RESEARCH PAPER

Accepted 27 July 2002
Revised 5 July 2002
Received 5 November 2001
Indian J. Pharm. Sci., 2002, 64(5): 465-471

QSAR Analysis of Heteroaryl Derivatives of 1,2-Diarylimidazole with Cyclooxygenase-2 Inhibitory Activity

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The human cyclooxygenase-2 inhibition activity for two series of compounds, namely the substituted 1,2-diarylimidazoles and the heteroaryl modified 1,2-diarylimidazoles is quantitatively analysed in relation to their physicochemical parameters and van der Waals volume, V_w. Significant correlations are obtained between the cyclooxygenase-2 inhibition activity and hydrophobic constant, π, molar refraction parameter and some indicator variables reflecting important structural binary variations in the first series of compounds. In the second series of compounds, however, the structural parameter V_w, along with indicator variables is found to play a significant role. Based on present findings, the strategy of substituent selection and possible modes of action of both series of compounds are discussed.

The chronic inflammatory conditions of arthritic patients may be checked[1] by nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin. Such drugs possess antiinflammatory, analgesic and antipyretic activities but are not always completely devoid of life-threatening side effects such as gastrointestinal haemorrhage, ulceration[1,2] and decreased renal function in some cases[3,4]. In view of such problems, efforts are being made to develop new NSAIDs that have improved antiinflammatory activity without the toxic side effects.

The important step in prostaglandin and thromboxane biosynthesis involves the conversion of arachidonic acid to prostaglandin H_2 (PGH_2). This reaction is catalyzed by the sequential action of the cyclooxygenase (COX) and peroxidase activities of prostaglandin endoperoxide synthase (PGHS) or COX. It was suggested[5-7] that COX activity originates from two distinct and independently regulated enzymes, namely COX-1 and COX-2. COX-1 is the constitutive isoform and is mainly responsible for the synthesis of cytoprotective prostaglandins in the gastrointestinal tract (GI) and of the proaggregatory thromboxane in blood platelets[2]. COX-2 is inducible and short-lived and its expression is stimulated in response to endotoxin, cytokines and mitogens[8-10]. This form also plays an important role in prostaglandin biosynthesis in inflammatory cells (monocytes/macrophases) and in the central nervous system[11-14]. These findings, therefore, suggest that COX-1 and COX-2 provide different physiological and pathophysiological functions. Classical NSAIDs inhibit both COX-1 and COX-2 to varying extents[15]. The differential tissue distribution of COX-1 and COX-2 provides a rationale for the development of selective COX-2 inhibitors as antiinflammatory and analgesic agents that lack the GI and haematologic liabilities exhibited by currently available NSAIDs. This hypothesis has been validated in animal models and has led to the marketing of new drugs as COX-2 inhibitors[16-22].

Of all NSAIDs, indomethacin, zomepirac, aspirin and flurbiprofen are the only examples of compounds that have been successfully elaborated into selective COX-2 inhibitors. More recently, celecoxib[23] and refecoxib[24] became the first COX-2 inhibitors to enter the market. However, the methodology utilized in NSAID modification is not general and consists of extensive modification of individual compounds. In view of this, Khanna *et al.*[25] have disclosed the synthesis and activity of heteroaryl derivatives of 1,2-diarylimidazoles (fig. 1 and 2) as selective COX-2 inhibitors.

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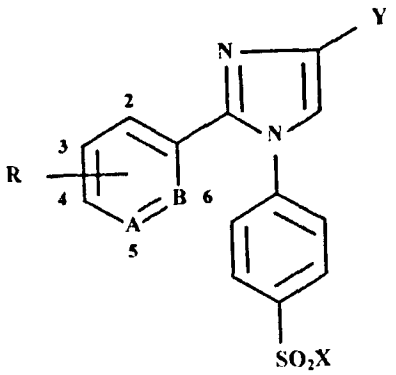

Fig. 1: Substituted 1,2-diarylimidazoles.

