

Molecular dynamics simulations of a set of isoniazid derivatives bound to InhA, the enoyl-acyl reductase from *M. tuberculosis*

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Ligand-receptor molecular dynamics simulations (MDSs) were carried out for a set of hydrazides bound to the enoyl-acyl reductase from *M. tuberculosis*, InhA (PDB entry code 1zid). It was presumed that all ligands investigated would act like the lead drug isoniazid, as reported by Rozwarski and co-workers (1998). After the hydrazide group is lost, the activated form (acylpyridine anion or radical) would be covalently attached to the C4 of the nicotinamide ring of the cofactor NAD, resulting in the formation of an acylpyridine-NAD adduct, which is a strongly bound inhibitor. The hypothesized active conformations resulting from a previous *receptor-independent* 4D-QSAR analysis and related optimum model/alignment [*J. Med. Chem.*, 47, 3755, 2004] were used in this study. The MDSs protocol employed 500000 steps for each ligand-receptor complex, the step size was 0.001ps (1fs), and the simulation temperature was 310 K, the same used in the biological assay. An output trajectory file was saved every 20 simulation steps resulting 25000 conformations. The hydration shell model was used to calculate the solvation energy of the lowest energy conformation obtained from each MDS. Structural parameters as well as binding energy contributions were considered in this analysis. The total energy contributions whose seem to be more relevant are van der Waals interaction energy and 1-4 interaction energy (Lennard-Jones). These findings can be meaningful for designing new antituberculosis agents.