4- and 5-Aroylindoles as Novel Classes of Potent Antitubulin Agents

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Received May 13, 2007

A novel series of 4- and 5-aroylindole derivatives was prepared and evaluated for antitumor activity. Several compounds showed excellent antiproliferative activity as inhibitors of tubulin polymerization. Compounds **13**, **14**, **15**, and **18**, with IC_{50} values of 1.9, 1.1, 1.2, and 1.8 μM, respectively, exhibited more potent inhibition of tubulin polymerization than colchicine. They also displayed antiproliferative activity, with IC_{50} values ranging from 10 to 43 nM in a variety of human cell lines from different organs.

Introduction

One of the recognized targets in oncology is represented by microtubules.[1] Microtubule-targeting agents such as taxanes and vinca alkaloids have played a central role in the treatment of diverse human cancers over the past decade.[2] However, many clinically useful chemotherapy drugs face substantial limitations, such as drug resistance, high systemic toxicity, complex syntheses, and isolation procedures. This has encouraged scientists to develop new antimitotic agents. Recent research reported compounds targeting the colchicine-binding domain can act as vascular-disrupting agents, rapidly depolymerizing microtubules of newly formed vasculatures to block the blood supply to tumors,[3] for example, drug candidates **2**, **3**, and **5** (Figure 1).

The encouraging antivascular/anticancer activity of compound **2** has stimulated significant interest in a number of diverse ligands designed and prepared to mimic combretastatins,[4] for instance, *z*-aminostilbene,[5] benzophenone,[6] benzothiophene,[7] benzofuran,[8] indole,[9] indazole,[10] carbazole,[11] thiophene,[12] and indolinone[13] moieties. Numbers of indole-containing compounds demonstrate strong antiproliferative and antitubulin activity.[9,14] Analysis of these combretastatin A-4 analogues or derivatives shows that the 3,4,5-trimethoxybenzoyl group or 3,4,5-trimethoxyphenyl group seems to play an important role for activity in this series. On the basis of these observations, we attempted to explore the structure−activity relationships between the indoles moiety and the aroyl group. Using the indole skeleton as a motif coupled with the 3,4,5-trimethoxybenzoyl group at different positions provided the regioisomers of aroylindoles and allowed evaluation of bioactivity. We herein describe the synthesis and structure−activity relationships of 4- and 5-aroylindoles as potent antitubulin agents in continuation of our search for anticancer agents (Figure 2).

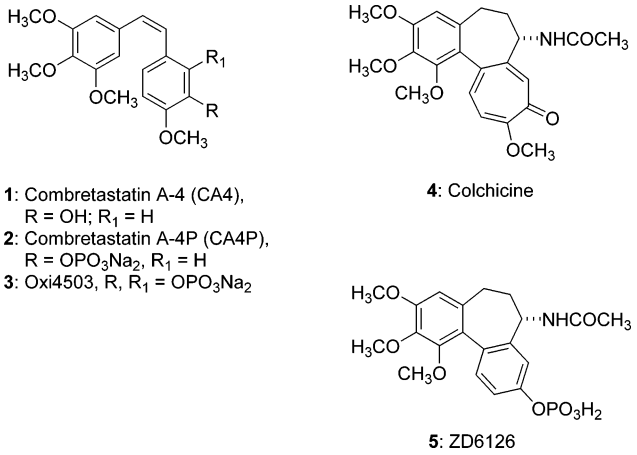

Figure 1.