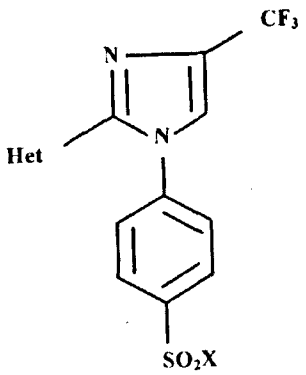

Fig. 2: Heteroaryl modified 1,2-diarylimidazoles.

The reported structure-activity relationship (SAR) was, however, directed only to alteration of the substituents at various positions in the structure and no rationale was provided to reduce the trial and error factors. Hence, a quantitative SAR (QSAR) on these drugs was conducted since QSAR not only provides the rationale for drug design but also illuminates the mechanism of action of drugs.

MATERIALS AND METHODS

First and foremost among the QSAR methods is the model, proposed by Hansch and co-workers[26-31]. It was the seminal contribution of this group to propose that the molar concentration (or dose) that elicits a constant biological response of a drug molecule is a linear function of its physicochemical parameters governing various types of interactions. Among others, three major physicochemical factors, namely, hydrophobic, steric and electronic, are recognized to play a pivotal role in drug-receptor interaction. Thus during such interaction either one, two or all three of these factors may be operative. To obtain the best QSAR, multiple regression analysis[32 33] (MRA) is used and the resulting correlations are assessed through a number of statistics obtained in conjunction with such calculations. The most important of these are the standard error of the estimate, s, the correlation coefficient, r (or the multiple correlation coefficient, R), and the F-ratio, which is a statistic for assessing the overall significance of the derived equation and the confidence intervals (usually 95%) for the individual regression coefficients in the derived equation.

The values of appropriate physicochemical parameters are taken directly from the compilation of Hansch and Leo[26]. Additionally, some indicator variables were also used to describe the effect of specific binary alterations. Further, the van der Waals volume, V_w a structural parameter accounting for the bulk of a molecule/substituent also emerged the most appropriate quantifying parameter for heteroaryl modified 1,2-diarylimidazoles. Its method of calculation has been described in one of our earlier publications[34] and is based on the original suggestion of Bondi[35]. For calculating V_w, according to Bondi, atoms are assumed to be spherical in shape. Necessary corrections are incorporated for the overlap of atomic orbitals and for the branching in hydrocarbon chain. The values of V_w are routinely reported as 10^2 Å^3 in QSAR works.

The activity data IC_{50} represents the concentration of a compound to accomplish 50% inhibition of the human COX-2. The same are further expressed as $-\log IC_{50}$ on molar basis. For the compounds under study, the biological effects along with explaining variables of the substituents are included in Tables 1 and 2. The best fit between $-\log IC_{50}$ and these explaining variables (or predictors) was found through MRA employing the method of least squares.

RESULTS AND DISCUSSION

MRA of the data for compounds in Table 1 yielded regression Eq. (1) for the COX-2 inhibition activity *versus* their different physicochemical parameters and indicator variables

$$-\log IC_{50} = 0.895(\pm0.26)\Sigma\pi + 1.029(\pm0.73)MR(R_4) - 0.476(\pm0.32)I_{A\text{-}B} - 0.738(\pm0.42)IR_2 + 0.583(\pm0.30)I_x + 4.693$$

$$n = 27,\ r = 0.899,\ s = 0.430,\ F(5, 21) = 17.752 \qquad (1)$$

the ± data within parentheses are the 90% confidence limits. The variable $\Sigma\pi$ represents the sum of hydrophobic contributions of Y and R_3 (R at 3-position) substituents. The molar refraction, accounting for steric/polar interaction of R_4 is indicated by $MR(R_4)$ parameter. For the present work, the values of this parameter are scaled to 0.1. Three additional predictors, $I_{A\text{-}B}$, IR_2 and I_x are the indicator variables,

TABLE 1: PREDICTOR VARIABLES AND CYCLOOXYGENASE-2 INHIBITION ACTIONS OF SUBSTITUTED 1,2-DIARYLIMIDAZOLES.

