Comparison of Topological, Physiochemical and Hydrophobic Parameters for QSAR Study on Flavonoid Derivatives as Tyrosins Kinase Inhibitors

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Introduction

QSAR studies on 104 flavonoid derivatives as p56lck protein tyrosine kinase inhibitors were performed using hydration energy and logP as predictor parameters. The results obtained demonstrate in detail, which specify that molar volume and density and polarisibility 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.

A **tyrosine kinase**[1] is an enzyme that can transfer a phosphate group from ATP to a protein in a cell. It functions as an "on" or "off" switch in many cellular functions.

Tyrosine kinases are a subclass of protein **kinase**. The phosphate group is attached to the amino acid **tyrosine** on the protein.**Tyrosine kinase inhibitors** (TKIs) block chemical messengers (enzymes) called **tyrosine kinases**. **Tyrosine kinases** help to send growth signals in cells, so blocking them stops the cell growing and dividing.

The set of 104 flavonoid derivatives is divided in three different sets based on the nature of substitution type of substitution and activity shown by the compounds. The flavonoids[2] with amino- and nitro- substituents were gathered (series comprises of 31 compounds) as a separate class (family) i.e., 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 1, set c).

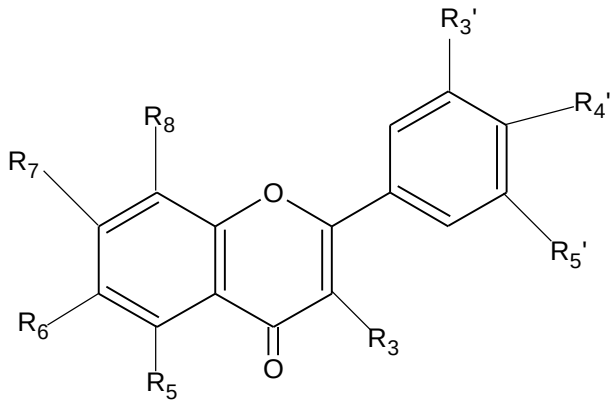


Figure 1. Parent structure of flavonoid derivatives used in present study.

Method:-
For the analysis of Tyrosin kinase inhibition activity we have calculated the various graph theoretical indices and physicochemical parameters[3] with the help of computer software Dragon, ACD labs and Hyperchem light. Along with these parameters we have tested the Octanol/Water partition coefficient and hydration energy for the flavonoid derivatives. These parameters and indices are recorded in Table 2 .These graph theoretical[4] indices represent the size, shape, connectivity and branching of the molecule.

The physicochemical parameters represent the volume of the compounds, refractive properties, surface properties and staric nature[5] of the molecule. Octanol/Water partition coefficient use to represent the hydrophobicity or lipophilicity of the molecule, it also can be used to explore the permeability properties for different biological barriers[6].

Table1. Structural details of Flavonoid derivatives and their biological activity log1/C.

No.	Substituents	log1/C(Obs.)	
1	5,7-OH,4-NH_2	5.13	a
2	3,5,7,3,4-OH	4.88	b
3	3,7,3,4-OH	4.86	b
4	5,7,4-OH	4.83	b
5	5,4-OH	4.80	b
6	6,3-OH	4.80	b
7	6-OH,5,7,4-NH_2	4.74	a
8	5,7-OH	4.71	b
9	4-OH,3,5-OCH_3	4.57	b
10	5,7,3,4-OH	4.46	b
11	7,3-OH	4.41	b
12	6-OH,5,7,3-NH_2	4.34	a
13	6-OMe,8,3-NH_2	4.25	a
14	6-OH,3,4,5-OCH_3	4.22	b
15	3,5,7,4-OH,3,5-OCH_3	4.16	b
16	3,5,7,3,5-OH	4.00	b
17	6,4-NH_2	3.99	a
18	6,8,4-NH_2	3.97	a
19	6-OH,8,4-NH_2	3.93	a
20	6,4-OH	3.93	b
21	7,4-OH,3,5-OCH_3	3.92	b
22	6-OH,4-OR	3.92	b
23	8,4-NH_2	3.91	a
24	6,4-OH,3,5-OCH_3	3.89	b
25	7-OH,4-NH_2	3.86	a
26	7-OH,6,4-NH_2	3.85	a
27	7,4-OH	3.78	b
28	7,8,3-OH	3.75	b
29	6,3-NH_2	3.70	a
30	4-NH_2	3.68	a
31	5-OH,6,4-NH_2	3.65	a
32	3,5,7-OH	3.53	b
33	5,4-OH,7-OCH_3	3.55	b
34	5,3-OH	3.50	b
35	7,8-OH	3.50	b
36	5-OH,8,4-NH_2	3.49	a
37	7-OH,8,4-NH	3.48	a

