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New Findings on the Vilsmeier-Haack Approach to Quinoline Derivatives

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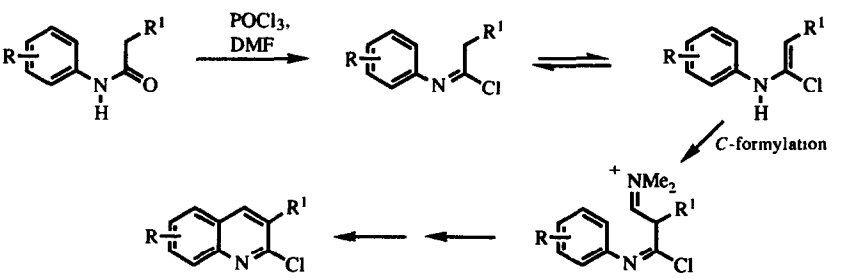
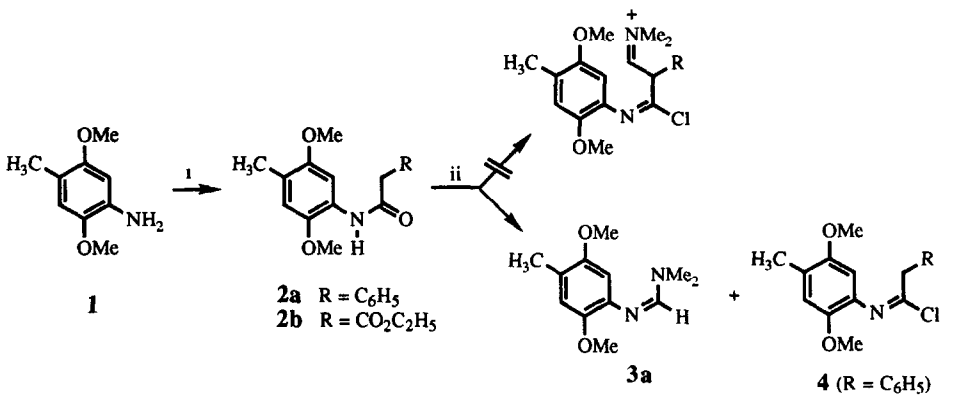
Abstract.- The presence of electron-releasing substituents on the aromatic ring of anilides, although necessary for the Vilsmeier-Haack cyclization to quinolines to proceed efficiently, can cause failure of the expected cyclization, leading to (*Z*) *N,N*-dimethylformamidines through an alternative course. A similar behaviour is observed when π-donor groups are introduced on the α position of the anilide, although in this case some cyclization to quinoline derivatives generally occurs.

The Vilsmeier-Haack reaction[1] involves treatment of a carbon nucleophile with a chloromethyleneiminium salt, normally generated from phosphorous oxychloride and dimethylformamide. When applied to anilides (Scheme 1), this reaction provides a versatile synthesis of quinolines[2] through *C*-formylation of the enamine tautomer of the iminochloride derived from the starting amide, followed by cyclization and subsequent aromatization with concomitant loss of dimethylamine. As expected, the cyclization step is favoured by the presence of electron-releasing groups in the aromatic ring.[3] Although the examples found in the literature do not include a wide range of substituents in the α position of the anilide, it can be concluded from the data available that alkyl and ω-haloalkyl-substituted anilides undergo satisfactory Vilsmeier-Haack cyclizations, but the α-chloro derivative gives an unusually low yield.[3]



Scheme 1

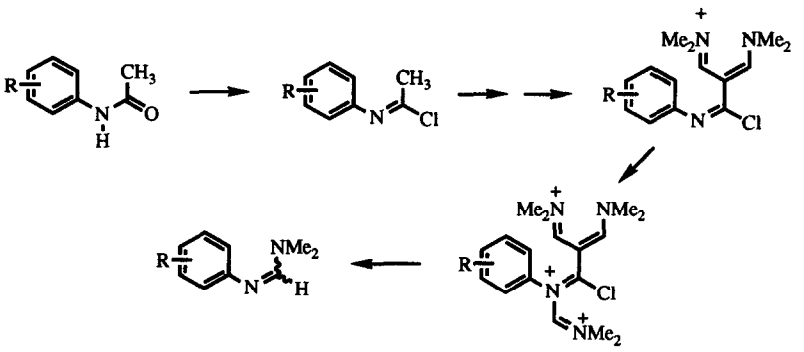
We have recently employed[4] this methodology for the synthesis of 3-substituted 2-chloro-5,8-dimethoxyquinolines, thus confirming the feasibility of using substrates with two electron-releasing groups on the aromatic ring and either electron-withdrawing or electron-releasing substituents of various sizes on the α position of the side chain (R = CH_3, CH_2CH_3, CH_2Cl, C_6H_5, $CO_2C_2H_5$). We now report that, in spite of these antecedents, the presence of a third electron-releasing group on the substrate, namely a methyl group in the *p*- position, causes the reaction to take a completely different course, where the main reaction products arise from *N*-formylation of the intermediate iminochloride (Scheme 2). Thus, acylation with phenylacetyl chloride of 4-methyl-2,5-dimethoxyaniline **1**, obtained by reduction of the corresponding nitro derivative,[5] led to 2-phenyl-*N*-(4-methyl-2,5-dimethoxyphenyl)acetamide **2a**. When this compound was treated with a mixture of phosphorous oxychloride and dimethylformamide, the corresponding *Z*-formamidine **3a** was the main product, together with a small amount (7 %) of the iminochloride (**4**) (Scheme 2), as shown by examination of the ^{1}H-NMR spectrum of the crude reaction product. Replacement of the phenyl group by an ethoxycarbonyl moiety (anilide **2b**) did not alter the outcome of the reaction, in spite of the expected increased ability of the intermediate iminochloride to enolize, and formamidine **3a** was the only product obtained (93 % yield). The corresponding anilides lacking the *p*-methyl substituent had given the expected quinolines in good yield.[4]



Reagents and conditions: i. RCH_2-COCl, r.t., 1 h; ii. $POCl_3$, DMF, 110 °C, 1 h

