Derivatives of Benzopyrans are Selective Estrogen Receptor beta Agonists (SERBAs): Molecular Modeling study of Benign Prostatic Hyperplasia

S. Gopalakrishna[1], S. Vastrad[1], V.S. Dasan[2], A. Kumar[3], M.A. Akinsaya[4], J. Bhatnagar[5], Asif Naqvi* [6]

[1] *Karnatak University, Dharwad, Karnataka, India*
[2] *Pharmaceutical Technology, University College of Engineering, Trichy, India*
[3] *Medical Biotechnology and Clinical Research, Vels University, Chennai, India.*
[4] *MONASH University, Selangor, Malaysia.*
[5] *Department of Biotechnology, CET-IILM Academy of Higher Learning, Greater Noida, India.*
[6] *BioDiscovery Group LifeSciences, India.(contactme.asif@gmail.com)**

ABSTRACT

Estrogen receptors play a significant role in the pathogenesis of prostate carcinoma (PCa) by estrogen signaling in normal and abnormal growth of the prostate gland. Estrogens directly target prostate tissue by specific estrogen receptors (ER). The human prostate is equipped with a dual system of ERs that undergoes profound remodeling during prostate cancer development and progression.

It was reported that ER-beta may play a significant role in prostate cell differentiation and proliferation and may modulate both the initial phases of prostate carcinogenesis and androgen-independent tumor growth.

A virtual screening and molecular docking study was conducted on 3500 benzopyrans for the development of new agonists for ER-beta. Molecular docking approach using Lamarckian Genetic Algorithm was carried out to find out the potent agonists for ER-beta on the basis of calculated ligand-protein pairwise interaction energies. The grid maps representing the protein were calculated using auto grid and grid size was set to 60*60*60 points with grid spacing of 0.375 Å. Docking was carried out with standard docking protocol on the basis of a population size of 150 randomly placed individuals; a maximum number of 2.5 *107 energy evaluations, a mutation rate of 0.02, a crossover rate of 0.80 and an elitism value of 1. Ten independent docking runs were carried out for each ligand and results were clustered according to the 1.0 Å RMSD criteria.

The docking result of the study of 3500 molecules demonstrated that the binding energies were in the range of -1.26 kcal/mol to -8.58 kcal/mol with the minimum binding energy of -8.58 kcal/mol. Three molecules showed promising ADMET properties.

Further in-vitro and in-vivo studies are required on these molecules as the binding mode provided hints for the future design of new inhibitors for ER-beta.

