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Elucidation of structure–activity relationships for 2- or 6-substituted-5,8-dimethoxy-1,4-naphthoquinones

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Abstract—1,4-Naphthoquinones have already been recognized to possess a wide range of biological activities. We have developed quantitative structure activity relationships (QSAR) for different series of 2- or 6-substituted-5,8-dimethoxy-1,4-naphthoquinones to understand the chemical–biological interaction governing antiproliferative/cytotoxic activities against L1210 cells. QSAR results have shown that these activities of 2- or 6-substituted-5,8-dimethoxy-1,4-naphthoquinones depend largely on their hydrophobicity.

1. Introduction

Naphthoquinones are ubiquitously distributed in nature and have been used for centuries in home remedies as well as in cosmetics. Henna is an important example, which is a paste, prepared from powdered leaves of the plant, *Lawsonia alba*, containing lawsone (2-hydroxy-1,4-naphthoquinone), used for coloring skin and hair.[1] Some naphthoquinone drugs, such as menadione (2-methyl-1,4-naphthoquinone), plumbagin (2-methyl-5-hydroxy-1,4-naphthoquinone), and lapachol (2-hydroxy-3-(3-methyl-2-butenyl)-1,4-naphthoquinone) having trypanocidal activities upon different trypanosomes and *Leishmania* responsible for several human diseases that includes African sleeping sickness (*Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*), Kala-azar (*Leishmania donovani*) and Chagas disease (*Trypanosoma cruzi*).[2] 1,4-Naphthoquinone derivatives also elicit several interesting and varied biological responses such as antibacterial,[3,4] antifungal,[3–6] anti-inflammatory,[3,6,7,16,17,19] antithrombotic[8,10] antiplatelet,[7–10,16,17,19] antiviral,[3,11–13] anticancer,[4,5,11,13–15] anti-allergic,[7,16–19] apoptosis,[20–22] lipoxygenase,[23,24] radical scavenging[25] and antiringworm[3] activities. 1,4-Naphthoquinone derivatives have been proved to be a human DNA topoisomerase I inhibitor.[15,25–29] It also has the ability to produce reactive oxygen species (ROS) such as semiquinone and hydroxyl radicals by enzymatic reduction (i.e., NADPH-cytochrome P 450 reductase).[30–32]

The biological activity of 1,4-naphthoquinone is mainly due to the presence of two carbonyl groups that have the ability to accept one and/or two electrons to form the corresponding radical anion or dianion species as well as their acid–base properties.[33] In a recent study, it was found that the presence of 5,8-dihydroxy groups, which facilitates the tautomerism in the structure of 1,4-naphthoquinone, should reduce the electrophilicity of the naphthoquinone ring. Thus the biological activity of naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) derivatives is dependent upon the electrophilicity of the quinone moiety. Since, naphthazarin occurs in a resonance equilibrium state, so that its electron density will disperse over the ring. Thus the methylation of naphthazarin to produce 5,8-dimethoxy-1,4-naphthoquinone (DMNQ) should increase the relative electrophilicity in C-2 and C-3 of the quinonoid moiety. This is as evidenced by the greater reactivity of glutathione with DMNQ, compared with naphthazarin.[28]

In the present paper, we have discussed the QSAR (quantitative structure activity relationship) studies of the different series of 2- or 6-substituted-5,8-dimethoxy-1,4-naphthoquinones with respect to their antiproliferative or cytotoxic activity in L1210 cells. In the past 42 years, the use of QSAR since its advent[34] has become increasingly helpful to understand the chemical–biological interactions in drug and pesticide research as well as in the areas of toxicology.[35] It is useful in elucidating the mechanisms of chemical–biological

Keywords: QSAR; Naphthoquinone; Hydrophobicity; CMR; MgVol.
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interaction in various biomolecules, particularly enzymes, membranes, organelles, and cells.[35,36] It has also been utilized for the evaluation of absorption, distribution, metabolism and excretion (ADME) phenomena in many organisms and whole animal studies. The QSAR approach employs extra-thermodynamically derived and computational-based descriptors to correlate biological activity in isolated receptors, cellular systems and in vivo. Three standard classifications routinely used in QSAR analysis: electronic, hydrophobic, and steric, including topological indices, are invaluable in helping to delineate a large number of receptor–ligand interactions that are critical to biological processes.[35] QSAR models can stand alone, augment other graphical approaches or be examined in tandem with equations of a similar mechanistic genre to establish the authenticity and reliability.[37]

2. Materials and methods

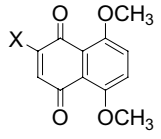
All the data for the different series of 2- or 6-substituted-5,8-dimethoxy-1,4-naphthoquinones have been collected from the literature (see individual QSAR for respective references). IC_{50} is the molar concentration of a compound that causes 50% inhibition. C is the molar concentration of a compound and $\log 1/C$ is the dependent variable that defines the biological parameter for QSAR equations. Similarly, ED_{50} is the molar concentration of a compound to produce a 50% reduction in the viability relative to the control. Physicochemical descriptors are auto-loaded, and multiregression analyses (MRA) to derive the QSAR are executed with the C-QSAR program.[38] For in-depth knowledge about the utility of QSAR program in comparative correlation analysis, the interested reader is referred to the earlier publications.[39–41] While comparing different QSAR, however, it must be borne in mind that variations in quality in testing in different laboratories will have an effect that cannot be estimated.

The parameters used in this paper have been already discussed in detail along with their applications.[35] $C\log P$ is a calculated partition coefficient in octanol/water system and is a measure of hydrophobicity of the whole molecule.[39] CMR is the calculated molar refractivity for the whole molecule. MR is calculated from the Lorentz–Lorenz equation and is described as follows: $(n^2 - 1/n^2 + 2)(MW/d)$, where n is the refractive index, MW is the molecular weight, and d is the density of a substance. Since there is a very little variation in n, MR is largely a measure of volume with a small correction for polarizability. MR can be used for a substituent or for the whole molecule. MgVol is the molar volume calculated by using the method of McGowan. π is the hydrophobicity of substituents. The indicator variable I is assigned the value of 1 or 0 for special features with special effects that cannot be parametrized and has been explained wherever used.

In QSAR equations, n is the number of data points, r is the correlation coefficient, r^2 is the square of the correlation coefficient, q is a measure of the quality of fit, q^2 is a measure of the Goodness of fit of the data and approaches the value of r^2 as the quality of the fit improves and s is the standard deviation. All the QSAR reported here are derived by us and were not given with the original data sets taken from the literature as referenced.

3. Results and discussion

3.1. QSAR for the antiproliferative/cytotoxic activity against L1210 cells by 2-X-5,8-dimethoxy-1,4-naphthoquinones



I

Song et al.[25] studied the antiproliferative activity of 2-(1-hydroxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells. We derived Eq. 1 from their results that indicates the hydrophobicity of the molecules has excellent correlation with their activity in a parabolic fashion. It shows that the hydrophobicity of the molecules initially increases activity up to an optimum $C\log P$ of 3.85 and then decreases.

3.1.1. ED_{50} of 2-(1-hydroxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 1).[25]

$$\begin{aligned}&\log 1/C = 0.21(\pm 0.04)C\log P - 0.03(\pm 0.004)C\log P^2 \\ &\qquad + 6.01(\pm 0.09)\\ &n = 12,\ r^2 = 0.971,\ q^2 = 0.956,\ s = 0.023\\ &\text{optimum } C\log P = 3.85(3.63\text{–}4.02)\\ &\text{range in } \log 1/C = 5.98\text{–}6.42\end{aligned} \quad (1)$$

It is our interest to note here that there is a high mutual correlation between $C\log P$ and CMR ($r^2 = 1.00$, $q^2 = 1.00$) and $C\log P$ and MgVol ($r^2 = 1.00$, $q^2 = 1.00$). Thus, the equation with CMR or MgVol will gave exactly the same statistics with that of $C\log P$. Now, it is very hard to predict, which is the most important hydrophobic or polarizability or volume effect. We prefer Eq. 1 because the variation at position-2 substituents in the compounds is only in the alkyl groups.

Chae et al.[26] studied the cytotoxic activity of 2-(1-azidoalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells. We derived Eq. 2 from their results, which gave a good correlation with $C\log P$. The negative coefficient of $C\log P$ suggests that an increase in the hydrophobicity should reduce the activity of the molecules.

