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EVALUATION OF THE TRYPANOCIDAL POTENTIAL OF THIOSEMICARBAZONE DERIVATIVES: A REVIEW

AVALIAÇÃO DO POTENCIAL TRIPANOCIDA DE DERIVADOS TIOSSEMICARBAZONAS: UMA REVISÃO

EVALUACIÓN DEL POTENCIAL TRIPANOCIDA DE LOS DERIVADOS DE LA TIOSEMICARBAZONA: UNA REVISIÓN

Daniel Lopes Araújo[1], José Eufrazino Junior[2], Vinicius Santos Silva[3], Carla Franco Mendonça de Araújo[4], Thaynara Hevellin Evangelista[5], Hilary Hevellin Evangelista[6], Geovana Maciel Lima[7], Ana Karoline Maciel Lima[8], Willian Moreira[9], Antônio Antunes Neto[10], Neusa Loise Nunes Albuquerque[11], Graziele Ferreira Nunes[12], Josué Brito Gondim[13], Emanuel Osvaldo de Sousa[14], Bruno Abilio da Silva Machado[15]

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ABSTRACT
Neglected diseases are a group of communicable diseases that mainly affect tropical regions in developing countries. Among this group of diseases is Chagas disease, which has been classified among the six most important parasitic diseases in the world, and it is estimated that more than one billion people are at risk in countries that are considered endemic. The aim of this study is to conduct a literature review on the trypanocidal activity of thiosemicarbazone derivatives. The study is a review research that used 31 articles to highlight the scientific findings on the trypanocidal activity of the derivatives in question. Articles were included in the time estimate between 2010 - 2021 (last 12 years). The search and selection of the reference studies was performed in Scielo, Science Direct, PubMed and Google Academic databases. The literature highlights that thiosemicarbazones are considered privileged compounds with a wide scientific interest due to their diverse chemical and biological properties, such as: antitumor, antibacterial, antiviral, antiprotozoal, and anti-chagasic. The studies presented here, which demonstrate the investigations of compounds of this class and their derivatives, are an important step towards the conception of therapeutic methods against *Trypanosoma cruzi*. New studies are necessary to elucidate in an even more specific way the effects of these derivatives *in vivo*, in order to obtain an alternative pharmacological therapy for Chagas disease.

KEYWORDS: Drug synthesis. Trypanocidal activity. *Trypanosoma cruzi.* Thiosemicarbazones

[1] Universidade Federal de Pernambuco
[2] Cristo Faculdade do Piauí
[3] Centro Universitário de Patos
[4] Centro Universitário Alfredo Nasser
[5] Universidade de Rio Verde Campus Aparecida de Goiânia - UNIRV
[6] Universidade de Rio Verde Campus Aparecida de Goiânia - UNIRV
[7] Universidade de Gurupi - UNIRG
[8] Universidade de Gurupi - UNIRG
[9] Univille Universidade
[10] Universidade do Estado do Amazonas
[11] Universidade Federal de Alagoas
[12] Faculdade Pitágoras São Luís
[13] Instituto Michelle Sales
[14] Graduado em Fisioterapia pelo Centro Universitário UniFacid/Wyden, Pós-graduado em Fisioterapia Traumato-ortopédica pela Universidade Estadual do Piauí - UESPI e Docência do Ensino Superior pela Faculdade Adelmar Rosado - FAR
[15] Graduado em Radiologia pelo Centro Universitário Mauricio de Nassau Teresina- UNINASSAU, Pós-graduado em Docência no Ensino Superior pela Faculdade Elesbão Veloso- FAEVE e MBA em Liderança, Inovação e Gestão pela Faculdade Venda Nova do Imigrante

