



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 order to know the relationship that exist 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 4million 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, and inflammation action with an improved profile is still a necessity (Rakesh *et al.*, 2017; Mabeka, 2017).

Anti-ulcer drugs exert their action by blocking the H^+/K^+ -ATPase enzyme, which is the final step of gastric acid secretion in the stomach (Anan and Wakode, 2017). *H. pylori* secrete CagA, (Cytotoxin-associated gene A), which is a poisonous substance produced by the bacterium after translocation into host cell, it alters cell shape, increase cell motility, redirect cell junction activity and thus responsible for gastric carcinomas and gastric ulcer (Kaur, *et al.*, 2012; Lanan, 2017). Therefore, the bacteria is also considered as a validated target for antiulcer agents. Benzo[d]thiazoles are bicyclic ring systems that are widespread and abundant in natural products

(Wang *et al.*, 2017). Today heterocyclic compounds, have attracted many attention of medicinal chemist. Which is attributed their diverse biological activities such as antimalarial, anti-inflammatory, antimicrobial, anticonvulsant, antioxidant, and antidiabetic 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 benzothiazole 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 IC_{50} (μM) were normalized and expressed in logarithmic scale as pIC_{50} ($pIC_{50} = \log_1/IC_{50}$). pIC_{50} was chosen as a reliable/dependent variable, which was correlated with the independent variable descriptors. Using Genetic function algorithm. The chemical structures and the IC_{50} (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 unrelying 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_{prd} 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.

$$LOF = SSE / (1 - \frac{c+dp}{M}) \quad (1)$$

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).

$$Y = a_1x_1 + a_2x_2 + a_3x_3 + b \quad (2)$$

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 file format. 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:

$$R^2 = 1 - \frac{\sum (Y_{obs} - Y_{pred})^2}{\sum (Y_{obs} - \bar{y}_{training})^2} \quad (3)$$

where Y_{pred}, Y_{obs} and Y_{mtraining} 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 varies directly with the increase in the number of repressors i.e. descriptors. 'Equation 4 shows the adjusted R² formula.

$$R^2 adj = 1 - (1 - R^2) \frac{n-1}{n-p-1} = \frac{(n-1) R^2 - p}{n-p+1} \quad (4)$$

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).

$$Q^2 = 1 - \frac{\sum (Y_p - Y)^2}{\sum (Y - Y_m)^2} \quad (5)$$

where Y_p explain predicted activity, and Y represent observed activity of the training set, and Y_{mtrng} is the average activity value of the training set (Abdulfatai *et al.*, 2017; Jalali-Heravi and Kyani, 2004).

