Antitumor Agents. 178.† Synthesis and Biological Evaluation of Substituted 2-Aryl-1,8-naphthyridin-4(1*H*)-ones as Antitumor Agents That Inhibit Tubulin Polymerization

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As part of our continuing search for potential anticancer drug candidates in the 2-aryl-1,8-naphthyridin-4(1*H*)-one series, we have synthesized two series of 3′-substituted 2-phenyl-1,8-naphthyridin-4(1*H*)-ones and 2-naphthyl-1,8-naphthyridin-4(1*H*)-ones. All compounds showed significant cytotoxic effects (log $GI_{50} < -4.0$; log molar drug concentration required to cause 50% growth inhibition) against a variety of human tumor cell lines of the National Cancer Institute's *in vitro* screen, including cells derived from solid tumors such as non-small cell lung, colon, central nervous system, melanoma, ovarian, prostate, and breast cancers. All 3′-substituted compounds demonstrated strong cytotoxic effects in almost all tumor cell lines. Introduction of an aromatic ring at the 2′- and 3′-positions also generated compounds with potent antitumor activity. Incorporation of an aromatic ring at the 3′- and 4′-positions produced compounds with reduced activity. Interestingly, introduction of a halogen at the 3′-position yielded compounds with different selectivity for the tumor cell lines tested. All 3′-halogenated compounds (**29**−**36**) and compounds **38** and **42**−**44** were potent inhibitors of tubulin polymerization with activities nearly comparable to those of the potent antimitotic natural products colchicine, podophyllotoxin, and combretastatin A-4. Active agents also inhibited the binding of [^{3}H]colchicine to tubulin.

Introduction

In our continuing search for antitumor agents, 2-phenyl-1,8-naphthyridin-4(1*H*)-ones were identified as antitumor agents interacting with tubulin at the colchicine site.[2] We have continued our synthesis and evaluation of related compounds, and in this paper, we describe new active agents, a series of 3′-substituted 2-phenyl-1,8-naphthyridin-4(1*H*)-ones (**29**−**41**) and 2-naphthyl-1,8-naphthyridin-4(1*H*)-ones (**42**−**52**). These compounds displayed strong inhibitory effects against a variety of human tumor cell lines, derived from solid tumors, when evaluated in the National Cancer Institute's (NCI) *in vitro* screen.[3,4] Like the initial members of the series,[2] the most potent 2-aryl-1,8-naphthyridin-4(1*H*)-ones (**29**−**31**, **33**−**36**, **43**−**46**) inhibited tubulin polymerization and colchicine binding to tubulin. These activities were comparable to those of the antimitotic natural products colchicine (Figure 1),[5,6] podophyllotoxin,[7,8] and combretastatin A-4.[9,10]

Our initial investigation of the structure−activity relationships of the 2-phenyl-1,8-naphthyridin-4(1*H*)-ones[2] indicated that a methoxy group at the 3′-position was required for potent cytotoxicity against most tumor cell lines. Substitution at the 2′- and 4′-positions yield compounds with little cytotoxic activity, although several agents with a 4′-methyl or 4′-chloro substituent retained significant, but reduced, antitubulin activity. The effects on activity of substitutions in ring A depended on the substitution in ring C, and this was most readily evaluated by comparing inhibitory effects on tubulin assembly. The work presented here describes the synthesis and evaluation of new 3′-substituted 2-phenyl-1,8-naphthyridin-4(1*H*)-ones and of 2-naphthyl-1,8-naphthyridin-4(1*H*)-ones in order to investigate further the steric and electronic effects of these positions for compound activity.

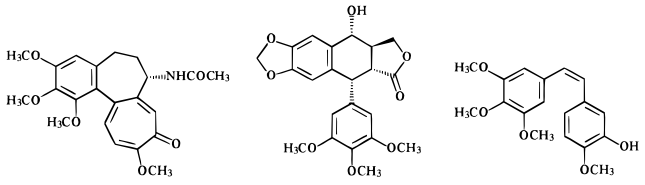

Figure 1.

Chemistry

The 3′-substituted 2-phenyl-1,8-naphthyridin-4(1*H*)-ones and 2-naphthyl-1,8-naphthyridin-4(1*H*)-ones were synthesized according to the previously reported methods.[2] In brief, condensation of substituted 2-aminopyridines (**1**) with substituted ethyl benzoylacetates (**2**) in the presence of polyphosphoric acid (PPA) formed the corresponding pyridopyrimidinones (**5**−**28**). Thermal rearrangement in mineral oil at 350 °C yielded the target compounds (**29**−**52**) (Scheme 1).[11] The starting substituted ethyl benzoylacetates (**2**) were prepared

† For part 177, see ref. 1.
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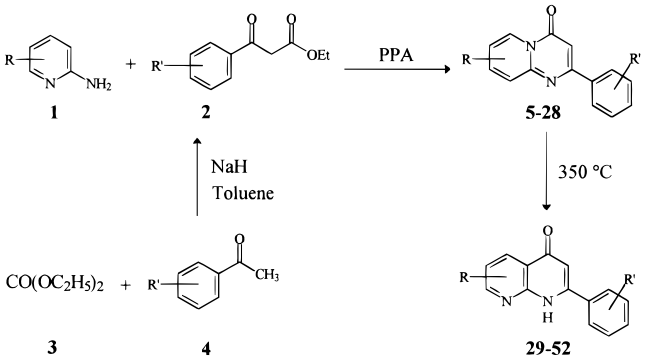
Scheme 1. Synthetic Route to 2-Aryl-1,8-naphthyridin-4(1*H*)-ones



according to a literature method.[12] Condensation of substituted acetophenones (**4**) with diethyl carbonate (**3**) in the presence of sodium hydride formed the required ethyl benzoylacetates. The structures and chemical features of newly synthesized compounds are summarized in Table 1.

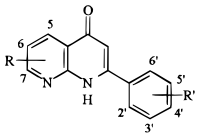
Results and Discussion

(a) Evaluation of the Cytotoxicity of 2-Aryl-naphthyridin-4(1*H*)-ones. The 2-aryl-1,8-naphthyridin-4(1*H*)-ones were submitted to the NCI for testing in its *in vitro* disease-oriented antitumor screen.[3,4] This assay involves determinations of a test agent's effect on growth parameters against a panel of approximately 60 human tumor cell lines, derived largely from solid tumors, including non-small cell lung, colon, central nervous system, renal, ovarian, prostate, and breast cancers, plus a few leukemia cell lines. The cytotoxic effects of each compound are presented as the molar drug concentrations required to cause 50% growth inhibition (GI_{50}) and total growth inhibition (TGI), respectively. The results are expressed as log GI_{50} values (Table 2) for each cell line and average log GI_{50} values (Table 1) and as log TGI values and average log TGI values (Table 3).

All compounds had cytotoxic activity (log $GI_{50} < -4.00$) against all cell lines tested. Among the three subseries of 2-phenyl-1,8-naphthyridin-4(1*H*)-ones, only compound **41** had limited activity, for compounds **29**−**40** were inhibitory toward most cell lines in the submicromolar (log GI_{50}'s of −7 to −6) to nanomolar (log GI_{50}'s of −8 to −7) range. Ignoring compound **41**, and considering only the average log GI_{50} values, which takes into account all the cell lines tested (not just those shown in Table 2), the agents with 3′-fluoride and methyl groups were slightly more cytotoxic than those with a 3′-chloride group. The 3′-fluoride compounds, in particular, have cytotoxicity comparable to that reported earlier for agents bearing a 3′-methoxy substituent.[2]

A fairly dramatic difference was observed between the 2-(α-naphthyl) (compounds **42**−**46**) and the 2-(β-naphthyl) (compounds **47**−**52**) derivatives. In the former group, except for compound **46**, low nanomolar GI_{50} values (log < −8) were observed with many cell lines. In the latter group, in contrast, submicromolar GI_{50} values were rarely obtained with any agent except