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RESUMO
As doenças negligenciadas são um conjunto de doenças transmissíveis que afetam principalmente regiões tropicais de países que estão em processo de desenvolvimento. Dentre esse conjunto de doenças se destaca a doença de Chagas, que foi classificada entre as seis doenças parasitárias mais importantes do mundo, e estima-se que mais de um bilhão de pessoas estão em risco em países que são considerados endêmicos. O objetivo deste estudo é de realizar uma revisão de literatura sobre a atividade tripanocida de derivados tiossemicarbazonas. O estudo trata-se de uma pesquisa de revisão que utilizou 31 artigos para evidenciar os achados científicos sobre a atividade tripanocida dos derivados em questão. Foram incluídos artigos na estimativa de tempo entre 2010 – 2021 (últimos 12 anos). A pesquisa e seleção dos estudos de referência foi realizada nas bases de dados Scielo, Science Direct, PubMed e Google Acadêmico. A literatura evidencia que as tiossemicarbazonas são compostos considerados privilegiados e com um amplo interesse científico devido a suas diversas propriedades químicas e biológicas, como por exemplo: antitumoral, antibacteriana, antiviral, antiprotozoária e anti-chagásiga. Os estudos aqui apresentados, que demonstram as investigações dos compostos dessa classe e seus derivados, desempenham um importante passo para a concepção de métodos terapêuticos frente ao *Trypanosoma cruzi.* Novos estudos são necessários para que seja elucidado de uma forma ainda mais específica os efeitos desses derivados in vivo, no intuito de se obter uma terapia farmacológica alternativa para a doença de Chagas**.**

PALAVRAS-CHAVE: Síntese de fármacos. Atividade tripanocida. *Trypanosoma cruzi.* Tiossemicarbazonas

RESUMEN
Las enfermedades olvidadas son un conjunto de enfermedades transmisibles que afectan principalmente a las regiones tropicales de los países que están en proceso de desarrollo. Entre este conjunto de enfermedades se encuentra la enfermedad de Chagas, que ha sido clasificada entre las seis enfermedades parasitarias más importantes del mundo, y se estima que más de mil millones de personas están en riesgo en los países que se consideran endémicos. El objetivo de este estudio es realizar una revisión bibliográfica sobre la actividad tripanocida de los derivados de tiosemicarbazona. El estudio es una investigación de revisión que utilizó 31 artículos para destacar los hallazgos científicos sobre la actividad tripanocida de los derivados en cuestión. Los artículos se incluyeron en la estimación temporal entre 2010 y 2021 (los últimos 12 años). La búsqueda y selección de los estudios de referencia se realizó en las bases de datos Scielo, Science Direct, PubMed y Google Academic. La literatura destaca que las tiosemicarbazonas son compuestos considerados privilegiados y con un amplio interés científico debido a sus diversas propiedades químicas y biológicas, tales como: antitumorales, antibacterianas, antivirales, antiprotozoarias y antichagásicas. Los estudios presentados aquí, que demuestran las investigaciones de los compuestos de esta clase y sus derivados, constituyen un paso importante hacia la concepción de métodos terapéuticos contra el *Trypanosoma cruzi*. Son necesarios nuevos estudios para dilucidar de forma aún más específica los efectos de estos derivados in vivo, con el fin de obtener una terapia farmacológica alternativa para la enfermedad de Chagas.

PALAVRAS-CLAVE: Síntesis de fármacos. Actividad tripanocida. *Trypanosoma cruzi.* Tiosemicarbazonas

INTRODUCTION

Neglected diseases are a group of communicable diseases that mainly affect tropical regions in developing countries. Populations living in poverty, without adequate sanitation, and in contact with

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infectious vectors are the most affected by these diseases. They are called "neglected" because there is little interest in the development of new treatments by the pharmaceutical industry (Araújo et al., 2021).

This fact can be attributed to the low financial return for these industries. Among this set of diseases is Chagas disease, which has been classified among the six most important parasitic diseases in the world, and it is estimated that more than one billion people are at risk in countries that are considered endemic (Who, 2017).

