Potential Antitumor Agents. 42. Structure–Activity Relationships for Acridine-Substituted Dimethyl Phosphoramidate Derivatives of 9-Anilinoacridine

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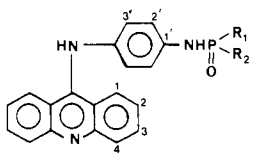
Replacement of the 1′-methanesulfonamide group of the 9-anilinoacridine class of antitumor agents with the 1′-(dimethyl phosphoramidate) group provides compounds that are generally more lipophilic and bind more tightly to DNA. On the average, the dimethyl phosphoramidates are twice as dose potent as the corresponding methanesulfonamide (AMSA) compounds against P388 leukemia in vivo, but also show about twice the acute toxicity and no resultant improvement in tumor cell selectivity (ILS_{max} values) is seen. A pairwise comparison of a range of acridine-substituted compounds shows that structure–activity relationships within each series are similar and dominated by the acridine substitution pattern.

An earlier investigation[1] of a variety of organophosphorus derivatives of 9-anilinoacridine, carried out as part of our program on analogues of the clinical antileukemic agent amsacrine (**30**),[2,3] showed the marked effect of oxygen atoms in the 1′-substituent on in vivo antileukemic activity. Thus, beginning with the inactive dimethylphosphinamide (**1**), progressive replacement of the

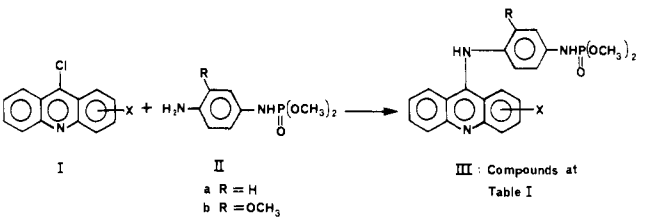


1 $R_1 = R_2 = CH_3$
2 $R_1 = CH_3$, $R_2 = OCH_3$
3 $R_1 = R_2 = OCH_3$

methyl groups with methoxy groups (to give compounds **2** and **3**) was accompanied by significant improvements in both in vitro cytotoxicity and in vivo antitumor activity at each stage. At the same time, the DNA-binding ability of the compounds decreased nearly 4-fold from **1** to **3** (**1**: log K = 6.81; **2**: log K = 6.34; **3**: log K = 6.26). This is at variance with results for other classes of 9-anilinoacridines, where increased biological activity generally correlates with increased DNA binding.[4,5]

When the 9-anilinoacridines bind to double-stranded DNA by intercalation of the acridine chromophore, the anilino side chain is probably constrained to lie in the minor groove,[4,6] with the 1′-substituent to the outside where it is well placed to participate in external hydrogen bonding interactions. Thus, the effects seen with the oxygenated phosphorus compounds were considered[1] to involve an enzyme or protein interaction that was triggered by false recognition of the drug oxygen atoms as those of a displaced DNA phosphate. A number of cyclic acid and acyclic oxygenated phosphorus derivatives were evaluated,[1] with the most active proving to be the 1′-(dimethyl phosphoramidate) (**3**). We were thus interested in further

Scheme I



I II III: Compounds at Table I
a R = H
b R = OCH_3

exploring structure-activity relationships for this class of 9-anilinoacridines and comparing them with the structure–activity relationships already observed for the well-studied 1′-methanesulfonamide (AMSA) series.

Earlier work[5] with the latter series of compounds showed that several factors are important for antitumor activity. These include the overall drug properties of lipophilicity, DNA binding, and acridine pK_a.

