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# INHIBITION OF α-GLUCOSIDASE BY NOVEL SERIES OF PIPERIDINYL COUMARIN DERIVATIVES FOR TYPE 2 DIABETES MELLITUS: IN SILICO DESIGN AND MOLECULAR DOCKING STUDIES

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## ABSTRACT

In the present study we report the inhibitory effect of piperidinyl coumarin derivatives on the activity of α-glucosidase through insilico studies. Inhibiting the action of such enzyme can significantly reduce post-prandial glucose levels in Type 2 diabetes. Molecular docking was carried out on α-glucosidase using AutoDock Vina in order to understand the molecular interaction of ligands with the active site of the enzyme. The derivatives (2A1-4C7) were analyzed for in silico ADMET properties and toxicity to establish oral drug like behavior and showed satisfactory results. The interactions of analogues showed that they could use as antidiabetic agent with suitable drug-like properties as compared to other active drugs for diabetes and therefore could be recommended for further studies, hopefully could discover a new specific leads in antidiabetic category as α-glucosidase inhibitor.

**KEYWORDS:** Piperidine, coumarin, α-glucosidase, autodock vina.

## INTRODUCTION

Diabetes mellitus is a metabolic disorder of glucose metabolism. People with diabetes may develop serious complications such as heart disease, stroke, kidney failure, blindness and premature death. The International Diabetes Federation recently reported that the number of people with diabetes is expected to rise from 382 million to 592 million by 2035.[1] Management of blood glucose level is the hallmark in the treatment of this disease. This may be achieved through the use of oral hypoglycemic drugs such as biguanides, insulin secretagogues, and α-glucosidase inhibitors. α-glucosidase is responsible for the hydrolysis of complex carbohydrates into simple absorbable glucose and causes postprandial hyperglycemia. α-glucosidase belong to the sub-subclass hydrolases that cause the hydrolysis of various substances in the body. α-glucosidase inhibition is thus the ideal target to prevent postprandial hyperglycemia. Inhibition of these enzyme systems helps to reduce the rate of digestion of carbohydrates.[2] α-glucosidase enzymes such as maltase, isomaltase and glucomaltase serve to hydrolyze the oligosaccharides on the intestinal wall.

Coumarin or 2H-chroman-2-one is an aromatic organic compound with formula $C_9H_60_2$. Plenty of in-vivo and in-vitro evidences demonstrate that coumarins can improve diabetes by means of antioxidative and anti-inflammatory action, improvement of pancreatic function, correction of abnormal insulin signaling and α-glucosidases inhibition.[3] As the multifactorial pathogenicity of diabetes demands a multimodal therapeutic approach, the diversity of coumarin targets is beneficial for antidiabetic application. Piperidine derivatives show effect on plasma glucose level. Piperidine also shows analgesic and anti-inflammatory activity.[4] Searching effective and safe drugs has always been a highlight for medicinal researchers, against diabetes and its complications. As Type 2 Diabetes accounts for approximately 90% of diabetes, more and more researchers are now focusing on drugs against Type 2 Diabetes that can ameliorate insulin resistance, such as insulin sensitizers and insulin mimetics, β-cell function or improve incretin system. Vipin Kumar *et al* developed Pharmacophore modeling and 3D-QSAR studies of α - glucosidase inhibitors as two hydrogen bond acceptor, one hydrogen bond donor and one aromatic ring as pharmacophoric features.[5,6]

In silico approaches, including virtual high throughput screening, and de novo structure-based rational drug design, have been established as tools in the drug discovery phase. Virtual screening emerged for finding novel drug-like compounds. In silico virtual screening has become a reliable, cost effective and time-saving technique that is complementary to in vitro screening for

the discovery and optimization of potent lead and hit compounds. Screening and optimizing ADME properties in the early stage of the drug development process are widely accepted.[7] Fast evaluation of ADME properties will save both time and expense. Toxicity tests aim to identify harmful effects caused by substances on humans, animals, plants or the environment through acute-exposure (single dose) or multiple-exposure (multiple doses). In silico toxicology (computational toxicology) is one type of toxicity assessment that uses computational resources. Drawback of the current α-glucosidase inhibitors (such as acarbose) is the presence of side effects such as abdominal bacterial fermentation of undigested carbohydrates in the colon. The purpose of the present study was to investigate the inhibitory effect of piperidinyl coumarin derivatives on isomaltase from Saccharomyces cerevisiae through virtual screening methods like molecular interactions with respect to molecular docking and ligand binding.

