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In silico design of new α-glucosidase inhibitors through 3D-QSAR study, molecular docking modeling and ADMET analysis

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Abstract

α-Glucosidase enzyme is a therapeutic target for diabetes mellitus and its inhibitors shown a crucial importance in the treatment of this disease. Twenty oxindole based oxadiazole molecules were studied based on the combination between 3D-QSAR and molecular docking approaches in order to develop new α-glucosidase inhibitors with high predicted activities. The proposed CoMFA and CoMSIA models exhibited important Q^2 values (0.544 and 0.605 respectively) and significant R^2 values (0.977 and 0.935 respectively). The CoMFA and CoMSIA models were undergone to an external validation to test their proficiency; the produced R^2test values are 0.950 and 0.804, respectively. Moreover, the contour maps produced by CoMFA and CoMSIA models have been exploited to determine the main groups influencing (decreasing or increasing) the *α*-glucosidase inhibitory activity. Therefore, two new oxindole based oxadiazole molecules with significant activities were proposed and designed. In a similar vein, molecular docking simulation was conducted to scrutinize the binding interactions between oxindole based oxadiazole molecules and *α*-glucosidase receptor (PDB code: **3A4A**). Finally yet importantly, ADMET properties were predicted to assess the oral bioavailability of the proposed new compounds and examine their toxicity.

Keywords: *Oxindole, oxadiazole, α-glucosidase, 3D-QSAR, molecular docking, ADMET*

1. Introduction

Diabetes mellitus is a life endangering and chronic metabolic turmoil, it is deemed one of the most common and grave disease of the 21st century. This illness is caused by deficient insulin secretion and marked by hyperglycemia [1]. High levels of glucose in blood lead to some acute problems to human organs such as nerves, kidney, heart and eyes [2]. Keeping in view the high difficulties of this obstacle, the inhibition of α-glucosidase is a cardinal scheme to control glucose level in blood which delaying the absorption of glucose [3]. α-Glucosidase is an enzyme located in the epithelium of small intestine and doing to transform the hydrolysis of disaccharides and polysaccharides into glucose[4]. Various α-glucosidase inhibitors such as acarbose, voglibose, and miglitol have been reported in the literature and are adopted to decrease the postprandial blood glucose levels [5-6]. Unfortunately, these drugs have many side effects such as diarrhea, abdominal pain and other gastrointestinal disorders in chronic therapy [7]. As a result, the discovery of new agents with high α-glucosidase inhibitory activity and weak side effects became of great importance. Compounds having an oxindole nucleus hint a diverse range of biological activities [8], such as antimicrobial activities [9], anticancer [10] and protein kinase activators [11]. The oxadiazole is deemed a cardinal class of heterocyclic scaffolds with large-spectrum of biological activities [12] and others uses as efficient corrosion inhibitors [13-15]. The three-dimensional quantitative structure-activity relationship (3D-QSAR) methodology is a crucial tool in modern medicinal chemistry [16,17], which involves generating models reflecting correlations between biological activities and several numerical parameters called descriptors using various statistical methods [18]. In the present study, 3D-QSAR and molecular docking approaches were conducted on a set of twenty oxindole based oxadiazole compounds in order to suggest new α-glucosidase inhibitors with more activity. Similarly, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis was put into effect to measure the oral bioavailability of the newly oxindole based oxadiazole molecules and assess their toxicity.

2. Material and methods

2.1. Dataset

The reliability of the QSAR study relies on the available dataset, the approaches of analysis and the validation techniques [19]. In the present study, a set of 20 oxindole based oxadiazole molecules which already evaluated for their α-glucosidase inhibitors, was extracted from the literature [20]. These molecules were taken into consideration to conduct the 3D-QSAR analysis; 15 compounds are selected randomly to mold the quantitative model (training set), and the 5 remaining molecules which are randomly chosen were applied to test the proficiency of the molded model (test set). The in vitro biological activities IC_{50} (µM) were turned into the corresponding pIC_{50} values ($pIC_{50} = -\log_{10}(IC_{50})$). Figure 1 and Table 1 embody the chemical structures of the 20 oxindole based oxadiazole derivatives and their α-glucosidase inhibitory activity.

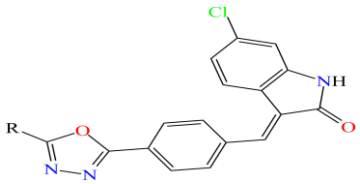
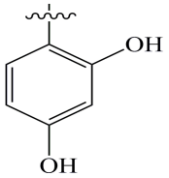
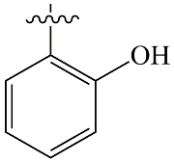
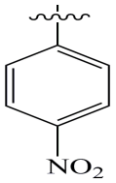
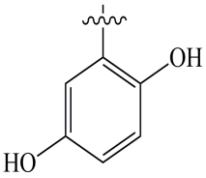
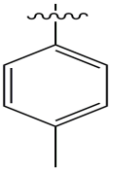
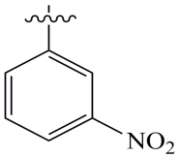
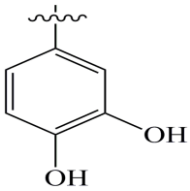
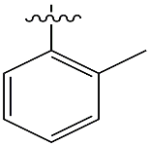
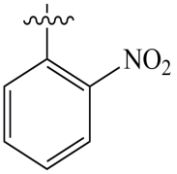
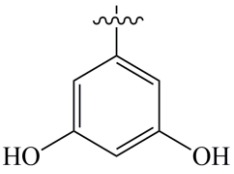
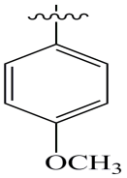
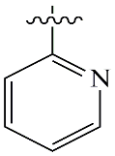
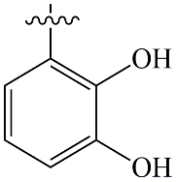
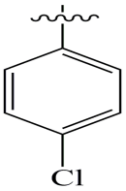
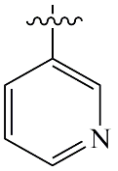
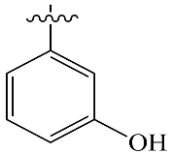
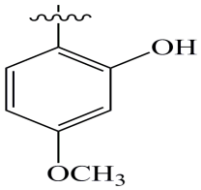
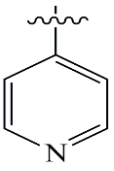
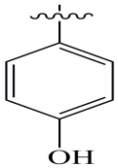
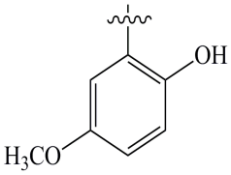


