HETEROCYCLES, Vol. 63, No. 3, 2004, pp. 529 - 537
Received, 4th November, 2003, Accepted, 8th January, 2004, Published online, 16th January, 2004

SYNTHESIS AND CYTOTOXIC EVALUATION OF CERTAIN TRICYCLIC BENZO[*g*]QUINOLIN-4(1*H*)-ONE AND BENZO[*g*]QUINOLINE-4,9,10-TRIONE DERIVATIVES

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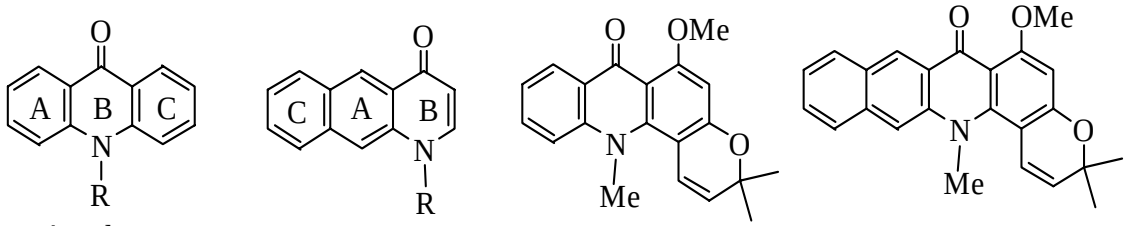
Abstract - The present report describes the synthesis and evaluation of tricyclic benzo[*g*]quinoline-4(1*H*)-one derivatives (*CAB* type) in which an additional aromatic ring is linearly fused on the antibacterial quinolone-3-carboxylic acid to maintain a free carboxylic acid (increase water-solubility) and a coplanar tricyclic DNA-intercalating chromophore (improve antitumor activity). 1*H*-Benzo[*g*]-quinoline-4,5,10-trione, 1-methyl-1*H*-benzo[*g*]quinoline-4,5,10-trione, and ethyl 1-methylbenzo[*g*]quinoline-4,5,10-trione-3-carboxylate exhibited significant cytotoxicity against all 60 cancer cells with mean GI_{50} values of 5.92, 7.75, and 2.52 μM respectively while 1-methylbenzo[*g*]quinoline-4,5,10-trione-3-carboxylic acid and 5-hydroxy-10-methoxy-1-methylbenzo[*g*]quinolin-4(1*H*)-one-3-carboxylic acid were inactive, indicated free carboxylic acid at C-3 position is unfavorable. The results have also implied the importance of carbonyl moieties at C-5 and C-10 due to the inactiveness of reduced products, ethyl 5-hydroxy-10-methoxy-1-methylbenzo[*g*]quinolin-4(1*H*)-one-3-carboxylate and ethyl 10-benzyloxy-5-hydroxybenzo[*g*]quinolin-4(1*H*)-one-3-carboxylate.

The tricyclic benzo[*g*]quinolin-4(1*H*)-ones (*CAB* type) can be considered as an isomer of acridone (*ABC* type) which constitute an important group of antitumor natural products, such as acronycine and glyfoline.[1-3] Early experiments suggested that acronycine interferes with the structure and function of cell-surface components.[4] However, a more recent investigation demonstrated that acronycine should interact with DNA, either by intercalation or by some other noncovalent process.[5] Intercalation with DNA is known to occur for

compounds possessing coplanar aromatic chromophores. The noticeable examples of DNA-intercalating agents are acridine derivatives such as amsacrine and anthraquinone anticancer drugs such as doxorubicin, daunorubicin, and mitoxantrone.[6-10] Due to poor water-solubility of anthraquinone skeletone, these drugs either bear aminosugar or long chain aminoalcohol to improve water-solubility.[10] Extensive SAR studies with DNA intercalating chromophores revealed a positive correlation between the strength of reversible DNA binding and the cytotoxic potency.[11-13] For example, benzoacronycine (IC_{50} = 1.9 μM), the acronycine analogue with an additional aromatic ring linearly fused on its A-ring to enhance DNA-intercalating capability, exhibited ten-fold more potent than the parent acronycine (IC_{50} = 19.9 μM) in inhibiting L1210 cell proliferatin.[14]



