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2D QSAR *In Silico* Analysis of Indole Derivatives with Their Cyclooxygenase-2 Inhibitory As an Anti-Inflammatory Activity

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ABSTRACT

A series of twenty two indole derivatives with their cyclooxygenase-2 inhibitory as an anti-inflammatory activity were subjected to quantitative structural activity relationship analysis to derive a correlation between biological activity as dependent variable and various descriptors as independent variables by using V-LIFE MDS3.5 software. The descriptors involved in building of 2D QSAR models slogP (partition coefficient), chi4 (molecular connectivity indices) and SaaCH count (total number of carbon atoms connected with a hydrogen along with two aromatic bonds), significant role in COX-2 inhibition. The best QSAR Model ($r^{2=}$0.843, q2=0.57 F=12.88, r^2se=0.305, q^2se=0.352, pred_r^2=0.690, pred_r^2se=0.321) has acceptable statistical quality and predictive potential as indicated by the value of cross-validated square of correlation coefficient (q2=0.57). Thus, this validated model brings important structural insight to aid the design of novel anti-inflammatory activity.

INTRODUCTION

The utility of non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of inflammation and pain is often limited by gastrointestinal liabilities including ulceration and bleeding. Inhibition of cyclooxygenase (COX), the enzyme that catalyzes arachidonic acid oxygenation, was initially considered to be responsible for the shared therapeutic benefits and gastrointestinal side effects of NSAIDs. However, the invention COX-2 provided important insights into NSAID side effects that translated into more effective drugs. COX-2 is inducible, short-lived, and produces at the site of inflammation. Its expression is stimulated by cytokines and mitogens. Importantly, COX-2 is responsible for inflammation due to the biosynthesis of prostaglandin. COX-1 is a constitutive enzyme responsible for the biosynthesis of cytoprotective prostaglandins in the gastric mucosa and the kidney. Classical NSAIDs inhibit both isoforms non-selectively. Selective inhibition of COX-2 provides therapeutic benefit in inflammation without gastric ulceration leading to improved safety profile allowing the use of these agents for long-term prophylaxis in certain chronic disease[1-7]

Certain indole derivatives with COX-2 inhibitory activity proved to possess analgesic, anti-inflammatory and anti-rheumatic activity. Several QSAR works have been carried out leading to development of selective COX-2 inhibitors. QSAR has been traditionally perceived as a means of establishing correlation between chemical structure modifications and respective changes in biological activity. Traditionally, the classic 2D QSAR model is only a rough approximation to the actual relationship as it mainly uses 2D molecular descriptors. The purpose of the present study was to explore the significant physiochemical parameters responsible for the anti-inflammatory activity of indole derivatives. Consequently, 2D QSAR analyses were carried out by multiple linear regressions (MLR).

Quantitative structure–activity relationships (QSARs) are an attempt to correlate the structural or property descriptors of compounds quantitatively with biological activities. The prime feature of QSAR is to establish a correlation between various molecular properties of a set of molecules with their experimentally known biological activity. 2D QSAR relationship is a rough approximation contains topological or two-dimensional (2D) information. It explains how the atoms are bonded in a molecule, both the type of bonding and the interaction of particular atoms

(e.g. total path count, molecular connectivity indices etc.). In search of new indole entities with improved anti-inflammatory activity present study deals with 2D QSAR approaches to find out structural features required for biological activity. [8-14]

MATERIALS AND METHODS

A dataset of twenty two indole derivatives [15]for their COX-2 inhibitory activity has been taken for present QSAR work given in Table 1. All molecular modeling techniques including 2D QSAR studies described herein were performed on molecular modeling software V-Life MDS 3.5. Each structure of the twenty two indole derivatives was built on a workspace, fully geometry optimized using standard Merck molecular force field (MMFF) with a distant dependent (1/r) dielectric function and energy gradient correlation ratio 0.001kcal/mol. Compounds having highest pIC_{50} values were selected as the template molecule and each molecule had to be superimposed onto template molecule (template-based alignment). These aligned molecules were placed into a three dimensional cubic lattice of 2Å grid. The electrostatic and steric fields were generated at each grid point using methyl probe (sp^3 hybridized) of charge +1 by kNN method with default energy of 30 kcal/mol and 10 kcal/mol respectively and partial atomic charges were generated using Gasteiger-Marsii method. The parameters slogP (38%) SaaCH count (28%), were contributed positively and chi4 (35%), were negatively contributed to antiinflammatory activity, Figure1.