Results and Discussion

Chemistry. The general method for the synthesis of aroylindoles **6**−**21** is depicted in Scheme 1. The 1-aroylindole, compound **6**, was synthesized by treating indole with 3,4,5-trimethoxybenzoyl chloride in the presence of KO*t*-Bu[a] in 85% yield. The preparation of 2-, 3-, 4-, 5-, 6-, and 7-aroylindoles (**7**−**12**) involved a four-step reaction sequence, with an overall yield of 30−41%. N1-protection of various commercially available indole-carboxyaldehydes (**23**−**28**) with benzenesulfonyl chloride yielded the corresponding indole-1-sulfonamides. These sulfonamides were subjected to a Grignard reaction with (3,4,5-trimethoxyphenyl) magnesium bromide followed by pyridinium dichromate (PDC) oxidation, and the reaction sequence was completed by NaOH-mediated deprotection to afford the desired aroylindoles **7**−**12**. The N1-alkyl-substituted compounds **13**−**17** were synthesized in 65−86% yields from compound **9** or **10** by allowing them to react with the corresponding alkyl halide at room temperature, utilizing KO*t*-Bu as base. Compound **18**, with a hydroxymethyl group at the N1-position, was prepared in 82% yield by treatment of compound **10** with KO*t*-Bu in THF, followed by stirring with 37% formaldehyde at room temperature. The 1-alkylcarboxylic

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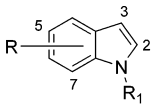
[a] Abbreviations: KO*t*-Bu, potassium *tert*-butoxide; PDC, pyridinium dichromate; CH_3CN, acetonitrile; Cs_2CO_3, cesium carbonate; DMF, *N*,*N*-dimethylformamide; THF, tetrahydrofuran; MDR, multidrug-resistant; LiOH, lithium hydroxide.

10.1021/jm070557q CCC: $37.00
Published on Web 08/08/2007



6: R = H; R_1 = 3',4',5'-trimethoxybenzoyl
7: R = 2-(3',4',5'-trimethoxybenzoyl); R_1 = H
8: R = 3-(3',4',5'-trimethoxybenzoyl); R_1 = H
9: R = 4-(3',4',5'-trimethoxybenzoyl); R_1 = H
10: R = 5-(3',4',5'-trimethoxybenzoyl); R_1 = H
11: R = 6-(3',4',5'-trimethoxybenzoyl); R_1 = H
12: R = 7-(3',4',5'-trimethoxybenzoyl); R_1 = H
13: R = 4-(3',4',5'-trimethoxybenzoyl); R_1 = CH_3
14: R = 5-(3',4',5'-trimethoxybenzoyl); R_1 = CH_3
15: R = 5-(3',4',5'-trimethoxybenzoyl); R_1 = C_2H_5
16: R = 5-(3',4',5'-trimethoxybenzoyl); R_1 = C_3H_7
17: R = 5-(3',4',5'-trimethoxybenzoyl); R_1 = *i*-C_3H_7
18: R = 5-(3',4',5'-trimethoxybenzoyl); R_1 = CH_2OH
19: R = 5-(3',4',5'-trimethoxybenzoyl); R_1 = CH_2CO_2H
20: R = 5-(3',4',5'-trimethoxybenzoyl); R_1 = $CH_2CH_2CO_2H$
21: R = 5-(3',4',5'-trimethoxybenzoyl); R_1 = $CH_2CH_2N(CH_3)_2$

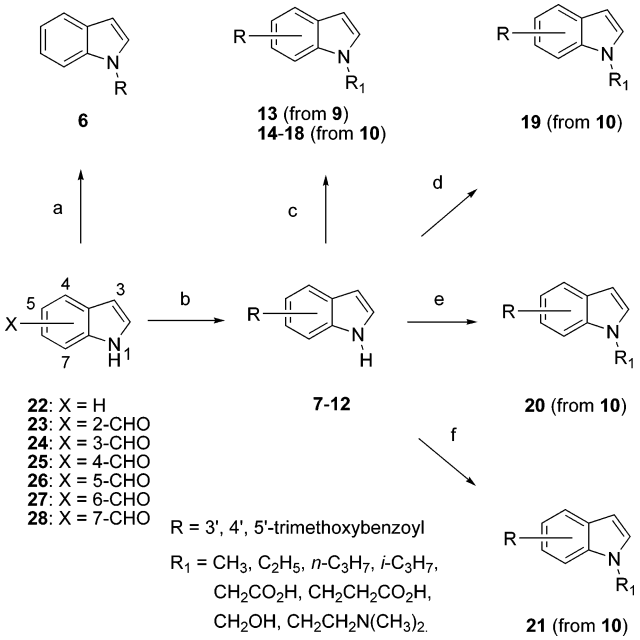
Figure 2.

