SYNTHESIS OF PROTECTED 5-FORMYLPYRIDO[2,3-*d*] PYRIMIDINE *VIA* A 2,3,4-TRISUBSTITUTED PYRIDINE USING AN ORTHO-LITHIATION STRATEGY; APPLICATION TO THE SYNTHESIS OF A FOLATE DERIVATIVE

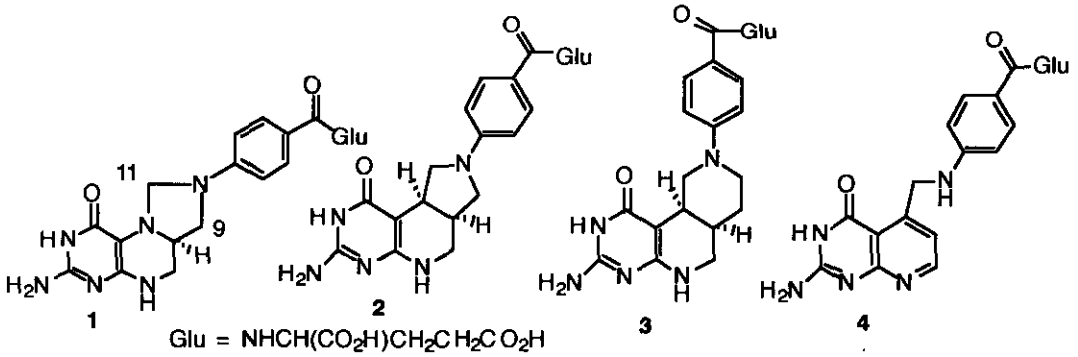
Samuel E. Watson* and Anatoly Markovich
Department of Chemistry,
Long Island University,
One University Plaza, Brooklyn, NY 11201, USA

Abstract - A convenient route for the preparation of a protected 5-formylpyrido[2,3-*d*]pyrimidine from 2,3,4-trisubstituted pyridines has been developed. The readily available diethylacetal of pyridine 4-carboxaldehyde is chlorinated at the 2-position and then treated with LDA and methyl chloroformate to give a 2,3,4-trisubstituted pyridine (**1 2**). Treatment of **1 2** with guanidine hydrochloride gives the pyrido[2,3-*d*]pyrimidine in good yield. A 4-aminobenzoylglutamic acid side chain is installed by means of a reductive amination step to provide a 5-substituted derivative that is, after deprotection, a conformationally unrestricted analog of 5,10-methylenetetrahydrofolate (**1**), the natural co-factor for thymidylate synthase, an important chemotherapeutic target in the treatment of cancer.

In studies aimed at the synthesis of novel folate derivatives as inhibitors of the enzyme thymidylate synthase as potential anti-tumor agents,[1] we have developed a practical, high yielding synthesis of the versatile intermediate, 5-formylpyrido[2,3-*d*]pyrimidine,[2] protected as the diethoxy acetal derivative. Our new methodology proceeds through a 2-chloro-3-carboethoxypyridine derivative, synthesized by an ortho-lithiation strategy that is similar to the work of Dormoy *et al.*[3] This methodology provides a succinct, high yielding route to synthetically useful 2,3,4-trisubstituted pyridines.

The ortho-lithiation strategy has been utilized to produce **4**, an analog of the natural thymidylate synthase co-

