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QSAR study of flavonoid derivatives as p56lck tyrosinkinase inhibitors

Abhilash Thakur,* S. Vishwakarma and Mamta Thakur

Department of Chemistry, Softvision Institute of Biotechnology, Indore, India

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Abstract—QSAR studies on 104 flavonoid derivatives as p56lck protein tyrosinekinase inhibitors were performed using hydration energy and logP as predictor parameters. The results obtained demonstrate in detail, which specify that hydration energy and hydrophobic parameters of the compounds play a significant role in developing QSAR models. The significance of presence and absence of substituents on particular position is successfully explored with the help of indicator parameters. The results are critically discussed on the basis of multiple linear regression parameters.

1. Introduction

Protein tyrosine kinases (PTKs) are well known for providing central switching mechanism in cellular signal transduction pathways by catalysing the transfer of the g-phosphate of either ATP or GTP to specific tyrosine residues in protein substrates.[1,2] They are important mediators of normal cellular signal transduction,[3–5] and enough evidence are now available which suggests that the inappropriate or elevated expression of these contribute to the transformed state of cells in many human malignancies.[6–8]

The importance of these class of enzymes in signal transduction and the association of aberrant PTK expression with proliferative disorders make substances which modulate the activity of PTKs attractive therapeutic agents.[9,10] Central to the function of all PTKs is the recognition and binding of a nucleoside triphosphate (usually ATP) and an appropriate tyrosyl-containing substrate, followed by the ensuing direct transfer of phosphate between the two.[11]

It is well known that flavonoids are a group of low molecular weight plant products, and are building block of flavone (2-phenyl-chromone, or 2-phenylbenzopyrone). A large number of natural and synthetic flavonoids have been tested for their PTK inhibitory activities. Kinetic analyses of the PTK Inhibition indicated that flavonoids were competitive inhibitors with respect to the nucleotide ATP.[12–18] Flavones and isoflavones differ in their inhibitory profiles both in their relative selectivity towards PTKs versus serine/threonine kinases and in their potencies among different PTKs.[13] Various synthetic flavonoid analogues have been prepared[14–16] with the goal of the development of PTK Inhibitors as chemotherapeutic agents.

Quantitative Structure–Activity Relationship (QSAR) study is basically concerned with the correlation of structure with property/activity. Several physicochemical descriptors, such as hydrophobicity, topology, electronic parameters and steric effects, are usually used in QSAR studies in many disciplines, with many pertaining to drug design and environmental risk assessments.[19,20] A large number of QSAR studies, involving flavonoids as PTKs inhibitors, have been published.[12–18]

Earlier, Nikolovska-Coleska and coworkers,[21] based on classical and quantum approach have shown that hydrophobic properties, molar refractivity and charge at phenyl ring region of the flavone molecule plays dominating role in developing QSAR models. Also, effect due to quantum parameters surface area of total electron density, net charge on the 3′ and 4′ positions, sum of charges on substituted carbon atom of the chrome moiety (C3, C5, C6, C7, C8) are also tested in developing QSAR of flavonoids. However, very poor statistic is obtained.

Keywords: QSAR; Flavonoid derivatives; p56lck protein tyrosinekinase; Hydration energy; logP.
* Corresponding author. Tel.: +91-731-2482454; fax: +91-731-2763618; e-mail: abhilashthakur@yahoo.com

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In view of the above, in the present work we describe QSAR study on flavonoids using hydration energy and hydrophobic parameters for entire set of 104 flavonoid derivatives, that inhibitors of p56 lck protein tyrosine kinase (Fig. 1).

2. Results and discussion

The flavones with amino- and nitro-substituents were gathered (series comprises of 31 compounds) as a separate class (family), that is, category-I. The second category-II includes 39 derivatives bearing *ortho*-, *meta*-, *para*-, and multiple-substituents of hydroxyl and methoxy group in benzopyrone and phenyl ring (Table 1, set b). The remaining 34 inactive compounds form the third category-III.

