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Novel application of Wiener vis-à-vis Szeged indices: Antitubercular activities of quinolones

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Abstract. The paper gives a brief account of the recently introduced Szeged index (Sz). Using this index antitubercular activities of N-2,4-difluorophenyl quinolones are subjected to quantitative structure–activity relationship analysis. The potential of Sz related to the Wiener index (W) is critically discussed. In addition, Huckel molecular orbital energies: E_{HOMO}, E_{LUMO} and E_{total} were also used for comparing and modelling antitubercular activities of the quinolones. The results, based on univariate as well as multivariate regressions, have shown that W, Sz and E_{total} give better results and that the correlations improve in multivariate regression analyses.

Keywords. Quantitative structure–activity relationship; Wiener and Szeged indices; antitubercular activity; fluorophenyl quinolones; modelling of drug activity.

1. Introduction

Quantitative structure–property–activity (QSPR, QSAR) relationships are certainly not a new field in chemistry. In fact, correlations between molecular properties and many kinds of molecular descriptors have been empirically sought for many years. Usually, molecular descriptors are chosen in an empirical way, that is, according to their ability to give good results in statistical models.

It has been known for some time that certain invariants of molecular graphs (carbon–hydrogen suppressed molecular structure of the organic molecules acting as drugs) – usually referred to as topological indices – can be used to establish quantitative structure–activity relationships (QSAR) of interest in pharmacology [1]. A number of successful QSAR studies have been made based on the Wiener index (W) [2–4] and its decomposition forms [5]. This index was introduced fifty years ago and looked upon as a measure of compactness of molecules but only recently [6] its relation with the molecular van der Waals area was demonstrated.

Recently [7,8] Gutman proposed a new index which was named the Szeged index (Sz). Many properties of Sz are discussed [9–11] but its applications in QSAR studies have not been thoroughly investigated.

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As part of a study optimize the quinolone antibacterials against *M. tuberculosis*, Renau and coworkers [12] have synthesized a series of N-2,4-difluorophenyl quinolones and evaluated a variety of C7 substituted quinolones with varying degrees of substitution and lipophilicity on the heterocyclic side chain (table 1). In order to investigate the relative antituberculotic activities of these compounds, they have calculated *c*log*P* values (table 1). However, no attempt has been made to investigate QSAR using molecular (topological and quantum mechanical) descriptors.

In view of the above, it was considered worthwhile to investigate the potential of Sz in QSAR studies. The main objective of this paper is to show how useful Sz can be in the QSAR field, both from the theoretical and the practical point of view. In order to investigate the relative potential of Sz over W in QSAR studies, an attempt is also made to study the role of W in modelling antitubercular activities of the quinolones. The Huckel orbital energies, the energy of the highest occupied molecular orbital (E_{HOMO}), the energy of the lowest unoccupied molecular orbital energy (E_{LUMO}) and total π-electron energy (E_{total}) are used as molecular descriptors. Note that the Wiener (W) and Szeged (Sz) indices are graph theoretical descriptors and these are merely topological in nature. On the other hand, HOMO and LUMO orbital energies are quantum chemical properties. These two parameters are not related (see table 2). However, we have used Sz and W indices because the potential of Sz in developing QSAR relationships is not well-known and this is our main objective. Another objective of the present investigation is to

Table 1. N-2,4-difluorophenyl quinolones used in the present study and their *c*log*P* values, Wiener (W)- and Szeged (Sz) indices (ref. figure 1).
R = substitution at R in figure 1; *c*log*P* = logarithm of partition coefficient (*P*) in octanol–water; W = Wiener index; Sz = Szeged index.

