SYNTHESIS OF 3-(4-METHOXYPHENYL)-5,7-DIMETHOXY-(1*H*)-QUINOLIN-2- OR 4-ONES AND DERIVATIVES

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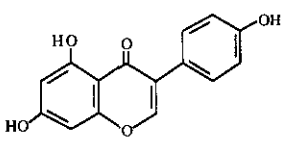
Abstract - Condensation of ethyl 2-(4-methoxyphenyl)-3-hydroxyacrylate with 3,5-dimethoxyaniline afforded, depending on experimental conditions, either 3-(4-methoxyphenyl)-5,7-dimethoxy-(1*H*)-quinolin-2-one or 3-(4-methoxyphenyl)-5,7-dimethoxy-(1*H*)-quinolin-4-one. Whereas chlorination with phosphorous oxychloride led to the corresponding 2- and 4- chloroquinolines derivatives, 2-chloro-3-(4-methoxyphenyl)-5,7-dimethoxyquinoline was also obtained by using the Meth Cohn method's.

Genistein (**1**) is a trihydroxyisoflavone which displays various interesting biological properties, e.g. anti-tyrosine kinase activity,[1] topoisomerase II inhibition [2] and estrogenic properties in the human breast cancer cell line MCF7.[3]

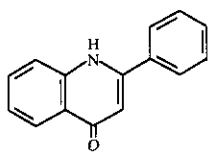
On the other hand 2-phenyl-(*1H*)-quinolin-4-ones (**2**) have recently received attention since several of them were reported to possess potent antitumor activity [4,5] while some 3-phenyl-(*1H*)-quinolin-2-ones (**3**) were described as efficient tools in the treatment of osteoporosis, an estrogen related disease .[6]

Although not directly related, both quinolinone series mentioned above share some structural features with genistein.



