MOLECULAR DOCKING STUDIES OF SOME SULFONAMIDE DERIVATIVES AS PBP-2X INHIBITORS AS ANTIBACTERIAL AGENTS

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Abstract. This paper deals with molecular docking studies of some synthesized sulfonamide derivatives with the penicillin-binding protein 2X (PBP-2X) protein. The simulation was done using a software package from Schrödinger (LLC, New York). The docking score is analyzed in comparison with the score of cefuroxime used as reference. The most promising derivatives present a score very close to that of cefuroxime. Hydrogen-bonding interactions of the studied sulfonamide compounds with the amino acids of the target protein have been analyzed.

Key words: docking studies, sulfonamides, binders, antibacterial studies.

INTRODUCTION

Antimicrobial agents consist of any of several synthetic organic compounds capable of inhibiting the growth of bacteria that require PABA (para-amino benzoic acid) which is structurally similar to sulphanilamide. Sulphonamides are the derivatives of sulfonic acids. Sulphonamides are chemically quite stable, they are weak acids compared to carboxylic acid amides. The acidic nature results from the ability of the SO_2 moiety to stabilize the nitrogen anion through resonance. The sulphonamide functional group is $–S(=O)_2–NH–$, a sulfonyl group connected to an amine group. The general formula is $RSO_2NH–$ where R is some organic group. Any sulfonamide can be considered as derived from a sulfonic acid by replacing a hydroxyl group with an amine group. In medicine, the term "sulfonamide" is sometimes used as a synonym for sulfa drug, a derivative or variation of sulfanilamide. Figure 1 shows the structural formula of sulfanilamide and Figure 2 shows the structural formula of PABA.

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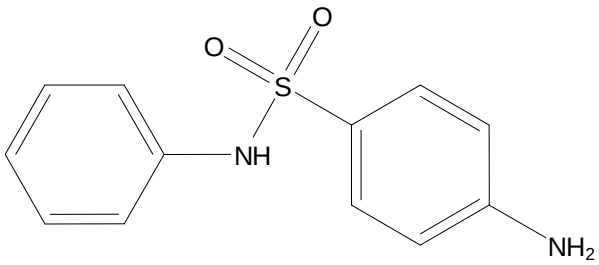


Fig. 1. Structural formula of sulfanilamide.

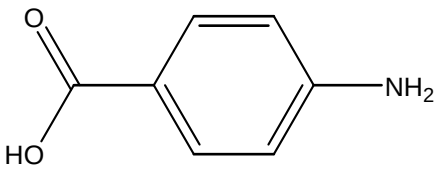


Fig. 2. Structural formula of PABA.

Sulfonamides are antibacterial agent. Hence, penicillin-binding protein (PBP-2X) is taken as the target protein for docking studies of sulfonamides. Docking is a method that predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex in three dimensional space. Docking is also helpful to find the orientation that maximizes the interaction while minimizing the total energy of the complex. Computers and programs (software) are used to predict or simulate the possible reaction (interactions) between two molecules based on the three dimensional structures. This method can therefore be used not only to predict possible binders or inhibitors, but also to predict how strong is the association existing between the molecules [2, 5, 6, 7, 8]. It is useful to compare the binding strength between groups of compounds or derivatives. Prediction of the binding affinity will be useful to synthesize the desired compounds. Because of its ability of predicting binding interactions and orientation, it is widely used in rational drug design and structure based on drug design processes.

The aim of this study is to analyze by docking methods the interaction of six sulphonamide derivatives with the PBP-2X in order to characterize their antimicrobial potential. The analysis was done with cefuroxime as reference molecule.

MATERIALS AND METHODS

In the present investigation we underwent the docking studies of synthesized series of sulfonamides with target protein penicillin-binding proteins (PBP-2X).

The primary targets for beta-lactam antibiotics are periplasmic membrane attached proteins responsible for the construction and maintenance of the bacterial cell wall. Bacteria have developed several mechanisms of resistance, one of which is the mutation of the target enzymes to reduce their affinity for beta-lactam antibiotics.

