SYNTHESIS OF 2,5,8(1*H*)-QUINOLINETRIONE DERIVATIVES THROUGH VILSMEIER-HAACK FORMYLATION OF 2,5-DIMETHOXYANILIDES

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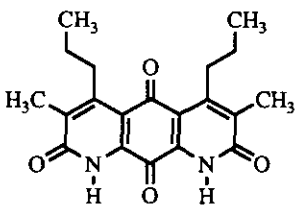
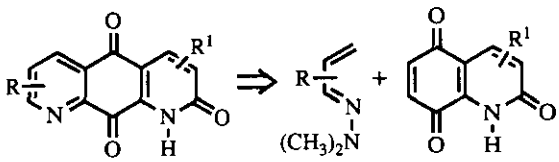
Abstract- The preparation of 2,5,8(1H)-quinolinetrione derivatives bearing both electron-withdrawing and electron-releasing groups at C_3 is described. The reaction sequence employed involves Vilsmeier-Haack cyclization of 2,5-dimethoxyanilides into 3-substituted 5,8-dimethoxy-2-chloroquinolines, followed by hydrolysis to the corresponding 2(1H)-quinolinones and oxidative demethylation with cerium ammonium nitrate.

Diazaquinomycin A[1] is a structurally novel *Streptomyces* metabolite with good activity as a thymidilate synthase inhibitor that departs from previous lead compounds in this field.[2] We have shown[3] that the hetero Diels-Alder reaction between 1-azadienes[4] and derivatives of the 2,5,8(1*H*)-quinolinetrione ("carbostyrilquinone") system provides ready access to diazaquinomycin analogues, many of which show excellent *in vitro* antitumour activity[3b] (Scheme 1).



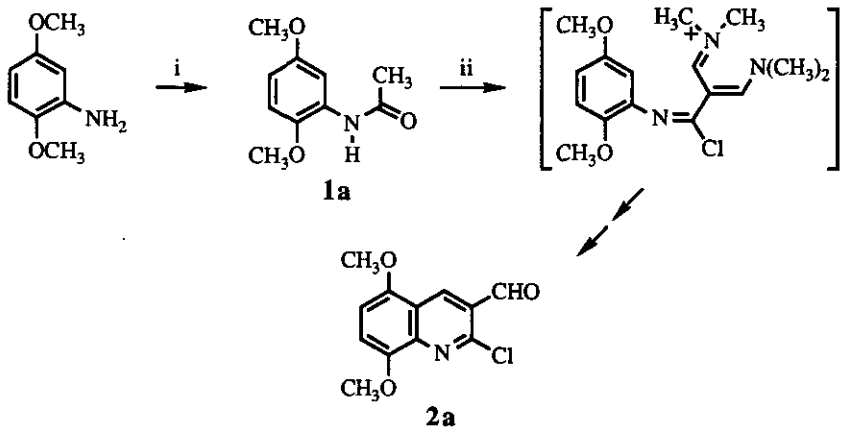
Diazaquinomycin A



Scheme 1

However, the use of the Diels-Alder approach for the systematic study of structure-activity relationships within this series of compounds is hampered by the lack of general methods for the synthesis of 3- or 4-substituted carbostyrilquinones.[5,6] We have recently developed[7] a Friedländer-based strategy that allows the efficient preparation of 2,5,8(1*H*)-quinolinetriones bearing electron-withdrawing groups at C_3 and now report an alternative, more general method that yields derivatives with both electron-withdrawing and electron-releasing groups at this position. This new approach is based on cyclization of 2,5-dimethoxyanilides under Vilsmeier-Haack conditions,[8] followed by hydrolysis of the 2-chloroquinolines thus obtained and oxidative demethylation.

Meth-Cohn and coworkers have shown[9] that treatment of acetanilides with the Vilsmeier-Haack reagent with phosphorous oxychloride as solvent allows the preparation of quinoline derivatives. In agreement with these antecedents, we observed that treatment of 2,5-dimethoxyacetanilide (**1a**) with phosphorous oxychloride and dimethylformamide afforded a 50 % yield of 5,8-dimethoxy-2-chloroquinoline-3-carbaldehyde (**2a**), presumably arising[9] from double Vilsmeier-Haack reaction of the anilide prior to cyclization (Scheme 2).

