SYNTHESIS OF 7-METHYL DERIVATIVES OF 5,10-DIDEAZA-5,6,7,8-TETRAHYDROFOLIC ACID (DDATHF), 5,10-DIDEAZA-5,6,7,8-TETRAHYDROHOMOFOLIC ACID (HDDATHF), AND LY254155

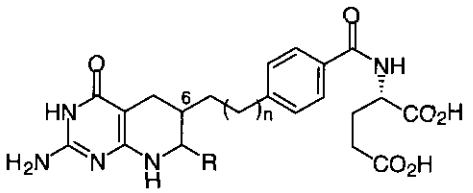
Edward C. Taylor* and Yao Wang
Department of Chemistry, Princeton University
Princeton, New Jersey 08544, U.S.A.

Abstract - 7-Methyl derivatives of DDATHF, homoDDATHF and the thiophene analog of DDATHF (LY254155) were prepared as potential antitumor agents.

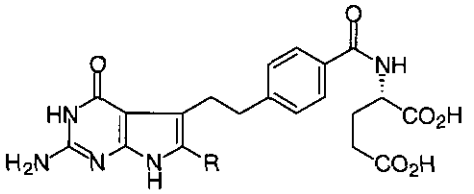
Recent work on the development of promising new antitumor agents which function as inhibitors of folate-dependent enzymes has included the discovery of DDATHF (**1**) and the subsequent clinical evaluation of its 6(*R*) diastereomer (lometrexol, **2**),[1] the discovery[2] and clinical development[3] of LY231514 (**5**) as a novel multitargeted antifolate,[4] and the introduction into clinical trials of (LY309887, **8**), the 6(*R*) diastereomer of the thiophene analog (LY254155, **7**) of DDATHF.[5] LY254155 is unusual in this triad of folate inhibitors in that intracellular polyglutamation by folylpolyglutamate synthetase (FPGS) appears to be unnecessary for its activity as a cell growth inhibitor; this feature could be significant in situations where the development of resistance has involved a decrease in the resistant cells' capability to convert monoglutamates to polyglutamates, or overexpression of γ-glutamyl hydrolase (which converts polyglutamates back to monoglutamates). We recently prepared the 6-methyl derivative (**6**) of LY231514[6a] and showed that it retained some cell growth inhibitory activity *in vitro*, although it was a poor substrate for FPGS.[6b] In order to examine this phenomenon further, we undertook the synthesis of 7-methyl-substituted derivatives of DDATHF, homoDDATHF[7] and LY354155 (**3**, **4** and **9** respectively). Provided that these 7-substituted derivatives retain cell growth activity but are poor substrates for FPGS, they would be of potential interest as chemotherapeutic agents against tumors which had developed resistance to **2** and/or **5**.

Our approach to target compounds (**3**), (**4**) and (**9**) was based on a cyclization strategy previously explored and exploited in our laboratory between 2,4-diamino-6(1H)-pyrimidinone and enamino ketones,[7] as illustrated in general terms in Scheme 1. For the synthesis of the 7-methyl derivative of DDATHF (**3**), we required the enamino ketone (**13a**), which was prepared as outlined in Scheme 2. The key methyl ketone (**10a**) was prepared by palladium acetate-catalyzed coupling of methyl 4-bromobenzoate with 4-hydroxy-1-

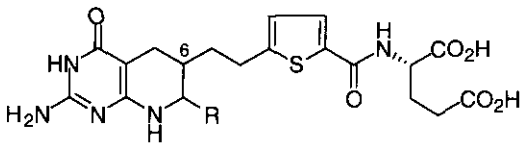
pentene in the presence of tetra-n-butylammonium chloride and lithium acetate.[9] Application of Miller's procedure for preparing thermodynamically favored enols (trimethylsilyl iodide and hexamethyldisilazane in



1, DDATHF 6(*R,S*), n = 1, R = H
2, lometrexol 6(*R*), n = 1, R = H
3, 6(*R,S*), n = 1, R = Me
4, 6(*R,S*), n = 2, R = Me

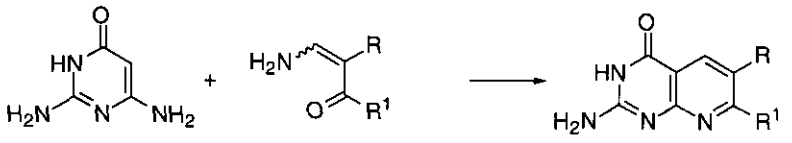


5, R = H
6, R = Me



7, LY254155, 6(*R,S*), R = H
8, LY309887, 6(*R*), R = H
9, 6(*R,S*), R = Me

Scheme 1



methylene chloride)[10] afforded the silyl enolate (**11a**), that with trimethyl orthoformate in the presence of $TiCl_4$ at -78 °C gave the β-keto enol (**12a**). Subsequent treatment of **12a** with saturated methanolic ammonia yielded the desired enamino ketone (**13a**), which was condensed with 2,4-diamino-6(1H)-pyrimidinone as previously described[8] to give the 5-deazapterin (**14a**).

Initial attempts to couple the acid (**15a**), readily obtained by saponification of **14a**, with diethyl L-glutamate were very discouraging because of the extreme insolubility of **15a**. This problem was alleviated

by initial acetylation to give **16a** (refluxing in acetic anhydride in the presence of DMAP, followed by mild basic hydrolysis of the intermediate mixed anhydride). Subsequent coupling of **16a** with diethyl L-glutamate in DMF, using 2-chloro-4,6-dimethoxy-1,3,5-triazine as the coupling agent and *N*-methylmorpholine as the base,[11] successfully gave **17a**. Hydrogenation of **17a** using PtO_2 in HOAc at room temperature then furnished **18a**, which was hydrolyzed with 1 N NaOH to give the target 7-methyl derivative (**3**) of DDATHF.[1,12]

The second target molecule, 7-methyl homoDDATHF (**4**),[12] was prepared by an analogous sequence of reactions starting from the homologous methyl ketone (**20**). This material was conveniently prepared by palladium-catalyzed coupling of hex-1-en-5-one with methyl 4-bromobenzoate to give **19**, followed by selective catalytic hydrogenation of the olefinic double bond.

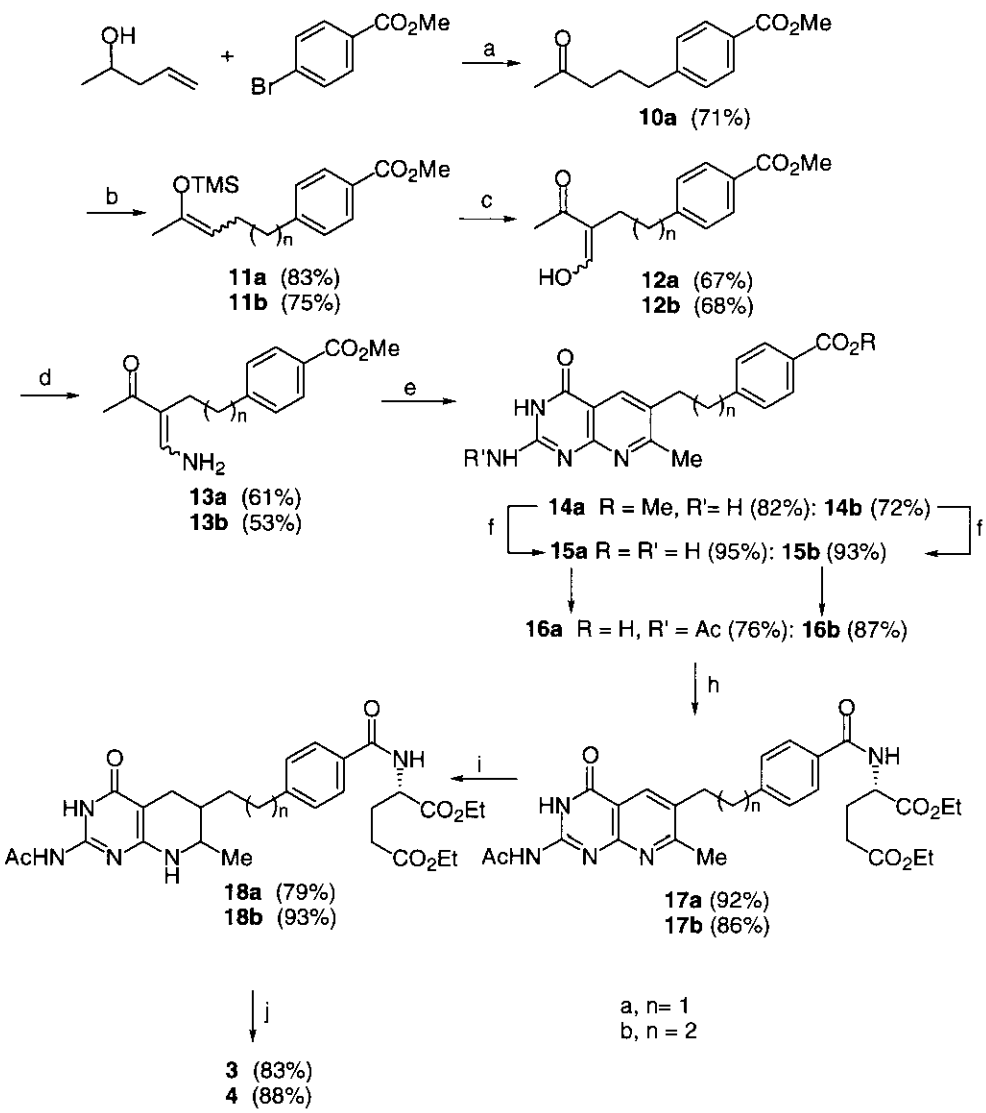
Preparation of the 7-methyl derivative of LY254155 (**9**) proved to be less straightforward. The thermodynamic silyl enolate (**30**) was prepared without incident from **29** (Scheme 4), but subsequent treatment with trimethyl orthoformate in the presence of $TiCl_4$ unexpectedly led to the dihydrobenzothiophene (**32**). It appears that the anticipated β-keto enol (**31**) had undergone a remarkably facile intramolecular Friedel-Crafts reaction. This untoward cyclization could, however, be avoided by removing $TiCl_4$ from the reaction mixture immediately after formation of the intermediate acetal (**33**). Thus, treatment of **30** with trimethyl orthoformate in the presence of $TiCl_4$ in methylene chloride at -78 °C for only 20 minutes, followed by a water quench, yielded **33**. The acetal functionality in **33** was then cleaved under neutral conditions using Jung's protocol (Me_3SiI, CH_2Cl_2, rt, 30 min)[13] to give **31** in 52% yield. Conversion of **31** to the desired β-keto enamine (**34**) was readily achieved with methanolic ammonia. Target molecule (**9**) was then obtained by a sequence of reactions analogous to those utilized and described above for the preparation of **3** and **4**.[12]

Full details of the biological evaluations of **3**, **4** and **9** will be published independently.

