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Original article

Theoretical modeling for predicting the activities of some active compounds as potent inhibitors against Mycobacterium tuberculosis using GFA-MLR approach

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ABSTRACT

Tuberculosis (TB) is of one the most infectious disease caused by *Mycobacterium tuberculosis* which remains a serious public health problem. Emergence of multi-drug resistant strains of *M. tuberculosis* led to development of new and more potent anti-tuberculosis agents. The aim of this study was to correlate the chemical structures of the inhibitory compounds with their experimental activities. In this study, analogs of 2,4-disubstituted quinoline derivatives as potent anti-tubercular agents was subjected to quantitative structure–activity relationship (QSAR) analysis in order to build a QSAR model for predicting the activities of these compounds. In order to build the regression model, Genetic Function Approximation (GFA) and Multi-linear Regression approach were used to predict the activities of inhibitory compounds. Based on the prediction, the best validation model was found to have squared correlation coefficient (R^2) of 0.9367, adjusted squared correlation coefficient (R^2 adj) value of 0.9223 and cross validation coefficient (Q^2_{cv}) value of 0.8752. The chosen model was subjected to external validations and the model was found to have (R^2 test) of 0.8215 and Y-randomization Coefficient (cR^2_p) of 0.6633. The proposed QSAR model provides a valuable approach for designing more potent anti-tubercular agents.

1. Introduction

Tuberculosis still remains a major infectious disease which causes human mortality. World Health Organization (WHO) estimates a marked increase in TB infections of 1.5 million deaths in 2014. Moreover, a marked increase of 6% in the TB incidence was reported in 2014 compared with the numbers reported in 2013 (Organization, 2016).

The widespread use of chemotherapeutics has resulted in the emergence of drug-resistant mutants that pose a continuing challenge to design new active compounds. The resistances of the *M. tuberculosis* toward the current drugs; isoniazid, rifampicin and enthambutol led to development of new approach that is fast and precise which could able to predict the biological activity for the new compounds against *M. tuberculosis.*

Quantitative structure activity relationships (QSARs), one of the most widely used computational method help in drug designing and prediction of drugs activities (Hansch et al., 2001). QSAR model is a mathematical linear equation which relates the molecular structures of the compounds and their biological activities. In this research, a data set of 2,4-diquinoline derivatives which had been synthesized and evaluated as anti-*mycobacterium tuberculosis* (Nayyar and Jain, 2008) have been selected for QSAR study. Few researchers; (Eric et al., 2016, n.d.; Joshi et al., 2014; Ogadimma and Adamu, 2016; Sharma et al., 2012) have carried QSAR studies to established relationship between some inhibitory compounds like Quinolone, chalcone, pyrrole and 7-methyijuglone. However QSAR study has not been established to relate the structures and activities of 2,4-disubstituted quinoline derivatives as potent anti-tubercular agents. Therefore, this study aimed to build a valid QSAR model that could predict the activities of 2,4-diquinoline derivatives against mycobacterium tuberculosis.

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2. Materials and methods

2.1. Data collection

Analogs of molecules of 2,4-disubstituted quinoline derivatives as potent anti-tubercular agents that were used in this studies were gotten from the literature (Nayyar and Jain, 2008).

2.2. Biological activities (pEC_{50})

The Biological activities of 2,4-disubstituted quinoline derivatives as potent anti-tubercular agents were initially expressed in percentage (%) and then converted to logarithm unit using Eq. (1) below in order to increase the linearity and approach normal distribution of the activity values. The observed structures and the biological activities of these compounds were presented in Table 1.

$$\mathrm{pBA} = \log\left[\left(\frac{Molecularweight_{(g/mol)}}{Dose_{(g/mol)}}\right)\left(\frac{\mathrm{percentage}(\%)}{100-\mathrm{percentage}(\%)}\right)\right] \quad (1)$$

2.3. Optimization

The chemical structures of the molecules were drawn with Chemdraw ultra Version 12.0 The molecular structures of the compounds were optimized in order to achieve a stable conformer for the inhibitory compounds by employing Density Function Theory (B3LYP/6-31G*) utilizing Spartan 14 Version 1.1.4 software.

2.4. Descriptor calculation

Molecular descriptor is a numerical value that gives chemical information about the molecule. Molecular descriptors for all the forty (40) molecules were calculated utilizing the PaDEL-Descriptor software Version 2.20. A total of 1875 molecular descriptors were calculated.

2.5. Normalization and data pretreatment

The calculated descriptors for the data set that made up the molecules were normalized using Eq. (1) in order to give each variable the same chance at the onset to influence the model (Singh, 2013).

$$\mathrm{X} = \frac{X_1 - X_{min}}{X_{max} - X_{min}} \quad (2)$$

where X_1 is the numeric value of each descriptor for a given molecule, Xmax and Xmin are the maximum and minimum value for each column of descriptors X. The normalized data were then subjected to pretreatment using Data Pretreatment software obtained from Drug Theoretical and Cheminformatics Laboratory (DTC Lab) in order to remove redundant data (Adeniji et al., 2018).

2.6. Data division

In order to generate a robust QSAR model that could predict the activity of the inhibitor against Mycobacterium tuberculosis, Kennard and Stone's algorithm was employed to divided the data set into training set and test set (Kennard and Stone, 1969). The training set is made up of 70% of the data set which were used to build the QSAR model while the remaining 30% of the data set (test set) were used to confirm the built model.

2.7. Generation of the model

The training set generated was imported to Material studio software version 8 to build the model by employing the Genetic Function Approximation and Multi-linear Regression (GFA-MLR) method.

2.8. Internal validation of model

Estimation of the validation parameter to access the built model was achieved with the aid of Material studio software version 8. Internal validation parameters calculated are as follows;

2.8.1. Friedman formula (LOF)

This parameter measures the fitness score of the model. LOF is defined as; (Friedman, 1991)

$$\mathrm{LOF} = \frac{SEE}{\left(1 - \frac{N+p\times k}{M}\right)^2} \quad (3)$$

N is the number of terms in the model, k is the number of descriptors, p is the user-defined smoothing parameter, and M is the number of compounds that made up the training set (Khaled, 2011).

The Standard Error of Estimation (SEE) is equivalent to the models standard deviation. It measures the model quality and a model is said to be a robust model if it has low SEE value. SEE is defined by equation below;

$$\mathrm{SEE} = \sqrt{\frac{\left(Y_{exp} - Y_{pred}\right)^2}{N - P - 1}} \quad (4)$$

Y_{exp} and Y_{pred} are the experimental activity and the predicted activity in the training set respectively (Tropsha et al., 2003).

