HETEROCYCLES, Vol. 55, No. 9, pp. 1679 - 1688, Received, 21st, May, 2001

SYNTHESIS OF 5-SUBSTITUTED PYRIDO[2,3-*d*]PYRIMIDINES AS ANALOGUES OF THE ANTIFOLATES METHOTREXATE, DDATHF AND PEMETREXED (LY231514)

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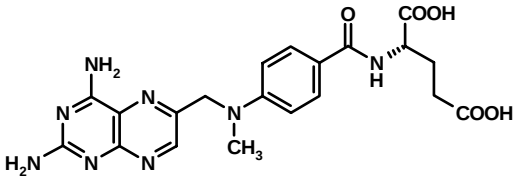
Abstract - The preparation of 5-substituted pyrido[2,3-*d*]pyrimidines **(18,19,21)** as analogues of the antifolates methotrexate **(1)**, DDATHF **(2)** and pemetrexed (LY231514) **(3)** is outlined, starting from methyl 4-(3-oxobutyl)benzoate **(4)**. Key steps involve high yielding *Knoevenagel* condensation of **4** with malononitrile **(5)**, treatment with dimethylformamide dimethyl acetal (DMF-DMA) **(7)**, cyclisation with hydrochloric acid and pyrimidine annulation with guanidine **(11)**. The resulting pyrido[2,3-*d*]pyrimidines **(13, 14)** are coupled with diethyl *L*-glutamate **(11)** and transformed to **18, 19** and **21**.

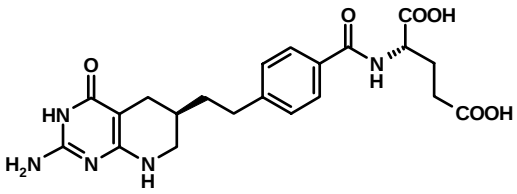
Antimetabolites are a widely used class of antineoplastic agents that interfere with enzymatic reactions in the synthesis of nucleic acids, purines, pyrimidines and their precursors.[1] Methotrexate (MTX) **(1)** has been long recognized as a clinical agent for the treatment of lymphocytic leukemia and choriocarcinoma.[2] It has served as a lead compound for structural modification since its introduction as an antitumor agent.[3] Numerous analogues of MTX **(1)** have been synthesized over a number of years with the aim of reducing the toxicity and improving the therapeutic activity against solid tumors.[4-9]

In 1985 *Taylor* and coworkers reported the synthesis of 5,10-dideazatetrahydrofolate (DDATHF) **(2)** as a new antileukemic agent.[10] It has been shown to be a potent antiproliferative folate antimetabolite with a mechanism of action other than dihydrofolate reductase (DHFR) inhibition: DDATHF **(2)** inhibits *de novo* purine biosynthesis, catalyzed by glycinamide ribonucleotide formyl transferase (GAR FTase), the first folate-dependent enzyme of this pathway.[11] Scientists at Lilly subsequently synthesized the pyrrolo-pyrimidine LY231514 **(3)** which represents a new generation of antifolates.[12] Recent sudies have revealed that **3** is a multitargeted antifolate inhibiting thymydilate synthase (TS), DHFR and murine GAR FTase as well as aminoimidazolecarboxamide ribonucleotide formyltransferase (AICAR FTase) and both domaines

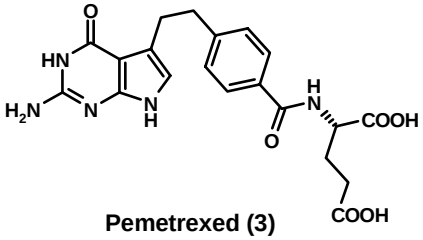
of C-1 tetrahydrofolate synthetase enzyme.[13]



Methotrexate (1)



DDATHF (2)



