Medicinal Chemistry Research (2019) 28:2099–2108
https://doi.org/10.1007/s00044-019-02453-y

MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Nitroheterocyclic derivatives: privileged scaffold for drug development against Chagas disease

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Received: 24 June 2019 / Accepted: 29 September 2019 / Published online: 11 October 2019

Abstract

Chagas disease or American trypanosomiasis is a major public health problem in Latin America. Approximately seven million people are currently infected worldwide. Despite the efforts to develop new drugs, only two nitroheterocyclic drugs (nifurtimox and benznidazole) are available for the treatment of Chagas disease, These drugs have been available since the 1970s, and no new drugs have been approved. Due to the lack of alternatives for the treatment of this disease, this review describes recent advances (2013–2019) concerning nitroheterocyclic compounds with activity against *T. cruzi* parasites, as well as new perspectives for future research.

Keywords Chagas disease · *T. cruzi* · Nitro compounds · New drugs

Introduction

Chagas disease, also known as American trypanosomiasis, is a neglected parasitic infection caused by the flagellated protozoan *Trypanosoma cruzi* (*T. cruzi*). This haemoflagelated parasite uses triatomine insects of the subfamily Triatominae as vectors. The parasite has different forms in vectors and mammals. It affects seven million people worldwide and is endemic in Latin America. It causes ~14,000 deaths each year worldwide. This tropical infection disease was first described in 1909 by Brazilian researcher Carlos Chagas (Sherlock 1999; Rassi et al. 2010; DNDi 2019; WHO 2019).

Currently, only two drugs are used to treat Chagas disease. These include the nitrocompounds nifurtimox (NFX, **1**) and benznidazole (BZN, **2**) (Fig. 1) (WHO 2002; Maya et al. 2010). Moreover, the present treatment is more effective during acute phases. Its effectiveness is extremely limited in the chronic phase of the infection. Its effectiveness also depends on the *T. cruzi* strain. However, the currently used nitro compounds (**1** and **2**) have serious adverse events (Morillo et al. 2015; de Andrade et al. 1996; Sosa-Estani et al. 1998; Castro et al. 2006; Andrade et al. 2013; Pan et al. 2013; Da Silva et al. 2014; Soy et al. 2015; Fernandez et al. 2016). Therefore, the development of new, safe, and effective drugs for treatment is urgent.

A few years ago, Francisco et al. showed in an in vivo model (bioluminescent CL-Brenner strain) that the nitroheterocyclic compound (BZN—100 mg/kg, **2**) demonstrated a 100% cure. This was compared with 15.8% reported by the drug posaconazole (20 mg/kg) during the acute stage after 20 consecutive days of treatment. This standard drug (BZN—100 mg/kg, **2**) presented a 100% cure when tested during the chronic stage after three different periods (5, 10, and 20 days of treatment), even after three exposures to cyclophosphamide. Posaconazole (20 mg/kg) showed no activity in any animal at this late stage of the disease. Thus, compared with posaconazole, the nitro compound (BZN, **2**) exhibited very powerful in vivo activity against transgenic parasites (bioluminescent CL-Brenner strain). Evaluations were performed by in and ex vivo imaging (Francisco et al. 2015).

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Supplementary information The online version of this article (https://doi.org/10.1007/s00044-019-02453-y) contains supplementary material, which is available to authorized users.

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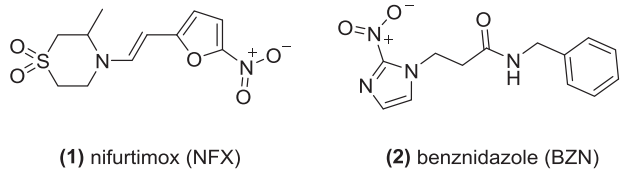


(1) nifurtimox (NFX) **(2)** benznidazole (BZN)

Fig. 1 NFX and BZN structures, antichagasic compounds

New nitroheterocyclic derivatives against *T. cruzi*

Several nitroheterocyclic compounds appear to be promising candidates for anti-*T. cruzi* drugs. These include nitroheterocyclic-based aryl, indazole, thiazole, triazole, benzofuroxan, and furoxan derivatives. Due to their chemical structure, these derivatives can display antiparasitic activity due to the formation of nitric oxide, generated by the molecule itself (Lancaster 2015). Also, some activity can be generated through inhibition of mitochondrial dehydrogenase. In summary, the mechanisms of action are still somewhat unclear for most of these compounds.