All chemical structures and their 2D QSAR study were performed using 239 physiochemical, alignment independent and atom type descriptors.[16-22] The various 2D descriptors were individual, retention index (chi), atomic valence connective index (chiv), path count, chi chain, chiv chain, chain path count, cluster, path cluster, kappa, element count, dipole moment, distance based topological, estate number, estate contributions, information theory index, semi-empirical, hydrophobicity XlogpA, hydrophobicity XlogpK, hydrophobicity SlogpA, hydrophobicity SlogpK, polar surface area, alignment independent and atom type descriptors class.

Models were generated using multiple regression techniques for 2D a study. The optimal training and test sets were selected by random selection method which uses the ratio of training to validation objects (test set) as 70%: 30%. The cross-validation analysis was performed using the leave-one-out method. The cross-correlation limit was set at 0.5 and the term selection criteria is

r^2. F value was specified to evaluate the significance of a variable. The higher the F value, the more stringent was the significance level. The variance cutoff was set at 0, and scaling was auto scaling in which the number of random iterations was set at 100. The following statistical parameters were considered for comparison of the generated QSAR models: correlation coefficient (r), squared correlation coefficient (r^2), internal cross-validation (q^2), predictive r^2 for external test set (pred r^2) for external validation, and Fischer's (F). Internal validation was carried out using leave-one-out (LOO) method. For calculating q^2, each molecule in the training set was eliminated once and the activity of the eliminated molecule was predicted by using the model developed by the remaining molecules. Plot of cross-validated calculated activity is given Figure 2.

RESULTS AND DISCUSSION

QSAR studies on indole series resulted in several QSAR equation using multiple linear regression technique. Selection of test and training sets was based on uni-column statistics. Seventeen compounds were placed in the training set and five (8a, 8e, 12a, 24a, 20a) compounds in the test set. Test and training set was chosen randomly such that low, moderate and high-activity compounds were present in approximately the same proportions in both sets, which were confirmed by the results of uni-column statistics. The uni-column statistical analysis is summarized in Table 2. Uni-column statistics showed that the results are interpolative (i.e. derived within the minimum–maximum range of the training set). The stepwise regression analysis generated a large number of QSAR equation, out of which the best equation (model 1) was found to be as given below

Model -1 (MLR)

Log (1/IC50) =0.6011(±0.1959) slogp +-0.5280(±.1792) chi4+0.1813(±0.0703) Saa-CH+6.6251 (n = 17, r^2= 0.84 q^2= 0.57, F test =12.88, r^2 se = 0.30, q^2se = 0.352 pred_r^2 = 0.69, pred_r^2se=0.321)

Model -2 (MLR)

Log(1/IC50)= +0.6177(±0.1624) slogp + [-0.0140(± 0.1276) chiV0] + 0.0990(±0.0088)SaaCHE-index+11.25)

(n = 17, r^2= 0.75 q^2= 0.68, pred_r^2 = 0.59, r^2 se = 0.30,)

Model -3 (MLR)

Log(1/IC50)= + 0.7275(± O.1367) slogp+ [– 0.0140(± 0.0066) Mw] +0.1809(±0.0677)Saa-CHcount+7.2120)

(n = 17, r^2= 0.70 q^2= 0.5068, pred_r^2 = 0.455 r^2 se = 0.270)

Among these models, model 1 was selected as best model because it showed higher cross validated regression coefficient (q^2) and correlation coefficient (r^2) and lower standard error than other models, reported in Table 3. Statistical measures used were n-number of compounds in regression, r-correlation coefficient, r^2-squared correlation coefficient, F- test (Fischer's value) for statistical significance, SD- standard deviation, q^2- cross validated correlation coefficient and correlation matrix to show correlation among the parameters.

The correlation coefficient values closer to 1.0 represent the better fit of the regression. High values of the F-test indicate that the model is statistically significant. Standard deviation is an absolute measure of quality of fit and should have a low value for the regression to be significant.

CONCLUSION

The study revealed that for anti-inflammatory activity, the parameter slogp, SaaCHcount were contributed positively and chi4 were negatively contributed to anti-inflammatory activity. This suggests that by modification in topological indices will be helpful for designing of more potent anti-inflammatory. Results of QSAR studies may be utilized for the rational designing of the compounds with expectation to obtain the potent anti-inflammatory, which would be patented in the near future. The work is planned to meet our challenges of complications arriving due to inflammatory.

