The Thai Journal of Pharmaceutical Sciences

Volume 40
Issue 2 *2016*

Article 2

1-1-2016

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TJPS 40 (2), April-June 2016: 72-81

Thai Journal of Pharmaceutical Sciences (TJPS)

Journal homepage: http://www.tjps.pharm.chula.ac.th

QSAR study on quinolinecarbaldehyde derivatives as potential anti-tubercular agents

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ARTICLE INFO
Article history:
Received: 8 October 2015
Revised: 24 November 2015
Accepted: 2 May 2016
Available online: 7 June2016

Keywords:

Anti-tubercular agents, tuberculosis, quantitative structure activity relationship, quinolinecarbaldehyde derivatives

ABSTRACT
This study investigated the quantitative structure–activity relationships (QSAR) for a range of substituted quinolinecarbaldehyde derivatives as anti-tubercular agent by multiple linear regression analysis. The derived QSAR models have been statistically validated internally by means of the Leave One Out (LOO) and Leave Many Out (LMO) cross-validation, and Y-scrambling techniques, as well as externally by means of an external prediction set. The statistical parameters endowed by the three developed MLR models were r2 = 0.982, 0.979 and 0.995, q2LOO = 0.976, 0.968 and 0.992, pred_r2 = 0.992, 0.981 and 0.997, and r2m average = 0.904, 0.970 and 0.992, respectively. Overall, these results suggest that the reported QSAR models are simple, reliable and robust tool for prediction and virtual screening of quinolinecarbaldehyde derivatives with good anti-tubercular activity. In addition, the calculated molar refractivity, calculated log P, hydrogen bond donor, polarizability and percentage of halogen atom in the molecules were found to possess high significant on the activity. Furthermore, the domain analysis was also carried out to evaluate the prediction reliability of the developed models. The developed models were found to be statistically robust and had good predictive power which can be successfully utilized for screening of new molecules.

Introduction

Tuberculosis is the most commonly encountered mycobacterial disease and is considered as one of the most dangerous chronic communicable disease by WHO and is responsible for at least 2 million deaths globally per year. It has been estimated that nearly 8 million people develop active TB every year and approximately 5,500 deaths per day (www.who.int/mediacentre/factsheets/fs104/en//). Due to demographic factors, socioeconomic trends, neglected tuberculosis control in many countries and HIV infection, this could be sited as reason for its present [1]. The major challenge for many anti-mycobacterial agents is the ability of Mycobacterium tuberculli strains to develop resistance. Effective new anti-TB drugs with new mechanism of action have not been identified in last forty years. In spite of its severe toxicity on repeated dosing, isoniazid is still considered as the first line of drug in treatment of tuberculosis.

Tuberculosis has been treated with combination therapy for over fifty years. Multiple drugs are used to treat

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TB (except in latent TB or chemoprophylaxis), and regimens that use only single drugs had resulted in rapid development of resistance that lead to treatment failure [2]. The rationale for using multiple drugs to treat TB is based on simple probability. In addition to the apparent risks factors (i.e., known exposure to a patient with MDR-TB) to MDR-TB, it also includes male sex, HIV infection, previous incarceration, failed TB treatment, failure to respond to standard TB treatment, and relapse following standard TB treatments are also considered as risk factors. People with HIV and latent TB infection need treatment as soon as possible to prevent from developing TB disease. People with HIV, and latent TB infection, are much more likely to progress to TB disease than people without HIV. Unfortunately, some people with HIV may not know that they are infected with TB. Similarly, one in five people with TB disease are unaware of their HIV status, although HIV status reporting for people with TB is improving. CDC recommends screening of HIV in those who have TB disease/ suspected of having TB disease, or in a contact of a TB patient [3].

Recent advances such as availability of TB genome sequence like, a gene probe for rpoB, katG [4] and mabA-inhA [5] have provided a wide range of novel targets for drug design [6], however no new specific effective drug has reached the market in past forty years [7]. This urges to discover new structural classes of anti-tuberculosis agents which may replace or supplement the currently avalable drugs.

The contribution of computational chemistry in rational drug design is an important factor to note. Quantitative structure activity relationship (QSAR) results in a prediction of quantitative relation between chemical structure and biological activity. Based on the literatures, it is learnt that several attempts have been made to build QSAR models for the design and development of anti-tubercular agents [8-19]. As a part of our investigation, for further optimizing quinolone's anti-bacterial activity against Mycobacterium tuberculosis, the QSAR studies were performed on quinolinecarbaldehyde derivatives to correlate their anti-tubercular activity with their various physico-chemical properties.

