SYNTHESES OF A REGIOISOMER OF N-{4-[2-(2-AMINO-4(3H)-OXO-7H-PYRROLO[2,3-d]PYRIMIDIN-5-YL)ETHYL]BENZOYL}-L-GLUTAMIC ACID (LY231514), AN ACTIVE THYMIDYLATE SYNTHASE INHIBITOR AND ANTITUMOR AGENT

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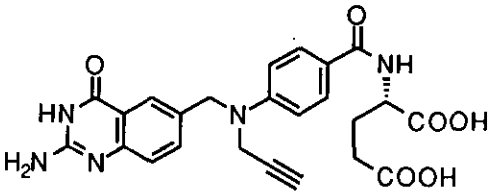
Abstract - Two independent routes to N-{4-[2-(2-amino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-6-yl)ethyl]benzoyl}-L-glutamic acid, a regioisomer of the potent TS inhibitor and antitumor agent LY231514, are described. Preliminary in vitro cell culture evaluation has shown that attachment of the ethanobenzoyl-glutamate moiety of LY231514 to position 6 of the pyrrolo-pyrimidine ring system rather than to position 5 results in complete loss of biological activity.

Thymidylate synthase (TS) is a critically important enzyme which catalyzes the conversion of 2'-deoxyuridine-5'-monophosphate (dUMP) to the corresponding 5-methyl derivative (2'-deoxythymidine-5'-monophosphate, (dTMP).[1] This biochemical methylation utilizes 5,10-methylenetetrahydrofolate both as the one-carbon donating agent and as a concomitant reducing agent. Since this TS-mediated reaction proceeds at a high rate in rapidly proliferating cells, but more slowly in normal cells, TS inhibition has long been recognized as a prime objective for the development of antitumor chemotherapeutic agents.[2] Notable among recently introduced inhibitors of TS are the quinazoline antifolates CB3717 (**1**)[3] and ICI D1694 (**2**),[4] the isoindoline derivative (**3**) (BW1843U89),[5] and the benzindole derivative (**4**) (AG-331).[6]

In the course of our program on the synthesis of inhibitors of folate-based biochemical processes as potential antitumor agents,[7-32] we recently prepared N-{4-[2-(2-amino4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic acid (**5**)[7]



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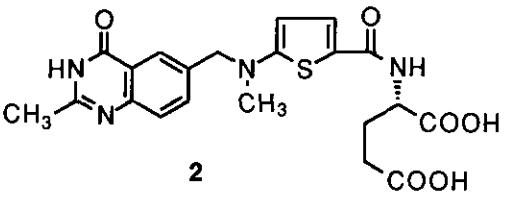

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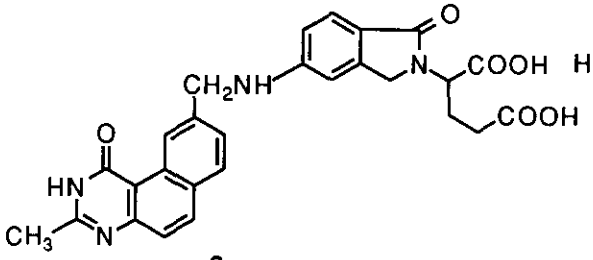

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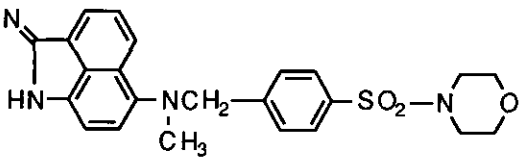

