Original Article

In Silico 2D-QSAR Analysis of 2-Aryl Pyridine Inhibitors of Mitogen-Activated Protein Kinase-2 as Anti-Rheumatoid Arthritis Agents

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ABSTRACT

A set of twenty-six compounds 2-Aryl pyridine derivatives with anti-rheumatoid activity was subjected to the two dimensional quantitative structure activity relationships studies using V life molecular drug design suit. Drug Designing module describe with various combinations of molecular connectivity indices, electro topological indices, alignment independent descriptors and other 2D descriptors. 2-Aryl pyridine taken as the lead molecule and QSAR model developed using multiple regression approach. For each set of descriptors, the best multi-linear QSAR equations were obtained by the stepwise variable selection method using leave-one-out cross-validation as selection criterion. Logarithmic inverse value of IC_{50} was taken as dependent variable and parameters slogP and T_C_O_2, T_T_N_1, T_N_Cl_4, T_N_F_6 topological parameter was taken as independent variable. The best QSAR model (r^2 = 0.8850, F = 23.08, r^2 se = 0.14, q^2 se = 0.222, Pred_r^2 = 0.2307, pred_r^2se = 0.3226) has acceptable statistical quality and predictive potential as indicated by the value of cross validated squared correlation coefficient (q^2 = 0.75. Thus this validated model brings important structural insight to aid the design of novel anti- rheumatoid activity.

Keywords: Anti-rheumatoid, 2D-QSAR, IC_{50}, Descriptors.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by an imbalance of proinflammatory and anti-inflammatory cytokines, autoimmunity, joint inflammation, and eventual joint destruction. Use of biologic therapeutics that neutralize these cytokines has shown some clinical success in reducing joint pain and inflammation while retarding joint destruction. Limits to the use of biologics in RA include the high cost of protein pharmaceuticals, parenteral administration,

loss of efficacy over time, risk of infection, and a significant portion of patients who show partial or no response to these agents[1-2].

Therefore, development of orally active small-molecule inhibitors that target signaling pathways regulating inflammatory cytokine production could add significant value to unmet medical need. p38_ kinase was identified as a target that regulates inflammatory cytokine biosynthesis. Since then, kinases have been hotly pursued as drugable targets that regulate inflammation signaling pathways[3-4]. Activation of the p38 kinase pathway in immune cells leads to the transcriptional and translational regulation of proinflammatory cytokine synthesis. Many p38 kinase inhibitors have subsequently been developed that demonstrate inhibition of TNF_, IL-1_, and IL-6 production and display anti-inflammatory efficacy in animal models[5-6].

Tumor necrosis factor-α (TNFα) is a cytokine that is overproduced in inflammatory disease states such as rheumatoid arthritis[7] (RA). Clinical efficacy of anti TNFα biological such as etanercept, infliximab and adalimumab demonstrate the importance of TNFα in inflammatory disease.[8-11]

Inhibitors of p38 MAP Kinase have been shown to play an important role in the regulation of the production of inflammatory cytokines such as TNFα[12-13]. More recently, VX-702 was reported as being efficacious for the treatment of RA in a phase II trial in combination with methotraxate.

The objective of present work is to determine the physicochemical parameters, which governs the anti- rheumatoid arthritis activity with a view to provide a better rational design of some more potent drugs in the present series. QSAR studies were performed to identify associated molecular properties and also to optimize their anti-rheumatoid activity.

MATERIALS AND METHODS

Selection of series

The series of twenty-one compounds of 2-Aryl pyridine derivative[14] were reported to have anti-rheumatoid activity. All the values of biological data's were expressed as IC_{50} values. For present biological activity data's were converted to –Log unit in mathematical operation mode to reduce skewness of data set. The general structure of these analogues is shown in "Figure 1" and compounds with their biological activity data are shown in (Table 1). The molecular modeling studies were performed using MDS 3.0, supplied by V Life science[3]. The structure of each compound was drawn in 2dappl mode of software and export in 3D mode for create 3D model. Energy minimization was performed of each model using MMFF. The basis of energy minimization is that the drug binds to effectors/receptor in the most stable form i.e. minimum energy state form.