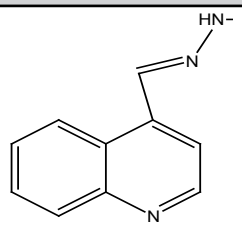
Materials and methods

Chem. Office 2004 (Cambridge Soft Corp., Cambridge, USA, http://www.cambridgesoft.com), Molecular Modeling Pro 6.1.0 (Trial version, ChemSW, Inc., www.chemsw.com) and Dragon 6 (TALETE srl, Milano,Italy) was used for molecular modeling studies and the QSAR models were executed with QSARINS 2.2 (www.qsar.it) software [20].

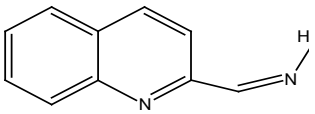
Biological data

In the present QSAR study, we have used biological and chemical data of twenty four quinolinecarbaldehydes reported by Nayyar et al. (2006) (Table 1) [21]. High structural diversity and a sufficient range of the biological activity in the selected series of quinolinecarbaldehyde derivatives were observed. Anti-tubercular activities used in the present study were expressed as -logMIC, where MIC is the micro molar concentration of the compounds producing minimum inhibition against Mycobacterium tuberculosis and stated as the means of at least two experiments. The total set of compounds was divided randomly into two sets as training and prediction set. Training set of compounds was used to develop QSAR models and prediction set compounds was used to externally validate the developed models.

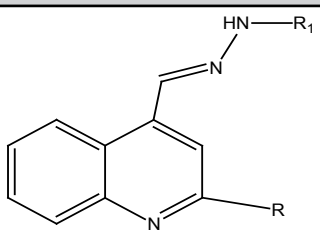
Table 1. Structures of quinolinecarbaldehydes



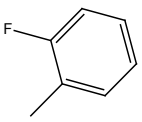
1-6

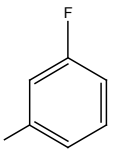
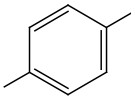
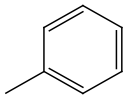
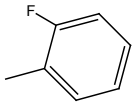
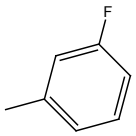
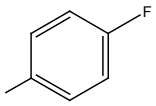
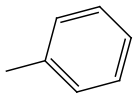
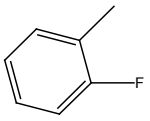
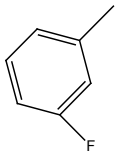
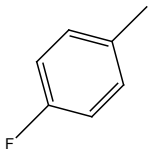


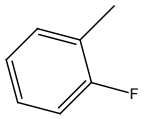
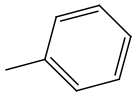
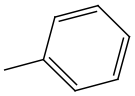
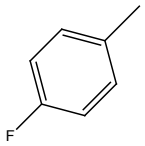
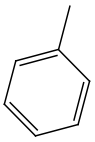
7-12



13-24

Compound No.	R	R_1
1	--	

Compound No.	R	R_1
2	--	
3	--	
4	--	CHO
5	--	$COCH_3$
6	--	
7	--	
8	--	
9	--	
10	--	CHO
11	--	$COCH_3$
12	--	
13	Adamantan-1-yl	
14	Adamantan-1-yl	
15	Adamantan-1-yl	
16	Adamantan-1-yl	CHO
17	Adamantan-1-yl	$COCH_3$

Compound No.	R	R_1
18	Adamantan-1-yl	
19	c-C_6H_{11}	
20	c-C_6H_{11}	
21	c-C_6H_{11}	
22	c-C_6H_{11}	CHO
23	c-C_6H_{11}	COCH3
24	c-C_6H_{11}	

Sketching of Molecules

The 2D structures of the compounds were drawn in the CS Chem. Office 2004 software using the drawing tools in it. The structures were then checked for errors and cleaned up, and saved as .mol files for computing various physico-chemical descriptors (Table 2). Some physico-chemical descriptors were calculated by using Molecular Modeling Pro 6.1.0. The 2D structures were converted into 3D structures and the geometry of the structures was optimized by AM1 and then followed by PM3 methods. The energy optimized 3D structures were utilized to calculate descriptors by Dragon 6 software.

