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ABSTRACT

Neglected parasitic diseases are a group of infections currently considered as a worldwide concern. This fact can be attributed to the migration of these diseases to developed and developing countries, associated with therapeutic insufficiency resulted from the low investment in the research and development of new drugs. In order to overcome this situation, bioprospecting supports medicinal chemistry in the identification of new scaffolds with therapeutically appropriate physicochemical and pharmacokinetic properties. Among them, we highlight the nitrogenous heterocyclic compounds, as they are secondary metabolites of many natural products with potential biological activity. The objective of this work was to review studies within a 10 year timeframe (2009-2019), focusing on the pharmacological application of nitrogen bioprospectives (pyrrole, pyridine, indole, quinoline, acridine, and their respective derivatives) against neglected parasitic infections (malaria, leishmania, trypanosomiases, and schistosomiasis), and their application as a template for semi-synthesis or total synthesis of potential antiparasitic agents. In our studies, it was observed that among the selected articles, there was a higher focus on the attempt to identify and obtain novel antimalarial compounds, in a way that an extensive amount of studies involving all heterocyclic nitrogen nuclei were found. On the other hand, the parasites with the lowest number of publications up until the present date have been trypanosomiasis, especially those caused by *Trypanosoma cruzi*, and schistosomiasis, where some heterocyclics have not even been cited in recent years. Thus, we conclude that despite the great biodiversity on the planet, little attention has been given to certain neglected tropical diseases, especially those that reach countries with a high poverty rate.

Keywords: Natural Products; Neglected Tropical Diseases; Molecular Design; Medicinal Chemistry; Semi-synthesis; Heterocyclic Compounds.

1. INTRODUCTION

The term bioprospecting, pioneered by Thomas T Eisner as "chemical prospecting", refers to the investigation of the biodiversity for the obtainment of commercially valuable genetic and biochemical resources. The exploration of the biodiversity for new medicines, foods, crops, insecticides, pesticides, and additional commercially relevant genetic and biological products and processes is growing, acknowledgments to the prominent development of biotechnology, mainly genomics, proteomics, transcriptomics, enzymatic and transgenic technologies [1].

The application of ethnopharmacology has supported medicinal chemistry in the discovery of novel chemical entities, mainly by the bioprospection of secondary metabolites from several natural products. Despite the significant efforts on employing combinatorial chemistry to identify new drugs, mostly due to the incompatibility of natural products with traditional high-throughput screening paradigms, the natural product libraries result in a higher hit rate than combinatory libraries [2-4]. The literature reports many biologically active compounds identified based on ethnopharmacological work, many resulting in approved medicines, mainly as chemotherapeutic compounds with antitumor [5-7], antibiotic [8, 9] and antiparasitic properties [10, 11]. In that sense, as an interesting example, artemisinin was first isolated from *Artemisia annua* and is categorized as a lead compound approved to malaria treatment [11].

Therefore, bioprospecting has become a useful and current alternative in the search for new sources of drugs, mainly through the isolation of secondary metabolites. Those are intended for multiple therapeutic purposes, including the cure of neglected diseases, whose treatment options are limited and associated with alarming resistance mechanisms developed by these parasites to existing and used drugs.

Parasitic diseases are responsible for thousands of deaths yearly, affect about one billion individuals and constitute a major obstacle to socioeconomic advance in many developing countries [12]. These diseases are caused by parasites, which are considered as organisms capable of obtaining their food by ingesting other organisms or their products in nature. As previously noted, these parasites are responsible for causing a high morbidity and mortality rate around the world, being mainly represented by Malaria, Leishmaniasis, Trypanosomiasis (Chagas disease and African sleeping sickness) and Schistosomiasis [13]. Strategies for the development of antiparasitic chemotherapeutics require many strategies, such as the identification of active compounds from natural sources, exploration of drugs already licensed for distinct pathologies, or validation of specific targets identified within key metabolic pathways, among others [12].

Malaria is the most common of the parasitic diseases in tropical and subtropical regions. The World Health Organization (WHO) has reported the occurrence of 216 million clinical cases of malaria and 445 thousand deaths in 2016 [14-19]. Despite being preventable and treatable, nowadays, this disease is responsible for almost half a million deaths of children and pregnant women per year in Africa [14-16]. It stands out for its high morbidity and mortality percentages in poor or underdeveloped countries. However, reports of the emergence of malaria in developed countries have attracted the attention of the world scientific community [20]. Malaria is caused by several species of the genus Plasmodium, a protozoan parasite that is transmitted to humans by Anopheles mosquitoes' bite. Within the five species of malaria parasites (*Plasmodium falciparum, P. vivax, P. ovale, P. malariae e P. knowlesi*) known for

affecting humans, the most virulent malaria parasite is *Plasmodium falciparum*. In the 1980s, this species was responsible for thousands of deaths in Africa, highter than any other parasitic disease [21]. Its treatment is usually conducted with the use of quinoline derivatives, designed from quinine structure, isolated from Cinchona bark, and, more recently, with artemisinin, which has been the drug of choice when standard treatments are insufficient. However, due to the widespread and ever-increasing resistance against antimalarial drugs, there is a growing need for novel therapeutic agents [22, 23].

Another neglected tropical disease is Leishmaniasis, which is included as one of the most relevant affections of the neglected tropical diseases, infecting millions of individuals worldwide. It is caused by different species of protozoa from the family Trypanosomatidae and the genus Leishmania [24]. In humans, the disease occurs in at least four major forms, depending on the parasite species and the cellular immune response of the patient, denominated as cutaneous leishmaniasis (CL), diffuse cutaneous leishmaniasis (DCL), mucocutaneous leishmaniasis (MCL) and visceral leishmaniasis (VL). VL caused by *Leishmania donovani* and *L. infantum* can be highlighted as the most severe form of leishmaniasis, while CL caused by *L. major*, *L. amazonensis, L. mexicana, L. braziliensis*, and *L. panamensis*, is significantly associated with morbidity [25, 26].

Nowadays, the drugs used for the treatment of leishmaniasis include pentavalent antimonials (sodium stibogluconate and meglumine antimoniate), amphotericin B, miltefosine, pentamidine and paromomycin. Many of these drugs exhibit high toxicity, the occurrence of side effects, and limitations due to the development of resistant strains. Besides, there are no effective vaccines; consequently, there is an urgent need to accelerate the development process of a new generation of more effective and safer antileishmanial compounds [26].

The third disease addressed in this review proposal is Chagas disease or American trypanosomiasis. This illness, caused by the flagellated protozoan *Trypanosoma cruzi*, represents a significant health problem in America and, due to human migration, is now a global public health issue. This disease is considered a neglected tropical disease, which means that it is associated with poverty and neglected by the socio-economic system and by policymakers [27, 28].

Chagas disease is characterized by an initial acute phase, which is fatal for 5% of the infected infants, followed by a long-term chronic phase, which can eventually be fatal due to associated cardiac problems [29]. Currently, only nifurtimox and benzimidazole, developed over four decades ago, are used as treatment for American trypanosomiasis. Both drugs cause multiple side effects and have efficacy, mainly, on patients in the chronical form of the disease. Thus, the development of drugs more efficient against *T. cruzi* is of high priority [29, 30].

Besides *Trypanosoma cruzi*, another type of trypanosomiasis has stood out. Human African Trypanosomiasis (HAT), also designated sleeping sickness, is caused by the parasite *Trypanosoma brucei* and affects people mainly in central Africa. This parasitic disease occurs subsequently the bite of a tsetse fly and develops in two clinical stages, a peripheral haemolymphatic stage (phase 1) followed by a meningoencephalitic stage (phase 2), in which the parasite crosses the blood-brain barrier and invades the central nervous system, leading to death [30, 31]. The HAT is caused by two subspecies of the parasite *Trypanosoma brucei* (T. b.), known as *T. b. rhodesiense* and *T. b. gambiense*. Currently, five drugs are used to treat HAT, depending on the stage. These include: Pentamidine, suramin, melarsoprol,

eflornithine and NECT (nifurtimox-eflornithine combination treatment). However, the current treatment is unsatisfactory due to pharmacokinetic limitations and considerable toxicity [31].

Last, but not least, we emphasize schistosomiasis. In an extensive review article published by Silva *et al*. (2017), schistosomiasis is defined as a group of diseases caused by helminths from the genus Schistosoma, and the most prevalent etiologic agents are the species *Schistosoma mansoni, S. intercalatum, S. haematobium, S. japonicum*, and *S. mekongi*. This disease is the most common within pathologies caused by worms in the world, being endemic in 78 countries, and affecting millions of people in Africa, Middle East, Southeast Asia, and South America as a result. Also, it is estimated that over 700 million people are living in areas that present a risk of contamination. Regions like America, Suriname, Venezuela, Caribbean Islands, and Brazil are considered endemic zones, and over 240 million people lack treatment for schistosomiasis. Currently, praziquantel is the first-line treatment against schistosomiasis and many other cestode infestations, while oxamniquine is used in case of treatment failure with praziquantel [32-34]. Table 1 summarizes the main compounds used to treat the parasitic agents cited in this review and, in some cases, their natural source compounds.

INSERT HERE THE TABLE 1.

Table 1. Main compounds used to treat the parasitic agents.

Despite the availability of some drugs for the treatment of neglected tropical diseases, there are strong reports of toxicity associated with these drugs, besides the emergence of resistance mechanisms, which includes, among others, drug efflux by ATP-binding cassette (ABC) transporters, target multation, decrease in drug uptake, transport defects and changes of membrane composition, that has made their use unfeasible, which is leading to treatment abandonment. For example, miltefosine is an antileishmanial drug that acts by achieving intracellular drug accumulation, however, a decrease in drug accumulation results in miltefosine resistance through two autonomous mechanisms: increased drug efflux by the overexpression of P-glycoprotein and decreased drug uptake by the inactivation of protein transporter LdMT [35, 36]. Thus, there is an urgent need for the discovery of new chemicals that can overcome these drawbacks, and bioprospection from natural compounds is an extremely valid alternative.

In the evaluation and search of molecules with biological potentials, heterocyclic compounds occupy a prominent place in the attention of several research groups worldwide. A variety of heteroatoms may be part of the constitution of these heterocycles, providing them unique properties, as interference in its chemical reactivities and physicochemical properties and the creation of new interactional places between these compounds and biological targets [37]. Over 90% of the drugs used in the overall therapy possess heterocyclic rings in their structure, in which 95% of these have at least one nitrogen atom incorporated [38, 39]. Among these, we highlight the pyrrole, pyridine, indole, quinolone, acridine, and their analogs as relevant nuclei for antiparasitic chemotherapeutic action [40]. These differ in terms of the number of members in the ring, which can provide a spectrum of structural characteristics that can make the compound more potent or more selective for a given pathogen.

In the compounds of natural origin, these heterocycles are classified into alkaloids group, responsible for a wide rate of biological activities [41-43]. In this topic of this review, we will focus our discussion in natural nitrogen heterocycles, whether from the direct isolation of the active substance, or

from semi-synthetic mechanisms, in the insertion and/or reproduction of nitrogen heterocyclic rings, or total synthesis of natural compounds and/or based on these.

For the design and development of synthetic routes for bioactive compounds based on natural products, several strategies are applied. Among which, stands out the molecular hybridization, based on the combination of chemical structures of known biological activity to generate a possibly more active hybrid compound [44]; and the bioisosterism, which aims the preservation or augmentation of the positive effects produced by a portion of the active molecule after their replacement by an isosteric group. In this last molecular modification strategy, nitrogen rings are usually well known to be bioisosteres of peptide bonds constituents, aromatic rings or double bonds [45-47]. This insertion of azole, pyridine, indoles, quinolones and acridine moieties in classes of natural products is, therefore, a good strategy for the obtainment of new biologically promising compounds [48, 49].

Among the potentialities of nitrogen heterocycles, their antiparasitic properties have some prominence [50, 51], of which some are the aim of our review. Therefore, this review included articles published within the last ten years (2009 – 2019) focused on the use of aforementioned nuclei derivatives, with potential antileishmanial, antiplasmodial, antitrypanosomal (*Trypanosoma cruzi* and *Trypanosoma brucei*) and antischistosomal activities. These key-words were included into the "ScienceDirect", "Pubmed" and "Periódicos Capes" platforms, focusing the attention and giving preference to the articles that included studies of natural products or based on these.

2. PYRROLE, IMIDAZOLE, TRIAZOLE AND TETRAZOLE DERIVATIVES

2.1. Antiparasitic mechanism of action

Heterocycle compounds such as pyrrole, imidazole, triazoles and tetrazole are reported in the literature with antiparasitic actions for different species of parasites, however, few are the studies that deeply address the antiparasitic mechanism of action of pyrrole, imidazole, triazole and tetrazole derivatives. But some studies provide evidence of possible molecular targets that show the route of action of these derivatives in their antiplasmodial, antileishmanial, antitrypanosomal and antischistosomal activities.

For antiplasmodial activity, some evaluation indicated that these compounds can act similarly to pyrrole atorvastatin, by inhibition of lactate dehydrogenase enzyme, an essential protein in the erythrocytic cycle period of *Plasmodium falciparum* [52]. For the compounds used to antileishmanial and antitrypanosomal activities (*Kinetoplastida* parasites), the literature indicates that some antifungal azoles can act similarly in their antiparasitic action mechanisms. Azole derivatives as imidazole and triazole act directly in the lipid biosynthesis, including membrane lipids, by cytochrome P450-dependent C14α sterol demethylase inhibition, leading non-formation of ergosterol, an important membrane steroid [53, 54]. For antitrypanosomal activity, the interference in the redox metabolism and formation of reactive oxygen species (ROS) on parasite be a mechanism of action known for the nitroimidazole drug Benznidazole, showing that this derivative class can have multiple biochemical targets in the growth inhibition of *Trypanosoma* sp. [55]. Finally, for the antischistosomal activity, azole derivatives represents, in the study of Botros *et al.* [56], a promising alternative for having, as therapeutic target, the cyclic nucleotide

phosphodiester of *Schistosoma* sp., allowing to kill the adult forms of the parasite, as well as to reduce the number os eggs.

2.2. Antiplasmodial activity

In recent years, the search by potent anti-*Plasmodium falciparum* agents has been directed at the insertion of azole rings in non-alkaloid natural compounds, the example of quinone derivatives, that is very used in obtaining a variety of bioactivity structures [57]. One naphtoquinone well known for their applications is Lapachol, that occurring in *Bignoniaceae* family [58], and was used by Brandão *et al.* (2018) [59] in the synthesis of molecules containing 1,2,3-triazole and evaluation of its potentialities against chloroquine-resistant strains of *Plasmodium falciparum*. The five-membered heterocyclic ring triazole is selected for the anti-negelcted diseases because of its ability to act as both hydrogen bond acceptor (HBA) and donor (HBD), structure rigidity and stability under oxidative and reductive conditions [60]. Click chemistry methodology was used in the junction of lapachol pharmacofore with other biological important structures, linked by a triazole ring. Of this series, the compound 1 (Figure 1) exhibited better antimalarial activities and selectivity index (SI) against HepG2 (hepatocellular carcinoma) cell line (IC_{50} = 5.2 μM, SI = 197.7) when compared to start lapachol (IC_{50} = 123.5 μM, SI ≥ 33.4; Figure 1). The additional molecular docking studies with *Plasmodium falciparum* dihydroorotate dehydrogenase (PfDHODH) performed by these authors, demonstrated that the 1,2,3-triazole moiety have a central role in the PfDHODH inhibition, for accomplish hydrophobic interactions with the enzyme amino acids, leading to conclusion that the insertion of the 1,2,3-triazol, was essential for increased potentiality.

INSERT FIGURE 1 HERE

Figure 1. Chemical structure of compound 1.

Artemisinin, a lactone sesquiterpene extracted from *Artemisia annua*, has antimalarial properties well established, however, it has been associated with resistance events by its target parasites [61, 62], which led to development of potent derivatives against Artemisinin-resistant strains, as trioxolanes and tetraoxanes, studied by Lobo *et al.* (2018) [63], that drawn and synthesized a library of new endoperoxide-derived compounds where the peroxide pharmacophore is part of a trioxolane (ozonide) or a tetraoxane moiety, flanked by adamantane and a substituted cyclohexyl ring including tetrazole rings in some of these. The library was evaluated for their anti-*P. falciparum* activity against chloroquine-susceptible (3D7) and multidrug-resistant (Dd2) strains. Among the eight more active compounds (sub-micromolar antimalarial activity with IC_{50} = 0.3-71.1 nM, no cross-resistance with artemisinin or quinolone derivatives and negligible cytotoxicity in hepatocellular carcinoma and hamster lung), four possessed a tetrazole ring (compounds 2-5, Figure 2). In addition, these four tetrazole derivatives demonstrated excellent *in vivo* results against *Plasmodium berghei*, with total parasite growth inhibition for the compounds 3 and 4, 94.46% for the compound 2 and 96.46% for the compound 5, after 10 days. Finally, 3 and 4 emerged as potential anti-malarial candidates; they show negligible toxicity towards mammalian cells, ability to kill intra-erythrocytic asexual stages of artemisinin-resistant *P. falciparum* and capacity to totally suppress *P. berghei* parasitaemia in mice. Hence, authors have attributed the potentiality of the derivatives to the presence of the tetrazole ring.

INSERT FIGURE 2 HERE

Figure 2. Compounds 2-5 of [63].

Prodigiosin (Figure 3), a known tripyrrole of bacterial pigment of *Serratia* spp., have its anti-*Plasmodium* spp. activity related [64], and for this reason was isolated, from *S. nematodiphila*, and evaluated by Rahul *et al.* (2015) [65] in their combinations with the gold and silver metals against chloroquine-resistant strains of *P. falciparum*, where the administration together with these nanoparticles reduced the IC_{50} values of isolated natural compound from 1.1±0.1 µg mL^{-1} to 0.36±0.014 e 0.4±0.028 µg mL^{-1} for the combinations with the silver and gold nanoparticles, respectively, showing a synergistic action.

