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COMPUTATIONAL STUDIES OF SOME BISCOUMARIN AND BISCOUMARIN THIOUREA DERIVATIVES AS α-GLUCOSIDASE INHIBITORS

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ABSTRACT

Quantitative structure-activity relationship (QSAR) and molecular docking studies of 35 compounds of Biscoumarins and Biscoumarins thiourea derivatives as α-glucosidase inhibitors was performed. Density Functional Theory (DFT) method was employed for complete geometry optimization of the α-glucosidase inhibitors. Genetic Function Algorithm (GFA) of the material studio was utilized to develop four models. Model 1 was found to be the best model with $R^2 = 0.914362$, $R^2_{adj} = 0.892953$, $Q^2_{cv} = 0.858197$ *and* $R^2_{pred} = 0.614745$. *The proposed model is robustness and predicted with good internal and external validation. The descriptors should be considered when improving the inhibitory activities of biscoumarin derivatives against α-glucosidase. The docking results showed that ligands having Ortho substituted phenyl ring have good interactions with active site residues and good inhibitory activities as compared to ligands having either Para or Meta substituted phenyl ring except ligand 16 which has the highest docking scores of -12.5 kcal/mol but undergoes para substitution on the phenyl ring and formed hydrogen bond, hydrophobic and electrostatic interactions with the active residues of the enzyme. The QSAR model and molecular docking results agree with each other and give way to the designing of new inhibitors with better activity against α-glucosidase.*

1. INTRODUCTION

α -glucosidase (EC.2.2.1.20) is an important enzyme that plays a crucial role in the metabolism of carbohydrates in the body. It speeds up the decomposition of glycosidic bonds in the non-reducing carbohydrate end, causing the release of excess glucose in the digestive tract of the body. It is located in the membranous tissue of the small intestine (Wang *et al.*, 2016b). α -glucosidase inhibitors are classes of drugs used to treat type 2 diabetes by inhibition of α-glucosidase (Taha *et al.*, 2015). α -glucosidase inhibitors are useful in the management of type 2 diabetes by preventing the decomposition of carbohydrates and thus reducing hyperglycemia (Kavitha *et al.*, 2017). α -glucosidase inhibitors can prevent viral infections in the body such as HIV, hepatitis, and cancer (Li *et al.*, 2004).

Biscoumarin is a dimeric type of coumarin with effective inhibitory activities (Aziz *et al.*, 2013). Natural and synthetic Biscoumarin have diverse biological activities which include antifungal, anti-inflammatory, and antioxidant activities (Khan *et al.*, 2014).

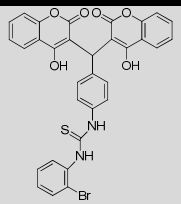
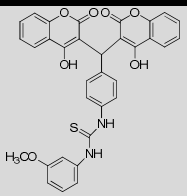
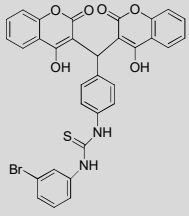
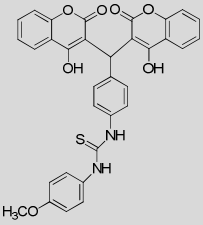
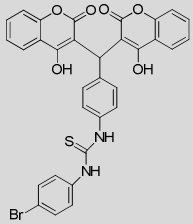
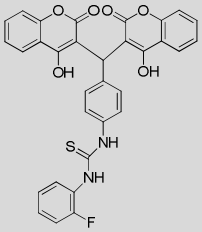
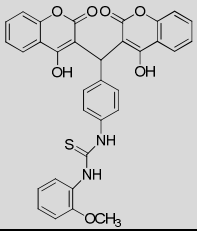
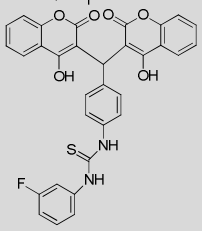
Computer-aided drug design is very important for mechanisms of action, experimental results and a new indication for synthesizing new molecules and can help reduce costs and save time in drug development (Bibi and Sakata, 2016) A large number of molecules have been identified using the computational method and have gotten to a clinical stage for drug development (Talele *et al.*, 2010). With the increase in computational power, an in-silico study has led to the development of new active drugs with a fewer side effect. QSAR and molecular docking studies were carried out to predict the activities of various compounds and elucidate the specific areas where interaction may decrease or increase the activity of the inhibitor molecules (Amit *et al.*, 2014); (Boukarai *et al.*, 2017); (Wang *et al.*, 2016a). QSAR establish a relationship between properties of various molecules and their biological activities while molecular docking is an in-silico method that helps in elucidating the interaction between the drug and protein (Abdulfatai *et al.*, 2017). This research focused on developing a QSAR model that will predict the activities of Biscoumarin derivatives against α -Glucosidase receptor and carry out molecular docking studies between the inhibitor compounds and α -Glucosidase receptor.

