SYNTHESIS OF A PYRIDO[2,3-d]PYRIMIDINE ANALOGUE OF THE MULTITARGETED ANTIFOLATE LY231514

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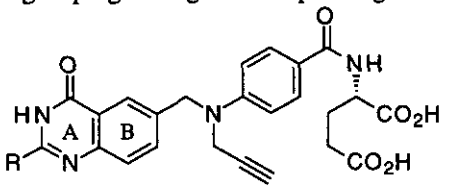
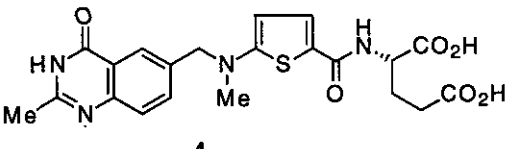
Abstract - Syntheses of pyrido[2,3-d]pyrimidines (**9**) and (**21**), ring-expanded analogues of the antitumor agent LY231514 (**7**), and its 4-amino analog, respectively, are described. Preliminary *in vitro* cell culture evaluation has shown that expansion of the pyrrole ring of the latter two pyrrolo[2,3-d]pyrimidines through introduction of a carbonyl group between positions 6 and 7 results in complete loss of cell growth inhibitory activity.

The *de novo* biosynthetic pathway for the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) is mediated by thymidylate synthase (TS).[1] This enzyme requires the folate coenzyme 5,10-methylene-5,6,7,8-tetrahydrofolic acid as the one-carbon donor and as the requisite reducing agent. Since rapidly dividing cells require an abundant supply of dTMP for the synthesis of DNA, inhibition of TS has been recognized as an attractive chemotherapeutic strategy for the treatment of cancer.[2] A number of TS inhibitors have, in fact, reached clinical trial. One of the earliest was the quinazoline antifolate CB3717 (**1**),[3] which was later withdrawn from further evaluation because of unexpected renal toxicity.[4] Newer TS inhibitors of continuing interest are second-generation quinazoline antifolates; e.g. the 2-desamino-,[5,6] 2-desamino-2-methyl- (ICI198583),[7-9] and 2-desamino-2-methyl thiophene (ZD1694, Tomudex)[10-13] analogues (**2**), (**3**) and (**4**), the non-classical quinazoline (**5**) (AG 337),[14] and the benzoquinazoline (**6**) (1843U89).[15] We recently prepared the pyrrolo[2,3-d]pyrimidine derivative (**7**) (LY231514) during a program directed at the synthesis of inhibitors of folate-dependent enzymes as potential antitumor agents. Initial investigations showed that this compound was a potent inhibitor, following intracellular polyglutamation, of both TS and dihydrofolate reductase (DHFR), and was an extremely effective cytotoxic agent against a broad range of solid tumors (**7** is currently in phase II clinical trials).[16] More recent studies have revealed that **7** is a *multitargeted antifolate* (MTA) exhibiting nanomolar activity against TS, DHFR and glycinamide ribonucleotide formyltransferase (GAR FTase), as well as micromolar activity against aminoimidazolecarboxamide ribonucleotide formyltransferase (AICAR TFase) and both domains of the C-1 tetrahydrofolate synthetase enzyme.[17] Our discovery of this new drug arose from an attempt to prepare an analogue of 5,10-dideazatetrahydrofolic acid[18] [DDATHF (**8**, 6RS), lometrexol (**8**, 6S)]

possessing the rigidity of the bicylic ring system present in **8**, an apparently requisite hydrogen bonding -NH grouping in ring B corresponding to N-8 in **8**, and no chiral center at the position joining ring B to



1; R = NH_2
2; R = H
3; R = Me



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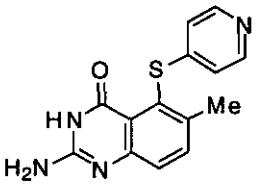

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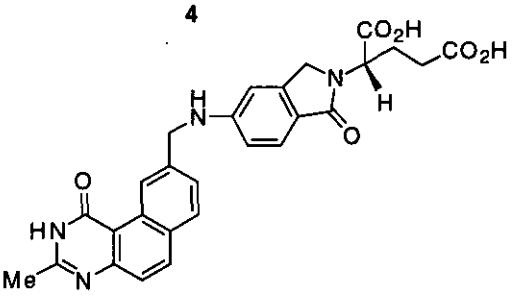

