J. Enzyme Inhibition, 1999, Vol. 14, pp. 277–288
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1,2-DIARYLIMIDAZOLES AS INHIBITORS OF CYCLOOXYGENASE-2: A QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIP STUDY

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(Received 3 September 1998)

The cyclooxygenase-2 (COX-2) enzyme inhibition activity of derivatives of 1,2-diarylimidazole is analysed through Fujita–Ban and Hansch approaches. The analyses have helped to ascertain the role of different substituents in explaining the observed inhibitory potency of these analogues. From both approaches it is revealed that the more hydrophobic X-substitutions that are present at the 3- and 4-positions of the aryl ring and are also non-hydrogen acceptor in character improve inhibitory action of a compound. The smaller substituent either H or F is preferred at the 2-X position as it is involved in steric interaction. Likewise, the substituent $-NH_2$ instead of Me at R is advantageous. Further, for a data set of 35 congeners, the selectivity ratio related to the constitutive COX-1 isozyme is also analysed through the Fujita–Ban approach. The derived contributions of parent moiety and various substituents have helped to predict the substitution pattern in the design of more effective compounds that were not in the original data set.

Keywords: Quantitative structure–activity relationship (QSAR); Inhibitors of cyclooxygenase-2 enzyme; 1,2-diarylimidazoles; Nonsteroidal anti-inflammatory drugs; Fujita–Ban and Hansch analyses

INTRODUCTION

It has been established that nonsteroidal anti-inflammatory drugs (NSAIDs) block the production of prostaglandins (PGs) via the cyclooxygenase pathway and elicit analgesic, antipyretic and anti-inflammatory activity.[1,2] The chronic usage of these drugs has, however, led to disruption

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of beneficial prostaglandin-regulated processes.[3,4] This causes the induction of gastrointestinal mucosal lesions, perforations, bleeding and decreased renal function[5] and therefore, restricts their therapeutic usefulness. Alternative treatment of inflammation with the steroidal anti-inflammatory drugs (gluco-corticoids) may also lead to a variety of unwanted side effects, especially in their use for long periods of treatment.[6]

Earlier, it was believed that cyclooxygenase (COX) was a single enzyme present constitutively in most cells, and inhibition of this enzyme would lead to both beneficial and detrimental effects.[7] Recently, it was suggested that the COX enzyme existed in two forms, namely, the inducible form (COX-2) that is expressed during inflammatory conditions and the constitutive isoform (COX-1) that produces physiologically important PGs present in gastrointestinal tract and kidney.[8–10] It is realised that it is the inhibition of COX-1 that causes the various side effects seen with NSAIDs. This finding coupled with the discovery of COX-2 has suggested that selective inhibitors of COX-2 might constitute a novel approach to the treatment of inflammation with minimal or no side effects.[11,12]

Previously we have quantitatively analysed the role of various substitutional parameters in explaining the observed COX-2 inhibition activities in two different series, the diarylspiro[2.4]heptenes[13] and the sulfones and sulfonamides of 1,2-diaryl-4,5-difluorobenzene.[14] Encouraged by the excellent derived quantitative relationships we have, in the present communication, expanded our study to another series of such inhibitors, reported more recently by Khanna *et al.*[15] They have synthesised a series of 1,2-diarylimidazoles which on evaluation were found to contain highly potent and selective inhibitors of the human COX-2 enzyme. Their structure–activity (SAR) studies on these analogues were aimed only at the alteration of substituents at different positions of the diarylimidazole moiety and provided no rationale to reduce the trial-and-error factors. Hence, a quantitative SAR (QSAR) study on these analogues was conducted so as to provide the rationale for drug-design and to explore the possible mechanism of their action.

MATERIALS AND METHODS

The reported compounds,[15] exemplified by Figure 1 and compiled in Table I, were subjected to QSAR analysis. Their biological inhibitory effects towards the human COX-2 enzyme and relevant physicochemical parameters are also listed in Table I. The activity data is based on IC_{50} values which represent the concentration of a drug to accomplish 50%

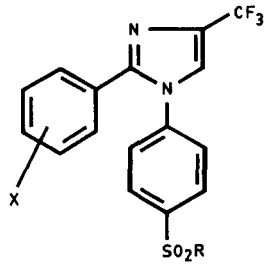

FIGURE 1 Structures of 1,2-diarylimidazoles.

inhibition of the human COX-2 enzyme. The same are expressed as $-\log IC_{50}$ on a molar basis.

