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Computer-Aided Design of Anticancer 1,4-Naphthoquinone Derivatives

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Authors' contributions

This work was carried out in collaboration between both authors. Author LHMA designed the study, performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript, managed the analyses of the study and the literature searches. Author AEMS revised the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: Evaluation the impact of *p*-naphthoquinones upon biological activities and extent based upon QSAR technique.
Study Design: QSAR Approach.
Methodology: About twelve - eleven naphthoquinones which have cytotoxic effect against eight cancer cell lines: L1210, P388, NCI-H358M, OVCAR-8, PC-3M DU145, T24 and MCF7 and partition coefficient descriptor was used to find good QSAR model.
Results: The biological activity and partition coefficient of naphthoquinones can be modeled with linear regression with negative coefficient and good satisfied statistical data for all these cancer cell lines
Conclusion: The inhibition of eight cancer cell lines is influenced mainly by partition coefficient.

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Keywords: Naphthoquinones; QSAR; partition coefficient; cytotoxic activity.

1. INTRODUCTION

Cancer is abnormal growth of the cells with the ability to spread in the other parts of the body, and in spite of the progress in the drugs field, but cancer still is the second cause of death in the world [1].

Quinones are defined as unsaturated cyclic diketones or tetraketones which derived from aromatic compounds by replacement of two or four H atoms into O atoms with any necessary rearrangement of double bonds which make them non-aromatic compounds although possessing a nucleus of six member ring of C-atoms [2]. Quinones are widely distributed in nature which can be isolated as dyes from the plant, microorganisms such as fungi, mosses and also from insects and marine organisms [3]. Quinones also present in many drugs which are used clinically in the therapy of solid cancers [1]. There are several studies on 1,4-quinone derivatives which demonstrate that the cytotoxic activities of 1,4-quinones depend on redox capability and lipophilicity [4].

The quinoid antitumor agents are oxidants which gain one or two electrons to give the corresponding semiquinone(Q^{-}) radical or hydroquinone(Q^{2-}) by reductase enzymes Fig. 1. The semiquinone radical anion can give its extra electron to dioxygen to give the original quinone(Q) and superoxide radical anion. This reaction sequence, initiated by bioreduction of the quinone followed by oxidation of the semiquinone, is known as redox-cycling, and it continues until the system becomes anaerobic. The hydroquinone formed via a two-electron reduction is stable and can undergo two pathways. It can be excreted by the organism in a detoxification pathway or can oxidizing with the original quinone to yield the semiquinone radical anion. Both the semiquinone and the superoxide radical anion can give the hydroxyl radical, which is the cause of DNA strand breaks [5,1].

Quinone derivatives may be toxic to cells by a number of mechanisms including redox cycling, arylation, intercalation, induction of DNA strands breaks, generation of free radicals and alkylation [6].

A number of quinone derivatives have been found to possess powerful pharmacological effects such as antibacterial [7,8,9], antifungal [10], anti-inflammatory [11], anti-malarials [12], antiproliferative [13], antineoplastic, antimycobacterial [14], antiprotozoal, antiviral [15], anti-tuberculosis [16-18,1,19-24].

Structure-property relationships are qualitatively or quantitatively empirically defined empirical relationships between molecular structure and observed properties. When this property is physical property as boiling point, it is called a Quantitative Structure-Property Relationship (QSPR) and a Quantitative Structure-Activity Relationship (QSAR) is called to biological activity [25] and QSTR (Quantitative Structure-Toxicity Relationship) is the name applied to correlate molecular structure to the toxicological data [26].

QSAR study saved the cost of product development and decreased the requirement for lengthy and expensive animal tests and reduced waste as green chemistry. The QSAR approach includes the following steps:

(1) collection of a data set; (2) sketching of the molecular structures; (3) minimization energy and geometry optimization of the structures; (4) generation of several molecular descriptors; (5) application of variable selection or/and methods data reduction of the calculated descriptors; (6) regression analysis; and finally (7) validation and prediction of the developed QSAR models [27].

