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Report

Correlation of Partitioning of Nitroimidazoles in the *n*-Octanol/Saline and Liposome Systems with Pharmacokinetic Parameters and Quantitative Structure–Activity Relationships (QSAR)

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The partitioning of a series of nine nitroimidazole drugs in liposomes (log K_m) of various compositions has been determined and compared to their partitioning in the *n*-octanol/saline system (log K) at 30°C. The log K_m ranged from 1.5 to 0.5 and was three- to fourfold greater than the log K; further, the linear correlation coefficient was greatest when cholesterol (CHOL)-free liposomes were used. Functional-group contributions were compared from their hydrophobic substituent constants and, except in the case of RO-07-2044 and iodoazomycin riboside, yielded negative values in all systems. Literature values of four pharmacokinetic parameters obtained in dogs and acute LD_{50} values of the nitroimidazoles in BALB/c mice were highly correlated with log K or log K_m only in CHOL-free liposomes. Comparing the relative sensitizing effect of the nitroimidazoles in murine EMT-6 or Chinese hamster V79 tumor cell cultures and their partition coefficients, the correlation in EMT-6 cells was poor, whereas the correlation in V79 cells was >0.9 when log K_m was used but <0.6 when log K was used. Thus, the liposome model is a better predictor of nitroimidazole activity than the *n*-octanol/saline system and, also, it is a more flexible model for selecting the optimum conditions for QSAR studies.

KEY WORDS: partitioning of nitroimidazoles; *n*-octanol/saline; liposomes; correlation analysis; quantitative structure–activity relationships (QSAR).

INTRODUCTION

The distribution of solutes in various oil/water systems and between aqueous and biological systems was first quantitatively described by Collander (1). Since these early studies it has become common practice to employ an oil/water system to predict the distribution of drugs or chemical toxicants into living cells. The concept of quantitative structure–activity relationships (QSAR) using the *n*-octanol–water distribution system, as developed by Hansch and co-workers (2), is well established. In addition to the oil/water systems, correlations have also been obtained using simple colloidal phospholipid dispersions, e.g., liposomes (3). More recently, thermodynamic approaches (4–7), QSAR studies (8), and nuclear magnetic resonance (NMR) studies (9) have shown unique behavior and differentiation among congeners in a drug series in liposomes not shown previously with the *n*-octanol/water system. Thus, the thermodynamics of the transfer process has been shown to be remarkably different in the oil/water and liposome systems, and certain liposome compositions have better predictability characteristics than others for particular groups of drugs (9). It is essential, therefore, that the liposome system be further examined as a model membrane for other classes of drugs in predicting pharmacokinetic behavior, membrane transport processes, pharmacologic activity, etc.

The nitroimidazoles are radiosensitizers and chemosensitizers which are used in the treatment of cancer. These drugs possess selective toxicity against hypoxic cells (10). There is concern whether chemopotentiation will occur with clinically relevant sensitizer doses of these agents. Consequently, drugs having improved physicochemical properties are continually being sought. The mechanisms involved, in addition to hypoxia, are believed to be enhanced DNA damage/reduced DNA repair capacity, reduction of intracellular sulfhydryl levels, and alterations of drug pharmacokinetics (10).

Generally, the more biologically active nitroimidazoles possess substantial water solubilities and have low partition coefficients. Thus, interactions of these solutes with biological membranes would be expected to be mainly through surface group interactions. Significant differentiation among many congeners in this series has not been found in the *n*-octanol/water system in which only bulk properties are manifest. Thus, studies of nitroimidazoles in liposomes have been conducted in order to assess the role of surface-group

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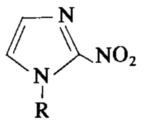
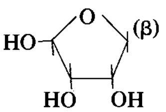
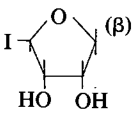
interactions and bilayer organization on partitioning and quantitative structure–activity relationships using pharmacokinetic and toxicity parameters. The *n*-octanol/water and liposome systems have been compared as appropriate distribution or membrane models in predicting the biological behaviors of members of this class of drugs.