Kancharla *et al.* (2015) [66] evaluated the antimalarial activity of analogs of the natural product undecylprodiginine (Figure 3) [67], getting a series of azole derivatives, of which the compounds 6 and 7 (Figure 3) were more active than undecylprodigine against all *P. falciparum* strain lines tested, with IC_{50} values of 6.1, 4.8 and 5.5 nM for the compound 6 and 6.5, 7.0 and 5.9 nM for the compound 7, against the D6, Dd2 and 7G8 lines, respectively. For evaluate de importance of the three pyrrole rings, this study performed a accurate chemical structure – biological activity relationships of these compounds, where conclude that the ring C is not essential and can be replaced by an alkylamine group retained/enhanced anti-*P. falciparum* potency, as example of KAR425 (Figure 3), a bipyrrole tambjamine derivative, with greater efficacy than prodiginine derivatives, providing 100% of protection to malaria-infected mice until day 28 at doses of 25 and 50 mg/kg /day, being also curative in this model in a single oral dose of 80 mg kg^{-1}.

INSERT FIGURE 3 HERE

Figure 3. Chemical structures of Prodigiosin, Undecylprodigiosin, Compounds 6, 7 and KAR425 of [66].

2.4. Antileishmanial activity

In the recent search for new antileishmanial agents, non-alkaloid natural molecules have been used in semi-synthesis strategies through the insertion of azole rings in their structures. Thus, eugenol (Figure 4), a natural product present in several aromatic plants, with *Eugenia caryophyllata* as their main source, and of high biological potentiality, was the object of study of Teixeira *et al.* (2018) [68], in an attempt to improve its already described leishmanicidal activity [69], by the insertion of triazole moieties via a click reaction strategy. The more active eugenol-triazole derivatives are also presented in Figure 4, with IC_{50} values against *Leishmania amazonensis* promastigotes of 30.2 (9), 59.4 (10), 49.2 (11), 37.9 (12), 32.2 (13) and 7.4 µmol L^{-1} (14), making them more active than eugenol alone (with the already related IC_{50} of 487 µmol L^{-1}). From these data, the more active compound 14 also demonstrated great results against amastigote intracellular forms, with IC_{50} values of 1.6 µmol L^{-1}, more active than the standard-drugs pentamidine and glucantime (table 1), besides showing lower toxicity than these, showing the increase of the anti-leishmanial potentiality obtained with the triazole moiety insertion.

INSERT FIGURE 4 HERE

Figure 4. Chemical structures of triazole-eugenol derivatives.

Flavonoids is another natural class well known for its leishmanicidal effects, with quercetin as one of their main representants, thus Dwivedi *et al.* (2015) [70] evaluated antileishmanial activity of triazole-linked *O*-benzylquercetin glycoconjugates, obtained via click chemistry reaction, against *Leishmania donovani* promastigote and amastigote forms. Between these, the compounds 15, 16 and 17 (Figure 5) were the most active for both promastigote and amastigote forms, with IC_{50} ± standard deviation values of 9.92±2.16 (15), 8.12±2.44 (16) and 7.76±2.44 (17) µg mL^{-1}, for promastigote forms, and 7.65±0.93 (15), 9.08±0.03 (16) and 6.08±0.03 (17) µg mL^{-1}, for amastigote forms. The more active 15 and 16 were evaluated according to their cytotoxicity effects and both demonstrated no toxicity in their IC_{50} active concentrations against macrophage lines, highlighting the important role of triazole moiety in the increased activity against *L. donovani*.

INSERT FIGURE 5 HERE

Figure 5. Chemical structure of triazole-quercetin derivatives.

Known antileishmanial tetrahydrofuran neolignans (Figure 6) were used by Cassamale *et al.* (2016) [71] as a bioisosteric strategic base in the replacement of its tetrahydrofuran portions by a 1,2,3-triazole core. Among the 16 derivatives obtained, 3 were more active against *Leishmania amazonensis* and *Leishmania infantum* promastigote forms. Compounds 18, 19 and 20 (Figure 6) presented with IC_{50} values of 1.1, 3.71 and 7.23 µM, for *L. amazonensis,* and 19.5, 15.4 and 5.2 µM, for *L. infantum*, respectively; being this results most promising that known tetrahydrofuran neolignans Veraguensin, Grandisin and Machilin G (Figure 6), that have antileishmanial activities related in the literature. In all these cases, the results of IC_{50} against *L. amazonensis* were more active than the standard-drug pentamidine (8.9 µM), besides being less cytotoxic than both standard-drug pentamidine and amphotericin B (Table 1). These results, when compared with the potentialities of tetrahydrofuran neolignans, lead to the conclusion that the replacement of a tetrahydrofuran ring by a 1,2,3-triazole moiety is responsible for increased antileishmanial activity of the analyzed products.

INSERT FIGURE 6 HERE

Figure 6. Chemical structure of compounds 17-19 of [71].

This study of Cassamale *et al.* [71] allowed conclude important scaffolds in molecular modification studies due to their antileishmanial activities on promastigote forms. So, this library of triazole derivatives was also evaluated by Costa *et al.* (2016) [72], for antileishmanial activity against *L. (L.) amazonensis* amastigote strains. The ability to inhibit the growth of parasites apparently depends on the index of molecular hydrophobicity (ClogP) of the compounds. A ClogP ranged from 2.8 to 3.4 reflect a lipophilicity/hydrossolubility rate suitable for transport across membranes. In particular, compounds 21 (Figure 7) and 20 (Figure 6) containing a trimethoxy group on ring B, were the most active (IC_{50} values of 5.6 and 4.4 µM, respectively), with low cytotoxicity on mammalian cell (SI = 14.1 and 10.6). These compounds induced nitric oxide production by the host macrophage cells, which could be suggested as the mechanism involved in the intracellular killing of parasite. It is important to highlight that the compound 20 also showed the best activity in promastigote forms of the Cassamale *et al.* (2016) study [71], confirming their potentiality in both parasite forms.

INSERT FIGURE 7 HERE

Figure 7. Compound 30 structure.

Hederagenin (Figure 8), a natural pentacyclic triterpene from *Sapindus saponaria*, presents significant activity against *Leishmania infantum* and *Leishmania tropica* [39]. So, Rodríguez-Hernández *et al.* (2016) [73] synthesized and evaluated the antileishmanial activity against *L. infantum* amastigote forms of esters and amides of hederagenin derivatives, with inclusion of triazole moieties as important pharmacophore. This study highlighted two amide derivatives (compounds 22 and 23 – Figure 8) with promising IC_{50} values of 2.0±0.16 and 6.0±0.06 μM, respectively. These were more active than hederagenin alone (IC_{50} = 61.6±0.25 μM). Even though the two derivatives obtained have shown higher toxicity for macrophage lines, compound 22 showed, however, just a little less toxicity than hederagenin for epithelial spleen-like.

The group also identified (2017) [74] two active ester derivatives bearing two triazole moieties 24 and 25 (Figure 8) with IC_{50} values of 5.6±0.14 and 7.4±0.12 μM, respectively. Both were non-cytotoxic to monkey African Green kidney and human hepatocytes.

INSERT FIGURE 8 HERE

Figure 8. Triazole-hederagenin derivatives.

A series of semi synthetic lupine triterpenoids of betulin and betulinic acid (Figure 9), known in some literature for its anti-*Leishmania* potentialities, have been used by Sousa *et al.* (2014) [75] for evaluation of their antileishmanial activity against *L. infantum*. Of the whole series of derivatives utilized, an imidazole carboxylic ester of betulin derivative (compound 26 – Figure 9) and a *N*-acylimidazole of betulinic acid derivative (compound 27 – Figure 9) were found to be the most active with IC_{50} values of 50.8 μM and 25.8 μM respectively. The superior anti-Leishmania activity of the compound 27 could be associated with the higher capacity as a Michael acceptor of this derivative. Drug interactions between these two active compounds and one currently antileishmanial drug miltefosine (Table 1), were also tested and the combination of 26/miltefosine and 27/miltefosine were more effective at reducing the viability of promastigotes relative to the derivatives alone. As an illustration, the combination of the 27 with miltefosine at 4μM induced decrease of the IC_{50} value from 25.8μM to 6.0μM. Finally, neither of these two derivatives (26 and 27) induced significant apoptosis/necrosis or induced death in macrophage cell lines. In addition they do not present any potential risk of toxicity for the host cells and so they can be considered as promising molecules in the development of new alternative therapies for leishmaniasis, including those involving combined-therapy with miltefosine.

INSERT FIGURE 9 HERE

Figure 9. Betulin and Betulinic Acid and their Derivatives evaluated by [75].

2.5. Antitrypanosomal activity: *Trypanosoma cruzi*

Zimmermann *et al.* (2018) [76], have drawn and synthesized analogs of natural lignans aiming to identify new trypanocidal compounds. In particular, they synthesized a series of bis-heterocyclic derivatives containing the isoxazole moiety and a triazole ring as a spacer group between the aromatic units (Figure 10). A qualitative structure activity relationship study using three dimensional descriptors was carried out and showed a correlation between growth inhibitory potency and the presence of i) a 3,4-di-OMe substitution on ring A and ii) a hydrophobic and highly flexible group located at ring D of the compounds. Compound 3-(3,4-dimethoxyphenyl)-5-((4-(4-pentylphenyl)-1*H*-1,2,3-triazol-1-

yl)methyl)isoxazole (28) was the most active in the series (GI_{50} 12.2 μM), showing, *in vitro,* low toxicity and potency similar to benznidazole (GI_{50} 10.2 μM) and a selectivity index to the parasite in a value greater than 49.1.

INSERT FIGURE 10 HERE

Figure 10. 1,2,3-Triazole-containing lignan derivative.

Cassamale *et al.* (2016) studies [71], above mentioned, also evaluated the anti-*T. cruzi* activity of their serie of triazole derivatives from the tetrahydrofurane neolignans, by bioisosteric modifications. Antitrypanosomal evaluations showed that some derivatives were only moderately active against parasite trypomastigote forms. Compounds 20 (Figure 6), 29 (Figure 11) and 30 (Figure 11) are the most active compounds with IC_{50} values of 56.1, 28.6 and 53.9 μM, respectively. Even though they have shown to be less active than the standard-drug benznidazole (IC_{50} of 7.3 μM) (Table 1), these results can provide important information in the search of great characteristics for the development of new antitrypanosomal drugs.

INSERT FIGURE 11 HERE

Figure 11. Compounds 29 and 30 of [71].

Gould *et al.* (2017) [77] have reported bis-tetrahydropyran 1,4-triazole analogs drawn as mimics of the annonaceous acetogenin natural product chamuvarinin (Figure 12), which maintained trypanocidal activity. This acetogenin compounds are polyketides found in *Annonaceae* spp [78]. In another manuscript, these researchers group evaluated trypanocidal activity of acetogenin derivatives with results that inspired the anti-leishmanial activities of analogs of this class, by retaining important structural and stereochemical features. Thus, this authors contructed triazole derivatives acetogenin-based from bioisosterism in the replacement of a tetrahydrofuran ring by a 1,2,3-triazole moiety, among others structural modifications. Among these, compound 31 (Figure 12) was the most promising in anti-*T. cruzi* essays, exhibiting an EC_{50} value of 3.1±0.2 μM. Moreover, compound 32 (Figure 12) showed the most prominent potential of the tested series against *Leishmania major*, with an EC_{50} of 7.8±0.3 μM, also still proving to be non-toxic for the HeLa and Vero cell lines. So, these modifications maintain the anti-neglected disease potentialities, beside provide a low cytotoxicity profile.

INSERT FIGURE 12 HERE

Figure 12. Chamuvarin and the promising triazole derivatives analyzed.

2.6. Antitrypanosomal activity: *Trypanosoma brucei*

The same work of Gould *et al*. (2017) [77], evaluated anti-*Trypanosoma brucei* activity of the chamuvarinin (Figure 12) analogs, where, of the whole series of triazole compounds obtained, only compound 31 (Figure 12) demonstrated an increase in the anti-*T. brucei* activity, when compared to chamuvirinin, with IC_{50} of 0.037±0.003 μM, not being cytotoxic in HeLa cells, but with an EC_{50} value of 4.5 ±0.3 μM in Vero cells, representing possible essential changes in the combat to *T. brucei* infection.

Similar studies were performed by Tulloch *et al.* (2017) [79], in which exclusively the compound 33 (Figure 13) showed potentiality comparable to chamuvarinin, with an EC_{50} value of 1.8±0.1 μM against blood forms of *T. brucei*, accompanying EC_{50} values of 7.0±1.0 μM for both HeLa and Vero cell lines.

INSERT FIGURE 13 HERE

Figure 13. Chamuvarin and triazole-chamuvarinin derivative.

Scott *et al*. (2016) [80] reported the azole action as a binder to DNA minor grooves, which inhibits the protein-DNA interaction, being of useful application in parasite infections treatment, among others diseases [81], by inducing apoptosis of invasive cells. Distamycin, a polyamide natural product which act as binder to DNA minor groves, was used as base for prepare a series of analogs, where five derivatives (Figure 14) demonstrated anti-*Trypanosoma brucei* activity in the nanomolar range (IC_{50} > 40 nM). These compounds showed high levels of selectivity to the parasite when compared to their activities in human embryonic kidney (HEK 293) cell line. Once the activity of distamycin was 48μM, these results allowed important conclusions for the optimization of molecules even more active in anti-parasitic modulation, with the parasite DNA as a possible target in the development of new minor groove binders.

INSERT FIGURE 14 HERE

Figure 14. Chemical structure of compounds 34, 35, 36, 37 and 38 of [80].

Prodigiosin (Figure 3) was also used by Rahul *et al.* (2015) [65] in gold and silver nanoparticles and evaluated for its anti-*Trypanosoma brucei gambiense* activity. The administration of prodigiosin in these nanoparticles improved its anti-*T. b. gambiense* potentiality in 4x approximately, reducing the IC_{50} value of the tripyrrole compound alone from 0.158±0.019 μg mL^{-1} to 0.044±0.014 μg mL^{-1}, for their combination with silver nanoparticles, and 0.046±0.006 μg mL^{-1}, for their combination with gold nanoparticles; besides maintaining their cytotoxic activity values without significant differences between them against PBMCs, HeLa and MCF7 cells.

2.7. Antischistosomal activity

Among the natural compounds evaluated for antischistosomal activity, some imidazole alkaloids that receive great notability can be obtained from plant species as *Pilocarpus microphyllus* [82-85]. Encouraged by this fact, Rocha *et al*. (2018) [86] performed molecular docking studies of known imidazole alkaloids (compounds Epiisopiloturine (39), Epiisopilosine (40), Isopilosine (41), Pilosine (42) and Macaubine (43), Figure 15) with some structurally known enzymes of *Schistosoma mansoni*, for identification of the imidazole ligand-protein target interaction mechanisms, that can clarify the anti-*S. mansoni* activities already reported in the literature for some of these molecules. Among the molecular targets studied, putative uridine phosphorylase (UP), involved in nucleotide metabolism, and thioredoxin glutathione reductase (TGR) enzymes, which possess an important role of parasite detoxification, demonstrated highest molecular affinities with Epiisopilosine (40). Additionally, TGR also showed good values of molecular affinity with Epiisopiloturine (39), Isopilosine (41), and Pilosine (42). Epiisopiloturine and Epiisopilosine were the most promising binders of purine nucleoside phosphorylase (PNP), acting in the purine and nucleotide bases recovery pathway, while the same Epiisopilosine, together with Isopilosine, were the most promising to interact with methylthioadenosine. Therefore, these could also be considered as potential antischistosomal targets.

INSERT FIGURE 15 HERE

Figure 15. Chemical structures of Epiisopiloturine (39), Epiisopilosine (40), Isopilosine (41), Pilosine (42) and Macaubine (43).

Portes *et al.* (2016) [87] synthesized metal compounds from the natural compound Epiisopiloturine (Figure 15) with Cu and Zn metals, demonstrating that the Cu coordinating compounds, in a concentration of 250 µM, were as active against *S. mansoni* as Epiisopiloturine in 1000 µM. However, those increased the worm mortality percentage from 20%, in Epiisopiloturine, to 60% in 250 µM of the tested metal compound. Besides that, both caused extensive changes in the parasite tegument. The parasite oviposition inhibition was also evaluated, keeping the Cu complexes as the most promising, inhibiting eggs laid for less than 25% at 62.5 µM, and totally at high concentrations, compared to suppression caused by Epiisopiloturine in 100 µg mL^{-1} obtained by Veras *et al.* (2012) [88].

Epiisopiloturine (Figure 15) was also the subject of study of Guimarães *et al.* (2015) [83], whose observed reducing the amount of juvenile worms in mice, after 21 days of infection, treated with doses of 40 and 300 mg kg^{-1}(reduction of 50.2% and 46.3%, respectively) of the compound under analysis. These promising results could also be seen in the anti-*S. mansoni* action of the lowest tested dose of Epiisopiloturine against their adult forms in mice after 45 days of infection, in doses of 40, 100 and 300 mg kg^{-1}, resulting in a reduction of 70%, 39.0%, and 46.7%, respectively. These authors also found the ability of oviposition inhibition and a dose-response inverse relationship in the *in vivo* studies at 40, 100 and 300 mg kg^{-1} concentrations, accompanied by the observation of decreased liver and spleen weight in mice after treatment with 40 mg kg^{-1} of Epiisopiloturine, which is the most advantageous concentration for the treatment, and of damage to the worms tegument after the administration of this natural product. This promising compound presented some acute toxicity only in concentrations equal to or greater than 530 mg kg^{-1}.