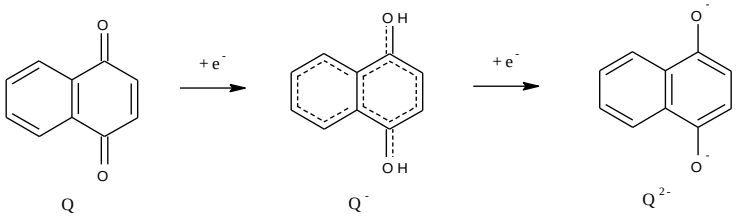


Fig. 1. Redox properties of naphthoquinones

Validation of QSAR models is a very important aspect to understand reliability of model for prediction of a new compound not present in the data set. There are two methods of validation internal validation and external validation [28].

On this basis, we modeled the biological activity of some selected naphthoquinones containing alkyl, amino, alkylamio groups and calculated octanol/water partition coefficient (logP) for these compounds. Then we evaluated of the impact of napthoquinones upon biological activities based upon QSAR technique.

2. MATERIALS AND METHODS

The biological activities of three different groups of naphthoquinone derivatives were collected from literatures [16,17,28,20] and these groups classified to alkylaminonaphthoquinones, alkylnaphthoquinones, and aminonaphthoquinones. The biological activities in these literatures express as ED_{50}, IC_{50} and $EC_{50}$where EC_{50}: Clinical efficacy of a drug, reported as the drug concentration required producing 50% of the maximum effect (may be inhibitory or stimulatory effect), IC_{50}: Concentration required producing 50% inhibition. The amount of inhibitor required depends on various factors, such as substrate concentration, target accessibility, cell permeability, duration of incubation, type of cells used, etc. and ED_{50} refers to the median effective dose (as opposed to concentration) at which 50% of individuals exhibit the specified quantal effect. It is a measure of reasonable expectance of a drug effect, but not necessarily equal to the prescribed dose [29].

The 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. The various regression equations were derived using multiple linear regression methods. In QSAR equations, r^2 is the square of correlation coefficient which reports the strength of the relationship between the set of independent variables and the dependent variable, [29], 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 [30].

Partition coefficients of alkylaminonaphthoquinone, alkylnaphthoquinone, and aminonaphthoquinone derivatives are calculated using the computer software ChemSketch/ ACDlab program version 12.01 as shown Tables 1, 2 and 3 respectively. 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 [24].

The best possible QSAR models were selected on the basis of the highest correlation coefficients r^2 and F-ratio, as well as the lowest standard deviations s. The selected models were additionally validated by cross validation method (leave one out) and plotted the observed activity (pC_{obsv}) against predicted activity (pC_{pred}) then the correlation coefficients q^2 were calculated.

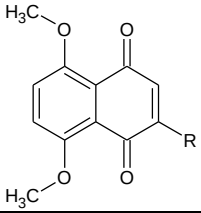
3. RESULTS AND DISCUSSION

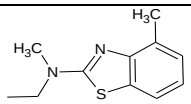
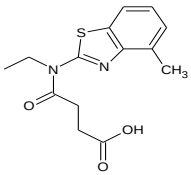
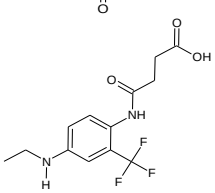
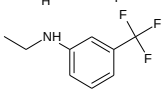
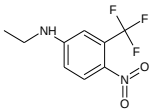
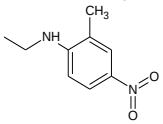
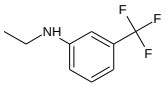
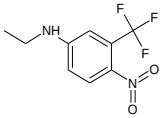
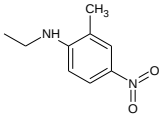
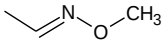
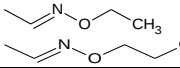
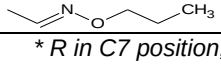
The values of calculated logP of alkylamino1,4-naphthoquinones are displayed within the range 2.17-5.09 and 4.49-11.41 for alkyl 1,4-naphthoquinones and 3.54-2.15 for amino1,4-naphthoquinones Tables 1, 2 and 3. According to these data, alkyl 1,4-naphthoquinones showed the lowest hydrophilicity and amino1,4-naphthoquinones the lowest hydrophobicity which confirm with the polarity of each substituent on them.