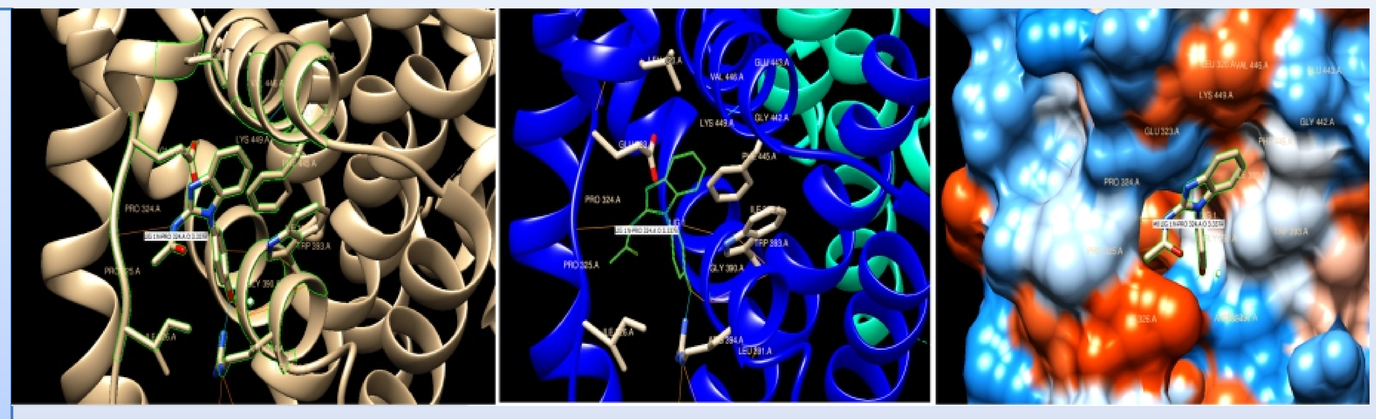
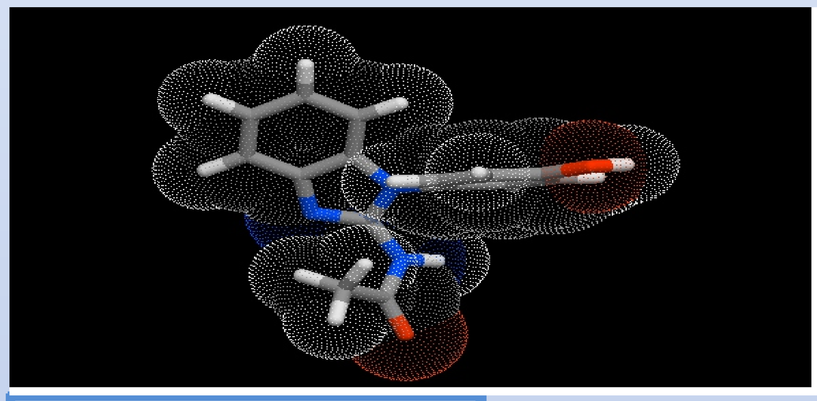
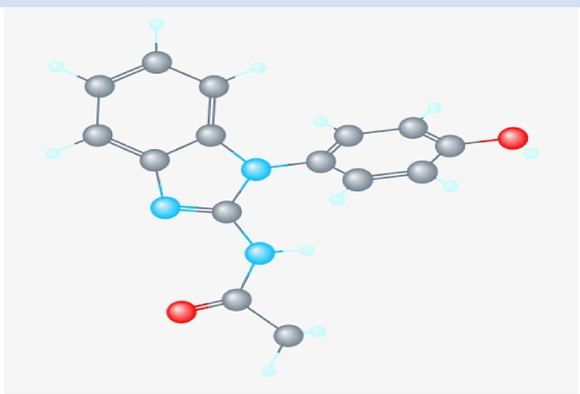


Fig 2: 3 D conformation of H-Bond Interaction of molecule JB-2





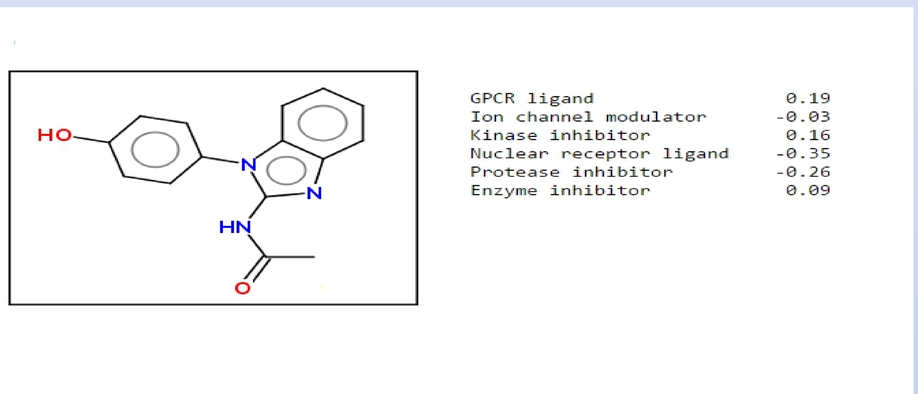


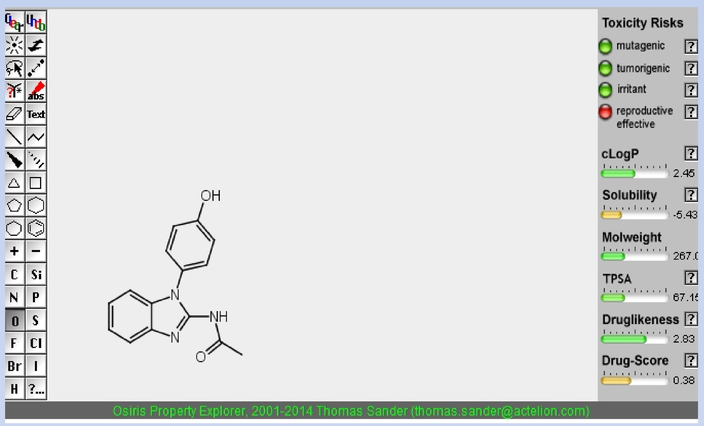
Fig 1: Structure and Bioactivity of JB-2

