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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

3D-QSAR CoMFA and CoMSIA studies on a set of diverse α_{1a}-adrenergic receptor antagonists

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Abstract The α-adrenergic receptors (α-ARs) modulate a number of intracellular processes and among these α_{1a}-adrenergic receptors play an important role in the regulation of physiological processes related to cardiovascular system. In view of its therapeutic potential, comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) studies were performed on a set of diverse α-AR antagonists to understand the structural factors affecting their antagonistic activity where both CoMFA ($q^2_{train} = 0.709$, $r^2_{train} = 0.962$, and $r^2_{predictive} = 0.629$) and CoMSIA ($q^2_{train} = 0.648$, $r^2_{train} = 0.949$, and $r^2_{predictive} = 0.656$) models gave statistical significant results. The generated CoMFA and CoMSIA models suggest that steric, electrostatic and hydrophobic interactions play an important role in describing the variation in antagonistic activity. Therefore, the models may be useful in the identification and optimization of novel scaffolds with potent α_{1a}-adrenergic receptor antagonistic activity.

Keywords Adrenergic receptors · 3D-QSAR · CoMFA · CoMSIA · Drug design

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Introduction

The α-adrenergic receptors (α-ARs) play a pivotal role in the regulation of a variety of physiological processes, particularly within the cardiovascular system and are divided into two main subtypes namely α_1- and α_2-ARs (Kulig *et al.*, 2009). The α_1-adrenergic receptors are widely distributed throughout the body and mediate number of physiological functions. The α_1-ARs are mainly present in blood vessels (postsynaptic), smooth muscle (postsynaptic), heart (postsynaptic), eyes (postsynaptic), liver (postsynaptic), CNS (postsynaptic), sympathetic neurons (presynaptic) (Jain *et al.*, 2008). In addition to blood pressure reduction, α_1-ARs antagonists also show beneficiary effect on plasma lipoproteins. Recent study revealed that activation of α_{1a}-ARs may be responsible for ischemia-induced cardiac arrhythmia (MacDougall and Griffith, 2006). Therefore, α_{1A}-ARs antagonists may be useful for the treatment of ischemia-induced cardiac arrhythmia.

There are relatively few publications reporting the application of QSAR analysis to α_1-AR species (Debnath *et al.*, 2003; Fumagalli *et al.*, 2005; Pallavicini *et al.*, 2006; Shakya *et al.*, 2004; Nowaczyk *et al.*, 2009). A general α_1-ARs pharmacophore developed by Barbaro *et al.* (2001) was based on pyridazinone derivatives (Fang *et al.*, 2003) while Li *et al.* (2005) developed an α_{1a} pharmacophore based on a diverse class of compounds. Recently, selective pharmacophore for α_1-ARs subtype was developed by MacDougall and Griffith (2006) while α_{1d}-ARs subtype specific pharmacophore was developed by Romeo *et al.* (2003). A CoMFA study on hexahydro and octahydropyrido[1,2-c]pyrimidine derivatives as α_{1a}-AR antagonists has been reported (Maciejewska *et al.*, 2006) while a self-organizing molecular field analysis (SOMFA) method to provide insight for the development

of α_1-adrenoceptor antagonists has been carried out by Li and Xia (2007)).

Since the exact crystal structure of α_{1a}-adrenoreceptor is unknown and a little attention has been given to the QSAR studies using diverse classes of adrenergic antagonists, it appeared of interest to develop a quantitative 3D-QSAR model using the diverse classes of α_{1a}-adrenoreceptor antagonists to find out the essential structural requirements for their antagonistic activity.

Materials and methods

The 3D-QSAR studies have been performed on a set of chemically diverse molecules belonging to 1,4-benzodioxane, 1,3-dioxolane, substituted piperazine, spiroethylphenylpiperazine, imido derivatives, non-imidospiro derivatives, spiroalkyl 2,5-dichlorophenylpiperazine and prazosin-related compounds reported in the literature (Quaglia *et al.*, 1999, 2002, 2005, 2008; Brasili *et al.*, 2003; Rosini *et al.*, 2003; Leonardi *et al.*, 2004; Franchini *et al.*, 2009; Sorbi *et al.*, 2009). The α_1-AR antagonistic activity/binding affinity data of these compounds are expressed as K_i value in the nanomolar (nM) range. The selected compounds with diverse structural features cover a wide range of biological activity spanning over more than 4 log units (0.05–2,684 nM). A correction factor for 20% lesser value of the activity data has been applied for the compounds reported in the paper (Leonardi *et al.*, 2004) since the reference compound BMY 7378 showed 20% higher activity value than reported in other papers considered in the QSAR study. The K_i values were converted into negative logarithm of K_i (pK_i) for the use in the QSAR studies.

