Original Article

3D QSAR Studies on Some 5-(*1H*-Indol-5-yl)-1, 3, 4-Thiadiazol-2 Amines as Potential PIM-1 Inhibitors

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ABSTRACT

Objective: Proviral integration site for moloney murine leukemia virus (PIM) kinases are among the contemporary targets for cancer chemotherapy as they play a pivotal role in inhibition of apoptosis and oncogenic signaling. Owing to their structural and functional dissimilarity to other kinases, they can be specifically targeted. The present study is an attempt to establish three dimensional quantitative structure activity relationship (3D QSAR) between some 5-(*1H*-Indol-5-yl)-1,3,4-thiadiazol-2-amines for their inhibitory activity against PIM by partial least squares regression (PLSR) analysis. **Method:** PLSR coupled with different variable selection methods such as stepwise (forward-backward) (SW), genetic algorithm (GA) and simulated annealing (SA) was performed to derive QSAR models and these models were validated for statistical significance internally and externally and robustness. **Results:** Two most significant models were generated through GA with optimum values of validation parameters. Among these model 1 exhibited q^2 and pred_r^2 values of 0.7523 and 0.8714 and model 2 evinced 0.6577 and 0.7675 respectively. The steric field point in model 1 suggests the need of more bulky group at this position and the positive coefficients of electrostatic field points at positions E_999, E_1162 respectively indicate the need of electronegative groups for favorable biological activity. Model 2 suggests the requirement of a positive hydrophobic group at H_564 and less electronegative and more electronegative group at E_157 and E_630

respectively for more potent biological activity. **Conclusion:** More bulky and/or hydrophobic R groups apart from the electrostatic contribution may be favorable for better PIM-1 inhibition of 5-(*1H*-indol-5-yl)-1,3,4-thiadiazol-2 amines.

Key words: 1,3,4-Thiadiazole-2-amine, PIM, QSAR, Anticancer, PLSR.

Key Message

The quantitative structure activity relationship analysis on 5-(*1H*-indol-5-yl)-1,3,4-thiadiazol-2 amines was carried out for PIM-1 inhibitory activity. The present study suggested the requirement of steric bulk and/or hydrophobic group at third position of indole ring for better activity.

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INTRODUCTION

Proviral integration site for moloney murine leukemia virus kinases (PIM) constitute a family with high sequence and structural similarity (PIM-1, PIM-2 and PIM-3) belonging to serine/threonine kinases.[1] They differ from other kinases in that they are constitutively activated and regulated at their post trascriptional and post translational levels. Another contrasting difference of PIMs to other kinases is the presence of proline residue in the hinge region of ATP binding pocket in the former which results in a unique molecular recognition site among the kinase family. They are primarily regulated by growth factor and cytokine signaling downstream of PTK/STAT activation.[2] The role of PIMs is implicated in tumor growth and activation of oncogenic MYC signaling. Their function in tumor growth is attributed to inhibition of apoptosis by targeting the proapoptotic B-cell lymphoma 2-associated death promoter (BAD). They activate the MYC signaling by phosphorylating the serine residue on histone H3 on the nucleosome of c-myc binding site, thus contributing to increased trascriptional activation of c-myc over expression or deregulation of PIM-1 and PIM-2 may result in different hematologic cancers such as diffuse large B-cell lymphoma, folicular lymphoma, hodgkin's lymphoma and mucosa-associated lymphoid tissue (MALT) and solid tumors while PIM-3 leads to adenocarcinomas.[3-5] Owing to the above, PIMs are perceived to be attractive therapeutic targets due to their role in inhibition of apoptosis and promoting cell proliferation.

Compounds having thiadiazole nucleus are reported to have a number of biological activities like antituberculosis,[6-8] antiproliferative,[9,10] antibacterial,[11,12] anticancer,[13-15] antifungal,[16,17] antihyperlipidemic,[18] and anti-inflammatory.[19] 5-(*1H*-indol-5-yl)-1,3,4-thiadiazol-2-amines were also reported as potent PIM inhibitors showing excellent potency against all three PIM isoforms.[20] Quantitative Structure Activity Relationship (QSAR) is a technique to establish the quantitative relationship between physiochemical or structural properties of congeneric series of compounds and their biological activity using statistical methods. It is a part of ligand based drug design which can be utilized for prediction of activity of hitherto experimentally untested compounds.[21-24] Thus it may prove to be a time and cost efficient method for new lead discovery. The present study is an attempt to determine QSAR between 5-(*1H*-indol-5-yl)-1,3,4-thiadiazol-2-amines and their PIM-1 inhibitory activity.