Figure 1: The general structure of the studied compounds

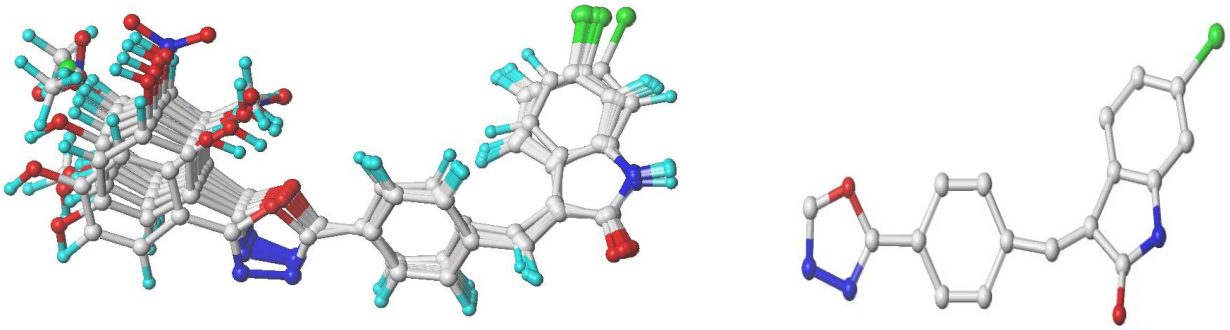
Table 1: Chemical structures of oxindole based oxadiazole derivatives used in this study and their experimental α-glucosidase inhibitory activity.

Nº	R	pIC_{50}	Nº	R	pIC_{50}	Nº	R	pIC_{50}
1		5.300	**8**		5.420	**15**		4.084
2*		5.019	**9**		4.049	**16**		3.637
3*		4.454	**10**		4.332	**17**		4.628
4		5.903	**11**		3.571	**18**		4.441
5*		4.376	**12**		4.366	**19**		3.576
6		4.755	**13**		4.869	**20**		3.808
7*		4.948	**14**		4.782		**Test set molecules*	

2.2. Molecular alignment

In CoMFA/CoMSIA analysis, alignment of compound is the first and critical step for elaborate the sturdy 3D-QSAR models. Every structure of 20 oxindole based oxadiazole was sketched and optimized using SYBYL program with Tripos force field [21] Gasteiger Huckel charges and with gradient convergence criteria 0.01

kcal/mol [22]. The common core was taken and the rest of the compounds were aligned to it using the ALIGN DATABASE algorithms available in SYBYL-X 2.0 software [23]. In this study, we have chosen the molecule **4** as template, because it's the more active molecule in database (Figure 2).



Aligned molecules Core

Figure 2: Superposition and alignment of the 20 studied compounds using compound **4** as a reference

2.3. Generation of 3D-QSAR models

CoMFA and CoMSIA procedures were conducted in this review to mold a trustworthy 3D-QSAR model. Both two methods were established basis on the idea of fields around the aligned compounds [24]. Indeed, the CoMFA procedure was done to compute the steric (S) and electrostatic (E) fields [25]. Whilst, the CoMSIA technique was put into practice to calculate the others fields like, hydrophobic, hydrogen bond acceptor and donor, as well as the steric and electrostatic fields [26]. In this analysis, the α-glucosidase values were utilized as dependent variables to compute CoMFA and CoMSIA techniques.

2.4. PLS analysis

The Partial Least Squares (PLS) [27] technique was put into practice to construct a linear correlation between the α-glucosidase activity and the CoMFA and CoMSIA descriptors. Hence, the PLS was conducted to provide the coefficient of cross-validation correlation (Q^2) and the optimum number of components (ONC) using leave-one-out cross-validation. In a similar vein, the non-cross-validation analysis was put into effect to afford the correlation coefficient (R^2), the standard error of estimate (SEE) and F-test value (F).

The cardinal values of Q^2 and R^2 and lower value of SEE were adopted to select the best 3D-QSAR model. The external validation was executed to assay the proficiency of the suggested model using 5 oxindole based oxadiazole molecules as a test set.

2.5. Molecular docking

Molecular docking is a popular approach adopted to scrutinize the types of interactions between a small molecule (ligand) and a macromolecule (receptor) [28,29]. In this work, molecular docking was put into practice using Surflex-dock existing in Sybyl X-2.0 software. The crystal structure of α-glucosidase does not exist yet, thus, we adopted the homology model as reported by Ming Liu et al [30]. All water molecules located in **3A4A** were deleted and polar hydrogen atoms added for protein preparation using the Discovery Studio 2016 software [31]. In this part, we conducted the molecular docking study of two molecules; molecule **4** (the more active compound) and molecule **T1** (The highest proposed compound) with the studied receptor.

