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3D-QSAR Analysis and Molecular Docking Studies on 3-Arylcoumarin Derivatives as Potential α- Glucosidase Inhibitors

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Abstract

α-glucosidase inhibitors (AGI) are the structural moieties that are found to be of utmost importance in the fields of pharmacy and which involves delaying the absorption of carbohydrates by blocking of alpha-glucosidase enzyme in the brush border of small intestine and plays an important role in constituting a promising therapeutic class against diabetic disease (Type II). In this study, the three-dimensional quantitative structure-activity relationship (3D-QSAR) and docking models were developed using Fujito-Ban analysis in VALSTAT software and Molegro Virtual Docker 6.0. The theoretical models were generated from 29 3-arylcoumarin inhibitors of α-glucosidase. A robust QSAR model with good prediction in internal and external verification was constructed, where r2 and q2 were 0.821 and 0.646 respectively. The QSAR study suggested that substitution of group at R1 position on 3-arylcoumarin ring with electron withdrawing group favourable for the anti-diabetic activity. Molecular docking studies were performed with the coordinates of the α-glucosidase crystal structure (PDB ID: 3WY2), as the results we found that the ligands would form the hydrogen bond interactions with Asp 202, Arg 400 and Glu 271 of the protein receptor generally. For better α–glucosidase inhibitory activity, dipole seems to give good results. These results of the QSAR analysis and molecular docking provided some useful information for designing new and effective α-glucosidase inhibitors in significance of stability and the binding interaction between ligand the receptor site by considering the validation parameters.

Keywords: Quantitative Structure-Activity Relationships (QSAR) • α-Glucosidase inhibitors • 3-arylcoumarin • Molecular docking • Drug design

Introduction

Diabetes is a disease that occurs in the case when your blood glucose, also called blood sugar, is too high. Diabetes is distinguished by chronic hyperglycemia (High blood glucose level) and the occurrence of micro-angiopathic problems such as neuropathy, nephropathy along with retinopathy and cardiovascular diseases [1]. Executing lifestyle changes can be a substantial challenge for patients with diabetes [2]. Besides, diabetes is supposed to become the seventh leading cause of death worldwide in next decade based on World Health Organization (WHO) report [3]. Diabetes mellitus defined as it is a metabolic state where no proper metabolism of carbohydrates, proteins, fats and lipids occurs due to disturbances in hormones [4]. Diabetes mellitus (DM) being the most usual endocrine disorder is a serious global health crisis [5,6]. There are two main regulatory components that govern glucose homeostasis: insulin secretion and insulin resistance.

Related studies have shown that α-glucosidase inhibitors (AGI) competitively inhibits the enzyme alpha glucosidase in the brush borders of the small intestine, which delays absorption of carbohydrates (absorbed in mid and distal portions of the small intestine instead). The outcome is the prevention of glucose production, thereby reducing postprandial hyperglycemia [7]. All recognized a-glucosidase inhibitors are excreted unchanged in the feces, obviating metabolic drug interactions [8,9]. AGIs can reduce body weight by 1-3 kg or help maintain weight if merged with insulinotropic anti-diabetic drugs [10]. 3-arylcoumarin is a category of naturally-occurring compounds act as anti-diabetic agent, the basic skeleton of which is arylbenzopyranones. It mainly includes 3-arylcoumarin and 4-arylcoumarin [11].

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The drug design implies the design of molecules that are complementary in shape and charge to the bio-molecular target with which they interact and therefore will bind to it [12,13]. Especially quantitative structure-activity relationship (QSAR) can be used to develop highly potent or less virulent compounds in the series, and it is generally considered to be the chief function of QSAR. Moreover, the correlation can be utilize to give some demonstration of the mechanism involved in the biological activity. In 3D QSAR, the correlation between 3D steric and electrostatic fields and biologically activity draws attention [14]. In this manuscript, we construct molecule based three-dimensional (3D)-QSAR models studies using 29 3-arylcoumarin derivatives to obtain key groups of α-glucosidase inhibitors, which was performed in the Fujito-Ban module of VALSTAT software. 3D-QSAR model suggested that the electron-withdrawing group and electrophilicity of inhibitors affected the α-glucosidase activity. To verify the conclusion of 3D-QSAR model, the molecular docking was carried out by Molegro Virtual Docker [15]. The main objective of molecular docking is to attain ligand-receptor complex with optimized conformation and with the intention of possessing less binding free energy [16].

