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Synthesis, anti-*Trypanosoma cruzi* activity and quantitative structure relationships of some fluorinated thiosemicarbazones

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ABSTRACT

Synthesis and spectroscopic characterization of ten fluorinated thiosemicarbazones are reported. All synthesized compounds were evaluated for their anti-*Trypanosoma cruzi* activity, and the IC_{50} values were obtained in the range of 5.64–29.19 $\mu g\,mL^{-1}$ in 24 h of cultures. Among all assayed thiosemicarbazones the 2,3,4-trifluoro-substituted compound showed the higher activity with $IC_{50} = 5.64\ \mu g\,mL^{-1}$. QSAR studies involving electronic and hydrophobic parameters, as well as the ^{13}C NMR chemical shifts of iminic carbon indicated that the deshielding effect caused by the fluorine atoms and their hydrophobicity are significant features for the anti-*T. cruzi* activity.

1. Introduction

The protozoan diseases such as Chagas disease and leishmaniasis are responsible for significant mortality of tropical and subtropical regions of the world. Additionally, the prevalence of the disease has been increasing in other areas such as North America and Europe due to human migration [1,2]. The protozoan parasites infect billion of humans, world-wide and are associated with large morbidity and economic impacts [3]. The trypanosomatids are parasitic protozoa of Kinetoplastida class that cause among others the Chagas disease by *Trypanosoma cruzi*. The Chagas disease affects around 25 million people which several effects such as cardiac, gastrointestinal or neurological commitment [4,5]. Chagas disease presents an initial acute phase followed by a chronic phase. The acute phase is generally asymptomatic, while the progression of disease into its chronic phase often results in cardiomyopathy, myocardium damage and other heart diseases [6].

For treatment of Chagas disease only two drugs, nifurtimox (Lampit™) and benzinidazole (Radanil™, Rochagan™) are decades old used and, curing at least 50% after long time of use with severe side-effects [7,8], further, are not uncommon the failure of treatment. In addition, the parasite naturally resistance to these compounds has been observed [9], including the induction of maintaining the parasite under prolonged drug exposition [10]. The search of new, safe and efficient anti-parasitic agents for the treatment of Chagas disease is an urgent need for health programs in all world.

Thiosemicarbazones are now well established class of nitrogen and sulphur donor ligands very attractive because of their structural, and diversified biological activities, such as, anticancer [11,12], antimicrobial [13,14], antiviral [15], antimalarial [16], anti-leishmanial [17] and anti-trypanosomal [16,18]. There are few years ago we reported the anti-*Trypanosoma cruzi* activity of some thiosemicarbazones, and the most efficient compound, 2-methoxy-styryl-thiosemicarbazone, demonstrated a significant decrease in nitric oxide synthase enzyme activity. Further, also was observed the absence of macrophage toxicity for any of the assayed compounds [19].

The fluorine moiety when present in biological active molecules led to very important increase of their biological effects [20,21]. In several times, the drug-receptor interactions are improved in the presence of fluorine moiety and the transport of drug is facilitated by the high lipophilicity of organofluorine compounds [22].

Thus, the early results of anti-*T. cruzi* effects by styrylaldehyde-thiosemicarbazones motivated us to prepare a series of thiosemicarbazones containing fluorine moieties in the benzaldehyde portion. Furthermore, the literature reports that among the thiosemicarbazones, assayed for anti-parasitic activities, fluorinated benzaldehydes-thiosemicarbazones have been rarely tested. So, in this paper we report the synthesis and full characterization

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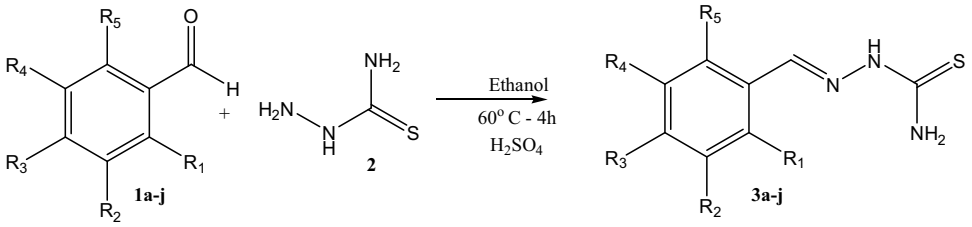

a: R_1=R_2=F, R_3=R_4=R_5=H
b: R_1=R_4=F, R_2=R_3=R_5=H
c: R_1=R_5=F, R_2=R_3=R_4=H
d: R_1=R_2=R_3=F, R_4=R_5=H
e: R_1=R_2=R_4=R_5=F, R_3=H
f: R_1=R_2=R_3=R_4=R_5=F
g: R_2=R_4=F, R_1=R_3=R_5=H
h: R_3=F, R_1=R_2=R_4=R_5=H
i: R_2=R_3=F, R_1=R_4=R_5=H
j: R_3=CF_3, R_1=R_2=R_4=R_5=H

Scheme 1. Synthesis of the compounds 3a–j.

by ^{1}H, ^{13}C and ^{19}F NMR, of ten fluoro-benzaldehyde-thiosemicarbazones (**3a–j**), the anti-*T. cruzi* epimastigotes effects and the preliminary quantitative structure activity relationship (QSAR).