Chagas disease (CD), or also called American trypanosomiasis, is configured as the human infection caused by the protozoan parasite *Trypanosoma cruzi* (Echeverria, 2019). There are about 6 to 7 million people in the world with the disease, mainly distributed among the 21 Latin American countries. Brazil contributes more than 1 million of these cases (Who, 2015). Regarding the epidemiological scenario in Brazil, according to data from the Ministry of Health (Brasil, 2018), in the period from 2007 to 2016, cases of acute Chagas disease were confirmed in most states, with an annual average of 200 cases. About 95% of these cases were registered in the North region, mainly in Pará where 85% of these cases are. Regarding the main probable forms of transmission in the country, most (69%) were attributed to oral transmission (Boletim epidemiológico, 2015).

Despite the lack of systematic data regarding the prevalence of the disease, in recent studies the prevalence estimate ranged from 1.0 to 2.4% of the population, which is equivalent to 1.9 to 4.6 million people infected with *T. cruzi* in the country. This is reflected in the high mortality from the disease in Brazil, as it is one of the four major causes of deaths from infectious and parasitic diseases (Lidani *et al*., 2019).

Between 2010 and 2011, Pernambuco had the largest outbreak of Chagas, the state even registered 14 occurrences, in five cities: Ibimirim, Pombos, Riacho das Almas, Salgueiro and Vertentes. In Pernambuco, 22 cities are considered priority in the monitoring of the disease and a total of 40 cities have registered the triatomine (barbeiro) infected, according to the program for confronting neglected diseases, Sanar (Program for Confronting Neglected Diseases) (Ses, 2020).

The treatment of Chagas disease consists of therapies that have several adverse effects and even long treatment periods leading about 15-20% of patients to drop out of treatment (Muller Kratz, 2018). Thus, the research and development of new drugs for neglected diseases are necessary (Jynior *et al.,* 2017).

Thiosemicarbazones are a class of compounds with medical potential due to their ability to inhibit the growth of various pathogens. These compounds have been shown to have antiviral (Pacca et al., 2017), antibacterial (Hassan et al., 2020), antitumor (Heffeter et al., 2019) properties. Moreover, studies regarding their biological activity suggest that these compounds are active against *T. cruzi* (Linciano *et al.,* 2018).

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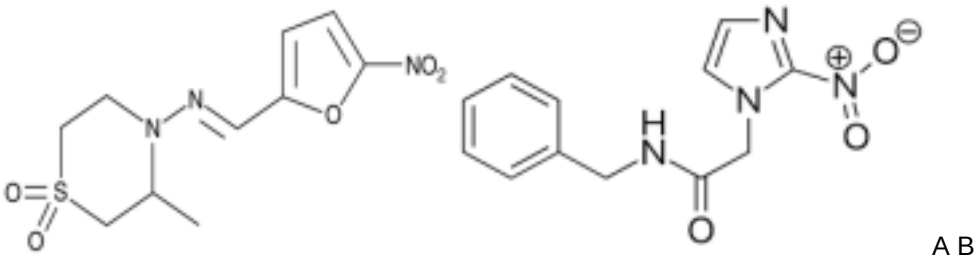
In this sense, taking into account the known antiparasitic activity of the mentioned nuclei, the present work proposes to conduct a literature review study on the trypanocidal activity of thiosemicarbazone derivatives.

2. THEORETICAL FOUNDATION

2.1 Treatment for Chagas disease

The options that currently exist as a form of treatment for CD are very limited, where only two nitroheterocyclic drugs are commercially available: Benzonidazole (Rochagan/LAFEPE and Abarax/ELEA) and Nifurtimox (LAMPIT/Bayer) (Figure 2). It is also worth noting that the sale of Nifurtimox is prohibited in Brazil. Adverse effects from this pharmacological therapy may include problems such as allergic dermatitis, pruritus, fever, gastrointestinal intolerance, among others (Bentran-Hortelano et al., 2020). Access to currently available treatments, including a clearer process to obtain them, has also been an issue. Thus, the actual number of patients treated remains very low (Oliveira, 2017; Arrúa *et al*., 2019).

