An Alternative Synthesis of Piritrexim, a Lipophilic Inhibitor of Human Dihydrofolate-Reductase

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Dedicated to Professor Dr. H. T. Roth (Karlsrühe) on the occasion of his 70th birthday

An alternative synthesis of the lipophilic antifolate piritrexim (**1**) is outlined. Starting from ketone **2**, treatment with phosphorus oxychloride and dimethylformamide gave the β-chlorocrotonaldehydes **3*E/Z***, which were reacted with cyanoacetamide (**6**) in the presence of sodium hydride to yield a 3-cyano-2-pyridone derivative **7**. Chlorination of **7** with thionyl chloride and subsequent reaction with guanidine (**9**) gave rise to piritrexim (**1**). The reaction of β-chlorocrotonaldehydes **3*E/Z***, with 2,4,6-triaminopyrimidine (**4**) yielded *iso*-piritrexim (**5**).

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Piritrexim (**1**), a new lipophilic inhibitor of human dihydrofolate-reductase [1], does not require an active transport mechanism and therefore overcomes Methotrexate-transport resistance [2].

In phase II clinical studies Piritrexim (**1**) has been evaluated as an anticancer agent against malignant melanomas, lung cancer, colon cancer, sarcoma and head and neck cancer [3]. In addition Piritrexim (**1**) is active as an antipsoriasis agent and as a drug against opportunistic infections with *Pneumocystis carinii* and *Toxoplasma gondii* [4]. Secondary infections with these organisms are the main cause of death for AIDS patients.

The original synthesis of Piritrexim (**1**) was described by Grivsky, Lee *et al.* in 1980 [1]. The key intermediate in this synthesis is 2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one which after chlorination with dimethylformamide/phosphorus oxychloride and reductive dehalogenation with hydrogen (Pd/C) yielded Piritrexim (**1**).

A second Piritrexim-synthesis was published in 1993 by Hill, Wisowaty and Darnofall [5]. The aim of this work was to label Piritrexim (**1**) in position 2 with carbon-14 for drug metabolism. The key step in this synthesis is the preparation of 2-bromo-5-(2,5-dimethoxybenzyl)-4-methylnicotinonitrile.

In the course of our syntheses of folate antagonists [6-9], we critically studied the existing syntheses of Piritrexim and found, that both routes have certain disadvantages. In the first mentioned Piritrexim synthesis the dehalogenation in the last step, proved to be relatively problematic in our hands. The strategy chosen by Hill *et al.* is in some steps not optimal because the yields are relatively small due to the formation of regioisomers. We therefore decided to devise an alternative synthesis of Piritrexim (**1**), based on cyclocondensation of an appropriate acyclic β-chlorovinylaldehyde with 2,4,6-triaminopyrimidine (**4**).

The reaction of cyclic β-chlorovinylaldehydes with 6-aminopyrimidines *e.g.* 2,4,6-triaminopyrimidine (**4**) was first reported by Gangjee *et al.* [10-14]. They found that the direction of ring closure of cyclic β-chlorovinylaldehydes with substituted 6-aminopyrimidines is dependent on the nature of the β-chlorovinylaldehyde, the 6-aminopyrimidine and the solvent. The desired β-chlorovinylaldehyde **3** could easily be prepared from 4-(2,5-dimethoxyphenyl)-2-butanone (**2**) [5,15] by reaction with dimethylformamide and phosphorus oxychloride at room temperature [16]. Theoretically the formylation can take place either at the methyl or the methylene group of ketone **2**, but it turned out that the ketone was formylated regioselectively at the methylene group (position 3) and transformed into the 3-chlorocrotonaldehydes **3*E*** and **3*Z*** (ratio 4:1). Compound **3*E/Z*** could be separated into its isomers by mplc. The configuration of **3*E*** and **3*Z*** was elucidated by means of NOE- measurements.

