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SOLID-PHASE SYNTHESIS OF 2-PHENYL-4-QUINOLINONE LIBRARY *VIA* FLAVYLIUM SALT

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Abstract — Fourteen 1-, 6-, 7-, 8-mono-, 7,8-di-, and 6,7,8-trisubstituted 2-(4'-hydroxy- and 4'-hydroxy-3'-methoxy)phenyl-4-quinolinones were conveniently synthesized by aqueous ammonia treatment of the flavylium salts obtained by the three-components condensation reaction of acetophenones, aldehydes, and ethyl orthoformate on a solid support with excellent purity and in overall yields of 11-59%.

It has recently been reported by K.-H. Lee *et al.*[1a,b,c] that 2-phenyl-4-quinolinone derivatives showed a potent inhibitory action against human antitumor cell lines, and a variety of substituted 2-phenyl-4-quinolinones were synthesized and subjected to screening for antitumor activity. However, some synthetic methods[1-5] have been used for the introduction of various substituents to the various positions of the 2-phenyl-4-quinolinones. We have recently developed a new two-step synthetic method using

flavylium perchlorates from acetophenones, aldehydes, and ethyl orthoformate in the presence of perchloric acid for the synthesis of various types of 2-phenyl-4-quinolinones.[6]

In order to supply many samples for biological screening, combinatorial chemistry using solid-phase synthesis has been developed and eagerly employed.[7a] It has been regarded as an important tool for the synthesis of a large number of medicinally interesting compounds.[7b,c] We then planned to apply this synthetic method to the solid-phase synthesis in order to prepare an expanded 2-phenyl-4-quinolinone library bearing versatile substituents in a short period.

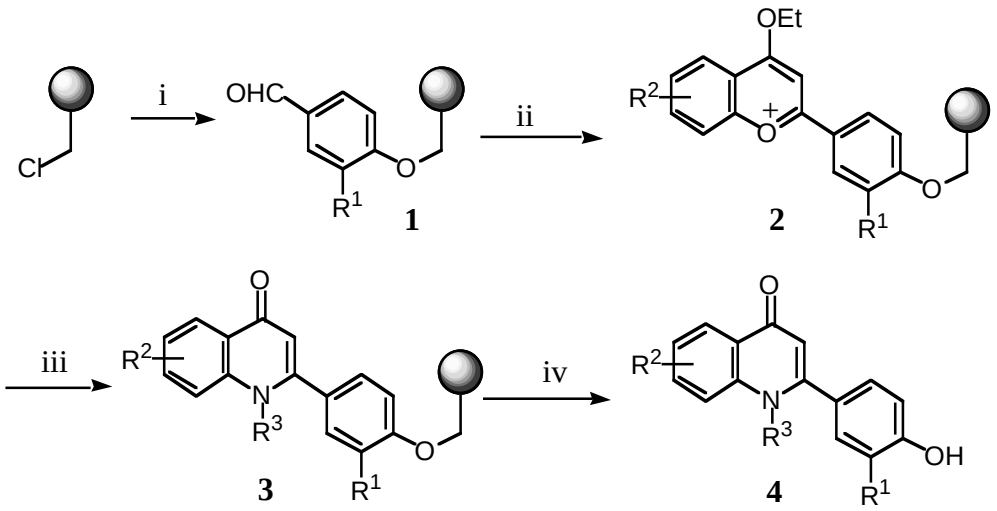
Since the higher antitumor activity of 2-phenyl-4-quinolinone is expected by change in substituents on the quinoline-ring rather than that on the 2-phenyl group,[1a,b,c] we planned a strategy that involved the preparation of a 2-phenyl-4-quinolinone library by coupling of a resin-bound benzaldehyde with various substituted acetophenones and ethyl orthoformate followed by conversion of the resulting flavylium salt with aqueous ammonia. The resin employed was the Merrifield® resin (1.36 mmol / g, Kokusan Chemical Co., Ltd.), which was one of the cheapest resins.

