

Synthesis of Novel 2,3-Dihydro-2-phenylquinolone Dimers Using β -Ketoester and *N*-Alkylaniline

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New dimer, *N,N'*-dialkyl-2,2',4'-trihydroxy-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolones were synthesized for the development of new candidates for anticancer drug through coupling of *N*-alkylanilines and ethyl benzoylacetate. A series of dimers was synthesized using an acid-catalyzed one-pot reaction involving condensation, cyclization, and dimerization. The formation of dimers was accomplished using *p*-toluenesulfonic acid (*p*-TSA) at 90-110 °C in toluene for 3.5-9 h in a Dean-Stark apparatus.

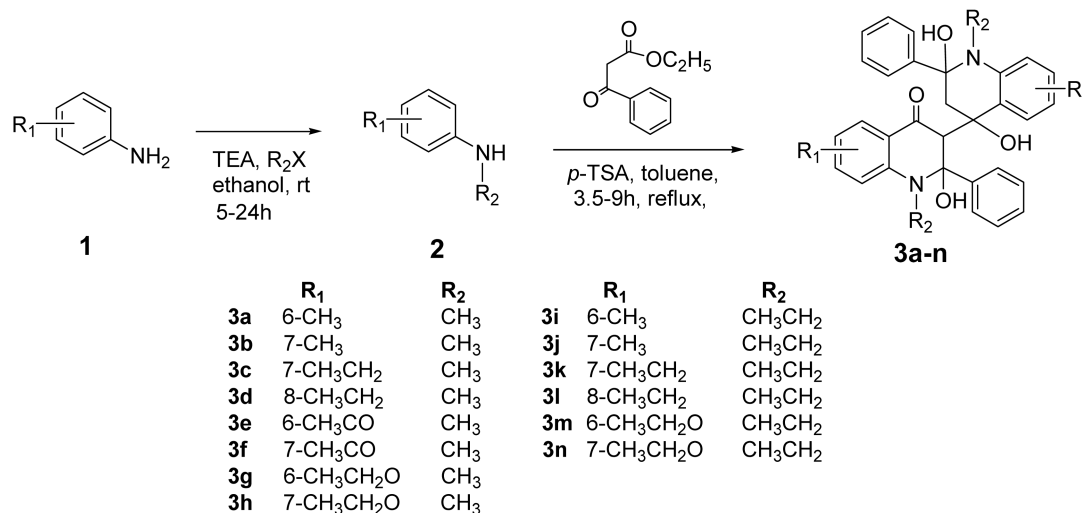
The *N*-alkylation of secondary amines with β -keto ester is not only important for the synthesis of tertiary amines, but is also essential for the preparation of a number of pharmaceuticals. Many reports have been published on the *N*-mono and *N,N*-dialkylation of anilines.¹⁻⁷ Even though synthetic pathways for 2-phenyl-4-quinolones were developed by Li *et al.*,⁸ Kuo *et al.*,⁹ Watterson *et al.*,¹⁰ Xia *et al.*,¹¹ and for 2,3-dihydro-2-phenyl-4-quinolones by Park *et al.*,¹² the synthesis of the dimers of 2,3-dihydro-2-phenyl-4-quinolones has not been reported until now. We applied a general method of preparing amines from a secondary amine and ketones² and a synthetic one-pot operation to produce dihydroquinolone, and previously described a catalytic method that allows the 2-phenylquinolones.¹² 2-Phenylquinolones have been extensively studied as potential antitumor compound.¹³

In our continuing study on the application of 2,3-dihydro-2-phenyl-4-quinolones, we examined *N*-alkylanilines as

