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In Silico Analysis of Quinoxaline Ligand Conformations on 1ZIP: Adenylate Kinase

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***Abstract*—**Adenylate kinase (AK) catalyse the phosphotransferase reaction plays an important role in cellular energy homeostasis. The inhibitors of bacterial AK are useful in the treatment of several bacterial infections. To the novel inhibitors of AK, docking studies performed by using the 3D structure of Bacillus stearothermophilus adenylate kinase from protein data bank (IZIP). 46 Quinoxaline analogues were docked in 1ZIP and selected the highly interacting compounds based on their binding energies, for further studies

***Keywords*—**Kinase, quinoxaline, homeostasis, inhibitor, nucleotide.

I. Introduction

TUBERCULOSIS (TB) has a long history. Its causative agent, Mycobacterium tuberculosis, may have killed more persons than any other microbial pathogen [1]. It is presumed that the genus Mycobacterium originated more than 150 million years ago [1]. The modern members of M. tuberculosis complex seem to have originated from a common progenitor about 15,000 - 35,000 years ago [2]. TB was documented in Egypt, India, and China as early as 5,000, 3,300, and 2,300 years ago, respectively [1]. Identification of genetic material from M. tuberculosis in ancient tissues has provided a powerful tool for the investigation of the incidence and spread of human TB in historic periods.

Therapy with anti-tuberculosis drugs was identified as the most effective measure for controlling patient's production of infectious particles and thus readily reversing infectivity [3]. Therefore, patients should only require isolation while they were sputum positive and before initiation of specific therapy. Hospitalization was either abolished or reduced to a few weeks for most patients [4]. Above all, the decline in TB control activities and the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic were two major factors fueling each other in the reemergence of TB. Supervised treatment, including sometimes direct observation of therapy (DOT), was proposed as a means of helping patients to take their drugs regularly and complete treatment, thus achieving cure and preventing the development of drug resistance. The Directly-Observed Treatment, Short-course (DOTS) strategy was promoted as the official policy of the WHO in 1991 [5]. Nowadays, treating TB is feasible and effective, even in low income countries, if based on reliable public health practice, including good laboratory infrastructure, appropriate treatment regimens, proper management of drug side-effects and resources to maintain adherence and prevent spread. It is also crucially important to intensify research efforts devoted to developing effective TB vaccines, as well as shortening the time required to ascertain drug sensitivity, improving the diagnosis of TB, and creating new, highly effective anti-tuberculosis medications. Hippocrates thought it was inherited, while Aristotle and Galen believed it was contagious [6]. The consequences of tuberculosis (TB) on society are immense. Worldwide, one person out of three is infected with Mycobacterium tuberculosis – two billion people in total. TB currently holds the seventh place in the global ranking of causes of death. Unless intensive efforts are made, it is likely to maintain that position through to 2020, despite a substantial projected decline in disease burden from other infectious diseases [7] – [8].

Drug design is the inventive process of finding new drug molecule based on the knowledge of a biological target. 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. 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.

II. Materials and Methods

Adenylate Kinase (AK) is a signal transuding protein; thus, the balance between conformations regulates protein activity. 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]

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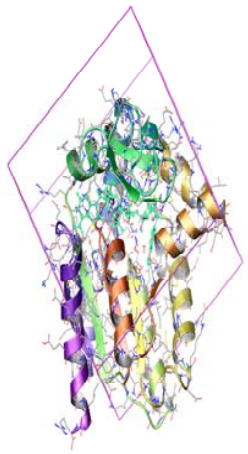

Fig. 1 3D structure of 1ZIP

The receptor protein was downloaded from Protein Data Bank [PDB] and refined using protein wizard of Schrodinger suit 2012. A typical structure file from the PDB is not suitable for immediate use in molecular modeling calculations. The tools of Schrodinger suite 2012 is used for the purpose [12] – [13]. 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. 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 [9] – [10]. 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.

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 [12]-[13]. 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.

