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Research Article

2D QSAR ANALYSIS ON OXADIAZOLE DERIVATIVES AS ANTICANCER AGENTS

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ABSTRACT

Two dimensional quantitative structure activity relationship (2D QSAR) study by means of partial least square regression (PLSR) method was performed on a series of 3-(aryl)-N-(aryl)-1,2,4-Oxadiazol-5-amines as antiproliferative agents using molecular design suite (VLifeMDS). This study was performed with 20 compounds (data set) using sphere exclusion (SE) algorithm and manual selection methods for the division of the data set into training and test set. PLSR methodology with stepwise (SW) forward-backward variable selection method was used for building the QSAR models. Statistically significant QSAR models were generated. Among them most significant model has squared correlation coefficient (r2), cross validated correlation coefficient (q2) and predictive correlation coefficient (pred_r2) 0.7937, 0.5754 and 0.8079 respectively. The QSAR model indicates that the descriptors SKMostHydrophilic [Most hydrophilic value on the van der Waals surface], T_C_N_7 [This is the count of carbon atoms (single or double bonded) separated from nitrogen atom (single or double bonded) by 7 bonds in a molecule] and AveragePotential [This descriptor signifies average of the total electrostatic potential on van der Waals surface area of the molecule] contributing (inversely) 40%, 31% and 28% respectively to biological activity.

Keywords: 3D-QSAR, PLSR, Antiproliferative agents, 1, 2, 4-Oxadiazoles

INTRODUCTION

Compounds containing the 1,2,4-oxadiazole nucleus has drawn interest due to the unique chemical structure and exhibits cytotoxic activities[1], antitumor[2], antineoplastic properties[3], tumor-selective and apoptosis-inducing agent[4,5], potent therapeutic agents for prostate cancer[6] and apoptosis-inducing anticancer agents[7,8]. Apart from anticancer activities, 1,2,4-Oxadiazoles also exhibit diverse biological activities e.g. hypocholesterolemic agents[9], antiviral agents[10], diuretic[11], antimicrobial[12], anti-inflammatory agents[13-16], anti-helmintic[17,18], etc. Oxadiazole ring has increased hydrolytic and metabolic stability, improved pharmacokinetic and *in vivo* performance are often observed, which makes this heterocycle an important structural moiety for the pharmaceutical industry.

In recent years, noteworthy advancement has been made by computational chemistry led new challenges to drug discovery. Quantitative structure activity relationship (QSAR) which has become an reputable tool for establishing quantitative relationship between biological activity and physicochemical properties of the compounds in a series using various statistical methods (linear regression and non- linear regression analysis) and it helps to calculate the biological activities of newly designed analogues contributing to the drug discovery process[19].

The core idea of the present study is the search for novel 1,2,4-Oxadiazoles that would show a promise to become useful as antiproliferative agents. A series of 3-(aryl)-N-(aryl)-1,2,4-oxadiazol-5-amines [6] which were reported as antiproliferative agents chosen for QSAR study in order to establish quantitative relationship between physiochemical properties and biological activities of the compounds using molecular design suite software (VlifeMDS)[20].

3-(Aryl)-N-(aryl)-1,2,4-oxadiazol-5-amines[6] reported as anti-cancer agents in the literature were selected for the present QSAR work in order to establish quantitative relationship between biological activity and various structural/physicochemical properties of the compounds using QSARPlus software.

MATERIALS AND MEHTODS

Data Set

In the present study a data set of 3-(aryl)-N-(aryl)-1,2,4-oxadiazol-5-amines as antiproliferative agents (20 molecules)[6] has been taken from the literature for QSAR studies (Table 1). The reported IC_{50} values (μM), have been converted to the logarithmic scale [pIC_{50} (moles)], for QSAR study.

