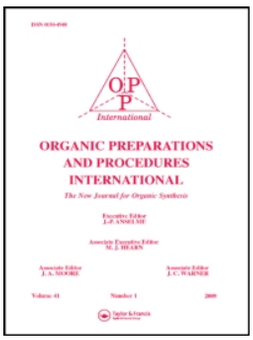

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# Synthesis of New Substituted Kynurenic Acids

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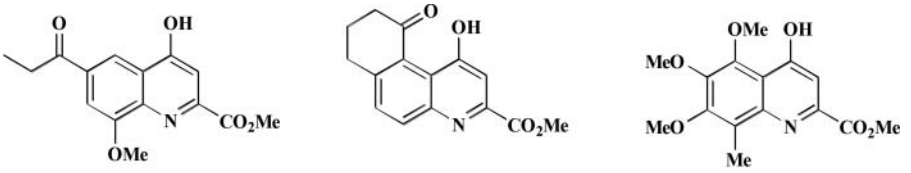
Kynurenic acid (4-hydroxyquinoline-2-carboxylic acid) and its derivatives play a crucial role in maintaining normal brain function.[1] Several kynurenic acid derivatives containing halo, amino, hydroxy and carboxy group in ring B have been prepared and their pharmalogical activities studies[2–9] and thus are attractive targets for organic synthesis. These findings encouraged us to synthesize three - to the best of ourknowledge - previously unreported kynurenic acid derivatives **1–3** (*Figure 1*) with propionyl, cyclo-hexanone and methoxy groups respectively on ring B with the hope that they too might also exhibit useful biological activities. The present article describes the prepa-ration of kynurenic acid derivatives **1, 2** and **3**.




1 2 3

**Figure 1**

The preparation of **1** was approached by condensation of the previously reported[10] aniline **4**, prepared from 3-methoxypropiophenone in four steps (Wolff-Kishner reduction, nitration, oxidation at the benzylic position and reduction of the nitro group), condensed with dimethylacetylene dicarboxylate **5** (DMAD) in methanol at room temperature to afford product **6** in 90% yield; its spectral data indicated the *trans*-configuration about the double bond.

Cyclization of **6** with polyphosphoric acid (PPA) yielded the kynurenic acid **1** (*Scheme 1*) in 60% (an overall yield 6% from 3-methoxypropiophenone). Although this type of cyclization had been performed[3,6,7] by heating in diphenyl ether (bp. 250°C) or in Dowtherm (bp. 235°C), the major disadvantages of these methods are the in-conveniently high temperature and potential problem in isolation; if the kynurenic acid derivative does not precipitate completely, then it becomes extremely difficult to isolate it from the reaction mixture by the usual work-up and the resulting product will remain contaminated with the solvents which are very difficult to remove.

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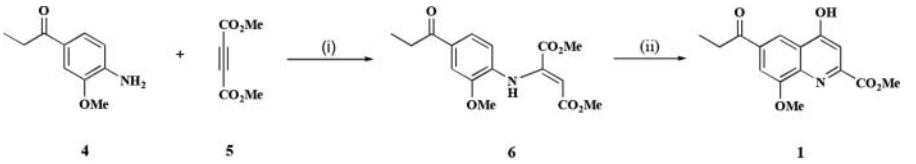
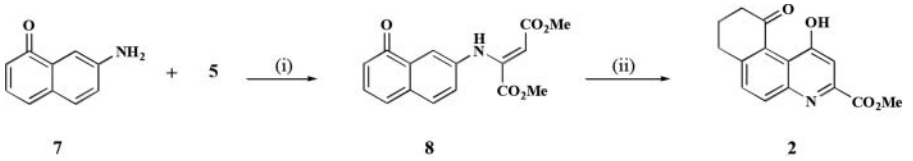



