Yogeeswari Perumal, Clin Exp Pharmacol 2018, Volume 8
DOI: 10.4172/2161-1459-C3-034

Multiple crystal structure modeling in structure-based drug discovery: Case studies on successful diverse lead identification

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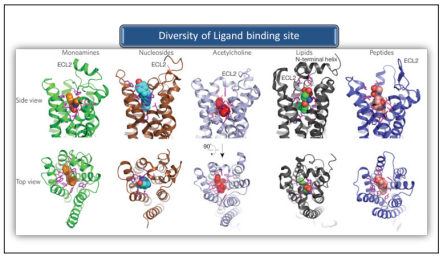

Structure-based drug design has played significant role in the design of various drug candidates. The most studied targets include the HIV protease, dihydrofolate reductase, beta secretase etc. for which there are number of crystal structures available in the protein databases (pdb). Our drug discovery research group initiated the strategy of utilizing multiple crystal structures in the design of diverse ligands of human beta secretase and was successful. In continuation to our efforts in this field, we report here the discovery of diverse ligands for various therapeutic classes utilizing structure-based design for those proteins where more than hundred crystal structures were available in the pdb. We rationalized the selection of crystal structures bound with different ligands based on the resolution of the structure, no mutation and only the wild type. About nine to 10 crystal structures were employed in the structure-based drug design to develop energy-based pharmacophore (e-pharmacophore) hypothesis based on the ligand interaction with the protein residues. Multiple e-pharmacophores were generated and validated using enrichment factor calculation. The validated pharmacophore hypothesis was utilized for filtering commercial database with pharmacophore fitness above 1.0. A high throughput screening combined with docking, analysis of binding amino acid residues and ADME parameters led to the identification of some potential diverse scaffolds that could be developed as novel inhibitors of HIV protease.

Recent Publications

1. J T Patrisha, D Manvar, S Kondepudi, M B Battu, D Sriram, A Basu, P Yogeeswari, N K Basu (2014) Multiple e-pharmacophore modeling, 3D-QSAR and High-throughput virtual screening of Hepatitis C Virus NS5B polymerase Inhibitors. *J. Chem. Inf. Model*; (ACS), 54: 539-552.
2. P Ravichand, D Sriram, P Yogeeswari, R Vadrevu (2013) Multiple E-Pharmacophore Modeling combined with High-Throughput Virtual Screening and Docking to Identify Potential Inhibitors of Beta Secretase. *Mol. Informatics*; 32: 2-15.

Biography

Yogeeswari Perumal is currently working as a Professor and Associate Dean (Sponsored Research and Consultancy Division), Department of Pharmacy, Birla Institute of Technology and Science, Pilani, Hyderabad Campus. She is the Founder of the Yogee'S Bioinnovations Pvt. Ltd, which is a drug discovery unit.

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