Antimitotic Activity of 5-Hydroxy-7-methoxy-2-phenyl-4-quinolones

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We report the synthesis of 5-hydroxy-7-methoxy-2-phenyl-4-quinolones and their biological activity as antitumor agents. These molecules were initially evaluated for their ability to induce cell cycle arrest in the G2/M phase. Compounds that showed significant G2/M cell cycle arrest were tested for antiproliferative activity using both the MTT assay and the NCI in vitro 60 cell line human tumor screen. The 5-hydroxy-7-methoxy-2-phenyl-4-quinolone (**3a**) and 2-(3-fluorophenyl)-5-hydroxy-7-methoxy-4-quinolone (**3f**) were the most active in the cell cycle arrest test whereas **3f** was found to be the most active in the MTT assay. In terms of structural requirements, we found that the presence of a 5-hydroxyl group, a 7-methoxy group, and an unsubstituted N1 were essential for the antimitotic activity. In accordance with the literature, a fluoro group at the 3′- or 2′-position and a methoxy or a chloro group at the 3′-position were found to be highly advantageous for both the cell cycle arrest and the antiproliferative activities.

Introduction

Low molecular weight natural products and analogues have been invaluable agents to induce arrest at specific points in the cell cycle.[1] Compounds such as vincristine, vinblastine, and taxol, which cause mitotic arrest, are of proven clinical utility.[2] These agents act by interfering with cytoskeletal dynamics, predominantly affecting the microtubules required for spindle formation.[3,4]

In this context, 2-phenyl-4-quinolones have been the subject of investigations as a new class of antitumor agents during the past 10 years. Lee and co-workers at the University of North Carolina have made a significant contribution in this field and developed 2-phenyl-4-quinolones with potent antitumor activity. These latter compounds seem to exert their antitumor effect through inhibition of tubulin polymerization involving binding to the colchicine binding site of tubulin.[5−9] Structure−activity studies led to the identification of 2-phenyl-4-quinolones possessing a pyrrolidine moeity at the 6- or 7-position and a 6,7-methylenedioxy and a fluoro or chloro substituent at the 3′-position as promising leads. Working on analogous compounds, Wiese and Pageva have recently reported quantitative structure−activity relationships in a variety of antimitotic 4-quinolones.[10]

Our group has studied the biological activities of flavones and their aza analogues.[11] From our studies and a review of the literature in different biological areas, we note that the most active flavones are often hydroxylated at the 5-position and hydroxylated or methoxylated at the 7-position.[12,13] Interestingly, this substitution pattern is frequently found in naturally occurring flavonoids and confirms that nature has evolved as an elegant solution to many complex biological processes.[14] There is an emerging consensus that the biological potency of 5-hydroxyflavones might be due to the ability of the 5-hydroxybenzofuran-4-one part to behave as an ATP competitive inhibitor by mimicry of the adenine moiety of ATP. The recent high-resolution cocrystallization of flavonoids with two kinases supports this mimicry phenomenon.[15,16]

The aim of the present study was to apply a similar approach to potentiate the antimitotic activity of 2-phenyl-4-quinolones. We therefore chose to target 2-phenyl-4-quinolones containing a hydroxyl at C-5 and a methoxy group at C-7 and possessing variant substitution patterns on the B ring. The C-3′ carbon was particularly targeted since its substitution has been reported as being the most critical for flavone and quinolone cytotoxicity.[6,7,9,12] We synthesized and evaluated 5-hydroxy-7-methoxy-2-phenyl-4-quinolones bearing *N*-substituents and determined the impact of these modifications on antimitotic activity. We also determined the influence of a spacer separating the B ring from the quinolone moiety by introducing a phenyl group, a double bond, or a methylene group as spacers. The phenyl and the double bond are meant to space the B ring from the quinolone moiety while maintaining the conjugation pattern whereas the methylene group is a rather small spacer, which breaks the conjugation between the phenyl group and the quinolone moiety. The structures of targeted compounds are shown in Figure 1.

Chemistry

The synthesis of compounds **3** and **4** is outlined in Scheme 1.[17] Briefly, condensation of 3,5-dimethoxyaniline with substituted benzoyl chlorides or benzoic acids affords amide **1**. Friedel−Crafts acylation with acetyl chloride and using $SnCl_4$ as a catalyst gave the *N*-(2-acetyl-3,5-dimethoxyphenyl)benzamides **2** and a

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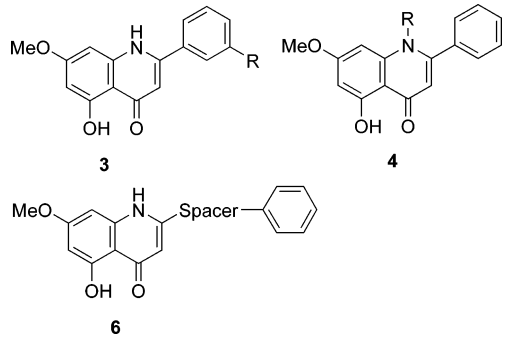
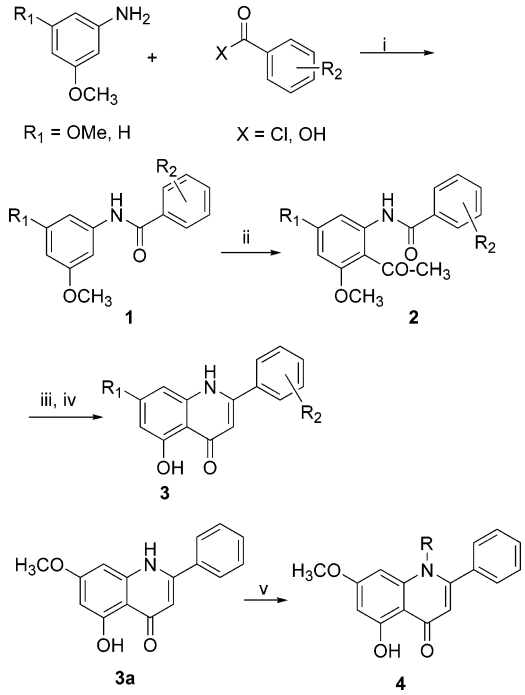


Figure 1. Structures of targeted compounds.

Scheme 1[a]

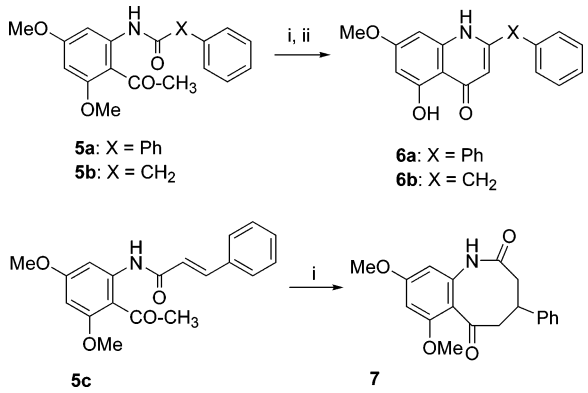


[a] Reagents: (i) X = Cl:Et_3N, THF. X = OH:EDC, HOBT, THF. (ii) Ac−Cl, $SnCl_4$, 1,2-dichloroethane. (iii) *t*-BuOK, *t*-BuOH, reflux. (iv) BBr_3, CH_2Cl_2. (v) K_2CO_3, R−X, DMF.

little amount of its regioisomer *N*-(4-acetyl-3,5-dimethoxy)benzamides **2′**, which can be easily separated. Basic cyclization affords 5,7-dimethoxyquinolones, which are selectively demethylated with a solution of BBr_3 in CH_2Cl_2 to afford 5-hydroxy-7-methoxy-4-quinolones **3**. *N*-Alkylquinolones **4** were obtained by alkylation of 5-hydroxyquinolones **3** as shown in Scheme 1.

