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TETRAHEDRON

Synthesis of *N*-{[4-(2-Amino-4(3*H*)-oxo-5,6,7,8-tetrahydro-(9*H*)-pyrimido[4,5-*b*]-azepin-6-yl)methyl]benzoyl}-L-glutamic Acid and Two of its Conformationally-Restricted Analogs †

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Abstract: Synthesis of the titled tetrahydropyrimidoazepine-based folate (**6a**) is described using a regiospecific γ-alkylation reaction between the dienolate generated from 3-carboethoxy-*N*-2,4-dimethoxybenzyl-1,5,6,7-tetrahydro-(1*H*)-azepin-2-one (**33**) and methyl 4-formylbenzoate, as the key step. The isoxazolinopyrimidoazepine and isoxazolopyrimidoazepine-based folates (**7a** and **8a** respectively) were also prepared (via intramolecular 1,3-dipolar cycloaddition chemistry) as conformationally-restricted analogs of **6a**. All three compounds were prepared as potential antitumor agents based on the known, structurally related, antitumor agent 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF). Both **7a** and **8a** were inactive in the human colon carcinoma (GC3c1) cell culture assay. Compound **6a**, however, was weakly active (IC_{50} = 2.0 μM) in the above assay.

Dihydrofolate reductase (DHFR), thymidylate synthase (TS), and glycinamide ribonucleotide formyltransferase (GARFT) are three folate requiring enzymes which play important roles in the biosynthesis of nucleotides. All three of these enzymes are attractive target sites for the development of anticancer agents.[1] The design and synthesis of folic acid (**1**) based antimetabolites as potential inhibitors of the above enzymes has received much interest over the past decade.[1-3] There are currently several antifolates at various stages of clinical development. [4] For example, 10-ethyl-10-deazaaminopterin (Edatrexate, **2**)[5] is an inhibitor of DHFR, while the pyrrolopyrimidine LY231514 (**3**)[6] inhibits TS and Lometrexol [7] [(**5**, the (6R)-diastereomer of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF; **4**)] is known to exert its cytotoxic effect *via* inhibition of GARFT.

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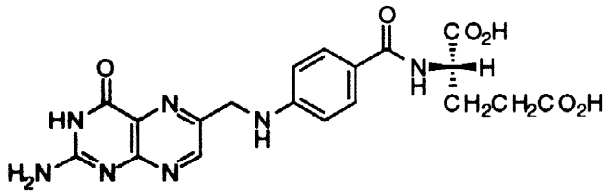
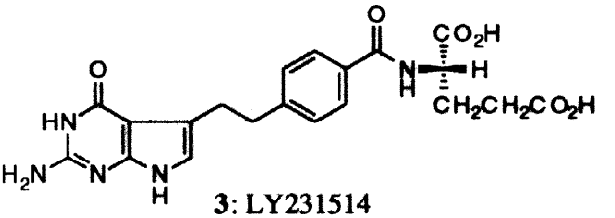
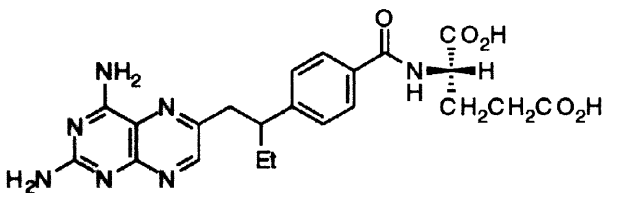


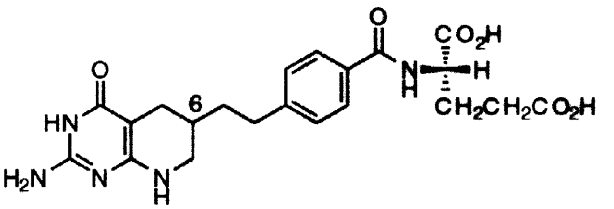
1: Folic Acid



3: LY231514



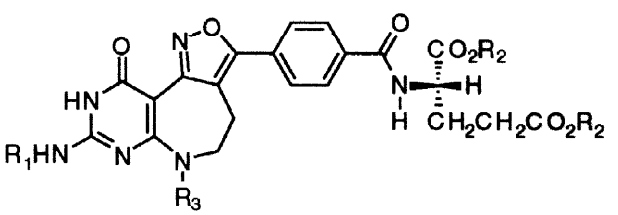
2: Edatrexate



4: DDATHF (6RS)
5: Lometrexol (6R)

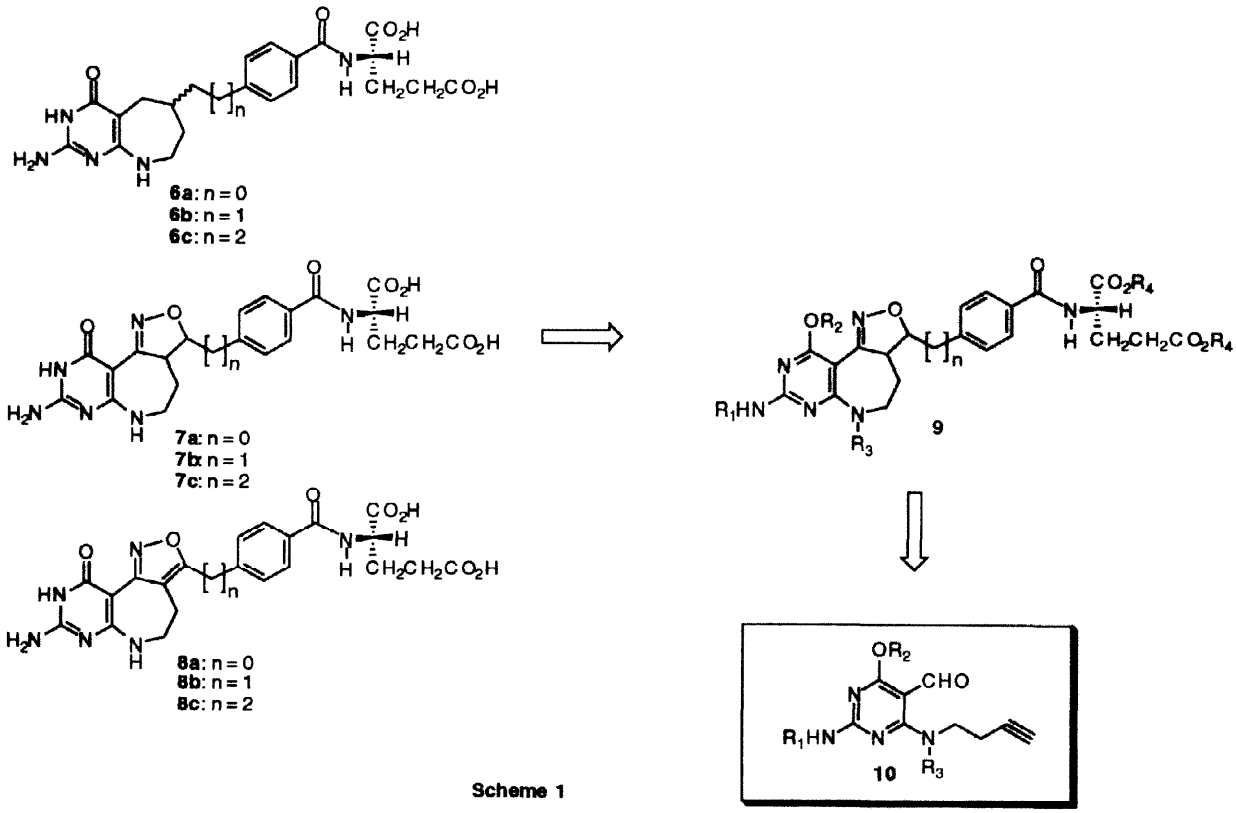
Over the last few years we have reported on our efforts to prepare pyrimidoazepine-based folates as potential antitumor agents *via* inhibition of GARFT and/or TS. [8-10] In this paper we report the synthesis of the title compound (**6a**) as well as two of its conformationally-restricted analogs (**7a** and **8a**; Scheme 1).

