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Molecular Mechanics-Based Quantitative Structure-Activity Relationship Study on the Inhibitory Activity of Some Schiff Bases against *Escherichia coli*

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Due to their high inhibitory action against *Escherichia coli* (*E. coli*), the rise of multidrug-resistant strains of the bacteria necessitates the testing and development of a new set of Schiff bases as anti-*E. coli* agents worldwide. In this study, the Genetic function approximation (GFA) Quantitative structure-activity relationship (QSAR) analyzes selected Schiff bases with anti-E. coli activity. This was done using different molecular descriptors and Hansch's approach, which results in the production of one statistically significant hepta parameter model as the strongest model with a squared correlation coefficient (R^2) = 0.828, adjusted squared correlation coefficient (R^2adj) = 0.775, cross-validated correlation coefficient (Q^2) = 0.691, Difference between R^2 and Q^2, Q^2 (R^2 - Q^2) = 0.137, external prediction (R^2pred.) = 0.751 and lack of fit (LOF) of 0.067 value were selected as the best model based on its sound statistical parameters. The development model demonstrated the predominance of the descriptors Minimum H E State (Hmin) and Valence path order 6 (VP-6) in influencing the observed anti-*E. coli* activity of Schiff bases. Insilico techniques can certainly provide

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a quick, inexpensive and safe quantitative risk assessment for this class of compounds. It is envisaged that the QSAR results discovered in this work will provide crucial structural insights towards the design of effective anti-*E. coli* drugs based on Schiff bases

Keywords: Escherichia coli; schiff bases; hansch's approach; QSAR; descriptor.

1. INTRODUCTION

"Schiff bases are characterized by an imine group **–N=CH**, which helps to elucidate the mechanism of transamination and racemization in biological systems" [1]. In terms of biological capabilities, it has an antibacterial and antifungal effect. In recent years, Schiff bases have received significant attention because of their physiological and pharmacological activities [2]. In both animals and people, antimicrobial drugs serve a key role in lowering illness and death caused by infectious diseases. However, selective pressure applied to existing antimicrobial drugs has hampered the development and spread of drug-resistance characteristics among disease-causing and commensal bacteria [3]. "*Escherichia coli* or *E. coli* are gram-negative bacilli of the family Enterobacteriaceae" [4]. E. coli is a common bacterium found in the large intestine of humans (it is a bacterium commonly found in the intestines of humans and animals). Of serious concern is the development of resistance by *Escherichia coli* or *E. coli* strains to the current antibiotics such as ampicillin, sulfonamide, gentamicin, streptomycin, ciprofloxacin, trimethoprim, amoxicillin [5-6]. E. coli is a common commensal bacterium in people and animals, but pathogenic forms can cause gastroenteritis, urinary tract infection, meningitis, peritonitis, and septicemia, among other illnesses [3]. This trend of resistance exhibited by this organism poses serious threat to human and animals health, necessitating the search for newer antibiotics [7]. This class of organic compounds have also demonstrated significant inhibitory activity against the growth of *E. coli* [8-11] making them a viable drug candidate in man's fight to combat the pathogenic microbe's alarming trend of multi-drug resistance [12].

Conventional drug discovery and development is characterized by a method based on a trial and error [13]. This is time-consuming, costly due to the enormous expense of failures of candidate drugs late in their development and a threat to green chemistry due to enormous waste released into the environment. "QSAR offers important structural insight into the design of novel anti-microbial drugs by exploring and harnessing the structural requirements controlling the observed anti-microbial activities as well as a providing predictive model for bio-activities of potential drug candidates, reducing the requirement for lengthy, costly and hazardous laboratory test" [14]. QSAR is based on the conception that there exists a close relationship between bulk properties of compounds and their molecular structure [15]. As a result, identifying these presumed correlations and then quantifying them is a key principle of chemistry, establishing a clear connection between the macroscopic and microscopic properties of matter [16].

By examining the correlations between the experimental pMIC of the compounds and their calculated molecular descriptors, this work aims to develop a statistically robust, predictive, and rational Genetic function approximation (GFA) based QSAR model for inhibitory activity of Schiff bases against *E. coli*.

2. MATERIALS AND METHODS

H.P 2000/computer system (Intel Pentium), 1.30GHz processor, 4GB RAM size on Microsoft Windows 13 Ultimate Operating System, Spartan 14 V.1.1.0, chem draw 12.0.1V, Padel descriptor tool kit, and Microsoft office Excel 2016 version Statistical software, Material Studio (modeling and simulation software) version 7.0, DTC are the materials used in this study [17]. QSAR investigations were carried out in this work using Hansch's method. According to Hansch's method, structural properties of compounds are determined in terms of several physicochemical parameters, and these parameters are then associated with biological activity using a regression analysis equation [18]. In Image 1, the many processes are depicted in a flowchart.

2.1 Data Collection

A data set comprising of series of 41 schiff bases *Escherichia coli* derivatives was taken from literature [8-11,19]. Table 1 shows the chemical structures and experimental minimum inhibitory concentration (pMIC) values of Schiff bases'

inhibitory activity against Escherichia coli. 70% of the data (31 compounds) was utilized as training set in model building, with the remaining 30% (14 compounds) serving as a test set for external validation of the most statistically significant QSAR model [20].