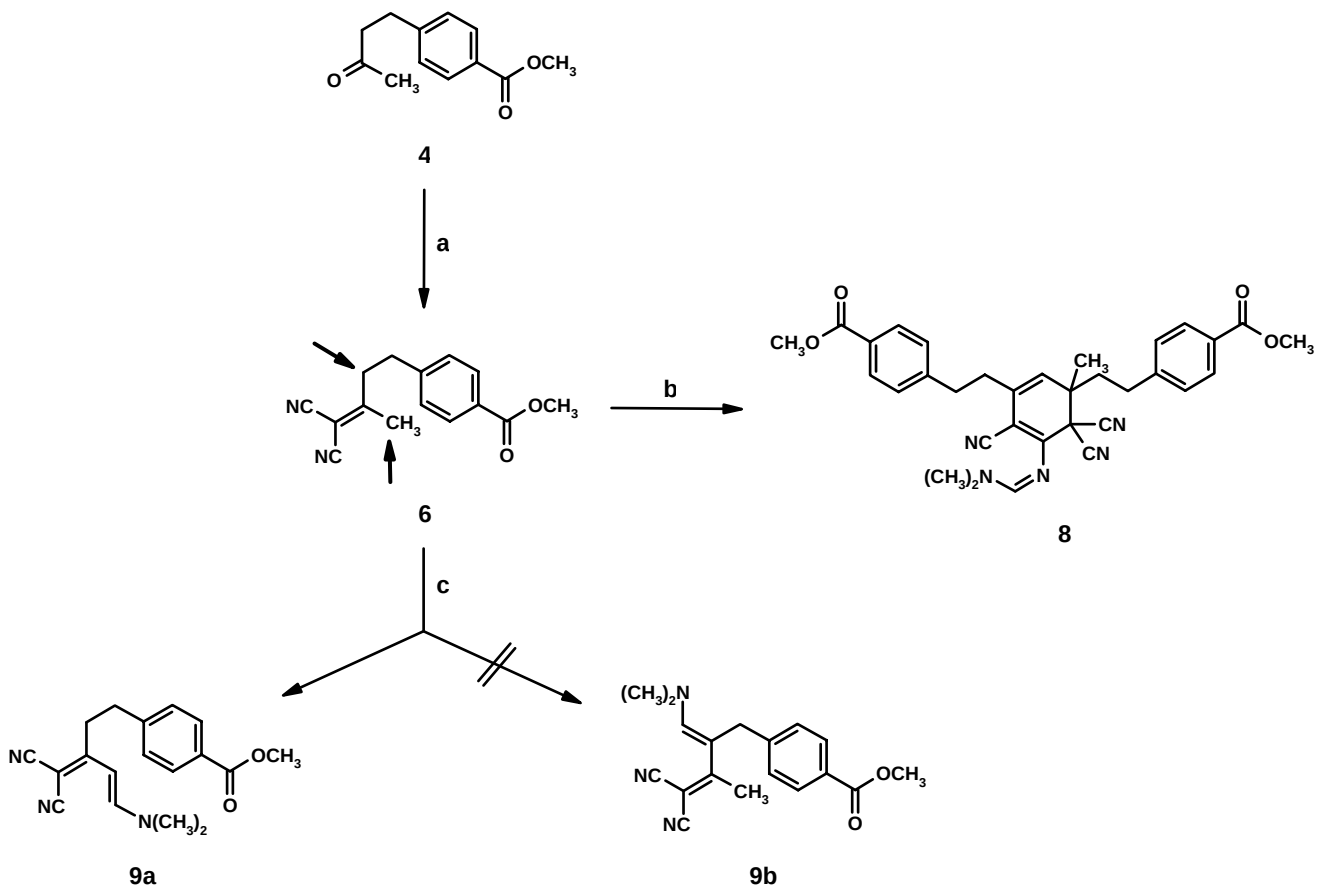
Pemetrexed (3)

CHEMISTRY

In the past many analogues of methotrexate possessing a 6-substituted pyrido[2,3-*d*]pyrimidine structure have been synthesized. But only a few antifolates bearing a substituent at the 5-position can be found in the literature.[14-18] Now we describe a versatile synthesis of 5-*phenethyl*-substituted 5-deazapteridines as potential inhibitors of DHFR, thymydilate synthase and GARFT following a strategy which has been used by *Kuyper et al.*[7] for the preparation of 5-phenyl-substituted pyrido[2,3-*d*]pyrimidines.

