Modelling of the interactions of some inhibitors with the Farnesyl Protein Transferase by BioDock- a Stochastic Approach to the Automated Docking of ligands to biomacromolecules.

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Oncogenic mutations of the mammalian Ras protooncogene have been implicated in 20%-30% of all human cancers. A key step in a series of posttranslational modifications of the oncogene product Ras is the S- farnesylation of a cystein residue near the C-terminus in a reaction catalyzed by the enzyme farnesyltransferase (FTase) using farnesyl diphosphate (FPP). This step is important for the association of the GTP-binding Ras protein to the inner surface of the plasma membrane, where it mediates cellular trasformations.Thus, FTase is a current target for small molecule inhibitors. Two types of FTase inhibitors have been designed on the basis of the structure of the two substrates of the reaction, farnesyl diphosphate mimics and Ras CAAX tetrapeptide mimics. Some well known inhibitors have been docked to the FTase structure, as recently obtained by X ray crystallographic analysis, in order to highlight possible interaction differences.