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Quantitative structure activity relationship studies of diarylimidazoles as selective COX-2 inhibitors

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Quantitative structure activity relationship approach using stepwise regression analysis has been applied to a series of 63 diarylimidazole derivatives as selective COX-2 inhibitors. For this purpose 49 compounds have been taken as training set and the rest as test set. These studies have produced good predictive models with high regression constant (r = 0.927), low standard deviation (0.279) and standard error of regression (0.30). A good correlation of various parameters like hydrophobicity (Π), electrophilicity (σ) and van der Waal's volume of various substituents has been established with COX-2 inhibitory activity. The impact of these structural parameters on the selectivity ratio (log COX-1/COX-2) has also been analyzed. The resulting correlation revealed that substitution at position A_3 with groups having low van der Waal's volume and high Π and σ values and substitution at A_5 and A_4 with groups having high Π and σ values are significant in increasing COX-2 inhibitory activity. Parameters for COX-2 enzyme selectivity have also been identified and on the basis of obtained correlation certain new compounds have been designed with much higher selectivity as COX-2 enzyme inhibitors in comparison to compounds reported in literature with retention of high inhibitory potency.

Keywords: QSAR, COX-2 inhibitors, diarylimidazole

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COX-1 and COX-2 are two isoforms of cyclo-oxygenase (COX)[1]. Their principal pharmacological effect is that they inhibit prostaglandin synthesis. This discovery led to the hypothesis that side effects such as ulcers and renal failure associated with the clinically used nonsteroidal anti-inflammatory drugs (NSAIDs) are caused by the inhibition of COX-1, whereas COX-2 is an inducible enzyme which is mainly produced during the inflammation process[2]. Study of selective inhibition of COX-2 led to a new class of anti-inflammatory, analgesic and antipyretic drugs with significantly reduced side effects. All these drugs have a common side effect of causing gastric mucosal damage[3]. A majority of the commonly used NSAIDS are non-selective towards COX-2. A new class of anti-inflammatory agents has emerged in the form of Coxibs (Celecoxib, Rofecoxib, *etc*.) which shows selectivity towards COX-2 over COX-1 enzyme. Drugs belonging to this class, such as Valdecoxib[4] and Etoricoxib[5] have also obtained FDA approval. Unfortunately, Rofecoxib has now been withdrawn from the market by Merck, following the premature cessation by the data and safety monitoring board, of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study. Incidences of serious thromboembolic adverse events (including heart attack and stroke) were observed[6]. Recent work also suggests that inhibiting COX-2 enzyme could be an important strategy for preventing certain types of cancers[7] and could also be used to delay or slow down the clinical expression of Alzheimer's disease[8]. Preclinical studies suggest that COX-2 may be involved in the molecular pathogenesis of some types of lung cancer. Treatment of humans with the selective COX-2 inhibitor Celecoxib has been shown to augment the anti-tumor effects of chemotherapy in patients with non-small cell lung cancer[9]. Research by neurologists at Columbia University suggests that COX-2 inhibitors like Celebrex and Vioxx may help in the treatment of patients suffering from Parkinson's disease by preventing death of neurons. Studies in mice suggest that Rofecoxib, the COX-2 inhibitor, doubled the number of surviving neurons: 88 per cent survived with the drug, while only 41 per cent survived without the drug[10]. Therefore, there is a need to develop more specific and efficient COX-2 inhibitors

possessing better safety profiles. A large number of research studies aimed at finding selective COX-2 inhibitors have been reported[11-14]. Many of these have been carried out using computer simulations to develop protocols and methods for designing new COX-2 inhibitors such as oxazoles, pyrazoles, pyrroles and imidazoles[15-19]. Recently Nunno and co-workers have synthesized novel 3,4-diarylisoxazole analogs of Valdecoxib as selective COX-2 inhibitors[20]. Some triphenylpyran-2-ones have also been synthesized and SAR studies on their suitability as selective COX-2 inhibitors have been carried out[21].

In a Fujita-Ban modified *de Novo* approach, three series of diaryl heterocycles namely, diaryl-imidazoles[22], diarylpyrazoles[23] and diaryloxazolones[24] were studied[25] and it was inferred that among the compounds of the three series, diarylimidazoles possess better selectivity for COX-2 over COX-1. Therefore, it was necessary to identify structural features in diarylimidazoles which were responsible for the observed selectivity towards COX-2. With this aim in mind Hansch analysis was planned on the given series of diarylimidazoles[22].