Acridone (*ABC* type) | Benzo[*g*]quinolone (*CAB* type) | Acronycine | Benzoacronycine

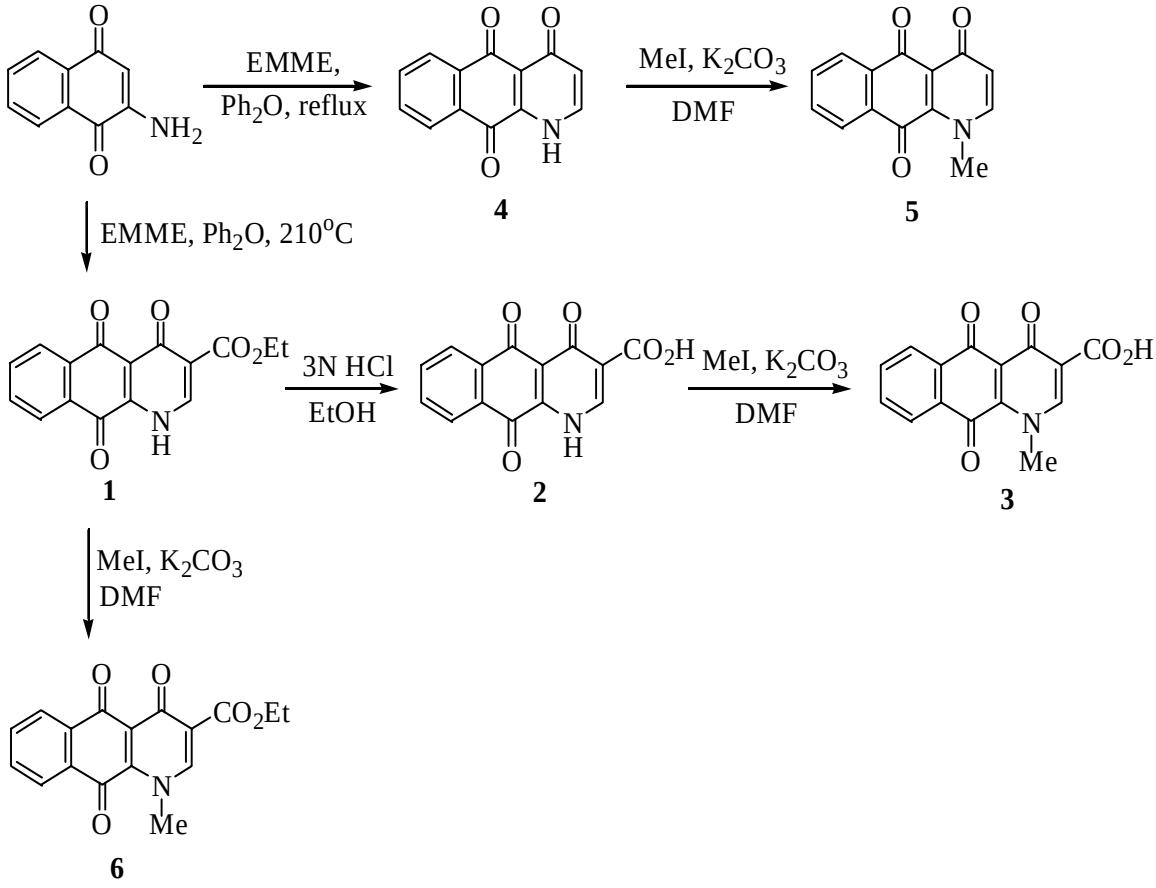
We have been interested in the synthesis and biological evaluation of quinolone-3-carbxylic acids.[15-18] These compounds are potent antibacterial agents that target the bacterial type II DNA topoisomerases (DNA gyrase and topoisomerase IV).[19] Due to structural and functional similarities between bacterial DNA gyrase and mammalian topoisomerase II, a series of modified tricyclic quinolones (*ABC* type) were synthesized in which the essential 3-carboxylic acid is surrogated by phenolic OH group in an attempt to shift the activity from antibacterial to antineoplastic.[20] The present report describes the synthesis and evaluation of tricyclic benzo[*g*]quinolin-4(1*H*)-one derivatives (*CAB* type) in which an additional aromatic ring is linearly fused on the antibacterial quinolone-3-carboxylic acid. The advantages of these *CAB*-type compounds are to maintain a free carboxylic acid (increase water-solubility) and a coplanar tricyclic DNA-intercalating chromophore (improve antitumor activity). Their hydroxyl, methoxy, benzyloxy, and carboxylate derivatives have also be synthesized and evaluated for antitumor activities.

