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2D QSAR STUDY OF INDOLE DERIVATIVES AS SELECTIVE COX-2 INHIBITORS

R. S. Chavan [*1], H. N. More [2] and A. V. Bhosale [1]

Department of Pharmaceutical Chemistry [1], Pune District Education Association's Seth Govind Raghunath Sable College of Pharmacy, Saswad, Pune - 412301, Maharashtra, India.
Bharati Vidyapeeth's College of Pharmacy [2], Kolhapur - 400614, Maharashtra, India.

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Correspondence to Author:
Dr. Mrs. Rajashree S. Chavan

Associate Professor, Department of Pharmaceutical Chemistry, PDEA's Seth Govind Raghunath Sable College of Pharmacy, Saswad, Pune - 412301, Maharashtra, India.

E-mail: rajchavan18@yahoo.co.in

ABSTRACT: The NSAIDs are popular in reducing acute and chronic inflammation as they have no abuse liability. QSAR (Quantitative structure-activity relationship) approach is a very useful and widespread technique for drug design. 2D QSAR models are based on descriptors derived from a two-dimensional graph representation of a molecule. The 2D QSAR study was performed on selected twenty-four compounds from synthesized indole derivatives for elucidating the structural requirements for COX-2 inhibition using multiple linear regression method. Statistically, significant models were generated using VLife Molecular Design Suite 3.5 software. The physicochemical parameters contributed significantly to biological activity. Amongst all the models generated, model 3 was found to be best with high r^2 (squared correlation coefficient) of 0.9382. Model is robust as q^2 (cross-validated squared correlation coefficient) value is also high as 0.8557 with good predictive power as indicated by pred_r^2 = 0.7443. The model showed two alignment independent (AI) descriptors T_2_O_0 and T_2_N_7 as well as two physicochemical descriptors –ve Potential Surface Area and SA Most Hydrophobic contributing for activity. The present study may prove to be helpful in the development and optimization of existing indole derivatives as anti-inflammatory agents with selective COX-2 inhibition.

INTRODUCTION: NSAIDs inhibit cyclo-oxygenase (COX), the enzyme responsible for the conversion of arachidonic acid to prostaglandins. COX exists in 2 isoforms. COX-1 is a ubiquitous constitutive isozyme producing prostaglandins responsible for homeostatic functions such as maintenance of GI mucosal integrity. COX-2 is largely a cytokine-induced isozyme producing prostaglandins that mediate pain and inflammation [1]. NSAIDs inhibit both COX-1 and COX-2 to varying degrees.

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Thus, the therapeutic effects of conventional NSAIDs are derived from the inhibition of COX-2, while the adverse effects of these agents, particularly in the upper GI tract, arise from inhibition of COX-1 activity [2]. Much recent effort thus has been made to produce selective inhibitors of cyclooxygenase-2 (COX-2) in the belief that these will lack the gastrointestinal damaging effects of traditional non-steroidal anti-inflammatory drugs (NSAIDs) [3, 4, 5].

Diarylheterocycle class of compounds has been investigated extensively as COX-2 inhibitors. Literature survey revealed that indole derivatives, pyrazoline derivatives, and pyrimidine derivatives independently possess good anti-inflammatory, analgesic activity, and selective COX-2 inhibitory effects [6, 7, 8, 9, 10, 11]. Hence, we focused at achieving greater selectivity for COX-2 enzymes with the use

of indole nucleus and other structural features of different COX-2 inhibitors (pyrazoline derivatives, pyrimidine derivatives, and sulfinyl methyl group) in the designed molecules. Thus, the concept of chemical derivatization of the indole nucleus with pyrazoline and pyrimidine was attempted. Three series of the target molecules are synthesized. The compounds synthesized were subjected to preliminary pharmacological evaluation for anti-inflammatory and analgesic activity by using models like carrageenin-induced rat paw edema method and acetic acid-induced writhing in mice, respectively. The compounds were also screened for acute ulcerogenicity by using Wistar rats. The compounds *viz*. IA7, IA9, IA11, IA12, IB3, IB7, IB12, IIA2, IIA3, IIA4, IIA5, IIA10, IIB2, IIB3, IIB4, IIB5, IIB7, IIIA4, IIIA10, IIIA11, IIIA17, IIIB10, IIIB11, IIIB17 showing comparable anti-inflammatory, analgesic activities with less ulceration were subjected to *in-vitro* cyclo-oxygenase (COX) inhibition assays using Celecoxib as the reference [12].