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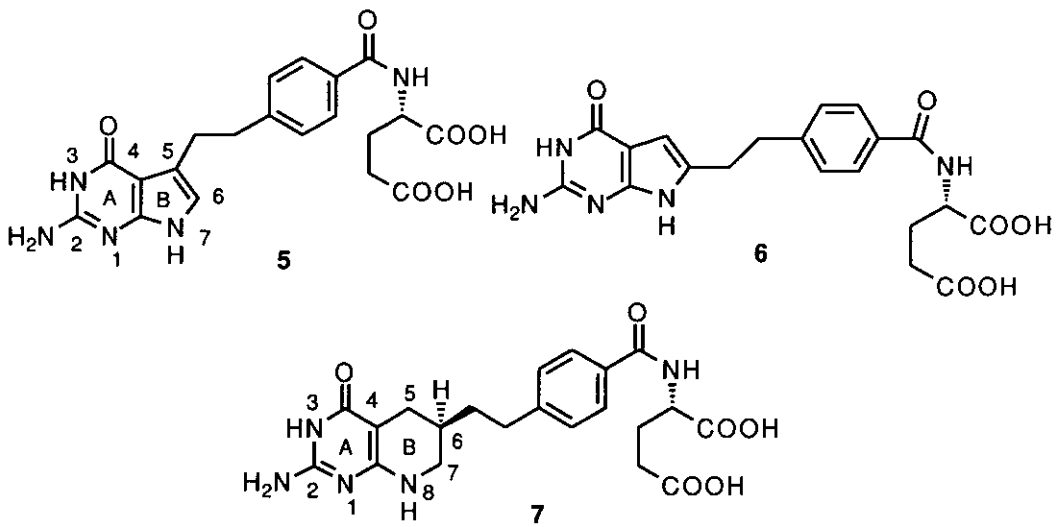
as a model for the quinazoline system in which a pyrrole ring was substituted for the annulated benzene B ring in CB3717, thereby introducing a hydrogen-bonding NH grouping. Indeed, this relatively simple 7-deazaguanine derivative proved not only to have increased water solubility compared to CB3717 itself, but it was also an extraordinarily potent inhibitor of TS, and a very active cytotoxic agent effective against a broad range of solid tumors. The present paper describes two independent syntheses of N-{4-[2-(2-amino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-6-yl)ethyl]benzoyl}-L-glutamic acid (**6**), a regioisomer of **5** in which the bridge between the pyrrolopyrimidine ring and the benzoylglutamate moieties is attached to position 6 rather than to position 5 of the pyrrolo[2,3-d]pyrimidine ring system. An added incentive to explore this structural change was the consideration that **6** may be considered an analog of DDATHF (Lometrexol, **7**)[8] in which the C-7 methylene group of the latter has been deleted, C-6 joined to N-8, and the B ring aromatized.

