**Computational Design of Novel Schiff Base Inhibitors Against Salmonella Typhi: Molecular Mechanics-Based QSAR Approach**

**ABSTRACT**

*Salmonella typhi*, a Gram-negative pathogen linked to typhoid disease, has shown concerning patterns of antibiotic resistance, highlighting the need for novel inhibitors. By using predicted Quantitative Structure-Activity Relationship (QSAR) models, this study aimed to identify the structural factors present in Schiff bases that have anti-*Salmonella typhi* activity. After a thorough collection of 43 Schiff bases was compiled, the minimum inhibitory concentrations (MIC) of each were transformed into pMIC values for analytical use. Molecular descriptors were obtained, and QSAR models were constructed using Genetic Function Approximation (GFA). Model 1 emerged as the most robust iteration, with validation metrics (R2 = 0.800, R2adj = 0.749, Q2 = 0.520, R2 - Q2 = 0.280, and R2pred = 0.642) reflecting substantial predictive capability. The developed model showed that the descriptors were predominant. The observed anti-*Salmonella typhi* activity of Schiff bases is influenced by directional WHIM, which is weighted by unit weights (Weta3.unity) about molecular weight. The findings highlight how molecular weight affects anti-Salmonella typhi efficacy, which lays the groundwork for the logical development of more potent Schiff base derivatives.

**Keywords:** *Salmonella typhi; QSAR; GFA; Descriptors; Inhibitors*

**1. INTRODUCTION**

*Salmonella typhi* is classified as a Gram-negative bacterium that is the etiological agent of typhoid fever. [1, 2], an endemic illness that is particularly prevalent in tropical and subtropical regions globally. This pathogen has emerged as a significant public health challenge in developing nations, with an alarming incidence of over 21.6 million cases and approximately 250,000 fatalities recorded annually[3], thereby representing a critical source of morbidity and mortality in these areas. The *Salmonella typhi* bacterium has developed resistance to several antibiotics, including ampicillin, ceftriaxone, cotrimoxazole, quinolones, penicillin, cephalosporins, macrolides, and others. In light of the escalating resistance of this pathogen to multiple antibiotics, there has been a growing interest among medicinal chemists in the development of novel inhibitors that exhibit enhanced bioactivity [4]. Consequently, there exists an urgent requirement for the discovery of more efficacious and less toxic anti-Salmonella typhi agents capable of overcoming the resistance mechanisms established by this bacterium.

Schiff bases are synthesized through the condensation of basic amines with carbonyl compounds in ketones or aldehydes, wherein an imine or azomethine functional group (–C = N–) replaces the carbonyl moiety (C = O) [5, 6]. The presence of the imine linkage within Schiff base molecules is pivotal for the manifestation of this compound’s extensive range of biological applications, including analgesic. [7], anticancer [8, 9], antimicrobial [10, 11], antitumor [12], antioxidant [13, 14], antiviral [15], and anti-inflammatory activities [16]. This category of organic compounds has also exhibited substantial inhibitory efficacy against *Salmonella typhi* growth, positioning them as promising drug candidates in the ongoing effort to mitigate the perilous trend of multi-drug resistance presented by this pathogenic microorganism [2, 17].

Traditional methodologies employed in drug discovery and development predominantly utilize a trial-and-error strategy that is both time-intensive and financially burdensome, primarily due to the substantial costs associated with late-stage drug candidate failures. This approach further poses challenges to the principles of green chemistry owing to the considerable waste generated during the process[18]. Quantitative structure-activity relationship (QSAR) analysis establishes a mathematical correlation between the physical, chemical, biological, or environmental activities of interest and quantifiable or computable parameters known as molecular descriptors. The fundamental premise of QSAR is that structurally analogous molecules are likely to exhibit similar activities, thereby allowing for the comparison of molecules with unknown properties to those with established characteristics [19]. The application of QSAR methodologies has the potential to substantially diminish the time and effort requisite for the discovery of new therapeutic agents or the enhancement of existing ones by circumventing the conventional trial-and-error paradigm. This approach aids in the elimination of improbable candidates and fosters green chemistry by reducing waste and enhancing efficiency [20].

The current investigation looks at the relationships between the compounds' computed molecular descriptors and experimental pMIC in order to develop reliable, logical, and predictive Genetic function approximation (GFA) based QSAR models for the inhibitory action of Schiff bases against *Salmonella typhi*.

