International Journal of Applied Chemistry.
ISSN 0973-1792 Volume 12, Number 1 (2016) pp. 1-9
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Docking Study of Some New 2, 5-Disubstituted-1, 3, 4-Thiadiazole Derivatives against Glucosamine-6-Phosphate Synthase

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Abstract

This article included the docking study of newly synthesized 2, 5-Disubstituted-1, 3, 4-thiadiazole derivatives against glucosamine-6-phosphate synthase, the target enzyme for the antimicrobial agents. Autodock 4. 2, the effective docking tool was used to study the interactions between the discovered hits and the binding pocket of enzyme.

Keywords: 1, 3, 4-thiadiazole, Docking, Antimicrobial

INTRODUCTION

Six-2, 5-Disubstituted-1, 3, 4-thiadiazole derivatives (1-6) were synthesized, characterized and published by our group as promising antimicrobial agents (Figure 1) [(1)]

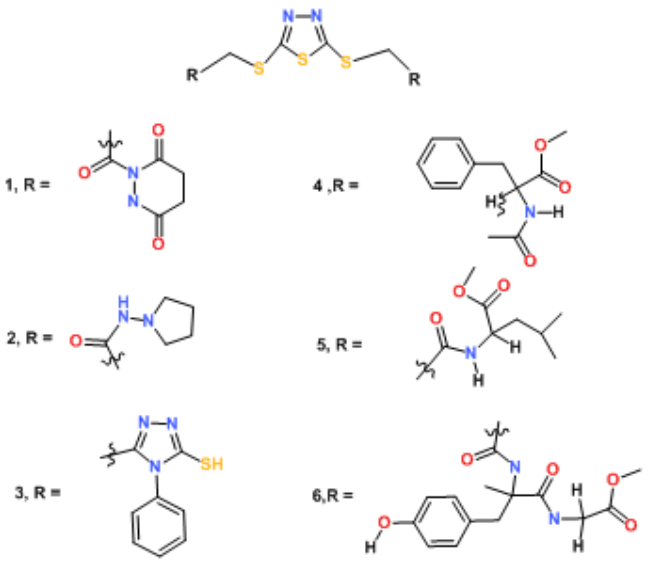

Figure 1: Chemical structures of discovered hits (1-6)

To explain the promising activity of these derivatives as antimicrobial agents (Table 1 and 2), this research includes the molecular docking of discovered hits within the binding pocket of *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. This enzyme 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-5-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)] Autodock4. 2, the effective tool for exploring the binding affinity of small molecule to enzyme target was used to study the interactions between the thiadiazole derivatives and the Glc N-6-P synthase binding site [(3)]

Table 1: Antibacterial activity of test compounds(1-6) at 100 µg /ml concentration

Compound	**Zone of Inhibition in mm**					
	S. aureus	***S. epidermidis***	***S. pyogenes***	***E. coli***	***P. aeruginosa***	***K. pneumonia***
1	11	-	-	-	-	-
2	-	-	-	-	-	-
3	-	11	9	-	11	11
4	10	-	9	12	-	13
5	-	-	-	11	-	-
6	-	7	8	-	-	-
Netilmicin 30	25	-	24	20	13	8
DMSO(control)	-	-	-	-	-	-

Table 2: Antifungal activities of test compounds (1-6) at 250 μg/ml concentration

Compound	Zone of inhibition in mm		
	Aspergillus niger	***Aspergillus terreus***	***Candida albicans***
1	**7. 5**	**-**	**-**
2	**8**	**16**	**-**
3	**4**	**3**	**-**
4	**9**	**6**	**-**
5	**8**	**7**	**-**
6	**-**	**22**	**-**
Fluconazole	**20**	**-**	**17**
DMSO	**-**	**-**	**-**

EXPERIMENTAL WORK

In this study we used AutoDock4. 2 package software to investigate the affinity of 2, 5-dimercaptothiadiazole derivatives (1-6) 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 (PDBcode1MOQ) 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 Chem Draw ultra 7. 0 as mol file and the energies of compounds were minimized then converted into the pdb format using open Babel 2. 3. 1 software. During the docking, the grid dimensions were 60 x 60 x 60A˚ with points separated by 0. 375A˚. 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 with10 runs, 150 population size, 2, 500, 000 maximum numbers of energy evaluations and 27, 000 maximum numbers of generations.