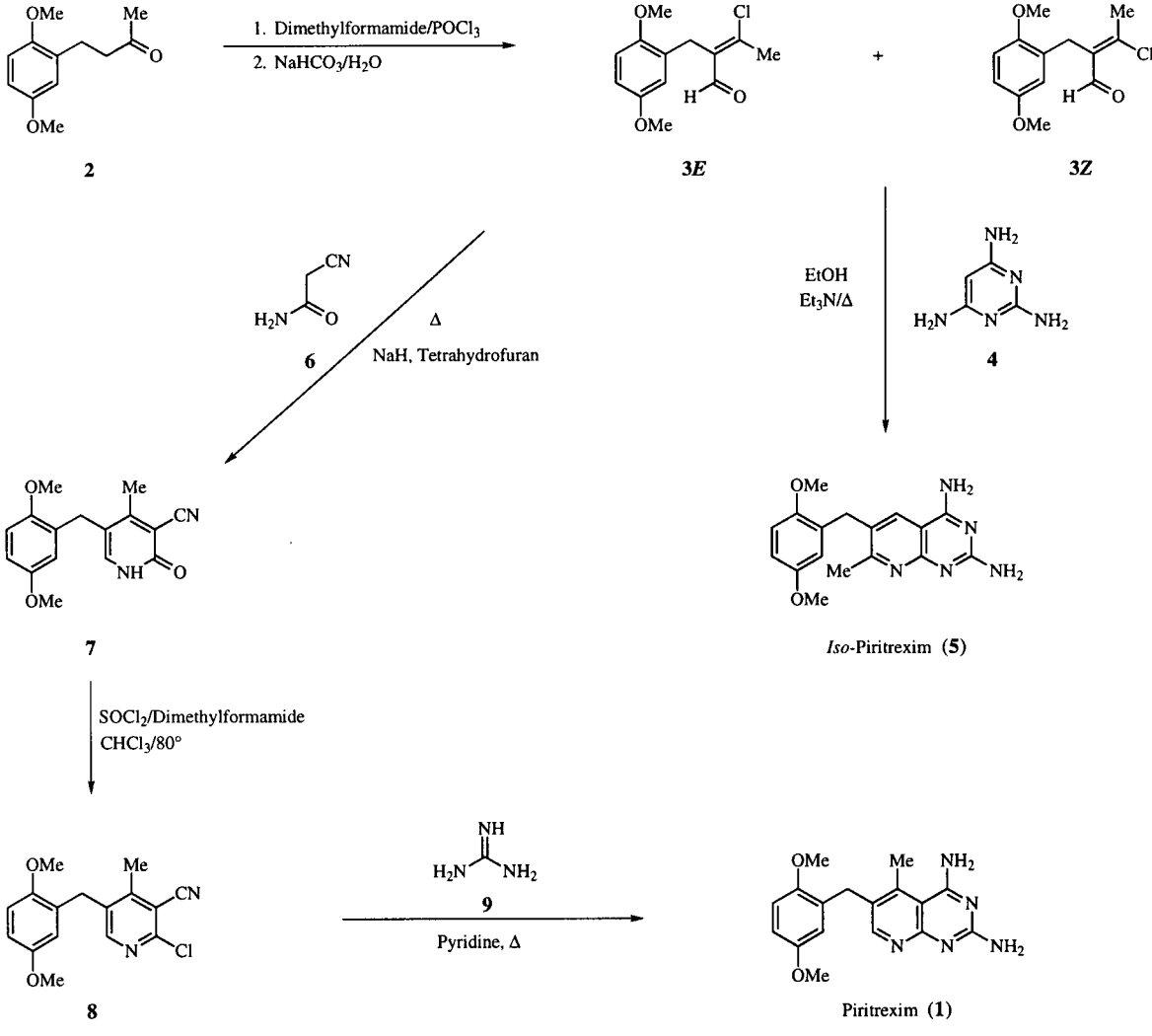
When β-chlorovinylaldehydes **3*E/Z*** were allowed to react with 2,4,6-triaminopyrimidine (**4**) in boiling ethanol/triethylamine, a single product was obtained. The ^{1}H nmr data revealed that *iso*-piritrexim (**5**) and not piritrexim (**1**) [8] had been formed. The reaction shows that the acyclic β-chlorovinylaldehydes **3*E/Z*** possess the same regioselectivity as the cyclic ones in cyclocondensation with 2,4,6-triaminopyrimidine (**4**). That means, the aldehyde carbon atom of **3*E/Z*** becomes C-5 in the pyrido[2,3-*d*]-pyrimidine **5**. For that reason we searched for a suitable acyclic 1,3-bisnucleophile that would react with 2-(2,5-dimethoxybenzyl)-3-chlorocrotonaldehydes **3*E/Z*** to give a functional 4-methylpyridine derivative, which could be finally cyclocondensed with guanidine to give piritrexim (**1**). A retrosynthetic analysis led to cyanoacetamide (**6**) as a suitable 1,3-bisnucleophile [17]. The treat-