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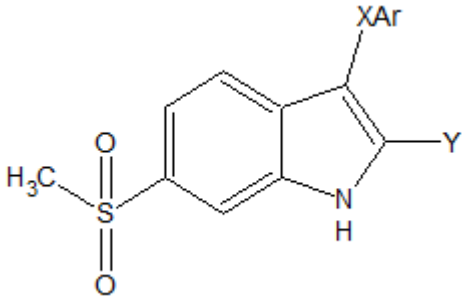
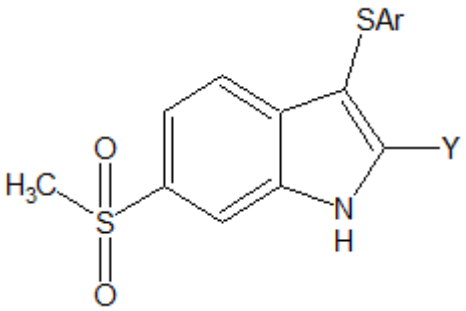
Table 1: Biological Activity of Data of of 6-Methylsulfonyl indole derivatives with their COX-2 inhibitory activity.



Compound	XAr	y	IC_{50} (µM)
8a	OPh(4-F)	CH_3	0.030
8b	OPh(2,4-DiF)	CH_3	0.11
8c	OPh(4-Cl)	CH_3	0.300
9d	OPh(4-OMe)	CH_3	0.200
8e	OPh(2,4-DiCl)	CH_3	0.11
12a	(C=O) OPh(4-F)	CH_3	0.664
12d	(C=O) OPh(4-OMe)	CH_3	1.09
13a	SPh(4-F)	CH_3	0.0200
13d	SPh(2,4-DiF)	CH_3	0.47
13f	S(2-Pyridyl)	CH_3	1.78
14a	CH_2 Ph(4-F)	CH_3	0.080
14b	CH_2 Ph(2,4-DiF)	CH_3	0.26
14c	CH_2 Ph(4-Cl)	CH_3	0.26
14d	CH_2 Ph(4-OMe)	CH_3	0.27
14g	CH_2 Ph(2-Cl)	CH_3	0.07



Compound	Ar moiety	Y	IC_{50} (µM)
20a	Ph(4-F)	CO_2Me	0.80
20b	Ph(2,4-DiF)	CO_2Me	0.38
22a	Ph(4-F)	$CONH_2$	1.21
22b	Ph(2,4-DiF)	$CONH_2$	2.24
24a	Ph(4-F)	CN	1.01
24b	Ph(2,4-DiF)	CN	0.94
24g	Ph(2-Cl)	CN	0.13
24h	Ph(2-Cl)	CN	0.33
25a	Ph(4-OMe)	CH_2OH	0.42

Table 2. Actual and Predicted Anti-inflammatory Activity of generated model 1

Compound no	Actual pIC_{50}	Predicted pIC_{50}	Residual pIC_{50}
8a*	7.523	7.039	0.483
8d	6.699	6.787	-0.088
8e*	6.959	6.987	-0.028
12*	6.178	6.491	-0.313
13a	7.699	7.070	0.628
13f	5.75	5.763	-0.013
14a	7.097	6.927	0.169
14b	6.585	6.610	-0.025
14c	6.585	7.060	-0.475
14d	6.569	6.675	-0.106
14g	7.155	7.060	0.094
20a*	6.097	6.118	-0.021
22a	5.917	5.846	0.070
24a*	5.996	6.621	-0.625
22b	5.65	5.528	0.121
24b	6.027	6.304	-0.277
24g	6.886	6.754	0.131
24h	6.481	6.369	0.111
25a	6.377	6.187	0.189
8b	6.959	6.722	0.236
12d	5.963	6.239	-0.276
13d	6.328	6.818	-0.490