RESULT AND DISCUSSION

The potent activity of 2, 5-Disubstituted-1, 3, 4-thiadiazole derivatives (1-6) as new antimicrobial agents, 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, Cys300, Gly301, Thr302, Ser303, Ser347, Gln348, Ser349, Thr352, Val399, Ser401, Ala602 and Lys603 as shown in **Figure 2**, which illustrates the *in silico* active pocket prediction of amino acid residues in binding with glucosamine-6-phosphate enzyme obtained from PDB sum [(4)].

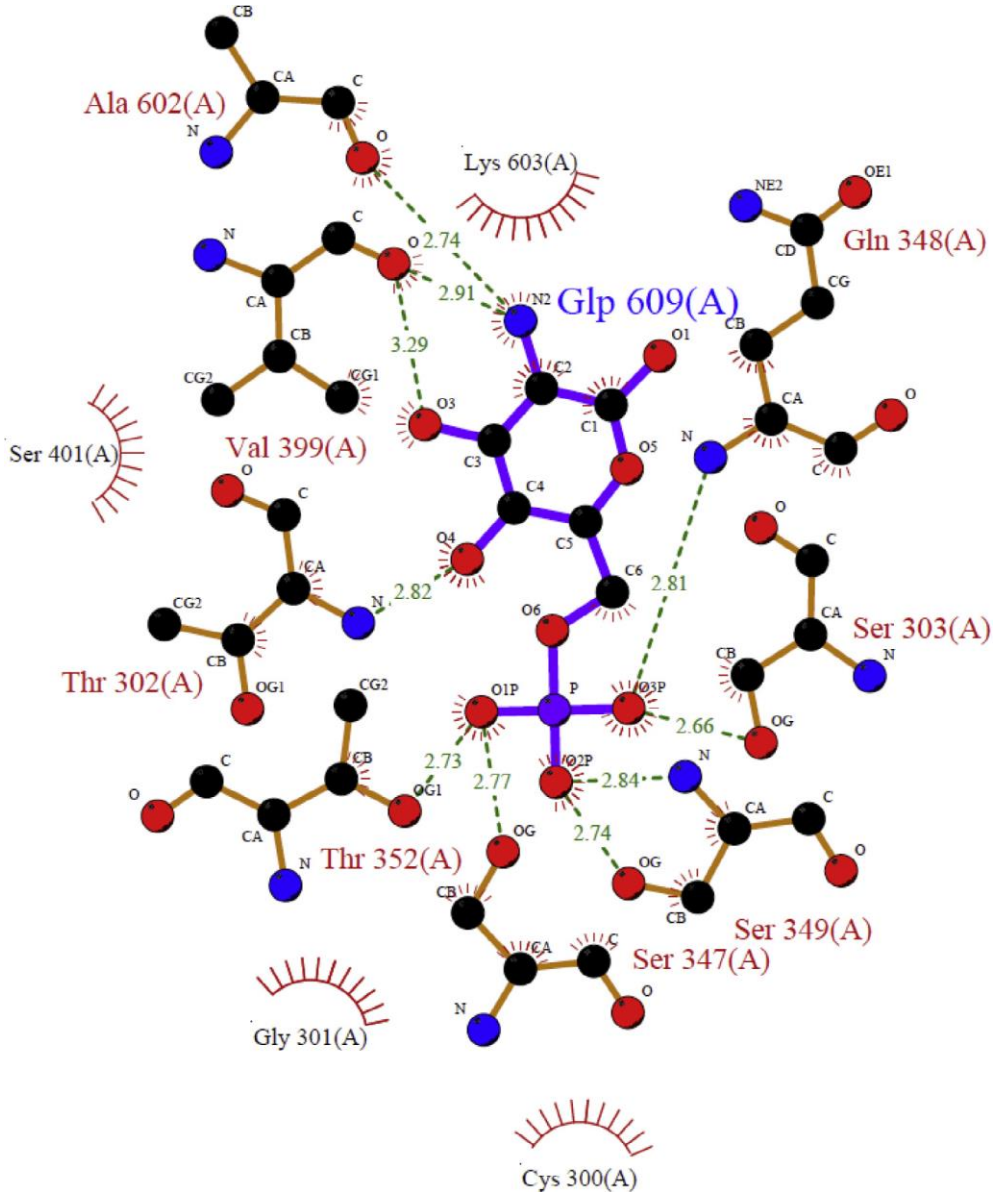

Figure 2: Ligplot of GlcN-6-P showing the binding of glucosamine-6-phosphate in an active site of enzyme.

