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Search for structurally diverse heterocyclic analogs as dual-acting antimalarial and antileishmanial agents: An overview

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ABSTRACT

Infections caused by protozoan parasites continue to be a significant cause of morbidity and mortality across the globe, with malaria and leishmaniasis forming the fulcrum of these infections. Decreased effectiveness of existing drugs and increasing cases of drug resistance have called for a multifaceted approach for the development of safe, efficacious, and affordable drugs for malaria and leishmaniasis. The present review article aims to unearth structurally diverse compounds as dual-acting antimalarial and antileishmanial agents. The current review article mainly focuses on the structure, biological activities, and structure-activity relationship (SAR) studies of synthetic and natural compounds that showed promising potential against malaria and Leishmania parasites in the past decade (2011–2021).

1. Introduction

Malaria is an infectious tropical disease that puts at risk approximately the health of half a billion people worldwide as of 2019. The geographical disparity in malaria incidence is vast at 94% of the cases and deaths in the WHO region of Africa [1]. Malaria susceptibility factors include infancy and age below five years (primarily due to the absence of protective immunity to the parasites), pregnancy, non-immune travelers, and HIV/AIDS patients. Around 67% of the total mortalities worldwide comprised children below the age of five in 2019 [1,2]. Malaria is caused by protozoa belonging to the genus *Plasmodium*. The species credited for transmitting human malaria include *P. falciparum, P. vivax, P. ovale, P. malariae,* and *P. knowlesi* [3]. *P. falciparum* causes the most severe form of infection, leading to cerebral malaria or severe anemia without treatment, and accounts for 99.7% of deaths in the WHO African region. The *P. vivax* species is the primary causative organism responsible for relapse and accounts for around 75% of the cases in the WHO region of the Americas.

Malaria infection proceeds once an infected female anopheles mosquito takes a blood meal and injects *Plasmodium* sporozoites into the host circulation. After a schizogonic hepatic phase, newly formed merozoites invade the red blood cells (RBC) and initiate an asexual reproductive phase which causes symptoms usually 10–15 days post-infection. The symptoms include fever, headache, and chills, and they occur every three or four days depending on the *Plasmodium* species and the length of the reproductive intraerythrocytic cycle. These are called “uncomplicated malaria cases.” In case of severe infections, cerebral malaria with coma, anemia, hypoglycemia, and respiratory distress may occur in children and multi-organ impairment in adults, as well [3]. The current mainstay treatment for uncomplicated malaria is represented by the artemisinin-based combination therapy (ACT), in which an artemisinin's derivative is co-formulated with a different antimalarial drug with a prolonged half-life compared to the artemisinin's derivative. For severe malaria, artesunate or quinine are the drugs of choice [4]. Overall, the antimalarial drugs currently used either for therapy or prophylaxis fall under the following categories viz. 4-aminoquinolines, 8-aminoquinolines, aryl-amino alcohols, antifolates, artemisinin's derivatives, antibiotics, and inhibitors of the cytochrome *bc*1 complex in the parasitic electron transport chain (ETC) [5]. Owing to the declining effectiveness

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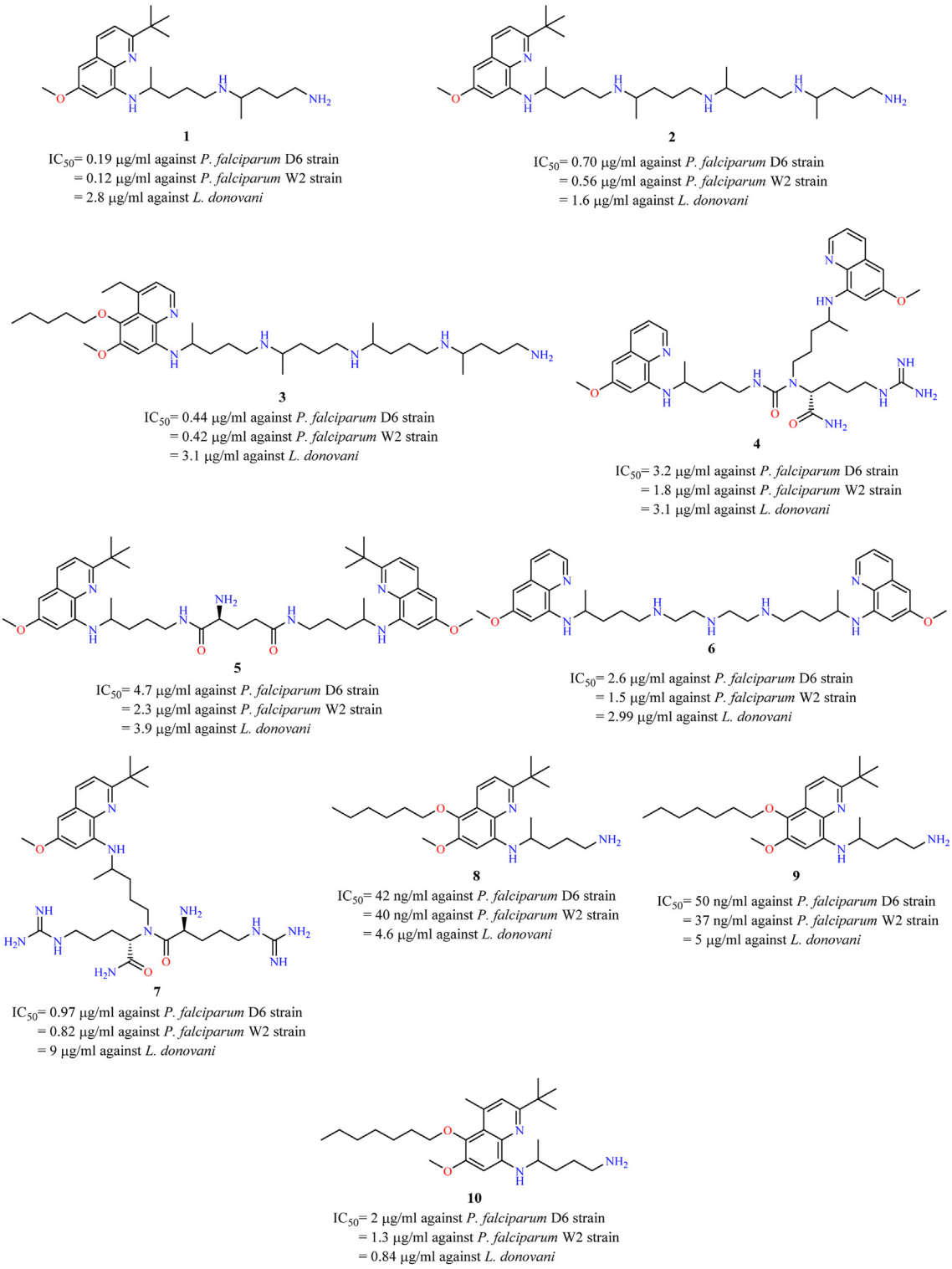


Fig. 1. Aminoquinoline derivatives (**1–10**) as dual-acting agents.

and raising resistance against current treatments, new molecular entities in the drug development pipeline include Arterolane, a synthetic peroxide targeting the membrane phospholipids which is under regulatory review in combination with piperaquine and Cipargamin, a *P. falciparum* ATPase inhibitor, which is under patient exploratory study [6]. Also, recently, covalent biotherapy has been explored wherein two or more pharmacophores are chemically linked to create a hybrid drug molecule that will possess multi-target activity that may lower the probability of inducing drug resistance [7]. The implementation of ACTs and vector control measures reduced malaria incidence and mortality significantly from 2000 to 2015 by 35% and 60%, respectively. However, since 2015 the progress stabilized, and the decrease was not as expected. The COVID-19 pandemic may aggravate the situation. The possible underneath reasons include reduced political pressure and financial support, parasite and vector resistance to drug and insecticides, respectively, and limited access to diagnosis and care [8].

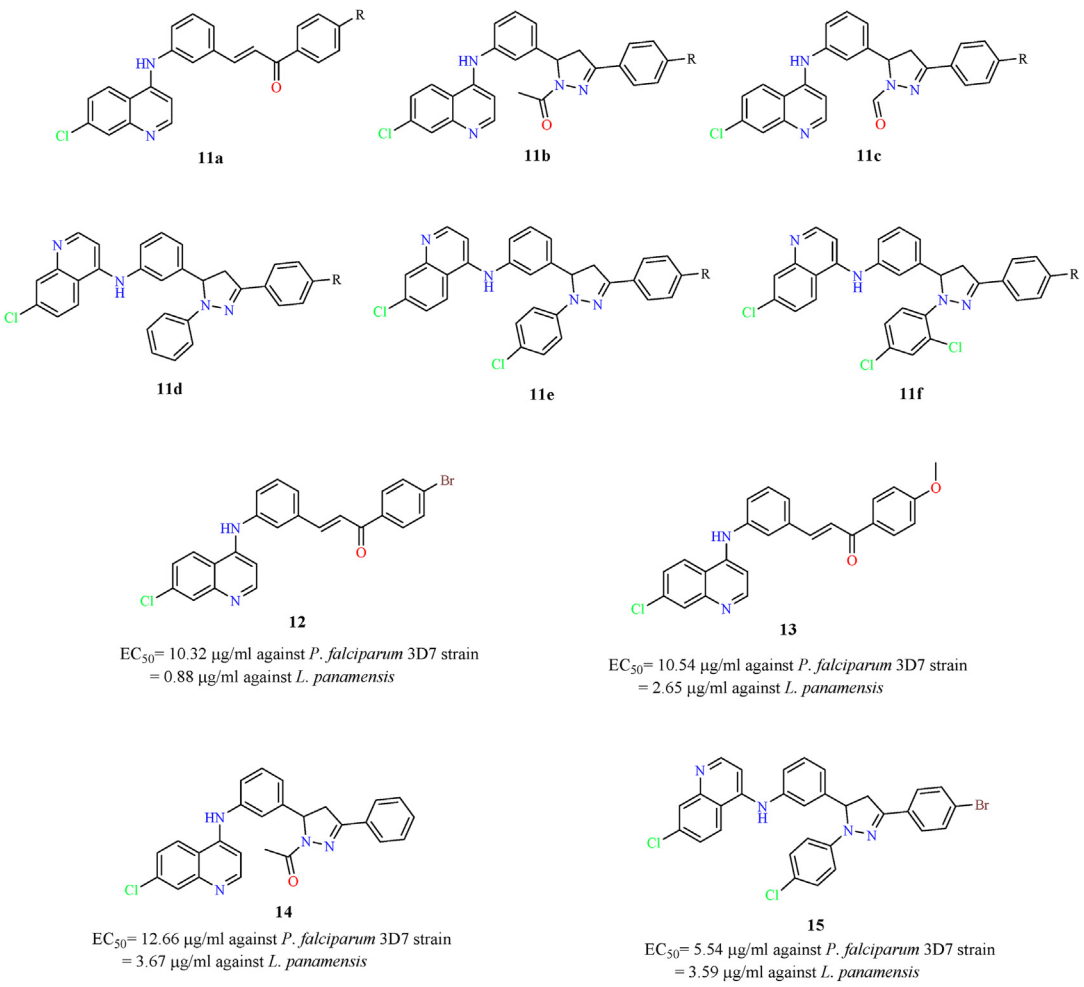


Fig. 2. Aminoquinoline based hybrid analogs (**11–15**) as dual-acting agents.

Moreover, after many decades of effort and investment, a highly effective malaria vaccine is unavailable. A pilot study has been authorized by WHO in three African countries, Malawi, Ghana, and Kenia, using Mosquirix™ GSK RTS,S/AS01, the only registered bivalent vaccine against malaria and hepatitis B, which in phase III studies demonstrated a 36% reduction of malaria cases in children and 28% in infants [9].

This calls for a multifaceted approach for the discovery and development of effective drugs for the treatment of malaria, which focuses on pathogen biology, druggable targets, and safety of the drug candidates to be suitable for treating pregnant women and children [2]. Moreover, an endemic overlap of other tropical diseases increases the rate of co-infections and, thus, complexities [5]. Current suggestions to treat malaria and delay the appearance of resistance in Africa include the triple ACT, using two additional compounds together with the artemisinin [10]. Therefore, additional research on novel entities and targets is continuously needed.

