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Research Article

3-Dimensional quantitative structure-activity relationship and molecular docking studies of tetrasubstituted pyrazole derivatives as inhibitors of cyclooxygenase-2

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ABSTRACT

Background: Design and development of new drugs is simplified and made more cost-effective because of the advances in the concepts of Quantitative Structure-Activity Relationship (QSAR) studies. A methodology of QSAR studies is one of the approaches to the rational drug design.
Methods: 3-Dimensional QSAR studies were performed on a series of tetrasubstituted pyrazole derivatives by using Scigress Explorer software suite. Docking studies of these compounds were also performed to understand the interactions with amino acid residues of COX-2 protein.
Results: The multiple linear regression analysis was used to correlate the physicochemical descriptors with the COX-2 inhibitory activity of 24 training set of compounds and the best QSAR model was developed. The best model was validated using leave-one-out method and found to be statistically significant, with coefficient of determination (r^2) of 0.835. This model was further used to predict the COX-2 inhibitory activity of 10 test set of compounds. Docking analysis revealed that most of the compounds formed H-bond interactions with amino acid residues of COX-2 protein (PDB ID: 1CX2). Predicted pIC50 value of one of the test compounds was 7.048 and it showed H-bond interactions with His90 & Tyr355 residues.
Conclusion: The present study shall help in rational drug design and synthesis of new selective COX-2 inhibitors with predetermined affinity and activity and provides valuable information for the understanding of interactions between COX-2 and the novel tetrasubstituted pyrazole derivative compounds.

Keywords: QSAR, Multiple linear regression, Physicochemical descriptors, Docking, COX-2, Scigress explorer, Molegro virtual docker

INTRODUCTION

Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) have been used to treat pain and inflammation in OA.[1] The anti-inflammatory effects of NSAIDs are mainly due to their ability to inhibit cyclooxygenase (COX), impairing production of prostaglandins, which are important mediators of the inflammatory response and pain. COX enzymes metabolize arachidonic acid, forming prostaglandin H_2, which is subsequently metabolized by prostaglandin E synthase into prostaglandin E2 (PGE_2).[2] However, numerous reported adverse drug reactions, case-control, and post-marketing surveillance studies have revealed that their use is frequently associated with a relatively high incidence of adverse reactions in the GI tract.[2-4] Traditional NSAIDs act by inhibiting both COX-1 and COX-2, thereby blocking the synthesis of PGs. Beneficial effects of NSAIDs are thought to be mediated by COX-2 inhibition, whereas unwanted gastrointestinal effects are caused by

inhibitory effects on COX-1.[5] The gastro-intestinal (GI) adverse events of NSAIDs are majorly due to the decrease in synthesis of the gastroprotective prostaglandins PGE_2 and PGI_2, which are mainly produced by COX-1.[2] To significantly reduce the GI toxicity of NSAIDs associated with acute and chronic use and to obtain similar or better efficacy, pharmaceutical companies conducted intensive international research which led to the development of selective COX-2 inhibitors.[6-7]

Selective COX-2 inhibitors are believed to reduce inflammation without influencing normal physiologic functions by inhibiting only COX-2. The first COX-2 selective NSAID approved by Food and Drug Administration (FDA) was celecoxib, which was followed by introduction of rofecoxib, valdecoxib, parecoxib, aceclofenac and etoricoxib.[8] Even though the GI toxicity profile of selective COX-2 inhibitors is better than the traditional NSAIDs, current evidences indicate that selective COX-2 inhibitors have important adverse cardiovascular and renal effects. In view of the adverse events of COX inhibitors and importance of these agents in the clinical management of arthritis, a Quantitative Structure-Activity Relationship (QSAR) analysis was performed on the COX-2 inhibitory activity of tetrasubstituted pyrazole derivatives. The present study was aimed at rationalizing the substituent variations of these analogues to provide insight for the future endeavours.