PENICILLIN-BINDING PROTEIN 2X STRUCTURE

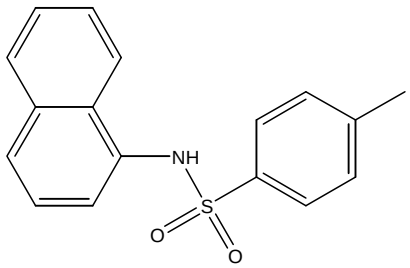
The Protein Data Bank is the single, global archive for information about the 3D structure of biomacromolecules and their complexes, as determined by X-ray crystallography, NMR spectroscopy and cryoelectron microscopy, and includes more than a few Nobel Prize winning structures. The crystal structure of the target protein, penicillin-binding protein 2X in complex with cefuroxime from human pathogen *Streptococcus pneumoniae* [3] was downloaded from the PDB (id: 1QMF) with the specific resolution.

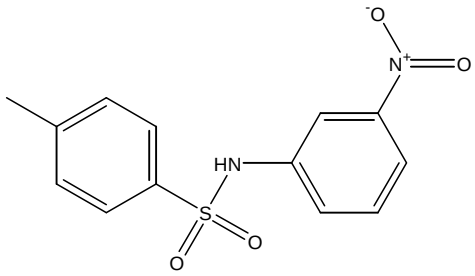
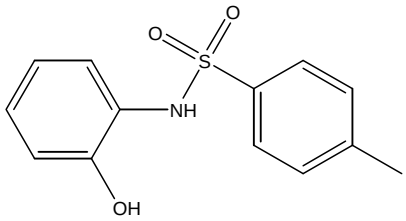
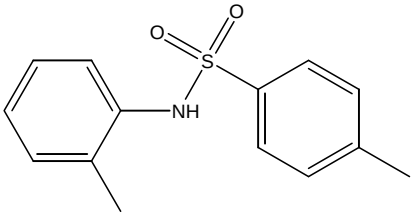
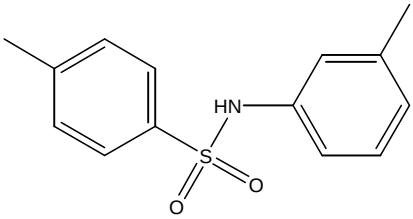
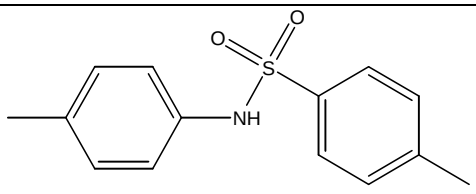
THE SULFONAMIDE DERIVATIVES (LIGANDS) STRUCTURES

The ligands compounds we studied are: 4-methyl-N-naphthalene1-yl benzene sulfonamide (4MNBS), 4-methyl-3-nitrophenyl benzene sulfonamide(4M3NPBS), 4-methyl-4-methylphenyl benzene sulfonamide (4M4MPBS), 4-methyl-3-methylphenyl benzene sulfonamide (4M3MPBS) 4-methyl-2-methylphenyl benzene sulfonamide (4M2MPBS), 4-methyl-2-hydroxyphenyl benzene sulfonamide(4M4HPBS). Their structures were drawn using Chemsketch and are listed in Table 1.

Table 1

Chemical structures of synthesized sulphonamide compounds

Sr. No	Molecular Code	Structures of synthesized compounds
1	4MNBS	 4-methyl-N(naphthalene 1-yl)benzene sulfonamide

2	4M3NPBS	 4-methyl-N(3-nitrophenyl)benzene sulfonamide
3	4M2HPBS	 4-methyl-N(2-hydroxyphenyl)benzene sulfonamide
4	4M2MPBS	 4-methyl-N(2-methylphenyl)benzene sulfonamide
5	4M3MPBS	 4-methyl-N(3-methylphenyl)benzene sulfonamide
6	4M4MPBS	 4-methyl-N(4-methylphenyl)benzene sulfonamide

MOLECULAR DOCKING

The studied sulfonamide compounds were screened using high throughput screening, and further subjected to induced fit docking studies Glide 4.0 and Induced Fit Docking (IFD, Suite 2006, Induced Fit Docking protocol; Prime version 1.5) script from Schrödinger (LLC, New York, 2005) is used as a primary docking engine. The docking algorithm in Glide utilizes a hierarchical search protocol. The structure was refined using OPLS forcefield and the energy minimized conformation was taken as starting conformation for docking studies [4]. The extra precision mode of Glide, which has higher penalties for unfavourable and unphysical interactions, was used for docking. Computations were carried out on a Linux with Redhat 9.0 computer platform. The pictures were taken using PyMOL (DeLano Scientific LLC, San Carlos, 1998–2004, California, USA).