2.8.2. The correlation coefficient (R^2)

Correlation coefficient (R^2) *defines* the fraction of the entire variation in the model. As the value of R^2 approaches 1.0, the stronger the model generated. R^2 is expressed as:

$$\mathrm{R2} = 1 - \left[\frac{\sum\left(Y_{exp-Y_{pred}}\right)^2}{\sum\left(Y_{exp-\bar{Y}_{training}}\right)^2}\right] \quad (5)$$

$\bar{Y}_{training}$ Y_{exp}, and Y_{pred} are the mean experimental activity, experimental activity and the predicted activity in the training set, respectively (Adeniji et al., 2018)

2.8.3. Adjusted R^2

Correlation coefficient (R^2) value varies directly with the increase in number of descriptors thus; R^2 is not reliable parameter to measure the robustness and stability of the model. Therefore, R^2 is adjusted in order to have a stable and reliable model. The R^2_{adj} is defined as:

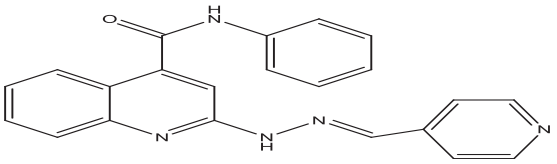
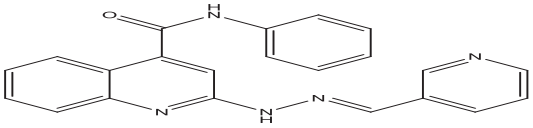
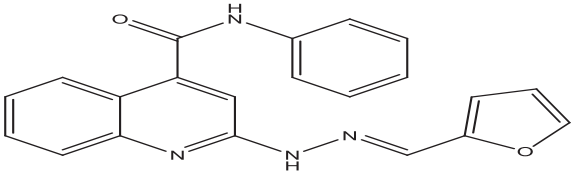
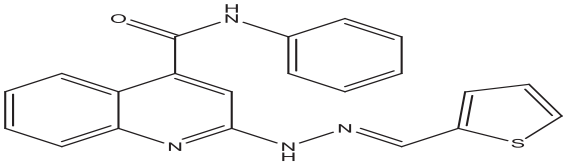
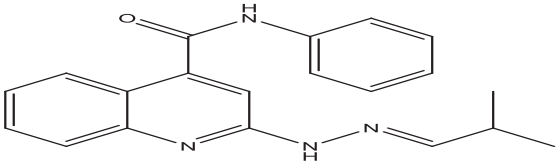
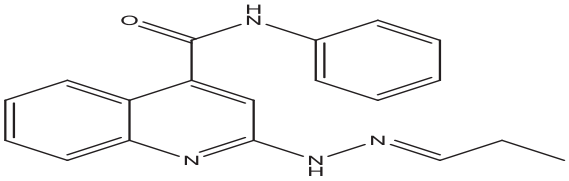
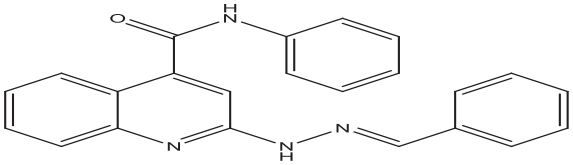
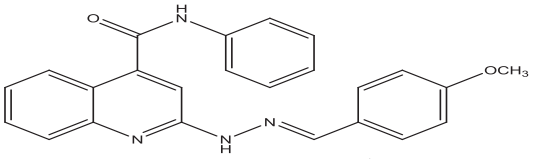
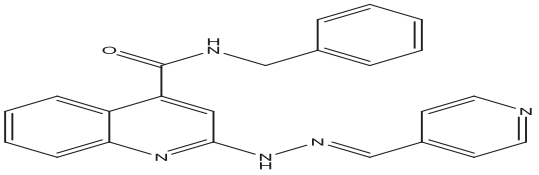
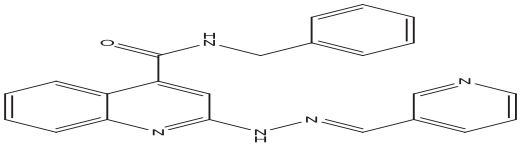
$$\mathrm{R^2adj} = \frac{R^2 - k(n-1)}{n - p + 1} \quad (6)$$

where k is the number of descriptors in the model and n is number compounds that made up the training set (Adeniji et al., 2018)

2.8.4. The cross-validation coefficient (Q^2_{cv})

The predictive ability of the QSAR model to predict the activity of inhibitor was determined using cross validation test. The cross-validation coefficient (Q^2_{cv}) is defined as:

Table 1
Molecular structures of inhibitor compounds and their derivatives as anti-tubercular agents.

S/N	IUPAC name	Molecular structure	Activity (%)	Activity (pA)
1[a]	(E)-N-phenyl-2-(2-(pyridin-4-ylmethylene) hydrazinyl)quinoline-4-carboxamide		14	6.9809
2	(E)-N-phenyl-2-(2-(pyridin-3-ylmethylene) hydrazinyl)quinoline-4-carboxamide		10	6.8150
3	(E)-2-(2-(furan-2-ylmethylene)hydrazinyl)-N-phenylquinoline-4-carboxamide		10	6.8018
4 [a]	(E)-N-phenyl-2-(2-(thiophen-2-ylmethylene) hydrazinyl)quinoline-4-carboxamide		26	7.3209
5 [a]	(E)-2-(2-(2-methylpropylidene)hydrazinyl)-N-phenylquinoline-4-carboxamide		11	6.8191
6	(E)-N-phenyl-2-(2-propylidenehydrazinyl) quinoline-4-carboxamide		12	6.8418
7 [a]	(E)-2-(2-benzylidenehydrazinyl)-N-phenylquinoline-4-carboxamide		11	6.8601
8 [a]	(E)-2-(2-(4-methoxybenzylidene)hydrazinyl)-N-phenylquinoline-4-carboxamide		99	9.4979
9	(E)-2-(2-(4-methoxybenzylidene)hydrazinyl)-N-phenylquinoline-4-carboxamide		14	6.9772
10	(E)-N-benzyl-2-(2-(pyridin-3-ylmethylene) hydrazinyl)quinoline-4-carboxamide		23	7.2608

(*continued on next page*)

Table 1 (*continued*)

