MOLECULAR DOCKING AND QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP (QSAR) STUDIES OF SOME SELECTED ANTI-ULCER INHIBITORS

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ARTICLE INFO
Article history:
Received 2018-04-25
Accepted 2018-06-11
Available online 2019-03-08

KEYWORDS
K+/H+AT-pase
Quantitative structure-activity relationship
Genetic function algorithm
Peptic ulcer diseases
Density functional theory (B3LYP/6-31G*)

ABSTRACT
Proton pump inhibitors portray the first choice for treating various ulcer disease, because they inhibit H+/K+-ATPase enzyme by covalently binding to a cysteine residue of either potassium or proton pump. Therefore, this enzyme is a validated target for anti-ulcer remedy/drugs. A quantitative structure-activity relationship and molecular docking studies have been made on 30 benzo[d]thiazole series as H+/K+-ATPase inhibitors. Density Functional Theory was used to optimize the geometry of the anti-ulcer compounds. Four types of molecular descriptors were generated in other to know the relationship that exit between anti-ulcer activity and structural properties of these compounds. The QSAR result revealed high statistically significant correlation coefficients $R^2 = 0.9401$, $R^2_{adj} = 0.9250$, $Q^2_{LOO} = 0.8842$ and $R^2_{pred} = 0.7975$. Our QSAR model showed an excellent predictive activity with the chemical properties of the compounds. The results of the docking analysis revealed that most of the compounds showed a very good relationship with the active receptor, with a better docking score of -9.1kcal/mol. The physicochemical parameters are to be considered when improving the inhibitory activities of benzo[d]thiazole against the enzyme that causes the ulcer (H+/K+-ATPase).
1. INTRODUCTION

An ulcer can be referred to as an area in the digestive system where the tissue has been damaged or destroyed by stomach juice or other digestive enzymes (Chaudary et al., 2015). Peptic ulcer disease is the “umbrella term” used to describe all gastrointestinal tract disorders (ulcers). Other various types of ulcer include acute and chronic ulcer (Rakesh et al., 2017), and can be ascribed to imbalances between aggressive factors such as acid and pepsin, and protective factors such as bicarbonates, blood flow and mucous membrane, in the stomach. This balance may be disturbed due to Helicobacter pylori infection (Skoglung, 2008; Rakesh et al., 2017; Wang et al., 2017), a gram-negative bacteria parasite, which has successfully colonized more than half of human population, and caused about 15-20% of pathologies such as adenocarcinomas, duodenal ulcer, and stomach lymphomas (Shi et al., 2016). Pain-killer drugs, such as ibuprofen, naproxen and diclofenac, which contain carboxylic groups are also believed to cause about 40% of peptic ulcer diseases (Fashner and Gitu, 2015; Shamsudeen et al., 2009). H⁺/K⁺-ATPase is a member of the class 2C P-type ion-transport ATPases. Also known as the primary gastric proton pump, which moves acid across parietal cells, and gastric mucosa (Rakesh et al., 2017). It was reported that H⁺/K⁺-ATPase (gastric proton/potassium pump) is the last passage of gastric acid secretion, and hypersecretion of this acid result in severe superior gastrointestinal bleeding (Wang et al., 2017). Common symptoms of the diseases include episodic gnawing, abdominal pain, vomiting and loss of appetite (Shamsudeen et al., 2009). The pain is typically alleviated when the stomach is empty, 2 to 5 hours after meals (Skoglung, 2008).

Peptic ulcer disease is one of the life-threatening diseases, that affect the large population of the world (Skoglung, 2008). Approximately 500,000 people are affected by the diseases in the United States, new 4 million cases of peptic ulcer complications, 1.8% lifetime prevalence (8-14%) with annual costs of $4.82 billion in the developing countries (Noor et al., 2017). Men are more vulnerable to peptic ulcer diseases compared to women, and this is due to their engagement in alcohol drinking, and cigarette smoking in the society (Rajesh et al., 2016). The widespread use of the antibiotic such as amoxicillin, clarithromycin, lansoprazole and omeprazole at present, is hardly effective due to increasing resistance of the bacterium to the classes of these drugs (Drini, 2017). Excess use of pain-killer drugs can cause mucosal injury, inflammation, intestinal permeability, protein loss, with a severe complication like anemia, obstruction diverticulum, ileal dysfunction and diaphragm structures (Utzeri & Usai, 2017). Therefore, in order to narrow the aforementioned problems, demand in search and design of novel compounds possessing anti-ulcer, anti-inflammatory, anti-microbial, anti-convulsant, antioxidant, and anti-diabetic activities (Rajesh et al., 2017; Ya-Li et al., 2015). Hydrazone Schiff bases are family of compounds that contain an azomethine group (–CH=N–) in their structure. Different derivatives of benzo[b]thiazole substituted at the 2 position have diverse therapeutic applications and anticancer effects.