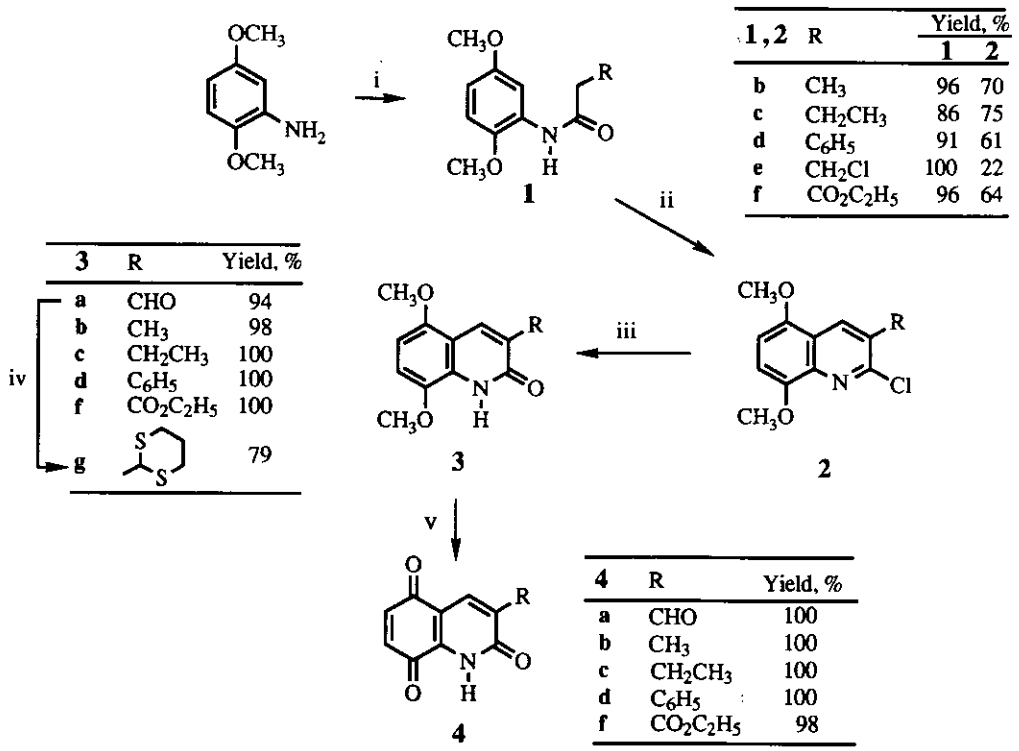


Reagents and conditions: i. $ClCOCH_3$, benzene, room temperature, 1 h
ii. DMF, $POCl_3$, 110 °C, 2 h

Scheme 2

The above mentioned double formylation is not possible if anilides higher than acetanilides are employed and therefore this method, although it has found little use in the literature,[10] should provide a good route to other 3-substituted 2-chloroquinolines. Our results, shown in Scheme 3, prove that 2,5-dimethoxyanilides (**1b-f**), bearing both electron-withdrawing and electron-releasing groups in the α position, can be efficiently cyclized to 3-substituted 2-chloroquinolines (compounds **2**). Clean, quantitative hydrolysis of **2**

to 5,8-dimethoxycarbostyrils (**3**) was achieved by heating in acetic acid containing a small amount of water, with the exception of the unstable compound (**2e**), which under the same conditions gave an intractable mixture. Aldehyde (**3a**) was fully characterized as its dithioketal (**3g**). Oxidative demethylation of compounds (**3**) to the desired quinones (**4**) was carried out by treatment with cerium ammonium nitrate[11] in acetonitrile-water at room temperature. An attempt to oxidize the protected derivative (**3g**) was unsuccessful, since it was insoluble in the reaction medium at room temperature and decomposed under forcing conditions; fortunately, oxidation of **3a** to quinone **4a** proceeded quantitatively without interference from the carbonyl group.



1,2	R	Yield, % 1	2
b	CH_3	96	70
c	CH_2CH_3	86	75
d	C_6H_5	91	61
e	CH_2Cl	100	22
f	$CO_2C_2H_5$	96	64

3	R	Yield, %
a	CHO	94
b	CH_3	98
c	CH_2CH_3	100
d	C_6H_5	100
f	$CO_2C_2H_5$	100
g		79

4	R	Yield, %
a	CHO	100
b	CH_3	100
c	CH_2CH_3	100
d	C_6H_5	100
f	$CO_2C_2H_5$	98

Reagents and conditions: i. ClCOR, benzene, room temperature, 1 h; ii. DMF, $POCl_3$, 75-100 °C, 1-3 h; iii. AcOH, H_2O, reflux, 1-5 h; iv. HS-$(CH_2)_3$-SH, HCl (g), 0 °C, 30 min; v. $(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, room temperature-50 °C, 15-30 min

Scheme 3

EXPERIMENTAL

Ir spectra were recorded on Perkin-Elmer 577 and Buck Scientific 500 spectrophotometers, with all compounds compressed into KBr pellets. Nmr spectra were obtained on Bruker AC-250 (250 MHz for ^1H, 63 MHz for ^{13}C) and Varian VXR-300 (300 MHz for ^1H, 75 MHz for ^{13}C) spectrometers; $CDCl_3$,

DMSO-d_6 and acetone-d_6 were used as solvents, and TMS was added in all cases as an internal standard. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer. Melting points were measured in open capillary tubes using a Büchi inmersion apparatus, and are uncorrected. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Scharlau Cf 530). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh and Scharlau Ge 048). All reagents were of commercial quality (Aldrich, Merck, SDS, Probus) and were used as received. Solvents were purified and dried using standard procedures. The expression "petroleum ether" refers to the fraction boiling at 40-60 °C.

General Synthesis of Anilides (**1**).

To a cooled solution of 2,5-dimethoxyaniline (1 g, 6.5 mmol) in dry benzene (7 ml) was dropwise added for 10 min a solution of the suitable acyl chloride (6.6 mmol) in dry benzene (7 ml). The reaction was stirred at room temperature for 1 h and was then quenched with cold 25 % aqueous sodium carbonate (10 ml). After vigorously stirring the two-phase system for 30 min, the benzene layer was separated and the aqueous phase was extracted with ether (3 x 50 ml). The combined organic layers were dried over sodium sulphate and evaporated, and the residue was crystallized from petroleum ether.

