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MOLECULAR MODELING AND DOCKING BASED STUDIES OF NOVEL CHALCONE SKELETON BASED COMPOUNDS ON GLUCOSAMINE-6-PHOSPHATE SYNTHASE ENZYME

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Key words:

Glucosamine-6-phosphate synthase, chalcone, antimicrobial, docking, binding energy, Molecular Interactions

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ABSTRACT: Glucosamine-6-phosphate synthase (G6PS) (EC 2.6.1.16), is an one of the drug target for the anti microbial species. Systemic anti bacterial and anti fungal infections are of the growing problems in contemporary medicines, however only limited anti bacterial agents are in clinical practice for selective action with low toxicity. Then there is an emergency need for more effective version of existing molecules as well as new potential target specific molecules. In this scenario, our present study is an attempt to find out specific molecules via in silico screening of novel chalcone based series of compounds targeting the glucosamine-6-phosphate synthase. Among the twenty five novel designed chalcones skeleton series of compounds, all of them have found to be successfully docking inside the active binding domain of G6PS target with a binding energy in a range of -7.35 to -9.99 Kcal/mol with predicted IC50 value range of 4.11 micro molar to 47.68 nano molar respectively.

INTRODUCTION: L-Glutamine:d-fructose-6-phosphate amidotransferase, also known as glucosamine-6-phosphate synthase (GlcN6P synthase) [1] , Glucosamine-6-phosphate synthase (L-glutamine: D-fructose- 6-phosphate aminotransferase (GlmS,1 EC 2.6.1.16)) 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 (**Scheme-1**).

GlcN-6-P is a precursor of uridine diphospho-N-acetylglucosamine from which other amino sugar-containing molecules are derived. One of these products, N-acetylglucosamine, is an important constituent of the peptido glycan layer of bacterial cell walls and fungal cell wall chitin.[2] Role of GlcN6P synthase in bacteria, eukaryotic organisms, glucose metabolism related to diabetes, cancer, inflammation and ulcer has been reviewed elsewhere. [3]

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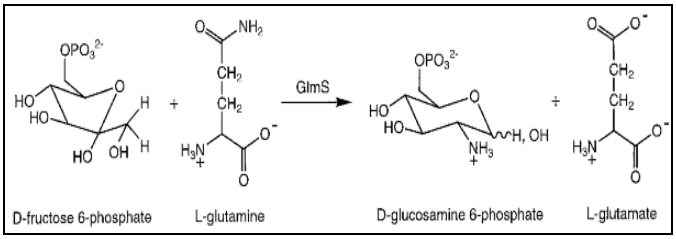


SCHEME: 1

On the other hand, chalcone nucleus having prominent activities against microbes is known [4-6]. A recent pharmaco-phore based studies by M.A. Baseer et al. [7] elucidated the potential of chalcone based compounds as promising drug like molecules. Therefore, it is of interest to design potential inhibitors using chalcone skeleton with appropriate modifications.

Computation methods:

Software and programs:

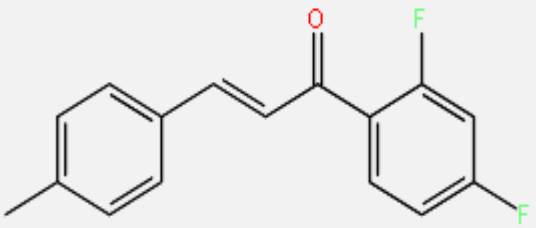
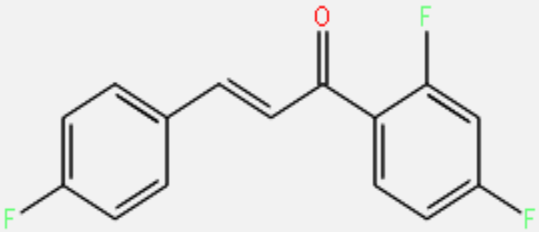
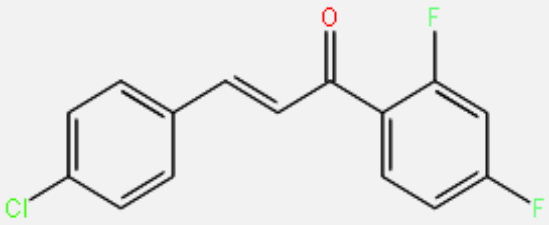
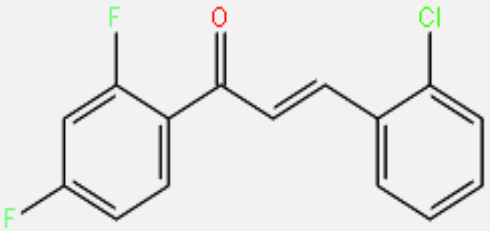
Accelry's Discovery studio ver 4.0 [8] is utilized to visualize the ligand structures, receptors, hydrogen bonding network and to render images. Chemsktech was used to draw the ligand compounds. Autodock 4.0 [9] is the primary docking program used in this work for the semi-flexible docking studies. Preparation of the ligands and protein receptors in pdbqt file and determination of the grid box size were carried out using Auto-Dock Tools version 1.5.6. Protocol used for performing protein and ligand preparation along with docking studies is same as followed elsewhere [10-12].