QSAR is a type of analysis where some measures of chemical properties are correlated with biological activity to derive a mathematical illustration of the underlying structure activity relationship (SAR).[9] QSAR studies are unquestionably of great importance in modern chemistry and biochemistry. To get an insight into the SAR we need molecular descriptors that can effectively characterize molecular size, molecular branching or the variations in molecular shapes, and can influence the structure and its activities.[10]

Design and development of new drugs is simplified and made more cost-effective because of the advances in the concepts of QSAR studies. A methodology of QSAR studies is one of the approaches to the rational drug design.[11]

The introduction of Hansch model, in early 1960, enabled chemists to describe the structure activity relationships in quantitative terms and check those using statistical methods.[12]

QSAR are statistically derived models that can be used to predict the biological activity of untested compounds from their molecular structures.[13, 14] This concept helps to understand the role of physicochemical descriptors of compounds in determining the biological activity and in estimating the characteristics of the new and potent compounds, without the chemical synthesis of the compounds.[12]

Docking various ligands to the protein of interest followed by scoring to determine the affinity of binding and to reveal the strength of interaction has also become increasingly important in the context of drug discovery.[15] Thus, the objective of the present work was to develop various QSAR models by multiple linear regression (MLR) methods and to use the best QSAR model for the prediction of COX-2 inhibitory activity of newly designed compounds by using Scigress Explorer software suite. We also performed the molecular docking of the newly designed compounds against COX-2 protein, 1CX2 (PDB ID) with bound ligand 1-Phenylsulfonamide-3-trifluoromethyl-5-parabromophenylpyrazole (S58) extracted from protein data bank (PDB), by utilizing fast, exhaustive docking software Molegro virtual docker.[16]

METHODS

Data set for 3D QSAR

The first step in developing QSAR equations was to compile a list of compounds for which the experimentally determined inhibitory activity was known. The COX-2 inhibitory activity data and chemical structures of tetrasubstituted pyrazole derivatives for training set were retrieved from literature.[17]

The biological activity (IC_{50}) of the molecules were converted to their corresponding pIC_{50} values,[18] and used as dependent variables in the QSAR calculations. The data set was divided into training set for model generation, and a test set for model validation, containing 24 and 10 compounds respectively (Table 1 & 2).

Chemical structure construction and optimization

The molecules were drawn using chemical drawing software 'ACD/ChemSketch',[19] and 3D optimization of molecules was done by 'ACD/3D viewer'.[20] Structure of the parent compound is illustrated in Figure 1. The molecules were first optimized to their lowest energy state using Merck molecular force field-3 (MMFF3) method,[21] using Scigress explorer software suite. To avoid the local stable conformations of the compounds, geometry optimization was run many times with different starting points of each molecule, and conformation with the lowest energy was considered for the calculation of the molecule descriptors.

Calculation of physicochemical descriptors

The structure of a molecule is expressed quantitatively in terms of its physicochemical descriptors, which are lipophilic, electronic and steric in nature. The aligned molecules were selected for calculation of the descriptors after inserting the biological activity as a dependent variable and the descriptors generated were selected as

independent variables. List of physicochemical descriptors used in this study are summarised in Table 3.

Table 1: Data set used in the generation of the QSAR models (Training set).

