QSAR MODELLING AND DOCKING ANALYSIS OF SOME THIAZOLE ANALOGUES AS α-GLUCOSIDASE INHIBITORS

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ABSTRACT

QSAR modelling and docking studies on 45 thiazole analogues were carried out. The studied compounds in this research were optimized adopting DFT method at B3LYP function with a 6-31G* basis set. The QSAR models were generated in material studio by MLR analysis (GFA method). Based on its statistical fitness, the first model was selected and reported as the best model and assessed with $R^2 = 0.906134$, $R^2_{adj} = 0.89049$, $Q^2_{cv} = 0.86149$ and $R^2_{pred} = 0.82581$ statistical parameters. The ligand with the highest binding energy of -11.0 kcal/mol among the other ligands was ligand 13 as indicated by the molecular docking. The standard drug (acarbose) was also docked to the binding pocket of α-glucosidase with -9.5kcal/mole docking score. The most active compound was found to be better than standard drug. The outcome of this findings paved way for predicting novel α-glucosidase inhibitors having improved potency toward their target enzyme.

KEYWORDS

QSAR
Molecular modelling
Molecular docking
Diabetes
1. INTRODUCTION

The essential role played by α-glucosidase in the breaking down of carbohydrate in the body makes it an important enzyme. It catalyzes the breaking down of carbohydrate, resulting in the discharge of too much sugar. It is situated inside the small bowel at the epithelium tissue of the small intestine (Wang et al., 2016). Inhibitors of α-glucosidase are kinds of small molecules (drugs) used in curing non-insulin dependent diabetes mellitus (NIDDM) by inhibiting α-glucosidase (Taha et al., 2015). Inhibitors of α-glucosidase are used in the treatment of NIDDM (Kavitha et al., 2017). Inhibitors of α-glucosidase can also stop some other diseases like hepatitis, cancer, and HIV (Li et al., 2004).

Thiazole is a five-membered azole heterocyclic organic compound containing a ring of 3 carbon atoms, a nitrogen and a sulphur (Taha et al., 2016). Thiazole and its derivatives have wide industrial application in pharmacy, liquid crystals, and polymers (de Souza, 2005). Thiazoles have several biological activities such as antioxidant, insecticidal, antitumor, anticonvulsant, anti-hyperlipidemic and anti-inflammatory (Khan et al., 2016).

Computer-aided drug design (CADD) is a unique area in drug discovery arena which apply the concept of molecular modelling to study the interaction between drugs and their target protein (Bibi and Sakata, 2016). QSAR is a molecular modeling technique widely used to correlate physicochemical properties of compounds and their experimentally determined activities (Alisi et al., 2018). While molecular docking is used to study the possible orientation of the target protein to the ligand when they bind to one another to form complex (Abdulfatai et al., 2017). This research is aimed at performing computational modelling and docking on thiazole analogues against α-Glucosidase receptor.

2. Materials and Method

2.1 QSAR studies

2.1.1 Sources of the Dataset

45 analogues of the studied compounds and their α-glucosidase inhibitory activities (IC_{50}) were downloaded from the work of (Rahim et al., 2015) and (Khan et al., 2016) for the purpose of this research. The inhibitory activities (IC_{50} (μM)) of the dataset were converted to pIC_{50} (Ibrahim et al., 2018a). 45 sets of the studied compounds and their inhibitory activities were presented in Table 1. (pIC_{50} = log_{10} IC_{50}).