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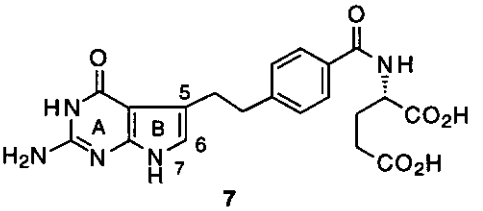

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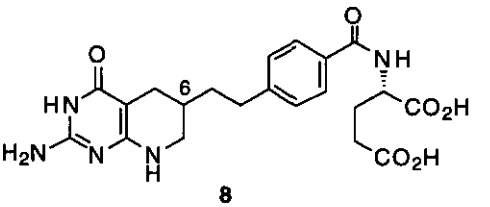

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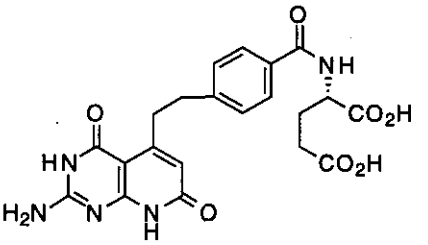

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the side chain (C-5 in **7**; C-6 in **8**). It is striking that other compounds possessing these same general structural features, such as the guanine[19] and the pyrazolopyrimidine[20] analogues of **7**, proved to be ineffective as inhibitors of cell growth.

In this paper we describe the synthesis of the 7-oxopyrido[2,3-d]pyrimidine (**9**) as a new modification of the lead compound (**7**). This molecule retains both the NH grouping in ring B and the sp^2 carbon at the point of side-chain attachment present in LY231514 (**7**), and thus may be viewed as a ring B-expanded analogue of **7** in which a carbonyl group has been inserted between positions 6 and 7 of the pyrrolopyrimidine ring system of **7**.

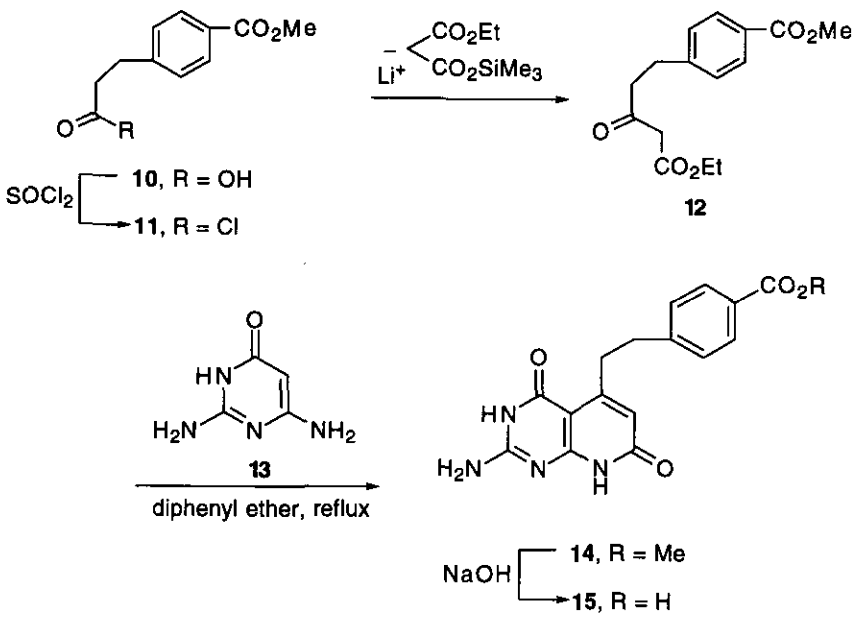
The synthesis of target compound (**9**) was initiated by construction of an appropriately substituted β-keto ester (**12**) (Scheme 1) by a methodology previously developed in our laboratory.[21] The acid chloride (**11**), which was readily prepared from 4-carbomethoxydihydrocinnamic acid (**10**),[22] was

reacted with the lithium enolate of ethyl trimethylsilylmalonate. Aqueous hydrolysis of the crude product followed by decarboxylation then gave **12** in good overall yield. An initial attempt to carry out a Reformatsky reaction of **11** with ethyl bromoacetate and zinc failed to give **12**, as might have been expected from literature precedents.[23]

