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INSILICO SCREENING OF BENZENE SULFONAMIDE DERTIVATIVES FOR TREATMENT OF DIABETES MELLITUS

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ABSTRACT

Diabetes mellitus is characterized by elevation in blood glucose level. It arises because the body is unable to produce enough insulin for its own needs, either because of impaired insulin secretion or impaired insulin action, or both. The present treatment of diabetes is focused on controlling and lowering blood glucose to a normal level. Several marketed drugs available for treatment of diabetes but with undesirable side effects. Naturally occurring flavanoids has profound effects on treating diabetes. In this study molecular docking and docking analysis was performed using molegro software which were used to predict and understand between alpha amylase inhibitors and six benzene sulphonamide derivatives.CV1 atomic coordinates was retrieved from protein data bank (PDB). All Ligands (Figure 1) were drawn by software chemsketch. Molegro virtual docker program that predicted interactions in terms of Dock score. The approach is applicable in engineering 3D structures of enzymatic models, and studying interactions of active site residues with ligands show that the three compounds: *N*-(4-phenyl-2,3-dihydro-1,3-thiazol-2-yl)methanesulfonamideCould be a potent anti-diabetic target molecule against CV1 which may be worth for further clinical trials.

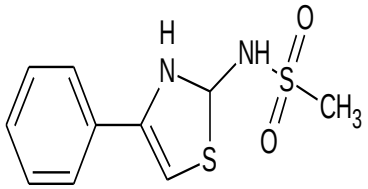
INTRODUCTION

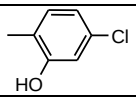
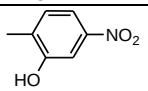
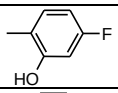
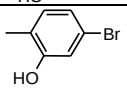
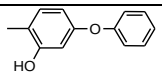
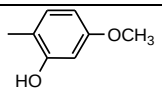
Diabetes mellitus is a metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, action, or both, currently affecting ca. 3% of the world population. This complex metabolic syndrome is a major human health concern in the world and is estimated to affect 300 million people by the year 2025 [1, 2]. Pharmaceutical intervention of hyperglycemia induced diabetic complications is actively pursued since it is very difficult to maintain normoglycemiaby any means in patients with diabetes mellitus [3, 4]. Several drugs such as sulfonylureas and biguanides are presently available to reduce hyperglycemia in diabetes mellitus. These drugs demonstrated significant side effects andthus searching for a new class of compounds is essential to overcome these problems [5]. Therefore, the urgent need to look for novel drug scaffold with minimal

side effects is still a challenge to the medicinal chemist [6].

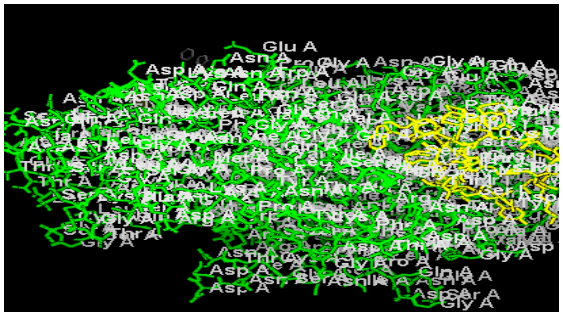
The clinical and medicinal importance of sulfonamides is well documented. The sulfonamide moiety (–SO2NH2) is an active pharmacophore, exhibiting a wide variety of pharmacological activities such as antimicrobial, antimalarial, insulin-releasing antidiabetic, anti-HIV, high ceiling diuretic, antithyroid, and antitumor [7-10].

General structure for ligand

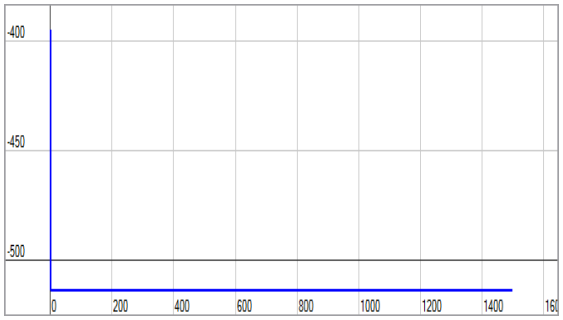


S. no	R SUBSTITUENTS	IUPAC NAME
1.		2-(2-chloro-5-hydroxyphenyl)-4*H*-sulfonamide
2.		2-[2-hydroxy-4-(nitromethyl)phenyl]-4*H*-sulfonamide
3.		2-(4-chloro-2-hydroxyphenyl)-4*H*-sulfonamide
4.		2-(4-bromo-2-hydroxyphenyl)-4*H*-sulfonamide
5.		2-(4-fluoro-2-hydroxyphenyl)-4*H*-sulfonamide
6.		2-(4-fluoro-2-hydroxyphenyl)-4*H*-sulfonamide

In the present study analogues are varied by different substitution to provide insight for future Endeavour's. The study also focuses on the comparison between the inhibitory potentials of the novel compounds on the CV1. Docking various ligands to the protein of interest followed by scoring to determine the affinity of binding and to reveal the strength of interaction has also become increasingly important in the context of drug discovery. The molecular docking was performed for newly designed compounds against CV1 protein, CV1 (PDB ID) with bound ligand(PCA) extracted from protein databank (PDB), by utilizing fast, exhaustive dockingsoftware Molegro virtual docker.



