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Topological Modeling of Acetophenones as Antibacterial Agents: A QSAR/QSPR Approach

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ABSTRACT

This paper describes QSAR analysis and biological evaluation of acetophenones derivatives as antibacterial agents. The most active amongst this group of compounds were 4-methyl, 2-hydroxy, 3-bromo, 4-ethoxy, 3-nitro and 4-nitro acetophenones. The models were generated on the E-Dragon software; Selected models showed a correlation coefficient (r^2) above 0.8 respectively. The activity contributions of these compounds to analyze the predictive ability of QSAR model were described. The generated model from 23 molecules revealed that an increase in topological descriptors for antibacterial activity.

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1. INTRODUCTION

The conception that there exists a close relationship between bulk properties and their molecular structure is quite rooted in chemistry. The basic tenet of chemistry to identify these assumed relationships between molecular structure and physiochemical properties and then to quantify them. QSAR approach including multivariate data analysis in combination with statistical design has been extensively employed.

Acetophenones have already been used as cytotoxic agents against renca and jurkat cells[1-2]. 3-Methoxy- and 2-hydroxy-3- methyl substituted 4-hydroxyacetophenones and their 4-O-glycosides have been used as antiasthmatics and anti-inflammatory agents [3]. Acronyculatins isolated from *Acronychia pedunculata* have been successfully tested for antioxidant and antityrosinase activities[4]. Tremetone and two of the other non-benzofuran acetophenones from *Ophryosporus axilliflorus* were evaluated as anti-inflammatory agents against carrageenan-induced mouse paw oedema[5]. Paeonol, 4-methoxy-2-hydroxy acetophenone, and its analogs have been tested for antiplatelet aggregation activity by one of the co-authors[6]. 3-Hydroxy-4-methoxy-acetophenone from *Cynanchum paniculatum* was used as an analgesic and as an inhibitory agent for gastric-motility[7]. One of the most successful approaches to the prediction of chemical properties starting only with molecular structural information is modeling of quantitative structure– activity/property relationships (QSAR/QSPR). The concept that there exists a close relationship between bulk properties of compounds and their molecular structure allows one to provide a yet unmeasured or even unknown [8-11]. A major step in constructing the QSAR models is finding a set of molecular descriptors that represent variations in the structural activity of the molecules. A wide variety of descriptors such as steric, electronic and distance based topological descriptors have been reported for use in QSAR analysis [12–18].

In most cases, it is more convenient to consider a linear relationship between activity/property and descriptors. Multiple linear regression (MLR), principal component regression (PCR), partial least squares (PLS) regression and artificial neural networks (ANN) are the most commonly used modeling methods in QSAR [18-21]. Clear connection between the macroscopic and the microscopic properties of matter. Quantitative structure–activity relationships are mathematical

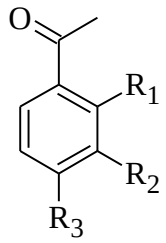
equations relating chemical structure to a wide variety of physical, chemical, biological, and technological properties [22-32].

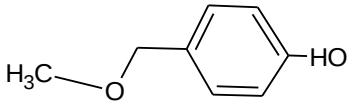
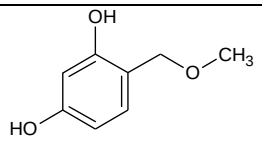
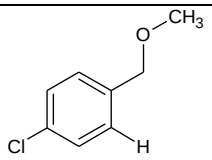
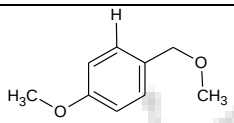
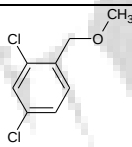
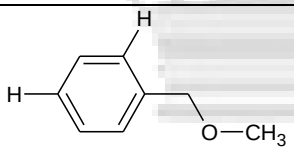
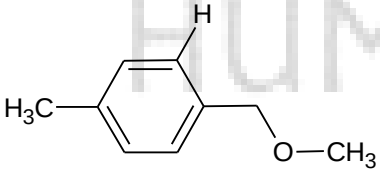
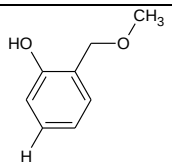
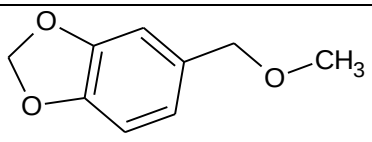
2. MATERIALS AND METHODS