| S/No | Structures | pIC_{50} | S/No | Structures | pIC_{50} |
|------|------------|---------|------|------------|---------|
| 1    | ![Structure1](image1) | 2.34    | 4    | ![Structure4](image4) | 2.59    |
| 2    | ![Structure2](image2) | 1.64    | 5    | ![Structure5](image5) | 2.31    |
| 3    | ![Structure3](image3) | 2.38    | 6    | ![Structure6](image6) | 2.24    |
| S/No | Structures | pIC<sub>50</sub> | S/No | Structures | pIC<sub>50</sub> |
|------|------------|----------------|------|------------|----------------|
| 7    | ![Structure](image) | 1.57 | 13   | ![Structure](image) | 2.28 |
| 8    | ![Structure](image) | 1.26 | 14   | ![Structure](image) | 2.09 |
| 9    | ![Structure](image) | 1.84 | 15   | ![Structure](image) | 2.35 |
| 10   | ![Structure](image) | 2.53 | 16   | ![Structure](image) | 2.35 |
| 11   | ![Structure](image) | 2.25 | 17   | ![Structure](image) | 2.29 |
| 12   | ![Structure](image) | 2.63 | 19   | ![Structure](image) | 2.09 |
| S/No | Structures | pIC50 | S/No | Structures | pIC50 |
|------|------------|-------|------|------------|-------|
| 20   | ![Structure 20](image) | 2.24  | 26   | ![Structure 26](image) | 1.92  |
| 21   | ![Structure 21](image) | 1.67  | 27   | ![Structure 27](image) | 1.54  |
| 22   | ![Structure 22](image) | 1.37  | 28   | ![Structure 28](image) | 1.42  |
| 23   | ![Structure 23](image) | 1.36  | 29   | ![Structure 29](image) | 1.15  |
| 24   | ![Structure 24](image) | 1.35  | 30   | ![Structure 30](image) | 1.25  |
| 25   | ![Structure 25](image) | 1.42  | 31   | ![Structure 31](image) | 1.43  |
| S/No | Structures | pIC<sub>50</sub> | S/No | Structures | pIC<sub>50</sub> |
|------|------------|----------------|------|------------|----------------|
| 32   | ![Structure 1](image1) | 1.28 | 39   | ![Structure 2](image2) | 1.51 |
| 33   | ![Structure 3](image3) | 0.98 | 40   | ![Structure 4](image4) | 1.69 |
| 34   | ![Structure 5](image5) | 1.11 | 41   | ![Structure 6](image6) | 1.7  |
| 35   | ![Structure 7](image7) | 1.08 | 42   | ![Structure 8](image8) | 1.86 |
| 36   | ![Structure 9](image9) | 1.23 | 43   | ![Structure 10](image10) | 1.86 |
| 37   | ![Structure 11](image11) | 1.1  | 44   | ![Structure 12](image12) | 1.67 |
| 38   | ![Structure 13](image13) | 1.21 |
2.1.2 Geometry optimization and Calculation of descriptors.

The 2D structures of these compounds were drawn using ChemDraw Ultra version 12.0. The studied compounds in this research were optimized utilizing B3LYP version of DFT method with 6-31G* basis set (Abdulfatai et al., 2017). PaDEL descriptor software was used to compute both thermodynamic, topological, autocorrelation constitutional, electronic, and geometric descriptors (Amin and Gayen, 2016) for further studies (Yap, 2011).

2.1.3 Dataset splitting and Correlation Analysis.

The dataset was randomly split into a model set (training set) of 36 molecules used to build the QSAR model and 9 validation set (test set) used for the validation of the built QSAR models (Cheng et al., 2014).

GFA method was employed for the correlation analysis using the normalized activities (pIC₅₀) as the response/dependent variable and the descriptors as independent variables (Arthur et al., 2016).

2.1.4 Validation of the QSAR Model.

The generated QSAR models were judged using leave-one-out cross validation coefficient Q²ₜₜₜₜ parameter. R² is an important parameter for validation of a QSAR model and it is given below:

\[ R^2 = 1 - \frac{\Sigma(y_{exp} - y_{pred})^2}{\Sigma(y_{exp} - y_{mean training})^2} \]

where Yₑ is the experimental activity, Yₑ_pred is the predicted activity, and Yₑ_mean training is the mean of the experimental activity of the model set (Adeniji et al., 2018).

The R²ₑ value of the generated model is also very paramount need to be calculated and is defined as:

\[ R^2ₑ = 1 - \frac{\Sigma(y_{exp} - y_{pred})^2}{\Sigma(y_{exp} - y_{mean training})^2} \]

where Yₑ is the experimental activity, Yₑ_pred is the predicted activity, and Yₑ_mean training is the mean of the experimental activity of the validation set (Tropsha et al., 2003).

2.1.5 Applicability domain

Applicability domain is carried out to investigate the compounds with cross-validated standardized residuals greater than 3√(N) (outliers) and compounds with leverages greater than the warning leverage (influential compounds)(Tropsha et al., 2003). In this regard, Leverage approach is used and is represented as hᵢ:

\[ hᵢ = (X^T X)^{-1} xᵢ xᵢ^T \] (i=K,…, P)

The threshold (h*) is given as:

\[ h* = 3(p+1)/N \]

where p represent the number of descriptors in the model and N is the number of compounds in the model set.