Computational design of novel molecule is a method that has been applied to speed drug discovery process, resulting in its acknowledgment and popularity. More also it inclination to reduce the classical trial and error approach (David et al., 2018). QSAR and molecular docking method are widely used to discover the novel blow for various therapeutic targets, and also help medicinal chemists to identify essential features associated to biological activities of molecules. (Pawar et al., 2014). QSAR studies also play a crucial role as predictive tools for a molecular development, and this is due to their low cost, little time involve in examining a large number of compounds (Castillo-Garit et al., 2012). Molecular docking show how two or more molecular structures interact with each other for example, determination of how a chemical substance and receptor are lock together in a model. This place demands on the use of the computational method, which must be quick and suitable (Abdulfatai et al., 2017). The main aim of this work is to search for effective anti-ulcer inhibitors (Shi et al., 2016), using QSAR and molecular docking studies.

2. MATERIAL AND METHOD

Experimental dataset collection

30 series of benzo[d]thiazole derivatives, identified from literature experimentally proven to inhibit H⁺/K⁺-ATPase were used for this study (Wang et al., 2017). The inhibitory activities of these compounds measured as IC₅₀ (μM) were normalized and expressed in logarithmic scale as pIC₅₀ (pIC₅₀ = log10(IC₅₀)). pIC₅₀ was chosen as a reliable independent variable, which was correlated with the independent variable descriptors. Using Genetic function algorithm. The chemical structures and the pIC₅₀ (anti-ulcer activities), of these compounds are shown in Table 1.

2.1 Dataset division

The biological data set was divided into a training and test set, in such a way that 70% (21) of the data set was made up of the training set while 30% (9) of the biological data was used as the validation test. Kennard- Stone Algorithm was used for the division of the biological data into a training set and validation/test set (Kennard and Stone, 1969).

2.2 Calculation of molecular descriptors

The Padel descriptor software version 2.18 was used for the generation of the 1D, 2D and 3D descriptors from the optimized structures of the Spartan files saved as sdf file format which is the recommended input file format for the Padel descriptor software (Yap 2011).
2.3 Model Building

The model was build using material studio software at Genetic Function Algorithms (GFA). The generated chemical descriptors from Padel software tool were submitted for regression analysis with the PIC₅₀ values chosen as the relying variable, while the descriptors were selected as unrellying variables. The regression equation was 4 which represent the number of the descriptors, 1000 was chosen for the Population, and 500 was input for the Generation parameter. The mutation probability was 0.1, and the top equation number was 4, smoothing parameter is 0.5. Friedman’s Lack of Fit (LOF) was used to score the model and other statistical parameters such as correlation coefficient matrix (R²) for the internal, and R² for external validation, statistical significance was determined using F test (Fischer’s value); Q² (cross-validated correlation coefficient). ‘Equation 1 shows the Friedman’s lack of fit formula.

\[ \text{LOF} = \frac{\text{SSE}}{(1 - \frac{c + d p}{m})} \]  (1)

SSE is the sum of square of errors, c refers to the number of terms in the model, other than constant time, p is the total number of descriptors, while d is a user-defined smoothing parameter. P is the total number of descriptors contained in all model terms, and M is the number of samples in the training set. Equation 2 show’s structure of the regression model formula (David et al., 2018).

\[ Y = a_1 x_1 + a_2 x_2 + a_3 x_3 + b \]  (2)

Y is the activity (pIC₅₀), where ‘a’s and ‘x’s are regression coefficients for a conforming Nonpartisan variable representing molecular descriptors of the molecules, the ‘a’s correspond to ‘x’s. While the last variable ‘c’ is the regression constant.

2.4 Geometry optimization

ChemDraw Ultra 12.0 software was used to sketch chemical (2D) structure of the molecules, and were saved as cdx format file. The structures were then converted to 3D using Spartan 14.0 version 1.1.2 software. The calculation was carried out using molecular mechanics force field (MM n+), to minimize the energy of the molecules prior to the quantum chemical calculations.

