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QSAR Studies of Pyrazolone-4-Oxadiazole Derivatives as Anti-inflammatory Agents

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Abstract: Novel 2-(5-((4,5-dihydro-3-methyl-5-oxo-1-aryl-1*H*-pyrazol-4-yl)methylene)-1,3,4-oxadiazol-2-ylthio)-1-(4-aryl phenyl)ethanone derivatives with anti-inflammatory activity were subjected for the two and three dimensional quantitative structure activity relationships (2D-QSAR and 3D-QSAR) studies. The 2D-QSAR models multiple linear regression, partial least square and principle component regression approach and 3D-QSAR model using the k nearest neighbour (kNN) approach were developed. The MLR, PLS and PCR model predicted the training data with r^2 of 0.9928, 0.9923 and 0.9703 together with q^2 estimating to 0.9733, 0.9021 and 0.9209 respectively. For 3D QSAR negative values in steric field descriptors indicated the requirement of negative steric potential, for enhancing the anti-inflammatory activity and more numbers of positive value in electrostatic descriptors suggested that electropositive groups were important for anti-inflammatory activity. Thus these validated models bring important structural insight to aid the design of effective anti-inflammatory agent.

INTRODUCTION

Many anti-inflammatory therapeutic agents have been developed; however, most have some limitations. [1] Most of the currently used anti-inflammatory drugs interfere with the action of pro-inflammatory mediators, whereas less is understood about the biochemical processes that resolve inflammation. Principally, selective activation of such a pathway might lead to an alternative treatment for inflammation. [1]

The cyclooxygenase (COX) enzymes, which catalyze the first step in arachidonic acid metabolism, [2] were identified as the molecular targets of all nonsteroidal anti-inflammatory drugs (NSAIDs). [3-5] COX-1, a constitutively expressed isoform, is found in platelets, kidneys and the gastrointestinal tract and is believed to be responsible for the homeostatic maintainance of the kidneys and GI tract. The COX-2 enzyme is the inducible isoform that is produced by various cell types upon exposure to cytokines, mitogens and endotoxins released during injury. [6] Pyrazolin-5-one derivative, 3-methyl-1-phenyl-2-pyrazolin-5-one has been reported to be a promising candidate for the treatment of neonatal hypoxic-ischemic encephalopathy [7] and paraquat poisoning [8] due to its free radical scavenging activity. Pyrazolones are associated with broad spectrum of biological activities including antimicrobial, [9] antioxidants, [10] anti-inflammatory, [11] analgesic, [11] antipyretic, [11] antiproliferative, [12] HIV-1 integrase inhibitors, [13] antitubercular, [14] antithrombotic, [15] antiviral, [16] antitumor [17] activities.

In this paper we reported 2D and 3D QSAR studies of 2-(5-((4, 5-dihydro-3-methyl-5-oxo-1-aryl-1*H*-pyrazol-4-yl) methylene)-1, 3, 4-oxadiazol-2-ylthio)-1-(4-aryl phenyl) ethanone by using Vlife MDS 4.0 software.

MATERIALS AND METHODS

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The anti-inflammatory activities of the compounds collected from the literature [18] were used in the 2D-QSAR and 3DQSAR studies. pIC50 values were calculated using the following equation. [19, 20]

$$pIC50 = -\log C + \log it$$

Where, C = molar concentration = [concentration (mg/ml) x 0.001/molecular weight], Log it = log [%inhibition/100 - %inhibition].

2D-QSAR Study

Synthesis and anti-inflammatory activities of novel pyrazolone-4-oxadiazole derivatives was carried out by our research group recently. [18] The structures of all the compounds along with their actual and predicted pharmacological activities are presented in (Table 1). To correlate the physicochemical properties of the synthesized compound with activity, the 2D-QSAR studies were performed using VlifeMDS 4.0>> QSAR. The structure of each compound was drawn in 2D dot mol format of software and exported in 3D mode. The energy minimization of each model was performed using Merks Molecular Force Field (MMFF).