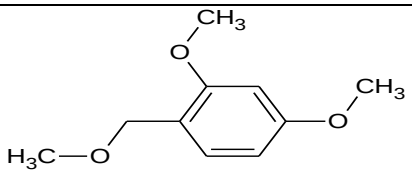
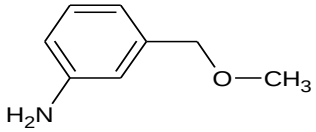
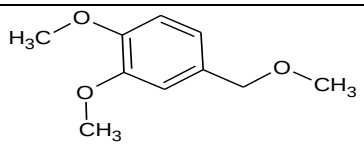
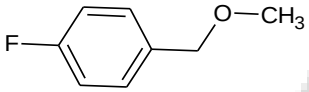
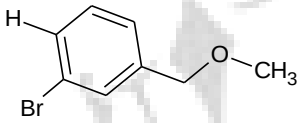
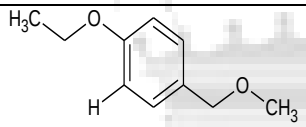
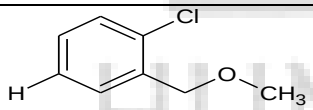
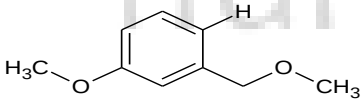
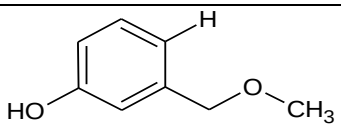
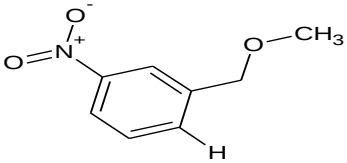
The QSAR model for the estimation of the pMIC of various anti-cancer drugs is established in the following six steps: the molecular structure input and generation of the files containing the chemical structures is stored in a computer readable format; quantum mechanics geometry is optimized with an ab initio method; structural descriptors are computed; structural descriptors are selected and the structure pMIC model is generated by the MLR and statistical analysis. The inhibitory activity of acetophenone derivatives is given in the form of minimum inhibitory concentrations expressed in μm which was evaluated by two fold dilution method. These data were converted to –log concentrations to obtain the pMIC value, which is used for developing the QSAR models. The inhibitory activities are taken from the work of Sivakumar et. al.[33].

All of the molecules were drawn into the E-Dragon Software. The E-Dragon software package was used for calculating the molecular descriptors. Some of the descriptors are obtained directly from the chemical structure, e. g. constitutional, geometrical, and topological descriptors. Other chemicals and physicochemical properties were determined by the chemical structure (lipophilicity, hydrophilicity descriptors, electronic descriptors, energies of interaction). One way to avoid data redundancy is to exclude descriptors that are highly inter-correlated with each other before performing statistical analysis.

Table 1: Structure of Acetophenone derivative



Com. No.	Name	Compound Name	pMIC
1.		4-Hydroxy acetophenone	0.338
2.		2,4-Dihydroxy acetophenone	0.386
3.		4-Chloroacetophenone	0.393
4.		4-Methoxy acetophenone	0.381
5.		2,4- Dichloroacetophenone	0.481
6.		Acetophenone	0.284
7.		4-Methylacetophenone	0.332
8.		2-Hydroxyacetophenone	0.338
9.		3,4-Methylenedioxy acetophenone	0.419

10.		2,4-Dimethoxyacetophenone	0.46
11.		3-Aminoacetophenone	0.335
12.		3,4-Dimethoxyacetophenone	0.761
13.		4-Fluoroacetophenone	0.344
14.		3-Bromoacetophenone	0.804
15.		4-Ethoxyacetophenone	0.721
16.		2-Chloroacetophenone	0.694
17.		3-Methoxyacetophenone	0.381
18.		3-Hydroxyacetophenone	0.338
19.		3-Nitroacetophenone	0.723

