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Computational Studies of N-1 Substituted Quinolone Derivatives as Potent Inhibitors of Gyr B subunit of *Escherichia coli* K-12

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ABSTRACT

It has been confirmed that 4-Quinolone derivatives associated with p-toluene sulphonamide group at 3 position are having bactericidal activity[10]. We have synthesized various derivatives of 1,4-dihydro-4-oxo-3-[1-oxo-2-hydrazino-3-{p-toluenenesulfon}] quinolines. These compounds were synthesized by the reaction of substituted quinolone carbohydrazide derivatives **1a,b** with p-toluene sulphonyl chloride in the presence of pyridine base. The compound was purified and characterized by IR, NMR (H^1 and C^{13}) and HRMS studies. Here we have conducted molecular docking of compounds **2a** and **2b** to explore their binding interactions on the active site of the target protein (PDB code: 6YD9).

Keywords: Quinolones, Softwares autodock 4 (AD_4) and Vina, Molecular docking.

INTRODUCTION

It has been observed that quinolone compounds are powerful antibacterial agents[1]. Based on this, various quinolone analogues have been discovered till today with improved bactericidal activity against both gram positive and gram negative bacteria[2-3]. Day by day increasing resistance power of bacteria, challenges the medicinal chemists to design and develop new more powerful antibacterial drugs. These drugs targets on bacterial DNA gyrase and topoisomerase IV[4] as they have structural and functional similarity. DNA gyrase and topoisomerase IV consist of twopairs of subunits:A2B2 (GyrA, GyrB) and C2E2 (ParC, ParE) respectively. GyrA and ParC subunits breaks and rejoins DNA strands thereby releasing torsional stress. On the other hand, GyrB and ParE provide energy to the enzyme by ATP hydrolysis. Quinolones works as GyrA inhibitors by forming DNA-enzyme complex, which resist the re-joining of broken DNA strands. However, due to its wide clinical use, side-effects and bacterial resistance have emerged. There is a need to research on designing and developing inhibitors having different mechanism of action.

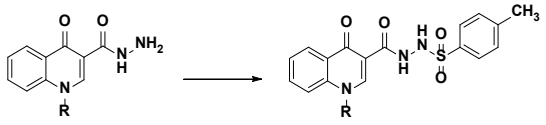
Since 1960, GyrB inhibitors have not been in clinical use due to their consequential side-effects[5]. Computational methods[6] are being used to analyse both unbound and bound structures which help in designing relevant structures useful for biological activity. Molecular docking is a competent

tool in studying various interactions between inhibitor molecules and active sites of the target receptor molecules[7]. Here in our work we have studied the binding interactions of **2a,b** with GyrB subunit of *Escherichia coli* K-12 (PDB code:6YD9) and compared the antibacterial activity obtained during our study[8-9]. We have evaluated binding affinities, root mean square deviation (rmsd), inhibition constant (Ki) and visualized different interactions such as hydrogen bonding, pi-anion, pi-alkyl, pi-cation, salt bridges in 3D as well as 2D.

MATERIALS AND METHODS

Synthetic approach

We have previously synthesized 4-oxo-1,4-dihydro-3-[1-oxo-2-hydrazino-3-{p-toluenesulfon}] quinoline N-R (R = H and Et) **2a,b** synthesized from N-R (R=H and Et) substituted 1,4-dihydro-4-oxoquinoline-3-carbohydrazide **1a,b** (Scheme 1) in our laboratory[8-9] and evaluated their antibacterial activity.



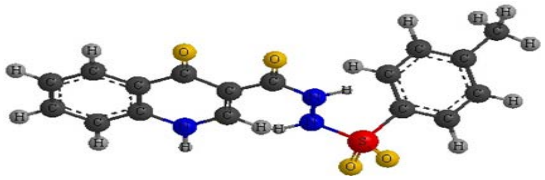
Scheme 1

Docking study

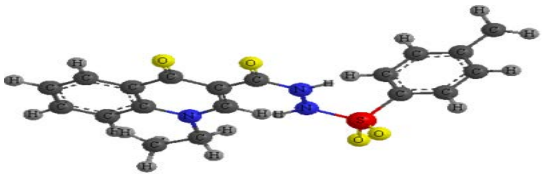
Molecular docking is a key tool used for structural analysis and computer aided drug design (CADD)[10]. It helps in predicting the binding modes of a ligand with a receptor molecule in three dimensional structure[11]. All the experiments were conducted using default parameters to get accurate results. We have performed docking with softwares Autodock4 (AD_4) and Vina[12]. The 3D and 2D visualization of the complex was assisted with Discovery Studio Visualizer software. The 3D structures of our molecules **2a** and **2b** is shown in Figure 1.

Preparation of Ligand and Receptor

GyrB subunit of *Escherichia coli* K-12 was selected as the receptor molecule which was obtained from Protein Data Bank file (PDB:6YD9). The water molecules and other heteroatoms bound to the receptor were removed, followed by addition of polar hydrogen atoms. The receptor molecule was further refined by checking missing atoms, adding Kollmann charges and completing the incomplete residues[13]. Autodock tools 1.5.7[14-15] were used to parameterize the rigidity of receptor and flexibility of ligands which were then saved in PDBQT file. Here Gasteiger-Marsili method, was used to estimate the charges[16].