Table 1. Physical Properties and Antimicrotubule Effects of Substituted 2-Aryl-1,8-naphthyridin-4(1*H*)-ones



compd	R_5	R_6	R_7	$R_{2'}$	$R_{3'}$	$R_{4'}$	ITP[a] IC_{50} (μM) ± SD	ICB[b] (% inhibition)	average[c] log GI_{50}	formula[d]	mp, °C	yield, %[e]
29	H	CH_3	H	H	F	H	0.63 ± 0.20	43 ± 1	−7.30	$C_{15}H_{11}FN_2O$	>300	57
30	H	H	CH_3	H	F	H	0.53 ± 0.08	41 ± 2	−7.37	$C_{15}H_{11}FN_2O$	270−272[f]	48
31	CH_3	H	CH_3	H	F	H	0.74 ± 0.06	29 ± 1	−7.07	$C_{16}H_{13}FN_2O$	236−238	57
32	H	H	H	H	Cl	H	1.50 ± 0.10		−6.64	$C_{14}H_9ClN_2O$	295−297[f]	26
33	CH_3	H	H	H	Cl	H	1.00 ± 0.03	32 ± 1	−6.80	$C_{15}H_{11}ClN_2O$	260−262	21
34	H	CH_3	H	H	Cl	H	0.72 ± 0.08	33 ± 2	−6.57	$C_{15}H_{11}ClN_2O$	290−292[f]	49
35	H	H	CH_3	H	Cl	H	0.89 ± 0.09	38 ± 1	−6.77	$C_{15}H_{11}ClN_2O$	255−257[f]	17
36	CH_3	H	CH_3	H	Cl	H	0.77 ± 0.20	22 ± 2	−6.46	$C_{16}H_{13}ClN_2O$	232−234	49
37	H	H	H	H	CH_3	H	3.30 ± 0.60		−7.02	$C_{15}H_{12}N_2O$	205−207	33
38	CH_3	H	H	H	CH_3	H	1.80 ± 0.50		−7.24	$C_{16}H_{14}N_2O$	175−177	32
39	H	CH_3	H	H	CH_3	H	1.50 ± 0.30		−6.19	$C_{16}H_{14}N_2O{\cdot}0.25H_2O$	223−225	36
40	H	H	CH_3	H	CH_3	H	1.90 ± 0.50		−7.01	$C_{16}H_{14}N_2O$	193−195	52
41	CH_3	H	CH_3	H	CH_3	H	2.30 ± 0.20		−4.42	$C_{17}H_{16}N_2O$	197−198	55
42	H	H	H	CH=CH−CH=CH		H	1.10 ± 0.30		−7.45	$C_{18}H_{12}N_2O$	282−283[f]	27
43	CH_3	H	H	CH=CH−CH=CH		H	0.93 ± 0.20	37 ± 4	−7.45	$C_{19}H_{14}N_2O$	228−230[f]	27
44	H	CH_3	H	CH=CH−CH=CH		H	0.55 ± 0.05	46 ± 3	−7.72	$C_{19}H_{14}N_2O$	236−238	25
45	H	H	CH_3	CH=CH−CH=CH		H	0.66 ± 0.10	40 ± 4	−7.18	$C_{19}H_{14}N_2O{\cdot}0.5H_2O$	240−242	34
46	CH_3	H	CH_3	CH=CH−CH=CH		H	0.78 ± 0.20	15 ± 10	−5.98	$C_{20}H_{16}N_2O$	276−278[f]	37
47	H	H	H	H	CH=CH−CH=CH		14.00 ± 2.00		−5.09	$C_{18}H_{12}N_2O$	259−261	38
48	CH_3	H	H	H	CH=CH−CH=CH		1.80 ± 0.06		−5.92	$C_{19}H_{14}N_2O$	217−219	29
49	H	CH_3	H	H	CH=CH−CH=CH		2.10 ± 0.50		−6.13	$C_{19}H_{14}N_2O$	255−257	34
50	H	H	CH_3	H	CH=CH−CH=CH		5.10 ± 0.90		−5.34	$C_{19}H_{14}N_2O$	244−246	45
51	CH_3	H	CH_3	H	CH=CH−CH=CH		>40		−4.87	$C_{20}H_{16}N_2O{\cdot}2H_2O$	149−151	59
52	H	Cl	H	H	CH=CH−CH=CH		2.50 ± 0.50		−5.24	$C_{18}H_{11}ClN_2O$	>300	51
colchicine							0.80 ± 0.07[g]		−7.24			
podophyllotoxin							0.46 ± 0.02[g]	76 ± 5	−7.54			
combretastatin A-4							0.53 ± 0.05[g]	91 ± 2	−8.18			

[a] ITB = inhibition of tubulin polymerization. [b] ICB = inhibition of colchicine binding and evaluated only when polymerization $IC_{50} \leq 1$ μM. [c] Data obtained from NCI's 60 human tumor cell line *in vitro* screen and calculated from all cell lines tested. [d] All compounds were analyzed for C, H, and N, and results agreed to ±0.4% of the theoretical values. [e] All yields were calculated from aminopyridines. [f] Decomposed. [g] Previously obtained data, see ref 16.

Table 2. Inhibition of *in Vitro* Tumor Cell Growth by Substituted 2-Aryl-1,8-naphthyridin-4(1*H*)-ones[a]

	cytotoxicity log GI_{50} (M)[b]										
compd	HL-60 (TB)[c]	NCI-H460	HCT-116	SF-295	U-251	SK-MEL-5	OVCAR-3	CAKI-1	PC-3	MDA-MB-435	MDA-N
29	−7.69	−7.41	−7.62	−7.56	−7.39	−7.55	−7.87	−7.55	−7.46	< −8.00	−7.93
30	−7.65	−7.48	−7.55	−7.54	−7.42	−7.65	−7.71	−7.34	−7.46	−7.91	−7.84
31	−7.43	−7.27	< −8.00	−7.48	−7.19	−7.43	−7.74	−7.45	−7.21	< −8.00	−7.89
32	−7.98	−7.06	−7.54	−7.20	−6.84	−7.28	−7.34	−7.25	−7.65	< −8.00	−7.76
33	< −8.00	−7.41	−7.80	−7.39	−7.28	−7.38	−7.50	−7.48	−7.81	< −8.00	−7.93
34	−7.51	−7.30	−7.52	−7.60	−7.16	−7.15	−7.65	−7.37	> −4.00	< −8.00	> −4.00
35	−7.54	−7.38	−7.59	−7.64	−7.19	−7.50	< −8.00	−7.38	> −4.00	< −8.00	> −4.00
36	−7.13	−6.65	−6.77	−7.32	−6.53	−6.93	−6.77	−6.69	−7.56	−7.88	−7.72
37	−7.72	−7.59	−7.65	−7.43	−7.35	−7.59	−7.38	−7.43	−7.37	<− 8.00	< −8.00
38	−7.74	−7.44	−7.33	−7.52	−7.27	−7.47	−7.65	−7.27	−7.48	< −8.00	−7.96
39	−6.76	−6.41	−6.39	−6.38	−6.77	−6.54	−6.60	−6.36	−6.51	<− 8.00	< −8.00
40	−7.57	−7.75	−6.92	−7.22	−6.70	−6.90	−6.31	−6.37	−6.86	−7.49	−7.50
41	−4.89	−4.35	−4.75	−4.19	−4.27	−4.46	−4.52	−4.25	−4.50	−4.70	−4.68
42	< −8.00	−7.41	< −8.00	< −8.00	−7.99	< −8.00	< −8.00	−7.82	−7.75	< −8.00	< −8.00
43	< −8.00	< −8.00	< −8.00	−7.97	< −8.00	< −8.00	< −8.00	−7.92	−7.70	< −8.00	< −8.00
44	< −8.00	< −8.00	< −8.00	< −8.00	< −8.00	< −8.00	< −8.00	< −8.00	< −8.00	< −8.00	< −8.00
45	< −8.00	−7.76	< −8.00	−7.62	−7.81	−7.86	< −8.00	−5.22	−7.52	< −8.00	< −8.00
46	−6.61	−6.20	−6.42	−6.23	−6.43	−6.33	−6.46	−5.02	−6.12	−6.72	−6.63
47	−5.74	−5.42	−5.42	−5.04	−5.36	−5.46	−5.08	−5.25	−4.98	−5.75	−5.78
48	−6.69	−5.98	−6.37	−5.83	−6.19	−6.36	−5.89	−5.62	−5.86	−6.69	−6.69
49	−6.85	−6.40	−6.33	−6.26	−6.33	−6.44	−6.45	−6.21	−6.39	−6.98	−6.88
50	−5.75	−5.42	−5.40	−5.42	−5.34	−5.48	−5.44	−5.27	−5.58	−5.80	−5.71
51	−5.46	−4.88	−4.90	−4.83	−4.80	−5.66	−4.70	−4.29	−5.26	−5.53	−5.49
52	−5.75	−5.39	−5.40	−5.26	−5.32	−5.53	−5.58	−5.12	−5.51	−6.07	−5.81

[a] Data obtained from NCI's *in vitro* disease-oriented human tumor cells screen (see refs 3 and 4 for details). [b] Log concentrations which reduced cell growth to 50% of level at start of experiment. [c] HL-60 (TB), leukemia cell line; NCI-H266, non-small cell lung cancer cell line; HCT-116, colon cancer cell line; SF-295, U251, CNS cancer cell lines; SK-MEL-5, melanoma cell line; OVCAR-3, ovarian cancer cell line; 786−0, renal cancer cell line; PC-3, prostate cancer cell line; MDA-MB-435, MDA-N, breast cancer cell lines.