## MATERIALS AND METHODS

### Protein preparation

The three-dimensional crystal structure of receptor was taken from Protein Data Bank (PDB) (http://www.rcsb.org/) and PDB ID is 3A4A. It was loaded in the Molegro virtual docker (MVD) with the removal of all water molecules. The standard Molegro algorithm was utilized for rendering the missing charges, protonation states, and assigning of polar hydrogen to the receptor.

### Ligand preparation

The ligand files for the molecular docking studies were prepared in Chem Draw Ultra software, Cambridge Soft Corporation, USA. Version-12.0, 1997-2010. It is a Chem Tech tool used for the drawing of ligand molecules. The compound structures drawn in ChemDraw software was converted to pdb format (.pdb file) using OPENBABEL program with the standard settings and further used for docking studies.

### Molinspiration

Molinspiration, an online tool, was employed to perform computational studies in order to identify potential activators of biological objects. It offers free online services for calculation of important molecular properties (LogP, polar surface area, number of hydrogen bond donors and acceptors), as well as prediction of the bioactivity score for the most important drug targets (www.molinspiration.com). These filters help in early preclinical development and could help in avoiding costly late step preclinical and clinical failure. Lipinski's rule of five was applied to select probable ligands.[8] The constituent that had more than one violation was eliminated from the present study. Lipinski rule analysis for proposed derivatives were given in Table 1.

### Calculation of ADME properties

On the basis of 2D structural models, drawn in ChemDraw Ultra version 12.0 software (Cambridge Software), ADME properties of studied compounds were calculated using online Pre ADME program[9] and Molinspiration program. The values of the observed properties are presented in Table 2 and toxicity datas are given in table 3.

### Molecular docking

For docking of ligands into intention protein binding pockets and to approximate the binding affinities of docked ligands, a molecular docking program AutoDock Vina[10] in PyRx Virtual screening tool (1.1.2) was worn in this cram. Docking studies were performed on developed protein and ligands. The active site of protein was obtained from FT Site Server. The protein PDB file was changed into the PDBQT format file containing the protein atom coordinates, partial charges and deliverance parameters and the ligands file (PDB) was distorted into PDBQT format. Auto Grid boxes (x, y, z coordinates 77.5, 51.05, 56.5) were predetermined around the active site of the protein. The look for grid was based on the Lamarickian genetic algorithm (LGA) and the obtained dock scores were reported in kcal/mol. The docking protocol utilized in the revise consisted of 10 autonomous runs per ligand. The outcome was analyzed on the source of ranked clusters of compound conformations. The various ligands binding energy values are shown in Table 4. Inhibitor -protein interactions were analyzed and visualized in Discovery Studio 4.0 client.[11,12]

## RESULTS AND DISCUSSION

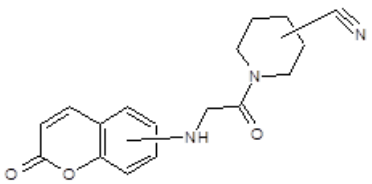


**Figure 1: Proposed structure of derivative.**

2A series represents piperidine derivatives, 4B series represents piperidine 2- carboxylic acid derivatives and 4C series represents piperidine 3- carboxylic acid derivatives. 1-7 coumarin derivatives are 3- amino coumarin, 4- amino coumarin, 6- amino coumarin, 7-amino coumarin, 3- amino -4-hydroxy coumarin, 6-amino 4-methyl coumarin and 7- amino 4-methyl coumarin derivatives respectively. In the present study, totally, 21 novel piperidinyl coumarin derivatives were designed and evaluated by various *in silico* tools.