PREPARATION OF PROTEIN

A typical PDB structure file consists only of heavy atoms and may include a co-crystallized ligand, water molecules, metal, ions and cofactors. Some structures are multimeric, and may need to be reduced to a single unit. Schrödinger has assembled a set of tools to prepare proteins in a form that is suitable for modelling calculations. The tools are combined in the Protein Preparation Wizard under Maestro**.**

PREPARATION OF LIGAND

The Schrödinger ligand preparation product LigPrep is designed to prepare high quality, all-atom 3D structures for large numbers of drug-like molecules.

GLIDE GRID GENERATION

Glide (Grid-based Ligand Docking with Energetics) is a ligand binding program provided by Schrödinger that searches for favourable interactions between one or more ligand molecules and a receptor molecule, usually a protein. It provides a complete solution for ligand-receptor docking. The combination of position and orientation of a ligand relative to the receptor, along with its conformation in flexible docking, is referred to as a ligand pose. The ligand poses that Glide generates pass through a series of hierarchical filters that evaluate the ligand's interaction with the receptor. Finally, the minimized poses are re-scored to generate the Glide score (G score) that is the sum of total various figures generated for each ligand during the docking process. The scoring function (G score), for computing binding affinity is an extension of an empirically based Chem-Score function of Eldridge *et al.* [1]. The best G Score is obtained as the most negative

value and the most active ligands in terms of G Score are enlisted in descending order [2].

RESULTS AND DISCUSSION

In the present investigation, *in silico* docking studies were performed using the crystal structure of penicillin-binding protein 2X to recognize the hypothetical binding mode of the six sulfonamide derivatives (ligands) with the receptor in order to know the correct binding site.

Structure based drug design involves detailed knowledge of the binding sites of targets (such as proteins) associated with the disease. A drug's effectiveness depends on the structural interaction with the receptor or target molecule. Molecular docking continues to hold great promise in the field of computer based drug design which screens small molecules by orienting and scoring them in the binding site of a protein.

The top score pose was selected for each analyzed compound and compared with cefuroxime, which was re-docked with the target protein using the same protocol. The IFD conformations are given in Table 2. The structure of the target protein 1QMF is shown in Figure 3 and the ligplot of 1QMF interactions with original ligand KEF (cefuroxime) is shown in Figure 4. Figures 5, 6 and 7 show hydrogen-bonding interactions of the compounds 4M3NPBS, 4M2HPBS and 4MNBS with the penicillin-binding protein 2X respectively.

It was interesting to observe that even though the core structure of all the compounds was the same, the degree of interaction and binding site were found to be different. The variation in the bioactivity is mainly attributed to the difference in their binding site. The binding sites of the compounds were found to be in close proximity to the binding site of the cefuroxime as evident from Figure 4. For instance, the docking studies showed that compounds 4M3NPBS, 4MNBS and 4M2HPBS showed comparable results with cefuroxime. It may be due to the fact that their binding site is close to the cefuroxime binding site when compared to other compounds as revealed by the docking studies.

The IFD conformations suggest that the three of the studied sulfonamide derivatives have favourable hydrogen bond interactions with the target penicillin-binding protein 2X. The compounds have binding orientation and interaction with aminoacids like GLY 664, VAL 662 and ARG 426 present in the active site compared with the standard drug cefuroxime. Among the six derivatives which were docked 4M3NPBS, 4M2HPBS and 4MNBS are more potent than the other derivatives with the Glide scores of –7.47, –7.17, –6.63 and Glide energies of –46.238, –44.476, –45.99 kcal/mol respectively. In all these complex conformations the hydrogen bond interaction limits are 2.5 to 3.5 Å which shows a good interaction and hence most likely to result in a strong inhibition.

