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Research Article

QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF PYRAZOLONE-BASED ANAPLASTIC LYMPHOMA KINASE (ALK) INHIBITORS

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ABSTRACT

Objective: Anaplastic lymphoma kinase (ALK) enzyme has important role in the development of several tumors. Quantitative structure-activity relationship (QSAR) study of some recently studied series of ALK inhibitors will provide the rationale to structure modification for the better efficacy and sensitivity to ALK inhibition. The main objective of the present work is to uncover the minimum structural requirements for ALK inhibitors containing Pyrazolone as scaffold using QSAR studies.

Methods: Quantitative structure-activity relationship (QSAR) study was performed using 23 ALK inhibitors containing pyrazolone scaffold. Descriptors such as Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied Molecular Orbital (LUMO) and calculated logP (cLogP) were calculated. QSAR models were derived and validated to judge the reliability of models.

Results: Present study offered good, predictive and statistically significant models. Among all the derived models, model-3 which correlates cLogP, HOMO and LUMO descriptors with ALK inhibition (r = 0.837) was found to be best model.

Conclusion: The best model obtained shows that cLogP, HOMO and LUMO properties of the molecules are the important parameters that needs to be considered while designing new potent ALK inhibitors.

Keywords: QSAR, Anaplastic Lymphoma Kinase inhibitors, Pyrazolone derivatives

INTRODUCTION

Anaplastic lymphoma kinase (ALK) enzyme is tyrosine kinase receptor and belong to insulin receptor subfamily. ALK enzyme is normally expressed in the central and peripheral nervous systems. ALK has important role in the development of several tumors. It is identified as fusion proteins comprised of nucleophosmin (NPM) and intracellular domain of ALK. This generated fusion (mutant protein), NPM-ALK responsible for oncogenic effect [1-3]. ALK has been a potential therapeutic target for cancer in several drug discovery programs [4, 5]. Various small molecules that inhibit ALK enzyme include methanesulfonamido-cyclohexylamine [6], aryloxyoxo pyrimidinone [7] 2, 3, 4, 5-tetrahydro-benzo[*d*]azepine derivatives of 2,4-diaminopyrimidine [8], pyrazolone derivatives [9] etc.

Current ALK inhibitors have several side effects like low levels of testesteron in male, nausea, diarrhea/constipation, dark/light vision changes and rare blood changes in liver tests etc. Keeping this in mind, in order to find highly potent ALK inhibitors with minimal side effects, a quantitative structure-activity relationship (QSAR) studies on some reported series of small molecules, will provide the rationale to structure modification for identification of the better potent ALK inhibitors. QSAR study not only provides minimum essential structural requirements but also it helps to optimize lead compounds to obtain newer more potent molecules [10-14]. Till date the discovery of newer, potent ALK inhibitors hampered due to lack of molecular modeling & computer-aided drug design studies. Considering the wealth of previously reported ALK inhibitors, it was thought to uncover the minimum structural requirements for ALK inhibitors containing Pyrazolone as scaffold based on preliminary QSAR studies.

MATERIALS AND METHODS

ALK inhibitory activity data IC_{50} (nM) was taken from the published work [9]. The experimental IC_{50} values were evaluated with VEGFR2 assay. The negative logarithm of the measured IC_{50} (nM) [pIC_{50} = -log (IC_{50})] was used as dependent variable for QSAR analysis. Compounds and their biological activity data have been shown in Table 1. Compounds having only definite activities were considered for the study. Compounds with insignificant activities were excluded from the dataset. Compounds were sketched using Chemdraw 8.0 and converted to 3D structures. Energy minimization and geometry optimization was carried out using standard force field up to 0.001 RMS gradients. Energy-minimized geometry of each compound was used for the calculation of descriptors.

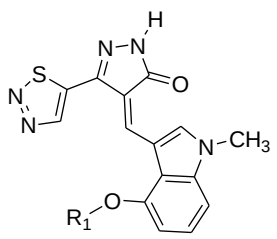
Regression analysis

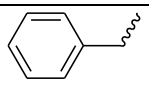
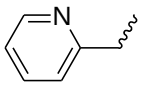
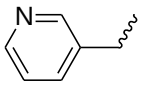
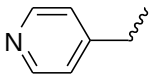
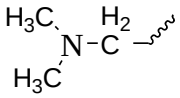
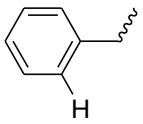
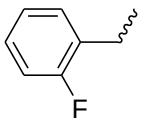
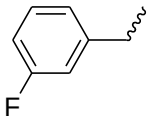
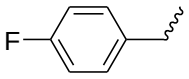
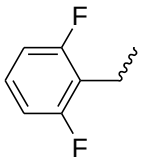
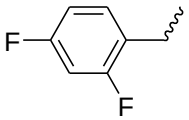
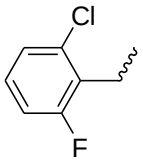
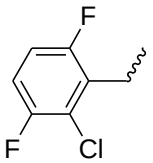
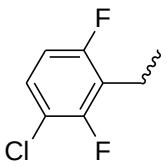
Regression analysis was performed using statistical methods as model building methods. QSAR models were generated using pIC_{50} values as the dependent variable and various descriptors values as independent variables.

