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5-Amino-2-Aroylquinolines as Highly Potent Tubulin Polymerization Inhibitors

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A series of aroylquinoline derivatives were synthesized and evaluated for anticancer activity. 5-Amino-6-methoxy-2-aroylquinoline **15** showed more potent antiproliferative activity (IC_{50} values ranging from 0.2 to 0.4 nM) as compared to **1a** (combretastatin A-4) (IC_{50} = 1.9−835 nM) against various human cancer cell lines and a MDR-resistant cancer cell line. Compound **15** (IC_{50} = 1.6 μM) exhibited more potent inhibition of tubulin polymerization than **1a** (IC_{50} = 2.1 μM) and showed strong binding property to the colchicine binding site of microtubules.

Introduction

Microtubules are dynamic structures that play a crucial role in cellular division and are recognized as an important target for anticancer therapy.[1]A number of naturally occurring compounds, such as paclitaxel, epothilone A, vinblastine, dolastatin 10, **1a** (combretastatin A-4), and **3** (colchicine), exhibit their anticancer properties by interfering with the dynamics of tubulin polymerization and depolymerization, resulting in mitotic arrest. Recent reports show that drugs binding to the colchicine domain are undergoing intensive investigation as vascular-disrupting agents for cancer therapy. For example, clinical candidates of the microtubule inhibitor, combretastatin A-4P (**1b**, Zybrestat) and AVE-8062 (**2b**, Ombrabulin), act as a vascular disrupting agent (VDA[a]) that rapidly depolymerize microtubules of newly formed vasculatures and subsequently shut down the blood supply to tumors.[2] In addition, the sulfonamide-containing small molecule compound, **4** (ABT-751), demonstrated efficacious antimitotic activity by inhibition of tubulin polymerization and is currently undergoing clinical trials.[3] (Figure 1)

The current available clinically used chemotherapeutic microtubule inhibitors have high toxicity, and their potential is limited by the development of multidrug resistance (MDR). Therefore, there has been great interest in identifying novel microtubule inhibitors that overcome various modes of resistance and exhibited improved pharmacology profiles.[4] The quinolines is a pharmacologically active class of heterocyclic compounds.[5] Analysis of these microtubule inhibitors, such as **1a**, **2a**, **3**, and **4**, indicates that the 3,4,5-trimethoxyphenyl/3,4,5-trimethoxybenzoyl and *para*-methoxyphenyl groups

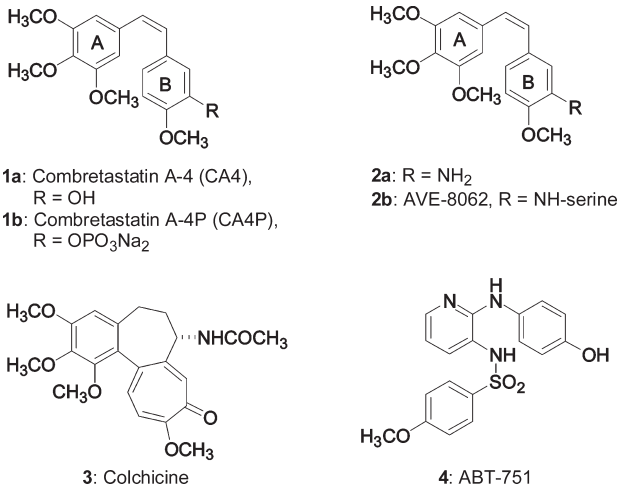

Figure 1

seem to play an important role in their bioactivity. Here we report our attempt to explore the quinoline core coupled with the 3,4,5-trimethoxybenzoyl group as tubulin polymerization inhibitors. The structure−activity relationship studies of series of aroylquinoline regioisomers led to the discovery of 5-amino-2-aroylquinolines as novel highly potent inhibitors of tubulin polymerization. (Figure 2)