The most suitable parameters were found to be the hydrophobic constant, π, Taft's steric parameter, Es and the hydrogen acceptor parameter, HA that were taken directly from the compilation of Hansch *et al.*[16] Besides these parameters, some dummy variables were also used to account for the effect of some specific alteration. Further, the COX-1 activities were reported only for a few compounds and for them the selectivity ratios, $S = IC_{50}(\text{COX-1})/IC_{50}(\text{COX-2})$, computed as $\log S$, are also included in Table I. Both Fujita–Ban and Hansch type of calculations were carried out for these compounds. In the Fujita–Ban approach,[17] which is based on an additivity principle, the biological activity, BA (either $-\log IC_{50}$ or $\log S$) is expressed as

$$BA_i = \sum a_j X_{ij} + \mu \tag{1}$$

where X_j is the jth substituent with a value of 1 if present and 0 if not, a_j is the contribution of the jth substituent (generally hydrogen) to BA_i and μ is the theoretical biological activity of the (unsubstituted) reference compound of the series. The linear equations generated using Equation (1) were solved by the method of least squares for the values of unknowns a_j and μ. For the variable $-\log IC_{50}(\text{COX-2})$, both the Fujita–Ban and Hansch type of approaches were used, while for the variable $\log S$ only a Fujita–Ban study was performed. For the latter variable, none of the electronic, hydrophobic, steric or van der Waals volume parameters was found suitable to correlate with it.

RESULTS AND DISCUSSION

The first sixty compounds (Nos. **1–60**) in Table I, only were retained in the construction of the Fujita–Ban matrix with compound **17** as the reference

TABLE I 1,2-Diarylimidazoles and their cyclooxygenase-2 inhibitory activities, selectivity ratio and physicochemical parameters (see Figure 1 for structures)

Compound no.	*R*	*X*	$\pi_{3,4}$	$HA_{3,4}$	Es(2)	I_R	$-\log IC_{50}$ (M)[a]				$\log S$[g]	
							Obsd.[b]	*Calcd.*			*Obsd.*[b]	*Calcd. F.B.*
								F.B.	*Equation* (6)	*Equation* (7)		
1	Me	2-F	0.00	0	−0.46	0	6.40	6.31	6.33	6.28	—[f]	—
2	Me	2-Me	0.00	0	−1.24	0	6.10	5.93	5.72	5.74	2.86	2.51
3	NH_2	2-F	0.00	0	−0.46	1	7.00	7.09	7.24	7.21	2.35[d]	—
4	NH_2	2-Me	0.00	0	−1.24	1	6.70	6.71	6.63	6.67	1.61	1.96
5	Me	3-Cl	0.71	0	0.00	0	7.22	7.26	6.98	6.96	3.78	3.80
6	Me	3-F	0.14	0	0.00	0	6.92	6.93	6.75	6.67	—[f]	—
7	Me	3-Br	0.86	0	0.00	0	7.10	7.16	7.04	7.03	—[f]	—
8	Me	3-Me	0.56	0	0.00	0	7.22	6.84	6.92	6.88	3.18	2.90
9	Me	3-OMe	−0.02	1	0.00	0	6.46	6.32	6.26	6.24	—[f]	—
10	Me	3-NMe_2	0.18	1	0.00	0	5.49	5.56	6.34	6.34	1.11[d]	—
11	NH_2	3-Cl	0.71	0	0.00	1	8.10	8.05	7.89	7.89	2.89	3.24
12	NH_2	3-F	0.14	0	0.00	1	7.52	7.72	7.66	7.60	3.35	3.31
13	NH_2	3-Br	0.86	0	0.00	1	8.15	7.95	7.95	7.96	2.81	2.87
14	NH_2	3-Me	0.56	0	0.00	1	7.52	7.62	7.83	7.81	2.03	2.35
15	Me	4-Cl	0.71	0	0.00	0	6.96	7.12	6.98	6.96	2.32	2.50
16	Me	4-F	0.14	0	0.00	0	7.00	6.85	6.75	6.67	2.56	2.78
17	Me	4-H	0.00	0	0.00	0	6.92	6.77	6.79	6.60	3.78	3.38
18	Me	4-Me	0.56	0	0.00	0	6.80	6.81	6.92	6.88	2.20	2.37
19	Me	4-OMe	−0.02	1	0.00	0	6.24	6.47	6.26	6.24	0.70	—[c]
20	Me	4-NHMe	−0.47	1	0.00	0	5.83	5.76	6.08	6.01	1.56[d]	—
21	Me	4-NMe_2	0.18	1	0.00	0	6.15	6.22	6.34	6.34	0.85	0.80
22	Me	4-SMe	0.61	0	0.00	0	6.80	6.81	6.94	6.91	1.11	1.39
23	NH_2	4-Cl	0.71	0	0.00	1	8.00	7.91	7.89	7.89	2.20	1.95
24	NH_2	4-F	0.14	0	0.00	1	8.00	7.63	7.66	7.60	2.28	2.22