Leishmaniasis remains one of the top three neglected tropical diseases of the world, endemic in 98 countries. The global disease burden estimates are soaring high, at 1.3 million new cases and 20,000–40,000 deaths per year [11]. The causative organism of leishmaniasis is the protozoan parasite of the class kinetoplastida and belongs to the subgenera *Leishmania* and *Viannia* [12]. Around 20 species of *Leishmania* are acknowledged to cause leishmaniasis in humans, which is transmitted by a sand fly vector. Approximately 90 species of the sandfly of the genus *Phlebotomus* and the genus *Lutzomyia* are responsible for transmission in the old World (Mediterranean region, Africa and India) or the New World (Central and South American regions), respectively [13,14]. The life cycle of the protozoan parasite is digenetic, involving a non-vertebrate and a vertebrate host. Parasitic infection in humans occurs when an infected female sandfly takes a blood meal and deposits the flagellated and extracellular promastigote form in the host skin, where it is taken up first by neutrophils, then by macrophages. Inside the phagolysosome compartment of phagocytes, promastigotes differentiate into round and intracellular amastigote which proliferate and subsequently infect neighboring dendritic cells and macrophages [15]. Clinical manifestations of leishmaniasis vary between the appearances of cutaneous lesions to a systemic infection causing impairment to the visceral organs. Based on this, leishmaniasis is categorized into Cutaneous Leishmaniasis (CL) and Visceral Leishmaniasis (VL), also referred to as Kala-Azar. The former is often self-healable, whereas the latter can prove fatal in the absence of therapeutic intervention(s) [16]. The Leishmania species such as *L. major, L. tropica, L. aethiopica, L. amazonensis, L. mexicana, L. braziliensis,* and *L. guyanensis* are the causative species for CL, whereas *L. infantum* and *L. donovani* species are responsible for VL in humans. The latter is endemic to the old world and is associated with Post Kala-azar Dermal Leishmaniasis (PKDL), which is a source of infection [14,16,17]. HIV co-infection elevates the risk of mortality and relapse in individuals who are immunocompromised. Leishmaniasis endangers approximately 1 billion people living in the endemic regions [18]. Susceptibility factors include poor housing, sanitation, population migration, malnutrition, environmental and climate changes that aid vector, parasite multiplication, and further transmission [19]. Despite the prevalence of an enormous clinical burden, effectively treating leishmaniasis still looms as a prospect. Effective vaccination is not available at present as leishmanization was withdrawn on unethical fronts. However, with the new genome editing

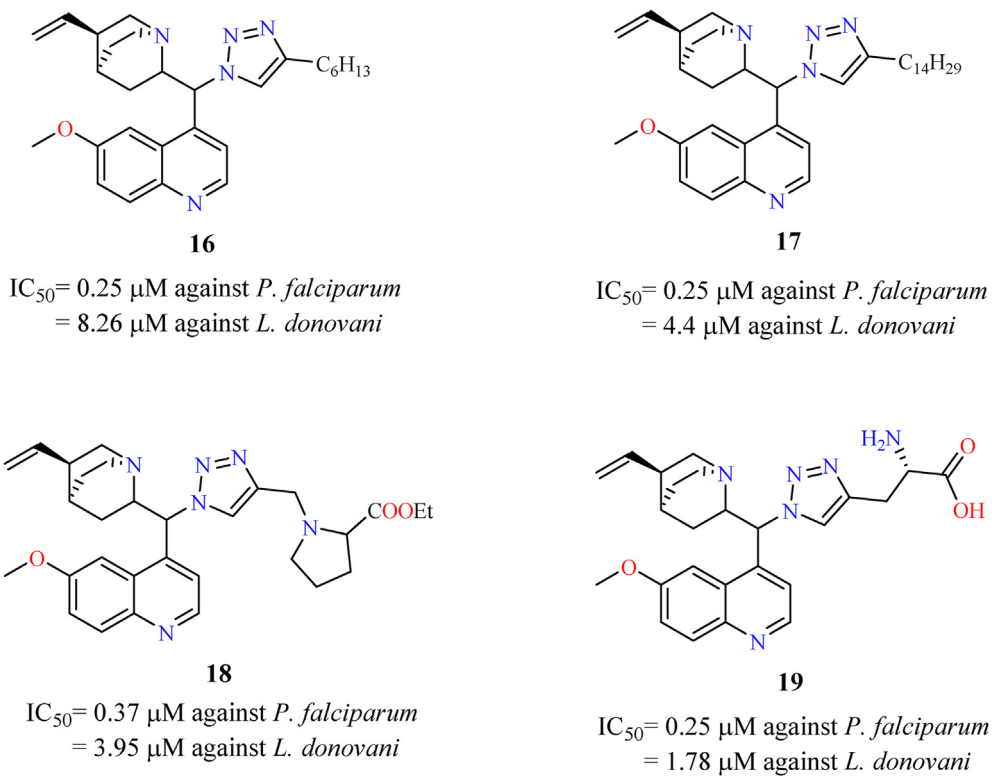


Fig. 3. Structure of quinine-triazolyl hybrid analogs (**16–19**) and their bioactivity.

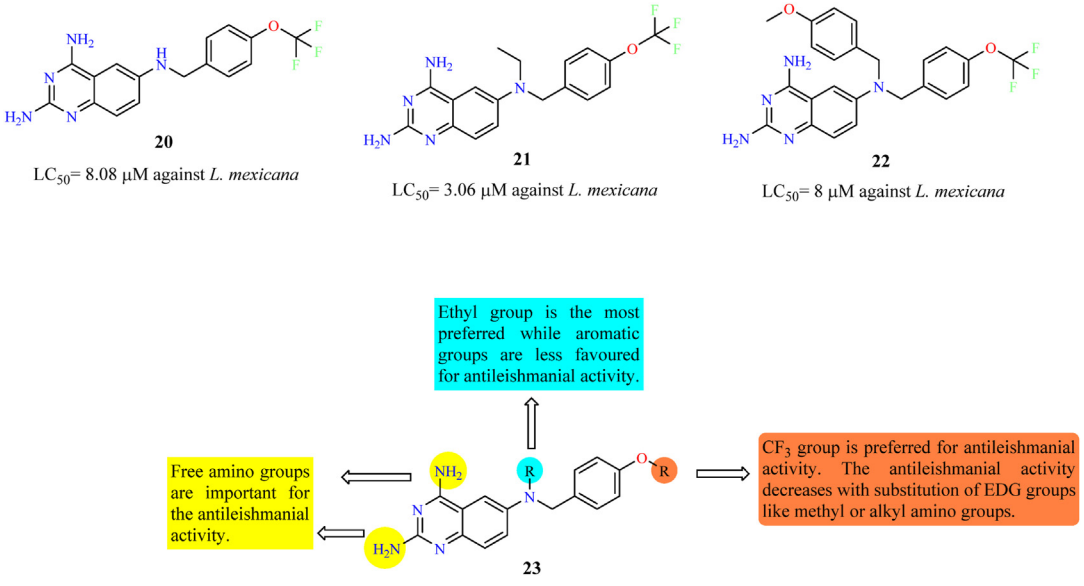
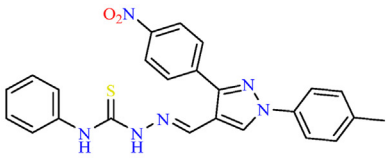


Fig. 4. Structure of quinazoline derivatives (**20–22**) and their SAR profile (**23**).

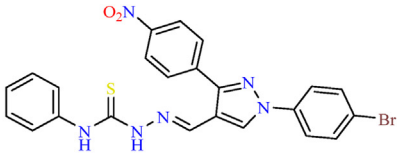
technologies, the possibility of inducing protective immunity using genetically attenuated strains of Leishmania, probably useful for a second-generation leishmanization [20]. Eradication of vectors also poses an impasse challenge; therefore, chemotherapy remains the go-to option in our hands [21,22]. Existing drugs include pentavalent antimonials, amphotericin-B, miltefosine, and paromomycin which often exhibit drug resistance, adverse effects associated with more extended treatment regimens, and treatment failure from time to time [13]. Challenges in treating leishmaniasis occur at every stage and encompass diverse areas. Vector and parasite complexity, pharmacokinetics, and pharmacodynamic nuances targeting the intracellular amastigote form pose hurdles from a drug discovery and development perspective [14]. Socioeconomic factors such as stigma associated with lesions, unavailability, and unaffordability of the only approved oral drug miltefosine present another setback. Recently, novel variants that account for atypical leishmaniasis and extend to other geographical areas have been discovered, leading to another point of concern [16,23].

At present, both malaria and leishmaniasis are at risk of increasing burden and lethality due to the subversion of control measures and investments caused by the COVID-19 pandemic. The latest World Malaria Report 2020 forecasts that due to COVID-19, the WHO's goals set for 2020 for the reduction of case incidence and mortality will be missed by



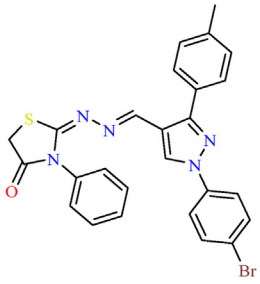
24

IC_{50}= 0.0378 μM against *P. falciparum* RKL9 strain
= 0.0241 μg/ml against *L. aethiopica* promastigotes
= 0.23 μg/ml against *L. aethiopica* amastigotes



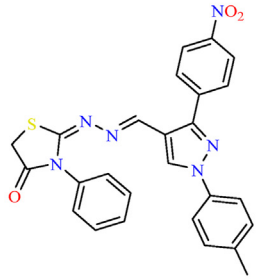
25

IC_{50}= 0.0384 μM against *P. falciparum* RKL9 strain
= 0.0214 μg/ml against *L. aethiopica* promastigotes
= 0.21 μg/ml against *L. aethiopica* amastigotes



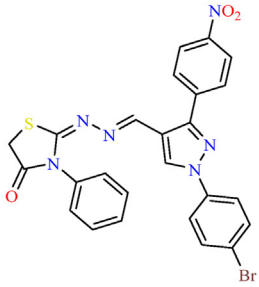
26

IC_{50}= 0.0364 μM against *P. falciparum* RKL9 strain
= 0.0341 μg/ml against *L. aethiopica* promastigotes
= 0.32 μg/ml against *L. aethiopica* amastigotes



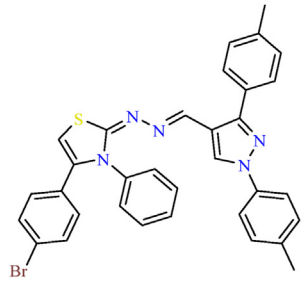
27

IC_{50}= 0.0402 μM against *P. falciparum* RKL9 strain
= 0.0201 μg/ml against *L. aethiopica* promastigotes
= 0.28 μg/ml against *L. aethiopica* amastigotes



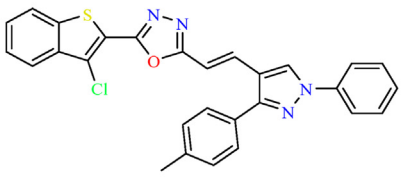
28

IC_{50}= 0.0392 μM against *P. falciparum* RKL9 strain
= 0.0224 μg/ml against *L. aethiopica* promastigotes
= 0.19 μg/ml against *L. aethiopica* amastigotes



29

IC_{50}= 0.0418 μM against *P. falciparum* RKL9 strain
= 0.0311 μg/ml against *L. aethiopica* promastigotes
= 0.30 μg/ml against *L. aethiopica* amastigotes

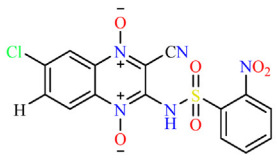


30

IC_{50}= 0.494 μg/ml against *P. falciparum* 3D7 strain
= 1.659 μg/ml against *P. falciparum* RKL9 strain
= 19 μg/ml against *L. donovani* promastigotes
= 73.1 μg/ml against *L. donovani* amastigotes

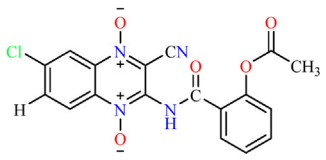
Fig. 5. Pyrazole based hybrid analogs (**24–30**) as dual-acting antimalarial and antileishmanial agents.

37% and 22%, respectively. International organizations such as WHO and non-profit initiatives such as Medicine for Malaria Venture (MMV, www.mmv.org) and Drug for Neglected Diseases Initiative (DNDi, https://dndi.org) are leading collaborative initiatives to mitigate the negative impact of the coronavirus in malaria and other vector-borne diseases [24]. The lack of affordable drugs, toxicity, and low efficacy of the existing drugs makes it even more difficult to contain these protozoan infections. Hence, an alternate approach to treat both leishmaniasis and malaria is urgently needed to contain these two vector-borne parasitic diseases successfully. This review provides an insight into compounds that have exhibited dual inhibitory action against malarial and leishmanial parasites. The first part of the review focuses on synthetic compounds, while the second part of the review focuses on the natural products that have been documented to exhibit dual activity against malaria and leishmaniasis.