In this paper an attempt has been made to correlate biological activity (COX-2 and COX-1 inhibition) with structural descriptors like Π (hydrophobicity), σ (electrophilicity) and van der Waal's volume for substituents present at different positions on the diarylimidazole skeleton[22].

Results and Discussion

The 63 compounds belonging to the diaryl-imidazole category (**Figure 1**) were divided in two sets, 49 compounds were taken into training set (**Table I**) and 14 compounds constituted the test set (**Table Ia**). The IC_{50} values for both COX-1 and COX-2 were transformed into $-\log [IC_{50}*10^6]$ *i.e.* pIC_{50}. Stepwise regression analysis was performed by taking pIC_{50} value as dependent variable and different structural descriptors as independent variables. A large number of equations were generated; the best equation out of them was Eqn 1, but even this equation was not statistically significant with large standard error of prediction (0.734).

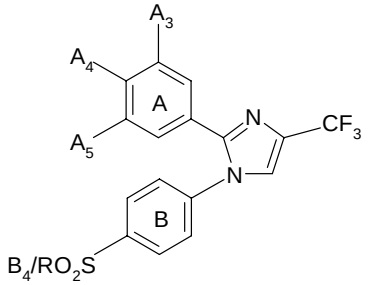

Figure 1 − Lead compounds for present study [A_3, A_4, A_5 and B_4 represent various positions of substituents on the basic skeleton].

pIC_{50} (COX-2) = $(0.8723 \pm 0.210)\ \Sigma\ \Pi\ (A_3 + A_4 + A_5) - (0.560 \pm 0.126)\ [\Sigma\ \Pi\ (A_3 + A_4 + A_5)]^2 + (0.575 \pm 0.280)\ \sigma\ [A_3 + A_5] - (0.807 \pm 0.610)\ \sigma\ B_4 - (0.0026 \pm 0.0020) V_w A_3 + (0.208 \pm 0.186)\ \sigma A_4 + (7.667 \pm 0.516)$ … (1)

n = 49, r = 0.583, S.E. = 0.734, S.D. = 0.60, r^2_{cv} = 0.274, F_{ratio} = 3.61.

This model is capable of explaining only 34 % of the variations. The cause of poor statistical figures were two compounds (**27** and **38**), whose calculated activities were showing too much deviation from the observed values and hence were considered to be outliers (**Table II**). After excluding these two compounds a much more robust model (Eqn. 2) with the same descriptors was obtained which could explain 85.7% of the variance in the observed activity values. The correlation matrix for descriptors influencing COX-2 inhibitory activity is shown in **Table III**. The predicted activity for the training set is shown in **Table IIa**.

pIC_{50} (COX-2) = $(0.639 \pm 0.173)\ \Sigma\ \Pi\ (A_3 + A_4 + A_5) - (0.3617 \pm 0.077)\ [\Sigma\ \Pi\ (A_3 + A_4 + A_5)]^2 + (0.994 \pm 0.212)\ \sigma\ [A_3 + A_5] - (5.834 \pm 0.648)\ \sigma\ B_4 - (0.020 \pm 0.0041)\ V_w A_3 + (0.6095 \pm 0.105)\ \sigma\ A_4 + (10.928 \pm 0.440)$ … (2)

n = 47, r = 0.927, S.E. = 0.302, S.D. = 0.279, r^2_{cv} = 0.546, F_{ratio} = 40.04.

This equation shows a positive correlation of $\Sigma\ \Pi\ (A_3 + A_4 + A_5)$ and $\sigma\ [A_3 + A_5]$ with COX-2 inhibition and negative correlation of $V_w A_3$ with COX-2 inhibitory activity. Eqn. 2 was used to predict the activity of the test set (**Table IIa**). The comparative graph of experimental *versus* predicted activity for the test set is shown in **Figure 2**. B_4 position is very critical for hydrogen bonding of the ligand in the COX-2 active site. Hence, only the reported substituents SO_2NH_2 and SO_2CH_3 could be analyzed.