Table 2

Energy and hydrogen-bond distance parameter for the sulfonamide compounds on binding with 1QMF protein

Molecule code	Docking score	Glide energy (kcal/mol)	Hydrogen bond interaction	Bond length (Å)
KEF (standard)	–7.54	–54.32	(ARG426)N–H…O O–H…O(VAL662) N–H…O(VAL662) (LYS420)N–H…O (N–H…O)GLY 664 (O–H…O)GLY666	2.801 2.923 2.931 2.996 3.372 2.825
4M3NPBS	–7.47	–46.238	(ARG463)N–H…O (ARG654)N–H…O (ARG426)N–H…O N–H…O(PRO424)	3.067 2.836 2.708 2.634
4M2HPBS	–7.17	–44.476	O–H...O(VAL662) N–H...O(VAL662) (ASP698)N–H...O (PRO697)	3.029 3.07 2.978
4MNBS	–6.63	–45.99	N–H…O(GLY664)	3.045
4M2MPBS	–3.73	–29.91	(ARG426)N–H…O	2.958
4M3MPBS	–4.95	–30.78	N–H…O(GLY664)	3.027
4M4MPBS	–4.22	–32.79	N–H…O(PRO420)	3.089

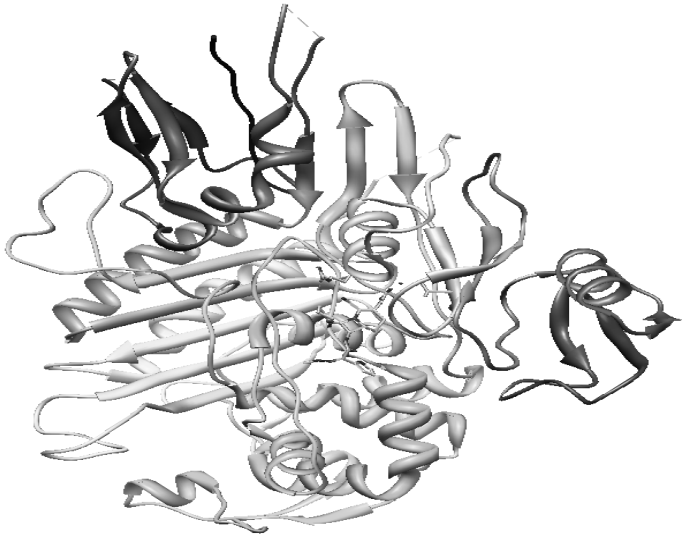


Fig. 3. The structure of the target protein 1QMF interactions with KEF (cefuroxime).

