Synthesis and Structure−Activity Relationships of 2-Amino-1-aroylnaphthalene and 2-Hydroxy-1-aroylnaphthalenes as Potent Antitubulin Agents[§]

Gadarla Randheer Reddy,[†,¶] Ching-Chuan Kuo,[‡,¶] Uan-Kang Tan,[||] Mohane Selvaraj Coumar,[†] Chi-Yen Chang,[‡] Yi-Kun Chiang,[†] Mei-Jung Lai,[⊥] Jiann-Yih Yeh,[†] Su-Ying Wu,[†] Jang-Yang Chang,[‡,§] Jing-Ping Liou,*[,⊥] and Hsing-Pang Hsieh*[,†]

Division of Biotechnology and Pharmaceutical Research, National Health Research Institutes, No. 35, Keyan Road, Zhunan Town, Miaoli County 350, Taiwan, Republic of China, National Institute of Cancer Research, National Health Research Institutes, Tainan 704, Taiwan, ROC, Department of Chemical and Materials Engineering, Technology and Science Institute of Northern Taiwan, Taipei 112, Taiwan, ROC, Division of Hematology/Oncology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan 704, Taiwan, ROC, and College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan, ROC

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A series of aroylnaphthalene derivatives were prepared as bioisosteres of combrestatin A-4 and evaluated for anticancer activity. 2-Amino-1-aroylnaphthalene and 2-hydroxy-1-aroylnaphthalene, **9** and **8**, respectively, showed strong antiproliferative activity with IC_{50} values of 2.1−26.3 nM against a panel of human cancer cell lines including multiple-drug resistant cell line. Compound **9** demonstrated better antiproliferative activity and has a comparable tubulin binding efficacy as that of colchicine.

Introduction

Microtubules play a pivotal role in mitosis and cell division and are recognized as an important target in cancer therapy.[1] Recent literature reveals that some antitubulin agents targeting colchicine-binding domain can act as vascular-disrupting agents.[2] For example, **2**, **4**, and **5** rapidly depolymerize microtubules of tumor vasculature by changing the morphology of the endothelial cellsm thereby blocking the blood supply to the tumors (Figure 1).

The pharmacological and clinical profiles of **4** as an antivascular/anticancer agent have drawn a lot of attention for medicinal chemists to develop a variety of derivatives or analogues in an effort to obtain better compounds.[3] The analysis of the structures of **3** analogues, for example, 2-aminobenzophenones,[4] 2-amino-3-aroylthiophenes,[5] 2-aroyl-3-aminothiophenes,[6] 2-amino- and 2′-aminocombretastatins,[7] 2-amino-3-aroylbenzothiophene,[8] and 2-aroyl-3-aminoindoles,[9] shows that the ortho relationship between the aroyl group (3,4,5-trimethoxybenzoyl) and amino group plays an important role in activity. Our work on 3-aroylindoles[10] (**6**) exploited the "endo enamine−ketone" conjugated indole ring as a bioisosteric replacement for the olefin functionality of the **3** structure. The methoxy substitution located at sixth position of indole ring contributed to the maximal activity by mimicking the methoxy group present at the para position to the double bond moiety in **3** (Figure 2). On the basis of the above observations, we synthesized amino or hydroxyl substituted 1- and 2-aroylnaphthalene derivatives utilizing the

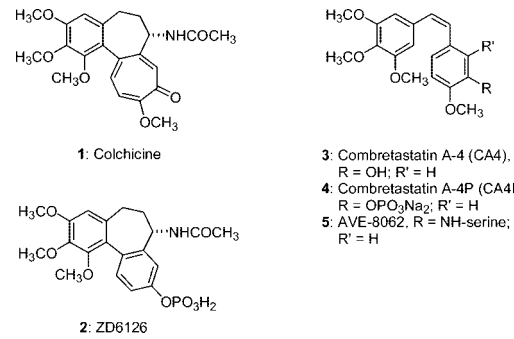

Figure 1. Antitubulin agents targeting colchicine-binding domain of tubulin.

