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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Synthetic compounds with sulfonamide moiety against *Leishmaniasis*: an overview

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Abstract
Leishmaniasis is listed by the World Health Organization as a neglected tropical disease. The medicines used to treat leishmaniasis are relatively expensive and therefore often unaffordable toxic. These drugs besides being toxic, confer resistance, few or no antileishmanial drugs are under development or have been approved for use recently. This review provides an overview of various synthetic compounds containing the sulfonamide group linked to heterocyclic rings that have been evaluated against *Leishmania spp*. and could be considered possible prototypes to develop new drugs to treat this disease.

Keywords Leishmaniasis · Sulfonamide

Introduction

Leishmaniasis can be caused by protozoan parasites from more than 20 *Leishmania* species and can be transmitted to humans by the bites of infected female phlebotomine sandflies of the genus *Phlebotomus* or *Lutzomyia*. The World Health Organization (WHO) considers this disease to be one of the most neglected diseases. The WHO reported 20,792 out of 22,145 (94%) of the new cases to be from seven countries: Kenya, Somalia, Ethiopia, India, South Sudan, and Brazil (WHO 2010).

According to the WHO, an estimated 700,000–1 million new *Leishmania* infections and ~26,000 to 65,000 deaths occur every year. In 2017, 97 countries and territories were considered endemic for leishmaniasis (WHO 2019). Leishmaniasis can manifest in the following four main forms: cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), visceral leishmaniasis (VL, also called "kala-azar"), and post-kala-azar dermal leishmaniasis (Glew et al. 1988). *Leishmania* parasites that cause CL, the most found form of the disease, and MCL are *L. Mexicana*, *L. tropica*, *L. braziliensis*, and *L. major*. However, *L. donovani*, *L. infantum*, and *L. chagasi* are responsible for VL, the most lethal form of the disease, which, if untreated, can be fatal (WHO 2019).

Treatment and diagnosis of leishmaniasis becomes difficult because there are different causative species and different clinical manifestations. A serious problem is related to coinfection with HIV/AIDS. Over the past few years, various drugs that were previously developed for other diseases have also been tested and showed variable efficacy (Cavalli and Bolognesi 2009; Tiuman et al. 2011; Croft and Yardley 2002; Mishra et al. 2009; Berman 2005; Micheletti and Beatriz 2012; Richard and Werbovetz 2010; Silva-López 2010).

Since the early 20th century, the pentavalent antimonial compounds Glucantime® (meglumine antimoniate) **(1)** and Pentostam® (sodium stibogluconate) **(2)** (Fig. 1) were the first choice for leishmaniasis treatment, despite their high cost and serious side effects (Rath et al. 2003). The incomplete treatment, misuse of those drugs and inappropriate prescription have been described as the major reasons for the emergence of resistance of *Leishmania* parasites against these pentavalent antimonials (Croft et al. 2006; Sundar et al. 2000; Sundar et al. 1994; Sundar 2001; Perez-Victoria et al. 2002; Integrity 2019).

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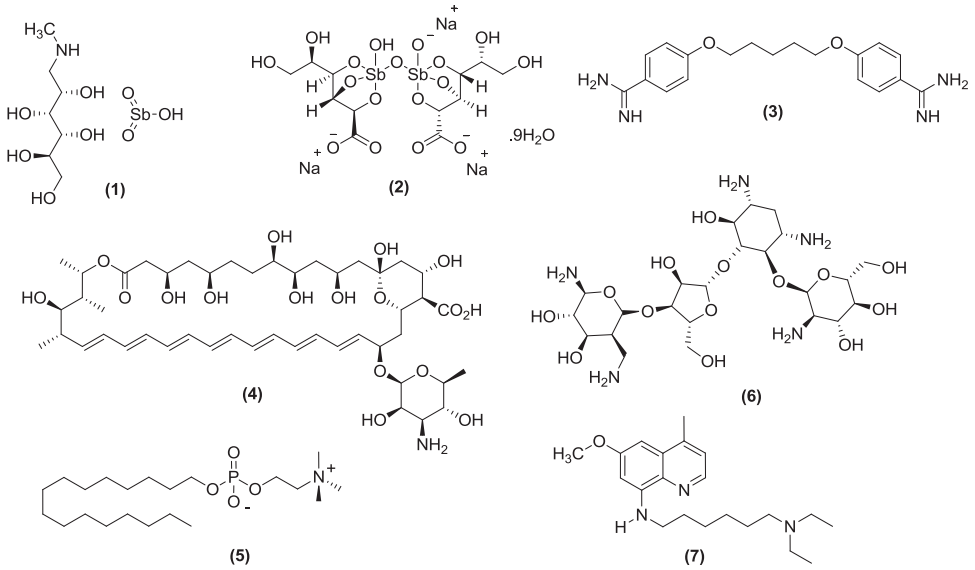

Fig. 1 Drugs used in the treatment of leishmaniasis

Pentamidine **(3)** (Fig. 1), produced by Sanofi–Aventis, launched in 1989. Over time the efficacy was declined, and serious adverse effects are associated with this drug (Thakur et al. 1991; Jha et al. 1991; Integrity 2019).

Amphotericin B **(4)** (Fig. 1) is used for VL. The following three new pharmaceutical formulations of amphotericin B, launched in 1995, are more effective and less toxic: liposomal ampho B (L-AmB: Ambisome®), amphotericin B colloidal dispersion (ABCD: Amphocil®), and amphotericin B lipid complex (ABL: Abelcit®) (Mishra et al. 1992; Thakur et al. 1999; Sundar et al. 2008; Thakur 2001; Sundar et al. 2003; Integrity 2019).