3.1.2. ED_{50} of 2-(1-azidoalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 2).[26]

$$\begin{aligned}&\log 1/C = -0.08(\pm 0.02)C\log P + 6.36(\pm 0.12)\\ &n = 12,\ r^2 = 0.892,\ q^2 = 0.841,\ s = 0.056\\ &\text{outlier: } CH(N_3)C_7H_{15}\\ &\text{range in } \log 1/C = 5.60\text{–}6.14\end{aligned} \quad (2)$$

Song et al.[27] reported the synthesis and ED_{50} data of 2-acyl-5,8-dimethoxy-1,4-naphthoquinones for their cytotoxic activity against L1210. From these data, we derived Eq. 3, which gave a parabolic correlation with $C\log P$. It shows that the hydrophobicity of the compounds initially increases activity up to an optimum value of 1.89 and then decreases.

3.1.3. ED_{50} of 2-acyl-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 3).[27]

$$\log 1/C = 0.15(\pm 0.13)C\log P - 0.04(\pm 0.02)C\log P^2 + 6.21(\pm 0.21)$$

$$n = 10,\ r^2 = 0.973,\ q^2 = 0.951,\ s = 0.049$$

optimum $C\log P = 1.89(0.40\text{–}2.48)$

outliers: COC_6H_{13}; $COC_{12}H_{25}$

range in $\log 1/C = 5.61\text{–}6.39$ (3)

In another attempt, Song et al.[28] studied the cytotoxic activity of 2-(1-hydroxyalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210. We derived Eq. 4 from their results. In Eq. 4, we obtained a bilinear correlation with $C\log P$.

3.1.4. ED_{50} of 2-(1-hydroxyalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 4).[28]

$$\log 1/C = 0.14(\pm 0.05)C\log P - 7.84(\pm 1.81) \times \log(\beta x 10^{C\log P} + 1) + 8.49(\pm 0.11)$$

$$n = 7,\ r^2 = 0.985,\ q^2 = 0.973,\ s = 0.024$$

optimum $C\log P = 3.47$

outlier: $CH(OH)C_6H_{13}$

$\log \beta = -5.20$

range in $\log 1/C = 8.52\text{–}8.93$ (4)

From this equation, it appears that hydrophobicity plays an important role. Activity of the compounds first increases with an increase in hydrophobicity to an optimum $C\log P$ of 3.47 and then decreases linearly.

The QSAR (Eqs. 1–4) for 2-substituted-5,8-dimethoxy-1,4-naphthoquinones gave a good correlation with hydrophobicity but not the similar way that is, linear, parabolic, and bilinear. This may be due to the present of steric hindrance at position-2 by different bulkier groups. We could not study the steric interaction of the substituents of the second position in all the four

Table 1. Biological and physicochemical parameters used to derive QSAR 1 for the antiproliferative activity of 2-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	$\log 1/C$	$\log 1/C$ (Eq. 1)		$C\log P$	CMR	MgVol
		Obsd	Calcd	Δ			
1	CH(=NOH)	6.27	6.27	0.00	1.56	6.61	1.82
2	$C(=NOH)CH_3$	6.33	6.32	0.01	2.0	7.07	1.96
3	$C(=NOH)C_2H_5$	6.35	6.36	−0.01	2.53	7.53	2.10
4	$C(=NOH)C_3H_7$	6.40	6.39	0.01	3.06	8.00	2.24
5	$C(=NOH)C_4H_9$	6.42	6.41	0.01	3.59	8.46	2.38
6	$C(=NOH)C_5H_{11}$	6.38	6.41	−0.03	4.12	8.93	2.52
7	$C(=NOH)C_6H_{13}$	6.36	6.39	−0.03	4.65	9.39	2.66
8	$C(=NOH)C_7H_{15}$	6.38	6.36	0.02	5.17	9.85	2.80
9	$C(=NOH)C_8H_{17}$	6.34	6.31	0.02	5.70	10.32	2.94
10	$C(=NOH)C_9H_{19}$	6.28	6.25	0.03	6.23	10.78	3.08
11	$C(=NOH)C_{10}H_{21}$	6.15	6.18	−0.02	6.76	11.24	3.22
12	$C(=NOH)C_{12}H_{25}$	5.98	5.98	0.00	7.82	12.17	3.51

Table 2. Biological and physicochemical parameters used to derive QSAR 2 for the cytotoxic activity of 2-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	$\log 1/C$	$\log 1/C$ (Eq. 2)		$C\log P$
		Obsd	Calcd	Δ	
1	CH_2N_3	6.04	6.11	−0.08	3.18
2	$CH(N_3)CH_3$	6.14	6.09	0.05	3.49
3	$CH(N_3)C_2H_5$	5.97	6.05	−0.07	4.02
4	$CH(N_3)C_3H_7$	5.95	6.0	−0.05	4.55
5	$CH(N_3)C_4H_9$	6.03	5.96	0.07	5.08
6	$CH(N_3)C_5H_{11}$	5.95	5.92	0.04	5.61
7	$CH(N_3)C_6H_{13}$	5.92	5.88	0.04	6.14
8	$CH(N_3)C_7H_{15}$	5.95[a]	5.84	0.11	6.67
9	$CH(N_3)C_8H_{17}$	5.82	5.79	0.03	7.20
10	$CH(N_3)C_9H_{19}$	5.75	5.75	0.00	7.73
11	$CH(N_3)C_{10}H_{21}$	5.65	5.71	−0.06	8.25
12	$CH(N_3)C_{12}H_{25}$	5.60	5.63	−0.03	9.31
13	$CH(N_3)C_5H_{11}$ (*iso*)	5.99	5.93	0.06	5.48

[a] Not included in the derivation of QSAR 2.

Table 3. Biological and physicochemical parameters used to derive QSAR 3 for the cytotoxic activity of 2-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	$\log 1/C$	$\log 1/C$ (Eq. 3)		$C\log P$
		Obsd	Calcd	Δ	
1	CHO	6.39	6.35	0.04	1.51
2	$COCH_3$	6.38	6.34	0.04	1.31
3	COC_2H_5	6.25	6.35	−0.10	1.84
4	COC_3H_7	6.34	6.34	−0.01	2.37
5	COC_4H_9	6.31	6.31	0.00	2.90
6	COC_5H_{11}	6.30	6.26	0.04	3.42
7	COC_6H_{13}	6.28[a]	6.18	0.09	3.95
8	COC_7H_{15}	6.11	6.08	0.02	4.48
9	COC_8H_{17}	5.94	5.96	−0.02	5.01
10	COC_9H_{19}	5.80	5.82	−0.02	5.54
11	$COC_{10}H_{21}$	5.66	5.65	0.01	6.07
12	$COC_{12}H_{25}$	5.61[a]	5.25	0.36	7.13

[a] Not included in the derivation of QSAR 3.

Table 4. Biological and physicochemical parameters used to derive QSAR 4 for the cytotoxic activity of 2-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	$\log 1/C$	$\log 1/C$ (Eq. 4)		$C\log P$
		Obsd	Calcd	Δ	
1	CH_2OH	8.68	8.68	0.00	1.33
2	$CH(OH)CH_3$	8.73	8.72	0.01	1.64
3	$CH(OH)C_2H_5$	8.73	8.75	−0.02	1.85
4	$CH(OH)C_3H_7$	8.85	8.82	0.03	2.38
5	$CH(OH)C_4H_9$	8.87	8.89	−0.02	2.91
6	$CH(OH)C_5H_{11}$	8.93	8.92	0.00	3.44
7	$CH(OH)C_6H_{13}$	8.66[a]	−22.03	30.69	3.97
8	$CH(OH)C_7H_{15}$	8.52	8.52	0.00	4.50

[a] Not included in the derivation of QSAR 4.

sets. This is because the steric parameters of the substituents are not available. Secondly, these data sets have a span of $\log 1/C$ values smaller than 1 log unit. For the better span of $\log 1/C$ value, we derived Eq. 5 (Table 11) by considering all the compounds, which were used in deriving Eqs. 1–4 (Tables 1–4). From Eq. 5, it appears that the effect of hydrophobicity is diminished as shown by small coefficient of $C\log P$ and greatly dominated by indicator variables. It is important to note here that this data set has a span of $\log 1/C$ values larger than 1 log unit that is, 3.33 log units.