Results and Discussion

Chemistry. The general method for the synthesis of aroylquinolines **5**−**11**, **14**, and **16**−**17** is depicted in the Scheme 1. The preparation of 2-, 3-, 4-, 5-, 6-, 7-, and 8-aroylquinolines (**5**−**11**) involved a concise two-step reaction sequence, with an overall yield of 57−72%. Grignard reaction of 3,4,5-trimethoxyphenylmagnesium bromide with various commercially available quinoline-carboxaldehydes (**18**−**24**) followed by pyridinium dichromate (PDC) oxidation afforded the desired aroylquinolines **5**−**11**. The 6-aroylquinoline **14**,

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[a] Abbreviations: MDR, multidrug-resistant; VDA, vascular disrupting agent; PDC, pyridinium dichromate; *m*-CPBA, *meta*-chloroperbenzoic acid; SeO_2, selenium dioxide; $POCl_3$, phosphorus oxychloride.

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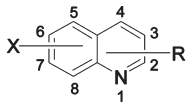
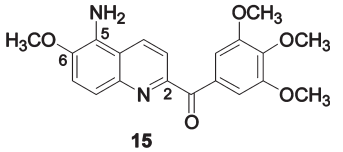
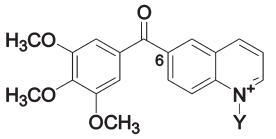


5: R = 2-(3',4',5'-trimethoxybenzoyl); X = H
6: R = 3-(3',4',5'-trimethoxybenzoyl); X = H
7: R = 4-(3',4',5'-trimethoxybenzoyl); X = H
8: R = 5-(3',4',5'-trimethoxybenzoyl); X = H
9: R = 6-(3',4',5'-trimethoxybenzoyl); X = H
10: R = 7-(3',4',5'-trimethoxybenzoyl); X = H
11: R = 8-(3',4',5'-trimethoxybenzoyl); X = H
12: R = 2-(3',4',5'-trimethoxybenzoyl); X = 6-OCH_3
13: R = 4-(3',4',5'-trimethoxybenzoyl); X = 8-OCH_3
14: R = 6-(3',4',5'-trimethoxybenzoyl); X = 2-OCH_3



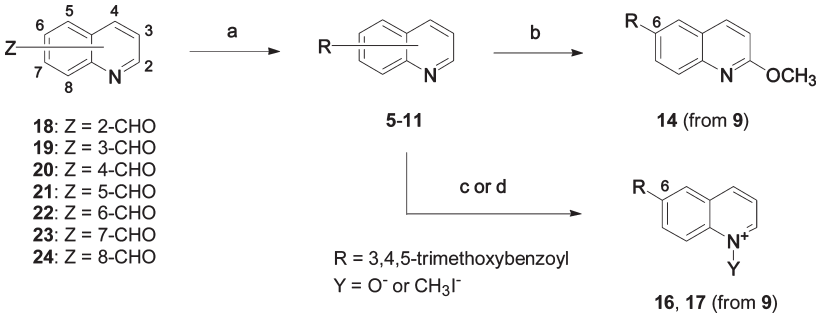
15



16: Y = O^-
17: Y = CH_3 (I^-)

Figure 2

Scheme 1[a]



18: Z = 2-CHO
19: Z = 3-CHO
20: Z = 4-CHO
21: Z = 5-CHO
22: Z = 6-CHO
23: Z = 7-CHO
24: Z = 8-CHO

5-11

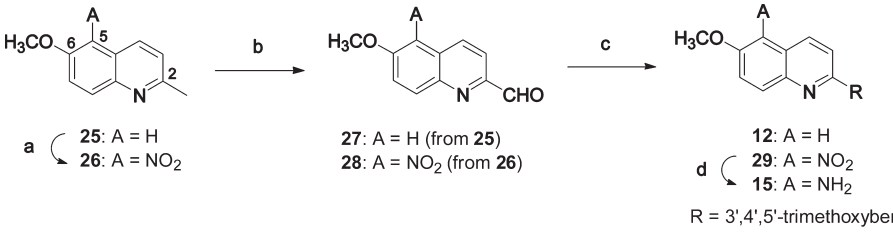
14 (from **9**)