MATERIALS AND METHODS

Materials. The nitroimidazoles used in these studies are described in Table I and were obtained as follows: SR-2508, SR-2555, RO-07-2044, RO-07-0741, misonidazole, and desmethylmisonidazole were provided by Dr. J. D. Chapman, Cross Cancer Institute, University of Alberta, Edmonton; azomycin, azomycin riboside, and iodoazomycin riboside were suppled by Dr. L. I. Wiebe, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton. L-α-Dimyristoylphosphatidylcholine (DMPC; 99%), L-α-dipalmitoylphosphatidylcholine (DPPC; $98^{+}\%$), cholesterol (CHOL), and dicetylphosphate (DCP) were purchased from Sigma Chemical Co., St. Louis, Mo., and used as received. All other solvents and chemicals were reagent grade. Water was deionized and glass-distilled.

Partition Coefficient Determinations. Partition coefficients of the nitroimidazoles in *n*-octanol/water or *n*-octanol/saline were previously determined (11,12; Chapman, personal communication). Experimental partition coefficients in liposomes were carried out as before (7). Briefly, films of phospholipids containing the nitroimidazoles were hydrated and dispersed from the walls of 50-ml round-bottom flasks with normal saline solution to form homogeneous multilamellar liposomes (MLVs) (10 mg/ml) yielding a concentration of nitroimidazole equivalent to 0.2 m*M*. After equilibration at 30°C for 24 hr, samples were centrifuged (143,000*g*, 30 min; Beckman L8-55 Ultracentrifuge) and the supernatant was analyzed by UV spectroscopy at the λ_{max} of each drug. Concentrations in the aqueous phases were determined from calibration curves, mass balance calculations were employed to obtain concentrations in the lipid phases, and molal partition coefficients (K_m) were calculated (7). Determinations were made in duplicate and the results averaged. Repeated analyses of stock solutions of nitroimidazoles confirmed their stabilities under the experimental conditions.

Table I. Chemical Structures and Molecular Weights of Nitroimidazoles

Nitroimidazole		Structure	MW
			
RO-07-0741	R =	$-CH_2CHOHCH_2F$	189
RO-07-2044		$-CH_2CHOHCH_2OCH_2CF_3$	269
SR-2508		$-CH_2CONHCH_2CH_2OH$	214
SR-2555		$-CH_2CON(CH_2CH_2OH)_2$	258
Misonidazole		$-CH_2CHOHCH_2OCH_3$	201
Desmethylmisonidazole		$-CH_2CHOHCH_2OH$	187
Azomycin riboside			245
			
Azomycin		$-H$	113
Iodoazomycin riboside			359
			

RESULTS AND DISCUSSION

The partition coefficients of nitroimidazoles in the aqueous *n*-octanol distribution system (log *K*) are compared to partition coefficients in liposomes of various compositions in Table II. It is apparent that log K_m is greater for all the nitroimidazoles than log *K*, a finding that has been reported for ionized phenothiazines (6), ionized beta blockers (7), and phenols (4,13). Also liposomes in the gel-state (DPPC) or fluid-state liposomes (DMPC) to which CHOL had been added yielded lower values of K_m than fluid-state DMPC liposomes. The log *K* increased in the order shown in Table II, whereas departures from this order occur with liposome systems. The log *K* of azomycin riboside was equal to that of SR-2508, whereas the log K_m of SR-2508 was significantly lower than that of azomycin riboside. Adding CHOL to the liposome causes a change in the rank order of the partition coefficients among several of the nitroimidazoles. These observations suggest that the organization and structure of liposomes exert an influence on the manner in which nitroimidazoles interact with membranes.

According to the earlier proposal by Collander (1) and linear free energy relationships (14,15), the partition coefficients of solutes in an oil/water system can be predicted from results of partitioning in a reference oil/water system. However, the extent to which this is applicable depends on the nature of the partitioning system (3,8). Correlations of log *K* and log K_m for the nitroimidazoles are summarized in Table

Table II. Partition Coefficients of Nitroimidazoles in the *n*-Octanol/Saline (log *K*) and Liposome Systems (log K_m) at 30°C[a]

		Log K_m for liposome composition[b]			
Nitroimidazole	log *K*	I	II	III	IV
SR-2555	−1.64	0.50	0.08	−0.32	−0.23
Azomycin riboside	−1.34	0.86	0.65	0.29	0.25
SR-2508	−1.34	0.66	0.37	0.16	0.14
Desmethylmisonidazole	−0.85	0.69	0.49	0.17	0.21
RO-07-0741	−0.52	0.80	0.60	0.42	0.10
Misonidazole	−0.37	0.92	0.74	0.12	0.14
Azomycin	0.16	1.13	0.83	0.54	0.40
Iodoazomycin riboside	0.32	1.29	0.92	0.44	0.34
RO-07-2044	0.46	1.47	1.06	0.62	0.50

[a] The maximum relative standard deviation (RSD) was 10%, although in most cases the RSD was <4.4%.

