RECEPTOR DEPENDENT (*RD*) LQTA-QSAR APPLIED TO A SET OF PHENOTHIAZINE DERIVATIVES AS INHIBITORS OF *T. cruzi* TRYPANOTHIONE REDUCTASE

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Introduction: A fundamental metabolic difference between mammalian host and trypanosomal parasite is the trypanothione redox-defense system. The enzyme trypanothione reductase (TR) is considered a potential target for the rational design of selective antitrypanosomal drugs. Parveen and co-workers (2005) reported that quartenization of the nitrogen atom of 2-amino-4-chlorophenyl phenyl sulfide analogues of chlorpromazine improved *T. cruzi* TR inhibition approximately 40-fold with a linear competitive K_i value in the μM range. **Purpose**: Application of *receptor-dependent* (*RD*) LQTA (Laboratório de Quimiometria Teórica e Aplicada)-QSAR formalism to a set of phenothiazine derivatives as inhibitors of *T. cruzi* TR. **Methodology**: A new approach of molecular alignment and (*RD*) 4D-QSAR methodology were applied to a preliminary set of thirty-three phenothiazine derivatives reported as potential inhibitors of *T. cruzi* TR. The ligand docking procedure into the active site of TR was followed by molecular dynamics (MD) simulations of the ligands-TR complexes. The alignment considered a conformational ensemble profile (CEP) of each ligand instead of one single conformation, and was based not only on the ligands' atoms, but also on key enzyme's atoms around the binding pocket. The QSAR models were built employing the ordered predictor selection (OPS) algorithm for variable selection, and the partial least squares (PLS) regression method. The **y**–randomization and leave–*N*–out cross-validation procedures were carried out in addition to the external validation. **Results**: Preliminary PLS models provided the following statistics: $q^2 = 0.84$, $r^2 = 0.91$ for 8 variables selected and 3 latent variables. Visualization of the 3D descriptors was successfully interpreted and provided an explanation regarding the binding mode of the set of ligands investigated. **Conclusions**: These findings support the applicability of this novel approach in the structure-based drug design of new potential and selective *T. cruzi* TR inhibitors.

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