R = 3,4,5-trimethoxybenzoyl
Y = O^- or CH_3I^-

16, **17** (from **9**)

[a]Reagents and conditions: (a) (i) 3,4,5-trimethoxyphenylmagnesium bromide, 0−25 °C; (ii) pyridinium dichromate (PDC), CH_2Cl_2, molecular sieves, rt; (b) (i) *m*-CPBA, CH_2Cl_2, (ii) $POCl_3$, CH_2Cl_2, reflux, (iii) sodium methoxide, CH_3OH, reflux; (c) *m*-CPBA, CH_2Cl_2; (d) CH_3I, CH_2Cl_2.

Scheme 2[a]



25: A = H
26: A = NO_2

27: A = H (from **25**)
28: A = NO_2 (from **26**)

12: A = H
29: A = NO_2
15: A = NH_2

R = 3',4',5'-trimethoxybenzoyl

[a]Reagents and conditions: (a) 65% HNO_3, H_2SO_4, 0−25 °C; (b) SeO_2, 1,4-dioxane, reflux; (c) (i) 3,4,5-trimethoxyphenylmagnesium bromide, 0−25 °C, (ii) pyridinium dichromate (PDC), CH_2Cl_2, molecular sieves, rt, (d) sodium sulfide nonahydrate, NaOH, ethanol, H_2O, reflux.

with a methoxy group at the C2-position, was synthesized in 51% yield by treatment of **9** with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 at room temperature, followed by a phosphorus oxychloride heating at reflux and sodium methoxide addition. The N1-substituted quaternary salt derivatives **16** and **17** were prepared in 95% and 91% yield from **9** by reaction with *m*-CPBA and CH_3I, respectively. The 6-methoxy-2-aroylquinolines **12** and **15** were prepared starting from the 6-methoxyquinaldine (**25**) as shown in the Scheme 2. The C2-methyl group of **25** was converted into the aldehyde followed by the treatment with Grignard reagent derived from 3,4,5-trimethoxyphenylmagnesium bromide and pyridinium dichromate (PDC)-mediated oxidation to give the 6-methoxy-2-aroylquinoline **12**. Compound **15**, with an additional amino group at the 5-position of the quinoline ring in **12**, was synthesized from the key intermediate **26**. Compound **25** was treated with the HNO_3/H_2SO_4-mediated nitration, giving the 2-methyl-6-methoxy-5-nitroquinoline (**26**) in 75% yield. The 5-nitroquinoline **26** was subject to a four-step reaction sequence, which involved the selenium dioxide-mediated C2-oxidation, Grignard reaction of 3,4,5-trimethoxyphenylmagnesium bromide, PDC-mediated oxidation, and Na_2S-mediated reduction, afforded the desired compound **15** (24% yield from **25**). The 8-methoxy-4-aroylquinoline **13** was obtained in 17% yield from commercially available *o*-anisidine (**30**) through a four-step synthesis. Treatment of **30** with methyl vinyl ketone in AcOH in the presence of ferric chloride and zinc chloride gave the 4-methylquinoline **31**, which on oxidation with selenium dioxide in *p*-xylene, followed by Grignard reaction with 3,4,5-trimethoxyphenylmagnesium bromide and PDC oxidation afforded the desired compound **13** (Scheme 3).

Biological Evaluation. A. In Vitro Cell Growth Inhibitory Activity. The synthesized aroylquinolines **5**−**17** were evaluated for antiproliferative activities against oral epidermoid carcinoma KB cells, non-small-cell lung carcinoma H460 cells, colorectal carcinoma HT29 cells, and stomach carcinoma MKN45 cells, as well as the MDR-positive cancer cell line, KB-vin10 cells, that overexpressed P-gp 170/MDR (Table 1).