Structure 2a



Structure 2b

Fig. 1. 4-oxo-1,4-dihydro-3-[1-oxo-2-hydrazino-3-{p-toluenesulfon}]quinoline 2a; $C_{17}H_{15}N_3O_4S$; M.M.=357.3837 1-Ethyl-4-oxo-1,4-dihydro-3-[1-oxo-2-hydrazino-3-{p-toluenesulfon}]quinoline 2b; $C_{19}H_{19}N_3O_4S$;M.M.=385.4336

Molecular Docking via AD_4

After the preparation of receptor, a grid box of size 100 x 100 x 100 (x,y and z) points and spacing 0.375Å was generated using Autogrid 4. The number of genetic algorithm (GA) was set to 10 with population size of 150. The GA number of evaluations were set to 2500000 which corresponds to *medium* option. Best conformers were searched by choosing Lamarckian genetic algorithm. AutoDock analyzer was used to investigate the results. The complex was visualized by using Discovery Studio visualizer for better interpretation. We have used standard docking protocol and the final result is reported for the conformer having lowest binding energy.

Molecular Docking via AutoDock Vina

Docking by Vina was conducted with same grid size as AD_4. The exhaustiveness was set to 8 (*short* option) and maximum energy range between the best and worst docking modes were set to 4 kcal/mol respectively. Docking was performed by using configuration file containing grid box properties and ligand-receptor information. The results were generated in a log file showing positional binding affinity (kcal/mol) along with root-mean-square deviation values. The conformer with lowest binding affinity was selected for the final results.

RESULTS AND DISCUSSION

Docking results using AutoDock (AD_4)

Molecular docking was performed by

following standard protocols. Summary of the results is listed in Table 1. Compound **2b** showed good activity '*In vitro*' against *E. coli* (ETEC)[9] and gave binding energy of -7.81 kcal/mol. It shows the occurrence of one hydrogen bonding of oxygen of SO_2 with Thr A:165 having bond length 1.92Å (Table 2). Other interactions such as salt bridge formation, pi-alkyl, pi-sigma are shown in Fig. 2. Compound **2a** showed a binding energy of -8.19 kcal/mol, showing the occurrence of one hydrogen bond with NH of hydrazide and Val A:43 having bond length 2.11 Å (Figure 2).

Docking results using AutoDock Vina

Compounds with lowest binding affinity is chosen as the best model for interpretation. Compounds **2a** and **2b** showed binding affinity of -5.9 and -5.7 kcal/mol respectively by using AutoDock Vina software (Table 1). Compound **2a** formed one hydrogen bond with Lys A:189 having bond length 2.62 Å. Compound **2b** formed one hydrogen bond with Arg A:190 having bond length 2.03 Å (Table 3). Other interactions such as pi-sigma, pi-alkyl, pi-cation, and pi-anion are also shown in Figure 3.

Table 1: Result Analysis by both AutoDock 4 and AutoDock Vina

Result Analysis	Receptor	Compound	Docking score	Amino acid residues
AutoDock 4	6YD9	**2a**	-8.19	ALA A: 47, ASN A : 46, GLU A : 50, ILE A:78, THR A:165, VAL A:43, VAL A: 71, VAL A:167
		2b	-7.81	ALA A:47, ASP A:73, GLU A:50, ILE A:78, ILE A:94, PRO A:79, VAL A:120, VAL A:167, THR A: 165
AutoDock Vina	6YD9	**2a**	-5.9	ARG A : 190, LYS A:189, THR A:34
		2b	-5.7	HIS A:38, ARG A:190, GLU A:193

Table 2: Docking results using AutoDock 4

Ligand	Binding Energy (kcal/mol)	Inhibition constant, Ki	No. of H-bonds	H-bond length (Å)	Amino acids
2a	-8.19	986.68 *nM*	1	2.11	ASN A: 46
2b	-7.81	1.88 μM	1	1.92	THR A:165

Table 3 : Docking results using AutoDock Vina

Ligand	Binding Affinity (kcal/mol)	No. of H-bonds	H-bond length (Å)	Amino acids
2a	-5.9	1	2.62	LYS A :189
2b	-5.7	1	2.03	ARG A:190