Rational division of training and test sets

The 108 compounds in the dataset were distributed into five clusters according to their biological activity data and the training set compounds were picked up from generated clusters. It has been suggested that the generated models should be tested on a sufficiently large test set to establish a reliable QSAR model (Prathipati and Saxena, 2003); therefore, the molecules were rationally divided into training set of 45 (Fig. 1; Tables 1–6) and test set of 63 compounds, respectively, in such a way that they cover almost entire range of biological activity.

Computational approach and molecular alignment

Molecular modeling studies viz. CoMFA and CoMSIA were done on a Silicon Graphics Octane R12000 workstation using SYBYL6.9 molecular modeling software (Tripos, St. Louis, MO). All compounds were built using the most active compound **31** as a template in the ISIS Draw 2.5 and thereafter imported in sybyl 6.9. The partial charges for all the compounds were calculated using Gasteiger–Huckel method and were optimized for their geometry using Tripos force field with a distance-dependent dielectric function and energy convergence criterion of 0.001 kcal/mol Å using 1,000 iterations and standard SYBYL settings. Alignment is a critical step in the CoMFA studies and among the three more commonly suggested alignments in the literature viz. maximum common structure (MCS)-based alignment, rigid body field fit alignment and multifit alignment; the MCS-based alignment was used in the present study as it had given the best results similar to our earlier studies (Roy *et al.*, 2008). The core (shown in bold) of the most active compound **31** (Fig. 2) was used for alignment (Fig. 3).

CoMFA studies

The steric (Lennard–Jonnes potentials) and electrostatic fields (Coulombic potentials) for CoMFA were calculated for the aligned molecules kept in 3D cubic lattice with a grid spacing of 2.0 Å in *x*, *y* and *z* directions using Tripos module in SYBYL. For each alignment a sp^3 carbon atom having a charge of +1 and a radius of 1.52 Å was used as a probe to calculate various steric and electrostatic fields. The influence of different parameter settings on CoMFA, various steric and electrostatic cutoffs and grid spacing was also tried as suggested by Crammer *et al.* (1988).

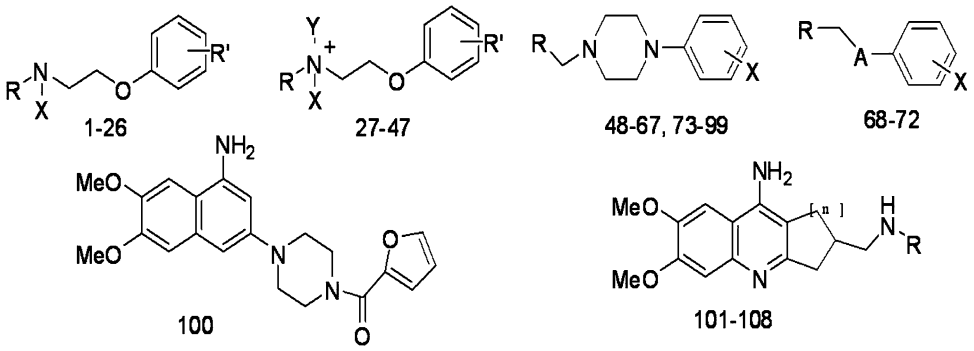


Fig. 1 Common structure of the α_{1a}-AR antagonists used in the 3D-QSAR study

Table 1 Structures of the training set molecules (1 to 47) used in the 3D QSAR study

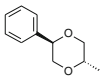
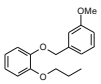
[a]C.N.	R	X	Y	R'	*Ki* (nM)	p*Ki*	Predicted p*Ki* (CoMFA)	Predicted p*Ki* (CoMSIA)
1		H	-	H	537.03	6.27	6.35	6.583
4		H	-	$2,6(OCH_3)_2$	512.86	6.29	6.616	6.533
5		H	-	H	407.38	6.39	6.143	6.194
8		H	-	$2,6(OCH_3)_2$	467.74	6.33	6.653	6.397
9		H	-	H	223.87	6.65	6.487	6.588
10		H	-	$2\text{-}OCH_3$	74.13	7.13	6.926	6.501
12		H	-	H	169.82	6.77	6.339	6.418
14		H	-	$2,6(OCH_3)_2$	338.84	6.47	6.651	6.682
16		H	-	$2,6(OCH_3)_2$	0.251	9.6	9.142	9.243
20		H	-	$2,6(OCH_3)_2$	1.99	8.7	9.033	9.108
22		H	-	$2,6(OCH_3)_2$	0.316	9.5	9.37	9.539
25		H	-	$2,6(OCH_3)_2$	1.99	8.7	8.523	8.813
29		H	CH_3	H	33.88	6.08	6.066	6.314
30		CH_3	CH_3	H	24.54	7.47	7.459	7.326
31		H	-	$2,6(OCH_3)_2$	0.05	10.3	10.047	9.966
32		H	-	$2,6(OCH_3)_2$	2.34	8.63	8.921	8.922