Initially, the coupling of *p*-hydroxybenzaldehyde (4 equiv.) with the Merrifield resin in DMF in the presence of NaH (4 equiv.) and tetrabutylammonium iodide (0.1 equiv.) was performed at 80°C for 18 h.[8a,b] The formation of the resin-bound *p*-hydroxybenzaldehyde (**1**) was assumed by its IR spectra showing a strong carbonyl stretching vibration at 1693 cm^{-1}. No solid-phase preparation of the flavylium salt was obtained under the same conditions as the solution method[6] in which ethyl orthoformate and perchloric acid were used as a solvent and acid, respectively. We then determined the best reaction conditions (see Table 1). A three-component coupling-reaction of the resin-bound benzaldehyde, 4-methoxyacetophenone and ethyl orthoformate was carried out using 1) trifluoroacetic acid or 2) trifluoromethanesulfonic acid as an acid, and 1) DMF 2) DMSO 3) CH_2Cl_2 or 4) ethyl orthoformate as a solvent. No flavylium salt was produced by using a polar solvent such as DMF or DMSO (Entries 2, 3, 6, 7, 10, 11). However, the corresponding flavylium salt was produced by using ethyl orthoformate or

Table 1 Syntheses of 6-methyl–2-(4’-hydroxy)phenyl-4-quinolinone on solid support using some acids and solvents

Entry	Acid	Solvent	Temp. (℃)	Time (h)	Overall yield (%)
1	70% $HClO_4$	$HC(OEt)_3$	50	48	0
2		DMF	50	48	0
3		DMSO	50	48	0
4		CH_2Cl_2	50	18	32
5	CF_3COOH	$HC(OEt)_3$	rt	18	0
6		DMF	rt	18	0
7		DMSO	rt	18	0
8		CH_2Cl_2	rt	18	0
9	CF_3SO_3H	$HC(OEt)_3$	rt	18	35
10		DMF	rt	18	0
11		DMSO	rt	48	0
12		CH_2Cl_2	rt	18	44

CH_2Cl_2 as a solvent and trifluoromethanesulfonic acid as an acid for 18 h. The progress of the reaction was confirmed by IR spectra, the carbonyl stretching vibration at 1693 cm^{-1} disappeared and two peaks at 1542 and 1525 cm^{-1} appeared. More than 20 equivalents of acetophenone and 2 equivalents of trifluoromethanesulfonic acid were required to prepare the flavylium salt. The conversion reaction of the flavylium trifluoromethanesulfonate to a 2-phenyl-4-quinolinone by 25% aqueous ammonia solution smoothly proceeded as well as using the solution method. Finally, cleavage was carried out in THF/CH_2Cl_2 (1:1) at room temperature overnight to afford 2-phenyl-4-quinolinones as a brown powder. The best yield of 6-methyl-2-(4’-hydroxy)phenyl-4-quinolinone was 44% (see Scheme 1).

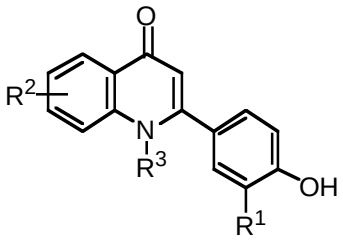


Scheme 1
Reagents and conditions: i) *p*-hydroxybenzaldehyde, NaH, in DMF, 80 °C, 18 h, ii) substituted acetophenone (20 equiv.), $HC(OEt)_3$ (20 equiv.), CF_3SO_3H (2 equiv.), in CH_2Cl_2, rt, 18 h, iii) 25% aq. NH_3, rt, 18 h, iv) CF_3CO_2H (2 equiv.), in CH_2Cl_2, rt, 18 h.

