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RESEARCH ARTICLE

Synthesis and antileishmanial activity of 5-(5-nitroaryl)-2-substituted-thio-1,3,4-thiadiazoles

Eskandar Alipour[1], Saeed Emami[2], Azadeh Yahya-Meymandi[3], Maryam Nakhjiri[3], Farnaz Johari[1], Sussan K. Ardestani[4], Fatemeh Poorrajab[4], Maryam Hosseini[1], Abbas Shafiee[3], and Alireza Foroumadi[5]

[1]Department of Chemistry, Islamic Azad University, Tehran-North Branch, Zafar St, Tehran, Iran, [2]Department of Medicinal Chemistry and Pharmaceutical Sciences Research Centre, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran, [3]Drug Design & Development Research Centre, Tehran University of Medical Sciences, Tehran, Iran, [4]Department of Biochemistry, Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran, and [5]Pharmaceutical Sciences Research Centre, Tehran University of Medical Sciences, Tehran, Iran

Abstract

A series of novel 2-substituted-thio-1,3,4-thiadiazoles bearing a 5-nitroaryl moiety including nitrofuran, nitrothiophene or nitroimidazole at the 5-position and a bulky residue attached to the 2-position of the thiadiazole ring were synthesised as potential antileishmanial agents. The target compounds were evaluated against the promastigote form of *Leishmania major* using the tetrazolium bromide salt (MTT) colorimetric assay. All test compounds exhibited high activity against *L. major* promastigotes with 50% inhibitory concentrations (IC_{50}) ranging from 1.11 to 3.16 μM. The structure-activity relationship study indicated that the *S*-pendant group attached to the 2-position of the thiadiazole ring has a high flexibility for structural alteration therefore retaining good antileishmanial activity.

Keywords: 1,3,4-Thiadiazole, 5-Nitrohetrocycles, leishmania major, leishmaniasis

Introduction

Leishmaniasis is caused by the *Leishmania* parasite which is transmitted to humans by sandflies [1]. The term leishmaniasis comprises three different clinical manifestations: generalised visceral (kala-azar), cutaneous, and mucocutaneous leishmaniasis [2]. While cutaneous leishmaniasis poses essentially cosmetic problems, mucocutaneous leishmaniasis leads to painful disfiguration, social stigmatisation and often severe secondary infections, visceral leishmaniasis is generally lethal if left untreated [3]. It is estimated that over 350 million people live at risk of infection [4]. In spite of the socioeconomic importance of this tropical infection, effort directed toward the discovery of new drugs and/or a vaccine against it, are underdeveloped [5,6].

The recommended drugs for treatment of leishmaniasis are the pentavalent antimonials, including sodium stibogluconate (Pentostam®) and meglumine antimoniate (Glucantime®) [3]. These drugs have been used clinically for more than 50 years and are still the first choice drug, for the treatment of leishmania [7]. The development of resistance against the antimonial compounds is of great concern, and poses a major impediment in the successful therapy of the disease [8]. In unresponsive cases, there are some alternative drugs to antimonial compounds such as amphotericine B, pentamidine [9] and in the case of visceral leishmaniasis the only orally adminstered drug is miltefosine [10]. However all these drugs are expensive, potentially toxic and require long term treatment. In addition, the development of drug resistance by the

Address for Correspondence: Alireza Foroumadi, Faculty of Pharmacy and Pharmaceutical Sciences Research Centre, Tehran University of Medical Sciences, Tehran, Iran. Tel: +98 21 66954708 Fax: +98 21 66461178 Email: aforoumadi@yahoo.com

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pathogens especially in an HIV-leishmania co-infection has aggravated the public health risk [11].

Thus the lack of an alternative chemotherapeutic approach to the treatment of leishmania requires urgent attention and a great number of synthetic compounds have been evaluated in recent years in antileishmanial assays [12–14].

