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Chapter 9

New Approaches for Chagas' Disease Chemotherapy

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Abstract

The latest advances concerning drug design and chemotherapy development to combat the Chagas' disease are discussed. This chapter is based on the metabolic differences between the pathogenic parasite and mammal hosts that led to the progress in the search for novel metabolic pathways in parasites that may be essential for parasite's survival but with no counterpart in the host. There is a considerable amount of work in the search of more promising molecular targets for drug design. However, the chemotherapy for this disease remains unsolved. It is based on old and fairly not specific drugs associated with long-term treatments, severe side effects, drug resistance, and different strains' susceptibility. Herein, a thorough analysis of selected molecular targets is described in terms of their potential usefulness for drug design. Therefore, rational approaches to the chemotherapeutic control of American trypanosomiasis describing some useful metabolic pathways are covered. Enzymes involved in ergosterol biosynthesis (squalene synthase, HMG-CoA reductase, farnesyl diphosphate synthase (FPPS), sterol 24-methyltransferase, and sterol 14α-demethylase), trypanothione system (glutathionyl-spermidine synthetase, trypanothione synthetase, and trypanothione reductase), cysteine proteases, trans-sialidase, and so on are discussed. The design of specific inhibitors of these metabolic activities as possible means of controlling the parasites without damaging the hosts is presented.

Keywords: *Trypanosoma cruzi*, drug development, molecular targets

1. Introduction

Chagas' disease or American trypanosomiasis is among the most prevalent parasitic diseases worldwide [1–3]. It has been estimated that around 20 million people are infected and over 40 million individuals are facing the risk of infection by the hemoflagellates protozoan *Trypanosoma cruzi*, the responsible agent of Chagas' disease. This disease is endemic in Latin

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American countries, but the migration of individuals and blood transfusions have made possible the occurrence of the Chagas' disease in developed countries. Currently, no vaccine is available, so the control of the disease is limited to its detection, vector control, screening of blood banks and organ donors, and case finding of infected pregnant women. Moreover, the development of a safer and more effective chemotherapeutic intervention is crucial for the treatment of Chagas disease.

This disease is characterized by three phases: (1) an early acute phase in which trypomastigotes circulate in blood and infect cells transforming into the asexually-multiplying amastigotes; (2) a subsequent intermediate phase where the cells are broken, parasites are released to the blood and infect other cells (in this phase there are unspecific symptoms like fever, allergic reactions, acute heart failure, or meningoencephalitis); (3) a late chronic phase, a prolonged, and asymptomatic indeterminate phase, where parasites establish in their target organs (during this stage patients may have nonspecific clinical manifestations or present major complications such as cardiomyopathy and/or megaesophagus and megacolon syndromes [4]. The absence of adequate treatment in the acute phase results in the development of the above-mentioned stages of the disease.

The existing chemotherapy remains deficient; it is based on two old drugs empirically discovered, (**1**) nifurtimox, actually discontinued, and (**2**) benznidazole (**Figure 1**). Although both of these compounds are able to cure at least 50% of recent infections, they present important drawbacks such as selective drug sensitivity on different *T. cruzi* strains, serious side effects including vomiting, anorexia, peripheral neuropathy, allergic dermopathy, and long-term treatment [2, 5, 6]. Moreover, these compounds are not effective in the chronic stage of the disease. Consequently, the development of novel, safe, and affordable compounds with potent antiparasitic activity is urgently needed [7, 8]. The existence of *T. cruzi* populations naturally resistant to benznidazole and nifurtimox led to the search for compounds with a different mechanism of action [2, 8]. The development of new drugs that are more effective and safer than those currently available is urgently necessary.

There is a considerable amount of work in the search of unique aspects of the biochemistry and physiology of *T. cruzi* intending to find specific molecular targets for drug design [9]. It can be thought that the selective inhibition of a biosynthetic pathway that leads to a crucial metabolite for parasite survival would not have any significant toxic effect on the host. Based on these facts, this chapter will discuss the search for new approaches based on metabolic differences between the pathogenic parasite and mammal hosts and the development of new potential antiparasitic drugs in the last years.

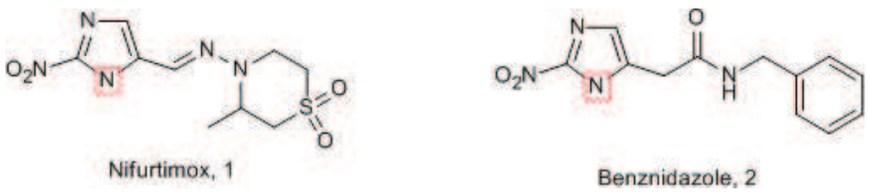

Figure 1. Drugs currently used for Chagas' disease treatment.

2. Molecular targets

There are many metabolic pathways and enzymes unique to *Trypanosoma cruzi* that constitute excellent molecular targets for drug development. However, despite the specificity of new compounds targeting parasite molecules, the effect of these drugs on mammalian metabolism must be carefully evaluated. A few of the most studied compounds targeting specific *T. cruzi* enzymes will be reviewed here.

2.1. Sterol biosynthesis

Isoprenoid biosynthetic pathway constitutes one of the most important metabolic pathways of all organisms because isoprenoids are essential for numerous biochemical functions. In trypanosomatides diverse enzymes of this biosynthetic pathway are involved in key process. Sterol biosynthesis in parasites differs from that in mammalian hosts since the final product is ergosterol instead cholesterol, the main sterol present in the mammals. As *T. cruzi* is entirely dependent on endogenously produced sterols for survival and proliferation, the sterol biosynthetic pathway constitutes an attractive target for drug development.