Table 2 records the six indicator parameters used in present study, that is, I_3, indicates presence of substituents at R3 position by $I_3 = 1$ otherwise zero, I_{NH} indicates presence of amino group by $I_{NH} = 1$, otherwise 0. I_1 indicates presence of –OH group at any position by $I_1 = 1$, otherwise 0. I_{OH} indicates presence of –OH group on phenyl ring by $I_{OH} = 1$ otherwise 0. I_{NO_2} indicates presence of nitro group by $I_{NO_2} = 1$, otherwise 0. I_{OMe} indicates presence of methoxy group by $I_{OMe} = 1$, otherwise 0.

In mono-, di-, tri- and tetra-parametric regressions a good correlation is obtained consisting of hydrophobic parameter (logP) and hydration energy (He), along with containing indicator parameters. The correlation matrix needed for the multiple regression analyses is shown in Table 3.

The regression analysis performed over set of 31 compounds yielded the following tri- and tetra-parametric models-

$$\log 1/IC_{50} = 0.1586(\pm 0.0784)\log P - 0.0799(\pm 0.0268)He + 0.6499 \times (\pm 0.2148)I_{NH} + 2.3047 \quad (1)$$

$n = 31,\ r = 0.8257,\ Se = 0.4067,\ F = 19.283,\ Q = 2.030$

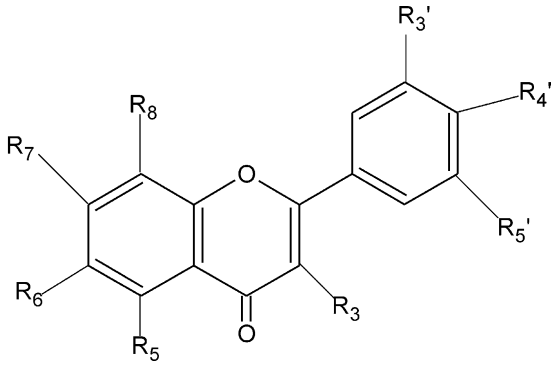

Figure 1. Parent structure of flavonoid derivatives used in present study.

$$\log 1/IC_{50} = 0.2071(\pm 0.0895)\log P - 0.1231(\pm 0.0473)He - 0.3169(\pm 0.2866)I_1 + 0.5420(\pm 0.2351)I_{NH} + 2.0029 \quad (2)$$

$n = 31,\ r = 0.8343,\ Se = 0.4050,\ F = 14.887,\ Q = 2.06$

Here and here after, n is the number of compounds, Se is the standard error of estimation, r is the correlation coefficient, F is the F-static and Q is the quality factor = R/Se.

In eqs 1 and 2, the positive coefficient of logP suggests that higher value of logP favors inhibitory action. In both the equations, negative coefficient of hydration energy (He) suggests that higher hydration energy reduces biological activity of compounds. I_{NH} with positive coefficient suggests that presence of amino group enhance the biological activity.

In eq 2, negative coefficient of I_1 indicates that the presence of –OH group decreases biological activity.

It is concluded, therefore, that compounds with higher logP, lower hydration energy, presence of amino group and absence of –OH group is favorable for the tyrosin kinase Inhibitory action of set a containing 31 flavonoid derivatives.

It is interesting to record that the tri- and tetra-parameters regressions obtained by Zaneta and coworkers[21] gave the following results:

Tri-parametric equation:

$r = 0.818,\ Se = 0.42,\ F = 17.47,\ Q = 1.947$

Tetra-parametric equation:

$r = 0.820,\ Se = 0.42,\ F = 12.78,\ Q = 1.950$

This shows that the models obtained by us are better model than those proposed by Nikolovska-Coleska and co-workers,[21] which is further confirmed by the value of Q factor.[22,23]

The regression analysis carried out on the another set of 39 compounds yielded the following models:

$$\log 1/IC_{50} = 0.1537(\pm 0.0940)\log P - 0.0803(\pm 0.0165)He - 0.4602(\pm 0.1711)I_3 + 2.8095 \quad (3)$$

