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DOCKING STUDY OF SOME *N*-[4-(4-ARYLIDENE)-2-(4-SUBSTITUTED-PHENYL)-5-OXO-4,5-DIHYDRO-IMIDAZOL-1-YL]-BENZENESULFONAMIDE DERIVATIVES AGAINST GLUCOSAMINE-6-PHOSPHATE SYNTHASE

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ABSTRACT

Docking study of *N*-[4-(4-arylidene)-2-(4-substituted-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]-benzenesulfonamide derivatives **(1-5)** against glucosamine-6-phosphate synthase, the target enzyme for the antimicrobial agents was achieved to explore and explain the affinity of discovered hits within the amino acid residues of the enzyme. The previously synthesized derivatives **(1-5)** exhibited moderate to potent activity against several bacterial species as well as *Candida albicans*, the common fungi species. In order to understand the interaction types of synthesized hits within the binding pocket of target enzyme, Autodock 4.2, the effective tools for the docking study of small molecules within the active side of enzyme was used.

Key words: Docking, Glucosamine, Imidazole, Benzenesulfonamide.

INTRODUCTION

Five derivatives of N-[4-(4-arylidene)-2-(4-substituted-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]-benzenesulfonamides **(1-5)** (Fig. 1) were synthesized, characterized and evaluated as new antimicrobial agents by our group[1]. The activity of the synthesized compounds against several gram +ve and –ve species as well as *Candida albicans* (Table 1)[1],

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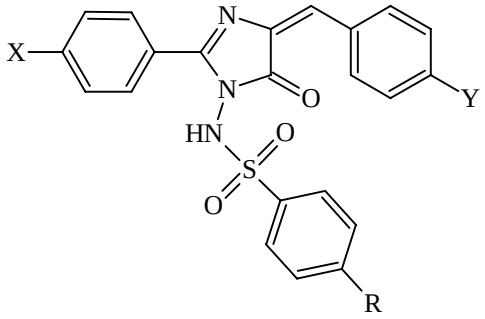
encouraged us to use autodock tool to study the binding of discovered hits inside the L-glutamine: D-fructose-6-phosphate amidotransferase, known under the trivial name of glucosamine-6-phosphate synthase (GlcN-6-P) which represents the effective target in antimicrobial chemotherapy. Glucosamine-6-phosphate synthase catalyzes the first step in hexosamine biosynthesis, converting D-fructose-6-phosphate (Fru-6-P) into D-glucosamine 6-phosphate (GlcN-6-P) using glutamine as the ammonia source and leading to the eventual formation of uridine 50-diphospho-N-acetyl-D-glucosamine (UDP-GlcNAc), the important point of metabolic control in the biosynthesis of amino sugar-containing macromolecules, which is necessary for the cell wall assembly in bacteria and fungi[2]. Autodock 4.2, the effective tool for exploring the binding affinity of small molecule to enzyme target[3-5] was used to study the interactions between the discovered hits and the GlcN-6-P synthase binding site.



(a) X = NO_2, Y = NO_2, R = H

(b) X = H, Y = Br, R = CH_3

(c) X = H, Y = Br, R = H

(d) X = H, Y = Cl, R = CH_3

(e) X = H, Y = NO_2, R = H

Fig. 1: The structures of N-[4-(4-arylidene)-2-(4-substituted-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]- benzenesulfonamides (1-5)

Docking study

In this study, AutoDock 4.2 package software has been used to investigate the affinity of *N*-[4-(4-arylidene)-2-(4-substituted-phenyl)-5-oxo-4, 5-dihydro-imidazol-1-yl]-benzene-sulfonamides **(1-5)** to the binding pocket of GlcN-6-P synthase. The pdb file format of enzyme as receptor was obtained from the RCSB Protein Data Bank (PDB code 1MOQ)

and used as a rigid molecule. Water molecules were removed and hydrogen atoms were added to the protein amino acids. All the docked compounds were drawn using ChemDraw ultra 7.0 as mol file and the energies of compounds were minimized and then converted into the pdb format using open Babel 2.3.1 software. During the docking, the grid dimensions were 60 × 60 × 60 Å 0.375 Å. The X, Y and Z coordinates were specified as 31.0, 17.0 and -2.0, respectively. Lamarckian Genetic Algorithm was employed as the docking algorithm with 10 runs, 150 population sizes, 2,500,000 maximum number of energy evaluations and 27,000 maximum number of generations.

