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Synthesis and Evaluation of the Schistosomicidal and Trypanocidal Properties of Thioxo-Imidazolidines and Thiazolidin-2, 4-Diones

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Authors' contributions

This work was carried out in collaboration between all authors. Authors JFO, ALS, ASAAJ and EFS designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors SAO, IRP and MCAL managed the literature searches. Author VBRS participated in chemical experiments. Authors ACS, AFB and VRAP participated in biological experiments. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Synthesis and evaluation of the schistosomicidal and trypanocidal properties of thioxo-imidazolidines and thiazolidin-2,4-diones.
Study Design: We tested this compounds by way of *in vitro* evaluation against the adult worms of *Schistosoma mansoni* and forms of *Trypanosoma cruzi*.
Place and Duration of Study: Departamento de Antibióticos, Universidade Federal de Pernambuco and Fundação Oswaldo Cruz/PE between January 2013 and March 2014.
Methodology: This study was approved by the Ethics Committee on Animal Use Research authorized by the license number. 38/2012. The thiazolidine (5a-h) and imidazolidine (7a-d) compounds tested for its cytotoxicity to mouse splenocytes. Then the compounds were evaluated against adult worms of *S. mansoni* by performing the activity *in vitro* at doses 5-100 µg/mL. In addition, the derivatives were evaluated against epimastigote and trypomastigote forms of *Trypanosoma cruzi* (1.23-100 µg/mL).
Results: It was found that 7a derivate imidazolidine and 5f thiazolidine caused a high efficiency in terms of the mortality of *S. mansoni* (100%) in the first 24 hours of the experiment. In the trypanocidal activity, the thiazolidine compounds 5f and 5h exhibited satisfactory activity through their high effectiveness against the epimastigote (0.98 and 1.36 µg/mL) and trypomastigote (0.43 and 1.58 µg/mL) forms. Of the imidazolidine compound tested, derivative 7d stood out from the others in terms of its activity against the trypomastigote form, with IC_{50} of 1.26 µg/mL.
Conclusion: The imidazolidine and thiazolidine derivatives tested are potential schistosomicidal and trypanocidal drugs, although more advanced experiments involving in vivo assays are still required.

Keywords: Schistosoma mansoni; Trypanosoma cruzi; chemoteraphy.

1. INTRODUCTION

Schistosomiasis and Chagas disease, whose etiological agents are the flatworm *Schistosoma mansoni* and the protozoon *Trypanosoma cruzi*, respectively, are parasitic diseases considered to be neglected and poses serious public health problems [1,2].

It is estimated that *S. mansoni* affects more than 597 million individuals around the world, especially in Latin America, Africa and Central America, while Chagas disease, according to the Pan American World Organization is known to be endemic, affecting around 10 million individuals and possibly causing roughly 14,000 deaths per year [3].

Schistosomiasis is still treated with praziquantel (PZQ), a pyrazino-isoquinoline derivative, which surpasses other schistosomicidal drugs in terms of effectiveness against all existing species of *Schistosoma*, and also has low toxicity for patients and is inexpensive to produce [4,5].

However, the continuing use of PZQ has raised controversy in various scientific studies of the possible resistance or temporary tolerance of strains of *S. mansoni* to this drug [6-8]. New studies have thus sought to shed light on the mechanism of action PZQ. Furthermore, medicinal chemistry has also been stepping up efforts to find new drugs that act on the various stages in the biological cycle of the parasite, since PZQ is only effective against the adult worms of *S. mansoni* [9].

For Chagas disease, the specific chemotherapy is based on benznidazole (Bzn) and nifurtimox (Nf) [10]. These drugs require prolonged treatment and are effective in the acute phase of parasitic infection, are sometimes poorly tolerated and exhibit limited effect in the chronic phase of the disease, which is the clinical form predominantly found in infected individuals [10,11].

The reasons for problems relating to treatment of *T. cruzi* are unknown, but there is evidence that the factors involved with different methods for evaluating treatment are susceptibility of the strain to the drugs, incomplete administration of treatment, and the immunological profile of the host [12].

New alternative treatments that act more broadly against parasitic infection are thus being developed by synthesizing and characterizing various compounds that are potential schistasomicidal and trypanocidal drugs [13-17].

This has given rise to the emergence of the imidazolidines and thiazolidines, bioisostere compounds which have a wide range of biological properties, such as antitumor [18], anti-inflammatory [19], antimicrobial [20], anti-hypertensive [21], schistosomicidal [22] and trypanocidal [16,17] activity.

As thiazolidines have properties similar to imidazolidines, inhibiting epimastigote growth, there is evidence that these compounds have the capacity to interfere in the biosynthesis of polyamine in the parasite and proteins involved in the production of trypanothione [16,23]. Trypanothione is a molecule responsible for reducing the oxidative stress the host puts on the parasite and is also involved in increasing the virulence of Chagas disease [24].

The mechanism of action of imidazolidines in relation to *S. mansoni* may be related to its action at the level of cholinergic receptors, making it possible to reduce or paralyze the motor activity of the parasite [25]. The thiazolidines, on the other hand, proliferator-activated receptor gamma agonists (PPARγ), are related to the reduction of liver fibrosis in individuals infected with schistosomiasis in the chronic phase [26,27].