2.1.6 MLR Y-randomization Test.

MLR Y-randomization test (Rᵧ)² of the best model was carried out to ensure that the model was not gotten by chance. The strength of the best model was confirmed by the high low R² and Q² values for many trials (Adedirin et al., 2018). Rᵧ² is given by equation 5.

\[ Rᵧ² = R*(R² - \text{average } Rᵢ )^{1/2} \] (5)

2.2.0 Docking analysis.

The interaction between the receptor (α-glucosidase) and the ligands (Thiazole analogues) was studied using molecular docking. The ligands were prepared by saving the structures of the studied compounds in pdb file format for this analysis (Abdulfatai et al., 2017). The crystal structure of the target enzyme (α-glucosidase) with this ID 3AJ7 was downloaded from Protein Databank (PDB). The receptor was prepared with the aid of Discovery studio software (Veerasamy et al., 2011) and save as PDB. The prepared structures of the ligand and the receptor were shown in Figures 1 and 2. Autodock vina of pyrex software was used to dock the ligands (Thiazole analogues) to the binding pocket of the target enzyme (α-glucosidase) (Trott and Olson, 2010). One of the limitations of docking with Auto-dock vina of Pyrex is that the ligand and the receptor separated (decoupled) after carrying out the docking. Therefore, chimera was utilized for the recoupling of the ligands and the α-glucosidase (rebuilding the complexes) and analyzed by the visualization of the complexes to study their nature of interactions.

**Figure 1** - 3D structure of the prepared Ligand.

**Figure 2** - 3D structure of the prepared Receptor.
3. Result and Discussion.

3.1 QSAR Results of the studied compounds

The MLR analysis was done employing GFA method to develop the models. The first model was selected as the studied model based on its statistical fitness as it has LOF value of 0.101072, $R^2$ value of 0.906134, $R^2_{\text{adj}}$ value of 0.89049, $Q^2_{\text{LOO}}$ value of 0.86149 and the $R^2_{\text{pred}}$ value of 0.825811. The minimum accepted values for a suitable QSAR model validation is given in Table 2 (Ibrahim et al., 2018b).

Table 2- The minimum accepted values for a suitable QSAR model validation

| Symbol | Name                          | Value                  |
|--------|-------------------------------|------------------------|
| $R^2$  | Co-efficient of determination | $\geq 0.6$             |
| $P_{(95\%)}$ | Confidence interval at 95% confidence level | $< 0.05$ |
| $Q^2$  | Cross-validation co-efficient | $\geq 0.5$             |
| $R^2$ - $Q^2$ | Difference between $R^2$ and $Q^2$ | $\leq 0.3$ |
| $N_{\text{ext.} \& \text{test (set)}}$ | Minimum number of external and test set | $\geq 0.5$ |
| $R^2_{\text{ext.}}$ | Co-efficient of determination of external and test set | $\geq 0.5$ |

Table 3-The names, definitions, and category of the descriptors that appear in the selected model

| S/No | Name      | Definition                                                                                     | Category |
|------|-----------|------------------------------------------------------------------------------------------------|----------|
| 1    | AATSC8p   | Average centered Broto-Moreau autocorrelation - lag 8 / weighted by polarizabilities.           | 2D       |
| 2    | SpMin7_Bhv| The largest absolute eigenvalue of Burden modified matrix - n 7 / weighted by relative van der Waals volumes. | 2D       |
| 3    | SpMax7_Bhe| The largest absolute eigenvalue of Burden modified matrix - n 7 / weighted by relative Sanderson electronegativities. | 2D       |
| 4    | SpMin7_Bhp| The smallest absolute eigenvalue of Burden modified matrix - n 7 / weighted by relative polarizabilities | 2D       |
| 5    | SpMax3_Bhi| The largest absolute eigenvalue of Burden modified matrix - n 3 / weighted by relative first ionization potential | 2D       |

The negative coefficient of these independent variables AATSC8p, SpMax3_Bhi, and SpMin7_Bhp in the model suggest that when the values of these independent variables in the thiazoles analogues are decreased, the inhibitory activity of these anti-diabetic compounds against α-glucosidase will be improved, whereas increasing such independent variables will reduce the inhibitory activity of these compounds against α-glucosidase, meaning that these independent variables contributed negatively to the inhibitory activity of these compounds. Also, the positive coefficient of SpMin7_Bhv and SpMax7_Bhe independent variables suggest that adding such independent variables will improve the activity of these anti-diabetic compounds against α-glucosidase. The higher the value of this independent variables, the better the anti-diabetic activity of these compounds against α-glucosidase. This implies that these independent variables contributed positively to the inhibitory activity of the thiazoles analogues. The names, definitions, and category of the descriptors in the selected model were presented in Table 3.

The graph of predicted activities of both the model building sets and validation sets versus the inhibitory activities (pIC₅₀) is presented in Figure 3. It can be seen from the graph that the internal validation $R^2$ value of the training set agrees with the $R^2$ value of 0.8061 extrapolated from the graph which affirmed the strength, reliability and robustness of the selected model.

In order to confirm the absence of systematic error in the selected model, Actual activities was plotted against standardized residuals. The even distribution of these residuals in Figure 4 on either side of zero indicates that the selected model was free from systematic error.

The high predictive ability of the selected model was confirmed by the low residual values observed between the Actual activities (pIC₅₀) and the Predicted activities (pIC₅₀) in Table 4.

