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QSAR Studies of Some 4-(Substituted)-Phenoxy-2-(4-Methyl-1-Piperazinyl)Quinazolines as Anticonvulsive Agents

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4-(Substituted)-phenoxy-2-(4-methyl-1-piperazinyl)quinazolines are reported to possess anticonvulsive properties. Therefore, QSAR studies were undertaken so as to evaluate the influence of the various physicochemical parameters on their biological activity, taking negative logarithmic value of effective dose (log $1/ED_{50}$) as dependent and different physicochemical and structural parameters (log P, MR and Dip-X) as independent variables. The results indicate that dipole moment (Dip-X, electronic factor) and log P (hydrophobic factor) contribute significantly in imparting the biological activity ($R = 0.85$, $F = 10.39$, $R^2_{cv} = 0.629$).

Key Word: QSAR studies, Substituted quinazolines.

INTRODUCTION

Quinazoline derivatives are known to be biologically versatile compounds. There are several reports on the biological activities of 2-(4-methyl-1-piperazinyl) quinazolines[1–4]. Some of them showed central nervous system activities. 4-(Substituted) phenoxy-2-(4-methyl-1-piperazinyl)quinazolines are reported to have the anticonvulsive properties[5]. There are several reports on QSAR studies of quinazoline derivatives[6–9]. In the present study, the structural features of drug molecules are quantified in terms of different parameters such as lipophilicity, electronic and steric which are correlated to biological data of congeneric structures using linear regression techniques to estimate the relative importance of structural features contributing to the biological effect, were undertaken for establishing structure-activity relationship quantitatively. A statistically sound QSAR regression equation can be used for lead optimization.

QSAR studies were undertaken on a number of 4-(substituted)-phenoxy-2-(4-methyl-1-piperazinyl)quinazolines[5] (Fig. 1) for their anticonvulsive activity so as to evaluate the influence of the physicochemical parameters on their biological activity. The structure of the compounds along-with their biological data and physicochemical parameters are reported in Table-1.

RESULTS AND DISCUSSION

From the listed compounds (Table-1), the softwares (MS Excel and SPSS) produced the mono-parametric QSAR equations using the data set and multi-parametric QSAR equations (Table-2). In QSAR equations, log $1/ED_{50}$ is the negative

logarithmic value of effective dose (ED_{50} on molar basis), n is the number of data points used in deriving the equation, R is the correlation coefficient, s is the standard deviation and F is ratio between the variances of calculated and observed activities (Table-2). Cross-validated parameters, PRESS (predicted residual sum of squares) and R^2_{cv} (cross-validated correlation coefficient) were also included in the Table-2, which determines the prediction power for the data not included in deriving the model and evaluate the model externally to avoid chance correlation completely. The predicted biological activity is given in Table-3.

TABLE-1
QSAR PARAMETERS AND BIOLOGICAL ACTIVITY OF THE 4-SUBSTITUTED PHENOXY-2-(4-METHYL-1-PIPERAZINYL) QUINAZOLINES

S. No.	R	ED_{50} (mg/kg)	$\log\left(\frac{1}{ED_{50}}\right)^a$	log P[b]	MR[c]	Dip-X[d]
1.	—H	20	4.20	4.19	95.78	1.68
2.	3-Cl	31	4.06	4.71	100.58	1.49
3.	4-Cl	31	4.06	4.71	100.58	2.93
4.	4-F	31	4.04	4.33	96.00	2.85
5.	3-OCH_3	20	4.24	3.94	102.24	1.59
6.	4-OCH_3	31	4.05	3.94	102.24	1.60
7.	3-CF_3	35	4.05	5.07	101.82	2.25
8.	4-CH_3	27	4.09	4.66	100.82	1.64
9.	4-$NHCOCH_3$	71	3.73	3.04	108.86	4.55
10.	3,4-Cl_2	41	3.98	5.22	105.39	2.79
11.	3-CH_3, 4-Cl	35	4.02	5.17	105.63	2.96