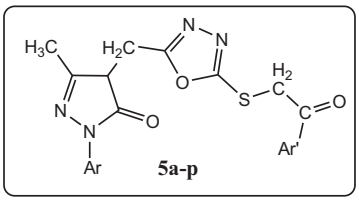
Descriptor Generation

Relationship between anti-inflammatory activity and various descriptors (physiochemical and alignment independent) were established by sequential multiple regression analysis (MLR) and principle component regression analysis (PCR) using MDS 4.0, in order to obtain QSAR models. The MDS 4.0 program was employed for the calculation of different quantum chemical descriptors including heat of formation, dipole moment, local charges and different topological elemental count including nitrogen count, chlorine count, path count and constitutional descriptors for each molecule. Physicochemical parameters including molar volume (V), molecular surface area (SA), hydrophobicity (log P), hydrogen acceptor count (HAC), hydration energy (HE) and molecular polarizability (MP) were also calculated.

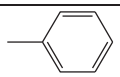
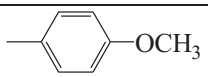
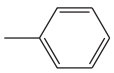
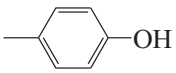
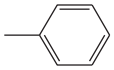
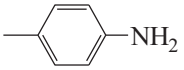
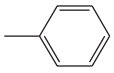
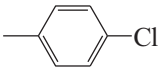
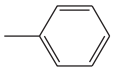
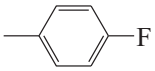
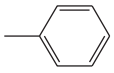
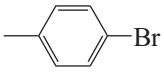
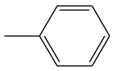
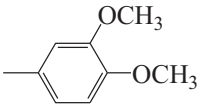
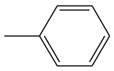
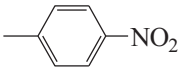
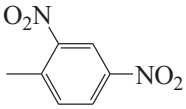
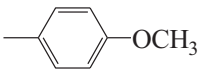
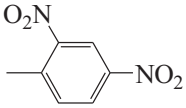
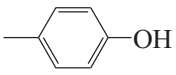
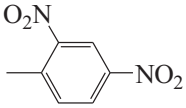
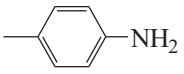
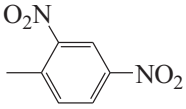
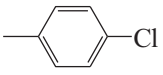
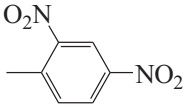
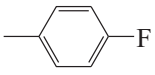
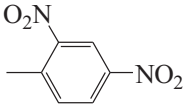
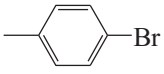
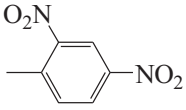
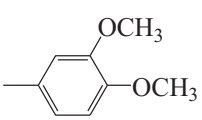
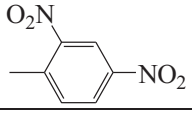
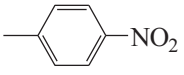
Model Development

The calculated descriptors were improved in a data matrix.

Table 1: Anti-inflammatory Activity Data with Actual and Predicted PIC_{50} Value



5a-p

Compound	Ar	Ar'	Actual PIC_{50} Value	Predicted PIC_{50} Value	Residual Value
5a			1.1059	1.10574	0.00016
5b			1.0646	1.09444	-0.02984
5c			1.1471	1.09444	0.05266
5d			0.3670	1.09444	-0.72744
5e			0.1673	0.21274	-0.04544
5f			0.0169	1.09444	-0.19584
5g			1.1395	1.13964	-0.00014
5h			0.2752	1.10574	-0.83054
5i			1.2233	1.20745	0.01585
5j			1.1657	1.19615	-0.03045
5k			1.1563	1.19615	-0.03985
5l			0.4503	1.19615	-0.74585
5m			0.3599	0.31445	0.04545
5n			-0.4997	1.19615	1.69585
5o			1.2244	1.24135	-0.01695
5p			0.4811	1.20745	-0.72635

