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MOLECULAR DOCKING STUDIES OF MurA INHIBITOR WITH MDR GRAM NEGATIVE PATHOGENS

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ABSTRACT

The problem of antimicrobial resistance was never taken to be such a threat to the management of infectious diseases. But gradually treatment failures were increasingly being seen in health care settings against first-line drugs and second line drugs or more. The bacterial cell wall is composed mainly of peptidoglycan and MurA catalyzes the first step in the biosynthesis of peptidoglycan. MurA transfers the enolpyruvyl group of phosphoenolpyruvate (PEP) to the 3'-hydroxyl group of UDP-Nacetylglucosamine (UNAG) to form UDP-Nacetylglucosamine (UDP-GlcNAc)- enolpyruvate. MurA is essential for cell growth, since deletion of the MurA gene in gram negative pathogens. There are three compounds docked with *Vibrio cholerae, Haemophilus influenzae, Bacillus anthraces, E. coli.* The compounds have good docking score and glide energy. These compounds will acts as leads compounds for gram negative MDR pathogens.

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INTRODUCTION

Multidrug resistance among many organisms has become a big challenge in the management of infectious disease. It is increasingly being reported in bacteria and is often mediated by genetic mobile elements such as plasmids, transposons, and integrons. The majority of genes encode antibiotic disinfectant resistance, including resistance to aminoglycosides, penicillins, cephalosporins, trimethoprim, tetracycline, erythromycin, and chloramphenicol. Resistance in Klebsiella pneumoniaee – common intestinal bacteria that can cause life-threatening infections – to a last resort treatment (carbapenem antibiotics) has spread to all regions of the world. K. pneumoniae is a major cause of hospital acquired infections such as pneumonia, bloodstream infections, and infections in newborns and intensive-care unit patients. In some countries, because of resistance, carbapenem antibiotics do not work in more than half of people treated for K.pneumoniae infections (Podschun and Ullmann, 1998). The gram-negative bacterium Klebsiella pneumoniaee is a leading cause of hospital-acquired (HA) infections and neonatal sepsis globally (Jones, 2010, Falade and Ayede 2011, Jarvis *et al*., 1985).

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Widely considered an opportunistic pathogen, K. pneumoniae can be carried asymptomatically in the intestinal tract, skin, nose, and throat of healthy individuals (Podschun and Ullmann, 1998) but can also cause a range. The bacterial cell wall is composed mainly of peptidoglycan and MurA catalyzes the first step in the biosynthesis of peptidoglycan. MurA transfers the enolpyruvyl group of phosphoenolpyruvate (PEP) to the 3'-hydroxyl group of UDP-Nacetylglucosamine (UNAG) to form UDP-Nacetylglucosamine (UDP-GlcNAc)-enolpyruvate (Bugg and Walsh, 1992). MurA is essential for cell growth, since deletion of the MurA gene in Escherichia coli or Streptococcus pneumoniae is lethal (Brown etal., 1995, Du *et al*., 2000). The indispensability of MurA and its universal presence in bacterial but not in mammalian cells make MurA an attractive target for antibiotic development. There are three compounds identified through screening methods and docking with MurA enzyme of *Vibrio cholerae, Haemophilus influenzae, Bacillus anthraces, E. coli.*

MATERIALS AND METHODS

In this study, docking software programs such as Glide Xp docking in schrodinger platform , ACD/ChemSketch and open Bable software was used to convert 2D file into 3D file of ligand molecule.

Protein preparation: All Energy minimisations was carried out by using Maestro 9.0.111 protein preparation wizard (Schrodinger,LLC, 2008, New York, NY) MurA similar proteins such as Vibrio cholera PDB ID: 4R7U, Bacillus subtilis PDB ID: 3SG1, Haemophilus influenzae PDB ID: 3SWE, E. coli PDB ID: 3KR6, preparation using Maestro protein preparation wizard (Schrodinger, 2008) where a brief relaxation was performed using an all-atom constrained minimisation with the Impref (Impact Refinement module), to alleviate steric clashes; bond orders were assigned and hydrogen's were added. The energy minimisation was carried out at the default cut off (Root Mean Square Deviation) RMSD value of 0.30 A using OPLS˚ 2001 force field (Salam *et al*., 2009). The possible conformation of the refined protein was obtained using procheck analysis visualised with the aid of Ramachandran plot (Laskowski *et al*., 1996 & Laskowsky *et al*., 199314) by checking the dihedral Phi and Psi angles of amino acid residues.