Reduction of endogenous sterols induces inhibition of the multiplication of *T. cruzi*. Then, the restriction of an enzyme of this biosynthetic pathway will inhibit the growth of the parasite [10, 11]. Sterol composition in *T. cruzi* is very similar to fungi with ergosterol and 24-ethylergosterol being the primary mature sterols in the epimastigote stage. Fungisterol and 24-ethylfurgisterol are the major sterols produced by the amastigote stage. In consequence, antifungal drugs are potentially capable of decreasing pathogen growth.

There are several interesting enzymes in the pathway as potential targets for anti-trypanosomal chemotherapy. For example, sterol 14α-demethylase, sterol 24-methyltransferase, farnesyl diphosphate synthase, squalene synthase, and HMG-CoA reductase.

2.1.1. Sterol 14α-demethylase (CYP51)

Sterol 14α-demethylase is a CYP monooxygenase that catalyzes the removal of the 14α-methyl group from eburicol. Unlike other hemoproteins, the hemo cofactor in CYP51 is coordinated to cysteine residue instead of histidine. Since it is an essential enzyme in sterol biosynthesis, the activity inhibition could be lethal in organisms requiring sterols for membrane function [12]. This enzyme constitutes an interesting target as it has the advantage of being inhibited by antifungal agents currently in clinical use. Azoles are the most efficient antifungal drugs and there have been reported numerous examples of its antiparasitic effects [13–15].

The first azoles such as ketoconazole (**3**), miconazole (**4**), or fluconazole (**5**) (**Figure 2**) were found to have potent *in vitro* activity but did not cure the *T. cruzi* infection. The mechanism of action involves binding to *T. cruzi* CYP51 and a disruption of sterol biosynthesis resulting in accumulation of 14-methylated sterols [16]. New azole drugs developed to combat fungal infections have been evaluated for the activity against *T. cruzi*. The experimental azole drug D0870 (**6**) was the first to cure the chronic infection in mice [17]. Unfortunately, D0870 was discontinued as an antifungal agent due to undesired side effects.

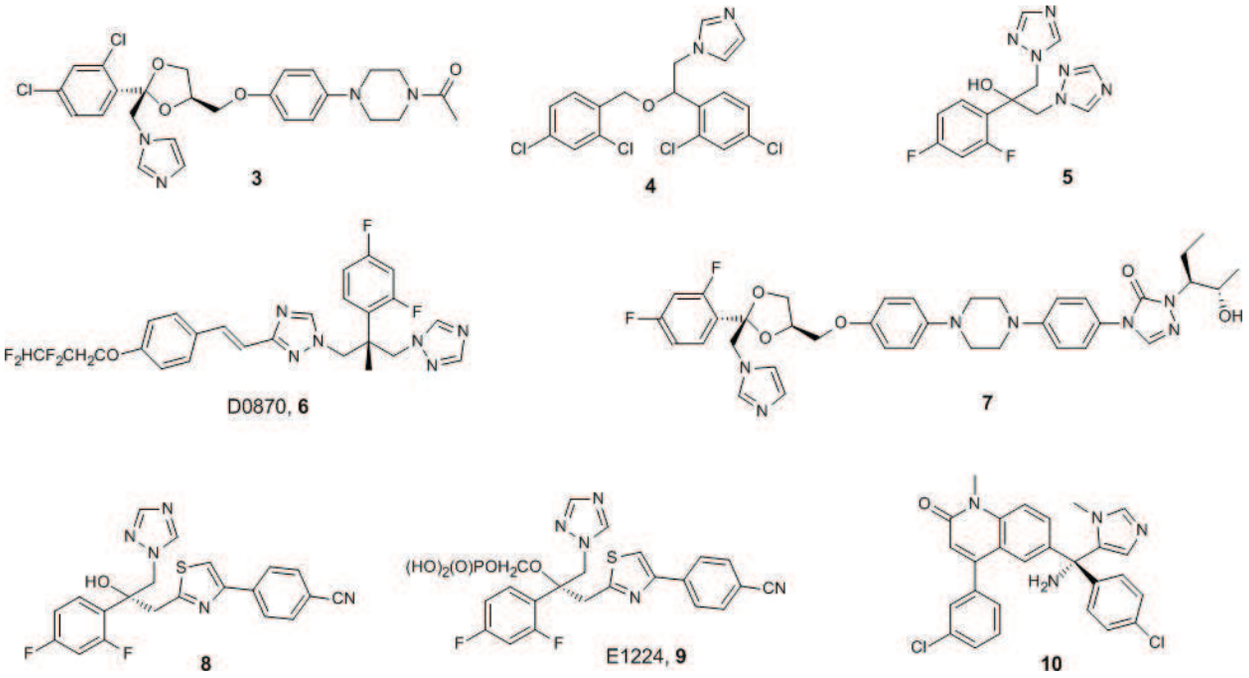

Figure 2. Structures of sterol 14α-demethylase (CYP51) inhibitors.