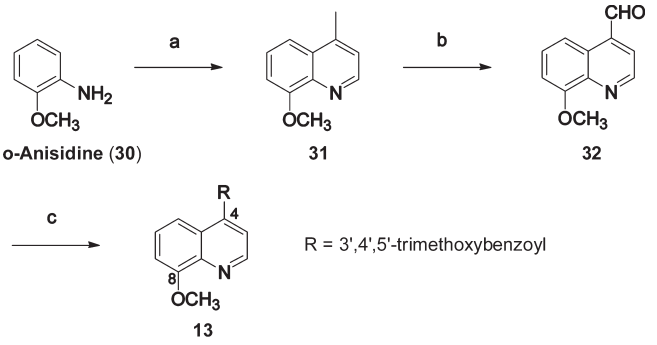
First, we evaluated the position effect of aroyl group (3,4,5-trimethoxybenzoyl) in the quinoline system. The regioisomers

Table 1. IC_{50} Values (nM ± SD[a]) of Compounds **5**−**17**, and Reference Compounds (**3** and **1a**)

	cell type (IC_{50} nM ± SD[a])				
compd	KB	H460	HT29	MKN45	KB-vin10
5	173.6 ± 33.1	180 ± 25.5	148 ± 17	245.5 ± 32.7	117.3 ± 23.7
6	1800 ± 100	1600 ± 380	1000 ± 210	562 ± 42	1100 ± 220
7	3500 ± 700	3800 ± 520	2300 ± 480	920 ± 90	2200 ± 600
8	2900 ± 400	3800 ± 620	2800 ± 310	1200 ± 150	2300 ± 400
9	24 ± 6.1	36 ± 5.5	24.6 ± 3	16.3 ± 4.5	21.5 ± 7.7
10	> 10000	> 10000	> 10000	> 10000	> 10000
11	8100 ± 700	5000 ± 920	4500 ± 1100	3200 ± 700	6000 ± 800
12	27.2 ± 9.8	61.5 ± 20.5	77 ± 5.7	150 ± 31.2	21.5 ± 0.6
13	155 ± 15.1	193 ± 35.3	162.5 ± 28.7	147 ± 25.4	165.2 ± 33
14	300.6 ± 64.4	256.5 ± 34.6	205.5 ± 4.9	138.5 ± 54.4	202.3 ± 26.2
15	0.3 ± 0.1	0.4 ± 0.3	0.4 ± 0.2	0.3 ± 0.2	0.2 ± 0.1
16	829.5 ± 171.5	1100 ± 150	872 ± 86.2	617.3 ± 85	764 ± 111.1
17	> 10000	> 10000	> 10000	> 10000	> 10000
3	12 ± 1.2	20.1 ± 3	13.2 ± 2.3	12.4 ± 2	128 ± 8
1a	2.4 ± 0.2	2.6 ± 0.3	835 ± 54	4.9 ± 0.2	1.9 ± 0.4

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

Scheme 3[a]



[a] Reagents and conditions: (a) ferric chloride, zinc chloride, CH_3COOH, methyl vinyl ketone, 70 °C-reflux; (b) SeO_2, *p*-xylene, reflux; (c) (i) 3,4,5- trimethoxyphenylmagnesium bromide, 0−25 °C, (ii) pyridinium dichromate (PDC), CH_2Cl_2, molecular sieves, rt.

2-, 3-, 4-, 5-, 6-, 7-, and 8-aroylquinolines (**5**, **6**, **7**, **8**, **9**, **10**, and **11**, respectively) were evaluated for antiproliferative activity against five human cancer cell lines. The 3,4,5-trimethoxybenzoyl group located at the C-2 and C-6 position on quinoline ring resulted in the most potent activity with 2-aroylquinoline (**5**) and 6-aroylquinoline (**9**) showing mean IC_{50} values of 172.8 and 24.4 nM against five cancer cell lines, respectively. Shifting of the aroyl group to the C-3, C-4, C-5, or C-8 position resulted in weak cytotoxicity at the μM level, while shifting to the C-7 position, as in **10**, resulted in the loss of cytotoxicity.