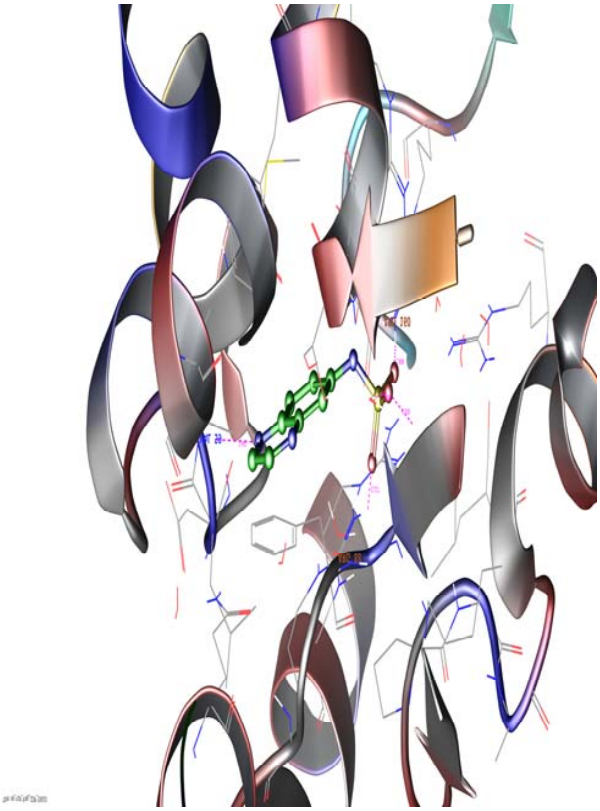

Fig. 2 The Optimal docking of q24 with 1ZIP

Default input parameters were used in all computations. 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 [12]- [13].

II. 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 I
DOCKING SCORE TABLE OF 10 MOITIES WITH HIGHEST DOCKING SCORE

Compound Name	Glide Score	Lipophilic EvdW	PhobEn	Hydrogen bond
quinoxalin-6-ylsulfamic acid (q24)	-9.78	-2.51	-1.5	-2.27
quinoxalin-6-ylphosphoramidic acid (q23)	-9.34	-2.12	-1.5	-3.63
oxy(quinoxalin-6-yl)suphonyl sodium (q39)	-6.15	-3.24	-1.5	-0.7
oxy(quinoxalin-6-yl)suphonyl potassium (q40)	-6.15	-3.24	-1.5	-0.7
quinoxaline-2,3,6-triamine (q16)	-5.75	-2.9	0.83	-1.19
quinoxalin-2-amine (q14)	-5.59	-3.24	-0.96	-0.64
quinoxaline-2-sulfonic acid (q25)	-5.21	-2.09	0	-3.31
potassium(quinoxlin-2yl)phosphoryl potassium (q36)	-5.11	-2.81	0	-1.33
(quinoxalin-2-ylcarbonyl)sodium (q42)	-5.07	-3.33	-0.79	-0.32
(quinoxalin-2-ylcarbonyl)potassium (q43)	-5.07	-3.33	-0.79	-0.32

From docking scores in Table I, the following conclusions were drawn. Quinoxalin-6 – yl- sulfamic acid(q24) shows the maximum glide score value of -9.78. The best dock fit is shown in Fig. 2. Quinoxalin - 6-yl - phosphoramidic acid shows the values of -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 [11]. The ligand q24 gives the value of the hydrophobic enclosure reward (-1.5). Glide score and the other values mentioned in the Table I shows that Quinoxalin-6yl-sulfamic acid (q24) is the best suitable ligand which well placed in the pocket of the receptor atom. This best fit is depicted in Fig. 3.

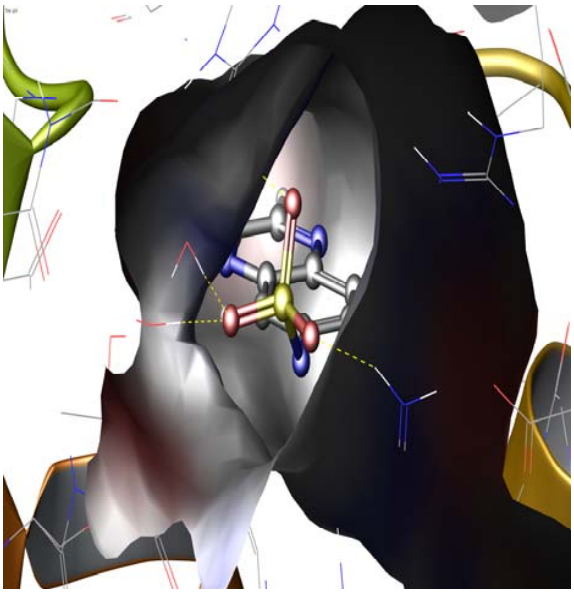

Fig. 3 Display showing 1ZIP – q24 best fit

In the case of hydrogen bond energy, q24 released -2.24. It can be inferred that the ligand q24, Quinoxalin-6yl-sulfamic acid is the potential ligand candidate among the other quinoxaline analogues docked against 1ZIP.

III. 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.

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