2.7 Applicability domain

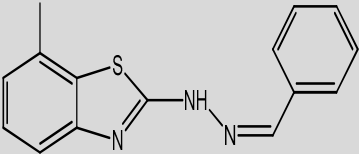
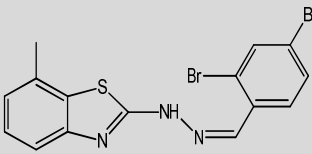
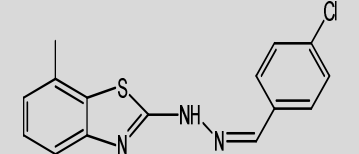
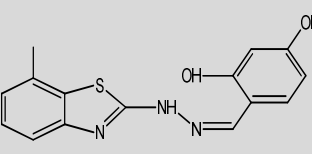
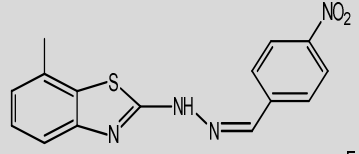
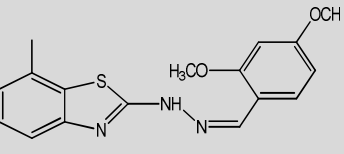
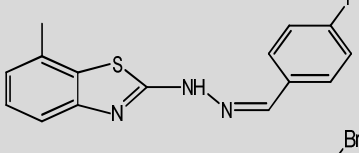
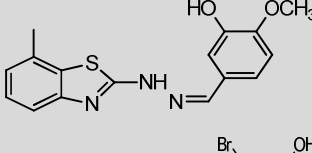
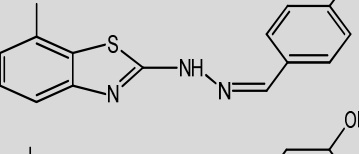
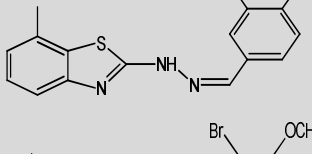
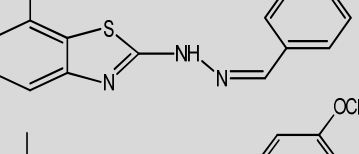
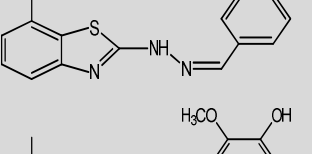
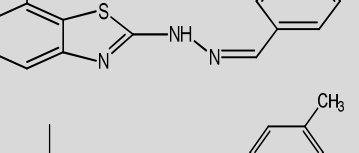
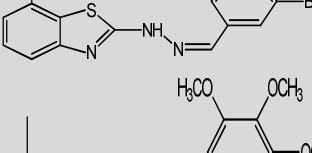
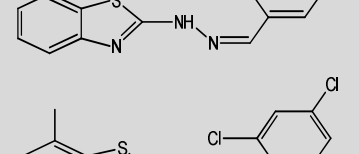
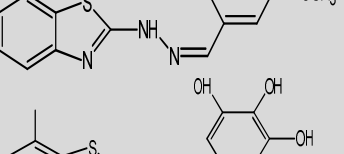
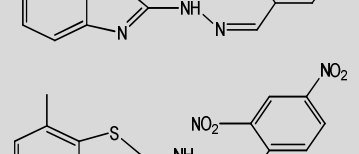
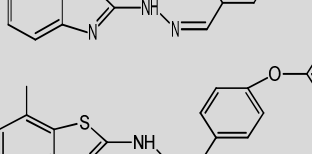
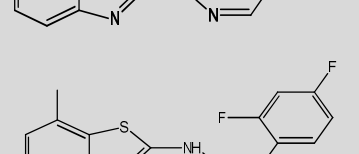
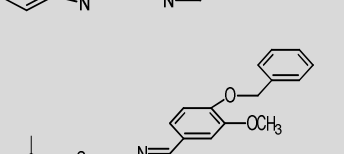
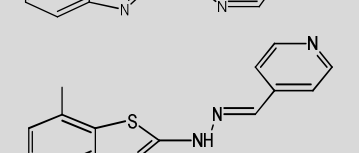
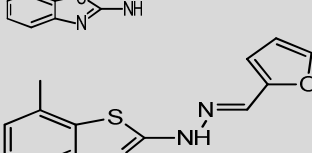

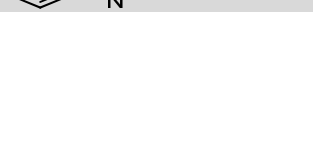
A QSAR model is an essential statistical tool used to determine whether a model make a good prediction within its applicability domain, and this can be determined from Williams plot (Tropsha *et al.*, 2003). There are some techniques for assessing the suitable space of a QSAR model, Leverage is one of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