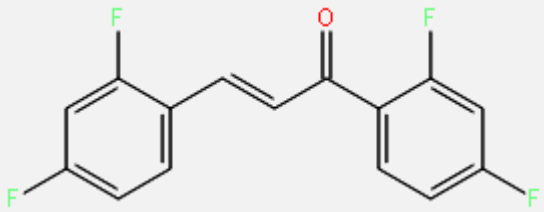
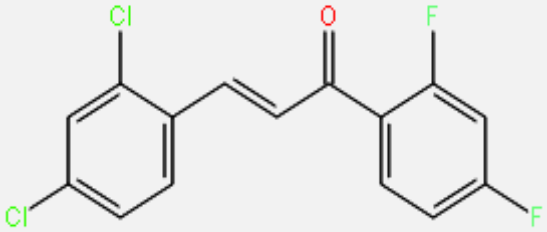
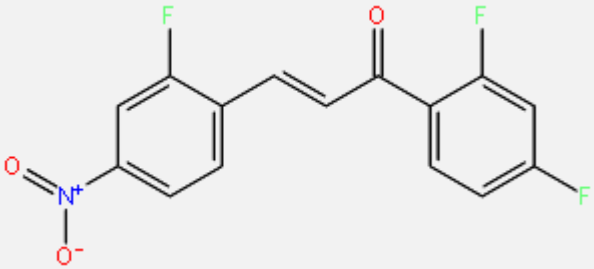
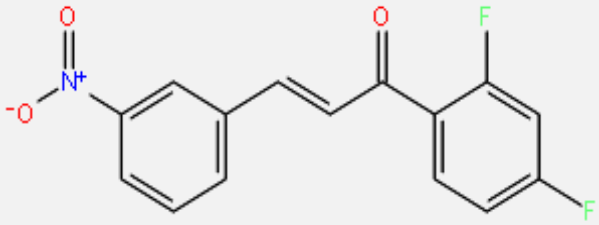
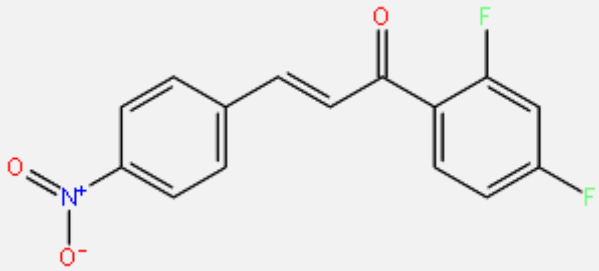
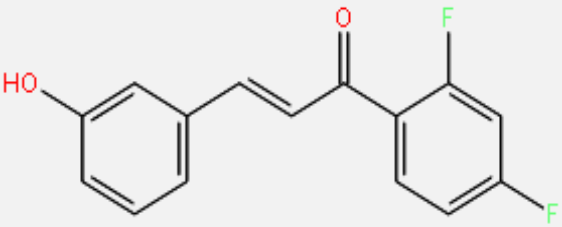
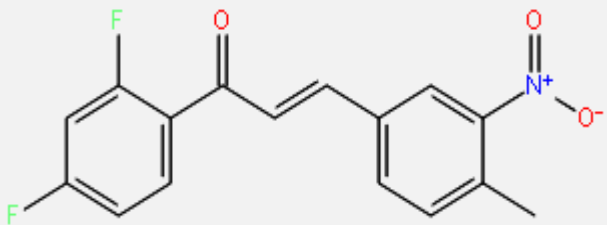
RESULTS AND DISCUSSION:

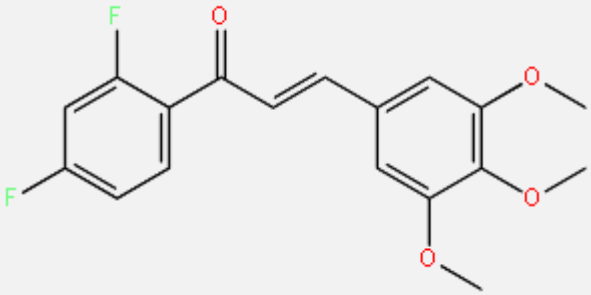
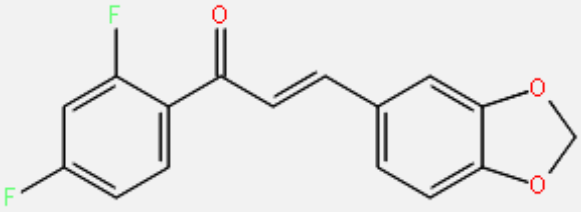
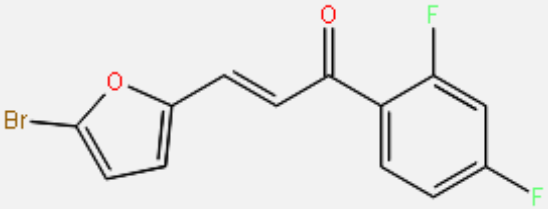
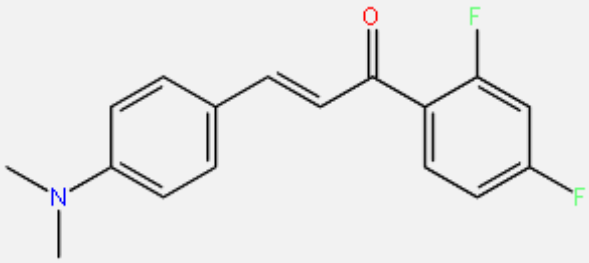
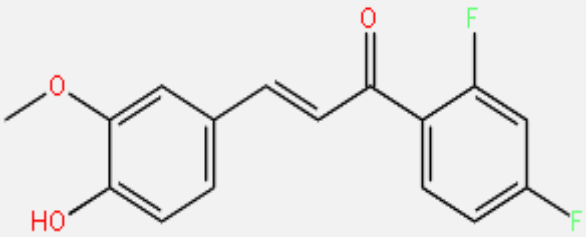
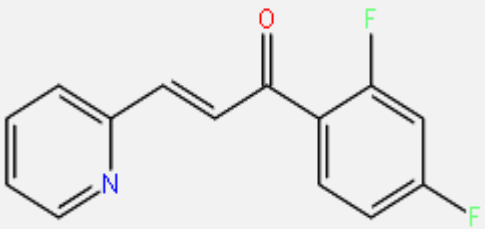
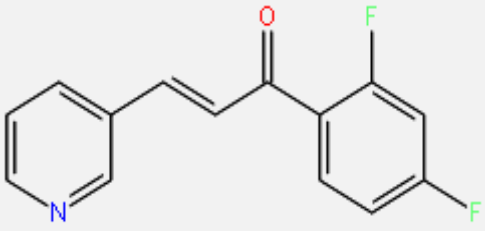
Docking and IC50 of the compounds with Glucosamine-6-phosphate synthase:

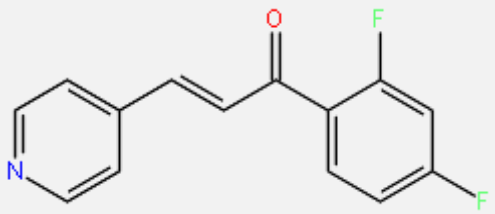
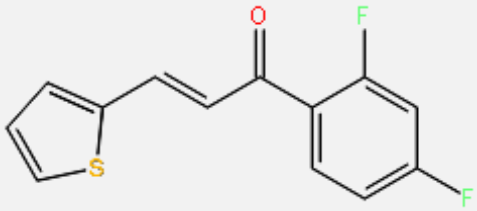
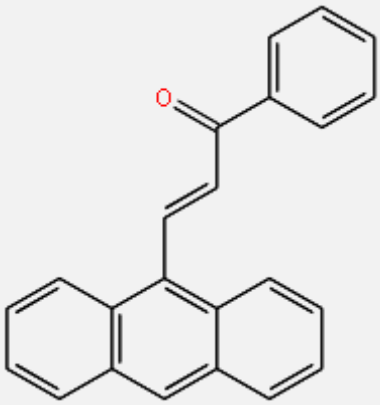
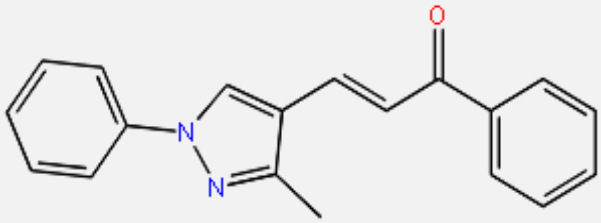
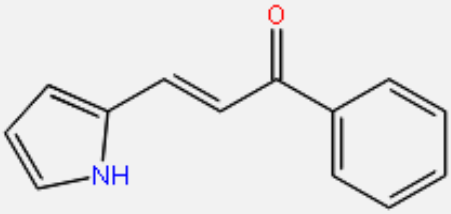
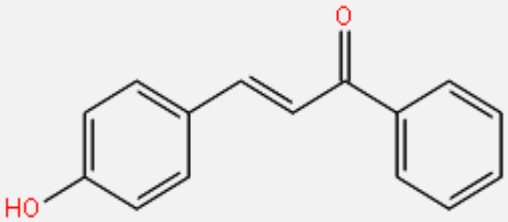
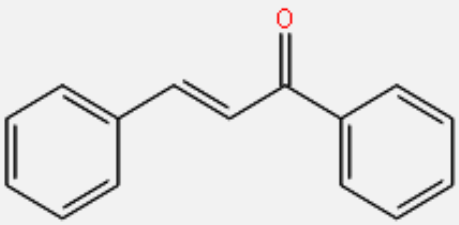
In order to know the binding energies involved in the protein ligand complex formation and to understand the molecular atomic level of interactions responsible for the target specific binding affinity of the compounds towards G6PS, we have performed the molecular docking studies for the present studied twenty compounds with the active binding site of G6PS protein target. Docking results have been are tabulated in **Table 1.**

TABLE 1: DOCKING RESULTS OF THE PRESENT STUDIED CHALCONE SERIES OF COMPOUNDS WITH GLUCOSAMINE 6-PHOSPHATE SYNTHASE

S.No	Compound	Docking energy (Kcal/mol)	pIC50 value (micromolar)
		-8.50	586.11 nM
		-7.66	2.44 uM
		-8.14	1.07 uM
		-8.54	550.62 nM

	-7.72	2.19 uM
	-8.60	492.79 nM
	-10.23	31.87 nM
	-9.03	238.48 nM
	-10.16	35.85 nM
	-9.06	227.60 nM
	-8.29	841.10 nM

	-8.37	735.03 nM
	-8.83	337.66 nM
	-8.47	623.66 nM
	-8.56	528.79 nM
	-8.54	552.93 nM
	-7.92	1.58 uM
	-8.25	890.75 nM

	-8.02	1.33 uM
	-8.04	1.29 uM
	-9.85	60.34 nM
	-9.29	154.81 nM
	-7.94	1.52 uM
	-8.45	635.57 nM
	-8.29	835.80 nM

All the twenty five compounds studied in this present work have shown to be successfully docking inside the active site of G6PS with a binding energy in a range of -7.66 to -10.16 Kcal/mol with predicted IC50 value range of 2.44 micro molar to 31.87 nano molar respectively. We have compared our docking results with some of the potent drug candidates for G6PS, as per the literature it is evident that Streptomycin and Glucose-6-phosphate were showing binding energy of -5.72 and -5.9 Kcal/mol respectively**.** Moreover, some other novel synthesized compound also shown potential antimicrobial activity targeting G6PS with a binding energy range of -4.37 to -9.75 kcal/mol **Table 2** (see supplementary material). When these docking results of these potent drug candidates compared with our compounds docking results, it was identified that compound 7 is showing better binding energies than these controls by showing -10.23 Kcal/mol of binding energy with a far better IC50 value prediction of 31.87 nano molar respectively **Table 1** (see supplementary material) for the G6PS target specific complex formation by forming hydrogen bonds with Trp74, Cys1, His77, Arg73, Thr76 residues repctively. a pi-pi and pi-cationic stacking with Trp74, His97, His86, His71 residues respectively **(Fig. 1).** Compounds interactions with the protein are tabulated in **Table 3**. Our *in silico* analysis revealed that these novel series of compounds have clearly demonstrated plausible high inhibitory potential for microbial targeting G6PS.