38	7-OH	3.47	b
39	6-OH,3,5-OCH_3,4-OR	3.43	b
40	6-OMe,8,4-NH_2	3.42	a
41	7,8-OH,3,4,5-OCH_3	3.40	b
42	3-COOMe,4-OH	3.36	b
43	4-OH	3.30	b
44	7-OH,6,3-NH_2	3.30	a
45	7-OH,6,8,4-NH_2	3.12	a
46	3-COOMe,4-NH_2	3.09	a
47	7-OH,4-OR	3.01	b
48	3-COOH,7-OMe,4-OH	2.99	b
49	7,4-OH,3,5-OCH_3	2.90	b
50	7-OH,3,5-OCH_3,4-OR	2.82	b
51	7-OH,6,8,4-NO_2	2.81	a
52	3-COOH,4-OH	2.80	b
53	5-OMe,8,4-NH_2	2.79	a
54	7-OH,8,4-NO_2	2.73	a
55	3-COOMe,3,4,5-OMe	2.70	b
56	3-COOMe,3,5-OMe	2.70	b
57	3-COOMe,3,4-OMe	2.70	b
58	3-COOMe,4-OBn	2.70	b
59	3-COOMe,7-OMe,4-OBn	2.70	b
60	3-COOMe,6-O4-OBn	2.70	b
61	3-COOH,4-Br	2.70	b
62	3-COOH,4-NO_2	2.70	a
63	3-COOH,7-OMe,4-NO_2	2.70	a
64	3-COOH,6-OMe,4-NO_2	2.70	a
65	3-COOH,5,7-OH,4-NO_2	2.70	a
66	4-NO_2	2.70	a
67	6,4-NO_2	2.70	a
68	8,4-NO_2	2.70	a
69	6-OMe,8,4-NO_2	2.70	a
70	5-OMe,8,4-NO_2	2.70	a
71	7-OH,4-OBn	2.70	c
72	7,8,3,4,5-OCH_3	2.70	c
73	7,8-OH,3,5-OCH_3,4-OR	2.70	c
74	7,8-OAc,3,5-OMe,4e	2.70	c
75	6,3,4,5-OCH_3	2.70	c
76	7-OH,3,4,5-OCH_3	2.70	c

77	7-OAc,3,5-OCH_3,4-OH	2.70	c
78	7-OAc,3,5-OCH_3,4-OR	2.70	c
79	7,3,4,5-OCH_3	2.70	c
80	3,5-OCH_3	2.70	c
81	5-OH,4-OBn	2.70	c
82	3,COOMe,4-OMe	2.70	c
83	3-COOMe,4-Br	2.70	c
84	3-COOMe,4-NO_2	2.70	c
85	3-COOMe,7-OMe,4-NO_2	2.70	c
86	3-COOMe,6-OMe,4-NO_2	2.70	c
87	3-COOMe,5,7-OBn,4-NO_2	2.70	c
88	3-COOH,3,4,5-OMe	2.70	c
89	3-COOH,3,5-OMe	2.70	c
90	3-COOH,3,4-OMe	2.70	c
91	3-COOH,4-OMe	2.70	c
92	3-COOMe,7-OMe,4-OH	2.70	c
93	3-COOMe,6-OMe,4-OH	2.70	c
94	3-COOMe,7-OMe,4-NHAc	2.70	c
95	3-COOMe,6-OMe,4-NHAc	2.70	c
96	7-OH,4-NO_2	2.70	c
97	6-OH,4-NO_2	2.70	c
98	5,7-OH,4-NO_2	2.70	c
99	7-OH,6,4-NO_2	2.70	c
100	5-OH,8,4-NO_2	2.70	c
101	6,8,4-NO_2	2.70	c
102	6-OH,8,4-NO_2	2.70	c
103	5-OH,6,4-NO_2	2.70	c
104	6-OH,5,7,4-NO_2	2.70	c

Table 2. Physicochemicalparameters of Flavonoid derivatives used.