Docking studies are computational techniques for the exploration of the possible binding modes of ligand to given receptor, enzyme or other binding site. In this study we used auto dock 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, auto grid that precalculates grid maps of interaction energies for various atom types of ligand with a macromolecule and auto dock, which performs the docking of the ligand to specified grids [(5)]. 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 auto-dock program such as inhibition constant, number of hydrogen bonds and others. **Figure 3** illustrates the binding of the best generated conformers for compounds (1-6) inside the binding pocket of target enzyme, while the molecular docking parameter shown in (Table 3) for all the docked hits.

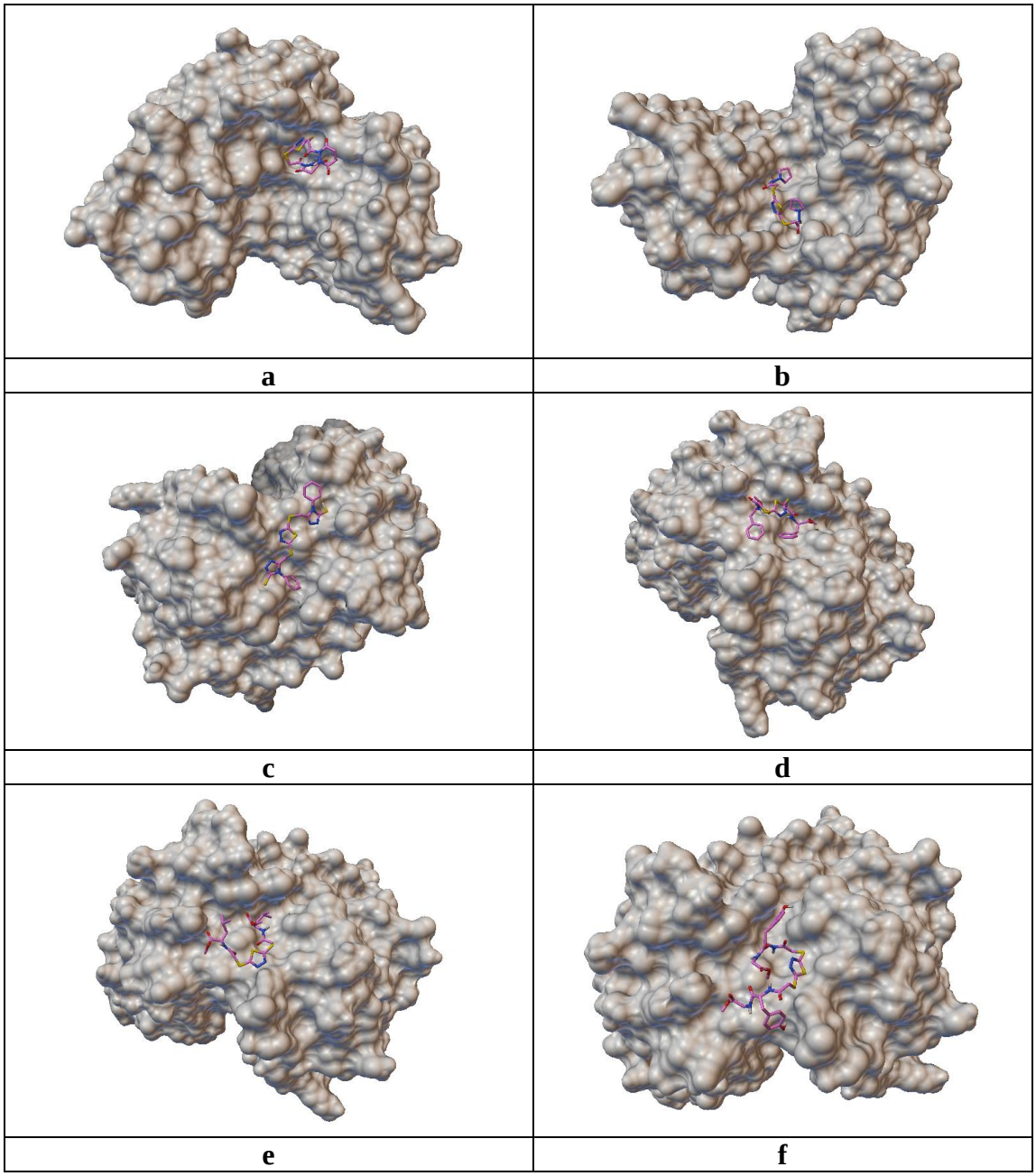

Figure 3: The binding of the best generated conformers (a-f) for compounds (1-6), respectively, inside the binding pocket of target enzyme.

Table (3): Molecular docking parameters of test compounds (1-6) with Glucosamine-6-phosphate synthase.