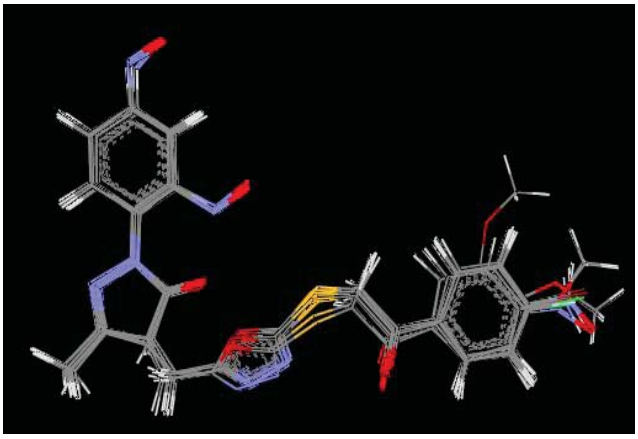


Figure 1: Aligned view of molecules (5a-p)

Table 2: Statistical Results of 2D QSAR Equation Generated by MLR, PLS and PCR Method

S. No.	Statistical Parameters	MLR Values	PLS Values	PCR Values
1	r^2	0.9928	0.9923	0.9703
2	q^2	0.9733	0.9021	0.9209
3	F test	41.57	37.00	28.30
4	r^2 se	0.0391	0.0374	0.0734
5	q^2 se	0.0751	0.1331	0.1197
6	pred_r^2	0.5613	0.5407	0.5651
7	pred_r^2se	0.9518	0.9451	0.9531
8	best_ran_r^2	0.05405	0.13748	0.10402
9	best_ran_q^2	0.62535	2.45690	0.22684
10	Z-Score	1.82364	1.73256	1.85291

The descriptors were verified for constant or near constant values and are selected for study. Then, the descriptors were correlated with each other and with the activity data. Finally, different regression analysis with stepwise selection and elimination of variables was applied to the development of QSAR models using software. The resulting models were validated by leave one-out cross-validation procedures to check their predictivity and robustness. The anti-inflammatory activity data and various parameters (physiochemical and alignment independent) were taken as dependent and independent variables respectively and correlation were established between them by employing multiple sequential regressions (MLR), partial least square (PLS) and multiple component regression (PCR) method, using random selection. In the generation of QSAR model, we have selected six test and fourteen training set. All calculations were run on a personal computer with the Windows XP operating system.

3D QSAR Methodology

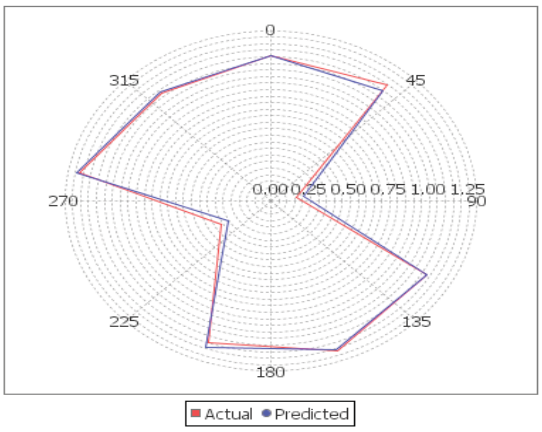
Like many 3D QSAR methods k-nearest neighbour molecular field analysis (kNN-MFA) requires suitable alignment of given set of molecules. This is followed by generation of a common rectangular grid around the molecules. The steric and electrostatic interaction energies are computed at the lattice points of the grid using a methyl probe of charge +1. These interaction energy values are considered for relationship generation and utilized as descriptors to decide nearness between molecules. The term descriptor is utilized in the following discussion to indicate field values at the lattice points. The optimal training and test sets were generated using the sphere exclusion algorithm. This algorithm allows the construction of training sets covering descriptor space occupied by representative points. Once the training and test sets were generated, kNN methodology was applied to the descriptors generated over the grid. [21]