N-(2',5'-Dimethoxyphenyl)acetamide (**1a**). Yield 86 %. mp 87-89 °C (petroleum ether) (lit.,[12] 91 °C). Ir (KBr): 3244 (NH); 1658 (C=O); 1225 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.10 (1H, d. J = 3.0 Hz, $C_{6'}$-H); 7.80 (1H, s, NH); 6.77 (1H, d, J = 9.0 Hz, $C_{3'}$-H); 6.50 (1H, dd, J = 9.0 and 3.0 Hz, $C_{4'}$-H); 3.82 (3H, s, $C_{5'}$-OCH_3); 3.79 (3H, s, $C_{2'}$-OCH_3); 2.19 (3H, s, C_2-H). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 168.13 (C_1); 153.72 ($C_{5'}$); 141.77 ($C_{2'}$); 128.27 ($C_{1'}$); 110.47 ($C_{3'}$); 108.12 ($C_{4'}$); 105.96 ($C_{6'}$); 56.03 and 55.66 (OCH_3); 24.88 (C_2).

N-(2',5'-Dimethoxyphenyl)propanamide (**1b**). Yield 96%. mp 65-67 °C (petroleum ether). Ir (KBr): 3235 (NH); 1660 (C=O); 1235 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.10 (1H, d, J = 3.0 Hz, $C_{6'}$-H); 7.80 (1H, s, NH); 6.70 (1H, d, J = 7.5 Hz, $C_{3'}$-H); 6.50 (1H, dd, J = 7.5 and 3.0 Hz, $C_{4'}$-H); 3.80 (3H, s, $C_{5'}$-OCH_3); 3.70 (3H, s, $C_{2'}$-OCH_3); 2.40 (2H, q, J = 7.5 Hz, C_2-H); 1.20 (3H, t, J = 7.5 Hz, C_3-H). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 171.87 (C_1); 153.80 ($C_{5'}$); 141.77 ($C_{2'}$); 128.34 ($C_{1'}$); 110.55 ($C_{3'}$); 108.34 ($C_{4'}$); 105.64 ($C_{6'}$); 56.10 and 55.68 (OCH_3); 30.98 (C_2); 9.55 (C_3). *Anal.* Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.36; H, 7.13; N, 6.89.

N-(2',5'-Dimethoxyphenyl)butanamide (**1c**). Yield 86%. mp 34 °C (petroleum ether). Ir (KBr): 3250 (NH); 1660(C=O); 1235 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.15 (1H, d, J = 3.0 Hz, $C_{6'}$-H); 7.80 (1H, s, NH); 6.78 (1H, d, J = 9.0 Hz, $C_{3'}$-H); 6.50 (1H, dd, J = 9.0 and 3.0 Hz, $C_{4'}$-H); 3.91 (3H, s, $C_{5'}$-OCH_3); 3.80 (3H, s, $C_{2'}$-OCH_3); 2.36 (2H, t, J = 7.2 Hz, C_2-H); 1.75 (2H, m, C_3-

H); 1.00 (3H, t, J = 7.2 Hz, C_4-H). ^{13}C-Nmr (75.4 Mz, $CDCl_3$) δ: 171.12 (C_1); 153.74 ($C_{5'}$); 141.77 ($C_{2'}$); 128.30 ($C_{1'}$); 110.51 ($C_{3'}$); 108.28 ($C_{4'}$); 105.65 ($C_{6'}$); 56.06 and 55.64 (OCH_3); 39.87 (C_2); 18.91 (C_3); 13.66 (C_4). *Anal.* Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found:C, 64.62; H, 7.48; N, 6.28.

N-(2',5'-Dimethoxyphenyl)-2-phenylacetamide (**1d**). Yield 91%. mp 85 °C (petroleum ether). Ir (KBr): 3310 (NH); 1660 (C=O); 1220 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.00 (1H, d, J = 3.0 Hz, $C_{6'}$-H); 7.80 (1H, s, N-H); 7.35 (5H, m, C_6H_5); 6.71 (1H, d, J = 9.0 Hz, $C_{3'}$-H); 6.50 (1H, dd, J = 9.0 and 3.0 Hz, $C_{4'}$-H); 3.75 (3H, s, $C_{5'}$-OCH_3); 3.65 (3H, s, $C_{2'}$-OCH_3); 2.10 (2H, s, C_2-H). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 168.89 (C_1); 153.89 ($C_{5'}$); 142.00 ($C_{2'}$); 134.45 ($C_{1''}$); 129.51($C_{2''}$, $C_{6''}$); 128.98($C_{3''}$, $C_{5''}$); 128.27 ($C_{1'}$); 127.42 ($C_{4''}$); 110.95 ($C_{3'}$); 108.68 ($C_{4'}$); 105.56 ($C_{6'}$); 56.29 and 55.73 (OCH_3); 45.13 (C_2). *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.53; H, 6.37; N, 5.33.