[b] I, DMPC; II, DPPC; III, DMPC:CHOL (1:1 mole ratio); IV, DMPC:CHOL:DCP (7:2:1 mole ratio).

Table III. Linear Regression Parameters Derived from Correlations of n-Octanol/Saline Partitioning (log K) and Liposome Partitioning (log K_m) of Nitroimidazoles[a]

Liposome composition[b]	a	b	r	P
DMPC	0.37	1.14	0.92	<0.01
DPPC	0.35	0.84	0.90	<0.01
DMPC:CHOL (1:1)	0.29	0.44	0.80	<0.01
DMPC:CHOL:DCP (7:2:1)	0.21	0.33	0.78	<0.05

[a] Linear regression parameters are as follows: a, slope; b, intercept; r, correlation coefficient. The two-sided t test was used to evaluate the significance of the coefficient of determination. A level of $P < 0.05$ was considered as being significant.

[b] Mole ratios in parentheses.

III, from which it can be seen that the correlation coefficient (r) was optimal in single phospholipid liposomes and least in CHOL-containing liposomes. Hydrophobic substituent constants (Π_x) (16) of the nitroimidazoles, where azomycin in this instance is regarded as the parent compound, are shown in Table IV. These data indicate that the lipophilic/hydrophilic properties of the substituents are not the only determinants of partitioning but that the structure and hydration of the partitioning phase also play important roles. In particular, the addition of CHOL to fluid-state liposomes is known to increase the structure and rigidity of the bilayers while also contributing to increased hydration at the liposome surfaces (17,18). The interaction at the membrane interface is, therefore, not a simple function of the polarity of the solute molecule and this is reflected in the lack of a systematic change of Π_x in CHOL-containing liposomes shown in Table IV.

Correlations of log K and log K_m with four pharmacokinetic parameters of the nitroimidazoles obtained from dogs and toxicities in BALB/c mice (19,20), defined in Table V, are described in Table VI. Only two of the pharmacokinetic parameters correlated significantly with log K or log K_m in DMPC liposomes, one with DPPC liposomes and none with DMPC:CHOL, 2:1, or DMPC:CHOL:DCP, 7:2:1, mole ratio liposomes. The best correlations occurred with peak plasma concentrations (PPC) and log K, plasma clearance rate (PCR) and log K_m (DMPC), and acute LD_{50} (ALD) and log K_m (DPPC).

Table IV. Hydrophobic Substituent Constants of Functional Groups of Nitroimidazoles in the n-Octanol/Saline (Π_o) and Liposome (Π_{I-IV}) Systems

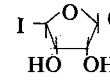
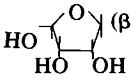
Functional group	Π_o	Π_I	Π_{II}	Π_{III}	Π_{IV}
H	—	—	—	—	—
$CH_2CHOHCH_2OCH_2CF_3$	0.30	0.34	0.23	0.08	0.10
	0.16	0.16	0.09	−0.10	−0.06
$CH_2CHOHCH_2OCH_3$	−0.53	−0.21	−0.09	−0.42	−0.26
$CH_2CHOHCH_2F$	−0.68	−0.33	−0.23	−0.12	−0.30
$CH_2CHOHCH_2OH$	−1.01	−0.44	−0.34	−0.37	−0.19
$CH_2CONHCH_2CH_2OH$	−1.50	−0.47	−0.46	−0.38	−0.26
	−1.50	−0.17	−0.18	−0.25	−0.15
$CH_2CON(CH_2CH_2OH)_2$	−1.80	−0.63	−0.75	−0.86	−0.63

Table V. Pharmacokinetic and Toxicity Parameters of Nitroimidazoles[a]

Nitroimidazole	Pharmacokinetic or toxicity parameter[b]				
	PP	PCR	UDU	OB	ALD
SR-2555	1.99	0.26	100.	19	34.5
SR-2508	1.82	0.21	88.8	86	22.9
Desmethylmisonidazole	1.06	0.19	74.7	57	18.3
Misonidazole	0.64	0.09	6.2	92	8.5

[a] Taken from Refs. 19 and 20.

