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Research Article

Exploring structure indenture for some Schiff bases as anti-*Salmonella typhi* drugs: A QSAR Approach

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Abstract

There are many drugs available in the market for treating typhoid infection, but the emergence of multi-drug resistant strain of *Salmonella typhi* (*S. typhi*) has necessitated the exploration and development of newer structural moiety of Schiff bases as anti-S. typhi agents owing to their enormous inhibitory activity against this bacterium. In this present study, a Genetic function approximation (GFA) QSAR analysis of some selected Schiff bases with anti-S. typhi activity was performed using OD,1D, 2D and 3D descriptors resulting in the generation of three statistically significant models from which an octa-parametric model was selected as the most robust model with $R^2 = 0.8589$, $R^2_{adj} = 0.8155$, $Q^2 = 0.7437$, $R^2 - Q^2 = 0.1152$, $r^2 – r_0^2 / r^2 = 0.00$, $r^2 – r'^2_0 / r^2 = 0.0263$, K = 1.0E-7, $K' = 0.1969$. The optimization model hinted the dominant influence of the size descriptor ETA-Eta-B (Branching index EtaB relative to molecular size) on the observed anti-*S. typhi* activity of Schiff bases. It is envisaged that the QSAR results identified in this study will offer important structural insight into designing novel anti-S.typhi drugs from Schiff bases.

Keywords: *Salmonella typhi*, QSAR, descriptors, Schiff bases, Typhoid infection.

1. Introduction

Salmonella Typhi is a Gram-negative bacterium responsible for typhoid fever [1-3] an endemic disease prevalent in the tropic and sub-tropical regions of the world. It has become a major public health concern in developing countries of the world with over 21.6 million cases and at least 250,000 deaths occurring annually [4], thus, constituting a serious source of morbidities and mortalities in these regions.

Many drugs such as ceftriaxone, chloramphenicol, ciprofloxacin/ofloxacin, cefixime, and ampicillin abound for the treatment of this infection. Regrettably, the overuse, misuse, and inappropriate antibiotic prescribing practices coupled with use of allopathic drugs as well as uncontrolled use of antibiotics in agriculture, animal husbandry and fisheries has led to the growth of multi-drug resistance strain of *S. typhi* [5-8]. Thus, there is an urgent need to develop new antibiotics that will arrest this dangerous trend of multi-drug resistance by this organism (*S. typhi*).

In recent years, Schiff bases have received considerable attention because of their physiological and pharmacological activities [9]. This class of organic compounds have also demonstrated significant inhibitory activity against the growth of *S. typhi* [10-13] making them potential drug candidate for man's quest to curb the dangerous trend of multi-drug resistance posed by this pathogenic micro-organism.

Quantitative structure activity relationship (QSAR) establishes the mathematical relationship between physical, chemical, biological or environmental activities of interest and measurable or computable parameters called molecular descriptors. Its main assumption is that structurally similar molecules tend to have similar activities and that molecules with unknown properties can be compared to structures with known properties [14]. The application of quantitative structure activity relationship (QSAR) methodologies has potential to decrease substantially the time and effort required to discover new medicines or to improve current ones in terms of their efficacy by avoiding the conventional trial and error approach employed in the discovery and development of novel medicines by avoiding leads

unlikely to be successful. Thus, promoting green and greener chemistry by reducing waste and increasing efficiency.

Aim of the present study is to build robust, rational, and predictive Genetic function approximation (GFA) based QSAR models for S. *typhi* inhibitory activity of Schiff bases.

2. Materials and Methods

The molecular modeling studies were performed using the molecular modeling program SPARTAN'14 V1.1.0 (www.wavefun.com) on H.P 650 computer system (Intel Pentium), 2.43GHz processor, 4GB ram size on Microsoft windows 7 Ultimate operating system. The molecules were first pre-optimized with the molecular mechanics procedure included in Spartan'14 V1.1.0 software and the resulting geometries were further refined by means of Semi-empirical (pm3). The lowest energy structure was used for each molecule to calculate their physicochemical properties (molecular descriptor).