Table 2. Physico-chemical parameters used in the present study

Physico-chemical parameters	
Molecular Weight (MW)	Moriguchi octanol-water partition coeff (logP)
Sum of atomic van der waals volumes (Sv)	Balaban distane connectivity index (J)
Sum of atomic polarizabilities (Sp)	Polarity number (Pol)
Mean atomic van der waals volume (Mv)	Global topological charge indix (JGT)
Mean atomic sanders on electonegativity (Me)	Modified Randic connectivity index (XMOD)
Mean atomic polarizability (Mp)	Dipole Length(μ)
Mean electropological state (Ms)	Highest occupied molecular orbital (HOMO)
Number of atoms (nAT)	Lowest unoccupied molecular orbital (LUMO)
Number of non-H atoms (nSK)	Percentage of halogen (X%)
Number of bonds (nBT)	Percentage of oxygen (O%)
Number of non-H bonds (nBO)	Percentage of nitrogen (N%)
Harmonic oscillator model of aromaticity index total	3D-Balaban index (J3D)
(HOMT)	3D-Harary index (H3D)
3D-Wiener index (W3D)	Hydrophilic factor (Hy)
	Ghose-grippen molar refractivity (AMR)

QSAR model- development and validation

In order to avoid co-linearity problems, descriptors were selected based on permutation and correlation matrices among it. Stepwise multiple linear regression analysis was used to achieve the best model.

The developed QSAR models are evaluated using the following statistical measures: n, (the number of compounds in regression); r^2, (the squared correlation coefficient); F test, (Fischer's value) for statistical significance; q^2, (cross-validated correlation coefficient); pred_r^2, (r^2 for external prediction set); RMSE (root mean square error); best_ran_q^2, (highest q+ value in the randomization test); best_ran_r^2, (highest r^2 value in the randomization test). The regression coefficient r^2 is the relative measure of fit by regression equation. It represents the part of variation in the observed data that is explained by the regression. However, a QSAR model is considered to be predictive, if the following conditions are satisfied: $r^2 > 0.6$, $q2 > 0.5$ and pred_$r^2 > 0.6$. The F-test reflects the ratio of variance explained by the model and variance due to the error in regression. High values of F-test indicate that the model is statistically significant. The low standard error of r2 (r^2_se), q^2 (q^2_se) and pred_r^2 (pred_r^2se) value shows absolute quality of fitness of the model.

Internal validation was carried out using 'leave-one-out' (q^2LOO) method [22]. The cross-validated coefficient, q^2, was calculated using the following equation

$$q^2 = 1 - \frac{\sum(y_i - \hat{y}_i)^2}{\sum(y_i - y_{mean})^2}$$

where y_i, and $\hat{y}_i$ are the actual and predicted activity of the i^{th} molecule in the training set, respectively and y_{mean} is the average activity of all molecules in the training set. However, a high q^2 value does not necessarily give a suitable representation of the real predictive power of the model for anti-tubercular activity. Hence, an external validation was carried out. The external predictive power of the model was assessed by predicting –logMIC value of the test set molecules, which were not included in the QSAR model development. The predictive ability of the selected model was also confirmed byr^2-$r^2$0/r^2, r^2-r'^{2}0/r^2, k and k'.

$$\text{pred}\_r^2 = 1 - \frac{\sum(y_i - \hat{y}_i)^2}{\sum(y_i - y_{mean})^2}$$

where y_i, and $\hat{y}_i$ are the actual and predicted activity of the ith molecule in the test set, respectively, and y_{mean} is the average activity of all molecules in the data set.

The external predictability of the selected model was also checked by r^2_m, which was proposed by Roy and Roy (2007) [23] and it was calculated by the following formula:

$$r_m^2 = r^2\left(1 - \sqrt{|r^2 - r_0^2|}\right)$$

$$r_m'^2 = r^2\left(1 - \sqrt{|r^2 - r_0'^2|}\right)$$

$$\overline{r_m^2} = \frac{r_m^2 + r_m'^2}{2}$$

where r^2 is the squared correlation coefficient between observed and predicted values and $r0^2$ is the squared correlation coefficient between observed and predicted values with intercept value set to zero. r^2m (overall) is the r^2m value calculated for both LOO and test set together. A value of r^2m is greater than 0.5 may be taken as an indicator for good external predictability.