Comp.No.	MR	MV	HE	IR	ST	D	Pol
1.	72.2	178.4	534.1	1.743	80.3	1.509	28.62
2.	73.31	167.9	549.9	1.823	114.8	1.799	29.06
3.	71.43	169.5	534.6	1.784	98.9	1.688	28.32
4.	69.85	174.5	521.4	1.732	79.5	1.548	27.69
5.	67.97	176.1	506.1	1.698	68.2	1.443	26.94
6.	67.97	176.1	506.1	1.698	68.2	1.443	26.94
7.	78.79	184.5	574.8	1.798	94.1	1.535	31.23

8.	67.97	176.1	506.1	1.698	68.2	1.443	26.94
9.	79.44	225.7	608.2	1.621	52.7	1.321	31.49
10.	71.73	172.9	536.6	1.767	92.5	1.654	28.43
11.	67.97	176.1	506.1	1.698	68.2	1.443	26.94
12.	78.79	184.5	574.8	1.798	94.1	1.535	31.23
13.	79.35	207.8	590.2	1.689	65	1.358	31.45
14.	86.12	249.7	666.8	1.606	50.8	1.314	34.14
15.	84.79	217.5	651.9	1.707	80.6	1.591	33.61
16.	73.31	167.9	549.9	1.823	114.8	1.799	29.06
17.	72.67	183.8	531.6	1.72	69.9	1.372	28.81
18.	76.91	186.1	559.6	1.764	81.7	1.436	30.49
19.	74.56	182.2	546.8	1.754	81	1.471	29.55
20.	67.97	176.1	506.1	1.698	68.2	1.443	26.94
21.	81.32	224.1	623.4	1.645	59.8	1.402	32.24
22.	104.61	320	806.2	1.567	40.2	1.151	41.47
23.	72.67	183.8	531.6	1.72	69.9	1.372	28.81
24.	81.32	224.1	623.4	1.645	59.8	1.402	32.24
25.	70.32	179.9	518.9	1.709	69	1.407	27.87
26.	74.56	182.2	546.8	1.754	81	1.471	29.55
27.	67.97	176.1	506.1	1.698	68.2	1.443	26.94
28.	69.85	174.5	521.4	1.732	79.5	1.548	27.69
29.	72.67	183.8	531.6	1.72	69.9	1.372	28.81
30.	68.44	181.5	503.7	1.677	59.2	1.306	27.13
31.	74.56	182.2	546.8	1.754	81	1.471	29.55
32.	69.55	171.1	519.4	1.747	84.9	1.579	27.57
33.	74.64	200.1	564.8	1.668	63.4	1.42	29.59
34.	67.97	176.1	506.1	1.698	68.2	1.443	26.94
35.	67.97	176.1	506.1	1.698	68.2	1.443	26.94
36.	74.56	182.2	546.8	1.754	81	1.471	29.55
37.	74.56	182.2	546.8	1.754	81	1.471	29.55
38.	66.08	177.7	490.9	1.666	58.2	1.34	26.19
39.	117.97	368	923.5	1.554	39.6	1.164	46.76
40.	79.35	207.8	590.2	1.689	65	1.358	31.45
41.	88	248.1	682	1.627	57	1.387	34.88
42.	77.03	213.3	592.8	1.641	59.6	1.388	30.53
43.	66.08	177.7	490.9	1.666	58.2	1.34	26.19
44.	73.87	185.5	544.9	1.727	74.3	1.445	29.28
45.	78.79	184.5	574.8	1.798	94.1	1.535	31.23
46.	79.38	217.1	605.6	1.651	60.4	1.359	31.47