$n = 39,\ r = 0.7948,\ Se = 0.4815,\ F = 17.125,\ Q = 1.650$

$$\log 1/IC_{50} = 0.1436(\pm 0.0942)\log P - 0.0739 \times (\pm 0.0174)He - 0.4184(\pm 0.1748)I_3 + 0.2110(\pm 0.1930)I_{OH} + 2.7485 \quad (4)$$

$n = 39,\ r = 0.8036,\ Se = 0.48,\ F = 13.677,\ Q = 1.674$

Table 1. Structural details of flavonoid derivatives and their biological activity log1/IC_{50}

No.	Substituents	log1/IC_{50} (obsd)	log1/IC_{50} (calc)	Residual		No.	Substituents	log1/IC_{50} (obsd)	log1/IC_{50} (calc)	Residual	
1	5,7-OH,4-NH_2	5.13	4.18	0.95	a	**53**	5-OMe,8,4-NH_2	2.79	3.66	−0.87	a
2	3,5,7,3,4-OH	4.88	4.38	0.50	b	**54**	7-OH,8,4-NO_2	2.73	2.89	−0.16	a
3	3,7,3,4-OH	4.86	4.20	0.66	b	**55**	3-COOMe,3,4,5-OMe	2.70	2.68	0.02	b
4	5,7,4-OH	4.83	4.19	0.63	b	**56**	3-COOMe,3,5-OMe	2.70	2.51	0.19	b
5	5,4-OH	4.80	3.98	0.82	b	**57**	3-COOMe,3,4-OMe	2.70	2.91	−0.21	b
6	6,3-OH	4.80	4.01	0.79	b	**58**	3-COOMe,4-OBn	2.70	2.67	0.03	b
7	6-OH,5,7,4-NH_2	4.74	3.97	0.77	a	**59**	3-COOMe,7-OMe,4-OBn	2.70	2.62	0.08	b
8	5,7-OH	4.71	3.40	1.31	b	**60**	3-COOMe,6-OMe,4-OBn	2.70	2.62	0.08	b
9	4-OH,3,5-OCH_3	4.57	3.47	1.10	b	**61**	3-COOH,4-Br	2.70	2.64	0.06	b
10	5,7,3,4-OH	4.46	4.42	0.04	b	**62**	3-COOH,4-NO_2	2.70	2.57	0.13	a
11	7,3-OH	4.41	4.01	0.40	b	**63**	3-COOH,7-OMe,4-NO_2	2.70	2.53	0.17	a
12	6-OH,5,7,3-NH_2	4.34	3.88	0.46	a	**64**	3-COOH,6-OMe,4-NO_2	2.70	2.54	0.16	a
13	6-OMe,8,3-NH_2	4.25	3.66	0.59	a	**65**	3-COOH,5,7-OH,4-NO_2	2.70	2.99	−0.29	a
14	6-OH,3,4,5-OCH_3	4.22	3.32	0.90	b	**66**	4-NO_2	2.70	2.89	−0.19	a
15	3,5,7,4-OH,3,5-OCH_3	4.16	3.84	0.32	b	**67**	6,4-NO_2	2.70	2.82	−0.12	a
16	3,5,7,3,5-OH	4.00	4.35	−0.35	b	**68**	8,4-NO_2	2.70	2.71	−0.01	a
17	6,4-NH_2	3.99	3.80	0.19	a	**69**	6-OMe,8,4-NO_2	2.70	2.67	0.03	a
18	6,8,4-NH_2	3.97	3.75	0.22	a	**70**	5-OMe,8,4-NO_2	2.70	2.66	0.04	a
19	6-OH,8,4-NH_2	3.93	3.95	−0.02	a	**71**	7-OH,4-OBn	2.70	2.97	−0.27	c
20	6,4-OH	3.93	4.03	−0.10	b	**72**	7,8,3,4,5-OCH_3	2.70	3.07	−0.37	c
21	7,4-OH,3,5-OCH_3	3.92	3.72	0.20	b	**73**	7,8-OH,3,5-OCH_3,4-OR	2.70	3.25	−0.55	c
22	6-OH,4-OR	3.92	3.09	0.83	b	**74**	7,8-OAc,3,5-OMe,4e	2.70	1.72	0.97	c
23	8,4-NH_2	3.91	3.72	0.19	a	**75**	6,3,4,5-OCH_3	2.70	3.04	−0.34	c
