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2D-QSAR Studies of Substituted Pyrazolone Derivatives as Anti-Inflammatory Agents

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Abstract

A QSAR study was performed on a series of substituted pyrazolone derivatives. The compounds in the selected series were characterized by spatial, molecular and electrotopological descriptors using QSAR module of molecular design suite (V-Life MDS 4.0). In present research paper we reported 2D-QSAR studies of substituted pyrazolone derivatives. Correlations between inhibitory activities and calculated predictor variables were established through partial least square regression (stepwise forward) method.

Keywords: 2D-QSAR; Anti-inflammatory; Pyrazolone

Introduction

Anti-inflammatory drugs are widely used for the treatment of pain, inflammation, rheumatoid arthritis and osteoarthritis. The common dose limiting toxicity of anti-inflammatory compounds is the increased risk of gastrointestinal ulceration, perforation and hemorrhage [1]. The enzyme cyclooxygenase (COX) catalyses the biooxygenation of arachidonic acid to prostaglandin G_2, which serves as a precursor for the synthesis of prostaglandins, prostacyclins and thromboxanes, which are collectively termed as prostanoids [2]. Non-steroidal anti-inflammatory drugs (NSAIDs), which are known to inhibit COX enzymes, are currently used as important therapeutic agents for the treatment of pain and inflammation. Celecoxib (aka: Celebrex®, Celebra®, Niflam®, and Onsenal®), a COX-2-selective NSAID is a pyrazole derivative. Celecoxib has relatively few gastrointestinal (GI) side effects but its long-term use is associated with cardiovascular injury, which limits its clinical applications [3]. Therefore, there is a need for the development of novel drugs with better safety profiles that could be used long-term to relieve chronic inflammatory conditions. A Quantitative Structure-activity Relationship (QSAR) study has been made on the inhibitions of some Matrix Metalloproteinases (MMPs) and Tumor Necrosis Factor-α Converting Enzyme (TACE) by benzodiazepine hydroxamic acid inhibitors [4]. Some QSAR studies also reported on some GSK-3α inhibitory 6-aryl-pyrazolo (3,4-*b*) pyridines [5].

Studying the Structure-Activity Relationships (SAR) for such compounds has been a fascination for scientists and efforts have been made to identify the essential physico-chemical requirements for the selective receptor [6]. QSAR can be performed by using Multiple Linear Regression (MLR) and Partial Least Square (PLS) analyses and molecular descriptors [7]. The results of QSAR were discussed critically on the basis of regression parameters [8].

The cyclooxygenase activity of the enzyme is the site of action of NSAIDs [9,10]. However, inhibition of prostanoid biosynthesis is associated with side effects such as ulceration and impairment of renal functions [11]. It has been well established that the cells express two isoforms of cyclooxygenases, namely cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) [12]. In previous study we reported molecular docking studies and synthesis of pyrazolone derivatives as anti-inflammatory agents [13].

Materials and Methods

Experimental methods

Molecular structure generation: All the molecular modeling and statistical analysis were performed using Vlife MDS 4.0 software [14]. The structures of the compounds were built using molecular sketching facilities provided in the modeling environment of Vlife engine and structures for 2D QSAR study selected from reported article [15]. Energy minimization and batch optimization was carried out using Merck Molecular force field. All the molecules were initially optimized and then used for the calculation of descriptors and further QSAR study.

QSAR study: All the 2D descriptors (thermodynamic, spatial, electronic and topological parameters) were calculated for QSAR analysis using Vlife MDS software. Thermodynamic parameters describe free energy change during drug receptor complex formation. Spatial parameters are the quantified steric features of drug molecules required for its complimentary fit with receptor. Electronic parameters describe weak non-covalent bonding between drug molecules and receptor [16,17].

Sr. No.	Statistical parameter	2D-QSAR Results
	r^2	0.9566
	r^2SE	0.0043
	q^2	0.8873
	q^2SE	0.0095
	Pred_r^2	0.5228
	Pred_r^2SE	0.1554
	F-Test	44.1002
	α $q2$	0.100
	Best-Rand $q2$	0.2341
	Z-score $q2$	2.2612
	N	10
	Contributing descriptors	+ 0.0356 chi2 + 0.0345 SdsNcount

Table 1: Statistical results of 2D-QSAR equation generated by Partial Least Square Regression method.

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Citation: Antre RV, Oswal RJ, Kshirsagar SS, Kore PP, Mutha MM (2012) 2D-QSAR Studies of Substituted Pyrazolone Derivatives as Anti-Inflammatory Agents. Med chem 2: 126-130. doi:10.4172/2161-0444.1000127

Stepwise partial least square regression was used to generate QSAR equations. Random Selection method and Sphere Exclusion Method were used for the selection of the training and test set (Table 1).

The maximum and minimum value in training and test set were compared in a way that [18]:

1. The maximum value of PIC_{50} of test set should be less than or equal to maximum value of PIC_{50} of training set.

2. The minimum value of PIC_{50} of test set should be higher than or equal to minimum value of PIC_{50} of training set.

