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3D QSAR Analysis on Oxadiazole Derivatives as Anticancer Agents

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ABSTRACT
Three dimensional quantitative structure activity relationship (3D 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 method used 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. Five predictive models were generated with sphere exclusion and two with manual data selection methods using PLSR. The most significant model is having correlation coefficient 0.9334 (squared correlation coefficient r2 = 0.8713) indicating noteworthy correlation between biological activity and descriptors. The model has internal predictivity 74.45% (q2 = 0.7445) and highest external predictivity 81.09 % (pred_r2 = 0.8109) and lowest error term for predictive correlation coefficient (pred_r2se = 0.1321). Model showed that steric (S_1278, S_751) and electrostatic (E_307) interactions play important role in determining antiproliferative activity. The molecular field analysis (MFA) contour plots provided further understanding of the relationship between structural features of substituted oxadiazole derivatives and their activities which should be applicable to design newer potential antiproliferative agents.

Keywords: 3D-QSAR, PLS, antiproliferative agents, 1, 2, 4-Oxadiazoles.

INTRODUCTION

Compounds containing the 1, 2, 4-oxadiazole scaffold has drawn interest due to the unique chemical structure and large variety of biological properties. 1, 2, 4-Oxadiazoles exhibit diverse biological activities. Oxadiazoles have often been described as bioisosteres for amides and esters. Due to increased hydrolytic and metabolic stabilities of the oxadiazole ring, improved pharmacokinetic and *in vivo* performance are often observed, which makes this heterocycle an important structural moiety for the pharmaceutical industry. As a result of these characteristics, oxadiazoles have often been the target of many drug discovery programs as tyrosine kinase inhibition [1], muscarinic agonism [2], histamine H3 antagonism [3], potent histamine H_2 receptor antagonists [4-5], hypocholesterolemic agents [6], antiviral agents [7], muscarinic receptor antagonists [8-9], anti-inflammatory agents [10-14], antimicrobial [15], antiviral [16], diuretic [17], anti-helmintic [18-19], interleukin-8 (IL-8) receptor antagonists [20], monoamine oxidase inhibition [21], anticonvulsant activity [22], cytotoxic activities [23], antitumor [24], antineoplastic properties [25], tumor-selective and apoptosis-inducing agents [26-27], potent therapeutic agents for prostate cancer [28] and apoptosis-inducing anticancer agents. [29-30]

In modern years, a significant advancement has been made by computational chemistry led new challenges to drug discovery by rational process. 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 and it helps to predict the biological activities of newly designed analogues contributing to the drug discovery processes. [31]

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 [28] 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). [32]

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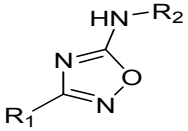
MATERIALS AND MEHTODS