The positive contribution of $\Sigma\ \Pi\ (A_3 + A_4 + A_5)$ indicates that substituents with higher Π values at position A_3, A_4 and A_5 would be favourable for the COX-2 inhibitory activity. The negative contribution of $V_w A_3$ clearly indicates that the van der Waal's volume of the subsituent at position A_3 must be as low as possible in order to be favourable for COX-2 inhibitory activity. The positive correlation of σA_4 also highlights the importance of electrophilicity of substituents at A_4, hence the substituents at this

Table I — Compounds with ring 'A' and 'B' substitutions and values of descriptors used in training set for COX-2 inhibitory activity

Compd	A-ring substitution			B-ring substitution	$\sum\prod$	V_wA_3	σ A_4	σ(A_3 + A_5)	σ B_4
	A_3	A_4	A_5		(A_3 + A_4 + A_5)				
1	H	F	H	Me	0.14	7.238	0.06	0.0	0.72
2	H	H	H	Me	0.0	7.238	0.0	0.0	0.72
3	H	Me	H	Me	0.56	7.238	-0.17	0.0	0.72
4	H	NMe_2	H	Me	0.18	7.238	-0.83	0.0	0.72
5	H	SMe	H	Me	0.61	7.238	0.0	0.0	0.72
6	H	SO_2Me	H	Me	-1.63	7.238	0.72	0.0	0.72
7	H	Cl	H	NH_2	0.71	7.238	0.13	0.0	0.57
8	H	H	H	NH_2	0.0	7.238	0.0	0.0	0.57
9	H	Me	H	NH_2	0.56	7.238	-0.17	0.0	0.57
10	Cl	H	H	Me	0.71	7.238	0.0	0.37	0.72
11	F	H	H	Me	0.14	7.238	0.0	0.34	0.72
12	Br	H	H	Me	0.86	22.44	0.0	0.39	0.72
13	CF_3	H	H	Me	0.88	31.05	0.0	0.43	0.72
14	OMe	H	H	Me	-0.02	26.60	0.0	0.12	0.72
15	SMe	H	H	Me	0.61	38.98	0.0	0.15	0.72
16	CH_2OMe	H	H	Me	-0.78	34.52	0.0	0.02	0.72
17	NMe_2	H	H	Me	0.18	43.57	0.0	-0.15	0.72
18	NO_2	H	H	Me	-0.28	52.42	0.0	0.71	0.57
19	Cl	H	H	NH_2	0.71	38.30	0.0	0.37	0.57
20	F	H	H	NH_2	0.14	21.02	0.0	0.34	0.57
21	Br	H	H	NH_2	0.86	31.43	0.0	0.39	0.57
22	Me	H	H	NH_2	0.56	22.44	0.0	-0.07	0.57
23	Cl	OMe	H	Me	0.69	12.24	-0.27	0.34	0.72
24	Cl	NMe_2	H	Me	0.89	26.67	-0.83	0.37	0.72
25	F	NMe_2	H	Me	0.32	22.44	-0.83	0.34	0.72
26	Cl	NHMe	H	Me	0.24	22.44	-0.84	0.37	0.72
27	F	Me	H	Me	0.70	22.44	-0.17	0.34	0.72
28	Me	F	H	Me	0.70	22.11	0.06	-0.07	0.72
29	Me	Cl	H	Me	1.27	22.44	0.23	-0.07	0.72
30	OMe	Cl	H	Me	0.69	12.24	0.23	0.12	0.72
31	NMe_2	Cl	H	Me	0.89	26.60	0.23	-0.15	0.72
32	F	F	H	Me	1.12	26.59	0.06	0.34	0.72
33	Me	H	Cl	Me	0.70	55.73	0.0	0.30	0.72
34	Me	H	F	Me	0.12	12.24	0.0	0.27	0.72
35	CF_3	H	F	Me	1.42	26.57	Out	0.77	0.72
36	Cl	H	Cl	Me	0.69	26.61	0.0	0.74	0.72
37	F	OMe	H	NH_2	0.69	34.53	-0.27	0.37	0.57
38	Cl	OMe	H	NH_2	0.84	38.96	-0.27	0.37	0.57
39	Br	OMe	H	NH_2	1.32	22.44	-0.27	0.39	0.57
40	Cl	SMe	H	NH_2	1.27	22.44	0.0	0.37	0.57
41	OMe	Cl	H	NH_2	0.28	22.44	0.23	0.12	0.57
42	F	F	H	NH_2	1.27	22.44	0.06	0.34	0.57
43	Me	H	F	NH_2	0.12	36.59	0.0	0.27	0.57
44	OMe	H	F	NH_2	0.26	12.24	Out	0.46	0.57
45	F	OMe	F	Me	1.40	26.52	-0.27	0.68	0.72
46	Cl	OMe	Cl	Me	1.70	26.68	-0.27	0.74	0.72
47	Br	OMe	Br	Me	1.10	34.45	-0.27	0.78	0.72
48	Cl	NMe_2	Cl	Me	0.26	12.24	-0.83	0.74	0.72
49	F	OMe	F	NH_2	0.26	31.05	-0.27	0.68	0.57