31

IC_{50} = 17.4 μM against *P. falciparum* FCR-3
= 3.1 μM against *L. amazonensis* axenic amastigotes



32

IC_{50} = 7.4 μM against *P. falciparum* FCR-3
= 7.3 μM against *L. amazonensis* axenic amastigotes

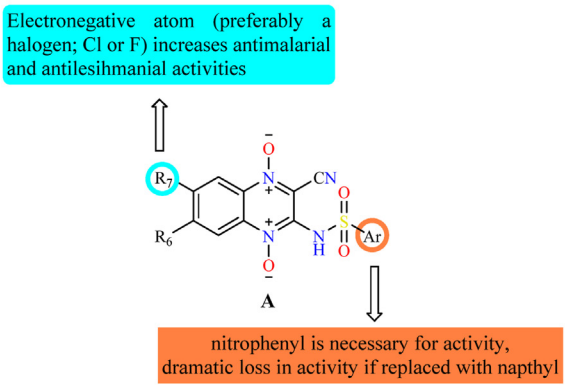
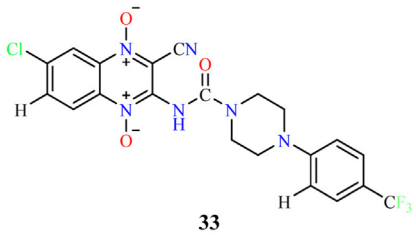
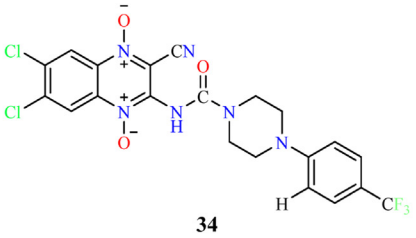


Fig. 6. Structure of quinoxaline-1,4-di-*N*-oxide derivatives (**31–32**) and their SAR pattern **A** and **B**.



33

IC_{50} = 18.6 μM against *P. falciparum* FCR-3
= 7.6 μM against *L. infantum* axenic amastigotes



34

IC_{50} = 18.5 μM against *P. falciparum* FCR-3
= 5.7 μM against *L. infantum* axenic amastigotes

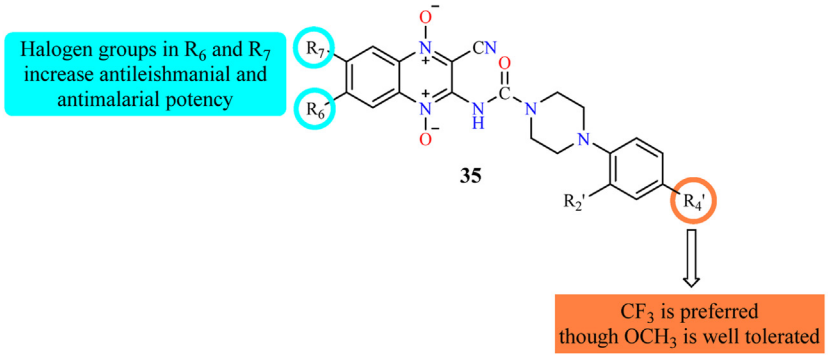
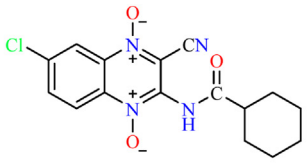


Fig. 7. Structure of 2-cyano-3-(4-phenylpiperazine-1-carboxamido)-quinoxaline-1,4-dioxide derivatives (**33–34**) and their SAR profile.

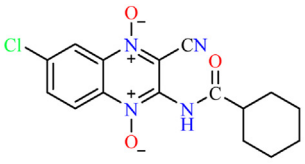
2. Synthetic analogs

Kaur et al. disclosed the synthesis of extended side chain analogs of primaquine and other 8-amino quinolines [25]. The synthesized analogs were found to exhibit sub-micromolar antimalarial potencies against *P. falciparum* D6 and W2 strains. Some of these analogs like **1–3** were also found to exhibit potent *in vitro* activity against promastigotes of *L. donovani*. The synthesized analogs also inhibited beta-hematin formation *in vitro*, providing corroboration to their antimalarial effects. The synthesized analogs were also evaluated *in vivo* against *P. berghei* infected mice model. Compounds **1–3** administered at doses of 10 mg/kg, 25 mg/kg, and 100 mg/kg once daily for four days resulted in the complete elimination of the malarial parasite from the mice's body, indicating their antimalarial prowess. Continuing their efforts to unearth novel antimalarial compounds, Kaur et al. synthesized three series of compounds based on the bis-(8-aminoquinolines) framework [26]. As



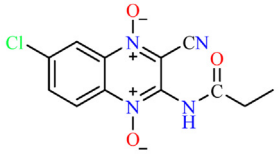
36

IC_{50} = 7.5 μM against *P. falciparum* FCR-3
= 2.5 μM against *L. infantum* axenic amastigotes



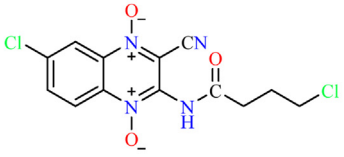
37

IC_{50} = 12.9 μM against *P. falciparum* FCR-3
= 3.4 μM against *L. infantum* axenic amastigotes



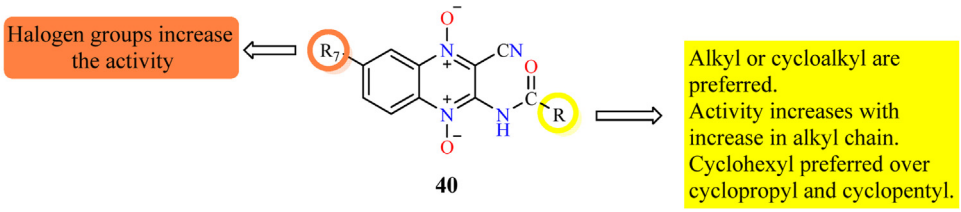
38

IC_{50} = 4.3 μM against *P. falciparum* FCR-3
= 4 μM against *L. amazonensis* axenic amastigotes



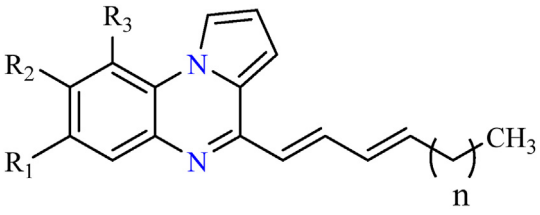
39

IC_{50} = 5.7 μM against *P. falciparum* FCR-3
= 0.7 μM against *L. amazonensis* axenic amastigotes



40

Fig. 8. Structure of quinoxaline-1,4-di-*N*-oxide derivatives (**36–39**) and their SAR analysis.



41a-g

Fig. 9. General structure of pyrrolo-[1,2-*a*]-quinoxaline derivatives (**41a-g**).

expected, the majority of the synthesized analogs were found to exhibit potent antimalarial activity. Some of the representative compounds **(4–6)** are shown in Fig. 1. Compound **6** also exhibited potent antimalarial activity *in vivo*. Compound **6** administered orally once a day for 4 days (at doses 10 mg/kg, 25 mg/kg, and 100 mg/kg) aided in complete clearance of the malarial parasite from the body of the mice. Additionally, compounds **4–6** were also conferred with good antileishmanial activity. The same group in their subsequent studies developed several novel analogs based on the 8-aminoquinoline framework as potential antiparasitic agents [27,28]. Modifications on the quinoline core as well as conjugation of the quinoline system with amino acids, pseudo peptides, and dipeptides, etc., lead to the generation of promising compounds exhibiting dual inhibitory actions against the parasites. Some of these analogs **(7–10)** and their IC_{50} values against the respective parasite are shown in Fig. 1.

This series of analogs developed on the 8-aminoquinoline scaffold has shown promising dual inhibitory actions against malaria and Leishmania parasites. More importantly, they are also devoid of any cytotoxicity. The above discussions show that some of these analogs have also shown good *in vivo* antimalarial activity. It remains to be seen whether the same could be said for their antileishmanial activity. Nevertheless, rigorous SAR

Table 1
Biological activity spectrum of pyrrolo-[1,2-*a*]-quinoxaline analogs **41a-g**.

Compound code	R_1	R_2	R_3	n	IC_{50} values (μM)				
					Leishmania promastigotes			*P. falciparum*	
					L. major	*L. mexicana*	*L. donovani*	W2	3D7
41a	H	H	H	0	4.7	7.6	9.8	2.5	2.4
41b	OCH3	H	H	0	3	3.3	5.3	3.4	3.3
41c	H	OCH3	H	0	2.7	3.7	5.4	2.4	1.5
41d	H	H	OCH3	0	3.3	8	7.2	2.6	3.2
41e	H	H	H	2	3.9	12.1	7.6	1.1	2.5
41f	OCH3	H	H	2	2.8	3.2	8.6	0.8	2.3
41g	H	H	OCH3	2	3.9	10.3	9.9	1.3	1.6

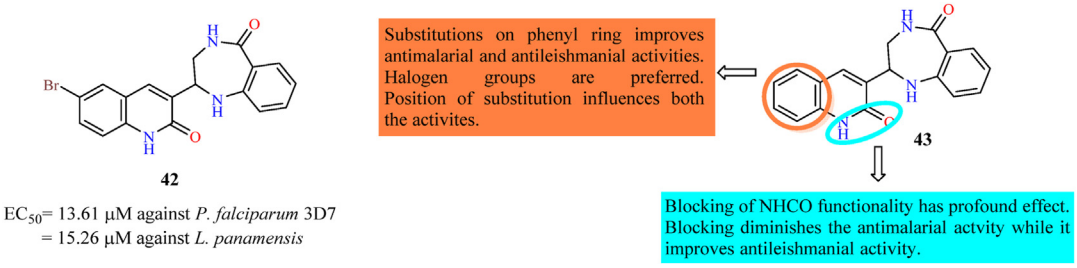


Fig. 10. SAR profile of quinoline-benzodiazepine hybrids (**42–43**).

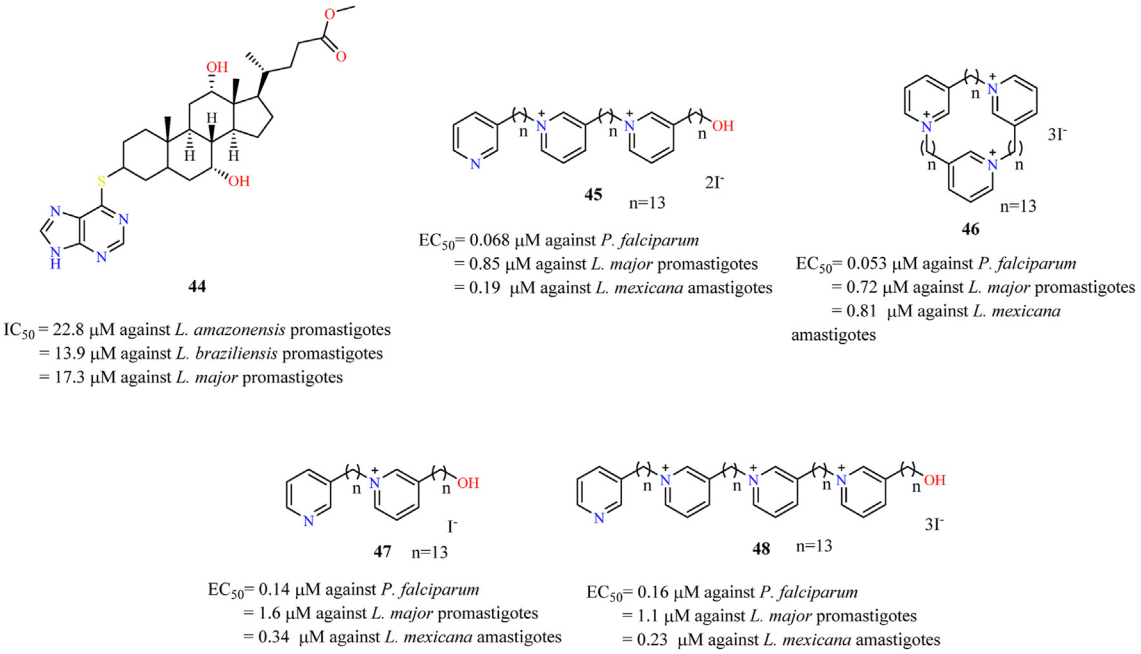


Fig. 11. Structure of 6-thiopurine-steroid hybrid (**44**) and tridecyl pyridinium alkaloids **(45–48)** and their biological activity.

studies and *in vivo* studies are required to corroborate the potential of 8-aminoquinolines as antiparasitic agents.

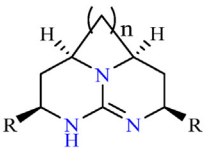
Six series of novel 4-aminoquinoline based hybrid analogs **(11a-f)** were synthesized and were evaluated for their antiprotozoal activity against *P. falciparum* 3D7 strain and intracellular amastigotes of *L. panamensis* [29]. Several compounds, including compounds with promising activities against these parasites, were discovered. Some of these compounds **(12–15)** and their biological activity is shown in Fig. 2. Notably, compounds **12–15** were found to be more potent than the standard drug chloroquine (EC_{50} of chloroquine = 18.9 μg/ml against *P. falciparum*). Therefore, these analogs warrant further *in vitro* and *in vivo* studies.