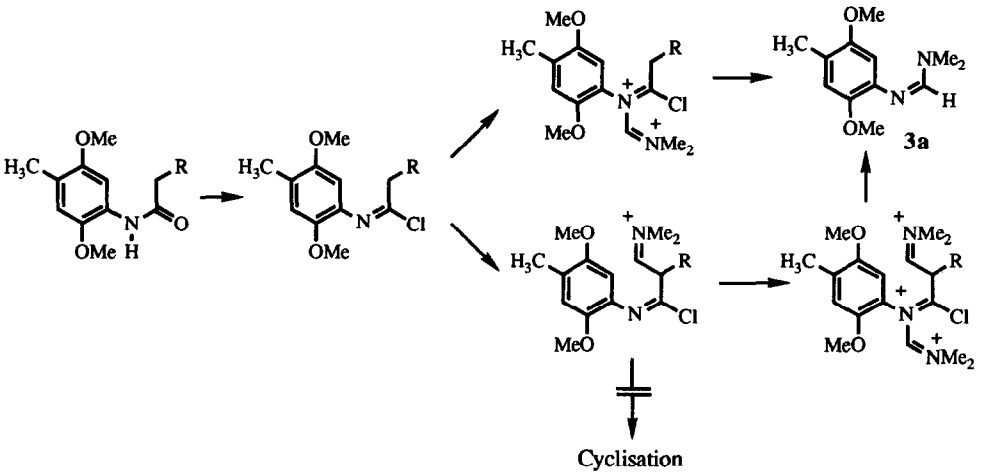
Scheme 2

Meth-Cohn and coworkers have isolated *N*,*N*-dimethylformamidine derivatives related to **3** in the Vilsmeier-Haack reaction of acetanilides (R = H) bearing electron-withdrawing groups on the aromatic ring, generally accompanied by the expected quinoline derivatives. On the basis of the isolation of certain reaction intermediates, these authors suggest[3b] the formation of a double *C*-formylated iminochloride which, due to its difficulty to cyclize imposed by the low electron density on the aromatic ring, undergoes *N*-formylation, probably aided by charge transfer from the enamino group to the imino nitrogen, followed by subsequent irreversible cleavage of the diformylated side chain (Scheme 3)



Scheme 3

Our own results can be explained through the combined effect of two factors. On one hand, the presence of an additional electron-releasing group (methyl) in the *p*- position with respect to the nitrogen atom in the intermediate iminochloride increases the electron density on the nitrogen atom to a point where *N*-formylation may be more favourable than *C*-formylation. On the other, the butressing effect of the methyl group may difficult the cyclisation step by creating additional steric hindrance at the C-6 position. In any case, subsequent hydrolytic cleavage of the side chain explains the isolation of **3a** (Scheme 4).



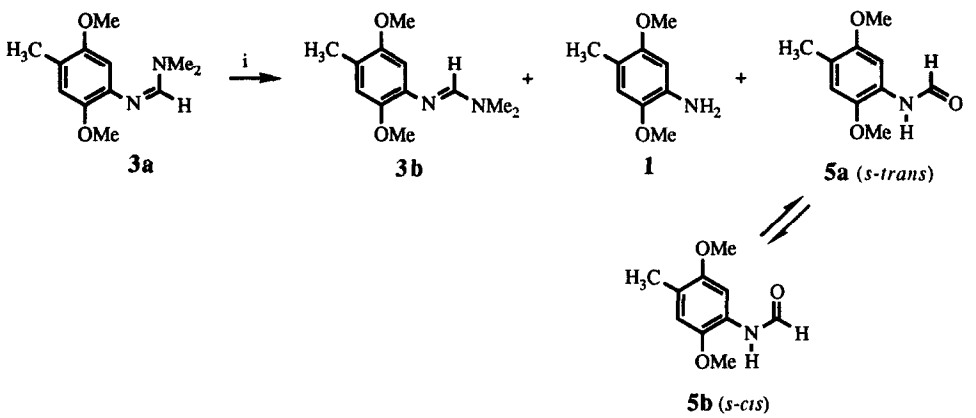
Scheme 4

Formation of the *Z* formamidine **3a** is potentially useful from a synthetic point of view, due to the scarcity of methods for the stereoselective synthesis of *Z*-formamidines.[6] Formamidines are an interesting class of compounds due to their biological properties,[7] including the good acaricidal,[8] insecticidal[9] and analgesic[10] activities found in many of them, and also due to their applications as synthetic intermediates.[11] Therefore, confirmation of the stereochemistry of **3a** was of interest.

Silica gel chromatography of **3a** led to its partial isomerization[12] to **3b** (48 %), and also to hydrolysis,

affording 4-methyl-2,5-dimethoxyaniline **1** (6 %) and formamide **5** (8 %) (Scheme 5). The latter compound was obtained as a 4:1 mixture of the *s-cis* (**5b**) and *s-trans* (**5a**) rotamers, whose structure was assigned through measurement of the coupling constants of the formamide proton (2.8 Hz in the *s-cis* structure and 11.6 Hz in the *s-trans* one). The non-equivalence of the nitrogen methyl groups in the ^{13}C-NMR spectrum of **3a**, suggesting restricted rotation around the C-N bond caused by steric compression between the dimethylamino group and the aromatic *ortho* hydrogen atom, supports the structural assignments of formamidines **3a** and **3b**. In this respect, it must be noted that electron-donating substituents on the aromatic ring of *N*-aryl formamidines are known to lower the rotational barrier around the C-N bond and allow free rotation at room temperature;[12b,13] therefore, the non-equivalence of the N-methyl groups in **3a** must be due to steric factors.[14]

Other spectral data[15] that agree with the structural assignment of amidines **3a** and **3b** are the shielding (*ca.* 0.2 ppm) of the protons of the dimethylamino group in **3a** relative to **3b**, which can be attributed to the effect on the *Z* structure of the nearby aryl group,[6] and the concomitant upfield displacement (*ca.* 0.3 ppm) of the H-6 aromatic proton.