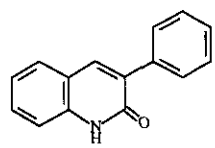
Genistein

1



4-quinolone

2



2-quinolone

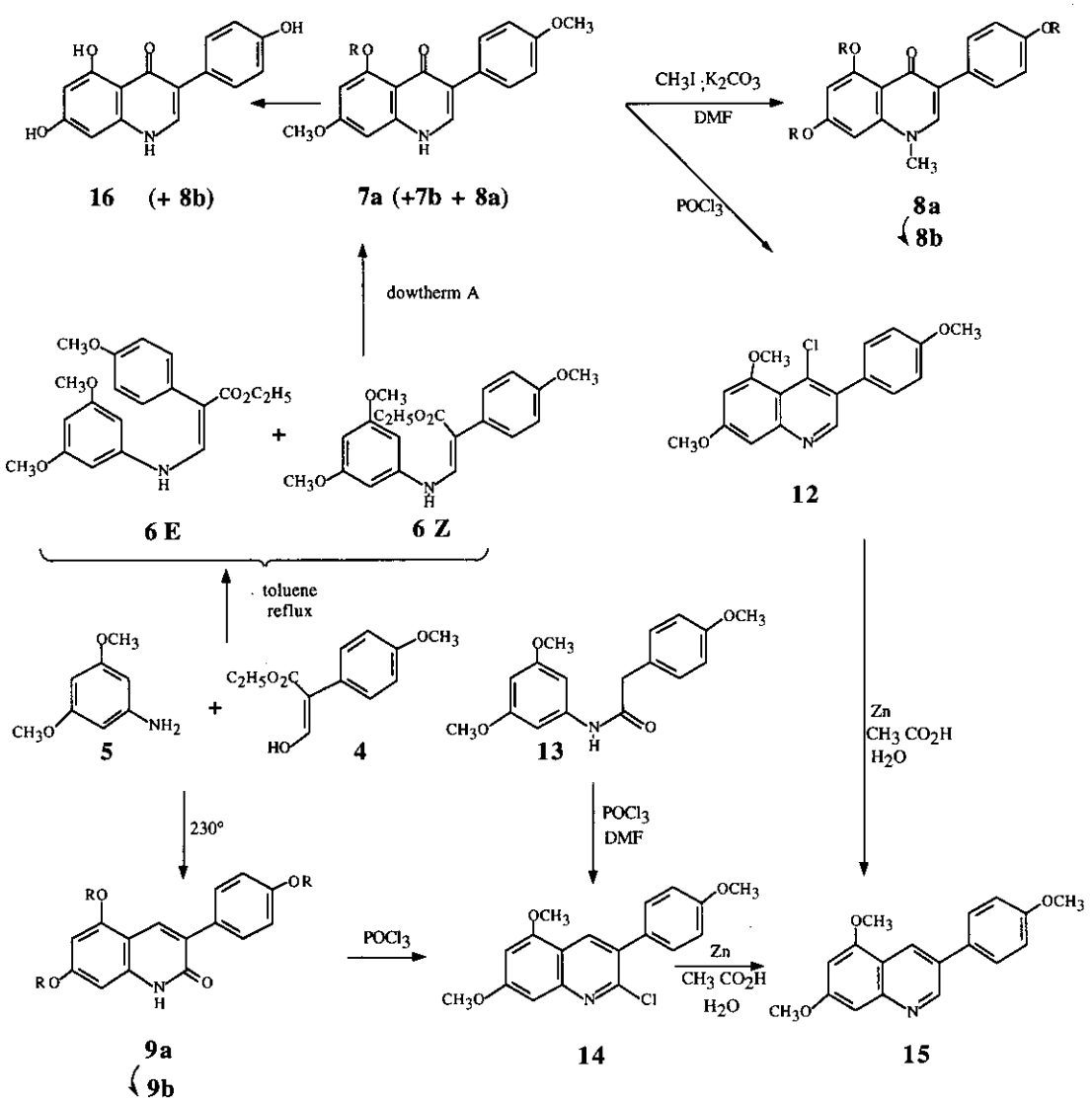
3

In the present work we describe the synthesis of 3-phenyl-(1*H*)-quinolin-2-(and -4)-one derivatives, the latter being nitrogen analogues of the isoflavone genistein.

Condensation of ethyl 2-(4-methoxyphenyl)-3-hydroxyacrylate (**4**) with 3,5-dimethoxyaniline (**5**) gave a mixture of ***Z*** and ***E*** ethyl 2-(4-methoxyphenyl)-3-(3,5-dimethoxyanilino)acrylate (**6**).

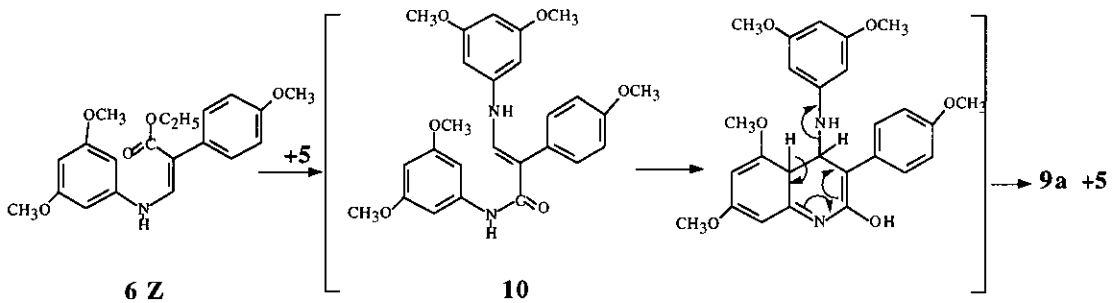
Depending on the experimental conditions of cyclization **6** ***Z*** afforded either 2 - oxo or 4-oxo- quinoline derivatives. Thus thermal cyclization of **6** ***Z*** in boiling dowtherm A (*biphenyl/diphenyl oxide mixture* 26.5 : 73.5) afforded the expected 3-(4-methoxyphenyl)-5,7-dimethoxy-(1*H*)-quinolin-4-one (**7a**) (55 %) together with compound (**7b**), which corresponded to a partial demethylation on C5 (5-OCH_3 → 5-OH)

and a *N*-methylated derivative (**8a**), whereas raising the temperature progressively decreased the yield (Scheme 1).