k-Nearest Neighbour (kNN) Method

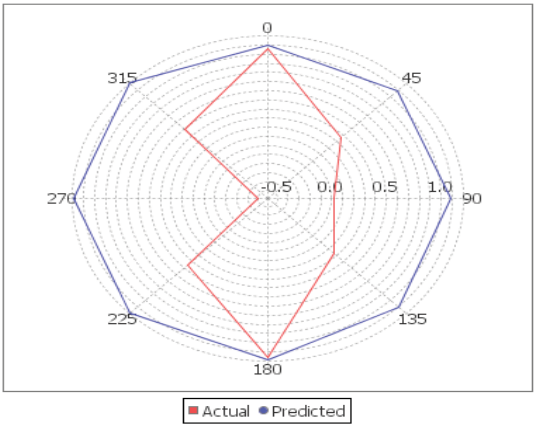
The kNN methodology relies on a simple distance learning approach whereby an unknown member is classified according to the majority of its k-nearest neighbours in the training set. The nearness is measured by an appropriate distance metric (e.g., a molecular similarity measure calculated using field interactions of molecular structures). The standard kNN method is implemented simply as follows. [22, 23] (1) Calculate distances between an unknown object (u) and all the objects in the training set. (2) Select k objects from the training set most similar to object u, according to the calculated distances. (3) Classify object u with the group to which the majority of the k objects belongs. An optimal k value is selected by optimization through the classification of a test set of samples or by leave-one out cross-validation. The variables and optimal k values were chosen using different variable selection method as described below:

1. kNN-MFA with Genetic Algorithm

Genetic algorithms (GA) first described by mimic natural evolution and selection. In biological systems, genetic information that determines the individuality of an organism is stored in chromosomes. Chromosomes are

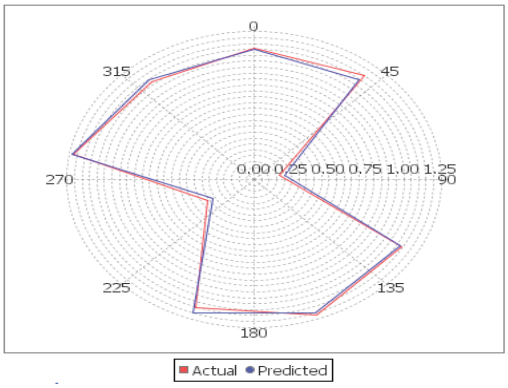


(2a)

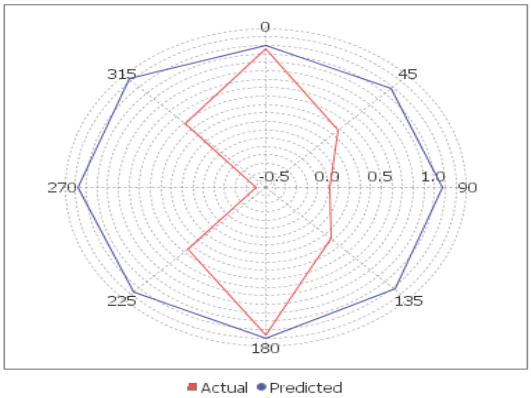


(2b)

Figure 2: Actual Vs predicted activity (2a) training set and (2b) test set by MLR method of 2D QSAR

