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In Silico Studies of Substituted α, β Unsaturated Ketones against α-Glucosidase and α-Amylase

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ABSTRACT

The molecular docking studies of novel chalcone derivatives with electron-withdrawing substituents (Cl, Br, F, NO2) against enzymes alpha-glucosidase (PDB code: 3WY1) and alpha-amylase (PDB code: 4W93) shown that all the 12 designed compounds have highest antidiabetic activity towards the enzyme alpha-glucosidase when compared to amylase. The compound with the free energy of binding -7.38 kcal/mol was considered as the lead/active molecule as it has the least binding energy and lowest toxicity as that of standard.

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INTRODUCTION

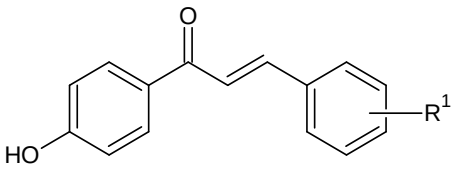
Diabetes mellitus [DM] is unshakingly increasing over the last few decades. In India 1 out of 11 people are formally diagnosed with either of the two cases of diabetes mellitus. It is estimated that 17% of the world's population with diabetes is from India. Diabetes mellitus is a group of metabolic disorders that result in increased blood sugar levels. It has many subclassifications including Type 1 diabetes mellitus (insulin-dependent or juvenile-onset diabetes mellitus) resulting from defective insulin secretion, Type 2 diabetes mellitus (non-insulin-dependent or adult-onset diabetes mellitus) where the body develops insulin resistance, and gestational diabetes which occurs during pregnancy.[1]

Diabetes mellitus can be controlled through a proper diet with regular exercise. Oral medications or insulin is the main treatment. Medication for Type 2 diabetes includes Metformin, Sulfonylureas, Thiazolidinediones, Dipeptidyl-peptidase 4 (DPP4) inhibitors, and insulin therapy. Other than these varieties of biomolecules are being investigated for their potential against diabetes mellitus. Chalcones (1,3-diphenyl-2-propen-1-one) are a group of natural precursors of flavonoids with activities including antibacterial, anti-inflammatory, antileishmanial, antidiabetic, and enzyme inhibitory action. Alpha-glucosidase is an enzyme that helps in digestion of starch and glucose. Alpha-Amylase is an enzyme that causes the degradation of starch molecules and hydrolyses them into small-chain dextrins. Inhibition of these enzymes plays a role in diabetes. Inhibition of the former inhibits the absorption of carbohydrates, while the latter prevents the breakdown of carbohydrates. Various lead compounds are being investigated to confirm their therapeutic usefulness. Molecular docking helps in predicting the predominant binding of a ligand with a three-dimensional protein structure and to determine the binding energy. In recent decades researchers' new docking software has been introduced into the world of chemistry, which has hastened up the process of new drug discovery and development.[2][3]

MATERIALS AND METHODS

Preparation of the ligands

The preparation of ligands and their energy minimization were done by using the software ACD/Chemsketch and Chemdraw ultra 8.0 respectively. The 3D structures of the designed molecules hence obtained were saved in PDB format and converted ligand from pdb to pdbqt format by Auto Dock.[4][5]