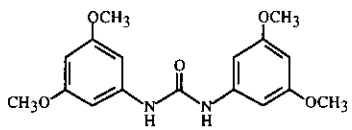
Scheme 1

On the other hand, one pot condensation of **4** with aniline (**5**) and thermal cyclization unexpectedly gave 3-(4-methoxyphenyl)-5,7-dimethoxy-(1*H*)-quinolin-2-one (**9a**) in a poor yield. This can probably be explained by amidation of the ester function which resulted, before cyclization, from the condensation of a second molecule of 3,5-dimethoxyaniline to gave amide (**10**) [7] whose aniline group was thermally eliminated. An hypothetic explanation of this result is depicted in Scheme 2.



Sheme 2

A similar result was recorded when purified **6 *Z*** and aniline (**5**) were heated together. Beside 2-quinolone (**9a**), however, urea (**11**) was also isolated. The formation of this last compound remains unexplained.



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The structures of the two compounds (**7a**) and (**9a**) were confirmed by ^{1}H NMR and IR spectral analyses. Thus, for **7a** a NOE response between the NH and proton H2 was observed whereas **9a** provided a specific response between the C5-OCH_3 and proton H4. Moreover IR spectra indicated a peak at 1624 cm^{-1} corresponding to the carbonyl group of a 4-pyridone ring for **7a** and a peak at 1651 cm^{-1} characteristic of a 2-pyridone system for **9a**.

Quinolones (**9a**) and (**7a**) were transformed by usual chlorination ($POCl_3$) into the 2-chloro and 4-chloro derivatives (**14**) and (**12**) respectively. 2-Chloroquinoline derivative (**14**) was also obtained by Meth-Cohn method's [8] by using acetanilide (**13**) and Vilsmeir's reagent. As expected reductive dechlorination of both 2-chloro and 4-chloro substituted quinolines (**12**) and (**14**) with zinc in warm acetic acid led to trimethoxyphenylquinoline (**15**).

Treatment of **7a** with CH_3I in the presence of K_2CO_3 in DMF led to **8a**. The assignment of **8a** as *N*-methyl derivative was based on ^{1}H NMR spectral evidence, which includes a NOE response between *N*-CH_3 and the two protons H8 and H2 and the appearance of a methyl signal at 3.8 ppm which remains after demethylation leading to compound (**8b**).

Demethylation of **7a**, **8a** and **9a** into **16**, **8b** and **9b** was achieved by reflux in pyridinium hydrochloride at 220°C. In the case of **7a**, beside **16,** the *N*-methylated compound (**8b**) was obtained in 7 % yield.

In conclusion, although various observed transformations were not fully explained, 3-aryl-(1*H*)-quinolin-4-one and -(1*H*)-quinolin-2-one derivatives have been obtained and conditions for their preparation were defined.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Microanalytical results were performed by CNRS, ICSN Gif sur Yvette. ^{1}H NMR spectra were recorded in a Bruker 200 AC (200 MHz) spectrometer. Chemical shifts are given in ppm relative to internal TMS (δ scale). IR spectra were obtained (KBr pellets) with a Nicolet MX-S FT.

Ethyl 2-(4-methoxyphenyl)-3-(3,5-dimethoxyanilino)acrylate (***6 Z*** + ***6 E***)

A mixture of 3,5-dimethoxyaniline (**5**) (12 g, 0.078 mol) and ethyl 2-(4-methoxyphenyl)-3-hydroxyacrylate (**4**) (18 g, 0.08 mol) in toluene (150 ml) was refluxed for 12 h. After cooling, the mixture was diluted with toluene (250 mL) and the unreacted amine was extracted with 6N HCl. About 1 g of aniline hydrochloride was filtered off. The organic layer was dried over $MgSO_4$ and the main part of the solvent removed under reduced pressure. The precipitate obtained was collected and identified as isomer (***6 Z***). The mother liquor contained a mixture of both isomers (***Z*** + ***E***). A chromatography on silica gel with CH_2Cl_2 as eluent gave successively isomer ***E*** and isomer ***Z***.