Elsewhere Sahu et al. synthesized novel quinine-triazolyl hybrid compounds and evaluated these analogs as potential antiprotozoal agents [30]. Almost 19 hybrid analogs were synthesized containing various substituents, viz. aromatic, heteroaromatic, aliphatic groups, etc., on the 4th position of the triazole nucleus. Out of the 19 derivatives that were synthesized, compounds **16–19** (Fig. 3) were shown to possess potent antimalarial and antileishmanial activity. Compounds **16–19** exhibited superior potency than the quinine (w.r.t antimalarial activity, IC_{50} of quinine = 0.62 μM against *P. falciparum*), while compounds **17–19** exhibited superior potency than amphotericin B (w.r.t antileishmanial activity, IC_{50} of amphotericin B = 5.55 μM against *L. donovani*). In-depth *in vitro* and *in vivo* toxicity studies shed light on the safety concerns of these analogs. The toxicity studies revealed that none of the compounds produced any toxic manifestations up to a dose of 1000 mg/kg. These studies highlight the promising potential of these series of compounds, and further *in vivo* studies are required to ascertain their efficacy.

Mendoza-Martínez et al. designed and synthesized novel quinazoline derivatives as potential antimalarial and antileishmanial agents [31]. The compounds were designed by performing molecular docking studies against two targets-dihydrofolate reductase (DHFR) and pteridine reductase (PTR). Three compounds, **20–22** (Fig. 4), inhibited the promastigotes of *L. mexicana* with IC_{50} values of 8.08 μM, 3.06 μM, and 8 μM, respectively. The *in vivo* anti-plasmodial activities of analogs **20–22** were evaluated on *P. berghei* murine model. Given orally at a dose of 50 mg/kg for 4 days, compounds **20–22** suppressed the parasitemia by 99.9%, 100% and 95.2%, respectively.

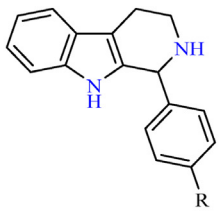
Several previous studies have identified the importance of folates for the growth of malarial parasites and how the malarial parasites can bypass folate inhibition by antimalarial antifolates like pyrimethamine when supplemented with a pool of folate derivatives. However, folate supplementation does not seem to affect the antimalarial activity of anticancer antifolates like methotrexate [32], and it would be interesting to see if folate supplementation has any effect on the antimalarial activities of compounds **20–22**.

Novel series of pyrazole hybridized with other heterocyclic scaffolds like thiazoles, thiazolidinones, 1,3,4-thiadiazoles, and pyrazolines were synthesized by Bekhit et al. [33]. The synthesized analogs were evaluated for their *in vivo* and *in vitro* antimalarial activity and *in vitro* antileishmanial activity. Collectively six compounds, **24–29** (Fig. 5), exhibited promising dual activity. Firstly, these compounds exhibited



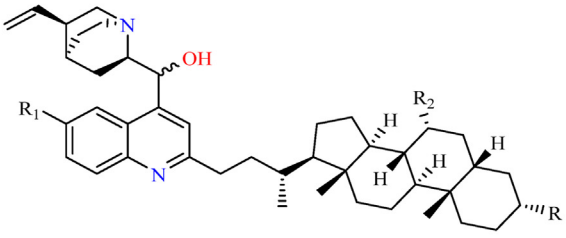
49, n=2, R= C_9H_{19}
50, n=3, R= C_9H_{19}
51, n=3, R= -CH_2CH_2Ph(m-Cl)
52, n=3, R= -CH_2CH_2Ph(m-CH_3)

Compound code	IC_{50} against *P. falciparum* D6 (μM)	IC_{50} against *P. falciparum* W2 (μM)	IC_{50} against *L. donovani* (μM)
49	1.48	1.43	2.39
50	1.39	1.76	2.78
51	1.25	1.64	7.23
52	1.37	2.26	7.71



53, R= CH_3
54, R= Cl
55, R= Br

Compound code	IC_{50} against *P. falciparum* W2 (μM)	IC_{50} against *L. donovani* (μM)
53	7.6	11.4
54	4.8	10.6
55	6.9	6.1



56-58

Compound code	R_1	OH- 9	R	R_2	IC_{50} against *P. falciparum* (*μg/ml*)	IC_{50} against *L. mexicana* (*μg/ml*)
56	OCH_3	R	OAc	OAc	0.69	3.49
57	H	R	OAc	OAc	0.21	3.91
58	H	S	OH	OH	0.09	3.39

Fig. 12. Structure of batzelladine K derivatives (**49–52),** beta-carboline analogs (**53–55**) and cinchona alkaloid hybrids (**56–58**) along with their biological activity.

potent *in vivo* activity with percentage suppression >90% (dose- 48.4 μM/kg/day). Then these compounds also demonstrated potent *in vitro* activity against the chloroquine-resistant strain of *P. falciparum* (RKL9). The IC_{50} values of compounds **24–29** against *P. falciparum* RKL9 strain ranged between 0.0364 μM and 0.0418 μM. These compounds also exhibited potent antileishmanial activity against the promastigote and amastigote forms of *L. aethiopica*. The obtained results were further corroborated by performing molecular docking studies against relevant antimalarial and antileishmanial drug targets- *P. falciparum* DHFR and *L. mexicana* PTR1. Finally, toxicity studies were performed to ascertain the safety of these analogs. The toxicity studies indicated that these compounds were safe and were tolerated by the animals parenterally up to 100 mg/kg and orally up to 300 mg/kg.

Elsewhere Verma et al. disclosed the synthesis and biological evaluation of pyrazole-1,3,4-oxadiazole hybrids [34]. Among the synthesized hybrids, compound **30** demonstrated potent antimalarial activity and moderate antileishmanial activity. Compound **30** exhibited IC_{50} values of 0.494 μg/ml and 1.659 μg/ml against chloroquine-sensitive 3D7 and chloroquine-resistant RKL 9 strains of *P. falciparum*, respectively. Moreover, compound **30** also inhibited falcipain-2 with an IC_{50} of 110 μM. On the other hand, compound **30** exhibited only moderate antileishmanial activity with IC_{50} values of 19.0 μg/ml and 73.1 μg/ml against promastigote and amastigote forms of *L. donovani*. Acute oral toxicity studies shed light on the safety of compound **30**. The studies determined that compound **30** was relatively safe as no signs of toxicity were observed in the biochemical and histological evaluations. Though compound **30** does

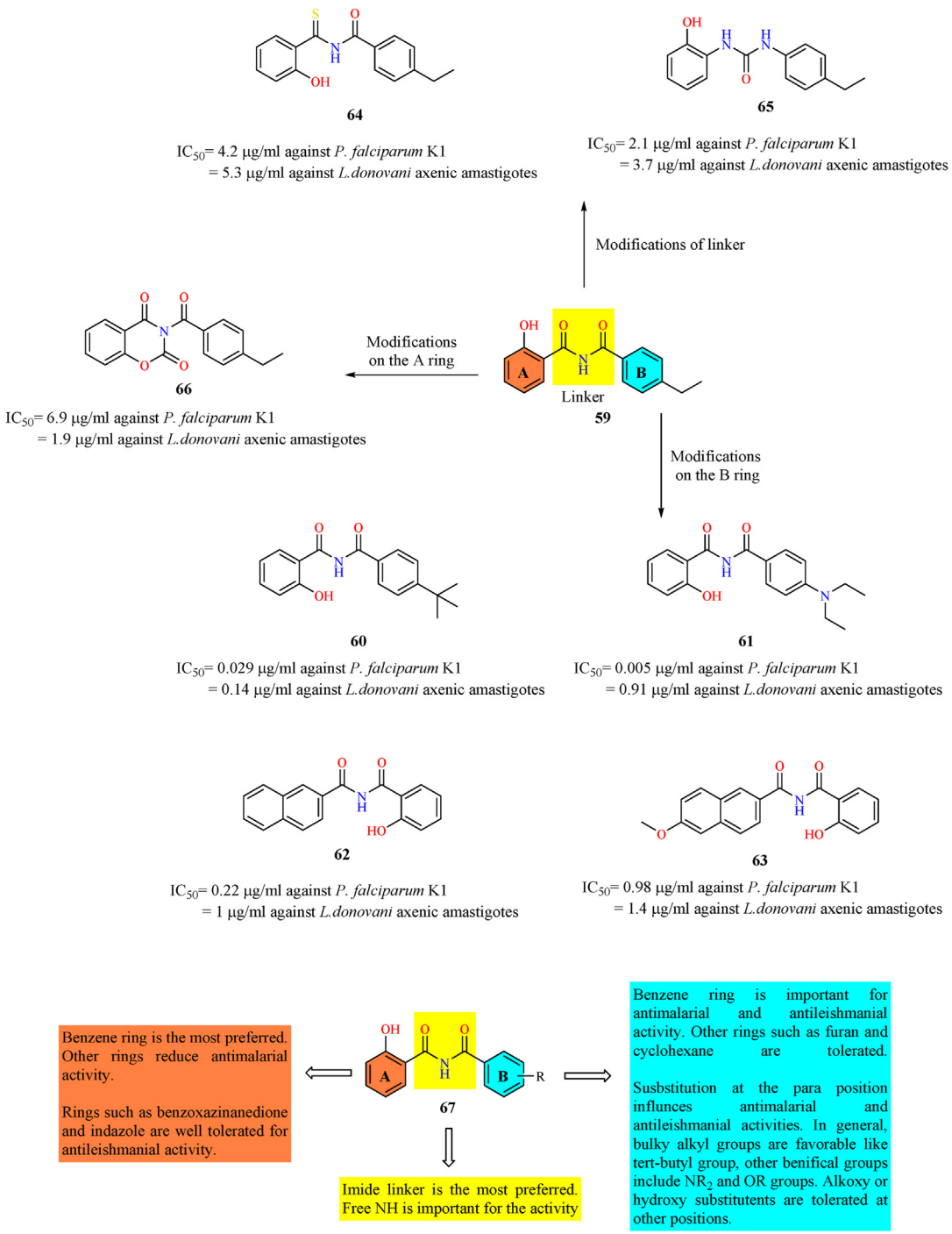


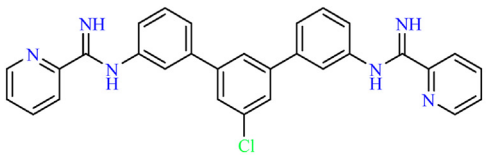
Fig. 13. Structure of *N*-benzoyl-2-hydroxybenzamide analogs (**59–66**) and their SAR studies (**67**).

not possess promising antileishmanial activity, it provides a structural framework for further SAR studies to obtain promising candidates with dual activity against leishmanial and malarial parasites.

Barea et al. designed and synthesized two series of quinoxaline-1,4-di-*N*-oxide derivatives **A** and **B** [35]. These quinoxaline analogs were evaluated against *P. falciparum* and *L. amazonensis*. Compound **31** belonging to the **A** series was found to exhibit low activity against *P. falciparum* FCR-3 strain (IC_{50} = 17.4 µM). In addition, this compound was found to exhibit good activity against axenic amastigotes of *L. amazonensis* with an IC_{50} value of 3.1 µM. Compound **32** belonging to series **B** was found to exhibit equipotent activity against malarial and *Leishmania* parasites. The SAR of the **A** and **B** series has been summarized in Fig. 6.

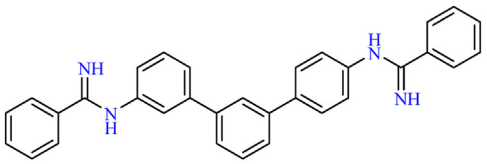
Continuing their efforts to develop antiparasitic agents exhibiting dual-inhibition, Barea et al. designed and synthesized novel analogs of 2-cyano-3-(4-phenylpiperazine-1-carboxamido)- quinoxaline-1,4-dioxide [36]. A couple of compounds, **33** and **34** (Fig. 7), were found to exhibit promising activity against *L. infantum* with IC_{50} values of 7.6 µM and 5.7 µM, respectively. However, they were only bestowed with weak antimalarial potency. Though the antimalarial potency exhibited by the analogs is not adequate, they provide a starting point for further structural modifications.

