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American Journal of Applied Sciences 7 (7): 902-905, 2010
ISSN 1546-9239

Density Functional Theory Based Quantitative Structure Activity Relationship Study of 2,5-Bis(1-Aziridinyl)-p-Benzoquinones with Lymphoid Leukemia

[1]Bahjat A. Saeed and [2]Rita S. Elias
[1]Department of Chemistry, College of Education,
[2]Department of Pharmaceutical Chemistry, College of Pharmacy,
University of Basrah, Iraq

Abstract: Problem statement: QSAR techniques increase the probability of success and reduce time and coast in drug discovery process. The study presented QSAR investigation on 32 bioactive aziridinylbenzoquinones that have activity against lymphoid leukemia. **Approach:** Molecular descriptors, molecular weight, total energy, hardness, chemical potential, electrophilicity index, HOMO and LUMO energies were calculated. Initial geometry optimizations were carried out with the AM1 Hamiltonian. The lowest energy conformations were subjected to single point calculations by the DFT method by employing Beck's Three-Parameter hybrid functional (B3LYP) and pvDZ basis set. Several models for the prediction of biological activity have been drawn up by using the multiple regression technique. **Results:** A model with hapta parametric linear equation with R^2 value of 0.886 was presented. **Conclusion:** The biological activity of the studied compounds can be modeled with quantum chemical molecular descriptors.

Key words: Aziridinyl benzoquenones, lymphoid leukemia, QSAR, DFT, electrophilicity

INTRODUCTION

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 (Parthasarthi *et al*., 2004). 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, semi empirical methods such as AM1 and PM3 mainly have been used (Cavalli *et al*., 2006; Shaik *et al*., 2005). However, DFT method has been used recently for the prediction of physiochemical and biological properties of organic molecules (Shaik *et al*., 2010; Lei *et al*., 2009; Siu and Che, 2006). A large number of quinones both synthetic and natural occurring have been screened for their antitumor activity in addition to a wide variety of other bioactivities (Bender *et al*., 2007; Bernardo *et al*., 2004; Hargreaves *et al*., 1999). The most prominent chemical feature of these compounds is their ability to undergo redox cycling to generate reactive oxygen species which can damage tumor cell (Fotie *et al*., 2010). Several aziridinylquinones have undergone clinical trials as potential antitumor drugs (Rajski and Williams, 1997; Mayalarp *et al*., 1996; Moret *et al*., 1996; Gupta, 1994). These compounds can be activated toward alkylation as a result of bioreduction by the electron reducing enzymes or by two electron reducing compounds (Aiello *et al*., 2005). Limited number of studies has investigated the QSAR of these quinones. The aim of this study is to build QSAR models using multiple regression method, to investigate the correlations between the experimental biological activity and calculated molecular descriptors of a series of 2,5-Bis(1-aziridinyl)-p-benzoquinones as inhibitors against lymphoid leukemia L1210 in BDF_1 mice.

Theory: Hardness (η), chemical potential (μ) and electronegetivity (χ) are defined as (Bultink *et al*., 2003):

$$\eta = 1/2\left(\frac{\partial^2 E}{\partial N^2}\right)V(r) = 1/2\left(\frac{\partial \mu}{\partial N}\right)V(r) \quad (1)$$

$$\mu = -\chi = -\left(\frac{\partial E}{\partial N}\right)V(r) \quad (2)$$

where, E and V(r) are electronic energy and external potential of an N-electron system, respectively.

Corresponding Author: Bahjat A. Saeed, Department of Chemistry, College of Education, University of Basrah, Iraq

Softness is a property of molecules that measures the extent of chemical reactivity. It is the reciprocal of hardness:

$$S = \frac{1}{\eta} \quad (3)$$

Using Koopmns' theorem for closed-shell molecules, η, μ and χ can be redefined as (Chattaraj *et al*., 2009):

$$\eta \approx ½ (I-A) \approx ½ (\varepsilon_{LUMO}-\varepsilon_{HOMO}) \quad (4)$$

$$\mu \approx ½ (I+A) \approx ½ (\varepsilon_{HOMO}-\varepsilon_{LUMO}) \quad (5)$$

$$\chi = \frac{I+A}{2} \quad (6)$$

$$I \approx -\varepsilon_{HOMO} \text{ and } A \approx -\varepsilon_{LUMO} \quad (7)$$

where, I and A are ionization potential and electron affinity of the molecules, respectively.

