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Research Article

QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP (QSAR) MODELING OF 2-X-5,8-DIMETHOXY-1,4-NAPHTHOQUINONES AGAINST L1210 CELLS

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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 quinones are mainly due to the inhibition of DNA topoisomerase-II. It is the necessity to develop the 1,4-Naphthoquinones analogues with impact Cytotoxic effect. Here 2-X-5,8-Dimethoxy-1,4-Naphthoquinones 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 of1,4-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.

Keywords: 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[1-4]. The well known members of the family are doxorubicin and daunorubicin, the first identified anthracyclines[5]. Synthetic epirubicin and mitoxantrone are well known examples of other quinines as anti-cancer agents[6].

Quinones too form a class of toxic metabolites generated by the metabolism of phenols, -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[7].

In the present study, we developed a Quantitative Structure Activity Relationship (QSAR) model on a series of 2-X-5,8-Dimethoxy-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[8]. The descriptors used by us for developing the QSAR model are Eccentric Connectivity Index (ECI)[9], Fragment complexity (FC)[10] and McGowan's volume (MG)[11].

MATERIALS AND METHOD

All the bioactivity values and information about 2D structure of **2-X-5,8-Dimethoxy-1,4-Naphthoquinones** derivatives were taken from literature[12]. IC_{50} is referred as the molar concentration of a compound that inhibits 50% growth of bacteria[8, 14]; 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[13] which incorporate CDK library for descriptor calculation have been used. For the development of QSAR model, Multiple Linear Regression has been employed[8].

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.

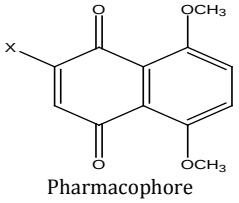
Model Validation

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

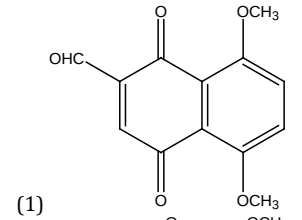
RESULT

The 2D structure of **2-X-5,8-Dimethoxy-1,4-Naphthoquinones** pharmacophore for which the QSAR model has been developed and the derivatives are shown in Table 1.

Table 1: 2D structure of 2-X-5,8-Dimethoxy-1,4-Naphthoquinones pharmacophore for which the QSAR model has been developed and the derivatives.



Pharmacophore



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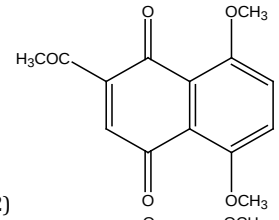

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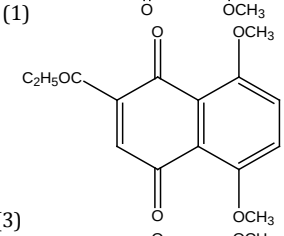

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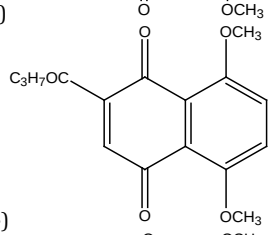

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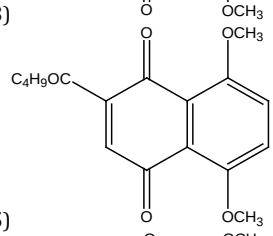

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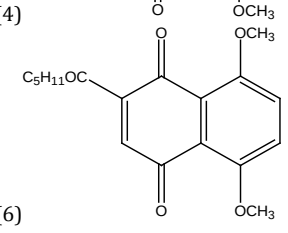

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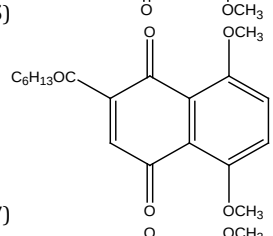

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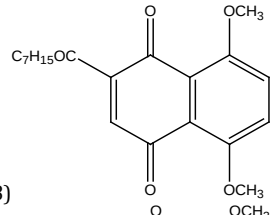