EXPERIMENTAL SECTION

Methyl 4-(4-Oxopentyl)benzoate (10a). To a 10 mL round-bottomed flask were added 0.22 g (1.0 mmol) of methyl 4-bromobenzoate, 0.13 g (1.5 mmol) of 4-hydroxy-1-pentene, 100 mg (0.45 mmol) of $Pd(OAc)_2$, 0.56 g (2.0 mmol) of tetra-*n*-butylammonium chloride, 0.04 g (1.0 mmol) of lithium chloride, 0.26 g (2.5 mmol) of lithium acetate dihydrate, and 2 mL of DMF. The mixture was stirred at 100 °C for 30 h. After cooling to rt, the mixture was diluted with 50 mL of brine and extracted with ether (2 x 50 mL). The ether layer was dried over anhydrous Na_2SO_4, solvent was removed under reduced pressure, and the residue was purified on a silica gel column (elution with 4:1 hexane/EtOAc) to give 0.16 g (71%) of **10a** as a colorless oil; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.91 (quintet, J = 7.4 Hz, 2 H), 2.11 (s, 3 H), 2.43 (t, J = 7.3 Hz, 2 H), 2.66 (t, J = 7.6 Hz, 2 H), 3.89 (s, 3 H), 7.23 (d, J = 8.6 Hz, 2 H), 7.95 (d, J

Scheme 2

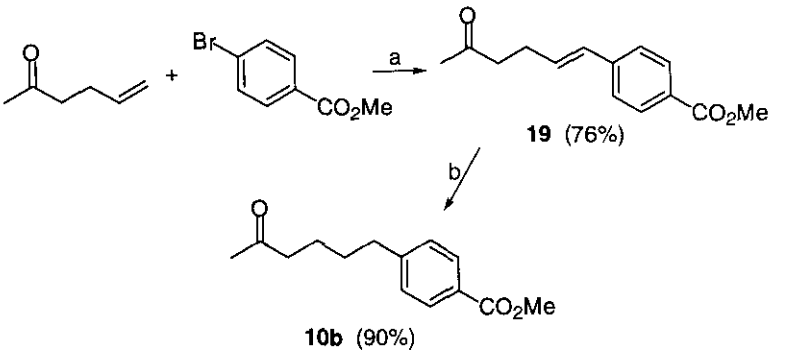


[a] $Pd(OAc)_2$, *n*-Bu_4NCl, LiCl, LiOAc, DMF, 100 °C; [b] Me_3SiI, $HN(SiMe_3)_2$, CH_2Cl_2, -20 °C to rt; [c] (i) $TiCl_4$, $HC(OMe)_3$, -78 °C; (ii) H_2O, rt; [d] NH_3/MeOH, 65 °C; e: HOAc/H_2O (2:1), 2,4-diamino-6(1H)-pyrimidinone, 110 °C, 2 h; [f] (i) OH^-, THF/EtOH/H_2O; (ii) H_3O^+; [f] (i) Ac_2O, DMAP, 130 °C, 2.5 h; (ii) 1 N NaOH; (iii) H_3O^+; [h] diethyl L-glutamate, 2-chloro-4,6-dimethoxy-1,3,5-triazine, NMM, DMF, 0 °C to rt; [i] H_2 (50 psi), PtO_2, HOAc, rt; [j] (i) OH^-, THF/H_2O, rt, 4 h; (ii) H_3O^+.

= 8.6 Hz, 2 H). This compound was identical in every way with an authentic sample prepared by a different route.[6a]

Methyl 4-[4-Trimethylsilyloxy-3-pentenyl]benzoate (11a). To a solution of 3.65 g (12.5 mmol) of **10a** in 80 mL of CH_2Cl_2 was slowly added 3.74 g (23.2 mmol) of $HN(SiMe_3)_2$ with stirring

Scheme 3

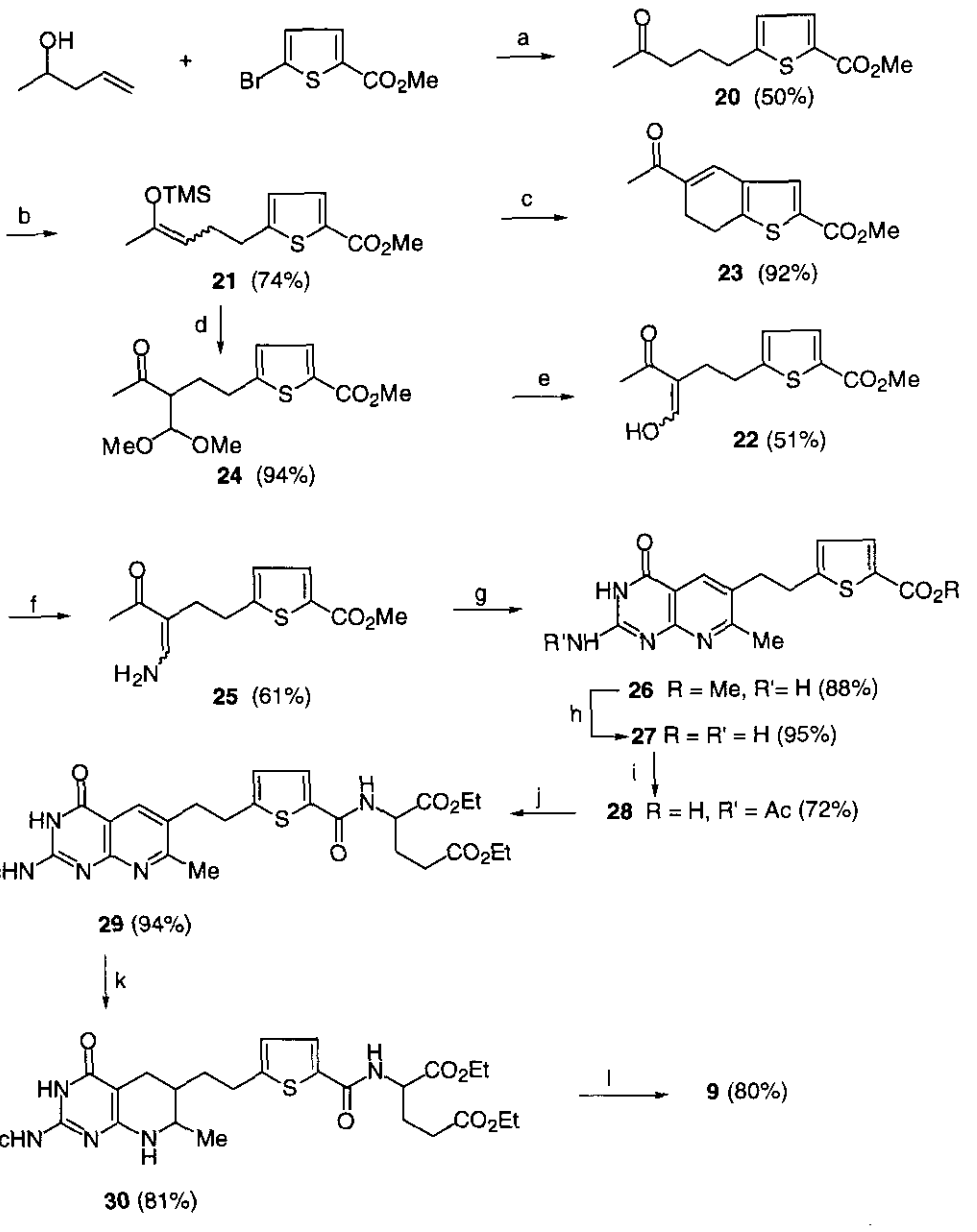


[a] $Pd(OAc)_2$, *n*-Bu_4NCl, KOAc, DMF, 80 °C; [b] 5% Pd/C, H_2 (1 atm), MeOH

under N_2 at -20 °C (ice-MeOH bath). To the mixture was added dropwise 3.94 g (1.2 eq) of Me_3SiI, and the resulting mixture was stirred at -20 °C for 20 min, then at 0 °C for 2 h. The reaction mixture was poured into 150 mL of cold saturated $NaHCO_3$ solution and extracted with ether (2 x 150 mL). The organic layer was dried over anhydrous Na_2SO_4, solvent was removed under reduced pressure, and the residue was purified on a silica gel column (elution with 8:1 hexane/EtOAc) to give 4.0 g (83%) of **11a** as a colorless oil; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.14 (s, 9 H, Z- isomer), 0.17 (s, 9 H), 1.63 (s, 3 H, Z-isomer), 1.75 (s, 3 H), 2.29 (q, J = 8.1 Hz, 2 H), 2.66 (t, J = 7.8 Hz, 2 H), 3.90 (s, 3 H), 4.43 (t, J = 7.2 Hz, 1 H), 4.63 (t, J = 7.6 Hz, 1 H, Z- isomer), 7.24 (d, J = 8.2 Hz, 2 H), 7.94 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 0.62, 22.5, 26.8, 36.0, 51.8, 107.2, 127.5, 128.3, 129.5, 147.2, 148.0, 167.0; IR (neat) 2953, 2922, 2857, 1725 (C=O), 1676, 1436, 1280, 1110 cm^{-1}; Anal. Calcd for $C_{16}H_{24}O_3Si$: C, 65.71; H, 8.27. Found: C, 65.67; H, 8.03.