Parr *et al*. (1999) have proposed electrophilicity index in terms of chemical potential and hardness. They defined electrophilicity index (ω) as follows:

$$\omega = \frac{\mu^2}{2\eta} \quad (8)$$

MATERIALS AND METHODS

The studied benzoquinones derivatives have been taken with their reactivity from literature (Gupta, 1994). Chemical structures and experimental biological activities are gathered in Table 1. The general formula for the chemical structures of the studied compounds is shown in Fig. 1.

Biological activities are represented as log(1/MED) for chronic treatment with daily injection for 12 days. All geometries of the aziridinylbenzoquinones are minimized using the Gaussian (2003) package with semi-empirical AM1 Hamiltonian. Single point calculations have also been made at the B3LYP/pvDZ level with the AM1 geometry. Using Koopmans' theorem for closed-shell system, the ionization potential (I) and electron affinity (A) are calculated using Eq. 7. Employing Eq. 4, 5 and 8, all the global chemical reactivity descriptors are obtained. Linear regression analyses are performed to find the best correlation between the various biological activity indices and the biological activities of the studied benzoquinones represented by their Loq(1/MED).

Table 1: The list of chemical structure of the compounds studied and their observed activities against lymphoid leukemia L1210 in BDF_1 mice

R_1	R_2	A_{obs}
C6H5	C6H5	4.43
CH_3	$(CH_2)_3C_6H_5$	4.47
C_5H_{11}	C_5H_{11}	4.63
$CH(CH_3)_2$	$CH(CH_3)_2$	4.77
CH_3	$CH_2C_6H_5$	4.85
C_3H_7	C_3H_7	4.92
CH_3	$CH_2OC_6H_5$	5.15
C_2H_5	C_2H_5	5.46
CH_3	$(CH_2)_2OCH_3$	5.57
OCH_3	OCH_3	5.59
CH_3	$CH(CH_3)_2$	5.60
C_3H_7	$CH(OCH_3)CH_2OCONH_2$	5.66
CH_3	CH_3	5.68
H	$CH(CH_3)_2$	5.68
CH_3	$CH(OCH_3)CH_2CH_3$	5.68
C_3H_7	$(CH_2)_2OCONH_2$	5.69
$(CH_2)_2OCH_3$	$(CH_2)_2OCH_3$	5.78
C_2H_5	$CH(OC_2H_5)CH_2OCONH_2$	5.86
CH_3	$(CH_2)_2OCOCH_3$	6.03
CH_3	C_2H_5	6.14
CH_3	$CH(OC_2H_2OCH_3)CH_2OCONH_2$	6.16
CH_3	$CH_2CH(CH_3)OCONH_2$	6.18
C_2H_5	$CH(OCH_3)CH_2OCONH_2$	6.18
CH_3	$CH(C_2H_5)CH_2OCONH_2$	6.18
CH_3	$CH(OC_2H_5)CH_2OCONH_2$	6.21
CH_3	$(CH_2)_3OCONH_2$	6.25
CH_3	$(CH_2)_2OCONH_2$	6.39
C_2H_5	$(CH_2)_2OCONH_2$	6.41
CH_3	$CH(CH_3)CH_2OCONH_2$	6.41
CH_3	$CH(OCH_3)CH_2OCONH_2$	6.45
$(CH_2)_2OH$	$(CH_2)_2OH$	6.54
H	$N(CH_2)_2$	6.77