MATERIALS AND METHODS

Three dimensional (3D) QSAR study was performed by Molecular design suite (VLife MDS) software on HCL computer with Intel Pentium dual core processor and Windows XP operating system.[25]

Data set

Twenty two thiadiazole derivatives reported by Wu *et al.* for their PIM-1 inhibitory activity were used as the data set for QSAR study (training set 75%, test set 25%).[1] The negative logarithmic scale values of concentration required for inhibition of 50% of enzyme [pIC_{50} (moles)] were utilized as dependent variable for QSAR analysis (Table 1).

Molecular modeling

2D Draw application of MDS was used to build the molecules that were converted into 3D structures for further analysis. Merck molecular force field (MMFF) was used to optimize the compounds by energy minimization and geometric optimization by considering distance-dependent dielectric constant of 1.0, convergence criterion or root-mean-square (RMS) gradient at 0.01 kcal/mole and the iteration limit to 10,000. The calculation of electrostatic, steric and hydrophobic fields on the lattice points of a grid around the molecules was performed on energy minimized structures. These fields were utilized as descriptors for QSAR generation.

Alignment of compounds

In order to obtain noteworthy results in 3D-QSAR study molecular alignment is a crucial step. The molecules were aligned by template based alignment. To this end a template was defined such that it represents a common fragment present in all the molecules of the data set (Figure 1).

Generation of training set and test set

In order for statistical significance a QSAR model has to be validated internally and externally. Leave one out cross validation procedure can be used for internal validation. Results of validation can be obtained in the form of cross validated R^2 (q^2) (the model is accepted if $q^2 > 0.5$). The data set has to be distributed into training set and test set for the purpose of external validation, where the model is developed with the help of the training set and its validation can be done by test set. In the present work the training and test sets were divided using random selection. The training set comprised of 75% of compounds and rest 25% of the compounds belonged to the test set.

Feature selection and model development

Different feature selection methods are available at the researcher's disposal in order to select descriptors for generation of the model from a large pool. Three variable selection methods were applied in for feature selection in this study: (1) Stepwise wearable selection (SW), (2) Genetic algorithm (GA) and (3) Simulated annealing (SA).

RESULTS AND DISCUSSION

3D QSAR study was performed on a series of thiadiazole derivatives for determination of structural features responsible for improved PIM inhibition. Random selection method was used for division of training and test sets. Partial least squares regression (PLSR) was applied for generation of a number of models from the deferent combination of training sets and test sets which were interpolative i.e. the compounds with maximum and minimum reported activities were in training set and the compound belonging to test set had values within this window. Unicolumn statistics of two most significant models are presented in Table 2. Some of the generated models were statically significant ($q^2 > 0.5$, $predr^2 > 0.5$) (Table 3). Further, the robustness of the models was checked by Y randomization test. The Y randomization test implies that the higher value of Z score at a given confidence interval α, the higher the ability of model to predict activity of an unknown compound within that confidence interval.
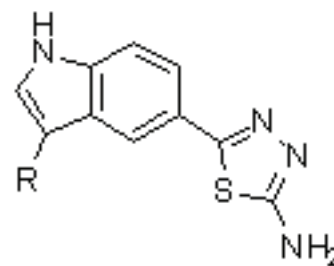
Table 1 : Series of 5-(1H-indol-5-yl)-1, 3, 4-thiadiazol-2-amines with pIC_{50} values