RESULTS AND DISCUSSION

The potent activity of synthesized compounds **(1-5)** as new antimicrobial agents (Table 1), prompted us to study the docking of these derivatives inside the active site of glucosamine-6-phosphate synthase, the potential target for antibacterial and antifungal agents. X-ray study of glucosamine-6-phosphate synthase with divergent inhibitors shows that the binding pocket of the enzyme include the following residues, Cys 300, Gly 301, Thr 302, Ser 303, Ser 347, Gln 348, Ser 349, Thr 352, Val 399, Ser 401, Ala 602 and Lys 603 as shown in Fig. 2, which illustrates the in silico active pocket prediction of amino acid residues in binding with glucosamine-6-phosphate enzyme obtained from PDB sum[6]. Docking studies are computational techniques for the exploration of the possible binding modes of a ligand to a given receptor, enzyme or other binding site. In this study we used autodock 4.2 to evaluate the binding energy of ligands inside the known 3D structure of target enzyme. Auto Dock 4.2 software consists of two main programs, autogrid that pre-calculates grid maps of interaction energies for various atom types of ligand with a macromolecule and autodock, which performs the docking of the ligand to specified grids[7]. For the typical systems, docking is carried out using a Lamarckian Genetic Algorithm (LGA). It is run several times to give several docked conformations (ten conformers by default) ranking according to their binding and intermolecular energies. Several parameters were also predicted by the autodock program such as inhibition constant, number of hydrogen bonds and others. Fig. 3 illustrates the binding of the best generated conformers for compounds **(1-5)** inside the binding pocket of target enzyme. Table 2 indicates the molecular docking parameters of compounds **(1-5)**. The high docking energies of all generated conformers of discovered hits are strongly proportional to the antibacterial activities as shown in Table 1. Inhibition constant Ki and intermolecular energy were also determined and depicted in Table 2. The docking study reveals that the high affinity of synthesized derivatives **(1-5)** within the binding pocket of glucosamine-6-phosphate synthase strongly enhanced the determined activities of these derivatives as potent antimicrobial agents.

Table 1: The antimicrobial activity of the discovered hits (1-5) at 1 mg/mL concentration

Compound	Zone of inhibition (mm)				
	Bacillus Spp.	***Staph. aureus***	***E. coli***	***Pseudomonas aeruginosa***	***Candida albicans***
1	15	18	10	-	17
2	20	-	12	15	14
3	19	-	13	18	15
4	17	20	11	10	16
5	11	-	12	15	12
Sulfamethaxazole	34	32	31	29	
Miconozole	-	-	-		**16**

