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Research Article

QSAR MODELING OF 2-[CH(OH)X]-5,8-$(OY)_2$-1,4-NAPHTHOQUININES AGAINST L1210 CELLS USING MULTIPLE LINEAR REGRESSION

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ABSTRACT

Quinones are present in many drugs such as anthracyclines, daunorubicin, doxorubicin, mitomycin, mitoxantrones and saintopin, which are used clinically in the therapy of solid cancers. The cytotoxic effects of these quinone are mainly due to the inhibition of DNA topoisomerase-II. It is the necessity to develop the 1,4-Naphthoquinone analogues with Cytotoxic effect. Here 2-[CH(OH)X]-5,8-$(OY)_2$-1,4-Naphthoquinines analogues have been used to correlate the cytotoxic activity with the Eccentric Connectivity index (ECI), Fragment Complexity (FC) and McGowan Volumes (MG) for studying the Quantitative Structure Activity Relationship (QSAR). Correlation may be an adequate predictive model which can help to provide guidance in designing and subsequently yielding greatly specific compounds that may have reduced side effects and improved pharmacological activities. We have used Multiple Linear Regression (MLR), one of the best methods for developing the QSAR model. Results from this QSAR study have suggested that ECI, FC and MG are the important descriptors for cytotoxic activities of 1,4-Naphthoquinones against L1210 cells. For the validation of the developed QSAR model, statistical analysis such as data point-descriptor ratio, fraction of variance, cross validation test, standard deviation, quality factor, Fischer's test; and internal validation such as Y-randomization test have been performed and all the tests validated this QSAR model.

Key words: 1,4-Naphthoquinones, QSAR, Eccentric connectivity index, Fragment complexity, McGowan Volume, Multiple Linear Regression

INTRODUCTION

Quinones of various chemical families serve as biological modulators and both synthetic and natural quinones are used as drugs (McIntire, 1998; Meganathan, 2001; Lee, 1999; Begleiter, 2000). The well known members of the family are doxorubicin and daunorubicin, the first identified anthracyclines (Di Marco *et al.,* 1981). Synthetic epirubicin and mitoxantrone are well known examples of other quinines as anti-cancer agents (Arcamone and Cassinelli, 1998).

Quinones also form a class of toxic metabolites generated by the metabolism of phenols, 1-naphthol, and diethyl-stilbesterol. The mechanisms by which quinones exert their toxic effects are complex, but two processes appear to be involved: the direct arylation of sulfhydryls, and the generation of active oxygen species via redox cycling. Certain quinones have been shown to be mutagenic via the active oxygen species and others via their conversion to DNA-binding semiquinone free radicals. Paradoxically, quinones are not only mutagenic and therefore potentially carcinogenic; they are also effective anticancer agents. The design of novel quinones that are more selective in their toxicity to human tumor cells and whose mechanism of action is understood seems a promising approach in cancer treatment, especially if host toxicity can be prevented via the use of chemo protective agents (Martyn and Smith, 1985).