Figure 1. Chemical structure of Benzonidazole (A) and Nifurtimox (B), current options for the treatment of Chagas disease.



A B

Source: PubChem (2021).

Benzonidazole (A) is the only drug used in Brazil and is recommended for patients with Chagas disease in the acute and indeterminate chronic phases (Da Silva et al., 2021). Benzonidazole treatment has a cure rate of 70% in patients with the acute phase of infection. However, the cure rate in patients in the indeterminate chronic phase is low, ranging from 10-33% (Tessarolo et al., 2018; Jackson, 2020; Losada Galvan et al., 2021).

2.2 Therapeutic Target

Without a shadow of a doubt, research for drugs useful in Chagas disease has evolved over the past two decades. In part, this has been possible due to the sequencing of the genome of *Trypanosoma cruzi*, the etiological agent of Chagas disease (De Sousa et al., 2019). An important

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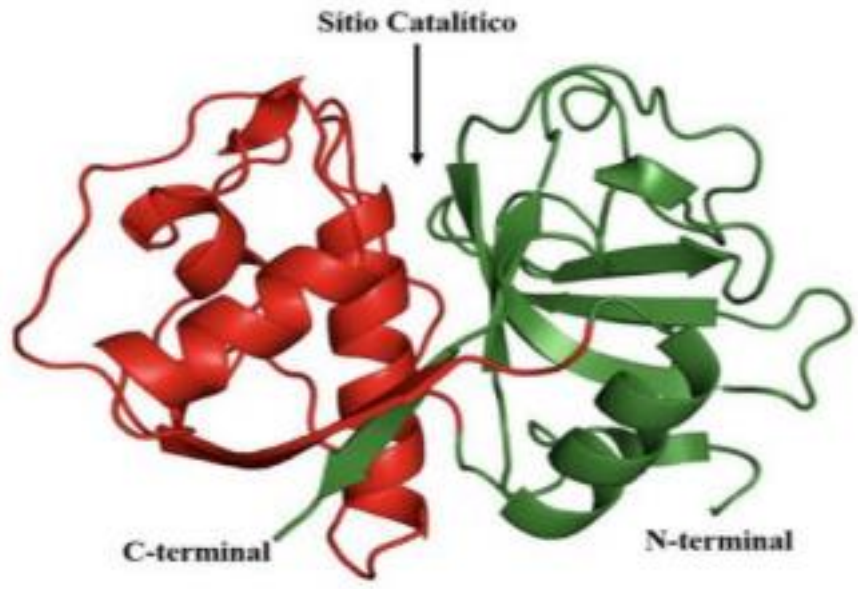
knowledge that has been gained after the genome sequencing of *T. cruzi* is the presence of genes expressing proteins that are potential molecular targets for drugs. The *T. cruzi* genome has a family of twenty genes that express cysteine proteases. To date, three *T. cruzi* cysteine proteases have been biochemically characterized: cruzain (gp57/51), cathepsin B (TccatB) and autophagin-4 (TcAtg4) (Costa, 2015; Herrera-Mayorga *et al*., 2019).

Cruzaine (Figure 2) is the main cysteine protease of the parasite *Trypanosoma cruzi*. It is expressed at all stages of the parasite's life cycle and plays a key role during host cell infection, replication and metabolism (Silva et al., 2020). For this reason, it is considered an important target for the development of new anti-*Trypanosoma cruzi* agents (Delgado-Maldonado *et al.,* 2020).

Figure 2. Enzyme cruzaine, one of the main therapeutic targets for experiments in the development of new drugs for CD.



S**ource**: Pauli (2016).

4. METHODOLOGY

This is an integrative literature review (IRL) with descriptive subsidy. In this sense, in the first moment it elaborated the following guiding question: what are the findings in the literature that can elucidate the trypanocidal mechanism of thiosemicarbazones and their derivatives?