Methyl 4-[3-Hydroxymethylene-4-oxopentyl]benzoate (12a). To a mixture of 15.4 mL of 1 N $TiCl_4$ in CH_2Cl_2 and 50 mL of CH_2Cl_2 was slowly added 1.54 g (14.5 mmol) of $HC(OMe)_3$ at -78 °C, followed by dropwise addition of 4.0 g (13 .7 mmol) of **11a** in 15 mL of CH_2Cl_2. The resulting mixture was stirred for 1 h, warmed to 0 °C, and 2 mL of water was added. The mixture was stirred at 0 °C for 1 h at rt overnight, and then poured into 100 mL of saturated $NaHCO_3$ solution and extracted with ether (2 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purified on a silica gel column (elution with 2:1 hexane/EtOAc) to give 2.28 g (67%) of **12a** as a white solid, mp 110-112 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.08 (s, 3 H), 2.50 (t, J = 7.5 Hz, 2 H), 2.78 (t, J = 7.5 Hz, 2 H), 3.91 (s, 3 H), 7.21 (d, J = 8.1 Hz, 2 H), 7.88 (d, J = 6.2 Hz, 1 H), 7.97 (d, J = 8.4 Hz, 2 H), 15.05 (d, J = 6.6 Hz, 1 H); IR ($CHCl_3$) 3156 (O-H), 2953, 2926, 2855, 1718 (C=O), 1637, 1437, 1284, 1113 cm^{-1}; Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.85; H, 6.45.

Scheme 4



[a] 10% $Pd(OAc)_2$, *n*-Bu_4NCl, LiCl, LiOAc, DMF, 100 °C; [b] Me_3SiI, $HN(SiMe_3)_2$, CH_2Cl_2, -20 °C to rt; [c] (i) $TiCl_4$, $HC(OMe)_3$, -78 °C; (ii) H_2O, rt: [d] $TiCl_4$, $HC(OMe)_3$, -78 °C, 20 min; [e] Me_3SiI, CH_2Cl_2, rt, 30 min; [f] NH_3/MeOH, 60 °C; [g] 2,4-diamino-6(1H)-pyrimidinone, 115 °C, 3h; [h] (i) OH^-, THF/EtOH/H_2O: (ii) H_3O^+; [i] (i) Ac_2O, DMAP, 130 °C, 3h; (ii) OH^-; (iii) H_3O^+: [j] diethyl L-glutamate, 2-chloro-4,6-dimethoxy-1,3,5-triazine, NMM, DMF, O °C to rt; [k] H_2 (50 psi), PtO_2, HOAc, rt; [l] (i) OH^-, THF/H_2O, rt, 4h; (ii) H_3O^+

Methyl 4-[3-Aminomethylene-4-oxopentyl]benzoate (13a). A solution of 1.80 g (7.25 mmol) of **12a** in 40 mL of saturated methanolic ammonia was heated to 65-70 °C and stirred overnight. After cooling to rt, the solvent and excess ammonia were removed under reduced pressure, and the residue was purified on a silica gel column (elution with 1:1 hexane/EtOAc) to give 1.10 g (61%) of **13a** as a off-white solid, mp 115-117 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.16 (s, 3 H), 2.48 (t, J = 7.6 Hz, 2 H), 2.71 (t, J = 7.5 Hz, 2 H), 3.88 (s, 3 H), 4.56 (d, J = 10.6 Hz, 2 H, NH_2), 7.26 (d, J = 7.9 Hz, 2 H), 7.33 (t, J = 10.9 Hz, 1 H), 7.91 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 24.2, 24.7, 34.0, 51.9, 112.8, 127.4, 128.4, 129.4, 146.2, 148.1, 167.1, 195.4; Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.19; H, 6.94; N, 5.43.

Methyl 4-[2-(2-Amino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl)ethyl]-benzoate (14a). To a mixture of glacial acetic acid (24 mL) and water (12 mL) were added 1.20 g (4.85 mmol) of **13a** and 0.62 g (4.92 mmol) of 2,4-diamino-6(1H)-pyrimidinone. The resulting mixture was stirred at 110 °C under N_2 for 2 h, cooled to rt and filtered. The collected solid was washed with water followed by MeOH and acetone, and then dried in a vacuum oven to give 1.34 g (82 %) of **14a** as a light yellow solid, mp 338 °C (decomp); ^{1}H NMR (CF_3COOD, 270 MHz) δ 2.73 (s, 3 H), 3.12 (m, 2 H), 3.19 (m, 2 H), 4.01 (s, 3 H), 7.24 (d, J = 7.9 Hz, 2 H), 8.00 (d, J = 7.9 Hz, 2 H), 8.68 (s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 17.1, 31.4, 34.5, 52.3, 111.7, 127.3, 128.3, 130.0, 133.3, 145.3, 150.6, 154.3, 159.0, 159.5, 170.6 (one peak overlapped); IR (KBr) 3237, 3192 (NH_2), 3063 (N-H), 2952, 2837, 1713 (C=O), 1674, 1603, 1416, 1284 cm^{-1}; Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.91; H, 5.38; N, 16.42.

4-[2-(2-Amino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl)ethyl]benzoic Acid (15a). To a mixture (45 mL) of THF/EtOH/water (1:1:1) were added 1.26 g (3.72 mmol) of **14a** and 15 mL of 1 N NaOH. The resulting mixture was stirred at rt for 3 h, an additional 10 mL of 1 N NaOH was added, and stirring was continued for an additional 2 h. The reaction mixture was then concentrated under reduced pressure, the residual aqueous solution was acidified with HCl to pH ~ 6, and the precipitate which formed was collected by filtration, washed with water followed by MeOH and acetone, and dried in a vacuum oven to give 1.15 g (95%) of **15a** as a light yellow solid, mp >360 °C (decomp); ^{1}H NMR (CF_3COOD, 270 MHz) δ 2.50 (s, 3 H), 2.90 (m, 2 H), 2.95 (m, 2 H), 7.04 (d, J = 8.1 Hz, 2 H), 7.82 (d, J = 8.1 Hz, 2 H), 8.46 (s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 20.1, 34.4, 37.6, 114.7, 129.3, 131.4, 133.6, 136.3, 148.3, 149.2, 153.7, 157.3, 162.0, 162.6, 175.7; IR (KBr) 3090 (br, O-H), 2954, 2838, 1691 (C=O), 1605, 1419, 1286, 1175 cm^{-1}; FABMS *m/z* 325 (MH^+), 307 (base), 289, 282, 273; Anal. Calcd for $C_{17}H_{16}N_4O_3 \cdot 0.2NaCl$: C, 60.76; H, 4.80; N, 16.67. Found: C, 60.59; H, 4.81; N, 16.60.

4-{2-[2-Acetylamino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl]ethyl}-benzoic Acid (16a). A suspension of **15a** (1.09 g, 3.36 mmol) in a mixture of 12 mL of acetic

anhydride and 60 mg of 4-dimethylaminopyridine was heated under gentle reflux for 2.5 h and then cooled to rt. To the mixture was added 15 mL of ether, and the separated solid was collected by filtration, washed with ether, dried, and then dissolved in 15 mL of 1 N NaOH and quickly filtered. The filtrate was acidified with acetic acid to pH ~ 6. The precipitate which formed was collected by filtration, washed with water, and vacuum dried to give 0.94 g (76%) of **16a** as a light brown solid, mp >340 °C (decomp); ^{1}H NMR (CF_3COOD, 270 MHz) δ 2.53 (s, 3 H), 2.89 (s, 3 H), 3.27 (m, 2 H), 3.31 (m, 2 H), 7.36 (d, J = 7.9 Hz, 2 H), 8.14 (d, J = 8.2 Hz, 2 H), 8.88 (s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 20.1, 25.2, 34.5, 37.3, 117.5, 129.2, 131.1, 133.3, 138.0, 147.9, 148.8, 154.5, 162.3, 175.5, 179.6 (two peaks overlapped); IR (KBr) 3106 (br, O-H), 2986, 2926, 2871, 1685 (C=O), 1626, 1607, 1420, 1268 cm^{-1}; HRMS calcd for $C_{19}H_{18}N_4O_4$ 366.1328, found 366.1331.

Diethyl *N*-[4-{2-[2-Acetylamino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl]ethyl}benzoyl]-L-glutamate (17a). Compound (**16a**) (0.90 g, 2.46 mmol) was dissolved in 50 mL of hot DMF. After cooling to 0 °C, 0.50 g (4.9 mmol) of *N*-methylmorpholine and 0.54 g (3.1 mmol) of 2-chloro-4,6-dimethoxy-1,3,5-triazine were added, and the reaction mixture was stirred at 0 °C for 2 h. An additional 0.50 g (4.9 mmol) of *N*-methylmorpholine and 0.71 g (3.49 mmol) of diethyl L-glutamate were added, and the mixture was stirred at 0 °C for 2 h and then at rt overnight. After removal of solvent under reduced pressure, the residue was triturated with water, filtered, washed with water and ether, and dried in a vacuum oven to give 1.24 g (92%) of **17a** as a light brown solid, mp >150 °C. ^{1}H NMR (CF_3COOD, 270 MHz) δ 1.42 (t, J = 7.2 Hz, 3 H), 1.49 (t, J = 7.2 Hz, 3 H), 2.44 (m, 1 H), 2.58 (s, 3 H), 2.63 (m, 1 H), 2.82 (t, J = 7.3 Hz, 2 H), 2.97 (s, 3 H), 3.27 (m, 2 H), 3.34 (m, 2 H), 4.38 (q, J = 7.2 Hz, 2 H), 4.50 (q, J = 7.2 Hz, 2 H), 5.07 (dd, J = 8.6 Hz, J = 4.7 Hz, 1 H), 7.45 (d, J = 7.9 Hz, 2 H), 7.91 (d, J = 7.9 Hz, 2 H), 9.00 (s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 14.7, 14.8, 20.2, 25.3, 28.9, 33.1, 34.6, 37.1, 56.1, 65.8, 66.8, 117.6, 130.6, 131.5, 132.5, 138.0, 147.7, 147.8, 154.6, 162.4, 174.7, 176.8, 179.5, 179.6 (two peaks overlapped); IR (KBr) 3176 (br, N-H), 2981, 2937, 1735 (C=O), 1679 (C=O), 1630, 1420, 1253, 1020 cm^{-1}; FABMS *m/z* 552 (MH+, base), 510, 478, 349, 307, 289.