Compounds with spacers can be prepared according to Scheme 1 and replacing benzoic acid by phenylbenzoic acid, phenylacetic acid, and cinnamic acid. In such conditions, intermediates **5a**−**c** (Scheme 2) were easily obtained. When subjected to cyclization conditions (*t*-BuOK/*t*-BuOH), derivatives **5a**,**b** were cyclized and selectively demethylated to yield targeted quinolones **6a**,**b**. In the same cyclization conditions, we were not able to convert **5c** to the expected quinolone, and instead, benzazocine **7** was isolated, certainly because the cyclization takes place at the β-carbon of the double bond and not at the carbonyl group. Attempts of other cyclization conditions (NaH/THF, K_2CO_3/acetone) failed to provide quinolone **6c**. The structures of synthesized compounds are summarized in Tables 1 and 2.

Scheme 2[a]



[a] Reagents: (i) *t*-BuOK, *t*-BuOH, reflux. (ii) BBr_3, CH_2Cl_2.

Results and Discussion

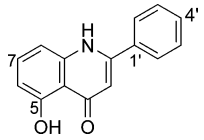
To identify compounds with antimitotic activity, the human leukemic K562 cell line, derived from a patient with acute myeloid leukemia, was exposed to test compounds continuously for 24 h at 5 μM concentration. The cells were then stained with propidium iodide and analyzed by flow cytometry. This test, which determines the distribution of the total population in the different phases of the cell cycle (G0/G1, S, and G2/M), indicates whether the molecule induces cell cycle arrest, but it does not evaluate the compound's cytotoxicity. The latter is measured by cell growth inhibition, which in this study was performed secondarily on those molecules that induced significant cell cycle arrest in the G2/M phase.

A preliminary screening on a set of representative compounds ruled out any cell cycle blocking activity for 5,7-dihydroxy-2-phenyl-4-quinolones and 5-unsubstituted and 4′-substituted quinolones (results not shown). The lead compound was 5-hydroxy-7-methoxy-4-quinolone, which induced a strong G2/M (66%) arrest comparable to that induced by taxol (71%) and a 2-fold higher arrest than that induced by vinblastine, which are both highly effective compounds used in the clinic. Methylation of the 5-hydroxy group (5,7-dimethoxy-2-phenyl-4-quinolones) or deletion of the 7-methoxy group (**3n**) led to a sensitive loss of activity (23 and 21%, respectively).

We decided to substitute the B ring with small substituents, especially at the 3′-position as this has been proven to enhance the efficacy of this type of compound. As shown in Table 1, in which various C-3′ substituents are compared, we can conclude that the antimitotic potency follows this order: hydrogen = fluorine > nitrogen atom > chlorine = methoxy groups. Because 3′- and 5′-positions are equivalent, we thought that their simultaneous substitution with a F, Cl, or OMe would enhance the activity. Unfortunately, as shown in Table 1, the 3′,5′-difluoro analogue (**3i**) did not possess any activity in the cell cycle assay. To confirm that the C′-3 is the most suitable position for substitution, 2′-fluoro and 4′-fluoro derivatives were synthesized and led to this order of potency: 3′-position > 2′ ≫ 4′. Substitution of C-3′ by a nitrogen (**3u**) reduced the cell cycle arrest from 70 to 45%, suggesting that a carbon atom is the most suitable atom at this position.

Insertion of a methylene as a spacer between the 4-quinolone moiety and the B ring led to complete loss

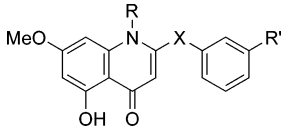
Table 1. Structures and Cell Cycle Arrest Activity of Synthesized Quinolones



	substitution				physical properties		% cells in each phase		
	7	**2′**	**3′**	**4′**	formula	mp (°C)	G0/G1	S	G2/M
3a	OMe	H	H	H	$C_{16}H_{13}NO_3$	257−259	7	26	66
3b	OMe	H	CF_3	H	$C_{17}H_{12}F_3NO_3$	219−221	41	38	20
3c	OMe	H	Cl	H	$C_{16}H_{12}ClNO_3$	250−252	33	35	32
3d	OMe	H	OCF_3	H	$C_{17}H_{12}F_3NO_4$	214−215	32	35	32
3e	OMe	H	OMe	H	$C_{17}H_{15}NO_4$	123−125	28	41	31
3f	OMe	H	F	H	$C_{16}H_{12}FNO_3$	272−274	9	30	60
3g	OMe	H	I	H	$C_{16}H_{12}INO_3$	264−266	44	50	6
3h	OMe	H	Br	H	$C_{16}H_{12}BrNO_3$	*a*	51	37	12
3i	OMe	H	3′,5′-F	H	$C_{16}H_{11}F_2NO_3$	152−154	42	40	18
3j	OMe	H	H	F	$C_{16}H_{13}NO_3$	257−259	54	36	10
3k	OMe	F	H	H	$C_{16}H_{12}FNO_3$	216−218	23	37	41
3l	6,7-OMe	H	H	H	$C_{17}H_{15}NO_4$	*a*	47	45	8
3m	5,6,7-OMe	H	H	H	$C_{18}H_{17}NO_4$	219−221	47	48	5
3n	H	H	H	H	$C_{15}H_{11}NO_2$	157−159	26	52	21
3o	H	H	F	H	$C_{15}H_{10}FNO_2$	172−174	17	33	49
3p	OMe	H	F	OMe	$C_{17}H_{14}FNO_4$	*a*	26	53	20
3q	OMe	H	F	Me	$C_{17}H_{14}FNO_3$	191−193	28	54	18
3r	OMe	H	CH_2Cl	H	$C_{17}H_{14}ClNO_3$	*a*	30	51	18
3s	OMe	H	H	Et	$C_{18}H_{17}NO_3$	230−232	26	48	25
3t	OMe	H	F	F	$C_{16}H_{11}F_2NO_3$	269−271	22	69	9
3u	OMe		nicotinyl		$C_{15}H_{12}N_2O_3$	199−201	24	31	45
			taxol				11	18	71
			vinblastine				33	30	37
			K562 (cells without antimitotic agent)				47	47	6

[a] Amorphous.

