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Quantitative Structure Activity Relationship and Biological Activity Studies of 4-Methyl-2-(4-substituted phenyl)quinoline Derivatives

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Quantitative structure activity relationship (QSAR) studies of some 4-methyl-2-(4-substituted phenyl)quinoline derivatives were carried out to determine their predicted biological activities. Numbers of descriptors were tested to adjudge a quantitative correlation between activity and structural features using training set and test set. Significant correlation was observed between activities and descriptors. The results were interpreted on the basis of linear regression analysis. Experimental antibacterial activities of the test set compounds were determined. The predicted biological activities generated by QSAR model were compared with the experimental antibacterial activities. The concurrence between the predicted and experimental biological activities validates the QSAR model. Thus, it can be concluded that the model under the present investigation can be applied for predicting the unknown biological activities of structurally similar molecules.

Keywords: Quantitative structure activity relationship, Quinoline derivatives, Biological activity.

INTRODUCTION

Quinoline and its derivatives are the important scaffold of biologically active compounds present in nature [1-6]. Many heterocyclic units contain quinoline scaffold as an integral part and show antiviral [7], antimalarial [8-10], antibacterial [8-13] and anticancer activities [14]. Conventional methods for the synthesis of quinoline and its derivatives reported in the literature include Skraup [15], Doebner-Von Miller [16], Friedlander [17] and Combes synthesis. Newer synthetic methods like microwave assisted organic synthesis [18] have come into play since the conventional methods suffer from drawbacks such as drastic conditions, use of hazardous chemicals and poor yield. The test set quinoline molecules under the present investigation have been synthesized by one pot microwave assisted organic synthesis approach which offer advantages like quick reaction time and improved yields.

Even after the synthesis of the potential drug molecule, one needs to test the biological efficacy of the molecule. The most difficult problem in the development of molecules as drug is the time and expenses involved in the development of the drug. It is reported that a single successful drug molecule takes nearly 14 to 16 years of research and clinical trial and that to at tremendous cost. The cost of more than 800 million dollars is expected to prove a molecule as the drug, which itself is a great problem for developing countries.

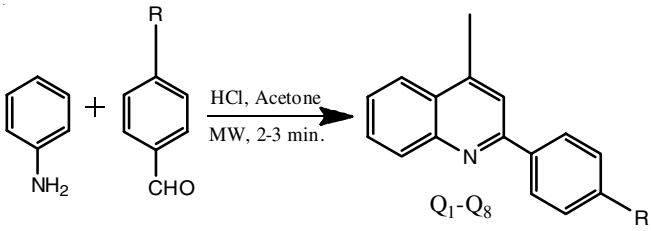
Quantitative structure activity relationships (QSARs) signifies computerized statistical method which correlates the activity of the compound with changes in the structure. The biological activity of compounds is considered as a function of various physico-chemical parameters. The biological activity can be optimized by choosing such substituents which would enhance desired physico-chemical properties. Agrawal *et al.* [19-28] have reported QSAR studies on different organic drug compounds.

QSAR deals the relationship of magnitude of various structural properties with the biological activity. Compounds which have similar structures to a pharmacologically active drug themselves are often biologically active. Even though the activity of these compounds may be either similar to that of the original compound but may differ in potency and may have unwanted side effects. The activity may completely differ from the original compound. These structurally related activities are commonly referred to as structure-active relationship (SAR) [29]. The mathematical and statistical analysis of QSAR data finally helps to reduce the number of molecules for study with respect to potent biological activity.

EXPERIMENTAL

All the chemicals/reagents used in this investigation were of chemically pure or analytical reagent grade. A number of quinoline derivatives were synthesized in accordance with the

Scheme-I. The structures of the derivatives were confirmed with ^{1}H NMR, IR and mass spectroscopy. The synthesised quinoline derivatives were used as test set for the calculation of antibacterial activities. The physico-chemical data of the synthesized compounds are given in Table-1.