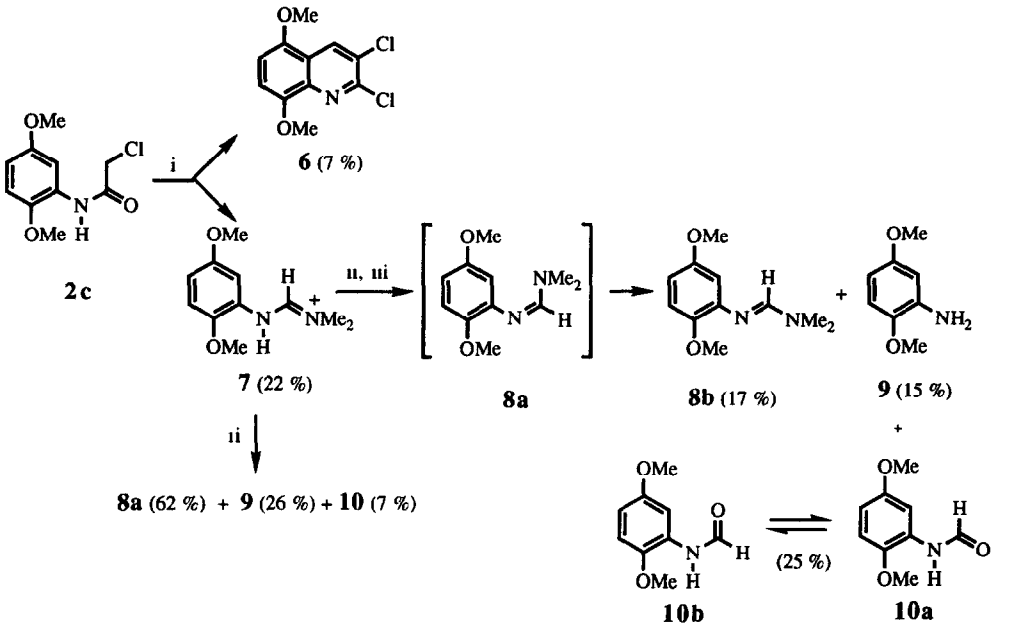
Reagents and conditions: i. Silica gel, r.t., 1 h

Scheme 5

In order to broaden the scope of the results outlined above, we next planned to examine the Vilsmeier-Haack reactions of anilides lacking the C_4-methyl group on the aromatic ring, but bearing π-donor groups in the α position of the anilide side chain, since these groups can transfer charge to the nitrogen atom through the intermediate vinylene chain in the enamine tautomer of the iminochloride.

The starting anilides **1c,d** (Z = Cl, OAc, Scheme 6) were prepared by acylation of 2,5-dimethoxyaniline, and compound **1e** (Z = NEt_2) was prepared by treatment of **1d** with diethylamine. When compounds **1c-1e** were submitted to Vilsmeier-Haack conditions, results consistent with those described above were obtained, since in all cases the main reaction products were those arising from *N*-formylation. Thus, the α-chloro derivative **1c**, on exposure to phosphorous oxychloride and dimethylformamide, yielded only minor amounts of

a product arising from *C*-formylation (7% of the 2,3-dichloroquinoline derivative **6**) (Scheme 6). The main reaction products, namely 17 % of (*E*) *N'*-(2,5-dimethoxyphenyl),*N*,*N*-dimethylformamidine (compound **8b**), 15 % of 2,5-dimethoxyaniline **9** and 25 % of *N*-(2,5-dimethoxyphenyl)formamide **10** (as a 3.3:1 mixture of the *s-cis* and *s-trans* rotamers **10b** and **10a**), derive from decomposition of the non-isolated *Z*-formamidine **8a** during continuous extraction and chromatography.



Reagents and conditions: i. $POCl_3$, DMF, 110 °C, 1.5 h; ii. NH_3,H_2O-$CHCl_3$, reflux, 14 h. iii. Silica gel, r.t., 1 h

