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Modeling Of Biological Activity of Thiazolidine-2, 4-Dione by Qsar Method

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ABSTRACT: A series of 21 thiazolidine-2,4-dione derivatives were used for quantitative structure–activity relationship (QSAR) studies. These compounds were introduced into two-dimensional (2D-QSAR), and three-dimensional (3D-QSAR) studies to find the structural requirements for PIM-2 kinase inhibitory activity. Results of statistical analysis found with value of Variance as 0.8191, Cross validated regression coefficient and Fisher-value as 0.7792 and 15.847 respectively which may be useful for (medicinal) chemists in selecting the most suitable substituent for the development of more potent, effective and selective Thiazolidine-2,4-dione based antitumor agents in future.

Key words: QSAR, Thiazolidine-2,4-dione, 2D QSAR.

I. INTRODUCTION

PIM enzymes regulate the cell communication pathways via Roman deity kinase (JAK)/signal electrical device and activator of transcription (STAT) pathway together with proliferation, migration and metabolism. The PIM kinases typically work as weak oncogenes once expressed as transgenes. The oncogenic potential increased on co-expression with c-Myc, a transcription issue plays a vital role in cell growth and differentiation. (Manoj Upadhyay et al.; wjpps; Volume 8, Issue 2, 662-678)

PIM-1 and PIM-2 kinases are over--expressed in kinds of cancer like myeloma, lymphomas, cancer of the blood and prostatic adenocarcinoma. PIM-3 over-expression is connected with solid tumors in duct gland, prostate, colon and alternative organelles. Consequently, the PIM kinases are also thought of as a possible target for cancer medical care. What is more, no severe aspect effects are ascertained once inhibiting of these kinases in associate experiment on mice. Novel substituted benzylidene-1,3-thiazolidine-2,4-diones (TZDs) are known as potent and extremely selective inhibitors of the PIM kinases.

Heterocycles play a very important role in cancer medical care particularly 5-membered ring heterocyclic that contain 3 carbon atoms, one chemical element atom, and one sulfur atom, referred to as thiazoles are of significant interest in numerous areas of healthful chemistry. Thiazolidine-2,4-dione (TZD), one among the foremost necessary heterocyclic systems has therapeutic importance and once combined with alternative heterocyclic rings it should turn out higher antitumor activity.

In literature several thiazolidine-2,4-diones have been synthesized and evaluated for their anti-cancer activity. In the present study, QSAR analysis was performed for 21 previously synthesized 5-benzylidene thiazolidine-2,4-dione analogues to establishing quantitative relationship between biological activity of derivatives and their physicochemical/structural properties. The aim of the present work is to generate best predictive and validated QSAR models which may help to medicinal chemist for designing and development of novel thiazolidine-2,4-dione derivatives. In this work widely used technique viz. stepwise forward-backward (SW-FB) with partial least square (PLS) analysis has been applied for the development of QSAR models as variable selection method. The generated models may provide insights into the influence of various interactive fields on the activity and thus, can help in designing and forecasting the inhibitory activity of novel anticancer agents.

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II. PRESENTATION OF DATA

In present study table-1 represents the structure of thiazolidine-2,4-dione derivatives, while table-2 shows the calculated connectivity descriptors with biological activity of thiazolidine-2,4-dione derivatives, table-3 represents the correlation matrix between different connectivity descriptors.

Descriptor and biological activity are given in table-2 and table-3 while table-4 represents the residual report from best model of topological & connectivity descriptors. Table-5 represent the Cross validation of best models. Ridge regression (fig-2) is representing the multicollinearity is not present in this study.

