# SYNTHESIS OF 6-FORMYL DERIVATIVES OF 5,8-DIMETHOXYCARBOSTYRYL

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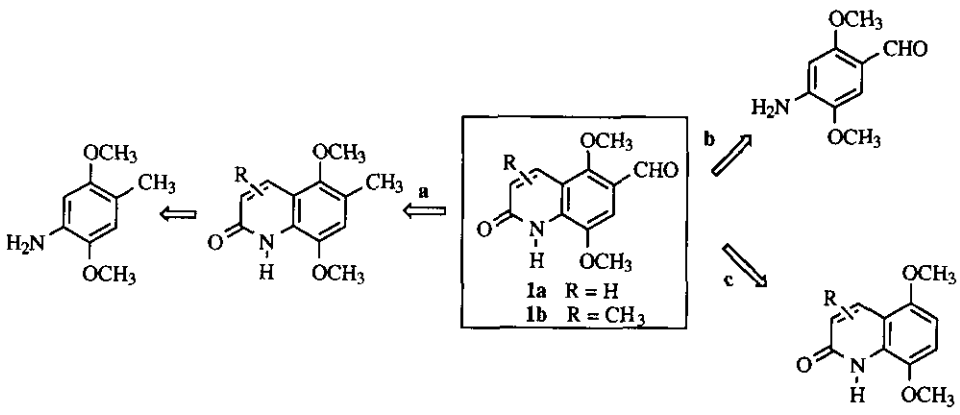
*Abstract- An efficient method is described for the preparation of 5,8-dimethoxy-2-oxo-1H-quinoline-6-carbaldehyde. Alternative strategies aimed at the synthesis of 4-methyl analogues are also studied.*

Heterocyclic quinones are increasingly important compounds due to their interesting and challenging chemistry and their relevant biological properties, including antitumour activity.[1] Some natural products, such as streptonigrin, lavendamycin[2] and diazaquinomycin[3] are particularly interesting in this respect, and intensive efforts are being devoted to their total synthesis and the preparation of analogues. Within the scope of our research on antitumour heterocyclic quinones bearing the 2,5,8-quinolinetrione moiety,[4] we required 6-formyl derivatives (**1**) as key synthetic intermediates.

The preparation of compounds (**1**) was planned according to several strategies, which are summarized in Scheme 1. Route *a* involves oxidation of 6-methyl-5,8-dimethoxycarbostyryl, prepared by cyclization of precursors obtained from 4-methyl-2,5-dimethoxyaniline (**2**), available in three quantitative steps from 2-methyl-hydroquinone.[5] Similar results might be achieved starting with 4-amino-2,5-dimethoxybenzaldehyde (route *b*). Finally, direct formylation[6] of 5,8-dimethoxycarbostyryls[7] (route *c*) must also be considered.

According to strategy *a*, 4-methyl-2,5-dimethoxyaniline (**2**) was acylated with 3,3-dimethoxypropionic acid[8] to give the diacetal (**3**). One-pot deprotection and Knorr cyclization of **3** afforded the precursor (**4**), which was oxidized to the desired aldehyde (**1a**) by benzylic bromination with *N*-bromosuccinimide followed by oxidation with *N*-methylmorpholine-*N*-oxide[9] without isolation of the intermediate bromide (**5**). The overall yield for the