N-(2',5'-Dimethoxyphenyl)-3-chloropropanamide (**1e**). Yield 100%. mp 97 °C (petroleum ether). Ir (KBr): 3320 (NH); 1680 (C=O); 1230 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.00 (1H, d, J = 2.7 Hz, $C_{6'}$-H); 7.90 (1H, s, N-H); 6.70 (1H, d, J = 9.0 Hz, $C_{3'}$-H); 6.50 (1H, dd, J = 9.0 and 2.7 Hz, $C_{4'}$-H); 3.80 (2H, t, J = 7.8 Hz, C_3-H) 3.79 (3H, s, $C_{5'}$-OCH_3); 3.73 (3H, s, $C_{2'}$-OCH_3); 2.80 (2H, t, J = 7.8 Hz, C_2-H). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 167.47 (C_1); 153.57 ($C_{5'}$); 142.52 ($C_{2'}$); 127.74 ($C_{1'}$); 110.86 ($C_{3'}$); 108.56 ($C_{4'}$); 106.04 ($C_{6'}$); 55.96 and 55.50 (OCH_3); 40.39 (C_3); 39.58 (C_2). *Anal.* Calcd for $C_{11}H_{14}NO_3Cl$: C, 54.22; H, 5.79; N, 5.75. Found: C, 53.91; H, 5.60; N, 5.64.

N-(2',5'-Dimethoxyphenyl)-2-ethoxycarbonylacetamide (**1f**). Yield 96%. mp 72 °C (petroleum ether). Ir (KBr): 3320 (NH); 1740 (CO_2Et); 1680 (CONH); 1230 (OCH_3 and OCH_2CH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.40 (1H, s, NH); 8,00 (1H, d, J = 3.0 Hz, $C_{6'}$-H); 6.70 (1H, d, J = 8.9 Hz, $C_{3'}$-H); 6.58 (1H, dd, J = 8.9 Hz, 3.0 Hz, $C_{4'}$-H); 4.21 (2H, q, J = 7.2 Hz, CO_2-C<u>H</u>$_2$-CH_3); 3.80 (3H, s, $C_{5'}$-OCH_3); 3.70 (3H, s, $C_{2'}$-OCH_3); 3.49 (2H, s, C_2-H); 1.30 (3H, t, J = 7. 2 Hz, CO_2-CH_2-C<u>H</u>$_3$). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 169.17 (<u>C</u>O_2-CH_2-CH_3); 162.78 (C_1); 153.72 ($C_{5'}$); 142.50 ($C_{2'}$); 127.99 ($C_{1'}$); 110.86 ($C_{3'}$); 108.77 ($C_{4'}$); 106.27 ($C_{6'}$); 88.31 (C_2); 61.76 (CO_2-<u>C</u>H_2-CH_3); 56.39 and 55.73 (OCH_3); 14.03 (CH_2-CO_2-CH_2-<u>C</u>H_3). *Anal.* Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.31; H, 6.31; N, 5.30.

3-Substituted 2-Chloro-5,8-dimethoxyquinolines (**2**). General Procedures.

Method A. Phosphorous oxychloride (77 to 100.1 mmol, 7 eq) was dropwise added to a stirred solution of the suitable anilide (**1**, 11 to 14.3 mmol, 1 eq) in dimethylformamide (16.5 to 21.5 mmol, 1.5 eq), kept under a nitrogen atmosphere and cooled in an ice bath. The solution was stirred at the required temperature for the time indicated in each case, while monitored by tlc (the desired product emited a characteristic blue

fluorescence upon excitation at λ = 366 nm). On completion of the reaction, the solution was poured on crushed ice, basified with 25 % aqueous ammonia and extracted with chloroform (3 x 50 ml). The combined organic layers were dried (sodium sulphate) and evaporated, and the residue was purified by flash column chromatography on silica gel.

Method B. A mixture of phosphorous oxychloride (3.36 to 35.7 mmol, 7.0 eq) and dimethylformamide (0.72 to 7.65, 1.5 eq) was stirred at -30 °C for 15 min, while kept in a nitrogen atmosphere. The suitable anilide(**1**)(0.48 to 5.1 mmol, 1 eq) was then added in one portion, and from this point the procedure was identical to that described in method A.

2-Chloro-5,8-dimethoxyquinoline-3-carbaldehyde (**2a**). Application of method B to 1 g (5.1 mmol) of anilide (**1a**) gave 650 mg (50 %) of **2a**, after stirring at 110 °C for 2 h. mp 159 °C (ethyl ether-petroleum ether). Ir (KBr): 1700 (CHO); 1275 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 10.55 (1H, s, CHO); 9.13 (1H, s, C_4-H); 7.13 (1H, d, J = 8.7 Hz, C_7-H); 6.83 (1H, d, J = 8.7 Hz, C_6-H); 4.04 (3H, s, C_8-OCH_3); 3.98 (3H, s, C_5-OCH_3). ^{13}C-RMN (75.4 MHz, $CDCl_3$) δ: 189.19 (CHO); 150.21 (C_2); 150.12 (C_5); 148.31 (C_8); 141.08 (C_{8a}); 135.93 (C_4); 125.77(C_3); 120.06 (C_{4a}); 112.16 (C_7); 105.23 (C_6); 56.31 and 55.94 (OCH_3). *Anal.* Calcd for $C_{12}H_{10}NO_3Cl$: C, 57.27; H, 4.01; N, 5.57. Found: C, 56.91; H, 3.96; N, 5.48.