The *p*-methoxy group substitution in the ring-B of *cis*-stilbene (**1a**)[6] and in the 3-benzenesulfonamide of pyridine (**4**)[7] are important for activity. Thus, we studied the effect of the addition of the methoxy group in aroylquinolines. The 2-, 4-, and 6-aroylquinolines were modified to introduce a methoxy group at the opposite site of the 3′,4′,5′-trimethoxybenzoyl group to afford 6-methoxy-2-(3′,4′,5′-trimethoxybenzoyl)quinoline (**12**), 8-methoxy-4-(3′,4′,5′-trimethoxybenzoyl)quinoline (**13**), and 2-methoxy-6-(3′,4′,5′-trimethoxybenzoyl)quinoline (**14**), respectively. All three compounds showed substantial antiproliferative activity against five cancer cell lines with mean IC_{50} values of 67, 164, and 220 nM, respectively. Introduction of a methoxy group at the C-6 and C-8 position of 2-aroylquinoline **5** and 4-aroylquinoline **7**, gave 6-methoxy-2-aroylquinoline **12** and 8-methoxy-4-aroylquinoline **13**, respectively, with increases in cell growth inhibition ability as compared to the parental compound. Compound **13** showed over an order of magnitude increase in activity over the parental compound **7**, while **12** showed improved of IC_{50} values to double digit nanomolar values in the KB, H460, HT29, and KB-vin10 cell lines. However, the addition of a methoxy group at the C-2 position in the 6-aroylquinoline system resulted in a decrease in potency as compared to the parental compound (**14** vs **9**). In an effort to increase the 2-aroylquinolines skeleton's polarity and activity, the 5-amino-substituted 2-aroylquinoline **15** was synthesized. It exhibited a mean IC_{50} value of 0.32 nM in all five cancer cell lines, thus displaying stronger cytotoxicity than **1a**. Interestingly, **15** with additional amino group showed approximately > 100-fold improvement in the IC_{50} value over its analogue **12** (**15** vs **12**). To further understand the underlying structure that give raise to the strong potency of 15, molecular modeling studies of **15**, **1a**, and **2a** were carried out. Compound **15**, **1a**, and **2a** were docked into the colchicine binding site of tubulin (PDB 1SA0) using Gold (version 4.0) in default mode. Results revealed that the hydrogen-binding seem play an important role in enhancing the potency of **15**. Compound **15** owned two hydrogen-binding reactions with the colchicine-binding domain, which were the 5-amino group of quinoline ring interaction with Thr 179 and the 2-carbonyl moiety of quinoline ring interaction with Leu 255. However, **1a** and **2a** had one hydrogen-binding reaction using their 3′-hydroxy and 3′-amino group of B-ring interaction with Val 181 and Thr 179, respectively, thus providing evidence for the potent activity of **15**. (Figure 3)

As the 6-aroylquinoline (**9**) demonstrated the best cytotoxicity stronger the other aroylquinolines, for instance, 2-aroylquinoline (**5**) and 3-aroylquinoline (**6**), two N_1-substituted derivatives, **16** and **17**, were further prepared. Compound **16** with *N*-oxide group reduced the activity by > 10-fold magnitude compared with **9** (**16** vs **9**), but substitution for *N*1-methyl group (**17**) resulted in drastic loss of activity (**17** vs **9**), thus revealing that the quaternary salts of alkylquinoline and quinoline *N*-oxide were not preferred.

B. Inhibition of Tubulin Polymerization and Colchicine Binding Activity. To examine whether aroylquinolines were microtubule inhibitors acting through the colchicine-binding

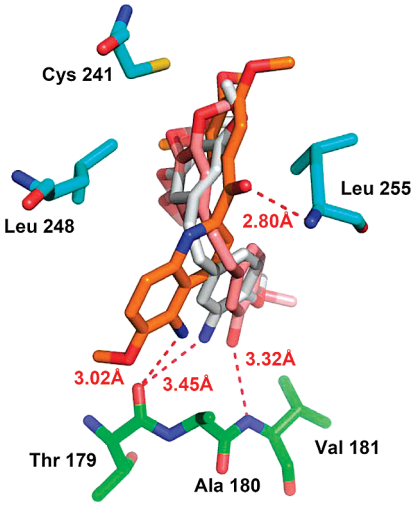


Figure 3. Superimposition of **15** (orange), **1a** (pink), and **2a** (gray) in colchicine binding site of tubule (PDB 1SA0) using Gold 4.0. Red dotted lines represent hydrogen bond.

