Pyrrolo[3,2-*d*]pyrimidine Folate Analogues: "Inverted" Analogues of the Cytotoxic Agent LY231514†

Edward C. Taylor* and Wendy B. Young‡

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

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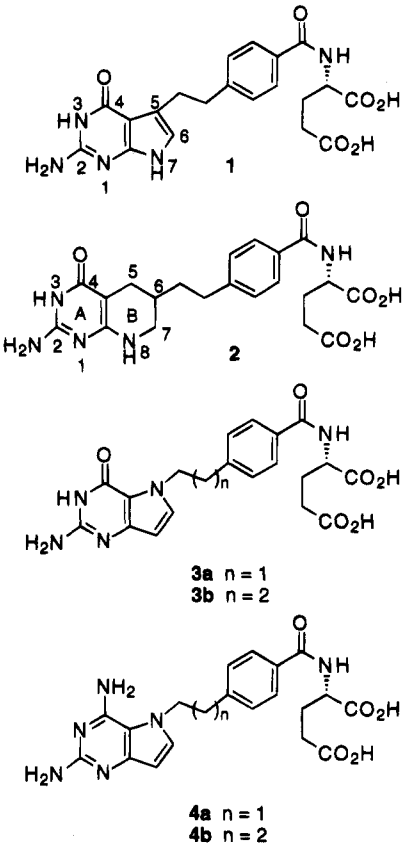
N-{4-[2-(2-Amino-4(3*H*)-oxo-5*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic acid (**3a**) and *N*-{4-[3-(2-amino-4(3*H*)-oxo-5*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl)propyl]benzoyl}-L-glutamic acid (**3b**) were synthesized as potential anticancer agents.

In the course of our program directed toward the design and synthesis of inhibitors of folate-dependent biochemical processes as antitumor agents,[1] we recently synthesized *N*-{4-[2-(2-amino-4(3*H*)-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic acid (**1**, LY231514)[2] as an analogue of DDATHF [(6RS)-**2**][1,3] in which C-5 of the latter was deleted and the B ring aromatized. This compound, which was found to be a potent inhibitor of tumor growth both in vitro and in vivo, primarily as a consequence of inhibition of thymidylate synthase, is currently in Phase II clinical trials.

Pyrrolo[3,2-*d*]pyrimidine **3a** is a structural isomer of LY231514 (**1**) in which the pyrrole ring has been inverted. This modification leaves the distribution of the steric bulk and electronics of the molecule intact, but removes a potential hydrogen bond donor from position 7. By extending the alkyl chain which connects the pyrrole ring with the *N*-benzoylglutamate moiety by one methylene unit, target molecule **3b** more closely approximates the length of the spacer chain in DDATHF (**2**). The synthesis and inhibitory activity against dihydrofolate reductase (DHFR) of the 2,4-diaminopyrrolo[3,2-*d*]pyrimidine derivatives **4a** and **4b** have recently been reported.[4]

The key steps envisioned for the preparation of our target compounds **3a** and **3b** are illustrated in Scheme 1. It was anticipated that an appropriate derivative of pyrrolo[3,2-*d*]pyrimidine **5**[5] could be substituted at N-5 using suitable alkylating reagents (i.e. the hydroxyethyl derivative **6a**, the bromoethyl derivative **6b**, or the iodopropyl derivative **6c**) and the N-alkylated products then converted to the target analogues **3a** and **3b** by previously exploited deprotection and amino acid coupling steps.[1,6–8]



A protected derivative of pyrrolopyrimidine **5**[5] was synthesized in four steps from the readily accessible 2-amino-6-methyl-5-nitro-4(3*H*)-pyrimidinone (**8**).[9] Our synthetic plan involving formylation of the 6-methyl group of **8**, followed by reductive ring closure, is a variant of the Batcho–Leimgruber indole synthesis.[10,11] However, treatment of **8** with DMF dimethylacetal at 60 °C unexpectedly gave the N-methylated derivative **9** in 92% yield (Scheme 2). The stereochemistry of the enamine side chain at position 6 was deduced as (*E*) on the basis of the observed coupling constant of 12.3 Hz for the two olefinic protons. The extraneous methyl group was assigned to N-3 based upon (1) the presence of a carbonyl IR stretch at 1661 cm^{-1}, indicating an intact lactam

† This paper is dedicated to Prof. Dr. Fritz Sauter, the Technical University, Vienna, on the occasion of his 65th birthday.

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(11) Batcho, A. D.; Leimgruber, W. *Organic Syntheses*; Wiley: New York, 1990; Vol. VII, p 34.

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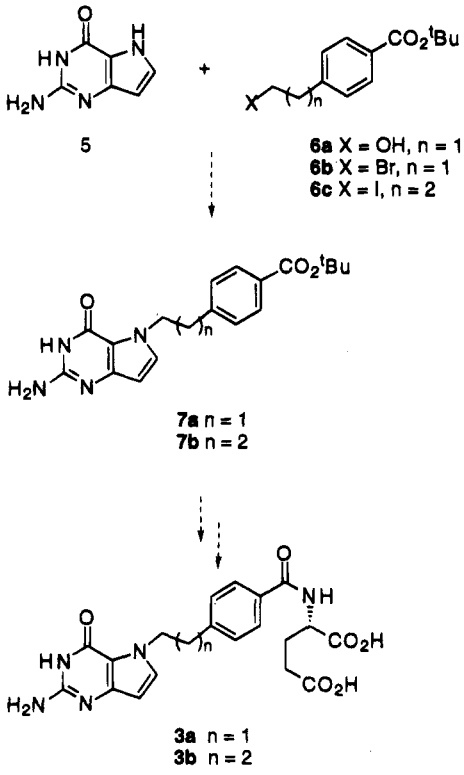
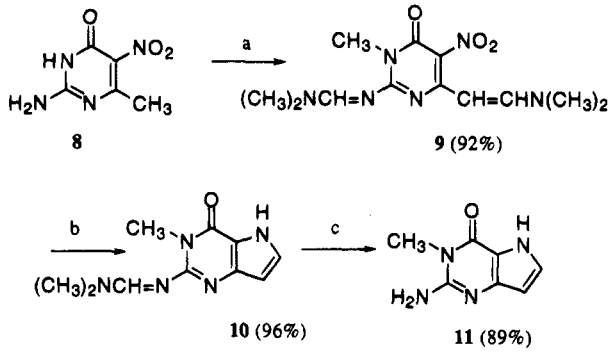
Scheme 1



