A Quantitative Structure-Activity Relationship Study of Novel Inhibitors of Cyclooxygenase-2: The 5-Aryl-2,2-dialkyl-4-phenyl-3(2*H*)furanone Derivatives

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The cyclooxygenase-2 enzyme inhibition activity of 5-aryl-2,2-dialkyl-4-phenyl-3(2*H*)furanone derivatives is quantitatively analyzed through Fujita-Ban and Hansch type of approaches. The analyses have helped to ascertain the role of different substituents in explaining the observed inhibitory activity of these congeners. From both approaches it is revealed that more hydrophobic susbtituents at 4-R_1, a non-hydrogen bond acceptor substitutent, preferably a -F substituent, at 3-R_1 in 4-phenyl ring of 3(2*H*)furanone scaffold improve inhibitory action of a compound. The substituents exhibiting collective molecular bulk smaller than spirocyclopentyl at *X* and *Y* positions are preferred as these geminal positions seems to be involved in steric interation. Similarly, 4-aminosulfonyl in 5-aryl ring of 3(2*H*)furanone moiety emerged as a better choice than 4-methylsulfonyl substitution.

Non-steroidal antiinflammatory drugs (NSAIDs), have been used to alleviate symptoms of arthritis, arthritis-associated disorders, fever, post-operated pain, migraine etc[1]. Despite their widespread uses and desirable therapeutic benefits, the long term usage of such drugs, however, led to disruption of beneficial prostaglandin-regulated processes[2,3]. The toxic effects causing induction of gastrointestinal mucosal lesions, perforations, bleeding and decreased renal function[4] have, therefore, restricted their therapeutic usefulness.

Earlier, it was believed that cyclooxygenase (COX) was a single enzyme present constitutively in various tissues including the gastrointestinal (GI) tract, the kidneys, and the platelets and its inhibition would lead to both beneficial and detrimental effects[5]. 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 prostaglandins (PGs) present in gastrointestinal tract and kidney[6-8]. It is realized that it is the inhibition of COX-1 that causes the various side effects seen with NSAIDs. Such findings coupled with the discovery of COX-2 suggested that selective inhibitors of COX-2 might constitute a novel approach to the treatment of inflammation with minimal or no side effects[9,10].

There are already several COX-2 inhibitors being used for chronic indications, and they mostly maintain a tricyclic structure as in rofecoxib[11], celecoxib[12], valdecoxib[13], and etoricoxib[14,15]. As more clinical data accumulate, it may become possible to differentiate profiles of COX-2 inhibitors based on efficacy and safety. There have been some, but not conclusive, attempts to differentiate profiles of COX-2 inhibitors[16,17].

More recently, the structure-activity relationship (SAR) and pharmacological properties of 4,5-diaryl-3(2*H*) furanone derivatives as a novel class of highly potent selective COX-2 inhibitors have been reported[18]. These analogues having 3(2*H*) furanone moiety are structurally similar to celecoxib and rofecoxib. Such a study was, however, aimed only at the alteration of substituents at different positions of 3(2*H*) furanone moiety on qualitative basis and provided no rationale to reduce the trial-and-error factors. Hence, a quantitative SAR (QSAR) study on these analogues was performed, so, as to provide the rationale for drug-design and to explore the possible mechanism of their action on molecular level.

MATERIALS AND METHODS

The reported compounds[18], depicted by Fig. 1 and listed in Table 1, were subjected to Fujita-Ban and Hansch

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type of analyses. The biological inhibitory effects towards the human COX-2 enzyme and appropriate physicochemical parameters are also listed in Table 1. The activity data, evaluated as IC_{50}, represent the concentration of a compound to accomplish 50% inhibition of the human COX-2 enzyme. The same are given as -logIC_{50} on molar basis. The most suitable descriptors were found to be the hydrophobic constant, π, and the hydrogen-bond acceptor parameter, *HA* that were taken directly from the compilation of Hansch *et al.*[19] Besides these parameters, some binary variables were also used to account for the effects due to specific variations in the parent structure.

