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Hierarchical virtual screening for identification of *Leishmania braziliensis N*-myristoyltraferase inhibitors

GALLO, J.C.C.[1*]; OLIVEIRA, L. M.[1]; SANTOS JUNIOR, M. C.[1]
Laboratório de Modelagem Molecular, Universidade Estadual de Feira de Santana-BA[1]
julianaccgallo@gmail.com

Abstract: Leishmaniasis is considered a neglected tropical disease with a limited therapeutic arsenal [1]. In order to overcome this problem, the enzyme N-myristoyltransferase of *Leishmania braziliensis* (*Lb*NMT) has been chosen as a molecular target, by catalyzing the transference of fatty acids, important in the constitution of parasite's cellular membrane [2]. Here, we report a combination of ligand- and structure-based screening approaches in finding *Lb*NMT inhibitors. Based on the published literatures, we collected five inhibitors as training set to generate pharmacophore models (PM), and six inhibitors as a test set to validate the PM. The test set were utilized for generating decoys in the DUD-E [3]. The PM were constructed in GALAHAD (SYBYL-X 2.0) [4]. 10 PM were generated and these were aligned to the test set and decoys, and then the Receiver Operating Characteristic Curve (ROC curve) was constructed in SigmaPlot 12.0 [5]. The PM01 showed the highest rate of recovery of active molecules, with AUC =1.0, indicating that PM distinguish between the molecules groups (true positives and false positives). This pharmacophore model show four hydrophobic centers, one positive nitrogen center and four hydrogen bond acceptor (Fig.1). The Biogenic Bank from Zinc15 [6] database was submitted to flexible alignment with PM01. 220 molecules were aligned to the PM01, the pharmacophoric match (QFIT) these molecules ranged from 6.0 to 47.9, these molecules were submitted to molecular docking approaches. Molecular docking was performed in DOCK 6.8 [7] program, using PDB [8] ID 5A27 receptor. Docking success was considered when the top scoring pose is within 2Å heavy atom Root-Mean-Square Deviation (RMSD) of the crystal ligand and AUC > 0.8 in ROC curve. 1.12Å RMSD is acceptable value, indicating that the pose generated by the DOCK 6.8 is close to that obtained by the crystallographic ligand**.** The AUC = 0.93 show perfect separation of the true positives/negatives molecules showing that Grid Score from DOCK 6.8 to be an effective score function. The molecules selected for the ligand-based method were submitted to molecular docking using Grid Score function. The top ranked molecules with their respective energy values (Kcal/mol) were ZINC85629024 (-105.79), ZINC85630510 (-98.04) and ZINC85630554 (-96.00). The ZINC85629024 forms hydrogen bonds acceptor with Tyr84, Met369 and Glu74, hydrogen bonds donor with Tyr209, Met369, Met412, Gly197 and π-stacking T-shaped with Tyr337 (Fig. 2). The combination of ligand and structure-based virtual screening allowed the identification of potential inhibitors of *Lb*NMT.

Figure 1. Hydrophobic Centers: cyan, Positive Nitrogen Center: red and Hydrogen Bonds Acceptors: green. The distance between the spheres was measured in Å.

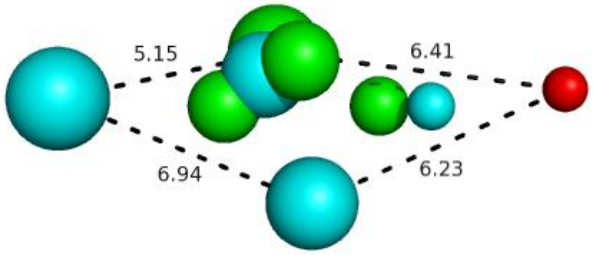
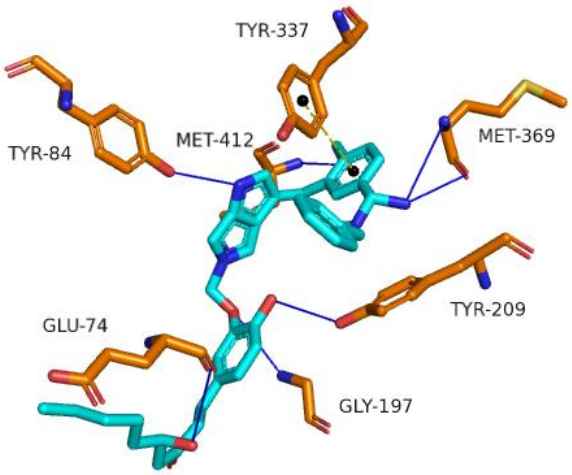


Figure 2. Intermolecular interactions between *Lb*NMT and the ZINC85629024 molecule. Hydrogen bonds (solid blue line) and π-stacking T-shaped (dashed yellow line).



Key-words: Pharmacophore model. Molecular docking. NMT. *Leishmania braziliensis.* Natural products.

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