Table 2. *N*-Alkylquinolones and Quinolones with Spacers



	substituent			physical properties		% cell in each phase		
entry	R	X	R′	formula	mp (°C)	G0/G1	S	G2/M
5a	H	C_6H_4−	H	$C_{22}H_{17}NO_3$	>300	46	45	9
5b	H	$-CH_2-$	H	$C_{17}H_{15}NO_3$		41	50	9
8a	Me		H	$C_{17}H_{15}NO_3$	187−189	46	50	4
8b	Et		H	$C_{18}H_{17}NO_3$	159−161	43	46	11
8c	Et		F	$C_{18}H_{16}FNO_3$		53	28	19

of activity (9%) suggesting the importance of an aryl-C3-aryl, analogous to biaryl systems that occur in natural products such as colchicine, podophyllotoxine, and combretastatins.[18,19] Replacing the methylene group by a phenyl led to the same loss of activity, which may indicate that steric hindrance is unfavorable.

Because the presence of a trimethoxyphenyl moiety is important for the antitumor activity of several antimitotics such as colchicine and podophylotoxins, we hypothesized that substituting a methoxy at the 6-position (compound **3l**) would lead to active quinolones. Unfortunately, we observed a complete loss of activity (Table 1). Our results show that *N*-unsubstituted quinolones are much more active than *N*-alkyl analogues (Table 2).

On the basis of the cell cycle results, we selected compounds **3a**,**e**,**f**,**k** and tested them for their antiproliferative effect using MTT assays in comparison with vinblastine, a potent antimitotic vinca alkaloid. As shown in Table 3, all compounds are more potent than vinblastine and 2-(3′-fluorophenyl)-5-hydroxy-7-methoxy-4-quinolone (**3f**) is the most active. However, polymerization assays of purified tubulin in vitro and immunocytochemistry of microtubules in cells exposed to these compounds were negative, suggesting that these compounds do not target microtubules (data not shown). When tested in the NCI primary in vitro human tumor cell screen for cytotoxicity, the compounds dis-

Table 3

compound	IC_{50} (μM)[a]	mean GI_{50} (μM)[b]
3a	1.8	8.7
3e	*c*	9.7
3f	0.8	14.5
3k	1.5	9.9
vinblastine	3	*c*

[a] Data obtained from MTT assay on K562 line. IC_{50}, inhibitory concentration 50% values. [b] Data obtained from NCIs in vitro 60 cell line human tumor screen. [b] GI_{50} values (growth inhibitory concentration 50%) are the concentrations that reduced cell growth by 50%. [c] Not available.

played moderate overall cytotoxicities; colon cancer was the most sensitive.[20−22]

In conclusion, this study shows that 5-hydroxy-7-methoxy-4-quinolones induce cell cycle arrest in G2/M and possess a significant antimitotic activity on tumor lines in vitro. These results reinforce previous studies and describe new structural requirements, which will be of use when conceiving new 2-phenyl-4-quinolone anticancer agents. Further evaluation of the cytotoxic activity, the antimitotic mechanism, and the in vivo activity of these compounds is warranted.

Experimental Section

Flow Cytometric Analysis of Cell Cycle. For analysis of DNA content and cell cycle distribution, cells were treated with the test compound at 5 μM for 24 h. After drug exposure, 10^6 cells/mL were resuspended in 2 mL of propidium iodide solution (50 mL/ml), incubated at 4 °C overnight, and then analyzed by flow cytometry. Flow cytometry was performed on a FACScalibur (Becton Dickinson, San Jose, CA). The cell cycle distribution was calculated after exclusion of cell doublets and aggregates on a FL2-area/FL2-width dot plot using Modfit LT 2.0 software (Verity Software Inc, Topsham, ME).

MTT and GTT Cytotoxicity Assays. The cell viability was determined in our laboratory on exponentially growing K562 cells using the MTT assay as previously described.[23] Briefly, asynchronously growing cells were transferred into 96 well cultures plates (Costar, Corning Inc., NY) in 100 μL of medium with a final cell concentration of 3×10^3 cells/well and incubated in media for 24 h. The corresponding drug concentrations were then added to each plate. After 72 h of drug exposure, 20 μL of MTT reagent (Sigma-Aldrich, 5 mg/mL) was added to each well. The cell viability was expressed as the percent of absorbance of treated wells relative to the untreated control wells. The inhibitory concentration 50 (IC_{50}) was defined as the drug concentration resulting in 50% loss of cell viability relative to untreated cells. The assays were performed in triplicate in at least three separate experiments. Compounds with significant antimitotic activity were analyzed at the National Cancer Institute using a similar assay, providing growth inhibitory 50% values (GI_{50} values) for 60 different cell lines representative of most types of human cancers.

