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An Efficient Synthesis of 1-Alkyl-2-phenyl-4-quinolones from 2-Halobenzoic Acids

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1-Methyl-2-phenyl-4-quinolones are naturally occurring alkaloids isolated from the leaves and stems of the plant family *Rutaceae*.[1] They have drawn considerable interest because of their potent pharmacological activities that include antifungal[1a] and antitumor activity,[2] inhibition of acetylcholinesterase (AChE),[3] and antimutagenic effect.[4]

Several methods have been developed to synthesize 1-alkyl-2-phenyl-4-quinolones from 2'-substituted acetophenones, anilines, and 2-halobenzoyl chlorides as starting materials.[5] The reaction of *N*-methylisatoic anhydride with the lithium enolate of an 4'-methoxyacetophenone afforded the 1-methyl-2-phenyl-4-quinolone in a short sequence, but the yield was low.[6] *N*-(2-Acetylphenyl)benzamides, prepared by Friedel-Crafts acylation of *N*-phenyl benzamides with acetyl chloride[7] or benzoylation of 2'-aminoacetophenones with benzoyl chlorides,[8] were cyclized with potassium *t*-butoxide to yield 2-aryl-4-quinolones, which were further alkylated with alkyl iodides to give 1-alkyl-2-aryl-4-quinolones. However, acylation was accompanied by formation of the regioisomer and alkylation yielded a mixture of *N*-alkylquinolones as the main products together with 4-alkoxyquinolines as minor products. On the other hand, *N*-methylated (2-acetylphenyl)benzamides, prepared from 2'-(*N*-methylamino)acetophenones and benzoyl chlorides, could be cyclized with sodium hydride in DMF to afford the 1-methyl-2-phenyl-4-quinolones in moderate yields.[9]

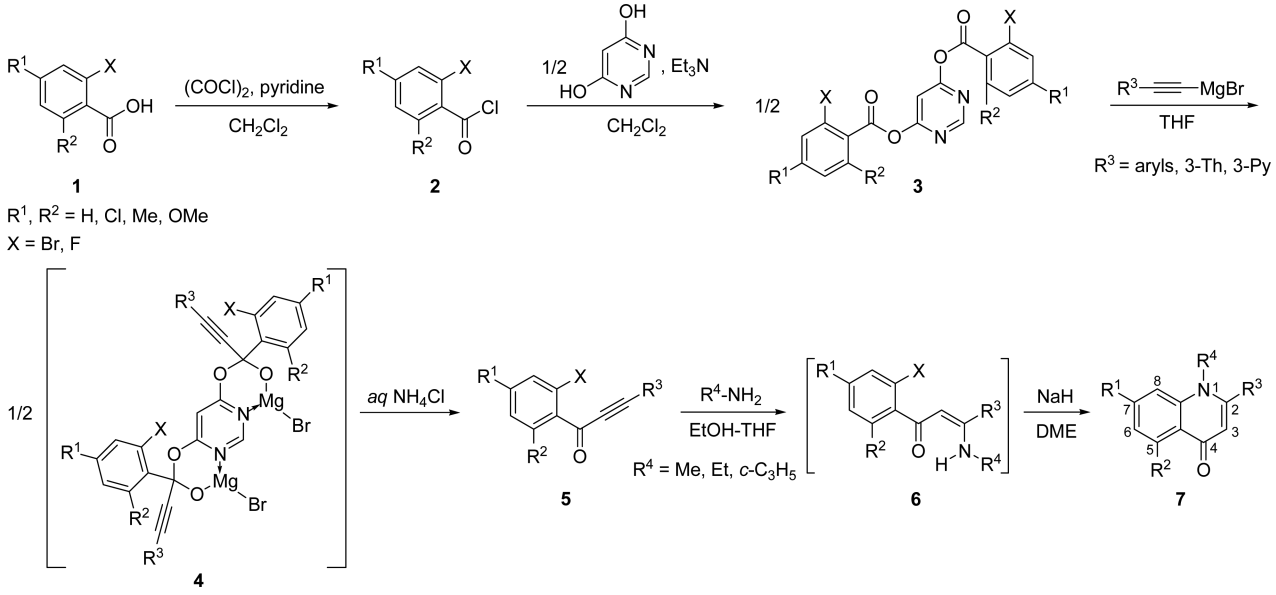
2'-(*N*-Alkylamino)chalcones, prepared by aldol condensation of 2'-aminoacetophenones and benzaldehydes followed by *N*-alkylation with alkyl halides, upon treatment with polystyrene-supported selenenyl bromide in the presence of $ZnCl_2$ afforded 2,3-dihydro-3-polystyrene-supported selenenyl-4-quinolones. These compounds were subsequently oxidized with H_2O_2 and eliminated to give 1-alkyl-2-phenyl-4-quinolones.[10] Palladium-catalyzed carbonylative coupling of 2-iodo-*N*-ethylaniline with phenylacetylene occurred smoothly to give a mixture of the corresponding enamine and the desired cyclic quinolone. Further cyclization of the enamine intermediate with sodium hydride in refluxing THF led to 1-ethyl-2-phenyl-4-quinolone.[11] Palladium-catalyzed tandem amination of 2-bromoalkynones, obtained by Sonogashira cross-coupling of arylacetylenes and 2-bromobenzoyl chlorides, with arylamines in refluxing dioxane was effective for the synthesis of 1-aryl-2-phenyl-4-quinolones.[12] Similarly, treatment of 2-halophenyl alkynones with arylamines afforded the corresponding 3-(*N*-arylamino) α,β-unsaturated ketones by conjugate addition. These compounds were then cyclized with K_2CO_3 in refluxing DMF for 52 h[13] or K_2CO_3/CuI and DMEDA as a ligand in DMSO[14] to give 1-phenyl-2-aryl-4-quinolones, but the scope of the synthesis of 1-alkyl-2-phenyl-4-quinolones was not fully investigated.

