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Key Contributions by the Swiss Tropical and Public Health Institute Towards New and Better Drugs for Tropical Diseases

Pascal Mäser*[ab], Sonja Bernhard[ab], Reto Brun[ab], Christian Burri[ab], Sébastien Gagneux[ab], Manuel W. Hetzel[ab], Marcel Kaiser[ab], Christian Lengeler[ab], Gerd Pluschke[ab], Elisabeth Reus[ab], Matthias Rottmann[ab], Jürg Utzinger[ab], Louisa Warryn[ab], Sergio Wittlin[ab], and Jennifer Keiser[ab]

Abstract: Thanks to its expertise in clinical research, epidemiology, infectious diseases, microbiology, parasitology, public health, translational research and tropical medicine, coupled with deeply rooted partnerships with institutions in low- and middle-income countries (LMICs), the Swiss Tropical and Public Health Institute (Swiss TPH) has been a key contributor in many drug research and development consortia involving academia, pharma and product development partnerships. Our know-how of the maintenance of parasites and their life-cycles in the laboratory, plus our strong ties to research centres and disease control programme managers in LMICs with access to field sites and laboratories, have enabled systems for drug efficacy testing *in vitro* and *in vivo*, clinical research, and modelling to support the experimental approaches. Thus, Swiss TPH has made fundamental contributions towards the development of new drugs – and the better use of old drugs – for neglected tropical diseases and infectious diseases of poverty, such as Buruli ulcer, Chagas disease, food-borne trematodiasis (*e.g.* clonorchiasis, fascioliasis and opisthorchiasis), human African trypanosomiasis, leishmaniasis, malaria, schistosomiasis, soil-transmitted helminthiasis and tuberculosis. In this article, we showcase the success stories of molecules to which Swiss TPH has made a substantial contribution regarding their use as anti-infective compounds with the ultimate aim to improve people's health and well-being.

Keywords: Drug research and development · Infectious diseases of poverty · Neglected tropical diseases · Product development partnership · Swiss TPH

The authors in the order of authorship, from left to right, top to bottom. Photos by Joachim Pelikan, Swiss TPH.

1. Introduction

The Swiss Tropical and Public Health Institute (Swiss TPH) has established, in its 80 years of history, a number of assets that placed it in a prime position for drug research and development (R&D), in particular for neglected tropical diseases and other infectious diseases of poverty.[1] These assets comprise expertise in clinical research, epidemiology, infectious diseases, microbiology, parasitology, public health, translational research and tropical medicine, and they range from capacity strengthening at field sites to molecular infectiology in highly specialized laboratories. Of foremost importance are (i) cell culture systems and animal models for the propagation of pathogens under physiological conditions, enabling drug efficacy testing *in vitro* and *in vivo*;[2] (ii) deeply rooted partnerships with institutions and sites in low- and middle-income countries (LMICs) that paved the way for high-standard clinical trials with local personnel; and (iii) clinical research and clinical operations expertise enabling translational medicine and evidence-based practice implementation in alignment with the UN Sustainable Development Goals (SDGs) 3 (good health and well-being) and 17 (partnerships for the goals).[3] Further enabling factors are Swiss TPH's expertise in modelling, pharmacokinetics (PK), bioinformatics, and molecular parasitology and microbiology (see the article by Meier *et al.* in this issue for a detailed overview).[3b] Thus, over the course of the past 30 years, Swiss TPH has made key contributions towards the development of new drugs – and the better use of old drugs – for neglected tropical diseases (*e.g.* Buruli ulcer, Chagas disease, food-borne trematodiasis, human African trypanosomiasis (HAT), leishmaniasis, schistosomiasis and soil-transmitted hel-

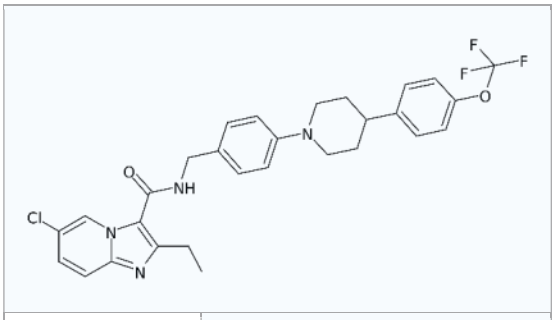
*Correspondence: Prof. P. Mäser, E-Mail: pascal.maeser@swisstph.ch
[a]Dept. Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, CH-4123 Allschwil, Switzerland; [b]University of Basel, CH-4001 Basel, Switzerland

minthiasis) and other infectious diseases of poverty (*e.g.* malaria and tuberculosis).

Developing new drugs requires multidisciplinary expertise, and effective partnerships are key to success. By working in drug R&D consortia, Swiss TPH is providing essential expertise along the value chain of innovation and validation to application, from the identification of new chemical hits over clinical trials to post-approval topics, such as access to medicines or pharmacovigilance. Our network of partnerships involves the Geneva-based product development partnerships (PDPs) Medicines for Malaria Venture (MMV) and Drugs for Neglected Diseases initiative (DND*i*), pharmaceutical companies from big pharma (*e.g.* Bayer, Merck and Novartis) to small and medium enterprises (SMEs), and a multitude of academic partners globally. Of particular note is the 20+ years of productive collaboration with Professor Kelly Chibale at the University of Cape Town in South Africa (Portrait in this issue[4]) and Professor Jonathan L. Vennerstrom at the University of Nebraska Medical Center in the United States of America (Portrait in this issue[5]) for developing new drugs against malaria and schistosomiasis.

In the following section, we present some of the success stories: old and new molecules to which Swiss TPH has made substantial contributions regarding anti-infective chemotherapy. Our article complements a companion piece by Meier and colleagues pertaining to repurposing know-how, published in this special issue of *CHIMIA*. Furthermore, our article is accompanied by interviews with Profs. Kelly Chibale[4] (University of Cape Town), Jonathan Vennerstrom[5] (University of Nebraska Medical Center) and Anna Hirsch (Helmholtz Institute for Pharmaceutical Research, Saarland)[123] to illustrate selected research partnerships.

