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The structural diversity and promise of antiparasitic marine invertebrate-derived small molecules

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Abstract

This review focuses on six important parasitic diseases that adversely affect the health and lives of over one billion people worldwide. In light of the global human impact of these neglected tropical diseases (NTDs), several initiatives and campaigns have been mounted to eradicate these infections once and for all. Currently available therapeutics summarized herein are either ineffective and/or have severe and deleterious side effects. Resistant strains continue to emerge and there is an overall unmet and urgent need for new antiparasitic drugs. Marine-derived small molecules (MDSMs) from invertebrates comprise an extremely diverse and promising source of compounds from a wide variety of structural classes. New discoveries of marine natural product privileged structures and compound classes that are being made via natural product library screening using whole cell *in vitro* assays are highlighted. It is striking to note that for the first time in history the entire genomes of all six parasites have been sequenced and additional transcriptome and proteomic analyses are available. Furthermore, open and shared, publicly available databases of the genome sequences, compounds, screening assays, and druggable molecular targets are being used by the worldwide research community. A combined assessment of all of the above factors, especially of current discoveries in marine natural products, implies a brighter future with more effective, affordable, and benign antiparasitic therapeutics.

Introduction

Today over one billion people worldwide are at risk for contracting and battling tropical infectious diseases caused by parasitic organisms. Scores of countries, mostly in the Third World, are impacted and the World Health Organization now classifies many of these ailments as neglected tropical diseases (NTDs) (Neglected tropical diseases; URL: http://www.who.int/neglecteddiseases/). For decades the natural products community has engaged in the quest to identify small molecule leads to develop robust chemo-therapeutics against NTDs. However, most of these efforts are nascent and must now be invigorated because the humanitarian benefit from a breakthrough could be enormous. For example, as we begin a new decade, it is unthinkable that in the Third World one child dies every 30 s due to Malaria (10 Facts on malaria; URL: http://www.who.int/features/factfiles/malaria/). The goal of this brief account, which covers the period January 2008–August 2010, is to focus on six important parasitic diseases. These constitute notable targets for discovery and pipeline-building based on compounds emerging from the study of marine-derived small molecules (MDSMs) from invertebrates.

In a review published in 1993 [1] we discussed the existence of relevant parasitic diseases caused by helminth (19 examples) and protozoal (12 examples) parasites that could be targets

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for the discovery of MDSMs. In this focused update, we present trends and opportunities through an important subset of six diseases —Malaria, Schistosomiasis, Chagas Disease, River Blindness, Leishmaniasis, and Sleeping Sickness. An overview of the various terms associated with these diseases, their causative parasite, the transferring host organism, and estimated global human impact is summarized in Table 1. Protozoan parasites transferred to a human host through an insect bite are the cause of Malaria, Chagas Disease, Leishmaniasis, and Sleeping Sickness. Helminth diseases are the category for the other two entries, Schistosomiasis and River Blindness. Trematodes (blood flukes) of the genus *Schistosoma* flourish inside freshwater snails and enter the human host directly through the skin causing schistosomiasis. Lastly, River Blindness is the result of a common endosymbiotic relationship between a bacterium (*Wolbachia pipientis*) and a nematode (*Onchocerca volvulus*), which enter the human bloodstream through a blackfly bite. For a more detailed overview of life cycles of these parasites and disease symptoms the reader is directed to the World Health Organization (WHO Fact Sheets; URL: http://www.who.int/mediacentre/fact-sheets) and the Centers for Disease Control and Prevention (CDC Index of Parasitic Diseases; URL: http://www.cdc.gov/ncidod/dpd/parasites/).

The answer to the obvious question — What current therapeutics exist for treating these diseases? — appears in the form of the 17 molecular structures shown in Figure 1. The compounds of this list represent ancient first generation drugs (see dates of their discovery — one can be traced back to 1921), many are somewhat toxic (see examples with As and Sb), several are difficult to administer, and almost all suffer from the continuing emergence of resistant parasite strains. Few among this list (only 31%) are based on a natural product, which is in contrast to the situation with anti-infectives where greater than 65% of clinical agents are of such origin [2].