**2. MATERIALS AND METHODS**

The following materials were used in this study: Chem draw 12.0.1V, Microsoft Office Excel 2016, Material Studio (modeling and simulation software) version 7.0, Padel descriptor tool kit, Dell Latitude 7480 computer system Intel(R) Core (TM) i7 7600 CPU @2.8GHz/2.9GHz, 16GB RAM size on Microsoft Windows 11 Pro, and DTC.

**2.1 Data Collection**

A compilation of 43 Schiff bases exhibiting significant anti-*Salmonella typhi* efficacy in vitro was derived from the existing literature [20–24] for this investigation. The minimum inhibitory concentration (MIC) values of the compounds were transformed to a logarithmic scale [pMIC = -logMIC (µg/ml)] to mitigate data dispersion and facilitate a linear response alongside optimal data fitting [2]. The chemical structures along with the experimental inhibitory concentration (pMIC) values of the Schiff bases against *Salmonella typhi* are presented in Table 1. Seventy percent of the dataset (29 compounds) was allocated as a training set for model development. In comparison, the remaining thirty percent (14 compounds) was designated as a test set for the external validation of the most statistically robust quantitative structure-activity relationship (QSAR) model.

Table 1. Chemical structures and experimental inhibitory concentration (pMIC) values of Schiff bases against S.typhi

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| S/N | Structures | pMIC | S/N | Structures | pMIC |
| 1 |  | 1.34 | 22 |  | 1.36 |
| 2 |  | 1.28 | 23 |  | 1.26 |
| 3 |  | 1.34 | 24 |  | 1.2 |
| 4 |  | 1.9 | 25 |  | 1.6 |
| 5 |  | 1.26 | 26 |  | 0.9 |
| 6 |  | 1.62 | 27 |  | 1.78 |
| 7 |  | 1.36 | 28 |  | 1.48 |
| 8 |  | 1.28 | 29 |  | 1.81 |
| 9 |  | 1.58 | 30 |  | 2.08 |
| 10 |  | 1.32 | 31 |  | 1.7 |
| 11 |  | 1.36 | 32 |  | 2.4 |
| 12 |  | 1.32 | 33 |  | 2.3 |
| 13 |  | 1.38 | 34 |  | 1.49 |
| 14 |  | 1.62 | 35 |  | 1.49 |
| 15 |  | 1.3 | 36 |  | 0.89 |
| 16 |  | 1.32 | 37 |  | 1.19 |
| 17 |  | 1.28 | 38 |  | 1.19 |
| 18 |  | 1.18 | 39 |  | 1.8 |
| 19 |  | 1.2 | 40 |  | 1.49 |
| 20 |  | 1.23 | 41 |  | 1.49 |
| 21 |  | 1.3 | 42 |  | 1.19 |
| 43 |  | 1.19 |  | | |

**2.2 Molecular optimization**

Finding a molecule's equilibrium or lowest energy geometry is known as optimization [25]. Each compound's chemical structure in the data set was drawn using ChemDraw Ultra V12.0 and saved as a \*cdx file. Using Chem 3D Pro's molecular mechanics (MM) process, the molecules were optimized. To determine the molecules' lowest energy or equilibrium geometry, optimization was carried out. For each molecule, the physicochemical parameters (molecular descriptor) were calculated using its lowest energy structure.

**2.3 Descriptor calculation**

Arithmetic values that characterize the characteristics of molecules derived from a well-defined algorithm or experimental process are known as molecular descriptors [25]. Using the Padel descriptor toolkit, the different 0D, 1D, 2D, and 3D descriptors were computed.

**2.4 Learning Process**

During this procedure, correlation analysis was performed using the Microsoft Excel program in Microsoft Office 2016 to determine the relationship between the compounds' biological activity (pMIC) and the computed descriptors. To choose the appropriate descriptors for this regression study, a model based on Pearson's correlation matrix was employed. In order to create QSAR models, the chosen descriptors were put through regression analysis using Genetic Function Approximation (GFA) in Material Studio software, with empirically determined activities as the dependent variable. To determine which model had the highest fitness score, the models were evaluated using the "lack of fit" (LOF) score, which was calculated using a slightly modified version of the original Friedman formula [2, 26]. The original Friedman formula is used to measure LOF [27].