The computer-aided prediction of biological activity about the chemical structure of a compound is now a commonly used technique in drug discovery. Computational chemistry represents molecular structures as a numerical model and simulates their behavior with the equations of quantum and classical physics. Available programs enable scientists to easily generate and present molecular data including geometries, energies, and associated properties (electronic, spectroscopic, and bulk). The usual paradigm for displaying and manipulating these data is a table in which compounds are defined by individual rows, and molecular properties (or descriptors) are defined by the associated columns [13, 14, 15].

QSAR (Quantitative structure-activity relationship) attempts to find consistent relationships between the variations in the values of molecular properties and the biological activity (% activity, IC_{50}, ED_{50}, MIC) for a series of compounds to generate a mathematical expression so that these rules can be used to evaluate new chemical entities. The mathematical expression can then be used to predict the biological response of other chemical structures. 2D QSAR models are based on descriptors derived from a two-dimensional graph representation of a molecule.

A QSAR generally takes the form of a linear equation:

Biological Activity = Const + $(C_1 \times P_1)$ + $(C_2 \times P_2)$ + $(C_3 \times P_3)$ +.....

Where the P_1 to Pn are physicochemical parameters value computed for each molecule in the series and C_1 to Cn are the coefficients of parameters. Physicochemical descriptors are based on the physicochemical properties of the molecule.

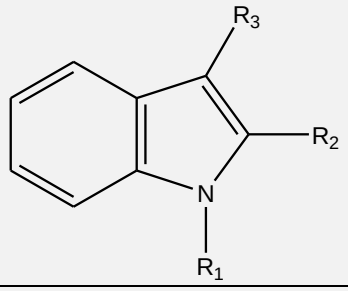
In the present research work, a data set of twenty-four molecules showing comparable COX-2 inhibitory activity was subjected to 2D quantitative structure-activity relationship (QSAR) analyses, in search of newer and potent anti-inflammatory agents with selective COX-2 inhibition. Statistically, significant models were generated, and the most robust models for 2D QSAR were obtained using partial least square regression method coupled with a stepwise forward-backward method using V-Life Molecular Design Suite software version 3.5.

MATERIALS AND METHODS:

Optimization of Molecules Structure: A data set of twenty-four molecules showing comparable COX-2 inhibitory activity measured was chosen for the present 2D QSAR study. **Table 1** the biological activity was expressed as IC_{50} values measured on COX-2 enzyme.

The structures of all the compounds were drawn in ChemDraw ultra 8.0 software in Mol format (mol file). These structures were imported in VLife MDS 3.5 software and converted to the mol2 format. Energy minimization was performed of each 3D model using Merck Molecular Force Field (MMFF) until the root mean square gradient values becomes smaller than 0.0001 kcal/mol Ao. For optimizing molecules using VLife MD, the set selected was 'Maximum number of cycles = 10000, convergence criteria (RMS gradient) = 0.01'. The distance-dependent function in the dielectric properties field was checked. 1.0 value was entered as constant. From force field drop down list MMFF was selected as a force field. Analytical as gradients type option was selected. In advanced button Non Bonded Cut Off dialog box, the values entered are as: Electrostatic as 20.00, vdW as 10.00 and vdW after iterations as 10.