R² = 0.906134 $R^2_{\text{adj}} = 0.89049$, $Q^2_{\text{LOO}} = 0.86149$, $N_{\text{trng}} = 36$, $R^2_{\text{test}} = 0.825811$, $N_{\text{test}} = 9$, LOF = 0.101072.
Table 4-The $pIC_{50}$, Predicted ($pIC_{50}$) and Residual of the selected Model

| S/No. | $pIC_{50}$ | Predicted $pIC_{50}$ | Residual |
|-------|------------|---------------------|----------|
| M001  | 2.34       | 2.163252            | 0.176748 |
| M002  | 1.64       | 1.671857            | -0.03186 |
| M003  | 2.38       | 2.473876            | -0.09388 |
| M004  | 2.59       | 2.577783            | 0.012217 |
| M005  | 2.24       | 2.10412             | 0.13588  |
| M007  | 1.57       | 1.485451            | 0.084549 |
| M008  | 1.26       | 1.261678            | -0.00166 |
| M009  | 1.84       | 2.028562            | -0.18856 |
| M011  | 2.25       | 1.973986            | 0.276014 |
| M012  | 2.63       | 2.379583            | 0.250417 |
| M013  | 2.28       | 2.400443            | -0.12044 |
| M014  | 2.16       | 2.141774            | 0.018226 |
| M016  | 2         | 1.986361            | 0.013639 |
| M017  | 2.09       | 2.092718            | -0.00272 |
| M018  | 1.74       | 2.129947            | -0.38995 |
| M019  | 2.35       | 2.262639            | 0.087361 |
| M021  | 1.67       | 1.849764            | -0.17976 |
| M022  | 1.37       | 1.379203            | -0.0092  |
| M023  | 1.36       | 1.500701            | -0.1407  |

S/No. | $pIC_{50}$ | Predicted $pIC_{50}$ | Residual |
|-------|------------|---------------------|----------|
| M024  | 1.35       | 1.340045            | 0.00955  |
| M026  | 1.92       | 1.82598             | 0.09402  |
| M027  | 1.54       | 1.45742             | 0.08258  |
| M028  | 1.42       | 1.163053            | 0.256947 |
| M029  | 1.15       | 1.127712            | 0.022288 |
| M031  | 1.43       | 1.653718            | -0.22372 |
| M032  | 1.28       | 1.230159            | 0.049841 |
| M033  | 0.98       | 1.03571             | -0.05571 |
| M034  | 1.11       | 1.320836            | -0.21084 |
| M036  | 1.23       | 1.222137            | 0.007863 |
| M037  | 1.1        | 1.181313            | -0.08131 |
| M038  | 1.21       | 1.204513            | 0.005487 |
| M039  | 1.51       | 1.393759            | 0.116241 |
| M041  | 1.7        | 1.791219            | -0.09122 |
| M042  | 1.86       | 1.774504            | 0.085496 |
| M043  | 1.86       | 1.790044            | 0.069956 |
| M044  | 1.67       | 1.704178            | -0.03418 |

Figure 3-The plot of $pIC_{50}$ and Predicted $pIC_{50}$ of both the model and validation sets of the selected model.

The predicted activities and residuals of the test set for the selected model were calculated and shown in Table 5 which further confirmed the high predictive ability of the selected model. The Computation of predictive $R^2$ shown in Table 6 further confirmed the robustness and reliability of the selected model.
Figure 4-The plot of the Residual and pIC\textsubscript{50} of the selected model.

Table 5-Computation of pIC\textsubscript{50} (predicted) and residuals of the validation set of the selected model

| pIC\textsubscript{50} | AATSC8p | SpMin7_Bhv | SpMax7_Bhe | SpMin7_Bhp | SpMax3_Bhi | Y\textsubscript{prd} | Y\textsubscript{prd}-Y\textsubscript{obs} |
|-----------------|---------|-------------|-------------|-------------|-------------|----------------|-----------------|
| 2.31            | 0.02102 | 1.12975     | 2.77182     | 1.05826     | 3.67607     | 2.25508        | -0.0549         |
| 2.53            | -0.035  | 1.00717     | 2.77182     | 0.96028     | 3.67238     | 2.29632        | -0.2337         |
| 2.29            | 0.01892 | 1.17481     | 2.95111     | 1.1323      | 3.69485     | 2.36787        | 0.07787         |
| 2.24            | 0.01171 | 1.13687     | 2.86851     | 1.10062     | 3.68024     | 2.22016        | -0.0198         |
| 1.42            | 0.01627 | 1.24737     | 3.00503     | 1.21827     | 3.86868     | 1.43454        | 0.01454         |
| 1.25            | -0.0102 | 1.25682     | 2.94436     | 1.23031     | 3.85148     | 1.54138        | 0.29138         |
| 1.08            | -0.0151 | 1.00717     | 2.87537     | 0.96028     | 3.84982     | 1.36791        | 0.28791         |
| 1.69            | -0.0292 | 1.33475     | 3.26554     | 1.40219     | 3.91931     | 1.27785        | -0.4121         |
| 1.69            | -0.0251 | 1.2809      | 3.13963     | 1.26558     | 3.90035     | 1.72007        | 0.03007         |