3.1.5. ED_{50} of 2-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 11).[25–28]

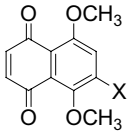
$$\log 1/C = -0.08(\pm 0.02)C\log P - 2.31(\pm 0.12)I - 2.59(\pm 0.13)I_1 - 2.55(\pm 0.12)I_2 + 8.97(\pm 0.11)$$

$$n = 45,\ r^2 = 0.987,\ q^2 = 0.983,\ s = 0.125$$

$$\text{range in } \log 1/C = 5.60\text{–}8.93 \qquad (5)$$

The indicator variables $I = 1$ is for those compounds of this series having X = 1-hydroxyiminoalkyl groups, $I_1 = 1$ for those compounds having X = 1-azidoalkyl groups and $I_2 = 1$ for those compounds having X = acyl groups, respectively.

3.2. QSAR for the antiproliferative/cytotoxic activity against L1210 cells by 6-X-5,8-dimethoxy-1,4-naphthoquinones



II

Song et al.[25] studied the synthesis and antiproliferative activity of 6-(1-hydroxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells. We derived Eq. 6 from their results, which gave a parabolic correlation with $C\log P$ of the molecules. It shows that the hydrophobicity of the molecules initially increases activity up to an optimum $C\log P$ of 4.02 and then decreases.

3.2.1. ED_{50} of 6-(1-hydroxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 5).[25]

$$\log 1/C = 0.41(\pm 0.10)C\log P - 0.05(\pm 0.01)C\log P^2 + 6.07(\pm 0.22)$$

$$n = 12,\ r^2 = 0.955,\ q^2 = 0.851,\ s = 0.061$$

$$\text{optimum } C\log P = 4.02(3.73\text{–}4.24) \qquad (6)$$

In another attempt, Song et al.[25] studied the synthesis and antiproliferative activity of 6-(1-propyloxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones against

L1210 cells for the purpose of protecting the oximes from a cellular reduction. We derived Eq. 7 from their results. In Eq. 7, we obtained a bilinear correlation with $C\log P$. From this equation, it appears that activity of the compounds first increases with an increase in hydrophobicity to an optimum $C\log P$ of 5.20 and then decreases linearly.

3.2.2. ED_{50} of 6-(1-propyloxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 6).[25]

$$\log 1/C = 0.16(\pm 0.06)C\log P - 0.41(\pm 0.09) \times \log(\beta x 10^{C\log P} + 1) + 6.06(\pm 0.25)$$
$$n = 12,\ r^2 = 0.966,\ q^2 = 0.929,\ s = 0.053$$
$$\text{optimum } C\log P = 5.20$$
$$\log \beta = -5.40$$
$$\text{range in } \log 1/C = 6.04\text{–}6.85. \quad (7)$$

Chae et al.[26] published the data for cytotoxic activity of 6-(1-azidoalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells. We derived Eq. 8 from their results, which gave a good correlation with $C\log P$. The negative coefficient of $C\log P$ suggests that an increase in the hydrophobicity should reduce the activity of the molecules.

3.2.3. ED_{50} of 6-(1-azidoalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 7).[26]

$$\log 1/C = -0.06(\pm 0.02)C\log P + 6.39(\pm 0.10)$$
$$n = 11,\ r^2 = 0.892,\ q^2 = 0.831,\ s = 0.038$$
$$\text{outliers: } CH_2N_3;\ CH(N_3)C_3H_7$$
$$\text{range in } \log 1/C = 5.83\text{–}6.18. \quad (8)$$

Song et al.[27] reported the synthesis and ED_{50} data of 6-acyl-5,8-dimethoxy-1,4-naphthoquinones for their cytotoxic activity against L1210. From these data, we derived Eq. 9, which gave a bilinear correlation with $C\log P$. It shows that the hydrophobicity of the compounds initially increases the activity up to an optimum value of 3.67 and then decreases linearly.

3.2.4. ED_{50} of 6-acyl-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 8).[27]

$$\log 1/C = 0.15(\pm 0.06)C\log P - 0.41(\pm 0.10) \times \log(\beta x 10^{C\log P} + 1) + 6.43(\pm 0.16)$$
$$n = 12,\ r^2 = 0.948,\ q^2 = 0.904,\ s = 0.06$$
$$\text{optimum } C\log P = 3.67$$
$$\log \beta = -3.90$$
$$\text{range in } \log 1/C = 6.18\text{–}6.96. \quad (9)$$

Song et al.[28] published the cytotoxic activity results of 6-(1-hydroxyalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells. We derived Eq. 10 from their results, which gave a bilinear correlation with $C\log P$.

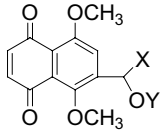
3.2.5. ED_{50} of 6-(1-hydroxyalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 9).[28]

$$\log 1/C = 0.71(\pm 0.54)C\log P - 1.29(\pm 0.83) \times \log(\beta x 10^{C\log P} + 1) + 8.41(\pm 0.96)$$
$$n = 7,\ r^2 = 0.907,\ q^2 = 0.714,\ s = 0.124$$
$$\text{optimum } C\log P = 2.57$$
$$\log \beta = -2.48$$
$$\text{outlier: } CH_2(OH)$$
$$\text{range in } \log 1/C = 9.10\text{–}9.83. \quad (10)$$

From this equation, it appears that activity of the compounds first increases with an increase in hydrophobicity to an optimum $C\log P$ of 2.57 and then decreases linearly.

Antiproliferative activity of 6-(1-acyloxyalkyl)-5,8-dimethoxy-1,4-naphthoquinones (**III**) against L1210 cells was studied by Kim et al.[29] Eq. 11 was obtained from their results, which gave a good correlation with MR_X (overall size and polarizability) of the X substituents. A negative MR_X shows that the overall size and polarizability of X substituents would interfere with the activity of naphthoquinones **III**. Therefore, bulkier X substituents are detrimental to the activity. The indicator variables $I = 1$ is for those compounds of this series having X = ethyl group. The negative coefficient of I shows that the presence of ethyl group is detrimental to the activity.

3.2.6. ED_{50} of 6-(1-acyloxyalkyl)-5,8-dimethoxy-1,4-naphthoquinones III against L1210 (Table 10).[29]



III

$$\log 1/C = -0.72(\pm 0.12)MR_X - 0.77(\pm 0.17)I + 8.24(\pm 0.25)$$
$$n = 22,\ r^2 = 0.901,\ q^2 = 0.871,\ s = 0.113$$
$$\text{outlier: } X = C_4H_9,\ Y = COC_2H_5$$
$$\text{range in } \log 1/C = 6.08\text{–}7.22. \quad (11)$$

It is of interest to note here that there is a high mutual correlation between MR_X and π_X ($r^2 = 1.00$, $q^2 = 0.999$). Considering π_X in the place of MR_X, we derived Eq. 11a.

$$\log 1/C = -0.62(\pm 0.11)\pi_X - 0.77(\pm 0.19)I + 8.13(\pm 0.25)$$
$$n = 22,\ r^2 = 0.889,\ q^2 = 0.857,\ s = 0.120. \quad (11a)$$

On comparison between Eqs. 11 and 11a, it is very hard to predict, which is the most important polarizability or hydrophobicity of X-substituents. We keep Eq. 11 because it has better statistics than that of Eq. 11a.

Now, we derived Eq. 12 (Table 11) by considering all the compounds, which were used in deriving Eqs. 6–11 (Tables 5–10). From Eq. 12, it appears that the effect of hydrophobicity is diminished and the activity is greatly dominated by the indicator variables. It is important to note that this data set has a span of $\log 1/C$ values more than 1 log unit that is 4 log unit.