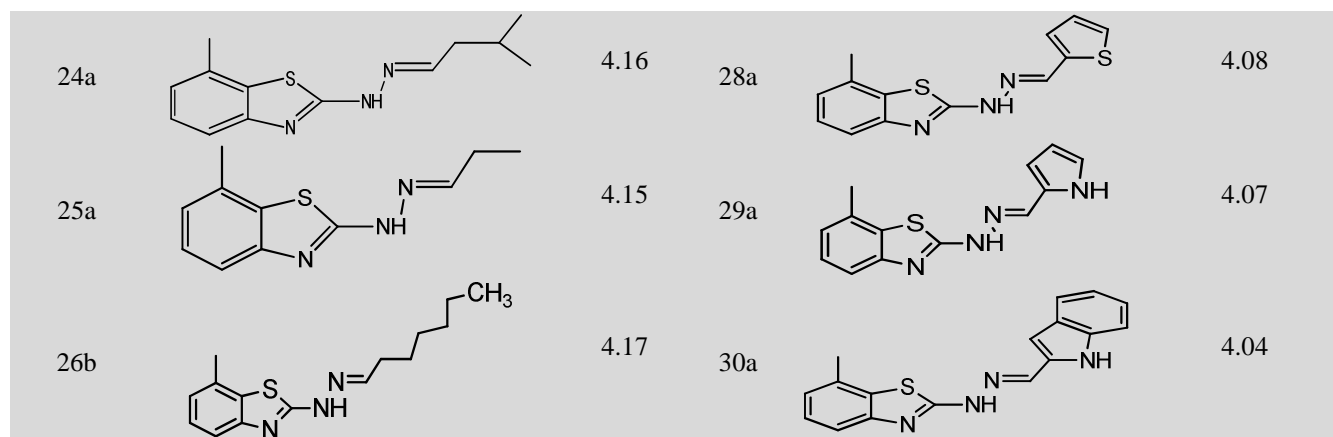
$$h_i = X_i^T (X^T X)^{-1} X_i \quad (6)$$

The x_i 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.

$$h^* = \frac{3(P+1)}{N} \quad (7)$$

Table 1- Shows the structures and the activity (pIC₅₀) of the benzo[d]thiazole derivatives.

S/NO	Molecular structure	pIC ₅₀	S/NO	Molecular structure	pIC ₅₀
1a		4.89	12a		4.41
2b		4.85	13a		4.39
3a		4.69	14b		4.37
4a		4.58	15a		4.37
5b		4.57	16a		4.36
6a		4.55	17b		4.31
7a		4.51	18a		4.26
8b		4.51	19a		4.24
9a		4.46	20b		4.22
10a		4.17	21a		4.15
11b		4.17	22a		4.09
23a		4.16	27a		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 residual 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
R^2	Coefficient of determination	≥ 0.5
$P_{(95\%)}$	Confidence interval at 95% confidence level	< 0.05
Q^2	Cross-validation coefficient	≥ 0.5
$R^2 - Q^2$	Difference between R^2 and Q^2	≤ 0.3
$N_{\text{ext. Test set}}$	Minimum number of external test set	≥ 5
R^2_{ext}	Coefficient of determination for external test set	≥ 0.5

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:

$$PIC_{50} = -0.329720059 * nBondsS3 - 0.999544315 * SCH-7 + 0.753890542 * Pubchem185 - 0.119244628 * Pubchem385 + 4.258196$$

on Hp G630 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. Saccharomyces cerevisiae isomaltase crystallographic structure (Resolution 1.30Å PDB code 3AJ7,) with 72.4% succession identity with the target was used as the mold for this study.

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 1.10.2 software 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 pIC_{50} for anti-ulcer compounds,

$$R^2_{\text{trng}}=0.940021, R^2_{\text{adj}}=0.925026, Q^2_{\text{LOO}}=0.884292, N_{\text{trng}}=21 \\ R^2_{\text{test}}=0.797578, N_{\text{test}}=9.$$

Table 3 – Show's 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.