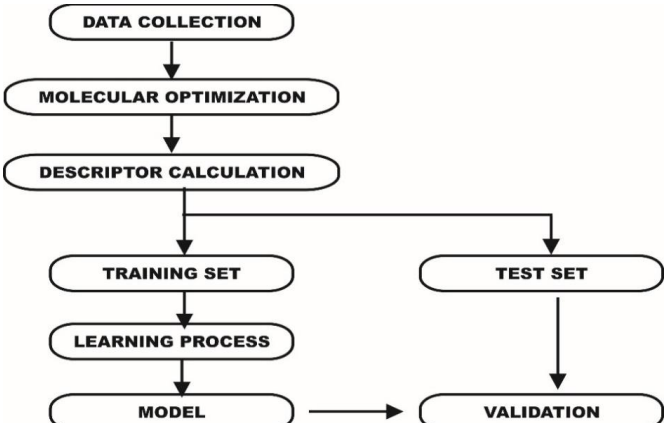

Image 1. QSTR Methodology flow chart (Source: [7])

Table 1. Chemical structures and experimental pmic values of anti-escherishia coli inhibitory activity

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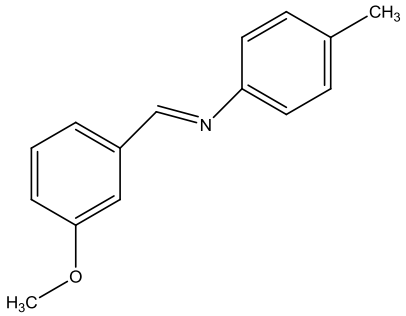
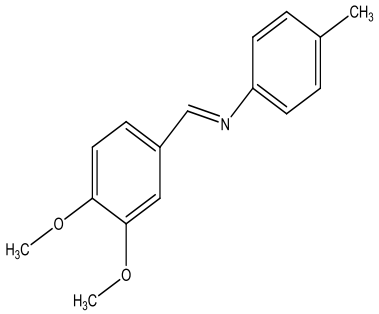
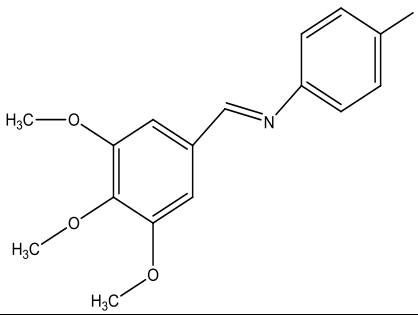
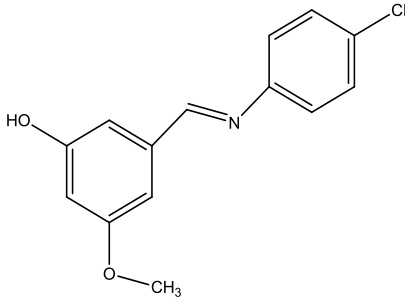
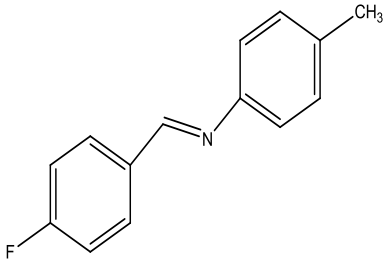
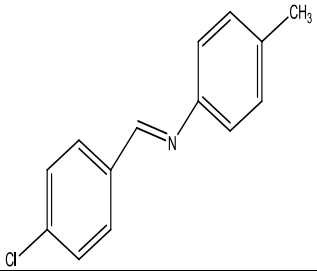
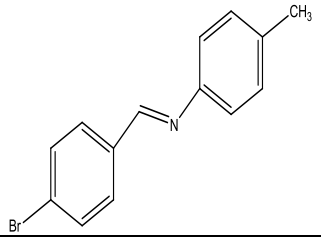
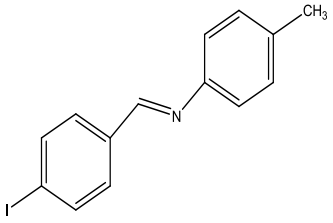
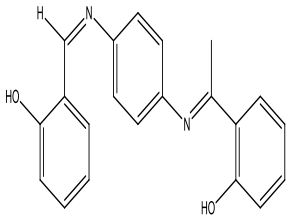
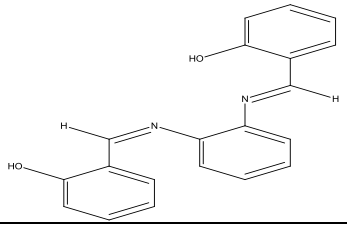
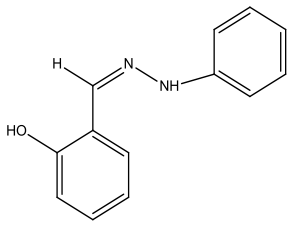
