Journal of Computational Intelligence in Bioinformatics
ISSN 0973-385X Volume 5, Number 3 (2012) pp. 193-200

http://www.ripublication.com/jcib.htm

Assessment of Binding Potentials of Quinoxaline Analogues against Adenylate Kinase

Arun Kumar V.A.[1] and Keshav Mohan

[1]Research Scholar, Department of S&H (Computer Applications), Sathyabama University, Chennai.
Email: [1]akva1234@yahoo.com

Abstract

Adenylate kinase (AK) catalyse the phosphotransferase reactions and plays important role in cellular energy homeostasis. The inhibitors of bacterial AK are useful in the treatment of several bacterial infections. Qunoxaline analogues were docked with 1ZIP and potential candidate compounds were identified based on their binding energies.

Keywords: nucleotide, kinase, quinoxaline, homeostasis

Introduction:

Tuberculosis is an infections disease caused by Mycobacterium tuberculosis. Tuberculosis can affect all organs of the body except hair and nail. Mycobacterium tuberculosis is a global health threat, infecting about one third of the human population and resulting in an annual casualty of 2 million people worldwide[1]. The chances of getting infected depend upon the duration, the frequency of exposure and the immune status of an individual. One fifth of the total global TB incidence is in India, ie., around 1.98 million cases. In India an estimated 2.76 lakh deaths occur from TB every year. TB is a serious public health problem in India causing immense morbidity, mortality and distress to individual and communities.

Present treatment requires a therapy involving four different drugs and for a period of 6–9 months. This often leads to poor patient compliance and subsequently to drug resistance[2]. In early 1990s, multi-drug resistant tuberculosis (MDR-TB) emerged and extensively drug-resistant tuberculosis (XDR-TB) cases were first reported in 2005[3,4]. Consequently, a renewed effort to develop new anti-tuberculosis drugs is necessary[5,6,7]. Accordingly, new therapeutic targets are to be precisely characterized to uncover their specific structural and functional features [8,9,10].

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, where as structure based drug design relies on the knowledge of the three dimensional structure of the biological target[11,12]. 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.

Materials and Methods

Large conformational changes in proteins play important roles in cellular signaling. Adenylate Kinase is a signal transducing protein; thus, the balance between conformations regulates protein activity. ADK has a locally unfolded state that becomes depopulated upon binding. The inhibitors of bacterial AK are useful in the treatment of several bacterial infections. Docking studies were performed using the 3 dimensional structure of Bacillus stearothermophilus adenylate kinase from protein databank (1ZIP) with a view to identify potential inhibitors in the class of novel quinoxaline analogues.[Fig.1]

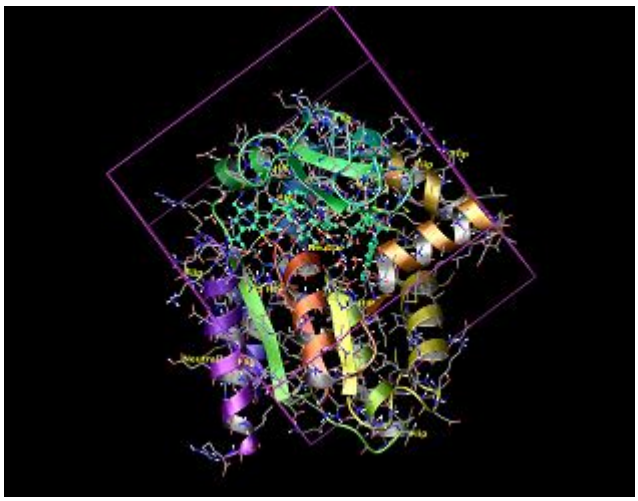


Fig.1. 3D structure of 1ZIP

The receptor protein was downloaded from Protein Data Bank [PDB] and refined using protein wizard of Schrodinger suit 2012[26,27]. A typical structure file from the PDB is not suitable for immediate use in molecular modeling calculations. Typical

PDB structure 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 is therefore needed to prepare proteins in a form that is suitable for modelling 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[13,14]. Quinoxaline, also called benzopyrazine has been considered as a wonder nucleus which posses almost all types of biological activities. 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[15-20]. 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.]

