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A quantitative structure-activity relationship study of novel, potent, orally active, selective VEGFR-2 and PDGFRα tyrosine kinase inhibitors: Derivatives of *N*-Phenyl-*N′*-{4-(4-quinolyloxy)phenyl}urea as antitumor agents

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Abstract

The tyrosine kinase inhibitory action of the derivatives of *N*-Phenyl-*N′*-{4-(4-quinolyloxy)phenyl}urea is quantitatively analyzed using multiple regression analysis. The analysis has helped to ascertain the role of different substituents in explaining the observed inhibitory actions of these compounds for two receptors, namely vascular endothelial growth factor receptor 2 (VEGFR-2) and platelet-derived growth factor receptor α (PDGFRα). From a derived significant correlation equation for inhibition of VEGFR-2, it was concluded that a less hydrophobic molecule with *ortho*-substituent(s), exerting less steric hindrance and *para*-substituent devoid of hydrogen-bond acceptor property augment the inhibition action. Besides, a 3-substituent transmitting a higher negative field effect is advantageous to improve the pIC_{50} value of a compound. The correlation equation, derived for the inhibition of PDGFRα, has revealed that a less hydrophobic molecule, having a 3-substituent which transmits a more negative resonance effect, is helpful in raising its activity. Likewise, in the middle phenyl ring, absence of a fluoro substituent augments the inhibitory activity. Based on derived QSAR equations pertaining to VEGF-2 and PDGFα receptors, the drawn guidelines for selection of substituents, may be used to synthesize potent compounds in future.

Keywords: N-*Phenyl*-N′-*{4-(4-quinolyloxy)phenyl}urea derivatives, VEGF-2 receptor, PDGFα receptor, QSAR, physicochemical properties, tyrosine kinase inhibitors*

Introduction

Angiogenesis play an important role in the growth of most solid tumors and the progression of metastasis [1,2]. Recently, it was reported that the growth of many types of solid tumors is suppressed by the specific inhibition of tumor-induced angiogenesis and thus it may prove a novel therapeutic approach against such tumors [3–5]. The vascular endothelial growth factor (VEGF) is a key angiogenic agent, which is secreted by malignant tumors, which induces the proliferation and the migration of vascular endothelial cells [6–10]. A number of compounds inhibiting the biological effect of VEGF has been reported and have been evaluated in a clinical trial. These include, antibodies to VEGF [11] or its receptor [12], small molecule receptor tyrosine kinase inhibitors [13,14] such as the 3-substituted indolinones [15–18], the 4-anilino- quinazolines [19–22] and the anilinophthalazines [23,24]. The latter studies have shown that an antiVEGF antibody exhibits significant effects in patients with colon and renal cancers [25,26].

More recently, a synthetic study was performed [27] with a view to find novel tyrosine kinase inhibitors for VEGF receptor 2 (VEGFR-2). Such inhibitors were identified through the screening with in-house compounds, which were synthesized earlier as platelet-derived growth factor receptor (PDGFR) tyrosine kinase inhibitors [28–31]. The inhibitory activities of these compounds for VEGFR-2 and PDGFRα phosphorylations were estimated through cell-based assay. The concentration of a molecule required to bring

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out 50% inhibition of the receptor concerned was expressed as IC_{50}. The initial structure-activity relationship (SAR) study on these compounds was, however, directed only to alteration of the substituents at different positions of the structure but no rationale was provided to reduce the trial-and-error factors. Hence, a quantitative SAR (QSAR) on these analogues has been performed since QSAR not only provides the rationale for drug design but also illuminates their plausible mechanism of action at the molecular level.

