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TWO DIMENSIONAL- QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIPS -2, 3 DIARYLTHIOPHENES AS SELECTIVE COX-1/-2 INHIBITORS

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A Quantitative Structure Activity Relationship Study on a series of substituted 2, 3 DIARYLTHIOPHENES AS SELECTIVE COX-2 AND COX-1 INHIBITORS was made using combination of various thermodynamic electronic and spatial descriptors. Several statistical expressions were developed using stepwise multiple liner regression analysis. The best quantitative structure activity relationship models were further validated by leave-one-out method of cross-validation. The best quantitative structure activity relationship COX-1 model was selected having a correlation coefficient (r) of 0.8672 and cross-validated correlation coefficient (Q^2) of 0.76 and COX-2 model was selected having a correlation coefficient (r) of. 0.9070 and cross-validated correlation coefficient (Q^2) of 0.85. The study indicates that thermodynamic descriptors (torsion energy, LogP, HF, Ovality, molar refractivity and Vander Waals energy) and electronic descriptor (HOMO, lowest unoccupied molecular orbital) play an important role for the non-steroidal anti-inflammatory drugs. The quantitative structure activity relationship study provides important structural insights in designing of COX -1/-2 Inhibitors.

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1. Introduction

Inhibition of prostaglandin production with non-steroidal anti-inflammatory drugs (NSAIDs) has been widely used for the treatment of both acute and chronic inflammatory diseases. [1] These compounds have had significant side effects which potentially limit their use in a large proportion of the potential patient population. [2] Arachidonic acid is converted to prostaglandins by at least two isoforms of the enzyme cyclooxygenase. [3, 4].The constitutive form of this enzyme (COX-l) is responsible for the normal production of prostaglandins. An inducible form of cyclooxygenase (COX-2) is primarily responsible for the production of prostaglandins at sites of inflammation. Non-steroidal anti-inflammatory agents (NSAID) are widely used in the treatment and management of pain and inflammation. These compounds inhibit the enzyme cyclooxygenase (COX) and thus prevent the formation of prostaglandins at elevated levels causing inflammation [5]. It has been reported that selective inhibition of second isoform of the enzyme, cyclooxygenase-2 (COX-2) (induced during inflammation) may provide the therapeutic benefit without causing gastric ulceration associated with the classical agents [6]. The improved safety profile of COX-2 inhibitors may allow the use of these new agents for long-term prophylactic use in certain chronic diseases [7]. This has led intense efforts in search for potent and selective COX-2 inhibitors, as the next generation of anti-inflammatory agents.Thus our main

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objective is to design specific inhibitors of COX-2 in the hope that these molecules may be further explored as powerful non-ulcerogenic anti-inflammatory agents.2, 3-diarylthiophenes In addition nowhere quantitative structure activity analysis has been reported for2, 3-diarylthiophenes. Thus such studies may help for the design and synthesis of better selective COX-2 inhibitors. The major objective of this study is to explore the physicochemical properties which are helpful in the designing of selective COX-1/ COX-2 inhibitors with better efficacy and reduced toxicity. The objective can be fulfilled by structural requirement which is explored through QSAR study and then exploited to optimize activity of compounds of selected series.