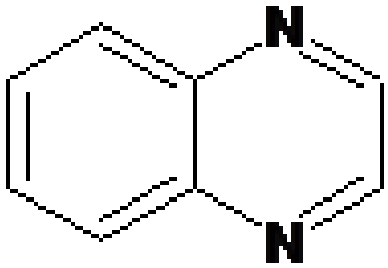


Fig.2. Typical Quinoxaline structure

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[26,27]. 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. The lowest-energy poses obtained in this fashion were subjected to a Monte Carlo procedure to obtain the final set of docking solutions. Glide uses two concentric boxes to generate the potential grids and define the binding site. The grids are computed within the space defined by the “outer box”, which encompasses all the ligand atoms. The “inner box” is defined as containing all acceptable positions for the ligand center upon docking.

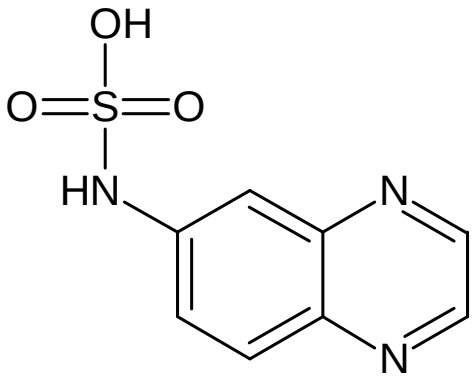


Fig. 3 : q24 : Quinoxalin-6 – yl- sulfamic acid

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. 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.

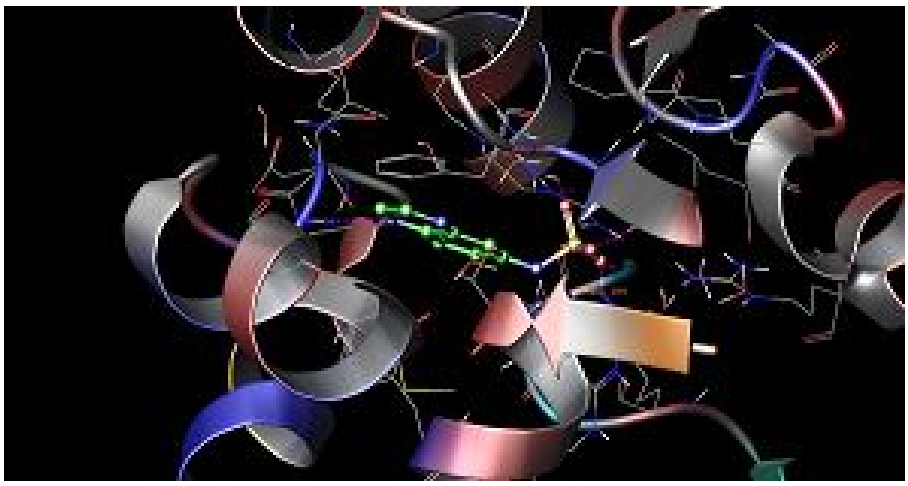
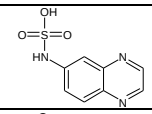
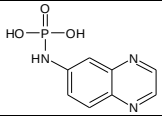
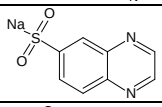
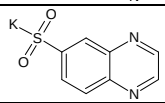
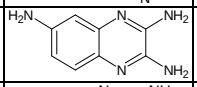
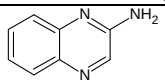
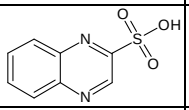
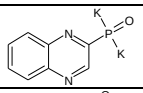
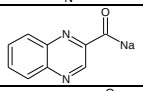
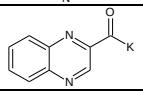


Fig.4 The Optimal docking of q24 with 1ZIP

Results & Discussions:

The following results were found in the docking process. The 10 moieties showed the maximum docking score are given below in the descending order.