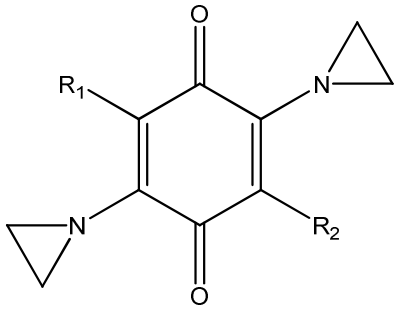

Fig. 1: The general formula for chemical structures of the studied compounds

RESULTS

Six QSAR models were produced in this study. Two models with hexa-parametric regression equations with very low R^2 values of 0.163 and 0.195. And three other hexa-parametric equations with R^2 values of 0.877, 0.875 and 0.851, as well as a hepta-parametric equation model with R^2 value of 0.886 which represents the predictive model that used to predict Log(1/MED).

Table 2: The values of DFT-based descriptors and their and their Predicted activity by Eq. 9

No.	Mw	TE	η	μ	ω	ε_{LUMO}	ε_{HOMO}	S	A_{pred}
1	342.391	-1109.098	1.490	-4.433	6.596	-2.943	-5.923	0.671	4.857
2	322.401	-1035.299	1.591	-4.446	6.213	-2.855	-6.038	0.628	4.602
3	330.464	-1040.130	1.613	-4.358	5.889	-2.746	-5.972	0.613	4.404
4	274.358	-882.858	1.658	-4.335	5.668	-2.677	-5.994	0.603	4.703
5	294.348	-956.660	1.579	-4.700	6.996	-3.121	-6.279	0.633	4.806
6	274.358	-882.870	1.539	-4.486	6.537	-2.947	-6.025	0.650	5.149
7	310.347	-1031.896	1.435	-4.645	7.548	-3.219	-6.088	0.700	4.972
8	246.305	-804.235	1.622	-4.422	6.027	-2.800	-6.043	0.616	5.415
9	262.304	-879.455	1.608	-4.505	6.311	-2.897	-6.113	0.622	5.776
10	250.251	-876.040	1.397	-4.701	7.909	-3.304	-6.097	0.716	6.022
11	246.304	-804.232	1.627	-4.495	5.834	-2.768	-6.022	0.614	5.841
12	218.252	-725.607	1.591	-4.471	6.282	-2.879	-6.062	0.629	5.812
13	232.278	-764.918	1.655	-4.558	6.275	-2.903	-6.214	0.604	5.388
14	276.331	-918.767	1.594	-4.519	6.405	-2.925	-6.113	0.627	5.596
15	319.356	-1087.519	1.620	-4.496	6.239	-2.876	-6.117	0.617	5.789
16	306.357	-1033.303	1.626	-4.511	6.259	-2.886	-6.137	0.615	5.742
17	290.314	-992.832	1.610	-4.569	6.483	-2.959	-6.180	0.621	5.983
18	232.278	-764.929	1.534	-4.546	6.736	-3.012	-6.080	0.652	5.800
19	365.381	-1277.036	1.450	-4.686	7.572	-3.235	-6.138	0.690	5.885
20	305.329	-1048.202	1.585	-4.543	6.511	-2.958	-6.128	0.631	6.117
21	335.355	-1162.737	1.616	-4.444	6.112	-2.828	-6.059	0.619	6.200
22	319.356	-1087.523	1.527	-4.581	6.871	-3.053	-6.108	0.655	5.762
23	335.355	-1162.746	1.621	-4.484	6.202	-2.863	-6.105	0.617	6.157
24	305.329	-1048.200	1.604	-4.480	6.256	-2.876	-6.084	0.623	6.127
25	291.302	-1008.888	1.608	-4.528	6.373	-2.920	-6.136	0.622	6.301
26	305.329	-1048.197	1.542	-4.478	6.502	-2.936	-6.021	0.648	6.328
27	248.278	-840.144	1.610	-4.542	6.407	-2.933	-6.152	0.621	6.153
28	305.329	-1048.192	1.581	-4.291	5.823	-2.710	-5.872	0.632	6.359
29	321.328	-1123.412	1.588	-4.454	6.246	-2.866	-6.042	0.630	6.568
30	231.251	-779.700	1.413	-4.260	6.423	-2.847	-5.673	0.708	6.604
31	278.304	-954.688	1.548	-4.609	6.861	-3.061	-6.157	0.646	6.198
32	245.277	-819.020	1.380	-4.213	6.433	-2.833	-5.593	0.725	6.351