2-Chloro-3-methyl-5,8-dimethoxyquinoline (**2b**). Application of method A to 3 g (14.3 mmol) of anilide (**1b**) gave 1.1 g of **2b** (50 %, calculated on unrecovered **1b**), after stirring at 75 °C for 2 h. Application of method B to 100 mg (0.48 mmol) of anilide (**1b**) gave 80 mg (70 %) of **2b**, after stirring at 110 °C for 1 h. mp 112 °C (ethyl ether-petroleum ether). Ir (KBr): 1280 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.34 (1H, s, C_4-H); 6.87 (1H, d, J = 8.5 Hz, C_7-H); 6.70 (1H, d, J = 8.5 Hz, C_6-H); 4.00 (3H, s, C_8-OCH_3); 3.94 (3H, s, C_5-OCH_3); 2.53 (3H, s, CH_3). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 151.56 (C_2); 148.43 (C_5); 148.01 (C_8); 138.45 (C_{8a}); 132.94 (C_4); 129.92 (C_3); 120.75 (C_{4a}); 107.04 (C_7); 104.08 (C_6); 55.69 and 55.91 (OCH_3); 20.12 (CH_3). *Anal.* Calcd for $C_{12}H_{12}NO_2Cl$: C, 60.64; H, 5.09; N, 5.89. Found: C, 60.66; H, 5.10; N, 5.86.

2-Chloro-3-ethyl-5,8-dimethoxyquinoline (**2c**). Application of method B to 1 g (4.5 mmol) of anilide (**1c**) gave 850 mg (75 %) of **2c**, after stirring at 110 °C for 2 h. mp 120 °C (ethyl ether-petroleum ether). Ir (KBr): 1265 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.35 (1H, s, C_4-H); 6.89 (1H, d, J = 8.0 Hz, C_7-H); 6.74 (1H, d, J = 8.0 Hz, C_6-H); 4.01 (3H, s, C_8-OCH_3); 3.95 (3H, s, C_5-OCH_3); 2.92 (2H, q, J = 7.5 Hz, $C\underline{H}_2$-CH_3); 1.30 (3H, t, J = 7.5 Hz, CH_2-$C\underline{H}_3$). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 151.34 (C_2); 148.39 (C_5*); 148.08 (C_8*); 138.29 (C_{8a}); 135.30 (C_3); 131.43 (C_4); 120.84 (C_{4a}); 106.99 (C_7); 103.97 (C_6); 55.65 and 55.91 (OCH_3); 26.52 ($\underline{C}H_2$-CH_3); 13.44 (CH_2-$\underline{C}H_3$). *Anal.* Calcd for $C_{13}H_{14}NO_2Cl$: C, 62.03; H, 5.61; N, 5.56. Found: C, 61.97; H, 5.76; N, 5.59. Interchangeable asignments are indicated with *.

2-Chloro-3-phenyl-5,8-dimethoxyquinoline (**2d**). Application of method A to 3 g (11 mmol) of anilide (**1d**) gave 800 mg of **2d** (33 %, calculated on the basis of unrecovered **1d**), after stirring at room temperature for 14 h. Application of method B to 1 g (3.7 mmol) of anilide (**1d**) gave 674 mg (61%) of **2d** (77 % calculated on the basis of unrecovered **1d**), after stirring at 75 °C for 3 h. mp 125 °C (ethyl ether-petroleum ether). Ir (KBr): 1270 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 8.49 (1H, s, C_4-H); 7.44-7.56 (5H, m, C_6H_5); 6.98 (1H, d, J = 8.4 Hz, C_7-H); 6.79 (1H, d, J = 8.4 Hz, C_6-H) ; 4.03 (3H, s, C_8-OCH_3); 3.94 (3H, s, C_5-OCH_3). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 149.31 (C_2); 148.60 (C_5*); 148.47 (C_8*); 138.88 (C_{8a}); 134.39 (C_4); 134.11 (C_3); 137.83 ($C_{1'}$); 129.68 ($C_{2'}$ and $C_{6'}$); 128.15 ($C_{3'}$, $C_{5'}$ and $C_{4'}$); 120.55 (C_{4a}); 108.15 (C_7); 104.46 (C_6); 56.09 and 55.78 (OCH_3). Interchangeable asignments are indicated with *. *Anal.* Calcd for $C_{17}H_{14}NO_2Cl$: C, 68.12; H, 4.71; N, 4.67. Found: C, 67.91; H, 4.67; N, 4.62.

2-Chloro-3-chloromethyl-5,8-dimethoxyquinoline (**2e**). Application of method B to 1 g (4.10 mmol) of anilide (**1e**) gave 250 mg (22 %) of **2e**, after stirring at 130 °C for 1.5 h. Its unstability in solution precluded further purification by crystallization or chromatography. Ir (KBr): 1280 (OCH_3) cm^{-1}. ^{1}H-Nmr (300MHz, $CDCl_3$) δ: 8.65 (1H, s, C_4-H); 7.10 (1H, d, J = 8.7 Hz, C_7-H); 6.79 (1H, d, J = 8.7 Hz, C_6-H); 4.80 (2H, s, CH_2-Cl); 4.00 (3H, s, C_8-OCH_3); 3.90 (3H, s, C_5-OCH_3). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 149.60 (C_2); 148.45 (C_5*); 148.32 (C_8*); 139.24 (C_{8a}); 134.19 (C_4); 128.74 (C_3); 120.40 (C_{4a}); 108.83 (C_7); 104.70 (C_6); 56.10 and 55.79 (OCH_3); 43.35 (CH_2-Cl). Interchangeable asignments are indicated with *.