Thus, fourteen types of 2-phenyl-4-quinolinones were synthesized in overall yields of 11-59% in the same way using eleven types of acetophenones (see Table 2). The purity of the quinolinones was high (>80%), which was estimated by HPLC. The structure assignment was confirmed by MS, IR, ^{1}H NMR spectra, and elemental analyses.[5] The bulkiness of the substituents such as the *sec*- and *tert*-butyl groups at the 6-position led to a decrease of yields (Entries 4 and 5, 11 and 18%, respectively). Substitution at the 8-position in comparison with that at the 6- or 7-position led to a slight decrease of yields (Entries 1, 7, and 9). Di- or tri-substitution at the 7,8- or 6,7,8-positions also resulted in a decrease of yields (Entries 11 and 12, 27 and 26%, respectively). The reaction on the resin-bound benzaldehyde bearing a methoxyl group at the *meta* position also resulted in a 50% decrease of yields (Entries 12 and 13, 44→21%, 41→26%). The substitution of a methyl group at the 1-position smoothly proceeded without a decrease of yields (Entries 13 and 14, 26 and 41%). Thus, we succeeded in the introduction of various substituents at the 1-, 6-, 7-, 8-

positions on the 4-quinolinone ring by the solid-phase method except for the 5-position, in which the corresponding precursor, 3-substituted acetophenones could not be prepared. However, the yields were lower in comparison to the solution method (42-93% except for 24% of **4c**).[6] The 1,6,7,8-tetrasubstituted, 7,8-disubstituted, and 6,7,8-trisubstituted (4'-hydroxy- and 4'-hydroxy-3'-methoxy)phenyl-4-quinolinones were able to be synthesized on a solid support. This method also made possible the introduction of various types of substituting group such as methyl, hydroxyl, methoxyl, acetyl, bromo, *sec*- or *tert*-butyl group on the solid support.

Table 2 Solid-phase synthesis of 2-phenyl-4-quinolinone derivatives



Entry	R^1	R^2	R^3	Compound	Overall yield (%)	Purity*(%)
1	H	6-Me	H	**4a**	44	88.7
2	H	6-OMe	H	**b**	48	86.8
3	H	6-OH	H	**c**	25	93.6
4	H	6-*sec*- Bu	H	**d**	11	96.7
5	H	6-*tert*-Bu	H	**e**	18	96.4
6	H	6-Br	H	**f**	59	84.9
7	H	7-Me	H	**g**	33	97.8
8	H	7-OMe	H	**h**	31	85.7
9	H	8-Me	H	**i**	26	94.3
10	H	7,8-OMe	H	**j**	27	88.3
11	H	6-Ac-7-OH-8-OMe	H	**k**	26	86.1
12	OMe	6-Me	H	**l**	21	80.4
13	OMe	6-Me	Me	**m**	26	97.9
14	H	6-Me	Me	**n**	41	98.8

* Purity was estimated by integration of the HPLC traces (ODS column, UV240 nm, mobile phase: methanol : water = 98 : 2)

Although this three-component coupling-reaction on the resin-bound aldehyde was key and the yield was moderate, one was able to prepare 2-phenyl-4-quinolinone libraries bearing various substituting groups by a simple method under mild conditions.

EXPERIMENTAL

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Elemental analyses were performed by Perkin-Elmer PE 2400 II. ^{1}H NMR spectra were measured at 200MHz on a Varian Mercury-200, and recorded in deuteriochloroform or/and deuteriodimethyl sulfoxide. Chemical shifts are reported in δ (ppm) units relative to the internal reference tetramethylsilane. IR spectra were recorded on a Horiba IR spectrophotometer FT 200 as potassium bromide pellets before recrystallization from acetic acid. MS spectra data were obtained by Fast Atom Bombardment (FAB) method using 3-nitrobenzyl alcohol as a matrix on a JEOL HX 100 mass spectrometer.

General procedure. To a resin-bound benzaldehyde (200 mg, 0.252 mmol) in CH_2Cl_2 (8 mL) was added 3-methylacetophenone (756 mg, 5.04 mmol) with stirring. To the stirring mixture, ethyl orthoformate (747 mg, 5.04 mmol) and trifluoromethanesulfonic acid (75 mg, 0.504 mmol) were added and the mixture was stirred at rt for 18 h. The resulting reaction mixture was filtered and washed with methanol (10 mL), acetone (50 mL), and ether (10 mL). The resin-bound flavylium salt was dried under reduced pressure and then added to 25% aqueous ammonia solution (8 mL) and the mixture was stirred at rt for 18 h. The resulting mixture was filtered and washed with water (40 mL), methanol (10 mL), acetone (20 mL), and ether (10 mL). The resin-bound quinolinone (209 mg) was treated with trifluoroacetic acid (4 mL) and CH_2Cl_2 (4 mL) at rt for 18 h. The resulting mixture was filtered and the filtrate was washed with CH_2Cl_2 (20 mL) and methanol (20 mL). The combined filtrate was evaporated *in vacuo*. The residual product was precipitated with hexane to afford 6-methyl-2-(4'-hydroxy)phenyl-4-quinolinone (28 mg, 44%) as a brown solid.