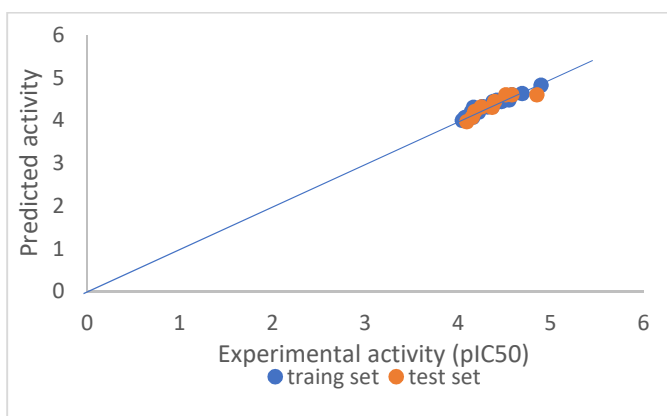
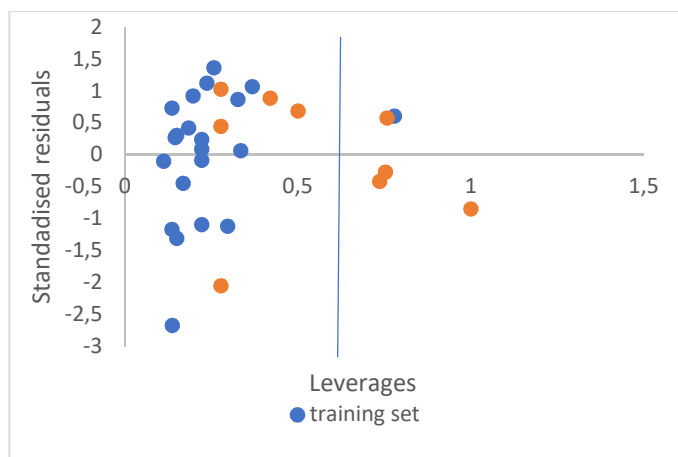


Figure 1 - The plot of the Experimental and predictive activity of both training and test set of the best model (1).

From the above plot of the developed model, we can say that the model is stable and robust, and this is because of the high linearity of the plot (straight line graph). More also the errors propagated on both side of the zero indicate the strength of the model, the prediction of the test set data was determined using the developed model equation. The plot of predicted values comprising both training set compounds and test sets against the experimental pIC_{50} values are shown in Figure 1. The studied predicted activity is in accordance with the experimental activity. Figure 2 illustrates the plot of standardized residual values versus leverages values (pIC_{50}).

A correlation matrix was performed on the descriptors of model 1, and found to be highly correlated which means that the descriptors used to build the model are very good. The result of the correlation matrix is shown in table 5.



$$h^* = 0.5$$

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

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, Pubchem finger print 185 and Pubchem finger print 185. 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 higher 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 results show that most of the molecules were found to potently block the efficient sites in the target protein ($H^+ / K^+ ATPase$ enzyme). Furthermore, almost all blockers/inhibitors showed high docking scores greater than the ones made by other researchers. For the target protein, the binding energy values range from -6.2 to -9.1 kcal/mol. Compound 22 is the most potent with the highest docking 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.

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	CLR300, CLR300	EU791, CLR3001	4.27784, 5.49472, 3.8696, 4.52792
5	-8.0	CLR3001, ILE36, CLR3001,		3.79241, 5.15969, 4.3678

11	8.0	LEU791 and CLR3001, CLR3001, ILE36, CLR3001, LEU791		5.42036, 4.84094, 4.27784, 5.49472, 3.86964
29	-6.2	GLN225, GLN232, ASP228, GLN225, and LEU262	ASP228, THR261, LYS221 and GLN229	2.06288, 2.99654, 2.81134, 2.79842

