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Understanding topoisomerase I and II in terms of QSAR

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Abstract—A variety of antitumor agents currently used in chemotherapy or evaluated in clinical trials are known to inhibit DNA topoisomerase I or II. We have developed sixteen quantitative structure–activity relationships (QSAR) for different sets of compounds that are camptothecin analogs, 1,4-naphthoquinones, unsaturated acids, benzimidazoles, quinolones, and miscellaneous fused heterocycles to understand chemical–biological interactions governing their inhibitory activities toward topoisomerase I and II.

1. Introduction

DNA topoisomerases (topo) are ubiquitous enzymes that control and modify the essential cellular functions involved in replication, recombination, transcription, chromosome condensation, and the maintenance of genome stability by catalyzing the passage of individual DNA strands (topo I) or double helices (topo II) through one another, which is manifested in the interconversion between topological isomers of DNA. Topoisomerase I breaks a single DNA strand, while topoisomerase II breaks both strands and requires ATP for full activity.[1–6] A variety of antitumor agents currently used in chemotherapy or evaluated in clinical trials are known to inhibit DNA topoisomerase I (topo I) or II (topo II). The antitumor drugs camptothecin, doxorubicin, etoposide, and teniposide are representative topoisomerase I or II inhibitors. It has been shown that bi- and ter-benzimidazole derivatives constitute a class of topoisomerase I and/or II inhibitors, indicating that a fused ring system in the structure is critical for the activity.[6–10] In the present paper, we have discussed the QSAR studies on the camptothecin analogs, 1,4-naphthoquinones, unsaturated acids, benzimidazoles, quinolones, and miscellaneous fused heterocycles for their topoisomerase I or topoisomerase II inhibiting activities.

Keywords: Hydrophobicity; Molar refractivity; Molar volume; NVE; QSAR; Topoisomerase inhibitor.
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2. Materials and methods

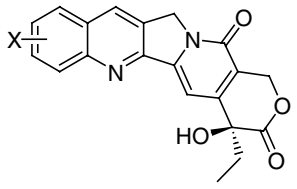
All the data have been collected from the literature (see individual QSAR for respective references). C is the molar concentration of a compound and log $1/C$ is the dependent variable that defines the biological parameter for QSAR equations. Physicochemical descriptors are auto-loaded, and multiregression analyses (MRA) used to derive the QSAR is executed with the C-QSAR program.[11] The parameters used in this report have already been discussed.[12] Briefly, C log P is the calculated octanol/water partition coefficient. MR is the molar refractivity and defined by the Lorentz–Lorenz equation: $MR = n^2 - 1/n^2 + 2(MW/\delta)$, where n = refractive index, δ = density, MW = molecular weight. CMR is the calculated molar refractivity.[11] Molar refractivity (MR) has a strong correlation with the molecular polarizability. Thus, it has been used as a measure of polarizability. MR can be used for a substituent or for the whole molecule. NVE (number of valence electrons) is a parameter[13] that was found to be another approach to understand polarizability and calculated by simply summing up the valence electrons in a molecule, for example, H = 1, C = 4, Si = 4, N = 5, P = 5, O = 6, S = 6, and halogens = 7. There are four commonly encountered electronic parameters: σ, σ^-, σ^+, and σ^* that account for specific electronic effects of substituents on a parent molecule. These parameters are known as the Hammett parameters and their application has been illustrated.[12] MgVol is the molar volume calculated by using the method of McGowan. I is an indicator variable that takes the value of 1 or 0 for structural features and cannot be defined by the normal parameters. In

QSAR equations, n is the number of data points, r is the correlation coefficient, r^2 is the goodness of fit, q^2 is the goodness of prediction 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. Inhibition of topoisomerase I

3.1.1. Inhibition of topoisomerase I by camptothecin analogs I. Data from Wall et al.[14] (Table 1).



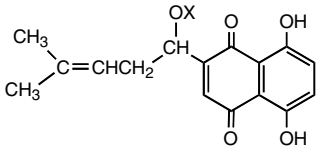
I

$$\log 1/C = 0.43(\pm 0.29)\mathrm{C}\log P - 0.43(\pm 0.22)\sigma_X^+ + 1.11(\pm 0.35)I - 0.89(\pm 0.40)\mathrm{MR}_9 + 6.37(\pm 0.19)$$
$$n = 17, \quad r^2 = 0.862, \quad s = 0.226, \quad q^2 = 0.681$$
$$\text{outliers : 9-Me; 9-Cl; 9,10-di-Cl; 9-NH}_2 \qquad (1)$$

$I = 1$ for substituent 10-OCH_2O-11.

σ^+ Represents a substituents ability to delocalize a positive charge. Its meaning has been discussed and illustrated.[15]

3.1.2. Inhibition of topoisomerase I by 2-CH(OX)-($CH_2CH{=}CMe_2$)-5,8-dihydroxy-1,4-naphthoquinones II. Data from Ahn and Sok.[16] (Table 2).



II

$$\log 1/C = 0.81(\pm 0.44)\mathrm{C}\log P - 1.48(\pm 0.64) \times \log(\beta \times 10^{\mathrm{C}\log P} + 1) + 1.59(\pm 1.39)$$
$$n = 8, \quad r^2 = 0.929, \quad s = 0.150, \quad q^2 = 0.883$$
$$\text{outlier : X} = \mathrm{COC_3H_7}$$
$$\text{optimum C}\log P = 4.34; \quad \log \beta = -4.26 \qquad (2)$$

Table 2. Biological and physicochemical constants used to derive QSAR Eq. 2 for the inhibition of topoisomerase I by 2-CH(OX)($CH_2CH{=}CMe_2$)-5,8-dihydroxy-1,4-naphthoquinones **II**