For QSAR purpose anti-inflammatory activity was selected as dependent variable and remaining variables considered as independent variables. Form Stepwise variable selection forward-backward method was used. A suitable statistical method coupled with a variable selection method allows analyses of this data in order to establish a QSAR model with the subset of descriptors that are most statistically significant in determining the biological activity [19,20]. The QSAR models were generated by Partial Least Square Regression method.

Results and Discussion

For QSAR analysis regression was performed using IC50 values as dependent variables and calculated parameters as independent variables. In any thorough investigation of the effects of molecular properties, it is essential to prove that the results are both statistically valid and make chemical sense. It would be appropriate to obtain insight into the physical meaning of the correlation obtained as an output of

the regression analysis. The magnitude of a descriptor could be used as a guideline to improve the anti-inflammatory activity of molecules.

The generated QSAR model was selected on the basis of various statistical parameters such as squared correlation co-efficient (r^2) which is relative measure of quality of fit. Fischer's value (F test) which represents F-ratio between the variance of calculated and observed activity, standard error (r^2_se) representing absolute measure of quality of fit, and cross-validated square correlation co-efficient (q^2), standard error of cross-validated square correlation co-efficient (q^2_se), predicted squared regression (pred_r^2) and standard error of predicted squared regression (pred_r^2se) to estimate the predictive potential of the models respectively.

The best QSAR equation is discussed below. The model consist of Training Set Size=4; Test Set Size=6 (Figure 1 and Figure 2 respectively).

Interpretation of QSAR studies

-LogIC50=+0.0356 chi2+0.0345 SdsNcount+0.6370

chi2: This descriptor signifies a retention index (second order) derived directly from gradient retention times. SdsNcount: This descriptor defines the total number of nitrogen connected with one single and one double bond.

The model fulfills the selection criteria's like correlation coefficient r^2>0.8 (0.9566) for anti-inflammatory activity with low standard error of squared correlation coefficient r^2_se<0.3 (0.0043) show the relative
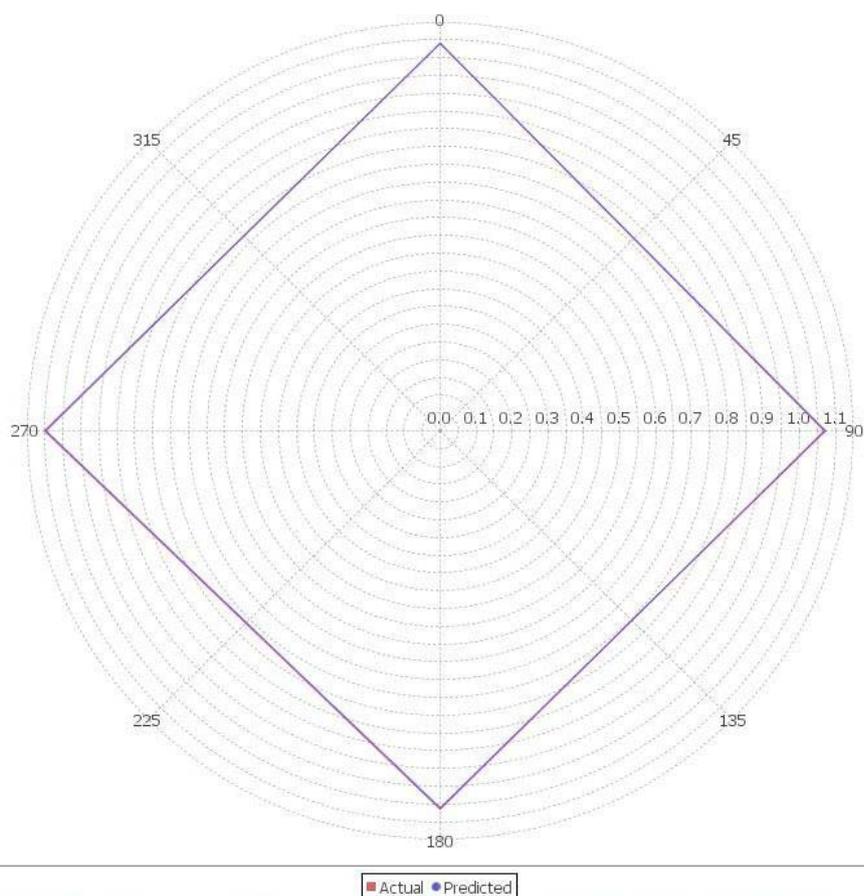