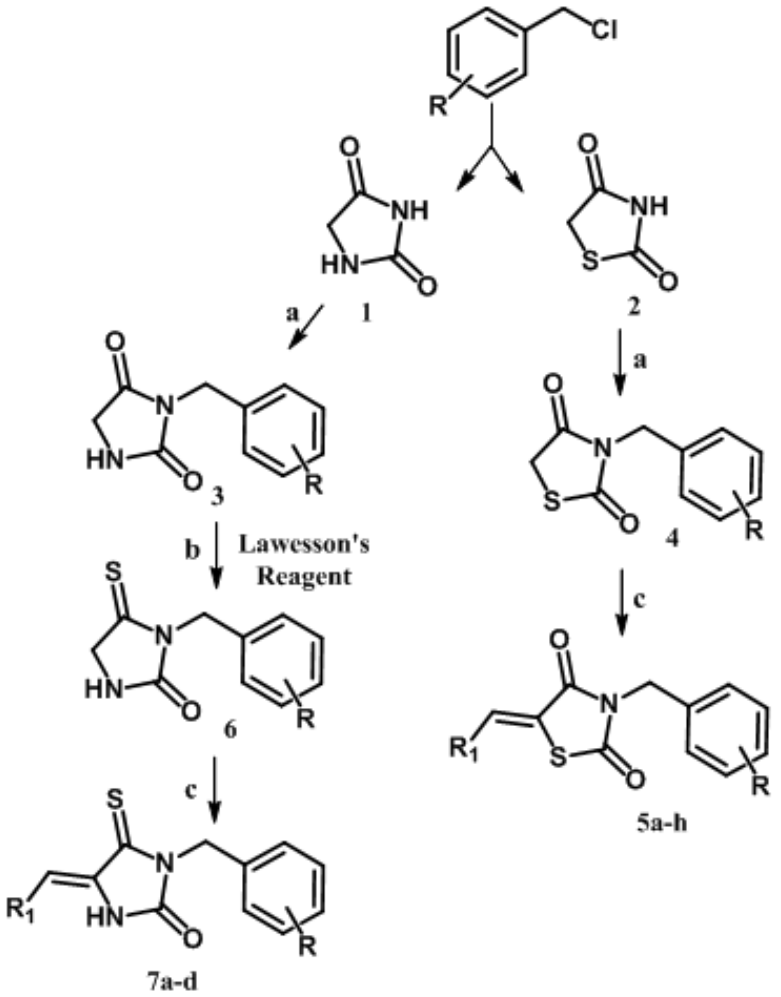
The present study thus aims to investigate the schistosomicidal and trypanocidal activity of duly synthesized and characterized thiazolidine and imidazolidine derivatives by way of cytotoxicity assays with spleen cells, tests with adult *S. mansoni* worms and parasitic forms of *T. cruzi* as a way of obtaining compounds that are candidates for the treatment of both Schistosomiasis and Chagas disease.

2. MATERIALS AND METHODS

2.1 Chemical

The thiazolidine (5a-h) and imidazolidine (7a-d) compounds were obtained from the Chemistry and Treatment Innovation Laboratory (LQIT) of the Federal University of Pernambuco (Brazil) and were duly identified using hydrogen nucleus magnetic resonance and infrared (IR) absorption spectroscopy. Scheme 1 shows the synthetic route for obtaining the compounds of interest. The starting reagents, imidazolidine-2,4-dione (1) and thiazolidine-2,4-dione (2), reacted with substituted benzyl halides under basic conditions to obtain the intermediaries 3-(benzyl)-imidazolidine-2,4-dione (3) and 3-(benzyl)-thiazolidine-2,4-dione (4) [28]. Compound 3 then reacted with Lawesson's reagent in anhydrous dioxane to produce 3-(benzyl)-4-thioxo-imidazolidine-2-one (6). The reaction mixture was heated under reflux for 24 hours [29]. Subsequently, 2-cyano-3-phenyl-acrilates [30], reacted, by way of a Michael type addition, with compounds 4 and 6, giving rise to the final thiazolidine (5a-h) and imidazolidine (7a-d) derivatives.

The reactions were monitored using analytical thin layer chromatography on a 0.25-mm silica gel plate (60F254, Merck, Germany) and viewed under UV light (254 nm). Melting points were determined using a Quimis 340.27 (Quimis, Diadema, SP, Brazil) capillary melting point apparatus and were not corrected. The infrared spectra were registered on KBr pellets using a Bruker IFS-66 IR (Bruker, USA) spectrophotometer. Nuclear magnetic resonance ^{1}H NMR and ^{13}C NMR spectra were registered on a VMMRS 300/75 MHz VARIAN (Varian, USA) spectrophotometer using tetramethylsilane (TMS) as the internal standard and DMSO-d6 as the solvent. Chemical shifts (δ, ppm) were assigned according to the internal standard signal of TMS in DMSO-d6 (δ, ppm). Coupling constants (*J*) are reported in Hz. ^{1}H NMR spectra are reported in the following order: chemical shift, multiplicity, number and type of proton and coupling constant(s). Mass spectra with MALDI-TOF Autoflex III (Bruker Daltonics, Billerica, MA, USA). Laser Nd: YAG, 355 nm. Freq. laser: 100 Hz. Derivatives 5a-h and 7a-d were isolated as single isomers. X-ray crystallographic studies and ^{13}C NMR demonstrated a preference for the *Z* configuration in 5-benzylidene-thiazolidinones [31-35]. The presence of the arylidene proton peak in ^{1}H NMR for the synthesized derivatives confirmed the completion of the nucleophilic addition reaction. The compound was also confirmed by MS data in negative mode. The IR spectrum of the compound showed the characteristic peaks of the carbonyl group and arylidene. Compounds 5a-h and 7a-d, were prepared using equimolar quantities of reagents in the presence of absolute ethyl alcohol (8 mL) as a solvent and morpholine (1 mL) as a catalyst. The reaction mixture was heated to 50°C for 8 hours and then cooled to room temperature. The solid precipitate was filtered under a vacuum and washed with water and absolute ethanol to form the final compounds.



Scheme 1. Synthesis of thiazolidine and imidazolidine derivative candidates for schistosomicidal and trypanocidal drugs. Reagents and conditions: (a) NaOH, absolute ethanol, reflux, 48 hours; (b) Lawesson's reagent, anhydrous 1,4-dioxane, reflux, 24 hours; (c) 2-cyano-3-phenyl-acrylates, absolute ethanol, morpholine, reflux, 8 hours

2.2 Biological Activity

2.2.1 Toxicity to mouse splenocytes

BALB/c mouse splenocytes were placed into a 96-well plate at a cell density of 5 x 10^6 cells/well in RPMI-1640 medium supplemented with 10% of FCS and 50 µg mL^{-1} of gentamycin. Each compound was tested at five concentrations in triplicate. An aliquot of test inhibitor suspended in DMSO was added to each well and to wells only containing solvent (untreated cells). The plate was incubated for 24 h at 37ºC and 5% CO_2. After incubation, [3H]-thymidine was added to each well and the plate was returned to the incubator. The plate was then transferred to a beta-radiation counter and the percentage of [3H]-thymidine was determined. Cell viability was measured as the percentage of [3H]-thymidine incorporation for treated cells in comparison to untreated cells.

