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QSAR Study on Some *p*-Arylthio Cinnamides as Antagonists of Biochemical ICAM-1/LFA-1 Interaction and ICAM-1/JY-8 Cell Adhesion in Relation to Anti-inflammatory Activity

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Abstract—In an attempt to find out the chemical and structural features of some *p*-arylthio cinnamides **1** as antagonists of biochemical ICAM-1/LFA-1 interaction as well as ICAM-1/JY-8 cell adhesion in relation to anti-inflammatory activity, QSAR study was performed. Steric effect on the arylthio ring and lipophilic substitutions at 2,3-positions, especially 2,3-disubstitution with Cl or CF_3 or both on cinnamides **1** were conducive to the activity, whereas simultaneous presence of methoxy group at arylthio ring and $NCOCH_3$ group at heterocyclic ring of cinnamides **1** were detrimental to activity in antagonism of biochemical ICAM-1/LFA-1 interaction. When inhibition of ICAM-1/JY-8 cell adhesion was considered, lipophilic substitution on ring B and simultaneous presence of CF_3 groups at 2 and 3 positions of the ring B were advantageous to antagonism. This QSAR study showed that B ring has played the most important role for both types of activities. © 2002 Elsevier Science Ltd. All rights reserved.

Introduction

Inflammation occurs after a number of events. The most important event is vasodilatation due to increased vascular permeability and exudation of fluid and plasma protein. Another important event is cell adhesion. In this process leukocytes first adhere to a specific region of the vascular endothelium and then cross the endothelial barrier to migrate to the inflamed tissue.[1] Adhesion molecule such as integrins, Ig supergene family members and selectins are involved in adhesion. Leukocyte function associated antigen-1 (LFA-1 or CD11a/CD18) belongs to a member of the β_2 integrin family of adhesion molecule $\alpha_L\beta_2$.[2] It is thought that LFA-1 interact with intercellular adhesion molecule ICAM-1 (CD54), an immunoglobulin expressed on endothelial cells, and this interaction promotes the migration of leukocytes rapidly into surrounding tissue. So, an agent which blocks the biochemical ICAM-1/LFA-1 interaction may suppress these early steps in the inflammation. It is also observed that JY-8 cells (a human EBV, i.e., Epstain–Barr Virus—transformed B cell line) express LFA-1 which adhere with ICAM-1 and that adhesion helps in inflammation. Thus, a molecule, which prevents this adhesion, may act as an anti-inflammatory agent.[3] The primary biochemical assay measures the ability of the compound to block the interaction between the integrin LFA-1 and its adhesion partner ICAM-1 in a time-resolved fluorescent ICAM-1/LFA-1 biochemical interaction assay. Biologically relevant activity of the compounds can be confirmed by using a cell-based adhesion assay, which measures the ability of a compound to block the adherence of JY-8 cells to immobilized ICAM-1.[3]

In this communication Quantitative Structure–Activity Relationship (QSAR) study was performed using Hansch approach[4] on some novel *p*-arylthio cinnamides **1** shown in Figure 1 as antagonists of ICAM-1/LFA-1 interaction as well as ICAM-1/JY-8 cell adhesion[5] as a part of our programme of rational drug design.[6]

Results and Discussion

The 50% Inhibitory Concentration (IC_{50}) of the biochemical ICAM-1/LFA-1 interaction and that of (i.e., IC_{50}) of ICAM-1/JY-8 Cell adhesion values of cinna-

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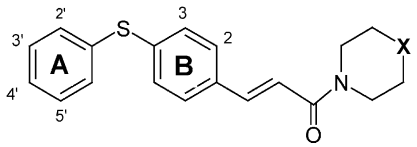

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Figure 1. The general structure of the *p*-arylthio cinnamides.

mides **1** are listed in Table 1. For using in Hansch model, biochemical IC_{50} and cell adhesion IC_{50} values were converted to negative logarithm form pC_1 and pC_2 respectively to get linear relationship with physicochemical parameters. The physicochemical parameters like hydrophobic parameter (π), Taft's steric parameter (Es), molar refractivity (MR), field effect (F), resonance effect (R) were collected from literature,[4] sum of molar refractivity for the A ring substituents ($\_MR_A$) was calculated from Chem sketch of ACD Labs software.[7]

