Application of enzymes to enhance drug action

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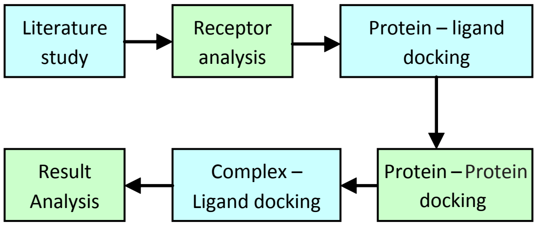
Customer type

A leading industrial enzyme manufacturing company

Software modules

VLife Engine
BioPredicta
MolSign



Application

Drug delivery

Techniques

Protein structure analysis
Protein - ligand docking
Protein - protein docking
Complex – ligand docking
Binding energy analysis

Background:

Enzymes play a key role in many biological functions by acting as catalysts in biochemical reactions. This role has ensured that the use of enzymes for analytical, industrial and scientific purposes has increased rapidly. Enzymes are also being increasingly used therapeutically to treat diseases while some enzymes are reported to have enhanced the effect of drugs in diseased conditions.

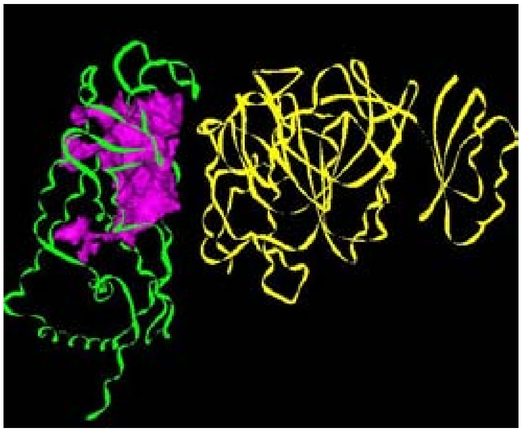
Design challenge:

Administering suitable enzymes with drugs can enhance the efficacy of the drug thereby bringing about a reduction in the required dosage of the drug. Enzymes can act as either drug carriers or by acting on the same target protein as the drug thereby eliciting the desired response or by changing the conformation of the target so that binding efficacy of drug towards the target is increased.

The customer, a leading manufacturer of industrial enzymes, wanted to determine an enzyme - drug combination that would help to reduce dosage of a drug thereby limiting its side effects. The project involved study of the drug - target, drug – enzyme and the target – enzyme - drug complexes.

Project work:

The crystal structures of the enzymes and targets collected from PDB were cleaned with respect to their bond orders and hydrogen was added. These cleaned files were optimized using MMFF force field.



An enzyme blocking the active site (hown in magenta) of a disease target

Drug docked into an enzyme

Drugs were docked into their respective targets using VLifeMDS.

Docking of drugs into the target – enzyme complex was performed using VLifeMDS while target – enzyme docking was performed using third party software.

Result analysis:

Target – enzyme docking was used to ascertain if the enzyme can block active site of the target and inhibit substrate binding whereas the enzyme – drug docking was performed to determine if the enzyme can bind the drug and hence act as drug carrier.

The binding energy of drug ligand towards the target protein or enzyme was calculated using the formula

$E_{bind} = E_{complex} – (E_{protein} + E_{ligand})$

where,

E_{bind} = Binding energy

$E_{complex}$ = Energy of complex (target - drug complex or target – enzyme complex)

$E_{protein}$ = Energy of protein and

E_{ligand} = Energy of ligand

The binding energy of the drug towards the target – enzyme complex was also calculated using the above formula, in which

$E_{complex}$ = Energy of ligand - target - enzyme complex and

$E_{protein}$ = Energy of target – enzyme complex

This binding energy indicated ability of the enzyme to enhance binding of drug to the target. Based on mode of binding and binding energies, the best enzyme – drug combinations for each therapeutic area were suggested to customer.