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A 3D-QSAR Study of Some Substituted Napthols as 5-Lipoxygenase Inhibitors

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In the present study, we have performed a three dimensional quantitative structure activity relationship study on two series of substituted naphthols as lipoxygenase inhibitors. Various physicochemical parameters were calculated using Cerius2 molecular modeling software. Quantitative structure activity relationship models were generated for lipoxygenase inhibitory activity using stepwise multiple regression and genetic function approximation analysis. Statistically significant models were obtained in both the series, series 1 having 15 compounds gave r^2 value as 0.818, whereas, with series 2 with 38 compounds, gave r^2 value as 0.857. The studies indicated that in series 1 the activity is dependent on thermodynamic and electronic descriptors. However, in series 2 the shape and electronic descriptors dominated the influence on the activity. Cross validation was performed using the leave-one-out method. The so obtained and validated models bring important structural insight to aid the design of novel 5-lipoxygenase inhibitors prior to their synthesis.

Non steroidal antiinflammatory agents are of current interest[1] because there are no drugs of choice for the treatment of most of the diseases like rheumatoid arthritis[2], allergic rhinitis, psoriasis[3,4], ulcerative colitis and asthma[5]. The two major approaches for design and synthesis of antiinflammatory agents are based on the inhibition of two enzymes[6], cyclooxygenase and lipoxygenase, which are involved in the metabolism of arachidonic acid (AA). Cyclooxygenase has been the common target for most of the antiinflammatory drugs but due to the association of some side effects such as ulceration and bleeding in gastrointestinal tract with cyclooxygenase inhibitors[7] and implication of leukotrienes in the above inflammatory and allergic disorders[8,9], the attention is focussed on the 5-lipoxygenase enzyme inhibitors, which restrict the synthesis of leukotrienes from AA via peroxidation of AA to 5-hydroperoxyeicoteranoic acid (5-HPETE) followed by dehydration to 5,6-epoxy leukotriene A_4 (LTA_4). No three dimensional quantitative structure activity relationship (3D QSAR) studies have been attempted so far on series of substituted naphthols derivative, it appeared of interest to perform 3D QSAR analysis employing Cerius2 software. The aim of this study was to find 3D QSAR models with good correlation between molecular structure and biological activity. Such an effort would facilitate the discovery and development of potent 5-lipoxygenase inhibitors.

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MATERIALS AND METHODS

The 5-lipoxygenase inhibitory data were taken from Batt *et al.*[10] All molecular modeling and 3D-QSAR studies were performed on a Silicon Graphics Indigo2 XZ employing Cerius2 software[11] (Version 3.5). The IC_{50} values originally expressed in micromole have been converted to kilomole and grammole for series 1 and 2, respectively for convenience of computation work. The molecular structure of all compounds (series 1 in Table 1 and series 2 in Table 2) were built using molecular sketching facilities provided in modeling environment of Cerius2. The molecular structures were minimized using the steepest descenf (SD), conjugate gradients[12] (CG) in sequence followed by truncated New-

TABLE 1: 5-LIPOXYGENASE INHIBITORY ACTIVITY DATA OF 2- SUBSTITUTED 1-NAPHTHOLS (SERIES 1).

Comp. No.	R	BA[a] RBL-1, $IC_{50}\mu M$	$(-LogIC_{50})^b$	Calculated $(-LogIC_{50})^c$
1	H	3.60	8.44	8.63
2	CH_3	0.13	9.89	10.02
3	$C(CH_3)_3$	0.18	9.74	9.30
4	$CH_2CH=CH_2$	0.06	10.25	10.04
5	$CH_2C_6H_5$	0.02	10.72	10.18
6	$CH(CH_3)C_6H_5$	0.07	10.15	10.47
7	$C(=O)C_6H_5$	20.0	7.70	7.84
8	$CH=CHC_6H_5$	0.16	9.80	10.65
9	$CH_2CH_2C_6H_5$	0.14	9.85	9.81
10	$COOC_2H_5$	25.0	7.60	7.91
11	$CH=CHCOOC_2H_5$	0.05	10.35	9.80
12	$CH_2CH_2COOC_2H_5$	0.06	10.24	9.60
13	$C(=NO_4)(CH_2)_3COOC_2H_5$	2.70	8.57	9.38
14	$(CH_2)_4COOC_2H_5$	0.01	10.96	10.89
15	$(CH_2)_4COOH$	4.20	8.38	8.12