*Reagents: (i) Methanol, rt. (ii) PPA, 100°C*

**Scheme 1**

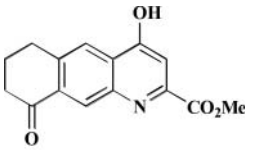
Treatment of the known[11] 7-amino-1-tetralone **7** (prepared from the commer-cially available 1-tetralone in two steps (43% yield) was similarly condensed with DMAD in methanol to afford the *trans* adduct **8** in 90% yield (*Scheme 2*). Conversion of **8** to kynurenic acid **2** in 60% yield




*Reagents: (i) Methanol, rt. (ii) PPA, 80°C*

**Scheme 2**

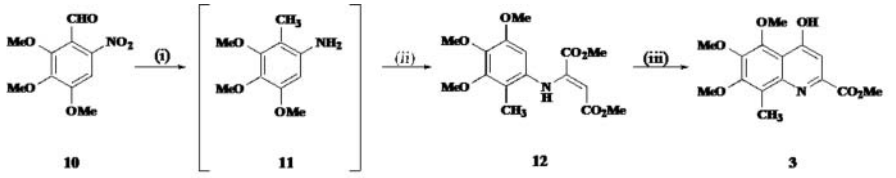
(overall yield 23%) was realized by cyclization using polyphosphoric acid. The struc-ture **2** was assigned to the resulting kynurenic acid on the basis of its $^1$H NMR and IR spectroscopic data. In assition to the signal at $\delta$ 13.46 for the phenolic hydrogen in $^1$H NMR spectrum, the presence of two doublets at $\delta$ 8.31 and 7.51 for hydrogens at C-7 and C-8 and a singlet at $\delta$ 7.65 (hydrogen at C-3) provide strong support for the structure **2** and thus indicating that cyclization had not occurred in the alternate direction to give compound **9**. If the compound **9** had been formed, then three singlets ascribable to three aromatic protons would have appeared in the $^1$H-NMR spectrum. Furthermore the IR spectrum also lent strong evidence in favor of the structure **2**. The absorption at 1727 cm$^{-1}$ was sassigned to the ester carbonyl group and the keto carbo-nyl group at 1642 cm$^{-1}$ was shifted to lower frequency (cyclohexanone absorbs at 1715 cm$^{-1}$) presumably because of the intramolecular bonding. These spectroscopic data clearly indicate the absence of the compound **9**.




**9**

Theoretical calculations performed in order to rationalize the formation of **2** in preference to **9** indicate that the intermediate leading to formation of **9** is not stable and cannot be formed but the intermediate to **2** maintains the cyclic conformation with an energetic cost of only 50 kcal/mol.[12]

Lastly for the synthesis of the kynurenic acid derivative **3** (*Scheme 3*), catalytic hydrogenation of the known[13] nitrobenzaldehyde **10** [surprisingly obtained in 75% yield by nitration of commercially available 2,3,4-trimethoxybenzaldehyde (*Scheme 3*)] led to the reduction of both the nitro and the aladehyde groups. Since the amino compound **11** has a strong tendency to decomposition,[14] the crude hydrogenation product was condensed was condensed with DMDA without purification to give **12** in 67% yield. Conversion of **12** to **3** proceeded in 75% yield and the overall yield to the kynurenic acid derivative **3** was 34% from 2,3,4-trimethoxybenzaldehyde.




10 11 12 3

*Reagents: (i) Pd/C, ethyl acetate, rt. (ii) DMAD, methanol, rt. (iii) PPA, 100°C*

**Scheme 3**

In conclusion, three new substituted kynurenic acids have been synthesized in good yields. No difficulty was experienced in the isolation of the hydroxyquinolines with the use of polyphosphoric acid as the cyclization agent. The biological activities of these kynurenic acid derivatives will be reported elsewhere at a later date.