6-311G* basis set, of density functional theory (DFT) using the B3LYP method was used for whole geometry optimization of the structures to obtain the lowest energy for all the compounds in this study (Abdulfatai et al., 2017). The DFT method uses Becke’s three-parameter functional (B3) with gradient correlation functional of Lee, Yang and Parr (LYP) which integrates a mixture of HF with DFT exchange terms.

2.5 Quality assurance of the model

The QSAR model exploits in this study, was evaluated through the use of internal and external validations parameters. The reliability and fatal capability of the model can also be determined using the parameter.

2.6 Validation of the model

The standard used to compare internal and external validation parameters of a particular QSAR model is shown in table 2 (Abdulfatai et al., 2017). Component of the total variation assign to the model is known through the square of the correlation coefficient (R²) parameter. R² is commonly used for internal validations, and the closer the R² to 0.1 the better the regression equation tell us more about Y variable. The expression for R² is given below:

\[ R^2 = 1 - \frac{\sum(y_{\text{obs}} - y_{\text{pred}})^2}{\sum(y_{\text{obs}} - y_{\text{training}})^2} \]  (3)

where Yₚₑᵈ, Yₜₒₖ and Yₙₜₑₜₕₐᵣₜₙᵢₜᵢₘᵢₜᵦᵢₙᵦᵢₙᵦᵢₖₜ are the predicted activity, the second is the experimental activity, while the latter represents the mean experimental activity of the sample in the training set compounds (Abdulfatai et al., 2017).

Adjusted R² (R² adj) value vary directly with the increase in the number of repressors i.e. descriptors. ‘Equation 4 shows the adjusted R² formula.

\[ R^2 \, \text{adj} = 1 - (1 - R^2) \frac{n-1}{n-p-1} = \frac{(n-1)R^2-p}{n-p+1} \]  (4)

The letter n is the number of training set compounds, p is the number of independent variables in the model (Brand and Orr 2015). Equation 5 shows the formula for leave one out cross validation coefficient (Q²).

\[ Q^2 = 1 - \frac{\sum(y_p-y)^2}{\sum(y-y_{\text{training}})^2} \]  (5)

where Yₚ explain predicted activity, and Y represent observed activity of the training set, Yₙₜₑₜₕₐᵣₜₙᵦᵢₙᵦᵢₖₜ is the average activity value of the training set (Abdulfatai et al., 2017; Jalali-Heravi and Kyani, 2004).

2.7 Applicability domain

A QSAR model is an essential statistical tool used to determine whether a model make a good prediction within its applicability domain, and this can be determined from Williams plot (Tropsha et al., 2003). There are some techniques for assessing the suitable space of a QSAR model, Leverage is one of them and is given for a chemical compound as hᵢ; ‘Equation 6 shows leverage formula.

\[ h_i = X_i^T(X^T X)^{-1} X_i \]  (6)

The xᵢ represents the row-vector of the compounds’ X is the number of times constant descriptors matrix of the training set compound. It’s used as the prediction tool of the warning leverages (h*) emulating the limit for X values. Thus (h*) is shown in equation 7 below.

\[ h^* = \frac{3(P+1)}{N} \]  (7)
Table 1 - Shows the structures and the activity ($\text{pIC}_{50}$) of the benzo[d]thiazole derivatives.

| S/NO | Molecular structure | $\text{pIC}_{50}$ | S/NO | Molecular structure | $\text{pIC}_{50}$ |
|------|---------------------|------------------|------|---------------------|------------------|
| 1a   | ![Structure 1a](image) | 4.89             | 12a  | ![Structure 12a](image) | 4.41             |
| 2b   | ![Structure 2b](image) | 4.85             | 13a  | ![Structure 13a](image) | 4.69             |
|      | ![Structure 14b](image) | 4.69             | 16a  | ![Structure 16a](image) | 4.36             |
| 4a   | ![Structure 4a](image) | 4.57             | 17b  | ![Structure 17b](image) | 4.31             |
| 5b   | ![Structure 5b](image) | 4.51             | 19a  | ![Structure 19a](image) | 4.51             |
| 6a   | ![Structure 6a](image) | 4.51             | 19a  | ![Structure 19a](image) | 4.24             |
| 7a   | ![Structure 7a](image) | 4.51             | 20b  | ![Structure 20b](image) | 4.22             |
| 9a   | ![Structure 9a](image) | 4.17             | 21a  | ![Structure 21a](image) | 4.15             |
| 10a  | ![Structure 10a](image) | 4.17             | 22a  | ![Structure 22a](image) | 4.09             |
| 11b  | ![Structure 11b](image) | 4.17             | 23a  | ![Structure 23a](image) | 4.09             |
The letter ‘a’ is the training set, while ‘b’ represents test set. The small letter is the number of training set compounds, while p is the number of descriptors that will be used to generate the model. Williams plot is the plot of standardized residuals against the leverages, which give information on the pertinent surface of the model in terms of chemical range. The compounds that lie outside the chemical domain (standardized residual no greater than 3 standard deviation units) are known as Y influential, while any compound that is above the chemical domain are called outliers.