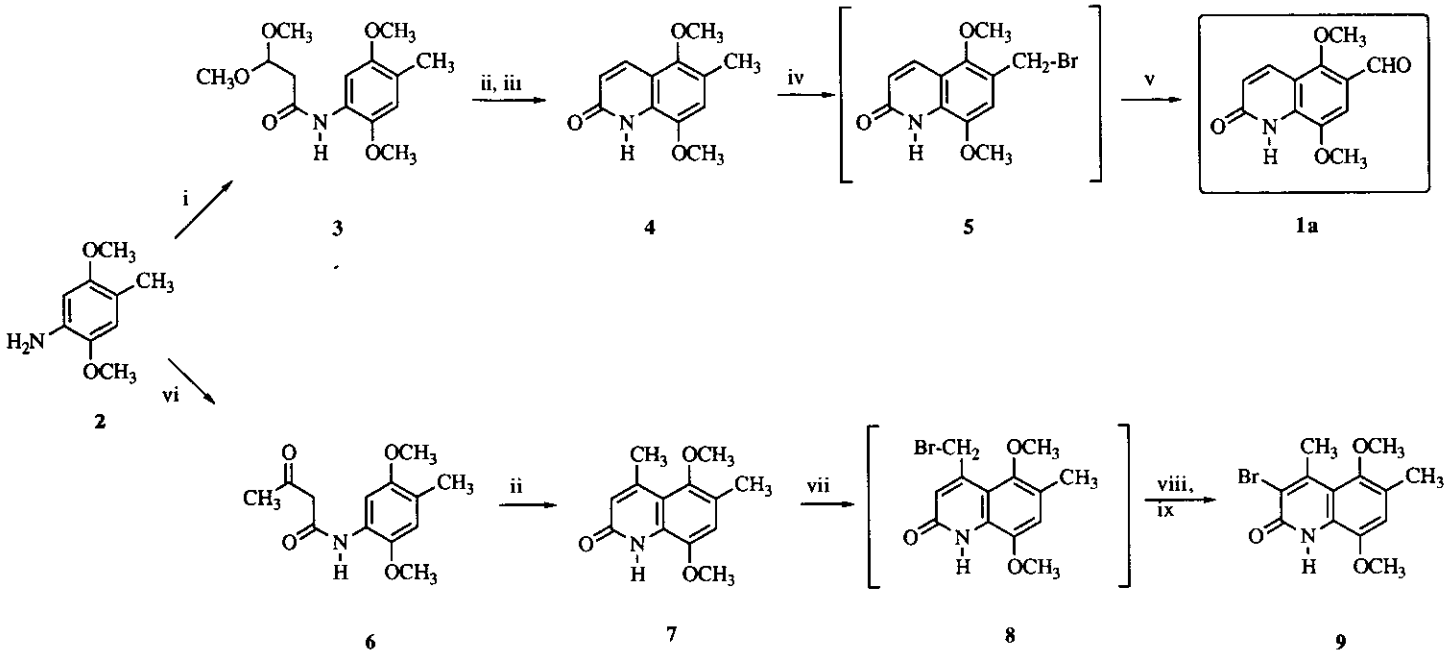



Scheme 1

complete route from commercially available 2-methylhydroquinone to **1a** was an excellent 75 % (Scheme 2).

The above strategy failed when applied to the synthesis of 4-methyl derivatives such as **1b**. Thus, acetoacetylation of amine (**2**) with 2,2,6-trimethyl-1,3-dioxin-4-one[7a,10] gave amide (**6**), which was cyclized to quinolinone (**7**) under Knorr conditions. An attempt to oxidize **7** by the method described above failed, since the first step afforded compound (**9**) through bromination at the more reactive $C_4$-Me group followed by allylic rearrangement under the purification conditions.

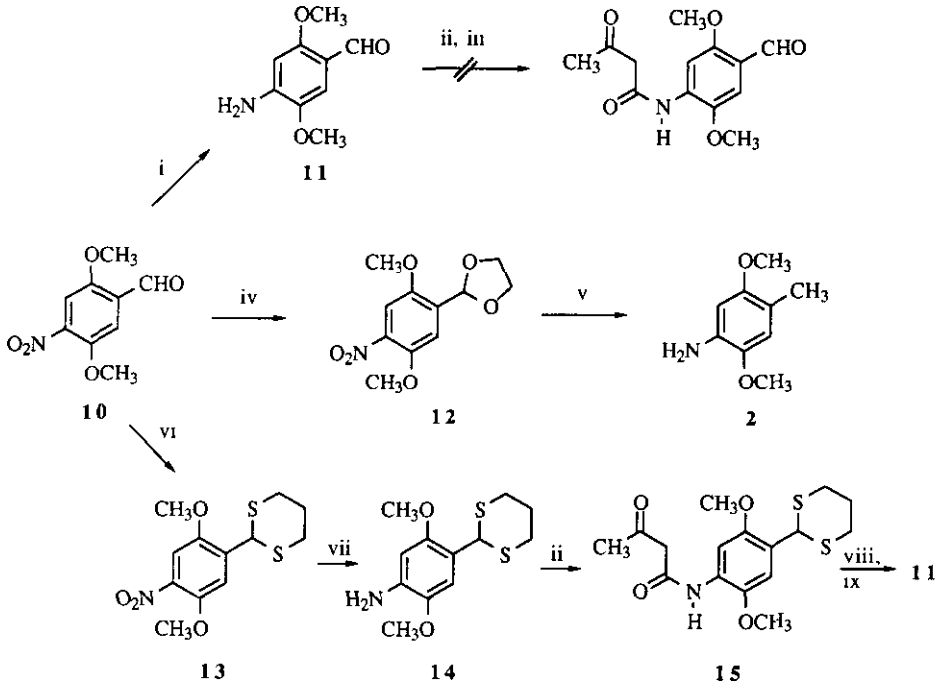
Therefore, the alternative strategy *b*, which relies on the cyclization of a 4-formyl-2,5-dimethoxyanilide or its synthetic equivalent, was attempted (Scheme 3). We initiated the synthesis of potential starting materials by attempting to reduce 4-nitro-2,5-dimethoxybenzaldehyde (**10**)[11] to the corresponding amine (**11**). In contrast with the relative ease of the reduction of 2-nitro-3,6-dimethoxybenzaldehyde,[7b] we found many difficulties in the isolation of **11**, and our best conditions (stirring at 100 °C for 4 h with stannous chloride in 35 % aqueous hydrochloric acid) gave only 21 % yield. Furthermore, all atempts to treat compound (**11**) with acetoacetylating reagents like 2,2,6-trimethyl-1,3-dioxin-4-one or *S-tert*-butylacetothioacetate[12] were unsuccessful. Therefore, the decision was taken to protect the carbonyl group prior to reduction. Since dimethylene acetals have been recently used as protective groups for aromatic aldehydes during catalytic hydrogenation steps,[13] we prepared compound (**12**) by treatment of **10** with ethylene glycol. However, hydrogenation of **12** over palladium on charcoal afforded a mixture, from which the only product that could be isolated was amine (**2**), arising from hydrogenolysis of the protection. A literature search revealed the existence of an early precedent of the hydrogenolysis of cyclic acetals derived from aromatic carbonyl compounds.[14] The change of the protective group to a 1,3-dithiane derivative (compound (**13**)) allowed the preparation of amine (**14**) by reduction with




**Reagents and conditions**: i. 3,3-dimethoxypropionic acid, DCC, $CH_2Cl_2$, room temperature, 12 h and reflux, 90 min. ii. 98 % $H_2SO_4$, room temperature, 30 min. iii. 35 % HCl, room temperature, 1 h. iv. *N*-bromosuccinimide, benzoyl peroxide, $CCl_4$, reflux, 5 h. v. *N*-methylmorpholine-*N*-oxide, powdered 4 Å molecular sieves, MeCN, room temperature, 2 h. vi. 2,2,6-trimethyl-1,3-dioxin-4-one, xylene, 130 °C, 30 min. vii. *N*-bromosuccinimide, benzoyl peroxide, $CCl_4$, reflux, 1 h. viii. EtOH, reflux, 20 min. ix. $SiO_2$, room temperature.