Miltefosine **(5)** (Fig. 1) is orally administered and was developed in 1993 for cancer treatment. In 2003, it was launched in India for the treatment of VL. Early clinical studies demonstrated a 94% cure rate, but the efficacy is variable for *Leishmania spp*. Miltefosine presents certain limitations, such as high-level teratogenicity, clinical resistance, and high cost (Berman 2008, 2006; Sundar et al. 2002; Integrity 2019).

Paromomycin **(6)** (Fig. 1) was indicated in 1960 for the treatment of acute and chronic intestinal amebiasis. The regulatory application filed in India was approved, in 2006, for use as an intramuscular injection for the treatment of VL. In 2010, the WHO Expert Committee on the Control of Leishmaniases recommended the combination of stibogluconate and paromomycin as first-line treatment for VL in East Africa. It is well tolerated, showing results comparable with amphotericin B. Phase III clinical trials are ongoing in combination with miltefosine or AmBisome. (Thakur et al. 2000; Sundar et al. 2007; Integrity 2019).

Sitamaquine (**7**) (Fig. 1) is in phase II clinical trials by the Walter Reed Army Institute in collaboration with GlaxoSmithKline. Sitamaquine has demonstrated oral efficacy against *L. donovani*, and studies are being conducted to characterize its pharmacokinetic profile, safety, and tolerability when compared with amphotericin B, but no recent development for this indication has been reported. (Sherwood et al. 1994; Yeates 2002; Wasunna et al. 2005; Jha et al. 2005; Integrity 2019).

Sulfonamides linked to heterocyclic rings as antileishmanial candidates

Discovered in the 1930s as a chemotherapeutic agent with antibacterial properties, the sulfonamide group is an important structural core in medicinal chemistry that shows a wide spectrum of pharmacological activities in many registered drugs for a variety of diseases (Smith and Jones 2008). In addition, compounds containing the sulfonamide group are described in the literature as having distinct biological activities, such as anticancer (Owa and Nagasu 2000), antiviral (Supuran et al. 2004), and antiparasitic (Hernández-Núñez et al. 2009; Bocanegra-Garcia et al. 2012; Pinheiro et al. 2015; Silva et al. 2016; Silveira et al. 2018; Zhao et al. 2019).

Several functional groups and heterocyclic rings have been associated as pharmacophoric groups with leishmanicidal activity (Kapil et al. 2018). Groups such as an amidine, diamidine, guanidine polyamine, and sulfonamide linked to heterocyclic rings are frequently found in leishmanicidal compounds (Boechat et al. 2014; Zhao et al. 2019).

This review presents various synthetic compounds containing the sulfonamide group linked to heterocyclic rings that have been evaluated against *Leishmania spp*.