Table Ia − Compounds with ring 'A' and 'B' substitutions and values of descriptors used in test set for COX-2 inhibitory activity

Compd	A-ring substitution			B-ring substitution	$\sum\prod(A_3+A_4+A_5)$	V_wA_3	σA_4	$\sigma(A_3+A_5)$	σB_4
	A_3	A_4	A_5						
50	H	Cl	H	Me	0.71	7.238	0.23	0.0	0.72
51	H	OMe	H	Me	-0.02	7.238	-0.27	0.0	0.72
52	H	NHMe	H	Me	-0.47	7.238	-0.84	0.0	0.72
53	H	SOMe	H	Me	-1.58	7.238	0.49	0.0	0.72
54	H	F	H	NH_2	0.14	7.238	0.06	0.0	0.57
55	Me	H	H	Me	0.56	12.24	0.0	-0.07	0.72
56	NHMe	H	H	Me	-0.47	52.42	0.0	-0.30	0.72
57	NH_2	H	H	Me	-1.23	55.62	0.0	-0.16	0.72
58	F	OMe	H	Me	0.12	31.05	-0.27	0.34	0.72
59	Cl	SMe	H	Me	1.32	12.24	0.0	0.37	0.72
60	Cl	Me	H	Me	1.27	12.24	-0.17	0.37	0.72
61	Me	Me	H	Me	1.27	12.24	-0.17	-0.07	0.72
62	OMe	H	F	Me	1.02	26.53	0.0	0.46	0.72
63	Cl	Me	H	NH_2	0.69	31.05	-0.17	0.37	0.57

Table II — Experimental and calculated biological activity of molecules used in training set for COX-2 inhibitors, with their selectivity ratio — *Contd*

Compd	COX-2 inhibitory activity			COX-1 inhibition		Selectivity $Log(IC_{50}COX\text{-}1/IC_{50}COX\text{-}2)^a$	Selectivity $Log(IC_{50}COX\text{-}1/IC_{50}COX\text{-}2)^b$
	IC_{50}	$pIC_{50}{}^a$	$pIC_{50}{}^b$	IC_{50}	$pIC_{50}{}^a$		
1	0.10	7.0	6.71	36	4.44	2.55	2.68
2	0.12	6.92	6.57	7.23	3.10	3.77	Outlier
3	0.16	6.79	6.77	26	4.58	2.21	1.98
4	0.70	6.15	6.17	5	5.30	0.85	0.81
5	0.16	6.79	6.90	2.1	5.67	1.11	Outlier
6	5.7	5.24	4.85	>100	-	-	-
7	0.01	8.00	7.95	1.6	5.79	2.20	2.37
8	0.04	7.39	7.45	19.3	4.71	2.68	2.50
9	0.04	7.39	7.65	4.6	5.33	2.06	1.71
10	0.06	7.22	7.29	360	3.44	3.77	3.35
11	0.12	6.92	7.01	>1000	-	-	-
12	0.08	7.0	7.02	>100	-	-	-
13	0.21	6.67	6.88	>100	-	-	-
14	0.35	6.45	6.27	>100	-	-	-
15	0.35	6.45	6.21	>100	-	-	-
16	68.1	4.16	5.21	>100	-	-	-
17	3.2	5.49	5.79	42.2	4.37	1.12	1.59
18	0.58	6.23	6.39	>100	-	-	-
19	0.0008	8.00	7.88	6.2	5.20	2.88	2.95
20	0.03	7.52	7.38	67.7	4.16	3.35	3.19
21	0.007	8.10	7.90	4.5	5.34	2.80	3.00
22	0.03	7.52	7.58	3.2	5.49	2.02	1.92

— *Contd*

Table II — Experimental and calculated biological activity of molecules used in training set for COX-2 inhibitors, with their selectivity ratio — *Contd*