TABLE 1: THE CHEMICAL STRUCTURES OF COMPOUNDS USED FOR 2D QSAR STUDY



S. no.	Compd	R_1	R_2	R_3
1	IA7	5-(4-methoxyphenyl)-1-phenylpyrazoline	4-chlorophenyl	H
2	IA9	1,5-diphenylpyrazoline	4-methoxyphenyl	H
3	IA11	5-(4-methoxyphenyl)-1-phenylpyrazoline	4-methoxyphenyl	H
4	IA12	5-(4-dimethyaminophenyl)-1-phenylpyrazoline	4-methoxyphenyl	H
5	IB3	4(4-methoxyphenyl) pyrimidin-2-amine	Phenyl	Phenyl
6	IB7	4(4-methoxyphenyl) pyrimidin-2-amine	4-chlorophenyl	Phenyl
7	IB12	4(4-(dimethylamino) phenyl)pyrimidin-2-amine	4-methoxyphenyl	Phenyl
8	IIA2	methylsulfonyl	5-(4-chlorophenyl)-1-phenylpyrazoline	Phenyl
9	IIA3	methylsulfonyl	(4-bromophenyl)-1-phenylpyrazoline	Phenyl
10	IIA4	methylsulfonyl	5-(4-methoxyphenyl)-1-phenylpyrazoline	Phenyl
11	IIA5	methylsulfonyl	5-(4-dimethyaminophenyl)-1-phenylpyrazoline	Phenyl
12	IIA10	Tosyl	(5-(4-methoxyphenyl)-1-phenylpyrazoline	Phenyl
13	IIB2	methylsulfonyl	4-(4-chlorophenyl) pyrimidin-2-amine	Phenyl
14	IIB3	methylsulfonyl	4-(4-bromophenyl) pyrimidine-2-amine	Phenyl
15	IIB4	methylsulfonyl	4-(4-methoxyphenyl) pyrimidin-2-amine	Phenyl
16	IIB5	methylsulfonyl	4-(4-(dimethylamino) phenyl)pyrimidin-2-amine	Phenyl
17	IIB7	Tosyl	4-phenylpyrimidin-2-amine	Phenyl
18	IIIA4	H	Phenyl	3-(4-hydroxyphenyl)-1-phenylpyrazoline
19	IIIA10	H	4-chlorophenyl	3-(4-hydroxyphenyl)-1-phenylpyrazoline
20	IIIA11	H	4-chlorophenyl	3-(4-aminophenyl)-1-phenylpyrazoline
21	IIIA17	H	4-methoxyphenyl	3-(4-aminophenyl)-1-phenylpyrazoline
22	IIIB10	H	4-chlorophenyl	4-(2-amino) pyrimidin-4-yl) phenol
23	IIIB11	H	4-chlorophenyl	4-(4-aminophenyl) pyrimidin-2-amine
24	IIIB17	H	4-methoxyphenyl	4-(4-aminophenyl) pyrimidin-2-amine

The optimization process was started. The energy and gradient of each iteration were reported in Output Window. After the successful termination of the optimization process, the final output in the Output Window dialog box showed both total energy details of the molecule before and after optimization. These structures were saved as energy minimized structures.

Calculation of Descriptors for QSAR: The 2D QSAR was launched by picking Modules in an appropriate sequence as per the manual. By selecting the QSAR Tool 'Calculate Descriptors' various physicochemical descriptors were selected. For performing QSAR analysis, descriptors that show variation for all the molecules are required. As the descriptors that were constant for all the molecules were not considered to contribute to QSAR and hence removed from the worksheet. Training and test set from the data were selected by manual selection method, ensuring the molecules have uniform spread (train and test) in terms of both activity and chemical space. In the generation of the QSAR model, we have selected eight molecules in test and sixteen in the training set. **Table 2** all calculations were run on a Pentium IV personal computer with the window XP operating system. Total of 213 Descriptors was evaluated.

TABLE 2: LIST OF SETS OF TRAINING AND TEST COMPOUNDS FOR QSAR STUDIES

Training Set (16 Molecules)	
IA7	IIA10
IA11	IIB4
IB3	IIB5
IB7	IIIA4
IB12	IIIA11
IIA3	IIIA17
IIA4	IIIB10
IIA5	IIIB11
Test Set (08 Molecules)	
IA9	IIB3
IA12	IIB7
IIA2	IIIA10
IIB2	IIIB17

Then data selection was done considering the negative log of IC_{50} values under the dependent variable and the remaining variables considered as independent. Regression methods selected were Multiple and Forward-Backward as the Stepwise Variable Selection from the Select Variable Selection Method panel. Stepwise parameter setting was done as cross-correlation limit =0.5, number of variable in final equation = 4, term selection criteria as r, F test in as 4 and F test out as 3.99. Additional parameter settings as: Variance Cut-Off = 0, Scaling option = Auto Scaling. The best model was selected based on various statistical parameters such as squared correlation coefficient (r^2), standard error of estimation (SE), sequential Fischer test (F). Quality and predictability of the model were estimated from the cross-validated squared correlation coefficient. The various 2D-QSAR models were developed using the MLR method. 2D-QSAR equations were selected by optimizing the statistical results generated along with a variation of the descriptors in these models. The fitness/pattern plots were also generated for evaluating the dependence of the biological activity on various types of descriptors **Fig. 1**.

