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Modeling of cyclooxygenase-2 and 5-lipooxygenase inhibitory activity of apoptosis-inducing agents potentially useful in prostate cancer chemotherapy: Derivatives of diarylpyrazole

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Abstract

The structure-activity models of the twenty derivatives for COX-2 and ten derivatives of 1,5-diarylpyrazole for 5-LOX inhibitory activity have been investigated using Combinatorial Protocol in Multiple Linear Regression (CP-MLR) with topological descriptors which were calculated from DRAGON software. Among the descriptor classes considered collectively in the study the COX-2 inhibitory activity was, however, correlated with topological (TOPO) and Galvez topological charge indices (GVZ). Modified Burden eigenvalues (BCUT) and 2D autocorrelations (2DAUTO) classes of descriptors have shown correlation to 5-LOX inhibitory activity. The developed models and participating descriptors in them have suggested that the substitutional modification in the diarylpyrazole moiety may have sufficient scope in optimization of prevailing inhibitory activities of these analogues.

Keywords: *QSAR, dragon descriptors, CP-MLR approach, 1,5-diarylpyrazole derivatives*

Introduction

The arachidonic acid metabolizing enzymes, which lead to the formation of various eicosanoids, are involved in a variety of human diseases, such as inflammation, fever, arthritis and cancer [1–4]. Cyclooxygenase-2 (COX-2) and lipooxygenases (LOXs), the arachidonic acid metabolizing enzymes, have been found to be implicated in a variety of cancers (such as colon, pancreas, breast, lung, skin, urinary bladder, or liver cancers), including prostate cancer [5]. The prostate cancer is usually fatal once the tumor cells invade the outer area of the gland because of the unavailability of the systemic therapies. COX-2 is involved in both, *in vitro* proliferation and *in vivo* tumor growth rate [6–9]. The potential use of COX inhibitors in the prevention and therapy of prostate cancer invasion [10] is due to the role played by COX-2 in disturbing the balance between matrix metalloproteinases (MMPs) and the tissue inhibitor of metalloproteinases (TIMPs) in prostate cancer cells. LOXs and their metabolic products also play different roles in carcinogenesis and chemoprevention [11]. One group of LOXs (which include 5-, 8- and 12-LOX) are procarcinogenic [11,12] whereas, 15-LOX metabolites have the opposite effect on the growth of prostatic adenocarcinoma cells [13]. 15-Hydroxyeicosatetraenoic acid (15-HETE), which is produced by 15-LOX-2, activates peroxisome proliferator-activated receptor γ (PPARγ) and inhibits proliferation [14]. On the other hand, (13*S*)-hydroxyoctadecadienoic acid (13*S*-HODE), which is a 15-LOX-1 metabolite, up-regulates the MAP kinase signaling pathway and then down-regulate PPARγ and increase tumorigenesis of the human prostate cancer cell line [15].

The COX-2/LOXs inhibitors, currently used in the treatment of pain and inflammation, have been tested *in vitro* and *in vivo* on cell growth and non-necrotic cell