Table 1. Docking score table of 10 moieties with highest docking score

Compound Name	Structures	*GScore*	*Lipophilic EvdW*	*PhobEn*	*Hbond*	*Electro*
q24		-9.78	-2.51	-1.5	-2.27	-3
q23		-9.34	-2.12	-1.5	-3.63	-1.74
q39		-6.15	-3.24	-1.5	-0.7	-0.22
q40		-6.15	-3.24	-1.5	-0.7	-0.22
q16		-5.75	-2.9	0.83	-1.19	-0.34
q14		-5.59	-3.24	-0.96	-0.64	-0.26
q25		-5.21	-2.09	0	-3.31	-2.31
q36		-5.11	-2.81	0	-1.33	-0.47
q42		-5.07	-3.33	-0.79	-0.32	-0.12
q43		-5.07	-3.33	-0.79	-0.32	-0.12

From docking scores in Table.1, the following conclusions were drawn. Quinoxalin-6 – yl- sulfamic acid(q24) shows the maximum glide score value of -9.78. The structure of q24 is shown in Fig.3. And the optimal docking of 1ZIP against q24 is shown in Fig.4. Quinoxalin-6-yl -phosphoramidic acid shows the docking score value, -9.34. q24 gives the Lipophillic van der Waal's energy of -2.51 whereas the nearest ligand q23 gives the energy value of -2.12. Hydrophobic enclosure reward is the cumulative hydrophobic interaction between the ligand and the receptor atom[28]. The ligand q24 gives the value of the hydrophobic enclosure reward (-1.5). Glide score and the other values mentioned in the Table 1. shows that Quinoxalin-6yl-sulfamic acid(q24) is the best suitable ligand which is well placed in the pocket of the receptor atom[28]. This best fit is depicted in Fig.5.

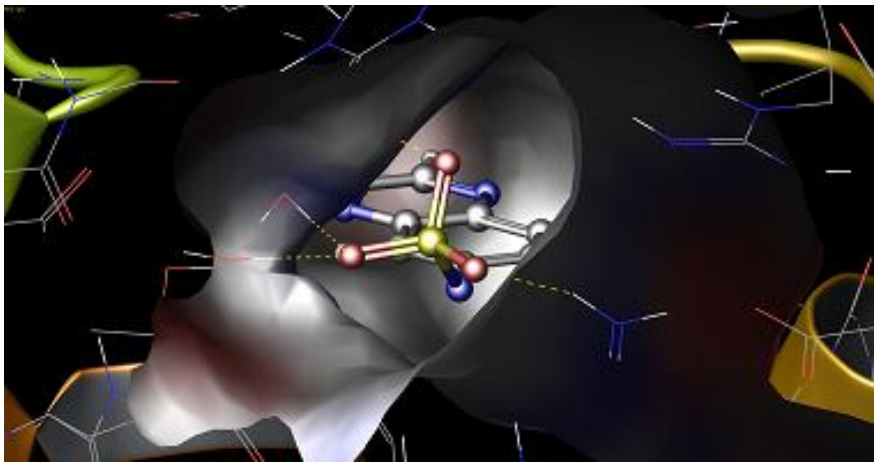


Fig.5. Display showing 1ZIP – q24 best fit

In the case of hydrogen bond energy released, q24 releases -2.24 less compared to the next ligand q23, but higher than of all other 44 ligands. q24 has the highest electrostatic reward compared to all the other 45 mioties. It can be inferred that the ligand q24, Quinoxalin-6yl-sulfamic acid is the potential ligand candidate among the quinoxaline analogues docked against 1ZIP.

Conclusion:

Quinoxalin-6yl-sulfamic acid (q24) binds effectively at the active site of 1ZIP with binding energy -9.78 (Kcal/mol). The *in silico* studies reveal that the molecule is potential candidate as a drug against 1ZIP which needs invites wet lab trials. Bioavailability, metabolic half life and lack of side effects etc are to be optimized before making it a safe and efficacious drug.

References:

[1] Dye, C., Scheele, S., Dolin, P., Pathania, V., and Raviglione, M.C. (1999).Consensus statement. Global burden of tuberculosis: estimated incidence,prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 282, 677–686.

[2] Tuberculosis. Scientific blueprint for tuberculosis drug development. Tuberculosis (Edinb) 2001;81 Suppl. 1:1-52.