The synthesis of target compounds **(19-21)** was initiated by condensation of the known[19] ketone **(4)** with malononitrile **(5)** under *Knoevenagel* conditions.[20] The resulting C-H acidic alkylidenemalononitrile **(6)** was heated with DMF-DMA **(7)** in presence of catalytic amounts of glacial AcOH[21] yielding exclusively dimeric type formamidine **(8)**.[22] After examination of a variety of conditions, we found that equimolar amounts of DMF-DMA **(7)** and AcOH were useful to prevent generation of **8**. In case of dinitrile **(6)** regioselective formation of the enamine **(9a)** was observed as the methyl group seemed to be the preferred reaction site for dimethylaminomethenylation. The isomeric aldehyde equivalent **(9b)** has not been formed (Scheme 1).

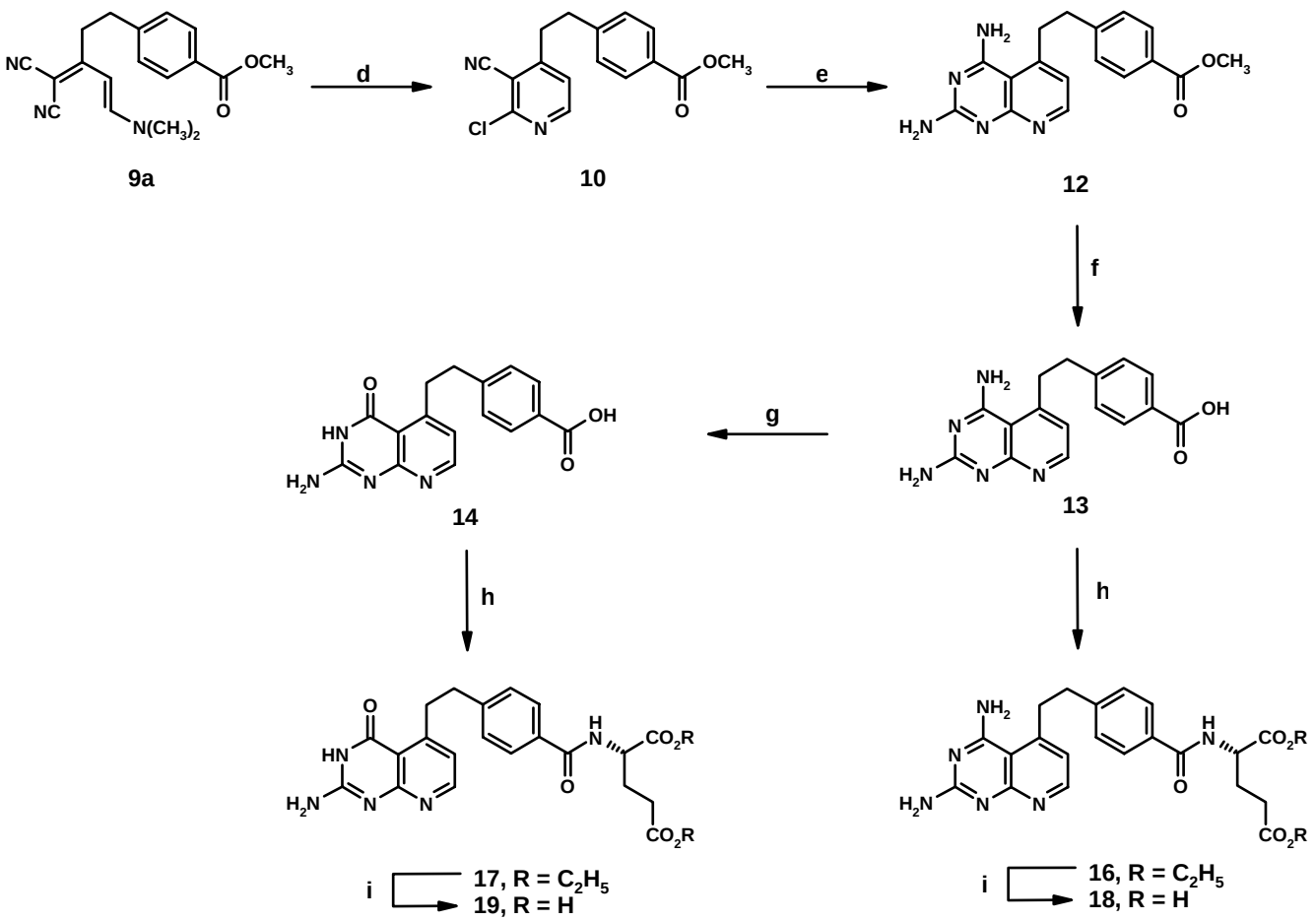
Scheme 1



a) malononitrile **(5)**, NH_4OAc/AcOH, toluene, reflux; b) DMF-DMA **(7)**, cat. amount of AcOH, reflux, 1 min;
c) DMF-DMA **(7)**/AcOH (1:1), reflux, 1 min

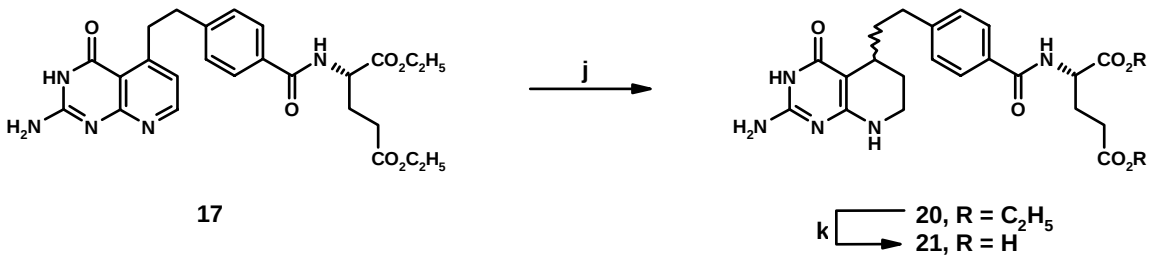