Table 5. Biological and physicochemical parameters used to derive QSAR 6 for the antiproliferative activity of 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	$\log 1/C$	$\log 1/C$ (Eq. 6)		$C\log P$
		Obsd	Calcd	Δ	
1	CH(=NOH)	6.64	6.55	0.09	1.43
2	C(=NOH)CH_3	6.66	6.75	−0.09	2.31
3	C(=NOH)C_2H_5	6.77	6.82	−0.05	2.84
4	C(=NOH)C_3H_7	6.89	6.87	0.02	3.37
5	C(=NOH)C_4H_9	6.92	6.90	0.02	3.89
6	C(=NOH)C_5H_{11}	6.82	6.89	−0.07	4.42
7	C(=NOH)C_6H_{13}	6.92	6.85	0.07	4.95
8	C(=NOH)C_7H_{15}	6.77	6.79	−0.02	5.48
9	C(=NOH)C_8H_{17}	6.72	6.69	0.03	6.01
10	C(=NOH)C_9H_{19}	6.59	6.57	0.02	6.54
11	C(=NOH)$C_{10}H_{21}$	6.46	6.42	0.04	7.07
12	C(=NOH)$C_{12}H_{25}$	5.98	6.03	−0.05	8.13

Table 6. Biological and physicochemical parameters used to derive QSAR 7 for the antiproliferative activity of 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	$\log 1/C$	$\log 1/C$ (Eq. 7)		$C\log P$
		Obsd	Calcd	Δ	
1	CH(=NOC_3H_7)	6.57	6.56	0.01	3.15
2	C(=NOC_3H_7)CH_3	6.59	6.58	0.00	3.30
3	C(=NOC_3H_7)C_2H_5	6.66	6.66	0.00	3.83
4	C(=NOC_3H_7)C_3H_7	6.68	6.73	−0.06	4.36
5	C(=NOC_3H_7)C_4H_9	6.85	6.79	0.07	4.89
6	C(=NOC_3H_7)C_5H_{11}	6.77	6.79	−0.02	5.42
7	C(=NOC_3H_7)C_6H_{13}	6.72	6.73	−0.01	5.95
8	C(=NOC_3H_7)C_7H_{15}	6.68	6.63	0.05	6.48
9	C(=NOC_3H_7)C_8H_{17}	6.54	6.51	0.03	7.00
10	C(=NOC_3H_7)C_9H_{19}	6.34	6.38	−0.04	7.53
11	C(=NOC_3H_7)$C_{10}H_{21}$	6.17	6.25	−0.08	8.06
12	C(=NOC_3H_7)$C_{12}H_{25}$	6.04	5.98	0.05	9.12

Table 7. Biological and physicochemical parameters used to derive QSAR 8 for the cytotoxic activity of 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	$\log 1/C$	$\log 1/C$ (Eq. 8)		$C\log P$
		Obsd	Calcd	Δ	
1	CH_2N_3	6.11[a]	6.21	−0.10	3.11
2	CH(N_3)CH_3	6.18	6.20	−0.02	3.42
3	CH(N_3)C_2H_5	6.10	6.17	−0.07	3.95
4	CH(N_3)C_3H_7	6.07[a]	6.13	−0.07	4.48
5	CH(N_3)C_4H_9	6.12	6.10	0.02	5.01
6	CH(N_3)C_5H_{11}	6.12	6.07	0.05	5.54
7	CH(N_3)C_6H_{13}	6.04	6.04	−0.01	6.07
8	CH(N_3)C_7H_{15}	6.07	6.01	0.05	6.60
9	CH(N_3)C_8H_{17}	5.97	5.98	−0.01	7.13
10	CH(N_3)C_9H_{19}	5.95	5.95	0.00	7.65
11	CH(N_3)$C_{10}H_{21}$	5.90	5.92	−0.02	8.18
12	CH(N_3)$C_{12}H_{25}$	5.83	5.86	−0.03	9.24
13	CH(N_3)C_5H_{11} (*iso*)	6.12	6.08	0.04	5.41

[a] Not included in the derivation of QSAR 8.

Table 8. Biological and physicochemical parameters used to derive QSAR 9 for the cytotoxic activity of 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	$\log 1/C$	$\log 1/C$ (Eq. 9)		$C\log P$
		Obsd	Calcd	Δ	
1	CHO	6.70	6.65	0.05	1.44
2	$COCH_3$	6.62	6.65	−0.03	1.46
3	COC_2H_5	6.72	6.73	−0.01	1.99
4	COC_3H_7	6.80	6.80	0.00	2.52
5	COC_4H_9	6.77	6.86	−0.09	3.05
6	COC_5H_{11}	6.96	6.90	0.06	3.58
7	COC_6H_{13}	6.96	6.88	0.08	4.11
8	COC_7H_{15}	6.80	6.80	0.00	4.64
9	COC_8H_{17}	6.62	6.68	−0.06	5.17
10	COC_9H_{19}	6.54	6.55	−0.01	5.70
11	$COC_{10}H_{21}$	6.40	6.42	−0.02	6.22
12	$COC_{12}H_{25}$	6.18	6.15	0.03	7.28

Table 9. Biological and physicochemical parameters used to derive QSAR 10 for the cytotoxic activity of 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	$\log 1/C$	$\log 1/C$ (Eq. 10)		$C\log P$
		Obsd	Calcd	Δ	
1	CH_2OH	9.60[a]	7.86	1.75	.95
2	$CH(OH)CH_3$	9.30	9.27	0.02	1.26
3	$CH(OH)C_2H_5$	9.51	9.58	−0.07	1.79
4	$CH(OH)C_3H_7$	9.83	9.77	0.06	2.32
5	$CH(OH)C_4H_9$	9.73	9.76	−0.03	2.85
6	$CH(OH)C_5H_{11}$	9.68	9.59	0.10	3.38
7	$CH(OH)C_6H_{13}$	9.18	9.33	−0.15	3.91
8	$CH(OH)C_7H_{15}$	9.10	9.03	0.07	4.44

[a] Not included in the derivation of QSAR 10.

Table 10. Biological and physicochemical parameters used to derive QSAR 11 for the antiproliferative activity of 6-CH(X)(OY)-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	Y	$\log 1/C$	$\log 1/C$ (Eq. 11)		MR_X	π_X	I
			Obsd	Calcd	Δ			
1	C_2H_5	$COCH_3$	6.66	6.73	−0.07	1.03	1.02	1
2	C_2H_5	$COCH_2CH_3$	6.92	6.73	0.19	1.03	1.02	1
3	C_2H_5	$CO(CH_2)_2CH_3$	6.77	6.73	0.04	1.03	1.02	1
4	C_2H_5	$CO(CH_2)_4CH_3$	6.62	6.73	−0.11	1.03	1.02	1
5	C_2H_5	$CO(CH_2)_5CH_3$	6.68	6.73	−0.05	1.03	1.02	1
6	C_3H_7	$COCH_3$	7.10	7.16	−0.06	1.50	1.55	0
7	C_3H_7	$COCH_2CH_3$	7.15	7.16	−0.01	1.50	1.55	0
8	C_3H_7	$CO(CH_2)_2CH_3$	7.15	7.16	−0.01	1.50	1.55	0
9	C_3H_7	$CO(CH_2)_4CH_3$	7.15	7.16	−0.01	1.50	1.55	0
10	C_3H_7	$CO(CH_2)_5CH_3$	6.96	7.16	−0.20	1.50	1.55	0
11	C_4H_9	$COCH_3$	7.05	6.83	0.22	1.96	2.13	0
12	C_4H_9	$COCH_2CH_3$	7.22[a]	6.83	0.39	1.96	2.13	0
13	C_4H_9	$CO(CH_2)_2CH_3$	6.96	6.83	0.13	1.96	2.13	0
14	C_4H_9	$CO(CH_2)_4CH_3$	6.77	6.83	−0.06	1.96	2.13	0
15	C_4H_9	$CO(CH_2)_5CH_3$	7.05	6.83	0.22	1.96	2.13	0
16	C_5H_{11}	$COCH_3$	6.55	6.49	0.06	2.42	2.63	0
17	C_5H_{11}	$COCH_2CH_3$	6.46	6.49	−0.04	2.42	2.63	0
18	C_5H_{11}	$CO(CH_2)_2CH_3$	6.41	6.49	−0.08	2.42	2.63	0
19	C_5H_{11}	$CO(CH_2)_4CH_3$	6.44	6.49	−0.05	2.42	2.63	0
20	C_5H_{11}	$CO(CH_2)_5CH_3$	6.43	6.49	−0.06	2.42	2.63	0
21	C_6H_{13}	$COCH_3$	6.19	6.16	0.03	2.89	3.16	0
22	C_6H_{13}	$COCH_2CH_3$	6.15	6.16	0.00	2.89	3.16	0
23	C_6H_{13}	$CO(CH_2)_2CH_3$	6.08	6.16	−0.08	2.89	3.16	0

[a] Not included in the derivation of QSAR 11.