Another term to check the external predictability of the selected model is CCC which was proposed by Chirico and Gramatica (2011) [24] and was calculated by the following formula:

$$CCC = \frac{2\sum(y_i - \bar{y})(\hat{y}_i - \bar{\hat{y}})}{\sum(y_i - \bar{y})^2 + \sum(\hat{y}_i - \bar{\hat{y}})^2 + n_{EXT}(\bar{y} - \bar{\hat{y}})^2}$$

Results and discussion

The best two models among several models obtained from the stepwise multiple linear regression analysis using the descriptors (Table 2) obtained from Chem. Office and Molecular Modeling Pro is given as below:

-logMIC = 4.247 (± 0.016) + 0.045 (± 0.001) CMR Eq. (1)

n = 15; r2 = 0.982; r^2_{adj} = 0.980; $RMSE_{tr}$ = 0.014; MAEtr = 0.012; CCC_{tr} = 0.991; LOF = 0.000; $F_{1,13}$ = 699.56; q^2LOO = 0.976; $RMSE_{cv}$ = 0.016; MAE_{cv} = 0.014; CCC_{cv} = 0.988; best rand r^2 = 0.072; best rand q^2 = -0.240

-logMIC = 4.151 (± 0.046) + 0.053 (± 0.002) Clog P + 0.082 (± 0.011) HD Eq. (2)

n = 15; r^2 = 0.979; r^2_{adj} = 0.975; $RMSE_{tr}$ = 0.014; MAE_{tr} = 0.010; CCC_{tr} = 0.989; LOF = 0.000; F2,12 = 272.59; q^2LOO = 0.968; $RMSE_{cv}$ = 0.018; MAEcv = 0.013; CCC_{cv} = 0.984; best rand r_2 = 0.143; best rand q^2 = -0.342

Eq. (1) could explain 98.2% of the variance of the anti-tubercular activity data. The parameters involved in the selected model (CMR) and the calculated anti-tubercular

activity by Eq. (1) are given in Table 3 and 4, respectively. The closeness between the actual and residual activity of the compounds in training and prediction set for Eq. (1) is shown in Figure 1. The selected model has shown good internal prediction (q^2LOO = 0.976). The robustness of this model was checked by Y–randomization test (maximum r2 value is 0.072 and maximum $q^2$is -0.240).

Table 3. Selected physico-chemical parameters

Compd. No	CMR	Clog P	HD	Sp	X%
1	8.020	3.986	3	22.762	3.10
2	8.020	3.986	3	22.762	3.10
3	8.020	3.986	3	22.762	3.10
4	5.993	0.453	4	16.756	0
5	6.457	1.238	4	18.517	0
6	8.005	3.737	3	22.824	0
7	8.020	4.406	3	22.762	3.10
8	8.020	4.406	3	22.762	3.10
9	8.020	4.406	3	22.762	3.10
10	5.993	0.453	4	16.756	0
11	6.457	1.658	4	18.517	0
12	8.005	4.157	3	22.824	0
13	12.424	7.793	3	38.091	1.80
14	12.424	7.793	3	38.091	1.80
15	12.424	7.793	3	38.091	1.80
16	10.400	4.260	4	32.086	0
17	10.400	5.045	4	33.847	0
18	12.408	7.544	3	38.154	0
19	10.625	6.606	3	32.569	2.10
20	10.625	6.606	3	32.569	2.10
21	10.625	6.606	3	32.569	2.10
22	8.598	3.073	4	26.563	0
23	9.062	3.858	4	28.324	0
24	10.610	6.357	3	32.631	0

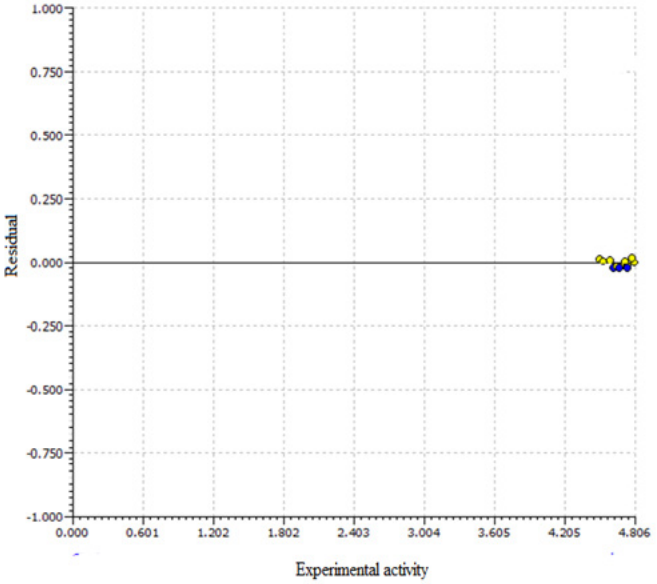


Figure. 1 Plot between experimental and residual anti-tubercular activities of quinolinecarbaldehyde derivatives by Eq. (1)