[a] Negative logarithm of effective dose ED_{50} on a molar basis.
[b] Logarithm of partition coefficient.
[c] Molar refractivity. [d] Dipole moment (X-axis)

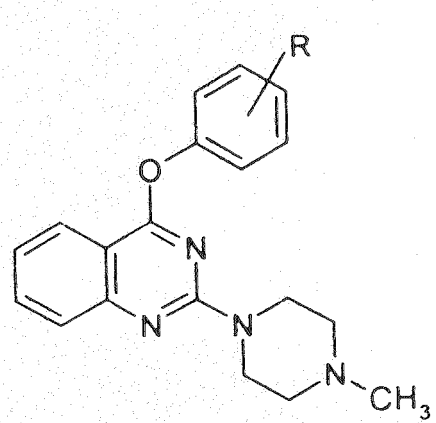

Fig. 1. General structure for quinazolines

TABLE-2
STATISTICALLY SIGNIFICANT QSAR MODELS

Eq. No.	Regression equation	Regression parameters				PRESS	R^2_{cv}
		n	R	R^2	F		
1	log 1/ED_{50} = 0.0597 (± 0.063) log P + 3.781 (± 0.284)	11	0.300	0.1306	0.892	0.42	–1.060
2	log 1/ED_{50} = –0.0228 (± 0.08) MR + 6.364 (± 0.828)	11	0.682	0.1001	7.842	0.18	0.135
3	log 1/ED_{50} = –0.117 (± 0.0245)Dip-X + 4.328 (± 0.063)	11	0.847	0.0727	22.898	0.48	0.478
4	log 1/ED_{50} = 0.04209 (±0.05) log P – 0.0218 (± 0.008) MR + 6.079 (± 0.906)	11	0.714	0.1017	4.157	0.37	–0.808
5	log 1/ED_{50} = 0.0134 (± 0.039) log P – 0.115 (±0.027) Dip-X + 4.262 (± 0.201)	11	0.850	0.0765	10.390	0.076	0.629
6	log 1/ED_{50} = –0.0098 (± 0.007) MR – 0.094 (± 0.028) Dip-X + 5.267 (± 0.658)	11	0.881	0.0688	13.820	0.23	–0.104

TABLE-3
OBSERVED AND CALCULATED BIOLOGICAL ACTIVITY

S. No.	Observed	Calculated from					
		Eq. 1	Eq. 2	Eq. 3	Eq. 4	Eq. 5	Eq. 6
1.	4.20	4.03	4.180	4.130	4.167	4.125	4.170
2.	4.06	4.06	4.075	4.153	4.085	4.154	4.141
3.	4.06	4.06	4.075	3.984	4.085	3.988	4.006
4.	4.04	4.04	4.180	3.994	4.168	3.992	4.116
5.	4.24	4.02	4.040	4.141	4.016	4.132	4.116
6.	4.05	4.02	4.040	4.140	4.016	4.131	4.115
7.	4.05	4.08	4.047	4.064	4.073	4.071	4.058
8.	4.09	4.06	4.070	4.136	4.077	4.136	4.125
9.	3.73	3.96	3.890	3.794	3.834	3.780	3.772
10.	3.98	4.09	3.966	4.001	4.001	4.011	3.972
11.	4.02	4.09	3.960	3.980	3.994	3.991	3.954

log P is the logarithmic value of the partition coefficient, which represents the hydrophobicity. Molar refractivity (MR) is a measure of steric bulk of molecules. Dipole moment reflects the strength and orientation behaviour of a molecule in electrostatic field. Equations reveal negative correlation of X-components of dipole moment of the molecules (Dip-X).