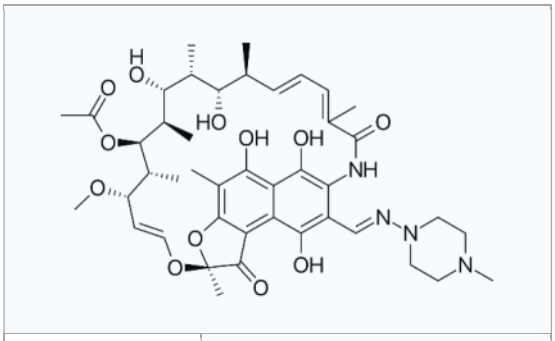
2. Telacebec



Name	**Telacebec**
Formula	$C_{29}H_{28}ClF_3N_4O_2$
Molecular weight	557.01
CAS No.	1334719-95-7
Indication(s)	Tuberculosis, leprosy, Buruli ulcer

Telacebec (Q203) is an inhibitor of cytochrome bc1 originally developed as a new lead for tuberculosis. As described in the accompanying article in this issue,[6] telacebec was subsequently found to be much more active against *Mycobacterium ulcerans* than *M. tuberculosis*, because *M. ulcerans* exclusively relies on cytochrome bc1 for oxidative phosphorylation, whereas an active cytochrome-bd oxidase bypass limits the potency of telacebec against *M. tuberculosis*.[7] Thus, the repurposing of telacebec for Buruli ulcer promises, at last, a faster treatment option for this elusive disease with fewer adverse events than the currently recommended antibiotic therapy.[8]

3. Rifampicin



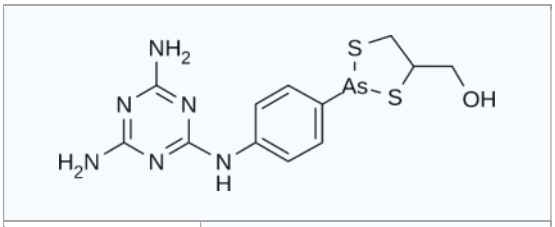
Name	**Rifampicin**
Formula	$C_{43}H_{58}N_4O_{12}$
Molecular weight	822.95
CAS No.	13292-46-1
Indication(s)	Tuberculosis

Rifampicin (also known as rifampin) was originally discovered in 1965.[9] In the 1970s, rifampicin became a cornerstone of the treatment against tuberculosis, allowing a reduction of the required treatment duration from an initial 2 years to 9 months when combined with isoniazid and ethambutol.[10] Today, rifampicin remains the most important component of the standard World Health Organization (WHO)-recommended 4-drug treatment regimen for drug-susceptible tuberculosis. In addition, rifampicin is also part of the standard treatment for leprosy[11] and Buruli ulcer.[12] As in most antibiotics, resistance to rifampicin started to emerge following the increasing roll-out of this drug.[13] In 1993, the first resistance-conferring mutations were described in *M. tuberculosis*,[14] and by now, the molecular basis of resistance to rifampicin has been elucidated in *M. tuberculosis* as well as in many other bacterial species.[15] Rifampicin binds to its target enzyme, the bacterial RNA polymerase, and thereby inhibits the transcription of DNA into RNA.[15] In *M. tuberculosis*, as in many other bacteria, rifampicin resistance is caused by mutations in RpoB, the β subunit of the RNA polymerase; these mutations reduce binding of the drug to its target, causing high- or low-level resistance, depending on the specific mutation.[15] Over the years, an increasing number of mutations have been identified in the rifampicin-resistance determining region of RpoB; these mutations are now being exploited as reliable diagnostic makers for rifampicin resistance in *M. tuberculosis*.[16]

While Swiss TPH was not involved in the development of rifampicin or in the original discovery of the main resistance mechanisms to this drug, researchers at Swiss TPH have made important contributions towards a deeper understanding of the biological and epidemiological consequences of rifampicin resistance in *M. tuberculosis*. It is widely acknowledged that antibiotic resistance can lead to a reduction in bacterial fitness in the absence of drug.[17] Swiss TPH researchers showed that, in the case of rifampicin, this fitness cost of resistance is not universal but its magnitude depends on the specific RpoB mutation.[18] Subsequently, the researchers discovered that secondary mutations in RpoA and RpoC of the mycobacterial RNA polymerase could compensate and reduce the initial fitness cost associated with rifampicin resistance-conferring mutations in RpoB.[19] Most recently, scientists at Swiss TPH and their collaborators used a combination of genomic epidemiology and phylodynamic modelling to show that these compensatory mutations also enhance the transmission potential of rifampicin-resistant *M. tuberculosis* between patients in the countries of Georgia[20] and South Africa.[21] Moreover, compensatory mutations were associated with a higher

number of drug resistance-conferring mutations, indicating that *M. tuberculosis* strains carrying compensatory mutations are more likely to acquire resistance to additional drugs compared to strains without compensatory mutations.[21] Taken together, these findings indicate that compensatory evolution plays an important role in the emergence and transmission of drug-resistant tuberculosis. In the light of the ongoing rollout of novel treatment regimens for drug-resistant tuberculosis,[22] surveillance should be implemented to identify the development and avoid the spread of additional drug resistance.

4. Melarsoprol



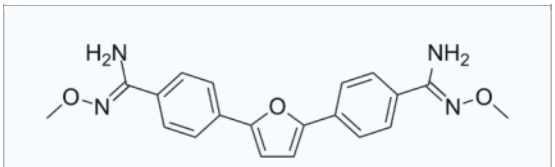
Name	**Melarsoprol**
Formula	$C_{12}H_{15}AsN_6OS_2$
Molecular weight	398.34
CAS No.	494-79-1
Indication(s)	Human African trypanosomiasis

Melarsoprol is used for the treatment of HAT, also known as sleeping sickness. HAT is caused by two subspecies of *Trypanosoma brucei*; *T. b. gambiense* in Western Africa and *T. b. rhodesiense* in Eastern Africa that are both transmitted by tsetse flies (*Glossina* spp.).[23] Due to the ability of the trypanosomes to cross the blood-brain barrier, the disease progresses from a first, haemolymphatic stage to the second, meningoencephalitic stage, which is generally fatal if untreated.

Introduced in 1949 by Erich Friedheim,[24] melarsoprol was the pinnacle in a long tradition of therapeutic arsenicals for HAT that had started with Livingstone's first mentioning of "arsenic as a remedy for the tsetse bite" in 1858.[25] Melarsoprol combined in a single molecule the melaminophenyl-based arsenical melarsen with an antidote of arsenic, dimercaptopropanol (British anti-Lewisite, BAL), whereby the arsenic was reduced to AsIII and complexed by the two thiol groups. Melarsoprol is highly active against *T. brucei* spp. and less toxic than other organic arsenicals. The selective activity of melaminophenyl arsenicals towards *T. brucei* is likely due to particular uptake routes in trypanosomes, *i.e.* the P2 aminopurine transporter[26] and the aquaglyceroporin AQP2,[27] which are absent from mammalian cells. The poor solubility of melarsoprol in water is a severe drawback, because the propylene glycol that is used as a solvent for intravenous injection causes thrombophlebitis and extreme pain.[28] Even more problematic than the solvent is the toxicity of melarsoprol itself (even though it is better tolerated than any other brain-permeable arsenical). The worst adverse event associated to melarsoprol is the encephalopathic syndrome (ES), which occurs in 5% to 10% of treated patients, and results in death in 10% to 50% of those in whom encephalopathy develops. Other severe adverse reactions reported are polyneuropathies, exfoliative dermatitis and neuropathies, which may occur in up to 10% of cases. Various, empirically developed, complicated treatment schedules were in use until the end of the last century. All consisted of three or four series of three to four injections, with intervening treatment free periods of 7 to 10 days. The total stay of 25 to 36 days not only limited hospital capacity but also imposed an immense burden on the accompanying families.[29] These issues, combined with a lack of alternative for melarsoprol, elicited the drug development activities at Swiss TPH.[3b] First, the PK and pharmacology of melarsoprol were elucidated and based on investigations in vervet monkeys and PK modelling, an abridged 10-day treatment schedule for melarsoprol was proposed. This proposed treatment schedule was tested in a pilot trial in the Democratic Republic of the Congo (DRC) and then in a large-scale clinical trial in Angola, followed by an implementation study in seven countries (Impamel I&II programmes; IMproved Application of MELarsoprol).[29,30] The efficacy of the abridged schedule was equal to the empirical schemes. In turn, this constituted a major socio-economic advantage, whereas the frequency of the ES remained at the same level. Later, the underlying cause for this severe adverse drug reaction was studied and the results supported the hypothesis that a genetically determined peculiar type of immune response confers susceptibility for ES.[31] In parallel, treatment failures started to emerge,[32] which corroborated the need for a completely new treatment approach and at the same time triggered research on the underlying resistance factors.

