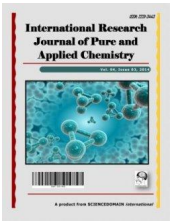

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QSAR Study of 3-Phenylamino-1,4-naphtoquinones Anti-cancer Activities

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: Evaluation the impact of quinones containing alkylamio groups upon biological activities and extent of napthoquinones based upon QSAR technique.
Study Design: QSAR Approach.
Place and Duration of Study: Data were collected from literature.
Methodology: About eleven naphthoquinones which have cytotoxic effect against DU145 Cancerous, MCF7 Cancerous and T24 Cancerous and 6 descriptors were used to find good QSAR model.
Results: The biological activity and surface tension of aminophenylnaphthoquinones can be modeled with linear regression with negative coefficient and satisfied statistical data for DU145 Cancerous r2=0.662, F=17.646, and s=0.34033
Conclusion: The inhabitation of DU145 Cancerous is influenced by surface tension.

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Keywords: Naphthoquinones; QSAR; surface tension; cytotoxic activity.

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 [4,5,1] and anticancer activities [6,7,8,9,10,11] they interfere with electron transport and oxidative phosphorylation processes and play roles in enzyme inhibition, and DNA cross linking [7].

Structure-property relationships are qualitatively or quantitatively empirically defined empirical relationships between molecular structure and observed properties. When the property being described is a physical property, such as the boiling point, this is referred to as a Quantitative Structure-Property Relationship (QSPR).When the property being described is a type of biological activity (such as a drug activity), this is referred to as a Quantitative Structure-Activity Relationship (QSAR) [12] and QSTR (Quantitative Structure-Toxicity Relationship) is the name applied to correlate molecular structure to the toxicological data [13].

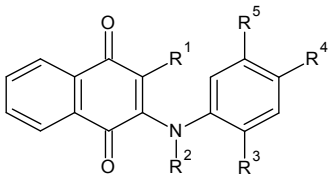
QSAR (Quantitative Structure Activity Relationships) have been applied for decades in the development of relationships between physicochemical properties of chemical substances and their biological activities to obtain a reliable mathematical and statistical model for prediction of the activities of new chemical entities [14].

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) [15].

2. MATERIALS AND METHODS

Biological data were obtained for Benites et al. [3] who reported the cytotoxicity of aminophenylnaphthaquinone derivatives against DU145 Cancerous, MCF7 Cancerous and T24 Cancerous (Table 1). The structures of these compounds (Table 2) 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, [16], 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 ED50 value (µg/mL) was defined as the concentration of compound which produced a 50% reduction in viability relative to the control in three independent experiments which defined the biological parameter for QSAR equations. Physicochemical parameters are calculated using the computer software ChemSketch/ ACDlab program version 12.01 (Table 1). 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 [17,18,19]. 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 [20,21].

Table 1. Structures of phenylaminonaphtoquinones derivatives



No.	R^1	R^2	R^3	R^4	R^5
1	H	H	H	H	H
2	Cl	H	H	H	H
3	H	H	Me	H	H
4	Cl	H	Me	H	H
5	H	H	H	OH	H
6	Cl	H	H	OH	H
7	H	H	H	OMe	H
8	H	H	OMe	H	OMe
9	Cl	H	OMe	H	OMe
10	H	Me	H	H	H
11	Cl	Me	H	H	H

3. RESULTS AND DISCUSSION

The correlation matrix of the used parameters MR, FW ,MV ST, RI , D and the biological activity for three cancer cell lines DU145, T24, and MCF7 shown on Table 4 which in the range between 0.814-0.07. It appears there is a strong relation between, MV,RI, ST and D same as relation between MR,FW,MV,RI and ST also as it between RI and ST with D. Also it appears that the biological activity for DU145 cancer cell line (pC_{DU145}) has good relation with RI, ST and D with Pearson correlation coefficient 0.691, 0.814 and 0.554 respectively. Same as the biological activity for MCF7cancer cell line (pC_{MCF7}) has good relation with Pearson correlation coefficient 0.512 and 0.554 against RI and ST respectively. Pearson correlation coefficient between pC_{MCF7} and descriptors less than 0.5 so that not used in employment of QSAR models. These features confirm with model on Table 5.

Table 2. Physicochemical parameters and biological activities of phenylaminonaphtoquinones derivatives for three cancer cell lines DU145 cancerous, MCF7 cancerous and T24 cancerous

No.	C_{DU145} (µg/mL)	C_{MCF7} (µg/mL)	C_{T24} (µg/mL)	Molar refractivity (cm^3)	Formula weight	Molar volume (cm^3)	Index of refraction	Surface tension (dyne/cm)	Density (g/cm^3)
1	4	2.6	1.2	72.12	249.26404	185.4	1.705	66.1	1.343
2	66.8	6.3	14.8	76.10	283.7091	202.9	1.673	59.7	1.39
3	7.7	0.8	7.7	76.95	263.29062	201.7	1.688	62.4	1.304
4	25.8	4.9	9.3	80.72	297.73568	218.6	1.659	57.5	1.36
5	0.9	0.8	2.3	74.00	265.26344	183.9	1.737	76.6	1.442
6	1.9	2.8	0.6	77.63	299.7085	199.8	1.704	70.6	1.49
7	7.6	3.7	8.1	78.80	279.29002	209.4	1.676	61.8	1.333
8	35.2	1.2	10.9	85.48	309.316	233.4	1.653	58.6	1.324
9	6	4.6	2.4	88.83	343.76106	246.6	1.639	58.2	1.39
10	20.9	7.8	8.4	76.83	263.29062	204.0	1.676	59.6	1.290
11	6.7	1.2	6	80.96	297.73568	217.9	1.665	58.2	1.36