2. Materials and methods

A part of our efforts to create QSAR models shows substantial predictive promise for the designing of new compounds with enhanced biological activity. In the present work, we correlated 2,3 DIARYLTHIOPHENES AS SELECTIVE COX-2 AND COX-1 INHIBITORS Yves Leblanc.et.al [8] (Table- 1).All computational work was performed on Pentium IV Dual Core Work station-using software In QSAR study, the logarithmic form of depending data set was considered which is having less skewness as compared to the non-logarithmic one. The inhibitory concentration (IC50 in μM) of COX-2, COX-1 was converted into pIC50 (negative logarithm of IC50 in mole) used as a dependent variable. The series was divided into a training set of 18 compounds including S-1 to S-18 (Table 1), and a test set of 7 compounds including T-1 to T-7 (Table 1), The molecular modelling study was performed using CS ChemOffice 6.1 [9], while the regression analysis was carried out on VALSTAT [10]. Structures of all compounds were sketched using builder module of the program. The sketched structures were subjected to energy minimization via steepest descent method using force field until the RMS gradient value become smaller than 0.001 kcal/molA° . The energy minimized molecules have been subjected to re-optimization via Austin model (AM1) [11] method until the RMS gradient attained a value lesser than 0.0001 kcal/molA° using MOPAC [12]. The geometry optimization of the lowest energy structure was carried out using EF routine. Calculated thermodynamic descriptors included critical temperature (T), ideal gas thermal capacity (C),Critical pressure (Pc), boiling point (BP), Henry's law constant (H), bend energy (Eb), heat of formation (Hf), total energy (TE), and partition coefficient (PC). Steric descriptors derived were Connolly accessible area (CAA), Connolly molecular area (CMA), Connolly solvent excluded volume (CSEV), exact mass (EM), molecular weight (MW), principal moment of inertia-X component (PMI-X), principal moment of inertia-Y component (PMIY), principal moment of inertia-Z component (PMI-Z), molar refractivity (MR), and Ovality (OVAL). Electronic descriptors such as dipole (DPL), electronic energy (ElcE), highest occupied molecular orbital energy (HOMO), lowest unoccupied molecular orbital energy (LUMO), repulsion energy (NRE),VDW-1,4-energy (E14), Non-1, 4-VDW energy (E), and total energy (E) were calculated. Multiple linear regression (MLR) analysis was used to investigate the correlation between biological activity and physicochemical properties. The MLR was performed by using the VALSTAT [11] by the stepwise method. The highest correlation of independent variables with dependent variable was chosen for deriving the QSAR model. The statistical values, multiple correlation coefficient (r), standard errors (s), cross validation r2 (q2) and standard error of prediction (SPRESS) were used to evaluate the obtained QSAR models.

Multiple linear regression analysis

The stepwise multiple regression analyses were carried out using the statistical software openstat2, version 6.5.1, designed and standardized by Bill Miller and Stat Val. Correlation matrix was obtained to justify the use of more than one variable in the study. The variables used were with maximum correlation to activity and minimum inter-correlation with each other. From the statistical viewpoint, the ratio of the number of samples (N) to the number of variables used (M) should not be very low; usually it is recommended that $N/M \geq 5$.

The QSAR equations were constructed for efficacy data of both species of malarial parasite with the physcio-chemical descriptors and indicator variables. The statistical quality of the equations[13] was judged by the parameters like correlation coefficient (r), explained variance (r^2),

standard error of estimate(s) and the variance ratio or overall significance value (F).The accepted equations are validated for stability and predictive ability using "leave –one-out" and cross validation technique. The statistical parameters used to access the quality of the models are the predictive sum of squares (PRESS) of validation. Finally, the standard cross-validation correlation coefficient r^2 and q^2 are also calculated.

$$PRESS = \Sigma (Ypred - Y\ obs)^2$$

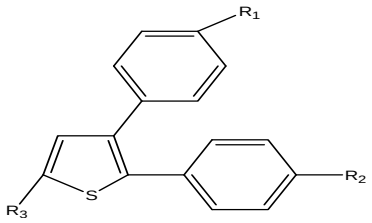
$$S_{press} = \sqrt{} PRESS/ (n-k-1)$$

n= no. of compounds used for cross-validation

y_i= experimental value of the physic-chemical property for the ith sample

y= value predicted by the model built without the sample i

Table-1: Physicochemical Parameters and Inhibitory Activity of 2, 3 diarylthiophenes as selective cox-1/-2 inhibitors