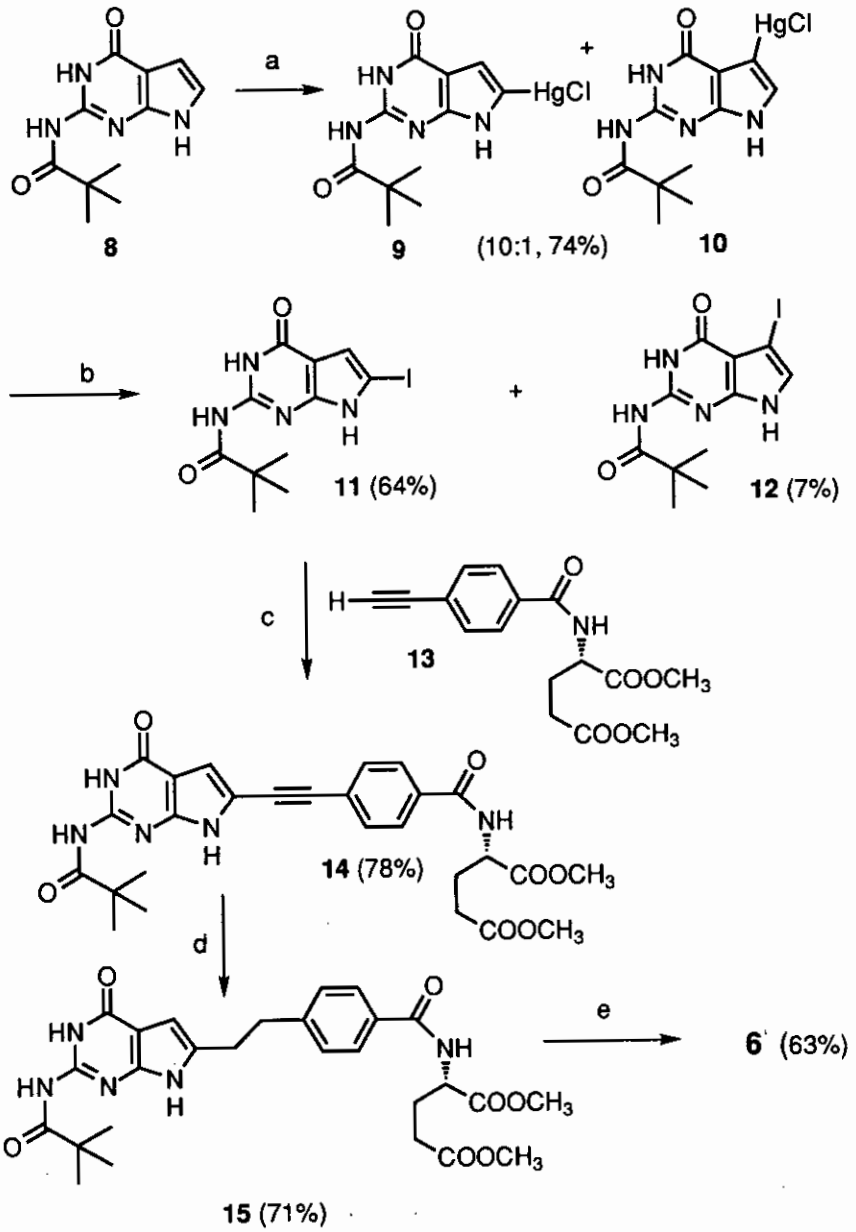
Chloromercuration of 2-pivaloylamino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidine (**8**)[7] yielded a 10:1 mixture of the 6-chloromercuri derivative (**9**) and the 5-chloromercuri derivative (**10**) in 74% overall yield (Scheme 1). Without separation, this mixture of chloromercuri derivatives was treated with iodine in dichloromethane to give the corresponding iodo derivatives (**11** and **12**) from which the desired 6-iodo compound (**11**) was readily separated in 64% yield by column chromatography. A palladium-



catalyzed carbon-carbon coupling reaction of this 6-iodopyrrolopyrimidine derivative (**11**) with dimethyl 4-ethynylbenzoyl-L-glutamate (**13**)[15a] led in 78% yield to the C-6 coupled derivative (**14**), which was then converted to the target analog (**6**) by a conventional series of reduction and deprotection steps.[15,17]

