CODEN IEJMAT *Internet Electronic Journal of Molecular Design* **2005**, *4*, 603–612 ISSN 1538–6414
BioChem Press http://www.biochempress.com

Inter*net* Electronic Journal of Molecular Design

September 2005, Volume 4, Number 9, Pages 603–612

Editor: Ovidiu Ivanciuc

Special issue dedicated to Professor Danail Bonchev on the occasion of the 65th birthday

Importance of Alignment in Developing 3–D QSAR Models of 1,5–Diaryl Pyrazoles for the Prediction of COX–2 Inhibitory Activity

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Received: November 22, 2004; Revised: April 7, 2005; Accepted: May 14, 2005; Published: September 30, 2005

Citation of the article:
R. Thilagavathi and A. K. Chakraborti, Importance of Alignment in Developing 3–D QSAR Models of 1,5–Diaryl Pyrazoles for the Prediction of COX–2 Inhibitory Activity, *Internet Electron. J. Mol. Des.* **2005**, *4*, 603–612, http://www.biochempress.com.

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Importance of Alignment in Developing 3–D QSAR Models of 1,5–Diaryl Pyrazoles for the Prediction of COX–2 Inhibitory Activity

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Received: November 22, 2004; Revised: April 7, 2005; Accepted: May 14, 2005; Published: September 30, 2005

Internet Electron. J. Mol. Des. **2005**, *4* (9), 603–612

Abstract

Motivation. A set of thirty–four 1,5–diaryl pyrazoles having selective COX–2 inhibitory activity were analyzed using Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA). One of the important steps in CoMFA is the derivation of active conformation and alignment of molecules. The success of CoMFA depends on the relative positioning of the ligands in the fixed lattice, prior to generation of the 3–D descriptors. Thus, we performed two different alignments such as as_is database alignment (the as_is option in the database alignment is used to align molecules to the template without changing the orientation**)** and the alignment based on FlexX docking. The first method is based solely on the selection of ligand atoms and the second method involves protein based docking and use of the docked conformations.

Method. CoMFA is one of the popular 3–D QSAR methods that relate the biological activity of a series of molecules with steric and electrostatic fields sampled at grid points defining a large 3–D box around the molecule. CoMSIA is a recently introduced 3–D QSAR method that includes additional parameters such as hydrophobicity, hydrogen bond donor and hydrogen bond acceptor properties along with steric and electrostatic fields. FlexX is one of the fast flexible docking methods that uses an incremental construction algorithm to place ligands into an active site. The scoring function (empirical binding free energy) of the FlexX is used to estimate the free binding energy of the protein–ligand complex.

Results. Compared to the alignment method involving the docked conformations, the atom–based alignment produced better CoMFA and CoMSIA results. Under the atom–based alignment, CoMFA produced a model (r^2_{cv} = 0.693, r^2_{conv} = 0.989, SEE= 0.196) better than that of CoMSIA (r^2_{cv} = 0.370, r^2_{conv} = 0.914, SEE= 0.519). The contour maps produced by CoMFA model could rationalize the COX–2 inhibitory activity profile of many compounds used in the present study.

Conclusions. The importance of alignment of molecules in deriving the 3–D QSAR model was revealed from a comparative study of atom–based alignment and alignment method involving the docked conformations. The resulted contour maps from CoMFA could be used to understand the important structural features responsible for COX–2 inhibitory activities of 1,5–diaryl pyrazoles.

Keywords. 3–D QSAR; CoMFA; Comparative Molecular Field Analysis; CoMSIA; Comparative Molecular Similarity Indices Analysis; FlexX; cyclooxygenase–2; COX–2; docking; alignment.

Dedicated on the occasion of the 65th birthday to Danail Bonchev. Presented in part at the Internet Electronic Conference of Molecular Design 2004, IECMD 2004.