When the biochemical ICAM-1/LFA-1 interaction inhibitory activity of cinnamides (pC_1) was studied with physicochemical parameters, the Model 1 obtained was as

$$pC_1 = -2.5599(\pm 0.2581) + 0.5449(\pm 0.2503)\_MR_A + 1.2630(\pm 0.1307)I_1 - 1.7621(\pm 0.2350)I_2 - 1.5973(0.2498)I_3 \quad (1)$$

$n = 28$; $r = 0.9611$; $\%EV = 92.36$; $r^2_A = 0.9103$; $F(4, 23) = 69.532$; $p < 0.00000$; S.E.E. $= 0.3109$; PRESS $= 3.4217$; SSY $= 29.0986$; $r^2_{CV} = 0.8824$; $S_{PRESS} = 0.3857$

where $\_MR_A$ is the sum of the molar refractivities of the substituents on the ring A, I_1 is the indicator variable for 2,3 disubstitution with either Cl or CF_3 or both on ring B, I_2 is the indicator variable for compounds with no substitution on ring B and I_3 is another indicator variable for simultaneous presence of 2′-OCH_3 on ring A and $NCOCH_3$ at the X position. The values of I_1 and I_3 are 1 for the presence of the corresponding groups and zero for their absence. The value of I_2 is 1 when there is no substitution on ring B and zero for the substitution on ring B. Among the statistical parameters '*n*' is the number of data points and '*r*', '%EV', 'r^2_A', '*F*', '*p*', 'S.E.E.', 'PRESS', 'SSY', 'r^2_{CV}', 'S_{PRESS}' are correlation coefficient, percentage of explained variance, adjusted r^2, ratio between the variances of observed and calculated activities, probability factor, standard error of estimate, predicted residual sum of squares, total sum of squares, cross validated r^2, standard error of PRESS respectively.[9] The value within the parenthesis is the standard error of the corresponding parameters. The statistical quality of eq 1 was

Table 1. The biochemical ICAM-1/LFA-1 interaction and ICAM-1/JY-8 cell adhesion inhibitory activities and physicochemical parameters of *p*-arylthio cinnamides **1**

Compd	A ring	B ring	X	Biochemical IC_{50} (nM)	Cell adhesion IC_{50} (nM)	MR_A	$\_\pi_B$
2	2′,4′-di Cl	H	$NCOCH_3$	4300	—[a]	0.965	0.000
3	2′,3′-di Cl	H	O	9100	—	0.965	0.000
4	2′,4′-di Cl	3-Cl	$NCOCH_3$	140	130	0.965	0.710
5	2′-CH_3O	3-Cl	O	150	40	0.637	0.710
6	3′,4′-OCH_2CH_2O	3-Cl	$NCOCH_3$	40	80	1.069	0.710
7	3′,4′-OCH_2CH_2O	3-Cl	CHCOOH	145	—	1.069	0.710
8	3′,4′-OCH_2CH_2O	3-CF_3	O	30	—	1.069	0.880
9	3′,4′-OCH_2CH_2O	3-CF_3	$NCOCH_3$	55	60	1.069	0.880
10	3′,4′-OCH_2CH_2O	3-CF_3	CHCOOH	50	—	1.069	0.880
11	3′,4′-OCH_2CH_2O	3-NO_2	$NCOCH_3$	139	—	1.069	−0.280
12	2′,3′-di Cl	3-NO_2	$NCOCH_3$	105	100	0.965	−0.280
13	2′-$CHMe_2$	3-NO_2	$NCOCH_3$	44	30	1.386	−0.280
14	2′-CH_3O	3-CH_3O	$NCOCH_3$	10700	—	0.637	−0.020
15	3′,4′-OCH_2CH_2O	2,3-di Cl	$NCOCH_3$	7	8	1.069	1.420
16	2′-CH_3O	2,3-di Cl	O	10	6	0.637	1.420
17	2′-CH_3O	2,3-di Cl	CHCOOH	8	8	0.637	1.420
18	2′-$CHMe_2$	2,3-di Cl	CHCOOH	10	6	1.386	1.420
19	3′,4′-OCH_2CH_2O	2,3-di Cl	CHCOOH	7	6	1.069	1.420
20	3′,4′-OCH_2CH_2O	2,3-di CF_3	CHCOOH	3	0.5	1.069	1.760
21	2′-CH_3O	2,3-di CF_3	CHCOOH	5	0.1	0.637	1.760
22	2′-CH_3O	2-CF_3, 3-Cl	O	8	5	0.637	1.590
23	2′-CH_3O	2-CF_3, 3-Cl	CHCOOH	6	4	0.637	1.590
24	3′,4′-OCH_2CH_2O	2-CF_3, 3-Cl	CHCOOH	5	2	1.069	1.590
25	2′-CH_3O	2,3-di CH_3	O	90	—	0.637	1.120
26	2′-$CHMe_2$	2,3-di F	CHCOOH	115	—	1.386	0.280
27	2′-CH_3O	2-F	$NCOCH_3$	3900	—	0.637	0.140
28	2′-CH_3O	2-CF_3	CHCOOH	265	—	0.637	0.880
29	2′-CH_3O	2-Cl	CHCOOH	1400	—	0.637	0.710

