QM 035 - RECEPTOR-DEPENDENT (*RD*) 3D-QSAR MODELS OF A SET OF ISONIAZID DERIVATIVES BOUND TO InhA, THE ENOYL-ACP REDUCTASE FROM *M. tuberculosis*, USING PLS REGRESSION AND GENETIC FUNCTION APPROXIMATION

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Introduction. Enoyl-acp reductase is a key regulatory step in fatty acid elongation. Biochemical evidence has suggested that isoniazid, a first-line drug for the treatment of tuberculosis (TB), blocks the mycolic acids biosynthesis in *M. tuberculosis*. These fatty acids, as well as the key enzyme responsible for their elongation (InhA), are considered attractive targets for the rational design of new anti-TB agents. **Purpose.** Construction of (*RD*) 3D-QSAR models, using PLS regression and genetic function approximation (GFA) formalism, for a set of isoniazid derivatives bound to InhA. **Methodology.** Ligand-receptor (L-R) molecular dynamics (MD) simulations were carried out for a set of 37 hydrazides bound to InhA (PDB entry code 1zid) at 310 K (biological assay temperature). The hypothesized active conformations resulting from a previously reported *receptor-independent* 4D-QSAR analysis were used as the molecular geometries of each ligand in this structure-based L-R binding research. Four water solvent molecules that participate in L-R interaction were maintained in the active site during the MD calculations. The dependent variable is the reported MIC values against *M. tuberculosis* var. *bovis*. The independent variables (descriptors) are scaled energy terms of a modified first-generation AMBER force field combined with a hydration shell aqueous solvation model. GFA and PLS regression were employed as the fitting functions to develop 3D-QSAR models, using the WOLF program (The Chem21 Group, Inc.). **Results.** The best model (N = 30) presented the following statistical measures: $r^2 = 0.77$; $q^2 = 0.61$; LOF = 0.58; LSE = 0.29. The bound ligand solvation energy, the sum in electrostatic and hydrogen bonding energies of the unbound ligand, the bending energy of the unbound ligand, the electrostatic intermolecular L-R energy, and the change in hydrogen bonding energy upon binding were found as the important energy contributions to the binding process. The external validation (test set = 6 hidrazides) was 83.33%. **Conclusion.** The 3D-QSAR model (310 K) has good internal and external predictability and may be regarded as representative of the binding process of ligands to InhA.