2.1 Data set: A data set comprising of series of 35 schiff bases with anti-*Salmonella typhi* activity was taken from reported articles [10-13] (Table 1) for the study.

Table 1: Anti-S.typhi activity of the compounds (MIC µg/ml and pMIC)

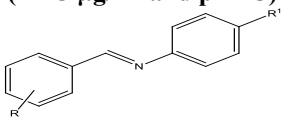
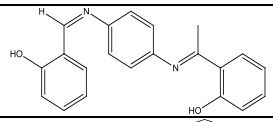
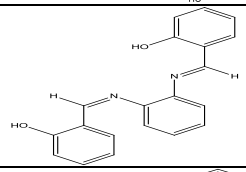
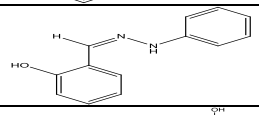
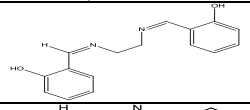
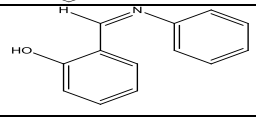


Figure 1: parent structure for compound 1-8.

cpd	R	R^1	MIC	pMIC
1	3-OCH_3	4-CH_3	18	1.26
2	3,4-OCH_3	4-CH_3	16	1.20
3	3,4,5-OCH_3	4-CH_3	40	1.60
4	3-OCH_3, 4-OH	4-CH_3	8	0.90
5	4-F	4-CH_3	60	1.78
6	4-Cl	4-CH_3	30	1.48
7	4-Br	4-CH_3	64	1.81
8	4-I	4-CH_3	120	2.08
9			50	1.70
10			250	2.40
11			200	2.30
12			100	2.00
13			200	2.30

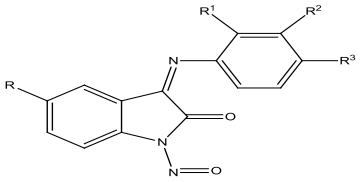


Figure 2: parent structure for compound 14-29

cpd	R	R^1	R^2	R^3	MIC	pMIC
14	H	H	H	Cl	22	1.34
15	H	H	H	Br	19	1.28
16	H	H	H	F	22	1.34
17	H	H	Cl	F	79	1.90
18	H	H	H	CH_3	18	1.26
19	H	H	H	OCH_3	42	1.62
20	H	H	H	NO_2	23	1.36
21	H	NO_2	H	NO_2	19	1.28
22	Br	H	H	Cl	38	1.58
23	Br	H	H	Br	21	1.32
24	Br	H	H	F	23	1.36
25	Br	H	Cl	F	21	1.32
26	Br	H	H	CH_3	24	1.38
27	Br	H	H	OCH_3	42	1.62
28	Br	H	H	NO_2	20	1.30
29	Br	NO_2	H	NO_2	21	1.32

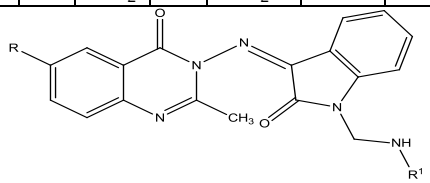
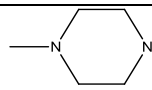
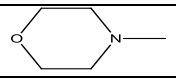


Figure 3: parent structure for compound 30-35

Cpd	R	R^1	MIC	pMIC
30	H	$N(CH_3)_2$	19	1.28
31	H	$N(C_2H_5)_2$	15	1.18
32	H	$N(C_6H_5)_2$	16	1.20
33	H	$N(C_6H_{11})_2$	17	1.23
34	H		20	1.30
35	H		23	1.36

2.2 Model building

The computed descriptors were subjected to regression analysis with the experimentally determined minimum inhibitory concentration on logarithmic scale (pMIC) as the dependent variable and the selected descriptors as the independent variables using Genetic function approximation (GFA) method in Material studio software. To develop the optimization model, 35 samples were included in the training set. The number of descriptors in the regression equation was set to 5, and Population and Generation were set to 1,000 and 5,000, respectively. The number of top equations returned was 5. Mutation probability was 0.1, and the smoothing parameter was 0.5. The statistical significance of the generated

models were assessed based on Friedman's LOF and the optimum model was selected based on this parameter.