[a]— Indicate that cell adhesion inhibitory activity of these compounds was not evaluated.

excellent as evidence from its high correlation coefficient ($r = 0.9611$). This equation explained 92.36% of the variances in the activity data. Positive coefficient of $\_MR_A$ indicated that steric effect at ring A might be conducive to the activity. These may be due to steric hindrance on ICAM-1 and thus blockade of the interaction of ICAM-1 with LFA-1 molecule. The presence of 2,3-disubstitution with either Cl or CF_3 or both on ring A might be helpful to the activity by way of binding with electropositive centers of ICAM-1 and/or LFA-1 molecules, which were in accordance with the observations as reported earlier.[5] The negative coefficients of I_2 and I_3 showed that no substitution at ring B and simultaneous presence of methoxy (OCH_3) group at 2′-position of the ring A and $NCOCH_3$ group at position X have detrimental effects to the biochemical interaction inhibitory activity.

When instead of I_1, the sum of hydrophobic constants of substituents at 2,3-positions on ring B, $\sum\pi_B$ was used to correlate with the biological activity in Model 2, a good correlation was found as shown in eq 2. $\_MR_A$ and $\sum\pi_B$ values of the compounds are shown in Table 1.

$$pC_1 = -3.3362(\pm0.4360) + 0.9652(\pm0.3707)\_MR_A + 0.9469(\pm0.1560)\sum\pi_B - 1.3914 \times (\pm0.3509)I_2 - 1.1456(\pm0.3816)I_3 \quad (2)$$

$n = 28$; $r = 0.9228$; %EV = 85.15; $r^2_A = 0.8257$; $F(4, 23) = 32.967$; $p < 0.0000$; S.E.E. = 0.4335; PRESS = 6.2867; SSY = 29.0986; $r^2_{CV} = 0.7840$; $S_{PRESS} = 0.5228$

Eq 2 explained the variances of the activity data up to 85.15%. The positive coefficient of the $\sum\pi_B$ indicated that lipophilic property of the substituents at 2,3-positions on ring B might play a major role through hydrophobic interactions with ICAM-1 and/or LFA-1 molecules in the biochemical interaction inhibitory activity of cinnamides **1**.

Deletion of the outliers (**29**, and **29** and **7** respectively), which may act through different mechanism of action, from Model 2 yielded eqs 3 and 4 with appreciable correlations as evidenced by statistical parameters.

$$pC_1 = -2.9067(\pm0.3907) + 0.6502(\pm0.3272)\_MR_A + 0.8621(\pm0.1340)\sum\pi_B - 1.5170 \times (\pm0.2981)I_2 - 1.3694(\pm0.3289)I_3 \quad (3)$$

DC = ***29***; $n = 27$; $r = 0.9449$; %EV = 89.28; $r^2_A = 0.8733$; $F(4, 22) = 45.791$; $p < 0.0000$; S.E.E. = 0.3651; PRESS = 4.3571; SSY = 27.3523; $r^2_{CV} = 0.8407$; $S_{PRESS} = 0.4450$

$$pC_1 = -2.9035(\pm0.3764) + 0.6857(\pm0.3160)\_MR_A + 0.8507(\pm0.1293)\sum\pi_B - 1.5544 \times (\pm0.2882)I_2 - 1.3945(\pm0.3172)I_3 \quad (4)$$

DC = **29**, **7**; $n = 26$; $r = 0.9511$; %EV = 90.45; $r^2_A = 0.8863$; $F(4, 21) = 49.731$; $p < 0.0000$; S.E.E. = 0.3518; PRESS = 3.9545; SSY = 27.2170; $r^2_{CV} = 0.8547$; $S_{PRESS} = 0.4339$

where DC is the deleted compounds. Eq 4 explained up to 90.45% of the variances of the activity data. The correlation matrix of eqs 1 and 4 are shown in Tables 2 and 3 respectively. The observed, calculated and residual values of the biochemical interaction inhibitory activity of cinnamides **1** for eqs 1 and 4 are shown in Table 4. The predictive powers of these two equations were confirmed by Leave-One-Out (LOO) method.[8] The LOO-predicted values of eqs 1 and 4 are shown in Table 4.