The Fujita-Ban approach[20] is based on an additivity principle, in which biological activity, BA is given as, $BA = \sum a_j X_j + \mu$ - (1), where X_j is the jth substituent with a value of 1 if present and 0 if not at some specific position. The numerals a_j and μ are respectively the contribution of the jth substituent (generally the hyrdrogen) to BA and theoretical biological activity of the (unsubstituted) reference compound of the series. The linear equations generated from Eqn. 1 were solved by the method of least squares for the values of unknown's a_j and μ. For

TABLE 1: QSAR PARAMETERS AND CYCLOOXYGENASE-2 INHIBITION ACTIVITY OF 5-ARYL-2,2-DIALKYL-4-SUBSTITUTED PHENYL-3(*2H*)FURANONE DERIVATIVES

S.No	*X*	*Y*	*Z*	R_1	R_2	π_{3+4}	HA_3	*IXY*	*IZ*	IR_1	-logIC_{50}[a] (M)				
											Obsd[b]	Cald Eq (2)	Cald F. B.	Prcd LOO	Prcd EVM
1	Me	Me	Me	H	H	0.00	0	0	0	0	7.30	7.20	7.29	7.20	7.17
2	Me	Me	Me	3-F	H	0.14	0	0	0	1	7.70	7.58	7.74	7.57	7.59
3	Me	Me	Me	3-Cl	H	0.71	0	0	0	0	8.00	7.42	7.64	7.39	7.38
4	Me	Me	Me	3-Cl,4-F	H	0.85	0	0	0	0	7.52	7.47	7.49	7.46	7.42
5	Me	Me	Me	3,5-F_2	H	0.14	0	0	0	1	7.30	7.58	7.53	7.62	7.59
6	Me	Me	Me	3,5-Cl_2	H	0.71	0	0	0	0	7.52	7.42	7.66	7.42	7.45
7	Me	Me	Me	3-CF_3	H	0.88	0	0	0	0	7.30	7.47	7.41	7.49	7.49
8	Me	Me	Me	4-i-Pr	H	1.53	0	0	0	0	7.52	7.67	7.45	7.71	7.65
9	Me	Me	Me	4-COMe	H	-0.55	0	0	0	0	6.52	7.04	6.91	7.17	7.15
10	Me	Me	Me	3-OMe	H	-0.02	1	0	0	0	7.00	6.76	6.89	6.52	6.52
11	Me	Et	Me	H	H	0.00	0	0	0	0	6.70	7.20	7.03	7.25	7.25
12	Me	Et	Me	3-Cl	H	0.71	0	0	0	0	7.52	7.42	7.38	7.42	7.44
13	Me	Et	Me	3,5-Cl_2	H	0.71	0	0	0	0	7.52	7.42	7.39	7.42	7.44
14	Me	Et	Me	3-CF_3	H	0.88	0	0	0	0	7.30	7.47	7.14	7.49	7.49
15	Me	Et	Me	3-OMe	H	-0.02	1	0	0	0	6.52	6.76	6.63	7.00	7.00
16	Et	Et	Me	H	H	0.00	0	1	0	0	5.30	5.81	5.52	6.00	5.92
17	Et	Et	Me	3-Me	H	0.56	0	1	0	0	6.30	5.99	6.08	5.88	6.08
18	Me	Me	NH_2	H	H	0.00	0	0	1	0	8.10	7.82	7.89	7.78	7.78
19	Me	Me	NH_2	3-F	H	0.14	0	0	1	1	8.52	8.20	8.33	8.15	8.13
20	Me	Me	NH_2	3-Cl	H	0.71	0	0	1	0	7.85	8.04	8.24	8.07	7.99
21	Me	Me	NH_2	3,4-F_2	H	0.28	0	0	1	1	8.18	8.24	8.18	8.25	8.28
22	Me	Me	NH_2	3-CF_3	H	0.88	0	0	1	0	7.96	8.09	8.01	8.12	8.12
23	Me	Me	NH_2	4-COMe	H	-0.55	0	0	1	0	7.89	7.65	7.50	7.58	7.56
24	Me	Me	Me	H	2-F	0.00	0	0	0	0	7.52	7.20	7.33	7.17	7.14
25	Me	Me	Me	3-F	2-F	0.14	0	0	0	1	7.52	7.58	7.78	7.59	7.59
26	Me	Me	Me	3-Cl	2-F	0.71	0	0	0	0	7.70	7.42	7.68	7.41	7.40
27	Me	Me	Me	3,5-F_2	2-F	0.14	0	0	0	1	7.52	7.58	7.57	7.59	7.59
28	Me	Me	Me	H	3-F	0.00	0	0	0	0	7.52	7.20	7.10	7.17	7.17
29	Me	Me	Me	3-F	3-F	0.14	0	0	0	1	7.52	7.58	7.55	7.59	7.58
30	Me	Me	Me	3-Cl	3-F	0.71	0	0	0	0	7.30	7.42	7.46	7.43	7.40
31	Me	Me	Me	3,5-F_2	3-F	0.14	0	0	0	1	7.52	7.58	7.35	7.59	7.50
32	Me	Me	NH_2	H	2-F	0.00	0	0	1	0	7.52	7.82	7.93	7.86	7.87
33	Me	Me	NH_2	3-F	2-F	0.14	0	0	1	1	8.52	8.20	8.37	8.15	8.13
34	Me	Me	NH_2	3,5-F_2	2-F	0.14	0	0	1	1	8.52	8.20	8.17	8.15	8.13
35	Me	Me	NH_2	H	3-F	0.00	0	0	1	0	7.52	7.82	7.70	7.86	7.87
36	Me	Me	NH_2	3-F	3-F	0.14	0	0	1	1	7.52[c]	-	-	-	-
37	Me	Me	NH_2	3,5-F_2	3-F	0.14	0	0	1	1	7.70	8.20	7.94	8.27	8.28
38	c-Pentyl			H	H	0.00	0	0	0	0	7.52	7.20	7.21	7.17	7.15
39	c-Pentyl			3-Me	H	0.56	0	0	0	0	7.52	7.38	7.77	7.37	7.36
40	c-Pentyl			4-i-Pr	H	1.53	0	0	0	0	7.30	7.67	7.37	7.77	7.74
41	c-Hexyl			H	H	0.00	0	1	0	0	5.70	5.81	5.72	5.86	5.69
42	c-Hexyl			3-Me	H	0.56	0	1	0	0	6.30	5.99	6.28	5.88	5.91