S. No.	Compound No.	R	IC_{50}	pIC_{50}
1	3	quinolin-3-yl	0.163	6.79
2	13	2,6-difluoro phenyl	0.177	6.75
3	14	6-amino pyridine-2-yl	0.865	6.06
4	15	6-(pyrrolidin-1yl)pyridine-2-yl	0.048	7.32
5	16	6-morpholino pyridin-2-yl	0.016	7.80
6	17	6-isopropylamino pyridin-2-yl	0.024	7.62
7	18	6-cyclopentylamino pyridine-2-yl	0.012	7.92
8	19	6-cyclohexylamino pyridine-2-yl	0.109	6.96
9	20	6-amino pyrazin-2-yl	0.142	6.85
10	21	6-pyrolidin-1-yl-pyrazin-2-yl	0.011	7.96
11	22	6-morpholinopyrazin-2-yl	0.005	8.30
12	23	6-isopropylamino pyrazin-2-yl	0.002	8.70
13	24	6-cyclopentylamino pyrazin-2-yl	0.001	9.00
14	25	6-cyclohexylamino pyrazine-2-yl	0.004	8.40
15	26	6-ethoxy pyridine-2-yl	0.017	7.77
16	27	6-isopropoxypyridin-2-yl	0.007	8.15
17	28	6-cyclopentyloxy pyridine-2-yl	0.015	7.82
18	29	6-cyclohexyloxy pyridine-2-yl	0.041	7.39
19	30	6-ethoxyl pyrazin-2-yl	0.021	7.68
20	31	6-isopropoxy pyrazin-2-yl	0.008	8.10
21	32	6-cyclopentyloxy pyrazin-2-yl	0.011	7.96
22	33	5-isopropoxy pyrazin-2-yl	0.262	6.58

Table 2 : Unicolumn statistics for most optimum models

Model no.	Data set	Average	Max	Min	Std Dev	Sum
1	Training	7.69	9.00	4.51	0.76	123.10
	Test	7.46	8.30	6.58	0.67	44.78
2	Training	7.71	9.00	6.61	0.75	123.44
	Test	7.41	8.30	6.58	0.69	44.44

Model 1:

pIC_{50} = 0.0387757 S_672 + 10.5355 E_1162 + 12.9437 E_999 + 8.49746

No. of training set compounds = 16, No. of test set compounds = 6, Degree of freedom = 13, q^2 = 0.7523, q^2se = 0.3995, pred_r^2 = 0.8714, pred_r^2se = 0.2762

The model shows a good internal (~75%) and external (~87%) validation capability with low standard error values. In this model, descriptor field points at E_999, E_1162 and S_672 are having coefficient values of 12.9437, 10.5355 and 0.0387757 respectively. These points correspond to the elec-

Table 3 : 3D QSAR analysis results by PLSR method by using random data selection (75% of training set)

S. No.	Test Set Molecules	PLSR								
		SW			GA			SA		
		r^2	q^2	pred r^2	r^2	q^2	pred r^2	r^2	q^2	pred r^2
1	16,17,20,28,31,33	0.76	0.62	0.91	0.83	0.66	0.15	0.70	0.52	0.68
2	20,23,25,28,32,33	0.84	0.75	0.47	0.80	0.70	0.63	0.74	0.45	-7.93
3	17,20,25,28,32,33	0.84	0.73	-5.89	0.77	0.65	0.67	0.67	0.42	0.67
4	17,19,27,30,32,33	0.91	0.85	0.21	0.89	0.81	0.20	0.78	0.62	0.05
5	15,17,22,28,30,33	0.84	0.77	-0.02	0.75	0.57	-0.24	0.64	0.46	0.34
6	13,19,23,27,32,33	0.89	0.81	0.60	0.88	0.76	0.29	0.80	0.70	0.08
7	15,16,21,29,31,33	0.87	0.81	-0.41	0.80	0.65	0.77	0.73	0.58	0.38
8	15,20,21,22,26,33	0.87	0.75	0.53	0.85	0.18	-0.28	0.80	0.67	0.07
9	13,15,22,29,31,33	0.82	0.74	0.34	0.85	0.75	0.87	0.66	0.43	0.48
10	16,18,19,20,22,33	0.89	0.81	-0.69	0.80	0.65	0.76	0.61	0.37	0.18

Table 4 : Statistical parameters for the two most significant models

Parameters	Model-1	Model-2
Size of training set	16	16
Size of test set	6	6
Degree of freedom	13	13
q^2	0.7523	0.6577
q^2_se	0.3995	0.4689
Pred_r^2	0.8714	0.7675
Pred_r^2se	0.2762	0.3735
Descriptor range	S_672 0.0387757	E_157 -0.762001
	E_1162 10.5355	E_630 1.0576
	E_999 12.9437	H_564 2.44615