Among second-generation azoles, posaconazole (**7**) is the most potent drug against *T. cruzi*; because of its broad-spectrum antifungal activity, it could potentially be repurposed for use in Chagas' disease (**Figure 2**) [14]. It has been demonstrated that posaconazole is curative in the chronic murine model. In addition, it has potent activity against benznidazole and nifurtimox resistant *T. cruzi* strains [18]. Recently, a case was reported in Spain, describing the cure of chronic infection by treatment with posaconazole in an immunosuppressed patient. This compound is currently in phase II clinical trial for Chagas' disease. [19, 20] Unfortunately, posaconazole is a very expensive drug, so its application becomes impractical for patients with limited resources.

Ravuconazole (**8**) is another azole antifungal drug that has been evaluated as an antiparasitic agent and it appeared to be very efficient in restraining the parasitemia *in vitro* against *T. cruzi* in murine models [21]. However, since the half-life is much longer in humans than in mice, it is possible that this drug has curative effects. In fact, a prodrug of ravuconazole (E1224 **9**) is in a phase II trial [20]. In addition, ravuconazole has a simpler chemical structure than posaconazole, so the cost might be lower (**Figure 2**).

Tipifarnib (**10**) is an antitumor agent inhibiting human protein farnesyl transferase (**Figure 2**). It has considerable *in vitro* activity against *T. cruzi*. It was determined that the drug produces restriction of sterol biosynthesis by inhibition of CYP51 [22]. Analogs of tipifarnib have been designed and synthesized with improved CYP51 inhibitory activity and excellent pharmacokinetic properties [23].

2.1.2. Sterol 24-methyltransferase (24-SMT)

This enzyme catalyzes the methenylation of zymosterol, an important step for the biosynthesis of ergosterol and other related 24-alkylated sterols, which are the main sterols

found in cell membranes of *T. cruzi* [24]. Azasterols are sterol compounds containing a nitrogen atom in the positions 23, 24, or 25 of the side chain. It was reported that these compounds inhibit the enzyme 24-SMT and demonstrated antiproliferative effects against trypanosomatids. 22, 26-azasterol (AZA, **11**), and 24, 25-epiminolanosterol (EIL, **12**) were the first azasterols reported to have trypanocidal activity [24, 25]. Different azasterols with modifications on their basic structure have been designed, synthesized, and biologically evaluated as antiparasitic agents [26, 27]. An important observation to take into account is that the 3β-OH group must be acylated. On the other hand, the nitrogen atom in the side chain can be located at the 23–25 position. The side chain can be attached via amine or amide bond and the presence of an ester moiety increased the activity [27]. General structures (**13**) of compounds, which have been developed as inhibitors of 24-SMT are shown in **Figure 3**.

2.1.3. 3-Hydroxy-3-methyl-glutaryl-coenzyme a reductase (HMG-CoA reductase)

The enzyme HMG-CoA reductase is involved in the first step in the pathway of isoprenoid biosynthesis and catalyzes the reduction of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate. Therefore, HMG-CoA reductase is a key enzyme and constitutes a valid molecular target since its inhibition will also prevent the synthesis of compounds of the mevalonate pathway.

Current cardiovascular drugs have been tested for the treatment of Chagas' disease but new therapeutic drugs based on statins with a new anti-inflammatory approach have arisen as potential antiparasitic agents. Statins are thought to be associated with their ability to reduce cholesterol synthesis [28]. It was observed that lovastatin (**14**) and simvastatin (**15**) (**Figure 4**) have inhibited the growth of epimastigotes of *T. cruzi* and simvastatin could potentially inhibit HMG-CoA reductase both in epimastigotes and trypomastigotes [29]. Moreover, the combination of lovastatin with ketoconazole allowed the elimination of the presence of parasites into the blood flow and, in this way, prevented host death [30].

2.1.4. Farnesyl diphosphate synthase (FPPS)

The enzyme farnesyl pyrophosphate synthase, also known as farnesyl diphosphate synthase (FPPS) belongs to the E-family of the prenyltransferases and it has a key role in the isoprenoid biosynthetic pathway. Isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP) are synthesized via mevalonate pathway from acetyl-CoA [31]. DMAPP is the precursor for the biosynthesis of different and very important isoprenoids like sterols, ubiquinones, triterpenoids, and prenylated proteins.

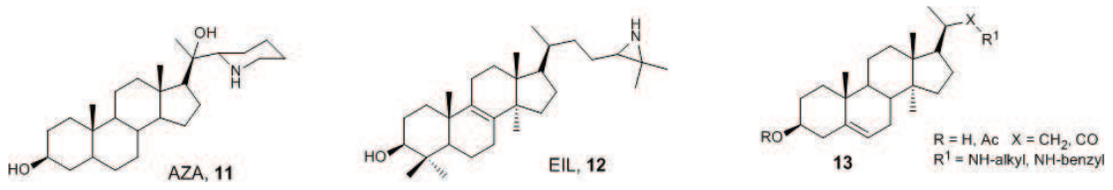

Figure 3. General structures of inhibitors of 24-SMT.