ton-Raphson (N-R) optimization techniques under universal force field[13]. The minimization terminates at which the root mean square (RMS) force on the molecule was less than 0.0001 Kcal/mol A°. The conformations were generated and its analysis for each compound was performed using GRID method. To generate the conformation, the energy cut off was set to 5 Kcal/mol. The number of conformation generated for each substrate was limited to a maximum of 100 and 150 for series 1 and 2, respectively. The conformations produced by the random conformation search were fully optimized and used immediately for further analysis. Among the so constituted conformational space, only the conformers above the lowest energy minima have kept for their geometry reoptimization with the semi-empirical MOPAC package version 6.0 using the Hamiltonian AMI. The lowest energy conformation for each compound was found. The descriptors were calculated using the lowest energy conformation.

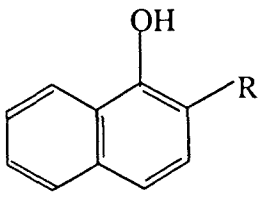

Fig. 1: 2-Substituted 1-Napthols.

For structures, [a]Rat Basophilic Leukemia (RBL-1) cell lysate 5-lipoxygenase inhibition measured by 5-HETE production, [b]IC_{50} values were expressed in terms of kilomoles, [c]Calculated $(-LogIC_{50})$ values using Eqn. 3.

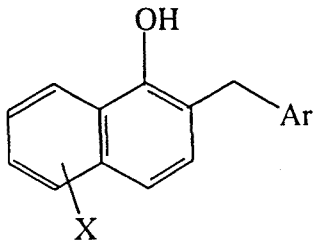

Fig. 2: 2-(Aryl methyl)-1-Naphthols.

For structures, [a]Rat Basophilic Leukemia (RBL-1) cell lysate 5-lipoxygenase inhibition measured by 5-HETE production, [b]IC_{50} values were expressed in terms of grammoles, [c]Calculated $(-LogIC_{50})$ values using Eqn. 8.

TABLE 2: 5-LIPOXYGENASE INHIBITORY ACTIVITY DATA OF 2-(ARYLMETHYL)-1- NAPHTHOLS (SERIES 2).

Comp. No.	Ar	X	BA[a] RBL-1, IC_{50} μM	(-LogIC_{50})[b]	Calculated (-LogIC_{50})[c]
1	C_6H_5	H	0.019	7.721	7.133
2	4-$CH_3C_6H_4$	H	0.024	7.619	7.161
3	2-$CH_3C_6H_4$	H	0.120	6.920	7.154
4	4-$CH_3OC_6H_4$	H	0.075	7.124	7.048
5	3-$CH_3OC_6H_4$	H	0.110	6.958	7.110
6	4-C_2H_5 OC_6H_4	H	0.062	7.207	7.099
7	3,4-$(CH_3O)_2C_6H_4$	H	0.051	7.292	7.09
8	3- C_6H_5 OC_6H_4	H	0.083	7.080	6.78
9	4-$C_6H_5CH_2OC_6H_4$	H	0.072	7.142	7.30
10	4-$CH_3SC_6H_4$	H	0.048	7.318	7.13
11	4-$(CH_3)_2NC_6H_4$	H	0.014	6.853	7.22
12	4-FC_6H_4	H	0.130	6.886	7.27
13	4-ClC_6H_4	H	0.039	7.408	7.84
14	3-ClC_6H_4	H	0.052	7.283	7.25
15	3,4-$Cl_2C_6H_4$	H	0.270	6.744	7.00
16	3-$CF_3C_6H_4$	H	0.048	6.568	6.36
17	4-$(CH_3SO_2)C_6H_4$	H	0.240	6.619	6.78
18	4-$NO_2C_6H_4$	H	0.048	7.318	7.24
19	2-naphthyl	H	0.058	7.236	7.15
20	2-thienyl	H	0.060	7.221	6.94
21	2-furyl	H	0.037	7.431	6.71
22	N-CH_3 2-pyrryl	H	0.140	6.853	7.06
23	2-pyridyl	H	0.390	6.408	6.77
24	3-pyridyl	H	0.230	6.638	6.73
25	4-pyridyl	H	0.140	6.852	7.00
26	C_6H_5	5-CH_3O	0.100	7.000	7.36
27	C_6H_5	5,7$(CH_3)_2$	0.062	7.207	7.380
28	C_6H_5	5,8$(CH_3)_2$	0.120	6.920	7.383
29	C_6H_5	4-CH_3	0.020	7.698	7.297
30	C_6H_5	4-C_6H_4	0.056	7.251	7.466
31	C_6H_5	4-OCH_3	0.031	7.508	7.499
32	C_6H_5	4-$COCH_3$	0.510	6.292	6.408
33	C_6H_5	4-COC_6H_4	0.054	7.267	6.905
34	C_6H_5	4-COOH	5.800	5.236	5.215
35	C_6H_5	4-SO_2CH_3	0.160	6.795	6.468
36	C_6H_5	4-SO_2CH_3	40.00	4.397	4.962
37	C_6H_5	4-SO_2NH_2	9.400	5.026	4.668
38	C_6H_5	4-NO_2	48.00	4.318	4.560

