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QSAR of Anticancer Compounds. Bis(11-oxo-11*H*-indeno [1,2-*b*]quinoline-6-carboxamides), Bis(phenazine-1-carboxamides), and Bis(naphthalimides)

Suresh Babu Mekapati,[a] William A. Denny,[b,*] Alka Kurup[a] and Corwin Hansch[a,*]

[a]*Department of Chemistry, Pomona College, Claremont, CA 91711, USA*
[b]*Auckland Cancer Society Research Center, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand*

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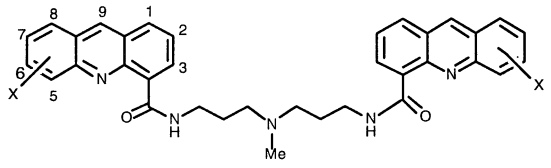
Abstract—QSAR have been developed for the anticancer activity (growth inhibition) of various tumor cells by bis(11-oxo-11*H*-indeno[1,2-*b*]quinoline-6-carboxamides), bis(phenazine-1-carboxamides), and bis(naphthalimides). Of the seven QSAR, positive hydrophobic interactions are found in only two examples: bis(naphthalimides) versus human colon cancer cells. This is consistent with other QSAR of anticancer compounds where hydrophobic interactions are found to be unimportant.

Introduction

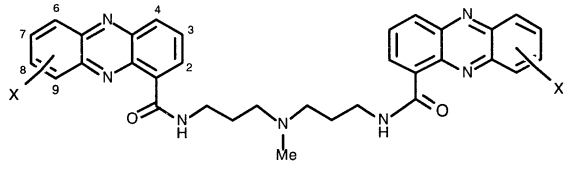
Interest in QSAR (quantitative structure–activity relationships) to help describe the interface between chemistry and biology has expanded exponentially since its advent at Pomona College in 1962 (currently there are almost 7000 web sites on the subject). The most important parameter in formulating these equations that give physicochemical bases for biological activity is the octanol/water partition coefficient, logP or its calculated equivalent ClogP. Out of 7450 QSAR currently in the Pomona database, the large majority (67%) contain either this term (4150) or the hydrophobic parameter for substituents, π (814).

We have become increasingly interested in the minority of QSAR that do not contain such hydrophobic terms. There are certain areas where hydrophobic terms are likely to be of lesser importance in such QSAR. One of these is in studies of compounds interacting with isolated receptors; currently of 1185 QSAR for receptors only 400 (34%) contain a logP term.[1–3] In contrast, the term appears more often in studies with whole animals (vertebrates), because of the greater diffusional barriers imposed; of 717 equations, 498 (69%) contain a logP term.

In a recent analysis of variations of the cell inhibitory properties of related dimeric DNA binding compounds (**I**) and (**II**), we found[4] that bis(acridines) (**I**) linked by a



I



II

*Corresponding author. Fax: +1-909-607-7726; e-mail: b.denny@auckland.ac.nz; atessier@pomona.edu

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$CONH(CH_2)_3NMe(CH_2)_3NHCO$ chain displayed a marginal negative dependence on ClogP, while the closely related bis(phenazines) (**II**) showed a very strong dependence on ClogP, with an optimum ClogP ($ClogP_0$) at 7.3. These compounds are of interest because they are representative of a new class of dimeric compounds, containing two lipophilic, functionally neutral, potentially DNA intercalating chromophores linked by a cationic chain. This broad class is effective topoisomerase poisons[5,6] that exhibit greatly increased inhibitory potency compared to the monomers they are comprised of,[7] and show excellent activity against human tumor xenografts in nude mice.[8,9]

In this paper we extend our previous QSAR study of compounds of this general type with an analysis of variations in further examples of bis(phenazines) (**IIa**), together with two different chromophore types, the bis(indeno[1,2-*b*]quinolines) (**III**) and the bis(naphthalimides) (**IV, IVa**).

