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Topological Designing of 4-Piperazinylquinazolines as Antagonists of PDGFR Tyrosine Kinase Family

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Abstract—Topological designing of a series of 4-piperazinylquinazolines as antagonists of platelet-derived growth factor receptor (PDGFR) tyrosine kinase family has been reported using a series of distance-based topological indices. Regression analysis of the data, using maximum R^2 method indicated that inhibitory activity, pIC_{50} (μm), in cellular PGDFR phosphorylation assay can be modelled excellently in multi-parametric model. The results are discussed critically using cross-validated parameters.

Introduction

Protein kinase are enzymes that play key roles in cell signal transduction, regulating pathways critical in differentiation, survival and death.[1]

The platelet-derived growth factor receptor (PDGFR) is one of the four receptor tyrosine kinases (RTKs) and is characterized by an extra-cellular ligand binding region, a single transmembrane spanning region, and intracellular tyrosine kinase domains.[2–14]

It is interesting to record that in Pandey paper[4] the compounds are described as PDGFR antagonists in the title and in the text. More careful reading of that paper reveals that the compounds act via ATP-competitive inhibition of the kinase domain. Furthermore they presented data for assay conditions with and without human plasma. However, in the present study, we have used the non-plasma data along with 11 cases of without organic plasma (W/O Plasma). The key issue of Pandey and coworkers research on the other hand was to present their efforts within the 4-piperazinylquinazoline class of PDGFR family inhibitors involving efforts to increase the potency of analogues in human plasma, obtaining and retaining appropriate kinase specificity of analogues, and achieving desirable pharmacokinetic properties including high oral bioavailability and long plasma half-life. Our issue is bit different from that of Pandey and coworkers[4] in that we have used the nonplasma data.

Consequent to the above, we report topological designing of 4-piperazinylqunazolines as antagonists of PDGFR tyrosine kinase family. We have adopted the inhibitory activity pIC_{50} (μm) βPGDFR phosphorylation assay (non-plasma data) for a large series of compounds (Table 1) reported by Pandey and coworkers.[4] The activity, that is IC_{50} (for non-plasma), is used by converting it to pIC_{50} unit. A large pool of topological indices[15–18] will be used for modeling pIC_{50}. The variation in R groups present in the data set is accounted for using indicator parameter.[19] Like topological indices indicator parameters are also considered as molecular descriptors. Usually they are used to account for the structural features not covered in topological indices and thus to better explain the data. However, unlike topological indices they assume only two values: 1 and 0. The value of indicator parameter equal to 1 is used when that structural feature (R groups in our case) are present in the molecule, otherwise it (indicator parameter) is zero. Such a study will help chemists, pharmaceutical and medicinal chemists to synthesize new compounds with still better activity. Also, such a QSAR study will identify structural features of such inhibitors that contribute to their specific βPGDFR inhibitory activity.

The results and discussion as given below show that interesting results are obtained in the present study.

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Table 1. Topological descriptors (W, B, $^1\chi$, J, logRB)and indicator parameter (Ip) and inhibitory activity ($\log IC_{50}$) of the kinase inhibitors