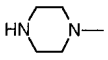
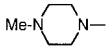
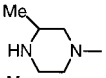
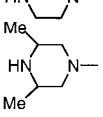
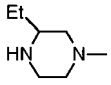
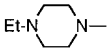
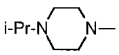
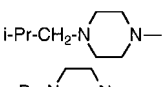
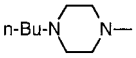
Compound	R	*c*log*P*	W	Sz	Sz/W
I		3·81	2302	4456	1·93571
II		4·67	2302	4456	1·93571
III		3·33	2437	4735	1·94296
IV		4·85	2468	5108	2·06969
V		4·86	2732	5242	1·91874
VI		5·20	2386	4622	1·93713
VII		5·51	2773	5285	1·90588
VIII		6·12	2965	5518	1·86105
IX		6·24	3200	5901	1·84406

Table 2. Correlation matrix for the correlation of *c*log*P* of N-2,4-difluorophenyl quinolones with various parameters used in the present study.
*c*log*P* = logarithm of partition coefficient (*P*) in octanol–water; W = Wiener index; Sz = Szeged index; E_{HOMO} = highest occupied molecular orbital energy, E_{LUMO} = lowest unoccupied molecular orbital energy, δE = energy difference between E_{HOMO} and E_{LUMO}; E_{total} = total π-electron energy, all energies in β units.

	*c*log*P*	W	Sz	E_{HOMO}	E_{LUMO}	E_{total}	δE
*c*log*P*	1·00000						
W	0·86762	1·00000					
Sz	0·84355	0·97050	1·00000				
E_{HOMO}	–0·22464	–0·06078	–0·16381	1·00000			
E_{LUMO}	0·04518	0·23644	0·17733	0·64958	1·00000		
E_{total}	0·96785	0·92913	0·93146	–0·17025	0·16018	1·0000	
δE	–0·33394	–0·28129	–0·36646	0·76213	0·00283	–0·36033	1·0000

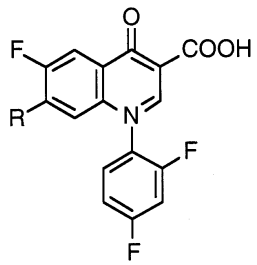


Figure 1. Structure of the quinolones under study.

compare the results obtained from Sz with those obtained from W. The reason for using E_{HOMO} and E_{LUMO} is that, most commonly, the dependence of biological activity on these parameters has been attributed to their being a measure of the ability of a molecule to serve as an electron donor (HOMO) or an electron acceptor (LUMO) in the formation of charge transfer (or electron donor–acceptor) complexes [13]. Dependence on the difference between these two energies may be accounted for by the relationship of this difference to the hardness in the context of hard and soft acids and bases [14,15]. Thus, the use of two types of unrelated parameters give two different types of information in developing QSAR models. The results are discussed below.

2. Computational procedure: Molecular modelling

Prompted by the observation [11] that N-2,4-difluorophenyl quinolones can be used in chemotherapy against *M. tuberculosis*, we studied a group of these quinolones (figure 1).

We studied these quinolones because they and their derivatives exhibit interesting biological and chemical properties which may eventually lead to useful applications. The nine quinolones selected for study are listed in table 1, along with values of the corresponding antitubercular activities (in terms of *c*log*P*), W and Sz. Modifications were allowed only at the C7 position. The size of the derivatives is varied by using different piperazyl and pyrrolidine side chains having varying degrees of alkyl substitution.

Our approach has been to calculate a number of Sz, W and molecular orbital energies, and to test each of these parameters using univariate as well as multivariate regression analyses. A correlation coefficient between 0·8 and 0·9 is considered "good" and values that are higher (> 0·98) are "excellent". Those parameters are retained which have at least good correlation with antitubercular activities and yield physically meaningful regressions. These relationships are then interpreted for their possible significance in formulating interesting models, and subsequently are used to develop multivariate regressions.