Energy minimized geometry was used for calculation of various thermodynamic, steric, topological and electronic descriptors. The relationship between biological activities and various descriptors is established by sequential multiple regression analysis (MLR) and Partial least square (PLS) using MDS 3.0, in order to obtain QSAR models. Anti-rheumatoid arthritis activity data and various physiochemical parameters were taken as independent and dependent variables respectively and correlation were established between them by employing multiple sequential regression (MLR) method. For the generation of the QSAR model we have selected the five test set and twenty one training set.

When these compounds were subjected to QSAR analysis, in order to develop QSAR models, various statistically significant two parametric models were obtained. The parameters T_C_O_2 (35%),

T_T_N_1 (18%), T_N_Cl_4 (10%) were contributed positively and slogP (28%), T_N_F_6 (10%) were negatively contributed in anti- rheumatoid arthritis activity, "Figure 3".

All chemical structures and their descriptors[15-21] i.e. molecular connectivity indices (MCI), electro topological indices (EI), alignment independent (AI) descriptors and other 2D descriptors such as logP (partition coefficient) etc. were calculated by using VLifeMDS software[16]. MCI descriptors are calculated on the basis of chemical graph theory. Calculated molecular descriptors have been used for the development of QSAR models. The whole data set was divided into 21 training and 5 test sets, (Table 2).

RESULTS & DISCUSSION

A quantitative structure activity relationship (QSAR) study on a series of analogs of 2-Aryl pyridine derivatives for their anti-rheumatoid activity has been made using combination of various descriptors. Different physicochemical parameters were taken for each substituent in order to obtain QSAR models. Following statistical parameters were considered to generate QSAR models: correlation coefficient (r), squared correlation coefficient (r^2), standard error of estimate (s) and Fisher's value (F), which represent F-ratio between the variance of calculated and observed activity. In order to validate the generated QSAR models leave one out (LOO) method was used. Squared cross-correlation coefficient (Q^2), standard deviation of sum of square of difference between predicted and observed value (S_{PRESS}) and standard deviation of error of prediction (S_{DEP}) were also used for each model to estimate the predictive potential of models.

All models were screened on the basis of intercorrelation with in the descriptors (<0.9) leave one out cross-validated squared correlation coefficient (q^2>0.6). Hence model 1 was considered as the best model with best statistical results (Table II).The stepwise regression analysis generated a large number of QSAR equation, out of which the best equation (model 1) was found to be as given below-

Model-1 (MLR)

Log_{10} (IC_{50}) = 0.3518 T_C_O_2 - 0.2933 slogP + 0.1315 T_T_N_1 + 0.3770 T_N_Cl_4- 0.3479 T_N_F_6 + 0.5166

(n = 21, r2 = 0.8850, F = 23.08, q^2 = 0.7486, r^2 se = 0.14, q^2 se = 0.222, Pred_r^2 = 0.2307, pred_r2se = 0.3226)

Model-2 (PLS)

Log_{10} (IC_{50}) = + 0.3985 T_C_O_2 -0.3266 slogp+ 0.1775 T_T_N_1+ 0.1364 T_T_Cl_4 + 0.1947

(n = 21, r2 = 0.8385, q2 = 0.7200, F test = 29.4282, r2 se = 0.1581, q2 se = 0.2083, pred_r2 = 0.6458, pred_r2se = 0.6226)

From the results (Model 1) obtained, it was concluded that parameters T_C_O_2 (count the number of carbon atom separated from any oxygen atom by two bond distance in a molecule), T_T_N_1 (count of number of nitrogen atom separated from any other nitrogen atom by single bond in a molecule), T_N_Cl_4 (count of number of oxygen atom separated from chlorine atom 4 bond distance in a molecule), contributes positively towards biological activity. Whereas slogP (signifies log of octanol/water partition coefficient), T_N_F_6 (count of number of nitrogen atom separated from Fluorine atom 6 bond distance in a molecule), contributes negatively towards biological activity. Low standard error of estimate of this model (se<0.3) demonstrates the accuracy of the model. Higher Q^2 value reflects good predictive potential of the model. To ascertain the predictivity of the model, internal validation using leave one out

cross validation process, bootstrapping technique test was performed. The model's Q^2>0.6 supported the predictive ability and significance model. The r^2 supported the robustness of the model, as well as indicated that, no single compound of the series contributed much more to the model.

