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In Silico Analysis of Indoles Against 1KE8 Inhibitors Using Autodock

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Authors' contributions

This work was carried out in collaboration between all authors. Author VAAK designed the study, wrote the protocol and wrote the first draft of the manuscript. Author KM verified the analyses of the study and the literature searches. All authors read and approved the final manuscript

Research Article

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ABSTRACT

1KE8 is known as a potential target for anti-cancer medication. Indoles are biologically active nitrogen heterocyclics known for broad spectrum activities. Modification of Indole ring system with selected structural descriptors has offered a high degree of stereo specificity and diversity in activity to the moiety.

Keywords: 1KE8; indoles; heterocyclic; anti cancer drugs.

1. INTRODUCTION

Cancer is a major health problem worldwide. Cancer disease starts when the cells in the body begin to grow out of control. Growth of cancer cells is different from the normal cell growth. They can grow into other tissues also. There are different types of cancer, but they all commence because of out-of-control growth of abnormal cells. The origin of the word cancer is credited to Hippocrates, who is considered as the "Father of Medicine." There are over 200 different known cancers that affect human cell type.

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The treatment of cancer involves surgery, radiation and chemotherapy. Clinical trials were used to develop new medical systems for cancer. Various studies revealed that about one-half of men and one-third of women in the US will develop cancer during their lifetimes. According to American cancer society, about 1,638,910 new cancer cases were diagnosed in 2012 and about 577,190 Americans were expected to die of cancer, which means that more than 1,500 people dies a day [1]. 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 in the world. Around 2.4 million new cases of cancer were diagnosed in EU countries in 2008 with 55% occurring among males and 45% among females [2]. Cancer has become one of the 8 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.

Computer aided drug discovery uses computational chemistry to discover, enhance, or study drugs and related biologically active molecules. The ultimate aim is to predict whether a given molecule will bind to a target and if so how strongly. 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. 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. There are two methods in computer aided drug design; Structure based drug design and Ligand Based drug design. Structure based drug design relies on the knowledge of the three dimensional structure of the biological target, whereas ligand based drug design depends on the knowledge of the molecules that bind to the biological target. Now these methods are very popular in the discovery of novel compounds [3,4].

2. MATERIALS AND METHODS

1KE8 is a cyclin dependent kinase and this docking study conducted for finding the 1KE8 inhibitor. 1KE8 belongs to a family of protein kinases first discovered for their role in regulating the cell cycle. Cyclin dependent kinases 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.

The crystal structure of CDK was selected and downloaded from the Protein Data Bank [PDBID: 1KE8]. The 3D structure of 1KE8 is shown in Fig.1. It is then refined using Autodock software [10,11]. A typical structure file from the PDB is not suitable for immediate use in molecular modeling calculations. It has heavy atoms and may include a co-crystallized ligand, water molecules, metal ions etc. The refining process involves fixing structures first, then deleting unwanted chains and waters, then fixing or deleting het groups, and finally performing some optimization of the fixed structure.

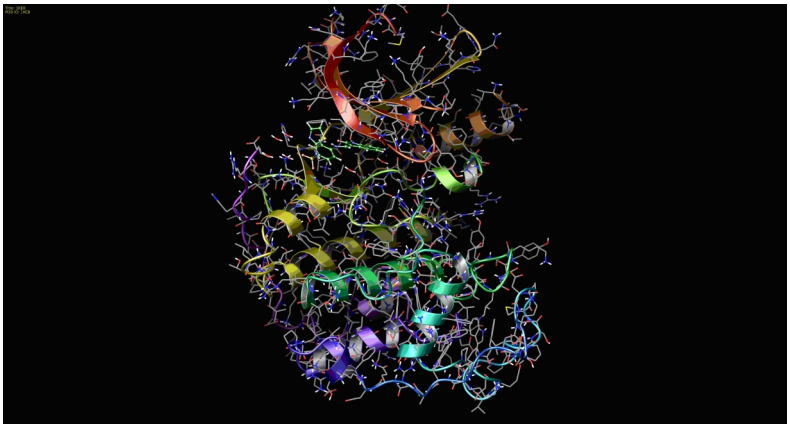


Fig. 1. 3D structure of 1KE8

Indoles are the most important nitrogen containing heterocyclic molecules. They found extensively in biological system and plays vital role in biochemical process. Indole is the commonly used name for the benzopyrrole ring system, consisting of a benzene ring fused to the 2, 3-positions of a pyrrole ring [5-8]. Indole ring system is found in many natural products. The interesting chemical properties of indole have inspired chemists to design and synthesize a variety of indole derivatives [9]. Indole derivatives are found to contain several biological activities those including antimicrobial, antibiotic, anti-inflammatory, antitumor, anti-malarial etc [10-16]. Modification in their structure has offered a high degree of diversity that has proven useful for the development of new therapeutic agents having improved potency and lesser toxicity.

Docking studies were carried out by using the Autodock. Autodock starts with a ligand molecule in an arbitrary conformation, orientation and position which finds favorable dockings in a protein binding site. It uses both simulating annealing and genetic algorithms. The program Autodock Tools (ADT), which has been released as an extension suite to the Python Molecular Viewer, was used to prepare the protein and the ligands.