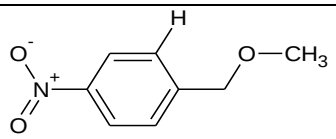
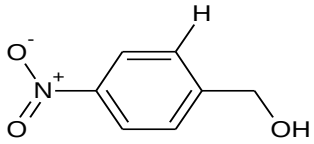
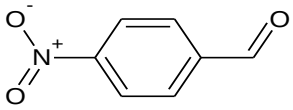
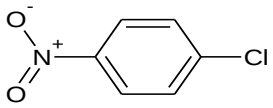
20.		4-Nitroacetophenone	1.024
21.		4-Nitrophenol	0.649
22.		4-Nitrobenzaldehyde	0.684
23.		4-Nitrochlorobenzene	-0.098

Table 2: Inhibitory Activity and Calculated Topological Descriptors of Acetophenone Derivatives

pMIC	W	Jhetv	Jhete	Jhetp	CIC_0	BIC_0
0.338	127	2.154	2.884	2.05	2.961	0.301
0.386	158	2.257	3.135	2.136	2.951	0.314
0.393	127	2.272	2.876	2.21	2.765	0.333
0.381	170	2.028	2.904	1.911	3.198	0.282
0.481	158	2.488	3.119	2.453	2.632	0.362
0.284	94	2.139	2.779	2.044	3.012	0.277
0.332	127	2.272	2.833	2.185	3.252	0.26
0.338	121	2.222	3.024	2.11	2.961	0.301
0.419	197	1.668	2.498	1.563	3.023	0.306
0.46	254	2.116	3.267	1.976	3.381	0.28
0.335	124	2.249	2.922	2.145	2.955	0.313
0.761	256	2.105	3.241	1.966	3.381	0.28
0.344	127	2.1	2.898	1.958	2.765	0.333
0.804	124	2.349	2.924	2.278	2.765	0.333
0.721	224	1.917	2.843	1.798	3.405	0.267

0.694	121	2.354	3.014	2.288	2.765	0.333
0.381	164	2.067	2.997	1.946	3.198	0.282
0.338	124	2.185	2.946	2.077	2.961	0.301
0.723	206	2.172	3.169	2.008	2.728	0.358
1.024	215	2.12	3.05	1.964	2.728	0.358
0.649	162	2.294	3.164	2.129	2.448	0.386
0.684	162	2.402	3.241	2.235	2.251	0.398
-0.098	120	2.375	3.32	2.221	1.822	0.476

3. RESULTS AND DISCUSSION

In the earlier times, QSAR study of acetophenone was mostly based on the Hansch approach. No QSAR study for acetophenone derivative using topological properties such as W, Jhetv, Jhete, Jhetp has been reported in the literature.

In view of this and in line with our earlier work, in the present study, an attempt was made to find the structural requirements for inhibition of different bacterial strains by acetophenone derivative using the QSAR approach with several topological descriptors, was made. The statistical quality of the regression equation was justified by parameters such as R^2, Se, F-Ratio, PRESS/SSY, PRESS, SSY, R^2cv, and Spress.

It was important for further analysis to develop a correlation matrix for the descriptors utilized and their correlations with the biological activities **(Table-3).** The results **(Table-3)** show that some of the descriptors are mutually correlated. Thus, if a combination of them is present in the regression expression, then the model may suffer from a defect due to collinearity. A perusal of **Table-3** shows that all chosen descriptors do not give significant correlation with antibacterial activity; meaning that in mono-parametric regression, those properties are not appropriate to obtain statistically significant results.

Table 3: Correlation Matrix between the Descriptors

	pMIC	W	Jhetv	Jhete	Jhetp	CIC_0	BIC_0
pMIC	1.0000						
W	0.5404	1.0000					
Jhetv	-0.0266	-0.4519	1.0000				
Jhete	0.1497	0.2823	0.5922	1.0000			
Jhetp	-0.0565	-0.5098	**0.9821**	0.4689	1.0000		
CIC_0	0.1135	0.3939	-0.5777	-0.3985	-0.5030	1.0000	
BIC_0	-0.0152	-0.1756	0.5245	0.5214	0.4332	-0.9679	1.0000

All topological descriptors **(Table-2)** are selected as independent variables and MIC as dependent values, and the stepwise multiple linear regression (MLR) used resulting in the following given below equation. Among the several models generated, five best are selected for the discussion. The selection based on the previously mentioned statistical parameters.