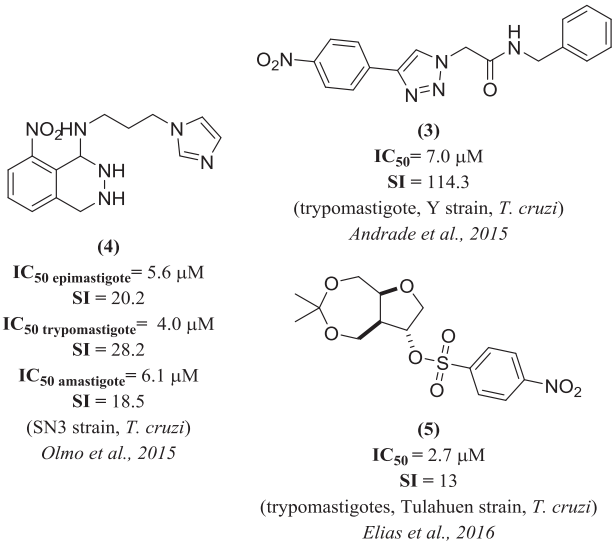
Nitro-Aryl compounds

Some authors have reported new BZN analogs with anti-*T. cruzi* activity. De Andrade et al. synthesized and evaluated a novel series of 1, 2, 3-triazole derivatives against *T. cruzi* parasites. Compound (**3**) has shown promising trypanocidal activity against trypomastigotes (Y strain), with IC_{50} values of 7.0 µM (selective index, SI = 114.3) (Fig. 2). However, this compound reported limited pharmacokinetics due to its poor water solubility (De Andrade et al. 2015).

Olmo and collaborators designed, synthesized, and evaluated a small series of four new phthalazine analogs containing imidazole with nitro groups in the benzene ring. The most promising compound (**4**) exhibited excellent IC_{50} values of 5.6 µM (SI = 20.2), 4.0 µM (SI = 28.2), and 6.1 µM (SI = 18.5) against epimastigote, trypomastigote, and amastigote forms of *T. cruzi* (SN3 strain), respectively (Fig. 2). Moreover, in animal models (in vivo), this compound was able to reduce the parasitaemia recrudescence during the post-treatment immunosuppression period in mice. Despite the nitro group that was present in the molecule, tissue damage was not shown in the histopathological analysis (Olmo et al. 2015).

In another work, Elias et al. reported a series of new xylitan analogs with anti-*T. cruzi* activity. When compared with BZN (**2**), the nitro-arylsulfonate xylitan (**5**) derivative appeared to be the most promising molecule and presented an IC_{50} value of 2.7 µM (SI = 13) against trypomastigote forms of *T. cruzi* (Tahahuen strain) (Fig. 2) (Elias et al. 2016).

Blau et al. identified a new small series of aryl thiosemicarbazones with anti-Chagas activity. Three analogs



(3)
IC_{50} = 7.0 µM
SI = 114.3
(trypomastigote, Y strain, *T. cruzi*)
Andrade et al., 2015

(4)
$IC_{50\ epimastigote}$ = 5.6 µM
SI = 20.2
$IC_{50\ trypomastigote}$ = 4.0 µM
SI = 28.2
$IC_{50\ amastigote}$ = 6.1 µM
SI = 18.5
(SN3 strain, *T. cruzi*)
Olmo et al., 2015

(5)
IC_{50} = 2.7 µM
SI = 13
(trypomastigotes, Tulahuen strain, *T. cruzi*)
Elias et al., 2016

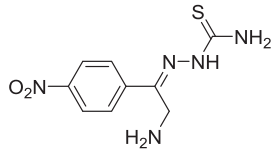
Fig. 2 Nitro-Aryl analogs obtained by Andrade et al. (2013), Olmo et al. (2015), and Elias et al. (2016)

(**6**–**8**) were reported as potent against epimastigote forms (Y strain), with IC_{50} values of 6.3 to 37.7 µM (Fig. 3). Moreover, these derivatives exhibited abilities to inhibit the cruzain enzyme, with an inhibition ranging from 10 to 50% when evaluated at 10 µM. This indicated that these analogs exerted their effects via iron superoxide dismutase (Fe-SOD) (Blau et al. 2013).

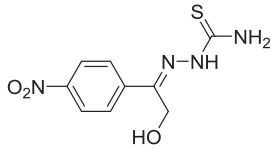
Moreno-Viguri et al. identified the arylaminoketone derivatives in screening libraries. They were synthesized and evaluated against three different *T. cruzi* strains (SN3, Arequipa, and Tulahuen). They reported a higher anti-*T. cruzi* effect (and were non-cytotoxic) when compared with BZN (**2**) (Moreno-Viguri et al. 2016). The arylaminoketone derivatives (**9**) (a nitro compound) had an excellent IC_{50} values of 10.8 µM (SI = 263) against the Arequipa strain of *T. cruzi* (Fig. 4). Their study was based on previous ^{1}H-Magnetic Nuclear Resonance (^{1}H-NMR) results (Moreno-Viguri et al. 2016).

Almeida et al. reported a small series of ten new nitroaromatic compounds with anti-*T. cruzi* activity. Compound (**10**) showed promising results in epimastigote forms (Y strain), with EC_{50} values of 14.09 µM (Fig. 5). It also has a moderate in vivo effect when evaluated in animals infected with the Y strain of *T. cruzi* (Almeida et al. 2018).