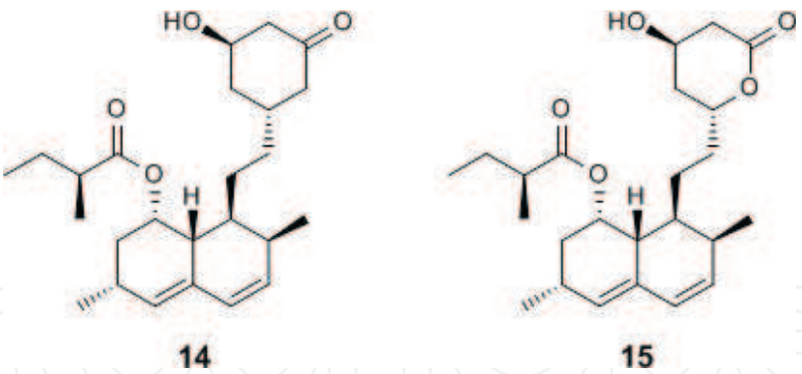

Figure 4. Chemical structures of inhibitors of the enzymatic activity of HMG-CoA reductase.

FPPS catalyzes two sequential steps: the addition of DMAPP to isopentenyl diphosphate (IPP) to form geranyl diphosphate (GPP) and the addition of DMAPP to geranyl diphosphate to produce farnesyl pyrophosphate (FPP). The inhibition or alteration of FPPS activity can regulate the isoprenoid metabolism. Therefore, FPPS has been selected as an excellent target for different disorders and anticancer, antibacterial, and antiparasitic drugs design among others [32–34].

Bisphosphonates act as inhibitors of bone resorption binding to the bone mineral. They are currently used for the treatment of several bone disorders like osteoporosis, Paget's disease, and hypercalcemia [35]. Bisphosphonates were the first FPPS inhibitors known and were reported as potent antiparasitic agents. Nitrogen-containing bisphosphonates like pamidronate (**16**), alendronate (**17**), risedronate (**18**), and ibandronate (**19**) were originally found to be effective against *T. cruzi* without toxicity to the host cells (**Figure 5**) [36]. Risedronate has shown a significantly increased survival of *T. cruzi*-infected mice *in vivo*. It was also found that diverse bisphosphonate derivatives were effective growth inhibitors of other pathogenic trypanosomatids and apicomplexan parasites [32, 37, 38].

Bisphosphonates have the disadvantage that they are highly polar and are rapidly removed from the circulatory system. Therefore, more lipophilic derivatives were developed (**20**) [38–40]. Bisphosphonates have a great potentiality as antiparasitic agents with characterized mechanisms of action involving the inhibition of FPPS, being very proper candidates to control and treat American trypanosomiasis. In addition, bisphosphonates have the advantage of being inexpensively synthesized and many compounds are FDA-approved drugs for the long-term treatment of several diseases.

2.1.5. Squalene synthase (SQS)

Squalene synthase (SQS) is also a key enzyme of ergosterol biosynthesis, which catalyzes the condensation of two farnesyl pyrophosphate molecules to form presqualene diphosphate and the subsequent loss of diphosphate, rearrangement, and reduction by NADPH to form squalene. Then, squalene epoxidase catalyzes the epoxidation of squalene affording oxidosqualene, which is cyclized by oxidosqualene cyclase to form lanosterol [41, 42]. Therefore,

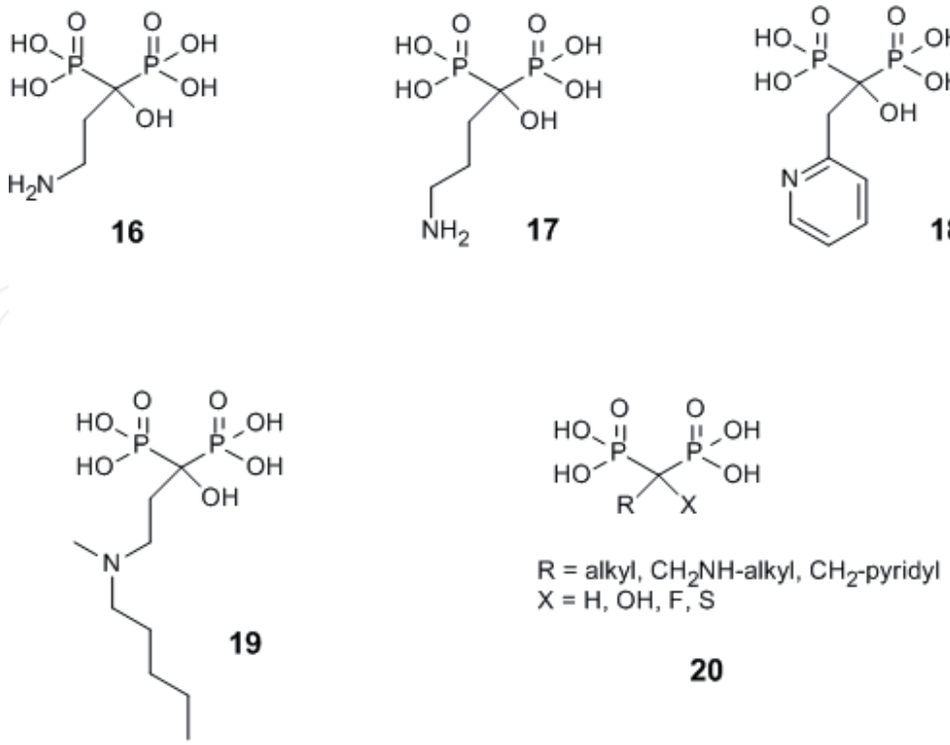

Figure 5. Chemical structures of representative bisphosphonates targeting FPPS.

any of these enzymes constitute an excellent molecular target for antitrypanosomal agent's development. SQS is also under intense study as a possible target for cholesterol-lowering drugs in humans [41].