Although several methods to synthesize 1-alkyl-2-phenyl-4-quinolones have been reported, they often suffer from harsh reaction conditions, multiple steps, and low yields. As part of an extension of our studies on azaflavonoids as potential drug candidates,[15] we report that novel 1-alkyl-2-phenyl-4-quinolones can be efficiently synthesized in high overall yields from 2-halobenzoic acids under relatively mild conditions.

2-Halobenzoyl chlorides (**2**) were efficiently prepared by treating 2-halobenzoic acids (**1**) with oxalyl chloride in the presence of pyridine in dichloromethane between 0 °C and 25 °C (Scheme 1). After stirring overnight, dichloromethane was evaporated, the residue was dissolved in anhydrous THF, and pyridinium hydrochloride was removed by filtration. The condensed residue was purified by vacuum distillation to give **2** (R^1=H, R^2=H, X=Br; 87%, R^1=Cl, R^2=H, X=Br; 97%, R^1=Me, R^2=H, X=Br; 93%, R^1=OMe, R^2=H, X=F; 75%, R^1=H, R^2=OMe, X=F; 91%).

Novel 4,6-pyrimidyl di(2-halobenzoates) (**3**) were prepared by acylation of 2 equiv of **2** with 4,6-dihydroxypyrimidine in the presence of 2 equiv of triethylamine in dichloromethane at 25 °C according to our previous similar method.[16] After evaporating dichloromethane, the mixture was dissolved in anhydrous THF, and triethylamine hydrochloride was removed by filtration. The condensed residue was purified by short-pathway silica gel (Davisil®, pH = 7) column chromatography or recrystallization from 75% EtOAc/*n*-hexane to give **3** (R^1=H, R^2=H, X=Br; 87%, R^1=Cl, R^2=H, X=Br; 85%, R^1=Me, R^2=H, X=Br; 94%, R^1=OMe, R^2=H, X=F; 87%, R^1=H, R^2=OMe, X=F; 93%).

