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Molecular docking based screening of G6PS with 1, 5 Benzothiazepine derivates for a potential inhibitor

Maruthi Malya Prasada Rao Chennu*[1], Rahaman Shaik Abdul[2], Rajendra Prasad Yejella[3]

[1]Department of Pharmaceutical Chemistry, QIS college of Pharmacy; JNTUK, Kakinada- 533003; [2]Department of pharmaceutical chemistry, Nirmala college of Pharmacy ,Mangalagiri; [3]Department of Pharmaceutical Chemistry, University college of Pharmaceutical Sciences, Andhra University, Visakhapatanam; Maruthi Malya Prasada Rao Chennu – Email: chennuprasad12@gmail.com; *Corresponding author

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Abstract:
Glucosamine-6-phosphate synthase (G6PS) (EC 2.6.1.16) is a known target for anti-bacterial and anti-fungal infections. Therefore, it is of interest to design potential inhibitors using 1, 5 benzo-thiazepine skeleton with appropriate modifications. We report the binding data for 20 derivatives of the skeleton molecule to G6PS having binding energy from -7.35 to -9.99 Kcal/mol with predicted IC50 value range of 4.11 to 47.68 nano-molar. It should be noted that this data should be further evaluated using in vitro and in vivo studies for safety, activity, efficacy and toxicity.

Keywords:
Glucosamine-6-phosphate synthase, 1,5 Benzothiazepine, antifungal, antimicrobial, docking, binding energy

Background:
L-Glutamine: d-fructose-6-phosphate amido-transferase, also known as glucosamine-6-phosphate synthase (GlcN6P synthase) **[1],** Glucosamine-6-phosphate synthase (L-glutamine: D-fructose-6-phosphate amino-transferase (GlmS, 1 EC 2.6.1.16)) catalyzes the first step in hexos-amine biosynthesis, an important constituent of the peptido-glycan layer of bacterial cell walls and fungal cell wall chitin **[2].** Purification, partial biochemical and dynamics characterization of glucosamine-6-phosphate synthase was reported by Gonzalez *et al.* **[3]** and Mouilleron *et al.* **[4]** and its ability to act as antifungal drug target has been evaluated using modeling and structure based drug design by Wojciechowski *et al.* **[5],** whereas its catalytic function was described by Durand *et al.* **[6].** Role of GlcN6P synthase in bacteria, eukaryotic organisms, glucose metabolism related to diabetes, cancer, inflammation and ulcer has been reviewed elsewhere **[7]** and hence, its potential as an anti-fungal target is known.

On the other hand, 1,5 benzo-thiazepines nucleus having prominent activities against microbes is known **[8-10].** A recent pharmaco-phore based studies by Bariwal *et al.* **[11]** elucidated the potential of 1,5 benzo-thiazepine based compounds as promising drug like molecules. Recently, Banerjee *et al.* **[12-13]** has demonstrated the use of peptide inhibitors for GlcN6P. Miszkiel *et al.* **[14]** performed long-range molecular dynamics simulation for understanding the molecular function of eukaryotic G6PS. Therefore, it is of interest todesign potential inhibitors using 1, 5 benzo-thiazepine skeleton withappropriate modifications.

Methodology:
Software and programs
Accelry's Discovery studio version 4.0 **[15]** is utilized to visualize the ligand structures, receptors and hydrogen-bonding networks. It is also used to render images. Chemsktech was used to draw the ligand compounds. Autodock 4.0 **[16]** is the primary docking program used for the semi-flexible

docking studies. Preparation of the ligands and protein receptors in pdbqt file and determination of the grid box size were carried out using Autodock Tools version 1.5.6. Protocol used for performing protein and ligand preparation along with docking studies is described elsewhere **[17-19]**.