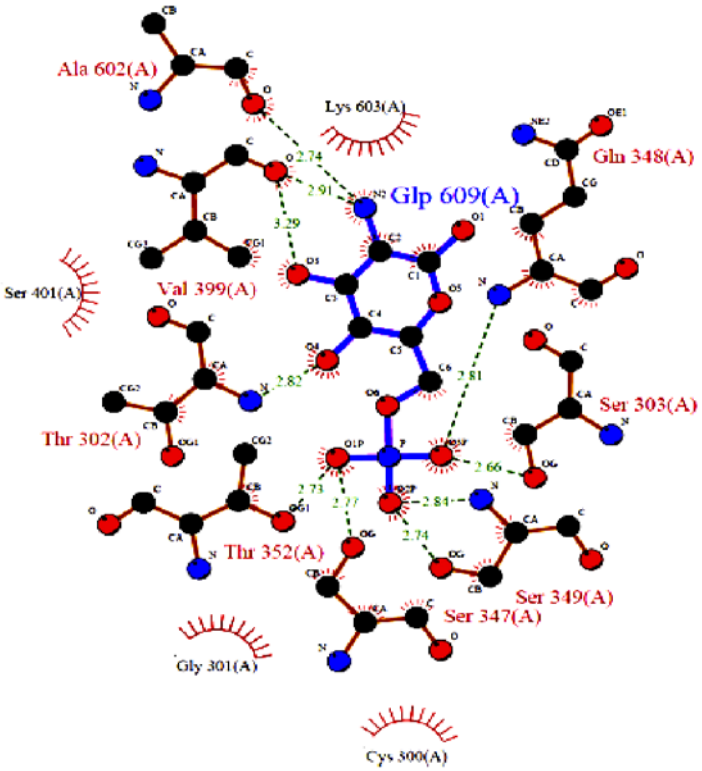


Fig. 2: Ligplot of GlcN-6-P showing the binding of glucosamine-6-phosphateinanactivesiteofenzyme