TABLE -1 – Structures of Thiazolidine-2,4-Dione Derivatives

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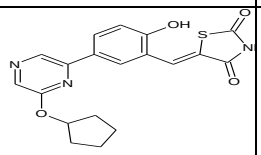
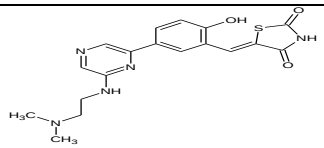
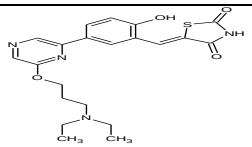
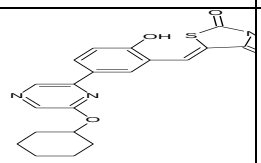
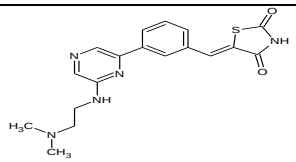
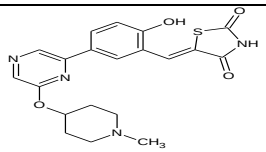
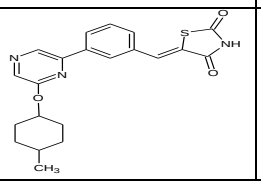
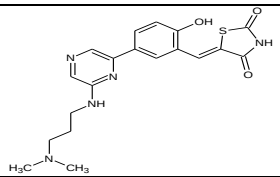
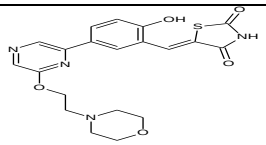
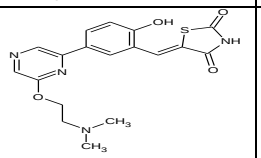
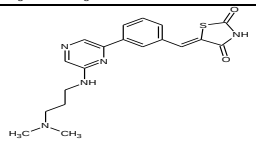
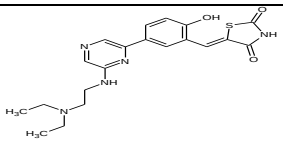
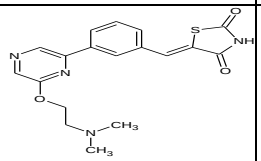
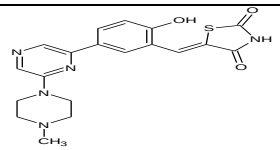
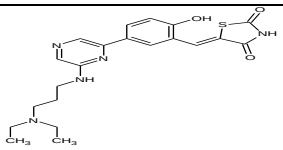
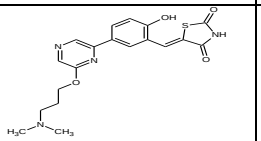
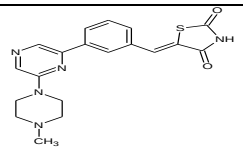
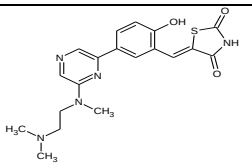
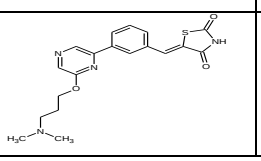
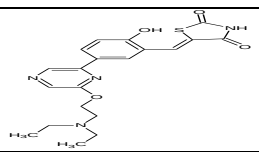
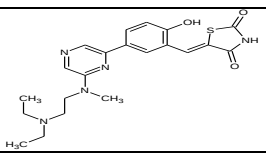
1		8		15	
2		9		16	
3		10		17	
4		11		18	
5		12		19	
6		13		20	
7		14		21	

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III. RESULT AND DISCUSSION

QSAR study of a series of Thiazolidine-2,4-dione derivatives was performed by using dragon software. In this study, biological activity (pIC_{50}) as dependent and various Connectivity descriptors taken as the independent variable and regression were established using MLR analysis. The models were selected on the basis of its statistical significance for further study. A data set of 21 compounds that the biological activities of all 21 compounds gave maximum and minimum value range of biological activities.

In order to understand experimental biological activity data of 21 thiazolidine -2,4-dione compound on theoretical basis, we established a QSAR study between biological activity and descriptor for connectivity properties of the molecules under consideration using multiple linear regression describing by Hansch and Fojity.

Developing a QSAR model requires a diverse set of a data and thereby a large number of descriptor have to be considered.

Descriptors are numerical values that encode different structural features of the molecules selection of set of appropriate descriptor from a large number of them require a method, which is able to discrimination between parameters.

The different molecular descriptors independent variables like Connectivity indices (X^0sol, X^1sol, X^2sol, XMOD) are calculated for heterocyclic compounds thiazolidine -2,4- dione presented in table-2.

Preliminary analysis was carried out in terms of correlation analysis (table-3). In general high co-linearity (r>81) was observed between different parameters.

It is clear from these table that Connectivity parameters are strongly correlated with biological activity with value of correlation coefficient more than 0.8 i.e. with X^0sol, XMOD, IR^1 and IR^2 strong auto correlation is also exist between X^0sol, XMOD, IR^1 and IR^2 etc. so correlation matrix indicated the predominance of Connectivity parameter in describing the biological activity heterocyclic compounds thiazolidine -2, 4-dione.

The data presented in table-3 demonstrated the low co-linearity between the parameters (r<81) indicated that these parameter could be combined to get multiples regression (MLR) models. The analysis of matrix revealed connectivity descriptors for the development of (MLR) models.

The best mono parametric model with Connectivity descriptor is as follows.