Scheme 2

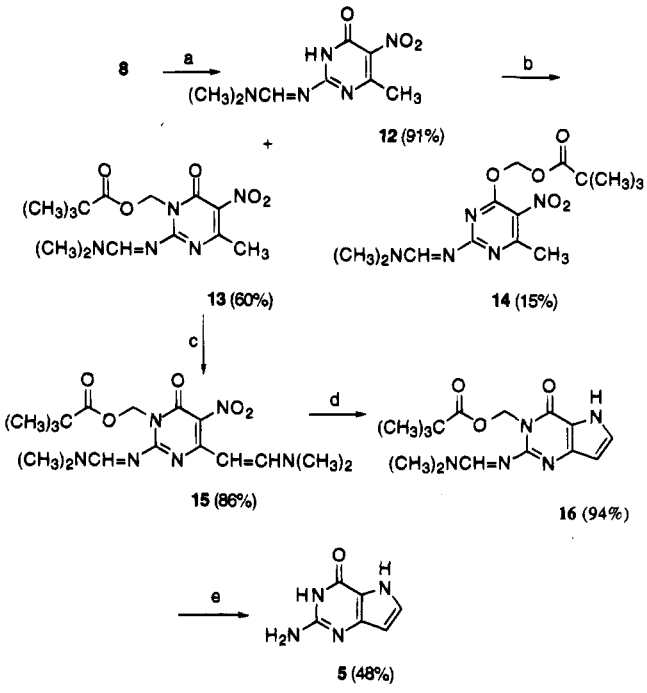


Reagents: a: DMF dimethylacetal, DMF; b: $Na_2S_2O_4$, THF/H_2O; c: 1N NaOH.

functionality, and thus the absence of O-methylation, and (2) the assumption that methylation had probably occurred at the sterically less congested ring nitrogen atom. Nevertheless, the feasibility of the projected pyrrole annulation reaction was readily demonstrated by reduction of **9** with sodium hydrosulfite to give in 96% yield the pyrrolo[3,2-*d*]pyrimidine **10**, which was then deprotected with 1 N NaOH to yield 1-methyl-9-deazaguanine (**11**).

Treatment of **8** with DMF dimethylacetal in CH_2Cl_2 at room temperature for 1 h generated compound **12** (91%, Scheme 3). Reaction of pyrimidine **12** with 1.1 equiv of sodium hydride followed by addition of excess chloromethyl pivalate produced a 4:1 mixture of **13** (60%) and its O-alkylated isomer **14** (15%), separated by column chromatography. The protected pyrimidine **13** was then converted to **15** in 86% yield with DMF dimethylacetal at room temperature.[12] Subsequent reduction of the nitro group of **15** led directly to **16** (94% yield), which was deprotected with 1 N NaOH to form 9-deazaguanine

Scheme 3



Reagents; a: DMF dimethylacetal, CH_2Cl_2; b: NaH, chloromethyl pivalate; c: DMF dimethylacetal, DMF; d: $Na_2S_2O_4$; e: 1N NaOH.

(**5**).[13,14] To the best of our knowledge there are only two previous syntheses of 9-deazaguanine (**5**). The method of Imai[13] is long and low-yielding (10 steps, <1% yield) while the method of Klein[14] failed in our hands. Furthermore, our synthesis produces the fully protected and soluble 2-amino-4(3*H*)-oxo-5*H*-pyrrolo[3,2-*d*]pyrimidine derivative **16** suitable for further transformations.

It was hoped that Mitsunobu coupling[15] of **16** with the hydroxyethyl derivative **6a**[16] would lead to pyrrolopyrimidine **17**. Disappointingly, however, Mitsunobu coupling of alcohol **6a** with the protected pyrrolopyrimidine **16** produced a mixture of the desired product **17** contaminated with a range of side products, and attempts to purify the material were fruitless. We thus turned to attempts to alkylate **16** with the primary bromide **6b**, which was prepared by esterification of 4-carboxyphenethyl bromide[17] with isobutylene/sulfuric acid. Addition of 1.1 equiv of NaH in DMF to pyrrolo[3,2-*d*]pyrimidine **16**, followed by bromide **6b**, gave the desired alkylation product **17** in only 10% yield, in addition to considerable recovered starting material **16** (83%) and a small amount (8%) of *tert*-butyl 4-vinylbenzoate[16,18,19] (8%) (Scheme 4).

(12) Reaction of the O-alkylated isomer **10** with DMF dimethylacetal led to mixtures of unidentified products along with unreacted starting material.

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(15) For a review see: Mitsunobu, O. *Synthesis* **1981**, 1.

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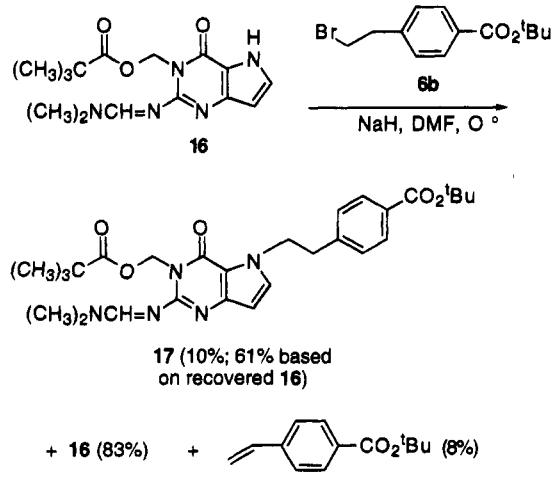
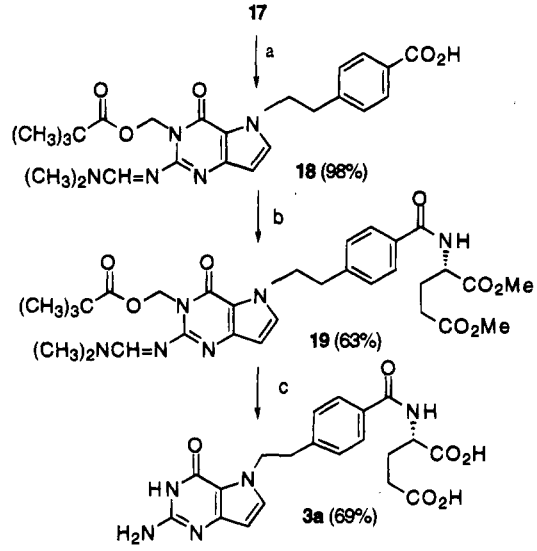
(19) *tert*-Butyl 4-vinylbenzoate, an intermediate in the synthesis of alcohol **6a** by standard hydroboration/oxidation,[16] was prepared by us from formaldehyde and 4-[(*tert*-butyloxycarbonyl)benzyl]triphenylphosphonium bromide (Rosowsky, A.; Forsch, R. A.; Moran, R. G. *J. Med. Chem.* **1989**, *32*, 709) and was thus available as an authentic sample.