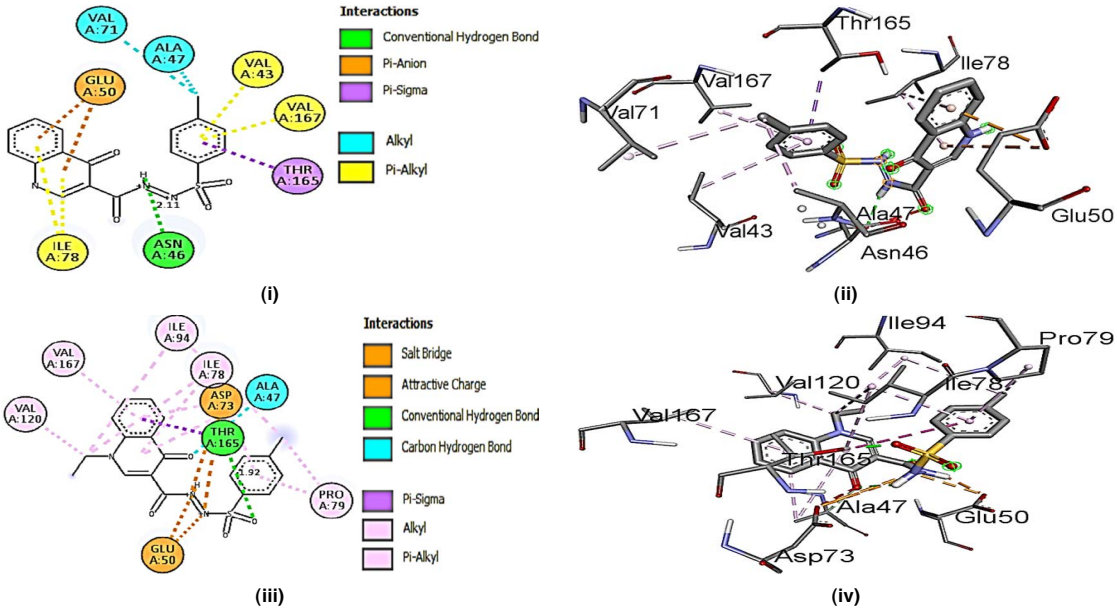


Fig. 2. Docking by AD_4 software; Images: Discovery Studio Visualizer; (i) 2D image of 2a (ii) 3D image of 2a (iii) 2D image of 2b (iv) 3D image of 2b

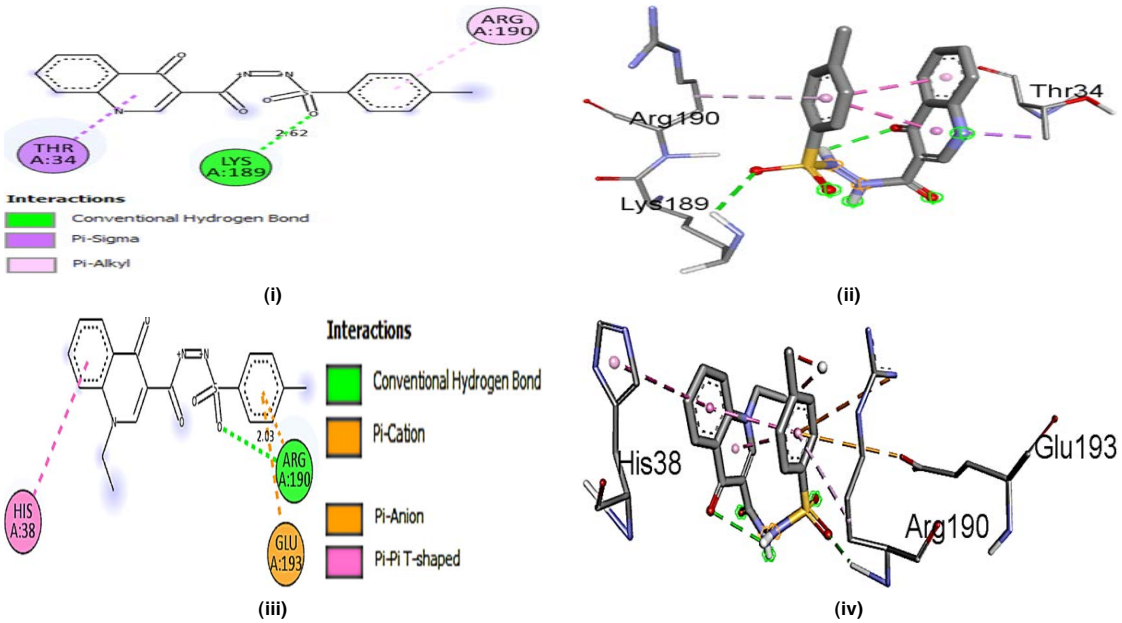


Fig. 3. Docking by Vina software; Images: Discovery Studio Visualizer; (i) 2D image of 2a (ii) 3D image of 2a (iii) 2D image of 2b (iv) 3D image of 2b

CONCLUSION

In this study we have explored the protein-ligand interactions of our synthesized quinolone derivatives **2a** and **2b**. Both AD_4 and Vina are popular tools in studying protein-ligand interactions. GyrB subunit of *Escherichia coli* K-12 was chosen for this study. Both the compounds were successfully docked with the receptor molecule. The best docking pose with lowest binding affinity was explored for protein-ligand interactions. The comparative study showed that both the moieties formed hydrogen bond at the active site. It can be inferred that the compounds can show antibacterial property. According to the docking results, both moieties have comparable binding affinities but **2b** formed shorter hydrogen bond (bond length = 1.92Å and 2.03 Å) with amino acid residues in comparison to **2a** (bond length = 2.11Å and 2.62 Å). Compound **2b** also showed significant antibacterial activity *In vitro* as compared to **2a**.

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Conflict of interests

The author(s) declare no conflict of interest, personal or financial.

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