In this regard, the use of nitroheterocycle scaffolds such as 5-nitrofurans, 5-nitrothiophenes and 5-nitroimidazoles in the development of anti-parasitic agents has been well established [15,16]. On the other hand, the anti-parasitic property of 1,3,4-thiadiazoles has been well documented and their attachment to other heterocycles often alters the bioactivity, depending upon the type of substituent and the position of the attachment [17,18]. Accordingly, in continuation of our previous papers [10,19] which were mostly devoted to the synthesis of diverse heterocycles with the emphasis on the role of 2,5-disubstituted-1,3,4-thiadiazole derivatives as anti-parasitic drugs, we decided to focus our attention toward the synthesis of new structures of 5-(5-nitroaryl)-2-substitutedthio-1,3,4-thiadiazoles to evaluate their antileishmanial activity against the promastigote form of *Leishmania major*.

Experimental

Chemistry

All the starting materials, reagents and solvents were purchased from Merck (Darmstadt, Germany). As illustrated in Figure 1, the key intermediate compounds, **4a–c** were synthesised according to the general methods previously described by us [20]. The purity of the synthesised compounds was confirmed by thin layer chromatography (TLC) using various solvents of different polarities. Merck silica gel 60 F_{254} plates were used for analytical TLC. The melting points were determined on a Kofler hot stage apparatus (C. Reichert, Vienna, Austria) and were uncorrected. The ^{1}H-NMR spectra were recorded using a Bruker 400 spectrometer (Rheinstatten, Germany), and chemical shifts expressed as δ (ppm) with tetramethylsilane (TMS) as the internal standard. The IR spectra were obtained on a Shimadzu 470 (Shimadzu, Tokyo, Japan) spectrophotometer (potassium bromide disks). The mass spectra were run on a Finigan TSQ-70 spectrometer (Finigan, San Jose, CA, USA) at 70 eV. Elemental analyses were carried out on a CHN-O-rapid elemental analyser (Heraeus, Hanau, Germany) for C, H and N, and the results are within ± 0.4% of the theoretical values.

General procedure for preparation of compounds 5–13

To a mixture of compounds **4a–c** (1 mmol) and KOH (1 mmol) in EtOH, the appropriate 2-bromo-1-(chlorophenyl) ethanone (1 mmol) were added. Then, the reaction mixture was allowed to stir overnight. The reaction was followed by TLC, which was accompanied by a colour change from red to yellow. The solvents were removed under reduced pressure, the residue was washed with water and crystallised from ethanol to give compounds **5–13**.

1-(2-Chlorophenyl)-2-(5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio)ethanone (5)

Yield 79%; mp 188–189°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (m, 1H, H_6 phenyl), 7.96–7.92 (m, 1H, H_3 phenyl), 7.9 (d, 1H, J = 4.4 Hz, H_4 thiophene), 7.64–7.6 (m, 1H, H_4 phenyl), 7.51–7.48 (m, 1H, H_5 phenyl), 7.36 (d, 1H, J = 4.4 Hz, H_3 thiophene), 5 (s, 2H, S-CH_2-CO). IR (KBr, cm^{-1}) ν_{max}: 1699 (C=O), 1517 and 1339 (NO_2). Anal. Calcd for $C_{14}H_8ClN_3O_3S_3$: C, 42.26; H, 2.03; N, 10.56. Found: C, 42.55; H, 2.16; N, 10.23.

1-(2-Chlorophenyl)-2-(5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-ylthio)ethanone (6)

Yield 54%; mp 178–179°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03–7.92 (m, 2H, H_4 and H_6 phenyl), 7.64 (d, 1H, J = 7.2 Hz, H_3 phenyl), 7.56–7.48 (m, 2H, H_5 phenyl and H_4 furan), 7.34 (d, 1H, J = 3.6 Hz, H_3 furan), 5.04 (s, 2H, S-CH_2-CO). IR (KBr, cm^{-1}) ν_{max}: 1705 (C=O), 1506 and 1347 (NO_2). MS (m/z, %): 381 (M^+, 81), 331 (10), 138 (100), 111 (80). Anal. Calcd for $C_{14}H_8ClN_3O_4S_2$: C, 44.04; H, 2.11; N, 11.01. Found: C, 44.22; H, 2.32; N, 10.85.