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death [16–19]. It is evinced that COX-2 inhibition, may, have no role in nonsteroidal anti-inflammatory drugs (NSAID)-mediated apoptotic cell death [18,20]. The apoptosis-inducing effects and anti-angiogenic activity of celecoxib may be partly ascribed to a COX-2 independent pathway [19,21] and thus the structural requirement for the induction of apoptosis in prostate cells seems different from those for COX-2 inhibition. Thus, in a new strategy to develop therapeutic treatments of prostate cancer, the drift of arachidonic acid metabolism toward the other pathway should be prevented to minimize side effects and specific cells possessing a high flux of arachidonic acid and its metabolites should be killed [22]. A new series of such dual COX-2/5-LOX inhibitors, the diarylpyrazole derivatives have recently been synthesized and evaluated for enzymatic potency by Pommery et al. [23]. However, the structure activity relationship (SAR) study on these congeners were mainly directed to only alteration of the substituents at different positions of the core structure and no justification was provided to reduce the trial-and-error factors. Hence, in the present communication, a 2D-quantitative SAR (2D-QSAR) study on these analogues has been conducted to provide the rationale for drug-design and to explore the possible mechanism of their action at molecular level. Several of the recent 3D-QSAR studies on similar type of inhibitors have been reported [24–29], using the molecular field analysis (MFA), the receptor surface analysis (RSA), the comparative molecular field analysis (CoMFA), and the comparative molecular similarity indices analysis (CoMSIA). These studies could reveal the importance of steric, electrostatic, hydrophobic and H-bond acceptor fields. Additionally the 3D-contour maps, obtained through these fields, were proposed to be used in the design of more potent COX-2/5-LOX inhibitors. Both the 2D- and 3D-QSAR studies are equally important if the developed statistical models under them have high predictive power for the new potential congeners. The emerged models from such studies may assist to identify the type of interactions involved between a drug molecule and the receptor sites. The possible mechanism of action of the compounds anticipated by one study may, therefore, be corroborated through the other one. However, a 2D-QSAR study is quite simple to interpret the biological data in terms of different descriptors obtained from the two dimensional structures of the compounds without involving energy minimization procedures. In a congeneric series, where a relative study is being carried out, the 2D- descriptors may play important role in deriving the significant correlations with biological activities of the compounds. Thus the novelty and importance of a 2D-QSAR study is mainly due to its simplicity for the calculations of different descriptors and their interpretation (in physical sense) to explain the inhibition actions of compounds in a congeneric series.

Material and methods

Data set

In the present study twenty analogues with COX-2 and ten analogues with 5-LOX inhibitory activities, respectively, have been considered from the literature report [23], in the form of logarithm of the inverse of inhibitory concentration (pIC_{50}, where IC_{50} is the concentration in moles per liter required to bring out 50% enzyme inhibiton). The compounds along with their biological effects are listed in Table I. DRAGON software [30] has been used for the parameterization of the compounds in this study as it offers several hundreds of descriptors for different perspectives corresponding to empirical, constitutional and topological indices characteristic to the molecules and their structural fragments under multi-descriptor class environment. The structures of all these congeners have been drawn in ChemDraw [31] and ported to DRAGON software for computing the parameters corresponding to 0D, 1D, and 2D-descriptors classes. The descriptor classes considered in the study along with their definitions and scope in addressing the structural features have been presented in Table II. As the total number of descriptors involved in this study is very large, only the names of descriptors classes and the actual descriptor involved in the models have been listed.

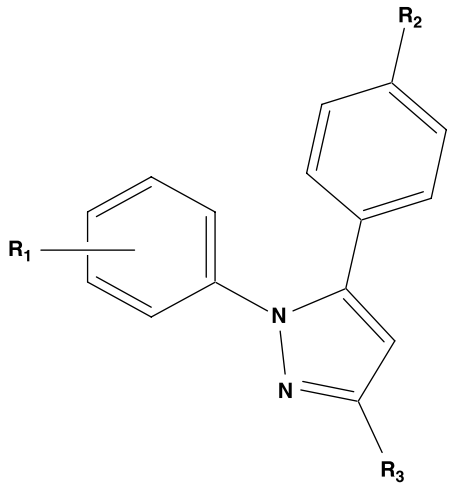
Computational procedure

The structures of the compounds under study have been drawn in 2D ChemDraw using the standard procedure. All these structures of respective compounds have been ported to DRAGON software for the computation of descriptors for the compounds in Table I. This software offers several hundreds of descriptors from different perspectives corresponding to 0D-, 1D-, and 2D-descriptor classes relating to empirical, constitutional and topological indices characteristic to the molecules under multi-descriptor class environment. The combinatorial protocol in multiple linear regression (CP-MLR) computational procedure has been used for present work in developing QSAR models. The brief description of this procedure is given below.