Methodology

The regression analysis and the calculation of ClogP, CMR and McGowan's molecular volume (MgVol) were done with Biobyte's (Claremont, CA 91711, USA) software version 4.0

MgVol is the molar volume calculated by the method of McGowan.[11] To obtain McGowan volume (MgVol) one simply multiplies the number of occurrences of each atom by the appropriate atom value; sums the results, and substracts a bond term (B). Bonds to hydrogen count, and no distinction is made for bond type (single, double, aromatic etc.). The bond count can be derived from the number of atoms (n) and the number of rings (r) by: $B=(n-1)+r$. The bond factor is: -6.56. The atom values are

H	8.71	C	16.35	N	14.39	O	12.43	F	10.48
Si	26.83	P	24.87	S	22.91	Cl	20.95	B	18.32
Ge	31.02	As	29.42	Se	27.81	Br	26.21		
Sn	39.35	Sb	37.74	Te	36.14	I	34.53		

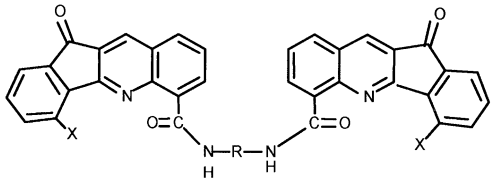
The final product: Σ (Atom value×No. of atoms) −6.56 B is divided by 100 for scaling purposes.

Linker chain lengths (L) were compared by computing the carboxamide N−N distances (in the fully extended form) using the 3-D module from Advanced Chemistry Development Inc., Toronto, Ontario M5H 3V9, Canada.

Results

QSAR 1 and 2 were developed for the growth inhibitory properties of bis(indenoquinolines) (**III**) against cell cultures, measured as IC_{50} values (the molar concentration of drug to reduce cell numbers to 50% of control cultures), using the data given in Table 1.

i. IC_{50} values of bis(indenoquinolines) (**III**) against Jurkat human leukemia[10] (Table 1).



$$\text{Log } 1/C = 2.09(\pm 0.48)\text{MgVol} - 2.48(\pm 2.51)$$
$$n = 10 \qquad r^2 = 0.925 \qquad s = 0.214$$
$$q^2 = 0.871 \qquad (1)$$

See Table 1 for two outliers. Almost the same correlation is obtained with calculated molar refractivity (CMR), where $r^2=0.921$. However using ClogP $r^2=0.472$.

Table 1. IC_{50} values (molar) of bis(indenoquinolines) (**III**) against Jurkat human leukemia cells [eq (1)] and P388 murine leukemia cells[10] [eq (2)]

No.	X	R	Log1/C (Jurkat)			Log1/C (P388)			MgVol
			Obsd	Calcd eq (1)	Δ	Obsd	Calcd eq (2)	Δ	
1	H	$(CH_2)_2NH(CH_2)_2$	6.62	6.87	−0.25	6.78	6.37	0.41	4.47
2	H	$(CH_2)_3NMe(CH_2)_3$	7.92	7.75	0.17	7.64	7.62	0.02	4.89
3	H	$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$[b]	7.85	7.66	0.19	8.60	7.50	1.10	4.85
4	H	$(CH_2)_2NMe(CH_2)_2NMe(CH_2)_2$[a]	7.48	8.25	−0.77	7.68	8.33	−0.65	5.13
5	H	$(CH_2)_2NH(CH_2)_3NH(CH_2)_2$[b]	8.33	7.96	0.37	9.13	7.91	1.21	4.99
6	Me	$(CH_2)_2NH(CH_2)_3NH(CH_2)_2$	8.30	8.55	−0.25	8.85	8.74	0.11	5.27
7	H	$(CH_2)_2NMe(CH_2)_3NMe(CH_2)_2$	8.57	8.55	0.02	9.46	8.74	0.71	5.27
8	Me	$(CH_2)_2NMe(CH_2)_3NMe(CH_2)_2$	9.16	9.14	0.02	9.75	9.58	0.17	5.55
9	Cl	$(CH_2)_2NMe(CH_2)_3NMe(CH_2)_2$	8.96	9.06	−0.10	9.44	9.47	−0.02	5.52
10	H	$(CH_2)_3NH(CH_2)_2NH(CH_2)_3$[a,b]	6.26	8.25	−1.99	6.81	8.33	−1.52	5.13
11	H	$(CH_2)_3$-pip-$(CH_2)_3$[c]	8.62	8.62	0.00	8.64	8.84	−0.20	5.30
12	H	$(CH_2)_3NH(CH_2)_4$	7.57	7.75	−0.18	7.08	7.62	−0.54	4.89

[a]Data points not included in deriving eq (1).
[b]Data points not included in deriving eq (2).
[c]pip: piperazinyl.