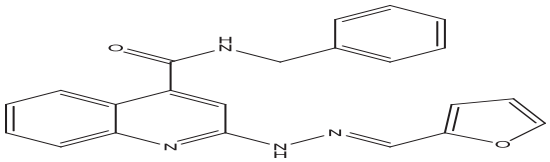
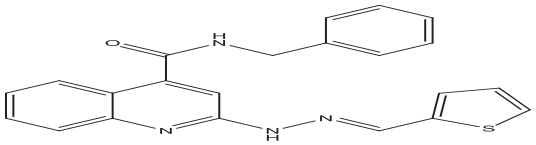
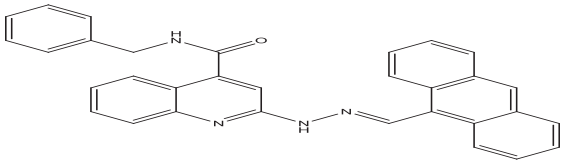
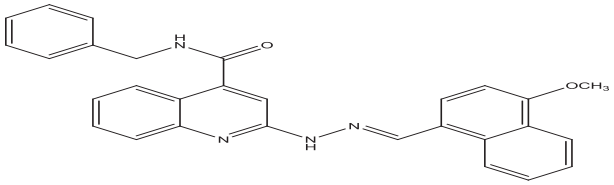
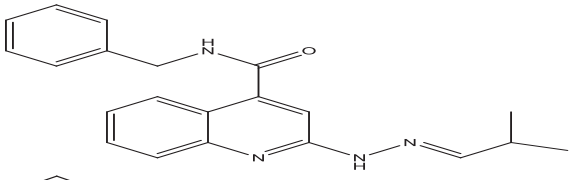
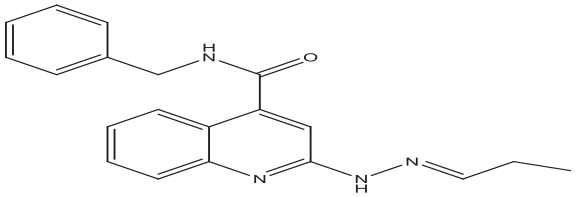
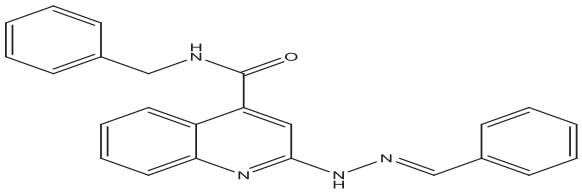
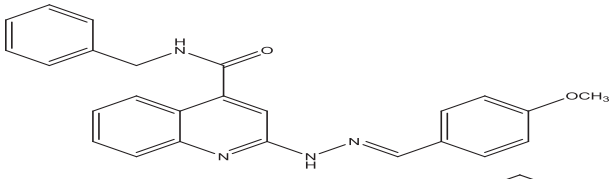
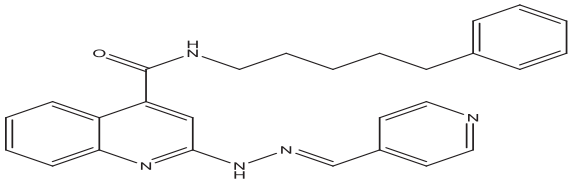
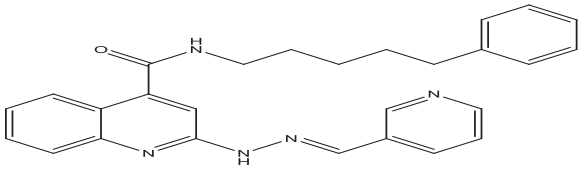
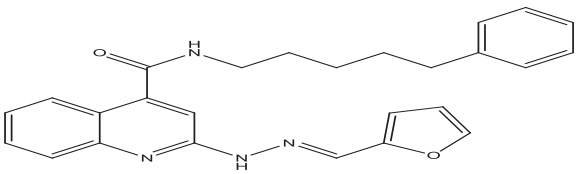
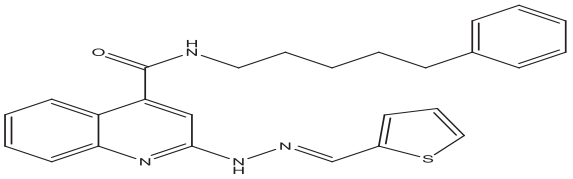
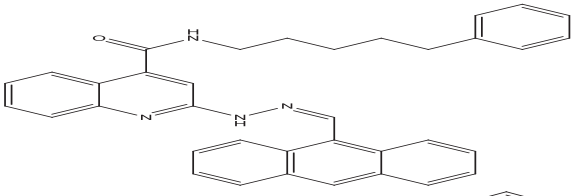
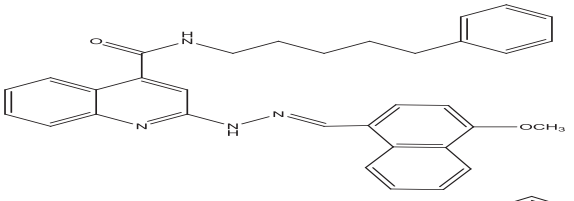
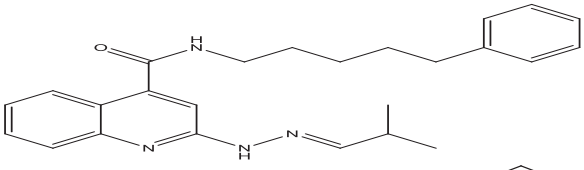
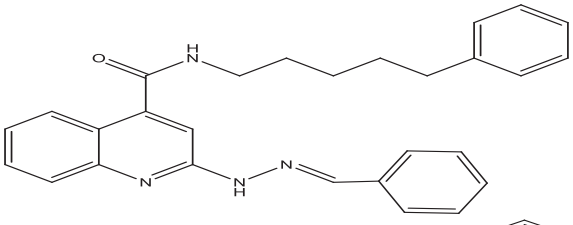
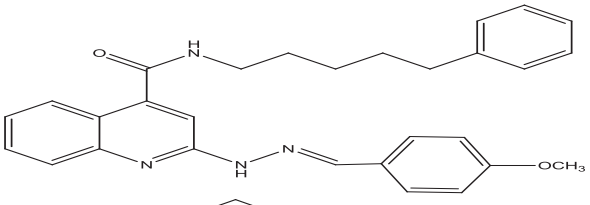
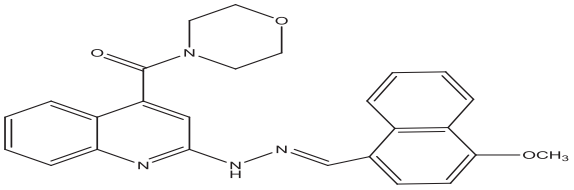
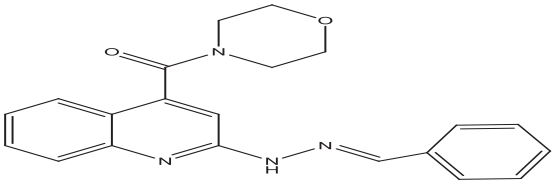
S/N	IUPAC name	Molecular structure	Activity (%)	Activity (pA)
11	(E)-N-benzyl-2-(2-(furan-2-ylmethylene) hydrazinyl)quinoline-4-carboxamide		20	7.1707
12 [a]	(E)-N-benzyl-2-(2-(thiophen-2-ylmethylene) hydrazinyl)quinoline-4-carboxamide		30	7.4233
13	(E)-2-(2-(anthracen-9-ylmethylene)hydrazinyl)-N-benzylquinoline-4-carboxamide		20	7.2838
14	(E)-N-benzyl-2-(2-((4-methoxynaphthalen-1-yl)methylene)hydrazinyl)quinoline-4-carboxamide		16	7.1472
15	(E)-N-benzyl-2-(2-(2-methylpropylidene) hydrazinyl)quinoline-4-carboxamide		42	7.6035
16	(E)-N-benzyl-2-(2-propylidenehydrazinyl) quinoline-4-carboxamide		27	7.2938
17	(E)-N-benzyl-2-(2-benzylidenehydrazinyl) quinoline-4-carboxamide		99	9.6090
18	(E)-N-benzyl-2-(2-(4-methoxybenzylidene) hydrazinyl)quinoline-4-carboxamide		21	7.2630
19	(E)-N-(5-phenylpentyl)-2-(2-(pyridin-4-ylmethylene)hydrazinyl)quinoline-4-carboxamide		30	7.4772
20	(E)-N-(5-phenylpentyl)-2-(2-(pyridin-3-ylmethylene)hydrazinyl)quinoline-4-carboxamide		10	6.8909

Table 1 (*continued*)