Mw: Molecular weight; TE: Total Energy (Hartree); η: Hardness; μ: Chemical potential; ω: Electrophilicity index; εLUMO: Energy of LUMO (eV); S: Softness; A_{pred}: Predicted biological activity expressed by Log(1/MED); MED: Minimum Effective Dose

DISCUSSION

The predictive model of QSAR study has been build up with help of the following descriptors:

Molecular weight (Mw), Total Energy (Hartree) (TE), LUMO energy (eV) (ε_{LUMO}), hardness (η), chemical potential (μ), electrophilicity index (ω) and Softness (S). The values of these descriptors for the studied benzoquenones have been calculated with help of DFT method. In the formation of the predictive model we employ all variables and the best-fitted equation of the model is hepta-parametric regression equation Eq. 9:

$$\begin{aligned} \text{Log}(1/\text{MED}) &= 59.695 - 0.078\ \text{Mw} - 0.0021\ \text{TE} \\ &+ 131.955\ \eta + 154.945\ \mu - 4.316 \\ &- 166.177\ \varepsilon_{LUMO} - 33.349 S \end{aligned} \quad (9)$$

$$R^2 = 0.886,\ F = 26.7,\ S^2 = 0.243$$

The predicted Log(1/MED) from Eq. 9 is reported in Table 2.

Hexa-parametric equations that not involve Mw or TE descriptors gave poor models with R^2 values for those models of 0.195 and 0.163 respectively. This indicates that both Mw and TE play major roles in the inhibiting activity against lymphoid leukemia L1210.

Less significant than Mw and TE (but of important effect on the R^2 value of the regression equation) is ω, which when not involved in the model equation the R^2 value dropped to 0.851 Eq. 10:

$$\begin{aligned} \text{Log}(1/\text{MED}) &= 97.131 - 0.008\ \text{Mw} - 0.0022\ \text{TE} \\ &+ 97.178\ \eta + 126.167\ \mu - 124.472\ \varepsilon_{LUMO} \end{aligned} \quad (10)$$

$$R^2 = 0.851,\ F = 23.9,\ S^2 = 0.272$$

Both ε_{LUMO} and μ are of comparable significance on the regression equation goodness and when these two parameters were excluded from the model (separately) two models with comparable R^2 values were obtained. They are represented by Eq. 11 and 12 respectively:

$$\text{Log}(1/\text{MED}) = 62.197 - 0.0761\ \text{Mw} - 0.0021\ \text{TE} - 33.288\ \eta - 10.121\ \mu - 3.972\ \omega - 35.298\ \text{S} \quad (11)$$

$$R^2 = 0.875,\ F = 29.3,\ S^2 = 0.250$$

$$\text{Log}(1/\text{MED}) = 61.158 - 0.0761\ \text{Mw} - 0.0021\ \text{TE} - 23.011\ \eta - 4.092\ \omega - 10.487\ \varepsilon_{\text{LUMO}} \quad (12)$$

$$R^2 = 0.877,\ F = 29.6,\ S^2 = 0.248$$

CONCLUSION

The study indicated that QSAR of biological activity represented by Log(1/MED) of aziridinyl benzoquenones to lymphoid leukemia in BDF_1 mice can be modeled with the DFT-based quantum mechanical molecular descriptors. The hepta-parametric regression equation is the best produced model with very good statistical fit as evident from its $R^2 = 0.886$, $F = 26.6$ and $S^2 = 0.243$. It is evident from the results that the inhibition of the leukemia is influenced mainly by molecular weight and total energy.

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