TABLE 3: CALCULATED DESCRIPTOR VALUES FOR SERIES 1.

Comp. No.	[a]Dipole-mag.	[b]Dipole-X	[c]AlogP	[d]HOMO	[e]Sr	[f]COSV
1	2.382	1.97	2.764	-10.598	0.701	121.61
2	2.243	1.77	3.231	-10.373	0.705	138.56
3	2.003	0.48	4.391	-10.359	1.840	153.90
4	2.250	1.14	3.809	-10.364	0.704	140.04
5	2.173	0.76	4.845	-10.343	0.495	139.47
6	1.992	0.62	5.175	-10.357	1.803	155.04
7	3.655	1.85	3.985	-10.629	1.240	138.64
8	2.004	0.38	4.981	-10.172	1.726	142.40
9	2.266	0.38	5.241	-10.335	1.873	140.33
10	2.142	1.86	2.837	-10.799	1.821	139.64
11	2.573	2.23	3.369	-10.541	0.495	140.32
12	2.347	1.92	3.165	-10.480	1.232	147.50
13	3.409	2.76	2.947	-10.490	0.703	145.37
14	3.009	2.31	3.958	-10.351	1.864	251.50
15	4.998	2.56	3.584	-10.355	1.238	141.20

[a]Dipole moment, [b]Dipole moment –X component, [c]Log of partition coefficient; [d]Energy of highest occupied molecular orbital, [e]Superdelocalizability, [f]Common overlap steric volume.

The following descriptors were calculated for 3D-QSAR study (values of only those descriptors which found place in the equations are given in Table 3 (series 1) and Table 4 (series 2). Thermodynamic descriptors such as, desolvation free energy for water (FH_2O)[14,15], desolvation free energy for octanol (FOCT)[14,15], Log of partition coefficient (AlogP)[14,15] and molecular refractivity (MR)[15,16]. Spatial descriptors such as, number of rotatable bonds (ROTBONDS)[15], molecular surface area (AREA)[17], radius of gyration (ROG), density (DENSITY)[17], molecular weight (MW)[17], molecular volume (VM)[17], principal moment of inertia (PMI)[18], principal moment of inertia–X component (PMI-X)[18], principal moment of inertia–Y component (PMI-Y)[18] and principal moment of inertia-Z component (PMI-Z)[18]. Electronic descriptors such as, sum of atomic polarizabilities (APOL)[19], dipole moment (dipole-mag)[19,20], dipole moment–X component (Dipole-X)[19,20], dipole moment–Y component (Dipole-Y)[19,20], dipole moment–Z component (Dipole-Z)[19,20], energy of highest occupied molecular orbital (HOMO)[21], energy of lowest unoccupied molecular orbital (LUMO)[21], superdelocalizability (Sr) and partial atomic charges[22].

Molecular shape descriptors, common overlap steric volume (COSV), difference volume (DIFFV), common overlap volume ratio (Fo), non-common overlap steric volume (NCOSV), RMS to shape reference (shape RMS), volume of shape reference (sr. vol.), vander waal's surface (vdws), were calculated to compare the common properties of the molecules and to measure molecular shape commonality. The conformers were used for computational calculation of different physico-chemical properties including atomic charges, electron density, HOMO, LUMO and dipole moments based on atomic contribution using MOPAC 6.0 (MNDO method). Partial charges were calculated using charge equilibration (Qeq) method[23]. Quantum mechanical descriptors such as, lowest unoccupied molecular orbital energy (LUMO_MOPAC), dipole moment (Dipole_MOPAC), highest occupied molecular orbital energy (HOMO_MOPAC), heat formation HF_MOPAC were calculated using MOPAC module. Connolly surface descriptor was derived with the probe radius at 1.40 A°, dot density at 8.0 A^2 and VDW scale factor at 1.