R_1: NO_2, Br, Cl, F

Fig 01: Substituted chalcone

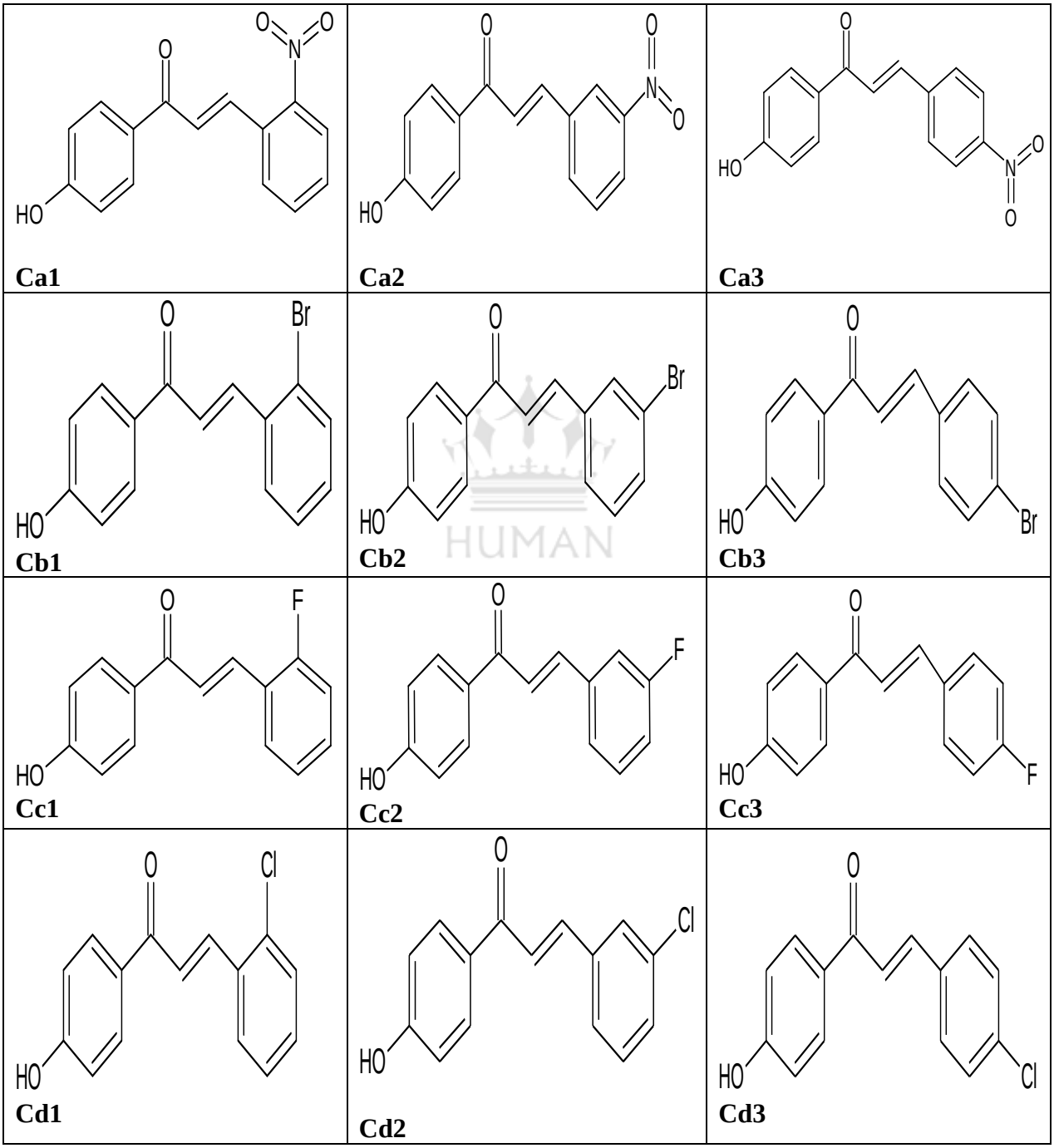


Figure 02: List of Designed Compounds

Validation of the ligands

Ligand validation was performed by analyzing the Lipinski rule of five, and all the designed ligands obey the rule. The pharmacokinetics and drug-likeness were analyzed by the SWISS ADME web tool and the related acute toxicities and LD_{50} by PRO TOX-II.

Preparation of macromolecules

The macromolecular targets for the particular ligands have been downloaded from RCSB PDB. The crystal structure of alpha-glucosidase (PDB ID: 3WY1) chain A and Human pancreatic alpha-amylase (PDB ID: 4W93) were downloaded and made suitable for docking by removing the ligand bound with the targets, water molecules, and hetero atoms using Biovia Discovery Studio.[6]

Validation of macromolecule

The Ramachandran plot is used to validate the macromolecule-based torsion angles.[7]

Molecular docking

The docking of the designed ligand molecules was done by using Auto Dock Vina in PyRx 0.8 software. The flexible docking was performed and the lead molecule was selected based on the least binding energy. The ligand-receptor interactions were visualized in the Biovia Discovery Studio visualizer.[8]

RESULT AND DISCUSSION

LIPINSKI RULE

Table no 01. Lipinski rule analysis of chalcone derivatives

S.NO	Compound code	M.W	HBD	HBA	Log P	MR
01	Ca1	269.00	1	4	2.826	72.457
02	Ca2	269.00	1	4	3.196	74.567
03	Ca3	269.00	1	4	2.706	74.382
04	Cb1	302.00	1	2	4.172	76.712
05	Cb2	302.00	1	2	4.050	75.613
06	Cb3	302.00	1	2	4.050	75.613
07	Cc1	242.00	1	2	3.427	67.871
08	Cc2	242.00	1	2	3.427	67.871
09	Cc3	242.00	1	2	3.427	67.871
10	Cd1	258.500	1	2	3.941	72.923
11	Cd2	258.500	1	2	3.169	69.992
12	Cd3	258.500	1	2	3.941	72.923

MW: Molecular weight, HBD: Hydrogen Bond Donor, HBA: Hydrogen Bond Acceptor, MR: Molar Refractivity

ORAL TOXICITY PREDICTION BY PROTOX II

All the compounds were predicted for their toxicities. The Oral LD50 values of the compounds range between 1048 to 3000 mg/kg. All the compounds come under toxicity classes IV and V.