Figure 1



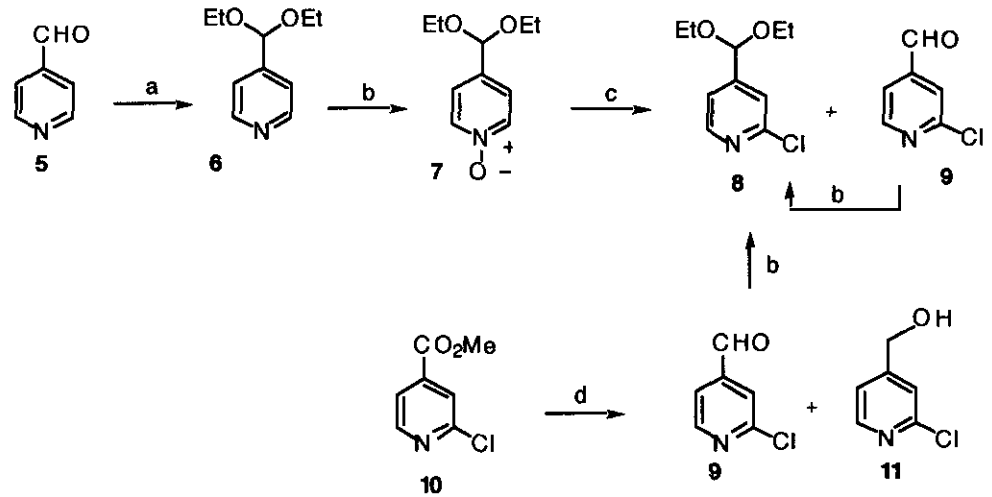
1 **2** **3** **4**

factor 5,10-methylenetetrahydrofolate (**1**) (Figure 1) in which the carbon at the 9-position has been removed and the tetrahydropyridine ring has been oxidized to the fully aromatic derivative. Inhibition of the enzyme thymidylate synthase has long been considered an effective strategy for the design of anti-tumor chemotherapeutic agents.[4] Tricyclic derivatives of 5,10-methylenetetrahydrofolate such as **2** and **3**, synthesized by Gangjee *et al.*,[5] have shown a disappointing lack of biological activity. Indeed, modeling studies of **2** and **3** have shown that the benzoylglutamic acid moiety, known to be a critical element for

recognition by the enzyme, lies in a considerably different orientation from that of the corresponding moiety in the natural co-factor. This could be a critical factor in the relatively poor recognition of **2** and **3** by the enzyme. It is hoped that **4**, an analog of 5,10-methylenetetrahydrofolate in which the side chain is unconstrained and the tetrahydropyridine ring is oxidized to the fully aromatic system will be able to sample a broader range of conformational space and as such will prove to be a more potent inhibitor of the enzyme. Indeed, molecular modeling studies indicate that **4** in which the pyridine ring is fully aromatized provides a better overlap with the natural co-factor than **2** or **3**.

Our synthetic studies began with commercially available pyridine-4-carboxaldehyde (**5**) (Scheme 1). We have developed two improved syntheses of the known 2-chloro-4-diethoxymethyl derivative (**8**).[6] Treatment of **5** with ethanolic toluene (1:1 mixture) in the presence of a catalytic amount of *p*-toluenesulfonic acid with azeotropic removal of water followed by treatment of the crude material with *m*-chloroperoxybenzoic acid in methylene chloride and chromatography over silica gel gave the diacetal *N*-oxide (**7**) in good yield (83% for the two steps). When **7** was boiled in phosphorus oxychloride[7] for several hours, the 2-chloro derivative (**8**) was obtained along with a varying amount of the aldehyde (**9**). Stirring the mixture of **8** and **9** in ethanolic toluene (1:1) in the presence of *p*-toluenesulfonic acid followed by chromatography over silica gel gave 2-chloro-4-diethoxymethylpyridine (**8**) in good yield.

Scheme 1



(a) cat. PTSA, EtOH/toluene (1:1), reflux, 2 d (b) *m*-CPBA, CH_2Cl_2, 4 °C, 0.5 h, rt for 2 h, 83% for two steps (c) $POCl_3$, 6 h, 66 % (d) LAH, THF, -78 °C, 2 h, 62 % for **9** and 21 % for **11**.

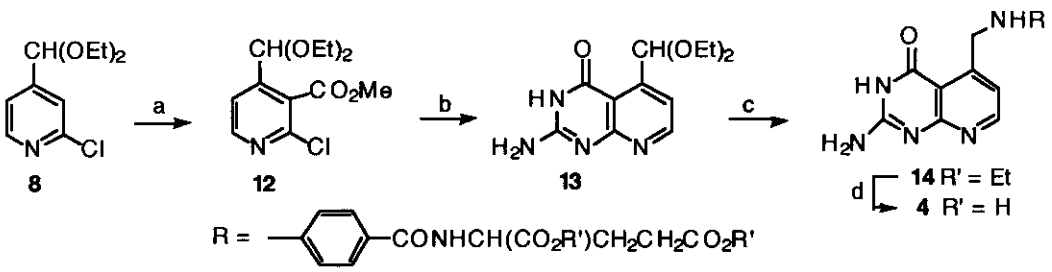
Alternatively, it was found that methyl 2-chloroisonicotinate (**10**)[8] could be reduced to the aldehyde (**9**) by treatment with lithium aluminum hydride at low temperature. About 20% of the over-reduced product (**11**) was also produced; this was most conveniently removed by chromatography after the acetalization step. This latter method was found to be more convenient for the large-scale production of **8**.