Ethyl 2-Chloro-5,8-dimethoxyquinoline-3-carboxylate (**2f**). Application of method B to 500 mg (1.87 mmol) of anilide (**1f**) gave 205 mg of **2f** (42 %, calculated on unrecovered **1f**) , after stirring at 75 °C for 4 h. Application of method B to 1 g of anilide (**1f**) gave 700 mg (64 %) of **2f**, after stirring at 110 °C for 1 h. mp 68 °C (ethyl ether-petroleum ether). Ir (KBr): 1730 (CO_2Et); 1270 and 1260 (OCH_3 and OCH_2CH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.01 (1H, s, C_4-H); 7.06 (1H, d, J = 8.7 Hz, C_7-H); 6.85 (1H, d, J = 8.7 Hz, C_6-H); 4.40 (2H, q, J = 7.2 Hz, CO_2-C<u>H</u>$_2$-CH_3); 4.02 (3H, s, C_8-OCH_3); 3.92 (3H, s, C_5-OCH_3); 1.40 (3H, t, J = 7.2 Hz, CO_2-CH_2-C<u>H</u>$_3$). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 164.76 (<u>C</u>O_2-CH_2-CH_3); 148.92 (C_2); 148.21 (C_5); 147.54 (C_8); 139.94 (C_{8a}); 136.73 (C_4); 123.99 (C_3); 119.25 (C_{4a}); 110.58 (C_7); 104.95 (C_6); 62.09 (CO_2-<u>C</u>H_2-CH_3); 56.15 and 55.83 (OCH_3); 14.18 (CO_2-CH_2-<u>C</u>H_3). *Anal.* Calcd for $C_{14}H_{14}NO_4Cl$: C, 56.86; H, 4.77; N, 4.74. Found: C, 56.66; H, 4.54; N, 4.61.

5,8-Dimethoxy-2(1*H*)-quinolinones (**3**). General Procedure.

A solution of the suitable 2-chloroquinoline (**2**) (0.24 to 0.80 mmol) in acetic acid (1.5 ml, 26.25 mmol per mmol of **2**) and water (0.05 ml, 2.77 mmol per mmol of **2**) was refluxed for 1-5 h. After evaporation of the solvent, the residue was dissolved in water, basified with 25 % aqueous ammonium hydroxide and

extracted with chloroform (3 x 25 ml). The combined chloroform layers were dried over sodium sulphate and evaporated, yielding an essentially pure residue. Analytical samples were obtained by crystallization.

1,2-Dihydro-5,8-dimethoxy-2-oxo-3-quinolinecarbaldehyde (**3a**). Starting from 60 mg (0.24 mmol) of **2a**, and heating the reactants for 5 h, a yield of 52 mg (94 %) of **3a** was obtained. Ir (KBr): 3200-2850 (NH); 1700 (CHO); 1675 (C=O); 1270 (OCH_3) cm^{-1}. ^{1}H-Nmr (250 MHz, $CDCl_3$) δ: 10.36 (1H, s, CHO); 9.28 (1H, s, NH); 8.77 (1H, s, C_4-H); 6.94 (1H, d, *J* = 8.7 Hz, C_7-H); 6.45 (1H, d, *J* = 8.7 Hz, C_6-H); 3.88 and 3.86 (6H, 2 s, OCH_3). ^{13}C-Nmr (63 MHz, $CDCl_3$) δ: 189.42 (CHO); 161.28 (C_2); 151.81 (C_5); 139.27 (C_8); 138.48 (C_4); 131.57 (C_{8a}); 124.84 (C_3); 113.88 (C_7); 110.37 (C_{4a}); 101.62 (C_6); 56.33 and 55.87 (OCH_3). Full analytical characterization of **3a** was performed on its dithioketal (**3g**).

3-Methyl-5,8-dimethoxy-2(1*H*)-quinolinone (**3b**). Starting from 100 mg (0.42 mmol) of **2b**, and heating the reagents for 3 h, a yield of 90 mg (98 %) of **3b** was obtained. mp 158 °C ($CDCl_3$). Ir (KBr): 3400 (NH); 1685 (C=O); 1220 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz; $CDCl_3$) δ: 9.24 (1H, s, NH); 7.95 (1H, s, C_4-H); 6.80 (1H, d, *J* = 8.7 Hz, C_7-H); 6.40 (1H, d, *J* = 8.7 Hz, C_6-H); 3.90 and 3.87 (6H, 2 s, OCH_3); 2.25 (3H, s, CH_3). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 162.53 (C_2); 149.13 (C_5); 139.47 (C_8); 131.68 (C_4); 129.59 (C_{8a}); 128.38 (C_3); 111.13 (C_{4a}); 108.96 (C_7); 101.05 (C_6); 56.13 and 55.76 (OCH_3); 16.97 (CH_3). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.68; H, 5.97; N, 6.25.