Recently we have developed an intramolecular nitrile oxide cycloaddition method, as a key step, to access the pyrimidoazepine system.[8-9] We have reported using this method to prepare the isoxazolopyrimidoazepine derivative **11**.[10] Since it is well known that the 8-NH of DDATHF and its derivatives is required for biological activity, [11] we wanted to prepare the conformationally-restricted target **8a**, from intermediate **13**. We anticipated that **13** would become available from intermediate **12** (which we had prepared previously)[10] *via* removal of the N-benzyl group. Unfortunately, we were unable to convert **12** to **13**.[12] Consequently, we revised our synthetic plan to include a *N-para*-methoxybenzyl (PMB) group in place of the offending *N*-benzyl group.



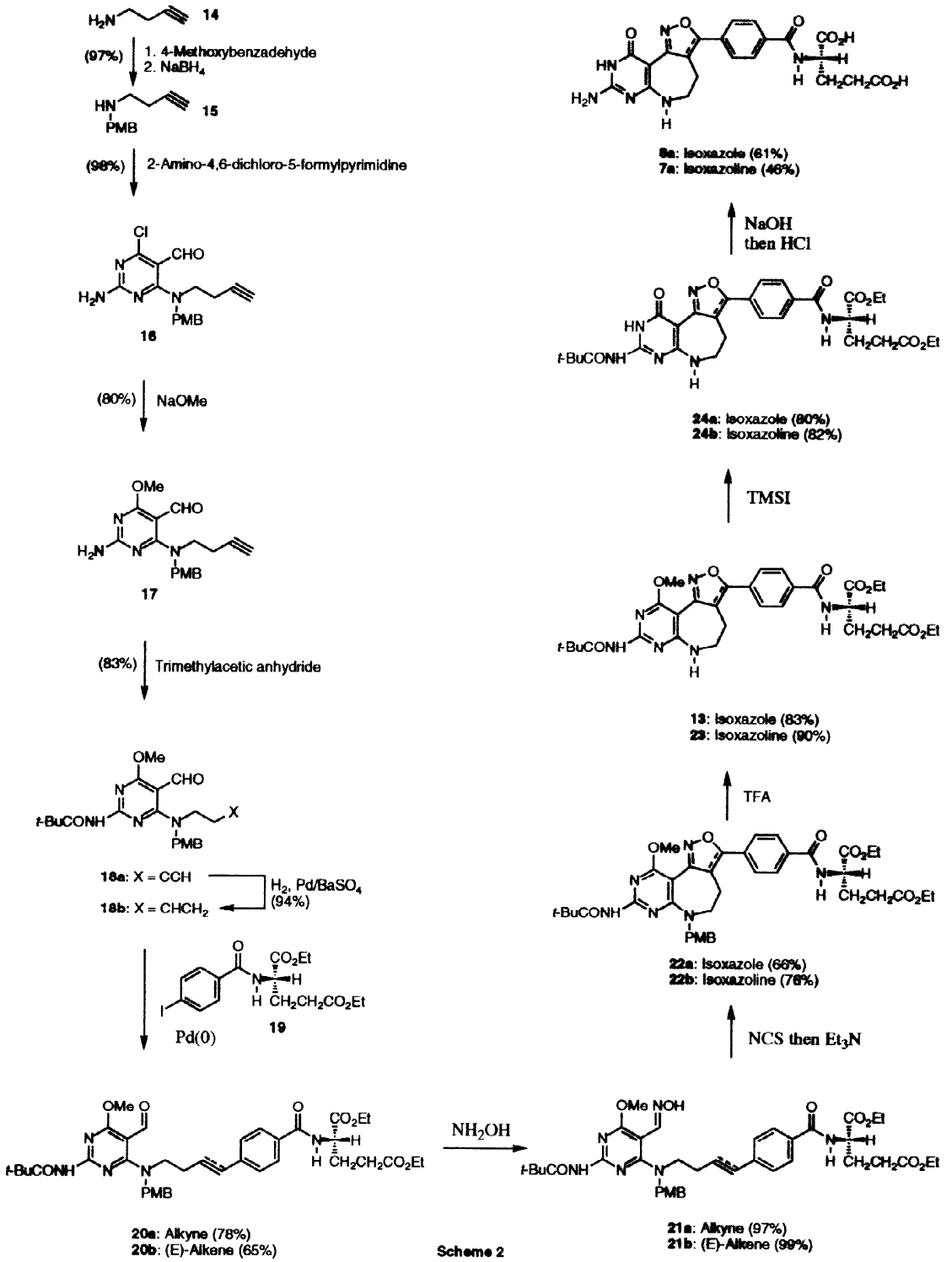
11: $R_1 = R_2 = H$, $R_3 = Bn$
12: $R_1 = COCMe_3$, $R_2 = Et$, $R_3 = Bn$
13: $R_1 = COCMe_3$, $R_2 = Et$, $R_3 = H$

Our strategy was to prepare a pyrimidine derivative of type **10** as a common intermediate, from which we envisioned the synthesis of the parent pyrimidoazepine-based folates **6a-6c**, as well as the conformationally-restricted isoxazolino- and isoxazolopyrimidoazepine-based folates (**7a-7c** and **8a-8c** respectively; Scheme 1).



Scheme 1

Using similar chemistry used to prepare the isoxazolopyrimidoazepine derivative **12**, we made the *N*-PMB derivative **22a** (Scheme 2). Thus, reductive alkylation of 4-amino-1-butyne (**14**) with 4-methoxybenzaldehyde gave the *N*-PMB protected amine **15** in 97% yield (Scheme 2). This reacted with 2-amino-4,6-dichloro-5-formylpyrimidine to give **16** in 98% yield as a colorless solid. Reaction of **16** with sodium methoxide in refluxing methanol led to the formation of the methyl ether **17** in 80% yield. We knew from previous experience that it would be advantageous to derivatize the 2-amino functionality of **17** as a pivaloylamino group to improve its solubility properties. Thus, reaction of **17** with trimethylacetic anhydride in refluxing toluene in the presence of a catalytic amount of 4-dimethylaminopyridine provided the 2-pivaloylamino derivative **18a**, our common intermediate, from which we planned to prepare all of the targets **6-8**. A palladium catalyzed coupling reaction of **18a** with diethyl 4-iodobenzoyl-L-glutamate (**19**) [13], provided the alkyne **20a** in 78% yield, after purification by chromatography on silica gel. Reaction of **20a** with hydroxylamine in ethanol at room temperature afforded the expected oxime **21a** in 97% yield, as a colorless solid. Treatment of this oxime with NCS in methylene chloride at room temperature followed by treatment with triethylamine led to the desired intramolecular 1,3-dipolar cycloaddition reaction (between the