(i) Wiener index (W): If d(u, $v|G$) is the distance [16] between the vertices u and v of the graph G (i.e. the number of edges in the shortest path that connects u and v), $V(G)$ is the vertex set of G, then

$$W = W(G) = \frac{1}{2} \sum_{e \in V(G)} \sum_{v \in V(G)} d(u, v|G). \tag{1}$$

For acyclic molecular graphs, Wiener [2] discovered a remarkably simple method for the calculation of W. Let e be an edge of an acyclic molecular graph G (= a tree). Let $n_1(e|G)$ and $n_2(e|G)$ be the number of vertices of G lying on two sides of the edge e. Then

$$W = W(G) = \sum_{e \in E(G)} n_1(e|G) n_2(e|G). \tag{2}$$

Here $E(G)$ denotes the edge set of the graph G.

(ii) Szeged index (Sz): In developing the Sz index, the quantities $n_1(e|G)$ and $n_2(e|G)$ are formally written as follows: Let e be an edge of a graph G (which may contain cycles or be acyclic) connecting the vertices u and v. Define two sets $N_1(e|G)$ and $N_2(e|G)$ as

$$N_1(e|G) = \{x \in V(G) | d(x, u|G) < d(x, v|G)\}, \tag{3}$$

$$N_2(e|G) = \{x \in V(G) | d(x, v|G) < d(x, u|G)\}. \tag{4}$$

The number of elements of $N_1(e|G)$ and $N_2(e|G)$ are denoted by $n_1(e|G)$ and $n_2(e|G)$ respectively. Thus, $n_1(e|G)$ counts the vertices of G lying closer to the vertex u than to vertex v. The meaning of $n_2(e|G)$ is analogous. Vertices equidistant from both ends of the edge uv belong neither to $N_1(e|G)$ nor to $N_2(e|G)$.

The Szeged index of the graph G is defined as:

$$Sz(G) = Sz = \sum_{e \in E(G)} n_1(e|G) n_2(e|G). \tag{5}$$

This generalization (5), was conceived by Gutman at the Attila Jozsef University in Szeged, and we propose that it be called the Szeged index, denoted by Sz [7].

The basic properties of Sz were recently established and it was found to be endowed with interesting and mathematically appealing features [6–11]. In this paper, we point out the potential of Sz in QSAR studies and in modelling the physiological activities of organic compounds acting as drugs i.e. the quinolones.

Table 3. Huckel molecular orbital energies: E_{HOMO}, E_{LUMO}, E_{total} and δE (= E_{HOMO}–E_{LUMO}) values for N-2,4-difluorophenyl quinolones.
E_{HOMO} = energy of highest occupied molecular orbital, E_{LUMO} = energy of lowest unoccupied molecular orbital, δE = energy difference between E_{HOMO} and E_{LUMO}, E_{total} = total π-electron energy, all in β units.

Compound	E_{HOMO}	E_{LUMO}	δE	E_{total}
I	0·5643	–0·0601	0·6248	61·7018
II	0·2303	–0·4528	0·6831	62·3158
III	0·2730	–0·2607	0·5337	62·7178
IV	0·0000	–0·3650	0·3650	63·9273
V	0·5643	–0·0540	0·6183	64·1928
VI	0·5643	–0·0528	0·6171	64·0648
VII	0·0000	–0·0564	0·0564	64·8805
VIII	0·0000	–0·3787	0·3787	66·1204
IX	0·5626	–0·0489	0·6115	66·5975

(iii) E_{HOMO}, E_{LUMO} and E_{total} orbital energies: Along with Sz, frontier orbital energies: the energy of the highest occupied molecular orbital, (E_{HOMO}), the energy of the lowest unoccupied molecular orbital energy (E_{LUMO}), and the total π-electron energy (E_{total}), were also used as molecular parameters for modelling the activities of N-2,4-difluorophenyl quinolones. These energies were calculated from the HMO version 1.1 supplied by Wissner [17]. The data so obtained are recorded in table 3. The values of these energies are given in terms of β.