Compd	COX-2 inhibitory activity			COX-1 inhibition		Selectivity Log(IC_{50}COX-1/ IC_{50} COX-2)[a]	Selectivity Log(IC_{50}COX-1/ IC_{50} COX-2)[b]
	IC_{50}	pIC_{50} [a]	pIC_{50} [b]	IC_{50}	pIC_{50} [a]		
23	0.13	6.86	6.71	296	3.52	3.35	2.69
24	0.32	6.49	6.48	1.56	5.80	0.68	1.37
25	0.33	6.48	6.27	17.1	4.76	1.71	Outlier
26	0.66	6.18	6.25	>100	-	-	-
27	0.11	6.95	6.84	>100	-	-	-
28	0.17	6.76	6.57	24.1	4.61	2.15	1.91
29	0.09	7.04	6.92	7.84	5.10	1.94	1.95
30	0.25	6.60	6.78	>100	-	-	-
31	1.04	5.98	6.55	>100	-	-	-
32	0.12	6.92	6.32	>100	-	-	-
33	0.08	7.09	7.12	>1000	-	-	-
34	0.11	6.95	6.52	>100	-	-	-
35	0.96	4.00	Outlier	67	4.17	-	-
36	0.17	6.76	7.09	>100	-	-	-

[a] experimental value, [b] predicted value

Table IIa — Experimental and calculated COX-2 inhibiting activity of molecules used in test set with their selectivity ratio

Compd	COX-2 inhibitory activity			COX-1 inhibition		Selectivity Log(IC_{50}COX-1/ IC_{50} COX-2)[a]	Selectivity Log(IC_{50}COX-1/ IC_{50} COX-2)[b]
	IC_{50}	pIC_{50} [a]	pIC_{50} [b]	IC_{50}	pIC_{50} [a]		
43	0.11	6.95	7.07	23	4.63	2.32	2.40
44	1.47	5.83	5.60	53.5	4.27	1.56	0.99
45	0.96	4.0	4.80	>100	-	-	-
46	0.01	8.0	7.59	1.9	5.72	2.27	2.45
47	0.92	6.03	5.00	>100	-	-	-
48	5.89	5.22	4.03	>100	-	-	-
49	0.15	6.82	6.33	49	4.30	2.51	2.62
50	0.04	7.39	7.20	>100	-	-	-
51	0.03	7.52	7.10	12	4.9	2.60	2.88
52	0.33	6.48	6.82	30	4.52	1.95	1.77
53	0.96	6.01	7.02	>100	-	-	-
54	0.003	8.52	7.56	0.57	5.45	2.27	2.90
55	0.04	7.39	7.52	>100	-	-	-
56	0.72	6.14	6.22	91	4.0	-	-

[a] experimental value, [b] predicted value by Eqn 5

Table III — Correlation matrix for descriptors influencing COX-2 inhibitory activity

	pIC_{50}	σA_4	$\sum\prod(A_3 + A_4 + A_5)$	$[\sum\prod(A_3 + A_4 + A_5)]^2$	$\sigma(A_3 + A_5)$	σB_4	V_wA_3
pIC_{50}	1.0						
σA_4	0.029	1.0					
$\sum\prod(A_3+A_4+A_5)$	0.518	0.194	1.0				
$[\sum\prod(A_3+A_4+A_5)]$	-0.039	0.219	0.379	1.0			
$\sigma(A_3+ A_5)$	0.228	0.390	0.318	0.226	1.0		
σB_4	-0.696	0.111	0.121	0.032	0.006	1.0	
V_wA_3	-0.205	0.069	0.191	0.127	0.366	0.091	1.0

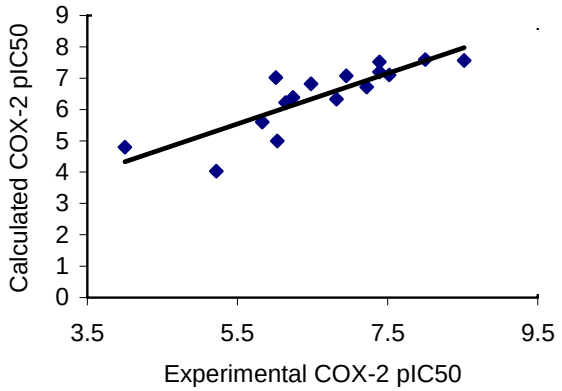

Figure 2 − Graph between experimental and predicted COX-2 inhibitory activity for compounds of test set

position should be more powerful electron withdrawing groups. Then, as per this model, the COX-2 inhibitory activity was calculated for the test set (**Table IIa**). A comparison of the experimental and calculated values (using Eqn. 2) for COX-2 inhibitory activity in the form of a graph is depicted in **Figure 2**.