CONCLUSION

The study revealed that for anti-rheumatoid activity, the parameters T_C_O_2, T_T_N_1, T_N_Cl_4 were contributed positively and slogP, T_N_F_6 were negatively contributed in anti-rheumatoid arthritis activity.

This suggests that by Modification in topological indices will be helpful for designing of more potent anti-rheumatoid agents. Results of the QSAR studies may be utilized for the rational designing of the compounds with expectation to obtain the potent anti-rheumatoid agents, which would be patented in the near future. The work is planned to meet out challenges of complications arriving due to inflammatory disorders.

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Table 1. Biological Activity of Data of 2-Aryl Pyridine Derivatives as Anti Rheumatoidal Agents.

S. No.	R in comp. (A)	(IC_{50} µM)	S. No.	R in comp. (B)	(IC_{50} µM)
1	H	19	**9**	2-OH	47
2	Cl	1.4	**10**	3-OH	36
3	4-Pridyne	23	**11**	4-OH	35
4	3-Pyridine	9.9	**12**	2-Cl	9
5	3-thienyl	6.8	**13**	3-Cl	2.6
6	3-Naphthyl	4.2	**14**	4-Cl	2.7
7	2-benzothienyl	5.7	**15**	2-F	4.8
8	3-quonoline	4.4	**16**	3-F	7.4
			17	4-F	2.4
			18	4-CF3	3.8
			19	4-Ac	18
			20	4-MeO	2.2
			21	4-NH2	12
			22	4-CONH-c-pentyl	23
			23	4-CONH-c-hex	10
			24	4-CONHCH2Ph	20
			25	4-CONH(CH)2Ph	11
			26	4-CON(Me)CH2Ph	15

Table 2. Actual and Predicted Anti-rheumatoidal Activity of generated model 1

	Training Set		Test Set	
S. No.	Actual	Predicted	Actual	Predicted
1	0.3802	0.3802	0.1461	0.7689
2	0.4314	0.5772	0.3424	1.4131
3	0.6435	0.8712	0.5798	0.5019
4	0.6628	0.5772	0.6232	0.4306
5	0.6812	0.7281	0.7559	0.7732
6	0.8325	0.7509		
7	0.8692	0.7281		
8	0.9542	0.9542		
9	0.9956	1.2094		
10	1.000	1.0721		
11	1.0141	1.0985		
12	1.0792	1.0230		
13	1.1761	1.1297		
14	1.2553	1.4700		
15	1.2788	1.2802		
16	1.3010	1.1555		
17	1.3617	1.1865		
18	1.3617	1.2094		
19	1.5441	1.5589		
20	1.5563	1.5589		
21	1.6721	1.5589		

