

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

Ramasamy Thilagavathi and Asit K Chakraborti*

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S. A. S Nagar, Punjab-160 062, India.

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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 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.

Methods. 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 ($r_{cv}^2 = 0.693$, $r_{conv}^2 = 0.989$, SEE= 0.196) better than that of CoMSIA ($r_{cv}^2 = 0.370$, $r_{conv}^2 = 0.914$, 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 guided to understand the important structural features responsible for COX-2 inhibitory activities of 1,5-diaryl pyrazoles.

Keywords. 3-D QSAR, CoMFA, CoMSIA, FlexX, cyclooxygenase-2, docking, alignment,

* Correspondence author; fax: :0172-2214692; E-mail: akchakraborti@niper.ac.in

Abbreviations and notations

NSAIDs, nonsteroidal anti-inflammatory drugs

COX-2, cyclooxygenase-2

PDB, protein data bank

Rdf, receptor description file

3-D QSAR, three-dimensional quantitative structure-activity relationships

1 INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of the symptoms of acute and chronic inflammatory disorders. Majority of the 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.

The first two lead compounds, Dup-697 [4] and NS-398 [5] (**Fig. 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, (**Fig. 1**) were marketed in 1998 [6, 7]. Valdecoxib, parecoxib sodium (a water soluble prodrug of valdecoxib) and etoricoxib (**Fig. 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.

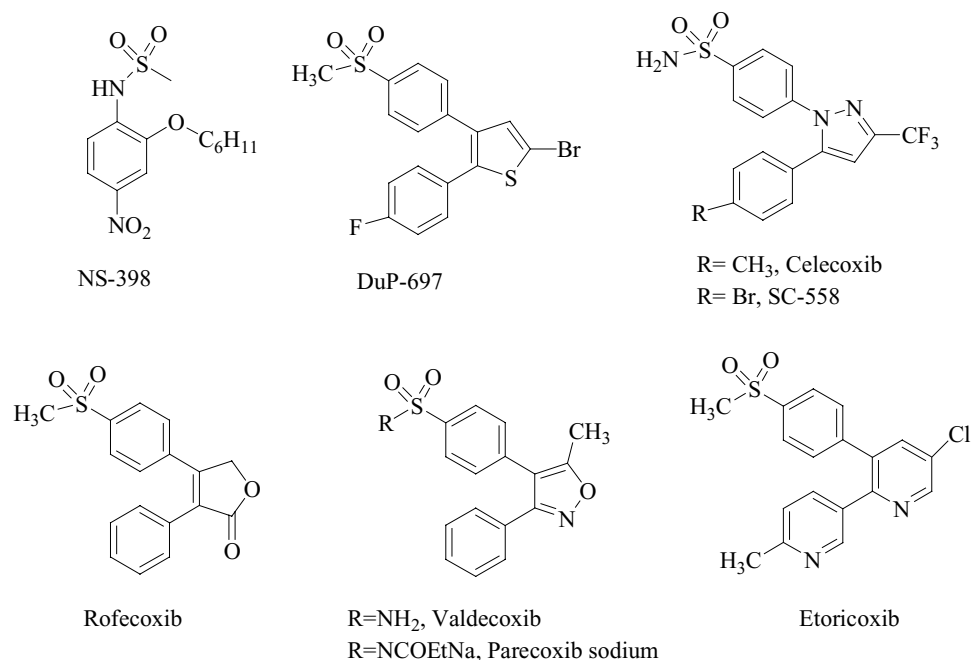


Figure 1. Structures of some selective COX-2 Inhibitors

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 perform 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 Preparation of Ligands

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 using recombinant human COX-2

enzyme were used for CoMFA studies. The biological activities were converted into the corresponding pIC₅₀ 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. 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. To obtain docked conformations, all the molecules were subjected to 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.

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 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 sp³ 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

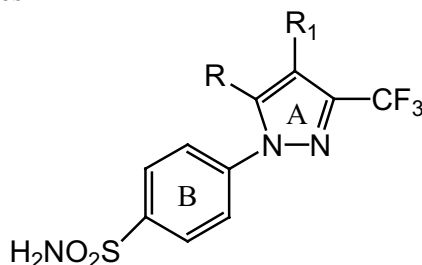
The CoMSIA method is based on molecular similarity indices. Using a common probe atom, similarity indices were calculated for a data set of prealigned molecules at regularly spaced grid points. There is sudden rise in energy when the atoms of the molecules approach the probe atom.