Scheme-I: Synthesis of test set quinoline derivatives

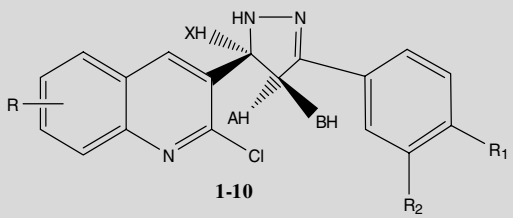
TABLE-1
SYNTHESIZED QUINOLINE DERIVATIVES WITH THEIR YIELDS AND MELTING POINTS

Compound	R	m.f.	Yield (%)	m.p. (°C)
Q_1	H	$C_{16}H_{13}N$	79	177-179
Q_2	CH_3	$C_{17}H_{15}N$	74	183-185
Q_3	OCH_3	$C_{17}H_{15}NO$	73	224-227
Q_4	OH	$C_{16}H_{13}NO$	77	288-290
Q_5	NO_2	$C_{16}H_{12}N_2O_2$	72	237-239
Q_6	Cl	$C_{16}H_{12}ClN$	86	218-221
Q_7	Br	$C_{16}H_{12}BrN$	87	248-252
Q_8	COOH	$C_{17}H_{13}NO_2$	76	360-362

QSAR studies

Generation of training set: The training set was constructed using a series of substituted quinoline based compounds as per literature method [30,31]. A total 30 molecules with different substitution on the quinoline scaffold were selected as training set with their known biological activities against bacteria and fungi. The biological activity data were in the form of reported zone of inhibition (ZOI) in millimetres. The details of the structure are given in Tables 2 and 3.

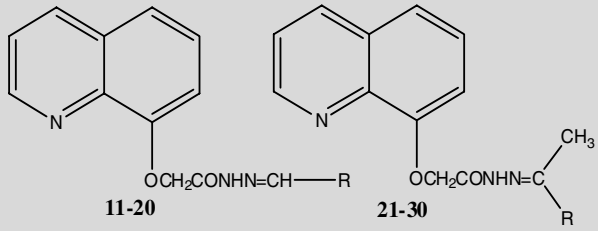
TABLE-2
COMPOSITION OF TRAINING DATA SET MOLECULES FROM 1-10



1-10

Compound No.	R	R^1/R^2
1	H	Cl
2	6-CH_3	Cl
3	7-CH_3	Cl
4	8-CH_3	Cl
5	6-OCH_3	Cl
6	H	OCH_3
7	6-CH_3	OCH_3
8	7-CH_3	OCH_3
9	8-CH_3	OCH_3
10	6-OCH_3	OCH_3

TABLE-3
COMPOSITION OF TRAINING SET MOLECULES FROM 11-30



11-20 **21-30**

Compound No.	R-CHO	Compound No.	R-$COCH_3$
11	C_6H_5	21	C_6H_5
12	*p*-Cl	22	*p*-Cl
13	*p*-OCH_3	23	*p*-OCH_3
14	*p*-CH_3	24	*p*-CH_3
15	*p*-$(CH_3)_2N$	25	*m*-NO_2
16	*o*-Cl	26	*p*-NO_2
17	*m*-Br	27	*p*-NH_2
18	*p*-OH	28	*p*-Br
19	*m*-OH	29	*p*-OH
20	*p*-Br	30	*o*-OH

Descriptor calculation: Datawarrier software [32] was used to calculate the various physico-chemical descriptors like constitutional, molecular, steric and electronic. The details of descriptors used to develop the model are listed Table-4 and the descriptors calculated for the training set compounds are given in Table-5.

TABLE-4
DESCRIPTORS USED FOR TRAINING AND TEST SET MOLECULES

Descriptor used	Symbol
Total molecular weight in g/mol; natural abundance	TMW
c log P; P; conc. (octanol)/conc. (water)	c log P
Total surface area (from polar and non-polar SAS approximation)	TSA
Drug likeness	Drug
Lipophilic ligand efficiency (LLE)	LLE
Ligand efficiency lipophilic price (LELP)	LELP
Molecular shape index	MSI
Rotatable bond count	RBC

Regression analysis: The linear regression was performed by using the software SPSS by stepwise method [33]. The best model derived from the regression analysis was used to predict the biological activity of the synthesised compounds. No outliers have been determined and the equations were derived using the entire training data set (n = 30). The resulting models are depicted in eqns. 1-3 and the derived equations as generated by the QSAR model were then used to calculate the predicted antibacterial activities.