Substituent groups on the acridine ring affect these overall drug properties, and thus biological activity, very profoundly. We therefore synthesized a number of acridine-substituted analogues of the dimethyl phosphoramidates (**3** and **29**). Physicochemical and biological data for these compounds are recorded in Table I, together with comparable data for the corresponding AMSA analogues. The choice and positioning of the acridine substituents were selected from combinations known to provide the greatest possible variation in antitumor activity in the AMSA series.[3]

Chemistry. The new dimethyl phosphoramidates described in Table I were prepared by usual[1] mild acid-catalyzed coupling of the appropriately substituted 9-chloroacridines with either dimethyl *N*-(4-aminophenyl)-phosphoramides or the corresponding 3-methoxy derivative in MeOH or MeOH/*N*-methylpyrrolidone mixtures (Scheme I). The chloroacridines were obtained by literature methods,[6] while the aniline components were produced by hydrogenation of nitro- and benzylurethane precursors, respectively.[1]

Results

Table I lists 20 pairs of 1′-(dimethyl phosphoramides) and 1′-methanesulfonamide derivatives of 9-anilinoacridine, together with relevant physicochemical properties and in vitro and in vivo antileukemic activity. ID_{50} values are the nanomolar concentration of drug required to reduce cell growth in vitro to 50% of the control values and are a measure of cytotoxicity. D_{50} values (in milligrams per kilogram) are the doses of drug needed to provide a percentage increase in life span of tumor-bearing mice of 50% compared to untreated controls and are determined from dose–response graphs by the method of ref 7. The ILS values quoted are those obtained at the optimal dose (OD).

(1) Rewcastle, G. W.; Baguley, B. C.; Cain, B. F. *J. Med. Chem.* **1982**, *25*, 1231.
(2) Arlin, Z. A.; Sklaroff, R. B.; Gess, T. S.; Kempin, S. J.; Howard, T.; Clarkson, B. D.; Young, C. W. *Cancer Res.* **1980**, *40*, 3304.
(3) Worrell, R. P.; Straus, D. J.; Young, C. W. *Cancer Treat. Rep.* **1980**, *64*, 1157.
(4) Denny, W. A., Baguley, B. C., Cain, B. F.; Waring, M. J. In "Molecular Aspects of the Action of Anticancer Agents"; Neidle, S.; Waring, M. J., Eds.; MacMillan: London, 1983.
(5) Baguley, B. C.; Denny, W. A.; Atwell, G. J.; Cain, B. F. *J. Med. Chem.* **1981**, *24*, 520.
(6) Denny, W. A.; Atwell, G. J.; Cain, B. F.; Hansch, C.; Panthananickal, A.; Leo, A. *J. Med. Chem.* **1983**, *25*, 276.

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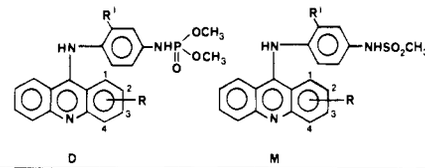
Table I: Physicochemical and Biological Data for Dimethyl Phosphoramidates (D) and Corresponding Methanesulfonamides (M)



