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Proceeding Paper

Insilico Evaluation of Chrome-4-One Derivatives as a Potential α-Glucosidase Inhibitor: Molecular Docking and ADMET Profiling [†]

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Abstract

Diabetes is a chronic metabolic disorder characterized by persistently high blood glucose levels due to insulin malfunction, defective insulin secretion, or both. Chromen-4-one, known to have diverse biological activity, is a core structure found in many natural products, particularly in the flavonoid and isoflavonoid families. The study aims to explore the potential of Chrome-4-one derivatives as a potential antidiabetic agent through the α-glucosidase inhibition mechanism. The compounds were retrieved from the PubChem database, optimized, and prepared using ChemDraw 12.0, Spartan14, and UCSF Chimera. The post-docking analysis was done using BIOVIA Discovery Studio. Theoretical oral bioavailability and toxicity predictions were performed using ADMETlab3.0. Molecular docking of the compounds against the α-glucosidase enzyme (PDB ID: 3A4A) was carried out using AutoDock Vina. According to Lipinski's rule of five (5), all the ligands passed the oral bioavailability and are druggable. The binding score of all the ligands was better than the native ligand (−5.7 Kcal/mol) but slightly lower than that of Acarbose (−9.0 Kcal/mol), except for L7 (Myricetin), which equals the standard drug. The ligands revealed good interaction with the enzyme's active site residues. The most notable interactions were hydrogen bonding, van der Waals, Pi-anion, Pi-cation, Pi-Pi T-shape, Pi-Sigma, and carbon-hydrogen bond. The ligands interacted with the key catalytic residues: Asp352, Glu277, Glu411, Trp158, and Arg442, which are responsible for α-glucosidase inhibition. The result of the study suggests that the chrome-4-one derivatives have the potential to be utilized as a lead molecule for orally available α-glucosidase inhibitors.

Keywords: α-glucosidase; chromen-4-one; molecular docking

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1. Introduction

Diabetes represents a prevalent condition impacting millions worldwide, distinguished by elevated blood glucose levels resulting from insulin-related complications [1]. Diabetes classification based on the WHO identifies two main types [2]: type 1, caused by the destruction of pancreatic β-cells, resulting in the inability to produce insulin, and type 2, primarily due to insufficient insulin secretion or malfunction [3]. Studies revealed that long-term diabetes has been associated with various health complications, including cardiovascular disease, kidney dysfunction, and neuropathy [4]. The inhibition of α-glucosidase, an enzyme responsible for the hydrolysis of starch into simple sugars, serves as a recognized and effective approach to regulating blood glucose levels in the management of type 2 diabetes [5]. Chromones (4H-Chromen-4-ones) represent a class of heterocyclic compounds characterized by a benzo-γ-pyrone framework [6]. The naturally occurring benzopyrones possess diverse biological properties like antiallergic, anti-inflammatory, and antidiabetic [7]. This study aims to explore the potential of Chrome-4-one derivatives as an antidiabetic agent through the α-glucosidase inhibition mechanism.

2. Methods

2.1. Ligand Preparation

Chromen-4-one derivatives used in this research were queried from the PubChem database. The 2D structures were generated using ChemDraw Ultra version 12.0.2, and Spartan 14v 114 was used to convert the 2D structures to 3D structures. The ligands were optimized and saved as mol2 files.

2.2. Receptor Preparation

The crystal structure of yeast α-glucosidase (PDB: 3A4A) protein was downloaded from the Protein Data Bank (PDB, http://www.rcsb.org). The enzyme was prepared by removing all non-residues, followed by the addition of hydrogen atoms and Gasteiger charges to the amino acid residues, using UCSF Chimera version 1.17.3 [8].

2.3. Molecular Docking

The prepared 3D ligands and the receptor were converted to pdbqt by utilizing AutoDockTool version 1.5.6 [9]. The molecular docking of the ligands and target enzyme was carried out using Autodock Vina [10] with the aid of Cygwin64 terminal. The docking calculations were viewed using UCFS chimera version 1.17.3 [8] and were saved in pdb format. The saved pdb files were viewed using Discovery Studio Visualizer version 20.1.0 for receptor-ligand interactions.

2.4. Theoretical Oral Bioavailability

The oral bioavailability prediction was carried out using an online web server (ADMETlab 3.0).