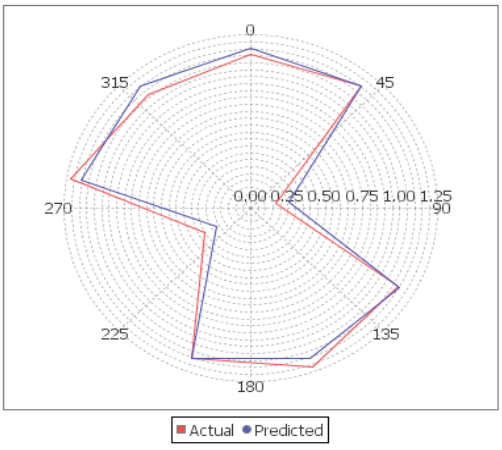


(3a)

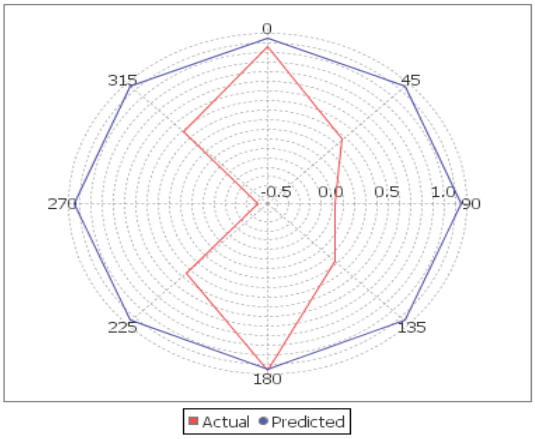


(3b)

Figure 3: Actual Vs predicted activity (3a) training set and (3b) test set by PLS method of 2D QSAR



(4a)



(4b)

Figure 4: Actual Vs predicted activity (4a) training set and (4b) test set by PCR method of 2D QSAR

replicated and passed onto the next generation with selection criteria depending on fitness. Genetic information can however be altered through genetic operations such as mutation and crossover. In GAs, each ‘‘chromosome’’ is a set of genes, which constitutes a candidate solution to the discrimination problem. Optimal or near optimal solutions are obtained through evolution over many generations. There are four major components of GA chromosome generation, fitness assessment, selection and mutation. This method employs a stochastic variable selection procedure, combined with kNN, to optimize (i) the number of nearest neighbours (k) and (ii) the selection of variables from the original pool as described in simulated annealing. The implementation of GA based kNN-MFA involved the following steps:

(1) Generate the initial population of chromosomes (candidate solutions) by randomly selecting genes (descriptors) from the pool of available genes. (2) Calculate pairwise Euclidean distances for all pair of molecules with respect to each chromosome. (3) Calculate the fitness of

Table 3: Statistical Results of kNN-MFA Method

S. No.	Parameters	kNN Method (Genetic Algorithm)
1	k Nearest Neighbour	2
2	N	8
3	Degree of freedom	7
4	q^2	0.6655
5	q^2_se	0.2446
6	Predr^2	-0.0701
7	pred_r^{2}se	0.8028
8	Descriptor	E_7 0.1382 0.2336 E_5 0.2206 0.2526 E_3 0.2385 0.3021 E_1 0.1199 0.1900 S_840 -0.0020 -0.0011 S_649 -0.0116 -0.0059 E_532 0.0860 0.2703 S_837 -0.0027 -0.0014 E_536 -0.0815 0.1354 E_830 -0.0837 0.0235