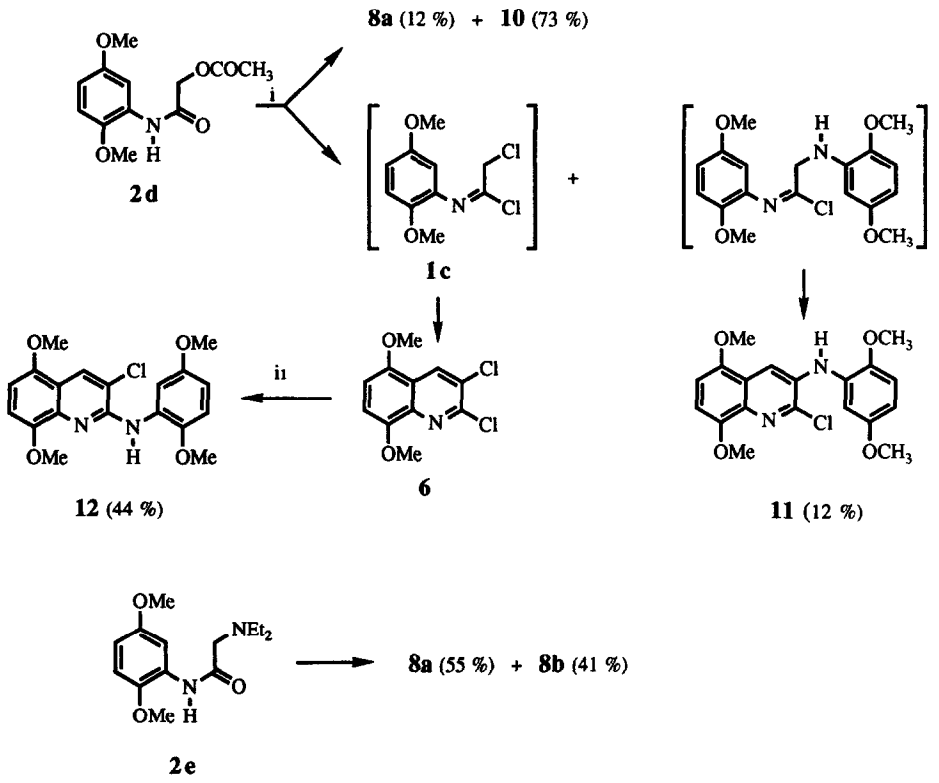
Scheme 6

Compound **8a** derives from of the previously unknown intermediate iminium salt **7**, which was isolated in 22 % yield after chromatography. This was proved by very careful neutralization of the reaction mixture and extraction at room temperature, which allowed the isolation of **7** as the only *N*-formylation product, together with a small amount of the *C*-formylation derivative **6**. Compound **7** was obtained as an *s-trans* rotamer, as proved by the observed coupling (J = 12.5 Hz) between the N-H and formamidine protons. Although compound **7** was stable to heating in the absence of a base, it was transformed into a mixture of **8a** (62 %), **9** (26 %) and **10** (7 %) when refluxed in a biphasic system containing 25 % aqueous ammonia and chloroform, thus confirming decomposition during continuous extraction. It is interesting to mention that none of the products **7**-**10** had been observed in the Vilsmeier-Haack reactions of 2,5-dimethoxyanilides.[4] Structural assignment of **8a** and **8b** was based on the same criteria as that of **3a** and **3b**.

Similar results were obtained in the case of *N*-(2,5-dimethoxyphenyl)-α-acetoxyacetamide **1d**, which under Vilsmeier-Haack conditions yielded a trace of the dichloro compound **6**, and also 12 % of a quinoline

derivative to which the structure **11** was assigned on the basis of spectral data and exclusion of the alternative structure **12** through its inequivocal synthesis from **6** and 2,5-dimethoxyaniline.

Formation of **6** can be rationalized as the consequence of displacement of the acetoxy group by a chloride anion, liberated in the reaction between phosphorous oxychloride and *N,N*-dimethyl-formamide[1a] to yield the iminochloride of compound **1c**, which, besides yielding *N*-formylation products as described above, would also cyclize to **6** through *C*-formylation (Scheme 7). The presence of small amounts of 2,5-dimethoxyaniline in the reaction medium, due to the existence of traces of water in it, explains the formation of a quinoline derivative through a similar mechanism, involving displacement of the 2-chloro group by the aniline to yield **11**. Water is necessary to account for the isolation of **11**, since this compound was formed in only trace amounts when moisture was rigorously excluded. Additional products obtained in the Vilsmeier-Haack reaction of **1d** were formamidine **8a** (12 %) and formamide **10** (73 %).



Reagents and conditions: i. $POCl_3$, DMF, 110 °C, 90 min; ii. 2,5-Dimethoxyaniline, AcOH, 130 °C, 4 h

Scheme 7

Finally, in the case of anilide **1e**, the presence of the strong diethylamino donor completely prevents *C*-formylation and subsequent cyclization and directs formylation to nitrogen, since the only products observed in the ^{1}H-NMR spectrum of the crude reaction product, after continuous extraction, were formamidines **8a** and **8b**

(Scheme 7).

In conclusion, we have shown the existence of unexpected effects in the Vilsmeier-Haack cyclization of anilides bearing electron-releasing groups in various positions, causing a previously unknown limitation in the use of this reaction for the synthesis of quinoline derivatives. This research has also uncovered a new stereoselective synthesis of *Z*-formamidines.

ACKNOWLEDGEMENT

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EXPERIMENTAL

Infra-red spectra were recorded on Perkin-Elmer 577 and Buck Scientific 500 spectrophotometers, with solid compounds compressed into KBr pellets and liquid compounds placed between NaCl plates. NMR spectra were obtained on Bruker AC-250 (250 MHz for ^{1}H, 63 MHz for ^{13}C) and Varian VXR-300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometers; $CDCl_3$ and DMSO-d_6 were used as solvents, and TMS was added in all cases as an internal standard. Interchangeable assignments are indicated with *. ^{13}C assignments were aided by DEPT experiments, when necessary. 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). Bulb-to-bulb distillations were carried out using a Büchi GKR-51 kugelrohr apparatus; the reported temperatures are those at the oven. All reagents were of commercial quality (Aldrich, Merck, SDS, Probus) and were used as received. The expression "petroleum ether" refers to the fraction boiling at 40-60 °C.

4-Methyl-2,5-dimethoxyaniline (1).

A suspension of 4-methyl-2,5-dimethoxynitrobenzene[5] (1 g, 5.95 mmol) and stannous chloride dihydrate (7.6 g, 40 mmol of $SnCl_2$) in 35 % aqueous hydrochloric acid was vigorously stirred at room temperature for 1 h. The cooled reaction mixture was basified with 20 % aqueous sodium hydroxide and extracted with chloroform (4 x 100 ml). The combined extracts were dried over sodium sulphate and evaporated, leaving 821 mg (100 %) of analytically pure **1**. Melting point, 109 °C (ethanol); lit.[5], 109 °C. ^{13}C-NMR (75 MHz, $CDCl_3$): 151.98 (C-5), 140.96 (C-2), 134.41 (C-1), 115.39 (C-4), 114.13 (C-3*), 114.08 (C-6*), 56.18 and 55.83 (OCH_3), 15.53 (CH_3).

General Synthesis of Anilides (2a-d).

To a cooled solution of 2,5-dimethoxyaniline or its 4-methyl derivative in dry benzene (7 ml per gram of aniline) was dropwise added for 10 min a solution of the suitable acyl chloride (1.05 eq.) in the same volume of dry benzene. 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 ethyl ether (3 x 50 ml). The combined organic layers were dried over sodium sulphate and evaporated, and the residue was purified by column chromatography on silica gel or by crystallization from petroleum ether.

2-Phenyl-*N*-(4'-methyl-2',5'-dimethoxyphenyl)acetamide (2a).

