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QSAR STUDY OF NOVEL N-SUBSTITUTED AZOLE DERIVATIVES OF NICOTINIC ACID MOIETY FOR THEIR ANTICANCER ACTIVITY

Anagha S. Patil, Tejaswi T. Kamble, S. K. Mohite, C. S. Magdum

Rajarambapu College of Pharmacy, Kasegaon, Tal. Walwa, Dist. Sangli, M.S., India.

Keywords:

QSAR, PCR, Anticancer Drug

For Correspondence:

Anagha S. Patil

Rajarambapu College of Pharmacy, Kasegaon, Tal. Walwa, Dist. Sangli, M.S., India.

E-mail:

patilanagha57@gmail.com

ABSTRACT

The development of anticancer drug has attracted much attention for the research. In this paper, an attempt was made to develop a quantitative structure–activity relationship (2D and 3D QSAR) on a novel series of 1, 3,4 oxadiazole. 2D QSAR was performed using multiple linear regression (MLR), principal component regression (PCR) and partial least squares regression (PLS) methods. Among these three methods, multiple linear regression (MLR) method has come out with a very promising result as compared to other two methods. According to Model-1 by MLR anticancer activity of oxadiazole derivatives were influenced by Electrostatic (Most +Ve And –Ve Potential Distance), Dipole Moment (Quadrupole2), Distance Based (Wiener Index) And Alignment Independent Descriptor (T_O_O_6) help in understanding the effect of substituent at different position of oxadiazole. The contribution plot of steric and electrostatic field interactions generated by 3D-QSAR shows interesting results in terms of internal and external predictability. Molecular field analysis was applied for the generation of steric and electrostatic descriptors based on aligned structures.

INTRODUCTION

Quantitative structure-activity relationships (QSAR) have been applied for decades in the development of relationships between physicochemical properties of chemical substances and their biological activities to obtain a reliable statistical model for prediction of the activities of new chemical entities. The fundamental principle underlying the formalism is that the difference in structural properties is responsible for the variations in biological activities of the compounds. In 2D QSAR, only 2D descriptor characteristics like molecular weight, slogP, hydrogen bond acceptor counts, rotating bond counts, etc. like this, 492 descriptors were analyzed. All these descriptors, which have the structural or the physicochemical significance, are used to predict the activity of that molecule. In the classical QSAR studies, affinities of ligands to their binding sites, inhibition constants, rate constants, and other biological end points, with atomic, group or molecular properties such as lipophilicity, polarizability, electronic and steric properties (Hansch analysis) or with certain structural features (Free-Wilson analysis) have been correlated. However such an approach has only a limited utility for designing a new molecule due to the lack of consideration of the 3D structure of the molecules. 3D-QSAR has emerged as a natural extension to the classical Hansch and Free-Wilson approaches, which exploits the three-dimensional properties of the ligands to predict their biological activities using robust chemo metric techniques such as PLS, G/PLS, KNN etc. It has served as a valuable predictive tool in the design of pharmaceuticals and agrochemicals. Although the trial and error factor involved in the development of a new drug cannot be ignored completely, QSAR certainly decreases the number of compounds to be synthesized by facilitating the selection of the most promising candidates. Several success stories of QSAR have attracted the medicinal chemists to investigate the relationships of structural properties with biological activity. This paper seeks to provide a bird's eye view of the different 2D and 3D-QSAR approaches employed within the current drug discovery community to construct predictive structure-activity relationships and also discuss the limitations that are fundamental to these approaches, as well as those that might be overcome with the improved strategies. The components involved in building a useful 3D-QSAR model are discussed, including the validation techniques available for this purpose.

2. MATERIALS AND METHODS

2.1. Methodology:

The anticancer activity data of 1, 3, 4 oxadiazole moiety which was taken from the reported work. A data set of 20 compounds for anticancer activity was used for the present QSAR study. The molar concentrations of the compounds required to produce binding at receptor site (in nm) converted to negative logarithm MIC values for undertaking the QSAR study. The biological activity data (IC50 in nm) were converted to their molar units and then further to negative logarithmic scale (pIC50) and subsequently used as the dependent variable for the QSAR analysis. Table 1 shows the structure of 20 such compounds along with their biological activity values. The 2D and 3D QSAR was carried out on the software namely: V-life MDS (Molecular Design Suite) .All the structures were constructed using the 2D draw application provided as a tool of main MDS window. The 2D structures were converted to 3D structures by sending them to MDS. Energy minimization and geometry optimization were conducted using Merck Molecular Force Field (MMFF) method with Root Mean Square (RMS) gradient set to 0.01 kcal/mol A° and iteration limit to 10 000. The 2D descriptors (physicochemical and alignment independent) were calculated for the optimized com- pounds on QSAR plus work sheet. The invariable descriptors (the descriptors that are constant for all the molecules) were re- moved, as they do not contribute to QSAR.