The obtained outcomes from surflex-dock were visualized using PyMol [32] and Discovery Studio 2016 [31] software's.

2.6. In silico ADMET prediction

The goal of this work is to propose new drugs with important α-glucosidase. These molecules may be toxic or not absorbed by the body. For this, we predicted the properties of the newly designed molecules using in silico ADMET in order to identify the effects sides of these drugs. The pkCSM [33] and SwissADME [34] online tools were adopted to predict the ADMET properties of the oxindole based oxadiazole molecules **T1** and **T2**.

3. Results and discussions

3.1. CoMFA and CoMSIA results

Among the goals of this study is to develop trustworthy 3D-QSAR model that is why CoMFA and CoMSIA techniques were conducted and their statistical outcomes were embodied in Table 2. Table 3 clarifies the observed and predicted pIC_{50} values of 20 oxindole based oxadiazole analogs.

It can be seen from Table 2, that the CoMFA model has important Q^2 value of 0.544, significant value of R^2 of 0.977, small SEE value (0.118) as well as 4 optimum number of components (ONC). Similarity, CoMSIA model presents high Q^2 of 0.605, R^2 of 0.935, very small SEE of 0.138 and 2 as an optimum number of components. Both CoMFA and CoMSIA models were checked for their proficiency using an external validation test; the $Rtest^2$ values obtained are 0.950 and 0.804, respectively. The main descriptors explained CoMFA model are steric and electrostatic with 0.518 and 0.482 ratios respectively. On the other hand, the principal contributions influencing the CoMSIA model are H-bond donor, electrostatic and H-bond acceptor with 0.323, 0.330 and 0.262 ratios, respectively. Outcomes of Table 3 reveal that the residual between the observed and predicted pIC_{50} values is very small which means the high correlation between them.

Table 2: The PLS statistical results of CoMFA and CoMSIA models

							Fractions				
Model	Q^2	R^2	SEE	F	ONC	R^2test	Ster	Elec	Acc	Don	Hyd
CoMFA	0.544	0.977	0.118	107.131	4	0.950	0.518	0.482	-	-	-
CoMSIA	0.605	0.935	0.183	85.917	2	0.804	0.035	0.330	0.262	0.323	0.052

R^2: Non-cross-validated correlation coefficient, Q^2: Cross-validated correlation coefficient, SEE: Standard error of the estimate, N: Optimum number of components, R^2test: External validation correlation coefficient, F: F-test value.

3.2. CoMFA contour map

The steric and electrostatic contour maps produced by CoMFA model were used to scrutinize the regions influencing the activity and their outcomes are embodied in Figure 3(a) and Figure 3(b), respectively.

The yellow contour around *ortho* position of the R moiety, hints that tiny groups might ameliorate the activity. On the other hand, green contours around *ortho* and *meta* positions of the resorcinol moiety point out that bulky groups have an important role to enhance the α-glucosidase activity (Figure 3(a)).

In CoMFA electrostatic contour maps (Figure 3(b)), the blue contour around *ortho* position of the resorcinol group suggests that the moieties with electro-donating character could raise the potency. Conversely, the two

red contours around *ortho* position and near *meta* and *para* positions of the resorcinol moiety, suggest that these positions are preferred by the substituents with electron-withdrawing nature to increase the α-glucosidase inhibitory activity.

Table 3: Observed and predicted α-glucosidase inhibitory activity of the 20 oxindole based oxadiazole derivatives

		CoMFA		CoMSIA	
Nº	pIC_{50}	Predicted	Residuals	predicted	Residuals
1	5.300	5.248	0.052	5.806	-0.506
2*	5.019	5.138	-0.119	4.632	0.387
3*	4.454	4.372	0.082	4.566	-0.112
4	5.903	5.939	-0.036	4.981	0.922
5*	4.376	4.504	-0.128	4.868	-0.492
6	4.755	4.731	0.024	4.403	0.352
7*	4.948	5.092	-0.144	5.044	-0.096
8*	5.420	5.278	0.142	5.106	0.314
9	4.049	4.189	-0.140	4.171	-0.122
10	4.332	4.365	-0.033	4.293	0.039
11	3.571	3.576	-0.005	4.215	-0.644
12	4.366	4.108	0.258	4.263	0.103
13	4.869	4.829	0.04	4.183	0.686
14	4.782	4.775	0.007	4.415	0.367
15	4.084	4.209	-0.125	4.185	-0.101
16	3.637	3.677	-0.04	4.153	-0.516
17	4.628	4.703	-0.075	4.221	0.407
18	4.441	4.409	0.032	4.251	0.190
19	3.576	3.694	-0.118	4.278	-0.702
20	3.808	3.733	0.075	4.283	-0.475

** Test set molecules*

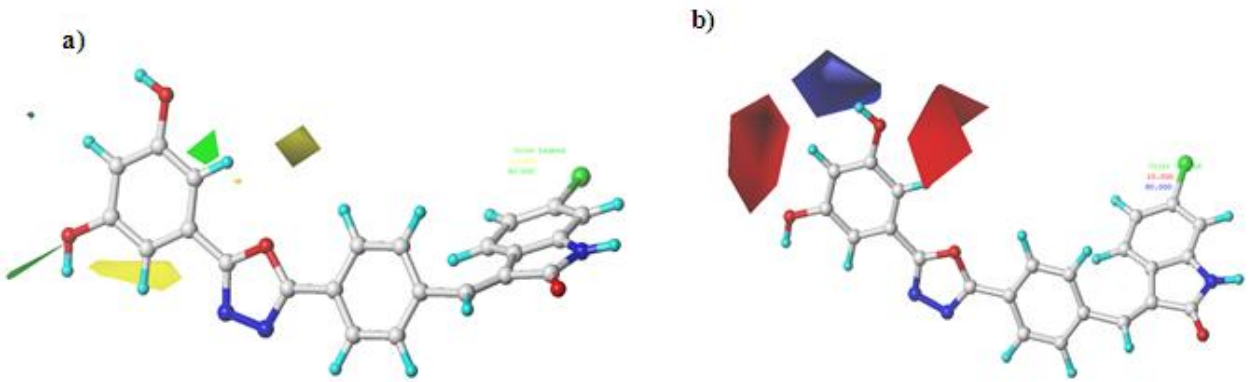


Figure 3: The steric (a) and electrostatic (b) contours maps generated by CoMFA model