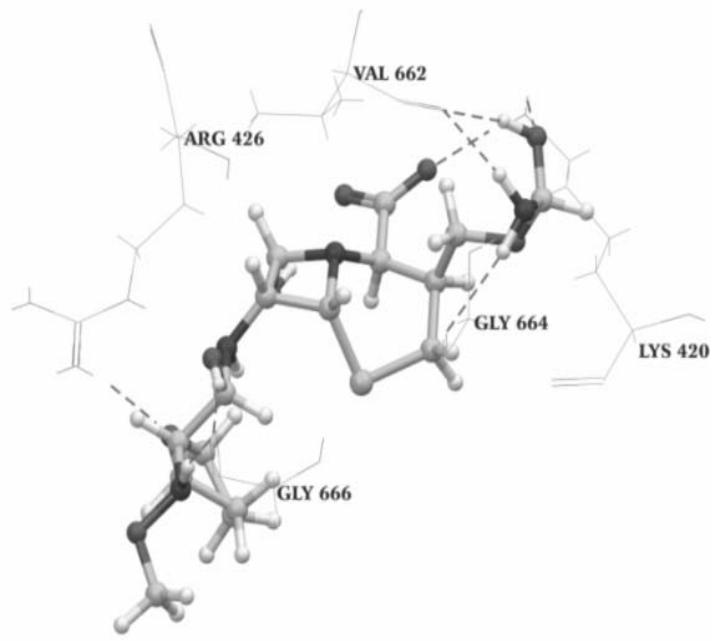


Fig. 4. Hydrogen bond interactions of KEF shown as dashed lines**.**

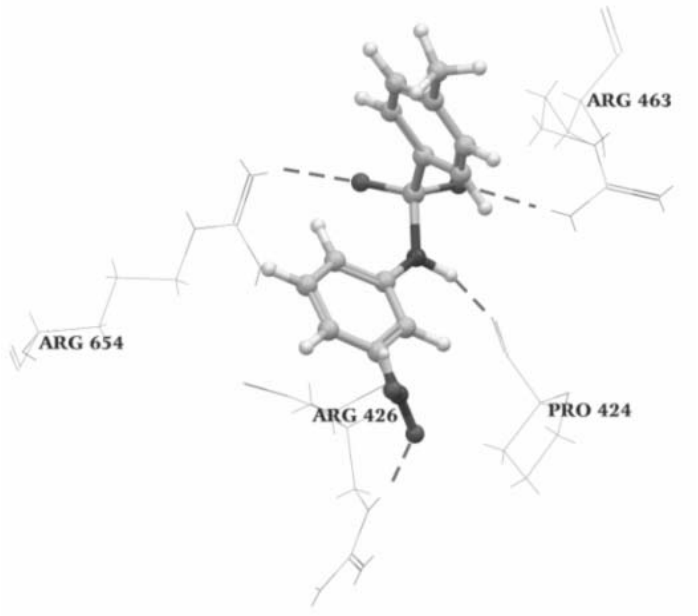


Fig. 5. Hydrogen bond interactions of compound 4M3NPBS shown as dashed line.

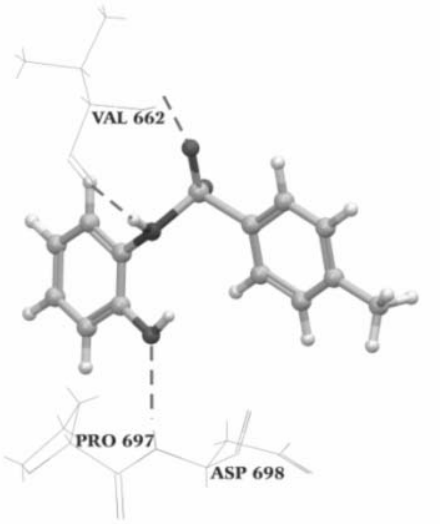


Fig. 6. Hydrogen bond interactions of compound 4M2HPBS shown as dashed line.

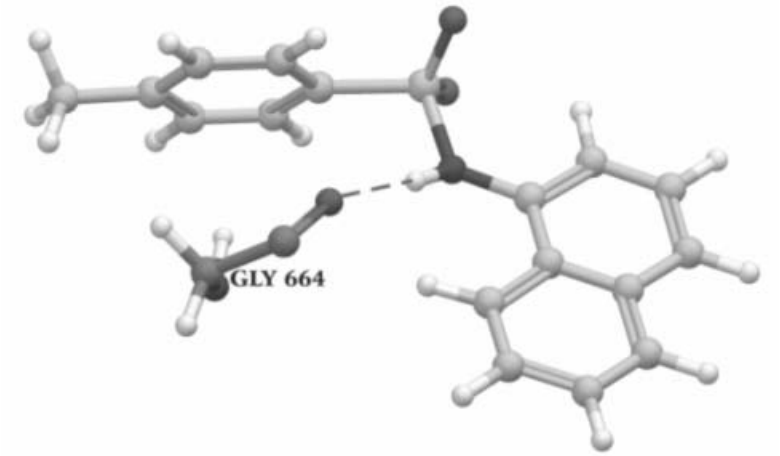


Fig. 7. Hydrogen bond interactions of compound 4MNBS shown as dashed line.

CONCLUSION

The docking studies results are found to be similar to those of solved complexes (penicillin-binding protein 2X in complex with cefuroxime) and the energy values are also comparable suggesting that three inhibitors: 4MNBS, 4M2HPBS and 4M3NPBS can be used as scaffold for designing new antimicrobial

drugs. The sulfonamide derivative having *meta* nitro group (4M3NPBS) got the maximum docking score for antibacterial activity.

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