Scheme 4

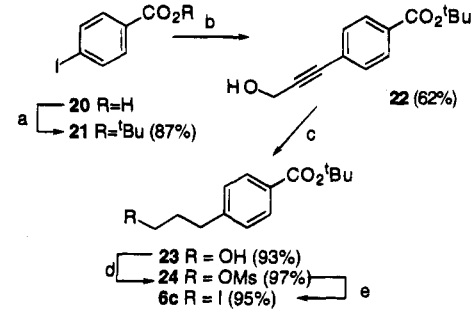


Scheme 5



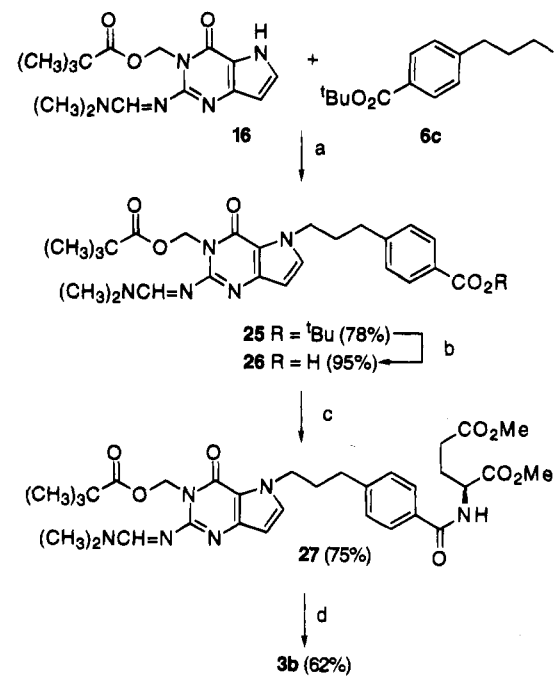
Reagents: a: TFA, CH_2Cl_2; b: N-methylmorpholine, 2-chloro-4,6-dimethoxy-1,3,5-triazine, dimethyl L-glutamate hydrochloride; c: 1N NaOH.

Scheme 6



Reagents: a: isobutylene, H_2SO_4, CH_2Cl_2; b: propargyl alcohol, $Pd(PPh_3)_4$, CuI, NEt_3, CH_2Cl_2; c: H_2, Pd/C, MeOH; d: MsCl, NEt_3; e: NaI, acetone.

Scheme 7



Reagents: a: NaH, DMF; b: TFA, CH_2Cl_2; c: N-methylmorpholine, 2-chloro-4,6-dimethoxy-1,3,5-triazine, dimethyl L-glutamate hydrochloride; d: 1N NaOH.

Despite the fact that all efforts to find conditions which would promote displacement over elimination (variations in solvent, use of crown ethers, different counter-anions, etc.) were unsuccessful, the yield of **17** *based upon recovered starting material* averaged 61%. Since the starting bromide **6b** was readily available, we decided to focus our attention on the final stages of our projected syntheses.

Scheme 5 illustrates the remaining reactions utilized to generate the target molecule **3a**. The *tert*-butyl ester **17** was converted to the free acid **18** with trifluoroacetic acid in CH_2Cl_2 (98% yield). Coupling of **18** with dimethyl L-glutamate using *N*-methylmorpholine and 2-chloro-4,6-dimethoxy-1,3,5-triazine[20] gave **19** in 63% yield. The final target antifolate **3a** was then obtained (69% yield) in the usual way by saponification with 1 N NaOH.

The synthesis of target molecule **3b** proved to be straightforward. The alkyl iodide **6c** was synthesized by a series of reactions (Scheme 6) previously utilized[21] to generate the corresponding methyl ester of **6c**.[22] Thus, commercially available 4-iodobenzoic acid (**20**) was esterified with sulfuric acid in isobutylene/methylene chloride to generate **21** (87%). A palladium-catalyzed coupling of **21** with propargyl alcohol gave the alkyne **22** in 62% yield. Reduction to the primary alcohol **23** (93%), conversion to the mesylate **24** (97%), and subsequent reaction with NaI in acetone then produced iodide **6c** (95%).

Addition of sodium hydride to pyrrolopyrimidine **16**, followed by iodide **6c**, gave **25** in 78% yield (Scheme 7). The free acid **26**, obtained in 95% yield from **25** with trifluoroacetic acid in CH_2Cl_2, was coupled with dimethyl L-glutamate hydrochloride as described above (75% yield), and final saponification then gave the target antifolate **3b** (62% yield).

The two target analogs **3a** and **3b** were tested for *in vitro* inhibition of human CCRF-CEM lymphoblastic leukemic cell growth and found to have IC_{50} values of 0.2 μg/mL and 0.4 μg/mL, respectively, some two orders of magnitude less than those of the lead compounds **1** (0.007 μg/mL) and **2** (0.007 μg/mL). These results suggest

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(21) Gillespie, P., Princeton University, Ph.D. Thesis, 1992.
(22) An alternative route to the iodide **6c** has recently been published; see ref 16.

that the hydrogen-bonding donor N−H at position 7 in LY231514 (1) may be critically important for maximum cell growth inhibitory activity.[23]

Experimental Section

2-Amino-6-methyl-5-nitro-4(3*H*)-oxopyrimidine (8).[9] In a 100 mL, round-bottom flask, open to the atmosphere, 2-amino-6-methyl-4(3*H*)-oxopyrimidine (20.0 g, 0.16 mmol) was dissolved in $H_2SO_{4(concd)}$ (100 mL) and cooled to 0 °C, and $HNO_{3(concd)}$ (17.6 mL) was added dropwise over 30 min. The mixture was warmed to rt, stirred for 3 h, and poured into Et_2O (1500 mL), and the precipitate was filtered and dissolved in 1 N NaOH. $HOAc_{(gl)}$ was added to precipitate product, and the solid was collected by vacuum filtration, washed with H_2O (2 × 10 mL), and air-dried overnight in a vacuum oven to yield 24.3 g (89%) of **8** as a pale yellow solid: mp > 300 °C, (lit.[9] mp > 300 °C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.60 (s, 1 H), 7.0 (br s, 2 H), 2.16 (s, 3 H).

6-[(2(*E*)-Dimethylamino)ethenyl]-2-[[(*N*,*N*-dimethylamino)methylene]amino]-3-methyl-5-nitro-4(3*H*)-oxopyrimidine (9). In a 50 mL round-bottom flask, flushed with nitrogen, were combined **8** (0.85 g, 5.0 mmol), DMF dimethylacetal (6 mL), and $DMF_{(anhyd)}$ (30 mL). The reaction mixture was stirred for 12 h at 60 °C and cooled, the solvent was removed under reduced pressure, Et_2O (5 mL) was added, the mixture was triturated, and the solid was collected by vacuum filtration. The crude product was purified by column chromatography on silica gel with 2% MeOH/CH_2Cl_2 as the eluent to yield 1.35 g (92%) of **9** as an orange solid: mp 232−235 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57 (s, 1 H), 7.88 (d, 1 H, J = 12.3 Hz), 5.61 (d, 1 H, J = 12.3 Hz), 3.47 (s, 3 H), 3.23 (s, 3 H), 3.14 (s, 3 H), 3.00 (br s, 6 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 159.15, 158.25, 157.22, 156.84, 152.60, 124.90, 90.32, 42.23, 35.96, 29.93; IR (KBr) 2921, 1661, 1618, 1598, 1534, 1499, 1471, 1443, 1379, 1323, 1288, 1098, 1076, 851, 795 cm^{-1}; MS *m/z* (relative intensity) 294 (M$^+$, 1), 277 (25), 262 (90), 235 (50); HRMS calcd for $C_{12}H_{18}N_6O_3$ 294.1442, found 294.1449. Anal. Calcd for $C_{12}H_{18}N_6O_3$: C, 48.97; H, 6.17; N, 28.56. Found: C, 48.67; H, 6.23; N, 28.46.