In their relentless pursuit to develop novel quinoxaline derivatives, Barea et al. evaluated novel amide derivatives of quinoxaline-1,4-di-*N*-oxide with promising leishmanial and antiplasmodial activities [37]. The



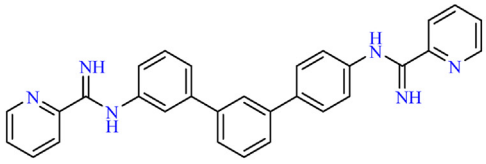
68

IC_{50}= 0.006 μM against *P. falciparum* K1 strain
= 0.095 μM against *L. donovani* amastigotes



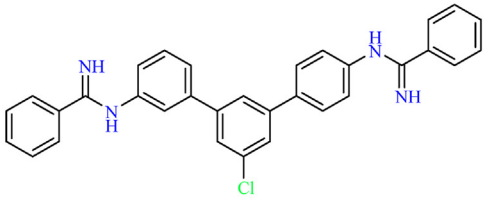
69

IC_{50}= 0.038 μM against *P. falciparum* K1 strain
= 0.907 μM against *L. donovani* amastigotes



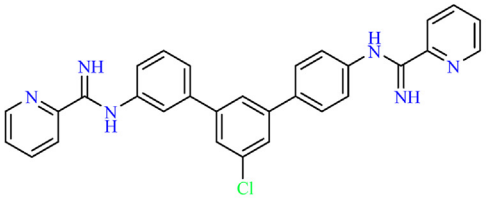
70

IC_{50}= 0.208 μM against *P. falciparum* K1 strain
= 0.123 μM against *L. donovani* amastigotes



71

IC_{50}= 0.039 μM against *P. falciparum* K1 strain
= 1.02 μM against *L. donovani* amastigotes



72

IC_{50}= 0.219 μM against *P. falciparum* K1 strain
= 0.211 μM against *L. donovani* amastigotes

Fig. 14. Structure of 4, 4″-diamidino-*m*-terphenyl derivatives (**68–72)** as promising dual-acting agents.

antimalarial IC_{50} values of the synthesized analogs ranged between 2.9 μM and 27.8 μM while their antileishmanial IC_{50} values ranged between 0.7 μM and 16.6 μM. Compounds **36–39** were some of the derivatives that were found to exhibit potent dual inhibitory properties, and their SAR pattern is depicted in Fig. 8.

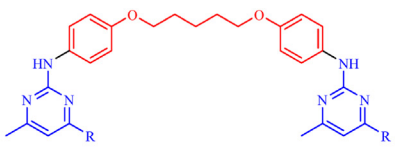
Continuing their efforts to develop bioactive molecules based on pyrrolo-[1,2-*a*]-quinoxaline heterocyclic framework, Ronga et al. designed and synthesized a novel series of 4-alkapolyenyl pyrrolo-[1,2-*a*]-quinoxaline derivatives [38]. The synthesized analogs were evaluated *in vitro* for their antileishmanial (against three different Leishmania species) and antimalarial activities (against two *P. falciparum* strains). Some of the compounds like **41a-g** (Fig. 9) were found to exhibit potent activity against Leishmania and malaria parasites, and their IC_{50} values against the tested species are highlighted in Table 1. It would be interesting to see if these compounds are also active against the more clinically relevant intracellular amastigotes. Nevertheless, these compounds could serve as the starting point for further SAR studies to develop compounds with dual inhibitory activity.

Novel benzodiazepine derivatives containing a quinoline motif were synthesized by Insuasty et al. Some of the compounds were screened for their antimalarial and antileishmanial activities [39]. Compound **42** was found to exhibit moderate activity against *P. falciparum* 3D7 (EC_{50} = 13.61 μg/ml) and intracellular amastigotes of *L. panamensis* (EC_{50} = 15.26 μg/ml). Substitutions on the quinoline core affect both these activities. Detailed SAR is discussed in Fig. 10.

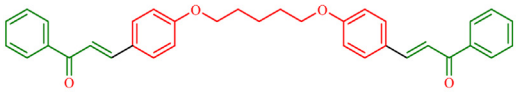
A series of novel 6-thiopurine derivatives containing 1,2,3-triazole or a steroid were synthesized, and their *in vivo* antimalarial activity and *in vitro* antileishmanial activity were examined [40]. Compound **44** (Fig. 11) containing 6-thiopurine motif conjugated with a steroid was found to possess good antimalarial potency *in vivo*. Given at a dose of 10 mg/kg, compound **44** inhibited parasite multiplication by 31% and 54% at the end of 7 and 9 days, respectively. Moreover, compound **44** exhibited better activity (% of inhibition = 65) than chloroquine (% of inhibition = 23) at the end of 12 days. This was the only compound that was found to have antileishmanial activity. In addition, compound **44** demonstrated moderate activity against the three tested leishmanial species (promastigotes), with *L. braziliensis* being the most susceptible.

Rodenko et al. disclosed the synthesis and antiprotozoal potential of marine-derived 3-tridecyl pyridinium alkaloids consisting of *N*-alkylated pyridinium units and saturated C_{13} alkyl chains [41]. All the alkaloids that were evaluated were found to possess sub-micromolar potency against both the Leishmania and malaria parasites. Compounds **45–48** were some of the alkaloids that were bestowed with potent dual-inhibitory properties. Notably, the tested analogs were also less cytotoxic as the toxicity towards human HEK293 cells was much lesser than their antiprotozoal activity. Given that all the compounds demonstrated promising dual-inhibitory properties, further SAR and mechanistic studies on these alkaloids will lead to the development of a lead compound effective against the protozoal diseases.

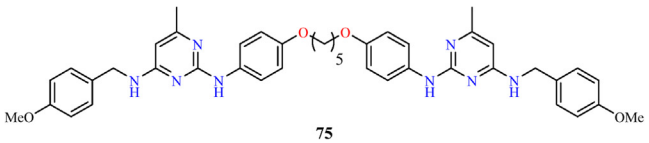
About 50 derivatives of batzelladine K were synthesized and evaluated for their antiprotozoal activity [42]. Batzelladines are a class of polycyclic marine alkaloids that consists of a guanidine group. The tricyclic guanidine analogs were evaluated against *P. falciparum* (D6 and W2 clones) and *L. donovani* promastigotes. Compounds **49–52** (Fig. 12) were some of the batzelladine K analogs that displayed potent antiprotozoal activity.



Pyrimidine-pentamidine hybrid **73**

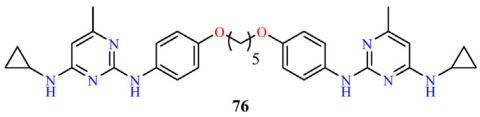


Chalcone-pentamidine hybrid **74**



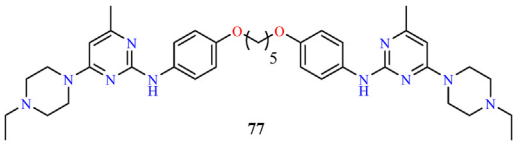
75

IC_{50}= 11.69 ng/ml against *P. falciparum* 3D7 strain, SI= 288.28
= 23.61 ng/ml against *P. falciparum* K1 strain
= 0.57 μM against *L. donovani*, SI= 3.70



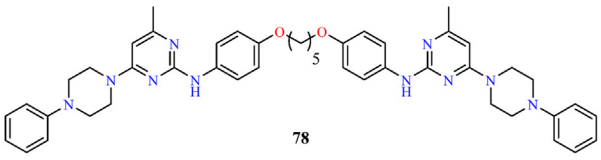
76

IC_{50}= 6.25 ng/ml against *P. falciparum* 3D7 strain, SI= 89.6
= 11.26 ng/ml against *P. falciparum* K1 strain
= 0.42 μM against *L. donovani*, SI= 6.38



77

IC_{50}= 45.15 ng/ml against *P. falciparum* 3D7 strain, SI= 157.9
= 22.13 ng/ml against *P. falciparum* K1 strain
= 0.30 μM against *L. donovani,* SI= 12.17



78

IC_{50}= 59.24 ng/ml against *P. falciparum* 3D7 strain, SI= 1688
= 53.06 ng/ml against *P. falciparum* K1 strain
= 1.72 μM against *L. donovani,* SI= >232

Fig. 15. Pentamidine based hybrid analogs (**73–78**) as dual-acting antimalarial and antileishmanial agents.

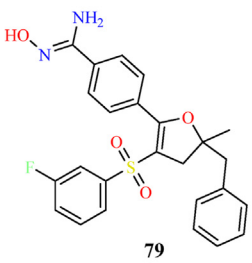
Gellis et al. disclosed the antiprotozoal activity of synthetic beta-carboline analogs [43]. Majority of the analogs that were evaluated exhibited selective activity against either *P. falciparum* W2 strain or promastigotes of *L. donovani*. However, certain compounds like **53–55** exhibited dual inhibition, with compound **55** exhibiting similar IC_{50} values against the malarial (IC_{50} = 6.9 μM) and leishmanial (IC_{50} = 6.1 μM) parasites.

A series of cinchona alkaloids hybridized with bile acids were synthesized and evaluated for their antiparasitic activity [44]. Cinchona alkaloids like quinine, quinidine, cinchonine and cinchonidine were conjugated with a bile acid-lithocholic or chenodeoxycholic acid via Barton-Zard radical decarboxylation reaction. Several hybrid molecules were found to possess good antiparasitic activity. Compounds **56–58** were some of the hybrid molecules exhibiting potent antimalarial and antileishmanial activity. However, these compounds were also found to exhibit similar levels of cytotoxicity against the normal cells. Therefore, further SAR studies are required to validate the promising antiparasitic effects of these hybrid analogs.

Stec et al. synthesized and evaluated a series of *N*-benzoyl-2-hydroxybenzamide analogs as potential antiprotozoal agents effective against *P. falciparum* K1 strain and *L. donovani* [45]. Initial studies lead to the identification of a moderately active compound **59**. Extensive SAR studies were conducted to modify compound **59** to improve antiprotozoal activity as well as to obtain a compound with good metabolic stability. In brief, compound **59** was modified at three sites: 4-ethylphenyl ring (B), the phenol ring (A) and the imide linker. These modifications lead to the identification of several analogs (**60-66**) exhibiting potent activity against the tested species. The SAR of these analogs is discussed in Fig. 13.

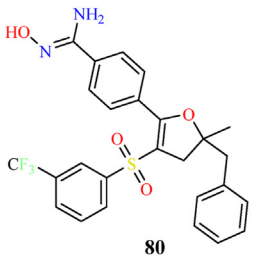
4,4″-diamidino-*m*-terphenyl and its analogs were screened for their antiparasitic activity against *P. falciparum* K1 strain and *L. amazonensis* amastigotes [46]. Predominantly, the evaluated analogs exhibited very potent activity (IC_{50} in the nanomolar range) against the Plasmodium. Certain derivatives (**68–72, Fig. 14**) were found to exhibit promising dual inhibitory effects. Compounds **68** and **69** were more lethal than standard drugs chloroquine (IC_{50} = 0.125 μM against *P. falciparum*) and amphotericin B (IC_{50} = 0.124 μM against *L. amazonensis*) against the tested species. Due to their promising antileishmanial activity, compounds **68, 69** and **71** were selected for *in vivo* studies. Unfortunately, all three compounds failed to show any promising activity. Compounds **68** and **69** were toxic for the mice and compound **71** demonstrated only modest inhibition of liver parasitemia (% inhibition of liver parasitemia = 23%).

Natural products influenced molecular hybridization technique was employed by Tyagi et al. for the design of novel pentamidine analogs as antiparasitic agents [47]. Important pharmacophores present in anno-montine (a naturally occurring beta-carboline alkaloid) and licochalcone A were used for the construction of two pentamidine hybrids-pyrimidine-pentamidine hybrid compound **73** and chalcone-pentamidine hybrid compound **74** (Fig. 15). Though the chalcone-pentamidine hybrids were found to exhibit potent antimalarial activity, they were devoid of antimalarial effects. However, the



79

IC_{50}= 7.16 μM against *P. falciparum* K1 strain
= 13.10 μM against *L. donovani*



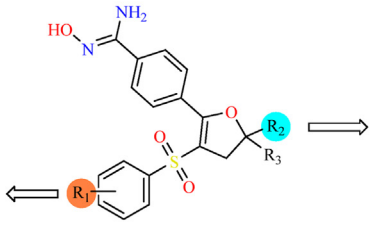
80

IC_{50}= 6.54 μM against *P. falciparum* K1 strain
= 11.89 μM against *L. donovani*

Nature of substituents influence antimalrial and antileishmanial activity.

Polysubstitution increases antimalarial activity while it decreases antileishmanial activity.

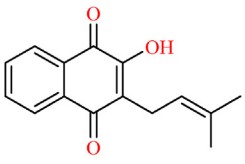
In general parasubstitution is preferred for both antimalarial and antileishmanial activities. Fluro group is preferred in the para position.