## Experimental Section

Unless otherwise stated all melting points are uncorrected and were determined on an Electrothermal melting point apparatus. Infrared (IR) spectra were recorded on a Nicolet-Fourier Transform (FT) instrument and NMR ($^1$H and $^{13}$C) spectra were determined on a Bruker AM-300 spectrometer in $CDCl_3$. Chemical shifts ($\delta$) are expressed in ppm. Mass spectra were recorded on Thermo Scientific TSQ Quantum Ultra AM Triple Quadrupole mass spectrometer. Column chromatography was carried out on silica gel 60 (Merck). Thin layer chromatography (TLC) plates were coated with silica gel and the spots were visualized using ultraviolet light. All organic solvents were dried over anhydrous $MgSO_4$ and evaporated *in vacuo.* Microwave irradiations were carried out using a monomode CEM Discovery Labmate microwave oven (2.45 GHZ, 300 W). Elemental analyses were performed on a Carlo-Erba 1108 Elemental Analyser.

### *trans-Dimethyl 2-[(2′-Methoxy-4′-propionylphenyl)amino]-2-butendioate (6)*

To a solution of the amine **4** (70 mg, 0.39 mmol) in methanol (2ml) was added DMAD **5** (0,05 ml, 0.40 mmol). The resulting solution was stirred for 24 h at room temperature and concentrated in *vacuo.* The residue was dissolved in chloroform and the solution was washed, dried and evaporated. The resulting oil on purification using preparative chromatography plate (hexane-ether 9:1) afforded the adduct **6** (113 mg, 90%), a pale yellow solid, mp. 73–75°C (hexane); IR ($cm^{-1}$): 1675, 1740 (CO); MS (m/z): 289 ($M^+$ - MeOH), 260 ($M^+$ - MeOH- Et), 200 (260 – HCOOMe); $^1$H NMR: $\delta$ 9.76 (bs, 1H, NH); 7.48 (d, 1H, $J = 1.77$ Hz) (H at C-5), 7.46–7.43 (dd, 1H, $J = 8.16$ Hz, $J = 1.77$ Hz) (H at

C- 3), 6.65 (d, 1H, $J = 8.16$ Hz) (H at C-2), 5.50 (s, 1H) (H at C-8), 3.91 (s, 3H, OMe), 3.73 (s, 3H,OMe), 3.71 (s, 3H, OMe), 2.91 (q, 2H, $J = 7.3$ Hz) (H at C-14), 1.16 (t, 3H, $J = 7.3$ Hz) (H at C-15); $^{13}$C NMR: $\delta$ 199.34 (C-13), 169.21 (C-9), 164.38 (C-11), 149.43 (C-6), 145.81 (C-7), 133.85 (C-1), 132.12 (C-4), 121.61 (C3), 117.34 (C-5), 109.63 (C-2), 96.18 (C-8), 55.71 (C-16), 52.76 (C-12), 51.32 (C-10), 31.28 (C-14), 8.34 (C-15).

*Anal*. Calcd for $C_{16}H_{19}NO_{6:}$ C, 59.81; H, 5.91. Found: C, 60.07; H, 6.06

### *4-Hydroxy-8-methoxy-6-propionylquinoline-2-carboxylic Acid Methyl Ester (1)*

To polyphosphoric acid (724 mg, 2.1 mmol) previously heated to and kept at 100°C was added adduct **6** (172 mg, 0.54 mmol) and the mixture was stirred for 2 h at 100°C. It was then cooled, quenched with water and extracted with chloroform. The organic extracts were washed, dried and evaporated. Preparative chromatography of the resulting residue (hexane-chloroform 9:1) afforded adduct **1** (92 mg, 60%), a pale yellow solid, mp. 183–185°C (hexane); IR ($cm^{-1}$): 3386 (OH), 1732 (CO), 1678 (CO); MS (m/z): 289 ($M^+$), 260 ($M^+$ - Et), 207 ($M^+ - C_5H_6O$),; $^1$H NMR: $\delta$ 9.46 (s, 1H, OH), 8.47 (s, 1H) (H at C-3), 7.72 (d, 1H, $J = 1.6$ Hz) (H at C-5), 7.01 (s, 1H, $J = 1.6$Hz) (H at C-7), 4.07 (s, 3H, OMe), 4.04 (s, 3H, COOMe), 3.11 (q, 2H, $J = 7.2$Hz), 1.23 (s, 3H, Me); $^{13}$C NMR: $\delta$ 199 (C-11), 179 (C-15), 162 (C-4), 148 (C-8), 135 (C-6), 133 (C-2), 132 (C-9), 126 (C-10), 119 (C-5), 113 (C-7), 109 (C-3), 56 (C-14), 53 (C-16), 31 (C-12), 8 (C-13).

