JOC Article

A New and Efficient Synthesis of Pyrrolo[2,3-*d*]pyrimidine Anticancer Agents: Alimta (LY231514, MTA), Homo-Alimta, TNP-351, and Some Aryl 5-Substituted Pyrrolo[2,3-*d*]pyrimidines

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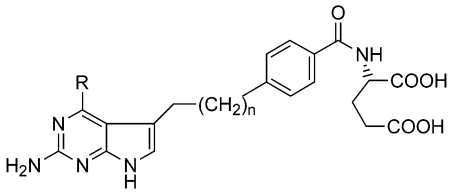
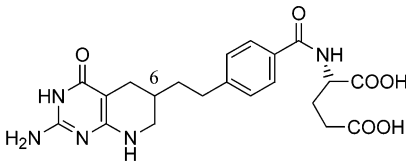
Received July 31, 2003

Alimta, as well as homo-Alimta, a nonbridged analogue of Alimta, and TNP-351 have been prepared by a new method that involves Michael addition of the appropriate 1-nitroalkene with 2,6-diamino-3*H*-pyrimidin-4-one or 2,4,6-triaminopyrimidine, followed by a Nef reaction of the resulting primary nitro Michael adduct. Spontaneous intramolecular cyclization of the resulting aldehyde with the pyrimidine 6-amino group yields the corresponding pyrrolo[2,3-*d*]pyrimidine. A series of previously unknown 5-arylpyrrolo[2,3-*d*]pyrimidines was prepared by the same methodology from the above pyrimidines and nitrostyrenes. It has been found that the intermediate primary nitro Michael adduct can be prepared in a single step by sonication of a mixture of an arylaldehyde, nitromethane, and the 6-aminopyrimidine in acetic acid containing ammonium acetate.

Alimta (pemetrexed) (**1**), N-{4-[2-(2-amino-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic acid disodium salt, is a unique antifolate that shows remarkable activity against a broad spectrum of solid tumors. This compound was initially prepared during a synthetic program to examine the biochemical consequences of removing the lometrexol (**3**) C-6 stereogenic center.[1] Although the antitumor activity of lomextrexol (and DDATHF, **2**) had been shown to be due primarily to inhibition of glycinamide ribonucleotide formyltransferase (GARFT) in the de novo purine biosynthetic pathway,[2] early studies on Alimta (**1**) indicated very surprisingly that its activity was against thymidylate synthase (TS).[1] More recent studies, however, have shown that following intracellular polyglutamation, Alimta (**1**) polyglutamate can reach high intracellular concentrations, and affects folate metabolism dramatically by inhibiting *at least five major folate-dependent enzymes*: thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT), aminoimidazole ribonucleotide formyltransferase (AICARFT), and C-1 tetrahydrofolate synthetase (C1-S).[3] Currently, Phase III clinical trials on Alimta (**1**) have been completed for mesothelioma and for second line treatment of non-small cell lung cancer, and are underway for pancreatic cancer; multiple additional trials of Alimta, both as a single agent and in combination with other oncolytic agents, are in progress for the treatment of a very broad range of solid tumors that includes bladder, breast, cervical, colon, colorectal, esophageal, gastric, genitourinary, head and neck, and renal cancer.[4] Alimta is now available on an expanded access basis (compassionate use) to medically eligible patients with malignant pleural mesothelioma, a devastating lung cancer usually associated with exposure to asbestos. The related 2,4-diamino derivative TNP-351 (**4**), originally synthesized by Miwa and co-workers at Takeda Industries,[5] is a dihydrofolate reductase (DHFR) inhibitor. Both **1** and **4** have a 5−6 bicyclic ring system that differs from the 6−6 bicyclic system of the well-known pteridine, deazapteridine, and quinazoline antifolates, and they represent a new class of inhibitors of folate-dependent enzymes.



1, ALIMTA (disodium salt), R = OH, n = 1
4, TNP-351, R = NH_2, n = 2,



2, DDATHF (6R, S)
3, lometrexol (6R)

During the past decade, several different synthetic strategies for the preparation of Alimta (**1**) and TNP-351 (**4**) have been disclosed by us and others (Schemes 1 and

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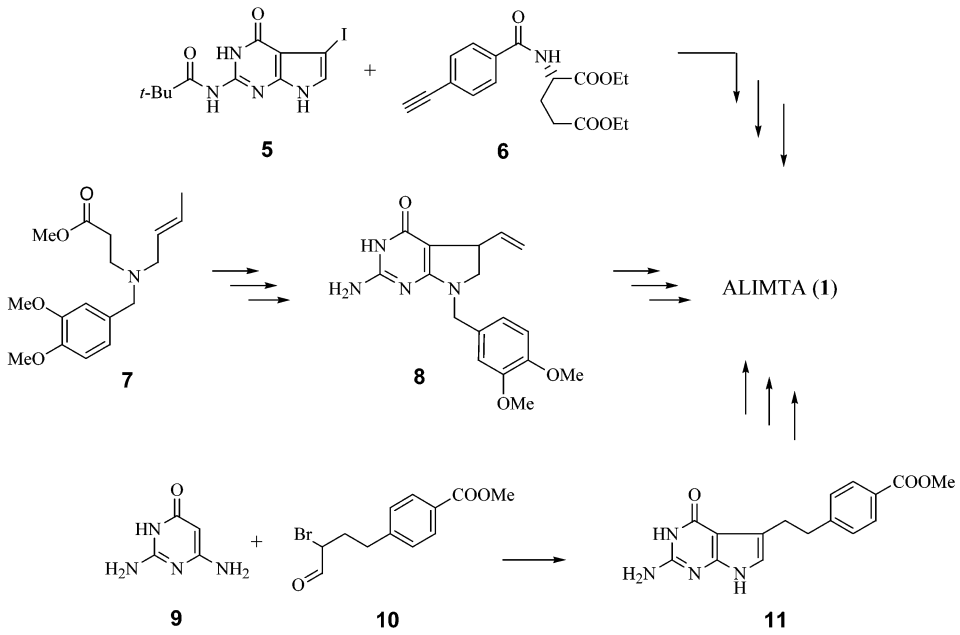
(1) Taylor, E. C.; Kuhnt, D.; Shih, C.; Rinzel, S. M.; Grindey, G. B.; Barredo, J.; Jannatipour, M.; Moran, R. G. *J. Med. Chem.* **1992**, *35*, 4450.

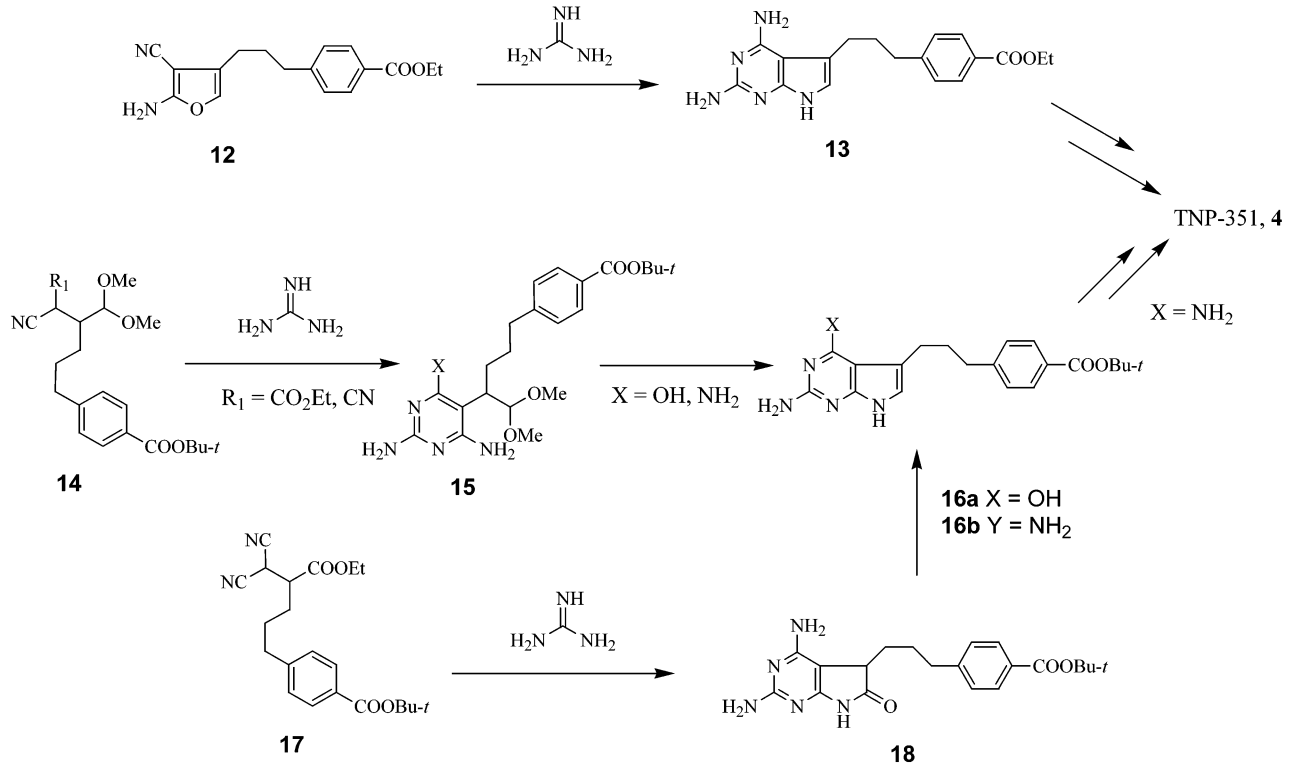
(2) (a) For the original synthesis of DDATHF, see: Taylor, E. C.; Harrington, P. J.; Fletcher, S. R.; Beardsley, G. P.; Moran, R. G. *J. Med. Chem.* **1985**, *28*, 914. (b) Beardsley, G. P.; Moroson, B. A.; Taylor, E. C.; Moran, R. G. *J. Biol. Chem.* **1989**, *264*, 328. (c) Moran, R. G.; Baldwin, S. W.; Taylor, E. C.; Shih, C. *J. Biol. Chem.* **1989**, *264*, 21042. (d) For reviews, see: Taylor, E. C. *J. Heterocycl. Chem.* **1990**, *27*, 1. Taylor, E. C. *Chemistry and Biology of Pteridines and Folates*; Ayling, J. E., Nair, M. G., Baugh, C. M., Eds.; Plenum Press: New York, 1993; p 387.

10.1021/jo030248h CCC: $25.00
Published on Web 11/22/2003

SCHEME 1



SCHEME 2



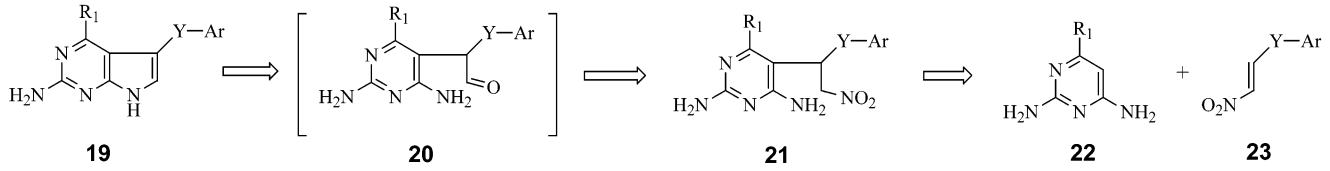
2). In our original synthesis of Alimta (**1**),[1] the complete molecular framework was constructed through a palladium-catalyzed Sonogashira coupling of the 2-amino-5-iodo-3*H*-pyrrolo[2,3-*d*]pyrimidin-4-one derivative **5** with diethyl 4-ethynylbenzoyl-L-glutamate (**6**) followed by reduction of the triple bond and final deprotection (Scheme 1). The starting material (**5**) was prepared from 2-pivaloylamino-3*H*-pyrrolo[2,3-*d*]pyrimidin-4-one by 5,6-diiodination with 2 equiv of *N*-iodosuccinimide (NIS) and

(3) Shih, C.; Chen, V. J.; Gossett, L. S.; Gates, S. B.; MacKellar, W. C.; Habeck, L. L.; Shackelford, K. A.; Mendelsohn, L. G.; Soose, D. J.; Patel, V. F.; Andis, S. L.; Bewley, J. R.; Rayl, E. A.; Moroson, B. A.; Beardsley, G. P.; Kohler, W.; Ratnam, M.; Schultz, R. M. *Cancer Res.* **1997**, *57*, 1116.