S.No	R1	R2	R3	IC_50 COX-2	IC_50 COX-1	PIC_50 COX-1	PIC_50 COX-2
1	SO_2Me	F	Br	0.005	0.60	5.78	3.70
2	F	SO_2Me	Br	0.02	1.1	6.04	4.31
3	SO_2Me	F	H	0.25	100	8	5.41
4	F	SO_2Me	H	4.3	50	7.69	6.64
5	SO_2Et	F	H	30	50	7.69	7.47
6	SO_2NH_2	F	H	0.03	1.3	6.12	4.48
7	F	SO_2NH_2	H	0.67	2.7	6.43	5.84
8	SO_2NH_2	$C(Me)_2OH$	H	30	50	7.67	7.47
9	SO_2NH_2	F	$CH(Me)_2$	0.01	0.23	5.37	4
10	SO_2NH_2	F	CO_2Me	0.07	1.0	6	4.85
11	SO_2NH_2	F	$C(Me)_2OH$	0.41	5.4	6.73	5.62
12	F	SO_2NH_2	$C(Me)_2OH$	1.6	50	7.69	6.21
13	F	SO_2NH_2	CO_2Me	30	50	7.69	7.47
14	SO_2NHMe	F	H	7.2	50	7.69	6.87
15	SO_2NHAc	F	H	5.4	50	7.69	5.75
16	SeO_2Me	F	H	0.55	32	7.51	3.69
17	$CONH_2$	F	H	30	3.2	6.51	7.47
18	COMe	F	H	30	0.75	8.75	7.47
19	CO_2H	F	H	30	50	7.69	7.47
20	CO_2Me	F	H	30	17	5.88	7.47
21	CHO	F	H	30	0.98	5.99	7.47
22	CN	F	H	30	0.21	5.32	7.47
23	CH_2OH	F	H	30	0.35	5.54	7.47
24	SMe	F	H	30	0.34	5.53	7.47
25	SOMe	F	H	30	15	7.17	7.47

Statistical Parameters[14]

The prime purpose of developing QSAR models is usually prediction of the activity. It is often assumed that provided the correlation is a "good" one (as indicated typically by a high correlation coefficient), then the QSAR can be used to give reliable predictions of bioactivity. QSAR analysis is based on regression analysis. Regression analysis correlates independent X variables (e.g., physiochemical parameters, indicator variables) and dependent Y variable (e.g., biological data). The equations obtained by regression analysis are analyzed by following parameters:

Correlation coefficient (r): It is the relative measure of quality of fit of the model because its value depends on the overall variance of the dependent variable. It ranges from 0 to 1. A value of 1 means there is perfect correlation between the biological data and the explanatory variables. A correlation coefficient of 0 means there is no correlation at all. A QSAR equation can be accepted if the 'r' is greater than 0.8 for in vivo biological data's and greater than 0.9 for in vitro biological data's and if standard deviation is not much larger than standard deviation of biological data.

Table 1. Comparisons of Observed and Leave One Out Predicted PIC50 Value of Compounds Used Equations …

Sr.no.	Obs.act (-PIC) COX1	Obs.act (-PIC)COX2	Pred. act Model-1 COX2	Pred. act Model-1 COX1
1	5.78	3.70	4.79051	5.82754
2	6.04	4.31	4.80594	6.11089
3	8	5.41	5.78665	8.13969
4	7.69	6.64	7.15339	7.71
5	7.69	7.47	7.8123	7.77821
6	6.12	4.48	7.8123	6.26312
7	6.43	5.84	5.64039	6.47855
8	7.67	7.47	7.8123	5.11085
9	5.37	4	4.73663	5.07918
10	6	4.85	4.945	6.14753
11	6.73	5.62	5.75145	6.8058
12	7.69	6.21	6.98459	7.71465
13	7.69	7.47	7.93371	7.71465
14	7.69	6.87	6.91945	7.71465
15	7.69	5.75	5.94775	7.71465
16	7.51	3.69	4.88451	7.53443
17	6.51	7.47	7.8123	6.58826
18	8.75	7.47	7.8123	5.92344
19	7.69	7.47	7.8123	7.16311
20	5.88	7.47	7.8123	7.21303
21	5.99	7.47	7.8123	5.87367
22	5.32	7.47	7.8123	5.18619
23	5.54	7.47	7.8123	5.6489
24	5.53	7.47	7.8123	5.6121
25	7.17	7.47	7.8123	7.213

Obs = observed activity, Pred= Predicted activity

Square of correlation coefficient (r^2): It is a measure of the explained variance, most often presented as a percentage value.

$$r2= 1-\Sigma\Delta2/Sy$$

S_{yy} = overall total variance

$$S_{yy} = \Sigma (y_{obs}-y_{mean})^2 = [\Sigma y2 – (\Sigma y)2]/n$$

$$\Sigma \Delta2 = SSQ = \text{sum of squared error}$$

Standard Error of Estimate (SEE): It is an absolute measure of the quality of fit. Its value considers the number of objects n and the number of variables k. Therefore, S depends not only on the quality of fit but also on the number of degree of freedom DF= n-k-1.

$$S2 = \Sigma \Delta2 / n-k-1 = (1-r2)\ Syy / n-k-1$$

Where, n-k-1 = Degrees of Freedom

Table 5. Cox-1 Cross Validation Parameters For Significant Equations.

