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QSAR STUDY OF 1, 2, 4 TRIAZOLE FOR THEIR ANTICANCER ACTIVITY

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ABSTRACT

Considerable attention has been given on the search for novel anticancer drugs with respect to the disease sequelae on human health and well-being. Triazole is considered to be an attractive scaffold possessing diverse biological activities. Structural modification on the privileged structures is noted as an effective strategy towards successful design and development of novel drugs. The quantitative structure–activity relationships (QSAR) is well-known as a powerful computational tool to facilitate the discovery of potential compounds. In this study, a series of eighteen 1,2,4-triazole derivatives (**1**–**18**) together with their experimentally measured cytotoxic activities against cancer cell lines i.e., MCF-7 (Breast cancer cell line) was used for QSAR analysis.. The study suggested crucial moieties and certain properties essential for potent anticancer activity and highlighted a series of promising compounds $5a_2$, $5a_3$, and $5a_8$ for further development as novel triazole-based anticancer agents.

1. INTRODUCTION

Our society is faced with challenges that can have a chemical solution. Examples include: bacterial drug resistance, new diseases like AIDS, and agricultural pest control. Characterizing the biological activity and properties of all the known compounds is impossible; hence, it is necessary to develop predictive tools for molecular properties and environmental setting. Quantitative structure activity relationships (QSAR) and quantitative structure properties relationships (QSPR) play a central role in this effort, and those methods are unquestionably of great importance in modern chemistry and biochemistry.

The concept of QSAR/QSPR is to transform searches for compounds with desired properties using chemical intuition and experience into a mathematically quantified and computerized form. Once a correlation between structure and activity/property is found, any number of compounds, including those not yet synthesized, can be readily screened on the computer in order to select a structure with the desired properties. It is then possible to select the most promising compounds for synthesis and testing in the laboratory.1,2,4-Triazole and its derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities.

The 1,2,4-triazole nucleus is associated with diverse pharmacological activities such as antibacterial, antifungal, hypoglycemic, antihypertensive, and analgesic . 1,2,4- triazole derivatives were used in this QSAR analysis. In this paper, an attempt was made to develop a quantitative structure–activity relationship (2D and 3D QSAR) on a1,2,4 triazole. 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 1,2,4- triazole derivatives were influenced by Electrostatic (Most +Ve And –Ve Potential Distance), Distance Based (Wiener Index) And Alignment Independent Descriptor (T_2_O_0, T_2_Cl_1, T_T_S_6) help in understanding the effect of substituent at different position of 1,2,4- triazole.

2. MATERIALS AND METHODS

2.1. Methodology:

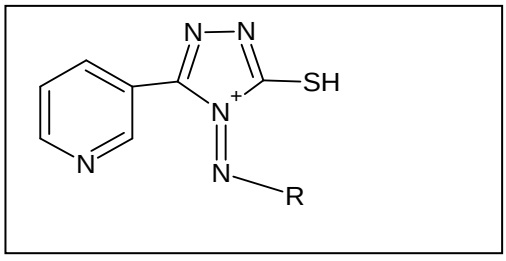
The anticancer activity data of 1, 2, 4 triazole moiety which was taken from the reported work. A data set of 18 compounds for anticancer activity was used for the present QSAR study. The molar concentrations of the compounds required to produce binding at receptor site (in nm)

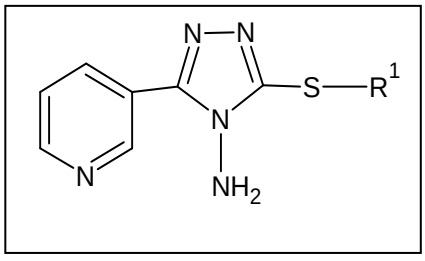
converted to negative logarithm MIC values for undertaking the QSAR study. The biological activity data (IC50 in nm) were converted to their molar units and then further to negative logarithmic scale (pIC50) and subsequently used as the dependent variable for the QSAR analysis. Table 1 shows the structure 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, 2, 4 triazole:

The medicinal importance, synthesis and use of 1, 2, 4 triazole as synthetic tools in organic chemistry. The 1, 2, 4 triazole functionality is much more widespread in pharmaceuticals . 1,2,4 triazole 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 18 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).