acids **19** and **20** were obtained through a two-step synthesis. Treatment of compound **10** with potassium *tert*-butoxide, KI, and methyl bromoacetate in CH_3CN at reflux followed by hydrolysis with LiOH in MeOH afforded the desired **19** in 65% yield (two steps). Michael addition of compound **10** to methyl acrylate at room temperature in the presence of Cs_2CO_3 followed by hydrolysis with LiOH/MeOH obtained the 1-(3-propanoic acid)-5-aroylindole **20** in 74% yield (two steps). Compound **10** was treated with 2-dimethylaminoethyl chloride hydrochloride in DMF in the presence of KO*t*-Bu and KI to afford the N1-alkylamino-substituted compound **21** in 48% yield.

Biological Evaluation. (A) In Vitro Cell Growth Inhibitory Activity. The synthesized aroylindoles **6**−**21** were evaluated for their antiproliferative activities against five types of human cancer cell lines, oral epidermoid carcinoma KB cells, colorectal carcinoma HT29 cells, non small cell lung carcinoma H460 cells, and two stomach carcinoma TSGH, MKN45 cells, as well the MDR-positive cell line KB-VIN10, with overexpressed P-gp 170/MDR (Table 1).

We first evaluated the effect of the 3,4,5-trimethoxybenzoyl group substitution on the indole ring for cytotoxic activity. Compounds **6**−**12** with a 3,4,5-trimethoxybenzoyl group at the C-1, C-2, C-3, C-4, C-5, C-6, and C-7 positions, respectively, on the indole ring were evaluated for antiproliferative activity. The SAR information indicates that the 3,4,5-trimethoxybenzoyl group located at the C-4 or C-5 position of the indole ring resulted in the best activity. Shifting the group to the C-6 or C-7 position resulted in moderate activity, while changing to

Scheme 1[a]



[a] Reagents and conditions: (a) 3,4,5-trimethoxybenzoyl chloride, KO*t*-Bu, THF, rt; (b) (i) NaOH, $PhSO_2Cl$, Bu_4NHSO_4, CH_2Cl_2, rt; (ii) (3,4,5-trimethoxyphenyl)magnesium bromide, 0−25 °C; (iii) pyridinium dichromate (PDC), CH_2Cl_2, molecular sieves, rt; (iv) 3N NaOH, EtOH, reflux; (c) alkyl halide or HCHO, KO*t*-Bu, THF, rt; (d) (i) methyl bromoacetate, KO*t*-Bu, KI, CH_3CN, reflux; (ii) LiOH, MeOH, H_2O, reflux; (e) (i) ethyl acrylate, Cs_2CO_3, CH_3CN, rt; (ii) LiOH, MeOH, H_2O, reflux; (f) 2-dimethylaminoethyl chloride hydrochloride, KO*t*-Bu, KI, DMF, 100−120 °C.

the C1−C3 position decreased the activity drastically. Notably, 4-aroylindoles (**9**) and 5-aroylindoles (**10**), namely, 4-(3′,4′,5′-trimethoxybenzoyl)indole and 5-(3′,4′,5′-trimethoxybenzoyl)-indole, respectively, showed IC_{50} values of 46−112 nM against five different human cancer cell lines, which was >2-fold more potent than the 6- and 7-aroylindoles (compounds **11** and **12**, respectively) and >10-fold more potent than 1-, 2-, and 3-aroylindoles (compounds **6**, **7**, and **8**, respectively). Interestingly, the 3′,4′,5′-trimethoxybenzoyl group located on the benzene part of the indole ring (C-4−C-7 positions) seems to be preferable to its location on the pyrrole part of the indole ring (C-1−C-3 position) (**9**, **10**, **11**, and **12** vs **6**, **7**, and **8**). In the 1-aroylindole and 3-aroylindole series, compound **6** and **8**, respectively, exhibit weak cytotoxicity with an IC_{50} value of