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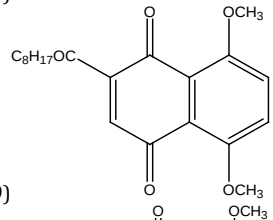

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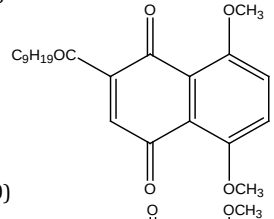

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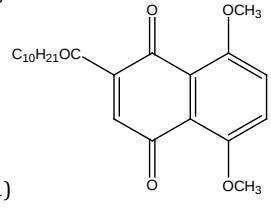

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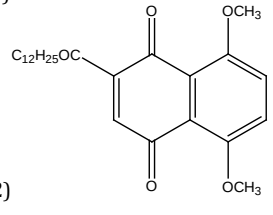

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Table 2: Descriptors used to derive QSAR equation along with bioactivities 2-X-5,8-Dimethoxy-1,4-Naphthoquinones analogues with substituents X

No.		log 1/C_{50}			ECI	FC	MG
	X	Observed	Predicted	Residuals			
1	CHO	6.39	6.36511	0.02489	221	535.05	1.7156
2	$COCH_3$	5.8	5.886438	-0.08644	686	2434.05	2.9837
3	COC_2H_5	5.66	5.771916	-0.11192	760	2725.05	3.1246
4	COC_3H_7	5.61	5.512141	0.097859	916	3355.05	3.4064
5	COC_4H_9	6.38	6.382126	-0.00213	236	682.05	1.8565
6	COC_5H_{11}	6.25	6.364917	-0.11492	275	845.05	1.9974
7	COC_6H_{13}	6.34	6.333718	0.006282	320	1024.05	2.1383
8	COC_7H_{15}	6.31	6.288527	0.021473	371	1219.05	2.2792
9	COC_8H_{17}	6.3	6.231594	0.068406	426	1430.05	2.4201
10	COC_9H_{19}	6.28	6.161795	0.118205	486	1657.05	2.561
11	$COC_{10}H_{21}$	6.11	6.082501	0.027499	548	1900.05	2.7019
12	$COC_{12}H_{25}$	5.94	5.989217	-0.04922	616	2159.05	2.8428

From the data in Table 2, QSAR equation have been developed where number of data point (n) is 12, is given below, here 95% confidence intervals are given in parentheses.

log (1/C) = 5.632753(±2.147214) - 0.0011241(±0.0107101)(ECI) - 0.0004529(±0.0030883)(FC) + 0.7129277(±1.13739)(MG)

Table 3: Results of statistical validation

n/p ≥ 4	r^2	q^2	s	r^2- q^2 < 0.3	Q	F	RMSD	variance
4	0.9275	0.9274	0.2755	0.0001	3.4954	34.1149	0.02136	0.008216

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 3.

Statistical Analysis

1. **n/p ratio**: $\frac{n}{p} \geq 4$, where n is the number of data points and p is the number of descriptors used in the QSAR model. The model obeys the condition.
2. **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[8, 15]. The value for this QSAR model is 0.9275.
3. **Cross-Validation Test (q^2):** A QSAR model must have $q^2 > 0.5$ for the predictive ability[8,16]. The value of q^2 for this QSAR model is 0.9274.
4. **Standard deviation (s):** The smaller s value is always required for the predictive QSAR model. The value of s for this QSAR model is 0.2755.
5. **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[8]. The value of r^2-q^2 for this QSAR model is 0.0001.
6. **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[8].
7. **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 34.1149 (where $F > F_{lit}$) suggests that the QSAR model is statistically significant at 95% level[8].

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 4. The values r^2<0.6 in Y-randomization test confirm the robustness of this QSAR model[8].