[a]IC_{50} represents the minimum concentration of a compound, required to bring about 50% inhibition of COX-2 enzyme; [b]Taken from Ref. (18); [c]The 'outlier' compound of present study.

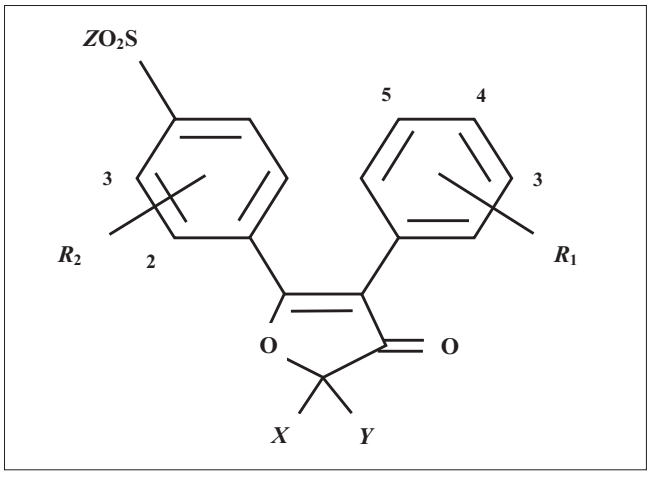

Fig. 1: 5-Aryl-2,2-Dialkyl-4-phenyl-3(2*H*)furanone Derivatives

present communication both the Fujita-Ban and the Hansch type of approaches were used to derive the QSAR results. The required software for these analyses were developed in our laboratory and are being extensively used in the QSAR studies as a part of our research programme pertaining to drug-design.

RESULTS AND DISCUSSION

Initially all compounds of Table 1 were used in the construction of the Fujita-Ban matrix with compound 1 as the reference congener. As per the requirement of this approach, all these compounds have similar substitutional variations at a given position, at least in two or more congeners. Tabulation of this matrix of 42 linear equations in 18 unknowns including the contribution of parent compound is avoided here for the sake of brevity. These equations were solved for the unknowns a_j and μ, employing multiple regression analysis (MRA). The contributions of various substituents obtained thereby are summarized in the third column of Table 2 and the statistical parameters of the study obtained are: n= 42, r^2= 0.880, s= 0.310, F (18,23)= 9.366, where n, r^2, s and F represent, respectively the number of data points, multiple correlation coefficient squared, standard error of estimate and F-ratio between the variances of calculated and observed activities. The±data mentioned within parentheses (Table 2) represent 90% confidence intervals of unknown variables. Obviously, these statistical parameters reflect the significance of derived results for a data set of 42 compounds. However, a close examination at the calculated activity values of these compounds has revealed that compound 36 is not following the trend similar to the other members of the series as its deviation from the observed activity value is comparatively much higher. This compound seems to have an error in the experimental determination of its activity and thus it was ignored in the follow up study. In doing so, the corresponding row was removed from the Fujita-Ban