Quinuclidines were developed as cholesterol-decreasing agents but actually, they also turned out to be potent SQS inhibitors. However, they showed poor SQS selectivity. It has also been reported that this class of compounds eliminated the parasite both *in vitro* and *in vivo* [43, 44].

SQ109 (**21**, **Figure 6**), an ethylenediamine currently in phase II clinical trials for the treatment of tuberculosis, is of great interest for the etiological treatment of Chagas' disease [45]. Studies have conveyed that SQ109 was an inhibitor of dehydrosqualene synthase from *Staphylococcus aureus*, a protein very similar to squalene synthase, suggesting that SQ109 might also inhibit *T. cruzi* SQS [46]. In fact, recently, it was determined that SQ109 is active against all life cycle stages of *T. cruzi*, detecting the most potent activity against the highly infective trypomastigote form. Furthermore SQ109 showed synergism with posaconazole [47].

Other very interesting SQS inhibitors that have been discovered include thiocyanates like WC-9 (**22**), which proved to be a potent inhibitor of this enzyme [48]. Fluorine-containing thiocyanate derivatives exhibited higher efficacy as inhibitors of *T. cruzi* proliferation (**23,24**) (**Figure 4**) [49]. Recently, the structures of human SQS and *T. cruzi* SQS bound to a substrate-like inhibitor were reported suggesting an interesting alternative for the development of selective drugs [50].

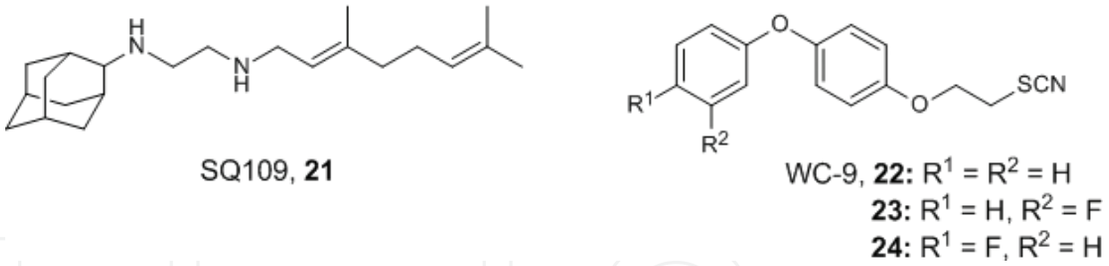

Figure 6. Chemical structures of inhibitors of the enzymatic activity of squalene synthase.

2.2. Cruzipain

Cruzipain is the main cysteine proteinase of *T. cruzi*, which is essential for the survival of the parasite. This enzyme is involved in different cellular functions such as nutrition, penetration into the host cell, defense, and differentiation processes [51]. It has been extensively studied as a valid target for new drug development [52, 53]. There are several three-dimensional structures of cruzipain with different inhibitors allowing the identification of structural regions of this enzyme that will enable the design of new agents [54, 55].

Numerous structurally varied compounds that inhibit proliferation of *T. cruzi* by inhibiting the enzymatic activity of cruzipain have been reported. Among the compounds tested, K777 (**25**), a vinyl sulfone derivative was active against a wide range of susceptible and resistant strains (**Figure 7**). Moreover, it was able to cure *T. cruzi* acute and non-acute infection in mice, showing also synergistic activity with benznidazole [56, 57].

