Computerized protein modeling and molecular docking analysis of human proto oncogene tyrosine protein kinase YES for discovery of novel lead molecules

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Introduction:

Human proto-oncogene tyrosine-protein kinase YES (YES) is a non receptor kinase belongs to Src family. This gene lies in close proximity to thymidylate synthase gene on chromosome 18. In hepatocellular carcinoma and colorectal carcinoma elevated human YES activity was observed. Inhibitors of human YES reported till date are in clinical trials and associated with several side effects. The present study was mainly aimed in homology modeling of YES and discovery of novel lead molecules that inhibit YES kinase more efficiently with less side effects. Virtual screening and docking techniques using Schrodinger software suite (Maestro 9.0) were applied to identify novel lead molecule of YES kinase. Ligand based virtual screening using modeled structure of YES protein resulted in identification of thirteen lead molecules.

METHOD:

Step-1
- Retrival of protein sequence from UNIPROT

Step-2
- Pathway analysis [Adherens junction and tight junction formation (KEGG)]

Step-3
- Homology modeling of human YES kinase using MODELLER 9v7
- Validation of modeled structure (PROCHECK)
- Visualization of modeled structure (PyMOL)

Step-4
- Lead identification
- Ligand based high through put virtual screening
- Docking studies using Schrodinger software

RESULTS:

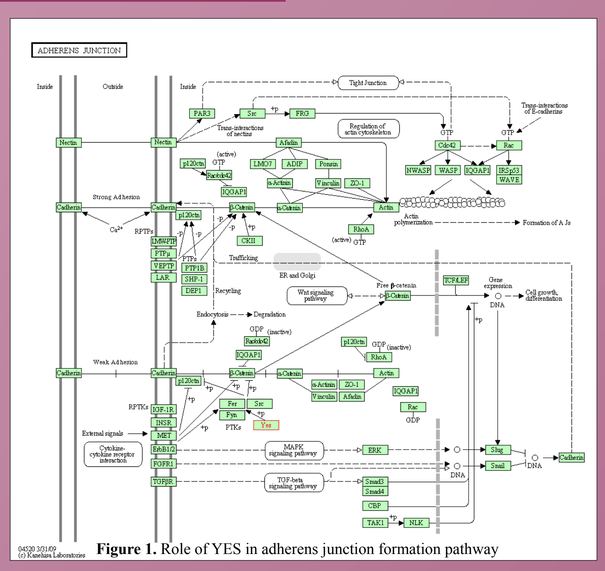

Figure 1. Role of YES in adherens junction formation pathway

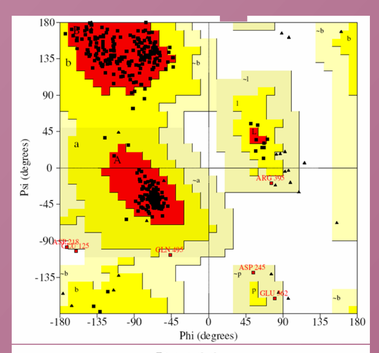

Figure 2. Ramachandran plot of modeled human YES kinase

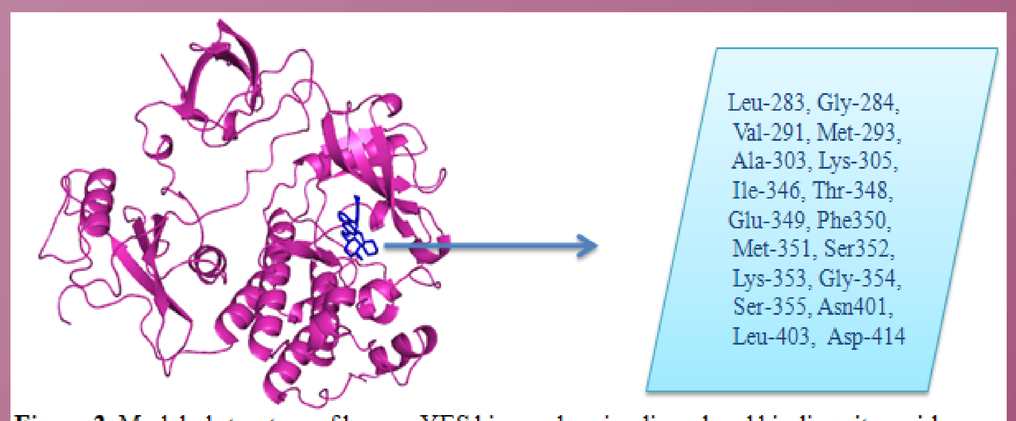

Figure 3. Modeled structure of human YES kinase showing ligand and binding site residues

