Quantitative Studies of Ligand-Receptor Interactions: A Rapid Evaluation of Binding Free Energies of Endothiapepsin To Its Inhibitors

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Abstract Computer-aided drug design can serve, at least in principle, as a complementary method to modern drug screening processes. It is a major challenge to develop methods for free energy calculations by the computer simulations that should provide quantitative results in reasonable execution times. Here, we compare the performance of several alternative methods: a Free Energy Perturbation (FEP) method, a Linear Response Approximation (LRA), a microscopic Protein Dipole Langevin Dipole (PDLD) method and a semi-macroscopic PDLD/S approach. The incorporation of these methods with molecular dynamics simulations in the POLARIS and ENZYMIX software packages is considered. Both ENZYMIX and POLARIS programs have been used for binding free energy calculations of endothiapepsin with eleven of its inhibitors as a general case study. It is found that FEP/MD calculations involved major convergence problems and lengthy execution times.[1] The LRA approach appeared to provide reasonable results for non polar inhibitors of the same family but it needs significant computing time. The PDLD and PDLD/S methods are more effective in reaching an energy convergence. The PDLD/S method seems to be the best approach to produce semi-quantitative results in a reasonable execution time.[2] It is also found that a linear regression approach that is based on all PDLD/S results can lead to useful insights into the correlation of different energy contributions to the total binding energy and give significant predictive power.

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2.Warshel,Tao,H.,Fothergill,M.,Chu,Z.T.,Isra.J.Chem.,1994,34:253-256