GRAPHICAL REPRESENTATION



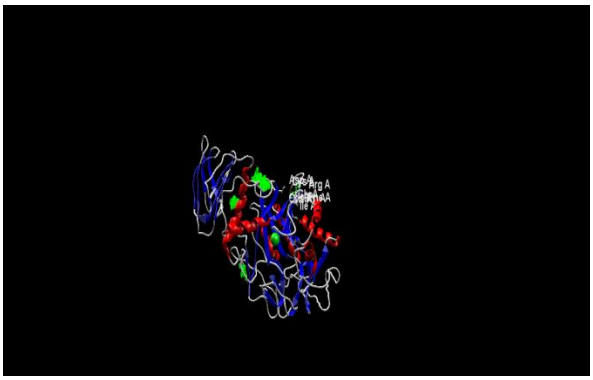
Materials and methods:

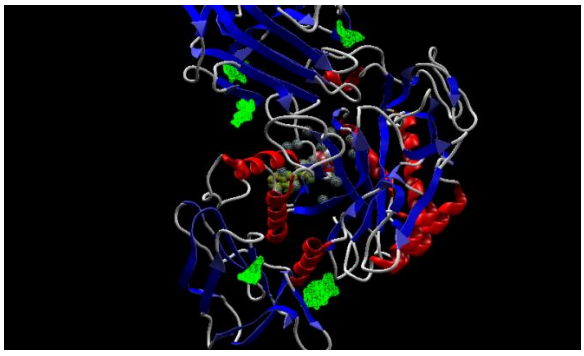
The preparation of the target enzyme with molegro tool involved in the addition of hydrogen atom to the target enzymes which is a necessary step for the computation of partial atomic charges alpha amylase enzyme complexed with selective inhibitors with two chains with $3.18A^0$ and $3.22A^0$ respectively. Computational analysis was carried out in chain A of CVI .Six molecules were selected to study associated protein ligand interactions. All ligands were drawn by using chem. Sketch software. Mol Dock Score scoring function was employed to predict the binding energy for active site residue-ligand interactions and docking studies computed for all ligands using Molegro virtual docker program that predicted interactions in terms of Dock score. All calculations were done on a Intel core I5 laptop with windows seven configuration. Docking was performed by using Molegro Virtual Docker (MVD) software package. MVD files performs flexible ligand docking, so the optimal geometry of the ligand will be determined during the docking. To obtain better potential binding sites in the alpha amylase (PDB ID: CV1), a maximum of five cavities was detected using default parameter

Moldocscore of ligand bind with target

Name of the Ligands	Mol. Dock score	Reranking score	H BOND ENERGY	H BOND IN A^0	RESIDUES
CV1-nAG	-9.39	78.54	-9.5	2.5 2.9 2.4	Asp63 Asn65 Ser199
PCA_1	-65.784	-54.27	-8.9	2.2 3.4 2.9	Gly238 Thr237 Phe239
2-(2-chloro-5-hydroxyphenyl)-4*H*-Sulfonamide	-40.20	18.19	-9.05	3.22	Thr237
2-[2-hydroxy-4-(nitromethyl)phenyl]-sulfonamide	-45.235	-22.5	-4.5	3.22 2.5 2.9 2.4	Thr 237 Asp63 Asn65 Ser199
2-(4-chloro-2-hydroxyphenyl)-4*H*-sulfonamide	-45.2356	-24.5	-4.5	-4.5 -1.1 1.4 -4.8	Thr237 Gly238 Phe239 Ly2
2-(4-bromo-2-hydroxyphenyl)-4*H*-sulfonamide	-60.032	85.065	-8.7	2.5 2.6	Asn12 Ly13
2-(4-fluoro-2-hydroxyphenyl)-4*H*-sulfonamide	-200.575	-1427.57	-2.9	2.5 2.9 2.4	Asp63 Ser199 Asn65
2-(4-hydroxy-2-hydroxyphenyl)-4*H*-sulfonamide	-74.45	-50.90	-5.12	2.5	Asp63

BEST DOCKED STRUCTURE





Study of Ligand- Substrate Interaction
RESULTS AND DISCUSSION

Study of Ligand-Substrate Interaction
The designed compounds were evaluated through docking techniques using MVD program. Designed compounds were docked on one of the crystal structures of alpha amylase and alpha glucosidase available through the RCSB Protein Data Bank. The compounds were scored based on the minimized ligand protein complexes. New ligands were docked into the empty binding site of alpha amylase and alpha glucosidase in order to compare the binding affinity. ACR_1003 ligand with surrounding active site residues within 3.5 A°, hydrogen bonding interactions and the spatial orientation in binding pocket is given in Figure 3. The interacting residues surrounding the ligand within 3.13 A° distance are Glu167 Asn613 Lys704 His412.The SIX ligand molecules having minimum energy were screened out as the possible inhibitors for alpha amylase given in the (Table 1).

