**QSAR-Based Design of Schiff Base Inhibitors for Drug-Resistant *Salmonella Typhi***

**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. Model 1 identified Weta3.unity, a molecular weight descriptor, as the dominant descriptor that influences the anti-*Salmonella typhi* activity of Schiff bases. The findings highlight how molecular weight affects the efficacy of anti-*Salmonella typhi*, laying 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 [4, 5]. 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 [6]. 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) [7, 8]. 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. [9], anticancer [10, 11], antimicrobial [12, 13], antitumor [14], antioxidant [15, 16], antiviral [17], and anti-inflammatory activities [18]. 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, 19].

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[20]. 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 [21]. 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 [22]. Although research using QSAR Schiff bases has been published for several bacteria[20, 23–26], there are still significant gaps in the particular targeting of drug-resistant *Salmonella typhi*.

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 [22, 27–30] 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 [31]. 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 [31]. Using the Padel descriptor toolkit, the different 0D, 1D, 2D, and 3D descriptors were computed.

**2.4 Learning Process**

The study used Microsoft Excel to analyze the relationship between compounds' biological activity (pMIC) and computed descriptors. A model based on Pearson's correlation matrix was used to select appropriate descriptors. Genetic Function Approximation (GFA) was used to create QSAR models, with empirically determined activities as the dependent variable. The "lack of fit" (LOF) score was used to evaluate the models, calculated using a modified version of the original Friedman formula [2, 32], which measures the number of terms other than the constant term, smoothing parameter, total number of descriptors, training set size, and sum of squares of errors [33]. The LOF measure prevents over-fitting by reducing the propensity to add more terms, unlike the widely used least squares measure[34].

**2.5 Model validation**

Internal and external validation factors were used to assess the best models' predictive power, stability, fitting ability, and reliability [31]. 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 [35].

**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 [35]. 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 [36].

***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 [20]. 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 [37].

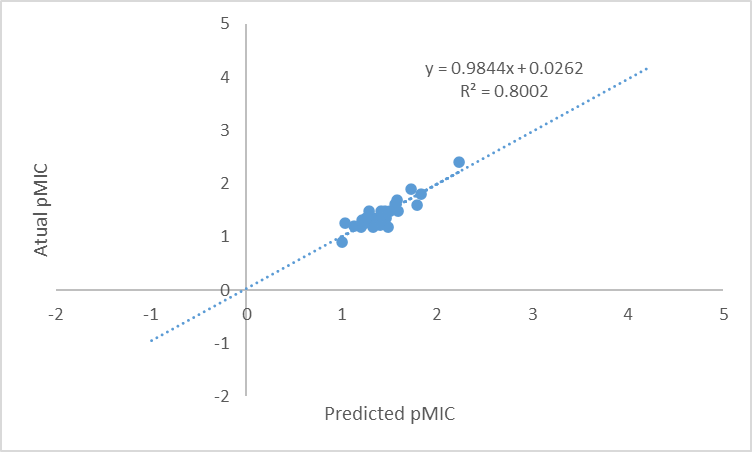


Fig.1. Plot of Actual pMIC against Predicted pMIC of Model 1(training set)

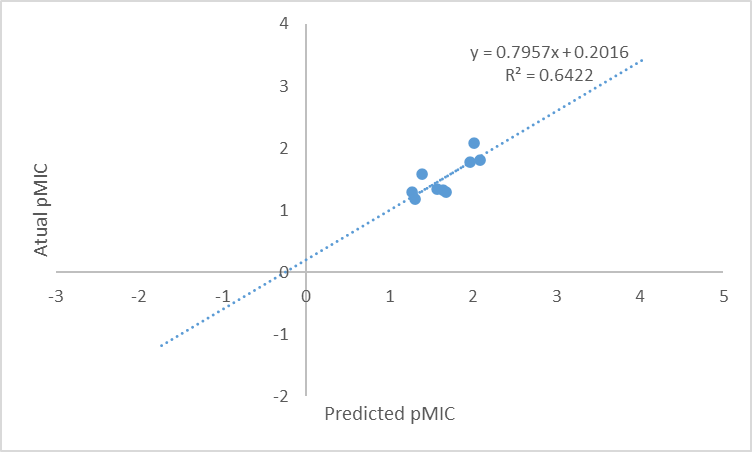


Fig.2. Plot of Actual pMIC against Predicted pMIC of Model 1(test set)

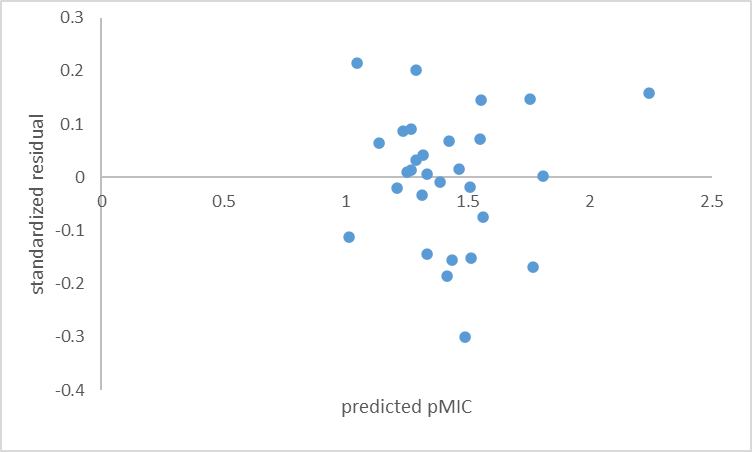


Fig.3. Residual Plot of Model 1

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, which is evidence that fluorine substitution decreases planarity is consistent with the minsF descriptor's positive correlation [38].

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 because large molecules have difficulty penetrating the outer membrane of *Salmonella typhi*, which is rich in lipopolysaccharides[39].

**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.

**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.

**RECOMMENDATION**

Model 1’s top-performing predicted Schiff bases should be validated through laboratory studies, both in vitro and in vivo, due to their effectiveness against *Salmonella typhi*. Expanding the dataset to include more structurally varied Schiff base derivatives should be a priority, along with the use of advanced machine learning methods or hybrid QSAR-docking techniques to improve prediction accuracy. Additionally, chemists should focus on synthesizing compounds with optimized molecular weights and electronegativities, as the model identified these features as key factors in bioactivity. Collaboration among computational chemists, microbiologists, and medicinal chemists can accelerate the development of these compounds into new anti-typhoid drugs, addressing the urgent need for new antibiotics against drug-resistant *Salmonella typhi*. Finally, applying green chemistry principles to the synthesis process could further align this research with sustainable drug development efforts. Connecting computational findings with real-world clinical impacts could ultimately help solve the critical shortage of antibiotics needed to combat drug-resistant *Salmonella typhi*.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that non-generative AI tools were used during the writing or editing of manuscripts.

Details of the AI usage are given below:

1. Grammarly was only used for spelling/grammar checks.
2. Quilbot (Paraphrasing Tool) was used to improve language clarity in non-technical areas, with all output verified by the authors.

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