2-[[(*N*,*N*-Dimethylamino)methylene]amino]-3-methyl-4(3*H*)-oxo-5*H*-pyrrolo[3,2-*d*]pyrimidine (10). In a 100 mL round-bottom flask a mixture of **9** (0.75 g, 2.55 mmol), $Na_2S_2O_4$ (2.78 g, 15.98 mmol), and THF/H_2O (2:1, 20 mL) was stirred at rt for 15 min. The solvent was removed under reduced pressure, H_2O (3 mL) was added, the solid was collected by filtration, washed with H_2O (2 × 10 mL), and air-dried, and the product was purified by column chromatography on silica gel with 2% MeOH/CH_2Cl_2 as the eluent to yield 0.54 g (96%) of **10** as a white powder: mp 241−242 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.95 (s, 1 H), 8.50 (s, 1 H), 7.20 (m, 1 H), 6.31 (d, 1 H, J = 1.9 Hz), 3.69 (s, 3 H), 3.15 (s, 3 H), 3.12 (s, 3 H); ^{13}C NMR (MeOD/$CDCl_3$, 300 MHz) δ 156.96, 156.74, 155.21, 144.62, 128.52, 114.95, 102.02, 41.25, 35.25, 30.17; IR (KBr) 3147, 3091, 2971, 2929, 1668, 1612, 1527, 1485, 1422, 1393, 1330, 1105, 1084, 1020, 978, 865, 774, 724, 583 cm^{-1}; MS *m/z* (relative intensity) 219 (M$^+$, 100), 175 (94), 148 (62), 108 (35); HRMS calcd for $C_{10}H_{13}N_5O_1$ 219.1122, found 219.1117.

2-Amino-3-methyl-4(3*H*)-oxo-5*H*-pyrrolo[3,2-*d*]pyrimidine (11). A sealed tube containing a mixture of **10** (250 mg, 1.14 mmol), 1 N NaOH (10 mL), and MeOH (2 mL) was heated at 100 °C for 5 h and cooled, $AcOH_{(gl)}$ was added to pH 7, the volume was reduced to 2 mL, and the product was collected by vacuum filtration and purified by column chromatography on silica gel with 5% MeOH/CH_2Cl_2 as the eluent to yield 170 mg (89%) of **11** as a white powder: 270−274 °C (dec.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.36 (s, 1 H), 7.10 (m, 1 H), 6.21 (s, 2 H), 5.88 (m, 1 H), 3.28 (s, 3 H); ^{13}C NMR (DMSO-d_6, 300 Mz) δ 155.02, 152.34, 145.84, 128.41, 113.08, 101.14, 28.84; IR (KBr) 3443, 3401, 3211, 3084, 1689, 1626, 1534, 1513, 1415, 1161, 767, cm^{-1}; MS *m/z* (relative intensity) 164 (M$^+$, 100), 134 (13), 119 (20), 108 (59), 83 (37); HRMS calcd for $C_7H_8N_4O_1$ 164.0699, found 164.0697.

2-[[(*N*,*N*-Dimethylamino)methylene]amino]-6-methyl-5-nitro-4(3*H*)-oxopyrimidine (12). In a 50 mL round-bottom flask flushed with nitrogen were combined **8** (1.0 g, 5.9 mmol), DMF dimethylacetal (4 mL), and CH_2Cl_2 (10 mL). The reaction mixture was stirred at rt for 5 h, the solvent was removed under reduced pressure, H_2O (5 mL) was added, the mixture was triturated, and the solid was collected by vacuum filtration. The crude product was purified by column chromatography on silica gel with 0.5−1% MeOH/CH_2Cl_2 as the eluent to yield 1.2 g (91%) of **12** as a yellow solid: mp 205−206 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.22 (s, 1 H), 8.69 (s, 1 H), 3.18 (s, 3 H), 3.04 (s, 3 H), 2.24 (s, 3 H); ^{13}C NMR (DMSO-d_6, 270 MHz) δ 160.31, 159.83, 158.89, 156.61, 132.05, 41.21, 35.13, 21.21; IR (KBr) 3182, 3069, 2978, 2929, 2802, 1647, 1541, 1492, 1415, 1344, 1323, 1210, 1090 cm^{-1}; MS *m/z* (relative intensity) 225 (M$^+$, 99), 208 (41), 98 (100), 83 (27); HRMS calcd for $C_8H_{11}N_5O_3$ 225.0863, found 225.0855. Anal. Calcd for $C_8H_{11}N_5O_3$: C, 42.67; H, 4.92; N, 31.10. Found: C, 42.58; H, 5.00; N, 31.25.

2-[[(*N*,*N*-Dimethylamino)methylene]amino]-6-methyl-5-nitro-4(3*H*)-oxo-3-[(pivaloyloxy)methyl]pyrimidine (13) and **2-[[(*N*,*N*-Dimethylamino)methylene]amino]-6-methyl-5-nitro-4-[(pivaloyloxy)methoxy]pyrimidine (14).** In a two-neck 100 mL round-bottom flask flushed with argon were placed NaH (0.34 g, 11.5 mmol, 80% in mineral oil) and $DMF_{(anhyd)}$ (20 mL). To this mixture was added **12** (2.35 g, 10.4 mmol) slowly. The mixture became viscous and was allowed to stir at rt for 1 h. Chloromethyl pivalate (2 mL) was added dropwise over 5 min, and the reaction was stirred for 12 h at rt, after which time it became fluid. Solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (50 mL), extracted with 5% AcOH (1 × 30 mL) and H_2O (1 × 30 mL), dried with $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The crude products were purified by column chromatography on silica gel with CH_2Cl_2−0.5% MeOH/CH_2Cl_2 as the eluent to yield 2.10 g (60%) of **13** as a pale yellow solid: mp 133−134 °C; [^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1 H), 6.21 (s, 2 H), 3.26 (s, 3 H), 3.14 (s, 3 H), 2.37 (s, 3 H), 1.15 (s, 9 H); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 177.25, 161.04, 159.57, 157.73, 155.64, 132.12, 65.27, 41.91, 38.78, 35.75, 26.96, 22.17; IR (KBr) 2964, 2929, 1682, 1626, 1478, 1408, 1323, 1126, 1112, 1070 cm^{-1}; MS *m/z* (relative intensity) 339 (M$^+$, 100), 226 (40), 225 (47), 210 (47); HRMS calcd for $C_{14}H_{21}N_5O_5$ 339.1544, found 339.1538. Anal. Calcd for $C_{14}H_{21}N_5O_5$: C, 49.55; H, 6.24; N, 20.64. Found: C, 49.38; H, 6.38; N, 20.79] and 0.53 g (15%) of **14** as a pale yellow gum: [^{1}H NMR ($CDCl_3$, 300 MHz) d 8.75 (s, 1 H), 6.16 (s, 2 H), 3.23 (s, 3 H), 3.21 (s, 3 H), 2.52 (s, 3 H), 1.17 (s, 9 H); IR (KBr) 2964, 2929, 1739, 1626, 1555, 1485, 1450, 1323, 1105, 1069, 1020 cm^{-1}; MS *m/z* (relative intensity) 339 (M$^+$, 35), 225 (24), 210 (49), 208 (100), 150 (23); HRMS calcd for $C_{14}H_{21}N_5O_5$ 339.1544, found 339.1537].