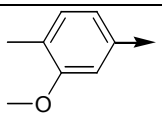
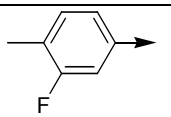
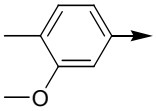
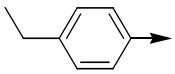
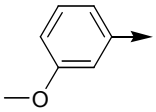
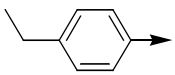
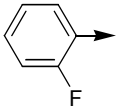
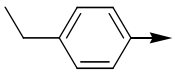
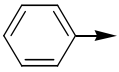
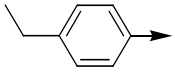
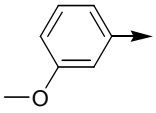
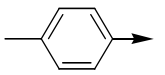
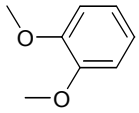
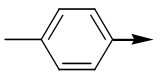
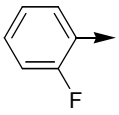
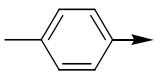
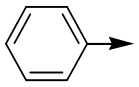
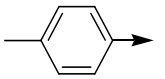
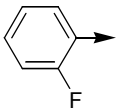
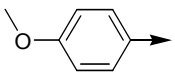
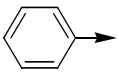
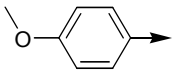
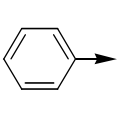
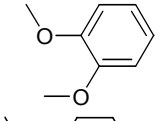
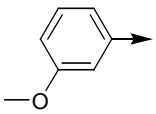
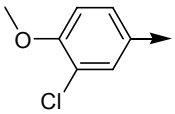
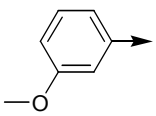
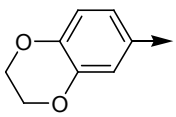
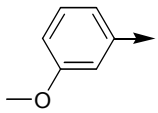
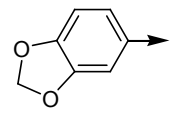
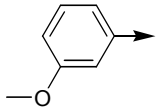
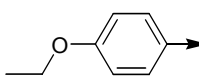
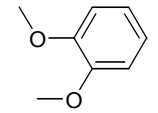
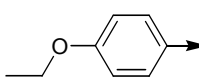
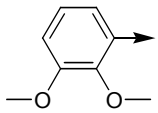
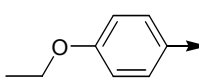
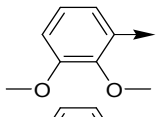
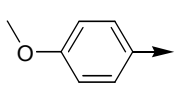
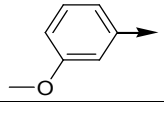
Data Set

In the present study a data set of 3-(aryl)-N-(aryl)-1, 2, 4-oxadiazol-5-amines as antiproliferative agents (20 molecules) [28] 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 Study

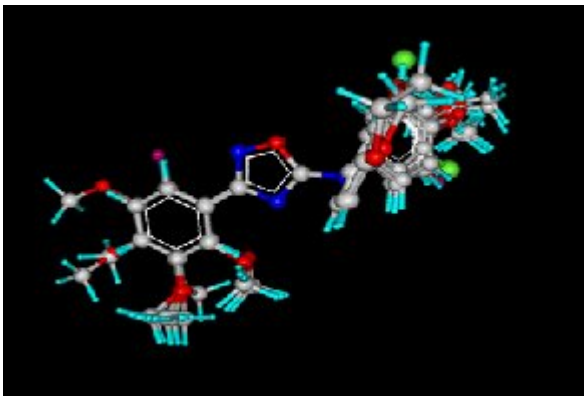
Molecular modeling and PLS studies were performed on HCL computer having genuine Intel Pentium Dual Core Processor and Windows XP operating system using the software Molecular Design Suite (MDS). Structures were drawn using the 2D draw application and converted to 3D structures. Structures were optimized 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. The selected dataset were aligned by using template based alignment method using most active molecule 2t as a reference molecule (**2**) and structure (**1**) as a template (Fig. 1). The alignment of all the molecules on the template is shown in Fig. 2. In the template based alignment method, a template structure was defined and used as a basis for alignment of a set of molecules.

Descriptor calculation:

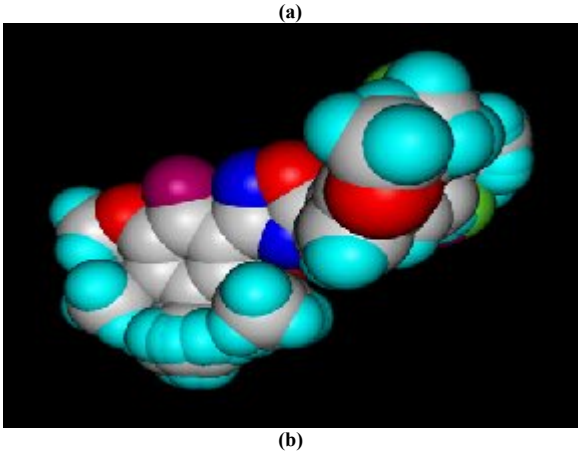
Once the molecules are aligned, a molecular field is computed on a grid of points in space around the molecule. This field provides a description of how each molecule will tend to bind in the active site. Descriptors representing the steric, electrostatic and hydrophobic interaction energies were computed at the lattice points of the grid using a methyl probe of charge +1.