More than 125 equations were employed between partition coefficient and biological activity for each cancer cell lines to find satisfies correlation. Between them eight QSAR models were produced which contain ClogP descriptor in this study. For all these eight selected models r^2 = 0.856, 0.756, 0.714, 0.869, 0.867, 0.756, 0.889 and 0.881 (which are more than 0.6) respectively. Also, the standard deviation s of these eight models are equal 0.30422 , 0.22261, 0.08805, 0.0739, 0.08404, 0.28937, 0.12594 and 0.16374 which less than standard deviation of the biological data 0.765142, 0.48401, 0.148477, 0.201894, 0.203906, 0.555591, 0.35889 and 0.444653 respectively. F values equal 59.557, 24.841, 17.495, 46.244, 58.483, 27.858, 72.027 and 52.022 with overall significance level is better than 95% respectively Table 4.

In order to confirm these eight models we used cross validation method and the observed and predicted activities of different compounds were plotted Figs. 1, 2, 3, 4, 5, 6, 7 and 8 and Tables 5, 6 and 7 respectively with q^2 values 0.7995,

Table 1. Structures, biological activities [16], [17] and partition coefficients of 5,8-Dimethoxy-1,4-naphthoquinone derivatives for two cancer cell lines L1210 and P388



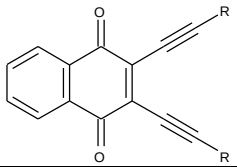
No.	R	C_{L1220} (µg/mL)	C_{P388} (µg/mL)	ClogP
1		1.21	0.56	4.67
2		4.76	4.19	4.09
3		8.92	0.36	2.17
4*		0.45	0.60	3.00
5*		0.61	0.21	3.50
6*		0.16	0.91	2.55
7		.18	0.67	4.59
8		0.19	0.13	5.09
9		0.05	2.24	4.14
10		4.97	2.29	2.39
11		5.10	2.76	2.92
12		5.28	0.56	3.46

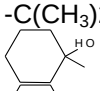
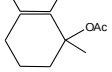
** R in C7 position,C is the concentration as* ED_{50} *against certain cancer cell lines*

0.5309, 0.5127, 0.8111, 0.7926, 0.6799, 0.8369 and 0.7928 respectively (more than 0.5). The standard deviation of residual activity 0.290218, 0.392425, 0.078773, 0.112002, 0.076577, 0.514244, 0.120466 and 0.163624 for eight models must be less than that of original data 0.765142, 0.48401, 0.148477, 0.201894, 0.203906, 0.555591, 0.35889 and 0.444653

respectively. These best-fitted mono-parametric models indicate that partition coefficient plays major roles in the inhibiting activity against lymphoid leukemia L1210, Lymphoid neoplasma P388, human ovarian adenocarcinoma (OVCAR-8), human metastatic prostate cancer (PC-3M), human bronchoalveolar lung carcinoma (NCI-H358M), DU145 (prostate), T24 (bladder) and MCF7 (breast) cancer cell lines. All models contain partition coefficient ClogP with negative sign which suggests that the compound with highly hydrophobic effect will be less active.Notice some models were modified by removed one or two compound from naphthoquinones set and this modification lead to better statistic values Table 4.

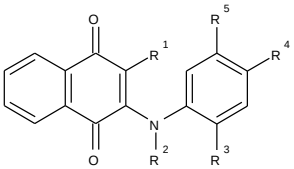
Table 2. Structures, biological activities [28] and partition coefficients of 2,3-Diyne-1,4-naphthoquinone derivatives for three cancer cell lines NCI-H358M, OVCAR-8 and PC-3M