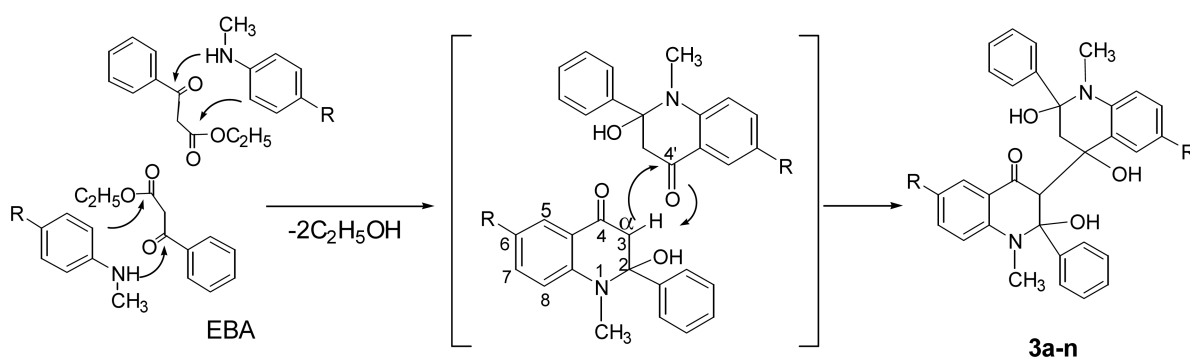
secondary amines in order to discover of novel compound and *N*-alkylanilines were effective to coupling with ethyl benzoylacetate to give the corresponding dimers. Here, we present our results concerning the coupling of *N*-alkylated anilines by β -keto ester, which provide access to quinolone dimers.

N-Alkylated anilines **2** were synthesized from various anilines **1** through selective *N*-monoalkylation using alkyl halide and triethylamine.¹⁴ Quinolones **3a-n** were prepared by coupling of *N*-alkylated anilines and ethyl benzoylacetate in toluene (Scheme 1).

We previously reported the synthesis of 2,3-dihydro-2-phenyl-4-quinolone using primary aniline.¹² The 2,3-dihydro-2-phenyl-4-quinolone derivatives were synthesized through dehydration, dealcoholation and hydration of related primary anilines and ethyl benzoylacetate. But we synthesized the dimers of quinolones without any monomer derivatives from related secondary anilines and ethyl benzoylacetate. In the formation of dimers, the monomers were not observed on the TLC monitoring. The proposed reaction mechanism for the formation of the final product involves cyclization between *N*-alkylated anilines and ethyl benzoylacetate (EBA) and intermolecular coupling between two quinolone molecules. When a β -keto ester is treated with a secondary amine in the presence of catalyst, reductive alkylation of the amine takes place to produce the ester intermediate. Ester was continuously converted to the appropriate quinolone by the removal of ethanol. The intermolecular reaction



Scheme 1. Synthesis of *N,N'*-dimethyl (or ethyl)-2,2',4'-hydroxy-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-quinolones **3a-n**.



Scheme 2. Proposed mechanism for dimer formation; compound **3a-n**.

appeared dependent on the nucleophilic properties of the 3-position. We thought that *N*-alkylaniline added to the β -ketoester to form a dipolar tetrahedral intermediate and proton transfer from nitrogen to oxygen produced a hemiaminal and the dimers were prepared through dealcoholation and rapid additional nucleophilic reaction of α -carbon to 4'-position of another molecule (Scheme 2).

The *p*-toluenesulfonic acid (*p*-TSA) assisted coupling of various *N*-methyl (or ethyl) anilines and EBA, resulting in cyclization and dimerization. A typical reaction is described as follows. A mixture of *N*-alkylaniline (11 mmol), EBA (10 mmol) and *p*-TSA (0.1 mmol) in anhydrous toluene was stirred under reflux for 3.5-9 h in a Dean-Stark apparatus. The reaction was carried out using 1 : 1.1 equivalents of EBA/*N*-alkylanilines. The moieties introduced to the aromatic nucleus of quinolones **3a-n** were 6-methyl, 7-methyl, 6-ethyl, 7-ethyl, 8-ethyl, 6-acetoxy, 7-acetoxy, 6-ethoxy, and 7-ethoxy.

EBA and *N*-methyl (or ethyl)-4(or 3)-toluidines and *N*-methyl (or ethyl)-3(or 2)-ethylanilines were reacted with *p*-TSA in toluene to form the corresponding dimer products in good yields. Similarly, *N*-methyl (or ethyl)-4(or 3)-phenetidines and *N*-methyl-4(or 3)-aminoacetophenones were converted into dimers in somewhat lower yields.

Product **3a-n** were identified by NMR, IR and FABMS. The 3-CH nmr peak of **3a-n** appeared at 5.13-5.45 ppm, and the 3'-CH₂ peak at 3.85-3.88 ppm. The ¹³C nmr peak of 4-carbonyl appeared at 194 ppm, the 3-CH peak at 86.33-87.68 ppm, and 3'-CH₂ peak at 44.03-46.54 ppm. Final products **3a-n** produced a monomer fragment in the MS spectra.