Table 4: Results of internal validation: Y-randomization test (5 runs)

S. No.	Shuffled observed log 1/C				
	Run 1	Run 2	Run 3	Run 4	Run 5
1	5.8	6.39	6.39	6.34	5.61
2	6.39	6.38	5.8	6.31	6.38
3	5.66	5.66	6.25	6.25	6.25
4	6.34	5.61	5.61	6.28	6.34
5	6.38	5.8	6.38	6.11	6.31
6	6.25	6.25	6.25	5.94	6.25
7	5.61	6.34	5.94	6.39	6.28
8	6.31	6.31	6.31	5.8	6.11
9	6.25	5.94	5.66	5.66	5.94
10	6.28	6.28	6.28	5.61	6.39
11	6.11	6.11	6.11	6.38	5.8
12	5.94	6.25	6.34	6.25	5.66
r^2	0.1291	0.5247	0.3338	0.2804	0.4681

DISCUSSION

According to the developed QSAR model, the 2-X-5,8-Dimethoxy-1,4-Naphthoquinones must have less or negative Eccentric Connectivity Index for enhanced cytotoxic action against L1210 cells at X substituent. A negative coefficient of Fragment Complexity containing X substituent also elevated the activity of 2-X-5,8-Dimethoxy-1,4-Naphthoquinones derivatives towards its cytotoxic action. Moving towards the effects of the McGowan Volume on the bioactivity of derivatives of 2-X-5,8-Dimethoxy-1,4-Naphthoquinones, the developed QSAR model suggest that an increment or positive elevation in MG at substituent X will definitely be favorable to the activity, as discussed by R. P. Verma and Corwin Hansch[8] in 2010, Ajeet et al[17] in 2012 and Ajeet[18] in 2012. A comparison (multiple linear regression plots) of observed values and predicted values of log(1/C) for 2-X-5,8-Dimethoxy-1,4-Naphthoquinones derivatives used for development of QSAR equation is shown in Figure 1 and multiple linear graph is shown in Figure 2.

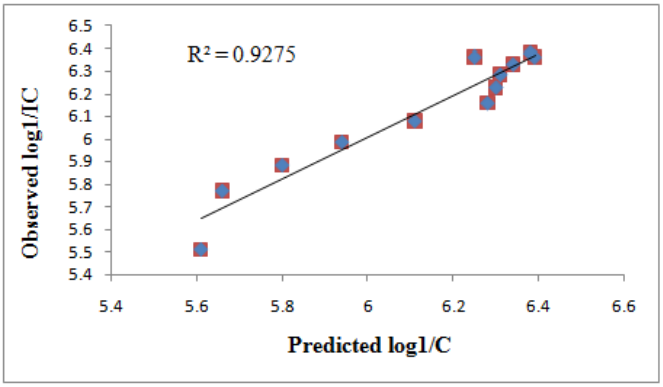

Fig. 1: Multiple linear regression plot for QSAR study

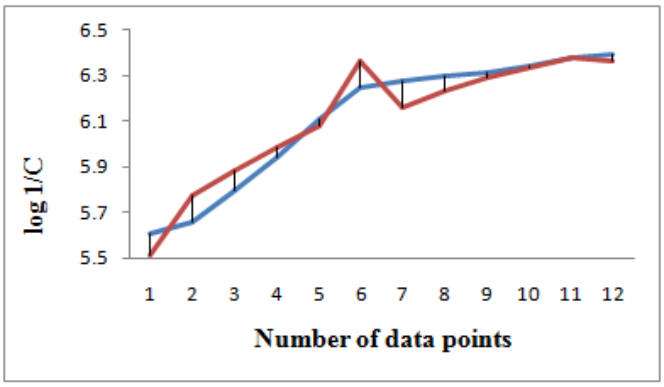

Fig. 2: Multiple linear graph between No. of data points and bioactivities

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-X-5,8-Dimethoxy-1,4-Naphthoquinones derivatives. The developed QSAR model equation suggest that cytotoxic activity in terms of inhibition concentration might be improved by decreasing the fragment complexity by making modification at X substituent of the 2-X-5,8-Dimethoxy-1,4-Naphthoquinones pharmacophore along with ensuring that eccentric connectivity index should be reduce simultaneously at the same X substituent while the substituent should enhance the McGowan Volume of the designed molecule.

