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Quantitative Structure Activity Relationship Studies on Imidazo[2,1-b][1,3,4]thiadiazole Derivatives as Murine Leukemia Cell Inhibitors

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A series of imidazo[2,1-b][1,3,4]thaidiazole derivatives was subjected to QSAR analysis and the generated models show good correlation between murine leukemic cell inhibitory activity and thermodynamic, electronic as well as steric properties of the derivatives. Most significant model was found to have squared correlation coefficient (r^2), cross validated correlation coefficient (Q^2) and predictive correlation coefficient (R^2_{pred}) 0.72, 0.56 and 0.72 respectively. The key descriptors are partition coefficient, cluster count and principal moment of inertia about X-axis (PMI-X). The negative coefficient value for partition coefficient and principal moment of inertia indicate that lower value leads to better murine leukemia cell inhibitory activity whereas higher value leads to decrease in activity. Positive coefficient value of cluster count indicates that higher value leads to better murine leukemia cell inhibitory activity whereas lower value leads to decrease in activity.

Keywords: Imidazothiadiazole, Murine leukemia, Anticancer, QSAR.

INTRODUCTION

Cell growth and differentiation are highly programmed processes and occur under rigorous biochemical control. Under normal physiological conditions the morbid cells are subjected to arrest and apoptosis (programmed cell death), but in cancer, some cells skip this regulatory mechanism and start growing aberrantly[1]. Development of anticancer drugs with fewer or no side effects is important for the treatment of cancer. Moreover, there has been wide interest in heterocyclic compounds containing imidazo[2,1-b][1,3,4]thiadiazole nucleus, because of their unique chemical structure and broad range of biological activity.

Imidazo[2,1-b][1,3,4]thiadiazole derivatives have often been target for many diseases like antibacterial and antifungal activity[2,3], antitubercular activity[4,5], anticonvulsant activity[6], anti-inflammatory, analgesic and antipyretic activity[7,8], carbonic anhydrase inhibition[9], diuretic activity[10], anticancer activity[11-13], antihelmentic and antiamebic activity[14,15], leishmanicidal activity[16], calcium channel blocking and local anesthetic activity[17].

Quantitative structure activity relationship (QSAR) which has become an accepted tool for establishing quantitative relationship between biological activity and descriptors representing physicochemical properties of the compounds in a series using statistical methods helps to predict the biological activities of newly designed analogues, thus contributing to the drug discovery process[18]. In the present study QSAR analysis was carried out on a series of imidazo[2,1-b][1,3,4]thiadiazoles[19].

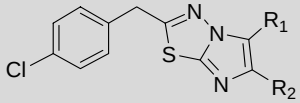
EXPERIMENTAL

Quantitative structure activity relationship studies were performed on HCl computer having genuine intel Pentium dual core processor and Windows XP operating system. Molecular modeling study was performed using Cambridge Soft ChemOffice Ultra 10.0[20] and statistical calculations were done by using VALSTAT software[21].

In the present study, a data set of 25 heterocyclic compounds belonging to a series of imidazo[2,1-b][1,3,4]-thiadiazoles having murine leukemia cancer cell line inhibitory activity was selected from literature[19] (Table-1). Quantitative structure activity relationship was performed on 25 out of 36 compounds from the data set because 11 compounds are either inactive or do not have defined biological activity. For QSAR analysis, descriptor values and pIC_{50} values were considered as independent and dependent variables respectively.

Molecular modeling and descriptor generation: Structures were drawn in CS ChemDraw and transferred to CS Chem 3D molecular modeling window. Each structure was subjected