The theoretical basis was based on electronic databases: International Literature in Health Sciences (MEDLINE) through the Regional Portal of the Virtual Health Library (VHL) and in virtual libraries: Scientific Eletronic Library Online (SciELO), ScienceDirect, and Google Academico.

The terms used were identified in Medical Subjects Headings (MeHS) and/or Health Science Descriptors (DeCS). The terms of drug syntheses, such as: Trypanocidal activity, *Trypanosoma cruzi*

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and Thiosemicarbazones, were used as keywords to direct the search strategy, given the specificity of the theme. The search strategies are presented in table 1.

Libraries and databases	Search Strategy
MEDLINE	*"Trypanocidal activity AND Trypanosoma Cruzi OR Thiosemicarbazones", "Trypanocidal activity AND Trypanosoma", "Trypanocidal activity OR Trypanosoma".*
SciELO, ScienceDirect e Google Academico.	*"Atividade tripanocida AND Trypanosoma Cruzi OR Thiosemicarbazones OR Atividade tripanocida AND Trypanosoma AND Atividade tripanocida OR Trypanosoma".*

Table 1 - Search strategies used in the databases selected for the study.
Source: Prepared by the authors, 2021.

The inclusion criteria were primary articles that presented the use of drug synthesis, such as: Trypanocidal activity, *Trypanosoma cruzi* and Thiosemicarbazones as a phenomenon of interest, theses, dissertations, clinical and randomized trials that had been published in English, Portuguese and available in full between the years 2010 and 2021 (last 10 years), due to be the years that most disassembled publications on the subject of interest.

The exclusion criteria were: editorials, review articles, those already selected in the search in another database, and those that did not answer the research question.

The search was performed simultaneously by two independent researchers, who standardized the sequence of use of descriptors and cross-references in each database and then compared the results obtained. The articles of the sample were selected through the sequence: reading the title, reading the abstract, and reading the full text.

A total of 119 articles were found from the search for the descriptors and the MeHS. Of this total, 18 were found in MEDLINE, 53 in SciELO, 28 in ScienceDirect, and 20 in Google Scholar. According to the eligibility criteria, 31 articles were selected for this review, as shown in Figure 1.

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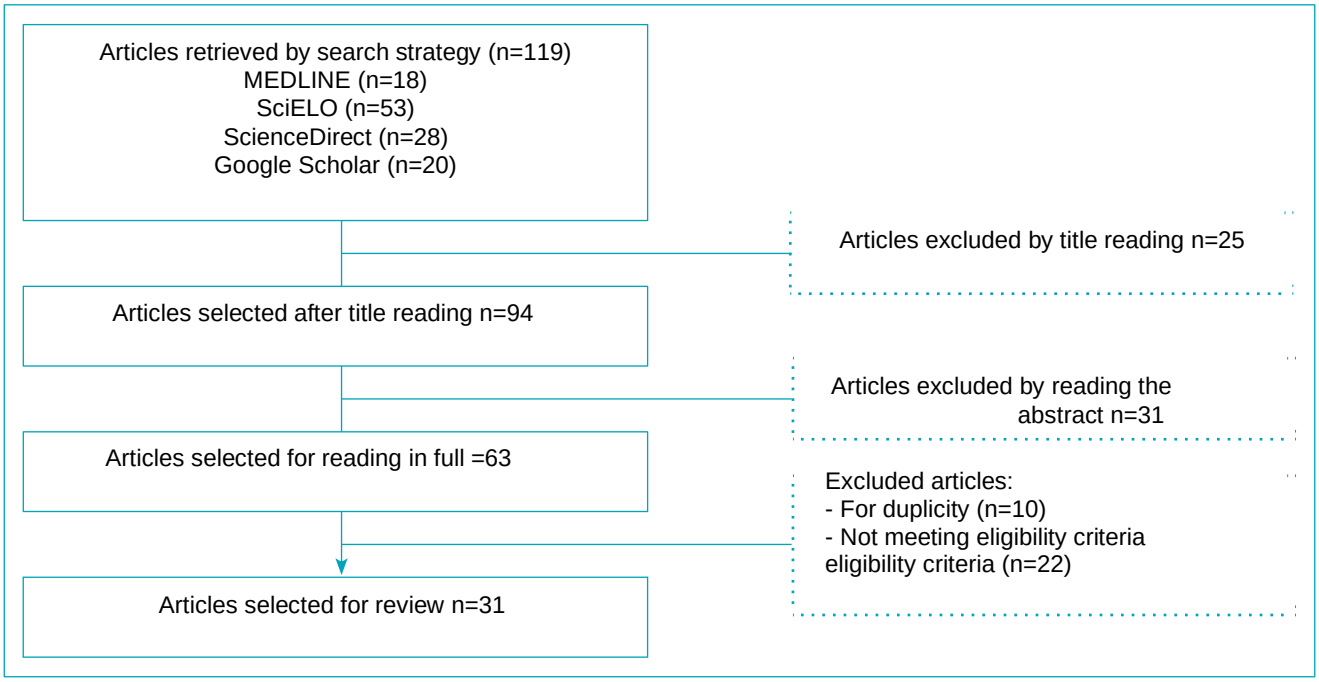