4-[(2(*E*)-Dimethylamino)ethenyl]-2-[[(*N*,*N*-dimethylamino)methylene]amino]-5-nitro-4(3*H*)-oxo-3-[(pivaloyloxy)-methyl]pyrimidine (15). In a 50-mL round-bottom flask flushed with nitrogen were combined **13** (1.1 g, 3.2 mmol), $DMF_{(anhyd)}$ (10 mL), and DMF dimethylacetal (2 mL). The reaction mixture was stirred for 12 h at rt, the solvent was removed under reduced pressure, 20% ether/hexanes was added, and the solid was filtered and dried under house vacuum. The product was purified by column chromatography on silica gel with CH_2Cl_2−0.5% MeOH/CH_2Cl_2 as the eluent to yield 1.1 g (86%) of **15** as an off-white solid: mp 206−207 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.59 (s, 1 H), 7.97 (d, 1 H, J = 12.2 Hz), 6.18 (s, 2 H), 5.72 (d, 1 H, J = 12.2 Hz), 3.22 (s, 3 H), 3.15 (br s, 3 H), 3.09 (s, 3 H), 2.96 (br s, 3 H), 1.15 (s, 9 H); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 176.94, 157.96, 156.97, 156.11, 154.77, 152.59, 122.74, 89.83, 64.71, 45.20 (br), 41.11, 38.18, 36.6 (br), 34.86, 26.46; IR (KBr) 2957, 2922, 1718, 1661, 1626, 1597, 1506, 1393, 1372, 1287, 1245, 1076, 957, 795 cm^{-1}; MS *m/z* (relative intensity) 394 (M$^+$, 4), 377 (27), 263 (35), 234 (12), 220(20); HRMS calcd for $C_{17}H_{26}N_6O_5$ 394.1967, found 394.1958.

(23) Alkylation of N-7 in LY231514 (1) results in loss of tumor inhibitory activity: Taylor, E. C.; Young, W. B.; Shih, C. J.; Gossett, L. S., unpublished observations. Also, replacement of N-7 in 1 by either sulfur or oxygen leads to loss of activity: Taylor, E. C., Patel, H. H.; Sabitha, G.; Chaudhari, R.; Young, W. B., manuscripts in progress.

Anal. Calcd for $C_{17}H_{26}N_6O_5$: C, 51.77; H, 6.64; N, 21.31. Found: C, 51.57; H, 6.75; N, 21.56.

2-[[(*N*,*N*-Dimethylamino)methylene]amino]-4(3*H*)-oxo-3-[(pivaloyloxy)methyl]-5*H*-pyrrolo[3,2-*d*]pyrimidine (16). In a 100 mL round-bottom flask were combined **15** (0.46 g, 1.17 mmol), $Na_2S_2O_4$ (1.20 g, 6.9 mmol), and THF/H_2O (2:1, 30 mL). The mixture was stirred at rt for 1 h, the solvent was removed under reduced pressure, H_2O (5 mL) was added, and the solid was collected by vacuum filtration and washed with H_2O (2 × 10 mL). The product was purified by column chromatography on silica gel with 2% MeOH/CH_2Cl_2 as the eluent to yield 0.35 g (94%) of **16** as a white powder: mp 267–268 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.91 (s, 1 H), 8.52 (s, 1 H), 7.23 (m, 1 H), 6.40 (s, 2 H), 6.31 (m, 1 H), 3.14 (s, 3 H), 3.05 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 178.34, 156.99, 156,10, 154.22, 145.45, 129.19, 115.04, 103.01, 66.55, 41.51, 39.42, 35.57, 27.71 (3); IR (KBr) 3203, 2964, 2922, 1725, 1668, 1619, 1485, 1337, 1140, 1098, 1027, 964, 781 cm^{-1}; MS *m/z* (relative intensity) 319 (M$^+$, 100), 218 (30), 206 (43), 190 (36), 149 (22), 119 (22), 85 (27), 69 (73); HRMS calcd for $C_{15}H_{21}N_5O_3$ 319.1646, found 319.1660. Anal. Calcd for $C_{15}H_{21}N_5O_3$: C, 56.41; H, 6.63; N, 21.93. Found: C, 56.29; H, 6.75; N, 21.85.

2-Amino-4(3*H*)-oxo-5*H*-pyrrolo[3,2-*d*]pyrimidine (5). In a 50 mL round-bottom flask were combined **16** (200 mg, 0.63 mmol), 1 N NaOH (6 mL) and THF (4 mL). The reaction mixture was stirred at rt for 4 days, the solvent was removed under reduced pressure, H_2O (1 mL) was added, $AcOH_{(gl)}$ was added to pH 5, and the precipitate was removed by filtration and purified by recrystallization from 20% MeOH/EtOAc to yield 45 mg (48%) of **5** as a white solid: mp 310–315 °C dec (lit.[13,14] >300 °C dec); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.41 (s, 1 H), 10.50 (s, 1 H), 7.08 (m, 1 H), 5.90 (m, 1 H), 5.77 (s, 2 H); MS *m/z* (relative intensity) 150 (M$^+$, 98), 133 (14), 108 (34), 78 (100); HRMS calcd for $C_6H_6N_4O$ 150.0543, found 150.0535.

***t*-Butyl 4-(2-Bromoethyl)benzoate (6b).** In a sealed tube 4-carboxyphenethyl bromide[17] (1.93 g, 8.46 mmol) was dissolved in CH_2Cl_2 (8 mL) and cooled to −78 °C. Isobutylene (~30 mL) was bubbled in, $H_2SO_{4(concd)}$ (3 drops) was added, the tube was sealed and warmed to rt, and the mixture was stirred for 24 h. The flask was recooled to −78 °C, the lid was removed, and the tube was warmed to rt to remove excess isobutylene. The remaining solution was poured into H_2O (100 mL), neutralized with 2 N NaOH, and extracted with CH_2Cl_2 (2 × 100 mL), the organic layers were combined, dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel with 5% EtOAc/hexanes as the eluent to yield 2.39 g (88%) of **6b** as a clear liquid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, 2 H, *J* = 8.1 Hz), 7.26 (d, 2 H, *J* = 8.1 Hz), 3.58 (t, 2 H, *J* = 7.4 Hz), 3.21 (t, 2 H, *J* = 7.4 Hz), 1.59 (s, 9 H); IR (neat) 2992, 2971, 2922, 1703, 1612, 1365, 1281, 1253, 1154, 1112, 1020, 844, 759, 696 cm^{-1}; MS *m/z* (relative intensity) 285 (M$^+$, 11), 230 (98), 229 (100), 213 (60), 215 (65), 149 (61), 135 (61), 103 (38), 77 (35), 97 (30); HRMS calcd for $C_{13}H_{17}BrO_2$ 284.0404, found 284.0412.