24	6,4-OH,3,5-OCH_3	3.89	3.72	0.17	b	**76**	7-OH,3,4,5-OCH_3	2.70	3.32	−0.62	c
25	7-OH,4-NH_2	3.86	3.99	−0.13	a	**77**	7-OAc,3,5-OCH_3,4-OH	2.70	2.71	−0.01	c
26	7-OH,6,4-NH_2	3.85	3.97	−0.12	a	**78**	7-OAc,3,5-OCH_3,4-OR	2.70	2.10	0.60	c
27	7,4-OH	3.78	4.03	−0.25	b	**79**	7,3,4,5-OCH_3	2.70	3.03	−0.33	c
28	7,8,3-OH	3.75	4.14	−0.39	b	**80**	3,5-OCH_3	2.70	2.88	−0.18	c
29	6,3-NH_2	3.70	3.78	−0.08	a	**81**	5-OH,4-OBn	2.70	3.17	−0.47	c
30	4-NH_2	3.68	3.74	−0.06	a	**82**	3,COOMe,4-OMe	2.70	2.61	0.09	c
31	5-OH,6,4-NH_2	3.65	3.80	−0.15	a	**83**	3-COOMe,4-Br	2.70	2.64	0.06	c
32	3,5,7-OH	3.53	3.36	0.17	b	**84**	3-COOMe,4-NO_2	2.70	2.57	0.13	c
33	5,4-OH,7-OCH_3	3.55	3.93	−0.38	b	**85**	3-COOMe,7-OMe,4-NO_2	2.70	2.68	0.02	c
34	5,3-OH	3.50	3.96	−0.46	b	**86**	3-COOMe,6-OMe,4-NO_2	2.70	2.54	0.16	c
35	7,8-OH	3.50	3.35	0.15	b	**87**	3-COOMe,5,7-OBn,4-NO_2	2.70	2.57	0.13	c
36	5-OH,8,4-NH_2	3.49	3.91	−0.42	a	**88**	3-COOH,3,4,5-OMe	2.70	2.76	−0.06	c
37	7-OH,8,4-NH_2	3.48	3.93	−0.45	a	**89**	3-COOH,3,5-OMe	2.70	2.57	0.13	c
38	7-OH	3.47	3.22	0.25	b	**90**	3-COOH,3,4-OMe	2.70	2.94	−0.24	c
39	6-OH,3,5-OCH_3,4-OR	3.43	3.12	0.31	b	**91**	3-COOH,4-OMe	2.70	2.61	0.09	c
40	6-OMe,8,4-NH_2	3.42	3.68	−0.26	a	**92**	3-COOMe,7-OMe,4-OH	2.70	3.41	−0.71	c
41	7,8-OH,3,4,5-OCH_3	3.40	3.45	−0.05	b	**93**	3-COOMe,6-OMe,4-OH	2.70	3.41	−0.71	c
42	3-COOMe,4-OH	3.36	3.44	−0.08	b	**94**	3-COOMe,7-OMe,4-NHAc	2.70	2.56	0.14	c
43	4-OH	3.30	3.78	−0.48	b	**95**	3-COOMe,6-OMe,4-NHAc	2.70	2.56	0.14	c
44	7-OH,6,3-NH_2	3.30	2.95	0.35	a	**96**	7-OH,4-NO_2	2.70	3.14	−0.44	c
45	7-OH,6,8,4-NH_2	3.12	3.89	−0.77	a	**97**	6-OH,4-NO_2	2.70	3.14	−0.44	c
46	3-COOMe,4-NH_2	3.09	3.41	−0.32	a	**98**	5,7-OH,4-NO_2	2.70	3.33	−0.63	c
47	7-OH,4-OR	3.01	3.09	−0.08	b	**99**	7-OH,6,4-NO_2	2.70	2.90	−0.20	c
48	3-COOH,7-OMe,4-OH	2.99	3.44	−0.45	b	**100**	5-OH,8,4-NO_2	2.70	2.90	−0.20	c
49	7,4-OH,3,5-OCH_3	2.90	3.47	−0.57	b	**101**	6,8,4-NO_2	2.70	2.61	0.09	c
50	7-OH,3,5-OCH_3,4-OR	2.82	3.12	−0.30	b	**102**	6-OH,8,4-NO_2	2.70	2.94	−0.24	c
51	7-OH,6,8,4-NO_2	2.81	2.65	0.16	a	**103**	5-OH,6,4-NO_2	2.70	2.85	−0.15	c
52	3-COOH,4-OH	2.80	3.48	−0.68	b	**104**	6-OH,5,7,4-NO_2	2.70	2.70	−0.00	c