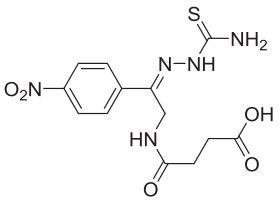
Costa et al. (through a virtual screening of a chemical library) reported a sizable series of novel hydrazine derivatives and evaluated their activity against amastigote forms (Tulahuen strain). Nitro compound (**11**) (IC_{50} = 1.62 µM/SI = 23.46) showed potential as a lead compound (Fig. 5) (Costa et al. 2016). In another study, Britta et al. discovered 4-nitrobenzaldehyde thiosemicarbazone (**12**, Fig. 5), an S-(-)-limonene analog with trypanocidal activity. The results demonstrated IC_{50} values of 1.43 µM (SI = 26.2) against



(6)
IC_{50} = 6.3 μM
(epimastigotes, Y strain, *T. cruzi*)
IC_{50}: % Inhibition of cruzain = 20
Blau et al., 2013

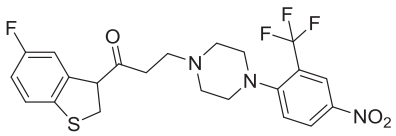


(7)
IC_{50} = 37.7 μM
(epimastigotes, Y strain, *T. cruzi*)
IC_{50}: % Inhibition of cruzain = 10
Blau et al., 2013



(8)
IC_{50} = 12.0 μM
(epimastigotes, Y strain, *T. cruzi*)
IC_{50}: % Inhibition of cruzain = 50
Blau et al., 2013

Fig. 3 Nitro-Aryl thiosemicarbazone derivatives described by Blau et al. (2013)

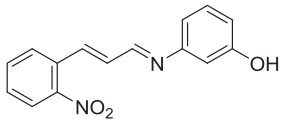


(9)
IC_{50} = 10.8 μM
SI = 263
Arequipa strain, amastigote form, *T. cruzi*
Moreno-Viguri et al., 2016

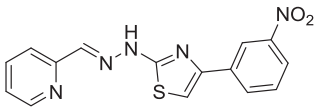
Fig. 4 Nitro-Aryl aminoketone derivatives evaluated by Moreno-Viguri et al. (2016)

trypomastigotes and 11.84 μM (SI = 11.6) for amastigote forms of *T cruzi* (Y strain) (Britta et al. 2015). This compound showed potential as a possible mitochondrion target analog.

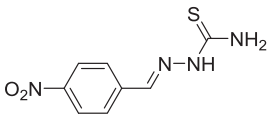
Moreno-Rodriguez et al. exhibited a small series of five novel 5-[(trifluoromethyl)phenylthio]-2-furaldehyde-thiosemicarbazone derivatives against epimastigote forms of



Compound **10**
EC_{50} = 14.09μM
(epimastigote, Y strain, *T. cruzi)*
Almeida et al. 2018



(11)
IC_{50} = 1.62 μM
SI = 23.46
(amastigotes, Tulahuen strain, *T. cruzi*)
Costa et al., 2016



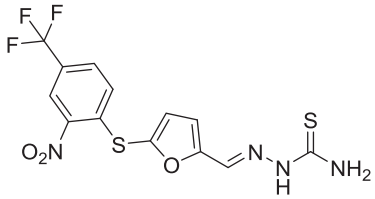
(12)
IC_{50} = 1.43 μM
SI = 26.2
(trypomastigotes, Y strain, *T. cruzi*)
IC_{50} = 11.84 μM
SI = 11.6
(amastigotes, Y strain, **T. cruzi**)
Britta et al., 2015

Fig. 5 Nitro-Aryl analogs obtained by Almeida et al. (2018), Costa et al. (2016), and Britta et al. (2015)

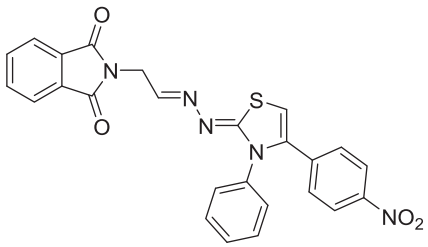
T. cruzi. Two new strains were used by the authors, isolated from 'Punta Lobos' (ITRI/MX/01/PL) and 'Queretaro' (ITRI/MX/86/Qro. Nitro Compound (**13**) demonstrated a potent effect against the strains, with LC_{50} values of 3.2 and 3.4 μM, respectively (Fig. 6) (Moreno-Rodríguez et al. 2014). Gomes et al. designed, synthesized, and evaluated a series of 20 new nitro thiazole analogs containing the phthalimide scaffold. Among the four most promising compounds, two (**14** and **15**) were nitro derivatives. Compounds (**14**) and (**15**) showed potency against trypomastigote forms (Y strain) of *T. cruzi*, with IC_{50} values of 3.2 (SI = 64.6) and 0.9 μM (SI = 114.8), respectively (Fig. 6) (Gomes et al. 2016).