3.3. CoMSIA contour map

In order to examine the hydrophobic, H-bond acceptor and H-bond donor fields as well as the steric and electrostatic fields, CoMSIA contour maps were made and their findings are clarified in Figure 4.

The CoMSIA steric field (Figure 4(a)) displays a huge green contour covering the resorcinol moiety which hints that these places are reserved only for the bulky moieties in order to raise the activity. Conversely, the yellow contour near *meta* position of the R group suggests that this region is preferred by the tiny moieties to increase the α-glucosidase activity. The analysis of CoMSIA electrostatic contour map is similarly to the explanation of CoMFA electrostatic field (Figure 4(b)). In CoMSIA hydrophobic field (Figure 4(c)); the huge white contour covering the resorcinol moiety hints that the addition of hydrophilic groups in these positions might be beneficial for increasing the inhibitory activity. On other hand, yellow contour around *meta* position of the R group suggests that moieties with hydrophobic character in this place might be essential for ameliorating the activity of compounds.

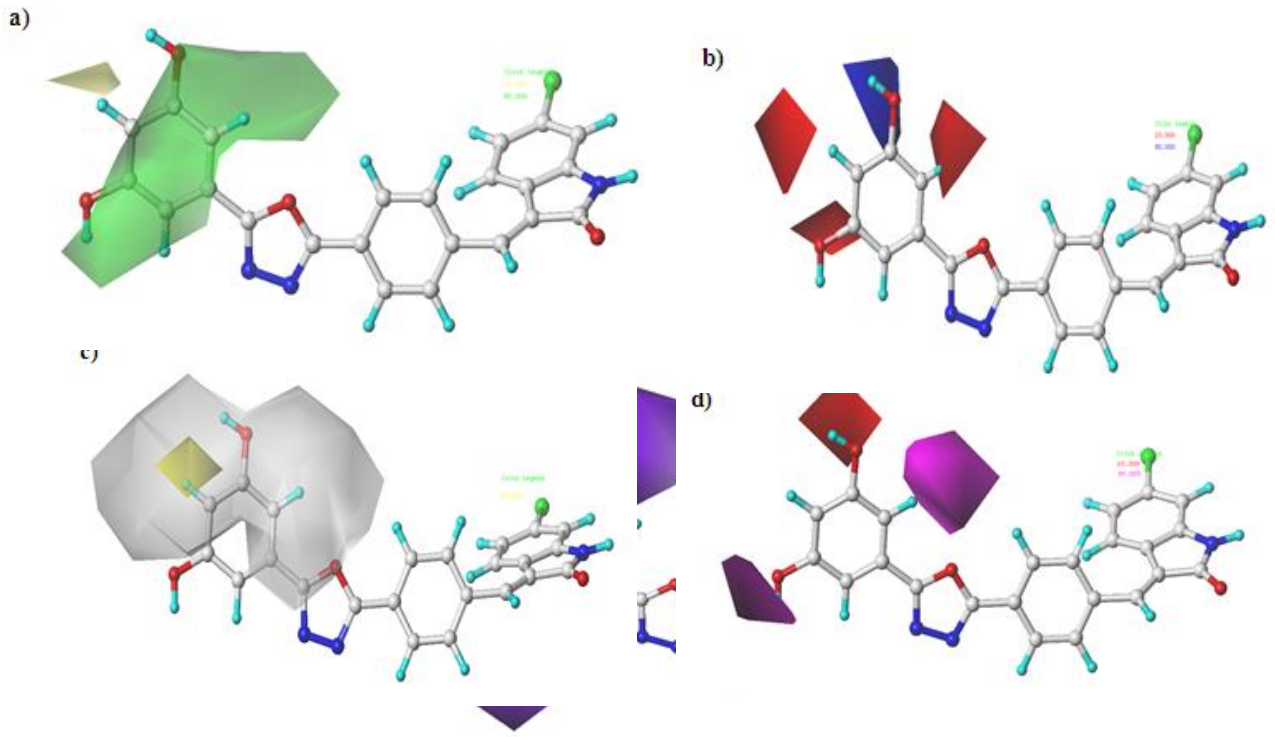


Figure 4: The steric (a), electrostatic (b), hydrophobic (c), H-bond acceptor (d) and H-bond donor (e) contours maps generated by CoMSIA model

The CoMSIA H-bond acceptor field (Figure 4(d)) put on show two magenta contours; one in *ortho* position of the resorcinol group and other in *meta* position of the same moiety indicating that moieties with hydrogen bond acceptor character could reduce the inhibitory activity. On the contrary, the red contour located in *meta* position of R group hints that groups with hydrogen bond acceptor nature could decrease the α-glucosidase activity. The bulky purple contour around the resorcinol moiety hints that substituents with hydrogen bond donor character in these regions could reduce the potency (Figure 4(e)). In Figure 5, we abstracted all information from CoMFA and CoMSIA contour maps results, which could be much helpful information which leads to identify the regions responsible for increasing or decreasing the α-glucosidase activity in order to propose new oxindole based oxadiazole compounds with better activity.