3. Results and Discussion

The result of theoretical oral bioavailability in Table 2 showed that all the designed ligands passed Lipinski's rule of five, meaning they are all druggable. All the ligands have a good synthetic accessibility score (<6). The binding score of all the ligands was better than the native ligand (−5.7 Kcal/mol) but slightly lower than that of Acarbose (−9.0 Kcal/mol), except for L7 (Myricetin), which equals the standard drug. The ligands revealed good interaction with the enzyme's active site residues. The most significant interactions were hydrogen bonding, van der Waals, Pi-anion, Pi-cation, Pi-Pi T-shape, Pi-Sigma, and carbon-hydrogen bond. The ligands interacted with the key catalytic residues: Asp352, Glu277, Glu411, Trp158, and Arg442, which are responsible for α-glucosidase inhibition. The molecular docking studies revealed that chromen-4-one derivatives have a promising inhibitory activity. This is in agreement with the work of Kumara *et al*., (2025), which reveals that chromones have the potential as α-glucosidase inhibitors with good pharmacokinetic properties [2]. The result in Table 2 correlates with the binding affinity (Figure 1). L7 shows higher lipophilicity (LogP value) in Table 2, which correlates with the binding affinity (related to biological activity) of −9.0 Kcal/mol, which has the best affinity.

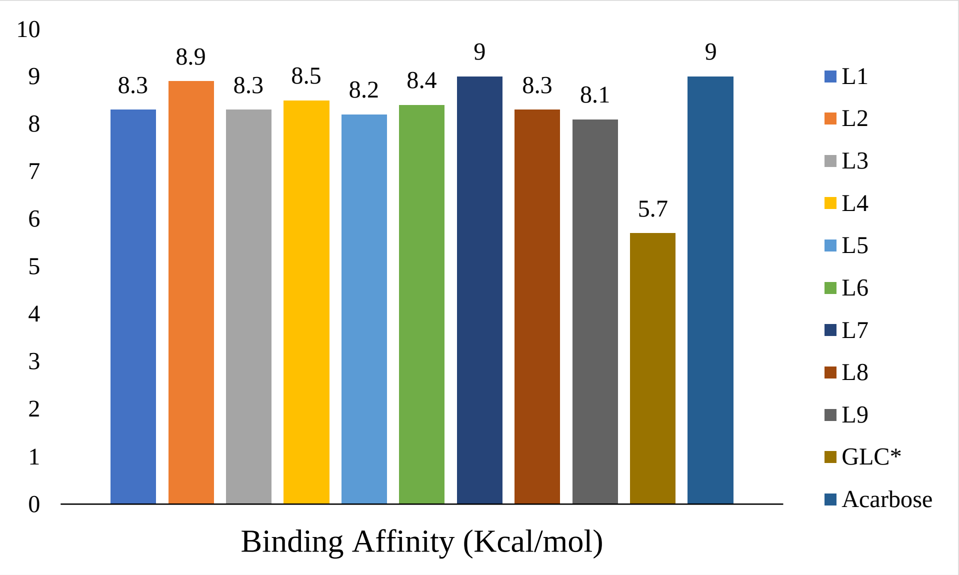


Figure 1. Binding affinities of the docked ligands (Chromen-4-one derivatives), native ligand (GLC*), and Acarbose (Standard drug).

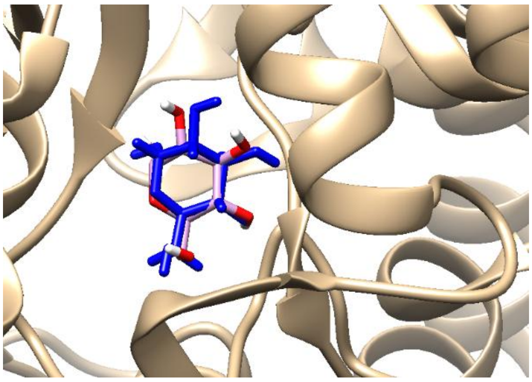


Figure 2. Crystal structure of α-glucosidase (blue) and re-docked ligand (pink-red edge) superimposed on the crystal structure for validation purposes.

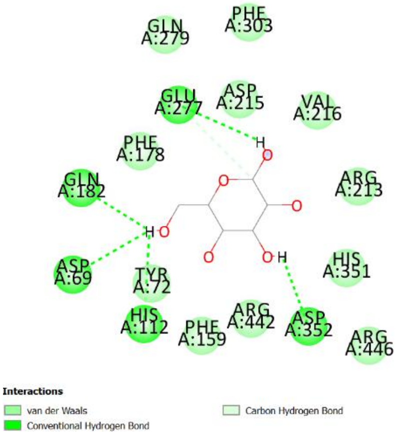


Figure 3. 2D pose interaction of native ligand at the active site of α-glucosidase.