Diethyl *N*-[4-{2-[2-Acetylamino-3,4-dihydro-4-oxo-7-methyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl]ethyl}benzoyl]-L-glutamate (18a). To a solution of **17a** (0.93 g, 1.69 mmol) in 80 mL of acetic acid was added 80 mg (0.2 eq) of PtO_2. Hydrogenation was carried out in a Parr apparatus at 50 psi and at rt for 24 h. After filtration of the mixture through Celite, solvent was removed under reduced pressure and the residue was purified on a silica gel column (elution with 2% MeOH in chloroform) to give 0.74 g (79%) of **18a** as an off-white solid, mp 205-210 °C (decomp); ^{1}H NMR (CF_3COOD, 270 MHz) δ 1.27 (d, J = 6.6 Hz, 3 H), 1.32 (t, J = 7.2 Hz, 3 H), 1.39 (t, J = 7.2 Hz, 3 H), 1.73 (m, 1 H), 1.85 (m, 1 H), 2.00 (m, 1 H), 2.31-2.55 (m, 3 H), 2.45 (s, 3 H), 2.72 (t, J = 7.4 Hz, 2 H), 2.83 (m, 3 H), 3.85 (m, 1 H), 4.29 (q, J = 7.2 Hz, 2 H), 4.41 (q, J = 7.2 Hz, 2 H), 4.98 (dd, J = 8.7 Hz, J = 4.7 Hz, 1 H), 7.37 (d, J = 7.9 Hz, 2 H), 7.78 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 14.8, 14.9, 16.9, 23.0, 25.3, 29.0, 33.3, 33.9, 35.3, 35.7, 53.2, 56.4, 65.9,

67.0, 93.5, 130.4, 131.3, 131.5, 150.4, 150.8, 155.7, 165.0, 175.4, 176.8, 179,3, 179.6; IR (KBr) 3343 (N-H), 3259 (N-H), 2977, 2933, 1736 (C=O), 1646 (C=O), 1616, 1472, 1256, 1194 cm^{-1}; FABMS *m/z* 556 (MH^+, base), 514, 353, 307; Anal. Calcd for $C_{28}H_{37}N_5O_7$: C, 60.53; H, 6.71; N, 12.60. Found: C, 60.61; H, 6.59; N, 12.32.

***N*-{4-[2-(2-Amino-3,4-dihydro-4-oxo-7-methyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)ethyl]benzoyl}-L-glutamic Acid (3).** To a solution of **18a** (0.50 g, 0.90 mmol) in 16 mL of THF/water (2:1) was added 8 mL of 1 N NaOH. The resulting mixture was stirred at rt for 4 h, filtered, and the filtrate was concentrated under reduced pressure and the residue acidified with acetic acid to *pH* ~ 6. The resulting precipitate was triturated with water, collected by filtration and dried in a vacuum oven to give 0.34 g (83%) of **3** as an off-white solid, mp >200 °C (decomp), shrinks at 170 °C; ^1H NMR (CF_3COOD, 270 MHz) δ 1.27 (d, J = 6.6 Hz, 3 H), 1.75-2.02 (br m, 3 H), 2.30-2.50 (m, 2 H), 2.62 (m, 1 H), 2.78-2.93 (br m, 5 H), 3.92 (m, 1 H), 5.11 (dd, J = 8.4 Hz, J = 4.4 Hz, 1 H), 7.41 (d, J = 7.9 Hz, 2 H), 7.80 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 13.4, 19.2, 25.4, 29.2, 31.2, 32.2, 32.9, 50.3, 52.6, 84.4, 127.2, 128.3, 128.4, 147.7, 149.4, 151.2, 159.6, 172.3, 176.2, 179.8; IR (KBr) 3335 (br, O-H), 2971, 2932, 1701 (C=O), 1646 (C=O), 1614, 1540, 1447 cm^{-1}; FABMS *m/z* 458 (MH^+), 346, 322, 307 (base), 289, 272; HRFABMS calcd for $C_{22}H_{28}N_5O_6$ (MH^+) 458.2040, found 458.2030; Anal. Calcd for $C_{22}H_{27}N_5O_6 \cdot 0.6H_2O$: C, 56.43; H, 6.07; N, 14.95. Found: C, 56.83; H, 6.06; N, 14.56.

Methyl 4-(5-Oxo-1-hexenyl)benzoate (19). To a 250 mL round-bottomed flask were added 10.0 g (46.5 mmol) of methyl 4-bromobenzoate, 9.13 g (93.0 mmol) of 1-hexen-5-one, 0.52 g (2.3 mmol) of $Pd(OAc)_2$, 12.9 g (47 mmol) of tetra-*n*-butylammonium chloride, 13.7 g (139 mmol) of potassium acetate, and 70 mL of DMF. The mixture was stirred at 80 °C overnight. After cooling to rt, the mixture was diluted with 500 mL of saturated $NaHCO_3$ solution and extracted with ether (2 x 500 mL). The ether extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and the residual solid purified on a silica gel column (elution with 4:1 hexane/EtOAc) to give 8.2 g (76%) of **19**, mp 62-63 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.18 (s, 3 H), 2.52 (q, J = 6.6 Hz, 2 H), 2.64 (t, J = 6.6 Hz, 2 H), 3.90 (s, 3 H), 6.33 (dt, J = 15.8 Hz, J = 6.3 Hz, 1 H), 6.45 (d, J = 15.8 Hz, 1 H), 7.37 (d, J = 8.6 Hz, 2 H), 7.95 (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 26.9, 29.8, 42.5, 51.8, 125.6, 128.3, 129.5, 129.6, 131.7, 141.7, 166.6, 207.3; IR (neat) 3002, 2959, 2903, 1716 (C=O), 1607, 1437, 1283, 1115 cm^{-1}; Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.39; H, 6.78.

Methyl 4-(5-Oxohexyl)benzoate (10b). To a solution of **19** (8.23 g, 35.4 mmol) in 200 mL of MeOH was added 0.90 g of 5% Pd/C. The resulting mixture was stirred at rt using a H_2 balloon for 2 h and then filtered. Evaporation of the solvent under reduced pressure provided 7.50 g (90%) of **10b** as a colorless oil; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.61 (m, 4 H), 2.11 (s, 3 H), 2.44 (t, J = 6.9 Hz, 2 H), 2.66 (t, J = 6.9 Hz, 2 H), 3.89 (s, 3 H), 7.23 (d, J = 8.2 Hz, 2 H), 7.93 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 23.1, 29.7, 30.3, 35.6, 43.2, 51.7, 127.6, 128.2, 129.4, 147.5, 166.8,

208.5; IR (neat) 3000, 2946, 2861, 1719 (C=O), 1610, 1436, 1280, 1110 cm^{-1}; Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.95; H, 7.93.

Methyl 4-[5-Trimethylsilyloxy-4-hexenyl]benzoate (11b). To a solution of 7.18 g (30.6 mmol) of **10b** in 140 mL of CH_2Cl_2 was slowly added 6.91 g (42.8 mmol) of $HN(SiMe_3)_2$ with stirring under N_2 at -20 °C (ice-MeOH bath). After 10 min, 7.34 g (36.7 mmol) of Me_3SiI was added dropwise. The mixture was stirred at -20 °C for 30 min, at rt overnight, and then poured into 300 mL of cold saturated $NaHCO_3$ solution. This solution was extracted with ether (2 x 300 mL) and the ether extracts were dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and the residue was purified on a silica gel column (elution with 16:1 hexane/EtOAc) to give 7.08 g (75%) of **11b** as a colorless oil; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.16 (s, 9 H), 0.19 (s, 9 H, *Z*- isomer), 1.63 (quintet, J = 7.6 Hz, 2 H), 1.70 (s, 3 H, *Z*- isomer), 1.77 (s, 3 H), 2.00 (m, 2 H), 2.66 (t, J = 7.6 Hz, 2 H), 3.90 (s, 3 H), 4.45 (t, J = 7.2 Hz, 1 H), 4.63 (t, J = 7.6 Hz, 1 H, *Z*- isomer), 7.24 (d, J = 8.2 Hz, 2 H), 7.94 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 0.68, 22.7, 25.0, 31.3, 35.7, 51.9, 108.1, 127.6, 128.5, 129.5, 147.0, 148.4, 167.2 (small peaks at 0.37, 17.8, 26.7, 31.8, 35.3, 107.6, 127.7, 128.4, 129.6, 148.1, 167.1 are attributed to the *Z*- isomer); IR (neat) 2948, 2861, 1721 (C=O), 1610, 1436, 1281, 1110 cm^{-1}; Anal. Calcd for $C_{17}H_{26}O_3Si$: C, 66.62; H, 8.55. Found: C, 66.92; H, 8.62.