No	X	Log 1/C (Eq. 2)			C log P
		Obsd	Calcd	Δ	
1	H	3.68	3.68	0.00	2.87
2	COMe	4.35	4.34	0.01	3.99
3	COC_2H_5	4.36	4.38	−0.02	4.52
4[a]	COC_3H_7	3.84	−2.00	5.84	5.05
5	COC_4H_9	3.79	3.92	−0.13	5.58
6	COC_5H_{11}	3.68	3.59	0.09	6.11
7	COC_6H_{13}	3.20	3.24	−0.04	6.63
8	$COCHMe_2$	4.08	4.21	−0.13	5.05
9	$COCH_2CH_2CH{=}CH_2$	4.40	4.19	0.21	5.09

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

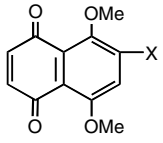
Table 1. Biological and physicochemical constants used to derive QSAR Eq. 1 for the inhibition of topoisomerase I by camptothecin analogs **I**

No	X	Log 1/C (Eq. 1)			C log P	σ_X^+	I	MR_9
		Obsd	Calcd	Δ				
1	10-OCH_2O-11	7.57	7.71	−0.14	0.08	−0.68	1	0.10
2[a]	9-Me	7.42	6.12	1.30	0.52	−0.07	0	0.56
3	9-NH_2, 10-OCH_2O-11	7.32	7.24	0.08	−0.27	−0.84	1	0.54
4	9-Cl, 10-OCH_2O-11	7.22	7.32	−0.11	0.58	−0.31	1	0.60
5[a]	9-Cl	7.07	6.03	1.03	0.83	0.37	0	0.60
6	10-OH	6.96	6.83	0.13	0.37	−0.92	0	0.10
7[a]	9,10-Cl_2	6.96	6.24	0.72	1.43	0.48	0	0.60
8[a]	9-NH_2	6.96	5.86	1.10	−0.23	−0.16	0	0.54
9	10-Br	6.89	6.74	0.15	1.23	0.15	0	0.10
10	10-NH_2	6.85	6.74	0.12	−0.23	−1.30	0	0.10
11	10-Cl	6.85	6.69	0.16	1.08	0.11	0	0.10
12	9-NO_2, 10-OCH_2O-11	6.82	6.65	0.17	−0.38	0.03	1	0.74
13	9-F	6.80	6.36	0.43	0.51	0.34	0	0.09
14	10-Me	6.52	6.76	−0.24	0.82	−0.31	0	0.10
15	10-F	6.43	6.53	−0.09	0.51	−0.07	0	0.10
16	10-NO_2	6.19	6.02	0.17	0.18	0.79	0	0.10
17	H	6.17	6.42	−0.25	0.32	0.00	0	0.10
18	9-OH	6.06	6.11	−0.05	0.10	0.12	0	0.29
19	10-COOH	6.00	6.25	−0.25	0.35	0.42	0	0.10
20	9-NMe_2, 10-OH	6.00	6.05	−0.05	1.41	−1.08	0	1.56
21	10-CN	5.72	5.95	−0.23	−0.12	0.66	0	0.10

[a] Not included in the derivation of QSAR Eq. 1.

The authors were seeking for alkylating agents as anticancer drugs. Presumably the X group would be activated by the carbonyl group. QSAR 2 is based on the bilinear model of Kubinyi.[17] It suggests that the activity of naphthoquinones **II** first increases linearly with an increase in hydrophobicity to an optimum C log *P* 4.34 and then decreases linearly in contrast to the usual parabolic relationship.

3.1.3. Inhibition of topoisomerase I by 6-X-5,8-dimethoxy-1,4-naphthoquinones III. Data from Song et al.[18] (Table 3).

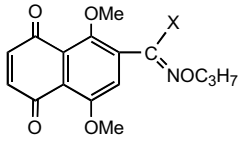


III

$$\begin{aligned}\log 1/C &= 0.19(\pm 0.04)\mathrm{C}\log P - 0.67(\pm 0.12) \\ &\quad \times \log(\beta \times 10^{\mathrm{C}\log P} + 1) + 4.10 + (0.12) \\ n &= 11, \quad r^2 = 0.967, \quad s = 0.049, \quad q^2 = 0.918 \\ \text{optimum C}&\log\ P = 3.97, \quad \log\beta = -4.36\end{aligned} \tag{3}$$

The authors could see that there was not a linear relation between the size of X and activity but had no idea what it was due to. QSAR 3 is a bilinear model of hydrophobicity. At first activity increases linearly with an increase in hydrophobicity to an optimum C log *P* 3.97 and then decreases linearly.

3.1.4. Inhibition of topoisomerase I by 6-C(=NOC$_3$H$_7$)X-5,8-dimethoxy-1,4-naphthoquinones IV. Data from Song et al.[19] (Table 4).



IV

Table 3. Biological and physicochemical constants used to derive QSAR Eq. 3 for the inhibition of topoisomerase I by 6-X-5,8-dimethoxy-1,4-naphthoquinones **III**

No	X	Log 1/*C* (Eq. 3)			C log *P*
		Obsd	Calcd	Δ	
1	CHO	4.42	4.37	0.05	1.44
2	$COCH_3$	4.40	4.38	0.02	1.46
3	COC_2H_5	4.42	4.48	−0.06	1.99
4	COC_3H_7	4.54	4.58	−0.04	2.52
5	COC_4H_9	4.68	4.67	0.01	3.05
6	COC_5H_{11}	4.74	4.74	0.00	3.58
7	COC_6H_{13}	4.80	4.76	0.03	4.11
8	COC_7H_{15}	4.72	4.69	0.04	4.64
9	COC_8H_{17}	4.49	4.51	−0.02	5.17
10	OCC_9H_{19}	4.23	4.29	−0.06	5.70
11	$COC_{10}H_{21}$	4.09	4.05	0.04	6.22

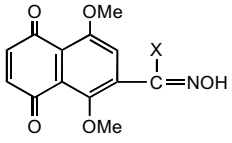
Table 4. Biological and physicochemical constants used to derive QSAR Eq. 4 for the inhibition of topoisomerase I by 6-C(=NOC$_3$H$_7$)X-5,8-dimethoxy-1,4-naphthoquinones **IV**