Sr. No.	A-B	R	X	Y	$\Sigma\pi$	MR[a](R_4)	I_{A-B}	IR_2	I_x	-logIC_{50}(M)	
										Obsd[b]	Calcd[c]
1	N-C	H	CH_3	CF_3	0.88	0.103	1	0	0	5.68	5.07
2	N-C	6-CH_3	CH_3	CF_3	0.88	0.103	1	0	0	5.02	5.07
3	N-C	4-CH_3	CH_3	CF_3	0.88	0.565	1	0	0	5.74	5.56
4	N-C	3-CH_3	CH_3	CF_3	1.44	0.103	1	0	0	5.74	5.68
5	N-C	2-CH_3	CH_3	CF_3	0.88	0.103	1	1	0	4.27	4.35
6	N-C	4-OCH_3	CH_3	CF_3	0.88	0.787	1	0	0	5.92	5.80
7	N-C	3-OCH_3	CH_3	CF_3	0.86	0.103	1	0	0	4.42	5.05
8	N-C	3-Br	CH_3	CF_3	1.74	0.103	1	0	0	6.02	6.00
9	N-C	H	NH_2	CF_3	0.88	0.103	1	0	1	6.21	5.62
10	N-C	6-CH_3	NH_2	CF_3	0.88	0103	1	0	1	5.55	5.62
11	N-C	4-CH_3	NH_2	CF_3	0.88	0.565	1	0	1	6.54	6.11
12	N-C	3-CH_3	NH_2	CF_3	1.44	0.103	1	0	1	6.29	6.22
13	N-C	2-CH_3	NH_2	CF_3	0.88	0.103	1	1	1	4.29	4.89
14	N-C	3-Br	NH_2	CF_3	1.74	0.103	1	0	1	6.47	6.54
15	C-N	5-CH_3	CH_3	CF_3	0.88	0.103	0	0	0	5.54	5.64
16	C-N	4-CH_3	CH_3	CF_3	0.88	0.565	0	0	0	5.89	6.13
17	C-N	3-CH_3	CH_3	CF_3	1.44	0.103	0	0	0	6.28	6.24
18	C-N	2-CH_3	CH_3	CF_3	0.88	0.103	0	1	0	5.24	4.91
19	C-N	5-CH_3	NH_2	CF_3	0.88	0.103	0	0	1	6.26	6.12
20	C-N	4-CH_3	NH_2	CF_3	0.88	0.565	0	0	1	6.14	6.65
21	C-N	3-CH_3	NH_2	CF_3	1.44	0.103	0	0	1	6.36	6.73
22	C-N	2-CH_3	NH_2	CF_3	0.88	0.103	0	1	1	5.81	5.44
23	C-N	2-CH_3	NH_2	CN	-0.57	0.103	1	0	0	4.61[d]	3.47
24	N-C	H	CH_3	CH_3	0.56	0.103	1	0	0	4.10	4.69
25	N-C	H	CH_3	CH_2OH	-1.03	0.103	1	0	0	3.03	2.97
26	N-C	H	CH_3	CHF_2	0.74[e]	0.103	1	0	0	4.68	4.89
27	N-C	H	NH_2	CHF_2	0.74[e]	0.103	1	0	1	5.74	5.49

[a]Values are scaled to 0.1; [b]the IC_{50} values are taken from ref. 25; [c]calculated using Eq. (2); [d]the 'outlier' compound of present study; [e]calculated as $\pi(CHF_2)=\pi(CF_3)-\pi(F)+\pi(H)$.

TABLE 2: PREDICTOR VARIABLES AND CYCLOOXYGENASE-2 INHIBITION ACTIONS OF HETEROARYL MODIFIED 1,2-DIARYLIMIDAZOLES.