To generate 3D-QSAR equations, stepwise multiple

TABLE 4: CALCULATED DESCRIPTOR VALUES FOR SERIES 2.

Comp No.	[a]vdws	[b]Dipole -Z	[c]ROG	[d]PM I-Y	[e]HOMO	[f]Fo	[g]NCO SV	[h]HOMO_ MOPAC	[i]Dipole -X	Dipole_ MOPAC
1	113	2.43	3.68	361	-10.3	0.92	19.09	-8.19	-0.46	1.16
2	118	2.54	3.97	445	-10.3	0.84	39.23	-8.17	-0.53	1.35
3	114	2.66	3.78	407	-10.4	0.81	46.40	-8.18	-0.44	1.24
4	123	1.67	4.15	544	-10.3	0.09	48.16	-8.18	-1.27	1.74
5	123	3.45	3.99	497	-10.4	0.47	133.1	-8.22	-0.21	1.36
6	131	1.63	4.48	656	-10.3	0.76	63.50	-8.17	-1.14	1.74
7	131	1.76	4.30	662	-10.4	0.73	75.01	-8.21	1.41	2.14
8	146	-0.02	4.99	1096	-10.4	0.49	154.8	-8.37	0.97	1.92
9	152	1.41	5.33	1313	-10.3	0.62	121.2	-8.19	-0.99	1.50
10	129	2.56	4.18	626	-10.4	0.78	57.71	-8.21	-1.53	1.67
11	128	1.99	4.35	616	-10.3	0.75	68.24	-8.14	-0.29	1.73
12	118	6.69	3.69	454	-10.4	0.49	116.7	-8.27	3.34	1.56
13	113	7.95	3.69	542	-10.5	0.48	124.5	-8.28	4.49	1.48
14	122	5.62	3.69	458	-10.5	0.53	112.2	-8.25	3.78	1.50
15	133	3.33	3.71	614	-10.5	0.79	51.70	-8.33	-2.68	2.21
16	129	-2.28	3.81	544	-10.5	0.78	56.32	-8.30	-3.91	2.54
17	133	1.90	4.34	770	-10.5	0.72	76.78	-8.39	-2.71	6.57
18	127	8.90	3.87	597	-10.6	0.40	133.6	-8.52	5.08	6.18
19	130	2.37	4.23	628	-10.3	0.76	64.40	-8.20	-0.50	1.14
20	112	3.41	3.53	357	-10.3	0.53	101.1	-8.20	-3.69	1.17
21	106	2.57	3.49	308	-10.3	0.53	95.92	-8.23	-3.45	1.01
22	112	2.21	3.75	380	-10.3	0.71	64.91	-8.14	-0.80	3.27
23	113	2.20	3.66	358	-10.4	0.51	108.4	-8.21	-3.25	2.19
24	112	0.96	3.64	362	-10.3	0.83	38.22	-8.28	-1.35	1.89
25	111	3.27	3.59	362	-10.4	0.90	22.86	-8.31	-0.62	1.91
26	121	1.31	4.09	497	-10.1	0.81	47.69	-7.97	0.05	0.41
27	124	2.28	4.06	459	-10.0	0.79	54.94	-8.04	-0.53	0.91
28	120	1.69	3.91	426	-10.0	0.78	56.45	-8.00	-0.31	1.13
29	119	2.24	3.77	377	-10.1	0.84	38.32	-8.09	-0.52	1.12
30	140	3.03	4.20	547	-10.0	0.68	93.49	-8.13	-0.45	1.13
31	123	1.72	3.83	389	-9.9	0.81	47.26	-7.93	-1.44	2.23
32	126	-0.92	3.88	422	-10.3	0.78	58.21	-8.38	-2.46	3.21
33	147	0.92	4.35	623	-10.2	0.64	113.3	-8.36	-3.21	3.19
34	124	-5.33	3.79	427	-10.6	0.49	136.1	-8.68	0.93	4.43
35	139	0.22	4.37	579	-10.5	0.70	85.69	-8.47	0.65	1.13
36	135	-4.84	4.03	495	-10.5	0.73	74.89	-8.95	-1.48	6.98
37	133	-6.03	3.97	501	-10.7	0.74	69.27	-8.02	-1.42	6.43
38	125	-6.85	3.76	419	-11.0	0.81	46.64	-8.99	-0.63	6.24