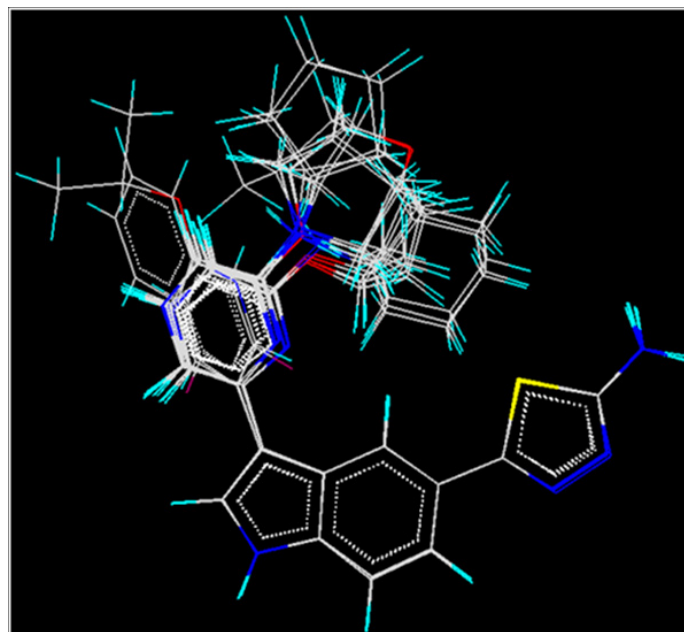**Figure 1:** Template based alignment of all the molecules.

trostatic contribution of E_999 and E_1122 and steric contribution of S_672 (Figure 2, Figure 3). The positive coefficient of the electrostatic field indicates that a more electronegative group is important for better activity. The positive value of the steric field point indicates that the substitution of more bulky group at this point will have favorable contribution for biological activity. This inference is supported by higher activities of compounds 22, 23, 24 and 25 with a bulky substituent at pyrazine nucleus as compared to their pyridine counterparts 16, 17, 18 and 19 respectively. Other compounds such as 3, 13, 14 and 20 have less bulky groups and are having less activities.

Model 2:

pIC_{50} = -0.762001 E_157 + 2.44615 H_564 + 1.0576 E_630 + 6.20693

No. of training set compounds = 16, No. of test set compounds = 6, Degree of freedom = 13, q^2 = 0.6577, q^2 se = 0.4689, pred_r^2 = 0.7675, pred_r^2se = 0.3735

In this model, the lattice points E_157, H_564, and E_630 show the hydrophobic and electrostatic field at points -0.762001, 2.44615 and

1.0576 respectively (Figure 4, Figure 5). The negative coefficient of electrostatic value of first lattice point is indicating that a less electronegative group at this point is favorable for more potent activity whereas positive coefficient of E_630 lattice point is indicating the need of a more electronegative group to be better for biological activity. The positive coefficient of hydrophobic field lattice point suggests the requirement of a hydrophobic group at this point. All the compounds with an alkyl or ring substituent around the hydrophobic field point have good potency, thus indicating that these groups are indeed necessary for better biological activity. E_157 is away from the substitution site which indicates that a more electronegative group at the substitution site would be favorable. On the other hand E_630 is near the main nucleus consisting of substituted thiadiazole moiety indicating the favorable electronegative group for the activity. The various statistical parameters of both the most significant models are given in Table 4. The Y-randomization test for both the models indicated that both the models were able to predict training set compounds with more than 99% and external compounds with 95% confidence. The robustness parameters are shown in Table 6.
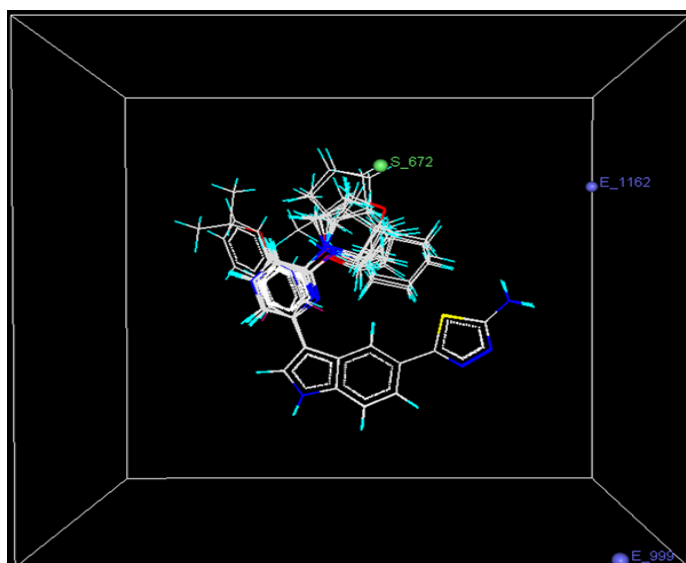
**Table 5 : Observed, predicted and residual values of the best models**