2-phenyl-4-quinolinones **4a**, **4b**, **4e**, **4g**, and **4l**: see ref. 2. **4a**: orange powder (methanol), mp 255-257°C. **4b:** orange powder (methanol), mp 281-283°C. **4e:** yellow prisms (acetic acid-MeCN), mp 194-195°C. **4g**: yellow powder (acetic acid-MeCN), mp 250-251°C. **4l:** brown powder (acetic acid), mp 165-167°C.

4c: yellow powder (acetic acid-MeCN), mp >300°C. MS *m/z*=254(M+1). IR (KBr) ν=3365, 3197, 1676, 1622, 1606, 1570, 1519, 1257, 1182, and 1030 cm^{-1}. ^1H NMR ($CDCl_3$+DMSO-d_6) δ=7.19(2H, d, *J*=9.0 Hz, H-3', 5'), 7.31(1H, s, H-3), 7.49(1H, dd, *J*=2.5 and 9.1 Hz, H-7), 7.64(1H, d, *J*=9.1 Hz, H-8), 7.73(1H, d, *J*=2.7 Hz, H-5), 9.92(2H, d, *J*=9.0 Hz, H-2', 6'). Anal. Calcd for $C_{15}H_{11}NO_3$·MeCOOH: C, 65.17; H, 4.83; N, 4.47. Found: C, 64.82; H, 4.77; N, 4.37.

4d: yellow powder (acetic acid-MeCN), mp 238-239°C. MS *m/z*=294(M+1). IR (KBr) ν=3353, 3188, 2964, 2933, 2875, 1676, 1622, 1606, 1564, 1510, 1261, 1178, and 1030 cm^{-1}. ^1H NMR (DMSO-d_6) δ=0.78(3H, t, *J*=7.4 Hz, CH_2CH_3), 0.89(3H, d, *J*=6.6 Hz, >$CHCH_3$), 1.60(2H, dt, *J*=7.4 and 6.6 Hz, CH_2CH_3), 2.70(1H, q, *J*=6.6 Hz, >$CHCH_3$), 6.68(1H, s, H-3), 6.82(2H, d, *J*=2.5 and 8.5 Hz, H-3', 5'), 7.45(1H, d, *J*=8.5 Hz, H-8), 7.49(1H, dd, *J*=2.5 and 8.5 Hz, H-7), 7.75(2H, d, *J*=8.5 Hz, H-2', 6'), 7.97(1H, d, *J*=2.5 Hz, H-5), 9.40(2H, br s, NH and OH). Anal. Calcd for $C_{19}H_{19}NO_2$·MeCOOH: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.50; H, 6.65; N, 3.91.

4f: reddish purple powder (acetic acid), mp 259-260°C. MS *m/z*=318(M+2), 316(M^+). IR (KBr) ν=3346, 3101, 1679, 1604, 1556, 1508, 1282, 1259, 1178, and 1030 cm^{-1}. ^1H NMR (DMSO-d_6) δ=6.94(1H, s, H-3), 6.94(2H, d, *J*=8.8 Hz, H-3', 5'), 7.76(1H, d, *J*=8.8 Hz, H-8), 7.98(1H, dd, *J*=2.7 and 8.8 Hz, H-7), 7.98(2H, d, *J*=8.8 Hz, H-2', 6'), 8.09(1H, d, *J*=2.7 Hz, H-5), 10.40(2H, br, OH and NH). Anal. Calcd for $C_{15}H_{10}NO_2Br$·0.25MeCOOH: C, 56.22; H, 3.35; N, 4.23. Found: C, 56.02; H, 3.23; N, 4.14.