When ICAM-1/JY-8 cell adhesion inhibitory activity of cinnamides **1** was considered for correlation with the physicochemical parameters, in Model 3, sum of the hydrophobic constants at 2,3-positions of the ring B ($\sum\pi_B$) and an indicator parameter I_4, which is related with ring B only, were having significant effects in the cell adhesion inhibitory activity as shown in eq 5.

Table 2. The correlation matrix for eq 1

	$\_MR_A$	I_1	I_2	I_3	pC_1
$\_MR_A$	1.00	−0.10	0.05	−0.31	0.18
I_1		1.00	−0.21	−0.21	0.76
I_2			1.00	−0.08	−0.53
I_3				1.00	−0.53
pC_1					1.00

Table 3. The correlation matrix for eq 4

	$\_MR_A$	$\_\pi_B$	I_2	I_3	pC_1
$\_MR_A$	1.00	−0.23	0.05	−0.33	0.14
$\sum\pi_B$		1.00	−0.36	−0.33	0.79
I_2			1.00	−0.08	−0.57
I_3				1.00	−0.57
pC_1					1.00

Table 4. The observed, calculated, residual and LOO-predicted values for eq 1

Compd	Observed value	Eq 1			Eq 4		
		Calcd	Res.	LOO-pred.	Calcd	Res.	LOO-pred.
2	−3.6334	−3.7962	0.1628	−3.9590	−3.7962	0.1628	−3.9590
3	−3.9590	−3.7962	−0.1628	−3.6330	−3.7962	−0.1628	−3.6330
4	−2.1461	−2.0341	−0.1120	−2.0260	−1.6378	−0.5083	−1.6090
5	−2.1760	−2.2129	0.0369	−2.2190	−1.8627	−0.3133	−1.8050
6	−1.6020	−1.9775	0.3755	−2.0090	−1.5665	−0.0355	−1.5640
7[a]	−2.1613	−1.9775	−0.1838	−1.9620	—	—	—
8	−1.4777	−1.9775	0.4998	−2.0190	−1.4219	−0.0559	−1.4190
9	−1.7403	−1.9775	0.2372	−1.9970	−1.4219	−0.3184	−1.4030
10	−1.6989	−1.9775	0.2786	−2.0010	−1.4219	−0.2770	−1.4050
11	−2.1430	−1.9775	−0.1655	−1.9640	−2.4087	0.2657	−2.4890
12	−2.0212	−2.0341	0.0130	−2.0350	−2.4800	0.4588	−2.6370
13	−1.6434	−1.8048	0.1613	−1.8400	−2.1913	0.5479	−2.3930
14	−4.0293	−3.8102	−0.2192	−3.5910	−3.8782	−0.1511	−3.7270
15	−0.8450	−0.7145	−0.1305	−0.6960	−0.9625	0.1175	−0.9750
16	−1.0000	−0.9499	−0.0501	−0.9420	−1.2587	0.2587	−1.2910
17	−0.9030	−0.9499	0.0469	−0.9570	−1.2587	0.3557	−1.3040
18	−1.0000	−0.5418	−0.4582	−0.3780	−0.7451	−0.2549	−0.6460
19	−0.8450	−0.7145	−0.1305	−0.6960	−0.9625	0.1175	−0.9750
20	−0.4771	−0.7145	0.2374	−0.7470	−0.6732	0.1961	−0.7120
21	−0.6989	−0.9499	0.2510	−0.9910	−0.9694	0.2705	−1.0140
22	−0.9030	−0.9499	0.0469	−0.9570	−1.1141	0.2111	−1.1430
23	−0.7781	−0.9499	0.1718	−0.9780	−1.1141	0.3360	−1.1610
24	−0.6989	−0.7145	0.0156	−0.7170	−0.8178	0.1189	−0.8350
25	−1.9542	−2.2129	0.2587	−2.2570	−1.5139	−0.4403	−1.4580
26	−2.0606	−1.8048	−0.2559	−1.7480	−1.7149	−0.3457	−1.6360
27	−3.5910	−3.8102	0.2192	−4.0290	−3.7421	0.1511	−3.8940
28	−2.4232	−2.2129	−0.2103	−2.1770	−1.7181	−0.7051	−1.6110
29[a]	−3.1461	−2.2129	−0.9332	−2.0530	—	—	—