Compd[a]	W	$B = {}^1\chi$	J	logRB	pIC_{50} (μM)	Ip
1 (**3**)	5892	18.7954	1.2633	1357.739	2.8539	0
2 (**4**)	5034	18.1221	1.2753	1191.380	0.7959	0
3 (**5**)	9733	22.6229	0.9318	2047.629	2.7959	1
4 (**6**)	9733	22.6229	0.9318	2047.629	3.3979	1
5 (**7**)	9877	22.6060	0.9192	2059.223	3.3979	1
6 (**8**)	9133	22.1229	0.9342	1941.160	3.0000	1
7 (**9**)	9133	22.1229	0.9342	1941.160	1.6990	1
8 (**10**)	7515	20.6400	1.0569	1646.564	2.0000	1
9 (**11**)	9990	22.2449	1.0278	2069.225	1.9208	1
10 (**12**)	8100	21.0335	1.0482	1748.022	2.5850	1
11 (**13**)	8100	21.0335	1.0482	1748.022	2.6198	1
12 (**14**)	5962	18.9779	1.2511	1365.420	1.3010	0
13 (**18**)	7716	20.6060	0.9092	1655.0450		
14 (**19**)	6911	19.6573	0.8855	1486.6140		
15 (**20**)	6194	19.1397	1.0365	1379.5500		
16 (**21**)	5510	18.1910	1.0037	1229.1410		
17 (**22**)	4025	16.6221	1.2494	969.8687	−0.1139	1
18 (**23**)	3524	15.6734	1.1998	848.5168	−0.0969	0
19 (**24**)	4833	17.4779	1.2240	1125.9400	0.3767	0
20 (**29**)	6684	20.1379	1.1157	1529.0760	−0.0414	0
21 (**30**)	7788	20.9955	1.0962	1727.8410	−0.6990	0
22 (**31**)	6684	20.1397	1.1157	1529.0760	0.3002	0
23 (**32**)	7788	20.9955	1.0962	1727.8410	0.7033	0
24 (**37**)	6752	20.1397	1.1047	1533.6130	1.1023	0
25 (**38**)	7864	20.9955	1.0858	1732.7340	1.0044	0
26 (**39**)	6282	19.6397	1.1071	1442.4220		
27 (**40**)	7346	20.4955	1.0871	1635.1860		
28 (**45**)	5611	18.6397	1.0692	1283.3850	−0.1492	0
29 (**46**)	5611	18.6397	1.0692	1283.3850	0.3726	0
30 (**47**)	6080	19.0334	1.0627	1370.8880	−0.7889	0
31 (**48**)	7572	20.5539	0.9339	1645.1140	0.4737	0
32 (**49**)	6080	19.0034	1.0627	1370.8880	−0.1367	0
33 (**50**)	5611	18.6397	1.0692	1283.3850	−0.8129	0
34 (**51**)	6080	19.0334	1.0627	1370.8880	0.1249	0
35 (**52**)	5611	18.6397	1.0692	1283.3850		
36 (**55**)	5177	18.1397	1.0747	1199.6420		
37 (**54**)	5177	18.1397	1.0747	1199.6420	−0.9127	0
38 (**55**)	5177	18.1397	1.0747	1199.6420		
39 (**24**)	4833	17.4779	1.2240	1125.9400	−0.3767	0
40 (**60**)	6603	19.4955	1.0506	1464.5370	−0.7033	0
41 (**61**)	6603	19.4955	1.0506	1464.5370	−0.0969	0
42 (**62**)	6121	18.9925	1.0547	1374.4370		
43 (**63**)	6121	18.9925	1.0547	1374.4370		
44 (**64**)	5177	18.1397	1.0747	1199.6420	−0.3502	0
45 (**65**)	5177	18.1397	1.0747	1199.6420	−0.0792	0
46 (**66**)	6551	19.3468	1.0593	1459.0840	−0.3284	0
47 (**67**)	7643	20.2026	1.0432	1653.1110		
48 (**68**)	6121	18.9955	1.0547	1374.4370		
49 (**69**)	6121	18.9955	1.0547	1374.4370		
50 (**70**)	6144	19.1397	1.0514	1377.6050		
51 (**71**)	6144	19.1397	1.0514	13,077.6050		
52 (**72**)	5674	18.6397	1.0582	12,089.6970		
53 (**73**)	5674	18.6397	1.0582	12,089.6970	−0.4487	0
54 (**74**)	5674	18.6397	1.0582	12,089.6970	0.0255	0
55 (**75**)	7190	19.9955	1.0356	15,065.3690		
56 (**76**)	7190	19.9955	1.0356	15,065.3690		
57 (**77**)	6670	19.4955	1.0409	14,071.0230		
58 (**78**)	6670	19.4955	1.0409	14,071.0230	−0.1614	0
59 (**79**)	6670	19.4955	1.0409	14,071.0230	0.0969	0
60 (**80**)	7158	19.8468	1.0395	15,061.5560		
61 (**81**)	8308	20.7026	1.0261	1762.3510		
62 (**82**)	8238	20.7026	1.0336	1756.7160		
63 (**83**)	7190	19.9955	1.0356	1565.3690		
64 (**84**)	6650	19.5335	1.0439	1469.2340	−2.3979	0
65 (**85**)	7748	20.3894	1.0295	1163.5140	−2.3979	0
66 (**86**)	6584	19.5504	1.0529	1463.4280	−2.3979	0
67 (**87**)	7678	20.4062	1.0375	1657.5480	−2.3979	0
68 (**90**)	6670	19.4955	1.0409	1471.0230	−1.0881	0
69 (**91**)	5713	18.3337	1.2121	1293.8320		
70 (**92**)	5713	18.3337	1.2121	1293.8320		
71 (**93**)	4833	17.4779	1.2240	1125.9400	−0.4928	0