No	X	Log 1/*C* (Eq. 4)			C log *P*
		Obsd	Calcd	Δ	
1	H	4.36	4.35	0.01	3.15
2	CH_3	4.36	4.37	0.00	3.30
3	C_2H_5	4.44	4.42	0.02	3.83
4	C_3H_7	4.40	4.47	−0.06	4.36
5	C_4H_9	4.57	4.51	0.06	4.89
6	C_5H_{11}	4.51	4.53	−0.02	5.42
7	C_6H_{13}	4.51	4.50	0.01	5.95
8	C_7H_{15}	4.37	4.38	0.00	6.48
9[a]	C_8H_{17}	4.36	0.26	4.10	7.00
10	C_9H_{19}	3.91	3.90	0.00	7.53

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

$$\begin{aligned}\log 1/C &= 0.10(\pm 0.04)\mathrm{C}\log P - 0.64(\pm 0.14) \\ &\quad \times \log(\beta \times 10^{\mathrm{C}\log P} + 1) + 4.03(\pm 0.19) \\ n &= 9, \quad r^2 = 0.973, \quad s = 0.040, \quad q^2 = 0.960 \\ &\text{outlier : X} = C_8H_{17} \\ \text{optimum C}&\log\ P = 5.44, \quad \log\beta = -6.16\end{aligned} \tag{4}$$

3.1.5. Inhibition of topoisomerase I by 6-C(=NOH)X-5,8-dimethoxy-1,4-naphthoquinones V. Data from Song et al.[19] (Table 5).



V

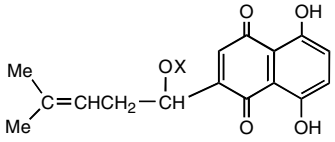
$$\begin{aligned}\log 1/C &= 0.07(\pm 0.04)\mathrm{C}\log P - 0.38(\pm 0.09) \\ &\quad \times \log(\beta \times 10^{\mathrm{C}\log P} + 1) + 4.28(\pm 0.15) \\ n &= 12, \quad r^2 = 0.951, \quad s = 0.06, \quad q^2 = 0.893 \\ \text{optimum C}&\log\ P = 4.71, \quad \log\beta = -5.36\end{aligned} \tag{5}$$

It is of interest to note here that there is a high mutual correlation between C log *P* and CMR ($r^2 = 0.998$, $q^2 = 0.996$), and C log *P* and MgVol ($r^2 = 0.998$, $q^2 = 0.996$). Thus, the equation with CMR or MgVol will give exactly the same statistics with that of C log *P*. Now, it is very hard to predict, which is the most important hydrophobic, polarizability or volume effect. We prefer Eq. 5 because the variation in X is only due to the alkyl groups.

3.1.6. Inhibition of topoisomerase I by 2-CH(OX)-(CH$_2$CH=CMe$_2$)-5,8-dihydroxy-1,4-naphthoquinones VI. Data from Ahn et al.[20] (Table 6).

Table 5. Biological and physicochemical constants used to derive QSAR Eq. 5 for the inhibition of topoisomerase I by 6-C(=NOH)X-5,8-dimethoxy-1,4-naphthoquinones **V**

No	X	Log 1/*C* (Eq. 5)			C log *P*
		Obsd	Calcd	Δ	
1	H	4.47	4.38	0.09	1.43
2	CH_3	4.39	4.44	−0.05	2.31
3	C_2H_5	4.39	4.47	−0.08	2.84
4	C_3H_7	4.47	4.51	−0.04	3.37
5	C_4H_9	4.53	4.54	−0.01	3.89
6	C_5H_{11}	4.60	4.56	0.03	4.42
7	C_6H_{13}	4.64	4.56	0.08	4.95
8	C_7H_{15}	4.53	4.52	0.01	5.48
9	C_8H_{17}	4.36	4.41	−0.06	6.01
10	C_9H_{19}	4.28	4.27	0.01	6.54
11	$C_{10}H_{21}$	4.12	4.12	0.00	7.07
12	$C_{12}H_{25}$	3.80	3.80	0.00	8.13



VI

$$\log 1/C = -1.55(\pm 0.40)\mathrm{MgVol} + 0.20(\pm 0.16)I + 8.25(\pm 1.12)$$
$$n = 13, \quad r^2 = 0.882, \quad s = 0.115, \quad q^2 = 0.746$$
outliers : monochloroacetyl; *n*-butanoyl; 4-pentenoyl (6)

$I = 1$ for X having a double bond which appears to make a small increase in potency. This is a usual search for anticancer agents.

3.1.7. Inhibition of topoisomerase I by 6-CH(R_1)(OR_2)-5,8-dimethoxy-1,4-naphthoquinones VII.

Data from Kim et al.[21] (Table 7).

Table 6. Biological and physicochemical constants used to derive QSAR Eq. 6 for the inhibition of topoisomerase I by 2-CH(OX)($CH_2CH{=}CMe_2$)-5,8-dihydroxy-1,4-naphthoquinones **VI**

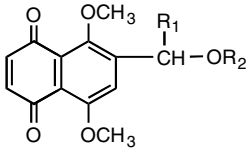
No	X	Log 1/*C* (Eq. 6)			MgVol	*I*
		Obsd	Calcd	Δ		
1	Acetyl	4.35	4.48	−0.14	2.44	0
2[a]	Monochloroacetyl	3.86	4.29	−0.43	2.56	0
3	Trichloroacetyl	3.94	3.91	0.02	2.80	0
4	*n*-Propanoyl	4.36	4.26	0.09	2.58	0
5[a]	*n*-Butanoyl	3.84	4.05	−0.21	2.72	0
6	Isobutanoyl	4.08	4.05	0.03	2.72	0
7	*n*-Pentanoyl	3.79	3.83	−0.04	2.86	0
8[a]	4-Pentenoyl	4.40	4.09	0.30	2.82	1
9	*trans*-2-Pentenoyl	4.10	4.09	0.00	2.82	1
10	*n*-Hexanoyl	3.68	3.61	0.07	3.00	0
11	*trans*-2-Hexenoyl	3.82	3.88	−0.06	2.96	1
12	*trans*-3-Hexenoyl	3.82	3.88	−0.06	2.96	1
13	2,4-Hexadienoyl	3.89	3.74	0.14	2.91	0
14	*n*-Heptanoyl	3.20	3.39	−0.19	3.14	0
15	2,6-Heptadienoyl	3.90	3.72	0.17	3.05	1
16	6-Heptenoyl	3.60	3.66	−0.06	3.10	1

[a] Not included in the derivation of QSAR Eq. 6.

