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Quantitative Structure-Activity Relationships (QSAR) Study of Some Schiff-base ligands

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Abstract

The Schiff-Base is known to have a variety of biological activities like antibacterial, anti-inflammatory and antimalarial activities. The study presents QSAR investigation on six bioactive Schiff-base ligands that have an activity against antibacterial. 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 properties, regression quality indicates that these descriptors provide valuable information and have significant role in the assessment of the activity of Schiff-base ligands. This model provides good results, when the model depends on two parameters[C=N STR+HOMO] and [C=N LENGTH + HOMO], with correlation coefficients R=0.979 and R=0.988 respectively. Second QSAR model depends on three parameters [LUMO+ E.GAP+C=N STR] and [C=N LENGTH + HOMO+D.M], this model also provides good results with R=0.977 and R=0.995 respectively.

Keywords. Schiff-base, Antibacterial, (QSAR) Model.

Introduction

The speciality of Schiff base is that many kinds of amine can be chosen to react with aldehyde or ketone to get the ligand with different structures as well as some variable properties [1-2]. In addition potential application in many fields such as antibacterial, antiviral, anticancer drugs, and electrochemistry[3].

Quantitative Structure activity relationship (QSAR) models are highly effective in describing the structural basis of biological activity, it is now widely used for the prediction of physicochemical properties and biological activities in chemical, environmental and pharmaceutical areas. [4]. The success of QSAR approach can be explained by the insight offered into the structural determination of chemical properties, and the possibility to estimate the properties of new chemical compounds without the need to synthesize and test them. [5]. Recently, development of useful QSAR models for antimicrobial activity have been reported [6] . In the field of QSAR, the main objective is to investigate these relationships by building mathematical models that explain the relationship in a statistical way with ultimate goal of prediction and/or mechanistic interpretation. QSAR are being applied in many disciplines like drug discovery and lead optimization, risk assessment and toxicity prediction, regulatory decisions and agrochemicals [7]. Quantitative structure Activity relationships (QSAR) are predictive tools for a preliminary evaluation of the activity of chemical compounds by using computer-aided models[8].

In this paper a theoretical technique has been discussed by which the biological activity of Schiff-base can be measured prior to their synthesis. This technique shall reduce the drug discovery cost, time and efforts. In this work we demonstrate the usefulness of some of the parameters in deriving predictive QSAR models. The relation between the antibacterial and quantum chemical calculated parameters, E

E_{HOMO}, E_{LOMO}, dipole moment, C7.Charge, N-Charge for Schiff-base bond C=N, Heat of Formation, ΔE, C=N STR, C=N Length investigated theoretically.

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Modeling and Geometry Optimization

Theoretical calculations were performed using hyperchem program version 7.5, running on a Pentium V PC-CPU 3400GHz. The geometries of the compounds were optimized first at level (MM+) by molecular mechanics force field theory and then at level (AM1) by semi- empirical theory[9].

Experimental

The antimicrobial data of 6 schiff-base have been taken from reference [10]. The structures of Schiff-bases are shown in Table 1, and identified by the following Figure 1.

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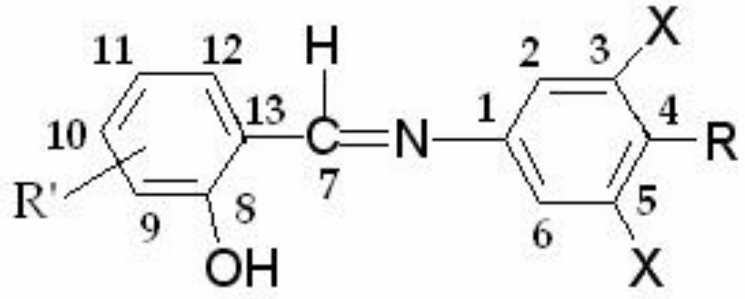

Figure 1. Molecular structure of Schiff-base used in the present study

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

Compound/Sub	HL1	HL2	HL1'	HL2'	HL1"	HL2"
R	Me	Me	Br	Br	OH	OH
R'	9-OMe	9-OH	9-OMe	9-OH	9-OMe	9-OH
X	H	H	H	H	t-Bu	t-Bu

Result and Discussion

The structures of the studied compounds is shown in Figure 1, and Table 1. In this study we used parameters in Table 2. to establish the statistical correlation, the physicochemical parameters were taken as independent variables and anti-bacterial activity as dependent variable. The data were transferred to statistical program datafit (version9.0.59) to generate the statistically significant QSAR models. 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[11].

