ABSTRACT AICHE 2005

Integration of *in-silico* Filters and Computational Quantum Chemistry for Structure Based COX-II Specific Drug Design and Screening

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In this work we investigated the molecular recognition of the interacting molecules with the chemical structure of active sites as a rational approach towards pharmaceutical drug design. The structure of target protein is known a priori. Considering the biological activity, the information gained from this study can be used as a method for virtual screening of drugs in the final stages of pre-clinical development and for design of new or improved drugs. We have employed a computational quantum chemistry approach using Gaussian 98, and the Jaguar software packages. Primary considerations during this investigation were geometrical characteristics, and protein–inhibitor interaction energy considerations. Various candidate molecules were built based on a known COX-II specific inhibitor. Molecular Mechanics calculations were performed on the candidate molecules for structure and energy optimization. First set of lead compounds were selected after passing them through empirical filters which assed their drug-like properties. Empirical filters such as Lipinski's rule of five were used which uses molecular properties like LogP, hydrogen bond donor and acceptor and molecular weight. To obtain these molecular properties we used group-contribution method with the application of Propred software and CHEM3D. For each successful candidate molecule, protein-ligand docking calculations were performed and free energy was estimated using the DOCK program. The candidate molecules were reported as lead compounds if free energy was negative otherwise the molecule was disregarded (as their free energy is positive and they don't successfully bind to the target protein). This method not only accelerates the drug discovery process but also allows development of novel compounds which might be better than existing COX-II inhibitor.

As a part of this study full quantum chemistry calculations were carried out on the protein–drug system where the protein of interest was decomposed into properly capped multiple amino acid fragments. The calculation at this scale was made possible by using a

recently developed technique called Molecular Fractionation using Conjugate Caps (MFCC) (Zhang et al., J. Chem. Phys, 2003). As a case study we considered aspirin and studied its therapeutic effect on serine. Serine is a protein, which is plays a significant role in the formation of prostaglandin H_2 synthase (PGHS), one of the factors associated with pain and inflammation. Aspirin binds to the serine molecule and prevents serine from producing PGHS. This reaction pathway was studied critically to find various transition states and energy calculations were performed using *ab-initio* and density functional methods (B3LYP). The binding ability between the target protein (in this case, COX-1 or COX-2) and the drug was calculated using the energy values. The computational results were compared with established experimental results to benchmark our study. The study was further extended to new drugs and candidate drugs were screened based on the protein-ligand binding energy.

The study revealed results, which can aid in screening the drugs based on their binding ability to the target protein. It also helped in understanding the drug behavior close to the protein by observing the potential energy surfaces of the protein-drug system. Further more, to make the study more realistic, water molecules were included explicitly to study the solvation effects on drugs. With the application of MFCC we can efficiently apply higher level of theory for a better approximation of the model, which is not possible otherwise.

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