The macromolecular structure was modified to get more logical and precise outcomes before performing docking. The existed ligands in the crystal were all omitted so that other molecules could be docked and also crystallographic water molecules in the structure were eliminated. Polar hydrogens were added, and then Kollman United Atom charges and atomic solvation parameters were assigned. The grid maps of docking studies were computed using the AutoGrid4 included in the Autodock4 distribution. Grid centers were placed on the active sites which were obtained by trial and error and the previous study done by L Zhang et al (Protein Sci. 2008) and 50x50x50 points with grid spacing of 0.375 was calculated. The GA-LS method was adopted to perform the molecular docking.

The parameters for GA were defined as follows: a maximum number of 250,000 energy evaluations; a maximum number of generations of 27,000; mutation and crossover rates of 0.02 and 0.8, respectively. Pseudo-Solis & Wets parameters were used for local search and 300 iterations of Solis & Wets local search were imposed. The number of docking runs was set to 50. Both Autogrid and Autodock computations were performed on Cygwin. After docking, all structures generated were assigned to clusters based on a tolerance of 1 A° all-atom RMSD from the lowest-energy structure. Hydrogen bonding and hydrophobic

interactions between docked potent agents and macromolecule were analyzed using ADT (Version 1.50).

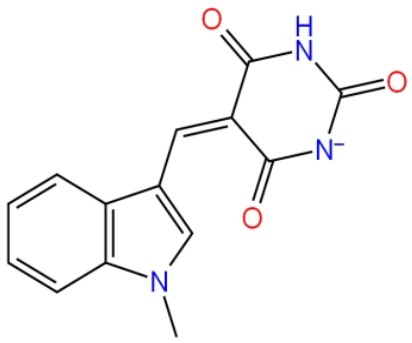


Fig. 2. Structure of I_1

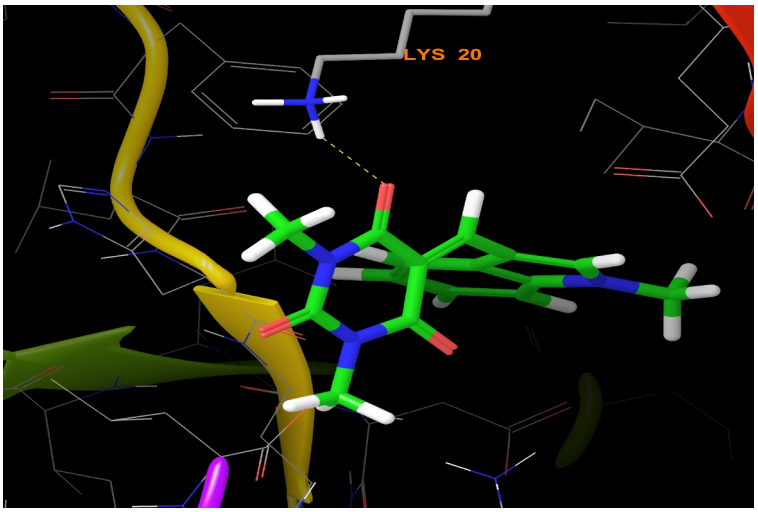


Fig. 3. The Optimal docking of I_1 with 1KE8

3. RESULTS AND DISCUSSIONS

Before running docking calculations, we have evaluated our docking protocol for its reproducibility by re-docking the co-crystal ligand of 1KE8 using Autodock. The docked pose of the co-crystal ligand obtained from Autodock is having only 0.504 Aº RMSD with co-crystal conformation and moreover all the interactions made by co-crystal is also reproduced in docking pose (Fig. 4). This validation shows that the Autodock generates accurate poses for 1KE8.