Table 7. Biological and physicochemical constants used to derive QSAR Eq. 7 for the inhibition of topoisomerase I by 6-CH(R_1)(OR_2)-5,8-dimethoxy-1,4-naphthoquinones **VII**

No	R_1	R_2	Log 1/*C* (Eq. 7)			C log *P*	*I*
			Obsd	Calcd	Δ		
1	Me	H	3.96	3.93	0.03	1.26	0
2	Me	$COCH_3$	4.08	4.01	0.06	2.12	0
3	Me	$COCH_2CH_3$	4.18	4.07	0.11	2.65	0
4	Me	$CO(CH_2)_2CH_3$	4.08	4.12	−0.04	3.18	0
5[a]	Me	$CO(CH_2)_4CH_3$	4.48	3.01	1.47	4.23	0
6[a]	Me	$CO(CH_2)_5CH_3$	4.94	2.91	2.02	4.76	0
7	C_2H_5	H	3.91	3.98	−0.07	1.79	0
8	C_2H_5	$COCH_3$	4.16	4.07	0.10	2.65	0
9	C_2H_5	$COCH_2CH_3$	4.24	4.12	0.12	3.18	0
10	C_2H_5	$CO(CH_2)_2CH_3$	4.02	4.17	−0.15	3.71	0
11	C_2H_5	$CO(CH_2)_4CH_3$	4.23	4.27	−0.04	4.76	0
12	C_2H_5	$CO(CH_2)_5CH_3$	4.25	4.28	−0.04	5.29	0
13	C_3H_7	H	3.89	4.03	−0.15	2.32	0
14	C_3H_7	$COCH_3$	4.07	4.13	−0.07	3.30	0
15	C_3H_7	$COCH_2CH_3$	4.18	4.17	0.01	3.71	0
16	C_3H_7	$CO(CH_2)_2CH_3$	4.26	4.22	0.03	4.23	0
17	C_3H_7	$CO(CH_2)_4CH_3$	4.39	4.28	0.11	5.29	0
18	C_3H_7	$CO(CH_2)_5CH_3$	4.27	4.26	0.01	5.82	0
19	C_4H_9	H	4.08	4.09	−0.01	2.85	0
20	C_4H_9	$COCH_3$	4.21	4.17	0.03	3.71	0
21	C_4H_9	$COCH_2CH_3$	4.13	4.22	−0.09	4.23	0
22	C_4H_9	$CO(CH_2)_2CH_3$	4.27	4.27	0.00	4.76	0
23	C_4H_9	$CO(CH_2)_4CH_3$	4.27	4.26	0.01	5.82	0
24	C_4H_9	$CO(CH_2)_5CH_3$	4.16	4.20	−0.03	6.35	0
25[a]	C_5H_{11}	$COCH_3$	4.16	2.51	1.65	4.23	1
26[a]	C_5H_{11}	$COCH_2CH_3$	4.01	2.41	1.59	4.76	1
27	C_5H_{11}	$CO(CH_2)_2CH_3$	3.80	3.78	0.02	5.29	1
28	C_5H_{11}	$CO(CH_2)_4CH_3$	3.63	3.70	−0.07	6.35	1
29	C_5H_{11}	$CO(CH_2)_5CH_3$	3.66	3.61	0.05	6.88	1
30	C_7H_{13}	$COCH_3$	4.33	4.27	0.07	4.76	0
31	C_6H_{13}	$COCH_2CH_3$	4.30	4.28	0.01	5.29	0
32	C_6H_{13}	$CO(CH_2)_2CH_3$	4.25	4.26	−0.01	5.82	0

[a] Not included in the derivation of QSAR Eq. 7.



VII

$$\log 1/C = 0.10(\pm 0.03)\mathrm{C}\log P - 0.29(\pm 0.16) \times \log(\beta \times 10^{\mathrm{C}\log P} + 1) - 0.50(\pm 0.13)I + 3.80(\pm 0.12)$$
$$n = 28, \quad r^2 = 0.867, \quad s = 0.077, \quad q^2 = 0.824$$
optimum $\mathrm{C}\log P = 5.29$, $\log\beta = -9.71$
outliers : $R_1 = Me$, $R_2 = COC_5H_{11}$;
$R_1 = Me$, $R_2 = COC_6H_{13}$;
$R_1 = C_5H_{11}$, $R_2 = COCH_3$;
$R_1 = C_5H_{11}$, $R_2 = COC_2H_5$ (7)

$I = 1$ for the presence of $R_1 = C_5H_{11}$

Table 8. Biological and physicochemical constants used to derive QSAR Eq. 8 for the inhibition of topoisomerase I by *cis*-unsaturated acids containing different numbers of double bonds

No	Compounds	Log 1/*C* (Eq. 8)			NVE
		Obsd	Calcd	Δ	
1	Oleic acid	4.51	4.53	−0.02	118
2	Linoleic acid	4.51	4.49	0.02	116
3	Linolenic acid	4.46	4.45	0.01	114
4	Eicosanoic acid	4.74	4.78	−0.03	130
5	Eicosadienoic acid	4.80	4.74	0.06	128
6	Eicosatrienoic acid	4.70	4.69	0.00	126
7	Eicosatertraenoic acid	4.62	4.65	−0.03	124
8[a]	Eicosapentaenoic acid	4.37	4.61	−0.25	122

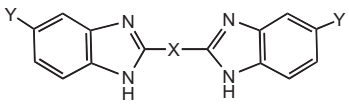
[a] Not included in the derivation of QSAR Eq. 8.