(4) For several recent extensive reviews of clinical studies on Alimta (originally referred to as LY231514, and then later as MTA (for MultiTargeted Antifolate)), see: (a) Bunn, P. A., Jr.; Smith, I. E., Guest Editors *Seminars Oncol.* **2002**, *29* (6), Suppl. 18, 1−75. (b) Bertino, J.; Allegra, C.; Calvert, H., Guest Editors *Seminars Oncol.* **1999**, *26* (2), Suppl. 6, 1−111. (c) Hanauske, A.-R.; Chen, V.; Paoletti, P.; Niyikiza, C. *The Oncologist* **2001**, *6*, 363−373.

(5) Miwa, T.; Hitaka, T.; Akimoto, H.; Nomura, H. *J. Med. Chem.* **1991**, *34*, 555.

SCHEME 3



19 **20** **21** **22** **23**

R_1 = OH, NH_2

then zinc-promoted de-iodination at C-6. It was later discovered that compound **5** could be prepared in excellent yield from 2-pivaloylamino-3*H*-pyrrolo[2,3-*d*]pyrimidin-4-one by first reacting with 2 equiv of *N*,*O*-bistrimethylsilylacetamide followed by treatment with 1 equiv of NIS in a one-pot operation.[6] An alternative route to **1** utilized manganic triacetate-induced cyclization of methyl *N*-crotyl-*N*-(3,4-dimethoxybenzyl)malonamide (**7**) to a pyrrolidinone intermediate that was then thiated and annulated with guanidine to 2-amino-7-(3,4-dimethoxybenzyl)-5-vinyl-3,5,6,7-tetrahydropyrrolo[2,3-*d*]pyrimidin-4-one (**8**). Palladium-catalyzed Heck coupling between **8** and diethyl 4-iodobenzoylglutamate was accompanied by a remarkable exocyclic-to-endocyclic double bond rearrangement. Deprotection of the 3,4-dimethoxybenzyl group with H_2SO_4/TFA at room temperature gave the ethyl ester analogue of **11**. This compound was then converted by standard reactions to Alimta (**1**).[7] This otherwise attractive route faltered, however, at the low-yielding (30%) deprotection step. Barnett and co-wokers[8] condensed 2,6-diamino-3*H*-pyrimidin-4-one (**9**) with the α-bromoaldehyde **10** to form 4-[2-(2-amino-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoic acid methyl ester (**11**). Hydrolysis of the methyl ester, glutamate coupling, and deprotection yielded Alimta (**1**) (Scheme 1). The α-bromoaldehyde **10** was originally synthesized from 3-butyn-1-ol by a four-step sequence, which includes a palladium-catalyzed coupling, reduction of the resulting alkyne, oxidation of the primary alcohol to an aldehyde, and bromination.[9] An improved route to **10** involves Heck coupling of 3-buten-1-ol with methyl 4-bromobenzoate to give 4-(4-carbomethoxyphenyl)butanal directly, followed by bromination.[10]

Miwa and co-workers synthesized TNP-351 (**4**) by generating the pyrrolo[2,3-*d*]pyrimidine fused ring system **16** from acyclic precursors **14** and **17**. In the first route, the pyrimidine derivative **15** was generated by reaction of **14** with guanidine, followed by formation of **16** through generation of the pyrrole ring by acidification.[11] In the second route, condensation of **17** with guanidine gave the 6-oxopyrrolo[2,3-*d*]pyrimidine derivative **18** that was reduced to **16** with BH_3—THF in THF.[5] Compound **14** was prepared through a photoinitiated free radical addition of bromomalononitrile to *tert*-butyl 4-(5-methoxy-4-pentenyl)benzoate in methanol, and compound **17** was synthesized by alkylation of malononitrile with ethyl 5-[4-(*tert*-butoxycarbonyl)phenyl]-2-iodopentanoate. Miwa and co-workers also reported the synthesis of **1** by appropriate modifications of both of the above routes. We have exploited a different concept for the synthesis of TNP-351 (**4**) by utilizing a one-pot ring-transformation/ring-annulation cascade through which the 2-amino nitrogen of the furan derivative **12** becomes the pyrrole nitrogen of the diaminopyrrolo[2,3-*d*]pyrimidine **13** (Scheme 2).[12]

We report in this paper new and efficient novel syntheses of Alimta (**1**) and TNP-351 (**4**), and the application of this new method to syntheses of homo and nonbridged analogues of Alimta (**1**) as well as some 5-aryl-substituted pyrrolo[2,3-*d*]pyrimidines. This new strategy couples the classical Nef reaction of primary

(6) Barnett, C. J.; Kobierski, M. E. *J. Heterocycl. Chem* **1994**, *31*, 1181.

(7) Taylor, E. C.; Liu, B. *J. Org. Chem*. **2001**, *66*, 3726.

(8) (a) Barnett, C. J.; Wilson, T. M.; Kobierski, M. E. In *Chemistry and Biology of Pteridiines and Folates 1997*; Pfleiderer, W., Rokos, H., Eds.; Blackwell Science: Berlin, Germany, 1997; p 123. (b) Barnett, C. J.; Wilson, T. M.; Kobierski, M. E. *Org. Process Res. Dev*. **1999**, *3*, 184.

(9) Taylor, E. C.; Harrington, P. M. *J. Org. Chem*. **1990**, *55*, 3222.

(10) Slattery, B. J.; Kjell, D. P. *Abstracts*; 218th ACS National Meeting, New Orleans, Aug. 22—26; American Chemical Society: Washington, DC, 1999; ORGN-130.

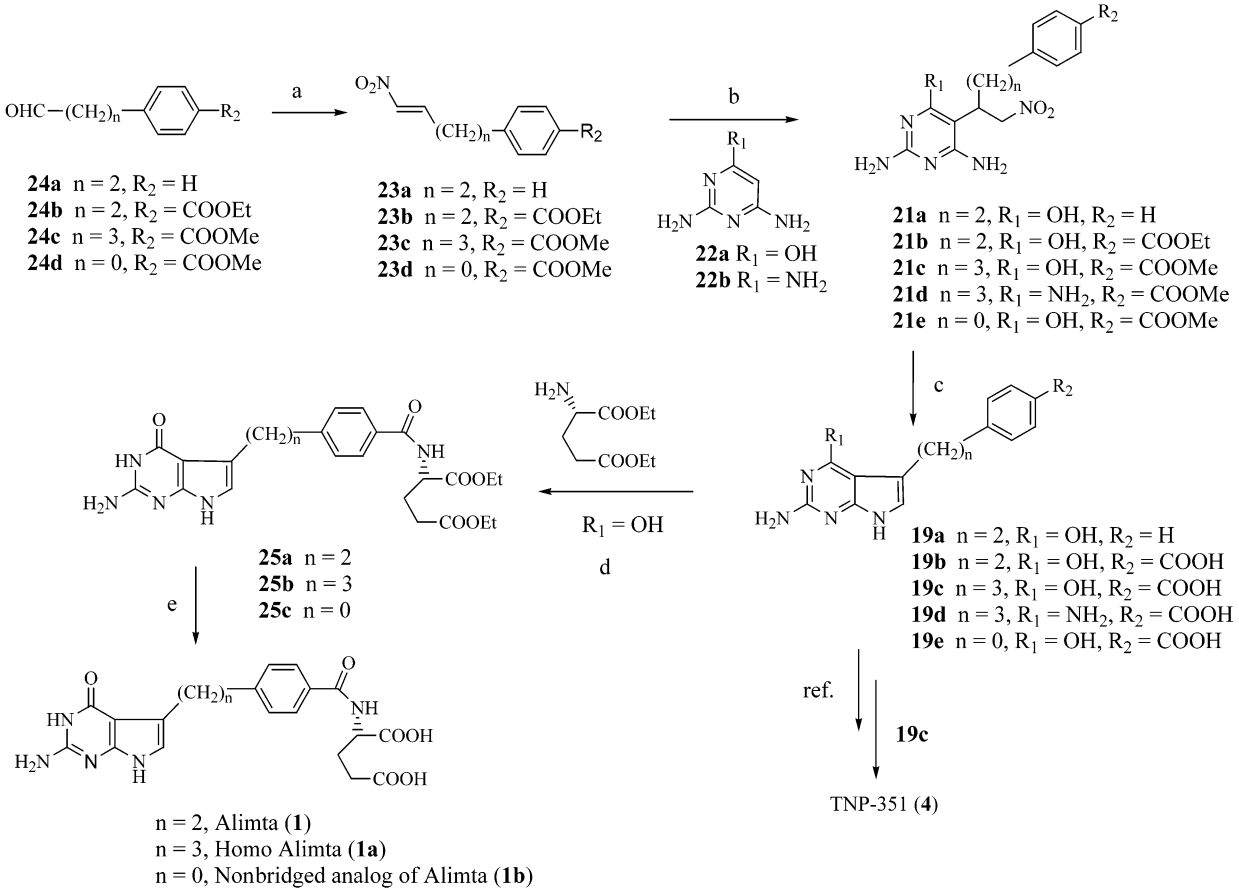
(11) Miwa, T.; Hitaka, T.; Akimoto, H. *J. Org. Chem*. **1993**, *58*, 1696.

(12) (a) Taylor, E. C.; Patel, H. H.; Jun, J.-G. *J. Org. Chem*. **1995**, *60*, 6684. (b) Taylor, E. C.; Mao, Z. *J. Org. Chem*. **1996**, *61*, 7973.