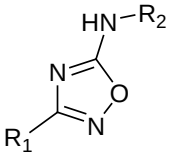
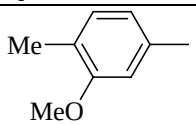
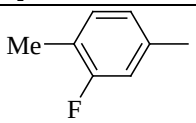
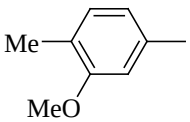
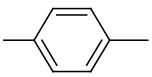
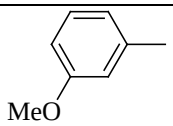
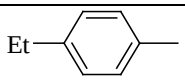
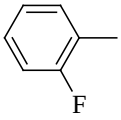
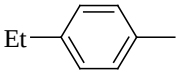
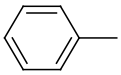
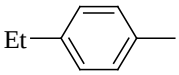
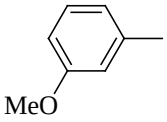
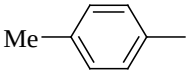
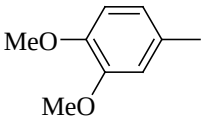
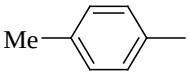
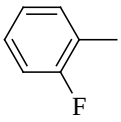
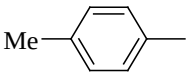
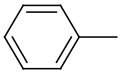
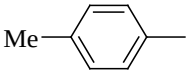
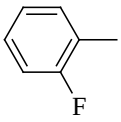
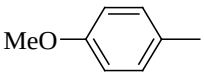
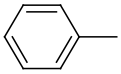
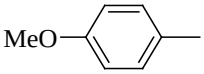
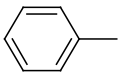
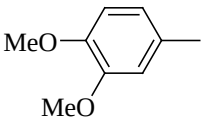
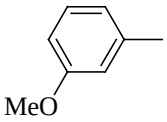
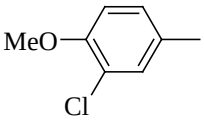
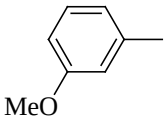
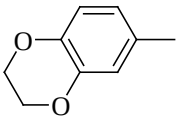
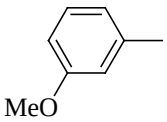
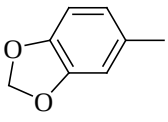
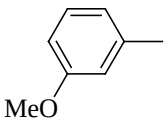
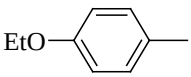
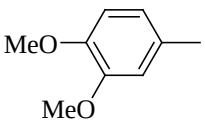
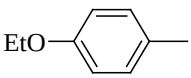
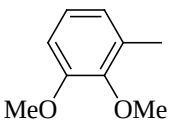
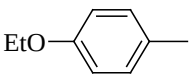
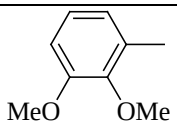
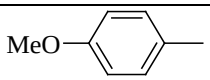
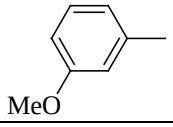
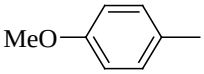


Table 1: General structure of the 3-(Aryl)-N-(Aryl)-1, 2, 4-Oxadiazol-5-amines and their biological activities (data set of 20 molecules)

S. No.	Compound	R_1	R_2	pIC_{50} (Mole)
1	2a			5.6576
2	2b			6.0655

3	2c			5.7959
4	2d			5.5850
5	2e			6.0000
6	2f			6.0000
7	2g			5.5686
8	2h			5.7959
9	2i			6.1938
10	2j			6.2596
11	2k			7.0757
12	2l			5.5686
13	2m			6.0177
14	2n			6.0315
15	2o			5.7447
16	2p			5.6778
17	2q			6.0410
18	2r			5.8239

19	2s			6.4202
20	2t			7.5376

Molecular modeling

Molecular modeling and PLS studies were performed on HCL computer having genuine Intel Pentium Dual Core Processor and Windows XP operating system using the software Molecular Design Suite (MDS). Structures were drawn using the 2D draw application and converted to 3D structures. Structures were optimized by energy minimization and geometry optimization was done using Dreiding Force Field method and Modified Qeq Charge with 10000 as maximum number of cycles, 0.01 as convergence criteria (root mean square gradient) and 1.0 as constant (medium's dielectric constant which is 1 for in vacuo) in dielectric properties. The default values of 30.0 and 10.0 Kcal/mol were used for electrostatic and steric energy cutoff.

Number of descriptors was calculated after optimization or minimization of the energy of the data set molecules. Various types of physicochemical descriptors were calculated: Individual (Molecular weight, H-Acceptor count, H-Donor count, XlogP, slogP, SMR, polarisablity, etc.), retention index (Chi), atomic valence connectivity index (ChiV), Path count, Chi chain, ChiV chain, Chain PathCount, Cluster, Pathcluster, Kappa, Element count (H, N, C, S count etc.), Distance based topological (DistTopo, ConnectivityIndex, WienerIndex, Balaban Index), Estate numbers (SsCH3count, SdCH2count, SssCH2count, StCHcount, etc.), Estate contribution (SsCH3-index., SdCH2-index, SssCH2-index , StCH index), Information theory based (Ipc, Id etc.) and Polar surface area.

More than 200 alignment independent descriptors were also calculated using the following attributes. A few examples are T_2_O_7, T_N_N_5, T_2_2_6, T_C_O_1, T_O_Cl_5 etc.

Structural descriptors	Selected Attributes
*Topological	2
Range	T (any)
Min – 0	C
Max. - 7	N
	O
	F
	Cl

Generation of training and test set of compounds

In order to evaluate the QSAR model, data set was divided into training and test set using Sphere Exclusion method. Training set is used to develop the QSAR model for which biological activity data are known. Test set is used to challenge the QSAR model developed based on the training set to assess the predictive power of the model which is not included in model generation.