*Anal*. Calcd for. $C_{15}H_{15}NO_5$: C, 62.28; H, 5.19. Found: C, 62.54; H, 5.32

### *Dimethyl (2Z)-2-[(8-Oxo-5,6,7,8-tetrahydronaphthalene-2-yl)amino]but-2-enedioate (8)*

To a solution of aminotetralone **7** (614 mg, 3.82 mmol) in methanol (10 ml) was added DMAD **5** (0.5 ml, 4.01 mmol) and the mixture was stirred at room temperature for 20 h and then heated under reflux in a microwave oven at 65W for 20 min. to complete the reaction. The solution was cooled and evaporated to afford an oil which was chromatographed (hexane-ethyl acetate 8:2) to give adduct **8** (1.04 g, 90%) as yellow liquid; IR ($cm^{-1}$): 3364 (NH), 1725 (CO), 1679 (CO); MS (m/z): 304 ($MH^+$); $^1$H NMR: $\delta$ 9.62 (s, 1H, NH), 7.47 (d, 1H, $J = 2.5$ Hz) (H at C-8) 7.13 (d, 1H, $J = 8.2$ Hz) (H at C-5), 6.98–6.95 (dd, 1H, $J = 8.2$ Hz, $J = 2.5$ Hz) (H at C-6), 5.38 (s, 1H,) (H at C-12), 3.70 (s, 3H) (H at C-16), 3.69 (s, 3H) (H at C-14)), 2.86 (t, 2H, $J = 6.1$ Hz) (H at C-2), 2.57 (t, 2H, $J = 6.1$ Hz) (H at C-4), 2.15–2.02 (m, 2H) (H at C-3); $^{13}$C NMR: $\delta$ 197 (C-1), 169 (C-13), 164 (C-15), 147 (C-7), 140 (C-11), 138 (C-9), 132 (C-10), 129 (C-5), 125 (C-6), 118 (C-8), 94 (C-12), 52 (C-16), 51 (C-14), 38 (C-2), 28 (C-4), 23 (C-3).

*Anal.* Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.61. Found: C, 63.61; H, 5.78.

### *Methyl 1-Hydroxy-9-oxo-7,8,9,10-tetrahydrobenzo[f]quinolone-3-carboxylate (2)*

To polyphosphoric acid (9.49 g, 28.08 mmol) heated to and kept at 80°C was added adduct **8** (2.13 g, 7.02 mmol) and the mixture was stirred at the same temperature for 1 h. It was then cooled, added to ice-cold water and extracted with chloroform. The organic extracts were washed with sodium bicarbonate solution (5%), water, dried and evaporated. The resulting oily material was chromatographed (hexane-$CHCl_3$ 6:4) to yield compound **2** (1.14 g, 60%) as yellow solid, mp.161–163°C (ether); IR ($cm^{-1}$): 1727

(CO), 1642 (CO); MS (m/z): 272 ($MH^+$); $^1$H NMR: $\delta$ 13.46 (s, 1H, OH), 8.31 (d, 1H, $J$ = 8.7 Hz) (H at C-7), 7.65 (s, 1H) (H at C-3), 7.51 (d, 1H, $J$ = 8.7 Hz) (H at C-8), 3.99 (s, 3H, OMe), 3.17 (t, 2H, $J$ = 6.1 Hz) (H at C-14), 2.87 (t, 2H, $J$ = 6.8 Hz) (H at C-12), 2.18–2.13 (m, 2H) (H at C-13),$^{13}$C NMR: $\delta$ 205 (C-11), 165 (C-15), 163 (C-4), 152 (C-2), 150 (C-10), 149 (C-6), 139 (C-7), 131 (C-8), 128 (C-9), 121 (C-5), 111 (C-3), 53 (C-16), 40 (C-12), 32 (C-14), 21 (C-13).