LOF = SS(1 – c + dp/m)2 ………………….…………………………… 1

In the model, c is the number of terms other than the constant term, d is the user-defined smoothing parameter, p is the total number of descriptors in all model terms (excluding the constant term), M is the number of samples in the training set, and SSE provides the sum of squares of errors [28]. Unlike the widely used least squares measure, the LOF measure is not always lowered by including additional terms in the regression model. The LOF metric prevents over-fitting by reducing the propensity to merely add more terms [29].

**2.5 Model validation**

Internal and external validation factors were used to assess the best models' predictive power, stability, fitting ability, and reliability [25]. Table 2 displays the minimum recommended value for a generally acceptable QSAR model, which was compared to the validation parameters.

Table 2. Validation Metrics for A Generally Acceptable QSAR Model.

|  |  |  |  |
| --- | --- | --- | --- |
| S/N | symbol | Name | Threshold |
| 1 | R2 | Coefficient determination | >0.6 |
| 2 | Q2 | LOO cross-validation coefficient | >0.5 |
| 3 | R2pred. | External test set’s coefficient of determination | >0.6 |
| 4 | R2 - Q2 | Different between R2 and Q2 | <0.3 |
| 5 | F value | Validation ratio | High |
| 6 | P95% | Confidence interval at 95% confidence level. | < 0.05 |
| 7 | VIF | Variance inflation factor | 1≤ VIF ≤10 |

**2.6 Internal validation parameters**

The data used to build the model was used for this validation. The square of the correlation coefficient (R2), Adjusted R2 (R2adj), Q2 (Leave one out cross validation coefficient), and validation ratio (F value) are the different internal validation parameters used in this study [30].

**2.6 External Validation**

A crucial stage in the creation of a QSAR model is internal validation. The model's improved stability and predictive ability are demonstrated by the intended internal validation results. For the external test set of molecules, it does not, however, demonstrate any true prediction ability. Thus, it is necessary to assess the best model's extrapolation and external predictive capacity [30]. R2pred is the external prediction parameter employed in this study.

**3. RESULTS AND DISCUSSION**

For the pMIC of anti-S. typhi compounds, the top three QSAR models developed from the Genetic Function Approximation are Models 1, 2, and 3. The best model for predicting the pMIC of anti-*Salmonella typhi* Schiff bases was determined to be Model 1, which had the lowest LOF. Additionally, its validation parameters and the typical validation metrics for a robust QSAR model agree well [31].

***Model 1:***

**pMIC = 0.052 \* minsF + 0.010 \* PNSA-3 - 9.772 \* Weta3.unity + 3.835 \* WK.unity - 0.727 \* Wnu2.eneg + 0.0182 \* Wlambda1.polar + 5.751**

Friedman LOF=0.046, R2=0.800, R2adj=0.749, R2cv=0.520, SR=Yes, Fvalue(C-SOR)= 14.958, C.Exp.error=2.561, Lack of fit point =22, Min non-exp.error LOFsign.= 0.112

***Model 2:***

**pMIC= 0.0415 \* minsF - 0.759 \* hmax - 8.622 \* Weta3.unity + 3.545 \* WK.unity + 0.018 \* Wlambda1.polar + 5.369**

Friedman LOF=0.049, R2=0.736, R2adj=0.678, R2cv=0.396, SR=Yes, Fvalue(C-SOR)= 12.809, C.Exp.error=2.663, Lack of fit point =23, Min non-exp.error LOFsign.= 0.128

***Model 3:***

**pMIC = - 1.736 \* BCUTc-1h + 0.040 \* minsF - 6.592 \* Weta3.unity - 0.800 \* Wnu2.eneg + 0.020 \* Wlambda1.polar + 5.356**

Friedman LOF=0.0494, R2=0.731, R2adj=0.672, R2cv=0.283, SR=Yes, Fvalue(C-SOR)= 12.481, C.Exp.error=2.663, Lack of fit point =23, Min non-exp.error LOFsign.= 0.129

Table 3. Definition of various descriptors used

|  |  |  |
| --- | --- | --- |
| S/N | Names of descriptors | Descriptors |
|  | minsF | Minimum atom-type E-State: -F |
|  | PNSA-3 | Charge-weighted partial negative surface area |
|  | Weta3.unity | Directional WHIM, weighted by unit weights |
|  | WK.unity | Non-directional WHIM, weighted by unit weights |
|  | Wnu2.eneg | Directional WHIM, weighted by Mulliken atomic electronegativities |
|  | Wlambda1.polar | Directional WHIM, weighted by atomic polarizabilities |