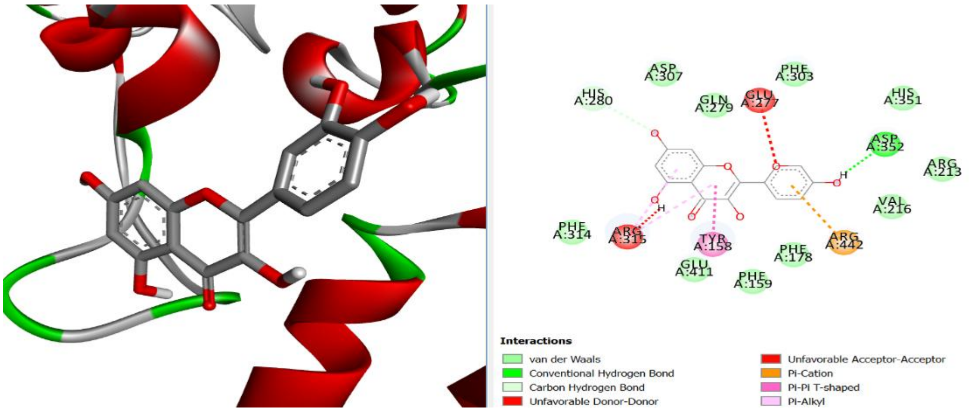


Figure 4. 3D and 2D pose interaction of L2 at the active site of *α*-glucosidase.

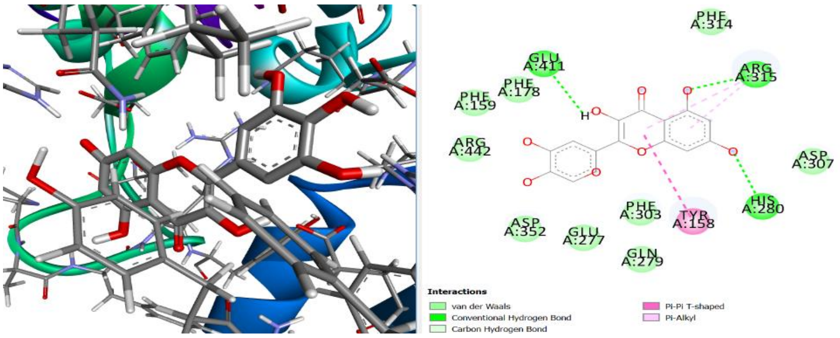


Figure 5. 3D and 2D pose interaction of L7 at the active site of *α*-glucosidase.

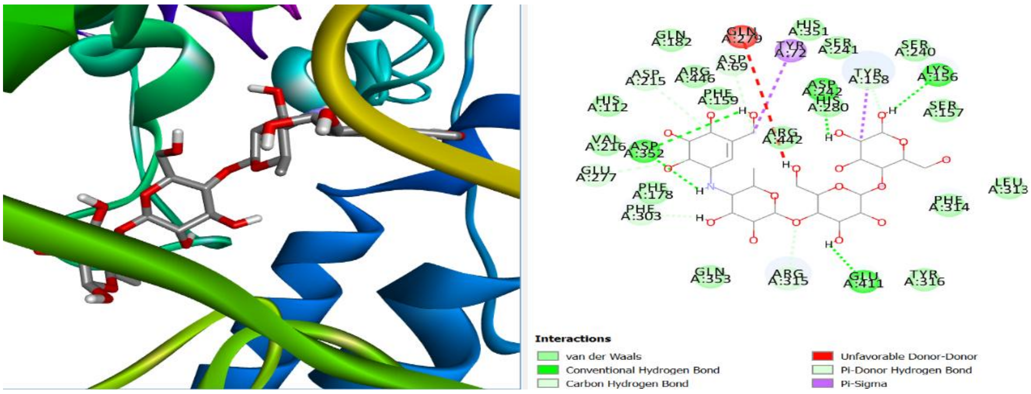
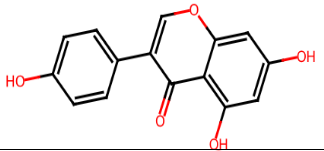
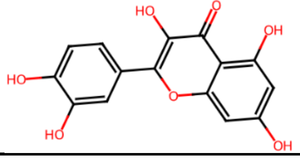


Figure 6. 3D and 2D pose interaction of Acarbose at the active site of *α*-glucosidase.