2. MATERIALS AND METHOD

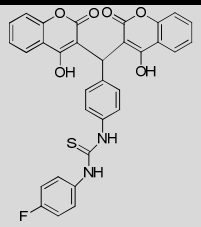
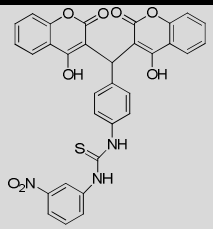
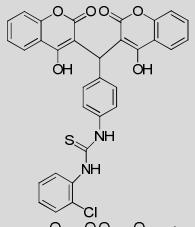
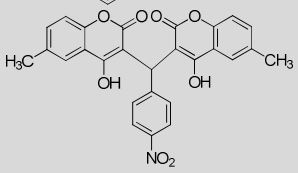
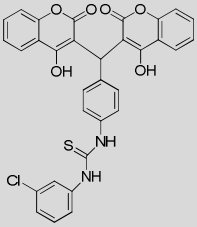
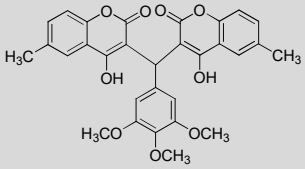
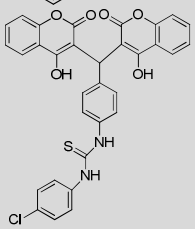
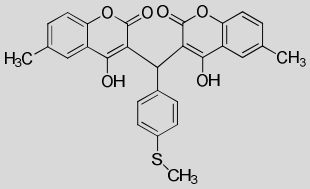
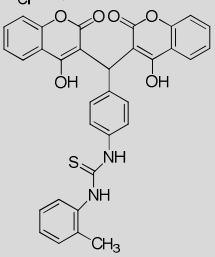
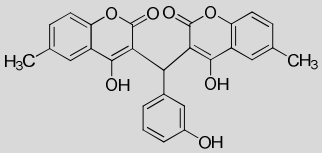
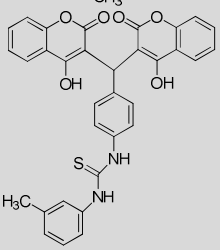
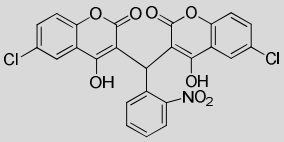
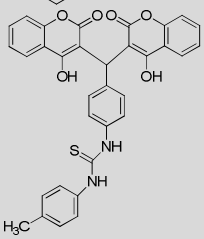
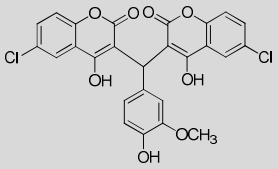
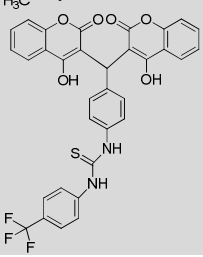
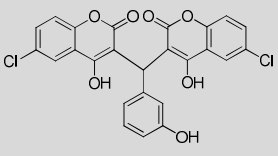
2.1 QSAR studies

Dataset collection: 35 sets of Biscoumarin and Biscoumarin thiourea derivatives and their inhibitory activities against α-glucosidase were gotten from the literature (Zawawi *et al.*, 2015) and (Khan *et al.*, 2014) and used for this study. The inhibitory activities of these compounds calculated as IC_{50} (μ M) were converted to pIC_{50} (pIC_{50} = $\log 1/IC_{50}$). The structures and the inhibitory activities of these molecules were shown in Table 1. The α-Glucosidase inhibitory activities of these molecules range from 1.13 to 2.59 (μM) as expressed in pIC_{50} logarithm scale.

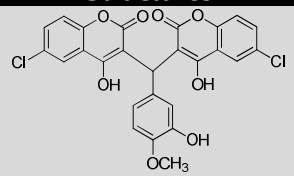
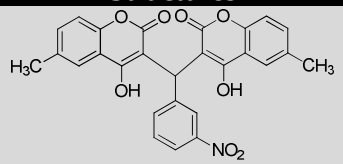
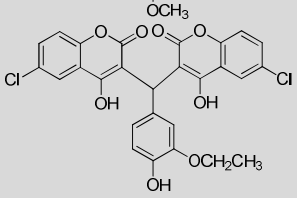
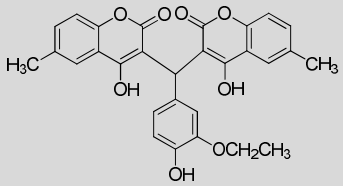
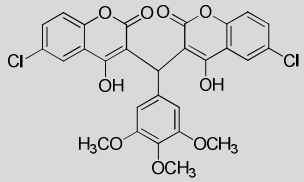
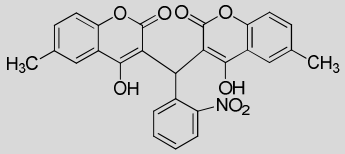
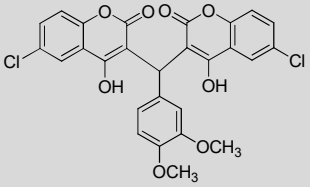
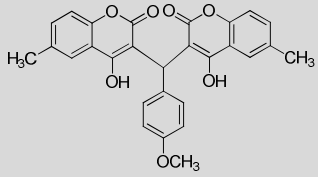
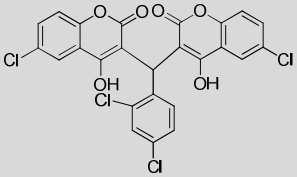
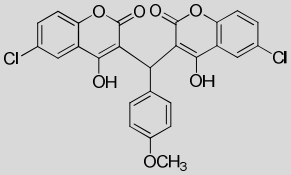
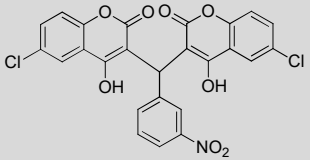
Table 1- Shows the structures and the activity (pIC_{50}) of the dataset.