Model development

The CP-MLR is a 'filter' based variable selection procedure for model development in QSAR studies [32–35]. The procedure employs a combinatorial strategy with MLR to result in selected subset regressions for the extraction of diverse structure-activity models, each having unique combination of descriptors from the generated data set of the

Table I. Structures and observed and modeled COX-2 and 5-LOX inhibitory activity of diarylpyrazole derivatives.



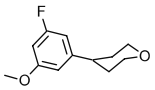
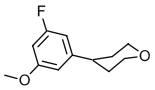
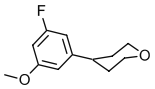
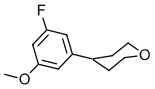
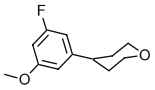
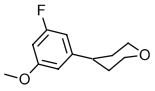
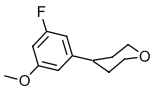
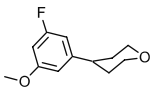
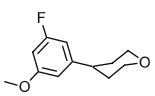
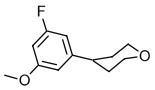
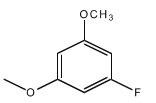
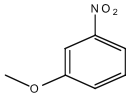
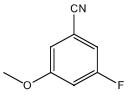
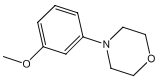
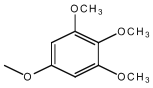
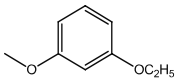
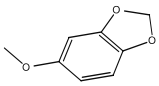
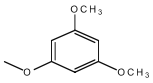
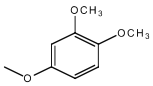
				pIC_{50}(M)					
				COX-2			5-LOX		
S. No.	R_1	R_2	R_3	Obsd.*	Calcd. Equation (3)	Pred. LOO	Obsd.*	Calcd. Equation (4)	Pred. LOO
1	4-CH_3SO_2	H		7.35	7.19	7.11	6.52	6.52	6.56
2	H	H		6.21	5.98	5.94	6.24	6.21	6.20
3	4-F	H		6.02	6.11	6.12	6.32	6.20	6.16
4	4-Cl	H		6.03	6.11	6.12	6.08	6.16	6.18
5	4-CH_3	H		6.03	6.11	6.12	6.14	6.12	6.12
6	4-CH_3O	H		6.52	6.30	6.28	6.11	6.07	6.06
7	3-CF_3O	H		6.09	6.36	6.40	6.07	6.12	6.12
8	4-NH_2SO_2	H		7.00	7.19	7.27	6.13	6.20	6.22
9	4,5-diCH_3	H		6.39	6.23	6.19	6.12	6.10	6.07
10	4,5-diCl	H		6.15	6.23	6.25	6.10	6.12	6.12
11	4-CH_3SO_2	H		6.51	6.57	6.59	–*	–	–

Table I – *continued*

				pIC_{50}(M)					
				COX-2			5-LOX		
S. No.	R_1	R_2	R_3	Obsd.*	Calcd. Equation (3)	Pred. LOO	Obsd.*	Calcd. Equation (4)	Pred. LOO
12	4-CH_3SO_2	H		6.13	6.22	6.23	–*	–	–
13	4-CH_3SO_2	H		6.24	6.41	6.48	–*	–	–
14	4-CH_3SO_2	H		6.04	6.08	6.08	–*	–	–
15	4-CH_3SO_2	H		6.66	6.54	6.50	–*	–	–
16	4-CH_3SO_2	H		6.05	5.91	5.87	–*	–	–
17	4-CH_3SO_2	H		6.35	6.21	6.19	–*	–	–
18	4-CH_3SO_2	H		6.06	6.09	6.09	–*	–	–
19	4-CH_3SO_2	H		6.15	6.28	6.30	–*	–	–
20†	4-NH_2SO_2	CH_3	CF_3	7.44	7.32	7.14	–*	–	–

* Taken from reference [23]; † Celecoxib.

compounds under study. The 'filters' set in CP-MLR are intended at (i) having inter-parameter correlation to a predefined cutoff value (filter-1; default acceptable value ≤ 0.3, (ii) optimize the variable entry to a model through t-value of regression coefficients (filter-2; default acceptable value ≥ 2.0, (iii) comparability of models (regression equations) with different number of descriptor in terms of square root of adjusted multiple correlation coefficient (filter-3; r-bar, default acceptable value ≥ 0.71), and (iv) addressing the external consistency of the model with leave-one-out (LOO) cross-validation as default option (filter-4; cross-validated Q^2 criteria, default acceptable limits are $0.3 \leq Q^2 \leq 1.0$). All these filters make the variable selection process efficient and lead to unique solution.

