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3D QSAR analysis of new 6-Methylsulfonyl indole derivative with their COX-2 Inhibitory as Anti-Inflammatory activity

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Abstract
Three-dimensional quantitative structure activity relationship studies were carried out on a series of 22, 6-Methylsulfonyl indole compounds to find out the structural requirements for anti-inflammatory activity using Molecular Design Suite (MDS) 3.0. The best predictions were obtained from the model where seventeen compounds were considered in the training set and remaining five compounds in the test set. 3D QSAR approach was developed based on principles of the k-nearest neighbor method combined with various variable selection procedures was used. The kNN-MFA approach was used to generate models for given data set and these models were used to predict the activity of test molecules.

Keywords: 3D QSAR; V-Life; 6-Methylsulfonyl indole; COX-2 inhibitors and Anti-inflammatory activity

1. Introduction

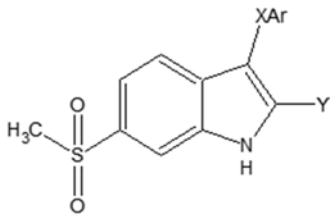
The utility of non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of inflammation and pain is often limited by gastrointestinal liabilities including ulceration and bleeding. Inhibition of cyclooxygenase (COX), the enzyme that catalyzes arachidonic acid oxygenation, was initially considered 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 [1-3]. 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 [4-7].

3D QSAR models are often sensitive to the particular alignment technique. The rapid increase in three-dimensional structural information (3D) of bioorganic molecules coupled with the development of fast methods for 3D structure alignment (e.g. active analogue approach), has led to the development of 3D structural descriptors and associated 3D QSAR methods. We report here the development of a new method (kNN-MFA) that adopts a k-nearest neighbor principle for generating relationships of molecular fields with the experimentally reported activity [8-11].

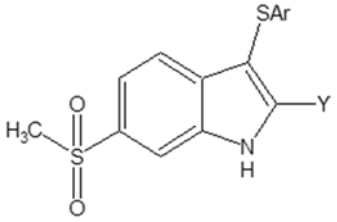
2. Materials and Methods

A dataset of twenty two indole derivatives [12] for their COX-2 inhibitory activity have been taken for present QSAR work reported in Table 1. All molecular modeling techniques including 3D QSAR studies described here and performed on molecular modeling software V-Life MDS. We hereby report the models, as generated by kNN-MFA utilizing SA and SW forward variable selection methods for this data set. In the kNN-MFA method, several models were generated for the given or selected members of training and test sets and the corresponding best models are reported here. The QSAR models developed by kNN-MFA include both the electronic and steric descriptors along with their range to indicate their importance for interaction in molecular field. Analysis of model suggested that both steric and electrostatic descriptors are important for interaction. All the QSAR models were evaluated on the basis of k i.e. no. of nearest neighbors; q2, i.e. cross validated r2 (by leave one out method) and pred_r2 for the external test set. In the dialog box, green points indicates steric region and blue indicates electronic [13-17].

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



Compound	X-Ar	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

3. Result and Discussion

QSAR studies on indole series resulted in several QSAR equation using partial least square (PLS) 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, 8d, 13f, 25a) 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. Selection of test and training set was based on uni-columns statistics. The best equation obtained by PLS in summarized here. The uni-column statistical analysis is summarized in Table 2. & Table 3.

Table 2: Uni-Column statistics for the 3D QSAR model

Data set	Average	Max	Min	SD	Sum
Training	6.4647	7.6990	5.6498	0.5323	109.8995
Test	6.6614	7.5229	5.7496	0.6604	0.6604

Table 3: Actual and Predicated Activity with Residual Activity of 3D QSAR best Model

