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ORIGINAL ARTICLE

Molecular modeling of 8-methoxy quinolone analogues by using quantitative structure activity relationship

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KEY WORDS

QSAR;
Steric parameters;
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Cytotoxicity

Abstract Quantitative structure activity relationship (QSAR) studies on a series of 8-methoxy quinolone are found to correlate well with steric parameters and electronic parameter. The results are critically discussed on the basis of regression data, Pogliani factor Q and cross validation technique. The results are found to be useful in discussing the mechanism of drug – receptor interaction. Steric parameter 'Mr' and electronic parameter 'Pz' gives the best model.

1. Introduction

Tuberculosis (TB) is a chronic infection caused by the bacteria *Mycobaterium tuberculosis*. It usually involves the lungs, but can also affect the central nervous system, the lymphatic system, the circulatory system, the genitourinary system, the gastrointestinal system, bones, joints and even the skin.

The classic symptoms of tuberculosis are a chronic cough with blood-tinged sputum, fever, night sweats and weight loss. Like common cold, TB spreads through the air. Today, TB tends to be concentrated among inner city dwellers, ethnic minorities and recent immigrants from areas of the world where the disease is still common. Alcoholic, who are often malnourished, are at high risk of developing the disease, as are people infected with HIV. It can occur anywhere, and no one is exempt from the threat of infection. TB is a global emergency in 1993 as declared by the World Health Organization (WHO) Ang et al., 2006. Tuberculosis treatment is difficult and requires long courses of multiple antibiotics. Contacts are also screened and treated if necessary. Antibiotics resistance is a growing problem in (extensively) multi-drug-resistant tuberculosis.

2. Experimental

In the present work, steric parameters such as molar refractivity (Mr), mean Weiner index (WA), Balaban connectivity distance index (J), and all the orders of molecular connectivity from ($^0\chi$ to $^5\chi$), and electronic parameter polarizability (Pz) have been used to study the relationship between parameters and properties.

Mr and Pz were calculated by ACD Lab Chem. Sketch Software whereas WA, J, $^0\chi$, $^1\chi$, $^2\chi$, $^3\chi$, $^4\chi$, $^5\chi$ were evaluated by DRAGON Software. The multiple regression used to derive the correlation was executed with the SPSS 7.5 version program.

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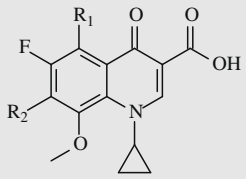
Table 1 Biological activity and physicochemical data for 8-methoxy quinolone analogues.