Guimarães *et al.* (2018) [89], in another manuscript, also evaluated the *in vivo* antischistosomal potential of Epiisopilosine (Figure 15). *S. mansoni* adult infected mice had a significant reduction of the number of worms in 400 mg kg^{-1} and 100 mg kg^{-1} of Epiisopilosine, with a reduction of 57.78% and 60.61%, respectively, thus, showing no significant difference, even with the decrease in the dose utilized. As seen in studies with Epiisopiloturine, alkaloid Epiisopilosine, at 100 mg kg^{-1}, demonstrated a reduction of the number of eggs collected in the feces of the infected mice (in this case, a reduction of 58%), decreasing of liver and spleen weight, when compared to control group, and changes in the morphology of *S. mansoni* adults tegument, mainly in male worms. *S. mansoni* juvenile forms also had their amounts in the infected mice reduced, in this case, a decrease of 58.06%. Epiisopilosine did not show significant cytotoxicity against the mammalian cells tested, in concentrations up to 512 µg mL^{-1}, nor *in vivo* toxicity.

By analyzing these studies, we can observe the importance of different isomers in the biological response and how it can affect the interaction with different targets, thus justifying their possible pharmacological responses. However, there is an evident shortage of compounds evaluated for this parasitosis associated with this core.

3. PYRIDINES, DIAZINES AND TRIAZINES DERIVATIVES

3.1. Antiparasitic mechanism of action

Based on the studies related to pyridine, diazine and triazine nucleus from the literature, these present a antiparasitc potential and the main mechanism of action for antiplasmodial and antileishmanial activity occurs by inhibiting the enzyme dihydrofolate reductase (DHFR) that affect the biosynthesis of purines and pyrimidines, DNA synthesis, cellular multiplication and nuclear division of the parasite [90-94]. Additionally, in some cases, the overexpression of pteridine reductase 1 (PTR1) can overcome the DHFR inhibition, thus becoming also a target of interest and its inhibition can corroborate for antileishmanial activity [95]. Another mechanism exhibited is the inhibition of hypoxantine with consequent growth interruption of the parasite as antiplasmodial activity [96]. Moreover, nitroreductases (NTRs) enzymes trigger the generation of toxic free radicals by bioactivating the nucleus of pyridine and its derivatives that is suggested as antileishmanial [30]. Regarding to antitrypanosomal activity the inhibition of CYP 51 is reported as lead mechanism of action, which is important to lanosterol's production by *Trypanosoma cruzi* [29, 97]. However, it is not described on the literature antischistosomal mechanisms related to the nucleus analyzed, thus might become a relevant subject to invest new researches.

3.2. Antiplasmodial activity

Heterocyclics are extensively present on the chemical structures of natural products, making them excellent starting points to the development of new drugs due to the diverse biological properties of these compounds. Secondary metabolites, especially alkaloids, terpenoids, flavonoids, and saponins with antimalarial activity already described can be highlighted [96, 97].

Azaguanine (44) (Figure 16), also known as pathocidin, was first isolated from fermentation broth of *Streptomyces albus* var. *pathocidicus* in 1961, bearing pyrimidine nucleus. This natural compound displays antimicrobial and cytotoxic properties against a wide range of bacteria, viruses, fungi and human cancer cell lines. Antimalarial activity occurs by the inhibition of hypoxanthine capitation (IC_{50} = 6.6 μM) and consequently, inhibition of parasite growth (IC_{50} = 18 μM), presenting itself a potential compound for the development of new antimalarial drugs [96].

INSERT FIGURE 16 HERE

Figure 16. Chemical structure of 8-Azaguanine (44)

Cassiarin A (45) (Figure 17) is a natural alkaloid isolated from *Cassia simea* [85], which bears pyridine ring in its skeleton and showed important antimalarial activity (IC_{50} of 0.005 μg mL^{-1}). Other members of this family, such as cassiarin C (46) (Figure 18), also have demonstrated vasorelaxant, anticancer and antimalarial activities [98].

INSERT FIGURE 17 HERE

Figure 17. Chemical structure of cassiarin A (45) e cassiarin C (46)

Rcognizing the pyridine nucleus and its derivatives obtained from natural products as potential antimalarials, studies were performed to synthesize new pyridine derivatives with promising antimalarial activity. In this context, Thipathi *et al*. (2019) synthesized, by hybridization, eighteen 4'-fluoro-amodiaquine-pyrimidine (FAQ-pyrimidines) (47) (Figure 18). Strains of *P. falciparum* NF54 were

sensitive to the reference drug, chloroquine (CQ), and strains of *P. falciparum* Dd2 were resistant to CQ. All FAQ-pyrimidines synthesized exhibited greater antiplasmodial potency against the resistant strain (Dd2) than the reference drug, except for intermediate 6b (48). Compound 8b (49) was the most active with an IC_{50} of 7.5 nM, demonstrating the importance of cyclic amines of FAQ-pyridines against these strains [16].

INSERT FIGURE 18 HERE

Figure 18. Chemical structure of FAQ-pyrimidine hybrid (47), (48) and (49)

Maurya *et al.* (2017) synthesized twenty-four 4-aminoquinoline-pyrimidine hybrids (Figure 19) and evaluated their antimalarial activity *in vitro* against chloroquine-sensitive and resistant strains of *Plasmodium falciparum* (D6 clone and W2 clone, respectively). Results demonstrated that most of the hybrids displayed great antimalarial activity against both strains of *P. falciparum*. The best activity, although, was performed in W2 strains, in which all hybrids, except 51 and 53 (IC_{50}= 0.454 and 0.506 µM, respectively), presented higher activity than the standard drug chloroquine (IC_{50}= 0.31µM), with IC_{50} values ranging from 0.039 to 0.257 µM [17].

INSERT FIGURE 19 HERE

Figure 19. Chemical structure of compounds 50, 51, 52, 53, 54, 55.

Le Manach *et al.* (2014) synthesized new imidazopyridazines identified from high throughput screening of SoftFocus kinase library, with antiplasmodial activity against K1 (multiple drug-resistant *P. falciparum* strain) and NF54 (sensitive *P. falciparum* strain). Structure-activity relationship (SAR) studies identified highly potent compounds against both cell lines, highlighting compound 56 (Figure 20) as lead compound with IC_{50} of 6.3 nM and 7.3 nM, against K1 and NF54, respectively, being comparable to the reference drug, artesunate (table 01). This compound also exhibited 98% *in vivo* activity against *P. berghei* mouse model, analyzed in mice, at 50 mg kg^{-1} dose by oral administration [99, 100].

INSERT FIGURE 20 HERE

Figure 20. Chemical structure of compound 56

Continuing his work, Le Manach *et al.* (2016) synthesized a new series of 2-aminopyrazine derivatives compounds, obtained through the introduction of water-solubilizing groups on the 5-phenyl ring of a 2-aminopyrazine series, and evaluated their biological activity against strains of K1 (multidrug-resistant *P. falciparum*) and NF54 (multidrug-sensitive *P. falciparum*). The authors observed that all compounds were equipotent against both strains, indicating no existing cross-resistance with the reference drug. Moreover, compound 57 (Figure 21) proved to be the most promising against *P. falciparum*, with IC_{50}= 5.2 nM and 5.4 nM, on K1 and NF54 strains, respectively [101].

INSERT FIGURE 21 HERE

Figure 21. Chemical structure of compound 57

Xue *et al.* (2019) synthesized 3,3'-Disubstituted 5,5'-Bi(1,2,4-triazine) derivatives and initially evaluated antiplasmodial activity of these compounds against erythrocytic stage of *Plasmodium Falciparum* 3D7 line, highlighting 58 (figure 22) as the most potent dimer with IC_{50} = 0.008 µM, and reference drug chloroquine with IC_{50} = 0.004 µM. This compound was evaluated also against strains of chloroquine-resistant (W2, IC_{50} CQ = 0.150 ± 0,03 µM) and artemisinin-resistant (MRA1240, IC_{50} CQ =

0.097 ± 0,021 µM) *P. falciparum,* obtaining promising values of IC_{50} = 0.0047 ± 0.0011 µM and IC_{50} = 0.0086 ± 0.0010. Researchers analyzed antimalarial potency of compound 58 on *P. falciparum* and *P. vivax* isolated from the blood of outpatients with uncomplicated malaria and observed that compound 58 had excellent potency with IC_{50} values of 0,022-0,034 µM and 0,0093-0,031 µM, respectively [90].

INSERT FIGURE 22 HERE

Figure 23. Chemical structure of compound 58

Pathak *et al.* (2017) synthesized twenty-six 2,4,6 s-triazine derivatives compounds. Analysis *in silico* based on ADME properties and docking studies selected compounds 59, 60 and 61 (Figure 23) to evaluate antimalarial activity against 3D7 strain line of *P. falciparum* (cycloguanil sensitive strain) and the possible inhibition of dihydrofolate reductase (DHFR). All three compounds (59, 60 and 61) presented potency 30 times better than the reference drug, cycloguanil, based on minimum inhibitory concentrations (MIC), in which, compounds 59, 60, 61, and cycloguanil presented values of 4.47 nM, 7.94 nM, 2.75 nM, and 255 nM, respectively. Compound 61 was the most active, while 60 the less active. The authors stated that the presence of electron-donating groups, the number of hydrogen bond formation, lipophilicity of ligands and charge of nitrogen in the triazine ring enhances the DHFR inhibition significantly [91].

INSERT FIGURE 23 HERE

Figure 24. Chemical structure of compounds 59, 60 and 61

3.3. Antileishmanial activity

The enzyme dihydrofolate reductase (DHFR) is an important target for antileishmanial compounds, acts by catalyzing the reduction of dihydrofolate to tetrahydrofolate. Tetrahydrofolate, when methylated is a vital cofactor to convert deoxyuridine monophosphate into thymidine monophosphate, and DHFR inhibition prevents biosynthesis of thymidine, leading to cell death, because these microorganisms do not have a mechanism of transport of this cofactor from the host. Most known DHFR inhibitors contain a heterocyclic aromatic ring, such as pyridine, that was substituted with alkyloxy groups of different chain lengths. These were synthesized and evaluated by Linãres *et al.* (2012), and three compounds (62, 63 and 64, Figure 24) presented potent results against *Leishmania mexicana* promastigotes with IC_{50} of 16, 12 and 20 µg mL^{-1}, respectively, better than the reference inhibitor geneticin (IC_{50} = 50 µg mL^{-1}). The acetylated compound 63, presenting 14 carbon atoms in the side chain, was the most potent, indicating that the presence of the acetyl group increased the inhibitory activity exhibited by compound 62 [92].

INSERT FIGURE 24 HERE

Figure 24. Chemical structure of compouds 62, 63 and 64

Annomontine (65) (Figure 25) is a pyrimidine-betacarboline alkaloid isolated from *Annona foetida* that presents an IC_{50} value of 34.8 µM against promastigote forms of *L. braziliensis*. Based on that activity, as stated by Acevedo *et al.* (2019), nine pyrimidine-pentamidine hybrids were synthesized and presented IC_{50} values, of *in vitro* tests against *L. donovani* amastigotes, ranging from 0.30 to 1.72 µM, demonstrating the importance of pyrimidine nucleus [102].

INSERT FIGURE 25 HERE

Figure 25. Chemical structure of compound 65

As stated by Suryawanshi *et al.* (2013), pyrimidine derivatives are known DHFR inhibitors, so a novel series of 4-S and 4-N-substituted pyrimidine derivatives were synthesized, 66 and 67 as lead compounds (Figure 26). According to their *in vitro* activity against *Leishmania donovani* amastigotes, compound 66 showed IC_{50}= 2.0 ± 0.1 µM and selectivity index (SI)= 188, while compound 67 obtained IC_{50}= 0.5 ± 0.1 µM and SI= 116, demonstrating superior results when compared to the reference drugs, pentamidine and sodium stibogluconate (table 01). Moreover, the *in vivo* activity of compounds 66 and 67 was similar to standard drugs [93].

INSERT FIGURE 26 HERE

Figure 26. Chemical structure of compounds 66 and 67

Small peptides (3-9 amino acid residues) find applications in diverse therapeutic areas, amino acid and dipeptide esters that contain at least one hydrophobic amino acid show leishmanicidal activities, moreover, triazines act as dihydrofolate reductase (DHFR) inhibitors. Therefore, Khattab *et al.* (2018) synthesized 1,3,5-triazino-peptide derivatives that against *Leishmania aethiopica* promastigotes, which had greater or comparable activity to miltefosine (IC_{50} = 7.8±0.34 µM). Among them, compound 68 (Figure 27), demonstrated the best activity (IC_{50} = 1.4±0.04 µM), also overcame miltefosine (IC_{50} = 0.74±0.04 µM) against *L. aethiopica* amastigote with IC_{50} = 0.22±0.02 µM and exhibited activity very close to amphotericin B (IC_{50} = 0.15±0.02 µM). Besides, it had the highest selective index (SI= 2457.88), and *in vivo* acute toxicity studies indicated their safety when administered orally and parenterally up to 250 and 100 mg kg^{-1} of body weight [94].

INSERT FIGURE 27 HERE

Figure 27. Chemical structure of compound 68

However, *Leishmania* is known to proficiently overcome DHFR inhibition by overexpressing pteridine reductase 1 (PTR1) and it is associated with the pterin and folate metabolism that is essential for the growth. Also, PTR1 is an excellent drug target due to the unusual salvage of pterin from the host while the host synthesizes pterin derivatives de novo from GTP and lack PTR1 activity. Using PTR1 as a target, Chauhan *et al.* (2013) synthesized triazine dimers and most of the compounds exhibited better potency than the reference drug pentamidine (IC_{50} =13.68 ± 1.57 µM) against *Leishmania donovani* intracellular amastigotes, also presenting low cytotoxicity. Compound 69 (Figure 28) showed very consistent and promising leishmanicidal activity with IC_{50} = 1.99 ± 0.31 µM and also displayed *in vivo* potential on *L. donovani* with good percentage inhibition (74.41 ± 10.26 %). As well, docking studies showed that compound 69 stood out due to its favorable hydrophobic and hydrogen bond interactions with binding domain of PTR1, presenting binding energy of -8.54 $kcal.mol^{-1}$, in contrast to -6.95 $kcal.mol^{-1}$ of reference drug pentamidine (table 01) [95].

INSERT FIGURE 28 HERE

Figure 28. Chemical structure of compound 69

The sequencing of the parasite genome provided new targets that can be potential to antileishmanial drugs, among them, *Leishmania* kinases. According to Castera-ducros *et al.* (2013), the inhibition of the parasite casein-kinase 1 by imidazo[1,2-a]pyridines demonstrated antileishmanial activity. Studies of several derivative's structure-activity relationships led to the characterization of 6-halo-3-nitro-2-phenylsulfonyl-methylimidazo[1,2-a]pyridine as pharmacophore, through substitutions emerged the lead compound 70 (Figure 29). When compared to the reference drugs, compound 70 presented a very good activity on *L. donovani and L. infantum* promastigotes with IC_{50} = 1.8 ± 0.8 µM and 3.3 ± 0.7 µM, respectively, being more active than standard compounds, pentamidine (IC_{50} = 6.0 ± 0.8 µM and 8.2 ± 0.1 µM) and miltefosine (IC_{50} = 3.1 ± 0.06 µM and 11.6 ± 0.4 µM). Promising results were reported also on *L. donovani* amastigotes with IC_{50} = 5.5 ± 0.2 µM, compared to pentamidine (IC_{50} > 20 µM) and miltefosine (IC_{50} = 6.8 ± 0.3 µM). Additionally, the selectivity index for *L. donovani* was higher than 17.2, which is more promising than pentamidine (SI = 0.4) and miltefosine (SI = 16.2) [103].

INSERT FIGURE 29 HERE

Figure 29. Chemical structure of compound 70

According to Marhadour *et al.* (2012), 2,3-diarylimidazo[1,2-a]pyridine based compounds were synthesized and evaluated on the promastigote stage of *Leishmania major*. Eight compounds displayed IC_{50} values below 10 µM, among the most active compounds on *L. major* promastigotes, the selectivity index of compounds 71, 72 and 73 (Figure 30) overcame the reference drug, pentamidine (SI = 3.13), with SI = 5.43, 5.51 and 3.85, respectively. The highest SI of the second series were exhibited by compounds 74 and 75 (Figure 30) with SI = 8.65 and 18.46, respectively. Moreover, compound 76 (Figure 30) remained active at concentration 1 µM, with low cytotoxicity on HeLa cells (IC_{50} = 67.0 ± 2.0µM). Furthermore, derivatives 71, 74 and 75 also presented activity comparable to pentamidine (99% inhibition with 10 µM concentration) against *L. major* amastigotes [25].

INSERT FIGURE 30 HERE

Figure 30. Chemical structure of compounds 71, 72, 73, 74, 75 and 76.

Secondary metabolites from marine microorganisms are important sources for the discovery of novel bioactive natural products. Indolepyrazines A (77) and B (78) (Figure 31) were isolated from a coastal mud sample of gram-negative bacterial strain *Acinetobacter sp.* ZZ1725. Both compounds showed inhibitory activities against the growth of MRSA, *Escherichia coli*, and *Candida albicans*, demonstrating the importance of pyrazine nucleus that was also included in the following synthesis [104].

INSERT FIGURE 31 HERE

Figure 31. Chemical structure compound 77 and 78

As a continuation to enhance previous results, Marchand *et al.* (2015) synthesized 2-phenyl-3-(pyridin-4-yl)imidazo[1,2-a]pyrazine (compound 79) that was starting point to two others sub-series with compounds 80 and 81. Both fluorine analogs have a polar substituent on C-8 position and are lead compounds (Figure 32). Tests *in vitro* on *L. major* promastigotes highlighted the stronger activity of compound 78, with IC_{50} = 2.8 ± 0.4 µM in comparison to pentamidine (IC_{50} = 4.6 ± 1.1 µM), 77 (IC_{50} = 20.1 ± 12.2 µM) and 79 (IC_{50} = 6.4 ± 0.2 µM). Also, cytotoxicity and selectivity index were comparable to the reference drug. The molecule 78 presented even better activity on *L. major* amastigotes, with IC_{50} =

0.2 ± 0.1 µM and SI = 466, followed by 79 (IC_{50}= 0.8 µM, SI= 52.5). Through these results, as stated by the authors, the introduction of fluorine atom and a polar substituent increased the activity [26].