D M

no.	type[a]	R^1	R	Rm[b]	log K[c]	L1210 in vitro: ID_{50}[d]	P388 in vivo		
							D_{50}[e]	OD[f]	ILS_{max}[g]
3	D	H	H	0.34	6.26	15	15	45	107
4	M	H	H	0.00	6.15	35	35	150	102
5	D	H	2-CH_3	0.43	6.09	286	*h*	20	36
6	M	H	2-CH_3	0.14	5.70	680	*h*	100	39
7	D	H	2-OCH_3	0.29	6.25	920	*h*	45	38
8	M	H	2-OCH_3	−0.04	6.00	2500	*h*	150	*i*
9	D	H	2-Cl	0.37	6.17	900	*h*	100	*h*
10	M	H	2-Cl	0.15	5.62	3800	*h*	150	*h*
11	D	H	3-CH_3	0.49	6.77	7	6	20	84
12	M	H	3-CH_3	0.24	6.41	8	27	50	73
13	D	H	3-Cl	0.46	7.00	16	35	45	62
14	M	H	3-Cl	0.14	6.89	50	60	65	53
15	D	H	3-Br	0.47	6.56	15	20	65	110
16	M	H	3-Br	0.16	6.93	16	*h*	100	33
17	D	H	3-SO_2CH_3	−0.14	5.63	>1500	*h*	150	*h*
18	M	H	3-SO_2CH_3	−0.20	5.30	>2200	*h*	150	*h*
19	D	H	3-NO_2	0.14	6.73	74	*h*	8.9	22
20	M	H	3-NO_2	−0.18	6.51	90	*h*	8.9	43
21	D	H	3-NH_2	0.06	6.90	385	5	5.9	58
22	M	H	3-NH_2	−0.18	6.82	10	8	8.9	67
23	D	H	4-CH_3	0.46	6.75	9	9	20	111
24	M	H	4-CH_3	0.07	6.52	17	50	66	75
25	D	H	4-OCH_3	0.33	6.53	20	45	45	50
26	M	H	4-OCH_3	0.01	6.24	45	125	150	58
27	D	H	4-$CONHCH_3$	0.18	6.46	97	60	66	56
28	M	H	4-$CONHCH_3$	−0.10	6.22	245	*h*	150	41
29	D	OCH_3	H	0.47	5.64	70	3.5	8.9	67
30	M	OCH_3	H	0.18	5.57	35	3	13.3	58
31	D	OCH_3	2-CH_3	0.55	5.28	985	*h*	30	25
32	M	OCH_3	2-CH_3	0.40	5.35	1400	*h*	69	34
33	D	OCH_3	3-Cl	0.61	6.40	12	5.5	13.3	91
34	M	OCH_3	3-Cl	0.32	6.06	70	5	20	232
35	D	OCH_3	3-Br	0.57	6.44	5	4	13.3	83
36	M	OCH_3	3-Br	0.34	6.29	50	4	20	133 (2)[j]
37	D	OCH_3	4-CH_3	0.44	6.16	18	3	8.9	106
38	M	OCH_3	4-CH_3	0.25	6.03	30	4	20	172 (3)
39	D	OCH_3	4-OCH_3	0.47	6.09	12	6	9	76
40	M	OCH_3	4-OCH_3	0.19	5.94	40	8	30	139 (5)
41	D	OCH_3	4-$CONHCH_3$	0.28	5.94	18	13	30	118
42	M	OCH_3	4-$CONHCH_3$	0.06	5.54	270	8	30	127

[a] D, dimethyl phosphoramidate; M, methanesulfonamide. [b] Rm is the chromatographic meausre of drug lipophilicity determined by liquid–liquid chromatrography on a cellulose support, as detailed in ref 7. Rm values are linearly related to log P (octanol) values.[6] [c] Log K values for the binding of drugs to poly[d(A-T)] were determined by the fluorometric methods given in ref 10, after allowing for quenching. [d] ID_{50} is the nanomolar concentration of drug that on 70-h incubation with cultures of murine L1210 leukemia cells reduces cell numbers to 50% of controls.[9] [e] D_{50} is the dose of drug, in milligrams per kilogram per day (administered intraperitoneally as a solution in 0.1 mL of 30%, v/v, EtOH/water on days 1, 58 and 9 after inoculation of 10^6 P388 leukemia cells), that provides a life extension of 50% compared to controls. D_{50} values can be determined from dose–response graphs as detailed in ref 7. [f] OD is the optimal (highest nonacutely toxic) dose of drug in milligrams per kilogram per day. [g] ILS_{max} is the percentage increase in life span of treated animals over that of tumor-bearing, untreated control animals injected with tumor alone, when given the optimal dose. Values of ILS greater than 20% are considered statistically significant. [h] An ILS of >50% could not be obtained at any dose level. [i] An ILS of >20% could not be obtained at any dose level. [j] Numbers in parentheses are the average number of animals (out of a group of six) that survived indefinitely when treated at the optimal dose.

For antitumor compounds, the OD is a reasonable approximation to the LD_{10}, provided that a full dose profile has been determined with escalations of 1.5-fold or less between doses and provided that a higher (and toxic) dose has been given.

