RECEPTOR-DEPENDENT 3D-QSAR APPROACH OF A SERIE OF *Trypanosoma cruzi* CYP51 INHIBITORS

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Introduction

The protozoan *Trypanosoma cruzi* (*T. cruzi*) is the etiological agent of Chagas disease. This disease is a serious public health problem due to the fact that 8 million people are infected worldwide, mostly in Latin America, where this disease is endemic (WHO, 2019). The treatment of Chagas disease is based on two nitroheterocyclic drugs: nifurtimox and benznidazole. Both are most effective in early stages of infection and have several side effects (Aldasoro et al., 2018; Miranda; Sayé, 2019). In the search for new drug candidates, the sterol 14α-demethylase cytochrome P450 (CYP51) has been evaluated as a drug target for *T. cruzi* due to its role in the ergosterol biosynthesis, essential for the parasite's survival (Lepesheva, Friggeri, Waterman, 2018). The present work focuses on the development of a receptor-dependent (RD) 3D-QSAR study of a series of CYP51 inhibitors described in the literature, aiming to provide some insight into the design of novel CYP51 inhibitors for Chagas disease treatment.

Method

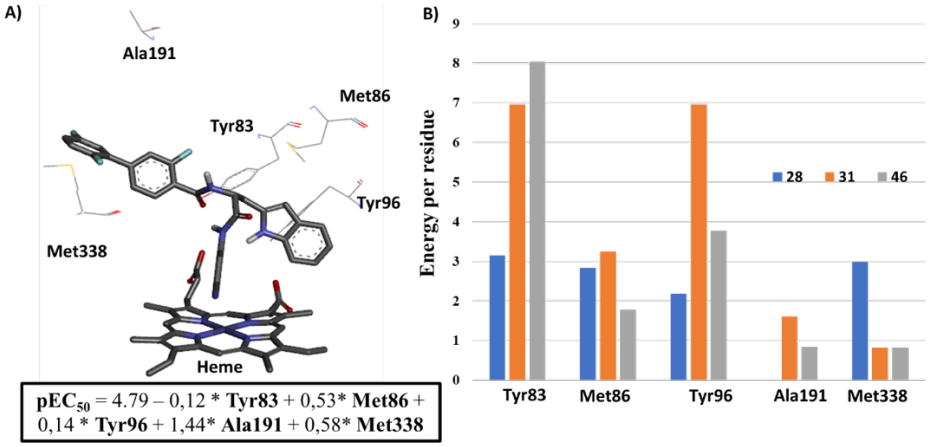
The RD-3D-QSAR models were built using a series of 50 CYP51 inhibitors (Andriani et al., 2013; Calvet et al., 2014; Vieira et al., 2014). The half-maximal effective concentration (EC_{50}) in nM of these compounds was converted to M and turned into the -log EC_{50} (pEC_{50}). This series of CYP51 inhibitors was split into a training set and a testing set in the proportion of 80:20, respectively. The Spartan 10 software was used to build the 3D structures of the inhibitors, which were optimized using the RM1 semi-empirical method. Molecular docking studies were performed using the GOLD 5.2 software, considering the ChemScore function (Jonnes et al., 1997). The energy per residue was extracted and used as independent descriptors to build the RD-3D-QSAR model. The influence of its descriptors in the predictive capability of RD-3D-QSAR models was estimated by the construction of four databases considering the different variance values (BDA=0.001, BDB=0.005, BDC=0.01 and BDD=0.05). The Kennard-Stone method was applied to select the training set and the test set compounds, considering the high dissimilarity regarding descriptors. The QSAR equations from 4 to 8 terms were generated in the WOLF software from the databases (Rogers; Hopfinger, 1994). The combined Genetic Function Approximation and Partial Least Squares (GFA/PLS) algorithm were used. The best equations were selected considering the follow statistic parameters: correlation coefficient (R^2), cross-validation correlation coefficient (q^2), root-mean-square deviation of the estimate (RMSEE), standard error of the estimate (SEE) and Spearman's correlation (ρ).

Results / Discussion

The 50 CYP51 inhibitors was successfully performed as described in the literature (Andriani et al., 2013; Calvet et al., 2014; Vieira et al., 2014), and the energy per residue from each pose was used as a descriptor to build the RD-3D-QSAR models. The WOLF software generated 2700 RD-3D-QSAR

models from all databases used (BDA, BDB, BDC, and BDD). The models with less variance showed a gradual reduction in the values of R^2 and q^2 according to the increase in the cutoff point of the variance and its interference in the predictive capacity of the models. Then, we selected the best 8 models from all databases using the parameters $R^2 > 0.6$, $q^2 > 0.5$ and RMSEE <1.0, The D-02 model (term=5; $R^2 = 0.727$; $q^2 = 0.618$ and RMSEE =0.712, **Figure 1A**) was chosen due to the low correlation between the descriptors of the model and better overall performance. Besides, two outliers were detected: **31** (Residual value = -1.44) and **46** (Residual value = 1.70), which were related to an underestimation and an overestimation, respectively. This result could be associated to the elevated interaction energy with **Tyr83** and **Tyr96** (**Figure 1B**). Moreover, this model showed a good agreement between experimental and predicted values ($\rho = 0.854$; $\mathbf{RMSEE_{train}} = 0.605$; and $\mathbf{RMSEE_{test}} = 0.776$).

Figure 1 – (A) Binding site interaction to model D-02 with the most active compound (**28**); (B) The energy per amino acid residue from the compounds **28**, **31**, and **46**



Conclusion

An RD-3D-QSAR model was developed based on the CYP51 inhibitors described in the literature. Eight models were selected from those generated by the WOLF software. From these, the D-02 was chosen as the best model, which presented better accuracy and better statistical parameters. This model highlighted the residues Tyr83, Met86, Tyr96, Ala191, and Met338 to describe the biological activity. These results can be used to predict the biological activities of potential anti-*T. cruzi* compounds.

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