47.	104.61	320	806.2	1.567	40.2	1.151	41.47
48.	83.71	237.3	651.5	1.623	56.8	1.374	33.18
49.	81.32	224.1	623.4	1.645	59.8	1.402	32.24
50.	117.97	368	923.5	1.554	39.6	1.164	46.76
51.	85.72	213.2	662.1	1.736	92.9	1.75	33.98
52.	72.19	187.9	549.4	1.694	73	1.501	28.61
53.	79.35	207.8	590.2	1.689	65	1.358	31.45
54.	79.17	201.3	605	1.715	81.5	1.629	31.38
55.	95.18	286.8	753.5	1.577	47.5	1.29	37.73
56.	88.51	262.8	694.9	1.588	48.8	1.294	35.08
57.	88.51	262.8	694.9	1.588	48.8	1.294	35.08
58.	95.73	288.4	756.5	1.578	47.3	1.221	37.95
59.	102.4	312.4	815.1	1.569	46.3	1.224	40.59
60.	102.4	312.4	815.1	1.569	46.3	1.224	40.59
61.	78	205.6	585.3	1.682	65.5	1.677	30.92
62.	76.85	201.3	591.3	1.688	74.3	1.545	30.46
63.	83.53	225.3	649.9	1.663	69.1	1.514	33.11
64.	83.53	225.3	649.9	1.663	69.1	1.514	33.11
65.	80.61	198.2	62 1.	71.748	96.8	1.731	31.95
66.	70.75	191.1	532.8	1.662	60.4	1.398	28.04
67.	77.29	202.9	589.8	1.686	71.3	1.538	30.64
68.	77.29	202.9	589.8	1.686	71.3	1.538	30.64
69.	83.97	226.9	648.4	1.661	66.6	1.508	33.29
70.	83.97	226.9	648.4	1.661	66.6	1.508	33.29
71.	97.61	286.8	771.7	1.596	52.4	1.284	38.69
72.	97.59	299.2	768.8	1.565	43.5	1.244	38.69
73.	119.85	366.4	938.7	1.567	43	1.213	47.51
74.	91.29	269.9	728	1.591	52.9	1.371	36.19
75.	90.92	275.2	710.2	1.574	44.3	1.243	36.04
76.	86.12	249.7	666.8	1.606	50.8	1.314	34.14
77.	86.31	247	675.7	1.615	55.9	1.385	34.21
78.	122.95	390.9	975.8	1.541	38.8	1.167	48.74
79.	90.92	275.2	710.2	1.574	44.3	1.243	36.04
80.	77.56	227.2	592.9	1.598	46.3	1.242	30.74
81.	97.61	286.8	771.7	1.596	52.4	1.284	38.69
82.	81.83	238.8	636.2	1.6	50.3	1.298	32.44
83.	82.84	231	628.7	1.636	54.8	1.554	32.84
84.	81.69	226.7	634.7	1.64	61.4	1.434	32.38
85.	88.37	250.7	693.3	1.622	58.4	1.417	35.03

86.	88.37	250.7	693.3	1.622	58.4	1.417	35.03
87.	122.85	373.7	992.4	1.571	49.7	1.256	48.7
88.	90.34	261.5	710.1	1.607	54.3	1.362	35.81
89.	83.66	237.5	651.5	1.622	56.6	1.373	33.16
90.	70.31	189.5	534.2	1.664	63.1	1.404	27.87
91.	76.98	213.5	592.8	1.64	59.4	1.387	30.52
92.	83.71	237.3	651.5	1.623	56.8	1.374	33.18
93.	83.71	237.3	651.5	1.623	56.8	1.374	33.18
94.	91.62	255.6	711.7	1.635	60	1.382	36.32
95.	91.62	255.6	711.7	1.635	60	1.382	36.32
96.	72.63	189.5	548	1.692	69.8	1.494	28.79
97.	72.63	189.5	548	1.692	69.8	1.494	28.79
98.	74.51	187.9	563.2	1.723	80.6	1.591	29.54
99.	79.17	201.3	605	1.715	81.5	1.629	31.38
100.	79.17	201.3	605	1.715	81.5	1.629	31.38
101.	83.84	214.7	646.9	1.709	82.2	1.663	33.23
102.	79.17	201.3	605	1.715	81.5	1.629	31.38
103.	79.17	201.3	605	1.715	81.5	1.629	31.38
104.	85.72	213.2	662.1	1.736	92.9	1.75	33.98

