DOCKING STUDIES OF QUINOXALINE ANALOGUES WITH 1KE8: A CYCLIN DEPENDENT KINASE [CDK]

Arun Kumar V.A[1], **Keshav Mohan** [2]

[1] Research Scholar, Sathyabama University, Chennai, India
[2]Professor, SVN College of Engineering, Kattachira, Alappuzha, India
Email: [1]adapihrd@gmail.com

Abstract

1KE8 is a Cyclin-dependent kinase (CDK) that belongs to a family of protein kinases. CDKs are considered a potential target for anti-cancer medication. Quinoxaline and its derivatives are an important class of benzoheterocycles displaying a broad spectrum of biological activities which have made them privileged structures in pharmacologically active compounds. 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. In the present work, attempts were made to identify leading quinoxaline moieties as candidate drugs against 1KE8 by carrying out docking experiments with 46 analogues and assigning docking scores. Structural features of the above quinoxaline analogues will be presented with a view to arrive at potential drug target for 1KE8.

Key words: CDK, Quinoxaline, Kinase, Anti Cancer drugs, Schrodinger Glide

I. INTRODUCTION

Cancer, medically known as malignant neoplasm, is a broad group of disease, involving different cell types in the human body with unregulated cell growth. In cancer, cells divide and grow uncontrollably forming tumors and invade near by cells and organs. The cancer may also spread to more distant part of the body through the lymphatic system or blood stream. There are over 200 different known neoplasm's that affect human cell type. Complex for our understanding is the cause of cancer.

Treatment protocol for cancer involved surgery, radiation and chemotherapy. Clinical trials are studies in which people volunteer to take part in tests of new drugs of medical procedures. Clinical trials are used to develop new medical regimes for cancer. 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. Cancer has become one of the 10 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 2010.

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. 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, a cyclin dependent kinase is selected for this study and docking exercises carried out for identifying 1KE8 inhibitor. 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.

The receptor protein was downloaded from Protein Data Bank [PDB] and refined using protein wizard of Schrodinger suit 2012[7-9]. A typical structure file from the PDB is not suitable for immediate use in molecular modeling calculations. Typical PDB structure

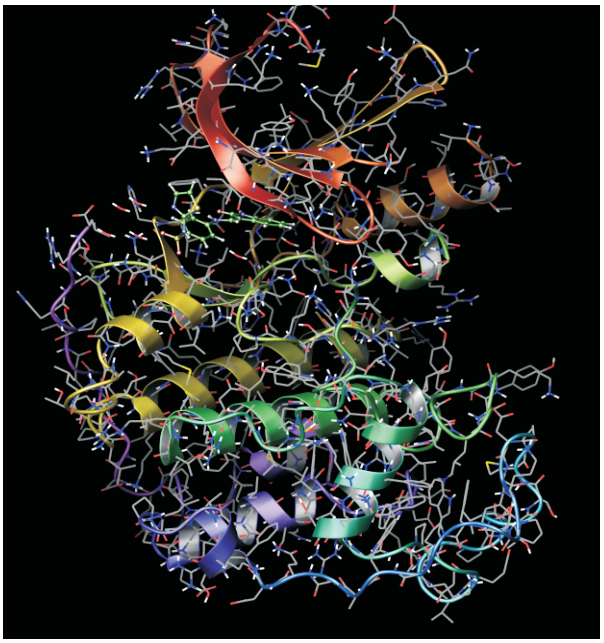

Fig. 1. 3D structure of 1KE8

file consists only of heavy atoms and may include a 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 first, then deleting unwanted chains and waters, then fixing or deleting het groups, and finally performing some optimization of the fixed structure.

Quinoxaline and its derivatives are an important class of benzoheterocycles displaying a broad spectrum of biological activities which have made them privileged structures in pharmacologically active compounds. Quinoxaline, also called benzopyrazine has been considered as a wonder nucleus which posses almost all types of biological activities[6]. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. They are clinically effective as antibacterial, antifungal, anti-inflammatory, anticancer, anti-tubercular and antineoplastic agents. Interestingly, it also shows anti-HIV and anti-proliferative activity. 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.

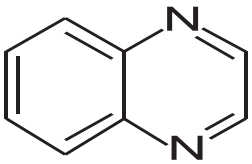

Fig. 2. Structure of Quinoxaline

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 docking calculations were carried out with Schrodinger Glide 2012. 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.