6 Z was recrystallized from methanol as colorless needles (14 g, 50 %), mp 95°C. Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21 ; H, 6.49 ; N, 3.92. Found : C, 66.89 ; H, 6.49 ; N, 3.96.^{1}H NMR ($CDCl_3$) δ : 10.23 (d, 1H, NH, J_{NH-CH} = 12.3 Hz) ; 7.30 (d, 1H, CH, J = 12.3 Hz) ; 7.24 (m, 2H, AA', $J_{AA'BB'}$ = 8.7 Hz) ; 6.87 (m, 2H, BB') ; 6.12 (m, 3H, H2 + H4 + H6) ; 4.24 (q, 2H, $C\underline{H}_2CH_3$, J_{CH-CH3}= 7.1 Hz, J_{H-H}= 14 Hz) ; 3.84, 3.81 and 3.76 (s, 9H, OCH_3) ; 1.29 (t, 3H, $CH_2C\underline{H}_3$, J = 7.1 Hz).

6 E was recrystallized from methanol as colorless needles (1,7 g ; 6 %), mp 108°C. Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21 ; H, 6.49 ; N, 3.92. Found : C, 66.86 ; H, 6.39 ; N, 4.10. ^{1}H NMR ($CDCl_3$) δ : 8.07 (d, 1H, CH, J_{CH-NH}= 13.5 Hz) ; 7.22 (m, 2H, AA', $J_{AA'-BB'}$ = 8.6 Hz) ; 6.97 (m, 2H, BB') ; 6.35 (d, 1H, NH, J = 13.5 Hz) ; 6.05 (m, 3H, H2 + H4 + H6) ; 4.20 (q, 2H, $C\underline{H}_2CH_3$, J_{CH-CH3} = 7.1 Hz, J_{H-H} = 14 Hz) ; 3.83 (s, 3H, OCH_3) ; 3.75 (s, 6H, OCH_3) ; 1.26 (t, 3H, $CH_2C\underline{H}_3$, J = 7.1 Hz).

3-(4-Methoxyphenyl)-5,7-dimethoxy-(1*H*)-quinolin-4-one (**7a**).

The anilino acrylate (***6 Z***) (5.1 g, 0.014 mol) was quickly added with stirring in small portions in dowtherm A (50 mL) at 250°C. After 10 min, the mixture was cooled to room temperature and diluted with n-hexane (100 mL). The precipitate was collected, washed with $CHCl_3$. Recrystallization from ethanol afforded **7a** (1.9 g, 43 %) as colorless needles, mp 261°C. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44 ; H, 5.50 ; N, 4.50. Found : C, 69.18 ; H, 5.44 ; N, 4.50. ^{1}H NMR (DMSO-d_6) δ : 11.49 (s, 1H, NH) ; 7.79 (s, 1H, H2) ; 7.56 (m, 2H, AA',$J_{AA'-BB'}$= 8.7 Hz) ; 6.94 (m, 2H, BB') ; 6.53 (d, 1H, H6, J_{H6-H8}= 2.19 Hz) ; 6.34 (d, 1H, H8, J = 2.19 Hz) ; 3.95 (s, 3H, OCH_3) ; 3.86 (s, 3H, OCH_3) ; 3.81 (s, 3H, OCH_3).

The mother liquor was evaporated under vacuum and the residue was chromatographed on a silica gel column. Elution with CH_2Cl_2 gave :

a) Colorless microcrystals from ethanol identified as 3-(4-methoxyphenyl)-5-hydroxy-7-methoxy-(1*H*)-quinolin-4-one (**7b**) (0.680 g, 16 %), mp 241°C. Anal. Calcd for $C_{17}H_{15}NO_4$ + C_2H_5OH (4 : 1) : C, 68.06 ; H, 5.39 ; N, 4.54. Found : C, 67.94 ; H, 5.16 ; N, 4.79.^{1}H NMR (DMSO-d_6) δ : 15.00 (s, 1H,