Starting from 0.56 g (3.35 mmol) of 4-methyl-2,5-dimethoxyaniline and 0.53 g (3.4 mmol) of phenylacetyl chloride, a yield of 0.86 g (90 %) of **2a** was obtained after crystallization from ethyl ether-petroleum ether (3:1). Melting point, 112-113 °C (ethyl ether-petroleum ether). IR, υ_{max} (KBr): 3350, 1730 and 1225 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.93 (1H, s, NH), 7.50-7.35 (6H, m, C_6H_5 and H-3'), 6.71 (1H, s, H-6'), 5.28 (2H, s, H-2), 3.89 and 3.78 (6H, 2 s, OCH_3), 2.29 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$, 63 MHz): 152.71 (C-1), 151.11 (C-5'), 140.65 (C-2'), 135.74 (C-1"), 128.03 and 127.71 (C-2",6" and C-3",5"), 127.68 (C-4"), 125.08 (C-1'), 119.43 (C-4'), 112.55 (C-3'), 101.55 (C-6'), 66.23 (C-2), 55.53 and 55.24 (OCH_3), 15.42 (CH_3). Found: C, 71.21; H, 6.65; N, 4.82. $C_{17}H_{19}NO_3$ requires C, 71.55; H, 6.71; N, 4.91.

2-Ethoxycarbonyl-N-(4'-Methyl-2',5'dimethoxyphenyl)acetamide (2b).

Starting from 0.51 g (3.01 mmol) of 4-methyl-2,5-dimethoxyaniline and 0.47 g (3.14 mmol) of ethyl malonyl chloride, a yield of 0.78 g (92 %) of **2a** was obtained after crystallization from ethyl ether-petroleum ether. Melting point, 88 °C (ethyl ether-petroleum ether). IR, υ_{max} (KBr): 3280, 1755, 1675, 1220 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 9.37 (1H, s, NH), 8.05 (1H, s, H-3'), 6.70 (1H, s, H-6'), 4.25 (2H, q, *J* 7.1 Hz, $CO_2\underline{CH_2}CH_3$), 3.87 and 3.80 (6H, 2 s, OCH_3), 3.46 (2H, s, H-2), 2.17 (3H, s, CH_3), 1.31 (3H, t, *J* 7.1 Hz, $CO_2CH_2\underline{CH_3}$). ^{13}C-NMR ($CDCl_3$, 63 MHz): 169.31 (CO_2Et), 162.77 (C-1), 151.50 (C-5'), 141.97 (C-2'), 125.57 (C-1'), 121.59 (C-4'), 113.26 (C-3'), 103.81 (C-6'), 61.87 (C-2), 56.61 and 56.07 (OCH_3), 42.65 ($\underline{CH_2}CH_3$), 16.24 ($CH_2\underline{CH_3}$) 14.17 (CH_3). Found: C, 59.77; H, 7.73; N, 5.13. $C_{14}H_{19}NO_5$ requires C, 59.75; H, 6.80; N, 5.00.

2-Chloro-*N*-(2,5-dimethoxyphenyl)acetamide (2c).

Starting from 2 g (13.1 mmol) of 2,5-dimethoxyaniline and 1.58 g (14.0 mmol) of chloroacetyl chloride, a yield of 2.89 g (96 %) of **2c** was obtained after washing the crude reaction product with petroleum ether. Melting point, 76 °C (petroleum ether). IR, υ_{max} (KBr): 3400, 1675, 1205 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.97 (1H, s, NH), 8.06 (1H, d, *J* 3.0 Hz, H-6'), 6.82 (1H, d, *J* 8.9 Hz, H-3'), 6.62 (1H, dd, *J* 8.9 and 3.0 Hz, H-4'), 4.20 (2H, s, H-2), 3.86 (3H, s, C_5-OCH_3), 3.78 (3H, s, C_2-OCH_3). ^{13}C-NMR ($CDCl_3$, 63 MHz): 163.77 (C-1), 153.67 (C-5'), 142.50 (C-2'), 127.11 (C-1'), 110.80 (C-3'), 109.27 (C-4'), 105.96 (C-6'), 56.30 and 55.74 (OCH_3), 43.06 (C-2). Found: C, 51.95; H, 5.38; N, 6.22. $C_{10}H_{12}NO_3Cl$ requires C, 52.28 ; H, 5.62; N, 6.55.

2-Acetoxy-*N*-(2,5-dimethoxyphenyl)acetamide (2d).

Starting from 1.0 g (6.5 mmol) of 2,5-dimethoxyaniline and 0.9 g (6.6 mmol) of 2-acetoxyacetyl chloride, a yield of 1.56 g (97 %) of **2d** was obtained, after recrystallization from petroleum ether. Melting point, 75 °C (petroleum ether). IR, υ_{max} (KBr): 3320, 1740, 1730 and 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.47 (1H, s, NH), 8.09 (1H, d, *J* 2.7 Hz, H-6'), 6.80 (1H, d, *J* 9.0 Hz, H-3'), 6.60 (1H, dd, *J* 9.0 and 3.0 Hz, H-4'), 4.70 (2H, s, H-α), 3.85 (3H, s, C_5-OCH_3), 3.78 (3H, s, C_2-OCH_3), 2.20 (3H, s, H-2). ^{13}C-NMR ($CDCl_3$, 63 MHz): 169.20 (C-1), 164.70 (CONH), 153.92 (C-5'), 142.20 (C-2'), 127.28 (C-1'), 110.88 (C-3'), 109.14 (C-4'), 106.18 (C-6'), 56.30 and 55.52 (OCH_3), 30.79 (C-α), 20.56 (C-2). Found: C, 56.93; H, 5.83; N, 5.55. $C_{12}H_{15}NO_5$ requires C, 56.91; H, 5.92; N, 5.53.

2-Diethylamino-N-(2,5-dimethoxyphenyl)acetamide (2e).