In conclusion, the combination of *N*-alkylated aniline/EBA/*p*-TSA was found to provide a convenient method for giving dimerized quinolones in satisfactory yields. The dimers of 2,3-dihydro-2-phenyl-4-quinolone **3a-n** were synthesized by condensation, cyclization, and nucleophilic reaction of *N*-substituted anilines with ethyl benzoylacetate in order to discover antitumor candidates.

Experimental Section

Chemicals were supplied by Aldrich, Sigma, Merck, and Tokyo Kasei. Melting points were determined in open

capillary tubes on a Büchi 535 melting point apparatus and uncorrected. The NMR spectra were recorded using a Bruker 300 MHz NMR spectrometer. Chemical shift values were reported in parts per million scales in deuteriochloroform or dimethyl-d₆ sulfoxide with tetramethylsilane as the internal standard. The NMR spin multiplicities were indicated by the symbols: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer using NaCl discs and pellets. Low and high-resolution FABMS (positive ion mode) mass spectra were determined on a JEOL 700 mass spectrometer.

General Procedure for the compounds 3a-n. Ethyl benzoylacetate (2.76 mL, 16 mmol), *p*-toluenesulfonic acid (38.0 mg, 0.2 mmol) and *N*-methyl-*p*-toluidine **2** (2.52 mL, 20 mmol) were refluxed for about 6.5 h in anhydrous toluene (35 mL) over the Dean-Stark apparatus until the starting material disappeared. The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure to remove the toluene. The residue was extracted with ethyl acetate (30 mL) and water (15 mL \times 3). The extracts were dried over anhydrous Na₂SO₄, and concentrated under a reduced pressure. The residue was purified by column chromatography (SiO₂, *n*-hexane : ethyl acetate) to give compound **3a** as high viscous oil. The oil was crystallized from methanol.

***N,N'*-Dimethyl-2,2',4'-trihydroxy-6,6'-dimethyl-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolone (3a):** Yield: 59.0%, mp 101-104 °C TLC [*n*-hexane : ethyl acetate (3 : 1)] R_f 0.35. ¹H NMR (300 MHz, CDCl₃) δ 14.77 (s, 1H, OH), 7.77 (d, *J* = 7.8 Hz, 2H, aromatic), 7.56-7.49 (m, 3H, aromatic+OH), 7.42-7.28 (m, 5H, aromatic+OH), 7.24 (d, *J* = 8.0 Hz, 2H, aromatic), 7.17-7.10 (m, 6H, aromatic), 5.39 (s, 1H, CH), 3.85 (s, 2H, CH₂), 3.33 (ss, 6H, N-CH₃ \times 2), 2.41 (s, 3H, CH₃), 2.32 (s, 3H, CH₃). ¹³C NMR (300 MHz, CDCl₃) δ 194.23 (C=O), 172.21, 170.01, 167.25 (C-O), 141.15, 140.80, 138.22, 137.69, 136.42, 134.72, 133.28, 130.47, 130.33, 128.78, 128.53, 128.31, 128.29, 127.08, 127.00, 125.88 (aromatic), 86.93 (CH), 45.49 (CH₂), 37.48 (N-CH₃ \times 2), 21.04 (CH₃ \times 2). IR (NaCl, cm⁻¹) 2923 (aromatic), 1691 (C=O), 1654, 1626, 1576 (C-O). HRMS (FAB, M+H) Calcd for C₃₄H₃₄N₂O₄ 534.2519, found 534.2524

***N,N'*-Dimethyl-2,2',4'-trihydroxy-7,7'-dimethyl-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolone (3b):** Yield: 45.8%, 111-116 °C TLC [*n*-hexane : ethyl acetate (3 : 1)] R_f 0.35. ¹H NMR (300 MHz, CDCl₃) δ 14.77 (s, 1H, OH), 7.77 (d, *J* = 7.8 Hz, 2H, aromatic), 7.56-7.49 (m, 3H, aromatic+OH), 7.42-7.28 (m, 5H, aromatic+OH), 7.24 (d, *J* = 8.0 Hz, 2H, aromatic), 7.17-7.10 (m, 6H, aromatic), 5.39 (s, 1H, CH), 3.85 (s, 2H, CH₂), 3.33 (ss, 6H, N-CH₃ \times 2), 2.41 (s, 3H, CH₃), 2.32 (s, 3H, CH₃). ¹³C NMR (300 MHz, CDCl₃) δ 194.23 (C=O), 172.21, 170.01, 167.25 (C-O), 141.15, 140.80, 138.22, 137.69, 136.42, 134.72, 133.28, 130.47, 130.33, 128.78, 128.53, 128.31, 128.29, 127.08, 127.00, 125.88 (aromatic), 86.93 (CH), 45.49 (CH₂), 37.48 (N-CH₃ \times 2), 21.04 (CH₃ \times 2). IR (NaCl, cm⁻¹) 2923 (aromatic), 1691 (C=O), 1654, 1626, 1576 (C-O). HRMS (FAB, M+H) Calcd for C₃₄H₃₄N₂O₄ 534.2519, found 534.2524