Chemistry. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument (200 MHz for ^{1}H, 50 MHz for ^{13}C). Chemical shifts are reported as δ values (ppm) relative to Me_4-Si as an internal standard. EI and DCI mass spectra were recorded on a Fisons Trio 1000 instrument. Elemental analyses were performed by the analytical department of CNRS (Vernaison, France). Thin-layer chromatography (TLC) was carried out using E. Merck silica gel F-254 plates (thickness, 0.25 mm). Flash chromatography was carried out using Merck silica gel 60, 200−400 mesh. All solvents were distilled prior to use. Chemicals and reagents were obtained from either Aldrich or ACROS companies and used according to the manufacturer's specifications.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)benzamides (2).** The preparation from benzoyl chloride derivatives has already been reported.[17] From benzoic acid derivatives: Benzoic acid derivative was dissolved in THF (4 mmol/mL) and treated with EDC (1.1 equiv) and then with HOBT (1.1 equiv). The mixture was stirred at room temperature for 1.5 h, and then, 3,5-dimethoxyaniline (1 equiv) was added. The solution was stirred at room temperature overnight and then hydrolyzed, and the precipitate was filtered off. The filtrate was diluted with ethyl acetate and washed with water and then brine, dried, and evaporated to yield pure benzamides **1**. A solution of **1** was prepared in 1,2-dichloroethane, cooled to 0 °C (ice bath), and successively treated by dropwise adding of $SnCl_4$ (2 equiv) and acetyl chloride (1.1 equiv). After it was stirred for 1.5 h, the solution was poured into crushed ice, extracted with AcOEt, washed with brine, dried over Na_2SO_4, and concentrated. The crude was purified by column chromatography eluted with AcOEt:cyclohexane (1:1) to obtain **2** as a white solid.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)benzamide (2a).** Yield 60%; mp 120 °C. ^{1}H NMR ($CDCl_3$): δ 8.25 (d, 1H, J = 2.0 Hz, H_6); 8.10 (dd, 2H, J_1 = 1.3 Hz, J_2 = 7.6 Hz, $H_{2'}$, $H_{6'}$); 7.55−7.48 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); 6.25 (d, 1H, J = 2.0 Hz, H_4); 3.92 (s, 3H, OCH_3); 3,88 (s, 3H, OCH_3); 2.65 (s, 3H, CH_3CO). MS m/z 300 $(M + 1)^+$. Anal. ($C_{17}H_{17}NO_4$) C, H, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-3-trifluoromethylbenzamide (2b).** Yield 65%; mp 142 °C. ^{1}H NMR ($CDCl_3$): δ 8.35 (sl, 1H, NH); 8.20 (d, 1H, J = 2.3 Hz, H_6); 7.83−7.79 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$); 7.69−7.62 (m, 1H, $H_{5'}$); 6.27 (d, 1H, J = 2.3 Hz, H_4); 3.94 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 2.65 (s, 3H, CH_3CO). MS m/z 367 $(M)^+$. Anal. ($C_{18}H_{16}F_3NO_4$) C, H, F, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-3-chlorobenzamide (2c).** Yield 65%; mp 95 °C. ^{1}H NMR ($CDCl_3$): δ 8.22 (d, 1H, J = 2.3 Hz, H_6); 7.95−7.72 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$); 7.57−7.30 (m, 1H, $H_{5'}$); 6.28 (d, 1H, J = 2.3 Hz, H_4); 3.95 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 2.67 (s, 3H, CH_3CO). MS m/z 333 (M^+). Anal. ($C_{17}H_{16}ClNO_4$) C, H, Cl, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-3-trifluoromethyloxybenzamide (2d).** Yield 69%; mp 105 °C. ^{1}H NMR ($CDCl_3$): δ 8.22 (d, 1H, J = 2.4 Hz, H_6); 7.98−7.93 (m, 2H, $H_{2'}$, $H_{6'}$); 7.55 (t, 1H, J = 8.1 Hz, $H_{5'}$); 7.42−7.38 (m, 1H, $H_{4'}$); 6.26 (d, 1H, J = 2.4 Hz, H_4); 3.95 (s, 3H, OCH_3); 3.93 (s, 3H, OCH_3); 2.65 (s, 3H, CH_3CO). MS m/z 383 (M^+). Anal. ($C_{18}H_{16}F_3NO_5$) C, H, F, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-3-methoxybenzamide (2e).** Yield 74%; mp 122°C. ^{1}H NMR (acetone-d_6): δ 8.20 (d, 1H, J = 2.5 Hz, H_6); 7.55−7.44 (m, 2H, $H_{2'}$, $H_{6'}$); 7.18−7.13 (m, 1H, $H_{5'}$); 6.42 (d, 1H, J = 2.4 Hz, H_4); 6.26−6.24 (m, 1H, $H_{4'}$); 3.91 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 3.77 (s, 3H, OCH_3); 2.59 (s, 3H, CH_3CO). MS m/z 330 $(M + 1)^+$. Anal. ($C_{18}H_{19}NO_5$) C, H, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-3-fluorobenzamide (2f).** Yield 69%; mp 126 °C. ^{1}H NMR ($CDCl_3$): δ 8.23 (d, 1H, J = 2.4 Hz, H_6); 7.84−7.72 (m, 2H, $H_{2'}$, $H_{6'}$); 7.54−7.44 (m, 1H, $H_{4'}$); 7.29−7.24 (m, 1H, $H_{5'}$); 6.26 (d, 1H, J = 2.4 Hz, H_4); 3.93 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 2.64 (s, 3H, CH_3-CO). MS m/z 317 (M^+). Anal. ($C_{17}H_{16}FNO_4$) C, H, F, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-3-iodobenzamide (2g).** Yield 72%; mp 122 °C. ^{1}H NMR ($CDCl_3$): δ 8.18 (d, 1H, J = 2.4 Hz, H_6); 8.0−7.75 (m, 1H, $H_{2'}$); 7.25−7.23 (m, 2H, $H_{4'}$, $H_{6'}$); 6.87 (m, 1H, $H_{5'}$); 6.24 (d, 1H, J = 2.4 Hz, H_4); 3.89 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 2.62 (s, 3H, CH_3CO). MS m/z 425 (M^+). Anal. ($C_{17}H_{16}INO_4$) C, H, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-3-bromobenzamide (2h).** Yield 67%; mp 140 °C. ^{1}H NMR ($CDCl_3$): δ 8.21 (d, 1H, J = 2.2 Hz, H_6); 7.95 (dd, 1H, J_1 = 1.0 Hz, J_2 = 7.8 Hz, $H_{2'}$); 7.68−7.66 (m, 2H, $H_{4'}$, $H_{6'}$); 7.39 (t, 1H, J = 7.8 Hz, $H_{5'}$); 6.26 (d, 1H, J = 2.2 Hz, H_4); 3.93 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 2.64 (s, 3H, CH_3CO). MS m/z 378 (M^+). Calcd ($C_{17}H_{16}$-$BrNO_4$) C, H, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-3,5-difluorobenzamide (2i).** Yield 73%; mp 118 °C. ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 1H, J = 2.4 Hz, H_6); 7.40−7.35 (m, 2H, $H_{2'}$, $H_{6'}$); 7.03−7.00 (m, 1H, $H_{4'}$); 6.27 (d, 1H, J = 2.4 Hz, H_4); 3.91 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 2.65 (s, 3H, CH_3CO). Anal. ($C_{17}H_{15}F_2NO_4$) C, H, F, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-4-fluorobenzamide (2j).** Yield 44%; mp 114 °C. ^{1}H NMR ($CDCl_3$): δ 8.23 (d, 1H, J = 2.2 Hz, H_6); 8.10−8.03 (m, 2H, $H_{2'}$, $H_{6'}$); 7.18 (t, 2H, J = 8,7 Hz, $H_{3'}$, $H_{5'}$); 6.25 (d, 1H, J = 2.3 Hz, H_4); 3.93 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 2.64 (s, 3H, CH_3CO). MS m/z 318 $(M + 1)^+$. Anal. ($C_{17}H_{16}FNO_4$) C, H, F, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-2-fluorobenzamide (2k).** Yield 66%; mp 75 °C. ^{1}H NMR ($CDCl_3$): δ 8.39 (sl, 1H, N−H); 8.12 (d, 1H, J = 2.1 Hz, H_6); 7.98−7,96 (m, 1H, $H_{6'}$); 7.49−7.47 (m, 1H, $H_{4'}$); 7.30−7.14 (m, 1H, $H_{5'}$); 6.90−6.88 (m, 1H, $H_{3'}$); 6.27 (d, 1H, J = 2.1 Hz, H_4); 3.89 (s, 3H, OCH_3); 3.75 (s, 3H, OCH_3); 2.57 (s, 3H, CH_3CO). MS m/z 318 $(M + 1)^+$. Anal. ($C_{17}H_{16}FNO_4$) C, H, F, N.

***N*-(2-Acetyl-3,4,5-trimethoxyphenyl)benzamide (2l).** Yield 15%. ^{1}H NMR ($CDCl_3$): δ 8.4 (s, 1H, H_6); 8.03−7.98 (m, 2H, $H_{2'}$, $H_{6'}$); 7.52−7.48 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); 3.98 (s, 3H,

OCH_3); 3.97 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 2.65 (s, 3H, CH_3CO). MS *m/z* 330 $(M + 1)^+$. Anal. ($C_{18}H_{19}NO_5$) C, H, N.

***N*-(2-Acetyl-3-methoxyphenyl)benzamide (2n).** ^1H NMR ($CDCl_3$): δ 8.08 (dd, 2H, $J_1 = 1.7$ Hz, $J_2 = 7.9$ Hz, $H_{2'}$, $H_{6'}$); 7.60−7.43 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); 7.36−7.28 (m, 1H, $H_{5'}$); 7.20−7.08 (m, 1H, H_6); 6.68 (dd, 1H, $J_1 = 2.3$ Hz, $J_2 = 8.9$ Hz, H_4); 3.87 (s, 3H, OCH_3); 2.65 (s, 3H, CH_3CO). MS *m/z* 269 (M^+). Anal. ($C_{16}H_{15}NO_3$) C, H, N.