For several decades, melarsoprol was the only trypanocidal drug that could pass the blood-brain barrier to a sufficient extent to efficiently cure late-stage infections, nonetheless at the cost of frequently fatal adverse drug reactions. Melarsoprol therefore remained the first-line treatment until nifurtimox-eflornithine combination therapy (NECT) became included in the WHO Model List of Essential Medicines in 2009 after considerable clinical trial efforts by Médecins sans Frontières (MSF), DND*i* and Swiss TPH.[33] Today, the use of melarsoprol is restricted to *T. b. rhodesiense*; as so far, no treatment alternatives exist. However, recruitment into phase II/III clinical trials on fexinidazole against this form of the disease has been concluded in 2022.[34]

5. Pafuramidine



Name	**Pafuramidine**
Formula	$C_{20}H_{20}N_4O_3$
Molecular weight	364.40
CAS No.	186953-56-0
Indication(s)	Human African trypanosomiasis

Diamidines are symmetrical molecules with an amidine group at either end, which will be protonated at physiological pH. The diamidines have been widely used as trypanocidal agents. Pentamidine, introduced in 1937, is still a recommended drug to treat the first stage of West-African sleeping sickness, *i.e.* haemolymphatic infections with *T. b. gambiense* before the parasites have crossed the blood-brain barrier.[35] Diminazene (Berenil) is used for the treatment of Nagana in cattle, which is caused by *T. congolense*, *T. vivax* or *T. b. brucei*. The earliest diamidine to be tested against trypanosomiasis was synthalin, one of the first antidiabetic drugs. Synthalin had been repurposed for HAT with the idea that its hypoglycaemic effect would starve out the parasites. This was based on the discovery that *T. brucei* bloodstream forms consume massive amounts of glucose (because they do not have an active mitochondrion and exclusively depend on glycolysis to produce ATP). This somewhat naive and rather risky rationale seemed to pay off when synthalin and other diamidines exhibited exquisite trypanocidal activity in the rabbit model of infection. However, once appropriate culture systems had been developed for drug

efficacy testing on the bloodstream-form of *T. brucei*, it became apparent that the diamidines are highly active also *in vitro*. This proved that they are intrinsically trypanocidal, acting directly against the trypanosomes rather than by an indirect effect on the host blood glucose level. However, in this context, it is not surprising that a common adverse reaction of diamidine drugs is hypoglycaemia. The exact mechanism of action of the diamidines remains to be elucidated and appears to involve mitochondrial targets.[36]

Pafuramidine is the latest diamidine derivative introduced to the chemotherapy of HAT. Originally, its active form DB75 was tested against multiple acquired immune deficiency syndrome (AIDS)-associated opportunistic pathogens, including *Pneumocystis jirovecii*, *Cryptococcus neoformans*, *Candida albicans* and *Cryptosporidium parvum*.[37] In 1977, the activity of DB75 against African trypanosomes was detected *in vivo*; however, DB75 was only poorly available when orally administered.[38]

The Consortium for Parasitic Drug Development (CPDD), a non-profit consortium founded in 1999 by academic and industrial partners, endeavoured to undertake the clinical development of diamidines against HAT and visceral leishmaniasis.[39] The main partners working on HAT were the University of North Carolina at Chapel Hill and the Georgia State University for chemical synthesis and drug design, Swiss TPH for drug efficacy testing and conducting clinical trials and Immtech Pharmaceuticals as an industrial partner supporting the preclinical and clinical development as well as regulatory affairs and chemistry, manufacturing and controls (CMC).[40] The CPDD was successful in optimizing diamidines and related molecules to better fit the target product profile (TPP) for HAT, in particular with respect to oral bioavailability. Furamidine (DB75) was a first lead compound that was more potent against African trypanosomes than pentamidine, well tolerated by mammalian cells, and curative at a single injection of 25 mg/kg in a mouse model of stage I infection with *T. brucei*.[41]

However, DB75 was limited to intravenous application and therefore a prodrug strategy was followed to render furamidine orally available, masking the positively charged amidines with methoxy groups that are metabolized after absorption through the gastrointestinal barrier. The resulting molecule pafuramidine (DB289) was curative in the same mouse model of stage I infection when administered *per os* at four doses of 10 mg/kg.[41] Even more promising diamidine prodrugs were subsequently identified.[42]

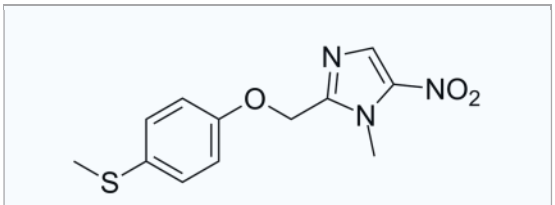
Initial phase I trials (single dose escalation, dose expansion with food effect and multiple dose escalation) were completed in 2001. A phase IIa study carried out in Angola and DRC with 32 patients demonstrated parasite eradication in the majority of subjects when treated orally with pafuramidine BID 100 mg for 5 days. Clinical tolerance was excellent in this study. A phase IIb study was then initiated in DRC, comparing oral pafuramidine to intramuscularly applied pentamidine. After observing treatment failures in the pafuramidine arm, the duration of this treatment was increased from 5 to 10 days (N=40 for DB289 5 days; N=30 for DB289 10 days). Pafuramidine was significantly better tolerated than pentamidine, and no treatment failures or relapses had been observed by the time the phase III study was initiated in 2005.[43]

The results of the phase III study carried out in Angola, DRC and South Sudan showed a non-inferior efficacy of pafuramidine compared to pentamidine in the general population (male and female participants older than 12 years); the same trend was observed in pregnant and lactating women (although sample size in these groups was too small for formal analysis). Generally, pafuramidine was well tolerated. However, three subjects experienced renal adverse events approximately 8 weeks post-treatment not judged to be related to the pafuramidine treatment by the investigator and the sponsor at the time, as other explanations for the adverse events were available. The patients who experienced renal toxicity recovered without sequelae, and the additional safety data obtained during the follow-up revealed no differences in abnormal biochemistry values between pafuramidine and pentamidine groups.[44]

While the phase III study was ongoing, an additional phase I study was conducted in South Africa to expand the limited safety data set. In this study, an extended treatment period of 14 days was tested to also cover the indication of *P. jirovecii*. Observed mild liver toxicity resulted in the hold of the clinical programme at the end of 2007.[45] While the reasons were explored, several treated participants developed severe kidney injury leading to the complete stop of the pafuramidine development programme in February 2008.