Material and Methods

Data set

Twenty nine 3-arylcoumarin derivatives (Figure 1) of α-glucosidase inhibitors (Table 1) were selected from the published work and used in our study [11]. Inhibitory potency of the compound was reported as IC_{50} (μM) values varying from 1.37 to 280.38 μM and then were converted to pIC_{50} using the formula pIC_{50} = -log IC_{50}. For 3D-QSAR, the original data set was randomly divided into training and test set comprising of 19 and 10 molecules for two models and 20 and 9 molecules for 1 model, respectively. The training set was used to build the 3D-QSAR model, and the test set was employ to verify the predictive ability of the model. All molecules have a common structural skeleton.

Construction of 3D-QSAR model

For sketching of structures of molecules ChemDraw Ultra 8.0 was used. The 2D structures were converted into 3D structures using module of the program (Chem3D Ultra 8.0). Then energy minimization of 3D structures

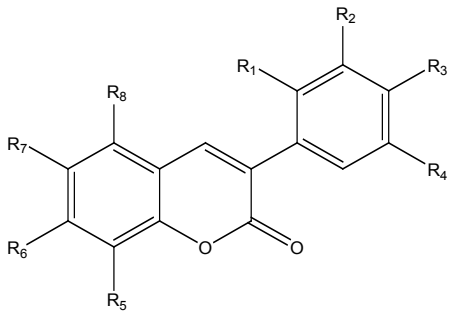

Figure 1. Structure of 3-arylcoumarin.

Table 1. Structures and bio-activities of 29 α-glucosidase inhibitors.

Comp.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	IC_{50} (μM)	pIC_{50}
1	H	H	H	H	H	OH	H	H	25.67	4.590
2	H	H	H	H	OH	H	H	H	280.38	3.552
3	H	H	OH	H	H	H	H	H	60.88	4.215
4	H	H	CH_3	H	OH	H	H	H	69.6	4.157
5	H	H	CH_3	H	H	OH	H	H	118.29	3.927
6	CH_3	H	H	H	H	OH	H	H	16.36	4.785
7	H	H	OH	H	H	OH	H	H	19.91	4.700
8	H	H	H	H	H	OH	H	OH	13.46	4.870
9	H	H	OH	H	OH	H	H	H	212.72	3.672
10	H	H	H	H	OH	OH	H	H	29.05	4.536
11	OH	H	H	H	H	OH	H	H	10.16	4.993
12	H	H	OH	H	H	H	OH	H	11.54	4.937
13	H	H	F	H	H	OH	H	H	86.91	4.060
14	H	H	CH_3	H	OH	OH	H	H	25.48	4.593
15	H	H	OCH_3	H	H	OH	H	H	27.42	4.561
16	H	H	CH_3	H	H	OH	H	OH	11.49	4.939
17	H	H	OH	H	H	H	OCH_3	H	70.26	4.153
18	H	H	OH	H	H	OH	H	OH	1.37	5.863
19	H	OH	OH	H	H	OH	H	H	29.89	4.524
20	H	H	OH	H	H	OH	H	H	19.04	4.720
21	H	H	F	H	H	OH	H	OH	19.08	4.719
22	H	H	OCH_3	H	OH	OH	H	H	18.8	4.725
23	H	H	OCH_3	H	H	OH	H	OH	10.81	4.966
24	H	OH	OH	H	OH	OH	H	H	247.34	3.606
25	H	OCH_3	OCH_3	H	OH	H	H	H	20.23	4.694
26	H	OCH_3	OCH_3	H	H	H	OH	H	13.09	4.883
27	H	H	OH	H	H	Et_2N	H	H	13.43	4.871
28	H	OCH_3	OCH_3	H	H	OH	H	OH	39.08	4.408
29	H	H	Br	H	OH	OH	H	H	35.71	4.447

was done using MOPAC (Molecular Orbital Package) until the value attained by RMS gradient will be 0.001 kcal/mol Å.

Then compute the properties, calculate the total energy and generate the QSAR model by correlating the pIC_{50} with some recognized properties. Various statistical methods were used for QSAR model building but here use of Multiple Linear Regression (MLR) method was done. We get statistical values lie r^2, q^2, etc.. for this compounds, which is then use to judge the quality of model.