TABLE 2: DOCKING RESULTS OF SOME OF THE DRUG CANDIDATE FOR G6PS

S.No	Ligand	Binding energy (Kcal/mol)	Reference
1.	Streptomycin	-5.72	Sumaiya et,al [13]
2.	Glucose-6-phosphate	-5.9	Arora et al.[14]
3.	2,4,5-triarylimidazole derivative (a)	-7.37	
4.	2,4,5-triarylimidazole derivative (b)	-7.62	Ivan et.al, [15]
5.	2,4,5-triarylimidazole derivative (c)	-7.61	
6.	N3-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid	-9.75	Banerjee et al. [16]
7.	N-benzyl-2,2,2-trifluoroacetamide	-4.37	Balachandran et.al, [17]

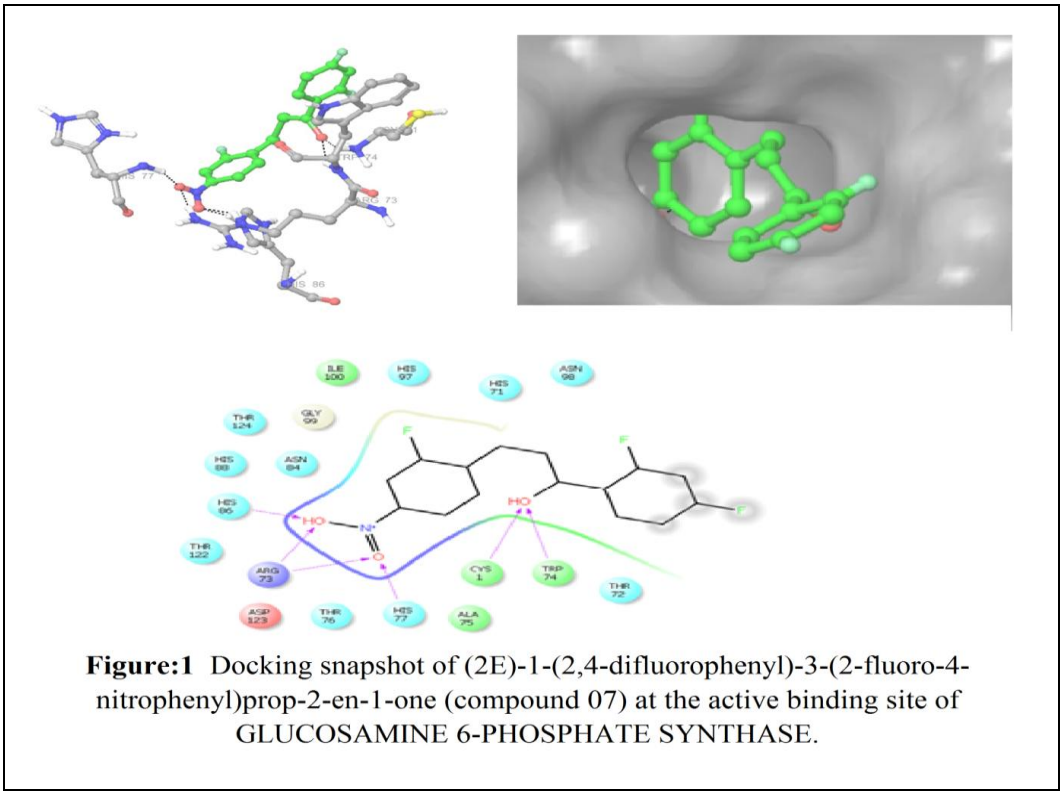