25	NH_2	4-H	0.00	0	0.00	1	7.40	7.55	7.60	7.53	2.68	2.83
26	NH_2	4-Me	0.56	0	0.00	1	7.40	7.60	7.83	7.81	2.06	1.82
27	Me	3-F,4-OMe	0.12	1	0.00	0	6.82	6.64	6.32	6.31	2.51	2.89
28	Me	3-Cl,4-OMe	0.69	1	0.00	0	6.89	6.97	6.55	5.59	3.36	2.82
29	Me	3-Cl,4-SMe	1.32	0	0.00	0	7.40	7.30	7.22	7.26	—[f]	—
30	Me	3-Cl,4-NMe_2	0.89	1	0.00	0	6.49	6.72	6.63	6.69	0.70	1.21
31	Me	3-F,4-NMe_2	0.32	1	0.00	0	6.48	6.39	6.40	6.41	1.72	1.27
32	Me	3-Cl,4-NHMe	0.24	1	0.00	0	6.18	6.25	6.36	6.37	—[f]	—
33	Me	3-Cl,4-Me	1.27	0	0.00	0	7.52	7.31	7.20	7.24	2.60	2.78
34	Me	3-F,4-Me	0.70	0	0.00	0	6.96	6.98	6.97	6.95	—[f]	—
35	Me	3-Me,4-F	0.70	0	0.00	0	6.77	6.92	6.97	6.95	2.15	2.29
36	Me	3-Me,4-Cl	1.27	0	0.00	0	7.05	7.19	7.20	7.24	1.94	2.01
37	Me	3-OMe,4-Cl	0.69	1	0.00	0	6.60	6.68	6.55	6.59	—[f]	—
38	Me	3-NMe_2,4-Cl	0.89	1	0.00	0	5.98	5.91	6.63	6.69	—[f]	—
39	Me	3,4-F_2	0.28	0	0.00	0	6.92	7.01	6.80	6.74	—[f]	—
40	Me	3,4-Me_2	1.12	0	0.00	0	6.48	6.88	7.14	7.16	1.96	1.89
41	NH_2	3-F,4-OMe	0.12	1	0.00	1	7.52	7.43	7.23	7.23	2.10	2.34
42	NH_2	3-Cl,4-OMe	0.69	1	0.00	1	7.70	7.75	7.46	7.52	2.46	2.27
43	NH_2	3-Br,4-OMe	0.84	1	0.00	1	7.52	7.66	7.52	7.59	1.96	1.90
44	NH_2	3-Cl,4-SMe	1.32	0	0.00	1	8.00	8.09	8.14	8.19	1.54	1.26
45	NH_2	3-Cl,4-Me	1.27	0	0.00	1	8.52	8.10	8.11	8.16	2.28	2.23
46	NH_2	3-OMe,4-Cl	0.69	1	0.00	1	7.70	7.47	7.46	7.52	2.63[d]	—
47	NH_2	3,4-F_2	0.28	0	0.00	1	7.52	7.80	7.72	7.67	3.00	2.70
48	Me	3-Me,5-Cl	0.56	0	0.00	0	7.10	6.75	6.92	6.88	—[f]	—
49	Me	3-Me,5-F	0.56	0	0.00	0	6.96	6.83	6.92	6.88	—[f]	—
50	Me	3-OMe,5-F	−0.02	1	0.00	0	6.02	6.31	6.26	6.24	—[f]	—
51	Me	3,5-Cl_2	0.71	0	0.00	0	6.77	7.17	6.98	6.96	—[f]	—
52	NH_2	3-Me,5-Cl	0.56	0	0.00	1	7.40	7.54	7.83	7.81	—[f]	—
53	NH_2	3-Me,5-F	0.56	0	0.00	1	7.52	7.61	7.86	7.81	3.44	3.26
54	NH_2	3-OMe,5-F	−0.02	1	0.00	1	6.34	—[c]	—[c]	—[c]	—[f]	—
55	Me	3,5-F_2,4-OMe	0.12	1	0.00	0	6.77	6.63	6.32	6.31	—[f]	—
56	Me	3,5-Cl_2,4-OMe	0.69	1	0.00	0	6.85	6.88	6.55	6.59	—[f]	—