Model 1, also known as the octa-parametric model, was chosen as the optimization model based on the validation parameters. With R2 = 0.800, R2adj = 0.749, Q2 = 0.520, R2 - Q2 = 0.280, and R2pred = 0.642, the Genetic Function Algorithm-derived QSAR model strongly agrees with the threshold displayed in Table 2. The low residual values shown in Table 4, which compares the compounds' observed and predicted pMIC, demonstrate the predictability of Model 1 [18]. Additionally, Fig.1's plot of predicted pMIC against observed pMIC shows that the model is well-trained and capable of predicting the compounds' pMIC. Additionally, as the propagation of residuals was seen on both sides of zero, the plot of observed pMIC versus residual pMIC (Fig. 3) shows that there was no systemic error in the model generation process [32].

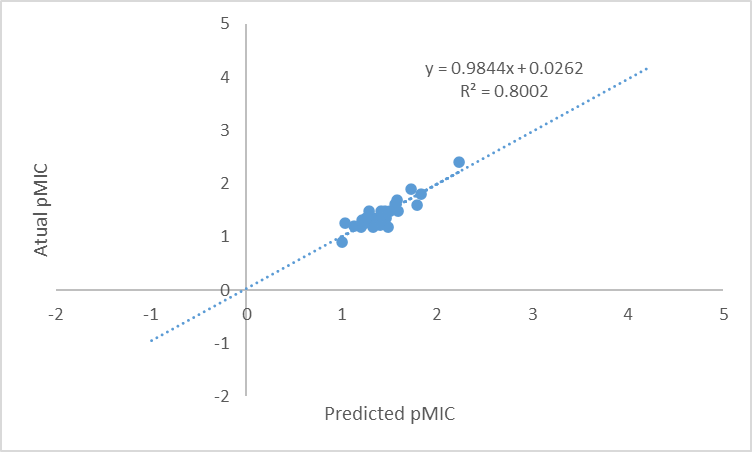


Fig.1. Plot of Actual pMIC against Predicted pMIC of Model 1(training set)

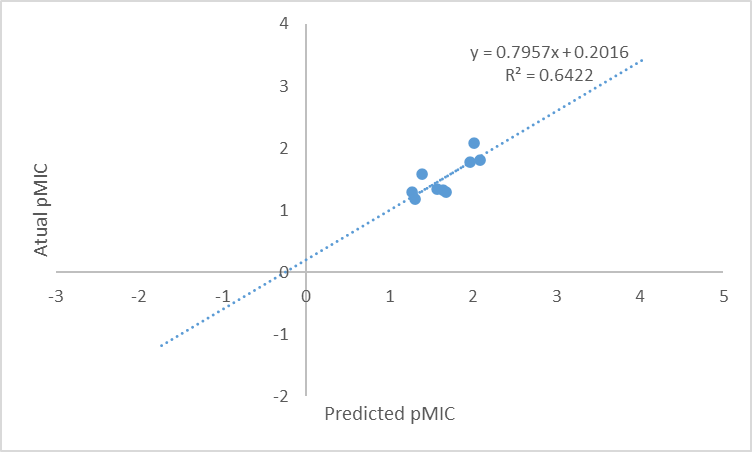


Fig.2. Plot of Actual pMIC against Predicted pMIC of Model 1(test set)

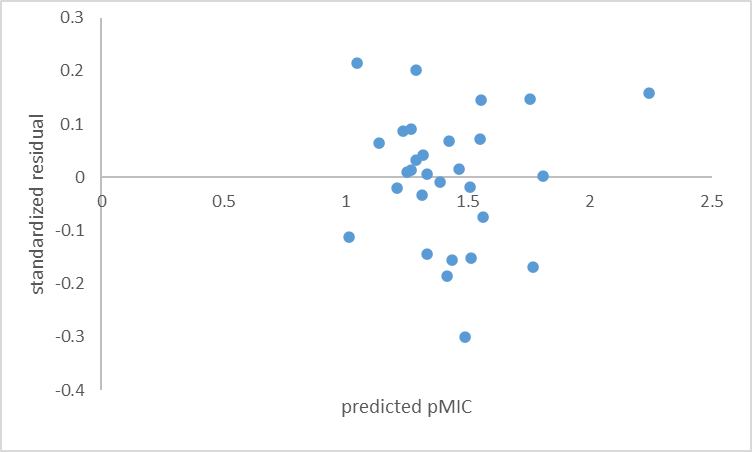


Fig.3. Residual Plot of Model 1

Table 4. Comparison between Actual pMIC and Predicted pMIC of Model 1 (training set)