Nitro-indazole, triazole, and thiazole compounds

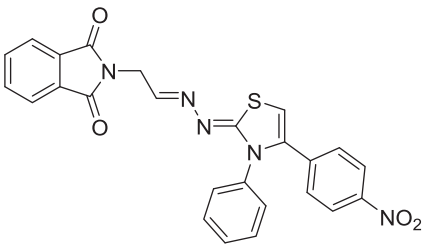
Fonseca-Berzal et al. have designed a novel series of 5-nitroindazole analogs. These were evaluated for their biological activity against the Y strain in amastigote forms, and the most potent compound (**16**) presented an IC_{50} value of 0.60 μM (SI = 166.67) (Fig. 7) (Fonseca-Berzal et al. 2016). In another study, Silva et al. exhibited a new series of 1,2,4-triazolic analogs against the Y strain. The most



(13)
LC_{50} ITRI/MX/01/PL= 3.2 μM
(epimastigotes, isolates 'Punta Lobos' strain, *T. cruzi*)
LC_{50} ITRI/MX/86/Qro = 3.4 μM
(epimastigotes, isolates 'Queretaro strain, *T. cruzi*)
Moreno-Rodriguez et al., 2014



(14)
IC_{50} = 3.4 μM
SI = 64.6
(trypomastigotes, Y strain, *T. cruzi*)
Gomes et al., 2016

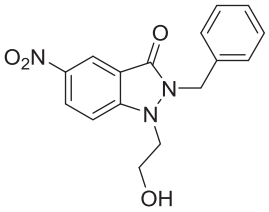


(15)
IC_{50} = 0.9 μM
SI = 114.8
(trypomastigotes, Y strain, *T. cruzi*)
Gomes et al., 2016

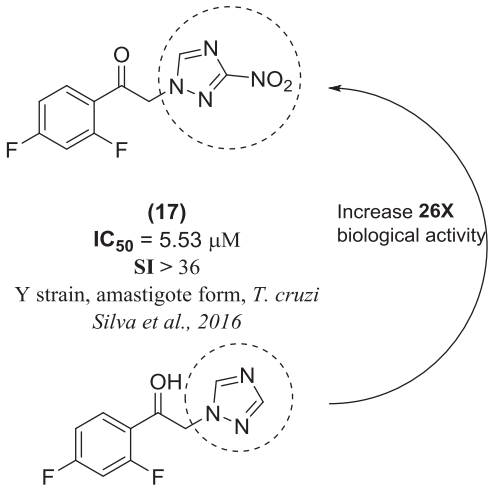
Fig. 6 Nitro-Aryl derivatives identified by Moreno-Rodriguez et al. (2014) and Gomes et al. (2016)

promising compound (**17**), a BZN bio-isosteric, reported an IC_{50} value of 5.53 μM (SI > 36) (Fig. 7), which was similar to the drug BZN (EC_{50} = 3.96, SI > 101). The same researchers identified a compound (**18**) that reduced *T. cruzi* activity, with an IC_{50} value of 144 μM (SI > 1.4) (Silva et al. 2016). Therefore, in this case, the presence of a nitro group was extremely important for generating anti-*T. cruzi* activity.

Papadopoulou et al. identified a novel group of 3-nitro-1*H*-1,2,4-triazole-based arylsulfonamides with potent



(16)
IC_{50} = 0.6 μM
SI > 166.67
Y strain, amastigote form, *T. cruzi*
Fonseca-Berzal et al., 2016



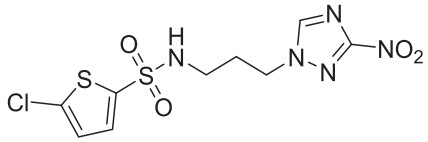
(17)
IC_{50} = 5.53 μM
SI > 36
Y strain, amastigote form, *T. cruzi*
Silva et al., 2016

(18)
IC_{50} = 144 μM
SI > 1.4
Y strain, amastigote form, *T. cruzi*
Silva et al., 2016

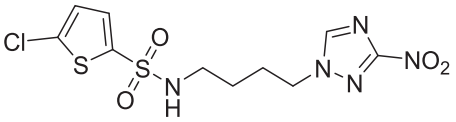
Fig. 7 Structures of Nitro triazoles and indazole analogs, investigated by Fonseca-Berzal et al. (2016) and Silva et al. (2016)

activity against *T. cruzi* in an in vitro assay. Nitro compounds (**19**–**23**) (Fig. 8) showed excellent IC_{50} values against amastigote forms of *T. cruzi* (Talahuen C4 strain) between 0.15 and 0.55 μM, and with SI values of 216–639 (Fig. 8) (Papadopoulou et al. 2014).