Treatment of **8** with 2.5 equivalents of lithium diisopropylamine at low temperature followed by the addition of 1.5 equivalents of methyl chloroformate proceeded to give **12** in 62% yields along with 20 - 25 %

recovered starting material on multi-gram scales after chromatography over silica gel. It was found that it was imperative to maintain the reaction for the full 2.5 hours after addition of the base and before addition of the electrophile so as to ensure complete formation of the anion.

Formation of the pyrimidine ring from the 2,3,4-trisubstituted pyridine (**12**) required considerable experimentation. Finally it was found that treatment of **12** with guanidine hydrochloride in refluxing ethanolic sodium ethoxide under forcing conditions [9] (5 days, sealed tube, 180 °C) gave 5-diethoxymethylpyrido[2,3-*d*]pyrimidine (**13**) in moderate but synthetically useful yields (55 - 60%) after work up and chromatography. It was found that hydrolysis of the acetal followed by reductive amination to produce **14** could be accomplished at the same time in one pot by stirring **13** with diethyl 4-aminobenzoyl-L-glutamate[10] in methanol at pH 4 to 5 in the presence of sodium cynanoborohydride. Saponification of the diethyl ester protecting groups produced the conformationally unrestricted folate derivative (**4**) without incident.

Scheme 2



(a) 2.5 equiv. LDA, THF, 2.5 h, -78 °C; then 1.5 equiv. $ClCO_2Me$, -78°C to rt, 3 h, 62 %. (b) guanidine hydrochloride, excess NaOEt, EtOH, 180 °C, 5 d, 56 %. (c) diethyl 4-aminobenzoyl-glutamate, $NaCNBH_3$, MeOH, pH 4-5, 42%. (d)1N NaOH, rt, 1 d, 65 %.

Overall this represents a succinct preparation of the versatile 5-formylpyrido[2,3-*d*]pyrimidine intermediate and represents a practical synthesis of the relatively inaccessible 2,3,4-trisubstituted pyridines. The reactions proceed in moderate yields but the overall synthesis can be performed on a multi-gram scale.

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EXPERIMENTAL

4-Diethoxymethylpyridine *N*-oxide (7). Pyridine 4-carboxaldehyde (5.0 g, 46.68 mmol) and a catalytic amount of PTSA (100 mg) in EtOH (50 mL) and toluene (50 mL) were heated at reflux with azeotropic removal of H_2O (Dean-Stark trap). The Dean-Stark trap was periodically emptied and additional EtOH and toluene were added to keep the reaction volume constant. After 48 h the reaction mixture was cooled and the solvents were removed under reduced pressure to give crude 4-diethoxymethylpyridine (**6**)

(8.42 g) as a pale oil suitable for use in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (m, overlapping triplets, 6H), 3.44 - 3.55 (m, overlapping quartets, 4H), 5.42 (s, 1H), 7.31 (d, J = 5.4 Hz, 2H), 8.52 (d, J = 5.4 Hz, 2H).

Crude 4-diethoxymethylpyridine (**6**) (1.0 g) was dissolved in dry CH_2Cl_2 (25 mL), cooled to 4 °C and *m*-CPBA (1.05 g, 6.08 mmol, 80-85% with benzoic acid) was added in portions. The solution was maintained at 4 °C for 30 min, warmed to rt and stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with 5% Na_2CO_3 (3 x 25 mL), dried (Na_2SO_4) and condensed to give a colorless oil that TLC indicated still contained some benzoic acid. Purification over silica gel (2.5% MeOH in CH_2Cl_2) gave **7** (0.86 g, 83% for two steps) as a colorless oil that slowly solidified on standing, mp 42 - 44 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 - 1.21 (m, overlapping triplets, 6H), 3.48 - 3.55 (m, overlapping quartets, 4H), 5.24 (s, 1H), 7.37 (d, J = 5.3 Hz, 2H), 8.19 (d, J = 5.3 Hz, 2H). MS m/z (relative intensity) 198 (21%), 197 (77%), 156 (13%), 153 (45%), 152 (96%), 136 (69%), 125 (41%), 124 100%). HRMS m/z calcd for $C_{10}H_{15}NO_3$ 197.1052, found 197.1037. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.74; H, 7.62; N, 7.19.