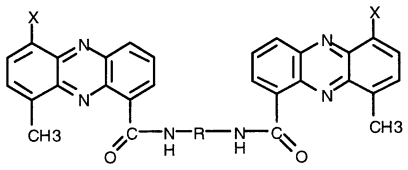
ii. IC_{50} values of bis(indenoquinolines) (**III**) against P388 murine leukemia cells[10] (Table 1).

$$\text{Log } 1/C = 2.95(\pm 1.11)\text{MgVol} - 6.79(\pm 5.74)$$
$$n = 9 \qquad r^2 = 0.848 \qquad s = 0.459$$
$$q^2 = 0.715 \qquad (2)$$

See Table 1 for three outliers. Almost the same correlation is obtained by using CMR, $r^2 = 0.839$. There is a high mutual correlation between MgVol and CMR (CMR versus MgVol $r^2 = 0.996$).

QSAR 3 to 5 were developed from the data in Tables 2 and 3 for bis(phenazine) derivatives.

iii. IC_{50} values of bis(phenazines) (**IIa**) against Jurkat human leukemia cells[12] (Table 2).



IIa

$$\text{Log } 1/C = -0.36(\pm 0.26)\text{CMR} - 0.18(\pm 0.11)L_R + 1.39(\pm 0.46)I_R + 16.56(\pm 4.10)$$
$$n = 13, \qquad r^2 = 0.936, \qquad s = 0.243,$$
$$q^2 = 0.868 \qquad (3)$$

See Table 2 for three outliers.

Table 2. IC_{50} values (molar) of bis(phenazine) (**IIa**) against Jurkat human leukemia cells [eq (3)] and Lewis lung carcinoma cells[12] [eq (4)]

No.	X	R	Log1/C (Jurkat)			Log1/C (Lewis)			CMR	L_R	I_R
			Obsd	Calcd eq (3)	Δ	Obsd	Calcd eq (4)	Δ			
1	H	$(CH_2)_3NMe(CH_2)_3$	8.25	8.50	−0.25	8.48	8.30	0.18	17.39	9.80	0
2	H	$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$	9.75	9.71	0.04	8.55	8.53	0.02	17.29	11.00	1
3	H	$(CH_2)_2NMe(CH_2)_2NMe(CH_2)_2$	8.28	7.98	0.29	7.70	7.78	−0.08	18.22	11.00	0
4	H	$(CH_2)_2NEt(CH_2)_2NEt(CH_2)_2$	7.80	7.65	0.15	7.32	7.37	−0.05	19.15	11.00	0
5	H	$(CH_2)_2NPr(CH_2)_2NPr(CH_2)_2$	7.34	7.31	0.03	6.92	6.95	−0.03	20.07	11.00	0
6	H	$(CH_2)_2NH(CH_2)_3NH(CH_2)_2$[b]	9.62	9.32	0.30	8.92	8.17	0.75	17.76	12.20	1
7	H	$(CH_2)_2NMe(CH_2)_3NMe(CH_2)_2$[a,b]	10.10	7.60	2.50	9.52	7.42	2.11	18.68	12.20	0
8	H	$(CH_2)_3NH(CH_2)_2NH(CH_2)_3$	8.77	8.92	−0.15	7.46	7.80	−0.35	18.22	13.50	1
9	H	$(CH_2)_2$-pip-$(CH_2)_2$[c]	7.96	8.17	−0.22	7.92	7.95	−0.02	18.04	10.30	0
10	H	$(CH_2)_3$-pip-$(CH_2)_3$[a,b]	8.89	7.44	1.45	9.34	7.25	2.09	18.97	12.50	0
11	H	$(CH_2)_4$-pip-$(CH_2)_4$[a,b]	8.96	6.62	2.34	9.47	6.49	2.98	19.90	15.20	0
12	H	$(CH_2)_3NH(CH_2)_3NH(CH_2)_3$	8.89	8.53	0.35	7.51	7.44	0.07	18.68	14.70	1
13	H	$(CH_2)_3NH(CH_2)_4NH(CH_2)_3$	8.06	8.13	−0.07	6.95	7.07	−0.12	19.15	16.00	1
14	H	$(CH_2)_4NH(CH_2)_4NH(CH_2)_4$	7.17	7.36	−0.19	6.54	6.35	0.19	20.07	18.40	1
15	Me	$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$	9.22	9.37	−0.15	8.41	8.12	0.29	18.22	11.00	1
16	Cl	$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$	9.22	9.35	−0.13	8.00	8.10	−0.10	18.27	11.00	1

[a]Data points not included in deriving eq (3).
[b]Data points not included in deriving eq (4).
[c]pip: piperazinyl.