**Table 1: Lipinski rule analysis of proposed derivatives.**

| S. No | Compound code | Log P | Molecular weight | H donor (n OH) | H acceptor (n OHNH) |
|---|---|---|---|---|---|
| 1 | 2A1 | 2.48 | 300.36 | 5 | 1 |
| 2 | 2A2 | 2.06 | 286.33 | 5 | 1 |
| 3 | 2A3 | 2.06 | 286.33 | 5 | 1 |
| 4 | 2A4 | 2.08 | 286.33 | 5 | 1 |
| 5 | 2A5 | 2.11 | 286.33 | 5 | 1 |
| 6 | 2A6 | 2.11 | 286.33 | 5 | 1 |
| 7 | 2A7 | 2.08 | 286.33 | 5 | 1 |
| 8 | 4B1 | 2.25 | 325.37 | 6 | 1 |
| 9 | 4B2 | 1.83 | 311.34 | 6 | 1 |
| 10 | 4B3 | 1.83 | 311.34 | 6 | 1 |
| 11 | 4B4 | 1.85 | 311.34 | 6 | 1 |
| 12 | 4B5 | 1.88 | 311.34 | 6 | 1 |
| 13 | 4B6 | 1.88 | 311.34 | 6 | 1 |
| 14 | 4B7 | 1.85 | 311.34 | 6 | 1 |
| 15 | 4C1 | 2.13 | 325.37 | 6 | 1 |
| 16 | 4C2 | 1.71 | 311.34 | 6 | 1 |
| 17 | 4C3 | 1.71 | 311.34 | 6 | 1 |
| 17 | 4C4 | 2.08 | 311.34 | 6 | 1 |
| 19 | 4C5 | 1.76 | 311.34 | 6 | 1 |
| 20 | 4C6 | 1.76 | 311.34 | 6 | 1 |
| 21 | 4C7 | 1.73 | 311.34 | 6 | 1 |

Various *in silico* tools such as ChemDraw, Molinspiration, Pre ADMET, Autodock vina, FT Site server, Discovery Studio visualiser etc were used in the designing of proposed analogs. All the proposed derivatives obeyed Lipinski rule of analysis and does not show any violations.

**Table 2: ADME prediction by Pre ADMET software.**

| Cpd Code | Human intestinal absorption | In Vitro CaCO-2 cell permeability | In vitro plasma protein binding |
|---|---|---|---|
| 2A1 | 95.79 | 24.60 | 70.80 |
| 2A2 | 95.66 | 37.54 | 78.31 |
| 2A3 | 95.76 | 19.25 | 72.29 |
| 2A4 | 95.76 | 24.51 | 50.65 |
| 2A5 | 95.77 | 28.46 | 73.95 |
| 2A6 | 95.77 | 21.46 | 66.28 |
| 2A7 | 95.75 | 21.45 | 72.89 |
| 4B1 | 98.40 | 22.99 | 100 |
| 4B2 | 97.96 | 22.41 | 100 |
| 4B3 | 98.45 | 23.97 | 100 |
| 4B4 | 98.40 | 22.47 | 100 |
| 4B5 | 98.40 | 22.47 | 100 |
| 4B6 | 98.42 | 22.45 | 100 |
| 4B7 | 98.43 | 22.45 | 100 |
| 4C1 | 98.40 | 21.96 | 100 |
| 4C2 | 98.40 | 21.68 | 100 |
| 4C3 | 98.40 | 2i.69 | 100 |
| 4C4 | 98.41 | 21.69 | 100 |
| 4C5 | 98.41 | 21.78 | 100 |
| 4C6 | 98.41 | 21.67 | 100 |
| 4C7 | 98.40 | 21.64 | 100 |

*In silico* molecular modification studies are one of the important preliminary steps in the rational designing of novel drugs. Data concerning toxicity, bioavailability and metabolism is necessary to determine the feasibility

and safety of the drug. Absorption, distribution, metabolism, excretion and toxicity (ADMET) properties play a very critical role in the bioavailability and duration of action of new drugs, thereby determining their clinical success. A careful study of ADMET properties at preclinical phase of drug design is extremely important since the majority of drug candidates fail clinical trials due to ADMET deficiencies.