2.2 A brief review on 1, 3, 4 oxadiazole:

The medicinal importance, synthesis and use of 1, 3, 4 oxadiazole as synthetic tools in organic chemistry. The 1, 3, 4 oxadiazole functionality is much more widespread in pharmaceuticals . 1,3,4 oxadiazole have been the subject of pharmaceutical interest as a result of their potent biological activities such as antihypertensive agent, , anticancer, anti-inflammatory and antiviral agents. A number of 20 derivatives having anticancer activity were considered in the present study. Biological activity expressed in terms of IC50 was converted in to pIC50 (pIC50= log 1/IC50).

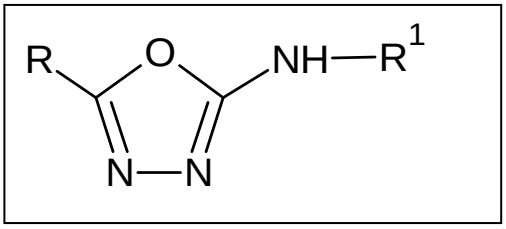

Table 1: Series of 1, 3, 4 oxadiazole derivatives with their biological activity

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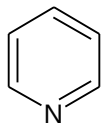
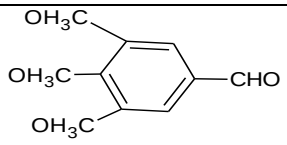
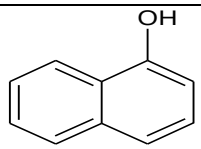
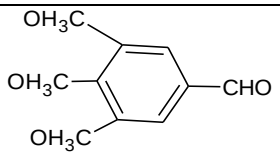
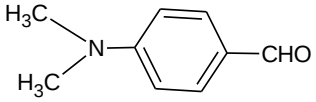
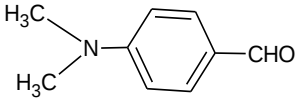
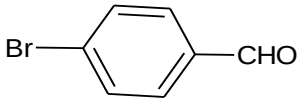
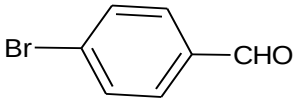
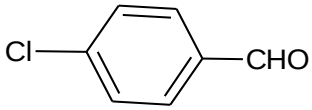
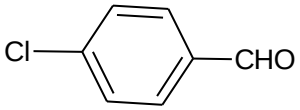
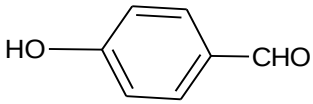
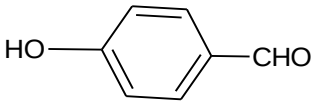
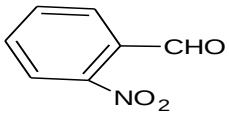
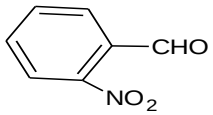
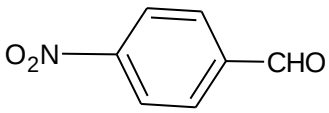
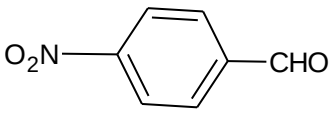
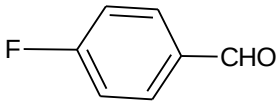
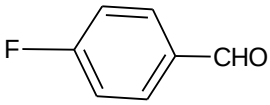
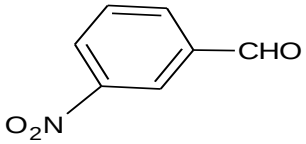
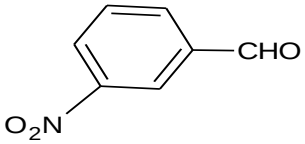
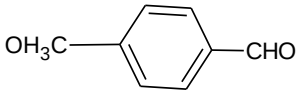
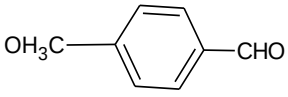
1			11		
2	-do-		12	-do-	
3	-do-		13	-do-	
4	-do-		14	-do-	
5	-do-		15	-do-	
6	-do-		16	-do-	
7	-do-		17	-do-	
8	-do-		18	-do-	
9	-do-		19	-do-	
10	-do-		20	-do-	