The requisite bicyclic pyrido[2,3-d]pyrimidine ring system was formed from **12** following the procedure described by Hitchings.[24] Thus, a mixture of **12** and 2,4-diamino-6(1H)-pyrimidinone (**13**) was heated in refluxing diphenyl ether to give the pyridopyrimidine (**14**), which was readily hydrolyzed in refluxing aqueous sodium hydroxide to the corresponding carboxylic acid (**15**). However, the extraordinary insolubility of **15** completely inhibited attempts to carry out peptide coupling with dimethyl glutamate. Even the 2-pivaloyl derivative of **15** was too insoluble to be useful.[25]

These results led us to construct the fully elaborated acyclic precursor (**17**) (Scheme 2). Thus, the benzoyl ester grouping of β-keto ester (**12**) was selectively hydrolyzed by treatment of **12** with two equivalents of lithium hydroxide in aqueous THF (use of excess of the base resulted in considerable decomposition presumably due at least in part to decarboxylation of the over-hydrolyzed product).

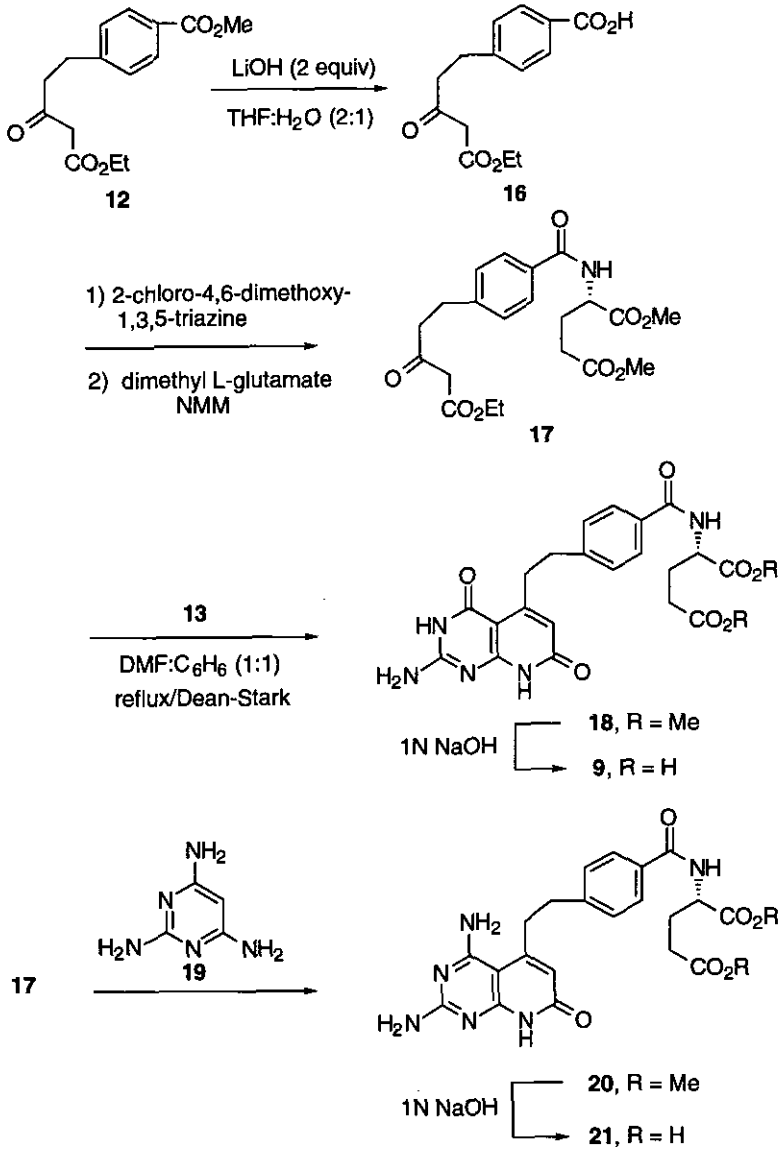
Scheme 1



Subsequent glutamate coupling afforded the requisite precursor (**17**) for attempted annulation of the pyridinone ring.

