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ORIGINAL ARTICLE

Inhibition of growth of *Leishmania donovani* promastigotes by newly synthesized 1,3,4-thiadiazole analogs

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KEYWORDS

Thiadiazoles;
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Abstract *Leishmania donovani*, the causative agent of visceral leishmaniasis, is transmitted by sand flies and replicates intracellularly in their mammalian host cells. The emergence of drug-resistant strains has hampered efforts to control the spread of the disease worldwide. Forty-four 1,3,4-thiadiazole derivatives and related compounds were tested *in vitro* for possible anti-leishmanial activity against the promastigotes of *L. donovani*. Micromolar concentrations of these agents were used to study the inhibition of multiplication of *L. donovani* promastigotes. Seven compounds were identified with potential antigrowth agents of the parasite. Compound **4a** was the most active at 50 μM followed by compound **3a**. These compounds could prove useful as a future alternative for the control of visceral leishmaniasis.

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1. Introduction

Leishmania parasites have a life cycle that includes an extracellular flagellated promastigote stage, and an obligatory intracellular, non-motile amastigote stage. The promastigotes are transmitted to mammalian hosts through the bite of sand flies and are rapidly transformed into non-flagellated amastigotes within mononuclear phagocytes.

Visceral leishmaniasis is one of the three clinical syndromes (visceral, cutaneous, and mucocutaneous leishmaniasis)

produced by *Leishmania* infection. Visceral leishmaniasis is caused by three related species or subspecies (*Leishmania donovani*, *L.d. infantum, L.d. chagasi*), which make up the *L. donovani* complex. These protozoan parasites produce a systemic and life-threatening infection by infecting reticuloendothelial cells and macrophages in all organs. More than 90% of visceral leishmaniasis cases occur in Bangladesh, Brazil, India and Sudan. It is a zoonotic disease using different reservoirs and sand fly vectors in different parts of the world. Infection may be subclinical but clinical disease is fatal if untreated (Lainson and Shaw, 1987; Rioux et al., 1990; Herwaldt, 1999).

Currently, the treatment of choice for visceral leishmaniasis is pentavalent antimonial compounds in the form of sodium stibogluconate and *N*-methylglucamine antimoniate. Cases of visceral leishmaniasis may also be treated by other agents such as pentamidine and paromomycin. Recently, other new potentially powerful drugs such as liposomal amphotericin B have been introduced, and the advantage is that lipsome-encapsulated drugs are more effective and less toxic. Several new compounds also show promising effects (Davis and Kedzierski, 2005; Singh and Sivakumar, 2004; Berman, 2005; Santos et al., 2008).

Within the last decade, the incidence of *Leishmania* infection has increased significantly due mainly to the high cost of drugs and emergence of immunosuppressive illnesses like AIDS (Paredes et al., 2003; Wolday et al., 1999; Pratlong et al., 2003). Drug resistance has been a major problem with about 25% of strains becoming resistant to antimonial treatment (Abdo et al., 2003; Faraut-Gambarelli et al., 1997; Henderson et al., 1992; Arevalo et al., 2001). These facts highlight the urgent need to develop new and more effective drugs to combat visceral leishmaniasis.

In our previous report (Al-Qahtani et al., 2005), pyrazoloquinoline derivatives were evaluated as leishmanicidal agents and a few of these compounds showed good potential activity against *L. donovani*. Furthermore, several recent reports have pointed out to the importance of 1,3,4-thiadiazole derivatives as potential treatment against the cutaneous form of leishmaniasis caused by *L. major* (Poorrajab et al., 2008; Behrouzi-Fardmoghadam et al., 2008). In this study, we tested a new family of 1,3,4-thiadiazoles and related compounds for their effect on the growth of *L. donovani* promastigotes. Few compounds showed an inhibitory effect on growth of the parasite.