(13) The reaction of 6-amino-3*H*-pyrimidin-4-ones and 4,6-diaminopyrimidines with Michael acceptors to give adducts at position 5, followed by intramolecular cyclization through participation of the pyrimidine 6-amino group, has been well documented in the literature. With α,β-unsaturated carbonyl compounds: (a) Warner, J. C. In *The Chemistry of Heterocyclic Compounds*; Delia, T. J., Taylor, E. C., Eds.; Wiley: New York, 1992; Vol. 24, Part 4, pp 17—25. (b) Anderson, G. L. *J. Heterocycl. Chem*. **1985**, *22*, 1469. (c) Mason, R. B. *J. Org. Chem*. **1977**, *42*, 1919. (d) Broom, A. D.; Shim, J. L.; Anderson, G. L. *J. Org. Chem*. **1976**, *41*, 1095. (e) Koen, M. J.; Gready, J. E. *J. Org. Chem*. **1993**, *58*, 1104. (f) Diaz, E.; Barrios, H.; Nava, J. L.; Enriquez, R. G.; Guzman, A.; Leon, G. L.; Fuentes, J. F.; Fuentes, B. A.; Quintero, A.; Solano, J. D. *J. Heterocycl. Chem*. **1997**, *34*, 1037. (g) Troschuetz, R.; Anders, E. *Arch. Pharm*. **1992**, *325*, 341. (h) Troschuetz, R. *Arch. Pharm*. **1984**, *317*, 709. (i) Cobo, J.; Garcia, C.; Melguizo, M.; Sanchez, A.; Nogueras, M. *Tetrahedron* **1994**, *50*, 10345. (j) Cobo, J.; Sanchez, A.; Nogueras, M. *Tetrahedron* **1998**, *54*, 5753. (k) El-Ahl, A. A. S.; El Bialy, S. A. A.; Ismail, M. A. *Heterocycles* **2001**, *55*, 1315. (l) Bagley, M. C.; Dale, J. W.; Hughes, D. D.; Ohnesorge, M.; Phillips, N. G.; Bower, J. *Synlett* **2001**, 1523. (m) Quiroga, J.; Insuasty, B.; Insuasty, H.; Abonia, R.; Ortiz, A.; Sanchez, A.; Nogueras, M. *J. Heterocycl. Chem*. **2001**, *38*, 339. (n) Bennett, G. B.; Mason, R. B. *J. Org. Chem*. **1977**, *42*, 1919. (o) Hughes, D. D.; Bagley, M. C. *Synlett* **2002**, 1332. (p) Kuwada, T.; Harada, K.; Nobuhiro, J.; Choshi, T.; Hibino, S. *Heterocycles* **2002**, *57*, 2081. (q) Bagley, M. C.; Singh, N. *Synlett* **2002**, 1718. (r) Taylor, E. C.; Dowling, J. E.; Schrader, T.; Bhatia, B. *Tetrahedron* **1998**, *54*, 9507. (s) Taylor, E. C.; Dowling, J. E.; Bhatia, B. *J. Org. Chem*. **1999**, *64*, 441. With activated azo compounds: (t) Taylor, E. C.; Sowinski, F. *J. Am. Chem. Soc*. **1968**, *90*, 1374. (u) Taylor, E. C.; Sowinski, *J. Am. Chem. Soc*. **1969**, *91*, 2143. (v) Yoneda, F.; Sakuma, Y.; Nagamatsu, T.; Mizumoto, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2398. (w) Yoneda, F.; Kawamura, M.; Matsumoto, S.; Higuchi, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2285. With nitrosoolefins: (x) Gibson, C. L.; Ohta, K.; Paulini, K.; Suckling, C. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3025. (y) Lang, A.; Dunn, C.; Paulini, K.; Gibson, C. L.; Rice, M. J.; Suckling, C. J. *Pteridines* **1995**, *6*, 90. With nitrolefins: (z) Prasad, A. S.; Sandhu, J. S.; Baruah, J. N. *J. Heterocycl. Chem*. **1984**, *21*, 1657. (aa) Taylor, E. C.; Liu, B. *Tetrahedron Lett*. **1999**, *40*, 4023. (bb) Taylor, E. C.; Liu, B. *Tetrahedron Lett*. **1999**, *40*, 4027. (cc) Edmont, D.; Williams, D. M. *Tetrahedron Lett*. **2000**, *41*, 8581. With 4,5-dichloro-5*H*-1,2,3-dithiazolium chloride: (dd) Chang, Y.-G.; Cho, H. S.; Kim, K, *Org. Lett*. **2003**, *5*, 507.

(14) This is the same general strategy for formation of the annulated pyrrole ring that was utilized by Miwa and co-workers for the synthesis of TNP-351 (**4**) and **1** (ref 11) and by us in our initial synthesis of **1** (ref 1).

SCHEME 4[a]



[a] Reagents and conditions: (a) (i) CH_3NO_2/NaOH/EtOH; (ii) CH_3SO_2Cl/Et_3N. (b) EtOAc/H_2O 1:1, 50 °C, 24 h. (c) (i) aq NaOH, rt, 2 h; (ii) add to aq H_2SO_4 at 0 °C, 3 h; (iii) aq NaOH to pH 7, rt, 1 h; HOAc, then filter. (d) NMM, 2,4-dimethoxy-6-chlorotriazine, DMF, rt. (e) NaOH, THF/H_2O.

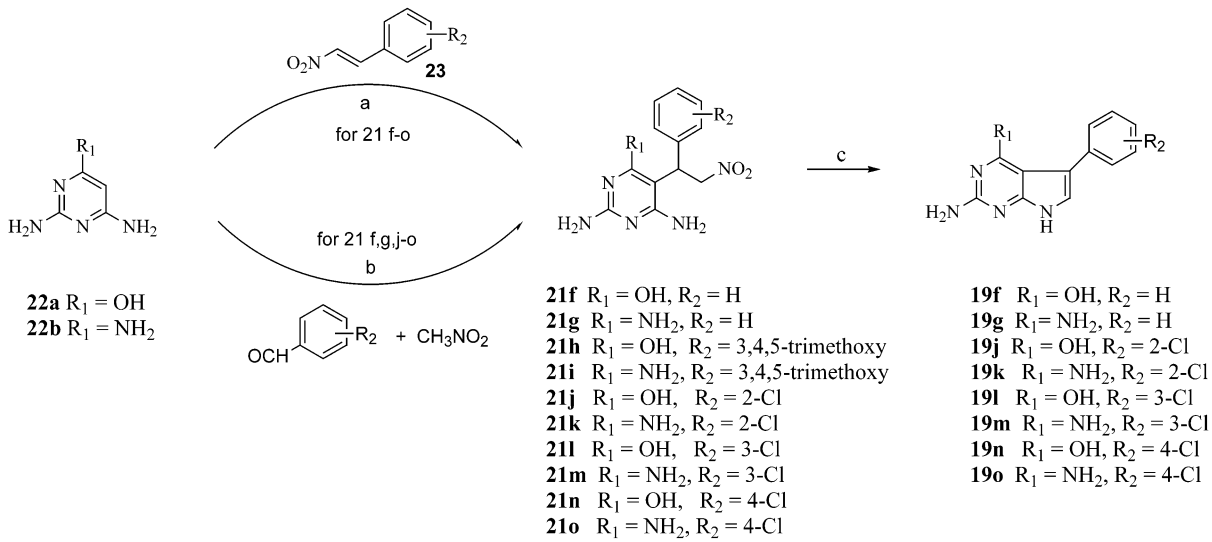
nitro compounds with the propensity of 2,6-diamino-3*H*-pyrimidin-4-one and 2,4,6-triaminopyrimidine to undergo Michael additions at their unsubstituted C-5 positions.[13]

This new strategy for the preparation of the pyrrolo-[2,3-*d*]pyrimidine 5−6 bicyclic ring system **19** is shown in Scheme 3. The pyrrole ring would be generated from the amino aldehyde **20** via intramolecular condensation.[14] The latter intermediate would be generated in situ through a Nef reaction with a primary nitro intermediate. We envisioned that the precursor **21** for this transformation could result from Michael addition of the 5-unsubstituted pyrimidines 2,6-diamino-3*H*-pyrimidin-4-one (**22a**) and 2,4,6-triaminopyrimidine (**22b**) with 1-nitroalkenes **23** acting as Michael acceptors (Scheme 3).[13z,aa,bb,cc]

We first chose **19a** as a target compound to test this approach (Scheme 4). The requisite Michael acceptor **23a** was prepared from commercially available hydrocinnamaldehyde (**24a)** by condensation with nitromethane and dehydration with methenesulfonyl chloride/triethylamine. Further condensation of this Michael acceptor **23a** with 2,6-diamino-3*H*-pyrimidin-4-one (**22a**) in a mixture of water and ethyl acetate at 50 °C smoothly afforded **21a** in excellent yield. A one-pot, *three-step* conversion of Michael addition product **21a** to the pyrrolo[2,3-*d*]pyrimidine derivative **19a**, which includes aldehyde formation from the nitroalkane by a Nef reaction followed by intramolecular condensation with the pyrimidine 6-amino group, was achieved by stirring **21a** with sodium hydroxide in water at room temperature for 2 h followed by rapid addition to aqueous sulfuric acid at 0 °C. After 3 h, the reaction mixture was neutralized by addition of aqueous sodium hydroxide and then acidified with acetic acid to afford **19a** in excellent overall yield. Encouraged by the success of this sequence, we then applied it to the synthesis of **1**, **4**, and analogues of **1**.

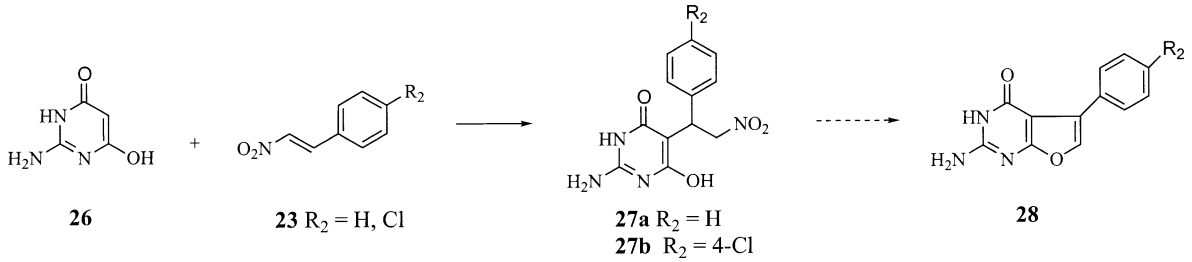
For the synthesis of Alimta (**1)**, the starting aldehyde, 4-(3-oxo-propyl)benzoic acid ethyl ester (**24b**), was prepared in nearly quantitative yield from ethyl 4-iodobenzoate and allyl alcohol through a palladium-catalyzed reaction as reported.[13aa] A Henry reaction of **24b** with nitromethane gave the expected nitro alcohol that was dehydrated by mesylation followed by treatment with triethylamine to yield 4-(4-nitrobut-3-enyl)benzoic acid ethyl ester (**23b**). Michael addition of 2,6-diamino-3*H*-pyrimidin-4-one (**22a**) to **23b** led to adduct **21b** in 91% yield, which was then converted to the 3*H*-pyrrolo[2,3-*d*]pyrimidin-4-one **19b** in 57% yield by means of a one-pot, *five-step* reaction as described above. It is worth noting that this one-pot operation efficiently resulted in both pyrrole ring formation and saponification of the benzoyl ester. Conversion of **19b** to Alimta (**1**) was achieved in good yield through conventional peptide coupling with diethyl L-glutamate/2-chloro-4,6-dimethoxy-

SCHEME 5[a]



[a] Reagents and conditions: (a) EtOAc/H_2O, 20−50 °C. (b) NH_4OAc, HOAc, ultrasound, 60−65 °C. (c) See conditions c in Scheme IV.

SCHEME 6



1,3,5-triazine/*N*-methylmorpholine, followed by saponification at room temperature in a mixture of 1 N NaOH and THF.

Homo-Alimta (**1a**) was then analogously prepared in good yield from the known 4-arylbutraldehyde **24c**, synthesized from 4-iodobenzoate and 1-hydroxy-3-butyne by a sequence of palladium-catalyzed coupling, reduction of the triple bond with H_2/Pd−C, and oxidation with PCC.[9] A Henry reaction of **24c** with nitromethane gave the expected nitro alcohol that was dehydrated to the nitroalkene **23c** by mesylation followed by dehydration. Michael addition with 2,6-diamino-3*H*-pyrimidin-4-one (**22b**) afforded adduct **21c** in 85% yield. This Michael adduct **21c** was smoothly converted to homo-Alimta (**1a**) in good yield. The nonbridged analogue **1b** was readily prepared from methyl 4-formylbenzoate (**24d**) through an analogous sequence of reactions. Interestingly, although homo-Alimta (**1a**) proved in initial cell growth inhibition studies to be approximately as active as Alimta (**1**), the nonbridged analogue **1b** was completely inactive as a cell growth inhibitor.

The 2,4-diaminopyrrolo[2,3-*d*]pyrimidine **19d**, an established penultimate precursor to TNP-351,[11,12b] was synthesized by a similar strategy through Michael condensation of 2,4,6-triaminopyrimidine (**22b**) with aryl nitroalkene **23c** to give **21d**, followed by the above sequence of a Nef reaction followed by intramolecular cyclization.