The conversion of ester (**17**) to pyridopyrimidine (**18**) did not proceed satisfactorily under the conditions originally described by Hitchings (e.g. reflux in diphenyl ether), which resulted in considerable decomposition along with very low yields of the desired product (**18**). Unlike compound

Scheme 2



(**12**), ester (**17**) slowly decomposed at the high temperature needed for the condensation in diphenyl ether. A much milder alternative to Hitching's procedure was therefore developed which involved heating the reaction partners at reflux in benzene-DMF with azeotropic removal of water. Under these conditions, ester (**17**) smoothly underwent condensation with 2,4-diamino-6(1H)-pyrimidinone (**13**) to

give **18** in good yield. Target compound (**9**) was then obtained by saponification of **18** with 1N sodium hydroxide.

By employing the latter sequence of reactions with 2,4,6-triaminopyrimidine and the common precursor (**17**), we have also prepared compound (**21**), a carbonyl-ring-expanded lower homolog of the DHFR inhibitor TNP-351.[26]

Preliminary *in vitro* biological evaluation of compounds (**9**) and (**21**) revealed that neither analogue was an effective inhibitor of cell growth (IC_{50} > 50 μg/mL).

EXPERIMENTAL SECTION

Methyl 3-Oxo-5-(4-carbomethoxyphenyl)pentanoate (12). To a solution of 4-carbomethoxydihydrocinnamic acid[22] (**10**, 2.08 g, 10 mmol) in $CHCl_3$ (30 mL) was added thionyl chloride (0.825 mL, 11.25 mmol) dropwise, and the mixture was heated at reflux for 30 min. After cooling to rt, the solvent and excess thionyl chloride were removed by evaporation under reduced pressure to give acid chloride (**11**). To a cooled solution of ethyl trimethylsilylmalonate (4.08 g, 20 mmol) in THF (100 mL) was added a solution of 1.6 M *n*-butyllithium (12.5 mL, 20 mmol) in hexane at - 78 °C. After the reaction mixture was stirred for 20 min, a solution of the acid chloride (**11**) in THF (20 mL) was added dropwise over 30 min, and the reaction mixture was allowed to warm to rt over 2 h. The reaction was quenched by addition of 50 mL of water, and the mixture was extracted with ether (3x40 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give **12** (2.53 g, 91%) as a yellow oil . This crude product was sufficiently pure to be used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.96 (d, 2 H, *J* = 7.9 Hz), 7.24 (d, 2 H, *J* = 7.9 Hz), 4.13 (q, 2 H, *J* = 7.1 Hz), 3.88 (s, 3 H), 3.41 (s, 2 H), 2.98 - 2.86 (m, 4 H), 1.24 (t, 3 H, *J* = 7.1 Hz). Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.53; H, 6.62.

Methyl 4-[2-(2-Amino-4,7(3H,8H)-dioxopyrido[2,3-d]pyrimidin-5-yl)ethyl]benzoate (14). A mixture of β-keto ester (**12**) (556 mg, 2.0 mmol), 2,4-diamino-6(1H)-pyrimidinone (277 mg, 2.2 mmol), and diphenyl ether (15 mL) was heated at 200 °C until no starting material (ester) was detected by TLC (*ca.* 7 days). The reaction mixture was cooled to rt, and the precipitated solid was collected by filtration and washed with MeOH. This crude product was washed with boiling water (3x15 mL) (to remove unreacted 2,4-diamino-6(1H)-pyrimidinone) and dried to give **14** (468 mg, 69%) as a brown solid; mp >260 °C; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 12.10 (s, 1 H), 11.05 (s, 1 H), 7.88 (d, 2 H, *J* = 8.0 Hz), 7.03 (d, 2 H, *J* = 8.0 Hz), 6.75 (br s, 2 H), 5.73 (s, 1 H), 3.85 (s, 3 H), 3.04 (m, 2 H), 2.71 (m, 2 H). HR FABMS: calcd for $C_{17}H_{17}N_4O_4$: 341.1250 (M^++H), found 341.1245. Anal. Calcd for $C_{17}H_{16}N_4O_4$: C, 59.98; H, 4.74; N, 16.47. Found: C, 59.70; H, 4.65; N, 16.22.