TABLE 2: SUBSTITUENTS CONTRIBUTIONS TO CYCLOOXYGENASE-2 INHIBITORY ACTIVITIES OF 5-ARYL-2,2-DIALKYL-4-SUBSTITUTED PHENYL-3(*2H*)FURANONE DERIVATIVES

Position	Substitution	Substituent contribution	
		n = 42	n = 41
X,Y	Et, Et	-1.809 (±0.49)	-1.768 (±0.48)
	Me, Et	-0.286 (±0.30)	-0.265 (±0.29)
	c-Hexyl	-1.610 (±0.49)	-1.569 (±0.48)
	c-Pentyl	-0.114 (±0.42)	-0.081 (±0.41)
Z	NH_2	0.554 (±0.21)	0.597 (±0.21)
3-R_1	CF_3	0.097 (±0.39)	0.120 (±0.37)
	Cl	0.330 (±0.31)	0.354 (±0.29)
	F	0.357 (±0.29)	0.445 (±0.29)
	Me	0.552 (±0.42)	0.558 (±0.40)
	OMe	-0.429 (±0.45)	-0.396 (±0.44)
4-R_1	COMe	-0.406 (±0.45)	-0.384 (±0.43)
	F	-0.115 (±0.43)	-0.149 (±0.42)
	i-Pr	0.135 (±0.45)	0.163 (±0.43)
5-R_1	Cl	0.002 (±0.46)	0.011 (±0.44)
	F	-0.105 (±0.32)	-0.201 (±0.32)
2-R_2	F	0.041 (±0.28)	0.041 (±0.27)
3-R_2	F	-0.276 (±0.28)	-0.188 (±0.28)
Parent contribution	μ	7.334(±0.26)	7.290(±0.25)

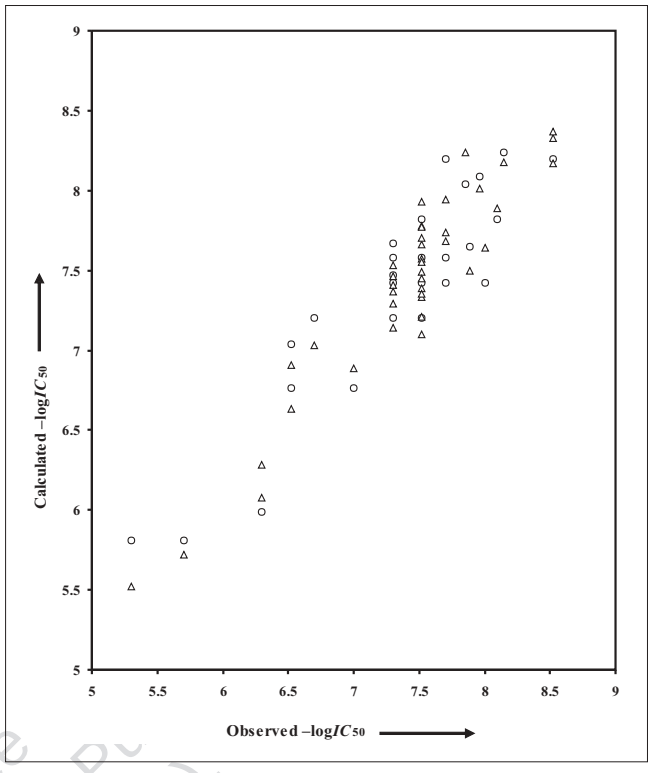

Fig. 2: Plot of Observed versus Calculated –logIC50 Values. The Calculated Activity Values are Obtained using Eqn. 2 (O) and Fujita-Ban (Δ)

matrix and the MRA of resulting matrix leads to the results listed in the last column of Table 2. The improved statistical parameters, accounting for better significance of the results are: n= 41, r^2= 0.894, s= 0.297, F (18,22)= 10.407. The r^2-value now accounts for 89% of the variance and the F-value obtained is significant at 99% level [$F_{18,22}$ (0.01)= 2.89]. The calculated values of logIC_{50}, listed in Table 1, are now in close agreement with the observed ones. The substituents, to be incorporated at different positions of the parent moiety, that make higher positive contributions to -logIC_{50} may be used to design more active compounds of the series in future.