S/N	IUPAC name	Molecular structure	Activity (%)	Activity (pA)
21	(E)-2-(2-(furan-2-ylmethylene)hydrazinyl)-N-(5-phenylpentyl)quinoline-4-carboxamide		15	7.0807
22	(E)-N-(5-phenylpentyl)-2-(2-(thiophen-2-ylmethylene)hydrazinyl)quinoline-4-carboxamide		21	7.2747
23	(Z)-2-(2-(anthracen-9-ylmethylene)hydrazinyl)-N-(5-phenylpentyl)quinoline-4-carboxamide		23	7.4091
24	(E)-2-(2-((4-methoxynaphthalen-1-yl) methylene)hydrazinyl)-N-(5-phenylpentyl) quinoline-4-carboxamide		40	7.7412
25 [a]	(E)-2-(2-(2-methylpropylidene)hydrazinyl)-N-(5-phenylpentyl)quinoline-4-carboxamide		42	7.6688
26 [a]	(E)-2-(2-benzylidenehydrazinyl)-N-(5-phenylpentyl)quinoline-4-carboxamide		21	6.2688
27	(E)-2-(2-(4-methoxybenzylidene)hydrazinyl)-N-(5-phenylpentyl)quinoline-4-carboxamide		40	7.6970
28	(E)-(2-(2-((4-methoxynaphthalen-1-yl) methylene)hydrazinyl)quinolin-4-yl) (morpholino)methanone		7	6.7741
29	(E)-(2-(2-benzylidenehydrazinyl)quinolin-4-yl) (morpholino)methanone		3	6.2513

(*continued on next page*)

Table 1 (*continued*)

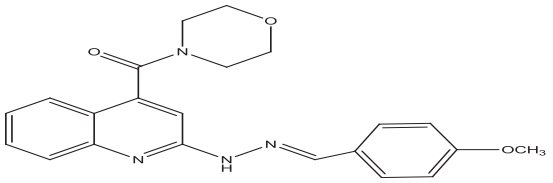
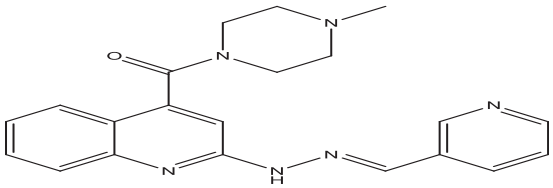
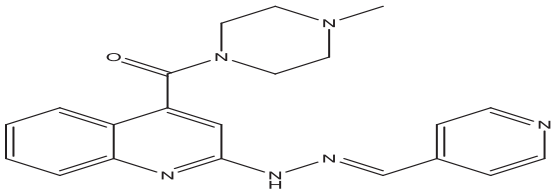
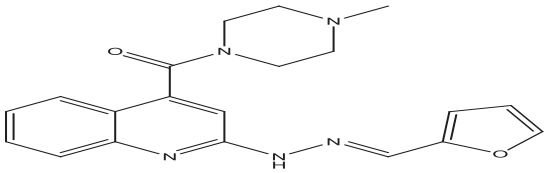
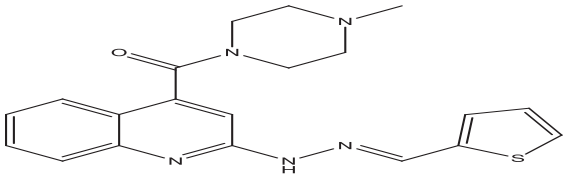
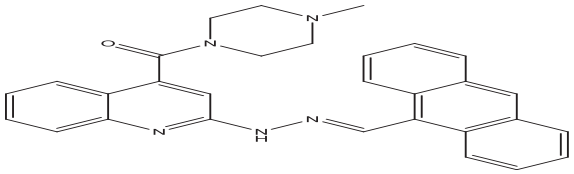
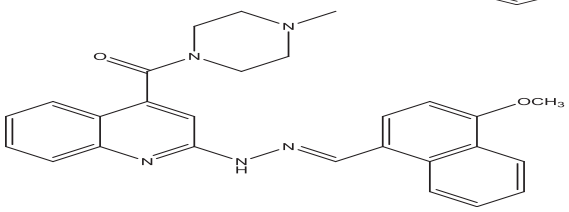
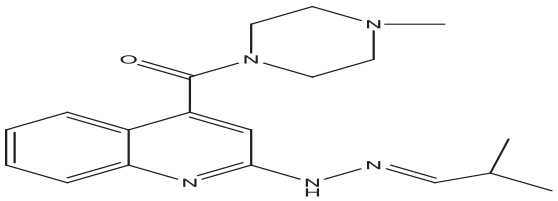
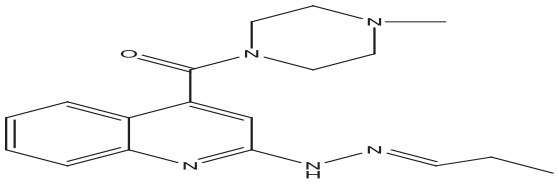
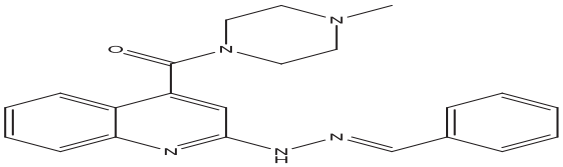
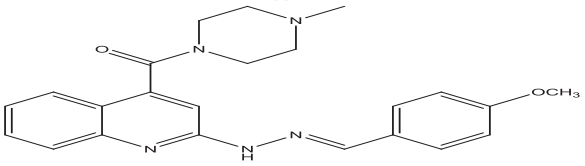
S/N	IUPAC name	Molecular structure	Activity (%)	Activity (pA)
30	(E)-(2-(2-(4-methoxybenzylidene)hydrazinyl) quinolin-4-yl)(morpholino)methanone		10	6.8414
31 [a]	(E)-(4-methylpiperazin-1-yl)(2-(2-(pyridin-3-ylmethylene)hydrazinyl)quinolin-4-yl) methanone		1	5.8000
32	(E)-(4-methylpiperazin-1-yl)(2-(2-(pyridin-4-ylmethylene)hydrazinyl)quinolin-4-yl) methanone		28	7.3673
33	(E)-(2-(2-(furan-2-ylmethylene)hydrazinyl) quinolin-4-yl)(4-methylpiperazin-1-yl) methanone		21	7.1891
34	(E)-(4-methylpiperazin-1-yl)(2-(2-(thiophen-2-ylmethylene)hydrazinyl)quinolin-4-yl) methanone		10	6.8291
35	(E)-(2-(2-(anthracen-9-ylmethylene)hydrazinyl) quinolin-4-yl)(4-methylpiperazin-1-yl) methanone		10	6.9253
36 [a]	(E)-(2-(2-((4-methoxynaphthalen-1-yl) methylene)hydrazinyl)quinolin-4-yl)(4-methylpiperazin-1-yl)methanone		18	7.2022
37	(E)-(4-methylpiperazin-1-yl)(2-(2-(2-methylpropylidene)hydrazinyl)quinolin-4-yl) methanone		52	7.7696
38 [a]	(E)-(4-methylpiperazin-1-yl)(2-(2-propylidenehydrazinyl)quinolin-4-yl) methanone		6	6.5216

Table 1 (*continued*)

S/N	IUPAC name	Molecular structure	Activity (%)	Activity (pA)
39	(E)-(2-(2-benzylidenehydrazinyl)quinolin-4-yl)(4-methylpiperazin-1-yl)methanone		9	6.7716
40	(E)-(2-(2-(4-methoxybenzylidene)hydrazinyl)quinolin-4-yl)(4-methylpiperazin-1-yl)methanone		30	7.4420