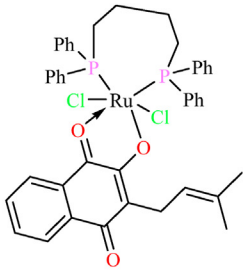
phenyl or ethyl group improves antimalarial activity in addition to methyl group

81

Fig. 16. Structure of dual-acting monoamidoxime derivatives (**79–80**) and their SAR analysis (**81**).



82



83

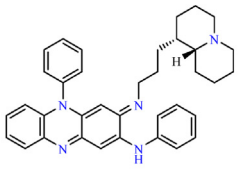
IC_{50}= 0.21 μM against *P. falciparum*
= 0.14 μM against *L. amazonensis* axenic promastigotes

Fig. 17. Ruthenium-Lapachol complexes (**82–83**) as promising dual-inhibitors.

pyrimidine-pentamidine hybrid analogs were bestowed with dual inhibitory effects. Some of the compounds like **75–78** exhibited potent antimalarial and antileishmanial activity. More importantly, these analogs were found to be more potent than the standard drugs such as chloroquine (IC_{50} = 2.45 ng/ml and 141.52 ng/ml against *P. falciparum* 3D7 and K1 strains, respectively), pentamidine (IC_{50} = 20.43 μM against *L. donovani*) and miltefosine (IC_{50} = 12.5 μM against *L. donovani*). Compounds **75–78** were also found to possess a good selectivity index (SI) value.

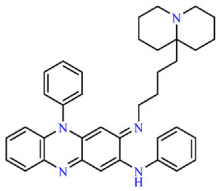
A novel series of monoamidoxime derivatives were screened for their inhibitory activity against *P. falciparum* K1 strain and *L. donovani* promastigotes [48]. A couple of compounds, **79–80,** were found to exhibit good antimalarial activity with IC_{50} values of 7.16 μM and 6.54 μM, respectively. They were also found to exhibit modest antileishmanial activity. The SAR of these analogs is discussed in Fig. 16.

Barbosa et al. synthesized and evaluated novel ruthenium/lapachol inorganic complexes as potential antiparasitic agents [49]. Lapachol (Lap) **82** and its complexes were evaluated for their ability to inhibit the proliferation of *L. amazonensis* promastigotes and intracellular amastigotes. Then they were evaluated for their antimalarial activity against the W2 strain of *P. falciparum*. Lapachol exhibited weak activity against the promastigote (IC_{50} = 12.49 μM) while it was completely inactive against the amastigote form of the Leishmania parasite. Its antimalarial activity was not convincing either, as it was found to exhibit a modest IC_{50} value of 11.3 μM. However, one of its ruthenium complexes [$RuCl_2$(Lap)(dppb)] **83** (Fig. 17) was found to exhibit potent antileishmanial and antimalarial activities. It inhibited the proliferation of both the promastigote (IC_{50} = 0.14 μM) and amastigote (IC_{50} = 0.57 μM) forms of *L. amazonensis*. The complex **83** was found to possess selective activity against the leishmanial parasite as it was found to be non-cytotoxic against the host cells J774 macrophages (LC_{50} of **83** = >10 μM and SI of **83** = >17). Additionally, complex **83** failed to cause 50% hemolysis of red blood cells (RBCs) at 200 μM suggesting



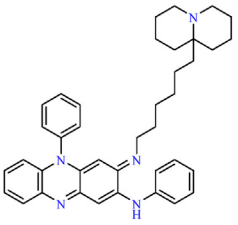
84

IC_{50}= 0.12 μM against *P. falciparum* D10 strain
= 0.063 μM against *P. falciparum* W2 strain
= 1.59 μM against *L. infantum*
=2.70 μM against *L. tropica*



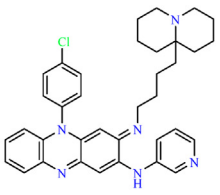
85

IC_{50}= 0.21 μM against *P. falciparum* D10 strain
= 0.27 μM against *P. falciparum* W2 strain
= 0.37 μM against *L. infantum*
= 0.22 μM against *L. tropica*
= 0.17 μM against *L. brasiliensis*



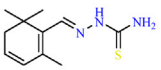
86

IC_{50}= 0.17 μM against *P. falciparum* D10 strain
= 0.21 μM against *P. falciparum* W2 strain
= 0.23 μM against *L. infantum*
= 0.12 μM against *L. tropica*
= 0.14 μM against *L. brasiliensis*



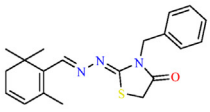
87

IC_{50}= 0.22 μM against *P. falciparum* D10 strain
= 0.18 μM against *P. falciparum* W2 strain
= 0.34 μM against *L. infantum*
= 0.34 μM against *L. tropica*



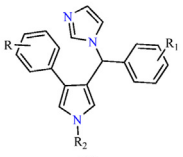
88

IC_{50}= 6.01 μg/ml against *P. falciparum* D10 strain
= 6.75 μg/ml against *P. falciparum* W2 strain
= 12.50 μg/ml against *L. infantum*
= 14.69 μg/ml against *L. tropica*

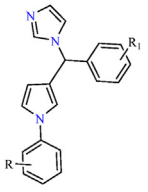


89

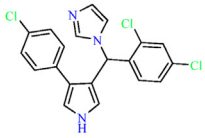
IC_{50}= 5.98 μg/ml against *P. falciparum* D10 strain
= 7.22 μg/ml against *P. falciparum* W2 strain
= 6.10 μg/ml against *L. infantum*
= 1.98 μg/ml against *L. tropica*



90a

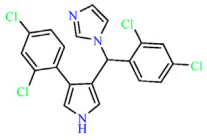


90b



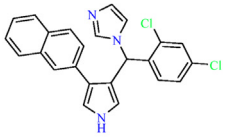
91

IC_{50}= 0.16 μM against *P. falciparum* K1 strain
= 3.77 μM against *L. donovani*



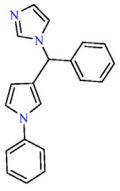
92

IC_{50}= 0.18 μM against *P. falciparum* K1 strain
= 1.19 μM against *L. donovani*



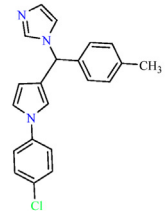
93

IC_{50}= 0.33 μM against *P. falciparum* K1 strain
= 1.91 μM against *L. donovani*



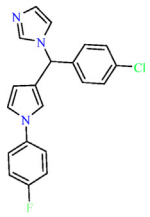
94

IC_{50}= 4.14 μM against *P. falciparum* K1 strain
= 14.53 μM against *L. donovani*



95

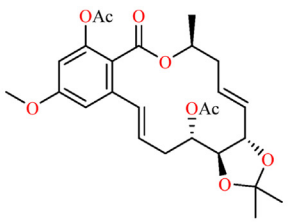
IC_{50}= 2.53 μM against *P. falciparum* K1 strain
= 12.53 μM against *L. donovani*



96

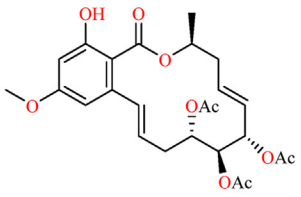
IC_{50}= 3.16 μM against *P. falciparum* K1 strain
= 10.43 μM against *L. donovani*

Fig. 18. Structure of dual acting clofazimine analogs **(84–87),** semi synthetic derivatives of safranal **(88–89)** and imidazole-based analogs **(91–96)** along with their biological activities.



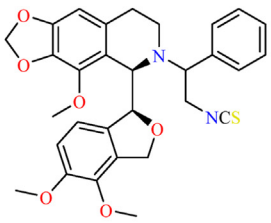
97

IC_{50}= 1.84 μM against *P. falciparum*
= 9.22 μM against *L. donovani*



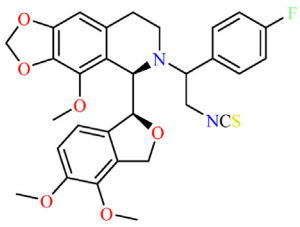
98

IC_{50}= 8.36 μM against *P. falciparum*
= 15.7 μM against *L. donovani*



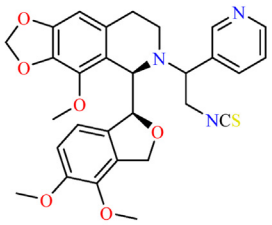
99

IC_{50}= 3.7 μM against *P. falciparum*
= 1 μM against *L. donovani*



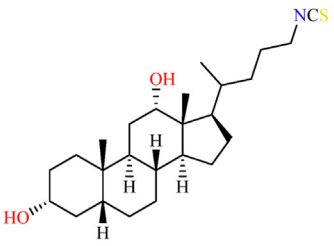
100

IC_{50}= 2.1 μM against *P. falciparum*
= 0.8 μM against *L. donovani*



101

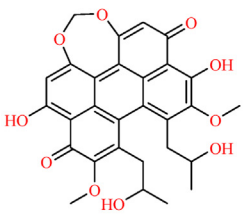
IC_{50}= 2.5 μM against *P. falciparum*
= 0.9 μM against *L. donovani*



102

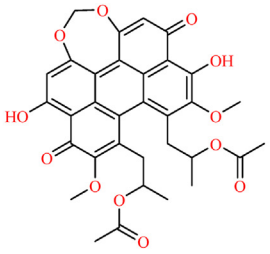
IC_{50}= 3.4 μM against *P. falciparum*
= 0.4 μM against *L. donovani*

Fig. 19. Structure of resorcylic acid lactone derivatives (**97–98)** and isothiocyanate based (**99–102**) analogs as promising antimalarial and antileishmanial agents.



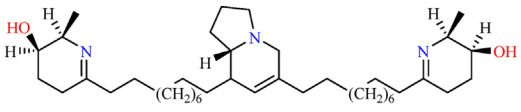
cercosporin 103

IC_{50}= 1.03 μM against *P. falciparum*
= 0.46 μM against *L. donovani*



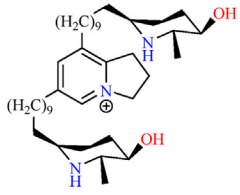
104

IC_{50}= 2.99 μM against *P. falciparum*
= 0.64 μM against *L. donovani*



Δ1,6-juliprosopine 105

IC_{50}= 560 ng/ml against *P. falciparum* D6
= 600 ng/ml against *P. falciparum* W2
= 1.83 μg/ml against *L. dononavi* axenic amastigotes
= 1.67 μg/ml against *L. dononavi* macrophage amastigotes



juliprosine 106

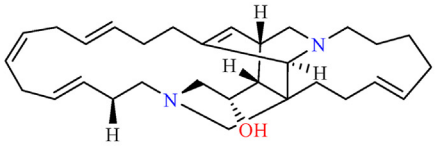
IC_{50}= 170 ng/ml against *P. falciparum* D6
= 150 ng/ml against *P. falciparum* W2
= 2.58 μg/ml against *L. dononavi* axenic amastigotes
= 3.08 μg/ml against *L. dononavi* macrophage amastigotes

Fig. 20. Structure of cercosporin (**103),** semisynthetic analog of cercosporin **(104)** and indolizidine alkaloids **(105–106)** as promising dual-acting agents.

that the antimalarial activity of complex **83** was not because of lysis of RBCs. The potent activity of compound **83** combined with its non-cytotoxic nature makes it an attractive compound for further exploration.

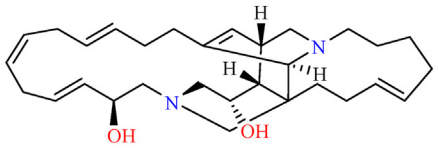
Two series of clofazimine derivatives were synthesized and were screened for their *in vitro* activity against chloroquine-sensitive and resistant strains of *P. falciparum* and against promastigotes of different leishmanial species [50]. Clofazimine is a riminophenazine drug that is used for the treatment of leprosy. Several clofazimine analogs such as **84–87** were found to exhibit good antimalarial and antileishmanial activity.

The antiparasitic effects of crocin and safranal, a couple of bioactive



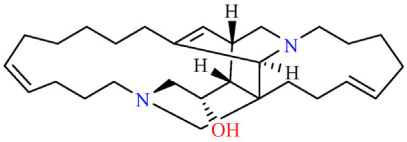
Ingamine A **107**

IC_{50} = 90 ng/ml against *P. falciparum* D6
= 72 ng/ml against *P. falciparum* W2
= 5.98 μg/ml against *L. dononavi* promastigotes



22-hydroxyingamine A **108**

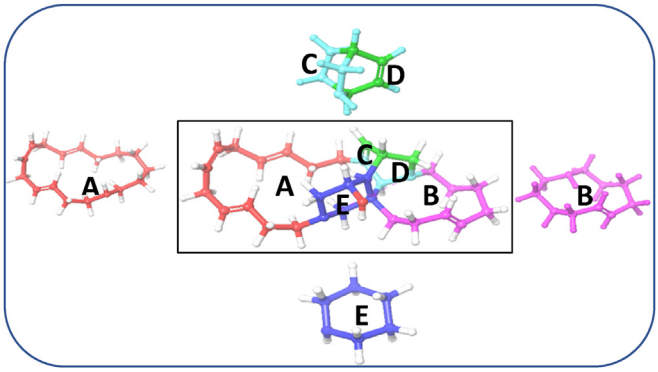
IC_{50} = 220 ng/ml against *P. falciparum* D6
= 140 ng/ml against *P. falciparum* W2
= 5.83 μg/ml against *L. dononavi* promastigotes



Dihydroingenamine D **109**

IC_{50} = 78 ng/ml against *P. falciparum* D6
= 57 ng/ml against *P. falciparum* W2
= 3.12 μg/ml against *L. dononavi* promastigotes

Fig. 21. Structure of pentacyclic ingamine alkaloids **(107–109)** and their biological activity.



