CoMFA vs. Topomer CoMFA, which One is better a Case Study with 5-Lipoxygenase Inhibitors

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Abstract

Quantitative structure-activity relationships (QSAR) have been applied for two decades in the development of relationships between physicochemical properties of chemical substances and their biological activities to obtain a reliable statistical model for prediction of the activities of new chemical entities. The fundamental principle underlying the QSAR is that the structural difference is responsible for the variations in biological activities of the compounds. In this work, we developed 3D-QSAR model for a series of 5-Lipoxygenase inhibitors, utilizing comparative molecular field analysis (CoMFA) and Topomer CoMFA methodologies. Our developed models addressed superiority of Topomer CoMFA over CoMFA. The CoMFA model was obtained with $q^2=0.593$, $r^2=0.939$, $Q^2=0.334$ with 6 optimum number of components (ONC). Higher statistical results were obtained with the Topomer CoMFA model ($q^2=0.819$, $r^2=0.947$, ONC=5). Further robustness of developed models was checked with the ANOVA test and it shows F=113 for CoMFA and F=162.4 for Topomer CoMFA model. Contour map analysis indicated that the more requirement of electrostatic parameter for improved potency.

Key words : CoMFA, Topomer CoMFA, 5-Lipoxygenase, 3D-QSAR

1. Introduction

Over forty years have elapsed since Hansch and Fujita published their pioneering work of quantitative structure-activity relationships (QSAR)[1,3]. Following the introduction of Comparative Molecular Field Analysis (CoMFA) by Cramer in 1998[4], other three-dimensional QSAR methods have been developed[5-8]. Currently, combination of classical QSAR and other computational techniques at three-dimensional level is of greatest interest and generally used in the process of modern drug discovery and design. During the last several decades, a number of different mythologies incorporating a range of molecular descriptors and different statistical regression ways[9-11] have been proposed and successfully applied in developing of new drugs, thus QSAR method has been proven to be indispensable in not only the reliable prediction of specific properties of new compounds, but also the help to elucidate the pos-

sible molecular mechanism of the receptor-ligand interactions.

The limiting factor in the development of QSARs is the availability of high quality experimental data. In QSAR analysis, it is imperative that the input data be both accurate and precise to develop a meaningful model. In fact, it must be realized that any resulting QSAR model that is developed is only as valid statistically as the data that led to its development.

The ideal QSAR should: (1) consider an adequate number of molecules for sufficient statistical representation, (2) have a wide range of quantified end-point potency (i.e. several orders of magnitude, at least 3) for regression models or adequate distribution of molecules in each class (i.e. active and inactive) for classification models, (3) be applicable for reliable predictions of new chemicals (validation and applicability domain) and (4) allow to obtain mechanistic information on the modeled end-point. Chemical descriptor(s) include empirical, quantum chemical or non-empirical parameters. Empirical descriptors may be measured or estimated and include physicochemical properties (such as for instance logP). Non-empirical descriptors can be based on individual atoms, substituents, or the whole molecule, they

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are typically structural features. They can be based on topology or graph theory and, as such, they are developed from the knowledge of 2D structure, or they can be calculated from the 3D structural conformations of a molecule.

In this paper, we report a 3D-QSAR study of 5-Lipoxygenase inhibitors utilizing CoMFA and Topomer CoMFA techniques. The aim of this study was to check the performance of CoMFA and Topomer CoMFA on the predictivity of QSAR model development.

2. Experimental Section

2.1. Data Set

Molecular datasets with congeneric compounds were selected from literature. The 5-Lipoxygenase inhibitors dataset consists of 51 molecules reported by Sogawa et. al[12]. Biological activities were reported in IC_{50} unit. Reported bioactivity values were converted to logarithmic scale to get linear QSAR model using following formula.

$$pIC_{50} = -\log IC50$$

The resultant logarithmic values (3.397-8.619) were utilized as a dependant variable in CoMFA and Topomer CoMFA. All the structures and their biological activities were reported in Table 1.
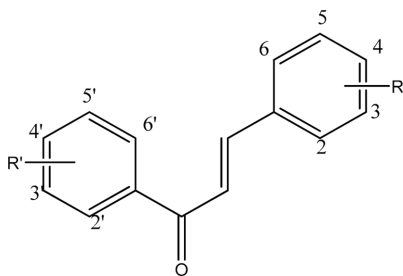