Table 3. IC_{50} of compound **II** against P388 murine leukemia cells[5]

No.	X	R	Log1/C			ClogP	L_R
			Obsd	Calcd eq (5)	Δ		
1	H	$(CH_2)_3NMe(CH_2)_3$	7.82	7.84	−0.02	6.93	9.80
2	H	$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$	7.68	8.08	−0.40	5.63	11.00
3	H	$(CH_2)_2NMe(CH_2)_2NMe(CH_2)_2$	7.48	7.48	−0.00	6.93	11.00
4	H	$(CH_2)_2NEt(CH_2)_2NEt(CH_2)_2$	6.77	7.00	−0.23	7.98	11.00
5	H	$(CH_2)_2NPr(CH_2)_2NPr(CH_2)_2$	6.60	6.51	0.09	9.04	11.00
6	H	$(CH_2)_2NH(CH_2)_3NH(CH_2)_2$	8.13	7.60	0.53	5.90	12.20
7	H	$(CH_2)_2NMe(CH_2)_3NMe(CH_2)_2$[a]	8.80	7.01	1.78	7.17	12.20
8	H	$(CH_2)_3NH(CH_2)_2NH(CH_2)_3$[a]	6.13	7.07	−0.93	6.21	13.50
9	H	$(CH_2)_2$-pip-$(CH_2)_2$[a,b]	5.65	8.44	−2.79	5.30	10.30
10	H	$(CH_2)_3$-pip-$(CH_2)_3$	7.32	7.60	−0.28	5.70	12.50
11	H	$(CH_2)_4$-pip-$(CH_2)_4$	7.02	6.87	0.15	5.53	15.20
12	H	$(CH_2)_3NH(CH_2)_3NH(CH_2)_3$	6.37	6.58	−0.22	6.48	14.70
13	H	$(CH_2)_3NH(CH_2)_4NH(CH_2)_3$	6.06	6.34	−0.29	6.15	16.00
14	H	$(CH_2)_4NH(CH_2)_4NH(CH_2)_4$	6.05	5.87	0.18	5.62	18.40
15	Me	$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$	8.08	7.62	0.46	6.62	11.00
16	Cl	$(CH_2)_2NH(CH_2)_2NH(CH_2)_2$	7.43	7.42	0.01	7.07	11.00

[a]Data points not used in deriving equation.
[b]pip: piperazinyl.

iv. IC_{50} values of bis(phenazines) (**IIa**) against Lewis lung carcinoma cells[12] (Table 2).

$$\text{Log } 1/C = -0.44(\pm0.22)\text{CMR} - 0.13(\pm0.09)L_R + 0.34(\pm0.39)I_R + 17.27(\pm3.44)$$
$$n = 12, \quad r^2 = 0.935, \quad s = 0.196, \quad q^2 = 0.844 \qquad (4)$$

See Table 2 for four outliers. There was a high collinearity between CMR versus MgVol in eqs (3) and (4) ($r^2 = 0.994$).

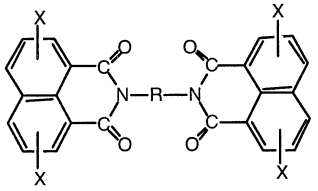
v. IC_{50} values of bis(phenazines) (**IIa**) against P388 murine leukemia cells[12] (Table 3).

$$\text{Log } 1/C = -0.46(\pm0.23)\text{ClogP} - 0.30(\pm0.09)L_R + 14.0(\pm2.3)$$
$$n = 13, \quad r^2 = 0.843, \quad s = 0.313, \quad q^2 = 0.744 \qquad (5)$$

See Table 3 for three outliers. There is no collinearity between ClogP and CMR or MgVol. In eqs (3)–(5) L_R is the calculated length (in Angstroms) of the linker chain between the two aromatic systems. The indicator variable I_R in eqs (3) and (4) takes the value of 1 for instances where two amino groups are present in the linker group R.