2-Chloro-4-diethoxymethylpyridine (8). 4-Diethoxymethylpyridine *N*-oxide (**7**) (5.0 g, 25.35 mmol) was dissolved in $POCl_3$ (30 mL) and heated at reflux for 6 h. The reaction mixture gradually darkened. The excess $POCl_3$ was removed under reduced pressure and the dark viscous syrup was dissolved while still hot in EtOAc (100 mL). The organic layer was washed with 1N NaOH (5 x 75 mL) until the aqueous layers remained basic and then with H_2O (50 mL) and brine (50 mL). It was dried ($MgSO_4$) and condensed to a dark oil that was immediately taken up in EtOH/toluene (1:1 mixture, 50 mL) containing a catalytic amount of PTSA (100 mg) and heated at reflux using a Dean-Stark trap as described above for the preparation of **6**. After 6 h the solvents were removed under reduced pressure and the residue was taken up in CH_2Cl_2 (75 mL). The organic layer was washed with H_2O and brine, dried (Na_2SO_4) and condensed to give a brown oil which after purification on silica gel (20% EtOAc in hexane) gave **8** (3.61 g, 66%) as a pale oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 - 1.18 (m, overlapping triplets, 6H), 3.44 - 3.53 (M, overlapping quartets, 4H), 5.39 (s, 1H), 7.23 (d, J = 5.1 Hz, 1H), 7.36 (s, 1H), 8.28 (d, J = 5.1 Hz, 1H). MS m/z (relative intensity) 218 (2%), 216 (6%), 187 (3%), 185 (7%), 174 (4%), 173 (40%), 172 (82%), 170 (96%), 158 (17%), 157 (17%), 144 (83%), 143 (48%), 142 (100%). HRMS m/z calcd for $C_{10}H_{15}NO_2Cl$ (MH^+) 216.0791, found: 216.0789. Anal. Calcd for $C_{10}H_{15}NO_2Cl$: C, 55.43; H, 6.98; N, 6.46. Found: C, 55.52; H, 7.02; N, 6.59.

2-Chloro-4-formylpyridine (9). Methyl 2-chloroisonicotinate (**10**)[8] (3.5 g, 20.41 mmol) was dissolved in dry THF (75 mL) with stirring under an N_2 atmosphere at -78 °C and LAH (22.4 mL, 1.0 M solution in THF) was added slowly dropwise over 45 min taking care to maintain the reaction temperature below -70 °C. The reaction mixture was warmed slowly to rt over 1 h, cooled to 4 °C and quenched with a mixture of AcOH (10 mL) and H_2O (10 mL) in THF (20 mL). The cooling bath was removed and the reaction mixture was stirred at rt until all of the solid aluminum salts had dissolved (1.5 h). The reaction

mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (2 x 75 mL). The organic layers were combined, washed with 5% Na_2CO_3 (2 x 50 mL), H_2O (50 mL), brine (30 mL), dried (Na_2SO_4) and condensed to give a pale oil that after chromatography over silica gel (20% EtOAc in hexane) gave **9** (1.79 g, 62%) as a colorless oil as well as **11** (0.62 g, 21%) as a colorless oil. For **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.71 (d, J = 4.8 Hz, 1H), 8.58 (d, J = 4.8 Hz, 1H), 9.98 (s, 1H). Anal. Calcd for C_6H_4NOCl: C, 50.91; H, 2.85; N, 9.89. Found: C, 51.05; H, 2.77; N, 9.96. For **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (br, 1H), 4.72 (m, 2H), 7.18 (d, J = 6.7 Hz, 1H), 7.34 (s, 1H), 8.18 (d, J = 6.7 Hz, 1H). Anal. Calcd for C_6H_6NOCl: C, 50.20; H, 4.21; N, 9.76. Found: C, 50.33; H, 4.13; N, 9.61.