Definitive explanations for the kidney injury mechanism remain unclear until today. However, in a mouse diversity panel (MDP) to predict drug toxicity, KIM-1, an indicator of kidney injury, was found to be increased in 38% of the mouse strains tested. KIM-1, also called HAVCR1 (hepatitis A virus cellular receptor 1) or TIM1 (T-cell immunoglobulin mucin receptor 1), is a membrane protein which is expressed in the kidney, liver and spleen and plays different roles in immune diseases and kidney injury. Variation in susceptibility to renal injury as assessed in the MDP by KIM-1 was associated with sequence variation in genes related to cell proliferation, lipid biosynthesis and transport, oxidative stress and cytokine signalling. The associated genes are assumed to control the rate of cell proliferation in response to tubular injury, but may also have a role in susceptibility to initial injury and progression. Unfortunately, DNA samples from participants of the clinical DB289 studies were not available to test in humans the hypotheses generated by the mouse models.[46] Whereas the pafuramidine programme has been stopped, the search for new diamidine analogues with antiprotozoal activity has continued to date.[47]

6. Fexinidazole



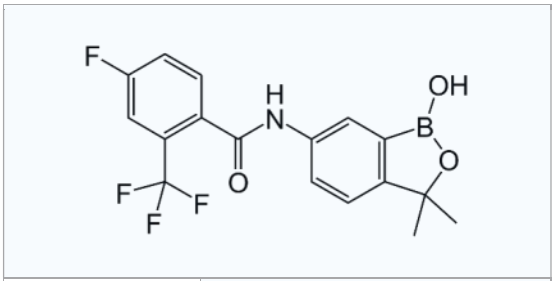
Name	**Fexinidazole**
Formula	$C_{12}H_{13}N_3O_3S$
Molecular weight	279.31
CAS No.	59729-37-2
Indication(s)	Human African trypanosomiasis

Fexinidazole was a breakthrough in the chemotherapy of HAT: the first oral drug, effective against stage I and stage II of the disease, and better tolerated than any other available treatment.[48] Given that the former 'gold' standard for stage II gambiense HAT, NECT,[49] still required 14 intravenous infusions (eflornithine monotherapy had even required 56 infusions), the introduction of the oral drug fexinidazole greatly improved the treatment of late-stage HAT. It also simplified the diagnostic algorithm: as a consequence of its good tolerability, fexinidazole can be given without prior lumbar puncture to verify the presence of trypanosomes in the cerebrospinal fluid. Thus, the introduction of fexinidazole as a first-line treatment facilitated the control of gambiense HAT, thereby increasing the coverage of infected individuals who will be treated and supporting the WHO goal of zero transmission of *gambiense* HAT by 2030.[46b]

Fexinidazole had originally been developed by Hoechst, now Sanofi, and was shown to be active against African trypanosomes *in vitro* and *in vivo*.[50] Based on the generally high trypanocidal activity and good oral bioavailability of the nitroimidazoles, DNDi launched a screening campaign to re-evaluate this old class of anti-infectives. Over 800 nitroimidazoles and related molecules were tested at Swiss TPH.[51] Starting from *in vitro* drug efficacy assays against different isolates of *T. brucei* subspecies, related pathogens and mammalian cell lines, promising molecules were selected for further evaluation in real-time assays that measured pharmacodynamic (PD) parameters such as onset-of-action and time-to-kill. Oral bioavailability and therapeutic efficacy against stage I or stage II infections was evaluated in different mouse models. This procedure finally identified fexinidazole as the best candidate for an oral drug against late-stage HAT.[51] Like most nitro-drugs, fexinidazole is a prodrug that is activated by chemical reduction of the nitro group. This is catalysed by nitroreductase I, an enzyme that is present in trypanosomatids and many bacteria but absent from mammalian cells.[52]

Swiss TPH also played an important role in the clinical development of fexinidazole. The centre piece was a pivotal phase II/III trial performed in DRC and the Central African Republic with second-stage HAT patients, flanked by two additional studies, one with first- and early second-stage patients and one with children aged above 6 years in any disease stage.[53] Based on the satisfactory performance regarding safety and efficacy, fexinidazole – formulated as 400 mg tablets – was granted a positive scientific opinion by the European Medicines Agency (EMA) in 2018. The WHO 2019 interim guidelines for the treatment of HAT already included fexinidazole,[54] allowing DRC to quickly approve and implement the new and better treatment option. Approval by the US Food and Drug Administration (FDA) for the treatment of both stages of West African sleeping sickness was granted in 2021.

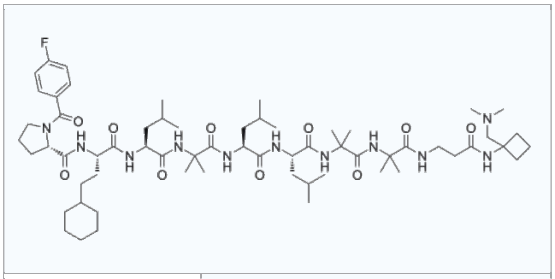
7. Acoziborole



Name	**Acoziborole**
Formula	$C_{17}H_{14}BF_4NO_3$
Molecular weight	367.11
CAS No.	1266084-51-8
Indication(s)	Human African trypanosomiasis

Acoziborole, originally called SCY-7158, is the lead compound of a series of boron-containing molecules originally developed by Anacor.[39] This company had specialized in the organic chemistry of boron. Based on the finding that several benzoxaboroles possess striking antitrypanosomal activity and are able to penetrate the blood-brain barrier, the class has the potential for a stage II drug against HAT (once the trypanosomes have invaded the cerebrospinal fluid).[39] Given the good oral bioavailability and long plasma half-life, there is hope for a single-dose oral cure of HAT. Swiss TPH was involved in the preclinical development of the benzoxaboroles, in particular regarding the *in vitro* assessment of drug efficacy against *T. b. gambiense* and *T. b. rhodesiense*, and PD parameters.[55] The lead compound acoziborole successfully passed a phase II/III clinical trial carried out by DND*i* against *gambiense* HAT in DRC and Guinea.[56] In DRC, study coordination and monitoring was done by Swiss TPH. Due to the declining number of cases, and as discussed with the EMA, the trial was performed non-randomized, *i.e.* without comparator treatment. Acoziborole compared favourably, in terms of both efficacy and tolerability, to data from previous trials with NECT in the same area (also supported by Swiss TPH).[33,49,57]