The regression analysis gave mono parametric models. Out of which one contain **IR^1** was found to give good results, the model obtained is as follows-

pIC_{50} = 7.7283, 0.6277(±0.2079) IR^1

……. [1]

N=21, MSE= 0.1852, R^2= 0.3242, AR^2= 0.2887, Q-VALUE= 1.7505

Here n is the number of compound, MSE is the means square error of estimation, R^2 is the regression coefficient, AR^2 Is the adjusted Regression coefficient and Q-value is the Quality factor. From above mono parametric model it is clear that average connectivity index of order 0 (IR^1) has a negative correlation influence on toxicity suggest that toxicity as expressed by log pIC_{50} decreases with increase in magnitude of average connectivity index of order 0.

Bi parametric correlations involves the indicator parameters **IR^1** and **IR^2** as-

pIC_{50} = 7.2217, 0.6074(±0.1827) IR^1, 0.6079(±0.2359) IR^2 ……[2]

N=21, MSE= 0.1427, R^2= 0.5064, AR^2= 0.4516, Q-VALUE= 3.5487

pIC_{50} = 13.1208, -0.4669(±0.2254) X^0sol, 0.8899(±0.2163) IR^1, 0.5757(±16.2567) IR^2 .. [3]

N=21, MSE= 0.1207, R^2= 0.6059, AR^2= 0.5364, Q-VALUE= 5.0198

pIC_{50} = 13.5633, 0.2003(±0.2536) X^1sol, -0.7126(±0.3856) X^2sol, 0.8800(±0.2191) IR^1, 0.5431(±0.2237) IR^2 …. [4]

N=21, MSE= 0.1234, R^2= 0.6207, AR^2= 0.5259, Q-VALUE= 5.0299

After deleted compound no 20 and 21, the best tetra parametric correlation involves the connectivity index X^0sol, XMOD and indicator IR^1, IR^2 as follows-

pIC_{50} = 7.7083, 0.6219(±0.2279) X^0sol, -0.1446(±0.0492) XMOD, 0.6948(±0.1603) IR^1, 0.4472(±0.1832) IR^2

…. [5]

N=19, MSE= 0.0605, R^2= 0.8191, AR^2= 0.7674, Q-VALUE= 13.5388

Finally in order to confirm out of the proposed models which is the most appropriated for modeling the biological activity? We calculated the pogliani's quality factor Q which is Ratio of R and MSE (means square error) among these Q value maximum value is found for Eq.5 as 13.5388. So Eq. 5 is the best model for modeling biological activity with connectivity parameters and a graph (fig-1) are plotted between observed vs. predicted values of biological activity from Eq. 5.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 672-677 www.ijprajournal.com ISSN: 2456-4494

We have undertaken a cross validation methodology for deciding the predictive power of the proposed model. It is necessary for a best model to have good statistics but this is not sufficient for good predictive potential.

The various cross validation parameters, calculated for the proposed models, are presented on Table-5 and are discussed below.

PRESS is an important parameter for cross validation for account a good estimate of the real predictive error of the model. When its value is less than the SSY, the model predicts better than by chance alone, and can be considered statistically significant and are better that chance.

For the QSAR model to be considered reasonable, PRESS/SSY should be smaller than 0.4 and the data presented in Table-5 indicate that model no. 5 proposed are significant. Finally in order to confirm our finding, biological activity were compared with the corresponding values reported in Table-2 and comparisons are shown in Table-4. The values agree well within experimental error. The residual is the difference between observed and calculated biological activity.

According the result of biological screening summary of Thiazolidine-2,4-dione derivatives graph is plotted between observed and predicted pIC_{50} (Fig-1). Ridge regression is more significant for analyzing best linear unbiased estimate in multiple linear regression analysis, value of variance inflation factor represents the effect of multicolinearity is admissible or not. Since all VIF's are less than 10, therefore multicollenerity is not a problem in present study.

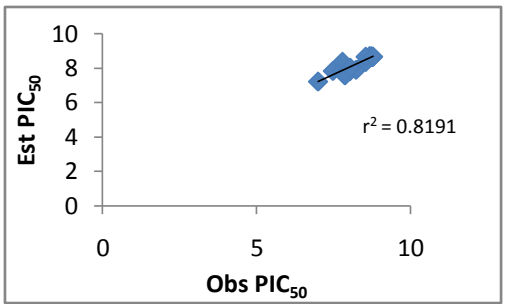

Fig. 1 - Plot of observed pIC_{50} versus experimentally pIC_{50}

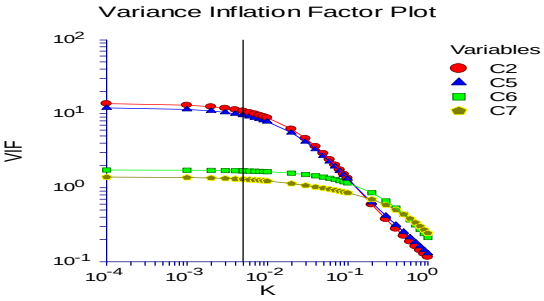

Fig. 2 - Ridge Regression Report.