Initiatives are now rapidly emerging to overcome the well-known hurdles (development expense, distribution to low income and remote populations, target finding) for developing antiparasitics to combat the entries of Table 1. Assisting in the push forward to encourage natural products based-discoveries are a multitude of opportunities headed by US federally funded International Cooperative Biodiversity Groups (ICBG), The Bill & Melinda Gates Foundation, the Drugs for Neglected Diseases Initiative (DNDi), the Special Program for Research and Training in Tropical Diseases (TDR), the Medicines For Malaria Venture (MMV), the Anti-Wolbachia (A-WOL) Consortium, the Institute for One World Health, the Seattle Biomedical Research Institute, and the Sandler Center for Basic Research in Parasitic Diseases at UC San Francisco. These and other programs will lead to the next generation of discoveries and we believe MDSMs will play an ever-expanding role because of proof-of-concept discoveries that have emerged during the last decade.

An important preamble

Before proceeding, it is important to mention some trends as well as milestone discoveries that provide a platform for future developments. First, very few compounds on the list in Table 1 have dates post 1990. This indicates there may be low-hanging molecular fruit as templates for future research. Second, several antiparasitic drugs in Figure 1 are derived directly from natural sources (amphotericin B, ivermectin) or are based on natural product scaffolds (artesunate, mefloquine, and doxycy-cline), demonstrating the power of natural products in the antiparasitic drug discovery pipeline. Third, recently, the screening of natural product libraries using whole cell *in vitro* assays proved to be an effective paradigm for Novartis to uncover a new antimalarial lead compound [3]. Fourth, several academic groups are also engaged in the screening of MDSMs for antiparasitic leads and encouraging results have emerged in the past decade. Strikingly, sponges have been a significant source of antimalarial active scaffolds

headed by compounds with diverse structures such as the manzamines, plakortins, isoaaptamines, axisonitriles, and homofascaplysins [4••,5••].

Despite the global relevance and lack of adequate therapeutics for Schistosomiasis and River Blindness (Table 1), screening of both plant and marine natural products has been focused only on *P. falciparum, T. brucei* sp., *Leishmania* sp. and *T. cruzi* and lead natural product scaffolds against these four protozoa have been outlined in a recent review [6]. Other reviews of interest include more specific reports covering drug resistance and natural product screening for *T. brucei* sp. [7], *P. falciparum* [8], and *Leishmania* sp. [9], with the main focus on plant metabolites. Natural products from medicinal plants with activity against *T. cruzi* were also highlighted [10], and two publications summarizing the discovery and development of marine antimalarials [4••,5••] recently appeared.

The synopsis in Figure 2 reflects these previous reviews and our supplemental literature searches. The 133 compounds included in this collection, discovered from 2008 to 2010, all displayed an IC_{50} below 30 μM against one or more parasites during *in vitro* screening. It is evident that marine sponges provide the majority of antiparasitic MDSMs with 87 compounds included in 30 publications between 2008 and 2010 [11–14,15•,16,[17],[18•],[19],[20•],[21_27],[28•],[29_31],[32•],[33],[34•],[35],[36•],37•,38•,39•,40]. Marine-derived fungi have produced the next largest set of 20 compounds, reported in only four papers [41–44] and cyanobacteria follow with 11 compounds included in eight reports [45–52]. Marine algae [53], actinomycetes [54–56], and hard corals [57–60] supplied four antiparasitic MDSMs each, and the final three metabolites were isolated from an ascidian [61•]. The remainder of this account will be focused on compounds from marine invertebrates (sponges, corals, and ascidians: 94 compounds, 70.7%) versus microorganism-derived molecules (fungi, cyanobacteria, actinomycetes, algae: 39 compounds, 29.3%) based on the special interest of this review.