"exo enamine− and enol−ketone" conjugated naphthalene ring to mimic the olefin functionality of **3**. In addition, the methoxy group was also introduced to optimize the activity. We herein describe the synthesis and structure−activity relationships of 1-aroyl- and 2-aroylnaphthalene derivatives as potent antitubulin agents in the continuation of our search for antitumor agents.

Results and Discussion

Chemistry. The general method for the synthesis of 1-aroylnaphthalenes **7**−**17** is shown in Scheme 1. The synthesis of 2-hydroxy-1-aroylnaphthalene (**8**) was carried out in six steps starting with formylation of 2,6-dimethoxynaphthalene (**22**) with *N*-methylformanilide and phosphoryl chloride to obtain 1-formyl-2,6-dimethylnaphthalene **23**.[11] The demethylation of **23** with 1-propanethiol followed by benzylation gave **24**[12] in 48% yield (three steps). Grignard reaction of 3,4,5-trimethoxyphenylmagnesium bromide with **24** followed by pyridinium dichromate (PDC) oxidation and Pd/C-mediated debenzylation afforded the desired 2-hydroxy-1-aroylnaphthalenes (**8**) (35% yield, three steps). 1-Aroylnaphthalene (**7**) was obtained from **8** in 24% yield by converting it into 2-triflate-1-aroylnaphthalene (**26**) with phenyl trifluoromethanesulfonate[13] and then reducing the triflate with Pd/C in Et_3N.[14] The C2-alkyl substituted compounds **15**−**17** were synthesized in 41−51% yield from triflate **26** by an iron-catalyzed coupling reaction with the corresponding

* To whom correspondence should be addressed. For J.-P.L.: (phone) 886-2-2736-1661, extension 6130; (fax) 866-2-27369558; (e-mail) jpl@tmu.edu.tw. For H.-P.H.: (phone) 886-37-246166, extension 35708; (fax) 886-37-586-456; (e-mail) hphsieh@nhri.org.tw.

§ This paper is dedicated to Professor Chun-Chen Liao, Department of Chemistry, National Tsing Hua University,Taiwan, on the occasion of his retirement.

† Division of Biotechnology and Pharmaceutical Research, National Health Research Institutes.

¶ These authors contributed equally to this work.

‡ National Institute of Cancer Research, National Health Research Institutes.

|| Technology and Science Institute of Northern Taiwan.

⊥ Taipei Medical University.

§ National Cheng Kung University Hospital.

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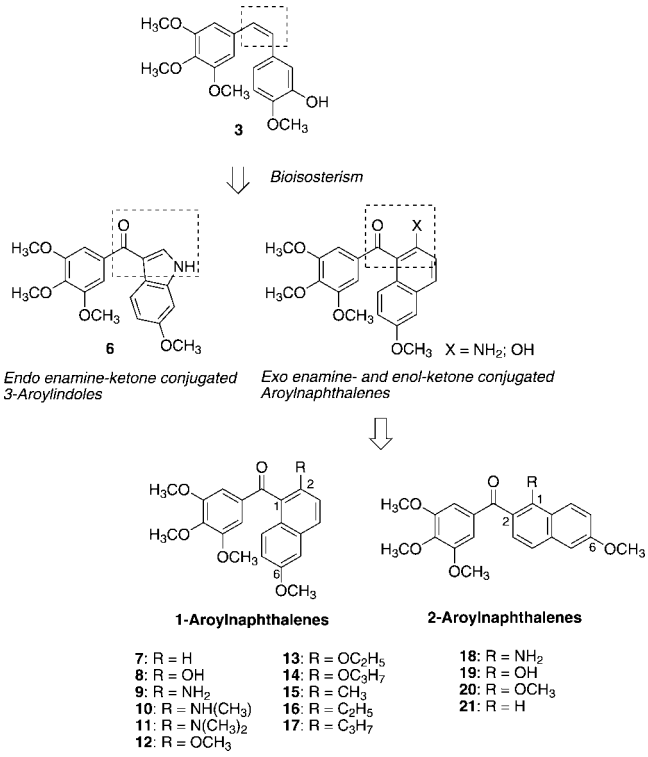
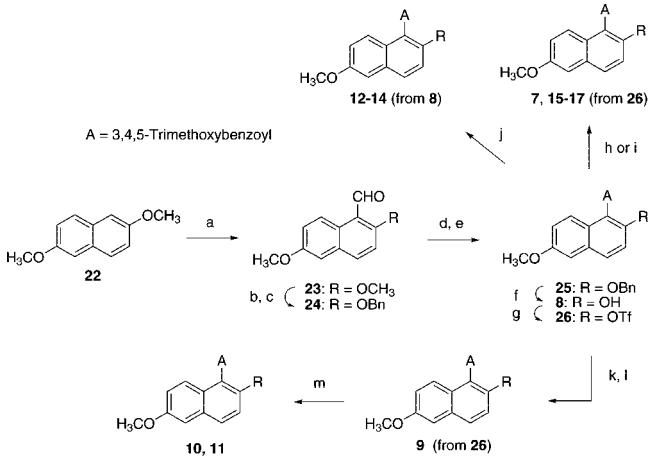