OH) ; 12.28 (s, 1H, NH) ; 8.12 (s, 1H, H2) ; 7.64 (m, 2H, AA', $J_{AA'-BB'}$ = 8.8 Hz) ; 7.00 (m, 2H, BB') 6.47 (d, 1H, H8, J_{H8-H6} = 2.1 Hz) ; 6.22 (d, 1H, H6, J = 2.1 Hz) ; 3.85 (s, 3H, OCH_3) ; 3.82 (s, 3H, OCH_3),

b) **7a** (0.550 mg, raising the overall yield to 55 %),

c) Elution with ethyl acetate and recrystallization from the same solvent gave compound (**8a**) (0.3 g, 6.8 %) as yellow needles, mp 175°C. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14 ; H, 5.89 ; N, 4.50. Found : C, 69.92 ; H, 5.75 ; N, 4.37.^{1}H NMR (DMSO-d_6) δ : 7.96 (s, 1H, H2) ; 7.57 (m, 2H, AA', $J_{AA'-BB'}$ = 8.7 Hz) ; 6.95 (m, 2H, BB') ; 6.53 (d, 1H, H6, J_{H6-H8}= 2.1 Hz) ; 6.47 (d, 1H, H8, J = 2.1 Hz); 3.95 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3) ; 3.79 (s, 3H, OCH_3) ; 3.80 (s, 3H, N-CH_3).

1-Methyl-5,7-dimethoxy-3-(4 -methoxyphenyl)-(1*H*)-quinolin-4-one (**8a**).

Compound (**7a**) (15 g, 4.8 mmol) was dissolved in dry DMF (35 mL) at 60°C. After cooling at room temperature the mixture was treated with potassium carbonate (5 g, 36 mmol) then methyl iodide (2 g, 14 mmol) was added dropwise and stiring was pursued for 8 h. Then the mixture was filtered and DMF removed under reduced pressure. Addition of water (50 mL) gave a precipitate corresponding to **8a** which was recrystallized from ethyl acetate as yellow needles (1.1 g, 72 %), mp 175°C, in all respects identical to that already isolated beside compounds (**7a**) and (**7b**).

3-(4-Methoxyphenyl)-5,7-dimethoxy-(1*H*)-quinolin-2-one (**9a**).

The mixture of 3,5-dimethoxyaniline (**5**) (6.12 g, 0.04 mol) and ethyl 2-(4-methoxyphenyl)-3-hydroxy acrylate (**4**) (9 g, 0.04 mol) was heated together, until all water was eliminated. The mixture (**6** ***Z*** and **6** ***E***) was transformed without further purification by heating at 210-222°C for 30 min and at 230-233°C for 5 min in a metal bath. After cooling, toluene was added and the precipitate filtered off. The crude material was purified by recrystallization in toluene as colorless needles (1.77 g, 14 %), mp 260°C. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44 ; H, 5.50 ; N, 4.50. Found : C, 69.79 ; H, 5.65 ; N, 4.45.^{1}H NMR (DMSO-d_6) δ: 11.74 (br s, 1H, NH) ; 8.00 (s, 1H, H4) ; 7.71 (m, 2H, AA', $J_{AA'-BB'}$ = 8.8 Hz) ; 7.00 (m, 2H, BB') ; 6.50 (d, 1H, H8, J_{H8-H6}= 2.1 Hz) ; 6.39 (d, 1H, H6, J = 2.1 Hz) ; 3.93 (s, 3H, OCH_3) ; 3.85 (s, 3H, OCH_3) ; 3.82 (s, 3H, OCH_3).

In the filtrate, beside ***6 E*** (1 g, 7 %) already described above, the urea (**11**) was also obtained (0.9 g, 10 %) as colorless microcrystals, mp 210°C from ethanol. Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61,44 ; H. 6.07 ; N, 8.43. Found : C, 61.81 ; H, 6.11 ; N, 8.19. ^{1}H NMR (DMSO-d_6) δ : 8.65 (s, 2H, NH) ; 6.69 (s, 4H, H2 + H5) ; 6.18 (s,2H, H4) ; 3.75 (s, 12H, OCH_3).

2-(4-Methoxyphenyl)-*N*-(3,5-dimethoxyphenyl)acetamide (**13**).