ment of cyanoacetamide (**6**) with β-chlorovinylaldehyde (**3*E*/*Z***) at room temperature in the presence of sodium methylate gave several products from tlc. After variation of the solvent and bases we found that the reaction of **6** with **3*E*/*Z*** proceeded well in boiling tetrahydrofuran with sodium hydride and gave rise to a mean product which proved to be pyridone **7**. The position of the methyl group in **7** was unequivocally established by $^{1/3}J$-$^{1}H/^{13}C$-correlation measurements. The regioselectivity of this reaction can be explained with high probability by the fact, that the nucleophilic cyanoacetamide anion (**6**$^{\ominus}$) is first added to the twofold activated electrophilic double bond of **3*E*/*Z*** to give an adduct which cyclized to the 3-cyano-2-pyridone **7** by elimination of chloride and water. The transformation of pyridone **7** into 2-chloronicotinonitrile **8** was carried out by treatment with dimethylformamide/thionyl chloride at elevated temperature (80°). Subsequent reaction of 2-chloronicotinonitrile **8** with guanidine (**9**) in boiling pyridine gave finally Piritrexim (**1**) in medium yield (45%).

EXPERIMENTAL

Melting points were determined on a Linström capillary melting point apparatus from Büchi (type 530) and are uncorrected. The boiling points were determined on a Kugelrohr-Destillation-apparatur from Büchi (type GRK 50). The ir spectra were recorded on a Perkin-Elmer infrared-fourier-transform-spectrophotometer (type 1740). The ^{1}H nmr spectra and the ^{13}C nmr spectra were recorded on ft-nmr spectrometers: Bruker AC 250 (at 250.13 MHz), Bruker AM 360 (at 360.13 MHz). The ^{13}C nmr spectra were recorded at 60.6 and 90.6 MHz; the solvent was dimethyl-d_6 sulfoxide (unless otherwise stated) with tetramethylsilane as the internal standard. The uv spectra were recorded on a Perkin-Elmer spectrophotometer (type Lambda 5). Solvent was methanol (UVasol® Merck). Mass spectra were recorded on a Finnigan TSQ 70 (electron impact; ionization-energy 70 eV). Microanalyses were carried out on a Heraeus-CHN-Rapid.

Scheme 1



2,4-Diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-*d*] pyrimidine (**1**).

To a stirred and cooled (0°) solution of 520 mg (23 mmoles) of sodium in 50 ml of methanol 2.5 g (26 mmoles) of guanidine hydrochloride (**9**) was added. The mixture was stirred at room temperature for 30 minutes. After filtration the filtrate was evaporated *in vacuo*. To the residue 5 ml of pyridine and 938 mg (3.3 mmoles) of 2-chloro-5-(2,5-dimethoxybenzyl)-4-methylnicotinonitrile (**8**) was added. The mixture was heated to 70° for 45 minutes and refluxed for another five hours. After cooling 25 ml of water was added. The precipitate was separated and crystallized from water/dimethylformamide to give 520 mg (49%), mp >310°; ir (potassium bromide): 3500-3000 (NH_2), 2996, 2962 (C-H), 2835 (OCH_3), 1646 (C=N), 1589, 1554, 1504 C=C) cm^{-1}; uv (methanol): (*p*H 1) λ max 333 (ε 3.613), 321 (ε 3.659), 282 (ε 3.770), 227 nm (ε 4.439); (*p*H 7): λ max 343 (ε 3.581), 298 (ε 3.643), 273 (ε 3.887), 250 (ε 4.139), 227 nm (ε 4.407); (*p*H 11): λ max 349 (ε 3.643), 298 (ε 3.620), 273 (ε 3.919), 248 nm (ε 4.191); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.55 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.89 (s, 2H, CH_2), 6.15 (s, br, 2H, NH_2, deuterium oxide-exchangeable), 6.43 (d, J = 3 Hz, 1H, 6'-H), 6.76 (dd, J_1 = 9 Hz, J_2 = 3 Hz, 1H, 4'-H), 6.90 (s, br, 2H, NH_2, deuterium oxide-exchangeable), 6.93 (d, J = 9 Hz, 1H, 3'-H), 8.33 ppm (s, 1H, 7-H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 17.8 (CH_3), 30.2 (CH_2), 55.2 (OCH_3), 55.7 (OCH_3), 105.3 (C-4a), 111.0, 111.5, 115.8 (C-3', C-4', C-6'), 126.5 (C-6), 129.2 (C-1'), 143.9 (C-5), 151.0, 153.0 (C-2', C-5'), 155.9, 161.3, 161.5, 164.0 ppm (C-2, C-5, C-7, C-8a); ms: (70 eV electron impact) m/z 325 (M^+), 310 (M^+-CH_3), 294 (M^+-OCH_3).