Sphere Exclusion method: In this method dissimilarity value provides an idea to handle training and test set size. It needs to be adjusted by trial and error until a desired division of training and test set is achieved. Increase in dissimilarity value results in increase in number of molecules in the test set.

Manual data selection method: Data set is divided manually into training and test sets on the basis of the result obtained in sphere exclusion method.

Partial least square regression (PLSR)

PLSR was used for model generation. PLSR is an expansion of the multiple linear regression (MLR) model. In its simplest form, a linear model specifies the (linear) relationship between a dependent (response) variable and a set of predictor variables. PLSR extends MLR without imposing the restrictions employed by discriminant analysis, principal component regression (PCR) and canonical correlation. In PLSR, prediction functions are represented by factors extracted from the Y'XX'Y matrix. The number of such prediction functions that can be extracted typically will exceed the maximum of the number of Y and X variables. PLSR is probably the least restrictive of the various multivariate extensions of the multiple linear regression model. This flexibility allows it to be used in situations where the use of traditional multivariate methods is severely limited, such as when there are fewer observations than predictor variables. PLSR can be used as an exploratory analysis tool to select suitable predictor variables and to identify outliers before classical linear regression. All the calculated descriptors were considered as independent variable and biological activity as dependent variable.

RESULTS AND DISCUSSION

Selected data set [3-(aryl)-N-(aryl)-1,2,4-oxadiazol-5-amines] was subjected to partial least square regression analysis method for model building. Result of PLSR analysis using sphere exclusion and manual data selection methods is shown in Table 2 and 3 respectively. The statistically significant model obtained is shown in Table 4.

Different training and test set of 3-(aryl)-N-(aryl)-1,2,4-oxadiazol-5-amines were constructed using sphere exclusion (dissimilarity level 9.0 to 11.5) and manual data selection methods. Training and test set were selected if they follow the Unicolumn statistics, i.e., maximum of the test is less than maximum of training set and minimum of the test set is greater than of training set, which is prerequisite for further QSAR analysis (Table-2). This result 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.

Partial least squares regression analysis (PLSR) in conjunction with stepwise (SW) forward-backward was applied for building QSAR models. Results of models developed by PLS using sphere exclusion and manual data selection methods are shown in Table 3 and 4 respectively. Significant QSAR models generated is shown in Table 5.

Table 2: Results of PLS analysis using sphere exclusion data selection method

Trials	Dissm. Value	Test set molecule	r2	q2	pred_r2	r2 se	q2 se	pred_r2se	F test
1	2.5	2f, 2r, 2i	0.7907	0.7047	-14.802	0.2699	0.3206	0.8168	26.4512
2	3	2f, 2q ,2i ,2h	0.8023	0.7097	-1.8314	0.2557	0.3099	0.5564	56.8290
3	3.2	2c, 2h, 2i,2p, 2q,2r	0.8115	0.6610	-1.0824	0.2724	0.3653	0.5236	23.6829
4	3.3	2b,2f,2h,2i,2q,2r,2h	0.7978	0.6278	-1.4119	0.2848	0.3864	0.4738	43.3950

Table 3: Results of PLS analysis using manual data selection method

Trials	Test set molecule	r2	q2	pred_r2	r2 se	q2 se	pred_r2se	F test
1	2i,2k,2l, 2p	0.8229	0.6202	**0.7566**	0.2189	0.3206	0.3420	30.2096
2	2i,2k,2l, 2p,2q	0.9103	0.8093	0.5612	0.1561	0.2277	0.4365	60.9104
3	2i,2k,2l, 2q	0.8864	0.7705	0.5632	0.1717	0.2440	0.4941	50.7004
4	2i,,2l, 2p,2q	0.8616	0.7400	-0.1671	0.2141	0.2935	0.5040	40.4750
5	2i,2k,2p, 2q	0.8667	0.6748	**0.6673**	0.1882	0.2939	0.4233	42.2611
6	2l,2k, 2p,2q	0.8292	0.5976	0.5423	0.2080	0.3192	0.5078	31.5526
7	2i, 2k,2l,	0.7937	0.5754	**0.8079**	0.2319	0.3327	0.3578	26.9289
8	2i, 2k,2p	0.7406	0.5309	0.4023	0.2631	0.3539	0.6123	19.9887
9	2i, 2l,2p	0.7719	0.6272	-1.0532	0.2708	0.3463	0.7108	23.6937
10	2k,2l,2p	0.7314	0.4716	0.2934	0.2604	0.3653	0.7080	19.0632
11	2i, 2k,2q	0.8407	0.6341	**0.6836**	0.2009	0.3045	0.5009	36.9476
12	2k,2q,2p	0.7939	0.4982	0.5186	0.2268	0.3538	0.6096	26.9588