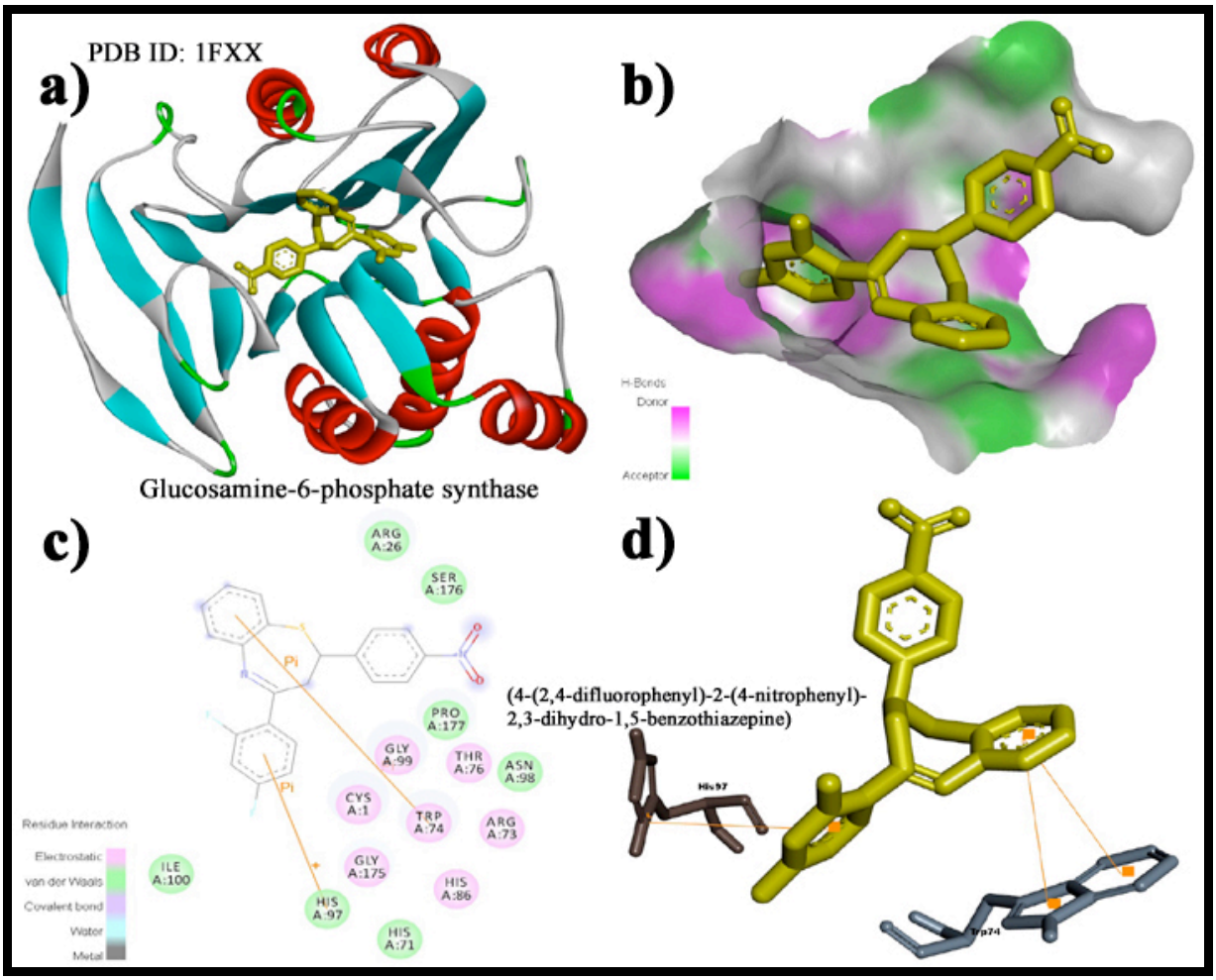

Figure 1: Docking snapshot of the G6PS in complex with compound 9 (4-(2,4-difluorophenyl)-2-(4-nitrophenyl)-2,3-dihydro-1, 5-benzothiazepine) is shown **(a)** protein-ligand complex represented in ribbon and stick, respectively; **(b)** showing binding pocket for the ligand fit with G6PS; **(c)** 2D representation of the molecular interaction; and **(d)** 3D representation of the molecular interactions.