3-Ethyl-5,8-dimethoxy-2(1*H*)-quinolinone (**3c**). Starting from 200 mg (0.80 mmol) of **2c**, and heating the reagents for 3 h, a yield of 185 mg (100 %) of **3c** was obtained. mp 160 °C (ethanol). Ir (KBr): 3240-2810 (NH); 1650 (C=O); 1245 (OCH_3) cm^{-1}. ^{1}H-Nmr (250 MHz, $CDCl_3$) δ: 9.18 (1H, s, NH); 7.90 (1H, s, C_4-H); 6.78 (1H, d, *J* = 8.7 Hz, C_7-H); 6.46 (1H, d, *J* = 8.7 Hz, C_6-H); 3.88 and 3.87 (6H, 2 s, OCH_3); 2.56 (2H, q, *J* = 9.0 Hz, CH_2-CH_3); 1.25 (3H, t, *J* = 9.0 Hz, CH_2-CH_3). ^{13}C-Nmr (63 MHz, $CDCl_3$) δ: 162.10 (C_2); 149.25 (C_5); 139.45 (C_8); 135.11 (C_{8a}); 129.83 (C_4); 128.19 (C_3); 111.14 (C_{4a}); 108.94 (C_7); 100.95 (C_6); 56.08 and 55.67 (OCH_3); 23.45 (CH_2-CH_3); 12.64 (CH_2-CH_3). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.47; H, 6.39; N, 5.78.

3-Phenyl-5,8-dimethoxy-2(1*H*)-quinolinone (**3d**). Starting from 200 mg (0.67 mmol) of **2d**, and heating the reagents for 3 h, a yield of 187 mg (100 %) of **3d** was obtained. mp 207 °C ($CDCl_3$). Ir (KBr): 1635 (C=O); 1250 (OCH_3) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.43 (1H, s, NH); 8.27 (1H, s, C_4-H); 7.79 (2H, d, *J* = 7.8 Hz, $C_{2'}$-H and $C_{6'}$-H); 7.40 (3H, m, $C_{3'}$-H, $C_{4'}$-H and $C_{5'}$-H); 6.87 (1H, d, *J* = 8.7 Hz, C_7-H); 6.51 (1H, d, *J* = 8.7 Hz, C_6-H); 3.94 and 3.91 (6H, 2 s, OCH_3). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 161.14 (C_2); 149.87 (C_5); 139.39 (C_8); 136.36 (C_4); 132.85 (C_{8a}); 131.83 (C_3);129.95 ($C_{1'}$); 128.79 ($C_{2'}$ and $C_{6'}$); 128.12 ($C_{3'}$ and $C_{5'}$); 127.93 ($C_{4'}$); 111.31 (C_7); 109.96 (C_{4a}); 101.08 (C_6); 55.75 and 55.63 (OCH_3). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C,

72.28; H, 5.44; N, 4.62.

Ethyl 1,2-Dihydro-5,8-dimethoxy-2-oxoquinoline-3-carboxylate (**3f**). Starting from 100 mg (0.34 mmol) of **2f**, and heating the reagents for 5 h, a yield of 93 mg (100 %) of **3f** was obtained. mp 189 °C (ethanol) (lit.[7], 189 °C).

5,8-Dimethoxy-3-(1,3-dithian-2-yl)-2(1*H*)-quinolinone (**3g**). A solution of **3a** (50 mg, 0.21 mmol) and 1,3-propanedithiol (22 µl, 0.23 mmol) in chloroform (50 ml) was placed in an ice bath and treated with a stream of dry, gaseous hydrogen chloride for 30 min, while magnetically stirred. The solvent was evaporated and the residue was recrystallized from methanol, filtered and washed with petroleum ether. Yield 55 mg (79 %). mp 269 °C (methanol). Ir (KBr): 3200-2850 (NH); 1645 (C=O); 1245 (OCH_3) cm^{-1}. ^{1}H-Nmr (250 MHz, $CDCl_3$) δ: 9.18 (1H, s, NH); 8.34 (1H, s, C_4-H); 6.80 (1H, d, J = 8.6 Hz, C_7-H); 6.40 (1H, d, J = 8.6 Hz, C_6-H); 5.61 (1H, s, $C_{2'}$-H); 3.83 and 3.81 (6H, 2 s, OCH_3); 3.10 (2H, m, $C_{4'}$-H and $C_{6'}$-$H_{ax.}$); 2.80 (2H, $C_{4'}$-H and $C_{6'}$-$H_{eq.}$); 1.90 (2H, m, $C_{5'}$-H). ^{13}C-Nmr (63 MHz, $CDCl_3$) δ: 159.80 (C_2); 149.98 (C_5); 139.30 (C_8); 134.18 (C_4); 129.91 (C_{8a}); 128.20 (C_3); 110.69 (C_7 and C_{4a}); 101.27 (C_6); 56.21 and 55.26 (OCH_3); 43.34 ($C_{2'}$); 32.22 ($C_{4'}$ and $C_{6'}$); 25.25 ($C_{5'}$). *Anal.* Calcd for $C_{15}H_{17}NO_3S_2$: C, 55.70; H, 5.30; N, 4.33. Found: C, 55.89; H, 5.56; N, 4.34.

3-Substituted 2,5,8(1*H*)-quinolinetriones (**4**). General Procedure.

Cerium ammonium nitrate (0.39 to 0.57, 2.2 eq) was added in small portions to a magnetically stirred suspension of the suitable carbostyril (**3**) (0.18 to 0.26 mmol, 1 eq) in water (2 ml, 0.11 mmol per mmol of **3**) and acetonitrile (2.5 ml, 47.8 mmol per mmol of **3**). The orange solution was stirred at the temperature and for the time indicated in each case, and was then diluted with water (10 ml) and extracted with chloroform (3 x 50 ml), yielding essentially pure compounds (**4**). Analytical samples were obtained by rapid chromatography on silica gel.