Table 1. Structures and biological activities of 5-Lipoxygenase inhibitors

S. No.	R'	R	$IC_{50}(\mu M)$	pIC_{50}
1	4'-OH	-	230	3.64
2	2',4'-OH	-	400	3.40
3	2',4',6'-OH	-	142	3.85
4	2'-OH	4-OH	42	4.38
5	2',4'-OH	4-OH	35	4.46
6	2',4',6'-OH	4-OH	100	4.00
7	-	3,4-OH	0.043	7.37
8	2'-OH	3,4-OH	0.023	7.64
9	3'-OH	3,4-OH	0.0042	8.38
10	4'-OH	3,4-OH	0.0040	8.40

Table 1. Continued

S. No.	R'	R	$IC_{50}(\mu M)$	pIC_{50}
11	2',4'-OH	3,4-OH	0.0046	8.34
12	2',4',6'-OH	3,4-OH	0.14	6.85
13	2-thienyl	3,4-OH	0.022	7.66
14	3-pyridyl	3,4-OH	0.21	6.68
15	2'-OH	3-OCH$_3$,4-OH	17	4.77
16	4'-Cl	3-OCH$_3$,4-OH	8.9	5.05
17	4'-OCH$_3$	3-OCH$_3$,4-OH	12	4.92
18	2'-Cl	3,4-OH	0.092	7.04
19	4'-Cl	3,4-OH	0.0085	8.07
20	4'-NO$_2$	3,4-OH	0.023	7.64
21	2'-CF$_3$	3,4-OH	0.058	7.24
22	3'-CH$_3$	3,4-OH	0.027	7.57
23	4'-CH$_3$	3,4-OH	0.076	7.12
24	2'-OCH$_3$	3,4-OH	0.027	7.57
25	3'-OCH$_3$	3,4-OH	0.0065	8.19
26	4'-OCH$_3$	3,4-OH	0.02	7.70
27	3'-N(CH$_3$)$_2$	3,4-OH	0.0098	8.01
28	4'- N(CH$_3$)$_2$	3,4-OH	0.0047	8.33
29	4'-OCH(CH$_3$)$_2$	3,4-OH	0.0041	8.39
30	2'-OH,4'-OCH$_3$	3,4-OH	0.015	7.82
31	2'-OH, 5'-OCH$_3$	3,4-OH	0.041	7.39
32	4'-OH,3'-OCH$_3$	3,4-OH	0.0090	8.05
33	2'-CH$_3$,4'-CH3	3,4-OH	0.017	7.77
34	2'-OCH$_3$,4'-OCH$_3$	3,4-OH	0.010	8.00
35	2'-OCH$_3$,5'-OCH$_3$	3,4-OH	0.0078	8.11
36	2'-OCH$_3$,6'-OCH$_3$	3,4-OH	0.370	6.43
37	3'-OCH$_3$,4'-OCH$_3$	3,4-OH	0.018	7.74
38	2'-CH$_3$,4'-CH$_3$, 6'-CH$_3$	3,4-OH	0.400	6.40
39	3'-OCH$_3$,4'-OCH$_3$,5'-OCH$_3$	3,4-OH	0.016	7.80
40	2',5'-OH	3,4-OH	0.064	7.19
41	2'-OH,5'-CH$_3$	3,4-OH	0.039	7.41
42	2'-OH,5'-OC$_2$H$_5$	3,4-OH	0.0053	8.28
43	2'-OH,5'-CH(CH$_3$)$_2$	3,4-OH	0.004	8.40
44	2'-OH,5'-OCH(CH$_3$)$_2$	3,4-OH	0.011	7.96
45	2'-OH,5'-OC$_4$H$_9$	3,4-OH	0.1	7.00
46	2',5'-CH$_3$	3,4-OH	0.016	7.80
47	2'-OCH$_3$,5'-CH$_3$	3,4-OH	0.024	7.62
48	2'-OCH3, 5'-OC$_2$H$_5$	3,4-OH	0.0038	8.42
49	2'-OCH$_3$,5'-OCH(CH$_3$)$_2$	3,4-OH	0.014	7.85
50	2'-OC$_2$H$_5$,5-OCH$_3$	3,4-OH	0.027	7.57
51	2'-OC$_2$H$_5$,5-OC$_2$H$_5$	3,4-OH	0.0024	8.62