INSERT FIGURE 32 HERE

Figure 31. Chemical structure of compounds 79, 80 and 81

The pyrazolopyridine derivatives revealed potential new drugs against *Leishmania* and 1*H*-Pyrazolo[3,4-b]pyridine is an example of a fused system, which is known to possess remarkable and significant biological and medicinal importance. Moreover, the introduction of a phosphoramidate group changes the physical and chemical properties, because it accentuates the polarization and intermolecular bonding characteristics, since the P=O group presents a significant role as a strong hydrogen bond acceptor, which is essential for the non-covalent bonding of proteins or other specific ligands to their substrates [105].

Based on that, Medeiros *et al.* (2018) synthesized a series of 1H-Pyrazolo[3,4-b]pyridine-phosphoramidates, in order to evaluate antileishmanial activity, tests on *Leishmania amazonensis* promastigotes highlighted cyano substituted molecules 82 (IC_{50} = 9.81 ± 3.10 µM) and 83 (IC_{50} = 6.44 ± 1.49 µM) as lead compounds (Figure 33) that obtained better results than pentamidine (IC_{50} = 13.00 µM), demonstrating the importance of phenyl substituent at position R1 of the pyrazole ring on compound 83. Furthermore, cytotoxicity responses on macrophages and selectivity index values were similar to the reference drug pentamidine [105].

INSERT FIGURE 33 HERE

Figure 32. Chemical structure of compounds 82 and 83

3.4. Antitrypanosomal activity: *Trypanosoma cruzi*

Pyridine derivatives, such as 1,2,4-triazine, obtained from synthetic and natural sources, possess different biological activities, being part of chemical structure of some natural antibiotics, such as fervenulin (planomycin), reumycin and toxoflavin (panthothricin), demonstrating the importance of this nucleus as starting point for discovery of new drugs with diverse biological activities [106]. Therefore, antitrypanosomal tests were performed with the alkaloid pyrimidine-β-carboline (annomontine – compound 65) (Figure 25), isolated from dichloromethane extract of *Annona foetida* (Annonaceae), that revealed strong activity against *T. cruzi* with IC_{50} of 4.2 ± 1,9 µg.mL^{-1} [107].

In this context, Lapier *et al.* (2019) synthesized twenty-four triazolopyridine derivatives and evaluated their trypanocidal activity, in which compound 84 (Figure 34) exhibited better trypanocidal activity than the reference drug nifurtimox (table 01), showing IC_{50} values of 6.8 ± 1.8 µM and 17.4± 1.3 µM, respectively, against *Trypanosoma cruzi* epimastigotes (DM28c strain) [27].

INSERT FIGURE 34 HERE

Figure 34. Chemical structure of compound 84

Braga *et al*. (2017) performed a molecular simplification of 8-chloro-*N*-(3-morpholinopropyl)-5H-pyrimido[5,4-b]indol-4-amine. Hence, five series were obtained: indole, pyrimidine, quinoline, aniline and pyrrole derivatives. Remarkably, compound 85 (Figure 35), a pyrimidine derivative, was

highly active against *T. cruzi*, presenting IC_{50} = 3.1±0 μM and selectivity index (SI) of 128, comparable to the reference drug benznidazole, IC_{50} = 3.8 ± 0.8 μM and SI = 626, demonstrating to be a promising trypanocidal agent [108].

INSERT FIGURE 35 HERE

Figure 35. Chemical structure of compound 85

3.5. Antitrypanosomal activity: *Trypanosoma brucei*

On the search for new efficient agents for the treatment of this disease, Fersing *et al.* (2018) synthesized twenty-one 6,8-dibromo-3-nitroimidazo[1,2-a]pyridine derivatives. Compounds 86 and 87 (Figure 36) demonstrated potent antiparasitic activity against *T. brucei,* presenting IC_{50} of 0.16 μM and 0.04 μM, respectively, in comparison to the reference drug suramin (IC_{50} = 0.03 μM) and eflornithine (IC_{50} = 13.3 μM), indicating a remarkable trypanocidal potential of this compounds [38].

INSERT FIGURE 36 HERE

Figure 36. Chemical structure of compounds 86 and 87

3.6. Antischistosomal activity

Natural products (NPs) are structurally diverse and a valuable source for new molecular scaffolds on the development of drugs. About 65% of all drugs are approved and classified as NPs or are inspired by NP nucleus, which was the case of ivermectin that is used for tropical neglected diseases with antihelmintic action, being a semi-synthetic drug obtained from monocyclic lactones produced by *Streptomyces avermitilis* [109]. In this context, given the lack of therapeutic arsenal for this pathology (schistosomiasis), the research of new drugs with antischistosomal activity is relevant, starting from the pyridine nucleus and its derivatives, due to diverse biological activity already demonstrated by this nucleus, including antiparasitic and antimicrobial. However, until the end of this work, the literature did not report any bioprospective derivatives of pyridine with this activity investigated.

4. INDOLE DERIVATIVES

4.1. Antiparasitic mechanism of action

A large number of compounds with the indole nucleus are described in the literature with significant activities against parasitic diseases, such as malaria, leishmaniosis, Chagas disease, sleeping sickness and schistosomiasis [20]. However, in most studies, the mechanisms of action of the indole compounds that have relevant activities are not reported. Even the drugs that are currently used as a standard (despite not containing the indole nucleus) do not have well-defined mechanisms [110]. However, the derivatives containing the indole nucleus that will be cited here may be related to the mechanisms of action involving DNA interactions and fragmentations [110, 111], topoisomerase II inhibition [112], inhibition of cysteine protease, and enzymatic inhibition [113-115].

4.2. Antiplasmodial activity

One of the first reports about antiplasmodial natural compounds is the alkaloid cryptolepine (88) (Figure 37), a hybrid of indole and quinoline that stood out as the main part of bloody *Cryptolepis* roots, a plant from Africa occidental used for malaria treatment [110]. *In vitro* studies of this isolated compound demonstrated activity against chloroquine-resistant *P. falciparum* strains with IC_{50} = 0.033 μg mL^{-1} [20]. *In vivo* study of cryptolepine demonstrated notable results to parasitemia reduction when administrated orally in a dose of 50 mg kg^{-1} during 4 days [116]. Moreover, cryptolepine and other 12 alkaloids containing a fusion between indole and quinoline rings were reported for antimalarial activity and other diseases [117]. Manzamine A (89) (Figure 37), another promising alkaloid containing an indole ring, is naturally found in sea sponges and was first isolated from *Okinawa Haliclona* sp. This compound has presented antimalarial activity with IC_{50} values of 13.5 ng mL^{-1} and 25 ng mL^{-1} against W2 and D6 *P. falciparum* strains, respectively [100].

INSERT FIGURE 37 HERE

Figure 37. Cryptolepine (88) and manzamine A (89) structures

New obtainment methods with semisynthetic and synthetic routes are described in the literature on the search for more efficient antimalarial compounds, with the indole nucleus from natural product as starting point. Pursuing this approach, Yadav *et al.* (2015) synthesized a series of *N*-aryl and heteroaryl sulfonamide derivatives of meridianins, which is an indolic alkaloid of marine origin, and evaluated their antimalarial activity against two *Plasmodium falciparum* strains (D6 and W2). Compound 90 (Figure 38) showed significant antiplasmodial activity against both strains with IC_{50} of 2.56 and 3.41 μM. These meridianin sulfonamide derivatives were also found to have no cytotoxicity against mammalian cell lines up to 25 μg mL^{-1}. The results sustain meridianin sulfonamide derivatives as potential candidates in the discovery of new antimalarial agents [118].

INSERT FIGURE 38 HERE

Figure 38. Compound 90 structure

Another natural product that has been frequently reported with antiplasmodial activity is tryptanthrin, compound 91 (Figure 39), despite its low solubility in water. In an attempt to solve this issue, Onambelle *et al.* (2015) synthesized tryptanthrin analogs and evaluated their antiplasmodial activity against *Plasmodium falciparum* in the asexual and sexual phase. The compound 92 (Figure 39) presented the best antiplasmodial activity (IC_{50} 30 nM; SI: 155.9) in both strains. In *in vivo* tests, compound was able to interfere with gametogenesis, decreasing microgamet exflagulation by 20% at IC_{90}. The results suggest tryptanthrin derivatives are able to eliminate the intraerythrocytic asexual stages and intervene in the parasite development in the sexual stage [119].

INSERT FIGURE 39 HERE

Figure 39. Compound 91 and 92 structures

A new class of glycine-extracted compounds with potential antimalarial activity was suggested by Svogie *et al.* (2016). A series of indolyl-3-ethanone-α-thioethers derivatives were synthesized and evaluated *in vitro*. Results emphasized compounds 93 and 94 (Figure 40) significant activities, both exhibited potent and selective antiplasmodial activity against chloroquine-sensitive strains of *Plasmodium*

falciparum (3D7), presenting IC_{50} of 0.24 and 0.09 μM, and SI of 2083 and 5556 μM, respectively. The SAR study further demonstrated that the *para*-substituted thiophenyl group is an indispensable pharmacophore for antiplasmodial activity, even though its mechanism of action is yet unknown [115].

INSERT FIGURE 40 HERE

Figure 40. Compound 93 and 94 structures

Another naturally occurring product containing the indole nucleus, found sponges and corals, is aplysinopsin, first isolated by Fusetani [120]. Based on its structure (95), Yadav *et al.* (2016) initially synthesized and evaluated several new indole derivatives against *Plasmodium falciparum*. SAR studies demonstrated that the activity increased when there were alkyl and carboxylate substitutions at the positions N1 and C2, and aryl substitution at the indole C3. Compound 96 (Figure 41) showed significant potency with MIC values below 0.70 μg mL^{-1}, which were better than standard drugs quinine (MIC 0.27 μg mL^{-1}) and chloroquine (MIC 0.02 μg mL^{-1}) [121].

INSERT FIGURE 41 HERE

Figure 41. Aplysinopsin structure (95) and indolic derivatives N1, C2 and C3 substituted (96)

A new class of C2-arylalkanimino tryptamine 97 (Figure 42) derivatives has been developed by Luthra *et al.* (2019), adopting as inspiration the structure of melatonin, a hormone naturally secreted by mammalian glands. Following a preliminary antimalarial *in silico*, a series of derivatives showed activity to inhibit the parasite intra-erythrocytic cycle progression, mainly interrupting the melatonin hormone-induced synchronization that induces parasite growth. Among the derivatives, compound 98 (Figure 42) stood out with the highest potential with IC_{50} of 0.74μM. The evaluation on MT1 melatonin receptor revealed that compound 98 binds to the enzyme, impacting on the improvement and elevation of the concentration of the molecules [122].

INSERT FIGURE 42 HERE

Figure 42. Tryptamine and compound 98 structures

Adamantane was isolated from petroleum by two Czech Chemists in 1932 [123] and has already been reported to treat several diseases [124, 125]. Based on its possible chemotherapeutic action, Devender *et al.* (2017) synthesized a series of fifty-three new adamantyl/cycloheptyl-indoleamide derivatives and evaluated their antiplasmodial activity *in vitro* against *P. falciparum* chloroquine-sensitive and resistant strains. The results highlighted compounds 99, 100, 101 and 102 (Figure 43) as promising, given their relevant antiplasmodial activity, with IC_{50} values of 1.87, 1.93, 2.0, 2.17 μM, respectively, against the chloroquine-sensitive strain (Pf3D7). Similar results were found against the chloroquine-resistant strain (Pfk1), with IC_{50} values of 1.69, 2.12, 1.60 and 2.19 μM, respectively. The SAR study also pointed out that the incorporation of large groups into sulfonamide derivatives favored antiplasmodial activity [126].

INSERT FIGURE 43 HERE

Figure 43. Indoleamide derivatives structures

Yeung *et al.* (2017) synthesized a series of cipargamine spiroindolones, based on GNF 493, a naturally occurring compound first identified as a potent *P. falciparum* growth inhibitor, and evaluated their antimalarial activity. Compound 103 (Figure 44) had a favorable oral pharmacokinetic (PK) profile

when evaluated in mice, showing Cmax = 3.6 mM and bioavailability of 59%. The same compound also exhibited notable activity against *Plasmodium falciparum* chloroquine-resistant strains NF54 and K1 (IC_{50} of 27 and 21nM, respectively) [127].

INSERT THE FIGURE 44 HERE

Figure 44. Spiroindolone derivative 103

The cryptolepine extracted from the native African *Cryptolepis sanguinolenta* plant and was first isolated in 1951 by Gellert *et al*. [128]. Through that, halogenated isocryptolepine derivatives were based on alkaloid isocryptolepine 104 (Figure 45) were synthesized and evaluated by Aroonkit *et al.* (2015) for *in vitro* antiplasmodial activity against *Plasmodium falciparum* strains K1, 3D7, SKF58 and SRIV35. Compound 105 showed the best results against the four strains with IC_{50} values 61.8, 37.9, 92.4 and 83.0 nM, respectively. Moreover, *in vitro* antiproliferative properties of isocryptolepine derivatives were evaluated against HepG2, HuCCA-1, MOLT-3, and A549 cancer cell lines, portraying derivatives 106 and 107 as potent and selective compounds against cancer cell lines [129].

INSERT THE FIGURE 45 HERE

Figure 45. Isocryptolepine derivatives

Chakka *et al.* (2015) evaluated a group of derivatives with the pyrrolidine fraction at T2 position showed potent inhibition of 2-falcipain. Compound 108 (Figure 46) displayed notable anti-parasitic activity (IC_{50} = 0.9 ± 0.1 μM), matching with its inhibitory activity against falcipain-2, with a Ki of 1.1 ± 0.1 μM. Furthermore, the same compound exhibited a potency against Dd2 and Mcamp isolates about 7 to 12 times greater than the laboratory strain (3D7), while compound 109 inhibited the growth of the drug resistant parasite Dd2 with more efficacy (EC_{50} = 1.7 μM) [130].

INSERT FIGURE 46 HERE

Figure 46. Compound 108 and 109 structures

Ugwu *et al.* (2017) performed *in silico* and *in vitro* studies to subsequently synthesize a series of twenty-four new carboxamide derivatives. Selected compounds with antimalarial potential were evaluated *in silico*, through molecular docking, against plasmepsin II enzyme and displayed good interaction with the target, indicating the possible mechanism of action. Among the derivatives, compound 110 (Figure 47), demonstrated better results with MIC value of 0.03 μM compared to chloroquine (0,06 μM). In addition, showed antioxidant action with IC_{50} of 0.045 mM comparable with 0.34 mM for ascorbic acid. The compound series synthesized presents a promising performance for reducing the oxidative stress caused by the malaria parasite [131].

INSERT FIGURE 47 HERE

Figure 47. Carboxamide derivative (110)

4.3. Antileishmanial activity

Antileishmanial molecules originated from isolated natural products are also reported in the literature. For example, staurosporine (111) (Figure 48), isolated from sponges of the Mediterranean Sea, showed activity against *Leishmania major* promastigotes with EC_{50} of 5.30 μM. Another alkaloid

resulting from bioprospection is the indole tryptophol, isolated from sponges *Spongia sp.* of Aegean Sea, displayed activity *in vitro* against *L. donovani* with EC_{50} of 5.30 μg mL^{-1} [132].

INSERT FIGURE 48 HERE

Figure 48. Staurosporine structure (111)

In this perspective, Ashok *et al*. (2016a) synthesized a series of 1-(thiophen-2-yl)-9*H*-pyrido[3,4-b]indole derivatives and evaluated their biological activity against promastigote and amastigote forms of *L. donovani* and also *L. amazonensis.* Two of the above compounds, 112 and 113 (Figure 49), expressed excelled *in vitro* activity against amastigotes forms of *L. donovani*, with IC_{50} values of 8.80 and 7.50 μM, respectively, therefore showing better results than the standard drugs, miltefosine and pentamidine (IC_{50} 15.70 and 32.70 μM respectively), in addition demonstrated an excellent selectivity [133].

INSERT FIGURE 49 HERE

Figure 49. Compound 112 and 113 structures

Ashok *et al.* (2016b) in another study, synthesized and evaluated a series of sixteen new tetrahydro-β-carboline derivatives against promastigote and amastigote forms of *Leishmania infantum*. Among the derivatives, compound 114 (Figure 50) displayed better effects, with high selectivity and potency for the amastigote form with IC_{50} value of 0.67 ± 0.05 μM and SI selectivity index higher than 298.5, values comparable to standard drug amphotericin B [134].

INSERT FIGURE 50 HERE

Figure 50. Tetrahydro-β-carboline derivative structure

Ashok *et al.* (2018), designed using the molecular hybridization strategy, synthesized (1-phenyl-9H-pyrido [3,4-b]indol-3-yl) (4-phenylpiperazin-1-yl)methanone derivatives and evaluated for cytotoxicity and inhibition activity against *L. infantum* and *L. donovani*. Compound 115 (Figure 51), in particular, is highlighted due to its EC_{50} values of 2.8 μM for axenic amastigote, and 4.0 μM for intracellular. These values are comparable to the standard drugs miltefosine (EC_{50} 1.6 and 23.7 μM) and pentamidine (EC_{50} 2.8 and 6.4 μM) (Table 1) [135].

INSERT FIGURE 51 HERE

Figure 51. Chemical structure of 115

In the sequence of the study described earlier, Ashok *et al.* (2019) synthesized and evaluated the anti-*Leishmania* activity of piperazinyl-β-carboline-3-carboxamide derivatives against *L. infantum* and *L. donovani*. Selected derivatives have shown significant inhibition against both promastigote and amastigote forms, exhibiting EC_{50} values of less than 3.73 μM for promastigote forms and less than 2.6 μM against amastigote forms of *L. infantum*, which outperforms standard drugs miltefosine and pentamidine. Compound 116 (Figure 52) showed the best inhibition of *L. donovani* promastigotes, axenic amastigotes and intracellular amastigotes with EC_{50} values of 0.91, 0.90, 1.30 μM, respectively [136].