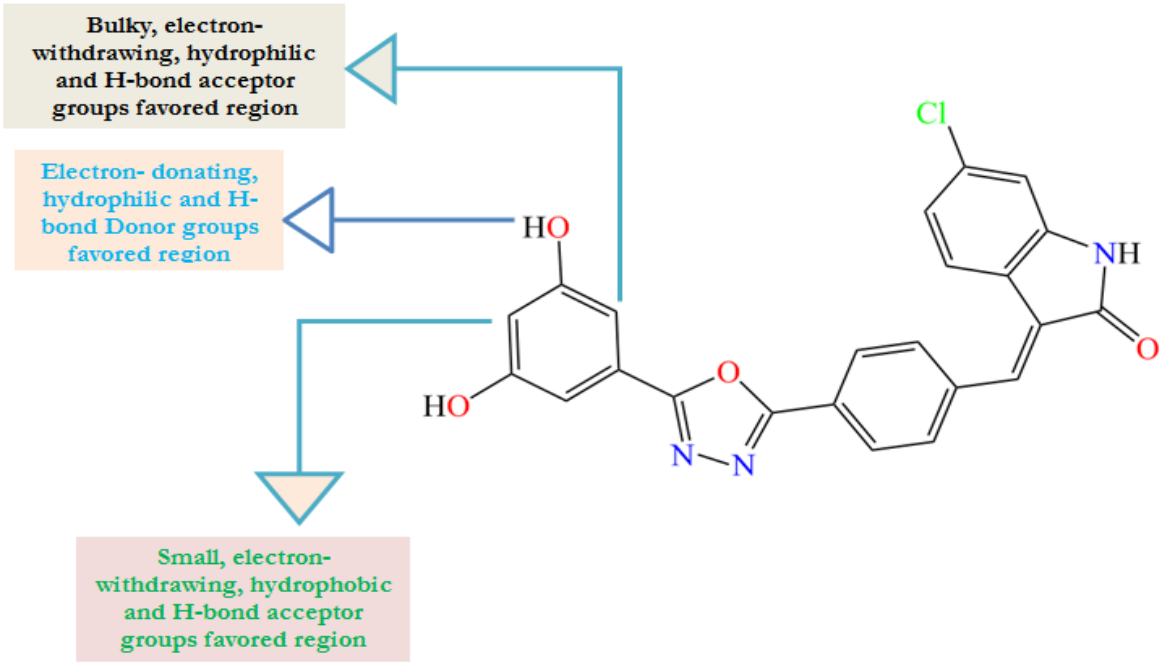


Figure 5: Summary of contour maps produced by CoMFA and CoMSIA models

3.4. Design of new α-glucosidase inhibitors

The principal target of the molecular modeling is to develop a new potent, safer, and inexpensive drug. Hence, this study was succeeded to propose new α-glucosidase with important inhibitory activity based to the crucial information extracted from CoMFA and CoMSIA models. The new oxindole based oxadiazole compounds were minimized and aligned to the database using the same way which was adopted in both training and test sets. The theoretical pIC_{50} values of the compounds **T1** and **T2** were predicted using the proposed CoMFA and CoMSIA models. The predicted pIC_{50} values of α-glucosidase inhibitors and their chemical structures are embodied in Table 4 and Figure 6.

Table 4: The predicted pIC_{50} values of newly designed compounds in comparison with compound **4**

N°	Predicted pIC_{50}		Compound **4**
	CoMFA	CoMSIA	Observed pIC_{50}
T1	6.207	5.783	5.903
T2	5.917	6.046	