Table 6-Computation of predictive R\textsuperscript{2} of the selected model

| S/No. | (Y\textsubscript{prd}-Y\textsubscript{obs})\textsuperscript{2} | Y\textsubscript{umd} | Y\textsubscript{obs}-Y\textsubscript{umd} | (Y\textsubscript{obs}-Y\textsubscript{umd})\textsuperscript{2} | \Sigma(Y\textsubscript{umd}-Y\textsubscript{obs})\textsuperscript{2}=0.4029 | \Sigma(Y\textsubscript{obs}-Y\textsubscript{umd})\textsuperscript{2}=2.313 |
|-------|-----------------------------|---------------------|-----------------------------|-----------------------------|--------------------------|--------------------------|
| 5     | 0.00302                    | 1.7244              | 0.5856                      | 0.34293                     | \Sigma(Y\textsubscript{umd}-Y\textsubscript{obs})\textsuperscript{2}=0.4029 | \Sigma(Y\textsubscript{obs}-Y\textsubscript{umd})\textsuperscript{2}=2.313 |
| 10    | 0.05461                    | 1.7244              | 0.8056                      | 0.64899                     | \Sigma(Y\textsubscript{umd}-Y\textsubscript{obs})\textsuperscript{2}=0.4029 | \Sigma(Y\textsubscript{obs}-Y\textsubscript{umd})\textsuperscript{2}=2.313 |
| 15    | 0.00606                    | 1.7244              | 0.5656                      | 0.3199                      | \Sigma(Y\textsubscript{umd}-Y\textsubscript{obs})\textsuperscript{2}=0.4029 | \Sigma(Y\textsubscript{obs}-Y\textsubscript{umd})\textsuperscript{2}=2.313 |
| 20    | 0.00039                    | 1.7244              | 0.5156                      | 0.26584                     | \Sigma(Y\textsubscript{umd}-Y\textsubscript{obs})\textsuperscript{2}=0.4029 | \Sigma(Y\textsubscript{obs}-Y\textsubscript{umd})\textsuperscript{2}=2.313 |
| 25    | 0.00021                    | 1.7244              | -0.3044                     | 0.09266                     | \Sigma(Y\textsubscript{umd}-Y\textsubscript{obs})\textsuperscript{2}=0.4029 | \Sigma(Y\textsubscript{obs}-Y\textsubscript{umd})\textsuperscript{2}=2.313 |
| 30    | 0.0849                     | 1.7244              | -0.4744                     | 0.22506                     | \Sigma(Y\textsubscript{umd}-Y\textsubscript{obs})\textsuperscript{2}=0.4029 | \Sigma(Y\textsubscript{obs}-Y\textsubscript{umd})\textsuperscript{2}=2.313 |
| 35    | 0.08289                    | 1.7244              | -0.6444                     | 0.41525                     | \Sigma(Y\textsubscript{umd}-Y\textsubscript{obs})\textsuperscript{2}=0.4029 | \Sigma(Y\textsubscript{obs}-Y\textsubscript{umd})\textsuperscript{2}=2.313 |
| 40    | 0.16987                    | 1.7244              | -0.0344                     | 0.00118                     | \Sigma(Y\textsubscript{umd}-Y\textsubscript{obs})\textsuperscript{2}=0.4029 | \Sigma(Y\textsubscript{obs}-Y\textsubscript{umd})\textsuperscript{2}=2.313 |
| 45    | 0.0009                     | 1.7244              | -0.0344                     | 0.00118                     | \Sigma(Y\textsubscript{umd}-Y\textsubscript{obs})\textsuperscript{2}=0.4029 | \Sigma(Y\textsubscript{obs}-Y\textsubscript{umd})\textsuperscript{2}=2.313 |

\[
R^2 = 1 - \frac{(0.4029/2.313)}{} = 0.8258
\]
The Pearson’s correlation was carried out on the independent variable that appear in the selected model (Table 7). This indicates that the independent variable utilized in generating the model were of good quality. Also, the importance and contribution of the independent variable that appear in the selected model were determine using their mean effect values (Table 7).