RESULTS AND DISCUSSION

Two-step thermal condensations of 2-aminobenzoquinone[21] with diethyl ethoxymethylenemalonate (EMME) gave ethyl 1*H*-benzo[*g*]quinoline-4,5,10-trione-3-carboxylate (**1**) in an 24 – 54% overall yield.[22,23] By heating 2-aminobenzoquinone with EMME at 210°C for 15 h, we were able to obtain **1** in a 66% yield. Hydrolysis of **1** with 3N HCl gave its free carboxylic acid (**2**) which was methylated with methyl iodide to afford 1-methylbenzo[*g*]quinoline-4,5,10-trione-3-carboxylic acid (**3**) in a fairly good overall yield. Similar

N-alkylation occurred when quinolone-esters were alkylated with methyl iodide[24] or benzyl chloride.[25] On the other hand, reaction of 2-aminobenzoquinone with EMME in diphenyl ether at 260-280^{o}C afforded benzo[*g*]quinoline-4,5,10-trione (**4**) which was subsequently methylated to give 1-methylbenzo[*g*]quinoline-4,5,10-trione (**5**). Methylation of **1** afforded ethyl 1-methylbenzo[*g*]quinoline-4,5,10-trione-3-carboxylate (**6**) as described in Scheme 1.

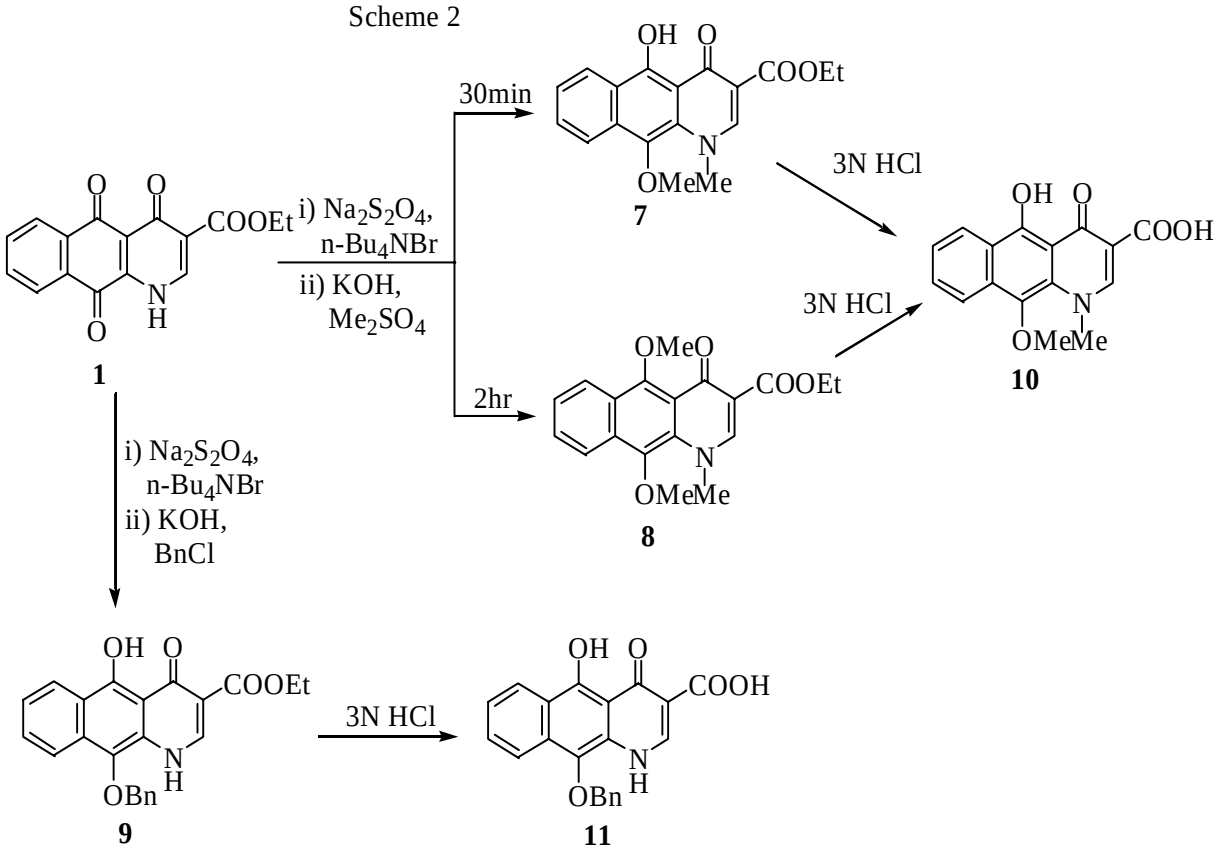
Scheme 1



The reductive methylation ($Na_2S_2O_4$, Me_2SO_4, KOH) of **1** by Kraus modification method[26] with a phase transfer catalyst [n-Bu_4NBr] gave ethyl 5-hydroxy-10-methoxy-1-methylbenzo[*g*]quinolin-4(1*H*)-one-3-carboxylate (**7**) or ethyl 5,10-dimethoxy-1-methylbenzo[*g*]quinolin-4(1*H*)-one-3-carboxylate (**8**) depending on the reaction time. Due to the formation of intramolecular hydrogen bonding between C-4 carbonyl and C-5 OH groups, C-10 hydroxy was more susceptible to methylation than C-5 OH. Hydrolysis of either **7** or **8** with 3N HCl afforded the same free carboxylic acid product, 5-hydroxy-10-methoxy-1-methylbenzo[*g*]quinolin-4(1*H*)-one-3-carboxylic acid (**10**) as depicted in Scheme 2. The presence of the intramolecular H-bonding signal at 14.87 ppm indicated the demethylation of **8** occurred at C-5 methoxy group. Accordingly, 10-benzyloxy-5-hydroxybenzo[*g*]quinolin-4(1*H*)-one-3-carboxylic acid (**11**) was prepared from **1** by the same reaction sequences *via* the reductive alkylation and hydrolysis. Selective *O*-benzylation at C-10 position to give ethyl 10-benzyloxy-5-hydroxybenzo[*g*]quinolin-4(1*H*)-one-

3-carboxylate (**9**) was confirmed by the presence of intramolecular H-bonding signal at 15.68 ppm.

Scheme 2



Benzo[*g*]quinoline derivatives (**3-11**) were evaluated *in vitro* against a 3-cell line panel consisting of MCF7 (Breast), NCI-H460 (Lung), and SF-268 (CNS). The results from Table 1 indicated some of them were active against the primary 3-cell line panel and exhibited good inhibitory activity against the growth of 60 cancer cell lines with GI_{50} values ranged from 2.52 to 29.2 μM. Compounds (**4-6**) exhibited significant cytotoxicity against all 60 cancer cells with mean GI_{50} values of 5.92, 7.75, and 2.52 μM respectively while compounds (**3**) and (**10**) were inactive indicated free carboxylic acid at C-3 position is unfavorable. The results have also implied the importance of carbonyl moieties at C-5 and C-10 due to the inactiveness of reduced products (**7**) and (**9**). Further study on the anticancer SAR of benzo[*g*]quinoline derivatives is ongoing.