Further, to find out any chance correlations associated with the models recognized in CP-MLR, each cross-validated model has been subjected to randomization test [36,37] by scrambling of the biological responses. The datasets with scrambled response vector have been reassessed by multiple regression analysis. The resulting regression equations, if any, with correlation coefficients better than or equal to the one corresponding to unscramble response data were counted. Every model has been subjected to 100 such simulation runs. This has been used as a measure to express the percent chance correlation of the model under scrutiny. The CP-MLR protocol has been applied with default filter thresholds to identify all the possible models that could emerge from the descriptors of compounds.

For a given set of compounds, the highest significant model was further subjected to external validation test. For this purpose, nearly 25 percent of the total compounds were removed to include in the test set and remaining in the training set. Thus for each model, three test sets were considered to validate it externally. Of the three test sets, two were generated in the SYSTAT [38] using the single linkage hierarchical cluster procedure involving the Euclidean distances of the respective descriptors or the activity as the case may be. The selection of the test set from the cluster tree was done in such a way to keep the test compounds at a maximum possible distance from

Table II. Descriptor classes used and identified categories for the analysis of COX-2 inhibitory activity of diarylpyrazole derivatives.

Descriptor class (acronyms)*	Definition and scope	Descriptors' category†
Constitutional (CONST)	Dimensionless or 0D descriptors; independent from molecular connectivity and conformations	III
Topological (TOPO)	2D-descriptor from molecular graphs andindependent conformations	I
Molecular walk counts (MWC)	2D-descriptors representing self-returning walks counts of different lengths	IV
Modified Burden eigenvalues (BCUT)	2D-descriptors representing positive and negative eigenvalues of the adjacency matrix, weights the diagonal elements and atoms	II
Galvez topological charge indices (GVZ)	2D-descriptors representing the first 10 eigenvalues of corrected adjacency matrix	II
2D-autocorrelations (2DAUTO)	Molecular descriptors calculated from the molecular graphs by summing the products of atom weights of the terminal atoms of all the paths of the considered path length (the *lag*)	III
Functional groups (FUN)	Molecular descriptors based on the counting of the chemical functional groups	IV
Atom centered fragments (ACF)	Molecular descriptors based on the counting of 120 atom centered fragments, as defined by Ghose-Crippen	IV
Empirical (EMP)	1D-descriptors represent the counts of nonsingle bonds, hydrophilic groups and ratio of the number of aromatic bonds and total bonds in an H-depleted molecule	III
Properties (PROP)	1D-descriptors representing molecular properties of a molecule	IV

* Reference [30]; † Descriptor categories identified at the end of second stage; in this the filter values are as follows: filter-1 as 0.3, filter-2 as 2.0, filter-3 as 0.71, and filter-4 as $0.3 \leq Q^2 \leq 1.0$, the number of compounds in each dataset is 20.

each other. The third test set of the compounds corresponds to the random selection procedure. With this, these test sets represent different cross-sections of compounds. The predictions of the test sets have been done with the models developed using remaining compounds in the training sets. The residuals of the predictions and the corresponding statistical parameters of each test set have also been derived.