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

	cell type (IC_{50} nM ± SD[a])					
cmpd	KB	KB-vin10	H460	HT29	TSGH	MKN45
6	>10 000	>10 000	>10 000	9600 ± 510	8400 ± 350	5200 ± 420
7	2900 ± 150	2800 ± 120	2100 ± 250	1700 ± 280	1800 ± 320	1500 ± 80
8	1600 ± 110	1500 ± 70	1700 ± 70	1000 ± 120	1100 ± 130	980 ± 90
9	50.7 ± 8	51.4 ± 2	53.8 ± 7	46.4 ± 4	54.4 ± 6	49.1 ± 8
10	104 ± 15	111 ± 6	112 ± 12	100 ± 7	103 ± 8	88 ± 11
11	510 ± 21	452 ± 8	520 ± 120	330 ± 18	430 ± 31	480 ± 22
12	310 ± 25	284 ± 12	295 ± 19	250 ± 24	310 ± 18	210 ± 11
13	22.1 ± 6	26.1 ± 2	28.8 ± 3	22.4 ± 4	26.9 ± 3	21.6 ± 4
14	13.6 ± 1	12.5 ± 3	14.1 ± 1	10.5 ± 2	13.4 ± 2	11.2 ± 3
15	36 ± 1	40 ± 2	38 ± 4	32 ± 6	41 ± 3	31 ± 4
16	1900 ± 120	2100 ± 480	2000 ± 520	1800 ± 350	1500 ± 180	680 ± 33
17	1800 ± 240	1600 ± 150	1600 ± 120	1200 ± 210	1100 ± 320	470 ± 51
18	39 ± 7	35 ± 4	39 ± 6	34 ± 3	43 ± 8	33 ± 4
19	520 ± 69	476 ± 16	530 ± 77	460 ± 58	548 ± 81	396 ± 38
20	>10 000	>10 000	>10 000	>10 000	>10 000	>10 000
21	5200 ± 380	4900 ± 210	5100 ± 620	4600 ± 310	4900 ± 610	2900 ± 320
colchicine	12 ± 2	120 ± 4	19 ± 3			13 ± 1

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

1−10 μM, but their activity could be significantly improved to the nanomolar range by the introduction of methoxy groups at the C-5 and C-6 positions of the indole moiety, respectively.[9a] A similar phenomenon was also observed in the case of the 2-aroylindole (**7**) series, where the introduction of a methoxy group at the C-5 position resulted in improvement of IC_{50} values to the nM level. [9b]

On the basis of these results, that the 5-aroylindole core demonstrating substantial antiproliferative activity, the N1-substituted 5-aroylindoles, compounds **14**−**21**, were synthesized and evaluated for activity. To understand the steric effect of alkyl substituents at the N1-position of 5-aroylindoles, the methyl-, ethyl-, propyl-, and isopropyl-substituted compounds **14**, **15**, **16**, and **17**, respectively, were prepared. Compound **14**, with a methyl group, displayed an apparent increase in activity with a mean IC_{50} value of 12 nM, being 8−10-fold more potent than the parent compound. However, compound **15**, with an ethyl group, retained substantial cytotoxicity, but a further increase in the bulkiness of the substituent resulted in a drastic decrease in potency to the micromolecular range, thus revealing that the steric effect of the substitutions at the N1-position of 5-aroylindoles influences cell growth inhibitory activities. The potency improvement by adding a methyl group at the N1-position observed in the 5-aroylindole series intrigued us to explore whether the 4-aroylindoles also exhibit this effect. A resemblance in the 4-aroylindole series showed that compound **13**, with an additional methyl group as compared to parent **9**, demonstrated an increased growth inhibition by a 1−2-fold magnitude in all six cell lines. Notably, compound **13** displayed IC_{50} values of 21−29 nM in five human cancer cells. In an attempt to increase the polarity of this series structure, compounds **18**, **19**, **20**, and **21**, with hydroxy, carboxylic acid, and amine functionalities, were prepared and evaluated for their cell growth inhibitory activity. The SAR data revealed that the activity of compounds with a polar group at the N1-position of a 5-aroylindole seems to be correlated with the steric effect. Compound **18**, with a methyl alcohol substitution, showed substantially increased antiproliferative activity, with an IC_{50} value of 34−43 nM against five human cancer cell lines, and was comparable to the 1-ethyl-5-(3′,4′,5′-trimethoxybenzoyl)-indole (**15**). The N1-alkylcarboxylic acid-substituted compounds **19** and **20**, modified with methylcarboxylic acid and ethyl carboxylic acid groups, displayed decreased antiproliferative activity relative to **10**. The ethanoic acid derivative **19** was 5-fold less potent than the parent, while the propanoic acid derivative **20** showed a dramatic loss of activity. The 2-(*N*,*N*-dimethylamino)ethyl substitution at the N1-position of parent (**10**) gave compound **21**, which resulted in decreased activity to micromolar IC_{50} values.