Table 3. Total Inhibition of *in Vitro* Tumor Cell Growth by 2-Phenyl-1,8-naphthyridin-4(1*H*)-ones (**29**−**36**)[a]

	Cytotoxicity log TGI (M)[b]							
cancer	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**
average	−5.29	−5.33	−5.25	−4.62	−4.59	−4.51	−4.67	−4.58
leukemia	−5.57	−5.56	−5.61	−4.41	> −4.00	−4.14	> −4.00	−4.09
non-small cell lung	−4.79	−5.24	−5.60	−4.07	> −4.00	−4.35	−4.61	> −4.00
colon	−6.49	−6.26	−5.93	−4.79	−4.92	−5.02	−5.51	−4.54
CNS	−5.51	−5.65	−5.01	−4.78	−4.74	−5.72	−5.71	−5.30
melanoma	−4.49	−4.62	−4.86	−4.01	−4.15	−4.32	−4.16	−4.14
ovarian	−4.57	−4.99	−5.26	−4.50	−4.56	−4.80	−4.89	−4.52
renal	−4.26	−4.19	−4.31	−4.31	−4.16	−4.06	> −4.00	−4.23
prostate	−6.16	−5.80	−4.31	−5.58	−5.63	> −4.00	> −4.00	−5.51
breast	−6.27	−6.24	−6.00	−5.93	−6.09	−4.89	−5.42	−5.91

[a] Data obtained from NCI's *in vitro* disease-oriented human tumor cells screen (see refs 3 and 4 for details). [b] log molar concentrations required to cause total growth inhibition.

compound **49**. Note, moreover, that 2-(β-naphthyl) derivative compound **49** was at least 50-fold less active than its 2-(α-naphthyl) congener compound **44**.

As in the earlier study,[2] substituents in the C ring altered substituent effects in the A ring. With a 3′-halogen, cytotoxicity was apparently unaffected by A ring substituents, within the limited range of available compounds. With a 3′-methyl group and with both 2-naphthyl series, cytotoxicity was unfavorably affected by methyl groups at both positions 5 and position 7. With a 3′-methyl group, a methyl group at position 6 was less favorable than either no substituent or a methyl group at positions 5 or 7. In the α-naphthyl series, a methyl substituent at position 5, 6, or 7 was equivalent, and cytotoxicity differed little from that of the unsubstituted compound. In the β-naphthyl series, greater activity was observed in the compounds with methyl groups at positions 5 or 6 than in the unsubstituted agent or that bearing a methyl group at position 7.

Interestingly, all 3′-halogenated compounds showed different selectivity in the tested tumor panels at the total growth inhibition (TGI) levels. Growth of cells from more sensitive panels was arrested at a concentration approximately 1−2 log concentrations lower than was growth of less sensitive panels. As summarized in Table 3, all 3′-halogenated compounds, except for compound **34**, exhibited a highly selective effect at the TGI level on the breast cancer panel. In the 3′-fluoro analogs, the compound with a methyl group at position 6 (**29**) showed high selectivity for the colon and breast panels and the two prostate cancer cell lines; the analog with a methyl group at position 7 (**30**) demonstrated high selectivity for the colon and breast panels; and the compound with methyl groups at positions 5 and 7 (**31**) exhibited highly selective effects on the colon and breast panels. In the 3′-chloro compounds, substitution of a methyl group at position 5 (**32**) or no substitution (**33**) in ring A produced high selectivity for the two prostate cancer cell lines and breast panel; a methyl at position 6 (**34**) conferred high selectivity for the CNS panel and moderate selectivity for the colon, ovarian, and breast panels; a methyl substituent at position 7 (**35**) gave highly selective effects on the colon, CNS, and breast panels; and methyl groups at positions 5 and 7 (**36**) produced high selectivity for the CNS and breast panels

as well as the provided two prostate cancer cell lines. The reasons for this selectivity of the 3′-halogenated derivatives and its modulation by ring A substituents are not clear.

(b) Interactions of 2-Aryl-1,8-naphthyridin-4(1*H*)-ones with Tubulin. In our previous study[2] we demonstrated that the most potently cytotoxic 2-phenyl-1,8-naphthyridin-4(1*H*)-ones (those with a 3′-methoxy substituent) strongly interacted with tubulin at the colchicine binding site. They inhibited the polymerization of 12 μM tubulin by 50% at concentrations below 1.0 μM, as did colchicine, podophyllotoxin, and combretastatin A-4, and they were potent inhibitors of radiolabeled colchicine binding to tubulin, showing 22−35% inhibition when present in an equimolar concentration with [^{3}H]colchicine. Data presented in Table 1 demonstrate that the new agents described here, both the new 2-phenyl-1,8-naphthyridin-4(1*H*)-ones and the 2-naphthyl derivatives, also interact with tubulin, with good correlation between their cytotoxic properties and their relative activity as inhibitors of tubulin assembly.

Among the compounds examined here, only one compound was inactive (**51**; $IC_{50} > 40$ μM), one weakly active (**47**; $IC_{50} = 14$ μM), and one moderately active (**50**; $IC_{50} = 5.1$ μM). These three compounds were among the least cytotoxic agents, in terms of the average log GI_{50} values. At the opposite extreme, eleven compounds (**29**−**31**, **33**−**36**, and **43**−**46**) were highly potent inhibitors of tubulin polymerization, with IC_{50} values of 1.0 μM or less. This is the group that has activity comparable to that observed with the natural products colchicine, podophyllotoxin, and combretastatin A-4. Six of these agents had average log GI_{50} values below −7, and the remainder fell between −7 and −6. The remaining 10 compounds (**32**, **37**−**42**, **48**, **49**, and **52**) inhibited tubulin assembly with IC_{50} values of 1.1−3.3 μM. Four of these compounds (**37**, **38**, **40**, and **42**) were among the most cytotoxic agents (log $GI_{50} = -7$), three (**32**, **39**, and **49**) were moderately cytotoxic with log GI_{50} values between −7 and −6, and three (**41**, **48**, and **52**) had little cytotoxicity (log $GI_{50} > -6$).

Considering structure−activity aspects solely from the point of view of inhibition of tubulin polymerization, the 3′-fluoride and 3′-chloride substituents appeared to be equivalent, differed little in their activity from the previously described 3′-methoxy series, and were more active than the analogous derivatives with the 3′-methyl substituent. With the 3′-halogen series and the 3′-methyl series, derivatives with different methyl substituents in the A ring all had nearly equivalent activity. In the chloride and methyl series the data suggest that the derivatives that are unsubstituted in the A ring (compounds **32** and **37**) were less active than those bearing methyl substituent(s).

The 2-(α-naphthyl) derivatives (compounds **42**−**46**) were comparable in activity to the 3′-halogen derivatives. In this series, too, substituents in the A ring had little effect on inhibitory activity. It was only in the less active 2-(β-naphthyl) series (compounds **47**−**52**) that A ring substitution affected the apparent interaction with tubulin. A methyl substituent at either position 5 (**48**) or 6 (**49**) decreased the IC_{50} value 7-fold relative to the value obtained with the unsubstituted compound **47**, while a methyl substituent at position 7 decreased the IC_{50} value 3-fold. In contrast, two methyl groups at positions 5 and 7 abolished activity. Finally, in the 2-(β-naphthyl) series, we found no significant difference between methyl and chloride substituents at position 6.

All compounds that inhibited tubulin assembly with IC_{50} values of 1.0 μM or less were compared with podophyllotoxin and combretastatin A-4 for inhibitory effects on the binding of [^{3}H]colchicine to tubulin (data summarized in Table 1). In these experiments inhibitor and colchicine were equimolar and in 5-fold molar excess over tubulin. All agents, except possibly compound **46**, significantly inhibited colchicine binding to tubulin, as had the previously studied active members of this group,[2] but none was as potent as either podophyllotoxin or combretastatin A-4. We believe the quantitative differences between the assembly assay and the [^{3}H]colchicine assay result from differences in relative rates of drug binding and dissociation from tubulin and from the stoichiometric character of the [^{3}H]colchicine assay versus the cooperative character of the assembly assay. However, the [^{3}H]colchicine binding assay does detect reduced activity in the 5,7-dimethyl derivatives that was not apparent in either the cytotoxicity or polymerization assays (*cf.* results with **31** *vs* **29** and **30**; with **36** *vs* **33**−**35**; and with **46** *vs* **43**−**45**).

(c) Summary. We found that the 3′-halogenated compounds were highly active in both antitumor and antitubulin assays. Substitution in ring A at different positions produced different selective cytotoxicity in the tumor types. The 2-(α-naphthyl)-1,8-naphthyridin-4(1*H*)-ones also exhibited high activities in both assays. However, the 2-(β-naphthyl)-1,8-naphthyridin-4(1*H*)-ones showed reduced and variable activity in the antitubulin polymerization assay and relatively weak cytotoxicity. Further structure−activity studies with additional compounds should provide new insights into the optimal substitution pattern in this new class of antineoplastic agents.

Experimental Section

General Experimental Procedures. Melting points were determined on a Fisher−John melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba EA 1108 elemental analyzer. ^{1}H NMR spectra were measured on a Bruker AC-300 spectrometer with TMS as internal standard. Chemical shifts are reported in δ (ppm). Mass spectra (MS) were obtained on a TRIO 1000 mass spectrometer EI. Flash column chromatography was performed on silica gel (mesh 25−150 μm) using a mixture of CH_2Cl_2 and EtOAc as eluant. Precoated silica gel plates (Kieselgel 60 F_{254} 0.25 mm, Merck) were used for TLC analysis. All substituted 2-aminopyridines were purchased from Aldrich Chemical Company.