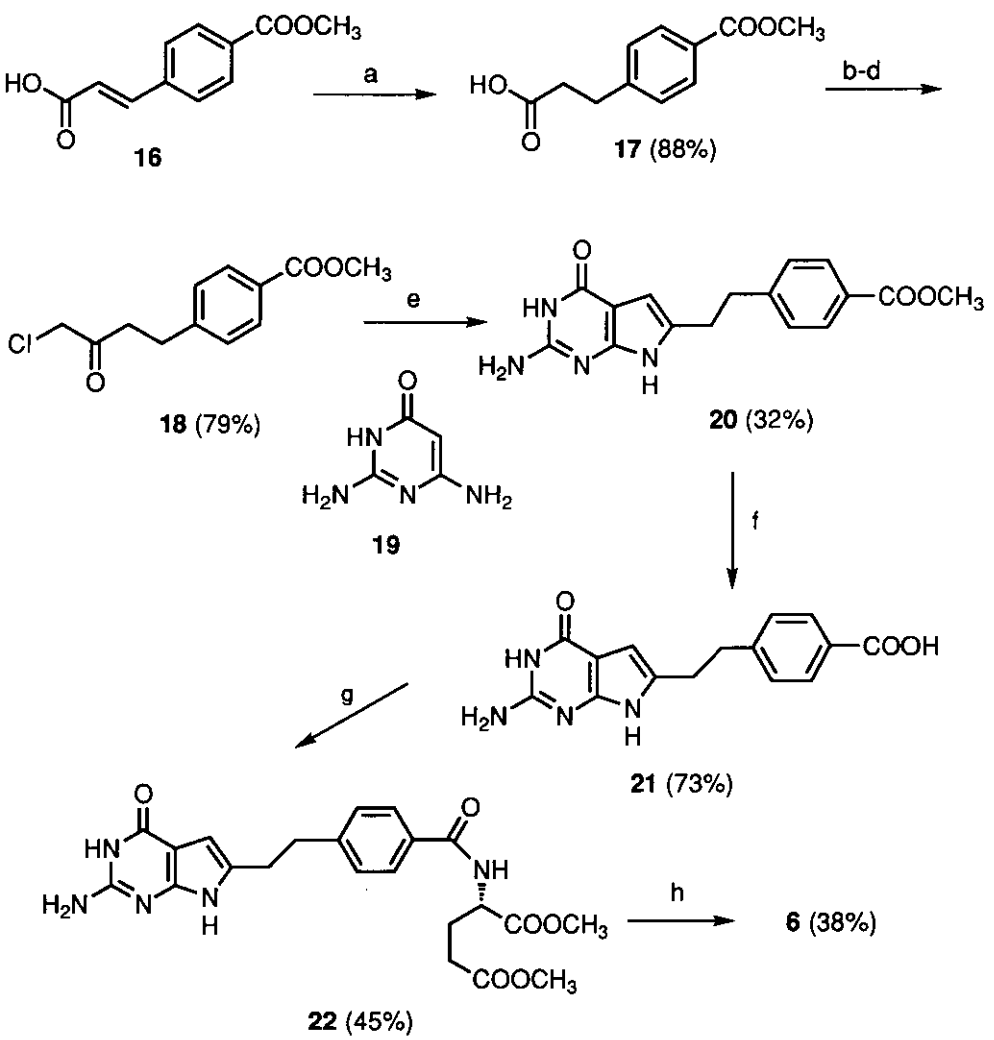
A second synthesis of **6** employed a completely different strategy and commenced with 4-carbomethoxycinnamic acid (**16**) (Scheme 2).[33] Catalytic reduction to the propionic acid (**17**), conversion to the acid chloride and treatment with diazomethane/HCl gave the chloromethyl ketone (**18**)[34] which was condensed with 2,4-diamino-6(1H)-pyrimidinone (**19**) in a mixture of aqueous sodium acetate and methanol to give the 6-substituted pyrrolo[2,3-d]pyrimidine derivative (**20**). The observed regiochemistry of this ring annulation reaction is a consequence of initial

Scheme 1



(a) $Hg(OAc)_2$, NaCl; (b) I_2; (c) $Pd(PPh_3)_4$, CuI, $N(C_2H_5)_3$; (d) Pd/C, H_2; (e) 1 N NaOH.

Scheme 2



(a) Pd/C, H_2; (b) $SOCl_2$; (c) CH_2N_2; (d) HCl; (e) NaOAc, CH_3OH;
(f) 1 N NaOH; (g) 4-methylmorpholine, 2,4-dimethoxy-6-chloro-1,3,5-triazine, dimethyl L- glutamate hydrochloride; (h) 1 N NaOH.

alkylation at the pyrimidine 5-position, followed by intramolecular cyclization. The 4-carbomethoxy grouping in **20** was converted to the corresponding acid (**21**); coupling with dimethyl L-glutamate hydrochloride and final saponification then gave **6**, identical in every respect with the material prepared by the first synthetic approach described above.