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REFERENCES

1. McIntire WS Newly discovered redox cofactors: possible nutritional, medical and pharmacological relevance to higher animals. Annu Rev Nutr 1998; 18:145–177.
2. Meganathan R Biosynthesis of menaquinone (vitamin K2) and ubiquinone (coenzyme Q): a perspective on enzymatic mechanisms. Vitam Horm 2001; 61:173–218.
3. Lee KH Novel antitumor agents from higher plants. Med Res Rev 1999; 19**:** 569–596.
4. Begleiter A Clinical applications of quinone-containing alkylating agents. Front Biosci 2000; 5**:** E153–E171.
5. Di Marco A, Cassinelli G, and Arcamone F The discovery of daunorubicin. Cancer Treat Rep 1981; 65**:** 3–8.
6. Arcamone F and Cassinelli G Biosynthetic anthracyclines. Curr Med Chem 1998; 5**:** 391–419.
7. Martyn T Smith Quinones as mutagens, carcinogens, and anticancer agents: Introduction and overview. Journal of Toxicology and Environmental Health 1985;16(5): DOI:10.1080/15287398509530776.
8. Verma Rajeshwar P, Hansch Corwin QSAR modeling of taxane analogues against colon cancer. Eur J Med Chem 2010; 45: 1470-1477.
9. Sardana S, Madan AK Topological models for prediction of antihypertensive activity of substituted benzylimidazoles. J Mol Struct (Theochem) 2003; 638: 41-49.
10. Gregg Siegal, Eiso AB, Jan Schultz. Integration of fragment screening and library design. Drug Discovery Today 2007; 12(23/24):1032-1039.
11. Michael H. Abraham, Adam Ibrahim, Andreas M. Zissimos, Determination of sets of solute descriptors from chromatographic measurements. Journal of Chromatography 2004; 1037:29–47.
12. Rajeshwar P. Verma, Anti-Cancer Activities of 1,4-Naphthoquinones: A QSAR Study, Anti-Cancer Agents in Medicinal Chemistry, 2006; 6:489-499.
13. Yap CW. PaDEL-descriptor: open source software to calculate molecular descriptors and fingerprints**.** J Comput Chem 2011; 32(7):1466-1474.
14. Chowdhury Abhishek, Dey Pradip, Sen Shantanu, Chetia Pankaj, Choudhury Manabendra Dutta And Dutta Sharma Gauri, An in silico appraisal of few bioactive compounds against kas-a for antitubercular drug efficacy, Asian J Pharm Clin Res, 2012; 5(1):60-62.
15. Sharma Brij Kishore, Singh Prithvi, Sarbhai Kirti A QSAR Study on 5-HT_7 Receptor Antagonists: Derivatives of (Phenylpiperazinyl-Alkyl) Oxindole. Int J Pharm Pharm Sci 2009; 1(1):227-239.
16. Sahu Satish, Kohli DV, Banerjee Lopamudra 3D-QSAR Studies of Some Thiazolidinesdiones as Peroxisome Proliferator Activated Receptor (PPARγ) Agonist. Int J Pharm Pharm Sci 2012; 4(1):148-153.
17. Ajeet, Kumar Vipul, Singh Brajpal QSAR modeling of gelatinase inhibitors: MLR approach, Int Res Jour of Pharm, 2012; 3(3):216-218.
18. Ajeet, QSAR modeling of recombinant human stromelysin inhibitors– MLR approach, Int J Adv Pharm Biol Sci, 2012; 2(2):171-175.