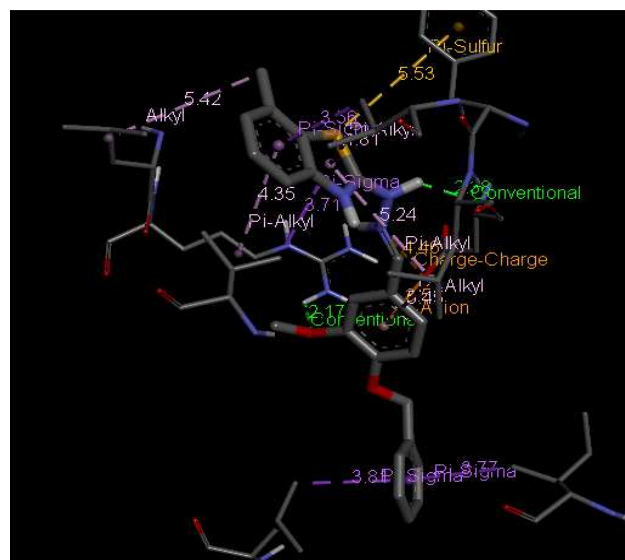
Table 7 - Binding Affinity, Hydrogen bond interaction and hydrophobic interaction formed between ligands with best binding energy and the active site of the H⁺/K⁺-ATPase receptor.

Ligands	Binding energy (Kcal/mol)	Residual interaction	Hydrogen bond	Hydrogen bond distance.
8	-8.1	TRP931, TRP988, ALA966, LEU30, TRP931, TRP988 and 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
9	-8.1	CLR3001, CLR3001, LEU791	Nil	4.27784, 5.49472, 3.86964, 5.27925
10	-8.2	LEU958, PHE999, TRP931, TRP931, ILE955	SER995, PHE999	2.21234, 2.10648, 3.81069, 3.97628, 4.05393, 4.90821, 5.21098, 5.10304

21	-8.8	LEU958, ILE935 and PHE959	ASP128	4.9788, 5.15371 4.86989, 5.40695 and 4.45631
22	-9.1	TRP988, TRP988 TRP988, TRP931 TRP931, PHE959, TRP931, LEU958, PHE959, PRO985 ALA966, VAL26, and TRP988	ASP128, ARG979	4.15222, 4.3862 3.99059, 4.74562 3.77045, 5.13493 4.87039, 5.0393 4.65917, 4.38884 5.11076, 4.55729 4.16245 and 4.27665
30	-8.5	VAL135, ILE322, LEU800, VAL805 TYR131, LEU978 LEU132, LEU132 VAL135 and VAL805	Nil	4.45696, 3.51146 2.37976, 2.16554 3.55938, 3.77113 3.80523, 3.71011 5.52512, 5.4223 5.45378, 5.2407 4.81062, and 4.35251
		TRP988, TRP988 TRP988, TRP931 TRP931, TRP988 ALA966, VAL26 VAL26, LEU30 TYR970, TRP988 and TRP988		5.68111, 3.86378 3.89773, 4.29311 4.7893, 4.456 4.88395, 3.73009 3.8604, 4.00719 5.47397, 5.39482 4.77903, 4.52037 and 4.42856



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



(b) Prepared structure of ligand (benzo[d]thiazole derivatives).

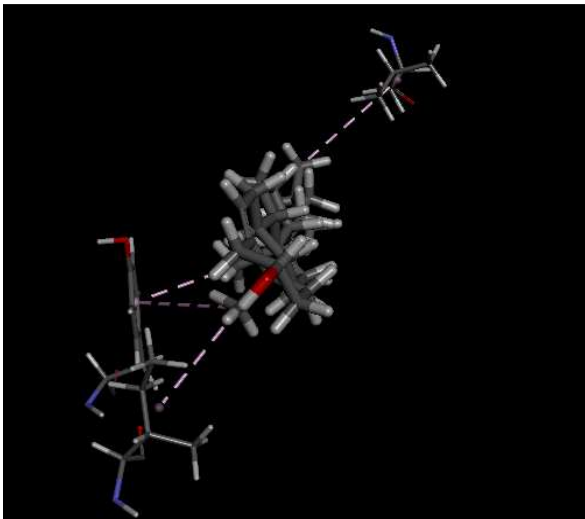


Figure 2 - 2D and 3D structure of Ligand-Receptor complex 22 (-9.1kcal/mol)

