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Research Article

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Quantitative Structure-Activity Relationships (QSAR) study and improving it of some schiff-base ligands as anticancer for prostate cancer

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ABSTRACT

The study presents rebuilding QSAR investigation on 12 Anticancer Schiff-base ligands that have an activity against prostate cancer. The geometries of the studied compounds were optimized first at level (MM+) by molecular mechanics force field theory and then at level (AM1) by semi- empirical theory. QSAR model includes some Molecular descriptors, regression quality indicates that these descriptors provide valuable information and have significant role in the assessment of the activity of Schiff-base ligands. Several models for the prediction of biological activity have been drawn up by using the multiple regression technique. Four models with R^2 ranges from 0.98-0.99 were predicted. A model was used to improving a predict the data the anticancer activities, shown it a better predictive equations and the agreement between the observed and the predicted values was excellent. Study has shown that the biological activity of the studied compounds affected by C=N properties.

Keywords: Schiff-base, Anticancer, prostate cancer, Rebuilding (QSAR) Model.

INTRODUCTION

The compounds carrying azomethine functional group –C=N- which are known as Schiff bases gain importance in medicinal and pharmaceutical field due to the most versatile organic synthetic intermediates and also showing a broad range of biological activities such as antituberculosis[1,2] anticancer[3,4] analgesic and antiinflamatory[5,6], anticonvulsant[7-9], antibacterial and antifungal[10,11]activities.In the recent years macrocyclic pyridinophanes (MCP, macroheterocycles including pyridine fragment in a ring) are being considered as the compounds with the potentially high pharmacological and biological activities[12]. Quantum chemical descriptors have been extensively used in Quantitave Structure-Activity Relationship studies in biochemistry. Numerous reviews have been published on the applications of quantum chemical descriptors [13]. The use of quantum chemical descriptors in the development QSAR has received attention due to reliability and versatility of prediction by these descriptors. For the calculation of the quantum chemical molecular descriptor used in QSAR studies[14]. Quantum chemical molecular descriptors used in QASR studies semi empirical methods such as AM1, PM3 and RM1, mainly have been used in prediction of physiological and biological properties of organic compounds[15].

Some previous results on studying multivariate higher order relationships to analyze several physical chemistry properties and biological activities has shown the convenience of resorting to higher-order equations in order to get suitable fitting equations giving satisfactory predictions In this paper we have chosen the same molecular set comprising 12 molecules as described in Ref.[16] and identical molecular descriptors to calculate R, S and F in order to be able to perform a comparison analysis between present results and those previously published. The present contribution presents the results on higher order polynomial calculations which improve previous results and so yields better predictive equations through the simple expedient of resorting to fitting equations computed at orders larger than one. The paper is organized as follows: next section deals with a brief sketch of the calculation scheme and some

previous antecedents. Then we present numerical results and discuss them, making suitable comparisons with previous published data. Finally, we give the conclusions on the proposed procedure and the evident advantages in resorting to this rather simple and direct method. In this work we demonstrate the usefulness and focus of some of the parameters in deriving predictive QSAR models. The relation between the anti prostate cancer and quantum chemical calculated parameters, N-Charge for C=N bond, C=N STR and C=N length investigated theoretically.

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Modeling and Geometry Optimization

Theoretical calculations were performed using Orca program version 2.4[17], running on a Pentium V PC-CPU 3400GHz. The full geometry of the compounds were optimized first at level (MM+) by molecular mechanics force field theory and then at level (AM1) by semi- empirical theory, no imaginary frequencies was found in the calculation spectra of the studied Schiff bases using AM1.

EXPERIMENTAL SECTION

The anticancer data of 12 schiff-base have been taken from reference [16]. The structures of Schiff-bases are shown in Table 1, and identified by the following Figure 1.