Overall drug lipophilicity, measured chromatographically for drug cations at pH 2 and recorded as Rm values,[7] shows that the dimethyl phosphoramidates are, on the average, more lipophilic than the corresponding AMSA compounds by 0.3 Rm unit. Since studies[8] with alkyl analogues of amsacrine (**30**) suggest this compound is already too lipophilic for optimal antileukemic activity, the increased lipophilicity (amounting to nearly 1.1 log P units[7]) could in itself have a deleterious effect upon the comparative activity of the dimethyl phosphoramidates.

The pK_a values (determined in 20% DMF) for the acridine nitrogen of the dimethyl phosphoramidates (**3**, 7.78; **29**, 8.21) are significantly higher than those for the corresponding sulfonamides (**4**, 7.19; **30**, 7.43). Given the excellent transmission of electronic effects through the 9-anilinoacridine system,[6] this suggests much greater electron-donating properties for the dimethyl phosphoramidate group. If the pK_a value for compound **3** and eq

(7) Denny, W. A.; Cain, B. F. *J. Med. Chem.* **1978**, *21*, 430.

2 of ref 6 are used, a σ_p value of −0.25 can be computed for the dimethyl phosphoramidate group. This compares to a value of 0.03 accepted (0.04 calculated by eq 2 of ref 6 from compound 4) for the methanesulfonamide group.

DNA-binding properties, as determined by equilibrium binding constants (K), display a similar relationship to structural changes in both series. Substitution in the 2-position generally leads to weaker binding than similar 3-substitution, and electron-donating groups provide more tightly binding compounds than electron-withdrawing groups. However, the dimethyl phosphoramidates (D) consistently show slightly tighter binding than the corresponding methanesulfonamide (M) analogues. This may be due partly to their higher pK_a values and is demonstrated by eq 1, relating the log K values for the 20 pairs of compounds in Table I.

$$\log K_D = 1.00 \log K_M + 0.15 \quad (1)$$

$$n = 20, r = 0.99, s = 0.02$$

The coefficient of unity confirms the similarity of binding behavior between the two series, while the intercept of 0.15 indicates the extent of the binding increment provided by the phosphoramidate group. In view of the known[5] relationship between activity and DNA binding for amsacrine derivatives, this effect might offset the higher lipophilicity of the dimethyl phosphoramidates.

A total of 12 monosubstituted acridine derivatives of the dimethyl phosphoramidate parent compound (**3**) were prepared, with substituents of widely varying lipophilic, electronic, and steric properties at the 2-, 3-, and 4-positions. In the AMSA series, such substituents have been shown to have substantial effects on in vivo L1210 antileukemic activity,[6] ranging from a 5-fold increase in potency over the parent compound (3-NH_2 and 3-CH_3) to abolition of activity even at doses of 500 mg/kg (3-SO_2CH_3). These broad structure–activity relationships are again followed by both series of monosubstituted compounds for in vivo P388 antileukemic activity (Table I). Thus, the 2-substituted compounds (**5–10**) are essentially inactive, as are the very polar 3-SO_2CH_3 derivatives (**17** and **18**); this may in part be due to lower DNA binding (see above). Improved activity over the parent compounds (**3** and **4**) in terms of higher dose potency D_{50} and/or higher ILS values is generally seen only with the lipophilic derivatives (3-CH_3, 3-halogen, and 4-CH_3; compounds **11–16**, **23**, and **24**).