	[a]bsr^2	[b]Q^2	[c]S_{PRESS}	[d]SDEP
Model-1	0.4612	0.2138	0.4276	0.1175
Model-2	0.6249	0.4397	0.3287	0.0267
Model-3	0.7791	0.4619	0.2718	0.3371
Model-4	0.6121	0.2710	0.1281	0.2318

Fischer's Value (F-value): It indicates F-ratio between the variance of calculated and observed activity. It is the measure of the level of statistical significance of the regression model. The number of variable being included to derive the model has stronger influence than in the case of the standard deviation so only F values being larger than the 95% significance limits are acceptable. The use of the model containing the larger number of variable is justified if the resulting partial F value indicates 95% significance for the new introduction of the new variable. If the calculated F-value is greater than the tabulated value then the equation is said to be significant at particular level of confidence.

$$F= r2(n-k-1) / k\ (1-r2)$$

Table-6 COX-2 cross validation parameters for significant equations.

	[a]bsr^2	[b]Q^2	[c]S_{PRESS}	[d]SDEP
Model-1	0.1461	0.1287	0.3182	0.5430
Model-2	0.2143	0.5512	0.3901	0.2145
Model-3	0.3206	0.6712	0.5721	0.3612

T-test: This is a method for determining the significance level of the regression coefficient particular parameter in a model. When the sample size and population standard deviation is unknown, t-value is calculated and the number obtained is compared to a table containing the Student's t-distribution at different confidence levels and degree of freedom. If the computed value is larger than the tabulated number then the coefficient can be considered as significant.

Validation of the models is crucial in order to assure their predictive potential. The predictive ability of a model (Internal validation) can be indicated by cross validation of the model generated by regression.

Table 7. Correlation matrix of model-cox-1

Parameters	HF	VDWE	MR
HF	1.0000		
VDWE	0.22164	1.0000	
MR	0.651751	0.729153	1.0000

Cross Validation: The most common form of cross-validation is 'leave one out' or Jack-knife method, in which each data value is left out in turn and a model is derived using the remainder of the data. A value can than be predicted for every data point in the set and compared with the true observed value. This is repeated for every data point in the set and permitted the calculation of a "cross-validated r2" also written as q2. Cross validation r2 values are typically lower than the normal but are considered more indicative of the predictive ability of the equation. Indeed q^2 can be negative values (unlike r^2). Thus, whereas r2 value is a measure of quality of fit, q2 is a measure of quality of prediction. A value greater than 0.6 is considered to be useful.

$q2 = 1\text{-PRESS} / \Sigma(y_{obs} - y_{mean})^2$

A more robust alterative to leave one out method is to divide the data set in to two or more groups while one as training set and another as test set. The model generated by the training set is used to calculate the activities of compounds of test set and compared with their biological activity. This is done for every data in test set and 'r^2pred' is calculated.

$pred\_ r^2 = SD - PRESS/ SD$

Where, SD is the sum of squared deviation between the biological activities of the test set and the mean activity of the training set molecules and PRESS is the sum of squared deviation between predicted and actual activity values from every molecule in the test set.

Table 8. Correlation Matrix Of Model-Cox-2

Parameters	MR	Ovality	HOMO
MR	1.0000		
Ovality	0.395950	1.0000	
HOMO	0.323234	0.446623	1.0000

PRESS: It is the predictive residual sum of squares or the predicted extra sum of squares. It is the sum of overall compounds of the squared difference between the actual and predicted values for the independent variables. Smaller the value of PRESS statistics indicates better prediction. If it is appreciably larger than the error sum of square of model, it is likely that there are outliers in data.

$$PRESS = \Sigma (Y_{pred} - Y_{obs})2$$

SPRESS: It is the standard deviation of prediction derived from the PRESS. It is the sum of squared error of prediction, divided by the number of degree of freedom. It is taken as the criterion for the optimum number of components in various techniques like PLS.

SDEP: It is the standard deviation of the error of predictions. It corresponds to SPRESS but the only difference being that the number of degree of freedom is not considered in the calculation of this value SDEP = PRESS/ n

Bootstrapped r^2: r^2bs is correlation coefficient obtained when regression is done using repeated data from the data set used to build the equation. During bootstrapping one data from the data set can be selected as many times while other can be left .Bootstrap r^2 should be near to the normal r^2. The three criteria r, s and f value refer to the fit of the data i.e., the predictive ability inside the model and others like PRESS, SPRESS etc., check the predictive ability outside the model.