Table 1. Common Name, PubChem ID, IUPAC Name, Chemical Structure, and SMILES of the selected Chrome-4-one Derivatives.

Common Name	Code	PubChem ID	IUPAC Name	Chemical Structure	SMILES
Genistein	L1	5280961	5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one		C1=CC(=CC=C1C2=COC3=CC(=CC(=C3C2=O)O)O)O
Quercetin	L2	5280343	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one		C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O

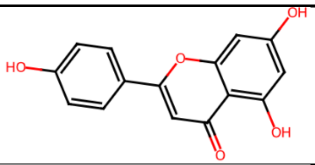
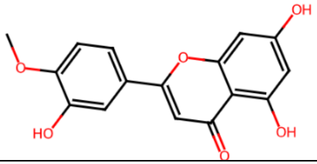
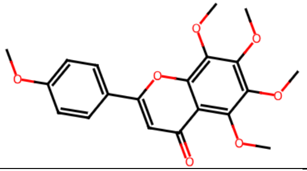
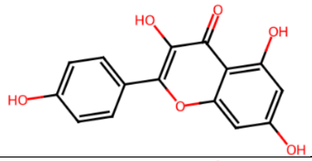
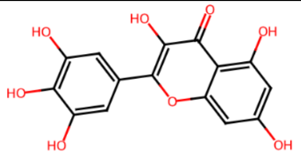
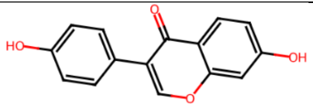
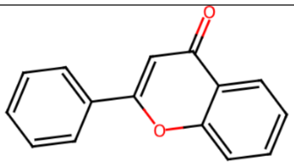
Apigenin	L3	5280443	5,7-dihydroxy-2-(4-hydroxyphenyl)chromen-4-one		C1=CC(=CC=C1C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O
Diosmetin	L4	5281612	5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)chromen-4-one		COC1=C(C=C(C=C1)C2=CC(=O)C3=C(C=C(C=C3O2)O)O)O
Tangeretin	L5	68077	5,6,7,8-tetramethoxy-2-(4-methoxyphenyl)chromen-4-one		COC1=CC=C(C=C1)C2=CC(=O)C3=C(O2)C(=C(C(=C3OC)OC)OC)OC
kaempferol	L6	5280863	3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one		C1=CC(=CC=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O
Myricetin	L7	5281672	3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one		C1=C(C=C(C(=C1O)O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O
Diadzein	L8	5281708	7-hydroxy-3-(4-hydroxyphenyl)chromen-4-one		C1=CC(=CC=C1C2=COC3=C(C2=O)C=CC(=C3)O)O
Flavone	L9	10680	2-phenylchromen-4-one		C1=CC=C(C=C1)C2=CC(=O)C3=CC=CC=C3O2

Table 2. Insilico theoretical oral bioavailability of the designed chromen-4-one derivatives.

S/No	Code	Mw (g/mol)	GI Absorption	LogP	n-HA	n-HD	SA Score	Lipinski's Violation	Inference
1	L1	270	High	2.07	5	3	2.0	0	Pass
2	L2	302	High	1.45	7	5	2.0	0	Pass
3	L3	270	High	2.98	5	3	2.0	0	Pass
4	L4	300	High	2.63	6	3	2.0	0	Pass
5	L5	372	High	2.45	7	0	2.0	0	Pass
6	L6	286	High	1.97	6	4	2.0	0	Pass
7	L7	318	High	1.12	8	6	2.0	1	Pass
8	L8	254	High	2.22	4	2	2.0	0	Pass
9	L9	222	High	3.80	2	0	2.0	0	Pass

Mw: Molecular weight; GI: Gastrointestinal; n-HA: Number of hydrogen bond acceptor; n-HD: Number of hydrogen bond donor; SA: Synthetic Accessibility.

4. Conclusions

The ligand interacts with amino acid residues at the enzyme's active site, which is responsible for α-glucosidase inhibition. This suggests that the chromen-4-one derivatives have the potential to be used as α-glucosidase inhibitors.

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