Biological evaluation of **6** indicated that it was an extremely poor TS inhibitor of cell growth (IC_{50} > 20 μg/ml). This is a particularly interesting result since **6** actually more closely resembles CB3717 in structure than does the extremely active regioisomer (**5**) (where the sidechain is separated from the pyrimidine ring by only one sp^2 carbon rather than by two sp^2 carbons).

The close structural resemblance of the 5,6-*dihydro* derivative of **6** with DDATHF is particularly striking, and a report on its synthesis and biological evaluation will appear independently.

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EXPERIMENTAL SECTION

6-Chloromercuri-4(3H)-oxo-2-pivaloylamino-7H-pyrrolo[2,3-d]pyrimidine (9) and 5-Chloromercuri-4(3H)-oxo-2-pivaloylamino-7H-pyrrolo[2,3-d]pyrimidine (10): To a solution of **8** (1.0 g, 4.3 mmol) dissolved in glacial acetic acid (100 ml) was added mercuric acetate (2.5 g, 7.9 mmol) which was completely dissolved in glacial acetic acid (100 ml). The mixture was stirred at room temperature for 10 min, poured into sat. NaCl (100 ml), and stirred for 30 min. The precipitate was vacuum filtered, washed with water (20 ml), followed by MeOH (20 ml), and dried. The precipitate was combined with MeOH (150 ml) and stirred at room temperature for 30 min to remove unreacted starting material to give 1.5 g (74%) of a 10:1 mixture of (**9**): ^{1}H Nmr (DMSO-d_6, 300 MHz) δ 11.75 (s, 1 H), 11.05 (s, 1 H), 10.79 (s, 1 H), 6.38 (s, 1 H), 1.20 (s, 9 H); and (**10**): ^{1}H Nmr (DMSO-d_6, 300 MHz) δ 11.76 (s, 1 H), 11.58 (s, 1 H), 11.38 (s, 1 H), 6.94 (d, J = 1.2 Hz, 1 H), 1.20 (s, 9 H). Anal. Calcd for $C_{11}H_{13}N_4O_2HgCl$: C, 28.15; H, 2.79; N, 11.94. Found: C, 28.38; H, 2.89; N, 11.74.

6-Iodo-4(3H)-oxo-2-pivaloylamino-7H-pyrrolo[2,3-d]pyrimidine (11) and 5-Iodo-4(3H)-oxo-2-pivaloylamino-7H-pyrrolo[2,3-d]pyrimidine (12). A mixture of **9** and **10** (2.0 g, 4.26 mmol), iodine (1.08 g, 4.26 mmol) and CH_2Cl_2 (75 ml) was stirred overnight. The solvent was removed under reduced pressure, the residue was washed with 3M $Na_2S_2O_3$ (2 x 50 ml), followed by water (2 x 50 ml), and dried in vacuo. The crude product was purified by column chromatography on silica gel with 3% MeOH/CH_2Cl_2 as the eluent to yield 0.98 g (64%) of **11** as a white solid: mp > 211 °C (decomp.); ^{1}H nmr (DMSO-d_6, 300 MHz) δ 12.08 (s, 1 H), 11.86 (s, 1 H), 10.83 (s, 1 H), 6.57 (s, 1 H), 1.19 (s, 9 H); ms m/z (relative intensity) 360 (M^+, 100), 276 (63), 234 (20); HRms calcd for $C_{11}H_{13}N_4O_2I$ 360.0085, found: 360.0073 and 0.11 g (7%) of **12** as a white solid: mp > 242 °C (decomp.); ^{1}H nmr (DMSO-d_6) δ 11.89 (s, 1 H), 11.79 (s, 1 H), 10.82 (s, 1 H), 7.12 (d, J = 1.8 Hz, 1 H), 1.20 (s, 9 H).[7]