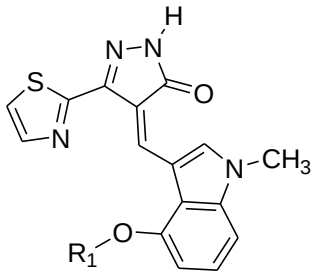
Statistical Validation

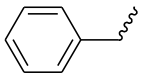
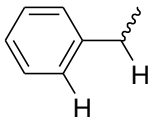
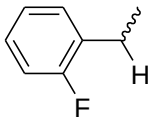
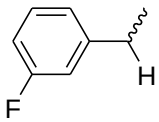
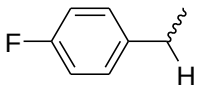
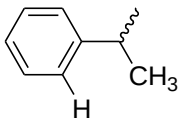
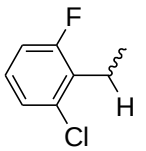
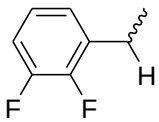
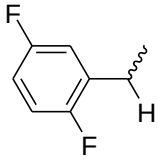
Developed models were subjected to statistical validation in terms of number of compounds in regression (n), correlation coefficient r, F-test (Fisher test value) for statistical significance (F), standard error (SE) of estimation, etc. The data set of 23 compounds [9] was used for the development of the QSAR models.

Table 1: Anaplastic lymphoma kinase inhibitors with their pIC_{50} values



S. No.	R_1	pIC_{50}			HOMO (eV)	LUMO (eV)	cLogP
		Observed	Estimated	Residual			
1.		7.6382	7.308	0.330	-8.22258	-1.94363	3.73
2.		6.8013	7.032	-0.231	-8.92251	-4.00544	2.233
3.		6.4634	6.808	-0.344	-9.02889	-1.21452	2.233
4.		7.2596	6.829	0.430	-9.06615	-1.26524	2.233
5.		6.5361	6.617	-0.080	-8.85614	-0.975633	2.0608
6.		7.6382	7.521	0.118	-8.91631	-0.944827	3.73
7.		7.886	7.597	0.289	-8.91592	-0.95566	3.873
8.		7.6989	7.62	0.073	-8.97973	-0.965881	3.873
9.		7.9208	7.633	0.288	-8.99044	-0.980766	3.873
10.		7.9208	7.671	0.250	-8.90508	-0.987133	4.016
11.		7.9208	7.709	0.212	-8.99046	-0.985889	4.016
12.		7.677	7.963	-0.286	-8.89252	-0.966536	4.586
13.		7.8538	8.075	-0.222	-8.96646	-1.00328	4.729
14.		8.301	8.057	0.244	-8.92851	-0.983072	4.729



S. No.	R_1	*p*IC_{50}			HOMO (eV)	LUMO (eV)	cLogP
		Observed	Estimated	Residual			
15.		7.3372	7.493	-0.156	-8.74467	-0.563756	3.893
16.		7.3372	7.492	-0.155	-8.72498	-0.644281	3.893
17.		7.3372	7.583	-0.245	-8.75409	-0.669295	4.036
18.		7.602	7.614	-0.012	-8.81459	-0.709224	4.036
19.		7.2006	7.617	-0.416	-8.83143	-0.663482	4.036
20.		7.3767	7.69	-0.313	-8.77526	-0.775948	4.202
21.		7.886	7.944	-0.058	-8.7205	-0.669587	4.749
22.		7.8538	7.662	0.192	-8.82703	-0.755158	4.109
23.		7.7695	7.692	0.078	-8.81675	-0.72562	4.179

RESULT AND DISCUSSION

Validation of QSAR Model

A quantitative assessment of model robustness was performed through model validation. All the statistical parameters of model validation have been calculated. These parameters as follows:

1. ***n*:** *n* is the number of data points. For a good QSAR model, at least 20 data points are required. (*n* = 23)
2. Standard Error **(*se*):** The smaller s value is always required for the predictive QSAR model. (*se* = 0.2697)
3. Fischer Statistics **(*F*):** The F value of the QSAR model suggests that the QSAR model is statistically significant. (*F*-value = 14.86)
4. Correlation coefficient **(*r*):** The value of correlation coefficient may vary between 0 (means model without explanatory power) and 1 (means perfect model). QSAR model having *r* > 0.6 will only be considered for validation [15, 16] (*r* = 0.837).