Scheme 2

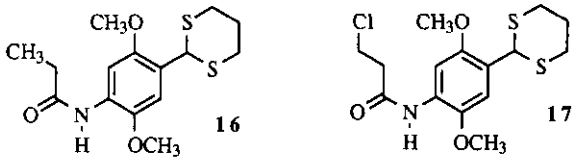
stannous chloride in hydrochloric acid. Acetoacetylation with 2,2,6-trimethyl-1,3-dioxin-4-one[5] gave **15** but, unfortunately, all attempts to effect its thermal cyclization were unsuccessful. In acidic media (Knorr synthesis),



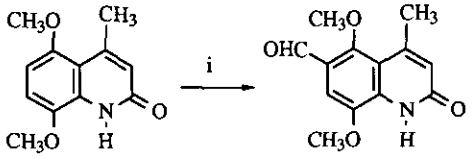
**Reagents and conditions:** i. $SnCl_2$, 20 % HCl, 100 °C, 4 h. ii. 2,2,6-trimethyl-1,3-dioxin-4-one, xylene, 130 °C, 30 min. iii. *S-tert*-butylacetothioacetate, $AgCF_3CO_2$, room temperature, 24 h. iv. $HO(CH_2)_2OH$, *p*-toluenesulfonic acid, benzene, reflux, 2 h. v. $H_2$, 10 % Pd-C, MeOH, 40 psi, room temperature, 15 min. vi. $HS(CH_2)_3SH$, $CHCl_3$, HCl (g), 0 °C to room temperature, 35 min. vii. $SnCl_2$, 35 % HCl, room temperature, 24 h. viii. 98 % $H_2SO_4$, room temperature, 15 min. ix. 98 % $H_2SO_4$, $P_2O_5$, room temperature, 15 min.

Scheme 3

hydrolysis of both the protective group and the side chain took place to yield the amine (**11**), even when moisture was excluded and the reaction was performed in the presence of a dehydrating agent (phosphorous pentoxide).[15] The deactivation of the aromatic ring was confirmed by the failure of the attempts to cyclize amide (**16**) through Vilsmeier-Haack reaction[16] and amide (**17**) through intramolecular Friedel-Crafts alkylation.[17]



Finally, the aldehyde (**1b**), was obtained by direct formylation of 4-methyl-5,8-dimethoxycarbostyryl (**18**), available in excellent yield from 2,5-dimethoxyaniline, [7a] (strategy *c*). This reaction was performed in 40 % yield by treatment with hexamethylenetetramine and trifluoroacetic acid (Scheme 4).[6b]




**18** **1b**

**Reagents and conditions**: i. hexamethylenetetramine, $CF_3CO_2H$, reflux, 12 h.

Scheme 4

## EXPERIMENTAL

Infrared spectra were recorded on Perkin-Elmer 577 and Buck Scientific 500 spectrophotometers, with all compounds compressed into KBr pellets. Nmr spectra were obtained on Varian VXR-300 (300 MHz for $^1H$, 75 MHz for $^{13}C$) and Bruker AC-250 (250 MHz for $^1H$ and 63 MHz for $^{13}C$) spectrometers; $CDCl_3$, *DMSO*-$d_6$ and pyridine-$d_5$ were used as solvents, and TMS was added as an internal standard. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer. Catalytic hydrogenations were carried out on a Parr 3920 reactor. 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.

*N*-(2',5'-Dimethoxy-4'-methylphenyl)-3,3-dimethoxypropionamide (**3**). To a solution of amine (**2**)[5] (1.82 g, 10.86 mmol) and 3,3-dimethoxypropionic acid[20] (1.46 g, 10.9 mmol) in dichloromethane (10 ml) at 0 °C was dropwise added a solution of dicyclohexylcarbodiimide (2.24 g, 10.86 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 12 h and was then refluxed for 90 min. The solvent was evaporated and the residue was washed with petroleum ether (4 x 25 ml). The organic washings were evaporated

to yield 2.82 g (92 %) of **3**. mp 51-52 °C (petroleum ether). Ir (KBr): 3320 (NH), 1660 (C=O), 1264 (Ar-OMe), 1216 ($C_3$-$(OMe)_2$) $cm^{-1}$. $^1$H-Nmr ( 250 MHz, $CDCl_3$) δ: 8.61 (br s, 1 H, NH); 8.07 (s, 1 H, $C_{6'}$-H); 6.68 (s, 1 H, $C_{3'}$-H); 4.79 (t, 1H, *J* = 5.3 Hz, $C_3$-H) 3.83 and 3.81 (2 s, 6 H, 2 Ar-OMe); 3.44 (s, 6H, $C_3$-$(OMe)_2$); 2.73 (d, 2 H, *J* = 5.3 Hz, $C_2$-H); 2.18 (s, 3 H, Ar-Me) ppm. $^{13}$C-Nmr (63 MHz, $CDCl_3$): 166.84 ($C_1$); 151.32 ($C_{5'}$); 141.39 ($C_{2'}$); 125.78 ($C_{1'}$); 120.80 ($C_{4'}$); 112.93 ($C_{3'}$); 103.39 ($C_{6'}$); 101.63 ($C_3$); 56.26 and 55.79 (2 OMe); 53.79 ($C_3$-$(OMe)_2$); 42.07 ($C_2$); 15.94 (Ar-Me) ppm. *Anal.* Calcd for $C_{14}H_{21}NO_5$: C, 59.36; H, 7.42; N, 4.95. Found: C, 59.22; H, 7.45; N, 5.03.