Structures used for QSAR study:





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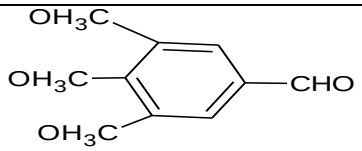
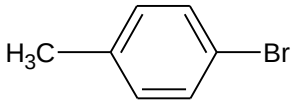
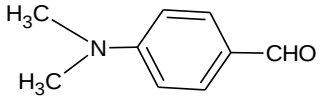
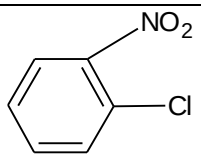
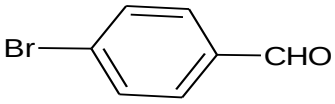
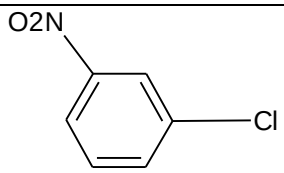
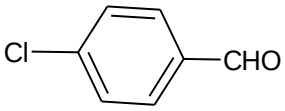
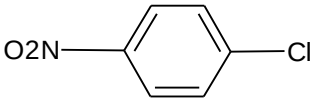
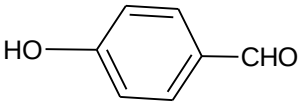
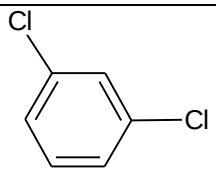
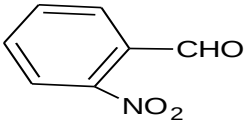
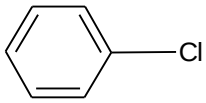
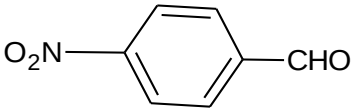
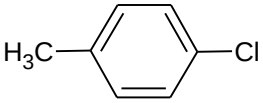
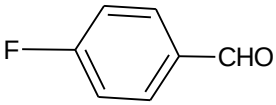
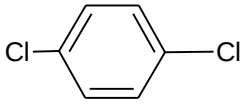
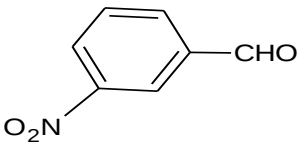
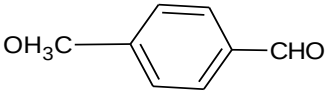
1		
2		
3		
4		
5		
6		
7		
8		
9		----
10		----

Table: Observation Table Of Observed And Predicted Value Of Synthesised Compound

Sr.no	Actual value	Predicted value	Residual value	IC50	PIC50
1	94.23	81.9846	12.2454	0.858	-0.066
2	75.83	66.7609	9.0691	1.066	0.027
3	62.45	73.4205	-10.9705	1.294	0.111
4	91.44	83.3387	8.1013	0.884	-0.053
5	71	69.2115	1.7885	1.138	0.056
6	46.09	47.61	-1.52	1.754	0.244
7	48.88	37.6	11.28	1.654	0.218
8	81.22	52.01	29.21	0.995	-0.0021
9	88.64	78.4648	10.1752	0.9121	-0.0399
10	71	73.4234	-2.4234	1.138	0.056
11	75.83	69.7159	6.1141	1.066	0.027
12	59.1	43.0609	16.0391	1.368	0.1360
13	85.68	72.7412	12.9388	0.943	-0.025
14	64.12	69.7141	-5.5941	1.260	0.100
15	68.43	67.5688	0.8612	1.181	0.072
16	83.08	72.5541	10.5259	0.973	-0.011
17	64.31	53.9437	10.3663	1.257	0.099
18	71	72.1197	-1.1197	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 eighteen molecules respectively, with dissimilarity value of compounds 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 12 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:

3.2.The results were as follows by Multiple regression analysis:

Multiple Regression

Training Set Size = 9

Test Set Size = 8

Selected Descriptors:

Most +ve &-ve Potentail Distance

T_2_O_0

T_2_Cl_1

T_T_S_6

Coefficient:

-0.0497(±0.0025)

-0.0651(±0.0096)

0.0660(±0.0132)

-0.0214(±0.0049)

Constant:

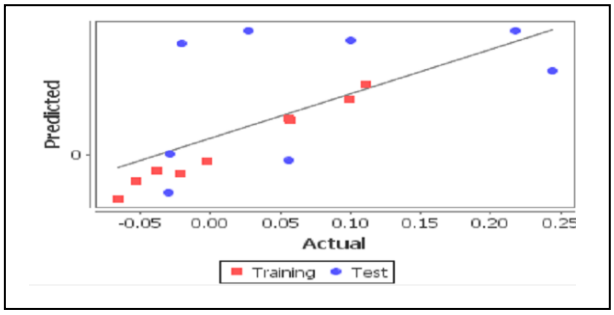
0.4778

Statistics:

Table no.2:Observation of k-NN MFA model using Multiple Regression selection method

N	9
Degree_of_freedom	4
r2	0.9840
q2	0.8067
F_test	61.4063
r2_se	0.0119
q2_se	0.0414
pred_r2	0.0951
pred_r2se	0.1179

3.3: Multiple 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

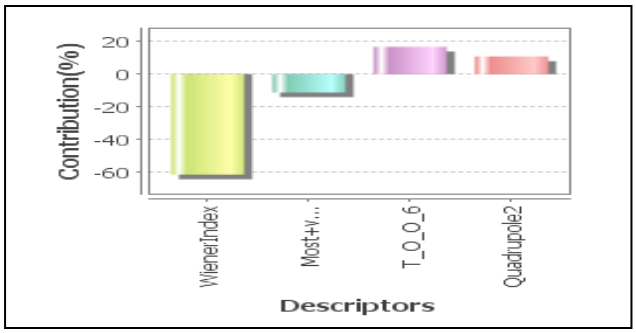
1Most+ve&-ve Potential Distance: This descriptor signifies the distance between points having the highest value of +ve and highest value of –ve electrostatic potential on van der Waals surface area of the molecule

2. T_2_O_0: This is the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from Oxygen atom by 0 bonds in a molecule.

3.T_2_Cl_1: This is the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from chlorine atom by 1 bonds in a molecule.

4.T_T_S_6 : This is the count of number of double bounded atoms (i.e. any double bonded atom, T_2) separated from Sulphar atom by 6 bonds in a molecule.

3.4.Contribution plot for 2D QSAR multiple regression method



From the above contribution plot , we can see that, Most positive and -ve potential should be lesser. T_2_O_0 , T_T_S_6 should be lesser and T_2_Cl_1 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. 1.3D QSAR
kNN Method

Training Set Size = 12

Test Set Size = 5

Selected Descriptors:

E_307

Statistics:

Table no3.:Observation of k-NN MFA model using variable selection method

k Nearest Neighbour	2
N	12
Degree_of_freedom	10
q2	0.4136
q2_se	0.1359
pred_r2	-3.2905
pred_r2se	0.2057

Descriptor Range:

E_307 -0.1257 -0.0080

kNN Method simulated

Training Set Size = 12

Test Set Size = 5

Selected Descriptors:

E_500

Statistics:

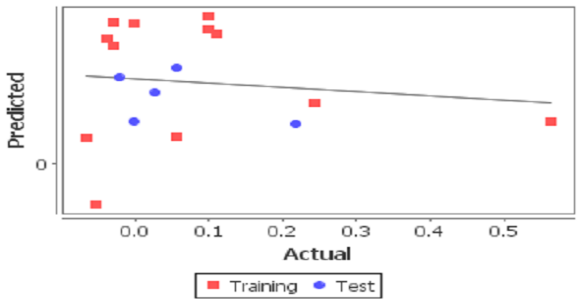
Table no.4:Observation of k-NN MFA model using Simulated anneling selection method

k Nearest Neighbour	5
N	12
Degree_of_freedom	10
q2	-0.1145
q2_se	0.1873
pred_r2	-1.6850
pred_r2se	0.1627

Descriptor Range:

E_500 10.0000 10.0000

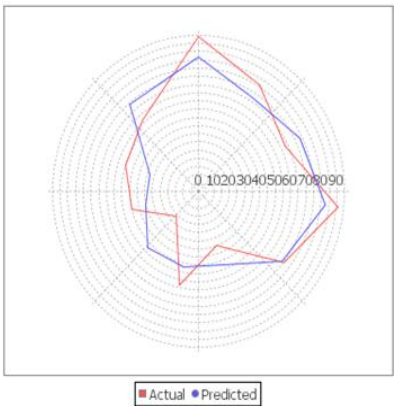
4.3.2.Fitness Plot for the training and test set:



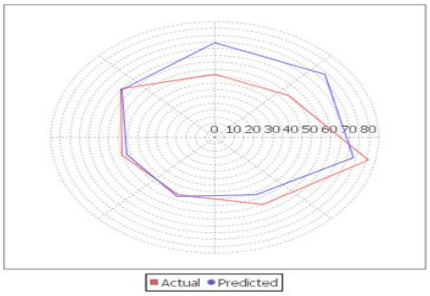
Interpretation:

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.