INSERT FIGURE 52 HERE

Figure 52. Compound 116 structure

Sangshetti *et al.* (2016) synthesized twelve new 3-(3-(1*H*-indol-3-yl)-3-phenylpropanoyl)-4-hydroxy-2*H*-chromen-2-one derivatives, from the fusion of two natural groups: indolic and coumarin

nucleus, natural product found in plants, bacteria and fungi [137]. All the synthesized compounds showed better activity than standard sodium stibogluconate (IC_{50} = 490 μg mL^{-1}) (Table 1). Among the derivatives, compound 117 (Figure 53) showed the most potent antileishmanial activity, with IC_{50} of 95.5 μg mL^{-1}, in addition presented excellent antioxidant activity (IC_{50} = 12.40 μg mL^{-1}) compared to hydroxytoluene (IC_{50}= 16.5 μg mL^{-1}) and ascorbic acid (IC_{50} = 12.8 μg mL^{-1}) as the standard. *In silico* studies of compound 117 exhibited a potential to inhibit pteridine reductase 1 enzyme, in addition to good pharmacokinetic parameters [114].

INSERT FIGURE 53 HERE

Figure 53. Compound 117 structure

Félix *et al.* (2016) also performed the fusion of groups from natural products, indole and aminothiophene nucleus, the last one found in oil and its derivatives in plants of the Family Asteraceae [138], thus synthesized thirty-two compounds containing cycloalka[b]thiophene and indole moieties that had their cytotoxic and antileishmanial activity evaluated against *L. amazonensis* promastigotes. Compound 118 (Figure 54) showed the most potent activity, with IC_{50} of 2.1 μg mL^{-1}. The compound also showed efficiency against trivalent antimony resistant parasitic strains. DNA fragmentation of *L. amazonensis* promastigotes justifies the activity of compound 118. Additionally, none of the thiophene-indole derivatives evaluated revealed cytotoxicity to human erythrocytes in the highest concentration tested (400 μg mL^{-1}) [111].

INSERT FIGURE 54 HERE

Figure 54. Compound 118 structure

Preclinical studies of thiophenic-indolics derivative were performed by Rodrigues *et al.* (2018) and evaluated on its acute toxicity, genotoxicity, *in vivo* oral efficacy in a murine model, and *in vitro* antileishmanial activity against an *L. amazonensis* SbIII-resistant strain. Compound 119 {2-[(5-bromo-1H-indol-3-ylmethylene)-amino]-4,5,6,7-tetrahydro-4H-benzo[b]thiophene-3-carbonitrile)} (Figure 55) demonstrated, at acute preclinical toxicity, LD_{50} of 2500 mg kg^{-1} orally. Also, it did not show genotoxicity *in vivo* at 2000 mg kg^{-1}. The results showed that after seven weeks of oral treatment, there was a reduction of over 50% in the paw lesion size and decreased the parasite load of the popliteal lymph node (42.57 ± 3.14%) and spleen (100%) at the highest dose tested (200 mg kg^{-1}). These results place the compound as a potential drug candidate [139].

INSERT FIGURE 55 HERE

Figure 55. Compound 119 structure

4.4. Antitrypanosomal activity: *Trypanosoma cruzi*

Researches have shown cryptolepine (88) and neocryptolepine (120) derivatives (Figure 56) to possess activity against *T. cruzi* and *T. brucei*, exhibiting IC_{50} of 2.01 and 2.23 μM, respectively. However, these values have not been superior the reference drugs, melarsoprol (IC_{50} = 0.004 μM) and benznidazole (IC_{50} = 1.50 μM) [100]. Studies since then were performed and the search for more effective molecules against neglected diseases are reported in the literature [140, 141].

INSERT FIGURE 56 HERE

Figure 56. Cryptolepine and neocryptolepine structures

A series of fourteen *N*-arylsulfonyl benzimidazole derivatives (NBSBZD) synthesized by Miana *et al.* (2019) and evaluated against epimastigote and amastigote forms of *Trypanosoma cruzi*. The compounds 121, 122 and 123 (Figure 57) showed the highest inhibitory potencies against epimastigote and amastigote forms of *T. cruzi*, with an increase in their bioactivities when compared to the reference compound BZN. There was also a significant increase in SI calculated for all reported compounds [142].

INSERT FIGURE 57 HERE

Figure 57. *N*-arylsulfonyl benzimidazole derivatives structures

Only the study described above was found using the indole nucleus in possible compounds with anti-*T. cruzi* activity.

4.5. Antitrypanosomal activity: *Trypanosoma brucei*

Besides the isolated alkaloid cryptolepine, another alkaloid, polysin (124) (Figure 58) was isolated from *Polyalthia suaveolens* (Annonaceae). Polysin demonstrated significant activity against *T. brucei*, by acting as a competitive reversible inhibitor (Ki = 10μM) of phosphofructokinase (PFK), while its derivative 3-O-acetyl greenwayodendrin presented selective inhibition of *T. brucei* aldolase with IC_{50} of approximately 0.5 μM [119].

INSERT FIGURE 58 HERE

Figure 58. Chemical structure of alkaloid polysin (124)

Karaman *et al.* (2018) describes Sirtuins as nicotinamide adenine dinucleotide (NAD+)-dependent class III histone deacetylases. Two inhibitors of sirtuin 1, 2 and 3 (sirt1–3), the bichalcones, known as rhuschalcone IV (125) and an analogue of rhuschalcone I (126), previously isolated from the medicinal plant Rhuspyroides, were shown to be active in the *in vitro* assay. The rhuschalcone I analogue showed the best activity against sirt1, with an IC_{50} value of 40.8 μM [143]. Similarly, Farahat *et al.* (2018) reported the synthesis of a new class of indole and benzimidazole bichalcophene diamidine hybrids, and biological evaluation against *T. brucei* parasites. Benzimidazole diamidines displayed antitrypanosomal activity against *Trypanosoma brucei rhodesiense* with IC_{50} values from 25 to 102 nM, being less effective than indole analogs, which were highly active against trypanosomes with IC_{50} values in the range of 2-15 nM. The indole analogs synthesized by the authors displayed SI ranging from 1046 to 5800 against *T. brucei rhodesiense*. Due to the excellent activity and *in vitro* selectivity of bichalcophenes indole diamidines, they were tested in the rigorous *T. brucei rhodesiense* STIB900 mouse model for the acute hemolymphatic stage of African trypanosomiasis at a daily intraperitoneal dose of 5 mg kg^{-1} four times daily. Compound 127 (Figure 59) was highly efficacious *in vivo* curing all *T. brucei rhodesiense* infected mice at a low dose of 4 x 5 mg kg^{-1} i.p., proving to be more active *in vivo* than the standard drug pentamidine [144].

INSERT FIGURE 59 HERE

Figure 59. Compound 125, 126 and 127 structures

Ferrigno *et al.* (2018) conducted an *in vitro* and SAR study on the selected set of compounds from previous work in the field of histone deacetylase inhibitors (HDAC). From the seven compounds substituted with indole nucleus, compound 128 (Figure 60), obtained using the bioisosterism strategy, was the most active in the initial study, showing low nanomolar (EC_{50} = 10 nM) activity in the *T. brucei* growth inhibition assay, and a large window between growth inhibition and cytotoxicity in HeLa cells (3 orders of magnitude). There was no activity in the biochemical assay against a panel of human HDACs (hHDAC1-9) up to a concentration of 5 μM [145].

INSERT THE PICTURE 60 HERE

Figure 60. Compound 128 structure

Hymenialdysine (129) is an alkaloid that was isolated in 1982 from a variety of marine sponges including Hymeniacidon species. Its synthetic structural, analog kenpaulone (130), has also been used as a prototype in the design of new protein kinase inhibitors [146]. Orban *et al.* (2016), aiming at the development of new drugs against *T. brucei* and starting from the observation that *N*-(5)-substituted paullone FS-554 (131) is a trypanothione synthase (TryS) inhibitor of parasites *L. infantum*, designed and synthesized, aryl-substituted alkyl 3-chlorokenpaullone derivatives as potentially improved trypanosomal inhibitors. Of the compounds obtained, compound 131 (Figure 61) showed EC_{50} = 40 nM and SI> 1000, exhibiting potent and selective antitrypanosomal activity, along with the absence of inhibitory activity against host kinases. Structure 131 can be considered promising against sleeping sickness and can be used as a prototype for the development of derivatives with better pharmacological properties [147].

INSERT THE FIGURE 61 HERE

Figure 61. Compound 129, 130, and 131 structure

4.6. Antischistosomal activity

Neocryptolepine derivatives (Figure 56), as stated previously as promising antiparasitic agents, showed relevant schistosomicidal activity in *in vitro* tests. In a review article, Bracca *et al.* (2014) presented a hybrid quinoline-indolic compound, designated 132 (Figure 62). This derivative stood out due to its IC_{50} of 1.26 and 4.05 μM against *S. mansoni* strains from Egypt and Puerto Rico, respectively [110]. These results will be better discussed in the quinolone derivatives section.

INSERT FIGURE 62 HERE

Figure 62. Compound 132 structure

Another natural compound widely used as starting point in synthesis is Isatisin A (133) (Figure 63), found in leaves of the Isatis plant found in China, and isolated in 2007 [148]. Based on this nucleus, Jiang *et al.* (2017), with an innovative methodology that had not yet been reported in the literature, synthesized a series of 2-(1H-indol-3-yl)-3-oxoindoline-2-carbonitrile derivatives via catalyzed oxidative homo-dimerization and evaluated their antischistosomicidal activity against *S. japonicum* adult worms. The compound 134 (Figure 63) displayed 100% inhibition within 24 hours at 10 μM [149].

INSERT FIGURE 63 HERE

Figure 63. Isatisin A and compound 134 structures

Almeida Junior *et al.* (2019) synthesized and evaluated *in vitro* schistosomicidal activity of indol-3-yl-thiosemicarbazones and 4-thiazolidinones derivatives against juvenile and adult worms of *S. mansoni*, in addition to *in silico* prediction of pharmacokinetic parameters and oral bioavailability. Compound 135 (Figure 64) caused 100% mortality at 24 and 48 hours in adult and juvenile worms. Moreover, this compound caused a reduction of viability of the adult parasites by 85% and 83% at concentrations of 200 and 100 μM. Similar results were obtained in juvenile worms, with a reduction in the viability of 85%, 81% and 64% at concentrations of 200, 100 and 50 μM, respectively. Furthermore, this compound presented good pharmacokinetic properties and satisfactory oral availability [112].

INSERT FIGURE 64 HERE

Figure 64. Compound 135 structure

5. QUINOLINE DERIVATIVES

5.1. Antiparasitic mechanism of action

Quinolinic compounds possess antiparasitic potential, being observed primarily as antimalarial compounds. In this sense, the general mechanism of action developed by quinoline compounds is properly elucidated in terms of antimalarial activity, taking into consideration reference quinoline drugs used in the treatment of malaria, which include, among others: chloroquine, quinine, and mefloquine [150]. Their mechanism of action involves the formation of quinoline heme complexes, responsible for inhibiting heme crystallization into hemozoin, leading to high levels of free heme and inducing pro-oxidant effects that culminate in parasite death [151].

Unlike antimalarial activity, there are no exact definitions of the mechanism of action generated by compounds containing quinoline nucleus in the other parasites aforementioned. The action of the studied derivatives has been attributed to a mechanism similar to that performed in *Plasmodium spp*. [151-153], as well as topoisomerase IB inhibition (LTopIB and hTopIB) [154] and increase in ROS levels and NO generation, which induces bioenergetic collapse and apoptosis of the parasite by decreasing ATP production and mitochondrial membrane potential [155].

5.2. Antiplasmodial activity

Chemotherapy for malaria based on natural products began with the isolation of quinine (Table 1), a quinoline derivative. In the mid-17th century, Europe used Cinchona bark from species of *Chincona* trees for the treatment of malaria. The alkaloid quinine, isolated in 1822, was the most effective against *Plasmodium* [23]. The quinine structure served as an excellent template for the development of structural analogs such as chloroquine, primaquine, mepacrine, and mefloquine (Table 1) that showed as effective antimalarial activity [20].

Nevertheless, in spite of widespread resistance to 4-aminoquinolines, quinoline scaffold is still considered very promising for the development of novel antimalarial agents. Therefore, many compounds containing the quinoline nucleus have been isolated and/or synthesized with this purpose [156].

Aiming naturally occurring compounds isolated from the roots of the West African plants *Cryptolepis sanguinolenta*, the alkaloid neocryptolepine was selected by El Sayed *et al.* (2009) as a lead

compound for the development of new antimalarial agents [157]. This alkaloid was previously described on its antiplasmodial activity by Cimanga *et al.* (1997), exhibiting IC_{50} of 35 ng mL^{-1}, 51 ng mL^{-1}, and 65 ng mL^{-1}, against *P. falciparum* D6, K1, and W2 strains, respectively [116]. Therefore, a series of chloro- and aminoalkylamino-substituted neocryptolepine was synthesized and evaluated for *in vitro* antiplasmodial activity against a chloroquine-sensitive *P. falciparum* strain and for cytotoxicity on a human cell (MRC5) line. Compound 136 displayed IC_{50} = 0.01 μM, value comparable to chloroquine, and SI = 1800 (Figure 65). It was also found that these compounds were able to inhibit β-hematin formation and to interact with DNA. Two selected derivatives were evaluated *in vivo* against *P. berghei* in Swiss mice, but they were not sufficiently potent or toxic to the animals [156].

Further exploration of the antimalarial potential of the neocryptolepine core through molecular modifications was also the objective of Mei *et al.* (2013). Several analogs were synthesized and evaluated *in vitro* against two *Plasmodium falciparum* strains (CQS, NF54; CQR, K1). A significant antimalarial activity was obtained by the urea derivatives, 2-Cl substituted 137 displayed excellent inhibition, with an IC_{50} value of 2.2 nM for CQS (NF54) and the highest SI value, among all the synthesized compounds, of 1400 (Figure 65). Against CQR (K1), almost all compounds were significantly more active than chloroquine, especially 138, which had an IC_{50} value of 2.2 nM for K1, SI of 1243 and resistance index value of 0.5 by K1/NF54. Three selected compounds were tested *in vivo* drug screening model against *Plasmodium berghei* in Swiss mice, however, they were not sufficiently potent or toxic to the mice. These results show the viability of the use of natural compounds as leads, even though further substitutions may be necessary to obtain active compounds *in vivo* [158].

Likewise, Wang *et al.* (2013) reported the synthesis of C2 or C8 and C11-disubstituted 6-methyl-5*H*-indolo[2,3-b]quinoline (neocryptolepine congener) derivatives. The best results of antiplasmodial activity against *P. falciparum* NF54 were achieved by compounds 139 and 140, which displayed IC_{50} values of 86 nM and 317 nM, and SI values of 20 and 370, respectively (Figure 65). Moreover, further experiments showed a linear correlation between β-hematin inhibition and cell growth inhibition in NF54 strain, as well as the influence of physicochemical factors related to solvation and polarity in the antiplasmodial activity [159].

INSERT FIGURE 65 HERE

Figure 65. Isolated compound, neocryptolepine, and its promising synthetic derivatives

Structurally related alkaloids ellipticine (141), cryptolepine triflate (142), cryptolepine synthetic derivative (143) and olivacine (144) were investigated for their antiplasmodial activity by Silva *et al.* (2012). Cryptolepine analog displayed IC_{50} values against *P. falciparum* K1 and 3D7 strains of 0.10 and 0.087 μM, respectively. However, *in vivo* studies against *P. berghei*-infected mice showed ellipticine as the most active compound, suppressing parasitemia by 100% and providing mean survival time of >40 days at an oral dose of 50 mg/kg/day. Besides *in vivo* tests, ellipticine and olivacine also proved to be less toxic than cryptolepine compounds (142, 143). These data reveal the potential of ellipticine and olivacine as antimalarial leads (Figure 66) [160].

INSERT FIGURE 66 HERE

Figure 66. Quinoline alkaloids isolated and synthetic analog

Followed by a screen of compounds containing structural features of natural products that are pharmacologically relevant, Roberts *et al.* (2017) selected 4-nitro styrylquinoline (145) as an antiplasmodial pharmacophore. It presented excellent antiplasmodial potency, with EC_{50} values of 67 nM against Dd2, 119 nM against 3D7 and 12.92 µM against HepG2 host cells, therefore displaying a selectivity index of 192. Furthermore, extensive experiments concluded that 145 does not interfere in β-hematin formation; blocks quickly at multiple stages of intraerythrocytic development of *P. falciparum*; displays novel mechanism of action by inhibiting merozoite invasion, and exhibits curative property in the rodent malaria model when administered orally. Accordingly, these results provide a strong indication that the styrylquinoline chemotype potentially is a new therapeutic alternative for malaria directed against unique cellular targets (Figure 67) [156].

INSERT FIGURE 67 HERE

Figure 67. Antiplasmodial scaffold 141

In order to solve chloroquine resistance issues, Çapcı *et al.* (2019) reported the synthesis of 17 novel artemisinin-isoquinoline and artemisinin-quinoline hybrids, and evaluation of antimalarial activity on the *P. falciparum* drug-sensitive strain (3D7) and in two multidrug-resistant strains (Dd2 and K1) (Figure 68). Within designed compounds, 146 gave EC_{50} values of 2.7 nM, 1.0 nM, and 780 pM against 3D7, Dd2, and K1 strains, respectively. *In vivo* evaluations against *Plasmodium berghei* in Swiss mice were conducted, demonstrating outstanding efficacy of hybrid 147, superior to artesunate. Applying a chemical proteomics approach, it was concluded that these hybrids affect important targets for the development and survival of blood-stage *P. falciparum*, such as the PfATP6 enzyme (responsible for artemisinin action) and the 40S ribosomal protein machinery (classically recognized for quinoline action) [161].