|  |  |  |  |
| --- | --- | --- | --- |
| Compound | Actual pMIC | Predicted pMIC | Residual Values |
| 1 | 1.34 | 1.339358 | 0.007101 |
| 2 | 1.28 | 1.443971 | -0.15595 |
| 4 | 1.9 | 1.721728 | 0.146945 |
| 5 | 1.26 | 1.240855 | 0.009619 |
| 7 | 1.36 | 1.325051 | 0.041633 |
| 8 | 1.28 | 1.252462 | 0.01311 |
| 10 | 1.32 | 1.272905 | 0.032902 |
| 11 | 1.36 | 1.463127 | -0.15141 |
| 13 | 1.38 | 1.39874 | -0.00793 |
| 14 | 1.62 | 1.559041 | 0.071824 |
| 16 | 1.32 | 1.21716 | 0.086602 |
| 17 | 1.28 | 1.308072 | -0.03361 |
| 19 | 1.2 | 1.126457 | 0.065111 |
| 20 | 1.23 | 1.405946 | -0.18624 |
| 22 | 1.36 | 1.258742 | 0.091397 |
| 23 | 1.26 | 1.038636 | 0.214726 |
| 25 | 1.6 | 1.788299 | -0.1684 |
| 26 | 0.9 | 1.003493 | -0.113 |
| 28 | 1.48 | 1.457055 | 0.015075 |
| 29 | 1.81 | 1.82734 | 0.002871 |
| 31 | 1.7 | 1.580521 | 0.144739 |
| 32 | 2.4 | 2.232743 | 0.158418 |
| 34 | 1.49 | 1.280793 | 0.202357 |
| 35 | 1.49 | 1.414518 | 0.067454 |
| 37 | 1.19 | 1.482615 | -0.29991 |
| 38 | 1.19 | 1.322937 | -0.14438 |
| 39 | 1.49 | 1.586191 | -0.07371 |
| 40 | 1.49 | 1.50212 | -0.01797 |
| 41 | 1.19 | 1.20038 | -0.01939 |

Table 5. Actual, Predicted, and Residual pMICof Model 1 (test set)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Compound | pMIC | Minsf | PNSA | Weta3-Unity | WK.Unity | Wnu2.eneg | Wlamba1.polar | Pred. pMIC |
| |  | | --- | | 3 | | 6 | | 9 | | 12 | | 15 | | 18 | | 21 | | 24 | | 27 | | 30 | | 33 | | 36 | | 39 | | 42 | | |  | | --- | | 1.34 | | 1.62 | | 1.58 | | 1.32 | | 1.3 | | 1.18 | | 1.3 | | 1.2 | | 1.78 | | 2.08 | | 2.3 | | 0.89 | | 1.8 | | 1.19 | | |  | | --- | | 12.86 | | 0 | | 0 | | 13.38 | | 0 | | 0 | | 0 | | 0 | | 12.65 | | 0 | | 0 | | 0 | | 13.19 | | 0 | | |  | | --- | | -39.28 | | -34.90 | | -45.88 | | -51.99 | | -45.70 | | -31.98 | | -31.28 | | -17.03 | | -20.31 | | -14.65 | | -20.55 | | -30.39 | | -23.62 | | -15.85 | | |  | | --- | | 0.56 | | 0.56 | | 0.54 | | 0.56 | | 0.56 | | 0.53 | | 0.56 | | 0.58 | | 0.58 | | 0.56 | | 0.53 | | 0.57 | | 0.57 | | 0.54 | | |  | | --- | | 0.32 | | 0.37 | | 0.32 | | 0.31 | | 0.34 | | 0.30 | | 0.35 | | 0.40 | | 0.41 | | 0.41 | | 0.27 | | 0.37 | | 0.38 | | 0.36 | | |  | | --- | | 0.23 | | 0.17 | | 0.01 | | 0.24 | | 0.20 | | 0.17 | | 0.14 | | 0.12 | | 0.11 | | 0.11 | | 0.68 | | 0.02 | | 0.02 | | 0.03 | | |  | | --- | | 0.09 | | 0.12 | | 10.97 | | 10.25 | | 11.50 | | 1.87 | | 22.80 | | 16.81 | | 0.03 | | 17.68 | | 0.58 | | 0.38 | | 0.27 | | 17.07 | | |  | | --- | | 1.57 | | 1.25 | | 1.39 | | 1.64 | | 1.26 | | 1.31 | | 1.68 | | 1.71 | | 1.97 | | 2.01 | | 0.89 | | 1.35 | | 2.08 | | 1.98 | |