1)] Rf 0.34. ^1H NMR (300 MHz, CDCl_3) δ 14.76 (s, 1H, OH), 7.76 (d, $J = 7.8$ Hz, 2H, aromatic), 7.57-7.50 (m, 3H, aromatic + OH), 7.41 (d, $J = 7.8$ Hz, 2H, aromatic), 7.36 (s, 1H, OH), 7.35-7.30 (m, 2H, aromatic), 7.27 (s, 1H, aromatic), 7.19 (t, $J = 7.4$ Hz, 2H, aromatic), 7.11-7.03 (m, 5H, aromatic), 5.40 (s, 1H, CH), 3.85 (s, 2H, CH_2), 3.33 (ss, 6H, $\text{N-CH}_3 \times 2$), 2.40 (s, 3H, CH_3), 2.30 (s, 3H, CH_3). ^{13}C NMR (300 MHz, CDCl_3) δ 194.25 (C=O), 172.11, 170.00, 167.12 (C-O), 143.62, 143.33, 140.03, 139.85, 136.43, 134.70, 133.30, 130.49, 129.66, 129.47, 128.97, 128.53, 128.31, 128.28, 127.86, 125.88, 124.38, 124.15 (aromatic), 86.95 (CH), 45.55 (CH_2), 37.41 ($\text{N-CH}_3 \times 2$), 21.33, 21.19 (CH_3). IR (NaCl, cm^{-1}) 3400 (OH), 2918 (aromatic), 1692 (C=O), 1655, 1626, 1600 (C-O). HRMS (FAB, M+H) Calcd for $\text{C}_{34}\text{H}_{34}\text{N}_2\text{O}_4$ 534.2519, found 534.2519.

***N,N'*-Dimethyl-2,2',4'-trihydroxy-7,7'-diethyl-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolone (3c):** Yield: 93.5%, Oil, TLC [*n*-hexane : ethyl acetate (3 : 1)] Rf 0.33. ^1H NMR (300 MHz, CDCl_3) δ 14.91 (s, 1H, OH), 7.74 (d, $J = 7.2$ Hz, 2H, aromatic), 7.36 (d, $J = 7.8$ Hz, 2H, aromatic), 7.49-7.43 (m, 1H, aromatic), 7.36-7.19 (m, 7H, aromatic+OH), 7.18 (d, $J = 7.2$ Hz, 1H, aromatic), 7.08-7.04 (m, 5H, aromatic), 5.45 (s, 1H, CH), 3.85 (s, 2H, CH_2), 3.33 (ss, 6H, $\text{N-CH}_3 \times 2$), 2.67 (q, $J = 7.5$ Hz, 2H, CH_2), 2.57 (q, $J = 7.5$ Hz, 2H, CH_2), 1.24 (t, $J = 7.5$ Hz, 1H, CH_3), 1.13 (t, $J = 7.5$ Hz, 3H, CH_3). ^{13}C NMR (300 MHz, CDCl_3) δ 194.22 (C=O), 172.03, 169.91, 167.08 (C-O), 146.26, 143.61, 143.27, 136.28, 134.59, 133.26, 130.47, 129.72, 129.54, 129.49, 128.27, 128.17, 127.73, 127.32, 126.58, 125.76, 124.40, 124.25 (aromatic), 86.86 (CH), 53.54 (CH_2), 45.90, 45.53 (N-CH_3) 28.60, 28.47 (CH_2), 15.46, 15.25 (CH_3). IR (NaCl, cm^{-1}) 3393 (OH), 2965 (aromatic), 1691 (C=O), 1655, 1626, 1601 (C-O). HRMS (FAB, M+H) Calcd for $\text{C}_{36}\text{H}_{38}\text{N}_2\text{O}_4$ 562.2832, found 562.2832.