EXPERIMENTAL

Melting points were determined on an Electrothermal IA9100 melting point apparatus and are uncorrected. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Varian Gemini 200 spectrometer or Varian-Unity-400 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard. TLC was performed on silica gel 60 F-254 plates purchased

from E. Merck and Co. The elemental analyses were performed in the Instrument Center of National Science Countil at National Cheng-Kung University and National Chung-Hsing University using Heraeus CHN-O Rapid EA.

Table 1. *In Vitro* Anticancer Assay of Benzo[*g*]quinoline Derivatives

Compd.	Growth Percentages[a)]			Mean GI_{50} (μM)[b)]
	NCI-H460 (Lung)	MCF7 (Breast)	SF-268 (CNS)	
3	39	18	28	98.2
4	0	1	2	5.92
5	0	0	1	7.75
6	0	0	1	2.52
7	101	58	130	nd[c)]
8	88	13	81	29.2
9	48	45	68	nd
10	103	35	119	nd
11	36	1	94	13.0

[a)] In this protocol, each cell line is inoculated and preincubated on a microtiter plate. Test agents are then added at a single concentration (100 μM) and the culture incubated for 48 h. End-point determinations are made with alamar blue.[27] Results for each test agent are reported as the percent of growth of the treated cells when compared to the untreated control cells. Compounds which reduced the growth of any one of the cell lines to 32% or less are passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range.[28]

[b)] Mean values over all 60 cell lines tested. Theses cell lines are: leukemia (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, PRMI-8226, and SR); non-small cell lung cancer (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, and NCI-H522); colon cancer (COLC 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, and SW-620); CNS cancer (SF-268, SF-295, SF-539, SNB-19, SNB-75, and U251); melanoma (LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, and UACC-257); ovarian cancer (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3); renal cancer (786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, and UO-31); prostate cancer (PC-3 and DU-145); and breast cancer (MCF7, MCF7/ADR-RES, MDA-MB-231/ ATCC, HS 578T, MDA-MB-435, MDA-N and T-47D).

[c)] Not determined.

Ethyl 1*H*-benzo[*g*]quinoline-4,5,10-trione-3-carboxylate (1). A mixture of 2-aminobenzoquinone (1.74 g, 10 mmol) and diethyl ethoxymethylenemalonate (EMME, 2.59 g, 12 mmol) in Ph_2O (15 mL) was stirred at 210°C for 15 h. The resulting brown mixture was cooled and then n-hexane (30 mL) was added. The precipitate was filtered and washed with n-hexane. The crude product was purified by flash column

chromatography (silica gel; CH_2Cl_2:n-hexane = 2:1) and crystallized from EtOAc to afford **1** (1.04 g, 66 %). mp: 224-226°C (lit.,[23] 224-226.5°C). ^{1}H NMR (DMSO-d_6) δ 1.29 (*t*, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 4.24 (*q*, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 7.82-8.20 (*m*, 5H-C(2, 6-9)), 12.43 (*br s*, NH).