***N*-(2-Acetyl-3-methoxyphenyl)-3-fluorobenzamide (2o).** Yield 22%; mp 155 °C. ^1H NMR ($CDCl_3$): δ 7.90−7.76 (m, 3H, H_6, H_5, $H_{6'}$); 7.52−7.49 (m, 2H, $H_{5'}$, $H_{2'}$); 7.31−7.23 (m, 1H, $H_{4'}$); 6.68 (dd, 1H, $J_1 = 2.6$ Hz, $J_2 = 8.9$ Hz, H_4); 3.94 (s, 3H, OCH_3); 2.66 (s, 3H, CH_3CO). MS *m/z* 287 (M^+). Anal. ($C_{16}H_{14}FNO_3$) C, H, F, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-(3-fluoro-4-methoxybenz)amide (2p).** Yield 35%. ^1H NMR ($CDCl_3$): δ 8.21 (d, 1H, $J = 2.4$ Hz, H_6); 7.85−7.76 (m, 1H, $H_{6'}$); 7.10−7.00 (m, 2H, $H_{2'}$, $H_{5'}$); 6.24 (d, 1H, $J = 2.4$ Hz, H_4); 3.89 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 2.65 (s, 3H, CH_3CO). MS *m/z* 347 (M^+). Anal. ($C_{18}H_{18}FNO_5$) C, H, F, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-3-fluoro-4-methylbenzamide (2q).** Yield 28%; mp 132 °C. ^1H NMR ($CDCl_3$): δ 8.49 (d, 1H, $J = 2.4$ Hz, H_6); 8.01−7.95 (m, 1H, $H_{6'}$); 7.63−7.46 (m, 2H, $H_{2'}$, $H_{5'}$); 6.52 (d, 1H, $J = 2.4$ Hz, H_4); 4.03 (s, 3H, OCH_3); 4.01 (s, 3H, OCH_3); 2.65 (s, 3H, CH_3CO); 2.62 (s, 3H, Ph-CH_3). MS *m/z* 331 (M^+). Anal. ($C_{18}H_{18}FNO_4$) C, H, F, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-3-chloromethylbenzamide (2r).** Yield 65%; mp 96 °C. ^1H NMR ($CDCl_3$): δ 8.24 (d, 1H, $J = 2.4$ Hz, H_6); 8.08−7.97 (m, 2H, $H_{2'}$, $H_{6'}$); 7.61−7.48 (m, 2H, $H_{4'}$, $H_{5'}$); 6.26 (d, 1H, $J = 2.4$ Hz, H_4); 4.68 (s, 2H, CH_2Cl); 3.93 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 2.64 (s, 3H, CH_3CO). MS *m/z* 347 (M^+). Anal. ($C_{18}H_{18}ClNO_4$) C, H, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-4-ethylbenzamide (2s).** Yield 32%; mp 115 °C. ^1H NMR ($CDCl_3$): δ 8.24 (d, 1H, $J = 2.2$ Hz, H_6); 7.94 (d, 2H, $J = 7.9$ Hz, $H_{2'}$, $H_{6'}$); 7.32 (d, 2H, $J = 7.9$ Hz, $H_{3'}$, $H_{5'}$); 6.21 (d, 1H, $J = 2.2$ Hz, H_4); 3.90 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 2.70 (q, 2H, $J = 7.6$ Hz, CH_2CH_3); 2.61 (s, 3H, CH_3CO); 1.25 (t, 3H, $J = 7.6$ Hz, CH_3CH_2). MS *m/z* 327 (M^+). Anal. ($C_{19}H_{21}NO_4$) C, H, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-3,4-difluorobenzamide (2t).** Yield 77%; mp 98 °C. ^1H NMR ($CDCl_3$): δ 8.17 (d, 1H, $J = 2.4$ Hz, H_6); 7.89−7.77 (m, 2H, $H_{2'}$, $H_{6'}$); 7.35−7.31 (m, 1H, $H_{5'}$); 6.25 (d, 1H, $J = 2.4$ Hz, H_4); 3.91 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 2.64 (s, 3H, CH_3CO). MS *m/z* 335 (M^+). Anal. ($C_{17}H_{15}F_2NO_4$) C, H, F, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)nicotinamide (2u).** Yield 48%; mp 136 °C. ^1H NMR ($CDCl_3$): δ 9.29 (d, 1H, $J = 1.6$ Hz, $H_{2'}$); 8.78 (dd, 1H, $J_1 = 1.6$ Hz, $J_2 = 4.9$ Hz, $H_{4'}$); 8.31 (ddd, 1H, $J_1 = 1.6$ Hz, $J_2 = 2.3$ Hz, $J_3 = 8.0$ Hz, $H_{6'}$); 8.21 (d, 1H, $J = 2.4$ Hz, H_6); 7.47 (dd, 1H, $J_1 = 4.8$ Hz, $J_2 = 7.8$ Hz, $H_{5'}$); 6.27 (d, 1H, $J = 2.4$ Hz, H_4); 3.93 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 2.64 (s, 3H, CH_3CO). MS *m/z* 301 $(M + 1)^+$. Anal. ($C_{16}H_{16}N_2O_4$) Calcd C, H, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-4-phenylbenzamide (4a).** Yield 37%; mp 165 °C. ^1H NMR ($CDCl_3$): δ 8.29 (d, 1H, $J = 2.4$ Hz, H_6); 8.15−8.11 (m, 2H, $H_{2'}$, $H_{6'}$); 7.76−7.63 (m, 4H, $H_{3'}$, $H_{5'}$, $H_{2''}$, $H_{6''}$); 7.51−7,39 (m, 3H, $H_{3''}$, $H_{4''}$, $H_{5''}$); 6.26 (d, 1H, $J = 2.4$ Hz, H_4); 3.94 (s, 3H, OCH_3); 3.91 (s, 3H, OCH_3); 2.65 (s, 3H, CH_3CO). MS *m/z* 376 $(M + 1)^+$. Anal. ($C_{23}H_{21}NO_4$) C, H, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)benzylamide (4b).** Yield 45%. ^1H NMR ($CDCl_3$): δ 7.98 (d, 1H, $J = 2.4$ Hz, H_6); 7.38−7.30 (m, 5H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$); 6.18 (d, 1H, $J = 2.4$ Hz, H_4); 3,84 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 3.55 (s, 2H, CH_2); 2.54 (s, 3H, CH_3CO). Anal. ($C_{18}H_{19}NO_4$) C, H, N.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)-*trans*-cinnamide (4c).** Yield 31%; mp 117 °C. ^1H NMR ($CDCl_3$): δ 8.45 (sl, 1H, NH); 8.19 (d, 1H, $J = 2.4$ Hz, H_6); 7.73 (d, 1H, $J = 15.6$ Hz, H_β); 7.60−7.55 (m, 2H, $H_{2'}$, $H_{6'}$); 7.40−7.37 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); 6.59 (d, 1H, $J = 15.6$ Hz, H_α); 6.22 (d, 1H, $J = 2.4$ Hz, H_4); 3.91 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 2.62 (s, 3H, CH_3CO). MS *m/z* 326 $(M + 1)^+$. Anal. ($C_{20}H_{21}NO_4$) C, H, N.