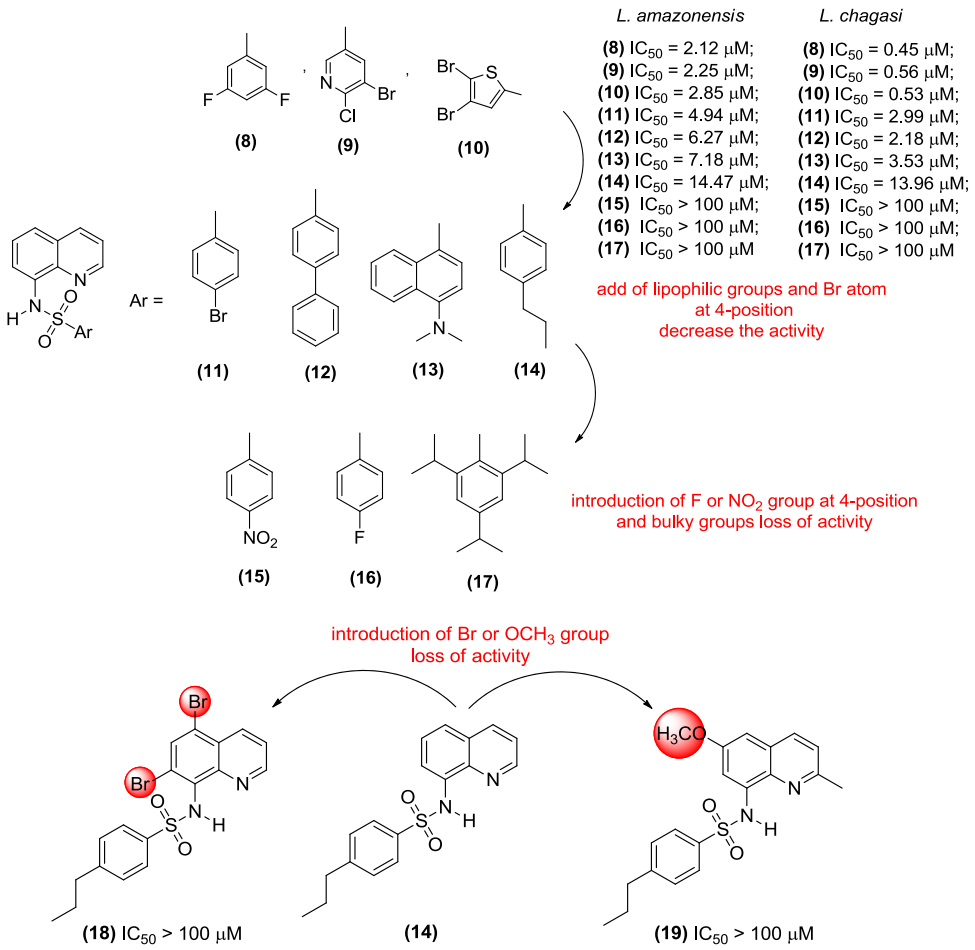

Fig. 2 Structures of quinolines **8–19**

Quinoline derivatives

A series of *N*-(quinolin-8-yl)benzenesulfonamide derivatives **(8–19)** (Fig. 2) was tested against *L. amazonensis* and *L. chagasi* (Silva et al. 2007). Dihalogen derivatives **8–10** were the most active compounds, with IC_{50} values ranging from 2.12 to 2.85 μM against the promastigote forms of *L. amazonensis* and 0.45–2.99 μM against *L. chagasi*, while amphotericin B showed IC_{50} values of 0.31 and 0.25 μM, respectively. Brominated derivative **11** and the derivatives **12–14**, that are the lipophilic compounds of the series, showed lower activities (IC_{50} 6.27–14.47 μM for *L. amazonensis* and IC_{50} 2.18–13.96 μM for *L. chagasi*).

Derivative **17**, containing bulky groups on the phenyl moiety, led to a loss of activity. A similar result was observed for compounds **15** (4-NO_2) and **16** (4-F). The bromine at the 4-position of the phenyl moiety shows activity. The introduction of substituents on the quinoline ring is another interesting finding. When the quinoline ring has substituents such as derivatives **18** (5-, 7-diBr) and **19** (2-CH_3, 6-OCH_3), this leads to a loss of activity (IC_{50} > 100 μM).

Compounds **6** and **17** were tested against the intracellular amastigote forms of *L. amazonensis* (infected macrophages). These compounds showed activity, with 67.1 and 88.2% reduction of cell infection at 5 μM, respectively, while amphotericin B presented a 97% reduction of infection at 10 μM.

Upadhayaya et al. screened a library of 39 compounds based on the quinoline and indenoquinolines scaffolds with various side chains for antiprotozoal activity. The quinoline–sulfonamide derivative **20** showed an IC_{50} of 8.11 μM against *L. infantum*. In this type of structure, when the 3-(trifluoromethyl)benzenesulfonamide group was replaced by a 1-(3-nitrophenyl)urea moiety as in compound **21**, the activity increased to give an IC_{50} of 1.70 μM (Fig. 3) (Upadhayaya et al. 2013).

Quinoline derivatives (Fig. 4) have been evaluated for their cytotoxicity in mammalian cells and for their in vitro activity against *L. amazonensis* for promastigote and intramacrophage amastigote forms (Antinarelli et al. 2015).

Among the five sulfonamide derivatives, compound **22** displayed significant antipromastigote (IC_{50} = 10.9 μg/mL) and intracellular amastigote (IC_{50} = 26.6 mg/mL) activities.

The absence of the pyridine ring, as in derivative **23**, or the exchange of this ring by other heterocycles, as in derivatives **24**–**26**, causes a loss of activity in both forms of *L. amazonensis*. The activity of this compound can be attributed to the presence of the pyridine ring. The hydrazine analogs **27** and **28** presented the highest activity against *L. amazonensis* promastigote and amastigote when compared with the sulfonamide derivatives.

The benzenesulfonyl-2-methyl-1,2,3,4-tetrahydroquinolines **(29–38)** (Fig. 5) were tested against *L. donovani* and showed IC_{50} values in the range of 18.87 to >271.02 µM (Pagliero et al. 2010). The addition of a benzenesulfonyl group increased the potency by ~35-fold with respect to 2-methyl-1,2,3,4-tetrahydroquinoline **(39)**. The activity increased when a substituent was added to the benzenesulfonyl group, with IC_{50} values between 18.8 and 167.0 µM, except for compound **38**, which has an NO_2 group at the 4-position (IC_{50} of 271.0 µM). When the nitro group is in the 3-position, the activity increases (IC_{50} of 24.9 µM). The halogenated compounds were the most active of the series, with 4-Cl and 4-Br showing IC_{50} values of 18.8 and 21.3 µM, respectively Fig. 6.

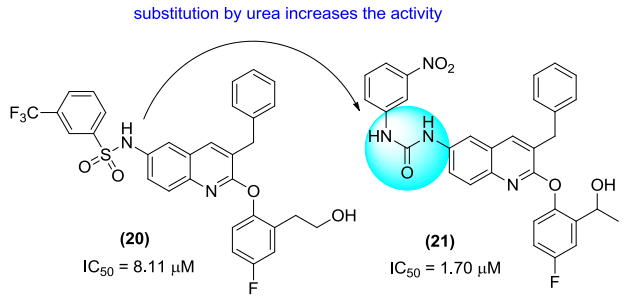

Fig. 3 Structures of quinolines **20** and **21**

Quinoxaline derivatives

A series of quinoxaline *N*,*N*′-dioxides, **40**–**46**, was tested in vitro against the promastigote form of *L. braziliensis* and showed IC_{50} values between >100 and 2.1 µM (Barea et al. 2011).