1*H*-Benzo[*g*]quinoline-4,5,10-trione-3-carboxylic acid (2). To a suspension of **1** (1.49 g, 5 mmol) in EtOH (50 mL) was added a solution of 3.0 N HCl (40 mL) and the mixture heated at reflux for 5 h. The mixture was evaporated under reduced pressure and then H_2O (200 mL) was added. This aqueous mixture was extracted with CH_2Cl_2 (3 x 100 mL), and the extract was dried ($MgSO_4$), and concentrated. The residual solid was crystallized from DMF to give **2** (0.80 g, 60%). mp > 300°C. ^{1}H-NMR (DMSO-d_6): 7.91 (*m*, 2H-C(7, 8)), 8.11 (m, 2H-C(6, 9)), 8.66 (s, 1H-C(2)). ^{13}C-NMR (DMSO-d_6): 119.66, 120.02, 126.23, 126.50, 131.02, 133.31, 133.72, 135.42, 147.06, 147.36, 166.08, 176.83, 179.97, 180.56. FAB-HRMS: Calcd for $C_{14}H_8NO_5$ (M+1): 270.0402. Found: 270.0407.

1-Methylbenzo[*g*]quinoline-4,5,10-trione-3-carboxylic acid (3). A mixture of **2** (0.54 g, 2 mmol), K_2CO_3 (1.10 g, 8 mmol), and MeI (1.36 g, 9.6 mmol) in DMF (50 mL) was heated at 120°C for 5 h. (TLC monitoring). The mixture was evaporated under reduced pressure and then H_2O (200 mL) was added. This aqueous mixture was extracted with CH_2Cl_2 (3 x 100 mL), and the extract was dried ($MgSO_4$), and concentrated. Flash column chromatography (FC, silica gel; n-hexane:EtOAc = 1:1) and crystallization from EtOAc gave **3** (0.37 g, 65%). mp 260-262°C. ^{1}H NMR (DMSO-d_6) δ 4.22 (*s*, NCH_3), 7.91 (*m*, 2H-C(7, 8)), 8.05 (*m*, 2H-C(6, 9)), 8.90 (*s*, 1H-C(2)). ^{13}C NMR (DMSO-d_6) δ 40.83, 119.32, 122.40, 125.80, 125.54, 132.07, 132.26, 134.01, 135.10, 146.81, 151.30, 164.66, 176.90, 180.09, 180.39. Anal. Calcd for $C_{15}H_9NO_2 \cdot 0.2\ H_2O$: C, 62.75; H, 3.27; N, 4.88. Found: C, 62.51; H, 3.31; N, 4.50.

1*H*-Benzo[*g*]quinoline-4,5,10-trione (4). A mixture of 2-amino-1,4-naphthoquinone[21] (1.74 g, 10 mmol) and EMME (2.59 g, 12 mmol) in Ph_2O (15 mL) was heated at 260-280°C for 5 h. The reaction mixture was cooled and then *n*-hexane (100 mL) was added. The resulting precipitate was collected, purified by FC (silica gel, CH_2Cl_2/MeOH = 100:1), and crystallized from EtOAc to afford **4** (0.68 g, 30%). mp 290-292°C [lit.,[22] > 300°C]. ^{1}H NMR (DMSO-d_6) δ 6.66 (*m*, 1H-C(2)), 7.85-8.12 (*m*, 5H-C(3, 6-9)), 12.17 (*br s*, NH). ^{13}C NMR (DMSO-d_6) δ 117.64, 121.13, 126.23, 126.37, 131.05, 132.73, 133.90, 135.25, 143.43, 145.30, 158.46, 172.20, 179.41.

1-Methyl-1*H*-benzo[*g*]quinoline-4,5,10-trione (5). Prepared from **4** by the same procedure as described for **3**. Compound (**5**) was obtained in a 55% yield. mp 248-250°C [lit.,[29] 238-239°C]. ^{1}H NMR (DMSO-d_6) δ 3.96 (*s*, CH_3-N(1)), 6.47 (*d*, *J* = 7.8 Hz, 1H-C(2)), 7.77-8.00 (*m*, 5H-C(3, 6-9)). ^{13}C NMR (DMSO-d_6) δ 45.30, 106.88, 121.25, 123.95, 125.53, 126.18, 132.13, 132.31, 133.29, 134.83, 145.24, 145.92, 174.63, 180.82,

182.09.