QSAR model for *E. coli*

Biological activity = (-9.462) + (-0.001*TMW) + (6.281* c log P) + (0.06*TSA) + (-0.068*Drug) + (-4.581*MSI) + (0.872*RBC) (1)

QSAR model for *S. aureus*

Biological activity = (2.96) + (0.001* TMW) + (-3.636* c log P) + (-0.037*TSA) + (0.012*Drug) + (19.186* MSI) + (-1.303* RBC) (2)

TABLE-5
VALUE OF DESCRIPTORS CALCULATED FOR THE TRAINING SET COMPOUNDS

Compound No.	TMW	c log P	TSA	Drug	LLE	LELP	MSI	RBC
1	376.673	5.3854	259.83	1.8974	3.6146	10.4680	0.58333	2
2	390.700	5.7293	272.09	1.8000	2.9697	12.0020	0.56000	2
3	390.700	5.7293	272.09	1.8000	2.7936	12.2500	0.60000	2
4	390.700	5.7293	272.09	1.8000	2.6686	12.4320	0.56000	2
5	406.699	5.3154	282.09	1.7961	2.9856	12.1360	0.57692	3
6	367.835	4.0334	273.51	1.7961	4.1884	9.2973	0.57692	4
7	381.862	4.3773	285.77	1.7352	3.7776	10.5640	0.55556	4
8	381.862	4.3773	285.77	1.7352	3.7196	10.6400	0.59259	4
9	381.862	4.3773	285.77	1.7352	3.6685	10.7070	0.55556	4
10	397.861	3.9634	295.77	1.7961	4.0366	10.1120	0.57143	5
11	305.336	3.0925	244.11	4.1966	4.8661	6.5145	0.65217	5
12	339.781	3.6985	259.53	4.2278	4.2223	8.1687	0.66667	5
13	335.362	3.0225	266.37	4.2013	4.8636	6.9844	0.68000	6
14	319.363	3.4364	256.37	4.1258	4.4175	7.6545	0.66667	5
15	348.405	2.9889	278.93	4.9362	4.8350	7.2401	0.65385	6
16	339.781	3.6985	259.53	4.2278	4.0974	8.2996	0.62500	5
17	384.232	3.8177	262.74	2.4066	3.9519	8.5961	0.62500	5
18	321.335	2.7468	250.46	4.1816	4.9979	6.2046	0.66667	5
19	321.335	2.7468	250.46	4.1816	4.9744	6.2235	0.62500	5
20	384.232	3.8177	262.74	2.4066	3.8813	8.6749	0.66667	5
21	319.363	3.0304	254.58	3.1347	4.6474	6.9049	0.62500	5
22	353.808	3.6364	270.00	3.1884	4.0212	8.6537	0.64000	5
23	349.389	2.9604	276.84	3.1842	4.6779	7.3453	0.65385	6
24	333.390	3.3743	266.84	3.1347	4.2455	8.0698	0.64000	5
25	364.360	2.1088	278.25	-1.9440	5.4933	5.4595	0.59259	6
26	364.360	2.1088	278.25	-1.9440	5.4762	5.4717	0.62963	6
27	334.378	2.3531	263.10	3.1166	5.2155	5.6656	0.64000	5
28	398.259	3.7556	273.21	1.3447	3.7972	9.0613	0.64000	5
29	335.362	2.6847	260.93	3.1430	4.8529	6.4906	0.64000	5
30	335.362	2.6847	260.93	3.1430	4.8382	6.5033	0.60000	5

QSAR model for *P. aeruginosa*

Biological activity = (28.883) + (-0.03* TMW) + (2.502* c log P) + (0.028*TSA) + (-0.236*Drug) + (-7.08*MSI) + (0.991*RBC) (3)

The predicted and experimental antibacterial activities are depicted in Table-5 and represented graphically in Fig. 1.