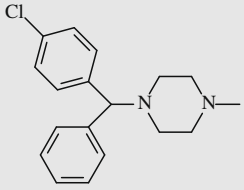
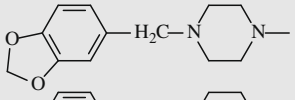
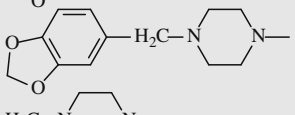
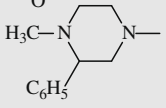
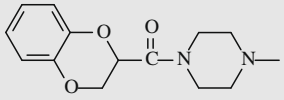
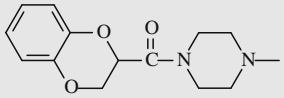
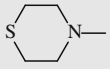
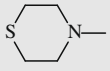
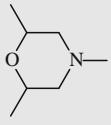
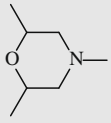
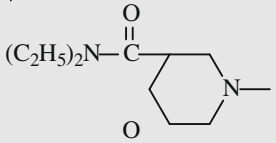
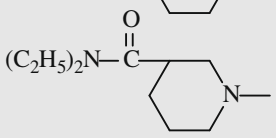
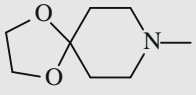
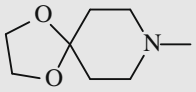
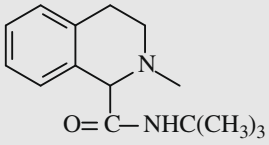
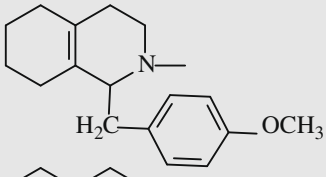
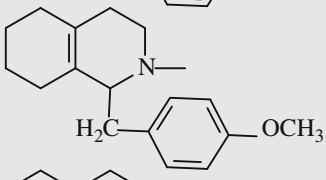
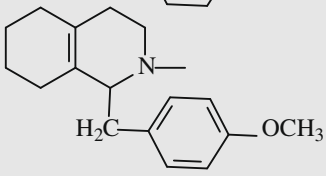
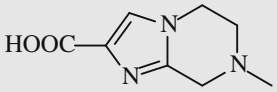
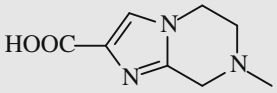
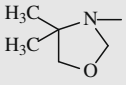
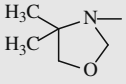
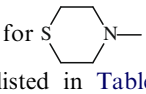
S. no.	R_1	R_2	Mr	Pz	WA	J	$^0\chi$	$^1\chi$	$^2\chi$	$^3\chi$	$^4\chi$	$^5\chi$	pIC_{50}	I_1	I_2
1	NO_2		155.16	61.51	6.841	1.227	30.413	20.706	19.159	16.154	14.519	12.478	3.987	0	0
2	H		125.48	49.74	6.511	1.122	24.974	17.457	16.170	13.985	12.547	10.424	3.899	1	0
3	NO_2		132.02	52.33	6.537	1.193	27.422	18.795	17.551	14.994	13.691	11.309	3.937	0	0
4	NO_2		125.85	49.89	5.597	1.474	25.723	17.239	16.101	13.548	12.220	10.383	3.900	0	0
5	H		129.74	57.43	6.855	1.109	26.551	18.367	17.019	14.868	12.944	11.038	3.923	1	0
6	NO_2		136.29	54.03	7.488	1.027	30.861	21.151	20.099	18.049	16.474	13.299	3.959	0	0
7	H		94.74	37.56	6.882	1.176	28.999	19.706	18.400	15.878	14.088	11.923	3.782	1	1
8	NO_2		101.29	40.15	4.594	1.741	20.870	13.887	12.887	10.644	9.779	8.230	3.831	0	1
9	H		97.60	38.69	4.754	1.629	20.162	13.312	12.785	10.199	9.440	7.629	3.796	1	0
10	NO_2		104.15	41.28	4.832	1.745	22.610	14.650	14.166	11.209	10.584	8.519	3.843	0	0
11	H		118.02	46.78	5.650	1.561	23.861	15.815	14.230	12.276	10.627	8.445	3.866	1	0
12	NO_2		124.56	49.38	5.689	1.672	26.309	17.154	15.611	13.285	11.771	9.332	3.907	0	0
13	H		102.56	40.65	5.209	1.374	21.043	14.438	13.652	11.740	10.379	8.557	3.826	1	0

Table 1 (*continued*)

S. no.	R_1	R_2	Mr	Pz	WA	J	$^0\chi$	$^1\chi$	$^2\chi$	$^3\chi$	$^4\chi$	$^5\chi$	pIC_{50}	I_1	I_2
14	NO_2		108.59	43.05	5.265	1.468	23.491	15.777	15.033	12.749	11.522	9.443	3.870	0	0
15	NO_2		139.77	55.41	5.749	1.563	29.093	18.851	18.758	14.363	13.602	11.290	3.946	0	0
16	H		143.47	56.87	6.147	1.277	27.258	18.905	17.252	15.022	13.226	11.588	3.931	1	0
17	NO_2		149.50	59.26	6.180	1.348	29.706	20.244	18.633	16.032	14.373	12.461	3.966	0	0
18	NO_2		147.08	58.31	6.132	1.307	28.129	19.333	17.671	15.647	13.638	11.899	3.943	0	0
19	H		106.83	42.35	5.500	1.370	22.731	15.295	14.676	12.319	10.846	9.283	3.850	1	0
20	NO_2		112.49	44.59	5.546	1.402	25.179	16.633	16.057	13.328	1.990	10.171	3.892	0	0
21	H		92.90	36.82	4.513	1.669	19.508	12.758	12.595	10.245	9.064	7.473	3.780	1	0
22	NO_2		99.44	39.42	4.609	1.782	21.955	14.096	13.976	11.254	10.213	8.326	3.829	0	0

3. Result and discussion

QSAR studies were performed on set of 22 compounds of 8-methoxy quinolone analogues, their activity data and the physicochemical parameter evaluated in the correlation are listed in Table 1. The biological activity (IC_{50}) is a measure of cytotoxicity (Senthilkumar et al., 2008). In order to study the role of different substituents at different positions, indicator parameters as I_1 for H at position R_1 and I_2 for  at position R_2 were introduced and are also listed in Table 1. These parameters have already been found to be useful in various QSAR studies performed earlier (Srivastava et al., 2008a; Srivastava et al., 2006; Srivastava et al., 2008b,c; Singh et al., 2008a,b).