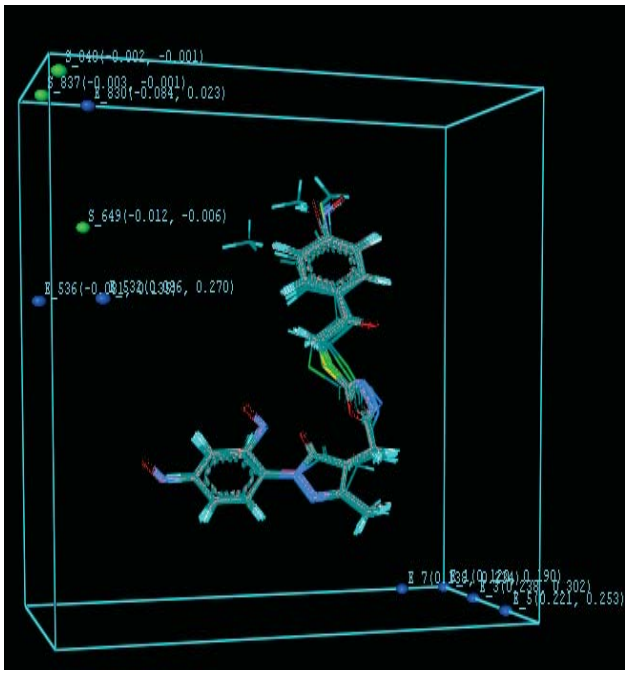


Figure 5: Stereo view of contribution plot showing steric and electrostatic field of interactions by kNN-MFA models

each chromosome using a weighted kNN cross-validation procedure. (4) Calculate fitness of each offspring using a weighted kNNcross-validation procedure. (5) Repeat steps until the convergence criteria or the maximum number of generations is reached.

Alignment of Molecules

Molecular alignment is a crucial step in 3D-QSAR study to obtain meaningful results. This method is based on moving of molecules in 3D space, which is related to the conformational flexibility of molecules. The goal is to obtain optimal alignment between the molecular structures necessary for ligand–receptor interactions. [24, 25] All molecules in the data set were aligned by template-based method using pyrazolone as template, where a template is built by considering common substructures in the series. A highly bioactive energetically stable conformation in this class of compounds is chosen as a reference molecule on which other molecules in the data set are aligned, considering template as a basis for the alignment.

RESULT AND DISCUSSION

With regard to QSAR modeling, as our goal was to establish a predictive model with a reasonable number of input features to ensure good generalization performance. While correlating various descriptors with biological activity is the most important means to study structure–activity relationships, the interest lies in deciding when to stop adding a new descriptor to the model. Thus, the optimal model should use the minimum number of descriptors to obtain the best fit. To achieve this, a well accepted method is to find out the saturation point, a point beyond which there is no considerable improvement in the regression coefficient (r^2 and q^2) values even if a new descriptor is

added (Table 2). MLR, PLS and PCR techniques was used in the present study for selecting a significant set of descriptors in order to build the significant models. The MLR, PLS and PCR model predicted the training data with r^2 of 0.9928, 0.9923 and 0.9703 together with q^2 estimating to 0.9733, 0.9021 and 0.9209 respectively. The plot of actual versus predicted values are shown in (Figure 2, 3, 4). The model gives the following equations:

Equation by MLR Model

pIC50 = -0.8817 (±0.0313) Fluorines count + 0.0113 (±0.0023) T_2_2_6 + 0.6876

Where Fluorines count (This descriptor signifies number of fluorine atoms in a compound) has negative contribution in the activity and T_2_2_6 (This is the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from any other double bonded atom by 6 bonds in a molecule) has positive contribution in the activity.

Equation by PLS Model

pIC50 = -0.8890 Fluorines count + 0.0271 H-Acceptor count + 0.9900

Where Fluorines count (This descriptor signifies number of fluorine atoms in a compound) has negative contribution in the activity and H-Acceptor count (Number of hydrogen bond acceptor atoms) has positive contribution in the activity.

Equation by PCR Model

pIC50 = -0.8890 Fluorine's count + 1.1526

Where Fluorine's count (This descriptor signifies number of fluorine atoms in a compound) has negative contribution in the activity.