A computational study of the proposed compounds were performed for prediction of ADMET properties. The absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of all the compounds were predicted using PreADMET software. Predicting human intestinal absorption (HIA%) of drugs is very important for identifying potential drug candidate. HIA% data are the sum of bioavailability and absorption evaluated from ratio of excretion or cumulative excretion in urine, bile and feces.[13] Caco-2 cell model have been recommended as a reliable *in-vitro* model for the prediction of oral drug absorption. Caco-2 cells, a well-differentiated intestinal cell line derived from human colorectal carcinoma, display many of the morphological and functional properties of the *in-vivo* intestinal epithelial cell barrier.[14] Degree of plasma protein binding (PPB%) of a drug influences on the drug's action, its disposition and efficacy. Therefore, the PPB% is an important pharmacokinetic factor and is determinant in the actual dosage regimen (frequency).[15] The analogs showed good intestinal absorption. Plasma protein binding was better for 2A series.

**Table 3: Toxicity prediction of analogs.**

| Compound code | TOXICITY | |
|---|---|---|
| | Mutagenicity | Carcinogenicity |
| 2A1 | *No risk* | *No risk* |
| 2A2 | *No Risk* | *No Risk* |
| 2A3 | *No Risk* | *No Risk* |
| 2A4 | *No Risk* | *No Risk* |
| 2A5 | *No Risk* | *No Risk* |
| 2A6 | *No Risk* | *No Risk* |
| 2A7 | *No Risk* | *No Risk* |
| 4B1 | *No Risk* | *No Risk* |
| 4B2 | *No Risk* | *No Risk* |
| 4B3 | *No Risk* | *No Risk* |
| 4B4 | *No Risk* | *No Risk* |
| 4B5 | *No Risk* | *No Risk* |
| 4B6 | *No Risk* | *No Risk* |
| 4B7 | *No Risk* | *No Risk* |
| 4C1 | *No Risk* | *No Risk* |
| 4C2 | *No Risk* | *No Risk* |
| 4C3 | *No Risk* | *No Risk* |
| 4C4 | *No Risk* | *No Risk* |
| 4C5 | *No Risk* | *No Risk* |
| 4C6 | *No Risk* | *No Risk* |
| 4C7 | *No Risk* | *No Risk* |

Currently many software and web servers can predict chemical toxicity before synthesis. Chemical carcinogenesis is of increasing importance in drug discovery for its serious effect on human health. The mechanism of carcinogenesis of chemicals can be due to genotoxicity, which are primarily caused by the mutagenicity of chemicals damaging DNA.[16] The proposed analogs does not show mutagenicity or carcinogenicity.

**Table 4: Binding interaction of piperidinyl coumarin derivatives.**

| Compound | Binding affinity | Compound | Binding affinity |
|---|---|---|---|
| 2A1 | -8.5 | 4B5 | -9.2 |
| 2A2 | -8.4 | 4B6 | -9.1 |
| 2A3 | -8. 1 | 4B7 | -9.0 |
| 2A4 | -8.5 | 4C1 | -8.7 |
| 2A5 | -8.6 | 4C2 | -8.6 |
| 2A6 | -8.4 | 4C3 | -8.4 |
| 2A7 | -8.2 | 4C4 | -8.6 |
| 4B1 | -8. 1 | 4C5 | -9.0 |
| 4B2 | -8.7 | 4C6 | -8.8 |
| 4B3 | -8.1 | 4C7 | -8.2 |
| 4B4 | -9.1 | Acarbose | -7.9 |

All the proposed derivatives show good binding affinity when compared with standard inhibitor acarbose and the results are tabulated in Table 4. 4B series shows more binding energy than other compounds and may be due to the nitrile group at 2nd position of piperidine. Figure 2 shows binding interaction of 4B6 with protein 3A4A and has hydrogen bond distance 2.60 Å with Arg A315. Figure 3 shows binding interaction of 2A7 with protein 3A4A and has hydrogen bond distance: 2.79 Å with Glu A 277.