Table no 02. Toxicological Insilico drug profile

SL NO	COMPOUNDS	PREDICTED LD50 (mg/kg)	H	C	I	M	CT
1	Ca1	3000	+	-	-	-	-
2	Ca2	3000	+	-	+	+	-
3	Ca3	3000	+	-	+	+	+
4	Cb1	1048	-	-	+	-	-
5	Cb2	1048	+	-	+	-	+
6	Cb3	1048	+	-	+	-	+
7	Cc1	1048	+	-	-	-	-
8	Cc2	1048	+	-	+	-	+
9	Cc3	1048	+	-	+	+	+
10	Cd1	1048	-	-	+	-	-
11	Cd2	1048	-	-	+	-	-
12	Cd3	1048	-	-	+	-	-

H: Hepatotoxicity, C: Carcinogenicity, I: Immunotoxicity, M: Mutagenicity,

CT: Cytotoxicity.

SWISS ADME

Table no 03. ADME properties and drug-likeness of chalcone derivates

S.NO	Compound Code	Log P	Pharmacokinetics		Drug likeness		Lead likeness
			GI absorption	BBB Permeant	Ghose Rule	Veber rule	
1	Ca1	1.69	High	No	Pass	Pass	Yes
2	Ca2	2.03	High	No	Pass	Pass	Yes
3	Ca3	1.79	High	No	Pass	Pass	Yes
4	Cb1	2.39	High	Yes	Pass	Pass	No
5	Cb2	2.57	High	Yes	Pass	Pass	No
6	Cb3	2.52	High	Yes	Pass	Pass	Yes
7	Cc1	2.26	High	Yes	Pass	Pass	No
8	Cc2	2.33	High	Yes	Pass	Pass	No
9	Cc3	2.27	High	Yes	Pass	Pass	No
10	Cd1	2.39	High	Yes	Pass	Pass	No
11	Cd2	2.47	High	Yes	Pass	Pass	No
12	Cd3	2.49	High	Yes	Pass	Pass	Yes

Docking results for Antidiabetic activity

Table no 04. Docking results with enzyme 3WY1(α-glucosidase) and 4W93(α-Amylase)

	3WY1		4W93
S.NO	Compound Code	Binding Energy (kcal/mol)	Binding Energy (kcal/mol)
01	Ca1	-7.77	-7.27
02	Ca2	-8.41	-7.12
03	Ca3	-8.27	-7.16
04	Cb1	-6.65	-6.70
05	Cb2	-8.47	-5.77
06	Cb3	-7.50	-6.52
07	Cc1	-6.22	-5.52
08	Cc2	-6.43	-6.40
09	Cc3	-6.38	-5.93
10	Cd1	-6.39	-6.74
11	Cd2	-7.38	-6.32
12	Cd3	-6.95	-6.67