TABLE I (*Continued*)

Compound no.	*R*	*X*	$\pi_{3,4}$	$HA_{3,4}$	Es(2)	I_R	$-\log IC_{50}$ (M)[a]				log *S*[g]	
							Obsd.[b]	*Calcd.*			*Obsd.*[b]	*Calcd. F.B.*
								F.B.	*Equation* (6)	*Equation* (7)		
57	Me	3,5-Me_2,4-OMe	0.54	1	0.00	0	6.14	5.98	6.48	6.51	2.10[d]	—
58	Me	3,5-Cl_2,4-NMe_2	0.89	1	0.00	0	6.85	6.63	6.63	6.69	—[f]	—
59	NH_2	3,5-F_2,4-OMe	0.12	1	0.00	1	7.52	7.41	7.23	7.23	3.07	3.25
60	Me	2,5-Me_2,4-OMe	−0.02	1	−1.24	0	4.91	5.07	5.29	5.37	—[f]	—
61	Me	2-Cl	0.00	0	−0.97	0	6.05[d]	—	5.93[e]	5.93	—[f]	—
62	Me	3-CF_3	0.88	0	0.00	0	6.68[d]	—	7.05[e]	7.04	—[f]	—
63	Me	3-SMe	0.61	0	0.00	0	6.46[d]	—	6.94[e]	6.91	—[f]	—
64	Me	3-CH_2OMe	−0.78	1	0.00	0	4.17[d]	—	5.95[e]	—[c]	—[f]	—
65	Me	3-NHMe	−0.47	1	0.00	0	6.04[d]	—	6.08[e]	6.03	—[f]	—
66	Me	3-NH_2	−1.23	1	0.00	0	5.23[d]	—	5.77[e]	5.63	—[f]	—
67	Me	3-NO_2	−0.28	1	0.00	0	6.24[d]	—	6.15[e]	6.11	—[f]	—
68	Me	4-SO_2Me	−1.63	1	0.00	0	5.24[d]	—	5.61[e]	5.43	—[f]	—
69	Me	3,4-OCH_2O–	−0.05	1	0.00	0	6.77[d]	—	6.25[e]	6.22	1.85[d]	—
70	Me	3,5-Br_2,4-OMe	−0.02	1	0.00	0	7.05[d]	—	6.26[e]	6.66	—[f]	—

[a]The COX-2 inhibition activity on a molar basis. [b]Taken from Ref. [15]. [c]'Outliers' of the present study. [d]Compound not considered in formulating Fujita–Ban matrix. [e]Predicted inhibition activity value, using Equation (6), for the compound in the test set. [f]The reported values of selectivity ratio were uncertain. [g]Defined as $S = IC_{50}(COX\text{-}1)/IC_{50}(COX\text{-}2)$.