Anal. Calcd. for $C_{17}H_{19}N_5O_2$ (325.38): C, 62.8; H, 5.89; N, 21.5. Found: C, 62.5; H, 5.67; N, 21.1.

(*E*/*Z*)-3-Chloro-2-(2,5-dimethoxybenzyl)crotonaldehyde (**3*E*/*Z***).

To 1.095 g (15 mmoles) of stirred and cooled (0°) dimethylformamide, 1.845 g (12 mmoles) of phosphorus oxychloride was added. The mixture was stirred for 30 minutes at room temperature and cooled (0°) again and 1.5 g (7.21 mmoles) of 4-(2,5-dimethoxyphenyl)butan-2-one (**2**) was added dropwise. After one hour the mixture was quenched by addition of ice, water and finally with sodium hydrogencarbonate solution (20%). The product was isolated by extraction with ether. The ether was dried (sodium sulfate) and evaporated to yield an orange-red oil.

(*Z*)-3-Chloro-2-(2,5-dimethoxybenzyl)crotonaldehyde (**3*Z***).

Isolation by mplc (cyclohexane:ethyl acetate (8:2), rf: 0.6) from **3*E*/*Z*** gave a yellow powder, 330 mg (18%), mp 75-76°; ir (potassium bromide): 3019, 3015 (Ar-H), 2938, 2912 (C-H), 2837 (OCH_3), 1718, 1677 (CHO), 1615, 1592, 1500 (C=C) cm^{-1}; uv (methanol): (*p*H 1) λ max 227 (ε 3.997), 254 (ε 4.023), 286 nm (ε 3.594); (*p*H 7) λ max 228 (ε 4.064), 245 (ε 3.965), 290 nm (ε 3.616); (*p*H 11) λ max 265 nm (ε 4.014); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.37 (s, 3H, CH_3), 3.54 (s, 2H, CH_2), 3.65 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 6.48 (d, J = 3 Hz, 1H, 6'-H), 6.74 (dd, J_1 = 9 Hz, J_2 = 3 Hz, 1H, 4'-H), 6.88 (d, J = 9 Hz, 1H, 3'-H), 10.16 ppm (s, 1H, CHO); ms: (70 eV, electron impact) m/z 254/256 (M^+), 219 (M^+-Cl).

Anal. Calcd. for $C_{13}H_{15}ClO_3$ (254.71): C, 61.3; H, 5.94. Found: C, 61.3; H, 5.74.

(*E*)-3-Chloro-2-(2,5-dimethoxybenzyl)crotonaldehyde (**3*E***).