2.2. Molecular Alignment

All the molecular modeling study was performed by SYBYL 8.1[13] molecular modeling package. Sketching of all structures was performed by SYBYL sketching program. The most active compound (51) of datasets was drawn using SYBYL and minimized with Tripos force field with distance dependant dielectric functions. CONFORT program was utilized to get bioactive conformation of the template molecule (51). We generated a single conformer for a template molecule to avoid selection problem among the multiple lowest energy conformers. Rest of the molecules from dataset was modeled based on the CONFORT generated conformation. Minimization of all the molecules was done with Tripos force field by keeping scaffold constrained. Variable parts of all molecules were searched systematically. Finally all the obtained conformations were subjected to PM6 minimization to ensure precise geometry for all molecules with global minimum energy conformations[14]. This procedure was done to ensure the systematic control of conformation in CoMFA and
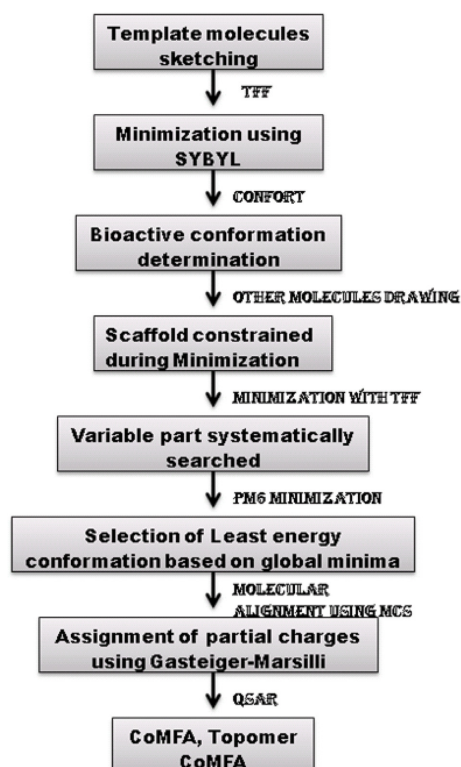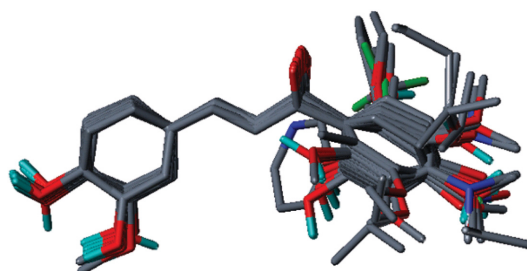

Fig. 2. Molecular superposition of all the molecules over template molecule using maximum common substructure algorithm.

given in flow chart (Fig. 1). Resultant molecules were further utilized for CoMFA and Topomer CoMFA analysis.

2.3. Molecular Alignment

Molecular alignment is considered to be a crucial part of 3D-QSAR analysis, and the resultant models predictivity depends on it. In this study, molecular alignment was performed by using maximum common substructure (MCS). MCS was calculated using MCS program. Partial atomic charges were assigned using Gasteiger-Marsilli method. Aligned 3D molecules for 5-lipoxygenase inhibitors were shown in Fig. 2.

2.4. CoMFA

For the alignment set, steric and electrostatic CoMFA field was calculated at each lattice intersection of a regularly spaced grid of 2.0 Å unit. The grid box dimensions were determined automatically in such a way that the region boundaries were extended beyond 4.0 Å in each direction. The steric and electrostatic interactions between probe and remaining molecules were calculated. The generated steric and electrostatic fields were scaled by CoMFA_STD scaling method in SYBYL with default energy of +30 kcal/mol. The electrostatic interactions are modeled by Columbic potential and van der Waals interaction using Lennard-Jones potential respectively, and calculated by using standard Tripos force field. The distance dependent dielectric constant 1.00 was used. A sp^3 hybridized carbon atom having +1 charge serves as a probe for calculating steric and electrostatic field.