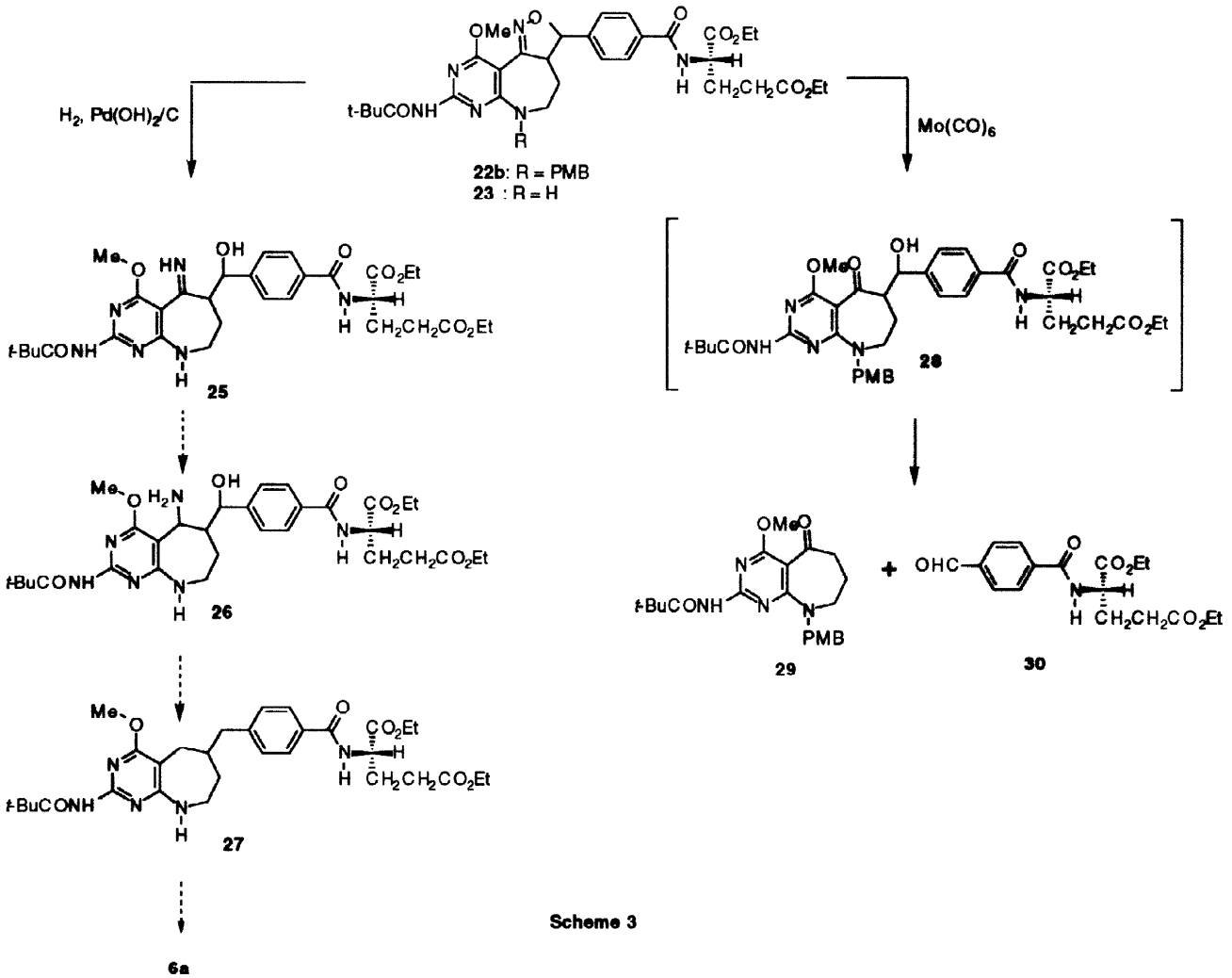

14
(97%) 1. 4-Methoxybenzadehyde 2. NaBH4
15
(98%) 2-Amino-4,6-dichloro-5-formylpyrimidine
16
(80%) NaOMe
17
(83%) Trimethylacetic anhydride
18a: X = CCH
18b: X = CHCH2
H2, Pd/BaSO4 (94%)
19
Pd(0)
20a: Alkyne (78%)
20b: (E)-Alkene (65%)
NH2OH
21a: Alkyne (97%)
21b: (E)-Alkene (99%)
NCS then Et3N
22a: Isoxazole (66%)
22b: Isoxazoline (76%)
TFA
23: Isoxazole (83%)
24a: Isoxazole (80%)
24b: Isoxazoline (82%)
TMSI
NaOH then HCl
8a: Isoxazole (61%)
7a: Isoxazoline (46%)

Scheme 2

corresponding nitrile oxide, generated in situ, and the tethered alkyne) to give the cycloadduct **22a**, which was isolated in 66% yield after chromatography on silica gel. Exposure of **22a** with neat TFA resulted in cleavage of the *N*-PMB group to give the corresponding N-H compound (**13**) in 83% yield. Reaction of **13** with iodotrimethylsilane in refluxing methylene chloride followed by quenching with methanol, led to cleavage of the methyl ether and gave the pyrimidin-4-one derivative **24a** in 80% yield. Finally, treatment of **24a** with 1% NaOH, followed by treatment with hydrochloric acid gave the desired isoxazolopyrimidoazepine-based folate (**8a**) in 61% yield.

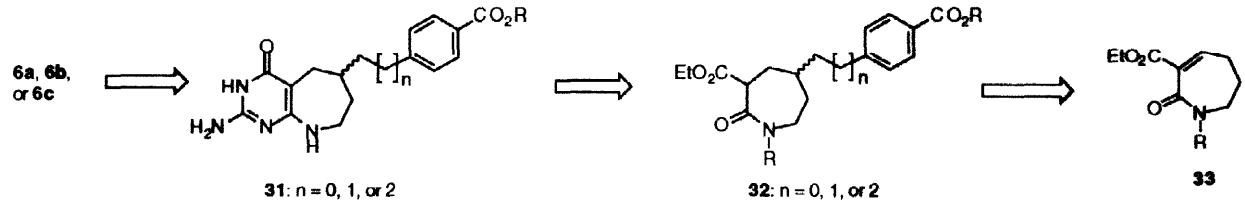
We also wanted to prepare the isoxazolinopyrimidoazepine-based folate **7a**, as another conformationally restricted analog of **6a**. Thus, reduction of the alkyne **18a** with hydrogen and $Pd/BaSO_4$ in pyridine gave the corresponding alkene (**18b**) in 94% yield (Scheme 2). This was converted to the desired target **7a** using similar chemistry as described above and is summarized in Scheme 2. Reaction of **18b** with diethyl 4-iodo-benzoyl-L-glutamate (**19**)[13] under Heck reaction conditions with a catalytic amount of Pd(0) gave the (*E*)-styrene derivative **20b** in 65% yield. We assigned the (*E*) stereochemistry for the double bond based on the observed coupling constant of 15.7 Hz for the olefinic protons. The aldehyde **20b** was smoothly converted to the oxime **21b** by reaction with hydroxylamine in ethanol at room temperature. The 1,3-dipolar cycloaddition chemistry gave the cycloadduct **22b** in 76% yield, as a mixture of two diastereomers which were not separated. Treatment of **22b** with TFA followed by treatment with iodotrimethylsilane gave the pyrimidone derivative **24b**. Saponification of **24b** in aqueous sodium hydroxide followed by acidification of the reaction mixture with hydrochloric acid gave the desired target **7a** as a mixture of two diasteromers.