Table No 2: Observation Table Of Observed And Predicted Value Of Synthesized Compound

Sr.no	Actual value	Predicted value	Residual value	Biological Activity	
				IC_{50}	PIC_{50}
1	88.64	78.4648	10.1752	0.9121	-0.039
2	71	73.4234	-2.4234	0.995	-0.0021
3	75.83	69.7159	6.1141	3.656	0.563
4	59.1	43.0609	16.0391	0.949	-0.022
5	85.68	72.7412	12.9388	1.257	0.099
6	64.12	69.7141	-5.5941	0.935	-0.029
7	68.43	67.5688	0.8612	1.260	0.100
8	83.08	72.5541	10.5259	1	0
9	64.31	53.9437	10.3663	1.138	0.056
10	71	72.1197	-1.1197	0.933	-0.030
11	64.12	82.1635	-18.0435	1.368	0.1360
12	22.11	61.6954	-39.5854	0.935	-0.029
13	85.3	80.05	5.25	0.99	-0.0043
14	81.22	75.0541	6.1659	1.077	0.0322
15	68.02	74.7756	-6.7556	1.138	0.056
16	78.8	66.2489	12.5511	0.973	-0.0118
17	86.43	74.8056	11.6244	0.943	-0.025
18	80.85	61.6321	19.2179	1.188	0.074
19	86.61	74.9061	11.7039	1.260	0.100
20	64.31	53.9437	10.3663	1.138	0.056

3 QSAR analysis

3.1. 2D QSAR:

Creation of training and test set:

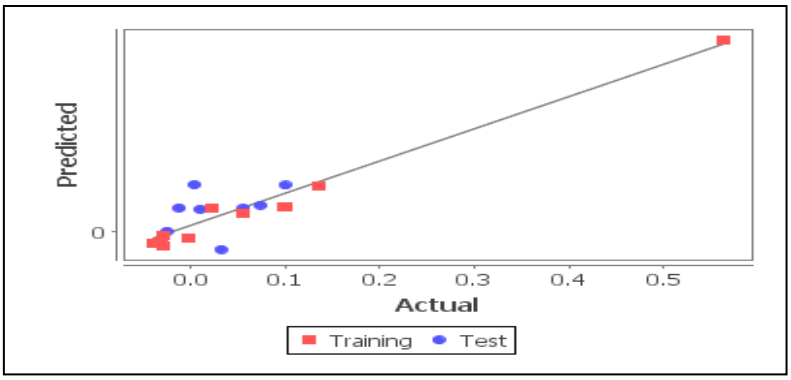
The sphere exclusion method was adopted for division of training and test data set comprising twenty nine and eleven molecules, respectively, with dissimilarity value of 8.1 where the dissimilarity value gives the sphere exclusion radius. In order to assess the similarity of the

distribution pattern of the molecules in the generated sets, statistical parameters (with respect to the biological activity), i.e., mean, maximum, mini- mum and standard deviation were calculated for the training and test sets. First 8 compounds, were used as test set while the remaining molecules were used as the training set.

The results were as follows by multiple linear regression analysis:

Statistical parameters	**Training Set 1**	**Training Set 2**
	Test set a	**Test set b**
r^2	0.8425	0.8174
r^2 se	0.0801	0.0807
Pred r^2	-0.0665	-0.8312
Pred r^2 se	0.0953	0.1249
	(+) VELY CONTRIBUTING	(-) VELY CONTRIBUTING
Descriptors	T_O_O_6 Quardrupole 2	Most +ve & ve Potential Distance Wiener index

3.2 Multiple linear Regression analysis of 2D QSAR:



Interpretation:

The training set is shown in red and the test set is shown in blue dots. There is not that much variance in the dependent variable between the test and training sets. The dominant descriptor's, which are important in predicting the IC50, are as follow,

1. Quadrupole2: This descriptor signifies magnitude of second tensor of quadrupole moments.

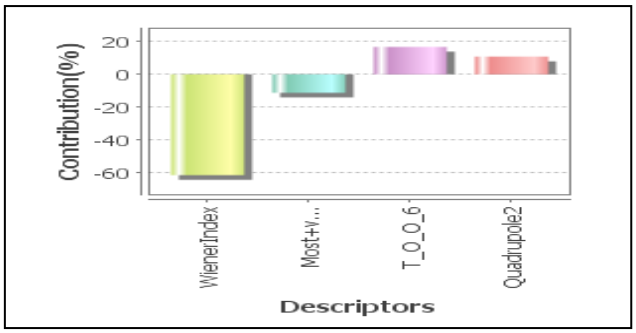
2.Most +ve &-ve Potential Distance: This descriptor signifies the distance between points having the highest value of +ve and highest value of –ve electrostatic potential on Vander Waals surface area of the molecule.