(continued on next page)

Table 1 (*continued*)

Compd[a]	W	B = $^1\chi$	J	logRB	pIC$_{50}$ (μM)	Ip
72 (**94**)	4833	17.4779	1.2240	1125.9400	−0.7474	0
73 (**95**)	8136	20.4350	1.2099	1748.3150	−0.3883	0
74 (**96**)	8666	20.8177	1.2121	1846.1270		
75 (**97**)	8707	20.9350	1.2073	1850.6600		
76 (**98**)	9322	21.4350	1.2029	1957.9890	−0.9508	0
77 (**99**)	9939	21.7908	1.2010	2066.0100		
78 (**100**)	9855	21.5814	1.2096	2057.4280		

[a]The number in parentheses is the corresponding number of the compound in Pandey's work.[4]

Methodology

The methodology used is to transform the chemical structure into its molecular graph. This can be done by depleting all the carbon–hydrogen as well as hetero–atom–hydrogen bonds of the chemical structure. The resulting molecular graph represents the topology of the molecule.

In the present investigation, initially we have used a large set of distance-based topological indices, out of which Wiener (W),[16] first-order connectivity ($^1\chi$),[17] Balaban(J),[18] and logRB[15] indices and their combinations were found useful.

The topological designing of 4-piperazinylquinazolines as antagonists of the PDGFR tyrosine kinase, using aforementioned topological indices is carried out by correlation analysis using maximum R^2 method.[19,20]

Results and Discussion

The structural details of a large series of 78 4-piperazonylquinazolines, along with their adopted inhibitory activities (pIC$_{50}$),[4] are presented in Table 1. For the compounds **64**–**67** no definite activity is reported,[4] therefore, they are deleted in the process of topological designing.

During the process of designing the activity we observed that compounds **1**, **7**, **9**, **21**, **30**, **33**, **58**, **63**, **68** and **76** (10 in all) are outliers. They are, therefore, further deleted from the process of topological designing. At present we can not provide convincing proof for deletion of these compounds. However, one of the promising reasons being that this set of compounds might have different type of mechanism and another reason being the set of compounds used is a combination of 'No Plasma' and 'W/O-plasma'. Otherwise, omission of these compounds is approximately 14% of the data set and is thus somewhat worrisome. However, it is important to record that dropping of these compounds is not for improving the statistical properties of a model. It is actually consequence of stepwise regression analysis and is quite usual. Therefore, it is not sound to believe that the omission of referred compounds mean that under given basis for activity has not been correctly identified.

In presenting the results we have used the following parameters: *n*, number of compounds used, SE, standard error of estimation, R, correlation coefficient, F, F-ratio and Q is the quality factor.

The maximum R^2 method[19] of designing involves recording of statistically the best two parametric, best three parametric, best tetra parametric models and so on using correlation matrix (Table 2). Such models obtained in the present case are summarized in Table 3. These results are the outcome of several such determinations.