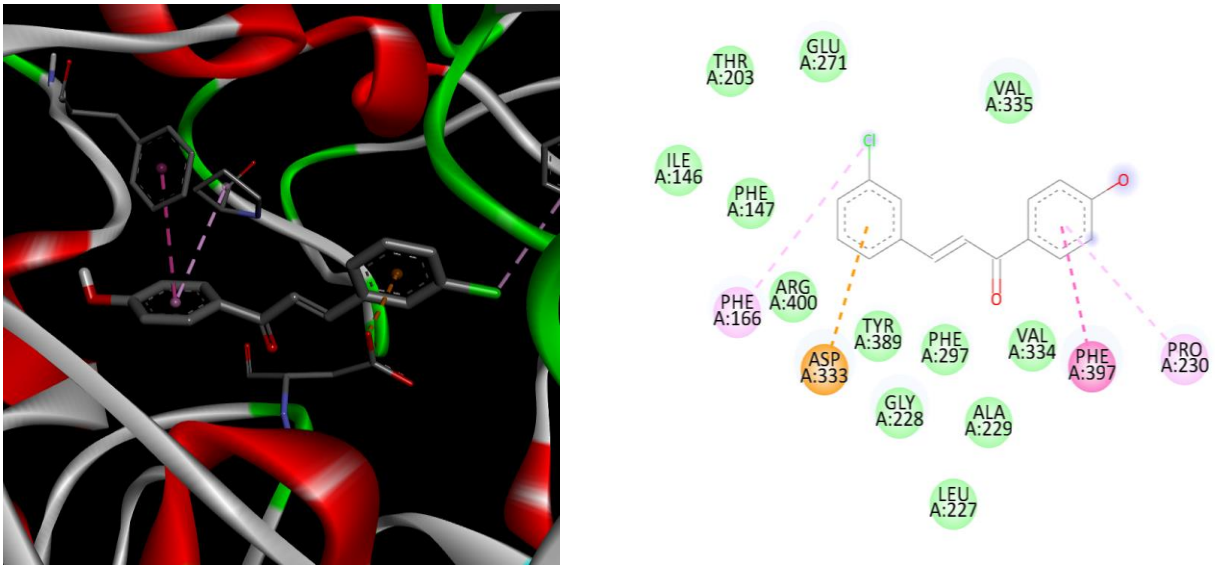


Fig 03: Binding of Cd2 with the crystal structure of alpha-glucosidase (3WY1)

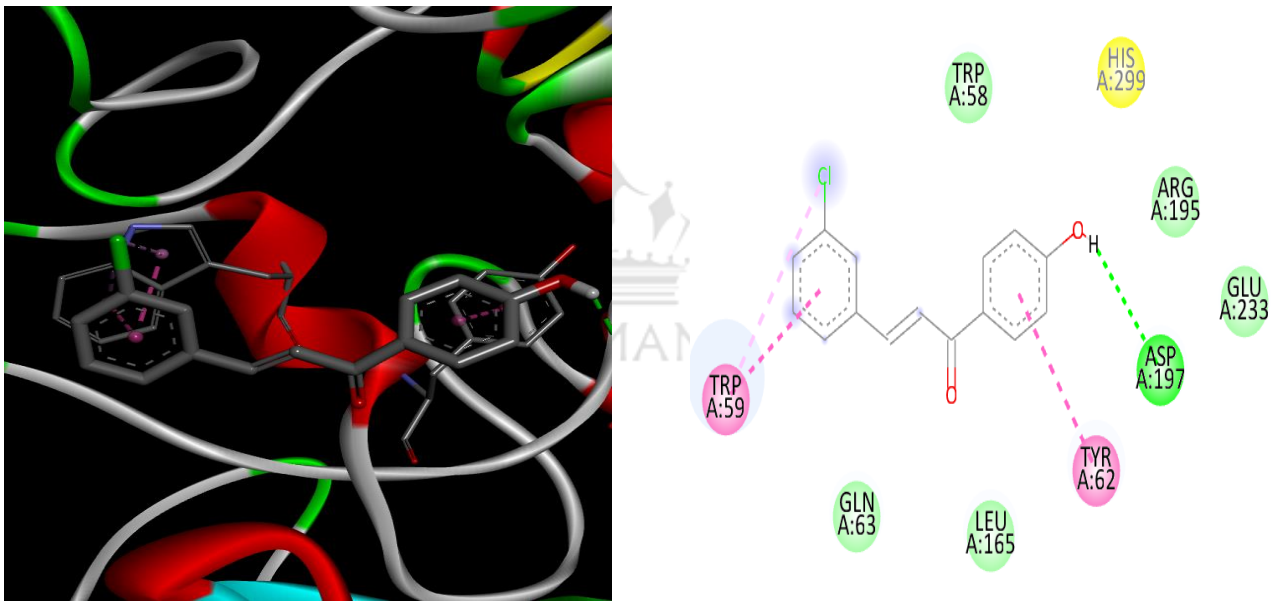


Fig 04: Binding of Cd2 with human pancreatic alpha-amylase (4W93)

CONCLUSION

The molecular docking process is where the binding of a ligand molecule with a target or macromolecule and the predominant binding with the best fit binding energy can be calculated. In this article, the binding energies of various chalcone derivatives with electron-withdrawing groups were compared against enzymes alpha glucosidase and alpha amylase which are involved in the inhibition of the absorption of carbohydrates and prevention of the breakdown of carbohydrates respectively. The binding energy of ligand macromolecule

complex containing electron withdrawing groups like halogens (Chlorine, Fluorine, Bromine) and Nitro groups were compared on ortho, meta, and para positions of Chalcone. The compound Cd2 with the free energy of binding -7.38 kcal/mol was considered as the lead/active molecule as it has the least binding energy and lowest toxicity.

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