● Prediction set, ○ Training set

Table 4. Experimetal, calculated and predicted anti-tubercular activity of quinolone carbaldehydes

Comp. No	Experimental activity (μM)	Eq. (1)		Eq. (2)		Eq. (3)	
		Calculated activity	Predicted activity	Calculated activity	Predicted activity	Calculated activity	Predicted activity
1[b,c]	4.628	4.609	-	4.607	-	4.626	4.625
2	4.628	4.609	4.607	4.607	4.603	4.626	4.625
3[d]	4.628	4.609	4.607	4.607	4.603	4.626	-
4	4.503	4.518	4.5218	4.503	4.503	4.514	4.518
5[b,c]	4.533	4.539	-	4.544	-	4.537	4.539
6	4.597	4.608	4.609	4.594	4.593	4.594	4.594
7[a]		-	-	-	-	-	-
8[d]	4.628	4.609	4.607	4.629	4.629	4.626	-
9[b,c]	4.628	4.628	4.609	-	4.629	4.626	4.625
10[d]	4.503	4.518	4.521	4.503	4.503	4.514	-
11	4.533	4.533	4.539	4.540	4.574	4.537	4.539
12	4.597	4.597	4.608	4.609	4.619	4.594	4.594
13	4.806	4.806	4.808	4.808	4.808	4.815	4.819
14[d]	4.806	4.806	4.808	4.808	4.808	4.815	-
15[a]		-	-	-	-	-	-
16	4.727	4.716	4.715	4.703	4.696	4.716	4.715
17	4.745	4.737	4.736	4.745	4.745	4.740	4.739
18	4.786	4.807	4.813	4.794	4.797	4.797	4.801
19[a]		-	-	-	-	-	
20[b,c]	4.745	4.727	-	4.745	-	4.745	4.745
21	4.745	4.727	-	4.745	-	4.745	-
22	4.653	4.635	4.634	4.641	4.638	4.643	4.643
23[b,c]	4.675	4.655	-	4.682	-	4.667	4.666
24	4.722	4.726	4.726	4.732	4.733	4.724	4.724

a - outliers, b - prediction set compounds for Eq. (1), c - prediction set compounds for Eq. (2), d - prediction set compounds for Eq. (3)

Eq. (2) could explain 97.9% of the variance of the anti-tubercular activity data. The parameters involved in the selected model [Clog P and hydrogen bond donor (HD)] and the calculated anti-tubercular activity by Eq. (2) are given in Table 3 and 4, respectively. The closeness between the actual and residual activity of the compounds in training and prediction set for Eq. (2) is shown in Figure 2. The selected model showed good internal prediction (q^2LOO = 0.968). The robustness of this model was checked by Y–randomization test (maximum r^2 value is 0.143 and maximum q^2 is -0.342). The low randomized r^2 and q^2 values indicate that the good results in our original model are not due to a chance correlation or structural dependency of the training set.