4-[2-(2-Amino-4,7(3H,8H)-dioxopyrido[2,3-d]pyrimidin-5-yl)ethyl]benzoic Acid (15). A suspension of pyridopyrimidine (**14**) (340 mg, 1.0 mmol) in 1N aqueous sodium hydroxide (5 mL) was heated at reflux for 30 min. The reaction mixture was cooled to rt and acidified with glacial

acetic acid. The precipitated solid was collected by filtration, washed with water and MeOH, and dried to give **15** (275 mg, 84%); mp >260 °C; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 12.05 (br s, 1 H), 10.94 (br s, 1 H), 7.86 (d, 2 H, J = 8.0 Hz), 7.42 (d, 2 H, J = 8.0 Hz), 6.66 (br s, 2 H), 5.74 (s, 1 H), 3.00 (m, 2 H), 2.68 (m, 2 H). HR FABMS: calcd for $C_{16}H_{15}N_4O_4$: 327.1093 (M^++H), found 327.1087.

Methyl 3-Oxo-5-(4-carboxyphenyl)pentanoate (16). To a solution of β-keto ester (**12**) (2.085 g, 7.5 mmol) in aqueous THF (1:2, 30 mL) was added lithium hydroxide monohydrate (630 mg, 15 mmol) in one portion, and the mixture was stirred for 2 h at rt. The resulting solution was washed with ether (20 mL), carefully acidified to pH 6 by slow addition of 0.2 N HCl, and extracted with ether (2x10 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give acid **16** (1.44 g, 73%) as a white solid. The analytical sample was recrystallized from ether and hexane; mp 125-127 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.00 (d, 2 H, J = 8.3 Hz), 7.28 (d, 2 H, J = 8.3 Hz), 4.17 (q, 2 H, J = 7.0 Hz), 3.43 (s, 2 H), 2.99 - 2.88 (m, 4 H), 1.25 (t, 3 H, J = 7.1 Hz). Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.39; H, 5.83.

Dimethyl [(4-Carbomethoxy)butan-3-on-1-yl]benzoyl-L-glutamate (17). A mixture of acid (**16**) (1.32 g, 5.0 mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (980 mg, 5.25 mmol), and N-methylmorpholine (0.66 mL, 6 mmol) in THF (50 mL) was stirred at rt for 30 min. Dimethyl L-glutamate hydrochloride (1.16 g, 5.5 mmol) and N-methylmorpholine (0.66 mL, 6 mmol) were sequentially added, and the mixture was allowed to stir for 2 h. The resulting white suspension was filtered through a pad of Celite and the filtrate was
concentrated. The residual oil was purified by flash column chromatography using 50% EtOAc and hexanes as eluent to give **17** (1.83 g, 87%) as a thick colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.71 (d, 2 H, J = 8.1 Hz), 7.22 (d, 2 H, J = 8.1 Hz), 7.12 (d, 1 H, J = 7.2 Hz), 4.77 (m, 1 H), 4.14 (q, 2 H, J = 7.1 Hz), 3.74 (s, 3 H), 3.62 (s, 3 H), 3.41 (s, 2 H), 2.93 - 2.86 (m, 4 H), 2.45 (m, 2 H), 2.26 (m, 1 H), 2.13 (m, 1 H), 1.23 (t, 3 H, J = 7.1 Hz). Anal. Calcd for $C_{21}H_{27}NO_8$: C, 59.85; H, 6.46; N, 3.32. Found: C, 59.69; H, 6.52; N, 3.60.

Dimethyl N-[4-[2-(2-Amino-4,7(3H,8H)-dioxopyrido[2,3-d]pyrimidin-5-yl)ethyl]-benzoyl]-L-glutamate (18). A homogeneous solution of **17** (321 mg, 1.0 mmol) and 2,4-diamino-6(1H)-pyrimidinone (126 mg, 1.0 mmol) in DMF (5 mL) and benzene (5 mL) was heated for 3 days at reflux, using a Dean-Stark water trap. After removal of the solvent by evaporation under reduced pressure, the oily residue was triturated with hot MeOH (20 mL). The remaining solid was collected by suction filtration, washed with hot MeOH, and dried under high vacuum to give **18** as a pale brown solid (305 mg, 80%); mp 258-260 °C; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 11.68 (s, 1 H), 10.85 (s, 1 H), 8.69 (d, 1 H, J = 7.3 Hz), 7.80 (d, 2 H, J = 7.9 Hz), 7.36 (d, 2 H, J = 7.9 Hz), 7.13 (br s, 2 H), 5,72 (s, 1 H), 4.44 (m, 1 H), 3.63 (s, 3 H), 3.57 (s, 3 H), 3.14 (m, 2 H), 2.84 (s, 2 H), 2.45 (t, 2 H, J = 7.6 Hz), 2.05 (m, 2 H). Anal. Calcd for $C_{23}H_{25}N_5O_7$: C, 57.14; H, 5.21; N, 14.49. Found: C, 56.93; H, 5.27; N, 14.41.