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Abbreviations and notations

NSAIDs, nonsteroidal anti–inflammatory drugs	Rdf, receptor description file
COX–1, cyclooxygenase–1	3–D QSAR, three–dimensional quantitative structure–activity relationships
COX–2, cyclooxygenase–2	
CoMFA, Comparative Molecular Field Analysis	CoMSIA, Comparative Molecular Similarity Indices Analysis

1 INTRODUCTION

Nonsteroidal anti–inflammatory drugs (NSAIDs) are widely used for the treatment of the symptoms of acute and chronic inflammatory disorders. The majority of currently available NSAIDs inhibit both COX–1 and COX–2 and exhibit selectivity in favor of COX–1 [1]. The discovery and characterization of COX–2 [2,3] suggested that selective inhibition of this enzyme might avoid the side effects of currently available NSAIDs. This hypothesis has generated a great deal of interest in this field and various laboratories are aggressively pursuing this objective.

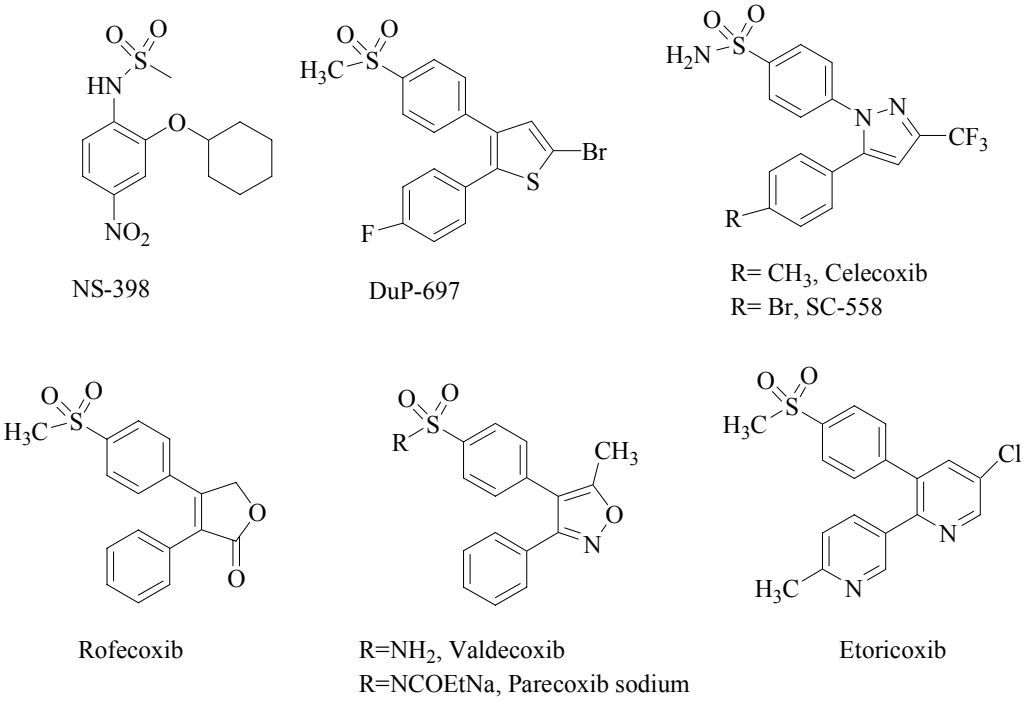


Figure 1. Structures of some selective COX–2 Inhibitors.

The first two lead compounds, DuP–697 [4] and NS–398 [5] (Figure 1), that provided non–ulcerogenic anti–inflammatory activity were reported by DuPont and Taisho, respectively. Successful outcome of the diaryl heterocycles, Celecoxib and Rofecoxib without any significant gastrointestinal injury, (Figure 1) were marketed in 1998 [6,7]. Valdecoxib, Parecoxib sodium (a water soluble prodrug of Valdecoxib) and Etoricoxib (Figure 1) were recently introduced [8,9]. However, Rofecoxib has been recently withdrawn from the market due to the cardiovascular problems [10]. Thus, there is a need for designing new compounds with optimum COX–1/COX–2 selectivity.

Recently we have reported 3–D QSAR and docking studies on selective COX–2 inhibitors [11–14]. The aims of the present work was to use ligand and structure based alignment methods and determine the effect of alignment in deriving the 3–D QSAR model for 1,5–diaryl pyrazole derivatives. This laboratory has been actively pursuing 3–D QSAR studies in determining new chemical entities for desired biological activities [15–17]. For the present study, we used CoMFA [18] and CoMSIA [19] 3–D QSAR methods. CoMFA relates the biological activity of a series of molecules with their steric and electrostatic fields sampled at grid points defining a large 3–D box around the molecule. The graphical representation (isocontour map) of CoMFA correlates the steric and electrostatic properties with the biological activity of the corresponding molecule in a data set. The basic principle of CoMSIA is the same as that of CoMFA, but includes some additional descriptors such as hydrophobicity, hydrogen bond donor and hydrogen bond acceptor.