6-Methyl-5,8-dimethoxy-2-(1*H*)quinolinone (**4**). Method A. A solution of amide (**3**) (690 mg, 2.44 mmol) in concentrated sulfuric acid (6 ml) was stirred at room temperature for 30 min and then poured on crushed ice (*ca.* 50 g) and vigorously stirred until the precipitation of a white solid was complete. This was filtered, washed with water and recrystallized from ethanol. Yield, 0.52 g (98 %). mp 116-117 °C (ethanol). Ir (KBr): 3150 (NH); 1648 (C=O); 1275 (OMe) $cm^{-1}$. $^1$H-Nmr (250 MHz, $CDCl_3$) δ: 9.42 (br s, 1H, NH); 7.97 (d, 1H, *J* = 9.7 Hz, $C_4$-H); 6.76 (s, 1H, $C_7$-H); 6.66 (d, 1H, *J* = 9.7 Hz, $C_3$-H); 3.92 and 3.79 (2 s, 6H, 2 OMe); 2.33 (s, 3H, $C_6$-Me) ppm. $^{13}$C-Nmr (63 MHz, $CDCl_3$) δ: 161.68 ($C_2$); 147.16 ($C_5$); 141.42 ($C_8$); 135.16 ($C_4$); 127.30 ($C_{8a}$); 122.79 ($C_3$); 121.95 ($C_6$); 114.13 ($C_{4a}$); 112.94 ($C_7$); 61.66 and 55.37 (2 OMe); 15.52 ($C_6$-Me) ppm. *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.52; H, 6.02; N, 6.33. Method B. Amide (**3**) (322 mg, 1.14 mmol) was added in small portions to 35 % hydrocloric acid (3 ml). The solution was stirred for 1 h and extracted with ether (4 x 5 ml). The combined organic layers were washed with water (2 x 5 ml), dried over sodium sulphate and evaporated. The residue was crystallized from ethanol, yielding 242 mg (98 %) of **4**.

5,8-Dimethoxy-2-oxo-1*H*-quinoline-6-carbaldehyde (**1a**). A solution of compound (**4**) (283 mg, 1.13 mmol), *N*-bromosuccinimide (462 mg, 2.6 mmol) and benzoyl peroxide (37 mg, 0.15 mmol) in carbon tetrachloride (30 ml) was refluxed for 5 h, while magnetically stirred. The reaction was cooled to 0 °C and the precipitated succinimide was filtered and washed twice for 30 min with carbon tetrachloride at 50 °C. The combined organic layers were evaporated and the residue was washed with acetone, thus precipitating an additional amount of succinimide. This was filtered off, the acetone was evaporated and the residue was dissolved in chloroform (30 ml) and washed with a cold 10 % aqueous solution of sodium carbonate (2 x 15 ml). The chloroform was dried (sodium sulphate) and evaporated, leaving 499 mg of a residue consisting of a mixture of 6-bromomethyl-5,8-dimethoxy-2-(1*H*)quinolinone (**5**)[18] and compound (**1a**). This mixture was dissolved in acetonitrile (30 ml) and *N*-methylmorpholine-*N*-oxide (429 mg, 3.68 mmol) and powdered 4 Å molecular sieves (25 mg) were added. The suspension was stirred at room temperature for 2 h and was filtered through a pad of silica gel. The solvent

was evaporated and the residue was crystallized from ethanol. Yield, 249 mg (83 %) of aldehyde (**1a**). mp 242 °C (ethanol). Ir (KBr): 3220-2800(NH), 1700 (CHO); 1685 ($C_2$=O), 1270 (OMe) $cm^{-1}$. $^1$H-Nmr (250 MHz, $CDCl_3$) δ: 10.37 (s, 1H, CHO); 9.48 (br s, 1H, NH); 8.05 (d, 1H, $J$ = 9.8 Hz, $C_4$-H); 7.45 (s, 1H, $C_7$-H); 6.75 (d, 1H, $J$ = 9.8 Hz, $C_3$-H); 4.03 and 4.02 (2 s, 6H, 2 OMe) ppm. $^{13}$C-Nmr (63 MHz, $CDCl_3$) δ: 187.73 (CHO); 161.58 ($C_2$); 155.97 ($C_5$); 142.30 ($C_8$); 134.59 ($C_4$); 134.49 ($C_{8a}$); 122.99 ($C_6$); 122.15 ($C_3$); 113.81 ($C_{4a}$); 106.73 ($C_7$); 66.16 and 56.27 (2 OMe) ppm. *Anal.* Calcd for $C_{12}H_{11}NO_4$: C, 61.79; H, 4.75; N, 6.01. Found: C, 61.53; H, 4.83; N, 5.88.