Successful synthesis of 1-(2-halophenyl)-3-(hetero)aryl-2-propyn-1-ones (**5**) was accomplished by reacting 1 equiv of **3** with 2 equiv of (hetero)arylethynylmagnesium bromide. The addition of 2 equiv of (hetero)arylethynylmagnesium bromide, generated from (hetero)arylacetylene and EtMgBr in THF for 0.5 h at 0 °C, to a solution of 1 equiv of **3** in THF at 0 °C led to the formation of a precipitate. The intermediate was hydrolyzed with saturated NH_4Cl solution to give **5**



Scheme 1

in 75-89% yields. The reaction seems to proceed *via* a 6-membered chelate **4**. Side products such as the corresponding alcohols, due to over-addition of (hetero)arylethynyl magnesium bromides to **5**, were not observed regardless of steric hindrance from 2-halo group in **3**.

The synthesis of 1-alkyl-2-phenyl-4-quinolones was carried out in a one-pot sequence of 1,4-addition of alkylamines to **5** and subsequent cyclization of the intermediate **6**. For example, the addition of methylamine to a solution of 1-(2-bromophenyl)-3-phenyl-2-propyn-1-one (**5a**) in EtOH/THF afforded the corresponding addition product **6a**, which was identified by some spectral data [characteristic values: ^{1}H NMR δ 11.14 (NH), 5.39 (=CH), 2.86 (CH_3); ^{13}C NMR δ 31.6 (CH_3); FT-IR 3445 (NH), 1598 (C=O) cm^{-1}; MS *m/z* 315 (M^+)]. After evaporation of the solvent, subsequent treatment of **6a** with sodium hydride in DME at 25 °C and further heating at 80 °C for 6 h gave 1-methyl-2-phenyl-4-quinolone (**7a**) by intramolecular nucleophilic substitution in 85% yield.

As shown in Table 1, various 1-alkyl-2-phenyl-4-quinolones were synthesized in high overall yields (39-68%) from starting material **1**. The presence of electron-withdrawing group, such as 7-chloro (**7c**, **7d**) in the condensed benzene ring accelerated the rate of cyclization. Moreover, a 2-fluoro group in **5** was more readily substituted than a 2-bromo group, which indicates that the initial addition of the enamino anion of **6** is slow. The reaction worked well regardless of the type and position of electron-withdrawing group (**7h**) and electron-donating groups (**7b**, **7c**, **7e**, **7f**, **7i**, **7j**) of the substituted phenyl rings at the 2-position under these reaction conditions. Furthermore, this method was applicable to the synthesis of **7** containing heteroaromatic groups, such as 3-thienyl (**7d**) and 3-pyridyl group (**7g**), in place of the substituted phenyl rings at the 2-position.

In conclusion, the present method offers an efficient synthesis of 1-alkyl-2-phenyl-4-quinolones from 2-halobenzoic acids. It has the advantages with respect to (i) synthesis of 2 equiv of alkynones **5** from 1 equiv of 4,6-pyrimidyl di(2-halobenzoates) **3**, (ii) synthesis of versatile 1-alkyl-2-phenyl-4-quinolones in high overall yields, and (iii) use of readily available and cheap starting materials. Therefore, this method could be utilized as a practical synthesis of 1-alkyl-2-phenyl-4-quinolones.

Experimental Section

Preparation of 4,6-Pyrimidyl di(2-bromo-4-chlorobenzoate) (3c). 2-Bromo-4-chlorobenzoyl chloride (2.54 g, 10.0 mmol) was added to a suspension of 4,6-dihydroxypyrimidine (560 mg, 5.0 mmol) and triethylamine (1.4 mL, 10.0 mmol) in dichloromethane (40 mL) at 25 °C. After stirring for 3 h, dichloromethane was evaporated *in vacuo*. The mixture was dissolved in anhydrous THF and triethylamine hydrochloride was removed by filtration. The residue was recrystallized twice from 75% EtOAc/*n*-hexane to give **3c** (2.32 g, 85%). mp 134-136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.11 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 0.8 Hz, 2H), 7.47 (dd, J_1 = 8.5 Hz, J_2 = 0.8 Hz, 2H), 7.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 161.1, 159.2, 140.4, 135.0, 133.6, 128.0, 127.1, 124.3, 105.4; FT-IR (KBr) 1762 (C=O) cm^{-1}.