A perusal of Table 3 shows that the best mono-parametric model involving $^1\chi$ (first-order connectivity) is found as:

$$\text{pIC}_{50}\ (\mu\text{M}) = -0.4893\ (\pm 0.0626)\ {}^1\chi + 8.7328$$
$$n = 64,\ \text{SE} = 0.7162,\ \text{R} = 0.7045,\ \text{F} = 61.099 \qquad (1)$$

The parameter $^1\chi$ conveys information about the number of atoms and first-order branching. The negative sign of the coefficient of $^1\chi$ in the above model indicates its negative contribution in modeling pIC$_{50}$ (μM). That is, first-order branching is not favourable for the exhibition of pIC$_{50}$.

Out of the several bi-parametric models attempted, the model consisting of $^1\chi$ and Ip was found to give better results than the monoparametric model discussed above. This model is as below:

$$\text{pIC}_{50}\ (\mu\text{M}) = -0.3117\ (\pm 0.0501)\ {}^1\chi - 1.4819\ (\pm 0.1899)\ \text{Ip} + 5.5213$$
$$n = 64,\ \text{SE} = 0.5106,\ \text{R} = 0.8648,\ \text{F} = 90.505 \qquad (2)$$

Table 2. Correlation matrix indicating correlatedness among topological indices and the inhibitory activity

	pIC$_{50}$	W	$^1\chi$ = B	J	logRB	Ip
pIC$_{50}$	1.0000					
W	−0.6810	1.0000				
$^1\chi$ = B	−0.7045	0.9755	1.0000			
J	0.5120	0.3709	0.4613	1.0000		
logRB	−0.6709	0.9980	0.9839	−0.3619	1.0000	
Ip	−0.7669	0.4207	0.4543	−0.5537	0.4052	1.0000

Table 3. Results of topological designing using maximum-R^2 method

Model	Parameters	Regression parameters and quality					
		SE	R	R^2	F	Q = R/SE	R^2_A
1	$^1\chi$	0.7162	0.7045	0.4963	61.099	0.9837	—
2	$^1\chi$, Ip	0.5106	0.8648	0.7479	90.505	1.6937	0.7397
3	$^1\chi$, W, J, Ip	0.5140	0.8653	0.7488	59.622	1.6835	0.7363
4	$^1\chi$, W, J, logRB	0.4791	0.8862	0.7854	53.973	1.8497	0.7708
5	$^1\chi$, W, J, logRB, Ip	0.4511	0.9017	0.8130	50.426	1.9989	0.7969

The negative sign of both the coefficients $^1\chi$ and Ip_1 indicated their retarding effect on the exhibition of pIC_{50} (μM). The physical significance of this model with respect to $^1\chi$ is similar to the above model (eq 1). The other parameter, that is, indicator parameter Ip indicates that smaller molecules are favourable for the exhibition of pIC_{50}.

The step-wise regression resulted into tri-parametric model consisting of $^1\chi$, W and Ip. Though the correlation coefficient R is slightly better than the bi-parametric model discussed above (eq 2) it is of statistically lower quality as the. coefficient of W term in the model was considerably lower than its standard deviation. Such models are not allowed statistically.[19]

A model consisting of $^1\chi$, W, J and logRB resulted into a tetra-parametric model having better quality than the models discussed above. This model is found as:

$$pIC_{50}\ (\mu M) = -5.6532\ (\pm 0.7055)\ {}^1\chi - 0.0124\ (\pm 0.0015)\ W - 9.6548\ (\pm 1.7456)\ J + 0.0912\ (\pm 0.0012)\ logRB + 67.8104$$
$$n = 64,\ SE = 0.1791,\ R = 0.8862,\ F = 53.973 \qquad (3)$$

As stated earlier, here also $^1\chi$ index conveys information regarding numbers of atoms and first-order connectivity. The Balaban index, J, on the other hand is highly discriminating index, whose values do not substantially increase with the molecular size and the number of ring presents. It represents extended connectivity and is a good descriptor for the shape of the molecules. The other two topological indices, W and log RB, are also responsible for shape, size and branching. Moreover, W in addition to size and shape also represents molecular structure-to-volume ratio as well as compactness of a given molecule. All these factors, taken together, reflect that the exhibition of the activity is favoured by smaller molecules.