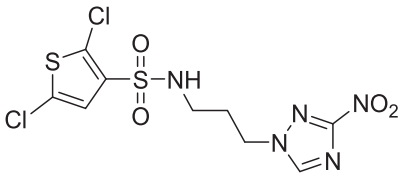
The same group synthesized and characterized a similar series of 3-nitrotriazole analogs, which reported IC_{50} < 0.5 μM against the Tulahuen C4 strain amastigote forms of *T. cruzi*. The most promising nitro compounds were (**24**) and (**25**) (Fig. 9). They presented SI values of 1194 and 2797, respectively. In the same year, a study by the same group optimized and identified two other potent 3-nitrotriazole analogs, Compounds (**26**) and (**27**) (Fig. 9). These demonstrated IC_{50} values of 8 nM (SI = 3615) and 36 nM (SI = 1954), respectively, against Tulahuen C4 strains of the amastigote forms. Moreover, in in vivo assays, these compounds (**24** to **27**) exhibited good results in decreasing parasitemic levels until they were sub-detectable. This shows the importance of this new class



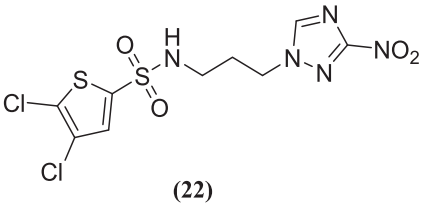
(19)
IC_{50} = 0.43 μM; **SI** = 556
(amastigotes - Talahuen C4 strain - *T. cruzi*)
Papadopoulou et al., 2014



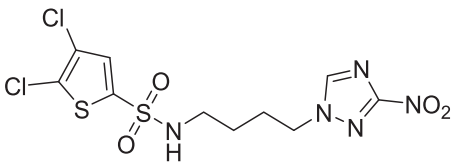
(20)
IC_{50} = 0.46 μM; **SI** = 278
(amastigotes - Talahuen C4 strain - *T. cruzi*)
Papadopoulou et al., 2014



(21)
IC_{50} = 0.55 μM; **SI** = 216
(amastigotes - Talahuen C4 strain - *T. cruzi*)
Papadopoulou et al., 2014



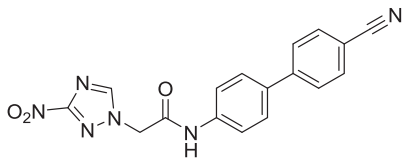
(22)
IC_{50} = 0.15 μM; **SI** = 639
(amastigotes - Talahuen C4 strain - *T. cruzi*)
Papadopoulou et al., 2014



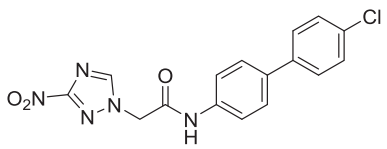
(23)
IC_{50} = 0.37 μM; **SI** = 261
(amastigotes - Talahuen C4 strain - *T. cruzi*)
Papadopoulou et al., 2014

Fig. 8 Nitro triazole-based sulfonamide analogs, evaluated by Papadopoulou et al. (2014)

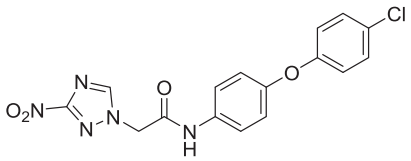
Fig. 9 Nitro triazole derivatives evaluated by Papadopoulou et al. (2015)



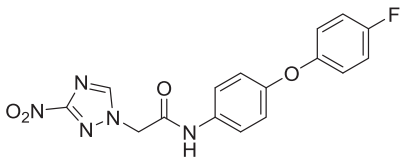
(24)
IC_{50} = 0.138 μM
SI = 1194
Tulahuen C4 strain, amastigote form, *T. cruzi*
Papadopoulou et al., 2015



(25)
IC_{50} = 0.045 μM
SI = 2797
Tulahuen C4 strain, amastigote form, *T. cruzi*
Papadopoulou et al., 2015



(26)
IC_{50} = 0.008 μM
SI = 3615
Tulahuen C4 strain, amastigote form, *T. cruzi*
Papadopoulou et al., 2015



(27)
IC_{50} = 0.036 μM
SI = 1954
Tulahuen C4 strain, amastigote form, *T. cruzi*
Papadopoulou et al., 2015

for the development of more active and promising drugs (Papadopoulou et al. 2015).

Using Imidazothiazole derivatives, Thompson et al. synthesized new derivatives with promising activity against *T. cruzi* strains. Imidazothiazole derivatives were also synthesized and assayed against *T. cruzi* strains. These included Compounds (**28**) ($IC_{50} = 0.04$ µM), (**29**) ($IC_{50} = 0.035$ µM), and (**30**) ($IC_{50} = 0.55$ µM) (Fig. 10), which had SI values ranging from 1163 to 1828. Compound (**30**), a bioisoster of delamanid (**31**), was the most potent derivative(Thompson et al. 2017). In the same year, Thompson et al. also exhibited a new series of 6-nitro-2,3-dihydroimidazo[2,1-b][1,3]-thiazoles. Only two compounds (**32** and **33**) showed potent activity against *T. cruzi* parasites. They presented IC_{50} values of 0.62 (SI = 206.45) and 0.49 µM (SI = 212.24), respectively (Fig. 11) (Thompson et al. 2017).