***N,N'*-Dimethyl-2,2',4'-trihydroxy-8,8'-diethyl-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolone (3d):** Yield: 68.8%, Oil, TLC [*n*-hexane : ethyl acetate (3 : 1)] Rf 0.34. ^1H NMR (300 MHz, CDCl_3) δ 14.89 (s, 1H, OH), 7.76 (d, $J = 8.3$ Hz, 2H, aromatic), 7.53-7.45 (m, 3H, aromatic+OH), 7.39-7.17 (m, 8H, aromatic+OH), 7.08 (d, $J = 8.4$ Hz, 1H, aromatic), 7.02 (d, $J = 9.3$ Hz, 4H, aromatic), 5.29 (s, 1H, CH), 3.85-3.75 (m, 6H, $\text{CH}_2 + \text{CH}_2 \times 2$), 2.38 (s, 3H, N-CH_3), 2.29 (s, 3H, N-CH_3), 1.21-1.13 (m, 6H, $\text{CH}_3 \times 2$). ^{13}C NMR (300 MHz, CDCl_3) δ 194.73 (C=O), 172.03, 170.40, 166.96 (C-O), 142.27, 141.98, 140.27, 136.82, 135.14, 133.65, 130.83, 129.94, 129.81, 129.47, 129.28, 129.18, 128.90, 128.68, 128.61, 126.21, 125.89, 125.66, 118.42 (aromatic), 87.68 (CH), 46.28 (CH_2), 44.55 ($\text{CH}_2 \times 2$), 21.72, 21.58 ($\text{N-CH}_3 \times 2$), 13.66, 13.44 (CH_3). IR (NaCl, cm^{-1}) 2974 (aromatic), 1691 (C=O), 1654, 1628, 1601 (C-O). HRMS (FAB, M+H) Calcd for $\text{C}_{36}\text{H}_{38}\text{N}_2\text{O}_4$ 562.2832, found 562.2832.

***N,N'*-Dimethyl-2,2',4'-trihydroxy-6,6'-diacetoxy-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolone (3e):** Yield: 35.5%, mp 87-89 °C TLC [*n*-hexane : ethyl acetate (1 : 1)] Rf 0.34. ^1H NMR (300 MHz, CDCl_3) δ 14.67 (s, 1H, OH), 8.05 (d, $J = 8.7$ Hz, 2H, aromatic), 7.96 (d, $J = 8.6$ Hz, 2H, aromatic), 7.84-7.81 (m, 5H, aromatic+OH), 7.58-7.56 (m,

2H, aromatic), 7.40-7.35 (m, 6H, aromatic+OH), 7.32 (s, 1H, aromatic), 6.55 (d, $J = 8.8$ Hz, 3H, aromatic), 5.47 (s, 1H, CH), 3.36 (s, 2H, CH_2), 2.88 (ss, 6H, $\text{N-CH}_3 \times 2$), 2.49 (s, 6H, $\text{CH}_3 \times 2$). ^{13}C NMR (300 MHz, CDCl_3) δ 197.02, 196.86, 196.42 (C=O), 171.90, 171.01 (C-O), 147.70, 147.59, 136.05, 135.89, 134.30, 133.62, 130.85, 130.75, 129.96, 129.83, 128.78, 128.66, 128.48, 128.41, 128.31, 127.32, 127.18, 126.45, 125.91 (aromatic), 86.56 (CH), 46.54 (CH_2), 30.05 ($\text{CH}_2 \times 2$), 26.69, 26.63 (CH_3). IR (NaCl, cm^{-1}) 3375 (OH), 2998 (aromatic), 1738, 1683, 1659 (C=O), 1625, 1599, 1574 (C-O). HRMS (FAB, M+H) Calcd for $\text{C}_{36}\text{H}_{34}\text{N}_2\text{O}_6$ 590.2418, found 590.2416.

