XIX SBQT
Simpósio Brasileiro de Química Teórica 2017
12 a 17/Nov, 2017, Águas de Lindóia/SP, Brasil

Molecular modeling in the inhibition of *M. tuberculosis* enzymes

Authors: Luis Mauricio S. Soares(*), Paulo Augusto Netz, Ícaro Ariel Simon, Vanessa Petry do Canto, Ricardo Fagundes da Rocha, Luis Andre Baptista
Address: Universidade Federal do Rio Grande do Sul. Instituto de Química, Grupo de Química Teórica. Av. Bento Gonçalves, 9500. Bairro Agronomia. Porto Alegre/RS.

Abstract: According to data from the World Health Organization (WHO), in the year 2015, occurred about 10.4 million of tuberculosis new cases; of these, 480 000 new cases of multidrug-resistant. Isoniazid (pyridine-4-carbohydrazide), a prodrug, used in tuberculosis treatment, has been known since 1952, as a potent agent against the *M. tuberculosis* bacillus; and is currently one of the main chemotherapeutics used to control this disease [1,2]. Among the *M. tuberculosis*'s mutant genes, about 75 to 85% of cases are related to the enzymes katG and inhA [3]. However studies have also found resistant strains of *M. tuberculosis*, with mutations in genes of the enzymes kasA (keto-acyl-synthase) and in ndh (NADH dehydrogenase) [4].
The present study aims to use computational methods to study of the interactions of isoniazid derivatives with enzymes of interest for the control of *M. tuberculosis* bacillus, focusing on resistant strains. Results of docking calculations carried out with the AutoDockVina program [5] using InhA and KatG enzymes as receptors are presented in this paper. The docking scores of about 104 docked molecules with different strains of the InhA and KatG enzymes were obtained and some of them are presented in the table below, compared with the reference isoniazid.

Enzyme	**InhA**			**KatG**			
PDB's id	4TRO*	4DTI**	2AQH**	1SJ2*	2CCD**	4C50**	4C51**
Ligands	Scores ($kcal.mol^{-1}$)						
isoniazid	**-7.1**	-5.2	-5.5	-6.3	-5.8	-6.5	-6.1
15	**-10.9**	-8.1	-8.8	-7.6	-7.1	-8.6	-7.3
19	**-10.5**	-8.5	-8.8	-9.0	-8.6	-9.4	-9.2
20R	**-9.8**	-7.5	-7.1	-7.7	-6.9	-6.9	-7.5
23S	**-10.7**	-8.3	-9.0	-9.1	-9.3	-8.9	-9.0
24R	**-10.5**	-8.6	-8.3	-9.2	-8.9	-8.4	-8.6
25	**-9.1**	-7.3	-7.6	-7.9	-7.2	-8.2	-8.2

*native isoform, **mutant isoform

The location, conformation and interactions of the ligands in the receptors were analyzed and it was also possible to verify a good correlation between the poses of lower energy, and their fit in the regions already defined by the literature as binding sites in these enzymes.

XIX SBQT
Simpósio Brasileiro de Química Teórica 2017
12 a 17/Nov, 2017, Águas de Lindóia/SP, Brasil

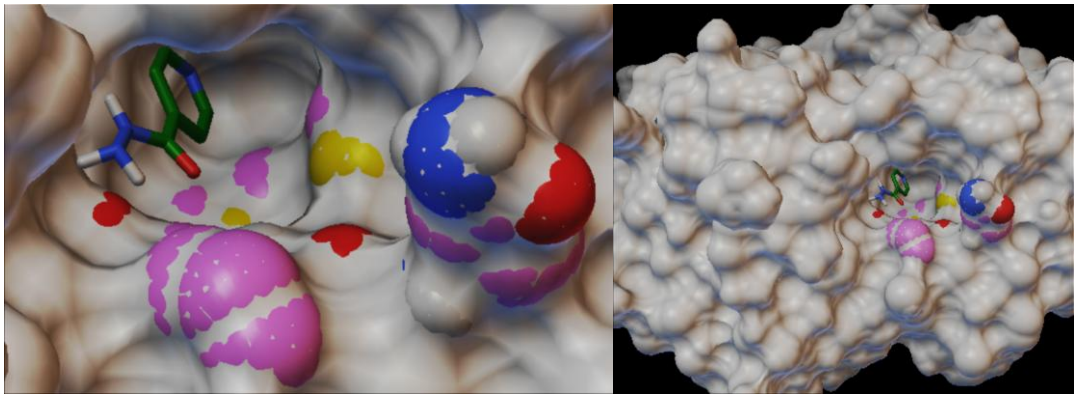

Figure 1 – Isonizid molecule fits to non-mutated Inha enzyme.

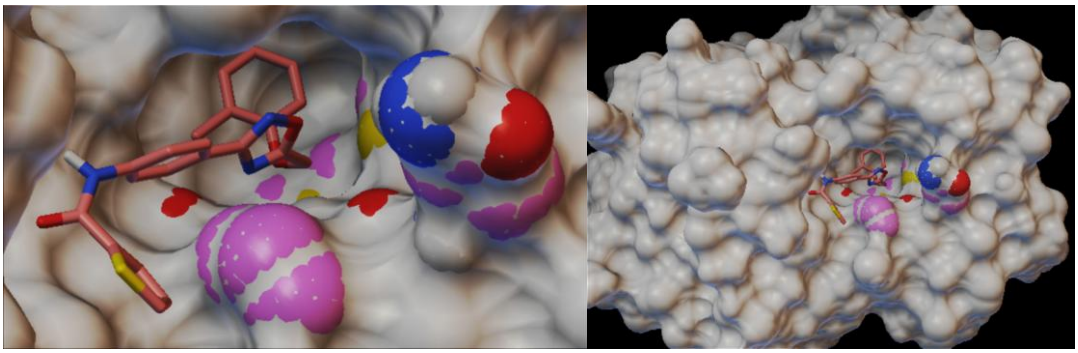

Figure 2 – Ligand 15, fits to same non-mutated Inha enzyme.

As second step of this study (already running), we expect to obtain, using molecular dynamics simulations, further insights regarding the interaction mechanisms of isoniazid-derived molecules, with different receptors, focusing InhA and KatG. Groups of molecules will also be selected and classified according to their topological characteristics, with aim of selecting molecules with larger pharmacological effect against *M. tuberculosis*.

Key-words: isoniazid, tuberculosis, Mycobacterium
Support: This work has been supported by Fundação de Amparo à Pesquisa do Rio Grande do Sul - FAPERGS, Universidade Federal do Rio Grande do Sul – UFRGS, Universidade Federal de Mato Grosso-UFMT.

References:

[1] Y. Zhang, A. Telenti, In: G.F. Hatfull, W.R.Jr. Jacobs, Washington, D.C ASM Press., p. 235-254 (2000).
[2] M.L.R. Rossetti et al. Revista Saúde Pública, v. 36, p. 525-532, 2002.
[3] N.L. Wengenack et al. Biochemistry. 37:15825-34. 1998.
[4] A. S. G. Lee, et al. Antimicrob. Agents Chemother. 45:2157–2159. 2001.
[5] O. Trott, A.J. Olson, J. Comp. Chem., v. 31, p. 455-461 (2010).