We had envisioned that we would be able to convert the isoxazoline intermediate **23** to the parent pyrimidoazepine target **6a** as shown in Scheme 3. Thus, we hoped that treatment of **23** with Pearlman's catalyst in acetic acid under 50 psi of hydrogen would result in the formation of the pyrimidoazepine derivative **27** *via* the following reactions: (i) reductive cleavage of the isoxazoline N-O bond; (ii) further reduction of the imine to the corresponding amine [14] and (iii) hydrogenolysis of the benzylic hydroxy and amino groups. In the event, however, we isolated the imino alcohol **25** in 30% yield after purification by column chromatography. We were unable to convert this to **27**. Even when we used a stoichiometric amount of palladium hydroxide in warm acetic acid with hydrogen at 50 psi for two weeks, we recovered **25** unchanged! We also attempted to further reduce the imino alcohol **25** using hydrogen and Adam's catalyst or 10% Pd/C in different solvents (ethyl acetate, ethanol and acetic acid). In each case the starting imino alcohol was recovered. We had also hoped that cleavage of the isoxazoline N-O bond of **22b** would result in the isolation of the β-hydroxy ketone **28** (Scheme 3) which, in principle, could be converted to the desired target **6a**. With this in mind, we treated the isoxazoline **22b** with molybdenum hexacarbonyl in aqueous acetonitrile, [15] but we were disappointed to isolate the ketone **29** and aldehyde **30** which clearly result from a reto-aldol reaction from the desired β-hydroxy ketone **28**. We had also attempted to prepare **28** from the treatment of **22b** with hydrogen and Raney-Nickel in aqueous methanol. [16] Unfortunately, these conditions led to the formation of several products, as evidenced by TLC, from which we were unable to isolate the desired β-hydroxy ketone **28**.



Scheme 3

While we were working on the above chemistry, we were also exploring alternative methods to access the parent tetrahydropyrimidoazepine targets **6a-6c**. The key step in one such strategy involves a regiospecific γ-alkylation of the dienolate generated from the azepinone derivative **33** to give **32** (Scheme 4). A ring annulation reaction of **32** with guanidine was expected to give the pyrimidoazepine derivative **31** and peptide coupling chemistry with L-glutamic acid diethyl ester followed by saponification was expected to provide the desired parent targets (**6a-6c**).

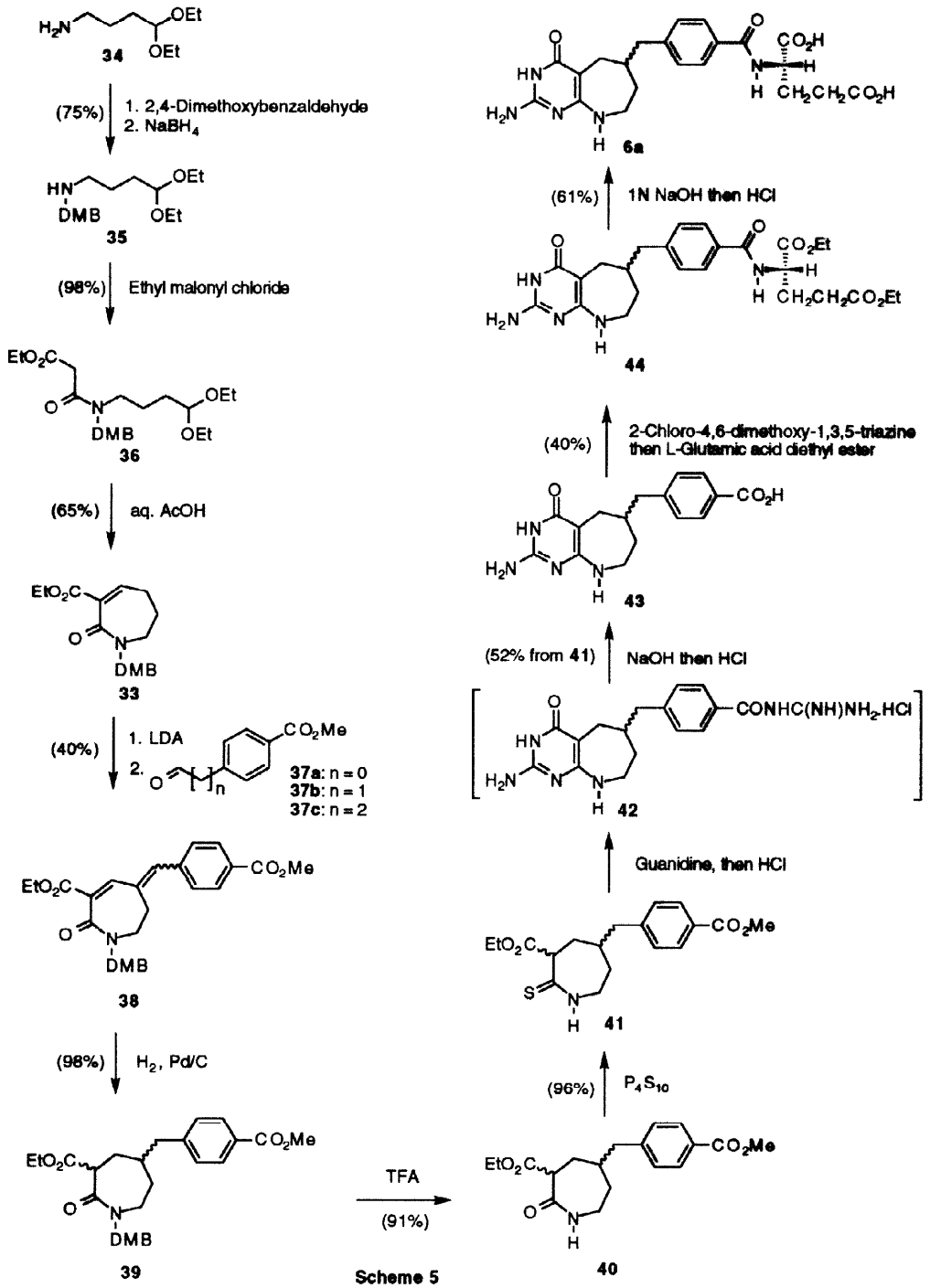


Scheme 4

We prepared the common intermediate **33** as shown in Scheme 5. Thus, reductive alkylation of aminobutyraldehyde diethyl acetal (**34**) with 2,4-dimethoxybenzaldehyde gave the 2,4-dimethoxybenzyl (DMB) protected amine **35** in 75% yield. Reaction of **35** with ethyl malonyl chloride gave the amide derivative **36** in 98% yield. When this was exposed to wet acetic acid, the azepinone derivative **33** was produced in good yield (65%) *via* an intramolecular acid catalyzed aldol reaction, followed by dehydration. Thebtaranonth and Yenjai have reported that the dienolate generated from 5,5-diphenyl-3-methyl-2-cyclopenteneone undergoes regiospecific γ-alkylation with aldehydes in the presence of zinc chloride.[17] Following their lead, we treated **33** with LDA followed by methyl 4-formylbenzoate in the presence of zinc chloride and after a mildly acidic workup we were gratified to isolate the diene **38**, albeit, in only modest yield (40%; as a mixture of (*E*) and (*Z*) isomers). No evidence of α-alkylation was observed. Reduction to the saturated system **39** was achieved easily in near quantitative yield with hydrogen and a catalytic amount of 10% Pd/C. The DMB group was cleaved smoothly by stirring at 40 °C in TFA for 0.5 h, which gave the lactam **40** in 91% yield. Reaction of **40** with phosphorus pentasulfide in warm THF gave the thiolactam **41** in 96% yield. Treatment of **41** with 5 equivalents of hot guanidine (in a manner similar to that reported by Barnett et. al.[18]), followed by acidification gave the acyl guanidine hydrochloride salt **42**. Basic hydrolysis of **42** gave, after acidification, the free carboxylic acid derivative **43**. Activation of the carboxylic acid group with 2-chloro-4,6-dimethoxy-1,3,5-triazine [19] followed by coupling with the diethyl ester of L-glutamic acid gave the tetrahydropyrimidoazepine-based folate **44** in 40% yield after purification by chromatography on silica gel. Finally, saponification in 1N sodium hydroxide, followed by acidification with hydrochloric acid gave the desired parent target **6a** in 61% yield as a mixture of two diastereomers.