[a]Compounds **29** and **7** are outliers for the Eq 4.

$$pC_2 = -1.9338(\pm 0.2010) + 0.7303(\pm 0.1677)\sum \pi_B + 1.2990(\pm 0.3211)I_4 \quad (5)$$

$n = 16$; $r = 0.9030$; %EV = 81.53; $r_A^2 = 0.7869$; $F(2, 13) = 28.698$; $p < 0.00002$; S.E.E. = 0.3920; PRESS = 3.7596; SSY = 10.8189; $r_{CV}^2 = 0.6525$; $S_{PRESS} = 0.5378$

where I_4 is the indicator parameter for the simultaneous presence of triflouromethyl (CF_3) groups at 2- and 3-positions of the ring B. The positive coefficient of this parameter showed that simultaneous presence of CF_3 groups at 2,3-positions on the ring B was conducive to the activity, may be due to interaction with ICAM-1 molecule and thereby block JY-8 cell for binding. $\sum\pi_B$ played an important role in the cell adhesion inhibitory activity. After deleting the outliers (**4**, **6** and **13**), which may be acting through a different mechanism, the statistical quality of the Model 3 was improved as shown in eq 6. The correlation matrix as well as the observed, calculated, residual and LOO-predicted values for eq 6 are listed in Tables 5 and 6 respectively.

Table 5. The correlation matrix for eq 6

	$\sum\pi_B$	I_4	pC_2
$\sum\pi_B$	1.00	0.38	0.80
I_4		1.00	0.77
pC_2			1.00

$$pC_2 = -2.0339(\pm 0.2018) + 0.8536(\pm 0.1534)\sum \pi_B + 1.1820(\pm 0.2288)I_4 \quad (6)$$

Table 6. The observed, calculated, residual and LOO-predicted values for eq 6

Compd	Observed value	Calculated value	Residual	LOO-predicted value
5	−1.6020	−1.4278	−0.1742	−1.3930
9	−1.7780	−1.2827	−0.4953	−1.2140
12	−2.0000	−2.2729	0.2729	−3.1720
15	−0.9030	−0.8218	−0.0813	−0.8120
16	−0.7780	−0.8218	0.0437	−0.8270
17	−0.9030	−0.8218	−0.0813	−0.8120
18	−0.7780	−0.8218	0.0437	−0.8270
19	−0.7780	−0.8218	0.0437	−0.8270
20	0.3010	0.6505	−0.3495	1.0000
21	1.0000	0.6505	0.3495	0.3010
22	−0.6990	−0.6766	−0.0224	−0.6730
23	−0.6020	−0.6766	0.0746	−0.6890
24	−0.3010	−0.6766	0.3756	−0.7370

$n = 13$; DC = ***4***, ***6***, ***13***; $r = 0.9499$;

%EV = 90.23; $r^2_A = 0.8828$; $F(2, 10) = 46.194$;

$p < 0.00001$; S.E.E. = 0.2758; PRESS = 2.9343;

SSY = 7.7872; $r^2_{CV} = 0.6232$; $S_{PRESS} = 0.5417$

Conclusion

The QSAR study clearly showed that in biochemical ICAM-1/LFA-1 interaction, compounds with lipophilic substitution at 2,3-positions, especially 2,3-disubstitution with either Cl or CF_3 or both on ring B were more active than any other substitution on the same ring. This might be due to the hydrophobic interaction or binding of Cinnamides **1** with electropositive centers of ICAM-1 and/or LFA-1 molecules. No substitution on ring B and simultaneous presence of 2′-OCH_3 on ring A and $NCOCH_3$ at X-position were resulted compounds with low active antagonists of this interaction. Steric effects on ring A was also fruitful to biochemical interaction inhibitory activity due to steric hindrance on ICAM-1 and thus may block the interaction. In case of ICAM-1/JY-8 cell adhesion inhibition, lipophilic substitutions on ring B were resulted compounds with high activity. Hydrophobic interaction with ICAM-1 molecule with active compounds might block JY-8 cell for binding. More active compounds obtained with 2,3-di triflouromethyl substitution on ring B of the *p*-arylthio cinnamides **1** so far cell adhesion inhibition is concerned. When both biochemical ICAM-1/LFA-1 interaction and ICAM-1/JY-8 cell adhesion inhibitions were considered ring B has played the most important role. This QSAR study will be beneficial for future tailoring of this type of compounds for such types of activities.