Ligand preparation: Three Ligands was retrieved from Enamine database**.** The 3D coordinates for the ligands were generated using Ligprep Module of Schrodinger Software in Maestro 9.0.111 (Schrodinger, NY) using a force field OPLS 2005. Five low energy conformers were generated per 14265, 5471 and 3291 compounds. Schrodinger utilities were used to remove salts, neutralise and ionise compounds at the physiological pH 7.0 ± 2.0. Default settings of Leather face protonation, tautomeric states and specified chiralities were retained before energy minimization, to result in a low energy conformer. The ligand poses that pass the initial screens were subjected to energy minimization on precompiled Van der Waals and electrostatic grids and pass through filters for the initial geometric and complementary fit between ligands and the receptor – MurA. (*Kawatkar et al*., 2009 & Friesner *et al*., 2006).

Receptor Grid Generation: The scoring grid was generated using a box size of 30 ˚A ×30 ˚A ×30 ˚A and centered on the centroid within a box of dimension 27 ˚A ×16 ˚A ×46 ˚A that encloses the entire groove near the active site to fit the ligands (Kawatkar *et al*., 2009).

Docking: Docking has become a promising tool for identifying active lead/active compounds and has combined with the pipeline of drug discovery in most pharmaceutical companies (Kawatkar *et al*., 2009). Glide (Louise-May *et al*., 2007) module has been used for all the docking protocol. The small molecules of enamine database that compounds have been used for screening and get less toxic compounds from the hits. The ligands were processed with the LigPrep program to assign the suitable protonation states at physiological pH= 7.2±0.2. Conformer generation was carried out with the ConfGen torsional sampling and Ligand docking used OPLS_2005 force field. The van der Walls radii were scaled using a default scaling factor of 0.80 and default partial cutoff charge of 0.15 to decrease the penalties. There XP in Glide modeule used for all docking studies.

RESULTS AND DISCUSSION

MurA is an essential enzyme that is conserved in both Gram-positive and Gram-negative bacteria and has no mammalian homolog. Deletion of the MurA gene bacteria leads to lethal mutants these properties make MurA an attractive target for the development of novel antibiotics. In these studies three compounds selected docking studies for gram negative pathogen MurA enzymes. This compounds retrieved enamine small molecule database. This compounds already best hits compounds for *Klebsiella pneumoniae* infection active Mur A inhibitors. The *Klebsiella pneumoniae* MurA was similarly other gram negative pathogens *Vibrio cholerae* MurA, Haemophilus influenza MurA, *Bacillus anthraces* MurA and E. *coli*. Mur A. So we selected compound 14265, compound 3291, and compound 5471 for molecular docking with other gram negative pathogens MurA enzymes. The XP docking was performed using Glide software in Schrodinger. the compounds 14265 was highly interact with *Vibrio cholerae* MurA, Haemophilus influenza MurA, *Bacillus anthraces* MurA and E. *coli*. MurA and docking result table 1. The lead compound 14265 was 5 hydrogen bond interactions with *Vibrio cholerae* MurA. The length of hydrogen bond formed of 2. 51 Å, 2.45 Å, 2.47Å, 2.53Å and 2.73 for HIE126, GLY165, ARG92, THR306 and ARG233 respectively amino acid of *Vibrio cholerae* MurA. The lead compound 14265 was highly interacting with active site region of *Vibrio cholerae* MurA. The docking score and glide energy and all hydrogen bond interaction results was showed Table 1 and Figure 1. The binding mode of this compound at the active site of *Haemophilus influenza* MurA the formed hydrogen bond with the key amino acids such as LYS22, ASN23, ARG122,ASP123,LEU126,SER164,VAL165,ASP307,ILE329 . The lead compound 14265 was 5 hydrogen bond interactions with *Haemophilus influenza* MurA. The hydrogen bonds formed were 2. 62 Å, 2 .64 Å, 2.60 Å, 2.71Å and 2.69 for ARG122, ARG122, ARG234, GLY163, and SER164 respectively amino acid of *Haemophilus influenza* MurA. The lead compound 14265 was highly interacting with active site region of *Haemophilus influenza* MurA. The docking score and glide energy and all hydrogen bond interaction results was showed Table 1 and Figure 2. The binding mode of this compound at the active site of *bacillus anthraces* MurA the formed hydrogen bond with the key amino acids such as LYS22, ASN23, ARG93, CYS117, ARG122, SER164, VAL165, THR305, ARG398. The lead compound 14265 was 6 hydrogen bond interactions with *bacillus anthraces* MurA. The length of hydrogen bond formed of 2. 76 Å, 2.72 Å, 2.78 Å, 2.81Å , 2.80Å and 2.67 Å for LY22, ARG93, GLN97, ARG122, PHE329, and ARG398 respectively amino acid of *bacillus anthraces* MurA. The lead compound 14265 was highly interacting with active site region of *bacillus anthraces MurA*. The docking score and glide energy and all hydrogen bond interaction results was showed Table 1and Figure 3.

