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Original article

Designing and exploring active *N*′-[(5-nitrofuran-2-yl) methylene] substituted hydrazides against three *Trypanosoma cruzi* strains more prevalent in Chagas disease patients

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ABSTRACT

Chagas disease affects around 8 million people worldwide and its treatment depends on only two nitroheterocyclic drugs, benznidazole (BZD) and nifurtimox (NFX). Both drugs have limited curative power in chronic phase of disease. Nifuroxazide (NF), a nitroheterocyclic drug, was used as lead to design a set of twenty one compounds in order to improve the anti-*Trypanosoma cruzi* activity. Lipinski's rules were considered in order to support drug-likeness designing. The set of *N*′-[(5-nitrofuran-2-yl) methylene] substituted hydrazides was assayed against three *T. cruzi* strains, which represent the discrete typing units more prevalent in human patients: Y (TcII), Silvio X10 cl1 (TcI), and Bug 2149 cl10 (TcV). All the derivatives, except one, showed enhanced trypanocidal activity against the three strains as compared to BZD. In the Y strain 62% of the compounds were more active than NFX. The most active compound was *N*′-((5-nitrofuran-2-yl) methylene)biphenyl-4-carbohydrazide (C20), which showed IC_{50} values of 1.17 ± 0.12 μM; 3.17 ± 0.32 μM; and 1.81 ± 0.18 μM for Y, Silvio X10 cl1, and Bug 2149 cl10 strains, respectively. Cytotoxicity assays with human fibroblast cells have demonstrated high selectivity indices for several compounds. Exploratory data analysis indicated that primarily topological, steric/geometric, and electronic properties have contributed to the discrimination of the set of investigated compounds. The findings can be helpful to drive the designing, and subsequently, the synthesis of additional promising drugs against Chagas disease.

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1. Introduction

Chagas disease (CD) is caused by the protozoan *Trypanosoma cruzi*, which can be transmitted by two predominant modes: vectorial, through infected feces/urine of triatomine bugs ('kissing bugs'), and by blood transfusion. Congenital transmission and oral infection by the ingestion of parasites in contaminated food, are also considered as important [1].

CD currently affects an estimated 8 million people in 21 countries in Latin America and is spreading by human migration to several countries in Europe, Canada, USA, Japan and Australia. It is considered the parasitic disease with the greatest socioeconomic impact in Latin America, being responsible for lost productivity costing US$ 1.2 billion annually [2].

CD is among the most neglected diseases. Since the 1970s, the treatment for Chagas disease is dependent on only two drugs, benznidazole (BZD, *N*′-benzyl-2-(2-nitroimidazolyl)acetamide) and nifurtimox (NFX, 3-methyl-4-(5-nitrofurfurylidene-amino)tetrahydro-4H-1,4-thiazine-1,1-dioxide) (Fig. 1A). Both nitroheterocyclic drugs require a prolonged treatment, cause severe side effects and have limited curative power in the chronic phase [1].

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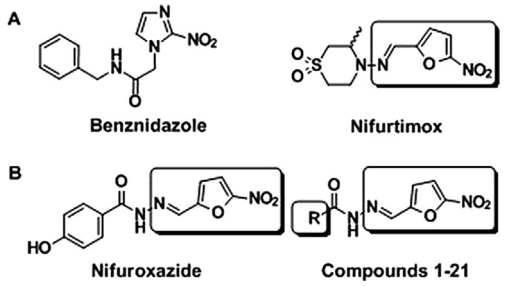

Fig. 1. (A) Chemical structure of benznidazole and nifurtimox. (B) Chemical structure of nifuroxazide, the lead compound, and scaffold of the designed compounds (c1–c21). Similar portions of nifuroxazide and nifurtimox structures were maintained in the designed compounds. The region where molecular modifications (R) were carried out is pointed out.

The reasons for treatment failures are unknown. NFX and BZD have shown different efficacies according to disease endemic areas [3]. In addition, experimental evidence in murine models indicates that both drugs exhibit a broad range of divergent activities against different *T. cruzi* strains, and natural resistance to NFX and BZD has been reported [4,5].

The biological and genetic diversity of *T. cruzi* strains have long been recognized. The strains are divided into six discrete typing units (DTUs) named as TcI to TcVI [6]. The ecological and epidemiological characteristics of *T. cruzi* DTUs have been recently reviewed [7–9]. DTUs TcI, TcII, TcV and TcVI are agents of human disease with dissimilar prevalence in different regions of Latin America. TcI is a major agent of human infection in Mexico, Central America, Amazonia and northern countries of South America. TcII predominates in patients in Brazil, whereas TcV and TcVI prevail in patients in the other countries of the Southern Cone region of South America. No apparent DTU association with natural resistance to BZD and NFX has been observed so far [10,11].

Given the unsatisfactory performance of the currently available drugs, new approaches on more specific chemotherapy for CD have been advanced in the last three decades and novel potential drug targets have already been described [2]. Ergosterol biosynthesis inhibitors, such as posaconazole and ravuconazole (E1224, prodrug), showed promising preliminary results [12]. Phase IIa clinical trials for evaluation of antiparasitic activity of both drugs in chronic patients have recently been concluded, but with unsatisfactory results [13,14]. An approach regarding the CD drug discovery and development scenery in 2013/2014 can be found elsewhere [15].

