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A 7 Dimensional-Quantitative Structure-Activity Relationship Approach Combining Quantum Mechanics Based Grid and Solvation Models to Predict Hotspots and Kinetic Properties of Mutated Enzymes: An Enzyme Engineering Perspective

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Abstract : Enzymes are molecular machines used in various industries such as pharmaceuticals, cosmetics, food and animal feed, paper and leather processing, biofuel, and etc. Nevertheless, this has been possible only by the breath-taking efforts of the chemists and biologists to evolve/engineer these mysterious biomolecules to work the needful. Main agenda of this enzyme engineering project is to derive screening and selection tools to obtain focused libraries of enzyme variants with desired qualities. The methodologies for this research include the well-established directed evolution, rational redesign and relatively less established yet much faster and accurate insilico methods. This concept was initiated as a Receptor Rependent-4Dimensional Quantitative Structure Activity Relationship (RD-4D-QSAR) to predict kinetic properties of enzymes and extended here to study transaminase by a 7D QSAR approach. Induced-fit scenarios were explored using Quantum Mechanics/Molecular Mechanics (QM/MM) simulations which were then placed in a grid that stores interactions energies derived from QM parameters (QMgrid). In this study, the mutated enzymes were immersed completely inside the QMgrid and this was combined with solvation models to predict descriptors. After statistical screening of descriptors, QSAR models showed > 90% specificity and > 85% sensitivity towards the experimental activity. Mapping descriptors on the enzyme structure revealed hotspots important to enhance the enantioselectivity of the enzyme.

Keywords : QMgrid, QM/MM simulations, RD-4D-QSAR, transaminase
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