No.	R	C $_{NCI-H358M}$ (μg/mL)	C $_{OVCAR-8}$ (μg/mL)	C $_{PC-3M}$ (μg/mL)	ClogP
1	Ph-	6.55	4.49	14.26	7.48
2	4-OMePh-	4.57	3.90	9.03	7.31
3	-C(CH_3)2OH	2.98	2.28	4.28	4.12
4	-C(CH_3)2OAc	4.95	5.63	5.74	5.91
5		5.07	5.98	6.56	5.79
6		2.74	3.09	5.26	7.59
7	-$(CH_2)_3CH_3$	6.23	6.56	8.94	7.16
8	- $(CH_2)_3OAc$	5.48	7.40	6.92	4.94
9	-$(CH_2)_2$ CH_3	8.03	9.01	9.17	6.10
10	-$(CH_2)_5$ CH_3	6.42	9.70	20.23	9.29
11	-$(CH_2)_7$ CH_3	3.99	7.53	17.70	11.41

C is the concentration as IC_{50} *against certain cancer cell lines*

Table 3. Structures, biological activities [20] and partition coefficients of phenylaminonaphtoquinones for three cancer cell lines DU145, MCF7 and T24



No.	R^1	R^2	R^3	R^4	C $_{DU145}$ (μg/mL)	C $_{MCF7}$ (μg/mL)	C $_{T24}$ (μg/mL)	ClogP
1	H	H	H	H	4	2.6	1.2	72.12
2	Cl	H	H	H	66.8	6.3	14.8	76.10
3	H	H	Me	H	7.7	0.8	7.7	76.95
4	Cl	H	Me	H	25.8	4.9	9.3	80.72
5	H	H	H	OH	0.9	0.8	2.3	74.00
6	Cl	H	H	OH	1.9	2.8	0.6	77.63
7	H	H	H	OMe	7.6	3.7	8.1	78.80
8	H	H	OMe	H	35.2	1.2	10.9	85.48
9	Cl	H	OMe	H	6	4.6	2.4	88.83
10	H	Me	H	H	20.9	7.8	8.4	76.83
11	Cl	Me	H	H	6.7	1.2	6	80.96

C is the concentration as EC_{50} *against certain cancer cell lines*

Table 4. The QSAR models between descriptors and biological activity

No.	QSAR model	r^2	F	s	sig.	Q^2	s activity	s residual
1	pC_{L1210}=6.714-0.0868ClogP	0.856	59.557	0.30422	0.000	0.856	0.765142	0.290218
2	pC_{P388}=6.490-0.0839ClogP	0.756	24.841	0.22261	0.001	0.729	0.48401	0.392425
3	$pC_{NCI-H358M}$ =5.602-0.00857ClogP	0.714	17.495	0.08805	0.004	0.726	0.148477	0.078773
4	$pC_{OVCAR-8}$=5.761 – 0.0136ClogP	0.869	46.244	0.07389	0.000	0.661	0.201894	0.112002
5	pC_{PC-3M} =5.308-0.00323ClogP	0.867	58.483	0.08404	0.000	0.869	0.203906	0.076577
6	pC_{DU145}=5.470-0.000778ClogP	0.756	27.858	0.28937	0.001	0.753	0.555591	0.514244
7	pC_{MCF7}=6.052-0.0447ClogP	0.889	72.027	0.12594	0.000	0.887	0.35889	0.120466
8	pC_{T24}= 5.978-0.0326ClogP	0.881	52.022	0.16374	0.000	0.865	0.444653	0.163624

r^2 is the square correlation coefficient, F is F-test, s is standard deviation, sig. significant value, Q^2 is the square cross-validated coefficient , s activity is the standard deviation of activities and s residual is the standard deviation of residuals

Table 5. Observed and predicted biological activities of 5,8-dimethoxy-1,4-naphthoquinone derivatives expressed by models 1 and 2