The significance of the QSAR equations were evaluated statistically with regard to their R, R^2, F and cross validated parameters, PRESS and R^2_{cv}. In mono-parametric QSAR equations (1 to 3), equation 3 was found to be highly

significant due to the higher R, R^2 and R^2_{cv}, highest F and lower PRESS value, indicating that electronic parameter has significant influence on the biological activity. Equation 2 also indicates that molar refractivity (steric parameter) influences the biological activity (R = 0.68, F = 7.84), but R^2_{cv} is less as compared to Eq. 3.

Multi-parametric QSAR equations 4–6 derived by taking log $1/ED_{50}$ as dependent and log P, MR; log P, Dip-X; and MR, log P as independent variables respectively. Multi-parametric QSAR equation 5, in which hydrophobic (log P) and electronic (Dip-X) parameters are correlated with the biological activity, was found to be highly significant due to the highest R, R^2 and R^2_{cv}, higher F and lowest PRESS value, indicating that hydrophobic as well as electronic parameters have significant influence on the biological activity. Thus, the present study clearly indicates that the physicochemical properties are necessary for the drug to impart the biological activity.

The correlation coefficient value R is more in equations 4–6 as compared to the mono parametric equation. In multi parametric QSAR equations 4–6, Eq. 5 has the highest correlation coefficient value R = 0.85, lowest standard deviation s = 0.076 with statistical significance value F = 10.39. Equation 5 has the highest cross-validated correlation coefficient (R^2_{cv}) among the multi-parametric QSAR equations 4–6 and the mutual correlation coefficient value is also less (Table-4). This clearly indicates the significance of hydrophobic (log P) and electronic parameter (Dip-X) in imparting the biological activity. The negative cross-validated correlation coefficient values (R^2_{cv}) for equations 1, 5 and 6 suggest that these equations are statistically insignificant.

TABLE-4
CORRELATION MATRIX FOR THE DESCRIPTORS USED IN EQ. 1-6

	log $1/ED_{50}$	log P	MR	Dip-X
log $1/ED_{50}$	1			
log P	0.300	1		
MR	0.680	0.136	1	
Dip-X	0.847	0.280	0.573	1

EXPERIMENTAL

A data set of 11 molecules has been taken from published results[5]. The structure and biological data of 4-(substituted)-phenoxy-2-(4-methol-1-piperazinyl) quinazolines along with their corresponding biological activity data for QSAR analysis are given in Table-1. For QSAR studies the software Hyperchem 7.5 (evaluation) was used for calculating the QSAR parameters. Using the MS Excel and SPSS software, statistical studies were done. Structures of compounds were sketched using Hyperchem. Every structure was subjected to geometry optimization process (min RMS gradient 0.10) using the MM^+ force field and Steepest Descent and Fletcher-Reeves (Conjugate gradient) algorithms.

QSAR studies in 4-(substituted)-phenoxy-2-(4-methyl-1-piperazinyl) quinazolines have been carried out by taking biological activity (log $1/ED_{50}$) as dependent

and different physico-chemical and structural parameters (log P, MR and Dip-X) as independent variables on Zenith PC using MS Excel 2000 and SPSS software (version 10.0). Mono and multi-parametric regression analysis was carried out for statistical studies to obtain sensitive and significant results. The correlation was established between different physico-chemical parameters like hydrophobic (log P), steric (MR) and electronic (Dip-X) as independent variables and biological activity (log $1/ED_{50}$) as dependent variable.

Regression analysis was used to generate QSAR equations (mono and multi-parametric). Statistical measures used are: n = number of samples in the regression, R = correlation coefficient, R^2 = squared correlation coefficient (coefficient of determination), s = standard deviation, F-test (Fischer's value) for statistical significance and correlation matrix to show mutual correlation among the parameters (Table-4). The ± data within parentheses represents standard error of coefficient.

Cross-validation was performed by using the common leave-one-out (LOO) method[10, 11]. In this method, one object (one biological activity value) is eliminated from the training set and a model is derived from the residual compounds. This model is used to predict the biological activity value of the compound, which was not included in the model. The cross-validation cycle is repeated until each compound has been excluded and predicted exactly once.

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