When COX-1 inhibitory data was subjected to regression analysis with those variables previously used for COX-2, a good correlation could not be obtained. The best correlation obtained here is shown in Eqn 3.

pIC_{50} (COX-1) = (0.1848 ± 0.168) Σ Π ($A_3 + A_4 + A_5$) – (0.2261 ± 0.143) [Σ Π ($A_3 + A_4 + A_5$)] ^{2} + (1.437 ± 0.394) σ [$A_3 + A_5$] – (6.938 ± 1.215) σ B_4 – (0.0024 ± 0.007) V_wA_3 + (0.9209 ± 0.322) σ A_4 + (9.0126 ± 0.824) … (3)

n = 35, r = 0.645, S.E. = 0.5612, S.D. = 0.515, F_{ratio} = 8.32, r^2_{cv} = 0.274.

This model explains only 55.5 % variance with high standard error of regression. Here, it can be seen that the contribution of V_wA_3 is very low. The role of summed Π values at A_3, A_4 and A_5 position is also ambiguous.

One of the aims of the present study was to identify the structural features which impart selectivity to these compounds for COX-2 enzyme over COX-1. To achieve this aim, structural descriptors used in Eqn 2 were regressed against selectivity ratio [log (IC_{50} COX-1/IC_{50} COX-2)].

log (COX-1/COX-2) = (0.7242 ± 0.230) Σ Π ($A_3 + A_4 + A_5$) – (- 0.115 ± 0.08) [Σ Π ($A_3 + A_4 + A_5$)] ^{2} + (3.225 ± 0.562) σ [$A_3 + A_5$] – (1.038 ± 0.392) σ B_4 – (0.0125 ± 0.0041) V_wA_3 +(2.050 ± 0.32) σ A_4 +(1.997 ± 0.462) … (4)

n = 26, r = 0.750, S.E. = 0.46, S.D. = 0.570, r^2_{cv} = 0.546, F_{ratio} = 6.05.

After removing outliers (**2**, **5** and **25**) and optimizing the number of descriptors Eqn 5 was obtained.

log (COX-1/COX-2) = (2.710 ± 0.20) - (0.722 ± 0.230) Σ Π ($A_3 + A_4 + A_5$) + (3.44 ± 0.510) σ [$A_3 + A_5$] – (0.012 ± 0.0084) V_wA_3 + (2.050 ± 0.32)σ A_4 … (5)

n = 23, r = 0.8539, S.E. = 0.40, S.D. = 0.4148, r^2_{cv} = 0.600.

This equation offered a much better correlation in terms of statistics. It is interesting to note that summed Π values of three positions in ring-A have now a negative contribution towards selectivity and the positive contribution of electronic parameter (σA_4) further increased to impart higher selectivity to the compounds. Eqn 5 was used to predict the selectivity of test compounds (**Table IIa**) and a plot of the experimental *versus* calculated values is shown in **Figure 3**.

Based on the correlations (Eqn. 2 and 5) obtained above, it was planned to design new molecules having the diarylimidazole skeleton with much higher selectivity than for those compounds which are reported[22]. In our earlier work[25] it was observed that SO_2CH_3 group had higher contribution over SO_2NH_2 for COX-2 inhibitory activity at B_4 position. So, all these compounds (**D1-10**, **Table IV**) have been designed with SO_2CH_3 group at B_4 position. All the designed compounds have much higher selectivity for COX-2 enzyme with retention of inhibitory activity.

Methodology

Data Sets

The structures (**Figure 1**) and activities at IC_{50} (IC_{50} is the concentration in μM for 50% inhibition of

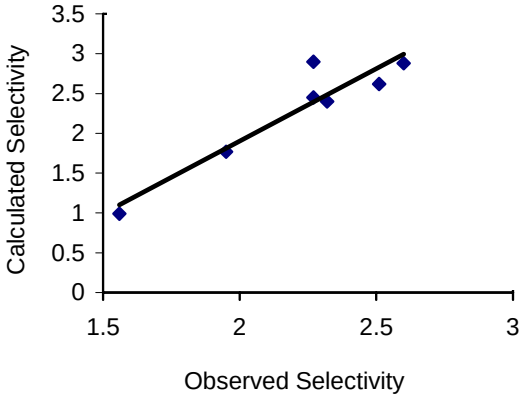

Figure 3 − Graph between experimental and predicted COX-2 selectivity for test set of compounds