5-Hydroxy-7-methoxy-4-quinolones (3). To a stirred solution of **2** in *t*-BuOH (5 mL/mmol) under N_2 atmosphere was added *t*-BuOK (5 equiv). The reaction mixture was then refluxed for 20 h and then cooled to room temperature before it was poured into a saturated solution of NH_4Cl. The solution was extracted with AcOEt, dried over Na_2SO_4, and evaporated and subjected to selective demethylation. A solution of 5,7-dimethoxyquinolone in anhydrous CH_2Cl_2 (5 mL/mmol) was cooled to 0 °C (ice bath) and treated with a solution of BBr_3 (1 M solution in CH_2I_2, 1.5 equiv). The mixture was stirred for 24 h at room temperature and then poured into iced water. After extraction with CH_2Cl_2, washing with H_2O, drying, and CH_2Cl_2 evaporation, the crude was purified by column chromatography using a gradient of cyclohexane:AcOEt (1:1 to 3:7) to yield quinolones **3** and **5** as yellow solids.

5-Hydroxy-7-methoxy-2-phenyl-4-quinolone (3a). Yield 80%. ^1H NMR (acetone-d_6): δ 13,35 (s, 1H, OH); 7.85−7.80 (m, 2H, $H_{2'}$, $H_{6'}$); 7.59−7.56 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); 6.61 (d, 1H, $J =$ 2.1 Hz, H_8); 6.27 (s, 1H, H_3); 6.18 (d, 1H, $J = 2.2$ Hz, H_6); 3.84 (s, 3H, OCH_3). MS *m/z* 268 $(M + 1)^+$. Anal. ($C_{16}H_{13}NO_3$) C, H, N.

5-Hydroxy-7-methoxy-2-(3-trifluoromethylphenyl)-4-quinolone (3b). Yield 75%. ^1H NMR (CD_3OD): δ 7.96−7.66 (m, 4H, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$); 6.52 (d, 1H, $J = 2.1$ Hz, H_8); 6.30 (s, 1H, H_3); 6.27 (d, 1H, $J = 1.9$ Hz, H_6); 3.92 (s, 3H, OCH_3). MS *m/z* 335 (M^+). Anal. ($C_{17}H_{12}F_3NO_3$) C, H, F, N.

2-(3-Chlorophenyl)-5-hydroxy-7-methoxy-4-quinolone (3c). Yield 65%. ^1H NMR ($CDCl_3$): δ 7.58−7.45 (m, 2H, $H_{2'}$, $H_{6'}$); 7.38−7.31 (m, 2H, $H_{4'}$, $H_{5'}$); 6.89 (d, 1H, $J = 2$ Hz, H_8); 6.67 (s, 1H, H_3); 6.45 (d, 1H, $J = 2$ Hz, H_6); 3.79 (s, 3H, OCH_3). MS *m/z* 301 (M^+). Anal. ($C_{16}H_{12}ClNO_3$) C, H, Cl, N.

5-Hydroxy-7-methoxy-2-(3-trifluoromethyloxyphenyl)-4-quinolone (3d). Yield 70%. ^1H NMR (acetone-d_6): δ 7,89−7,68 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$); 7.56−7.52 (m, 1H, $H_{5'}$); 6.60 (d, 1H, $J = 1.2$ Hz, H_8); 6.32 (s, 1H, H_3); 6.19 (d, 1H, $J = 1.2$ Hz, H_6); 3.84 (s, 3H, OCH_3). MS *m/z* 351 (M^+). Anal. ($C_{17}H_{12}F_3NO_4$) C, H, F, N.

5-Hydroxy-7-methoxy-2-(3-methoxyphenyl)-4-quinolone (3e). Yield 35%. ^1H NMR (CD_3OD): δ 7.49−7.31 (m, 3H, $H_{2'}$, $H_{5'}$, $H_{6'}$); 7,14−7.10 (m, 1H, $H_{4'}$); 6.57 (d, 1H, $J = 2.2$ Hz, H_8); 6.29 (s, 1H, H_3); 6.19 (d, 1H, $J = 2.2$ Hz, H_6); 3.86 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3). Anal. ($C_{17}H_{15}NO_4$) C, H, N.

2-(3-Fluorophenyl)-5-hydroxy-7-methoxy-4-quinolone (3f). Yield 71%. ^1H NMR (DMSO-d_6): δ 11.89 (sl, 1H, OH); 7.73−7.60 (m, 2H, $H_{2'}$, $H_{6'}$); 7.46−7.43 (m, 2H, $H_{4'}$, $H_{5'}$); 6.64 (d, 1H, $J = 1.3$ Hz, H_8); 6.35 (s, 1H, H_3); 6.20 (d, 1H, $J = 1.2$ Hz, H_6); 3,81 (s, 3H, OCH_3). MS *m/z* 286 $(M + 1)^+$. Anal. ($C_{16}H_{12}FNO_3$) C, H, F, N.

5-Hydroxy-2-(3-iodophenyl)- 7-methoxy-4-quinolone (3g). Yield 52%. ^1H NMR (DMSO-d_6): δ 8.18−8.16 (m, 1H, $H_{2'}$); 7.93 (dd, 1H, $J_1 = 1,7$ Hz, $J_2 = 8$ Hz, $H_{6'}$); 7.83 (dd, 1H, $J_1 = 1.7$ Hz, $J_2 = 7.6$ Hz, $H_{4'}$); 7.36 (t, 1H, $J = 7.7$ Hz, $H_{5'}$); 6.61 (d, 1H, $J = 2.1$ Hz, H_8); 6.17 (d, 1H, $J = 2.1$ Hz, H_6); 3.81 (s, 3H, OCH_3). MS *m/z* 394 $(M + 1)^+$. Anal. ($C_{16}H_{12}INO_3$). Calcd: C, 48.88; H, 3.08; I, 32.28; N, 3.56. Found: C, 48.51; H, 3.10; I, 31.24; N, 3.53.

2-(3-Bromophenyl)-5-hydroxy-7-methoxy-4-quinolone (3h). Yield 52%. ^1H NMR (DMSO-d_6): δ 8.05 (sl, 1H, NH); 7.82−7.75 (m, 2H, $H_{2'}$, $H_{6'}$); 7.60−7.51 (m, 2H, $H_{4'}$, $H_{5'}$); 6.51 (d, 1H, $J = 2.1$ Hz, H_8); 6.31 (s, 1H, H_3); 6.23 (d, 1H, $J = 2.1$ Hz, H_6); 4.05 (s, 3H, OCH_3). MS *m/z* 346 $(M + 2)^+$. Anal. ($C_{16}H_{12}BrNO_3$). Calcd: C, 55.51; H, 3.49; Br, 23.08; N, 4.05. Found: C, 55.35; H, 3.42; Br, 22.14; N, 4.00.