In models expressed by eqs 3 and 4, the role of logP and hydration energy He is the same for the models expressed by eqs 1 and 2. The negative coefficient of indicator I_3 in the above eqs 3 and 4 suggests that the substitution at R_3 inhibits the tirosinkinase inhibitory action for this set of flavonoid derivatives. The positive coefficient of indicator parameter I_{OH} in eq 4 expressed that the presence of –OH group on phenyl moiety is favorable for the tirosinkinase Inhibitory action of these flavonoid derivatives.

The results obtained by Nikolovska-Coleska and coworkers[21] on the same set of compound gave the following statistics:

Tri-parametric model

$r = 0.729$, Se $= 0.53$, $F = 13.60$, $Q = 1.375$

Tetra-parametric model

$r = 0.789$, Se $= 0.48$, $F = 14.47$, $Q = 1.643$

Therefore, here also our results are better than those reported by Nikolovska-Coleska and coworkers.[21]

We now report our results on the combined set of (30 + 40) 70 compounds. The best model obtained being:

Table 2. Hydrophobic parameters and Indicator parameters of flavonoid derivatives used

Compd	logP	He	I_1	I_3	I_{OH}	I_{NH}	I_{NO_2}	I_{OMe}	Compd	logP	He	I_1	I_3	I_{OH}	I_{NH}	I_{NO_2}	I_{OMe}
1	−2.78	−22.21	1	0	0	1	0	0	**53**	−3.44	−14.62	0	0	0	1	0	0
2	−4.01	−34.51	1	1	1	0	0	0	**54**	−5.53	−18.37	1	0	0	0	1	0
3	−2.99	−29.01	1	1	1	0	0	0	**55**	−2.54	−11.20	0	1	0	0	0	1
4	−0.03	−18.88	1	0	1	0	0	0	**56**	−1.46	−5.59	0	1	0	0	0	1
5	−1.06	−17.48	1	0	1	0	0	0	**57**	−1.46	−12.69	0	1	0	0	0	1
6	−1.06	−18.06	1	0	1	0	0	0	**58**	0.74	−3.40	0	1	0	0	0	1
7	−3.47	−20.14	1	0	0	1	0	0	**59**	−0.25	−4.77	0	1	0	0	0	1
8	−1.06	−17.16	1	0	0	0	0	0	**60**	−0.25	−4.89	0	1	0	0	0	1
9	−2.02	−10.78	1	0	1	0	0	1	**61**	0.58	−3.22	0	1	0	0	0	0
10	−3.11	−29.93	1	0	1	0	0	0	**62**	−2.22	−8.41	0	1	0	0	1	0
11	−1.06	−18.07	1	0	1	0	0	0	**63**	−3.21	−10.05	0	1	0	0	1	0
12	−5.19	−22.49	1	0	0	1	0	0	**64**	−3.21	−10.16	0	1	0	0	1	0
13	−3.44	−14.55	0	0	0	1	0	0	**65**	−4.27	−20.62	1	1	0	0	1	0
14	−3.02	−20.12	1	0	0	0	0	1	**66**	−1.76	−9.79	0	0	0	0	1	0
15	−4.97	−27.31	1	1	1	0	0	1	**67**	−4.51	−14.72	0	0	0	0	1	0
16	−4.01	−34.04	1	1	1	0	0	0	**68**	−4.51	−12.78	0	0	0	0	1	0