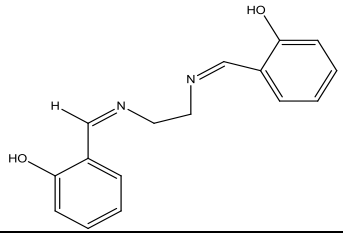
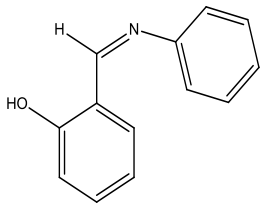
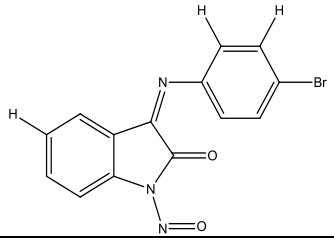
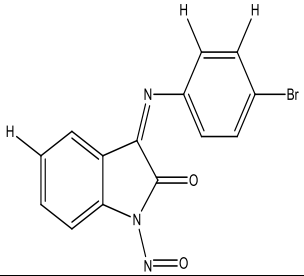
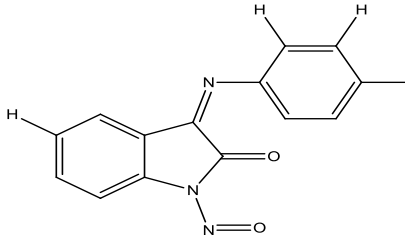
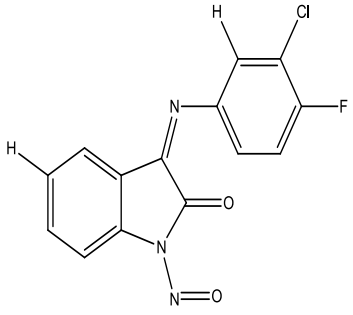
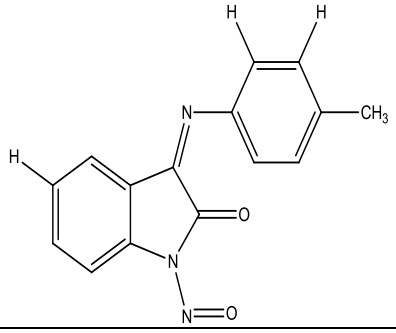
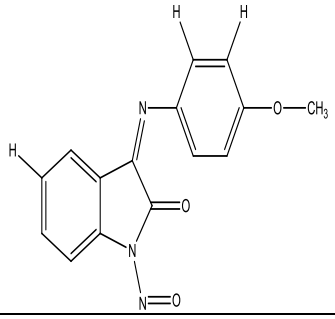
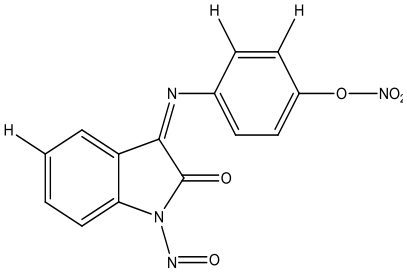
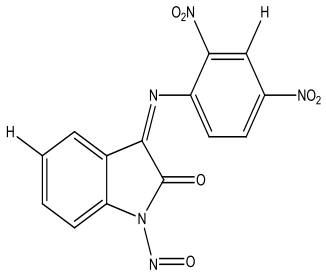
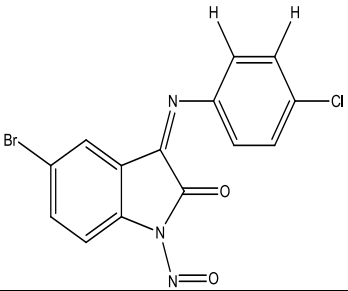
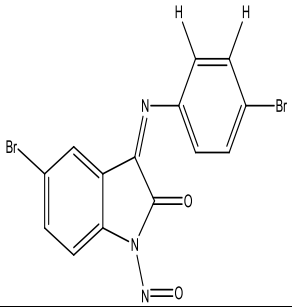
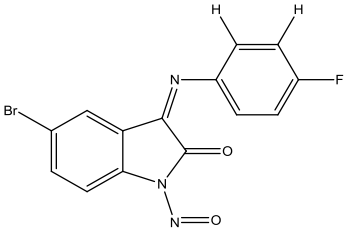
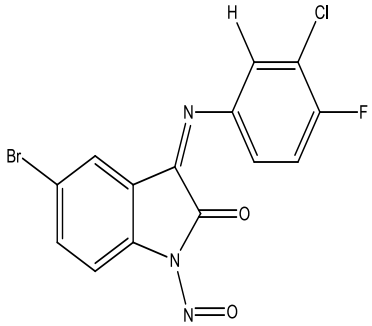
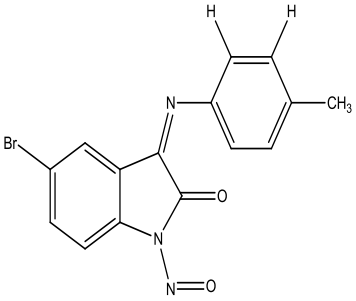
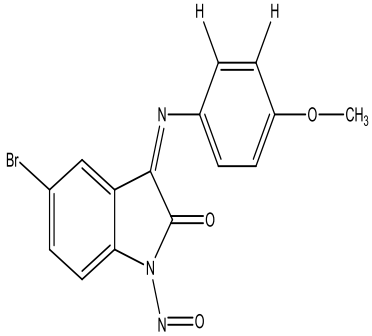
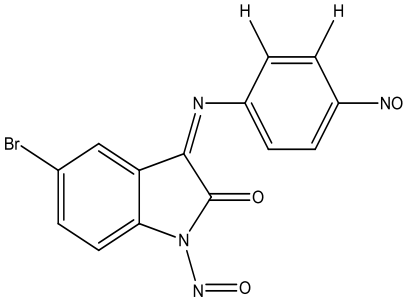
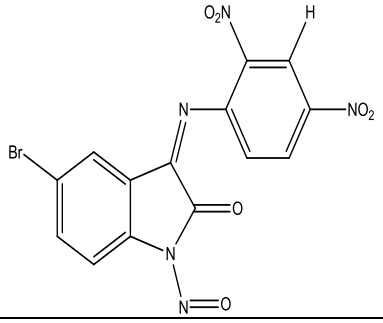