2. Results and discussion

2.1. Chemistry

A series of ten fluoro-benzaldehyde-thiosemicarbazones (**3a–j**), in which the compounds **3a, 3d**, **3e** and **3f** are described here for the first time, was prepared from the fluorinated benzaldehydes (**1a–j**) with thiosemicarbazide (**2**) in ethanol, as solvent, and few drops of H_2SO_4 at 60 °C within 4 h, according to literature, [17] as shown in the Scheme 1. The products were recrystallized from methanol in 92–96% yield. The infrared spectra show the band at 1500–1530 cm^{-1} and 1030–1097 cm^{-1} related to ν C=S and ν (C=N), respectively, as reported in the literature [23]. ^{1}H, ^{13}C and ^{19}F NMR spectra (Supplementary data) permitted the full characterisation of all thiosemicarbazones.

The ^{13}C NMR spectra showed that all the chemical shift values of C-1′ to the fluorinated-benzaldehyde thiosemicarbazones (**3a–j**) have upfield shift ($\Delta\delta < 0$) when compared to benzaldehyde thiosemicarbazone (**TH**), as can be observed in Table 1. In addition, when there is at least one fluorine atom is present in *ortho* position, the shielding is most pronounced ($\Delta\delta \geq |8{\cdot}9|$). Moreover, other increase in shielding is observed of $\Delta\delta = -11{\cdot}3$ and $\Delta\delta = -12{\cdot}0$ to compounds with 4 (**3e**) and 5 (**3f**) fluorine atoms, respectively. The C-1 (*ipso* carbon) also stay shielding ($\Delta\delta < 0$), with exception of the compound **3g** (two fluorine atoms in *meta* position) and **3j** (4-CF_3). The difference of chemical shifts ($\Delta\delta$) these carbon atoms are higher than C-1′ atoms, and the polyfluorinated compounds, **3e** and **3f**, present values of $\Delta\delta = -19{\cdot}9$ and $\Delta\delta = -24{\cdot}6$, respectively, when compared to benzaldehyde thiosemicarbazone. These results can be attributed to mesomeric and polar effects caused by fluorine atom in the *ortho* position. A dependence linear was obtained ($r^2 = 0.89$) between Δδ C-1′ and Δδ C-1, with two outliers, **3b** and **3h**.

The ^{1}H NMR shifts for azomethine hydrogen (H-1′) present two tendencies, when there is one or more fluorine atom are present in *orto* position; the chemical shift of H-1′ atom is downfield ($\Delta\delta > 0$), and the opposite effect is observed to C-1′ atom. It can be due to anisotropic effect caused by N atom, since another compounds (**3g–j**) are upfield ($\Delta\delta < 0$) with exception of compound **3j**. This same tendency was observed for chemical shifts of the Schiff bases [24]. The hydrogens of the NH_2 group present different chemical shifts, indicating that these not is homotopic, probably due to establishing of an intramolecular hydrogen bond (Scheme 2) with the N-5′ of azomethine group. However, as can be observed in Table 1, at least one H-5′ is more deshielding than the corresponding hydrogen of the benzaldehyde-thiosemicarbazone (δ 8.22). The presence of an intramolecular strong hydrogen bond can be the cause of this hydrogen chemical shift in downfield, highlight the compounds **3e** and **3f** that present the chemical shifts in δ 8.54 and δ 8.52, respectively. The ^{19}F NMR chemical shifts present δ −162.7 to −109.4 according with the contribution of electronic effect due the fluorine atoms at *ortho*, *meta*, and *para* position, with exception the compound **3j** (R_3 = CF_3, δ = −65.0). Further, were observed values of F–F coupling in the range of 5 Hz to 25 Hz due to distance between the fluorine atoms. The ^{19}F NMR chemical shifts as F–F coupling were in concordance with the literature [25].

Table 1
Some ^{1}H and ^{13}C chemical shifts for compounds **3a–j** in DMSO-d_6.

Entry	Comp.	Substituent					δ C-1′	Δδ C-1′-C-1′[a]	δ C-1	Δδ C-1-C-1[a]	δ H-1′	Δδ H-1′-H-1′[a]	H-5′
		R_1	R_2	R_3	R_4	R_5							
1	**TH**[a]	H	H	H	H	H	142.8	0	134.6	0	8.05	0	8.22/8.01
2	**3a**	F	F	H	H	H	133.9	−8.9	124.6	−10.0	8.26	0.21	8.38/8.15
3	**3b**	F	H	H	F	H	134.3	−8.4	123.5	−11.1	8.21	0.16	8.36/8.16
4	**3c**	F	H	H	H	F	133.8	−9.7	111.1	−23.4	8.21	0.16	8.43/7.36
5	**3d**	F	F	F	H	H	133.2	−9.6	120.6	−14.0	8.18	0.13	8.36
6	**3e**	F	F	H	F	F	131.5	−11.3	114.7	−19.9	8.16	0.11	8.54/7.42
7	**3f**	F	F	F	F	F	130.8	−12.0	110.0	−24.6	8.12	0.07	8.52/7.43
8	**3g**	H	F	H	F	H	139.8	−3.0	138.6	+4.0	7.98	−00.7	8.33/8.28
9	**3h**	H	H	F	H	H	141.6	−1.2	131.1	−3.5	8.04	−001	8.24
10	**3i**	H	F	F	H	H	140.2	−2.6	132.6	−2.0	8.00	−0.05	8.27/8.21
11	**3j**	H	H	CF_3	H	H	140.7	−2.1	138.7	+4.1	8.10	0.05	8.36/8.20

[a] Phenyl-thiosemicarbazone.