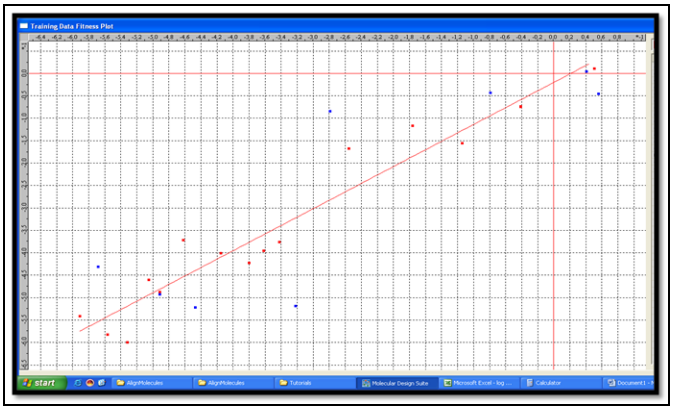


FIG. 1: FITNESS GRAPH OF OBSERVED AND PREDICTED IC_{50} DATA FOR ALL 24 COMPOUNDS DERIVED FROM MODEL NO. 3

The frequency of use of a particular descriptor in the population of equations indicated the relevant contributions of the descriptors. Contribution chart **Fig. 2** signifies that the descriptors below the zero line have negative contribution and above the zero lines has a positive contribution. The best regression equation obtained is represented as model 3.

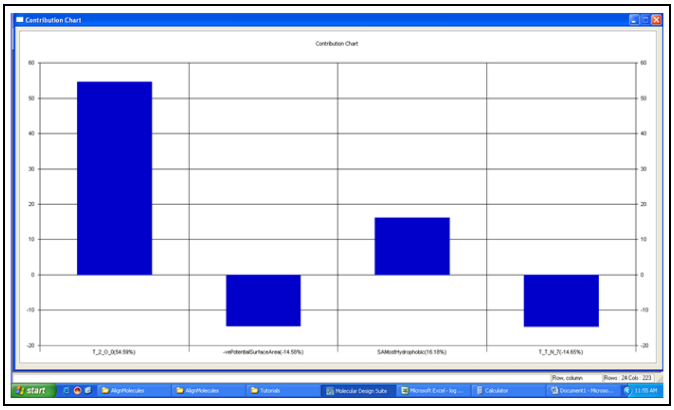


FIG. 2: CONTRIBUTION PLOT DERIVED IN MODEL NO. 3

RESULTS AND DISCUSSION: The results of *in-vitro* COX inhibition assay on the most active twenty-four molecules from all the series shows that these compounds are more selective towards COX-2 than COX-1. Compound IIA3, IIB2, and IIB4 from series II showed selectivity index of

54.60, 56.70 and 52.54 for COX-2 *vs.* COX-1. The compounds IIIB11 and IIIB17 from series III also showed a selectivity index of 29.75 and 35.27, respectively. The remaining compounds in series IA, IB, IIIA and IIIB have shown less selectivity index as compared to compounds in IIA and IIB series. The results show that the presence of a sulfonyl group in series IIA and IIB is favorable for maximum drug-receptor interactions. In the compounds IIIB11 and IIIB17, presence of hydrogen bonding groups is important for optimum drug-receptor interactions **Table 3**.

TABLE 3: *IN-VITRO* COX-INHIBITION DATA OF COMPOUNDS

S. no.	Compound	COX-1[a] (IC_{50}, µM)	COX-2 (IC_{50}, µM)	COX-2 SI[b] (Selectivity Index)
01	Celecoxib	28.6	0.09	317.77
02	IA7	37.8	2.2	17.18
03	IA9	51.2	3.7	13.83
04	IA11	46.8	3.2	14.62
05	IA12	49.6	2.8	17.71
06	IB3	48.1	3.6	13.36
07	IB7	51.5	3.1	16.61
08	IB12	45.6	2.4	19
09	IIA2	39.5	0.91	43.40
10	IIA3	48.6	0.89	54.60
11	IIA4	54.1	1.1	49.18
12	IIA5	47.8	1.3	36.76
13	IIA10	56.9	1.8	31.61
14	IIB2	49.9	0.88	56.70
15	IIB3	48.6	1.2	40.5
16	IIB4	53.6	1.02	52.54
17	IIB5	57.5	1.3	44.23
18	IIB7	52.8	1.9	27.78
19	IIIA10	44.6	3.1	14.38
20	IIIA11	48.1	3.9	12.33
21	IIIA17	50.6	2.6	19.46
22	IIIA4	49.1	3.4	14.44
23	IIIB10	39.6	2.3	17.21
24	IIIB11	47.6	1.6	29.75
25	IIIB17	38.8	1.1	35.27