1-(2-Chlorophenyl)-2-(5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazol-2-ylthio)ethanone (7)

Yield 93%; mp 178–180°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.1 (s, 1H, H imidazole), 8.03 (m, 1H, H_6 phenyl), 7.98–7.92 (m, 1H, H_3 phenyl), 7.66–7.6 (m, 1H, H_5 phenyl), 7.53–7.46 (m, 1H, H_4 phenyl), 5.03 (s, 2H, S-CH_2-CO), 4.53 (s, 3H, N-CH_3). IR (KBr, cm^{-1}) ν_{max}: 1684 (C=O), 1523 and 1338 (NO_2). Anal. Calcd for $C_{14}H_{10}ClN_5O_3S_2$: C, 42.48; H, 2.55; N, 17.69. Found: C, 42.37; H, 2.62; N, 17.72.

1-(3-Chlorophenyl)-2-(5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio)ethanone (8)

Yield 43%; mp 185–187°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (s, 1H, H_2 phenyl), 7.96–7.91 (m, 1H, H_6 phenyl), 7.9 (d, 1H, J = 4.4 Hz, H_4 thiophene), 7.64–7.59 (m, 1H, H_4 phenyl), 7.52–7.46 (m, 1H, H_5 phenyl), 7.35 (d, 1H, J = 4.4 Hz, H_3 thiophene), 5 (s, 2H, S-CH_2-CO). IR (KBr, cm^{-1}) ν_{max}: 1693 (C=O), 1518 and 1344 (NO_2). Anal. Calcd for $C_{14}H_8ClN_3O_3S_3$: C, 42.26; H, 2.03; N, 10.56. Found: C, 42.37; H, 1.94; N, 10.63.

1-(3-Chlorophenyl)-2-(5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-ylthio)ethanone (9)

Yield 84%; mp 177–179°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12–8.08 (m, 1H, H_2 phenyl), 8.04–8 (m, 1H, H_6 phenyl), 7.89 (d, 1H, J = 4 Hz, H_4 furan), 7.8–7.74 (m, 1H, H_5 phenyl), 7.63 (d, 1H, J = 8 Hz, H_4 phenyl), 7.6 (d, 1H, J = 4 Hz, H_3 furan), 5.22 (s, 2H, S-CH_2-CO). IR (KBr, cm^{-1}) ν_{max}: 1698 (C=O), 1503 and 1347 (NO_2). MS (m/z, %): 381 (M^+, 8), 331 (23), 139 (100). Anal. Calcd

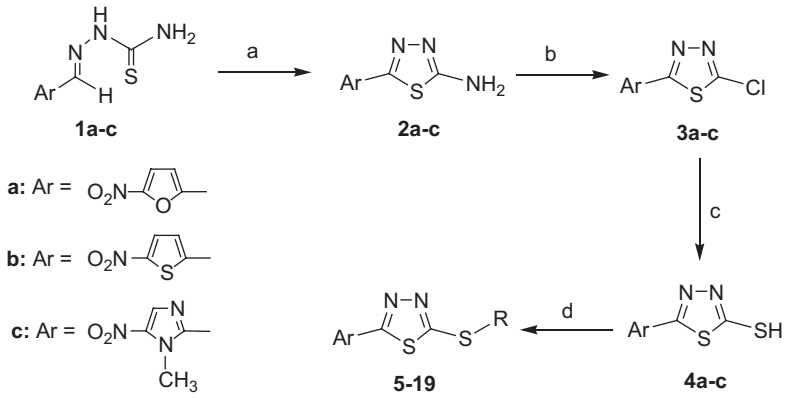


Figure 1. Synthesis of 5-(5-nitroaryl)-2-substituted-1,3,4-thiadiazoles. Reagents and conditions; (a) $NH_4Fe(SO_4)_2$, H_2O, reflux; (b) $NaNO_2$, HCl, Cu; (c) Thiourea, EtOH, reflux, then HCl; (d) R-X, ethanol, KOH, rt.

for $C_{14}H_8ClN_3O_4S_2$: C, 44.04; H, 2.11; N, 11.01. Found: C, 44.15; H, 2.06; N, 10.94.