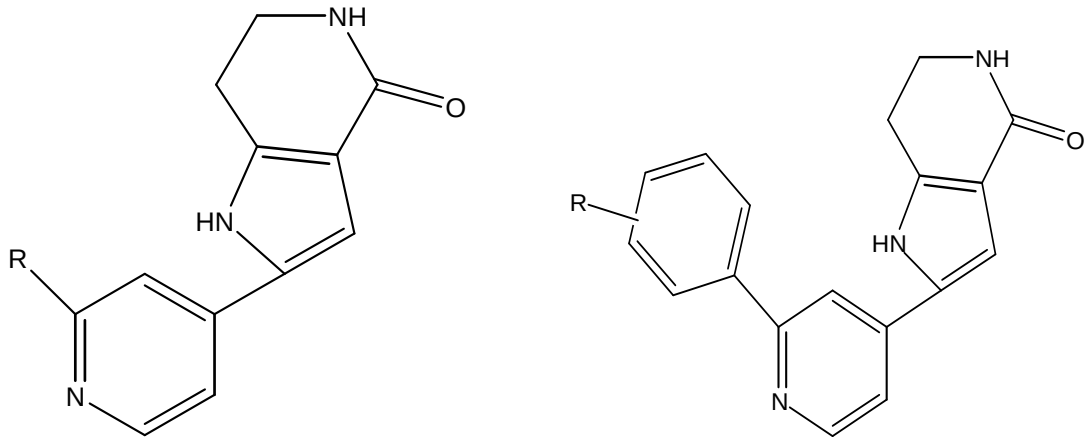

Figure.1. General structure of 2-Aryl Pyridine derivatives.

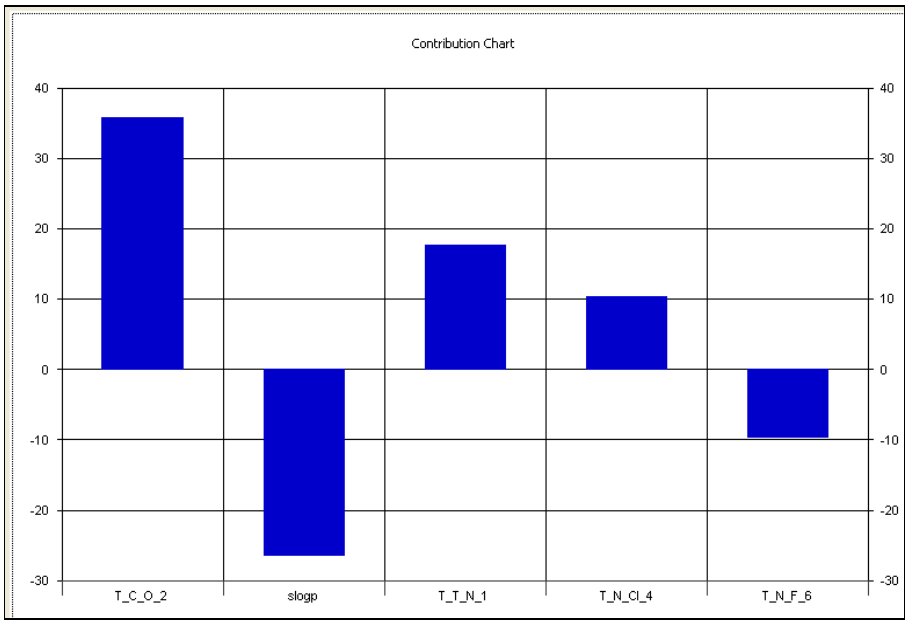

Figure.2. Contribution chart of descripter for model 1(MLR method)

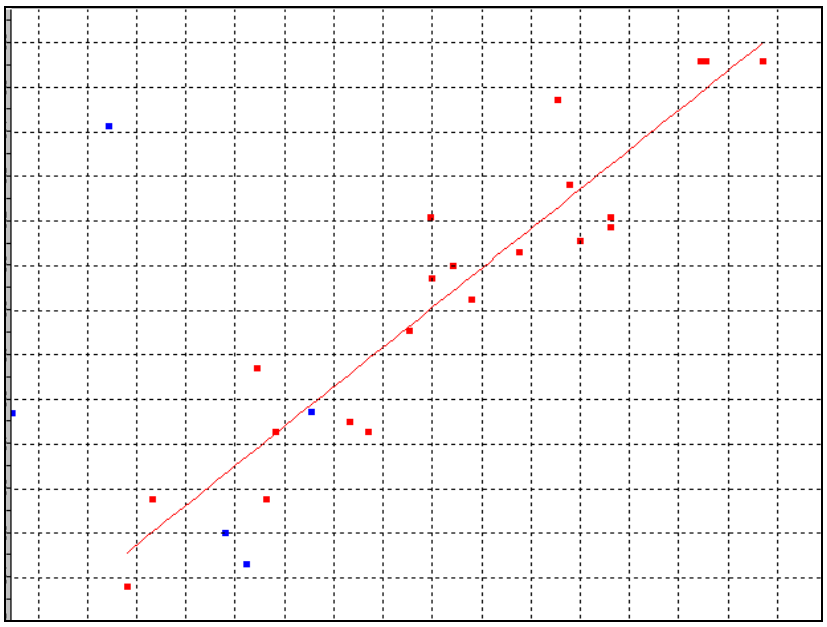

Figure.3. Plot of cross-validated calculated activity obtained (model 1)