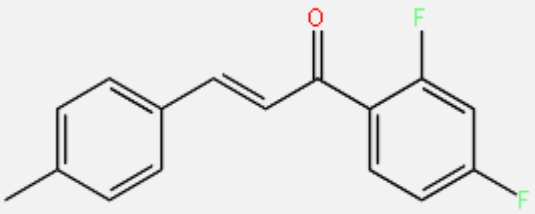
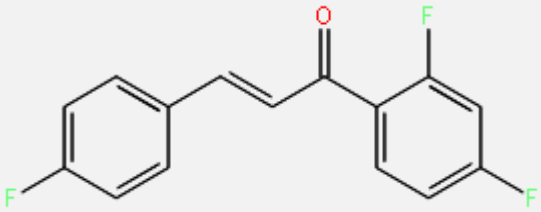
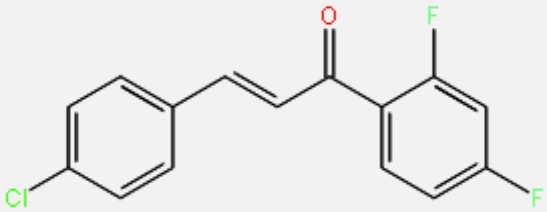
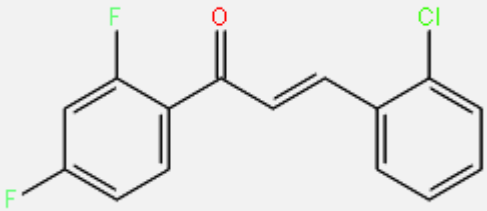
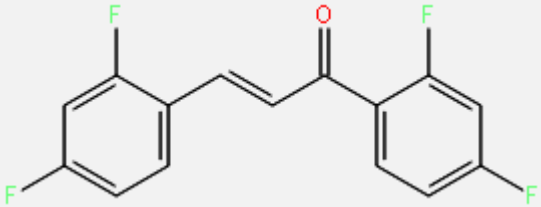
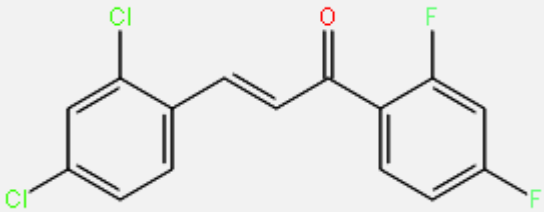
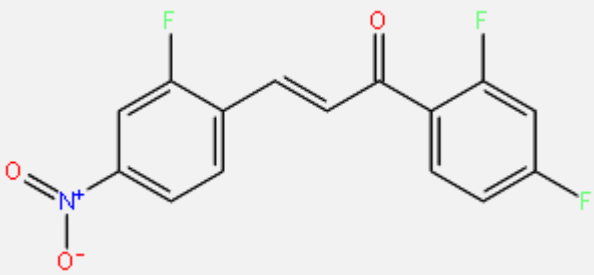
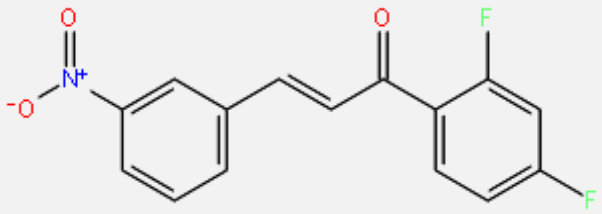
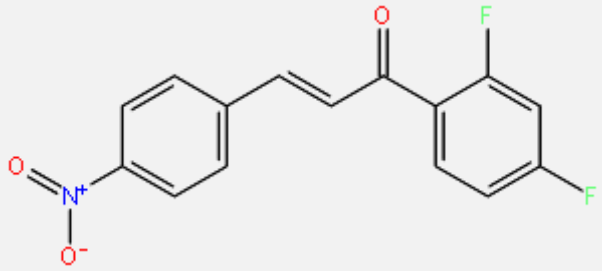
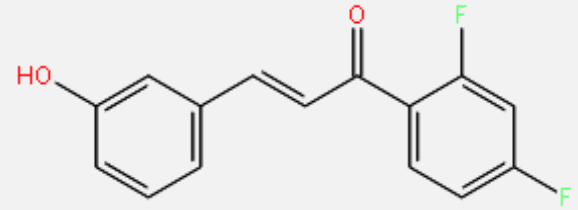
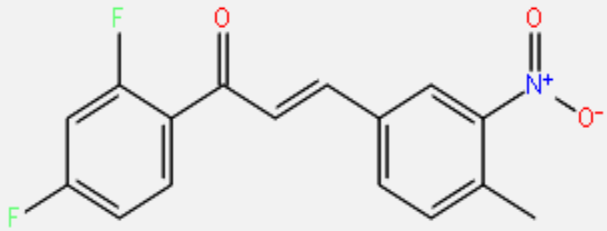
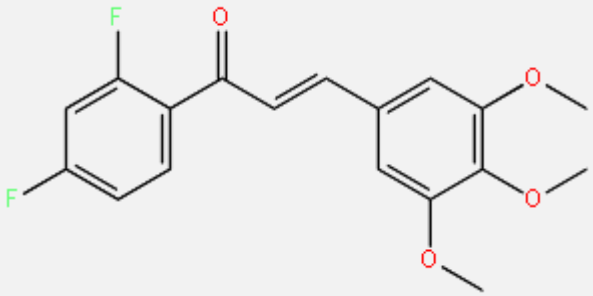
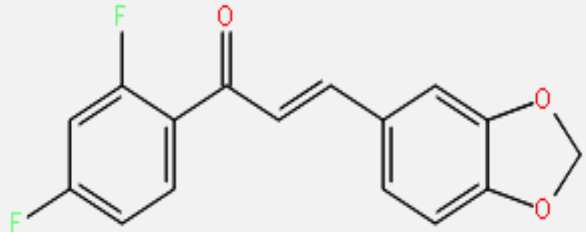
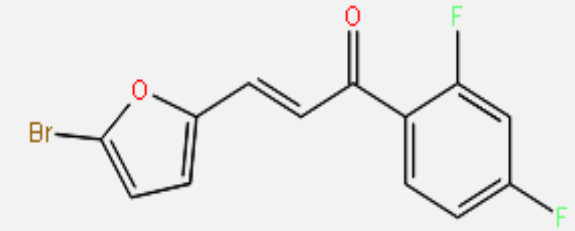