Descriptors generation

The thermodynamic, steric and electronic parameters are shown in Table 2 were calculated for QSAR analysis [17]. Free energy change during drug receptor complex formation was described by thermodynamic parameters. Steric features were used to quantify spatial parameters of drug molecules required for its complementary fit with the receptor. Weak non-covalent bonding between drug molecules and the receptor were described by electronic parameters.

Statistical analysis

Firstly, the descriptors were recognized for constant or near constant values and those detected were discarded from original data matrix. With the activity set and with each other, correlation of descriptors was setup. Among the collinear parameters detected, the one which is more specifically correlated with activity was kept and the remaining was excluded. Using simple linear regression analysis by VALSTAT software, various descriptors to biological activity were studied and, due to interference of collinearity among descriptors, individual amalgamation of descriptors were subjected to sequential and stepwise multiple regression analysis. Statistical quality of models were assessed by using the parameters: number of compounds (n), correlation coefficient (r), squared correlation coefficient (r^2), standard error of estimate (s), variance, Fischer F-test for quality of fit.

In order to validate the derived QSAR models, the leave-one-out (LOO) method was used. Once the model was determined, each compound was eliminated from the remaining compounds and the eliminated compound was predicted from this model. The same procedure was repeated after elimination of next compound, until all the compounds had been eliminated once. The predictability of each model was assessed by using cross validated correlation coefficient (q^2).

Molecular docking

To investigate the interaction between 3-arylcoumarin derivatives and key parts of the α-glucosidase, molecular docking study was performed with Molegro virtual docker 6.0. For sketching of structures of molecules ChemDraw Ultra 8.0 was used. The 2D structures were converted into 3D structures using module of the program (Chem3D Ultra 8.0). Then energy minimization of 3D structures was done using MOPAC (Molecular Orbital Package) until the value attained by RMS gradient will be 0.001 kcal/mol Å. The coordinates of the α-glucosidase crystal structure (PDB ID: 3WY2) at the resolution of 1.47 Å were acquired from the Protein Data Bank and

Table 2. The various descriptors calculated using chem.-office software.

Steric descriptors	Thermodynamic descriptors	Electronic descriptors
Connolly accessible area (SAS)	Critical temperature (Tc)	Dipole (DPL)
Connolly molecular area (MS)	Ideal gas thermal capacity (Cp)	Electronic energy (ElcE)
Connolly solvent excluded volume (CSEV)	Critical pressure (Cp)	Highest occupied molecular orbital energy (HOMO)
Principal moment of inertia-X component (Pmix)	Henry's law constant (H)	Lowest unoccupied molecular orbital energy (LUMO)
Principal moment of inertia-Y component (Pmiy)	Bend energy (Eb)	Repulsion energy (NRE)
Principal moment of inertia-Z component (Pmiz)	Heat of formation (Hf)	VDW-1,4-Energy (E14)
Molar refractivity (MR)	Total energy (Et)	Non-1,4-VDW Energy (Ev)
Ovality (Oval)	Partition coefficient (PC)	Dipole length (DPLL)
Balaban index (BIndx)	Critical volume (Vc)	Total energy (TotE)
Cluster count (ClsC)	Dipole-dipole energy (Ed)	
Diameter (Diam)	Log P	
Molecular topological index (TIndx)		
Sum of valence degrees (SVDe)		
Total valence connectivity (TVCon)		

prepared with Protein Preparation Wizard in Molegro Virtual Docker 6.0 software [18]. During the preparation of protein, all other water molecules and co-factors were deleted except the water molecules which were near to binding domain.

Many a times PDB files also have missing or poor assignment of explicit hydrogen's and no accommodation of bond order information in PDB file format. Set assign all below to always. Warning (if any) must be removed and rectified. Surface was created and cavities were detected and selection of the cavity of largest volume. As the PDB was imported, in the same manner all the molecules from the series are imported which were saved into .mol format. Docking must be carried out as mentioned in 'Docking Wizard' option. Thus the docking of molecules was done. The output poses were evaluated by scoring functions, including Mol-dock score, Re-rank score and H-bond score. Generally, the higher the Mol-dock score, the better the selectivity of the resulted pose.

Results

The correlation between the different physicochemical descriptors as independent variable and the negative log of the observed activity as dependent variable was examines using VALSTAT while determining the statistically significant relationships to study the selectivity requisites among these compounds. The inter-correlation between all the descriptors was also determined and good orthogonality was ensured during quantitative model building. Some of the statistically significant models are discussed below.

