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Synthesis of the Lipophilic Antifolate Piritrexim via a Palladium(0)-Catalyzed Cross-Coupling Reaction

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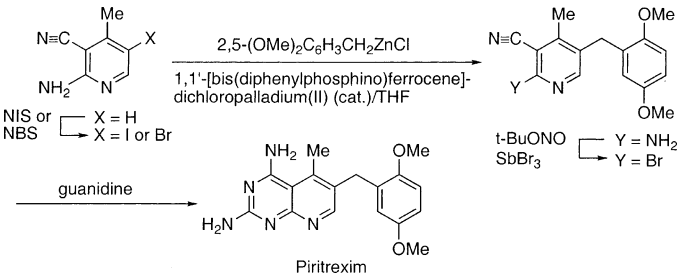
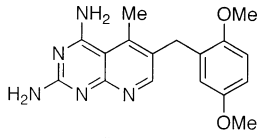
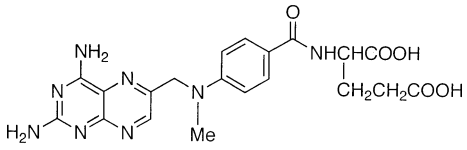


A regiospecific and convergent route the lipophilic antifolate piritrexim (PTX) is described in which a key step is a Pd(0)-catalyzed cross-coupling reaction between 2-amino-3-cyano-4-methyl-5-bromopyridine and 2,5-dimethoxybenzylzinc chloride to form 2-amino-4-methyl-5-(2,5-dimethoxybenzyl)nicotinonitrile. To complete the synthesis, the amino group is replaced by a more reactive bromine atom via nonaqueous diazotization with *tert*-butyl nitrite, and the resultant bromo nitrile is cyclized with guanidine.

Piritrexim (**1**, PTX) is a nonclassical antifolate which was first synthesized by Grivsky and co-workers[1a,b] as a lipophilic analogue of the anticancer drug methotrexate (MTX) (Figure 1). Extensive in vitro and in vivo preclinical studies were subsequently carried out by a number of investigators with a view to exploring the mechanism and scope of action of **1** relative to MTX.[2a−g] Phase I[3a−c] as well as single- and multi-agent Phase II clinical trials have been performed with **1** in patients with several types of cancer including soft tissue sarcoma,[4] malignant melanoma,[5a,b] and carcinomas of the head and neck,[6a−c] lung,[7] breast,[8] bladder,[9a−c] and brain.[10] Other diseases against which **1** has been used clinically include psoriasis[11a,b] and AIDS-related opportunistic parasitic infections such as *Pneumocystis carinii* pneumonia.[12,13] For this reason, new and/or improved synthetic routes to **1** and its congeners continue to be of interest.



PTX



MTX

FIGURE 1. Structures of piritrexim (PTX, **1**) and methotrexate (MTX).

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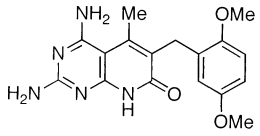
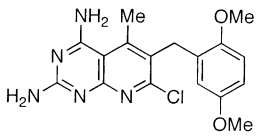
Three synthetic routes to **1** have been reported in the literature,[1a,14,15] all of which suffer from various limitations. In the Grivsky synthesis,[1a] 2,4,6-triaminopyrimidine is condensed with ethyl 2-(2,5-dimethoxybenzyl)-3-oxobutanoate to afford the dicyclic lactam **2**, whereupon chlorination ($SOCl_2$/DMF) followed by catalytic dechlorination (H_2/Pd−C/KOH) yields **3** and **1**, respectively. This route suffers from the capricious nature of the chlorination step and from fact that the diaminoheterocyclic intermediates **2** and **3** are difficult to purify on a large scale because of their poor solubility in organic solvents other than DMF or DMSO.

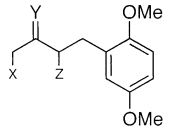


2

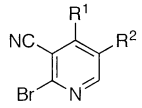


3

In the Hill synthesis,[14] which was designed to avoid some of the foregoing problems and also provide access to [^{14}C]PTX, Knoevenagel condensation of 4-(2,5-dimethoxyphenyl)-2-butanone (**4**) with malononitrile, followed by reaction of the resulting ylidenemalononitrile **5** with diethoxymethyl acetate (DEMA), yielded the isomeric acetals **6** and **7**. Without being separated, the latter were then converted directly to the 2-bromonicotinonitriles **8** and **9** (HBr/AcOH). After removal of the unwanted isomer **9**, bromo nitrile **8** was cyclized with guanidine. The lack of regiospecificity in the DEMA reaction necessitated careful optimization of this step by HPLC and ultimately separation of **8** and **9** by flash chromatography and crystallization.