Compounds **6a**, **7a** , and **8a** were all tested in a human colon carcinoma (GC3c1) cell culture assay. While **7a** and **8a** were totally inactive in this assay, the tetrahydropyrimidoazepine **6a** showed marginal activity (IC_{50} = 2.0 μM) and will be further evaluated in other human tumor cell lines. It is noteworthy that Taylor and Dowling have recently reported the synthesis of **6b** (as a mixture of two diastereomers, via a synthetic strategy involving a Beckmann rearrangement as a key step), and found it to have significant activity in the human CCRF-CEM lymphoblastic leukemia cell culture assay (IC_{50} = 47 nM). [20] It was found to be virtually equipotent to DDATHF as an inhibitor of GARFT isolated from murine L1210 leukemia cells. We are currently investigating the regiospecific γ-alkylation reaction of **33** with the one and two carbon extended

aldehydes (**37b** and **37c**) as a method to prepare targets **6b** and **6c** respectively. We are also exploring the 1,3-dipolar cycloaddition methodology to prepare two conformationally-constrained analogs of **6b**, namely **7b** and **8b**.



Scheme 5

Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected. All NMR spectra were recorded on either a Varian VXR-300 (proton: 300 MHz; and carbon: 75 MHz) or a JEOL JNM GSX270 (proton: 270 MHz; carbon: 67.5 MHz) spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane. Column chromatography was performed on Merck silica gel 60 (240-400) mesh; silica gel plates were routinely used for TLC determinations. Elemental analyses were performed by Desert Analytics, Tucson, AZ, and were within ±0.4% of the theoretical values. Low resolution mass spectra were obtained by using electrospray ionization technique on a Micromass Inc., Platform II single quadrupole mass spectrometer. High resolution mass spectral data [either fast atom bombardment (FAB) or electron ionization (EI)] were obtained from the Nebraska Center for Mass Spectrometry.

***N*-4-Methoxybenzyl-4-amino-1-butyne (15).** To a mixture of 4-amino-1-butyne hydrochloride [21] (9.0g, 0.0857 mole) and anhydrous methanol (300 mL), triethylamine (11.92 mL, 0.0857 mole) was added dropwise. The resulting solution was allowed to stir at room temperature for 1 h. 4-Methoxybenzaldehyde (10.42 mL, 0.0857 mole) was added and the mixture was stirred at rt for an additional 1 h. The solution was then cooled in an ice bath and sodium borohydride (6.51g, 0.1714 mole) was added in small portions over 1 h, and the reaction mixture was stirred an additional 1 h. Water (150 mL) was slowly added and the mixture was extracted with methylene chloride. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed by rotary evaporation to yield 15.8 g (97.5%) of a colorless oil which was used without further purification. ^{1}H NMR ($CDCl_3$): δ 2.00 (t, 1 H, J = 2.6 Hz), 2.38 (dt, 2 H, J = 2.6, 6.6 Hz), 2.75 (t, 2 H, J = 6.6 Hz), 3.72 (s, 2 H), 3.76 (s, 3 H), 6.85 (d, 2 H, J = 8.7 Hz), 7.23 (d, 2 H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$): δ 19.16, 46.87, 52.41, 54.94, 69.42, 82.19, 113.52, 129.04, 131.79, 158.39.

2-Amino-6-(*N*-3-butynylamino-*N*-4-methoxybenzyl)-4-chloro-5-formyl-pyrimidine (16). A mixture of 2-amino-4,6-dichloro-5-formylpyrimidine [22] (13.0g, 0.0681 mole), **15** (12.864g, 0.0681 mole), triethylamine (9.50 mL, 0.0681 mole) and ethanol (300 mL) was heated at reflux for 6 h under a nitrogen atmosphere. After cooling to rt, the ethanol was removed by evaporation under reduced pressure. The resulting residue was partitioned between methylene chloride and water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed by evaporation under reduced pressure to yield 22.88 g (98%) of a colorless solid. An analytical sample was obtained by choromatography on silica gel, eluting with 35% ethyl acetate in hexane to give a colorless solid: mp 135-137 °C. ^{1}H NMR ($CDCl_3$): δ 1.97 (t, 1 H, J = 2.6 Hz), 2.47 (dt, 2 H, J = 2.6, 7.3 Hz), 3.58 (t, 2 H, J = 7.3 Hz), 3.79 (s, 3 H), 4.65 (s, 2 H), 5.90 (br s, 2 H), 6.85 (d, 2 H, J = 8.7 Hz), 7.11 (d, 2 H, J = 8.7 Hz), 10.10 (s, 1 H); ^{13}C NMR ($CDCl_3$): δ 17.41, 48.64, 53.98, 55.18, 70.11, 81.12, 105.45, 113.99, 128.07, 128.99, 158.96, 160.74, 163.61, 167.27, 185.12. Anal. Calcd. for $C_{17}H_{17}ClN_4O_2$: C, 59.22; H, 4.93; N, 16.25. Found: C, 59.13; H, 4.75; N, 16.07.

2-Amino-6-(*N*-3-butynylamino-*N*-4-methoxybenzyl)-5-formyl-4-methoxy-pyrimidine (17). To a freshly prepared solution of sodium methoxide (1.633 g, 0.071 moles of sodium in 200 mL anhydrous methanol) was added **16** (22.2 g, 0.0645 mole) and the mixture was heated at reflux under nitrogen for 3.5 h. After cooling the mixture to rt, the solvent was removed by evaporation under reduced pressure. The resulting residue was partitioned between methylene chloride and water and the organic layer was separated, dried over magnesium sulfate, and the solvent removed under reduced pressure. The oily residue was chromatographed on silica gel, eluting with 50% ethyl acetate in hexane to give 17.33 g (80%) of a light yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.94 (t, 1 H, J = 2.6 Hz), 2.45 (dt, 2 H, J = 2.6, 7.4 Hz), 3.58 (t, 2 H, J = 7.4 Hz), 3.78 (s, 3 H), 3.94 (s, 3 H), 4.68 (s, 2 H), 5.27 (br s, 2H), 6.83 (d, 2 H, J = 8.7 Hz), 7.13 (d, 2 H, J = 8.7 Hz), 9.92 (s, 1 H); ^{13}C NMR ($CDCl_3$): δ 17.58, 48.41, 53.96, 54.11, 55.17, 69.71, 81.70, 95.83, 113.86, 128.92, 129.22, 158.75, 162.14, 164.59, 174.43, 183.74. HRMS (EI) calcd. for $C_{18}H_{20}N_4O_3$: 340.1535 (M^+). Found: 340.1531.

6-(*N*-3-Butynylamino-*N*-4-methoxybenzyl)-5-formyl-4-methoxy-2-pivaloylamino pyrimidine (18a). A mixture of **17** (16.75 g, 0.0493 mole), trimethylacetic anhydride (50 mL, 0.246 mole), 4-dimethylaminopyridine (100 mg, 8.2 mmole), and toluene (500 mL) was heated at reflux for 2 days. The reaction mixture was cooled to rt, and the toluene and excess trimethylacetic anhydride were removed under reduced pressure. The residue was dissolved in methylene chloride and washed with a saturated solution of sodium bicarbonate, dried over anhydrous magnesium sulfate, and the solvent was removed by evaporation under reduced pressure. The residue was chromatographed on silica gel, eluting with 50% ethyl acetate in hexane to afford 17.4 g (83%) of a colorless solid: mp 42-45 °C. ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 9 H), 1.93 (t, 1H, J = 2.6 Hz), 2.50 (dt, 2 H, J = 2.7, 7.1 Hz), 3.65 (t, 2 H, J = 7.1 Hz), 3.77 (s, 3 H), 4.03 (s, 3 H), 4.76 (s, 2 H), 6.81 (d, 2 H, J = 8.7 Hz), 7.11 (d, 2 H, J = 8.7 Hz), 7.82 (br s, 1 H), 10.01 (s, 1 H); ^{13}C NMR ($CDCl_3$): δ 17.54, 27.34, 40.38, 48.71, 54.14, 54.74, 55.17, 69.92, 81.47, 97.86, 113.89, 128.52, 129.07, 156.65, 158.87, 163.38, 174.21, 175.52, 184.74. Anal. Calcd. for $C_{23}H_{28}N_4O_4$: C, 65.08; H, 6.65; N, 13.20. Found: C, 65.09; H, 6.33; N,12.84.