It is important to mention that the non-parametric approach such as Fujita-Ban or Free-Wilson cannot extrapolate beyond the substituents used in the training set whereas the parametric Hansch type of approach, followed next for the same training set can do so. For this purpose, a number of physicochemical descriptors in conjunction with binary variables were employed to obtain the final correlation equation. Initially, the physicochemical descriptors such as hydrophobic, π, hydrogen bond donor/acceptor, *HD/HA*, molar refraction, *MR*, electronic, σ, field, *F*, resonance, *R*, Taft's steric, E_S were chosen for the substituents of each of the varying positions. Besides these, the structural descriptors namely the van der Waals volume, V_W and simple and valence connectivity of the first-order, $^1\chi$, $^1\chi^v$ were also used for this purpose. In this way a large number of correlation equations were derived, using necessary computer programs, RGANLS, developed in our QSAR laboratory. Once the appropriate parameters were found then their combinations for different positions were also attempted to reduce the number of independent descriptors to account for meaningful correlations. The descriptors accounting for significance of results in statistical sense were then retained for exploration of further QSAR through the MRA. The stepwise development of such QSAR equations [(i)-(v)] are documented in Table 3 and the last equation included therein is reproduced as Eqn. 2, -logIC_{50}= 0.307 (±0.19) π_{3+4} -0.437 (±0.39)HA_3 - 1.390 (±0.28)*IXY* + 0.615 (±0.19)*IZ* + 0.334 (±0.20)IR_1 + 7.204, n= 41, r^2= 0.828, s = 0.301, F (5,35)= 33.747, q^2 = 0.745 -(2) for further discussion. Here, the hydrophobic constants for the substituents of 3- and 4- (*meta*- and *para*-) positions in 4-phenyl ring of 3 (2H)furanone scaffold were added to give π_{3+4} descriptor while the hydrogen bond acceptor, HA_3 parameter for 3-substituents in the same ring appeared to be an important descriptor. The binary variable, *IXY*, is accounting for collective molecular bulk of *XY*-substituents bigger than spirocyclopentyl moiety. Thus a value equal to 1 was arbitrarily taken for Et, Et and spirocyclohexyl moiety and 0 for other substituents. It is to be noted that the spirocyclopentyl moiety occupies a smaller space than the diethyl substitutions. Consideration of such a descriptor has steeply increased the significance of QSAR [Eqn. 3, Table 3]. The second binary variable, *IZ* accounted for the presence of -NH_2 substituent at *Z*. Thus a value equal to 1 or 0 for *IZ*, in that order, identifies the presence of 4-aminosulfonyl or 4-methylsulfonyl substitution in 5-aryl ring of 3 (2H) furanone moiety. This variable also added significantly to increase the *R*-value [Eqn. 4]. The third indicator variable, IR_1, selected for 3-F substituent of R_1. A value 1 or 0 for this descriptor accounted, respectively, for presence or absence of 3-F substituent in 4-phenyl ring of 3(2H)furanone. Inclusion of IR_1 has further improved the significance of QSAR Eqn. 2 [or Eqn. 5, Table 3]. The r^2-value accounts for 83% of variance in observed activity values and F-value remained significant at 99% level [$F_{5,35}$(0.01)= 3.56]. The calculated activity values, using Eqn. 2 and listed in Table 1, are in close agreement with the observed ones. The plot of observed versus calculated -logIC_{50}s using Eqn. 2 and the Fujita-Ban study is also given in fig. 2 to demonstrate the goodness of fit and to show systematic variations of observed versus calculated activities in the present congeneric series. That the variables used in Eqn. 2 have no mutual correlation is shown in Table 4.