When the two series of compounds are compared pairwise to examine the influence of the dimethyl phosphoramidate group, the initial[1] observation of higher in vivo dose potency in the dimethyl phosphoramidate series is borne out. For the six sets of compounds for which D_{50} values are available, they are related by eq 2. Equation

$$D_{50}\ (D) = 0.37 D_{50}\ (M) + 0.31 \quad (2)$$

$$n = 6, r = 0.90, s = 0.02$$

2 shows that, on the average, the dimethyl phosphoramidates are more than twice as potent as the methanesulfonamides. The relationships for the optimal doses (used as a crude indication of acute toxicity) shows a similar trend (eq 3), In contrast to this significant difference

$$OD\ (D) = 0.49 OD\ (M) - 0.40 \quad (3)$$

$$n = 13, r = 0.67, s = 0.06$$

in potency and acute toxicity between the series, the maximum ILS values (a measure of tumor cell selectivity[6]) obtained are similiar in both series, varying much more with acridine substitution pattern than with the 1′-substituent.

In the methanesulfonamide series, substitution of the parent compound (**4**) with a 3′-methoxy group to give amsacrine (**30**) provides more than a tenfold increase in both dose potency and acute toxicity. To explore if this remarkable enhancement was carried over into the already more dose-potent dimethyl phosphoramidate series, we prepared a group of acridine-substituted derivatives of **3** and compared them pairwise with the corresponding amsacrine analogues. The data in Table I for five sets of substituted compounds (**31–42**) show that the above trends do continue, with the phosphoramidates having at least twice the acute toxicity of the corresponding methanesulfonamides (eq 4 for compounds **29–42**). Although D_{50}

$$OD\ (D) = 0.38 OD\ (M) + 5.26 \quad (4)$$

$$n = 7, r = 0.73, s = 0.03$$

values for these seven sets of compounds are about the same, over the whole data base of evaluable compounds the dimethyl phosphoramidates are generally much more dose potent and acutely toxic (eq 5 and 6) However, in

$$D_{50}\ (D) = 0.34 D_{50}\ (M) + 3.00 \quad (5)$$

$$n = 12, r = 0.90, s = 0.08$$

$$OD\ (D) = 0.48\ OD\ (M) + 1.63 \quad (6)$$

$$n = 20, r = 0.75, s = 0.04$$

contrast to the 3′-H compounds, the 3′-OCH_3 dimethyl phosphoramidate derivatives did not provide ILS values as high as those for the corresponding methanesulfonamide (amsacrine) analogues. The latter derivatives, especially those bearing lipophilic substituents, showed very high levels of selectivity, providing, on the average, 30 to 80% of long-term survivors with the dosage protocol (days 1, 5, and 9) chosen.

We conclude from these results that, in general, the structure–activity relationships of both the dimethyl phosphoramidates and the methanesulfonamides studied here are dominated by the acridine substitution patterns, with these giving about a 10-fold range in potency and toxicity in both series of 3′-H compounds (and lesser ranges in the 3-′OCH_3 compounds). In addition, there is good evidence (summarized by eq 5 and 6) that the 1′-phosphorus substituent provides compounds about twice as potent (but also twice as toxic) as the corresponding 1′-sulfur compounds.

This colinear increase in both potency and toxicity demonstrates again one of the primary dilemmas in the development of antitumor drugs: that if increases in potency are accompanied by similar increases in toxicity, little of therapeutic value has been gained. The dimethyl phosphoramidate substituent is a novel one, clearly compatible with high antitumor activity in the 9-anilinoacridine class of compounds. However, the concomitant increases in acute toxicity means that, at least for the leukemias, the resulting 3′-H compounds do not have better tumor cell selectivity to the methanesulfonamide analogues, and the 3′-OCH_3 compounds are clearly inferior. Furthermore, the changes in biological activity are small compared to those effected by acridine substitution[5,8] and substitution at the 3′-position of the anilino ring.[5] It seems likely that changes of the latter two types made within the 4-(9-acrydinylamino)methanesulfonanilide series (com-

(8) Denny, W. A.; Atwell, G. J.; Cain, B. F. *J. Med. Chem.* **1979**, 22, 1453.