Statistically significant results for growth inhibition activity of acetophenone derivatives against bacterial species using three to four descriptors have been given below.

$$\mathbf{pMIC = 0.0059175 + 0.0027(\pm 0.0009)W}$$

n = 23 R^2 = 0.2921 R^2A = 0.2584 F-Ratio = 8.665…….1

For antibacterial activity, the developed QSAR model (Eq-1) demonstrates the importance of wiener index (topological descriptor) with antibacterial activity of acetophenone. The positive coefficient of wiener index reveals that as the value of W increases the antibacterial activity also increases. The correlation coefficient between the topological descriptor and antibacterial activity is (r=0.54) which is very low with the variance of only 29.21% indicates that the model is not significant and addition of topological descriptors results in the development of biparametric model.

$$\mathbf{pMIC = -0.8220 + 0.0033(\pm 0.0010)W + 0.3579(\pm 0.2643)Jhetv}$$

n = 23 R^2 = 0.3516 R^2A = 0.3946 F-Ratio = 5.422…….2

The QSAR model Eq-3 stated that with the addition of topological parameters results increase in the correlation coefficient from (r = 0.54) Eq-1 to (r = 0.59) which is slightly improved with the variance of 35.16%. The positive coefficient of both topological descriptors indicate that value of both parameters are directly proportional with the antibacterial activity.

pMIC = -0.4761+0.0058(±0.0014)W+ 1.2370(±0.4404)Jhetv-0.8917(±0.3758)Jhete

n = 23 R^2 = 0.4998 R^2A = 0.4208 F-Ratio = 6.328…….3

pMIC = -0.3805+0.0071(±0.0014)W+ 5.4379(±2.0265)Jhetv-

1.7133(±0.5198) Jhete-3.3847(±1.5998)Jhetp

n = 23 R^2 = 0.5994 R^2A = 0.5104 F-Ratio = 6.7323……..4

The developed QSAR model Eq-3 and Eq-4, describe the importance of topological descriptors with antibacterial activity. According to the developed model Eq-3 and Eq-4 Jhete show the negative coefficient while all topological descriptors show positive coefficient. The correlation coefficient between the topological descriptors and the antibacterial activity in Eq-3 is (r = 0.70) and Eq-4 is (r = 0.77) with the variance of 49.98% and 59.94% which is good but not best. The "rule of thumb" indicates that no further addition of descriptors will take place. There are three serious outliers are present and after deleting it, the resulting QSAR model Eq-5 is given below.

After deletion of compound no.7, 11 and 16.

pMIC = -0.0091+ 0.0083(±0.0011)W+ 8.0223(±1.6229)Jhetv-

2.4312(±0.4304) Jhete-5.3025(±1.2688)Jhetp

n = 20 R^2 = 0.8013 R^2A = 0.7483 F-Ratio = 15.119…….5

Initial regression analysis indicated that out of six molecular descriptors used, in combination with other topological descriptors. Jhetv plays a dominant role in shaping antibacterial activity (The greatest value of regression coefficient). The positive coefficient of Jhetv indicates that the activity increases as the magnitude of those descriptors increases (Eq-2 toEq-5). The correlation coefficients were found to be good (0.89) in Eq-5 and the standard error of estimation is 0.11. An

excellent correlation was obtained in Eq-5, where the correlation coefficient is maximum with a minimum se value.