congener. These compounds have identical substitutional variations at a given position, at least in two or more congeners. Tabulation of this matrix of 60 linear equations in 20 unknowns including the contribution of parent compound is avoided here for the sake of brevity. These equations were solved by the method of least squares for the unknowns μ and a_j. The contributions of various substituents obtained thereby are summarised in the first column of Table II and the resulting statistical parameters of the study are

$$n = 60, \quad r = 0.957, \quad s = 0.244, \quad F(20, 39) = 21.202,$$

where n, r, s and F are respectively the number of data points, multiple regression coefficient, standard error of estimate and F-ratio between the variances of calculated and observed activities. The data point **54** is the only compound whose calculated activity value was found to be slightly higher than the observed value. This data point was, therefore, ignored to improve the results further but no specific reason is immediately apparent for its 'outlier' behaviour. In doing so, the corresponding row was removed from the Fujita–Ban matrix and the MRA of resulting matrix leads to the results summarised in the last column of Table II. The improved statistical

TABLE II Substituents contributions to cyclooxygenase-2 inhibitory activities of 1,2-diarylimidazoles

Position	*Substitution*	*Substituent contribution*	
		$n = 60$	$n = 59$
X	2-F	−0.447	−0.459
	2-Me	−0.824	−0.839
	3-Cl	0.504	0.497
	3-F	0.191	0.169
	3-Br	0.409	0.398
	3-Me	0.098	0.071
	3-OMe	−0.567	−0.443
	3-NMe_2	−1.238	−1.209
	4-Cl	0.406	0.358
	4-F	0.074	0.080
	4-Me	0.043	0.046
	4-OMe	−0.276	−0.296
	4-NHMe	−1.017	−1.009
	4-NMe_2	−0.552	−0.541
	4-SMe	0.043	0.041
	5-Cl	−0.103	−0.088
	5-F	−0.107	−0.012
	5-Me	−0.606	−0.561
R	NH_2	0.754	0.788

parameters of the study are:

$$n = 59, \quad r = 0.964, \quad s = 0.226, \quad F(20,38) = 24.760.$$

The r^2-value now accounts for 93% of the variance and the F-value obtained is significant at 99% level [$F_{20,38}(0.01) = 2.40$]. The calculated values of $-\log IC_{50}$(COX-2), listed in Table I, are now in close agreement with the observed ones. The substituents, to be incorporated at various positions of the parent moiety, that make higher positive contributions to activity may be used to design more active compounds of the series in future. A simple suggested compound with substituents such as R = NH_2 and X = 3-Cl, 4-F may possess the theoretical activity value nearly one order of magnitude higher than the highest active compound of the present series.

It is important to note that the Fujita–Ban (or the Free-Wilson) approach cannot extrapolate beyond the substituents used in the training set whereas the Hansch approach, attempted next for the same data set of 60 compounds, can do so. The steps of the development of the final QSAR are described through follow up correlations. In this approach, the binary variation either $-NH_2$ or $-$Me at R may be described by a dummy variable, I_R. Its value of 1 or 0, in that order, indicates the presence or absence of $-NH_2$ at R and the resulting correlation in it is given by Equation (2)

$$-\log IC_{50} = 0.945(\pm 0.140)I_R + 6.629,$$
$$n = 60, \quad r = 0.664, \quad s = 0.517, \quad F(1,58) = 45.666. \qquad (2)$$

The added hydrophobicity constant, $\pi(3+4)$ due to 3-X and 4-X substituents have further improved the above equation as follows:

$$-\log IC_{50} = 0.750(\pm 0.130)\pi(3+4) + 0.943(\pm 0.112)I_R + 6.270,$$
$$n = 60, \quad r = 0.804, \quad s = 0.414, \quad F(2,57) = 52.086. \qquad (3)$$