2 MATERIALS AND METHODS

2.1 Ligand Preparation

All the molecular modeling studies were performed on a Silicon Graphics Octane 2 workstations using Sybyl 6.9 [20]. Thirty–four compounds (Table 1) were selected based on structural diversity [6]. The COX–2 inhibitory activities reported from *in vitro* assay obtained with recombinant human COX–2 enzyme were used for CoMFA studies. The biological activities were converted into the corresponding pIC_{50} values. The most active compound **8** [modeled from the bioactive conformation of SC–558 (1CX2.pdb)] was used as template. Molecules were optimized using MMFF94 method [21] including MMFF94 charges till the gradient convergence 0.05 kcal/mol was reached.

2.2 Alignment Rules

One of the important steps in CoMFA and CoMSIA methods is the determination of active conformation and alignment of molecules. The success of CoMFA and CoMSIA methods entirely depend on the relative positioning of the ligands in the fixed lattice, prior to the generation of 3–D descriptors. We have performed two different alignments such as as_is database alignment using QSAR>>Manage CoMFA>>Alignments... and FlexX method [22] to derive docked conformations. Database method is one of the alignment methods used to align some or all of the molecules in a database with a template molecule also in the database. All the molecules in the selected database that contain the indicated substructure will be aligned with the selected template molecules. The substructure indicates the atoms to be used for alignment and their connectivity. The as_is option in the database alignment is used to align molecules to the template without changing their orientation. For the as_is database method we used atoms of ring A and B. Compound **8** was used as a template and rest of the molecules were aligned to it.

In the second method, to obtain docked conformations, all the molecules were subjected to FlexX docking. The COX–2–SC–558 (1CX2.pdb) complex [23] was used for docking. Amino acid residues within 6.5 Å distance from the inhibitor SC–558 were selected for the preparation of rdf file. All the selected ligands were docked into the active sites of COX–2. The lowest energy conformations obtained from FlexX docking of ligands were used as input files for CoMFA. The charges were calculated using MMFF94 method.

2.3 CoMFA Interaction Energy Fields

The basic assumption of CoMFA is that compounds having similar pharmacophoric pattern will orient and interact with the receptor/enzyme in a similar fashion. To mimic such interactions, a 3–D grid box was put around the molecules taken for the study and CoMFA interaction fields were calculated at each lattice intersection of a regularly spaced grid of 2.0 Å by employing Lennard–Jones and Coulomb potentials. The CoMFA fields, depicting the steric and electrostatic interaction with an sp^3 carbon atom with +1.0 charge as the probe were calculated using Tripos force field. The steric and electrostatic fields were truncated at ± 30.0 kcal/mol and the electrostatic fields were ignored at points with maximal steric interactions.

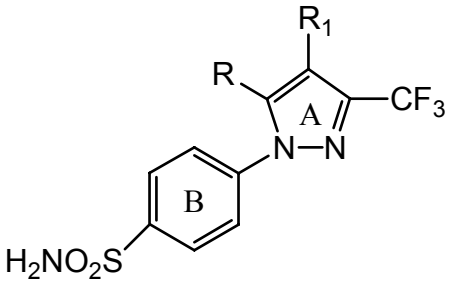
2.4 CoMSIA Interaction Energy Fields

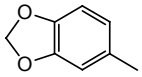
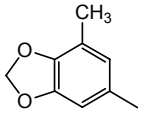
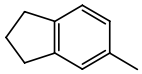
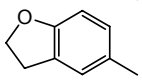
The CoMSIA method is based on molecular similarity indices. Using a common probe atom, similarity indices were calculated for a data set of pre–aligned molecules at regularly spaced grid points. There is a sudden rise in energy when the atoms of the molecules approach the probe atom. Therefore, the cut–off value of >30 kcal/mol is included in CoMFA. This restriction may give some false interaction energy field values, which sometimes lead to error in the predictions. The 'gaussian' type distance dependent functional forms used by CoMSIA method to calculate such properties overcome this problem. Similarity indices were calculated at all grid points inside and outside the molecules and evaluated in a PLS analysis following the usual CoMFA protocol.