Table 4: Cross Validation Statistical parameters

Model	n	PRESS	SSY	PRESS/SSY	R^2_{cv}	R^2_{adj}	S_{press}
1	23	1.0043	0.3362	2.98	0.1276	0.2584	0.2089
2	23	0.9859	0.4047	2.43	0.1436	0.2867	0.2070
3	23	0.9762	0.5259	1.85	0.1520	0.4208	0.2060
4	23	0.8523	0.6900	1.23	0.2596	0.5104	0.1925
5	20	0.3171	0.8494	**0.32**	0.5121	0.7483	**0.1259**

We have undertaken a cross-validation methodology for deciding the predictive power of the proposed model (Eq-1 to Eq-5). This was needed because a model with good statistics may not have good predictive potential. The various cross-validation parameters, calculated for the proposed models, are presented in **Table-4** and are discussed below. PRESS appears to be an important cross-validation parameter accounting for a good estimate of the real predictive error of the model. When its value is less than SSY, the model predicts better than by chance alone, and can be considered statistically significant and are better that chance. For QSAR model to be considered reasonable, PRESS/SSY should be smaller than 0.4 and the data presented in **Table-4** indicate that model no.5 proposed are significant. Finally in order to confirm our finding, antibacterial activity was compared with the corresponding values reported in Table-2. These comparisons are shown in **Table-6.** The values agree well within experimental error. The residual is the difference between observed and calculated antibacterial activity.

The real usefulness of QSAR models is not just their ability to reproduce known data, verified by their fitting power (R^2), but is mainly their potential for predictive application. For this reason, the model calculations were performed by maximizing the explained variance in prediction, verified by the leave-one-out cross- the possibility of overestimating the model predictivity by

using R^2 procedure, as is strongly recommended for QSAR modeling. This indicates that the obtained regression model has a good internal and external predictive power.

In order to investigate the existence of a systemic error in developing the QSAR models, the residuals of the predicted activity was plotted against the observed activity value **(Figure-2).** The propagation of the residuals on the both sides of the zero axis indicates that no systemic error in the development of regression models exists.

Table 6: Antibacterial Screening Summary

Com.	Actual	Predicted	Residual
1	0.338	0.366	-0.028
2	0.386	0.385	0.001
3	0.393	0.484	-0.091
4	0.381	0.403	-0.022
5	0.481	0.596	-0.115
6	0.284	0.258	0.026
7	0.338	0.203	0.135
8	0.419	0.572	-0.153
9	0.46	0.582	-0.122
10	0.761	0.627	0.134
11	0.344	0.387	-0.043
12	0.804	0.599	0.205
13	0.721	0.71	0.011
14	0.381	0.254	0.127
15	0.338	0.296	0.042
16	0.723	0.7	0.023
17	1.024	0.88	0.144
18	0.649	0.682	-0.033
19	0.684	0.799	-0.115
20	-0.01	0.114	-0.124

A plot between the predicted and observed MIC values is shown in Figure 1.

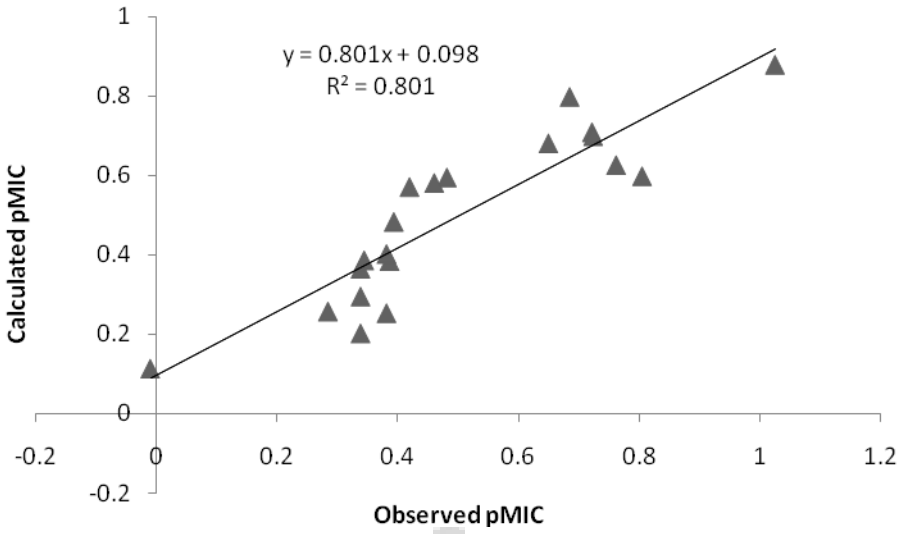


Figure 1: Plots of Predicted v/s experimentally observed inhibitory activity of Acetophenone