Figure 2. Design of 1- and 2-aroylnaphthalenes as antimitotics.

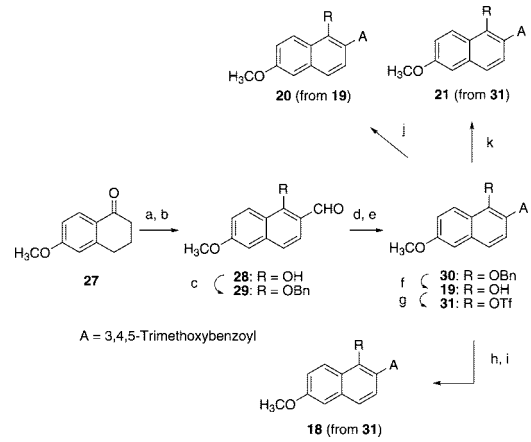
Scheme 1[a]



[a] Reagents and conditions: (a) *N*-methylformanilide, $POCl_3$; (b) 1-propanethiol, NaH, DMF, 50−60 °C; (c) BnBr, K_2CO_3, acetone, reflux; (d) 3,4,5-trimethoxyphenylmagnesium bromide, THF, 0 °C → room temp; (e) PDC, CH_2Cl_2, 4 Å molecular sieves, room temp; (f) 10% Pd/C, EtOAc, room temp; (g) phenyl trifluoromethanesulfonamide, triethylamine, CH_2Cl_2, room temp; (h) Pd/C, Et_3N, CH_3OH, room temp; (i) $Fe(acac)_2$, *N*-methylpyrrolidine, methyl- or ethyl- or propylmagnesium iodide, THF; (j) CH_3I or C_2H_5I or C_3H_7I, K_2CO_3, acetone, reflux; (k) $Pd(OAc)_2$, BINAP, $Ph_2C{=}NH$, Cs_2CO_3, THF, 65−70 °C; (l) NaOAc, $NH_2OH{\cdot}HCl$, CH_3OH, room temp; (m) CH_3I, K_2CO_3, DMF, reflux.

alkylmagnesium halides in the presence of iron(II) acetylacetonate and *N*-methylpyrrolidine.[15] A series of 2-alkoxy-1-aroylnaphthalenes were prepared from **8** in 70−81% yield. Compound **8** was treated with the corresponding alkyl halides in the presence of potassium carbonate in acetone to afford 2-alkoxy-1-aroylnaphthalenes (**12**−**14**). The 2-amino-1-aroylnaphthalene (**9**) was synthesized by palladium-catalyzed amination of triflate.[16] 1-Trifluorosulfonyl-2-aroylnaphthalene (**26**) was reacted with palladium acetate/benzophenoimine to give imine, which on treatment with NaOAc/$NH_2OH{\cdot}HCl$ afforded

Scheme 2[a]



[a] Reagents and conditions**:** (a) HCO_2Et, $NaOCH_3$, Ph-H, room temp; (b) DDQ, 1,4-dioxane, room temp, (c) BnBr, K_2CO_3, DMF, reflux; (d) 3,4,5-trimethoxyphenylmagnesium bromide, THF, 0 °C → room temp; (e) PDC, 4 Å molecular sieves, CH_2Cl_2, room temp; (f) 10% Pd/C, EtOAc; (g) phenyl trifluoromethanesulfonamide, Et_3N, CH_2Cl_2, room temp; (h) $Pd(OAc)_2$, BINAP, Cs_2CO_3, $Ph_2C{=}NH$, THF, 65−70 °C; (i) NaOAc, $NH_2OH{\cdot}HCl$, CH_3OH, room temp; (j) CH_3I, K_2CO_3, acetone, reflux; (k) 10% Pd/C, Et_3N, CH_3OH.