### Table 7-Pearson’s correlation analysis of the descriptors in the studied model

|        | AATSC8p | SpMin7_Bhv | SpMax7_Bhe | SpMin7_Bhp | SpMax3_Bhi | MF    |
|--------|---------|------------|------------|------------|------------|-------|
| AATSC8p | 1       |            |            |            |            | 0.001173 |
| SpMin7_Bhv | 0.001986 | 1          |            |            |            | -0.74996 |
| SpMax7_Bhe | -0.3452 | 0.837262   | 1          |            |            | -0.47028 |
| SpMin7_Bhp | -0.13042 | 0.981499   | 0.904859   | 1          |            | 0.658535 |
| SpMax3_Bhi | -0.45466 | 0.448907   | 0.64831    | 0.516989   | 1          | 0.679415 |

The applicability domain was shown by plotting the Williams plot (standardized residuals against leverages) as shown in Figure 5. It can be seen from the plot that 6 compounds in the test set have their leverages value greater than the threshold value h*(h*=0.5). These compounds are called influential compounds and they are not considered when designing new other ones with improved activities because the model cannot predict their activities. The MLR Y-randomization test is carried to assess the robustness of the selected model. It is shown in Table 8 that the selected model was robust and was not obtained by chance because the new parameter (cRp^2) obtained was greater than 0.5 (0.606241).

### Table 8-MLR Y-randomization result

| Model | R     | R^2    | Q^2    |
|-------|-------|--------|--------|
| Original | 0.817486 | 0.668283 | 0.543764 |
| Random 1 | 0.435427 | 0.189597 | -0.07775 |
| Random 2 | 0.596614 | 0.355949 | -0.07775 |
| Random 3 | 0.581513 | 0.338158 | 0.11225 |
| Random 4 | 0.231249 | 0.053476 | -0.24571 |
| Random 5 | 0.227931 | 0.051953 | -0.24571 |
| Random 6 | 0.320037 | 0.102423 | -0.25776 |
| Random 7 | 0.382972 | 0.146668 | -0.14174 |
| Random 8 | 0.317907 | 0.101065 | -0.21706 |
| Random 9 | 0.282764 | 0.079956 | -0.25776 |
| Random 10 | 0.063417 | 0.004022 | -0.34226 |