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.

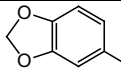
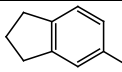
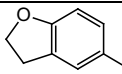
2.5. PLS analysis

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 weightage was assigned to steric and electrostatic fields. 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 molecules of 1, 5-diaryl pyrazoles



Mol	R	R ₁	Actual pIC ₅₀	Predicted pIC ₅₀	Residual	Mol	R	R ₁	Actual pIC ₅₀	Predicted pIC ₅₀	Residual
1	4-CH ₃ C ₆ H ₄	H	7.40	6.98	0.42	18	4-OCH ₃ C ₆ H ₄	H	8.10	7.99	0.11
2	4- CF ₃ C ₆ H ₄	H	5.08	5.35	-0.27	19		H	7.28	7.31	-0.03
3 ^a	4-OCH ₃ C ₆ H ₄	H	6.12	6.36	-0.24	20 ^e	5-methyl- 2-furyl	H	5.48	5.50	-0.02
4	4-SCH ₃ C ₆ H ₄	H	8.04	8.28	-0.24	21	4-NH ₂ C ₆ H ₄	H	6.47	6.54	-0.07

5	4-Cl C ₆ H ₄	Cl	8.27	8.08	0.19	22 ^f	4-F C ₆ H ₄	H	4.00	4.04	-0.04
6	4-COOH C ₆ H ₄	H	4.95	5.07	-0.12	23 ^e	4- SO ₂ CH ₃	H	4.00	3.97	0.03
7		H	7.62	7.86	-0.24	24 ^e	4-COOH C ₆ H ₄	H	4.33	4.37	-0.04
8	4-NMe ₂	H	8.33	8.18	0.15	25 ^e	4-CN C ₆ H ₄	H	4.53	4.67	-0.14
9	5-bromo- 2-thienyl	H	7.92	7.66	0.26	26	2-NMe ₂	H	4.84	5.56	-0.72
10 ^b	4-F C ₆ H ₄	H	4.00	3.88	0.12	27 ^g	4-F C ₆ H ₄	H	4.00	4.61	-0.61
11	4-Cl C ₆ H ₄	Me	7.66	7.83	-0.17	28	4-Cl C ₆ H ₄	Et	7.55	8.01	-0.46
12	C ₆ H ₅	OH	5.45	5.32	0.13	29	3-CH ₃	H	6.96	6.42	0.54
13	5-chloro- 2-thienyl	H	7.58	7.63	-0.05	30		H	7.51	7.21	0.30
14 ^c	C ₆ H ₅	H	4.00	3.89	0.11	31		H	7.68	7.00	0.68
15 ^d	4-F C ₆ H ₄	H	4.00	3.80	0.20	32	2-pyridyl	H	4.34	6.53	-2.19
16	3,4-OMe C ₆ H ₃	H	6.22	6.16	0.06	33	3-pyridyl	H	4.35	6.07	-1.72
17	4- CH ₂ OH C ₆ H ₄	H	4.03	4.14	-0.11	34	4-pyridyl	H	4.19	5.17	-0.98

^a replacement of SO₂NH₂ by OMe, ^b replacement of SO₂NH₂ by COCF₃, ^c replacement of SO₂NH₂ by H, ^d replacement of CF₃ by COOH, ^e replacement of CF₃ by CH₂F, ^f replacement of SO₂NH₂ by NO₂, ^g replacement of CF₃ 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). 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 (**Fig. 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.