Table 4: Statistical significant models generated

Model	Trial no. (Manual)	Test set molecules	Equation
1	7	2i,2k,2l	pIC_{50} = - 2.7966 SKMostHydrophilic - 0.3478 T_C_N_7 - 58.5564 AveragePotential + 7.8242 Optimum Components = 2; n = 17; Degree of freedom = 14; r2 = 0.7937; q2 = 0.5754; r2 se = 0.2319; q2 se = 0.3327; pred_r2 = 0.8079; pred_r2se = 0.3578; F test = 26.9289 Alpha Rand R^2 = 0.01; Alpha Rand Q^2 = 0.05; Alpha Rand Pred R^2 = 0.00000
2	1	2i,2k,2l,2p	pIC_{50} = -2.7573 SKMostHydrophilic -0.3533 T_C_N_7 -60.0618 AveragePotential +7.8384 Optimum Components = 2; n = 16; Degree of freedom = 13; r2 = 0.8229; q2 = 0.6202; r2 se = 0.2189 ; q2 se = 0.3206; pred_r2 = 0.7566; pred_r2se = 0.3420; F test = 26.9289 Alpha Rand R^2 = 0.01; Alpha Rand Q^2 = 0.05; Alpha Rand Pred R^2 = 0.00000
3	11	2i,2k,2q	pIC_{50} = -2.7410 SKMostHydrophilic -0.3737 T_C_N_7 -56.2360 AveragePotential +7.8603 Optimum Components = 2; n = 17; Degree of freedom = 14; r2 = 0.8407 ; q2 = 0.6341 ; r2 se = 0.2009; q2 se = 0.3045; pred_r2 = 0.6836; pred_r2se = 0.5009 F test = 36.9476 Alpha Rand R^2 = 0.01; Alpha Rand Q^2 = 0.05; Alpha Rand Pred R^2 = 0.00000
4	5	2i,2k,2p,2q	pIC_{50}= - 2.7034 SKMostHydrophilic - 0.3784 T_C_N_7 - 58.4140 AveragePotential + 7.8674 Optimum Components = 2; n = 16; Degree of freedom = 13; r2 = 0.8667; q2 = 0.6748; r2 se = 0.1882; q2 se = 0.2939; pred_r2 = 0.6673; pred_r2se = 0.4233; F test = 42.2611; Alpha Rand R^2 = 0.01; Alpha Rand Q^2 = 0.05; Alpha Rand Pred R^2 = 0.00000

Data fitness plot for model 1 is shown in Fig. 3. Result of the observed and predicted biological activity for the training and test compounds for the Model 1 is shown in Table 6. The plot of observed vs. predicted activity of training and test sets for model 1 is shown in Fig. 4**.** From the plot it can be seen that model is able to predict the activity of training set quite well (all points are close to regression line) as well as external.

In the above QSAR equations, n is the number of molecules (Training set) used to derive the QSAR model, r2 is the squared correlation coefficient, q2 is the cross-validated correlation coefficient, pred_r2 is the predicted correlation coefficient for the external test set, *F* is the Fisher ratio, reflects the ratio of the variance explained by the model and the variance due to the error in the regression. High values of the F-test indicate that the model is statistically significant. r2 se, q2 se and pred_r2se are the standard errors terms for r2, q2 and pred_r2 (smaller is better).

The QSAR model was obtained by using partial least squares regression method using sphere exclusion data selection method (for training and test set).

From Table 3, model 1 explains 83.69 % (r2= 0.8369) of the total variance in the training set as well as it has internal (q2) and external (pred_r2) predictive ability of 72.06% and 80.03% respectively. The F-test = 24.36 shows the statistical significance of 99.98% of the model. In addition randomization test shows confidence of 99.9% that the generated model is not random and hence it can be selected as the QSAR model. Model 2 explains 87.73% (r2= 0.8773) of the total variance in the training set as well as it has internal (q2) and external (pred_r2) predictive ability of 80.40% and 55.32% respectively. Model 3 explains 78.40% (r2= 0.7840) of the total variance in the training set as well as it has internal (q2) and external (pred_r2) predictive ability of 56.31% and 75.00% respectively. Model 4 explains 83.36% (r2= 0.8336) of the total variance in the training set as well as it has internal (q2) and external (pred_r2) predictive ability of 65.18% and 74.81% respectively.

Table 4 represents the actual and predicted biological activity for the models 1 and 2. Descriptors used in the most significant model (Model-01) is shown in Table 05. Correlation between descriptors used in the model 1 is shown in Table 6.

Table 5: Actual and predicted biological activity for the models 1and 2.