3.2.7. ED_{50} of 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 11).[25–29]

$$\log 1/C = -0.08(\pm 0.03)C\log P - 0.55(\pm 0.15)I_1 + 2.65(\pm 0.19)I_3 + 7.04(\pm 0.16)$$
$$n = 80,\ r^2 = 0.941,\ q^2 = 0.936,\ s = 0.235$$
$$\text{range in } \log 1/C = 5.83\text{–}9.83. \quad (12)$$

The indicator variables $I_1 = 1$ is for those compounds of this series having X = 1-azidoalkyl groups and $I_3 = 1$ for those compounds having X = 1-hydroxyalkyl groups, respectively.

3.3. QSAR for the antiproliferative/cytotoxic activity against L1210 cells by 2- or 6-X-5,8-dimethoxy-1,4-naphthoquinones

Finally, we derived Eq. 13 (Table 11) for better understanding and conclusive QSAR results, by considering all 2-X- and 6-X- derivatives of 5,8-dimethoxy-1,4-naphthoquinones, which were used in deriving Eqs. (1)–(4), (6)–(11) (Tables 1–10).

3.3.1. ED_{50} of 2- or 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 11).[25–29]

$$\log 1/C = -0.06(\pm 0.03)C\log P - 0.47(\pm 0.16)I_1 + 2.49(\pm 0.19)I_3 + 6.79(\pm 0.17)$$
$$n = 123,\ r^2 = 0.891,\ q^2 = 0.883,\ s = 0.319$$
$$\text{outliers: 2-CH}_2\text{OH; 6-CH}_2\text{OH}$$
$$\text{range in } \log 1/C = 5.60\text{–}9.83. \quad (13)$$

The indicator variables $I_1 = 1$ is for those compounds of this series having X = 2 or 6-(1-azidoalkyl) groups and $I_3 = 1$ for those compounds having X = 2 or 6-(1-hydroxyalkyl) groups, respectively. The span of $\log 1/C$ values for this data set is more than 1 log unit, that is, 4.23 log units.

The equations with combined data (Eqs. 5, 12, 13) gave contradictory results as compared to that of the individual one (Eqs. 1–4 and 6–11) that is, the effect of the main parameter hydrophobicity is greatly diminished as shown by the small coefficient of $C\log P$. The combined equations are actually dominated by indicator variables. This may be due to the fact that the combined equations (Eqs. 5, 12, 13) were formulated by the combination of data of 5,8-dimethoxy-1,4-naphthoquinones having various functional groups at position-2 or -6. Particularly, the data of 2- or 6-(1-hydroxyalkyl)-5,8-dimethoxy-1,4-naphthoquinones (Tables 4 and 9) which showed dramatic increase in potency (2–3 log units more potent) that it overwhelms all other effects in the combined equations, and thus the predominant factor in the combined equations are the indicator variables.

The activities of these naphthoquinones are dependent on their hydrophobocity can be further supported by deriving equations by combining the data of those naphthoquinones having the same functional groups either at position-2 or -6.

We formulated Eq. 14 (Table 12) by combining the data of 2- or 6-(1-hydroxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones, which was used in deriving Eqs. 1 and 6 (Tables 1 and 5).

3.3.2. ED_{50} of 2- or 6-(1-hydroxyiminoalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 12).[25]

$$\log 1/C = 0.32(\pm 0.08)C\log P - 0.04(\pm 0.01) \times C\log P^2 - 0.40(\pm 0.06)I + 6.22(\pm 0.17)$$
$$n = 24,\ r^2 = 0.947,\ q^2 = 0.891,\ s = 0.068$$
$$\text{optimum } C\log P = 3.96(3.69\text{–}4.17)$$
$$I = 1 \text{ for those compounds having X = 2-(1-hydroxyiminoalkyl) group.} \quad (14)$$

The effect of a hydroxyalkyl group either at position-2 or -6 is so great (2–3 log units more potent) but these analogs are also interacting with the receptor in a similar manner as compared to the other analogs. This can be supported by the Eq. 15 (Table 13) that was derived by combining the data of 2- or 6-(1-hydroxyalkyl)-5,8-dimethoxy-1,4-naphthoquinones, which was used in deriving Eqs. 4 and 10 (Tables 4 and 9). The Eq. 15 is quite similar to that of Eqs. 4, 7, 9 and 10.

3.3.3. ED_{50} of 2- or 6-(1-hydroxyalkyl)-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 13).[28]

$$\log 1/C = 0.22(\pm 0.17)C\log P - 0.76(\pm 0.41) \times \log(\beta x 10^{C\log P} + 1) - 0.76(\pm 0.16)I + 9.18(\pm 0.33)$$
$$n = 16,\ r^2 = 0.923,\ q^2 = 0.844,\ s = 0.141$$
$$\text{optimum } C\log P = 2.77,\ \log\beta = -3.16$$
$$I = 1 \text{ for those compounds having X = 2-(1-hydroxyalkyl)group.} \quad (15)$$

This equation also supported that the activities of these naphthoquinones are dependent on their hydrophobocity.

A correlation with hydrophobicity was also achieved by deriving Eq. 16 (Table 14) from the dataset, which comprised the high and low values from each subset (Tables 1–10).

3.3.4. ED_{50} of 2- or 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 (Table 14).[25–29]

$$\log 1/C = -0.56(\pm 0.17)C\log P - 1.82(\pm 1.15)I - 2.49(\pm 1.16)I_1 + 10.59(\pm 1.12)$$
$$n = 17,\ r^2 = 0.812,\ q^2 = 0.725,\ s = 0.648$$
$$\text{outliers: 2-CHO, 6-COC}_5\text{H}_{11}\text{, 6-CH(C}_6\text{H}_{13}\text{)OCOC}_3\text{H}_7$$
$$I = 1 \text{ for those compounds having X = 2- or 6-C(=NOH)C}_4\text{H}_9 \text{ group}$$
$$I_1 = 1 \text{ for those compounds having X = 2- } or \text{ 6-CH(N}_3\text{)CH}_3 \text{ group.} \quad (16)$$