Compound	Binding energy (kcal mol^{-1})	Inhibition constant (mM)=K*i*	Intermolecular (kcal mol^{-1})	H-bonds	Bonding
Compound 1					
1	**-4. 00**	**1. 18**	**-5. 78**	**2**	**1MOQ:A:GLP609: H1:LIGAN: O 1MOQ:A:GLP609: H23:LIGAN: N**
2	**-3. 90**	**1. 38**	**-5. 69**	**3**	**1MOQ:A:GLY301:NH:LIGAN:O 1MOQ:A:GLP602:H23:LIGAN:O LIGAN:H:1MOQ:A:ALA602:N**
3	**-5. 08**	**0. 187**	**-6. 87**	**0**	**-**
4	**-4. 04**	**1. 09**	**-5. 83**	**1**	**1MOQ:A:GLP609:H1 LIGAN: O**
5	**-4. 43**	**0. 566**	**-6. 22**	**2**	**1MOQ:A:GLP609: H1:LIGAN: O 1MOQ:A:GLP609: H23:LIGAN: O**
6	**-4. 06**	**1. 06**	**-5. 85**	**2**	**1MOQ:A:GLP609: H1:LIGAN: O 1MOQ:A:GLP609: H23:LIGAN: O**
7	**-3. 82**	**1. 58**	**-5. 61**	**1**	**1MOQ:A:SER604:HN:LIGAN: N**
8	**-3. 51**	**2. 66**	**-5. 30**	**1**	**LIGAN:H:1MOQ:A:GLP609: O1**
9	**-2. 88**	**7. 75**	**-4. 67**	**1**	**1MOQ:A:SER604:HN:LIGAN: O**
10	**-4. 99**	**0. 219**	**-6. 78**	**2**	**1MOQ:A:SER328:HG:LIGAN: O 1MOQ:A:GLP609: H1:LIGAN: O**
Compound 2					
1	**-4. 42**	**0. 577**	**-6. 80**	**3**	**LIGAN:H:1MOQ:A:GLU488:OE 2 1MOQ:A:GLY301:NH:LIGAN:O 1MOQ:A:GLP602:H23:LIGAN:O**
2	**-3. 59**	**2. 33**	**-5. 98**	**2**	**LIGAN:H:1MOQ:A:SER604:O 1MOQ:A:SER604: HN:LIGAN:N**
3	**-5. 09**	**0. 185**	**-7. 48**	**2**	**LIGAN:H:1MOQ:A:ASP354:ODE 1MOQ:A:GLP609: H23:LIGAN:O**
4	**-4. 60**	**0. 428**	**-6. 98**	**2**	**LIGAN:H:1MOQ:A:GLP609:O1, O5 1MOQ:A:GLY301: HN:LIGAN:O**
5	**-3. 32**	**3. 68**	**-5. 71**	**2**	**LIGAN:H:1MOQ:A:SER604:O LIGAN:H:1MOQ:A:ILE397:O**
6	**-2. 71**	**10. 24**	**-5. 10**	**1**	**1MOQ:A:SER604: HN:LIGAN:N**
7	**-3. 32**	**3. 70**	**-5. 70**	**1**	**1MOQ:A:SER604: HN:LIGAN:N**
8	**-4. 80**	**0. 301**	**-7. 19**	**0**	**-**