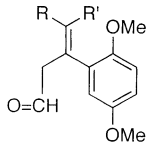


4: X = Z = H; Y = O
5: X = Z = H; Y = $C(CN)_2$
6: X = H, Z = $CH(OEt)_2$, Y = $C(CN)_2$
7: X = $CH(OEt)_2$, Z = H, Y = $C(CN)_2$

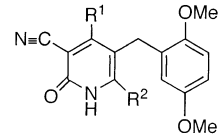


8: R^1 = Me, R^2 = 2,5-dimethoxybenzyl
9: R^1 = 2-(2,5-dimethoxyphenyl)ethyl, R^2 = H

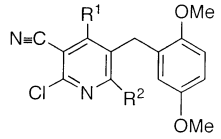
In the Troschütz synthesis,[15] **4** was subjected to a Vilsmeier reaction ($POCl_3$/DMF) to obtain an approximately 3:1 mixture of **10a** and **10b**, the crude mixture was condensed directly with cyanoacetamide to obtain 4-methylpyridone-3-carbonitrile (**11**), and after extensive purification via a combination of chromatography and recrystallization, **11** was subjected to chlorination ($SOCl_2$/DMF) followed by treatment with guanidine to form **12** and **1**, respectively. However, the reaction of **10a/10b** with cyanoacetamide was said to afford more than one product,[15] one of which we surmised might be **13**. Thus a possible drawback of this route is that unless **11** and **12** are entirely free of their respective regioisomers **13** and **14** the final product could be a difficulty separable mixture of PTX and the corresponding 7-methyl isomer, i.e., "isoPTX".[16]



10a: R = Me, R' = Cl
10b: R = Cl, R' = Me



11: R^1 = Me, R^2 = H
13: R^1 = H, R^2 = Me



12: R^1 = Me, R^2 = H
14: R^1 = H, R^2 = Me

An inefficient feature of all the previously described routes[1,14,15] to **1** is that they are nonconvergent. That is, for the synthesis of every 2,4-diamino-5-methyl-6-(substituted benzyl)pyrido[2,3-*d*]pyrimidines, a different ethyl 2-(substituted benzyl)-3-oxobutanoate, 4-(substituted phenyl)-3-butanone, or 3-(substituted phenyl)-1-propanone

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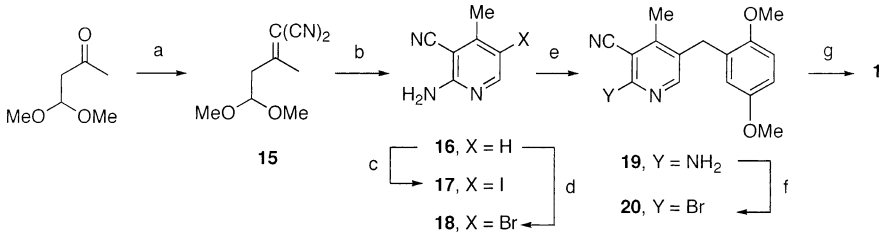
SCHEME 1[a]



[a] Reagents: (a) $CH_2(CN)_2$/piperidine/AcOH; (b) NH_3/MeOH; (c) NIS/DMF; (d) NBS/DMF; (e) 2,5-$(MeO)_2C_6H_3CH_2ZnCl$/$PdCl_2$(dppf)·CH_2Cl/THF; (f) $SbBr_3$/*t*-BuONO/CH_2Br_2; (g) $H_2NC(=NH)NH_2/C_5H_5N$.

must be used. It therefore seemed of interest to devise a strategy for the synthesis of **1**, and potentially its congeners,[17] that would be *both regiospecific and convergent.* To this end we took advantage of a Pd(0)-catalyzed organozinc coupling reaction[18] we had used earlier to prepare 2,4-diamino-6-(substituted benzyl)quinazolines[19] and 2,4-diamino-6-(substituted benzyl)pyrido[2,3-*d*]pyrimidines.[20] In the latter instance, the poor solubility of unprotected 2,4-diaminopyrido[2,3-*d*]pyrimidines necessitated the use of 2,4-bis(pivaloylamino) derivatives in the coupling reaction. Accordingly, to avoid the extra protection and deprotection steps that would be needed with a preformed 2,4-diamino-6-halo-5-methylpyrido[2,3-*d*]pyrimidine we decided to perform the Rieke reaction at an early stage of the sequence where solubility would be less of a problem.