N-(2',5'-Dimethoxy-4-methylphenyl)acetoacetamide (**6**). A stirred solution of amine (**2**) (710 mg, 5.14 mmol) in xylene (1 ml) was placed in an open flask and heated in a bath at 130 °C. 2,2,6-Trimethyl-1,3-dioxin-4-one (730 mg, 5.14 mmol) was added dropwise. The reaction was maintained under the above conditions for 30 min and cooled to give a precipitate of **6**, which was filtered and washed with petroleum ether. The xylene layer was evaporated and the residue was crystallized from petroleum ether, yielding an additional amount of **6**. Yield, 1.20 g (93 %). mp 132-133 °C (petroleum ether). Ir (KBr): 3290 (NH); 1740, 1670 (C=O); 1230 (OMe) $cm^{-1}$. $^1$H-Nmr ( 250 MHz, $CDCl_3$) δ: 9.16 (s, 1 H, NH); 8.18 (s, 1 H, $C_{6'}$-H); 6.78 (s, 1 H, $C_{3'}$-H); 3.86 and 3.81 (2 s, 6 H, 2 OMe); 3.59 (s, 2 H, $C_2$-H); 2.33 (s, 3 H, $C_4$-H); 2.19 (s, 3 H, Ar-Me) ppm. $^{13}$C-Nmr (63 MHz, $CDCl_3$) δ: 204.29 ($C_3$); 163.11 ($C_1$); 151.35 ($C_{5'}$); 141.82 ($C_{2'}$); 125.42 ($C_{1'}$); 121.52 ($C_{4'}$); 113.15 ($C_{3'}$); 103.72 ($C_{6'}$); 56.44 and 55.93 (2 OMe); 50.77 ($C_2$); 31.01 ($C_4$); 16.07 (Ar-Me) ppm. *Anal.* Calcd for $C_{13}H_{17}O_4N$: C, 62.14; H, 6.81; N, 5.58. Found: C, 61.70; H, 6.65; N, 5.44.

4,6-Dimethyl-5,8-dimethoxy-2-(1*H*)-quinolinone (**7**). A solution of compound (**6**) (550 mg, 2.19 mmol) in 98 % sulphuric acid (6 ml) was stirred at room temperature for 30 min and poured on crushed ice (50 g). The precipitate was filtered and washed with water, yielding 510 mg (100 %) of **7**. An analytical sample was obtained by recrystallization from ethanol. mp 86 °C (ethanol). Ir (KBr): 3430 (NH); 1680 (C=O); 1280 (O Me) $cm^{-1}$. $^1$H-Nmr (250 MHz; $CDCl_3$) δ: 9.05 (s, 1H, NH); 6.75 (s, 1H, $C_3$-H); 6.41 (s, 1H, $C_7$-H); 3.88 and 3.66 (s, 6H, 2 OMe); 2.63 (s, 3H, $C_4$-Me); 2.32 (s, 3H, $C_6$-Me) ppm. $^{13}$C-Nmr (63 MHz; $CDCl_3$) δ: 161.24 ($C_2$); 149.45 ($C_5$); 149.08 ($C_8$); 141.70 ($C_4$); 127.84 ($C_{8a}$); 123.85 ($C_6$); 122.93 ($C_3$); 114.89 ($C_{4a}$); 113.03 ($C_7$); 61.59 and 56.17 (2 OMe); 23.10 ($C_4$-Me); 16.19 ($C_6$-Me) ppm. *Anal.* Calcd for $C_{14}H_{15}O_3N$: C, 66.95; H, 6.48; N, 6.00. Found: C, 66.84; H, 6.24; N, 5.83 .

Bromination of 7. A solution of compound (**7**) (74 mg, 0.32 mmol), *N*-bromosuccinimide (113 mg, 0.64 mmol) and benzoyl peroxide (5 mg, 0.022 mmol) in carbon tetrachloride (5 ml) was refluxed for 1 h. The precipitate obtained by cooling the reaction mixture at 0 °C was filtered off and washed with carbon tetrachloride (30 ml) at

50 °C for 30 min. The combined organic layers were dried over sodium sulphate and evaporated. The residue was dissolved in chloroform (25 ml), washed with water (2 x 2 ml), dried over sodium sulphate and evaporated. The residue[19] was chromatographed on silica gel, eluting with 1:1 ethyl acetate-petroleum ether, to yield 60 mg (60 %) of 3-bromo-4,6-dimethyl-5,8-dimethoxy-2-(1*H*)-quinolinone (**9**). mp 190 °C (ethanol). $^1$H-Nmr (250 MHz, $CDCl_3$) δ: 9.40 (br s, 1H, NH); 6.82 (s, 1H, $C_7$-H); 3.94 and 3.68 (2 s, 6H, 2 OMe); 2.95 (s, 3H, $C_4$-Me); 2.37 (s, 3H, $C_6$- Me) ppm. $^{13}$C-Nmr (63 MHz; $CDCl_3$) δ: 157.03 ($C_2$); 148.21 ($C_5$); 147.73 ($C_8$); 141.61 ($C_4$); 126.26 ($C_{8a}$); 124.80 ($C_{4a}$); 122.13 ($C_6$); 114.98 ($C_3$); 113.06 ($C_7$); 61.60 and 56.28 (2 OMe); 22.73 ($C_4$-Me); 16.42 ($C_6$-Me) ppm. *Anal.* Calcd for $C_{12}H_{12}NO_3Br$: C, 48.32; H, 4.03; N, 4.70. Found: C, 48.41; H, 4.00; N, 4.65.

4-Amino-2,5-dimethoxybenzaldehyde (**11**). To a suspension of the nitro derivative (**10**) (200 mg, 0.95 mmol) in 20 % aqueous hydrochloric acid (4.5 ml) was added stannous chloride dihydrate (0.9 g, 3.8 mmol of $SnCl_2$). The suspension was stirred at 100 °C for 4 h and was then basified with 6*N* aqueous sodium hydroxide and extracted with chloroform (3 x 30 ml). The combined chloroform layers were dried over sodium sulphate and evaporated. The residue was purified by chromatography on silica gel, eluting with ether, to yield 35 mg (21 %) of **11**, as an oil. Ir (KBr): 3325 (NH), 1665 (C=O), 1240 (OMe) cm$^{-1}$. $^1$H-Nmr (300 MHz, $CDCl_3$) δ: 10.20 (s, 1H, CHO); 7.23 (s, 1H, $C_6$-H); 6.22 (s, 1H, $C_3$-H); 4.54 (s, 2H, $NH_2$); 3.84 and 3.83 (2 s, 6H, 2 OMe) ppm. $^{13}$C-Nmr (75 MHz; $CDCl_3$) δ: 187.34 (CHO); 159.35 ($C_2$); 144.70 ($C_4$); 140.97 ($C_5$); 114.94 ($C_1$); 108.11 ($C_6$); 96. 44 ($C_3$); 55.82 (2 OMe) ppm. *Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.67; H, 6.07; N, 7.73. Found: C, 59.39; H, 6.13; N, 7.79.