Table 2. Inhibition of Tubulin Polymerization and Colchicine Binding by Compounds **5**, **9**, **12**, **14**, **15**, and Reference Compounds (**1a** and **3**)

	tubulin[a]	colchicine binding[b] (% ± SD)	
	IC_{50} ± SD (μM)		
compd		1 μM inhibitor	5 μM inhibitor
5	> 10		
9	2.9 ± 0.5	51 ± 3	72 ± 3
12	3.5 ± 0.6	40 ± 3	68 ± 2
14	> 10		
15	1.6 ± 0.2	90 ± 0.5	97 ± 1
3	4.2 ± 0.6		
1a	2.1 ± 0.3	87 ± 1	95 ± 2

[a]Inhibition of tubulin polymerization.[8] [b]Inhibition of [^{3}H]colchicine binding.[9] Tubulin was at 1 μM; [^{3}H]colchicine was at 5 μM.

site, the 2-aroylquinoline (**5**, **12**, and **15**), 6-aroylquinoline (**9** and **14**), and reference compounds (**1a** and **3**) were evaluated for antitubulin activity and the ability to compete for the colchicine-binding site. (Table 2) Compounds **9**, **12**, and **15** were effective in inhibiting microtubule assembly with IC_{50} values of 2.9, 3.5, and 1.6 μM, respectively. Compound **15** showed more potent antitubulin activity as compared to **1a** (IC_{50} = 2.1 μM) and **3** (IC_{50} = 4.2 μM), which positively correlated with its antiproliferative activity. Unexpectedly, the moderate cytotoxic compounds **5** and **14** did not inhibit microtubule assembly up to 10 μM. Results of the [3H]-colchicine binding assay indicated that the 5-amino-6-methoxy-(3′,4′,5′-trimethoxybenzoyl)quinoline (**15**) was strongly bound to the colchicine-binding domain of tubule with binding affinity comparable to **1a**.

Conclusion

Synthesis and structure−cell inhibitory activity[10] studies for 2-, 3-, 4-, 5-, 6-, 7-, 8-aroylquinolines as anticancer agents were performed. 2-Aroylquinolines (**12**, **15**) and 6-aroylquinolines (**9**) were identified as a novel class of potent microtubule inhibitors acting through the colchicine-binding site of tubulin. The lead compound 5-amino-6-methoxy-2-aroylquinoline **15** displayed potent antiproliferative activity, with IC_{50} values ranging from 0.2 to 0.4 nM in a diverse set of human cancer cell lines from different organs, including the MDR-positive resistant cell line (KB-vin 10). It also showed stronger activity against microtubule assembly than **3** and slightly superior activity than **1**. The SAR information revealed that the aroyl group (3′,4′,5′-trimethoxybenzoyl moiety) located at the position 2 and 6 on the quinoline ring significantly contributed more in activity than in position 3−5 and 7−8 (**5** and **9** vs **6**, **7**, **8**, **10**, and **11**). The addition of a methoxy group at the C-6 or C-8 position of the 2- and 4-aroylquinolines (**5** and **7**, respectively) increased potency in both series (**12** and **13**), but an additional methoxy group at the C-2 position of 6-aroylquinoline **9** resulted in a decrease in activity (**14** vs **9**). In summary, 5-amino-6-methoxy-2-aroylquinoline (**15**) exhibited a strong activity in inhibiting tubulin polymerization and tumor cell growth with potential for further investigation as an anticancer agent.