All derived QSAR equations were further subjected to a validation test[21] by leave-one-out (LOO) procedure. This method creates a number of modified data sets by taking away one compound from the parent data set in such a

TABLE 3: STEPWISE DEVELOPMENT OF REGRESSION EQN. 2; –logIC_{50} = $A_1\pi_{3+4}$ + a_2HA_3 + a_3IXY + a_4IZ + a_5IR_1 + b

a_1	a_2	a_3	a_4	a_5	b	r	s	F^a	q^2	Eqn.
0.170 (±0.40)					7.348	0.115	0.682	0.525	-0.072	(i)
0.117 (±0.40)	-0.633 (±0.84)				7.397	0.231	0.677	1.072	-0.052	(ii)
0.056 (±0.26)	-0.831 (±0.54)	-1.709 (±0.39)			7.594	0.788	0.434	20.222	0.525	(iii)
0.225 (±0.20)	-0.559 (±0.42)	-1.487 (±0.30)	0.661 (±0.21)		7.325	0.887	0.330	33.300	0.702	(iv)
0.307 (±0.19)	-0.437 (±0.39)	-1.390 (±0.28)	0.615 (±0.19)	0.334 (±0.20)	7.204	0.910	0.301	33.747	0.745	(v)

[a]The $F^a_{k,\ n-k-1}$-statistics obtained for n (=41) data points and k (= 1,2,3,4,5) independent variable(s).

TABLE 4: THE INTER-CORRELATION MATRIX[a] AMONGST THE PREDICTOR VARIABLES OF EQN. 2

	π_{3+4}	HA_3	IXY	IZ	IR_1
π_{3+4}	1.000	0.031	0.002	0.048	0.059
HA_3		1.000	0.005	0.019	0.019
IXY			1.000	0.040	0.040
IZ				1.000	0.065
IR_1					1.000

[a]The matrix elements are the r^2-values.

way that each observation is taken away once and once only. Then one model is developed for each reduced data set and the activity value of the deleted observation is predicted from the model. The squared difference between predicted and observed activity values are added to give the predictive residual sum of squares (PRESS). The cross-validation index, q^2 was calculated from the ratio of PRESS to the sum of squares of the observed values (SSY). To be a reasonable QSAR model, q^2 should be greater than 0.6, while a value ³ 0.9 represents an excellent model. Eqn. 2 was further subjected to bootstrap analysis by making use of the external validation method (EVM). In this approach, a few compounds were considered in the test set and were left out to derive a correlation equation on remainders. The equation was then used to predict the activities of compounds in the test set. In this way, several equations were obtained and are listed in Table 5 corresponding to left out compounds of test set. The predicted activities for these compounds are given in Table 1 for the sake of comparison. These activities were found in close agreement with the observed ones.

From Eqn. 2, it appears that the hydrophobic nature of 3-R_1 and 4-R_1 substituents in 4-phenyl ring of 3(2*H*)furanone scaffold is one of the important quantifying parameter governing the COX-2 inhibition activity. The substituents of these two positions having relatively higher π-values are leading improved value of inhibition activity. Additionally, a-F substitution in 3-position in this ring is also a valid option to improve COX-2 activity (positive regression coefficient of IR_1 in Eqn. 2). However, hydrogen bond acceptor substituent at 3-R_1 contributed negatively (negative coefficient of HA_3 in Eqn. 2) to activity and is, therefore, least preferred. Alternatively, it may be stated that a non-hydrogen bond acceptor substituent such as a -F at 3-R_1 and a more hydrophobic substituent at 4-R_1 are the preferred substitutions of 4-phenyl ring attached to 3(2*H*)furanone moiety. The roles of remaining structural variations in parent structure are also evident from the regression coefficient associated with binary variable. The negative coefficient of *IXY*, demands for the substituents exhibiting collective molecular bulk smaller than spirocyclopentyl at *X* and *Y* positions. Similarly, the positive coefficient of *IZ* reflects that 4-aminosulfonyl is a better substitution than 4-methylsulfonyl in 5-aryl ring of 3(2*H*)furanone moiety. Such guidelines may, further be used to synthesize more effective inhibitors of COX-2. Following above strategy with reference to QSAR Eqn. 2, a few new compounds listed in Table 6, may be designed which have activity values higher than the calculated activity values of compounds reported in the original data set.