***N,N'*-Dimethyl-2,2',4'-trihydroxy-7,7'-diethoxy-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolone (3h):** Yield: 27.3%, mp 85-86 °C TLC [*n*-hexane : ethyl acetate (2 : 1)] Rf 0.38. ^1H NMR (300 MHz, CDCl_3) δ 14.73 (s, 1H, OH), 7.78 (d, $J = 8.5$ Hz, 1H, aromatic), 7.58-7.55 (m, 2H, aromatic), 7.53 (s, 1H, OH), 7.42-7.28 (m, 7H, aromatic+OH), 7.26 (s, 2H, aromatic), 6.68-6.82 (m, 2H, aromatic), 6.81-6.77 (m, 3H, aromatic), 5.44 (s, 1H, CH), 4.05 (q, $J = 6.9$ Hz, 2H, O- CH_2), 3.96 (q, $J = 6.9$ Hz, 2H, O- CH_2), 3.88 (s, 2H, CH_2), 3.34 (ss, 6H, $\text{N-CH}_3 \times 2$), 1.45-1.35 (m, 6H, $\text{CH}_3 \times 2$). ^{13}C NMR (300 MHz, CDCl_3) δ 194.28 (C=O), 172.07, 167.07, 159.94, 144.48, 136.39, 134.66, 133.34, 130.56, 130.52, 130.39, 128.56, 128.31, 125.90, 119.47, 119.11, 114.50, 114.00, 113.52, 113.39 (aromatic), 86.93 (CH), 63.74, 63.69 (O- CH_2), 45.47 (CH_2), 43.35, 36.64 (N-CH_3), 14.74, 14.67 (CH_3). IR (NaCl, cm^{-1}) 3400 (OH), 2979 (aromatic), 1692 (C=O), 1657, 1626, 1598, 1586, 1575 (C-O). HRMS (FAB, M+H) Calcd for $\text{C}_{36}\text{H}_{38}\text{N}_2\text{O}_6$ 594.2731, found 594.2751.

***N,N'*-Diethyl-2,2',4'-trihydroxy-6,6'-dimethyl-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolone (3i):** Yield: 45.7%, mp 123-125 °C TLC [*n*-hexane : ethyl acetate (3:1)] Rf 0.35. ^1H NMR (300 MHz, CDCl_3) δ 14.91 (s, 1H, OH), 7.75 (d, $J = 8.4$ Hz, 2H, aromatic), 7.40-7.37 (m, 3H, aromatic+OH), 7.26-7.23 (m, 7H, aromatic+OH), 7.14-7.08 (m, 6H, aromatic), 5.29 (s, 1H, CH), 3.85-3.75 (m, 6H, $\text{CH}_2 + \text{CH}_2 \times 2$), 2.41 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 1.16 (q, $J = 6.9$ Hz, 6H, $\text{CH}_3 \times 2$). ^{13}C NMR (300 MHz, CDCl_3) δ 194.72 (C=O), 172.14, 170.41, 167.08 (C-O), 139.74, 139.40, 138.70, 138.28, 136.82, 135.17, 133.63, 130.81, 130.77, 130.72, 128.90, 128.66, 128.57, 128.49, 126.22 (aromatic), 87.65 (CH), 46.24, 44.57, 43.99 (CH_2), 21.56, 21.44 (CH_3), 13.60, 13.41 (CH_3). IR (NaCl, cm^{-1}) 2976 (aromatic), 1650 (C=O), 1628, 1598 (C-O). HRMS (FAB, M+H) Calcd for $\text{C}_{36}\text{H}_{38}\text{N}_2\text{O}_4$ 562.2832, found 562.2831.

***N,N'*-Diethyl-2,2',4'-trihydroxy-7,7'-dimethyl-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolone (3j):** Yield: 55.5%, Oil, TLC [*n*-hexane : ethyl acetate (3 : 1)] Rf 0.32. ^1H NMR (300 MHz, CDCl_3) δ 14.89 (s, 1H, OH), 7.74 (d, $J = 8.5$ Hz, 2H, aromatic), 7.51-7.48 (m, 3H, aromatic+OH), 7.37-7.32 (m, 4H, aromatic), 7.31 (s, 1H, OH), 7.29-7.24 (m, 6H, aromatic), 7.18-7.15 (m, 3H, aromatic), 5.18 (s, 1H, CH), 3.74 (s, 2H, CH_2), 3.27 (ss, 6H, $\text{CH}_3 \times 2$), 2.66-2.54 (m, 4H, $\text{CH}_2 \times 2$), 1.28-1.17 (m, 6H, $\text{CH}_3 \times 2$). ^{13}C NMR (300 MHz, CDCl_3) δ 194.30 (C=O), 172.72, 170.53, 167.86 (C-O), 142.00, 141.96, 141.65, 141.53, 136.85, 134.96, 133.66,

130.91, 130.12, 130.08, 129.42, 129.24, 128.91, 128.68, 128.63, 127.84, 127.80, 126.18 (aromatic), 86.98 (CH), 45.49 (CH₂), 37.21, 36.46, 24.06, 23.78, 14.96, 14.91 (CH₃). IR (NaCl, cm⁻¹) 3435 (OH), 3053 (aromatic), 1692 (C=O), 1626, 1575 (C-O). HRMS (FAB, M+H) Calcd for C₃₆H₃₈N₂O₄ 562.2832, found 562.2826.