2.5 PLS Analysis

The regression analysis of CoMFA field energies was performed using the partial least squares (PLS) algorithm with the leave–one–out (LOO) method adopted for cross–validation. The optimum number of components to be used in conventional analyses was chosen from (*i*) the analysis with the highest cross validated r^2 value, and (*ii*) the model with the smallest standard error of prediction for component models with identical r^2 values. The column filtering value (σ) was set to 2.0 for cross–validated runs. Equal weights were assigned to steric and electrostatic fields. A final analysis was carried out to calculate the conventional r^2 value using the optimum number of components.

Table 1. The structures, actual/predicted inhibitory activities (pIC_{50}) for the training and test set of 1,5–diaryl pyrazoles

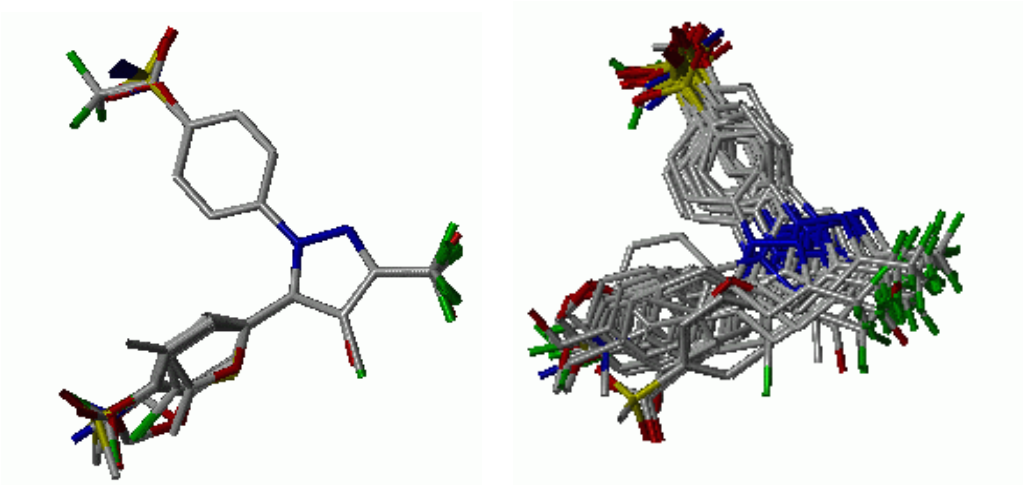


Compound	R	R_1	IC_{50} (μM)	Actual pIC_{50}	Predicted pIC_{50}	Residual
1	4–CH_3–C_6H_4	H	0.040	7.40	6.98	0.42
2	4–CF_3–C_6H_4	H	8.23	5.08	5.35	–0.27
3 [a]	4–OCH_3–C_6H_4	H	0.75	6.12	6.36	–0.24
4	4–SCH_3–C_6H_4	H	0.009	8.04	8.28	–0.24
5	4–Cl–C_6H_4	Cl	0.0053	8.27	8.08	0.19
6	4–COOH–C_6H_4	H	11.2	4.95	5.07	–0.12
7		H	0.024	7.62	7.86	–0.24
8	4–NMe_2	H	0.0047	8.33	8.18	0.15
9	5–bromo–2–thienyl	H	0.012	7.92	7.66	0.26
10 [b]	4–F–C_6H_4	H	100	4.00	3.88	0.12
11	4–Cl–C_6H_4	Me	0.022	7.66	7.83	–0.17
12	C_6H_5	OH	3.58	5.45	5.32	0.13
13	5–chloro–2–thienyl	H	0.026	7.58	7.63	–0.05
14 [c]	C_6H_5	H	100	4.00	3.89	0.11
15 [d]	4–F–C_6H_4	H	100	4.00	3.80	0.20
16	3,4–OMe–C_6H_3	H	0.60	6.22	6.16	0.06
17	4–CH_2OH–C_6H_4	H	93.3	4.03	4.14	–0.11
18	4–OCH_3–C_6H_4	H	0.008	8.10	7.99	0.11
19		H	0.052	7.28	7.31	–0.03
20 [e]	5–methyl–2–furyl	H	3.29	5.48	5.50	–0.02
21	4–NH_2–C_6H_4	H	0.34	6.47	6.54	–0.07
22 [f]	4–F–C_6H_4	H	100	4.00	4.04	–0.04
23 [e]	4–SO_2CH_3	H	100	4.00	3.97	0.03
24 [e]	4–COOH–C_6H_4	H	46.8	4.33	4.37	–0.04
25 [e]	4–CN–C_6H_4	H	29.7	4.53	4.67	–0.14
26	2–NMe_2	H	14.3	4.84	5.56	–0.72
27 [g]	4–F–C_6H_4	H	100	4.00	4.61	–0.61
28	4–Cl C_6H_4	Et	0.028	7.55	8.01	–0.46
29	3–CH_3	H	0.11	6.96	6.42	0.54
30		H	0.031	7.51	7.21	0.30
31		H	0.021	7.68	7.00	0.68
32	2–pyridyl	H	45.6	4.34	6.53	–2.19
33	3–pyridyl	H	45.0	4.35	6.07	–1.72
34	4–pyridyl	H	64.7	4.19	5.17	–0.98