***t*-Butyl 4-[2-[2-[[(*N*,*N*-Dimethylamino)methylene]amino]-4(3*H*)-oxo-3-((pivaloyloxy)methyl)-5*H*-pyrrolo[3,2-*d*]-pyrimidin-5-yl]ethyl]benzoate (17).** To a mixture of NaH (43 mg, 1.72 mmol) and $DMF_{(anhyd)}$ (10 mL) at 0 °C was added dropwise **16** (500 mg, 1.56 mmol) in DMF (2 mL), and the mixture was stirred for 20 min. Bromide **6b** (530 mg, 1.87 mmol) was added all at once, and the mixture was stirred for 2 h at 0 °C, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel with 1% MeOH/CH_2Cl_2 as the eluent to yield 80 mg (10%) of **17** as a white powder: shrinks 65 °C, melts 120–121 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (s, 1 H), 7.87 (d, 2 H, *J* = 8.2 Hz), 7.14 (d, 2 H, *J* = 8.2 Hz), 6.69 (d, 1 H, *J* = 2.7 Hz), 6.38 (s, 2 H), 6.09 (d, 1 H, *J* = 2.7 Hz), 4.56 (t, 2 H, *J* = 7.0 Hz), 3.18 (t, 2 H, *J* = 7.0 Hz), 3.13 (s, 3 H), 3.04 (s, 3 H), 1.58 (s, 9H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 177.16, 165.21, 155.77, 154.69, 153.44, 144.68, 142.73, 130.94, 129.84, 129.11, 128.33, 112.84, 100.53, 80.32, 65.15, 49.79, 40.37, 38.28, 37.90, 34.45, 27.69 (3), 26.59 (3); IR (KBr) 2971, 2922, 1704, 1661, 1619, 1541, 1492, 1407, 1287, 1161, 1133, 1105 cm^{-1}; MS *m/z* (relative intensity) 523 (M$^+$, 54), 332 (64), 218 (25), 149 (80), 148 (78), 72 (100); HRMS calcd for $C_{28}H_{37}N_5O_5$ 523.2797, found 523.2797. Anal. Calcd for $C_{28}H_{37}N_5O_5$: C, 64.23; H, 7.12; N, 13.38. Found: C, 64.21; H, 7.18; N, 13.23;. Also isolated were 0.42 g (83%) of **16** and 25 mg (8%) of *tert*-butyl 4-vinylbenzoate.[16,18,19]

4-[2-[2-[[(*N*,*N*-Dimethylamino)methylene]amino]-4(3*H*)-oxo-3-[(pivaloyloxy)methyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl]ethyl]benzoic Acid (18). In a 50 mL round-bottom flask flushed with argon were combined **17** (295 mg, 0.56 mmol), TFA (2 mL), and CH_2Cl_2 (4 mL). The mixture was stirred for 2 h, the solvents were removed under reduced pressure, Et_2O (5 mL) was added, the mixture was triturated, the white precipitate was collected by vacuum filtration, and the product was air-dried on a house vacuum overnight to yield 310 mg (98%) of **18** as a white solid: mp 185–186 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.51 (s, 1 H), 8.93 (s, 1 H), 7.93 (d, 2 H, *J* = 8.1 Hz), 7.19 (d, 2 H, *J* = 8.1 Hz), 6.85 (d, 1 H, *J* = 2.7 Hz), 6.32 (d, 2 H, J = 2.7 Hz), 6.27 (s, 2 H), 4.46 (t, 2 H, *J* = 7.3 Hz), 3.33 (s, 3 H), 3.17 (s, 3 H), 3.10 (t, 2 H, J = 7.3 Hz), 1.19 (s, 9 H); ^{13}C NMR ($CDCl_3$/MeOH, 270 MHz) δ 176.96, 167.93, 157.41, 153.21, 152.14, 142.19, 135.09, 132.21, 129.36, 128.33, 128.10, 110.98, 97.19, 64.67, 49.34, 40.81, 38.09, 37.24, 34.84, 26.05; IR (KBr) 3464, 2964, 2936, 2872, 1703, 1668, 1562, 1387, 1189, 1126, 971, 724 cm^{-1}; FABMS calcd for $C_{24}H_{30}N_5O_5$ 468.2247, found 468.2245.

Dimethyl {4-[2-[2-[[(*N*,*N*-Dimethylamino)methylene]-amino]-4(3*H*)-oxo-3-[(pivaloyloxy)methyl]-5*H*-pyrrolo-[3,2-*d*]pyrimidin-5-yl]ethyl]benzoyl}-L-glutamate (19). To a 20 mL round-bottom flask, flushed with argon, were combined **18** (150 mg, 0.27 mmol), *N*-methylmorpholine (2 mL), 2-chloro-4,6-dimethoxy-1,3,5-triazine (49 mg, 0.28 mmol), and CH_2Cl_2 (5 mL), and the mixture was stirred at rt for 1 h. Dimethyl L-glutamate hydrochloride (59 mg, 0.28 mmol) was added, and the mixture was stirred for 12 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel with 1% MeOH/CH_2Cl_2 as the eluent to yield 100 mg (63%) of **19** as an off-white solid: mp 62–64 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (s, 1 H), 7.71 (d, 2 H, *J* = 8.2 Hz), 7.18 (d, 2 H, *J* = 8.2 Hz), 7.00 (d, 1 H, *J* = 7.32 Hz), 6.69 (d, 1 H, *J* = 2.8 Hz), 6.38 (s, 2 H), 6.08 (d, 1 H, *J* = 2.8 Hz), 4.83–4.76 (m, 1 H), 4.55 (t, 2 H, *J* = 7.0 Hz), 3.78 (s, 3 H), 3.65 (s, 3 H), 3.18 (t, 2 H, *J* = 7.0 Hz), 3.12 (s, 3 H), 3.04 (s, 3 H), 2.55–2.40 (m, 2 H), 2.38–2.13 (m, 1 H), 2.12–2.07 (m, 1 H), 1.16 (s, 9 H); MS *m/z* (relative intensity) 624 (M$^+$, 23), 332 (44), 255 (100), 223 (28), 195 (38), 91 (30); HRMS calcd for $C_{31}H_{40}N_6O_8$ 624.2910, found 624.2888.