2.2.2 Parasites and definitive hosts

Infection of each mouse was performed percutaneously using 100 *S. mansoni* cercariae (Strain LE - Belo Horizonte) from *Biomphalaria glabrata* freshwater snails maintained at Departamento de Malacologia do Centro de Pesquisa Aggeu Magalhães (CPqAM). Fifty albino Swiss mice (*Mus musculus*) (25 days of age) were used. After 60 days, a parasitological

examination of the feces of the mice was conducted to provide a positive identification of infection. For the anti-*Trypanosoma* cruzi activity (epimastigote and trypomastigote) were utilized Dm28c strain. This study was approved by the Animal Ethics Committee of the Centro de Pesquisa Aggeu Magalhães/Fundação Oswaldo Cruz (CPqAM/FIOCRUZ) and authorized by license no. 38/2012.

2.2.3 Anti-*Schistosoma mansoni* activity

Adult *S. mansoni* worms were obtained from mice after 60 days of infection. The animals were intraperitoneally anesthetized with ketamine hydrochloride (115 mg/kg) in combination with xylazine hydrochloride (10 mg/kg). After anesthesia, the animals were subjected to perfusion of the hepatic portal vein to remove the worms, which were then separated on Petri dishes with 0.85% saline, counted and categorized according to the gender and vitality.

The parasites removed from the infected mice were washed with a medium (RPMI-1640 containing 20 mM HEPES pH 7.5, 100 UI/mL penicillin, 100 µg/mL streptomycin and 10% FBS). After washing, the adult worms were transferred to tissue culture plates containing 2 mL of medium. Each well received two worms and all wells were incubated at 37ºC in a 5% CO_2 humidified atmosphere. After a 2-hour period of adaptation to the environment, the imidazolidine and thiazolidine derivatives were added at concentrations of 100 µg/mL, 80 µg/mL, 40 µg/mL, 20 µg/mL, 10 µg/mL and 5 µg/mL. The parasites were kept in culture for 6 days and monitored every 24 hours for evaluation of their motility, mortality and tegumental changes. PZQ was the standard drug for the experiment (positive control). The worms from the negative control group were treated only with dimethyl sulfoxide (DMSO) in an RPMI medium. The motility of the parasites was analyzed and scored according to the criteria proposed by Horiuchi et al. [36]. The scoring system was as follows: 3 - normal body movement; 1.5 - partial body movement; and 0 - dead.

2.2.4 Anti-*Trypanosoma* cruzi activity (epimastigotes)

Epimastigotes (Dm 28 c) in LIT media were counted in a hemocytometer and then seeded 10^6 cells/well in a 96-well plate. Compounds were dissolved in DMSO and then diluted in LIT medium in a serial dilution (1.23,3.70,11.11, 33.33 and 100 mg/mL) and added to respective wells, in triplicate. The final DMSO concentration in the plate was 1%. The plate was incubated for 5 days at 26ºC, aliquots of each well were collected, and the number of viable parasites counted in a Neubauer chamber and compared to the untreated parasite culture. The inhibitory concentration for 50% (IC_{50}) was calculated using nonlinear regression on Prism 4.0 GraphPad software. Benznidazole and nifurtimox were used as the reference drugs.

2.2.5 Anti-*Trypanosoma cruzi* activity (trypomastigotes)

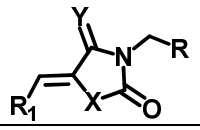
Metacyclic trypomastigotes were collected from the supernatant of infected LLC-MK2 cells and then seeded in 4 x 10^5 cells/well in an RPMI-1640 medium. All compounds were dissolved in DMSO and then serially diluted in RPMI-1640 medium (1.23, 3.70, 11.11, 33.33 and 100 mg/mL) and added to the respective wells, in triplicate. The final DMSO concentration was 1%. The plate was incubated for 24 h at 37ºC and 5% CO_2. Aliquots of each well were collected and the number of viable parasites was counted in a Neubauer chamber. The percentage of inhibition was calculated in relation to untreated cultures. The cytotoxic concentration for 50% (CC_{50}) calculation was also carried out using nonlinear regression on Prism 4.0 GraphPad software. Benznidazole and nifurtimox were used as the reference drugs.

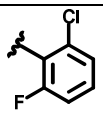
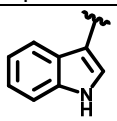
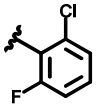
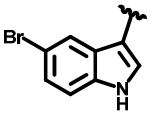
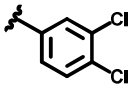
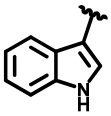
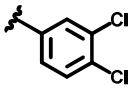
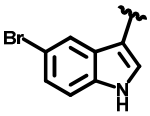
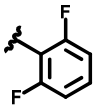
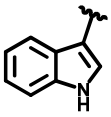
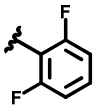
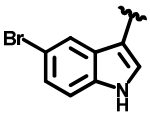
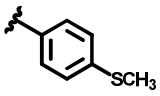
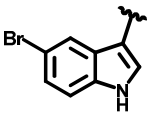
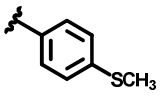
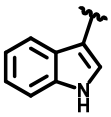
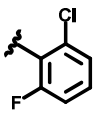
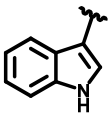
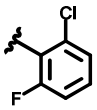
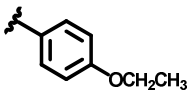
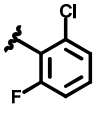
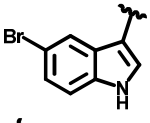
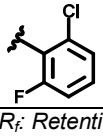
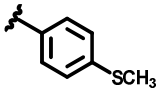
3. RESULTS AND DISCUSSION

3.1 Physicochemical Characterization of Thioxo-Imidazolidines and Thiazolidin-2, 4-Diones Derivatives

The table below shows the physical-chemical characterization of the compounds evaluated in this study (Table 1). You can see that all the compounds showed satisfactory reaction yields demonstrating the effectiveness of the employed synthetic route. Regarding the characterization, the structures were confirmed by methods such as nuclear magnetic resonance (NMR ^1H and ^{13}C) and infrared (IR).