Model 1: BA = [9.87675 (± 3.5559)] -DPL [0.190832 (± 0.127166)] + LUMO [2.38031 (± 1.72422)] -Ev [0.00233565 (± 0.00191963)]

n=19, r=0.886, r^2=0.785, std=0.335, F=18.256

Model 2: BA = [1.51912 (± 2.55024)] + LogP [0.229416 (± 0.337251)] + MS [0.0138723 (± 0.0115592)] -DPL [0.177714 (± 0.135981)]

n=19, r=0.894, r^2=0.801, std=0.269, F=20.125

Model 3: BA = [-1.37524 (± 5.61273)] + MS [0.0270713 (± 0.0210838)]-DPL [0.263521 (± 0.158952)] -Homo [0.387891 (± 0.506097)] -Mass [0.00746546 (± 0.0135831)]

n=20, r=0.906, r^2=0.821, std=0.0901, F=20.639, q^2=0.646

Discussion

Interpretation of descriptors

Model 1 explains only 78.5% variance in the α-glucosidase inhibitor binding activity. It shows that descriptor Dipole (DPL) and non-1,4 van der Waals energy (Ev) contribute negatively and lowest unoccupied molecular orbital (LUMO) contribute positively towards α-glucosidase inhibitor binding activity. It is not a very good significant equation therefore new model required having good explained variance.

Model 2 explains 80.1% variance in the α-glucosidase inhibitor binding activity. It shows that descriptor Log P and Connolly molecular area (MS) contribute positively and dipole (DPL) contribute negatively towards αglucosidase inhibitor binding activity. It is not also a very good significant equation therefore new model required having good explained variance.

Model 3 explains 82.1% variance in the α-glucosidase inhibitor binding activity. Model 3 have low standard error (0.0901) shows the relative good fitness of the model. It has the characters of large F value (20.639), r^2 and q^2 values close to 0.9. Model-3 is reliable and highly predictive and it was proved by internal and external validation. It shows that descriptor Connolly molecular area (MS) contribute positively while dipole (DPL), highest occupied molecular orbital (HOMO), and exact mass (Mass) contribute negatively towards α-glucosidase inhibitor binding activity. The DPL is the crucial indicator of molecular reactivity and properties. The negative contribution of dipole (DPL) indicates its low value favor the activity. The significance of DPL indicates, the high electronegativity of the compound, and there by holding electrons tightly to its orbital, would help them to increase biological activity. Highest occupied molecular orbital (HOMO), an electronic parameter, which is negatively correlated, indicates that electrophilicity or electron withdrawing group on the compound would increase the binding affinity. Negative value of mass indicates that, with increase in the exact mass of the compound, biological activity decreases.

The Figure 2 shows plot of observed and calculated biological activity for training set molecules (Model 3) and Figure 3 shows plot of observed and predicted biological activity for same set (Model 3).

Statistical analysis of descriptors

The inter-correlation matrix of descriptors of QSAR equation is given in Table 3, the predictor variables with p value >0.05 were eliminated while deriving the QSAR models in order to ensure their statistical reliability.

Molecular docking analysis

To evaluate and validate the docking reliability, crystal structure of protein (3WY2) with the cognate ligand was re-docked. As reference ligand, the cognate ligand was taken out of its protein-ligand complex (3WY2) and re-docked back into its binding site. As shown in Figure 4, it can be seen that the re-docked ligand and the reference ligand are almost completely superimposed together. Both of them are having basically similar rotational tendency. The result shows that the docking method is rational and reliable.

Figure 5 represents the dock result of the re-docked ligand. As can be seen from Figure 5, the key residue Arg 200, Arg 400, Asp 62, Asp 202, Asp 333, Glu 271 and His 332 in chain interact with the inhibitor by hydrogen bond.

Considering the training molecules as the ligands and 3WY2 as the receptor, 195 output poses were obtained. The higher the Mol-dock-score, the better the selectivity of the output poses. The best output pose of each molecule with good Mol-dock score and H-score was selected. Compound

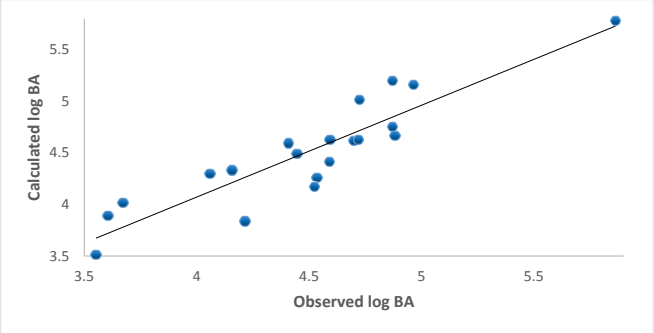

Figure 2. Discrete plot of training between *observed* and calculated biological activity by leave-one-out-validation values (Model 3).