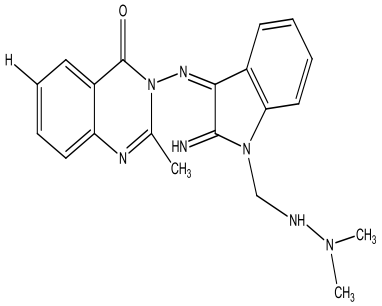
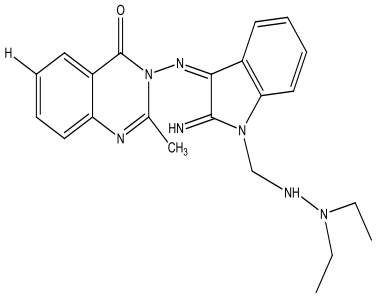
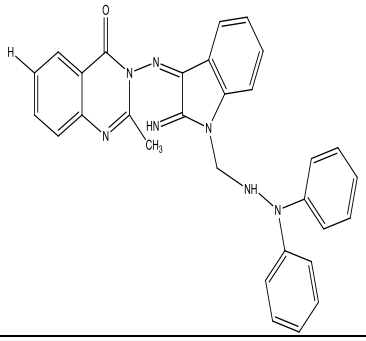
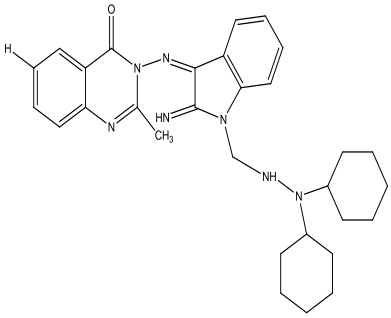
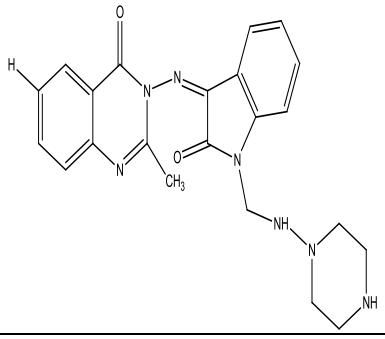
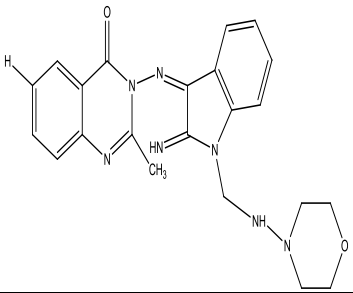
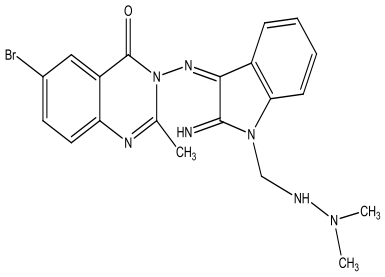
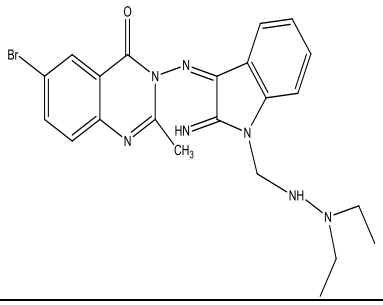
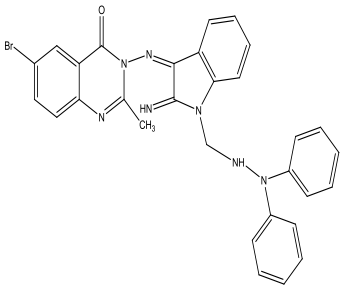
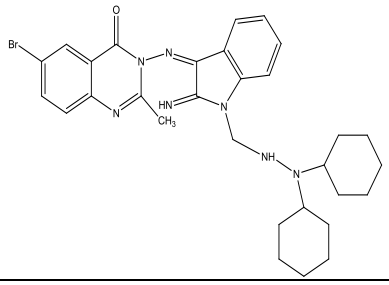
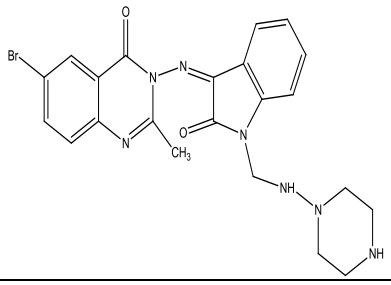
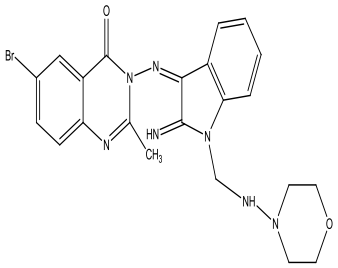
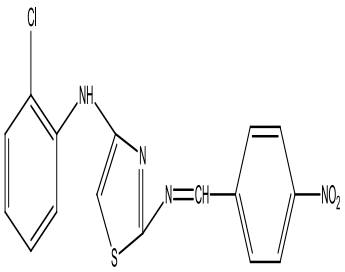
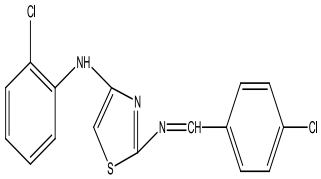
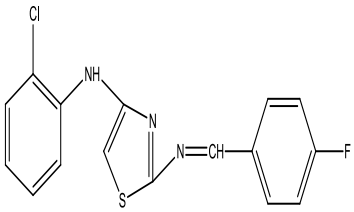
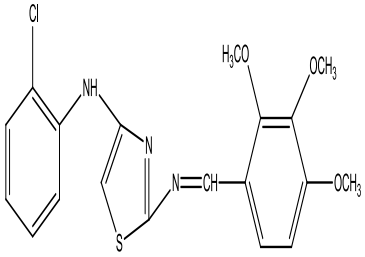
1.		1.342	2.		1.255
3.		1.556	4.		1.079
5.		1.806	6.		1.415