1-(3-Chlorophenyl)-2-(5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazol-2-ylthio)ethanone (10)

Yield 52%; mp 189–191°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.1 (s, 1H, H imidazole), 8.04 (s, 1H, H_2 phenyl), 7.98–7.92 (m, 1H, H_6 phenyl), 7.66–7.6 (m, 1H, H_4 phenyl), 7.52–7.46 (m, 1H, H_5 phenyl), 5.03 (s, 2H, S-CH_2-CO), 4.53 (s, 3H, N-CH_3). IR (KBr, cm^{-1}) ν_{max}: 1685 (C=O), 1522 and 1344 (NO_2). Anal. Calcd for $C_{14}H_{10}ClN_5O_3S_2$: C, 42.48; H, 2.55; N, 17.69. Found: C, 42.37; H, 2.34; N, 17.82.

1-(4-Chlorophenyl)-2-(5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio)ethanone (11)

Yield 62%; mp 182–184°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8 (d, 2H, J = 8.8 Hz, H_2 and H_6 phenyl), 7.9 (d, 1H, J = 4.4 Hz, H_4 thiophene), 7.51 (d, 2H, J = 8.8 Hz, H_3 and H_5 phenyl), 7.35 (d, 1H, J = 4.4 Hz, H_3 thiophene), 5 (s, 2H, S-CH_2-CO). IR (KBr, cm^{-1}) ν_{max}: 1747 (C=O), 1522 and 1379 (NO_2). Anal. Calcd for $C_{14}H_8ClN_3O_3S_3$: C, 42.26; H, 2.03; N, 10.56. Found: C, 42.13; H, 2.27; N, 10.37.

1-(4-Chlorophenyl)-2-(5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol-2-ylthio)ethanone (12)

Yield 90%; mp 187–189°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, 2H, J = 8.4 Hz, H_2 and H_6 phenyl), 7.58–7.5 (m, 3H, H_4 furan and H_3 and H_5 phenyl), 7.34 (d, 1H, J = 3.6 Hz, H_3 furan), 5.04 (s, 2H, S-CH_2-CO). IR (KBr, cm^{-1}) ν_{max}: 1672 (C=O), 1527 and 1347 (NO_2). MS (m/z, %): 381 (M^+, 3), 138 (100), 110 (27). Anal. Calcd for $C_{14}H_8ClN_3O_4S_2$: C, 44.04; H, 2.11; N, 11.01. Found: C, 43.84; H, 2.33; N, 11.23.

1-(4-Chlorophenyl)-2-(5-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,3,4-thiadiazol-2-ylthio)ethanone (13)

Yield 91%; mp 202–205°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (s, 1H, H imidazole), 8.1 (d, 2H, J = 8.8 Hz, H_2 and H_6 phenyl), 7.67 (d, 2H, J = 8.8 Hz, H_3 and H_5 phenyl), 5.23 (s, 2H, S-CH_2-CO), 4.33 (s, 3H, N-CH_3). IR (KBr, cm^{-1}) ν_{max}: 1674 (C=O), 1588 and 1359 (NO_2). Anal. Calcd for $C_{14}H_{10}ClN_5O_3S_2$: C, 42.48; H, 2.55; N, 17.69. Found: C, 42.16; H, 2.74; N, 17.51.

General procedure for the preparation of compounds 14–19

To a mixture of compounds **4a,b** (1 mmol) and KOH (1 mmol) in EtOH, 3- chloro-1-phenylpropan-1-one or 2-chloro-1-phenylpropan-1-one or (1-chloroethyl) benzene (1 mmol) were added and the reaction mixture was allowed to stir overnight. The progress of the reaction was followed by TLC, which was accompanied by a colour change from red to yellow. The solvents were removed under reduced pressure and the residue was washed with water and crystallised from ethanol to give compounds **14**–**19**.