3.1.8. Inhibition of topoisomerase I by *cis*-unsaturated acids containing different numbers of double bonds. Data from Suzuki et al.[22] (Table 8).

$$\log 1/C = 0.020(\pm 0.006)\mathrm{NVE} + 2.13(\pm 0.75)$$
$$n = 7, \quad r^2 = 0.936, \quad s = 0.037, \quad q^2 = 0.875 \qquad (8)$$
$$\text{outlier : Eicosapentaenoic acid}$$

3.2. Inhibition of topoisomerase II

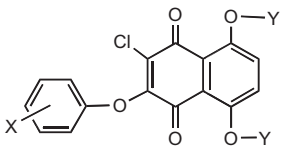
3.2.1. Inhibition of topoisomerase II by benzimidazole derivatives VIII. Data from Dykstra et al.[23] (Table 9).



VIII

$$\log 1/C = 3.28(\pm 0.60)\mathrm{MgVol} - 4.59(\pm 1.76)$$
$$n = 7, \quad r^2 = 0.975, \quad s = 0.180, \quad q^2 = 0.963$$
$$\text{outliers : X} = (\mathrm{CH_2})_2, \mathrm{Y} = \mathrm{C(=NH)NH_2};$$
$$\mathrm{X} = \mathrm{CH_2CH_2CH_2}, \mathrm{Y} = \text{  };$$
$$\mathrm{X} = \mathrm{CH{=}CH}, \mathrm{Y} = \mathrm{C(=NH)NH_2} \qquad (9)$$

3.2.2. Inhibition of topoisomerase II by 1,4-naphthoquinone derivatives IX. Data from Chang et al.[24] (Table 10).



IX

$$\log 1/C = -52.4(\pm 26.8)\mathrm{MgVol} + 10.39(\pm 5.45) \times \mathrm{MgVol}^2 + 67.4(\pm 32.8)$$
$$n = 7, \quad r^2 = 0.897, \quad s = 0.334, \quad q^2 = 0.630$$
$$\text{outliers : X} = \text{3-OH, Y} = \text{H; X} = \text{3-OMe, Y} = \text{H; X} = \text{3, 5-di-OMe, Y} = \text{COMe}$$
$$\text{optimum MgVol} = 2.52(2.46\text{–}2.63) \qquad (10)$$

QSAR 10 brings out an allosteric reaction.[25] This means, at first the activity declines as MgVol increases, but then the exponential term takes over and activity begins to increase. This implies a change in receptor structure or binding mode.

Table 10. Biological and physicochemical constants used to derive QSAR Eq. 10 for the inhibition of topoisomerase II by 1,4-naphthoquinone derivatives **IX**

No	X	Y	Log 1/*C* (Eq. 10)			MgVol
			Obsd	Calcd	Δ	
1	H	H	3.60	3.44	0.16	2.07
2[a]	3-OH	H	2.00	2.92	−0.92	2.12
3	3,5-Di-OH	H	2.30	2.47	−0.17	2.18
4[a]	3-OMe	H	2.90	1.96	0.94	2.27
5	3,5-Di-OMe	H	1.70	1.31	0.39	2.47
6	3-OH	Me	1.00	1.42	−0.42	2.41
7	3-OMe	Me	1.30	1.29	0.02	2.55
8	3,5-Di-OMe	Me	2.00	1.80	0.20	2.75
9	3-OMe	COMe	2.30	2.47	−0.17	2.86
10[a]	3,5-Di-OMe	COMe	1.70	4.28	−2.59	3.06

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

Table 9. Biological and physicochemical constants used to derive QSAR Eq. 9 for the inhibition of topoisomerase II by benzimidazole derivatives **VIII**

No	X	Y	Log 1/*C* (Eq. 9)			MgVol
			Obsd	Calcd	Δ	
1	CH_2	C(=NH)NH_2	3.40	3.40	0.00	2.44
2	CH_2	$C_3N_2H_5$	4.21	4.53	−0.33	2.78
3[a]	$(CH_2)_2$	C(=NH)NH_2	6.20	3.86	2.34	2.58
4	$(CH_2)_2$	$C_3N_2H_5$	5.00	5.00	0.00	2.93
5	$(CH_2)_3$	C(=NH)NH_2	4.52	4.32	0.20	2.72
6[a]	$(CH_2)_3$	$C_3N_2H_5$	4.30	5.46	−1.16	3.07
7	$(CH_2)_4$	C(=NH)NH_2	4.90	4.78	0.12	2.86
8	$(CH_2)_4$	$C_3N_2H_5$	5.90	5.92	−0.02	3.21
9[a]	–CH=CH–	C(=NH)NH_2	5.90	3.72	2.18	2.34
10	–CH=CH–	C(=NH)N(*iso*-Pr)	6.51	6.49	0.02	3.38

[a] Not included in the derivation of QSAR Eq. 9.

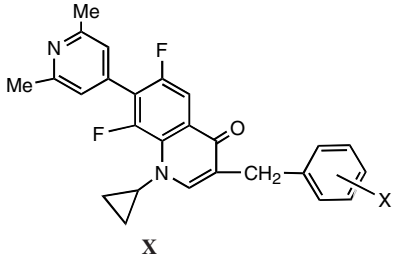
Table 11. Biological and physicochemical constants used to derive QSAR Eq. 11 for the inhibition of topoisomerase II by quinolone derivatives **X**

No	X	Log 1/*C* (Eq. 11)			σ^-	*I*
		Obsd	Calcd	Δ		
1	H	5.41	5.06	0.35	0.00	0
2	4-Cl	5.11	4.95	0.16	0.19	0
3	4-OCH_3	4.85	5.21	−0.36	−0.26	0
4[a]	4-OH	5.92	6.58	−0.66	−0.37	1
5	4-NH_2	5.14	5.42	−0.28	−0.63	0
6	3-OCH_3	4.85	4.99	−0.14	0.12	0
7	3-OH	5.96	6.30	−0.34	0.12	1
8	2-OCH_3	4.85	5.21	−0.36	−0.26	0
9	2-OH	6.48	6.58	−0.10	−0.37	1
10	2-CH_2OH	5.17	5.02	0.15	0.08	0
11[a]	2-COOH	3.70	4.62	−0.92	0.77	0
12	2-NH_2	5.68	5.42	0.25	−0.63	0
13	2-$NHCOCH_3$	5.29	5.06	0.23	0.00	0
14	2,3-Di-OH	6.44	6.51	−0.07	−0.25	1
15	2,4-Di-OH	6.80	6.79	0.00	−0.74	1
16	2,5-Di-OH	6.80	6.51	0.28	−0.25	1
17	2,6-Di-OH	7.02	6.79	0.22	−0.74	1
18	2,4,6-Tri-OH	7.01	7.01	0.00	−1.11	1

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

3.2.3. Inhibition of topoisomerase II by quinolone derivatives X.

Data from Eissenstat et al.[26] (Table 11).