[a] replacement of SO_2NH_2 by OMe; [b] replacement of SO_2NH_2 by $COCF_3$; [c] replacement of SO_2NH_2 by H; [d] replacement of CF_3 by COOH; [e] replacement of CF_3 by CH_2F; [f] replacement of SO_2NH_2 by NO_2; [g] replacement of CF_3 by H.

3 RESULTS AND DISCUSSION

Molecules **1–25** were used to construct the training set and the remaining compounds were considered as test set (Table 1).



(*a*) (*b*)

Figure 2. Alignment of 1,5–diarylpyrazoles: (*a*) database method, (*b*) docked conformations derived by FlexX.

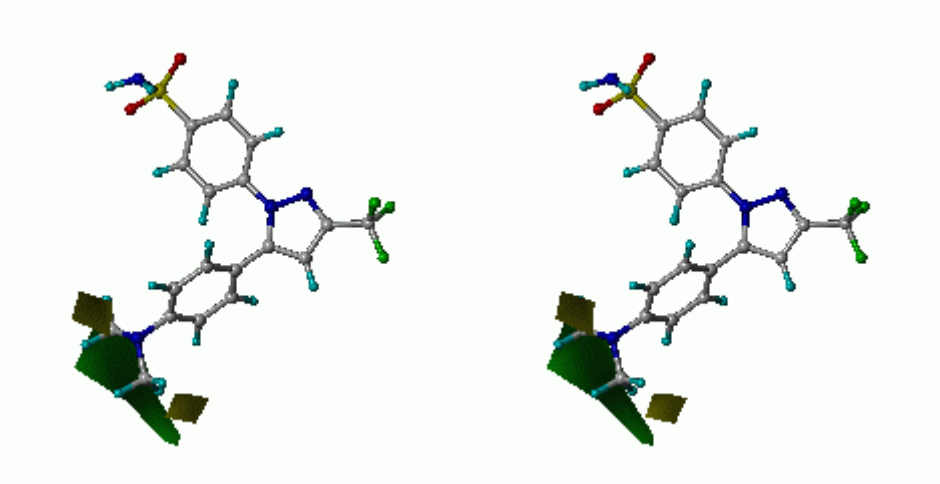


Figure 3. Stereoview of CoMFA steric contour plot (STDEV*COEFF). The most active molecule **8** is displayed in the background for reference.

The database of 1,5–diarylpyrazole analogues was subjected to FlexX docking. Two different alignment methods were used. One is database alignment method (using atoms of ring A and B) and the other FlexX docking method (Figure 2). Molecules **9** and **13** could not be docked into the active site of COX–2 enzyme. The resulted conformations of other molecules were used for further CoMFA and CoMSIA studies. However, the alignment based on FlexX docking method produced poor CoMFA (r^2 = –0.018) and CoMSIA (r^2 = –0.242) results. The atom based alignment method was found to be better than the structure based alignment method. CoMFA with 25 molecules in the

training set produced a cross–validated r^2 of 0.693 with minimum standard error and optimum number of components. This analysis was used for the final non–cross–validated run, giving a good correlation coefficient with a very low standard error of estimate (Table 2). The actual and calculated inhibitory activities and the residual values for both training and test sets are given in Table 1.