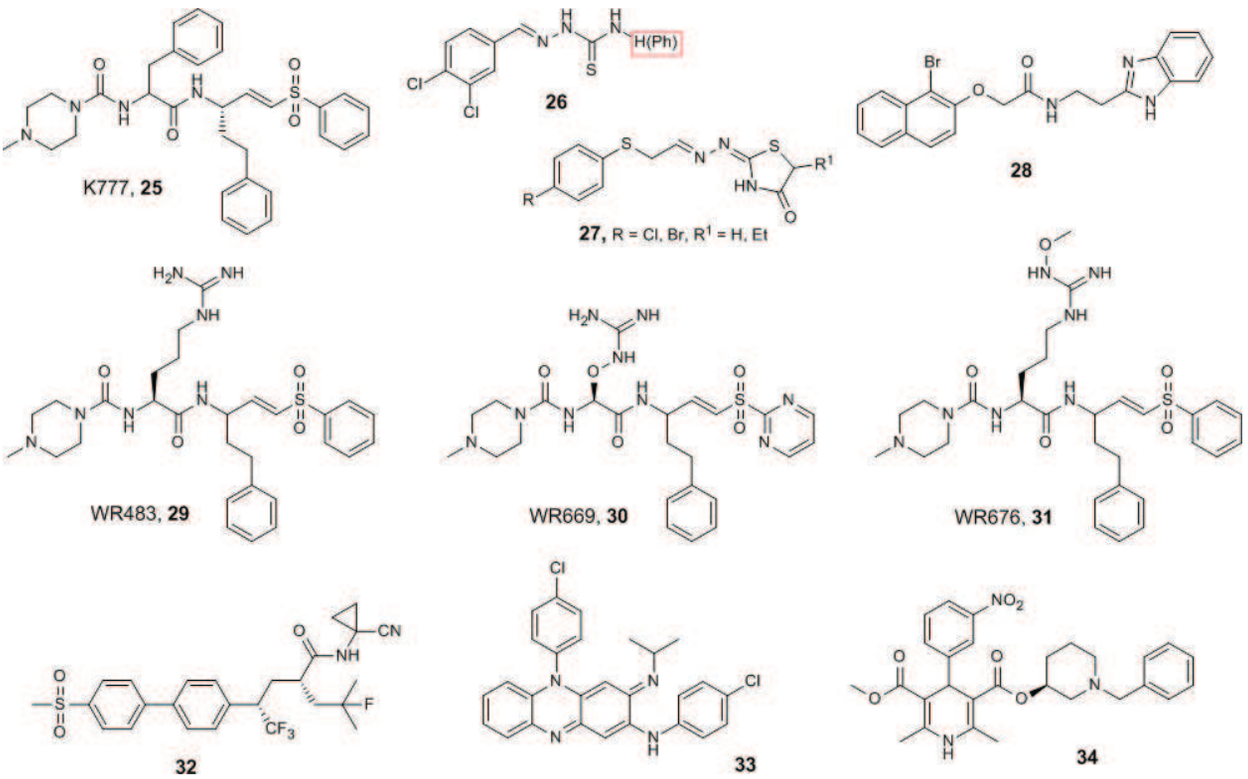

Figure 7. Structures of inhibitors of cruzipain activity.

Molecules containing thiosemicarbazones have been extensively explored [58–60]. Among these, 3, 4-dichlorophenyl thiosemicarbazone (**26**) is one of the most potent cruzipain inhibitor [61]. Recently, thiazolidinone derivatives (**27**) were identified as strong antiparasitic compounds (**Figure 7**) [62, 63].

Benzimidazoles have also been studied as cruzipain inhibitors and various derivatives have been synthesized and evaluated. *N*-(2-(1H-benzo[d]imidazol-2-yl) ethyl)-2-(1-bromonaphthalene-2-yloxy) acetamide (**28**) was the most potent enzyme inhibitor but it showed moderate trypanocidal activity [64, 65].

Other very potent cruzipain inhibitors have been developed such as oxyguanidine derivatives WRR-483, WRR-669, and WRR-676 (**29–31**). Some of these compounds showed suitable metabolic stability and a remarkable trypanocidal activity [66].

Very recently a series of peptidyl nitroalkenes was designed, synthesized, and evaluated as cruzipain inhibitors. Several compounds showed high activity against the enzyme observing the peptidic nature to be the determinant for their inhibitory activity [67].

Odanacatib (**32**), clofazimine (**33**), and benidipine (**34**) are examples of drug repurposing for the development of novel therapeutics for the Chagas' diseases (**Figure 5**). Odanacatib is a cathepsin K inhibitor used for the treatment of postmenopausal osteoporosis; it is a potent cysteine protease inhibitor, which is in Phase III clinical trials [68]. Clofazimine is an antibiotic applied to the treatment of leprosy [69] and benidipine is a calcium channel-blocking agent employed in the treatment of hypertension [70]. Clofazimine and benidipine were recently tested in a murine model of chronic Chagas' disease infection. Both compounds have reduced the parasitemia and the inflammatory effects have been well tolerated [71].

2.3. *Trans*-sialidase

The enzyme *trans*-sialidase (TS) belongs to the group of enzymes that are secreted by the parasite involved in the processes of cell invasion and immune evasion [72]. *T. cruzi* incorporates sialic acid (**35**) from exogenous sialoglycoconjugates by a trans-glycosylation reaction [73]. TS catalyze this transfer from host sialoglycoconjugates to glycoconjugates or mucins, which are attached to the cell membrane of *T. cruzi* via glycophosphatidylinositol anchors [74, 75]. Added to its important role, the absence of this enzyme in mammalian organisms makes it an excellent molecular target.

Within TS' inhibitors it can be mentioned fluorinated compounds like 9-benzoyl-3-fluoro-N-acetylneuraminic acid (**36**), and 3-fluorosialyl fluoride (**37**) selectively bind to the active site of the enzyme [76]. Sulfonamide-containing hydroxylated chalcones (**38**) and quinolones (**39**) are also specific inhibitors of *T. cruzi* TS, being dihydroxylated more potent than monohydroxylated derivatives (**Figure 8**) [77].

Some approved FDA drugs were evaluated on trypomastigotes deriving out of a computational screening protocol. The anti-inflammatory sulfasalazine (**40**) showed potent antiparasitic effects in *in vivo* assays, but with moderate TS inhibition. However, this drug and sulfonamide-containing compounds could be used as leading drugs in the development of new TS inhibitors [78].