Figure 2. Flowchart of the number of articles found and selected after applying the inclusion and exclusion criteria.
Source: Prepared by the authors, 2021.

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5. RESULTS AND DISCUSSION

5.1 Trypanocidal activity of thiosemicarbazones

Table 1. Summary of some studies reporting trypanocidal activity of thiosemicarbazones and derivatives.

Manuscript title	Periodical	Objective
Evaluation of thiosemicarbazones and semicarbazones as potential agents anti-*Trypanosoma cruzi* (2011).	Experimental Parasitology	To evaluate synthetic thiosemicarbazones and semicarbazones for *Trypanosoma cruzi* obtained from LLC-MK2 cell cultures.
In vitro antiparasitic activity of new thiosemicarbazones in strains of *Trypanosoma cruzi* (2014).	European Journal of Medicinal Chemistry	The objective of the study was to identify the trypanocidal properties of thiosemicarbazones obtained from 5-[(trifluoromethyl)phenylthio]-2-furaldehyde
Synthesis of New Thiosemicarbazones and Semicarbazones Containing the 1,2,3-1H-triazole-isatin Scaffold: Trypanocidal, Cytotoxicity, Electrochemical Assays, and Molecular Docking	Medicinal Chemistry	Perform the synthesis and evaluation of the antitrypanosomal activities of a series of thiosemicarbazones and semicarbazones containing 1,2,3-1H isothermal triazole scaffold.
Synthesis, anti-*Trypanosoma cruzi* activity and quantitative structure relationships of some fluorinated thiosemicarbazones	Journal of Fluorine Chemistry	This work was carried out in order to do the synthesis and spectroscopic characterization of ten fluorinated thiosemicarbazones against *T. cruzi*.

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Thiosemicarbazones and thiadiazines derived from fluorinated benzoylthioureas: Synthesis, crystal structure and anti-*Trypanosoma cruzi* activity	Journal of Fluorine Chemistry	Evaluate the activity of halogenated compounds against the *Trypanosoma cruzi* parasite.
Synthesis, characterization and antichagasic evaluation of thiosemicarbazones prepared from chalcones and dibenzalacetones	Journal of Molecular Structure	The work aimed to describe the synthesis of new thiosemicarbazones derived from chalcones and dibenzalacetones as potential drugs for the treatment of Chagas disease.

Source: Prepared by the author (2021).

Soares and co-workers (2011) investigated the trypanocidal potential of thiosemicarbazones using Swiss mice (male, weight 20-25 g). In this experiment, 5 compounds (figure 2) derived from thiosemicarbazone were tested. The authors evidenced that among all the tests, compound four obtained a higher accuracy than the others that were also tested. It is worth noting that none of the compounds showed macrophage toxicity, suggesting that the mechanisms presented were specific to the parasite forms investigated. The drug benzonidazole was used as a reference drug, and this showed considerably relative levels of toxicity.