*Anal*. Calcd. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.79. Found: C, 66.65; H, 4.93.

***Dimethyl 2[(2′-Methyl-3′, 4′, 5′,-trimethoxyphenyl)amino]-2-butendioate (12)***

A solution of the nitrobenzaldehyde **10** (608 mg, 2.52 mmol) in ethyl acetate (25 mL) was hydrogenated in presence of (164 mg) Pd-C (10%) at room temperature for 3 h at atmospheric pressure. Removal of the catalyst and solvent afforded an crude oil (532 mg) which was dissolved in methanol (10 mL) and treated with DMAD **5** (0.33 ml, 2.65 mmol). The reaction mixture was stirred at room temperature for 20 h and then heated under reflux in a microwave oven at 65W for 20 min. The solution was cooled, evaporated and the residue afforded adduct **12** as a yellow oil (574 mg, 67%) after preparative chromatography (hexane-ether 6:4). MS (m/z): 339 ($M^+$), 324 ($M^+$–Me), 307 ($M^+$ - MeOH), 280 ($M^+$ - $CO_2$Me); $^1$H NMR: $\delta$ 9.38 (s, 1H, NH), 6.11 (s, 1H) (H at C-6), 5.27 (s, 1H) (H at C-8), 3.78 (s, 3H, OMe at C-5), 3.77 (s, 3H, OMe at C-3), 3.68 (s, 3H) (H at C-12), 3.67 (s, 3H, OMe at C-4), 3.60 (s, 3H) (H- at C-10), 2.10 (s, 3H) (H at C-13); $^{13}$C NMR: $\delta$ 170 (C-9), 164.8 (C-11), 152.2 (C-3), 151.1 (C-5), 149.1 (C-1), 139.7 (C-7), 134.4 (C-4), 117.1 (C-2), 102.1 (C-6), 91.9 (C-8), 60.8 (C-15), 60.5 (C-14), 55.8 (C-16), 52.6 (C-12), 50.9 (C-10), 10.1 (C-13).

*Anal*. Calcd for $C_{16}H_{21}NO_{7:}$ C, 56.63; H, 6.19. Found: C, 56.88; H, 6.37.

***2-Carboxymethyl-4-hydroxy-5,6,7-trimethoxy-8-methylquinoline (3)***

To polyphosphoric acid (1.42 g, 4.2 mmol) heated to and kept at 100°C was added adduct **12** (356 mg, 1.05 mmol) and the mixture was stirred for 2 h at that temperature. It was then cooled, diluted with cold water and extracted with chloroform. The organic extracts were washed with a solution of sodium bicarbonate (5%), dried and evaporated. The resulting yellow oily material on preparative chromatography (hexane-ether 6:4) yielded the product **3** (242 mg, 75%) as pale yellow solid, mp.105–107°C (hexane); IR ($cm^{-1}$) 3407(OH), 1726(CO); MS (m/z): 307 ($M^+$), 292 ($M^+$ - Me), 261($M^+$ - Me - OMe), 232 ($M^+$ - Me - HCOOMe); $^1$H NMR: $\delta$ 10.1 (s, 1H, OH), 7.44 (s, 1H) (H at C-3), 3.98 (s, 6H) (H at C-11, C-16) 3.90 (s, 6H) (H at C-12, C-13); 2.66 (s, 3H) (H at C-14); $^{13}$C NMR: $\delta$ 162.5 (C-15), 153.9 (C-9), 147.9 (C-7), 145.5 (C-5), 144.9 (C-4), 143.5 (C-2), 127.1 (C-6), 112.5 (C-10), 105.6 (C-3), 62.4 (C-12), 61.2 (C-13), 60.9 (C-11), 52.8 (C-16), 10.7 (C-14).

*Anal*: Calcd for $C_{15}H_{17}NO_{6:}$ C, 58.63; H, 5.53. Found: C, 58.82; H, 5.65

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