Before under taking multiparametric regression, autocorrelation was checked and the resulting matrix is given in Table 2. Multiple regression analysis of the data gave several regression models of which the following equations were found to be the most significant

$$pIC_{50} = 0.002(\pm 0.000)\mathrm{Mr} - 0.020(\pm 0.053)I_1 - 0.015(\pm 0.024)I_2 + 3.560,$$
$$n = 22, R = 0.978, R^2 = 0.957, R_A^2 = 0.950, \mathrm{S.E.} = 0.013, F_{(3-18)} = 134.605, Q = 75.231 \quad (1)$$

$$pIC_{50} = 0.007(\pm 0.001)\mathrm{Pz} - 0.020(\pm 0.013)I_1 - 0.015(\pm 0.024)I_2 + 3.560,$$
$$n = 22, R = 0.978, R^2 = 0.957, R_A^2 = 0.950, \mathrm{S.E.} = 0.013, F_{(3-18)} = 134.596, Q = 75.231 \quad (2)$$

Table 2 Correlation matrix between physicochemical parameters and indicator parameters.

	pIC_{50}	Mr	Pz	WA	J	$^0\chi$	$^1\chi$	$^2\chi$	$^3\chi$	$^4\chi$	$^5\chi$	I_1	I_2
pIC_{50}	1.000												
Mr	0.965	1.000											
Pz	0.965	1.000	1.000										
WA	0.659	0.662	0.662	1.000									
J	−0.510	−0.521	−0.521	−0.910	1.000								
$^0\chi$	0.800	0.811	0.811	0.869	−0.661	1.000							
$^1\chi$	0.801	0.821	0.821	0.915	−0.753	0.989	1.000						
$^2\chi$	0.783	0.785	0.785	0.885	−0.724	0.986	0.983	1.000					
$^3\chi$	0.765	0.773	0.773	0.938	−0.813	0.962	0.986	0.972	1.000				
$^4\chi$	0.775	0.768	0.768	0.914	−0.773	0.970	0.981	0.987	0.989	1.000			
$^5\chi$	0.779	0.792	0.793	0.895	−0.785	0.962	0.983	0.981	0.985	0.986	1.000		
I_1	−0.476	−0.349	−0.349	0.004	−0.215	−0.347	−0.269	−0.313	−0.231	−0.309	−0.277	1.000	
I_2	−0.412	−0.372	−0.372	−0.015	0.051	−0.035	−0.029	−0.055	−0.041	−0.038	−0.015	0.058	1.000

$$pIC_{50} = 0.047(\pm0.015)WA - 0.055(\pm0.028)I_1 - 0.078(0.046)I_2 + 3.640,$$
$$n = 22, R = 0.896, R^2 = 0.803, R_A^2 = 0.770, \text{S.E.} = 0.029, F_{(3-18)} = 24.466, Q = 30.896 \quad (3)$$

$$pIC_{50} = 0.167(\pm0.071)J - 0.071(\pm0.033)I_1 - 0.072(\pm0.053)I_2 + 4.159,$$
$$n = 22, R = 0.859, R^2 = 0.738, R_A^2 = 0.694, \text{S.E.} = 0.034, F_{(3-18)} = 16.883, Q = 25.265 \quad (4)$$

$$pIC_{50} = 0.012(\pm0.003)^0\chi - 0.025(\pm0.027)I_1 - 0.078(\pm0.044)I_2 + 3.581,$$
$$n = 22, R = 0.908, R^2 = 0.824, R_A^2 = 0.794, \text{S.E.} = 0.027, F_{(3-18)} = 28.025, Q = 33.630 \quad (5)$$

$$pIC_{50} = 0.017(\pm0.004)^1\chi - 0.031(\pm0.025)I_1 - 0.078(\pm0.040)I_2 + 3.607,$$
$$n = 22, R = 0.924, R^2 = 0.855, R_A^2 = 0.830, \text{S.E.} = 0.025, F_{(3-18)} = 35.289, Q = 36.960 \quad (6)$$

$$pIC_{50} = 0.018(\pm0.006)^2\chi - 0.029(\pm0.029)I_1 - 0.075(\pm0.047)I_2 + 3.601,$$
$$n = 22, R = 0.895, R^2 = 0.800, R_A^2 = 0.767, \text{S.E.} = 0.029, F_{(3-18)} = 24.042, Q = 30.862 \quad (7)$$