Figs. 22. 3D model of pentacyclic Ingamine A alkaloid **107**.

compounds present in *Crocus sativus*, and their semisynthetic derivatives were disclosed by Monte et al. [51]. Both the naturally occurring crocin and safranal were found to be inactive against the tested species of malarial and leishmanial parasites. However, a couple of semisynthetic derivatives **88–89** exhibited potential antimalarial and antileishmanial activity. Compound **88,** a thiosemicarbazone derivative, exhibited good antimalarial activity, although its antileishmanial potency was comparatively low. A thiazolidinones derivative of safranal, **89,** exhibited potent activity against *L. tropica* (1.98 μg/ml) and demonstrated good activity against the malarial strains.

Two series of imidazole-based analogs (**90a-90b**) were synthesized and evaluated against *P. falciparum* K1 strain and axenic amastigotes of *L. donovani* [52]. In general, compounds belonging to the **90a** series were found to exhibit better antiprotozoal activity than **90b** series of analogs. Most of the compounds belonging to the **90a** series were bestowed with sub-micromolar potency against the Plasmodium and low micromolar potency against the Leishmania parasite. Some of the representative compounds of **90a** (**91–93**) and **90b** (**94–96**) series are highlighted in Fig. 18.

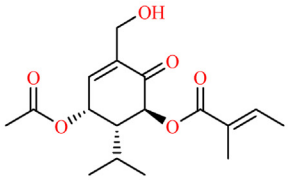
A series of resorcylic acid lactone derivatives were semi-synthesized and were evaluated for their antiparasitic properties against *P. falciparum* and *L. donovani* [53]. The 14-membered resorcylic acid lactones are a class of fungal secondary metabolites that have broad biological properties [54,55]. While most of the derivatives were either inactive or selectively toxic to one parasite, a couple of derivatives, **97–98** were found to inhibit both the parasites with good selectivity. Compound **97** exhibited strong antiplasmodial and antileishmanial activities with IC_{50} values of 1.84 μM and 9.22 μM, respectively, while compound **98** was comparatively less potent towards these parasites.

Novel isothiocyanate analogs of noscapine, bile acids, amino acids and a few other aromatic amines were synthesized and screened for their antiprotozoal activities [56]. These analogs were found to exhibit excellent antileishmanial activity and strong antimalarial activity. The antileishmanial IC_{50} values of these analogs ranged between 0.4 μM and 7.1 μM, while the antimalarial IC_{50} values ranged between 1.1 μM and 10.3 μM. Some of the highly active compounds, **99–102,** against these parasites are exhibited in Fig. 19. The isothiocyanate group was unearthed as an essential pharmacophore for the antileishmanial activity as the parent analogs that were devoid of the group were totally inactive against *L. donovani*.

3. Natural products

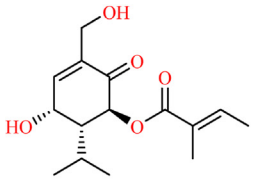
Moreno et al. isolated a novel chemical compound from an endophytic fungus ***Mycosphaerella* sp. nov**. and evaluated their bioactivity against Leishmania and malaria parasites [57]. The isolated compound was identified as cercosporin **103** (Fig. 20)**.** *In vitro* studies indicate that cercosporin possesses potent antileishmanial (IC_{50} = 0.46 μM against *L. donovani* amastigotes) and antimalarial (IC_{50} = 1.03 μM against *P. falciparum*) activities. A semisynthetic analog of cercosporin, compound **104** was synthesized by acetylation to determine the importance of the OH group. No dramatic change in the bioactivities was observed for compound **104**, indicating that the OH group may not have an essential role in the bioactivity of cercosporin.

A couple of indolizidine alkaloids **105** and **106** were isolated from the leaves of ***Prosopis glandulosa*** var. by Rahman et al. [58]. The structures of **105** and **106** were elucidated using a combination of nuclear magnetic resonance (NMR) and mass spectrometry (MS) methods. Both the compounds exhibited potent activity against both the chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum,* with **106** being more potent than **105**. They were also found to be active against the



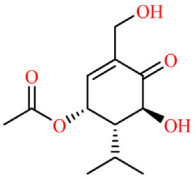
3-acetoxy-7- hydroxy-5-tigloyloxycarvotacetone 110

IC_{50} = 1.40 μg/ml against *P. falciparum* D6
= 2 μg/ml against *P. falciparum* W2
= 0.70 μg/ml against *L. dononavi* axenic amastigotes



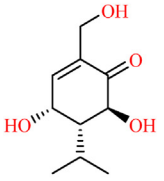
3,7-dihydroxy-5-tigloyloxycarvotacetone 111

IC_{50} = 0.79 μg/ml against *P. falciparum* D6
= 0.90 μg/ml against *P. falciparum* W2
= 3 μg/ml against *L. dononavi* axenic amastigotes



3-acetoxy-5,7-dihydroxycarvotacetone 112

IC_{50} = 0.60 μg/ml against *P. falciparum* D6
= 0.68 μg/ml against *P. falciparum* W2
= 0.70 μg/ml against *L. dononavi* axenic amastigotes



3,5,7-trihydroxy-carvotacetone 113

IC_{50} = 3.40 μg/ml against *P. falciparum* D6
= 2.80 μg/ml against *P. falciparum* W2
= 17 μg/ml against *L. dononavi* axenic amastigotes

Fig. 23. Structure of carvotacetone derivatives (**110–113)** as dual-acting antimalarial and antileishmanial agents.

L. donovani promastigotes and amastigotes.

Three pentacyclic ingamine alkaloids **107–109** (Fig. 21) with antiparasitic properties were isolated from a marine sponge ***Petrosid Ng5 Sp5*** [59]**.** The isolated compounds exhibited promising activities against *P. falciparum* D6 and W2 strains and *L. donovani* promastigotes, with compound **109** being the most active against both the parasites. Importantly, these compounds were devoid of toxicity toward mammalian cells (up to 10 μg/ml). The energy minimized 3D model of pentacyclic ingamine A alkaloids **107** is represented in Fig. 22. The distance between two nitrogen atoms present in A and D ring was observed to be 5.09 Å.

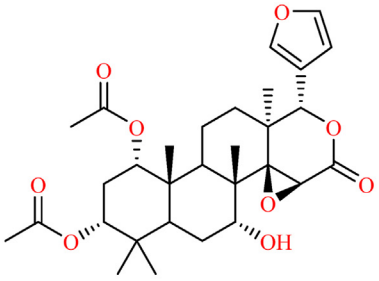
Seventeen secondary metabolites were isolated from the aerial parts of ***Sphaeranthus bullatus*** by Machumi et al. [60]. Of the seventeen metabolites, four carvotacetone derivatives **110–113** (Fig. 23) displayed promising antiparasitic activities. All four derivatives were active against Leishmania and malaria parasites, with their IC_{50} values being less than 5 μg/ml against the tested parasites.

Two tetraterpenoid limonoid compounds-7-deacetylkhivorin **114** and grandifolione **115** (Fig. 24) were isolated from the seeds of ***Khaya anthotheca*** by Obbo et al. and were evaluated for their antiparasitic properties [61]. Compounds **114** and **115** were found to exhibit potent activity against *P. falciparum* with IC_{50} values of 1.37 μg/ml and 0.732 μg/ml, respectively. However, both compounds exhibited only weak antileishmanial activity (IC_{50} of compound **114** and **115** = 36.71 μg/ml and 13.31 μg/ml, respectively, against *L. donovani*). Compound **116**, a triterpenoid saponin ester was isolated from the stem bark of ***Pittosporum mannii*** [62]. Compound **116** displayed pronounced activity against *P. falciparum* and *L. donovani* with IC_{50} values of 1.02 μg/ml and 1.80 μg/ml, respectively. Gadetskaya et al. isolated 11 natural products from the aerial parts of ***Limonium caspium*** and evaluated their antiparasitic properties against malaria and Leishmania parasites [63]. Myricetin **117** was found to exhibit dual inhibitory properties. Myricetin exhibited similar potency against the sensitive and resistant strains of *P. falciparum* with IC_{50} values of 1.51 μg/ml and 1.82 μg/ml, respectively. It also exhibited good activity against *L. donovani* promastigotes (IC_{50} = 7.67 μg/ml).

Tasdemir et al. investigated the phytochemical constituents of ***Origanum onites*** essential oil [64]. A combination of Gas Chromatography-Flame Ionization Detector (GC-FID) and Gas Chromatography-Mass Spectrometry (GC-MS) analysis led to the identification of almost 71 compounds in various proportions. The main component of the oil, carvacrol **118** (Fig. 25), and a minor component, thymol **119,** were evaluated for their antiparasitic properties. Carvacrol and thymol exhibited good activity against *P. falciparum* with IC_{50} values of 6.4 μg/ml and 5.7 μg/ml, respectively. They were also found to exhibit moderate activity against *L. donovani*. Due to their potential antiparasitic activity, methyl ether derivatives of carvacrol **120** and thymol **121** were also evaluated for their antiparasitic activity. Surprisingly, compounds **120** and **121** exhibited less antileishmanial potency than their parent analogs. Moreover, they were also devoid of any antimalarial activity.

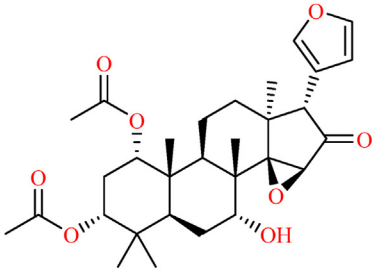
Imperatore et al. investigated the antiparasitic properties of sesquiterpene avarone **122** (Fig. 26) and its reduced form avarol **123** [65]. These marine-derived metabolites were isolated from the ***Dysidea avara*** sponge. Both the analogs were found to exhibit potent antimalarial potency against *P. falciparum* D10 and W2 strains. Furthermore, both analogs were evaluated against *P. falciparum* stage V gametocytes, the sexual stage of the parasite in the bloodstream, to determine their transmission-blocking potential. Avarone and avarol were found to exhibit moderate potency toward *P. falciparum* gametocytes stage V (IC_{50} of avarone and avarol = 15.53 μM and 9.30 μM, respectively). In all these evaluations, the reduced form, avarol, exhibited better potency than the oxidized form avarone. A similar trend was also observed for the antileishmanial potency of these analogs. Avarol was found to exhibit superior potency (IC_{50} = 3.19 μM) than avarone (IC_{50} = 7.64 μM) against *L. infantum* amastigotes.

A combination of lignans, amides and saponins were isolated from a Sudanese medicinal plant ***Haplophyllum tuberculatum*** by Mahmoud et al. [66]. The phytochemical investigation led to the isolation of 13 compounds, which were evaluated for their antimalarial and antileishmanial potentials. Nectandrin B **124** was the only compound that was found to possess dual inhibition property (IC_{50} = 4.5 μM and 9.5 μM against *L. donovani* axenic amastigotes and *P. falciparum*, respectively). However, the promising potential of nectandrin B against axenic



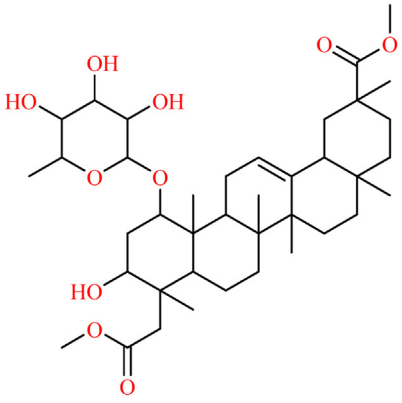
7-deacetylkhivorin 114

IC_{50}= 1.37 μg/ml against *P. falciparum*
= 36.71 μg/ml against *L. donovani*



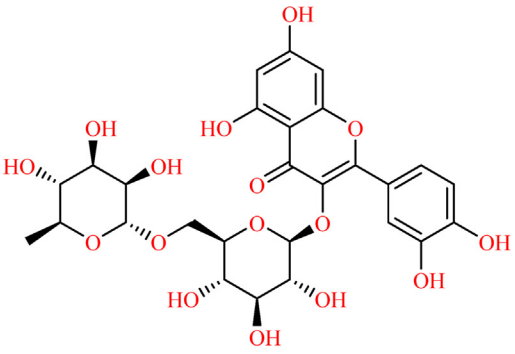
grandifolione 115

IC_{50}= 0.732 μg/ml against *P. falciparum*
= 13.31 μg/ml against *L. donovani*



1-O-[apha- L-(Rhamnopyranosyl]-23-acetoxyimberbic acid 29-methyl ester 116

IC_{50}= 1.02 μg/ml against *P. falciparum*
= 1.80 μg/ml against *L. donovani*



myricetin 117

IC_{50} = 1.51 μg/ml against *P. falciparum* D6
= 1.82 μg/ml against *P. falciparum* W2
= 7.67 μg/ml against *L. dononavi* promastigotes

Fig. 24. Structure of naturally obtained tetraterpenoids (**114–115**), triterpenoid saponin ester **116** and myricetin **(117)** with their bioactivity.