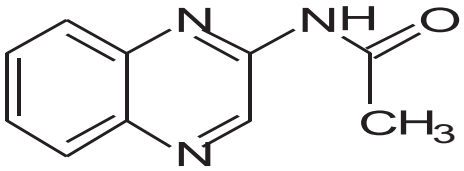

Fig. 3. Structure of q22
(N-(quinoxaline-2-yl)acetamide)

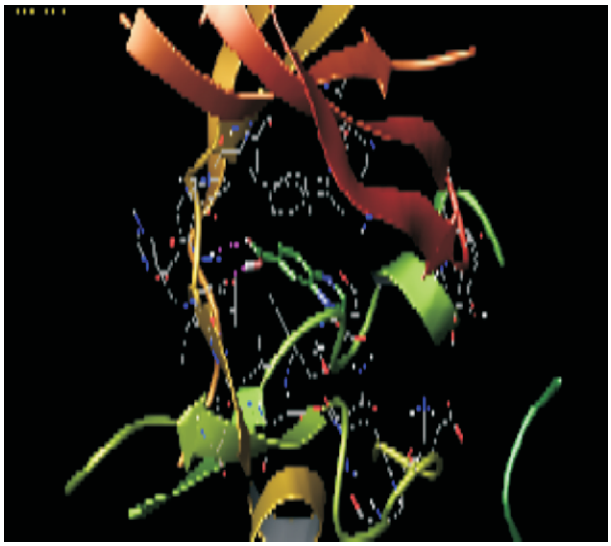

Fig. 4. The Optimal docking of q22 with 1KE8

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 standard-precision (SP) mode[1,3,4]. 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. The top- ranked compounds obtained in this way were docked and scored again with the Glide extra-precision (XP) mode, and the best of 10 XP-docked structures was finally selected as final docking solution[7,8,9].

III. RESULTS AND DISCUSSIONS

The results of docking experiments of the first 10 lead drug candidates are tabulated below in the order of decreasing Glide score.

From docking scores in Table.1, the following conclusions can be drawn. N-(quinoxaline-2-yl) acetamide (q22) shows the maximum glide score value of – 6.69. The nearest two ligands i.e. (Quinoxaline-6ylcarbonyl)sodium (q45) and (Quinoxaline-6ylcarbonyl)potassium (q46) give the value of – 6.14. q22 gives the Lipophillic van der Waal's energy of – 3.24 where as the nearest ligands (q45 and q46) give the energy value of – 2.72. Hydrophobic enclosure reward is the cumulative hydrophobic interaction between the ligand and the receptor atom[2]. The ligand q22 gives the maximum value of the hydrophobic enclosure reward (– 0.82). This shows that N-(quinoxaline-2-yl)acetamide (q22) is the best suitable ligand which is well placed in the pocket of the receptor atom[5]. This best fit is depicted in Fig.5.

In the case of hydrogen bond energy released, q22 releases less compared with q45 and q46. They show the value of -0.75. The electrostatic energy of q22 is -0.19, which is higher than the other two ligands.

Table I. Docking score for 10 selected ligands
(1- GScore, 2- LipophilicEvdW, 3-PhobEn, 4-Hbond, 5-Electro)

Ligands	1	2	3	4	5
N-(quinoxalin-2-yl)acetamide (q22)	– 6.69	– 3.24	– 0.82	– 0.61	– 0.19
(Quinoxaline-6-ylcorbonyl)sodium (q45)	– 6.14	– 2.72	– 0.75	– 0.7	– 0.15
(Quinoxaline-6ylcarbonyl)potassium (q46)	– 6.14	– 2.72	– 0.75	– 0.7	– 0.15
[Hydroxy(quinoxaline-2-yl)phophoryl]sodium(q33)	– 5.68	– 2.58	– 0.57	– 0.7	– 0.32
[Hydroxy(quinoxaline2yl)phophoryl]potassium(q32)	– 5.65	– 2.57	– 0.57	– 0.7	– 0.3
Quinoxaline -2-ylsulfamic acid (q18)	– 5.39	– 2.04	– 0.2	– 1.3	– 1.06
Quinoxaline 6-ylphosphoramidic acid (q23)	– 5.38	– 1.72	0	– 2.34	– 0.96
Quinoxaline -2-ylphosphoramidic acid (q19)	– 5.89	– 1.48	0	– 1.42	– 2.49
Quinoxaline 6-yl-sulfamic acid (q24)	– 5.21	– 2.03	0	– 1.32	– 1.08
2,3,6,7 tetrachloroquinoxaline (q9)	– 5.11	– 3.54	– 1.05	0	– 0.08