1,2,5,8-Tetrahydro-2,5,8-trioxo-3-quinolinecarbaldehyde (**4a**). Starting from 60 mg (0.26 mmol) of **3a**, a yield of 52 mg (100 %) of **4a**, was obtained after stirring for 20 min at room temperature. mp could not be obtained because compound (**4a**) decomposed on heating. Ir (KBr): 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$, 250 MHz) δ: 10.37 (1H, s, CHO); 9.85 (1H, s, NH); 8.61 (1H, s, C_4-H); 7.04 (2H, s, C_6-H and C_7-H). ^{1}H-Nmr (250 MHz, acetone-d_6) δ: 11.45 (1H, s, NH); 10.28 (1H, s, CHO); 8.42 (1H, s, C_4-H); 7.16 (1H, d, J = 10.4 Hz, C_7-H); 7.08 (1H, d, J = 10.4 Hz, C_6-H). ^{13}C-Nmr ($CDCl_3$, 63 MHz) δ: 188.92 (CHO); 182.70 (C_8); 180.01 (C_5); 161.53 (C_2); 142.86 (C_{8a}); 139.26 (C_6); 137.29 (C_3); 136.77 (C_7); 130.09 (C_4); 114.54 (C_{4a}). *Anal.* Calcd for $C_{10}H_5NO_4$: C, 59.12; H, 2.48; N, 6.89. Found: C, 58.95; H, 2.85; N, 6.84.

3-Methyl-2,5,8(1*H*)-quinolinetrione (**4b**). Starting from 50 mg (0.23 mmol) of **3b**, a yield of 43 mg (100 %) of **4b** was obtained after stirring for 15 min at room temperature. The analytical sample was obtained by

chromatography on silica gel, eluting with ether. mp 212 °C. Ir (KBr): 1640 (C=O) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.50 (1H, s, NH); 7.79 (1H, d, *J* = 1.0 Hz, C_4-H); 6.88 (2H, m, C_7-H and C_6-H); 2.27 (3H, d, *J* = 1.0 Hz, CH_3). ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 182.41 (C_8); 179.37 (C_5); 161.78 (C_2); 138.30 (C_{8a}); 138.10 (C_6); 135.60 (C_3); 134.60 (C_7); 131.84 (C_4); 114.98 (C_{4a}); 17.36 (CH_3). *Anal.* Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.40. Found: C, 63.41; H, 4.08; N, 7.34.

3-Ethyl-2,5,8(1*H*)-quinolinetrione (**4c**). Starting from 50 mg (0.21 mmol) of **3c**, a yield of 44 mg (100 %) of **4c** was obtained after stirring for 15 min at room temperature. The analytical sample was obtained by chromatography on silica gel, eluting with ether. mp 168 °C. Ir (KBr): 1650 (C=O) cm^{-1}. ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 9.60 (1H, s, NH); 7.75 (1H, s, C_4-H); 6.87 (2H, m, C_7-H and C_6-H); 2.66 (2H, q, *J* = 7.8 Hz, CH_2-CH_3); 1.26 (3H, t, *J* = 7.8 Hz, CH_2-CH_3) ^{13}C-Nmr (75.4 MHz, $CDCl_3$) δ: 177.92 (C_8); 174.79 (C_5); 156.81 (C_2); 138.98 (C_{8a}); 133.50 (C_6); 130.57 (C_3); 129.96 (C_7); 125.33 (C_4); 110.39 (C_{4a}); 19.17 (CH_2-CH_3); 7.33 (CH_2-CH_3). *Anal.* Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.33; H, 4.59; N, 6.78.

3-Phenyl-2,5,8(1*H*)-quinolinetrione (**4d**). Starting from 50 mg (0.18 mmol) of **3d**, a yield of 45 mg (100 %) of **4d** was obtained after stirring for 15 min at 50 °C. mp 185 °C. Ir (KBr): 1645 (C=O) cm^{-1}. ^{1}H-Nmr (250 MHz, DMSO-d_6) δ: 12.20 (1H, s, NH); 7.91 (1H, s, C_4-H); 7.73 (2H, m, $C_{2'}$-H and $C_{6'}$-H); 7.43 (3H, m, $C_{3'}$-H, $C_{4'}$-H and $C_{5'}$-H); 6.99 (1H, d, *J* = 9.3 Hz, C_7-H); 6.92 (1H, d, *J* = 9.3 Hz, C_6-H). ^{13}C-Nmr (75.4 MHz, DMSO-d_6) δ: 183.17 (C_8); 179.93 (C_5); 161.00 (C_2); 141.77 (C_{8a}); 137.48 (C_6); 136.25 (C_7); 135.35 (C_3); 132.17 (C_4); 131.58 ($C_{1'}$); 128.71 ($C_{2'}$ and $C_{6'}$); 128.42 ($C_{3'}$ and $C_{5'}$); 128.30 ($C_{4'}$); 114.39 (C_{4a}). *Anal.* Calcd for $C_{15}H_9NO_3$: C, 71.71; H, 3.61; N, 5.58. Found: C, 71.36; H, 3.96; N, 5.86.

Ethyl 1,2,5,8-Tetrahydro-2,5,8-trioxo-3-quinolinecarboxylate (**4f**). Starting from 46 mg (0.17 mmol) of **3f**, a yield of 40 mg (98 %) of **4f** was obtained after stirring for 15 min at room temperature. The analytical sample was obtained by chromatography on silica gel, eluting with ethyl acatate-ethanol. mp 158 °C (lit.,[7] 158 °C).

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