Methyl 4-[4-Hydroxymethylene-5-oxohexyl]benzoate (12b). To a mixture of 9.4 mL of 1 N $TiCl_4$ in CH_2Cl_2 and 25 mL of CH_2Cl_2 was slowly added 0.91 g (8.58 mmol) of $HC(OMe)_3$ under N_2 at -78 °C. After 10 min, 2.40 g (7.83 mmol) of **11b** in 5 mL of CH_2Cl_2 was added dropwise. The resulting mixture was stirred at this temperature for 1 h, warmed to 0 °C, and 1 mL of water was added. Stirring was continued at 0 °C for 1 h, and then at rt overnight. The reaction mixture was poured into 100 mL of saturated $NaHCO_3$ solution, extracted with ether (2 x 150 mL), and the ether extracts were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified on a silica gel column (elution with 2:1 hexane/EtOAc) to give 1.39 g (68% yield) of **12b**, mp 60-61 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.77 (quintet, J = 7.3 Hz, 2 H), 2.10 (s, 3 H), 2.19 (t, J = 7.3 Hz, 2 H), 2.70 (t, J = 7.5 Hz, 2 H), 3.91 (s, 3 H), 7.24 (d, J = 8.3 Hz, 2 H), 7.95 (d, J = 4.0 Hz, 1 H), 7.97 (d, J = 8.6 Hz, 2 H), 14.98 (d, J = 6.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 23.8, 27.2, 32.1, 35.2, 52.0, 112.3, 128.0, 128.4, 129.8, 147.1, 167.0, 177.1, 194.7; IR (neat) 3422 (br, O-H), 3004, 2952, 2865, 1717 (C=O), 1611, 1436, 1283, 1112 cm^{-1}; FABMS *m/z* 263 (MH^+), 245, 231, 217, 205, 191 (base), 161, 149; Anal. Calcd for $C_{15}H_{18}O_4 \cdot 0.1NaCl$: C, 67.19; H, 6.76. Found: C, 67.20; H, 6.58.

Methyl 4-[4-Aminomethylene-5-oxohexyl]benzoate (13b). A mixture of 1.33 g (5.07 mmol) of **12b** in 30 mL of saturated methanolic ammonia was heated to 65 °C and stirred overnight. After cooled to rt, the solvent and the excess ammonia were removed under reduced pressure and the residue was purified on a silica gel column (elution with 2:1, then 1:1 hexane/EtOAc) to give 0.70 g (53 %) of **13b** as a off-white solid, mp 89-90 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.69 (quintet, J = 7.9 Hz, 2 H), 2.17 (s, 3 H), 2.21 (t, J = 7.9 Hz, 2 H), 2.69 (t, J = 7.6 Hz, 2 H), 3.89 (s, 3 H), 4.23 (d, J = 10.6 Hz, 2 H, NH_2),

7.25 (d, J = 8.2 Hz, 2 H), 7.31 (t, J = 10.6 Hz, 1 H), 7.94 (d, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 22.4, 24.4, 29.2, 35.9, 52.1, 114.2, 127.7, 128.5, 129.7, 145.7, 148.3, 167.1, 195.7; IR (neat) 3354 and 3216 (NH_2), 2946, 1716 (C=O), 1653, 1609, 1573, 1436, 1283, 1112 cm^{-1}; FABMS *m/z* 262 (MH^+), 230, 154 (base).

Methyl 4-[3-(2-Amino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl)propyl]-benzoate (14b). To a mixture of glacial acetic acid (40 mL) and water (20 mL) were added 2.01 g (7.69 mmol) of **13b** and 0.97 g (7.69 mmol) of 2,4-diamino-6(1H)-pyrimidinone. The resulting mixture was stirred at 110 °C under N_2 for 3 h, and then cooled to rt. To the mixture was added 20 mL of water, and the solid which separated was collected by filtration, washed with water followed by MeOH and acetone, and dried in a vacuum oven to give 1.96 g (72%) of **14b** as a light yellow solid, mp 336 °C (decomp); ^{1}H NMR (CF_3COOD, 270 MHz) δ 2.26 (quintet, J = 7.6 Hz, 2 H), 2.95 (s, 3 H), 3.05 (m, 4 H), 4.19 (s, 3 H), 7.49 (d, J = 8.2 Hz, 2 H), 8.18 (d, J = 8.2 Hz, 2 H), 8.98 (s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 19.8, 32.2, 32.3, 37.2, 55.0, 114.5, 129.4, 130.9, 132.5, 137.5, 147.6, 150.1, 153.0, 156.9, 161.7, 162.3, 173.7; IR (KBr) 3232 and 3198 (NH_2), 3030 (N-H), 2951, 2837, 1722 (C=O), 1672, 1604, 1420, 1286 cm^{-1}; FABMS *m/z* 353 (MH^+, base), 321, 307, 282, 273.

4-[3-(2-Amino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl)propyl]benzoic Acid (15b). To a mixture (60 mL) of THF/EtOH/water (1:1:1) were added 1.90 g (5.39 mmol) of **14b** and 20 mL of 1 N NaOH. The resulting mixture was stirred at rt overnight and then concentrated under reduced pressure. The residual aqueous solution was acidified with acetic acid to pH ~ 6, and the precipitate which formed was collected by filtration, washed with water followed by MeOH and acetone, and dried in vacuo to give 1.70 g (93%) of **15b** as a light yellow solid, mp >340 °C (decomp); ^{1}H NMR (CF_3COOD, 270 MHz) δ 2.09 (quintet, J = 7.6 Hz, 2 H), 2.78 (s, 3 H), 2.88 (m, 4 H), 7.35 (d, J = 8.2 Hz, 2 H), 8.05 (d, J = 8.2 Hz, 2 H), 8.80 (s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 20.1, 32.4, 32.6, 37.5, 114.7, 128.4, 131.2, 133.3, 137.6, 147.7, 151.3, 153.2, 157.1, 161.9, 162.5, 176.1; IR (KBr) 3234, 3063 (br, O-H), 2938, 2854, 1688 (C=O), 1605, 1420, 1238, 1175 cm^{-1}; HRMS calcd for $C_{18}H_{18}N_4O_3$ 338.1379, found 338.1390.

4-{3-[2-Acetylamino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl]propyl}benzoic Acid (16b). A suspension of **15b** (1.70 g, 5.02 mmol) in a mixture of 20 mL of acetic anhydride and 0.1 g of 4-dimethylaminopyridine was heated under gentle reflux for 4.5 h and then cooled to rt . To the mixture was added 30 mL of ether. The solid which separated was collected by filtration, washed with water and ether, dried in the air, and then dissolved in 20 mL of 1 N NaOH. The resulting solution was quickly filtered, and the filtrate was acidified with acetic acid to pH ~ 6. The precipitate that formed was collected by filtration, washed with water and dried in a vacuum oven to give 1.66 g (87%) of **16b** as a light brown solid, mp >258 °C (decomp); ^{1}H NMR (CF_3COOD, 270 MHz) δ 2.20 (quintet, J = 7.6 Hz, 2 H), 2.53 (s, 3 H), 2.92 (s, 3 H), 2.99 (m, 4 H), 7.43 (d, J = 8.2 Hz, 2 H), 8.13 (d, J = 8.2 Hz, 2 H), 8.98 (s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 20.2, 25.4, 32.4, 32.8,

37.5, 117.7, 128.5, 131.2, 133.3, 139.4, 147.5, 151.2, 154.4, 154.5, 162.5, 163.3, 176.1, 179.7; IR (KBr) 3176 (br, O-H), 2939, 2866, 1685 (C=O), 1626, 1603, 1419, 1235, 1176 cm^{-1}; FABMS m/z 381 (MH+, base), 365, 339, 322, 307, 282, 273; Anal. Calcd for $C_{20}H_{20}N_4O_4 \cdot 0.4H_2O$: C, 61.97; H, 5.41; N, 14.45. Found: C, 61.88; H, 5.35; N, 14.55.

Diethyl *N*-[4-{3-[2-Acetylamino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl]propyl}benzoyl]-L-glutamate (17b). Compound (**16b**) (1.60 g, 4.2 mmol) was dissolved in 80 mL of hot DMF, the solution was cooled to 0 °C, and to the solution were added 0.85 g (8.4 mmol) of *N*-methylmorpholine and 0.92 g (5.2 mmol) of 2-chloro-4,6-dimethoxy-1,3,5-triazine. The mixture was stirred at 0 °C for 2 h, and then an additional 0.85 g (8.4 mmol) of *N*-methylmorpholine and 1.21 g (5.96 mmol) of diethyl L-glutamate were added. The resulting mixture was stirred at rt overnight, the solvent was removed under reduced pressure, and the residue was dissolved in 100 mL of $CHCl_3$/MeOH (4:1). A small amount of silica gel was added and the sovent was evaporated under reduced pressure. The impregnated silica gel was applied to the top of a silica gel column, and the product (mixed with some 2-hydroxy-4,6-dimethoxy-1,3,5-triazine) was eluted with $CHCl_3$/MeOH (95:5). This mixture was triturated with water, filtered, and the collected solid was washed with water and a small amount of acetone and dried in a vacuum oven to give 2.05 g (86%) of **17b** as a light yellow solid, mp 138-144 °C; ^{1}H NMR (CF_3COOD, 270 MHz) δ 1.37 (t, J = 7.1 Hz, 3 H), 1.45 (t, J = 7.1 Hz, 3 H), 2.18 (quintet, J = 7.2 Hz, 2 H), 2.42 (m, 1 H), 2.54 (s, 3 H), 2.58 (m, 1 H), 2.79 (t, J = 7.1 Hz, 2 H), 2.94 (s, 3 H), 2.98 (m, 4 H), 4.34 (q, J = 7.1 Hz, 2 H), 4.47 (q, J = 7.1 Hz, 2 H), 5.04 (dd, J = 8.6 Hz, J = 4.7 Hz, 1 H), 7.45 (d, J = 8.1 Hz, 2 H), 7.86 (d, J = 8.1 Hz, 2 H), 9.01 (s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 15.0, 15.1, 20.4, 25.6, 29.1, 32.6, 33.0, 33.4, 37.5, 56.5, 66.0, 67.1, 117.9, 130.6, 131.8, 139.5, 147.7, 150.3, 154.6, 154.7, 162.7, 163.6, 175.4, 177.0, 179.8, 179.9 (one peak overlapped); IR (KBr) 3318 (N-H), 3172 (N-H), 2982, 2937, 1741 (C=O), 1733 (C=O), 1694 (C=O), 1632, 1609, 1420, 1252, 1233 cm^{-1}; HRMS calcd for $C_{29}H_{35}N_5O_7$ 565.2536, found 565.2552; Anal. Calcd for $C_{29}H_{35}N_5O_7$: C, 61.58; H, 6.24; N, 12.38. Found: C, 61.43; H, 6.15; N, 12.55.