8. Lefleuganan



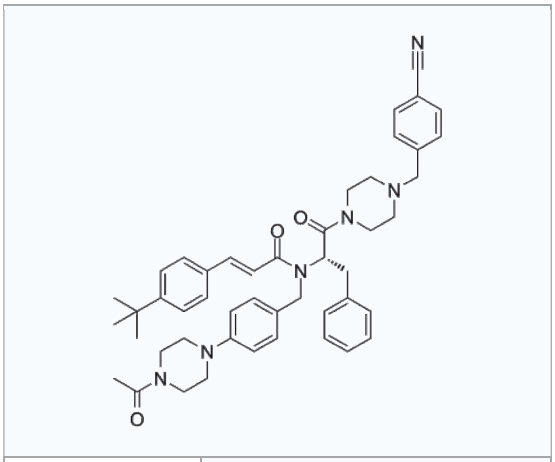
Name	**Lefleuganan**
Formula	$C_{62}H_{102}FN_{11}O_{10}$
Molecular weight	1180.54
CAS No.	2233558-98-8
Indication(s)	Cutaneous leishmaniasis

Lefleuganan, originally called ZHAWOC6027 or BAC6027,[58] is a novel type of antiparasitic drug candidate. It is a synthetic derivative of leucinostatin A, a natural nonapeptide from the fungus *Purpureocillium lilacinum* with broad antimicrobial activity.[59] Leucinostatin A has subnanomolar IC50 values against malaria parasites and African trypanosomes.[58] However, it is too toxic for use as a therapeutic agent.[60]

Under the lead of the company Bacoba AG, a consortium including the Zurich University of Applied Sciences (ZHAW) and Swiss TPH aimed to optimize leucinostatin A derivatives to reduce their toxicity while maintaining its antitrypanosomatid potency. This was achieved based on a detailed dissection of the structure–activity relationship (SAR).

The final candidate, lefleuganan, was as active as leucinostatin A against trypanosomatid parasites but less toxic to mammalian cells – and much easier to synthesize.[58] Lefleuganan appears to specifically target the trypanosomatid mitochondrion.[58] What exactly causes this selectivity remains to be elucidated. Trypanosomatid mitochondria are different from those of other eukaryotes regarding morphology, metabolism and gene expression.[61] Lefleuganan has the potential for a new, topical treatment of cutaneous leishmaniasis, the most widespread form of leishmaniasis. Cutaneous leishmaniasis is not lethal, but it is a disfiguring and stigmatizing disease of urgent need for better therapeutics. A clinical phase I trial for topical application of lefleuganan is currently under way.

9. ACT-451840

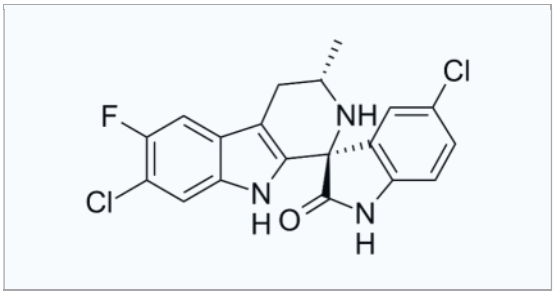


Name	**ACT-45180**
Formula	$C_{47}H_{54}N_6O_3$
Molecular weight	750.97
CAS No.	1984890-99-4
Indication(s)	Malaria

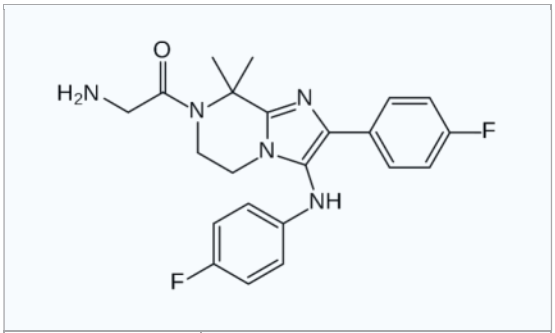
The antimalarial drug candidate ACT-451840 is the fruit of the collaboration between Actelion Ltd., Switzerland, and Swiss TPH.[62] A screening campaign against *Plasmodium falciparum* identified phenylalanine derivatives as promising starting points. Chemical optimization of the scaffold, based on extensive SAR studies, resulted in molecules with low nanomolar activity against *P. falciparum* and favourable drug metabolism and pharmacokinetics (DMPK) values for oral therapeutics.[63] ACT-451840 showed excellent activity in the *P. falciparum* SCID mouse model of infection (but, like all molecules of the series, lower activity against *P. berghei*).[63] The phenylalanine derivatives had originally been conceived as protease inhibitors, directed in particular against *P. falciparum* plasmepsins. However, ACT-451840 has a different mode of action, possibly involving inhibition of the *P. falciparum* transporter protein MDR1.[64] The clinical development of ACT-451840 was pursued under the auspices of MMV.

ACT-451840 exhibited good safety and tolerability in phase I testing.[65] Unfortunately, though, it had a rather strong food effect, *i.e.* higher drug levels in the fed than in the fasted state.[65] Tests in an experimental infection model with human volunteers (in the fed state) confirmed the rapid onset of action of ACT-451840 and also its gametocytocidal property.[66]

10. Cipargamin and Ganaplacide



Name	**Cipargamin**
Formula	$C_{19}H_{14}Cl_2FN_3O$
Molecular weight	390.24
CAS No.	1193314-23-6
Indication(s)	Malaria



Name	**Ganaplacide**
Formula	$C_{22}H_{23}F_2N_5O$
Molecular weight	411.46
CAS No.	1261113-96-5
Indication(s)	Malaria

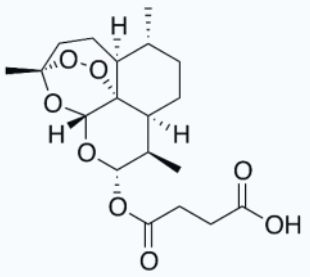
Cipargamin and ganaplacide are two antimalarial drug candidates that have been developed by a consortium of the Novartis Institute for Tropical Diseases in Singapore (now in Emeryville, CA, USA), Novartis in Basel, the Biomedical Primate Research Center in the Netherlands and Swiss TPH with financial support by the Wellcome Trust. Both molecules were developed from initial hits that had emerged from automated high-throughput phenotypic screens of Novartis chemical libraries against *P. falciparum*. Researchers at Swiss TPH supported the hit-to-lead optimization with their panel of antimalarial *in vitro* assays and *in vivo* models. Cipargamin and ganaplacide have the potential for novel kinds of malaria therapies: both have low nanomolar efficacy against malaria parasites – including mutants resistant to the current antimalarials, are well tolerated in humans and orally applicable.[67]

Cipargamin (originally called NITD609) was curative in the *P. berghei* mouse model of infection at a single oral dose, and it also showed transmission-blocking activity in mosquito feeding assays.[68] Cipargamin entered phase II clinical trials against malaria in 2013.[69] Currently, it is undergoing clinical evaluation in a phase II monotherapy (intravenous) study in patients with severe malaria. A striking feature of cipargamin is its ultrafast action *in vivo*.[69] It targets the ATPase PfATP4, an essential Na^+ pump of *P. falciparum*.[67a] The resulting accumulation of Na^+ ultimately kills the parasites. However, even before that, the disturbance in Na^+ homeostasis increases the rigidity of the infected erythrocyte, leading to its removal in the spleen. Hence, cipargamin displays

a faster antimalarial action *in vivo* than anticipated based on *in vitro* assays.