| S. No.	Compound No.	Actual Values	Model 1		Model 2	
			Predicted Value	Residual Values	Predicted Value	Residual Values
1	3	6.79	6.99	-0.20	6.73	0.05
2	13	6.75	6.78*	-0.02*	6.64	0.11
3	14	6.06	6.02	0.04	6.50	-0.44
4	15	7.32	6.89*	0.43*	7.53	-0.21
5	16	7.80	7.74	0.06	7.36*	0.44*
6	17	7.62	7.81	-0.19	7.98	-0.36
7	18	7.92	8.26	-0.34	7.99*	-0.07*
8	19	6.96	7.41	-0.45	7.52*	-0.55*
9	20	6.85	6.79	0.06	7.13*	-0.29*
10	21	7.96	8.20	-0.24	8.24	-0.29
11	22	8.30	8.11*	0.20*	8.26*	0.04*
12	23	8.70	8.49	0.21	8.42	0.28
13	24	9.00	8.74	0.26	8.80	0.20
14	25	8.40	8.03	0.37	8.23	0.16
15	26	7.77	7.37	0.40	7.15	0.62
16	27	8.16	7.69	0.46	7.53	0.62
17	28	7.82	7.71	0.11	7.75	0.07
18	29	7.39	7.71*	-0.32*	7.74	-0.35
19	30	7.68	7.86	-0.18	7.91	-0.24
20	31	8.10	8.28*	-0.19*	8.05	0.05
21	32	7.96	8.31	-0.35	8.25	-0.29
22	33	6.58	6.71*	-0.13*	6.92*	-0.33*

* Test set compounds

Table 6 : Robustness statistics for both the most significant models

Model No.	ZScore R^2	ZScore Q^2	Best Rand R^2	Best Rand Q^2	Alpha Rand R^2	Alpha Rand Q^2	Z Score Pred R^2	Best Rand Pred R^2	alpha Rand Pred R^2
1	4.05	3.70	0.67	0.44	0.00	0.00	1.86	0.43	0.05
2	4.07	2.81	0.63	0.34	0.00	0.01	2.11	0.62	0.05