2-amino-1-aroylnaphthalene (**9**) (31% yield, two steps). The C2-amino-1-aroylnaphthalene (**9**) was converted into C2-methylamino **10** and C2-dimethylamino **11** derivatives in 18% and 30% yields, respectively, by reacting with iodomethane in the presence of potassium carbonate and DMF.

The syntheses of 2-aroylnaphthalenes (**18**−**21**) are depicted in the Scheme 2. Starting from commercially available 6-methoxy-1-tetralone (**27**), the preparation of **19** was carried out in six steps through ethyl formate mediated formylation, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ[a]) mediated aromation,[17] protection with the benzyl group, Grignard reaction of 3,4,5-trimethoxyphenylmagnesium bromide followed by alcohol oxidation with pyridinium dichromate and then deprotection with Pd/C. Similar to the synthesis of 2-amino-1-aroylnaphthalene (**9**), 1-amino-2-aroylnaphthalene (**18**) was obtained from the key intermediate **31**. The 1-hydroxy-6-methoxy-2-(3′,4′,5′-trimethoxybenzoyl)naphthalene (**19**) was treated with phenyl trifluoromethane sulfonamide in trimethylamine to give 1-triflate **31**. Palladium-catalyzed imination of **31** in the presence of benzophenoneimine and cesium carbonate followed by cleavage of imine moiety with NaOAc/$NH_2OH{\cdot}HCl$ afforded **18** in 12% yield (three steps). Compound **20**, with a methoxy group at the C1-position of the naphthalene ring, was prepared in 82% yield by treatment of **19** with iodomethane in acetone, utilizing K_2CO_3 as base. Compound **21**, a dehydroxy analogue of **19**, was prepared by treatment of triflate **31** with Pd/C in triethylamine in 51% yield.

Biological Evaluation. A. In Vitro Cell Growth Inhibitory Activity. The synthesized 1-aroylnaphthalenes **7**−**17**, 2-aroylnaphthalenes **18**−**21**, and reference compounds **1** and **6** were evaluated for their antiproliferative activities against five human cancer cell lines, cervical carcinoma KB cells, colorectal carcinoma HT29 cells, non-small-cell-lung carcinoma H460 cells, and stomach carcinoma MKN45 cells, as well as MDR-positive cell line, KB-vin10 cells, which overexpress P-gp 170/MDR (Table 1).

[a] Abbreviations: BINAP, (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; $POCl_3$, phosphorus(III) oxychloride; Cs_2CO_3, cesium carbonate; $Pd(OAc)_2$, palladium(II) acetate; DMF, *N,N*-dimethylformamide; THF, tetrahydrofuran; MDR, multidrug-resistant.

Table 1. IC_{50} Values (nM ± SD[a]) of Compounds **6**−**21** and **1**

	cell type (IC_{50} ± SD,[a] nM)				
compd	KB	KB-vin10	H460	HT29	MKN45
6	4.6 ± 0.4	6.2 ± 1	7.1 ± 2	5.9 ± 1.5	3.2 ± 0.2
7	72.9 ± 22	58 ± 38	85.5 ± 29	69.4 ± 13.2	44.1 ± 22
8	8.2 ± 0.9	11 ± 4	12.6 ± 9	26.3 ± 7.1	21 ± 5.4
9	2.9 ± 1.1	3.3 ± 2.2	3.6 ± 0.2	15.4 ± 10.7	2.1 ± 0.3
10	381 ± 6	364 ± 12	416 ± 18	512 ± 30	338 ± 26
11	>10000	>10000	>10000	>10000	>10000
12	65 ± 19	70 ± 32	84 ± 24	144 ± 102	53 ± 15
13	1000 ± 50	912 ± 52	1210 ± 120	1134 ± 204	874 ± 76
14	2600 ± 400	2431 ± 610	2716 ± 318	2851 ± 541	1762 ± 412
15	276 ± 14	263 ± 29	321 ± 56	412 ± 38	254 ± 25
16	600 ± 100	512 ± 10	764 ± 32	667 ± 62	320 ± 71
17	1000 ± 102	1104 ± 57	987 ± 65	1320 ± 512	840 ± 50
18	8800 ± 200	7910 ± 367	>10000	9850 ± 760	7432 ± 850
19	>10000	>10000	>10000	>10000	>10000
20	>10000	>10000	>10000	>10000	>10000
21	510 ± 83	530 ± 28	716 ± 21	548 ± 30	462 ± 12
1	11 ± 2	116 ± 15	18 ± 7	10 ± 2	13 ± 4