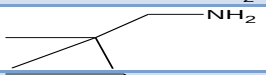
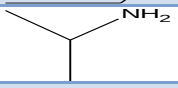
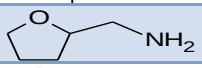
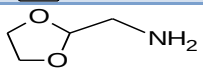
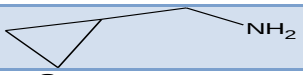
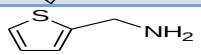
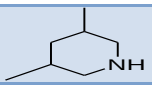
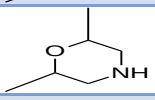
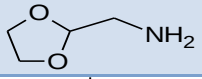
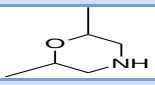
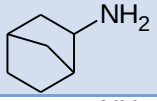
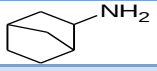
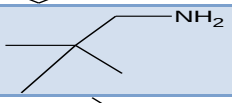
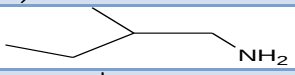
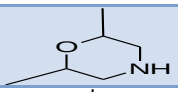
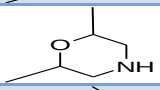
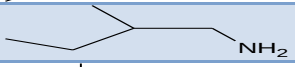
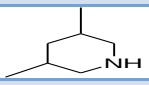
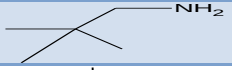
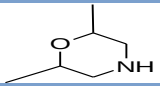
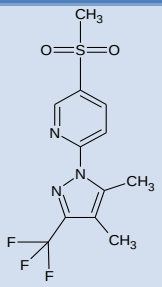
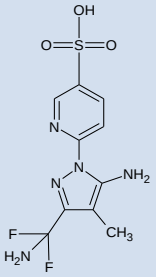
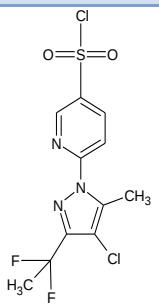
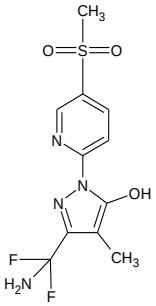
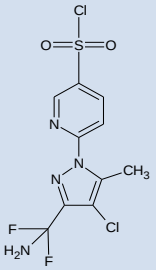
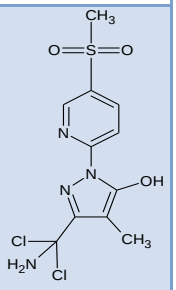
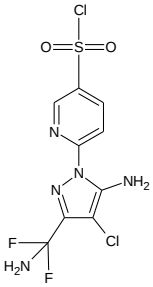
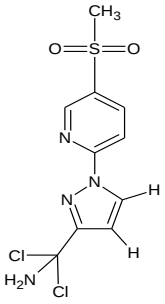
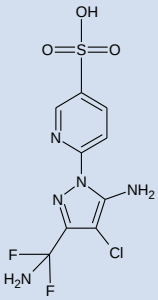
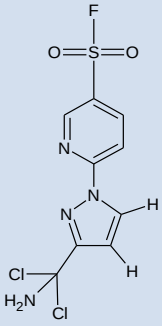
Compound	R	R^1	R^2	R^3	pIC_{50} (µM)
1	F	CH_3	CN		6.879
2	F	CH_3	CN		6.638
3	F	CH_3	CN		6.705
4	F	CH_3	CN		6.443
5	F	CH_3	CN		7.200
6	F	CH_3	CN		6.899
7	F	CH_3	CN		6.958
8	F	CH_3	CN		6.903
9	F	CH_3	CN		7.022
10	F	CH_3	CN		6.853
11	F	CH_3	H		6.508
12	H	CH_3	CN		6.886
13	H	CH_3	CN		6.721
14	H	CH_3	CN		6.619
15	H	CH_3	CN		6.376
16	F	NH_2	CN		6.853
17	F	NH_2	CN		6.886
18	F	NH_2	CN		6.721
19	F	NH_2	CN		5.728
20	F	NH_2	CN		5.102
21	H	NH_2	CN		6.698
22	H	NH_2	CN		6.677
23	H	NH_2	CN		6.443
24	H	NH_2	CN		5.301

Table 2: Data set used for the validation of QSAR models (Test set).

Compound	Structure	Compound	Structure
1		6	
2		7	
3		8	
4		9	
5		10	

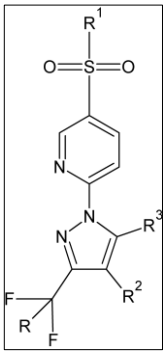


Figure 1: Structure of parent compound used for QSAR analysis. R1 & R2 positions were substituted to obtain 10 test set of compounds.

Development and validation of QSAR models

The QSAR studies were carried out to correlate physicochemical descriptors of 24 derivatives from the training set with their COX-2 inhibitory activity. The physicochemical descriptors were taken as the independent variables and the COX-2 inhibitory activity was taken as the dependent variable. Various QSAR models were developed by correlating more than one (stepwise MLR analysis implemented in Scigress explorer's "Project Leader" program) physicochemical descriptors at a time, with COX-2 inhibitory activity of the compounds. Validation parameter, predictive r^2 (r^2 pred) was calculated for evaluating the predictive capacity of the models. The models were then cross-validated by the 'leave one out' scheme,[22] where a model was built with n-1 compounds and the nth compound was predicted. Each compound was left out of the model derivation and predicted in turn. An indication of the performance of the model was obtained from the cross-validated r^2_{CV} (or predictive q^2) coefficient which is defined as:

$$q^2 = (SD\text{-}PRESS/SD)$$

Where, SD is the sum of squares deviation for each activity from the mean. PRESS (or predictive sum-of-squares) is the sum of the squared difference between the actual and that of the predicted values when the compound is omitted from the fitting process. Cross-validation coefficient q^2 is considered as an indicator of the predictive performance and stability of a model. For a reliable model, the square of cross-validation coefficient q^2 should be ≥ 0.5.[23] The COX-2 inhibitory activity of 24 compounds in the training set and 10 compounds in the test set was predicted using the best QSAR model (Equation 1). For further validation of the accuracy of the predicted values by the best QSAR model, the experimental COX-2 inhibitory of the 24 training set compounds was correlated with their predicted COX-2 inhibitory activity.