$$\log 1/C = -0.0558(\pm 0.0068)He - 0.7861(\pm 0.1168)I_{NO2} + 2.6470 \quad (1)$$

n = 104, r = 0.7162, Se = 0.5011, F = 53.176, Q = 1.429

$$\log 1/C = 6.1570(\pm 0.7285)RI - 0.8498(\pm 0.1161)I_{NO2} - 6.8178 \quad (2)$$

n = 104, r = 0.7242, Se = 0.4951, F = 55.694, Q = 1.462

Table 3. Observed and Calculated activity obtained from Eq. 2.

No.	$\log 1/IC_{50}$(Obs.)	$\log 1/IC_{50}$(Calc)	Residual.	
1	5.13	4.18	0.95	a
2	4.88	4.38	0.50	b
3	4.86	4.20	0.66	b
4	4.83	4.19	0.63	b
5	4.80	3.98	0.82	b
6	4.80	4.01	0.79	b
7	4.74	3.97	0.77	a
8	4.71	3.40	1.31	b
9	4.57	3.47	1.10	b
10	4.46	4.42	0.04	b

11	4.41	4.01	0.40	b
12	4.34	3.88	0.46	a
13	4.25	3.66	0.59	a
14	4.22	3.32	0.90	b
15	4.16	3.84	0.32	b
16	4.00	4.35	-0.35	b
17	3.99	3.80	0.19	a
18	3.97	3.75	0.22	a
19	3.93	3.95	-0.02	a
20	3.93	4.03	-0.10	b
21	3.92	3.72	0.20	b
22	3.92	3.09	0.83	b
23	3.91	3.72	0.19	a
24	3.89	3.72	0.17	b
25	3.86	3.99	-0.13	a
26	3.85	3.97	-0.12	a
27	3.78	4.03	-0.25	b
28	3.75	4.14	-0.39	b
29	3.70	3.78	-0.08	a
30	3.68	3.74	-0.06	a
31	3.65	3.80	-0.15	a
32	3.53	3.36	0.17	b
33	3.55	3.93	-0.38	b
34	3.50	3.96	-0.46	b
35	3.50	3.35	0.15	b
36	3.49	3.91	-0.42	a
37	3.48	3.93	-0.45	a
38	3.47	3.22	0.25	b
39	3.43	3.12	0.31	b
40	3.42	3.68	-0.26	a
41	3.40	3.45	-0.05	b
42	3.36	3.44	-0.08	b
43	3.30	3.78	-0.48	b
44	3.30	2.95	0.35	a
45	3.12	3.89	-0.77	a
46	3.09	3.41	-0.32	a
47	3.01	3.09	-0.08	b
48	2.99	3.44	-0.45	b
49	2.90	3.47	-0.57	b