The 94 invertebrate-derived structures are divided into eight classes on the basis of their molecular formulas and structural motifs as shown in Figure 3. Compounds containing only carbon, hydrogen and oxygen (47 compounds, 50%) are the most abundant and have been divided into four classes: endoperoxides, oxoterpenes, polyketides, and steroids. Nitrogen-containing compounds (32 compounds, 34%) are also divided into subclasses of alkaloids, peptides, and isonitrile (*CN*-R) terpenes and the unique structures possessing halogen atoms comprise their own class (15 compounds, 16%).

A snapshot of selected natural products

Twenty compounds were chosen to represent the outstanding structural diversity of antiparasitic MDSMs from invertebrates and they are displayed in Figure 4 along with the IC_{50} (μM) results obtained from *in vitro* screening. Our discussion will be limited to the most potent compounds of each molecular type, and the reader is encouraged to examine the cited literature for a more comprehensive overview. Assay standards listed in Table 2 provide the benchmark for comparison of *in vitro* bioassay data for the MDSMs discussed below.

Compounds containing carbon, hydrogen and oxygen

Endoperoxides [18•,20•,22,27,32•,35]. These polyketide and terpenoid compounds display activities against *P. falciparum* and *T. brucei* in the nanomolar range, and also inhibit growth of *T. cruzi* at concentrations that are comparable with current assay standards. These multiple activities mirror the use of pentamidine and nifurtimox for the treatment of more than one parasitic disease. Interestingly, the antimalarial endoperoxy polyketide manadoperoxide A (**1**) showed a greater growth inhibition of a chloroquine resistant (CQR) strain of *P. falciparum* versus a chloroquine sensitive (CQS) strain [18•]. Compounds isolated from *Plakortis* sp. and *Diacarnus bismarckensis* displayed activity against *T. brucei*, although the

polyketide **2** [20•] surpassed other terpenes in potency, including compound **4** [32•]. Limited screening of this compound class has been completed versus *T. cruzi*; however, endoperoxide **3** demonstrated growth inhibition equal with that of nifurtimox (Table 2) [22] and also showed modest activity against *L. donovani*.

Terpenes [21,30,59,60], *Steroids*, [26,31,37•], *and Polyketides* [17,25,35]. Other oxygen-containing terpenes display broad spectrum antiparasitic activities similar to the endoperoxy group, albeit with much less effectiveness. Two examples are the coral-derived compound **5** [60] and compound **6** from a *Spongia* sp. [30]. Compound **7**, from a group of steroidal saponins, showed high potency against *L. donovani*. This represents a 20-fold improvement over the assay standard benznidazole; however, the selectivity for **7** between mammalian cells (IC_{50} = 0.2 μM, rat myoblast) and the parasite was relatively low (SI = 4.0) [31]. Another antileishmanial steroid **8** was isolated from a *Crella* sp. sponge collected in Antarctica, but was less potent than **7**. Recent reports on antiparasitic polyketides focus on screening against *P. falciparum*. One highlight is the sulfonated compound **9** that showed excellent growth inhibition of CQR strains and little cytotoxicity versus mammalian cells (IC_{50} = 45.0 μM, MCF-7, SI = 512).

Compounds containing nitrogen

Alkaloids [11,13,15•,23,[34•],36•,39•,57,61•] and *CN-R terpenes* [37•,38•]. Like the endoperoxide group of structures, alkaloids from invertebrates exhibited powerful bioactivity in multiple antiparasitic screens, with greatest potency against *T. brucei* and *P. falciparum*. Notable compounds include the pyridoacridone compounds **10** [61•] and **11** [13], a terpene alkaloid (**12**) [36•], the β-carboline **13**, and guanidine alkaloids **14** [23] and **15** [34•]. Other nanomolar growth inhibitors of *P. falciparum* include the isonitrile-containing terpenes **16** [37•] and **17** [38•]. An outstanding selectivity index of (>154) was observed between the *P. falciparum* CQR strain and human fibroblast cells (IC_{50} = 13.9 μM) for compound **16**.

