International Journal of
Science and Engineering Investigations vol. 2, issue 13, February 2013
ISSN: 2251-8843

In Silico Identifications of Potential Drug Candidates Against 1KE8 using Indoles

Arun Kumar V.A[1], Keshav Mohan[2]
[1]Research Scholar, Department of S&H (Computer Applications), Sathyabama University, Chennai, India
[2]Professor & Executive Director, SVN College of Engineering, Alappuzha, India
([1]akva1234@yahoo.com)

***Abstract*-** Cyclin-dependent kinasse (CDK2) are considered as potential target for anti-cancer medication. Indoles are important nitrogen containing heterocyclics known for broad spectrum of biological activities. Modification in basic indole with stereospecific structural descriptors has offered a high degree of diversity that has proven useful for the development of new therapeutic agents having improved potency and lesser toxicity.

***Keywords*-** *Indoles, CDK, Kinase.*

I. INTRODUCTION

Cancer, also called malignancy, is a class of diseases characterized by out-of-control cell growth. Cancer cells can spread to other parts of the body through the blood and lymph systems. Cancer harms the body when damaged cells divide uncontrollably to form lumps or masses of tissue called tumors (except leukemia).There are over 200 different known malignant neoplasm's that affect human cell type. Complex for our understanding is the cause of cancer.

Cancer treatment includes chemotherapy, radiation and surgery. The treatment of cancer varies with its type and stage. The stage refers to the growth and spreading of tumor from its original location. It is estimated that about 9 million new cancer cases are diagnosed every year and over 4.5 million people die from cancer each year worldwide. Around 2.4 million new cases of cancer were diagnosed in EU countries in 2008 with 55% occurring among males and 45% among females [1]. Cancer is one of the leading causes of death in India; officially recorded over half a million deaths due to cancer in 2011 — 5.35 lakh as against 5.24 lakh in 2008.

Drug design is the inventive process of finding new drug molecule based on the knowledge of a biological target. The drug is an organic small molecule that activates or inhibits the function of a bio-molecule such as a protein, which in turn results in therapeutic benefit to the patient. Ligand based drug design depends on the knowledge of the molecules that bind to the biological target, whereas structure based drug design relies on the knowledge of the three dimensional structure of the biological target [2,3]. In contrast to traditional methods of drug discovery, which rely on trial-and error testing of chemical substances on cultured cells or animals, and matching the apparent effects to treatments, computer aided drug design begins with a hypothesis that modulation of a specific biological target may have therapeutic value. Computer-aided drug design uses computational chemistry to discover, enhance, or study drugs and related biologically active molecules. The most fundamental goal is to predict whether a given molecule will bind to a target and if so how strongly.

II. MATERIALS AND METHODS

1KE8 is a cyclin dependent kinase. This study carried out for identifying 1KE8 inhibitors thru molecular docking. 1KE8 belongs to a family of protein kinases first discovered for their role in regulating the cell cycle. It is also involved in regulating transcription, mRNA processing, and the differentiation of nerve cells. CDKs are considered a potential target for anti-cancer medication. If it is possible to selectively interrupt the cell cycle regulation in cancer cells by interfering with CDK action, the cell will die. A CDK inhibitor is a chemical that inhibits the function of CDKs.

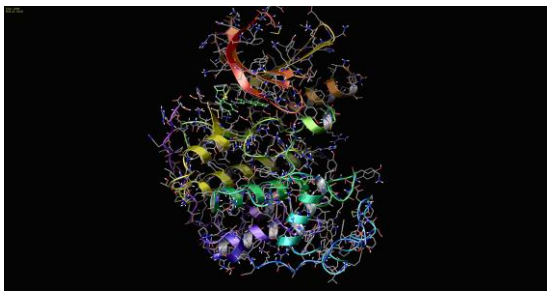


Fig.1. 3D structure of 1KE8

The receptor protein, 1KE8 was downloaded from the Protein Data Bank [PDB] (Fig.1) and refined using protein wizard of Schrodinger suit 2012 [21,22]. A typical structure file from the PDB is not suitable for immediate use in molecular modeling calculations. It consists of heavy atoms, cocrystallized ligand, water molecules, metal ions and cofactors. Some structures are multimeric, and may need to be

reduced to a single unit. It is therefore needed to prepare proteins in a form that is suitable for modeling calculations. The tools of Schrodinger suite 2012 is used for the purpose. The refining process involves fixing structures, deleting unwanted chains and waters, fixing or deleting het groups, and finally performing some optimization of the fixed structure.

Indoles are the most important nitrogen containing heterocyclic molecules, which play vital role in biochemical process. It found extensively in biological systems also. Indole is the commonly used name for the benzopyrrole, consisting of a benzene ring fused to the 2, 3-positions of a pyrrole ring [4-6]. Indole ring system is found in many natural products, pharmaceuticals agents and polymer materials. The interesting chemical properties of indole have inspired chemists to design and synthesize a variety of indole derivatives [7]. Indole derivatives are found to contain several biological activities those including antimicrobial, antibiotic, anti-inflammatory, analgesic, anticonvulsant, antimalarial, etc. [8-17]. Modification in their structure has offered a high degree of diversity, useful for the development of new therapeutic agents having improved potency and lesser toxicity.