Ganaplacide (originally called KAF156) is in phase III clinical development in combination with lumefantrine (Swiss TPH supports Novartis with study management, monitoring, and logistics of the clinical phase II/III in DRC). Its exact mechanism of action remains to be elucidated. Like cipargamin, it showed transmission-blocking activity in mosquito feeding assays.[70] In addition, ganaplacide is also active against the *P. falciparum* liver stages and thus has the potential for malaria prophylaxis.[70]

11. Artesunate

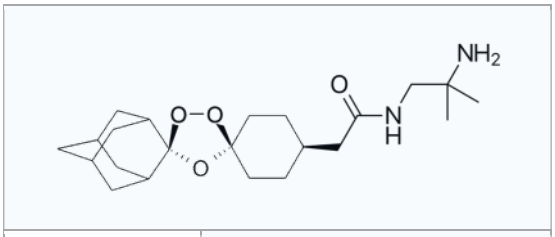


Name	**Artesunate**
Formula	$C_{19}H_{28}O_8$
Molecular weight	384.43
CAS No.	88495-63-0
Indication(s)	Malaria

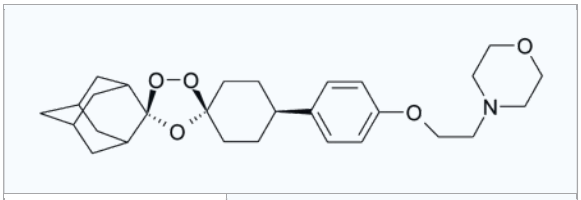
Derivatives of artemisinin extracted from the herb *Artemisia annua* form the backbone of present-day malaria treatment strategies worldwide.[71] The active metabolite dihydroartemisinin rapidly clears *Plasmodium* spp. parasites from the peripheral blood, though the compound is less effective against late-stage gametocytes.[72] The parenteral administration of artesunate is the recommended first-line treatment for severe malaria.[71] It was shown in randomized trials to be superior to quinine.[73] Rectal artesunate was shown to effectively clear malaria parasites[74] and in a randomized trial it reduced case fatality from severe malaria when provided to children <6 years of age before transfer to a referral facility compared to referral without treatment.[75] The WHO therefore recommends pre-referral rectal artesunate for children in this age group who suffer from suspected severe malaria in remote areas without prompt access to injectable antimalarials.[71]

In the context of a large-scale real-world roll-out of treatment interventions, aspects additional to treatment safety and efficacy are of operational importance as they may impact on treatment effectiveness and population-wide impact. In the MATIAS study, Swiss TPH and partners in DRC demonstrated that parenteral artesunate acted faster, was easier to use, and less costly to implement than parenteral quinine, providing strong supportive evidence for rapid national scale-up of injectable artesunate.[76] In the CARAMAL project on the other hand,[77] Swiss TPH and partners in DRC, Nigeria and Uganda found that the use of rectal artesunate by community-based health care providers may not extend the life-saving effect documented in a clinical trial setting. The project found serious shortfalls along the continuum of care such as incomplete referral and inadequate post-referral treatment at hospitals in addition to relatively high implementation costs.[78] The WHO subsequently issued information notes emphasizing the need to ensure a functioning continuum of care wherever rectal artesunate is implemented as pre-referral treatment.[79]

12. Arterolane and Artefenomel



Name	**Arterolane**
Formula	$C_{22}H_{36}N_2O_4$
Molecular weight	392.54
CAS No.	664338-39-0
Indication(s)	Malaria



Name	**Artefenomel**
Formula	$C_{28}H_{39}NO_5$
Molecular weight	469.61
CAS No.	1029939-86-3
Indication(s)	Malaria

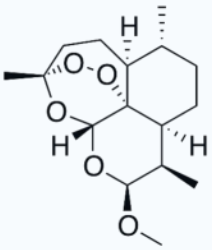
Artefenomel and arterolane are synthetic antimalarials that stem from the collaboration of the University of Nebraska Medical Center in the United States of America, Hoffmann-La Roche Ltd. and Basilea Pharmaceutica in Basel, Monash University in Australia, MMV in Geneva and Swiss TPH. The molecules were designed by Jonathan L. Vennerstrom, who has been collaborating with Swiss TPH for over a quarter of a century.[5] Artefenomel and arterolane are trioxolanes sandwiched by a conserved adamantane part and cyclohexane with a variable substituent. The ozonide pharmacophore resembles that of the natural artemisinins and, indeed, the mechanism of action is thought to be the same for both: these antimalarials are prodrugs that need to be activated by chemical reduction of the endoperoxide bridge.[80] This only happens in the malaria parasites, because the required electron is donated by ferrous haem, the end-product of haemoglobin degradation by the parasite inside the erythrocyte. This reduction then leads to the formation of radicals and ultimately to uncontrolled, stochastic alkylation of *P. falciparum* proteins and haeme itself.[81]

While the natural artemisinins and the synthetic ozonides have the same mechanism of action, the latter have two major advantages: they are easier to produce and they can be chemically optimized, in particular regarding their PK properties. The goal of the consortium, with the guidance of MMV, was to make a new drug that is as effective and as well tolerated as artemisinin but has a longer half-life in the human body, so that it may provide a single-dose cure for malaria. A first drug candidate, arterolane (OZ277), was highly promising but turned out to have a shorter half-life of excretion in malaria patients than in uninfected individuals.[82] Nevertheless, Ranbaxy Laboratories Ltd. (now Sun Pharmaceuticals) went ahead and registered arterolane-piperaquine combination therapy under the brand name Synriam, which is being used as a new antimalarial in India, Cameroon, Côte d'Ivoire, Guinea, Kenya, Nigeria, Senegal and Uganda. It is worth highlighting that OZ277 was also tested against *Schistoso-*

ma mansoni and *S. haematobium* in a proof of concept clinical trial,[83] following laboratory investigations in line with the in depth investigations of antimalarials on schistosomiasis,[84] which will be discussed in more detail below.

Meanwhile, the Consortium had synthesized second-generation ozonides with prolonged half-lives in the human body also in the presence of malaria parasites. The frontrunner artefenomel (OZ439) was curative in the mouse model of infection at a single oral dose[85] and has passed phase I and phase II clinical trials.[86] As a result of its better PK profile, artefenomel is more potent than arterolane or artemisinin also against Kelch-13 mutant *P. falciparum*.[87] However, the hope for a single-dose cure for malaria has so far not been realized due to the difficulty of formulation.[88] Still, artefenomel offers a replacement option of artemisinin in antimalarial combination therapy.[89]

13. Artemether

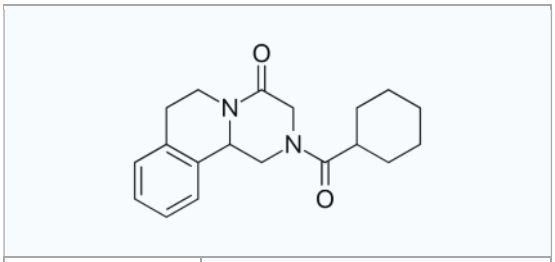


Name	**Artemether**
Formula	$C_{16}H_{26}O_5$
Molecular weight	298.38
CAS No.	71963-77-4
Indication(s)	Malaria, schistosomiasis

Artemether – like artesunate – is a semi-synthetic derivative of artemisinin, the active principle in the leaves of *A. annua*, a plant that is widespread in the People's Republic of China and has been utilized in traditional medicine for thousands of years. Artemisinin was isolated in the early 1970s,[90] underwent detailed laboratory investigation and clinical trials, and became the most important class of antimalarials, particularly in the frame of artemisinin-based combination therapy (ACT).[91] Currently, a new paediatric formulation with adapted ratio of artemether:lumefantrine (1:12) is in clinical development as the first treatment of malaria in babies below 5 kg bodyweight in several African countries. Swiss TPH is in charge of study management, monitoring and logistics in DRC.