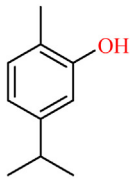
amastigotes was not reproduced against *L. donovani* intracellular amastigotes as it was found to be inactive until 30 μM. In a subsequent study conducted by the same group, a total of 13 natural products were isolated from ***Croton gratissimus*** and ***Cuscuta hyaline*** [67]**.** Quercetin-3, 7-dimethyl ether **125** exhibited good potency against *P. falciparum* (IC_{50} = 7.3 μM) and *L. donovani* axenic amastigotes (IC_{50} = 4.5 μM). Ayanin **126**, a possible congener, was also found to exhibit moderate activity against leishmanial (IC_{50} = 8.2 μM against *L. donovani* axenic amastigotes) and malarial parasite (IC_{50} = 7.8 μM against *P. falciparum*). Like nectandrin, quercetin-3,7-dimethyl ether was also found to be inactive against *L. donovani* intracellular amastigotes. This may be due to lack of penetration or decreased stability of nectandrin B and quercetin-3, 7-dimethyl ether in macrophages. Nevertheless, the promising potential of nectandrin B and quercetin-3,7-dimethyl ether against malarial and antileishmanial parasites provides ample scope for the generation of novel nectandrin B and quercetin analogs. The dual inhibitory potential of natural products is summarized in Table 2.

4. Conclusion

Despite numerous efforts to curtail the devastating effects of malarial and leishmanial diseases, they continue to be a major public health concern. The existing treatments have been marred by increasing resistance and drug adverse effects. This calls for the development of novel treatment strategies to effectively manage both malaria and leishmaniasis using a single therapeutic molecule. In recent years, structurally diverse compounds of synthetic and natural origin have been explored for their potential antimalarial and antileishmanial activities. In the present review article, an attempt has been made to unearth structurally diverse compounds exhibiting dual activity against malaria and Leishmania parasites. Structurally, such reported compounds belong to different classes of heterocyclics such as quinoline, quinazoline, quinoxaline, pyrazoles, etc. Several synthetic compounds reported in this review, such as **19, 24, 25, 29, 45, 47, 50, 69, 71, 77, 83, 84–87, 91–93,** etc. have demonstrated potent dual inhibitory activity providing a foundation for future drug discovery ventures. Natural products belonging to different classes like alkaloids, flavonoids, terpenoids, etc. have also demonstrated promising dual activity that warrants further studies. We hope the information provided in this article will encourage researchers to discover and develop novel dual-acting inhibitors against malarial and leishmanial parasites.

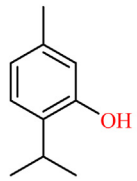
5. Future directions

From the above reported and compiled information, it is evident that there are lot of novel molecules with dual inhibitory activity have been reported by various researchers across the globe. However, most of the molecules, albeit a few, were not developed as dual-acting agents in the first place. Therefore, the information amassed in this review suggests that it is indeed possible to design and develop a novel compound that



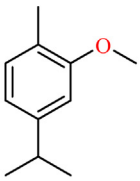
carvacrol 118

IC_{50}= 6.4 μg/ml against *P. falciparum*
= 13.1 μg/ml against *L. donovani*



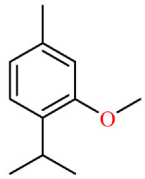
thymol 119

IC_{50}= 5.7 μg/ml against *P. falciparum*
= 17.3 μg/ml against *L. donovani*



carvacrol methyl ether 120

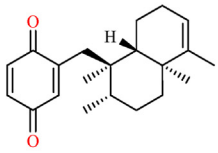
IC_{50}= >20 μg/ml against *P. falciparum*
= 17.5 μg/ml against *L. donovani*



thymol methyl ether 121

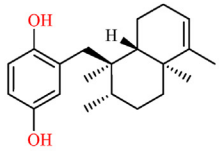
IC_{50}= >20 μg/ml against *P. falciparum*
= 86 μg/ml against *L. donovani*

Fig. 25. Structure of carvacrol (**118**), thymol (**119**) and their derivatives (**120–121**) as dual-acting agents.



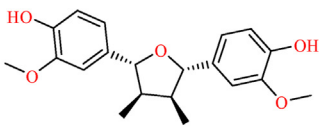
avarone 122

IC_{50} = 2.74 μM against *P. falciparum* D10
= 2.09 μM against *P. falciparum* W2
= 15.53 μM against *P. falciparum* gametocytes stage V
= 7.64 μM against *L. infantum* amastigotes



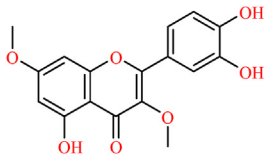
avarol 123

IC_{50} = 0.96 μM against *P. falciparum* D10
= 1.10 μM against *P. falciparum* W2
= 9.30 μM against *P. falciparum* gametocytes stage V
= 3.19 μM against *L. infantum* amastigotes



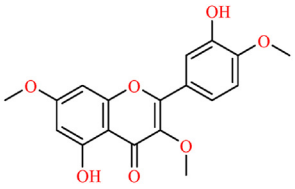
nectandrin B 124

IC_{50}= 9.5 μM against *P. falciparum*
= 4.5 μM against *L. donovani* axenic amastigotes



quercetin 3,7-dimethyl ether 125

IC_{50}= 7.3 μM against *P. falciparum*
= 4.5 μM against *L. donovani* axenic amastigotes



ayanin 126

IC_{50}= 7.8 μM against *P. falciparum*
= 8.2 μM against *L. donovani* axenic amastigotes

Fig. 26. Structure of naturally obtained sesquiterpenes (**122–123**), lignan **124** and flavonoids (**125–126**) with their biological activity.

can target both malarial and Leishmanial parasites. This can be done in four ways. The first approach would be to identify the most appropriate heterocyclic nucleus and critical fragments for significant dual activity. Then with further SAR, QSAR studies, it is possible to develop a novel

Table 2
Summary of naturally obtained compounds exhibiting dual activity against malaria and leishmaniasis.

S. No	Natural product	Source	Biological activity		Reference
			IC_{50} against *P. falciparum*	IC_{50} against *L. donovani*	
1	Cercosporin	***Mycosphaerella* sp**	0.55 μg/ml	0.24 μg/ml	[57]
2	Δ1,6-juliprosopine	***Prosopis glandulosa***	0.560 μg/ml (D6 strain), 0.600 μg/ml (W2 strain)	1.83 μg/ml (axenic amastigotes), 1.67 μg/ml (amastigotes)	[58]
3	Juliprosine	***Prosopis glandulosa***	0.170 μg/ml (D6 strain), 0.150 μg/ml (W2 strain)	2.58 μg/ml (axenic amastigotes), 3.08 μg/ml (amastigotes)	[58]
4	Ingamine A	***Petrosid Ng5 Sp5***	0.090 μg/ml (D6 strain), 0.072 μg/ml (W2 strain)	5.98 μg/ml (promastigotes)	[59]
5	22-hydroxyingamine A	***Petrosid Ng5 Sp5***	0.220 μg/ml (D6 strain), 0.140 μg/ml (W2 strain)	5.83 μg/ml (promastigotes)	[59]
6	Dihydroingenamine D	***Petrosid Ng5 Sp5***	0.078 μg/ml (D6 strain), 0.057 μg/ml (W2 strain)	3.12 μg/ml (promastigotes)	[59]
7	3-acetoxy-7- hydroxy-5-tigloyloxycarvotacetone	***Sphaeranthus bullatus***	1.40 μg/ml (D6 strain), 2 μg (W2 strain)	0.70 μg/ml (axenic amastigotes)	[60]
8	3,7-dihydroxy-5-tigloyloxycarvotacetone	***Sphaeranthus bullatus***	0.79 μg/ml (D6 strain), 0.90 μg (W2 strain)	3 μg/ml (axenic amastigotes)	[60]
9	3-acetoxy-5,7-dihydroxycarvotacetone	***Sphaeranthus bullatus***	0.60 μg/ml (D6 strain), 0.68 μg (W2 strain)	0.70 μg/ml (axenic amastigotes)	[60]
10	3,5,7-trihydroxy- carvotacetone	***Sphaeranthus bullatus***	3.40 μg/ml (D6 strain), 2.80 μg (W2 strain)	17 μg/ml (axenic amastigotes)	[60]
11	7-deacetylkhivorin	***Khaya anthotheca***	1.37 μg/ml	36.71 μg/ml	[61]
12	Grandifolione	***Khaya anthotheca***	0.732 μg/ml	13.31 μg/ml	[61]
13	1-*O*-[apha- L-(Rhamnopyranosyl]-23-acetoxyimberbic acid 29-methyl ester	***Pittosporum mannii***	1.02 μg/ml	1.80 μg/ml	[62]
14	Myricetin	***Limonium caspium***	1.51 μg/ml (D6 strain), 1.82 μg (W2 strain)	7.67 μg/ml (promastigotes)	[63]
15	Carvacrol	***Origanum onites***	6.4 μg/ml	13.1 μg/ml	[64]
16	Thymol	***Origanum onites***	5.7 μg/ml	17.3 μg/ml	[64]
17	Carvacrol methyl ether	***Origanum onites***	>20 μg/ml	17.5 μg/ml	[64]
18	Thymol methyl ether	***Origanum onites***	>20 μg/ml	86 μg/ml	[64]
19	Avarone	***Dysidea avara***	0.85 μg/ml (D10 strain) 0.65 μg/ml (W2 strain)	2.38 μg/ml (*L. infantum* amastigotes)	[65]
20	Avarol	***Dysidea avara***	0.30 μg/ml (D10 strain) 0.34 μg/ml (W2 strain)	1 μg/ml (*L. infantum* amastigotes)	[65]
21	Nectandrin B	***Haplophyllum tuberculatum***	3.26 μg/ml	1.54 μg/ml (axenic amastigotes)	[66]
22	Quercetin-3,7-dimethyl ether		3.26 μg/ml	1.48 μg/ml (axenic amastigotes)	[67]
23	Ayanin		2.68 μg/ml	2.82 μg/ml (axenic amastigotes)	[67]

molecule with balanced dual inhibitory activities against both malaria and leishmaniasis. The second approach would be to identify antimalarial pharmacophore and antileishmanial pharmacophore initially. Then, these individual pharmacophores can be linked/fused/merged to develop a novel hybridized molecule that may exhibit dual inhibitory activity. Third approach would be isosteric/bio-isosteric replacement of already existing dual active lead molecules to get an optimized lead molecule with improved potency and reduced toxic effects. The fourth method could be using structure-based drug design utilizing the common molecular target motifs. While implementing such approaches, we may end up with significant activity against any one of the protozoa and less/weak activity against the other protozoa. So, appropriate measures must be taken to get an analog with balanced inhibitory activity against both the parasites.

As discussed in the present review article, several heterocyclic analogs have demonstrated dual-inhibitory activity. Analogs of these molecules can be modified to study their antimalarial and antileishmanial effects. A key feature of compound **93** is a substituted naphthalene ring on the pyrrole nucleus. It will be quite interesting to analyze what happens to the activity against both malarial and leishmanial parasites when naphthalene ring is replaced with other bicyclic systems like quinoline and tetrahydroisoquinoline. Pentamidine was fused with amino pyrimidines (a pharmacophore in annomontine) to generate compounds **75–78**, and the resultant molecules exhibited promising antimalarial and antileishmanial activity. In a similar way, pentamidine can be hybridized with chromone, an important pharmacophore found in several flavonoids. Also, substituting a triazole or imidazole scaffold in the pyrrole moiety in compounds **91**–**96** may lead to superior molecules exhibiting dual antimalarial and antileishmanial properties. These suggested modifications may give insights for the future directions towards newer potential antimalarial and antileishmanial candidates.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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