4.3.4. Radar plot of training set:



4.3.5. Radar plot of test set:



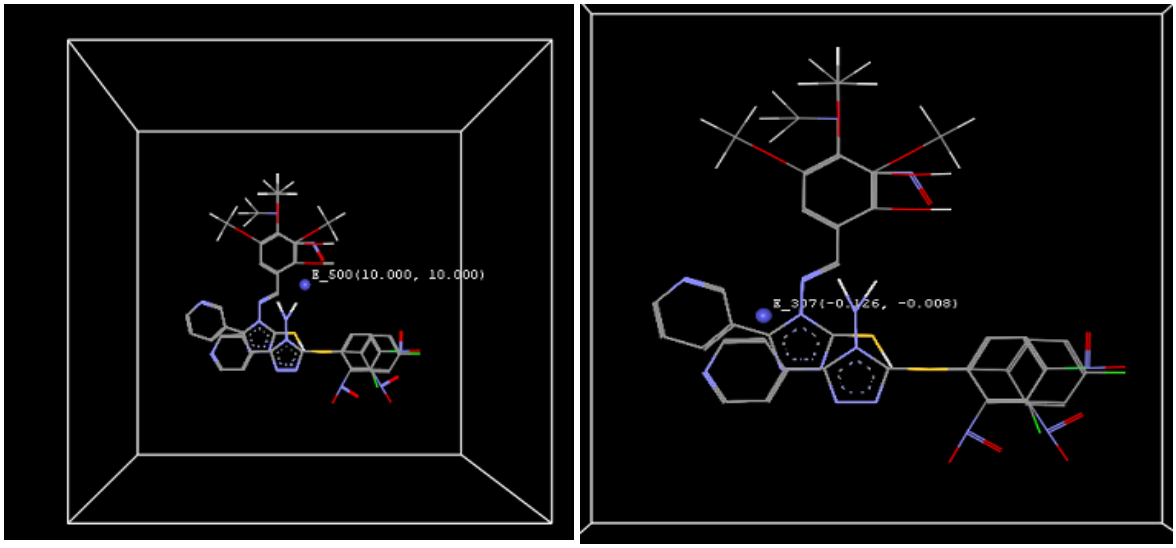
Interpretation:

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.

4.4 Interpretation of kNN MFA models:

In the above results it can be seen that the kNN MFA models shows that electrostatic interactions plays major role in determining biological activity. Plot of the kNN MFA which shows the relative position and ranges of the corresponding important electrostatic fields in the model. Point generated in 3D QSAR model is electronic E_307 -0.1257 -0.0080, E_500 10.0000 10.0000

Model Summary dialog box:



Negative moderate value of electrostatic data point

-Indicate the requirement of low to moderate electronegative substituent's enhancing biological activity.

Eg- -Cl,- Br,-OH etc

4.5 Result and Discussion:

In the above results it was observed that most of the active molecules have electrostatic field values at E_307 -0.1257 -0.0080, E_500 10.0000 10.0000, contributed negatively (-0.1257 -0.0080) for the activity. So increasing electro negativity of the substituent group may enhance the Anticancer activity.

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 triazole derivatives was influenced by electrostatic(most +ve and –ve potential distance),dipole moment(quadrupole2),and alignment independent descriptor(T_2_O_0, T_2_Cl_1, T_T_S_6)help in understanding the effect of substituent at different position of triazole.

In 3D QSAR kNN-MFA model it is observed that electrostatic field with negative coefficient (E-307), on triazole moiety ,indicating that electronegative group are favorable on this site and electronegative groups increases the activity of triazole compounds and electro Positive coefficient (E-500), range indicates that positive electrostatic potential is favorable for increase in the activity and hence a less electronegative substituent group is preferred in that region.

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