***N,N'*-Diethyl-2,2',4'-trihydroxy-7,7'-diethyl-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolone (3k)**: Yield: 61.0%, Oil, TLC [*n*-hexane : ethyl acetate (3 : 1)] Rf 0.32. ¹H NMR (300 MHz, CDCl₃) δ 15.09 (s, 1H, OH), 7.60 (s, 2H, aromatic), 7.40 (s, 1H, OH), 7.17-6.92 (m, 15H, aromatic+OH), 5.25 (s, 1H, CH), 3.66 (s, 4H, N-CH₂ × 2), 2.51-2.40 (m, 4H, CH₂ × 2), 1.06-0.97 (m, 12H, CH₃ × 4). ¹³C NMR (300 MHz, CDCl₃) δ 192.35, 190.63 (C=O), 169.80, 168.16, 164.58 (C-O), 144.28, 140.23, 139.85, 134.60, 132.89, 131.34, 128.63, 127.84, 127.78, 126.65, 126.47, 126.34, 125.95, 125.87, 125.73, 123.88, 123.77, 123.67 (aromatic), 85.33 (CH), 44.03 (CH₂), 42.21, 41.75 (N-CH₂), 26.79, 26.68 (CH₂), 13.72, 13.51, 11.40, 11.25 (CH₃). IR (NaCl, cm⁻¹) 3468 (OH), 2968 (aromatic), 1691 (C=O), 1654, 1628, 1600 (C-O). HRMS (FAB, M+H) Calcd for C₃₈H₄₂N₂O₄ 590.3145, found 590.3147.

***N,N'*-Diethyl-2,2',4'-trihydroxy-8,8'-diethyl-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolone (3l)**: Yield: 77.6%, Oil, TLC [*n*-hexane : ethyl acetate (8 : 1)] Rf 0.23. ¹H NMR (300 MHz, CDCl₃) δ 15.01 (s, 1H, OH), 7.71 (d, *J* = 8.4 Hz, 1H, aromatic), 7.49 (d, *J* = 8.2 Hz, 3H, aromatic+OH), 7.38-7.23 (m, 11H, aromatic+OH), 7.15-7.13 (m, 3H, aromatic), 5.13 (s, 1H, CH), 4.22-4.15 (m, 2H, CH₂), 2.63-2.53 (m, 3H, CH₃). ¹³C NMR (300 MHz, CDCl₃) δ 194.11 (C=O), 171.95, 170.18, 166.98 (C-O), 141.87, 141.31, 139.51, 134.61, 133.21, 130.44, 129.62, 129.40, 128.92, 128.77, 128.72, 128.47, 128.44, 128.25, 128.22, 127.01, 126.92, 125.72 (aromatic), 87.32 (CH), 45.91, 43.70, 43.15, 23.44, 23.20 (CH₂), 14.47, 14.36, 13.04, 12.75 (CH₃). IR (NaCl, cm⁻¹) 3470 (OH), 2971 (aromatic), 1691 (C=O), 1654, 1627, 1599 (C-O). HRMS (FAB, M+H) Calcd for C₃₈H₄₂N₂O₄ 590.3145, found 590.3140.

***N,N'*-Diethyl-2,2',4'-trihydroxy-7,7'-diethoxy-4-oxo-2,2',3,3'-tetrahydro-2,2'-diphenyl-4,4'-diquinolone (3n)**. Yield: 65.5%, Oil, TLC [*n*-hexane : ethyl acetate (3 : 1)] Rf 0.35. ¹H NMR (300 MHz, CDCl₃) δ 14.92 (s, 1H, OH), 7.76 (d, *J* = 7.3 Hz, 2H, aromatic), 7.56-7.47 (m, 3H, aromatic+OH), 7.40-7.28 (m, 7H, aromatic+OH), 6.81-6.80 (m, 1H, aromatic), 6.77-6.75 (m, 5H, aromatic), 5.34 (s, 1H, CH), 4.09 (q, *J* = 7.1 Hz, 2H, O-CH₂), 4.02 (q, *J* = 6.9 Hz, 2H, O-CH₂), 3.94 (q, *J* = 6.9 Hz, 2H, CH₂), 3.85 (s, 2H, CH₂), 3.79 (q, *J* = 7.1 Hz, 2H,