Compound no.	Actual pIC_{50}	Predicted pIC_{50}	Residual pIC_{50}
12a	6.177	6.142	0.035
22a	5.917	5.856	0.060
20b	6.420	6.474	-0.054
20a	6.096	5.827	0.269
14g	7.154	7.094	0.060
14d	6.568	6.582	-0.013
14c	6.585	6.721	-0.136
14b	6.585	6.536	0.0487
14a	7.096	7.0921	0.004
13f*	5.749	5.916	-0.167
13a	7.698	7.612	0.086
12d	5.962	5.980	-0.017
8e*	6.958	6.870	0.088
8d*	6.698	7.033	-0.334
8c	6.522	6.610	-0.087
8b	6.958	6.914	0.043
8a*	7.522	6.666	0.855
25a*	6.376	6.176	0.199
24h	6.481	6.487	-0.005
24b	6.026	6.243	-0.216
24a	5.995	5.872	0.123
22b	5.649	5.850	-0.200

Test set*

Partial Least Square Analysis Result of 3d QSAR Models

Above model was chosen as the best model as it showed a good correlation coefficient (r^2 = 0.950) which explain 95% of the variance. The model showed an internal predication (q^2= 0.874) of 87% and predicivity for the external test (pred r^2=0.5251) of 52%. The overall statistical significance level was found to be exceed 99.9% with fitness (F=83.060).

Log (1/IC50) =0.0732(E_594) +0.0186(S_766) +0.0231(S_707) +0.0410(E_664) +6.182

(n = 17, F= 83.06, r^2= 0.9504, q^2= 0.8742, r^2Se = 0.1315, pred r^2= 0.5251)

The Negative coefficient (-0.0732) at E_594 position indicates that more electronegative substitutions (CF_3, Cl, F, Br) are favorable for activity, while positive coefficient (0.0231) at S_707 indicates substitution of a bulky group like phenyl are favorable for activity. Contribution chart is reported in, Fig. 1.

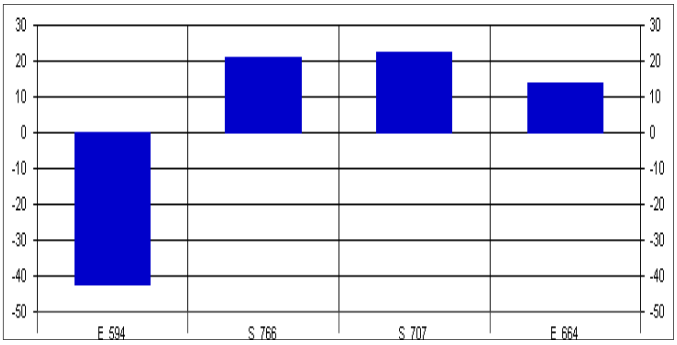


Fig 1: Contribution Chart of 3D QSAR

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 Fig. 2. The kNN-MFA models provide direction for the design of new molecules in a rather convenient way. The points which contribute to the SW kNN-MFA and SA kNN-MFA models in data sets are displayed in Fig.3. And Fig.4.

Fig 2: Plot of cross-validated calculated activity of 3D QSAR mode

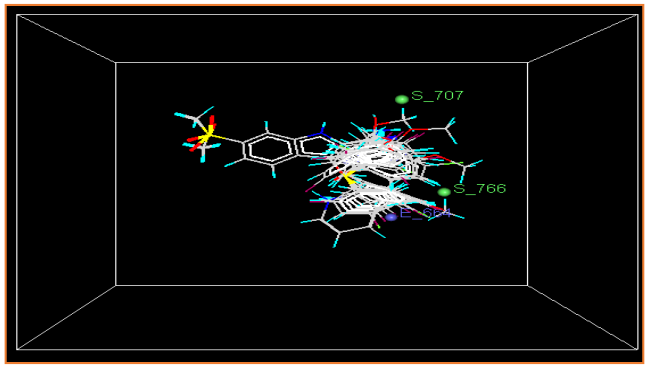
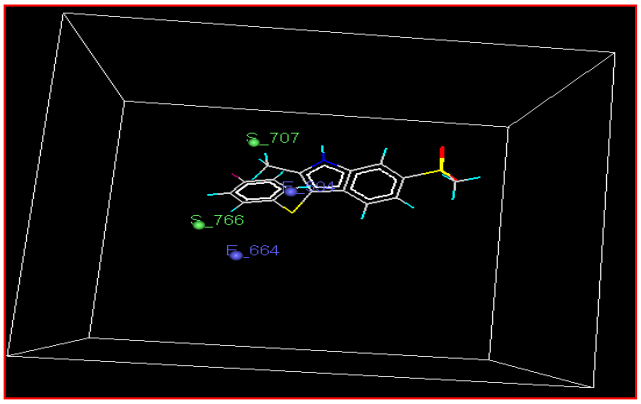