S. No.	Compound	pIC_{50} (Mole)	Model - 1	Model - 2
1	2a	5.6576	5.6691	5.6855
2	2b	6.0655	5.9863	6.0128
3	2c	5.7959	5.8553	5.8831
4	2d	5.5850	5.7423	5.7740
5	2e	6.0000	5.7888	5.8239
6	2f	6.0000	6.1112	6.1371
7	2g	5.5686	5.5125	5.5208
8	2h	5.7959	5.7332	5.7674
9	2i	6.1938	5.9078*	5.9444*
10	2j	6.2596	6.3904	6.4134
11	2k	7.0757	6.6765*	6.7110*
12	2l	5.5686	5.6904*	5.7063*
13	2m	6.0177	5.7033	5.7169
14	2n	6.0315	6.0384	6.0539
15	2o	5.7447	5.9234	5.9362
16	2p	5.6778	6.0230	6.0473*
17	2q	6.0410	6.1450	6.1675
18	2r	5.8239	6.2503	6.2648
19	2s	6.4202	6.2500	6.2663
20	2t	7.5376	7.3983	7.4193

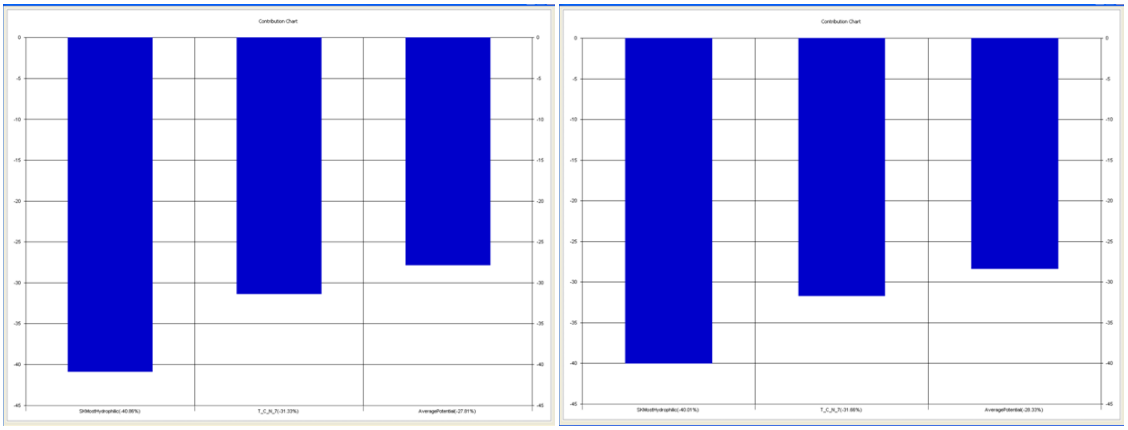
* indicates that compound are in the test set and rest of the compounds are in the training set.

Table 5: List of descriptors for the training set compounds used in the most significant model (model-01)

S. No.	Compound	SKMostHydrophilic	T_C_N_7	AveragePotential
1	2a	0.427628	3	-0.001435
2	2b	0.44437	3	-0.007652
3	2c	0.486441	3	-0.007425
4	2d	0.548184	3	-0.008443
5	2e	0.567751	3	-0.010172
6	2f	0.409914	3	-0.00814
7	2g	0.329563	5	-0.005955
8	2h	0.572534	3	-0.009451
9	2j	0.350116	2	-0.004113
10	2m	0.423838	2	0.0041
11	2n	0.333352	3	-0.00324
12	2o	0.336009	3	-0.001402
13	2p	0.416066	3	-0.006927
14	2q	0.341632	4	-0.011394
15	2r	0.244299	4	-0.008545
16	2s	0.29154	3	-0.004856
17	2t	0.099113	2	-0.009337

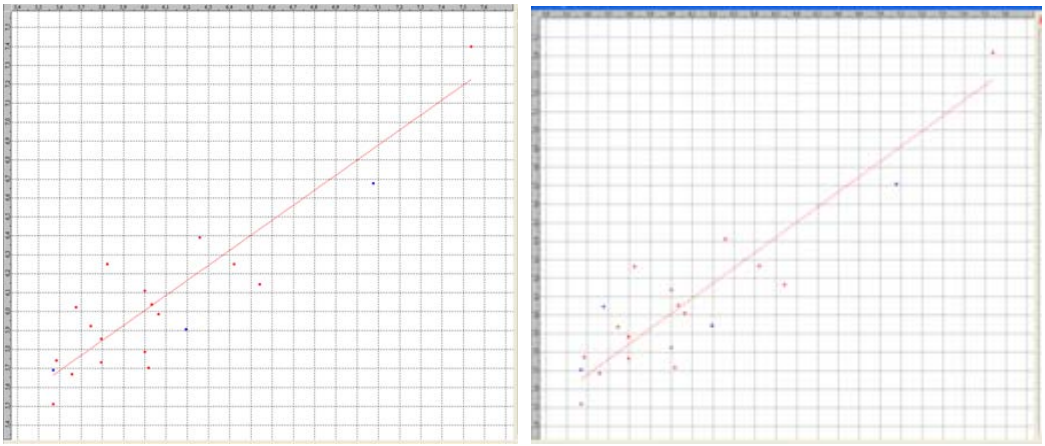
Contribution chart for models 1-2 is represented in Figure-1. Data fitness plot for models 1-2 is shown in Figure-2. The plot of observed vs predicted activity provides an idea about how well the model was trained and how well it predicts the activity of the external test set.