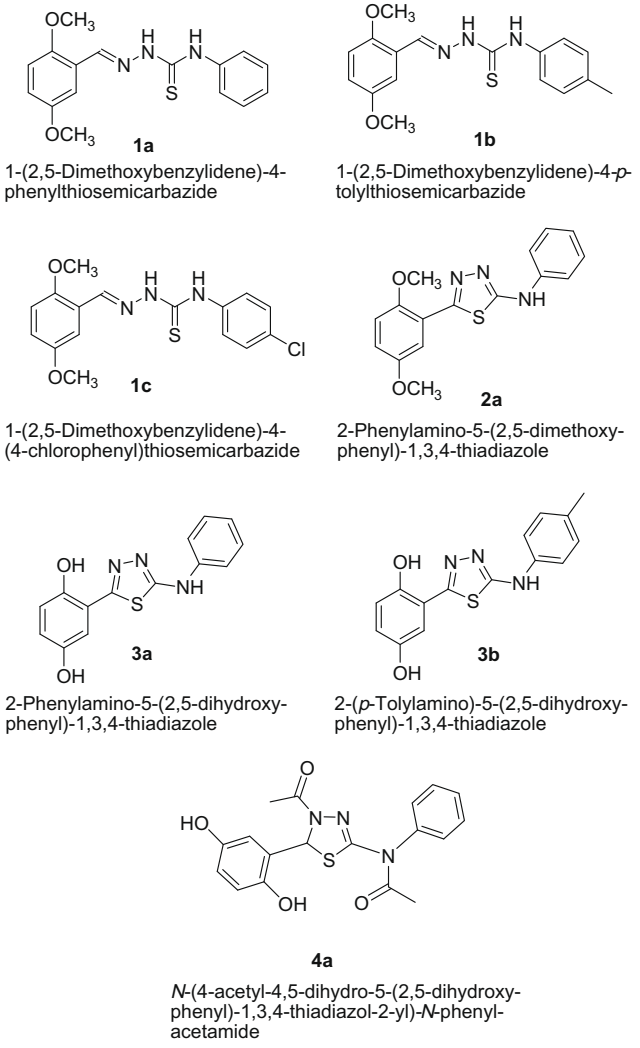

Figure 1 Chemical structures of 1,3,4-thiadiazole derivatives and related compounds which showed activity against *L. donovani*.

2. Materials and methods

2.1. Compounds

Forty-four 1,3,4-thiadiazole analogs were synthesized according to the method described by Chaaban et al. (2007). Seven of these compounds were found to possess antileishmanial activity. The chemical structures of these seven compounds are presented in Fig. 1.

2.2. Parasites

Leishmania donovani strain DD8 was a kind gift from Dr. May Al-Jaser, Zoology Department, College of Science, King Saud University, Riyadh, Saudi Arabia. The parasites were cultured in Medium 199 (Invitrogen, Bethesda, MD, USA) supplemented with 10% fetal bovine serum and penicillin and streptomycin added at a concentration of 100 IU/ml and 100 μg/ml, respectively. All incubations were carried on at 26 °C. Stock solutions of these compounds were made in dimethyl sulfoxide (DMSO) (Merck, Germany) and stored in the dark at −20 °C.

2.3. Assay for antileishmanial activity

After 5 days of incubation, the promastigote culture was centrifuged at 2000*g* for 10 min at room temperature. The pellet was suspended in Schneider's insect medium (Sigma Chemical Company, St. Louis, MO, USA) supplemented with 10% fetal bovine serum. The number of promastigotes was adjusted to 1×10^7 cell/ml. Ninety-six well plates (Nunc, Denmark) were inoculated with 50 μl/well of the parasite culture. Stock solutions of 1,3,4-thiadiazole compounds were dissolved in Scheineder's medium and 50 μl of different concentrations were added to the culture in triplicate. Maximum concentration of DMSO in promastigote cultures (with or without the thiadiazole derivates) did not exceed 0.4%, which is within a safe limit for the parasites. After 2 days of incubation, wells in 96-well plates were examined microscopically for the motility of prom-

astigotes. Growth of the para-sites was monitored using tetrazolium (MTS) colorimetric assay purchased from Promega, Madison WI, USA (Cory et al., 1991). Plates were incubated at 37 °C for 4–5 h and the absorbance was read at 490 nm wavelength according to manufacturer's instructions. Amphotericin B at a concentration of 50 μM was used in the test protocol as a control.

2.4. Statistical analysis

Absorbance values from the test and control wells were analyzed using two-sample *t*-test. All *p*-values $\leqslant 0.005$ were considered significant.

3. Results and discussion

Forty-four new 1,3,4-thiadiazole analogs were tested for their antileishmanial activity. These compounds were previously tested for their antimicrobial activity (unpublished results). Out of the forty-four compounds tested, only seven showed strong antileishmanial activity and their antiproliferative effects were comparable, at equimolar concentration, to that of the positive control, e.g. amphotericin B, a potent antileishmanial agent (Table 1).

Compounds **1a**, **2a**, **3a**, **3b** and **4a** showed very promising antileishmanial effects, even at concentrations as low as 50 μM. Compound **4a** was the most active at low concentration (50 μM). However, at higher concentrations, compound **3a** showed the strongest activity against the growth of the parasite. Compounds **1a**, **2a** and **3b** were also effective, especially at higher concentrations (i.e., 200 μM and 400 μM). Two compounds **1b** and **1c** also affected growth of the parasites at (400 μM) but at 50 μM, they were completely ineffective. The microscopic observation revealed that promastigotes were non-motile when incubated with the test compounds while the controls (with no compound) were actively motile.

Some 1,3,4-thiadiazole derivatives have received recognition because they have been shown to possess potential antimicrobial and antiviral agents (Gadad et al., 2000; Kristanida et al., 2002; Invidiata et al., 1996). A few of these compounds have been described to be very potent in inhibiting reverse transcriptase in HIV-1 (Hanasaki et al., 1995).