2-(3,5-Difluorophenyl)-5-hydroxy-7-methoxy-4-quinolone (3i). Yield 55%. ^1H NMR ($CDCl_3$): δ 7.82 (s, 1H, H_3); 7.59−7.54 (m, 2H, $H_{2'}$, $H_{6'}$); 7.42 (d, 1H, $J = 2.3$ Hz, H_8); 7.24−7.19 (m, 1H, $H_{4'}$); 6.80 (d, 1H, $J = 2.2$ Hz, H_6); 4.31 (s, 3H, OCH_3). MS *m/z* 303 (M^+). Anal. ($C_{16}H_{11}F_2NO_3$) C, H, F, N.

2-(4-Fluorophenyl)-5-hydroxy-7-methoxy-4-quinolone (3j). Yield 55%. ^1H NMR ($CDCl_3$): δ 7,58−7,56 (m, 2H, $H_{2'}$, $H_{6'}$); 7,25 (d, 1H, $J = 2,2$ Hz, H_8); 7,11 (t, 2H, $J = 8,2$ Hz, $H_{3'}$, $H_{5'}$); 6,37 (s, 1H, H_3); 6,19 (d, 1H, $J = 2,2$ Hz, H_6); 3,76 (s, 3H, OCH_3). MS *m/z* 286 $(M + 1)^+$. Anal. ($C_{16}H_{12}FNO_3$) C, H, F, N.

2-(2-Fluorophenyl)-5-hydroxy-7-methoxy-4-quinolone (3k). Yield 47%. ^1H NMR (DMSO): δ 12.59 (sl, 1H, O−H); 12.0 (sl, 1H, N−H); 7,71−7,60 (m, 2H, $H_{4'}$, $H_{6'}$); 7.47−7.38 (m, 2H,

$H_{3'}$, $H_{5'}$); 6.51 (d, 1H, J = 2.3 Hz, H_8); 6.20 (d, 1H, J = 2.2 Hz, H_6); 6.12 (s, 1H, H_3); 3.79 (s, 3H, OCH_3). MS m/z 286 ($M + 1$)$^+$. Anal. ($C_{16}H_{12}FNO_3$) C, H, F, N.

6,7-Dimethoxy-5-hydroxy-2-phenyl-4-quinolone (3l). Yield 15%. ^{1}H NMR (DMSO-d_6): δ 8.04−8.01 (m, 2H, $H_{2'}$, $H_{6'}$); 7.55−7.51 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); 7.10 (s, 1H, H_3); 7.01 (s, 1H, H_8); 3.95 (s, 3H, OCH_3); 3.72 (s, 3H, OCH_3). MS m/z 298 ($M + 1$)$^+$. Anal. ($C_{17}H_{15}NO_4$) C, H, N.

2-Phenyl-5,6,7-trimethoxy-4-quinolone (3m). Yield 49%. ^{1}H NMR ($CDCl_3$): δ 8.06−8.01 (m, 2H, $H_{2'}$, $H_{6'}$); 7.49−7.45 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); 7.30 (s, 1H, H_3); 7.11 (s, 1H, H_8); 4.19 (s, 3H, OCH_3); 4.01 (s, 3H, OCH_3); 3.96 (s, 3H, OCH_3). MS m/z 312 ($M + 1$)$^+$. Anal. ($C_{18}H_{17}NO_4$) C, H, N.

5-Hydroxy-2-Phenyl-4-quinolone (3n). Yield 80%. ^{1}H NMR (CD_3OD): δ 8.29 (d, 1H, J = 9.1 Hz, H_8); 7.94−7.89 (m, 2H, $H_{2'}$, $H_{6'}$); 7.71−7.66 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); 7.41 (dd, 1H, J_1 = 2.3 Hz, J_2 = 9 Hz, H_7); 7.33−7.27 (dd, 1H, J_1 = 2.2 Hz, J_2 = 9.1 Hz, H_6); 7.15 (s, 1H, H_3). MS m/z 238 ($M + 1$)$^+$. Anal. ($C_{15}H_{11}NO_2$) C, H, N.

2-(3-Fluorophenyl)-5-hydroxy-2-phenyl-4-quinolone (3o). Yield 70%. ^{1}H NMR (CD_3OD): δ 8.28 (d, 1H, J = 9.1 Hz, H_8); 7.74−7,68 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{6'}$); 7.51−7.44 (m, 1H, $H_{5'}$); 7.40 (dd, 1H, J_1 = 2.1 Hz, J_2 = H_7); 7.33−7.28 (dd, 1H, J_1 = 2.2 Hz, J_2 = 9.1 Hz, H_6); 7.14 (s, 1H, H_3). MS m/z 256 ($M + 1$)$^+$. Anal. ($C_{15}H_{10}FNO_2$) C, H, F, N.

2-(3-Fluoro-4-methoxyphenyl)-5-hydroxy-7-methoxy-4-quinolone (3p). Yield 15%. ^{1}H NMR (CD_3OD): δ 8.54 (d, 1H, J = 2.1 Hz, $H_{6'}$); 7.61−7.56 (m, 2H, $H_{2'}$, $H_{5'}$); 6.63 (d, 1H, J = 3.1 Hz, H_8); 6.30 (s, 1H, H_3); 6.24 (d, 1H, J = 3.1 Hz, H_6); 3.85 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3). MS m/z 316 ($M + 1$)$^+$. Anal. ($C_{17}H_{14}FNO_4$) C, H, F, N.

2-(3-Fluoro-4-methylphenyl)-5-hydroxy-7-methoxy-4-quinolone (3q). Yield 70%. ^{1}H NMR (DMSO-d_6): δ 11.81 (sl, 1H, OH); 7.69−7,45 (m, 3H, $H_{2'}$, $H_{5'}$, $H_{6'}$); 6.64 (d, 1H, J = 1.8 Hz, H_8); 6.34 (s, 1H, H_3); 6.19 (d, 1H, J = 1.8 Hz, H_6); 3.81 (s, 3H, OCH_3); 2.32 (s, 3H, CH_3). MS m/z 300 ($M + 1$)$^+$. Anal. ($C_{17}H_{14}FNO_3$) C, H, F, N.

2-(3-Chloromethylphenyl)-5-hydroxy-7-methoxy-4-quinolone (3r). Yield 21%. ^{1}H NMR (CD_3OD): δ 7.81−7.53 (m, 4H, $H_{2'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$); 6.96 (d, 1H, J = 2.2 Hz, H_8); 6.60 (s, 1H, H_3); 6.25 (d, 1H, J = 2.2 Hz, H_6); 4.67 (s, 2H, CH_2Cl); 3.86 (s, 3H, OCH_3). Anal. ($C_{17}H_{14}ClNO_3$) C, H, Cl, N.

2-(4-Ethylphenyl)-5-hydroxy-7-methoxy-4-quinolone (3s). Yield 26%. ^{1}H NMR (CD_3OD): δ 7.66 (d, 2H, J = 8.2 Hz, $H_{2'}$, $H_{6'}$); 7.40 (d, 2H, J = 8.1 Hz, $H_{3'}$, $H_{5'}$); 6.58 (d, 1H, J = 2.2 Hz, H_8); 6.30 (s,1H, H_3); 6.23 (d, 1H, J = 2,1 Hz, H_6); 3.86 (s, 3H, OCH_3); 2,72 (q, 2H, J = 7,6 Hz, CH_2CH_3); 1.27 (t, 3H, J = 7,6 Hz, CH_3CH_2). MS m/z 296 ($M + 1$)$^+$. Anal. ($C_{18}H_{17}NO_3$) C, H, N.