(1) (2)

Fig 1: Structure of template (1) and reference molecule (2) used in template based alignment



(a)



(b)

Fig 2: 3D-Allignment of molecules (a) ball and stick model, (b) space fill model

Data selection

In order to evaluate the QSAR model externally, data set was divided into training and test set using sphere exclusion and manual data selection methods. 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 effectiveness of the model which is not included in model generation.

Sphere exclusion algorithm was used for design of training and test sets. The entire data set was separated into training and test sets by means of sphere exclusion algorithm. [33] This algorithm allows constructing training sets covering all descriptor space areas occupied by representative points. The higher the dissimilarity level, the smaller the training set is and the larger the test set is and vice versa. It is anticipated that the predictive ability of QSAR models generally decrease when the dissimilarity level increases. Once the training and test sets are generated, partial least square regression method is applied to descriptors generated over grid.

Manual data selection method was also used on the basis of results obtained in sphere exclusion method.

Model Building

Models were generated by using partial least squares regression analysis (PLSR) in conjunction with stepwise (SW) forward-backward variable selection method with pIC_{50} activity field as dependent variable and descriptors as independent variable. [34-35]

Validation of the models

Models were validated internally and externally. In internal validation (cross validation), a compound is eliminated in the training set and its biological activity is predicted. This step is repeated until every compound in the training set has been eliminated and its activity is predicted once. External validation [(pred_r2)] is done by calculating predicted correlation coefficient (pred_r2) value using following equation, where y_i and y_* are the actual and predicted activities of the i^{th} compound in test set, respectively and y_{mean} is the average activity of all compounds in the training set. Both summations are over all compounds in the test set. The obtained pred_r^2 value is indicative of the predictive power of the QSAR model for external test set.

$$\text{pred\_ r2} = 1 - \sum (y_i - y_*)^2 / \sum (y_i - y_{mean})^2$$

RESULTS AND DISCUSSION

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 model generated is shown in Table-5.

Table 2: Uni-Column Statistics for Model 1 for training and test set activity

Column Name	Average	Max	Min	StdDev	Sum
Training set	6.1109	7.5376	5.5686	0.5415	103.8852
Test set	5.8245	6.0000	5.6777	0.1631	17.4735

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.

Table 3: Results of 3D-QSAR analysis using PLSR method by sphere exclusion selection method

Trial	Dissimilarity value	Test Set	Stepwise – forward backward (SW-FB)						
			r2	q2	Pred_r2	r2 se	q2 se	Pred_r2 se	F test
01	9.0	2c, 2e	0.8713	0.7445	0.8109	0.2044	0.2880	0.1321	50.7680
02	9.5	2c, 2d, 2e	0.8900	0.7296	0.6176	0.1901	0.2981	0.2761	56.6499
03	10.0	2c, 2d, 2e, 2p	0.8949	0.7245	0.6593	0.1885	0.3053	0.2761	55.3712
04	11.0	2c, 2e, 2h, 2p	0.8761	0.7279	0.7869	0.2090	0.3098	0.1782	45.9684
05	11.5	2c, 2e, 2h, 2p, 2n	0.8897	0.6895	0.6794	0.2051	0.3441	0.1951	48.4003

Table 4: Results of 3D-QSAR analysis using PLSR method by manual data selection method