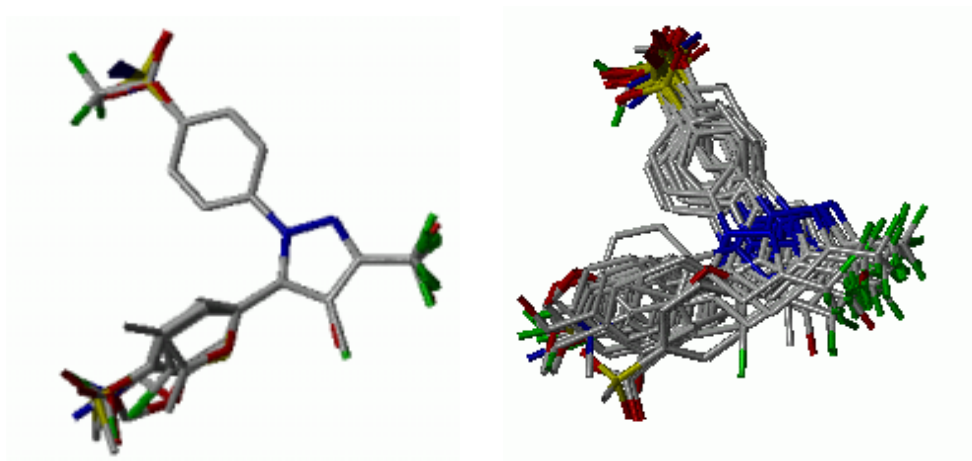


Figure 2. Alignment of 1,5-diarylpyrazoles: a) Database method, b) docked conformations derived by FlexX method

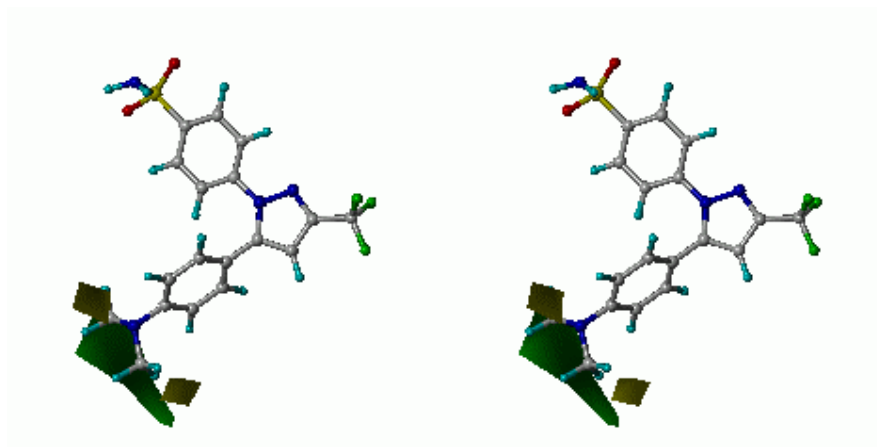


Figure 3. Stereoview of CoMFA steric contour plot (STDEV*COEFF). The most active molecule **8** is displayed in the background for reference

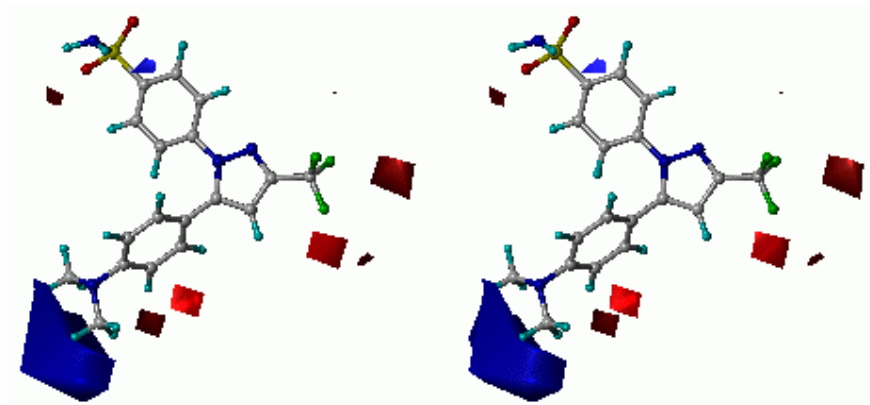


Figure 4 Stereoview of CoMFA electrostatic contour plot (STDEV*COEFF). The most active molecule **8** is displayed in the background for reference