The activity of artemisinin and its derivatives artemether and artesunate against *Schistosoma japonicum* was discovered in the early 1980s.[92] In contrast to praziquantel (the current treatment of choice for all species of Schistosoma), *in vivo* studies found highest activities against schistosomula (the juvenile developing stages), while adult worms were less affected by the artemisinins. Subsequent studies found that the artemisinins were also active against *S. mansoni* and *S. haematobium*, particularly against schistosomula.[93] In the 1990s, a series of randomized controlled trials were carried out in the People's Republic of China with individuals infected by *S. japonicum* who were treated with repeated doses of artemether (or artesunate). Data from more than 17,000 people revealed high efficacy (60–100%). Researchers at Swiss TPH with colleagues from Côte d'Ivoire conducted the first randomized placebo-controlled clinical trials with artemether for prevention of *S. mansoni* and *S. haematobium*. Repeated oral artemether at a dose 6 mg/kg, administered to school-aged children every 3 or 4 weeks was well tolerated and resulted in efficacies of 50% and 25%, respectively.[94] In recent years, additional studies with artemether (and artesunate), given alone or in combination with praziquantel or other antimalarials, have been conducted with mixed results.[95] Hence, our conclusion is that the artemisinins show some promise against schistosomiasis. However, praziquantel clearly remains the drug of choice for schistosomiasis.

14. Praziquantel



Name	**Praziquantel**
Formula	$C_{19}H_{24}N_2O_2$
Molecular weight	312.41
CAS No.	55268-74-1
Indication(s)	Schistosomiasis, food-borne trematodiasis

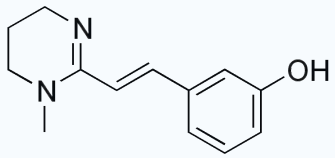
Praziquantel is the drug of choice against all schistosome species infecting humans and several species of food-borne trematodes.[96] The discovery of the antischistosomal properties of praziquantel goes back to the early 1970s, when Bayer pursued *in vivo* screening of some 400 pyrazinoisoquinoline derivatives that were synthesized at Merck.[97] Data from comprehensive laboratory studies published in 1977 revealed a broad spectrum of activity of praziquantel against the different *Schistosoma* species investigated in different animal models. Interestingly, drug susceptibility was largely restricted to the invasive stages and the adult worms, while schistosomula were less susceptible.[98] Subsequent clinical trials conducted in Brazil, the Philippines and Zambia with individuals infected with *S. mansoni*, *S. japonicum* and *S. haematobium*, respectively, found that praziquantel is efficacious and safe.[96a] To date, hundreds of millions of people have been treated with praziquantel, mainly through preventive chemotherapy campaigns targeting school-aged children in schistosomiasis-endemic countries.

Over the past 30 years, Swiss TPH contributed to numerous studies in the laboratory and in clinical trials to deepen the understanding of the safety and efficacy profile of praziquantel. Specifically, the efficacy has been determined using rigorous diagnostic approaches[99] and through modelling in the absence of a diagnostic 'gold' standard.[100] The efficacy of praziquantel was assessed according to pre-treatment infection intensity[101] and the effect of two closely spaced praziquantel treatments was determined in terms of cure and egg reduction rates and adverse events.[101,102] Praziquantel-based combination therapies (*i.e.* praziquantel-mefloquine and praziquantel-mefloquine-artesunate) were tested in patients, but did not augment the therapeutic efficacy when compared to praziquantel alone.[103]

In the absence of a paediatric formulation, researchers at Swiss TPH and colleagues tested the efficacy of crushed praziquantel tablets in preschool-aged children in Côte d'Ivoire[104] and a praziquantel syrup registered in Egypt and in preschool-aged children in Niger.[105] The development of a child-friendly formulation, substituting racemic praziquantel with its active (*R*)-enantiomer (alternatively called (–)-PZQ or L-PZQ), was launched

over a decade ago. Within the frame of the Paediatric Praziquantel Consortium, led by Merck, Swiss TPH managed the phase II and phase III trials with an orally dispersible tablet of L-PZQ that is seeking approval by EMA. Moreover, researchers at Swiss TPH were involved in a series of cluster randomized trials to gain and sustain schistosomiasis control and to break transmission in Côte d'Ivoire and Zanzibar, facilitated by the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) with funding from the Bill & Melinda Gates Foundation.[106]

15. Oxantel Pamoate

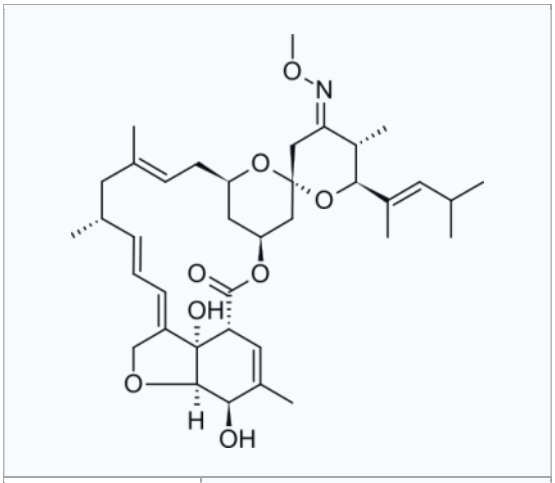


Name	**Oxantel**
Formula	$C_{13}H_{16}N_2O$
Molecular weight	216.28
CAS No.	36531-26-7
Indication(s)	*Trichuris trichiura* infection

Few anthelminthics are available to treat soil-transmitted helminthiasis with two benzimidazoles (*i.e.* albendazole and mebendazole) being the most widely used drugs. Administered at a single oral dose, the regimen applied in preventive chemotherapy programmes, both albendazole and mebendazole show a low efficacy against *Trichuris trichiura* (whipworm) infections.[107]