Table 1 continued

[a]C.N.	R	X	Y	R'	*Ki* (nM)	p*Ki*	Predicted p*Ki* (CoMFA)	Predicted p*Ki* (CoMSIA)
33		H	-	$2,6(OCH_3)_2$	0.08	10.05	10.138	10.198
37		H	-	$2,6(OCH_3)_2$	0.426	9.37	9.232	9.49
40		H	-	$2,6(OCH_3)_2$	8.7	8.06	8.176	7.759

a C.N.= Compound name

CoMSIA studies

The CoMSIA technique is based on the molecular similarity indices with the same lattice box used for the CoMFA calculations (Klebe *et al.*, 1994). It is considered superior to CoMFA technique in certain aspects such as the results remain unaffected to both, region shifts as well as small shifts within the alignments, it does not require steric cutoffs and more intuitively interpretable contour maps. So, in the present study, standard settings of CoMSIA (probe with charge +1, radius 1 Å and hydrophobicity +1, hydrogen-bond donating +1, hydrogen-bond accepting +1, attenuation factor of 0.3 and grid spacing 2 Å) were used to calculate five different fields viz steric, electrostatic, hydrophobic, acceptor and donor.

Partial least square analysis

PLS is used to correlate α_{1a}-adrenoreceptor antagonistic activity with the CoMFA and CoMSIA values containing magnitude of steric, electrostatic and hydrophobic potentials. The leave one out (LOO) cross-validation procedure by SAMPLS method was used to assess the models as implied in SYBYL (Bush and Nachbar, 1993). In addition to LOO cross-validation, a group cross-validation using 30 groups, repeating the procedure 30 times was also carried out. The mean of 30 readings is given as $r^2_{cv(mean)}$. The full PLS analysis was carried out with a column filtering of 2.0 kcal/mol to speed up the calculation and reduce the noise.

Results and discussion

CoMFA and CoMSIA techniques were used to derive 3D-QSAR models on a set of 108 chemically diverse α_{1a}-adrenoreceptor antagonists. The lowest energy conformation of all the compounds was considered for database alignment. Various 3D-QSAR models were generated and the best one was selected based on the statistically significant parameters obtained. The predictive power of the generated 3D-QSAR models was assessed by predicting biological activities of the test set molecules. The results of the CoMFA, CoMSIA studies have been summarized in Table 7.

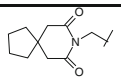
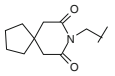
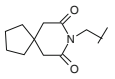
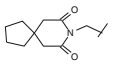
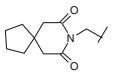
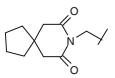
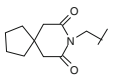
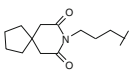
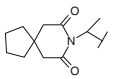
CoMFA analysis

In CoMFA and CoMSIA studies though a q^2 value of 0.3 is considered statistically significant (Bohm *et al.*, 1999) but a $q^2 > 0.5$ can be considered statistically more significant. The Tripos standard (TS) field showed the highest q^2 of 0.709 using five principal components with a high conventional r^2 value of 0.962 and low standard error of estimate (0.247) indicating it to be a statistically highly significant model. To further assess the robustness of this model, bootstrapping analysis (30 runs) was performed to give r^2_{bs} of 0.979 ($SD_{bs} = 0.009$) thus establishing the strength of the model. In addition to LOO, a group cross-validation was further done to assess the internal predictive ability of the model. The cross-validation for 30 times was performed with 30 groups and the mean r^2_{CV} of 0.714 (TS) revealed that the model has good internal predictability and the results has no chance correlation (Table 3). A test set of 63 molecules was used to evaluate the predictivity of the generated model and a predictive r^2 of 0.629 showed good predictive ability of the generated model (Fig. 4a). The predictive pK_i value of the training as well as test set molecules based on the CoMFA model has been included in Tables 1–6.