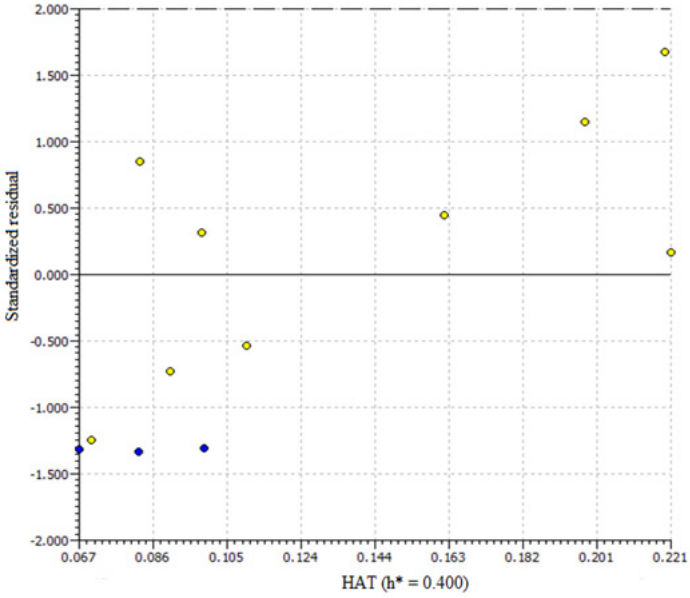


Figure 2. Williams plot for Eq. (1): plot of standardized residuals (Y-axis) versus leverages (hat values; X-axis) for each compound
● Prediction set, ○ Training set

The best model among several models obtained from the stepwise multiple linear regression analysis using the descriptors obtained from Dragon 6 is given as below:

-logMIC = 4.293 (± 0.076) + 0.013 (± 0.000) Sp + 0.011 (± 001) X% Eq. (3)

n = 15; r^2 = 0.995; r^2_{adj} = 0.994; $RMSE_{tr}$ = 0.006; MAE_{tr} = 0.005; CCC_{tr} = 0.997; LOF = 0.000; $F_{2,12}$ = 1231.24; q^2LOO = 0.992; $RMSE_{cv}$ = 0.008; MAE_{cv} = 0.006; CCC_{cv} = 0.996; best rand r^2 = 0.133; best rand q^2 = -0.323

Eq. (3) explains 99.5% of the variance of the anti-tubercular activity data. The parameters involved in the selected model (Sp and X%) and the calculated anti-tubercular activity by Eq. (3) are given in Table 3 and 4, respectively. The closeness between the actual and residual activity of the compounds in training and prediction set for Eq. (3) is shown in Figure 3. The selected model has shown good internal prediction (q^2LOO = 0.992). The robustness of this model was checked by Y–randomization test (maximum r^2 value is 0.133 and maximum $q^2$is -0.323).

The low randomized r^2 and q^2 values indicate that the good results in our original model are not due to a chance correlation or structural dependency of the training set. The significance and predictive ability of the proposed QSAR model [Eq. (1), (2) and (3)] was confirmed as it satisfies the conditions mentioned in Table 5.

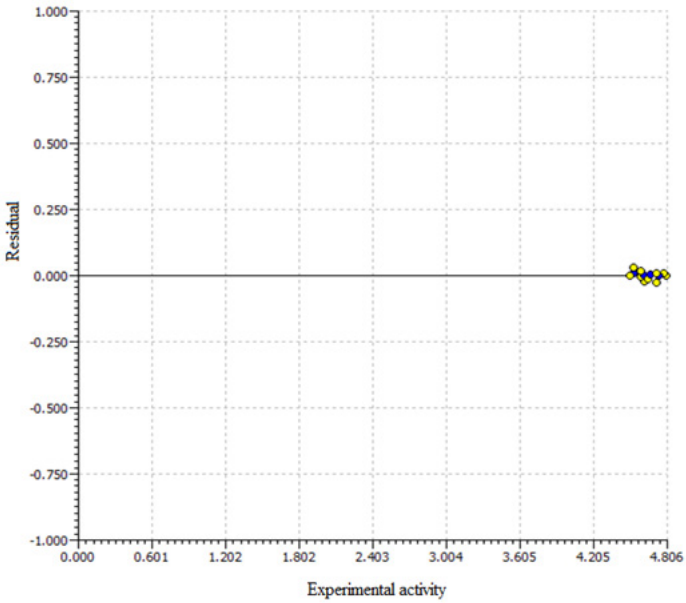


Figure 3. Plot between experimental and residual anti-tubercular activities of quinolinecarbaldehyde derivatives by Eq. (2)
● Prediction set, ○ Training set