Table 2. Calculated physico-chemical parameters of the compounds

Name	C=N STR Cm^{-1}	ΔE ev	LUMO ev	HOMO ev	Dipole. Moment μ Debye	Heat of Formation KCAL/MOL	Total. Energy CAL/MOL	Mulliken Charge on C7.atom	Mulliken Charge on N.atom	C=N A^o
HL1	1999.49	8.44538	-0.27696	-8.7223	4.654	-15.79657	-68573.80469	0.023	-0.152	1.28
HL2	1970.09	8.36518	-0.38271	-8.7479	4.16	-21.17036	-64992.33984	0.011	-0.143	1.284
HL1'	2001.27	8.5638	-0.4247	-8.9885	5.186	-3.67553	-72811.39063	0.033	-0.159	1.28
HL2'	2001.37	8.51812	-0.50537	-9.0235	4.655	-9.87747	-69230.75781	0.031	-0.157	1.28
HL1"	1996.32	8.20818	-0.25346	-8.4616	4.477	-103.2833	-108291.9766	0.019	-0.147	1.28
HL2"	2006.33	8.42962	-0.05538	-8.4845	5	-107.3451	-104709.1953	0.007	-0.133	1.278

All variables are in Table 2. examinant to build the best model, the best model were selected on the basis of statistical parameters viz., Standard error of estimate (s), and sequential Fischer value (F), and correlation coefficient(R), were used to evaluate the obtained QASR. Acceptability of the regression model was judged by examining the correlation coefficient(R), fischer value (F) and standard error of estimate (s), performing multiple liner regression analysis results in statistically significant QASR models against anti-bacterial. The model when depends on only one parameter[C=N STR] or [N-CHARGE] gave (R=0.921, R=0.934) respectively, when HL2" outlier[12]. The percentage of correlation coefficient(R) increases when using two parameters as shown in eq. 1

Model-1 = Eq 1. = a+b*x1+c*x2……..(1)

Model -1 shows very good correlation coefficient with (R=0.979 and R=0.988)) respectively, a significant F-value, and a low standard deviation, when the model depends on two parameters, as equation 1. model A & B, Table 3. shows best correlation coefficient.

Equation 1. when depends on two parameters[C=N STR+HOMO].
Model A ……. Y= -295.3454 – 6.6645HOMO+0.12381 $C=N_{STR}$

Equation 1. when depends on two parameters[C=N LENGTH + HOMO].
Model B……Y= 1030.4951- 853.2065$C=N_{LENGTH}$- 8.2276HOMO

Table 3. Correlation matrix of used molecular descriptors with two parameters
Eq 1. = a+b*x1+c*x2 . .

Descriptor		R	S	F
X_1	X_2			
C=N LENGTH	DELT GAP	0.813	1.27	6.554
*HOMO	C=N STR	0.979	0.444	61.139
LUMO	C=N STR	0.876	1.034	10.648
T.E	C=N STR	0.844	1.159	8.175
DELT GAP	C=N STR	0.864	1.083	9.572
CHARGE on C-ATOM	N- CHARGE	0.832	1.203	7.475
HEAT FORMATION	C=N LENGTH	0.852	1.131	6.656
C=N LENGTH	LUMO	0.878	1.026	10.831
*C=N LENGTH	HOMO	0.988	0.31	133.321

*= best correlation coefficient

The good relationship between the experimental deta and predicted antibacterial is reported in Table 4.