[b] PPC, peak plasma concentration (mol/ml); PCR, plasma clearance rate (liters/kg · hr); UDU, unchanged drug in urine (%) after i.v. injection of saline solutions of drug in dogs; OB, oral bioavailability (%) after administration of 400 mg drug in a size 00 hard gelatin capsule; ALD, acute LD_{50} (mmol/kg) after i.v. injection of saline solutions of drug in dogs.

Predictions of ALD and PCR from log K or log K_m of different phospholipid compositions are shown in Table VII. These were obtained from the regression equations of Table VI. Thus, predicted values of PCR in the n-octanol/saline system or liposomes of various compositions were in good agreement with the literature value for SR-2555, the most hydrophilic nitroimidazole in the series, but greater deviations were observed as the compounds became more lipophilic. In particular, liposomes to which CHOL or CHOL and DCP were added yielded the greatest deviation of predicted PCR from the literature values. Overall, liposomes of DMPC provided the most consistent predictions of PCR. Similarly, predicted ALD values deviated increasingly from literature values with increases in lipophilicity, particularly with liposomes consisting of lipid combinations as described. However, in this instance DPPC liposomes yielded predicted values which were almost coincidental with the literature values.

In QSAR studies linear relationships between the concentration of a solute required to produce a given rate of response (C) or a minimal biologic activity and partitioning in the n-octanol/water system have been obtained (2). Where the correlations have not been very successful, mathematical treatments have been applied to improve the correlations even though these have no relationship to the model being tested (21). However, it is more reasonable to expect that for a given chemical entity or in a particular set of congenors, differences in membrane interaction are due to specific membrane component interactions with the solute molecules which result in a change in the partitioning environment due to membrane reorganization and not just a hydrophilic/lipophilic solubility phenomenon. Depending on the solute species, the significance of membrane structure may be high or low. As a test of this hypothesis the relative radiosensitizing effects[4] of five nitroimidazoles in either murine EMT-6

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[4] Concentration of drug in complete media required to produce a sensitizer enhancement ratio at 10% survival of 1.5 (taken from Refs. 12 and 22 and unpublished results from D. Chapman).

Table VI. Linear Regression Parameters Derived from Correlations of log K or log K_m(I–IV) with Pharmacokinetic or Toxicity Parameters of Nitroimidazoles ($N = 4$)[a]

Pharmacokinetic or toxicity parameter[b]	a	b	r	P
	log K			
PPC	−1.13	0.19	−0.99	<0.01
PCR	−0.12	0.06	−0.96	<0.05
UDU	−70.2	−6.27	−0.93	—
OB	40.5	106.	0.68	—
ALD	−18.8	1.28	−0.97	<0.05
	log K_m(I)			
PPC	3.33	3.68	−0.91	—
PCR	−0.41	0.47	−1.00	<0.01
UDU	−233.	229.	−0.96	<0.05
OB	160.	−47.0	0.83	—
ALD	−61.2	63.4	−0.98	<0.05
	log K_m(II)			
PPC	−2.17	2.29	−0.93	—
PCR	−0.25	0.20	−0.97	<0.05
UDU	−139.	126.	−0.90	—
OB	101.	21.3	0.83	—
ALD	−39.4	37.6	−1.00	<0.01
	log K_m(III)			
PPC	−1.60	1.43	−0.59	—
PCR	−0.18	0.19	−0.61	—
UDU	−78.5	70.0	−0.44	—
OB	121.	59.6	0.85	—
ALD	−35.9	22.19	−0.78	—
	log K_m(IV)			
PP	−2.09	1.51	−0.65	—
PCR	−0.22	0.20	−0.62	—
UDU	−96.8	73.7	−0.46	—
OB	134.	54.8	0.80	—
ALD	−43.5	23.9	−0.80	—

[a] I, DMPC; II, DPPC; III, DMPC:CHOL (1:1 mole ratio); IV, DMPC:CHOL:DCP (7:2:1 mole ratio). SeeTable III, footnote a, for definitions of linear regression parameters.

[b] See Table V, footnote b, for definitions.

or Chinese hamster V79 tumor cell cultures were examined for correlations with the n-octanol–saline system or liposomes of various compositions. These are described in Equations (1)–(10) (see Table II for definitions of I, II, III, and IV).