Table 5. Statistical significance and validation parameters

Statistical parameters	Conditions	Models		
		Eq. (1)	Eq. (2)	Eq. (3)
r^2	> 0.6	0.982	0.976	0.995
CCC_{TR}	> 0.85	0.991	0.989	0.997
q^2LOO	> 0.5	0.976	0.968	0.992
CCC_{cv}	> 0.85	0.989	0.984	0.996
q^2LMO	> 0.5	0.974	0.964	0.991
pred_r^2	> 0.6	0.992	0.981	0.997
CCC_{ex}	> 0.85	0.972	0.990	0.998
q2-F1	> 0.6	0.948	0.981	0.996
q2-F2	> 0.6	0.948	0.981	0.996
q2-F3	> 0.6	0.972	0.990	0.995
r^2m	> 0.5	0.912	0.980	0.994
r'^2m	> 0.5	0.896	0.961	0.991
Δr^2m	< 0.2	0.014	0.019	0.003
r^2m average	> 0.5	0.904	0.970	0.992
k'	0.85 < k' < 1.15	0.997	1.000	1.000
k	0.85 < k' < 1.15	1.003	1.000	0.999
r^2-$r^2$0/r^2	< 0.1	0.009	0.000	0.000
r^2-$r'^2$0/ r^2	< 0.1	0.006	0.000	0.000
r^2p	> 0.5	0.937	0.000	0.000
r^2m(overall)	> 0.5	0.943	0.971	0.943
r'^2m(overall)	> 0.5	0.926	0.951	0.926
r^2m average (overall)	> 0.5	0.934	0.961	0.934
Δr^2m (overall)	< 0.2	0.017	0.020	0.017

Finally, the applicability domain was established for all the developed models by determining the leverage values for each compound. Figure 4, 5 and 6 shows the Williams plot; i.e. plot of standardized residuals (*y*-axis) *versus* leverages (*x*-axis) for each compound of the training and prediction set of all the three models. From these plot, the applicability domain was established inside a squared area within ± 2.00 standard deviations for Eq. (1) and Eq. (3), ± 2.50 standard deviations for Eq. (2), and a leverage threshold $h^* = 0.400$, 0.600 and 0.563 ($h^* = 3p'/n$, being p' the number of model parameters + 1, and n the number of compounds) for all the three models. All compounds of training set and prediction set were inside of the square area as seen in Figure 4, 5 and 6.

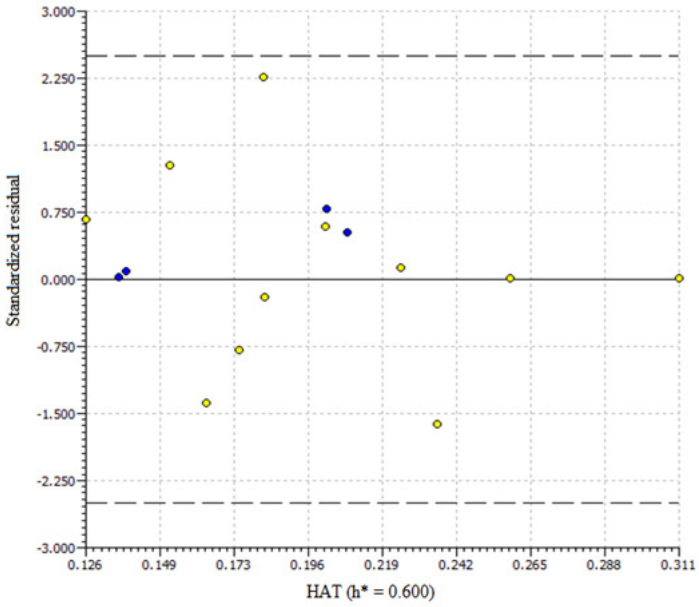


Figure 4. Williams plot for Eq. (2): plot of standardized residuals (Y-axis) versus leverages (hat values; X-axis) for each compound

● Prediction set, ○ Training set

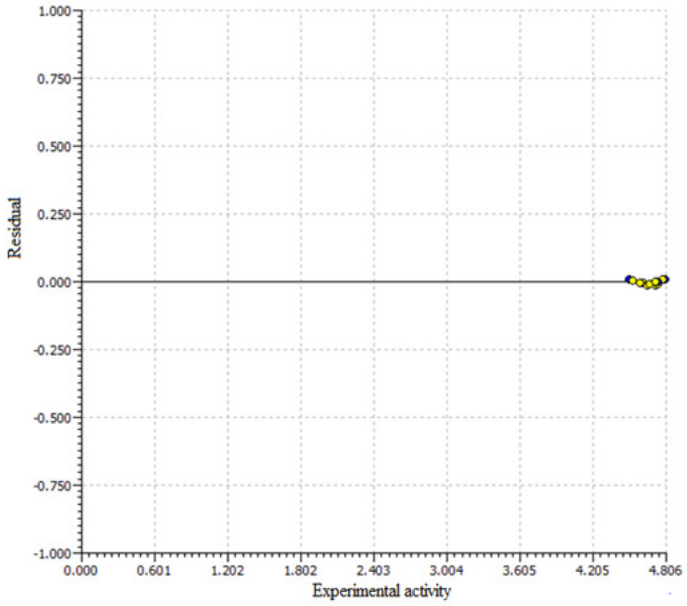


Figure 5. WPlot between experimental and residual anti-tubercular activities of quinolinecarbaldehyde derivatives by Eq. (3)