Table 2 - Show’s the general lowest acceptable value for the evaluation of the quantitative QSAR model.

| Name       | Symbols | Value          |
|------------|---------|----------------|
|            | R²      | Coefficient of determination ≥0.5 |
|            | P95     | Confidence interval at 95% <0.05 |
|            | Q²      | Cross-validation coefficient ≥0.5 |
|            | ΔR²     | Difference between R² and Q² ≤0.3 |
| N_ext Test | Minimum number of ≥5 external test set |
| R²_ext     | Coefficient of determination ≥0.5 for external test set |

2.8 Molecular Docking studies

Docking of protein-ligand of some benzo[d]thiazole derivatives was evaluated in order to investigate the interaction between the active site of H⁺/K⁺-ATPase enzyme and the ligands and this was based on the internal validation statistical parameters of the model as it is in line with the recommended validation parameters for QSAR models. The result of the model 1 is given below:

\[ \text{PIC}_{50} = -0.329720059 \times \text{nBondsS3} - 0.999544315 \times \text{SCH-7} + 0.753890542 \times \text{Pubchem185} -0.119244628 \times \text{Pubchem385} + 4.258196 \]

2.9 Preparation of Ligands and Receptor for Docking

The 2D structure of the compounds (benzo[d]thiazole) derivatives, were sketch using ChemDraw Ultra 12.0 software. Which were later converted to 3D structures for geometry optimization of the compounds, using Spartan'14 software. PaDEL Descriptor version 2.18 (Yap, 2011; Anonymous, 2013). The structure of gastric proton pump inhibitors, with the PDB code 2Zex receptor was downloaded from Protein Databank (PDB). The 3D structure receptor was prepared by discarding water molecules and cofactors using Discovery studio software (Ravinchandran et al., 2011) and save as Pdb.

2.9.1 Docking using Autodock version 4.0 of Pyrx software

The docking of the ligands (benzo[d]thiazole derivatives) and the receptor (H⁺/K⁺-ATpase) was perform using Autodock version 4.0 of pyrx software (Trott and Olson, 2010). Chimera version 1.10.2 was used to form the complex (ligand-receptor) since the receptor and the ligand separate after carrying out the docking with autodock vina of pyrx. The complexes were visualized to view their interactions using Discovery studio software.

3. RESULT AND DISCUSSION

Four QSAR models were developed using material studio software (Genetic Function Algorithm). And out of these four models, model 1 was selected as the preferable model for predicting the pIC₅₀ for anti-ulcer compounds,

\[ R^2_{trng} = 0.940021, \quad R^2_{adj} = 0.925026, \quad Q^2_{LOO} = 0.884292, \quad N_{trng} = 21, \quad R^2_{test} = 0.797578, \quad N_{test} = 9. \]
Table 3 – Shows the list of the descriptors, their description, and classes for model 1.

| S/N | Symbols     | Name of descriptors                                      | Class |
|-----|-------------|---------------------------------------------------------|-------|
| 1   | nBondsS3   | Total number of single bonds, (excluding bonds to hydrogens and aromatic bonds) | 2D    |
| 2   | SCH-7      | Simple chain, order 7.                                   | 2D    |
| 3   | Pubchem185 | Pubchem finger print 185.                                | 2D    |
| 4   | Pubchem185 | Pubchem finger print 185                                | 2D    |

The high $Q^2$ LOO cross verification coefficient calculated (0.8842), for pIC$_{50}$ shows a valid internal validation of the model, the test set containing 30% of the biological data set were used for the external verification of the model. The result was found to be 0.7975 which is better than the standard $cR^2_p$ parameter value 0.50 for the model.

From the above plot, it can be deduced that four compounds were found outside the applicability domain, which includes three training set compounds with pIC$_{50}$ of 4.05, 4.89, 4.69 and one test set compound with pIC$_{50}$ 4.39. The plot also shows that compounds found outside the threshold value $h^*$, have very few of the chemical descriptors, and are structurally different when compared to other compounds within the complete data set, i.e. these compounds which could be related to those in the model.