Finally, QSAR 6 and 7 were formulated from the data in Tables 4 and 5 respectively, for bis(naphthalimides) (**IV** and **IVa**).[13,14]

vi. IC_{50} values of bis(naphthalimides) (**IV**) against HT-29 human colon cancer cells[13] (Table 4).



IV

$$\text{Log } 1/C = 4.91(\pm1.95)\text{ClogP} - 0.41(\pm0.21)(\text{ClogP})^2 - 1.73(\pm0.51)\text{MgVol} + 0.73(\pm0.51)I_R - 1.04(\pm4.22)$$
$$n = 23 \quad r^2 = 0.893 \quad s = 0.273 \quad q^2 = 0.830 \qquad (6)$$

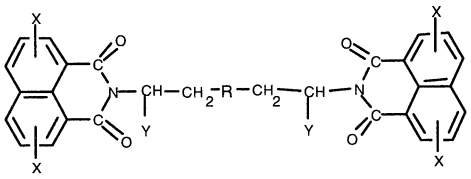
$\text{ClogP}_0 = 6.05$ (5.41 to 7.50). See Table 4 for four outliers.

Table 4. IC_{50} values (molar) of bis(naphthalimides) (**IV**) against HT-29 human colon cancer cells[13]

No.	X	R	Log1/C			ClogP	MgVol	I_R
			Obsd	Calcd eq (6)	Δ			
1	3-NO_2	NH	6.29	6.68	−0.39	4.67	3.68	0
2	3-NH_2	NH	4.52	4.54	−0.02	3.25	3.53	0
3	3-NO_2,6-NO_2	NH[a]	6.57	5.64	0.93	4.32	4.03	0
4	3-NO_2	NMe[a]	5.61	6.98	−1.37	5.31	3.82	0
5	3-NO_2	$NHCH_2$	6.68	6.71	−0.03	4.94	3.82	0
6	3-NH_2	$NHCH_2$	4.81	4.88	−0.07	3.53	3.68	0
7	3-NO_2	$NMeCH_2$	7.16	6.87	0.29	5.56	3.97	0
8	3-NO_2	CH_2NHCH_2	6.80	6.68	0.12	5.22	3.97	0
9	3-NH_2	CH_2NHCH_2	5.31	5.17	0.14	3.80	3.81	0
10	3-NO_2,6-NO_2	CH_2NHCH_2	5.64	5.80	−0.16	4.87	4.31	0
11	4-NO_2	CH_2NHCH_2[a]	5.56	6.68	−1.13	5.22	3.97	0
12	3-NO_2	CH_2NMeCH_2	6.62	6.70	−0.08	5.82	4.11	0
13	3-NH_2	CH_2NMeCH_2	5.73	5.88	−0.15	4.40	3.96	0
14	3-NHAc	CH_2NMeCH_2	5.13	5.35	−0.22	4.83	4.55	0
15	3-NO_2,6-NO_2	CH_2NMeCH_2	6.11	5.98	0.13	5.47	4.45	0
16	3-NO_2,6-NH_2	CH_2NMeCH_2	5.77	5.44	0.33	4.53	4.31	0
17	3-NO_2	CH_2NHCMe_2	6.54	6.47	0.07	5.93	4.25	0
18	3-NO_2	$CH_2NH(CH_2)_2$	6.72	6.47	0.25	5.27	4.11	0
19	3-NO_2	$CMe_2NH(CH_2)_2$	6.01	6.22	−0.22	5.97	4.39	0
20	3-NH_2	$CH_2NH(CH_2)_2NHCH_2$	5.46	5.42	0.04	3.71	4.20	1
21	H	$CH_2NH(CH_2)_4NHCH_2$[a]	5.57	7.29	−1.73	5.33	4.28	1
22	3-NH_2	$CH_2NH(CH_2)_4NHCH_2$	4.41	4.82	−0.41	3.65	4.48	1
23	3-NO_2	$CH_2NH(CH_2)_4NHCH_2$	6.14	6.51	−0.36	5.06	4.63	1
24	3-NO_2,6-NO_2	$CH_2NH(CH_2)_4NHCH_2$	5.40	5.58	−0.18	4.72	4.98	1
25	3-NO_2,6-NH_2	$CMe_2NH(CH_2)_4NHCMe_2$	5.35	5.29	0.06	5.19	5.39	1
26	3-NO_2	CH_2-pip-CH_2[b]	6.64	6.33	0.31	4.68	4.52	1
27	3-NH_2	CH_2-(1,4-diazo-cy-heptyl)-CH_2	5.64	5.09	0.55	3.82	4.51	1

[a]Data points not used in deriving equation.
[b]pip: piperazinyl.

vii. IC_{50} of bis(naphthalimides) (**IVa**) against HT-29 human colon cancer cells[14] (Table 5).



