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Point-Mutation in a Rationally Engineered Esterase Inverts its Enantioselectivity

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Abstract : Enzymes are safe and selective catalysts. They skillfully catalyze chemical reactions; however, the native form is not usually suitable for industrial applications. Enzymes are therefore engineered by several techniques to meet the required catalytic task. Clopidogrel is recorded among the five best selling pharmaceutical in 2010 under the brand name Plavix. The commonly used route for production of the drug on an industrial scale is the synthesis of the racemic mixture followed by diastereomeric resolution to obtain the pure S isomer. The process consumes a lot of solvents and chemicals. We have evaluated a biocatalytic cleaner approach for asymmetric hydrolysis of racemic clopidogrel. Initial screening of a selected number of hydrolases showed only one enzyme EST to exhibit activity and selectivity towards the desired stereoisomer. As the crude EST is a mixture of several isoenzymes, a homology model of EST-1 was used in molecular dynamic simulations to study the interaction of the enzyme with R and S isomers of clopidogrel. Analysis of the geometric hindrances of the tetrahedral intermediates revealed a potential site for mutagenesis in order to improve the activity and the selectivity. Single point mutation showed dramatic increase in activity and inversion of the enantioselectivity (400 fold change in E value).

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