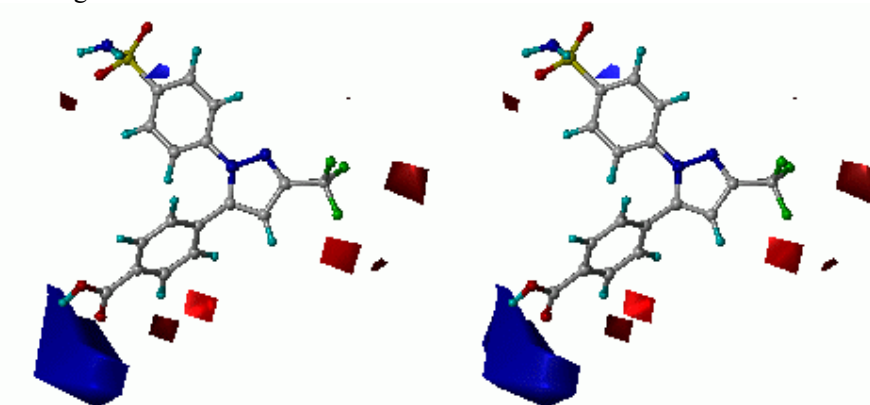


Figure 5 Stereoview of CoMFA electrostatic contour plot (STDEV*COEFF). Molecule **6** is displayed in the background for reference

The final model demonstrated a good predictive ability by predicting the activities of test set (**26-31**, **34**) molecules ($r^2_{\text{pred}} = 0.8291$) 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.

Table 2. The summary of results of CoMFA-CoMSIA

	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	
F value	338.374		74.577	
r^2_{pred}	0.8291		-	

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

CoMFA produced a green contour (**Fig. 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 CH₃, SCH₃, Cl, NMe₂, Cl, OCH₃, and Cl, respectively, at this position possessed better biological activities. On similar reason, the better 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. Since the 3D-QSAR model did not produce any colour contour near the region of C-4 of the central pyrazole ring and near the region occupied by SO₂NH₂ 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 SO₂NH₂ group in **14** do not contribute significantly to the cause of inferior biological activities of these compounds. The red contours projected near to the CF₃ group of **8** indicated the importance of electronegative atom in this region. Therefore, as **27** is devoid of the CF₃ group it exhibit poor biological activity. The cluster of blue contour (**Fig. 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-CF₃, 4-COOH, 4-SO₂Me, and 4-CH₂OH, respectively, were oriented towards the blue contour (**Fig. 5**). In case of **24**, the replacement of the CF₃ by CH₂F 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 CF₃ 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 SO₂NH₂ of the aryl substituent at N-1 by COCF₃ and NO₂, respectively, in **10** and **22** do not contribute significantly in decreasing the activity of these compounds as no contour is shown by the QSAR model in the region of the SONH₂ 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 CF₃ group by CH₂F.

4 CONCLUSIONS

We have carried out CoMFA, 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, 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 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 projected any colour contour in the region occupied by the SONH₂ group provides rational for designing non-sulfonyl COX-2 inhibitors¹³ that might circumvent the problem of side effect associated with the SONH₂ group. In fine, this study will be useful for the design of novel selective COX-2 inhibitors.

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Biographies

Ramasamy Thilagavathi has completed B.Pharm at Sri Ramakrishna Institute of Paramedical Sciences (SRIPMS),

Coimbatore, Tamilnadu, India. Then she moved to the department of medicinal chemistry, National Institute of Pharmaceutical Education and Research (NIPER), S. A. S. Nagar, India and obtained the degree M.S. (pharm). She is currently pursuing Ph.D in the same department under the supervision of Prof. Asit K. Chakraborti. Her research interests include rational drug design, CADD, 3-D QSAR, docking, pharmacophore mapping and synthesis of heterocyclic compounds.

Asit K. Chakraborti is professor and head of the department of medicinal chemistry at NIPER S. A. S. Nagar, Punjab, India. After obtaining a Ph.D. degree in organic chemistry from the Indian Association for the Cultivation of Science (IACS), Kolkata, India Dr. Chakraborti undertook postdoctoral research with Professor R. K. Dieter in the Department of Chemistry at Clemson University, Clemson, South Carolina, U. S. A. and Professor Mark Cushman in the Department of Medicinal Chemistry and Pharmacognosy at Purdue University, West Lafayette, Indiana, U. S. A. Dr. Asit K Chakraborti has published several original research papers in international journals in chemistry and reviewed research articles submitted to *J. Org. Chem.*, *Bioorg. Med. Chem. Lett.*, *Bioorg. Med. Chem.* and *Internet. Electron. J. Mol. Design*. More recently, Dr. Chakraborti has collaborated on projects dealing with computer aided design and synthesis of anti-asthma agents with internationally renowned pharmaceutical industry.