Table II. Analytical Data for the New Compounds of Table I

no.	mp, °C	formula	anal.
5	278–279	$C_{22}H_{22}N_3O_3P$·HCl	C, H, N, Cl
7	272–275	$C_{22}H_{22}N_3O_4P$·HCl	C, H, N, Cl
9	265–267	$C_{21}H_{19}ClN_3O_3P$·HCl	C, H, N, Cl
11	250	$C_{22}H_{22}N_3O_3P$·HCl	C, H, N, Cl
13	>350	$C_{21}H_{19}ClN_3O_3P$·HCl	C, H, N, Cl
15	>350	$C_{21}H_{19}BrN_3O_3P$·HCl	C, H, N, Cl
17	264–266	$C_{22}H_{22}N_3O_5PS$·HCl	C, H, N, Cl
19	218–219	$C_{21}H_{19}N_4O_5P$	C, H, N
21	>350	$C_{21}H_{21}N_4O_3P$·HCl·1/2H_2O	C, H, N, Cl
23	225–227	$C_{22}H_{22}N_3O_3P$	C, H, N
25	238–240	$C_{22}H_{22}N_3O_4P$·HCl	C, H, N, Cl
27	232–235	$C_{23}H_{23}N_4O_4P$·HCl	C, H, N, Cl
28	295–297	$C_{22}H_{20}N_4O_3S$·HCl	C, H, N, Cl
31	297–281	$C_{23}H_{24}N_3O_4P$·HCl	C, H, N, Cl
33	201–205	$C_{22}H_{21}ClN_3O_4P$·HCl	C, H, N, Cl
35	210–212	$C_{22}H_{21}BrN_3O_4P$·HCl	C, H, N, Cl
37	181–183	$C_{23}H_{24}N_3O_4P$	C, H, N
39	177–178	$C_{23}H_{24}N_3O_5P$	C, H, N
41	220–223	$C_{24}H_{25}N_4O_5P$·HCl	C, H, N, Cl

pound 4) will be more likely to provide 9-anilinoacridine derivatives superior to amsacrine as antitumor agents.

Experimental Section

Where analyses are indicated only by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Analyses were performed by Dr. A. D. Campbell, Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on an Electrothermal melting point apparatus with the marker's supplied stem-corrected thermometer; melting points are as read.

To monitor the progress of reactions, purification of products, etc., we used TLC on SiO_2 (Merck SiO_2, F_{254}). The most convenient solvents were the top phase of *n*-BuOH-HOAc-H_2O (5:1:4, v/v) and $CHCl_3$ containing 10% MeOH.

9-Chloroacridines. The substituted 9-chloroacridines were prepared from the appropriate 9(10*H*)-acridones by reaction with thionyl chloride and a trace of DMF as previously described.[6]

Dimethyl *N*-(4-Aminophenyl)phosphoramidate (IIa). Hydrogenation of dimethyl *N*-(4-nitrophenyl)phosphoramidate[1] over Pd on C in MeOH gave amine IIa in quantitative yield, mp 125 °C (MeOH–EtOAc). Anal. ($C_8H_{13}N_2O_3P$) C, H, N, P.

Dimethyl *N*-(4-Amino-3-methoxyphenyl)phosphoramidate (IIb). Reduction of dimethyl *N*-[4-[(benzyloxy)carboxamido]-3-methoxyphenyl]phosphoramidate[1] as above gave the methoxyamine IIb, mp 122–124·C, Anal. ($C_9H_{15}N_2O_4P$) C, H, N.

Standard Coupling Procedure To Give the Compounds (III) of Table I. A solution of the substituted 9-chloroacridine (I; 5 mmol) in 50 mL of methanol (or *N*-methylpyrrolidone and methanol) containing 1 drop of concentrated NH_3 (aq) was combined with a methanolic solution of the phosphoramidate amine component (II) (5.25 mmol), and two drops of concentrated HCl were added to initiate the reaction, which was evidenced by the appearance of a deep red color. After 5-10 min, the solution was concentrated to a small volume and allowed to stand as crystallization commenced. After being diluted with ethyl acetate to ensure complete crystallization, the mixture was filtered, and the dark-red hydrochloride salt was washed well with dry acetone. The product was purified by recrystallization from MeOH–EtOAc. Where necessary, conversion of the hydrochloride salt to the free base was achieved by the addition of 1.1 equiv of $KHCO_3$ to an aqueous methanolic solution of the salt.