Ethyl 1-methylbenzo[*g*]quinoline-4,5,10-trione-3-carboxylate (6). Prepared from **1** by the same procedure as described for **3**. Compound (**6**) in was obtained in a 60% yield. mp 191-193°C. ^{1}H NMR (DMSO-d_6) δ 1.29 (*t*, *J* = 7.2, $OCH_2C\underline{H}_3$), 4.03 (*s*, NCH_3), 4.24 (*q*, *J* = 7.2, $OC\underline{H}_2CH_3$), 7.87 (*m*, 2H-C(7, 8)), 8.00 (*m*, 2H-C(6, 9)), 8.38 (*s*, 1H-C(2)). ^{13}C-NMR (DMSO-d_6): δ 14.12, 45.51, 60.59, 123.24, 124.31, 125.53, 126.15, 132.02, 132.14, 133.45, 134.80, 145.51, 148.74, 163.69, 170.80, 180.60, 181.48. Anal. Calcd for $C_{17}H_{13}NO_5 \cdot 0.5\ H_2O$: C, 64.78; H, 4.25; N, 4.44. Found: C, 64.82; H, 4.23; N, 4.19.

Ethyl 5-hydroxy-10-methoxy-1-methylbenzo[*g*]quinolin-4(1*H*)-one-3-carboxylate (7). To a solution of **1** (1.49 g, 5 mmol), n-Bu_4NBr (0.38 g, 1.16 mmol), THF (50 mL), and H_2O (20 mL) was added 20 mL of aqueous $Na_2S_2O_4$ (5.22 g, 30 mmol). After 15 min at rt, a solution of KOH (6.16 g, 110 mmol) in H_2O (5 mL) was added. After 2 min, Me_2SO_4 (10 mL, 105 mmol) was added and the mixture was stirred for 30 min. The product was extracted by partitioning between H_2O (200 mL) and CH_2Cl_2 (3 x 100 mL). The CH_2Cl_2 fractions were combined, dried ($MgSO_4$), and concentrated. The residue was purified by FC (silica gel, n-hexane:EtOAc = 1:1) and crystallized from EtOH to give **7** (1.06 g, 65%). mp 170-171°C. ^{1}H NMR (DMSO-d_6 + TFA-d) δ 1.32 (*t*, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$), 3.85 (s, CH_3-N(1)), 4.23 (s, OCH_3), 4.27 (*q*, *J* = 7.0 Hz, $OC\underline{H}_2CH_3$), 7.57 and 7.77 (two *m*, 2H-C(7, 8)), 8.12 and 8.35 (two *m*, 2H-C(6, 9)), 8.64 (*s*, 1H-C(2)). ^{13}C NMR (DMSO-d_6 + TFA-d) δ 14.40, 46.31, 59.98, 63.74, 105.26, 108.70, 121.05, 121.69, 123.49, 125.25, 128.58, 130.25, 131.05, 134.96, 155.11, 163.61, 180.90. Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.70; H, 5.23; N, 4.25.

Ethyl 5,10-dimethoxy-1-methylbenzo[*g*]quinolin-4(1*H*)-one-3-carboxylate (8). Prepared from **1** by the same procedure as described for **7** except the mixture was stirred for 2h to afford **8** in 60% yield. mp 152-153°C. ^{1}H NMR (DMSO-d_6) δ 1.28 (*t*, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 3.84 (s, CH_3-N(1)), 3.93 (s, OCH_3), 4.09 (s, OCH_3), 4.21 (*q*, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 7.62 and 7.73 (two *m*, 2H-C(7, 8)), 8.15 and 8.28 (two *m*, 2H-C(6, 9)), 8.46 (*s*, 1H-C(2)). ^{13}C NMR (DMSO-d_6) δ 14.40, 45.67, 59.57, 63.02, 63.44, 108.46, 119.87, 121.66, 123.71, 125.59, 126.35, 129.17, 129.90, 130.82, 140.90, 152.78, 153.48, 164.46, 173.67. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.91; H, 5.69; N, 4.08.