17	−2.45	−14.71	0	0	0	1	0	0	**69**	−5.50	−14.38	0	0	0	0	1	0
18	−4.17	−17.86	0	0	0	1	0	0	**70**	−5.50	−14.18	0	0	0	0	1	0
19	−3.47	−19.75	1	0	0	1	0	0	**71**	1.20	−4.45	1	0	0	0	0	1
20	−1.06	−18.36	1	0	1	0	0	0	**72**	−1.99	−13.38	0	0	0	0	0	1
21	−3.05	−17.52	1	0	1	0	0	1	**73**	−3.37	−19.73	1	0	0	0	0	1
22	−0.36	−9.97	1	0	0	0	0	0	**74**	−3.89	5.91	0	0	0	0	0	1
23	−2.45	−13.28	0	0	0	1	0	0	**75**	−2.99	−15.16	0	0	0	0	0	1
24	−3.05	−17.51	1	0	1	0	0	1	**76**	−3.02	−20.13	1	0	0	0	0	1
25	−1.76	−16.59	1	0	0	1	0	0	**77**	−3.47	−0.59	1	0	1	0	0	1
26	−3.47	−20.11	1	0	0	1	0	0	**78**	−2.76	1.84	0	0	0	0	0	1
27	−1.06	−18.37	1	0	1	0	0	0	**79**	−2.99	−15.01	0	0	0	0	0	1
28	−2.09	−22.70	1	0	1	0	0	0	**80**	−1.00	−7.86	0	0	0	0	0	1
29	−2.45	−14.41	0	0	0	1	0	0	**81**	0.18	−10.31	1	0	0	0	0	1
30	−0.73	−9.84	0	0	0	1	0	0	**82**	−0.46	−5.13	0	1	0	0	0	1
31	−2.45	−14.71	1	0	0	1	0	0	**83**	0.58	−3.22	0	1	0	0	0	0
32	−1.96	−21.71	1	1	0	0	0	0	**84**	−2.22	−8.41	0	1	0	0	1	0
33	−2.06	−18.91	1	0	1	0	0	0	**85**	−4.63	−15.87	0	1	0	0	1	0
34	−1.06	−17.18	1	0	1	0	0	0	**86**	−3.21	−10.16	0	1	0	0	1	0
35	−1.06	−16.17	1	0	0	0	0	0	**87**	−2.00	−8.01	0	1	0	0	1	0
36	−3.47	−19.09	1	0	0	1	0	0	**88**	−2.48	−12.37	0	1	0	0	0	1
37	−3.47	−19.32	1	0	0	1	0	0	**89**	−1.49	−6.79	0	1	0	0	0	1
38	−0.04	−11.54	1	0	0	0	0	0	**90**	−1.49	−13.24	0	1	0	0	0	1
39	−2.34	−15.07	1	0	0	0	0	1	**91**	−0.46	−5.13	0	1	0	0	0	1
40	−3.44	−14.85	0	0	0	1	0	0	**92**	−1.49	−11.67	1	1	1	0	0	0
41	−4.04	−24.76	1	0	0	0	0	1	**93**	−1.49	−11.78	1	1	1	0	0	0
42	−0.50	−10.03	1	1	1	0	0	0	**94**	−2.56	3.59	0	1	0	1	0	0
43	−0.04	−11.62	1	0	1	0	0	0	**95**	−2.56	3.47	0	1	0	1	0	0
44	−3.35	−17.66	1	1	0	0	0	0	**96**	−2.83	−16.54	1	0	0	0	1	0
45	−5.19	−22.62	1	0	0	1	0	0	**97**	−2.78	−16.53	1	0	0	0	1	0
46	−1.19	−8.28	0	1	0	1	0	0	**98**	−3.81	−22.16	1	0	0	0	1	0
47	−0.36	−9.98	1	0	0	0	0	0	**99**	−5.53	−18.52	1	0	0	0	1	0
48	−1.52	−12.35	1	1	1	0	0	0	**100**	−5.53	−18.62	1	0	0	0	1	0
49	−2.02	−10.78	1	0	1	0	0	1	**101**	−7.25	−17.41	0	0	0	0	1	0
50	−2.34	−15.08	1	0	0	0	0	1	**102**	−5.53	−19.18	1	0	0	0	1	0
51	−8.28	−20.40	1	0	0	0	1	0	**103**	−5.53	−17.71	1	0	0	0	1	0
52	−0.53	−10.72	1	1	1	0	0	0	**104**	−8.02	−20.77	1	0	0	0	1	0