For Emt-6 cells

$$\log 1/C = 0.071 \log K + 0.126, \qquad r = 0.220 \tag{1}$$

$$\log 1/C = 0.179 \log K_m(\mathrm{I}) - 0.086, \qquad r = 0.227 \tag{2}$$

$$\log 1/C = 0.366 \log K_m(\mathrm{II}) - 0.175, \qquad r = 0.334 \tag{3}$$

$$\log 1/C = 0.696 \log K_m(\mathrm{III}) - 0.157, \qquad r = 0.558 \tag{4}$$

$$\log 1/C = 0.297 \log K_m(\mathrm{IV}) + 0.027, \qquad r = 0.206 \tag{5}$$

For V79 cells

$$\log 1/C = 0.189 \log K + 0.200, \qquad r = 0.588 \tag{6}$$

$$\log 1/C = 0.885 \log K_m(\mathrm{I}) - 0.653, \qquad r = 0.920 \tag{7}$$

$$\log 1/C = 0.591 \log K_m(\mathrm{II}) - 0.286, \qquad r = 0.950 \tag{8}$$

$$\log 1/C = 0.651 \log K_m(\mathrm{III}) - 0.065, \qquad r = 0.947 \tag{9}$$

$$\log 1/C = 0.789 \log K_m(\mathrm{IV}) - 0.091, \qquad r = 0.937 \tag{10}$$

Overall, the relative radiosensitizing effect in EMT-6 tumor cells correlated poorly with the partitioning behavior in any system, consistent with earlier observations that lipophilicity or lipid solubility of nitroaromatic drugs did not correlate with either toxicity or sensitizing effectiveness in studies with mammalian cells growing *in vitro* (23–25). It is significant to note, however, that a DMPC:CHOL (1:1 mole ratio) liposome composition yielded a better correlation than all other liposome compositions or the n-octanol/saline system. In contrast, the relative radiosensitizing effect of the same five nitroimidazoles in Chinese hamster V79 tumor cells yielded high correlations with partitioning in liposomes but not the n-octanol/saline system, suggesting that membrane transport of drug into the cells is governed by the structural properties of the membrane.

The interaction of drug molecules with transport across cell membranes involves a complex series of events incorporating such parameters as electronic and steric substituent effects, influences of molecular volume and shape of the drug molecules on the organization and architecture of the membrane, and the energetics of the transfer process. In any particular situation, certain of these phenomena may exert predominance in the final course of events. For instance, it has been reported that biological activities of a series of chloramphenicol congeners or their liposome/saline hydrophobicities showed little dependence on electronic and steric substituent parameters (26). Also, the partitioning of phenols in liposome systems has been found to be highly correlated with their partitioning in the n-octanol/saline system but contributions of enthalpy and entropy to the free energy of partitioning showed radical differences in these two systems (4,5,13). Recently, it has been pointed out that under certain conditions n-octanol and n-hexane are satisfactory surrogates for biological phases but that molecular volume and shape affect activity coefficients in a membrane differently than in a bulk oil phase, these differences becoming larger with increasing solute size (27). Thus, in a group of relatively polar compounds, such as the nitroimidazoles, the above arguments may also be expected to apply. The evidence indicates that a membrane in which CHOL is present in significant amounts is a more formidable barrier to nitroimidazole interaction than CHOL-free membranes and their relative radiosensitizing effects in tumor cells correlate quite well with this model. It is now becoming recognized that there are many situations in which liposome partition coefficients are more reliable for predictions in QSAR studies than a bulk oil/water system. By making an appropriate choice of liposome composition, refinements in the accuracy of predictability are possible.

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Table VII. Relative Error in Predictions of Plasma Clearance Rate (PCR) or Acute LD_{50} (ALD) of Nitroimidazoles from *n*-Octanol/Saline (log *K*) or Liposome (log K_m) Systems[a]

Nitroimidazole	*n*-Octanol–saline system	Liposomes[b] I	II	III	IV	Literature value[c]
		Predicted PCR (liters/kg · hr)				
SR-2555	0.26	0.27	0.27	0.25	0.25	0.26
SR-2508	0.22	0.20	0.20	0.16	0.17	0.21
Desmethylmisonidazole	0.16	0.19	0.17	0.16	0.19	0.19
Misonidazole	0.10	0.09	0.10	0.17	0.17	0.09
Average % error	11	2	8	25	223	
		Predicted ALD (mmol/kg)				
SR-2555	32.1	32.8	34.4	33.7	33.8	34.5
SR-2508	26.4	23.0	23.0	16.5	17.8	22.9
Desmethylmisonidazole	17.3	21.2	18.3	16.1	14.7	18.2
Misonidazole	8.24	7.11	8.42	17.9	17.8	8.50
Average % error	8	10	0.5	27	27	

[a] Using regression equations from Table VI.