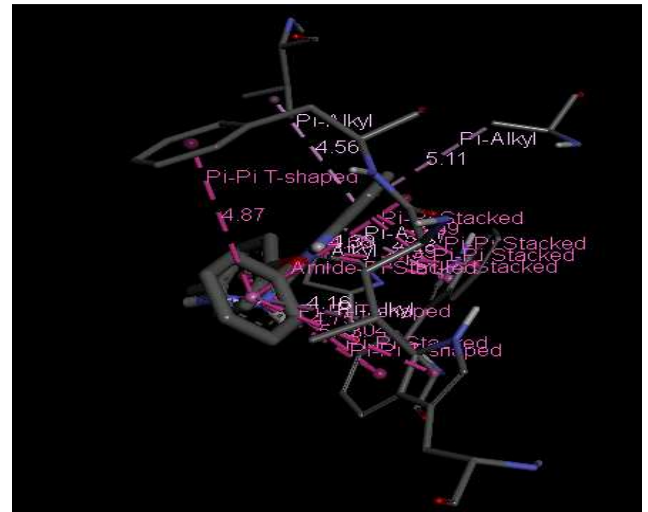
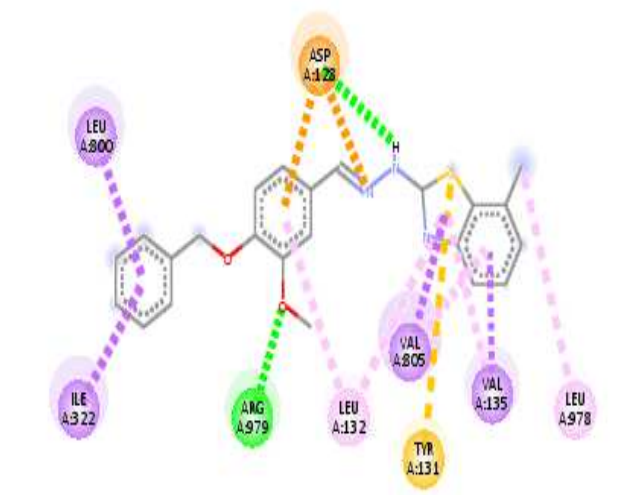
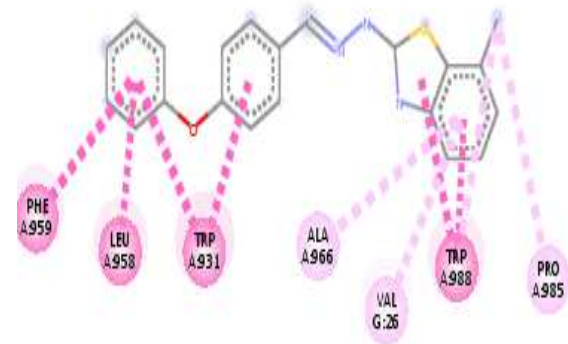


Figure 3 - 2D and 3D structure of Ligand-Receptor complex 21 (-8.8kcal/mol).



Interactions

- Attractive Charge
- Conventional Hydrogen Bond
- Pi-Anion
- Pi-Sigma
- Pi-Sulfur
- Alkyl
- Pi-Alkyl



Interactions

- Pi-Pi Stacked
- Pi-Pi T-shaped
- Amide-Pi Stacked
- Alkyl
- Pi-Alkyl

3.3 Adherence site of Blockers/inhibitors

Table 6 and 7 show the least and the best binding scores, hydrogen bond length (\AA), hydrophobic interaction, and the reactive sediment entangled in the configuration of docking inhibitors at the feasible side of H^+/K^+ -ATPase. Figure 1b and 1c is the prepared H^+/K^+ -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 (2.379\AA) and ARG979 (2.165\AA). However, the binding energy value generated in this 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^+/K^+ -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 better the drug inhibits the target enzyme (H^+/K^+ -ATPase), thus explaining that benzo[d]thiazole derivatives are very good inhibitors.

In addition, all the benzo[d]thiazole derivatives docked with H^+/K^+ -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 R^2 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^+/K^+ -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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