Diethyl *N*-[4-[4-(5-formyl-4-methoxy-2-pivaloylaminopyrimidin-4-yl)-*N*-4-methoxybenzylamino]-1-butynyl]benzoyl-L-glutamate (20a). A mixture of **18a** (1.15 g, 2.70 mmoles), diethyl 4-iodobenzoyl-L-glutamate [13] (1.24 g, 2.98 mmoles), palladium acetate (0.025 g, 0.11 mmoles), triphenylphosphine (0.057 g, 0.22 mmoles), copper(I) iodide (0.021 g, 0.11 mmoles), and triethylamine (10 mL) was stirred in acetonitrile (40 mL) at rt for 36 h. The solution was passed through a pad of celite and the solvent was removed by evaporation under reduced pressure. The resulting residue was partitioned between methylene chloride and water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under pressure. The reddish-brown residue was chromatographed on silica gel, eluting with 50 % ethyl acetate in hexane to yield 1.41 g (78% based on the recovery of 0.10g of starting material) of a colorless solid: mp 61-64 °C. ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 3 H, J = 7.1 Hz), 1.30 (t, with overlapping s, 12 H, J = 7.1 Hz), 2.16 (m, 1 H), 2.29 (m, 1 H), 2.46 (m, 2 H), 2.75 (t, 2 H, J = 6.9 Hz), 3.76 (t, 2 H, J = 7.0 Hz), 3.78 (s, 3 H), 4.03 (s, 3 H), 4.11 (dq, 2 H, J = 1.7, 7.1 Hz), 4.23 (q, 2 H, J = 7.1 Hz), 4.77 (m, 1 H), 4.83 (s, 2 H), 6.83 (d, 2 H, J = 8.2 Hz),

7.11 (d, 1 H, J = 7.2 Hz), 7.15 (d, 2 H, J = 8.2 Hz), 7.39 (d, 2 H, J = 8.5 Hz), 7.73 (d, 2 H, J = 8.5 Hz), 7.86 (s, 1 H), 10.05 (s, 1 H); ^{13}C NMR ($CDCl_3$): δ 14.04, 14.06, 18.64, 27.02, 27.30, 30.40, 40.35, 48.70, 52.34, 54.16, 54.69, 55.14, 60.75, 61.64, 81.46, 90.02, 97.87, 113.87, 126.86, 127.11, 128.52, 129.08, 131.58, 132.42, 156.61, 158.84, 163.46, 166.38, 171.79, 173.17, 174.19, 175.48, 184.62. Anal. Calcd. for $C_{39}H_{47}N_5O_9$: C, 64.18; H, 6.49; N, 9.59. Found: C, 63.91; H, 6.29; N, 9.74.

Diethyl *N*-[4-[4-(4-methoxy-5-oximinomethyl-2-pivaloylaminopyrimidin-4-yl)-*N*-4-methoxybenzyl-amino]-1-butynyl]benzoyl-L-glutamate (21a). A mixture of **20a** (2.0 g, 0.00274 mole), hydroxylamine hydrochloride (0.21 g, 0.003 mole), and pyridine (0.25 mL, 0.0031 mole) was stirred in absolute ethanol (50 mL) for 5 h at rt under nitrogen. The solvent was removed under reduced pressure and the residue was partitioned in methylene chloride and water. The organic layer was separated, dried over anhydrous magnesium sulfate, and removed under reduced pressure. The yellow residue was chromatographed on silica gel, eluting with 50% ethyl acetate in hexane to give 1.98g (97%) of a colorless solid: mp 64-67 °C. ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 3 H, J = 7.1 Hz), 1.30 (t, with overlapping s, 12 H, J = 7.1 Hz), 2.15 (m, 1 H), 2.30 (m, 1 H), 2.46 (m, 2 H), 2.76 (t, 2 H, J = 6.9 Hz), 3.71 (t, 2 H, J = 6.9 Hz), 3.77 (s, 3 H), 3.95 (s, 3 H), 4.10 (dq, 2 H, J = 1.7, 7.1 Hz), 4.24 (q, 2 H, J = 7.1 Hz), 4.74 (s, 2 H), 4.77 (m, 1 H), 6.82 (d, 2 H, J = 8.7 Hz), 7.09 (d, 1 H, J = 8.9 Hz), 7.14 (d, 2 H, J = 8.4 Hz), 7.37 (d, 2 H, J = 8.4 Hz), 7.70 (d, 2 H, J = 8.4 Hz), 7.82 (s, 1 H), 8.06 (br s, 1 H), 9.20 (br s, 1 H); ^{13}C NMR ($CDCl_3$): δ 14.07, 14.09, 18.58, 27.07, 27.42, 30.44, 40.25, 48.78, 52.36, 54.01, 54.47, 55.18, 60.80, 61.73, 81.38, 90.55, 91.21, 113.90, 126.93, 127.19, 128.78, 129.22, 131.56, 132.36, 144.46, 154.81, 158.79, 164.02, 166.46, 169.32, 171.95, 173.21, 175.61. Anal. Calcd. for $C_{39}H_{48}N_6O_9$: C, 62.89; H, 6.49; N, 11.28. Found: C, 62.52; H, 6.63; N, 11.14.

Diethyl 4-[(10-methoxy-6-(4-methoxybenzyl)-8-pivaloylamino)-4,5-dihydroisoxazolo[3,4-*d*]-pyrimido[4,5-*b*]azepin-3-yl] benzoyl-L-glutamate (22a). A mixture of **21a** (3.2 g, 0.0043 mole), *N*-chlorosuccinimide (0.633 g, 0.0047), and anhydrous methylene chloride (40 mL) was stirred at rt under nitrogen for 3 h. Triethylamine (0.70 mL, 0.005 mole) was added and the solution was allowed to stir an additional 2 h. Water was added to the reaction mixture and the organic layer was separated, dried over anhydrous magnesium sulfate, and the solvent was removed via evaporation under reduced pressure. The residue was chromatographed on silica gel, eluting with 75% ethyl acetate in hexane to give 2.1 g (66%) of a colorless solid: mp 84-87 °C. ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3 H, J = 7.2 Hz), 1.31 (t, with overlapping s, 12 H, J = 7.2 Hz), 2.18 (m, 1 H), 2.31 (m, 1 H), 2.48 (m, 2 H), 2.85 (m, 2 H), 3.43 (m, 2 H), 3.82 (s, 3 H), 4.12 (q, 2 H, J = 7.0 Hz), 4.17 (s, 3 H), 4.25 (q, 2 H, J = 7.0 Hz), 4.79 (m, 1 H), 4.99 (s, 2 H), 6.87 (d, 2 H, J = 8.5 Hz), 7.23 (d, 1 H, J = 7.4 Hz), 7.30 (d, 2 H, J = 8.6 Hz), 7.75 (d, 2 H, J = 8.4 Hz), 7.84 (br s, 1 H), 7.92 (d, 2 H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$): δ 14.08, 14.13, 26.02, 26.96, 27.46, 30.47, 40.30, 49.62, 52.53, 54.01, 54.89, 55.23, 60.90, 61.78, 87.36, 113.61, 113.88, 126.62, 127.65, 129.75, 129.88, 131.07, 134.11, 153.76, 157.54, 158.96, 162.37, 164.82, 166.17, 170.22, 171.79, 173.38, 175.73. Anal. Calcd. for $C_{39}H_{46}N_6O_9$: C, 63.06; H, 6.24; N, 11.31. Found: C, 63.20; H, 6.22; N, 11.19.