[a]Vander waals surface, [b]Dipole moment – Z component, [c]Radius of gyration, [d]Principal moment of inertia – Y component, [e]Energy of highest occupied molecular orbital, [f]Common overlap volume ratio, [g]Non-common overlap steric volume, [h]Highest occupied molecular orbital energy, [i]Dipole moment – X component, [j]Dipole moment.

regression analysis and genetic function approximation analysis (GFA) methods were used. GFA was used since it generates a population of equations for correlation between biological activity and physicochemical properties. GFA developed by Rogers involves combination of Friedman's multiple adaptive regression splines (MARS) algorithm with Holland's genetic algorithm to evolve a population of equations that best fit the data. A distinctive feature of GFA that instead of generating single model, as do most other statistical methods, it produces a population of models. The range of variation in this population gives added information on the quality of fit and importance of descriptors[11]. The cross validation was performed using the leave-one-out method procedure. The following statistical measures were used: the number of samples in regression (n), squared correlation coefficient (r^2), F-test for statistical significance (F), Friedman's lack of Fitness (LOF), cross-validated squared correlation coefficient (cvr^2), boot strapped squared correlation coefficient (bsr^2).

RESULTS AND DISCUSSION

When all the calculated parameters and –Log IC_{50} of compounds for both series 1 and 2 were subjected to stepwise multiple parameter regression analysis and genetic function approximation analysis. The following significant Eqns. 1 and 2 were obtained by stepwise multiple regression analysis for series 1(2-substituted 1-napthols).

(1) -LogIC_{50}=49.2818–0.647632*Dipole-mag.+3.83845*HOMO-0.80425*Sr+0.0199562*COSV
n=15, r^2=0.848, F=13.944, press=14.77, cvr^2=0.098, bsr^2=0.852

(2) -Log IC_{50}=47.9231–0.561242*Dipole-mag+3.73406*HOMO+ 0.0136159*COSV
n=15, r^2=0.711, F=9.042, press=8.96, cvr^2=0.452, bsr^2=0.715
On genetic function approximation analysis significant Eqn. 3 was obtained for series 1,

(3) -LogIC_{50}=54.822+1.12761*AlogP+1.89147*Dipole-X+4.68747*HOMO–1.40912
Dipole-mag.
n=15, r^2=0.818, F=11.242, LOF=0.912, press=7.03, cvr^2=0.571,bsr^2= 0.821

Considering the Eqns. 1 to 3 for series 1, we find that Eqn. 1 suggests better correlation (r^2=0.848) between parameters and biological activity. In addition to this, Eqn. 1 has good statistical significance (>99.9%) with the F-value $F_{(4,10)}$=13.94, against the value of 99.9% significance ($F_{(4,10}$ $\alpha_{0.001)}$=11.3). The R^2 accounts for 84.8% variance in activity values. Even then, cross validation correlation coefficient (cvr^2=0.098) is poor. Statistical data were also obtained for Eqn. 2, such as, r^2=0.711, cvr^2=0.452 and bsr^2=0.715. The squared correlation coefficient value of Eqn. 2 is less than the Eqn. 1, whereas its cross-validated squared correlation coefficient value is better than the Eqn. 1. In addition, the F-value obtained for Eqn. 2 is significant at 99% level ($F_{(3,4}$ $\alpha_{0.01)}$=6.22) and R^2 accounts for 71.1% variance in activity values. In both the equations (Eqns. 1 and 2) HOMO and COSV contributed positively for the 5-lipoxygenase inhibitory activity, while the dipole-mag is not favorable for activity in both Eqns. 1 and 2. It is also clear from Eqn. 1 that Sr. parameter also contributes negatively for activity.

Eqn. 3 has better statistical significance>99% with the F-value ($F_{(3,10)}$=11.242) against the value of 99% significance ($F_{(3,10}$ $\alpha_{0.001)}$=5.97). R^2 has 81.8% variance in the biological activity values. The boot strap r^2 (bsr^2=0.821), values reflect the accuracy of the models. Log of the partition coefficient (A log P), Dipole–X and HOMO contribute positively in the order of 0.24:0.40:1 for 5-lipoxygenase inhibitory activity in series 1, while the dipole-mag is not favorable for activity. The relative contributions of thermodynamic and electronic descriptors were 14.6% and 85.4%, respectively.