Preparation of Substituted Ethyl Benzoylacetates. The substituted ethyl benzoylacetates (**2**) were prepared according to procedures described by Krapcho *et al.*[12] To a vigorously stirring suspension of NaH and $CO(OEt)_2$ (**3**) in toluene was added dropwise a solution of substituted acetophenone (**4**) in toluene under reflux. The mixture was allowed to reflux and was stirred for 20 min after the addition was complete. When cooled to room temperature, the mixture was acidified with glacial HOAc. After ice-cold water was added, the mixture was extracted with toluene. The extract was then dried over $MgSO_4$. After the toluene was evaporated at atmospheric pressure, the residue was distilled *in vacuo* to give the corresponding substituted ethyl benzoylacetates.

Procedures for Preparation of 2-Arylpyrido[1,2-*a*]pyrimidin-4-ones (5−28) and 2-Aryl-1,8-naphthyridin-4(1*H*)-ones (29−52).[11] A mixture of substituted 2-aminopyridine (**1**),

substituted ethyl benzoylacetate (**2**), and polyphosphoric acid was heated at 125 °C with stirring. The reaction was monitored by TLC. After the reaction was complete, the mixture was cooled to room temperature and neutralized with 4 M NaOH. After extraction with CH_2Cl_2, the extract was passed through a silica gel column to give the 2-arylpyrido[1,2-*a*]pyrimidin-4-one. The 2-arylpyrido[1,2-*a*]pyrimidin-4-one was added to liquid paraffin at 350 °C with stirring. The oil was maintained at 350 °C for 2 h after the addition was complete. The cooled mixture was subjected to silica gel column chromatography, and elution with CH_2Cl_2−EtOAc gave the corresponding 2-aryl-1,8-naphthyridin-4(1*H*)-one.

2-(3′-Fluorophenyl)-7-methylpyrido[1,2-*a*]pyrimidin-4-one (5) was obtained from ethyl (3′-fluorobenzoyl)acetate and 2-amino-5-picoline: amorphous, mp 163−165 °C; ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1 H, H-6), 7.85 (d, J = 8.5 Hz, 1 H, H-6′), 7.83 (s, 1 H, H-2′), 7.71 (d, J = 9.0 Hz, 1 H, H-9), 7.65 (dd, J = 9.0, 1.5 Hz, 1 H, H-8), 7.48 (m, 1 H, H-5′), 7.19 (dt, J = 2.0, 8.5 Hz, 1 H, H-4′), 6.88 (s, 1 H, H-3), 2.46 (s, 3 H, CH_3-7); MS m/z 254 (M^+). Anal. C, H, N.

2-(3′-Fluorophenyl)-6-methylpyrido[1,2-*a*]pyrimidin-4-one (6) was obtained from ethyl (3′-fluorobenzoyl)acetate and 2-amino-6-picoline: amorphous, mp 145−146 °C; ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J = 7.5, Hz, 1 H, H-6′), 7.80 (d, J = 1.5, Hz, 1 H, H-2′), 7.51 (d, J = 7.5 Hz, 1 H, H-9), 7.48 (m, 1 H, H-5′), 7.45 (dd, J = 7.5, 6.0 Hz, 1 H, H-8), 7.18 (dt, J = 2.5, 8.0 Hz, 1 H, H-4′), 6.72 (s, 1 H, H-3), 6.69 (d, J = 6.0 Hz, 1 H, H-7), 3.10 (s, 3 H, CH_3-6); MS m/z 254 (M^+). Anal. C, H, N.

2-(3′-Fluorophenyl)-6,8-dimethylpyrido[1,2-*a*]pyrimidin-4-one (7) was obtained from ethyl (3′-fluorobenzoyl)-acetate and 2-amino-4,6-dimethylpyridine: amorphous, mp 162−164 °C; ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 1 H, H-6′), 7.79 (d, J = 1.0 Hz, 1 H, H-2′), 7.45 (m, 1 H, H-5′), 7.30 (br s, 1 H, H-9), 7.17 (dt, J = 2.5, 8.0 Hz, 1 H, H-4′), 6.64 (s, 1 H, H-3), 6.53 (br s, 1 H, H-7), 3.07 (s, 3 H, CH_3-6), 2.37 (s, 3 H, CH_3-8); MS m/z 268 (M^+). Anal. C, H, N.

2-(3′-Chlorophenyl)pyrido[1,2-*a*]pyrimidin-4-one (8) was obtained from ethyl (3′-chlorobenzoyl)acetate and 2-aminopyridine: amorphous, mp 160−161 °C; ^{1}H NMR ($CDCl_3$) δ 9.08 (d, J = 7.2 Hz, 1 H, H-6), 8.15 (t, J = 1.5 Hz, 1 H, H-2′), 7.94 (td, J = 7.0, 1.5 Hz, 1 H, H-6′), 7.79 (m, 2 H, H_2-8, 9), 7.46 (m, 2 H, H_2-4′, 5′), 7.17 (dt, J = 6.5, 1.5 Hz, 1 H, H-7), 6.90 (s, 1 H, H-3); MS m/z 256 (M^+). Anal. C, H, N.

2-(3′-Chlorophenyl)-8-methylpyrido[1,2-*a*]pyrimidin-4-one (9) was obtained from ethyl (3′-chlorobenzoyl)acetate and 2-amino-4-picoline: prisms, mp 142−144 °C; ^{1}H NMR ($CDCl_3$) δ 8.97 (d, J = 7.2 Hz, 1 H, H-6), 8.13 (t, J = 2.0, 1 H, H-2′), 7.92 (td, J = 7.5, 2.0 Hz, 1 H, H-6′), 7.54 (br s, 1 H, H-9), 7.45 (m, 2 H, H_2-4′, 5′), 7.00 (dd, J = 7.2, 2.0 Hz, 1 H, H-7), 2.52 (s, 3 H, CH_3-8); MS m/z 270 (M^+). Anal. C, H, N.

2-(3′-Chlorophenyl)-7-methylpyrido[1,2-*a*]pyrimidin-4-one (10) was obtained from ethyl (3′-chlorobenzoyl)acetate and 2-amino-5-picoline: prisms, mp 175−176 °C; ^{1}H NMR ($CDCl_3$) δ 8.89 (s, 1 H, H-6), 8.13 (s, 1 H, H-2′), 7.92 (td, J = 7.0, 1.0 Hz, 1 H, H-6′), 7.69 (d, J = 9.0 Hz, 1 H, H-9), 7.64 (dd, J = 9.0, 1.5 Hz, 1 H, H-8), 7.45 (m, 2 H, H_2-4′, 5′), 6.86 (s, 1 H, H-3), 2.46 (s, 3 H, CH_3-7); MS m/z 270 (M^+). Anal. C, H, N.

2-(3′-Chlorophenyl)-6-methylpyrido[1,2-*a*]pyrimidin-4-one (11) was obtained from ethyl (3′-chlorobenzoyl)acetate and 2-amino-6-picoline: needles, mp 150−152 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (t, J = 1.5 Hz, 1 H, H-2′), 7.91 (td, J = 8.0, 1.5 Hz, 1 H, H-6′), 7.52 (d, J = 7.0 Hz, 1 H, H-9), 7.48 (dd, J = 8.0, 7.0 Hz, 1 H, H-8), 7.45 (m, 2 H, H_2-4′, 5′), 6.70 (s, 1 H, H-3), 6.68 (d, J = 8.0 Hz, 1 H, H-7), 3.10 (s, 3 H, CH_3-6); MS m/z 270 (M^+). Anal. C, H, N.

2-(3′-Chlorophenyl)-6,8-dimethylpyrido[1,2-*a*]pyrimidin-4-one (12) was obtained from ethyl (3′-chlorobenzoyl)-acetate and 2-amino-4,6-dimethylpyridine: prisms, mp 125−126 °C; ^{1}H NMR ($CDCl_3$) δ 8.09 (t, J = 2.0 Hz, 1 H, H-2′), 7.89 (dd, J = 6.7, 2.0 Hz, 1 H, H-6′), 7.43 (m, 2 H, H_2-4′, 5′), 7.31 (br s, 1 H, H-9), 6.63 (s, 1 H, H-3), 6.53 (br s, 1 H, H-7), 3.07 (s, 3 H, CH_3-6), 2.37 (s, 3 H, CH_3-8); MS m/z 284 (M^+). Anal. C, H, N.

2-(3′-Methylphenyl)pyrido[1,2-*a*]pyrimidin-4-one (13) was obtained from ethyl (3′-methylbenzoyl)acetate and 2-aminopyridine: needles, mp 118−120 °C; ^{1}H NMR ($CDCl_3$) δ 9.09 (d, J = 7.0 Hz, 1 H, H-6), 7.94 (s, 1 H, H-2′), 7.87 (d, J = 7.5, Hz, 1 H, H-6′), 7.76 (d, J = 3.5 Hz, 2 H, H_2-8, 9), 7.41 (t, J = 7.5 Hz, 1 H, H-5′), 7.32 (d, J = 7.5 Hz, 1 H, H-4′), 7.15 (ddd, J = 7.0, 3.5, 1.5 Hz, 1 H, H-7), 6.92 (s, 1 H, H-3), 2.47 (s, 3 H, CH_3-3′); MS m/z 236 (M^+). Anal. C, H, N.