Fig. 1. Protocol for the molecular conformation determination.

2.5. Topomer CoMFA

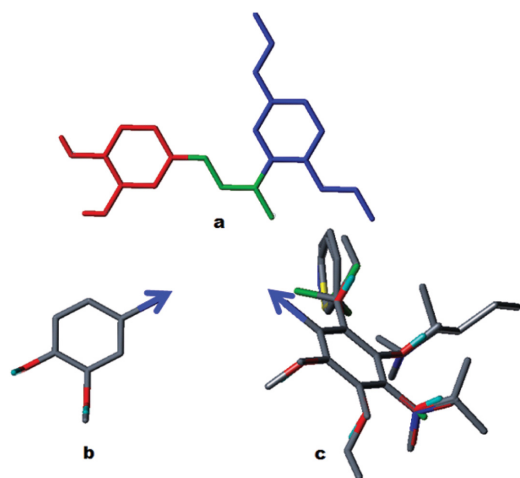A Topomer CoMFA technique merges CoMFA[4] and

Fig. 3. (a) Fragmentation pattern for all the molecules in dataset using Topomer CoMFA, red color denotes R1 fragment, blue color denotes R2 fragment and green color represents common part. (b) Molecular superposition of all the R1 fragments. (c) Molecular superposition of all R2 fragments.

topomer technology, to overcome the alignment problem of CoMFA[15]. Topomer CoMFA includes alignment of structural fragments. Structural fragments by definition contain a common feature, the "open valence" or "attachment bond". The Topomer methodology overlaps this common feature to provide an absolute orientation for any fragment. A Topomer is an invariant three-dimensional (3D) representation of molecular subunit generated from its two-dimensional (2D) topology by topomer alignment in topomer CoMFA[16].

In Topomer CoMFA analysis, all molecules of dataset were divided into two fragments, shown as R1 (red) and R2 (blue) groups and common scaffold in green color in Fig. 3a. Each Topomer fragment was applied with topomer alignment to make a 3D invariant representation[17]. In Topomer CoMFA, atomic charges were calculated by the Gasteiger-Marsilli method for the topomer structure. Topomer CoMFA acts in two different ways for the calculation of molecular fields. An 'attenuation factor' reduces the field contributions of fragment atoms more distant from the attachment bond. Finally, the r^2 is calculated by using the same optimum number of component obtained from leave-one-out (LOO) cross validation analysis. Topomer CoMFA steric and electrostatic fields were calculated at a regular space grid of 2 Å, and were fixed automatically into a

1000 point cube to contain a Topomer. A sp^3 hybridized carbon atom was used as a probe atom for the steric field calculation and a negative oxygen atom was used as a probe for electrostatics field.

2.6. Topomer CoMFA

The relationship between structural parameters and biological activities of compounds under study has been quantified using a PLS algorithm[9-11]. CoMFA and Topomer CoMFA descriptors were used as independent variable and biological activity as a dependent variable. The cross-validation analysis was performed by using the LOO method, in which one molecule is removed from the dataset and its activity is predicted by using the model derived from rest of the molecules in the dataset. The q^2 resulted in an optimum number of components and the lowest standard error of prediction.

3. Result

3.1. CoMFA Model Analysis

We developed a reasonable CoMFA models for both 5-Lipoxygenase and T-type calcium channel inhibitors. Quality of the developed models was accessed by LOO cross validation (q^2) and progressive scrambling (Q^2). CoMFA model for 5-Lipoxygenase shows q^2=0.593, r^2=0.939 ONC=6. Developed CoMFA model shows 0.973 as standard error of predictions (SDEP) and 0.376 standard error of estimate (SEE). ANOVA test for model shows satisfactory result (113.1). Robustness of CoMFA model was checked with progressive scrambling of 50 runs, with maximum 10 numbers of bins and minimum 2 bins. The model showed good correlation after response randomization (Q^2=0.334).