3. Results and discussion

The 25 compounds belonging to diaryl furanones category (Table.1) were divided into two sets, 18 compounds were taken in the training set and 7 compounds were taken in the test set (Table 1). The biological activities data for diaryl furanone derivatives were taken from literature [8]. The IC_{50} values for both COX-1 and COX-2 were transformed into –log [PIC50*10-^{6}] i.e. pIC50. Stepwise regression analysis was performed by taking pIC50 as dependent variable and descriptors calculated from chemoffice 6.1 as independent variables.

COX-1

BA= [4.04601(± 0.859089)] +HF [-0.0323814(± 0.0185784)] +logP [0.0203999(± 0.0223441)] +Ovality [0.0100504(± 0.00661578)] +TE [-0.0093099(± 0.0251623)]

n=18, r=0.8867, r^2=0.79357, *q*2 = 0.71,variance=0.115275, std=0.339522,F=31.7973

The tetravariant model No. 1 explained 88.6% of the variance in activity. The standard error of estimate of the derived coefficients is less in making a higher *t* value, hence rendering the terms statistically significant. The observed *t* values of the descriptors HC, logP, Ovality and DE are greater than the tabulated *t* value at 95% confidence interval. The data showed an overall internal statistical significance level better than 99.9%. The dependency among the physicochemical parameters was checked by observing an inter correlation amongst the parameters (i.e., ICAP).The tetravariant model No. 1 was also found to be statistically significant with a comparatively lesser r^2 value. The model was found to have a fairly good predictive ability, as reflected by the cross-validation data. Internal consistency of the models was tested by exploiting leave-one-out and bootstrapping methods of cross-validation. The models were found to be robust having a fairly good predictive ability, as evident from the higher q2 (0.71), and low SPRESS and SDEP values. The model was tested further for outliers by utilizing the Z score values and no compound was found to be an outlier, which suggested that the model is able to explain the structurally diverse analogues. The r^2 bs is at par with the conventional squared correlation coefficient (r2). Randomization test data (Chance < 0.001) revealed that the results were not based on chance correlation.

BA= [3.74773(± 0.755394)] +LogP [-0.0287275(± 0.0160425)] +Ovality [0.0208738(± 0.0191271)] +BE [0.0125142(± 0.00584014)]

n=18, r=0.83696,r^2=0.7704, *q*2 = 0.80,variance=0.0842067,std=0.290184,F=26.542

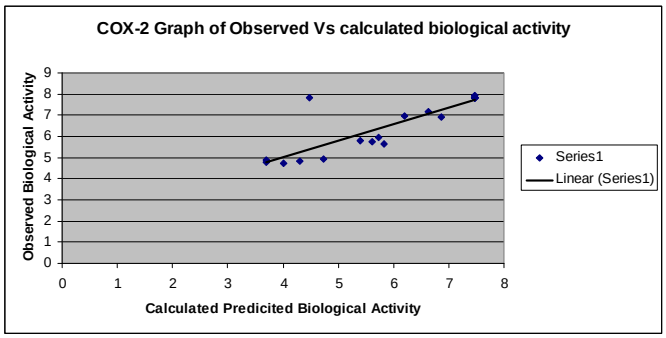


Fig. A plot between observed activity and predicted activity for COX-2

The trivariant model No.2 explained 77.04% of the variance in activity. The standard error of estimate of the derived coefficients is less in making a higher *t* value, hence rendering the terms statistically significant. The observed *t* values of the descriptors logP, Ovality and BE are greater than the tabulated *t* value at 95% confidence interval. The data showed an overall internal statistical significance level better than 99.9%. The trivariant model No. 2 was also found to be statistically significant with a comparatively lesser r^2 value. The model was found to have a fairly good predictive ability. Internal consistency of the models was tested by exploiting leave-one-out and bootstrapping methods of cross-validation. The models were found to be robust having a fairly good predictive ability, as evident from the higher q2 (0.80), and low S_{PRESS} and SDEP values. The model was tested further for outliers by utilizing the Z score values and no compound was found to be an outlier, which suggested that the model is able to explain the structurally diverse analogues. The r^2 bs is at par with the conventional squared correlation coefficient (r2). Randomization test data (Chance < 0.001) revealed that the results were not based on chance correlation.