From the plot (Figure-03) it can be seen that the model is able to predict the activity of the training set quiet well as well as external test set, providing confidence of the model.



(Model -1) (Model -2)

Fig. 1: Contribution chart for models 1-2 showing contribution of different descriptors.



(Model -1) (Model -2)

Fig. 2: Data fitness plot for models 1-2.

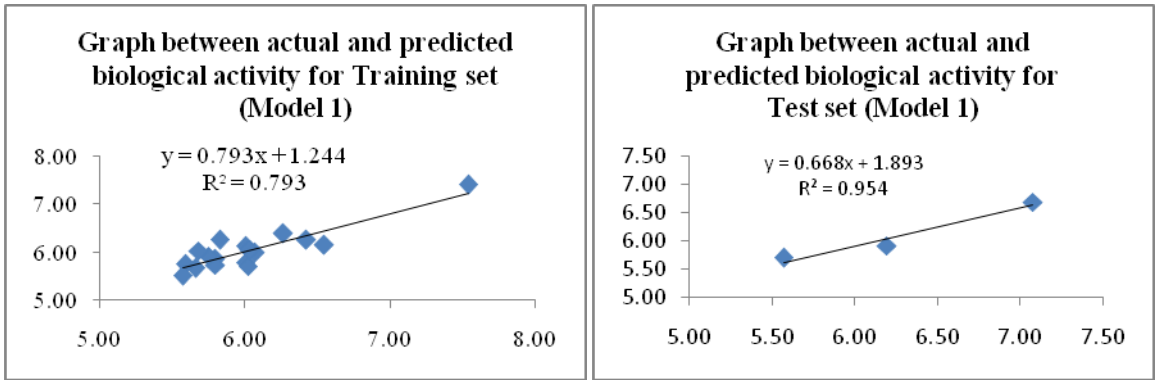


Fig. 3: Graph between actual and predicted biological activity of training and test set for Model-1.

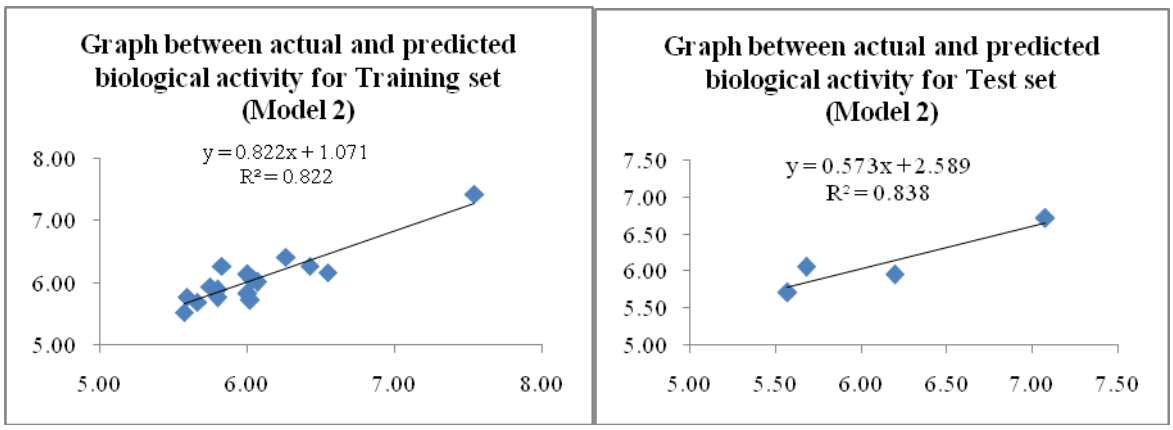


Fig. 4: Graph between actual and predicted biological activity of training and test set for Model-2.

Interpretation of the Model 01 (Most significant)

Among the four significant models generated (Table-04), model 1 is the most significant one. The equation explains 79% (r2 = 0.7937) of the total variance in the training set and has an internal (q2) and external (pred_r2) predictive ability of ~58% and ~81% respectively. The F test shows the statistical significance of 99.99 % of the model which means that probability of failure of the model is 1 in 10000. In addition, the randomization test shows confidence of 99.9999 (Alpha Rand Pred R^2 = 0.00000) that the generated model is not random and hence chosen as the QSAR model.