IVa

$$\text{Log } 1/C = 4.40(\pm 1.61)\text{ClogP} - 0.32(\pm 0.14)(\text{ClogP})^2 - 0.59(\pm 0.28)\sigma^+ + 3.12(\pm 1.00)\text{I} + 1.67(\pm 0.82)\text{I}_y - 8.37(\pm 4.85)$$

$$n = 24 \qquad r^2 = 0.870 \qquad s = 0.475$$

$$q^2 = 0.807$$

$$\text{ClogP}_0 = 6.95 \text{ (6.52 to 7.93)} \qquad (7)$$

See Table 5 for four outliers

In eq (7), the indicator variable I_Y takes the values of 1 for instances where Y is H, and indicator variable I takes the value of 1 for the instances where 3-NH_2 group is present in X.

Discussion

In the present study we are again surprised that no evidence for any hydrophobic effect could be found in describing the activity of bis(indenoquinolines) (**III**) and bis(phenazines) (**IIa**) against leukemia cell lines.

Eqs (1) and (2) are quite similar in that CMR and molar volume yield essentially the same result. Two data points are outliers (all of the sets contain outliers), with no obvious reasons. However, given that these structures are complex and difficult to parameterize for QSAR, the results are better than we expected. The most important factor is overall bulk, and when the two aromatic systems are moved apart by increasing the size of *R*, they seem to encounter no specific effects. Adding a squared term to eqs (1) or (2) does not make a significant improvement in the correlation, hence increasing the size might yield more potent congeners.

In the case of bis(phenazines) (**IIa**) [eqs (3) and (4)] it is surprising to see the negative term in CMR. Strong hydrophobic interactions were observed in bis(phenazines) (**II**) against leukemia cell lines where the linker chain is same and substituents are varying at different position in the aromatic ring.[4] In the present case, the bis(phenazines) (**IIa**) congeners have varying linker chains, with no substituents in the aromatic ring, except for compound **15** (X = Me) and compound 16 (X = Cl).

Table 5. IC_{50} values (molar) of bis(naphthalimides) (IVa) against HT-29 human colon cancer cells[14] [eq (7)]