To our surprise, it appears that 5-aryl-substituted pyrrolo[2,3-*d*]pyrimidines, as a class, have been virtually unknown. We have synthesized several representative examples by exploitation of a modification of the above method (Scheme 5). Nitrostyrenes **23** were prepared as before from the corresponding aldehydes and nitromethane. Michael addition of pyrimidines **22a** and **22b** to **23** furnished adducts **21f**−**o** in excellent yields. The Michael adducts **21f**,**g**,**j**−**o** were then converted in moderate to good yields to 5-aryl-substituted pyrrolo[2,3-*d*]-pyrimidines **19f**,**g**,**j**−**o** under the conditions described above. However, this transformation failed to afford the expected products from methoxy-substituted precursors such as **21h** and **21i**. Moreover, Michael addition of 2-amino-6-hydroxy-3*H*-pyrimidin-4-one **(26)** to 1-nitro-2-phenyl- and 1-nitro-2-(4-chlorophenyl)ethylene smoothly afforded adducts **27a** and **27b**, but these compounds failed to generate the corresponding furo[2,3-*d*]pyrimidines **28** under the above conditions (Scheme 6).

It was reported recently that nitrostyrenes bearing electron-donating substituents in the aromatic ring can be obtained in a single step by ultrasound-promoted reaction of the corresponding arylaldehyde with nitromethane. Arylaldehydes bearing electron-withdrawing substituents gave only the intermediate nitro alcohols. We have found not only that both classes of nitrostyrenes can be obtained in a single step by sonication of the nitromethane/aryaldehyde mixture at 60−65 °C, but that a mixture of 2,6-diamino-3*H*-pyrimidin-4-one (**22a**) or 2,4,6-triaminopyrimidine (**22b**), the arylaldehyde, and nitromethane in acetic acid containing ammonium acetate, upon sonication at 60−65 °C, led *in one smooth*

step to the Michael adducts **21** (Scheme 5). With 3,4,5-trimethoxybenzaldehyde, however, adduct **21h** was not obtained, and only a small amount (12% yield) of **21i** was isolated.. The reaction sequence failed with aliphatic aldehydes. Nevertheless, this one-pot, three-component reaction provides easy access to the precursors for the above 5-aryl-substituted pyrrolo[2,3-*d*]pyimidines.

In summary,we have developed a concise and economical method for the synthesis of pyrrolo[2,3-*d*]pyrimidine derivatives. We have successfully utilized this new method for the synthesis of Alimta (**1**), homo-Alimta (**1a**), and the nonbridged analogue (**1b**), and for a formal synthesis of TNP-351 (**4**). A series of 5-aryl-substituted pyrrolo[2,3-*d*]pyrimidines has also been prepared by utilizing this method. Further studies of this efficient route to pyrrolo[2,3-*d*]pyrimidines are currently underway in our laboratory.

Experimental Section

General. All commercial reagents were used without further purification. Tetrahydrofuran was distilled from benzophenone ketyl. Methylene chloride, *N*,*N*-dimethylformide (DMF), and triethylamine were distilled from calcium hydride. Melting points were uncorrected.

Methyl 4-(4-hydroxybutyl)benzoate: A Parr flask was charged with 3.25 g (15.9 mmol) of methyl 4-(4-hydroxy-1-butynyl)benzoate and 0.26 g (8 wt % equiv) of 10% palladium on carbon catalyst in 40 mL of ethanol. Hydrogenation was carried out at 50 psi of hydrogen for 18 h. The mixture was filtered though a silica gel pad, which was washed with ethanol. The filtrate was concentrated to give 3.20 g (97%) of product as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.99 (2 H, d, J = 8.0 Hz), 7.27 (2 H, d, J = 8.0 Hz), 3.94 (3 H, s), 3.71 (2 H, t, J = 6.0 Hz), 2.74 (2 H, t, J = 7.3 Hz), 1.82−1.57 (4 H, m), 1.51 (1 H, s).

4-(4-Oxobutyl)benzoic acid methyl ester (24c): To a mixture of 4.97 g (23 mmol) of pyridine chlorochromate and 1.23 g (15 mmol) of sodium acetate in 100 mL of dry methylene chloride was added 3.2 g (15.3 mmol) of methyl 4-(4-hydroxybutyl)benzoate in 50 mL of methylene chloride at room temperature. The resulting mixture was stirred at room temperature for 3 h, diluted with 150 mL of ethyl ether, filtered through a silica gel pad, and concentrated. The residue was purified by column chromatorgaphy (silica gel/hexane: EtOAc = 4:1) to give 2.85 g (90%) of the product as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 10.01 (1 H, s), 8.21 (2 H, d, J = 8.1 Hz), 7.50 (2 H, d, J = 8.1 Hz), 4.15 (3 H, s), 2.96 (2 H, t, J = 7.2 Hz), 2.72 (2 H, t, J = 6.6 Hz), 2.40−2.15 (2 H, m); MS m/z 206 (M^+), 175, 162, 131, 103, 91, 63.

4-Nitro-3-hydroxybutylbenzene: To a stirred mixture of 15 g (200 mmol, 14.4 mL) of nitromethane, 7.8 mL of ethanol, and 0.39 mL of 10.0 N aqueous NaOH was added 26.8 g (200 mmol, 26.3 mL) of hydrocinnamaldehyde at room temperature. After two-thirds of the aldehyde was added, 0.39 mL of 10 N aqueous NaOH and 1.5 mL of water were added, then the remainder of the aldehyde was added. The resulting mixture was stirred at 38 °C for 65 h and then neutralized with 2 N aqueous HCl. A yellow precipitate was collected, washed with hexane, and dried under vacuum to give 35.0 g (90%) of product as a yellow solid: IR (KBr) 3375, 2952, 1558, 1445, 1385, 1196, 1090, 878, 753, 704, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35−7.20 (5 H, m), 4.32 (2 H, d, J = 9.0 Hz), 4.30 (1 H, m), 3.00−2.54 (2 H, m), 1.92−1.62 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 140.8, 128.8, 128.6, 126.4, 80.7, 70.0, 35.3, 31.5; EIMS m/z 195 (M^+), 177, 170, 160, 147, 133, 130, 115, 105, 91, 77; Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 62.01; H, 7.00; N, 7.10.

4-(3-Hydroxy-4-nitrobutyl)benzoic acid ethyl ester: To a stirred mixture of 2.25 g (37 mmol) of nitromethane, 1.2 mL of ethanol, and 0.06 mL of 10 N aqueous NaOH solution was added 7.18 g (37 mmol) of 4-(3-oxopropyl)benzoic acid ethyl ester at room temperature. After addition of the aldehyde, 0.06 mL of 10 N aqueous NaOH and 0.23 mL of ethanol were added. The resulting mixture was stirred at 38 °C for 48 h. The mixture was poured into a mixture of ethyl acetate (100 mL) and hexanes (100 mL), washed with water (2 × 20 mL), dried with Na_2SO_4, and then concentrated. The residue was purified by column chromatography (silica gel/EtOAc:hexanes = 1:4) to afford 6.8 g (68%) of product as a white solid: IR (KBr) 3439, 2929, 1700, 1619, 1553, 1362, 1289, 1180, 1137, 1105, 1019, 882, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.98 (2 H, d, J = 8.5 Hz), 7.28 (2 H, d, J = 8.0 Hz), 4.42 (2 H, d, J = 5.5 Hz), 4.38 (2 H, q, J = 7.0 Hz), 4.34−4.29 (1 H, m), 3.03 (1 H, br s), 2.96−2.90 (1 H, m), 2.84−2.78 (1 H, m), 1.92−1.78 (2 H, m), 1.40 (3 H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 166.9, 146.4, 131.0, 128.7, 128.6, 80.8, 67.9, 61.1, 35.0, 31.5, 14.5; EIMS m/z 267 (M^+), 265, 252, 249, 232, 222, 206, 177, 161, 149, 133, 105, 91, 77; HRMS calcd for $C_{13}H_{17}NO_5$ 267.1107, found 267.1095. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.69; H, 6.37; N, 5.29.

4-(4-Hydroxy-5-nitropentyl)benzoic acid methyl ester: isolated in 61% as a light yellow solid: IR (KBr) 3503, 3025, 2944, 1701, 1557, 1289, 1102, 761, 699; ^{1}H NMR ($CDCl_3$) δ 7.97 (2 H, d, J = 8.0 Hz), 7.25 (2 H, d, J = 8.0 Hz), 4.43−4.35 (3 H, m), 3.92 (3 H, s), 2.86 (1 H, d, J = 3.5 Hz), 2.73 (2 H, t, J = 8.0 Hz), 1.95−1.86 (1 H, m), 1.79−1.70 (1 H, m), 1.62−1.49 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 167.3, 147.3, 130.0, 128.6, 128.2, 80.8, 68.6, 52.2, 35.6, 33.2, 26.75; EIMS m/z 267 (M^+), 249, 218, 206, 187, 175, 162, 149, 131, 121, 103, 91, 77; HRMS calcd for $C_{13}H_{17}NO_5$ 267.1107, found 267.1104. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.27; H, 6.61; N, 5.42.

4-(1-Hydroxy-2-nitroethyl)benzoic acid methyl ester: isolated in 90% yield as a light yellow solid: mp 79−80 °C; IR (KBr) 3448, 3005, 2955, 1717, 1699, 1613, 1559, 1437, 1380, 1288, 1193, 1112, 1082, 1018, 964, 899, 863, 771, 727, 704, 649 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.96 (2 H, d, J = 8.0 Hz), 7.44 (2 H, d, J = 8.0 Hz), 5.50 (1 H, dt, J = 9.5 and 3.5 Hz), 4.60−4.55 (1 H, AB, J = 13.0 and 9.5 Hz), 4.54−4.50 (1 H, AB, J = 13.0 and 3.5 Hz), 3.90 (1 H, d, J = 3.5 Hz), 3.89 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 167.0, 143.8, 130.35, 130.2, 126.1, 81.1, 70.6, 52.45; EIMS m/z 207($M^+ - H_2O$), 192, 176, 164, 148, 133, 129, 104, 102, 89, 77; HRMS calcd for $C_{10}H_9NO_4$ ($M^+ - H_2O$) 207.0532, found 207.0539.

4-(Nitrobut-3-enyl)benzene (23a): To a solution of 5.85 g (30.0 mmol) of 1-nitro-4-phenyl-2-butanol in 40 mL of dry methylene chloride at 0 °C was added 3.44 g (30.0 mmol) of methanesulfonyl chloride followed by addition of 6.07 g (60.0 mmol) of triethylamine. The mixture was warmed to room temperature, stirred for 20 min, then poured into 40 mL of water and extracted with 50 mL of methylene chloride. The organic extract was dried with Na_2SO_4 and concentrated, and the residue was purified by column chromatography (silica gel/EtOAc:hexanes = 1:9) to afford 2.75 g (52%) of product as a yellow oil that slowly decomposes at room temperature and therefore was used immediately for the next reaction: IR (neat) 3028, 2930, 1648, 1555, 1524, 1497, 1454, 1351, 1176, 953, 931, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35−7.26 (4 H, m), 7.21 (2 H, d, J = 7.5 Hz), 7.00 (1 H, dt, J = 13.5 Hz), 2.87 (2 H, t, J = 8.0 Hz), 2.63 (2 H, q, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 141.55, 140.2, 139.7, 128.9, 128.5, 126.8, 34.2, 30.3; EIMS m/z 177 (M^+), 160, 143, 133, 130, 115, 103, 91, 77; HRMS calcd for $C_{10}H_{11}NO_2$ 177.0790, found 177.0802. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 68.00; H, 6.13; N, 7.75.

4-(4-Nitrobut-3-enyl)benzoic acid ethyl ester (23b): A procedure similar to that used for the preparation of **23a** was employed for the conversion of 4.89 g (18.1 mmol) of 4-(3-hydroxy-4-nitrobutyl)benzoic acid ethyl ester to **23b**; yield 4.1 g (90%) obtained as a light yellow solid: mp 42−43 °C; IR (KBr) 3112, 2982, 1713, 1647, 1610, 1519, 1424, 1417, 1353,

1277, 1178, 1104, 1021, 954, 935, 857, 766, 706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (2 H, d, J = 8.5 Hz), 7.28 (1 H, dt, J = 14.0 and 7.5 Hz), 7.27 (2 H, d, J = 8.5 Hz), 6.98 (1 H, d, J = 14.0 Hz), 4.39 (2 H, q, J = 7.0 Hz), 2.92 (2 H, t, J = 7.5 Hz), 2.64 (2 H, q, J = 8.0 Hz), 1.42 (3 H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 166.55, 144.9, 140.9, 140.4, 130.2, 129.3, 128.5, 61.2, 34.1, 29.0, 14.5; EIMS m/z 249 (M^+), 204, 202, 163, 135, 129, 118, 107, 90, 77; HRMS calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.1029. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.63; H, 6.26; N, 5.70.