3D QSAR Modeling

In the present study, kNN-MFA model is developed coupled with stepwise variable selection method to develop 3D-QSAR models 2-(5-((4,5-dihydro-3-methyl-5-oxo-1-aryl-1*H*-pyrazol-4-yl)methylene)-1,3,4-oxadiazol-2-ylthio)-1-(4-aryl phenyl)ethanone based on steric and electrostatic fields. A highly bioactive energetically stable conformation in this class of compounds is chosen as a reference molecule on which other molecules in the data set are aligned, considering template as a basis for the alignment. The aligned view 2-(5-((4,5-dihydro-3-methyl-5-oxo-1-aryl-1*H*-pyrazol-4-yl)methylene)-1,3,4-oxadiazol-2-ylthio)-1-(4-aryl phenyl)ethanone is presented in (Figure 1). In this study we have presented equation to this of the best regression model of the whole set. The kNN-MFA model showed significant k-Nearest Neighbour=2, N=8, Degree of freedom=7, q^2=0.6655, q^2_se=0.2446, Predr^2=-0.0701 and pred_r^{2}se=0.8028 proved a good conventional statistical correlation which have been obtained (Table 3). The contribution plot arising out of 3D-QSAR studies provide some useful insights for better understanding of the structural features of these compounds responsible for producing significant COX-2 inhibitory activity.

The points generated in SA KNN MFA 3D QSAR model are E_7 0.1382 0.2336, E_5 0.2206 0.2526, E_3 0.2385 0.3021, E_1 0.1199 0.1900, S_840 -0.0020 -0.0011, S_649 -0.0116 -0.0059, E_532 0.0860 0.2703, S_837 -0.0027 -0.0014, E_536 -0.0815 0.1354, E_830 -0.0837 0.0235 that is, steric and electrostatic interaction field at lattice points 50, 30, 10, 840, 649, 532, 837, 536, 830 respectively (Figure 5). These points suggested the significance and requirement of electrostatic and steric properties as mentioned in the ranges in parenthesis for structure–activity relationship and maximum anti-inflammatory activity of 2-(5-((4,5-dihydro-3-methyl-5-oxo-1-substituted phenyl-1H-pyrazol-4-yl)methyl)-1,3,4-oxadiazol-2-ylthio)-1-(4-substituted phenyl)ethanone analogues.

Negative values in steric field descriptors indicated the requirement of negative steric potential, for enhancing the anti-inflammatory activity of 2-(5-((4,5-dihydro-3-methyl-5-oxo-1-aryl-1*H*-pyrazol-4-yl)methylene)-1, 3,4-oxadiazol-2-ylthio)-1-(4-aryl phenyl)ethanone analogues. Therefore less steric substituents were preferred at the position of generated data points S_840 -0.0020 -0.0011 S_649 -0.0116 -0.0059, S_837 -0.0027 -0.0014 respectively around 2-(5-((4,5-dihydro-3-methyl-5-oxo-1-aryl-1*H*-pyrazol-4-yl)methylene)-1, 3,4-oxadiazol-2-ylthio)-1-(4-aryl phenyl)ethanone pharmacophore. Similarly the positive and negative values of electrostatic descriptors suggested the requirement of electropositive and electronegative groups at the position of generated data point E_7 0.1382 0.2336, E_5 0.2206 0.2526, E_3 0.2385 0.3021, E_1 0.1199 0.1900, E_532 0.0860 0.2703, E_536 -0.0815 0.1354, E_830 -0.0837 0.0235 respectively around 2-(5-((4, 5-dihydro-3-methyl-5-oxo-1-aryl-1*H*-pyrazol-4-yl)methylene)-1,3,4-oxadiazol-2-ylthio)-1-(4-aryl phenyl) ethanone pharmacophore for maximum activity. So more numbers of positive value in electrostatics descriptor suggested that electropositive groups important for anti-inflammatory activity. Results obtained and points generated around 2-(5-((4,5-dihydro-3-methyl-5-oxo-1-aryl-1*H*-pyrazol-4-yl)methylene)-1,3,4-oxadiazol-2-ylthio)-1-(4-aryl phenyl)ethanone pharmacophore using the 3D QSAR studies was used for correlation chemical nature of substituent's around pyrazolone attached oxadiazol rings with their observed activity.

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