**3.1 Significance of the Descriptors in Model 1**

The descriptors' positive coefficient follows: The value of the pMIC of these compounds against *Salmonella typhi* increases as the values of the following descriptors increase: Minimum atom-type E-State: -F (minsF), Charge-weighted partial negative surface area (PNSA-3), Non-directional WHIM, weighted by unit weights (WK.unity), Directional WHIM, weighted by Mulliken atomic electronegativities (Wnu2.eneg), and Directional WHIM, weighted by atomic polarizabilities (Wlambda1.polar). Therefore, the biological activity of these compounds against *Salmonella typhi* increases with the values of these descriptors, and vice versa.

Minimum atom-type E-State: -F (minsF) is a descriptor of the electronegativity of Flourine. The result of the QSAR optimization model shows that the inhibitory activity of the studied Schiff bases increases with compounds having fewer numbers of fluorine atoms.

Charge-weighted partial negative surface area (PNSA-3), Non-directional WHIM, weighted by unit weights (WK.unity), Directional WHIM, weighted by Mulliken atomic electronegativities (Wnu2.eneg), and Directional WHIM, weighted by atomic polarizabilities (Wlambda1.polar) are descriptors of molecular weights.

The Directional WHIM, weighted by unit weights (Weta3.unity), is also a descriptor of molecular weight. Its negative correlation with pMIC of the molecule, as shown in the best model (model 1), indicates that the biological activity of the studied compounds against *Salmonella typhi* increases with a decrease in molecular weight of the compounds. Therefore, for an enhanced anti-*Salmonella typhi* biological activity from Schiff bases, the weight of the molecules should be minimal.

**3.2 Summary of Findings**

Models 1, 2, and 3 reflect the optimal QSAR models that were produced in order to investigate the structural requirements controlling the observed biological activities of Schiff bases. The strongest prediction model for Schiff bases' pMIC against *Salmonella typhi* is Model 1. Directional WHIM, weighted by unit weights (Weta3.unity) relative to molecular weight, was found to have a significant impact on the observed pMIC of the compounds against Salmonella typhi. This descriptor accounts for 48.46% of the molecules' observed inhibitory activity against *Salmonella typhi*. According to model 1, the descriptors' positive coefficients indicate that a molecule's activity against *Salmonella typhi* increases with the descriptors' value and vice versa.

**RECOMMENDATION**

Model 1’s top-performing predicted Schiff bases should be experimentally validated through in vitro and in vivo studies, given their effectiveness against *Salmonella typhi*. Expanding the dataset to include more structurally diverse Schiff base derivatives should be prioritized, along with the application of advanced machine learning techniques or hybrid QSAR-docking approaches to refine accuracy in predictions. Moreover, chemists must prioritize the synthesis of compounds with optimized molecular weights and electronegativities, given that the model cited these features as critical in determining bioactivity. Integrating computational chemists, microbiologists, and medicinal chemists could rapidly accelerate the development of these compounds into novel anti-typhoid drugs, meeting the critical need for new antibiotics targeting drug-resistant Salmonella typhi. Finally, the application of green chemistry principles to the synthesis could further enhance the alignment of this research with sustainable drug discovery initiatives.

**CONCLUSION**

The study successfully developed and validated QSAR models to predict the anti-*Salmonella typhi* activity of Schiff bases. Model 1's exceptional statistical performance demonstrated the importance of descriptors like minsF, PNSA-3, and WHIM-based factors in controlling biological activity. The negative relationship between molecular weight (Weta3.unity) and pMIC suggests that lighter molecules may have stronger inhibitory effects. These findings are consistent with the urgent need for novel antimicrobial medications to combat drug-resistant *Salmonella typhi*. In addition to saving time and money when compared to traditional drug development, the QSAR method also complies with green chemistry principles by minimizing experimental waste.