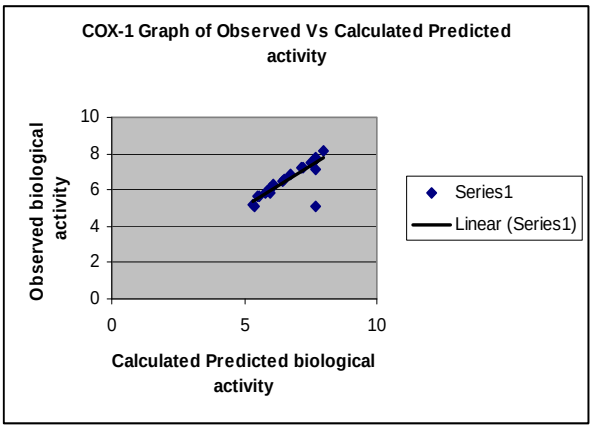


Fig. A plot between observed activity and predicted activity for COX-1

BA= [3.89782(± 0.674334)] +HF [-0.0295238(± 0.0154761)] + VDWE [0.0130842(± 0.0178486)] +MR [0.0116066(± 0.00508151)].3n=18,r=0.86728,r^2=0.8217, *q*2 = 0.76,variance=0.081009,std=0.284621,F=30.5305

The model No. 3 obtained for COX-1 inhibition is found to explain 82.1% of the variance in activity. It is statistically significant with an F value exceeding 99.9% confidence level. The model is having good predictive ability, which is evident from the obtained q2 and r^2bs values. The low values of SPRESS, SDEP, and Sbs also reflect the statistical significance of the model.

Descriptors calculated for the Equations		
S. No.	Descriptor	Type
1	Heat of Formation (HF)	Thermodynamic
2	Boiling Point (BP)	Thermodynamic
3	Critical Pressure (CP)	Thermodynamic
	Critical Temperature (CT)	Thermodynamic
5	Critical Volume (CV)	Thermodynamic
7	Henry's Law Constant (HLC)	Thermodynamic
8	Ideal Gas Thermal Capacity (IGTC)	Thermodynamic
9	LogP	Thermodynamic
10	Melting Point (MP)	Thermodynamic
11	Molar Refractivity (MR)	Thermodynamic
12	Standard Gibbs Free Energy (SGFE)	Thermodynamic
13	Connolly Accessible Area (CAA)	Steric
14	Connolly Molecular Area (CMA)	Steric
15	Connolly Solvent-Excluded Volume (CSEV)	Steric
16	Ovality (OVA)	Steric
17	Principal Moment of Inertia - X (PMI-X)	Steric
18	Principal Moment of Inertia - Y (PMI-Y)	Steric
19	Principal Moment of Inertia - Z (PMI-Z)	Steric
20	Dipole Moment (D)	Electronic
21	Dipole Moment -X Axis (DX)	Electronic
22	Dipole Moment -Y Axis (DY)	Electronic
23	Dipole Moment -Y Axis (DZ)	Electronic
24	Electronic Energy (EE)	Electronic
25	HOMO Energy (HOMO)	Electronic
26	LUMO Energy (LUMO)	Electronic
27	Repulsion Energy (RE)	Electronic
28	Bend Energy (E_b)	Thermodynamic
29	Charge-Charge Energy (CCE)	Thermodynamic
30	Charge-Dipole Energy (CDE)	Thermodynamic
31	Dipole— Dipole Energy (DDE)	Thermodynamic
32	Non-1, 4 VDW Energy (E_v)	Thermodynamic
33	Stretch Energy (SE)	Thermodynamic
34	Stretch-Bend Energy (SEE)	Thermodynamic

35	Torsion Energy (E_t)	Thermodynamic
36	Total Energy (E)	Thermodynamic
37	Van der Waals e 1,4 Energy (VDWE)	Thermodynamic
38	VDW 1,4 Energy (VDWE)	Thermodynamic

COX-2

BA= [4.67922(± 0.636593)] +LogP [-0.0331651(± 0.0201496)] +MR [0.00850745(± 0.00745097)] +BE [0.0988542(± 0.195762)]

n=18, r=0.84047, r^2=0.75605, , $q2$ = 0.69,variance=0.191668, std=0.4378, F=23.2285

Model 4 has good correlation between biological activity and parameters as r = 0.84 and explains 75% variance in COX-2 activity. Low standard deviation of the model demonstrates accuracy of the model. The model showed overall significance level better than 99%, with the F = 23.2285 .Value of chance is less than 0.01, which shows there is significant relationship between LogP, MR (Molar- Refractivity), BE (Bend Energy) and biological activity.