* TEST SET

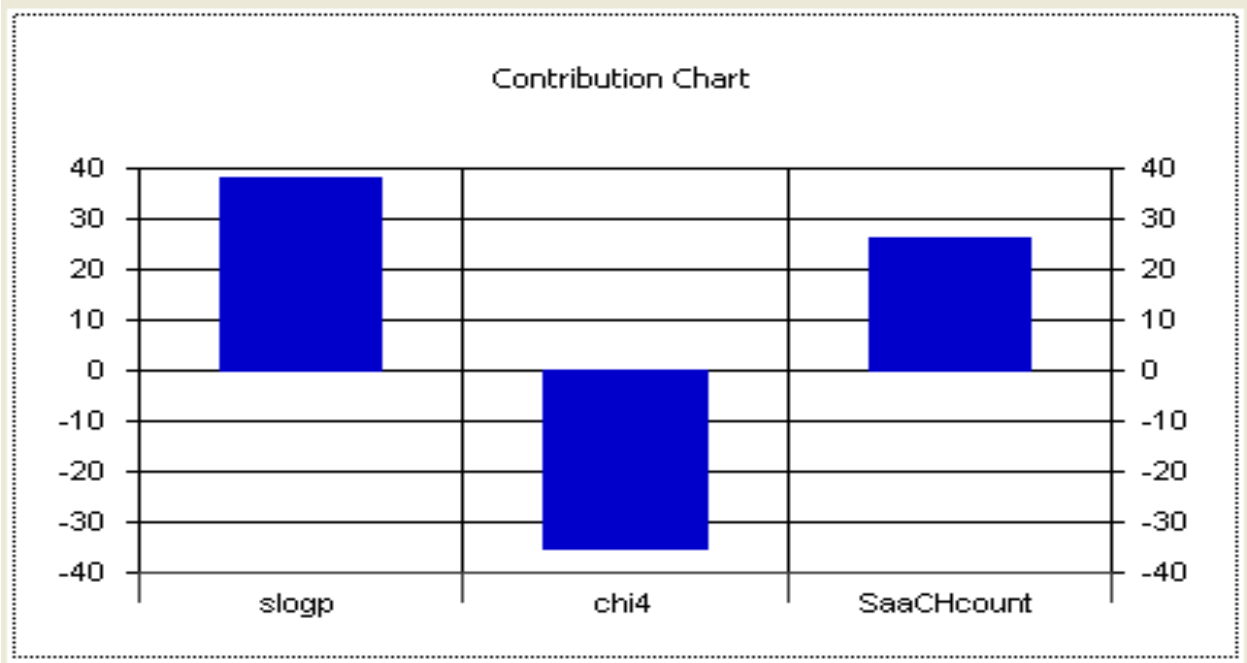


Figure.1. Contribution chart of descriptor for model 1 (MLR method)

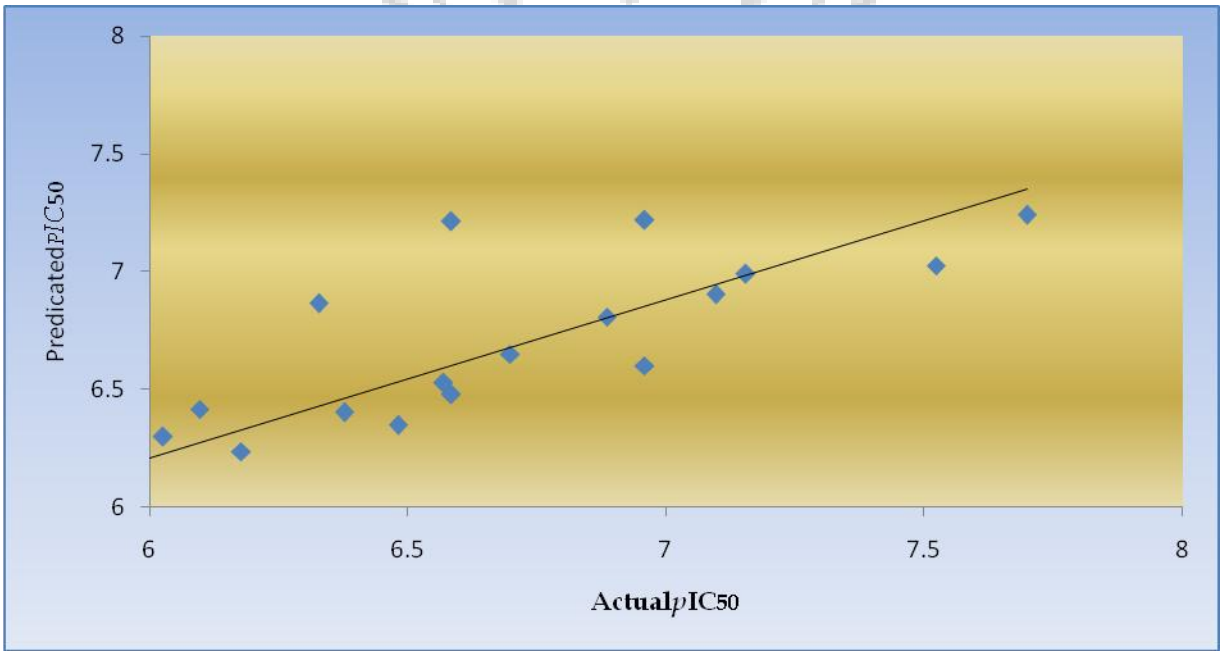


Figure.2. Plot of cross-validated calculated activity obtained (model 1)

Table 3: Statistical data of all three model

Model	n	r^2	q^2	Pred r^2	r^2Se
1	17	0.8430	0.5728	0.6909	0.3055
2	17	0.7516	0.6832	0.5872	0.4520
3	17	0.7086	0.5068	0.4552	0.2705