Trial	Test Set	Stepwise – forward backward (SW-FB)						
		r2	q2	Pred_r2	r2 se	q2 se	Pred_r2 se	F test
01	2c, 2h, 2p	0.8278	0.7862	0.3796	0.2379	0.2651	0.3578	33.6483
02	2e, 2h, 2p	0.7982	0.6940	0.4638	0.2512	0.3093	0.2835	59.3193
03	2c, 2e, 2p	0.8414	0.7843	0.7698	0.2227	0.2597	0.1856	79.5787
04	2c, 2e, 2h	0.8888	0.7854	0.8039	0.1948	0.2707	0.1405	55.9384
05	2c, 2e, 2h, 2p	0.8396	0.7870	0.4305	0.2379	0.2741	0.2913	34.0145
06	2c, 2e, 2h, 2n	0.8600	0.8202	0.0226	0.2267	0.2570	0.2639	39.9226
07	2c, 2e, 2n, 2p	0.8706	0.8270	-0.5823	0.2159	0.2497	0.4076	43.7504
08	2c, 2h, 2n, 2p	0.8694	0.8199	0.3132	0.2148	0.2522	0.3155	43.2743
09	2e, 2h, 2n, 2p	0.8708	0.8265	-0.5781	0.2158	0.2501	0.4074	43.8164
10	2c, 2d, 2j, 2t	0.8838	0.8389	-2.0259	0.1465	0.1724	1.6253	49.4186

Table 5: Statistical significant models (best 4) generated

Parameters	Model-1 (SE-Trial-1)	Model-2 (Manual-Trial-4)	Model-3 (SE-Trial-4)	Model-4 (Manual-Trial-3)
Training Set Size (n)	18	17	16	17
Test set size	2	3	4	3
Test set	2c, 2e	2c, 2e, 2h	2c, 2e, 2h, 2p	2c, 2e, 2p
Optimum Components	2	2	2	1
Degree of freedom	15	14		15
r2	0.8713	0.8888	0.8761	0.8414
r2 se	0.2044	0.1948	0.2090	0.2227
q^2	0.7445	0.7854	0.7279	0.7843
q^2se	0.2880	0.2707	0.3098	0.2597
pred_r^2	**0.8109**	**0.8039**	**0.7869**	**0.7698**
pred_r^2se	0.1321	0.1405	0.1782	0.1856
F test	50.7680	55.9384	45.9684	79.5787
Descriptor	S_1278	S_1278	S_1278	S_1278
	S_751	S_377	S_751	S_567
	E_307	S_424	E_307	E_653
Coefficient	0.0355	0.0404382	0.0347	0.0271
	0.9733	1.25954	0.9375	-30.4803
	-0.2252	0.0390321	-0.2274	-0.0342
Alpha Rand R^2	0.00003	0.00100	0.00023	0.00100
Alpha Rand Q^2	0.05000	0.01000	0.10000	0.05000
Alpha Rand Pred R^2	0.00000	0.05000	0.05000	0.05000

Table 6: Actual and predicted biological activity for training set and test set

S. No.	Compound	Actual	Predicted
1	2a	5.66	5.71
2	2b	6.07	5.87
3	2c*	6.00	6.08
4	2d	5.59	5.91
5	2e*	5.80	5.90
6	2f	6.00	5.89
7	2g	5.57	5.68
8	2h	5.80	5.91
9	2i	6.19	6.08
10	2j	6.26	6.43
11	2k	7.08	7.11
12	2l	5.57	5.86
13	2m	6.02	5.87
14	2n	6.03	5.75
15	2o	5.74	5.71
16	2p	5.68	5.88
17	2q	6.54	6.66
18	2r	5.82	5.79
19	2s	6.42	6.03
20	2t	7.54	7.42

*Indicates compounds are in the test set

Interpretation of Model

The result shown in Table 5 indicates model equation as -

pIC_{50} = 0.0355 S_1278 + 0.9733 S_751 − 0.2252 E_307 + 6.2416

n = 18	Degree of freedom = 15	F test = 50.7680
r2 = 0.8713	q2 = 0.7445	pred_r2 = 0.8109
r2 se = 0.2044	q2 se = 0.2880	pred_r2 se = 0.1321
Alpha Rand r2 = 0.00003	Alpha Rand q2 = 0.05	Alpha Rand pred_r2 = 0.00000

Optimum components = 2

The equation explains 87% (r2 = 0.8713) of the total variance in the training set and has an internal (q2) and external (pred_r2) predictive ability of ~74% 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 99.999 (Alpha Rand r2 = 0.00003) that the generated model is not random and hence chosen as the QSAR model.