CoMSIA analysis

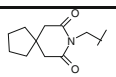
Various CoMSIA models were generated considering all possible combinations of field descriptors. In this study, steric (S), electrostatic (E) and hydrophobic (H) field

Table 2 Structures of the training set molecules (48 to 67) used in the 3D QSAR study

[a]C.N.	R	X	*Ki* (nM)	p*Ki*	Predicted p*Ki* (CoMFA)	Predicted p*Ki* (CoMSIA)
48		H	2684	5.57	6.123	6.23
50		2-OCH(CH3)$_2$	2.832	8.55	8.861	8.56
52		2-CN	170.88	6.77	6.635	6.415
57		2-Cl, 5-CH$_3$	100.44	7	6.64	6.456
58		2,5-(CH$_3$)$_2$	95.424	7.02	7.512	7.473
62		2-CN, 5-Cl	402.56	6.39	6.694	6.528
63		2-Cl, 5-F	86.16	7.06	7.147	7.228
66		2,5-dichloro	1.448	8.84	9.019	8.793
67		2,5-dichloro	149.344	6.82	6.789	6.887

a C.N.= Compound name

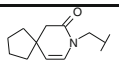
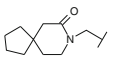
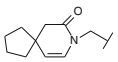
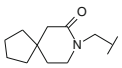
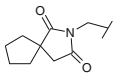
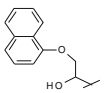
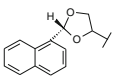
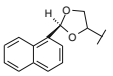
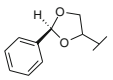
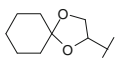
Table 3 Structures of the training set molecules (70) used in the 3D QSAR study

[a]C.N.	R	A	X	*Ki* (nM)	p*Ki*	Predicted p*Ki* (CoMFA)	Predicted p*Ki* (CoMSIA)
70			2-Cl	236.08	6.63	6.633	6.461

a C.N.= Compound name

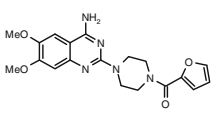
descriptors were found to have an important role in the modulation of biological activity. The model having steric, electrostatic and hydrophobic fields gave the highest q^2 of 0.648 at five components and a conventional non-cross-validated r^2 of 0.949 among all the generated CoMSIA models (Table 4). To further assess the statistical ability and robustness of the model, bootstrapping analysis (30 runs) was performed where r^2_{bs} of 0.966 with low standard deviation of 0.012 were obtained thus showing the robustness of the model. Similar to CoMFA, internal predictive ability of the model was accessed by group cross-validation performed with 30 groups. The mean r^2_{cv} value of 0.649 revealed that the model has high internal predictivity. Further predictive r^2 of 0.656 for the 63 test set

Table 4 Structures of the training set molecules (73 to 99) used in the 3D QSAR study

[a]C.N.	R	X	*Ki* (nM)	p*Ki*	Predicted p*Ki* (CoMFA)	Predicted p*Ki* (CoMSIA)
82		2-Cl	43.144	7.36	7.302	7.276
83		2-Cl	70.04	7.15	7.18	6.897
84		2-OMe	23.4	7.63	7.659	7.896
87		2,5-dichloro	33.928	7.47	7.462	7.348
88		2,5-dichloro	54.608	7.26	7.164	7.207
89		2-OMe	5.88	8.23	8.221	8.33
90		2-OMe	36.3	7.44	7.601	7.506
91		2-OMe	7.94	8.1	7.817	7.576
94		2-OMe	28.84	7.54	7.538	7.263
97		2-OMe	91.2	7.04	7.164	6.98

a C.N.= Compound name

Table 5 Structures of the training set molecules (100) used in the 3D QSAR study

[a]C.N.	Structure	*Ki* (nM)	p*Ki*	Predicted (CoMFA)	p*Ki*	Predicted (CoMSIA)	p*Ki*
100		0.588	9.23	8.972		9.215	

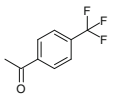
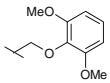
a C.N.= Compound name

compounds showed the usefulness of the model (Fig. 4b). The Predictive pK_i values of the training as well as test set molecules based on the CoMSIA model are included in Tables 1, 2, 3, 4, 5, 6.