Treatment of ylidenenitrile **(9a)** with hydrochloric acid in glacial AcOH[23] provided the 2-chloro-nicotinonitrile **(10)** in good yield. Pyrimidine annulation with guanidine **(11)** in dimethyl sulfone at 130 °C afforded methyl 4-[2-(2,4-diaminopyrido[2,3-*d*]pyrimidin-5-yl)ethyl]benzoate **(12)** which was saponified with aqueous sodium hydroxide[24] at room temperature. Subsequent refluxing of the intermediate **(13)** in 2N-NaOH[25] gave the corresponding 2-amino-4-oxopyrido[2,3-*d*]pyrimidine **(14)** which also was not isolated. Both intermediates **(13)** and (**14)** were coupled with diethyl *L*-glutamate **(15)** using 6-chloro-2,4-dimethoxy-1,3,5-triazine/*N*-methylmorpholine.[26] Final alkaline hydrolysis of the esters **(16)** and **(17)** followed by acidification with acetic acid yielded the glutamic acid derivatives **(18)** and **(19)**[15] (Scheme 2). The diethyl ester **(19)** could be readily converted to the tetrahydro derivative **(20)** by catalytic reduction in trifluoroacetic acid as solvent utilizing Pd/C as catalyst.[27] Mild hydrolysis of **20** with sodium hydroxide in THF-H_2O afforded isolometrexol **(21)** (Scheme 3).