As shown in Scheme 1, commercially available 4,4-dimethoxy-2-butanone was condensed with malononitrile to form the ylidenemalononitrile **15**[21] (cf. also refs 22−24), and the latter was cyclized to 2-amino-4-methyl-3-carbonitrile (**16**) with ammonia in methanol. Halogenation of **16** with *N*-iodosuccinimide or *N*-bromosuccinimide in anhydrous DMF[23] afforded the 5-iodo and 5-bromo derivatives **17** and **18**, respectively. As expected, the pair of doublets for C_5 (δ 6.56) and C_6 (δ 8.07) protons in the ^{1}H NMR spectrum of **16** was replaced by a singlet at δ 8.42 in the case of **17** and δ 8.24 in the case of **18**. The larger downfield shift of the C_6 proton in the iodide **17** ($\Delta = -0.35$ ppm) than in the bromide **18** ($\Delta = -0.17$ ppm) relative to **16** was qualitatively consistent with the chemical shifts of the corresponding singlet in 3-iodo-4-methylpyridine (δ 8.9)[25] and 3-bromo-4-methylpyridine (δ 8.5),[26] respectively.

Reaction of **17** in dry THF with 2,5-dimethoxybenzylzinc chloride and 1,1′-bis[(diphenylphosphino)ferrocene]-dichloropalladium(II)·CH_2Cl_2 [$PdCl_2$(dppf)·CH_2Cl_2] under an inert atmosphere afforded the desired 5-(2,5-dimethoxybenzyl) derivative **19**. Interestingly, the reaction of **18** appeared to be much more efficient than that of **17**. Thus, when the reaction of the bromide was worked up after just 4 h in refluxing THF the yield of **19** was 59%, whereas in the case of the iodide the yield was only 36% even after 24 h. Moreover, the ^{1}H NMR spectrum of crude **19** obtained via **17** indicated the likely presence of some **16**, presumably formed by reductive deiodination. It thus appears that despite the better yields sometimes observed with aryl iodides in Pd(0)-catalyzed coupling reactions, the bromide was clearly superior to the iodide in this case.

While we had hoped that treatment of **19** with guanidine would yield **1**, we were disappointed to find that the desired ring closure did not occur despite a number of attempts to vary the temperature and/or duration of the reaction. We suspect that this was probably due to a combination of two factors. The first is that the nucleophilic reactivity of the NH_2 group is diminished because it is simultaneously flanked by a ring nitrogen and C≡N group. The other is that the electrophilic reactivity of the nitrile may be compromised by steric hindrance by the methyl group at C_4 and the additional buttressing effect of the arylmethyl group at C_5. Faced with this hurdle, we decided to replace the NH_2 group by Br via a Sandmeyer-type reaction in the hope that the bromo nitrile would be more reactive. Accordingly, nonaqueous diazotization of **19** with *t*-BuONO and $SbBr_3$ in CH_2Br_2 via a slight modification of the excellent method of Robins and Uznanski[27] led to the required bromo nitrile intermediate **20** (43%), which on further treatment with guanidine was successfully cyclized to **1** (38%).

In summary, while we did not optimize the yields of the various steps in Scheme 1, we believe that our route to **1** is a novel alternative to other approaches used in the past because it involves fewer overall steps, avoids capricious Vilsmeier-type reactions, and is by its very nature *both regiospecific and convergent*. Thus, an inter-

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(21) This reaction is reported in a patent[22] to yield a mixture of **15** and a second compound identified as 4-methoxy-3-methyl-1,3-butadienylidenemalonitrile, presumably formed by loss of a molecule of MeOH during distillation. The products were used without separation, but the reactions disclosed in the patent did not include cyclization with ammonia. Interestingly, the ^{1}H NMR spectrum of our double-distilled product showed no evidence of an enol ether byproduct. The *diethyl* acetal analogue of **15** is known[23] and can also be used to make **16**. However, unlike **15**, the diethyl acetal is not commercially available and its synthesis from 1,1-dicyano-2-methylpropene (acetonylidenemalonitrile), triethyl orthoformate, acetic anhydride, and $ZnCl_2$ catalyst laboratory adds an extra step. Compound **16** has also been synthesized previously by a multistep route from 2-amino-4-methylpyridine,[24] but the method described here is superior.
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esting feature of this strategy is that is has the potential to be used in the construction of libraries of piritrexim analogues by parallel synthesis.