Graphical analysis

Graphical analysis was performed using Scigress explorer's plotting facilities to display molecules that were outliers in the database. Through scatter plot there was evaluation of regression in the graph. By plotting the actual activities along X-axis versus the predicted activities along Y-axis, the predicted ability of the model was assessed. From the regression line it was easy to predict the number of molecules lie on and away from regression line.

Receptor X-ray structure

The 3D coordinates of the crystal structure of COX-2 in complex with 1-phenylsulfonamide-3-trifluoromethyl-5-parabromophenylpyrazole (PDB code: 1CX2) extracted from the protein data bank (www.rcsb.org/) was selected as the receptor model for docking experiments.

Docking analysis

We used the template docking available in Molegro virtual docker software and evaluated MolDock, Rerank and protein-ligand interaction scores from MolDock and MolDock [GRID] options. Template docking is based on extracting the chemical properties like the pharmacophore elements of a ligand bound in the active site and using that information for docking structurally similar analogues. We used the default settings, including a grid resolution of 0.30 Å for grid generation and a 15 Å radius from the template as the binding site. We used the MolDock optimizer as a search algorithm, and the number of runs was set to 10. A population size of 50, maximum iteration of 2000, scaling factor of 0.50, crossover rate of 0.90 and a variation based termination scheme for parameter settings were used. The maximum number of poses was set to a default value of 5.

RESULTS

Physicochemical descriptors listed in Table 3 were calculated for the training set of molecules using the Scigress explorer's "Project Leader" program. COX-2 inhibitory activity (experimental activity) of all the training compounds was added manually in the data set and was correlated with the different physicochemical descriptors by stepwise MLR analysis and QSAR models were generated. The best model (equation 1) was validated using leave-one-out method and found to be statistically significant, with coefficient of determination (r^2 pred) of 0.835 and cross-validated r^2CV (or predictive q^2) coefficient of 0.703.

Equation 1 (Model 1): M=0.0787994*SE-0.690428*HF-0.488229*HOMO-0.305929*POL+0.0468046*SASA-0.0565615*DP +0.13061*TE-3.10224*IP-0.0260347*MR+1.72358*1X+34.0088 r^2CV=0.703813 r^2=0.835596

Table 3: List of physicochemical descriptors selected for this study.

Abbreviation	Full name	Description
SE	Steric energy	The steric energy of a molecule is the sum of the molecular mechanics potential energies calculated for the bonds, bond angles, dihedral angles, non-bonded atoms and so forth.
HF	Heat of formation	The energy released or used when a molecule was formed from elements in their standard states
LOG P	Log p	The octanol-water partition coefficient
HOMO	HOMO Energy	The energy required to remove an electron from the highest occupied molecular orbital (HOMO)
POL	Polarizability	The molecule's average alpha polarizability
SASA	Solvent Accessible Surface Area	The molecular surface area accessible to a solvent molecule
DP	Dipole moment	It can be defined as the product of magnitude of charge and distance of separation between the charge
TE	Total Energy	The total energy contained in an object was identified with its mass, and energy (like mass)
IP	Ionization potential	The energy per unit charge needed to remove an electron from a given kind of atom or molecule to an infinite distance
MR	Molecular refractivity	It is measure of the total polarizability of a mole of a substance and was dependent on the temperature, the index of refraction and the pressure
^{1}X	Connectivity index (order 1)	It is the information in any molecular formula or model regarding the order in which the constituent atoms of the molecule were linked, irrespective of the nature of the linkage.
EA	Experimental activity	A measured activity such as therapeutic activity or catalytic activity

Ten QSAR models were generated and equation 1 was considered as the best model to predict the activities of 10 test set of molecules (Table 4).