INSERT FIGURE 68 HERE

Figure 68. Most promising artemisinin-quinoline hybrid evaluated for antiplasmodial activity by Capci *et al.* (2019)

Okanya *et al.* (2011) isolated six marinoquinoline alkaloids from gliding bacterium *Ohtaekwangia kribbensis*. These compounds were evaluated for their antiprotozoal activity against several parasites *in vitro* and performed promising activity against *P. falciparum* K1. For example, compound 148 (marinoquinoline B) presented good antimalarial activity (IC_{50} = 1.8 µM) associated with low cytotoxicity against L6 cells (IC_{50} = 58.7 µM) (Figure 69) [162].

Isolated from marine sponge *Zyzza* sp., pyrroloiminoquinones alkaloids displayed potent antiplasmodial activity in Davis *et al.* (2012) report. Tested against *P. falciparum* 3D7 and Dd2 strains, new bispyrroloiminoquinone alkaloid, compound 149 (tsitsikammamine C), presented itself as the most efficient compound, due to its IC_{50} of 13 nM (3D7) and 18 nM (Dd2), and SI > 200 against HEK293 host cells. Moreover, in *in vitro* stage specific assays, tsitsikammamine C inhibited both ring and trophozoite stages of the malaria parasite life cycle. Sufficient quantities of alkaloids makaluvamines J and makaluvamines G were available for additional biological studies to be performed. Therefore, *in vivo* tolerability and efficacy studies were undertaken, and results showed that makaluvamine G was not toxic to mice and suppressed parasite growth in *P. berghei* infected mice following subcutaneous

administration at 8 mg kg^{-1} day^{-1}, indicating that this structure class has promising antimalarial activity (Figure 69) [163].

INSERT FIGURE 69 HERE

Figure 69. Isolated pyrroloquinolines, marinoquinoline B and tsitsikammamine C, evaluated against *P. falciparum.*

Ferroquine (SSR97193) (Figure 70), a ferrocenic derivative of chloroquine, is an antimalarial drug candidate, currently in phase IIb combination clinical trials with artefenomel, an antiparasitic trioxolane, formulated for children as a single dose [164]. It was first designed in 1994 by Biot and co-workers at the University of Lille, and has previously shown potent activity against chloroquine-sensitive and resistant *P. falciparum* strains, efficient curative effect in mice infected with *P. vinckei*, absence of significant cross sensitivity with other antimalarials currently used, action in hematin and inhibition of hemozoin formation, and presence of highly active metabolite (*N*-monodemethylated) [165, 166]. Mombo-Ngoma *et al.* (2011) report two clinical phase I trials in asymptomatic young males with *P. falciparum* infection, which aimed to assess the clinical, and laboratory safety and tolerability profile of ferroquine. Results showed a favorable tolerability and safety profile up to 1,600 mg when administered as a single dose. Moreover, adverse events were mainly gastrointestinal and nervous system disorders. Consequently, further clinical development of ferroquine is highly warranted and currently underway [165].

Stringer *et al.* (2019) aimed at the synthesis of two ferroquine-derived polyamines (compounds 150 and 151) that target a resistant strain of *P. falciparum* (Figure 70). Both compounds displayed similar antimalarial activity against chloroquine-sensitive (NF54) and resistant (K1) strains. Compound 150 revealed a two-fold more prominent activity than compound 151 in both sensitive and resistant strains, presenting IC_{50} values of 0.305 and 0.328 μM, respectively. Their mechanism of action appears not to be involved with inhibition of haemozoin formation, but with the capacity to generate reactive oxygen species [164].

INSERT FIGURE 70 HERE

Figure 70. Antimalarial drug candidate ferroquine and analogs

Chalcones are naturally occurring key structural motifs among biologically active compounds, characterized as key intermediates for combinatorial assembly of heterocyclic scaffolds. Therefore, based on the remarkable progress of ferroquine as an antimalarial agent and chalcones' promising broad biological activity spectrum, which includes oxygenated chalcone Licochalcone A as a potential antimalarial agent, Raj *et al*. (2015) proposed the synthesis, using molecular hybridization and expansion strategies, and biological evaluation of amide tethered 7-chloroquinoline chalcones and 7-chloroquinoline-ferrocenyl chalcones. The most potent of the synthesized compounds, the chalcone derivative N-[6-(7-chloro-quinolin-4-ylamino)-hexyl]-2-{4-[3-(4-methoxy-phenyl)-acryloyl]-phenoxy}-acetamide (152), exhibited activity comparable to that of chloroquine, with an IC_{50} value of 17.8 nM against *P. falciparum* W2 strain (Figure 71) [167].

INSERT FIGURE 71 HERE

Figure 71. Amide tethered 7-chloroquinoline chalcone

Several additional studies involve the evaluation of the antiplasmodial action of quinoline compounds. This fact reflects the relevance of this nucleus in the treatment of this neglected disease, thus rendering it indispensable for such purpose.

5.3. Antileishmanial activity

Given the extensive biological activity of chalcones, along with quinoline nucleus potential, as presented previously in this article by Raj *et al.* (2015) [167] in the investigation of their antimalarial activity, Coa *et al.* (2017) reported the synthesis and biological activities (cytotoxicity, leishmanicidal and trypanocidal) of six quinoline-chalcone and five quinoline-chromone hybrids. Compound 153 was the most active against *L. (V) panamensis*, with EC_{50} = 6.11 ± 0.26 µg mL^{-1}/16.91 µM (Figure 72). These derivatives, however, proved to be toxic against human macrophages (U937 cells). Nonetheless, they may still have potential to be considered as candidates to antileishmanial drug development [168].

INSERT FIGURE 72 HERE

Figure 72. Quinoline-chromone hybrid

Based on the fact that steroid transporters have been reported as able to accept and carry a variety of drugs and its derivatives are known to exhibit antimicrobial activities, Antinarelli *et al.* (2012) proposed increasing leishmanicidal activity of aminoquinoline compounds through conjugation with cholic acid. Three aminoquinoline/steroid conjugates (154, 155, and 156), along with their respective alkyne intermediates, were tested against promastigote forms of *L. major* and *M. tuberculosis*. Focusing on the antileishmanial assay, all conjugates displayed better results than their intermediates, particularly compound 154 (IC_{50} = 10.6 µM). Intracellular antiamastigote tests also evidenced that the addition of a steroid group to aminoquinoline molecules once more enhanced the biological activity of the compounds. Results showed that compounds 155 and 156 exhibited higher inhibition of parasite burden, of 64% and 80%, respectively. Hence, these results highlight the importance of steroids as carriers (Figure 73) [169].

INSERT FIGURE 73 HERE

Figure 73. Aminoquinoline/steroid (bile acid) conjugate products 154, 155, and 156.

Oxoaporphine alkaloids are widely found in nature and known for their pharmacological activities as antiparasitic agents. Given their potential, Sobarzo-Sánchez *et al.* (2013) aimed to investigate, for the first time, *in vitro* and *in vivo* leishmanicidal activity of several novel synthetic oxoisoaporphine compounds. *In vitro* assays of axenic amastigotes from *L. amazonensis* evidenced compounds 157 (IC_{90} < 0.05 µg mL^{-1}, IC_{50} < 0.05 µg mL^{-1}) and 158 (IC_{90} < 0.025 µg mL^{-1}, IC_{50} < 0.025 µg mL^{-1}) as the fittest for further evaluations to determine the *in vitro* effectiveness against promastigotes of four species of *Leishmania* representative of the main clinical forms of the disease (*L. infantum, L. amazonensis, L. braziliensis,* and *L. guyanensis*) (Figure 74). Both compounds were active against promastigote forms of these species, especially against *L. guyanensis* (IC_{50} of 16.3 and 1.8 µg mL^{-1}, respectively). These were also tested against intracellular amastigotes using *L. infantum* and *L. amazonensis.* In both assays, 158 was more active but more cytotoxic against J774.2 cell line. Finally,

both *in vitro* active compounds were tested *in vivo* in BALB/c mice infected with *L. infantum*. Compound 157 caused, in a dose of 10 mg kg^{-1}, 99.62% and 78±33% of reduction of the parasite in livers and spleens, respectively [170].

INSERT FIGURE 74 HERE

Figure 74. Novel oxoisoaporphine derivatives

Quinazolinone is a building block of naturally occurring alkaloids and is utilized as a druglike scaffold in several natural products. In that sense, Sharma *et al.* (2013) synthesized four series of quinazolinone hybrids via the introduction of heterocyclic systems previously reported as potent antileishmanial agents (pyrimidine, triazine, tetrazole, and peptide). Fifty-three compounds were synthesized and evaluated against *L. donovani* intracellular amastigotes. Most of these molecules displayed potent antileishmanial activity (IC_{50} from 0.65 ± 0.2 to 7.76 ± 2.1 μM), in which compounds 159, 160, and 161 showed very consistent and promising leishmanicidal activity against intracellular amastigotes and *in vivo* efficacy in the golden hamster model (Figure 75). In conclusion, these analogs are good candidates for a lead optimization for identifying new analogs as possible antileishmanial agents [171].

INSERT FIGURE 75 HERE

Figure 75. Quinazolinone-triazine (159, 160) and quinazolinone-peptide (161) derivatives

Subsequently, Sharma *et al.* (2014) designed and synthesized a series of triazino indole-quinoline hybrids as potential antileishmanial chemotherapeutics. Evaluated against *L. donovani* amastigotes and promastigotes, compound 162, particularly, exhibited good antipromastigote activity (IC_{50} = 6.27 ± 0.65 μM), high antiamastigote action (IC_{50} = 0.36 ± 0.10 μM), and low cytotoxicity (CC_{50} > 400 μM) (Figure 76) [172].

INSERT FIGURE 76 HERE

Figure 76. Structure of triazino indole-quinoline derivative

A series of novel triazolyl 2-methyl-4-phenylquinoline-3-carboxylate analogs were designed and synthesized via molecular hybridization approach by Upadhyay *et al.* (2018). Compound 163 presented high activity against promastigote forms of *L. donovani*, obtaining an IC_{50} value of 3 μM, but proved to be inactive against intracellular amastigote. Among synthesized compounds, 164 and 165 displayed significant antiamastigote activity, both presenting an IC_{50} of 7 μM, and lower cytotoxicity against J77A.1 cell line in comparison to standard drugs (miltefosine and sodium stibogluconate). Compound 165 also demonstrated promising *in vivo* leishmanicidal activity (Figure 77). Thereupon, these results revealed the therapeutic potential of the novel synthesized compounds as potential antileishmanial agents [173].

INSERT FIGURE 77 HERE

Figure 77. Structure of triazolylquinoline 165

Consecutively, Upadhyay *et al.* (2019) designed and synthesized a series of quinoline-metronidazole hybrid compounds. Antileishmania *in vitro* evaluation against *L. donovani* highlighted compound 166 due to its IC_{50} values against promastigote (IC_{50} = 5.42 μM) and amastigote (IC_{50} = 3.75 μM) stages of the parasite (Figure 78). Further experiments revealed that compound 166 effectively inhibited the parasite burden in the liver and spleen (>80%) of infected BALB/c model of visceral

leishmaniasis, and triggers oxidative stress by enhancing ROS and NO generation. These results suggest the potential of quinoline-metronidazole derivatives for the future development of specific clinical agents for counteracting leishmaniasis and other neglected parasitic diseases [155].

INSERT FIGURE 78 HERE

Figure 78. Chemical structure of the most promising quinoline-metronidazole conjugate as an antileishmanial agent

Almandil *et al.* (2019) reported the synthesis of quinoline-based thiadiazole hybrid analogs and their excellent *in vitro* leishmanicidal activity against *L. major promastigotes* (JISH118). Fourteen compounds exhibited higher inhibition than standard compound, pentamidine (IC_{50} = 7.02 μM). Structure-activity relationship study indicated that dihydroxylated compounds displayed better activity, especially compound 167, a 2,3-dihydroxy analogue (IC_{50} = 0.04 μM) (Figure 79) [174].

INSERT FIGURE 79 HERE

Figure 79. Quinoline based thiadiazole derivative

Valdivieso *et al.* (2018) evaluated previously synthesized drugs 168 and 169 for their antileishmanial activity against *L. donovani* strain (Figure 80). Antipromastigote assay demonstrated that both compounds were able to inhibit the parasite proliferation, displaying IC_{50} values of 13.03 ± 3.4 (168) and 7.90 ± 0.6 μM (169). These were also active against intracellular amastigotes, as 168 showed an IC_{50} value of 0.66 ± 0.2 μM, while for derivative 169 resulted in an IC_{50} of 1.02 ± 0.17 μM. The derivatives were evaluated in combined therapy with miltefosine and amphotericin B, and presented a synergistic effect for both combinations, with a Fractional Inhibitory Concentration (FIC) Index lower than 1 for promastigotes and less than 0.3 for intracellular amastigotes. Therefore, beyond presenting two molecules as potential leishmanicidal compounds, this research validates the combination of drugs as an effective alternative to potentiate the action of antileishmania agents [175].

INSERT FIGURE 80 HERE

Figure 80. Structures of tested 4-aryloxy-7-chloroquinoline compounds 168 and 169

Novel hybrid tetrahydroquinoline and quinoline derivatives with phosphorus substituents have been synthesized by Tejería *et al.* (2019) (Figure 81). The tetrahydroquinolylphosphine sulfide 170 presented a good antipromastigote activity (IC_{50} = 10.66 μM), the lowest EC_{50} value against amastigotes forms, of 0.61 μM, and the highest selectivity index (56.87). The compounds were also evaluated on inhibition of recombinant LTopIB and hTopIB activities *in vitro*, being 171 the most active compound with IC_{50} = 23.64 μM, whereas compounds 170 presented an IC_{50} = 93.73 μM. This result suggests that the antileishmanial activity of some of these compounds could be explained partially by the inhibition of TopIB [154].

INSERT FIGURE 81 HERE

Figure 81. Structure of 1,2,3,4-tetrahydroquinolinyl-phosphine sulfide derivatives

5.4. Antitrypanosomal activity: *Trypanosoma cruzi*

Waltheria indica L. (Malvaceae) is a short-lived shrub commonly used in traditional medicine. Throughout the analysis of dichloromethane extracts of the aerial parts and roots of *W. indica*, Cretton *et al*. (2014) isolated 10 quinoline alkaloids from the roots. The isolated molecules presented excellent activity when evaluated against protozoan causer of Chagas disease, *T. cruzi,* with IC_{50} values ranging from 0.02 to 3.1 µM. Compound 172 (waltherione G) was found to be the most promising alkaloid, due to its exceptional antitrypanosomal activity (IC_{50} = 0.02 µM) associated with the highest selectivity index displayed by these molecules (33.8), when tested for cytotoxicity against mouse skeletal L-6 cells (Figure 82) [176].

INSERT FIGURE 82 HERE

Figure 82. Isolated alkaloid waltherione G

Ensuing, Cretton *et al.* (2015) isolated two novel quinoline alkaloids, Waltherione A (173) and Waltherione C (174), from the dichloromethane extract from the roots of *W. indica*. Waltherione C showed a potent antitrypanosomal activity towards *T. cruzi* with an IC_{50} value of 1.93 µM, correlated with low cytotoxicity towards L6 cell line (IC_{50} = 101.23 µM) (Figure 83). This resulted in a selectivity index superior to 50, meaning this alkaloid falls into the criteria required by the WHO/TDR for *T. cruzi* to be considered as a hit. As a result of promising outcomes, *in vivo* studies with waltherione C (174) are in progress and further investigations are required to determine cellular target(s) [177].

INSERT FIGURE 83 HERE

Figure 83. Structure of the alkaloid waltherione C

Ramírez-Prada *et al.* (2017) synthesized a novel series of quinoline–based 4,5–dihydro–1*H*–pyrazoles from quinoline–chalcones and determined its biological activity as potential anticancer, antifungal, antibacterial and antiprotozoal agents (Figure 84). Most compounds displayed satisfying *in vitro* antitrypanosomal activity against *T. cruzi*, with EC_{50} ranging from 0.70 to 22.58 µg mL^{-1}, for active compounds. Compound 175 was highly active, displaying with EC_{50} = 0.70 µg mL^{-1}, superior to standard drug benznidazole (EC_{50} = 10.7 µg mL^{-1}) [178].

INSERT FIGURE 84 HERE

Figure 84. *N*–substituted 2–pyrazoline derivative 175

Studies performed by Coa *et al.* (2015) presented quinoline-hydrazone hybrids as potential trypanocidal agents [116]. Compounds 176 and 177 presented activity against *T. cruzi* with EC_{50} values of 1.4 ± 0.3 µg mL^{-1}/4.8 µM and 6.6 ± 0.3 µg mL^{-1}/4.6 µM, respectively. Besides, these compounds presented better activity against *T. cruzi* than antitrypanosomal drug, benznidazole (EC_{50} = 10.5 ± 1.8 µg mL^{-1}/ 40.3 µM). As previously mentioned, Coa *et al.* (2017) also evaluated the antitrypanosomal activity of quinoline-chalcone and quinoline-chromone hybrids. Compound 178 presented itself as the best hybrid derivative against *T. cruzi*, exhibiting EC_{50} value >2 µg mL^{-1}/>4.63 µM (Figure 85) [179].

INSERT FIGURE 85 HERE

Figure 85. Antitrypanosomal compounds synthesized by Coa *et al.* (2015) and Coa *et al*. (2017)

Synthetic 2-alkylaminomethylquinoline derivatives were obtained and tested for their trypanocidal activity by Muscia *et al.* (2011). A series of ten analogous derivatives were tested towards epimastigotes, trypomastigotes, and amastigotes stages of *T. cruzi*. Among them, compound 179 showed remarkable activity, with IC_{50} values of 3.4, 3.1 and 12.8 μM, respectively. Moreover, this molecule presented low cytotoxicity against COS-7 cell line (CC_{50} = 770.9 μM). Given the promising results obtained *in vitro* with compound 179, *in vivo* studies were conducted. Compound 179-treated mice presented a threefold reduction in the number of parasites when compared to untreated ones (1.5 and $4.5x10^6$, respectively). Therefore, these outcomes classify this derivative as an excellent candidate for additional studies (Figure 86) [180].