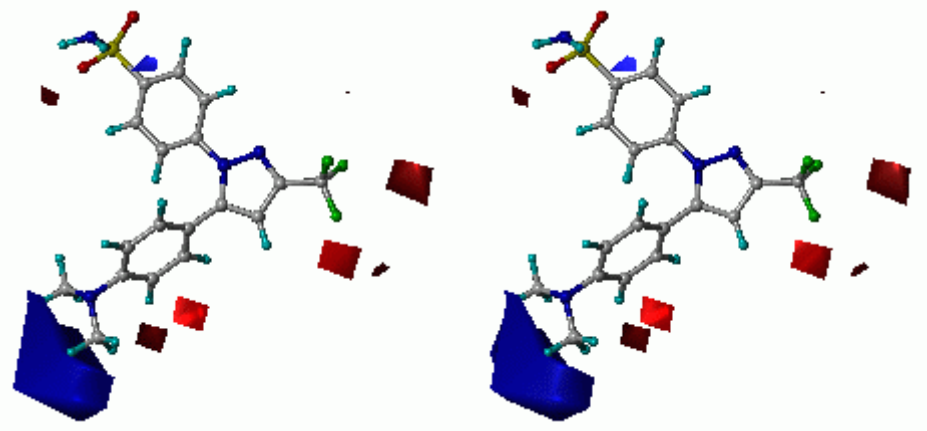


Figure 4. Stereoview of CoMFA electrostatic contour plot (STDEV*COEFF). The most active molecule **8** is displayed in the background for reference.

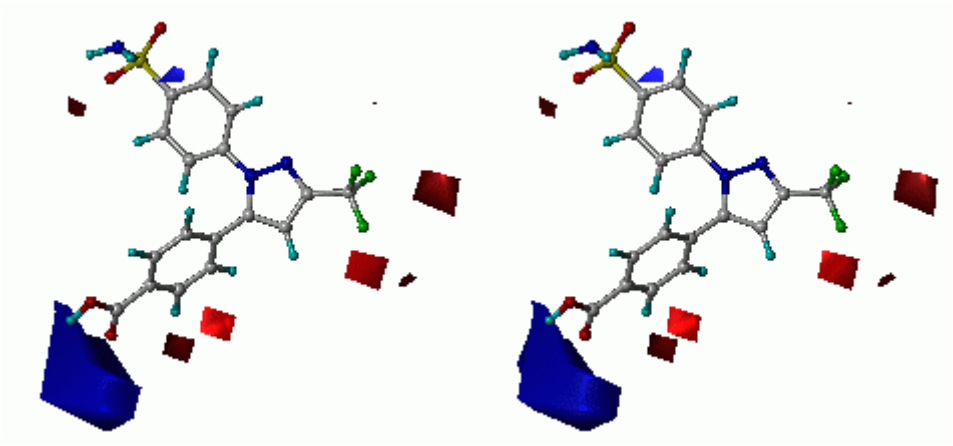


Figure 5. Stereoview of CoMFA electrostatic contour plot (STDEV*COEFF). Molecule **6** is displayed in the background for reference.

The final model demonstrated a good predictive ability by predicting the activities of test set (**26–31**, **34**) molecules (r^2_{pred} = 0.8291) that were not included in the training set. Molecules with 2–pyridyl (**32**) and 3–pyridyl (**33**) moieties were over–predicted by CoMFA method and were considered as outliers.