Compounds **40** and **41** inhibited 50% of parasite growth with approximate IC_{50} values of 2.1 and 3.1 µM, respectively, showing 10–15 times less activity than the reference drug amphotericin B. When $R_2 = Cl$, the compounds have better activity, except for derivative **44**. When $R_1 = R_2$, as in compounds **42**, **43**, and **46**, the activity decreases. A Cl

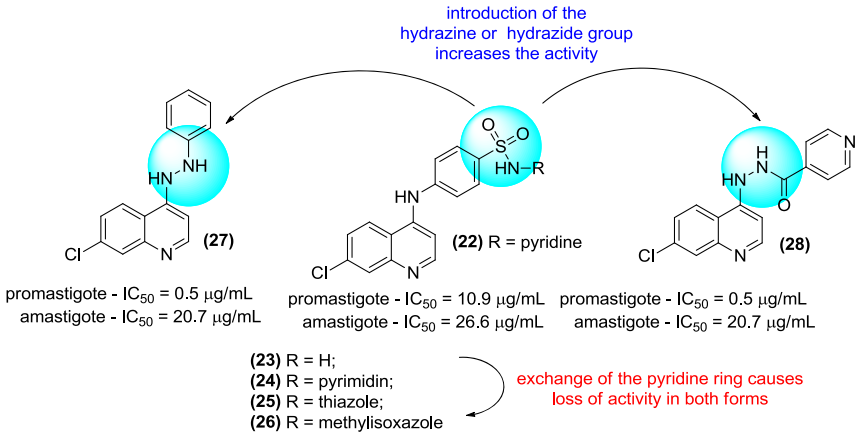

Fig. 4 Structures of quinolines **22**–**28**

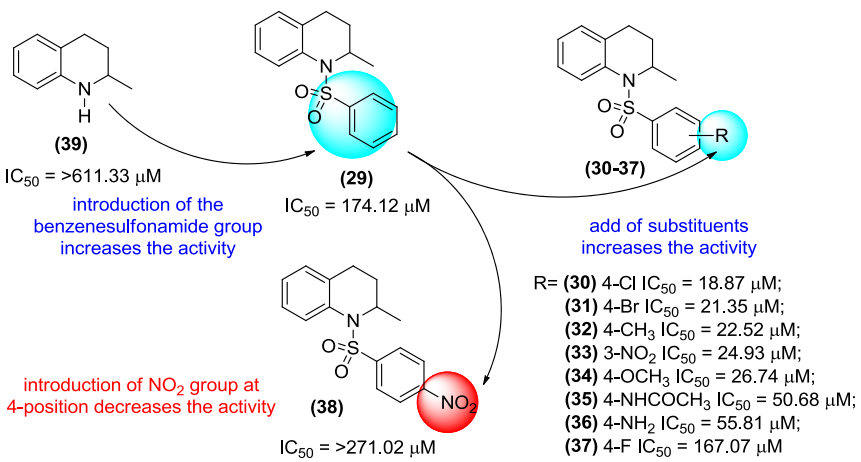

Fig. 5 Structures of tetrahydroquinolines **29**–**39**

atom at the 6-position is responsible for the activity in association with the 4-nitrophenylsulfonamide substituent because once this group is changed to a naphthalene-2-sulfonamide group, the activity decreases.

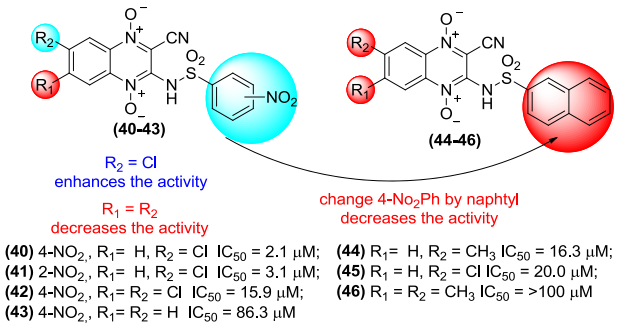

Fig. 6 Structures of the quinoxaline *N*,*N*′-dioxides **40–46**

Azole derivatives

Pyrimidines, pyrazine, pyridine, thiazole, isoxazole, pyrazole, indazole, indane, guanidine, imidazolidinone, and aniline sulfonamide derivatives **47–73** (Fig. 7) were evaluated in vitro against promastigotes of *L. infantum* and showed 92.7–85% growth inhibition (Dea-Ayuela et al. 2009; Bilbao-Ramos et al. 2012; Galiana-Rosello et al. 2013). The most active compounds were found have IC_{50} values between 224 and <1 μM, with the exception of the guanidines and an imidazolidinones series were inactive on the growth of *L. infantum*.

From the pyrimidine series, NO_2 derivative **47** is the most potent. With the electron withdrawing effects from the NO_2 group, compound **48** (R = H), or replacement of this group by an electron-donating group, such as in derivative **49** ($R = OCH_3$), causes a decrease in the activity or a loss of activity (**50** $R = NH_2$). The exchange of the NO_2 group by