Where superscript **a** represent the test set.

$$Q^2_{cv} = 1 - \left[\frac{\sum\left(Y_{pred-Y_{exp}}\right)^2}{\sum\left(Y_{exp-\bar{Y}_{training}}\right)^2}\right] \quad (7)$$

$\bar{Y}_{training}$ Y_{exp}, and Y_{pred} are the mean experimental activity, experimental activity and the predicted activity in the training set respectively (Adeniji et al., 2018)

2.9. External validation of the model

Model built was validated to assessed R^2_{test} value. As the value of R^2_{test} approaches 1.0, the robust the model generated. The R^2_{test} is defined by as;

$$R^2_{test} = 1 - \frac{\sum\left(Ypred_{test} - Y_{exp_{test}}\right)^2}{\sum\left(Ypred_{test} - \bar{Y}_{training}\right)^2} \quad (8)$$

where $Ypred_{test}$ and $Y_{exp_{test}}$ are the predicted and experimental activity test set. While $\bar{Y}_{training}$ is the training set mean values of the experimental activity (Tropsha et al., 2003).

The external validation test for the developed QSAR model was further subjected to Golbraikh and Tropsha criteria listed below:

a. |r0^2 − r′0^2| (Threshold value < 0.3)
b. $r^2 - r^2_o/r^2$ (Threshold value < 0.1)
c. $r^2 - r'^2_o/r^2$ (Threshold value < 0.1)
d. k (Threshold value $0.85 \leq k \leq 1.15$)
e. k′ (Threshold value $0.85 \leq k \leq 1.15$) (Roy et al., 2013; Tropsha et al., 2003)

where r^2 is the square correlation coefficients of the plot of experimental activity against predicted activity values, r^2_o is the square correlation coefficients of the plot of experimental activity against predicted activity values at zero intercept, r'^2_o is the square correlation coefficients of the plot of predicted activity against experimental activity at zero intercept, k is the slope of the plot of experimental activity against predicted activity values at zero intercept and k′ is the slope of the plot of predicted against experimental activity at zero intercept.

2.10. Y-Randomization test

Y-randomization test was carried out on the training set in order to confirmed that the built QSAR model is strong, robust, reliable and not gotten by chance (Tropsha et al., 2003). For the developed QSAR model to reliable and robust, the model is expected to have a low R^2 and Q^2 values for numbers of trials. Coefficient of determination (cR^2_p) for Y-randomization test is another external validation parameter with (Threshold value >0.5) for passing this test.

$$cR^2_p = R \times \left[R^2 - (R_r)^2\right]^2 \quad (9)$$

R is determination coefficient for Y-randomization and Rr is average 'R' of random models (Tropsha et al., 2003).

2.11. Determination of outlier and influential molecule

The applicability domain approach was employed to determination of outlier and influential molecule. Any compound outside the applicability domain space of ±3 is said to be an outlier. The leverage approach was employed in defining and describing the applicability domain of the built QSAR models (Veerasamy et al., 2011). Leverage of a given molecule *hi*, is defined as;

$$hi = Xi\left(X^TX\right)^{-1}X_i^T \quad (10)$$

Xi is training set matrix of *i*. *X* is the n × k descriptor matrix of the training set compound and X^T is the transpose of the training set (*X*). X_i^T is the transpose matrix X_i used to build the mode. The warning leverage h^* is the limit values to check for influential molecule. The warning leverage h^* is defined as;

$$h^* = 3\frac{(j+1)}{m} \quad (11)$$

where *j* is the number of descriptors in the build model and *m* is the number of compounds that made up the training set.

2.12. Intelligent consensus prediction

An intelligent consensus prediction is performed on multiple **QSAR** models developed against a particular response and compares them with the prediction quality obtained from the individual models. Further, the quality of predictions is judged based on several external validation metrics such as Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, CCC, r^2_m and *MAE* that might help in improving the quality of prediction for a query molecule. The optimum settings can be fixed using the available QSAR models and corresponding external set compounds with known response values, while the same setting can be later employed for predictions of newly designed query molecules (Roy et al., 2018).

2.13. Assessment of the built model

The robustness, reliability, fitness, stability, and predictability of the generated models were evaluated by subjecting the model to validation parameters. The minimum Threshold value for internal and external validation parameters for a generally acceptable QSAR model (Veerasamy et al., 2011) is presented in Table 2.

3. Results and discussion

QSAR approach was used to predict the activities of 2,4-disubstituted quinoline derivatives as potent inhibitor against *Mycobacterium tuberculosis*. The data set which comprises of 40 compounds were divided into a training set of 28 compounds and test set 12 compounds by employing Kennard-Stone algorithm. The training set compounds were used to build the model while the test set compounds were used to validate the built model.

Descriptive analysis of the training set and the test set were reported in Table 3. This shows that the mean value and the standard deviation value of the training set were similar to that of test set. Thus, Kennard-Stone algorithm used in dividing the dataset generate a test set compounds that is a good reflection of the training set compounds

The Genetic Function Algorithm (GFA) was employed in this study to select the best descriptor that could better predict the activities of the inhibitory compounds while Multi-linear Regression (MLR) method was used as modeling technique in generating the QSAR model. GFA-MLR led to selection of five descriptors and five QSAR models.

Model 1

pBA = −6.515153698 * AATS5e + 0.056593117 * VR3_Dzp + 0.001891166 * VR1_Dzi + 0.000132807 * VR1_Dzs − 6.230058484 * SpMin7_Bhe + 61.731402188.

Model 2

pBA = −5.983214203 * AATS5e + 0.065340929 * VR3_Dzp + 0.001930689 * VR2_Dzi + 0.004049607 * VR1_Dzs − 6.084763724 * SpMin7_Bhe + 57.265328066.

Model 3

pBA = −6.738118716 * AATS5e + 0.008743880 * VR3_Dzv + 0.001819903 * VR1_Dzi + 0.000135235 * VR1_Dzs − 5.680009813 * SpMin7_Bhe + 63.776142838.

Model 4

pBA = −6.148961522 * AATS5e + 0.077745375 * VR3_Dzp + 0.058288135 * VR1_Dzi + 0.000140171 * VR2_Dzs − 5.605672315 * SpMin7_Bhe + 57.795782473.

Model 5

pBA = −6.730758918 * AATS5e + 0.008667299 * VR3_Dzv + 0.001822324 * VR1_Dzi + 0.004064233 * VR1_Dzs − 5.596564878 * SpMin7_Bhe + 63.634320925.

Internal validation parameters to confirm that the built QSAR model is stable and robust were reported in Table 4. These parameters were in agreement with validation parameters presented in Table 2. Based on these validation parameters, model one was selected as the optimum model and used to predict the activities of 2,4-disubstituted quinoline derivatives.

The QSAR model generated in this research was compared with the model obtained in the literature (Shola et al., 2018; Ogadimma and Adamu, 2016) as shown below;

pBA = −0.307001458(**AATS7s**) + 1.528715398(**nHBint3**) + 3.976720227(**minHCsatu**) + 0.016199645(**TDB9e**) + 0.089381479 (R**DF90i**) − 0.107407822(**RDF110s**) + 4.057082751 $N_{train} = 35$, $R^2 = 0.92023900$, $R_{adj} = 0.91017400$, $Q^2_{cv} = 0.89538600$ *and the external validation for the test set was found to be* R^2-*pred = 0.8842* (Shola et al., 2018).

pIC50 = −2.040810634 * nCl − 19.024890361 * MATS2m + 1.855704759 * RDF140s + 6.739013671 $N_{train} = 27$, $R^2 = 0.9480$,

Table 2
Generally accepted value for the validation parameters for a given QSAR model.