(iv) Regression analysis: Regression analysis for modelling the activities of N-2,4-difluorophenyl quinolones was carried out using Regress-1 software. The correlation matrix derived from this program is given in table 2. Regression parameters as well as the quality of different monovariate and multivariate correlations are recorded in table 4. The extent of modelling is summarized in table 5.

3. Results and discussion

Renau and coworkers [12,16–18] have reported the effect of changes in the lipophilicity of N-phenyl substituted fluoroquinolones against microbacteria. The issue of penetration of these compounds into microbacteria is important in the design of new antitubercular agents since it is well-known that surface-associated lipids of microbacteria form a transport barrier when compared to the cell wall of true bacteria. They have demonstrated that increasing the lipophilic character of the side chain at C7 may be more important in exhibiting antitubercular activities of the quinolones.

To test the aforementioned possibilities a quantitative model of the structure–activity relation must be found. The choice of the structural parameters is necessarily somewhat arbitrary. However, for the reasons mentioned earlier we have chosen topological indices W and Sz as well as frontier orbital energies. To make correlation calculation possible, carbon–hydrogen suppressed molecular graphs of the quinolones were considered.

It is worthy of mention that higher values of hardness at constant chemical potential indicate higher stability [13–15,19,20]. A perusal of table 2 indicates that HOMO, LUMO orbital energies from this point of view (i.e. E_{HOMO}–E_{LUMO} = δE) do not correlate with the

Table 4. Regression parameters and the quality of correlation of *c*log*P* with Sz, E_{HOMO}, E_{LUMO}, E_{total} and δE in univariate and multivariate regressions for N-2,4-difluorophenyl quinolones.
A, *B* = regression parameters, SD = standard deviation (standard error of estimation), *R* = correlation coefficient, *c*log*P* = logarithm of partition coefficient (*P*) in octanol–water, W = Wiener index, Sz = Szeged index, E_{HOMO} = highest occupied molecular orbital energy, E_{LUMO} = lowest unoccupied molecular orbital energy, δE = energy difference between E_{HOMO} and E_{LUMO}, E_{total} = total π-electron energy, all energies in β units.

Correlation parameters used	Slope A_i i = 1–4	Intercept *B*	SD	*R*	*F*-ratio
W	A = 0·0022	–0·6476	0·4241	0·8676	21·314
Sz	A = 0·0013	–0·6703	0·4581	0·8435	17·269
E_{total}	A = 0·4692	–24·9891	0·2145	0·9679	103·652
W E_{HOMO}	A_1 = 0·0022 A_2 = –0·5233	–0·4181	0·4297	0·8846	10·789
W E_{LUMO}	A_1 = 0·0023 A_2 = –0·7937	–1·0641	0·4323	0·8831	10·628
W δE	A_1 = 0·0021 A_2 = –0·3891	–0·2726	0·4491	0·8727	9·581
W E_{total}	$A_1 = -5{\cdot}821 \times 10^{-4}$ A_2 = 0·5734	–30·1425	0·2179	0·9716	50·630
Sz E_{HOMO}	A_1 = 0·0013 A_2 = –0·2694	–1·4715	0·4882	0·8481	7·686
Sz E_{LUMO}	A_1 = 0·0014 A_2 = –0·5049	–1·9200	0·4851	0·8502	7·824
Sz δE	A_1 = 0·0013 A_2 = –0·1143	–1·5249	0·4942	0·8440	7·427
Sz E_{total}	$A_1 = -6{\cdot}9445 \times 10^{-4}$ A_2 = 0·6669	–34·1581	0·1793	0·9809	76·206
δE E_{total}	A_1 = 0·0679 A_2 = 0·4721	–25·2134	0·2313	0·9680	44·612
W Sz E_{total}	$A_1 = 6{\cdot}7709 \times 10^{-4}$ A_2 = –0·0010 A_3 = 0·6421	–32·6369	0·1861	0·9828	47·335
W E_{HOMO} E_{total}	$A_1 = -5{\cdot}0797 \times 10^{-4}$ A_2 = – 0·1255 A_3 = 0·5567	–29·2286	0·2354	0·9724	28·924
W E_{LUMO} E_{total}	$A_1 = -4{\cdot}2490 \times 10^{-4}$ A_2 = –0·4570 A_3 = 0·5528	–29·3236	0·2193	0·9761	33·644
W δE E_{total}	$A_1 = -6{\cdot}1367 \times 10^{-4}$ A_2 = 0·1277 A_3 = 0·5846	–30·8435	0·2368	0·9721	28·599
Sz E_{HOMO} E_{total}	$A_1 = -6{\cdot}9846 \times 10^{-4}$ A_2 = –0·1942 A_3 = 0·6627	–33·8131	0·1858	0·9828	47·499