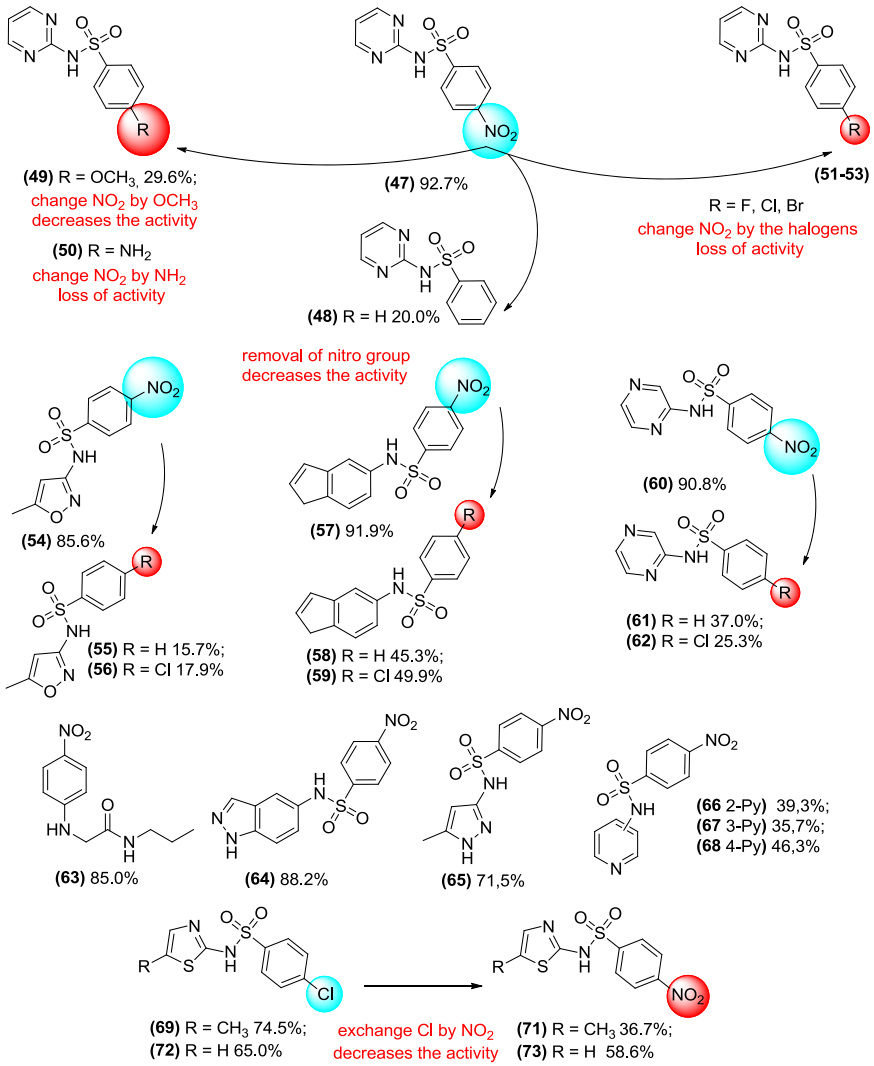

Fig. 7 Structures of compounds **47–73**

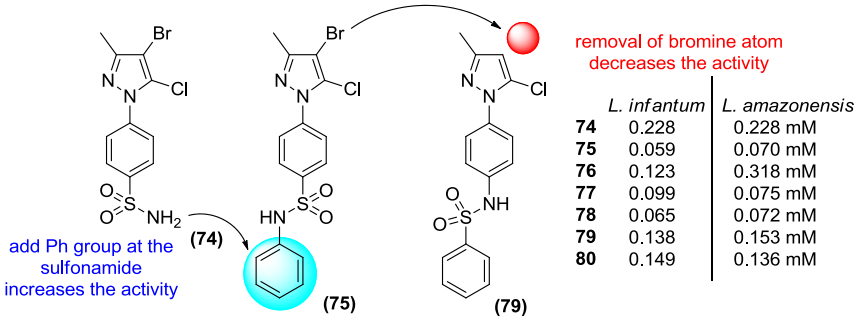

Fig. 8 Structures of pyrazoles **74–80**

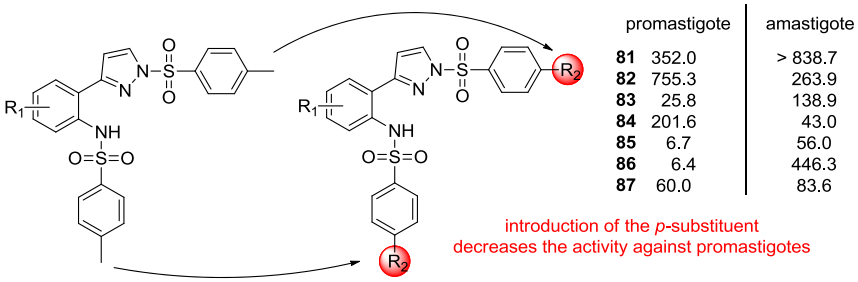

Fig. 9 Structures of pyrazoles **81–87**

halogens in compounds **51–53** also resulted in loss of activity.

The series of isoxazoles **54–56**, 1*H*-indenes **57–59** and pyrazines **60–62** show the same pattern of activity, where the nitro derivatives are the most potent in the series. Sulfonamide derivatives nitroaniline **63**, indazole **64**, and pyrazole **65** showed inhibition of 85.0%, 88.2%, and 71.5%, respectively. The pyridine series, **66–68**, were less potent, showing inhibition rates between 35.7 and 46.3%. It was observed from these series that the compounds with the NO_2 group were the most potent against the parasites, but it did not apply to the thiazole series **69–73**, in which chlorinated compounds are the most active.

Sulfonamides **47**, **60**, and 4-nitroaniline **63** were tested in vivo and displayed high levels of activity (99.89–97.58%) without signs of toxicity. Compound **47** was the most potent, with IC_{50} values of 76.4, 48.8, 46.4, and 68.6 µM for *L. infantum*, *L. braziliensis*, *L. guyanensis*, and *L. amazonensis*, respectively.