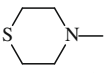
$$pIC_{50} = 0.019(\pm0.006)^3\chi - 0.036(\pm0.027)I_1 - 0.076(\pm0.045)I_2 + 3.644,$$
$$n = 22, R = 0.902, R^2 = 0.813, R_A^2 = 0.782, \text{S.E.} = 0.028, F_{(3-18)} = 26.071, Q = 32.214 \quad (8)$$

$$pIC_{50} = 0.021(\pm0.007)^4\chi - 0.029(\pm0.029)I_1 - 0.077(\pm0.047)I_2 + 3.638,$$
$$n = 22, R = 0.894, R^2 = 0.800, R_A^2 = 0.767, \text{S.E.} = 0.029, F_{(3-18)} = 23.995, Q = 30.828 \quad (9)$$

$$pIC_{50} = 0.024(\pm0.007)^5\chi - 0.031(\pm0.027)I_1 - 0.080(\pm0.044)I_2 + 3.652,$$
$$n = 22, R = 0.910, R^2 = 0.828, R_A^2 = 0.799, \text{S.E.} = 0.027, F_{(3-18)} = 28.872, Q = 33.704 \quad (10)$$

where, n is the number of data points, R is correlation coefficient, R^2 is the coefficient of determination, S.E. is the standard error of estimate, R_A^2 represents adjusted R^2. F is variance ratio (Studies for molecular descriptors and Diudea, 2000; Bikash et al., 2003), Q is quality of fit (Pogliani, 1994, 1996) and data within the parenthesis for the 95% confidence intervals.

The positive signs of the coefficients of Mr and WA indicate that bulkier group is favorable for the activity. Signs of the coefficients of all the orders of molecular connectivity from zero order to fifth order are positive implying that groups having more branching are conducive for the activity. The negative coefficient of J in the above model is probably due to its high co-linearity with other parameters. All these results indicate that the steric factor is more dominating towards the activity. The sign of coefficient of electronic parameter Pz is positive which implies that more polar groups are beneficial for the activity.

The sign of coefficient of both the indicator parameter I_1 and I_2 is negative showing that the group H for indicator I_1 and  for indicator I_2 at R_1 and R_2-position, respectively, are strictly avoided for the future drug modeling.

The statistical details of the QSAR model given above speak for its good statistical quality.

4. Cross validation

The cross validation analysis was performed using leave one out (LOO) method (Cramer et al., 1988; Poolgar and Ferguson, 2000), in which one compound is removed from the data set and the activity is correlated using the rest of the data set. The cross-validated R^2 in each case was found to be very close to the value of R^2 for the entire data set and hence these models can be termed as statistically significant.

Cross validation provides the values of PRESS, SSY and R_{CV}^2 and PSE from which we can test the predictive power of the proposed model. It is argued that PRESS, is a good estimate of the real predictive error of the model and if it is smaller than SSY the model predicts better than chance and can be considered statistically significant. Furthermore, the ratio PRESS/SSY can be used to calculate approximate confidence intervals of prediction of new compound. To be a reasonable QSAR model PRESS/SSY should be smaller than 0.4. Also, if PRESS value is transformed in a dimension less term by

Table 3 Comparison between observed and predicted activities and their residual values.

S. no.	pIC_{50}	Pred.	Resi.
1	3.987	3.991	−0.004
2	3.899	3.889	0.010
3	3.937	3.927	0.010
4	3.900	3.910	−0.010
5	3.923	3.900	0.023
6	3.959	3.939	0.020
7	3.782	3.787	−0.005
8	3.831	3.826	0.005
9	3.796	3.811	−0.015
10	3.843	3.849	−0.006
11	3.866	3.868	−0.002
12	3.907	3.906	0.001
13	3.826	3.825	0.001
14	3.870	3.862	0.008
15	3.946	3.948	−0.002
16	3.931	3.939	−0.008
17	3.966	3.975	−0.009
18	3.943	3.969	−0.026
19	3.850	3.837	0.013
20	3.892	3.872	0.020
21	3.780	3.798	−0.018
22	3.829	3.836	−0.007

relating it to the initial sum of squares, we obtain R^2_{CV} i.e. the complement to the traces on of unexplained variance over the total variance. The PRESS and R^2_{CV} have good properties. However, for practical purposes of end users the use of square root of PRESS/N, which is called predictive square error (PSE), is more directly related to the uncertainty of the predictions. The PSE values also support our results. The calculated cross-validated parameters confirm the validity of the models. All the requirements for an ideal model have been fulfilled by model no. 1, that's why, we have considered as the best model.