[3] WHO. Global Tuberculosis Control: Epidemiology, Strategy, Financing: WHO report 2009. WHO Press; 2009.

[4] Jassal M, Bishai WR. Extensively drug-resistant tuberculosis. Lancet Infect. Dis. 2009;9:19-30.

[5] Janin YL. Antituberculosis drugs: ten years of research. Bioorg. Med. Chem. 2007;15:2479-2513.
[6] Rivers EC, Mancera RL. New anti-tuberculosis drugs in clinical trials with novel mechanisms of action. Drug Discov. Today 2008;13:1090-1098.
[7] Sacchettini JC, Rubin EJ, Freundlich JS. Drugs versus bugs: in pursuit of the persistent predator Mycobacterium tuberculosis. Nat. Rev. Microbiol. 2008;6:41-52.
[8] Mdluli K, Spigelman M. Novel targets for tuberculosis drug discovery. Curr. Opin. Pharmacol. 2006;6:459-467.
[9] Zhang Y. The magic bullets and tuberculosis drug targets. Annu. Rev. Pharmacol. Toxicol. 2005;45:529-564.
[10] Zhang Y, Post-Martens K, Denkin S. New drug candidates and therapeutic targets for tuberculosis therapy. Drug Discov. Today 2006;11:21-27.
[11] Blundell T.L. Structure-based drug design. Nature. 1996;384(6604 Suppl.):23–26
[12] I.D. Kuntz, Science, 257, 1078 (1992). "Structure-based strategies for drug design and discovery".
[13] Shivaji, V. M.; Sastry, M. N. V.; Wang, C. C.; Ching-Fa Y. *Tetrahedron Lett.* 2005, *46*, 6345-6348.
[14] Hui, X.; Desrivot, J.; Bories, C.; Loiseau P. M.; Franck, R.; Hocquemiller, R.; Figadere, B. *Bioorg. Med. Chem. Lett.* 2006, *16*, 815-820.
[15] Undevia SD, Innocenti F, Ramirez J, et al. A phase I and pharmacokinetic study of the quinoxaline antitumour Agent R(+)XK469 in patients with advanced solid tumours. *European Journal of Cancer*. 2008;44(12):1684–1692.
[16] . Corona P, Carta A, Loriga M, Vitale G, Paglietti G. Synthesis and in vitro antitumor activity of new quinoxaline derivatives. *European Journal of Medicinal Chemistry*. 2009;44(4):1579–1591.
[17] . Urquiola C, Gambino D, Cabrera M, et al. New copper-based complexes with quinoxaline N1,N4-dioxide derivatives, potential antitumoral agents. *Journal of Inorganic Biochemistry*. 2008;102(1):119–126.
[18] Weng Q, Wang D, Guo P, et al. Q39, a novel synthetic Quinoxaline 1,4-Di-N-oxide compound with anti-cancer activity in hypoxia. *European Journal of Pharmacology*. 2008;581(3):262–269.
[19] Wagle S, Adhikari AV, Kumari NS. Synthesis of some new 4-styryltetrazolo[1,5-a]quinoxaline and 1-substituted-4-styryl[1,2,4]triazolo[4,3-a]quinoxaline derivatives as potent anticonvulsants. *European Journal of Medicinal Chemistry*. 2009;44(3):1135–1143.
[20] Prasad *et al.* Anti Inflammatory Activity of Some New Thio-Ether Derivatives of Quinoxaline. 2011. *Pharmacologyonline* 1: 1023-1030
[21] Maestro, Version 8.5, Schrödinger, LLC, New York, NY, 2012.
[22] Glide, Version 5.7, Schrödinger, LLC, New York, NY, 2012
[23] Friesner, R. A.; Murphy, R. B.; Repasky, M. P.; Frye, L. L.; Greenwood, J. R.; Halgren, T. A.; Sanschagrin, P. C.; Mainz, D.T., , Extra precision glide:

Docking and scoring incorporating a model of hydrophobic enclosure for protein-ligand complexes. J. Med. 2006 Chem., 49 (21), 6177-6196