Het	X	V_w (x 10^2 Å^3)	I_x	$I_{s(2)}$	-logIC_{50}(M)	
					Obsd[a]	Calcd[b]
3-Pyridyl	CH_3	0.919	0	0	5.77	5.41
3-Isoquinolyl	CH_3	1.057	0	0	5.92	6.05
1-Isoquinolyl	CH_3	1.057	0	0	5.77	6.05
3-Quinolyl	CH_3	1.057	0	0	6.20	6.05
N-Methyl-3-indolyl	CH_3	1.345	0	0	5.96[c]	7.37
5-Benzodioxyl	CH_3	1.153	0	0	6.55	6.49
4-Benzodioxyl	CH_3	1.153	0	0	6.33	6.49
3-Thienyl	CH_3	0.699	0	0	4.29	4.40
2-Thienyl	CH_3	0.699	0	1	6.33	6.43
2-Thienyl	NH_2	0.699	1	1	7.16	7.27
4-Bromo-2-thienyl	CH_3	0.905	0	1	7.59	7.38
3-Methyl-2-thienyl	CH_3	0.853	0	1	5.96[c]	7.14
2-Methyl-4-thiazolyl	CH_3	0987	0	0	6.03	5.72
2-Methyl-4-thiazolyl	NH_2	0.987	1	0	6.28	6.56
2-Methyl-5-thiazolyl	NH_2	0.987	1	0	6.37	6.56
4-Methyl-2-thiazolyl	NH_2	0.987	1	0	6.96	6.56
2-Methyl-4-oxazolyl	CH_2	0.984	0	0	5.38	5.71
5-Methyl-3-isoxazolyl	NH_2	0.906	1	0	6.39	6.19

[a]The IC_{50} values are taken from ref. 25; [b]calculated using Eq. (5); [c]the 'outlier' compound of present study.

accounting for binary variations of A-B incision, R_2 and X positions respectively. A value of 1 or 0 for $I_{A\text{-}B}$, in that order, shows the presence of N-C and C-N moiety in the aryl ring. The presence or absence of a CH_3 substituent at R_2 is assigned respectively, a value of 1 or 0 to the variable IR_2. Likewise, a CH_3 or NH_2 substitution at X is accounted for by the variable I_x, having the assigned value of 0 and 1 for them. The F-value obtained in Eq. (1) is significant at 99% level [$F_{5,21}(0.01) = 4.04$] and r^2-value takes care of 81% of the variance in the observed activity values. Though these statistical parameters hint at a high level of significance of above equation but the calculated activity value using it for compound 23 (Table 1) is largely deviating from the observed one. This is the lone compound containing a highly reactive CN substitution at Y that may get hydrolysed prior to interaction at the active site and exhibit unusual biological response. This compound is, therefore, eliminated to derive the follow up correlation Eq. (2)

$$-\log IC_{50} = 1.082(\pm0.27)\Sigma\pi + 1.148(\pm0.66)MR(R_4) - 0.484(\pm0.29)I_{A\text{-}B} - 0.679(\pm0.38)IR_2 + 0.599(\pm0.27)I_x + 4.453$$

$$n = 26,\ r = 0.921,\ s = 0.385,\ F(5, 20) = 22.285 \qquad (2)$$

The statistical parameters of above equation are significantly improved. The s-value is lowered, the r-value and F-value, still significant at 99% level [$F_{5,20}(0.01) = 4.10$] are increased and 85% of the variance in observed activity values is now accounted for by r^2. In addition, the variables used in obtaining Eq. (2) are mutually orthogonal. The same is shown by inter-correlation matrix included in Table 3. This equation was further subjected to a validation study[36] by the

leave-one-out method (LOO). The method creates a number of modified data sets by taking away one compound from the parent data set in such a way that each observation is taken away once and once only. Then one model is developed for each reduced data set and the response values of the deleted observations are predicted from the model. The squared differences between predicted and actual values are added to give the predictive residual sum of squares, PRESS. From the ratio of PRESS to the sum of squares of the response values (SSY), the index q^2 was calculated. The value equals 0.957, obtained for this index, indicated an excellent model. The highly significant correlation Eq. (2) was, therefore, used to calculate the $-\log IC_{50}$ values for entire data set. These calculated activity values, except for compound 23, are in close agreement with the observed ones (Table 1). It also follows from Eq. (2) that the highly hydrophobic substituents at Y and R_2 combined, highly polar/bulky substituents at R_4 and NH_2 substituent at X are essential to improve the activity of a compound. In addition, the C-N moiety at incision A-B and unsubstitution at R_2, possibly due to steric reasons are also essential to raise the activity. These guidelines may, therefore, be used in the design of some more active compounds of this series.