4-(5-Nitropent-4-enyl)benzoic acid methyl ester (23c): isolated in 96% yield as a light yellow oil: IR (neat) 3103, 2950, 1719, 1649, 1610, 1524, 1436, 1352, 1281, 1197, 1101, 1020, 962, 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (2 H, d, J = 8.5 Hz), 7.29 (2 H, dt, J = 13.5 and 7.5 Hz), 7.26 (2 H, d, J = 8.5 Hz), 7.00 (1 H, dt, J = 13.5 and 1.5 Hz), 3.93 (3 H, s), 2.76 (2 H, t, J = 7.5 Hz), 2.31 (2 H, qd, J = 7.5 and 1.5 Hz), 1.90 (2 H, quintet, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 167.2, 146.5, 141.95, 140.1, 130.1, 128.6, 128.5, 52.25, 35.3, 29.1, 27.95; EIMS m/z 249 (M^+), 232, 218, 202, 187, 171, 163, 149, 143, 131, 118, 103, 91, 77; HRMS calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.0992. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.44; H, 5.97; N, 5.31.

4-(2-Nitrovinyl)benzoic acid methyl ester (23d): isolated in 85% yield as a yellow solid: mp 176−178 °C; IR (KBr) 3105, 2960, 1720, 1636, 1521, 1500, 1426, 1347, 1285, 1108, 960, 850, 772, 716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.14 (2 H, d, J = 8.5 Hz), 8.04 (1 H, d, J = 14.0 Hz), 7.65 (1 H, d, J = 14.0 Hz), 7.64 (2 H, d, J = 8.5 Hz), 3.93 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 166.2, 138.9, 137.8, 134.4, 133.2, 130.7, 129.2, 52.7; EIMS m/z 207 (M^+), 194, 178, 164, 133, 129, 120, 105, 91, 77; HRMS calcd for $C_{10}H_9NO_4$ 207.0532, found 207.0529.

2,6-Diamino-5-(1-nitromethyl)-3-phenylpropyl)-3*H*-pyrimidin-4-one (21a): To a mixture of 1.85 g (10.5 mmol) of (4-nitrobut-3-enyl)benzene (**23a**) in a mixture of 20 mL of water and 20 mL of ethyl acetate at room temperature was added 1.16 g (9.0 mmol) of 2,6-diamino-3*H*-pyrimidin-4-one. The resulting mixture was stirred for 18 h, 100 mL of ethyl acetate was added, and the organic layer was separated, dried, and concentrated to afford a yellow solid that was washed with 2% ethyl acetate in hexane and dried to give 2.64 g (96%) of product as a yellow solid: 189 °C dec; IR (KBr) 3473, 3402, 2913, 1622, 1537, 1493, 1450, 1376, 1003, 781, 742, 696 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.81 (1 H, s), 7.25 (2 H, t, J = 7.0 Hz), 7.16−7.11 (3 H, m), 6.06 (2 H, br s), 5.96 (2 H, br s), 5.03 (1 H, t, J = 10.0 Hz), 4.77 (1 H, dd, J = 12.0 and 6.5 Hz), 3.41 (1 H, m), 2.58 (1 H, td, J = 13.0 and 5.0 Hz), 2.47 (1 H, td, J = 12.5 and 5.0 Hz), 2.15−2.07 (1 H, m), 1.73−1.66 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 162.85, 161.9, 153.5, 142.4, 128.25, 128.0, 125.6, 84.0, 77.65, 35.1, 33.0, 31.85; EIMS m/z 303 (M^+), 268, 254, 242, 163, 151, 126, 109, 91, 77; HRMS calcd for $C_{14}H_{17}N_5O_3$ 303.1331, found 303.1339.

4-[3-(2,4-Diamino-6-oxo-1,6-dihydropyrimidin-5-yl)-4-nitrobutyl]benzoic acid ethyl ester (21b): The mixture of 1.41 g (5.7 mmol) of **23b** and 0.72 g (5.7 mmol) of 2,6-diamino-3*H*-pyrimidin-4-one in 20 mL of water and 20 mL of ethyl acetate was stirred at 50 °C for 24 h. The solid slowly disappeared. The reaction mixture was poured into 200 mL of ethyl acetate, washed with water (2 × 40 mL), dried with Na_2SO_4, and then concentrated. The residue was purified by column chromatorgaphy (silica gel/ethyl acetate:methanol = 8:1) to afford 1.95 g (91%) of product as a light yellow solid: mp 126−128 °C; IR (KBr) 3461, 3368, 3198, 2922, 1704, 1611, 1545, 1436, 1375, 1281, 1177, 1101, 1013, 784, 761 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.84 (1 H, br s), 7.83 (2 H, d, J = 8.0 Hz), 7.25 (2 H, d, J = 8.0 Hz), 6.09 (2 H, br s), 5.97 (2 H, br s), 5.00 (1 H, t, J = 10.0 Hz), 4.76 (1 H, dd, J = 12.0 and 6.5 Hz), 4.27 (2 H, q, J = 7.0 Hz), 3.39 (1 H, m), 2.65 (1 H, td, J = 11.5 and 5.5 Hz), 2.50 (1 H, td, J = 11.5 and 5.0 Hz), 2.17−2.09 (1 H, m), 1.70 (1 H, m), 1.29 (3 H, t, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6) δ 165.7, 162.6, 161.9, 153.5, 148.15, 129.2, 128.4, 127.4, 83.9, 77.6, 60.5, 35.0, 32.6, 31.3, 14.2; EIMS m/z 375 (M^+), 357, 240, 328, 283, 202, 180, 163, 151, 145, 136, 109, 98, 90, 77, 68. Anal. Calcd for $C_{17}H_{21}N_5O_5$: C, 54.39; H, 5.64; N, 18.66. Found: C, 54.20; H, 6.02; N, 18.19.

4-[4-(2,4-Diamino-6-oxo-1,6-dihydropyrimidin-5-yl)-5-nitropentyl]benzoic acid methyl ester (21c): isolated in 85% yield as a light yellow solid: mp 102−104 °C; IR (KBr) 3483, 3374, 3196, 2947, 1708, 1622, 1541, 1428, 1377, 1277, 1179, 1110, 791, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.77 (1 H, s), 7.84 (2 H, d, J = 8.0 Hz), 7.29 (2 H, d, J = 8.0 Hz), 6.03 (2 H, br s), 5.93 (2 H, br s), 4.97 (1 H, br t), 4.71 (1 H, dd, J = 12.0 and 6.5 Hz), 3.82 (3 H, s), 3.43−3.25 (1 H, br s), 2.67−2.47 (2 H, m), 1.94−1.82 (1 H, m), 1.62−1.44 (2 H, m), 1.43−1.34 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 166.2, 162.8, 161.9, 153.5, 148.3, 129.2, 128.6, 127.1, 84.15, 77.8, 51.9, 35.15, 34.7, 29.2, 28.4; EIMS m/z 375 (M^+), 341, 328, 297, 218, 190, 180, 164, 151, 126, 109, 99, 91, 77, 68; HRMS calcd for $C_{17}H_{21}N_5O_5$ 375.1542, found 375.1559. Anal. Calcd for $C_{17}H_{21}N_5O_5$: C, 54.39; H, 5.64; N, 18.66. Found: C, 54.53; H, 6.01; N, 18.42.

4-[5-Nitro-4-(2,4,6-triaminopyrimidin-5-yl)pentyl]benzoic acid methyl ester (21d): isolated in 91% yield as a light yellow solid: mp 68−70 °C; IR (KBr) 3481, 3394, 3184, 2949, 1709, 1613, 1569, 1437, 1286, 1180, 1114, 801, 766 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7,86 (2 H, d, J = 8.5 Hz), 7.30 (2 H, d, J = 8.0 Hz), 5.70 (2 H, br s), 5.60 (2 H, br s), 5.38 (2 H, s), 4.81 (2 H, m), 3.82 (3 H, s), 3.55 (1 H, m), 2.63 (2 H, q, J = 6.5 Hz), 1.84−1.76 (1 H, m), 1.64−1.44 (3 H, m); ^{13}C NMR (DMSO-d_6) δ 166.2, 163.4, 161,25, 160.8, 148.1,. 129.2, 128.6, 127.2, 82.1, 77.2, 51.95, 35.0, 33.8, 28.7, 28.5; EIMS m/z 376 ($M + 2^+$), 374 (M^+), 366, 258, 342, 328, 314, 232, 218, 202, 187, 163, 149, 140, 132, 125, 98, 92, 85, 77, 67. Anal. Calcd for $C_{17}H_{22}N_6O_4$: C, 54.54; H, 5.92; N, 22.45. Found: C, 53.99; H, 6.28; N, 22.13.

4-[1-(2,4-Diamino-6-oxo-1,6-dihydropyrimidin-5-yl)2-nitroethyl]benzoic acid methyl ester (21e): isolated in 84% yield as a light yellow solid by column chromatography (silica gel/EtOAc: MeOH = 5:1): mp 124−126 °C; IR (KBr) 3476, 3365, 3208, 2954, 1713, 1625, 1549, 1492, 1438, 1377, 1289, 1192, 1116, 1019, 794, 776, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.87 (1 H, s), 7.84 (2 H, d, J = 8.5 Hz), 7.62 (2 H, d, J = 8.5 Hz), 6.23 (2 H, br s), 6.12 (2 H, br s), 5.44 (1 H, AB, J = 12.5 and 7.5 Hz), 5.38 (1 H, AB, J = 12.5 and 7.5 Hz), 5.67 (1 H, t, J = 7.5 Hz), 3.82 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 166.2, 162.4, 162.1, 153.8, 147.0, 128.9, 128.0, 127.7, 85.4, 77.1, 52.0, 39.1; EIMS m/z 286 ($M^+ - HNO_2$), 255, 216, 207, 192, 176, 160, 151, 149, 129, 126, 118, 102, 89, 68.

2-Amino-5-phenethyl-3,7-dihydropyrrolo[2,3-*d*]pyrimidin-4-one (19a): To an aqueous solution of NaOH (0.34 g, 8.1 mmol) in 5 mL of water was added 0.148 g (1.58 mmol) of **21a** at room temperature. The mixture was stirred for 2 h, and then was slowly added to an aqueous solution of 1.37 g (14 mmol) of sulfuric acid (98%) in 5 mL of water at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and at room temperature for 1 h. The color of the mixture changed to gray. Concentrated NH_4OH was added at 0 °C to adjust the pH to 7. The precipitated solid was collected and purified by column chromatography (silica gel/EtOAc:MeOH = 9:1) to give 0.2 g (50%) of product as a light yellow solid: IR (KBr) 3510, 3399, 3197, 2927, 1665, 1635, 1604, 1525, 1436, 1376, 783, 755, 701, 699 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.61 (1 H, s), 10.15 (1 H, s), 7.25 (2 H, t, J = 7.0 Hz), 7.20 (2 H, d, J = 7.0 Hz), 7.15 (1 H, t, J = 7.0 Hz), 6.32 (1 H, s), 6.01 (2 H, br s), 2.93−2.87 (2 H, m), 2.86−2.81 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 159.3, 152.15, 151.2, 142.5, 128.3, 128.1, 125.5, 118.0, 113.3, 98.75, 36.3, 28.3; EIMS m/z 254 (M^+), 163, 146, 121, 91, 78, 69; HRMS calcd for $C_{14}H_{14}N_4O$ 254.1168, found 254.1175. Anal. Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 65.88; H, 5.66; N, 21.69.