Moreno-Rodríguez *et al.,* (2014) studied s thiosemicarbazone derivatives of 5-[(trifluoromethyl)phenylthio]-2-furaldehyde, which in this case were synthesized and evaluated in terms of their efficiency in challenging the growth of epimastigote forms of *Trypanosoma cruzi,* the etiological agent of Chagas disease. Several compounds have been synthesized from 5-bromo-2-furfuraldehyde using nucleophilic aromatic substitution. When tested with *T. cruzi*, they showed a stronger reaction, similar to nifurtimox and benznidazole. The trypanocidal activity of these substances represents a good starting point for a medicinal chemistry program aimed at therapy for Chagas disease.

Santos *et al.,* (2017) conducted a study with fluorinated thiosemicarbazones against *T. cruzi*. IC50 values were obtained in the range of 5.64-29.19 µg mL-1 in 24 h of cultures. Among all the thiosemicarbazones tested, the 2,3,4-trifluoro-substituted compound showed the highest activity with IC50 = 5.64 µg mL-1.

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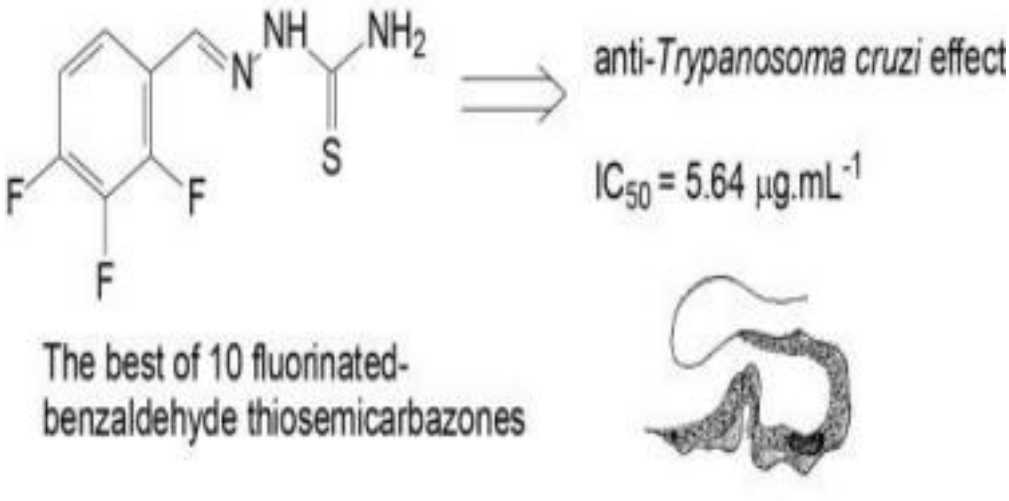
Figure 3. Graphical summary of the experiment.



Source: Santos *et al.,* (2017).

Salsi *et al.,* (2018) conducted a study of the activity of halogenated compounds against the parasite *Trypanosoma cruzi*. A series of thiosemicarbazones were obtained by condensation of N-(diethylaminothiocarbonyl)benzimidoyl halogenated chlorides (3b 3h) with 4,4-dimethyl-3-thiosemicarbazide. The halogen substitution was found to increase the antiparasitic activity in most cases. The metafluorinated compound (4g) was identified as the most potent (IC50= 9.0 µM, CC50 > 200 µM), having a selectivity index (SI = IC50/CC50), which is 4 times higher than that of the unsubstituted compound.

