# 24-c-sterol-methyltransferase as a target for the design of new anti-trypanosomatids drugs

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*Trypanosoma brucei* is the etiologic agent of sleeping sickness, a neglected tropical disease (NTD) affecting mostly low-income populations in tropical countries. The last product of sterol biosynthesis in parasitic is ergosterol and 24-alkylated sterols are major cell membrane components of parasites, in contrast to cholesterol in mammals. Their biosynthesis requires an alkylation, catalyzed by an S-adenosyl-L-methionine: Δ24- sterol methyltransferase (Tb24-SMT), a key difference between cholesterol and ergosterol biosynthesis, presenting an opportunity for the rational design of anti- infective agents. Its inhibition prevents the survival of parasites and is an important target for design of anti-trypanasomatids drugs. However, a limiting factor for the structural-based drug design is the absence of a Tb24-SMT 3D model for an appropriate active site mapping and pharmacophore models. In this work, we built 100 3D models candidate for Tb24-SMT, using comparative modeling and threading approach, based on the structure of 4'-O-methyltransferase from *L. aerocolonigenes* (PDBid 3BUS) with 60% coverage, 23% identity and 41% similarity between sequences. The best model was chosen and validated through the parameters: Ramachandran plot where the highest value of R1 (residue in most favored regions) was 95.2%, the average deviation between template and model (RMSD) was 0.37Å. The active site residues being mapped as N134, Q139, D162, F163, M163, M166, I179. Molecular docking studies were performed with derivatives of azasterol inhibitors by AutoDock and Vina softwares. We conclude that sequential analyses identified the binding site residues and showed it is conserved between template and model. Molecular docking studies for all inhibitors showed more than 32% of conformations in the same cluster. The azasterol+3C (-12.90 kcal/mol), 22-piperidin-3yl-pregnan-22(S),3b-diol (-12.43 kcal/mol) and 24-b-aminolanosterol (-12.06 kcal/mol) inhibitors demonstrated the best results with lower docking energy, better than the natural substrate zimosterol (-10.10 kcal/mol) and lanosterol (-10.40 kcal/mol) results for this enzyme. The amino acids participating in the interaction between enzyme and compounds were mapped. Next step consists in MD simulations for providing detailed information on the interaction and fluctuations in each complex with compounds for further experimental purposes.

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