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QSAR Studies on Hetaryl Imidazoles Derivatives as Novel Dual Inhibitors of Vascular Endothelial Growth Factor Receptors I and II

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The QSAR studies have been carried out on 19-hetaryl imidazoles derivatives, which were reported as inhibitor of vascular endothelial growth factor receptors (VEGFR). The present study was undertaken to determine the physico chemical parameters, which govern the anticancer activity of the given series of drug molecules. The best QSAR model thus obtained, have high statistical significance (> 99.9 %) and moderate correlation coefficient (r = 0.85) led us to know that the activity of these compounds is mainly influenced by substitutions (R) done at *meta* position of benzene ring and presence of 4-pyridine group at Ar position is found to be important for activity of given series of drug molecules.

Key Words: QSAR, Hetaryl imidazoles derivatives, Vascular endothelial growth factor receptors.

INTRODUCTION

Vascular endothelial growth factor (VEGF), secreted by malignant tumor, is a key angiogenic factor[1]. Angiogenesis is the formation of new vasculature from the existing vascular network[2], causes growth of solid tumor. Thus inhibitors of angiogenesis are considered to be novel therapeutic approach in oncology and ophthalmology[3,4]. A number of compounds, which inhibit the activity of VEGF, have been produced, as small molecule inhibitors inhibit VEGFR phosphorylation by directly competing with ATP binding site of respective intracellular kinase domain and finally lead to death of endothelial cells[1]. In this paper we report the QSAR[5-7] study on hetaryl imidazoles derivatives (Fig. 1) to determine the physicochemical parameters that influence the anticancer activity of series.

EXPERIMENTAL

Hetaryl imidazoles derivatives were prepared by several steps process[1]. Imidazole was heated in presence of H_2SO_4/HNO_3 mixture for 3 h at 70 ºC. The resulting product (4-nitro-5-chloro derivative) was then treated with

KCN/KI in EtOH to obtain **2**. Compound **2** was then heated in aqueous H_2SO_4 to hydrolyze nitrile group and obtain respective acid **3**. Compound **3** was converted to 1,3,4-oxadiazoles (**4**) *via* published route[8]. The nitro group of **4** was reduced to amine by hydrogenation. The amines thus obtained were treated with aldehydes in dry MeOH to obtain respective Schiff base, which were further reduced with $NaBH_4$ to obtain hetaryl imidazoles derivatives.

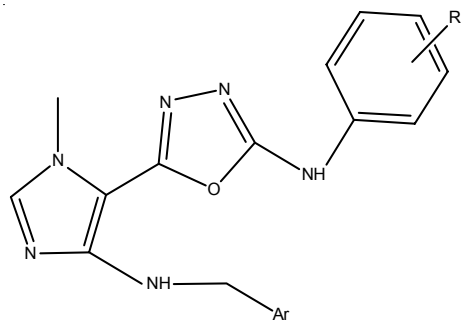
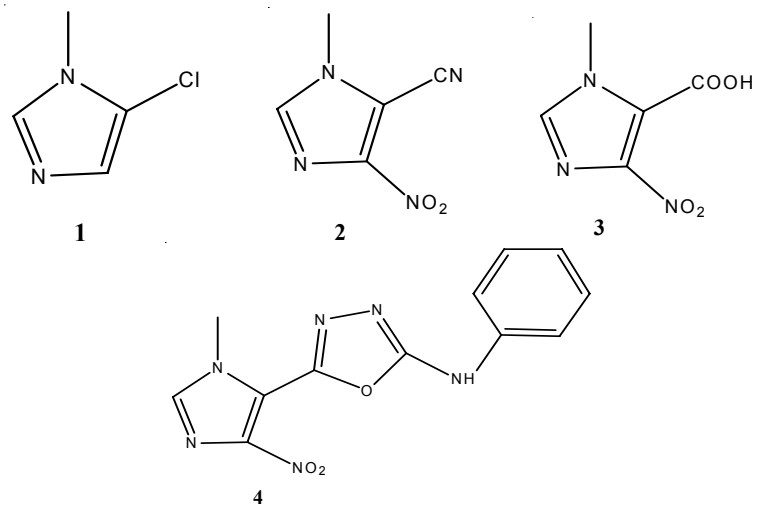


Fig. 1. Hetaryl imidazoles derivatives



The inhibitory activity data of hetaryl imidazole derivatives have been collected from literature[1] and calculated as -log BA.The values of physico-chemical parameters for the substituents at R position are calculated as hydrophobic (π), steric (MR), electronic (σm, σp), resonance (R) and field effect (F). We considered different physico-chemical parameters as independent and inhibitory activity of hetaryl imidazole derivatives as dependent parameter in regression analysis for deriving QSAR equations[9], using Systat Software version 10.2. An indicator variable (I) having values 1 or 0, is also introduced to indicate the presence or absence of 4-pyridine group at

position Ar, respectively. The parameters that showed some significant correlation during multi regression analysis are given in Table-1 along with the biological activities of all the compounds of the series.

