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Molecular properties and docking studies of Certain Novel Isoxazole incorporated Coumarin Derivatives as potent *α- Amylase* Inhibitory Agents

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ABSTRACT

Alpha amylase is one of the important targets in the treatment of diabetes mellitus that work by preventing the digestion of carbohydrates. Many alpha amylase inhibitors with diverse chemical structures and modes of protein interaction have been designed on the basis of their ability to compete with alpha amylase enzyme. This study involves the molecular docking of certain novel isoxazole incorporated coumarin derivatives as potent alpha amylase inhibitory agents. The compounds were computationally designed and optimized with the docking to investigate the interactions between the target compounds and the amino acid residues of theα-amylase enzyme. The inhibitory activities against human alpha amylase enzyme were investigated by molecular docking using the autodock software. All the designed compounds were showed good binding energy when compared with the binging energies of standard drugs such as acarbose (for anti-diabetic activity). Among all the designed compounds, compoundI1 and I3 have more binding energy values when compared with standard drugs. Here we also studied the molecular properties of designed compound using molinspiration software. Further we planned to synthesis these isoxazole derivatives and screen for *in vitro*anti diabetic activity.

Keyword: Alpha amylase, isoxazole derivatives, docking, autodock.

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INTRODUCTION

Over the last decade, the pursuit of alpha amylase inhibitors has received an extraordinary level of attention in the pharmaceutical industry and in the medicinal chemistry community. A unique combination of well-established pharmacology, clinical efficacy and the opportunity to utilize structure-based drug designhas made this a highly attractive target for therapeuticintervention.T here is overwhelming evidence indicating that inhibition ofα-amylase can lead to reduction in post-prandial hyperglycemia in diabetic condition. Blocking this α-amylasemay offer an effective therapy for treating many diabetes diseases.

However great number of heterocyclic compounds display interesting anti diabetic activity especially isoxazole and coumarin derivatives having important role in this concern. Coumarins are secondary metabolites found widely in plants and used mainly in anticoagulant and antithrombic therapy. Over the past two decades, literature related to the effects of coumarins and their derivatives on diabetes and its complications are reported. The search for new coumarins against diabetes and its complications, either isolated from traditional medicine or chemically synthesized, has been constantly expanding. The cellular and molecular mechanisms include protecting pancreatic beta cells from damage, improving abnormal insulin signaling, reducing oxidative stress/inflammation, activating AMP-activated protein kinase (AMPK), inhibiting alpha amylase and alpha glycosidase. Hence we are planned to incorporate isoxazole into coumarin nucleus by several synthetic methods, scheme and structure of the designed compound were represented in figure 1 and table 1 respectively. The designed compound were evaluated for their molecular properties by the "Lipinski's rule of 5" and further their ability to bind in the active site region of α-amylaseidentified using molecular docking approach.

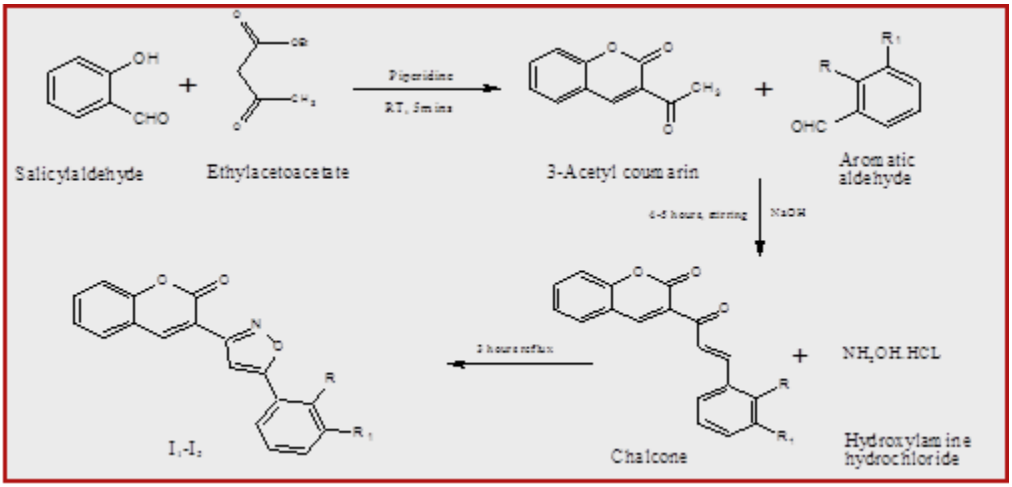

Figure 1: proposed scheme for designed compounds

Table 1: Structure of the designed compounds

Code	I_1	I_2	I_3	I_4	I_5
R	H	Cl	NO_2	OCH_3	OH
R_1	H	H	H	OCH_3	OCH_3

MATERIALS AND METHOD[9, 10]

For this present study we have used bioinformatics tools, biological databases like PDB (Protein Data Bank) and software's like autodock and ACD chemsketch. The PDB is the single worldwide archive of structural data of biological macromolecules, established in Brookhaven National Laboratories (BNL). It contains structural information of the macromolecules determined by X-ray crystallographic, NMR methods etc. Auto dock is an automated docking tool. It is designed to predict how small molecules such as substrates bind to a receptor of known 3D structures.