**REFERENCE**

1. Bouchrif B, Paglietti B, Murgia M, Piana A, Cohen N, Ennaji MM, Rubino S, Timinouni M (2009) Prevalence and antibiotic-resistance of Salmonella isolated from food in Morocco. The Journal of Infection in Developing Countries. https://doi.org/10.3855/jidc.103

2. Adawara SN, Alisi IO, Sani S (2015) Modelling of some Schiff bases as anti-Salmonella typhi drugs: A QSAR approach.

3. Ameji JP, Femi E, Oluwaseye A, Sabitu O (2016) Exploring structure indenture for some Schiff bases as anti-Salmonella typhi drugs: A QSAR Approach. International Journal of Advances in Scientific Research 2:48–053

4. Glomb T, Świątek P (2021) Antimicrobial Activity of 1,3,4-Oxadiazole Derivatives. Int J Mol Sci 22:6979

5. Abdel Aziz AA, Ramadan RM, Sidqi ME, Sayed MA (2023) Structural characterisation of novel mononuclear Schiff base metal complexes, DFT calculations, molecular docking studies, free radical scavenging, DNA binding evaluation and cytotoxic activity. Appl Organomet Chem. https://doi.org/10.1002/aoc.6954

6. Babaei P, Rezvan VH, Gilani NS, Mansour SR (2024) Molecular docking and in vitro biological studies of a Schiff base ligand as anticancer and antibacterial agents. Results Chem. https://doi.org/10.1016/j.rechem.2024.101517

7. Yassen TM, AL-Azzawi AM (2023) Synthesis and Characterization of New Bis-Schiff Bases Linked to Various Imide Cycles. Iraqi Journal of Science 1062–1070

8. Yuosra Khalaf Alasadi, Fawzi Hameed Jumaa, Mohammed Ghanam Mukhlif (2023) Preparation, Characterization, Anti-cancer and Antibacterial Evaluation of New Schiff base and Tetrazole Derivatives. Tikrit Journal of Pure Science 28:12–19

9. Aroua LM, Alhag SK, Al-Shuraym LA, Messaoudi S, Mahyoub JA, Alfaifi MY, Al-Otaibi WM (2023) Synthesis and characterization of different complexes derived from Schiff base and evaluation as a potential anticancer, antimicrobial, and insecticide agent. Saudi J Biol Sci 30:103598

10. Alfonso‐Herrera LA, Rosete‐Luna S, Hernández‐Romero D, Rivera‐Villanueva JM, Olivares‐Romero JL, Cruz‐Navarro JA, Soto‐Contreras A, Arenaza‐Corona A, Morales‐Morales D, Colorado‐Peralta R (2022) Transition Metal Complexes with Tridentate Schiff Bases (O N O and O N N) Derived from Salicylaldehyde: An Analysis of Their Potential Anticancer Activity. ChemMedChem. https://doi.org/10.1002/cmdc.202200367

11. Awolope RO, Ejidike IP, Clayton HS (2022) Schiff base metal complexes as dual antioxidant and antimicrobial agents. J Appl Pharm Sci. https://doi.org/10.7324/JAPS.2023.91056

12. Rezaei MT, Keypour H, Hajari S, yaghoobi F, Moazzami Farida SH, Saadati M, Gable RW (2023) Theoretical and solid-state structures of three new macroacyclic Schiff base complexes and the investigation of their anticancer, antioxidant and antibacterial properties. RSC Adv 13:9418–9427

13. Aytac S, Gundogdu O, Bingol Z, Gulcin İ (2023) Synthesis of Schiff Bases Containing Phenol Rings and Investigation of Their Antioxidant Capacity, Anticholinesterase, Butyrylcholinesterase, and Carbonic Anhydrase Inhibition Properties. Pharmaceutics 15:779

14. Abd El‐Hamid SM, Sadeek SA, Mohammed SF, Ahmed FM, El‐Gedamy MS (2023) N 2 O 2 ‐chelate metal complexes with Schiff base ligand: Synthesis, characterisation and contribution as a promising antiviral agent against human cytomegalovirus. Appl Organomet Chem. https://doi.org/10.1002/aoc.6958