Preparation of 1-(2-Bromo-4-chlorophenyl)-3-(4-methoxyphenyl)-2-propyn-1-one (5c). 4-Methoxyphenylethynylmagnesium bromide, generated from 4-methoxyphenylacetylene (397 mg, 3.0 mmol) and EtMgBr (1.0 M in THF, 3.0 mL, 3.0 mmol) in THF (9 mL), was slowly added to a solution of **3c** (820 mg, 1.5 mmol) in THF (10 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 0.5 h at 0 °C and was then quenched with saturated NH_4Cl solution (5 mL). After evaporating THF, the mixture was poured into saturated NH_4Cl solution (30 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic phases

Table 1. Preparation of 1-(2-halophenyl)-3-(hetero)aryl-2-propyn-1-ones **5** and 1-alkyl-2-phenyl-4-quinolones **7** from 2-halobenzoic acids **1**

Entry	X	R^1	R^2	R^3	R^4	Reaction time, h[a]	Isolated yields, %[b]	
							5[c]	**7**[d]
a	Br	H	H	C_6H_5	Me	6	81	85 (52)
b	Br	H	H	4-MeO-C_6H_4	Me	8	89	81 (55)
c	Br	Cl	H	4-MeO-C_6H_4	Et	2	83	90 (62)
d	Br	Cl	H	3-thienyl	*c*-C_3H_5	7	85	80 (56)
e	Br	Me	H	4-Me-C_6H_4	Me	18	85	89 (66)
f	Br	Me	H	2-MeO-C_6H_4	Me	18	88	89 (68)
g	Br	Me	H	3-pyridyl	Et	30	78	75 (51)
h	F	OMe	H	3-Cl-C_6H_4	Me	1	82	87 (47)
i	F	OMe	H	3,5-$(MeO)_2$-C_6H_3	*c*-C_3H_5	7	80	74 (39)
j	F	H	OMe	2-MeO-C_6H_4	Me	1	75	86 (55)

[a]Reaction time indicates the conversion of **6** to **7**. [b]The numbers in parentheses indicate the overall yields from 2-halobenzoic acids **1**. [c]Chromatographically pure. [d]Recrystallized yields.

were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized twice from 10% EtOAc/*n*-hexane to give **5c** (871 mg, 83%). mp 131-133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 1.8 Hz, 1H), 7.60 (d, J = 8.9 Hz, 2H), 7.43 (dd, J_1 = 8.4 Hz, J_2 = 1.9 Hz, 1H), 6.93 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 162.0, 138.9, 136.1, 135.3, 134.6, 133.5, 127.7, 121.9, 114.5, 111.5, 96.1, 87.9, 55.5; FT-IR (KBr) 2196 (C≡C), 1641 (C=O) cm^{-1}; Ms *m/z* (%) 352 (M^++4, 21), 350 (M^++2, 85), 348 (M^+, 67), 324 (13), 322 (54), 320 (42), 159 (100).