Materials and methods

The QSAR analysis was carried out on a reported series [27] comprising of the derivatives of *N*-Phenyl-*N'*-{4-(4-quinolyloxy)phenyl}urea. These compounds, having the general structure shown in Figure 1, along with their biological effects for VEGFR-2 and PDGFRα are compiled in Table I. The biological effects, evaluated by cell-based assay and measured as IC_{50} for the two receptors, are expressed on the negative logarithmic scale, pIC_{50}, on a molar basis. The suitable quantifying parameters, used to derive final equations, are only listed in this Table. Amongst them, the partition parameter, *P*, the measure of hydrophobicity of the molecule, was calculated as Clog*P* using ChemDraw software [32]. Whereas the physicochemical parameters, the Taft's steric, *Es*, resonance, *R*, hydrogen-bond acceptor, *HA* are taken from the literature [33–35] and are given in Table I along with an indicator variable, reflecting upon some special structural feature present in the compounds. The subscripted numerals associated to the descriptors represent the varying positions in the titled compounds. The multiple regression analysis (MRA), employing the method of least squares, is used to derive significant correlation equations to ascertain the predictive power of the study and to explore the possible mode of action. The derived significant QSAR equations were further validated by the leave-one-out (LOO) method [36]. This method is frequently employed for internal validation of a statistical model equation. The derived parameter q^2, from LOO, then accounts for the predictivity or more precisely the robustness of the model. The method has been discussed briefly in one of our earlier publications [37].

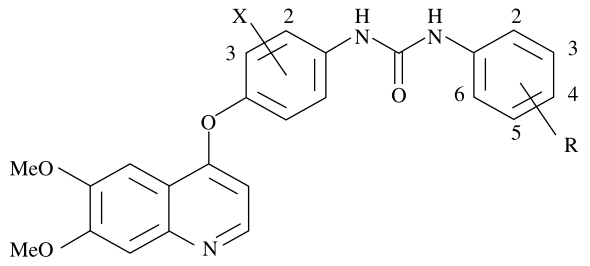

Figure 1. The derivatives of *N*-Phenyl-*N'*-{4-(4-quinolyloxy) phenyl}urea.

Results and discussion

Table I lists the compounds where the alteration in substituents occurred at the middle and terminal phenyl rings attached to the two ends of the urea moiety. To account for the effects produced by different substituents, a large number of descriptors related to hydrophobic, electronic and steric interactions were initially examined for the varying positions of both phenyl rings. In the preliminary attempt, the selected parameters for various substituents for varying positions were hydrophobicity, π, hydrogen-bond donor or acceptor, *HD* or *HA*, electronic (*meta* and *para*), σ, field, *F*, resonance, *R*, dipole moment, μ, Taft's steric, *Es*, molar refraction, *MR*, molecular weight, *MW* and van der Waals volume, V_w. This resulted into a large number of QSAR equations, which were then subjected to different statistical tests. The correlation equations, which returned the highest correlation coefficient, *r* and *F*-statistic and lowest standard deviation, *s* were finally retained for further discussion. The inhibition activity for VEGFR-2 correlating different quantifying parameters is finally shown in Equation (1) and its development steps [(i) – (iii)] are given in Table II.

$$\begin{aligned} \mathrm{p}IC_{50}(\mathrm{VEGFR}-2) = & 12.852 \\ & - 0.589(\pm 0.17)\mathrm{C}\log P \\ & + 0.789(\pm 0.16)Es_2 \\ & - 1.085(\pm 0.44)\mathrm{F3} \\ & - 1.017(\pm 0.34)HA_4 \\ & + 1.279(\pm 0.43)Es_6 \\ n = 29, r = 0.933, s = & 0.254, \\ F(5,23) = 30.772, q^2 = & 0.752 \end{aligned} \quad (1)$$

In the above and subsequent correlation equations, *n* is the number of data points, *F* is the *F*-ratio between the variances of calculated and observed activities, and the ± data within the parentheses are the 90% confidence intervals. Except the parameter, Clog*P* which was calculated for the whole molecule, the remaining quantifying parameters of Equation (1) stand for R-substituents of the terminal phenyl ring. From this equation it appears that the 2- and 6-substituents exert steric hindrance, the 3-substituents are involved in electronic interactions and the 4-substituents are engaged in hydrogen-bond acceptor interaction. Besides other interactions, the Clog*P*, accounting for hydrophobicity of a molecule appears to play an important role in the inhibition action. The statistical parameters of Equation (1), are sound enough to indicate significant results as the r^2 value accounts for 86% of the variance in the observed activities and 99% level of significance

Table I. QSAR parameters and inhibitory activities of *N*-Phenyl-*N'*-{4-(4-quinolyloxy) phenyl}urea derivatives for VEGFR-2 and PDGFRα (see Figure 1 for structures).