X

$$\log 1/C = -0.57(\pm 0.43)\sigma^- + 1.31(\pm 0.32)I + 5.06(\pm 0.20)$$
$$n = 16, \quad r^2 = 0.912, \quad s = 0.263, \quad q^2 = 0.865$$
$$\text{outliers} : \text{X} = \text{4-OH, 2-COOH} \qquad (11)$$

I = 1 for the presence of X = OH. It seems to make little difference where the OH is positioned or if there is more than one. The positive coefficient with *I* implies OH makes for stronger inhibition. This suggests a polar region in the receptor that is confirmed by the negative σ^- (sigma) term. What is strange is that *I* takes the value of 1 for 1, 2, or 3 OH units.

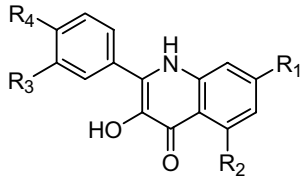
Table 12. Biological and physicochemical constants used to derive QSAR Eq. 12 for the inhibition of topoisomerase II by quinolone derivatives **XI**

No	R_1	R_2	R_3	R_4	Log 1/*C* (Eq. 12)			CMR
					Obsd	Calcd	Δ	
1	OH	OH	OH	OH	7.78	8.03	−0.25	7.66
2	F	F	OH	OH	7.52	7.31	0.21	7.38
3	CH_3	CH_3	OH	OH	9.63	9.66	−0.04	8.28
4	H	OH	OH	OH	8.01	7.63	0.38	7.50
5[a]	OH	H	OH	OH	8.40	7.63	0.77	7.50
6	H	OH	H	H	6.52	6.83	−0.30	7.20

[a] Not included in the derivation of QSAR Eq. 12.

3.2.4. Inhibition of topoisomerase II by quinolone derivatives XI.

Data from Sui et al.[27] (Table 12).



XI

$$\log 1/C = 2.63(\pm 1.31)\text{CMR} - 12.07(\pm 9.95)$$
$$n = 5, \quad r^2 = 0.932, \quad s = 0.339, \quad q^2 = 0.845$$
$$\text{outlier} : \text{R}_1 = \text{R}_3 = \text{R}_4 = \text{OH}, \quad \text{R}_2 = \text{H} \qquad (12)$$

3.2.5. Inhibition of topoisomerase II by miscellaneous fused heterocycles XII–XVI (Fig. 1) and etoposide.

Data from pinar et al.[6] (Tables 13 and 14).

From these data, we are not able to get a meaningful QSAR, because it has a large number of outliers indicating that these compounds may be interacting with the receptor in two different modes. Thus, we removed all the outliers from the data set of QSAR 13 to make it useful. After that these outliers was used in the formulation of a different QSAR 14. It is interesting to note here that both QSAR Eqs. 13 and 14 have good statistics, and not have any outlier. By comparing QSAR 13 and 14, it has been confirmed that these two data sets must be interacting with the receptor in two different modes.

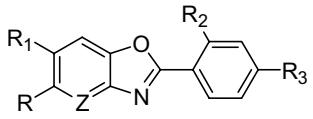
$$\log 1/C = -0.57(\pm 0.15)\text{C}\log P - 0.02(\pm 0.005) \times \text{NVE} + 8.02(\pm 1.08)$$
$$n = 13, \quad r^2 = 0.874, \quad s = 0.215, \quad q^2 = 0.781 \qquad (13)$$

$$\log 1/C = 1.04(\pm 0.27)\text{CMR} - 1.58(\pm 0.40) \times \log(\beta \times 10^{\text{CMR}} + 1) - 3.24(\pm 1.93)$$
$$n = 11, \quad r^2 = 0.926, \quad s = 0.156, \quad q^2 = 0.902,$$
$$\text{optimum CMR} = 8.48, \quad \log\beta = -8.20 \qquad (14)$$

3.2.6. Inhibition of topoisomerase II by quinolone derivatives XVIIa–XVIIx (Fig. 2).

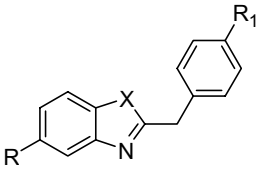
Data from Stanton[28] (Table 15 and 16).

From the data of Stanton, again we are unable to obtain a good QSAR due to the presence of a large number of outliers. As similar to the QSAR 13 and 14, this data set was also divided into two data sets that gave QSAR Eqs. 15 and 16 with good statistics.