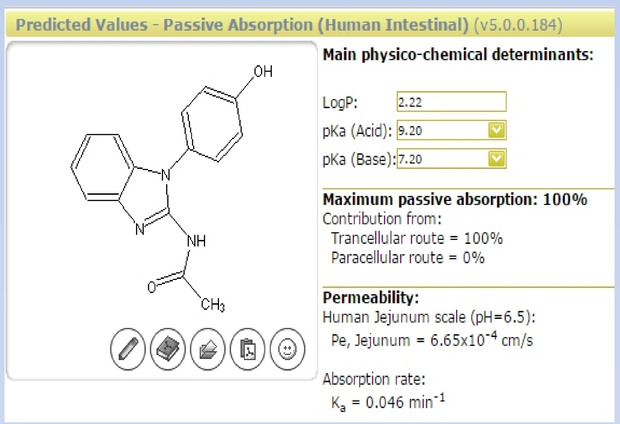
INTRODUCTION

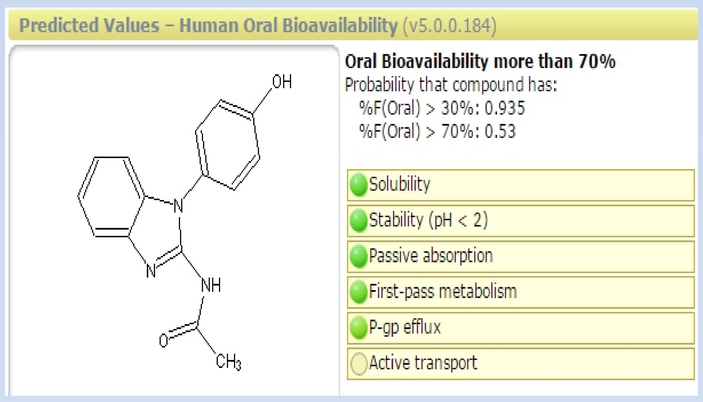
Prostate carcinoma is the development of cancer in the prostate gland. The inner part of the prostate (around the urethra) often keeps growing as men get older, which can lead to a common condition called benign prostatic hyperplasia (BPH). Estrogen receptors are believed to play a significant role in the pathogenesis of prostate carcinoma (PCa).[1] The prostate expresses both estrogen receptor alpha and estrogen receptor beta. Ricke et al. demonstrated in mice that, androgen, estrogen, aromatase and ERA are all required for prostate carcinogenesis. There is a growing body of evidence to suggest that estrogen signaling also plays a significant role in normal and abnormal growth of the prostate gland. Estrogens directly target prostate tissue by specific estrogen receptors (ER).

It was reported that ER-β may play a significant role in prostate cell differentiation and proliferation and modulate both the initial phases of prostate carcinogenesis and androgen-independent tumor growth.[2]

Hence, it becomes a target for the molecular modeling study to see the binding mode of small molecules with this biological target of Prostrate Carcinoma.