The following 3D-QSAR Eqns. 4 to 7 were generated by stepwise multiple regression analysis for series 2 (2-(aryl methyl)-1-naphthols).

(4) -LogIC_{50}=22.1385+0.104179*Dipole-Z+1.865*HOMO

n=38, r^2=0.830, F=85.254, press=4.90, cvr^2=0.797, bsr^2=0.830

(5) -LogIC_{50}=5.37107–0.0779649*Dipole-X+0.178269 *Dipole-Z+0.387054*ROG–0.174287*Dipole_MOPAC

n=38, r^2=0.841, F=43.573, press=5.50, cvr^2=0.772, bsr^2 = 0.841

(6) -LogIC_{50}=21.4715+0.0106872*vdws+0.108456 *Dipole-Z+1.94776*HOMO_MOPAC

n =38, r^2=0.849, F=63.534, press=4.653, cvr^2=0.807, bsr^2=0.848

(7) -LogIC_{50}=15.8315+0.137275*Dipole-Z+0.000607239 *PMI-Y+0.888898*HOMO–0.14235*Dipole_MOPAC

n=38, r^2=0.832, F=40.989, press=5.76, cvr^2=0.761,

bsr^2=0.832

The following 3D-QSAR Eqn. 8 was obtained by genetic functional approximation analysis for series 2,

(8) $-LogIC_{50}$=17.5829+0.124249*Dipole-Z+0.013485 *NCOSV+1.75508*HOMO_MOPAC +3.67723*Fo

n=38, r^2=0.857, F=49.754, LOF=0.145, press=4.81, cvr^2=0.801, bsr^2=0.858

Eqn. 4 obtained for series 2 has good correlation (r^2=0.830) between the parameters and biological activity. Statistical parameters were obtained for Eqn. 4, viz., r^2=0.830, F=85.25, cvr^2=0.797 and bsr^2=0.830. It shows better statistical significance >99.9% with $F_{(2,35)}$=85.25 against the value for 99.9% significance ($F_{(2,35}\,\alpha_{0.001)}$=8.47). The R^2 accounts for 83% variance in the activity values. In Eqn. 4, both parameters such as, Dipole-Z and HOMO contributed positively for activity. By evaluation of this model, we can conclude that electronic parameters play an important role in the activity.

In addition to the above equations, some statistically improved equations (Eqns. 5 to 7) were also obtained for series 2. Eqns. 5 and 7 have good statistical significance>99.9% with the F-values $F_{(4,33)}$=43.57 and $F_{(4,33)}$ =40.989, respectively against the value of 99.9% significance ($F_{(4,33}\,\alpha_{0.001)}$=5.11). The F-value obtained for Eqn. 6 is significant at 99.9% level ($F_{(3,34}\,\alpha_{0.001)}$=6.79). The R^2 accounts for 84.1%, 84.9%, and 83.2% variance in activity values for Eqns 5, 6 and 7, respectively. Among three equations, Eqn. 6 was found better and indicated that vander waals surface (vdws), Dipole-Z and HOMO_MOPAC played an important role for activity.

Among all the 3D-QSAR equations for series 2, Eqn. 8 was statistically significant. This model has good predictive power according to the statistical results (r^2=0.857, cvr^2=0.801, bsr^2=0.858). The goodness of the structure activity correlation was estimated by r^2 (r^2=0.857). The lack of fitness value is very less (0.145). The F value has a high statistical significance>99.9% with $F_{(3,33)}$=49.75, against the value for 99.9% significance ($F_{(4,33}\,\alpha_{0.001)}$=5.88). The R^2 accounts for 85.7% variance in the biological activity values. The cross validated (cvr^2=0.801) values reflect predictive power of the equation. The boot strap r^2 (bsr^2=0.858) results reflect accuracy of the model. The Dipole-Z, NCOSV, HOMO_MOPAC and Fo contributed positively for activity in the order of 0.03:0.003:0.47:1 for series 2. From the above analysis, it may be inferred that Eqns. 3 and 8 for series 1 and 2, respectively can be used for theoretical prediction of 5-lipoxygenase inhibitory activity of the new molecules.

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