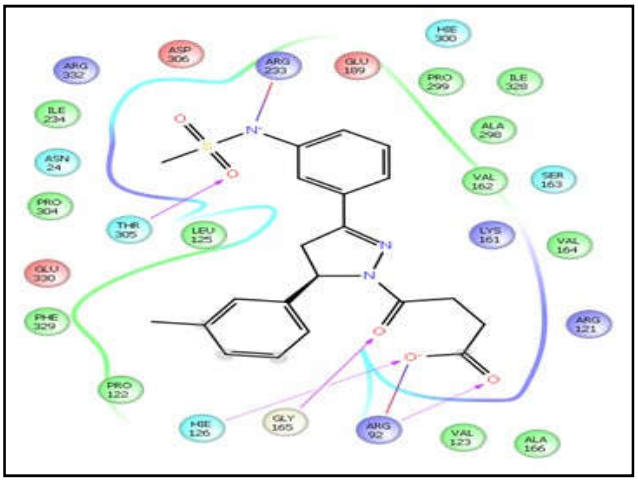

Figure 1. LIG-Plot interaction of XP docking of 14265 with *Vibrio cholera* MurA

Figure 2. LIG-Plot interaction of XP docking of 14265 with *Haemophilus influenza* MurA

Organism name	Docking score	Glide energy	Interaction residues	Distances (Å)
Vibrio cholerae	-6.9	-57.99	HIE126 N-H...O	2.51
			GLY165 N-H...O	2.45
			ARG92 N-H...O	2.47
			THR306 N-H...O	2.53
			ARG233 N-H...O	2.73
Haemophilus influenza	-6.9	-52	ARG122 N-H...O	2.62
			ARG122 N-H...O	2.64
			ARG234 N-H...O	2.60
			GLY163 N-H...O	2.71
			SER164 N-H...O	2.69
Bacillus anthraces	-6.	-50	LYS22N-H...O ARG93N-H....O	2.76
				2.72
			GLN97 N-H....O	2.78
			ARG122 N-H....O	2.81
			PHE329 N-H...O	2.80
			ARG398N-H...O	2.67
E. coli	-6	-51	ASN23 N-H...O	2.80
			ARG91 N-H...O	2.83
			SER161 N-H...O	2.81
			VAL163 N-H...O	2.86
			GLY164 N-H...O	2.63
			ARG234 N-H...O	2.51

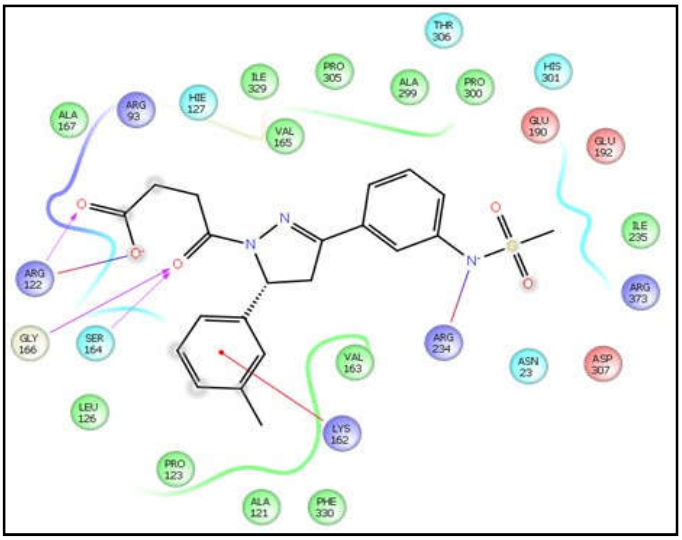

Figure 2. LIG-Plot interaction of XP docking of 14265 with *Haemophilus influenza* MurA