TABLE-1
PHYSICOCHEMICAL PARAMETERS AND INHIBITORY ACTIVITY OF HETARYL IMIDAZOLE DERIVATIVES

C. No.	R	Ar	σ_m	I	-log BA_{cal}		-log BA_{obs}
					eqn. 3	eqn. 4	
1	4-Cl	4-Pyridine	0.00	1.00	0.532	0.632	0.602
2	4-Cl	Piperonyl	0.00	0.00	-0.294	-0.294	0.018
3	4-Cl	3,4-Di-F (C_6H_3)	0.00	0.00	-0.294	-0.294	-0.270
4	4-Cl	5-Imidazole	0.00	0.00	-0.294	-0.294	-0.375
5	4-Cl	5-Quinoline	0.00	0.00	-0.294	-0.294	-0.549
6	4-*t*-Bu	4-Pyridine	0.00	1.00	0.532	0.632	0.420
7	4-*i*-Pr	4-Pyridine	0.00	1.00	0.532	0.632	0.357
8	4-ClF_2CO	4-Pyridine	0.00	1.00	0.532	0.632	0.886
9	4-F_3CO	4-Pyridine	0.00	1.00	0.532	0.632	1.032
10	4-F_3C	4-Pyridine	0.00	1.00	0.532	0.632	1.137
11	3-F_3CO	4-Pyridine	0.38	1.00	1.219	1.216	1.337
12	3-Me	4-Pyridine	-0.07	1.00	0.405	0.524	0.149
13	3-MeO	4-Pyridine	0.12	1.00	0.749	0.816	0.886
14	3,4 di Cl	4-Pyridine	0.37	1.00	1.200	1.201	0.745
15	3,4 di MeO	4-Pyridine	0.12	1.00	0.749	0.816	1.284
16	4-Cl, 3-CF_3	4-Pyridine	0.43	1.00	1.309	1.293	1.367
17	4-F, 4-Me	4-Pyridine	0.00	1.00	0.532	0.632	0.585
18	4-Br	4-Pyridine	0.00	1.00	0.532	0.632	0.137
19	4-Ph	4-Pyridine	0.00	1.00	0.532	–	-0.508

RESULTS AND DISCUSSION

During regression analysis we considered 4-pyridine group as indicator parameter and is assigned the value of 1 or 0 for its presence or absence at Ar position, respectively. The parameters, which showed some correlation are described in Table-2.

TABLE-2
PEARSON CORRELATION MATRIX

	F	σ_m	σ_p	I	-log BA
F	1				
σ_m	0.586	1			
σ_p	0.235	0.001	1		
I	0.175	0.252	0.179	1	
-log BA	0.200	0.569	0.209	0.658	1

Since no satisfactory results were obtained by linear regressions analysis, multiregression analysis was performed. Thus several permutations and combinations of the above parameters were tried keeping in view the inter correlation ($r < 0.5$) among the parameters used in same equation.

$$-\log BA = 0.702 (\pm 0.374) F1 + 1.073 (\pm 0.260) I - 0.582 \quad (1)$$
$$n = 19, r = 0.732, f = 9.229, s = 0.454$$

$$-\log BA = 1.028 (\pm 0.523)\sigma_p + 1.079 (\pm 0.258) I - 0.530 \quad (2)$$
$$n = 19, r = 0.737, f = 9.526, s = 0.451$$

$$-\log BA = 1.808 (\pm 0.679)\sigma_m + 0.825 (\pm 0.243) I - 0.294 \quad (3)$$
$$n = 19, r = 0.779, f = 12.366, s = 0.418$$

where n = no. of data points, r = correlation coefficient, f = variance ratio between the calculated and observed activities and s = standard error of estimation.

On analyzing the above equations, eqn. 3 was found to be statistically significant (> 99 %) with moderate correlation coefficient ($r > 0.77$).

On careful analysis of eqn. 3, compound number 19 was identified as an outlier having residual value three times more than the standard error. Thus the removal of compound number 19 from eqn. 3 led to eqn. 4 with significant improved correlation coefficient ($r > 0.85$).

$$-\log BA = 1.537 (\pm 0.539)\sigma_m + 0.926 (\pm 0.193) I - 0.294 \quad (4)$$
$$n = 18, r = 0.857, f = 20.785, s = 0.328$$

Since the coefficient of parameters in eqn. 4 possess positive sign which indicates their positive contribution to activity. Thus substitution (R) by group or atom, at *meta* position of benzene ring and presence of 4-pyridine group at Ar position play a crucial role in enhancing the activity of given series on drug molecule.

In conclusion, the above QSAR studies on hetaryl imidazole derivatives highlight the important parameters which affect its activity and thus, led us to know that substitution at meta position of benzene ring (R) by atom or group contribute positively to activity and presence of 4-pyridine group at Ar position will also be helpful in designing new drug molecule or enhancing the activity of given series of compounds.

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