Diethyl 4-[(10-methoxy-8-pivaloylamino)-4,5-dihydro-(6*H*)-isoxazolo[3,4-*d*]pyrimido[4,5-*b*]azepin-3-yl]-benzoyl-L-glutamate (13). Isoxazole **22a** (0.615 g, 0.83 mmoles) was dissolved in TFA (7 mL) and the mixture stirred at room temperature for five days under a calcium chloride drying tube. The TFA was removed by evaporation under reduced pressure, and the residue was chormatographed on silica gel eluting with ethyl acetate to yield 0.425 g (83%) of product as colorless plates: mp 132-135 °C. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 3 H, J = 7.15 Hz), 1.32 (t, with overlapping s, 12 H, J = 7.1 Hz), 2.32 (m, 2 H), 2.56 (t, 2 H, J = 7.4 Hz), 2.98 (m, 2 H), 3.46 (m, 2 H), 4.10 (s, 3 H), 4.14 (q, 2 H, J = 7.1 Hz), 4.26 (q, 2 H, J = 7.1 Hz), 4.79 (m, 1 H), 6.80 (t, 1 H, J = 5.0 Hz), 7.65 (d, 2 H, J = 8.4 Hz), 7.82 (d, 1 H, J = 7.5 Hz), 7.9 (s, 1 H), 7.92 (d, 2 H, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$): δ 13.96, 26.00, 26.47, 27.20, 30.53, 40.09, 43.49, 52.52, 54.58, 60.60, 61.56, 85.98, 114.76, 126.75, 127.59, 130.38, 134.35, 154.48, 156.96, 162.22, 163.10, 166.55, 169.31, 172.14, 173.03, 176.13. HRMS (FAB) calcd. for $C_{31}H_{38}N_6O_8$ *m/z*: 623.2751 (MH^+). Found : 623.2831.

Diethyl 4-[(10(9*H*)-oxo-8-pivaloylamino)-4,5-dihydro-(6*H*)-isoxazolo[3,4-*d*]pyrimido[4,5-*b*]azepin-3-yl]-benzoyl-L-glutamate (24a). To a solution of **13** (300 mg, 0.48 mmoles) in 5 mL anhydrous methylene chloride was added iodotrimethylsilane (0.138 mL, 0.96 mmoles) and the resulting mixture was refluxed under nitrogen for 2 h. The reaction was cooled to rt, quenched with 5 mL of methanol, and stirred for an additional 0.5 h. The dark brown solution was then passed through a pad of celite and the solvents were removed in vacuo. The residue was chromatographed on silica gel, eluting with 7% methanol in methylene chloride to give 0.235 g (80%) of pale orange plates: mp 198-201 °C. ^{1}H NMR (CD_3OD): δ 1.25 (two overlapping t and one s, 15 H, J = 7.1 Hz), 2.13 (m, 1 H), 2.30 (m, 1 H), 2.52 (m, 2 H), 3.00 (m, 2 H), 3.40 (m, 2 H), 4.13 (q, 2 H, J = 7.1 Hz), 4.23 (q, 2 H, J = 7.1 Hz), 4.66 (m, 1 H), 7.65 (d, 2 H, J = 8.2 Hz), 7.92 (d, 2 H, J = 8.2 Hz), 11.87 (br s, 1 H). HRMS (FAB) calcd. for $C_{30}H_{36}N_6O_8$ *m/z*: 609.2594 (MH^+). Found : 609.2664.

4-[(8-Amino-10(9*H*)-oxo)-4,5-dihydro-(6*H*)-isoxazolo[3,4-*d*]pyrimido[4,5-*b*]azepin-3-yl]benzoyl-L-glutamic Acid (8a). A suspension of **24a** (85 mg, 0.14 mmoles) in 3 mL of 1% NaOH was stirred at rt for 7 days. The solution was filtered and the filtrate was cooled in ice-water and acidified by the dropwise addition of conc. HCl. The colorless precipitate was filtered at the pump, and washed with a small portion of ice cold water, and dried under reduced pressure to yield 40 mg (61%) of a colorless solid: mp >230 °C. ^{1}H NMR (DMSO-d_6): δ 1.96 (m, 1 H), 2.09 (m, 1 H), 2.36 (t, 2 H, J = 7.5 Hz), 2.94 (m, 2 H), 3.32 (m, 2 H), 4.42 (m, 1 H), 6.82 (br s, 2 H), 7.45 (br s, 1 H), 7.78 (d, 2 H, J = 8.1 Hz), 8.03 (d, 2 H, J = 8.4 Hz), 8.77 (d, 1 H, J = 8.1 Hz), 10.54 (br s, 1 H). HRMS (FAB) calcd. for $C_{21}H_{20}N_6O_7$ m/z: 469.1393 (MH^+). Found: 469.1466.

6-(*N*-3-Butenylamino-*N*-4-methoxybenzyl)-5-formyl-4-methoxy-2-pivaloylamino pyrimidine (18b). A 100 mL 3-necked flask was charged with **18a** (5.60g, 0.0132 mole), pyridine (50 mL), and $Pd/BaSO_4$ (50 mg). The resulting solution was stirred at rt under 1 atm of hydrogen for 5 h. The solution was passed through a small pad of celite and the pyridine was removed in vacuo. The residue was partitioned between methylene chloride and water, the organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The residue was chromatographed on silica gel, eluting with 50% ethyl acetate in hexane

gave 5.29 g (94%) of a colorless solid: mp 88-90 °C. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9 H), 2.32 (q, 2 H, J = 7.2 Hz), 3.56 (t, 2 H, J = 7.3 Hz), 3.78 (s, 3 H), 4.04 (s, 3 H), 4.73 (s, 2 H), 4.99 (m, 2 H), 5.69 (m, 1 H), 6.82 (d, 2 H, J = 8.6 Hz), 7.12 (d, 2 H, J = 8.6 Hz), 7.81 (br s, 1 H), 10.02 (s, 1 H); ^{13}C NMR ($CDCl_3$): δ 27.35, 31.80, 40.36, 49.45, 53.76, 54.66, 55.16, 97.71, 113.82, 116.69, 128.79, 129.03, 135.03, 156.56, 158.79, 163.38, 174.25, 175.49, 184.54. Anal. Calcd. for $C_{23}H_{30}ClN_4O_4$: C, 64.77; H, 7.09; N, 13.17. Found: C, 64.42; H, 6.68; N, 13.07.