Table 11. Biological and physicochemical parameters used to derive QSAR 5, 12 and 13 for the antiproliferative/cytotoxic activity of 2- or 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	$\log 1/C$	$\log 1/C$ (Eq. 5)		$\log 1/C$ (Eq. 12)		$\log 1/C$ (Eq. 13)		$C\log P$	I	I_1	I_2	I_3
		Obsd	Calcd	Δ	Calcd	Δ	Calcd	Δ					
1	2-CH(=NOH)	6.27	6.53	−0.26			6.70	−0.43	1.56	0	0	0	0
2	2-C(=NOH)CH_3	6.33	6.50	−0.17			6.68	−0.35	2.00	1	0	0	0
3	2-C(=NOH)C_2H_5	6.35	6.46	−0.11			6.65	−0.30	2.53	1	0	0	0
4	2-C(=NOH)C_3H_7	6.40	6.41	−0.01			6.62	−0.22	3.06	1	0	0	0
5	2-C(=NOH)C_4H_9	6.42	6.37	0.05			6.58	−0.16	3.59	1	0	0	0
6	2-C(=NOH)C_5H_{11}	6.38	6.33	0.05			6.55	−0.17	4.12	1	0	0	0
7	2-C(=NOH)C_6H_{13}	6.36	6.29	0.07			6.52	−0.16	4.65	1	0	0	0
8	2-C(=NOH)C_7H_{15}	6.38	6.24	0.14			6.49	−0.11	5.17	1	0	0	0
9	2-C(=NOH)C_8H_{17}	6.34	6.20	0.14			6.46	−0.12	5.70	1	0	0	0
10	2-C(=NOH)C_9H_{19}	6.28	6.16	0.12			6.43	−0.15	6.23	1	0	0	0
11	2-C(=NOH)$C_{10}H_{21}$	6.15	6.12	0.03			6.40	−0.25	6.76	1	0	0	0
12	2-C(=NOH)$C_{12}H_{25}$	5.98	6.03	−0.05			6.34	−0.36	7.82	1	0	0	0
13	2-CH_2N_3	6.04	6.12	−0.08			6.61	−0.57	3.18	0	0	0	0
14	2-CH(N_3)CH_3	6.14	6.10	0.04			6.12	0.02	3.49	0	1	0	0
15	2-CH(N_3)C_2H_5	5.97	6.06	−0.09			6.09	−0.12	4.02	0	1	0	0
16	2-CH(N_3)C_3H_7	5.95	6.01	−0.06			6.06	−0.11	4.55	0	1	0	0
17	2-CH(N_3)C_4H_9	6.03	5.97	0.06			6.03	0.00	5.08	0	1	0	0
18	2-CH(N_3)C_5H_{11}	5.95	5.93	0.02			5.99	−0.04	5.61	0	1	0	0
19	2-CH(N_3)C_6H_{13}	5.92	5.89	0.03			5.96	−0.04	6.14	0	1	0	0
20	2-CH(N_3)C_7H_{15}	5.95	5.84	0.11			5.93	0.02	6.67	0	1	0	0
21	2-CH(N_3)C_8H_{17}	5.82	5.80	0.02			5.90	−0.08	7.20	0	1	0	0
22	2-CH(N_3)C_9H_{19}	5.75	5.76	−0.01			5.87	−0.12	7.72	0	1	0	0
23	2-CH(N_3)$C_{10}H_{21}$	5.65	5.71	−0.06			5.84	−0.19	8.25	0	1	0	0
24	2-CH(N_3)$C_{12}H_{25}$	5.60	5.63	−0.03			5.78	−0.18	9.31	0	1	0	0
25	2-CH(N_3)$(CH_2)_2CH(CH_3)_2$	5.99	5.94	0.05			6.00	−0.01	5.48	0	1	0	0
26	2-CHO	6.39	6.30	0.09			6.71	−0.32	1.51	0	0	0	0
27	2-$COCH_3$	6.38	6.31	0.07			6.72	−0.34	1.31	0	0	1	0
28	2-COC_2H_5	6.25	6.27	−0.02			6.69	−0.44	1.84	0	0	1	0
29	2-COC_3H_7	6.34	6.23	0.11			6.66	−0.32	2.37	0	0	1	0
30	2-COC_4H_9	6.31	6.19	0.12			6.63	−0.32	2.90	0	0	1	0
31	2-COC_5H_{11}	6.30	6.14	0.16			6.59	−0.29	3.42	0	0	1	0
32	2-COC_6H_{13}	6.28	6.10	0.18			6.56	−0.28	3.95	0	0	1	0
33	2-COC_7H_{15}	6.11	6.06	0.05			6.53	−0.42	4.48	0	0	1	0
34	2-COC_8H_{17}	5.94	6.02	−0.08			6.50	−0.56	5.01	0	0	1	0
35	2-COC_9H_{19}	5.80	5.97	−0.17			6.47	−0.67	5.54	0	0	1	0
36	2-$COC_{10}H_{21}$	5.66	5.93	−0.27			6.44	−0.78	6.07	0	0	1	0
37	2-$COC_{12}H_{25}$	5.61	5.85	−0.24			6.38	−0.77	7.13	0	0	1	0
38	2-CH_2OH	5.68[a]	8.86	−0.18			6.72	1.96	1.33	0	0	0	0
39	2-CH(OH)CH_3	8.73	8.84	−0.11			9.19	−0.46	1.64	0	0	0	1
40	2-CH(OH)C_2H_5	8.73	8.82	−0.09			9.18	−0.45	1.85	0	0	0	1
41	2-CH(OH)C_3H_7	8.85	8.78	0.07			9.15	−0.30	2.38	0	0	0	1
42	2-CH(OH)C_4H_9	8.87	8.73	0.14			9.12	−0.25	2.91	0	0	0	1
43	2-CH(OH)C_5H_{11}	8.93	8.69	0.24			9.08	−0.15	3.44	0	0	0	1
44	2-CH(OH)C_6H_{13}	8.66	8.65	0.01			9.05	−0.39	3.97	0	0	0	1
45	2-CH(OH)C_7H_{15}	8.52	8.61	−0.09			9.02	−0.50	4.50	0	0	0	1
46	6-CH(=NOH)	6.64			6.93	−0.29	6.71	−0.07	1.43	0	0	0	0
47	6-C(=NOH)CH_3	6.66			6.87	−0.21	6.66	0.00	2.31	1	0	0	0
48	6-C(=NOH)C_2H_5	6.77			6.82	−0.05	6.63	0.14	2.84	1	0	0	0
49	6-C(=NOH)C_3H_7	6.89			6.78	0.11	6.60	0.29	3.37	1	0	0	0
50	6-C(=NOH)C_4H_9	6.92			6.74	0.18	6.57	0.35	3.89	1	0	0	0
51	6-C(=NOH)C_5H_{11}	6.82			6.70	0.12	6.54	0.28	4.42	1	0	0	0
52	6-C(=NOH)C_6H_{13}	6.92			6.66	0.26	6.51	0.41	4.95	1	0	0	0
53	6-C(=NOH)C_7H_{15}	6.77			6.62	0.15	6.47	0.30	5.48	1	0	0	0
54	6-C(=NOH)C_8H_{17}	6.72			6.58	0.14	6.44	0.28	6.01	1	0	0	0
55	6-C(=NOH)C_9H_{19}	6.59			6.54	0.05	6.41	0.18	6.54	1	0	0	0
56	6-C(=NOH)$C_{10}H_{21}$	6.46			6.50	−0.04	6.38	0.08	7.07	1	0	0	0
57	6-C(=NOH)$C_{12}H_{25}$	5.98			6.42	−0.44	6.32	−0.34	8.13	1	0	0	0
58	6-CH(=NOC_3H_7)	6.57			6.80	−0.23	6.61	−0.04	3.15	0	0	0	0
59	6-C(=NOC_3H_7)CH_3	6.59			6.79	−0.20	6.60	−0.01	3.30	0	0	0	0
60	6-C(=NOC_3H_7)C_2H_5	6.66			6.75	−0.09	6.57	0.09	3.83	0	0	0	0
61	6-C(=NOC_3H_7)C_3H_7	6.68			6.71	−0.03	6.54	0.14	4.36	0	0	0	0
62	6-C(=NOC_3H_7)C_4H_9	6.85			6.67	0.18	6.51	0.34	4.89	0	0	0	0
63	6-C(=NOC_3H_7)C_5H_{11}	6.77			6.63	0.14	6.48	0.29	5.42	0	0	0	0

(*continued on next page*)

Table 11 (*continued*)