Table 1. Physicochemical characteristics of thiazolidines and imidazolidines derivatives with potential schistosomicidal and trypanocidal activity



Compound	X	Y	R	R_1	M.p.* (ºC)	Yield	R_f**
5a	S	O			239-41	45%	0.68; 6:4
5b	S	O			244-46	51%	0.54; 6:4
5c	S	O			258-60	45%	0.61; 6:4
5d	S	O			280-82	72%	0.55; 6:4
5e	S	O			245-47	56%	0.64; 6:4
5f	S	O			259-61	44%	0.47; 6:4
5g	S	O			180-82	46%	0.5; 6:4
5h	S	O			210-11	40%	0.55; 6:4
7a	NH	S			269	26%	0.52; 1:1
7b	NH	S			217	71%	0.53; 7:3
7c	NH	S			207-08	43%	0.6; 1:1
7d	NH	S			202-03	65%	0.7; 6:4

**M.p.: Melting point; **R_f: Retention factor on eluting system n-hexane/ethyl acetate 6:4*

3.1.1 5-((1*H*-indol-3-yl)methylene)-3-(2-chloro-6-fluorobenzyl) thiazolidine-2, 4-dione (5a)

IR (KBr, cm^{-1}): 1449, 1668, 1726, 3241. NMR ^{1}H 400 MHz (d ppm, DMSO-d_6): 4.96 (s, 2H, CH_2), 7.32 (d, 2H, indole, *J*= 8 Hz), 7.38 (t, 1H, benzyl, *J*= 6.4 Hz), 7.40 (t, 2H, benzyl, *J*= 8 Hz), 7.50 (d, 1H, indole, *J*= 8 Hz), 7.79 (s, 1H, CH), 7.88 (d, 1H, indole, *J*= 8 Hz), 8.16 (s, 1H, CH/indole), 12.19 (s, 1H, NH). NMR ^{13}C (100 MHz, DMSO-d_6): 37.06, 110.40, 112.46, 113.13, 114.72, 118.39, 120.77, 121.20, 123.17, 125.65, 126.01, 126.80, 129.14, 130.62, 134.19, 136.22, 162.71, 164.84, 166.36.

3.1.2 5-((5-bromo-1*H*-indol-3-yl) methylene)-3-(2-chloro-6-fluorobenzyl) thiazolidine-2, 4-dione (5b)

IR (KBr, cm^{-1}): 1601, 1678, 1733, 3296. NMR ^{1}H 400 MHz (d ppm, DMSO-d_6): 4.97 (s, 2H, CH_2), 7.23 (t, 1H, benzyl, *J*= 9.6 Hz), 7.33 (d, 1H, *J*= 8.4, benzyl), 7.34 (s, 1H, indole), 7.39 (m, 1H, indole), 7.45 (d, 1H, *J*= 8.4, benzyl), 7.82 (s, 1H, CH), 8.17 (d, 1H, indole, *J*= 4.4 Hz), 12.30 (s, 1H, NH). NMR ^{13}C (100 MHz, DMSO-d_6): 37.09, 110.09, 113.99, 114.45, 114.68, 120.70, 120.86, 121.18, 125.58, 125.72, 128.63, 130.06, 130.50, 130.59, 134.22, 134.92, 162.69, 164.67, 166.22.

3.1.3 5-((1*H*-indol-3-yl) methylene)-3- (3, 4-dichlorobenzyl) thiazolidine-2, 4-dione (5c)

IR (KBr, cm^{-1}): 1593, 1672, 1729, 3250. NMR ^{1}H 400 MHz (d ppm, DMSO-d_6): 4.83 (s, 2H, CH_2), 7.20 (t, 1H, benzyl, *J*= 8 Hz), 7.26 (t, 1H, benzyl, *J*= 8 Hz), 7.29 (dd, 1H, benzyl, J_1= 8.4 Hz, J_2= 1,6), 7.51 (d, 1H, indole, *J*= 8 Hz), 7.61 (d, 2H, indole, *J*= 8.4 Hz), 7.82 (s, 1H, CH), 7.91(d, 1H, indole, *J*= 8 Hz), 8.22 (s, 1H, indole), 12.21 (s, 1H, NH). NMR ^{13}C (100 MHz, DMSO-d_6): 43.35, 110.43, 112.49, 113.34, 118.43, 121.25, 123.21, 126.37, 126.79, 127.98, 129.32, 129.85, 130.44, 130.88, 131.15, 136.26, 136.88, 165.36, 167.20.

3.1.4 5-((5-bromo-1*H*-indol-3-yl) methylene)-3-(3,4-dichlorobenzyl) thiazolidine-2, 4-dione (5d)

IR (KBr, cm^{-1}): 1603, 1672, 1727, 3399. NMR ^{1}H 400 MHz (d ppm, DMSO-d_6): 4.83 (s, 2H, CH_2), 7.29 (dd, 1H, benzyl, J_1= 8.4 Hz, J_2= 2Hz), 7.35 (dd, 1H, benzyl, J_1= 8.4 Hz, J_2= 1.6 Hz), 7.46 (d, 1H, benzyl, *J*= 8.8 Hz), 7.59 (d, 1H, indole, *J*= 1.2 Hz), 7.61 (s, 1H, indole), 7.84 (s, 1H, CH), 8.18 (d, 1H, indole, *J*= 1.6 Hz), 8.22 (s, 1H, indole), 12.03 (s, 1H, NH). NMR ^{13}C (100 MHz, DMSO-d_6): 43.37, 110.14, 113.93, 114.21, 114.44, 121.21, 125.75, 126.11, 127.98, 128.64, 129.86, 130.26, 130.46, 130.86, 131.15, 135.00, 136.81, 165.24, 167.10.