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.

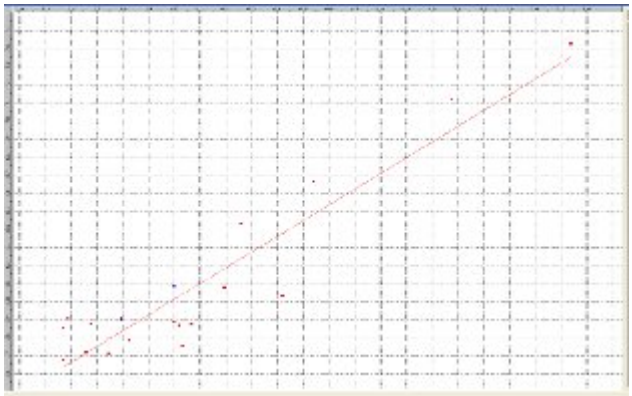
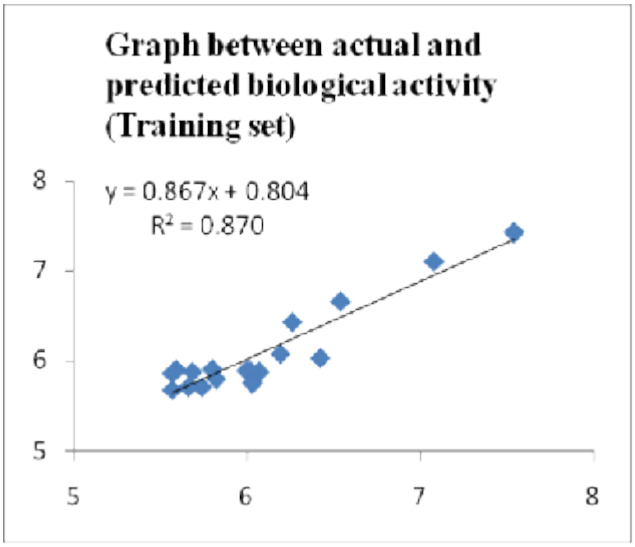


Fig 3: Data fitness plot for Model 1



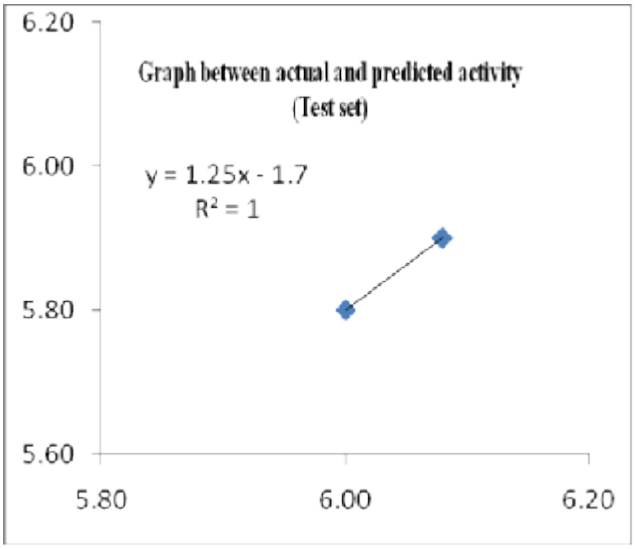


Fig 4: Graph between actual and predicted biological activity of training and test set for Model 1

