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QSAR STUDY OF 2,3-DIYNE-1,4-NAPHTHOQUINONE DERIVATIVES ANTI-CANCER ACTIVITIES

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ABSTRACT: QSAR study on 11 of 2,3-Diyne-1,4-naphthoquinone derivatives with anti-cancer activities IC_{50} has been made using seven physicochemical parameters to evaluate the chemical-biological interactions. Multiple linear regression techniques were used to select the descriptors and to generate the several QSAR models and even in multi-parametric regression these physicochemical parameters don't give significant results but the mono-parametric regression shown that the cytotoxic activities of 2,3-Diyne-1,4-naphthoquinone derivatives depend on their hypophilictiy.

KEYWORDS: 1,4-naphthoquinone, QSAR, descriptors, hypophilicity

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1. INTRODUCTION

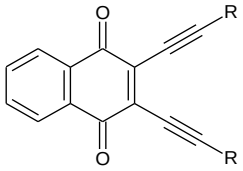
Quinones are widely spread in plants, fungi, and some animals and many drugs containing quinone nucleus have clinical importance, such as anthracyclines, mitoxantrone and saintopin, show the excellent anticancer activity. These anticancers have a great impact on the living cell because they are good electron acceptors which able to accept one or two electrons to form the corresponding radical anion or dianion species, and also have acid-base properties. They are effective inhibitors of DNA topoisomerase, and it is generally known that the cytotoxicity of quinone analogues results from the inhibition of DNA topoisomerase II [1], [2], [3] .1,4-naphthoquinones have a biological activities as

well as antifungal, antibacterial, and anticancer activities, they interfere with electron transport and oxidative phosphorylation processes and play roles in enzyme inhibition, and DNA cross linking [4]. QSAR (Quantitative Structure Activity Relationships) have been applied for decades in the development of relationships between physicochemical properties of chemical substances and their biological activities to obtain a reliable mathematical and statistical model for prediction of the activities of new chemical entities [5].Quantitative structure-activity relationships (QSARs) correlate within congeneric series of compounds, affinities of ligands to their binding sites, inhibition constants, rate constants and other biological activities either with certain structural features (Free-Wilson analysis) or with atomic, group or molecular properties such as lipophilicity, polarizability, electronic and steric properties (Hansch analysis) [6].

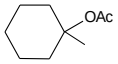
2. MATERIALS AND METHODS

Biological data were obtained for Silva *et al.*, 2013[7] who reported the diynes were evaluated as potential cytotoxic agents against three tumor cell lines: human ovarian adenocarcinoma (OVCAR-8), human metastatic prostate cancer (PC-3M) and human bronchoalveolar lung carcinoma (NCI-H358M), presenting, in general, satisfactory results for inhibition of cell growth (Table 1). The

Table (1): Structures, Physicochemical Parameters and Biological Activities of 2,3-Diyne-1,4-naphthoquinone derivatives for three cancer cell lines NCI-H358M, OVCAR-8 and PC-3M.



No.	R-	IC_{50} / μM			Calculated Log P	Molar Refractivity (cm^3)	Formula Weight	Molar Volume (cm^3)	Index of Refraction	Surface Tension (dyne/cm)	Density(g/cm^3)
		$C_{NCI-H358M}$	$C_{OVCAR-8}$	C_{PC-3M}							
1	Ph-	6.55	4.49	14.26	7.48	106.88	358.39	274.4	1.707	67.1	1.30
2	4-OMePh-	4.57	3.90	9.03	7.31	119.61	418.44	317.7	1.676	65.1	1.31
3	$-C(CH_3)_2OH$	2.98	2.28	4.28	4.12	88.32	322.35	249.1	1.627	64.0	1.29
4	$-C(CH_3)_2OAc$	4.95	5.63	5.74	5.91	107.49	406.43	324.9	1.575	54.3	1.25

5		5.07	5.98	6.56	5.79	112.03	402.48	308.5	1.646	68.1	1.30
6		2.74	3.09	5.26	7.59	131.20	486.56	384.0	1.599	58.8	1.26
7	$-(CH_2)_3CH_3$	6.23	6.56	8.94	7.16	94.50	318.41	286.0	1.574	49.4	1.11
8	$-(CH_2)_3OAc$	5.45	7.40	6.92	4.94	107.48	406.43	324.1	1.577	56.7	1.25
9	$-(CH_2)_2 CH_3$	8.03	9.01	9.17	6.10	85.24	290.36	253.6	1.586	51.1	1.14
10	$-(CH_2)_5 CH_3$	6.42	9.70	20.23	9.29	113.02	374.52	350.7	1.557	47.0	1.06
11	$-(CH_2)_7 CH_3$	3.99	7.53	17.70	11.41	131.55	430.62	415.2	1.546	45.6	1.03