Isolation by mplc (cyclohexane:ethyl acetate (8:2), rf: 0.4) from **3*E*/*Z*** gave a yellow oil, 900 mg (49%), bp 170-190° (3 hPa); ir (potassium bromide): 3020, 3012 (Ar-H), 2976, 2909 (C-H), 2837 (OCH_3), 1674 (CHO), 1618, 1500 (C=C) cm^{-1}; uv (methanol): (*p*H 1) λ max 228 (ε 4.007), 251 (ε 4.041), 287 nm (ε 3.543); (*p*H 7) λ max 229 (ε 4.133), 243 (ε 4.106), 289 nm (ε 3.546); (*p*H 11) λ max 227 (ε 4.125), 248 (ε 4.089), 278 nm (ε 3.443); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.71 (s, 3H, CH_3), 3.58 (s, 2H, CH_2), 3.64 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 6.38 (d, J = 3 Hz, 1H, 6'-H), 6.72 (dd, J_1 = 9 Hz, J_2 = 3 Hz, 1H, 4'-H), 6.86 (d, J = 9 Hz, 1H, 3'-H), 10.07 ppm (s, 1H, CHO); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 22.5 (CH_3), 26.7 (CH_2), 55.2 (OCH_3), 55.7 (OCH_3), 110.3, 111.2, 114.7, 126.9 (C-1', C-3', C-4', C-6'), 135.8 (C-2), 151.0, 153.0 (C-2', C- 5'), 155.3 (C-3), 189.0 ppm (C-1); ms: (70 eV, electron impact) m/z 254/256 (M^+), 219 (M^+-Cl).

Anal. Calcd. for $C_{13}H_{15}ClO_3$ (254.71): C, 61.3; H, 5.94. Found: C, 61.5; H, 6.14.

2,4-Diamino-6-(2,5-dimethoxybenzyl)-7-methylpyrido[2,3-*d*]-pyrimidine (**5**).

To a solution of 750 mg (3.0 mmoles) of 3-chloro-2-(2,5-dimethoxybenzyl)crotonaldehyde (**3*E*/*Z***) in 5 ml of ethanol and 300 mg of triethylamine 250 mg (2.0 mmoles) of 2,4,6-triaminopyrimidine (**4**) was added. The mixture was heated at reflux for 3 hours. On cooling a product precipitated which was separated. Purification by mplc (chloroform:methanol 7:3) and crystallization from water/dimethylformamide gave a yellow powder, 155 mg (24%), mp >310°; ir (potassium bromide): 3328, 3153 (NH_2), 2997 (Ar-H), 2925 (CH_3), 2834 (OCH_3), 1684 (C=N), 1605, 1504 cm^{-1} (C=C); uv (methanol): (*p*H 1) λ max 224 (ε 4.294), 275 (ε 3.708), 320 (ε 3.694), 330 nm (ε 3.512); (*p*H 7) λ max 225 (ε 4.247), 247 (ε 4.035), 272 (ε 3.714), 297 (ε 3.525), 333 (ε 3.525), 352 (ε 3.415); (*p*H 11) λ max 247 (ε 4.032), 272 (ε 3.714), 297 (ε 3.525), 348 (ε 3.562); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.45 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.91 (s, 2H, CH_2), 6.51 (d, J = 3 Hz, 1H, 6'-H), 6.79 (dd, J_1 = 8.5 Hz, J_2 = 3 Hz, 1H, 4'-H), 6.93 (d, J = 8.5 Hz, 1H, 3'-H), 7.46 (s, br, 2H, NH_2, deuterium oxide-exchangeable), 8.35 (s, 1H, 5-H), 8.48 ppm (s, br, 2H, NH_2, deuterium oxide-exchangeable); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 22.6 (CH_3), 31.9 (CH_2), 55.2 (OCH_3), 55.7 (OCH_3), 103.0 (C-4a), 111.3, 111.7, 116.2, 128.1 (C-1', C-3', C-4', C-6'), 129.4 (C-6), 134.4 (C-5), 149.3 (C-4), 151.0, 153.0 (C-2', C-5'), 158.1 (C-2), 163.0 (C-8a), 164.1 ppm (C-7); ms: (70 eV, electron impact) m/z 325 (M^+), 310 (M^+-CH_3), 294 (M^+-OCH_3).

Anal. Calcd. for $C_{17}H_{19}N_5O_2$ (325.37): C, 62.8; H, 5.89; N, 21.5. Found: C, 62.6; H, 5.89; N, 21.3.

5-(2,5-Dimethoxybenzyl)-3-cyano-4-methyl-2-pyridone (**7**).