TABLE-1
SERIES OF IMIDAZO[2,1-b][1,3,4]THIADIAZOLES WITH THEIR PHYSICOCHEMICAL PROPERTIES AND pIC_{50} VALUES



S. No.	Compound	PC	ClsC	PMI-X	ShpA	Substituents		pIC_{50}
						R_1	R_2	
1	**2d**	5.1210	24	794.00	22.04	H	4-OCH_3-Ph	4.42
2	**2f**	6.2889	24	1033.97	22.04	H	2,4-di-Cl-Ph	3.61
3	**2h**	4.8562	25	2058.70	23.04	H	4-NO_2-Ph	3.67
4	**3d**	5.6846	25	1488.67	23.04	Br	4-OCH_3-Ph	4.20
5	**3f**	6.8517	25	1404.79	23.04	Br	2,4-di-Cl-Ph	4.51
6	**3h**	5.4187	26	2810.13	24.04	Br	4-NO_2-Ph	4.03
7	**3i**	5.1640	28	1603.27	26.04	Br	Coumarin-3-yl	5.28
8	**4a**	4.9990	25	1114.86	23.04	CHO	4-F-Ph	4.70
9	**4b**	5.6860	25	1177.67	23.04	CHO	4-Cl-Ph	4.82
10	**4c**	5.8360	25	1252.39	23.04	CHO	4-Br-Ph	5.34
11	**4d**	4.8650	26	1108.54	24.04	CHO	4-OCH_3-Ph	5.28
12	**4e**	5.3552	25	1127.99	23.04	CHO	4-CH_3-Ph	4.64
13	**4f**	6.1491	26	1775.26	24.04	CHO	2,4-di-Cl-Ph	4.09
14	**4g**	4.9728	24	1047.91	22.04	CHO	Ph	4.70
15	**4h**	4.5996	27	2281.45	25.04	CHO	4-NO_2-Ph	4.82
16	**4i**	4.4519	29	1254.44	27.03	CHO	Coumarin-3-yl	6.05
17	**5a**	5.6688	26	1654.19	24.04	SCN	4-F-Ph	4.64
18	**5b**	6.2389	26	1737.50	24.04	SCN	4-Cl-Ph	4.31
19	**5c**	6.3889	26	1684.51	24.04	SCN	4-Br-Ph	4.09
20	**5d**	5.5347	27	1585.79	25.04	SCN	4-OCH_3-Ph	4.80
21	**5e**	6.0240	26	1644.79	24.04	SCN	4-CH_3-Ph	4.49
22	**5f**	6.0246	26	1644.79	24.04	SCN	2,4-di-Cl-Ph	4.31
23	**5g**	6.7020	27	1580.10	25.04	SCN	Ph	4.62
24	**5h**	5.5256	25	1541.00	23.04	SCN	4-NO_2-Ph	4.30
25	**5i**	5.2689	28	2483.06	26.04	SCN	Coumarin-3-yl	5.89

to energy minimization by using MM2 force field taking RMS gradient of 0.01. Thus, energy minimized structures were used for calculation of various physicochemical properties like thermodynamic, steric and electronic by using compute properties option available in CS Chem 3D window. These properties were used as descriptors for conventional QSAR analysis.

Once the descriptors were generated, multiple linear regression (MLR) analysis was performed on the generated data using the calculated descriptors as independent variables and pIC_{50} values as dependent variables. The dataset was divided into training and test sets using random selection method (80 %). MLR analysis was carried out using VALSTAT. The statistical models were validated using leave one out (LOO) cross validation method internally and external validation was performed for the selected test set.

Statistical parameters considered for evaluation of QSAR models were the number of compounds in regression n, regression coefficient r^2, F-test (Fisher test value) for statistical significance, cross validated correlation coefficient Q^2, SPRESS (predicted residual sum of squares) and SDEP (standard deviation error of prediction). The predictive power of the models was ascertained by Q^2 and predictive correlation coefficient (R^2_{pred}).

RESULTS AND DISCUSSION

The QSAR study in the present work was performed by multiple linear regression (MLR) analysis using VALSTAT software.

Imidazo[2,1-b][1,3,4]thiadiazole derivatives were subjected to multiple linear regression analysis for generation of statistically significant models. Different QSAR models were developed using random selection of data set (training set 80 % and test set 20 %). Training and test set were selected if they follow the uni-column statistics shown in Table-2. Table-2 shows that the test is interpolative *i.e.* derived from the min-max range of training set. The mean and standard deviation of the training and test set provides insight to the relative difference of mean and point density distribution of the two sets. The results of MLR analysis are shown in Table-3. The models in terms of statistical significance are shown in Table-4.