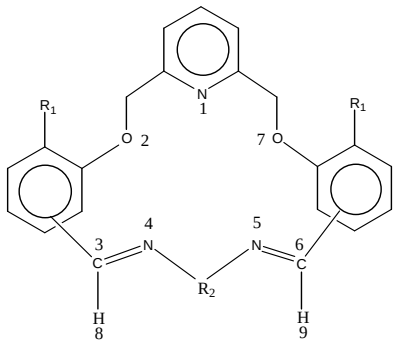

Figure 1. Molecular structure of Schiff-base used in the present study

Comounds	R_1	R_2
I	H	$(CH_2)_2NH(CH_2)_2$
II	H	4,4'-$C_6H_4C_6H_4$
III	H	$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$
IV	H	1,4-C_6H_4
V	H	$(CH_2)_2NH(CH_2)_2$
VI	H	$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$
VII	H	1,4-C_6H_4
VIII	H	4,4'-$C_6H_4C_6H_4$
IX	Me O	$(CH_2)_2NH(CH_2)_2$
X	Me O	$(CH_2)NH(CH_2)NH(CH_2)_2$
XI	Me O	1,4-C_6H_4
XII	Me O	4,4'-$C_6H_4C_6H_4$

Table 1: The list of chemical structure of the Schiff-base compounds

RESULTS AND DISCUSSION

To establish the relation between structural characteristics of molecule and its properties the mathematical methods can be used. Multiple linear regression (MLR) is one of the mathematical methods which have an extent application. Four QSAR models were produced in this study. The model of QSAR study has been build up with help of the descriptors N-Charge, vibration of C=N STR and C=N length was investigated. The predictive model of QASR study has been built up with the help of the following descriptors in Table 2. These descriptors for the Schiff-bases under study were calculated.

Table 2. Calculated physico-chemical descriptors of the compounds

Mol	N4-charge	N5-charge	[a]C6=N5 Length	[b]C6=N5 STR	C3=N4 STR	C3=N4 Length	C3-[c]H8 STR	C6-H9 STR
I	-0.2351	-0.24684	1.289	2061	2063	1.289	3088	3098
II	-0.189878	-0.18822	1.297	2040	2042	1.295	3085	3071
III	-0.28051	-0.27629	1.29	2060	2060	1.289	3095	3099
IV	-0.184592	-0.21782	1.283	2109	2117	1.281	3103	3120
V	-0.255019	-0.25334	1.285	2075	2069	1.287	3091	3108
VI	-0.237339	-0.24145	1.28	2109	2111	1.279	3121	3131
VII	-0.181709	-0.1817	1.295	2044	2044	1.295	3078	3078
VIII	-0.189771	-0.18836	1.297	2040	2042	1.29	3085	3072
IX	-0.254769	-0.24952	1.287	2075	2069	1.285	3092	3109
X	-0.237476	-0.24051	1.28	2110	2111	1.279	3131	3120
XI	-0.180453	-0.18046	1.296	2042	2043	1.296	3072	3077
XII	-0.193162	-0.19403	1.296	2037	2036	1.298	3066	3082

Definition of Descriptors Used in This Study.
a = Length of C=N = Length Bond of the Azomethin Group (C=N) in Angstrom. **b**, **c**= Stretching vibration of the Azomethin Group (C=N) in cm^{-1}, and Stretching vibration of the C-H bond in cm^{-1}.

Table 3. Statistical parameters of the lineal regressions models obtained for the 8 kinds of descriptors

Model type	descriptors								R2	S	F
	1	2	3	4	5	6	7	8			
IX	N5-CHARGE								0.533	20.602	11.450
2X	C6=N5 STR	N5-CHRAGE							0.592	20.295	6.552
3X	C6=N5 STR	N5-CHARGE	C3=N4 STR						0.807	14.785	11.216
4X	C3=N4 STR	C6=N5 STR	C6=N5 LENGTH	N5-CHARGE					0.929	9.573	23.087
5X	C3=N4 STR	C6=N5 STR	C6=N5 LENGTH	N5-CHARGE	N4-CHARGE				0.930	10.239	16.168
6X	C3=N4 STR	C6=N5 STR	C6=N5 LENGTH	N5-CHARGE	N4-CHARGE	C3=N4 LENGTH			0.934	10.957	11.805
7X	C3=N4 STR	C6=N5 STR	C6=N5 LENGTH	N5-CHARGE	N4-CHARGE	C3=N4 LENGTH	C6-H9 STR		0.934	12.189	8.182
8X	C3=N4 STR	C6=N5 STR	C6=N5 LENGTH	N5-CHARGE	N4-CHARGE	C3=N4 LENGTH	C6-H9 STR	C3-H8 STR	0.934	12.189	8.182