Compounds containing halogen atoms

Halogenated metabolites [13,14,16,19,24,28•,33,40]. Secondary metabolites containing halogen atoms are commonly isolated from marine organisms and these compounds often elicit biological responses. Girolline (**18**), a relatively simple structure, is no exception, showing strong growth inhibition effects in several strains of *P. falciparum* in the nanomolar range. A similar pattern was reported for discorhabdin A (**20**), which showed equal activity in CQS and CQR strains of *P. falciparum*. The complex polycyclic alkaloid dibromopalau'amine (**19**) exhibited low micromolar IC_{50}'s for *P. falciparum*, *T. brucei rhodiense* and *L. donovani* and showed modest selectivity (SI = 9.8) for *T. brucei rhodesiense* versus mammalian cells (rat myoblast, IC_{50} = 7.8 μM) [33]. A greater selectivity index of 27.2 was reported for compound **18** between Vero cells (IC_{50} = 2.1 μM) and a CQR strain *P. falciparum* [12].

Concluding remarks

The prospects for structure–activity relationship (SAR)-driven mining of MDSM-derived pharmacophores as antiparasitics against the targets shown in Table 1 are significant. Considerable structural diversity is represented in the 94 relevant structures we examined (as illustrated by the subset in Figure 4) and is the basis for the recommendation of six structural classes that are ripe for further development. This final list is based on biological properties of potency and/or selectivity, on new insights gained during the last 2.5 years on previously studied pharmacophores, plus new insights obtained for analogs based on structures examined in the past. The scaffolds among this list shown in Table 3 include: endoperoxides, guanidine alkaloids, β-carboline alkaloids, pyridoacridone alkaloids, isonitrile (*CN*-R) terpenes, and terpene alkaloids.

Comparing the information in the two center columns of Table 3 illustrates that, while no significant new structure types have been identified, significant interest and effort is being devoted to enhancing the lead potential of legacy pharmacophores. Here are some specific examples to underscore this point. The antimalarial activity of plakortin (**21**) was discovered in 2003 (IC_{50} = 0.87 μM (*P. falciparum* D10-CQS), IC_{50} = 0.41 μM (*P. falciparum* W2-CQR)) [62] and its potency against *P. falciparum* has not been surpassed by any other endoperoxide (such as **1**–**4**). Significantly, endoperoxide **2** represents a *new lead compound* for Sleeping Sickness; it possesses nanomolar potency against *T. brucei* and 100-fold selectivity versus mammalian cells (HEK293) [20•]. Similarly, in 2000 manzamine A (**23**) (original structure published in 1986) was found to have antimalarial properties [63]. Its recent re-isolation along with the zamamadine (**13**) series of compounds [39•] not only showed that manzamine A is still the most potent antimalarial β-carboline alkaloid, but also uncovered its trypanocidal properties (IC_{50} = 0.07 μM, *T. brucei rhodesiense*). However, concerns about the cytotoxicity of **23** remain unresolved. Among the guanidine alkaloids, crambescidin 800 (**24**) (IC_{50} = 0.16 μM (*P. falciparum* 3D7-CQS), IC_{50} = 0.24 μM (*P. falciparum* FCR3-CQR)) [64] is more potent than batzelladines (compounds **14**, **15**). New prospects have been discovered for the pyridoacridone class, whose analogs have been poorly studied. In particular, ascididemin (**22**) exhibits nM activity against *Plasmodium* and *Trypanosoma* [61•,65]. The isonitrile-containing terpenoids represent a class known since 1973 and while kalihinol A (**25**) is exquisitely potent (*P. falciparum* IC_{50} = 0.001 μM) [66] this activity level is matched by that of amphilectenes (**16**, **17**). The isonitrile functionality is the warhead for activity, putatively by disruption of heme [67]. The known agelasine class represents a new opportunity for further study; however, compound **12** is less potent than other legacy compounds.