(B) Inhibition of Tubulin Polymerization and Colchicine Binding Activity. To investigate whether the 4- and 5-aroylindoles were tubulin inhibitors through the colchicine-binding domain, compounds **9**, **10**, **13**, **14**, **15**, **18**, and reference compounds (colchicine and combretastatin A-4) were evaluated for antitubulin activities and colchicine binding activities (Table 2). The data showed that 4- and 5-aroylindoles have good antitubulin activity and correlated with their cellular growth inhibitory activity. As shown in Table 2, compounds **9**, **10**, **13**−**15**, **18** were effective in inhibiting tubulin assembly, with IC_{50} values of 2.0, 2.2, 1.9, 1.1, 1.2, and 1.8 μM, respectively. These values were comparable or superior to the reference compounds, combretastatin A-4 and colchicine (IC_{50} = 1.3 and 2.9, respectively). In the [^{3}H] colchicine-competing assay, our data in Table 2 revealed that 4- and 5-aroylindoles derivatives were bound to the colchicine binding site.

Table 2. Inhibition of Tubulin Polymerization and Colchicine Binding by Compounds **9**−**10**, **13**−**15**, **18**, Colchicine, and CA4

cmpd	tubulin[a] $IC_{50} \pm$ SD (μM)	colchicine binding[b] (% ± SD)
9	2.0 ± 0.2	74 ± 3
10	2.2 ± 0.3	71 ± 4
13	1.9 ± 0.2	75 ± 3
14	1.1 ± 0.1	84 ± 2
15	1.2 ± 0.3	81 ± 3
18	1.8 ± 0.2	78 ± 4
colchicine	2.9 ± 0.4	
CA4	1.3 ± 0.2	89 ± 2

[a] Inhibition of tubulin polymerization.[15] [b] Inhibition of [^{3}H] colchicine binding.[15,16] Tubulin was at 1 μM and both [^{3}H]colchicine and inhibitor were at 5 μM.

Conclusion

The 4- and 5-aroylindole derivatives have been identified as a novel class of potent antitubulin agents acting through the colchicine binding site on microtubules. The lead compound **14** exhibits antiproliferative activity, with IC_{50} values ranging from 10 to 15 nM in a diverse set of human cancer cell lines from different organs, including the MDR-positive resistant line (KB-vin10). It also demonstrates greater antitubulin activity than colchicine and comparable activity to combretastatin A-4. The SAR information indicated that the 3,4,5-trimethoxybenzoyl substituent at position-4 or -5 of the indole ring contributed to a significant extent to maximal activity, rather than the other positions, such as positions 1−3 and 6−7 (**9** and **10** vs **6**, **7**, **8**, **11**, and **12**). Adding a methyl group at the N1-position in the 4- and 5-aroylindoles increases potency in both series (**13** and **14**). But a further increase in the bulkiness of the N1-position of 5-aroylindoles resulted in a tendency to decrease activity (**16**, **17**, **19**, and **20** vs **10**). In summary, 4-aroylindoles (**13**) and 5-aroylindoles (**14**, **15**, and **18**) constitute a strong antimitotic agent with the potential to be further investigation for cancer treatment.