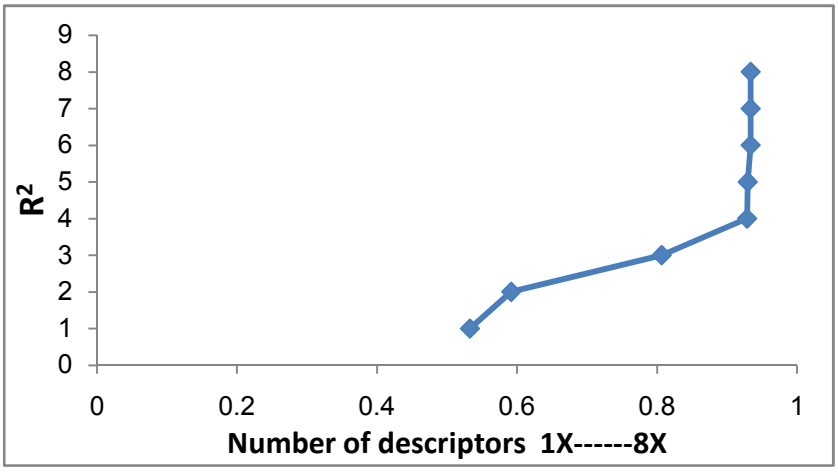

Fig. 2. Influence of number of descriptors on R2 of MLR model

The prediction set, consisted of 12 molecules, was used to evaluate the generated model. It is clear that many MLR models will result using stepwise multiple regression procedure; among them we have to choose the best one. It is common to consider four statistical parameters for this purpose. These parameters are the number of descriptors, correlation coefficient (R^2) for training and prediction sets, standard error (SE) for training and prediction sets, and F statistic. A reliable MLR model is one that has high R^2 and F values, low SE and least number of descriptors. In addition to these, the model should have a high predictive ability. The discussion here will focus only on the influence

the C=N [STR, LENGTH] C-H STR and N-Charge on R^2 value depends on some previous results[14]. Consequently, among different models, the best model was chosen, whose specifications are presented in Table 3. It is obvious that as the number of descriptors increase the R^2 will increase. Fig. 2, shows the effect of increasing the number of descriptors on R^2 values[18]. It can be seen from this figure that increasing the number of parameters only up to six has a large influence on improving correlation. Therefore, we have chosen eight descriptors as optimum number of parameters. four- and five-parameter models for each of shiff base, which it has less standard error (SE) high F values.

The four- and five- parameter correlations of the shiff base were given in eq. (1) and eq. (2) respectively, while depicted in Figures 3and 4.[19-22]

The. Eq 1. of the biological activity of shiff base compounds are best predicated by the depend on only 5 parameter gave good model with correlation coefficient R^2 values for this model of 0.929.

Y=(-7.035+/-4.262) C3=N4STR+(10.530+/-6.649) C6=N5STR+(13840.545+/-13933.631) C6=N5LENGHT+ (652.847+/-600.155) N5CHARGE-(24853.897+/-24074.177) …….Eq(1)

n = 12 R^2= 0.929 F= 23.087 S= 9.573

The excellent relationship between the experimental data and predicted antibacterial activities**.** In this model depends on values of C3=N4 STR, C6=N5 STR, C6=N5 Length and N5-Charge suggest that the activity increases with increase values of these descriptors.

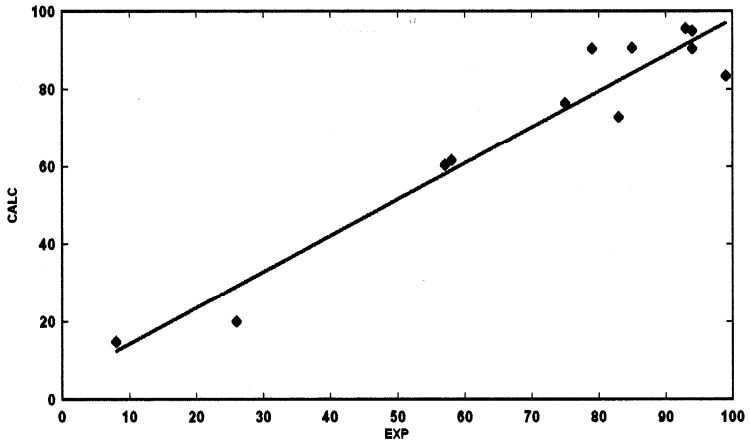

Fig. 3. Observed vs. predicted biological activities of Schiff base compounds calculated by Eq.1.