4-[2-(2-Amino-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoic acid (19b): To a mixture of 0.24 g (6.0 mmol) of NaOH in 3.0 mL of water was added 0.375 g (1.0 mmol) of **21b** at room temperature. The mixture was stirred at room temperature for 2 h and then was slowly added to 0.98 g (10.0 mmol) of H_2SO_4 in 4.0 mL of water at 0 °C.

After 3 h, aqueous sodium hydroxide (2.0 N) was added to adjust the pH to 7. The mixture was stirred at room temperature for another 1 h. Acetic acid (0.5 mL) was added and the precipitated solid was collected by filtration, washed with water followed by ethyl acetate, and dried under vacuum to give 0.17 g (57%) of product as a light green solid that is used without further purification for the next reaction: IR (KBr) 3467, 3328, 3198, 2919, 1645, 1536, 1431, 1381, 1273, 1172, 1072, 839, 779, 759 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.61 (1 H, s), 10.16 (1 H, s), 7.83 (2 H, d, J = 8.0 Hz), 7.31 (2 H, d, J = 7.5 Hz), 6.31 (1 H, s), 6.00 (2 H, br s), 2.98 (2 H, t, J = 8.0 Hz), 2.85 (2 H, t, J = 8.0 Hz); ^{13}C NMR (DMSO-d_6) δ 167.3, 159.0, 152.0, 150.1, 147.75, 129.2, 128.4, 128.2, 117.7, 113.6, 98.7, 36.2, 27.8; EIMS m/z 298 (M^+), 210, 170, 169, 163, 151, 142, 139, 126, 105, 91, 77, 69.

4-[3-(2-Amino-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)propyl]benzoic acid (19c): 257 mg (0.66 mmol) of **21c** was used and 107 mg (50.7% yield) of product was obtained as a light blue solid that was used for the next step without further purification. IR (KBr) 3490, 3375, 2950, 1700, 1657, 1544, 1428, 1276, 1180, 780 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.71 (1 H, s), 10.25 (1 H, s), 7.84 (2 H, d, J = 8.0 Hz), 7.31 (2 H, d, J = 8.0 Hz), 6.39 (1 H, s), 6.15 (2 H, br s), 2.65 (2 H, t, J = 7.5 Hz), 2.58 (2 H, t, J = 7.5 Hz), 1.92 (2 H, quintet, J = 7.5 Hz); EIMS m/z 312 (M^+), 252, 207, 190, 170, 164, 150, 135, 126, 119, 107, 105, 98, 78, 64; HRMS calcd for $C_{16}H_{16}N_4O_3$ 312.1222, found 312.1242.

4-[3-(2,4-Diamino-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)propyl]benzoic acid (19d):[12b] 300 mg (0.80 mmol) of **21d** was used and 110 mg (44% yield) of product was obtained as a white solid: mp 210 °C; IR (KBr) 334, 3202, 2931, 164, 1549, 147, 1328, 1272, 1111, 780, 620 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.61 (1 H, br s), 10.66 (1 H, s), 7.85 (2 H, d, J = 8.0 Hz), 7.32 (2 H, d, J = 8.0 Hz), 6.50 (1 H, s), 6.38 (2 H, br s), 5.80 (2 H, br s), 2.71 (2 H, t, J = 7.5 Hz), 2.69 (2 H, t, J = 7.5 Hz), 1.84 (2 H, quintet, J = 7.5 Hz); EIMS m/z 311 (M^+), 229, 183, 163, 151, 149, 125, 117, 109, 91, 78; HRMS calcd for $C_{16}H_{17}N_5O_2$ 311.1382, found 311.1391.

4-[2-Amino-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]benzoic acid (19e): To a solution of 0.48 g (12 mmol) of sodium hydroxide in 4 mL of water was added 0.4 g (1.2 mmol) of **21e**. The mixture was stirred at room temperature for 3 h and then added slowly to a solution of 1.76 g (18 mmol) of H_2SO_4 in 4 mL of water at 0 °C. The resulting mixture was stirred for 3 h at 0 °C, neutralized with 0.1 N NaOH, and stirred for 1 h. Acetic acid (2 mL) was added and the collected solid was washed with water, ethyl acetate, and methanol, then dried under vacuum to give 0.31 g (96% yield) of crude product (>95% yield by NMR) as a light green solid. This sample was used in the next step without further purification: mp 290 °C; IR (KBr) 3464, 3336, 3209, 1683, 1642, 1604, 1405, 1288, 1119, 757, 638, 616 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.90 (1 H, br s), 11.39 (1 H, s), 10.39 (1 H, s), 8.14 (2 H, d, J = 8.0 Hz), 7.85 (2 H, d, J = 8.0 Hz), 7.23 (1 H, d, J = 1.5 Hz), 6.19 (2 H, br s); ^{13}C NMR (DMSO-d_6) δ 167.9, 159.5, 153.5, 151.0, 140.0, 129.5, 127.45, 127.4, 119.05, 117.4, 97.5; EIMS m/z 270 (M^+), 253, 225, 210, 182, 170, 155, 141, 128, 115, 105, 91, 83, 77, 73, 69; HRMS calcd for $C_{13}H_{10}N_4O_3$ 270.0753, found 270.0737.

***N*-{4-(2-Amino-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic acid diethyl ester (25a):** To a suspension of 185 mg (0.62 mmol) of **19b** in 15 mL of dry DMF were added 0.08 mL (0.74 mmol) of 4-methylmorpholine and 130 mg (0.74 mmol) of 2-chloro-4,6-dimethoxy-1,3,5-triazine. The resulting mixture was stirred at room temperature for 2 h, and 0.08 mL of 4-methylmorpholine and 221 mg (0.93 mmol) of diethyl L-glutamate hydrochloride were added. The reaction mixture was stirred for another 3.5 h at room temperature. Solvent was evaporated under vacuum and the residue was purified by column chromatography (silica gel/CH_2Cl_2:MeOH = 9:1) to give 185 mg (62%) of product as an off-white solid: mp 84−86 °C; IR (KBr) 3340, 3216, 2979, 1728, 1635, 1538, 1499, 1437, 1371, 1204, 1095, 1021, 785, 668 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.64 (1 H, s), 10.21 (1 H, s), 8.64 (1 H, d, J = 5.0 Hz), 7.79 (2 H, d, J = 7.5 Hz), 7.30 (2 H, d, J = 8.0 Hz), 6.32 (1 H, s), 6.07 (2 H, br s), 4.44 (1 H, q, J = 5.0 Hz), 4.11 (2 H, q, J = 7.0 Hz), 4.05 (2 H, q, J = 7.0 Hz), 2.99 (2 H, t, J = 8.0 Hz), 2.87 (2 H, t, J = 8.0 Hz), 2.44 (2 H, t, J = 7.5 Hz), 2.15−2.08 (1 H, m), 2.05−1.97 (1 H, m), 1.19 (3 H, t, J = 6.5 Hz), 1,17 (3 H, t, J = 6.5 Hz); ^{13}C NMR (DMSO-d_6) δ 172.2, 171.9, 166.7, 159.25, 152.2, 151.0, 146.3, 131.1, 128.19, 127.4, 117.7, 113.5, 98.75, 60.5, 59.9, 52.0, 36.1, 30.2, 28.0, 25.7, 14.1 (two carbons); EIMS m/z 483 (M^+), 321, 281, 252, 191, 163, 141, 129, 119, 100, 91, 84; HRMS calcd for $C_{24}H_{29}N_5O_6$ 483.2118, found 483.2119. Anal. Calcd for $C_{24}H_{29}N_5O_6$: C, 59.62; H, 6.05; N, 14.48. Found: C, 58.99; H, 5.94; N, 14.05.

***N*-{4-[3-(2-Amino-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)propyl]benzoyl}-L-glutamate diethyl ester (25b):** isolated in 51% yield as a off-white solid: mp 56−58 °C; ^1H NMR ($CDCl_3$) δ 10.96 (1 H, s), 9.33 (1 H, s), 7.74 (1 H, d, J = 7.5 Hz), 7.67 (2 H, d, J = 8.0 Hz), 7.18 (2 H, d, J = 8.0 Hz), 6.38 (1 H, s), 5.37 (2 H, br s), 4.84 (1 H, q, J = 7.0 Hz), 4.23 (2 H, t, J = 7.0 Hz), 4.11−4.04 (2 H, m), 2.68 (2 H, t, J = 7.0 Hz), 2.61 (2 H, t, J = 7.0 Hz), 2.54−2.40 (2 H, m), 2.32−2.24 (1 H, m), 2.20−2.12 (1 H, m), 2.02−1.92 (2 H, m), 1.29 (3 H, t, J = 7.0 Hz), 1.19 (3 H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 173.6, 173.2, 168.2, 161.2, 152.4, 151.8, 146.9, 131.5, 128.9, 127.5, 119.3, 114.3, 99.7, 62.1, 61.1, 52.6, 35.6, 31.2, 30.9, 27.5, 26.0, 14.3 (two carbons); EIMS m/z 497 (M^+), 451, 334, 309, 295, 266, 192, 177, 164, 131, 100, 84; HRMS calcd for $C_{25}H_{31}N_5O_6$ 497.2274, found 497.2290.

***N*-{4-(2-Amino-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)benzoyl]-L-glutamic acid diethyl ester (25c):** isolated as a light yellow solid in 59% yield: mp 112−114 °C; IR (KBr) 3339, 3216, 2982, 1732, 1637, 1514, 1373, 1024, 1204, 1102, 1021, 827, 765, 672 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.37 (1 h, br s), 10.50 (1 H, br s), 8.64 (1 H, d, J = 7.5 Hz), 8.11 (2 H, d, J = 8.5 Hz), 7.82 (2 H, d, J = 8.5 Hz), 7.20 (1 H, s), 6.30 (2 H, br s), 4.47−4.43 (1 H, m), 4.11 (2 H, qm, J = 7.0 Hz), 4.04 (2 H, q, J = 7.0 Hz), 2.45 (2 J, t, J = 7.5 Hz), 2.16−2.09 (1 H, m), 2.07−1.99 (1 H, m), 1.19 (3 H, t, J = 7.0 Hz), 1.16 (3 H, t, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6) δ 172.25, 171.9, 166.6, 159.1, 153.0, 152.6, 138.1, 130.0, 127.2, 126.7, 118.7, 116.4, 97.1, 60.5, 59.9, 52.0, 30.2, 25.7, 14.1 (two carbons); EIMS m/z 455 (M^+), 297, 281, 222, 210, 194, 181, 157, 130, 127, 113, 100, 84; HRMS calcd for $C_{22}H_{25}N_5O_6$ 455.1805, found 455.1825.

***N*-{4-[2-(2-Amino-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]benzoyl}-L-glutamic acid (Alimta, 1):** To a solution of 80 mg of **25a** in 3.0 mL of THF was added 1.0 mL of 1 N aqueous NaOH at room temperature. The resulting mixture was stirred for 3.5 h. Solvent was evaporated under reduced pressure and the mixture was acidified by addition of acetic acid. The precipitate was collected, washed with water (3 × 10 mL) and EtOAc (3 × 10 mL), and dried under vacuum to afford 50 mg (73%) of **1** as an off-white solid: ^1H NMR (DMSO-d_6) δ 12.48 (2 H, s), 10.60 (1 H, s), 10.51 (1 H, s), 8.48 (1 H, d, J = 7.0 Hz), 7.78 (2 H, d, J = 7.5 Hz), 7.29 (2 H, d, J = 7.5 Hz), 6.30 (1 H, s), 6.00 (2 H, br s), 4.38 (1 H, q, J = 4.5 Hz), 2.97 (2 H, t, J = 7.0 Hz), 2.85 (2 H, t, J = 7.0 Hz), 2.35 (2 H, t, J = 7.0 Hz), 2.12−2.02 (1 H, m), 1.97−1.92 (1 H, m); ^{13}C NMR (DMSO-d_6) δ 173.9, 173.45, 166.5, 159.25, 152.2, 151.0, 146.2, 131.3, 128.15, 127.4, 117.6, 113.4, 98.7, 51.9, 36.1, 30.4, 21.02, 25.9.

