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Synthesis, docking and *in vitro* activity of thiosemicarbazones and acyl-thiazolidones against *Trypanosoma cruzi*

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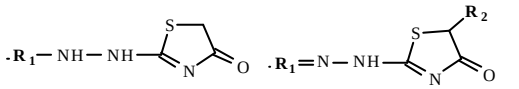
Introduction

Chagas' disease is a serious health problem that affects around 20 million people in Central and South America, and results in 50,000 yearly deaths. Development of new anti-chagasic drugs is a must. Cruzain is the major cysteine protease of *T. cruzi* and appears to have potential for new antitrypanosomal chemotherapy. Some derivatives with thiosecarbazones scaffolds have been related for their ability to interaction with cruzain. These data suggest a promising direction for the development of new antitrypanosome chemotherapy. Here we report here the synthesis of thiosemicarbazones and acyl-thiazolidone and the *in vitro* evaluation of their ability to inhibit the growth of epimastigote and trypomastigote forms of *T. cruzi*, as well as a docking analysis under *Trypanosoma cruzi* cruzain (TCC). The compounds designed were thus analyzed as potential ligands for cruzain[1].

Results and Discussion

The novel compounds were prepared as described in reference 2 and showed below.



5a R_1 = Gly* 10a R_1 CH-CH_2-S-p Cl-C_6H_5 R_2 = CH_3
5b R_1 = Phe 10b R_1 C(CH_3)-CH_2-S-C_6H_6 R_2= CH_3
5c R_1 = Pro 10c R_1 CH-CH_2-S-pCH_3-C_6H_5 R_2 = H.

* Entry represent the Boc-amino acids residues.

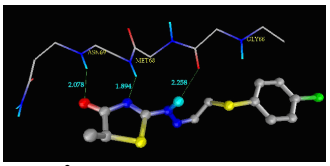
These compounds were tested at non-cytotoxic concentrations on the epimastigote form of Y strain. The free energy of binding (ΔG) values for complexes (most stable docking solutions) between compounds and target (TCC) are presented in Table, along with the pIC_{50} (equals –log IC_{50} of the Y strain epimastigotes) values. In the case of acyl-thiazolidones derivatives, the compound **5c** (a proline derivative) was more active than analogues **5a** and **5b**, however, inactive against the Colombian strain (data not shown). With regard to the aryl-thiazolin-hydrazones series, biological analyses revealed that **10b** (in racemic form), was the least cytotoxic and the most active against the Colombian strain in a high concentration (data not shown). Yet compound **10a** was the most active at the concentrations tested. This compound possesses a chlorine substituent in the phenyl ring system and has shown itself to be active against epimastigote, when compared with benznidazole.

Table: Biological and Docking results.

Comp.	Y epimastigote (%)[a]	IC_{50}[b]	pIC_{50}[c]	? G[d] (kcal/mol)
5a	0.0	**73.4**	4.13	-5.27
5b	8.7	**83.3**	4.08	-6.88
5c	65.2	**30.5**	4.52	-7.01
10a	89.0	**31.9**	4.50	-6.92 (R) and -7.10
10b	100.0	**128.4**	3.89	-7.02 (R) and -7.01
10c	92.3	**45.0**	4.35	-6.67

[a] (%) growth inhibition, [b]μmol/L, [c]-log IC_{50} with IC_{50} in mol/L, [d] is free energy of binding values.

The docking analysis was carried out using the AutoDockTools (ADT) v1.1 and Autodock v3.0.5 programs. The active site was treated as a rigid molecule, whereas the ligands were treated as flexible, which means that all non-ring torsions were maintained (active).The compound that produced the best result (i.e. the most stable complex) in docking analysis, the S enantiomer of molecule **10a**, was analyzed in details. Important interactions found include three hydrogen bonds and also hydrophobic interactions between ligand and target residues (see figure).



HB distances in Å (blue) and residues names (yellow).

Conclusions

In summary, some derivatives exhibit significant in vitro activity against epimastigote T. cruzi, particularly compounds **5c** and **10a.** These results confirm that the thiosemicarbazone scaffold is a potential anti-T. cruzi agent.

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[1] *Leite, A. C.; Santos, L. M. F.; Lima, R. S.; Cardoso, M. V. O. Moreira, D. R.M.; Brito, A. C. G.; Hernandes, M. Z.; Kiperstok, A., Lima, R. S.; Soares, M. B. P.* Bioorg. Med. Chem. ***2006***, *14*, in

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