BA= [4.12797(± 0.386667)] +MR [-0.0259112(± 0.0115931)] +OVALITY [0.0131825(± 0.00439019)] + HOMO [0.166785(± 0.112537)]
n=18,r=0.907058,r^2=0.802754,$q2$=0.85,variance=0.0618087,std=0.248614,F=47.96

Equation explains 80.2% of the variance in activity with low standard error of estimation. The model showed overall significance level better than 99%, with the F = 47.96 .Value of chance is less than 0.01, which shows there is significant relationship between MR (Molar- Refractivity), BE (Bend Energy) VDWE, and biological activity.

Table. Descriptors Used Qsar Equations

S. N	HOMO	[b]Ovality	[c]logp	[d]BE	[e]TE	LUMO	HF	MR
1	-9.03911	1.66721	5.5932	19.6669	-3.6144	-0.937434	26.5457	14.9055
2	-9.05988	1.69255	4.4175	21.4386	2.19236	-0.677617	29.1047	13.6483
3	-9.22597	1.77186	6.2837	18.5811	-3.69162	-0.906798	29.342	15.3969
4	-9.07392	1.7535	6.3977	18.0953	-2.51626	-0.895331	29.5672	15.8331
5	-9.10245	1.70207	5.222	21.7702	3.24286	-0.68178	29.1408	14.5759
6	-9.15363	1.73609	4.8395	12.8389	-10.7322	-0.885528	21.0903	14.1973
7	-9.1028	1.59765	3.6638	15.4426	4.04463	-8.26792	23.8189	12.9401
8	-9.60331	1.74131	5.53	13.5939	-9.79753	-9.34106	20.4546	14.6887
9	-8.69329	1.63072	5.7954	17.428	-6.16985	-0.4886	29.611	14.6167
10	-8.00458	1.59323	4.051	15.6408	5.51998	-0.29779	22.6602	13.4039
11	-8.1345	1.62998	5.985	13.2643	-2.88737	-1.50493	24.769	14.4636
12	-8.88987	1.64804	3.7857	14.4966	4.66737	-0.674764	15.9496	13.2508
13	-9.23619	1.58615	4.8012	15.2438	22.7475	-1.00958	31.8985	14.9854
14	-8.90007	1.70839	3.942	21.4703	-0.8644	-1.21176	42.9158	13.9726
15	-9.3558	1.8442	5.6439	13.2496	-1.55999	-1.01765	34.8464	15.7208
16	-9.24992	1.73621	4.5381	12.5012	1.22963	-0.947252	31.9908	14.5216
17	-7.50826	1.71617	3.3624	428.494	0.796735	-2.34849	25.64356	13.2644
18	-9.32468	1.81316	5.3808	12.9805	-5.02994	-0.986669	33.3215	15.257
19	-9.06656	1.63896	3.2351	12.8511	26.4875	-0.325483	39.5644	12.1006
20	-9.06818	1.6282	5.3491	11.8906	28.3449	-0.943651	44.3221	12.1636
21	-9.23272	1.58815	4.1852	10.5134	24.2551	-1.0876	42.6045	11.2084
22	-8.77935	1.60122	4.9546	11.2551	23.1178	-0.873245	38.2313	11.6641
23	-9.27997	1.61001	5.086	11.2891	22.4226	-0.856412	41.6869	11.6998
24	-9.05705	1.58346	4.9583	11.371	23.521	-1.04938	42.4844	11.6722
25	-8.97787	1.6421	5.1483	10.6832	20.5362	-1.12411	40.8298	11.5191

BA= [3.95633(± 0.439126)] +BE [-0.0229962(± 0.0113975)] +LUMO [0.0111466(± 0.0100943)] +Part.coeff. [0.0131032(± 0.00359353)]

n=18, r=0.812038, r^2=0.759406, *q*2=0.63 variance=0.0753585, std=0.274515, F=38.7209

Model shows good correlation coefficient (r=0.812 between descriptors such as BE, MR, Partt.coff). Squared correlation coefficient (r^2) of 0.7594, which explains 63.4% variance in biological activity. Model also indicates statistical significance >99.9% with F-values F= 38.72 Cross-validated Square correlation coefficient of the model was 0.6026, which shows good internal predictivity of the model.