										pIC_{50}(M)[a]		
										VEGFR-2		PDGFRα
S. No.	X	R	Clog*P*	Es_2	F_3	R_3	HA_4	Es_6	I_X	Obsd	Cald Eq(1)	Obsd	Cald Eq(3)
1	H	H	5.233	0.00	0.00	0.00	0	0.00	0	9.70	9.77	8.44	8.41
2	H	2-OMe	5.336	−0.55	0.00	0.00	0	0.00	0	9.70	9.27	8.24	8.33
3	H	3-OMe	5.336	0.00	0.26	−0.51	0	0.00	0	> 9.00[b]	–	8.70	8.73
4	H	4-OMe	5.336	0.00	0.00	0.00	1	0.00	0	8.96	8.69	8.36	8.33
5	H	2-Me	5.172	−1.24	0.00	0.00	0	0.00	0	8.64	8.82	8.44	8.46
6	H	3-Me	5.732	0.00	−0.04	−0.13	0	0.00	0	9.70	9.52	8.48	8.14
7	H	4-Me	5.732	0.00	0.00	0.00	0	0.00	0	9.30	9.47	7.44[c]	8.04
8	H	2-NO_2	5.624	−2.52	0.00	0.00	0	0.00	0	7.72	7.55	8.17	8.12
9	H	3-NO_2	5.624	0.00	0.67	0.16	0	0.00	0	8.96	8.81	7.74	8.00
10	H	4-NO_2	5.624	0.00	0.00	0.00	1	0.00	0	8.25	8.52	7.77	8.12
11	H	2-F	5.228	−0.46	0.00	0.00	0	0.00	0	9.30	9.41	8.41	8.41
12	H	3-F	5.678	0.00	0.43	−0.34	0	0.00	0	8.92	9.04	8.19	8.34
13	H	4-F	5.678	0.00	0.00	0.00	0	0.00	0	9.40	9.51	8.24	8.08
14	H	3-Cl	6.248	0.00	0.41	−0.15	0	0.00	0	8.80	8.72	7.62	7.77
15	H	4-Cl	6.248	0.00	0.00	0.00	0	0.00	0	9.70	9.17	8.00	7.66
16	H	2,3-F_2	5.407	−0.46	0.43	− 0.34	0	0.00	0	9.15	8.84	8.80	8.54
17	H	2,4-F_2	5.477	−0.46	0.00	0.00	0	0.00	0	9.15	9.26	8.47	8.23
18	H	2,5-F_2	5.477	−0.46	0.00	0.00	0	0.00	0	9.40	9.26	8.33	8.23
19	H	2,6-F_2	5.027	−0.46	0.00	0.00	0	−0.46	0	8.74	8.94	8.46	8.56
20	H	3,4-F_2	5.857	0.00	0.43	−0.34	0	0.00	0	8.96	8.93	8.17	8.21
21	H	3,5-F_2	5.927	0.00	0.43	− 0.34	0	0.00	0	8.74	8.89	8.00	8.16
22	H	2,3-Cl_2	6.387	−0.97	0.41	− 0.15	0	0.00	0	7.57	7.88	7.62	7.67
23	H	2,4-Cl_2	6.507	−0.97	0.00	0.00	0	0.00	0	8.25	8.25	7.43	7.46
24	H	2,5-Cl_2	6.507	−0.97	0.00	0.00	0	0.00	0	8.22	8.25	7.37	7.46
25	H	2,6-Cl_2	5.947	−0.97	0.00	0.00	0	−0.97	0	7.43	7.34	> 8.00[b]	–
26	H	3,4-Cl_2	6.947	0.00	0.41	− 0.15	0	0.00	0	8.43	8.31	7.26	7.25
27	H	3,5-Cl_2	7.067	0.00	0.41	− 0.15	0	0.00	0	8.05	8.24	7.12	7.16
28	2-F	2,4-F_2	5.207	−0.46	0.00	0.00	0	0.00	1	9.05	9.42	7.17	7.56
29	2-Cl	2,4-F_2	5.667	−0.46	0.00	0.00	0	0.00	0	9.40	9.15	> 8.52[b]	–
30	3-F	2,4-F_2	5.457	−0.46	0.00	0.00	0	0.00	1	> 9.00[b]	–	7.77	7.38
31	3-Cl	2,4-F_2	5.997	−0.46	0.00	0.00	0	0.00	0	8.59	8.95	7.89	7.84

[a]Inhibition concentration, on molar scale, measured by cell-based assay; taken from Ref. [27]; [b]Reported activity is uncertain; [c]"Outlier" compound in the present study.