The regression plot for best model (i.e. model-3) is depicted in Figure 1. This also suggests the significance of the QSAR model. The observed activity on abscissa and estimated activity on ordinate yields a linear regression with slope Y=0.999X.

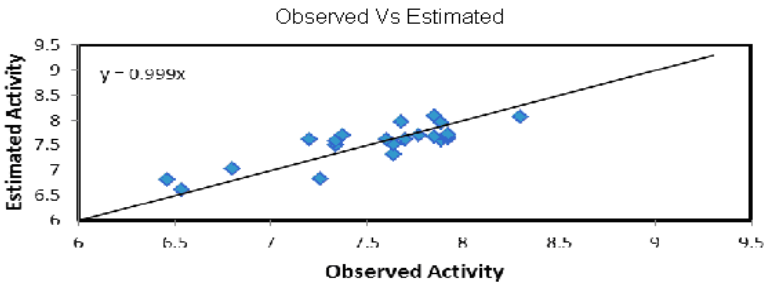


Fig. 1: Correlation between observed and predicted activity

Structures and their biological activities of ALK inhibitors are shown in Table 1. Descriptor values for each compound are also shown in Table 1. Initially, a QSAR model was developed using cLogP as an independent variable. The model obtained is as follows:

pIC_{50} = 0.4635*cLogP + 5.7768……Model 1

n = 23, *F*-ratio = 41.86, Std. Error = 0.2713, Correlation Coefficient <*r*> = 0.816

Values of *r*, *F*, Std. Error proved that QSAR model obtained was statistically significant and showed variation in biological activity (*Y*-variance=66.6%). Model 1 correlates cLogP property with the biological activity with correlation coefficient <*r*> = 0.816. This model suggests that lippophilicity character of ALK inhibitors is an important criterion for designing new and potent ALK inhibitors.

Energies of HOMO & LUMO are very popular descriptors in building QSAR models. The orbitals play major role in many chemical reactions & binding interactions of ligands to the enzymes. Keeping this in mind, another model was developed with HOMO & CLogP as descriptors. The model thus obtained is as follows:

pIC_{50} = 0.4810*clogP -0.3851*HOMO+ 2.3001…… Model 2

n = 23, *F*-ratio = 21.76, Std. Error = 0.2699, Correlation coefficient <r> = 0.828

The above model indicates that HOMO descriptor along with cLogP correlates with biological activity with <*r*> = 0.828. This value was found to be better than that of model no. 1. This suggests that both the descriptors (HOMO & cLogP) are important for contributing ALK inhibitory activity. It may be concluded from the above results that ALK inhibitors considered in the present study can interact with the enzyme by the attack of electrophiles present in the enzymes.

Another QSAR model was developed to check the contribution of LUMO along with other descriptors i.e. HOMO, cLogP. The model obtained is as follows:

*p*IC50 = 0.5273*cLogP-0.4465*HOMO-0.0974*LUMO + 1.4806 Model 3

n = 23, *F*-ratio = 14.86, Std. Error = 0.2697, Correlation coefficient <*r*> = 0.837

The model indicates that along with cLogP and HOMO, LUMO descriptor correlate well with the biological activity. The higher significance of this model is proved by the better correlation coefficient value (*r* = 0.837 in Model 3). *Y*-variance for this data set was found to be 70.1%. This model implies that these ALK inhibitors can interact with enzymes by attack of nucleophiles.

Table 2: Correlation matrix for best QSAR model (Model 3)

	pIC_{50}	HOMO	LUMO	CLogP
pIC_{50}	1.000			
HOMO	0.042	1.000		
LUMO	0.331	-0.33	1.000	
CLogP	0.416	0.217	0.512	1.000

The actual and predicted activities along with their residuals are shown in Table 1. The correlation matrix for three descriptors with biological activities is shown in Table 2. This suggests that there is no or less interdependency among the descriptors used in the study.

The correlation graph for actual and predicted ALK inhibitory activities is shown in Figure 1.

CONCLUSION

It can be suggested that cLogP, HOMO & LUMO properties of pyrazolone-based ALK inhibitors are the important properties that have to be checked while developing new potent ALK inhibitors as they are deciding factors for their activity. It may be concluded from the above results that since HOMO and LUMO properties of ALK inhibitors are well correlated with biological activity, they can interact with the enzyme by the attack of electrophiles present in the enzymes and/or inhibitors can interact with enzymes by attack of nucleophiles.

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