In summary, our analysis of the discovery of active invertebrate-derived MDSMs suggests the following trends: First, most of the information gained from *in vitro* screening studies in the last three years has provided additional structure–activity information for established antimalarial compounds [4••]. Second, several known antimalarial MDSMs and their congeners also have potent trypanocidal activity versus *T. brucei.* Third, there are no significant lead compounds under advanced evaluation against the other four parasitic diseases of Table 1 (Entries 2–5).

Gazing into our crystal ball

Scientists and philanthropists are becoming united in their belief that curing the six parasite diseases discussed here can occur by a fusion of the structural diversity inherent in natural products and the new insights being accumulated from breakthroughs in molecular biology. Thus, we expect that the investigation of new and known MDSMs in the context of antiparasitic research will thrive in coming years. Furthermore, such research activities will expand beyond the core tasks of natural product-derived library screening. As illustrated above, MDSM leads are in hand for Malaria and Sleeping Sickness, therefore a shift in effort is needed on two different fronts. First, accelerated screening must occur against *Leishmania* sp. and *T. cruzi* using well-established assays. Second, programs need to be initiated employing the schistosomiasis parasite utilizing assays for medium-throughput [68] and high-throughput [69••] screening that have recently been described. Likewise, current awareness searches should be directed to assays employing the River Blindness causative organisms — *Wolbachia pipientis* and *Onchocercus volvulus*.

The climate to promote rapid discovery has arrived. The impact of genomics and the availability of publicly accessible, open and shared databases such as Collaborative Drug Discovery (CDD) (URL: http://www.collaborative-drug.com/) represent new important milestones to facilitate future research based on deeper understanding of parasite biology and host interactions, and the potential for small molecules to modulate these processes. The CDD database and similar

tools are rapidly expanding with voluminous screening and compound data being added by researchers worldwide, such as the GlaxoS-mithKline open-access collection of 13 500 antimalarial compounds. The complete sequences for the genomes of each parasite in Table 1 have been published [70,71••,72–75]. Transcriptome and proteomic analyses provide additional insights into parasite life cycles, environmental responses, parasite–host interactions, and identification of new druggable targets [71••]. Indeed, the synergy of efforts by the research community and the age of genomics have already greatly enhanced our understanding of these diseases and potential curative agents. Thus, our summary of the recent literature here serves not only as an overview of what has been accomplished, but also as a wake-up call to the global natural products community in the tasks that remain before us!

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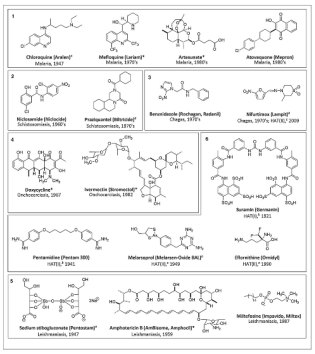

Figure 1.

Examples of current therapeutics against important parasitic diseases with trade names, target disease (entries **1**–**6**, Table 1), and year of discovery. *Natural product or based on a natural product scaffold. [a]Administered as a mixture of stereoisomers. [b]HAT(I): First stage of Human African trypanosomiasis; [c]HAT(II): Second stage of Human African trypanosomiasis.

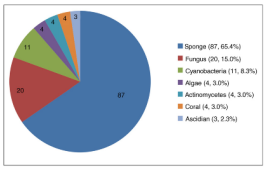

Figure 2.
Overview of marine organism sources of 133 antiparasitic small molecules parasite targets include all entries from Table 1 except River Blindness.

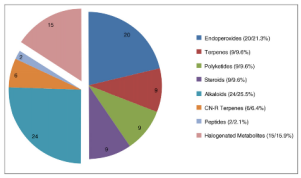

Figure 3.
Structure types and the tally among eight classes of MDMS's from invertebrates reported 2008–2010.