4h: yellow powder (acetic acid-MeCN), mp 196-197°C. MS *m/z*=268(M+1). IR (KBr) ν=3349, 3226, 1668, 1635, 1606, 1529, 1261, 1246, 1180, and 1230 cm^{-1}. ^1H NMR (DMSO-d_6) δ=4.00(3H, s, OCH_3), 7.04(2H, d, *J*=9.0 Hz, H-3', 5'), 7.20(1H, s, H-3), 7.37(1H, dd, *J*=9.3 and 2.4 Hz, H-6), 7.60(1H, d, *J*=2.4 Hz, H-8), 8.03(2H, d, *J*=9.0 Hz, H-2', 6'), 8.36(1H, d, *J*=9.3 Hz, H-5), 10.00 and 10.60(each 1H, br s, OH

and NH). Anal. Calcd for $C_{16}H_{13}NO_3$·2MeCOOH: C, 62.01; H, 5.46; N, 3.62. Found: C, 62.04; H, 5.01; N, 3.98.

4i: yellow powder (acetic acid-MeCN), mp 268-269°C. MS *m/z*=252(M+1). IR (KBr) ν=3353, 3224, 1672, 1625, 1604, 1575, 1261, 1178, and 1030 cm^{-1}. ^1H NMR (DMSO-d_6) δ=2.65(3H, s, $ArCH_3$), 7.06(2H, d, *J*=8.8 Hz, H-3', 5'), 7.31(1H, s, H-3), 7.64(1H, t, *J*=7.8 Hz, H-6), 7.94(1H, d, *J*=7.8 Hz, H-7), 8.04(2H, d, *J*=8.8 Hz, H-2', 6'), 8.28(1H, d, *J*=7.8 Hz, H-5), 10.26 and 10.81(each 1H, br s, OH and NH). Anal. Calcd for $C_{16}H_{13}NO_2$·MeCOOH: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.67; H, 5.43; N, 4.35.

4j: yellow powder (acetic acid-MeCN), mp 182-183°C. MS *m/z*=298(M+1). IR (KBr) ν=3307, 3226, 2947, 2846, 1672, 1625, 1598, 1567, 1535, 1465, 1292, 1182, 1130, and 1030 cm^{-1}. ^1H NMR ($CDCl_3$-DMSO-d_6) δ=4.06 and 4.08(each 3H, s, OCH_3 x 2), 7.04(2H, d, *J*=9.0 Hz, H-3', 5'), 7.28(1H, d, *J*=9.3 Hz, H-6), 7.31(1H, s, H-3), 7.96(2H, d, *J*=9.0 Hz, H-2', 6'), 8.24(1H, d, *J*=9.3 Hz, H-5), 9.99(2H, s, OH and NH). Anal. Calcd for $C_{17}H_{15}NO_4$·MeCOOH: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.65; H, 5.28; N, 3.84.

4k: brown powder (acetic acid-MeCN), mp >300°C. MS *m/z*=310(M+1). IR (KBr) ν=3365, 3107, 1675, 1651, 1629, 1604, 1575, 1516, 1465, 1438, 1411, 1365, 1300, 1180, and 1031 cm^{-1}. ^1H NMR (DMSO-d_6) δ=2.37(3H, s, CH_3), 2.75(3H, s, $COCH_3$), 7.04(2H, d, *J*=8.8 Hz, H-3', 5'), 7.09(1H, s, H-3), 7.97(2H, d, *J*=8.8 Hz, H-2', 6'), 8.83(1H, s, H-5), 9.86 and 10.08(each 1H, br s, 4-OH and NH), 10.74(1H, br s, chelated OH). Anal. Calcd for $C_{18}H_{15}NO_4$·1.5MeCOOH: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.34; H, 5.21; N, 3.56.