In QSAR models, r^2 is squared correlation coefficient. Predictive ability of generated QSAR model was evaluated by Q^2 employing leave-one out method internally. F value reflects ratio of variance explained by models and variance due to error in regression. High F value indicates that model is statistically significant. All the generated QSAR models have low standard deviation and high F value, which indicates that the model is statistically significant. Predictive ability of QSAR models was also confirmed by external validation of test set compounds denoted by R^2_{pred}. Actual and predicted pIC_{50} is shown in Table-5. Plot of actual *versus* predicted pIC_{50} value is shown in Figs. 1 and 2.

Interpretation of model 1: Model 1 explains 72.28 % (r^2 = 0.7228) of the total variance in the training as well as it has internal (Q^2) and external (R^2_{pred}) predictive ability of 56.96

TABLE-2
UNI-COLUMN STATISTICS OF THE BEST MODELS

Model No.	Data set	Average	Max	Min	Std Dev	Sum
1	Training	4.57	6.05	3.61	0.630527	91.42
	Test	4.83	5.28	4.42	0.419976	24.17
2	Training	4.57	6.05	3.61	0.630527	91.42
	Test	4.83	5.28	4.42	0.419976	24.17

TABLE-3
QSAR MODELS GENERATED USING MLR (RANDOM SELECTION, 80 %)

S. No.	Test set compounds	Trial	R^2	Q^2	R^2_{pred}	F test	SPRESS	SDEP
1	17, 1, 7, 20, 9	1a	0.741	0.605	0.514	15.295	0.444	0.397
		1a*	0.828	0.704	0.539	24.225	0.380	0.338
		1b	0.741	0.605	0.513	15.291	0.444	0.397
		1b*	0.828	0.704	0.539	24.214	0.381	0.338
2	7, 11, 21, 1, 8	2a	0.732	0.605	0.580	14.589	0.432	0.386
		2b	0.723	0.570	0.721	13.912	0.451	0.403
		2c	0.723	0.569	0.721	13.907	0.451	0.404
3	1, 14, 9, 4, 21	3	0.776	0.655	-0.961	18.430	0.422	0.377
4	10, 1, 6, 14, 19	4	0.850	0.764	-0.722	30.195	0.329	0.294
5	17, 9, 13, 6, 1	5	0.772	0.688	-2.648	18.051	0.389	0.348
6	19, 18, 10, 22, 1	6	0.872	0.787	-1.253	36.411	0.316	0.282
7	12, 5, 20, 21, 6	7	0.775	0.664	-0.850	18.341	0.413	0.369
8	9, 1, 18, 8, 7	8a	0.740	0.594	0.625	15.167	0.449	0.401
		8a*	0.825	0.692	0.707	23.695	0.388	0.344
		8b	0.740	0.593	0.625	15.162	0.449	0.401
		8b*	0.825	0.692	0.707	23.684	0.388	0.345
9	15, 21, 7, 23, 4	9a	0.748	0.620	0.475	15.812	0.432	0.387
		9b	0.733	0.566	0.748	14.657	0.462	0.413
		9b*	0.825	0.667	0.705	23.667	0.402	0.357
		9c	0.733	0.565	0.748	14.650	0.462	0.414
		9c*	0.825	0.667	0.705	23.653	0.402	0.357
10	18, 21, 22, 3, 19	10	0.741	0.498	-3.433	15.292	0.465	0.415

*Indicates that compound 10 is outlier.