No	X	log 1/*C*	log 1/*C* (Eq. 5)		log 1/*C* (Eq. 12)		log 1/*C* (Eq. 13)		*C*log *P*	*I*	I_1	I_2	I_3
		Obsd	Calcd	Δ	Calcd	Δ	Calcd	Δ					
64	6-C(=NOC$_3$H$_7$)C$_6$H$_{13}$	6.72			6.58	0.14	6.45	0.27	5.95	0	0	0	0
65	6-C(=NOC$_3$H$_7$)C$_7$H$_{15}$	6.68			6.54	0.14	6.42	0.26	6.48	0	0	0	0
66	6-C(=NOC$_3$H$_7$)C$_8$H$_{17}$	6.54			6.50	0.04	6.39	0.15	7.00	0	0	0	0
67	6-C(=NOC$_3$H$_7$)C$_9$H$_{19}$	6.34			6.46	−0.12	6.36	−0.02	7.53	0	0	0	0
68	6-C(=NOC$_3$H$_7$)C$_{10}$H$_{21}$	6.17			6.42	−0.25	6.32	−0.15	8.06	0	0	0	0
69	6-C(=NOC$_3$H$_7$)C$_{12}$H$_{25}$	6.04			6.34	−0.30	6.26	−0.22	9.12	0	0	0	0
70	6-CH$_2$N$_3$	6.11			6.25	−0.14	6.61	−0.50	3.11	0	0	0	0
71	6-CH(N$_3$)CH$_3$	6.18			6.23	−0.05	6.12	0.06	3.42	0	1	0	0
72	6-CH(N$_3$)C$_2$H$_5$	6.10			6.19	−0.09	6.09	0.01	3.95	0	1	0	0
73	6-CH(N$_3$)C$_3$H$_7$	6.07			6.15	−0.08	6.06	0.01	4.48	0	1	0	0
74	6-CH(N$_3$)C$_4$H$_9$	6.12			6.11	0.01	6.03	0.09	5.01	0	1	0	0
75	6-CH(N$_3$)C$_5$H$_{11}$	6.12			6.07	0.05	6.00	0.12	5.54	0	1	0	0
76	6-CH(N$_3$)C$_6$H$_{13}$	6.04			6.03	0.01	5.97	0.07	6.07	0	1	0	0
77	6-CH(N$_3$)C$_7$H$_{15}$	6.07			5.99	0.08	5.94	0.13	6.60	0	1	0	0
78	6-CH(N$_3$)C$_8$H$_{17}$	5.97			5.94	0.03	5.91	0.06	7.13	0	1	0	0
79	6-CH(N$_3$)C$_9$H$_{19}$	5.95			5.90	0.05	5.88	0.07	7.65	0	1	0	0
80	6-CH(N$_3$)C$_{10}$H$_{21}$	5.90			5.86	0.04	5.84	0.06	8.18	0	1	0	0
81	6-CH(N$_3$)C$_{12}$H$_{25}$	5.83			5.78	0.05	5.78	0.05	9.24	0	1	0	0
82	6-CH(N$_3$)(CH$_2$)$_2$CH(CH$_3$)$_2$	6.12			6.08	0.04	6.01	0.11	5.41	0	1	0	0
83	6-CHO	6.70			6.93	−0.23	6.71	−0.01	1.44	0	0	0	0
84	6-COCH$_3$	6.62			6.93	−0.31	6.71	−0.09	1.46	0	0	1	0
85	6-COC$_2$H$_5$	6.72			6.89	−0.17	6.68	0.04	1.99	0	0	1	0
86	6-COC$_3$H$_7$	6.80			6.85	−0.05	6.65	0.15	2.52	0	0	1	0
87	6-COC$_4$H$_9$	6.77			6.81	−0.04	6.62	0.15	3.05	0	0	1	0
88	6-COC$_5$H$_{11}$	6.96			6.77	0.19	6.59	0.37	3.58	0	0	1	0
89	6-COC$_6$H$_{13}$	6.96			6.73	0.23	6.55	0.41	4.11	0	0	1	0
90	6-COC$_7$H$_{15}$	6.80			6.69	0.11	6.52	0.28	4.64	0	0	1	0
91	6-COC$_8$H$_{17}$	6.62			6.64	−0.02	6.49	0.13	5.17	0	0	1	0
92	6-COC$_9$H$_{19}$	6.54			6.60	−0.06	6.46	0.08	5.70	0	0	1	0
93	6-COC$_{10}$H$_{21}$	6.40			6.56	−0.16	6.43	−0.03	6.22	0	0	1	0
94	6-COC$_{12}$H$_{25}$	6.18			6.48	−0.30	6.37	−0.19	7.28	0	0	1	0
95	6-CH$_2$OH	9.60[a]			9.62	−0.02	6.74	2.86	0.95	0	0	0	0
96	6-CH(OH)CH$_3$	9.30			9.60	−0.30	9.21	0.09	1.26	0	0	0	1
97	6-CH(OH)C$_2$H$_5$	9.51			9.55	−0.04	9.18	0.33	1.79	0	0	0	1
98	6-CH(OH)C$_3$H$_7$	9.83			9.51	0.32	9.15	0.68	2.32	0	0	0	1
99	6-CH(OH)C$_4$H$_9$	9.73			9.47	0.26	9.12	0.61	2.85	0	0	0	1
100	6-CH(OH)C$_5$H$_{11}$	9.68			9.43	0.25	9.09	0.59	3.38	0	0	0	1
101	6-CH(OH)C$_6$H$_{13}$	9.18			9.39	−0.21	9.06	0.12	3.91	0	0	0	1
102	6-CH(OH)C$_7$H$_{15}$	9.10			9.35	−0.25	9.03	0.07	4.44	0	0	0	1
103	6-CH(C$_2$H$_5$)OCOCH$_3$	6.66			6.84	−0.18	6.64	0.02	2.65	0	0	0	0
104	6-CH(C$_2$H$_5$)OCOCH$_2$CH$_3$	6.92			6.80	0.12	6.61	0.31	3.18	0	0	0	0
105	6-CH(C$_2$H$_5$)OCO(CH$_2$)$_2$CH$_3$	6.77			6.76	0.01	6.58	0.19	3.71	0	0	0	0
106	6-CH(C$_2$H$_5$)OCO(CH$_2$)$_4$CH$_3$	6.62			6.68	−0.06	6.52	0.10	4.76	0	0	0	0
107	6-CH(C$_2$H$_5$)OCO(CH$_2$)$_5$CH$_3$	6.68			6.63	0.05	6.49	0.19	5.29	0	0	0	0
108	6-CH(C$_3$H$_7$)OCOCH$_3$	7.10			6.80	0.30	6.61	0.49	3.18	0	0	0	0
109	6-CH(C$_3$H$_7$)OCOCH$_2$CH$_3$	7.15			6.76	0.39	6.58	0.57	3.71	0	0	0	0
110	6-CH(C$_3$H$_7$)OCO(CH$_2$)$_2$CH$_3$	7.15			6.72	0.43	6.55	0.60	4.23	0	0	0	0
111	6-CH(C$_3$H$_7$)OCO(CH$_2$)$_4$CH$_3$	7.15			6.63	0.52	6.49	0.66	5.29	0	0	0	0
112	6-CH(C$_3$H$_7$)OCO(CH$_2$)$_5$CH$_3$	6.96			6.59	0.37	6.46	0.50	5.82	0	0	0	0
113	6-CH(C$_4$H$_9$)OCOCH$_3$	7.05			6.76	0.29	6.58	0.47	3.71	0	0	0	0
114	6-CH(C$_4$H$_9$)OCOCH$_2$CH$_3$	7.22			6.72	0.50	6.55	0.67	4.23	0	0	0	0
115	6-CH(C$_4$H$_9$)OCO(CH$_2$)$_2$CH$_3$	6.96			6.68	0.28	6.52	0.44	4.76	0	0	0	0
116	6-CH(C$_4$H$_9$)OCO(CH$_2$)$_4$CH$_3$	6.77			6.59	0.18	6.46	0.31	5.82	0	0	0	0
117	6-CH(C$_4$H$_9$)OCO(CH$_2$)$_5$CH$_3$	7.05			6.55	0.50	6.42	0.63	6.35	0	0	0	0
118	6-CH(C$_5$H$_{11}$)OCOCH$_3$	6.55			6.72	−0.17	6.55	0.00	4.23	0	0	0	0
119	6-CH(C$_5$H$_{11}$)OCOCH$_2$CH$_3$	6.46			6.68	−0.22	6.52	−0.06	4.76	0	0	0	0
120	6-CH(C$_5$H$_{11}$)OCO(CH$_2$)$_2$CH$_3$	6.41			6.63	−0.22	6.49	−0.08	5.29	0	0	0	0
121	6-CH(C$_5$H$_{11}$)OCO(CH$_2$)$_4$CH$_3$	6.44			6.55	−0.11	6.42	0.02	6.35	0	0	0	0
122	6-CH(C$_5$H$_{11}$)OCO(CH$_2$)$_5$CH$_3$	6.43			6.51	−0.08	6.39	0.04	6.88	0	0	0	0
123	6-CH(C$_6$H$_{13}$)OCOCH$_3$	6.19			6.68	−0.49	6.52	−0.33	4.76	0	0	0	0
124	6-CH(C$_6$H$_{13}$)OCOCH$_2$CH$_3$	6.15			6.63	−0.48	6.49	−0.34	5.29	0	0	0	0
125	6-CH(C$_6$H$_{13}$)OCO(CH$_2$)$_2$CH$_3$	6.08			6.59	−0.51	6.46	−0.38	5.82	0	0	0	0

[a]Not included in the derivation of QSAR 13.