3,5-Dimethoxyaniline (**5**) (4 g, 0.026 mol) in toluene (80 mL) containing triethylamine (3.3 mL, 0.039 mol) and 4-methoxyphenylacetyl chloride (4.8 g, 0.026 mol) in toluene (20 mL) were heated at reflux for 3 h. After cooling, the solution was washed with an aqueous solution of $NaHCO_3$, then with water. The organic layer was dried over $MgSO_4$ and evaporated under *vacuum*. Amide (**13**) was recrystallized from toluene as colorless microcrystal (5.7 g, 73 %), mp 150°C. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76 ; H,

6.36 ; N, 4.65. Found : C, 67.88 ; H, 6.31 ; N, 4.69.^{1}H NMR ($CDCl_3$) δ : 7.33 (s, 1H, NH) ; 7.25 (m, 2H, AA') ; 6.93 (m, 2H, BB') ; 6.71 (m, 2H, H2 + H6) ; 6.23 (m, 1H, H_4) ; 3.84, 3.78, 3.75 (s, 9H, OCH_3) ; 3.66 (s, 2H, CH_2).

2-Chloro-3-(4-methoxyphenyl)-5,7-dimethoxyquinoline (**14**).

Method A. Compound (**9a**) (1.04 g ; 3.34 mmol) in $POCl_3$ (20 mL) was refluxed for 2.5 h. After cooling at room temperature, $POCl_3$ was evaporated under reduced pressure, then the residue was poured into ice-water and a saturated aqueous K_2CO_3 solution was added. **14** was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated under *vacuum*. The chloro compound (**14**) was recrystallized from cyclohexane as colorless needles (0.640 g, 58 %), mp 168°C. Anal. Calcd for $C_{18}H_{16}NO_3Cl$: C, 65.56 ; H, 4.89 ; N, 4.25. Found : C, 65.58 ; H, 4.71 ; N, 3.96.^{1}H NMR (DMSO-d_6) δ : 8.27 (s, 1H, H4) ; 7.51 (m, 2H, AA', $J_{AA'-BB'}$= 8.5 Hz) ; 7.08 (m, 2H BB') ; 7.03 (d, 1H, H8, J_{H8-H6}= 1.9 Hz) ; 6.78 (d, 1H, H6, J = 1.9 Hz) ; 3.99, 3.86 (s, 6H, OCH_3).

Method B. To dimethylformamide (1.16 mL, 0.015 mol) cooled at 0°C $POCl_3$ (6.44 mL, 0.07 mol) was added dropwise, under stirring. After 0.5 h, anilide **13** (3 g, 0.01 mol) was added and after 5 min the mixture was heated at 80°C for 4 h. The mixture was cooled and poured into ice-water. After stirring for 0.5 h, the chloro compound (**14**) was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over $MgSO_4$ and the solvant evaporated under *vacuum*. The residue was chromatographed on silica gel. Elution with methylene chloride gave **14** (1 g, 30.5 %).

4-Chloro-3-(4-methoxyphenyl)-5,7-dimethoxyquinoline (**12**).

By using the method A described for obtention of compound (**14**), **7a** (3.1 g, 0.01 mol) gave **12** (2.50 g, 77 %) as colorless needles, mp 124°C (from cyclohexane). Anal. Calcd for $C_{18}H_{16}NO_3Cl$: C, 65.56 ; H, 4.89 ; N, 4.25. Found : C, 65.30 ; H, 4.89 ; N, 4.09. ^{1}H NMR (DMSO-d_6) δ : 8.59 (s, 1H, H2) ; 7.41 (m, 2H, AA', $J_{AA'-BB'}$= 8.7 Hz) ; 7.04 (m, 2H, BB') ; 7.05 (d, 1H, H8, J_{H8-H6}= 2.4 Hz) ; 6.77 (d, 1H, H6, J = 2.4 Hz) ; 3.91, 3.90, 3.61 (s, 9H, OCH_3).

3-(4-Methoxyphenyl)-5,7-dimethoxyquinoline (**15**)