TABLE- 2 – Calculated Connectivity descriptors and biological activity of Compound

Comp. No.	pIC_{50}	X^0sol	X^1sol	X^2sol	XMOD	IR^1	IR^2
1	8.03	19.156	13.489	12.768	86.431	1	0
2	7.84	19.863	13.989	13.121	89.431	1	0
3	7.01	19.863	13.972	13.225	88.752	0	0
4	8.66	19.742	13.327	12.706	86.333	1	1
5	7.49	18.872	12.916	12.188	83.292	0	1
6	8.77	20.449	13.827	13.06	89.333	1	1
7	7.77	19.579	13.416	12.542	86.292	0	1
8	8.74	19.742	13.327	12.706	85.879	1	1
9	8.24	18.872	12.916	12.188	82.838	0	1
10	8.68	20.449	13.827	13.06	88.879	1	1
11	7.98	19.579	13.416	12.542	85.838	0	1
12	7.8	20.027	13.899	13.295	89.35	1	1
13	7.88	19.156	13.489	12.778	86.309	0	1
14	8.66	21.156	14.403	12.995	92.62	1	1
15	8.68	21.863	14.903	13.348	95.62	1	1
16	8.55	20.734	14.383	13.743	92.491	1	1
17	8.05	21.278	14.989	13.816	97.135	1	1
18	8.55	21.156	14.403	12.995	92.166	1	1

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 672-677 www.ijprajournal.com ISSN: 2456-4494

19	8.79	21.863	14.903	13.348	95.166	1	1
20	8.05	20.612	13.738	13.224	88.548	1	1
21	7.49	22.027	14.814	13.513	94.835	1	1

X^0sol = Solvation connectivity index of order 0, X^1sol = Solvation connectivity index of order 1,
X^2sol = Solvation connectivity index of order 2, XMOD = Modified Randic index,
IR^1 = is one if hydroxyl group is present in place of R1, otherwise it is zero.
IR^2 = is one if nitrogen is present in place of R2, otherwise it is zero.

TABLE -3- Correlation matrix

	pIC_{50}	X^0sol	X^1sol	X^2sol	XMOD	IR^1	IR^2
pIC_{50}	1						
X^0sol	0.5515	1					
X^1sol	0.3237	0.9407	1				
X^2sol	0.1965	0.753	0.8752	1			
XMOD	0.3646	0.9464	0.9939	0.8800	1		
IR^1	0.6719	0.6342	0.5783	0.6112	0.6157	1	
IR^2	0.5169	0.2596	0.0467	-0.0678	0.1044	0.0163	1

TABLE – 4 - Residual Report

Row	Est. pIC_{50}	Obs. pIC_{50}	Residual
1	8.03	7.822	0.208
2	7.84	7.828	0.012
3	7.01	7.231	-0.221
4	8.66	8.647	0.013
5	7.49	7.851	-0.361
6	8.77	8.653	0.117
7	7.77	7.857	-0.087
8	8.74	8.713	0.027
9	8.24	7.917	0.323
10	8.68	8.719	-0.039
11	7.98	7.923	0.057
12	7.8	8.388	-0.588
13	7.88	7.592	0.288
14	8.66	8.618	0.042
15	8.68	8.624	0.056
16	8.55	8.374	0.176
17	8.05	8.041	0.009
18	8.55	8.683	-0.133
19	8.79	8.689	0.101

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 672-677 www.ijprajournal.com ISSN: 2456-4494

TABLE – 5 – Result of Cross Validation

Model No	N	PRESS	SSY	PRESS/SSY	R^2	R^2_{CV}	PSE	S_{press}
1	21	3.5188	1.6884	2.0841	0.3242	0.0	0.0893	0.4303
2	21	2.5702	2.6369	0.9747	0.5064	0.0253	0.0763	0.3777
3	21	2.0521	3.1551	0.6504	0.6059	0.3496	0.0682	0.3474
4	21	1.9751	3.2321	0.6110	0.6207	0.389	0.0669	0.3512
5	19	0.8475	3.8373	0.2208	0.8191	0.7792	0.0484	0.2459

IV. CONCLUSION

The following conclusions are obtained from this analysis:

(1) Connectivity parameters are used for modeling of these compounds.

(2) Connectivity parameters are more effective in this QSAR study.

(3) X^0sol, X^1sol, X^2sol, XMOD, IR^1 and IR^2 parameters issued.

(4) The highest value R^2 = 0.8191 are obtained in QSAR models.

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