[a] Values are means of two determinations acquired using an ovine COX-1/COX-2 assay kit and the deviation from the mean is <10% of the mean value. [b] *In-vitro* COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).

2D-QSAR Equation Interpretation: Among the generated QSAR models; model 3 was selected based on various statistical parameters such as squared correlation coefficient (r^2), which is a relative measure of the quality of fit.

Fischer's value (F test) which represents F-ratio between the variance of calculated and observed activity, standard error (r^2_se) representing absolute measure of quality of fit, and cross-validated square correlation coefficient (q^2), standard error of cross-validated square correlation coefficient (q^2_se), predicted squared regression (pred_r^2) and standard error of predicted squared regression (pred_r^2se) to estimate the predictive potential of the models, respectively.

Model 1:

IC_{50} = 3.4687 (± 1.1887) SA Most Hydrophobic + 10.9861(± 4.2795) Average +ve Potential -3.5648.

Statistical Data: n = 16, Degree of freedom = 13, r^2 = 0.8120, q^2 = 0.6542 F test = 21.4359, r^2 se = 0.1728, q^2 se = 0.2937, pred_r^2 = 0.6180, pred_r^2se = 0.1883.

Model 2:

IC_{50} = -2.2496 (± 0.0314) XA Most Hydrophilic + 4.5372 (± 1.1283) SA Most Hydrophobic + 13.7287 (±5.1352) Average +ve Potential -2.3174.

Statistical Data: n = 16, Degree of freedom = 12, r^2 = 0.8636, q^2 = 0.7264, F test = 36.6845, r^2 se = 0.1278, q^2 se = 0.1145, pred_r^2 = 0.7180, pred_r^2se = 0.1183.

Model 3:

IC_{50} = 0.2167 (±0.0015) T_2_O_0 - 0.0014 (±0.0000) –ve Potential Surface Area + 4.0448 (±0.9698) SA Most Hydrophobic -0.0143 (±0.0000) T_2_N_7 -1.1256.

Statistical Data: n = 16, Degree of freedom = 11, r^2 = 0.9382 , q^2 = 0.8557, F test = 41.7199, r^2 se = 0.0596, q^2 se = 0.0911, pred_r^2 = 0.7443, pred_r^2se = 0.1274.

Interpretation of Model 3: Several models were generated for 2 D QSAR model development. Model 3 was found to be best with high r^2 of 0.9382. Model is robust as q^2 value is also high as 0.8557 with good predictive power as indicated by pred_r^2=0.7443. The model showed two alignment independent (AI) descriptors T_2_O_0 and T_2_N_7 as well as two physicochemical descriptors -ve Potential Surface Area and SA Most Hydrophobic contributing for activity. From the derived QSAR model, it can be concluded that anti inflammatory activity of indole derivatives is strongly influenced by physicochemical descriptors.

Alignment Independent (AI) Descriptors: T_2_O_0 is the count of a number of double bounded atoms (*i.e.*, any double bonded atom, T_2) separated from oxygen atom by 0 bonds in a molecule and is positively contributing (54.59%). This indicates that double bonded oxygen atoms should be more for increasing activity. Thus, it can be predicted that the sulfonyl group in series II is responsible for high COX-2 selectivity of the few of the compounds in the series. T_2_N_7 (-14.65% contribution) is the count of the number of double bounded atoms (*i.e.*, any double bonded atom, T_2) separated from nitrogen atom by seven bonds in a molecule and is negatively contributing (-14.65%). This indicates that a reduction in double bond characteristics surrounding nitrogen of indole ring at a 7th bond distance will lead to an increase in activity.

Physicochemical Descriptor: -ve Potential Surface Area is the descriptor which signifies total van der Waals surface area with the negative electrostatic potential of the molecule. This is contributing negatively (-14.58%) indicate that negative electrostatic potential on the surface should be reduced by attaching electron donating groups.