Finally, a penta-parametric model containing $^1\chi$, W, J, logRB and Ip is found to be the best model for the modeling of pIC_{50} (μM). This model is found as below:

$$pIC_{50}\ (\mu M) = -3.9975\ (\pm 0.8725)\ {}^1\chi - 0.0086\ (\pm 0.0019)\ W - 7.2414\ (\pm 1.8914)\ J + 0.0634\ (\pm 0.0142)\ logRB - 0.7361\ (\pm 0.2515)\ Ip + 18.9742$$
$$n = 64,\ SE = 0.1511,\ R = 0.9017,\ F = 50.426 \qquad (4)$$

In the aforementioned models (eqs 3 and 4) all the topological indices but logRB are found to correlate negatively with pIC_{50}. The positive sign of logRB is due to its correlatedness with other indices. Also that contribution of logRB relative to $^1\chi$ and J is quite small. Furthermore, discussed models show that $^1\chi$ plays dominating role in exhibiting pIC_{50}. Similarly, the negative correlation of the aromatic indicator variable (Ip) is likewise of great concern. The overall physical significance of the model (eq 4) is similar to earlier models discussed above and further supports that small molecules are favorable for kinase inhibition.

At this stage, it is interesting to comments on R^2_A (adjustable R^2). It takes into accounts of adjustment of R^2. Therefore, if a variable is added that does not contribute its fair share, the R^2_A will actually decline. The magnitude of R^2_A presented in Table 3 indicates that except for the tri-parametric model containing $^1\chi$, W and Ip, R^2_A goes on increasing. The R^2_A value of this tri-parametric model (0.7363) is lower than the value of (0.7397) for the bi-parametric model containing $^1\chi$ and Ip. It means that the added parameter W does not contribute its fair share and, thus this tri-parametric model needs to be neglected. The results, does, show that combinations of topological indices and indicator variable is quite useful in designing compounds.

It is worthy to mention that statistically significant model may or may not have best predictive potential. Therefore, the proposed model be finally judged by evaluating their respective predictive potential. One such simple measure of the evaluation of predictive potential is the quality factor, Q, (Q = R/SE) introduced in the literature.[20] This shows that the lower the standard error of estimation (SE), the larger the correlation coefficient R, the higher will be Q, and the better will be the predictive potential of the model. The Q value recorded in Table 3 shows that the most significant penta-parametric model has the highest Q value. Thus, this model has the highest predictive potential.

However, the use of quality factor Q in deciding predictive potential of the model is recently criticized by Todeschini.[21] Thus, according to Todeschini,[21] the quality factor Q does not appear to be common place for QSAR applications.

Consequent to the above, we have performed cross-validation to validate the statistical and predictive qualities of the models.[19,22–25] The statistical quality of the

Table 4. Cross-validated parameters for the proposed models (refer. Table 3)

Model	Number of parameters	PRESS	SSY	PRESS/SSY	R^2_{CV}	S_{PRESS}	PSE
2	2	15.9049	17.1957	0.9249	0.0750	0.5106	0.4985
4	4	13.5432	19.5574	0.6925	0.3075	0.4791	0.4600
5	5	11.8010	51.2996	0.2300	0.7700	0.4511	0.4294

PRESS, predictive error sum of squares derived from leave-one-out-method; SSY, variance of biological activity of the molecules around the mean value; R^2_{CV}, overall predictive ability; S_{PRESS}, uncertainty of the prediction; PSE, predictive square error.

model(s) appear to require improvement in terms of its ability to correlate the chosen descriptors with the activity of the complete set. On the other hand the predictive quality of the models needs to be demonstrated by leaving out parts of the training set using a cross validation method.

We have, therefore, estimated cross-validation parameters and the same are recorded in Table 4. PRESS (predicted residual sum of squares) is a good estimate of the real prediction error of the model. If PRESS is smaller than sum of the squares of response value, that is SSY the model predict better than chance can be considered statistically significant. In this regard all the models (Table 4) are statistically significant. Furthermore, the ratio PRESS/SSY should be smaller than 0.4, and value of this ratio smaller than 0.1 indicates an excellent model with high predictive potential.[26–30]

In view of the above we observed that (Table 4) only the model 5 is an excellent model and it alone has the excellent predictive potential. The highest value of cross-validation correlation coefficient (R^2_{cv}) further confirms this finding.