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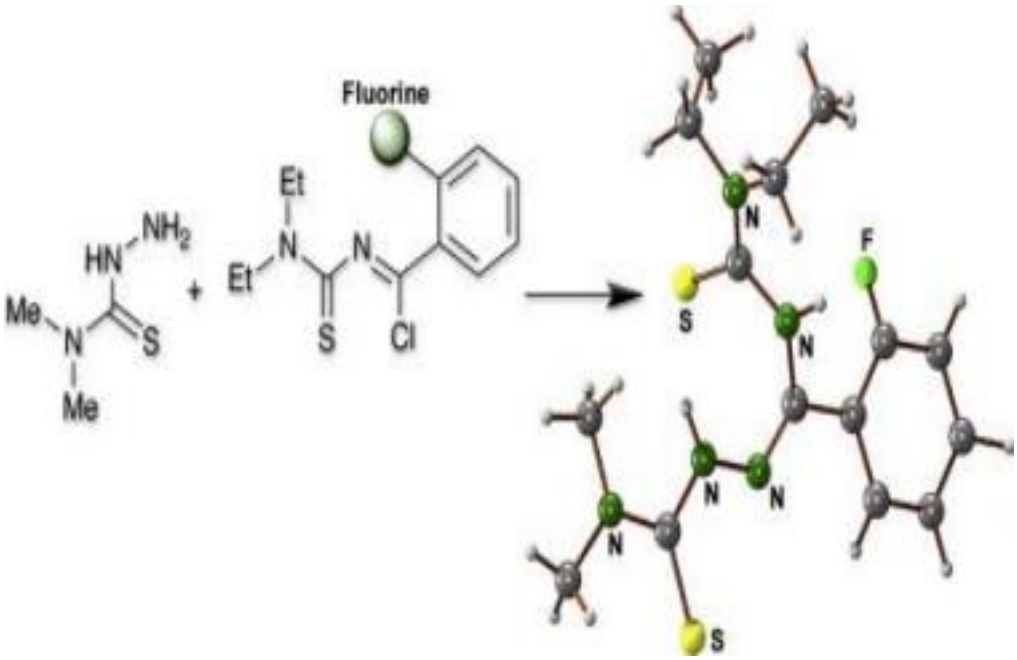
Figure 4. The fluorinated thiosemicarbazones derived from N- (diethylaminothiocarbonyl)benzimidoyl chlorides that show considerable activity against *Trypanosoma cruzi.*



S**ource:** Salsi *et al.,* (2018).

Silva and colleagues (2019) proposed the investigation of carbonylated derivatives with thiosemicarbazide and hydrochlorinated semicarbazide. The compounds were tested for *in vitro* trypanocidal activity against *Trypanosoma cruzi*, the etiological agent of Chagas disease. Among the 37 compounds evaluated, 18 were found to be active, in particular thiosemicarbazones containing a non-polar saturated alkyl chain (IC50 = 24.1, 38.6 and 83.2 µM; SI = 11.6, 11.8 and 14.0, respectively). To further clarify the mechanism of action of these new compounds, the redox behavior of some active and inactive derivatives was studied by cyclic voltammetry.

Silva *et al.,* (2021), analyzed the trypanocidal potential of thiosemicarbazones derived from chalcones and dibenzalacetones. To do so, thiosemicarbazones that were derived from chalcone were tested against the intracellular amastigote form of the protozoan *Trypanosoma cruzi* and had their cytotoxicity evaluated using LLC-MK2 cells. One of the compounds showed better activity than the others, suggesting a satisfactory inhibitory concentration (IC50 = 12.25 µM), thus, this compound showed the best activity when compared to the standard drug benznidazole, which was used as a reference drug (IC50 = 5.64 µM).

6. FINAL CONSIDERATIONS

According to the compilation of information described in this review work, it is noticeable that thiosemicarbazones and their derivatives widely described in the literature for the most diverse

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pharmacological activities are also responsible for triggering trypanocidal mechanisms. This fact is due to the satisfactory values of the inhibitory concentration or parasite load developed by these compounds.

This work brings us the reflection about the thought of new studies, with other approaches, in order to elucidate in an even more specific way the effects of these compounds. It is true that *in vivo* studies can favor the detailing of this parameter, in order to develop additional pharmacological alternatives with anti-*T. cruzi* potential, thus obtaining new prototypes for the therapy of Chagas disease.

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