For each model, derived in n data points, a number of statistical parameters were obtained to access its overall statistical significance. These are the multiple correlation coefficient, r, the standard deviation, s, the F-value representing the ratio of the variances of calculated to observed activities and the cross-validated Q^2, obtained by LOO method, addressing the external consistency (or the robustness) of the model. Additional statistical parameters such as, the Akaike's information criterion, AIC [39,40], the Kubinyi function, FIT [41,42] and the Friedman's lack of fit, LOF [43], have also been calculated to further validate the derived models. The AIC takes into account the statistical goodness of fit and the number of parameters that have to be estimated to achieve that degree of fit. The FIT, closely related to the F-value, proved to be a useful parameter for assessing the quality of the models. A model which is derived in k independent descriptors, its F-value will be more sensitive if k is small while it becomes less sensitive if k is large. The FIT, on the other hand, will be less sensitive if k is small whereas it becomes more sensitive if k is large. The model that produces the lowest AIC value and highest FIT value is considered potentially the most useful and the best. The LOF factor takes into account the number of terms used in the equation and is not biased, as are other indicators, toward large number of parameters.

Results and discussion

Initially, the COX-2 inhibitory activity of 20 diarypyrazole derivatives was investigated with a variety of 0D-, 1D- and 2D-descriptors obtained from DRAGON software. The calculated DRAGON descriptors for the diarylpyrazole derivatives listed in Table I, were subjected to CP-MLR for category analysis, considering the default value of 0.71 for filter-3. The identified categories are included in Table II. Only the TOPO class has emerged in the primary category while BCUT and GVZ in the secondary category. The CONST, 2DAUTO and EMP classes contributed at the tertiary stage whereas all other classes (MWC, FUN, ACF and PROP) remained noncontributory. A total number of 12 models, in one and two descriptors belonging to primary contributing (TOPO) class have emerged. The highest significant model derived in such descriptors is shown through Equation (1)

$$\begin{aligned} pIC_{50}(COX-2) &= 0.004(\pm 0.002)T(O..O) \\ &\quad + 0.044(\pm 0.010)T(S..F) \\ &\quad + 5.984(\pm 0.172) \\ n = 20, r = 0.861, s &= 0.233, \\ F = 24.312, Q^2_{LOO} &= 0.620, \\ FIT = 3.998, LOF &= 0.019, AIC = 0.034 \end{aligned} \quad (1)$$

The ± data within parenthesis represents the 90% confidence intervals associated with regression coefficient. The participated descriptors have accounted for

74 per cent ($r^2 = 0.741$) of variance in observed activity values. From above Equation, it is apparent that sum of topological distances between oxygen-oxygen [descriptor T(O..O)] and sulphur-fluorine [descriptor T(S..F)] contribute positively to COX-2 inhibitory activity of the diarylpyrazole derivatives and higher values of these topological distances, are beneficiary to activity.

In search of higher statistical significant models, the equations in three descriptors were further derived. For this purpose, the identified relevant descriptors were categorized under two different pools. Firstly, the 223 descriptors from TOPO class, which emerged from the category analysis as primary contributors, were subjected to CP-MLR. The resulting best model, in three descriptors, from this pool is shown in Equation (2)

$$\begin{aligned} pIC_{50}(COX-2) &= 0.319(\pm 0.173)VEA1 \\ &\quad + 0.005(\pm 0.002)T(O..O) \\ &\quad + 0.049(\pm 0.009)T(S..F) \\ &\quad + 4.369(\pm 0.883) \\ n = 20, r &= 0.918, s = 0.187, \\ F = 28.700, Q^2_{LOO} &= 0.625, \\ FIT = 2.969, LOF &= 0.057, AIC = 0.052 \end{aligned} \quad (2)$$

The parameters s, LOF and AIC of Equation (2), compared to Equation (1), have been lowered and the F, FIT and r parameters have been increased to account for the superiority of Equation (2). From Equation (2), it appeared that the sum of topological distances between O..O and S..F along with the other TOPO class descriptor VEA1 (Eigenvector coefficient sum from adjacency matrix) are positive contributors to activity. A higher value of these descriptors would enhance the activity.