3.1.5 5-((1*H*-indol-3-yl) methylene)-3- (2, 6-difluorobenzyl) thiazolidine-2, 4-dione (5e)

IR (KBr, cm^{-1}): 1593, 1672, 1729, 3314. NMR ^{1}H 400 MHz (d ppm, DMSO-d_6): 4.91 (s, 2H, CH_2), 7.09 (t, 2H, benzyl, *J*= 8 Hz), 7.19 (t, 1H, indole, *J*= 7.2 Hz), 7.25 (t, 1H, indole, *J*= 7.2 Hz), 7.41 (q, 1H, benzyl, *J*= 8 Hz), 7.51 (d, 1H, indole, *J*= 8 Hz), 7.89 (d, 1H, indole, *J*= 8 Hz), 7.79 (s, 1H, CH), 8.18 (s, 1H, CH/indole), 12.19 (s, 1H, NH). NMR ^{13}C (100 MHz, DMSO-d_6): 33.34, 110.35, 111.10, 111.44, 111.69, 112.39, 113.12, 118.33, 121.14, 123.11, 126.02, 126.74, 129.10, 130.32, 136.18, 159.69, 162.16, 164.71, 166.29.

3.1.6 5-((5-bromo-1*H*-indol-3-yl) methylene)-3-(2,6-difluorobenzyl) thiazolidine-2, 4-dione (5f)

IR (KBr, cm^{-1}): 1598, 1669, 1728, 3297. NMR ^{1}H 400 MHz (d ppm, DMSO-d_6): 4.91 (s, 2H, CH_2), 7.09 (t, 1H, benzyl, *J*= 8.4 Hz), 7.35 (d, 1H, indole, *J*= 8.4 Hz), 7.41 (t, 1H, benzyl, *J*= 8.4 Hz), 7.45 (d, 1H, indole, *J*= 8.4 Hz), 7.81 (s, 1H, CH), 8.15 (s, 1H, indole) 8.18 (s, 1H, indol), 12.30 (s, 1H, NH). NMR ^{13}C (100 MHz, DMSO-d_6): 33.49, 110.06, 110.88, 111.07, 111.25, 111.50, 111.69, 113.85, 114.00, 114.33, 121.15, 125.75, 128.60, 130.34, 134.91, 159.70, 162.17, 164.59, 166.20.

3.1.7 5-((5-bromo-1*H*-indol-3-yl) methylene)-3-(4-(methylthio)benzyl) thiazolidine-2, 4-dione (5g)

IR (KBr, cm^{-1}): 1603, 1659, 1731, 3430. NMR ^{1}H 400 MHz (d ppm, DMSO-d_6): 2.41 (s, 3H, SCH_3); 4.75(s, 2H, CH_2); 7.22 (q, 4H, benzyl, *J*= 8.8 Hz); 7.33 (dd, 1H, indole, J_1= 8.4 Hz, J_2= 1.6 Hz); 7.43 (d, 1H, indole, *J*= 8.4 Hz); 7.81 (s, 1H, CH); 8.16 (d, 1H, indole, *J*= 1.6 Hz); 8.19 (s, 1H, indole); 12.31 (s, 1H, NH). NMR ^{13}C (100 MHz, DMSO-d_6): 14.64, 44.08, 110.13, 113.91, 114.28, 114.39, 121.21, 125.73, 125.92, 126.07, 128.44, 128.62, 130.15, 132.33, 134.95, 137.79, 165.25, 166.96.

3.1.8 5-((1*H*-indol-3-yl) methylene)-3-(4-(methylthio) benzyl) thiazolidine-2, 4-dione (5h)

IR (KBr, cm^{-1}): 1596, 1662, 1729, 3412. NMR ^{1}H 400 MHz (d ppm, DMSO-d_6): 2.43 (s, 3H, SCH_3); 4.77 (s, 2H, CH_2); 7.19 (d, 2H, indole, *J*= 8 Hz); 7.24 (q, 4H, benzyl, *J*= 8 Hz); 7.51 (d, 1H, indole, *J*= 8 Hz); 7.89 (s, 1H, CH); 7.90 (d, 1H, indole, *J*= 7.6 Hz); 8.21 (s, 1H, indole); 12.22 (s, 1H, NH). NMR ^{13}C (100 MHz, DMSO-d_6): 14.64, 44.06, 110.43, 112.46, 113.39, 118.40, 121.21, 123.17, 126.07, 126.18, 126.78, 128.45, 129.20, 132.38, 136.22, 137.78, 165.37, 167.06.

3.1.9 4-((1*H*-indol-3-yl) methylene)-1-(2-chloro-6-fluorobenzyl) -5-thioxoimidazolidin-2-one (7a)

IR (KBr, cm^{-1}): 1525, 1637, 1720, 3445. NMR ^{1}H (400 MHz, DMSO-d_6): 5.06 (s, 2H, CH_2), 7.15-7.22 (m, 2H, benzyl), 7.28-7.32 (m, 1H, benzyl), 7.36 (s, 1H, CH), 7.43-7.47 (m, 1H, indole), 7.58-7.61 (m, 1H, indole), 7.74-7.76 (m, 1H, indole), 8.29 (d, 1H, indole, *J*= 3 Hz), 8.32 (d, 1H, indole, *J*= 2.1 Hz), 10.93 (s, 1H, NH/imidazolidine), 12.14 (s, 1H, NH/indole). NMR ^{13}C (100 MHz, DMSO-d_6): 120.73, 120.83, 122.70, 125.43, 127.14, 127.14, 127.9, 128.46, 129.54, 129.66, 129.94, 133.85, 135.82, 135.92, 152.47, 154.79, 159.89, 162.36, 179.88, 186.09.

3.1.10 1-(2-chloro-6-fluorobenzyl)- 4- (4-ethoxybenzylidene)- 5-thioxoimidazolidin-2-one (7b)

IR (KBr, cm^{-1}): 1510, 1595, 1731, 3227. NMR ^{1}H (300 MHz, DMSO-d_6): 1.33 (t, 3H, CH_3, *J*= 6.6 Hz), 4.09 (q, 2H, OCH_2, *J*= 6.9 Hz), 5.16 (s, 2H, CH_2), 6.94 (1H, s, CH), 6.97 (d, 2H, ArH, *J*= 8.7Hz), 7.15-7.21 (m, 1H, benzyl), 7.29-7.40 (m, 2H, benzyl), 7.66 (d, 2H, ArH, *J*= 9.3 Hz), 11.17 (s, 1H, NH). NMR ^{13}C (75 MHz, DMSO-d_6): 14.53, 63.33, 114.41, 114.72, 114.95, 115.96, 120.45, 120.65, 125.26, 125.56, 130.09, 130.21, 131.46, 132.01, 134.03, 155.27, 159.50, 162.85, 187.97.