The 1*H*-pyrazolo sulfonamides **74–80** (Fig. 8) were evaluated against the promastigote forms of *L. infantum* and *L. amazonensis* and showed IC_{50} values ranging from 0.059 to 0.228 mM and 0.070–0.228 mM, respectively (Marra et al. 2012). The addition of a sulfonamide to the brominated compounds **74–80** enhanced the antileishmanial activity of this series, and the removal of the bromine atom decreased the activity of sulfonamides **79** and **80**. Compounds **78** and **79** showed the most active in vitro profile against the infective *L. amazonensis* promastigote forms with $IC_{50} = 0.070$ mM and 0.072 mM, respectively as well as against *L. infantum* (*L. chagasi* syn.) ($IC_{50} = 0.059$ mM and 0.065 mM, respectively).

Pyrazolyl benzenesulfonamide derivatives **81–87** (Fig. 9) were evaluated in vitro against *L. amazonensis* promastigotes and axenic amastigotes (Borges et al. 2014). Compound **85**, with $R_1 = 2\text{-}CH_3$ and $R_2 = H$ was the most active compound against promastigotes. The introduction of phenyl substituents decreased activity against the promastigote form. However, compound **84**, substituted in the 4-position ($R_1 = 4\text{-}Br/R_2 = CH_3$), was more effective against the axenic amastigote form.

A series of 3-nitro-1*H*-1,2,4-triazole-based amides and sulfonamides **88–90** (Fig. 10) were characterized for their in vitro antileishmanial and antitrypanosomal activities (Papadopoulou et al. 2012). Three nitrotriazole amides displayed mild activity against *L. donovani* axenic form with IC_{50} values of 4.68–5.91 µM. Nitrotriazole sulfonamides **88–90** showed IC_{50} values of 7.54, 7.79, and 7.80, respectively, with slightly less activity than amides.

Miscellaneous

Chalcone derivatives

Sulfonamide 4-methoxychalcones **91–99** (Fig. 11) demonstrated inhibition against *L. braziliensis* with IC_{50} values of 3.5–69.0 µM (Andrighetti-Fröhner et al. 2009; Souza et al. 2009). Although the compounds showed lower activity than amphotericin B, they were more active than pentamidine drug. Only, with The addition of an aniline substituent group on the sulfonamide group, compound **99**, showed a decrease in the inhibitory activity on the growth of *L. braziliensis* promastigote forms ($IC_{50} = 69$ µM) compared to 4-methoxychalcone **100**. All of the other substitutions at

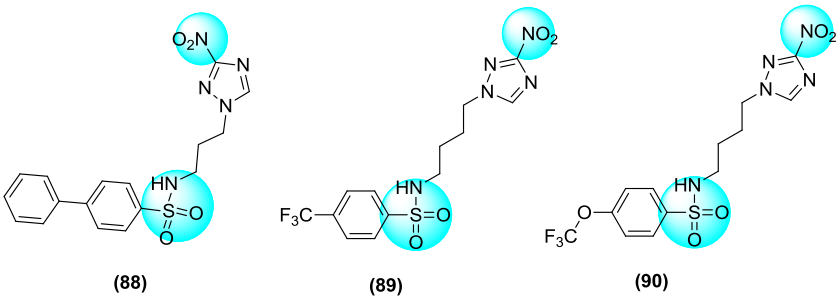

Fig. 10 Structures of triazoles **88–90**

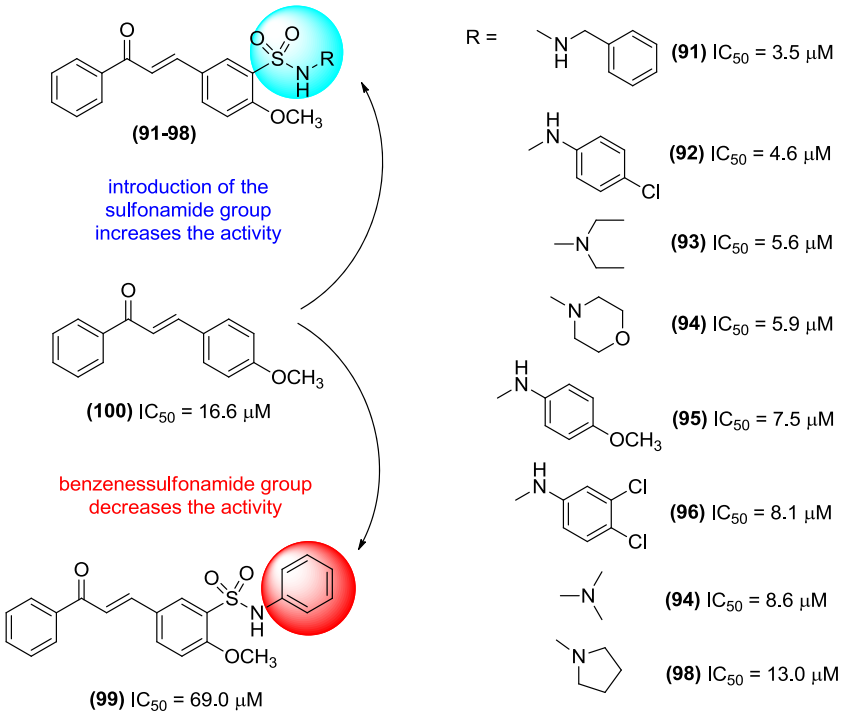

Fig. 11 Structures of chalcones **91–100**

the sulfonamide moiety maintained the antileishmanial profile, suggesting the feasibility of new interactions in these positions. Compound **92** with a benzylamino substituent on the sulfonamide showed the best activity ($IC_{50} = 3.5$ μM).

