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Poster presentation

In silico prediction system of CYP450-mediated metabolism profile

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The Cytochrome P450 (CYP450) enzymes represent an ideal subject for the investigation of metabolic drug. drug interactions. CYP450 is considered to be the most important single enzyme family in drug metabolism. This superfamily of enzymes is thought to metabolize approximately 90% of all marketed drugs. It is essential for the purpose of reducing time and resources of drug design and development to predict metabolism occurrence and regioselectivity. However, the lack of quantitative experimental metabolic data and substrate specificity, and the fact that CYP450 system depends on both steric effect and electronic reactivity indicate that metabolism prediction is difficult. In this study, we tried three approaches using statistical methods to classify substrate, empirical model to predict the activation energy of CYP450 reaction and combination of docking method and semi-empirical molecular orbital calculations to determine the binding mode of CYP450 enzyme-substrate complex. Each model gives a lot of insights to describe CYP450-mediated system *in vivo*. Statistical method is useful to separate potential substrates and non-substrate with only two dimensional descriptors. Empirical model can explain aliphatic hydroxylation and aromatic hydroxylation which altogether constitute most reactions mediated by CYP450 using AM1 quantum mechanical calculations. Third model gives major metabolic positions of substrates in CYP450. Further, collection knowledge of appropriate ligand and its binding site of CYP450 will help to follow up pharmacokinetics of novel compounds.

Conclusion

Statistical method is useful to separate potential substrates and non-substrates with only two dimensional descriptors. Empirical model can explain aliphatic hydroxylation and aromatic hydroxylation which altogether constitute most reactions mediated by CYP450 using AM1 quantum mechanical calculations. In regioselectivity prediction, we predict 55% for the first position, 82% for including the second and third positions using the feature mapping, SAS and electronic energy. Further, combination of diverse methods will help to follow up pharmacokinetics of novel compounds.

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