Dimethyl *N*-[4-[(3-Amino-9-acridinyl)amino]phenyl]-phosphoramide (21). A methanolic solution of the free base of dimethyl *N*-[4-(3-nitro-9-acridinyl)amino)phenyl]phosphoramidate (19) was hydrogenated over Pd/C to give the amine (21), which was converted to its hydrochloride salt by bubbling HCl gas into the concentrated solution. Dilution with EtOAc gave the crude product, which was recrystallized from MeOH–EtOAc (see Table II for data).

Antitumor Testing. F1 hybrid (DBA/2J × C57BlJ) mice (19–21 g) of either sex were inoculated with 10^6 P388 murine leukemia cells on day 0. Drugs, normally as solutions but at the highest doses as suspensions (sonicated) in 30% aqueous ethanol, were administered intraperitoneally in a volume of 0.1 mL on days 1, 5, and 9. Average survival times were measured for each group of six mice, and the percentage increase in life span was calculated with respect to the control animals (20–30 mice). Control animals survived 11.0 days on average. Drug doses ranged from a toxic level downwards at 0.67-fold intervals.

Cultures of L1210 leukemia cells were used to test drug cytotoxicity over a 3-day incubation time. Conditions for cell culture and drug addition were identical with those previously described.[9]

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Registry No. **5**, 90171-90-7; **5**·HCl, 90194-65-3; **7**, 90194-66-4; **7**·HCl, 90171-91-8; **9**, 90171-92-9; **9**·HCl, 90171-93-0; **11**, 90171-94-1; **11**·HCl, 86187-20-4; **13**, 90171-95-2; **13**·HCl, 86187-21-5; **15**, 90171-96-3; **15**·HCl, 86187-23-7; **17**, 90171-97-4; **17**·HCl, 90194-67-5; **19**, 86187-25-9; **21**, 90171-98-5; **21**·HCl, 90171-99-6; **23**, 86187-30-6; **25**, 90172-00-2; **25**·HCl, 86187-26-0; **27**, 90172-01-3; **27**·HCl, 86187-28-2; **28**, 90172-02-4; **28**·HCl, 90172-03-5; **31**, 90172-04-6; **31**·HCl, 90172-05-7; **33**, 90172-06-8; **33**·HCl, 86187-22-6; **35**, 90172-07-9; **35**·HCl, 86187-24-8; **37**, 86187-31-7; **39**, 86187-27-1; **41**, 90172-08-0; **41**·HCl, 86187-29-3; I (X = 2-CH_3), 16492-09-4; I (X = 2-OCH_3), 16492-13-0; I (X = 2-Cl), 1019-14-3; I (X = 3-CH_3), 16492-10-7; I (X = 3-Cl), 35547-70-7; I (X = 3-Br), 35547-72-9; I (X = 3-SO_2CH_3), 90172-09-1; I (X = 3-NO_2), 1744-91-8; I (X = 3-NH_2), 40505-23-5; I (X = 4-CH_3), 16492-11-8; I (X = 4-OCH_3), 16492-15-2; I (X = 4-$CONHCH_3$), 63178-97-2; I (X = H), 1207-69-8; IIa, 82720-54-5; IIb, 86187-37-3; dimethyl *N*-(4-nitrophenyl)phosphoramidate, 78258-13-6; dimethyl *N*-[4-(benzyloxy)carboxamido]-3-methoxyphenyl]phosphoramidate, 86187-36-2.

(9) Baguley, B. C.; Nash, R. *Eur. J. Cancer* **1981**, *17*, 671.
(10) Baguley, B. C.; Denny, W. A.; Atwell, G. J.; Cain, B. F. *J. Med. Chem.* **1981**, *24*, 170.