Listed data in Table 2 were subjected to MRA and the derived correlation between $-\log IC_{50}$ values and the quantifying parameters, V_w and I_x is as in Eq. (3)

$$-\log IC_{50} = 0.620(\pm1.77)V_w + 0.672(\pm0.64)I_x + 5.392$$

$$n = 18,\ r = 0.431,\ s = 0.680,\ F(2,15) = 1.710 \qquad (3)$$

In this equation, V_w is the van der Waals volume of heterocyclic part only (*i.e.*, Het substitution; fig. 2) and I_x is the indicator variable, discussed earlier. It takes care of a CH_3 or NH_2 substituent at X. Obviously, the activity is poorly correlated with both of these parameters and the equation as such requires further improvement in the statistical parlance. This was achieved by considering one additional indicator variable $I_{s(2)}$ that accounts for a sulfur atom insertion present alone in the heterocyclic ring at position 2. Thus compounds having 2-thienyl ring (*e.g.*, compounds S. No. 9-12; Table 2) were assigned a value I for $I_{s(2)}$ and 0 otherwise. The resulting correlation in aforesaid independent variables is shown in Eq. (4)

$$-\log IC_{50} = 2.939(\pm1.48)V_w + 0.894(\pm0.44)I_x + 1.453(\pm0.57)I_{s(2)} + 2.762$$

$$n = 18,\ r = 0.817,\ s = 0.450,\ F(3,14) = 9.382 \qquad (4)$$

The statistical parameters of this equation are certainly improved over that of Eq. (3). The equation also hinted at the sensitivity of inserted sulfur atom at position 2 in a five membered ring. Further, two congeners (S. No. 5 and 12) of this series exhibited off-the-trend behavior and were thus ignored in deriving the subsequent correlation Eq. (5)

$$-\log IC_{50} = 4.610(\pm1.12)V_w + 0.841(\pm0.27)I_x + 2.030(\pm0.40)I_{s(2)} + 1.174$$

$$n = 16,\ r = 0.947,\ s = 0.268,\ F(3,12) = 34.918 \qquad (5)$$

to which the F-value obtained is significant at 99% level [$F_{3,12}(0.01) = 5.95$] and r^2 value accounted for nearly 90% of the variance in the observed activity values. The LOO method, in addition, resulted into a cross-validated q^2 = 0.934. Obviously, the model predicts better than chance and can be considered statistically significant. Also, the predictor variables of this equation were shown to have mutual orthogonal relationships. This highly significant correlation equation was, therefore, used to calculate the activity values of all the compounds. Except for the "outlier" compounds, the calculated and the observed activity values have now reached parity (Table 2). To have more potent compound, Eq. (5) as such favors a bulky heterocyclic ring having a higher value of V_w in addition to an NH_2 substituent at X. Additionally, a sulfur atom insertion at position 2 is also essential in this ring system. Thus, sulfonamide analogue containing a 2-benzo[b]thienyl substituent ($V_w = 1.122 \times 10^2$ Å^3) as the heterocyclic moiety, not synthesized yet, may have theoretical activity value nearly 1.6 order of magnitude higher than the highest active compound of the present series. The reason for "outlier" behavior of compound 12 is not immediately apparent. Compound 5, however, is the only compound in the series that contains a methyl substituent, directly attached to the ring nitrogen. This may raise the electron den-

TABLE 3: THE INTERCORRELATION MATRIX AMONG THE PREDICTOR VARIABLES OF EQ. (2)[a].

	$\Sigma\pi$	MR (R_4)	I_{A-B}	IR_2	I_x
$\Sigma\pi$	1.000	0.003	0.013	0.002	0.037
MR(R_4)		1.000	0.003	0.042	0.003
I_{A-B}			1.000	0.032	0.011
IR_2				1.000	0.004
I_x					1.000

[a]The matrix elements are the r^2-values, that satisfy the orthogonality conditions among the predictor variables.

sity through inductive effect at the nitrogen atom in the ring and thus the compound seems to elicit a different behavior from other congeners.

In conclusion, the present QSAR study on two congeneric series provides the ground for rationalizing the substituent selection in designing more potent inhibitors of the human COX-2.

ACKNOWLEDGEMENTS

Authors are grateful to the Department of Chemistry and the Institution for providing necessary facilities for this work.

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