Table II. Stepwise development of Equation (1); $pIC_{50} = a_0 + a_1 ClogP + a_2 Es_2 + a_3 F_3 + a_4 HA_4 + a_5 Es_6$

a_0	a_1	a_2	a_3	a_4	a_5	r	s	$F^a_{k,n-k-1}$	q^2	
12.197	−0.581(±0.35)					0.476	0.572	07.909	0.134	(i)
12.764	−0.633(±0.27)	0.652(±0.26)				0.743	0.444	15.983	0.466	(ii)
12.306	−0.532(±0.29)	0.726(±0.26)	−0.682(±0.73)			0.770	0.431	12.149	0.479	(iii)
12.727	−0.579(±0.24)	0.847(±0.23)	−0.934(±0.63)	−0.949(±0.48)		0.850	0.363	15.677	0.561	(iv)
12.852	−0.589(±0.17)	0.789(±0.16)	−1.085(±0.44)	−1.017(±0.34)	1.279(±0.43)	0.933	0.254	30.772	0.752	(v)

[a] *F*-statistics obtained for $n = 29$ data points and k (= 1, 2, 3, 4, and 5) independent variable(s).

[$F_{4,23}(0.01) = 4.264$]. The higher value obtained for q^2 expressed the robustness of the QSAR model. That the variables used in deriving Equation (1) had no mutual correlation is shown in Table III. The calculated activity values, using this equation and listed in Table I, are in close agreement with the observed ones. The plot between observed *versus* calculated and predicted activities is shown in Figure 2 to identify their systematic variations and to understand the goodness of fit directed by the model equation. From Equation (1), it appears that a less hydrophobic molecule with *ortho*-substituent(s), exerting less steric hindrance and *para*-substituent devoid of hydrogen-bond acceptor property augment the inhibition action. Besides, a 3-substituent transmitting a higher negative field effect is advantageous to improve the pIC_{50} value pertaining to VEGFR-2.

Further, the PDGFR tyrosine kinase inhibition activity of the title compounds was also analyzed quantitatively in terms of the QSAR parameters (Table I). Such parameters have revealed a correlation Equation (2), whose development is given in Table IV.

$$pIC_{50}(\text{PDGFR}\alpha) = 12.258 - 0.741(\pm 0.14)\text{C}\log P - 0.858(\pm 0.50)\text{R}_3 - 0.835(\pm 0.30)I_X$$

$$n = 29,\ r = 0.888,\ s = 0.231,\ F(3,25) = 30.954,\ q^2 = 0.613 \quad (2)$$

This equation highlights the importance of hydrophobicity of the molecule and the resonance effect of 3-substituents of the terminal phenyl ring. Occurrence of a fluoro-substituent reflected through the indicator variable, I_X, in the middle phenyl ring is also predominant in governing the inhibitory activity of a compound. A value either 1 or 0 for I_X, in that order, indicates the presence or absence of a fluoro-substituent in the middle phenyl ring. The significant role played by the variable I_X, is apparent in steps (ii and iii; Table IV) in developing the above model equation. Except the *r*-value which is accounting for 79% ($r^2 = 0.788$) of the variance, the other statistical parameters of Equation (2) tune to a high level of significance. The *F*-value remained significant at 99% level [$F_{3,25}(0.01) = 4.676$] while q^2 expressed a reasonable QSAR model. Equation (2), as such, reflects upon the parametric requirement and needs further improvement. The residuals [pIC_{50} (obsd.) − pIC_{50}(calcd.; Equation 2)] obtained for all the data points were, therefore, further analyzed to trace out unusual behavior of certain congeners. Compound **7** was the lone analogue whose calculated activity value largely deviated from the observed one. The 4-methyl, being a non-polar substituent, enhances hydrophobicity of this molecule, which may not allow effective binding with some hydrophilic

Table III. Intercorrelation Matrix[a] among the predictors of Equation (1)

	Clog*P*	Es_2	F_3	HA_4	Es_6
Clog*P*	1.000	0.074	0.377	0.164	0.069
Es_2		1.000	0.305	0.202	0.184
F_3			1.000	0.176	0.165
HA_4				1.000	0.069
Es_6					1.000

[a]Matrix elements are the *r*-values.