To a stirred and cold (0°) solution of 147.8 mg (1.76 mmoles) of cyanoacetamide (**6**) in 15 ml of tetrahydrofuran, 42.2 mg (1.76 mmoles) of sodium hydride was added in small portions. After 1 hour stirring at room temperature, the mixture was cooled to -10° and 225 mg (0.88 mmole) of (*E*/*Z*)-3-chloro-2-(2,5-dimethoxybenzyl)crotonaldehyde (**3*E*/*Z***) in 5 ml of tetrahydrofuran was slowly added. Then the mixture was heated slowly to reflux for 10 hours. After cooling and addition of 5 ml of water the mixture was evaporated *in vacuo*. The residual solid was purified by mplc on silica gel (chloroform:methanol = 97:3) to give 90 mg (36%). Crystallization from ethanol gave colorless crystals, mp 212-213°; ir (potassium bromide): 3149 (NH), 3005

(Ar-H), 2965, 2907 (C-H), 2842 (OCH_3), 2223 (CN), 1656 (C=N), 1618, 1533, 1499 cm^{-1} (C=C); uv (methanol): (*p*H 7) λ max 216 (ε 4.539), 242 (ε 3.942), 297 (ε 3.792), 332 nm (ε 3.987); (*p*H 11) λ max 245 (ε 4.107), 291 (ε 3.763), 337 nm (ε 3.951); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.28 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3), 6.57 (d, J = 3 Hz, 1H, 6'-H), 6.79 (dd, J_1 = 9 Hz, J_2 = 3 Hz, 1H, 4'-H), 6.93 (d, J = 9 Hz, 1H, 3'-H), 7.31 (s, 1H, 6-H), 12.20 ppm (br, 1H, N-*H* deuterium oxide-exchangeable); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 18.6 (CH_3), 28.8 (CH_2), 55.3 (OCH_3), 55.8 (OCH_3), 103.2 (C-3), 111.6, 111.8, 115.9, 116.1, 116.8 (C-3', C-4', C-6', C-5, CN), 127.9 (C-1'), 139.6 (C-4), 151.0, 153.2 (C-2', C-5'), 159.7, 160.50 ppm (C-2, C-6); ms: (70 eV, electron impact) m/z 284 (M^+), 269 (M^+-CH_3), 253 (M^+-OCH_3).

Anal. Calcd. for $C_{16}H_{16}N_2O_3$ (284.32): C, 67.6; H, 5.67; N, 9.85. Found: C, 67.5; H, 5.69; N, 10.1.

2-Chloro-5-(2,5-dimethoxybenzyl)-4-methylnicotinonitrile (**8**).

To a stirred and cooled (0°) solution of 7.3 ml (95 mmoles) of dimethylformamide in 50 ml of dry chloroform 11.9 g (0.1 mole) of thionyl chloride in 20 ml of dry chloroform was added dropwise, keeping the temperature below 5°. At the end of the exothermic reaction 2.84 g (0.01 mole) of **7** was added within 10-15 minutes. The reaction mixture was first stirred at room temperature and then heated at reflux for 3 hours. After cooling, the mixture was quenched with ethanolic potassium hydroxide solution (10%) and then was diluted with water. The organic layer was separated, dried (sodium sulfate) and evaporated *in vacuo*. The residue was separated by mplc (cyclohexane:ethyl acetate = 8:2). Crystallization from ethanol yielded a yellow powder, 2.21 g (72%), mp 90°; ir (potassium bromide): 2999 (Ar-H), 2938 (C-H), 2835 (OCH_3), 2231 (CN), 1612, 1591, 1568, 1504 cm^{-1} (C=C); uv (methanol): (*p*H 7) λ max 209 (ε 4.513), 225 (ε 4.234), 278 (ε 3.660), 287 (ε 3.724), 299 nm (ε 3.585); ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.48 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.95 (s, 2H, CH_2), 6.64 (d, J = 3 Hz, 1H, 6'-H), 6.81 (dd, J_1 = 9 Hz, J_2 = 3 Hz, 1H, 4'-H), 6.94 (d, J = 9 Hz, 1H, 3'-H), 8.30 ppm (s, 6-H); ms: (70 eV, electron impact) m/z 302/304 (M^+), 287/289 (M^+-CH_3), 271 (M^+-OCH_3).

Anal. Calcd. for $C_{16}H_{15}N_2O_2Cl$ (302.77): C, 63.5; H, 5.00; N, 9.25. Found: C, 63.7; H, 4.75; N, 9.16.

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