Scheme 2



d) HCl_{gas}, AcOH, rt, 12 h; e) guanidine **(11)**, dimethyl sulfone, 130 °C, 10 min; f) 1. 1N-NaOH, MeOH, rt, 12 h 2. AcOH; g) 1. 1N-NaOH, reflux, 2 h 2. AcOH; h) 1. *N*-methylmorpholine, 6-chloro-2,4-dimethoxy-1,3,5-triazine, DMF, rt, 1 h 2. diethyl *L*-glutamate **(15)**, rt, 2 h; i) 1N-NaOH, THF, rt, 2 h 2. AcOH

Scheme 3



j) H_2, 5% Pd/C, TFA; k) 1N-NaOH, THF, rt, 2 h 2. AcOH

BIOLOGICAL EVALUATION

Compound **(18)** has been tested at the National Cancer Institute, Bethesda (USA) in an anticancer drug screen utilizing a panel of 60 human tumor cell lines.[28] The concentrations of **18** ranged from 10^{-4} M to 10^{-8} M and the concentration at which growth of each cell line was inhibited by 50% (GI_{50}), was determined. The average potency has been calculated and compared to Methotrexate (MTX) **(1)**.

The biological evaluation revealed that compound **(18)** was an effective inhibitor of cell growth (average $GI_{50} = 10^{-7.1}$ M), better than MTX (average $GI_{50} = 10^{-6.5}$ M). Compounds **(19)** and **(21)** will be tested soon and the results published independently.

EXPERIMENTAL SECTION

Methyl 4-[(4,4-Dicyano-3-methylbut-3-enyl)]benzoate (6). Malononitrile **(5)** (2.38 g, 36 mmol), glacial AcOH (1.1 mL) and NH_4OAc (700 mg) were added to a solution of **4** (6.19 mg, 30 mmol) in toluene (80 mL). The reaction mixture was heated under reflux for 2 h and then cooled and diluted with H_2O (100 mL). The layers were separated, the aqueous layer was extracted with toluene (2 x 100 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by recrystallization from EtOH to obtain 6.87 g (90 %) of **6** as colorless needles; mp 78 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.88-2.98 (m, 4H), 3.92 (s, 3H), 7.26-7.28 (m, 2H), 8.00-8.02 (m, 2H); EIMS, *m/z* (relative intensity) 254 (M^+, 2), 223 (5), 149 (100), 121 (19); Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 71.08; H, 5.85; N, 11.21.

***N,N*-Dimethyl-*N'*-{3,5-bis-[2-(4-methoxycarbonylphenyl)ethyl]-2,6,6-tricyano-5-methylcyclohexa-1,3-dienyl}formamidine (8).** DMF-DMA **(7)** (1.79 g, 15 mmol), **6** (2.54 g, 10 mmol) and glacial AcOH (60 mg, 1 mmol) were heated under reflux for 1 min, cooled and diluted with H_2O. The precipitated solid was filtered, washed with EtOH and chromatographed on silica gel eluting with 30% EtOAc/hexane. Fractions containing the product were combined and evaporated to give 3.16 g (56 %) of **8** as a yellow powder; mp 136 °C (*i*-PrOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 3H), 1.78-1.87 (m, 1H), 1.98-2.06 (m, 1H), 2.47-2.74 (m, 4H), 2.83-2.97 (m, 2H), 3.16 (s, 3H), 3.19 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.25 (s, 1H) 7.17-7.20 (m, 2H), 7.31-7.33 (m, 2H), 7.95-7.98 (m, 4H), 8.06 (s, 1H); EIMS, *m/z* (relative intensity) 563 (M^+, 4), 375 (15), 347 (11), 149 (100), 121 (60); Anal. Calcd for $C_{33}H_{33}N_5O_4$: C, 70.32; H, 5.90; N, 12.42. Found: C, 70.49; H, 6.27; N, 12.23.