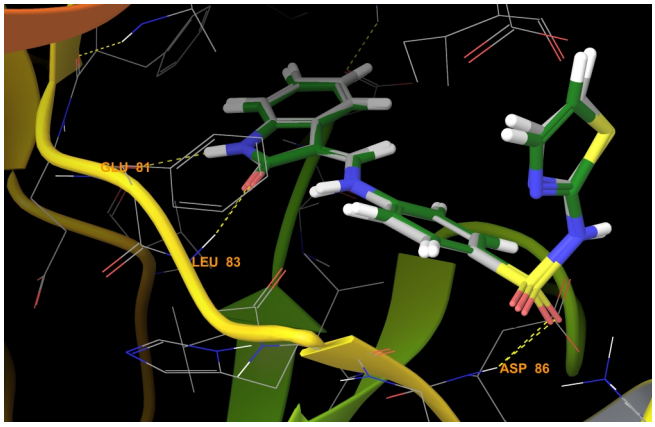


Fig. 4. Re-docking of the co-crystal ligand using Autodock

The co-crystal ligand is showing strong hydrogen bond interactions with hinge region amino acids (Glu81 and Leu83) and also with Asp86 Similar protocol was used to dock all the 15 indole analogues into ATP site of CDK2 receptor and the results of the study was shown in the Table 1. Most of the indole analogs were docked well inside the pocket of CDK2 receptor, especially the indole moiety was making hydrogen bond with hinge region amino acids of the receptor. (The structure of compound I_1 is shown in Fig. 2.) Autodock energy was ranging from -8.89 Kcal/mol to -3.88 kcal/mol for these compounds. The compound I_1 was showing high binding affinity of -8.89 kcal/mol due to strong hydrogen bond interactions with respect to the receptor binding site amino acids. The backbone CO group of Glu81 and backbone NH of Leu83 present in the hinge region of the receptor formed a hydrogen bond with NH and CO group of the pyrimidinetrione moiety of the compound I_1. Similar interactions in the hinge region are also observed in co-crystal ligand. Further the total moiety was surrounded by the hydrophobic amino acids including Phe82,Ala31, Phe80, Val18, Ala144, Leu134,Val64, Leu83 (Fig. 5). The optimal docking is shown in Fig. 3. Due to these combinations of both hydrophobic and hydrogen bond interactions the compound I_1 was tightly bind to the receptor. The best fit of I_1against 1KE8 is shown in Fig. 6.

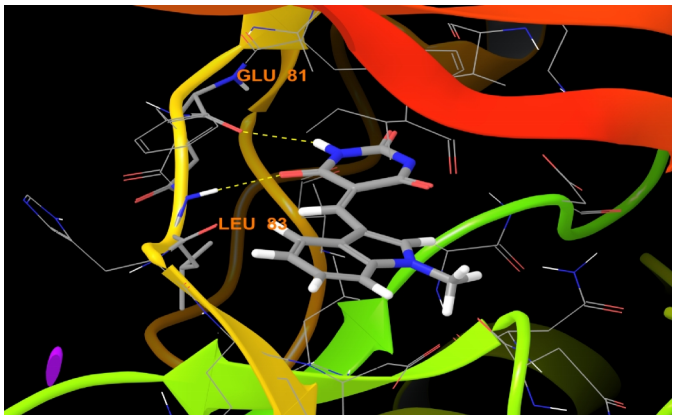
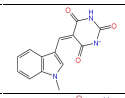
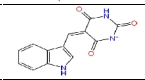
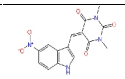
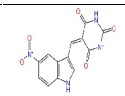
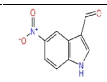
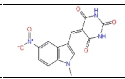
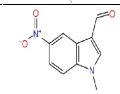
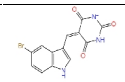
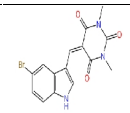
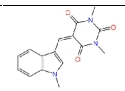
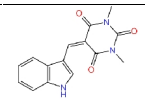
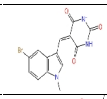
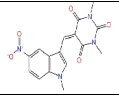


Fig. 5. Hydrogen bond interactions (represented in yellow dotted lines) formed by the Autodock docking pose of compound I_1 with the binding site amino acids of CDK2 receptor

The table below shows the docking scores of Indole compounds docked with 1KE8 using AutoDock software.

Table 1. Docking score of Indole analogues against 1KE8

Compound Name	Structures	Binding Energy
I_1		-8.89
I_2		-7.52
I_3		- 3.91
I_4		-4.39
I_5		-3.88
I_6		-5.21
I_7		-8.75
I_8		-8.17
I_9		-5.00
I_{10}		-5.28
I_{11}		-4.94
I_{12}		- 8.89
I_{13}		-5.06
I_{14}		-5.93
I_{15}		-8.12

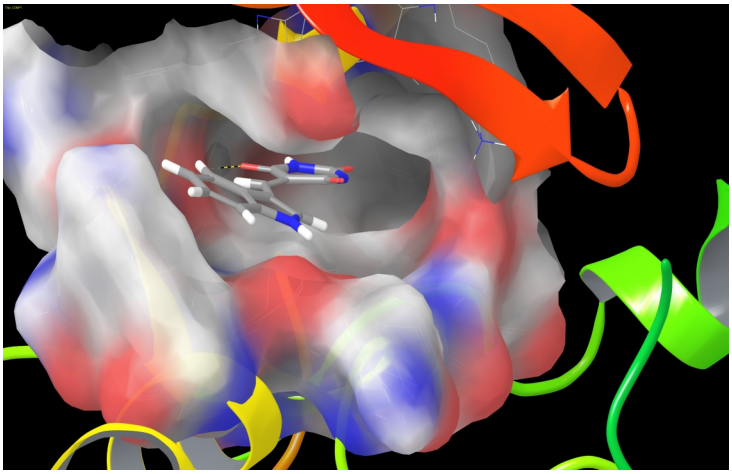


Fig. 6. Display showing 1KE8 – I_1 best fit

4. CONCLUSION

(5E)-5-[(1-methyl-1H-indol-3-yl)methylidene]-2,4,6-trioxotetrahydro-2H-pyrimidin-1-ide, (I_1) binds effectively at the active site of 1KE8 with binding energy -8.89 (Kcal/mol). There is no extensive study carried out in the ligand, (5E)-5-[(1-methyl-1H-indol-3-yl)methylidene]-2,4,6-trioxotetrahydro-2H-pyrimidin-1-ide. 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.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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