S/n	Structure	pMIC	S/n	Structure	pMIC
7.		1.806	8.		2.093
9.		2.301	10.		2.301
11.		2.398	12.		2.000
13.		2.301	14.		1.362
15.		1.322	16.		1.380
17.		1.623	18.		1.301

S/n	Structure	pMIC	S/n	Structure	pMIC
19.		1.591	20.		1.342
21.		1.204	22.		1.602
23.		1.255	24.		1.342
25.		1.301	26.		1.322
27.		1.380	28.		1.230

S/n	Structure	pMIC	S/n	Structure	pMIC
29.		1.362	30.		1.301
31.		1.204	32.		1.301
33.		1.279	34.		1.342
35.		1.415	36.		1.204
37.		1.255	38.		1.230

S/n	Structure	pMIC	S/n	Structure	pMIC
39.		1.279	40.		1.322
41.		1.431	42.		1.255
43.		1.279	44.		1.279
45		1.000			

2.2 Molecular Optimization

Chemdraw ultra V12.0 was used to draw the chemical structure of each compound in the data sets, which was then identified and stored as a *cdx file. Chem 3D Pro's molecular mechanics (MM) technique was used to optimize the compounds. The goal of optimization was to discover the molecule's equilibrium or lowest energy geometry. “For each molecule, the lowest energy structure was employed to calculate its physicochemical parameters (molecular descriptors)” [18].

2.3 Descriptors Calculation

The (Pharmaceutical Data Exploration Laboratory) PaDEL descriptor tool kit [21] was utilized to calculate the molecular descriptors used in this QSAR modeling. For this project, almost 1000 descriptors ranging from 0D through 1D, 2D, and 3D were used [18].

2.4 Data Normalization

Table 1 shows the chemical structures of the compounds as well as their experimental pMIC. Data normalization was performed on the dependent variable (MIC) by converting the experimental MIC values to logarithmic scale [pMIC = $\log_{10}$ MIC]. This was done to get a more linear response and reduced data dispersion.

2.5 Learning Process

Using the Microsoft Excel package in Microsoft Office 2016, the correlation between biological

activities (pMIC) of the compounds and the computed descriptors was achieved during this approach. In order to pick the appropriate descriptors for this regression study, Pearson's correlation matrix was employed as a model. To create QSAR models, the selected descriptors were subjected to regression analysis [12] using Genetic Function Approximation (GFA) in material studio software [22] with empirically determined activities as the dependent variable. The models were evaluated using a "lack of fit" (LOF) score, which was calculated using a modest version of Friedman's original formula, with the best model receiving the highest fitness score [23,24]. The original Friedman formula is used to calculate the LOF [25] shown in equation 1.

'LOF = SSE(1-c+dp/m)2---------- (1)

SSE stands for sum of squared errors, while 'c' stands for the number of terms in the model (excluding the constant term), 'd' stands for the user-defined smoothing parameter, 'p' stands for the total number of descriptors contained in all model terms (ignoring the constant term), and'm' stands for the number of samples in the training set' [26]. In contrast to the commonly used least squares measure, the LOF measure cannot always be decreased by adding more terms to the regression model [27]. The LOF measure prevents overfitting by minimizing the tendency to simply add more terms [28].

2.6 Model Validation

Internal and external validation factors were used to assess the best models' fitting ability, stability, dependability, and predictive ability. Table 2 shows a comparison of the validation parameters to the lowest required value for a generally acceptable QSAR model [29].

2.7 Internal Validation Parameters

This validation was carried out using the same data that was used to develop the model [30]. The square of the correlation coefficient (R^2), Adjusted R^2 (R^2adj), Q^2 (Leave one out cross validation coefficient, Validation ratio (F value)) are some of the internal validation metrics used in this study [31].

2.8 External Validation Parameters

Internal validation is a crucial phase in the creation of a QSAR model. The model's internal validation findings suggest that it has a higher level of stability and predictability. However, it shows no genuine capacity to predict molecules in an external test set. As a result, the best model's external forecasting power and extrapolation should be assessed [23]. R^2pred is the external prediction parameter employed in this study.

Table 2. Validation metrics for a generally acceptable QSAR model [22]

S/N	Symbol	Name	Threshold
1	R^2	Coefficient determination	$\geq$0.6
2	Q^2	Cross validation coefficient	>0.5
3	$R^2_{pred.}$	External test set's coefficient of determination	$\geq$0.6
4	R^2 - Q^2	Different between R^2 andQ^2	$\leq$0.3
5	F value	Validation ratio	High
6	P95%	Confidence interval at 95% confidence level.	< 0.05

Sources : [22,23]

3. RESULTS AND DISCUSSION

Model 1 Equation;

$$pMIC = 1.186X1 - 3.486X2 - 0.329X3 - 6.116X4 + 0.091X5 - 0.078X6 + 0.540X7 + 3.872.$$

Friedman LOF = 0.073, R^2 =0.828, R^2_{adj} =0.775, Q^2=0.691, S.R = yes, F_{value} =15.777, C.Exp.error =0.069, Minimum error = 0.000.

Table 3. Definition of various descriptors used

S/N	Descriptor	Symbol	Definition
1	X_1	VPC-4	Valence path cluster, order 4
2	X_2	VP-6	Valence path, order 6
3	X_3	maxsCH3	Maximum atom-type E-State:-CH3
4	X_4	Hmin	Minimum H E-State
5	X_5	ETA_Eta	Composite index Eta
6	X_6	WT.eneg	Non-directional WHIM, weighted by Mulliken atomic electronegativites
7	X_7	WK.eneg	Non-directional WHIM, weighted by Mulliken atomic electronegativites

3.1 Plot of Experimental Versus Predicted pMIC of Model 1

The optimization model's agreement between experimental and predicted pMIC values for molecules employed in the training and validation set compounds is shown in Fig. 1 and Fig. 2, respectively.