From both the approaches, a few conclusions are now evinced. The more hydrophobic substituent at 4-positions, a non-hydrogen bond acceptor substituent such as a -F at 3-position of 4-phenyl ring of 3(2*H*)furanone moiety improve the inhibitory action of a compound. The Fujita-

TABLE 5: QSAR MODEL EQUATIONS USING BOOTSTRAP ANALYSIS

Compounds in test set	Derived correlation equations from remaining compounds	*n*	r^2	*s*	F^a
1,2,3,4,5	$-\log IC_{50}$ = 0.291(±0.20)π_{3+4} -0.405 (±0.39) HA_3 -.353 (±0.29)*IXY* +0.631(±0.20)*IZ* +0.377(±0.21)IR_1 +7.171	36	0.850	0.300	33.894
6,7,8,9,10	$-\log IC_{50}$ = 0.239 (±0.23)π_{3+4} -0.758 (±0.53) HA_3 -.450 (±0.29) *IXY* +0.570 (±0.20) *IZ* + 0.285 (± 0.20) IR_1 +7.283	36	0.846	0.298	33.127
11,12,13,14,15	$-\log IC_{50}$ = 0.273 (±0.20)π_{3+4} -0.245(±0.54) HA_3 -.427(±0.29) *IXY* +0.588 (±0.20) *IZ* + 0.304 (±0.20) IR_1 + 7.250	36	0.839	0.301	31.492
16,17,18,19,20	$-\log IC_{50}$ = 0.289 (±0.19)π_{3+4} -0.451 (± 0.38) HA_3 -.298(±0.37) *IXY* +0.563 (±0.21) *IZ* + 0.310 (±0.20) IR_1 +7.217	36	0.766	0.291	19.550
21,22,23,24,25	$-\log IC_{50}$ = 0.390 (±0.22)π_{3+4} -0.369 (±0.41) HA_3 -.346 (±0.30) *IXY* +0.635 (±0.23) *IZ* +0.395 (±0.23) IR_1 +7.137	36	0.830	0.312	29.141
26,27,28,29,30	$-\log IC_{50}$ = 0.324 (±0.20)π_{3+4} -0.402 (±0.41) HA_3 -.359(±0.30) *IXY* +0.631(±0.21) *IZ* +0.370 (±0.22) IR_1 +7.168	36	0.839	0.314	31.122
31,32,33,34,35	$-\log IC_{50}$ = 0.266 (±0.19)π_{3+4} -0.484(±0.39) HA_3 -.424(±0.28) *IXY* +0.621(±0.23) *IZ* +0.217 (±0.22) IR_1 +7.250	36	0.828	0.300	28.859
37,38,39,40,41,42	$-\log IC_{50}$ = 0.390 (±0.21) π_{3+4} -0.377(±0.38) HA_3 -.454 (±0.37) *IXY* +0.682 (±0.20) *IZ* +0.401 (±0.20)IR_1 +7.145	35	0.824	0.291	27.333

[a]The $F^a_{k,\ n-k-1}$-statistics obtained for *n* (=41) data points and *k* (= 1,2,3,4,5) independent variable(s).

TABLE 6: PREDICTED ACTIVITIES OF THE COMPOUNDS WHICH ARE NOT REPORTED IN ORIGINAL DATA SET

S. No.	X	Y	Z	R_1	R_2	-logIC_{50}[a] (M)
1	Me	Me	NH_2	3-F,4-Cl	H	8.37
2	Me	Me	NH_2	3-F,4-Br	H	8.41
3	Me	Me	NH_2	3-F,4-I	H	5.50
4	Me	Me	NH_2	3-F,4-i-Pr	H	8.62
5	Me	Me	NH_2	3-F,4-CF_2CF_3	H	8.65
6	Me	Me	NH_2	3-F,4-t-Bu	H	8.76
7	Me	Me	NH_2	3-F,4-n-Bu	H	8.81

[a]Predicted -logIC_{50} values using Equation (2).

Ban study, in conformity with this assigned higher substitutional contributions to such substituents. But, if the substituent at 3-position also possesses a hydrogen-bond acceptor property in addition then it may cause a detrimental effect. The hydrogen-bond acceptor property, adding negatively, counter-balances the incremental effect to activity produced by the hydrophobic effect. The substituents smaller than Et, Et and spirocyclohexyl moiety at *XY*-positions (both together) are preferred substitutions in raising the activity value. The Fujita-Ban study, in agreement with this inference has assigned less negative contribution to such a substituent. The substituent -NH_2 at *Z* having a positive substituent contribution relative to Me, enhanced the activity of a compound. The same is also reflected by the positive regression coefficient associated with the indicator variable *IZ* in the Eqn. 2. 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.

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