TABLE-4
SIGNIFICANT MODELS GENERATED USING MLR (RANDOM SELECTION, 80 %)

Model No.	Trial	Training set (%)	Test set molecules	Equation
1	2(b)	80	7, 11, 21, 1, 8	BA= [0.161769(± 4.02485)] +PC [-0.314085(± 0.285227)] +Clsc [0.287083(± 0.128717)] +PMI-X [-0.000793457(± 0.000406154)] n=20, r=0.850, r^2=0.722, variance=0.131, std=0.361, F=13.912, Q^2=0.569, SPRESS=0.451, SDEP=0.403, r^2pred=0.721
2	2(c)	80	7, 11, 21, 1, 8	BA = [0.717408(± 3.80397)] +PC [-0.314447(± 0.28522)] +PMI-X [-0.000794282(± 0.000406344)] +ShpA [0.287528(± 0.128947)] n=20, r=0.850, r^2=0.722, variance=0.131, std=0.362, F=13.907, Q^2=0.569, SPRESS=0.451, SDEP=0.403, r^2pred=0.720

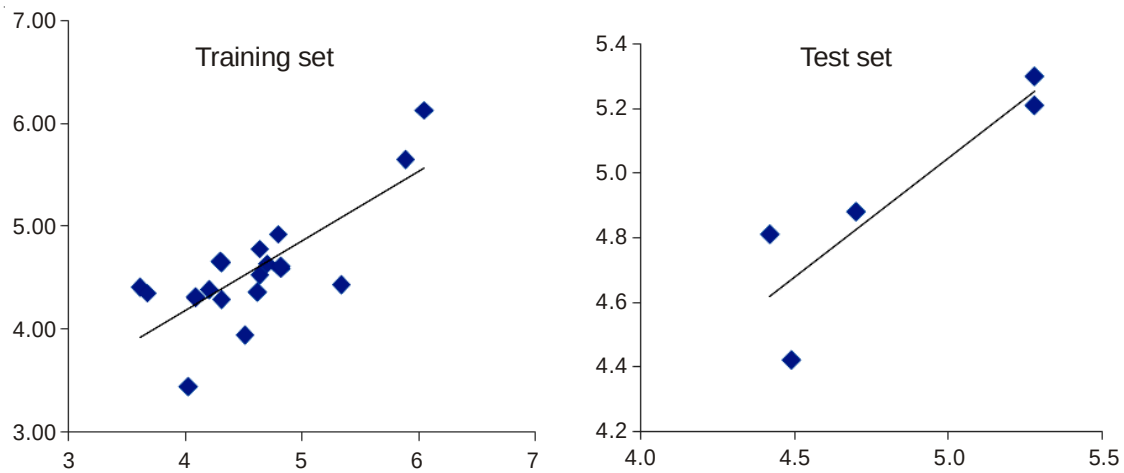


Fig. 1. Graph between actual and predicted biological activity for training and test set (model 1)

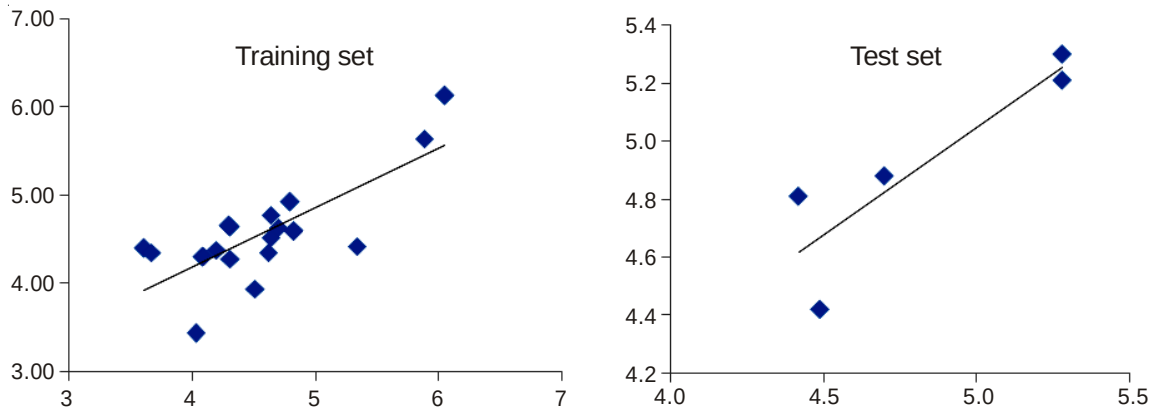


Fig. 2. Graph between actual and predicted biological activity for training and test set (model 2)