2,5-Dimethoxy-4 (1',3'-dioxolan-2'-yl)nitrobenzene (**12**). A solution of the nitro aldehyde (**10**) (1 g, 4.73 mmol), ethylene glycol (5.45 g, 87.9 mmol) and *p*-toluenesulphonic acid (2.2 g, 11.5 mmol) in anhydrous benzene (100 ml) was refluxed for 2 h with simultaneous removal of water by means of a Dean-Stark trap. After addition of solid sodium carbonate (2.6 g) and brine (50 ml), the mixture was extracted with chloroform (4 x 50 ml), and the combined organic layers were dried over sodium sulphate. The solvent was evaporated and the residue was recrystallized from ethanol, yielding 490 mg (41%) of **12**. Evaporation of the ethanol gave 500 mg (50%) of unreacted **10**. mp 110 °C (ethanol). Ir (KBr): 1520, 1395, 1370 ($NO_2$); 1220 (OMe); 1035 (C-O) cm$^{-1}$. $^1$H-Nmr (300 MHz,$CDCl_3$) δ: 7.43 (s, 1 H, $C_6$-H); 7.34 (s, 1 H, $C_3$-H); 6.11 (s, 1 H, $C_{2'}$-H); 4.18 and 4.11 (2 m, 4 H, $C_{3',4'}$-H); 3.96 and 3.89 (2s, 6 H, 2 OMe) ppm. $^{13}$C-Nmr (75 MHz, $CDCl_3$) δ: 150.83 ($C_5$); 147.35 ($C_2$); 139.27 ($C_1$); 132.38 ($C_4$); 112.79 ($C_3$); 108.19 ($C_6$); 98.19 ($C_{2'}$); 65.45 ($C_{4'}$, $C_{5'}$); 57.12 and 57.02 (2 OMe) ppm. *Anal.* Calcd for $C_{11}H_{13}NO_6$: C, 51.76; H, 5.09; N, 5.49. Found: C, 51.32; H, 5.17; N,

5.30.

Catalytic Hydrogenation of **12**. 10 % Palladium on charcoal (12 mg) was added to a solution of **12** (425 mg, 1.59 mmol) in methanol (100 ml). The suspension was hydrogenated at room temperature and *40 psi* for *20 min* and filtered through celite. The solvent was evaporated and the residue was chromatographed on silica gel, eluting with 2:1 petroleum ether-ether, affording 65 mg (25 %) of amine (**2**). mp 109 °C (ethanol). lit.,[5] 108-109 °C. $^{13}$C-Nmr (63 MHz, $CDCl_3$) δ: 151.98 ($C_5$); 140.96 ($C_2$); 134.41 ($C_1$); 115.39 ($C_3$); 114.08 ($C_4$); 99.32 ($C_6$); 56.19 and 55.83 (2 OMe); 15.53 ($C_4$-Me) ppm.

2,5-Dimethoxy-4-(1',3'dithian-2'-yl)nitrobenzene (**13**). Dry hydrogen chloride was bubbled through a solution of **1** (1 g, 4,73 mmol) and 1,3-propanedithiol (0.51 g, 0.47 ml, 4.73 mmol) in chloroform (6 ml) cooled at 0 °C for 5 min. The reaction mixture was stirred at room temperature for 30 min and the solvent was then evaporated. The residue was purified by recrystallization from methanol. The precipitate was filtered and washed with petroleum ether. Yield, 1.30 g (87 %). mp 162-163 °C (methanol). Ir (KBr): 1525, 1395, 1360 ($NO_2$), 1230 (OMe) $cm^{-1}$. $^1$H-Nmr (250 MHz, $CDCl_3$) δ: 7.41 (s, 1 H, $C_6$-H); 7.34 (s, 1H, $C_3$-H); 5.65 (s, 1 H, $C_{2'}$-H); 3.95 and 3.88 (2s, 6 H, 2 OMe); 3.12 (m, 2H, $C_{4',6'}$-$H_{eq}$); 2.94 (m, 2H, $C_{4',6'}$-$H_{ax}$); 2.16 (m, 1H, $C_{5'}$-$H_{eq}$); 1.97 (m, 1H, $C_{5'}$-$H_{ax}$) ppm.$^{13}$C-Nmr (63 MHz, $CDCl_3$) δ: 148.70 ($C_5$); 147.83 ($C_2$); 138.39 ($C_1$); 134.27 ($C_4$); 115.19 ($C_3$); 108.16 ($C_6$); 57.10 and 56.53 (2 OMe); 43.13 ($C_{2'}$); 32.16 ($C_{4',6'}$); 24.98 ($C_{5'}$) ppm. *Anal.* Calcd for $C_{11}H_{13}NO_6$: C, 47.84; H, 4.98; N, 4.65. Found: C, 47.76; H, 4.92; N, 4.72 .