Successive inclusion of hydrogen acceptor property, $HA_{3,4}$ for 3-X or 4-X substitutions and Taft's steric parameter, Es(2) for 2-X substitution are described respectively by correlation Equations (4) and (5):

$$-\log IC_{50} = 0.631(\pm 0.123)\pi(3+4) - 0.380(\pm 0.104)HA_{3,4}$$
$$+ 0.877(\pm 0.103)I_R + 6.502,$$
$$n = 60, \quad r = 0.845, \quad s = 0.376, \quad F(3,56) = 46.586, \qquad (4)$$

$$-\log IC_{50} = 0.440(\pm 0.112)\pi(3+4) - 0.456(\pm 0.090)HA_{3,4}$$
$$+ 0.754(\pm 0.159)Es(2) + 0.868(\pm 0.088)I_R + 6.685,$$
$$n = 60, \quad r = 0.893, \quad s = 0.320, \quad F(4,55) = 53.961. \qquad (5)$$

And, finally eliminating, compound **54** (the 'outlier' of Fujita–Ban study), MRA resulted in the significant correlation Equation (6):

$$-\log IC_{50} = 0.403(\pm 0.107)\pi(3+4) - 0.423(\pm 0.087)HA_{3,4} + 0.782(\pm 0.152)Es(2) + 0.914(\pm 0.085)I_R + 6.690,$$
$$n = 59, \quad r = 0.904, \quad s = 0.304, \quad F(4, 54) = 60.227. \qquad (6)$$

The parameters, r, s and F have now improved in a statistical sense and this equation as such reflects the parameteric requirement of various substitutions at different positions in the 1,2-diarylimidazoles as inhibitors of the COX-2 enzyme. The r^2-value accounts for 82% of variance in the observed activity values and the F-value is significant at 99% level [$F_{4,54}(0.01) = 3.70$]. The calculated activity values, using Equation (6) and listed in Table I, are in close agreement with the observed ones. In addition, the activities of ten compounds (test set, Nos. **61–70**) that were outside the training set, are also calculated using this equation. Their predicted values, in this way, are found nearly related to the observed ones. That the variables used have no mutual correlation is shown in Table III. The validity of Equation (6) is strengthened further through consideration of all the compounds of Table I. The test set that was outside the training set earlier was also combined to give a relatively larger data set. The MRA on complete data have resulted into correlation Equation (7) with one more compound (No. **64**) as the 'outlier'.

$$-\log IC_{50} = 0.499(\pm 0.079)\pi(3+4) - 0.356(\pm 0.085)HA_{3,4} + 0.698(\pm 0.139)Es(2) + 0.929(\pm 0.085)I_R + 6.602,$$
$$n = 68, \quad r = 0.909, \quad s = 0.312, \quad F(4, 63) = 74.998. \qquad (7)$$

The statistical significance of Equation (7) is similar to that of Equation (6) and reflects improved results, as in the above equation, derived for a larger data set, the r-value obtained accounts for 83% of variance and the F-value, significant at 99% level [$F_{4,63}(0.01) = 3.63$], is also increased. The mutual orthogonality conditions among the independent variables of Equation (7) shown in Table IV and the calculated activity values that closely resemble the

TABLE III The intercorrelation matrix amongst the independent variables of Equation (6)

	$\pi(3+4)$	$HA_{3,4}$	Es(2)	I_R
$\pi(3+4)$	1.000	0.244	0.337	0.032
$HA_{3,4}$		1.000	0.070	0.205
Es(2)			1.000	0.016
I_R				1.000

TABLE IV The intercorrelation matrix amongst the independent variables of Equation (7)

	$\pi(3+4)$	$HA_{3,4}$	Es(2)	I_R
$\pi(3+4)$	1.000	0.346	0.224	0.124
$HA_{3,4}$		1.000	0.120	0.230
Es(2)			1.000	0.006
I_R				1.000

observed ones are listed in Table I. For the compounds in the test set, the predicted and the calculated activities using Equation (6) and Equation (7) respectively are nearly the same. This inference reveals a better indication of the predictiveness of Equation (6). Either of these equations may, therefore, be used to synthesise more effective inhibitors of COX-2 enzyme in future.