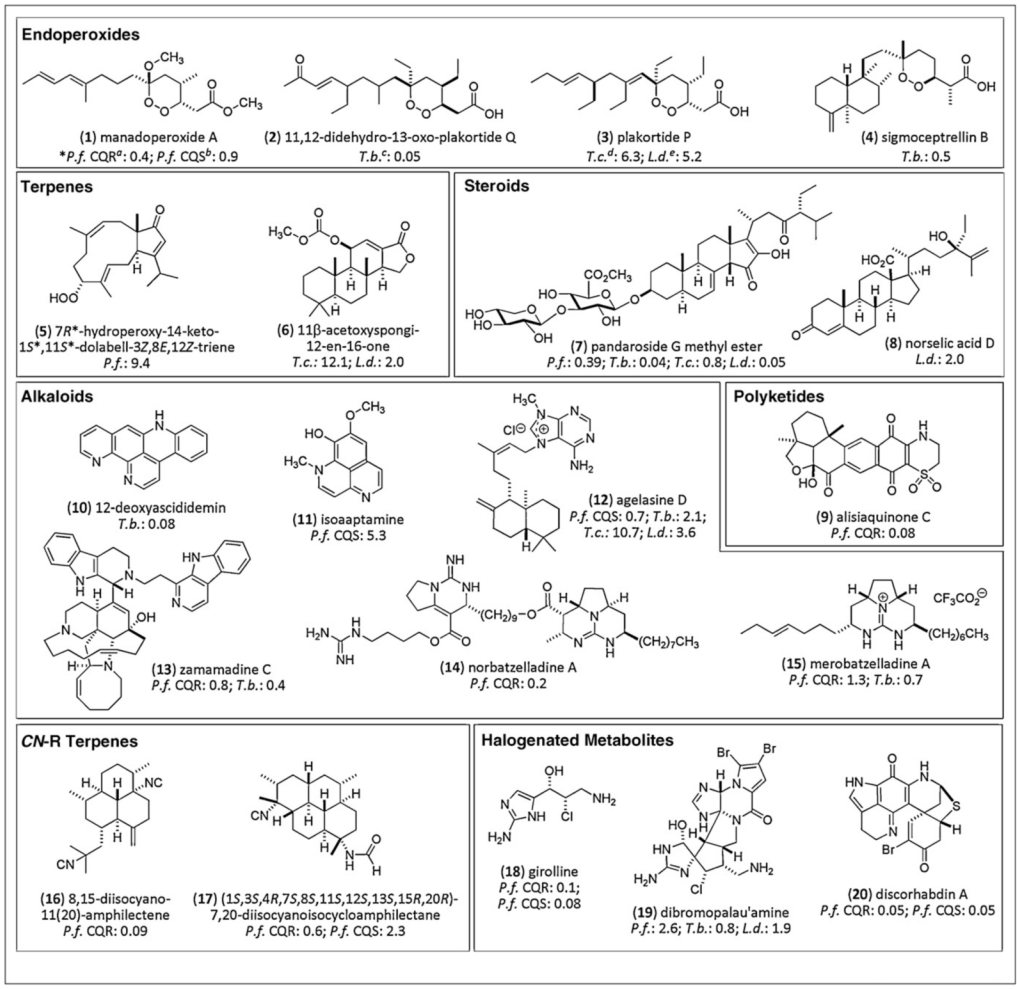

Figure 4.

Twenty selected lead structures from 94 MDSM's and their antiparasitic IC_{50}'s (μM) *Parasite: IC_{50} (μM) result from *in vitro* screening; [a]*P.f.* CQR = *P. falciparum* chloroquine-resistant strain; [b]*P.f.* CQS = *P. falciparum* chloroquine-sensitive strain; [c]*T.b. = T. brucei*; [d]*T.c. = T. cruzi*; [e]*L.d. = L. donovani*.