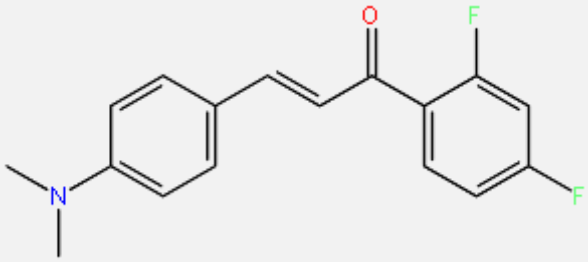
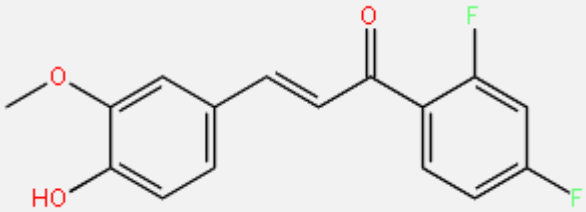
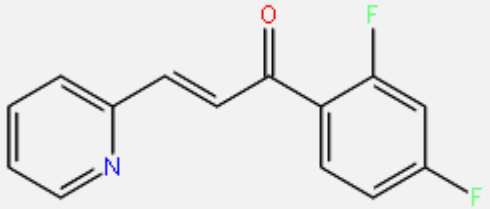
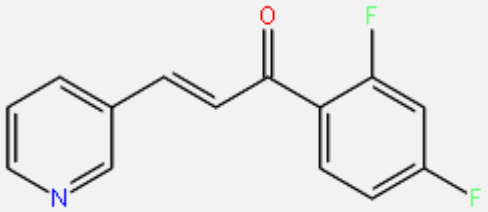
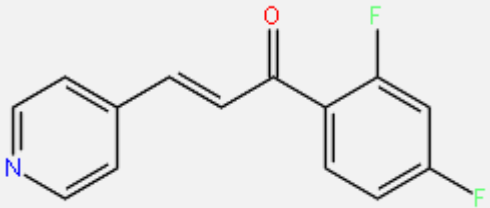
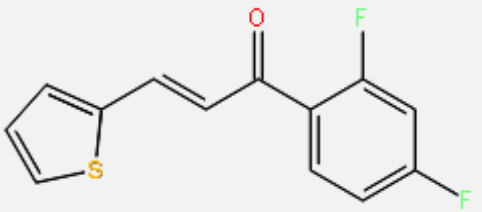
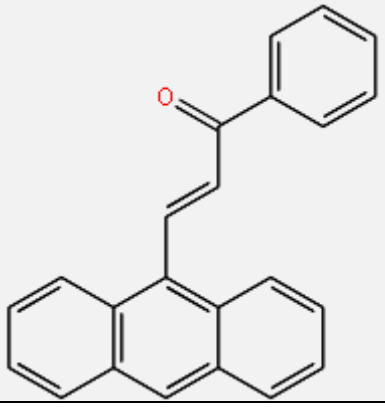
Figure:1 Docking snapshot of (2E)-1-(2,4-difluorophenyl)-3-(2-fluoro-4-nitrophenyl)prop-2-en-1-one (compound 07) at the active binding site of GLUCOSAMINE 6-PHOSPHATE SYNTHASE.