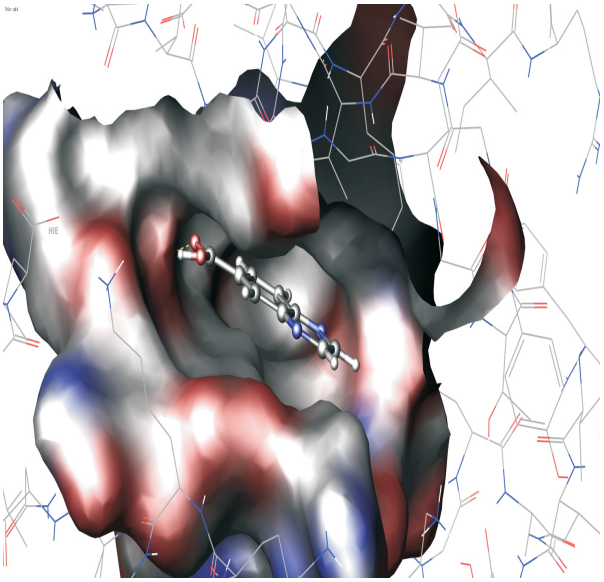

Fig. 5. Display showing 1KE8 – q22 best fit

So we can conclude that the ligand q22 i.e. N-(quinoxalin-2-yl)acetamide is the best ligand among the other 46 ligands docked against the inhibitor, 1KE8.

The amide further showed considerably higher hydrogen bond [-0.61] and electrostatic attraction[-0.19] compared to the carbamic acid analogue, quinoxaline-2-ylcarbamic acid (q20). It is also noted that Sodium and Potassium salts [q45, 46] of quinoxaline -6-carboxylic acid [q44] have excellent binding affinity to the receptor 1KE8.

Table 2. Docking score for 3 selected ligands (1-GScore, 2- LipophilicEvdW, 3- PhobEn, 4-Hbond, 5- Electro)

Ligand	1	2	3	4	5
(Quinoxalin-2-ylcarbonyl)sodium (q42)	– 4.32	– 2.5	– 1.18	0	0
(Quinoxaline-2ylcarbonyl)potassium (q43)	– 4.32	– 2.5	– 1.18	0	0
Quinoxaline-2carboxylic acid (q41)	– 4	– 2.15	– 0.93	0	0

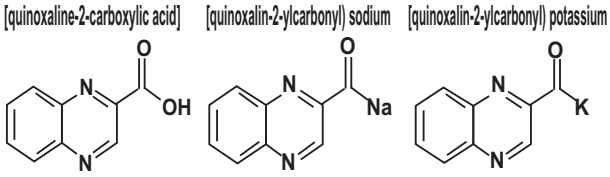

Fig. 6. Structure of q41, q42 & q43

It is observed that introducing caboxylic functional at position 2 did not improve binding affinity of the ligand moieties [q41,q42,q43]. Refer the table 2.

IV. CONCLUSION

N-(quinoxaline-2-yl)acetamide (q22) binds effectively at the active site of 1KE8 with binding energy -6.69 (Kcal/mol). There is no extensive study carried out in the ligand, N-(quinoxaline-2-yl) acetamide. So this result of the *in silico* studies reveal that the molecule is potential candidate for drug, which needs to undergo wet lab trials.

REFERENCES

[1] 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, accurate docking and scoring. 1. Method and assessment of docking accuracy. J. Med. Chem. 47 (7), 1739-1749.

[2] Friesner, R. A.; Murphy, R. B.; Repasky, M. P.; Frye, L. L.; Greenwood, J. R.; Halgren, T. A.; Sanschagrin, P. C.; Mainz, D.T., 2006, Extra precision glide: Docking and scoring incorporating a model of hydrophobic enclosure for protein-ligand complexes. J. Med. Chem., 49 (21), 6177-6196.

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

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

[5] Sherman, W.; Day, T.; Jacobson, M. P.; Friesner, R.A.; Farid, R., 2006, Novel Procedure for Modeling Ligand/Receptor Induced Fit Effects. J. Med. Chem., 49, 534.

[6] Prasad et al., 2011, Anti Inflammatory Activity of Some New Thio-Ether Derivatives of Quinoxaline. Pharmacologyonline 1: 1023-1030.

[7] MOE, Version 2008.10, Chemical Computing Group, Inc., www.chemcomp.com.(2008)

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

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