SA Most Hydrophobic is the most hydrophobic value on the vdW surface, which is positively contributing (16.18%) indicates that more bulky groups will further increase the activity by increasing surface hydrophobicity.

TABLE 4: INTERCORRELATION MATRIX OF DESCRIPTORS USED IN MODEL NO. 3

Parameter	T_2_O_0	–ve Potential Surface Area	SA Most Hydrophobic	T_2_N_7	IC_{50}
T_2_O_0	1				
–ve Potential Surface Area	0.2081	1			
SA Most Hydrophobic	-0.1463	0.1695	1		
T_2_N_7	0.1678	0.1986	0.3151	1	
IC_{50}	0.5192	-0.12674	-0.1687	-0.1378	1

TABLE 5: OBSERVED AND PREDICTED IC_{50} VALUE DATA FOR TRAINING SET COMPOUNDS (16 MOLECULES) OBTAINED FROM MODEL NO. 3

Compound Code	Observed Value	Predicted Value	Residual Value	Residual Variance
IA7	-0.342423	-0.376169	0.033746	0.0043
IA11	-0.505150	-0.460390	-0.04476	0.1590
IB3	-0.556303	-0.582001	0.025698	0.0044
IB7	-0.491362	-0.486880	-0.004482	0.0049
IB12	-0.380211	-0.422895	0.042684	0.1770
IIA3	0.050610	0.010688	0.039922	0.0019
IIA4	-0.041393	-0.074962	0.033569	0.0035
IIA5	-0.176091	-0.116537	-0.059554	0.0006
IIA10	-0.255273	-0.167558	-0.087715	0.0060
IIB4	-0.041393	-0.073966	0.032573	0.0573
IIB5	-0.113943	-0.155171	0.041228	0.0535
IIIA4	-0.531479	-0.599633	0.068154	0.0093
IIIA11	-0.591065	-0.541233	-0.049832	0.0157
IIIA17	-0.414973	-0.400449	-0.014524	0.0002
IIIB10	-0.361728	-0.395808	0.03408	0.0104
IIIB11	-0.462398	-0.371676	-0.090722	0.0624

TABLE 6: OBSERVED AND PREDICTED IC_{50} VALUE DATA FOR TEST SET COMPOUNDS (08 MOLECULES) OBTAINED FROM MODEL NO. 3

Compound Code	Observed Value	Predicted Value	Residual Value	Residual Variance
IA9	-0.568202	-0.430638	-0.137564	0.1900
IA12	-0.447158	-0.522218	0.07506	0.0409
IIA2	0.040959	0.004411	0.036548	0.0713
IIB2	0.055517	-0.045410	0.100927	0.0803
IIB3	-0.079181	-0.043709	-0.035472	0.0122
IIB7	-0.278754	-0.084583	-0.194171	0.0049
IIIA10	-0.491362	-0.492239	0.000877	0.0924
IIIB17	-0.322219	-0.518414	0.196195	0.0557

The plot of observed versus predicted activity provides an idea about how well the model was trained and how well it predicts the activity of the external test set **Table 5** and **Table 6**. From the plots it can be seen that the model is able to predict the activity of training set quite well (all points are close to regression line) as well as external test set up to 62% (only few points are relatively apart from the regression line) providing confidence in predictive ability of the model **Fig. 1**.

CONCLUSION: The present work describes the 2D QSAR study which generated an equation which signifies that the count of number of double bounded atoms separated from oxygen atom by 0 bonds in a molecule is positively contributing thus indicating double bonded oxygen atoms should be more for increasing activity and total van der Waals surface area with negative electrostatic potential of the molecule contributing negatively indicating that negative electrostatic potential on surface should be reduced by attaching electron donating groups.

It also signifies that most hydrophobic value on the vdW surface positively contributing and thus indicating that more bulky groups will further increase the activity by increasing surface hydrophobicity. It further signifies the count of the number of double bounded atoms (*i.e.* any double bonded atom, T_2) separated from nitrogen atom by seven bonds in a molecule which is negatively contributing (-14.65%). Thus, the results obtained can be used for further modification and optimization of the indole derivatives for better anti-inflammatory activity with selective COX-2 inhibition.

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CONFLICT OF INTEREST: All authors have none to declare.

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