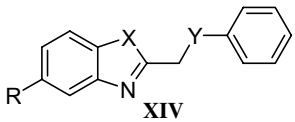
XII

No	R	R_1	R_2	R_3	Z
XIIa	H	NO_2	OMe	H	CH
XIIb	H	Me	NO_2	H	CH
XIIc	NO_2	H	H	H	CH
XIId	H	H	H	CMe_3	N
XIIe	H	Me	F	H	CH
XIIf	NH_2	H	H	Et	CH
XIIg	Me	H	Me	Me	CH
XIIh	Me	H	H	NHMe	CH
XIIi	NO_2	H	H	OEt	CH



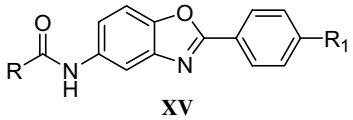
XIII

No	R	R_1	X
XIIIa	Me	Me	NH
XIIIb	H	OMe	O
XIIIc	Me	NH_2	NH



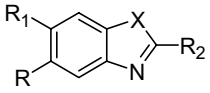
XIV

No	R	X	Y
XIVa	Me	NH	S
XIVb	NO_2	NH	O
XIVc	H	S	O
XIVd	COOMe	NH	S



XV

No	R	R_1
XVa	$CH_2C_6H_4$(4-NO_2)	H
XVb	$CH_2C_6H_5$	F
XVc	C_6H_4(4-F)	H
XVd	$CH_2C_6H_4$(4-Br)	Et



XVI

No	R	R_1	R_2	X
XVIa	Cl	NO_2	cy-C_6H_{11}	O
XVIb	Cl	H	CH_2-cy-C_6H_{11}	NH
XVIc	H	H	CH_2CH_2-cy-C_5H_9	NH

Figure 1.

$$\log 1/C = 12.38(\pm 4.11)\mathrm{CMR} - 0.65(\pm 0.22)\mathrm{CMR}^2 - 0.91(\pm 0.21)I - 57.63(\pm 19.51)$$
$$n = 18, \quad r^2 = 0.901, \quad s = 0.167, \quad q^2 = 0.847$$
$$\text{optimum CMR} = 9.48(9.35\text{–}9.60) \qquad (15)$$

Table 13. Biological and physicochemical constants used to derive QSAR Eq. 13 for the inhibition of topoisomerase II by miscellaneous fused heterocycles **XII–XVI** and etoposide

No	Compounds	Log 1/*C* (Eq. 13)			C log *P*	NVE
		Obsd	Calcd	Δ		
1	**XIIa**	4.77	4.89	−0.12	2.84	100
2	**XIIb**	4.73	4.44	0.29	3.79	94
3	**XIIc**	4.49	4.76	−0.27	3.39	88
4	**XIId**	3.97	4.15	−0.18	4.25	96
5	**XIIIa**	3.99	4.02	−0.02	4.63	90
6	**XIVa**	4.56	4.27	0.29	4.19	90
7	**XIVb**	4.55	4.71	−0.16	3.16	100
8	**XIVc**	4.94	4.60	0.34	3.77	84
9	**XVa**	3.38	3.41	−0.03	4.43	138
10	**XVb**	3.38	3.32	0.06	4.85	128
11	**XVIa**	3.99	4.07	−0.08	4.27	100
12	**XVIb**	3.51	3.65	−0.13	5.27	90
13	Etoposide	4.66	4.63	0.03	0.03	226

Table 14. Biological and physicochemical constants used to derive QSAR Eq. 14 for the inhibition of topoisomerase II by miscellaneous fused heterocycles **XII–XVI**

No	Compounds	Log 1/*C* (Eq. 14)			CMR
		Obsd	Calcd	Δ	
1	**XIIe**	3.36	3.35	0.02	6.37
2	**XIIf**	3.94	4.14	−0.20	7.19
3	**XIIg**	4.35	4.22	0.13	7.28
4	**XIIh**	3.89	4.14	−0.25	7.19
5	**XIIi**	4.65	4.46	0.19	7.58
6	**XIIIb**	4.06	3.94	0.12	6.97
7	**XIIIc**	4.33	4.32	0.01	7.40
8	**XIVd**	4.77	4.81	−0.04	8.49
9	**XVc**	4.62	4.61	0.01	9.29
10	**XVd**	3.50	3.50	0.00	11.44
11	**XVIc**	3.66	3.64	0.02	6.66

$I = 1$ for the presence of piperazine substituent at position-7.

$$\log 1/C = -2.33(\pm 1.01)\mathrm{C}\log P - 1.33(\pm 0.88)$$
$$n = 6, \quad r^2 = 0.910, \quad s = 0.281, \quad q^2 = 0.800 \qquad (16)$$

By comparing Eq. 15 and 16, it is clear that these two sets of quinolone derivatives **XVIIa–XVIIr**, and **XVIIs–XVIIx** may be interacting with the receptor in two different modes.

4. Conclusion

An analysis of our QSAR results on topoisomerases brings up a number of points of interest. On considering topoisomerase I for this paper, only two QSAR (Eqs. 6 and 8) out of eight individual QSAR, lack hydrophobic terms. It is interesting, all the five QSAR (Eqs. 2–5 and 7) out of six are for 1,4-naphthoquinone derivatives where we get bilinear C log *P* term. Optimum C log *P* for these equations is 4.34, 3.97, 5.44, 4.71, and 5.29, respectively. Recently, we found that the antiproliferative/cytotoxic activities for different series of 2- or