S/No	Structures	pIC_{50}	S/No	Structures	pIC_{50}
1		1.57	5		1.4
2		1.55	6		1.13
3		1.59	7		1.96
4		2.02	8		1.74

Continued Table 1

S/No	Structures	pIC_{50}	S/No	Structures	pIC_{50}
9		1.73	17		1.71
10		1.7	18		1.9
11		1.45	19		2.59
12		1.43	20		1.57
13		1.7	21		1.72
14		1.89	22		1.91
15		1.64	23		2.05
16		1.5	24		1.92

Continued Table 1

S/No	Structures	pIC_{50}	S/No	Structures	pIC_{50}
25		1.92	31		1.83
26		1.76	32		2.35
27		2.11	33		2.11
28		1.96	34		2.03
29		1.22	35		1.88
30		1.43			

Geometry Optimization: ChemDraw Ultra version 12.0 software was used to draw the 2D structure of the compounds and save as cdx file format. The structures were then converted to 3D using Spartan 14.0 version 1.1.2 software. Density functional theory (DFT) using the B3LYP version and 6-311G* basis set, was employed for complete geometry optimization of the structures (Abdulfatai *et al.*, 2016).

Molecular Descriptors calculation: 0D, 1D, 2D and 3D descriptors were calculated using PaDEL descriptor software version 2.18 and saved as sdf file format from the optimized structures of the Spartan files, (Yap, 2011).

Dataset division: Kennard–Stone Algorithm was used to split the dataset into training and test set using (Kennard and Stone, 1969). 75% of the dataset goes to the training set used and the remaining 25% as the test sets used for external validation of the built model.

Model Building: Regression analysis was performed using Genetic Function Algorithm (GFA) method in material studio software with the biological activities (pIC_{50}) as the dependent variable and the physicochemical properties (descriptors) as independent variables.

Internal validations: The built models were assessed using Friedman's Lack of Fit (LOF) which served as a measure of fitness of a model. Below is the revised formula for the Friedman's lack of fit.

$$LOF = \frac{SEE}{(1 - \frac{C+dp}{M})^2} \quad (1)$$

where SEE is the standard error of estimation, p is the total number of descriptors in the model, d is a user-defined smoothing parameter, c is the number of terms in the model, and M is the number compound in the training set.

SEE is the standard error of estimation which equals to the standard deviation of the model and a model is said to be good when it has lower SEE value. SEE is given as:

$$SEE = \sqrt{\frac{(Y_{exp} - Y_{pred})^2}{N-P-1}} \quad (2)$$

The structure of the regression model takes the form(Arthur et al., 2016)

$$Y = a1x1 + a2x2 + a3x3 + b \quad (3)$$

where Y is the biological activity (pIC_{50}), 'a's are regression coefficients for the corresponding 'x's which are the independent variables representing molecular descriptors of the molecules, the last variable 'c' is the regression constant.

R^2 gives an account of the fragment of total variation of the model. The nearer the R^2 value is to 1.0, the better the model developed. The most frequently used internal assessment parameter for QSAR model is R^2 and is shown below:

$$R^2 = 1 - \frac{\sum(Y_{exp} - Y_{prd})^2}{\sum(Y_{exp} - Y_{mntrng})^2} \quad (4)$$

where Y_{exp}, Y_{pred}, and $Y_{mntraining}$ are the observed activity, the predicted activity and the average observed activity of the training set (Adeniji *et al.*, 2018).

Adjusted R^2 (R^2_{adj}) value changes directly with an increament in the number of descriptors; R^2 is not suitable for measuring the stability of a model. In order to have a reliable and stable model, R^2 needs to be adjusted. The adjusted R^2 is defined as follows:

$$R^2 = 1 - (1 - R^2)\frac{(n-1)}{n-p-1} = \frac{(n-1)(R^2-P)}{n-p+1} \quad (5)$$

Where n is the number of compounds in the training set, p= number of descriptors in the model (Abdulfatai *et al.*, 2017).