3.2 Residual Plot of Model

The measure of the dispersion of residual pMIC values from the predicted pMIC values is shown in Fig. 3.

3.3 Comparison of Actual and Predicted pMIC

Table 4 shows the comparison of the model's predicted pMIC with their experimental values [32].

3.4 External Validation of the Model

Table 5 shows the actual, predicted and residual pMIC values of the test set compounds [33].

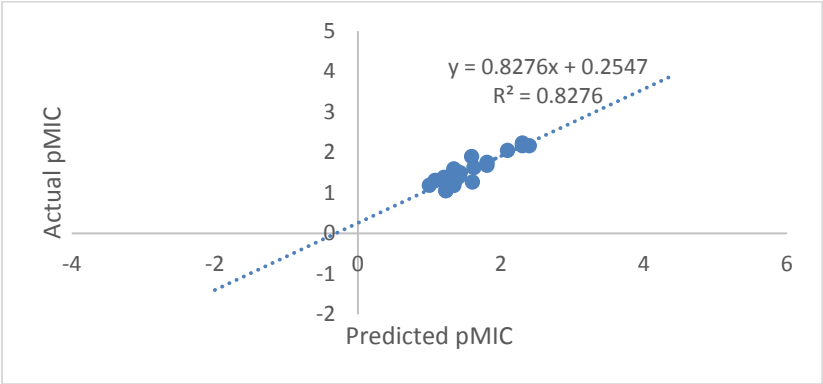


Fig. 1. Plot of actual versus predicted pMIC (Training set)

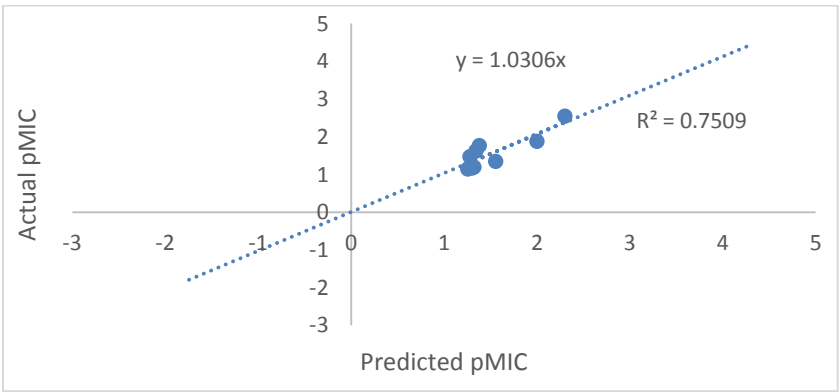


Fig. 2. Plot of actual versus predicted pMIC (Test set)

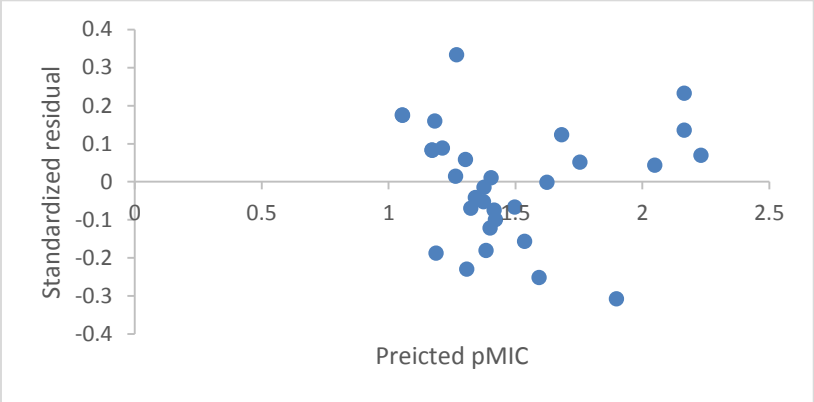


Fig. 3. Residual plot of model

Table 4. Actual, predicted and residual pMIC of model (training set)

Compound	Actual pMIC	Equation 1: predicted values	Equation 1: residual values
1	1.342	1.182	0.160
2	1.255	1.324	-0.069
4	1.079	1.308	-0.229
5	1.806	1.754	0.052
7	1.806	1.682	0.124
8	2.093	2.049	0.044
10	2.301	2.165	0.136
11	2.398	2.165	0.233
13	2.301	2.231	0.070
14	1.362	1.303	0.059
16	1.380	1.536	-0.156
17	1.623	1.624	-9.090e-004
19	1.591	1.898	-0.307
20	1.342	1.593	-0.251
22	1.602	1.268	0.334
23	1.255	1.171	0.084
25	1.301	1.342	-0.041
26	1.322	1.421	-0.099
28	1.230	1.054	0.176
29	1.362	1.376	-0.014
31	1.204	1.384	-0.180
32	1.301	1.212	0.089
34	1.342	1.416	-0.074
35	1.415	1.404	0.011
37	1.255	1.172	0.083
38	1.230	1.055	0.175
40	1.322	1.374	-0.052
41	1.431	1.497	-0.066
43	1.279	1.400	-0.121
44	1.279	1.264	0.015
45	1.000	1.187	-0.187

Table 5. Actual, predicted and residual pMIC of model (test set)

