In silico evaluation of phenothiazine derivatives as trypanothione reductase inhibitors

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Background: American trypanosomiasis is caused by parasite *Trypanosoma cruzi*, and it is considered a worldwide health problem. Current treatment consists of benznidazole and nifurtimox, which are not fully effective against both disease stages and have adverse effects. There is thus a need to find parasite-specific alternative treatments. Search of specific inhibitors of parasite-exclusive crucial enzymes is a known strategy. Trypanothione reductase (TR) enzyme is central in parasite's redox system both for detoxification of reactive oxygen and nitrogen species as well as amino acid and nucleotide biosynthesis. Phenothiazine scaffold is known by pharmacologists as a very versatile structure and its derivatives have shown TR inhibition. A virtual screening of phenothiazine derivatives from PubChem database may permit finding potential TR inhibitors. **Methodology**: TR crystal was obtained from the PDB database (1GXF). A total of 100 phenothiazine derivatives complying with Lipinski's rules were docked in TR active site using AutoDock Vina 1.1.2. Binding energy and interaction profiles, determined with PLIP (Protein-Ligand Interaction Profiler) server, were used to discriminate among derivatives. **Results**: Binding energy was found to be in the range of -10.9 to -6.1 kcal/mol compared to -8.8 kcal/mol of natural ligand trypanothione disulfide (TS_2). Forty-two compounds showed a binding energy greater than or equal to natural ligand, top ten were determined interactions. Main interactions were found with residues important to TS_2 binding: Phe396, Leu399, His461, Glu466 and Glu467. **Conclusion**: Best ranked compounds both by binding energy and interactions may be proposed as TR inhibitors and assayed *in vitro* to test effectivity.