The cross-validation coefficient (Q_{cv}^2) is used to determine the power of a QSAR model to predict the activity of new compounds. Q_{cv}^2 is represented as:

$$Q_{cv}^2 = 1 - \frac{\sum(Y_{prd} - Y_{exp})^2}{\sum(Y_{exp} - Y_{mntrng})^2} \quad (6)$$

where Y_{pred} and Y_{exp} represent the predicted and experimental activity (pIC_{50}) respectively of the training set and Y_{mntrng} the average activity value of the training set(Jalali-Heravi and Kyani, 2004).

External validation: The external validation of the generated model is based on the R^2 test value and is defined as:

$$R^2_{test} = 1 - \frac{\sum(Y_{prd} - Y_{exp})^2}{\sum(Y_{exp} - Y_{mntrng})^2} \quad (7)$$

where Y_{pred} and Y_{exp} represent the predicted and biological activity (pIC_{50}) respectively of the test set and Y_{mntrng} the mean activity value of the test set (Tropsha *et al.*, 2003).

Applicability domain: Applicability domain of a QSAR model is employed to determine outliers and influential compounds and to affirm the reliability and robustness of the model generated (Tropsha *et al.*, 2003). Leverage is one of the techniques used in evaluating the applicability domain of a QSAR model and is given for a chemical compound as h_i:

$$h_i = x_i(X^TX)^{-K}x_i^T \quad (i = K, \cdots, P) \quad (8)$$

where x_i is the training compound matrix *I*, X is $n \times k$ descriptor matrix of the training set compounds and X^T is the transpose matrix X used to build the model. As a prediction tool, the warning leverage (h^*) which is the limit for X values and it's defined as:

$$h^* = \frac{3(p+1)}{n} \quad (9)$$

where *n* is the number of training compounds, and p is the number of descriptors in the model.

Y-randomization Test: In Y-randomization test, random Multi Linear regrasion models are built by randomly moving the activity while keeping the descriptors unchanged. The R^2 and Q^2 values for the new QSAR models built for many trials are expected to be very low, which confirm that the developed QSAR models are robust. Another parameter, cR^2_p is also calculated which should be more than 0.5 for passing this test.

$$CR_P = R(R^2 - (average\ R_r)^2)^{\frac{1}{2}} \quad (10)$$

Quality assurance of the model: Internal and external validations parameters are used to assess the reliability and predictive ability of a QSAR model. Table 2 gives the general minimum requirement values for the assessment of a QSAR model (Veerasamy *et al.*, 2011).

Table 2 - General minimum recommended value for the evaluation of QSAR model.

Symbol	Name	Value
R^2	Co-efficient of determination	≥0.6
$P_{(95\%)}$	Confidence interval at 95% confidence level	<0.05
Q^2	Cross-Validation Co-efficient	≥0.5
R^2- Q^2	Difference between R^2 and Q^2	≤0.3
$N_{(ext,\ and\ test\ set)}$	Minimum number of external and test set	≥ 05
$R^2_{ext.}$	Co-efficient of determination of external and test set	≥0.5

Molecular docking studies: Protein-Ligand docking studies on 35 Biscoumarin derivatives were performed to study the interaction between the binding pocket of α-glucosidase enzyme and the ligands on Hp G62 computer system, with Intel ® Core™ i3 Dual CPU, M330 @2.13 GHz 2.13GHz, 4GB of RAM using Auto dock vina 4.2 of pyrex virtual screening software, Chimera version 1.10.2 and Discovery studio software.

Ligands Preparation: The optimized structures of the compounds from Spartan'14 were saved as PDB file format for the docking studies(Abdulfatai *et al.*, 2017). Figure1 shows the 3D structure of the prepared ligand.

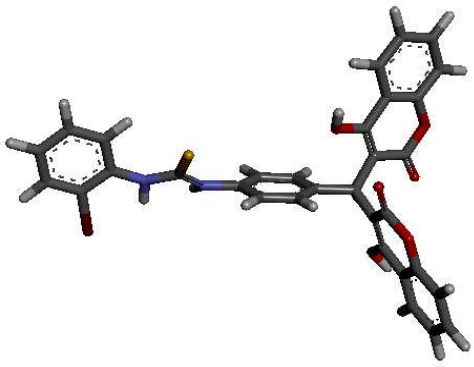


Figure 1 - 3D structure of the prepared Ligand.

Preparation of receptor: The 3D structure of the receptor (Saccharomyces cerevisiae isomaltase) with the PDB code 3AJ7 was retrieved from Protein Databank (PDB). Discovery studio software was to prepare the receptor by removing water molecules and cofactors (Veerasamy *et al.*, 2011) and save as PDB file format. Figure 2 shows the 3D structure of the prepared Receptor.