CoMFA and CoMSIA contour maps

The CoMFA and CoMSIA contour map analyses provided good insight into the SAR by providing a visual display of

Table 6 Structures of the training set molecules (101 to 108) used in the 3D QSAR study

[a]C.N.	R	n	*Ki* (nM)	p*Ki*	Predicted p*Ki* (CoMFA)	Predicted p*Ki* (CoMSIA)
101		2	95.49	7.02	6.811	6.925
102		1	158.49	6.8	6.849	6.884
105		2	85.11	7.07	6.937	6.976
107		2	2570.4	5.59	5.469	5.936
108		2	1698.2	5.77	5.502	5.969

a C.N.= Compound name

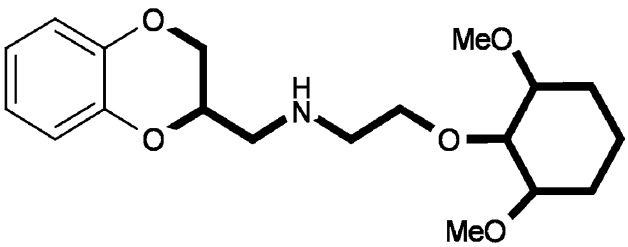


Fig. 2 The core of the most active compound 31 used for the alignment (shown in *bold*)

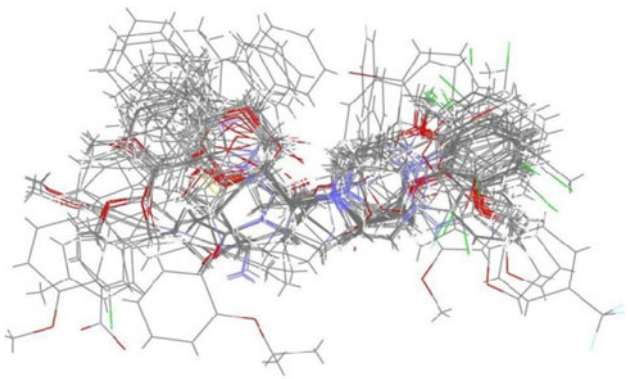


Fig. 3 The overall alignment of the molecules used in the 3D-QSAR study

favored and disfavored positions. The steric and electrostatic features of the final CoMFA and the steric, electrostatic and hydrophobic features of CoMSIA models are displayed as contour maps of the PLS regression coefficients at each CoMFA/CoMSIA region grid point (Fig. 5). They are generated using the field type SD × coefficient to show the contribution for favorable and unfavorable interactions with the receptor in terms of steric (80% green,

Table 7 PLS statistics of CoMFA (TS) and CoMSIA (SEH) models

Parameters	CoMFA (TS)	CoMSIA (SEH)
q^2	0.709	0.648
PRESS	0.687	0.756
r^2	0.962	0.949
SEE	0.247	0.287
F	199.628	146.269
N	5	5
Fractions		
S	0.515	0.211
E	0.485	0.459
H	–	0.330
r^2_{bs} (30 runs)	0.979	0.966
SD_{bs}	0.009	0.009
$r^2_{CV\ (mean)}$ (30 runs)	0.714	0.649
r^2_{pred}	0.629	0.656

q^2 leave one out cross-validation correlation coefficient, *PRESS* LOO cross-validated standard error, r^2 conventional correlation, *SEE* standard error of estimate, *F* degree of freedom, *N* optimal number of component, r^2_{bs} bootstrapping correlation, SD_{bs} bootstrapping standard deviation, $r^2_{CV(mean)}$ group cross-validation, *TS* Tripos standard, *SEH* Steric, electrostatic and hydrophobic