3.1.11 4-((5-bromo-1*H*-indol-3-yl) methylene)-1-(2-chloro-6-fluorobenzyl)- 5-thioxo-imidazolidin-2-one (7c)

IR (KBr, cm^{-1}): 1510, 1638, 1721, 3457. NMR ^{1}H (300 MHz, DMSO-d_6): 5.18 (s, 2H, CH_2); 7.18-7.22 (m, 1H, benzyl), 7.29-7.39 (m, 2H, benzyl), 7.37 (d, 1H, ArH, *J*= 8.4 Hz), 7.42 (s, 1H, indole), 7.44 (d, 1H, benzyl, *J*= 8.7 Hz), 7.46 (s, 1H, indole), 7.92 (s, 1H, CH), 10.90 (s, 1H, NH/ imidazolidine), 12.27 (s, 1H, NH/indole). NMR ^{13}C (75 MHz, DMSO-d_6): 108.19, 109.55, 113.90, 114.70, 115.19, 121.00, 121.37, 125.83, 126.03, 129.44, 130.09, 130.49, 130.61, 134.41, 135.19, 155.41, 160.02, 163.33, 186.77.

3.1.12 1-(2-chloro-6-fluorobenzyl) -4 -(4-(methylthio) benzylidene)-5-thioxo-imidazolidin-2-one (7d)

IR (KBr, cm^{-1}): 1588, 1640, 1725, 3207. NMR ^{1}H (400 MHz, DMSO-d_6): 2.50 (s, 3H, SCH_3); 5.15 (s, 2H, CH_2); 6.90 (s, 1H, CH); 7.17 (m, 1H, benzyl); 7.29 (d, 2H, ArH, *J*= 8.4 Hz); 7.32-7.39 (m, 1H, benzyl); 7.62 (d, 2H, ArH, *J*= 8 Hz); 11.23 (s, 1H, NH) NMR ^{13}C (100 MHz, DMSO-d_6): 14.11, 114.24, 114.46, 114.69, 120.43, 120.57, 125.59, 129.17, 130.14, 130.25, 130.42, 132.56, 133.98, 134.03, 140.55, 155.35, 159.96, 162.45, 188.11.

3.2 Effect of New Compounds on Adult *S. mansoni* Survival

The cytoxicity of the thiazolidine (5a-d) (Table 2), (5e-h) (Table 3) and imidazolidine (7a-d) (Table 4) compounds tested were found to be less cytotoxic than praziquantel (<1 µg/mL). Twelve derivatives containing thiazolidine and imidazolidine nuclei were tested for schistosomicidal properties (Table 2 and 3). Throughout the 144 hours of observation, all the adult *S. mansoni* worms incubated in absence of any drug (negative control group) and exhibited the typical wavy and peristaltic movement along the body axis, with occasional adherence to the bottom of the culture plate by the ventral sucker (score=3). Compounds were evaluated at a concentration of 5 to 100 µg/mL every 24 h for a period of 144 h, and the mortality, motility, and egg-laying of worms were observed.

Derivative 7a showed the greatest effectiveness of the imidazolidine compounds tested in terms of mortality (score=0) of parasites (100%) after the sixth hour subsequent to administration (100 µg/mL) and was lethal (score=0) to the worms at other concentrations (5,10,20,40 e 80 µg/mL) within the first 24 hours of observation. All tests with compound 7c showed a low mortality level for *S. mansoni*, reaching only 40% lethality (score=0) at a concentration of 100 µg/mL on the sixth day of observation, while the other concentrations were capable only of reducing the motility of the parasites (score=1.5).

The administration of compounds 7a and 7c acted directly on the normal physiology of the

parasites, which were not capable of laying eggs and were found to be incapable of mating or using their suckers. In vitro tests using 7b and 7d produced no results in terms of mortality, motility and egg-laying in any of the adult *S. mansoni* worms (score=3).

Of the thiazolidine compounds, the 5f derivative caused the death of all the parasites at a dose of 100 µg/mL (score=0) in the first 24 hours of the experiment. This mortality rate remained unchanged at doses of 80 (48 hours), 40 (96 hours) and 20 µg/mL (144 hours) over the days of the evaluation. 5d also killed 100% (score=0) of worms at doses of 100 and 80 µg/mL after 48 hours of evaluation. 5 g achieved the maximum mortality rate (score=0) after 72 hours at the highest dose used in the experiments. The last compound (5b), which has the same substitution profile, achieved 100% mortality only at the highest dose (100 µg/mL) after 120 hours of exposure. The other compounds evaluated (5c, 5e and 5h) could be found only to alter the motility of parasites (score=1.5), except for 5a, which caused 83.33% mortality after 144 hours of observation. Similarly to evidenced with imidazolidine compounds (7a-d), the thiazolidines derivatives (5a-h) were also able to interfere with the egg laying and adherence of the suckers.

By contrast, the worms exposed to the antischistosomal drug of choice, praziquantel (positive control group), exhibited severe muscle contraction with partial movements or remained immobile but alive (score=1.5). This occurred immediately subsequent to praziquantel administration. During the first 24 hours of praziquantel treatment all doses killed 100% of worms (score=0).

3.3 Effect of New Compounds on *T. cruzi* Survival

Compounds 7a-d and 5a-h were evaluated against epimastigotes and trypomastigotes of *T. cruzi*. Antiparasitic activity was determined by counting the parasite number in a Neubauer chamber and calculating the concentration of the test compound resulting in 50% inhibition (IC_{50}, epimastigotes) or 50% cytotoxicity (IC_{50}, trypomastigotes). Benznidazole was used as the reference antiparasitic drug and exhibited an IC_{50} of 12.7 and 1.63 µg/mL against trypomastigotes and epimastigotes, respectively.