To explore models superior to the model in Equation (2), a second pool of descriptors was formulated from all the 6 contributing classes considered collectively. This pool now comprising of 425 descriptors, was able to generate 53 models through the CP-MLR analysis. In these models, the number of participated descriptors was 36. However, the highest significant model that was emerged is shown in Equation (3)

$$\begin{aligned} pIC_{50}(COX-2) &= 0.005(\pm 0.002)T(O..O) \\ &\quad + 0.047(\pm 0.009)T(S..F) \\ &\quad + 0.282(\pm 0.112)GGI2 \\ &\quad + 4.960(\pm 0.424) \\ n = 20, r &= 0.939, s = 0.162, \\ F = 40.099, Q^2_{LOO} &= 0.802, \\ FIT = 4.148, LOF &= 0.043, AIC = 0.039 \end{aligned} \quad (3)$$

All the statistical parameters of Equation (3) have improved over to that of Equation (2). This in turn, reflected upon the superiority of newly derived model. The descriptors are now able to account for 88 percent of variance in observed COX-2 inhibitory activity values. The s-value is lowered and F-value remained significant at 99 percent level. Additionally, the value of FIT function has increased whereas the LOF and AIC have decreased and the higher value obtained for Q^2 index hints towards a robust QSAR model. Further, the independent variables emerged in these models showed poor inter-correlation among themselves (Table III). The calculated pIC_{50} values using Equation (3) and predicted from LOO approach are in close agreement with the observed ones (Table I). The plot of observed versus calculated and predicted pIC_{50} values is given in Figure 1 to demonstrate the goodness of fit and to show systematic variations between them in the present congeneric series. From Equation (3), it has appeared that the topological distances between oxygen-oxygen and sulphur-fluorine plays a pivotal role in optimization of COX-2 inhibitory activity. The newly appeared descriptor GGI2, which belong to GVZ class of descriptors, is topological charge index of order 2. A higher value of this index along with higher values of topological distances between O and O and S and F is helpful to augment the activity.

Equation (3) was further validated through three test sets, each containing 5 compounds out of the 20 compounds listed in Table I. These test sets, which were based on the descriptor, activity and random selection procedure, represent different cross-sections of all the compounds in present series. The remaining 15 data points in each of the three training sets were then used to derive new models. These models were

Table III. Cross-correlation matrix* amongst identified descriptors of the models.

Equation (2)				Equation (3)				Equation (4)		
	VEA1	T(O..O)	T(S..F)		T(O..O)	T(S..F)	GGI2		BELe7	MATS2v
VEA1	1.000	0.225	0.248	T(O..O)	1.000	0.136	0.261	BELe7	1.000	0.153
T(O..O)		1.000	0.136	T(S..F)		1.000	0.130	MATS2V		1.000
T(S..F)			1.000	GGI2			1.000			

* Matrix elements are the r-values.

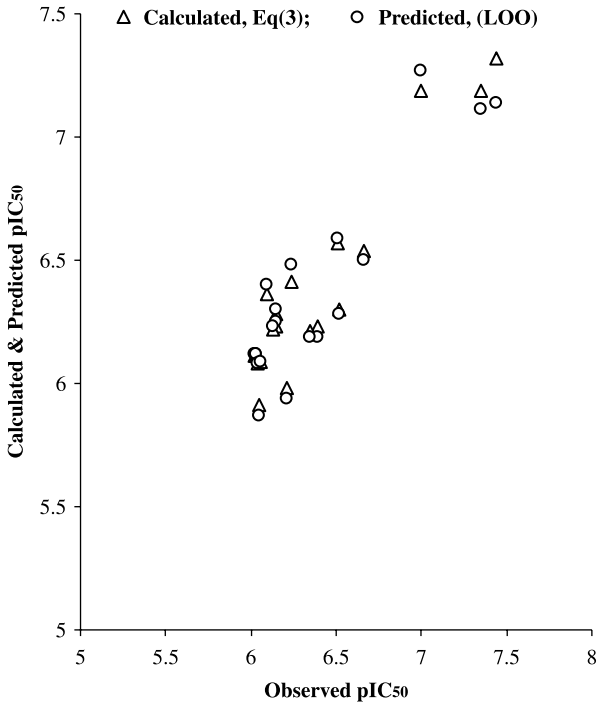


Figure 1. Plot of observed versus calculated [Equation (3)] and predicted (LOO) pIC_{50}(COX-2) values.

next used to predict activities of compounds in corresponding test sets. The calculated activities of the test and training compounds along with corresponding predictive r^2, s, Q^2 and F-values have been given in Table IV. The predictions for compounds corresponding to three test sets are within the reasonable limits of their actual values.