2.3 Model Validation: A reliable validation procedure is required in order to confirm the existence of chance correlations as well as ascertaining the fitting ability, stability, reliability and predictive ability of the developed models. The optimum model was validated and its validation parameters were compared with the standards shown in Table 2.

Table 2: **Validation metrics for a generally acceptable QSAR model**

S/n	Metric symbol	Name	Threshold
1	R^2	Coefficient of determination	≥ 0.6
2	Q^2	LOO cross validation coefficient	< 0.5
3	$R^2_{pred.}$	External test set's coefficient of determination	≥ 0.6
4	$R^2 - Q^2$	Difference between R^2 and Q^2	≤ 0.3
5	F value	Variation ratio	High
6	$r^2 - r_0^2 / r^2$	Golbraikh and Tropsha condition	< 0.1
7	$r^2 - r'^2_0 / r^2$	Golbraikh and Tropsha condition	< 0.1
8	K and K'	Intercept	$0.85 \leq k$ or $k' \leq 1.15$

Source: [15-17]

2.3.1 Validation parameters

R^2 (the square of the correlation coefficient): describes the fraction of the total variation attributed to the model. The closer the value of R^2 is to 1.0, the better the regression equation explains the Y variable. R^2 is the most commonly used internal validation indicator and is expressed as follows:

$$R^2 = 1 - \frac{\sum(Yobs - Ypred)^2}{\sum(Yobs - Ytraining)^2} \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where, Yobs; Ypred ;Ytraining are the experimental property, the predicted property and the mean experimental property of the samples in the training set, respectively .

Adjusted R^2 (R^2_{adj}): R^2 value varies directly with the increase in number of regressors i.e. descriptors, thus, R^2 cannot be a useful measure for the goodness of model fit. Therefore, R^2 is adjusted for the number of explanatory variables in the model. The adjusted R^2 is defined as:

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

Where p = number of independent variables in the model [18]

Q^2 (Leave one out cross validation coefficient): The LOO cross validated coefficient (Q^2) is given by;

$$Q^2 = 1 - \frac{\sum(Yp - Y)^2}{\sum(Y - Ym)^2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Where Yp and Y represent the predicted and observed activity respectively of the training set and Y_m the mean activity value of the training set [18].

Variance Ratio (F): this parameter is used to judge the overall significance of the regression coefficient. It is the ratio of regression mean square to deviations mean square defined as:

$$F = \frac{\frac{\sum(Ycal - Ym)^2}{p}}{\frac{\sum(Yobs - Ycal)^2}{N-P-1}} \quad \ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Where Y_{obs} stands for the observed response value, while Y_{calc} is the model-derived calculated response and Y_m is the average of the observed response values. The F value has two degrees of freedom: p, N − p − 1. The computed F value of a model should be significant at $p < 0.05$. A high F value is an indication that the regression coefficients are significant [15].

Standard error of estimate (s): Low standard error of estimate is an indication of a good model. It is defined as follows:

$$S = \sqrt{\frac{(Yobs - Ycal)^2}{N-P-1}} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Its degree of freedom is N-p-1 [15].

Leave one out cross validation (LOOCV): in this cross validation approach, the model is repeatedly refit leaving out a single observation and then used to derive a prediction for the left-out observation**.** For good predictability, $Q^2 > 0.5$ and $R^2 - Q^2$ value should not exceed 0.3. The equation for CV is:

$$Q^2 = 1 - \frac{PRESS}{\sum(Yi - Ym)^2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (6)$$

$$PRESS = \sum (Ypred, i - Yi) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (7)$$

Q^2 = LOOCV cross validation coefficient, R^2 = coefficient of determination.

