ABSTRACT

Crystal Structure of cytochrome p450 2B4 has 476 amino acids through docking approach we have attempted to explain the specificity of CYTP450, total 28 imidazole drug were used for the studies as antifungal drugs in which binding interaction (reference) shows the binding energy of -6.67 kcal/mol. Compound Miconazole shows the minimum binding energy of -10.45 kcal/mol. The 2B4-imidazole structure identified 10 residues (ALA 298, 2GLY 299, GLU 301, THR 302, LLE 365, VAL 292) within 6.5 Å of the active site of bilin. GLU 301, THR 302 are also located in 6.5 Å of the bound ligand in 2B4 structure. Due to the presence of the multiple binding sites in cytochrome p450 2B4 acts as the important target of many drugs in antifungal metabolism.

INTRODUCTION

Cytochrome P450 family of enzymes plays a major role in xenobiotic metabolism in all classes of living beings. Cytochrome P450 (EC 1.14.13.) mainly involved in the detoxification of many drugs, environmental pollutants, xenobiotic, fatty acids and bile acids, and, frequently, also activation of endogenous Cytochromes P450 (CYPs) are superfamily of xenosoluble enzymes which differ in their substrate specificity and are regulated by numerous factors including age, sex, and exposure to certain CYP inducers. P450s range in size from 40-50 KD and contain a single heme group. The CYPs are nitrogens, a change of O-O bond forming an imidazole linked oxygen in cytochrome P450 which prevents protein oxidation. This can perform both the stereospecific hydroxylation of a wide variety of endogenous and exogenous organic molecules. The binding feature of these enzymes is their ability to bind ligands of various sizes and shapes.

Cytochrome P450 is an electron donor protein for several oxygen enzymes found on the endoplasmic reticulum of most eukaryotic cells. These oxygen enzymes include the cytochromes P450 enzymes involved in metabolization of drugs, hormone, xenosoluble toxic substances and cellular homeostasis.

MATERIAL & METHODS

To elucidate the specificity of the cytochrome p450 docking approach have been attempted. Docking is used to predict the binding orientation of drug to the protein target in order to interpret the affinity & activity of drug which includes docking of ligands onto the above target proteins. The imidazole drug were identified using azole ring bind to their respective derivative. Total no of imidazole used for the studies was 28 in number having bilin in the active site. The docking/drug in the Lipinski's rule of five required are converted using the open-16 affordable. Protein have been modeled to get the alignment pattern of the drug using Modeller which models three-dimensional structures of proteins from three-dimensional structures of atomic coordinates. Modeller implements an automated approach for comparative protein structure modeling, the input are from the PDB atom files of cytochrome p450 2B4 and their alignment with the drug. The output is modeled for the drug that includes all non-hydrogen atoms, Modelled proteins were classified into two categories 10-Molled proteins with HADM 3.0 residue 2D-Molled with proteins with HADM 3.5 residue.

AutoDock was used for the docking study combined with the Lamarckian genetic algorithm to search for the globally optimized conformation. The grid spacing was set to 0.375 Å, each grid spacing and each grid map consists of a 64x64x64 grid point. For every protein, the center of the grid was set to the position of the HADM 3.0. During each docking experiment 15 ms were carried out & the rest of the parameters were set at the default value. At the end of the docking experiment with multiple runs, a cluster analysis was performed. Docking solutions with aligned all atoms mean square deviation to 0.0 Åms then clustered together & ranked by lowest binding energy.

The compounds ranked as per the lowest binding energy are Miconazole, Sertaconazole, Tioconazole, Econazole, Econazole, Econazole.

REFERENCES


Email: arpit.tandon@gmail.com

ACKNOWLEDGEMENT

We thank to Department of Bioinformatics, Biotechnology Park, Lucknow and Dr B.N. Mishra Institute of Engineering & Technology, Uttar Pradesh Technical University, Lucknow for their support and all ACS staff members for helpful comments on the poster and stimulating discussion and practical help. We also thank Mr. Muthu for invaluable support.