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CORRELATION STUDY BETWEEN STRUCTURE AND ANTIBACTERIAL ACTIVITY OF SUBSTITUTED 1, 3, 4-OXADIAZOLE COMPOUNDS

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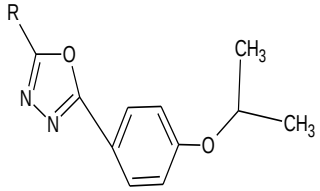
ABSTRACT

Correlation study between activity data of substituted 1, 3, 4-oxadiazole compounds and their structural property data set has been carried out with stepwise regression analysis (regression analysis estimates the relationships among variables through a statistical process). Repeated activity data has been eliminated wherever was possible, and finally it became possible to find out good correlation between activity data and physical descriptors depends on structure e.g. Heat of formation, Torsion energy, and LUMO[1], which is presented as QSAR equation Y =78.05 +1035.59*X_1 + 0.9949*X_2 + 297.7474*X_3.

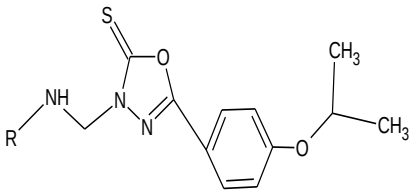
Keywords: 1, 3, 4-oxadiazole compounds, QSAR studies, physical descriptors, antibacterial activity data, regression analysis.

INTRODUCTION

In current era mankind are struggling to fight against new challenges in form of stubborn diseases like cancer, aids, liver cirrhosis ect. To overcome such challenges obviously it is require for chemists, pharmacists and scientists to go through number of aggressive chemical processes. QSAR studies helps to design novel drugs with improved biological activities with diminishing side-effects. QSAR technique is very useful to correlate the activity data and structure of the compounds through their physical properties. From liable QSAR equation one can predict activity of designed compound to be synthesized. With the help of such type of study we can avoid unnecessary labour, waste of chemicals, time, etc. Thus, this field supports the research in the era of "GREEN CHEMISTRY".



2-(4-ISOPROPOXYPHENYL)-5-(ARYL)-1,3,4-OXADIAZOLE
(**SERIES CODE:- JJTABLE 2)**



2-(4-ISOPROPOXYPHENYL)-3-N-(ARYL) AMINO METHYL-1,3,4-OXADIAZOLE-5(4H)-THIONE
(**SERIES CODE:- JJTABLE 3)**

MATERIALS AND METHODS

QSAR studies of some of the titled compounds have resulted in the identification of structural and physicochemical parameters (Torsion energy, Heat of formation, and LUMO) contributing to antimicrobial activity of substituted 1, 3, 4-oxadiazoles [2].

In order to establish Quantitative Structure-Activity Relationship (QSAR) the antibacterial activity data are taken as minimal bactericidal concentration (MBC) in µl at different dilution and were used as dependent variables by selection with attention that it should not to be repeated as much as possible.

Activity data were first correlated with different type of parameters such as steric parameters (i.e. Connolly Accessible Area, Connolly Molecular Area, Connolly Solvent-Excluded Volume), electronic parameters (i.e. HOMO, LUMO,) and

thermodynamic properties (i.e. Heat of Formation, Molar Refractivity, Torsion Energy, Partition Coefficient). Activity data and different type of parameters are presented in Table-1. All parameters were calculated from Chemdraw Ultra 3D (version 8.0). Statistical study including multi parameter regression analysis was carried out on Compaq Presario V3702 using KYplot (2.0) statistical software [3, 4].

RESULTS AND DISCUSSION

At primary stage, no significant relationship could have been established among activity data and physicochemical parameters. But later with regression analysis activity data and physicochemical parameters the relationship was showed. To improve the correlation between activity data and physicochemical parameters we led to minimize the activity data set.

On secondary stage of multivariate correlation analysis; some of the parameters (independent variables e.g. Connolly Solvent-Excluded Volume, Exact mass, Molar Refractivity) showed less correlation (r = -0.39 to -0.32) with E.coli activity data. Stepwise regression analysis of different combinations of these parameters were studied, which resulted in derivation of the following equation-1, with very good correlation (r^2 =0.86) of high statistical significance > 86 % (F=30.76). Which shows that physical parameters like torsion energy, heat of formation and LUMO are in good statistically agreement with biological activity against E.coli bacteria; (Equation 1). "Table-2" and "comparative graph of measured and predicted activity data" also support the statistical relationship between physical parameters and activity data against E.coli bacteria.

The calculated activities for the compounds by equation (1) were in good agreement.

$$Y = 78.05 + 1035.59*X_1 + 0.9949*X_2 + 297.7474*X_3 \quad \text{---- ----} \rightarrow \quad 1)$$

Where; n = 07, r^2 = 0.86, F = 30.76

X_1= Torsion Energy, X_2 = Heat of Formation, X_3 = LUMO

The general tendency of correlation between Torsion Energy and Activity data is that as Torsion Energy increases the activity data of compound decreases and vice-versa. In general comparison to LUMO contribution, it has been observed that as contribution of LUMO decreases the activity of compounds decreases in oxadiazoles contain only alkyl substitution (JJTABLE2J to JJTABLE2C @ TABLE-3).