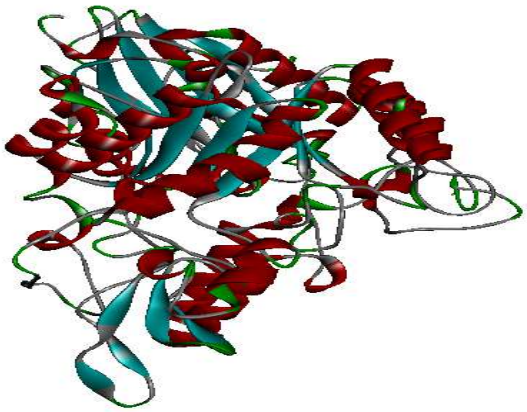


Figure 2 - 3D structure of the prepared Receptor.

Docking of the ligands with the receptor using Autodock version 4.0 of pyrex software: The docking of ligands (Biscoumarin derivatives) with the receptor (α-glycosidase) was done using Autodock version 4.0 of pyrex software (Trott and Olson, 2010). Chimera 1.10.2 software was used to build the complex (ligand-receptor) since the receptor and the ligand decoupled after carrying out docking with the autodock vina of pyrex. The ligand-receptor were visualized to view their interactions utilizing Discovery studio visualizer.

3. RESULT AND DISCUSSION

3.1 QSAR results.

Genetic Function Algorithm (GFA) of material studio software was employed to generate four QSAR models. Out of these four models, based on the internal assessment statistical parameters for QSAR models, model 1 was chosen as the best model**.** The best model equation is given below:

Model 1

$$\mathbf{pIC50} = 0.288289720\ \mathbf{HBD\ Cnt} - 0.018409794\ \mathbf{AATS8m} + 4.204618239\ \mathbf{AATSC5i} - 0.003870369\ \mathbf{ECCEN} + 8.911608832\ \mathbf{MWC5} - 65.32884998$$

R^2 =0.9144 R^2_{adj} = 0.8929, Q^2_{LOO} =0.8582, N_{trng} = 26, R^2_{test} = 0.614745, N_{test} = 9

The positive coefficient of the descriptors in model 1 such as **HBD Count. (**Hydrogen bond donor count), **AATSC5i** (Average centered Broto-Moreau autocorrelation - lag 5 / weighted by first ionization potential) and **MWC5** (Molecular walk count of order 5 (ln (1+x)) will increase the inhibitory activities of these Biscoumarins against α-glycosidase enzymes responsible for the breakdown of carbohydrate. Furthermore, the negative coefficient of **AATS8m** (Average Broto-Moreau autocorrelation - lag 8 / weighted by mass) and **ECCEN** (Eccentric connectivity index) implies that the inhibitory activities of these Biscoumarins against α-glycosidase will be more with the decrease in such descriptors. Table 3 gives the symbols, descriptions, and classes of the descriptors used in the model.

Table 3 - List of the descriptors, their description, and classes for model 1

S/no	Name	Description	Class
1	**HBDCnt.**	Hydrogen bond donor count.	2D
2	**AATS8m**	Average Broto-Moreau autocorrelation - lag 8 / weighted by mass	2D
3	**AATSC5i**	Average centered Broto-Moreau autocorrelation - lag 5 / weighted by first ionization potential	2D
4	**ECCEN**	Eccentric connectivity index	2D
5	**MWC5**	Molecular walk count of order 5 (ln(1+x)	2D

The high calculated R^2 value (0.9144), R^2_{adj} value (0.8929) and Q_{cv}^2 LOO value (0.8582) of the model indicates a good internal assessment of the model. R^2 for the external assessment of the model was also calculated for the test set containing 25% of the data and was found to be 0.6147. Table 4 and 5 give the external validation and calculation of the predictive R^2 of model 1.

Table 6 present the experimental and predicted activities of α-glycosidase inhibitors as a potent anti-diabetic and the residual values. The high predictive power of the model is indicated by the low residual value between experimental and predicted activities

Correlation matrix of the descriptors in the best model: A correlation matrix was performed on the descriptors that appear in the best model and found to be highly correlated which means that the descriptors used to build the model are very good. Table 7 gives the result of the correlation matrix.

Table 4 - External validation of model 1.

S/No.	pIC_{50}	HBD Cnt.	AATS8m	AATSC5i	ECCEN	MWC5	Yprd	Yprd-Yobs
3b	1.59	4	71.62441	-0.09696	1331	8.120589	1.314125	-0.27587
7b	1.96	4	68.58793	-0.05797	1263	8.1277	1.860515	-0.09948
11b	1.45	4	70.53864	-0.08223	1265	8.121183	1.656818	0.206818
15b	1.64	4	65.44368	-0.08198	1331	8.120589	1.490894	-0.14911
19b	2.59	2	78.37368	-0.13035	797	8.111028	2.454472	-0.13553
23b	2.05	3	89.98194	-0.11343	734	8.034955	2.166103	0.116103
27b	2.11	2	85.45815	-0.08617	797	8.111028	2.509814	0.399814
31b	1.83	2	75.47388	-0.19613	734	8.027803	1.733458	-0.09654
35b	1.88	2	88.52307	-0.13147	717	7.996654	1.553316	-0.32668

Table 5 - Calculation of the predictive R^2 of model 1.