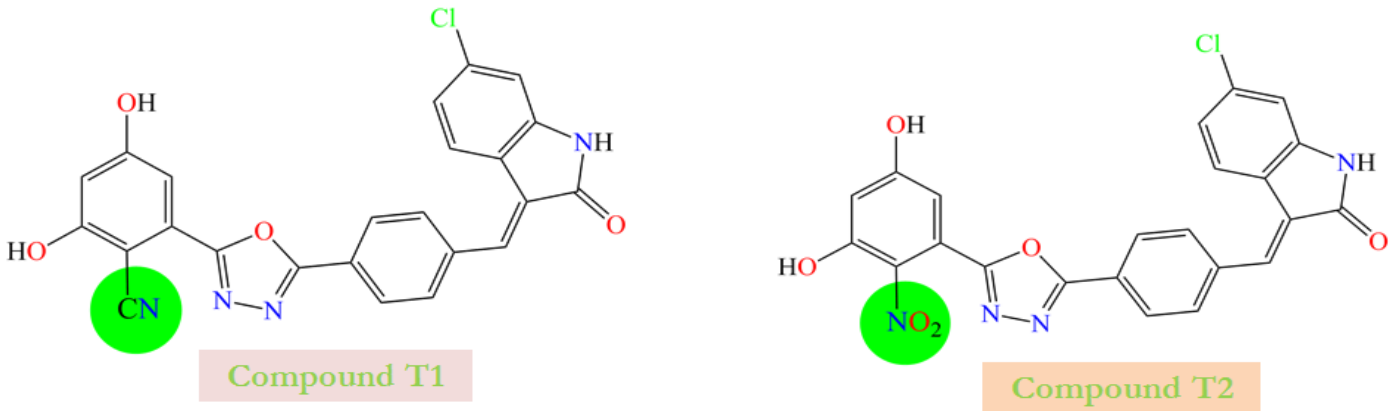


Figure 6: Chemical structures of the proposed α-glucosidase inhibitors**.**

3.5. Molecular docking results

Docking simulation was conducted on compounds **4** and **T1**, which have showed a high potent inhibitory activity among the entire series. Docking routcomes of compound **4** and compound **T1** in the active site of α-glucosidase receptor (PDB code: 3A4A) are shown in Figures 7, 8, 9 and 10. The compound **4** which is the most active molecule in dataset presents alkyl and pi-alkyl interactions with Val216 (5.05Å) and Arg315 (5.10 Å, 4.22 Å, 5.24 Å) residues. Asp215 (1.96 Å) and His351 (2.42 Å) were seen making hydrogen bonds with the hydroxyl moiety of the resorcinol group of the molecule. The resorcinol moiety of the molecule **4** provides also a pi-lone pair interaction with Tyr72 (2.80 Å) residue. The oxindole moiety afforded hydrogen bond interaction with Pro312 (2.45 Å) residue. The 6-chloroindolin-2-one moiety provides a carbon hydrogen bond interaction with Phe314 (3.26 Å) residue. Glu277 (4.13Å and 4.24 Å) formed pi-anion with oxadiazole group of the compound. The phenyl ring which is near oxadiazole moiety offers a pi-pi-T-shaped with Phe303 (2.45 Å) residue. These several interactions affirmed the high inhibitory activity of the compound **4**.

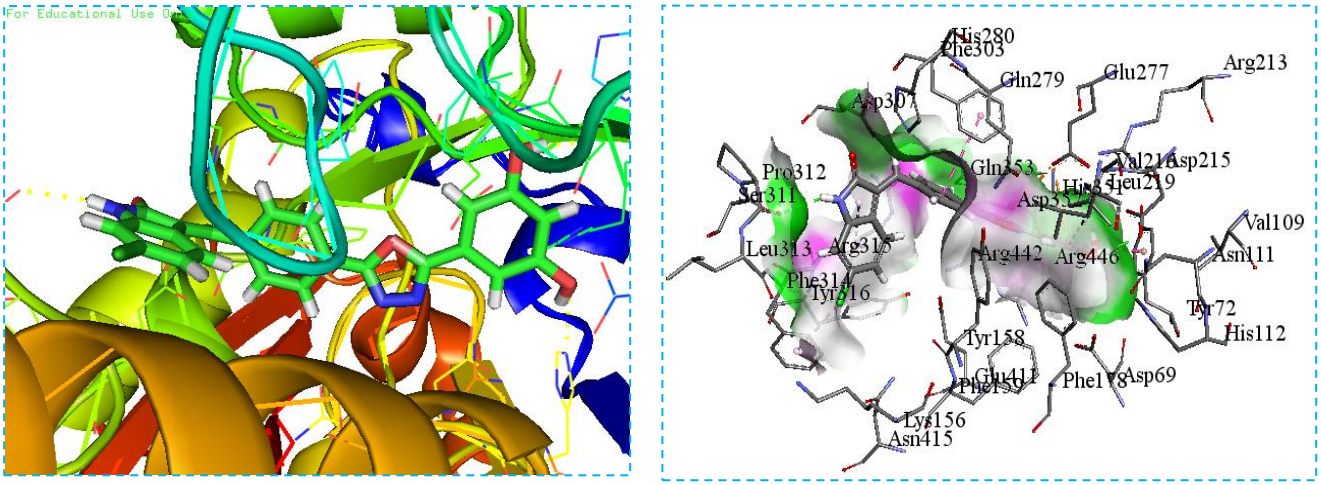


Figure 7: Position of the best conformation of the compound **4** in the binding pocket of α-glucosidase receptor.

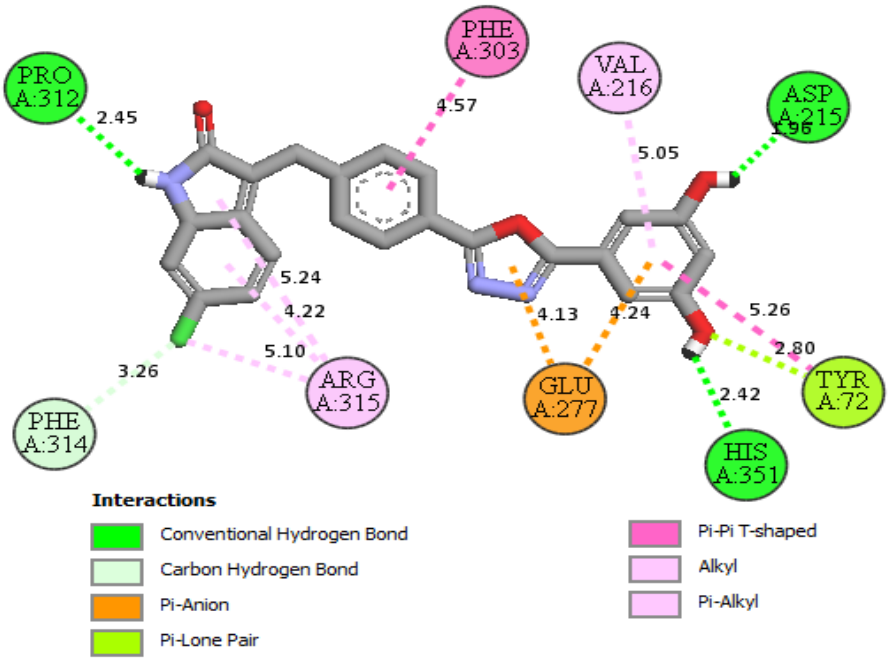


Figure 8: Docking interactions between the compound **4** and the α-glucosidase receptor.