The docking experiments provide with structure which can bind the protein with least energy. Such a structure is considered as lead drug. In this case, all the docking calculations were carried out with Schrodinger Glide 2012 [21, 22]. This program performs a hierarchical search of ligand conformations undergoing a filtering procedure and finally minimizes in the field of the receptor using the OPLS-AA force fields in conjunction with a distance-dependent dielectric model. Glide uses two concentric boxes to generate the potential grids and define the binding site.

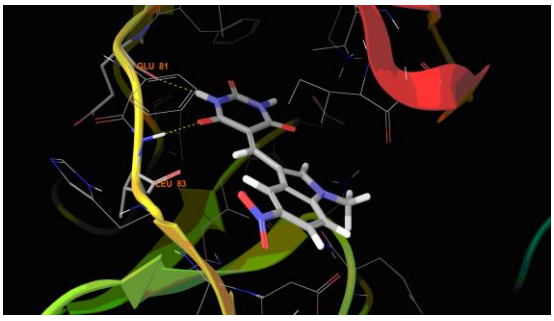


Fig.2. The Optimal docking of I_8 with 1KE8

Default input parameters were used in all computations (no scaling factor for the van der Waals radii of non-polar protein atoms and a scaling factor of 0.8 for non-polar ligand atoms). All compounds were docked and scored using the Glide extra precision (XP) mode [18-20]. Upon completion of each docking calculation, 30 poses per ligand were saved. The best-docked structures were ranked using a model energy score (Emodel) derived from a combination of Glide Score (Gscore, a modified and extended version of the empirically based ChemScore function), Coulombic, and van der Waals energies, and the strain energy of the ligands.

III. Results and Discusions

Fifteen indole analogues were docked into ATP site of CDK2 receptor and the results of the study were shown in the Table 1. Most of the indole derivaties are not docked well inside the pocket of CDK2 receptor. The docking scores are in the range of -8.04 Kcal/mol to -5.1 kcal/mol. Many compounds were showing a weak hydrophobic and hydrogen bond interactions with receptor. The presence of indole moiety should favours the interaction with receptor due to pyrimidinetrione group the compound cannot have proper complementarity with receptor and hence all the compounds unable to enter into the pocket and cannot have strong interaction with receptor. The Compound I_1 was showing only one hydrogen bond interaction with receptor and the glide score of this compound is less (-5.1 Kcal/mol) (Fig. 3). The oxygen atom of CO group present in pyrimidinetrione moiety of compound I_8 is forming and hydrogen bond with side chain NH2 group of Lys20. The Compound I_8 showed a good interaction with the receptor, 1KE8. Compound I_8 had given the maximum dock score, -8.04. The optimal docking fit is depicted in Fig.2. The compound I_8 is well placed in the hydrophobic enclosure also. The best fit of I_8 against 1KE8 is shown in Fig.4.

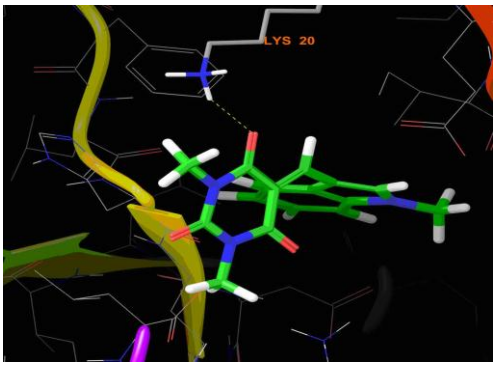


Fig.3 Hydrogen bond interactions (represented in yellow dotted lines) formed by the Glide docking pose of compound I_1 with the binding site amino acids of CDK2

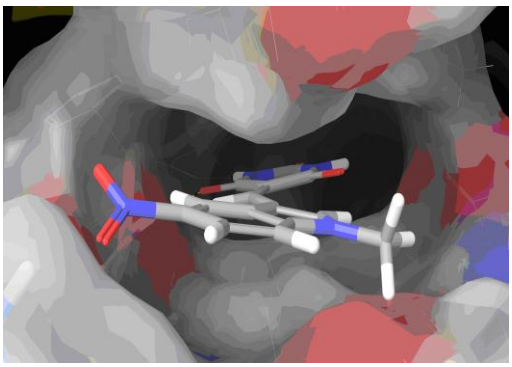
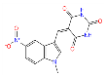


Fig. 4. Display showing 1KE8 – I_8 best fit

The table below shows the docking scores of 15 Indole compounds docked against 1KE8 using Schrodinger Glide.