***N*-{4-[3-(2-Amino-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)propyl]benzoyl}-L-glutamic acid (homo-Alimta, 1a):** isolated in 68% yield as an off-white solid; IR (KBr) 3289, 2929, 1693, 1651, 1541, 1502, 1400, 1337, 1302, 1236, 1109, 1095, 765, 680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.36 (2 H, br s), 10.63 (1 H, s), 10.10 (1 H, s), 8.48 (1 H, d, J = 7.5 Hz), 7.79 (2 H, d, J = 8.0 Hz), 7.29 (2 H, d, J = 8.0 Hz), 6.36 (1 H, s), 5.97 (2 H, s), 4.38 (1 H, q, J = 5.0 Hz), 2.64 (2 H, t, J = 7.5 Hz), 2.58 (2 H, t, J = 8.0 Hz), 2.34 (2 H, t, J = 7.0 Hz), 2.12−2.02 (1 H, m), 1.98−1.94 (1 H, m), 1.92 (2 H, quintet, J = 7.0 Hz); ^{13}C (DMSO-d_6) δ 173.9, 173.5, 166.4, 159.2, 152.1,

151.3, 146.1, 131.4, 128.2, 127.5, 118.1, 113.2, 98.75, 51.9, 34.8, 31.45, 30.5, 26.0, 25.7; FABMS *m/z* 442 (MH^+), 396, 309, 295, 275, 155, 135, 119; HRFABMS calcd for $C_{21}H_{24}N_5O_6$ (MH^+) 442.1648, found 442.1723. Anal. Calcd for $C_{21}H_{23}N_5O_6$: C, 57.14; H, 5.25; N, 15.86. Found: C, 56.94; H, 5.31; N, 15.48.

***N*-[4-(2-Amino-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)benzoyl]-L-glutamic acid (nonbridged analogue of Alimta, 1b):** To a mixture of 110 mg (0.247 mmol) of **25c** in 2.0 mL of THF at room temperature was added 1 mL of 1 N NaOH. The mixture changed to deep blue immediately, and was stirred for 3 h. Acetic acid (0.11 mL, 2.0 mmol) was added. The mixture was evaporated to dryness and 3 mL of methanol was added. The solid was collected by filtration, washed with ethyl acetate, and dried under vacuum to give 90 mg (80% yield) of **1b** as a light blue solid (Note: **1b** is soluble in water): mp 176 °C dec; IR (KBr) 3375, 3204, 2955, 1639, 1600, 1514, 1403, 1298, 1007, 959, 862, 823, 766, 679 cm^{-1}; ^1H NMR (DMSO-d_6/D_2O) δ 7.97 (2 H, d, J = 8.0 Hz), 7.76 (2 H, d, J = 8.0 Hz), 7.09 (1 H, s), 4.13 (1 H, m), 2.04−1.95 (3 H, m), 1.86 (1 H, m); ^{13}C NMR (DMSO-d_6/D_2O) δ 178.5, 176.05, 166.4, 160.0, 153.25, 153.15, 138.1, 131.8, 127.6, 127.5, 119.4, 117.0, 97.55, 55.5, 34.3, 29.5; FABMS *m/z* 399 (M^+); FABHRMS calcd for 399.1179, found 399.1164.

2,6-Diamino-5-(2-nitro-1-phenethyl)-3*H*-pyrimidin-4-one (21f): isolated in 92% yield as a light solid: mp 146 °C dec; IR (KBr) 3379, 3187, 2912, 1622, 1546, 1494, 1436, 1376, 1253, 793, 773 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.90 (1 H, s), 7.50 (2 H, d, J = 8.0 Hz), 7.25 (2 H, t, J = 7.5 Hz), 7.17 (1 H, t, J = 7.5 Hz), 6.12 (4 H, s), 5.46 (1 H, dd, J = 13.0 and 7.5 Hz), 5.30 (1 H, dd, J = 13.0 and 7.5 Hz), 4.56 (1 H, t, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 162.3, 153.8, 141.5, 128.0, 127.8, 126.4, 118.65, 86.2, 78.0, 39.35; MS 276 (MH^+); EIMS *m/z* 228 ($M^+ - HNO_2$), 180, 149, 126, 102, 91, 77.

2,4,6-Triamino-5-(2-nitro-1-phenethyl)pyrimidine (21g): isolated in 90% yield as a light yellow solid: mp 127 °C dec; IR (KBr) 3460, 3342, 3192, 1635, 1554, 1496, 1447, 1377, 1339, 1253, 1044, 700, 651 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.34−7.29 (2 H, m), 7.27−7.22 (3 H, m), 5.46 (1 H, dd, J = 13.0 and 6.5 Hz), 5.16 (1 H, dd, J = 13.0 and 9.0 Hz), 5.05 (1 H, dd, J = 13.0 and 6.5 Hz); ^{13}C NMR (DMSO-d_6) δ163.2, 161.8, 140.3, 129.65, 128.0, 127.8, 85.5, 76.59, 38.4; MS 275 (MH^+).

2,6-Diamino-5-[2-nitro-1-(3,4,5-trimethoxyphenyl)ethyl]-3*H*-pyrimidin-4-one (21h): isolated in 84% yield as a light yellow solid: mp 208 °C dec; ^1H NMR (DMSO-d_6) δ 9.94 (1 H, s), 6.99 (2 H, s), 6.14 (2 H, br s), 6.12 (2 H, br s), 5.51 (1 H, dd, J = 12.5 and 8.0 Hz), 5.24 (1 H, dd, J = 12.5 and 8.0 Hz), 4.43 (1 H, t, J = 8.0 Hz), 3.71 (6 H, s), 3.61 (3 H, s); ^{13}C NMR (DMSO-d_6) δ 162.4, 162.3, 153.6, 153.0, 137.2, 136.2, 135.6, 86.1, 77.9, 59.9, 55.8, 39.7; EIMS *m/z* 318 ($M^+ - HNO_2$); 306, 287, 217, 177, 152, 126, 98, 67; HRMS calcd for $C_{15}H_{18}N_4O_4$ ($M^+ - HNO_2$) 318.1328, found 318.1324.

2,4,6-Triamino-5-[2-nitro-1-(3,4,5-trimethoxyphenyl)-ethyl]pyrimidine (21i): isolated in 75% yield as a light yellow solid: mp 176 dec; IR (KBr) 3475, 3377, 3188, 2942, 1614, 1569, 1508, 1447, 1376, 1331, 1241, 1126, 999, 909, 794, 733 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.56 (2 H, s), 5.51 (4 H, s), 5.47 (2 H, s), 5.46 (1 H, m), 5.16 (1 H, m), 4.96 (1 H, m), 3.73 (6 H, s), 3.63 (3 H, s); ^{13}C NMR (DMSO-d_6) δ 163.4, 162.05, 154.0, 137.4, 135.8, 105.8, 85.2, 76.9, 61.1, 57.1, 38.9; EIMS *m/z* 364 (M^+), 318, 239, 207, 192, 177, 149, 125, 98, 84, 67; HRMS calcd for $C_{15}H_{20}N_6O_6$ 364.1495, found 364.1513.

2, 6-Diamino-5-[2-nitro-1-(2-chlorophenyl)ethyl]-3 *H*-pyrimidin-4-one (21j): isolated in 81% yield as a light yellow soild: mp 158 °C dec; IR (KBr) 3492, 3395, 3339, 3205, 2850, 1628, 1597, 1547, 1445, 1389, 1038, 794, 763 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.93 (1 H, s), 7.68 (1 H, d, J = 7.5 Hz), 7.40 (1 H, d, J = 7.5 Hz), 7.25 (2 H, q, J = 8.5 Hz), 6.19 (2 H, br s), 5.84 (2 H, br s), 5.54 (1 H, dd, J = 13.0 and 7.5 Hz), 5.22 (1 H, dd, J = 13.0 and 7.5 Hz), 4.78 (1 H, t, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 162.4, 153.8, 137.6, 132.6, 130.0, 129.2, 128.25, 126.9, 86.3, 75.8, 36.9; EIMS *m/z* 309 (M^+), 291, 275, 262, 260, 243, 218, 192, 183, 164, 151, 136, 126, 101, 89, 75, 68; MS (MH^+) 310; HRMS calcd for $C_{12}H_{12}ClN_5O_3$ 309.0628, found 309.0610.

2,4,6-Triamino-5-[2-nitro-1-(2-chlorophenyl)ethyl]pyrimidine (21k): isolated in 89% yield as a light yellow solid: 153 °C dec; IR (KBr) 3636, 3502, 3398, 3351, 1619, 1569, 1433, 1378, 1069, 862, 766, 706 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.60 (1 H, d, J = 7.5 Hz), 7.42 (1 H, d, J = 7.5 Hz), 7.32 (2 H, q, J = 6.5 Hz), 5.52−5.43 (1 H, m), 5.36 (6 H, br s), 5.31−4.80 (2 H, m); ^{13}C NMR (CD_3COOD) δ 159.3, 154.8, 135.8, 135.6, 132.5, 130.7, 128.9, 127.7, 82.4, 73.75, 37.1; EIMS *m/z* 308 (M^+), 262, 248, 224, 212, 195, 183, 168, 140, 125, 118, 101, 89, 75, 67; MS (MH^+) 309; HRMS calcd for $C_{12}H_{13}ClN_6O_2$ 308.0788, found 308.0792.

2, 6-Diamino-5-[2-nitro-1-(3-chlorophenyl)ethyl]-3 *H*-pyrimidin-4-one (21l): isolated in 86% yield as a light yellow solid: 180 °C dec; IR (KBr) 3489, 3402, 3168, 2910, 1630, 1594, 1540, 1493, 1446, 1377, 1174, 1082, 1001, 785, 679 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.89 (1 H, s), 7.59 (1 H, s), 7.50 (1 H, d, J = 7.5 Hz), 7.29 (1 H, t, J = 7.5 Hz), 7.24 (1 H, d, J = 8.0 Hz), 6.24 (2 H, br s), 6.13 (2 H, br s), 5.42 (1 H, dd, J = 12.5 and 7.5 Hz), 5.35 (1 H, dd, J = 12.5 and 7.5 Hz), 4.36 (1 H, t, J = 7.5 Hz); ^{13}C NMR ((DMSO-d_6) δ 162.3, 162.2, 153.7, 143.9, 132.6, 129.8, 127.6, 126.5, 126.4, 85.5, 77.4, 39.0; EIMS *m/z* 309 (M^+), 291, 274, 262, 260, 238, 225, 208, 192, 183, 151, 126, 113, 101, 86, 75, 68; HRMS calcd for $C_{12}H_{12}ClN_5O_3$ 309.0628, found 309.0622.

2,4,6-Triamino-5-[2-nitro-1-(3-chlorophenyl)ethyl]pyrimidine (21m): isolated in 81% yield as a light yellow solid: 182 °C dec; IR (KBr) 3498, 3482, 3381, 3199, 1639, 1608, 1561, 1473, 1438, 1382, 804, 682 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.37 (1 H, t, J = 8.0 Hz), 7.30 (2 H, d, J = 8.5 Hz), 7.24 (1 H, d, J = 8.0 Hz), 5.54 (4 H, br s), 5.51 (1 H, dd, J = 13.5 and 5.0 Hz), 5.44 (2 H, br s), 5.18 (1 H, dd, J = 13.5 and 9.0 Hz), 5.04 (1 H, t, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 162.35, 161.4, 141.85, 133.7, 130.15, 127.0, 126.55, 125.7, 83.6, 75.4, 37.2; MS *m/z* 308 (M^+), 262, 258, 248, 231, 206, 183, 140, 125, 113, 102, 89, 75, 67; HRMS calcd for $C_{12}H_{13}ClN_6O_2$ 308.0788, found 308.0776.