CONCLUSION

It has been observed that among the number of physical descriptors some of them possess fine correlation with activity data. It has been observed that compounds with appropriate substitutional group at proper posion, increases value of Heat of formation and LUMO and decreases the value of torsion energy of the compounds, possess good anti microbial activity against E.coli. e.g. meta nitrophenyl substituted 1, 3, 4-oxadiazole compounds (JJTABLE3G)[Table-3]. They also predicted very good extent of activity against E. coli (MTCC 442) species as compare to other compounds which have been substituted by pera methoxyphenyl and phenyl functional groups.

From experimental data given in Table-3, it has been observed that the compounds containing sulphur element showed comparatively good antibacterial activity. Apart from this, oxadiazoles containing both sulphur and alkyl substitution posses less torsion energy than that of oxadiazoles contain only alkyl substitution.

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Table–1 "Activity data and different type of parameters"

Sr. no.	SAMPLE SERIES CODE	E.COLI MTCC 442	TORSION ENERGY	HEAT OF FORMATION	LUMO	MIN. STERIC ENERGY	LogP	CM AREA	CSE VOLUME	EXACT MASS	PARTION COEFFICIENT	HOMO	MR (CLOGP)
1	JJTABLE2A	1000	0.3829	21.27	-1.28	15.84	3.67	313.39	265.55	310.13	3.6	-8.9	8.6
2	JJTABLE2B	500	0.332	36.9	-1.18	14.77	3.799	284.34	239.92	280.121	3.55	-8.87	8.047
3	JJTABLE2C	1000	0.2291	-135.68	-1.805	8.53	NA	319.87	269.188	325.106	3.34	-9.094	8.66
4	JJTABLE2J	250	0.0288	-52.61	-0.227	12.76	3.2	294.777	255.14	290.11	2.31	-8.75	8.02
5	JJTABLE3A	250	0.0414	122.51	-1.05	9.59	4.63	360.15	327.69	371.13	4.9	-8.94	10.57
6	JJTABLE3D	500	0.169	145.95	-1.04	9.96	5.73	366.498	333.54	369.15	5.75	-8.885	10.88
7	JJTABLE3G	250	0.02	228.73	-1.22	7.19	NA	352.88	322.45	389.105	5.19	-9.12	10.56
8	r =		0.797448	-0.5791	-0.676	.3021	-0.1004	-0.2602	-0.3931	-0.3212	-0.2658	-.2293	-0.38434

Table-2 : Comparative data activity set (measured and predicted)

Table-2			
Compound number	Compound code	Measured activity	Predicted activity
1	JJTABLE2J	250	227.657
2	JJTABLE3G	250	234.45
3	JJTABLE3A	250	311.673
4	JJTABLE3D	500	417.516
5	JJTABLE2B	500	736.496
6	JJTABLE2A	1000	834.533
7	JJTABLE2C	1000	987.7257

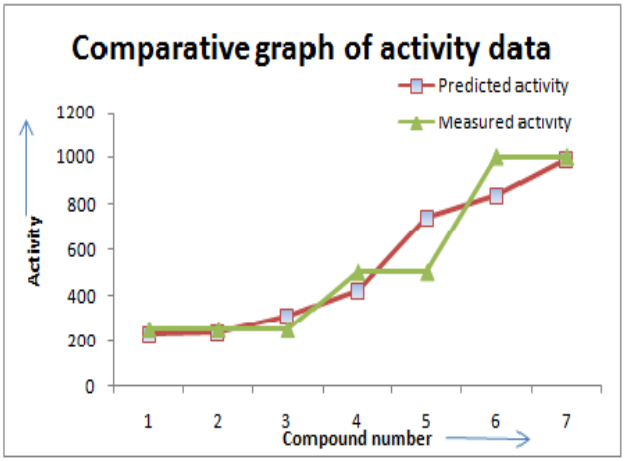
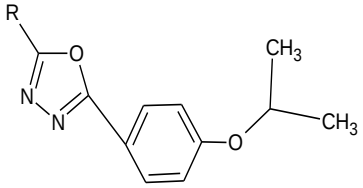


Table-3 : General tendency of correlation between Activity data and physical parameters.

Sample series Code	Predicted activity against E.coli	E.coli MTCC 442	Torsion Energy	Heat of formation	LUMO	Substitutional group R=
JJTABLE2J	227.657	250	0.0288	-52.61	-0.2265	C_4H_7S-
JJTABLE3G	234.450	250	0.0200	228.73	-1.22	3-NO_2-C_6H_4-
JJTABLE3A	311.673	250	0.0414	122.51	-1.05	4-OCH_3-
JJTABLE3D	417.516	500	0.169	145.95	-1.04	4-$(CH_3)_2$-
JJTABLE2B	736.496	500	0.332	36.90	-1.18	-C_6H_5
JJTABLE2A	834.533	1000	0.3829	21.27	-1.28	4-OCH_3-
JJTABLE2C	987.7257	1000	0.229	-135.68	-1.805	3-NO_2-C_6H_4-



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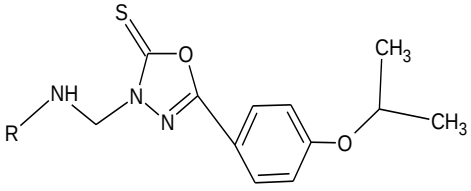

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