2-(3′-Methylphenyl)-8-methylpyrido[1,2-*a*]pyrimidin-4-one (14) was obtained from ethyl (3′-methylbenzoyl)acetate and 2-amino-4-picoline: amorphous, mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 8.97 (d, J = 7.2 Hz, 1 H, H-6), 7.92 (s, 1 H, H-2′), 7.86 (d, J = 7.5, 1 H, H-6′), 7.54 (s, 1 H, H-9), 7.40 (t, J = 7.5 Hz, 1 H, H-5′), 7.31 (d, J = 7.5, Hz, 1 H, H-4′), 6.98 (d, J = 7.2 Hz, 1 H, H-7), 6.85 (s, 1H, H-3), 2.51 (s, 3 H, CH_3-8), 2.45 (s, 3 H, CH_3-3′); MS m/z 250 (M^+). Anal. C, H, N.

2-(3′-Methylphenyl)-7-methylpyrido[1,2-*a*]pyrimidin-4-one (15) was obtained from ethyl (3′-methylbenzoyl)acetate and 2-amino-5-picoline: prisms, mp 158−160 °C; ^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1 H, H-6), 7.92 (s, 1 H, H-2′), 7.86 (d, J = 7.7, 1 H, H-6′), 7.69 (d, J = 9.0 Hz, 1 H, H-9), 7.62 (dd, J = 9.0, 2.0 Hz, 1 H, H-8), 7.40 (t, J = 7.7, Hz, 1 H, H-5′), 7.31 (d, J = 7.7, Hz, 1 H, H-4′), 6.90 (s, 1 H, H-3), 2.47 (s, 3 H, CH_3-7), 2.46 (s, 3 H, CH_3-3′); MS m/z 250(M^+). Anal. C, H, N.

2-(3′-Methylphenyl)-6-methylpyrido[1,2-*a*]pyrimidin-4-one (16) was obtained from ethyl (3′-methylbenzoyl)acetate and 2-amino-6-picoline: prisms, mp 152−154 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1 H, H-2′), 7.84 (d, J = 7.7, 1 H, H-6′), 7.51 (d, J = 8.5, Hz, 1 H, H-9), 7.46 (dd, J = 8.5, 6.4 Hz, 1 H, H-8), 7.39 (t, J = 7.5 Hz, 1 H, H-5′), 7.30 (d, J = 7.7, Hz, 1 H, H-4′), 6.73 (s, 1 H, H-3), 6.66 (d, J = 6.4 Hz, 1 H, H-7), 3.09 (s, 3 H, CH_3-6), 2.46 (s, 3 H, CH_3-3′); MS m/z 250(M^+). Anal. C, H, N.

2-(3′-Methylphenyl)-6,8-dimethylpyrido[1,2-*a*]pyrimidin-4-one (17) was obtained from ethyl (3′-methylbenzoyl)-acetate and 2-amino-4,6-dimethylpyridine: prisms, mp 145−147 °C; ^{1}H NMR ($CDCl_3$) δ 7.88 (br s, 1 H, H-2′), 7.82 (d, J = 7.5, Hz, 1 H, H-6′), 7.38 (t, J = 7.5 Hz, 1 H, H-5′), 7.35 (br s, 1 H, H-9), 7.28 (d, J = 7.5, Hz, 1 H, H-4′), 6.66 (s, 1 H, H-3), 6.50 (br s, 1 H, H-7), 3.07 (s, 3 H, CH_3-6), 2.45 (s, 3 H, CH_3-3′), 2.36 (s, 3 H, CH_3-8); MS m/z 264 (M^+). Anal. C, H, N.

2-(α-Naphthyl)pyrido[1,2-*a*]pyrimidin-4-one (18) was obtained from ethyl (α-naphthylbenzoyl)acetate and 2-aminopyridine: amorphous, mp 169−170 °C; ^{1}H NMR ($CDCl_3$) δ 9.19 (d, J = 7.0 Hz, 1 H, H-6), 8.24 (dd, J = 6.5, 2.5 Hz, 1 H, H-8′), 7.97 (d, J = 8.5 Hz, 1 H, H-2′), 7.95 (m, 1 H, H-5′), 7.81 (d, J = 2.5 Hz, 2 H, H_2-8, 9), 7.72 (d, J = 6.5 Hz, 1 H, H-4′), 7.58 (dd, J = 8.5, 6.5 Hz, 1 H, H-3′), 7.52 (m, 2 H, H_2-6′, 7′), 7.24 (m, 1 H, H-7), 6.80 (s, 1 H, H-3); MS m/z 272 (M^+). Anal. C, H, N.

2-(α-Naphthyl)-8-methylpyrido[1,2-*a*]pyrimidin-4-one (19) was obtained from ethyl (α-naphthylbenzoyl)acetate and 2-amino-4-picoline: needles, mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 9.08 (d, J = 7.2 Hz, 1 H, H-6), 8.24 (dd, J = 6.5, 2.5 Hz, 1 H, H-8′), 7.96 (d, J = 8.7 Hz, 1 H, H-2′), 7.93 (m, 1 H, H-5′), 7.71 (d, J = 6.8 Hz, 1 H, H-4′), 7.62 (br s, 1 H, H-9), 7.58 (dd, J = 8.7, 6.8 Hz, 1 H, H-3′), 7.53 (m, 2 H, H_2-6′, 7′), 7.08 (dd, J = 7.2, 1.5 Hz, 1 H, H-7), 6.72 (s, 1H, H-3), 2.54 (s, 3 H, CH_3-8); MS m/z 286 (M^+). Anal. C, H, N.

2-(α-Naphthyl)-7-methylpyrido[1,2-*a*]pyrimidin-4-one (20) was obtained from ethyl (α-naphthylbenzoyl)acetate and 2-amino-5-picoline: amorphous, mp 138−140 °C; ^{1}H NMR ($CDCl_3$) δ 8.99 (s, 1 H, H-6), 8.24 (dd, J = 6.5, 2.5 Hz, 1 H, H-8′), 7.96 (d, J = 8.7 Hz, 1 H, H-2′), 7.93 (m, 1 H, H-5′), 7.72 (d, J = 7.0 Hz, 1 H, H-4′), 7.70 (d, J = 9.0 Hz, 1 H, H-9), 7.66 (dd, J = 9.0, 1.5 Hz, 1 H, H-8), 7.56 (dd, J = 8.7, 6.8 Hz, 1 H, H-3′), 7.50 (m, 2 H, H_2-6′, 7′), 6.77 (s, 1 H, H-3), 2.49 (s, 3 H, CH_3-7); MS m/z 286(M^+). Anal. C, H, N.

2-(α-Naphthyl)-6-methylpyrido[1,2-*a*]pyrimidin-4-one (21) was obtained from ethyl (α-naphthylbenzoyl)acetate and 2-amino-6-picoline: prisms, mp 149−150 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, J = 5.0, 2.5 Hz, 1 H, H-8′), 7.95 (d, J = 8.3 Hz, 1 H, H-2′), 7.92 (m, 1 H, H-5′), 7.71 (d, J = 6.5 Hz, 1 H, H-4′), 7.56 (dd, J = 8.7, 6.8 Hz, 1 H, H-3′), 7.52 (m, 2 H, H_2-8, 9), 7.50 (m, 2 H, H_2-6′, 7′), 6.74 (d, J = 5.5 Hz, 1 H, H-7), 6.61 (s, 1 H, H-3), 3.16 (s, 3 H, CH_3-6); MS m/z 286 (M^+). Anal. C, H, N.

2-(α-Naphthyl)-6,8-dimethylpyrido[1,2-*a*]pyrimidin-4-one (22) was obtained from ethyl (α-naphthylbenzoyl)acetate and 2-amino-4,6-dimethylpyridine: prisms, mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 8.27 (dd, J = 5.0, 2.5 Hz, 1 H, H-8′), 7.94 (d, J = 7.5 Hz, 1 H, H-2′), 7.92 (m, 1 H, H-5′), 7.70 (d, J = 7.5 Hz, 1 H, H-4′), 7.54 (t, J = 7.5 Hz, 1 H, H-3′), 7.51 (m, 2 H, H_2-6′, 7′), 7.35 (br s, 1 H, H-9), 6.60 (br s, 1 H, H-7), 6.53 (s, 1 H, H-3), 3.13 (s, 3 H, CH_3-6), 2.39 (s, 3 H, CH_3-8); MS m/z 300 (M^+). Anal. C, H, N.

2-(*β*-Naphthyl)pyrido[1,2-*a*]pyrimidin-4-one (23) was obtained from ethyl (*β*-naphthylbenzoyl)acetate and 2-aminopyridine: amorphous, mp 201−202 °C; ^{1}H NMR ($CDCl_3$) δ 9.11 (d, J = 7.0 Hz, 1 H, H-6), 8.68 (s, 1 H, H-1′), 8.18 (dd, J = 8.5, 1.0 Hz, 1 H, H-3′), 7.99 (m, 1 H, H-8′), 7.98 (d, J = 8.5 Hz, 1 H, H-4′), 7.91 (m, 1 H, H-5′), 7.81 (m, 2 H, H_2-8, 9), 7.57 (m, 2 H, H_2-6′, 7′), 7.17 (dt, J = 7.0, 2.0 Hz, 1 H, H-7), 7.08 (s, 1 H, H-3); MS m/z 272 (M^+). Anal. C, H, N.