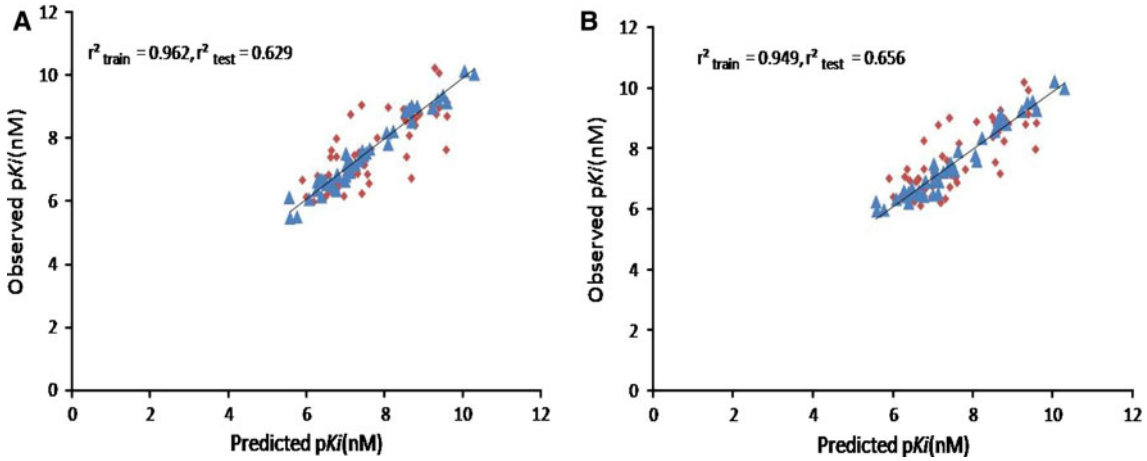


Fig. 4 Correlation graph between observed and predicted activities of training set molecules (triangular points) and test set molecules (square points): **a** CoMFA and **b** CoMSIA

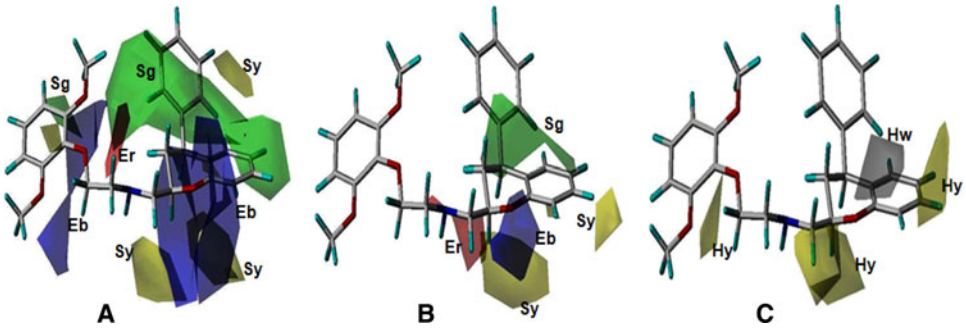


Fig. 5 **a** Steric and electrostatic contours of CoMFA **b** Steric and electrostatic contours of CoMSIA and **c** hydrophobic contours of CoMSIA displayed around the most active compound **31**. [Sg = Steric green; Sy = Steric yellow; Eb = Electrostatic blue; Er = Electrostatic red; Hw = Hydrophobic white; Hy = Hydrophobic yellow] (color figure online)

20% yellow), electrostatic (80% blue and 20% red), hydrophobic (80% yellow, 20% white), donor (80% cyan, 20% purple) and acceptor (80% magenta, 20% red).

The surfaces near the template molecule **31** indicated the regions where the increase (green region) or decrease (yellow region) in steric bulk as well as increase (blue region) or decrease (red region) in electrostatic field would be important for the improvement of binding affinity. The yellow polyhydra in the hydrophobic contours show the region where an increase in hydrophobicity is favorable for α_{1a}-adrenoreceptor antagonistic activity while white polyhydra denote the region where hydrophobicity is unfavorable for activity. The advantage of CoMSIA contour maps over CoMFA is that they are easier to interpret.

The CoMFA contours mainly showed four types of regions (Fig. 5a). The first and largest region is shown by green polyhedra (near the phenylchroman group) signified the importance of bulky steric group at this region which may be important for hydrophobic interactions with the receptor. The second one is blue polyhedra near the chroman moiety and phenoxy oxygen atom of the molecule **31** showed that there could be possibility of H-bond interactions at the binding site involving the oxygen atom of this molecule. The third yellow and fourth red polyhedral regions described the undesired steric group. Fourth red polyhedral region showed that the addition of negatively charged group at this region may increase in adrenergic antagonistic activity. The steric and electrostatic CoMSIA contours are also in well agreement with the CoMFA contours as shown in Fig. 5b. The contour plot of hydrophobic field as shown by white polyhydra (Fig. 5c) also suggested the importance of hydrophobic interaction near the phenylchroman group of the most active molecule **31** of the dataset.

Conclusion

The CoMFA and CoMSIA method has been applied successfully to rationalize the structurally diverse α_{1a}-ARs

antagonists covering a wide range of biological activity and structural features in terms of their steric, electrostatic and hydrophobic properties. The developed models showed good statistical significance in internal (q^2, group cross-validation and bootstrapping) validation and performed very well in predicting the biological activity (pK_i) of the compounds in the test set. In view of the above, it may be concluded that the developed CoMFA and CoMSIA model can further be applied for the identification and optimization of novel scaffolds with potent α_{1a}-adrenergic receptor antagonistic activity.

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