Diethyl *N*-{4-[3-[2-Acetylamino-3,4-dihydro-4-oxo-7-methyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl]propyl]benzoyl}-L-glutamate (18b). A solution of **17b** (1.28 g, 2.26 mmol) in 100 mL of acetic acid with 105 mg (0.2 eq) of added PtO_2 was hydrogenated in a Parr apparatus at 50 psi of H_2 and at rt for 20 h. After filtration of the reaction mixture through Celite, the filtrate was concentrated under reduced pressure and the product was precipitated by addition of hexane/EtOAc, triturated with hexane, filtered, and dried in a vacuum oven to give 1.20 g (93%) of **18b** as an off-white solid, mp 179-183 °C; ^{1}H NMR (CF_3COOD, 270 MHz) δ 1.23 (d, J = 6.6 Hz, 3 H), 1.34 (t, J = 6.9 Hz, 3 H), 1.41 (t, J = 6.9 Hz, 3 H), 1.54 (m, 2 H), 1.80 (m, 2 H), 2.02 (m, 1 H), 2.30-2.56 (m, 3 H), 2.47 (s, 3 H), 2.76 (m, 5 H), 3.86 (m, 1 H), 4.30 (q, J = 6.9 Hz, 2 H), 4.43 (q, J = 6.9 Hz, 2 H), 5.00 (dd, J = 8.5 Hz, J = 4.7 Hz, 1 H), 7.37 (d, J = 7.9 Hz, 2 H), 7.78 (d, J = 7.9 Hz, 2 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 14.1, 16.5, 22.3, 24.1, 27.1, 28.9, 29.9, 30.5, 34.7, 35.8, 49.1, 52.4, 60.8, 61.7, 88.5, 127.1, 128.4, 131.1, 146.5, 148.5, 158.5, 160.7, 167.3, 172.1, 173.2, 173.3 (one peak

overlapped); IR (KBr) 3334 (N-H), 3251 (N-H), 2970, 2934, 1737 (C=O), 1647 (C=O), 1614, 1571, 1472, 1260, 1191 cm^{-1}; HRMS calcd for $C_{29}H_{39}N_5O_7$ 569.2849, found 569.2840; Anal. Calcd for $C_{29}H_{39}N_5O_7$: C, 61.15; H, 6.90; N, 12.29. Found: C, 61.12; H, 6.92; N, 12.40.

***N*-{4-[3-(2-Amino-3,4-dihydro-4-oxo-7-methyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)propyl]benzoyl}-L-glutamic Acid (4).** A *suspension of* **18b** (0.80 g, 1.4 *mmol) in* 24 mL of 1:1 THF/water and 12 mL of 1 N NaOH was stirred at rt for 4 h and then filtered. The filtrate was concentrated under reduced pressure and then acidified with acetic acid to pH ~ 6. The precipitate that separated was collected by filtration, washed with water and ether, and dried in a vacuum oven to give 0.58 g (88%) of **4** as an off-white solid, mp 180-184 °C; ^{1}H NMR (CF_3COOD, 270 MHz) δ 1.23 (d, J = 5.9 Hz, 3 H), 1.50 (m, 2 H), 1.80 (m, 2 H), 2.00 (m, 1 H), 2.28 (m, 1 H), 2.45 (m, 1 H), 2.65 (m, 1 H), 2.83 (m, 5 H), 3.90 (m, 1 H), 5.11 (m, 1 H), 7.40 (d, J = 7.6 Hz, 2 H), 7.80 (d, J = 7.3 Hz, 2 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 14.8, 16.6, 22.4, 28.4, 30.7, 32.3, 36.6, 37.9, 53.5, 55.8, 87.8, 130.1, 130.7, 131.7, 151.9, 152.4, 154.3, 162.4, 175.7, 179.1, 182.7; IR (KBr) 3300 (br, O-H), 2974, 2934, 1701 (C=O), 1652 (C=O), 1542, 1447, 1201 cm^{-1}; FABMS m/z 472 (MH^+), 346, 325, 307 (base); HRFABMS calcd for $C_{23}H_{30}N_5O_6$ (MH^+) 472.2196, found 472.2192; Anal. Calcd for $C_{23}H_{29}N_5O_6 \cdot 0.8H_2O$: C, 56.85; H, 6.35; N, 14.41. Found: C, 56.92; H, 6.02; N, 14.13.

Methyl 5-(4-Oxopentyl)thiophene-2-carboxylate (20). To a 250 mL round-bottomed flask were added 10.0 g (45.2 mmol) of methyl 5-bromothiophene-2-carboxylate, 5.87 g (68.2 mmol) of 4-hydroxy-1-pentene, 1.0 g of $Pd(OAc)_2$, 25.3 g (92.4 mmol) of tetra-*n*-butylammonium chloride, 1.93 g (45.5 mmol) of lithium chloride, 11.6 g (113.7 mmol) of lithium acetate dihydrate, and 90 mL of DMF. The mixture was stirred at 100 °C for 24 h, cooled to rt, diluted with 500 mL of saturated $NaHCO_3$ solution, and extracted with ether (2 x 500 mL). The combined ether extracts were dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and the residue was purified on a silica gel column (elution with 4:1 hexane/EtOAc) to give 5.15 g (50%) of **20** as a pale yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.95 (quintet, J = 7.3 Hz, 2 H), 2.12 (s, 3 H), 2.48 (t, J = 7.3 Hz, 2 H), 2.84 (t, J = 7.3 Hz, 2 H), 3.84 (s, 3 H), 6.77 (d, J = 3.6 Hz, 1 H), 7.61 (d, J = 3.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 25.0, 29.4, 30.0, 42.2, 51.9, 125.5, 130.9, 133.7, 152.5, 162.6, 207.9; IR (neat) 2999, 2952, 1714 (C=O), 1540, 1463, 1292, 1265, 1097 cm^{-1}; Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24; S,14.17. Found: C, 58.10; H, 6.22; S, 13.90.

Methyl 5-[4-Trimethylsilyloxy-3-pentenyl]thiophene-2-carboxylate (21). To a solution of 3.75 g (16.6 mmol) of **20** in 80 mL of CH_2Cl_2 was slowly added 3.75 g (23.2 mmol) of $HN(SiMe_3)_2$ with stirring under N_2 at -20 °C (ice-MeOH bath). After 10 min, 3.98 g (19.9 mmol) of Me_3SiI was added dropwise, and the resulting mixture was stirred at -20 °C for 30 min, then at rt overnight. The reaction mixture was poured into 200 mL of cold saturated $NaHCO_3$ solution and extracted with ether (2 x 200 mL). The combined ether extracts were dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and the residue was purified on a silica gel column (elution with 16:1 hexane/EtOAc) to give 3.64

g (74%) of **21** as a pale yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.16 (s, 9 H, *Z*- isomer), 0.19 (s, 9 H), 1.68 (s, 3 H, *Z*- isomer), 1.77 (s, 3 H), 2.35 (q, J = 7.8 Hz, 2 H), 2.83 (t, J = 7.6 Hz, 2 H), 3.86 (s, 3 H), 4.46 (t, J = 6.9 Hz, 1 H), 4.65 (t, J = 7.0 Hz, 1 H, *Z*- isomer), 6.79 (d, J = 3.6 Hz, 1 H), 7.62 (d, J = 3.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 0.68, 22.6, 27.3, 30.6, 51.9, 106.6, 125.1, 130.5, 133.6, 147.9, 153.6, 162.7; IR (neat) 2953, 2920, 2850, 1715 (C=O), 1540, 1462, 1291, 1264, 1254, 1097 cm^{-1}; Anal. Calcd for $C_{14}H_{22}O_3SSi$: C, 56.34; H, 7.43; S, 10.74. Found: C, 56.06; H, 7.36; S, 10.87.

2-Methoxycarbonyl-5-acetyl-6,7-dihydrobenzo[*b*]thiophene (23). To a mixture of 13.4 mL of 1 N $TiCl_4$ in CH_2Cl_2 and 45 mL of CH_2Cl_2 was slowly added 1.30 g (12.3 mmol) of $HC(OMe)_3$ at -78 °C, followed by dropwise addition of 3.35 g (11.2 mmol) of **21** in 15 mL of CH_2Cl_2. The resulting mixture was stirred for 1 h, warmed to 0 °C, and 2 mL of water was added. The mixture was stirred at 0 °C for 1 h, then at rt overnight, and poured into 100 mL of saturated $NaHCO_3$ solution and extracted with ether (2 x 100 mL). The organic extracts were dried over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purified on a silica gel column (elution with 2:1 hexanes/EtOAc) to give 2.43 g (92%) of **23** as a light yellow solid, mp 115-118 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3 H), 2.73 (t, J = 8.6 Hz, 2 H), 2.96 (t, J = 8.6 Hz, 2 H), 3.88 (s, 3 H), 7.35 (s, 1 H), 7.67 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 20.9, 22.7, 25.2, 52.2, 129.9, 131.0, 132.4, 134.6, 134.9, 148.4, 161.6, 197.5; FABMS *m/z* 236 (M^+), 221, 193, 176, 161, 134 (base), 97, 83, 69.