A solution of anilide **2c** (0.5 g, 2.17 mmol) in diethylamine (1 g, 13.7 mmol) was refluxed for 14 h. The cooled reaction was diluted with water (5 ml) and extracted with chloroform (3 x 5 ml). The extracts were dried

over sodium sulphate and evaporated, leaving a residue that was purified by bulb-to-bulb distillation to yield 450 mg (78 %) of **2e**. Boiling point, 245-250 °C (0.01 torr). IR, υ_{max} (NaCl): 3300, 1675, 1210 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 9.97 (1H, s, NH), 8.15 (1H, d, *J* 3.0 Hz, H-6'), 6.79 (1H, d, *J* 9.0 Hz, H-3'), 6.56 (1H, dd, *J* 9.0 and 3.0 Hz, H-4'), 3.84 (3H, s, C_5-OCH_3), 3.78 (3H, s, C_2-OCH_3), 3.16 (3H, s, H-2), 2.62 (4H, q, *J* 7.1 Hz, N-$C\underline{H}_2CH_3$), 1.12 (6H, t, *J* 7.1 Hz, N-$CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$, 63 MHz): 170.15 (C-1), 153.74 (C-5'), 142.53 (C-2'), 128.09 (C-1'), 110.83 (C-3'), 108.25 (C-4'), 105.61 (C-6'), 58.61 and 56.15 (OCH_3), 55.63 (C-2), 48.51 (N-$\underline{C}H_2CH_3$), 12.50 (N-$CH_2\underline{C}H_3$). Found: C, 62.97; H, 7.99; N, 10.50. $C_{14}H_{22}N_2O_3$ requires C, 63.15; H, 8.27; N, 10.52.

Vilsmeier-Haack Reactions. General Procedure.

A mixture of phosphorous oxychloride (7.0 eq) and dimethylformamide (1.5 eq) was stirred at -30 °C for 15 min, while kept in a nitrogen atmosphere. The suitable anilide **2** (1 eq) was then added in one portion. The solution was stirred at the required temperature for the time indicated in each case, while monitored by tlc (the desired product emitted 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.

Vilsmeier-Haack Reaction of Anilide 2a.

Starting from 1.52 g (5.33 mmol) of **2a**, and heating the reactants at 110 °C for 1 h, a yield of 1.34 g of a mixture of (*Z*) *N*-(4'-methyl-2',5'-dimethoxyphenyl)formamidine (**3a**) and 2,5-dimethoxy-4-methyl-*N*-(1-chloro-2-phenyl-ethylidene)aniline (**4**) was obtained (**3a**:**4** ≈12:1, as measured in the ^{1}H-NMR spectrum of the crude reaction product). Column chromatography on silica gel, eluting with 1:1 ethyl ether-petroleum ether, yielded 83 mg (7 %) of **4**, 48 mg (4 %) of starting anilide **2a**, 72 mg (6 %) of 4-methyl-2,5-dimethoxyaniline **1**, 100 mg (8 %) of *N*-(4-methyl-2,5-dimethoxyphenyl)formamide **5**, 243 mg (20 %) of **3a**, and 578 mg (48 %) of its *E* isomer, **3b**.

Data for **3a**. IR, υ_{max} (KBr): 1655, 1210 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.51 (1H, s, H-1), 6.63 (1H, s, H-3'), 6.37 (1H, s, H-6'), 3.73 (6H, s, OCH_3), 2.97 (6H, br. s, $N(CH_3)_2$), 2.09 (3H, s, Ar-CH_3). ^{13}C-NMR ($CDCl_3$, 63 MHz): 153.88 (C-1), 151.54 (C-5'), 145.49 (C-2'), 139.40 (C-1'), 119.68 (C-4'), 114.46 (C-3'), 105.33 (C-6'), 56.18 and 56.68 (OCH_3), 39.88 and 34.13 ($N(CH_3)_2$), 15.60 (Ar-CH_3).

Data for **3b**. IR, υ_{max} (KBr): 1655, 1210 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.90 (1H, s, H-1), 6.74 (1H, s, H-3'), 6.71 (1H, s, H-6'), 3.78 (6H, s, OCH_3), 3.16 (6H, br. s, $N(CH_3)_2$), 2.18 (3H, s, Ar-CH_3). ^{13}C-NMR ($CDCl_3$, 63 MHz): 154.18 (C-1), 151.72 (C-5'), 145.13 (C-2'), 121.59 (C-1'), 114.67 (C-4'), 113.99 (C-3'), 105.86 (C-6'), 56.41 and 56.17 (OCH_3), 35.00 ($N(CH_3)_2$), 15.46 (Ar-CH_3).

Data for **4**. IR, υ_{max} (KBr): 1630, 1215 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.45-7.10 (5H, m, C_6H_5), 6.58 (1H, s, H-3'), 6.21 (1H, s, H-6'), 4.33 (2H, s, H-2), 3.78 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.13 (3H, s, Ar-CH_3). ^{13}C-NMR ($CDCl_3$, 63 MHz): 152.04 (C-1), 140.60 (C-5'), 139.54 (C-2'), 136.64 (C-1"), 128.47 (C-2",6"), 128.01 (C-4'), 127.43 (C-3",5"), 127.02 (C-4"), 113.23 (C-3'), 113.00 (C-6'), 96.27 (C-1'), 56.15 and 56.09 (OCH_3), 48.37 (C-2), 15.34 (Ar-CH_3).

Data for **5**. Melting point, 96-97 °C. IR, υ_{max} (KBr): 3270, 1715, 1210 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz, 80 % *s-cis* rotamer **5b**, 20 % *s-trans* rotamer, **5a**): 8.68 (1H, d, *J* 11.6 Hz, H-1, **5a**), 8.40 (1H, d, *J* 2.8 Hz, H-1, **5b**), 8.01 (1H, s, H-6, **5a** and **5b**), 7.73 (1H, s, NH, **5b**), 7.55 (1H, s, NH, **5a**), 6.71 (1H, s, H-3, **5a**), 6.67 (1H, s, H-3, **5b**), 3.80 and 3.79 (6H, 2 s, OCH_3, **5b**), 3.75 and 3.71 (6H, 2 s, OCH_3, **5a**), 2.17

(3H, s, Ar-CH_3, **5b**), 2.14 (3H, s, Ar-CH_3, **5a**). ^{13}C-NMR (63 MHz, $CDCl_3$): 161.63 (C-1, **5a**), 158.76 (C-1, **5b**), 154.28 (C-5', **5a**), 151.51 (C-5', **5b**), 146.10 (C-2', **5a**), 141.41 (C-2', **5b**), 124.91 (C-4', **5b**), 123.37 (C-4', **5a**), 121.81 (C-1', **5b**), 120.15 (C-1', **5a**), 114.64 (C-3', **5a**), 113.12 (C-3', **5b**), 105.75 (C-6', **5a**), 104.11 (C-6', **5b**), 56.63 and 56.55 (OCH_3, **5a**), 56.23 and 56.10 (OCH_3, **5b**), 16.26 (Ar-CH_3, **5a**), 15.38 (Ar-CH_3, **5b**). Found: C, 61.29; H, 6.49; N, 7.17. $C_{10}H_{13}NO_3$ requires C, 61.49; H, 6.71; N, 7.18.