2-(5-(5-Nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio)-1-phenylpropan-1-one (14)

Yield 68%; mp 158°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (d, 2H, J = 7.6 Hz, H_2 and H_6 phenyl), 7.9 (d, 1H, J = 4.4 Hz, H_4 thiophene), 7.64 (t, 1H, J = 7.6 Hz, H_4 phenyl), 7.52 (t, 2H, J = 7.6 Hz, H_3 and H_5 phenyl), 7.35 (d, 1H, J = 4.4 Hz, H_3 thiophene), 5.9 (q, 1H, J = 7.2 Hz, CHMe), 1.8 (d, 3H, J = 7.2 Hz, CH_3). IR (KBr, cm^{-1}) ν_{max}: 1671 (C=O), 1510 and 1352 (NO_2). Anal. Calcd for $C_{15}H_{11}N_3O_3S_3$: C, 47.73; H, 2.94; N, 11.13. Found: C, 47.55; H, 3.13; N, 10.98.

2-(5-(5-Nitrofuran-2-yl)-1,3,4-thiadiazol-2-ylthio)-1-phenylpropan-1-one (15)

Yield 45%; mp 182–183°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (d, 2H, J = 7.4 Hz, H_2 and H_6 phenyl), 7.45 (d, 1H, J = 3.8 Hz, H_4 furan), 7.39–7.34 (m, 2H, H_3 and H_5 phenyl), 7.33–7.28 (m, 2H, H_4 phenyl and H_3 furan), 5.13 (q, 1H, J = 7 Hz, CHMe), 1.87 (d, 3H, J = 7 Hz, CH_3). IR (KBr, cm^{-1}) ν_{max}: 1685 (C=O), 1530 and 1347 (NO_2). Anal. Calcd for $C_{15}H_{11}N_3O_4S_2$: C, 49.85; H, 3.07; N, 11.63. Found: C, 50.03; H, 3.19; N, 11.87.

3-(5-(5-Nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio)-1-phenylpropan-1-one (16)

Yield 64%; mp 187°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8 (d, 2H, J = 7.6 Hz, H_2 and H_6 phenyl), 7.85 (d, 1H, J = 4.4 Hz,

H_4 thiophene), 7.61 (t, 1H, J = 7.6 Hz, H_4 phenyl), 7.5 (t, 2H, J = 7.6 Hz, H_3 and H_5 phenyl), 7.18 (d, 1H, J = 4.4 Hz, H_3 thiophene), 4.8 (t, 2H, J = 7.2 Hz, S-CH_2), 3.6 (t, 2H, J = 7.2 Hz, CH_2-CO). IR (KBr, cm^{-1}) ν_{max}: 1685 (C=O), 1514 and 1351 (NO_2). Anal. Calcd for $C_{15}H_{11}N_3O_3S_3$: C, 47.73; H, 2.94; N, 11.13. Found: C, 47.51; H, 2.87; N, 11.47.

3-(5-(5-Nitrofuran-2-yl)-1,3,4-thiadiazol-2-ylthio)-1-phenylpropan-1-one (17)

Yield 59%; mp 177°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8 (d, 2H, J = 7.6 Hz, H_2 and H_6 phenyl), 7.61 (t, 1H, J = 7.6 Hz, H_4 phenyl), 7.5 (t, 2H, J = 7.6 Hz, H_3 and H_5 phenyl), 7.41 (d, 1H, J = 4 Hz, H_4 furan), 7 (d, 1H, J = 4 Hz, H_3 furan), 4.82 (t, 2H, J = 7.2 Hz, S-CH_2), 3.65 (t, 2H, J = 7.2 Hz, CH_2-CO). IR (KBr, cm^{-1}) ν_{max}: 1685 (C=O), 1526 and 1324 (NO_2). Anal. Calcd for $C_{15}H_{11}N_3O_4S_2$: C, 49.85; H, 3.07; N, 11.63. Found: C, 49.74; H, 3.15; N, 11.39.

2-(5-Nitrothiophen-2-yl)-5-(1-phenylethylthio)-1,3,4-thiadiazole (18)

Yield 41%; mp 96–97°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, 1H, J = 4 Hz, H_4 thiophene), 7.46 (d, 2H, J = 7.2 Hz, H_2 and H_6 phenyl), 7.4–7.32 (m, 3H, H_3, H_4 and H_5 phenyl), 7.31 (d, 1H, J = 4 Hz, H_3 thiophene), 5.16 (q, 1H, J = 7.2 Hz, SCH), 1.87 (d, 3H, J = 7.2 Hz, CH_3). IR (KBr, cm^{-1}) ν_{max}: 1507 and 1347 (NO_2). Anal. Calcd for $C_{14}H_{11}N_3O_2S_3$: C, 48.12; H, 3.17; N, 12.02. Found: C, 47.82; H, 3.06; N, 12.17.