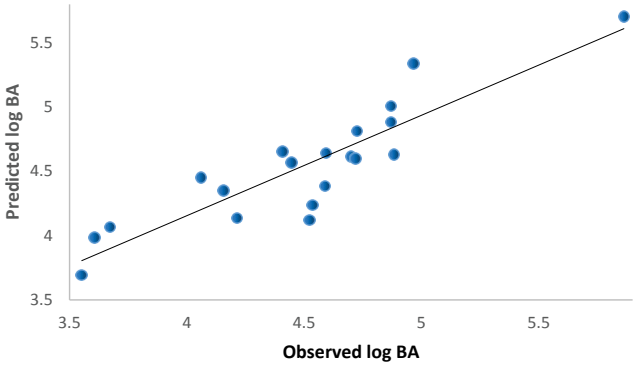

Figure 3. Discrete plot of training between *observed* and *predicted* biological activity by leave-one-out-validation values (Model 3).

27 shows higher Mol-dock score (-132.86) but it interacts less with protein as compared to compounds 16 and 18 with Mol-dock score of -113.09 and -112.06, respectively. Therefore, the pose of molecules 16 and 18 were choosing to explain the binding mode between the protein receptor and inhibitors, and the docking results are shown in Figures 6A and 6B, respectively. As can be seen from Figure 6A, the molecule forms hydrogen-bonding interactions with Asp 62, Asp 202, Arg 400, His 332, Glu 271 of the protein receptor. Meanwhile, in Figure 6B, we find hydrogen-bonding interactions at the active sites, including Arg 400, Asp 202, Asp 333 and Glu 271 of the protein receptor.

Molecule 26 is the most inactive compound and shows hydrogen-bonding interaction with Glu 271 of the protein receptor as shown in Figure 7. The results indicate that the ligands would form the hydrogen-bonding interactions with Asp 202, Arg 400 and Glu 271 of the protein receptor generally.

Table 3. Pearson correlation matrix of the descriptors used in all models.

Parameters	BA	DPL	LUMO	Ev	LogP	MS	HOMO	MASS
BA	1.000							
DPL	0.534	1.000						
LUMO	0.129	0.255	1.000					
Ev	0.027	0.177	0.186	1.000				
LogP	0.096	0.316	0.641	0.187	1.000			
MS	0.105	0.433	0.514	0.153	0.415	1.000		
HOMO	0.139	0.013	0.823	0.181	0.544	0.362	1.000	
MASS	0.168	0.440	0.178	0.033	0.037	0.575	0.215	1.000

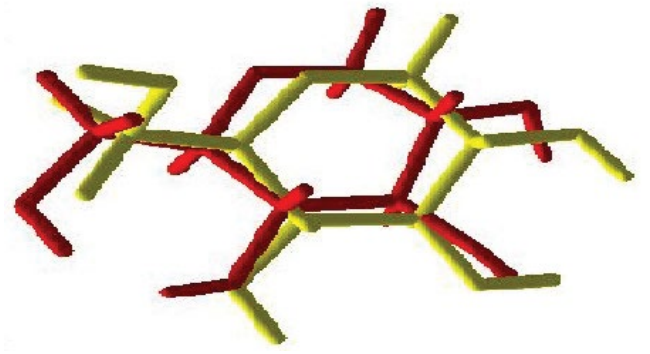

Figure 4. Superimposition of the reference ligand (the yellow stick represents the re-docked ligand; the red stick represents the reference ligand).