Preparation of 1-Ethyl-7-chloro-2-(4'-methoxyphenyl)-4-quinolone (7c): To a solution of **5c** (699 mg, 2.0 mmol) in EtOH/THF (12/12 mL) was added ethylamine (1.5 mL, 2.0 M in MeOH, 3.0 mmol) at 25 °C and stirred for 8 h. After evaporation of the solvents, a solution of the intermediate **6c** in DME (15 mL) was added to a suspension of sodium hydride (88 mg, 60% dispersion, 2.2 mmol) in DME (10 mL) at 25 °C. Stirring was continued for 0.5 h and the resulting solution was refluxed for a further 2 h. The mixture was quenched with H_2O (5 mL) and the solvent was evaporated *in vacuo*. The mixture was poured into 5% NaCl solution (30 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized twice from 10% EtOAc/*n*-hexane to give **7c** (562 mg, 90%). mp 214-216 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, J = 8.6 Hz, 1H), 7.55 (d, J = 1.6 Hz, 1H), 7.35 (dd, J_1 = 8.6 Hz, J_2 = 1.6 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 6.21 (s, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.89 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 160.4, 154.7, 141.1, 138.6, 129.5, 128.8, 127.9, 125.7, 124.1, 116.0, 114.2, 113.7, 55.4, 43.2, 14.3; FT-IR (KBr) 1625 (C=O) cm^{-1}; Ms *m/z* (%) 315 (M^++2, 34), 313 (M^+, 100), 298 (52), 287 (16), 285 (47).

1-Methyl-2-phenyl-4-quinolone (7a): mp 144-145 (lit.[6] 145-147 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 1H), 7.69-7.75 (m, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.47-7.52 (m, 3H), 7.40-7.45 (m, 3H), 6.30 (s, 1H), 3.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 154.7, 141.9, 135.9, 132.4, 129.6, 128.8, 128.6, 126.9, 126.7, 123.7, 116.0, 112.7, 37.3; FT-IR (KBr) 1622 (C=O) cm^{-1}; Ms *m/z* (%) 235 (M^+, 100), 207 (82).

1-Methyl-2-(4'-methoxyphenyl)-4-quinolone (7b): mp 145-146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 8.0 Hz, 1H), 7.68-7.73 (m, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H), 6.29 (s, 1H), 3.98 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 160.5, 154.7, 142.0, 132.2, 130.1, 128.2, 126.9, 126.7, 123.6, 116.0, 114.2, 112.8, 55.5, 37.4; FT-IR (KBr) 1615 (C=O) cm^{-1}; Ms *m/z* (%) 265 (M^+, 100), 237 (82).

1-Cyclopropyl-7-chloro-2-(3-thienyl)-4-quinolone (7d): mp 227-228 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 1.8 Hz, 1H), 7.56 (dd, J_1 = 2.9 Hz, J_2 = 1.2 Hz, 1H), 7.46 (dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 1H), 7.27-7.31 (m, 2H), 6.35 (s, 1H), 3.29-3.36 (m, 1H), 1.06 (d, J = 7.0 Hz, 2H), 0.63 (d, J = 3.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 150.6, 143.7, 138.0, 136.9, 128.0, 127.7, 126.4, 125.9, 125.2, 124.2, 117.6, 113.2, 32.2, 12.7; FT-IR (KBr) 1623 (C=O) cm^{-1}; Ms *m/z* (%) 303 (M^++2, 21), 301 (M^+, 64), 275 (25), 273 (87), 266 (100).

1,7-Dimethyl-2-(4'-methylphenyl)-4-quinolone (7e): mp 163-164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J = 8.2 Hz, 1H), 7.22-7.32 (m, 6H), 6.25 (s, 1H), 3.58 (s, 3H), 2.53 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 154.6, 143.0, 142.2, 139.6, 133.2, 129.4, 128.5, 126.6, 125.2, 124.8, 115.8, 112.5, 37.2, 22.3, 21.3; FT-IR (KBr) 1626 (C=O) cm^{-1}; Ms *m/z* (%) 263 (M^+, 100), 235 (89).

1,7-Dimethyl-2-(2'-methoxyphenyl)-4-quinolone (7f): mp 199-201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J = 8.2 Hz, 1H), 7.45-7.50 (m, 1H), 7.27-7.33 (m, 2H), 7.23 (d, J = 8.1 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.22 (s, 1H), 3.80 (s, 3H), 3.52 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 156.4, 152.1, 142.8, 141.8, 131.3, 130.4, 126.7, 125.1, 125.0, 124.8, 121.1, 115.7, 112.6, 110.9, 55.6, 35.9, 22.3; FT-IR (KBr) 1625 (C=O) cm^{-1}; Ms *m/z* (%) 279 (M^+, 88), 250 (14), 148 (100).