2, 6-Diamino-5-[2-nitro-1-(4-chlorophenyl)ethyl]-3 *H*-pyrimidin-4-one (21n): isolated in 80% yield as a light yellow solid: mp 92 °C dec; IR (KBr) 3480, 3390, 3196, 2916, 1624, 1547, 1490, 1436, 1376, 1256, 1093, 1015, 793 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.98 (1 H, s), 7.53 (2 H, d, J = 7.5 Hz), 7.30 (2 H, d, J = 7.5 Hz), 6.21 (2 H, br s), 6.13 (2 H, br s), 5.41 (1 H, t, J = 7.5 Hz), 5.32 (1 H, t, J = 7.5 Hz), 4.56 (1 H, t, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 162.3, 162.2, 153.7, 140.4, 131.0, 129.7, 127.9, 85.75, 77.5, 38.7; EIMS *m/z* 309 (M^+), 291, 274, 262, 249, 233, 206, 192, 183, 151, 142, 126, 102, 89, 75, 68; HRMS calcd for $C_{12}H_{12}ClN_5O_3$ 309.0639, found 309.0642.

2,4,6-Triamino-5-[2-nitro-1-(4-chlorophenyl)ethyl]pyrimidine (21o): isolated in 87% yield as a light yellow solid: mp 80 °C dec; IR (KBr) 3476, 3372, 3188, 1617, 1568, 1444, 1375, 1235, 1092, 1014, 802 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.40 (2 H, d, J = 7.5 Hz), 7.29 (2 H, d, J = 7.5 Hz), 5.60 (4 H, br s), 5.50 (2 H, br s), 5.47 (1 H, m), 5.17 (1 H, t, J = 8.5 Hz), 5.04 (1 H, t, J = 8.5 Hz); ^{13}C NMR (DMSO-d_6) δ 162.3, 161.25, 138.1, 131.2, 128.9, 128.25, 83.75, 75.5, 37.0; EIMS *m/z* 308 (M^+), 262, 248, 231, 217, 206, 189, 183, 168, 150, 140, 125, 113, 101, 84, 75, 67; HRMS calcd for $C_{12}H_{13}ClN_6O_2$ 308.0788, found 308.0771.

Compounds **19f**−**o** were cyclized as described above for the conversion of **21a** to **19a**.

2-Amino-5-phenyl-3,7-dihydropyrrolo[2,3-*d*]pyrimidin-4-one (19f): isolated in 42% yield as a light yellow solid: ^1H NMR (DMSO-d_6) δ 11.19 (1 H, s), 10.31 (1 H, br s), 7.91 (2 H, d, J = 7.5 Hz), 7.26 (2 H, t, J = 7.6 Hz), 7.12 (1 H, t, J = 6.8 Hz), 7.03 (1 H, d, J = 2.4 Hz), 6.11 (2 H, br s); ^{13}C NMR (DMSO-d_6) δ 158.9, 152.45, 152.15, 134.7, 127.6, 127.2, 125.1, 119.4, 115.097.0; MS 227 (MH^+).

2,4-Diamino-5-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (19g): isolated in 46% yield as a light yellow solid: ^1H NMR (CD_3-OD) δ 7.45−7.40 (4 H, m), 7.33−7.29 (1 H, s), 6.79 (1 H, s);

^{13}C NMR (CD_3OD) δ 160.39, 159.60, 154.41, 137.07, 130.02, 129.66, 127.89, 118.77, 118.22, 95.76; MS 226 (MH^+); EIMS *m*/*z* 225 (M^+), 212, 197, 179, 140, 104, 86, 77, 69.

2-Amino-5-(2-chlorophenyl)-3,7-dihydropyrrolo[2,3-*d*]-pyrimidin-4-one (19j): isolated in 41% yield as a light blue solid: IR (KBr) 3337, 3159, 1676, 1516, 1473, 1419, 1248, 1112, 1051, 756, 615 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.30 (1 H, s), 10.41 (1 H, s), 7.62−7.40 (4 H, m), 6.89 (1 H, s), 6.25 (2 H, br s); ^{13}C NMR (DMSO-d_6) δ 159.8, 153.1, 152.7, 137.8, 131.9, 128.95, 127.1, 125.0, 124.1, 118.8, 116.7, 97.2; EIMS *m*/*z* 260 (M^+), 238, 225, 213, 206, 196, 183, 162, 148, 136, 126, 118, 101, 78, 69; HRMS calcd for $C_{12}H_9ClN_4O$ 260.0465, found 260.0466.

2,4-Diamino-5-(2-chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (19k): isolated in 43% yield as a yellow soild: IR (KBr) 3339, 3104, 1659, 1543, 1454, 1383, 1393, 967, 819, 759, 615 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.04 (1 H, s), 7.57 (1 H, d, J = 7.0 Hz), 7.41−7.36 (3 H, m), 6.78 (1 H, s), 5.63 (2 H, br s), 5.39 (2 H, br s); ^{13}C NMR (DMSO-d_6) δ 160.8, 158.5, 154.7, 135.5, 134.2, 133.5, 130.9, 129.9, 128.5, 118.7, 113.2, 97.6; EIMS *m*/*z* 295 (M^+), 242, 224, 217, 207, 197, 180, 169, 155, 137, 127, 112, 102, 94, 89, 78, 69; HRMS calcd for $C_{12}H_{10}ClN_5$ 259.0625, found 259.0638.

2-Amino-5-(3-chlorophenyl)-3,7-dihydropyrrolo[2,3-*d*]-pyrimidin-4-one (19l): isolated in 41% yield as a light green solid: IR (KBr) 3144, 1695, 1520, 1477, 1418, 1311, 1114, 981, 775, 759, 683, 622 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.34 (1 H, s), 10.38 (1 H, s), 8.20 (1 H, d, J = 1.5 Hz), 7.90 (1 H, t, J = 8.0 Hz), 7.18 (1 H, s), 7.15−7.12 (2 H, m), 6.14 (2 H, br s); ^{13}C NMR (DMSO-d_6) δ 159.2, 153.0, 152.6, 137.15, 132.8, 129.8, 127.0, 125.4, 124.9, 118.1, 116.3, 96.9; EIMS *m*/*z* 260 (M^+), 243, 218, 208, 189, 183, 180, 162, 156, 136, 127, 113, 99, 78, 69; HRMS calcd for $C_{12}H_9ClN_4O$ 260.0465, found 260.0471.

2,4-Diamino-5-(3-chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (19m): isolated in 40% yield as a yellow solid: IR (KBr) 3349, 3180, 1653, 1473, 1382, 1090, 784, 616 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.37 (1 H, s), 7.52−7.30 (4 H, m), 7.04 (1 H, s), 6.15 (4 H, br s). ^{13}C NMR (CD_3COD/DMSO-d_6) δ 157.5, 156.7, 153.1, 127.5, 134.0, 130.9, 127.9, 126.8, 126.5, 118.8, 115.9, 93.5; EIMS *m*/*z* 259 (M^+), 242, 217, 207, 183, 165, 156, 152, 139, 125, 116, 111, 102, 89, 78, 69; HRMS calcd for $C_{12}H_{10}ClN_5$ 259.0625, found 259.0613.

2-Amino-5-(4-chlorophenyl)-3,7-dihydropyrrolo[2,3-*d*]-pyrimidin-4-one (19n): isolated in 49% yield as a light green solid: IR (KBr) 3391, 3201, 1635, 1520, 1490, 1447, 1091, 1015, 964, 837, 784 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.20 (1 H, s), 10.31 (1 H, s), 8.11 (2 H, d, J = 8.0 Hz), 7.34 (2 H, d, J = 8.0 Hz), 7.05 (1 H, s), 6.21 (2 H, br s); ^{13}C NMR (DMSO-d_6) δ 159.1, 152.8, 152.5, 133.8, 129.0, 128.9, 127.7, 118.3, 115.7, 97.0; EIMS *m*/*z* 260 (M^+), 243, 231, 219, 181, 150, 137, 111, 102, 94, 78, 63; HRMS calcd for $C_{12}H_9ClN_4O$ 260.0465, found 260.0459.

2,4-Diamino-5-(4-chlorophenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (19o): isolated in 54% yield as a yellow solid: IR (KBr) 3466, 3335, 3173, 1661, 1540, 1455, 1385, 1092, 825, 617 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.48 (1 H, s), 7.48 (2 H, d, J = 8.0 Hz), 7.44 (2 H, d, J = 8.0 Hz), 6.98 (1 H, s), 6.45 (4 H, br s); ^{13}C NMR (DMSO-d_6) δ 155.4, 155.1, 152.55, 133.6, 131.2, 129.7, 128.9, 118.8, 116.0, 92.8; EIMS *m*/*z* 259 (M^+), 242, 217, 182, 153, 139, 125, 112, 94, 78, 63; HRMS calcd for $C_{12}H_{10}ClN_5$ 259.0625, found 259.0621.

General Procedure for the Preparation of 21 by the Ultrasound-Promoted One-Pot Three-Component Reaction. A mixture of the arylaldehyde (10 mmol), 2,4,6-triaminopyrimidine or 2,6-diamino-3*H*-pyrimidin-4-one (10 mmol), nitromethane (7 mL), NH_4OAc (2 g), and acetic acid (5 mL) was sonicated at 60−65 °C. After starting material was consumed, the mixture was poured into ethyl acetate and washed with an excess amount of saturated aqueous solution of Na_2CO_3. The organic layer was separated and dried. The solvent was removed and the residue was purified by chromatography on silica gel to afford **21**.

2-Amino-6-hydroxy-5-(2-nitro-1-phenethyl)-3*H*-pyrimidin-4-one (27a): To a mixture of 0.51 g (4.0 mmol) of 2-amino-6-hydroxy-3*H*-pyrimidinone and 0.57 g (4.0 mmol) of 1-nitro-2-phenylethylene in 10 mL of ethyl acetate and 5 mL of water was added 0.56 mL (4.0 mmol) of triethylamine. The resulting mixture was stirred at 60 °C for 20 h. Acetic acid (2 mL) was added, and the white solid was collected, washed with a mixture of ethyl acetate and hexane (1:1), and dried to give 0.77 g (70% yield) of product: IR (KBr) 3270, 3086, 2850, 2696, 1621, 1548, 1420, 1379, 1163, 1108, 839, 703 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.60 (2 H, br s), 7.37 (2 H, t, J = 7.0 Hz), 7.24 (2 H, t, J = 8.0 Hz), 7.16 (1 H, t, J = 7.5 Hz), 6.77 (2 H, br s), 5.30−5.22 (2 H, m), 4.79 (1 H, t, J = 8.0 Hz); ^{13}C NMR (DMSO-d_6) δ 162.7, 152.0, 141.9, 128.0, 127.55, 126.2, 87.9, 77.8, 37.6; EIMS *m*/*z* 227 (M^+), 214, 185, 172, 152, 115, 99, 86, 77.

2-Amino-6-hydroxy-5-[2-nitro-1-(4-chlorophenyl)ethyl]-3*H*-pyrimidin-4-one (27b): isolated in 78% yield as a light yellow solid: IR (KBr) 3085, 2692, 1624, 1550, 1489, 1417, 1384, 1299, 1108, 1091, 1015, 803, 738 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.67 (2 H, br s), 7.39 (2 H, d, J = 9.0 Hz), 7.28 (2 H, d, J = 9.0 Hz), 7.00 (2 H, br s), 5.33−5.16 (3 H, m), 4.78 (1 H, t, J = 9.0 Hz); EIMS *m*/*z* 227 ($M^+ - HNO_2$), 207, 187, 170, 169, 133, 127, 117, 105, 103, 99, 91; HRMS calcd for $C_{12}H_9N_3O_2$ 227.0649, found 227.0695.

Acknowledgment. We are indebted to Eli Lilly & Company both for financial support of this work and for the in vitro cell growth inhibition studies.

JO030248H