Experimental Section

Infrared (IR) spectra using KBr disks or NaCl plates were obtained on a double-beam recording spectrophotometer. Mass spectra (MS) were provided by the Molecular Biology Core Facility of the Dana-Farber Cancer Institute. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 200 MHz. Each peak is denoted as a singlet (s), broad singlet (br s), doublet (dd), or triplet (t). The ^{13}C NMR spectrum of **1** was recorded at 125 MHz field strength, with peak assignments made by means of the attached proton test.[28] TLC analyses were on glass plates coated with silica gel containing a fluorescent dye, and spots were visualized by illumination at 254 nm. Column chromatography was on flash-grade silica gel (40 μm particle size). Chemicals were of the best grade available from commercial suppliers, and were used without additional purification. Elemental analyses were performed by a commercial laboratory.

4,4-Dicyano-3-methyl-3-butenal Dimethyl Acetal (15). Malononitrile (25 g, 0.38 mmol) was added in portions over 20 min to a stirred solution of 4,4-dimethoxy-2-butanone (50 g, 0.38 mol) in toluene (150 mL) containing acetic acid (2.2 mL, 0.038 mmol) and piperidine (3.8 mL, 0.038 mol). Stirring was continued at room temperature overnight, and the resulting dark red solution was washed with H_2O (50 mL). The organic layer was evaporated and the residue double-distilled to obtain a colorless oil (52 g, 76%).[29] A center-cut (77−79 °C/0.03 mm) was set aside for spectroscopic and microchemical analysis, and the remainder was used directly in the next step: IR (NaCl) ν 2930, 1840, 2240 (C≡N), 1680, 1600, 1440, 1360, 1340, 1120, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H, CH_3), 2.87 (d, 1H, J = 5.2 Hz, CH_2), 3.39 (s, 6H, OCH_3), 4.57 (t, 1H, J = 5.2 Hz, CH). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.69; H, 6.72; N, 15.82.

2-Amino-3-cyano-4-methylpyridine (16). Ammonia gas was bubbled without external cooling through a solution of **15** (8.0 g, 44 mmol) in MeOH (300 mL), and the deep-red solution was stirred at room temperature overnight. The solvent was evaporated, and the residue partitioned between 1 N HCl (300 mL) and EtOAc (300 mL). The aqueous layer was added carefully (caution: foaming) to ice-cold concd $NaHCO_3$ (600 mL), and the precipitate was filtered to obtain a beige solid (3.0 g, 33%). Recrystallization of a portion of the solid from EtOAc-cyclohexane gave yellow needles: mp 154−155 °C (lit.[24] mp 150−152.5 °C); MS calcd *m/z* 134.06, found 133.94 (M + 1); IR (KBr) ν 3400, 3340, 3160, 2220 (C≡C), 1650, 1560, 1480, 1370, 1330, 1260, 1250, 800, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H, CH_3), 5.18 (bs s, 2H, NH_2), 6.56 (d, 1H, J = 5.2 Hz, H_5), 8.07 (d, 1H, J = 5.2 Hz, H_6). Anal. Calcd for $C_7H_7N_3$: C, 63.14 H, 5.30; N, 31.56. Found: C, 63.13; H, 5.32; N, 31.56.

2-Amino-3-cyano-4-methyl-5-iodopyridine (17). A solution of *N*-iodosuccinimide (15 g, 66 mmol) in dry DMF (125 mL) was added dropwise to a solution of **16** (8.3 g, 63 mmol) in DMF (125 mL) at 0 °C. When addition was complete, the solution was allowed to come to room temperature and stirred overnight. The volume was reduced in half by rotary evaporation (vacuum pump), the dark-brown solution poured slowly into 3 M NaOH (1 L), and the precipitate collected. Silica gel flash chromatography (9:1 CH_2Cl_2−EtOAc) furnished a beige solid (5.6 g, 34%): mp 203−204 °C (*i*-PrOH); MS calcd *m/z* 259.05, found 259.80 (M + 1); IR (KBr) ν 3400, 3320, 3320, 2200 (C≡N), 1640, 1570, 1470, 1450, 1360, 1330, 1260, 830, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H, CH_3), 5.20 (br s, 2H, NH_2), 8.42 (s, 1H, H_6). Anal. Calcd for $C_7H_6IN_2$: C, 32.46; H, 2.33 N, 16.22. Found: C, 32.34; 2.43; N, 15.99.