contd

Table 4. (*Contd*)

Correlation parameters used	Slope A_i i = 1–4	Intercept B	SD	R	F-ratio
Sz E_{LUMO} E_{total}	$A_1 = 6{\cdot}6051 \times 10^{-4}$ $A_2 = -0{\cdot}4718$ $A_3 = 0{\cdot}6650$	–34·3017	0·1690	0·9859	57·742
Sz δE E_{total}	$A_1 = -6{\cdot}9389 \times 10^{-4}$ $A_2 = 0{\cdot}0061$ $A_3 = 0{\cdot}6670$	–34·1707	0·1964	0·9809	42·337
E_{HOMO} E_{LUMO} E_{total}	$A_1 = 0{\cdot}0996$ $A_2 = -0{\cdot}6350$ $A_3 = 0{\cdot}4824$	–25·9896	0·2264	0·9745	31·444
E_{HOMO} δE E_{total}	$A_1 = -0{\cdot}5354$ $A_2 = 0{\cdot}6350$ $A_2 = 0{\cdot}4824$	–25·9896	0·2264	0·9745	31·444
W Sz δE E_{total}	$A_1 = 7{\cdot}7369 \times 10^{-4}$ $A_2 = -0{\cdot}0011$ $A_3 = -0{\cdot}1048$ $A_4 = 0{\cdot}6367$	–32·2018	0·2065	0·9831	28·855
W E_{LUMO} δE E_{total}	$A_1 = -4{\cdot}5780 \times 10^{-4}$ $A_2 = -0{\cdot}4617$ $A_3 = 0{\cdot}1399$ $A_4 = 0{\cdot}5649$	–30·0829	0·2424	0·9766	20·665
W E_{HOMO} δE E_{total}	$A_1 = -4{\cdot}5780 \times 10^{-4}$ $A_2 = -0{\cdot}4617$ $A_3 = 0{\cdot}6016$ $A_4 = 0{\cdot}5649$	–30·0829	0·2424	0·9766	20·665
E_{HOMO} E_{LUMO} δE E_{total}	$A_1 = 0{\cdot}0996$ $A_2 = -0{\cdot}6350$ $A_3 = -7{\cdot}0000 \times 10^{-15}$ $A_4 = 0{\cdot}4824$	–25·9896	0·2264	0·9745	31·444
W E_{HOMO} E_{LUMO} E_{total}	$A_1 = -4{\cdot}5780 \times 10^{-4}$ $A_2 = 0{\cdot}1399$ $A_3 = -0{\cdot}6016$ $A_4 = 0{\cdot}5649$	–30·0829	0·2424	0·9766	20·665
Sz E_{HOMO} E_{LUMO} E_{total}	$A_1 = -6{\cdot}5682 \times 10^{-4}$ $A_2 = 0{\cdot}0375$ $A_3 = -0{\cdot}5123$ $A_4 = 0{\cdot}6657$	–34·3806	0·1887	0·9859	34·742

antitubercular activities of quinolones. However, moderate collinearities exist between δE and $E_{HOMO.}$ Also, it may be of interest to know the values of the local quantities, like charge, Fukui function or local softness at the active sites of the compounds and how these are related to the activity. However, we could not make such calculations due to unavailability of software. Furthermore, such local counterparts to the topological indices, Wiener or Szeged, are not known.

