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MOLECULAR MODELLING OF HUMAN ALDEHYDE OXIDASE AND IDENTIFICATION OF THE KEY INTERACTIONS IN THE ENZYME-SUBSTRATE COMPLEX

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Abstract:

Aldehyde oxidase (EC 1.2.3.1), a cytosolic enzyme containing FAD, molybdenum and iron-sulphur cluster, is a member of non-cytochrome P-450 enzymes called molybdenum hydroxylases which is involved in the metabolism of a wide range of endogenous compounds and many drug substances. Drug metabolism is one of the important characteristics which influences many aspects of a therapeutic agent such as routes of administration, drug interaction and toxicity and therefore, characterisation of the key interactions between enzymes and substrates is very important from drug development point of view. The aim of this study was to generate a three-dimensional model of human aldehyde oxidase (AO) in order to assist us to identify the mode of interaction between enzyme and a set of phethalazine/quinazoline derivatives. Both sequence-based (BLAST) and inverse protein fold recognition methods (THREADER) were used to identify the crystal structure of bovine xanthine dehydrogenase (pdb code of 1FO4) as the suitable template for comparative modelling of human AO. Model structure was generated by aligning and then threading the sequence of human AO onto the template structure, incorporating the associated cofactors, and molecular dynamics simulations and energy minimization using GROMACS program. Different criteria which were measured by the PROCHECK, QPACK, VERIFY-3D were indicative of a proper fold for the predicted structural model of human AO. For example, 97.9 percentages of phi and psi angles were in the favoured and most favoured regions in the ramachandran plot, and all residues in the model are assigned environmentally positive compatibility scores. Further evaluation on the model quality was performed by investigation of AO-mediated oxidation of a set of phthalazine/quinazoline derivatives to develop QSAR model capable of describing the extent of the oxidation. Substrates were aligned by docking onto the active site of the enzyme using GOLD technology and then HASL method were used to generate a 3D-QSAR model. Correlation coefficient (r2) between the test set actual and predicted Km values was 0.65.

Keywords:

Aldehyde oxidase ، Molecular modeling ، 3D-QSAR ، genetic algorithm

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