Methyl 5-[3-Dimethoxymethyl-4-oxopentyl]thiophene-2-carboxylate (24). To a mixture of 12.2 mL of 1 N $TiCl_4$ in 40 mL of CH_2Cl_2 and 1.47 g (13.9 mmol) of $HC(OMe)_3$ at - 78 °C was added 3.64 g (12.2 mmol) of **21** in 10 mL of CH_2Cl_2. The resulting mixture was stirred at this temperature for 20 min and then poured into a mixture of ether (200 mL) and half saturated $NaHCO_3$ solution (200 mL). The ether layer was separated, the aqueous layer was extracted with ether (200 mL), and the combined ether extracts were dried over anhydrous Na_2SO_4. After removal of the ether under reduced pressure, the residue was purified on a silica gel column (elution with 4:1 followed by 2:1 hexane/EtOAc) to give 3.45 g (94%) of **24** as a pale yellow oil; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.88-2.10 (m, 2 H), 2.19 (s, 3 H), 2.49 (t, J = 7.1 Hz, 1 H), 2.70-2.97 (m, 2 H), 3.32 (s, 3 H), 3.33 (s, 3 H), 3.86 (s, 3 H), 4.39 (d, J = 7.6 Hz, 1 H), 6.79 (d, J = 3.6 Hz, 1 H), 7.63 (d, J = 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 27.9, 29.2, 31.7, 42.2, 52.0, 54.1, 55.4, 105.3, 125.6, 131.0, 133.6, 152.1, 162.5, 209.0; IR (neat) 2996, 2952, 2835, 1712 (C=O), 1540, 1462, 1292, 1265, 1096 cm^{-1}; Anal. Calcd for $C_{14}H_{20}O_5S$: C, 55.98; H, 6.71. Found: C, 56.21; H, 6.50.

Methyl 5-[3-Hydroxymethylene-4-oxopentyl]thiophene-2-carboxylate (22). To a solution of **24** (3.83 g, 12.8 mmol) in 50 mL of CH_2Cl_2 was added 3.06 g (15.3 mmol) of Me_3SiI under N_2 at rt. The resulting mixture was stirred at rt for 30 min, poured into 200 mL of saturated $NaHCO_3$ solution, and extracted with ether (2 x 200 mL). The ether extracts were dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and the residue purified on a silica gel column (elution with 2:1 hexane/EtOAc) to

give 1.67 g (51%) of **22** as an off-white solid, mp 100-102 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.11 (s, 3 H), 2.55 (t, J = 7.6 Hz, 2 H), 2.95 (t, J = 7.6 Hz, 2 H), 3.87 (s, 3 H), 6.78 (d, J = 4.0 Hz, 1 H), 7.63 (d, J = 4.0 Hz, 1 H), 7.94 (d, J = 6.6 Hz, 1 H), 15.10 (d, J = 6.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 23.5, 29.6, 31.6, 52.0, 111.0, 125.9, 131.3, 133.6, 150.9, 162.4, 178.4, 193.9; IR (chloroform) 3155 (O-H), 2953, 2847, 1709 (C=O), 1637, 1588, 1462, 1296, 1271, 1100 cm^{-1}; Anal. Calcd for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55; S, 12.61. Found: C, 56.45; H, 5.35; S, 12.53.

Methyl 5-[3-Aminomethylene-4-oxopentyl]thiophene-2-carboxylate (25). A solution of 1.12 g (4.4 mmol) of **22** in 30 mL of saturated methanolic ammonia was heated to 60 °C and stirred overnight. After cooling to rt, the solvent and excess ammonia were removed under reduced pressure. The residue was purified on a silica gel column (elution with 1:1 hexane/EtOAc) to give 0.67 g (61%) of **25** as a light yellow solid, mp 110-112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.19 (s, 3 H), 2.53 (t, J = 7.2 Hz, 2 H), 2.90 (t, J = 7.2 Hz, 2 H), 3.85 (s, 3 H), 4.45 (d, J = 10.8 Hz, 2 H, NH_2), 6.80 (d, J = 3.7 Hz, 1 H), 7.37 (t, J = 10.8 Hz, 1 H), 7.60 (d, J = 3.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.0, 24.8, 28.4, 51.7, 111.8, 125.3, 130.4, 133.5, 147.1, 153.5, 162.6, 195.3; IR (neat) 3358, 3291, 3219, 2951, 2850, 1703 (C=O), 1654, 1577, 1459, 1295, 1274, 1100 cm^{-1}; FABMS *m/z* 254 (MH+), 222, 196, 165, 154 (base).

Methyl 5-[2-(2-Amino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl)ethyl]-thiophene-2-carboxylate (26). To a mixture of glacial acetic acid (14 mL) and water (7 mL) were added 0.65 g (2.58 mmol) of **25** and 0.36 g (2.85 mmol) of 2,4-diamino-6(1H)-pyrimidinone. The resulting mixture was stirred at 115 °C under N_2 for 3 h, cooled to rt , and diluted with 10 mL of water. The solid which precipitated was collected by filtration, washed with water followed by MeOH and acetone, and dried in a vacuum oven to give 0.78 g (88%) of **26** as a light yellow solid, mp 306 °C (decomp); ^{1}H NMR (CF_3COOD, 270 MHz) δ 2.77 (s, 3 H), 3.27 (m, 2 H), 3.31 (m, 2 H), 3.97 (s, 3 H), 6.89 (d, J = 3.3 Hz, 1 H), 7.75 (d, J = 3.0 Hz, 1 H), 8.77 (s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 20.0, 31.6, 34.4, 55.2, 114.7, 129.6, 133.2, 135.3, 138.1, 148.1, 153.6, 153.8, 157.2, 162.0, 162.5, 168.7; IR (KBr) 3236, 3198, 3057, 2953, 2838, 1704 (C=O), 1674, 1604, 1564, 1480, 1292, 1098 cm^{-1}; HRMS calcd for $C_{16}H_{16}N_4O_3S$ 344.0943, found 344.0958; Anal. Calcd for $C_{16}H_{16}N_4O_3S$: C, 55.80; H, 4.68; N, 16.27. Found: C, 55.97; H, 4.65; N, 16.04.

5-[2-(2-Amino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl)ethyl]thiophene-2-carboxylic Acid (27). A mixture of 21 mL of THF/EtOH/water (1:1:1), 0.70 g (2.03 mmol) of **26** and 7 mL of 1 N NaOH was stirred at rt for 3 h and then concentrated under reduced pressure. The residual aqueous solution was acidified with acetic acid to pH ~ 6, and the precipitated solid was collected by filtration, washed with water followed by MeOH and acetone, and dried in a vacuum oven to give 0.64 g (95%) of **27** as a light yellow solid, mp >340 °C (decomp); ^{1}H NMR (CF_3COOD, 270 MHz) δ 2.92 (s, 3 H), 3.42 (m, 2 H), 3.47 (m, 2 H), 7.07 (d, J = 4.0 Hz, 1 H), 7.98 (d, J = 4.0 Hz, 1 H), 8.92 (s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 20.2, 31.9, 34.6, 114.8, 130.0, 132.2, 135.3, 139.7, 148.1,

154.2, 155.3, 157.5, 162.2, 162.6, 170.8; IR (KBr) 3394, 3315, 3075 (br, O-H), 2959, 2934, 1672 (C=O), 1635, 1604, 1541, 1465, 1263, 1197 cm^{-1}; FABMS *m/z* 331 (MH^+, base), 307, 289.

5-{2-[2-Acetylamino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl]ethyl}-thiophene-2-carboxylic Acid (28). A solution of 0.58 g (1.76 mmol) of **27** and 35 mg of 4-dimethylaminopyridine in 15 mL of hot acetic anhydride was heated under gentle reflux for 3 h, cooled to rt, and concentrated under reduced pressure. The solid which separated upon addition of 20 mL of ether was collected by filtration, washed with ether, dried in the air, and then dissolved in 15 mL of 0.5 N NaOH. Filtration and addition to the filtrate of acetic acid to ~pH 6 gave a precipitate which was collected by filtration, washed with water and ether, and dried in a vacuum oven to give 0.47 g (72%) of **28** as a yellow solid, mp 252-254 °C; ^1H NMR (CF_3COOD, 270 MHz) δ 2.54 (s, 3 H), 2.94 (s, 3 H), 3.40 (m, 4 H), 7.00 (d, J = 4.0 Hz, 1 H), 7.91 (d, J = 4.0 Hz, 1 H), 8.97 (s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 20.3, 25.4, 31.8, 34.7, 117.7, 129.9, 132.2, 137.3, 139.6, 148.0, 154.7, 154.8, 155.1, 162.3, 163.2, 170.8, 179.7; IR (KBr) 3436, 3218, 3159 (br, O-H), 2960, 2873, 1686 (C=O), 1621, 1560, 1463, 1262 cm^{-1}; FABMS *m/z* 373 (MH^+), 346, 307 (base), 289; Anal. Calcd for $C_{17}H_{16}N_4O_4S$: C, 54.83; H, 4.33; N, 15.04. Found: C, 54.73; H, 4.37; N, 14.79.

Diethyl *N*-{5-[2-[2-Acetylamino-3,4-dihydro-4-oxo-7-methylpyrido[2,3-*d*]pyrimidin-6-yl]ethyl]thienoyl}-L-glutamate (29). A mixture of **28** (0.45 g, 1.2 mmol), 0.25 g (2.5 mmol) of *N*-methylmorpholine and 0.26 g (1.5 mmol) of 2-chloro-4,6-dimethoxy-1,3,5-triazine in 25 mL of DMF at 0 °C was stirred at 0 °C for 2 h. An additional 0.25 g (2.5 mmol) of *N*-methylmorpholine and 0.35 g (1.72 mmol) of diethyl L-glutamate were then added, and the reaction mixture was stirred at 0 °C for 2 h and at rt overnight. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4 and purified on a silica gel column (elution with 2.5% MeOH in $CHCl_3$) to give 0.63 g (94%) of **29** as a yellow solid, mp 110-116 °C, along with 0.15 g of 2-hydroxy-4,6-dimethoxy-1,3,5-triazine; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.23 (t, J = 7.2 Hz, 3 H), 1.30 (t, J = 7.2 Hz, 3 H), 2.14 (m, 1 H), 2.27 (m, 1 H), 2.38 (s, 3 H), 2.48 (dt, J = 5.6 Hz, J = 7.4 Hz, 2 H), 2.59 (s, 3 H), 3.08 (m, 2 H), 3.19 (m, 2 H), 4.11 (q, J = 7.2 Hz, 2 H), 4.23 (q, J = 7.2 Hz, 2 H), 4.73 (ddd, J = 7.6 Hz, J = 7.6 Hz, J = 4.6 Hz, 1 H), 6.74 (d, J = 3.6 Hz, 1 H), 7.03 (d, J = 7.6 Hz, 1 H), 7.38 (d, J = 3.9 Hz, 1 H), 8.24 (s, 1 H), 12.26 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 14.0 (two carbon peak), 22.9, 24.5, 27.0, 30.1, 30.5, 33.7, 52.2, 60.7, 61.7, 113.0, 125.6, 128.5, 132.1, 135.1, 136.3, 146.1, 156.3, 159.7, 160.9, 161.5, 165.0, 172.0, 173.1, 173.9; IR (KBr) 3164, 3106, 2978, 2935, 1735 (C=O), 1684 (C=O), 1628, 1563, 1476, 1374, 1258 cm^{-1}; FABMS *m/z* 558 (MH^+, base), 460, 355, 307, 289.