4. Conclusions

The descriptor HOMO, LUMO, MR, Ovality, VDEW, LogP, TE in the models represents the sum of electrostatic, Thermodynamics, terms resulting from the interaction of three dipoles. The descriptor bears a positive coefficient, which suggests significance of dipole–dipole interactions for the COX-1, COX-2 activity. The Van der Waals energy is a thermodynamic parameter which can be defined as the sum of pair wise Vander Waals interaction energy terms for atoms separated by exactly four chemical bonds, related to the structure of the molecule itself. The coefficient of the descriptor VDWE bears a positive sign in the COX-1 model 1 which indicates that increase in the HF,LogP,TE between atoms separated by 3 chemical bonds is conducive to the activity, which in the present case is applicable to the substituents in the Sulphur atoms COX-1, COX-2 moiety. The descriptor bears negative coefficient in the model, suggesting increase in the bulkiness of the substituents and molecular solvent accessible surface area is not conducive to the activity. Predicted activity data of model-1, COX-1 and Model 3 COX-2 were shown in (Table-3) and results of the leave-one-out cross validation for model-1, 2, 3 and 4 are shown in Table-5 and 6.It is evident from the QSAR studies that in COX-1 model-3, thermodynamic descriptors (HF, VDWE, MR). Negative contribution of Heat Formation (attractive forces between active substituents and enzyme-binding sites) and positive contribution VDEW, MR in biological activity indicates that minimizing parameters with suitable substituents enhances the activity. COX-2 Molar Refractivity Negative contribution of total energy (electron density in the enzyme cavity) to the biological activity indicates that minimizing the total energy of the molecule decreases the activity, HOMO positive biological activity indicates that minimizing parameters with suitable substituents enhances the activity. Based on the QSAR model obtained from series, for the design of the new molecules.

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References

[1] Vane, J. R. Nature (New Biol.) **231**,232, (1971).
[2] Allison, M. C.; Howatson, A. G.; Torrance, C. J.; Lee, F. D.; Russell, R. I. N. Engl. J. Med,**327**, 749, (1992).
[3] Maier, J. A.; Hla, T.; Maciag, T. J. Biol. Chem., **265**, 10805,(1990).
[4] O'Banion,M.K.;Winn, V. D.; Young, D. A. Proc. Natl. Acac£ Sci. USA, **89**, 4888,(1992).
[5] J.R. Vane, Nature 231 232, (1971).
[6] B. Barttisini, R. Botting,Y.S. Bakhle, Drug News Prospects **7** ,501,(1994).
[7] S. Kargman, G.P. O'Neil, P.J. Vickers, J.F. Evans, J.A. Mancini,S. Jothy, Cancer Res. **55** 2356,(1995).
[8] Yves Leblanc, JacquesYves Gauthier, Diane Ethier, Jocelyne Guay, Joseph Mancini, Denis Riendeau, Philip Tagari, Philip Vickers, Elizabeth Wong and Petpiboon Prasit Bioorganic &

Medicinal Chemistry Letter **5**(18), 2123 (1995).
[9] CS ChemOffice, Version 8.0, Cambridge Soft Corporation, Software Publishers Association, 1730 M Street, Suite 700, Washington D.C. 20036 (202) 452-1600, U.S.A.
[10] A.K. Gupta, B.M. Arockia, S.G. Kaskhedikar, Indian J. Pharm. Sci. 66396e,402,(2004)
[11] M.J.S. Dewar, E.G. Zoebisch, E.F. Healey, J.J.P. Stewart, J. Am. Chem.Soc. 107 3902,(1985).
[12] J.J.P. Stewart, MOPAC 6.0, QCPE 455, Indiana University, Bloomington, IN 47405, (1990).
[13] H.Kubinyi.Quant.Struct.Act.Relat., 13,285.1994
[14] D. M. Viltaria, M. Orazio, P. Engenio, C. Anionia, G. Federico and B. Adde, J. Med. Chem., **35**, 2910 (1992).