Table 1

Important parasitic diseases and their human impact

Entry #	Disease name	Organism		Source/transmission	Estimated global relevance
1	Malaria	*Plasmodium falciparum*	PS[a]	Mosquito	247 million[d]
		P. vivax		*Anopheles* sp.	
		P. malariae			
		P. ovale			
		P. knowlesi			
2	Schistosomiasis	*Schistosoma mansoni*	H[b]	Freshwater snail	207 million[d]
		S. haematobium		*Biomphalaria* sp.	
		S. japonicum			
		S. mekongi			
		S. intercalatum			
3	Chagas Disease (American Trypanosomiasis)	*Trypanosoma cruzi*	PK[c]	Triatomine bug	16–18 million[e]
				Triatoma sp.	
				Reduviidae sp.	
4	River Blindness (Onchercerciasis)	*Onchocerca volvulus*	H	Black fly	17.7 million[e]
		Wolbachia pipientis		*Simulium* sp.	
5	Leishmaniasis (Kala-Azar)	*Leishmania* sp.	PK	Sand fly	12 million[f]
				Phlebotomus sp.	
6	Sleeping Sickness (Human African Trypanosomiasis)	*Trypanosoma brucei*	PK	Tsetse fly	50–70 000[e]
		T. brucei gambiense		*Glossina* sp.	
		T. brucei rhodesiense			

[a] PS: protozoan parasite, sporozoan subclass.

[b] H: helminth parasite.

[c] PK: protozoan parasite, kinetoplastid subclass.

[d] Data from the World Health Organization; URL: http://www.who.int/mediacentre/factsheets/.

[e] Data from the Centers for Disease Control and Prevention; URL: http://www.cdc.gov/ncidod/dpd/parasites/.

[f] Data from Ref. [10].

Table 2

Examples of *in vitro* bioactivity data for assay standards

Disease target	Assay standard	IC_{50} (μM)	Organism target	Reference
Malaria	Chloroquine	0.05	*P. falciparum* (D6 CQS[a])	[27]
		5.3	*P. falciparum* (W2 CQR[b])	[27]
	Artemesinin	0.01	*P. falciparum* (K1 CQR)	[37•]
	Atovaquone	0.0005	*P. falciparum* (D6 CQS)	[38•]
		0.002	*P. falciparum* (W2 CQR)	[38•]
Schistosomiasis	Niclosamide	4.6[c]	*Biomphalaria glabrata*	[50]
Chagas	Benznidazole	1.2	*T. cruzi*	[33]
	Nifurtimiox	10.0	*T. cruzi*	[52]
River Blindness	None			
Leishmaniasis	Amphotericin B	0.07	*L. donovani*	[27]
	Miltefosine	0.5	*L. donovani*	[33]
	Sodium stibogluconate	44.7	*L. donovani*	[51]
Sleeping Sickness	Pentamidine	0.03	*T. brucei brucei*	[20•]
	Melarsoprol	0.01	*T. brucei rhodesiense*	[33]

[a] CQS = chloroquine sensitive strain.

[b] CQR = chloroquine-resistant strain.

[c] LC_{100} value.

Table 3

MDSM lead compound classes for antimalarial and trypanocidal development

Target parasite	Lead compound classes and compound numbers[a]	Legacy compound(s) and year of antiparasitic discovery	References
P. falciparum; T. brucei sp.	Endoperoxides (1–4, 21)	plakortin (2002)	[18•,20•,22,27,32•,62]
P. falciparum	Guanidine alkaloids (14, 15, 24)	crambesidin 800 (2006)	[23,34•,64]
P. falciparum	β-Carboline alkaloids (13, 23)	manzamine A (2000)	[39•,63]
P. falciparum	Pyridoacridone alkaloids (10, 11, 22)	ascididemin (2003)	[13,28•,61•,65]
P. falciparum	*CN*-R terpenes (16, 17, 25)	kalihinol (1998)	[37•,38•,66]
P. falciparum; T. brucei sp.	Terpene alkaloids (12)	agelasine D (2008)	[11,15•,36•]

[a] See Figure 3 and structures below.