In the QSAR model 1, the negative coefficient value of SKMostHydrophilic [Most hydrophilic value on the van der Waals surface] on the biological activity indicated that lower value leads to better antiproliferative activity (compound 2t,2s, 2n, 2q etc.) whereas higher value leads to decrease antiproliferative activity (compound 2h, 2d, 2c, 2a etc.). Negative coefficient value of T_C_N_7 [This is the count of carbon atoms (single or double bonded) separated from nitrogen atom (single or double bonded) by 7 bonds in a molecule] on the biological activity indicated that lower values leads to good antiproliferative activity (compound 2j, 2m, 2t, 2s) while higher value leads to reduced antiproliferative activity

(compound 2g, 2r etc.). Negative coefficient value of AveragePotential [This descriptor signifies average of the total electrostatic potential on van der Waals surface area of the molecule] on the biological activity indicated that lower values leads to better antiproliferative activity (compound 2t, 2q, 2e) while higher value leads to reduced antiproliferative activity (compound 2o, 2a, 2g, 2p etc.). Contribution chart for model 1 reveals that the descriptors SKMostHydrophilic, T_C_N_7 and AveragePotential contributing 26.08%, 27.11% and 9.44 % respectively. Two more descriptors T_N_O_6 and +ve PotentialSurfaceArea are contributing inversely 40%, 31% and 28% respectively to biological activity.

The observed vs. predicted activity provides an idea about how well the model was trained and how well it predicts the activity of the external test set. From the plot it can be seen that model is able to predict the activity of training set quite well (all points are close to the regression line) as well as external test set providing confidence in the predictive ability of the model.

CONCLUSION

Two dimensional quantitative structure activity relationship (2D QSAR) study by means of partial least square regression (PLSR) method was performed on a series of 3-(aryl)-N-(aryl)-1,2,4-Oxadiazol-5-amines as antiproliferative agents using molecular design suite (VLifeMDS). This study was performed with 20 compounds (data set) using sphere exclusion (SE) algorithm and manual selection methods for the division of the data set into training and test set. PLSR methodology with stepwise (SW) forward-backward variable selection method was used for building the QSAR models. Statistically significant QSAR models were generated. Among them most significant model has squared correlation coefficient (r2), cross validated correlation coefficient (q2) and predictive correlation coefficient (pred_r2) 0.7937, 0.5754 and 0.8079 respectively. The QSAR model indicates that the descriptors SKMostHydrophilic [Most hydrophilic value on the van der Waals surface], T_C_N_7 [This is the count of carbon atoms (single or double bonded) separated from nitrogen atom (single or double bonded) by 7 bonds in a molecule] and AveragePotential [This descriptor signifies average of the total electrostatic potential on van der Waals surface area of the molecule] contributing (inversely) 40%, 31% and 28% respectively to biological activity. The negative coefficient value of SKMostHydrophilic, T_C_N_7 and AveragePotential on the biological activity indicated that lower value leads to better antiproliferative activity whereas higher value leads to decrease antiproliferative activity. Structural information obtained can be used for predicting the activity of the newer compounds with more potent activity.