4m: yellow powder (acetic acid-MeCN), mp 186-187°C. MS *m/z*=282(M+1). IR (KBr) ν=3348, 3193, 1676, 1620, 1604, 1566, 1508, 1288, and 1028 cm^{-1}. ^1H NMR (DMSO-d_6) δ=2.54(3H, s, $ArCH_3$), 3.38(3H, s, NCH_3), 3.96(3H, s, OCH_3), 7.08(1H, d, *J*=8.4Hz, H-5'), 7.48(1H, s, H-3), 7.83(1H, d, *J*=2.2 Hz, H-2'), 7.88(1H, dd, *J*=1.7 and 8.8 Hz, H-7), 7.94(1H, dd, *J*=2.2 and 8.5 Hz, H-6'), 7.97(1H, d, *J*=8.8 Hz, H-8'), 8.24(1H, br s, H-5), 10.48(2H, br s, OH x 2). **4m** may exist in 4-quinolinol form in DMSO. Anal. Calcd

for $C_{18}H_{17}NO_3 \cdot 0.6CF_3SO_3H$: C, 57.97; H, 4.60; N, 3.63. Found: C, 58.20; H, 4.34; N, 3.33.

4n: yellow powder (acetic acid-MeCN), mp 244-246°C. MS *m/z*=266(M+1). IR (KBr) ν=3427, 3216, 3099, 1681, 1627, 1602, 1560, 1525, 1442, 1380, 1280, 1263, 1180, and 1031 cm^{-1}. ^1H NMR (DMSO-d_6) δ=2.55(3H, s, $ArCH_3$), 3.40(3H, s, NCH_3), 7.04(2H, d, *J*=8.8 Hz, H-3', 5'), 7.17(1H, s, H-3), 7.70(1H, d, *J*=9.0 Hz, H-8), 7.74(1H, dd, *J*=2.0 and 9.0 Hz, H-7), 8.08(2H, d, *J*=8.8 Hz, H-2', 6'), 8.33(1H, br s, H-5). Anal. Calcd for $C_{17}H_{15}NO_2 \cdot 0.75CF_3SO_3H$: C, 56.42; H, 4.20; N, 3.71. Found: C, 56.66; H, 4.19; N, 3.57.

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REFERENCES

1. (a) S.-C. Kuo, H.-Z. Lee, J.-P. Juang, Y.-T. Lin, T.-S. Wu, J.-J. Chang, D. Lednicer, K. D. Paull, C. M. Lin, E. Hamel, and K.-H. Lee, *J. Med. Chem.,* 1993, **36**, 1146. (b) L. Li, H.-K. Wang, S.-C. Kuo, T.-S. Wu, D. Lednicer, C. M Lin, E. Hamel, and K.-H. Lee, *J. Med. Chem*., 1994, **37**, 1126. (c) L. Li, H.-K. Wang, S.-C. Kuo, T.-S. Wu, A. Mauger, C. M. Lin, E. Hamel, and K.-H. Lee, *J. Med. Chem*., 1994, **37**, 3400.
2. A. Kasahara, T. Izumi, H. Watanabe and S.-I. Takahashi, *Chem. Ind. (London)*, 1981 , 121.
3. B.–C., Chen, X. Huang, and J. Wang, *Synthesis*, 1987, 482.
4. R. J. Chong, M. A. Siddiqui, and V. Snieckus, *Tetrahedron Lett*., 1986, **27** , 5323.
5. B. Staskun, and S. S. Israelstam, *J. Org. Chem.,* 1961, **26**, 3191.
6. S. Sato, T. Watanabe, H. Kumagai, N. Kitamura, S. Matsuba, T. Kumazawa, J. Onodera, and M. Suzuki, *J. Heterocycl. Chem*., 1999, **36**, 1189.
7. (a) P. H. H. Hermkens, H. C J. Ottenheijm, and D. Rees, *Tetrahedron*, 1996, **52**, 4527. (b) E. M. Gordon, R. W. Barrett, W. J. Dower, S. P. A. Fodor, and M. A. Gallop, *J. Med. Chem*., 1994, **37**, 1385.

(c) L. A. Thompson and J. A. Ellman, *Chem. Rev*., 1996, **96**, 555.

8. (a) A. Routledge, C. Abell, and S. Balasubramanian, *Tetrahedron Lett*., 1997, **38**, 1227. (b) K. C. Nicolaou, N. Watanabe, J. L. J. Pastor, and N. Winssinger, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1559.