INSERT FIGURE 86 HERE

Figure 86. Structure of 2-alkylaminomethylquinoline derivative

Upadhayaya *et al.* (2013) reported the identification of new lead compounds based on quinoline and indenoquinolines. Fifty-seven compounds were evaluated against *T. cruzi, T. brucei, T. brucei rhodesiense,* and *L. infantum*. Particularly for *T. cruzi,* compound 180, which possesses an imidazole substitution, appeared to be the most active and promising, with an IC_{50} value of 0.25 μM and a selectivity index of 125.76 (Figure 87). Thus, this compound constitutes a new 'lead' for further structure-activity studies as a potential active trypanocidal agent [181].

INSERT FIGURE 87 HERE

Figure 87. Chemical structure of compound 180

Based on the mechanism of action of quinoline antimalarial drugs, Lechuga *et al.* (2016) synthesized and evaluated the activity of a series of 4-arylaminoquinoline-3-carbonitrile derivatives against all forms of *T. cruzi in vitro*. Among tested compounds, 181 presented an $IC_{50} < 1$ μM towards epimastigote forms when combined with hemin (Figure 88). Additionally, it also inhibited the viability of trypomastigotes and intracellular amastigotes, especially with the addition of hemin to the culture medium. These results suggest that the mechanism of action displayed by these molecules towards *T. cruzi* is similar to what occurs in *Plasmodium* spp. Therefore, the elucidation of the mechanism involving interactions with heme is an open field of research that can improve and guide rational drug development and combination strategies [151].

INSERT FIGURE 88 HERE

Figure 88. Quinoline derivative 181

Likewise, Chanquia *et al.* (2019) reported the synthesis of a series of 2- and 3-arylaminoquinoline derivatives, trypanocidal evaluation and the participation of heme in the mechanism of action of these compounds. 3-arylaminoquinoline derivatives proved to be more active against *epi*-, trypo- and amastigote forms of *T. cruzi*, especially fluorine and chlorine derivatives 182, 183 and 184. These compounds did not show cytotoxicity against Vero cells. Moreover, they were capable to inhibit the degradation of heme, inducing intracellular oxidative damage, which is not countered by the antioxidative defense system of the parasite (Figure 89) [152].

INSERT FIGURE 89 HERE

Figure 89. Aryl 3-aminoquinoline derivatives synthesized by Chanquia *et al*. (2019)

5.5. Antitrypanosomal activity: *Trypanosoma brucei*

Based on alkaloids isolated from *Cryptolepis sanguinolenta*, such as cryptolepine, neocryptolepine, isocryptolepine, and isoneocryptolepine, previously commented on the antimalarials topic, Baelen *et al.* (2009) designed and evaluated novel derivatives against *T. brucei rhodesiense.* Compound 184 (Figure 90) and its hydroiodide salt were found to be more active and displayed IC_{50} values of 0.72 and 0.55 μM, respectively. Even though these analogs demonstrated strong trypanocidal activities, they exhibited cytotoxicity towards L6 cells (IC_{50} = 1.48 and 2.2 μM, respectively) [182].

INSERT FIGURE 90 HERE

Figure 90. Chemical structure of 6-methyl-6H-indolo[3,2-c]isoquinoline (184)

As a complementation of antiprotozoal activity evaluation of neocryptolepines analogs, Mei *et al.* (2013) tested selected compounds towards *T. brucei rhodesiense* strain. These compounds presented IC_{50} values ranging from 1373 to 868.4 nM. Molecule 185 displayed the best result of the equivalent to 1.373 μM (Figure 91). However, all compounds were proved to be more effective against chloroquine-sensitive and resistant *P. falciparum* strains [158].

INSERT FIGURE 91 HERE

Figure 91. Structure of neocryptolepine analog 185

Aiming the polipharmacotherapy against sleeping sickness, Krstin *et al.* (2015) explored the potential synergism of mutual combinations of bioactive alkaloids and alkaloids with a membrane-active steroidal saponin. Within the selected alkaloids, chelerythrine (186), a quinoline derivative (Figure 92), was evaluated against *T. brucei brucei* alone and in combinations. The trypanocidal activity of this alkaloid is high, presenting an IC_{50} of 0.33 μM. Furthermore, chelerythrine was able to synergistically enhance the activity of berberine lowering the IC_{50} value from 6.85 to 2.80 μM, with a combination index value below 1. Likewise, the combination of chelerythrine with piperine lowered the IC_{50} of chelerythrine from 0.33 to 0.20 μM. Therefore, this study gives an insight into which combinations could be interesting for *in vivo* combination studies, to better understand the pharmacokinetics and pharmacodynamics of the corresponding drug combinations [183].

INSERT FIGURE 92 HERE

Figure 92. Structure of chelerythrine

Di Pietro *et al.* (2015) reported the synthesis of novel quinoline-based analogs of a benzonapthyridine compound, previously reported as a hit compound by Di Pietro *et al.* (2014). Compound 187 presented an IC_{50} of 1 μM against *T. brucei*, being 3-fold more potent than benzonapthyridine 1 (IC_{50} = 3.33 μM), an IC_{90} of 1.19 μM, and a selectivity index of 6.8 (IC_{50} *T. brucei*/IC_{50} L6 cells). This particular molecule had its structure modified by N_1-debenzylation, A-ring contraction and expansion, bioisosteric NH/O replacement at position 1, and substitution of the 5-(4-aminomethyl)phenyl group by 5-(2-furyl) and 5-(2-thienyl), originating novel analogs. Within new

molecules, the pyrrolo[3,2-c] quinoline 188 presented IC_{50} and IC_{90} values of 0.92 μM and 1.19 μM, respectively. Therefore, based on this data, these tricyclic heterofused quinolines exhibited an interesting trypanosomatid profile (Figure 93) [184].

INSERT 93 HERE

Figure 93. Benzonaphthyridine 187 and heterofused quinoline analog 187

A series of 32 new synthetic *Cinchona* alkaloids and bile acids hybrids, added to a series of the 16 derivatives previously prepared from lithocholic and chenodeoxycholic acids, was tested *in vitro* for antiparasitic activities by Leverrier *et al.* (2015). All the examined hybrids displayed good activities against *T. brucei*, with IC_{50} values ranging from 0.48 to 5.39 μM and selectivity indices from 1.3 to 12.3. From the quinine hybrid compounds, molecule 189 presented the best trypanocidal activity (IC_{50} = 0.45 μM/SI = 8.3). Among quinidine hybrids, 192 presented itself as the most efficient compound (IC_{50} = 0.55 μM/SI = 5.3). Molecule 190, a cinchonine hybrid, showed an IC_{50} of 0.51 μM and a SI of 8.3. Lastly, of the cinchonidine hybrid compounds, 191 exhibited an IC_{50} of 0.52 μM and a SI of 7.2. In summary, the hybridization of bile acids with *Cinchona* alkaloids had a favorable effect on the trypanocidal activity for some of the compounds (Figure 94) [185].

INSERT FIGURE 94 HERE

Figure 94. Structures of the synthesized and most promising hybrids of *Cinchona* alkaloids

Noscapine is a phthalideisoquinoline alkaloid isolated from *Papaver somniferum* that has attracted the attention of research groups due to its anticancer capabilities. Based on the structure of this alkaloid, Harikandei *et al.* (2019) synthesized two series of novel *N*-substituted cyclic ether derivatives of *N*-nornoscapine. Most derivatives displayed promising activity against *T. b. rhodesiense*, with IC_{50} values between 2.5-10.0 μM and selectivity index (SI) ranged from 0.8 to 13.2. Compound 193 was responsible for showing the highest potency (Figure 93). Moreover, molecular docking studies concluded that 194 showed the most significant docking score (-8.59 kcal mol^{-1}) for the ligand-TbTR protein complex, mainly by the formation of two hydrogen bonding interactions between MET333 and THR335 and the ligand amide side chain. Furthermore, compound 195 (Figure 95) showed the highest docking score (-8.86 kcal mol^{-1}) with the TbUDPGE enzyme, the primary interaction was among the 3-phenoxyphenyl group of the ligand 6b2 and hydrophobic residues containing TYR173, ALA100, LEU102, MET98, ILE12, and ALA9. Thus, according to these results, these novel semi-synthetic analogs represent potential drug candidates, being viable further researches for its optimization as an antitrypanosomal agent [186].

INSERT FIGURE 95 HERE

Figure 95. *N*-substituted *N*-nornoscapine derivatives 193 and 195

5.6. Antischistosomal activity

Two plant-derived compounds, plumbagin and sanguinarine (196), were evaluated for their antischistosomal activity by Zhang *et al.* (2013). Sanguinarine (Figure 96), a quinoline derivative, is obtained from the root of *Sanguinaria* spp. and possesses a broad spectrum of biological assets, as well as

antimicrobial, antioxidant and anti-inflammatory properties. The compound 196, at a concentration of 10 µM (equivalent to 3.68 µg mL^{-1}), caused a 100% of mortality at 48h. Moreover, it was found that sanguinarine does not cause morphological changes in worms from both sexes, but can cause tegumental alterations through severe erosion and disintegration of the tegumental surface between tubercles. Hence, obtained results meet the World Health Organization's (WHO) criterion of "hit" compound for the treatment of schistosomiasis [187].

INSERT FIGURE 96 HERE

Figure 96. Structure of evaluated alkaloid sanguinarine

Aiming the knowledge expansion about biological properties of the alkaloids of *Cryptolepsis sanguinolenta*, known for their antimalarial activity, semi-synthetic aminoalkylamino substituted neo- and norneocryptolepine analogs were evaluated for their schistosomicidal and molluscicidal activities by El Bardicy *et al.* (2012). The schistosomicidal bioassay showed that 8 compounds (6 neocryptolepines, and 2 norneocryptolepines) exhibited 100% worm mortality at the concentration of 5 µg mL^{-1} after 5 days. Compounds 197 and 198 presented the lowest IC_{50} and IC_{90} values against *S. mansoni* Egyptian strain (1.26 and 4.05 µM, 1.77 and 4.55 µM, respectively) and the Puerto Rico strain (3.54 and 6.83 µM, 3.29 and 5.57 µM, respectively) (Figure 97) [188].

INSERT FIGURE 97 HERE

Figure 97. Neocryptolepine derivatives 197 and 198

Soares *et al.* (2009) investigated the activity of three antimalarial compounds (quinine, quinidine and quinacrine), along with new synthetic quinolines, in a murine schistosomiasis model through the utilization of a combination of biochemical, cell biology and molecular biology approaches. All commercial quinolines and synthetic C7 and C10 inhibited heme crystallization, exhibiting IC_{50} values of 4.63, 2.41, 13.38, 9.00 and 17.50 µM, respectively. *In vivo* assays were carried out with commercial compounds, and results were promising, especially for the compounds quinine and quinidine. These were injected in daily doses of 75 mg/kg/day, through intraperitoneal route in *S. mansoni*-infected female Swiss mice from the 11th to 17th day after infection, they caused significant decreases in worm burden (39%–61%) and egg production (42%–98%). Therefore, these results suggest that interference with hemozoin formation in *S. mansoni* represents an important mechanism of schistosomicidal action of these compounds and points out the heme crystallization process as a valid chemotherapeutic target to treat schistosomiasis [153].

Eweas *et al.* (2013) reported the synthesis and biological evaluation of two 8-hydroxyquinoline derivatives (199 and 200) *In vitro* anti-schistosomal assay against *Schistosoma* (S.) *mansoni* adult worms revealed that, at 200 µg mL^{-1} concentration, both compounds displayed potent activity by reducing the motor activity and caused their death within 24 h. However, at lower concentrations (50 and 100 µg mL^{-1}), both compounds presented unsatisfactory potency when compared to standard drug praziquantel [189] (Table 1). Therefore, Eweas *et al*. (2013b) aimed at the synthesis of more potent anti-schistosomal 8-hydroxyquinoline-5-sufonyl 1,4-diazepine derivatives. Among all evaluated derivatives, 201 presented the most potent anti-schistosomal activity (Figure 96). This compound at 50 and 100 µg mL^{-1} concentrations caused 100% death of all worms after 72 h and 48 h, respectively. At 200 µg mL^{-1} and

after 24h of incubation, this compound caused 75% and 100% death of male and female worms, respectively. Moreover, docking studies suggest that the schistosomicidal action developed by this molecule is possibly through the inhibition of thioredoxin-glutatione reductase, in view that 201 has performed high binding energy (ΔG = -101.33 kcal mol^{-1}). Furthermore, 201 completely diminished egg deposition [190].

Subsequently, the same group published *in vivo* evaluation of 201 in *S. mansoni*-infected mice, along with two other promising compounds reported in the previous paper (Figure 98). Allam *et al.* (2013) affirmed that 201 reduced adult male and female count by 83.2% and 79.25%, respectively; reduced the count of immature female by 56.84%; decreased eggs per gram liver and intestine by 54.22% and 67.26%, respectively; reduced granuloma volume by 72.09%, etc. Once more, this compound was the most effective, in a way that it can be useful for the development of a new schistosomicidal drug [191].

INSERT FIGURE 98 HERE

Figure 98. Lead 8-hydroxyquinoline derivative against *S. mansoni*

6. ACRIDINE DERIVATIVES

6.1. Antiparasitic mechanism of action

The mechanism of action performed by acridine compounds with antiparasitic activity has been mostly related to their ability to intercalate between the bases of DNA [192-194]. This mechanism of action is well-known to acridine compounds with chemotherapeutic action, considering the structure of the nucleus, which characterized as polyaromatic and planar, with a positively charged heteroatom inserted into the ring system, which assists in relocating the molecule to the center of the DNA [195, 196].

In addition to this mode of interaction with the parasites, distinct mechanisms responsible for the activity developed by acridine derivatives has been reported, especially concerning the antimalarial action, such as the interference in the formation of hematin, inhibition of DNA decatenation performed by the enzyme topoisomerase II, interference with the food vacuole of the parasite, inhibition of falcipain-2, among others [197, 198].

6.2. Antiplasmodial activity

Acridine derivatives have shown remarkable activity as antimalarial agents. It all starts in the 1930s, during the II World War, with the clinical introduction of mepacrine (also known as quinacrine or atebrine) as the first synthetic antimalarial blood schizontocide. This 9-aminoacridine replaced quinine in the treatment of non severe malaria and was mainly used in malaria prophylaxis [199, 200]. Similarly, a Mannich base derivative of mepacrine was developed in the late 1970s. Pyronaridine, also referred to as '7351' and Malaridine®, showed high efficacy against drug-resistant *Plasmodium falciparum* and has been used in China for the treatment of malaria as a single agent for the past 30 years, also being used as a fixed-dose combination with artesunate [197, 201, 202].

Following the rational strategy of molecular design based on a privileged structure, Fonte *et al.* (2019) proposed the development of a multi-step synthetic route towards N^4,N^9-disubstituted 4,9-

diaminoacridines. Considering mepacrine's historical relevance associated with its extensive biological spectrum, interest in mepacrine derivatives has aroused due to growth in the percentage of chloroquine-resistant strains. These derivatives maintain the 9-amino-2-methoxy-6-chloroacridine core while altering moieties linked to the 9-amino groups. Hence, the research group aimed the synthesis of unpublished mepacrine derivatives, by embedding both the chloroquine and the primaquine moieties. Compound 202 was obtained as the final molecule, with an excellent yield in its final step (100%) (Figure 99). Although it has not yet been biologically tested, this multi-step synthetic route is unprecedented and may pave the way towards novel bioactive compounds, which are likely to possess a multi-stage antimalarial activity, considering its distinct features of chloroquine, which acts on blood-stage parasites, and primaquine, that targets parasite liver-stage forms and gametocytes [203].

INSERT FIGURE 99 HERE

Figure 99. Final product of multi-step synthetic route (202)

Based on pyronaridine, an antimalarial drug, Sereekhajornjaru *et al*. (2014) synthesized pynacrine (203) and compared its hematin-targeting properties with pyronaridine (204), to understand the relevance of the benzonaphthyridine in the structure of the latter in its antiplasmodial property (Figure 100). The results of pynacrine were comparable to pyronaridine. It showed an IC_{50} value of 5.5 ± 0.1 nM against intra-erythrocytic growth of *P. falciparum* K1 strains, a minimum concentration of 2.0 ± 0.1 nM to enhance hematin-induced human RBC lysis, MIC of GSH-induced degradation of hematin of 2.5 ± 0.5 µM, and the 1:2 stoichiometry of its interaction with hematin. Even though pynacrine was as potent as pyronaridine, it was 50-fold less effective in inhibiting β-hematin formation, which suggests that it has other off-target(s) effects [204].

INSERT FIGURE 100 HERE

Figure 100. Structure of pyronaridine and its analogue, pynacrine

Silva *et al.* (2018) realized the synthesis of four acridine derivatives through an addition reaction between cyanoacetohydrazide and 6,9-dichloro-3-methoxyacridine (205), followed by treatment of the product with aromatic aldehydes (206-208). All synthesized compounds were active against *P. falciparum* W2 with IC_{50} values ranging from 0.90 ± 0.08 to 3.20 ± 0.20 µM (derivative 206 and 207, respectively), and were less toxic than reference drugs against HepG2 cells. Even though they were all less potent than mefloquine (IC_{50} = 0.04 ± 0.01 µM, SI = 295), derivative 206 demonstrated IC_{50} comparable to amsacrine (IC_{50} = 0.80 ± 0.10 µM, SI = 6.5) and selectivity index 14 times higher, and also proved to be more efficient than primaquine in both aspects (IC_{50} = 1.70 ± 0.10 µM, SI = 49) (Figure 101) [205].