No.	Model 1 for L1220			Model 2 for P338		
	$pC_{obsrv.}$	$pC_{pred.}$	ΔpC	$pC_{obsrv.}$	$pC_{pred.}$	ΔpC
1	5.92	6.22	-0.30	6.25	6.15	0.10
2	5.32	5.02	0.30	5.38	5.82	-0.44
3*	5.05	5.03	0.02	4.39	4.21	0.18
4	6.35	6.60	-0.25	6.44	6.19	0.26
5	6.21	6.53	-0.32	6.22	6.16	0.06
6	6.80	6.68	0.12	6.68	6.20	0.48
7	6.74	6.64	0.10	6.04	6.12	-0.07
8	6.72	6.63	0.09	6.17	6.13	0.04
9	7.30	6.70	0.60	6.89	6.20	0.69
10	5.30	5.68	-0.38	5.65	6.09	-0.44
11	5.29	5.42	-0.13	5.64	6.06	-0.42

** Outlier in eq.2*

Table 6. Observed and predicted biological activities of 2,3-diyne-1,4-naphthoquinone expressed by derivatives models 3, 4 and 5.

No.	Model 3 for NCI-H358M			Model 4 for OVCAR-8			Model 5 for PC-3M		
	$pC_{obsrv.}$	$pC_{pred.}$	ΔpC	$pC_{obsrv.}$	$pC_{pred.}$	ΔpC	$pC_{obsrv.}$	$pC_{pred.}$	ΔpC
1	5.18	5.21	-0.03	5.35	5.32	0.02	4.85	4.96	-0.11
2	5.34	5.33	0.01	5.41	5.36	0.05	5.04	5.09	-0.05
3	5.53	5.49	0.04	5.64	5.48	0.16	5.37	5.25	0.12
4	5.31	5.36	-0.05	5.25	5.33	-0.08	5.24	5.20	0.04
5	5.29	5.36	-0.07	5.22	5.32	-0.09	5.18	5.19	-0.01
6	5.56	5.43	0.13	5.51	5.39	0.12	5.28	5.18	0.10
7	5.21	5.24	-0.03	5.18	5.24	-0.06	5.05	5.10	-0.05
8	5.26	5.38	-0.12	5.13	5.31	-0.17	5.16	5.20	-0.04
9	5.10	5.21	-0.11	5.05	5.19	-0.14	5.04	5.13	-0.09
10	5.19	5.13	0.06	5.01	4.96	0.05	4.69	4.70	-0.01
11*	5.40	5.24	0.16	5.12	4.99	0.13	4.75	4.66	0.09

** Outlier in eq.3*

Table 7. Observed and predicted biological activities of phenylaminonaphtoquinones derivatives expressed by models 6, 7 and 8

No.	Model 6 for DU145			Model 7 for MCF7			Model 8 for T24		
	$pC_{obsrv.}$	$pC_{pred.}$	ΔpC	$pC_{obsrv.}$	$pC_{pred.}$	ΔpC	$pC_{obsrv.}$	$pC_{pred.}$	ΔpC
1	5.18	5.21	-0.03	4.85	4.96	-0.11	5.35	5.32	0.02
2	5.34	5.33	0.01	5.04	5.09	-0.05	5.41	5.36	0.05
3	5.53	5.49	0.04	5.37	5.25	0.12	5.64	5.48	0.16
4	5.31	5.36	-0.05	5.24	5.20	0.04	5.25	5.33	-0.08
5	5.29	5.36	-0.07	5.18	5.19	-0.01	5.22	5.32	-0.09
6	5.56	5.43	0.13	5.28	5.18	0.10	5.51	5.39	0.12
7	5.21	5.24	-0.03	5.05	5.10	-0.05	5.18	5.24	-0.06
8	5.26	5.38	-0.12	5.16	5.20	-0.04	5.13	5.31	-0.17
9	5.10	5.21	-0.11	5.04	5.13	-0.09	5.05	5.19	-0.14
10	5.19	5.13	0.06	4.69	4.70	-0.01	5.01	4.96	0.05
11*	5.40	5.24	0.16	4.75	4.66	0.09	5.12	4.99	0.13