TABLE-5
ACTUAL AND PREDICTED VALUES OF BEST MODELS

S. No.	Comp. No.	Comp. Name	Actual values	Predicted value	
				Model 1	Model 2
1	1	2d	4.42	4.81*	4.81*
2	2	2f	3.61	4.41	4.40
3	3	2h	3.67	4.35	4.35
4	4	3d	4.20	4.39	4.39
5	5	3f	4.51	3.94	3.94
6	6	3h	4.03	3.44	3.44
7	7	3i	5.28	5.3*	5.3*
8	8	4a	4.70	4.88*	4.88*
9	9	4b	4.82	4.59	4.59
10	10	4c	5.34	4.43	4.43
11	11	4d	5.28	5.21*	5.21*
12	12	4e	4.64	4.78	4.78
13	13	4f	4.09	4.31	4.31
14	14	4g	4.70	4.64	4.64
15	15	4h	4.82	4.61	4.61
16	16	4i	6.05	6.13	6.13
17	17	5a	4.64	4.53	4.53
18	18	5b	4.31	4.29	4.29
19	19	5c	4.09	4.31	4.31
20	20	5d	4.80	4.93	4.93
21	21	5e	4.49	4.42*	4.42*
22	22	5f	4.31	4.65	4.65
23	23	5g	4.62	4.36	4.36
24	24	5h	4.30	4.66	4.66
25	25	5i	5.89	5.65	5.65

*Compound in test set

and 72.13 % respectively. The F test value is 13.91. The descriptors involved in model 1 are Partition coefficient (PC), Cluster count (ClsC) and Principal moment of inertia at X-axis (PMI-X).

Partition coefficient and principal moment of inertia at X-axis are contributing negatively and Cluster count contribute positively to the model. If the value of partition coefficient of the compound is increased, the biological activity will be decreased. Thus greater the lipophilicity of the compound, lesser the biological activity will be. Principal moment of inertia at X-axis is contributing negatively to the model, which shows that less bulky group will enhance the biological activity if it is substituted at X-axis. Cluster count is contributing positively to the model, *i.e*. increase in the value of cluster count will result in increase in biological activity.

Interpretation of model 2: Model 2 explains 72.28 % (r^2 = 0.7228) of the total variance in the training as well as it has internal (Q^2) and external (R^2_{pred}) predictive ability of 56.93 % and 72.08 % respectively. The F test value is 13.90. The descriptor involved in this model are Partition coefficient (PC), Shape attributes (ShpA) and Principal moment of inertia at X-axis (PMI-X).

Partition coefficient and principal moment of inertia at X-axis contributing negatively and Shape attribute contribute positively to the model. If we increase the value of partition coefficient of the compound then the biological activity will be decreased. It means that, greater the lipophilicity of the compound, lesser the biological activity will be. Principal moment of inertia at X-axis is contributing negatively to the model, which shows that less bulky groups will enhance the biological activity if it is substituted at X-axis. Shape attributes contribute positively to the model indicating that increasing the value of Shape attribute will result in increased biological activity.

The above models were cross validated using leave one out method and the results of cross validation are summarized in Table-4. Error terms, SPRESS and SDEP are lower in both models and Q^2 and R^2_{pred} have value greater than 0.5. The models pass the Fischer's F-test for 99.9 % confidence level and show very small standard deviations, which indicates the acceptability and predictivity of the models. Thus the structural features increasing the value of Shape attribute and lower the value of Partition coefficient and Principal moment of inertia at X-axis would prove to be favourable for increasing the biological activity.

Conclusion

In the present study, quantitative structure activity relationship (QSAR) analysis was performed on various heterocyclic compounds *i.e*. imidazothiadiazole analogues using Chem Office and VALSTAT. Statistically significant QSAR models were generated. Among them most significant model has squared correlation coefficient (r^2), cross validated correlation coefficient (Q^2) and predictive correlation coefficient (R^2_{pred}) 0.72, 0.56, 0.72 respectively. The key descriptors for this model were found to be partition coefficient (PC), cluster count (ClsC) and Principal moment of inertia about X-axis (PMI-X). The negative coefficient value of partition coefficient and Principal

moment of inertia on the biological activity indicate that lower value leads to better murine leukemia cell inhibitory activity whereas higher value leads to decrease in activity. Positive coefficient value of cluster count indicates that higher value leads to better murine leukemia cell inhibitory activity whereas lower value leads to decrease in activity.