#### Docking studies Results

45 sets of thiazole analogues (Ligands) were docked against α-glucosidase (receptor). The results of the docking analysis in Table 9 clearly showed that ligand number 13 has the highest binding energy of -11.0 kcal/mole and formed hydrogen bond interactions with ARG442 (2.5752 Å), hydrophobic interactions with active residues such as TYR158, LYS156, ARG315, LYS156, electrostatic interaction with HIS280 and carbon-hydrogen bond with ASP215 (3.5158 Å), ASP352 (3.5652 Å). The standard drug (acarbose) was also docked to the binding pocket of α-glucosidase with -9.5 kcal/mole docking score. It formed 8 hydrogen bond interactions with GLU421 (2.36494 Å), ASN417 (2.22115 Å), SER162 (2.51822 Å), THR165 (2.12267 Å), ARG176 (3.03496 Å), ARG176 (2.58199 Å), ASN414 (2.36034 Å) and SER162 (3.7388 Å) of α-glucosidase. Figure 6A and B showed the 2D interaction between ligand 13- receptor and Standard drug - receptor.
| Ligands-Receptor | Binding Energy (kcal/mol) | Hydrophobic Interaction | Electrostatic Interaction/Others | Hydrogen Bonds | Hydrogen Bond Distance (Å) |
|-----------------|--------------------------|-------------------------|---------------------------------|----------------|---------------------------|
| 1               | -8.5                     | SER311, ARG315 and PRO312 | ASP307                          | ASP307 and ARG442 | 2.8858 and 2.3897       |
| 2               | -8.7                     | PHE303, TYR158, VAL216, TYR72, PHE178, and HIS280 | GLU27 and ASP35 | SER24 and SER240 | 2.0339 and 3.0898       |
| 3               | -8.5                     | TRP15, ILE262, ARG263 and ILE272 | GLU271                          | ILE272         | 3.0922                    |
| 4               | -9.7                     | ASP307, VAL308, PRO312, ARG315 and PHE303 | ASP307                          | SER311, ASP307 and THR310 | 2.1107 and 2.7360       |
| 5               | -8.2                     | TYR158, ASP307, VAL308, PRO312 and ARG315 | ASP307                          | ASP307, THR310 and SER311 | 2.8322                    |
| 6               | -9.3                     | ARG315, VAL308 and ALA329 | ASP307                          | THR310 and ASP307 | 2.7397 and 2.2357       |
| 7               | -9.1                     | VAL308, TYR158, ARG315, PRO312 and PHE178 | GLU411 and ASP352 | GLU411    | 2.9724                    |
| 8               | -9.3                     | VAL216, ARG315, TYR72, HIS112, TYR158, PHE178 and PHE314 | LYS156 and TRP238 | ASN415, GLY161, SER157 and PHE314 | 2.2854, 2.6837, 3.7     |
| 9               | -9.4                     | TYR158, PHE314, PHE314, LYS156 and ALA418 | GLU411, ASP352, and PHE314 | ASP307, THR310, SER311 and ASP325 | 2.5887, 2.0332, 2.4954 and 3.6392 |
| 10              | -9.1                     | VAL216, ARG315, LYS156, TYR158, and PHE178 | LYS156 and TRP238 | ASP415, GLY161, SER157 and PHE314 | 2.5364, 2.6937, 2.5569 and 2.6233, 2.6399, 3.5288 and 3.4713 |
| 11              | -9.1                     | PHE303, TYR158 and PHE315, LYS156, ALA418 and ILE419 | LYS156 and TRP238 | ASP242, ARG442, ASP252, and ASP352 | 2.5752, 3.5158, 3.5652 and 3.55 |
| 12              | -9.4                     | VAL308, TYR158, ARG315, PHE178 and ALA329 | HIS280                          | GLU411, ASP219 and ASP352 | 2.5332, 2.1136, and 3.3652 |
| 13              | -11.0                    | TYR158, LYS156, ARG315 and LYS156 | HIS280                          | ASP307, THR310, SER311 and ASP325 | 2.5887, 2.0332, 2.4954 and 3.6392 |
| 14              | -8.2                     | TYR158, ASP307, VAL308, PRO312, ARG315 and PRO312 | ASP307                          | ASP307, THR310, SER311 and ASP325 | 2.5887, 2.0332, 2.4954 and 3.6392 |
| 15              | -9.8                     | TYR158, PHE178, ARG315, LYS156, and VAL216 | GLU411, ASP352, PHE314 and TYR316 | GLU411, ASP242 and TYR158 | 2.6801, 2.9945, and 3.6015 |
| 16              | -9.4                     | TYR158, ASP307, VAL308, PRO312 and ARG315 | ASP307 and ASP352 | ASP307 and ASP352, PHE303 | 2.607, 2.1655, 2.5259 and 2.0355, 2.3695, 2.3610, 2.6801, 2.0895, and 3.0553 |
| 17              | -8.8                     | ARG315, PRO312 and PHE303 | ASP307                          | THR310, SER311, ASP307 and THR310, SER311 | 2.607, 2.1655, 2.5259 and 2.0355, 2.3695, 2.3610, 2.6801, 2.0895, and 3.0553 |
| 18              | -8.9                     | LYS156 and TYR158 | ASP242, HIS280 and PHE303 | ASP307, THR310, SER311 and ASP325 | 2.607, 2.1655, 2.5259 and 2.0355, 2.3695, 2.3610, 2.6801, 2.0895, and 3.0553 |
| 19              | -9.0                     | ALA292, TRP15, LEU297, SER298, VAL266, ARG263, ILE272 and LYS13 | ASP242, HIS280 and PHE303 | ILE272, ASN259, and GLU111 | 1.9759, 3.6456, and 3.4362 |
| 20              | -8.8                     | ALA292, TRP15, SER291, ILE262 and ARG263 | THR274                          | ASN259, GLU296, THR290, SER298, THR274, ARG263 and LEU297 | 2.7351, 2.3154, 1.9711, 2.9548, 2.3927, 3.4650, and 3.5142 |
| 21              | -9.2                     | TYR158, ARG315 and LYS156 | GLU411, ARG442, ASP352, PHE314 and TYR316 | GLU277 and ASP352 | 2.1094 and 2.3821 |
| 22              | -9.4                     | TYR158 | ASP307 and ASP352 | ASP307 and ARG442 | 3.0021 and 3.6732 |
| 23              | -9.6                     | TYR158 | ASP307 and ASP352 | ASP307 and ARG442 | 3.0815 and 3.4567 |
| 24              | -9.3                     | TYR158 | ASP307 & ASP242 | ASP307 and ARG442 | 3.0287 and 2.2548 |
| Ligands-Receptor | Binding Energy(kcal/mol) | Hydrophobic Interaction | Electrostatic Interaction/Others | Hydrogen Bonds | Hydrogen Bond Distance (Å) |
|------------------|--------------------------|-------------------------|--------------------------------|----------------|-------------------------|
| 25               | -8.4                     | HIS280, TYR158 and PRO312 | ASP242 and ASP307             | ASP242         | 2.1545                  |
| 26               | -9.3                     | TYR158 and PHE159       | ASP307 and ASP242             | ASP307         | 3.0050                  |
| 27               | -8.7                     | PHE321, LEU323, LEU318, LEU439, TRP326 and PHE360 | THR358 and GLY361 | 2.4937 and 2.1589 |
| 28               | -9.0                     | TYR158 and PHE178       | ASP242                         | PRO312, LYS156 and SER240 | 2.0603, 2.1594 |
| 29               | -8.9                     | ARG315 and PRO312       | ASP307 and ASP242             | GLY160 and ASN415 | 2.989 and 2.1150 |
| 30               | -8.9                     | TYR158, LYS156 and ARG315 | ASP307 and ASP242             | SER241 and ASP307 | 1.7843 and 2.5307 |
| 31               | -9.1                     | ARG315 and TYR158       | ASP307                         | PRO312, LYS156 and SER240 | 1.9013 |
| 32               | -8.8                     | SER240 and TYR158       | ASP242                         | SER240 and ARG315 | 1.8459 |
| 33               | -9.1                     | ARG315,TYR158 and PHE159 | ASP242                         | PRO312         | 1.8991                  |
| 34               | -9.8                     | PRO312, TYR158, HIS280, ARG315 and HIS280 | ASP307                         | ASP307, SER311, SER241, SER240 and ARG315 | 2.9473, 2.7324 |
| 35               | -9.1                     | HIS280, VAL232, ARG315 and TYR158 | ASP307                         | SER311, SER241 and ARG315 | 1.8218, 3.0827, 2.9212 |
| 36               | -9.9                     | PRO312, TYR158, PRO312, ARG315 and HIS280 | ASP307                         | SER311, SER241 and ARG315 | 2.7322 |
| 37               | -8.9                     | HIS280, VAL232, LEU313, TYR158 and PHE159 | ASP242                         | SER240 and ARG315 | 1.8313, 3.0822 |
| 38               | -9.1                     | PHE303, LYS156, TYR158 and PHE178 | ASP307                         | ARG315         | 2.9219                  |
| 39               | -8.4                     | ARG263, VAL266, and ALA292 | ASP242 and ASP307             | ASP307, THR290, ARG315 and ARG315 | 2.4738, 3.3492 |
| 40               | -8.3                     | PHE321                   | TRP581                         | GLY361, LEU323, LYS523 and ASP363 | 2.7081 |
| 41               | -8.1                     | PHE321, LEU323, and LYS523 | ASP242                         | ASP242, ARG176 and ARG315 | 2.3735, 2.1644, 2.3789 |
| 42               | -7.7                     | ALA418 and LYS148        | GLU421, ARG176, and PHE173    | TRP164, ASN414, and ARG176 | 1.9111 |
| 43               | -9.0                     | HIS280, TYR158, PHE303, VAL232, LEU313, PRO312, ARG315 and HIS280 | ASP242, ASP307 and TYR158 | 2.6508, 2.7899 |
| 44               | -7.7                     | ALA418 and LYS148        | GLU421, ARG176, and PHE173    | TRP164, ASN414, and ARG176 | 3.4268 |
| 45               | -9.0                     | TYR158, VAL216, ARG315, PHE159, PHE178, and PHE303 | ASP307, ASP242, and HIS280 | 2.6530, 2.7260, 3.4199 |