Yi is the data value(s) not used to construct the CV model, PRESS is the predictive residual sum of the squares, Ym = mean of the experimental bioactivity (pMIC), $Ypred, i$ is the predicted Yi [16].

3. Result and Discussion

Table 3: GFA derived QSAR models for the pMIC of the selected Schiff bases.

Model	Equation	Definition of terms
1.	*p*MIC = - 37.716609524 * X64 + 0.001733366 * X124 - 0.048104300 * X125 - 0.110389586 * X144 + 0.208049019 * X159 + 0.024540633 * X165 + 0.486019870 * X200 + 0.447687106 * X216 + 0.936108571	X64 : BN : ETA_EtaP_B X124 : DV : PNSA-2 X125 : DW : PNSA-3 X144 : EP : RNCS X159 : FE : LOBMIN X165 : FK : MOMI-YZ X200 : GT : Wnu2.volume X216 : HN : WK.eneg
2.	*p*MIC = - 39.324866343 * X64 + 0.001432639 * X124 - 0.047261292 * X125 - 0.112261024 * X144 + 0.197812171 * X158 + 0.023705510 * X164 + 0.431956515 * X216 - 0.230144398 * X229 + 0.939841671	X64 : BN : ETA_EtaP_B X124 : DV : PNSA-2 X125 : DW : PNSA-3 X144 : EP : RNCS X158 : FD : LOBMAX X164 : FJ : MOMI-XZ X216 : HN : WK.eneg X229 : IA : WK.polar
3.	*p*MIC = - 38.895205619 * X64 + 0.001469090 * X124 - 0.047159174 * X125 - 0.111871139 * X144 + 0.190408175 * X159 + 0.023663077 * X165 + 0.431644505 * X216 - 0.222354151 * X229 + 0.989289993	X64 : BN : ETA_EtaP_B X124 : DV : PNSA-2 X125 : DW : PNSA-3 X144 : EP : RNCS X159 : FE : LOBMIN X165 : FK : MOMI-YZ X216 : HN : WK.eneg X229 : IA : WK.polar

Table 4: Validation Parameters of the models

S/n	Parameters	Model 1	Model 2	Model 3
1	Friedman LOF	0.04476700	0.04478200	0.04482100
2	R-squared	0.85894600	0.85889800	0.85877500
3	Adjusted R-squared	0.81554500	0.81548200	0.81532200
4	Cross validated R-squared	0.74371600	0.74497200	0.74483600
5	Significant Regression	Yes	Yes	Yes
6	Significance-of-regression F-value	19.7908300	19.7830200	19.76297400
7	Critical SOR F-value (95%)	2.32534900	2.32534900	2.32534900
8	Replicate points	0	0	0
9	Computed experimental error	0.00000000	0.0000000	0.00000000
10	Min expt. error for non-significant LOF (95%)	0.07859400	0.07860800	0.07864200

The GFA algorithm makes use of a population of many models rather than generating a single model. The models are scored using Friedman's "lack of fit" (LOF) measure as the evaluation function [19, 20] as well as other validation parameters as shown in Table 4 above. Based on statistical significance, model 1 is selected as the optimization model for predicting the minimum inhibitory concentration (MIC) of anti-*Salmonella typhi* Schiff bases because it has the least LOF score, highest R-squared, adjusted R-squared, Cross validated R-squared and F-value.

Table 5: Detailed definition of descriptors

S/n	Descriptor symbol	Definition
1	ETA_EtaP_B	Branching index EtaB relative to molecular size
2	PNSA-1	Partial negative surface area -- sum of surface area on negative parts of molecule
3	PNSA-2	Partial negative surface area * total negative charge on the molecule
4	RNCS	Relative negative charge surface area -- most negative surface area.
5	LOBMIN	The L/B ratio for the rotation that results in the minimum area
6	MOMI-YZ	Moment of inertia along Y/Z axis
7	Wnu2.volume	Directional WHIM, weighted by van der Waals volumes
8	WK.eneg	Non-directional WHIM, weighted by Mulliken atomic electronegativites.