The Eq 2.of the biological activity of shiff base compounds are best predicated by the depend on only 6 parameter gave good model with correlation coefficient R^2 values for this model of 0.930.

Y=(-6.642+/-6.421) C3=N4STR+(10.105+/-8.817) C6=N5 STR +(13566.078+/-16063)

C6=N5LENGTH+(845.676N5+/-2184.913)N5CHARGE-(183.61+/-1977.143)N4 CHARGE-(24430.669+/-27657.776) …….Eq (2).

n=12 R^2= 0.930 F= 16.168 S= 10.239

Eq.2, indicate a strong dependency of the activity on this parameters in Tabl.2 with R^2= 0.930, This value became high when a double parameter regression equation including both C=N Length and the C=N STR IN AZOMETHEN GROUP, N4 and N5-CHARGE was used as shown in Eq .2 [14]

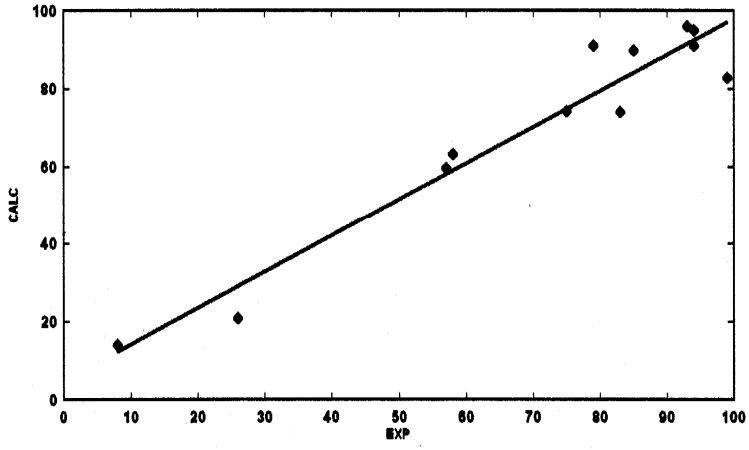

Fig. 4. Observed vs. predicted biological activities of Schiff base compounds calculated by Eq.2.

In the Table 4. The predicted biological activity values obtain from Eq. 1-2 in this study and comparable with the previously study in the Reference [16]. It is obvious from Table 3. that the Relations between descriptors which calculations in this study and experimental biological activity values are excellent[23].

Table 4. Predicated Experimental data depends on Eq 1. & Eq 2.

No molecule	Calc in this work Model 5x	Calc in this work Model 4x	Calc ref(16)	Exp ref(16) PROSTATE CANCER
1	13.97	14.80	17	8
2	91.05	90.39	87	79
3	20.79	19.99	15	26
4	74.20	76.25	71	75
5	59.49	60.41	63	57
6	63.06	61.51	65	58
7	95.07	95.02	81	94
8	90.91	90.30	96	94
9	89.81	90.59	74	85
10	73.98	72.66	76	83
11	95.89	95.65	92	93
12	82.71	83.38	108	99

CONCLUSION

In the present study we investigated and recomputed descriptors for 12 schiff base activity against prostate cancer have been correlated with their activity. The good regression coefficients R^2, depends on Eq2. And the best of model which depends on the parameters in Eq.2, have a significant role in the biological activity of the studied Schiff base compound. We have improving the value of R^2 and compared QASR results of the anticancer activity with previously study, and attempt to build the best successful QSAR models. The descriptors understudy including [C=N], showed insignificant role in the anticancer activity of schiff base. QSAR analysis produced one- to- tow-parameter equations that could be working properly to predict the potency of unknown activity Schiff base. C=N STR and C=N Length descriptors constituted the major variables in the correlated models. A model was used to improving a predict the data the anticancer activities, shown it a better predictive equations, with the values of R^2 =0.966, F=11.805, S=10.957, from Eq.2, compare with previous study [16] with values of R^2=0.95, F=41.6, S=11. the observed and the predicted values was excellent. This study may be helpful for the medicinal chemists in understanding antimicrobial activity of Schiff bases ligand as anticancer.

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