Ethyl 10-benzyloxy-5-hydroxybenzo[*g*]quinolin-4(1*H*)-one-3-carboxylate (9). Prepared from **1** and benzyl chloride by the same procedure as described for **7** except the mixture was stirred for 2 h at 90°C to afford **9** in 18% yield. mp 190-192°C. ^{1}H NMR (DMSO-d_6) δ 1.30 (*t*, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 4.24 (*q*, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 5.06 (*s*, OCH_2Ph), 7.36-7.46 (*m*, 3H-Ar), 7.53-7.60 (*m*, 2H-Ar), 7.51 and 7.70 (two *m*, 2H-C(7,8)), 7.98 and 8.32 (two *m*, 2H-C(6, 9)), 8.47 (*s*, 1H-C(2)), 12.15 (*br s*, NH), 15.68 (*s*, OH). ^{13}C NMR (DMSO-d_6) δ 14.33, 59.82, 75.93, 105.20, 107.70, 119.79, 120.78, 123.43, 124.50, 127.68, 128.23, 128.35

(4C), 129.64, 129.84, 131.73, 136.69, 147.74, 156.89, 163.66, 181.39. Anal. Calcd for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60. Found: C, 71.16; H, 5.03; N, 3.57.

5-Hydroxy-10-methoxy-1-methylbenzo[*g*]quinolin-4(1*H*)-one-3-carboxylic acid (10). Hydrolysis of **7** or **8** with 3N HCl by the same procedure as described for **2** afforded **10** in a 30-40 % yield. mp 258-260°C. ^{1}H NMR (DMSO-d_6) δ 3.86 (*s*, CH_3-N(1)), 4.30 (*s*, OCH_3), 7.63 and 7.82 (two *m*, 2H-C(7, 8)), 8.15 and 8.34 (two *m*, 2H-C(6, 9)), 8.85 (*s*, H-C(2)), 13.09 (*br s*, COOH), 14.87 (*br s*, 5-OH). ^{13}C NMR (DMSO-d_6) δ 46.72, 63.91, 103.50, 107.49, 120.91, 121.83, 123.32, 125.88, 128.32, 130.68, 131.21, 135.97, 155.23, 156.73, 164.65, 181.93. Anal. Calcd for $C_{16}H_{13}NO_3 \cdot 0.1\ H_2O$: C, 63.78; H, 4.38; N, 4.64. Found: C, 63.76; H, 4.42; N, 4.62.

10-Benzyloxy-5-hydroxybenzo[*g*]quinolin-4(1*H*)-one-3-carboxylic acid (11). Hydrolysis of **9** with 3N HCl by the same procedure as described for **2** afforded **11** in a 34% yield. mp 236-238°C. ^{1}H NMR (DMSO-d_6) δ 5.09 (*s*, OCH_2), 7.38-7.79 (*m*, 5H-Ar and 2H-C(7, 8)), 8.02 and 8.34 (two *m*, 2H-C(6, 9)), 8.56 (*s*, H-C(2)), 12.78 (*br s*, NH), 13.19 (*br s*, COOH), 13.89 (*s*, 5-OH). ^{13}C NMR (DMSO-d_6) δ 76.16, 103.86, 106.57, 119.87, 121.00, 123.39, 125.20, 127.57, 128.22 (2C), 128.36 (2C), 129.92, 130.30, 132.92, 136.55, 147.75, 155.39, 164.94, 182.75. Anal. Calcd for $C_{21}H_{15}NO_5 \cdot 0.1\ H_2O$: C, 69.39; H, 4.19; N, 3.90. Found: C, 69.21; H, 4.34; N, 4.24.

ACKNOWLEDGMENTS

Financial support of this work by the *National Science Council of the Republic of China* is gratefully acknowledged. We also thank *National Cancer Institute (NCI)* of the United States for the anticancer screenings and the *National Center for High-Performance Computing* for providing computer resources and chemical database services.

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