structures of these compounds were sketched using the computer software ChemSketch/ACDlab program version 12.01. Data were transferred to the statistical program SPSS version 20 and a correlation matrix was constructed showing the correlation between various descriptors as well as between descriptors and biological activity (Table 2). The various regression equations were derived using multiple linear regression methods. In QSAR equations, r2 is the square of correlation coefficient which reports the strength of the relationship between the set of independent variables and the dependent variable, [8], s is the standard deviation which shows how far the activity values are spread about their average and F assesses the statistical significance of the regression equation. The IC_{50} value (μg/mL) was defined as the concentration of the inhibitor where the response (or binding) is reduced by half which defined the biological parameter for QSAR equations. Physicochemical parameters are calculated using the computer software ChemSketch/ ACDlab program version 12.01 (Table 1). Octanol/water partition coefficient (logP) is the most frequently used measure of hydrophobicity (or lipophilicity) of chemicals, which, in turn, is a very important property in medicinal chemistry, toxicology, and pharmaceutical and environmental sciences [9]. Molar Volume (derived from liquid density) MV= FW/D, or the parachor (derived from density and surface tension) Pc=ST1/4.MV/D where D is a surface tension. Refraction Index (RI) of the medium is the ratio of the velocity of light in the vacuum to the velocity of light in the medium and it is an important property of the structural arrangement of atoms in the molecule. The molar refractivity (MR) can be determined using Lorentz-Lorentz equation: MR= [(RI2-1)/ (RI2+2)](FW/D) where RI is the refractive index, FW is the formula weight, δ is the density of the substance[10],[11] .Surface Tension (ST) or Inter facial tension is the cumulative effect of the different intra and intermolecular forces of two different surfaces: $ST= (Pc/MV)^4$ [12].

3. RESULTS AND DISCUSSION

The correlation matrix of the used parameters and their correlation with the biological activity for three cancer cell lines NCI-H358M, OVCAR-8 and PC-3M (Table 2) explain that the mono-parametric regression equations between logP, MR, FW ,MV ST, RI or D and activities with a small value of Pearson correlation coefficient which gave poor models except those of ST and D against biological activity for human metastatic prostate cancer (PC-3M) and that of log P against biological activity for human bronchoalveolar lung carcinoma (NCI-H358M). This matrix shows the relation between different descriptors and it's clear that there is a poor relation between log P, FW, and RI also between MV, FW and MR. Also, each of MR, FW and MV not related to RI, ST and D. The partition coefficient is affected by the biological activities for one cancer cell line (NCI-H358M with the good value of Pearson correlation coefficient of 0.810.

Table (2): Correlation matrix of the physicochemical parameters used and the activity for OVCAR-8, PC-3M and NCI-H358M cancer cell lines.

	pC_3	pC_4	pC_5	logP	MR	FW	MV	RI	ST	D
pC_3	1.000									
pC_4	0.762	1.000								
pC_5	0.516	0.629	1.000							
logP	-0.036	-0.382	-0.810	1.000						
MR	0.448	0.043	-0.269	0.653	1.000					
FW	0.576	0.197	0.071	0.344	0.927	1.000				
MV	0.389	-0.189	-0.326	0.725	0.912	0.828	1.000			
RI	0.015	0.545	0.141	-0.300	-0.058	-0.039	-0.459	1.000		
ST	0.255	0.665	0.475	-0.543	-0.039	0.112	-0.410	0.900	1.000	
D	0.301	0.690	0.661	-0.686	-0.067	0.183	-0.394	0.774	0.935	1.000

About 147 mono- and multi-parametric regression equations were employed between selected descriptors and biological activity to find satisfy correlation. Between them only mono-parametric regression equation eq.1 was produced for human bronchoalveolar lung carcinoma (NCI-H358M) in this study with a high r2 value of 0.656 and the overall significant level and those of all individual regression coefficients are better than 95%.

$$pC = 5.669 - 0.0869 logP \qquad \text{eq.1}$$

In order to confirm this model was calculated the predicted activates of different compounds and plot the later against observed activities fig1 which give r2= 0.6786 and that indicate to the hypophilicity of 2,3-Diyne-1,4-naphthoquinone derivatives plays major role in inhabitation of NCI-H358M cancer

cell line and there is inverse proportional between the activity of these compounds and their partition coefficient.

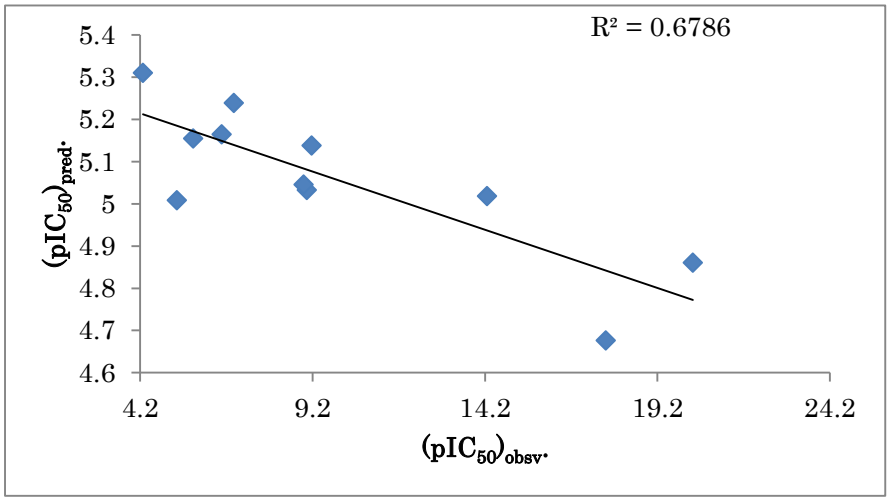


Figure (1): Internal Validation of eq.1.

4. CONCLUSION

The study indicated that QSAR of biological activity represented by pIC50 of 2,3-Diyne-1,4-naphthoquinone derivatives human bronchoalveolar lung carcinoma (NCI-H358M) can be modeled using molecular descriptors. The best mono-parametric regression equation which involves logP with good statistical fit as evident from its r2=0.656, F=17.153 and s=0.13500 and the inhabitation of human bronchoalveolar lung carcinoma is influenced mainly by hypophilicity.

CONFLICT OF INTEREST

The authors declare that no competing financial interests exist.

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