Virtual screening: The six ligand molecules having minimum energy were screened out as the possible inhibitors for alphaamylase inhibitor sgiven in the (Table 1). 2-(4-bromo-2-hydroxyphenyl)-4*H*-sulfonamide it had highest moldoc score of -40.20.It had one hydrogen bond.The Thr237 of protein formed hydrogen bond with oxygen of chromone group of ligand.The bond length was found to be 3.22 A^0.The active binding site of the alpha amylase inhibitors was found to have bond length of 2.2 A^O ,3.4 $A^{0,}$2.9 A^0 of Gly238 ,Thr237 ,Phe239 aminoacids respectively which has molecular docking score of -65.784 and its hydrogen bond energy was found to be -8.9. 2-(4-bromo-2-hydroxyphenyl)-4*H*-sulfonamide had mol doc score -60.032.It had two hydrogen bond formed between Asn 12 and hyroxy group of sulfonyl derrivatives.The bond length was found to

be 2.5 A^0.The aromatic aldehyde derivative formed between Ly13 and hydroxyl of aldehyde of sulfonamides the bond length was found to be 2.6 near aromatic substitution of sulfonyl substitution. 2-(4-fluoro-2-hydroxyphenyl)-4*H*-chromen-4-one had mol doc score -200.575.It had two hydrogen bond formed between Asp 63 and hyroxy group of sulfonyl derivatives derivatives.The bond length was found to be 2.5 A^0.The aromatic aldehyde derivative formed between Asp 63 and hydroxyl of aldehyde of sulfonylthe bond length was found to be 2.5 near aromatic substitution of sulfonyl substitution. The other hydrogen was found between Ser199 and hyroxy group of chromone derivatives.The bond length was found to be 2.9 A^0.The aromatic aldehyde derivative formed between Ser199and hydroxyl of aldehyde of chromones,the bond length was found to be 2.9 A^0 near aromatic substitution of chromone derivatives. 2-(4-chloro-2-hydroxyphenyl)-4*H*-chromen-4-one had mol doc score -45.23Kcal/mol.It had four hydrogen bond formed between Thr 237 and hyroxy group of sulfonyl derivatives.The bond length was found to be -4.5 A^0.The aromatic aldehyde derivative formed between Thr 237 and hydroxyl of aldehyde of sulfonyl,the bond length was found to be -4.5 A^0 near aromatic substitution of sulfonyl substitution. The other hydrogen was found between Gly238 and hyroxy group of sulfonyl derivatives.The bond length was found to be-1.1A^0.The aromatic aldehyde derivative formed between Gly238 and hydroxyl of aldehyde of sulfonyl ,the bond length was found to be -1.1 near aromatic substitution of sulfonylsubstitution. The aromatic aldehyde derivative formed between Phe239 and hydroxyl of aldehyde of sulfonyl,the bond length was found to be 1.4A^0 near aromatic substitution of sulfonyl substitution. The other hydrogen was found between Ly2 and hyroxy group of sulfoyl derivatives.The bond length was found to be—4.8 A^0 aromatic substitution of sulfonyl derivatives. The active site is present in A ring of the protein. The residue bind with the ligand is same as that of the standard compounds docked. The residues found in the active sites are as follows Gly238,Thr237 ,Phe239, Thr 237 ,Asp63,Asn65, Ser199, Thr237,Ly2.

CONCLUSION:

By using computational approaches derivatives designed showed good interactions with alpha amylase inhibitors protein. *N*-(4-phenyl-2,3-dihydro-1,3-thiazol-2-yl) methanesulfonamide 200.575 kcal/mol against CV1 (PDB ID) in docking analysis. Docking studies confirm that the main interaction of CV1 inhibitors with enzyme is Hydrogen bond and Hydrophobic interactions with the binding pockets made by N and H group of sulfonamides and aromatic aldehyde substitution of the ligands. This information has potential implications to understand the mechanism of CV1 related enzymatic inhibition reactions, and also applicable in the prediction of more effective inhibitors and engineering 3D structures of other enzymes as well.Hence, it is concluded that *N*-(4-phenyl-2,3-dihydro-1,3-thiazol-2 yl) dimethane sulfonamide that could be a potent anti-diabetic target molecule against CV1 which may be worth for further clinical trials. In this study, computations on the interactions at the active site of CV1 were carried out for Six ligands. In future, it may be necessary to explore the development of potential new alpha amylase inhibitors for treating diabetis The present study shall help in rational drug design and synthesis of new selective alphaamylase inhibitors with predetermined affinity and activity and provides valuable information for the understanding of interactions between CV1 and the novel 4 aromatic sulphonamides.

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