The trend may be explained by the existence of a variance inflation factor (VIF). The VIF value was calculated for $1/1\text{-}r^2$, where r^2 is the squared multiple correlation coefficient of one parameter effect on the remaining parameter. VIF values are greater than 5, indicate the presence of unacceptably large multicollinearity between the parameters in the correlation. The VIF value of Eq.3 is closer to 5 and may be responsible for the marginal increase in its r value.

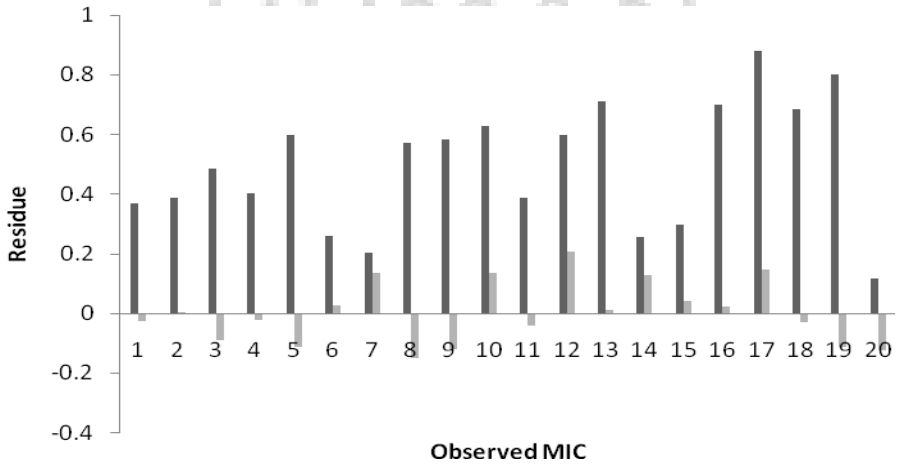


Figure 2: Plots of residual value against the experimentally observed activity of Acetophenone

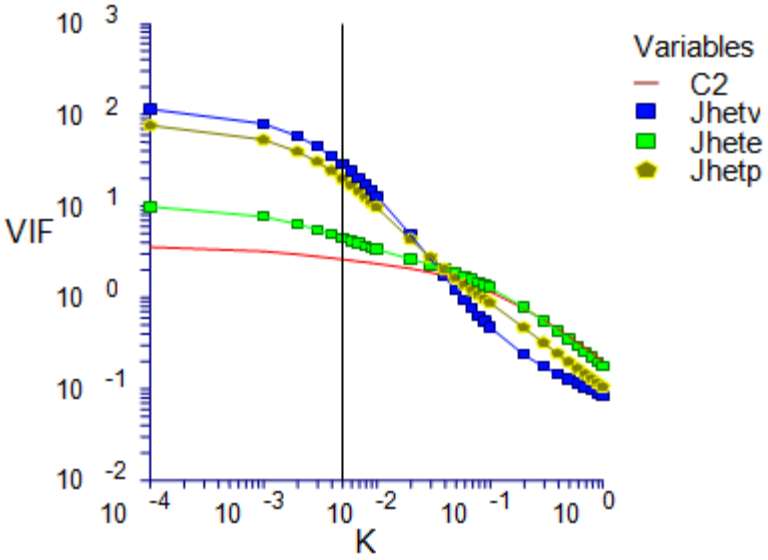


Figure 3: Plot between VIF and K

4. CONCLUSION

Spurred by the need for new antibacterial agents and the fact that many effective drugs, insecticides and fungicides possess in their structure. In view of the results and discussions above, we conclude that topological descriptors such as W, Jhetv, Jhete and Jhetp can be successfully used for modeling acetophenone derivative as antibacterial drugs. These results will help medical as well as agricultural scientists in the design and prediction of compounds with increased activity and thus the synthesis of new acetophenone exhibiting better activities than those reported in this result.

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