When tested against *L. amazonensis*, compounds **92**, **95**, and **96** with 4-Cl, 4-OCH_3, and 3,4-diCl substituents, respectively, were the most active, with IC_{50} values of 4.3, 5.5, and 5.6 μM, respectively. Compound **92** with the 4-Cl substituent showed a more potent profile against the amastigote form of *L. amazonensis* ($IC_{50} = 2.0$ μM).

Chloralin derivatives

Trifluralin **(101)**, a commercial herbicide, and its industrial precursor chloralin **(102)** (Fig. 12), was effective against *Leishmania* (Chan et al. 1995). Both compounds present the potential for carcinogenicity due to the presence of a nitro group. Therefore, to discover other compounds that retains the activity of chloralin without its corresponding toxicity, 11 chloralin analogs (**103–113**) were synthesized (Fig. 12) that have a sulfonamide group in place of the nitro group. The evaluation in vitro against amastigote *L. donovani* parasites indicates that the chlorinated derivatives was more potent than the fluorinated derivatives, with only one exception, analog **113**, with an IC_{50} of 199 μM.

The analogs that incorporated a sulfonamide nitrogen into a 5–7 membered heterocyclic ring had good activity, with IC_{50} values in the 44–418 μM range. Halogenated derivative 2-pyridylpiperazyl **104** showed the lowest IC_{50} value of 44 μM, while its fluorinated analog was inactive. Dipyrrolidine analog **103** showed the greatest potency against *L. donovani* parasites with $IC_{50} = 23$ μM. The introduction of amino, methylamino, and diethylenediamine groups made the compounds inactive (Pitzer et al. 1998).

Oryzalin **(114)** (Fig. 13), which contains a sulfonamide group in the place of the trifluoromethyl functionality present in trifluralin **(101)**, was used as a lead compound to

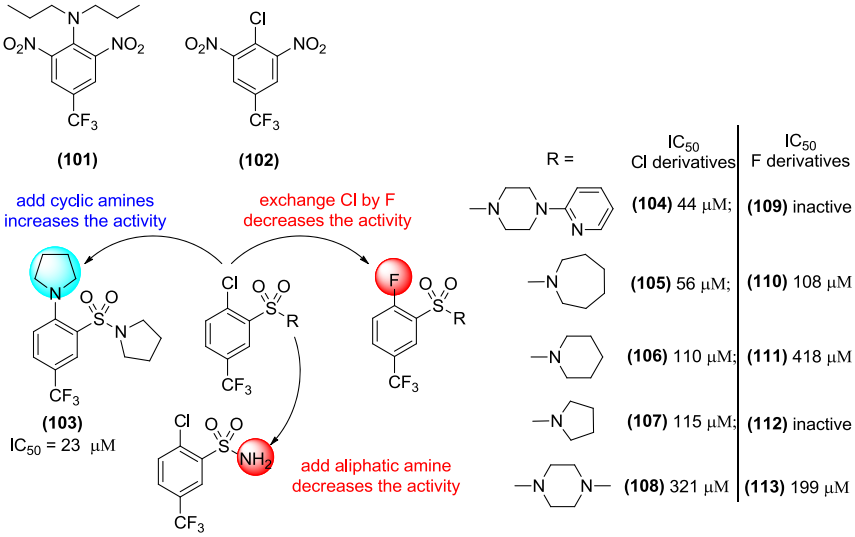

Fig. 12 Structures of trifluralin and derivatives **101–113**

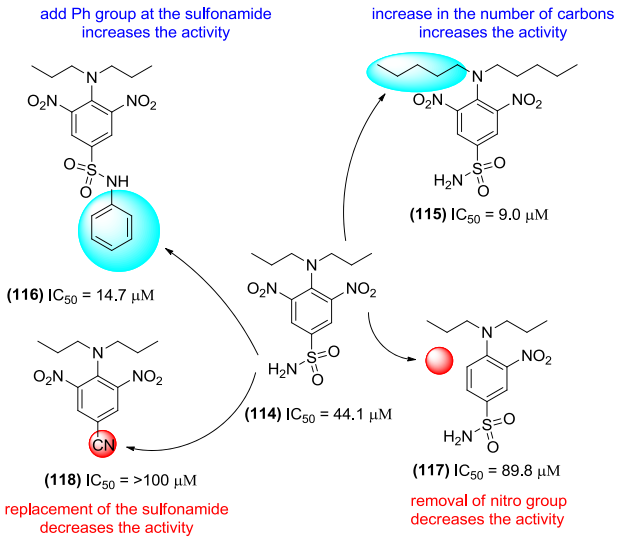

Fig. 13 Structures of oryzalin and derivatives **114–118**

prepare a series of ten analogs, **115–121**. This series was tested against the growth of *L. donovani* parasites. Oryzalin showed moderate antiparasitic activity against promastigotes and amastigotes, with IC_{50} values of 44.1 and 72.5 μM, respectively.