The data presented in table 2, i.e. the correlation matrix, are important for investigating statistically significant QSAR models as well as the inter-collinearities existing between (i) W and Sz, (ii) W and E_{total}, and (iii) Sz and E_{total}. A good correlation exists between E_{HOMO} and δE.

Table 5. Comparison of estimated *c*log*P* values of the quinolones with those reported in table 1.
Residue = difference between observed and estimated *c*log*P*

		Estimated *c*log*P*					
		I		II		III	
Compound	Obs. *c*log*P*	(7)	Residue	(8)	Residue	(9)	Residue
I	3·81	3·96	–0·15	3·90	–0·09	3·82	–0·01
II	4·67	4·26	0·41	4·33	0·34	4·44	0·23
III	4·33	4·44	–0·11	4·38	–0·05	4·41	–0·08
IV	4·85	5·00	–0·15	4·93	–0·08	5·01	–0·16
V	4·86	5·13	–0·27	5·01	–0·15	4·95	–0·09
VI	5·20	5·07	0·13	5·36	–0·16	5·28	–0·08
VII	5·51	5·45	0·06	5·44	0·06	5·38	0·13
VIII	6·12	6·03	0·09	6·11	0·01	6·21	–0·09
IX	6·25	6·26	–0·01	6·16	0·09	6·11	0·14

Similarly, the correlation matrix shows that high collinearity exists between E_{total} and log*P*; while good collinearity is found between W and log*P* as well as Sz and log*P*. Thus, monoparametric QSAR models are possible with each of these three molecular descriptors i.e. W, Sz and E_{total} and that multiparametric correlations involving these parameters will be statistically significant.

Several univariate as well as multivariate correlations between the structural parameters mentioned above and *c*log*P* are presented in table 4.

As seen from the correlation matrix (table 2), W, Sz and E_{total} are the best suited parameters for univariate correlation analysis. Regression parameters and correlations given in table 4 confirm this finding.

Hence, if *TI* stands for one of the parameters W, Sz or E_{total} then,

$$c\log P = ATI + B, \tag{6}$$

here *A* and *B* represent the corresponding regression coefficients.

A perusal of table 4 indicates that E_{total} is an excellent parameter for correlating *c*log*P* values of the quinolones. Therefore,

$$c\log P = (0{\cdot}4692)E_{total} - 24{\cdot}9894. \tag{7}$$

In bivariate correlation analyses also, the correlations involving E_{total} and W or Sz are found to be excellent. However, bivariate correlations involving Sz were found to be better than those in which W is involved. Excellent correlation (0·9809) is obtained when in bivariate correlation Sz and E_{total} were used. The correlation is expressed as:

$$c\log P = (6{\cdot}9445 \times 10^{-4})\mathrm{Sz} + (0{\cdot}6669)E_{total} - 34{\cdot}1581. \tag{8}$$

An excellent correlation is also obtained in tervariate correlations involving W, Sz and E_{total} on the one hand and Sz , E_{HOMO} and E_{total} on the other. The correlation coefficients in both the cases were found to be approximately the same (0·9828), the standard deviation of the latter (0·1858) was found to be slightly smaller than the standard deviation in the former (0·1861). This indicates that the tervariate correlation: Sz – E_{HOMO} – E_{total} is better than the correlation W – Sz – E_{total}.