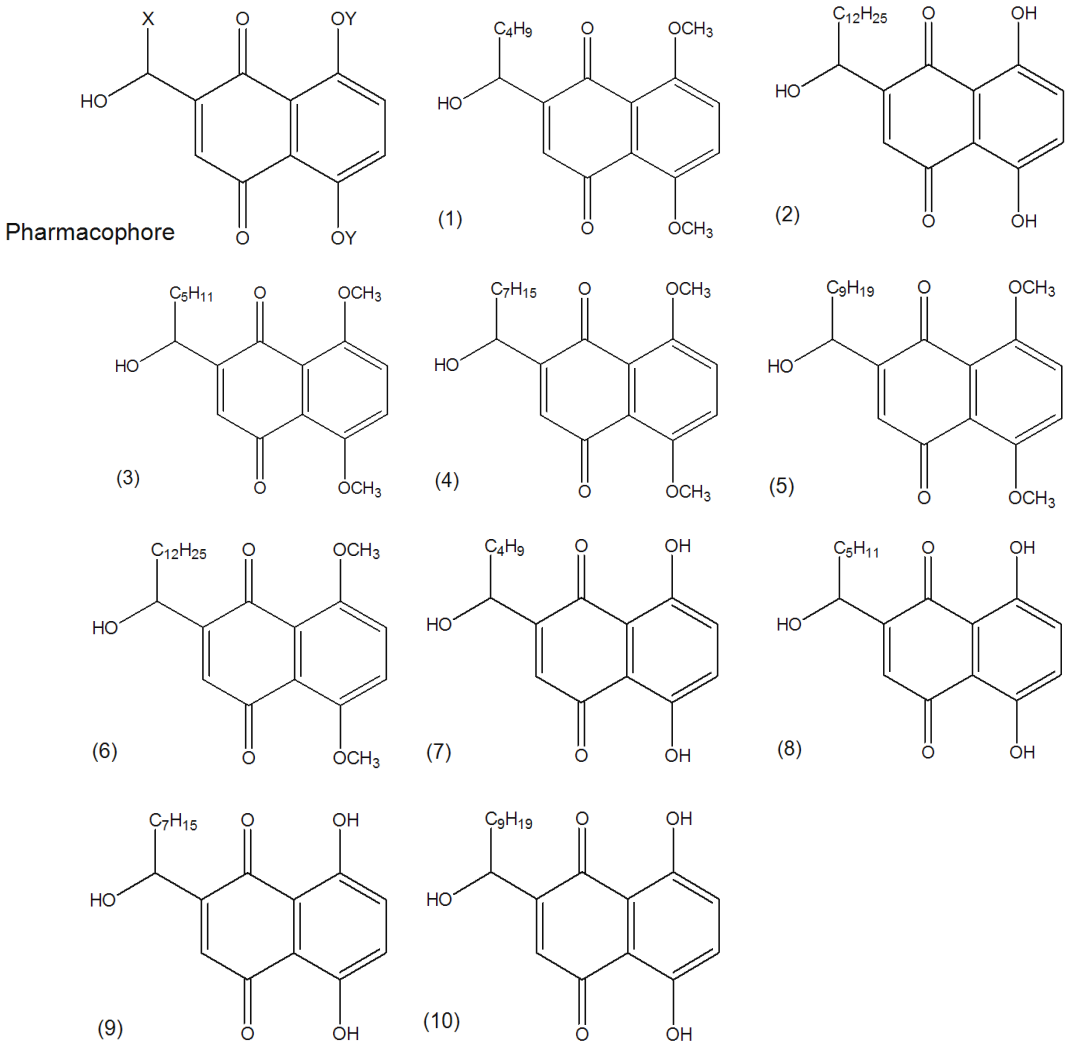

Figure 1. 2D structure of 2-[CH(OH)X]-5,8-(OY)$_2$-1,4-Naphthoquinones pharmacophore for which the QSAR model has been developed and the derivatives

In the present study, we developed a Quantitative Structure Activity Relationship (QSAR) model on a series of 2-[CH(OH)X]-5,8-(OY)$_2$ -1,4-Naphthoquinones with respect to their cytotoxity against L1210 Cells. The QSAR studies are perfect tool for understanding the drug design process in terms of their chemical-pharmacological activity interaction, along with it is also used in toxicology and pesticide research. QSAR studies can focus on mechanism of action of ligands with human, bacteria, virus, membranes, enzymes etc. It can also be used for the evaluation of the metabolism, absorption, distribution and excretion phenomena. The QSAR methodology comprises of computationally derived descriptors to correlate with pharmacological activities. These descriptors are principally of four types such as electronic, stearic, hydrophobic and topological indices (Verma *et al.,* 2010). The descriptors used by us for developing the QSAR model are Eccentric Connectivity Index (ECI) (Sardana and Madan, 2003), Fragment complexity (FC) (Gregg, *et al.,* 2007) and McGowan's volume (MG) (Michael *et al.,* 2004).

METHODOLOGY

All the bioactivity values and information about 2D structure of 2-[CH(OH)X]-5,8-$(OY)_2$ -1,4-Naphthoquinones derivatives were taken from literature (Rajeshwar and Verma, 2006). IC_{50} is referred as the molar concentration of a compound that inhibits 50% growth of bacteria (Verma *et al.,* 2010; Chowdhury *et al.*, 2012); log1/C is subsequent variable that comprises the bioactivity parameter for the QSAR model. In order to calculate the 2D molecular descriptors, PaDEL descriptor software (Yap, 2011) which incurporate CDK library for descriptor calculation have been used. For the development of QSAR model, Multiple Linear Regression has been employed (Verma *et al.,* 2010).