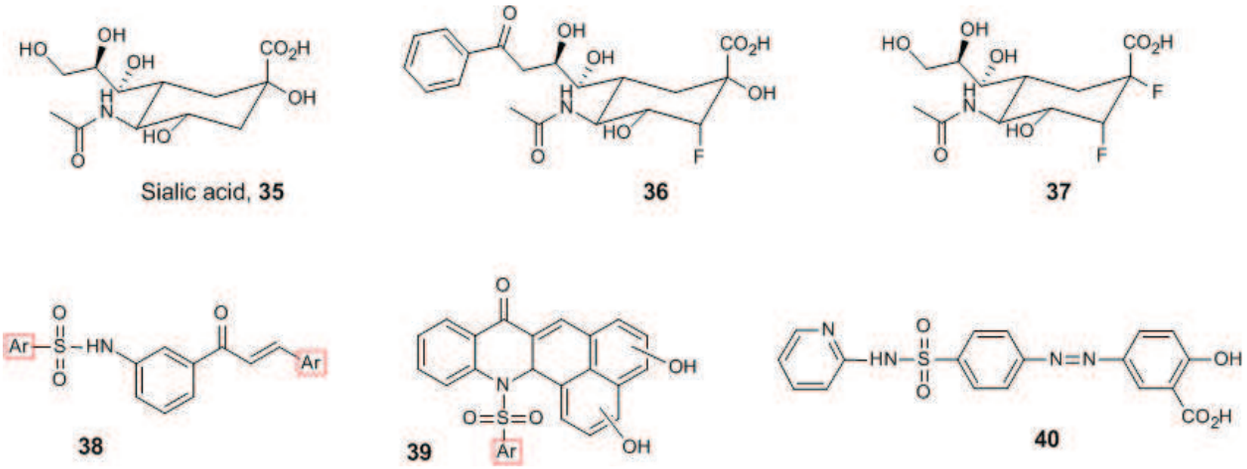

Figure 8. Representative inhibitors of *trans*-sialidase.

2.4. Trypanothione system

Trypanothione ($T[SH]_2$ or N^1, N^8-bis-(glutathionyl)spermidine, (**41**)) is a dithiol, which is responsible for the thiol metabolism in trypanosomatids by maintaining the intracellular redox balance [79]. Trypanothione is responsible for the protection against oxidative stress in *T. cruzi* trapping reactive oxygen species [80].

The protective reactions involve two key enzymes, which keep the trypanothione system operating: trypanothione reductase (TryR), homologous to mammal glutathione reductase and trypanothione synthetase (TryS) [81]. TryR catalyzes the reduction of trypanothione disulfide ($T[S]_2$, **42**) to $T[SH]_2$ (**Figure 9**); TryS catalyzes the synthesis of $T[SH]_2$ from glutathione and spermidine, keeping the amount of total trypanothione constant [82]. Taking into account the fact that trypanothione system is essential to the survival of parasites, these enzymes emerge as valid molecular targets for the search of new chemotherapeutics agents. In addition, TryS has no counterpart in mammals, making even more interesting to the design more specific and safer inhibitors [2].

Various reports have conveyed that different classes of compounds have selective enzyme inhibition activity such as tricyclic ring structures, bicyclic, and heterocyclic compounds or polyamines among others.

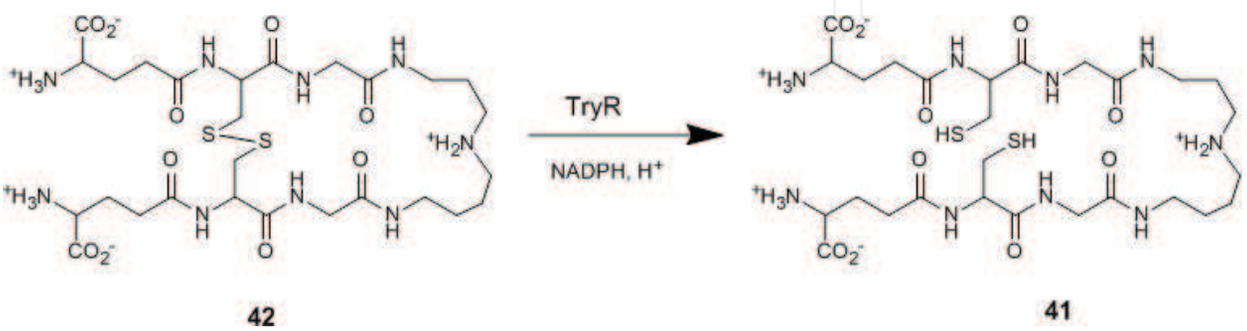

Figure 9. Structures of the oxidized and reduced forms of trypanothione.

Mepacrine (**43**) is a tricyclic antimalarial, which showed TryR inhibition without affecting human glutathione reductase and several mepacrine derivatives have been prepared. Although these derivatives presented greater potency, they turned out to be toxic to human cells [83].

Tricyclic phenothiazine-containing drugs are currently used as an antidepressant and have additionally exhibited antimicrobial activity [84]. Some phenothiazines demonstrated inhibitory activity against TryR [85]. Within them, thioridazine (**44**) is one of the most potent TryR inhibitors as investigations have suggested [86]. Clomipramine (**45**) [87] is another psychiatric drug with inhibiting action towards TryR. Both thioridazine and clomipramine seem to have *in vivo* effects against *T. cruzi* (**Figure 10**).

Library screening has allowed the identification of other classes of inhibitors that could be useful for the development of more potent TryR inhibitors. Some examples of these compounds are indatraline (**46**), a monoamine transporter inhibitor, 1-(2-(benzhydryloxy)ethyl)-4-(3-phenylpropyl)piperazine (GBR-12935, **47**) and a benzothiophene-piperidine derivative (BTCP **48**) [88]. Other or additional, studies allowed finding analogs of these compounds, which have increased the potency against TryR exhibiting higher selectivity [89]. The most interesting compounds were a piperazine-phenothiazine derivative of GBR-12935 (**49**) and a diaryl sulfide BTCP derivative [50, 88, 90].