Results & Discussion:

We have performed the molecular docking studies for twenty compounds with the active binding site of G6PS protein target is completed. The binding energies involved in the protein ligand complex formation are determined. The molecular atomic level of interactions responsible for the target specific binding affinity of the compounds towards G6PS is extracted (Table 1 see supplementary material). The twenty compounds have shown the successful docking inside the active site of G6PS with a binding energy of -7.35 to -9.99 Kcal/mol with predicted IC50 value range of 4.11 micro molar to 47.68 nano molar. We compared the predicted docking data with known G6PS inhibitors such Streptomycin and Glucose-6-phosphate having binding energy of -5.72 and -5.9 Kcal/mol, respectively. Moreover, some other known synthesized compound also show potential antimicrobial activity targeting G6PS with a binding energy range of -4.37 to -9.75 kcal/mol **Table 1 (see supplementary material) [20-24].** Compound 9 with binding energy -9.99 Kcal/mol and predicted IC50 value of 47.68 nano molar **Table 2 (see supplementary material)** for G6PS is found interesting when compared to known compounds. The pi-pi and pi-cationic stacking with Trp74 and His97 residues respectively in this complex is shown in **Figure 1**.

Conclusion:

G6PS is a known target for anti-bacterial and anti-fungal infections. We present the binding data for 1, 5 Benzothiazepine derivatives with G6PS in this report. This data should be further evaluated using in vitro and in vivo studies for safety, activity, efficacy and toxicity.

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Supplementary material:

Table 1: Docking results of some of the drug candidate for G6PS

No	Ligand	Binding energy (Kcal/mol)	Reference
1.	Streptomycin	-5.72	Sumaiya *et,al* [11]
2.	Glucose-6-phosphate	-5.9	Arora *et al*. [12]
3.	2,4,5-triarylimidazole derivative (a)	-7.37	
4.	2,4,5-triarylimidazole derivative (b)	-7.62	Ivan *et al*. [13]
5.	2,4,5-triarylimidazole derivative (c)	-7.61	
6.	N3-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid	-9.75	Banerjee *et al*. [14]
7.	N-benzyl-2,2,2-trifluoroacetamide	-4.37	Balachandran et al, [15]

Table 2: Binding energy for G6PS drug candidates with interaction data

No	Compound Name	Docking energy (Kcal/mol)	pIC50 value (nanomolar)	H-bond	Pi-Pi interaction	Pi-Cation	Salt Bridge
1.	4"-methyl phenyl	-8.49	598.86nM	-	-	-	-
2.	4"-fluorophenyl	-7.67	2.39uM	Gly99	His86	His97	--
3.	4"-chlorophenyl	-8.45	638.9nM	--	Trp74	--	--
4.	2"-chlorophenyl	-7.94	1.5uM	Gly99	Trp74	His97	--
5.	2",4"-difluorophenyl	-7.65	2.49uM	Gly99	Trp74, His86	His97	--
6.	2",4"-dichlorophenyl	-8.04	1.28uM	Gly99	Trp74	His97	--
7.	2"-chloro-5"-nitrophenyl	-8.85	327.3nM	Gly99	--	--	Cys1
8.	3"-nitrophenyl	-9.67	81.23nM	Gly99 Cys1 Trp74	--	Cys1	--
9.	4"-nitrophenyl	-9.99	47.68nM	--	Trp74	His97	--
10.	3"-hydroxyphenyl	-7.99	1.4uM	Cys1 Trp74	Trp74	--	--
11.	3"-nitro-4"methylphenyl	-9.75	71.66nM	Trp74 Gly99	Agr26	--	Cys1
12.	3",4",5"-trimethoxyphenyl	-7.35	4.11uM	--	Agr216	--	--
13.	3",4"-methelenedioxyphenyl	-9.54	100.94nM	Arg73 His86 Thr76	Trp74	--	--
14.	5"-bromofuran-2"-yl	-8.87	314.53	Cys1 Trp74	--	Cys1	--
15.	4"-dimethylaminophenyl	-8.32	795.04	Trp74	--	Cys1	--
16.	3"-methoxy-4"-hydroxyphenyl	-8.34	767.42nM	Trp74 Gly99	Trp74	--	--
17.	2"-pyridinyl	-8.2	983.65nM	Cys1	Trp74	--	--
18.	3"-pyridinyl	-7.56	2.89uM	Gly99	Trp74	His97	--
19.	4"-pyridinyl	-7.56	42.87uM	Gly99	Trp74	His97	--
20.	2"-thienyl	-7.44	3.54uM	Gly99	Trp74	--	--