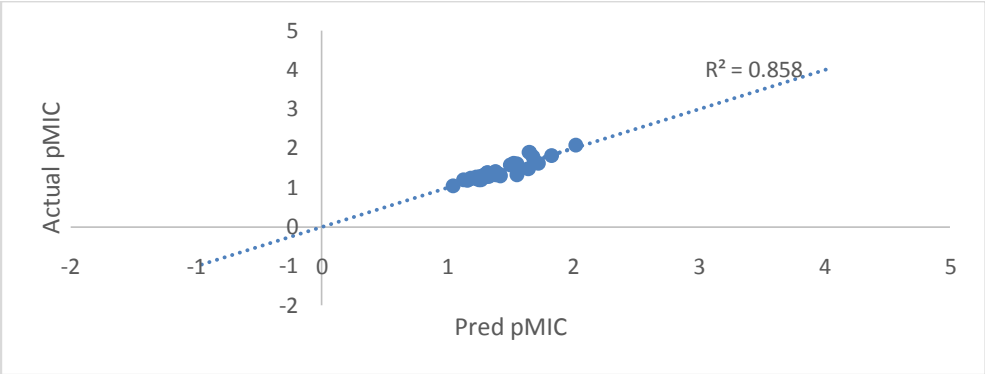


Figure 4: Plot of actual pMIC against predicted pMIC

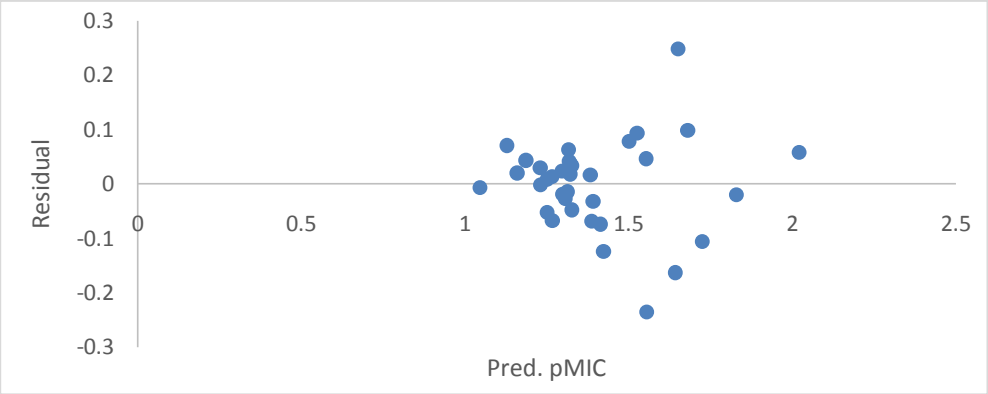


Figure 5: Residual plot of model 1

Table 6: Comparison of actual pMIC and pred. pMIC of model 1

Name	Actual pMIC	Pred. pMIC	Residual
C1	1.26000000	1.22993400	0.03006600
C2	1.20000000	1.26706200	-0.06706200
C3	1.60000000	1.55333400	0.04666600
C4	1.78000000	1.68084500	0.09915500
C5	1.48000000	1.64276800	-0.16276800
C6	1.81000000	1.82952800	-0.01952800
C7	2.08000000	2.02124300	0.05875700
C8	1.34000000	1.32147100	0.01852900
C9	1.28000000	1.30665100	-0.02665100
C10	1.34000000	1.41377200	-0.07377200
C11	1.90000000	1.65144800	0.24855200
C12	1.26000000	1.25118600	0.00881400
C13	1.62000000	1.52615200	0.09384800
C14	1.36000000	1.32214100	0.03785900
C15	1.28000000	1.26582800	0.01417200
C16	1.58000000	1.50109200	0.07890800
C17	1.32000000	1.38774800	-0.06774800
C18	1.36000000	1.39150200	-0.03150200
C19	1.32000000	1.55495900	-0.23495900
C20	1.38000000	1.31617400	0.06382600
C21	1.62000000	1.72525300	-0.10525300
C22	1.30000000	1.31383600	-0.01383600
C23	1.32000000	1.29592300	0.02407700
C24	1.28000000	1.29827400	-0.01827400
C25	1.18000000	1.15951900	0.02048100
C26	1.20000000	1.25165800	-0.05165800
C27	1.23000000	1.23132400	-0.00132400
C28	1.30000000	1.42351200	-0.12351200
C29	1.36000000	1.32615200	0.03384800
C30	1.20000000	1.12883300	0.07116700
C31	1.28000000	1.32735700	-0.04735700
C32	1.04000000	1.04602200	-0.00602200
C33	1.23000000	1.18633000	0.04367000
C34	1.40000000	1.38313500	0.01686500
C35	1.36000000	1.31803300	0.04196700