S/No.	$(Y_{prd}-Y_{obs})^2$	$\bar{Y}_{trng}$	$Y_{obs}-\bar{Y}_{trng}$	$(Y_{obs}-\bar{Y}_{trng})^2$
3b	0.076107	1.7258	-0.1358	0.018442
7b	0.009897	1.7258	0.2342	0.05485
11b	0.042774	1.7258	-0.2758	0.076066
15b	0.022233	1.7258	-0.0858	0.007362
19b	0.018368	1.7258	0.8642	0.746842
23b	0.01348	1.7258	0.3242	0.105106
27b	0.159851	1.7258	0.3842	0.14761
31b	0.00932	1.7258	0.1042	0.010858
35b	0.106722	1.7258	0.1542	0.023778
	$\Sigma(Y_{prd}-Y_{obs})^2=0.4588$			$\Sigma(Y_{obs}-\bar{Y}_{trng})^2=1.1909$
				$R^2=(1-0.4588/1.1909)=0.614745$

Table 6 - Comparison of Experimental (pIC_{50}), Predicted (pIC_{50}) and Residual of Model 1.

S/no	pIC_{50}	predicted pIC_{50}	Residual
1	1.57	1.572693	-0.00269
2	1.55	1.524139	0.025861
4	2.02	1.883073	0.136927
5	1.4	1.468213	-0.06821
6	1.13	1.189773	-0.05977
8	1.74	1.795393	-0.05539
9	1.73	1.645647	0.084353
10	1.7	1.715159	-0.01516
12	1.43	1.420691	0.009309
13	1.7	1.8595	-0.1595
14	1.89	1.863038	0.026962
16	1.5	1.461293	0.038707
17	1.71	1.683683	0.026317
18	1.9	1.899039	9.61E-04
20	1.57	1.662324	-0.09232
21	1.72	1.817606	-0.09761
22	1.91	1.917366	-0.00737
24	1.92	1.879253	0.040747
25	1.92	2.026843	-0.10684
26	1.76	1.730718	0.029282
28	1.96	2.006411	-0.04641
29	1.22	1.170741	0.049259
30	1.43	1.463729	-0.03373
32	2.35	2.288598	0.061402
33	2.11	2.138544	-0.02854
34	2.03	1.786534	0.243466

Table 7 - Pearson's correlation matrix of the descriptors in model 1.

	HBD Cnt.	*AATS8m*	*AATSC5i*	*ECCEN*	*MWC5*
HBD Cnt.	1				
AATS8m	-0.71498	1			
AATSC5i	0.690063	-0.33956	1		
ECCEN	0.931779	-0.85799	0.68082	1	
MWC5	0.599984	-0.68793	0.711074	0.747915	1

Figure 3 shows the plot of predicted activities of both training and test sets against Experimental activities, the reliability of model 1 was confirmed by high Linearity of this plot which indicates the high predictive power of the model.

The measure of the dispersion of standardized residual values from the Experimental activity (pIC_{50}) values is presented in Figure 4. The propagation of the errors on both sides of zero is an indication of the robustness of model 1

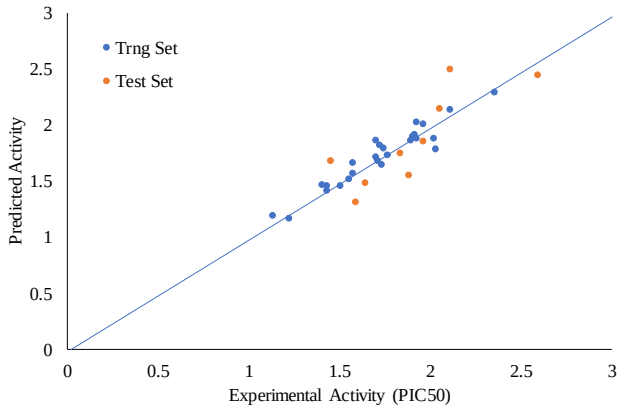


Figure 3 – The plot of the Experimental and Predicted activity of both the training and test sets of model 1.

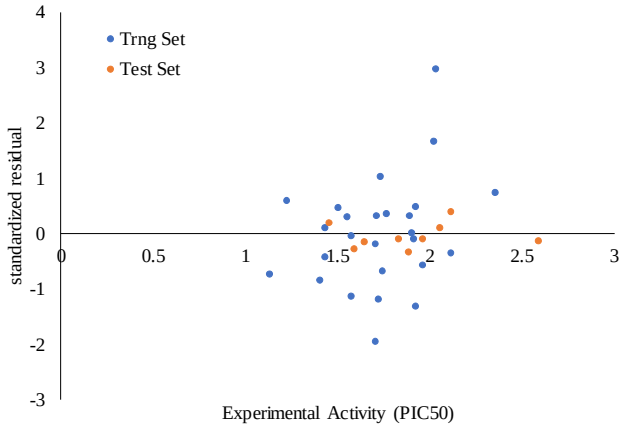


Figure 4 – The plot of the standardized residual and Experimental activity (pIC_{50}) of model 1.