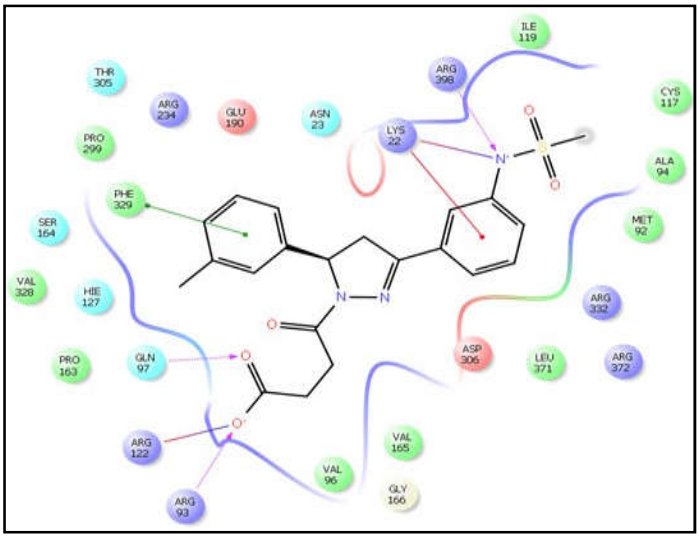

Figure 3. LIG-Plot interaction of XP docking of 14265 with Bacillus anthraces MurA

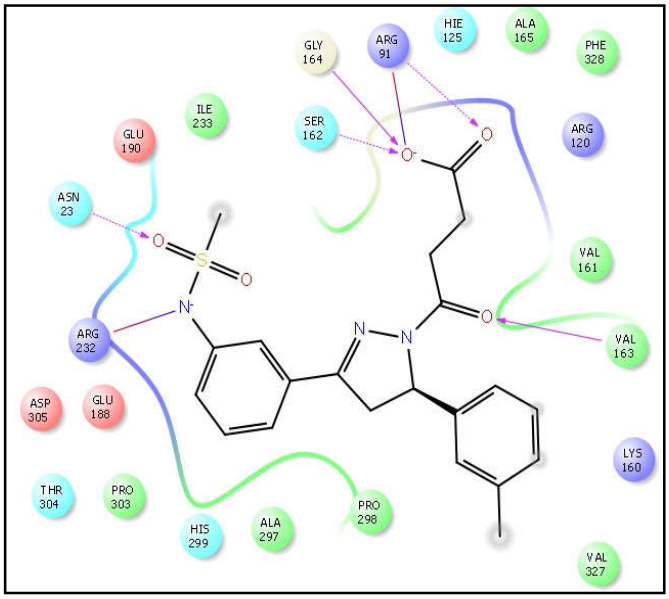

Figure 6. LIG-Plot interaction of XP docking of 14265 with *E. coli* MurA

The binding mode of this compound at the active site of *E. coli* MurA the formed hydrogen bond with the key amino acids such as LYS22, ASN23, ARG91, CYS117, VAL161, GLY164, THR305, ARG232. The lead compound 14265 was 6 hydrogen bond interactions with *E. coli* MurA. The length of hydrogen bond formed of 2. 80 Å, 2.83 Å, 2.81 Å, 2.86Å, 2.63Å and 2.51 Å for ASN23, ARG91, SER161, VAL163, GLY164, and ARG232 respectively amino acid of *E. coli* MurA. The lead compound 14265 was highly interacting with active site region of *E. coli* MurA. The docking score and glide energy and all hydrogen bond interaction results was showed Table 1 and Figure 4.

Conclusion

The present study was carried out to identify binding interactions of compounds 14265, 5471 and 3291 compounds with *Vibrio cholerae* MurA, Haemophilus influenza MurA, *Bacillus anthraces* MurA and E. *coli*. The enamine database compounds 14265, 5471 and 3291 compounds binds to *Vibrio cholerae, Haemophilus influenzae, Bacillus anthraces, E. coli*. The compounds 14265 highly interact with all organism. This docking studies proven to result in improved inhibition of *Vibrio cholerae* MurA, Haemophilus influenza MurA, *Bacillus anthraces* MurA, E. *coli* and active amino acid residues, which will be useful in designing other potent drugs and drug analogs. This study provides new insights into the identification of drugs in the in vitro laboratory. The novel molecular entities have the potential as leads which certainly aid in designing anti bacterial molecules in short span of time. As whole results throw light for future development of more potent and drug like inhibitors for MurA.

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