***N*-[4-[2-(2-Amino-4,7(3H,8H)-dioxopyrido[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic Acid (9).** A suspension of diester (**18**) (115 mg, 0.3 mmol) in 1 N NaOH (1 mL) was

stirred overnight at rt. The resulting clear solution was carefully acidified with glacial HOAc, and MeOH (1 mL) was added with vigorous stirring. The resulting jelly-like suspension was centrifuged and water/MeOH was decanted off. This process was repeated twice with MeOH, and the collected solid was dried under high vacuum to give **9** (57 mg, 66%) as a pale brown solid; mp >260 °C; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 12.31 (s, 1 H), 11.32 (s, 1 H), 8.05 (d, 1 H, J = 6.7 Hz), 7.77 (d, 2 H, J = 8.2 Hz), 7.37 (d, 2 H, J = 8.2 Hz), 6.73 (s, 2 H), 5,78 (s, 1 H), 4.26 (m, 1 H), 3.10 (m, 2 H), 2.80 (m, 2 H), 2.21 (m, 2 H), 1.97 (m, 2 H). HR FABMS: calcd for $C_{21}H_{22}N_5O_7$: 456.1519 (M^++H), found 456.1535. Anal. Calcd for $C_{21}H_{21}N_5O_7$: C, 55.38; H, 4.65; N, 15.38. Found: C, 55.11; H, 4.68; N, 15.21.

Dimethyl *N*-[4-[2-(2,4-Diamino-7(8H)-oxopyrido[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamate (20). This compound was prepared as a pale yellow solid in 76% yield from 2,4,6-triaminopyrimidine (277 mg, 2.2 mmol) and β-keto ester (**17**) (642 g, 2 mmol) by the procedure described above for the preparation of **18**: mp 249-251 °C; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 11.95 (s, 1 H), 8.67 (d, 1 H, J = 7.3 Hz), 7.77 (d, 2 H, J = 7.7 Hz), 7.32 (d, 2 H, J = 7.7 Hz), 6.83 (br s, 2 H), 6.73 (s, 2 H), 5,78 (s, 1 H), 4.42 (m, 1 H), 3.62 (s, 3 H), 3.55 (s, 3 H), 3.17 (m, 2 H), 2.93 (s, 2 H), 2.43 (t, 2 H, J = 7.2 Hz), 2.06 (m, 2 H). Anal. Calcd for $C_{23}H_{26}N_6O_6 \cdot 0.5H_2O$: C, 56.21; H, 5.54; N, 17.10. Found: C, 56.12; H, 5.42; N, 17.23.

***N*-[4-[2-(2,4-Diamino-7(8H)-oxopyrido[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic Acid (21).** This compound was prepared in 83% yield as a yellow solid from diester (**20**) (115 mg, 0.3 mmol) by the procedure described above for the preparation of **9**: mp >260 °C; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 11.32 (s, 1 H), 8.07 (d, 1 H, J = 6.7 Hz), 7.75 (d, 2 H, J = 8.0 Hz), 7.32 (d, 2 H, J = 8.0 Hz), 6.58 (s, 2 H), 6.44 (s, 2 H), 5,78 (s, 1 H), 4.28 (m, 1 H), 3.14 (m, 2 H), 2.93 (s, 2 H), 2.37 (m, 1 H), 2.19 (m, 1 H), 1.95 (m, 2 H). HR FABMS: calcd for $C_{21}H_{23}N_6O_6$: 455.1679 (M^++H), found 455.1696. Anal. Calcd for $C_{21}H_{22}N_6O_6$: C, 55.49; H, 4.88; N, 18.5. Found: C, 55.19; H, 4.99; N, 18.21.

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