3.2. Topomer CoMFA Model Analysis

Topomer CoMFA analysis displayed better results than CoMFA. Topomer CoMFA model for 5-lipoxygenase dataset shows that it gaves good internal predictive ability. Developed model shows q^2 of 0.819 and SDEP =0.64 with ONC=5.

The non-cross-validated correlation coefficient (r^2) for developed model was 0.947 and SEE=0.350. Higher value of ANOVA test (162.4) implies that model is robust and predictive. Statistical results of both the models were given in Table 2. Graph plot of predicted versus actual activities for both CoMFA and Topomer

Table 2. Statistical summary of CoMFA and Topomer CoMFA models

	CoMFA	Topomer CoMFA
q^2	0.593	0.819
ONC	6	5
SDEP	0.973	0.640
r^2	0.939	0.947
SEE	0.376	0.350
ANOVA	113.0	162.4

q^2-LOO cross-validated correlation coefficient, ONC-optimum number of components, SDEP-standard error of prediction, r^2-non-cross-validated correlation coefficient, SEE-standard error of estimate, ANOVA-ANOVA test value.
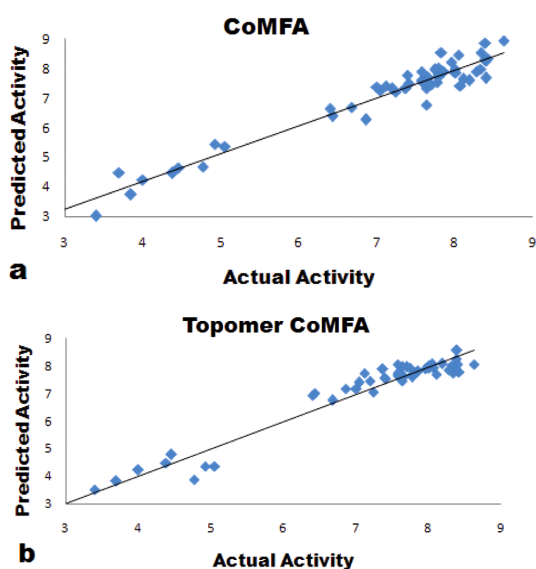
Fig. 4. Graph plot of predicted versus actual activities of all the molecules in dataset for (a) CoMFA and (b) Topomer CoMFA model.

CoMFA models was given in Fig. 4. Actual and predicted activities along with residual values for CoMFA and Topomer CoMFA models were given in Table 3.

3.3. Contour Map Analysis

Contour maps shows spatial requirement of steric and electrostatics field for enhancing the inhibitory potency. Steric field is denoted by green and yellow contour maps. Green contour indicates that steric bulk is favorable for increasing inhibitory potency which is corresponds to increase in Lennard-Jones potential. Whereas, yellow contour denotes that decrease in Lennard-Jones

Table 3. Actual and predicted activities for CoMFA and Topomer CoMFA models along with residual values