Compound	pMIC	VPC-4	VP-6	Maxs CH3	hmin	ETA_ Eta	WT. eneg	WK. eneg	pred. Pmic
3	1.556	0.854	0.541	2.083	0.097	11.356	16.271	-0.247	1.348
6	1.415	0.846	0.615	0	0.072	15.826	12.251	-0.150	2.693
9	2.301	0.412	0.298	0	0.144	7.991	10.182	0.327	2.546
12	2	0.890	0.648	0	0.129	11.982	13.415	-0.082	1.879
15	1.322	0.964	0.720	1.575	0.100	13.230	16.858	-0.125	1.196
18	1.301	1.383	1.039	0	0.065	16.168	13.818	-0.072	1.848
21	1.204	1.522	1.064	0	0.076	17.585	14.045	-0.071	1.968
24	1.342	1.349	1.049	0	0.100	16.126	15.912	0.349	1.620
27	1.38	1.830	1.330	2.078	-5.95E-04	28.200	18.322	-0.181	1.766
30	1.301	1.730	1.427	1.715	0.028	27.871	21.432	0.171	1.170
33	1.279	2.177	1.562	2.084	-0.017	32.487	15.928	0.009	2.144
36	1.204	1.830	1.330	2.078	-5.95E-04	28.201	18.322	-0.181	1.766
39	1.279	1.191	0.899	0	0.069	16.509	20.789	-0.250	1.472
42	1.255	0.610	0.442	2.065	0.105	10.737	18.325	-0.246	1.146

3.5 Molecular Optimization and Descriptor Calculation

The molecules used for this study were successfully optimized at each stage. The optimization time for each level of theory follows Molecular mechanics. The molecular properties (descriptors) computed from each optimized structure include the Chemdraw 12.0.1V software, PaDEL descriptor toolkit listed above. The successful optimization of the studied molecules indicates that their structures correspond to their real or natural geometry. Thus, all the descriptors derived from these structures are reliable.

3.6 GFA Derived QSAR Model for SCHIFF Bases Against *Escherichia coli*

Model-1 was chosen as the best model for estimating the pMIC of Schiff bases molecules based on the model with the best statistical parameters [12]. To anticipate the inhibitory activity of Schiff bases against E. coli, Model-1 was created. The GFA QSAR model's result is consistent with the standard stated in Table 2, as R^2 = 0.828, R^2_{adj} =0.775, Q^2 = 0.691, R^2_{pred}. = 0.751. This demonstrates the model's strength.

The coefficient of determination (R^2) being near to 1.0 indicates that the model described a significant portion of the response variable (descriptor), which is sufficient for a robust QSAR model [18]. "The model's strong adjusted R^2 (R^2adj) value and closeness in value to R^2 indicates that it has excellent explanatory power for the descriptors in it. In addition, the high and close proximity of Q^2 to R^2 indicated that the model was not overfit. The model's high R^2pred. indicates that it can make accurate predictions for novel compounds that fall within its applicability domain" [34]. The overall significance of the regression coefficients is determined by the F value The model's high F value indicates that the regression coefficients are significant. Table 3 shows a comparison of the compounds' observed and expected inhibitory actions. The low residual values in the Table demonstrate the predictability of model 1. The comparison of observed pMIC vs projected pMIC (Fig. 1) also has a strong linearity (R^2 = 0.828), indicating the model's high predictability [18]. 'The measured pMIC was plotted against the residual pMIC to see if there was a systematic error in the model construction (Fig. 3). The absence of systemic error in model development was evidenced by the propagation of residuals on both sides of zero' [12].

3.7 The Significance of Descriptors in Model 1

The positive coefficients of the descriptors X1, X5, and X7 imply that as the values of these descriptors rise, so does the magnitude of the pMIC of these compounds against E. coli. As a result, the lower the biological activity of these compounds against E. coli, and vice versa, the higher the values of these descriptors in these molecules.

Molecular electronegativity descriptors X6 and X7 (Non-directional WHIM, weighted by Mulliken atomic electronegativites (WT.eneg), Non-directional WHIM, weighted by Mulliken atomic electronegativites (WK.eneg)). The E. coli

inhibitory activity of the compounds increases as the electronegativity of the compounds decreases, according to the QSAR optimization model.

X_1 and X_2 (Valence path cluster, order 4(VPC-4), Valence path, order 6(VP-6)) is a descriptor of molecular size. Its correlation with pMIC of the molecule as shown in the model indicate that the biological activity of the studied compounds against *E. coli* increases with a decrease in the size of the compounds. Therefore, for an enhanced biological activity from Schiff bases against *E. coli*, the size of molecules should be minimal.

3.8 Summary of Findings

The model above represents the developed optimum QSAR models used to investigate the structural requirements influencing the reported biological activities of Schiff bases. This model gives the best predictive model for pMIC of Schiff bases against *E. coli*. The observed pMIC of the compounds against *E. coli* was found to be heavily influenced by X_2 and X_4. These descriptors account for roughly 61.16 percent of the compounds' anti-E. coli inhibitory action. The negative correlations of the descriptors indicate that the lesser the value of such descriptors in such a molecule, the greater the pMIC and the lesser the molecule's biological activity against *E. coli*, and vice versa.

4. RECOMMENDATIONS

Based on this research, it is suggested that in the prospective discovery and development of new Schiff bases as anti-*E. coli* drugs, the compounds be made as small as possible because the molecular size is negatively associated with the bioactivity of the compounds, as shown in the GFA derived model. In order to produce a reasonable anti-E. coli activity, the amount of hydrogen atoms in the constituent or parent structure should be high. In addition, more QSAR work on the pharmacokinetic aspects of these drugs is needed. Because drug treatment may not only be a product of its action, but also of how the human body will react to the medication, it must be safe and effective.