2-Chloro-4-diethoxymethylpyridine (8). Crude 2-chloro-4-formylpyridine (**9**) (3.45 g, containing approximately 20% of **11** by NMR) was dissolved in absolute ethanol (25 mL) and toluene (25 mL) as described above for the preparation of **6**. A catalytic amount of PTSA (100 mg) was added and the mixture was heated at reflux with azeotropic removal of H_2O (Dean-Stark trap). The Dean-Stark trap was periodically emptied and additional EtOH and toluene added to keep the reaction volume constant. After 36 h the reaction mixture was cooled and the solvents were removed under reduced pressure to give a pale oil that after chromatography over silica gel (20% EtOAc in hexane) gave **8** (2.57 g, 58% for two steps from methyl 2-chloroisonicotinate (**10**)) and **11** (0.60 g, 20% for two steps from **10**) that by ^{1}H NMR was identical to the material prepared by the *N*-oxide route described above.

3-Carbomethoxy-2-chloro-4-diethoxymethylpyridine (12). n-BuLi (19.3 mL, 1.6 M solution in hexane) was added slowly with stirring under an N_2 atmosphere at -78 °C to a solution of freshly distilled diisopropylamine (4.33 mL, 30.89 mmol) in dry THF (20 mL). The mixture was stirred 15 min and 2-chloro-4-diethoxymethylpyrimidine (**8**) (2.5 g, 11.59 mmol) in dry THF (15 mL) was added slowly while maintaining the reaction temperature below -65 °C. The reaction mixture was stirred 2.5 h at -78 °C and quenched with the addition of methyl chloroformate (4.67 g, 49.4 mmol) in dry THF (10 mL). The reaction mixture was allowed to warm slowly to rt over 3 h, diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (2 x 60 mL). The organic layers were combined, dried (Na_2SO_4) and condensed to give an amber oil which after purification over silica gel (7% EtOAc in hexane) gave **12** (1.97 g, 62%) as a pale oil and recovered **8** (0.80 g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (m, overlapping triplets, 6H), 3.52 (m, overlapping quartets, 4H), 3.94 (s, 3H), 5.64 (s, 1H), 7.49 (d, J = 5.1 Hz, 1H), 8.41 (d, J = 5.1 Hz, 1H). MS m/z (relative intensity), 214 (3%), 212 (3%), 186 (2%), 184 (3%), 172 (22%), 171 (16%), 170 (67%), 144 (33%), 142 (100%). HRMS m/z calcd. for $C_{12}H_{16}NO_4Cl$ 273.0768, found: 273.0774. Anal. Calcd for $C_{12}H_{16}NO_4Cl$: C, 52.66; H, 5.89; N, 5.12. Found: C, 52.53; H, 5.73; N, 5.01.

5-Diethoxymethyl-5-deazapterin (13). Na (0.157 g, 6.81 mmol) was dissolved in dry EtOH (6 mL) with stirring under an N_2 atmosphere and guanidine hydrochloride (0.542 g, 5.68 mmol) was added. After 30 min 3-carbomethoxy-2-chloro-4-diethoxymethylpyridine (**12**) (0.62 g, 2.27 mmol) in dry EtOH (2 mL) was added and the mixture was heated at 180 °C for 5 d in a sealed tube. Removal of the volatiles under

reduced pressure, trituration with water, drying under high vacuum and chromatography over silica gel (5% MeOH - CH_2Cl_2) gave **13** (0.336 g, 56%) as a pale yellow powder: mp > 241 °C (decomp). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 - 1.39 (m, overlapping triplets, 6H), 4.20 - 4.38 (m, overlapping quartets, 4H), 5.52 (s, 1H), 6.02 (br, 1H), 7.04 (d, J = 5.0 Hz, 1H), 8.21 (d, J = 5.0 Hz, 1H), 8.52 (br, 2H). MS m/z (relative intensity) 264 (4%), 250 (5%), 222 (30%), 220 (13%), 241 (18%), 212 (22%), 208 (30%), 178 (35%), 168 (100%). HRMS m/z calcd for $C_{12}H_{16}N_4O_3$ 264.1224, found: 264.1217. Anal. Calcd for $C_{12}H_{16}N_4O_3$: C, 54.54; H, 6.10; N, 5.30. Found: C, 54.40; H, 6.01; N, 5.28.