Table 7: Golbraikh and Tropsha validation parameters for model 1

s/n	Parameter	Value
1	r^2	0.8589
2	r'^2_0	0.8363
3	r_0^2	0.8589
4	k	1.0E-7
5	K'	0.1969

Based on the parameters above;

$$r^2 - r_0^2 / r^2 = \frac{0.8589 - 0.8589}{0.8589} = 0.00$$

$$r^2 - r'^2_0 / r^2 = \frac{0.8589 - 0.8363}{0.8589} = 0.0263$$

Tables 3, 4, and 5 give the GFA derived QSAR models for predicting the minimum inhibitory concentration of some selected anti-*Salmonella typhi* Schiff bases, validation parameters of the models, and detailed definition of the descriptors used in the models respectively. Based on the validation parameters, the octa-parametric model (model 1) was selected as the optimization model. The Genetic Function Algorithm derived QSAR model is in good agreement with the threshold shown in Table 2 as R^2 = 0.8589, R^2_{adj} = 0.8155, Q^2 = 0.7437, R^2 - Q^2 = 0.1152 and the Golbraikh and Tropsha criteria (Table 7) are also met. The predictability of model 1 is evidenced by the low residual values observed in Table 6 which gives the comparison of observed and predicted pMIC of the molecules. Also, the plot of predicted pMIC against observed pMIC shown in Figure 4 indicates that the model is well trained and it predicts well the

pMIC of the compounds. Furthermore, the plot of observed pMIC versus residual pMIC (Figure 5) indicates that there was no systemic error in model development as the propagation of residuals was observed on both sides of zero [21].

The result of the QSAR modelling hinted the predominance of the size descriptor ETA-Eta-B (Branching index EtaB relative to molecular size) over other descriptors in the model in influencing the anti-*salmonella typhi* bioactivity of the studied Schiff bases owing to its relatively high numerical coefficient. The negative value of the coefficient of the descriptor implies that the minimum inhibitory concentration (MIC) of schiff bases is inversely proportional to the value of this descriptor. Thus, the inhibitory activity of Schiff bases increases with the increase in value of this descriptor since activity of drug varies inversely with its minimum inhibitory concentration.

However, high molecular sized drugs have enhanced bioavailability and prolonged plasma half-life due to their increased hydrodynamic volume that reduces the kidney clearance [22]. Thus, the enhanced MIC of Schiff base with increased in branching index relative to molecular size descriptor as shown in the optimization model (model 1) may be due to its increased hydrodynamic volume orchestrated by increased molecular size.

3. Conclusion

A QSAR study was conducted with a series of anti-*Salmonella typhi* agents, and some useful molecular models were obtained. The molecular descriptors; ETA_EtaP_B, PNSA-1, PNSA-2, RNCS, LOBMIN, MOMI-YZ, Wnu2.volume and WK.eneg were found to have important role in governing the observed anti-*Salmonella typhi* activity of Schiff bases. The robustness and applicability of the optimum QSAR equation has been established by various validation techniques. It is hoped that this QSAR model (s) will provide better insight into the design of more potent anti-*Salmonella typhi* agents in future prior to their synthesis.

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