Validation Parameter	Definition	Threshold value
R^2	Coefficient of determination	≥0.6
$P_{(95\%)}$	Confidence interval at 95% confidence level	<0.05
Q^2_{cv}	Cross validation coefficient	>0.5
$R^2 - Q^2_{cv}$	Difference between R^2 and Q^2_{cv}	≤0.3
$N_{ext.\ test\ set}$	Minimum number of external test set	≥5
cR^2_p	Coefficient of determination for Y-randomization	>0.5

Table 3
Descriptive statistics of the inhibition data.

Statistical parameters	Activity	
	Training set	Test set
Number of sample points	28	12
Range	3.5617	1.8688
Maximum	6.2513	8.2854
Minimum	4.7441	4.9074
Mean	7.339114	6.498873
Median	7.19905	6.1213
Variance	0.609039	0.866467
Standard deviation	0.78041	0.93084
Mean absolute deviation	0.5672	0.703515
Skewness	2.323993	0.87066
Kurtosis	6.13018	0.153415

Table 4
Validation parameters for each model using Genetic Function Approximation (GFA).

Internal Validation Parameters	Model 1	Model 2	Model 3	Model 4	Model 5
Friedman LOF	0.214357	0.31676	0.32802	0.33227	0.33506
R-squared	0.936651	0.90639	0.90306	0.90181	0.90098
Adjusted R-squared	0.922254	0.88511	0.88103	0.87949	0.87848
Cross validated R-squared	0.875177	0.79575	0.77394	0.76346	0.74815
Significant Regression	Yes	Yes	Yes	Yes	Yes
Significance-of-regression F-value	65.05654	42.6022	40.9893	40.4092	40.0358
Critical SOR F-value (95%)	2.684036	2.684036	2.684036	2.684036	2.684036
Replicate points	0	0	0	0	0
Computed experimental error	0	0	0	0	0
Lack-of-fit points	22	22	22	22	22
Min expt. error for non-significant LOF (95%)	0.175074	0.21282	0.21657	0.21796	0.21888

R_{adj} = 0.9350, Q^2_{cv} = 0.87994 and R^2pred = 0.76907. (Ogadimma and Adamu, 2016).

From the above models the validation parameters reported in this work and those reported in the literature were all in agreement with parameters presented in Table 2 which actually confirmed the robustness of the model generated.

3.1. Interpretation of descriptors in the built model

AATS5e is Average Broto-Moreau autocorrelation – lag 5/ weighted by I-state auto-correlation descriptor. It's based on spatial dependent autocorrelation function which measures the strength of the relationship between observations (atomic or molecular properties) and space separating them (lag). This descriptor is obtained by taking the molecule atoms as the set of discrete points in space and an atomic property as the function evaluated at those points. When this descriptor is calculated on molecular graph, the lag coincides with the topological distance between any pair of the vertices. AATS5e is defined on the molecular graphs using atomic masses (m), Sanderson electronegativity (e) and inductive effect respectively of pairs of atoms 5 bond apart as the weighting scheme. These observations suggested that atomic masses and electronic distribution of atoms that made up the molecule had significant effect on the anti-tubercular activity of the dataset. In addition, the signs of the regression coefficients for each descriptor indicated the direction of influence of the descriptors in the models such that, negative regression coefficient associated to a descriptor will diminish the activity of the compound.

VR1_Dzi is Randic-like eigenvector-based index from Barysz matrix/weighted by first ionization potential while **VR1_Dzs** is Randic-like eigenvector-based index from Barysz matrix/weighted by I-state. From the model generated in this study, these descriptors have positive coefficient and positive mean effect value. Thus, the interpretation of this model shows that each of this descriptor with positive coefficient is directly proportional to the activities of these molecules. Descriptor **VR3_Dzp** (Logarithmic Randic-like eigenvector-based index from Barysz matrix/weighted by polarizabilities) with positive mean effect also contribute positively to the activities of the inhibitory compounds.

SpMin7_Bhe is one of the Burden modified eigen values descriptors. The SpMin7_Bhe descriptors have been proposed as chemical structure descriptors derived from a new representation of molecular structure. SpMin7_Bhe is the smallest absolute eigenvalue of Burden modified matrix – n 1/weighted by relative van der Waals volumes. The SpMin7_Bhe mean effect has a positive sign. This sign suggests that the anti-tubercular activity is directly related to this descriptor.

Experimental activities, predicted activities of the inhibitors and the residual values were reported in Table 5. The low residual values between experimental activities and predicted activities indicate that the model generated has a high predictive power (Adeniji et al., 2018).

Calculated descriptors for training set and test set in generating Model 1 were reported in Tables 6 and 7. The statistical parameters that influences the selected descriptors used in generating the QSAR model were reported in Table 8. Standard regression coefficient (b_j^s) and the mean effect (ME) values reported in Table 8 provides vital information on the effect of the descriptors and the degree of influence in the developed model. The signs and the magnitude of these descriptors combined with their mean effects indicate their individual strength and direction in influencing the activity of a compound. Variance Inflation Factor (VIF) calculated for all the five descriptors in the model were all less than 4 which shows that the descriptors selected were orthogonal and model generated was significant. The P-values less than 0.05 shows that there is significant relationship between the descriptors used to build the model and the activities of the inhibitory molecules.

Table 5
Experimental, Predicted and Residual values for 2,4-disubstituted quinoline derivatives.

Molecule	Experimental Activity	Predicted Activity	Residual
1	6.9809	6.971917	0.008983
2	6.815	7.035605	−0.2206
3	6.8018	6.835969	−0.03417
4	7.3209	7.405311	−0.08441
5	6.8191	6.812504	0.006596
6	6.8418	6.794876	0.046924
7	6.8601	7.14979	−0.28969
8	9.4979	9.780245	−0.28235
9	6.9772	6.981565	−0.00436
10	7.2608	7.023143	0.237657
11	7.1707	7.447515	−0.27682
12	7.4233	7.223165	0.200135
13	7.2838	7.473957	−0.19016
14	7.1472	7.201502	−0.0543
15	7.6035	7.567027	0.036473
16	7.2938	7.373105	−0.0793
17	9.6090	9.116462	0.4925
18	7.813	7.55099	0.26201
19	7.4772	7.22946	0.24774
20	6.8909	6.854689	0.036211
21	7.0807	7.201935	−0.12124
22	7.2747	7.265469	0.009231
23	7.4091	7.611252	−0.20215
24	7.7412	7.249363	0.491837
25	7.6688	7.666948	0.001852
26	6.2688	6.399172	−0.13037
27	7.697	7.838932	−0.14193
28	6.7741	6.4254	0.3487
29	6.2513	6.153244	0.098056
30	6.8414	7.044018	−0.20262
31	5.8	5.750218	0.049782
32	7.3673	7.102889	0.264411
33	7.1891	7.133475	0.055625
34	6.8291	6.94336	−0.11426
35	6.9253	6.907757	0.017543
36	7.2022	6.641454	0.560746
37	7.7696	7.382345	0.387255
38	6.5216	6.814865	−0.29327
39	6.7716	6.792383	−0.02078
40	7.442	7.501349	−0.05935

Pearson's correlations of the five descriptors selected in building the QSAR Model were reported in Table 9. The low correlation coefficient indicates that there is no significant inter-correlation among the selected descriptors.