50	2.82	3.12	-0.30	b
51	2.81	2.65	0.16	a
52	2.80	3.48	-0.68	b
53	2.79	3.66	-0.87	a
54	2.73	2.89	-0.16	a
55	2.70	2.68	0.02	b
56	2.70	2.51	0.19	b
57	2.70	2.91	-0.21	b
58	2.70	2.67	0.03	b
59	2.70	2.62	0.08	b
60	2.70	2.62	0.08	b
61	2.70	2.64	0.06	b
62	2.70	2.57	0.13	a
63	2.70	2.53	0.17	a
64	2.70	2.54	0.16	a
65	2.70	2.99	-0.29	a
66	2.70	2.89	-0.19	a
67	2.70	2.82	-0.12	a
68	2.70	2.71	-0.01	a
69	2.70	2.67	0.03	a
70	2.70	2.66	0.04	a
71	2.70	2.97	-0.27	c
72	2.70	3.07	-0.37	c
73	2.70	3.25	-0.55	c
74	2.70	1.72	0.97	c
75	2.70	3.04	-0.34	c
76	2.70	3.32	-0.62	c
77	2.70	2.71	-0.01	c
78	2.70	2.10	0.60	c
79	2.70	3.03	-0.33	c
80	2.70	2.88	-0.18	c
81	2.70	3.17	-0.47	c
82	2.70	2.61	0.09	c
83	2.70	2.64	0.06	c
84	2.70	2.57	0.13	c
85	2.70	2.68	0.02	c
86	2.70	2.54	0.16	c
87	2.70	2.57	0.13	c
88	2.70	2.76	-0.06	c

89	2.70	2.57	0.13	c
90	2.70	2.94	-0.24	c
91	2.70	2.61	0.09	c
92	2.70	3.41	-0.71	c
93	2.70	3.41	-0.71	c
94	2.70	2.56	0.14	c
95	2.70	2.56	0.14	c
96	2.70	3.14	-0.44	c
97	2.70	3.14	-0.44	c
98	2.70	3.33	-0.63	c
99	2.70	2.90	-0.20	c
100	2.70	2.90	-0.20	c
101	2.70	2.61	0.09	c
102	2.70	2.94	-0.24	c
103	2.70	2.85	-0.15	c
104	2.70	2.70	-0.00	c

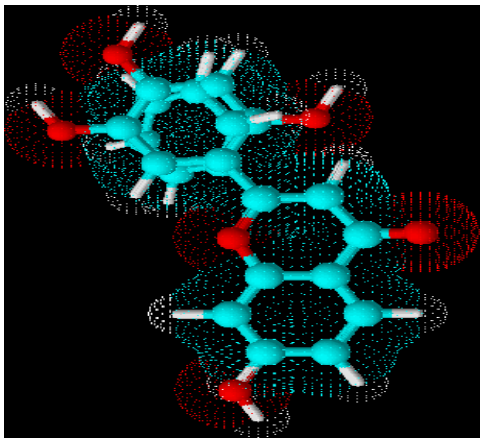
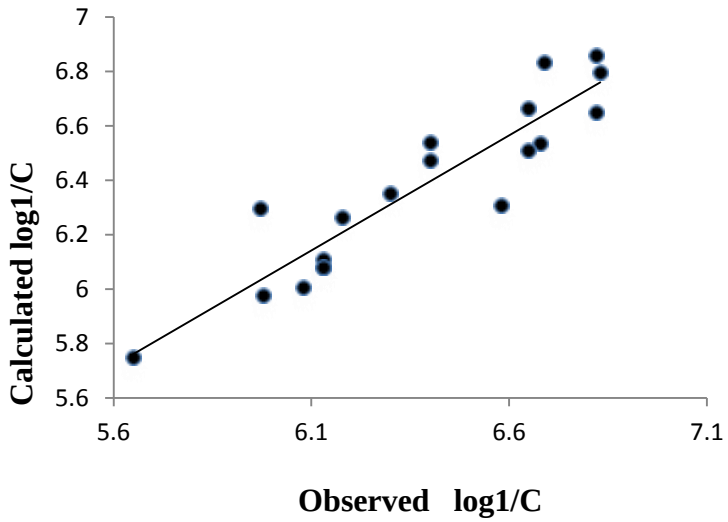


Figure 66. Molecular superimposing of compound no 66 on parent molecule.



Result and Discussion

1. Flavonoid derivatives under study, showing the dependence over the hydration energy and refractive properties in performing the PTK inhibition activity.
2. Presence of NO_2 substitution on the derivatives, make the ridge of the molecule little rigid due to lone pair of electron and double bong conjugation.
3. As nitro group is hydrophobic in nature when associated with cyclic structures it increases the effort required for hydration of these molecules or derivatives.
4. It is also revels from the study that the presence of NO_2 will increase the amount of hydration energy and also increases the biological activity.

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