***N*-{4-[2-(2-Amino-4(3*H*)-oxo-5*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic Acid (3a).** In a 20 mL round-bottom flask were combined **19** (75 mg, 0.12 mmol), 1 N NaOH (4 mL), and THF (1 mL). The solution was stirred at rt for 4 days, the solvent reduced to 1 mL under reduced pressure, $AcOH_{(gl)}$ (5 drops) added, and the precipitate collected by vacuum filtration, washed with H_2O (2 × 2 mL), CH_2Cl_2 (2 × 2 mL), Et_2O (2 × 2 mL), and air-dried on a house vacuum overnight to yield 35 mg (69%) of **3a** as a white solid: mp > 175 °C dec; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 12.3 (br s, 2 H), 10.40 (br s, 1 H), 8.47 (d, 1 H, *J* = 7.6 Hz), 7.73 (d, 2 H, *J* = 8.3 Hz), 7.18 (d, 2 H, *J* = 8.3 Hz), 6.95 (d, 1 H, *J* = 2.6 Hz), 5.77 (d, 1 H, *J* = 2.6 Hz), 5.74 (s, 2 H), 4.40 (t, 2 H, *J* = 7.1 Hz), 4.36–4.29 (m, 1 H), 3.04 (t, 2 H, *J* = 7.1 Hz), 2.32 (t, 2 H, *J* = 7.1 Hz), 2.07–1.86 (m, 2 H); MS *m/z* (relative intensity) 624 (M$^+$, 23), 332 (44), 255 (100), 223 (28), 195 (38), 91 (30); FABMS calcd for $C_{20}H_{22}N_5O_6$ 428.1570, found 428.1575. Anal. Calcd for $C_{20}H_{21}N_5O_6$: C, 56.05; H, 5.18; N, 16.35. Found: C, 55.97; H, 5.01; N, 16.08.

***t*-Butyl 4-Iodobenzoate (21).** In a sealed tube 4-iodobenzoic acid (**20**) (2.90 g, 11.7 mmol) and CH_2Cl_2 (50 mL) were combined and cooled to −78 °C with a dry ice/acetone bath. Isobutylene (~100 mL) was bubbled in, $H_2SO_{4(concd)}$ (3 drops) was added, the tube was sealed and warmed to rt, and the mixture was stirred for 72 h. The flask was recooled to −78 °C, the lid was removed, and the tube was warmed to rt to remove excess isobutylene. The remaining solution was poured into H_2O (100 mL), neutralized with 1 N NaOH, and

extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined, dried with $MgSO_4$, and filtered, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel with 3% EtOAc/hexanes as the eluent to yield 3.10 g (87%) of **21** as a clear liquid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (d, 2 H, J = 8.4 Hz), 7.69 (d, 2 H, J = 8.4 Hz), 1.59 (s, 9 H); MS *m/z* (relative intensity) 304 (M^+, 16), 248 (100), 231 (55), 203 (16), 76 (26); HRMS calcd for $C_{11}H_{13}O_2I$ 303.9962, found 303.9959.

***t*-Butyl 4-(3-Hydroxy-1-propynyl)benzoate (22).** In a 100 mL round-bottom flask flushed with argon and equipped with a reflux condenser were combined **21** (3.00 g, 9.9 mmol), $Pd(PPh_3)_4$ (0.57 g, 0.49 mmol), CuI (0.09 g, 0.49 mmol), NEt_3 (2.51 g, 24.7 mmol), propargyl alcohol (1.66 g, 29.6 mmol), and CH_2Cl_2 (50 mL). The mixture was refluxed for 5 min and cooled, the solvent removed under reduced pressure, and the crude material purified by column chromatography on silica gel with CH_2Cl_2 as the eluent to yield 1.41 g (62%) of **22** as a yellow liquid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (d, 2 H, J = 8.2 Hz), 7.47 (d, 2 H, J = 8.2 Hz), 4.53 (s, 2 H), 1.67 (s, 1 H), 1.59 (s, 9 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 166.01, 132.01, 129.87, 129.87, 127.53, 90.95, 85.24, 82.12, 51.82, 28.72; IR (neat) 3408 (br), 2964, 2922, 2859, 1703, 1598, 1288, 1154, 1112, 1027, 1013, 774 cm^{-1}; MS *m/z* (relative intensity) 232 (M^+, 43), 177 (31), 176 (77), 175 (30), 159 (86), 132 (25), 131 (100), 103 (53), 77 (50); HRMS calcd for $C_{14}H_{16}O_3$ 232.1100, found 232.1111. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.45; H, 7.12.

***t*-Butyl 4-(3-Hydroxy-1-propyl)benzoate (23).** A mixture of **22** (1.38 g, 5.94 mmol), 10% Pd–C (250 mg), and MeOH (75 mL) was shaken under 50 psi of hydrogen for 4 h and then poured through Celite, and the solvent was removed under reduced pressure to yield 1.30 g (93%) of **23** as a clear liquid: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.91 (d, 2 H, J = 8.1 Hz), 7.24 (d, 2 H, J = 8.1 Hz), 3.67 (t, 2 H, J = 6.4 Hz), 2.76 (m, 2 H), 1.89 (m, 2 H), 1.59 (s, 9 H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 166.60, 147.71, 130.15, 128.91, 81.43, 62.27, 34.50, 32.70, 28.78; IR (neat) 3396, 2968, 2924, 2866, 1698, 1604, 1285, 1154, 1103, 849, 762 cm^{-1}; MS *m/z* (relative intensity) 236 (M^+, 8), 181 (61), 180 (46), 164 (21), 163 (95), 162 (99), 136 (38), 135 (53), 118 (43), 117 (100), 91 (53), 77 (33); HRMS calcd for $C_{14}H_{20}O_3$ 236.1413, found 236.1423. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.54. Found: C, 71.14; H, 8.66. This compound, whose spectroscopic data correspond in all respects with those reported for this material prepared via a different route,[16] was carried on to the iodide **6c** as previously described.[16]

***t*-Butyl 4-[3-[2-[[(Dimethylamino)methylene]amino]-3-[(pivaloyloxy)methyl]-4(3*H*)-oxo-5*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl]propyl]benzoate (25).** To a mixture of NaH (12 mg, 0.4 mmol, 80% in mineral oil) and $DMF_{(anhyd)}$ (5 mL), was added **16** (0.12 g, 0.4 mmol) in $DMF_{(anhyd)}$ (2 mL) all at once, the mixture was stirred for 2 h at rt, and **6c** (500 mg, 1.4 mmol) in $DMF_{(anhyd)}$ (3 mL) was added dropwise over 10 min. The mixture was stirred for 2 h, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography on silica gel with 2% MeOH/CH_2Cl_2 as the eluent to yield 157 mg (78%) of **25** as a white powder: mp 124–126 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.59 (s, 1 H), 7.89 (d, 2 H, J = 8.0 Hz), 7.21 (d, 2 H, J = 8.0 Hz), 6.97 (d, 1 H, J = 2.6 Hz), 6.35 (s, 2 H), 6.22 (d, 1 H, J = 2.6 Hz), 4.39 (t, 2 H, J = 6.9 Hz), 3.14 (s, 3 H), 3.04 (s, 3 H), 2.68 (m, 2 H), 2.17 (m, 2 H), 1.58 (s, 9 H), 1.16 (s, 9 H); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 177.57, 165.65, 156.15, 155.04, 153.76, 146.07, 144.79, 130.98, 129.77, 129.49, 128.09, 113.63, 101.19, 80.63, 65.57, 48.17, 40.78, 38.69, 34.83, 32.81, 32.56, 28.11, 27.00; IR (KBr) 3105, 2964, 2922, 1703, 1675, 1619, 1548, 1492, 1281, 1105, 774 cm^{-1}; FABMS calcd for $C_{29}H_{40}N_5O_5$ 538.3029, found 538.3024.