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References and Notes

1. (a) Springer, T. A. *Nature* **1990**, *346*, 425. (b) Hynes, R. O. *Cell* **1992**, *69*, 11. (c) Carlos, T. M.; Harlan, J. M. *Blood* **1994**, *84*, 2068. (d) Liu, G.; Link, J. T.; Pei, Z; Reilly, E. B.; Leitza, S.; Nguyen, B.; Marsh, K.; Okasinski, G. F.; von Geldern, T. W.; Ormes, M.; Fowler, K.; Gallatin, M. *J. Med. Chem.* **2000**, *43*, 4025.
2. Cotran, R. S.; Moyadas-Norton, T. *Pathol. Biol.* **1998**, *46*, 164.
3. (a) Carlos, T. M.; Harlen, J. M. *Blood* **1994**, *84*, 2068. (b) Liu, G.; Huth, J. R.; Olejniczak, E. T.; Mendoza, R.; DeVries, P.; Leitza, S.; Reilly, E. B.; Okasinski, G. F.; Fesik, S. W.; von Geldern, T. W. *J. Med. Chem.* **2001**, *44*, 1202. (c) Pei, Z.; Xin, Z.; Liu, G.; Li, Y.; Reilly, E. B.; Lubbers, N. L.; Huth, J. R.; Link, J. T.; von Geldern, T. W.; Cox, B. F.; Leitza, S.; Gao, Y.; Marsh, K. C.; DeVries, P.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 2913.
4. (a) Hansch, C.; Leo, A.; Hoekman, D. In *Exploring QSAR: Hydrophobic, Electronic and Steric Constants*; ACS: Washington, DC, 1995. (b) Hansch, C.; Leo, A. In *Exploring QSAR: Fundamentals and Applications in Chemistry and Biology*; ACS: Washington, DC, 1995. (c) Hansch, C.; Leo, A. In *Substitution Constants for Correlation Analysis in Chemistry and Biology*; John Wiley & Sons: New York, 1979.
5. Winn, M.; Reilly, E. B.; Liu, G.; Huth, J. R.; Jae, H. S.; Freeman, J.; Pei, Z.; Xin, Z.; Lynch, J.; Kester, J.; von Geldern, T. W.; Leitza, S.; DeVries, P.; Dickinson, R.; Mussatto, D.; Okasinski, G. F. *J. Med. Chem.* **2001**, *44*, 4393.
6. (a) Debnath, B.; Srikanth, K.; Banarjee, S.; Jha, T. *Internet Electron. J. Mol. Des.* **2002**, *1*, 488. (b) Srikanth, K.; Kumar, C. A.; Ghosh, B.; Jha, T. *Bioorg. Med. Chem.* **2002**, *10*, 2119. (c) Srikanth, K.; Debnath, B.; Jha, T. *Bioorg. Med. Chem.* **2002**, *10*, 1841. (d) Srikanth, K.; Debnath, B.; Jha, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 899. (e) Srikanth, K.; Kumar, Ch. A.; Goswami, D.; De, A.U.; Jha, T. *Indian J. Biochem. Biophys* **2001**, *38*, 120. (f) Jha, T. In *Frontiers of Pharmaceutical Technology*, Gupta, J. K., Jha, T., Eds.; Jadavpur University: Calcutta, 1999; p. 87 (g) Purkayastha, S. K.; Jha, T.; Pal, D. K.; De, A. U. *Anticancer Drug Des* **1993**, *8*, 95.
7. Chem sketch program of ACD Labs software: http://www.acdlabs.com
8. (a) Schaper, K. J. *Quant. Struct-Act. Relat* **1999**, *18*, 354. (b) Tetko, I. V.; Tanchuk, V. Y.; Villa, A. E. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 1407.
9. (a) Snedecor, G. W.; Cochran, W. G. *Statistical Methods*; Oxford and IBH: New Delhi, 1967. (b) Rawlings, J. O. *Applied Regression Analysis*; Wadsworth: CA, USA, 1988. (c) Darper, N. R.; Smith, H. *Applied Regression Analysis*; John Wiley & Sons: New York, 1981. (d) Lien, E. J. Drug Design; In *Quantitative Correlations Using Multiple Regression and Substituent Constants*; Ariens, E. J. Ed.; Academic: New York, 1975; Vol. V, p 84.