logP, octenol/water partition coefficient; He, hydration energy; I_1, presence of –OH group at any position by 1, otherwise 0; I_3, presence of substituents at R3 position by 1 otherwise 0; I_{OH}, presence of –OH group on phenyl ring by 1 otherwise 0; I_{NH}, presence of amino group by 1 otherwise 0; I_{NO_2}, presence of nitro group by 1 otherwise 0; I_{OMe}, presence of Methoxy group by 1 otherwise 0.

Table 3. Correlation matrix for the parameters and log1/IC_{50} of flavonoid derivatives

log1/IC_{50}	logP	He	I_1	I_3	I_{OH}	I_{NH}	I_{NO_2}	I_{OMe}	
log1/IC_{50}	1.0000								
logP	0.0796	1.000							
He	−0.5427	0.4492	1.000						
I_1	0.4372	−0.0774	−0.5727	1.000					
I_3	−0.2831	0.2503	0.2731	−0.3524	1.000				
I_{OH}	0.4416	0.1995	−0.2769	0.4723	0.0279	1.000			
I_{NH}	0.3115	−0.1164	−0.0357	−0.1127	−0.2061	−0.2829	1.000		
I_{NO_2}	−0.4337	−0.5578	−0.0602	−0.1425	−0.0037	−0.3081	−0.2755	1.000	
I_{OME}	−0.2537	0.2079	0.2964	−0.1785	0.0697	−0.0714	−0.3277	−0.3569	1.000

$$\log 1/IC_{50} = 0.2214(\pm 0.0385)\text{logP} - 0.0901(\pm 0.0102)\text{He} - 0.4746(\pm 0.1252)I_3 + 2.8080 \quad (5)$$

$n = 70,\ r = 0.7896,\ \text{Se} = 0.4603,\ F = 34.225,\ Q = 1.710$

$$\log 1/IC_{50} = 0.2360(\pm 0.0375)\text{logP} - 0.0924(\pm 0.0098)\text{He} - 0.3664(\pm 0.1283)I_3 + 0.3205(\pm 0.1309)I_{NH} + 2.6814 \quad (6)$$

$n = 70,\ r = 0.8107,\ \text{Se} = 0.4428,\ F = 29.238,\ Q = 1.83$

Eq 5 suggests that substituents at R3 position decreases $\log 1/IC_{50}$.

From the above results, we concluded that presence of amino- group and absence of substituents at R_3 is preferable over presence of –OH at phenyl moiety or absence of –OH in a molecule for a set of 70 flavonoids.

The results obtained by Nikolovska-Coleska and co-workers[21] for the same set of 70 compounds are given below:

Tri-parametric model

$n = 70,\ r = 0.715,\ \text{Se} = 0.52,\ F = 23.05,\ Q = 1.375$

Tetra-parametric model

$n = 70,\ r = 0.789,\ \text{Se} = 0.46,\ F = 26.80,\ Q = 1.710$

Thus, our results are slightly better than those reported by Nikolovska-Coleska and co-workers.[21]

Finally, for the entire set of 104 flavonoid derivatives, eqs 7 and 8 were the best suited:

$$\log 1/IC_{50} = 0.0497(\pm 0.0068)\text{He} - 0.9622(\pm 0.1159)I_{NO_2} - 0.4557(\pm 0.1172)I_{OMe} + 2.9154 \quad (7)$$