Vilsmeier-Haack Reaction of Anilide 2b.

Starting from 423 mg (2.04 mmol) of **2b**, and heating the reactants at 110 °C for 1 h, a yield of 310 mg (93 %) of essentially pure **3a** was obtained.

Vilsmeier-Haack Reaction of Anilide 2c.

a) Starting from 1 g (4.35 mmol) of **2c**, and heating the reactants at 110 °C for 90 min, the reaction mixture was poured on ice (10 g) and basified with 25 % aqueous ammonia, which was extracted with chloroform (3 x 15 ml). This extract was dried over sodium sulphate and evaporated, leaving a residue of 500 mg that was purified by column chromatography on silica gel, eluting with 1:1 petroleum ether-ethyl ether, to yield compounds **6** (80 mg, 7 %), **7** (200 mg, 22 %) and **10** (50 mg, 6 %). The aqueous layer was re-extracted overnight with 200 ml of chloroform in a continuous extractor. Drying and evaporation of the chloroform layer afforded 500 mg of a residue that was chromatographed as above, yielding compounds **8b** (150 mg, 17 %), **9** (100 mg, 15 %) and **10** (150 mg, 19 %, 25 % overall).

b) Starting from 1 g (4.35 mmol) of **2c** and performing the reaction as above, the reaction mixture was poured on ice (10 g) and neutralized with 25 % aqueous ammonia while cooled in a bath at -5 °C. Extraction with chloroform (10 x 15 ml), drying of the extracts and evaporation afforded a residue weighing 1 g, which consisted of a mixture of compounds **6** and **7** (**7/6** ≈ 15:1, as determined by ^{1}H-NMR). When 100 mg of this mixture were refluxed overnight in chloroform (15 ml), no appreciable changes occurred. However, when the same sample was added to 25 % aqueous ammonia (15 ml) and refluxed overnight while vigorously stirred, evaporation of the dried organic phase left a residue which was proved by ^{1}H-NMR to be a mixture of compounds **7**, **9** and **10** (**7/9/10** ≈ 8.7:3.7:1).

Data for **6**: Melting point, 160 °C (petroleum ether). IR, υ_{max} (KBr): 1620, 1265 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.61 (1H, s, H-4), 6.97 (1H, d, *J* 8.5 Hz, H-6), 6.81 (1H, d, *J* 8.5 Hz, H-7), 4.03 and 3.97 (6H, 2 s, OCH_3). ^{13}C-NMR (63 MHz, $CDCl_3$): 148.44 (C-8), 147.98 (C-2), 147.67 (C-5), 132.95 (C-4), 127.30 (C-8a), 124.79 (C-3), 121.11 (C-4a), 108.45 (C-7), 105.26 (C-6), 56.16 and 55.88 (2 OCH_3). Found: C, 50.82; H, 3.25; N, 5.37. $C_{11}H_9NO_2Cl_2$ requires C, 51.16; H, 3.48; N, 5.42.

Data for **7**: IR, υ_{max} (KBr): 3400, 1700, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 11.74 (1H, d, *J* 12.5 Hz, NH), 8.42 (1H, d, *J* 12.5 Hz, H-1), 7.41 (1H, d, *J* 2.9 Hz, H-6'), 6.87 (1H, d, *J* 9.0 Hz, H-3'), 6.73 (1H, dd, *J* 9.0 and 2.9 Hz, H-4'), 3.81 and 3.76 (6H, 2 s, OCH_3), 3.52 and 3.42 (6H, 2 s, $N(CH_3)_2$). ^{1}H-NMR (d_6-DMSO, 250 MHz): 10.79 (1H, br. s, NH), 8.48 (1H, br. s, H-1), 7.12 (1H, d, *J* 9.0 Hz, H-3'), 7.06 (1H, d, *J* 2.9 Hz, H-6'), 6.90 (1H, dd, *J* 9.0 and 2.9 Hz, H-4'), 3.81 and 3.74 (6H, 2 s, 2 OCH_3), 3.31 and 3.24 (6H, 2 s, $N(CH_3)_2$). ^{13}C-NMR ($CDCl_3$, 63 MHz): 168.72 (C-1), 154.96 (C-5'), 154.15 (C-2'), 144.94 (C-1'), 114.10 (C-3'), 113.60 (C-4'), 109.45 (C-6'), 56.84 and 56.21 (2 OCH_3), 44.55 and 38.84 ($N(CH_3)_2$). Found: C, 45.94; H, 6.12; N, 9.67. $C_{11}H_{17}N_2O_2.1/2Cl^-.1/2PO_2Cl_2^-$ requires C, 46.23; H, 5.95; N, 9.80.

Data for **8a**: IR, υ_{max} (KBr): 1660, 1225 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.54 (1H, s, H-1), 6.77

(1H, d, *J* 8.7 Hz, H-3'), 6.50 (1H, dd, *J* 8.7 and 3.0 Hz, H-4'), 6.45 (1H, d, *J* 3.0 Hz, H-6'), 3.79 and 3.76 (6H, 2 s, OCH_3), 3.04 (6H, br. s, $N(CH_3)_2$). ^{13}C-NMR (d_6-DMSO, 63 MHz): 154.17 (C-1), 153.95 (C-5'), 146.63 (C-2'), 138.87 (C-1'), 113.37 (C-3'), 108.01 (C-4'), 106.70 (C-6'), 56.34 and 55.34 (2 OCH_3), 34.10 (N-CH_3; the other N-CH_3 signal was hidden by the DMSO resonance). ^{13}C-NMR ($CDCl_3$, 63 MHz): 153.89 (C-1), 153.55 (C-5'), 146.67 (C-2'), 141.87 (C-1'), 111.69 (C-3'), 108.26 (C-4'), 106.54 (C-6'), 56.14 and 55.43 (OCH_3), 40.10 and 34.36 ($N(CH_3)_2$).