From both the approaches, the following conclusions may now be drawn:

1. More hydrophobic substituents that are not hydrogen acceptors in nature present at the 3- and 4-positions of the aryl ring improve the inhibitory action of a compound. The Fujita–Ban study, in conformity with this, assigned higher substitutional contributions to such substituents. But, if the substituent at either of these two positions also possesses a hydrogen acceptor property in addition then it may cause a detrimental effect. The hydrogen acceptor property, adding negatively, counterbalances the incremental effect to activity produced by the hydrophobic effect.
2. The 2-X substituents of the aryl ring are engaged in steric interaction. Compared to H and F, the other bulkier substituents having more negative Es(2) values are undesirable and the Fujita–Ban study has predicted a more negative substituent contribution for them.
3. All substituents at 5-X have negative substituent contributions, suggesting that this position should remain unsubstituted.
4. The substituent $-NH_2$ at R having a positive substituent contribution relative to Me, enhances the activity of a compound. The same is also reflected by the positive regression coefficient associated with the indicator variable I_R in both the Equations (6) and (7).

An attempt was also made to correlate the selectivity ratio, log S with various physicochemical (σ, π, MR and Es) and structural (van der Waals volume, Vw) parameters in different combinations, but none of these could give any meaningful correlations. Interestingly, the Fujita–Ban approach has delineated some important conclusions for this dependent variable. This data set consists of only those compounds in which the frequency of occurrence of certain group, at a given position, is more than one. For this reason,

only 35 compounds (Nos. **2**, **4**, **5**, **8**, **11–19**, **21–28**, **30**, **31**, **33**, **35**, **36**, **40–45**, **47**, **53** and **59**) in Table I were selected for the construction of the Fujita–Ban matrix and their $\log S$ values as the dependent variable. The matrix, subjected to MRA resulted in the solution of 14 independent variables that are the contributions of parent compound and various substituents present at R, 2-X, 3-X, 4-X, and 5-X. The same are listed in Table V and the statistical parameters of study are

$$n = 35, \quad r = 0.894, \quad s = 0.467, \quad F(14, 20) = 5.656.$$

This could account for 80% ($r^2 = 0.799$) of variance. The calculated $\log S$ values obtained by adding requisite contributions of substituents to μ were reasonably in close agreement, except for compound **19**. When this lone compound was deleted, the contributions of substituents and parent moiety obtained in that way are also included in Table V. The improved statistical parameters emerging from the study are

$$n = 34, \quad r = 0.936, \quad s = 0.351, \quad F(14, 19) = 9.565.$$

The r^2-value is now greatly increased and accounts for 88% of the variance. Likewise, the F-value, significant at 99% level [$F_{14,19}(0.01) = 3.20$], is also increased and the observed and calculated values of $\log S$ have reached parity (Table I). From Table V, it appears that the substituents of the aromatic ring only at 3-X (F, Cl, Br), and 5-X (F) have positive contributions, while the substitutions at remaining positions of this ring have negative contributions. Further, the substitution $-NH_2$ instead of $-Me$ at

TABLE V Substituents contributions to selectivity ratio of 1,2-diarylimidazoles

Position	*Substitution*	*Substituent contribution*	
		$n = 35$	$n = 34$
X	2-Me	−0.691	−0.872
	3-Cl	0.643	0.412
	3-Me	−0.359	−0.484
	3-F	0.773	0.477
	3-Br	0.352	0.040
	4-Cl	−0.735	−0.884
	4-F	−0.532	−0.608
	4-Me	−0.941	−1.010
	4-OMe	−1.292	−0.973
	4-NMe_2	−2.555	−2.589
	4-SMe	−1.922	−1.988
	5-F	1.016	0.914
R	NH_2	−0.494	−0.551

R, having a negative contribution, is also undesirable now. It is important to note that any substitutions at 5-X and –Me at R that were undesirable for having improved COX-2 inhibition activity have now become important for the raising of the selectivity ratio. Thus, substitutions such as 3,5-F_2 or 3-Cl, 5-F (for X in aromatic ring) and –Me at R may lead to the highest theoretical value (= 4.77) of log *S*.

In conclusion, the two analyses in the present study provide the ground for rationalizing the substituent selection in designing more potent compounds of the series.

Acknowledgement

The financial assistance provided by the UGC, Central Regional Office, Bhopal, through the sanction of a minor research grant to P.S. is thankfully acknowledged.

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