An increase in the number of carbons in the dialkylamine group, such as in compound **115**, led to greater activity against *L. donovani* compared with **114**, as **115** showed 5.5-fold greater activity against promastigotes with $IC_{50} =$ 8.0 μM and 8.1-fold greater activity against amastigotes with $IC_{50} = 9.0$ μM. The analogs with a monopropylamino group ($IC_{50} = 67.0$ μM) and a diethylamino group ($IC_{50} = 69.3$ μM) were less potent against promastigotes. Cyclic amines such as morpholino and pyrrolidino showed decreased activity against promastigotes ($IC_{50} > 100$ and 97.1 μM, respectively).

Compound **116**, substituted with a benzenesulfonamide group, was threefold more active than oryzalin against promastigotes with an IC_{50} value of 14.7 μM and was 13.4-fold more potent against amastigotes with an IC_{50} of 5.41 μM. Removal of one nitro group, as in **117**, decreased the potency against promastigotes ($IC_{50} = 89.8$ μM) and lost activity against amastigotes. Replacement of the sulfonamide group with a cyano group, amide, or amidoxime group as in **118** render these derivatives inactive against amastigotes (Bhattacharya et al. 2002).

Lead compound **116** was used for the synthesis of other derivatives, **119–126** (Fig. 14), possessing variations in the oryzalin sulfonamide, although it has already been shown that modifications at the *N*4 position can enhance the antiparasitic activity (Bhattacharya et al. 2004).

As previously mentioned, an increase in the carbonic chain in the dialkylamine group increases the activity, and compound **119** with an *N*-(dibutylamino) group had the lowest IC_{50} of the series (2.6 μM).

Meta-substituted compounds **120–122** were more potent against the amastigote form of *L. donovani* than those molecules containing a *para*-substituent (**123–125**).

The 3,5-diCl-substituted compound **126** had the strongest antileishmanial activity ($IC_{50} = 3.7$ μM), being more potent than the 3-Cl **120** ($IC_{50} = 5.5$ μM) and the unsubstituted **114**.

1-Napthalene Sulfonamides **(127–131)** were evaluated for inhibitory effects against *Leishmania tarentolae* promastigotes in culture (Katinas et al. 2017).

Sulfonamides *N*-(2′-methylphenyl)-1-napthalene sulfonamide **(129)** at 100 μM and *N*-(4′-carboxy-2′-methylphenyl)-1-naphthalene sulfonamide **(130)** inhibited *Leishmania* viability in vitro 70–96%, but likely by different mechanisms Fig. 15.

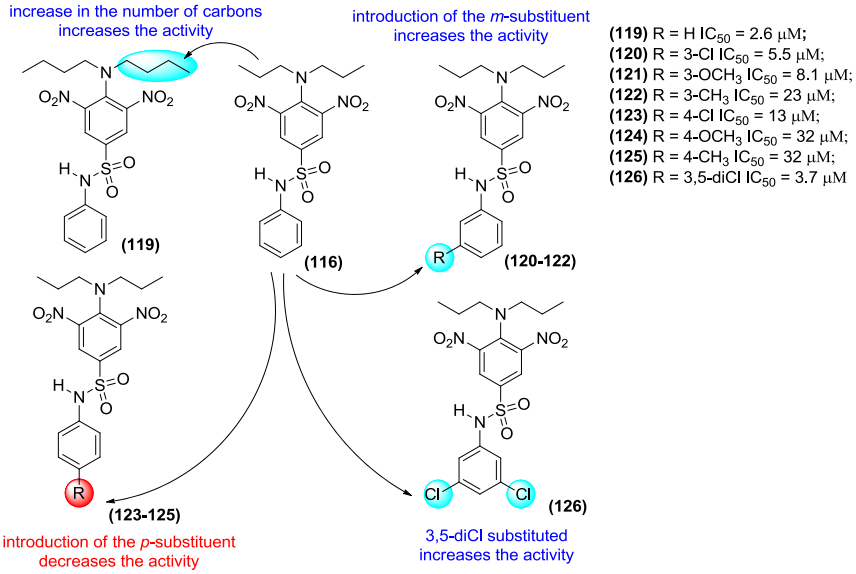

Fig. 14 Structures of oryzalin derivatives **119–126**

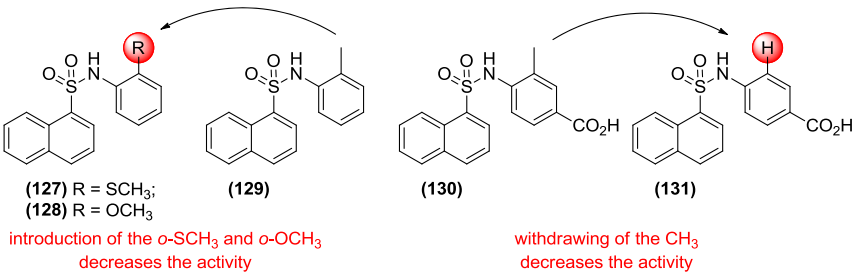

Fig. 15 Structures of 1-napthalene sulfonamides derivatives **127–131**

The methyl group proved to be important for inhibition making compound **129** more potent than **127** and **128**, as well as **130** was more potent than **131**.

The carboxyl group at 4-position proved to be important role in at least one inhibition mechanism.

Conclusions

Here, we presented various synthetic compounds with a sulfonamide group that have been tested against *Leishmania spp*. The sulfonamide functional group has been associated with leishmanicidal activity and could be considered a possible pharmacophore group that can be incorporated into the structure of lead compounds to enhance the activity against *Leishmania* and contribute to the search and development of new drugs and alternative treatments that could cure this disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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