2,5-Dimethoxy-4-(1',3'dithian-2'-yl)aniline (**14**). A suspension of **13** (1 g, 0,33 mmol) and stannous chloride dihydrate (4.32 g, 27.5 mmol of $SnCl_2$) in 35 % hydrochloric acid (13 ml) was stirred at room temperature for 24 h. The reaction was basified with 20 % sodium hydroxide and extracted with chloroform (4 x 25 ml). The combined organic layers were dried over sodium sulphate and evaporated under reduced pressure to yield 856 mg (95 %) of **14**. An analytical sample was obtained by recrystallization from methanol. mp 163-164 °C (methanol). Ir (KBr): 3350 ($NH_2$); 1205 (OMe) $cm^{-1}$. $^1$H-Nmr (250 MHz, $CDCl_3$) δ: 7.01 (s, 1 H, $C_3$-H); 6.28 (s, 1H, $C_6$-H); 5.63 (s, 1 H, $C_{2'}$); 3.87 (s, 2H, $NH_2$); 3.83 and 3.77 (2 s, 6 H, 2 OMe); 3.10 (m, 2 H, $C_{4',6'}$-$H_{eq}$); 2.87 (m, 2H, $C_{4',6'}$-$H_{ax}$); 2.16 (m, 1 H, $C_{5'}$-$H_{eq}$); 1.93 (m, 1 H, $C_{5'}$-$H_{ax}$) ppm. $^{13}$C-Nmr (75 MHz, $CDCl_3$) δ: 150.11 ($C_5$); 141.40 ($C_2$); 137.06 ($C_1$); 115.94 ($C_3$); 111.42 ($C_4$); 99.24 ($C_6$); 56.40 and 55.14 (2 OMe); 43.64 ($C_{2'}$); 32.48 ($C_{4',6'}$); 25.23 ($C_{5'}$) ppm. *Anal.* Calcd for $C_{10}H_{17}NO_2S_2$: C, 53.13; H, 6.27; N, 5.16. Found: C, 53.45; H, 6.28; N, 5.01.

*N*-[2',5'-dimethoxy-4'-(1",3"-dithian-2"-yl)phenyl]acetoacetamide (**15**). To a stirred solution of amine (**14**) (849 mg, 6.14 mmol) in anhydrous xylene (50 ml) at 130 °C was dropwise added 2,2,6-trimethyl-1,3-dioxin-4-

one (872 mg, 6.14 mmol). After 30 min, the reaction mixture was cooled and the resulting solid was filtered off and purified by column chromatography on silica gel, eluting with ether-petroleum ether (1:1). Yield, 1.01 g (91 %) of **15**. mp 190-191 °C (ether-petroleum ether). Ir (KBr): 3227 (NH); 1705, 1638 (C=O); 1228 (OMe) $cm^{-1}$. $^1$H-Nmr (250 MHz, $CDCl_3$) δ: 9.26 (s, 1H, NH); 8.13 (s, 1H, $C_{3'}$-H); 7.08 (s, 1 H, $C_{6'}$-H); 5.66 (s, 1 H, $C_{2''}$-H); 3.88 and 3.82 (2 s, 6H, 2 OMe); 3.57 (s, 2H, $C_2$-H); 3.09 (m, 2 H,$C_{4'',6''}$-$H_{eq}$); 2.86 (m, 2 H, $C_{4'',6''}$-$H_{ax}$); 2.29 (s, 3 H, $C_4$-H); 2.16 (m, 1 H, $C_{5''}$-$H_{eq}$); 1.93 (m, 1 H, $C_{5''}$-$H_{ax}$) ppm. $^{13}$C-Nmr (75 MHz, $CDCl_3$) δ: 203.61 ($C_3$); 163.39 ($C_1$); 148.89 ($C_{5'}$); 141.89 ($C_{2'}$); 127.49 ($C_{1'}$); 121.33 ($C_{4'}$); 110.40 ($C_{3'}$); 103.60 ($C_{6'}$); 55.93 (2 OMe); 50.12 ($C_2$); 42.99 ($C_{2''}$); 31.78 ($C_{4'',6''}$); 30.38 ($C_4$); 24.68 ($C_{5''}$) ppm. *Anal.* Calcd for $C_{16}H_{21}NO_4S_2$: C, 54.08; H, 5.91; N, 3.94. Found: C, 54.12; H, 5.91; N, 3.60.

*N*-[2',5'-Dimethoxy-4'-(1'',3''-dithian-2''-yl)phenyl]propanamide (**16**). To a stirred solution of **14** (500 mg, 1.84 mmol) in anhydrous benzene (4 ml) was dropwise added a solution of propionyl chloride (274 mg, 2.0 mmol) in anhydrous benzene (4 ml) in 10 min. The reaction mixture was stirred for an additional hour and was then added to a 8 % solution of sodium carbonate (7 ml) with vigorous stirring. Extraction with ether (3 x 50 ml), evaporation of the combined organic layers and recrystallization from petroleum ether gave 573 mg (95 %) of **16**. mp 126 °C (petroleum ether). Ir (KBr): 3335 (NH); 1670 (C=O); 1220 (OMe) $cm^{-1}$. $^1$H-Nmr (250 MHz, $CDCl_3$) δ: 8.20 (s, 1H, $C_{6'}$-H); 7.82 (s, 1 H, NH); 7.08 (s, 1 H, $C_{3'}$-H); 5.69 (s, 1 H, $C_{2''}$-H); 3.87 and 3.85 (2 s, 6 H, 2 OMe); 3.12 (m, 2 H, $C_{4'',6''}$-$H_{eq}$); 2.88 (m, 2 H, $C_{4'',6''}$-$H_{ax}$); 2.42 (q, 2 H, $J$ = 7.7 Hz, $C_2$-H); 2.15 (m, 1 H, $C_{5''}$-$H_{eq}$); 1.94 (m, 1 H, $C_{5''}$-$H_{ax}$); 1.24 (t, 3 H, $J$ = 7.7 Hz, $C_3$-H) ppm. $^{13}$C-Nmr (63 MHz, $CDCl_3$) δ: 172.06 ($C_1$); 149.61 ($C_{5'}$); 141.68 ($C_{2'}$); 128.36 ($C_{1'}$); 121.01 ($C_{4'}$); 110.51 ($C_{3'}$); 103.60 ($C_{6'}$); 56.41 and 56.26 (2 OMe); 43.59 ($C_{2''}$); 32.41 ($C_{4'',6''}$); 31.01 ($C_2$); 25.24 ($C_{5''}$); 9.53 ($C_3$) ppm. *Anal.* Calcd for $C_{15}H_{21}NO_3S_2$: C, 55.01 ; H, 6.46; N, 4.28. Found: C, 54.89 ; H, 6.14 ; N, 4.70.