[a] SD: standard deviation. All experiments were independently performed at least three times.

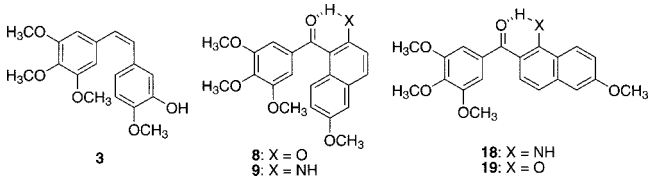


Figure 3. 2D-Conformation of **3** and intramolecular bonded **8**, **9**, **18**, and **19**.

We evaluated the effect of the substitution of 2-hydroxy or 2-amino group on the naphthalene ring in the 1-aroyl-6-methoxynaphthalene series on the antiproliferative activity. Compounds **8** and **9** with hydroxyl and amino groups, respectively, demonstrated strong cytotoxicity with mean IC_{50} values of 15.8 and 5.4 nM, respectively, against a panel of human cancer cell lines. The antiproliferative activity of 2-amino-1-aroylnaphthalene (**9**) was superior to **1** and comparable to 3-aroylindole **6**. Compound **7**, with no substitution at the C2 position, showed double-digit nanomolar IC_{50} values against five cell lines. To understand the steric effect of alkyl substitution on the amino function at the C2 position, methylamino and *N*,*N*-dimethylamino substituted compounds **10** and **11** were synthesized. Compound **10** exhibited a decreased cytotoxicity in comparison with **9** with a mean IC_{50} of 402 nM, but an increase in the bulkiness of the substitution, for example, **11**, resulted in a dramatic loss of activity, thus revealing the influence of the steric effect of the substituent at the C2 position of the naphthalene ring on cell growth inhibitory activity.

A similar phenomenon was also observed with the C2-alkoxy substituents (**12**−**14**) and C2-alkyl substituents (**15**−**17**) 1-aroylnaphthalene derivatives. Compounds **12**, **13**, and **14** with a methoxy, ethoxy, and propyloxy group at the C2 position of naphthalene ring, respectively, showed cytotoxicity with mean IC_{50} values of 83, 1026, and 2472 nM, respectively. The alkylation at the C2 position in 1-aroyl-6-methoxynaphthalenes, for instance, **15**, **16**, and **17** with methyl, ethyl, and propyl moieties, respectively, resulted in moderate activity against all five cell lines with IC_{50} values of 254−1320 nM.

A comparison of the structures of **7**−**9** indicated that an intramolecular hydrogen-bonding interaction between the 3′,4′,5′-trimethoxybenzoyl carbonyl group and hydroxyl/amino group on the naphthalene ring (Figure 3) would lock the conformation of **8** and **9** to mimic **3** better than unsubstituted compound **7**, leading to enhanced potency (**8** and **9** vs **7**). In addition, the presence of a methoxy group at the C6 position of 1-aroylnaphthalenes would mimic the methoxy group present at the position para to the olefin double bond of z-stilbene (**3**), resulting in maximum cytotoxicity (Figure 3). However, *N*,*N*-dimethylamino (**11**), C2-alkoxy (**12**−**14**), or alkyl substituted (**15**−**17**) compounds do not have this conformation restricting intramolecular hydrogen-bonding interaction to mimic the conformation of **3**, resulting in decreased activity for these compounds. Even though compounds without intramolecular hydrogen-bonding interaction, like **7**, **12**, and **15**, have good antiproliferative activity, an increase in steric bulk at this position leads to lower antiproliferative activity as in the case of **13** and **14** vs **12** and of **16** and **17** vs **15**. Moreover, complete inactivity of **11** indicates that the *N*,*N*-dimethylamino substitution through steric bulk prevents the molecule from taking up the conformation of **3**. Thus, unsubstituted **7**'s activity is maximized by the presence of conformation restricting intramolecular hydrogen-bonding interaction as in the case of **8** and **9**.