Table 4: Predicted activity values of 10 test set of compounds calculated from the best QSAR model (equation 1).

Test compound	Predicted activity from model 1
Compound (1)	5.783
Compound (2)	6.969
Compound (3)	6.546
Compound (4)	5.807
Compound (5)	6.448
Compound (6)	7.048
Compound (7)	6.915
Compound (8)	6.626
Compound (9)	6.449
Compound (10)	6.227

Table 5: Values of actual, predicted & residual activities of 24 training set of compounds.

Compound	Actual activity	Predicted activity	Residual activity
Compound (1)	6.879	6.862	0.017
Compound (2)	6.638	6.553	0.085
Compound (3)	6.705	6.624	0.081
Compound (4)	6.443	6.475	-0.032
Compound (5)	7.200	7.258	-0.058
Compound (6)	6.899	7.008	-0.109
Compound (7)	6.958	6.868	0.090
Compound (8)	6.903	6.872	0.031
Compound (9)	7.022	6.903	0.119
Compound (10)	6.853	6.81	0.043
Compound (11)	6.508	6.006	0.502
Compound (12)	6.886	7.028	-0.142
Compound (13)	6.721	6.125	0.596
Compound (14)	6.619	7.06	-0.441
Compound (15)	6.376	6.746	-0.370
Compound (16)	6.853	6.905	-0.052
Compound (17)	6.886	7.008	-0.122
Compound (18)	6.721	6.804	-0.083
Compound (19)	5.728	5.831	-0.103
Compound (20)	5.102	5.845	-0.743
Compound (21)	6.698	6.287	0.411
Compound (22)	6.677	6.348	0.329
Compound (23)	6.443	6.095	0.348
Compound (24)	5.301	5.18	0.121

*Predicted and the experimental activities closely matches as evidenced by low values of residual activity (difference between experimentally observed activity and QSAR predicted activity)

In order to validate our results we correlated the predicted activities of 24 molecules of the training set using the model expressed by equation 1 and compared with the experimental values. Predicted and the experimental activities were very close to each other evidenced by low values of residual activity (difference between experimentally observed activity and QSAR predicted activity) (Table 5).

The graph between predicted and experimental activity of training set compounds by using model 1 is illustrated in Figure 2. Through this scatter plot, the compounds aligned on and around the regression line showed good correlation level between the predicted and experimental activity and compounds which were deviated from the regression line showed low correlation level between the predicted and experimental activity of training set of compounds. Variations in residual activity of training set of compounds are illustrated in Figure 3.

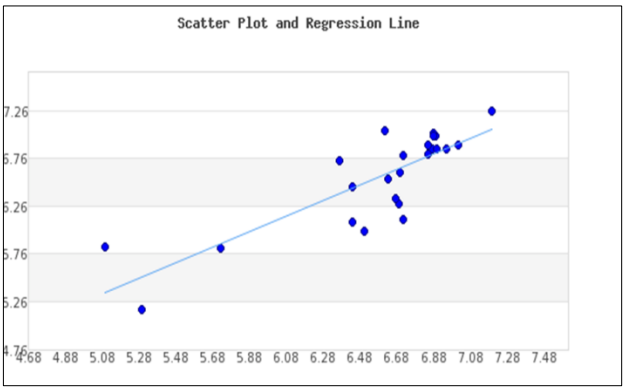


Figure 2: Graph between predicted (vertical axis) and experimental activity (horizontal axis) of training set of compounds by using equation 1. Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 17, 18, 19 & 24 were aligned on and around the regression line showed good correlation level between the predicted and experimental activity.

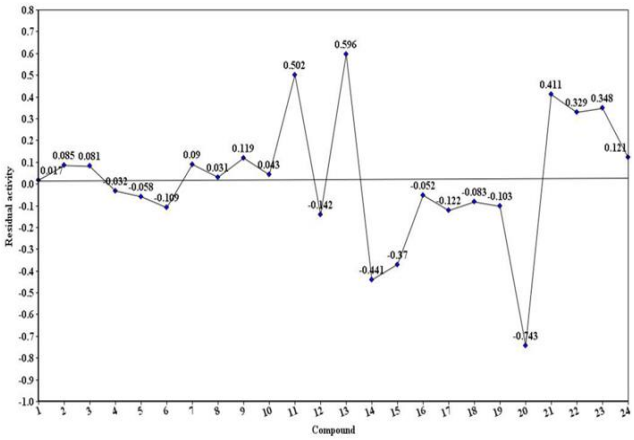


Figure 3: Graphical illustration of variation in residual activity (difference between actual and predicted activity) of 24 training set of compounds.