Figure 2: Contribution 3D plot for model 1.
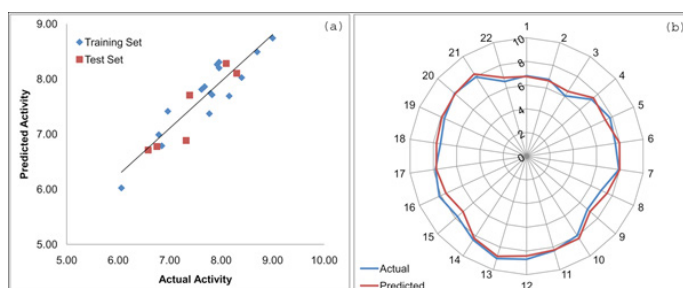
Figure 3: (a) Graph of observed vs. predicted activities for model 1 (b)Comparison of actual and predicted activities for all the compounds for the same model (blue line: actual activity, red line: predicted activity).
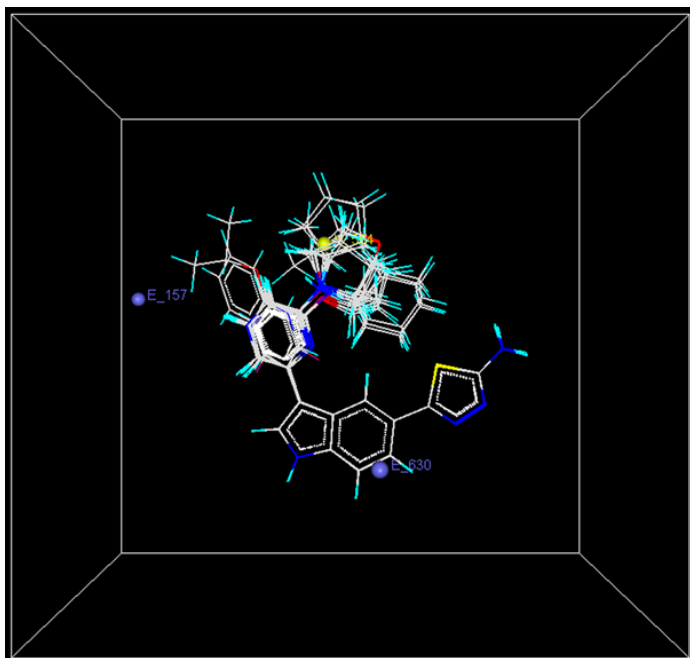
Figure 4: Contribution 3D plot for model 2.
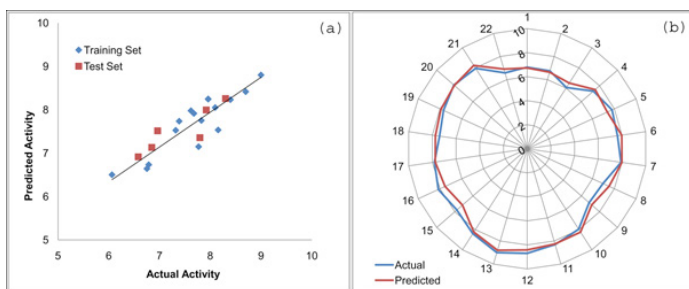
Figure 5: (a) Graph of observed vs. predicted activities for model 2.
(b) Comparison of actual and predicted activities for all the compounds for the same model (blue line: actual activity, red line: predicted activity).

CONCLUSION

The present study attempts to establish 3D QSAR between a set of 1,3,4-thiadiazol-2-amines and their PIM inhibitory activity. Steric, electrostatic and hydrophobic descriptors were considered for model development through PLSR. The compounds were divided into training and test sets (75% training set and 25% test set) by random selection method. Three types of Variable selection methods were applied (1) Stepwise Variable selection (SW), (2) Genetic algorithm (GA) and (3) Simulated annealing (SA) with individually ten trials run. Two most significant models generated by GA were selected among the developed models for description on the basis of their internal and External validation parameters and robustness (q^2 and pred_r^2 respectively). Model 1 and 2 have q^2 values of 0.7523 and 0.6577 and pred_r^2 values of 0.8714 and 0.7675 respectively. The steric field point in model 1 suggests the need of more bulky group at this position and the positive coefficients of electrostatic field points at positions E_999, E_1162 respectively indicate the need of electronegative groups for favorable biological activity and model 2 suggest the requirement of a positive hydrophobic group at H_564 and less electronegative and more electronegative group at E_157 and E_630 respectively for more potent biological activity. Thus more bulky and/or hydrophobic R groups apart from the electrostatic contribution may be favorable for better PIM-1 inhibitory activity of 5-(1*H*-

indol-5-yl)-1, 3, 4-thiadiazol-2 amines. For designing of the newer PIM inhibitors with better anticancer activity the structural information from this study may be helpful.

CONFLICTING INTEREST

No conflict of interest are declared.

ABBREVIATION USED

ATP: Adenosine triphosphate; **BAD:** B-cell lymphoma 2-associated death promoter; **MALT:** mucosa-associated lymphoid tissue, MYC: myelocytomatosis; **PIM:** Proviral integration site for moloney murine leukemia virus; **PLSR:** partial least squares regression; **PTK/STAT:** Protein tyrosine kinase/signal transducer and activator of transcription; **QSAR:** Quantitative structure activity relationship.

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