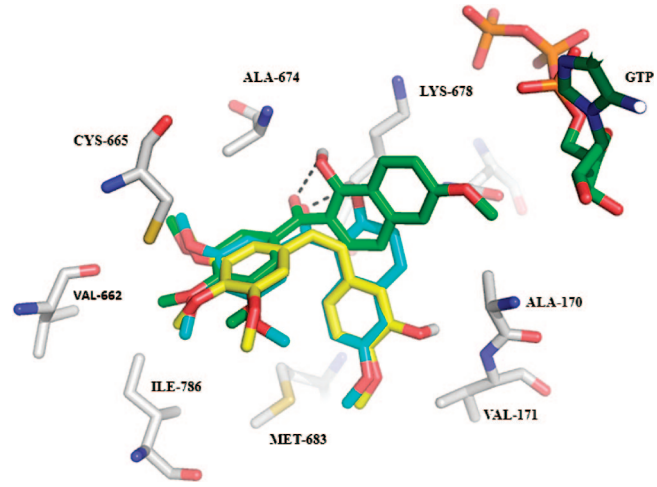


Figure 4. Superimposition of **8** (blue) and **19** (green) over **3** (yellow) in colchicine binding site of tubulin (PDB code 1SA0) using Gold 4.0. Dark-gray dotted lines represent intramolecular hydrogen bond.

Since 1-aroylnaphthalenes, such as **7**−**9** and **12**, demonstrated substantial activity, we attempted to evaluate the effect of switching the functional groups at C1 and C2 positions of 1-aroylnaphthalenes with each other to prepare the 2-aroylnaphthalene derivatives **18**−**21**. Results indicated exchanging C1 aroyl group and C2 amino moiety of 1-aroylnaphthalenes (**9**) with each other, as in **18**, led to a dramatic loss of activity against KB, KB-vin10, H460, HT29, and MKN45 lines. A similar phenomenon was also observed in the cases of **19** and **20**. Unexpectedly, 2-aroylnaphthalene **21**, namely, 6-methoxy-2-(3′,4′,5′-trimethoxybenzoyl)naphthalene, showed moderate activity with a mean IC_{50} of 553 nM against five cell lines. Similar to 1-aroylnaphthalene derivatives **8** and **9**, 2-aroylnaphthalene compounds **18** and **19** possess conformation restricting intramolecular interaction between the C2 carbonyl group and C1 amino (or hydroxyl) group. However, the 1-amino- and 1-hydroxy-2-aroyl-6-methoxynaphthalenes, **18** and **19**, respectively, would adopt a conformation that is different from **3**, thereby causing inactivity in the 2-aroylnaphthalene series by the presence of conformation restricting intramolecular interaction (Figure 3). The moderate antiproliferative activity of **21** without substitution at the C1 position and intramolecular hydrogen-bonding interaction might be due to its flexible structure conformation. Presence of intramolecular hydrogen bonding as discussed above is evidenced from the appearance of an OH proton at a downfield position (~δ 10.5) from the

Table 2. Growth Inhibition of Compounds **8** and **9** against Drug-Resistant Cell Lines

		IC_{50}				
cell lines	resistant type	vincristine, nM	paclitaxel, nM	VP-16, μM	**8**, nM	**9**, nM
KB	Parental	0.4 ± 0.1	3.3 ± 1.2	1.1 ± 0.2	8.2 ± 0.9	2.9 ± 1.1
KB-VIN10	P-gp170/MDR ↑	90.1 ± 7.4	16500 ± 707	23 ± 3	11 ± 4	3.3 ± 2.2
KB-TAX50	P-gp170/MDR ↑	17.6 ± 2.2	273 ± 15	3.5 ± 0.3	15 ± 2.5	3.1 ± 1.6
KB-7D	MRP ↑	1.2 ± 0.4	7.9 ± 0.5	54 ± 3.5	16.9 ± 3.1	3.5 ± 1.4