Methyl 4-[4,4-Dicyano-3-(2-dimethylaminovinyl)but-3-enyl]benzoate (9a). DMF-DMA **(7)** (2.15 g, 18 mmol), glacial AcOH (1.08 g, 18 mmol) and **6** (3.05 g, 12 mmol) were heated under reflux for 1 min and then diluted with *i*-PrOH (20 mL). After cooling, a yellow precipitate was formed which was filtered and washed with *i*-PrOH. The residue was purified by recrystallization from *i*-PrOH to obtain 3.04 g (82 %) of **9a** as yellow needles; mp 138 °C (*i*-PrOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.81-2.85 (m, 2H), 2.91-2.96 (m, 2H), 2.92 (s, 3H), 3.05 (s, 3H), 3.91 (s, 3H), 5.54 (d, *J* = 13 Hz, 1H), 6.86 (d, *J* = 13 Hz, 1H), 7.27-7.29 (m, 2H), 7.96-7.98 (m, 2H); EIMS, *m/z* (relative intensity) 309 (M^+, 100), 278 (9), 205 (42), 149 (100), 121 (77), 71 (70); Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.83; H, 6.40; N, 13.70.

Methyl 4-[2-(2-Chloro-3-cyanopyrid-4-yl)ethyl]benzoate (10). Methyl 4-[4,4-dicyano-3-(2-dimethyl-aminoethenyl)but-3-enyl]benzoate **(9a)** (3.09 g, 10 mmol) was dissolved in acetic acid (100 mL). Through this solution was bubbled HCl gas at a rapid rate for 2 min. The solution was stirred at rt overnight and then poured onto ice (100 g). The solid which preciptated was collected by filtration, washed with water and recrystallized from EtOH to yield 2.83 g (94 %) of **10** as colourless needles; mp 94 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.04-3.08 (m, 2H), 3.17-3.21 (m, 2H), 3.91 (s, 3H), 7.08 (d, *J* = 5 Hz, 1H), 7.23-7.25 (m, 2H), 7.97-7.99 (m, 2H), 8.41 (d, *J* = 5 Hz, 1H); EIMS, *m/z* (relative intensity) 300 (M^+, 14), 149 (100), 121 (22), 89 (14); Anal. Calcd for $C_{16}H_{13}N_2O_2Cl$: C, 63.90; H, 4.36; N, 9.31. Found: C, 64.23; H, 4.66; N, 9.07.

Methyl 4-[2-(2,4-Diaminopyrido[2,3-*d*]pyrimidin-5-yl)ethyl]benzoate (12). Methyl 4-[2-(2-chloro-3-cyanopyrid-4-yl)ethyl]benzoate **(10)** (2.11 g, 7 mmol) was dissolved in dry DMSO (5 mL). Guanidine base **(11)** (2.07 g 35 mmol) was added and the solution stirred at 80 °C overnight. The reaction mixture was diluted dropwise with water until a crude product precipitated. The solid was filtered, washed with boiling water and chromatographed on silica gel eluting with 10% MeOH/$CHCl_3$. Fractions containing the product were combined and evaporated to give **12** (1.22 g 54 %) as a white powder; mp > 300 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.97-3.05 (m, 2H), 3.39-3.46 (m, 2H), 3.83 (s, 3H), 6.27 (s, 2H, exchangeable with D_2O), 6.70 (d, *J* = 5 Hz, 1H), 6.98 (s, 2H, exchangeable with D_2O), 7.37-7.39 (m, 2H), 7.86-7.88 (m, 2H), 8.45 (d, *J* = 5 Hz, 1H); EIMS, *m/z* (relative intensity) 323 (M^+, 69), 174 (75), 161 (70), 149 (100), 121 (43); Anal. Calcd for $C_{17}H_{17}N_5O_2$: C, 63.15; H, 5.30; N, 21.66. Found: C, 63.32; H, 5.66; N, 21.58.