Data for **8b**: IR, υ_{max} (KBr): 1680, 1210 cm^{-1}. ^{1}H-NMR (d_6-DMSO, 250 MHz): 7.92 (1H, s, H-1),. 6.88 (1H, d, *J* 8.6 Hz, H-3'), 6.60 (2H, m, H-4' and H-6'), 3.68 and 3.67 (6H, 2s, 2 OCH_3), 3.07 and 3.02 (6H, 2 s, $N(CH_3)_2$). ^{13}C-NMR (d_6-DMSO, 63 MHz): 154.82 (C-1), 153.77 (C-5'), 146.43 (C-2'), 137.03 (C-1'), 113.48 (C-3'), 108.91 (C-4'), 108.81 (C-6'), 56.47 and 55.59 (2 OCH_3).

Data for **10**: Melting point, 78 °C (petroleum ether-ethyl ether); lit.,[15] 79-80 °C. IR, υ_{max} (KBr): 3270, 1715, 1210 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz, 77 % *s-cis* rotamer, **10a**, 23 % *s-trans* rotamer, **10b**): 8.73 (1H, d, *J* 11.6 Hz, H-1, **10b**), 8.44 (1H, d, *J* 1.5 Hz, H-1, **10a**), 8.08 (1H, d, *J* 3.0 Hz, H-6', **10a**), 7.95 (1H, br. s, NH, **10a**), 7.81 (1H, br. s, NH, **10b**), 6.82 (1H, H-6', **10b**), 6.83 (1H, d, *J* 8.5 Hz, H-3', **10b**), 6.80 (1H, d, *J* 8.4 Hz, H-3', **10a**), 6.62 (1H, m, H-4', **10b**), 6,60 (1H, dd, *J* 8.4 and 3.0 Hz, **10a**), 3.82 (3H, s, OCH_3, **10a**), 3.81 (3H, s, OCH_3, **10b**), 3.77 (s, OCH_3, **10a** and **10b**).

Vilsmeier-Haack Reaction of Anilide 2d.

Starting from 500 mg (1.97 mmol) of **2d** and heating the reactants at 110 °C for 1 h, a yield of 40 mg (12 %) of **8a**, 260 mg (73 %) of **10** and 90 mg (14 %) of **11** were obtained, after purification by column chromatography on silica gel, eluting with ethyl ether-petroleum ether (1:1).

Data for **11**: Melting point, 70 °C (ethanol). IR, υ_{max} (KBr): 3300 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.59 (1H, s, H-4), 6.96 (1H, d, *J* 8.6 Hz, H-7), 6.78 (1H, d, *J* 8.6 Hz, H-6), 6.71 (1H, d, *J* 8.7 Hz, H-3'), 6.33 (1H, d, *J* 2.9 Hz, H-6'), 6.24 (1H, dd, *J* 8.7 and 2.9 Hz, H-4'), 4.02, 3.95, 3.80, 3.73 (12H, 4 s, OCH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): 154.28 (C-5'), 148.39 (C-8), 147.63 (C-5), 141.80 (C-2'), 137.74 (C-8a), 137.09 (C-3), 132.95 (C-2), 132.88 (C-4), 127.24 (C-4a), 121.07 (C-4a), 111.23 (C-7), 108.45 (C-6), 105.24 (C-6'), 102.04 (C-3'*), 101.33 (C-4'*), 56.11, 55.97, 55.53 and 55.39 (OCH_3). Found: C, 59.32; H, 6.33; N, 5.77. $C_{19}H_{19}N_2O_4Cl.2\ C_2H_5OH$ requires C, 59.16; H, 6.65; N, 6.00.

Vilsmeier-Haack Reaction of Anilide 2e.

Starting from 200 mg (0.75 mmol) of **2e**, and heating the reactants at 110 °C for 1h, followed by basification and continuous extraction with chloroform for 8 h, a yield of 150 mg (95 %) of a mixture of **8a** and **8b** (55 % of **8a** and 40 % of **8b**, by ^{1}H-NMR) was obtained.

2-Chloro-5,8-dimethoxy-3-(2,5-dimethoxyphenylamino)quinoline (12).

A solution of compound **6** (20 mg, 0.073 mmol) and 2,5-dimethoxyaniline (11.2 mg, 0.073 mmol) in glacial acetic acid (0.1 ml) was refluxed in an oil bath at 130 °C for 4 h. The solvent was evaporated under reduced pressure and the residue was dissolved in water (1 ml), basified with 25 % aqueous ammonia and extracted with chloroform (3 x 3 ml). The combined extracts were dried over sodium sulphate and evaporated, and the residue was purified by column chromatography on silica gel eluting with ethyl ether-petroleum ether (1:1), yielding 12 mg (44 %) of **12**. Melting point, 122 °C. IR, υ_{max} (KBr): 3440, 1635, 1610, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): 9.25 (1H, d, *J* 3.0 Hz, H-6'), 8.40 (1H, s, H-4), 8.34 (1H, br. s, NH), 6.89 (1H, d, *J* 8.6 Hz, H-6), 6.85 (1H, d, *J* 8.9 Hz, H-7), 6.58 (1H, d, *J* 8.6 Hz, H-3'), 6.56 (1H, dd, *J* 8.8 and 3.1 Hz, H-4'), 3.98 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 3.89 (6H, s, 2 OCH_3). ^{13}C-NMR (63 MHz,

$CDCl_3$): 154.03 (C-2), 148.30 (C-5*), 148.23 (C-8*), 148.19 (C-5'*), 142.02 (C-2'), 137.44 (C-8a), 130.52 (C-4), 130.42 (C-1'), 117.92 (C-4a), 116.75 (C-3), 110.77 (C-7), 108.19 (C-6), 107.44 (C-3'), 103.44 (C-4'), 101.55 (C-6'), 56.60, 56.04, 55.68, 55.52 (4 OCH_3).

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