● Prediction set, ○ Training set

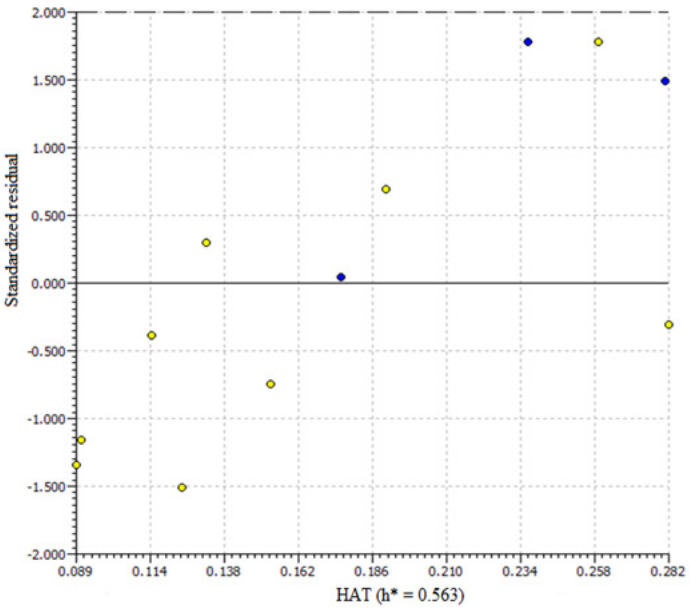


Figure 6. Williams plot for Eq. (3): plot of standardized residuals (Y-axis) versus leverages (hat values; X-axis) for each compound

● Prediction set, ○ Training set

For future investigations, the predicted anti-tubercular activity data must be considered reliable only for those molecules that fall within the applicability domain on which the model was constructed [25].

Moreover, it is not possible to use the reported QSAR models to predict the activity of any type of molecules vs. anti-tubercular activity. The applicability domain of the derived QSAR models is applicable only to the substituted quinolinecarbaldehyde derivatives. However, it is very important to point out an eventual QSAR models disappointments: like activity cliffs [26]. It is possible because similar molecules can show significantly different biological activity. Activities are often mispredicted for these molecules, even when the overall prediction of the models is high.

In Eq. (1) the positive coefficient of CMR suggests that the activity increases with increase in size of the molecules, thus the bulky molecules may perfectly fit into the active site. This finding was supported by compounds 13-24. In Eq. (2) the positive coefficient of Clog P indicates that the hydrophobicity of the compounds is positively persuading to the anti-tubercular activity, thus the strong hydrophobic groups may responsible to bind with active site. This finding was supported by compounds 13-15 and 18 which are having adamantan-1-yl substitution on second position of quinolone and fluorinated aromatic ring substitution on –NH-R1 position. The positive coefficient of HD indicates that the hydrogen bond donor groups in the compounds are positively affect the anti-tubercular activity, thus the hydrogen bond donor groups may responsible to bind with active site. This phenomenon was found to be supported by compounds 16, 17, 22 and 23 which are having additional hydrogen bond donor groups on –NH-R1 position.

Conclusion

In this study we had developed three QSAR models for a set of twenty four quinolone carbaldehyde derivatives having Mycobacterium tuberculosis inhibitory activity. The LOO cross-validation methods and Y-randomization technique indicated that the models were significant, robust and has good internal predictability. These findings could be utilized in development and optimization of new anti-tubercular agents. The reported QSAR models might be used for predicting the anti-tubercular activity of quinolinecarbaldehyde derivatives only. It can be concluded thar 3D QSAR and docking studies should be carried out to understand the mechanisms of chemical–biological interactions of quinolinecarbaldehydes against Mycobacterium tuberculosis.

Acknowledgment

Authors are thankful to AIMST University for providing the necessary facilities to carry out this work.

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