*N*-[2',5'-Dimethoxy-4'-(1'',3''-dithian-2''-yl)phenyl]-3-chloropropanamide (**17**) Starting from 500 mg (1.84 mmol) of **14** and 254 mg (2.0 mmol) of 3-chloropropionyl chloride, following the method described above, 605 mg (95 %) of **17** were obtained. mp 156-157 °C (petroleum ether). Ir (KBr): 3367 (NH); 1700 (C=O); 1225 (OMe) $cm^{-1}$. $^1$H-Nmr ( 250 MHz, $CDCl_3$) δ: 8.31 (s, 1 H, $C_{6'}$-H); 8.17 (s, 1 H, NH); 7.10 (s, 1 H, $C_{3'}$-H); 5.69 (s, 1 H, $C_{2''}$-H); 3.93 and 3.86 (m, 8 H, 2 OMe and $C_3$-H); 3.13 (m, 2 H, $C_{4'',6''}$-$H_{eq}$); 2.94 (m, 2H, $C_{4'',6''}$-$H_{ax}$); 2.91 (s, 2H, $C_2$-H); 2.19 (m, 1 H, $C_{5''}$-$H_{eq}$); 1.98 (m, 1 H, $C_{5''}$-$H_{ax}$) ppm. $^{13}$C-Nmr ( 63 MHz, $CDCl_3$) δ: 167.64 ($C_1$); 149.60 ($C_{5'}$); 141.80 ($C_{2'}$); 127.82 ($C_{1'}$); 121.73 ($C_{4'}$); 110.68 ($C_{3'}$); 103.79 ($C_{6'}$); 56.47 and 56.34 (2 OMe); 43.55 ($C_{2''}$); 40.73 ($C_3$); 39.62 ($C_2$); 32.40 ($C_{4'',6''}$); 25.22 ($C_{5''}$) ppm. *Anal.* Calcd for $C_{15}H_{20}NO_3ClS_2$: C, 49.78; H, 5.57; N, 3.87. Found: C, 49.83; H, 5.43; N, 3.54.

5,8-Dimethoxy-4-methyl-2-oxo-1*H*-quinoline-6-carbaldehyde (**1b**). A solution of compound (**18**)[7a] (3.26 g, 14.85 mmol) and hexamethylenetetramine (2.09 g, 14.85 mmol) in trifluoroacetic acid (24 ml) was refluxed for 12 h. The solution was evaporated *in vacuo* and the residue was made basic with 10 % sodium carbonate. The solution was extracted with chloroform (4 x 10 ml). The combined organic layers were dried over sodium sulphate and evaporated, and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate, yielding 1.31 g (40 %) of **1b**. mp 204-205 °C (acetone). Ir (KBr): 3480 (NH); 1675 (C=O); 1235 (OMe) $cm^{-1}$. $^1$H-Nmr ( 250 MHz, $CDCl_3$) δ: 10.36 (s, 1 H, CHO); 9.32 (s, 1 H, NH); 7.40 (s, 1 H, $C_7$-H); 6.52 (br s, 1 H, $C_3$-H); 4.00 and 3.93 (2 s, 6 H, 2 OMe); 2.70 (d, 1H, $J$ = 1.1 Hz, $C_4$-$CH_3$) ppm. $^{13}$C-Nmr (63 MHz, $CDCl_3$) δ: 188.16 (CHO); 161.64 ($C_2$); 148.84 ($C_8$); 142.41 ($C_5$); 135.02 ($C_4$); 123.64 ($C_3$); 122.85 ($C_6$); 116.96 ($C_{4a}$); 106.91 ($C_7$); 66.93 and 56.29 (2 OMe); 22.86 ($C_4$-Me) ppm. *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.29; N, 5.69. Found: C, 63.12; H, 5.29; N, 5.53.

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18. $^1$H-Nmr data of **5**: (250 MHz, $CDCl_3$) δ: 7.97 (d, 1H, $J$ = 10 Hz, $C_4$-H); 6.98 (s, 1H, $C_7$-H), 6.71 (d, 1H, $J$ = 10 Hz, $C_3$-H); 4.79 (s, 2H, $CH_2Br$); 4.04 and 3.99 (2 s, 6H, 2 OMe) ppm.

19. The $^1$H-Nmr spectrum (250 MHz, $CDCl_3$) of this crude reaction product showed signals due to succinimide and the following ones, attributed to **8**: 6.90 (s, 1H, $C_7$-H); 6.67 (s, 1H, $C_3$-H); 3.99 and 3.74 (2 s, 6H, 2 OMe); 2.76 (s, 2H, $CH_2$-Br); 2.41 (s, 3H, Me) ppm.

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