Diethyl *N*-{4-[2-(2,4-Diaminopyrido[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-*L*-glutamate (16). To a suspension of **12** (618 mg, 2 mmol) in MeOH (25 mL) was added 1N-NaOH (10 mL) and the mixture was

allowed to stir at rt for 12 h. It was then acidified with glacial AcOH and the solid was filtered, washed with water and dried. The crude product was suspended in DMF (30 mL) at 25 °C and *N*-methylmorpholine (0.26 mL, 2.38 mmol) was added followed by 6-chloro-2,4-dimethoxy-1,3,5-triazine (448 mg, 2.4 mmol). The resulting solution was stirred at 25 °C for 1 h. *N*-Methylmorpholine (0.33 mL, 3.04 mmol) was added to the solution followed by diethyl *L*-glutamate hydrochloride (509 mg, 2.4 mmol), and the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was taken up in CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was washed with 5% $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with 10% MeOH/$CHCl_3$. Fractions containing the product were combined and evaporated to give 663 mg (67 %) of **16** as a white solid; mp 195-200 °C (decomp); ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.16 (t, *J* = 7 Hz, 3H), 1.19 (t, *J* = 7 Hz, 3H), 1.94-2.15 (m, 2H), 2.41-2.43 (m, 2H), 2.98-3.02 (m, 2H), 3.41-3.45 (m, 2H), 4.05 (q, *J* = 7 Hz, 2H), 4.11 (q, *J* = 7 Hz, 2H), 4.39-4.45 (m, 1H), 6.45 (s, 2H, exchangeable with D_2O), 6.85 (d, *J* = 5 Hz, 1H), 7.14 (s, 2H, exchangeable with D_2O), 7.31-7.34 (m, 2H), 7.78-7.80 (m, 2H), 8.44 (d, *J* = 5 Hz, 1H), 8.64 (d, *J* = 8 Hz, 1H, exchange-able with D_2O); EIMS, *m/z* (relative intensity) 494 (M^+, 2), 421 (13), 292 (12), 189 (16), 174 (8), 84 (100); Anal. Calcd for $C_{25}H_{30}N_6O_5$: C, 60.72; H, 6.11; N, 16.99. Found: C, 61.03; H, 6.26; N, 16.77.

Diethyl *N*-{4-[2-(2-Amino-3,4-dihydro-4-oxopyrido[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-*L*-glutamate (17). A suspension of **12** (618 mg, 2 mmol) in 2 *N* NaOH (10 mL) was heated under reflux for 2 h. It was then acidified with glacial AcOH and the solid was filtered, washed with water and dried. The crude product was coupled with diethyl *L*-glutamate hydrochloride (509 mg, 2.4 mmol) as described above (silica gel chromatography, eluting with 10% MeOH/$CHCl_3$) to give 792 mg (80 %) of **17** as a white solid; mp 225-228 °C (decomp); ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.18 (t, *J* = 7 Hz, 3H), 1.19 (t, *J* = 7 Hz, 3H), 1.95-2.17 (m, 2H), 2.41-2.47 (m, 2H), 2.88-2.95 (m, 2H), 3.37-3.49 (m, 2H), 4.05 (q, *J* = 7 Hz, 2H), 4.11 (q, *J* = 7 Hz, 2H), 4.40-4.47 (m, 1H), 6.71 (s, 2H, exchangeable with D_2O), 6.86 (s, 1H), 7.35-7.38 (m, 2H), 7.79-7.82 (m, 2H), 8.41 (s, 1H), 8.65 (d, *J* = 8 Hz, 1H, exchangeable with D_2O), 11.11 (s, 1H, exchangeable with D_2O); FABMS, *m/z* 495 (M^+); Anal. Calcd for $C_{25}H_{29}N_5O_6 \times 1.5\ H_2O$: C, 57.46; H, 6.17; N, 13.40. Found: C, 57.52; H, 6.08; N, 13.40.