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REFERENCES

1. Luthman K, Borg S, Hacksell U. Synthesis and Use of Pseudopeptides Derived from 1,2,4-Oxadiazole-, 1,3,4-Oxadiazole-, and 1,2,4-Triazole-based Dipeptidomimetics. Methods Mol Med 1999; 1-23.
2. Zhang HZ, Kasibhatla S, Kuemmerle J, Kemnitzer W, Ollis-Mason K, Qiu L, Crogan-Grundy C, Tseng B, Drewe J, Cai SX. Discovery and Structure-Activity Relationship of 3-Aryl-5-Aryl-1,2,4-Oxadiazoles as a New Series of Apoptosis Inducers and Potential Anticancer Agents. J Med Chem 2005; 48: 5215-5223.
3. Matsumoto J, Takahashi T, Agata M, Toyofuku H, Sasada N. A Study of the Biological Pharmacology of IFO, A New Selective and Reversible Monoamine Oxidase-B Inhibitor. Jpn J Pharmacol 1994; 65: 51-57.
4. Boys ML, Schretzman LA, Chandrakumar NS, Tollefson MB, Mohler SB, Downs VL, Wang Y, Dalton CR, Norring SA. Convergent, Parallel Synthesis of a Series of β-Substituted 1,2,4-Oxadiazole Butanoic Acids as Potent and Selective αvβ3 Receptor Antagonists. Bioorg Med Chem Lett 2006; 16: 839-844.
5. Jessen KA, English NM, Wang JY, Maliartchouk S, Archer SP, Qiu L, Brand R, Kuemmerle J, Zhang HZ, Gehlsen K, Drewe J, Tseng B, Cai SX, Kasibhatla S. The Discovery and Mechanism of Action of Novel Tumor-Selective and Apoptosis-Inducing 3,5-Diaryl-1,2,4-Oxadiazole Series Using a Chemical Genetics Approach. Mol Cancer Ther 2005; 4(5): 761-771.
6. Krasavin M, Rufanov KA, Sosnov AV, Karapetian R, Godovykh E, Soldatkina O, Lavrovsky Y, Gakh AA. Discovery and SAR Exploration of N-Aryl-N-(3-Aryl-1,2,4-Oxadiazol-5-yl)Amines as Potential Therapeutic Agents for Prostate Cancer. Chem Centr J 2010; 4: 4-10.
7. Than GN, Turoczy T, Sumegi B, Than NG, Bellyei S, Bohn H, Szekeres G. Over Expression of Placental Tissue Protein 17b/TIP47 in Cervical Dysplasias and Cervical Carcinoma. Anticancer Res 2001; 21: 639-642.
8. Kemnitzer W, Kuemmerle J, H-Zhang Z , Kasibhatla S, Tseng B, Drewe J, Cai SX. Discovery of 3-Aryl-5-Aryl-1,2,4-Oxadiazoles as A New Series of Apoptosis Inducers. 2. Identification of More Aqueous Soluble Analogs as Potential Anticancer Agents. Bioorg. Med. Chem. Lett 2009; 19: 4410-4415.
9. Yurugi S, Miyake A, Fushimi T, Imamiya E, Matsamura H, Imai Y. Studies on the Synthesis of N-Heterocyclic Compounds. 3. Hypocholesterolemic 1,2,4-Oxadiazole Derivatives. Chem Pharm Bull 1973; 21: 1641-1650.
10. Diana GD, Volkots DL, Nitz TJ, Bailey TR, Long MA, Vescio N, Aldous S, Pevear DC, Dutko FJ. Oxadiazoles as Ester Bioisosteric Replacements in Compounds Related to Disoxaril-Antirhinovirus Activity. J Med Chem 1994; 37: 2421-2436.
11. Watthey JWH, Desai M, Rutledge R, Dotson R. Synthesis and Diuretic Profile of 3-(3-Amino-1,2,4-Oxadiazol-5-yl)-5-Chloro-2,6-Pyrazinediamine, An Amiloride-Type Diuretic. J Med Chem 1980; 23: 690-692.
12. Leite ACL, Vieira RF, de Faria AR, Wanderley AG, Afiatpour P, Ximenes ECPA, Srivastava RM, Oliveira CF, Medeiros MV, Antunes E, Brondani DJ. Synthesis, Anti-inflammatory and Antimicrobial Activities of New 1,2,4-Oxadiazoles Peptidomimetics. Farmaco 2000; 55: 719-724.
13. Unangst PC, Shrum GP, Connor DT, Dyer RD, Schrier DJ. Novel 1,2,4-Oxadiazoles and 1,2,4-Thiadiazoles as Dual 5-Lipoxygenase and Cyclooxygenase Inhibitors. J Med Chem 1992; 35: 3691-3698.
14. Song Y, Connor DT, Sercel AD, Sorenson RJ, Doubleday R, Unangst PC, Roth BD, Beylin VG, Gilbertsen RB, Chan K, Schrier DJ, Guglietta A, Bornemeier DA, Dyer RD. Synthesis, Structure Activity Relationships and *in vivo* Evaluations of Substituted Di-Tert-Butylphenols as a Novel Class of Potent, Selective and Orally Active Cyclooxygenase-2 Inhibitors. 1. Thiazolone And Oxazolone Series. J Med Chem 1999; 42: 1151-1160.
15. Farooqui M, Bora R, Patil CR. Synthesis, Analgesic and Anti-inflammatory Activities of Novel 3-(4-Acetamido-Benzyl)-5-Substituted-1,2,4-Oxadiazoles. Eur J Med Chem 2009; 44: 794-799.
16. Nicolaides DN, Fylaktakidou KC, Litinas KE, Hadjipavlou-Litina D. Synthesis and Biological Evaluation of Several Coumarin-4-Carboxamidoxime and 3-(Coumarin-4-yl)-1,2,4-Oxadiazole Derivatives. Eur J Med Chem 1998; 33: 715-724.
17. Haugwitz RD, Martinez AJ, Venslavsky J, Angel RG, Maurer BV, Jacobs GA, Narayanan VL, Cruthers LR, Szanto J. Antiparasitic Agents. 6. Synthesis and Anthelmintic Activities of Novel Isothiocyanatophenyl-1,2,4-Oxadiazoles. J Med Chem 1985; 28: 1234-1241.
18. Ainsworth C, Buting WE, Davenport J, Callender ME, McCowen MC. Anthelmintic Activity of 1,2,4-Oxadiazoles. J Med Chem 1967; 10: 208-211.
19. Ferreira MMC. Multivariate QSAR. J Braz Chem Soc 2002; 13: 742.
20. VLifeMDS 3.5, Molecular Design Suite, Vlife Sciences Technologies Pvt. Ltd., Pune, India (2009), www.vlifesciences.com.