2-(*β*-Naphthyl)-8-methylpyrido[1,2-*a*]pyrimidin-4-one (24) was obtained from ethyl (*β*-naphthylbenzoyl)acetate and 2-amino-4-picoline: amorphous, mp 168−169 °C; ^{1}H NMR ($CDCl_3$) δ 9.00 (d, J = 7.2 Hz, 1 H, H-6), 8.66 (s, 1 H, H-1′), 8.16 (d, J = 8.5 Hz, 1 H, H-3′), 7.99 (s, 1 H, H-9), 7.98 (m, 1 H, H-8′), 7.97 (d, J = 8.5 Hz, 1 H, H-4′), 7.90 (br d, J = 7.0 Hz, 1 H, H-5′), 7.57 (m, 2 H, H_2-6′, 7′), 7.01 (s, 1H, H-3), 6.99 (d, J = 7.2 Hz, 1 H, H-7), 2.54 (s, 3 H, CH_3-8); MS m/z 286 (M^+). Anal. C, H, N.

2-(*β*-Naphthyl)-7-methylpyrido[1,2-*a*]pyrimidin-4-one (25) was obtained from ethyl (*β*-naphthylbenzoyl)acetate and 2-amino-5-picoline: needles, mp 228−229 °C; ^{1}H NMR ($CDCl_3$) δ 8.93 (s, 1 H, H-6), 8.66 (s, 1 H, H-1′), 8.17 (dd, J = 8.7, 1.0 Hz, 1 H, H-3′), 7.99 (m, 1 H, H-8′), 7.97 (d, J = 8.7 Hz, 1 H, H-4′), 7.90 (m, 1 H, H-5′), 7.75 (d, J = 9.0 Hz, 1 H, H-9), 7.65 (dd, J = 9.0, 1.2 Hz, 1 H, H-8), 7.56 (m, 2 H, H_2-6′, 7′), 7.06 (s, 1 H, H-3), 2.47 (s, 3 H, CH_3-7); MS m/z 286(M^+). Anal. C, H, N.

2-(*β*-Naphthyl)-6-methylpyrido[1,2-*a*]pyrimidin-4-one (26) was obtained from ethyl (*β*-naphthylbenzoyl)acetate and 2-amino-6-picoline: prisms, mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1 H, H-1′), 8.14 (d, J = 8.6 Hz, 1 H, H-3′), 7.99 (m, 1 H, H-8′), 7.96 (d, J = 8.6 Hz, 1 H, H-4′), 7.90 (m, 1 H, H-5′), 7.55 (m, 2 H, H_2-6′, 7′), 7.53 (d, J = 8.8 Hz, 1 H, H-9), 7.49 (dd, J = 8.8, 6.5 Hz, 1 H, H-8), 6.88 (s, 1 H, H-3), 6.68 (d, J = 6.5 Hz, 1 H, H-7), 3.12 (s, 3 H, CH_3-6); MS m/z 286 (M^+). Anal. C, H, N.

2-(*β*-Naphthyl)-6,8-dimethylpyrido[1,2-*a*]pyrimidin-4-one (27) was obtained from ethyl (*β*-naphthylbenzoyl)acetate and 2-amino-4,6-dimethylpyridine: needles, mp 189−190 °C; ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1 H, H-1′), 8.12 (d, J = 8.9 Hz, 1 H, H-3′), 7.98 (m, 1 H, H-8′), 7.94 (d, J = 8.9 Hz, 1 H, H-4′), 7.89 (m, 1 H, H-5′), 7.55 (m, 2 H, H_2-6′, 7′), 7.36 (br s, 1 H, H-9), 6.81 (s, 1 H, H-3), 6.53 (br s, 1 H, H-7), 3.09 (s, 3 H, CH_3-6), 2.38 (s, 3 H, CH_3-8); MS m/z 300 (M^+). Anal. C, H, N.

2-(*β*-Naphthyl)-7-chloro-pyrido[1,2-*a*]pyrimidin-4-one (28) was obtained from ethyl (*β*-naphthylbenzoyl)acetate and 2-amino-5-chloro-pyridine: amorphous, mp 227−229 °C; ^{1}H NMR ($CDCl_3$) δ 9.12 (d, J = 2.0 Hz, 1 H, H-6), 8.66 (s, 1 H, H-1′), 8.15 (dd, J = 8.7, 1.5 Hz, 1 H, H-3′), 8.00 (m, 1 H, H-8′), 7.97 (d, J = 8.7 Hz, 1 H, H-4′), 7.90 (m, 1 H, H-5′), 7.75 (d, J = 9.3 Hz, 1 H, H-9), 7.70 (dd, J = 9.3, 2.0 Hz, 1 H, H-8), 7.57 (m, 2 H, H_2-6′, 7′), 7.09 (s, 1 H, H-3); MS m/z 306(M^+). Anal. C, H, N.

2-(3′-Fluorophenyl)-6-methyl-1,8-naphthyridin-4(1*H*)-one (29) was obtained from compound **5**: needles; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 8.48 (d, J = 2.0 Hz, 1 H, H-5), 8.47 (d, J = 2.0 Hz, 1 H, H-7), 7.52 (m, 2 H, H_2-2′, 5′), 7.45 (dd, J = 8.0, 2.0 Hz, 1 H, H-6′), 7.25 (m, 1 H, H-4′), 6.57 (s, 1 H, H-3), 2.47 (s, 3 H, CH_3-6); MS m/z 254 (M^+). Anal. C, H, N.

2-(3′-Fluorophenyl)-7-methyl-1,8-naphthyridin-4(1*H*)-one (30) was obtained from compound **6**: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.90, (br s, 1 H, NH-1), 8.56 (d, J = 8.0 Hz, 1 H, H-5), 7.52 (m, 2 H, H_2-2′, 5′), 7.41 (d, J = 9.5 Hz, 1 H, H-6′), 7.29 (m, 1 H, H-4′), 7.23 (d, J = 8.0 Hz, 1 H, H-6), 6.57 (s, 1 H, H-3), 2.64 (s, 3 H, CH_3-7); MS m/z 254 (M^+). Anal. C, H, N.

2-(3′-Fluorophenyl)-5,7-dimethyl-1,8-naphthyridin-4(1*H*)-one (31) was obtained from compound **7**: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.86, (br s, 1 H, NH-1), 7.50 (m, 2 H, H_2-2′, 5′), 7.39 (dd, J = 9.3, 1.8 Hz, 1 H, H-6′), 7.24 (m, 1 H, H-4′), 6.92 (s, 1 H, H-6), 6.49 (s, 1 H, H-3), 2.93 (s, 3 H, CH_3-5), 2.51 (s, 3 H, CH_3-7); MS m/z 268 (M^+). Anal. C, H, N.

2-(3′-Chlorophenyl)-1,8-naphthyridin-4(1*H*)-one (32) was obtained from compound **8**: needles; ^{1}H NMR ($CDCl_3$) δ 8.66 (dd, J = 4.5, 2.0 Hz, 1 H, H-5), 8.63 (dd, J = 8.0, 2.0 Hz, 1 H, H-7), 7.72 (t, J = 1.5 Hz, 1 H, H-2′), 7.61 (td, J = 7.0, 1.5 Hz, 1 H, H-6′), 7.48 (m, 2 H, H_2-4′, 5′), 7.36 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 6.58 (s, 1 H, H-3); MS m/z 256 (M^+). Anal. C, H, N.

2-(3′-Chlorophenyl)-5-methyl-1,8-naphthyridin-4(1*H*)-one (33) was obtained from compound **9**: needles; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 8.37 (d, J = 5.0 Hz, 1 H, H-7), 7.70 (t, J = 2.0 Hz, 1 H, H-2′), 7.59 (td, J = 7.2, 2.0 Hz, 1 H, H-6′), 7.46 (m, 2 H, H_2-4′, 5′), 7.02 (d, J = 5.0 Hz, 1 H, H-6), 6.49 (s, 1 H, H-3), 2.91 (s, 3 H, CH_3-5); MS m/z 270 (M^+). Anal. C, H, N.

2-(3′-Chlorophenyl)-6-methyl-1,8-naphthyridin-4(1*H*)-one (34) was obtained from compound **10**: amorphous; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 8.49 (d, J = 2.0 Hz, 1 H, H-5), 8.42 (d, J = 2.0 Hz, 1 H, H-7), 7.72 (t, J = 1.5 Hz, 1 H, H-2′), 7.61 (td, J = 7.2, 1.5 Hz, 1 H, H-6′), 7.48 (m, 2 H, H_2-4′, 5′), 6.57 (s, 1 H, H-3), 2.46 (s, 3 H, CH_3-6); MS m/z 270 (M^+). Anal. C, H, N.

2-(3′-Chlorophenyl)-7-methyl-1,8-naphthyridin-4(1*H*)-one (35) was obtained from compound **11**: amorphous; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 8.54 (d, J = 8.0 Hz, 1 H, H-5), 7.72 (t, J = 2.0 Hz, 1 H, H-2′), 7.61 (td, J = 6.8, 2.0 Hz, 1 H, H-6′), 7.50 (m, 2 H, H_2-4′, 5′), 7.23 (d, J = 8.0 Hz, 1 H, H-6), 2.64 (s, 3 H, CH_3-7); MS m/z 270 (M^+). Anal. C, H, N.