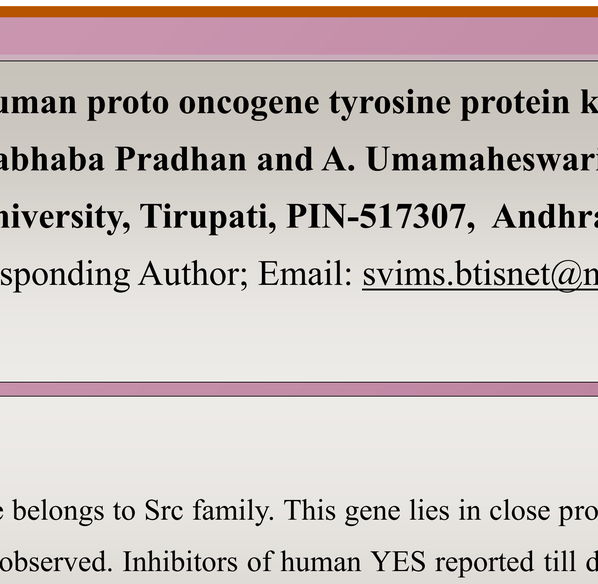

Figure 4. 76th pocket showing information about active site residues

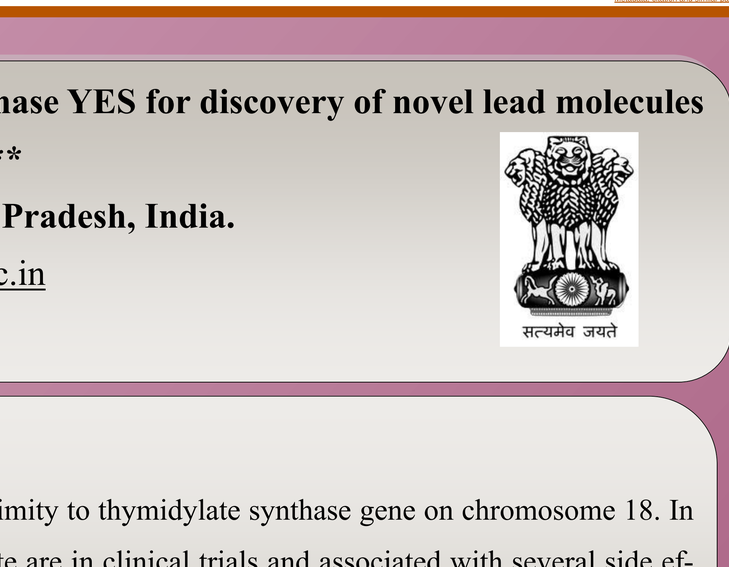

Figure 5. Virtual screening of published inhibitors giving rise to potent lead molecule

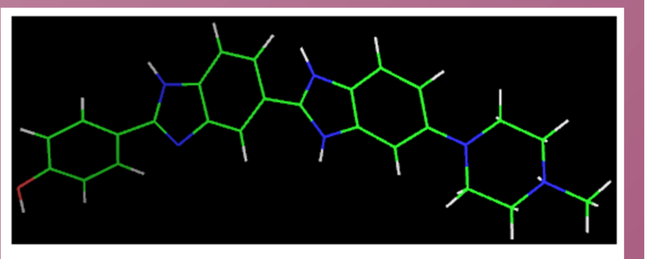

Figure 6. **Lead '1'** molecule with XP Gscore 12.07 Kcal/mol

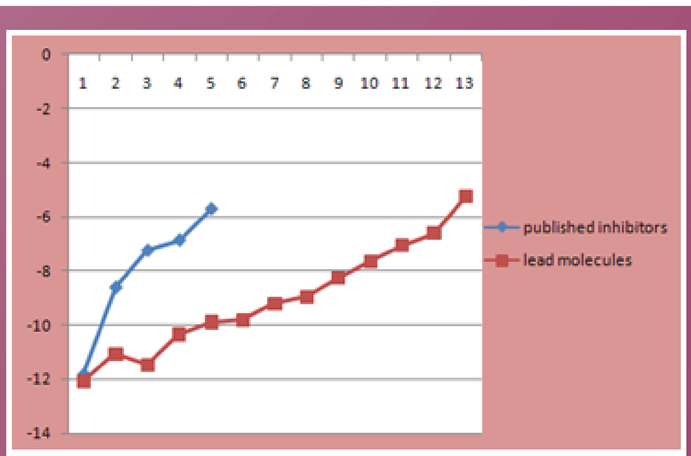

Figure 7. Graph comparing the XP Gscore of inhibitors and lead molecules

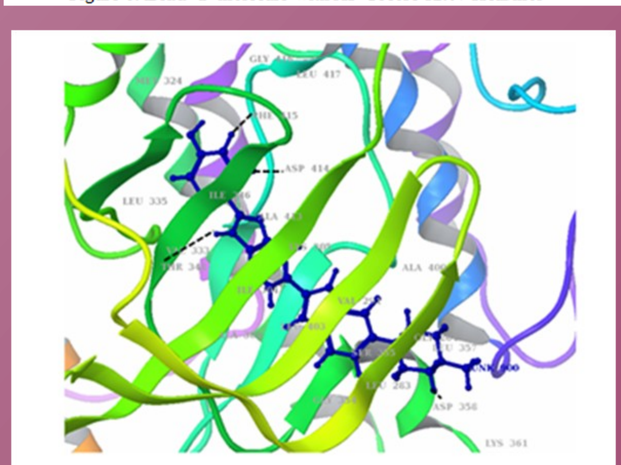

Figure 8. Hydrogen bonds formed by human YES with lead '1' molecule Thr-348, Asp-358, Asp-414 and Phe-415 residues were involved in formation of hydrogen bond network

Docking complex of human YES kinase and Lead '1' had deciphered that the amino acid residues of YES kinase such as Leu-283, Gly-284, Val-291, Ala-303, Ile-304, Lys-305, Met-324, Val-333, Leu-335, Ile-346, Thr-348, Gly-354, Ser-355, Leu-361, Ala-400, Leu-403, Ala-413, Asp-414, Phe-415, Gly-416 and Leu-417 are involved in molecular interaction.

Conclusion: Compared to five published inhibitors **Lead '1'** molecule was having least XP Gscore of -12.07 Kcal/mol and molecular weight 424.51 Daltons. Therefore **Lead '1'** can be raised into potential inhibitors after binding assays and passing several phases of clinical trials.

Acknowledgements: It gives me an immense pleasure to express my deep sense of gratitude to the honorable Dr. A. Umamaheswari, Coordinator of BIF & Head of the Department Bioinformatics, SVIMS, Tirupati, for her able guidance. I am thankful to DBT, ministry of science and technology, Govt. of India for providing all the necessary facilities to carry out the project work.