R^2_A takes into account the adjustment of R^2. R^2_A is a measure of the percentage explained variation in the dependent variable that takes into account the relationship between the number of cases and the number of independent variables in the regression model, whereas R^2 will always increase when an independent variable is added. R^2_A will decrease if the added variable does not reduce the unexplained variable enough to offset the loss of decrease of freedom.

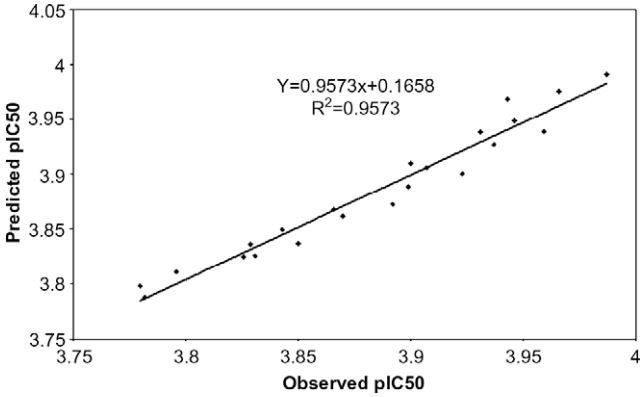


Figure 1 A plot showing comparison between observed plC50 and predicted plC50 for the best model.

5. Predictive error of coefficient of correlation (PE)

The predictive error of coefficient of correlation (PE) (Chatterjee et al., 2000) is yet another parameter used to decide the predictive power of the proposed models. We have calculated PE value of all the proposed models and they are reported in Table 4. It is argued that of

(i) $R <$ PE, then correlation is not significant;
(ii) $R >$ PE; several times (at least three times), then correlation is indicated; and if;
(iii) $R >$ 6PE, then the correlation is definitely good.

For all the models developed the condition $R >$ 6PE is satisfied and hence they can be said to have a good predictive power.

Predicted and residual activity values for model no. 1 are given in Table 3. The graph plotted between predicted activity obtained with model (1) and observed activity (Fig. 1) produced a high value of R^2 pred. = 0.957 and indicates about the reliability of prediction based on this model.

6. Conclusion

On the basis of the above discussion following conclusions are drawn:

(1) More branched, Bulkier groups should be used.
(2) More polar groups are favorable for the activity.

Table 4 Cross validated parameters and predictive error of coefficient of correlation (PE) for the proposed model.

Model no.	n	Parameters used	PRESS	SSY	PRESS/SSY	R^2_{CV}	PSE	R	$1-R^2$	PE	6PE
1	22	Mr + I_1 + I_2	0.003	0.076	0.039	0.961	0.012	0.978	0.044	0.006	0.036
2	22	Pz + I_1 + I_2	0.003	0.076	0.039	0.961	0.012	0.978	0.044	0.006	0.036
3	22	WA + I_1 + I_2	0.015	0.063	0.238	0.762	0.026	0.896	0.197	0.028	0.168
4	22	J + I_1 + I_2	0.021	0.059	0.356	0.644	0.030	0.859	0.262	0.037	0.222
5	22	$^0\chi$ + I_1 + I_2	0.014	0.065	0.215	0.785	0.025	0.924	0.146	0.021	0.126
6	22	$^1\chi$ + I_1 + I_2	0.011	0.067	0.164	0.836	0.022	0.908	0.176	0.025	0.150
7	22	$^2\chi$ + I_1 + I_2	0.016	0.064	0.250	0.750	0.027	0.895	0.199	0.028	0.168
8	22	$^3\chi$ + I_1 + I_2	0.015	0.065	0.231	0.769	0.026	0.902	0.186	0.026	0.156
9	22	$^4\chi$ + I_1 + I_2	0.016	0.064	0.250	0.750	0.026	0.894	0.201	0.029	0.174
10	22	$^5\chi$ + I_1 + I_2	0.014	0.066	0.212	0.788	0.025	0.910	0.172	0.024	0.144

(3) H at position R_1 and group  at position R_2 should be strictly avoided.

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