2-(5-Nitrofuran-2-yl)-5-(1-phenylethylthio)-1,3,4-thiadiazole (19)

Yield 54%; mp 125–126°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (d, 2H, J = 7.8 Hz, H_2 and H_6 phenyl), 7.43 (d, 1H, J = 3.2 Hz, H_4 furan), 7.38–7.33 (m, 2H, H_3 and H_5 phenyl), 7.32–7.28 (m, 2H, H_4 phenyl and H_3 furan), 5.12 (q, 1H, J = 6.8 Hz, SCH), 1.86 (d, 3H, J = 6.8 Hz, CH_3). IR (KBr, cm^{-1}) ν_{max}: 1536 and 1355 (NO_2). Anal. Calcd for $C_{14}H_{11}N_3O_3S_2$: C, 50.44; H, 3.33; N, 12.6. Found: C, 50.71; H, 3.28; N, 12.45.

In vitro antileishmanial activity

The vaccine strain of *L. major* (MRHO/IR/75/ER) was obtained from the Pasteur Institute (Tehran, Iran). The promastigote form of the parasite was grown in blood agar cultures at 25°C. For the experiments described here, the stationary phase of the promastigotes were washed with phosphate buffered saline and then re-cultured in RPMI 1640 medium (Sigma, St Louis, MO, USA) at a density of 2×10^6 cells/mL, supplemented with 10% of heat-inactivated fetal bovine serum, 2 mM glutamine (Sigma), pH ~7.2, 100 U/mL penicillin (Sigma) and 100 μg/mL streptomycin (Sigma). The growth curve of the *L. major* strain was determined daily using a light microscope and counting in a Neubauer's chamber. To determining the 50% inhibitory concentrations (IC_{50}), the tetrazolium bromide salt (MTT) assay was used. Briefly, promastigotes (2×10^6 /mL) from the early log phase of growth were seeded in 96-well plastic cell culture trays, containing serial dilutions of the compounds and phenol red free RPMI 1640 medium, supplemented with 10% of FCS, 2 mM glutamine, pH ~7.2 and antibiotics, in a volume of 200 μL. After 24 h of incubation at 25°C, the media was renewed with 100 μg /well of MTT (0.5 mg/mL) and the plates were further incubated for 4 h at 37°C. The plates were centrifuged (2000 rpm × 5 min) and the pellets were dissolved in 200 μL of DMSO. The samples were read using an ELISA plate reader (Bio-Rad Laboratories, Hercules, CA, USA) at a wavelength of 492 nm. Two or more independent experiments in triplicate were performed to determine the sensitivity to each drug, the IC_{50} were calculated by linear regression analysis, expressed as the mean. Control cells were incubated with culture medium supplemented with DMSO [21].

Results and discussion

Chemistry

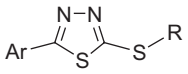
The synthesis of the target compounds **5**–**19** was accomplished through an efficient process as outlined in Figure 1. The starting compounds **1a** and **1b** were obtained from the corresponding 5-nitro-2-arylidene diacetate; whereas the starting compound **1c** was prepared from 1-methyl-5-nitroimidazole-5-carboxaldehyde according to the previously described procedure [22,23]. The oxidative cyclisation of **1a**–**c** in the presence of $NH_4Fe(SO_4)_2$ caused the formation of 2-amino-1,3,4-thiadiazoles **2a**–**c**. The diazotation and the subsequent chlorination of **2a**–**c** in hydrochloric acid in the presence of $NaNO_2$ and copper powder afforded **3a**–**c**, which then reacted with an equivalent amount of thiourea in refluxing EtOH to produce **4a**–**c** [20]. The reaction of compound **4a**–**c** with appropriate phenacyl bromide in stirring KOH/EtOH gave the target compounds **5**–**13**; while the treatment of **4a,b** with 3-chloro-1-phenylpropan-1-one, 2-chloro-1-phenylpropan-1-one or (1-chloroethyl)benzene in stirring KOH/EtOH afforded target compounds **14**–**19**.