RESULTS AND DISCUSSION

Calculation of molecular properties

The molecular properties were calculated on the basis of simple molecular descriptors used by 'Lipinski's rule of 5'. The five properties consist of molecular weight, hydrogen bond donor, hydrogen bond acceptors, log P, and Total polar surface area (TPSA) which was calculated using the online cheminformatics tool molinspiration (http://www.molinspiration.com/) 18 and the results were shown in **Table 2**.

Table 2: Molecular descriptor properties of designed compounds

Compound Code	Log P	Molecular weight	Hydrogen acceptors	Hydrogen donors	No. of violation
I1	3.35	291.31	4	1	0
I2	3.98	329.27	4	1	0
I3	3.43	336.30	7	0	0
I4	2.99	351.36	6	1	0
I5	3.36	335.31	6	1	0

DRUGLIKENESS PROPERTIES OF DESIGNED ISOXAZOLE DERIVATIVES[11]

The molinspiration virtual screening is fast (100,000 molecules may be screened in about 30 minutes) and therefore allows processing of very large molecular libraries. Validation tests performed on various target classes (including kinase inhibitors, various GPCR targets, different enzymes etc.,) show 10 to 20- fold increases in hit rate in comparison with standard / random selection of molecules for screening. The data's for drug likeness properties were depicted in table 3.

Table 3: Drug likeness properties of designed compounds

Compound Code	GPCR Ligand	Ion channel Modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
I1	-0.31	-0.47	-0.39	-0.20	-0.14	-0.01
I2	-0.31	-0.49	-0.49	-0.16	-0.23	-0.10
I3	-0.17	-0.49	-0.77	-0.21	-0.28	-0.07
I4	-0.31	-0.59	-0.38	-0.20	-0.28	-0.14
I5	-0.26	-0.17	-0.24	0.12	-0.29	-0.04

MOLECULAR DOCKING STUDY[12-15]

In order to gain more insight on the binding mode of the compounds with α-amylasedocking studies using Auto Dock 4.0.1 were carried out. Topscoring molecules from the largest cluster were considered for interaction studies. The crystallographic structure ofα-amylase, which is retrieved from the RCSB Protein Data Bank (PDB code 1UA7) serves as docking receptor, and all the designed compounds are selected as ligand molecules. Before docking the screened ligands in to the protein active site, the protein was prepared by deleting the substrate cofactor as well as the crystallographic ally observed water molecules and then protein was defined for generating the grid. All molecules were drawn using ChemDraw Ultra 8.0 tool and energy minimized using Chem 3D Ultra 8.0 software.

AUTO DOCK 4.0.1 PROCEDURE

Automated docking was used to locate the appropriate binding orientations and conformations of various inhibitors into the 1UA7binding pocket. To perform the task, the powerful genetic algorithm method implemented in the program Auto Dock 4.0.1 was employed. Gridmaps were generated by AutoGrid program. Eachgrid was centered at the crystal structure of the corresponding 1G2A and 2GT1 separately. Lamarckian genetic algorithm was employed asthe docking algorithm. The grid dimensions were60 Å X 60 Å X 60 Å with points separated by 0.375Å. For all ligands, random starting positions ,random orientations and torsions were used. During docking, grid parameters were specified for x, y and z axes as 38.808, 30.946 and 42.249 respectively. The docking parameters number of genetic algorithm (GA) runs: 25, population size: 150, maximum number of evaluation: 2,500,000, maximum number of generation: 27,000 were used for this study. The structure with the lowest binding free energy and the most cluster members was chosen for the optimum docking conformation.

Table 4: Energy minimization table of Ligand and MAP kinase Interaction

Code	Binding Energy (Kcal/mol)	Inhibition Constant	Vdw. Desolvation Energy	Intermol Energy	Ligand efficiency	Electrostatic Energy	Total internal
I1	-7.79	2.04	-7.66	-8.96	-0.31	-1.3	1.19
I2	-7.05	6.75	-7.83	-8.25	-0.27	-0.42	0.32
I3	-7.28	6.42	-6.95	-8.28	-0.26	-1.33	-0.44
I4	-6.41	20.04	-7.48	-7.6	-0.25	-0.12	-.044
I5	-7.19	5.36	-8.71	-8.38	-0.28	-0.32	-0.42
Acarbose	-10.41	2.36	-9.44	-10.01	-0.11	-2.45	-0.32