C is the concentration as ED50 against certain cancer cell lines

Table 3. Correlation matrix of the physicochemical parameters used and the activity

	pC_{DU145}	pC_{MCF7}	pC_{T24}	MR	FW	MV	RI	ST	D
pC_{DU145}	1.000								
pC_{MCF7}	0.476	1.000							
pC_{T24}	0.812	0.137	1.000						
MR	-0.289	-0.083	-0.295	1.000					
FW	-0.159	-0.164	-0.231	0.923	1.000				
MV	-0.420	-0.184	-0.370	0.986	0.896	1.000			
RI	0.691	0.399	0.512	-0.839	-0.728	0.918	1.000		
ST	0.814	0.419	0.544	-0.610	-0.448	-0.729	0.933	1.000	
D	0.554	0.070	0.291	-0.048	0.305	-0.148	0.366	0.594	1.000

pC=-logC, MR molar refractivity, FW formula weight, MV molar volume, RI refractive index, ST surface tension and D density

Table 4. Observed and predicted biological activities of phenylaminonaphthoquinone derivatives expressed by model for cancer cell line DU145 cancerous

No.	$pC_{obsrv.}$	$pC_{pred.}$	ΔpC
1	5.4	5.31	0.09
2	4.18	4.93	-0.75
3	5.11	5.04	0.07
4	4.59	4.70	-0.11
5	6.05	6.18	-0.13
6	5.72	5.63	0.09
7	5.12	4.99	0.13
8	4.45	4.81	-0.36
9	5.22	4.65	0.57
10	4.68	4.86	-0.18
11	5.17	4.66	0.51

Table 5. The QSAR models between descriptors and biological activity

QSAR model	r2	F	s	sig.	Q2	s activity	s residual
pC_{DU145}=0.412+0.0742ST	0.662	17.646	0.34033	0.002	0.5657	0.555591	0.371482

r2 is the square correlation coefficient, F is F-test, s is standard deviation, sig. significant value, Q2 is the square cross-validated coefficient , s activity is the standard deviation of activities and s residual is the standard deviation of residuals

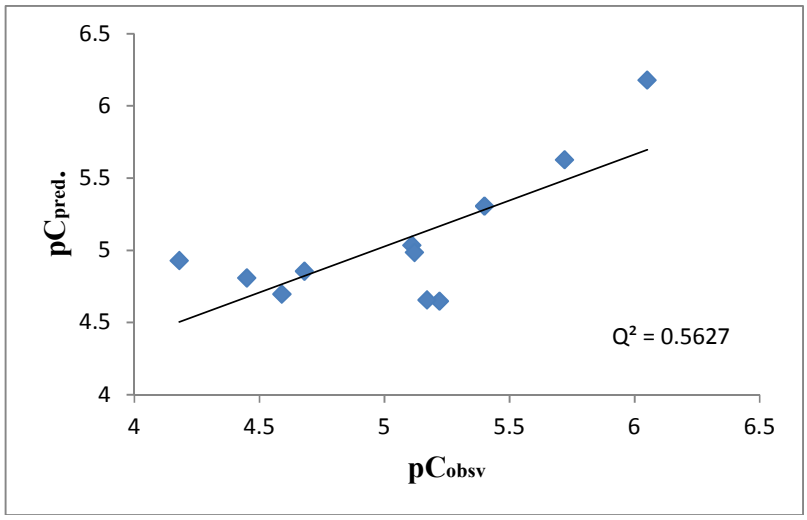


Fig. 1. Cross validation of model

More than 50 equations were employed between one-three descriptors and biological activity for each cancer cell line to find satisfy correlation. Between them, one QSAR models with mono-parametric regression equations (Table 5) were produced for DU145 cancer cell line in this study with accepted r2 value of 0.662, F= 17.646 and the overall significant level is better than 95%. This model contains ST descriptor Table 5. In order to confirm this model we used leave one out cross validation method Fig. 1 and the value of q2 is satisfied 0.5627.

The value of residual activity show in Table 5 and the standard deviation of all of them 0.371482 (Table 3) less than that of observed activities 0.555591. we suggest that surface tension of naphthoquinones plays major roles in the inhibiting activity against DU145 Cancerous.

4. CONCLUSION

The QSAR study of phenylaminonaphtoquinones for cancer cell line: DU145 (prostate) can be modeled using ST descriptor used to generate

model with very good statistical fit as evident from its r2=0.662, F=17.646, and s=0.34033 and we can suggest that the inhabitation of human prostate carcinoma is influenced mainly by, surface tension.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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