The proposed molecule **T1** was observed having good interactions and good pIC_{50} value (See Table 4). The resorcinol moiety forms three conventional hydrogen bond interactions with Gln239, Thr245 and Ser241 residues at distances 2.56 Å, 245 Å, 1.99 Å, respectively of the target enzyme as displayed in Figures 9 and 10. Likewise, the ring of the resorcinol group affords two types of interactions like pi-donor hydrogen bond and pi-anion with Ser240 (3.54 Å) and Asp242 (4.74 Å) residues, respectively. The compound **T1** affords pi-anion interaction Asp242 (4.74 Å and 4.78 Å). The 6-chloroindolin-2-one moiety offers four types of interactions; pi-sigma, pi-anion, alkyl and pi-alkyl with Pro312 (2.84 Å, 4.25 Å and 3.61 Å) and Asp307 (4.52 Å) residues. These crucial interactions explain the high activity and good stability of the compound **T1** in the active site of α-glucosidase receptor.

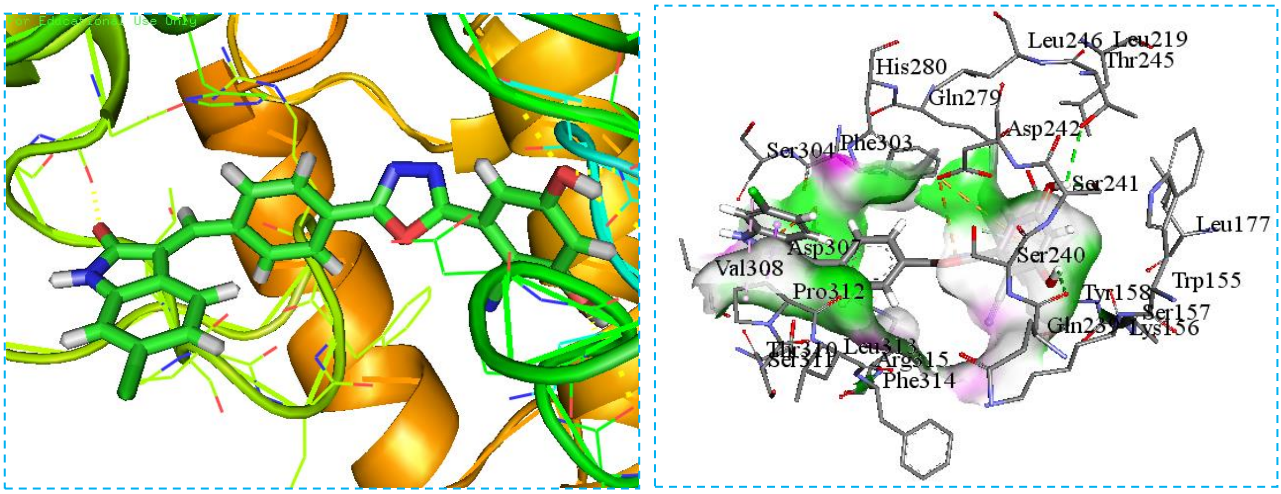


Figure 9: Position of the best conformation of the proposed compound **T1** in the binding pocket of α-glucosidase receptor.

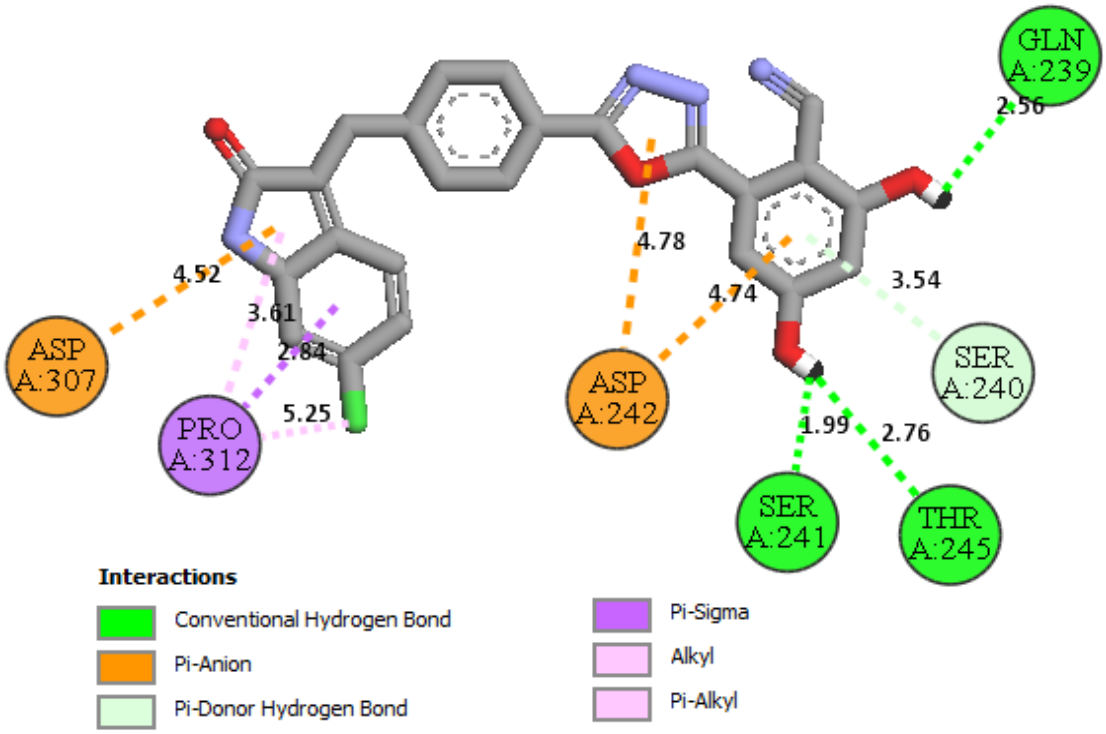


Figure 10: Docking interactions between the proposed compound **T1** and the α-glucosidase receptor.