4-[3-[2-[[(*N*,*N*-Dimethylamino)methylene]amino]-4(3*H*)-oxo-3-[(pivaloyloxy)methyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl]propyl]benzoic Acid (26). In a 50 mL round-bottom flask flushed with argon were combined **25** (150 mg, 0.28 mmol), TFA (1 mL), and CH_2Cl_2 (10 mL). The mixture was stirred for 2 h, the solvents were removed under reduced pressure, and the crude material was purified by column chromatography on silica gel with 2% MeOH/CH_2Cl_2 as the eluent to yield 128 mg (95%) of **26** as a white powder: shrinks 130 °C, melts 145–147 °C; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 12.80 (s, 1 H), 8.50 (s, 1 H), 7.79 (d, 2 H, J = 7.9 Hz), 7.34 (d, 1 H, J = 2.6 Hz), 7.25 (d, 2 H, J = 7.9 Hz), 6.13 (s, 2 H), 6.06 (d, 1 H, J = 2.6 Hz), 4.30 (t, 2 H, J = 6.8 Hz), 3.10 (s, 3 H), 2.93 (s, 3 H), 2.57 (m, 2 H), 2.04 (m, 2 H), 1.05 (s, 9 H); ^{13}C NMR ($CDCl_3$/MeOD, 300 MHz) δ 178.57, 169.92, 157.42, 155.11, 154.74, 147.06, 143.08, 132.68, 130.48, 129.24, 128.80, 113.59, 100.83, 66.31, 48.52, 41.47, 39.36, 35.49, 33.31, 33.15, 27.37; IR (KBr) 3422, 2964, 2929, 1710, 1668, 1626, 1605, 1415, 1386, 1203, 1126, 710 cm^{-1}; FABMS calcd for $C_{25}H_{32}N_5O_5$ 482.2403, found 482.2421.

Dimethyl *N*-{4-[3-[2-[[(*N*,*N*-Dimethylamino)methylene]amino]-4(3*H*)-oxo-3-[(pivaloyloxy)methyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl]propyl]benzoyl}-L-glutamate (27). In a 20 mL round-bottom flask flushed with argon were combined **26** (145 mg, 0.30 mmol), *N*-methylmorpholine (2 mL), 2-chloro-4,6-dimethoxy-1,3,5-triazine (34 mg, 0.33 mmol), and CH_2Cl_2 (5 mL). The mixture was stirred at rt for 2 h, dimethyl L-glutamate hydrochloride (70 mg, 0.33 mmol) was added, and the mixture was stirred for 12 h at rt. The solvent was then removed under reduced pressure, and the crude product was purified by column chromatography on silica gel with 1% MeOH/CH_2Cl_2 as the eluent to yield 144 mg (75%) of **27** as a gum which crystallized upon standing: mp 65–67 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (s, 1 H), 7.72 (d, 2 H, J = 8.1 Hz), 7.00 (d, 1 H, J = 10.0 Hz), 6.99 (d, 2 H, J = 8.1 Hz), 6.97 (d, 1 H, J = 2.9 Hz), 6.35 (s, 2 H), 6.19 (d, 1 H, J = 2.8 Hz), 4.79 (m, 1 H), 4.39 (t, 2 H, J = 7.0 Hz), 3.77 (s, 3 H), 3.64 (s, 3 H), 3.12 (s, 3 H), 3.03 (s, 3 H), 2.68 (t, 2 H, J = 8.0 Hz), 2.46 (m, 2 H), 2.30 (m, 1 H), 2.17 (m, 3 H), 1.15 (s, 9 H); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 177.62, 173.59, 172.39, 166.93, 156.24, 155.07, 153.84, 145.51, 144.74, 131.32, 131.04, 128.52, 127.24, 113.66, 101.22, 77.21, 65.62, 52.53, 52.18, 51.85, 48.23, 40.86, 38.74, 34.90, 32.87, 32.52, 30.16, 27.03; IR (neat) 3337, 2943, 2921, 2865, 1724, 1675, 1668, 1618, 1541, 1492, 1429, 1408, 1344, 1238, 1154, 1126, 1105, 1027 cm^{-1}; FABMS calcd for $C_{32}H_{43}N_6O_8$ 639.3142, found 639.3126.

***N*-{4-[3-(2-Amino-4(3*H*)-oxo-5*H*-pyrrolo[3,2-*d*]pyrimidin-5-yl]propyl]benzoyl}-L-glutamic Acid (3b).** In a 20 mL round-bottom flask were combined **27** (70 mg, 0.11 mmol), 1 N NaOH (2.2 mL), and THF (2 mL). The solution was stirred at rt for 5 days, the solvent reduced to 1 mL under reduced pressure, $AcOH_{(gl)}$ (5 drops) added, and the precipitate collected by vacuum filtration, washed with H_2O (3 × 5 mL), CH_2Cl_2 (2 × 10 mL), and acetone (2 × 5 mL), and air-dried on a house vacuum overnight to yield 30 mg (62%) of **3b** as a white solid: mp 184–187 °C dec; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 12.5 (s br, 2 H), 10.50 (s, 1 H), 8.46 (d, 1 H, J = 7.9 Hz), 7.65 (d, 2 H, J = 7.9 Hz), 7.23 (d, 2 H, J = 7.9 Hz), 7.16 (d, 1 H, J = 2.8 Hz), 5.85 (d, 1 H, J = 2.8 Hz), 5.79 (s, 2 H), 4.34 (m, 1 H), 4.21 (t, 2 H, J = 6.8 Hz), 2.56 (m, 3 H), 2.30 (t, 2 H, J = 7.5 Hz), 2.06–1.91 (m, 3 H); FABMS calcd for $C_{21}H_{24}N_5O_6$ 442.1727, found 442.1727. Anal. Calcd for $C_{21}H_{23}N_5O_6$: C, 56.99; H, 5.47; N, 15.83. Found: C, 56.53; H, 5.61; N, 15.64.

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