2-(3,4-Difluorophenyl)-5-hydroxy-7-methoxy-4-quinolone (3t). Yield 73%. ^{1}H NMR (DMSO-d_6): δ 11.89 (sl, 1H, OH); 8.04−7.95 (m, 1H, $H_{6'}$); 7.71−7.63 (m, 2H, $H_{2'}$, $H_{5'}$); 6.63 (d, 1H, J = 2,0 Hz, H_8); 6,35 (s, 1H, H_3); 6.20 (d, 1H, J = 2,1 Hz, H_6); 3.81 (s, 3H, OMe). MS m/z 303 (M^+). Anal. ($C_{16}H_{11}F_2NO_3$) C, H, F, N.

5-Hydroxy-7-methoxy-2-(3-nicotinyl)-4-quinolone (3u). Yield 35%. ^{1}H NMR (DMSO-d_6): δ 12.0 (sl, 1H, OH); 9.0 (d, 1H, J = 1.5 Hz, $H_{2'}$); 8.76 (dd, 1H, J_1 = 1.5 Hz, J_2 = 4.6 Hz, $H_{4'}$); 8.23 (ddd, 1H, J_1 = J_2 = 1.7 Hz, J_3 = 8.1 Hz, $H_{6'}$); 7.61 (dd, 1H, J_1 = 4.8 Hz, J_2 = 7.8 Hz, $H_{5'}$); 6.61 (d, 1H, J = 2.6 Hz, H_8); 6.38 (s, 1H, H_3); 6.22 (d, 1H, J = 2.6 Hz, H_6); 3.82 (s, 3H, OCH3). MS m/z 269 ($M + 1$)$^+$. Anal. ($C_{15}H_{12}N_2O_3$) C, H, N.

***N*-Alkyl-5-hydroxy-7-methoxy-4-quinolones (4).** To a stirred solution of quinolone **3** in anhydrous DMF (5 mL/mmol) were successively added the alkyl halide (1.5 equiv) and K_2CO_3 (3 equiv). The reaction mixture was stirred at room temperature for 2 h and then heated at 80 °C for 3 h. After it was heated, the reaction mixture was poured into water, extracted with EtOAC, and concentrated. Purification by chromatography column eluted with cyclohexane:AcOEt (9:1) or by preparative TLC (cyclohexane: AcOEt 7:3) afforded *N*-alkylquinolones **7** as white solids.

5-Hydroxy-7-methoxy-1-methyl-2-phenyl-4-quinolone (4a). Yield 56%. ^{1}H NMR ($CDCl_3$): δ 7.53−7.50 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); 7.41−7,38 (m, 2H, $H_{2'}$, $H_{6'}$); 6.42 (d, 1H, J = 2.1 Hz, H_8); 6.32 (d, 1H, J = 2.1 Hz, H_6); 6.13 (s, 1H, H_3); 3.90 (s, 3H, OCH_3); 3.49 (s, 3H, NCH_3). Anal. ($C_{17}H_{15}NO_3$) C, H, N.

1-Ethyl-5-hydroxy-7-methoxy-2-phenyl-4-quinolone (4b). Yield 21%. ^{1}H NMR ($CDCl_3$): δ 7.52−7.48 (m, 3H, $H_{3'}$, $H_{4'}$, $H_{5'}$); 7.40−7.35 (m, 2H, $H_{2'}$, $H_{6'}$); 6.41 (d, 1H, J = 2.1 Hz, H_8); 6.35 (d, 1H, J = 2.1 Hz, H_6); 6.06 (s, 1H, H_3); 3.94 (q, 2H, J = 7.1 Hz, N−CH_2); 3,89 (s, 3H, OCH_3); 1.26 (t, 3H, J = 7.1 Hz, CH_3CH_2). MS m/z 295 (M^+). Anal. ($C_{18}H_{17}NO_3$) C, H, N.

1-Ethyl-2-(3-fluorophenyl)-5-hydroxy-7-methoxy-4-quinolone (4c). Yield 22%. ^{1}H NMR ($CDCl_3$): δ 7.55−7.34 (m, 1H, $H_{6'}$); 7.22−7.14 (m, 3H, $H_{2'}$, $H_{4'}$, $H_{5'}$); 6.41 (d, 1H, J = 1.9 Hz, H_8); 6.35 (d, 1H, J = 1.7 Hz, H_6); 6.04 (s, 1H, H_3); 3.94 (q, 2H, J = 7.1 Hz, NCH_2); 3.89 (s, 3H, OCH_3); 1.27 (t, 3H, J = 7.1 Hz, CH_3CH_2). MS m/z 313 (M^+). Anal. ($C_{18}H_{16}FNO_3$) C, H, F, N.

2-(1,4-Biphenyl)-5-hydroxy-7-methoxy-4-quinolone (6a). Yield 25%. ^{1}H NMR ($CDCl_3$): δ 7.74−7.72 (m, 2H, $H_{2'}$, $H_{6'}$); 7.63−7.59 (m, 2H, $H_{2''}$, $H_{6''}$); 7.53−7.41 (m, 5H, $H_{3'}$, $H_{5'}$, $H_{3''}$, $H_{4''}$, H5″); 6.41 (s, 1H, H_3); 6.34 (d, 1H, J = 2.5 Hz, H_8); 6.27 (d, 1H, J = 2.5 Hz, H_6); 3.87 (s, 3H, OCH_3). MS m/z 344 ($M + 1$)$^+$. Anal. ($C_{22}H_{17}NO_3$) C, H, N.

2-Benzyl-5-hydroxy-7-methoxy-4-quinolone (6b). Yield 35%. ^{1}H NMR (CD_3OD): δ 7.40−7.16 (m, 6H, $H_{2'-6'}$, H_3); 6.36 (d, 1H, J = 2.2 Hz, H_8); 6.29 (d, 1H, J = 2.2 Hz, H_6); 3.84 (s, 3H, OCH_3); 2.39 (s, 2H, CH_2). MS m/z 282 ($M + 1$)$^+$. Anal. ($C_{17}H_{15}NO_3$) C, H, N.

7,9-Dimethoxy-4-phenylbenzazocin-3,6-dione (7). Yield 10%. ^{1}H NMR (DMSO-d_6): δ 9.75 (sl, 1H, NH); 7.29−7.20 (m, 5H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$); 6.58 (d, 1H, J = 1.7 Hz, H_{10}); 6.28 (d, 1H, J = 1.7 Hz, H_8); 3.79 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3); 3.0−2.86 (m, 2H, $COCH_2CHPh$); 2.68 (dd, 2H, J_1 = 3.7 Hz, J_2 = 9.1 Hz, $NHCOCH_2CHPh$); 2.28 (bd, 1H, J = 11.8 Hz, CH−Ph). MS m/z 326 ($M + 1$)$^+$. Anal. ($C_{19}H_{19}NO_4$) C, H, N.

Supporting Information Available: Elemental analyses of target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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