3.5. ADMET prediction and drug likeness

The principal goal of this study is to propose new α-glucosidase inhibitors with excellent activities. Therefore, to ensure that the designed compounds are viable drugs, we calculated the pharmacokinetic parameters ADMET and drug likeness of these newly molecules. The pkCSM [33] and SwissADME [34] are online tools adopted to predict the ADMET properties of new oxindole based oxadiazole molecules. Table 5 displays the Lipinski's properties of the new proposed molecules, while the Table 6 reveals the in silico ADMET properties of the new compounds **T1** and **T2**. For a given compound with logP not more than 5, molecular weight (MW) less than 500 Da, hydrogen-bond acceptors (HBA) not more than 10 and Hydrogen bond donors (HBD) less than 5, are deemed as best absorption drugs (Lipinski's rule of five) [35]. In addition, compounds with total polar surface area (TPSA) not more than 140 Å and rotatable bonds (nrotb) less than 10, display good bioavailability [36]. It can be seen from Table 5 that the molecules **T1** and **T2** have a logP less than 5, MW not more than 500 Da, HBA less than 10 and HBD not more than 5, indicating that these compounds have a best absorption and good bioavailability respecting Lipinski's rule.

Table 5: Lipinski's properties of the new proposed α-glucosidase inhibitors.

Compounds	Property					
	Log P	HBD	HBA	TPSA	nrotb	MW
Compound **T1**	4.83	3	7	132.27	3	456.845
Compound **T2**	4.86	3	8	154.30	4	476.83

Table 6: In silico ADMET prediction of the new designed compounds **T1** and **T2**

Compounds	Absorption (**A**)		Distribution (**D**)	Metabolism (**M**)							Excretion (**E**)	Toxicity (**T**)	Synthetic accessibility
	Water solubility	Intestinal absorption (human)	Blood-brain barrier permeability	CYP							Total clearance	AMES toxicity	
				2D6 substrate	3A4 substrate	1A2 inhibitor	2C19 inhibitor	2C9 inhibitor	2D6 inhibitor	3A4 inhibitor			
	(log mol/l)	Numeric (% absorbed)	(logBB)	Categorical (Yes/No)							Numeric Log ml/min/kg)	(Yes/No)	Numeric
T1	−4.02	90.75	−1.252	No	Yes	Yes	Yes	Yes	No	Yes	-0.069	No	3.36
T2	−3.512	90.69	−1.442	No	Yes	No	Yes	Yes	No	Yes	-0.088	Yes	3.42

Absorbance value more than 30% signifies good absorbance [37]; outcomes of Table 6 clarify that all new compounds revealing a value above 90%, which indicates a good absorbance in the human intestine. Blood brain barrier (BBB) is main interfaces separating the central nervous system (CNS) and the blood circulation; it's a cardinal property since it controls if drugs can pass the blood-brain barrier or not and also exerts its effect on the brain [38]. Outcomes of Table 6 8 show non-penetrating BBB for new compounds **T1** and **T2**. In addition, water solubility is given in log (mol/L) (insoluble ≤10 < poorly soluble ≤ 6 < moderately ≤ 4 < soluble ≤ 2 < very soluble < 0< highly soluble), from the Table 6, we notice that two molecules are very soluble. Moreover, Cytochrome P450s is deemed as a cardinal enzyme system for drugs metabolism in liver.

The CYP3A4 and CYP2D6 are the two principal subtypes of cytochrome P450. The molecules **T1** and **T2** are both CYP3A4 Inhibitors and substrates. On the other hand, the proposed molecules **T1** and **T2** reveal an inhibition for both CYP3A4 and CYP2D6 substrates and Inhibitors. These outcomes hint that the new compounds **T1** and **T2** can be easily metabolized in the liver. Furthermore, knowledge the toxicity of the compounds is important property because a potent drug should be no-toxic [39]. To that end, the compounds **T1** and **T2** were examined for their toxicity using Ames test. The findings of Table 6 exhibit no toxicity for compound **T1**, which means that this compound can be adopted as an inhibitor for diabetes mellitus. The α-glucosidase inhibitors **T1** and **T2** were assessed for their synthetic accessibility. These compounds reveal a values about 3, thus, it can be synthetic them easily; especially the compound **T1**.

Conclusion

A series of 20 oxindole based oxadiazole derivatives was studied using 3D-QSAR study and molecular docking simulation. The CoMFA and CoMSIA models provided important statistical outcomes (Q^2= 0.544, R^2= 0.977 and R^2test= 0.949) and (Q^2= 0.605, R^2= 0.991 and R^2test= 0.804), respectively. Moreover, the contour maps made by CoMFA and CoMSIA models were a good support to propose two new α-glucosidase inhibitors with important predicted activities. In a similar vein, molecular docking simulation was done to study the possible binding modes of oxindole based oxadiazole molecules at the active site of α-glucosidase receptor (PDB: 3A4A). The findings hinted that the molecule **T1** is stabilized by hydrogen bond with Gln239 (2.56Å), Thr245 (2.76Å) and Ser241 (1.99Å) residues. ADMET analysis showed good pharmacokinetic properties and oral bioavailability for the new oxindole based oxadiazole molecules, in particular compound **T1** which showed no toxicity in the Ames test. Therefore, this study allowed us to identify new α-glucosidase inhibitors that will be of great importance in the treatment of diabetes mellitus.

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