SAR, Molecular Modeling and *in silico* Toxicological Studies of Thiosemicarbazone Inhibitors of Rhodesain, Falcipain and Cruzain

Raphaela P. Valiati (IC)[1], Helena C. Castro (PQ)[2], Carlos R. Rodrigues (PQ)[3], Monique A. de Brito (PQ)[1]* (moniquebrito@vm.uff.br)

[1] Lab. de Química Medicinal Computacional, Faculdade de Farmácia, UFF. [2] LaBioEMol, Instituto de Biologia, UFF. [3] ModMolQSAR, Faculdade de Farmácia, UFRJ.

Key Words: Molecular Modeling, Structure-Activity Relationship, Tropical Diseases, Thiosemicarbazone Derivatives.

Introduction

Parasitic diseases are major causes of human disease and mortality in most tropical countries, affecting mainly marginalized populations.[1] Chagas disease, malaria and sleeping sickness are the main examples of such diseases.[2] They affect millions of people in the non-developed areas of the world.

All drugs on the market for these tropical diseases are very old and toxic.[2] Therefore, there is a need in the research of new drugs to combat these diseases.

Structure-Activity Relationship (SAR) molecular modeling and *in silico* toxicological studies are important areas with the aim of improving and designing new drug candidates.

Results and Discussion

In this study we have worked with 15 thiosemicarbazone inhibitors[3] of the rhodesain, cruzain and falcipain enzymes, which were used to develop the SAR.

The descriptors used for the SAR study were dipole moment (μ), energies of the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO), molecular weight (M.W.), area, volume, number of atoms acceptors of hydrogen bond and number of atoms donors of hydrogen bond. We also compared the electrostatic potential maps (E.P.M.) of the inhibitors. All the calculations were performed using Sartan Pro (Wavefunction Inc. Irvine, CA, 2000).

The structural profile of the inhibitors was shown in Figure 1, where R_1 and R_2 are different substituents.

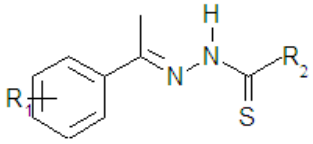


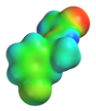
Figure 1. Structural profile of the inhibitors.

Our molecular modeling results showed that compound **3d**, the more active inhibitor (IC_{50} and E.P.M. showed in Table 1), has the lowest E_{HOMO}= -8.85 eV. It also has shown E_{LUMO}= -0.58 eV, μ= 3.91 D, M.W.= 272.17 g/mol, area of 267.90 Å² and volume of 247.22 Å³. These properties may be implicated in SAR.

In silico toxicological properties (tumorigenicity, mutagenicity, reproductive and irritating effects) was obtained with Osiris® Property Explorer (Actelion Pharmaceuticals Ltd.). All compounds of the series showed good results, except the compound **2c** (which has lower activity).

Parameters like cLogP, solubility, *drug-score* and *drug-likeness* were also analyzed and showed good results. The value of cLogP for the most active compound, **3d**, is 2.32.

Table 1. Electrostatic potential map for the more active inhibitor (**3d**) of cruzain and rhodesain.

#	IC_{50} (μM) cruzain	IC_{50} (μM) rodesain	E.P.M.
3d	0,06	0,05	

Conclusion

The SAR study done with 15 inhibitors of cruzain, rhodesain and falcipain-2, showed some relationship with the descriptors analyzed, mainly with the E_{HOMO}, which presented the lowest value for the more active compound. The toxicological properties also showed good results.

Acknowledgements

PROPPi (UFF), FAPERJ, CNPq, and the professor Estela M. F. Muri (UFF).

---

[1] Hotez, P. J.; Fenwick, A.; Savioli, L.; Molyneux, D. H. *The Lancet*, **2009**, *373*, 1570.
[2] Hotez, P. J.; Molyneux, D. H.; Fenwick, A.; Kumaresan, J.; Sachs, S. E.; Sachs, J. D.; Savioli, L. *N. Engl. J. Med*., **2007**, *357*, 1018.
[3] Greenbaum, D. C.; Mackey, Z.; Hansell, E.; Doyle, P.; Gut, J.; Caffrey, Conor R.; Lehrman, J.; Rosenthal, Philip J.; McKerrow, James H. and Chibale, K. *J. Med. Chem*., **2004**, *47* , 3212.