Figure 1: Actual activity V/S predicted activity for training set.
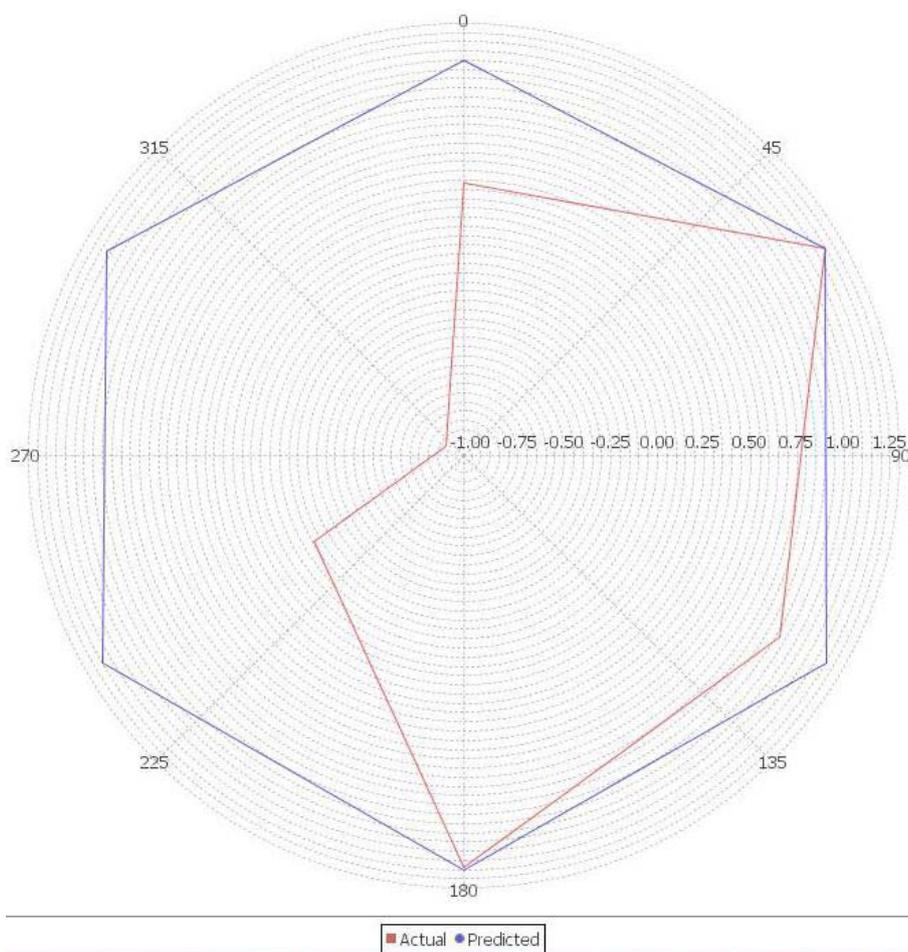
Figure 2: Actual activity V/S predicted activity for test set.

Compound Code	Structure	Actual Activity PIC_{50}	Predicted Activity PIC_{50}	Residual	logP
5a		1.0898	1.09099	-0.00119	2.69
5b		0.4345	1.0981	-0.6631	-0.48

5c		1.0678	1.07214	-0.00434	3.08
5d		1.0662	1.06277	0.00343	2.82
5e		1.1002	1.0981	0.0021	3.49
5f		1.2037	1.19737	0.00633	-0.77
5g		0.92281	1.20491	-0.2821	-0.56
5h		1.1927	1.20449	-0.01179	0.32
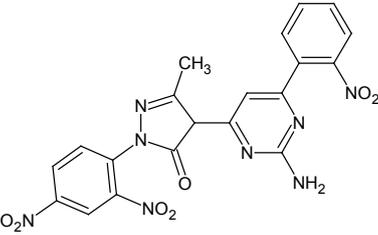
5i		-0.10841	1.20226	-1.13067	-0.56
5j		-0.9338	1.7251	-2.6589	0.1
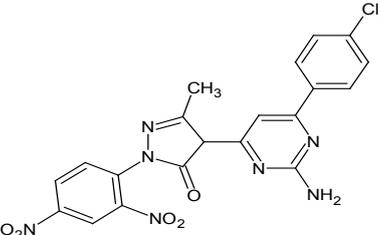
Table 2: Actual Activity, Predicted Activity, Residual and logP for compounds (5a-5j**).

good fitness of the model and F value>11 times than tabulated F value show the 99% statistical significance of the regression model.

The validation criteria for selection of the model are cross validated squared correlation coefficient q^2>0.8 (0.8873) for training set and pred_r^2>0.40 (0.5228) for test set. This model fulfill all validation criteria with low standard error of cross validated squared correlation coefficient q^2_se<0.3 (0.0095) and standard error of pred_r^2se< 0.3(0.1554), which show accuracy of the statistical calculation. The cross correlation limit is 0.5 which show inter-pair correlations among the selected descriptors are very low. Two descriptors as chi2 and SdsNcount contribute positively to model.

Conclusion

The above QSAR study revealed that for anti-inflammatory activity, Chi2 and SdsNcount contributes positively. This suggests that by change in number of chi2 and SdsNcount will be helpful for designing of more potent anti-inflammatory agents. Consequently this study may prove to be helpful in development and optimization of existing anti-inflammatory activity of this class of compounds (Table 2).

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