Dimethyl N-{4-[2-(2-Pivaloylamino-4(3H)-oxo-7H-pyrrolo[2,3-d])pyrimidine-6-yl]-ethynyl}-L-glutamate (14). In a 3-neck 200 ml round-bottom flask, equipped with a reflux condenser and nitrogen inlet, **11** (0.70 g, 1.94 mmol), **13** (0.89 g, 2.94 mmol), copper iodide (0.07 g, 0.37 mmol, 20%), triethylamine (0.49 g, 4.8 mmol), tetrakis(triphenylphosphine)palladium(0) (0.113 g, 0.09 mmol, 5%), and DMF (15 ml) were all combined and stirred at 60 °C for 4 h. The solvent was concentrated to 5 ml under reduced pressure, poured into water (100 ml), and triturated. The precipitate was filtered, dried, and purified by column chromatography on silica gel with 1% - 4% MeOH/CH_2Cl_2 as the eluent to yield 0.81 g (78%) of **14** as a pale yellow solid: mp > 210 °C (decomp.); ^{1}H nmr (DMSO-d_6, 300 MHz) δ 12.25 (s, 1 H), 11.93 (s, 1 H), 10.95 (s, 1 H), 8.85 (d, J = 7.7 Hz, 2 H), 7.90 (d, J = 6.9 Hz, 2 H), 7.62 (d, J = 6.9 Hz, 2 H), 6.81 (s, 1 H), 4.45-4.42 (m, 1 H), 3.61 (s, 3 H), 3.55 (s, 3 H), 2.54-2.41 (m, 2 H), 2.10-1.98 (m, 2 H), 1.21 (s, 9 H); ms m/z (relative intensity) 535 (M^+, 100), 451 (21), 360 (24), 277 (21), 150 (10), 84 (28); HRms calcd for 535.2069, found 535.2081. Anal. Calcd for $C_{27}H_{29}N_5O_7$: C, 60.55; H, 5.46; N, 13.08. Found: C, 60.36; H, 5.57; N, 13.23.

Dimethyl N-{4-[2-(2-Pivaloylamino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-6-yl)ethyl]-benzoyl}-L-glutamate (15). A solution of **14** (0.5 g, 0.93 mmol), 5% Pd/C (0.40 g), CH_2Cl_2 (100 ml) and MeOH (100 ml) was stirred for 48 h under 50 psi of hydrogen at room temperature. The solution was filtered through Celite and washed with MeOH (200 ml). The filtrate was reduced to 5 ml under reduced pressure, water (20 ml) was added and the precipitate was filtered. The solid was dried overnight in a vacuum oven to yield 0.36 g (72%) of **15** as an orange solid: mp 135-137 °C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 11.76 (s, 1 H), 11.38 (s, 1 H), 10.73 (s, 1 H), 8.65 (d, J = 7.2 Hz, 1 H), 7.76 (d, J = 7.9 Hz, 2 H), 7.29 (d, J = 7.9 Hz, 2 H), 6.06 (s, 1 H), 4.41-4.38

(m, 1 H), 3.60 (s, 3 H), 3.53 (s, 3 H), 2.94 (t, J = 6.0 Hz, 2 H), 2.92 (t, J = 6.0 Hz, 2 H), 2.53-2.38 (m, 2 H), 2.10-1.99 (m, 2 H), 1.20 (s, 9 H); ms m/z (relative intensity) 539 (M^+, 4), 262 (21), 247 (100), 199 (23), 84 (16); HRms calcd for $C_{27}H_{33}N_5O_7$ 539.2382, found 539.2388. Anal. Calcd for $C_{27}H_{33}N_5O_7$: C, 60.10; H, 6.16; N, 12.98. Found: C, 60.35; H, 6.04; N, 12.71.