Experimental Section

General Procedure for the Preparation of 4- and 5-Aroylindoles (9, 10). 4-(3′,4′,5′-Trimethoxybenzoyl)indole (9). Benzenesulfonyl chloride (1.76 mL, 13.77 mmol) was added slowly to a well-stirred suspension of 4-formylindole (**25**) (1 g, 6.88 mmol), potassium hydroxide (1.16 g, 20.66 mmol), and tetra-*n*-butylammonium hydrogen sulfate (0.23 g, 0.68 mmol) in CH_2Cl_2 (20 mL) at room temperature. After 18 h, the reaction mixture was quenched with saturated $NaHCO_3$ (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuum to give a residue, which was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 1:1) to afford the N1-phenylsulfonamide-indoles product. The N1-sulfonamide compound was dissolved in THF (20 mL) and cooled to 0 °C with stirring. A solution of 3,4,5-trimethoxyphenylmagnesium bromide (10.33 mL, 1.0 M in THF, prepared in advance) was added dropwise to the reaction mixture over 10 min with vigorous stirring for 1 h. The mixture was quenched with ice water, neutralized with saturated NH_4Cl solution, and extracted with EtOAc (15 mL × 2) and CH_2Cl_2 (15 mL × 2). The combined organic extracts was dried over $MgSO_4$ and evaporated to give a crude residue, which was dissolved in CH_2Cl_2 (60 mL). Molecular sieves (4 Å, 5.2 g) and pyridinium dichromate (5.20 g, 13.78 mmol) were added to the reaction mixture with stirring at room temperature for 16 h. The reaction mixture was diluted with diethyl ether (40 mL) and stirred for another 1 h, and then filtered through a pad of celite and washed three times by

CH_2Cl_2 (50 mL). The filtrate was concentrated in vacuum, and the residue was further treated with 3 N sodium hydroxide (23 mL, 68.88 mmol) in EtOH (30 mL) and heated at reflux for 16 h. The solution was evaporated and extracted with EtOAc (20 mL × 2) and CH_2Cl_2 (20 mL × 2). The combined organic layers were dried and evaporated to give a residue that was purified by silica gel flash column chromatography (ethyl acetate/*n*-hexane = 1:1) and recrystallized (CH_2Cl_2/EtOAc) to afford compound **9**, yield 39%; mp 94.8−95.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 6H), 3.95 (s, 3H), 6.94 (m, 1H), 7.14 (s, 2H), 7.22 (t, J = 8.0 Hz, 1H), 7.31 (t, J = 2.8 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 8.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 60.9, 103.1, 107.6, 115.5, 120.5, 124.0, 126.5, 127.2, 129.1, 134.0, 136.5, 141.5, 152.6, 196.6. MS (EI) *m*/*z* 311 (M^+, 100%), 144 (95%), 116 (38%). HRMS (EI) calcd for $C_{18}H_{17}NO_4$ (M^+), 311.1162; found, 311.1160. Anal. ($C_{18}H_{17}NO_4 \cdot 0.25H_2O$) C, H, N.

5-(3′,4′,5′-Trimethoxybenzoyl)indole (10). The title compound was obtained in 41% overall yield from 5-formylindole (**26**) and 3,4,5-trimethoxyphenylmagnesium bromide; mp 147.2−148.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 6H), 3.94 (s, 3H), 6.62−6.63 (m, 1H), 7.09 (s, 2H), 7.27−7.28 (m, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.75 (dd, J = 8.4, 1.5 Hz, 1H), 8.16 (s, 1H), 9.55 (s, 1H). MS (EI) *m*/*z* 311 (M^+, 100%), 195 (39%), 144 (90%). HRMS (EI) calcd for $C_{18}H_{17}NO_4$ (M^+), 311.1145; found, 311.1151. Anal. ($C_{18}H_{17}NO_4$) C, H, N.