Statistical parameters

In the QSAR model, number of data points is denoted as n, squared correlation coefficient as r^2 (fraction of variance), cross-validated r^2 is denoted as q^2, s is standard deviation, RMSD is root mean square deviation, variance. Q is quality factor, where Q= r/s (here r is correlation coefficient and s is standard deviation). Fischer statistics is denoted by F.

Model validation

The QSAR model validation was carried with statistical analysis and with internal validation.

RESULT AND DISCUSSION

The 2D structure of 2-[CH(OH)X]-5,8-$(OY)_2$-1,4-Naphthoquinones pharmacophore for which the QSAR model has been developed and the derivatives are shown in figure 1. From the data in table I, QSAR equation have been developed where number of data point (n) is 10, is given below, here 95% confidence intervals are given in parentheses.

log(1/C) = 11.103 (± 6.302) + 0.01 (± 0.005) (ECI) - 0.001 (± 0.0024732) (FC) - 2.85 (± 3.976) (MG)

Validation of QSAR model

A quantitative assessment of model robustness has been performed through model validation. All the statistical results of model validation have been given in table II.

Fraction of variance (r^2)

The value of fraction of variance may vary between 0 (means model without explanatory power) and 1 (means perfect model). QSAR model having $r^2 > 0.6$ will only be considered for validation (Verma *et al.,* 2010; Sharma *et al.*, 2009). The value for this QSAR model is 0.9293.

Cross-validation test (q^2)

A QSAR model must have $q^2 > 0.5$ for the predictive ability (Verma *et al.,* 2010; Sahu *et al.*, 2012). The value of q^2 for this QSAR model is 0.9293.

Standard deviation (s)

The smaller s value is always required for the predictive QSAR model. The value of s for this QSAR model is 0.57.

r^2-q^2 < 0.3

The difference between r^2 and q^2 should never be exceed by 0.3. A large difference suggests the following: presence of outliers, over-fitted model, and presence of irrelevant variables in data (Verma *et al.,* 2010). The value of r^2-q^2 for this QSAR model is 0.

Quality factor (Q)

Over fitting and chance correlation, due to excess number of descriptors, can be detected by Q value. Positive value for this QSAR model suggests its high predictive power and lack of overfitting (Verma *et al.,* 2010).

Fischer statistics (F)

The F value of QSAR model was compared with their literature value at 95% level. The F value of this QSAR model is 26.2885 (where $F > F_{lit}$) suggests that the QSAR model is statistically significant at 95% level (Verma *et al.,* 2010).

Internal validation
Y-Randomization test

To establish the QSAR model robustness, this technique is being used widely. For this test, the dependent variable vector is randomly shuffled, and a new QSAR model is developed using the unchanged independent variable. This process was repeated for five times. The statistical data of r^2 for five runs are given in table III.

Table I. Descriptors used to derive QSAR equation along with bioactivities 2-[CH(OH)X]-5,8-$(OY)_2$ -1,4-Naphthoquinones analogues with substituents X , Y

X	Y	log 1/IC			ECI	FC	MG
		Obs.	Pred.	Resid.			
C_4H_9	CH_3	6.52	6.226286	0.293714	371	1387.05	2.3222
$C_{12}H_{25}$	H	6.1	6.131223	-0.03122	825	2965.05	3.1676
C_5H_{11}	CH_3	6.05	6.056366	-0.00637	426	1610.05	2.4631
C_7H_{15}	CH_3	5.54	5.768087	-0.22809	548	2104.05	2.7449
C_9H_{19}	CH_3	5.43	5.548557	-0.11856	686	2662.05	3.0267
$C_{12}H_{25}$	CH_3	5.37	5.275251	0.094749	916	3619.05	3.4494
C_4H_9	H	6.85	7.076011	-0.22601	317	989.05	2.0404
C_5H_{11}	H	7	6.923798	0.076202	369	1180.05	2.1813
C_7H_{15}	H	6.7	6.650101	0.049899	483	1610.05	2.4631
C_9H_{19}	H	6.52	6.42432	0.09568	611	2104.05	2.7449

Table II. Results of statistical validation

r^2	q^2	s	$r^2 - q^2 < 0.3$	Q	F	RMSD	variance
0.9293	0.9293	0.57	0	1.6912	26.2885	0.0480491	0.0384786

Table III. Results of internal validation: Y-randomization test (5 runs)