It is interesting to note that the tervariate correlation involving $Sz - E_{HOMO} - E_{total}$ (0·9859) is excellent in all the 27 correlations investigated by us. The tetravariate correlation involving $Sz - E_{HOMO} - E_{LUMO} - E_{total}$ has the same correlation potential (0·9859). However, its standard deviation (0·1887) is much higher than the trivariate correlation discussed above (0·1690). This clearly indicates that the antitubercular activity of the quinolones under the present study is excellently modelled by the tervariate correlation. Thus, the correlation expression can be written as:

$$c\log P = (-6{\cdot}6051E \times 10^{-4})Sz - (0.4718)E_{LUMO} + (0.6650)E_{total} - 34.3017. \quad (9)$$

The data presented in table 4 clearly indicate that the quality of correlation increases as we pass from univariate to tetravariate correlations. Also, the results indicate that multiple correlations give better estimates than the univariate correlations and that the multivariate correlations wherein Sz is involved are better than those correlations where W is involved.

As seen from table 4, it is possible to quite accurately estimate the values of *c*log*P* (expressing antitubercular activities) of the quinolones under present study. Thus, using the distance-based topological indices W and Sz as well as molecular orbital energies, it is possible to infer the pharmacological activities of these substances. All the five molecular descriptors (W, Sz, E_{HOMO}, E_{LUMO} and E_{total}) have practically the same predictive ability, the Szeged index (Sz) being slightly better (in multivariate correlations) than the remaining molecular descriptors.

All the tetravariate correlations involving E_{HOMO} and E_{LUMO} have correlation coefficients approximately of the order of 0·9766. This suggests a possibility of charge transfer (CT) from the drug (quinolones) to the receptor. Of greater interest is the fact that the energy difference δE ($= E_{HOMO} - E_{LUMO}$) also gives excellent results in multivariate correlations. This indicates that potency increases with decreasing gap magnitude and a concerted CT is suggested between the drug's (quinolone's) π-HOMO and an unoccupied orbital of the receptor, and the drug's (quinolone's) π-LUMO and an occupied orbital of the receptor.

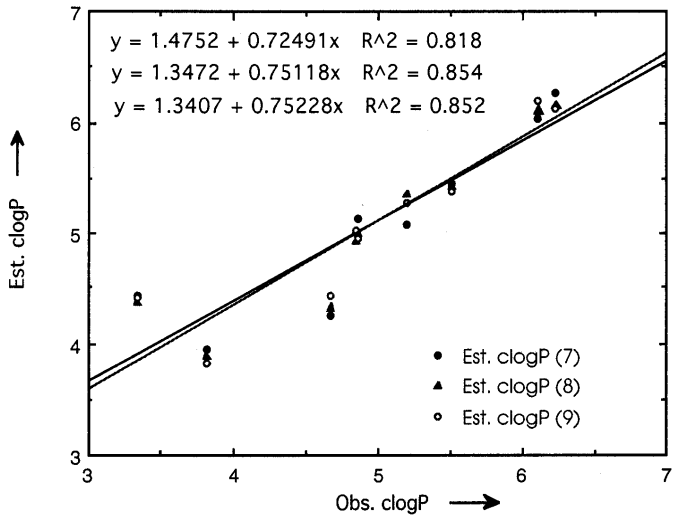


Figure 2. Correlation of observed with estimated *c*log*P*.

Finally, in order to confirm our findings, antitubercular (*c*log*P*) activities predicted by (7), (8) and (9) are compared with the corresponding *c*log*P* values reported in table 1. Such a comparison is shown in table 5. Within experimental error, the values agree well.

Finally, a plot is obtained between the observed and estimated *c*log*P* as shown in figure 2 wherein all the three equations (7), (8) and (9) are used for estimating *c*log*P* respectively. R^2 values (0·818, 0·854, and 0·852) obtained for each of these equations confirm our findings.

4. Conclusion

Analysis of this limited set of quinolone molecules allowed us to build a model of antitubercular activity in which W, Sz, E_{HOMO}, E_{LUMO}, dE and E_{total} are important factors. This, in turn, will help pharmacologists as well as medicinal chemists in the prediction of increased activity and thus the synthesis of hitherto unknown quinolone(s) exhibiting better antitubercular activities than those reported in this paper.

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