TABLE 1. DOCKING SCORE OF 15 INDOLES AGAINST 1KE8

Compound Name	Structure	Dock score
I_1		-5.11
I_2		-5.98
I_3		-5.21
I_4		-6.98
I_5		-7.15
I_6		-5.56
I_7		-5.53
I_8		-8.04
I_9		-6.17
I_{10}		-7.50
I_{11}		-5.53
I_{12}		-5.50
I_{13}		-5.49
I_{14}		-6.72
I_{15}		-6.94

IV. CONCLUSION

5-[(1-methyl-5-nitro-1*H*-indol-3-yl) [methylidene] pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione, (I_8) binds effectively at the active site of 1KE8 with binding energy -8.04 (Kcal/mol). There is no extensive study carried out in the ligand, 5-[(1-methyl-5-nitro-1*H*-indol-3-yl)methylidene] pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione. So this result of the *in silico* studies reveal that the molecule is potential candidate for drug, which needs to undergo wet lab trials. Further the compound should be optimized to have better bioavailability, optimum metabolic half-life and with minimal side effects etc before making it a safe and efficacious drug.

REFERENCES

[1] Ferlay J, Shin HR, Bray F, et al. Cancer Incidence and Mortality Worldwide, International Agency for Research on Cancer, Lyon. (2010). GLOBOCAN 2008 v1.2.

[2] P. Diaz, S.S. Phatak, J. Xu, F. Astruc-Diaz, C.N. Cavasotto, M. Naguib, 6-MethoxyN-alkyl isatin acylhydrazone derivatives as a novel series of potent selective cannabinoid receptor 2 inverse agonists: design, synthesis, and binding mode prediction, J. Med. Chem. 52 433–444 (2009).

[3] S. Costanzi, On the applicability of GPCR homology models to computer-aided drug discovery: a comparison between in silico and crystal structures of the beta(2)-adrenergic receptor, J. Med. Chem. 51. 2907–2914 (2008).

[4] Sundberg, R. J. 1970.The Chemistry of Indoles, Academic Press, New York.

[5] Joule, J. A.; Mills, K. 2000. Heterocyclic Chemistry, 4th ed., Blackwell Science, Oxford.

[6] Gribble, G. W. J. 2000: Recent developments in indole ring synthesis-methodology

[7] Zhang H.Z.: J. Med. Chem. 48, 5215 (2005).

[8] Ashok Kumar, Hemlata Kaur, Sunil Kumar , "Synthesis, Antipsychotic and Anticonvulsant Activityof some new pyrazolinyl/isoxazolinylindol-2-ones" Int. J. Chem. Tech. Res. Vol.2, No.2, pp 1010-1019, April-June 2010.

[9] Samosorn S., Bremner J. B., Ball Lewis A.K.: Bioorg. Med. Chem. 14, 857 (2006).

[10] Chang, X., Tou, J.C., Hong, C., Kim, H.A., Riby, J.E., Firestone, G.L.,Bjeldanes, F., 2005. 3,3-diindolylmethane inhibits angiogenesis and the growth of transplantable human breast carcinoma in athymic mice. Carcinogenesis 26, 771–778.

[11] Chen, D.Z., Qi, M., Auborn, K.J., Carter, T.H., 2001. Indole-3-carbinoland diindolylmethane induce apoptosis of human cervical cancer cells and in murine HPV16-transgenic preneoplastic cervical epithelium.Journal of Nutrition 131, 3294–3302.

[12] Chinni, S.R., Li, Y., Upadhyay, S., Koppolu, P.K., Sarkar, F.H., 2001.Indole-3-carbinol (I3C) induced cell growth inhibition, G1 cell cycle arrest and apoptosis in prostate cancer cells. Oncogene 20, 2927–2936.

[13] Qi, M., et al. Indole-3-carbinol prevents PTEN loss in cervical cancer in vivo. Mol Med, 2005. 11(1-12): p. 59-63.

[14] Naik, R., et al. A randomized phase II trial of indole-3-carbinol in the treatment of vulvar intraepithelial neoplasia. Int J Gynecol Cancer, 2006. 16(2): p. 786-90.

[15] Bell, M.C., et al. Placebo-controlled trial of indole-3-carbinol in the treatment of CIN. Gynecol Oncol, 2000. 78(2): p. 123-9.

[16] Kietpeerakool, C., and Srisomboon, J. Medical treatment of cervical intraepithelial neoplasia II, III: an update review. Int J Clin Oncol, 2009. 14(1): p. 37-42.

[17] Kim. Y.S., and Milner, J.A. Targets for indole-3-carbinol in cancer prevention. J Nutr Biochem, 2005. 16(2): p. 65-73

[18] Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S., 2004, Glide: A new approach for rapid,

[19] Krovat, E. M.; Steindl, T.; Langer, T., 2005, Recent Advances in Docking and Scoring. Curr. Comput.-Aided Drug Des., 1, 93-102.

[20] Kontoyianni, M.; McClellan, L. M.; Sokol, G. S., 2004, Evaluation of Docking Performance: Comparative Data on Docking Algorithms. J. Med. Chem., 47, 558-565

[21] Maestro, Version 9.2, Schrödinger, LLC, New York, NY, (2012).

[22] Glide, Version 5.7, Schrödinger, LLC, New York, NY, (2012).