Further, the 5-LOX inhibition activity of title compounds, listed in Table I, was also analyzed quantitatively in terms of DRAGON descriptors. For this purpose all the descriptor classes were considered collectively. A total number of 419 such descriptors were subjected to CP-MLR. In this process the value of filter-3 was set at 0.71 and two models were generated in one and two descriptors and the highest significant model is shown through Equation (4)

$$\begin{aligned} pIC_{50}(5-LOX) &= 4.327(\pm 1.783)BELe7 \\ &\quad - 2.091(\pm 1.538)MATS2v \\ &\quad + 1.647(\pm 1.916) \\ n = 10, r = 0.906, s &= 0.068, \\ F = 16.076, Q^2_{LOO} &= 0.693, \\ FIT = 2.297, LOF &= 0.009, AIC = 0.009 \end{aligned} \quad (4)$$

Table IV. Observed and calculated inhibitory activities of compounds with training and test sets statistics.

S. No.	COX-2 Inhibition				5-LOX inhibition			
	Obsd.*	Calcd.†	Calcd.‡	Calcd.¶	Obsd.*	Calcd.†	Calcd.‡	Calcd.¶
1	7.35	7.11§	7.17§	7.11§	6.52	6.52	6.52	6.52
2	6.21	5.92§	5.99§	6.00	6.24	6.20§	6.20§	6.20§
3	6.02	6.01	6.12	6.10	6.32	6.20	6.19	6.19
4	6.03	6.01	6.12§	6.10	6.08	6.16	6.16	6.15
5	6.03	6.01	6.12	6.10§	6.14	6.13	6.12	6.12§
6	6.52	6.21§	6.31	6.28	6.11	6.09	6.08	6.07
7	6.09	6.26	6.38§	6.33	6.07	6.12§	6.12	6.11
8	7.00	7.11	7.17	7.11	6.13	6.20	6.20	6.19
9	6.39	6.11§	6.25	6.20§	6.12	6.11	6.10	6.10
10	6.15	6.11	6.25	6.20	6.10	6.12	6.12§	6.11
11	6.51	6.59	6.55§	6.58	–	–	–	–
12	6.13	6.20	6.22	6.24	–	–	–	–
13	6.24	6.42	6.39	6.44	–	–	–	–
14	6.04	6.06	6.08	6.10§	–	–	–	–
15	6.66	6.49	6.54	6.52	–	–	–	–
16	6.05	5.92	5.90	5.96	–	–	–	–
17	6.35	6.19	6.21	6.22	–	–	–	–
18	6.06	6.10§	6.08	6.13	–	–	–	–
19	6.15	6.25	6.29	6.29§	–	–	–	–
20	7.44	7.27	7.28	7.26	–	–	–	–
Training set r^2		0.919	0.893	0.862		0.824	0.819	0.826
s		0.134	0.151	0.171		0.076	0.078	0.078
F		41.582	30.698	22.810		11.725	11.343	11.858
LOF		0.036	0.047	0.060		0.014	0.015	0.015
FIT		5.198	3.837	2.851		1.954	1.890	1.976
AIC		0.031	0.040	0.051		0.013	0.013	0.013
Q^2_{LOO}		0.756	0.680	0.668		0.527	0.589	0.592
Test set r^2		0.726	0.859	0.902		–‖	–‖	–‖
s		0.123	0.368	0.151		–‖	–‖	–‖
F		21.807	2.556	17.671		–‖	–‖	–‖

* Taken from Ref. [23]; † Test set from the cluster analysis of all descriptors used in deriving Equation (3) for COX-2 and Equation (4) for 5-LOX; ‡ Test set from the cluster analysis of the respective activity of the compounds; ¶ Test set from random selection of the compounds. The training models have 15 and 8 compounds each for COX-2 and 5-LOX respectively; § Calculated activities of test set compounds; ‖ Values cannot be determined as the number of data-points in test set were two only.