Diethyl *N*-{5-[2-[2-Acetylamino-3,4-dihydro-4-oxo-7-methyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl]ethyl]thienoyl}-L-glutamate (30). To a solution of **29** (0.55 g, 0.99 mmol) and 0.13 g of 2-hydroxy-4,6-dimethoxy-1,3,5-triazine, obtained as the crude product mixture as described above, in 50 mL of acetic acid was added 0.34 g (1.5 mmol) of PtO_2. Hydrogenation was

carried out in a Parr apparatus at 50 psi of H_2 and rt for 24 h. An additional equivalent of PtO_2 was added, and the hydrogenation was continued for an additional 24 h. After filtration through Celite, the solvent was removed under reduced pressure and the residue was purified on a silica gel column (elution with 2% MeOH in $CHCl_3$) to give 0.45 g (81%) of **30** as a light yellow solid, mp >190 °C (decomp). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.09 (d, J = 6.6 Hz, 3 H), 1.22 (t, J = 7.2 Hz, 3 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.52-1.71 (m, 2 H), 1.84 (br s, 2 H), 2.08-2.32 (m, 2 H), 2.26 (s, 3 H), 2.45 (m, 2 H), 2.60 (m, 1 H), 2.78-2.97 (m, 2 H), 3.50 (m, 1 H), 4.10 (q, J = 7.2 Hz, 2 H), 4.22 (q, J = 7.2 Hz, 2 H), 4.76 (ddd, J = 7.9 Hz, J = 7.6 Hz, J = 5.0 Hz, 1 H), 5.81 (s, 1 H), 6.74 (d, J = 3.3 Hz, 1 H), 7.01 (d, J = 7.6 Hz, 1 H), 7.37 (d, J = 3.6 Hz, 1 H), 10.24 (br s, 1 H), 11.33 (br s, 1 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 15.2 (two carbon peak), 17.3, 23.2, 25.6, 29.2, 30.2, 33.6, 34.4, 35.7, 53.4, 56.4, 66.2, 67.2, 93.6, 129.3, 134.7, 135.2, 150.8, 156.0, 156.5, 165.3, 168.7, 177.4, 179.5, 180.0; IR (KBr) 3339, 3251, 2977, 2933, 1736 (C=O), 1648 (C=O), 1573, 1472, 1376, 1259 cm^{-1}; FABMS *m/z* 562 (MH^+, base), 460, 359, 307.

***N*-{5-[2-(2-Amino-3,4-dihydro-4-oxo-7-methyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)ethyl]thienoyl}-L-glutamic Acid (9).** A solution of **30** (0.35 g, 0.62 mmol) in 12 mL of 2:1 THF/water and 6 mL of 1 N NaOH was stirred at rt for 4 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure and acidified with acetic acid to pH ~ 6. The precipitate which separated was triturated with water, collected by filtration, and dried in vacuo to give 0.23 g (80%) of **9** as an off-white solid, mp >190 °C, shrinks at 170 °C; ^{1}H NMR (CF_3COOD, 270 MHz) δ 1.32 (d, J = 6.9 Hz, 3 H), 1.80-2.10 (br m, 3 H), 2.33-2.51 (m, 2 H), 2.61 (m, 1 H), 2.86 (m, 3 H), 3.08 (m, 2 H), 3.94 (m, 1 H), 5.07 (dd, J = 8.6 Hz, J = 4.9 Hz, 1 H), 6.99 (d, J = 3.3 Hz, 2 H), 7.70 (d, J = 3.6 Hz, 2 H); ^{13}C NMR (CF_3COOD, 67.9 MHz) δ 16.4, 22.2, 28.2, 29.7, 32.2, 34.3, 35.6, 53.1, 55.4, 87.2, 128.8, 134.2, 134.7, 152.4, 154.0, 155.9, 162.7, 168.3, 179.3, 182.8; IR (KBr) 3324 (br, O-H), 3109, 2971, 2932, 1701 (C=O), 1645 (C=O), 1547, 1460, 1383, 1247 cm^{-1}; HRFABMS calcd for $C_{20}H_{26}N_5O_6S$ (MH^+) 464.1604, found 464.1609; Anal. Calcd for $C_{20}H_{25}N_5O_6S \cdot 0.5H_2O$: C, 50.84; H, 5.55; N, 14.82. Found: C, 51.12; H, 5.55; N, 14.55.

ACKOWLEDGEMENT

We are endebted to Eli Lilly & Company, Indianapolis, IN, for financial support of this work.

REFERENCES AND NOTES

1. (a) E. C. Taylor, P. J. Harrington, S. R. Fletcher, G. P. Beardsley, and R. G. Moran, *J. Med. Chem.*, 1985, **28**, 914; (b) E. C. Taylor, *J. Heterocycl. Chem.*, 1990, **27**, 1; (c) E. C. Taylor, *Adv. Exp. Med. Biol.*, 1993, **338**, 387.
2. (a) E. C. Taylor, US Patent 5,344,932, Sept. 6, 1994; (b) E. C. Taylor, D. Kuhnt, C. Shih, S. M. Rinzel, G. B. Grindey, J. Barredo, M. Jannatipour, and R. G. Moran, *J. Med. Chem.*, 1992, **35**,

4450. (c) E. C. Taylor, D. Kuhnt, and C. Shih, In *Chemistry and Biology of Pteridines and Folates 1997,* ed. by W. Pfleiderer and H. Rokos, Blackwell Science, Berlin, 1997, p. 83.

3. (a) D. A. Rinaldi, H. A. Burris, F. A. Dorr, J. R. Woodworth, J. G. Kuhn, J. G.; J. R. Eckardt, G. Rodriguez, S. W. Corso, S. M. Fields, C. Langley, G. Clark, D. Faries, P. Lu, and D. D. Van Hoff, *J. Clin. Oncol.*, 1995, **13**, 2842. (b) D. E. Thornton, W. John, P. Loerher, and E. Eisenhauer, In *Chemistry and Biology of Pteridines and Folates 1997,* ed by W. Pfleiderer and H. Rokos, Blackwell Science, Berlin,1997, p. 195.

4. (a) C. Shih, V. J. Chen, L. S. Gossett, S. B. Gates, W. C. MacKellar, L. L. Habeck, K. A. Shackelford, L. G. Mendelsohn, D. J. Soose, V. F. Patel, S. L. Andis, J. R. Bewley, E. A. Rayl, B. A. Moroson, G. P. Beardsley, W. Kohler, M. Ratnam, and R. M. Schultz, *Cancer Res.*, 1997, **57**, 1116. (b) C. Shih, G. P. Beardsley, V. J. Chen, W. J. Ehlhardt, W. C. MacKellar, L. G. Mendelsohn, M. Ratnam, R. M. Schultz, E. C. Taylor, and J. F. Worzella, In *Chemistry and Biology of Pteridines and Folates 1997,* ed.by W. Pfleiderer and H. Rokos, Blackwell Science, Berlin, 1997, p. 181.

5. (a) C. Shih and E. C. Taylor, US Patent 4,882,334, Nov. 21, 1989; (b) L. L. Habeck, T. A. Leitner, K. A. Shackelford, L. S. Gossett, R. M. Schultz, S. L. Andis, C. Shih, G. B. Grindey, and L. G. Mendelsohn, *Cancer Res.*, 1994, **54**, 1021.

6. (a) E. C. Taylor and B. Hu, *Heterocycles*, *1996*, *43*, 323; (b) Subsequent studies on this compound showed that it was a very poor substrate for FPGS (C. Shih, Eli Lilly & Co., Indianapolis, IN, private communcication).

7. E. C. Taylor and P. M. Harrington, *J. Org. Chem.*, 1990, **55**, 3222.

8. (a) E. C. Taylor and S. R. Fletcher, *J. Org. Chem.*, 1984, **49**, 3226. (b) E. Stark and E. Breitmaier, *Tetrahedron*, 1973, **29**, 2209.

9. R. C. Larock, W.-Y. Leung, and S. Stolz-Dunn, *Tetrahedron Lett.*, 1989, **30**, 6629.

10. R. D. Miller and D. R. McKean, *Synthesis*, 1979, 730.

11. Z. J. Kaminski, *Tetrahedron Lett.*, 1985, **26**, 2901.

12. The resulting mixture of diastereomers was not separated, since previous studies have indicated that preliminary but reliable cell growth inhibitory information in this series can be obtained by evaluation of diastereomeric mixtures; see, for example, (a) R. G. Moran, S. W. Baldwin, E. C. Taylor, and C. Shih, *J. Biol. Chem.*, 1989, **264**, 21047; (b) E. C. Taylor and C.-m. Yoon, *J. Org. Chem.*, 1994, **59**, 7096; (c) E. C. Taylor, G. S. K. Wong, S. R. Fletcher, P. J. Harrington, G. P. Beardsley, and C. J. Shih, In *Chemistry and Biology of Pteridines*; ed. by B. A. Cooper and V. M. Whitehead, Walter de Gruyter, Berlin, 1986, p. 61; (d) ref. 1

13. M. E. Jung, W. A. Andrus, and P. L. Ornstein, *Tetrahedron Lett.*, 1977, 4175.

Received, 24th March, 1998