Before the docking experiments, the protocol was validated. 1CX2 (PDB ID) bound ligand 1-phenylsulfonamide-3-trifluoromethyl-5-parabromophenylpyrazole was docked into the binding pocket of COX-2 protein to obtain the docked pose and the RMSD (Root Mean Square Deviation) of all atoms between these two conformations indicating that the parameters for docking simulation were good in reproducing the X-ray crystal structure. Therefore, tetrasubstituted pyrazole derivatives (10 test set of molecules) were docked into the binding pocket of COX-2 protein. 1CX2 co-crystallized 1-phenylsulfonamide-3-trifluoromethyl-5-parabromophenylpyrazole ligand resulted in MolDock score of -139.507kcal/mol. Therefore, any molecule from the dataset which shows a score lower than -139.507kcal/mol would be regarded as ligand with higher binding affinity and would act as inhibitor against COX-2 protein. Our approach identified three compounds from the test set of molecules with better energy scores than the 1CX2 bound co-crystallized ligand. The docked energies (Moldock score) and H-bond interaction data of the three best compounds from the 10 test set of molecules are given in Table 6.

Table 6: Interaction parameters of 1CX2 with the three best test set of compounds and co-crystallized 1-phenylsulfonamide-3-trifluoromethyl-5-parabromophenylpyrazole (Reference ligand).

Compound	MolDock score (kcal/mol)	Rerank Score	H-Bond
Compound (6)	-141.457	-115.507	-3.49944
Compound (7)	-141.008	-109.672	-0.975495
Compound (2)	-140.368	-98.3467	-0.0447294
Reference ligand	-139.507	-126.035	-3.52043

*H-Bond stands for Hydrogen Bond interaction score, Compound (6), in particular, showed high binding affinity with MolDock score (binding score) of -141.457kcal/mol against 1CX2 (PDB ID) in docking analysis

Out of 10 test set of molecules, the best one was molecule 6th with predicted pIC50 value of 7.048 and binding energy score of -141.457kcal/mol This compound was docked within the binding pocket of COX-2 protein (PDB ID: 1CX2) forming H-bond interactions with His90 & Tyr355 residues. Interaction parameters of COX-2 with 6th test compound are illustrated in Figure 4.

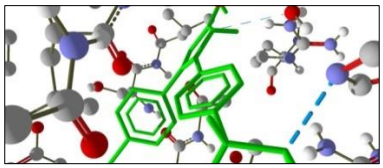


Figure 4: Interactions between the COX-2 (PDB id: 1CX2) and test compound 6. Blue dashed lines - hydrogen bonds (image generated using Molegro virtual docker software).

DISCUSSION

Finding novel compounds at starting points for lead optimization is a major challenge in drug discovery. The number of methods and softwares which use the QSAR and docking approaches are increasing at a rapid pace. It has been clearly demonstrated that the approach utilized in this study was successful in finding novel COX-2 inhibitors from the data set developed by computational methods. The model generated from various physicochemical descriptors corresponds to the essential structural features of tetrasubstituted pyrazole derivatives and found to have significant correlation (coefficient of determination (r^2) of (0.835) with COX-2 inhibiting activity. Tetrasubstituted pyrazole derivatives designed by using computational approaches also showed good interactions with COX-2 protein. Compound (6), in particular, showed high binding affinity with MolDock score of -141.457kcal/mol against 1CX2 (PDB ID) in docking analysis and predicted pIC_{50} value of 7.048 in QSAR analysis. The ligand was docked deeply within the binding pocket region forming hydrogen bond interactions with His90 & Tyr355. This study shall help in rational drug design and synthesis of new selective COX-2 inhibitors with predetermined affinity and activity and provides valuable information for the understanding of interactions between COX-2 and the novel compounds and might pave the way towards discovery of novel COX-2 inhibitors with improved efficacy and safety. The physicochemical descriptors used in QSAR analysis in this study were important in further lead optimization of the tetrasubstituted pyrazole derivatives.

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