Previous data from our group have shown that some nifuroxazide (NF), 4-hydroxy-*N*′-(5-nitro-2-furfuryliden) benzohydrazide derivatives (Fig. 1B), show trypanocidal activity against epimastigote forms of the Y (DTU TcII) strain [16–18]. In addition, we have also reported that benzofuroxan derivatives and 5-nitro-2-furfuriliden derivatives are active against multidrug-resistant *Staphylococcus aureus* strains [16–20]. Although the NF mode of action is not fully elucidated, previous studies have suggested that NF antimicrobial activity would be related to the nitro group reduction and formation of free radical toxic species [16–18]. Being *T. cruzi* partially deficient in free radical detoxification mechanisms, these intermediates could affect its metabolism. The trypanocidal activity of NFX involves the generation of nitro anion radical by nitroreductases which, in the presence of oxygen, form reactive intermediates deleterious to the parasite [19,21–23]. Nifurtimox and eflornithine combination therapy have been considered the first-line treatment in second-stage gambiense human African trypanosomiasis (HAT) [24]. This fact would support the interest to investigate the trypanocidal action of new nitroderivative compounds.

NF analogs were synthesized (Fig. 1B), herein, in order to identify more active compounds against strains representing the DTUs more prevalent in human patients: TcI, TcII, and TcV [15]. Molecular modifications on the phenol group of NF scaffold were carried out in order to obtain physicochemical diversity. 'Lipinski's Rule of 5' was considered to support the design of drug-likeness [25–28]. The (5-nitrofuran-2-yl)methanamine moiety remained unchanged in order to preserve the similarity with the pharmacophoric group of NF and NFX. The energetically favorable conformation of each compound was selected by applying molecular modeling methods. Then, molecular properties of distinct nature (electronic, steric, hydrophobic, topological and geometric) were calculated to perform exploratory data analysis, which comprises hierarchical cluster analysis (HCA) and principal component analysis (PCA) [29,30]. The compounds were discriminated based on either similarity indices (HCA) or linear combination (PCA) in order to establish some qualitative structure–activity relationships.

2. Results and discussion

2.1. Chemistry

The set of 5-nitro-2-furfuriliden derivatives was obtained as shown in Scheme 1A. Molecular modifications were based on the influence of physicochemical properties, mainly hydrophobicity, represented by the calculated *n*-octanol/water partition coefficient (ClogP) [27,28] and steric/hydrophobic properties, represented by molar refractivity (MR) [31] in order to achieve structure diversity with the inclusion of aryl, alkyl and cicloalkyl substituent groups (Fig. 1). Recently, ClogP was pointed out as an important descriptor for anti-*T. cruzi* activity, showing high correlation with IC_{50} values against epimastigote forms of *T. cruzi* (Y strain) [18]. Furthermore, the designed compounds presented high degree of drug-likeness, regarding 'Lipinski's Rule of 5' [25,26] (see Scheme 1B).

The hydrazides were obtained from carboxylic acids through consecutive esterification and hydrazinolysis reactions, without isolating the corresponding methyl esters [32]. The hydrazinolysis reactions provided yields from 67 to 97%. 5-nitro-2-furfuriliden derivatives (c1–c21) were obtained by nucleophilic addition of hydrazides with 5-nitro-2-furaldehyde, and the yield ranged from 65 to 98%, as previously reported [18,33]. Regarding the nucleophilic addition step, compounds with low ClogP, i.e. high solubility in water, such as compounds c1 [$-CH_3$], c2 [$-C_5H_{11}$], c3 [$-C_5H_9$], c4 [$-O(tert\text{-}C_4H_9)$], c6 [$-C_6H_{11}$], and c11 [$-C_8H_{17}$], were synthesized using ethanol as reaction medium. Among the advantages of this method are: the isolation process, the reduction of impurities, and the improvement of yield. However, this approach requires more reaction time, and can be used only for hydrophilic compounds [34].

The structural elucidation of compounds c1–c21 was confirmed through ^1H and ^{13}C NMR spectra analysis, considering chemical shifts (δ) related to the residual solvent peak or internal standard (see Supplementary Material). Compounds showed characteristic NMR spectra, and compound c19 [$-C_6H_4\text{-}4\text{-}OC_4H_9$] was chosen to illustrate the analysis (Fig. 2). Regarding ^1H NMR spectrum of compound c19 (Fig. 2A), singlet signals can be observed around δ 12 ppm and δ 8 ppm, indicating the protons of *N*-acylhydrazones group (see Fig. 2: H_8 and H_6, respectively). The ^{13}C NMR spectrum of compound c19 has two characteristic peaks, as illustrated in Fig. 2B, one around δ 170 ppm, related to C_9 (carboxyl carbon), and other near 130 ppm, which is characteristic of C_6 (azomethine carbon).

2.2. Anti-T. cruzi activity assays

The biological activity of compounds c5, c9, c10 and c15 against

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