$n = 104,\ r = 0.7783,\ \text{Se} = 0.4611,\ F = 48.148,\ Q = 1.688$

$$\log 1/IC_{50} = 0.1221(\pm 0.0292)\text{logP} - 0.0595(\pm 0.0077)\text{He} + 0.5677(\pm 0.1215)I_{OH} + 0.7633(\pm 0.1145)I_{NH} + 2.4257 \quad (8)$$

$n = 104,\ r = 0.8032,\ \text{Se} = 0.4398,\ F = 42.267,\ Q = 1.826$

The positive coefficient of I_{OH} and I_{NH} favors the presence of the amino-group and presence of –OH group on phenyl moiety for the tyrosinkinase inhibition activity. Due to other substituents the positional significance of indicator I_3 or third position were decreases and the role of –OH group on phenyl moiety enhance for the tyrosinkinase inhibition activity.

The statistics obtained from the tri- and tetra-parametric models for the set of 104 compounds by Nikolovska-Coleska and co-workers[21] are found as below:

$n = 104,\ r = 0.750,\ \text{Se} = 0.48,\ F = 42.79,\ Q = 1.56$

$n = 104,\ r = 0.747,\ \text{Se} = 0.48,\ F = 31.20,\ Q = 1.556$

Hence, the results obtained by us for this set of 104 compounds are again of better quality.

Finally, the penta-parameteric model gave slightly better statistics:

$$\log 1/IC_{50} = 0.1300(\pm 0.0291)\text{logP} - 0.0568(\pm 0.0077)\text{He} - 0.188(\pm 0.0999)I_3 + 0.5591(\pm 0.1199)I_{OH} + 0.7137(\pm 0.1159)I_{NH} + 2.5666 \quad (9)$$

$n = 104,\ r = 0.8115,\ \text{Se} = 0.4337,\ F = 35.485,\ Q = 1.870$

3. Conclusion

The statistical analyses based on logP and hydration energy He with indicator parameters led us to propose the explanation of the structure–activity relationships, which covers a wide range of substituents as well as a verity of physicochemical interaction involve in the enzyme–inhibitors complex. The models proposed in present work are more useful in describing QSAR of flavonoid derivatives as p56lck Protein Tyrosinkinase Inhibitors than that of Nikolovska-Coleska et al.[21]

4. Experimental

4.1. Molecular descriptors

In the present study, the parameters used in the present work are He, an energy released when water molecules surrounds any flavonoids and logP is the logarithm of octanol/water partition coefficient accounts for hydrophobic nature of drug molecules. These are calculated from software hyperchem 7 (demo version)[24] and shown in Table 2.

4.2. Indicator parameters

Six indicator parameters, I_3, I_{NH}, I_1, I_{OH}, I_{NO2} and I_{OMe} are used and also recorded in the Table 2. I_1 is used for presence of –OH group at any position by 1, I_3 is the

account for the presence of substituents at the R3 position, I_{OH} indicate the presence of –OH group on phenyl ring by 1, I_{NH} is account of amino group by 1, I_{NO_2} is used for the presence of nitro group by 1, I_{OMe} is the account of presence of methoxy group by 1 otherwise 0.

4.3. Biological activity

The biological assay data used in our study are results of in vitro tests for Inhibitory activity against protein-tyrosine kinase p56lck, a lymphoid cell lineage-specific PTK of the src family which taken from literature.[21,25,26] Molecular structure and numbering of the substituents in the flavonoid derivatives are represented in Figure 1 and structures of the used flavone derivatives (natural and synthetic) along their Inhibitory data, are summarized in Table 1.

4.4. Regression analysis

In the present study linear mathematical models are developed to study Quantitative structure/property–activity relationship (QSARs). Multiple linear regressions are used to develop these models.

Step-wise regression has been performed for obtaining the best model. The predictive potential of these models are discussed on the basis of quality factor (Q).[22]

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