***N*-{4-[2-(2,4-Diaminopyrido[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-*L*-glutamic acid (18).** To a solution of **16** (494 mg, 1 mmol) in 6 mL of THF-H_2O (2:1) was added a 1 M aqueous solution of NaOH (3 mL). After beeing stirred for 2 h, the organic solvent was removed in vacuo, and to the remaining aqueous solution was added 1 mL of AcOH. The resulting colourless precipitate was ultrasonicated, filtered,

washed with water and dried to give 215 mg (49 %) of **18** as a white solid; mp 178-183 °C (decomp); ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.87-2.12 (m, 2H), 2.34 (t, J = 7 Hz, 2H), 2.99 (m, 2H), 3.44 (m, 2H), 4.34-4.40 (m, 1H), 6.71 (s, 2H, exchangeable with D_2O), 6.88 (d, J = 5 Hz, 1H), 7.28 (s, 2H, exchangeable with D_2O), 7.30-7.32 (m, 2H), 7.77-7.79 (m, 2H), 8.43 (s, 1H, exchangeable with D_2O), 8.45 (d, J = 5 Hz, 1H); FABMS, *m/z* 438 (M^+); Anal. Calcd for $C_{21}H_{22}N_6O_5\times0.5\ H_2O$: C, 56.37; H, 5.20; N, 18.78. Found: C, 56.72; H, 5.57; N, 18.92.

***N*-{4-[2-(2-Amino-3,4-dihydro-4-oxopyrido[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-*L*-glutamic acid (19).** Compound **(17)** (248 mg, 0.5 mmol) was saponified as described above to give 123 mg (56 %) of **19** as a white solid; mp 273-276 °C (decomp); ^{1}H NMR (250 MHz, CF_3COOD) δ 2.39-2.50 (m, 1H), 2.60-2.71 (m, 1H), 2.84-2.89 (m, 2H), 3.16-3.22 (m, 2H), 3.81-3.87 (m, 2H), 5.10-5.15 (m, 1H), 7.45-7.48 (m, 3H), 7.84-7.87 (m, 2H), 8.58 (d, J = 5 Hz, 1H); FABMS, *m/z* 439 (M^+); Anal. Calcd for $C_{21}H_{21}N_5O_6\times4\ H_2O$: C, 49.31; H, 5.71; N, 13.69. Found: C, 49.69; H, 5.77; N, 13.61.

Diethyl *N*-{4-[2-(2-Amino-3,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-*L*-glutamate (20). To a solution of **17** (495 mg, 1 mmol) in 20 mL of TFA was added 200 mg of 5% Pd/C. Hydrogenation was carried out in a parr apparatus at 50 psi at rt for 24 h. After filtration of the mixture through Celite, solvent was removed under reduced pressure. The residual solid was triturated with 30 mL of 2 N Na_2CO_3 solution and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with 10% MeOH/$CHCl_3$. Fractions containing the product were combined and evaporated to give 414 mg (83 %) of **20** as a white solid; mp 194-196 °C (decomp); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.21 (t, J = 7 Hz, 3H), 1.30 (t, J = 7 Hz, 3H), 1.51-3.77 (m, 13H), 4.10 (q, J = 7 Hz, 2H), 4.23 (q, J = 7 Hz, 2H), 4.75-4.85 (m, 1H), 5.19 (d, J = 8 Hz, 1H, exchangeable with D_2O), 5.46 (s, 2H, exchangeable with D_2O), 7.22-7.28 (m, 2H), 7.66-7.72 (m, 2H); FABMs, *m/z* 499 (M^+); Anal. Calcd for $C_{25}H_{33}N_5O_6\times H_2O$: C, 58.02; H, 6.82; N, 13.53. Found: C, 58.37; H, 7.07; N, 13.21.

***N*-{4-[2-(2-Amino-3,4,5,6,7,8-hexahydro-4-oxopyrido[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-*L*-glutamic acid (21).** Compound **(20)** (250 mg, 0.5 mmol) was saponified as described above to give 95 mg (43 %) of **21** as a white solid; mp 249-253 °C (decomp); ^{1}H NMR (250 MHz, CF_3COOD) δ 1.78-3.77 (m, 13H), 5.10-5.16 (m, 1H), 7.42-7.46 (m, 2H), 7.80-7.84 (m, 2H); FABMS, *m/z* 495 (M^+); Anal. Calcd for $C_{21}H_{25}N_5O_6\times2.5\ H_2O$: C, 51.63; H, 6.19; N, 14.34. Found: C, 51.89; H, 6.15; N, 14.08.

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