The test set was subjected to external validation in order to validate the model built. Model 1 passed all the validation parameters reported in Table 10. This can be infer that the model developed is robust and reliable to predict the activities of 2,4-disubtituted quinoline.

Y-Randomization test was reported in Table 11. The low R^2 and Q^2 values for numbers of trials confirm that the built QSAR model is robust, stable, and reliable. While the Coefficient of determination cR^2_p value greater than 0.5 guaranteed that the built model is powerful and not inferred by chance.

Intelligent consensus prediction performed on multiple **QSAR** models developed against a particular response compared with the prediction quality obtained from the individual models has been analyzed and reported. The quality of the predictions judged based on several external validation metrics such as Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, CCC, r^2_m and *MAE* that might help in improving the quality of prediction for a query molecule were reported in Table 12.

Graphical representations for internal and external validation test were shown in Fig. 1 and Fig. 2 respectively. The squared

Table 6
Calculated descriptors for training set in generating Model 1.

Molecule	AATS5e	VR3_Dzp	VR1_Dzi	VR1_Dzs	SpMin7_Bhe	Predicted Activity
10	7.7372	17.70549	511.3397	642.028	1.0157	7.023143
11	7.791068	17.47607	962.9099	309.0707	1.025939	7.447515
13	7.608921	21.68556	870.1052	873.1568	1.226739	7.473957
14	7.659644	20.41834	627.2396	3328.826	1.18583	7.201502
15	7.739571	20.32523	238.2739	219.4391	0.857759	7.567027
16	7.713336	14.36154	211.4342	208.8292	0.843563	7.373105
17	7.723033	17.69381	522.9963	524.6427	1.01531	7.116462
18	7.652887	18.32748	1468.024	1691.794	1.01613	9.55099
19	7.573325	21.86432	404.1937	380.1573	1.14638	7.22946
2	7.840335	15.98099	517.8681	688.3532	0.898044	7.035605
20	7.564849	21.84717	200.1304	380.1454	1.151469	6.854689
21	7.596019	19.21292	881.1454	449.1	1.251748	7.201935
23	7.520498	31.07208	669.6331	605.408	1.320635	7.611252
24	7.542017	26.40663	635.8836	544.9153	1.297562	7.249363
27	7.536545	27.71683	518.8696	391.9847	1.180847	7.838932
28	7.727577	19.4227	344.8825	537.3151	1.085863	6.4254
29	7.817869	15.1251	398.1442	782.1284	1.018928	6.153244
3	7.907036	16.80212	520.6419	433.798	0.869388	6.835969
30	7.735461	16.0337	546.1729	1172.182	1.018928	7.044018
32	7.711552	16.12091	508.9688	1034.445	1.018928	7.102889
33	7.745807	20.73024	526.963	316.0941	1.018928	7.133475
34	7.712288	15.85823	480.0661	421.0379	1.018928	6.94336
35	7.595979	20.95833	382.0186	591.7095	1.164737	6.907757
37	7.702071	14.90617	597.3325	222.4993	0.979925	7.382345
39	7.689397	16.46417	250.0237	1282.517	1.018928	6.792383
40	7.631576	16.87745	474.5457	558.9262	1.018928	7.501349
6	7.823736	18.6672	253.5776	210.2844	0.888366	6.794876
8	7.734472	16.85365	479.7148	18835.13	0.948795	9.780245

Table 7
Calculated descriptors for test set in generating Model 1.

Molecule	AATS5e	VR3_Dzp	VR1_Dzi	VR1_Dzs	SpMin7_Bhe	Predicted Activity
1	7.852957	17.18093	400.8908	527.9417	0.86626	6.971917
12	7.751904	17.26382	674.0365	408.3237	1.012727	7.223165
22	7.567618	19.01451	834.7073	743.5662	1.270478	7.265469
25	7.560045	16.95123	544.0738	292.8519	1.097381	7.666948
26	7.589404	14.07973	258.4521	233.0907	1.156111	6.399172
31	7.789627	14.02771	123.6455	675.4873	1.018928	5.750218
36	7.641038	19.59175	364.7305	583.3535	1.153024	6.641454
38	7.704655	15.62959	245.2209	200.6652	0.978235	6.814865
4	7.798773	16.07059	477.8878	694.5818	0.870197	7.405311
5	7.848879	15.28019	316.6029	346.5946	0.849395	6.812504
7	7.824782	16.21208	532.6217	511.4705	0.898009	7.14979
9	7.748697	17.71338	511.449	635.1386	1.014425	6.981565

Table 8
Statistical parameters that influence the model.

Descriptor	Standard regression coefficient (b_j)	MeanEffect (ME)	P-Value (Confidence interval)	VIF	Standard Error
AATS5e	−0.2769	−0.31421	0.000527	1.8931	7.19166E−06
VR3_Dzp	0.67675	0.153246	3E−12	1.2779	1.53188E−07
VR1_Dzi	0.987436	0.58264	8.84E−11	3.6622	1.56739E−09
VR1_Dzs	0.338438	0.351968	4.48E−06	1.3493	1.11976E−10
SpMin7_Bhe	1.097495	−0.34097	3.25E−10	3.0968	6.03594E−06

Table 9
Pearson's correlation coefficient for the descriptor used in the QSAR model.

Inter-correlation					
	AATS5e	*VR3_Dzp*	*VR1_Dzi*	*VR1_Dzs*	*SpMin7_Bhe*
AATS5e	1				
VR3_Dzp	−0.07133	1			
VR1_Dzi	−0.15418	0.10971	1		
VR1_Dzs	0.071375	−0.11793	0.015657	1	
SpMin7_Bhe	−0.52256	0.0747094	0.301044	−0.11617	1

Table 10
External validation parameters to validate the built QSAR model.

External Validation Parameter	Threshold value	Model 1	Model 2	Model 3	Model 4	Model 5
K	0.85 < k < 1.15	1.00018	1.00234	1.03762	1.08732	1. 10,234
K′	0.85 < k < 1.15	0.9989	0.93229	0.89233	0.85423	0.84292
$/r_0^2 - r'^2_0/$	<0.3	0.01487	0.06523	0.06234	0.18766	0.32566
$\frac{r^2-r_0^2}{r^2}$	<0.1	0.00363	0.007632	0.08341	0.92301	0.14938
$\frac{r^2-r'^2_0}{r^2}$	<0.1	0.02176	0.05478	0.08432	0.92310	0.16738
R^2 test	>0.6	0.8215	0.7145	0.6822	0.6734	0.6598

Table 11
Y-Randomization Parameters test.