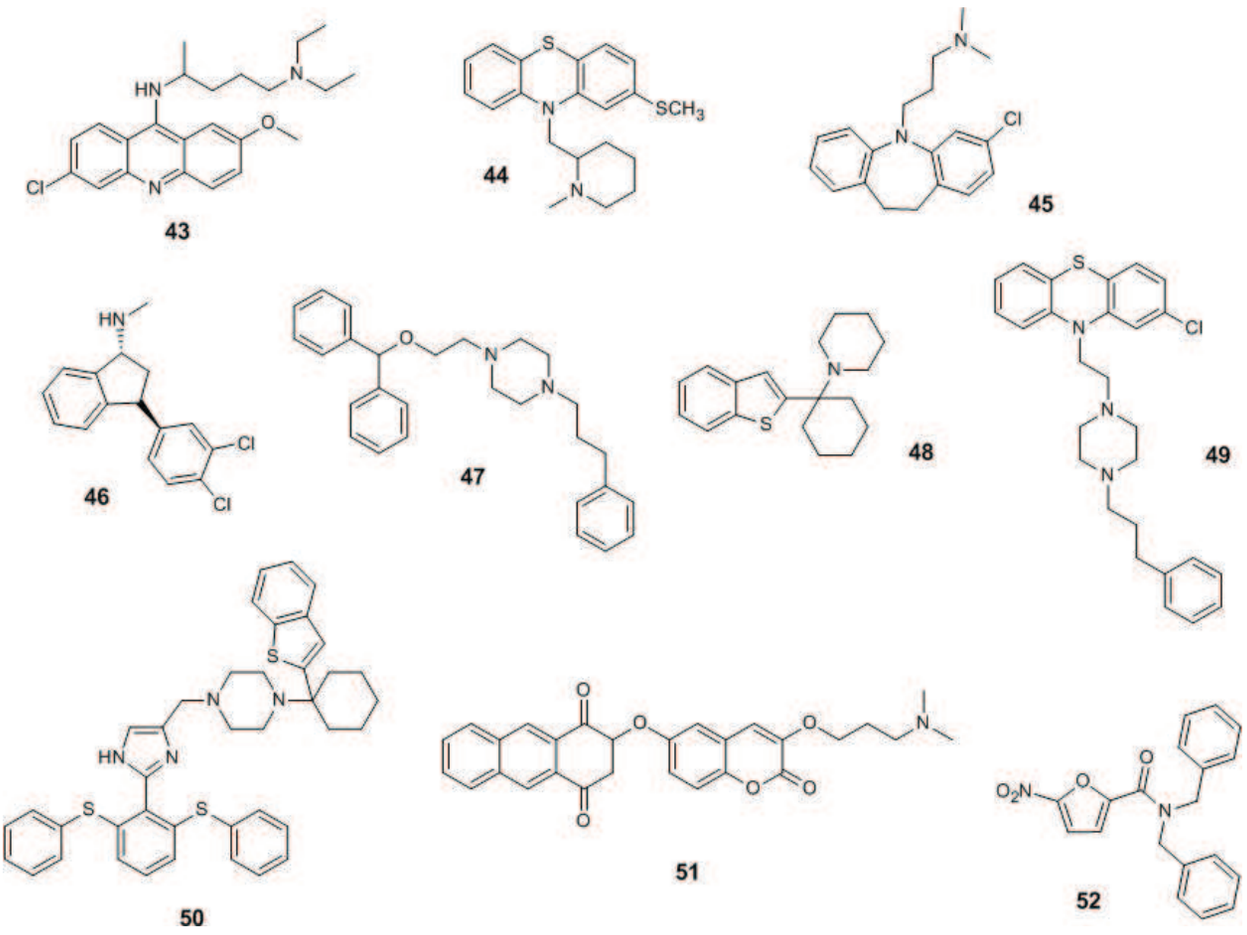

Figure 10. Chemical structures of relevant compounds targeting trypanothione reductase.

Different compounds can behave as TryR inhibitors when turning into reactive radical species through the reduction single-electron step [83, 91]. Within these structures, 1, 4 naphthoquinones and nitrofurans have been largely studied [92, 93]. The most potent derivative of 1,4 naphthoquinone was a quinone–coumarin hybrid [51] despite showing toxicity against rat skeletal myoblasts [94].

Between nitrofurans compounds, several 5-nitrofuroic acid derivatives have been synthesized and evaluated against *T. cruzi*. The best compound was 5-nitro-furan-2-carboxylic acid dibenzyl amide [52], which it significantly increased the trypanocidal nifurtimox activity being TryTR your molecular target [95].

3. Conclusions

Currently, the chemotherapy of American trypanosomiasis remains a serious problem in the field of neglected tropical diseases. There are no vaccines, and chemotherapy is limited to old drugs, which present important drawbacks. Taking into account that this disease is associated with poor populations and bad housing conditions, pharmaceutical companies have no economic motivations. Therefore, all efforts to the development of new drugs must be made by academic and/or governmental institutions and new chemotherapies are needed urgently. In order to search new, safer and efficient drugs for the Chagas' treatment, an overview of possible molecular targets based on specific features of the biochemistry of *Trypanosoma cruzi* was given. Although there are numerous potentially valid targets, only the more representative ones were discussed here. Furthermore, some of the new potential antiparasitic drugs as well as drugs applied to other human illness were described in this work. However, despite numerous efforts and progress in the searching of new or repositioned compounds for American trypanosomiasis chemotherapy, no ideal drugs are yet available for human treatment

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