Experimental Section

General Procedure for the Preparation of 2- and 6-Aroylquinolines (9, 12). 6-(3′,4′,5′-Trimethoxybenzoyl)quinoline (9). A solution of 3,4,5-trimethoxyphenylmagnesium bromide (10 mL, 1.0 M in THF, prepared in advance) was added slowly to the corresponding 6-quinoline-carboxaldehyde (**22**) (1.57 g, 10 mmol) in tetrahydrofuran (10 mL) at 0 °C. The reaction mixture was warmed to room temperature, and stirring was continued for another 1 h. A saturated NH_4Cl solution was slowly added to hydrolyze the adduct at 0 °C 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 (50 mL). Molecular sieves (4 Å, 7.52 g) and pyridinium dichromate (7.52 g, 20 mmol) were added to the reaction mixture with stirring at room temperature for 16 h. The reaction mixture was filtered through a pad of celite. The filtrate was evaporated to give a residue that was purified by silica gel flash column chromatography (EtOAc:*n*-hexane = 2:3) and recrystallized (CH_3OH) to afford the desired compound **9**, yield 72%; R_f 0.32, mp 132−134 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 6H), 3.96 (s, 3H), 7.11 (s, 2H), 7.51 (dd, J = 4.3, 8.2 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.22 (d, J = 8.7 Hz, 1H), 8.26−8.27 (m, 2H), 9.03−9.04 (m, 1H). MS (EI) m/z: 323 (M^+, 100%). HRMS (EI) for $C_{19}H_{17}NO_4$ (M^+): calcd, 323.1158; found, 323.1153. Anal. ($C_{19}H_{17}NO_4 \cdot 0.5H_2O$) C, H, N.

6-Methoxy-2-(3′,4′,5′-trimethoxybenzoyl)quinoline (12). The title compound was obtained in 68% overall yield from 3,4,5-trimethoxyphenylmagnesium bromide and 6-methoxy-2-quinolinecarboxaldehyde (**27**) in a similar manner as described for the preparation of **9**; TLC (EtOAc:*n*-hexane = 3:2), R_f 0.37, mp 143−145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (s, 6H), 3.96 (s, 3H), 3.98 (s, 3H), 7.15 (d, J = 2.7 Hz, 1H), 7.44 (dd, J = 4.0, 9.1 Hz, 1H), 7.64 (s, 2H), 8.06−8.12 (m, 1H), 7.96 (d, J = 8.1 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H). MS (EI) m/z: 353 (M^+, 100%). HRMS (EI) for $C_{20}H_{19}NO_5$ (M^+): calcd, 353.1263; found, 353.1262. Anal. ($C_{20}H_{19}NO_5$) C, H, N.

5-Amino-6-methoxy-2-(3′,4′,5′-trimethoxybenzoyl)quinoline (15). To a stirred suspension of **29** (0.2 g, 0.5 mmol), sodium sulfide nonahydrate (0.87 g, 3.61 mmol) and sodium hydroxide (0.34 g, 8.48 mmol) in ethanol (4 mL) and water (11 mL) was heated at reflux for 16 h and then left to stand overnight. The resulting precipitate was collected by filtration and repeatedly washed with water. Recrystallization from methanol afforded the desired product **15**, yield 78%; TLC (EtOAc:*n*-hexane = 1:1), R_f 0.33, mp 184.3−185.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 6H), 3.96 (s, 3H), 4.03 (s, 3H), 4.34 (br, 2H), 7.51 (d, J = 9.2 Hz, 1H), 7.64 (s, 2H), 7.69 (d, J = 9.1 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 8.30 (d, J = 8.8 Hz, 1H). MS (EI) m/z: 368 (M^+, 100%). HRMS (EI) for $C_{20}H_{20}N_2O_5$ (M^+): calcd, 368.1373; found, 368.1374. Anal. ($C_{20}H_{20}N_2O_5 \cdot 0.25H_2O$) C, H, N.

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Supporting Information Available: Spectral data of compounds **5**−**8**, **10**−**11**, **13**−**14**, **16**−**17**, **26**−**29**, and **31**−**32**, experimental procedures for synthesis and biological evaluations, and elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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