Fig 3: Distribution of chosen points in the SW kNN-MFA model



- Electrostatic region
- Steric region.

Fig 4: Distribution of chosen points in the SA kNN-MFA model

The range of property values for the chosen points may aid in the design of new potent molecules. The range is based on the variation of the field values at the chosen points using the most active molecule and its nearest neighbor set. Negative range indicates that negative electrostatic potential and steric potential are favorable for increase in the activity and hence more electronegative substituent group is preferred in that region. Positive electro potential and steric potential are favorable for increase in activity and hence a less electronegative group is preferred in this region. Hence, this method is expected to provide a good alternative for the drug design.

In the dialog box, green points indicates steric region and blue indicates electronic. Negative coefficient (-0.0732) at position E_594 indicates that more electronegative substitutions (CF_3, Cl, F, Br) are favorable for activity, while positive coefficient (0.0231) at S_707 indicates substitution of a bulky group like phenyl are favorable for activity. Statistical data for SW kNN-MFA and SA kNN-MFA model was given in Table 4.

Table 4: Statistical Result of 3D QSAR Model For Of 6-Methylsulfonyl Indole Derivatives

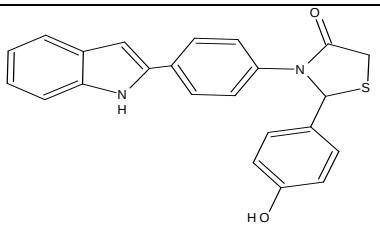
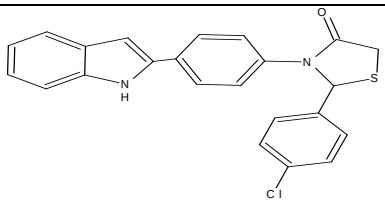
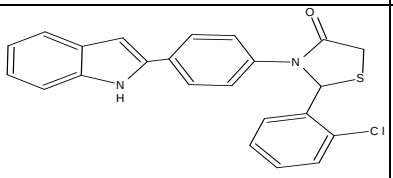
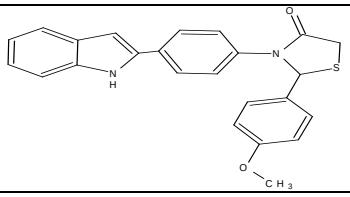
kNN-MFA Method	Descriptors	Statistical Parameter
Stepwise (SW) Variable Selection	E_594 (-0.0732) S_766(-0.0186) S_707(0.0231) E_664(-0.0410) Constant =6.182	r^2=0.950, q^2=0.874, F Test= 83.06, r^2se=0.131, q^2se=0.209, Pred_r^2=0.525, pred_r^2se=0.371, test size= 5 n=17

4. Conclusion

The compounds were designed by using 3D QSAR study. The descriptors E_594, E_664 and S_707, S_766 were found to be responsible for the activity. New compounds have been designed on the basis of above facts and the prediction of activities for designed compounds was found to be more than the previous reported compounds

Anti-Inflammatory Activities of the newly designed (6-methylsulfonyl indole) were predicted by using the best model obtained from the 3D QSAR. On the basis of the developed model 3D QSAR, four molecules are newly designed which are found to be more potent and effective. On the basis of above results, the new compounds were designed and given in Table 5.

Table 5: The new designed compounds based 3D QSAR model

S. No.	Compound	Calculated activity 3D (pIC_{50})
1.		8.792293
2.		7.973703
3.		8.4224532
4.		7.5368

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