Nitro-furoxan and benzofuroxan compounds

Serafim et al. exhibited a series of novel furoxan derivatives with a potent anti-*T. cruzi* effect. Two nitro compounds, methyl-furoxan (**34**) and phenyl-furoxan (**35**), reported IC_{50} values of 2.88 and 2.90 µM against the Tulahuen strain C2C4, respectively. This strain obtained from the b-galactosidase (Lac Z) gene of the amastigote forms of *T. cruzi* (Fig. 12). Moreover, the researchers showed that these compounds inhibit cysteine protease (the cruzain enzyme), which is very important for *T. cruzi* parasites. Compounds (**34**) and (**35**) reported IC_{50} values of 11.2 and 15.1 µM in the cruzain inhibition assay, respectively (Serafim et al. 2014).

In another study, Arias et al. synthesized, characterized, and biologically evaluated a series of 13 new compounds of 5-nitro-2-furoic acid derivatives against epimastigote forms of *T. cruzi* (Dm28c strain). Compound (**36**) demonstrated a potent parasitic inhibition capacity, with an IC_{50} value of 1.0 µM (SI = 70) (Fig. 12). Moreover, this compound was an excellent inhibitor of trypanothione reductase (TcTR inhibition = 68U) when compared with the standard drugs (NFX, TcTR inhibition = 245U) (Fig. 12) (Arias et al. 2017). Palace-Berl et al. identified four nitro-furoxan derivatives (compounds **37**–**40**, Fig. 13) as promising antichagasic agents. These compounds showed potent IC_{50} values ranging from 0.67 to 3.77 µM against four different *T. cruzi* strains (epimastigote forms): Silvio X10 cl1, Y, Bug 4129cl10, and the Colombiana strain (Palace-Berl et al. 2018). Therefore, in addition to the other nitroheterocyclic classes shown here, these furoxan and benzofuroxan classes are also important pharmacophore groups to consider in the search for potent lead compounds against Chagas disease.

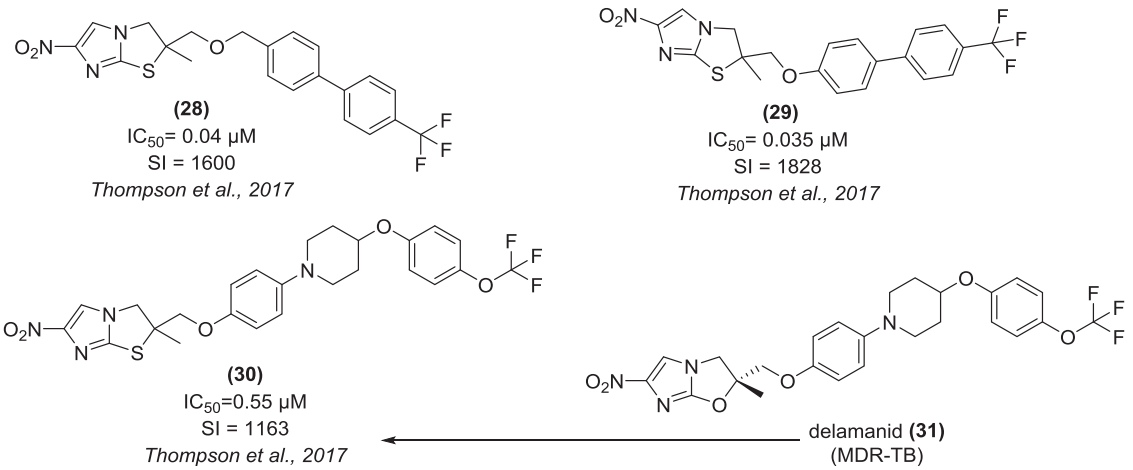
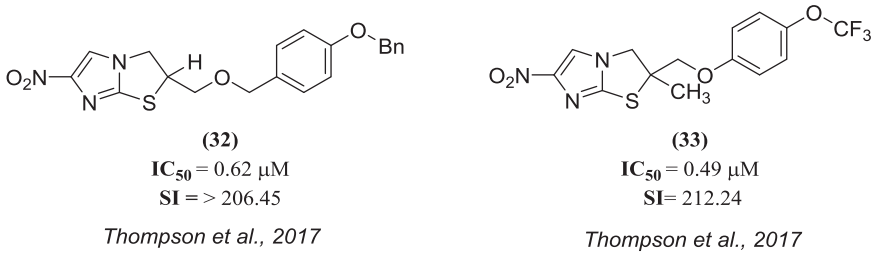
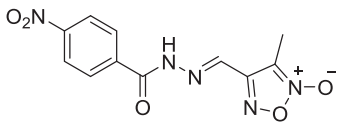


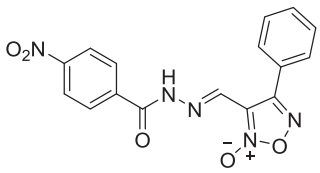
Fig. 10 Nitro Imidazothiazole analogs exhibited by Thompson et al. (2017)

Fig. 11 Nitro Thiazole derivatives obtained by Thompson et al. (2017)