Diethyl 4-(2-amino-4-hydroxypyrido[2,3-*d*]pyrimidin-5-yl)methylamino-benzoyl-L-glutamate (14). 5-Diethoxymethyl-5-deazapterin (**13**) (0.30 g, 1.096 mmol) was dissolved in EtOH (15 mL) and 1N HCl (2.5 mL) and stirred at rt for 24 h. Diethyl *p*-aminobenzoyl-L-glutamate[10] (0.55 g, 1.71 mmol) was added all at once followed by addition of $NaCNBH_3$ (87 mg, 1.36 mmol) slowly in portions. Stirring was continued at rt while the pH was maintained at 4 - 5 by periodic addition of 1N HCl. After 2 d the solution was neutralized with 1N NaOH, diluted with H_2O (25 mL), cooled to 4 °C and filtered to give a yellow solid. After air drying, chromatography of this material over silica gel (10% MeOH- CH_2Cl_2) gave **14** (0.237 g, 42%) as a pale yellow solid: mp 168 - 174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 - 1.44 (m, overlapping triplets, 6H), 2.12 - 2.62 (m, 4H), 3.50 (s, 2H), 4.13 (q, J = 6.3 Hz, 2H), 4.37 (q, J = 6.4 Hz, 2H), 4.86 (m, 1H), 6.42 (br, 1H), 6.73 (d, J = 7.3 Hz, 2H), 6.80 (d, J = 6.8 Hz, 1H), 7.45 (br, 2H), 7.71 (d, J = 7.3 Hz, 2H), 8.22 (d, J = 6.8 Hz, 1H), 8.88 (br, 1H). MS m/z (relative intensity) 299 (4%), 272 (5%), 247 (4%), 218 (8%), 208 (12%), 207 (60%), 198 (14%). FABMS 496 (8%), 495 (22%(, 473 (13%), 329 (110%), 307 (94%), 289 (58%). Anal. Calcd for $C_{24}H_{28}N_6O_6$: C, 58.04; H, 5.69; N, 16.93. Found: C, 57.92; H, 5.42; N, 16.27.

4-{1-[2-Amino-4-hydroxypyrido[2,3-*d*]pyrimidin-5-yl]methylamino}benzoyl-L-glutamic acid (4). Dimethyl 4-(2-amino-4-hydroxypyridino[2,3-*d*]pyrimidin-5-yl)-methylaminobenzoyl-L-glutamate (**14**) (0.152 g, 0.309 mmol) was suspended in 1N NaOH (2.5 mL) and stirred at rt for 24 h. The reaction mixture was carefully neutralized with conc. HCl. The reaction mixture was concentrated (to 1 mL) under reduced pressure and the residue was applied to a short column of Dowex 50-X4 ion exchange resin. Elution with conc. NH_4OH (15 mL) and treatment as before gave **4** (0.088 g, 65%) as a pale tan solid: mp > 293 °C (decomp); $[\alpha]^{23}_{589}$ +16 ±2°(*c* 0.5, 0.1 N NaOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13 - 2.61 (m, 4H), 3.64 (s, 2H), 4.91 (m, 1H), 6.58 (br, 1H), 6.92 (d, J = 7.4 Hz, 2H), 7.17 (d, J = 7.2 Hz, 1H), 7.56 (br, 2H), 7.83 (d, J = 7.4 Hz, 2H), 8.41 (d, J = 6.7 Hz, 1H), 8.92 (br, 1H). MS m/z (relative intensity) 440 (2%), 311(3%), 306 (2%), 163 (13%), 162 (62%). HRMS m/z calcd for $C_{20}H_{20}N_6O_6$ 440.1795, found: 440.1811. Anal. Calcd for $C_{20}H_{20}N_6O_6$: C, 52.40; H, 4.84; N, 18.33. Found: C, 52.61; H, 4.89; N, 18.41.

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