[b] I, DMPC; II, DPPC; III, DMPC:CHOL (1:1 mole ratio); IV, DMPC:CHOL:DCP (7:2:1 mole ratio).

[c] From Ref. 19 for PCR and from Ref. 20 for ALD.

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REFERENCES

1. R. Collander. *Physiol. Plant* 7:420–445 (1954).
2. C. Hansch and T. Fujita. *J. Am. Chem. Soc.* 86:1616–1626 (1964).
3. Y. Katz and J. M. Diamond. *J. Membrane Biol.* 17:121–154 (1974).
4. J. A. Rogers and S. S. Davis. *Biochim. Biophys. Acta* 598:392–404 (1980).
5. N. H. Anderson, S. S. Davis, M. James, and I. Kojima. *J. Pharm. Sci.* 72:443–448 (1983).
6. M. S. Ahmed, F. H. Ahmed, and I. W. Kellaway. *Pharm. Res.* 2:119–124 (1985).
7. G. V. Betageri and J. A. Rogers. *Int. J. Pharm.* 36:165–173 (1987).
8. G. V. Betageri and J. A. Rogers. *Int. J. Pharm.* 46:95–102 (1988).
9. G. V. Betageri, Y. Theriault, and J. A. Rogers. 2nd National Meeting, AAPS, Boston (1987).
10. D. W. Siemann. In J. D. Chapman and G. F. Whitmore (eds.), *Chemical Modifiers of Cancer Treatment. Part 2,* Pergamon Press, Toronto, 1984, pp. 1585–1594.
11. J. M. Brown and P. Workman. *Radiat. Res.* 82:171–190 (1980).
12. D. C. Jette, L. I. Wiebe, R. J. Flanagan, J. Lee, and J. D. Chapman. *Radiat. Res.* 105:169–179 (1986).
13. J. A. Rogers and A. Wong. *Int. J. Pharm.* 6:339–348 (1980).
14. N. B. Chapman and J. Shorter. In J. D. Chapman and J. Shorter (eds.), *Advances in Linear Free Energy Relationships,* Plenum Press, New York, 1972, pp. 71–117.
15. J. Shorter. In J. Shorter (ed.), *Correlation Analysis in Organic Chemistry. An Introduction to Linear Free Energy Relationships,* Oxford University Press, 1973, pp. 8–31.
16. C. Hansch and A. Leo. *Substituent Constants for Correlation Analysis in Chemistry and Biology,* John Wiley & Sons, New York, 1979.
17. J. de Gier, M. C. Blok, P. W. M. van Dijck, C. Mombers, A. J. Verkley, E. C. M. van der Neut-Kok, and L. L. van Deenen. *Ann. N.Y. Acad. Sci.* 308:85–99 (1978).
18. L. Ter-Minassian-Saraga and G. Madelmont. *FEBS Lett.* 137:137–140 (1982).
19. R. A. S. White, P. Workman, and J. M. Brown. *Radiat. Res.* 84:542–561 (1980).
20. J. M. Brown, N. Y. Yu, D. M. Brown, and W. W. Lee. *Int. J. Radiat. Oncol. Biol. Phys.* 7:695–703 (1981).
21. E. R. Cooper, B. Berner, and R. D. Bruce. *J. Pharm. Sci.* 70:57–59 (1981).
22. J. D. Chapman, J. Lee, and B. E. Meeker. *Int. J. Radiat. Oncol.,* in press (1988).
23. J. D. Chapman, J. A. Raleigh, J. Borsa, R. G. Webb, and R. Whitehouse. *Int. J. Radiat. Biol.* 17:475–482 (1972).
24. J. A. Raleigh, J. D. Chapman, J. Borsa, W. Kremers, and A. P. Reuvers. *Int. J. Radiat. Biol.* 23:377–387 (1973).
25. G. E. Adams, I. R. Flockhart, C. E. Smithen, I. J. Stratford, P. Wardman, and M. E. Watts. *Radiat. Res.* 67:9–20 (1976).
26. R. E. Brown and B. J. Brown. In *QSAR Des. Bioact. Compd.,* Prous, Barcelona, Spain, 1984, pp. 13–24.
27. F. A. P. C. Gobas, J. M. Lahittete, G. Garofalo, W. Y. Shiu, and D. MacKay. *J. Pharm. Sci.* 77:265–272 (1988).