Table 4. Experimental and predicated of antibacterial by using Eq 1.

*Exp. of Antibacterial	Calc. by-Model A	Calc. by-Model B
10	10.350	10.155
7	6.88	6.952
12	12.344	12.344
13	12.59	12.632
8	8.22	8.01
10	9.612	9.904

*= The experimental inhibitory reference [10].

The second QASR model has been formed with the help of descriptors in Table 2. and test against anti-bacterial[13]. The models are shown in eq. 2

Model-2= Eq 2.= a*x1+b*x2+c*x3+d…..(2)

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By using three parameters, as equation 2. model A & B, we have got very good models with (R=0.989 and R=0.995)) respectively. Table 4. shows best correlation coefficient.

Equation 2. when depends on three parameters[LUMO+ E.GAP+C=N STR]

Model A ……. Y= -8.7081LUMO+7.6862ΔE-879.0812C=N $_{LENGTH}$+1068.0299

Equation 2. when depends on three parameters[C=N LENGTH + HOMO+D.M]

Model B…… Y= -1005.435C=N $_{LENGTH}$ – 8.8207HOMO – 0.9567D.M + 1224.7029

Table 5. Correlation matrix of used molecular descriptors with three parameters Eq 2.= a*x1+b*x2+c*x3+d

Descriptor			R	S	F
X_1	X_2	X_3			
LUMO	DELT GAP	C=N STR	0.977	0.541	28.872
C –CHARGE	DELT GAP	C=N LENGTH	0.933	0.931	9.321
C=N STR	HOMO	D.M	0.976	0.547	28.239
*C=N LENGTH	HOMO	D.M	0.995	0.249	138.231
*LUMO	DELT GAP	C=N LENGTH	0.989	0.367	63.337

*= best correlation coefficient

The good relationship between the experimental deta and predicted antibacterial is reported in Table 6.

Table 6. Experimental and predicated of antibacterial by using Eq 2.

*Exp. of Antibacterial	Calc. by-Model A	Calc. by-Model B
10	10.131	10.229
7	6.919	6.905
12	12.327	12.068
13	12.67	12.885
8	8.103	8.099
10	9.838	9.811

*= The experimental inhibitory reference [10].

Conclusion

The quantum chemical calculated parameters can be successfully used for the prediction of QSAR. The study indicated that biological activity for Schiff-base compounds can be modeled by using three parameters. The good correlation coefficients R, depends on eq2. And the best of model which depend on the parameters D.M, HOMO, C=N LENGTH.

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العلاقة بين الفعالية البايلوجية و الخواص الالكترونية لقواعد شف باستعمال الموائمة الهندسية وتقنيات qasr

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الملخص :

مركبات قواعد شف معروفة بامتلاكها مدى واسع من الفعالية البايلوجية ضد antibacterial, anti-inflammatory antimalarial activities. الدراسة تقدم العلاقة التركيبية ل QSAR لستة مركبات من قواعد شف التي تمتلك فعالية بايلوجية ضد antibacterial. استخدم كيمياء الكم لحساب الموصوفات لتتبأ بخواص QSAR لستة مركبات من ليكاندات قواعد شف. الموائمة الهندسية لهذه التراكيب أنجزت أولا بطريقة (+MM)ومن ثم أكملت الموائمة الهندسية بطريقة التشبه تجريبية MINDO. موديل QSAR تضمن بعض خواص الالكترونية والجزيئية لتتبئ بخواص الفعالية البايلوجية لقواعد شف. الموديل الأول الذي اعتمد على متغيرين هما [C=N LENGTH + HOMO], [C=N STR+HOMO] أعطى نتائج جيدة مع قيمه عالية ل R=0.979 ، R=0.988 على التوالي. الموديل الثاني اعتمد على ثلاثة متغيرات هما [LUMO+ E.GAP+C=N STR] [C=N LENGTH + HOMO+D.M], الذي أيضا أعطى نتائج جيدة مع قيمه عالية ل R=0.977، R=0.995.