2-Amino-3-cyano-4-methyl-5-bromopyridine (18). A solution of NBS (1.8 g, 10 mmol) in dry DMF (10 mL) was added dropwise to a solution of **16** (1.3 g, 9.8 mmol) in dry DMF (10 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred overnight, and poured slowly into 3 M NaOH (150 mL). After dilution with H_2O (150 mL), the solid was collected and dried to obtain a product (1.9 g, 92%) that was pure enough to be used directly in the next step. A small sample recrystallized from cyclohexane gave fine beige needles: mp 198−200 °C; MS calcd *m/z* 212.05 (based on natural distribution of Br isotopes), found 211.85, 213.85 (M + 1); IR (KBr) ν 3520, 3360, 3200, 2220 (C≡N), 1640, 1570, 1480, 1390 1250, 840, 770 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3H, CH_3), 6.99 (br s, 2H, NH_2, exchangeable with D_2O), 8.20 (s, 1H, H_6); ^{1}H NMR ($CDCl_3$) δ 2.52, (s, 3H, CH_3), 5.19 (br s, 2H, NH_2), 8.24 (s, 1H, H_6). Anal. Calcd for $C_7H_6BrN_2$: C, 39.65; H, 2.85; N, 19.82; Br, 37.68. Found: C, 39.56; H, 2.65; N, 19.58; Br, 37.57.

2-Amino-3-cyano-4-methyl-5-(2,5-dimethoxybenzyl)pyridine (19). Method A. A mixture of the bromide **18** (1.6 g, 7.5 mmol) and $PdCl_2$(dppf)·CH_2Cl_2 (308 mg, 0.75 mmol) in dry THF (10 mL) was stirred at room temperature for 5 min in a thoroughly dried three-necked flask under argon. 2,5-Dimethoxybenzylzinc chloride (30 mL of 0.5 M solution in THF, 2 molar equiv) was then added via a transfer needle, the mixture refluxed for 4 h, and the solvent evaporated under reduced pressure. The black solid was applied to the top of a flash silica gel column, which was eluted with CH_2Cl_2 and then 8:1 CH_2Cl_2−EtOAc to obtain a reddish solid (1.3 g, 59%). Recrystallization from *i*-PrOH gave colorless needles: mp 173−174 °C; MS calcd *m/z* 283.33, found 283.96 (M + 1); IR (KBr) ν 3480, 3310, 3160, 2980, 2220 (C≡N), 1640, 1480, 1250, 1220, 1210, 1050, 1050, 1020, 800, 710 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 3.69 (s, 5H, OCH_3 and CH_2), 6.44 (d, 1H, J = 2.8 Hz, $H_{6'}$), 6.55 (br s, 2H, NH_2), 6.69 (dd, 1H, J = 2.8 Hz, J = 8.8 Hz, $H_{4'}$), 6.85 (d, 1H, J = 9.0 Hz, $H_{3'}$), 7.85 (s, 1H, pyridine H_6); ^{13}C NMR (DMSO-d_6) δ 17.3 (CH_3), 29.2 (CH_2), 55.2 (CH_3), 55.7 (CH_3), 90.4 (C), 111.2 (CH), 111.5 (CH), 115.8 (CH), 116.5 (C), 122.3 (C), 28.7 (C), 150.6 (C), 151.0 (C), 152.9 (C), 153.0 (C), 159.3 (CH). Anal. Calcd for $C_{16}H_{17}N_3O_2$·$0.55H_2O$: C, 65.54; H, 6.22; N, 14.33. Found: C, 65.74; H, 6.22; N, 14.04.

Method B. The same procedure using iodide **17** (1.3 g, 5 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (410 mg, 0.5 mmol) in dry THF (20 mL), and 2,5-dimethoxybenzylzinc chloride (50 mL of 0.05 M solution in THF, 5 molar equiv) afforded **21** (510 mg, 36%). Microanalytical and spectroscopic data indicated that this product and the one obtained via method A were the same.