Table 2. Cytotocity and percentage of mortality and motility of the adult *S. mansoni* worms from thiazolidines derivatives 5a-5d

Compound	Time	Concentration (µg.mL^{-1})						Cytotoxicity (µg.mL^{-1})
		100	80	40	20	10	5	
		Mortality and motility (%)						
5a	24 h	0	0	0	0	0	0	
	48 h	0	0	0	0	0	0	
	72 h	33.3	0	0	0	0	0	
	96 h	41.6	33.3	0	0	0	0	10
	120 h	50	50	41.6	8.3	0	0	
	144 h	83.3	50	41.6	25	8.3	0	
5b	24 h	8.3	8.3	0	0	0	0	
	48 h	33.3	33.3	16.6	8.3	8.3	0	
	72 h	50	50	41.6	33.3	25	0	
	96 h	50	50	41.6	41.6	25	0	5
	120 h	100	66.7	58.3	58.3	50	16.7	
	144 h	100	83.3	66.7	66.7	50	33.3	
	24 h	0	0	0	0	0	0	
	48 h	0	0	0	0	0	0	
5c	72 h	0	0	0	0	0	0	
	96 h	8.3	0	0	0	0	0	50
	120 h	16.7	16.7	16.7	16.7	0	0	
	144 h	25	25	16.7	16.7	0	0	
	24 h	25	25	8.3	8.3	0	0	
	48 h	100	100	50	8.3	0	0	
5d	72 h	100	100	75	33.3	0	0	5
	96 h	100	100	100	66.7	0	0	
	120 h	100	100	100	83.3	0	0	
	144 h	100	100	100	100	0	0	

As a cut-off, compounds with IC_{50} equivalent to that of benznidazole against trypomastigotes and epimastigotes were considered potent anti-*T. cruzi* compounds. The results are reported in Table 5.

Antiparasitic activity against trypomastigotes and epimastigotes was analyzed. The imidazolidine derivative 7a, with an indole group substitute, was active but less potent than benznidazole. Compound 7b, with an ethoxy group, exhibited a high level of trypanocidal activity against epimastigote forms but produced no results against trypomastigotes. The 7c derivate, which has a bromoindole substitute, exhibited no significant activity in for either of the forms tested. However, 7d (methylsulfanyl), despite not being active against epimastigote forms, was found to be a potent compound anti-*T. cruzi* compound against trypomastigote forms (IC_{50}= 1.26 µg/mL).

The thiazolidine derivate compounds 5a (indole; 2-chloro, 6-fluoro), 5c (indole; 3, 4-dichloro), 5d (bromo-indole; 3, 4-dichloro), 5e (indole; 2,6-difluoro) and 5g (bromo-indole, methylsulfanyl) did not exhibit satisfactory trypanocidal activity against epimastigote and trypomastigote forms, compared to the reference compound benznidazole. However, derivative 5b (bromo-indole; 2-chloro, 6-fluoro) produced a good result, but only against the epimastigote forms, with an IC_{50} of 2.89 µg/mL. Compounds 5f (bromo-indole, 2,6-difluoro) and 5h (indole; methylsulfanyl) exhibited very promising activity a more efficient performance against both epimastigotes and trypomastigotes than benznidazole, with IC_{50} values lower than 12.7 µg/mL (epimastigotes) and 1.63 µg/mL (trypomastigotes).

Imidazolidines and thiazolidines are bioisostere compounds that have been proposed as drugs with a potential to combat Schistosomiasis and Chagas disease. The action of these molecules on the adult *S. mansoni* and *T. cruzi* parasites has been studied and produced promising results [15-17]. Although some studies have been conducted to discover how imidazolidines and thiazolidines act on the mortality, motility and egg-laying ability of parasites, the action mechanism has still not been explained.

Table 3. Cytotocity and percentage of mortality and motility of the adult *S. mansoni* worms from thiazolidines derivatives 5e-5h

Compound	Time	Concentration (µg.mL^{-1})						Cytotoxicity (µg.mL^{-1})
		100	80	40	20	10	5	
		Mortality and motility (%)						
	24 h	8.3	8.3	8.3	0	0	0	
	48 h	8.3	8.3	16.7	0	0	0	
	72 h	16.7	8.3	16.7	0	0	0	>100
5e	96 h	16.7	8.3	25	16.7	0	0	
	120 h	16.7	8.3	25	25	0	0	
	144 h	16.7	25	33.3	33.3	0	0	
	24 h	100	83.3	50	50	0	0	
	48 h	100	100	91.7	58.3	16.7	0	
	72 h	100	100	100	75	25	0	1
5f	96 h	100	100	100	91.7	66.7	0	
	120 h	100	100	100	91.7	75	8.3	
	144 h	100	100	100	100	83.3	8.3	
	24 h	0	0	0	0	0	0	
	48 h	33.3	33.3	16.7	8.3	0	0	
5g	72 h	100	83.3	58.3	16.7	0	0	
	96 h	100	100	91.7	50	0	0	10
	120 h	100	100	100	75	0	0	
	144 h	100	100	100	91.7	0	0	
	24 h	0	0	0	0	0	0	
	48 h	0	0	0	0	0	0	
5d	72 h	0	0	0	0	0	0	10
	96 h	0	0	0	0	0	0	
	120 h	16.7	8.3	0	0	0	0	
	144 h	25	16.7	16.7	0	0	0	

Table 4. Cytotocity and percentage of mortality and motility of the adult *S. mansoni* worms from imidazolidines derivatives 7a-7d

Compound	Time	Concentration (μg.mL^{-1})						Cytotoxicity (μg.mL^{-1})
		100	80	40	20	10	5	
		Mortality and motility (%)						
	24 h	100	100	100	100	100	100	
	48 h	100	100	100	100	100	100	
	72 h	100	100	100	100	100	100	
7a	96 h	100	100	100	100	100	100	5
	120 h	100	100	100	100	100	100	
	144 h	100	100	100	100	100	100	
	24 h	0	0	0	0	0	0	
	48 h	0	0	0	0	0	0	
	72 h	0	0	0	0	0	0	
7b	96 h	0	0	0	0	0	0	25
	120 h	0	0	0	0	0	0	
	144 h	0	0	0	0	0	0	
	24 h	0	10	0	0	0	0	
	48 h	10	10	0	0	0	0	
7c	72 h	10	10	0	0	0	0	
	96 h	10	10	16,6	0	0	0	5
	120 h	30	10	33,3	0	0	0	
	144 h	40	30	33,3	0	0	0	
	24 h	0	0	0	0	0	0	
	48 h	0	0	0	0	0	0	
7d	72 h	0	0	0	0	0	0	
	96 h	0	0	0	0	0	0	25
	120 h	0	0	0	0	0	0	
	144 h	0	0	0	0	0	0	