1-Ethyl-7-methyl-2-(3-pyridyl)-4-quinolone (7g): mp 218-219 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (dd, J_1 = 4.8

Hz, J_2 = 1.4 Hz, 1H), 8.71 (d, J = 1.6 Hz, 1H), 8.39 (d, J = 8.2 Hz, 1H), 7.77 (dd, J_1 = 7.8 Hz, J_2 = 1.9 Hz, 1H), 7.47 (dd, J_1 = 7.8 Hz, J_2 = 4.9 Hz, 1H), 7.34 (s, 1H), 7.25 (d, J = 8.2 Hz, 1H), 6.16 (s, 1H), 4.06 (q, J = 7.1 Hz, 2H), 2.55 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 150.6, 150.4, 148.7, 143.3, 140.5, 135.7, 132.1, 127.0, 125.5, 125.3, 123.4, 115.7, 113.5, 43.0, 22.4, 14.3; FT-IR (KBr) 1626 (C=O) cm^{-1}; Ms *m/z* (%) 264 (M^+, 100), 249 (81), 236 (33).

1-Methyl-7-methoxy-2-(3'-chlorophenyl)-4-quinolone (7h): mp 206-207 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 8.1 Hz, 1H), 7.41-7.50 (m, 3H), 7.27-7.32 (m, 1H), 7.01 (dd, J_1 = 8.9 Hz, J_2 = 2.2 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.17 (s, 1H), 3.95 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 163.1, 152.8, 143.6, 137.6, 134.8, 130.2, 129.7, 128.7 (overlapped), 126.8, 121.2, 112.6, 112.0, 99.1, 55.7, 37.3; FT-IR (KBr) 1635 (C=O) cm^{-1}; Ms *m/z* (%) 301 (M^++2, 33), 299 (M^+, 96), 273 (16), 271 (45), 258 (34), 256 (100).

1-Cyclopropyl-7-methoxy-2-(3',5'-dimethoxyphenyl)-4-quinolone (7i): mp 215-217 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 8.9 Hz, 1H), 7.31 (d, J = 2.1 Hz, 1H), 6.99 (dd, J_1 = 8.9 Hz, J_2 = 2.2 Hz, 1H), 6.65 (d, J = 2.1 Hz, 2H), 6.54 (d, J = 2.0 Hz, 1H), 6.26 (s, 1H), 3.95 (s, 3H), 3.83 (s, 6H), 3.21-3.33 (m, 1H), 0.99 (d, J = 6.5 Hz, 2H), 0.65 (d, J = 3.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 162.4, 160.7, 155.1, 144.9, 138.7, 128.2, 121.1, 113.0, 112.0, 106.8 (overlapped), 100.9, 55.6 (overlapped), 32.5, 12.6; FT-IR (KBr) 1623 (C=O) cm^{-1}; Ms *m/z* (%) 351 (M^+, 100), 322 (65), 320 (77), 308 (36).

1-Methyl-5-methoxy-2-(2'-methoxyphenyl)-4-quinolone (7j): mp 188-189 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.59 (m, 1H), 7.43-7.49 (m, 1H), 7.28-7.33 (m, 1H), 7.03-7.10 (m, 2H), 6.97 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.19 (s, 1H), 4.00 (s, 3H), 3.80 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 160.9, 156.5, 150.3, 144.4, 132.2, 131.3, 130.5, 124.8, 121.1, 117.5, 115.1, 110.8, 107.9, 104.6, 56.4, 55.6, 36.8; FT-IR (KBr) 1623 (C=O) cm^{-1}; Ms *m/z* (%) 295 (M^+, 95), 280 (35), 164 (100).

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