Oxantel pamoate, a tetrahydropyrimidine, is marketed in combination with pyrantel pamoate to treat soil-transmitted helminth infections in several South American and Asian countries. The drug is also widely used in veterinary medicine. Researchers at Swiss TPH have thoroughly characterized oxantel pamoate against *Trichuris muris*, *Ancylostoma ceylanicum* and *Necator americanus* both *in vitro* and *in vivo* and compared the activity of the drug to the standard anthelminthics (*e.g.* albendazole and mebendazole).[108] Oxantel pamoate showed a significantly higher activity compared to the standard anthelminthics against *T. muris* but lacked activity against hookworm. In a subsequent step, combination chemotherapy was explored in laboratory studies.[108] These findings set the stage for numerous phase II investigator-initiated trials sponsored by Swiss TPH assessing the efficacy and safety of the combination of albendazole-oxantel pamoate.[109] In comparison to monotherapy with the recommended albendazole or mebendazole, albendazole-oxantel pamoate showed a broad-spectrum of activity against soil-transmitted helminthiasis. Hence, oxantel pamoate lends itself as an important addition to the depleted drug armamentarium for *T. trichiura* infections. Additionally, having an alternative anthelminthic drug with a different mechanism of action than albendazole and mebendazole is crucial to delay the development and spread of resistance to existing drugs. In order to advance oxantel pamoate towards mono registration at a stringent regulatory authority for the use against *T. trichiura*, the EU-funded HELP project is preparing a regulatory phase Ib study sponsored by Swiss TPH in Tanzania that is scheduled to be completed in 2024. For the study, a chewable tablet formulation with 250 mg oxantel pamoate was developed.

16. Moxidectin



Name	**Moxidectin**
Formula	$C_{37}H_{53}NO_8$
Molecular weight	639.83
CAS No.	113507-06-5
Indication(s)	Broad-spectrum anthelminthic

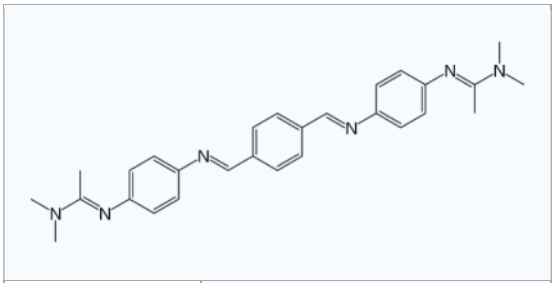
The macrocyclic lactone moxidectin was approved in 2018 for the treatment of onchocerciasis (river blindness). Following a drug repurposing approach and given the low number of drugs for soil-transmitted helminthiasis, researchers at Swiss TPH were interested to evaluate moxidectin against infections with *Strongyloides stercoralis* and *T. trichiura*.

Studies conducted by Swiss TPH using *Strongyloides ratti* as a laboratory model of *Strongyloides* spp. found excellent activity of moxidectin *in vitro* and *in vivo*. Hence, it was suggested to explore moxidectin for the treatment of human strongyloidiasis.[110]

A dose-ranging phase IIa study conducted in Lao People's Democratic Republic (PDR) in 209 *S. stercoralis*-infected participants defined 8 mg of moxidectin as the optimum dose for *S. stercoralis* infection due to a flattening dose–response curve at this level (cure rate = 83%, larval reduction rate = 98%).[111] Phase IIb studies in Lao PDR and Cambodia comparing moxidectin to the treatment of choice against strongyloidiasis (*i.e.* ivermectin) are currently ongoing. In the framework of the clinical trials, PK studies were conducted to run population-based pharmacometric modelling, which supported the use of the 8 mg weight independent dose of moxidectin.[112]

Swiss TPH acted as the sponsor in clinical trials against *T. trichiura* to determine in a first step the dose-response of moxidectin monotherapy and combination chemotherapy (8, 16 or 24 mg of moxidectin monotherapy; 8, 16 or 24 mg of moxidectin plus 400 mg of albendazole combination therapy). Moxidectin-albendazole was found to be superior to moxidectin and doses of 8 mg moxidectin plus 400 mg albendazole defined for further evaluation.[113] A recent head-by-head clinical evaluation of moxidectin-albendazole and ivermectin-albendazole against *T. trichiura* showed inferiority of moxidectin and albendazole to ivermectin and albendazole against *T. trichiura* but superiority to monotherapy.[114]

17. Tribendimidine

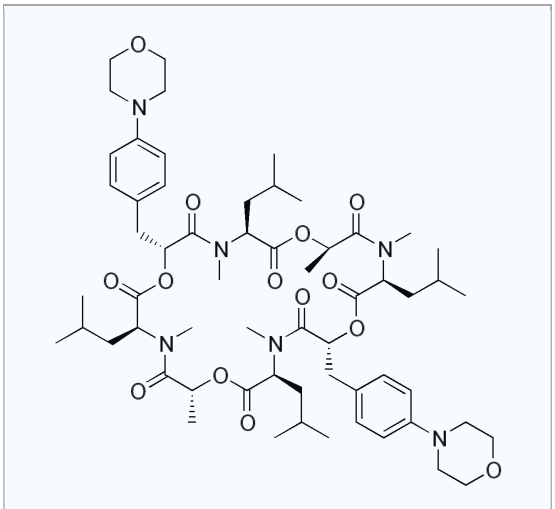


Name	**Tribendimidine**
Formula	$C_{28}H_{32}N_6$
Molecular weight	452.61
CAS No.	115103-15-6
Indication(s)	Broad-spectrum anthelminthic

Tribendimidine is an anthelminthic marketed in the People's Republic of China, characterized by a broad spectrum of activity. It is a derivative of amidantel.[115] The drug has not only activity against nematodes, including *Ascaris lumbricoides* (roundworm) and hookworm, but also high activity against the liver flukes *Clonorchis sinensis* and *Opisthorchis viverrini*.[116]

Swiss TPH contributed to a range of preclinical and clinical studies with tribendimidine.[117] For example, phase IIa and IIb studies were conducted against both *C. sinensis* and *O. viverrini* highlighting that the drug has a remarkable efficacy and might serve as a treatment alternative to praziquantel.[118] With regard to the indication of soil-transmitted helminthiasis dose-ranging studies[119] and clinical trials using tribendimidine as combination chemotherapy were carried out.[109c]

18. Emodepside



Name	**Emodepside**
Formula	$C_{60}H_{90}N_6O_{14}$
Molecular weight	1119.41
CAS No.	155030-63-0
Indication(s)	Gastrointestinal nematodes

The veterinary drug emodepside is used in cats and dogs for helminth infections. The cyclooctadepsipeptide has a unique mechanism of action on the calcium-activated potassium (SLO) channel. More than a decade ago, the drug was considered as an interesting drug development candidate for soil-transmitted helminth infections.[120]

Preclinical studies at Swiss TPH with emodepside revealed high activity in laboratory models for human soil-transmitted helminth infections.[121] The development of a tablet formulation by Bayer and the completion of phase I trials by Bayer and DNDi against onchocerciasis provided a strong foundation on which Swiss TPH launched two phase IIa trials against hookworm and *T. trichiura* infections among adult participants in Pemba, Tanzania. At the lowest dose tested (5 mg) emodepside showed high efficacy against *T. trichiura* (cure rate above 80%), while complete cure of all patients was achieved with a dose of 15 mg. Against hookworm infections 25–30 mg of emodepside revealed the highest activity.[122] Phase IIb and PK studies have been launched. The ultimate goal is to register the drug with an indication against soil-transmitted helminth infection at the Food and Drug Administration (FDA), for which a regulatory phase III trial is planned.

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