S. No.	pIC$_{50}$	CoMFA		Topomer CoMFA	
		Predicted	Residual	Predicted	Residual
1	3.64	4.48	0.84	3.82	0.18
2	3.40	3.02	-0.38	3.52	0.12
3	3.85	3.74	-0.11	2.96	-0.89
4	4.38	4.46	0.08	4.49	0.11
5	4.46	4.64	0.18	4.77	0.31
6	4.00	4.25	0.25	4.22	0.22
7	7.37	7.32	-0.05	7.87	0.50
8	7.64	6.77	-0.87	7.45	-0.19
9	8.38	8.29	-0.09	8.25	-0.13
10	8.40	7.67	-0.73	8.03	-0.37
11	8.34	8.52	0.18	7.73	-0.61
12	6.85	6.26	-0.59	7.18	0.33
13	7.66	7.67	0.01	7.59	-0.07
14	6.68	6.69	0.01	6.75	0.07
15	4.77	4.67	-0.11	3.87	-0.90
16	5.05	5.35	0.30	4.35	-0.70
17	4.92	5.44	0.52	4.37	-0.55
18	7.04	7.25	0.21	7.39	0.35
19	8.07	7.41	-0.66	7.93	-0.14
20	7.64	7.32	-0.32	7.95	0.31
21	7.24	7.20	-0.04	7.06	-0.18
22	7.57	7.61	0.04	8.05	0.48
23	7.12	7.42	0.30	7.72	0.60
24	7.57	7.55	-0.02	7.63	0.06
25	8.19	7.59	-0.61	8.07	-0.12
26	7.70	7.45	-0.25	7.95	0.25
27	8.01	7.85	-0.16	8.00	-0.01
28	8.33	7.96	-0.37	8.00	-0.33
29	8.39	8.84	0.45	8.55	0.16
30	7.82	8.52	0.70	7.77	-0.05
31	7.39	7.78	0.39	7.56	0.17
32	8.05	8.44	0.39	8.09	0.04
33	7.77	7.53	-0.24	7.58	-0.19
34	8.00	7.98	-0.02	7.91	-0.09
35	8.11	7.63	-0.48	7.69	-0.42
36	6.43	6.39	-0.04	7.00	0.57
37	7.74	7.95	0.21	7.93	0.19
38	6.40	6.64	0.24	6.93	0.53
39	7.80	8.00	0.20	7.68	-0.12
40	7.19	7.31	0.11	7.44	0.25
41	7.41	7.47	0.06	7.54	0.13
42	8.28	7.89	-0.39	7.84	-0.44
43	8.40	8.25	-0.15	7.79	-0.61
44	7.96	8.20	0.24	7.89	-0.07
45	7.00	7.38	0.38	7.16	0.16
46	7.80	7.71	-0.09	7.66	-0.14
47	7.62	7.55	-0.07	7.67	0.05
48	8.42	8.33	-0.09	7.76	-0.66
49	7.85	7.89	0.04	7.79	-0.06
50	7.57	7.89	0.32	7.71	0.14
51	8.62	8.94	0.32	8.05	-0.57

potential resulted in loss of inhibitory activity. Electrostatic contour maps are represented by red and blue contour. Electrostatic red contour indicates that region where increase in Columbic potential leads to increase in activity by electronegative group.

Whereas, electrostatic blue color designate that increase in Columbic potential by electropositive group favored for inhibitory potency.

A CoMFA contour map for steric and electrostatic fields for template molecule (51) is shown in Fig. 5. It shows that molecule is surrounded with the favorable as well as unfavorable contours. On the right side of molecule, we can see 2,5-diethoxyphenyl substituent is surrounded by favorable and unfavorable contours. A small yellow contour near 2-ethoxy group indicated that this position is unfavorable for sterically bulky group, and increase in bulk at this position may decrease in activity. The big green contour in vicinity of 4th and 5th position of phenyl ring indicated that this position is favorable for sterically bulky groups and substitution of bulky group might increase bioactivity of molecules. However, blue and red contour also observed at same position, which indicates that this position is favorable for electropositive and electronegative substituents.

On left side of molecule i.e. 3,4-dihydroxyphenyl group is surrounded by sterically favorable green and unfavorable yellow contour. It indicates that meta and para position of phenyl ring should be substituted with sterically smaller bulkier group to enhance biological activity. Electrostatic red contour near 'O' of 3,4-dihydroxy group indicates that for higher bioactivity of molecules electronegative group at particular position is important. Electropositive blue contour represents that

the group like methoxy is favorable for retaining activity.

Topomer CoMFA contour maps for R1 and R2 fragments are shown in Figure 6. Blue arrow indicates the attachment point to the common substructure. Contour map showed that R1 fragment (Fig. 6a) of template molecule was surrounded by big red and blue contour near meta and para substituents. It indicated that electronegative nature of 'O' is favorable for inhibitory activity and electropositive nature of methyl group is also required for higher bioactivity. This result is in line with the CoMFA result. A small yellow contour observed beneath the meta position indicates that substituents penetrating at this direction are unfavorable for activity.