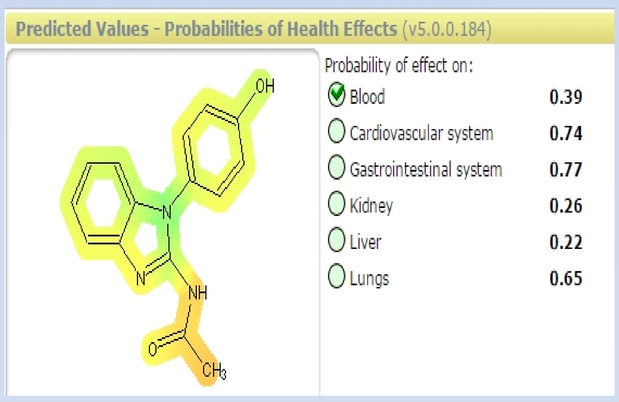


Fig 3: ADMET Properties of molecule JB-2

MATERIALS & METHODS

3500 molecules were taken from PubChem and ChemBank molecule database. The ligands were generated in-silico by ACD ChemSketch; files were saved in MDL Molfiles, and then converted to .pdb format by Open Babel GUI. X-ray diffraction PDB structure of resolution 2.90 Å was taken from Protein Data Bank as target for docking and, Protein Optimization was performed by removing I0G. Energy Minimization using Steepest Descent method was executed on SPDBV. Later, Molecular docking using Lamarckian Genetic Algorithm[3] was carried out to find out the binding mode of 3500 molecules with the biological target, on the basis of calculated ligand-protein pairwise interaction energies. The grid maps representing the protein were calculated using auto grid, and the grid size was set to 60*60*60 points with grid spacing of 0.375 Å. Docking was carried out with standard docking protocol on the basis of a population size of 150 randomly placed individuals; a maximum number of 2.5 *107 energy evaluations, a mutation rate of 0.02, a crossover rate of 0.80 and an elitism value of 1. Ten independent docking runs were carried out for each ligand and results were clustered according to the 1.0 Å RMSD criteria.

RESULTS

Docking result of 3500 molecules showed the binding energies were in the range of -1.26 kcal/mol to -8.58 kcal/mol with the minimum binding energy of -8.58 kcal/mol. We report molecule JB-2 (Fig-1) showed least binding energy and H-Bonds interactions with binding pocket residues 394 (Fig-2). The molecule showed no indication for being mutagenic, tumorigenic and irritant effects (Fig-3). Maximum passive absorption calculated as 100% which was 100% from Transcellular route. The permeability for Human Jejunum scale (pH=6.5) was equal to 6.65×10^{-4} cm/s and absorption rate $K_a = 0.046$ min^{-1} (Fig-3).

Also, Oral bioavailability was more than 70% and docked conformations were rated by scoring functions that include terms for Van der Waals', hydrogen bond & electrostatic interactions, plus internal energy of ligands. The solubility of the docked compound was related with the binding energy, with the help of log P value.

CONCLUSIONS

Based on the Molecular Docking study of 3500 molecules, we reported three molecules that showed H-bond interaction with the binding pocket residue of the protein, and also exhibited promising ADMET results. Here, we report only one molecule JB-2, which showed Estimated Free Energy of Binding of -7.19 kcal/mol and Estimated Inhibition Constant, Ki of 5.35 µM (micromol). The molecule also showed better affinities with the active site residue of the protein. The molecule follows Lipinski's Rule of 5 and Final Intermolecular Energy of -8.09 kcal/mol with vdW + Hbond + desolv Energy of -7.09 kcal/mol. The Human Oral Bioavailability of the compound JB-2 is between 30% and 70% , and Probability that compound has: %F(Oral) > 30%: 0.935 and %F(Oral) > 70%: 0.53.

The magnitude of work stretches to the in-silico approach for determining the binding mode. This, further necessitates to generate in-vitro & in-vivo activities with the established data; to synthesize & test, so as to design new drugs with better specificity & metabolism.

ACKNOWLEDGMENTS

We are thankful to the staff of BioDiscovery Group LifeSciences, India, for providing us the opportunity to work in this project. Their training & continuous guidance has led this research to be accomplished on time. We are grateful for their suggestions and kind support.

REFERENCES

1. Expression of Estrogen Alpha and Beta Receptors in Prostate Cancer and Hyperplasia: Immunohistochemical Analysis. J.A.Al-Maghrabi[1], T. M. Hassan[1, 2], T. A. Abdel-Meguid[3, 4], H. A. Mosli[3]. African Journal of Urology, 1110-5704, Vol. 16, No.3, 2010, 79-87.
2. Estrogen receptor beta in prostate cancer: Friend or Foe? Adam W Nelson[1,2], Wayne D Tilley[1,3], David E Neal[1,2,4] and Jason S Carroll[1,4]. Endocr Relat Cancer. 2014 Aug; 21(4): T219-234. doi: 10.1530/ERC-13-0508. Epub 2014 Jan 8.
3. Automated docking using a Lamarckian genetic algorithm and empirical binding free energy function. Garrett M. Morris[1], David S. Goodsell[1], Robert S. Halliday[2], Ruth Huey[1], William E. Hart[3], Richard K. Belew[4], Arthur J. Olson[1]. J. Comp Chem. 19, 1639-1662 (1998).