The chloroquinoline (**12**) or (**14**) (0.5 g, 1.5 mmol) in acetic acid (10 mL) and water (0.85 mL) was heated to 75°C. Zinc (0.4 g, 6.15 mmol) was added, and the stirred mixture was maintained at 75°C for 1 h. Water (50 mL) was added and the mixture was basified with aqueous sodium hydroxide (40 % w/v) and extracted with CH_2Cl_2. The dried ($MgSO_4$) extract was evaporated and the residue chromatographed on silica gel. Elution with CH_2Cl_2 and recrystallization gave **15** (350 mg, 78 %) as colorless needles, mp 135°C (from cyclohexane). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20 ; H, 5.80 ; N, 4.74. Found : C, 73.02 ; H, 6.01 ; N, 4.79. ^{1}H NMR ($CDCl_3$) δ : 9.03 (d, 1H, H2, J_{H2-H4}= 2.4 Hz) ; 8.55 (d, 1H, H4, J = 2.4 Hz) ; 7.65 (m, 2H, AA', $J_{AA'-BB'}$= 8.8 Hz) ; 7.02 (m, 2H, BB') ; 7.03 (d, 1H, H8, J_{H8-H6}= 2.2 Hz) ; 6.53 (d, 1H, H6, J = 2.2 Hz) ; 3.98, 3.94, 3.86 (s, 9H, OCH_3).

General procedure for the synthesis of trihydroxy compounds (**16**, **8b** and **9b**)

The trimethoxy derivatives (**7a**), (**8a**) and (**9a**) (1 g) were refluxed in a large excess of pyridine hydrochloride (10 g) for 0.5 h for **7a-8a** or 1 h for **9a**. After cooling, water was added and the precipitate filtered off, washed with water and recrystallized.

3-(Hydroxyphenyl)-5,7-dihydroxy-(1*H*)-quinolin-2-one (**9b**) was recrystallized from aqueous ethanol (1/1) as pale yellow leaves (700 mg, 86 %), mp > 280°C. Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.91 ; H, 4.12 ; N, 5.20. Found : C, 66.57 ; H, 4.20 ; N, 5.28. ^{1}H NMR (DMSO-d_6) δ : 11.53, 10.28, 9.90 (s, 3H, OH) ; 9.48 (s, 1H, NH) ; 7.95 (s, 1H, H4) ; 7.57 (m, 2H, AA', $J_{AA'-BB'}$= 8.6 Hz) ; 6.81 (m, 2H, BB') ; 6.28 (d, 1H, H8, J_{H8-H6}= 1.9 Hz) ; 6.16 (d, 1H, H6, J = 1.9 Hz).

3-(4-Hydroxyphenyl)-5,7-dihydroxy-(1*H*)-quinolin-4-one (**16**). The filtrate contained a mixture of **7b** and **16** which can be separated by chromatography on silica gel using CH_2Cl_2 + 10 % methanol as eluent. Compound (**7b**) was obtained in the first fraction (60 mg, 7 %). The second fraction gave **16** (300 mg, 37 %) as pale yellow leaves, mp > 320°. Anal. Calcd for $C_{15}H_{11}NO_4$ + 1 H_2O : C, 62.72 ; H, 4.56 ; N, 4.88. Found : C, 62.42 ; H, 4.59 ; N, 4.80. ^{1}H NMR (DMSO-d_6) δ : 15.0 (s, 1H, OH) ; 12.1 (br s, 1H, NH) ; 10.25 (br s, 1H, OH) ; 9.4 (br s, 1H, OH) ; 7.97 (s, 1H, H2) ; 7.50 (m, 2H, AA', $J_{AA'-BB'}$= 8.6 Hz) ; 6.81 (m, 2H, BB') ; 6.33 (d, 1H, H8, J_{H8-H6}= 2.1 Hz) ; 6.05 (d, 1H H6, J = 2.1 Hz).

1-Methyl-3-(4-hydroxyphenyl)-5,7-dihydro-(1*H*)-quinolin-4-one(**8b**) was recrystallized from ethanol as pale yellow leaves (563 mg, 66 %), mp 316°C. Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84 ; H, 4.63 ; N, 4.94. Found : C, 67.45 ; H, 4.63 ; N, 5.01. ^{1}H NMR (DMSO-d_6) δ : 15.5 (s, 1H, OH) ; 10.45 (br s, 1H, OH) ; 9.45 (br s, 1H, OH) ; 8.18 (s, 1H, H2) ; 7.50 (m, 2H, AA', $J_{AA-BB'}$= 8.7 Hz) ; 6.82 (m, 2H, BB') ; 6.29 (d, 1H, H8, J_{H8-H6}= 2.1 Hz) ; 6.17 (d, 1H, H6, J = 2.1 Hz) ; 3.79 (s, 3H, CH_3).

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