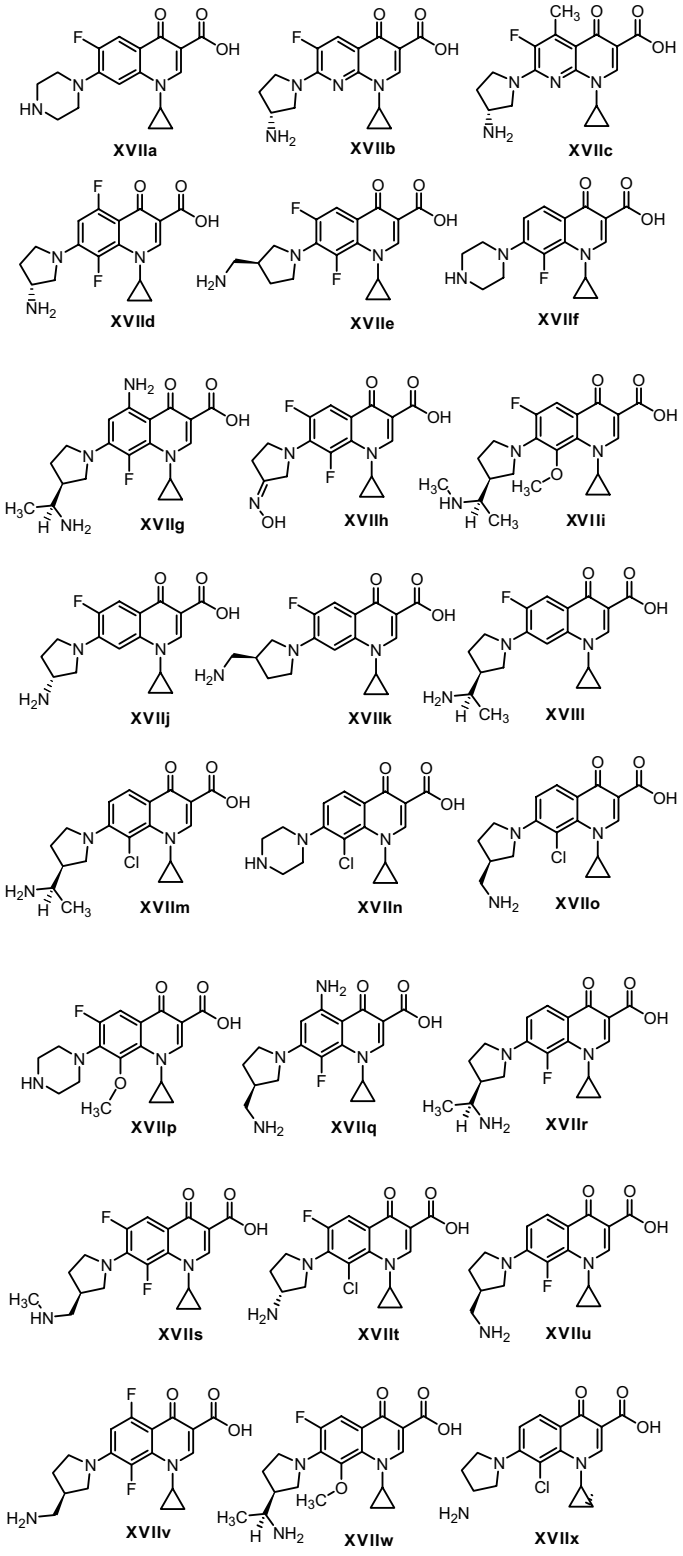


Figure 2.

6-substituted-5,8-dimethoxy-1,4-naphthoquinones depend largely on their hydrophobicity.[29] QSAR 1 for camptothecin analogs is linear in C log *P* showing new possibilities for increased activity. MR and electronic parameter (σ^+) of substituents are also important for these analogs. QSAR 6 has MgVol term and interestingly with negative coefficient. QSAR 8 that is linear in NVE also indicates the possibilities for more active analogs.

On considering topoisomerase II, only two QSAR (Eqs. 13 and 16) out of eight having hydrophobic term and also with negative coefficient. NVE term is present in

Table 15. Biological and physicochemical constants used to derive QSAR Eq. 15 for the inhibition of topoisomerase II by quinolone derivatives **XVIIa–XVIIr**

No	Compounds	Log 1/*C* (Eq. 15)			CMR	*I*
		Obsd	Calcd	Δ		
1	**XVIIa**	−0.18	−0.26	0.08	8.72	1
2	**XVIIb**	0.35	0.42	−0.07	8.50	0
3	**XVIIc**	0.94	0.87	0.07	8.97	0
4	**XVIId**	0.54	0.67	−0.13	8.73	0
5	**XVIIe**	0.96	0.98	−0.03	9.20	0
6	**XVIIf**	−0.08	−0.26	0.17	8.72	1
7	**XVIIg**	0.97	0.85	0.12	10.01	0
8	**XVIIh**	0.94	0.79	0.15	8.86	0
9	**XVIIi**	0.00	0.02	−0.01	10.72	0
10	**XVIIj**	0.52	0.66	−0.14	8.72	0
11	**XVIIk**	1.06	0.98	0.08	9.18	0
12	**XVIIl**	0.78	1.02	−0.24	9.64	0
13	**XVIIm**	0.73	0.77	−0.04	10.12	0
14	**XVIIn**	0.06	0.07	0.00	9.19	1
15	**XVIIo**	0.96	1.01	−0.06	9.66	0
16	**XVIIp**	−0.14	0.11	−0.25	9.33	1
17	**XVIIq**	0.95	1.03	−0.08	9.55	0
18	**XVIIr**	1.38	1.02	0.36	9.64	0

Table 16. Biological and physicochemical constants used to derive QSAR Eq. 16 for the inhibition of topoisomerase II by quinolone derivatives **XVIIs–XVIIx**

No	Compounds	Log 1/*C* (Eq. 16)			C log *P*
		Obsd	Calcd	Δ	
1	**XVIIs**	0.67	0.90	−0.23	−0.96
2	**XVIIt**	−0.04	−0.34	0.30	−0.42
3	**XVIIu**	1.54	1.59	−0.05	−1.26
4	**XVIIv**	1.56	1.24	0.32	−1.11
5	**XVIIw**	−0.19	−0.10	−0.09	−0.53
6	**XVIIx**	−0.24	0.01	−0.24	−0.57

Eq. 13 with negative coefficient, suggesting electron repulsion between ligand and receptor. QSAR 9 is linear in MgVol implies that more potent compound could be made. Of course how much more potent is not possible to say. One would have to make compounds with small increments until the limit was found. The same possibility exists for Eq. 12 based on CMR. The role of molar refractivity is brought out by Eqs. 14 and 15 where we get bilinear and parabolic CMR term. Optimum CMR values are 8.48 and 9.48, respectively. An electronic term (σ^-) of substituents for quinolone derivatives is present in Eq. 11. It is interesting that Eq. 10 brings out an allosteric reaction in terms of MgVol for 1,4-naphthoquinone derivatives that means, at first activity declines as MgVol increases, but then the exponential term takes over and activity begins to increase. This implies a change in receptor structure or binding mode.

Finally, we can say that the inhibition of topoisomerase I is largely dependent on the hydrophobicity of compounds, with a bilinear correlation being the most important. On the other hand, polarizability (CMR or NVE) and molar volume (MgVol) of the compounds are important for topoisomerase II inhibition.

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