It is evident that there is a growing interest in 1,3,4-thiadiazole derivatives as potential antileishmanial compounds. Foroumadi et al. showed that thiadiazole derivatives have leishmanicidal activity against *L. major* (Foroumadi et al., 2005a,b). Also, da Silva et al. tested a group of similar compounds against *L. amazonensis* and observed effective killing of the parasites (da Silva et al., 2002). The effect observed could be related to modulation and/or inhibition of G protein-coupled receptors in the parasite as it has been shown that some thiadiazole analogs are strong modulators of such cell molecules (Fawzi et al., 2001). *Leishmania* was shown to possess G protein-coupled receptors similar to those found in mammalian cells (Cassel et al., 1991; Fu et al., 1998). One possible explanation for the inhibitory effect of these compounds on the parasite may be attributed to their interference with the redox potential in the cells (Li et al., 2003). There are several similar available compounds shown to be effective against the growth of *Trypanosoma cruzi* (Maya et al., 2003) and *T. brucei* (Bouteille et al., 1995). It was suggested these compounds might exert antiproliferative effects through production of nitro radical anions (Bouteille et al., 1995). However, we would like to suggest that there could be other mechanisms by which these thiadiazole analogs work, since compounds described in this study do not have nitro groups. The antileishmanial effect of these compounds could be attributed to the functional groups which are capable of formation of free radicals such as 1,4-dimethoxyphenyl group (i.e., compounds **1a**, **1b**, **1c** and **2a**) or 1,4-dihydroxyphenyl group (i.e. compounds **3a**, **3b**, and **4a**). These compounds could permeate through the cell plasma membrane and damage nucleic acids and/or proteins inside the cell (Enanga et al., 2003). Alternatively, they might damage proteins or other molecules essential for the growth of the parasite located at the extracellular space of the plasma membrane such as adenosine receptors (Hansen et al., 1986; van Muijlwijk-Koezen et al., 2001). Furthermore, 1,3,4-thiadiazole analogs might exert their effect through modification of sulfhydryl groups of cysteine residues in some essential enzymes and other important proteins as they have been shown to be strong sulfhydryl modifying agents (Goblyos et al., 2005).

In conclusion, 1,3,4-thiadiazole derivatives have been shown to possess a promising antileishmanial effect *in vitro*. However, these compounds have to be thoroughly appraised for their acute toxicity and genotoxicity. Furthermore, their effect *in vivo* in experimental animals should be performed to

Table 1 Effect of 1,3,4-thiadiazole analogs and related compounds on growth of *L. donovani* promastigotes.

		400 μM	200 μM	100 μM	50 μM
Control (untreated)	0.859 ± 0.016				
Control (amphotericin B-treated cells)		–	–	–	0.381 ± 0.057
Compound **1a**		0.330 ± 0.020	0.337 ± 0.010	0.430 ± 0.030	0.610 ± 0.070
Compound **1b**		0.290 ± 0.020	0.380 ± 0.002	0.680 ± 0.04	1.060 ± 0.050**
Compound **1c**		0.303 ± 0.003	0.402 ± 0.010	0.690 ± 0.040	1.070 ± .0400**
Compound **2a**		0.324 ± 0.004	0.360 ± 0.006	0.580 ± 0.010	0.630 ± 0.030
Compound **3a**		0.260 ± 0.008	0.270 ± 0.003	0.340 ± 0.010	0.538 ± 0.050
Compound **3b**		0.370 ± 0.014	0.330 ± 0.014	0.590 ± 0.070	0.670 ± 0.080
Compound **4a**		0.449 ± 0.032	0.424 ± 0.031	0.426 ± 0.013	0.495 ± 0.050

Parasites were seeded in complete medium containing indicated concentration of each compound and the viability of cells was estimated using MTS assay. Each number represents the mean and standard deviation of three reading.
All other values are statistically significant compared to the untreated control when calculated at a 95% confidence level. *P*-value $\leqslant 0.005$.
** Not significant.

draw a meaningful conclusion. Both lines of experiments are underway in our laboratory.

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تثبيط نمو الليشمانية الدونوفانية المشيقة بواسطة مضاهيات 1، 3، 4- ثياديازول مشيدة حديثاً

أحمد القحطاني[1]، يوسنس الصديقي[1]، عدنان بخيت[2] ، علا السيد[2]،
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ملخص البحث

تنتقل الليشمانية الدونوفانية، المسببة لداء الليشمانيات الحشوية، بواسطة ذبابة الرمل وتتكاثر داخل خلايا مضيفها من الثدييات. ولقد أعاق ظهور سلالات مقاومة للدواء الجهود المبذولة لمكافحة انتشار المرض في جميع بلدان العالم. وقد تم عمل الاختبار المعملي لأربعة وأربعين مركباً من مشتقات 1،3، 4- ثياديازول ومركبات وثيقة الصلة بها لفاعليتها المضادة لليشمانية المحتملة ضد مشيقات الليشمانية الدونوفانية (مرحلة من دورة حياة الطفيليات). وتم استخدام تراكيز ميكرومولارية من هذه المركبات لدراسة تثبيط تكاثر المشيقات. وتم التعرف على سبعة مركبات لها فاعلية واعدة مضادة لنمو الطفيل. وكان المركب 4a أكثرها فاعلية عند تركيز 50 ميكرومولار تلاه المركب 3a . وربما أثبتت هذه المركبات فائدتها كبدائل مستقبلية لمكافحة داء الليشمانية الحشوية.

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