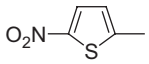
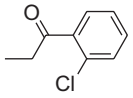
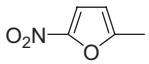
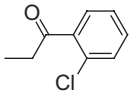
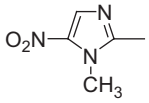
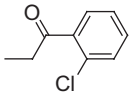
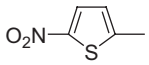
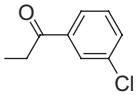
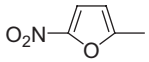
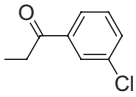
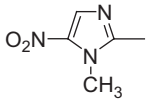
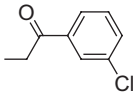
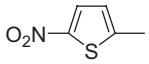
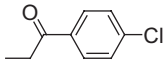
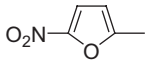
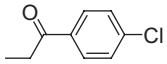
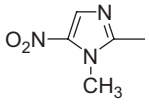
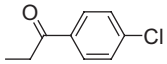
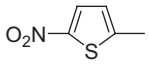
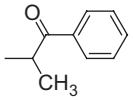
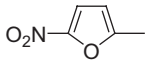
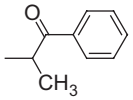
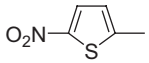
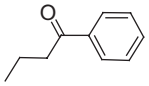
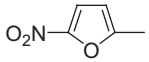
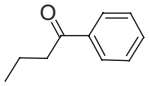
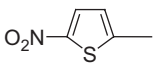
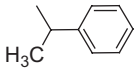
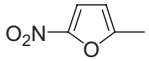
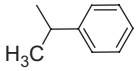
Antileishmanial activity

The antileishmanial activity of all the target compounds **5**–**19** against *Leishmania major* is shown in Table 1. In addition, the activity of the clinically used drug Glucantime® is also shown as a standard drug. The inhibitory concentrations for 50% of inhibition (IC_{50}) of parasitic growth, at the third day of incubation, were calculated based on a linear regression and reported as a mean.

These data indicated that all the compounds exhibited a high activity against *L. major* promastigotes with IC_{50} values ranging from 1.11 to 3.16 μM. For the structure-activity relationship study, the type of nitroheterocyle and pendant bulky group attached to the 1,3,4-thiadiazole ring was varied. The comparison of IC_{50} values for the different nitroaryl derivatives including furan, thiophene, and *N*-methylimidazole revealed that these compounds are close in activity and the differences observed were not very significant. Regio-isomeric chlorine substitution and α-methyl branching of the phenacylthio-pendant group did not improve activity at concentrations less than 1.11 μM. The results for the two α-methyl benzyl derivatives

Table 1. Structures and in vitro activities of compounds **5**–**19** against the promastigote form of *L. major*.



Compound	Ar	R	IC_{50} (μM)[a]
5			1.51
6			1.76
7			3.16
8			2.62
9			1.57
10			1.31
11			1.26
12			1.52
13			1.77
14			1.85
15			1.11
16			2.65
17			2.21
18			2.86
19			1.43

[a]The values represent the mean. The IC_{50} of glucantime was 30 ± 0.19 mg/mL as the standard drug.

(compounds **18** and **19**) and the α-methylphenacyl analogs (compounds **14** and **15**) suggested that the carbonyl group may not be essential for optimum activity. Replacement of the phenacyl group with a propiophenone homologue retained the activity for compounds **16** and **17**.

In conclusion, we have identified a series of 2,5-disubstituted-1,3,4-thiadiazoles bearing a 5-nitroaryl moiety including nitrofuran, nitrothiophene or nitroimidazole at the 5-position and a bulky residue attached to the 2-position of thiadiazole ring as promising antileishmanial agents. The structure-activity relationships for this series indicated that in all type of 5-(5-nitroaryl)-2-thio-1,3,4-thiadiazoles, the *S*-pendant group have a high flexibility with the structural alteration retaining a good antileishmanial activity.

Declaration of interest

The authors have declared no conflict of interest.

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