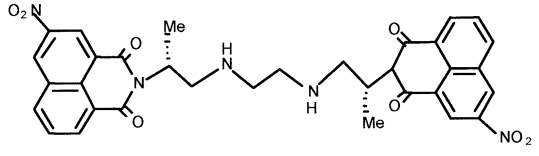
No.	X	Y	Z	Log1/C			ClogP	σ^+	I	I_Y
				Obsd	Calcd eq (7)	Δ				
1	H	H	$NH(CH_2)_2NH$	7.14	7.17	−0.03	4.85	0	0	1
2	H	H	$NH(CH_2)_3NH$	7.85	7.50	0.35	5.12	0	0	1
3	H	H	$N(CH_2)_4NH$	7.77	7.09	0.68	4.79	0	0	1
4	H	H	$NMe(CH_2)_3NMe$	7.47	8.46	−0.99	6.38	0	0	1
5	H	H	cy-$[N(CH_2)_3NCH_2]$	8.70	8.06	0.64	5.69	0	0	1
6	H	Me	$NH(CH_2)_2NH$	6.22	6.20	0.02	5.47	0	0	0
7	H	H	$[NH(CH_2)_2]_2$-NH	6.60	7.04	−0.44	4.75	0	0	1
8	H	H	$[NH(CH_2)_2]_3$-NH	6.30	6.91	−0.61	4.66	0	0	1
9	3-NO_2	H	$NH(CH_2)_2NH$[a]	8.55	5.95	2.61	4.58	1.42	0	1
10	3-NO_2	H	$NH(CH_2)_3NH$[a]	8.40	6.33	2.07	4.85	1.42	0	1
11	3-NO_2	H	$NMe(CH_2)_3NMe$	7.19	7.50	−0.32	6.11	1.42	0	1
12	3-NO_2	H	$NMe(CH_2)_2NMe$	7.40	7.36	0.04	5.87	1.42	0	1
13	4-NO_2	H	$NH(CH_2)_3NH$	6.70	6.24	0.46	4.85	1.58	0	1
14	3-NH_2	H	$NH(CH_2)_2NH$	7.47	7.32	0.15	3.16	−0.32	1	1
15	3-NH_2	H	$NH(CH_2)_3NH$	7.82	7.95	−0.13	3.43	−0.32	1	1
16	3-NH_2	Me	$NH(CH_2)_2NH$	7.00	7.02	−0.02	3.78	−0.32	1	0
17	3-NHAc	H	$NH(CH_2)_2NH$	4.40	4.75	−0.35	3.59	0.42	0	1
18	3-NHAc	H	$NH(CH_2)_3NH$	5.26	5.30	−0.04	3.86	0.42	0	1
19	3-NHAc	Me	$NH(CH_2)_2NH$[a]	5.82	4.27	1.55	4.21	0.42	0	0
20	3-Br	H	$NH(CH_2)_3NH$	8.85	8.11	0.75	6.96	0.78	0	1
21	4-Br	H	$NH(CH_2)_3NH$	8.26	8.39	−0.13	6.96	0.30	0	1
22	4-Cl	H	$NH(CH_2)_3NH$	7.82	8.41	−0.59	6.66	0.22	0	1
23	2-OH	H	$NH(CH_2)_3NH$	8.35	8.09	0.25	4.73	−1.84	0	1
24	3-OH	H	$NH(CH_2)_3NH$	6.82	6.67	0.15	4.60	0.24	0	1
25	4-OH	H	$NH(CH_2)_3NH$[a]	5.07	7.90	−2.83	4.60	−1.84	0	1
26	2-Me	H	$NH(CH_2)_3NH$	8.70	8.71	−0.01	6.12	−0.62	0	1
27	4,5-di-Me	H	$NH(CH_2)_3NH$	9.26	9.29	−0.03	7.12	−1.24	0	1
28	4,5-di-Me	H	$NMe(CH_2)_3NMe$	8.82	8.66	0.16	8.38	−1.24	0	1

[a]Data points not included in deriving equation.

Equation (5) is a surprise since it is now seen that ClogP replaces CMR. ClogP and MgVol are not collinear ($r^2 = 0.17$) so that nature of the binding site in the P388 murine leukemia is obviously different. Moreover, the I term is also lacking. L and ClogP are quite independent ($r^2 = 0.14$). We have often noted a lack of hydrophobic interaction of ligands interacting with DNA. We have noted before that in the case of cancer cells, small changes in structure can cause surprisingly large changes in QSAR.[4] The same holds true for other systems.[15]

Equations (3)–(5) also contains small but negative coefficients of L_R (the length of linker chain). This indicates that increases in the separation of chromophores are detrimental to the activity. This confirms a previous, more linked study[12] of analogues bearing linker chains $(CH_2)_xNH(CH_2)_nNH(CH_2)_x$, that showed a highly significant inverse correlation between potency and linker length. The reason for this is most likely the unfavourable entropic effects on DNA binding of a long and flexible linker chain.[16] The positive coefficient of I_R in eqs (3) and (4) indicates that presence of two amino groups in the linker group R may be beneficial to the activity.

Equations (6) and (7) focus on the bis(naphthalimides) (**IV** and **IVa**). These are the most extensively studied subgroup of dimeric DNA binders,[8,9,13,14] with two examples in clinical trial; DMP 840 (**V**)[8] and LU 79553 (elinafide; compound **2** of Table 4).[17] The QSAR for these compounds for inhibition of HT-29 human colon carcinoma cells were also heavily dependent on a parabolic relationship with ClogP. A 3-NH_2 substituent was highly beneficial, from the size of the coefficient for the I variable in eq (7). The positive coefficient with I_Y in eq (7) that takes the value of 1 when Y = H and 0 when Y = Me shows that H is superior to Me. Presumably this has to do with the comparative size of the two possible substituents.



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