INSERT FIGURE 101 HERE

Figure 101. Chemical structure of acridine derivative 206

In the article "Synthesis, characterization and antimalarial evaluation of new β-benzoylstyrene derivatives of acridine", Prajapati *et al.* (2017) synthesized a series of eighteen acridine derivatives and evaluated their antimalarial activity against chloroquine-sensitive strain (3D7) and chloroquine-resistant strain (Dd2) of *P. falciparum* through *in vitro* red blood cell based culture using the SYBR Green I fluorescence assay. Three compounds (209, 210, 211) were the most potent against both strains, showing

values of IC_{50} ranging from 0.30 to 0.52 µM against 3D7 strain and values on the range of 0.15-0.32 µM against Dd2 strain (Figure 102). Unexpectedly, some derivatives exhibited more potency against CQ-resistant strain in comparison to CQ-sensitive strain, with values of resistance index in the range of 0.15-0.7. All compounds were found to be selective to *P. falciparum*, in which the three most potent presented selectivity index in the range of 80-520. Therefore, this research exhibited very good antimalarial activity, high selectivity and promising resistance indices, where further exploration and optimization of these derivatives could provide novel antimalarial molecules [206].

INSERT FIGURE 102 HERE

Figure 102. Structure of β-benzoylstyrene derivatives of acridine 209, 210, and 211

Exploring *Zanthoxylum simullans* Hance, a popular natural spice from the Rutaceae family, Wang *et al*. (2014) isolated, from the root bark MeOH extract, five acridone alkaloids: normelicopidine (212), normelicopine (213), melicopine (214), melicopidine (215), and melicopicine (216) (Figure 103). All acridone alkaloids were isolated from this plant for the first time and were evaluated for their antimalarial activity against *P. falciparum* chloroquine-sensitive strain 3D7 and chloroquine-resistant strain Dd2. These compounds displayed IC_{50} values in a range of 18-42 µg mL^{-1} against 3D7 and Dd2, in which normelicopidine showed the strongest activity against Dd2 (IC_{50} = 18.9 µg mL^{-1}), while melicopine was the more active compound against 3D7 (IC_{50} = 25.5 µg mL^{-1}). All compounds tested showed no cytotoxicity against HEK293 up to 100 µg mL^{-1} [207].

INSERT FIGURE 103 HERE

Figure 103. Chemical structure of acridone alkaloids 212-216.

Since the 1940s, the antimalarial activity of 1,2,3,4-tetrahydroacridin-9(10H)-ones (THAs) has been known. Cross *et al.* (2011) synthesized several series of THA derivatives and examined each compound for its antimalarial activity against *P. falciparum* multidrug-resistant malarial strains W2 and TM90-C2B. Of all compounds synthesized, several potent compounds (EC_{50} < 100 nM) were identified, in which biaryl ether compound (217) demonstrated to be the most active by presenting EC_{50} of 12.2 nM for W2, 9.1 nM for TM90-C2B and resistance index of 0.75 (Figure 104). Furthermore, the entire THA series did not show any cytotoxicity to J774 mammalian cells at 20 µM. Structure activity and structure property relationship studies concluded that the discovery that the 6- or 7-position of the THA scaffold tolerates aryl substituents provides opportunities for next generation designs [198].

INSERT FIGURE 104 HERE

Figure 104. THA analogue 217

Based on the tacrine (1,2,3,4-tetrahydroacridine), a clinically used drug in the treatment of Alzheimer's disease that exhibited antimalarial activity in an antiprotozoal screening (IC_{50} = 12.5 µM against chloroquine-sensitive strain 3D7), Schmidt *et al.* (2016) synthesized new dimeric tacrine derivatives. All compounds were found to have a good antiplasmodial activity, especially dimers, which showed IC_{50} in the nanomolar range, however, most of them presented low selectivity index. Nevertheless, derivative 218 demonstrated promising antimalarial activity due to its IC_{50} (3D7) = 0.02 ± 0.014 µM associated with its high selectivity index (1250) (Figure 105). Besides, the compound was tested against falcipain-2, showing an inhibition rate of 56.7% in a concentration of 20 µM, giving an IC_{50}

(FP-2) = 5.2 μM. Given that this enzyme is essential for parasite growth, these results indicate that falcipain-2 represents at least one target of the compound studied [208].

INSERT FIGURE 105 HERE

Figure 105. Structure of dimeric tacrine 218

Novel 9-aminoacridine derivatives linked to different cinnamic acids, previously noted to improve antimalarial activity, through an aminobutyl chain were designed and synthesized by Pérez *et al.* (2013). All seven compounds demonstrated mid-nanomolar against *P. falciparum* W2 strain, with values of IC_{50} ranging from 126 ± 3 to 892 ± 152 nM. Compound 219 (*Pf* W2 IC_{50} = 138 ± 2 nM) showed greater active against liver-stage parasites of the rodent parasite *P. berghei* than the reference drug primaquine (IC_{50} = 8 μM), with an IC_{50} = 3.2 μM (Figure 106). All compounds were found to be non-toxic to human hepatoma cells at up to 5 μM. Therefore, this study establishes 9-(*N*-cinnamoylbutyl)aminoacridines as a novel class of dual-stage antimalarial leads [209].

INSERT FIGURE 106 HERE

Figure 106. Hybrid aminoacridine-cinnamic acid 219

Synthesis and evaluation of antimalarial activity of new acridinone derivatives were performed by Fernández-Calienes *et al.* (2011). Most compounds were inactive or marginally activity against *P. falciparum* GHA-strain, exhibited $IC_{50} \geq 64$ μM. However, three compounds (220, 221, 222) showed IC_{50} below 0.5 μg mL^{-1} and selectivity index greater than 39. Moreover, inhibition of β-hematin formation was investigated using spectrophotometric assay, nevertheless, all compounds showed IC_{50} values over 20 Meq, while the reference drug, chloroquine, presented IC_{50} = 1.2 ± 0.5 Meq. Besides, mitochondrial bc_1 complexes were isolated from *S. cerevisiae* and bovine heart cells to test derivatives' inhibitory activity, which displayed moderate inhibition of the *cyt* bc_1 complex from bovine and yeast. The study has gotten to a "hit" for an antimalarial drug (222) and work is underway to elucidate the mechanism of action and to evaluate *in vivo* efficacy in murine models of malaria (Figure 107) [210].

INSERT FIGURE 107 HERE

Figure 107. Hit acridinone derivative synthesized by Fernández-Calienes *et al.* (2011).

6.2. Antileishmanial activity

Based on the structure of mepacrine, two series of novel thiophene-acridine derivatives were synthesized and evaluated for antileishmania activity by Serafim *et al.* (2018) against promastigote *Leishmania amazonensis* strains. The eight new compounds demonstrated good antipromastigote activity, associated with hemolysis index> 1000μM, particularly compounds 223 and 224, which exhibited better results than positive control drugs (tri and pentavalent antimonial), with IC_{50} of 9.60 ± 3.19 and 10.95 ± 3.96 μM, respectively (Figure 108). These were selected for further evaluation against antimony-resistant *L. amazonensis* strains and presented the respective IC_{50} values of 14.83 ± 0.44 and 16.36 ± 1.72 μM. Additionally, spectroscopic techniques revealed DNA intercalation as a mechanism of action executed by these molecules due to its binding constant of 10^4 M^{-1}. The results suggested these compounds are promising as potential drug candidates [193].

INSERT FIGURE 108 HERE

Figure 108. Potential antileishmanial acridine derivatives 223 and 224

Baquedano *et al*. (2016) achieved the synthesis of a new series of selenocyanates and diselenides bearing bioactive scaffolds, in which the acridine nucleus was included. Two acridine analogs were synthesized, 225 and 226, and examined for their antiprotozoal activity against amastigotes of the pathogenic *L. infantum* and had their cytotoxicity determined using human THP-1 cells (Figure 109). These presented ED_{50} of 7.40 ± 0.60 and 5.46 ± 0.01 μM, respectively, combined with low selectivity. Consequently, no additional studies were performed with these derivatives. However, joining all the results from each bioactive scaffold, it's supposed that analogs with the diselenide unit were more active than those with the selenocyanate moiety, and was observed that, in this scenario, tricyclic nitrogenated rings, such as acridine, are detrimental to the biological activity and selectivity compared with bicyclic nitrogenated rings [211].

INSERT FIGURE 109 HERE

Figure 109. Acridine analogs 225 and 226

Considering leishmaniasis as an important public health issue, Astelbauer *et al.* (2011) investigated the antileishmanial activity of 13 plant-derived compounds. Two acridones, 5-hydroxynoracronycine (227) and yukocitrine (228), isolated from *Glycosmis trichanthera* stembark, first reported by Vajrodaya *et al.* (1998) [212, 213], revealed antipromastigote activity when tested against *L. infantum* (Figure 110). Results after 24h of exposure were EC_{50} = 34.84 and 29.76 μM, EC_{90} = 447.58 and 327.58 μM, respectively. Likewise, results after 48h of exposure were EC_{50} = 4.42 and 0.88 μM, EC_{90} = 20.77 and 9.94, respectively. Hence, yukocitrine (228) showed lower EC_{50} after 48h of exposure than the reference compound, miltefosine (EC_{50} = 1.1 μM). These compounds also showed low hepatotoxic activity (EC_{50} = 201.87 and 147.06 μM, respectively) and no hemolytic activity in concentrations ranging from 150 to 1.56 μM. According to the authors, both acridones can be chemically synthesized with high yield, which is an advantage for the performance of further investigations [213].

INSERT FIGURE 110 HERE

Figure 110. Isolated alkaloids 5-hydroxynoracronycine (227) and yukocitrine (228)

In the article "Development of an *Ex Vivo* Lymph Node Explant Model for Identification of Novel Molecules Active against *Leishmania major*", Peniche *et al*. (2014) describe the development and application of a medium-throughput screening approach to identify new drug candidates for cutaneous leishmaniasis using an *ex vivo* lymph node explant culture (ELEC) derived from the draining lymph nodes of *Leishmania major*-infected mice. For that purpose, a collection of 334 compounds, which included several molecules shown previously to have antileishmanial activity, especially against *L. donovani*, were screened in a concentration of 2.5 μM. Throughout this process, it has been identified eight 9-aminoacridines derivatives as hits (>50% inhibition). In parallel, cytotoxicity quantification of the hits using human hepatocyte cell line and calculation of *in vitro* therapeutic index (IVTI) were investigated, in the presence and absence of S9 liver enzyme fraction. Four 9-aminoacridine derivatives (CID: 14169, 3131604, 3122093, and 2790597), considered most promising, showed values of EC_{50} ranging from 0.05 to 0.49 μM, in the absence of S9, and EC_{50} varying between 0.11-0.51 μM, in the

presence of S9. IVTI values were in the range of 188.8-770.2, in the absence of S9, and between 227.8-583, in the presence of S9. The incorporation of the S9 liver enzyme fraction showed a decrease of IVTI in some cases (CID: 14169, and 3131604), attesting the need for medicinal chemistry approaches in lead optimization to protect against hepatic metabolism. Besides, according to PubChem searches, most of these compounds had not previously been reported to be active against *Leishmania* sp., except for 2790597 [214].

Using a known acridine derivative, acriflavine, Makwali *et al*. (2012) examined the influence of combination and monotherapy on *L. major* infection in BALB/c mice using plant extracts and herbicides. Firstly, used as a monotherapy in a single 0.2 mg kg^{-1} dose, acriflavine showed 85.4% of reduction in liver amastigote burden on day 7 and 80.44% on day 56 post-treatment. Moreover, within 7 days of treatment, control of liver infection was obtained with acriflavine (1.25 mg kg^{-1}) with a reduction of 90.8%. However, body weight loss was noted in all the animals and the spleen remained positive for amastigotes. When tested in combination with plumbaginacea extract, triterpenoid saponin extract, and trinfluralin, resulted in complete clearance of parasitemia from the lesion site and internal organs of *L. major*-infected BALB/c mice. Therefore, the authors suggest combination therapy as a promising approach for the treatment of *L. major* infection [215].

6.3. Antitrypanosomal activity: *Trypanosoma cruzi*

Chromatographic separation of the leaves of *Teclea trichocarpa* (Engl.) Engl. (Rutaceae) led Mwangi *et al.* (2010) to the isolation of acridone, furoquinoline alkaloids, and triterpenoids, in addition to other compounds. From the dichloromethane extract, three acridone alkaloids (melicopicine (229), normelicopicine (230), and arborinine (231)) were isolated and used in the antiprotozoal (against *Plasmodium falciparum, Trypanosoma brucei rhodesiense, Trypanosoma cruzi,* and *Leishmania donovani*) and cytotoxicity assay (Figure 111). Results of these compounds against *T. cruzi* (Tulahuen C4 strain) were not satisfying, showing low or no activity with an IC_{50} value equal to or greater than 30 µg mL^{-1}. However, they have demonstrated to be more promising against other parasites, with values ranging from 1.61 to 12.45 µg mL^{-1} for *P. falciparum* (K1 strain, chloroquine resistance), from 5.24 to 23.52 µg mL^{-1} for *T. b. rhodesiense* (STIB 900 strain), and from 1.08 to >30 µg mL^{-1} for *L. donovani* (MHOM-ET-67/L82 strain). However, most data corroborate to the fact that compound 230 is a potential lead compound, since it has shown low IC_{50} against the parasites in this study and a high MIC (>90 µg mL^{-1}) against myoblasts in the cytotoxicity assay [216].

INSERT FIGURE 111 HERE

Figure 111. Isolated alkaloids 229-231.

6.4. Antitrypanosomal activity: *Trypanosoma brucei*

Two known acridone alkaloids, compound 227 (Figure 110) and 231 (Figure 112), were isolated from the methanolic extract of *Citropsis articulata* Root Bark, by Lacroix *et al.* (2011). Both were tested against *T. b. brucei*, but have not shown significant activity (125 µg mL^{-1}). Nonetheless, the two compounds showed promising antimalarial activity against *P. falciparum*, with IC_{50} values of 0.9 and 3.0

μg mL^{-1}, respectively, both having a selectivity index of around 10. They have also displayed antileishmanial activity against *L. donovani*, with EC_{50} values of 11.2 and 20.4 μg mL^{-1}, respectively [217].

INSERT FIGURE 112 HERE

Figure 112. Structure acridone alkaloid 231

In the article "Antiprotozoal Activity and DNA Binding of Dicationic Acridones", published by Montalvo-Quirós *et al.* (2015), several series of acridone derivatives were synthesized and had their antiparasitic activity evaluated. These exhibited IC_{50} in the nanomolar range against *T. b. rhodesiense* STIB900 trypomastigotes, associated with high selectivity (>1000). Compound 232 in particular was as active as melarsoprol *in vitro* and also curative in the STIB900 mouse model of stage 1 HAT (Figure 113). Furthermore, some of these compounds have presented antimalarial activity in the submicromolar range against wild type (NF54) and resistant (K1) strains of *P. falciparum*. Additionally, antiparasitic assays against *T. cruzi* and *L. donovani* were performed, however, no significant activity was detected. Subsequently, UV spectrophotometric titrations and circular dichroism (CD) experiments were conducted, revealing binding constants with DNA in the 10^4 M^{-1} range, and binding mode mainly by intercalation. No apparent correlation was observed between antitrypanosomal activity and DNA binding affinity, which suggests that there may be additional mechanisms of action involved in the activity of these acridone derivatives against *T. brucei* [194].

INSERT FIGURE 113 HERE

Figure 113. Acridone derivative 232

6.5. Antischistosomal activity

According to our findings and to the best of our knowledge, no researches involving acridine derivatives with antischistosomal activity were published within the timeframe established. This fact might be explained by the lack of satisfying results evolving this scenario. Khalil *et al.* (1934) have concluded, during an extensive clinic trial, that acriflavine doesn't present a curative effect on schistosomiasis due to *Schistosoma haematobium* or *S. mansoni* [218]. Similar results were found by Newsome (1953), through an experiment with four aminoacridines on *S. mansoni* infections in baboons, which revealed that these compounds were not effective at the dosages used [219]. However, a 9-acridanone-hydrazone, compound 233 (10-2-(Diethylamino) ethyl-9-acridanone(2-thiazoline-2-yl)hydrazine), has had its effects against schistosomiasis widely studied since 1984 and it's recognized as an interesting drug candidate, obtaining attention over the years from the academia, the World Health Organization and, recently, a company (http://selvarx.com/selva/) (Figure 114) [220-224].

INSERT FIGURE 114 HERE

Figure 114. Drug candidate 233

7. CONCLUSION

The recent studies here addressed confirmed the biological potentiality attributed to heterocyclic nitrogenous nuclei, focusing on their application in the search for new antiparasitic agents capable of combating the main neglected diseases. The results obtained by the articles presented in this review showed that natural origin compounds have an important role in this pursuit, whether in the analyzes of the isolated natural product; obtained from total synthesis strategies; or obtained through the utilization of semi-synthetic routes to produce derivations of natural products, which, oftentimes, has been used as an strategy to insert nitrogenous rings in non-alkaloid natural compounds, aiming to increase their biological potentiality. Therefore, these strategies have shown as important alternatives, not only in the development of new antiparasitic agents but also in the observation of essential structural properties of these molecules, allowing the rational design of new pharmacophores.

According to our findings, several studies evolving heterocyclic nitrogenous compounds, such as pyrrole, pyridine, indole, quinoline, and acridine derivatives, focus their research mainly on the exploration of possible antimalarial drugs, among the neglected diseases group. This conclusion might be justifiable due to the preexistence of drugs containing some of these scaffolds directed to *Plasmodium spp.* parasites, and the high morbidity and mortality rate associated with the disease, which promotes efforts to fill the void of the need for novel antiplasmodials.

Nevertheless, in contrast, a limited quantity of recent studies directed to schistosomiasis was found. Concomitantly, few studies seek to elucidate the mechanism of action developed by the compounds evaluated. It is also observed the lack of investment, mainly by the pharmaceutical industry, for the development and obtainment of new candidates for drugs aimed at neglected parasitic diseases, which, in turn, increases the obstacles associated with these parasites and their consequences for public health.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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