Table 3. Inhibition of Tubulin Polymerization and Colchicine Binding by Compounds **7**−**9**, **12**, **15**, **18**, **1**, **6**, and **3**

compd	tubulin,[a] $IC_{50} \pm$ SD (μM)	colchicine binding,[b] % ± SD
6	2.8 ± 0.2	85 ± 3
7	4.3 ± 0.1	68 ± 4
8	2.6 ± 0.3	75 ± 2
9	2.4 ± 0.3	85 ± 3
12	2.7 ± 0.1	52 ± 2
15	2.9 ± 0.4	67 ± 1
18	>10	
1	3.2 ± 0.3	
3	1.3 ± 0.2	93 ± 2

[a] Inhibition of tubulin polymerization.[18] [b] Inhibition of [^{3}H]colchicine binding.[18−20] Tubulin was at 1 μM. [^{3}H]Colchicine and inhibitor were both at 5 μM.

usual in the ^{1}H NMR spectra of **8** and **19**. To further validate our hypothesis for conformation restricting intramolecular hydrogen-bonding playing an important role in enhancing the potency, molecular modeling studies of **8** and **19** were carried out. Compounds **8** and **19** were docked into the colchicine binding site of tubulin (PDB code 1SA0) using Gold, version 3.1, in default docking mode. The results showed that **8** overlapped well with **3**; however, **19** did not overlap well over **3** (Figure 4), further providing evidence for the potent activity of **8** and inactivity of **19**.

In an effort to further understand the efficacy of 2-amino- and 2-hydroxy-1-aroylnaphthalenes against drug-resistant cell lines, **8** and **9** were evaluated for antiproliferative activity in various resistant lines as shown in the Table 2. Despite the high level of expression drug-resistant efflux protein (MDR/P-gp or MRP) in KB-Vin 10, KB-TAX50, and KB-7D cells, **8** and **9** showed similar cytotoxic efficacy between parental cells and these resistant lines. **8** and **9** were also evaluated for antiproliferative activity in normal cells, human fibroblast Detroit 551 cells. Data found that their IC_{50} values toward cultured fibroblast Detroit 551 were >1000 nM. This result indicated that **8** and **9** possessed great selectivity between normal and cancer cells.

B. Inhibition of Tubulin Polymerization and Colchicine Binding Activity. To investigate whether the activities of these aroylnaphthalenes were related to interactions with microtubule system, the selected compounds **7**−**9**, **12**, **15**, **18** and reference compounds **1**, **3**, and **6** were evaluated for their antitubulin activities and colchicine binding activities (Table 3). The results indicated that the compounds' antiproliferative activity correlated with the inhibition of tubulin polymerization. Compounds **8**, **9**, **12**, and **15** were efficacious in inhibiting microtubulin assembly, with IC_{50} values of 2.6, 2.4, 2.7, and 2.9 μM, respectively. These values were comparable to reference compounds **1** and **6**. In the [^{3}H]colchicine-binding assay, results indicated that 1-aroylnaphthalenes were bound to the colchicine-binding site.

Conclusion

Synthesis and structure−activity relationships studies for 1-aroylnaphthalenes and 2-aroylnaphthalenes as anticancer agents were carried out. The 2-amino- and 2-hydroxy-6-methoxy-1-aroylnaphthalenes were identified as a novel class of potent antitubulin agents acting through the colchicine binding site of the microtubule. Compounds **8** and **9** demonstrated antiproliferative activities with mean IC_{50} values of 15.8 and 5.4 nM, respectively, in a diverse set of human cancer cell lines, including the MDR/MRP-positive drug resistant cell line. They also exhibited substantial inhibition of tubulin polymerization with IC_{50} values of 2.6 and 2.4 μM, respectively, which were comparable to those of reference compounds **1** and **6**. The SAR information indicated that the introduction of the amino or hydroxyl group at the C2-position of 6-methoxy-1-aroylnaphthalenes resulted in an increased activity compared with unsubstituted compound (**8** and **9** vs **7**), thus revealing that the C2-amino or C2-hydroxyl substitution in the 1-aroylnaphthalene core plays an important role for maximal activity. Using a bioisosterism approach via an exo enamine− and enol−ketone conjugated naphthalene ring to mimic the olefin functionality of **3**, we effectively prepared potent antimitotic agents, 2-amino and 2-hydroxy-1-aroylnaphthalenes (**8** and **9**), which would be further evaluated as potential anticancer agents.