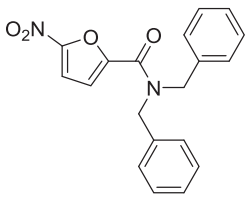




(34)
IC_{50}= 2.88 μM
cruzain inhibition = 11.2 μM
(trypomastigote, Tulahuen strain C2C4, *T. cruzi*)
Serafim et al., 2014



(35)
IC_{50}= 2.9 μM
cruzain inhibition = 15.1 μM
(trypomastigote, Tulahuen strain C2C4, *T. cruzi*)
Serafim et al., 2014



(36)
IC_{50} = 1.1 μM
SI = 70.1
TcTR inhibition = 68U
(epimastigotes, Dm28c strain, *T. cruzi*)
Arias et al., 2017

Fig. 12 Nitro-benzofuroxan and furoxan derivatives as antichagasic agents, exhibited by Serafim et al. (2014) and Arias et al. (2017)

Physicochemical parameters

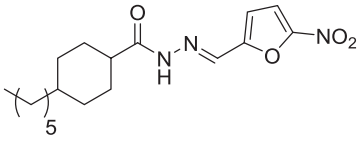
The evaluation of the physicochemical parameters of potentially active compounds in the early stages of drug discovery plays an important role when ensuring adequate pharmacokinetics (Curatolo 1998; Leeson and Springthorpe 2007; Wenlock and Barton 2013). Computational chemistry software also is essential in the early stages, as it helps predict several in silico physicochemical and ADME/T properties based on mathematical formulas and compound databases. All of these features can be used in the free online platform pkCSM, for example (Tetko 2005). The physicochemical parameters of nitroheterocyclic analogs apply Lipinski's rule (Lipinski et al. 1997, 2001). While using the online program pkCSM, we calculated theoretical partition coefficient (cLog*P*) values, rotatable bonds, the numbers of hydrogen bond donors and hydrogen bond acceptors, surface areas, and molecular weights. Most of the nitroheterocyclic analogs presented acceptable physicochemical parameters, according to Lipinski's rule (Table S1—Supplementary Material) (Waring 2010; Chen et al. 2013; Tarcsay and Keseru 2013; Manjunatha and Smith 2015).

The correlation between SI values with cLog*P* (Fig. 14) demonstrated that seven nitroheterocyclic compounds presented SI values above 1000 and all compounds presented cLog*P* up to 5.68. In summary, the validity of this study is based on its potential to assist researchers in the medical chemistry field concerning their knowledge on novel nitroheterocyclic compounds against *T. cruzi*. Though these compounds comply with Lipinski's rule, this rule may be violated by some compounds. However, these cases are exceptions and don't need to be excluded in later studies.

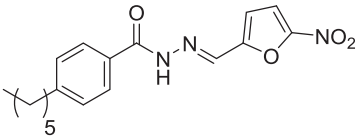
Perspectives against Chagas disease

Recently, Francisco et al. reported the antichagasic activity of the nitroheterocyclic compound Fexinidazole (**41**), and its active analog fexinidazole sulfone (**42**, Fig. 15) in the Balb/c and C3H mouse models. These models were infected with two different bioluminescence strains of *T. cruzi*—CL Brener and JR. The results have shown that both nitroheterocyclic compounds were more effective than the standard drugs (BZN and NFX) during both stages of the disease. Therefore, the nitro compounds (**41** and **42**) exhibited potent anti-*T. cruzi* activity in bioluminescence strains of *T. cruzi* (Francisco et al. 2016). However, they were withdrawn from phase II clinical trials due to toxicity levels.

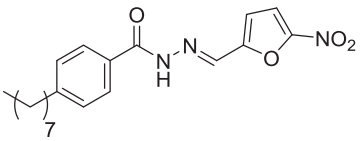
Hydroxymethylnitrofurazone (NFOH) (**43**, Fig. 15) is a new nitrofurazone derivative that has shown high in vitro and in vivo trypanocidal activity in both trypomastigotes and amastigotes. It was also recorded lower mortality rates in the acute phase when compared with BZN (**2**) (Guido et al. 2001; Chung et al. 2003; Davies et al. 2010). Similar concentrations of nitrofurazone and NFOH inhibited 30 and 60% of the cruzain, respectively (PDB code: 1ME4) (Trossini et al. 2010). Davies et al. (2014) evaluated the short-term (21 days) and long-term (60 days) hepatotoxicity of NFOH (150 mg/Kg/day) in an acute phase animal model treated 5 days post-infection. They noted lower liver infiltration compared with BZN treatment, but there were no significant alterations in other hepatic markers (Davies et al. 2014). Using the transgenic *T. cruzi* Brazil Luc strains expressed by the firefly luciferase, researchers reported 78.5% trypanocidal activity after four days of NFOH treatment (50 mg/kg) (Ekins et al. 2015). These encouraging studies indicate that NFOH can be a potential candidate for clinical studies. Moreover, when using Balb/C mice infected with the Y strain, Scarim et al. showed that the NFOH (150 mg/kg) could reduce the intensity of tissue parasitism and inflammation (when compared with BZN group, 100 mg/kg) during the indeterminate form of the chronic