3.1 Interpretation of descriptors in model 1

$nBondsS3$ and $SCH-7$ have defined as 2D Total number of single bonds (excluding bonds to hydrogens and aromatic bonds) descriptor and Simple chain, order 7. It has been clearly shown that an increase in the molecular descriptor $nBondsS3$ and $SCH-7$ with decrease in the molecular descriptor $Pubchem185$ and $Pubchem385$ will actually increase the anti-ulcer activity of (benzo[d]thiazole derivatives) against $H^+$/K$^+$-ATPase enzymes. The high the binding score of the ligand-receptor complex formed, the better the drug inhibits the target enzyme ($H^+$/K$^+$-ATPase), thus explaining that benzo[d]thiazole derivatives are very good inhibitors.

3.2 Molecular docking studies

Molecular docking studies between the target protein ($H^+/K^+$-ATPase enzyme) and the benzo[d]thiazole derivatives (ligands) were performed. The result shows that most of the molecules were found to potently block the efficient sites in the target protein ($H^+/K^+$-ATPase enzyme). Furthermore, almost the blockers/inhibitors showed high docking scores greater than the ones made by other researchers. For target protein, the binding energy values range from -6.2 to -9.1 kcal/mol. Compound 22 is the most potent with the high docked score of -9.1 kcal/mol. Compound 21, and 30 also showed a better docking score of -8.8 kcal/mol and -8.5 kcal/mol. Other compounds of the series have average docking scores as shown in table 6 above, while ligands with the best binding energy values are shown in table 7.

Figure 1 - The plot of the Experimental and predictive activity of both training and test set of the best model (1).

Figure 2- The plot of the standardized residuals versus the leverage value of both the training set and test set of model 1.

$h^* = 0.5$
Table 5 - Pearson’s correlation matrix for the selected

|          | NBondsS3 | SCH-7  | PubchemFP185 | PubchemFP382 |
|----------|----------|--------|--------------|--------------|
| NBondsS3 | 1        |        |              |              |
| SCH-7    | -0.19603 | 1      |              |              |
| PubchemFP185 | -0.50753 | 0.888975 | 1           |              |
| PubchemFP382 | 0.562168 | 0.50792 | 0.316228     | 1            |

Table 6 – Show’s the binding energy value, hydrophobic interaction and hydrogen bond interaction formed between ligands with the active site of the H⁺/K⁺-ATPase receptor.

| Ligands | Binding energy (Kcal/mol) | Residual interaction | Hydrogen bond | Hydrogen bond distance |
|---------|--------------------------|----------------------|---------------|------------------------|
| 4       | -8.0                     | CLR30 0, CLR30 0, EU791, CLR30 01 | 4.2778        | 4, 5.4947 2, 3.8696 4, 5.2792 5 | 4.3678 |
| 5       | -8.0                     | CLR30 01, ILE36, CLR30 01 | 3.7924        | 1, 5.1596 9 | 4.3678 |
| 11      | 8.0                      | CLR30 01, ILE36, CLR30 01, LEU79 1 | 4.2778        | 4, 5.4947 2, 3.8696 4, 5.2792 5 | 4.3678 |
| 29      | -6.2                     | GLN22, ASP22 5, 8, THR26 1, 4, ASP22 1 and GLN22 4 and 2.21234, 2.10648 4, 3.89628, 4.32655 3.89628, 4.32655 | 2.0628        | 4, 2.9965 4 and 2.8113 4 and 2.7984 2 |

Table 7 - Binding Affinity, Hydrogen bond interaction and hydrophobic interaction formed between ligands with best binding energy and the active site of the H⁺/K⁺-ATPase receptor.

| Ligands | Binding energy (Kcal/mol) | Residual interaction | Hydrogen bond | Hydrogen bond distance |
|---------|--------------------------|----------------------|---------------|------------------------|
| 8       | -8.1                     | TRP931, TRP931, TRP988, TRP988 - ALA966, VAL26, LEU30, VAL26, TRP931, TYR970, TRP988 and CLR3001, CLR3001, LEU791 | SER995, PHE999 | 4.53035, 4.78732 3.72203, 3.97043 3.86645, 4.0203 5.46087, 5.2563 4.49187, 4.91557 4.456 and 4.32655 | 4.3678 |
| 9       | -8.1                     | LEU958, LEU958, PHE999, TRP931, TRP931, PHE959, TRP931, ILE955 | SER995, PHE999 | 2.21234, 2.10648 3.81069, 3.97628 4.05393, 4.90821 5.21098, 5.10304 | 4.3678 |
| 10      | -8.2                     | LEU958, LEU958, PHE999, TRP931, TRP931, PHE959, TRP931, ILE955 | SER995, PHE999 | 2.21234, 2.10648 3.81069, 3.97628 4.05393, 4.90821 5.21098, 5.10304 | 4.3678 |
LEU958, ILE935 and PHE959
4.9788, 5.15371
4.86989, 5.40695
and 4.45631