15. Pore A, Gaikwad G, Hegade S, Jadhav Y, Mane R, Kumbhar R (2023) Analyzing the Impact of the Substituent on the Quinazolinone Schiff Base and the Interaction of the Fe (III) and Cr (III) with Different Quinazolinone Schiff Base for Antioxidant and Anti-inflammatory Activity. Analytical Chemistry Letters 13:39–59

16. Krishna GA, Dhanya TM, Shanty AA, Raghu KG, Mohanan PV (2023) Transition metal complexes of imidazole derived Schiff bases: Antioxidant/anti-inflammatory/antimicrobial/enzyme inhibition and cytotoxicity properties. J Mol Struct 1274:134384

17. Muhammad H, Sharif A, Ahmed D, Mir H (2015) Antimicrobial salicylaldehyde Schiff bases: Synthesis, characterization and evaluation.

18. Juliet OI, Onize IB, Praise ET, Ojodomo AI, Aminat Y, Raimi N (2022) Molecular Mechanics-Based Quantitative Structure-Activity Relationship Study on the Inhibitory Activity of Some Schiff Bases against Escherichia coli. Asian Journal of Chemical Sciences 44–56

19. Rathod AK (2011) Antifungal and Antibacterial activities of Imidazolylpyrimidines derivatives and their QSAR Studies under Conventional and Microwave-assisted.

20. Ameji PJ, Adamu U, Gideon AS (2016) Insilico design of highly potent anti-salmonella typhi drug candidates from schiff bases. Albanian Medical Journal 4:19–22

21. Adeel-Sharif HM, Ahmed D, Mir H (2015) Antimicrobial salicylaldehyde Schiff bases: synthesis, characterization and evaluation. PubMed 28:449–455

22. Kumar BS, Parthiban KG (2011) Synthesis of Schiff bases of some  novel n-nitrosoisatin derivatives as potential antimicrobial  agents. Asian J Pharm Clin 4:137–40

23. Rajasekaran S, Gopalkrishna R (2012) Scholars Research Library Synthesis, antibacterial and antioxidant activity of some 2, 3-susbtituted quinazolin-4(3H)-ones.

24. Singh M, Sellamuthu S, Singh SK, Gangwar M, Nath G, Singh SK (2017) Antimicrobial Potency and Molecular Mechanism of Benzothiazole Schiff Base Hybrids. Saudi Journal of Medical and Pharmaceutical Sciences. https://doi.org/10.36348/sjmps.2017.v03i12.017

25. Ameji JP, Chinweuba OC, Sabitu O (2015) Quantitative structure activity relationship study on the inhibitory activity of Schiff bases against Escherichia coli (E.coli). Journal of Computational Methods in Molecular Design 5:84–96

26. Wu W, Zhang C, Lin W, Chen Q, Guo X, Qian Y, Zhang L (2015) Quantitative Structure-Property Relationship (QSPR) Modeling of Drug-Loaded Polymeric Micelles via Genetic Function Approximation. PLoS One 10:e0119575

27. Abdulfatai U, Uzairu A, Uba S (2017) Quantitative structure-activity relationship and molecular docking studies of a series of quinazolinonyl analogues as inhibitors of gamma amino butyric acid aminotransferase. J Adv Res 8:33–43

28. Chai H-H, Lim D, Chai H-Y, Jung E (2013) Molecular Modeling of Small Molecules as BVDV RNA-Dependent RNA Polymerase Allosteric Inhibitors. Bull Korean Chem Soc 34:837–850

29. Tropsha A (2010) Best Practices for QSAR Model Development, Validation, and Exploitation. Mol Inform 29:476–488

30. Abdulfatai U, Uzairu A, Uba S (2018) Molecular docking and QSAR analysis of a few Gama amino butyric acid aminotransferase inhibitors. Egyptian Journal of Basic and Applied Sciences 5:41–53

31. Veerasamy R, Rajak H, Jain A, Sivadasan S, Varghese CP, Agrawal RK (2011) Validation of QSAR Models - Strategies and Importance. International Journal of Drug Design and Discovery 2:511–519

32. Mahmud AW, Shallangwa GA, Uzairu A (2020) QSAR and molecular docking studies of 1,3-dioxoisoindoline-4-aminoquinolines as potent antiplasmodium hybrid compounds. Heliyon 6:e03449