2-Bromo-3-cyano-4-methyl-5-(2,5-dimethoxybenzyl)pyridine (20). A solution of $SbBr_3$ (300 mg, 0.83 mmol) in CH_2Br_2 (2 mL) was added dropwise to a stirred solution of **19** (150 mg, 0.53 mmol) in CH_2Br_2 (10 mL) at 0 °C under dry argon. When addition was complete, the brown solution was treated dropwise with freshly distilled *t*-BuONO (1 mL). The reaction mixture was kept at 4−10 °C (internal) for 6 h, then brought back down to 4 °C, and poured into ice-cold concentrated $NaHCO_3$ solution. The product was extracted three times into CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and evaporated to dryness. Column chromatography on flash-grade silica gel using CH_2Cl_2 as the eluent gave a pale-orange solid (80 mg, 43%). Recrystallization from cyclohexane gave an off-white solid: mp 113−115 °C (lit.[14] mp 108−110 °C); MS calcd *m/z* 347.21 (based on natural distribution of Br isotopes), found 346.94, 348.93 (M + 1); IR (KBr) ν 2980, 2850, 2400, 1590, 1560, 1510, 1430, 1230, 1050, 1020, 880, 800, 720 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.46 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.91 (s, 2H, CH_2), 6.61 (d, 1H, J = 2.8 Hz,

(28) Cobas, J. C.; Sardina, F. J. *Concept. Magn. Reson.* **2003**, *19A*, 80.

(29) The once-distilled product was pale-greenish in color. The twice-distilled product was initially colorless, became straw-colored on standing overnight at room temperature, and turned orange after being kept at 4 °C under argon for a week. Freshly distilled product should be used.

$H_{6'}$), 6.76 (dd, 1H, J = 2.8 Hz, 8.8 Hz, $H_{4'}$), 6.90 (d, 1H, J = 8.8 Hz, $H_{3'}$), 8.25 (s, 1H, pyridine H_6). Anal. Calcd for $C_{16}H_{15}BrN_2O_2$: C, 55.35; H, 4.35; N, 8.07. Found: C, 55.14; H, 4.15; N, 7.95.

2,4-Diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido-[2,3-*d*]pyrimidine (PTX, 1). Sodium metal (46 mg, 2 mmol) was dissolved in absolute MeOH (2 mL), the solution was chilled, guanidine hydrochloride (191 mg, 2 mmol) was added, the mixture was stirred for 15 min, the fine white precipitate of NaCl was suction filtered, and the filtrate was evaporated to dryness under reduced pressure. To the residue were then added **20** (138 mg, 0.4 mmol) and dry pyridine (1.8 mL), and the mixture was refluxed for 3 h. After being cooled to room temperature, the solution was diluted with H_2O (30 mL) and cooled to 0 °C. The beige precipitate was collected by suction filtration, and another crop was recovered from the filtrate by extracting it several times with CH_2Cl_2 and evaporating the pooled extracts to dryness. Column chromatography (flash-grade silica gel, 95:5 $CHCl_3$−MeOH) afforded **1** as a white solid (50 mg, 38%): mp 273−274 °C (lit.[1a,b] mp 252−254 °C, lit.[15,30] mp >310 °C); MS calcd *m/z* 326.37, found 326.04 (M + 1); IR (KBr) ν 3480, 3340, 3120, 1650, 1590, 1550, 1500, 1500, 1460, 1230, 1050, 830 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.52 (s, H, CH_3), 3.59 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.87 (s, 2H, CH_2), 6.15 (br s, 2H, NH_2, exchangeable with D_2O), 6.39 (d, 1H, J = 3.0 Hz, $H_{6'}$), 6.70 (dd, 1H, J = 3.0 Hz, 8.8 Hz, $H_{4'}$), 6.87 (d, 1H, J = 3.0 Hz, 8.8 Hz, $H_{3'}$, with an underlying br s, 2H, NH_2, exchangeable with D_2O), 8.32 (s, 1H, pyridine H_6); ^{13}C NMR (DMSO-d_6) δ 17.9 (CH_3), 30.3 (CH_2), 55.2 (CH_3), 55.8 (CH_3), 105.4 (C), 111.0 (CH), 111.4 (CH), 115.9 (CH, 126.5 (C), 129.2 (C), 151.0 (C), 153.0 (C), 156.0 (CH), 161.3 (C), 161.6 (C), 164.0 (C). Anal. Calcd for $C_{17}H_{19}N_5O_2 \cdot H_2O$: C, 59.46; H, 6.16; N, 20.40. Found: C, 59.66; H, 6.04; N, 20.09.

(30) The observed melting or decomposition temperature of condensed diaminopyrimidine derivatives can vary considerably depending on the drying method, particle size, type of melting point apparatus, and rate at which the sample is heated. The lower melting point of our sample of **1** relative to that reported by Troschütz and co-workers[15] may be due to a small difference in the method of determination or to the fact that our material, unlike theirs, was solvated with a molecule of H_2O.

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Supporting Information Available: ^{13}C NMR spectra for piritrexim (**1**) and the synthetic intermediates **15**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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