TRP988, TRP988
4.15222, 4.3862
TRP988, TRP931
3.99059, 4.74562
TRP931, PHE959,
3.77045, 5.13493
TRP931, LEU958,
4.87039, 5.0393
PHE959, PRO985
4.65917, 4.38884
ALA966, VAL26, and
5.11076, 4.55729
TRP988
4.16245 and
4.27665

TRP988, TRP988
4.45696, 3.51146
ASP128
4.2.37976, 2.16554
TRP988
3.55938, 3.77113
ASP128, ARG979
3.80523, 3.71011
TRP988
5.52512, 5.4223
LEU978
5.45378, 5.2407
LEU978
4.81062, and
5.3251
TRP988
3.86378
LEU978
3.89773, 4.29311
ASP128
4.7893, 4.456
TRP988
4.88395, 3.73009
VAL26, LEU30
3.8604, 4.00719
TRP988
5.47397, 5.39482
TYR970, TRP988 and
4.77903, 4.52037
TRP988
4.42856

Figure 1 - (a) Prepared Structure of (H⁺/K⁺-ATPase).

(b) Prepared structure of ligand (benzo[d]thiazole derivatives).
Figure 2 - 2D and 3D structure of Ligand-Receptor complex 22 (-9.1 kcal/mol).

Figure 3 - 2D and 3D structure of Ligand-Receptor complex 21 (-8.8 kcal/mol).
3.3 Adherence site of Blockers/inhibitors

Table 6 and 7 show the least and the best binding scores, hydrogen bond length (A˚), hydrophobic interaction, and the reactive surface entangled in the configuration of docking inhibitors at the feasible side of H+/-ATPase. Figure 1b and 1b is the prepared H+/-ATPase and ligand benzo[d]thiazole structures, compound 22 being the most active molecules form three types of interaction these are Hydrophobic, electrostatic, and hydrogen bond. Benzo[d]thiazole ring was bounded by hydrophobic pockets consisting of amino residues such as VAL135, ILE322, LEU800, VAL805 TYR131, LEU978 LEU132, LEU132 VAL135, VAL805 with two hydrogen bonding of ASP128 (2.379A˚) and ARG979 (2.165 A˚). However, the binding energy value generated in thus study was found to be better than the work of (wang et al., 2017), the docked models revealed that N-2 and C-16 of benzo[d]thiazole ring forms a hydrogen bond with amino backbone residue.

4. CONCLUSION

It has been clearly shown that an increase in the molecular descriptor nBondsS3 and SCH-7, with the decrease in the molecular descriptor Pubchem185 and Pubchem385 will actually increase the anti-ulcer activity of (benzo[d]thiazole derivatives). Against the H+/-ATPase enzymes, This is in agreement with the result obtained from the molecular docking analysis in which compound 22a (Fig. 2 and 3) in particular, showed a very good binding affinity of -9.1kcal/mol, along with the hydrophobic pocket interaction of amino residues. The high the binding score of a ligand-receptor complex formed, the lower the drug inhibits the target enzyme (H+/-ATPase), thus explaining that benzo[d]thiazole derivatives are very good inhibitors.

In addition, all the benzimidazole derivatives docked with H+/-ATPase enzyme were better than even the standard anti-ulcer drug (omeprazole). The physicochemical parameter used for molecular docking and quantitative structure-activity relationship (QSAR) in this study, were essential parameters to look into especially in improving the chance of new anti-ulcer drug as benzo[d]thiazole derivatives. Our QSAR result with high correlation coefficient R2 of 0.7975 and molecular docking result of -9.1kcal/mol correspond with each other and give direction for design of ulcer inhibitors. This study gives room for the synthesis of a new selective H+/-ATPase inhibitor with predetermined affinity and activity of the compound.

Acknowledgments.

The authors sincerely acknowledge department of chemistry, Ahmadu Bello University, Zaria for its technical support and Dr. Sani Uba and Mr. Usman Abdulfatai for their advice in the course of this research.

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