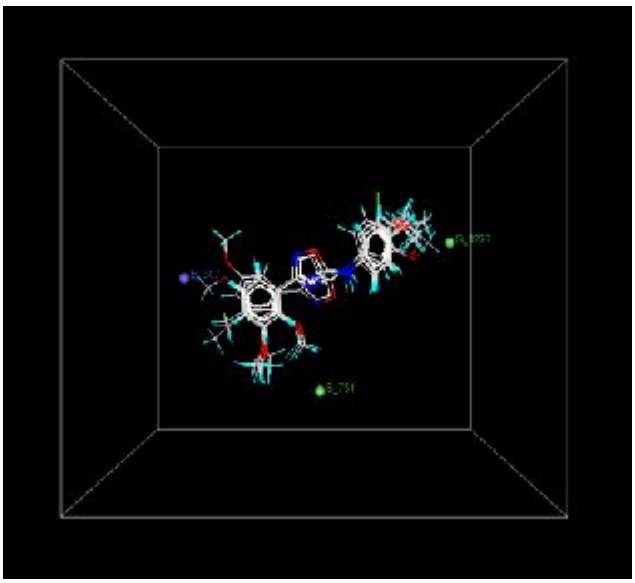


Fig 5: MFA result (Show points): 3D-alignment of molecules with the important steric and electrostatic points contributing [Model 1] with ranges of values shown in parenthesis

Model obtained by PLSR shows that steric interactions (2 of 3) plays major role in determining biological activity. Statistically model is better with respect to squared correlation coefficient (r2), cross validated correlation coefficient (q2 or r2cv) and predictive correlation coefficient (pred_r2). It uses two steric field descriptors and one electrostatic field descriptor with two optimum components to evaluate the activity of new molecule. Contribution chart indicates that the descriptors S_1278, S_751 and E_307 are contributing 48%, 28% and 23% respectively (Total steric contribution is 77% and electrostatic contribution is 23%).

Result plot in which 3D-alignment of molecules with the important steric and hydrophobic points contributing in the model with ranges of values shown in parenthesis represented in Fig. 5.

It shows the relative position and ranges of the corresponding important steric and electrostatic fields in the model provides guidelines for new molecule design as follows –

(i) Steric field:

(a) Steric field, S_1278 has positive range indicates that steric potential is favorable for increase in the activity and hence more bulky substituent group is preferred in that region.

(b) Steric field, S_751 also has positive range indicates that steric potential is favorable for increase in the activity and hence more bulky substituent group is preferred in that region.

(ii) Electrostatic field, E_307 has negative range indicates that negative electrostatic potential is favorable for increase in the activity and hence more electronegative substituent group is preferred in that region.

Taking clues from the above mentioned guidelines and looking at the developed model field plot and corresponding important steric and electrostatic fields range which shows the ranges are towards positive side (S_1278 and S_751) meaning more bulky substituent group is preferred and negative side for (E_307) meaning more electronegative substituent group is preferred at the respective sites.

Finally, it is hoped that the work presented here will play an important role in understanding the relationship of physiochemical parameters with structure and biological activity. By studying the QSAR model one can select the suitable substituent for active compound with maximum potency.

Five and two predictive model was generated with sphere exclusion and manual data selection methods respectively. Models developed to predict the structural features of 3-(aryl)-N-(aryl)-1, 2, 4-oxadiazol-5-amines as antiproliferative agents reveals useful information about the structural features requirement for the molecule. The master grid obtained for the model show that positive range in steric descriptor indicates bulky substituents group is preferred in that region. Negative range in electrostatic field descriptor indicates that negative electronic potential is favorable for increase in activity and hence more electronegative substituent group is preferred in that region. On the basis of electronic and steric potential contributions to the developed model in this work is useful in describing QSAR of 3-(aryl)-N-(aryl)-1, 2, 4-oxadiazol-5-amines as antiproliferative agents and can be employed to design new derivatives with potent inhibitory activity.

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