Experimental Section

2-Hydroxy-6-methoxy-1-(3′,4′,5′-trimethoxybenzoyl)naphthalene (8). Compound **25** (2.2 g, 4.8 mmol) was dissolved in ethyl acetate (10 mL). Then 10% Pd/C (0.1 g) was added to the reaction solution, and then the reaction mixture under Parr hydrogenator was shaken for 4 h at room temperature. The mixture was filtered through a Celite pad and the organic layer evaporated under reduced pressure. The remaining residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 1:4) to afford the desired **8**, yield 78%. ^{1}H (300 MHz, $CDCl_3$) δ 3.72 (s, 6H), 3.88 (s, 3H), 3.93 (s, 3H), 6.90 (s, 2H), 6.88 (dd, J = 2.7, 9.6 Hz,1H), 7.08 (d, J = 3.0 Hz,1H), 7.21 (d, J = 9.0 Hz, 1H), 7.28 (d, J = 9.3 Hz,1H), 7.82 (d, J = 9.0 Hz, 1H), 10.58 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 56.4, 61.3, 107.2, 107.3, 114.9, 118.7, 119.7, 127.3, 127.9, 129.7, 135.1, 135.2, 142.3, 153.2, 156.0, 159.3, 199.2. HRMS (EI) for $C_{21}H_{20}O_6$ (M^+): calcd, 368.1260; found, 368.1247. Anal. ($C_{21}H_{20}O_6$) C, H.

2-Amino-6-methoxy-1-(3′,4′,5′-trimethoxybenzoyl)naphthalene (9). A stirred solution of **26** (0.5 g, 1.09 mmol), palladium(II) acetate (5 mg, 0.022 mmol), (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (20 mg, 0.032 mmol), benzophenoneimine (0.23 g, 1.31 mmol), and cesium carbonate (0.49 g, 1.50 mmol) in THF (20 mL) was heated under 65−70 °C with stirring for 16 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with brine, dried over $MgSO_4$, and evaporated to give a crude residue, which was dissolved in methanol (15 mL). Sodium acetate (0.26 g, 3.27 mmol) and hydroxyamine hydrochloride (0.15 g, 2.18 mmol) were added to the reaction mixture with stirring at room temperature for 16 h. The reaction solution was neutralized with 0.1 M and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extracts were dried and evaporated to give a residue that was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:4) to afford the desired **9**, yield 31%. ^{1}H (300 MHz, $CDCl_3$) δ 3.73 (s, 6H), 3.86 (s, 3H), 3.91 (s, 3H), 4.58 (s, 2H), 6.88 (dd, J = 2.7, 9.0 Hz, 1H), 6.94 (d, J = 8.7 Hz, 1H), 7.02 (s, 2H), 7.03 (d, J = 2.7 Hz, 1H), 7.21 (d, J = 9.0 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 56.4, 61.2, 107.0, 107.4, 115.8, 118.9, 119.6, 124.7, 126.7, 128.1, 128.5, 131.4, 134.4, 143.3, 153.3, 155.3, 198.1. HRMS (EI) for $C_{21}H_{21}NO_5$ (M^+): calcd., 367.1420; found, 367.1429. Anal. ($C_{21}H_{21}NO_5 \cdot 0.5H_2O$) C, H, N.

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Supporting Information Available: Spectral data of **7**, **10**–**12**, **13**−**21**, **23**−**26**, **28**−**31**; experimental procedures for synthesis and biological evaluations; [^{3}H]vinblastine competition-binding assay and dose response curve of colchicine competition binding for **8** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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