Williams plot of model 1: Figure 5 shows the Williams plot of the standardized residual against leverages of both the training and test sets of model 1. Four compounds of the test set were found to be influential because their leverage values are greater than the warning leverages (h*= 0.692). This is because their molecular structure is different from other compounds of the dataset.

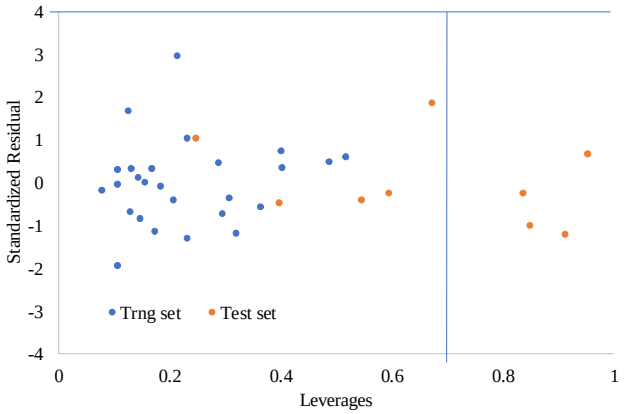


Figure 5 – Williams plot of the standardized residual and leverages of both the training and test sets of model 1.

Y-randomization test of model 1: The Y-randomization test presented in table 8 showed that the model is not obtained by chance it is robust and good because it has significantly low R^2 and Q^2 values for several trials and also ${}^{C}R^{2}{}_{P}$ value is greater than 0.5.

3.2 Results of molecular docking studies of the Biscoumarins derivatives.

Molecular docking studies of 35 Biscoumarin and Biscoumarin thiourea derivatives was carried out against α-glucosidase to find out their docking scores and their interactions. Ligands with the best docking scores were presented in table 9 and the docking scores were found to correlate with their experimentally determined inhibitory activities. Ligand 16 with the best docking scores of -12.5 kcal/mol showed hydrogen bond interaction with ASP352 (3.6970Å), ARG315(2.6445Å) and ARG442(2.5865Å) active sites. Also, it forms a hydrophobic interaction with HIS280, TYR158, LYS156, PRO312, ARG315, TYR72 and PHE178 active site of the receptor. In addition, it forms an electrostatic interaction with GLU277, ASP307, ARG315, ARG442, ASP352, ASP69 and ASP215 residues. Figure 6 and 7 give the 3D, 2D and H-bond interaction between α-glucosidase and ligand 16. From the docking studies, it is shown that ligand 16 has the highest docking scores and showed very good interaction with the active site residue of the receptor as compared to other ligands.

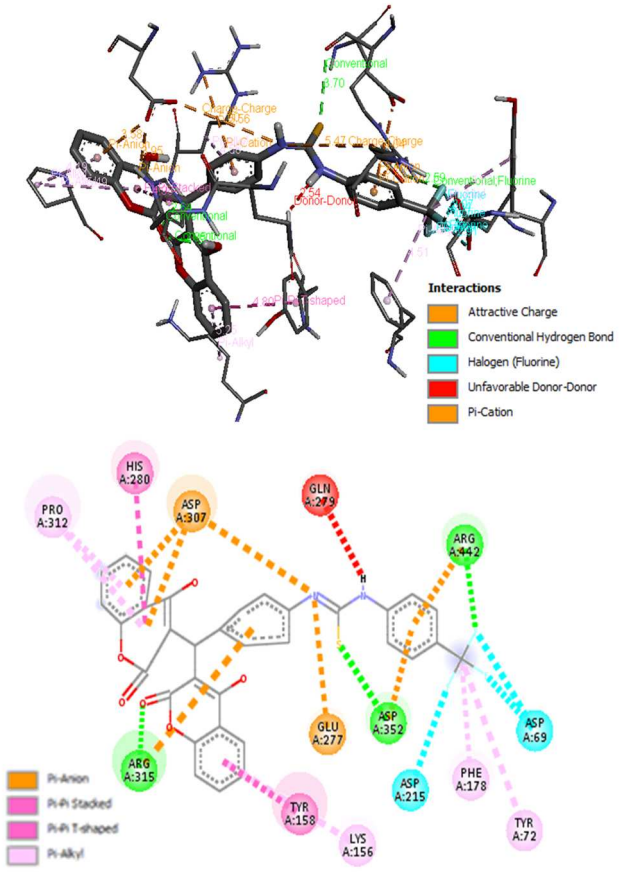


Figure 6 – 3D and 2D interaction between α-glucosidase and Ligand 16.