Table 5. Trypanocidal activity of thiazolidines and imidazolidines compounds against epimastigote and trypomastigotes forms

Compound	Trypanocidal activity IC_{50}^{*} (μg.mL^{-1})	
	Epimastigote (Cepa Dm 28c)	Trypomastigote (Cepa Y)
5a	21.15	7.0
5b	2.89	7.3
5c	27.7	5.0
5d	27.7	5.96
5e	ND**	6.0
5f	0.98	0.43
5g	6.65	ND**
5h	1.36	1.58
7a	25.36	10.11
7b	2.11	21.71
7c	32.59	20.05
7d	27.24	1.26
Benznidazole	12.7	1.63
Nifurtimox	1.64	0.79

*IC_{50}: Represents the concentration required to give 50% inhibition; **ND: means not determined, because the lack of activity in the tested concentrations did not allow us to calculate the IC_{50} values*

However, there is evidence that imidazolidines act on the cholinergic receptors causing flaccid paralysis that leads to the death of *S. mansoni* [25,37,38]. On the other hand, other studies report the activity of imidazolidine derivatives interfering in the biosynthesis of polyamines of *T. cruzi* and affecting their mitochondrial integrity [23,16].

The difference in therapeutic potential observed in the imidazolidine and thiazolidine derivatives tested may result from variation in the radicals present in the chemical structures of each compound. Starting out from an imidazolidine structural skeleton, the following substituents were added indole (7a), ethoxy (7b), bromo-indole (7c), methyl-sulfanyl (7d). In the case of the thiazolidine compounds, the substituents to the molecular skeleton were 5a (indole; 2-chloro, 6-fluoro), 5b (bromo-indole; 2-chloro, 6-fluoro), 5c (indole; 3,4-dichloro), 5d (bromo-indole; 3,4-dichloro), 5e (indole; 2,6-difluoro) 5f (bromo-indole, 2,6-difluoro), 5g (bromo-indole, methyl-sulfanyl) and 5h (indole; methyl-sulfanyl). Of the four imidazolidine derivatives tested *in vitro*, compound 7a exhibited greater schistosomicidal activity, causing a mortality rate of 100% in the first 24 hours. The same occurred with the thiazolidine compound 5f, with indole and the halogens fluorine and bromine on its structure, producing 100% mortality in the first 24 hours of contact with *S. mansoni* parasites.

The indole radical is of great importance in the structure of the molecule, since it possesses a wide range of properties associated with this heterocyclic, such as anti- fungal [39]; anti-inflammatory [40] and anti-tuberculosis activity [41]. The indole radical is also a bioisostere of quinoline, as structure found in trioxaquines and mefloquine, which have schistosomicidal properties, as proved by the high level of mortality of adult *S. mansoni* worms [42-45].

Likewise, it is possible to draw an analogy between mefloquine, trioxaquine and indole on the grounds that the structure of trioxaquines has a chlorine atom and, in mefloquine, a trifluoromethyl radical directly linked to the quinolone nucleus, just as, in the compounds evaluated here that produced the best results, a bromine atom is attached to the indole nucleus. The presence of this electronegative/electron-stripping substituent on the heterocyclic ring significantly changes the results of the present study.

The presence of the indole substituent and halide compounds such as bromine and chlorine can be seen in studies of anti-*T. cruzi* activity against trypomastigote, epimastigote and amastigote forms, with promising results when using imidazolidine compounds NN-52 (3-indole; 4-nitrobenzyl), NN-100 (3-indole; 4-bromobenzyl) and the thiazolidine derivative SF-29 (5-(3,4-dichlorobenzylidene)-3- (4-nitrobenzyl) -thiazolidine-2,4-dione) [16,17]. The incorporation of halogens as substituents makes the derivative more lipophilic and hence less soluble in water [46]. This factor may help to increase the activity of imidazolidine and thiazolidine derivatives with halogenated substituents in their structure, as can be seen in the present study in the case of derivative 5b (bromo-indole; 2-chloro, 6-fluoro) which produced a good outcome against epimastigote forms, as was also the case in assays with the 5f (bromo-indole, 2,6-difluoro) and 5h (indole; methyl-sulfanyl) compounds, which proved to be promising in terms of high effectiveness against epimastigote and trypomastigote forms, being more active than benznidazole.

Benznidazole is the trypanocidal drug currently used as the main treatment of Chagas disease, as praziquantel is for Schistosomiasis. However, these drugs have a limited chemotherapeutical effect, in so far as benznidazole is effective only during the acute phase of infection and has various side-effects and praziquantel is only active against the adult forms of *S. mansoni*, having no effect on immature forms, in addition to the fact that there a possible cases of resistant strains around the world [6,10,11].

There is therefore a need to search for new broad-spectrum schistosomicidal and trypanocidal drugs. The promising results obtained in the present study suggest that imidazolidines and thiazolidines are strong candidates for use as drugs against these parasites that pose a great risk to public health. However, there is still a need for further in vivo and more in-depth studies of their mechanism of action.

4. CONCLUSION

The imidazolines and thiazolidines compounds evaluated in this study highlight schistosomicidal and trypanocides activities satisfactory. The compounds 7a imidazolidine and 5f thiazolidine caused a high efficiency in terms of the mortality of *S. mansoni* (100%) in the first 24 hours of the experiment. In the trypanocidal activity, the thiazolidine compounds 5f and 5h exhibited satisfactory activity through their high effectiveness against the epimastigote (0.98 and 1.36 µg/ml) and trypomastigote (0.43 and 1.58 µg/ml) forms. Of the imidazolidine compound tested, derivative 7d stood out from the others in terms of its activity against the trypomastigote form, with ic_{50} of 1.26 µg/ml. Thereby, the results

of this study lead to the conclusion that the imidazolidine and thiazolidine derivatives tested are potential schistosomicidal and trypanocidal drugs, although more advanced experiments involving *in vivo* assays are still required.

CONSENT

The present study did not involve patients.

ETHICAL APPROVAL

This project was approved by the Animal Ethics Committee from Centro de Pesquisa Aggeu Magalhães/ Fundação Oswaldo Cruz (CPqAM/ FIOCRUZ) and authorized by the license no. 21/2011.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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