	Shuffled observed log 1/C				
	Run 1	Run 2	Run 3	Run 4	Run 5
1	5.43	6.1	6.85	5.54	7
2	6.52	6.52	7	5.43	6.7
3	7	7	6.7	5.37	6.52
4	6.7	6.7	6.52	6.85	5.43
5	6.52	6.52	6.52	7	5.37
6	5.37	5.37	6.1	6.7	6.85
7	6.85	6.85	6.05	6.52	6.52
8	6.05	6.05	5.54	6.52	6.1
9	5.54	5.54	5.43	6.1	6.05
10	6.1	5.43	5.37	6.05	5.54
r^2	0.0757	0.2048	0.2944	0.1209	0.3758

The values $r^2<0.6$ in Y-randomization test confirm the robustness of this QSAR model (Verma *et al.,* 2010).

According to the developed QSAR model, the 2-[CH(OH)X]-5,8-$(OY)_2$-1,4-Naphthoquinones must have positive Eccentric Connectivity Index for enhanced cytotoxic action against L1210 cells at X and Y substituents. A negative coefficient of Fragment Complexity containing X and Y substituents also elevate the activity of 2-[CH(OH)X]-5,8-$(OY)_2$ -1,4-Naphthoquinones derivatives towards its cytotoxic action. Moving towards the effects of the McGowan Volume on the bioactivity of derivatives of 2-[CH(OH)X]-5,8-$(OY)_2$ -1,4-Naphthoquinones, the developed QSAR model suggest that a negative elevation in MG at substituent X and Y will definitely be favorable to the activity, as discussed by R. P. Verma and Corwin Hansch (Verma *et al.,* 2010) in 2010, Ajeet *et al.,* (2012) in 2012 and Ajeet (Ajeet, 2012) in 2012. A comparison (multiple linear regression plots) of observed values and predicted values of log(1/C) for 2-[CH(OH)X]-5,8-$(OY)_2$-1,4-Naphthoquinones derivatives used for

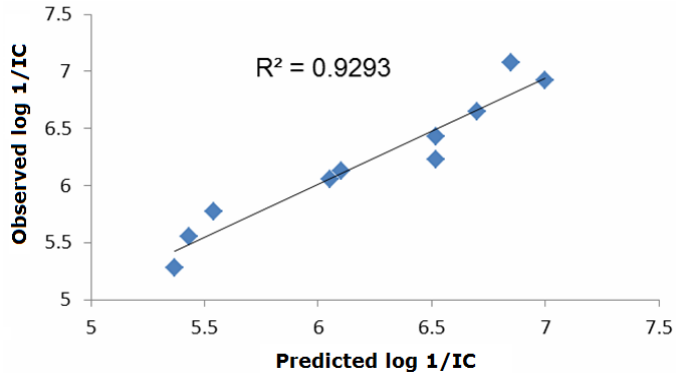

Figure 2. Multiple linear regression plot for QSAR study

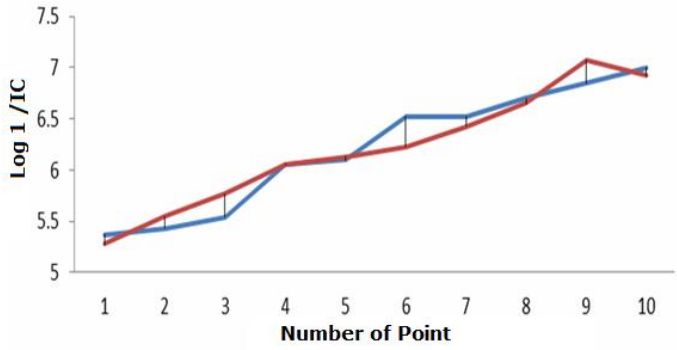

Figure 3. Multiple linear graph between No. of data points and bio-activities

development of QSAR equation is shown in Figure 2 and multiple linear graph is shown in Figure 3.

CONCLUSION

An analysis of developed QSAR model reflects a number of important points. Firstly it reveals that ECI, FC and MG are essential descriptors for the development of 2-[CH(OH)X]-5,8-$(OY)_2$-1,4-Naphthoquinones derivatives. The developed QSAR model equation suggest that cytotoxic activity in terms of inhibition concentration might be improved by increasing the eccentric connectivity index by making modification at X, Y substituents of the 2-[CH(OH)X]-5,8-$(OY)_2$-1,4-Naphthoquinones pharmacophore along with ensuring that fragment complexity and McGowan Volume should be reduced simultaneously at the same X, Y substituents.

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