CH₂), 1.41 (t, *J* = 6.9 Hz, 3H, N-CH₃), 1.36 (t, *J* = 6.9 Hz, 3H, N-CH₃), 1.23 (t, *J* = 7.0 Hz, 3H, CH₃), 1.16 (t, *J* = 7.0 Hz, 3H, CH₃). ¹³C NMR (300 MHz, CDCl₃) δ 194.70 (C=O), 171.93, 171.38, 170.40, 166.83, 160.27 (C-O), 143.39, 143.09, 136.73, 135.03, 133.64, 130.83, 130.80, 130.69, 128.88, 128.65, 128.57, 126.16, 120.89, 120.56, 114.50, 114.89, 114.85, 114.80, 114.40 (aromatic), 87.58 (CH), 53.93 (O-CH₂), 46.16 (CH₂), 44.45, 43.92 (N-CH₂), 15.06, 15.00, 14.53, 13.44 (CH₃). IR (NaCl, cm⁻¹) 3400 (OH), 2978 (aromatic), 1692 (C=O), 1656, 1627, 1599, 1585 (C-O). HRMS (FAB, M+H) Calcd for C₃₈H₄₂N₂O₆ 622.3044, found 622.3064.

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References

- Smith, M. B.; March, *J. March's Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: New York, U.S.A, 2001; p 1185 and references cited therein.
- Hunig, S.; Lucke, E.; Brenninger, W. *Organic Synthesis*, Collective Vol; 1973; Vol. V, p 808.
- Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463.
- Abdel-Magid, F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
- Hayat, S.; Rahman, A.; Choudhary, M. I.; Khan, K. M.; Schumann, W.; Bayer, E. *Tetrahedron* **2001**, *57*, 9951.
- Fache, F.; Valot, F.; Milenkovic, A.; Lemaire, M. *Tetrahedron* **1996**, *52*, 9777.
- Chen, B. C.; Sundeen, J. E.; Guo, P.; Bednarz, M. S.; Zhao, R. *Tetrahedron Lett.* **2001**, *42*, 1245.
- Li, L.; Wang, H. K.; Kuo, S. C.; Wu, T. S.; Mauger, A.; Lin, C. M.; Hamel, E.; Lee, K. H. *J. Med. Chem.* **1994**, *37*, 3400.
- Kuo, S. C.; Lee, H. Z.; Juang, J. P.; Lin, Y. T.; Wu, T. S.; Chang, J. J.; Lednicer, D.; Paull, K. D.; Lin, C. M.; Hamel, E.; Lee, K. H. *J. Med. Chem.* **1993**, *36*, 1146.
- Watterson, S. H.; Carlsen, M.; Dhar, T. G. M.; Shen, Z.; Pitts, W. J.; Gu, H. H.; Norris, D.; Chorba, J.; Chen, P.; Chen, D.; Witmer, M.; Fleener, C. A.; Rouleau, K.; Townsend, R.; Hollenbaugh, D. L.; Iwanowicz, E. J. *Bioorganic & Medicinal Chemistry Lett.* **2003**, *13*, 543.
- Xia, Y.; Yang, Z. Y.; Xia, P.; Bastow, K. F.; Nakanishi, P. N.; Hamel, E.; Brossi, A.; Lee, K. H. *Bioorganic & Medicinal Chemistry Lett.* **2003**, *13*, 2891. (b) Xia, Y.; Yang, Z. Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S. C.; Hamel, E.; Hackl, T.; Lee, K. H. *Bioorganic & Medicinal Chemistry Lett.* **1998**, *41*, 1155.
- Park, M. S.; Lee, J. I. *Bull. Korean Chem. Soc.* **2004**, *25*, 1269.
- Zhao, Y. L.; Chen, Y. L.; Chang, F. S.; Tzeng, C. C. *Eur. J. Med. Chem.* **2005**, *40*, 792.
- Kim, J. H.; Park, M. S. *Yakhak Hoeji* **2005**, *49*, 162.