Table 12. Biological and physicochemical parameters used to derive QSAR 14 for the antiproliferative activity of 2- or 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	log 1/*C*	log 1/*C* (Eq. 14)		*C*log *P*	*I*
		Obsd	Calcd	Δ		
1	2-CH(=NOH)	6.27	6.22	.05	1.56	0
2	2-C(=NOH)CH_3	6.33	6.30	.03	2.0	1
3	2-C(=NOH)C_2H_5	6.35	6.38	−.03	2.53	1
4	2-C(=NOH)C_3H_7	6.40	6.43	−.03	3.06	1
5	2-C(=NOH)C_4H_9	6.42	6.45	−.03	3.59	1
6	2-C(=NOH)C_5H_{11}	6.38	6.46	−.08	4.12	1
7	2-C(=NOH)C_6H_{13}	6.36	6.44	−.08	4.65	1
8	2-C(=NOH)C_7H_{15}	6.38	6.40	−.02	5.17	1
9	2-C(=NOH)C_8H_{17}	6.34	6.33	.01	5.70	1
10	2-C(=NOH)C_9H_{19}	6.28	6.25	.03	6.23	1
11	2-C(=NOH)$C_{10}H_{21}$	6.15	6.14	.01	6.76	1
12	2-C(=NOH)$C_{12}H_{25}$	5.98	5.85	.13	7.82	1
13	6-CH(=NOH)	6.64	6.60	.04	1.43	0
14	6-C(=NOH)CH_3	6.66	6.75	−.09	2.31	0
15	6-C(=NOH)C_2H_5	6.77	6.81	−.04	2.84	0
16	6-C(=NOH)C_3H_7	6.89	6.84	.05	3.37	0
17	6-C(=NOH)C_4H_9	6.92	6.86	.06	3.89	0
18	6-C(=NOH)C_5H_{11}	6.82	6.85	−.03	4.42	0
19	6-C(=NOH)C_6H_{13}	6.92	6.82	.10	4.95	0
20	6-C(=NOH)C_7H_{15}	6.77	6.76	.01	5.48	0
21	6-C(=NOH)C_8H_{17}	6.72	6.68	.04	6.01	0
22	6-C(=NOH)C_9H_{19}	6.59	6.58	.01	6.54	0
23	6-C(=NOH)$C_{10}H_{21}$	6.46	6.46	.0	7.07	0
24	6-C(=NOH)$C_{12}H_{25}$	5.98	6.14	−.16	8.13	0

Table 13. Biological and physicochemical parameters used to derive QSAR 15 for the cytotoxic activity of 2- or 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells

No	X	log 1/*C*	log 1/*C* (Eq. 15)		*C*log *P*	*I*
		Obsd	Calcd	Δ		
1	2-CH_2OH	8.68	8.71	−.03	1.33	0
2	2-CH(OH)CH_3	8.73	8.78	−.05	1.64	1
3	2-CH(OH)C_2H_5	8.73	8.82	−.09	1.85	1
4	2-CH(OH)C_3H_7	8.85	8.90	−.05	2.38	1
5	2-CH(OH)C_4H_9	8.87	8.92	−.05	2.91	1
6	2-CH(OH)C_5H_{11}	8.93	8.83	.10	3.44	1
7	2-CH(OH)C_6H_{13}	8.66	8.64	.02	3.97	1
8	2-CH(OH)C_7H_{15}	8.52	8.38	.14	4.50	1
9	6-CH_2OH	9.60	9.39	.21	.95	0
10	6-CH(OH)CH_3	9.30	9.46	−.16	1.26	0
11	6-CH(OH)C_2H_5	9.51	9.56	−.05	1.79	0
12	6-CH(OH)C_3H_7	9.83	9.65	.18	2.32	0
13	6-CH(OH)C_4H_9	9.73	9.68	.05	2.85	0
14	6-CH(OH)C_5H_{11}	9.68	9.60	.08	3.38	0
15	6-CH(OH)C_6H_{13}	9.18	9.42	−.24	3.91	0
16	6-CH(OH)C_7H_{15}	9.10	9.17	−.07	4.44	0

4. Conclusion

An analysis of our QSAR results on 2- or 6-X-5,8-dimethoxy-1,4-naphthoquinones brings up a number of points of interest. On considering the most important factor, that is, hydrophobicity for this paper containing 10 individual biological QSARs, only one of the QSAR (Eq. 11) lack hydrophobic term. Equation 11 gave a good correlation with MR_X (overall size and polarizability of the X substituents). The term MR_X in Eq. 11 can be replaced by π_X (hydrophobicity of the X substituents) and represented by Eq. 11a. Seven QSARs (Eqs. 1, 3, 4, 6, 7, 9 and 10) have positive hydrophobic terms whereas two QSARs (Eqs. 2 and 8) have negative hydrophobic terms. These results suggest that the antiproliferative/cytotoxic activities of 2- or 6-X-5,8-dimethoxy-1,4-naphthoquinones against L1210 cells are mainly dependent on their hydrophobicity. Because of each data set of these naphthoquinones are dominated by the variation of alkyl groups, there is a high correlation between *C*log *P*, CMR, and MgVol. Thus the importance of their CMR and MgVol cannot be ignore. The

Table 14. Biological and physicochemical parameters used to derive QSAR 16 for the antiproliferative/cytotoxic activity of 2- or 6-X-5,8-dimethoxy-1,4-naphthoquinones having high and low values from each subset (Tables 1–10) against L1210 cells

No	X	log 1/*C*	log 1/*C* (Eq. 16)		*C*log *P*	*I*	I_1
		Obsd	Calcd	Δ			
1	2-C(=NOH)C_4H_9	6.42	6.75	−0.33	3.59	1	0
2	2-C(=NOH)$C_{12}H_{25}$	5.98	6.20	−0.22	7.82	0	0
3	2-CH(N_3)CH_3	6.14	6.14	0.00	3.49	0	1
4	2-CH(N_3)$C_{12}H_{25}$	5.60	5.36	0.24	9.31	0	0
5	2-CHO	6.39[a]	9.74	−3.35	1.51	0	0
6	2-$COC_{12}H_{25}$	5.61	6.58	−0.97	7.13	0	0
7	2-CH(OH)C_5H_{11}	8.93	8.66	0.27	3.44	0	0
8	2-CH(OH)C_7H_{15}	8.52	8.06	0.46	4.50	0	0
9	6-C(=NOH)C_4H_9	6.92	6.59	0.33	3.89	0	0
10	6-C(=NOH)$C_{12}H_{25}$	5.98	6.02	−0.04	8.13	0	0
11	6-C(=NOC_3H_7)C_4H_9	6.85	7.84	−0.99	4.89	0	0
12	6-C(=NOC_3H_7)$C_{12}H_{25}$	6.04	5.47	0.57	9.12	0	0
13	6-CH(N_3)CH_3	6.18	6.18	0.00	3.42	0	1
14	6-CH(N_3)$C_{12}H_{25}$	5.83	5.40	0.43	9.24	0	0
15	6-COC_5H_{11}	6.96[a]	8.58	−1.62	3.58	0	0
16	6-$COC_{12}H_{25}$	6.18	6.50	−0.32	7.28	0	0
17	6-CH(OH)C_3H_7	9.83	9.29	0.54	2.32	0	0
18	6-CH(OH)C_7H_{15}	9.10	8.09	1.01	4.44	0	0
19	6-CH(C_4H_9)$OCOC_2H_5$	7.22	8.21	−0.99	4.23	0	0
20	6-CH(C_6H_{13})$OCO(CH_2)_2CH_3$	6.08[a]	7.32	−1.24	5.82	0	0

[a] Not included in the derivation of QSAR 16.

steric interactions of the substituents at either position-2 or position-6 are also important. Unfortunately, the steric contribution of these substituents was not predicted due to the unavailability of the steric parameters. The domination of the hydrophobic effect is further supported by combined equations (Eqs. 14–16).

In the combined equations (Eqs. 5, 12 and 13), the hydrophobic effect is diminished and the indicator variables are dominated. This may be due to the fact that the combined equations were formulated by the combination of data of 5,8-dimethoxy-1,4-naphthoquinones having various functional groups at position -2 or -6. Particularly, the data of 2- or 6-(1-hydroxyalkyl)-5,8-dimethoxy-1,4-naphthoquinones, which showed dramatic increase in potency (2–3 log units more potent) that it overwhelms all other effects in the combined equations, and thus the predominant factor in the combined equations are the indicator variables. By comparing Eq. 15 with that of 4, 7,9, and 10, it is clear that 2- or 6-(1-hydroxyalkyl)-5,8-dimethoxy-1,4-naphthoquinones are interacting with the receptor in a similar manner as the other analogs do.

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