General Procedure for the Preparation of 1-Substituted 4- and 5-Aroylindoles Derivatives (13−15, 18). 1-Methyl-4-(3′,4′,5′-trimethoxybenzoyl)indole (13). Potassium *tert*-butoxide (0.36 g, 3.21 mmol) was added to a solution of **9** (0.5 g, 1.60 mmol) in THF (20 mL) under vigorous stirring at room temperature. Stirring was continued for 20 min followed by the addition of iodomethane (0.5 mL, 8.03 mmol). After 3 h, the reaction mixture was evaporated and extracted with EtOAc (15 mL × 2) and CH_2Cl_2 (15 mL × 2). The combined organic layers were dried over $MgSO_4$ and evaporated to give a residue, which was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 1:3) to afford compound **13**, yield 86%; mp 105.2−106.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 6H), 3.86 (s, 3H), 3.94 (s, 3H), 6.85 (d, J = 3.2 Hz, 1H), 7.13 (s, 2H), 7.19 (d, J = 3.2 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.0, 56.2, 60.9, 101.8, 107.6, 113.4, 120.2, 123.6, 127.8, 129.4, 130.9, 134.0, 137.3, 141.5, 152.7, 196.3. MS (EI) *m*/*z* 325 (M^+, 100%), 282 (17%), 158 (49%). HRMS (EI) calcd for $C_{19}H_{19}NO_4$ (M^+), 325.1332; found, 325.1323. Anal. ($C_{19}H_{19}NO_4$) C, H, N.

1-Methyl-5-(3′,4′,5′-trimethoxybenzoyl)indole (14). The title compound was obtained in 84% yield from **10** and iodomethane; mp 119.6−120.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.84 (s, 6H), 3.94 (s, 3H), 6.60 (d, J = 2.8 Hz, 1H), 7.08 (s, 2H), 7.14 (d, J = 3.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.79 (dd, J = 8.8, 1.6 Hz, 1H), 8.14 (d, J = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.0, 56.2, 60.8, 102.8, 107.4, 108.9, 123.7, 125.0, 127.5, 129.1, 130.3, 134.1, 138.8, 141.1, 152.6, 196.3. MS (EI) *m*/*z* 325 (M^+, 100%), 158 (43%). HRMS (EI) calcd for $C_{19}H_{19}NO_4$ (M^+), 325.1328; found, 325.1321. Anal. ($C_{19}H_{19}NO_4$) C, H, N.

1-Ethyl-5-(3′,4′,5′-trimethoxybenzoyl)indole (15). The title compound was obtained in 76% yield from **10** and iodoethane; mp 103.5−104.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (t, J = 7.6 Hz, 3H), 3.87 (s, 6H), 3.94 (s, 3H), 4.22 (q, J = 7.6 Hz, 2H), 6.60 (d, J = 3.2 Hz, 1 H), 7.08 (s, 2H), 7.21 (d, J = 3.2 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.79 (dd, J = 8.8, 1.6 Hz, 1H), 8.14 (d, J = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 41.1, 56.2, 60.8, 102.9, 107.4, 109.0, 123.5, 125.2, 127.7, 128.6, 129.1, 134.1, 137.8, 141.1, 152.6, 196.2. MS (EI) *m*/*z* 339 (M^+, 85%), 172 (100%). HRMS (EI) calcd for $C_{20}H_{21}NO_4$ (M^+), 339.1463; found, 339.1467. Anal. ($C_{20}H_{21}NO_4$) C, H, N.

1-Hydroxymethyl-5-(3′,4′,5′-trimethoxybenzoyl)indole (18). The title compound was obtained in 82% yield from **10** and 37% formaldehyde; mp 162.1−163.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 6H), 3.93 (s, 3H), 5.65 (s, 2H), 6.57 (d, J = 3.2 Hz, 1H), 7.02 (s, 2H), 7.26 (d, J = 3.6 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 8.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.1, 60.9, 69.8, 104.1, 107.5, 109.4, 124.1, 124.9, 128.3, 129.0, 129.7, 133.7, 138.0, 141.3, 152.6, 196.8. MS (EI) *m*/*z* 341 (M^+, 65%), 311 (100%). HRMS (EI) calcd for $C_{19}H_{19}NO_5$ (M^+), 341.1257; found, 341.1260. Anal. ($C_{19}H_{19}NO_5 \cdot 0.5H_2O$) C, H, N.

Acknowledgment. This research were supported by the National Science Council of the Republic of China (Grant No. NSC 95-2320-B-038-008 and NSC 95-2752-B-400-001-PAE), and National Health Research Institutes, Taiwan (Grant No. 95A1CAPP06-1).

Supporting Information Available: Spectral data of compounds **6**−**8**, **11**, **12**, **16**, **17**, **19**−**21** and experimental procedures for synthesis and biological evaluations. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM070557Q