Model	R	R^2	Q^2
Original	0.85791	0.736009	0.361481
Random 1	0.263469	0.069416	-0.42957
Random 2	0.634931	0.403137	-3.21615
Random 3	0.44027	0.193838	-1.71176
Random 4	0.45403	0.206144	-0.7079
Random 5	0.642442	0.412732	-4.71577
Random 6	0.116309	0.013528	-0.3569
Random 7	0.24943	0.062215	-0.2046
Random 8	0.296007	0.08762	-0.42455
Random 9	0.270977	0.073429	-0.37515
Random 10	0.351074	0.123253	-0.38131
Random Models Parameters			
Average r:	0.371894		
Average r^2:	0.164531		
Average Q^2:	-1.25236		
cRp^2:	0.663262		

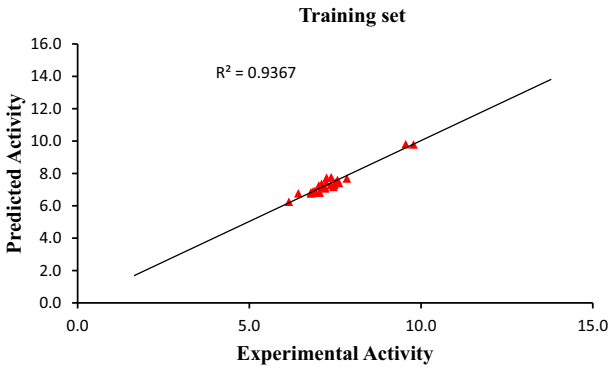


Fig. 1. Plot of predicted activity against experimental activity of training set.

correlation coefficient (R2) of 0.9367 for training set and (R^2test) of 0.8215 for test set reported in this study were in agreement with Genetic Function Approbation (GFA) derived R^2 value reported in Table 2 and Table 10. This confirmed the stability, robustness and reliability of the model. The dataset used in this study were within the limit range of ±2.5 as shown in Fig. 3. This indicates that dataset were evenly distributed.

In order to determine the outliers and influential compound in the dataset standardized residual for the all the compounds that made up the dataset were plotted against their leverage values. The Williams plot of the standardized residuals against the leverage values is an evident that all the compounds were within the square space ±3 as shown in Fig. 4. Therefore no compound is said to be an outlier. It is also an evident that no compound is said to be an influential compound since all their leverage values are less than the warning leverage (h^* = 0. 64).

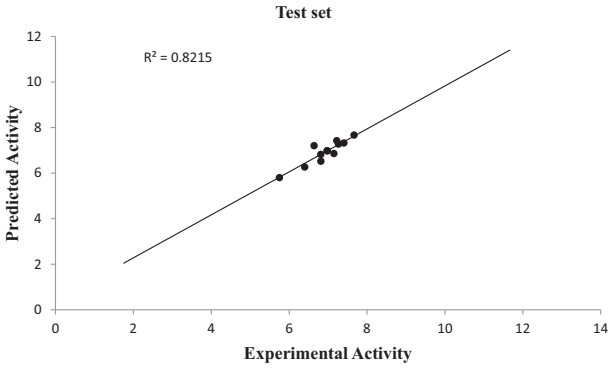


Fig. 2. Plot of predicted activity against experimental activity of test set.

Table 12
Intelligent consensus predictions compared with the prediction quality obtained from the individual (MLR) models.

Type of Model	N Comp Ext	Q2f1 (100%)	Q2f2 (100%)	Q2f3 (100%)	CCC (100%)	Avg Rm2 (100%)	Delta Rm2 (100%)	MAE (100%)	MAE (95%)	PRESS (100%)	PRESS (95%)	SDEP (100%)	SDEP (95%)
Individual Model 1	12	0.8915	0.8185	0.9218	0.9056	0.7506	0.05595	0.1366	0.0980	0.5512	0.2368	0.2143	0.1467
Individual Model 2	12	0.8883	0.8132	0.9195	0.8957	0.7197	0.15706	0.1463	0.1085	0.5675	0.2509	0.2175	0.1510
Individual Model 3	12	0.7801	0.632	0.8415	0.7901	0.4998	0.26599	0.2417	0.2118	1.1172	0.7922	0.3051	0.2684
Individual Model 4	12	0.7664	0.6092	0.8316	0.7709	0.562	0.12429	0.2456	0.2112	1.187	0.7976	0.3145	0.2693
Individual Model 5	12	0.7466	0.5761	0.8173	0.7469	0.4125	0.32315	0.2553	0.2266	1.2877	0.9618	0.3276	0.2957
CM0 (Average; Original)	12	0.8657	0.7754	0.9032	0.8667	0.6188	0.19871	0.1725	0.1378	0.6822	0.3748	0.2384	0.1846
CM 1 (Average; Modified)	12	0.8657	0.7754	0.9032	0.8667	0.6188	0.19871	0.1725	0.1378	0.6822	0.3748	0.2384	0.1846
CM 2 (Weighted Average)	12	0.8701	0.7828	0.9064	0.8740	0.6442	0.18763	0.1619	0.1263	0.6599	0.3534	0.2345	0.1792
CM 3 (Using Best Model)	12	0.8924	0.820	0.9224	0.9145	0.7740	0.05941	0.1577	0.1209	0.5469	0.2303	0.2135	0.1447

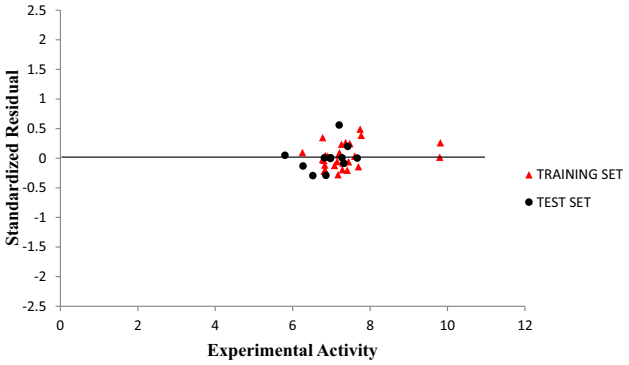


Fig. 3. Plot of Standardized residual activity versus experimental activity.

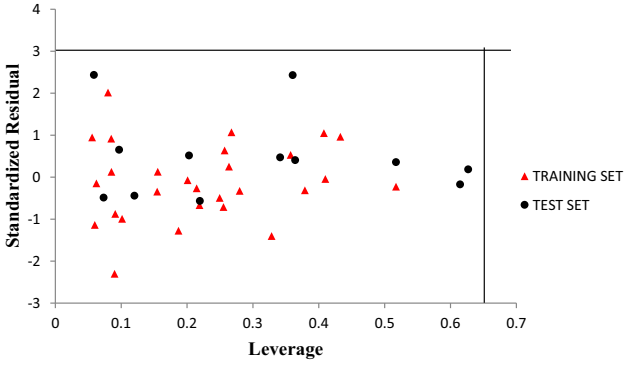


Fig. 4. The Williams plot of the standardized residuals versus the leverage value.

4. Conclusion

This study generates a QSAR model for a dataset of 2,4-disubstituted quinoline derivatives as potent inhibitors against *Mycobacterium tuberculosis*. The internal and external validation test confirmed that the built QSAR model is significant, robust and reliable. From the results, it is concluded that 2,4-disubstituted quinoline derivatives can be modeled using molecular descriptors; AATS5e, VR3_Dzp, VR1_Dzi, VR1_Dzs and SpMin7_Bhe. The built QSAR model will be useful for pharmaceutical as well as medicinal chemists to design and synthesis new drugs with better activities against *M. tuberculosis*.

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