Contour map for R2 fragment is shown in Figure 6b. Steric contour revealed that the 2-ethoxy group might interact sterically and substituents with more bulkier nature are unfavorable at this position for improved potency. However, 5-ethoxy group was surrounded by the sterically favored green contour and indicated that bulky substitution are most welcomed at this position, which is quite similar to CoMFA contour. Another big green contour was observed in vicinity to 3rd and 4th position of phenyl ring indicated that bulkier substitution are favored at this region for improved potency, which is quite evident through R2 fragments alignment (Fig. 3b). Electrostatics red contour indicated that molecule needs more requirements of electronegative groups for inhibitory potency, which is quite evident through big red contours around ortho, meta and para
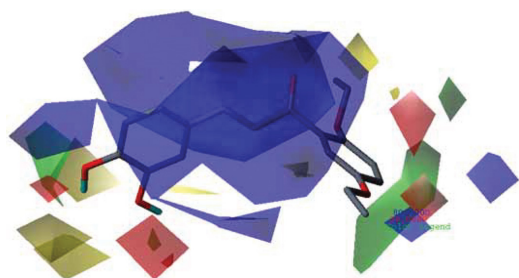

Fig. 5. GSteric and electrostatic contour map for CoMFA model, highly active molecule was displayed in background. Steric favor/disfavor denoted by green/yellow color whereas, electrostatic red indicates favorable for electronegative group and blue color denotes favorable for electropositive group.
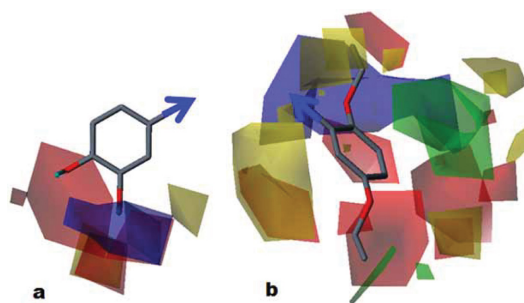

Fig. 6. Topomer CoMFA contour maps for fragments. (a) Contour map for R1 fragment and (b) contour map for R2 fragment. Steric favor/disfavor denoted by green/yellow color whereas, electrostatic red indicates favorable for electronegative group and blue color denotes favorable for electropositive group.

positions. Here, sizes of red contours are bigger than the CoMFA contour sizes. It is clear indication of more requirements of electronegative property of substituents for higher inhibitory activity.

4. Discussion

In this study, we developed good predictive CoMFA and Topomer CoMFA models in terms q^2, r^2 and Q^2 for 5-Lipoxygenase inhibitors. Our developed models showed Topomer CoMFA is superior over the CoMFA. In CoMFA there could be many sources of error, such as bioactive conformation determination, alignment of molecules, which would remarkably changes CoMFA result. But, in Topomer CoMFA both these problems were addressed by completely objective and universal methodology for generating a structural alignment, both a conformation and its orientation in a Cartesian space[15]. This might be the reason why Topomer CoMFA results are better than CoMFA. There could be some chances of ignoring specific receptor requirement by this method, which in turn results in degraded QSAR model.

As we can see some time CoMFA alignment introduces more noise than that of the signal into input data. In our study, molecular alignment used for CoMFA study was shown in Fig. 2. From the aligned molecules, we can see that the variable parts are oriented diversely in 3D space and could be acted as a potential source of noise introduction in QSAR model. In Topomer CoMFA, this supposition could be conveniently evaluated, because there already exists an objective and universal "Topomer" methodology for generating an alignment of a structural fragment[17]. In case of Topomer CoMFA, alignment of all the R1 and R2 fragments are shown in Fig. 3a, b. It indicated that all the aligned R1 and R2 fragments oriented in same 3D plane, with little difference in substituents. This is why Topomer CoMFA gaves higher statistical results than the CoMFA model.

5. Conclusions

We developed predictive CoMFA and Topomer CoMFA models in terms of q^2, r^2 and Q^2 for 5-Lipoxygenase inhibitors. Our generated models show that Topomer CoMFA has better predictive ability than the

CoMFA. The differences in statistical results aroused from the determination of bioactive conformation and molecular alignment. So, while performing 3D-QSAR, one may consider these issues seriously to get reliable and predictive QSAR model.

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