***in vitro* Antimicrobial activity**: The *in vitro* antibacterial activities of 2,4-substituted quinoline derivatives have been investigated against three strains of bacteria. Nutrient agar media was employed for the bacterial growth. Bacterial plate was incubated at 37 ºC for 24 h. Three microbial strains *viz*. *E. coli*, *S. aureus* and *P. aeruginosa* were used in antimicrobial assay. Streptomycin was used as standard. Most of the synthesised compounds were tested for their antimicrobial potency as compared to reference drug within a MIC range of 25-50 µg/mL. The screening results are tabulated in Table-6.

RESULTS AND DISCUSSION

A series of 4-methyl-2-(4-substituted phenyl)quinoline derivatives (**Q1-Q8**) have been successfully synthesized. The purity of the synthesized compounds was established by TLC and determination of the melting points. The structures of the synthesised compounds were elucidated by IR, ^{1}H NMR and mass spectral data. The synthesized compounds were screened for their antibacterial activities by cup method against various strains of gram positive and gram negative bacteria. All the derivatives were significantly active against *E. coli*. None of the derivative has shown profound activity against *S. aureus* whereas all quinoline derivatives have shown significant activity against *P. aeruginosa*.

Conclusion

4-Methyl-2-(4-substituted phenyl)quinoline derivatives have shown remarkable anti biological activities. QSAR studies

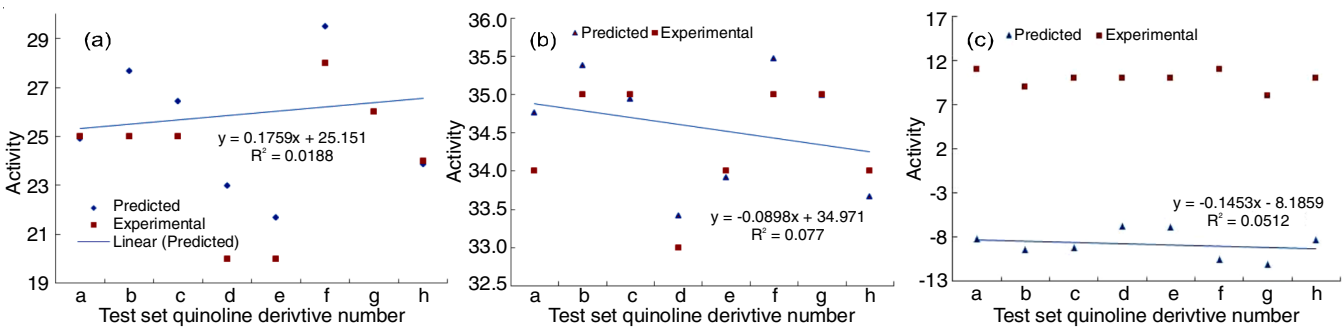


Fig. 1. Predicted and experimental biological activities of test set quinoline compounds (a) *E. coli*, (b) *P. aeruginosa*, (c) *S. aureus*

TABLE-6
ANTIBACTERIAL SCREENING OF THE SYNTHESIZED QUINOLINE DERIVATIVES

Compound	Diameter of zone of inhibition (mm)					
	E. coli		*S. aureus*		*P. aeruginosa*	
	Predicted	Experimental	Predicted	Experimental	Predicted	Experimental
Q_1	24.90	25	-8.27	11	34.76	34
Q_2	27.68	25	-9.52	9	35.38	35
Q_3	26.43	25	-9.28	10	34.94	35
Q_4	22.98	20	-6.79	10	33.42	33
Q_5	21.66	20	-6.89	10	33.91	34
Q_6	29.48	28	-10.57	11	35.47	35
Q_7	30.51	26	-11.10	8	34.99	35
Q_8	23.87	24	-8.32	10	33.66	34
Streptomycin	25		24		28	

performed on these compounds have revealed that descriptors used to generate the model correlates the structure with biological activity significantly. QSAR studies revealed that the hydrophobic parameter *i.e*. partition coefficient corroborated towards the enhanced biological activity except against *S. aureus*. The concordance between QSAR predicted and experimental antibacterial activities validates the constructed QSAR model. For *S. aureus*, some different descriptors seems to plays important roles as the generated QSAR model predicts negative biological activity.

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