2-(3′-Chlorophenyl)-5,7-dimethyl-1,8-naphthyridin-4(1*H*)-one (36) was obtained from compound **12**: needles; ^{1}H NMR ($CDCl_3$) δ 7.67 (t, J = 1.5 Hz, 1 H, H-2′), 7.58 (td, J = 7.0, 1.5 Hz, 1 H, H-6′), 7.50 (m, 2 H, H_2-4′, 5′), 6.93 (s, 1 H, H-6), 6.49 (s, 1 H, H-3), 2.94 (s, 3 H, CH_3-5), 2.53 (s, 3 H, CH_3-7); MS m/z 284 (M^+). Anal. C, H, N.

2-(3′-Methylphenyl)-1,8-naphthyridin-4(1*H*)-one (37) was obtained from compound **13**: prisms; ^{1}H NMR ($CDCl_3$) δ 10.57, (br s, 1 H, NH-1), 8.70 (dd, J = 8.0, 2.0 Hz, 1 H, H-5), 8.18 (dd, J = 4.5, 2.0 Hz, 1 H, H-7), 7.54 (d, J = 1.5 Hz, 1 H, H-2′), 7.53 (d, J = 7.5 Hz, 1 H, H-6′), 7.45 (t, J = 7.5, Hz, 1 H, H-5′), 7.40 (d, J = 7.5 Hz, 1 H, H-4′), 7.27 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 6.60 (s, 1 H, H-3), 2.44 (s, 3 H, CH_3-3′); MS m/z 236 (M^+). Anal. C, H, N.

2-(3′-Methylphenyl)-5-methyl-1,8-naphthyridin-4(1*H*)-one (38) was obtained from compound **14**: needles; ^{1}H NMR ($CDCl_3$) δ 9.77, (br s, 1 H, NH-1), 8.10 (d, J = 4.8 Hz, 1 H, H-7), 7.52 (s, 1 H, H-2′), 7.50 (br d, J = 6.0 Hz, 1 H, H-6′), 7.43 (t, J = 7.5, Hz, 1 H, H-5′), 7.37 (d, J = 7.5 Hz, 1 H, H-4′), 6.98 (d, J = 4.8 Hz, 1 H, H-6), 6.52 (s, 1 H, H-3), 2.98 (s, 3 H, CH_3-5), 2.45 (s, 3 H, CH_3-3′); MS m/z 250 (M^+). Anal. C, H, N.

2-(3′-Methylphenyl)-6-methyl-1,8-naphthyridin-4(1*H*)-one (39) was obtained from compound **15**: prisms; ^{1}H NMR ($CDCl_3$) δ 10.78, (s, 1 H, NH-1), 8.50 (d, J = 2.0 Hz, 1 H, H-5), 7.92 (d, J = 2.0 Hz, 1 H, H-7), 7.52 (br s, 2 H, H_2-2′, 6′), 7.45 (t, J = 7.5, Hz, 1 H, H-5′), 7.40 (d, J = 7.5 Hz, 1 H, H-4′), 6.57 (s, 1 H, H-3), 2.43 (s, 3 H, CH_3-3′), 2.38 (s, 3 H, CH_3-6); MS m/z 250 (M^+). Anal. C, H, N.

2-(3′-Methylphenyl)-7-methyl-1,8-naphthyridin-4(1*H*)-one (40) was obtained from compound **16**: amorphous; ^{1}H NMR ($CDCl_3$) δ 9.23, (br s, 1 H, NH-1), 8.57 (d, J = 8.0 Hz, 1 H, H-5), 7.49 (br s, 2 H, H_2-2′, 6′), 7.42 (t, J = 7.2, Hz, 1 H, H-5′), 7.36 (d, J = 7.2 Hz, 1 H, H-4′), 7.20 (d, J = 8.0 Hz, 1 H, H-6), 6.60 (s, 1 H, H-3), 2.58 (s, 3 H, CH_3-7), 2.43 (s, 3 H, CH_3-3′); MS m/z 250 (M^+). Anal. C, H, N.

2-(3′-Methylphenyl)-5,7-dimethyl-1,8-naphthyridin-4(1*H*)-one (41) was obtained from compound **17**: amorphous; ^{1}H NMR ($CDCl_3$) δ 9.14, (br s, 1 H, NH-1), 7.47 (br s, 2 H, H_2-2′, 6′), 7.40 (t, J = 7.5, Hz, 1 H, H-5′), 7.34 (d, J = 7.5 Hz, 1 H, H-4′), 6.89 (s, 1 H, H-6), 6.50 (s, 1 H, H-3), 2.94 (s, 3 H, CH_3-5), 2.42 (s, 3 H, CH_3-7), 2.47 (s, 3 H, CH_3-3′); MS m/z 264 (M^+). Anal. C, H, N.

2-(α-Naphthyl)-1,8-naphthyridin-4(1*H*)-one (42) was obtained from compound **18**: plates; ^{1}H NMR ($CDCl_3$) δ 8.67 (dd, J = 8.0, 1.5 Hz, 1 H, H-5), 8.08 (d, J = 8.0 Hz, 1 H, H-2′), 7.99 (d, J = 8.0 Hz, 1 H, H-8′), 7.97 (d, J = 8.0 Hz, 1 H, H-5′),

7.68 (d, J = 8.0 Hz, 1 H, H-4′), 7.62 (t, J = 8.0 Hz, 1 H, H-3′), 7.57 (d, J = 8.0 Hz, 1 H, H-6′), 7.52 (d, J = 8.0 Hz, 1 H, H-7′), 7.49 (d, J = 4.5 Hz, 1 H, H-7), 7.11 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 6.56 (s, 1 H, H-3); MS m/z 272 (M^+). Anal. C, H, N.

2-(α-Naphthyl)-5-methyl-1,8-naphthyridin-4(1*H*)-one (43) was obtained from compound **19**: amorphous; ^{1}H NMR ($CDCl_3$) δ 11.37, (br s, 1 H, NH-1), 8.06 (d, J = 7.8 Hz, 1 H, H-2′), 7.97 (d, J = 8.5 Hz, 2 H, H_2-5′, 8′), 7.65 (br d, J = 6.5 Hz, 1 H, H-4′), 7.62 (t, J = 7.8 Hz, 1 H, H-3′), 7.56 (d, J = 7.5 Hz, 1 H, H-6′), 7.48 (d, J = 7.5 Hz, 1 H, H-7′), 7.00 (d, J = 4.8 Hz, 1 H, H-7), 6.71 (d, J = 4.8 Hz, 1 H, H-6), 6.46 (s, 1 H, H-3), 2.93 (s, 3 H, CH_3-5); MS m/z 286 (M^+). Anal. C, H, N.

2-(α-Naphthyl)-6-methyl-1,8-naphthyridin-4(1*H*)-one (44) was obtained from compound **20**: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.39 (d, J = 1.0 Hz, 1 H, H-5), 8.10 (dd, J = 7.5, 1.5 Hz, 1 H, H-2′), 7.99 (d, J = 8.0 Hz, 1 H, H-8′), 7.88 (d, J = 8.0 Hz, 1 H, H-5′), 7.66 (br d, J = 7.0 Hz, 1 H, H-4′), 7.65 (d, J = 1.0 Hz, 1 H, H-7), 7.63 (t, J = 7.5 Hz, 1 H, H-3′), 7.54 (t, J = 7.5 Hz, 1 H, H-6′), 7.44 (t, J = 7.5 Hz, 1 H, H-7′), 6.50 (s, 1 H, H-3), 2.12 (s, 3 H, CH_3-6); MS m/z 286 (M^+). Anal. C, H, N.

2-(α-Naphthyl)-7-methyl-1,8-naphthyridin-4(1*H*)-one (45) was obtained from compound **21**: amorphous; ^{1}H NMR ($CDCl_3$) δ 10.78, (br s, 1 H, NH-1), 8.48 (d, J = 8.0 Hz, 1 H, H-5), 7.97(d, J = 8.0 Hz, 1 H, H-2′), 7.92 (d, J = 8.0 Hz, 1 H, H-8′), 7.85 (d, J = 8.0 Hz, 1 H, H-5′), 7.58 (dd, J = 7.0, 1.0 Hz, 1 H, H-4′), 7.51 (t, J = 8.0 Hz, 1 H, H-3′), 7.43 (dt, J = 7,0, 1.0 Hz, 1 H, H-6′), 7.32 (dt, J = 7.0, 1.0 Hz, 1 H, H-7′), 6.93 (d, J = 8.0 Hz, 1 H, H-6), 6.50 (s, 1 H, H-3), 2.06 (s, 3 H, CH_3-7); MS m/z 286 (M^+). Anal. C, H, N.