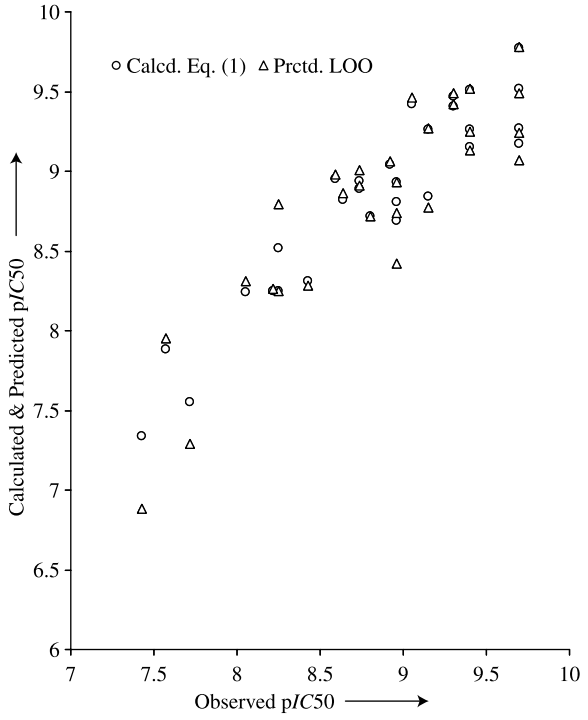

Figure 2. Plot showing variation of observed versus calculated and predicted pIC_{50} values.

Table IV. Stepwise development of Equation (2); $pIC_{50} = b_0 + b_1 ClogP + b_2 R_3 + b_3 I_X$

b_0	b_1	b_2	b_3	r	s	$F^a_{k,n-k-1}$	q^2	
11.576	−0.620(±0.21)			0.697	0.346	25.458	0.420	(i)
11.701	−0.657(±0.19)	−1.038(±0.67)		0.771	0.313	19.905	0.527	(ii)
12.258	−0.741(±0.14)	−0.858(±0.50)	−0.835(±0.30)	0.888	0.231	30.953	0.613	(iii)

[a]*F*-statistics obtained for $n = 29$ data points and k (= 1, 2, and 3) independent variable(s).

pocket present at the receptor. Compound **15** still has a more hydrophobic 4−Cl substituent, but being polar in nature, may favor interaction with a hydrophilic pocket leading to enhancement of activity. The predicted activity of this compound, therefore, becomes closer to the observed one. Elimination of compound **7** further revealed the correlation shown in Equation (3)

$$pIC_{50}(\text{PDGFR}\alpha) = 12.302 - 0.744(\pm 0.13)\text{C}\log P - 0.774(\pm 0.44)R_3 - 0.866(\pm 0.26)I_X$$

$$n = 28,\ \ r = 0.913,\ \ s = 0.204,\ \ F(3, 24) = 39.915,\ \ q^2 = 0.654 \qquad (3)$$

The statistical parameters, r, F and q^2 are increased while the s and 90% confidence intervals associated to regression coefficients are lowered. All these parameters now account for highly significant results. The calculated pIC_{50} values using Equation (3), listed in Table I, are in close agreement with the observed ones. The required orthogonality conditions amongst predictor variables of this equation are evinced in Table V. From Equation (3), it appears that a less hydrophobic molecule having a 3-substituent which transmits a more negative resonance effect, is helpful in raising its activity. Likewise, in the middle phenyl ring, absence of a fluoro- substituent augments the inhibitory activity. At present, the substitutional pattern in the middle phenyl ring cannot be concluded precisely as the reported data set has a limited number of substituents in this ring.

The conclusions deduced from Equations (1) and (3) may serve as guidelines and assist in obtaining more potent analogues in a further synthesis of similar compounds. The present study, therefore, provides a basis for rationalization of substituent selection in designing more potent analogs of *N*-Phenyl-*N*′-{4-(4-quinolyloxy)phenyl}urea.

Table V. Intercorrelation Matrix[a] among the predictors of Equation (3)

	Clog*P*	R_3	I_X
Clog*P*	1.000	0.124	0.224
R_3		1.000	0.160
I_X			1.000

[a]See foot-note under Table III.

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