**Std drg-Recptor**

-9.0

GLU421, ASN417, SER162, THR165, ARG176, ARG176, ASN414 and SER162

2.36494, 2.2211, 5.2, 2.3822, 2.12267, 3.0349, 2.25819, 2.36, 0.34, and 2.7388
4. Conclusion.

Computational Studies on 45 studied compounds as α-glucosidase inhibitors were carried out. Based on the assessment carried out, the first model was selected as the studied model and assessed with LOF value of 0.101072, $R^2$ value of 0.906134, $R^2_{adj}$ value of 0.89049, $Q^2_{LOO}$ value of 0.86149 and the $R^2_{pred}$ value of 0.825811. The QSAR result of this study indicates the effects of the descriptors $AATSC8p$, $SpMax3_{Bhi}$, and $SpMin7_{Bhp}$ as they contributed negatively to the inhibitory activities of the thiazole analogues. While $SpMin7_{Bhv}$ and $SpMax7_{Bhe}$ have positive effects toward the inhibitory activities of the compounds. The docking study clearly showed that ligand number 13 has the highest binding energy (-11.0 kcal/mole) and formed hydrogen bonding with ARG442 (2.5752Å), hydrophobic interaction with active residues such as TYR158, LYS156, ARG315, LYS156, electrostatic interaction with HIS280 and carbon-hydrogen bond with ASP215 (3.5158 A˚), ASP352 (3.5652 A˚). The standard drug (acarbose) was also docked to the binding pocket of α-glucosidase with -9.5kcal/mole docking score. The most active compound was found to be better than standard drug acarbose. We hope this research may give the basis for the designing of new thiazole derivatives with better inhibitory activities.

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