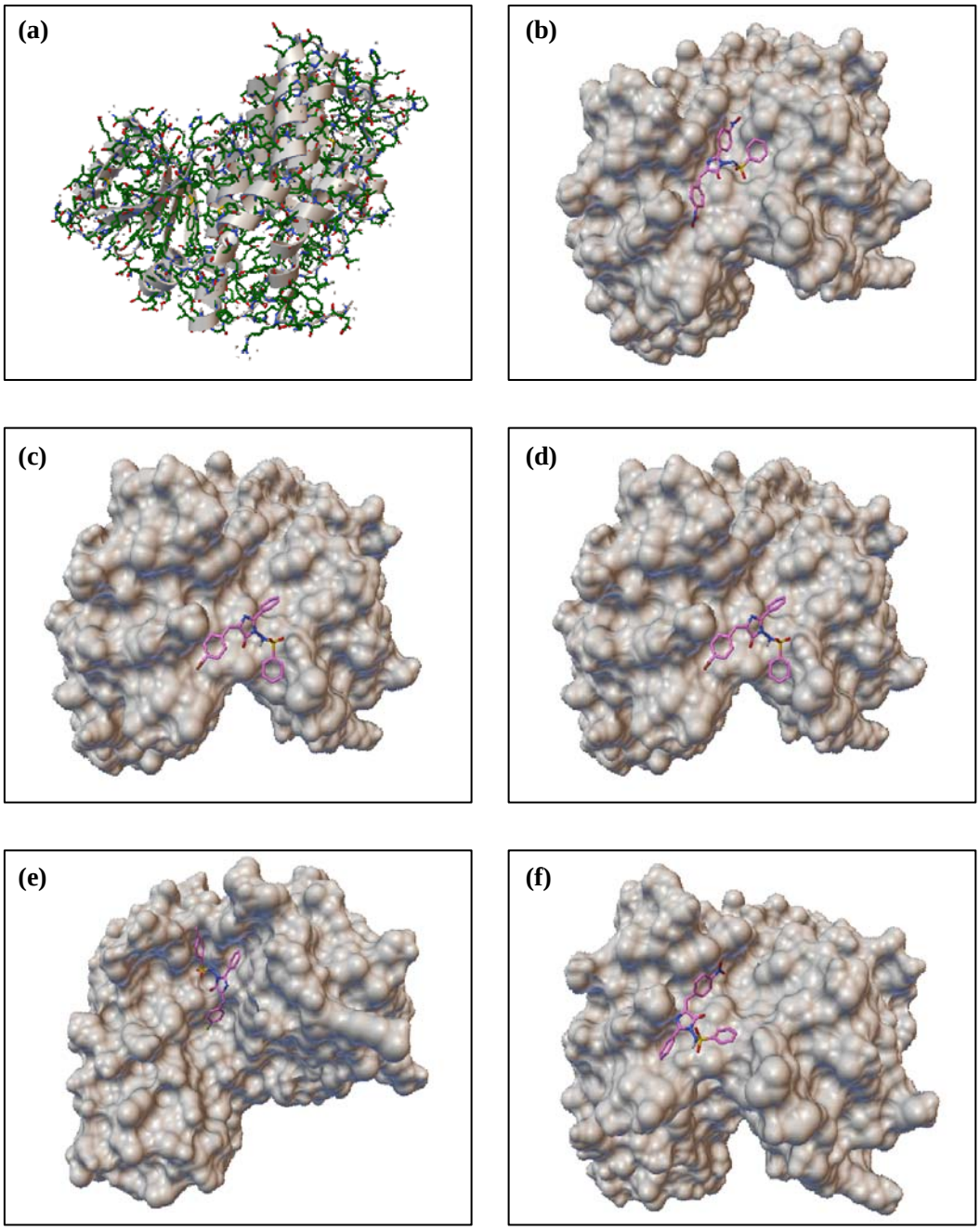


Fig. 3: (a) 3D structure of GlcN-6-P synthase. (b-f) Binding of the high ranking generated conformers for compounds (1-5), respectively inside the binding pocket of GlcN-6-p-synthase

Table 2: Molecular docking parameter of N-[4-(4-arylidene)-2-(4-substituted-phenyl)-5-oxo-4, 5-dihydro-imidazol-1-yl]-benzenesulfonamide derivatives with glucosamine-6-phosphate synthase

Compound	Binding energy (kcal mol^{-1})	Inhibition constant (μM)	Intermolecular (kcal mol^{-1})
Compound 1			
1	-6.39	20.54 uM	-8.48
2	-6.23	27.00	-8.32
3	-5.27	136.76	-7.36
4	-4.92	246.97	-7.01
5	-5.49	94.04	-7.58
6	-6.30	24.19	-8.39
7	-5.25	141.63	-7.34
8	-4.98	225.27	-7.06
9	-5.96	42.94	-8.05
10	-6.08	34.68	-8.17
Compound 2			
1	-5.95	43.54	-7.14
2	-6.30	23.99	-7.50
3	-5.57	82.84	-6.76
4	-6.08	35.03	-7.27
5	-5.96	42.98	-7.15
6	-5.75	61.41	-6.94
7	-6.46	18.53	-7.65
8	-6.28	24.76	-7.48
9	-6.79	10.55	-7.98
10	-6.76	11.01	-7.96

Cont…

Compound	Binding energy (kcal mol^{-1})	Inhibition constant (μM)	Intermolecular (kcal mol^{-1})
Compound 3			
1	-6.74	11.48	-8.23
2	-5.86	50.80	-7.35
3	-6.34	22.45	-7.83
4	-6.08	34.83	-7.57
5	-6.75	11.25	-8.24
6	-6.21	28.04	-7.70
7	-6.06	36.33	-7.55
8	-5.73	62.55	-7.23
9	-5.86	50.36	-7.35
10	-6.83	9.90	-8.32
Compound 4			
1	-6.00	40.11	-7.49
2	-5.77	58.69	-7.26
3	-6.20	28.37	-7.69
4	-6.25	26.42	-7.74
5	-6.26	25.93	-7.75
6	-6.50	17.13	-7.99
7	-7.27	4.71	-8.76
8	-6.57	15.19	-8.06
9	-6.11	33.35	-7.60
10	-6.97	7.79	-8.46

Cont…

Compound	Binding energy (kcal mol^{-1})	Inhibition constant (μM)	Intermolecular (kcal mol^{-1})
Compound 5			
1	-6.40	20.41	-8.19
2	-5.75	60.53	-7.54
3	-6.46	18.55	-8.24
4	-6.00	39.92	-7.79
5	-6.24	26.57	-8.03
6	-5.71	65.07	-7.50
7	-6.11	33.34	-7.90
8	-5.92	45.51	-7.71
9	-5.39	112.49	-7.18
10	-6.10	33.55	-7.89

CONCLUSION

Docking study of N-[4-(4-Arylidene)-2-(4-substituted-phenyl)-5-oxo-4,5-dihydro-imidazol-1-yl]- benzenesulfonamide derivatives (1-5) against glucosamine-6-phosphate synthase was achieved to explain the binding affinity against the target enzyme using Auto dock 4.2. Docking outcomes strongly enhanced the discovered hits as promising antimicrobial agents.

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