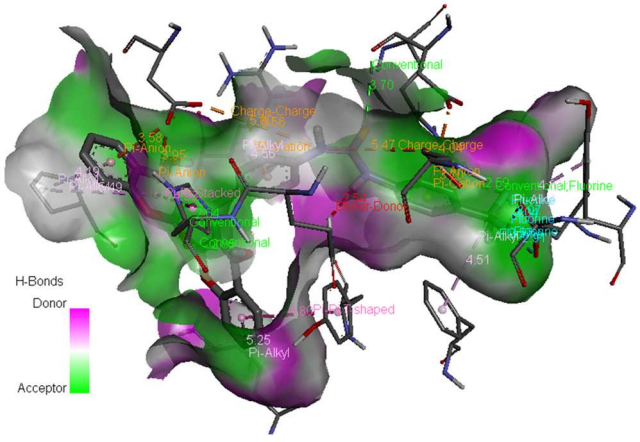


Figure 7 – The Hydrogen-bond interaction between ligand 16 and α-glucosidase

Table 8 - Result Y randomization test

Model	R	R^2	Q^2
Original	0.881884	0.777719	0.608842
Random 1	0.649304	0.421596	0.069882
Random 2	0.258633	0.066891	-0.42333
Random 3	0.218202	0.047612	-0.63194
Random 4	0.562411	0.316306	-0.06344
Random 5	0.1465	0.021462	-0.58996
Random 6	0.497656	0.247662	-0.20249
Random 7	0.197324	0.038937	-0.51371
Random 8	0.459429	0.211075	-0.15327
Random 9	0.284061	0.080691	-0.40922
Random 10	0.489127	0.239246	-0.11405
Random Models Parameters			
Average :	0.376265		
Average r^2 :	0.169148		
Average Q^2 :	-0.30315		
cRp^2 :	0.703378		

Table 9- Binding energy, hydrophobic interactions, Electrostatic/other interactions, Hydrogen bonds and Hydrogen bond distance of α-glycosidase and the ligands with highest docking scores.

Ligand-Receptor	Binding Energy(kcal/mol)	Hydrophobic interaction	Electrostatic Interaction/Others	Hydrogen Bonds	Hydrogen Bond Distance (Å)
1	-11.4	TYR158, HIS280, LYS156 and ARG315	ASP307	THR310, SER311, THR310 and ASP307	2.5128, 2.6980,3 .5082 and 2.0744
2	-11.8	HIS280, SER15, TYR158, VAL216, LYS156, PRO312, ARG315 and PHE178	GLU277, ASP307, ASP215, ARG315, ARG442, ASP307 and ASP352,	ASP352, GLN353, ARG315 and ARG315	3.0663, 3.7505, 2.6071 and 2.68669
5	-12.0	TYR158, SER157, LYS156, PRO312 and ARG315	ARG31, GLU277, ASP307 and ASP352	SER311, ASP352, GLU411, ARG315, ARG315, ARG442 and ASP215	2.1412, 3.5428, 3.6486, 2.5651, 2.8086, 2.3801 and 3.6394
9	-11.4	TYR158, ARG315, LYS156 and ARG315	ASP307, ASP307 and SER304	HIS280	4.1192
16	-12.5	HIS280, TYR158, LYS156, PRO312, ARG315, TYR72 and PHE178	GLU277, ASP307, ARG315, ARG442, ASP352, ASP69 and ASP215	ASP352, ARG315 and ARG442	3.6970, 2.6448 and 2.5865
17	-11.8	HIS280, TYR158, SER157, LYS156, PRO312 and ARG315	GLU277, ARG315, ARG442 and ASP307	SER311, ASP352, ARG315 and ARG315	2.0858, 3.1577, 2.592 and 2.8519
24	-11.0	SER157 , PRO312, LYS156, ARG315 and TYR158	ASP307	THR310, SER311 and ARG315	3.0061, 2.2284 and 2.5721
30	-11.4	HIS280, SER311, PRO312, LYS156, ARG315 and TYR158	ASP307	THR310 and ARG315	2.2917 and 2.5050

.

4. CONCLUSION

QSAR and molecular docking studies of 35 compounds of Biscoumarin and Biscoumarin thiourea derivatives as α-glucosidase inhibitors was performed. Density Functional Theory (DFT) method was employed for complete geometry optimization of the α-glucosidase inhibitors. Genetic Function Algorithm (GFA) of the material studio was utilized to develop four models. Model 1 was found to be the best model with $R^2 = 0.9144$, $R^2_{adj} = 0.8929$, $Q^2 = 0.8582$ and the external validation $R^2_{pred} = 0.6147$. As a result of the negative and positive coefficient of the descriptors in the model, it indicates that decrease in descriptors with negative coefficients such as **AATS8m** and **ECCEN** with increase in **HBD count**, **AATSC5i** and **MWC5** descriptors with positive coefficient will increase

the inhibitory activity of these molecules against α-glucosidase key enzymes responsible for the breaking down of carbohydrate. From the docking studies, it is shown that ligand 16 has the highest docking scores of -12.5 kcal/mol and formed hydrogen bond, hydrophobic and electrostatic interactions with the active site of the receptor. The QSAR model and molecular docking results correlate with one another and give room for designing new α-glucosidase inhibitors with better activity.

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