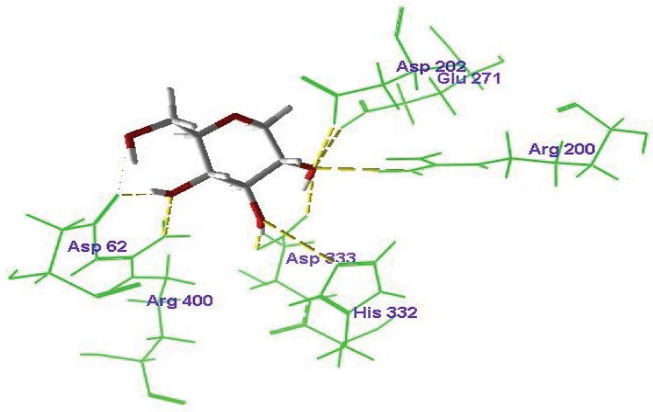

Figure 5. The hydrogen-bond interaction (the ligand was represented by sticks, the amino acid residues were represented by lines, the hydrogen bonds were represented by dotted lines).

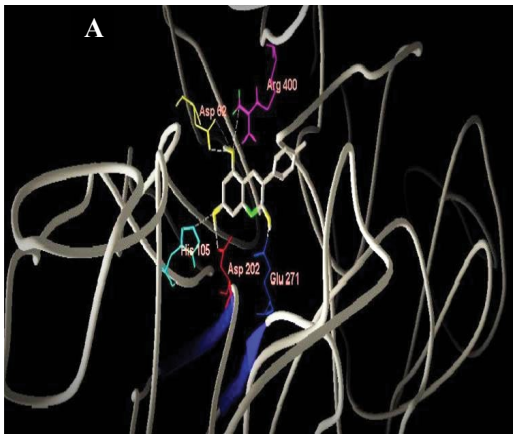

Figure 6A. The hydrogen-bond interaction between compound 16 and 3WY2 (the grey dotted lines represent the hydrogen bonding).

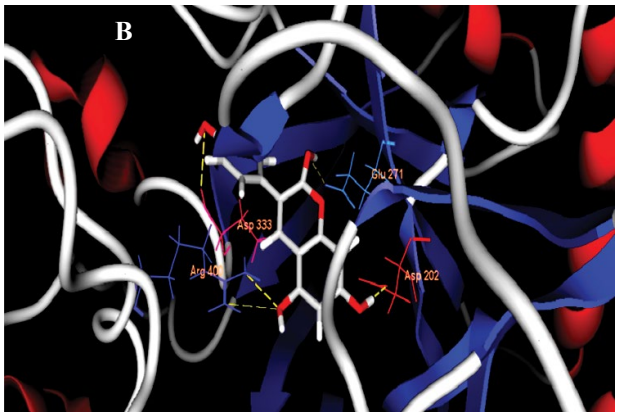

Figure 6B. The hydrogen-bond interaction between compound 18 and 3WY2 (the yellow dotted lines represent the hydrogen bonding).

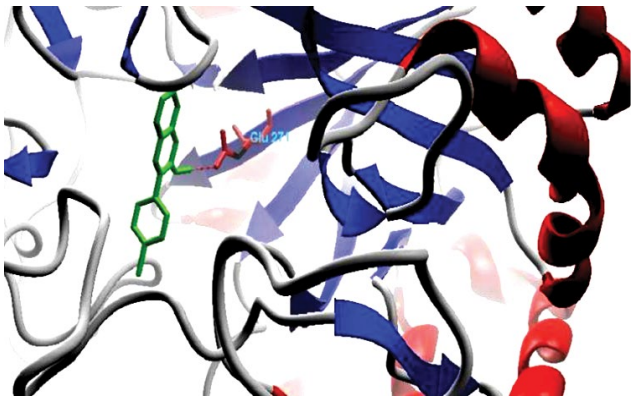

Figure 7. The hydrogen-bond interaction between compound 26 and 3WY2.

Conclusion

We developed QSAR model of 3-arylcoumarin derivatives for their α-glucosidase inhibitory activity. It may be concluded that α-glucosidase inhibitory activity of 3-arylcoumarin derivatives is strongly influenced by the electronic nature of the substituents. Based on the developed QSAR model, it can be determined that Dipole (DPL) is to be considered while designing newer compounds, for their potential enzyme inhibitory activity. In order to further understand the binding modes and activity trend, the molecular docking studies were conducted on the series of α-glucosidase inhibitors. Best ligands interactions with respect to the binding site were identified by docking analysis. The active compounds 16 and 18 depicted significant interactions with the crucial residues of binding site. The docking scores against α-glucosidase in this study could be utilized for

further computational studies. The results explained here may give rise to recognition of other series of new and more potent α-glucosidase inhibitors.

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The authors declare no competing financial interest.

Conflict of Interest

The authors declare that they have no conflict of interest.

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