3. T_O_O_6: This is the count of number of oxygen atoms (single double or triple bonded) separated from any other oxygen atom (single double or triple bonded) by 6 bonds in a molecule.

4. Wiener Index: This descriptor signifies the sum of the numbers of edges in shortest paths in a chemical graph between all pairs of non-hydrogen atoms in a molecule.

The biological activity is dominantly dependent upon above descriptors out of the 492 calculated descriptors for 22 molecules.

3.3. Contribution plot for 2D QSAR multiple linear regression method:



Interpretation:

From the contribution plot above, we can see that Wiener Index is the most Dominant descriptor according to the multiple linear regression analysis. Wiener index should be lesser. Most positive and –ve potential should be lesser. T_O_O_6 and quadrupole 2 should be higher, in order to get the better biological activity.

4. 3D QSAR:

3D QSAR methods kNN-MFA requires suitable alignment of set of molecules. This is followed by generation of a common rectangular grid around the molecules. The steric and electrostatic energies are computed at the lattice points of the grid using methyl probe of charge +1. These interaction energy values at the grid points are considered for relationship generation using kNN method and utilized as descriptors for obtaining distances within this method.

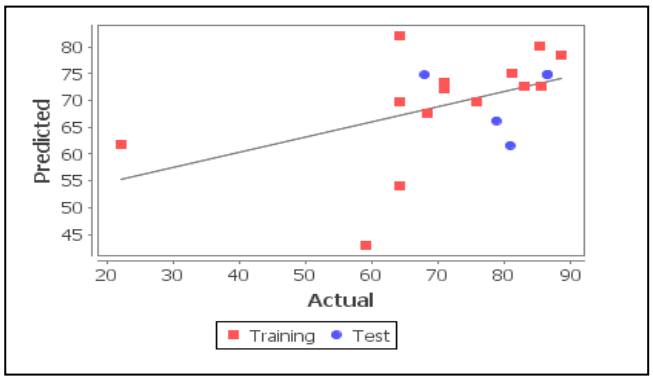
4.1 Table no 3: Observation of k-NN MFA model using variable selection method

Statistical parameters	**Training set 1 SA-kNN MFA**	**Training set 2 SW-kNN MFA,**
	Test set a	**Test set b**
kNN	5	5
n	10	10
Degree_of_freedom	8	8
q^2	0.0885	0.1692
q^2 se	0.1722	0.1644
Pred r^2	-0.9990	-0.0353
Pred r^2 se	0.1122	0.0807
	(+) VELY CONTRIBUTING	(-) VELY CONTRIBUTING
Descriptors	E_130 (0.1295 0.9763)	E_661 (-1.1552 0.9389) E_892 (-0.6722 -0.0105) S_771 (-0.0726 4.4244)

4.2. Observation Table no 4:3D QSAR activity predictions of molecule:

Compounds	**E_130**	**E_661**	**E_892**	**S_771**
1	0.976	-1.155	-0.01	-0.073
2	0.531	1.434	0.214	-0.0441
3	-0.201	-4.078	0.222	-0.394
4	0.16	-4.888	-0.546	-0.477
5	-0.0327	1.02	-0.067	30
6	-0.166	-0.23	-0.164	-0.406
7	-0.123	-0.204	-0.24	-0.431
8	2.223	-3.855	-0.815	-0.053
9	0.129	0.939	-0.672	4.424
10	-0.254	-0.54	0.022	-0.305

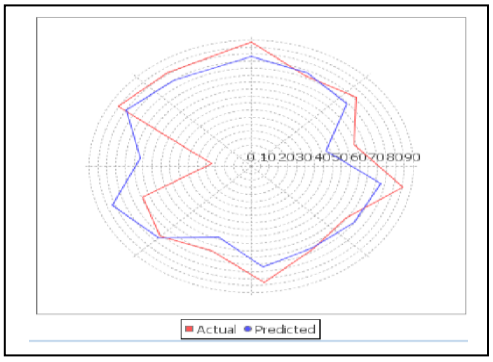
4.3.Fitness Plot for the training and test set:



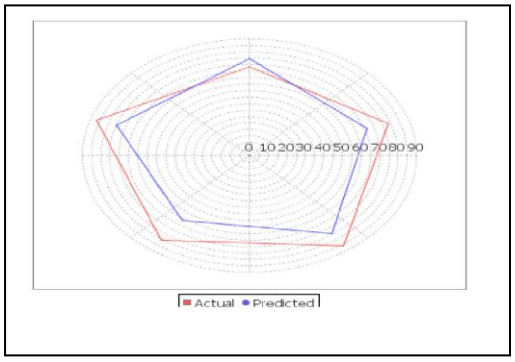
Interpretation:

All points for training and test set lies on or near the regression line hence confirming that there is not that much variance between test and training set.

4.4. Radar plot of training set:



4.5. Radar plot of test set:

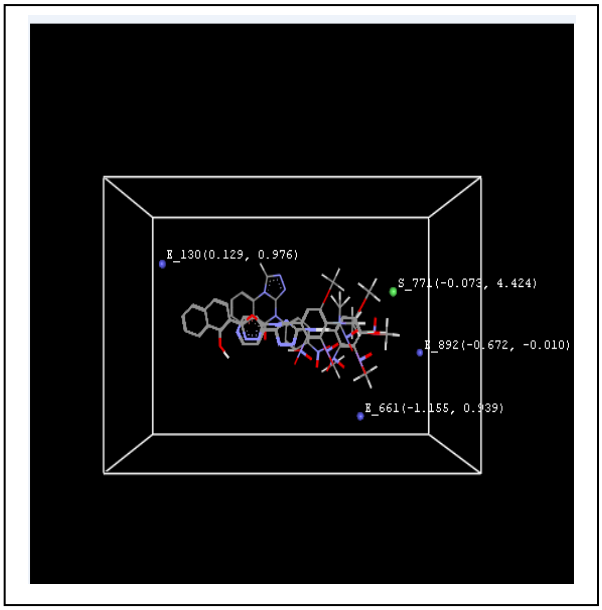


Interpretation:

Red color indicates the actual PIC50 values while blue color indicates the predicted PIC50 values and both don't differ much so the model is validated.

4.5 Interpretation of kNN MFA models:

3D QSAR was used to optimize electrostatic, steric and hydrophobic requirement around oxadiazole pharmacophore.The value generated grid points helped us to design potent anticancer drugs. The ranges of data point values were based on the variation of field values at chosen points using most active molecule of data set and its nearest neighbor set. Point generated in 3D QSAR model is electrostatic E_661 (-1.1552 0.9389), E_892 (-0.6722 -0.0105), E_130 (0.1295 0.9763) and steric S_771 (-0.0726 4.4244).



Grid point (E+s) generated in 3D rectangular grid

Negative value of electrostatic data point	**Negative value of streic data point**	**Positive value of electrostatic data point**
-Indicate the requirement of more electronegative group is preferred in that region.. E.g. - -Cl,-Br,-OH etc.	-Indicates the requirement of less bulky substituent group is preferred in that region. E.g.- $-C_6H_5$, $-CH_2$ etc.	-Indicate the requirement of less electronegative substituent's enhancing biological activity. E.g- -Cl,-Br,-OH etc.

4.6 RESULT AND DISCUSSION

In the present 2D QSAR study all proposed models were statistically significant .However multiple regression analysis could considered as best .According to model anticancer activity of oxadiazole derivatives was influenced by

1. Electrostatic (Most +Ve And –Ve Potential Distance),
2. Dipole Moment (Quadrupole2),
3. Distance Based (Wiener Index) And
4. Alignment Independent Descriptor (T_O_O_6)

These Help in understanding the effect of substituent at different position of oxadiazole. From the contribution plot, we can see that Wiener Index is the most dominant descriptor according to the multiple regression analysis. Wiener index should be lesser. Most positive and -ve potential should be lesser. T_O_O_6 and quadrupole 2 should be higher, in order to get the better

biological activity. In 3D QSAR kNN-MFA model it is observed that electrostatic field with negative coefficient E_661 and E_892 on oxadiazole moiety, indicating that electronegative group are favorable on this site and electronegative groups increases the activity of oxadiazole compounds. Electrostatic field with positive coefficient E_130 on oxadiazole moiety, indicating that electropositive group is favorable on this site and electropositive groups increases the activity of oxadiazole compounds. Presence of steric field with negative coefficient (S_771) indicates that negative steric potential is favorable for increase in the activity and hence less bulky substituent group is preferred in that steric region.

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