2-(α-Naphthyl)-5,7-dimethyl-1,8-naphthyridin-4(1*H*)-one (46) was obtained from compound **22**: amorphous; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J = 7.5 Hz, 1 H, H-2′), 7.95 (d, J = 8.0 Hz, 1 H, H-8′), 7.88 (d, J = 8.0 Hz, 1 H, H-5′), 7.60 (dd, J = 6.5, 1.0 Hz, 1 H, H-4′), 7.53 (t, J = 7.5 Hz, 1 H, H-3′), 7.49 (dt, J = 6.0, 2.0 Hz, 1 H, H-6′), 7.38 (dt, J = 7.0, 1.0 Hz, 1 H, H-7′), 6.69 (s, 1 H, H-6), 6.45 (s, 1 H, H-3), 2.91 (s, 3 H, CH_3-5), 2.10 (s, 3 H, CH_3-7); MS m/z 300 (M^+). Anal. C, H, N.

2-(β-Naphthyl)-1,8-naphthyridin-4(1*H*)-one (47) was obtained from compound **23**: amorphous; ^{1}H NMR ($CDCl_3$) δ 9.98 (br s, 1H, NH-1), 8.71 (dd, J = 8.0, 1.5 Hz, 1 H, H-5), 8.44 (d, J = 4.5 Hz, 1 H, H-7), 8.24 (d, J = 1.0 Hz, 1 H, H-1′), 8.04 (d, J = 8.5 Hz, 1 H, H-4′), 7.94 (m, 2 H, H_2-5′, 8′), 7.80 (dd, J = 8.5, 2.0 Hz, 1 H, H-3′), 7.63 (m, 2 H, H_2-6′, 7′), 7.28 (dd, J = 8.0, 4.5 Hz, 1 H, H-6), 6.76 (s, 1 H, H-3); MS m/z 272 (M^+). Anal. C, H, N.

2-(β-Naphthyl)-5-methyl-1,8-naphthyridin-4(1*H*)-one (48) was obtained from compound **24**: needles; ^{1}H NMR ($CDCl_3$) δ 10.09, (br s, 1 H, NH-1), 8.21 (d, J = 1.0 Hz, 1 H, H-1′), 8.08 (d, J = 5.0 Hz, 1 H, H-7), 8.01 (d, J = 8.5 Hz, 1 H, H-4′), 7.93 (m, 2 H, H_2-5′, 8′), 7.79 (dd, J = 8.5, 2.0 Hz, 1 H, H-3′), 7.61 (m, 2 H, H_2-6′, 7′), 6.93 (d, J = 5.0 Hz, 1 H, H-6), 6.67 (s, 1 H, H-3), 2.99 (s, 3 H, CH_3-5); MS m/z 286 (M^+). Anal. C, H, N.

2-(β-Naphthyl)-6-methyl-1,8-naphthyridin-4(1*H*)-one (49) was obtained from compound **25**: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 2.0 Hz, 1 H, H-5), 8.21 (d, J = 1.0 Hz, 1 H, H-1′), 8.03 (d, J = 8.5 Hz, 1 H, H-4′), 7.97 (m, 2 H, H_2-5′, 8′), 7.87 (d, J = 1.0 Hz, 1 H, H-7), 7.79 (dd, J = 8.5, 2.0 Hz, 1 H, H-3′), 7.62 (m, 2 H, H_2-6′, 7′), 6.72 (s, 1 H, H-3), 2.24 (s, 3 H, CH_3-6); MS m/z 286 (M^+). Anal. C, H, N.

2-(β-Naphthyl)-7-methyl-1,8-naphthyridin-4(1*H*)-one (50) was obtained from compound **26**: needles; ^{1}H NMR ($CDCl_3$) δ 9.32, (br s, 1 H, NH-1), 8.59 (d, J = 8.0 Hz, 1 H, H-5), 8.19 (d, J = 2.0 Hz, 1 H, H-1′), 8.01 (d, J = 8.5 Hz, 1 H, H-4′), 7.92 (m, 2 H, H_2-5′, 8′), 7.76 (dd, J = 8.5, 2.0 Hz, 1 H, H-3′), 7.61 (m, 2 H, H_2-6′, 7′), 7.21 (d, J = 8.0 Hz, 1 H, H-6), 6.74 (s, 1 H, H-3), 2.60 (s, 3 H, CH_3-7); MS m/z 286 (M^+). Anal. C, H, N.

2-(β-Naphthyl)-5,7-dimethyl-1,8-naphthyridin-4(1*H*)-one (51) was obtained from compound **27**: amorphous; ^{1}H NMR ($CDCl_3$) δ 9.20, (br s, 1 H, NH-1), 8.17 (d, J = 1.5 Hz, 1 H, H-1′), 7.99 (d, J = 8.5 Hz, 1 H, H-4′), 7.92 (m, 2 H, H_2-5′, 8′), 7.75 (dd, J = 8.5, 1.5 Hz, 1 H, H-3′), 7.60 (m, 2 H, H_2-6′, 7′), 6.90 (s, 1 H, H-6), 6.65 (s, 1 H, H-3), 2.96 (s, 3 H, CH_3-5), 2.50 (s, 3 H, CH_3-7); MS m/z 300 (M^+). Anal. C, H, N.

2-(β-Naphthyl)-6-chloro-1,8-naphthyridin-4(1*H*)-one (49) was obtained from compound **28**: amorphous; ^{1}H NMR ($CDCl_3$) δ 8.59 (d, J = 2.5 Hz, 1 H, H-5), 8.56 (d, J = 2.5 Hz, 1 H, H-7), 8.22 (d, J = 1.0 Hz, 1 H, H-1′), 7.95 (d, J = 8.5 Hz, 1 H, H-4′), 7.91 (m, 1 H, H-8′), 7.86 (m, 1 H, H-5′), 7.74 (dd, J = 8.5, 2.0 Hz, 1 H, H-3′), 7.55 (m, 2 H, H_2-6′, 7′), 6.68 (s, 1 H, H-3); MS m/z 306 (M^+). Anal. C, H, N.

Cytotoxicity Assays. Compounds **5**−**28** were assayed for *in vitro* cytotoxicity in a panel of human and murine tumor cell lines at the School of Medicine, University of North Carolina at Chapel Hill, and according to procedures described previously.[13] The cell lines include human epidermoid carcinoma of the nasopharynx (KB), lung carcinoma (A-549), ileocecal carcinoma (HCT-8), melanoma (PRMI-7951), and medulloblastoma (TE-671), as well as one murine leukemia cell line (P-388). The results (data not shown) demonstrated that essentially all 2-arylpyrido[1,2-*a*]pyrimidin-4-ones (**5**−**28**) were inactive (EC_{50} > 4 μg/mL); only a few compounds showed marginal activity. Compounds **29**−**52** were submitted to NCI and assayed in the NCI's *in vitro* disease-oriented antitumor screen, which involves determination of a test compound's effects on the growth of approximately 60 human tumor cell lines.[3,4] These lines include leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate, and breast cancers. The cytotoxic effects of each compound were obtained as GI_{50} or TGI values, which represent the molar drug concentrations required to cause 50% inhibition or total growth inhibition, respectively.

Antimicrotubule Assay. Electrophoretically homogeneous bovine brain tubulin was purified as described previously.[14] Combretastatin A-4 was a generous gift of Dr. G. R. Pettit, Arizona State University.

The tubulin polymerization assay was performed as described previously.[15] In brief, tubulin at 1.2 mg/mL (12 μM) was preincubated for 15 min at 26 °C in a 0.24-mL volume of 0.8 M monosodium glutamate (pH 6.6 with NaOH in a 2 M stock solution) with varying drug concentrations. The drug stock solutions were in DMSO, and the final solvent concentration was 4% (v/v). All concentrations are in terms of the final reaction volume (0.25 mL). The reaction mixtures were chilled on ice, and 10 μL of 10 mM GTP was added to each reaction mixture. Samples were transferred to cuvettes held at 0 °C by an electronic temperature controller in Gilford spectrophotometers. Baselines were established at 350 nm, and polymerization was initiated by a temperature jump to 26 °C. The jump took about 50 s to complete. After 20 min, turbidity readings were recorded, and the temperature controller was set to 0 °C. When depolymerization was complete, turbidity readings were again recorded. Generally, turbidity readings were about 90% cold-reversible, and the cold-reversible turbidity was taken to represent the extent of assembly for each reaction mixture. IC_{50} values were obtained graphically from inhibition of polymerization by different drug concentrations. Four spectrophotometers were used for each experimental sequence, with two control reactions (no drug) in each set. Generally, the control reactions were within 5% of their average and IC_{50} values obtained with this polymerization assay are usually highly reproducible. Generally, standard deviations were within 20% of the mean values, but in some cases, the standard deviations were 30−35% of the mean. Therefore, we can conservatively estimate that a 50% difference in IC_{50} values represents a difference in the relative activity of two agents.

Colchicine Binding Assay. The binding of radiolabeled colchicine to tubulin was measured by the DEAE−cellulose filter technique, as described previously.[16] In brief, each 0.1-mL reaction mixture contained 0.1 mg (1.0 μM) of tubulin, 1.0 M commercial monosodium glutamate (pH 6.6 with HCl), 1 mM $MgCl_2$, 0.1 mM GTP, 5.0 μM [^{3}H]colchicine, 5% (v/v) DMSO, and 5.0 μM inhibitor. Incubation was for 20 min at 37 °C. Each reaction mixture was filtered under reduced vacuum through a stack of two DEAE−cellulose paper filters that were washed with water, and the radioactivity was quantitated in a liquid scintillation counter.

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