CoMFA produced a green contour (Figure 3) near the C–4 position of non–sulphonyl ring (represented by the substituent R in the general structural formula) indicating that the presence of a bulky substitution at this position should improve the biological activity. This was supported by the

observations that the molecules **1**, **4**, **5**, **8**, **11**, **18**, and **28** having CH_3, SCH_3, Cl, NMe_2, Cl, OCH_3, and Cl, respectively, at this position possessed better biological activities. Similarly, the higher biological activities of **7**, **19**, **30** and **31** can be explained due to the presence of fused dioxole, dihydropyran or cyclopentene rings having ring residue at C–4 of the phenyl ring. The good biological activity of **9** and **13** is ascribed to the bulkier substituent bromine and chlorine atoms, respectively, at C–5 of the heterocyclic ring. The importance of the presence of a bulky substituent at C–4 of the non–sulfonyl aryl moiety of the pyrazole is further supported by the poor biological activities of **12** and **14** with unsubstituted phenyl ring at the corresponding position of the central pyrazole ring.

Table 2. Summary of Results of CoMFA–CoMSIA QSAR

	CoMFA		COMSIA	
	1	2	1	2
r^2_{cv}	**0.693**	–0.018	0.370	–0.242
NOC	**5**	2	3	1
SEP	**1.032**	1.739	1.402	1.875
r^2_{conv}	**0.989**		0.914	
SEE	**0.196**		0.519	

1 Database alignment; 2 FlexX based alignment, $r^2_{cv} = r^2$ cross–validated, NOC= number of components SEP=standard error of prediction, $r^2_{conv} = r^2$ conventional, SEE = standard error of estimate

Since the 3D–QSAR model did not produce any color contour near the region of C–4 of the central pyrazole ring and near the region occupied by SO_2NH_2 of the aryl substituent at N–1 it may be presumed that the presence of the OH group in **12** and the absence of the SO_2NH_2 group in **14** do not contribute significantly to the cause of inferior biological activities of these compounds. The red contours projected near to the CF_3 group of **8** indicate the importance of electronegative atom in this region. Therefore, as **27** is devoid of the CF_3 group it exhibits poor biological activity. The cluster of blue contour (Figure 4) observed surrounding the C–4 of the non–sulphonyl ring (the substituent R at the central pyrazole ring) indicates the necessity of the presence of electropositive group at this region in imparting the desired biological activity. It explains the inferior biological activity of **2**, **6**, **17**, **23**, and **24** in which the electronegative fluorine/oxygen atoms of 4–CF_3, 4–COOH, 4–SO_2Me, and 4–CH_2OH, respectively, were oriented towards the blue contour (Figure 5). In the case of **24**, the replacement of the CF_3 by CH_2F may also add to the cause of its decreased biological activity. The observed inferior biological activities of **10**, **15**, **22** and **27** may be accounted for by the dual reason of the lack of the presence of a bulky substituent and the presence of the fluorine atom at C–4 of the non–sulfonyl aryl moiety. Thus, for **27** the overall decreased biological activity is due to the lack of the CF_3 group at the central pyrazole ring and the presence of F at C–4 in the non–sulfonyl aryl group. It may be assumed that the replacement of the SO_2NH_2 of the aryl substituent at N–1 by $COCF_3$ and NO_2, respectively, in **10** and **22** does not contribute significantly in decreasing the activity of these compounds as no contour is shown by the QSAR model in the region of the $SONH_2$ group. The poor biological activity of **25** bearing the CN group at C–4 of the non–sulfonyl

aryl moiety may be explained due to multivariable factors such as the lack of a bulky group at C–4, the electronegative nitrogen present in the CN group at C–4 and the replacement of the CF_3 group by CH_2F.

4 CONCLUSIONS

We have carried out CoMFA and CoMSIA studies for thirty–four 1,5–diaryl pyrazoles as selective COX–2 inhibitors. The obtained 3–D QSAR models using two different alignment methods (as_is atom–based, and use of docked conformations derived from FlexX docking) were compared. The atom–based alignment method provided better CoMFA and CoMSIA models indicating the importance of alignment in deriving 3–D QSAR models. The resulted contour maps gave rational for the COX–2 inhibitory profile of the structurally diverse 1,5–diaryl pyrazoles. The fact that the 3–D QSAR model did not project any color contour in the region occupied by the $SONH_2$ group provides rational for designing non–sulfonyl COX–2 inhibitors [13] that might circumvent the problem of side effect associated with the $SONH_2$ group. Finally, this study will be useful for the design of novel selective COX–2 inhibitors.

Acknowledgment

RT thanks to CSIR for the award of SRFship (No. 9/727/(19)/2002–EMR–I).

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