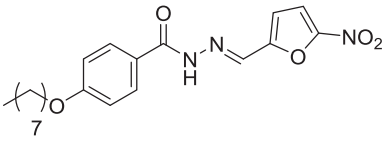
(BSF-37)
IC_{50} = 2.3 µM
Silvio X10 cl1 strain
IC_{50} = 2.5 µM
Y strain
IC_{50} = 1.27 µM
Bug 4129cl10 strain
IC_{50} = 1.47 µM
Colombiana strain
(epimastigotes, *T. cruzi*)
Palace-Berl et al., 2018



(BSF-38)
IC_{50} = 3.77 µM
Silvio X10 cl1 strain
IC_{50} = 2.55 µM
Y strain
IC_{50} = 1.99 µM
Bug 4129cl10 strain
IC_{50} = 1.76 µM
Colombiana strain
(epimastigotes, *T. cruzi*)
Palace-Berl et al., 2018



(BSF-39)
IC_{50} = 1.98 µM
Silvio X10 cl1 strain
IC_{50} = 1.37 µM
Y strain
IC_{50} = 0.67 µM
Bug 4129cl10 strain
IC_{50} = 1.05 µM
Colombiana strain
(epimastigotes, *T. cruzi*)
Palace-Berl et al., 2018



(BSF-40)
IC_{50} = 1.99 µM
Silvio X10 cl1 strain
IC_{50} = 1.47 µM
Y strain
IC_{50} = 0.85 µM
Bug 4129cl10 strain
IC_{50} = 1.09 µM
Colombiana strain
(epimastigotes, *T. cruzi*)
Palace-Berl et al., 2018

Fig. 13 Novel *N*'-[(5nitrofuran2-yl)methylene] substituted hydrazide derivatives identified by Palace-Berl et al. (2018)

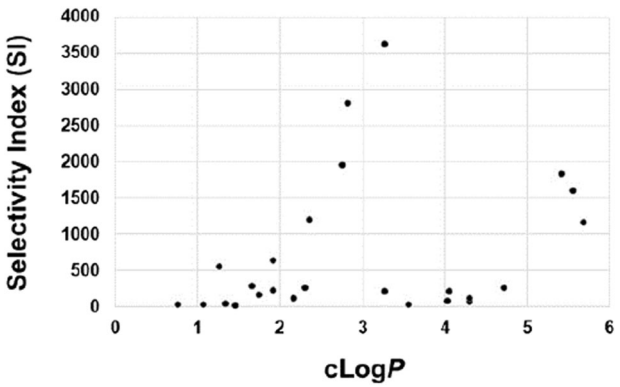
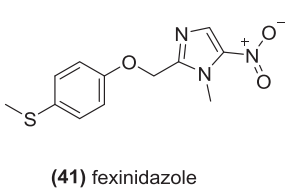
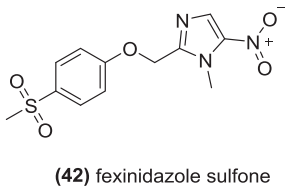


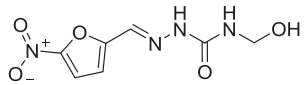
Fig. 14 Correlation between SI (IC_{50}/CC_{50}) values and cLog*P* for the nitroheterocyclic analogs against Chagas disease; cLog*P*: calculated partition coefficient



(41) fexinidazole



(42) fexinidazole sulfone



(43) hydroxymethylnitrofurazone (NFOH)

Fig. 15 Structures of fexinidazole (41), fexinidazole sulfone (42), and hydroxymethylnitrofurazone (NFOH, 43)—a new antichagasic compounds

stage of Chagas disease. After 60 days of treatment, the animals were immunosuppressed, and NFOH and BZN prevented the reactivation of parasitaemia (Scarim et al. 2018).

Overall, nitroheterocyclic compounds occupy a considerable space in the medicinal chemistry field (Paula et al. 2009). In recent years, these pharmacophore groups have shown important biological activities. These include anticoagulant, profibrinolytic, anti-inflammatory, anti-oxidant, analgesic, antimicrobial, antitubercular, antiviral, anticonvulsant, neuroprotective (Alzheimer's disease), antiparasitic, anti-tumor, anti-cancer, and antidiabetic activities

and/or properties. Thus, the exploration of this class for its potential against parasites (such as *T. cruzi*) is justified, especially considering the urgency to find an effective treatment for Chagas disease (Dias et al. 2009; Ferreira 2012; Do Amaral et al. 2017).

Acknowledgements This work was financed in part by the Coordenação de Aperfeiçoamento Pessoal de Nível Superior—Brasil (**CAPES**)—Finance code 001. Moreover, the authors would like to thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (**FAPESP—**2016/10847-9) for the research fellowship assistance.

Compliance with ethical standards

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

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