

***In silico* prediction of metabolism by human carboxylesterase-1 (hCES1) combining docking analyses and MD simulations.**

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Because metabolic problems lead to too many failures during clinical trials, much effort is now devoted to *in silico* models to predict metabolic stability and metabolites. Such models are well known for cytochromes P450 and various conjugating enzymes, and they enjoy a relative success. In contrast, little has been done to predict the hydrolyzing activity of human esterases, although these play a key role in the hydrolytic metabolism of xenobiotics and in the activation of most prodrugs.

On these grounds, the present study was undertaken to develop a computational approach able to predict the hydrolysis of new chemical entities by the human carboxylesterase hCES1. The first step of the study involves docking analyses of several known hCES1 substrates with a view to develop predictive models also incorporating new scoring functions designed to take hydrophobic interactions into account. In a second step, MD simulations of complexes revealed the behavior and trajectory of substrates and products, demonstrating in particular the influence of their ionization state.

The results emphasize some crucial properties of the catalytic cavity of hCES1. Thus, the region that accommodates the alcohol group is rich in negatively charged residues and markedly rigid. In contrast, the cavity which harbors the acyl moiety contains several residues with alkyl side-chains and shows a significant flexibility. These observations suggest that hCES1 prefers substrates with small polar alcohol groups and large hydrophobic acyl moieties. Also, the docking results confirm the usefulness of the here proposed score for hydrophobic interactions, which allows a robust prediction of hCES1 catalysis. Finally, the MD simulations clearly discriminate between substrates and products and suggest that basic substrates interact with the enzyme in their neutral form.

In summary, the combined approach exemplified here analyses at atom level the dynamic profile of enzyme-substrate and enzyme-product complexes, resulting in useful predictions of the substrate specificity of hCES1.