9	**-3. 34**	**3. 55**	**-5. 73**	**2**	**LIGAN:H:1MOQ:A:SER604:O 1MOQ:A:SER604: HN:LIGAN:O**
10	**-4. 01**	**1. 16**	**-6. 39**	**1**	**1MOQ:A:GLY301: HN:LIGAN:O**
Compound 3					
1	**-3. 28**	**3. 96**	**-6. 26**	**3**	**LIGAN:H:1MOQ:A:LEU601:O LIGAN:H:1MOQ:A:SER349:O 1MOQ:A:SER604: HG:LIGAN:N**
2	**-4. 28**	**0. 730**	**-7. 26**	**2**	**LIGAN:H:1MOQ:A:SER328:OG 1MOQ:A:GLP609: H23:LIGAN:N, N**
3	**-6. 40**	**0. 0204**	**-9. 38**	**0**	**-**
4	**-5. 67**	**0. 069**	**-8. 66**	**2**	**LIGAN:H:1MOQ:A:GLU488:OE 2 1MOQ:A:GLP609: H23:LIGAN:S**
5	**-3. 82**	**1. 59**	**-6. 80**	**0**	**-**
6	**-2. 29**	**21. 07**	**-5. 27**	**1**	**LIGAN:H:1MOQ:A:THR606:OG 1**
7	**-4. 20**	**0. 833**	**-7. 18**	**2**	**LIGAN:H:1MOQ:A:GLU488:OE 2 1MOQ:A:GLP609: H1:LIGAN:N**
8	**-3. 84**	**1. 53**	**-6. 82**	**1**	**LIGAN:H:1MOQ:A:GLU396:N**
9	**-2. 93**	**7. 17**	**-5. 91**	**1**	**LIGAN:H:1MOQ:A:GLP609:O1**
10	**-3. 88**	**1. 44**	**-6. 86**	**0**	**-**
Compound 4					
1	**-2. 39**	**17. 72**	**-7. 16**	**1**	**LIGAN:H:1MOQ:A:GLU396:O**
2	**-1. 02**	**179. 55**	**-5. 79**	**0**	**-**
3	**-1. 07**	**164. 33**	**-5. 84**	**1**	**1MOQ:A:SER604: HN:LIGAN:O**
4	**-1. 44**	**87. 35**	**-6. 22**	**0**	**-**
5	**-1. 58**	**69. 81**	**-6. 35**	**1**	**1MOQ:A:SER604: HN:LIGAN:O**
6	**-1. 13**	**147. 41**	**-5. 91**	**1**	**1MOQ:A:SER609: HN:LIGAN:O**
7	**-3. 11**	**5. 23**	**-7. 89**	**0**	**-**
8	**-0. 09**	**864. 98**	**-4. 86**	**0**	**-**
9	**-2. 31**	**20. 10**	**-7. 09**	**0**	**-**
10	**-1. 33**	**106. 61**	**-6. 10**	**0**	**-**
Compound 5					
1	**-**	**-**	**-**	**-**	**-**
2	**-2. 01**	**33. 76**	**-6. 78**	**1**	**1MOQ:A:SER604: HN:LIGAN:O**
3	**-0. 79**	**263. 26**	**-5. 56**	**1**	**1MOQ:A:SER604: HN:LIGAN:N**
4	**-1. 66**	**60. 77**	**-6. 43**	**1**	**1MOQ:A:SER604: HN:LIGAN:O**
5	**-1. 78**	**49. 35**	**-6. 56**	**1**	**1MOQ:A:SER604: HN:LIGAN:O**
6	**-0. 91**	**213. 81**	**-5. 69**	**0**	**-**

7	**-0. 93**	**207. 32**	**-5. 71**	**0**	**-**
8	**-0. 73**	**291. 15**	**-5. 50**	**0**	**-**
9	**-3. 16**	**4. 86**	**-7. 93**	**1**	**1MOQ:A:GLY604: HN:LIGAN:O**
10	**-1. 15**	**143. 81**	**-5. 92**	**0**	**-**
Compound 6					
1	**-1. 59**	**68. 49**	**-8. 15**	**2**	**LIGAN:H:1MOQ:A:ASN375:O LIGAN:H:1MOQ:A:SER604:O**
2	**-2. 37**	**18. 24**	**-8. 94**	**1**	**LIGAN:H:1MOQ:A:SER604:OG**
3	**-0. 79**	**263. 22**	**-7. 35**	**1**	**LIGAN:H:1MOQ:A:SER604:OG**
4	**-1. 40**	**93. 77**	**-7. 96**	**1**	**LIGAN:H:1MOQ:A:LEU601:O**
5	**-0. 26**	**648. 37**	**-6. 82**	**0**	**-**
6	**-1. 16**	**140. 96**	**-7. 72**	**1**	**LIGAN:H:1MOQ:A:GLN348:OE 1**
7	**+2. 02**		**-4. 54**	**2**	**LIGAN:H:1MOQ:A:GLU396:O LIGAN:H:1MOQ:A:ASN600:O**
8	**+0. 42**		**-6. 15**	**0**	**-**
9	**+0. 48**		**-6. 08**	**2**	**LIGAN:H:1MOQ:A:SER604:O 1MOQ:A:SER604: HN:LIGAN:O**
10	**-1. 91**	**40. 11**	**-8. 47**	**0**	**-**

The moderate ranking binding energies of some generated conformers were-4. 99,-5. 09,-6. 04,-3. 01,-2. 01 and-2. 37 kcal/mol for compounds 1 to 6, respectively. The high docking energies of all generated conformers of compound 1 are strongly proportional to the antibacterial activities as shown in Table (1). Inhibition constant (K*i*), intermolecular energy and hydrogen bonds were also determined and depicted in Table (3)

ACKNOWLEDGMENT

This study was supported by the Department of Pharmaceutical Chemistry, College of Pharmacy. Baghdad University, Baghdad, Iraq.

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