N-[4-[2-(2-Amino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-ethyl]benzoyl]-L-glutamic Acid (6). (Scheme 1) A solution of **15** (0.20 g, 0.37 mmol) in 1N NaOH (4 ml) was stirred at room temperature for 3 days. Conc. HCl (3 ml) was added, the solvent was concentrated to 1 ml under reduced pressure, water (10 ml) was added and the white precipitate which formed was collected by filtration, washed with water (2 x 20 ml), acetone (2 x 20 ml), MeOH (2 x 20 ml), CH_2Cl_2 (2 x 20 ml), and hexanes (2 x 20 ml), and dried overnight in a vacuum oven to yield 0.10 g (63%) of **6** as an off-white solid: mp 210-213 °C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 12.6-12.3 (br s, 2 H,), 10.90 (s, 1 H), 10.18 (s, 1 H), 8.50 (d, J = 7.7 Hz, 1 H), 7.75 (d, J = 8.1 Hz, 2 H), 7.28 (d, J = 8.1 Hz, 2 H), 6.06-6.01 (s, 2 H), 5.83 (s, 1 H), 4.38-4.34 (m, 1 H), 2.92 (t, J = 6.0 Hz, 2 H), 2.94 (t, J = 6.0 Hz, 2 H), 2.36-2.01 (m, 2 H), 1.93-1.91 (m, 2 H); FABms calcd for (MH^+) $C_{20}H_{21}N_5O_6$ 428.1570, found 428.1554. Anal. Calcd for $C_{20}H_{21}N_5O_6$: C, 56.20; H, 4.95; N, 16.39. Found: C, 56.10; H, 4.88; N, 16.15.

(Scheme 2) A suspension of **22** (160 mg, 0.364 mmol) and 1N NaOH (4 ml) was stirred at room temperature for 7 days. The resulting clear solution was neutralized with conc. HCl, the precipitate was collected by filtration, washed with water (2 x 5 ml), and dried in vacuo to give 60 mg (38%) of **6**. Spectral data were identical with those reported above.

3-(4-Carbomethoxyphenyl)propionic Acid (17). A mixture of 4-carbomethoxy-cinnamic acid (**16**)[33] (10.3 g, 50.0 mmol), 5% Pd/C (0.540 g), methanol (250 ml), and acetic acid (5 ml) was hydrogenated at 50 psi for 3 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The crude product was recrystallized from benzene to give 9.1 g (88%) of **17** as a white crystalline solid: mp 114-115 °C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 7.83 (d, J = 8.1 Hz, 2 H), 7.33 (d, J = 8.1 Hz, 2 H), 3.79 (s, 3 H), 2.85 (t, J = 7.5 Hz, 2 H), 2.52 (t, J = 7.5 Hz, 2 H); ms m/z (relative intensity) 208 (M^+, 82), 177 (91), 162 (77), 149 (83), 131 (73); HRms calcd for $C_{11}H_{12}O_4$ 208.0735, found 208.0745. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.46; H, 5.81. Found: C, 63.71; H, 5.95.

1-Chloro-4-(4-carbomethoxyphenyl)-2-butanone (18).[34] A mixture of **17** (10.4 g, 50.0 mmol) and $SOCl_2$ (35 ml) was refluxed for 1.5 h and excess $SOCl_2$ was removed under reduced pressure. The resulting acid chloride was dissolved in ether (50 ml) and added dropwise to a solution of diazomethane (150 mmol, from 45 g of Diazald)

in ether (350 ml) at -5 °C. The reaction mixture was stirred at -5 °C for 1 h and dry HCl was bubbled in for 30 min. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel with 20% ethyl acetate/hexanes as the eluent to give 9.5 g (79%) of **18** as a colorless solid: mp 76-77 °C; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 7.95 (d, J = 8.1 Hz, 2 H), 7.25 (d, J = 8.1 Hz, 2 H), 4.04 (s, 2 H), 3.89 (s, 3 H), 2.92-3.01 (m, AA'BB', J = 6.6 and 5.6 Hz, 4 H); ms m/z (relative intensity) 240 (M^+, 33), 209 (45), 191 (84), 163 (68), 149 (100); HRms calcd for $C_{12}H_{13}O_3$ Cl 240.0553, found 240.0561. Anal. Calcd for $C_{12}H_{13}O_3Cl$: C, 59.89; H, 5.44; Cl, 14.73. Found: C, 59.85; H, 5.53; Cl, 15.10.