5. CONCLUSION

The produced QSAR models were used to investigate the structural requirements governing the antibacterial characteristics reported. The objectives of the study have been met. Internal and external validation procedures have shown the QSAR models' resilience and usefulness. It was discovered that the structural characteristics X1, X2, X3, X4, X5, X6, and X7 (Valence path cluster, order 4 (VPC-4), Valence path, order 6 (VPC-6) were important for the inhibitory effect of Schiff bases against E. coli (VP-6), The dominant structural characteristics responsible for the studied inhibitory activity of the molecules against E. coli were Maximum atom-type E-State: CH3 (maxsCH3), Minimum H E-State (Hmin), Composite index Eta (ETA Eta), Non-directional WHIM, measured by Mulliken atomic electronegativites (WT.eneg) as well as Non-directional WHIM, measured by Mulliken atomic electronegativites (WK.en). Furthermore, the amount of knowledge contained in these models is expected to enable a quick, cost-effective, and environmentally friendly means of developing novel and less hazardous bioactive Schiff base chemicals to combat the growing trend of multidrug-resistant *E. coli* strains.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Asma A Alothman, Eida S Al-Farraj, Wedad A Al-Onazi, Zainab M Almarhoon, Amal M Al-Mohaimeed. Spectral characterization, electrochemical, antimicrobial and cytotoxic studies on new metal (II) complexes containing N2O4 donor hexadentate Schiff base ligand. Arabian Journal of Chemistry; 2020.
2. Misbah UR, Muhammad I, Muhammad A, Amer J. 2013;1(4):5966.
3. Available:www.academic journals.org
4. Available:cwww.intechopen.com
5. Blaettler L, Mertz D, Frei R, Elzi L, F, A, Battegay M. M. Infection. 2009;534–9.
6. Kronvall G. Antimicrobial resistance. APMIS. 2010;118:621–39.
7. John PA, Onoyima CC, Olusupo SB. Quantitative structure activity relationship study on the inhibitory activity of Schiff bases against *Escherichia coli* (*E. coli*). Journal of Computational Methods in Molecular Design; 2015.

8. Hafiz MA, Dildar A, Hira M Pak. J. Pharm. Sci. 2015;28(2):449-455.
9. Malik A, Sher KS, Wajid R, Zonera HA, Muhammad I. African J. Biotechnol. 2011;10(2).
10. Santhosh KB, Parthiban KG. Asian J. Pharm. Clin. Res. 2011;4(4).
11. Sahu SK, Afzal MD, Banerjee M, Acharrya S, Behera CC, Si S, Braz J. Chem. Soc. 2008;19(5).
12. Available:www.ishp.gov.al
13. Available:www.kenkyugroup.org
14. Shola Elijah Adeniji. Anti-tubercular modelling via QSAR approach, in silico design and virtual docking screening of designed hypothetical inhibitors against DNA gyrase Protein Current Computer-Aided Drug Design. 2021l1450-7188.
15. Available:mafiadoc.com
16. Sabitu Babatunde Olasupo. Density functional theory (B3LYP/6-31G*) study of toxicity of polychlorinated dibenzofurans. International Journal of Computational and Theoretical Chemistry; 2017.
17. Available:ijasre.net
18. Karki R, Rao GK, Gupta A, Mariappan G, Adhikari S. Synthesis, characterization and antimicrobial activities of schiff bases of 2-amino-4-(O-chloroanilino)-1, 3-thiazole. J App Pharm Sci. 2013;3(07):093-096.
19. In Silico Methods for Predicting Drug Toxicity. Springer Science and Business Media LLC; 2016.
20. Available:bnrc.springeropen.com
21. Available:ssjournals.com
22. Available:www.tandfonline.com
23. Wu W, Zhang C, Lin W, Chen Q, Guo X, Qian Y. Quantitative structure property relationship (QSPR) modeling of drug-loaded polymeric micelles via genetic function approximation. PLoSONE. 2015; 10(3):35-43.
24. Usman Abdulfatai, Adamu Uzairu, Sani Uba. Quantitative structure activity relationship study of anticonvulsant activity of _substituted acetamido-Nbenzylacetamide derivatives. Cogent Chemistry; 2016.
25. Usman Abdulfatai, Adamu Uzairu, Sani Uba. Quantitative structure-activity relationship and molecular docking studies of a series of quinazolinonyl analogues as inhibitors of gamma amino butyric acid aminotransferase. Journal of Advanced Research; 2017.
26. Han-Ha Chai, Dajeong Lim, Hee-Yeoul Chai, Eunkyoung Jung. Molecular modeling of small molecules as BVDV RNA-Dependent RNA polymerase allosteric inhibitors. Bulletin of the Korean Chemical Society; 2013.
27. Available:www.mdpi.com
28. Available:www.hindawi.com
29. Available:thesis.univ-biskra.dz
30. Usman Abdulfatai, Adamu Uzairu, Gideon Adamu Shallangwa, Sani Uba. *In-silico* molecular design and dynamic binding energy assessments of some multifunctional lubricating oil additives. South African Journal of Chemical Engineering; 2020.
31. Usman Abdulfatai, Adamu Uzairu, Sani Uba. Molecular docking and QSAR analysis of a few Gama amino butyric acid aminotransferase inhibitors. Egyptian Journal of Basic and Applied Sciences; 2019.
32. Usman Abdulfatai, Adamu Uzairu, Sani Uba. Molecular docking and QSAR analysis of a few Gama amino butyric acid aminotransferase inhibitors. Egyptian Journal of Basic and Applied Sciences; 2018.
33. Available:www.ftstjournal.com
34. Sabitu Babatunde Olasupo, Adamu Uzairu, Gideon Adamu Shallangwa, Sani Uba. Chemoinformatic studies on some inhibitors of dopamine transporter and the receptor targeting schizophrenia for developing novel antipsychotic agents. Heliyon; 2020.
35.

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