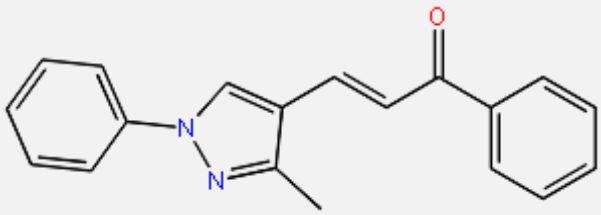
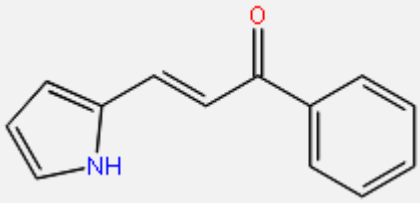
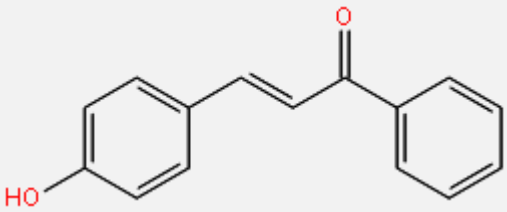
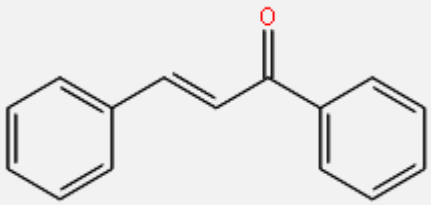
FIG.1: DOCKING SNAPSHOT OF (2E)-1-(2,4-DIFLUOROPHENYL)-3-(2-FLUORO-4-NITROPHENYL)PROP-2-EN-1-ONE (COMPOUND 07) AT THE ACTIVE BIMDING SITE OF GLUCOSAMINE 6-PHOSPHATE SYNTHASE

TABLE 3: MOLECULAR INTERACTIONS OF CHALCONE SERIES OF COMPOUNDS WITH GLUCOSAMINE 6-PHOSPHATE SYNTHASE

S.No	Compound	H Bond	Pi-Pi interaction	Pi cation Interaction	Salt bridge
1.		Trp74 Cys1	Arg73 His86 Asn98	His71	
2.		Trp74 Cys1	Arg73 His97	His71 His77 His86	
3.		Trp74 Cys1	Arg73 His97	His71 His77 His86	
4.		Trp74 Cys1	Arg73 His97	His71	
5.		Trp74 Cys1	Arg73 His86	His71	
6.		Trp74 Cys1		His86	
7.		Trp74 Cys1 His77 Arg73 Thr76	Trp74 His97	His86 His71	

8.		His77 Thr76 Arg73 His86	Trp74		
9.		Trp74 Cys1		His86	Arg73
10.		Thr76 Arg73 His77 Gly99	His97 Trp74	His86	
11.		Trp74 Cys1	His97 His86 Arg73	His71 Cys1	
12.		Trp74 Cys1	His97 Trp74	His71 His77 His86	
13.		Thr76 His86 Arg73	Trp74	His97	
14.		Thr76 Trp74 Cys1	Arg73		

15.		Trp74 Cys1	His97 Trp74	His71 His86
16.		Thr76 His86 Arg73	Trp74	His97
17.		Trp74 Cys1	Trp74	His86 His71
18.		Trp74 Cys1 Thr76	Trp74 His86	His77
19.		Trp74 Cys1	Trp74	His86
20.		Trp74 Cys1	His86 His97 Arg73 Trp74	His77
21.		Trp74 Cys1	Trp74 His97	His71 His77 His86

22.		Trp74 Cys1	Arg26	His86
23.		Trp74 Cys1 Thr76 His77	His86 Arg73	
24.		Trp74	His86	
25.		Trp74 Cys1	Trp74 His97	His71 His86

All present studied compounds have been evaluated as good ADMET compiling compounds according to Lipinski's rule of five. The data have been presented in elsewhere.[8]

CONCLUSION: Our *In silico* studies provides a rationalization to the ability of present studied chalcones skeleton based series of compounds as a valuable small ligand molecule with strong binding affinity towards G6PS for plausible anti-microbial activity involving large value of negative binding energy by forming various interactions with the residues, all or some of which fall under catalytic active site important residues consolidating their complex's thermodynamic stability. Moreover, predicted IC50 values further substantiated our hypothesis that these compounds have the potential to inhibit G6PS. The knowledge gained through this present study could be of high value for computational screening of target specific G6PS domain inhibitors by understanding the molecular interaction basis between ligand and receptor. The present investigated chalcone skeleton based series of compounds offers the possibility of expedient additional modifications that could give rise to lead structures with enhanced inhibitory activity and selectivity towards anti-microbial activity targeting drug targets like G6PS.

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