Docking Analysis

The newly designed molecules are energy minimized and the resulting molecules are considered for docking analysis using Auto Dock 4.0.1. Auto dock is employed to study the docking molecules within active site region of 1UA7 and the H-bond interaction. Docked scores of newly designed molecules along with inhibition constant, Vdw. desolvation Energy, ligand efficacy and electrostatic energy and hydrogen bonds are represented in Table 4 and table 5 respectively. Among the studied compounds, compound I1 have highest binding score (-7.745 K Cal/mol with one hydrogen bond) when compared with standard drugs such as Acarbose -10.41K Cal/mol (for anti- diabetic) followed by compound I3 with score of -7.28 K Cal/mol with one hydrogen bond, compound I5 with score of -7.29 K Cal/mol with one hydrogen bond, compound I2 have score of –7.05 with two hydrogen bond and lastly compound I4 with score of -6.41. KCal/mol with one hydrogen bond.

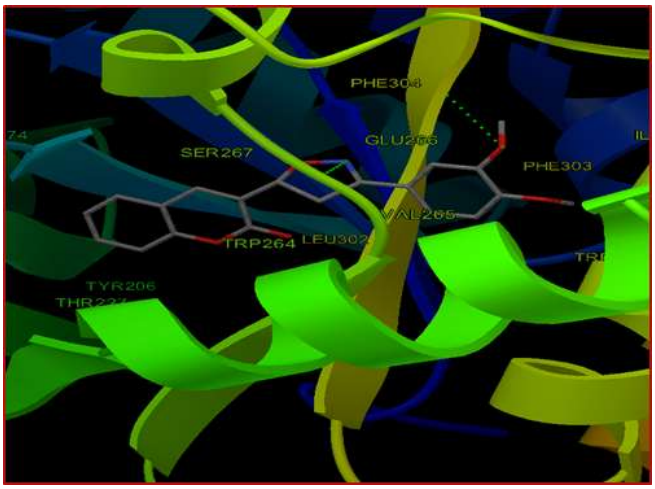

Figure 2: Docking pose of compound I1against alpha amylase as target enzyme

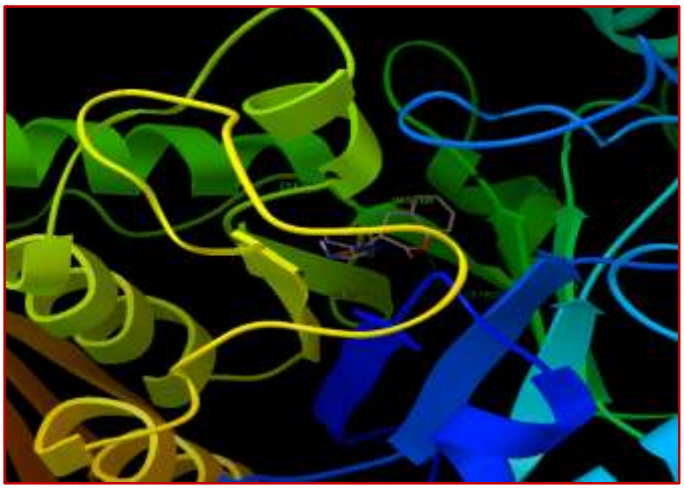

Figure 3: Docking pose of compound I3against alpha amylase as target enzyme

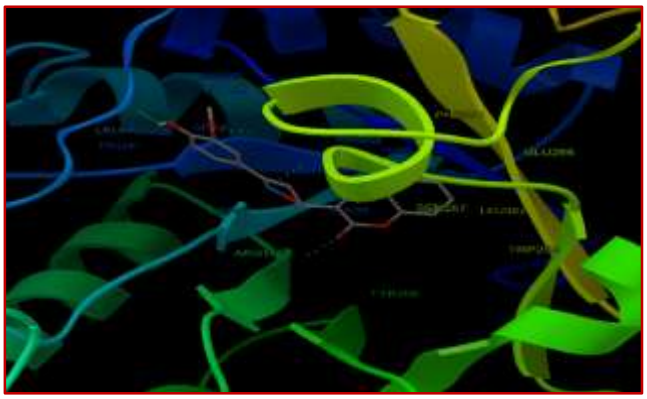

Figure 4: Docking pose of compound I5against alpha amylase as target enzyme

Figure 5: Docking pose of standard drug (acarbose)against alpha amylase as target enzyme

CONCLUSION

In current study, an approach of molecular docking is widely used to identify the potential inhibitor of α-amylase by measuring their binding energies. Applying Lipinski's rule of five to these coumarin derivatives to evaluate drug-likeness, there was no violations of the rule determining drugs pharmacological activity in the body. The docking study showed that derivative I4 and I1 possess the highest potential binding affinity into the binding site of 3D macromolecule of α-amylase compared to the standard known inhibitors. Thus, this study will be useful for the design of α-amylase inhibitors as anti- Diabetic agents.

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