Methyl N-4-[2-(2-Amino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-6-yl)ethyl] benzoate (20). A mixture of 2,4-diamino-6(1H)-pyrimidinone (**19**) (1.26 g,10.0 mmol) and sodium acetate (1.64 g, 20.0 mmol) in water (20 ml) was heated at 100 °C with stirring until the solution became clear. To this solution **18** (2.4 g, 10.0 mmol) in methanol (20 ml) was added and the mixture was stirred at 100 °C for 10 days. The solvent was removed under reduced pressure, the residue was washed with water (15 ml), dried, and the crude product was purified by flash chromatography on silica gel with 5% MeOH/CH_2Cl_2 as the eluent to give 1.0 g (32%) of **20** as a pale yellow solid: mp 235-237 °C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 10.88 (s, 1 H), 10.12 (s, 1 H), 7.83 (d, J = 7.6 Hz, 2 H), 7.34 (d, J = 7.6, 2 H), 5.96 (s, 2 H), 5.80 (s, 1 H), 3.79 (s, 3 H), 2.94 (t, J = 7.0 Hz, 2 H), 2.77 (t, J = 7.0 Hz, 2 H); ms m/z (relative intensity) 312 (M^+, 42), 177 (24), 163 (100); HRms calcd for $C_{16}H_{16}N_4O_3$ 312.1222, found 312.1229.

N-4-[2-(2-Amino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-6-yl)ethyl]benzoic Acid (21). A suspension of **20** (1.0 g, 3.2 mmol) in 1N NaOH (7 ml) was heated with stirring at 80 °C for 8 h. The resulting clear solution was cooled to room temperature and neutralized with acetic acid to give 0.7 g (73%) of **21** as a white solid: mp 312-314 °C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 12.6 (br s, 1 H), 10.88 (s, 1 H), 10.17 (s, 1 H), 7.81 (d, J = 6.5 Hz, 2 H), 7.29 (d, J = 6.5 Hz, 2 H), 5.98 (s, 2 H), 5.82 (s, 1 H), 2.69-2.92 (m, 4 H); ms m/z (relative intensity) 298 (M^+, 14), 164 (100), 122 (32); HRms calcd for $C_{15}H_{14}N_4O_3$ 298.1066, found 298.1065.

Dimethyl N-{4-[2-(2-Amino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-6-yl)ethyl]benzoyl}-L-glutamate (22). Under a nitrogen atmosphere, 4-methylmorpholine (0.143 ml, 1.3 mmol) was added to a solution of **21** (298 mg, 1 mmol) in DMF (10 ml). The mixture was stirred at 0 °C while 2,4-dimethoxy-6-chloro-1,3,5-triazine (176 mg, 1.0 mmol) was added, and stirring was continued for 2 h at 0 °C. To the reaction mixture was added 4-methylmorpholine (0.143 ml, 1.3 mmol) and dimethyl L-glutamate hydrochloride (212 mg, 1.0 mmol). The reaction mixture was stirred for an

additional 2 h at 0 °C and for 12 h at room temperature. The DMF was removed under reduced pressure, and the resulting residue was purified by flash chromatography on silica gel with 5% MeOH/CH_2Cl_2 as the eluent to give 0.20 g (44%) of **22** as a pale yellow solid: mp 125-126 °C; ^{1}H nmr (DMSO-*d6*, 300 MHz) δ 10.90 (s, 1 H), 10.32 (s, 1 H), 8.71 (d, *J* = 6.7, 1 H), 7.76 (d, *J* = 7.7 Hz, 2 H), 7.28 (d, *J* = 7.7 Hz, 2 H), 6.19 (s, 2 H), 5.80 (s, 1 H), 4.40-4.38 (m, 1 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 2.99-2.76 (m, 4 H), 2.46-2.22 (m, 2 H), 2.07-1.97 (m, 2 H); HRms calcd for $C_{22}H_{26}N_5O_6$ 456.1883, found 456.1896.

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