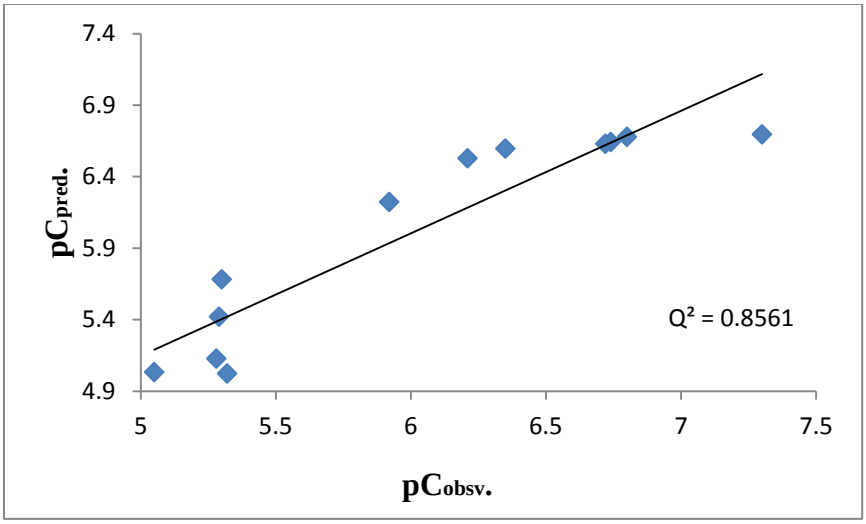


Fig. 2. Cross validation of model 1

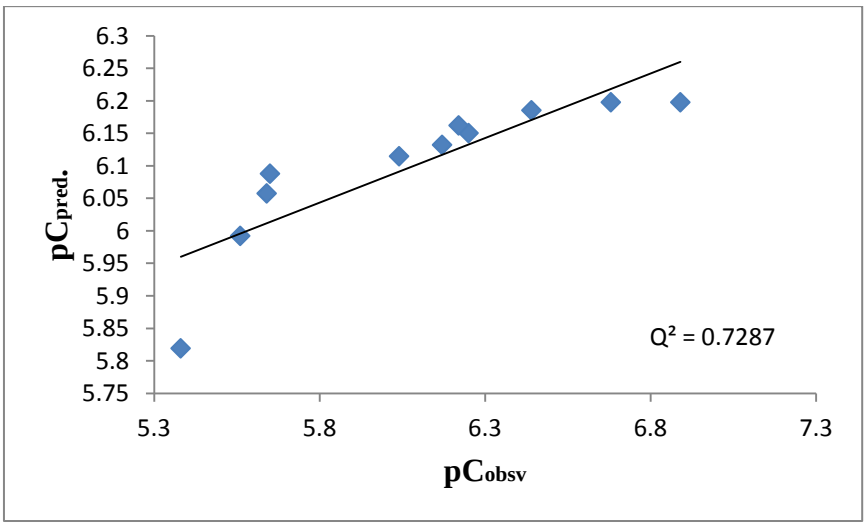


Fig. 3. Cross validation of model 2

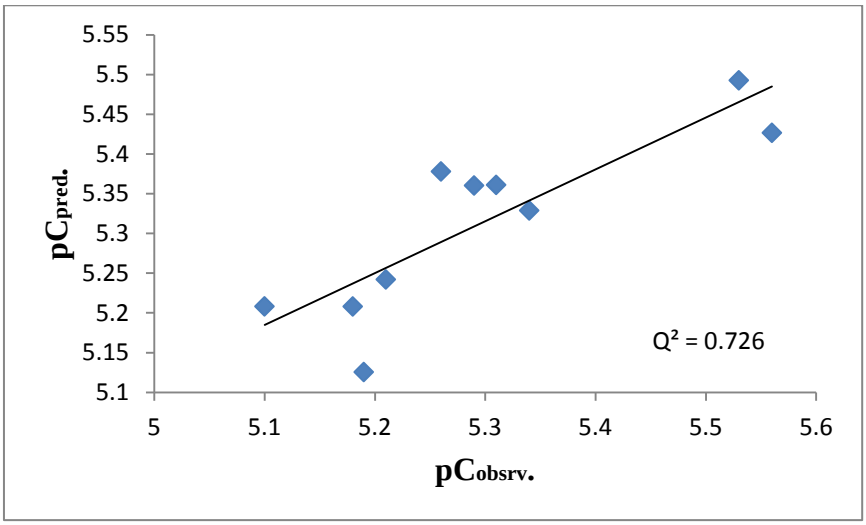


Fig. 4. Cross validation of model 3

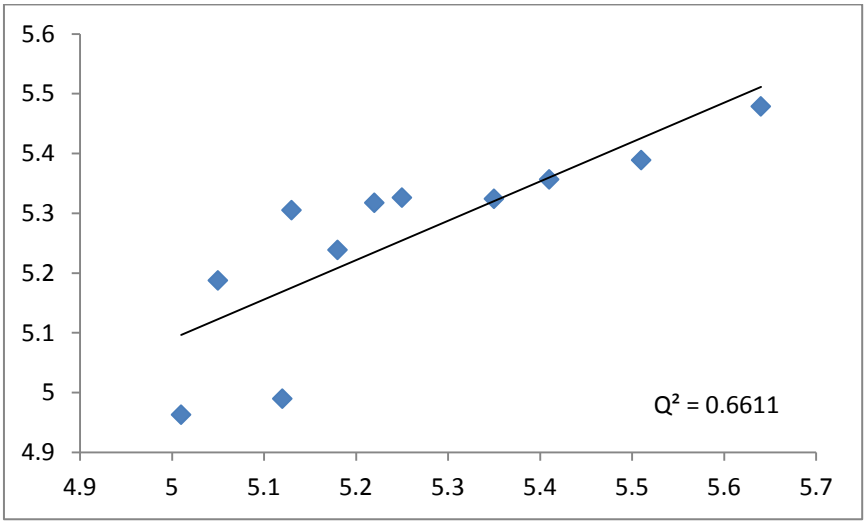


Fig. 5. Cross validation of model 4

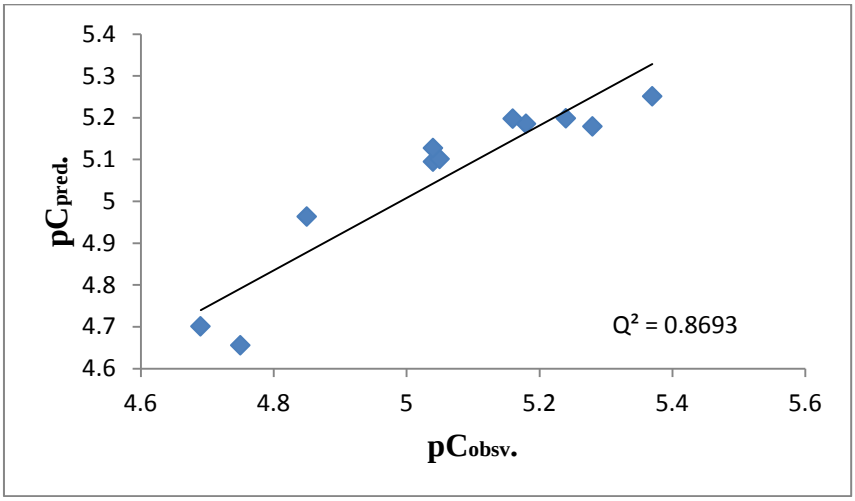