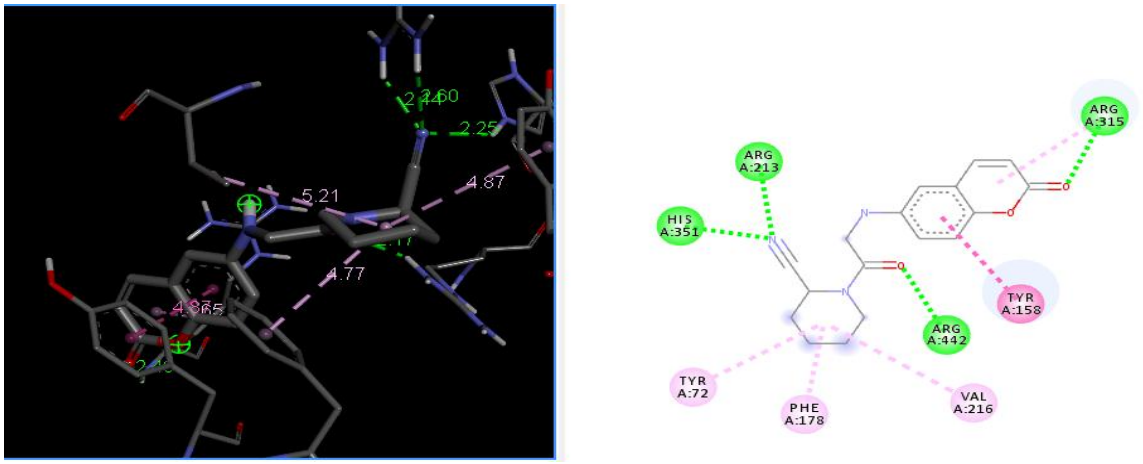


**Figure 2: Binding interaction of 4B6 with 3A4A.**

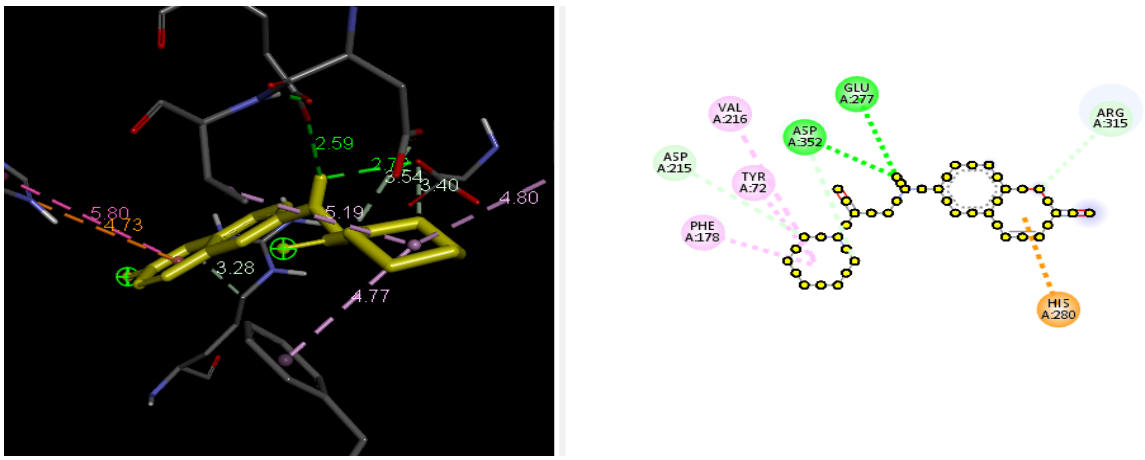


**Figure 3: Binding interaction of 2A7 with 3A4A.**

## CONCLUSION

α- glucosidase activity has been positively correlated to post-prandial blood glucose levels and has been identified as a viable target for inhibition and the development of therapeutics towards the treatment of diabetes and obesity. Inhibition of the α-glucosidase enzyme causes inhibition of glucose absorption. Molecular docking studies were carried out to identify their mode of binding, which revealed that further

chemical modifications on these molecules could have resulted in lead molecules with high degree of inhibitory activity and selectivity towards α-glucosidase enzyme.

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