Table IV — Structures, descriptors, selectivity ratio and COX-2 inhibitory activity of the designed compounds

Compd	A_3	A_4	A_5	(Pi)*	$[Pi)^*]^2$	$\sigma(A_3 + A_5)$	V_wA_3	σA_4	(S)*	pIC_{50} COX-2
D1	Cl	SO_2CF_3	F	1.4	1.96	0.71	22.449	0.93	5.24	7.93
D2	Cl	SCOEt	F	1.49	2.22	0.71	22.449	0.44	4.12	7.54
D3	Cl	SO_2CF_3	Cl	1.97	3.88	0.74	22.449	0.93	4.92	7.72
D4	Br	SO_2CF_3	Cl	2.12	4.49	0.77	31.059	0.93	4.77	7.47
D5	Br	SO_2CF_3	F	1.55	2.4	0.73	31.059	0.93	5.06	7.72
D6	Br	SO_2CF_3	Br	2.27	5.15	0.78	31.059	0.93	4.69	7.36
D7	SMe	SO_2CF_3	F	1.30	1.69	0.49	43.578	0.93	4.35	7.55
D8	SMe	SO_2CF_3	Cl	1.87	3.49	0.52	43.578	0.93	4.02	7.38
D9	SMe	SCOEt	Cl	1.96	3.84	0.52	43.578	0.44	3.95	6.70
D10	SMe	SO_2CF_3	Br	2.02	4.08	0.55	43.578	0.93	4.0	7.32

(S)*- Refers to selectivity ratio calculated by Eqn 5
$(Pi)^* = \sum \prod (A_3 + A_4 + A_5)$

the COX-2 or COX-1 enzyme) for diarylimidazoles extracted from literature[22] and gathered in **Tables I**, **Ia, II** and **IIa**, respectively.

Molecular Modeling

Molecular modeling was performed on Alchemy 2000 to calculate various parameters, for the purpose of using them in correlations. All compounds were drawn on builder module of Alchemy 2000. Compounds were then subjected to conformational analysis and energy minimization with RMS gradient of 0.001 and iteration limit of 10000 using MM2 force field. Conformations have a dramatic effect on the biological activity and hence, the lowest energy conformers of all the compounds were considered while calculating the descriptors. Parameters like surface area, van der Waal's volume, ovality, dipole moment in different directions, ionization potential, HOMO and LUMO energies were calculated for different molecules using MM2 force field or MOPAC. Partial charges for all atoms in the molecules were also calculated. Constants like Π (hydrophobicity), σ_m and σ_p (electronic parameter) for the existing groups were taken from the literature[26,27]. The correlations between biological activity (pIC_{50}) and descriptors were obtained by stepwise regression analysis using QSAR easy software developed in the department[28]. Following statistical measures were used: n = number of samples, r = regression constant, S.E. = standard error of regression, S.D. = standard deviation and percentage of variance explained by regression analysis.

Conclusion

The series of diarylimidazoles discussed in this paper are very potent (IC_{50} = 10-100nm) and selective inhibitors of human COX-2 enzyme. The quantitative structure activity relationship data suggests that the COX-2 inhibitory activity and selectivity are greatly influenced by the functional groups attached to different positions of the molecule and also by their properties like electrophilicity (Π), hydrophobicity (σ) and van der Waal's volume. Eqn 2 clearly shows the positive contribution of $\Sigma\ \Pi\ (A_3 + A_4 + A_5)$ and $\sigma\ (A_3 + A_5)$ which indicates that increase in the Π and σ value of the substituents at position A_3, A_4 and A_5 will be favourable for COX-2 inhibitory activity. The effect of van der Waal's volume of the substituent at A_3 was significant. It was observed that whenever the van der Waal's volume at A_3 is increased the selectivity was decreased (**Table IV**). Interestingly, the summed 'Π' contribution at all the three positions in ring-A had negative contribution for COX-2 selectivity. Based on the developed QSAR relationships certain compounds could be designed with very high COX-2 selectivity while retaining high inhibitory potency. The study provides further structural insights in the development of newer COX-2 inhibitors to be used as potential anti-inflammatory/anticancer agents or those used for the control of Alzheimer's disease.

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