Fig. 6. Cross validation of model 5

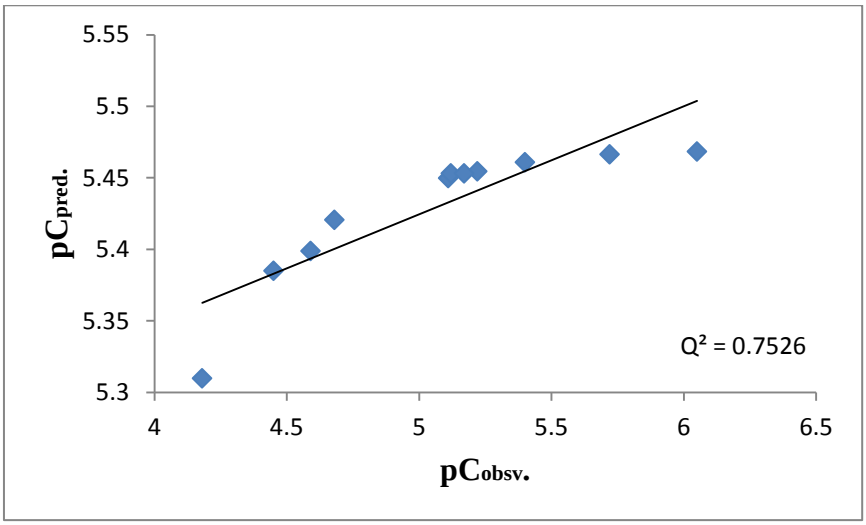


Fig. 7. Cross validation of model 6

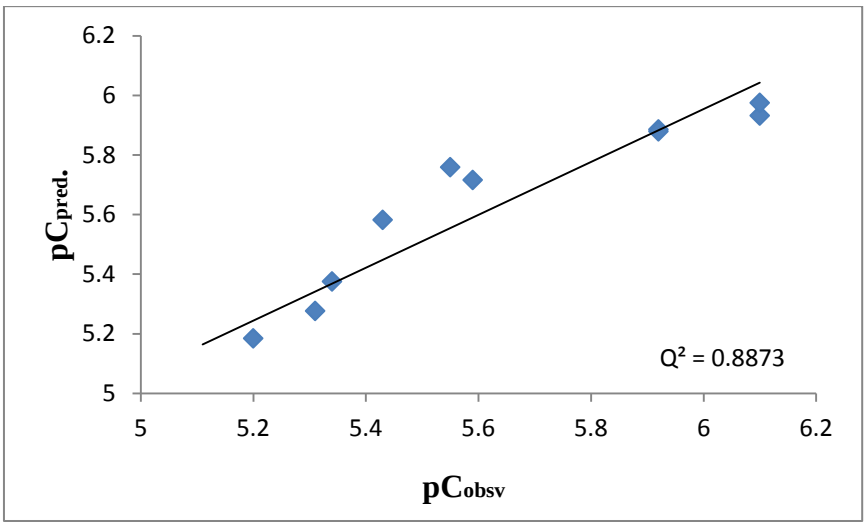


Fig. 8. Cross validation of model 7

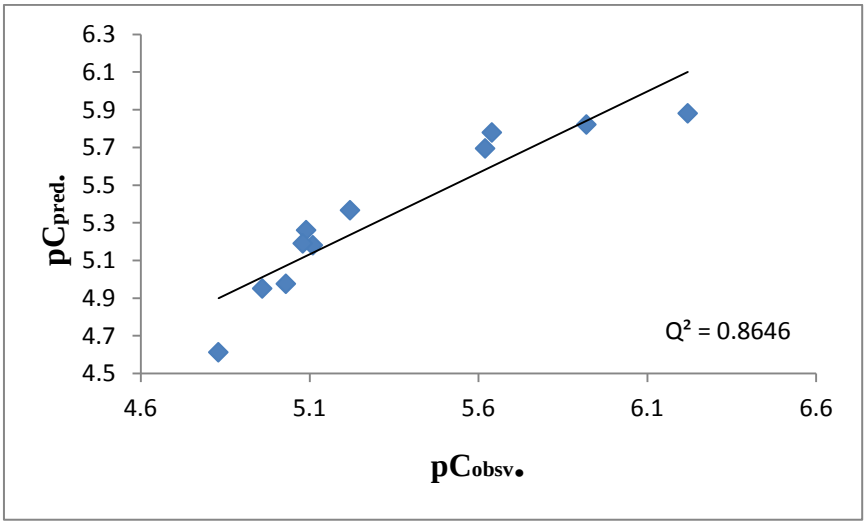


Fig. 9. Cross validation of model 8

4. CONCLUSION

The study indicated that QSAR of biological activity represented of 1,4-naphthaquinone derivatives against different cancer cell lines can be modeled using ClogP. These models are linear models The inhibition of eight different cancer cell lines is influenced mainly by hydrophobicity.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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