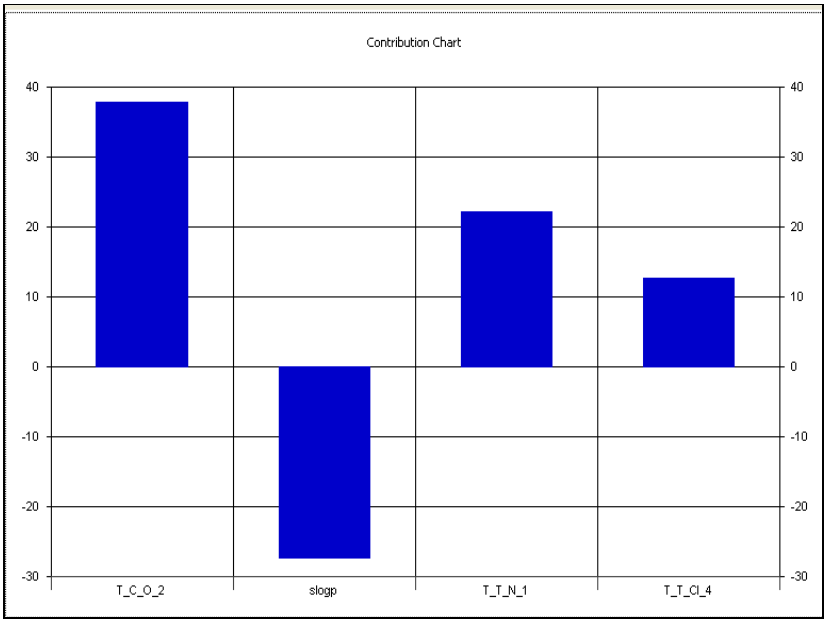

Figure.4. Contribution chart of descriptor for Model 2 (PLS method).

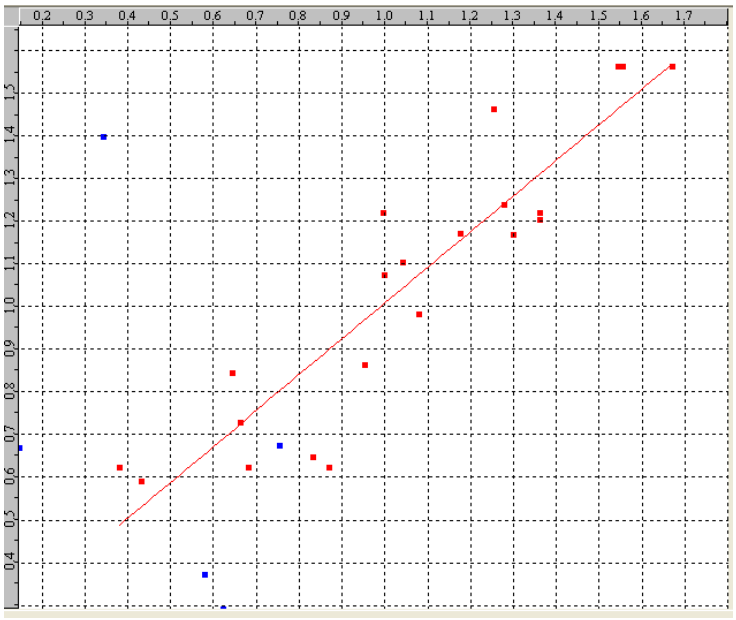

Figure.5. Plot of cross-validated calculated activity obtained (model 2)