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REFERENCES

1. T.L. Lemke, D.A. Williams, V.F. Roche and S.W. Zito, Foye's Principles of Medicinal Chemistry, Lippincott Williams and Wilkins, New Delhi, edn 6, p. 1147 (2008).
2. A.K. Gadad, I.M. Khazi and C.S. Mahajanshetti, *Indian J. Heterocycl. Chem.*, **2**, 125 (1992).
3. A.K. Gadad, C.S. Mahajanshetti, S. Nimbalkar and A. Raichurkar, *Eur. J. Med. Chem.*, **35**, 853 (2000).
4. G. Kolavi, V. Hegde, I.A. Khazi and P. Gadad, *Bioorg. Med. Chem.*, **14**, 3069 (2006).
5. A.K. Gadad, M.N. Noolvi and R.V. Karpoormath, *Bioorg. Med. Chem.*, **12**, 5651 (2004).
6. I.M. Khazi, C.S. Mahajanshetti, A.K. Gadad, A.D. Tarnalli and C.M. Sultanpur, *Arzheim. Forsch.*, **46**, 949 (1996).
7. V.B. Jadhav, M.V. Kulkarni, V.P. Rasal, S.S. Biradar and M.D. Vinay, *Eur. J. Med. Chem.*, **43**, 1721 (2008).
8. A.K. Gadad, M.B. Palkar, K. Anand, M.N. Noolvi, T.S. Boreddy and J. Wagwade, *Bioorg. Med. Chem.*, **16**, 276 (2008).
9. I.T. Barnish, P.E. Cross, R.P. Dickinson, B. Gadsby, M.J. Parry, M.J. Randall and I.W. Sinclair, *J. Med. Chem.*, **23**, 117 (1980).
10. A. Andreani, M. Rambaldi, A. Locatelli, S. Malandrino and G. Pifferi, *Arzneimittelforschung*, **29**, 339 (1994).
11. N. Terzioglu and A. Gursoy, *Eur. J. Chem.*, **38**, 781 (2003).
12. S.S. Karki, K. Panjamurthy, S. Kumar, M. Nambiar, S.A. Ramareddy, K.K. Chiruvella and S.C. Raghavan, *Eur. J. Med. Chem.*, **46**, 2109 (2011).
13. M.N. Noolvi, H.M. Patel, N. Singh, A.K. Gadad, S.S. Cameotra and A. Badiger, *Eur. J. Med. Chem.*, **46**, 4411 (2011).
14. A. Marin, N. Valls, B.F. Javier, M.T. Alonson, M.A. Ramon and M.M. Mercedes, *J. Farmaco*, **47**, 63 (1992).
15. C.S. Andotra, T.C. Langer, S. Dham and P. Kour, *Proc. Ind. Natl. Sci. Acad.*, **63**, 589 (1993).
16. V.J. Ram and N. Haque, *Indian J. Chem.*, **35B**, 238 (1996).
17. P.J. Sanfilippo, M. Urbanski, J.B. Press, B. Dubinsky and J.B. Moore, *J. Med. Chem.*, **31**, 2221 (1988).
18. M.M.C. Ferreira, *J. Braz. Chem. Soc.*, **13**, 742 (2002).
19. S. Kumar, M. Hegde, V. Gopalakrishnan, V.K. Renuka, S.A. Ramareddy, E. De Clercq, D. Schols, A.K. Gudibabande Narasimhamurthy, S.C. Raghavan and S.S. Karki, *Eur. J. Med. Chem.*, **84**, 687 (2014).
20. CambridgeSoft ChemOffice Ultra 10.0, www.cambridgesoft.com.
21. A.K. Gupta, M.A. Babu and S.G. Kaskhedikar, *Indian J. Pharm. Sci.*, **66**, 396 (2004).