The participated descriptors, in above Equation, hold scope to explain the 82 per cent variance in observed activity values. The BCUT class descriptor, BELe7, is lowest eigenvalue n.7 of Burden Marix/weighted by atomic Sanderson electronegativities. The positive regression coefficient of this descriptor suggested that the higher value of it would be beneficiary to activity. MATS2v, a descriptor from 2DAUTO class, is the atomic van der Waals volumes weighted Moran autocorrelation of *lag* 2. A more negative or less positive value of it would be helpful to augment the 5-LOX inhibitory activity. The calculated pIC_{50} values, using Equation (4) and predicted from LOO procedure are in close agreement with the observed ones (Table I, Figure 2). That the predictor variables have poor cross-correlation is shown in Table III. Above Equation was further validated through three test sets based on strategy discussed earlier. Two compounds out of ten active ones, listed in Table I, were considered in each test set. The activity predictions for the compounds corresponding to three test sets are within the reasonable limits of their actual values (Table IV).

In conclusion the present study has provided structure-activity relationship of the COX-2 and 5-LOX inhibitory activity of diarylpyrazole derivatives in terms of structural requirements. The inhibitory activity has, therefore become the function of the cumulative effect of different structural features which were identified in terms of individual descriptors. In order to improve the COX-2 inhibitory activity of a compound, the descriptors, T(O..O) and T(S..F) have advocated, respectively, the longer topological distances between oxygen-oxygen and sulphur-fluorine atoms while the descriptor GGI2 emphasized the requirement of topological charge of order 2. For the 5-LOX inhibitory activity of titled compounds, the derived model suggested the role of electronic content (BELe7) and van der Waals volumes (MATS2v) in optimization of the activity. The derived models and participating descriptors in them have evinced that the substituents of diarylpyrazole moiety have sufficient scope for further modification. Thus, our study may provide a ground for modeling of diarylpyrazoles as the dual COX-2/5-LOX inhibitors.

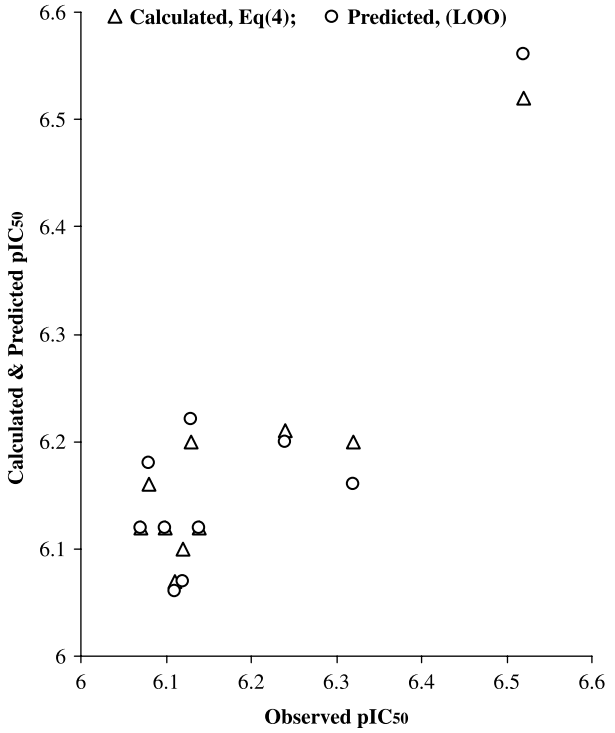


Figure 2. Plot of observed versus calculated [Equation (4)] and predicted (LOO) pIC_{50}(5-LOX) values.

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