Another useful cross-validation parameter is the uncertainty of prediction (S_{PRESS}). However, in the present case this parameter is of no use as its magnitude is the same as that of standard error of estimation (SE). In such cases an important cross-validation parameter named as predictive square error (PSE) is available (Table 4). This parameter is more directly related to the uncertainty of the predictions. The lowest value of PSE for the model 5 also confirms its excellent predictive potential.

In order to further confirm aforementioned finding we have estimated predictive correlation coefficient (R^2_{pred}) in that the observed activity is correlated with the estimated activity. We have, therefore, obtained R^2_{pred} for the tetra- and penta-parametric models (Figs. 1 and 2) giving R^2_{pred} as 0.7853, and 0.8130, respectively, indicating again that the latter model has the best predictive potential.

It is worth recording that Pandey and coworkers[4] used the inhibitory activity in terms of IC_{50} (μM); while in the present case we have converted this activity as pIC_{50} (−log IC_{50}). Consequently; the excellent model proposed by as (eq 4) supports the physical consequences of SAR study arrived at by Pandey and coworkers.[4] Our study further favours the synthesis of new compounds analogues to compound **75** (compound **55** in our case) proposed by Pandey and coworkers.[4]

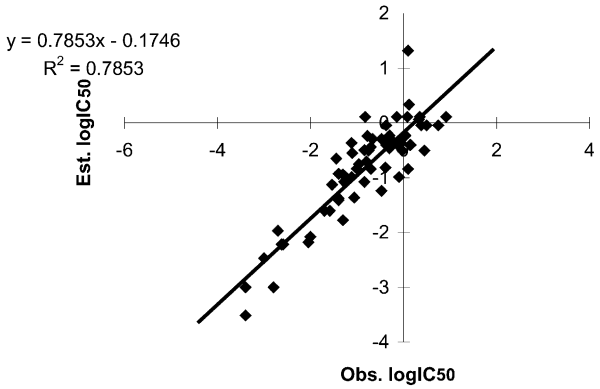

Figure 1. Correlation of observed and estimated pIC_{50} (μM) using model 4 (refer. Table 3).

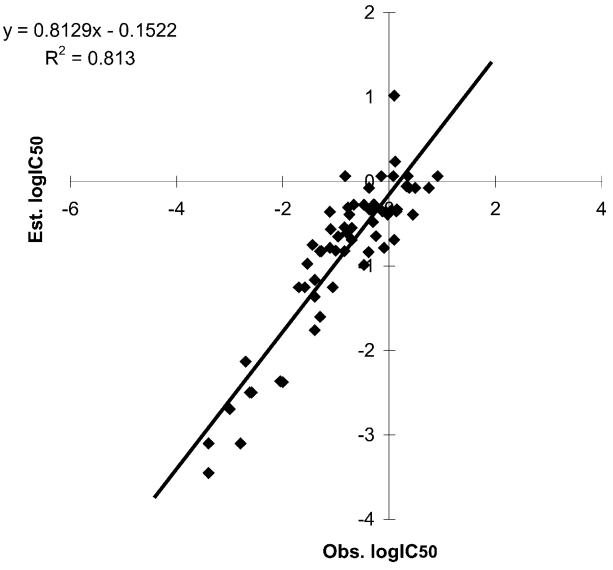

Figure 2. Correlation of observed and estimated pIC_{50} (μM) using model 5 (refer. Table 3).

Conclusions

As stated by Pandey and coworkers[4] kinase inhibition represents a novel mechanism-based approach to selectivity block signaling pathways that are known to mediate disease processes. The present study show that the same can be designed using distance-based topological indices. The designing carried out in the present study supports the findings of Pandey and coworkers[4] that the development of the small molecules RTK as potential treatment of AMC. The topological designing used by us can be

conveniently extended to model diseases that are mediated by the PGDFR family of RTKs.

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