(*E*)-Diethyl *N*-[4-[4-(5-formyl-4-methoxy-2-pivaloylaminopyrimidin-4-yl)-*N*-4-methoxybenzylamino]-1-butenyl]benzoyl-L-glutamate (20b). A mixture of **18b** (4.0 g, 0.0094 mole), diethyl 4-iodobenzoyl-L-glutamate [13] (4.25 g, 0.0098 mole), palladium acetate (0.025 g, 0.11 mmoles), triphenylphosphine (0.057 g, 0.22 mmoles), copper(I) iodide (0.021 g, 0.11 mmoles), and triethylamine (20 mL) was stirred in acetonitrile (200 mL) heated at sandbath temperature of 55°C for 4 days. The solution was cooled to room temperature and passed through a pad of celite. The solvent was removed in vacuo, and the resulting residue was partitioned in methylene chloride and water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel, eluting with 50 % ethyl acetate in hexane to yield 3.60 g (65% based on the recovery of 0.725 g starting material) of a pale yellow solid: mp 62-64 °C ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 3 H, J = 7.1 Hz), 1.31 (t, with overlapping s, 12 H, J = 7.1 Hz), 2.14 (m, 1 H), 2.2-2.58 (m, 5 H), 3.68 (t, 2 H, J = 7.1 Hz), 3.79 (s, 3 H), 4.02 (s, 3 H), 4.11 (dq, 2 H, J = 1.5, 7.0 Hz), 4.23 (q, 2 H, J = 7.0 Hz), 4.72 (s, 2 H), 4.78 (m, 1 H), 6.12 (m, 1 H), 6.39 (d, 1 H, J = 15.7 Hz), 6.83 (d, 2 H, J = 8.6 Hz), 7.01 (d, 1 H, J = 7.5 Hz), 7.13 (d, 2 H, J = 8.6 Hz), 7.33 (d, 2 H, J = 8.4 Hz), 7.72 (d, 2 H, J = 8.4 Hz), 7.80 (br s, 1 H), 10.02 (s, 1 H); ^{13}C NMR ($CDCl_3$): δ 14.08, 14.11, 27.21, 27.37, 30.45, 31.33, 40.38, 49.27, 52.29, 54.26, 54.66, 55.19, 60.74, 61.64, 97.73, 113.89, 126.02, 127.28, 128.75, 129.16, 129.60, 130.93, 131.84, 140.92, 156.53, 158.89, 163.48, 166.73, 171.95, 173.18, 174.26, 175.47, 184.53. HRMS (FAB) calcd. for $C_{39}H_{49}N_5O_9$ *m/z*: 732.3530 (MH^+). Found : 732.3611.

(*E*)-Diethyl *N*-[4-[4-(4-methoxy-5-oximinomethyl-2-pivaloylaminopyrimidin-4-yl)-*N*-4-methoxybenzylamino]-1-butenyl]benzoyl-L-glutamate (21b). A mixture of **20b** (2.70 g, 0.0037 mole), hydroxylamine hydrochloride (0.285 g, 0.0041 mole), pyridine (0.40 mL, 0.005 mole) and absolute ethanol (45 mL) was stirred at rt under a nitrogen atmosphere for 3 h. The ethanol was removed under reduced pressure and the residue was partitioned between methylene chloride water. The organic layer was dried over anhydrous magnesium sulfate and removed in vacuo to yield 2.74 g (99%) of a colorless solid. An analytical sample was prepared using column chromatography on silica gel, eluting with 50% ethyl acetate in hexane, which gave a colorless solid: mp 72-74 °C. ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3 H, J = 7.2 Hz), 1.31 (t, with overlapping s, 12 H, J = 7.2 Hz), 2.14 (m, 1 H), 2.25-2.6 (m, 5 H), 3.58 (t, 2 H, J = 7.4 Hz), 3.78 (s, 3 H), 3.95 (s, 3 H), 4.12 (q, 2 H, J = 7.0 Hz), 4.23 (q, 2 H, J = 7.0 Hz), 4.68 (s, 2 H), 4.78 (m, 1 H), 6.26 (m, 1 H), 6.39 (d, 1 H, J = 16.0 Hz), 6.82 (d, 2 H, J = 8.7 Hz), 7.04 (d, 1 H, J = 7.6 Hz), 7.14 (d, 2 H, J = 8.7 Hz), 7.31 (d,

2 H, J = 8.4 Hz), 7.71 (d, 2 H, J = 8.4 Hz), 7.77 (s, 1 H), 8.1 (s, 1 H), 8.71 (br s, 1 H); ^{13}C NMR ($CDCl_3$): δ 14.11, 14.13, 27.24, 27.47, 30.49, 31.35, 40.27, 49.77, 52.31, 53.51, 54.41, 55.21, 60.77, 61.70, 90.77, 113.88, 126.00, 127.34, 128.90, 129.50, 129.74, 130.95, 131.83, 140.94, 144.81, 154.83, 158.79, 164.10, 166.76, 169.41, 172.06, 173.20, 175.55. Anal. Calcd. for $C_{39}H_{50}N_6O_9$: C, 62.72; H, 6.75; N, 11.25. Found: C, 62.71; H, 6.53; N, 10.93.

Diethyl 4-[(10-methoxy-6-(4-methoxybenzyl)-8-pivaloylamino)-3,4,5,6-tetrahydroisoxazolino[3,4-*d*]-pyrimido[4,5-*b*]azepin-3-yl] benzoyl-L-glutamate (22b). To a well stirred solution of **21b** (2.5 g, 0.00335 mole) in anhydrous methylene chloride (60 mL), *N*-chlorosuccinimide (0.469 g, 0.0035 mole) was added in small portions over a fifteen minute period. The solution was stirred at rt under nitrogen for 3 h. Triethylamine (0.60 mL, 0.0043 mole) was added and the solution was allowed to stir an additional 3 h. Water was added to the reaction mixture and the organic layer was separated, dried over anhydrous magnesium sulfate, and the solvent was removed via rotary evaporation. The residue was chromatographed on silica gel, eluting with 70% ethyl acetate in hexane to give 1.89g (76%) of a colorless solid: mp 85-87 °C. ^{1}H NMR ($CDCl_3$): δ 1.25 (two overlapping t, and one s, 15 H, J = 7.1 Hz), 1.92 (m, 1 H), 2.14 (m, 2 H), 2.31 (m, 1 H), 2.44 (m, 2 H), 3.26 (dd, 1 H, J = 4.2, 15.0 Hz), 3.36 (dt, 1 H, J = 3.0, 9.1 Hz), 3.63 (dt, 1 H, J = 4.7, 14.0 Hz), 3.82 (s, 3 H), 4.04 (s, 3 H), 4.12 (q, 2 H, J = 6.7 Hz), 4.23 (q, 2 H, J = 7.1 Hz), 4.47 (d, 1 H, J = 14.5 Hz), 4.77 (m, 1 H), 5.18 (d, 1 H, J = 2.8 Hz), 5.25 (d, 1 H, J = 14.4 Hz), 6.85 (d, 2 H, J = 8.4 Hz), 7.05 (d, 1 H, J = 7.3 Hz), 7.23 (d, 2 H, J = 8.6 Hz), 7.32 (d, 2 H, J = 8.4 Hz), 7.75 (br s, 1 H), 7.78 (d, 2 H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ 14.10, 14.12, 27.15, 27.42, 30.45, 34.55, 40.26, 48.88, 52.36, 52.72, 54.83, 55.25, 57.82, 60.80, 61.70, 86.16, 87.35, 113.92, 125.25, 127.43, 129.74, 130.12, 133.21, 144.78, 153.29, 154.97, 159.10, 165.75, 166.59, 168.19, 171.88, 173.22, 175.58. Anal. Calcd. for $C_{39}H_{48}N_6O_9$: C, 62.89; H, 6.49; N, 11.28. Found: C, 63.26; H, 6.44; N, 11.25.

Diethy 4-[(10-methoxy-8-pivaloylamino)-3,4,5,6-tetrahydro-(6*H*)-isoxazolino[3,4-*d*]pyrimido[4,5-*b*]-azepin-3-yl] benzoyl-L-glutamate (23). Isoxazoline **22b** (0.530 g, 0.711 mmoles) was dissolved in TFA (10 mL) and allowed to stir at 45 °C for 3 days. The solvent was removed by evaporation under reduced pressure and the residue was chromatographed on silica gel eluting with neat ethyl acetate to yield 0.400 g (90%) of a colorless solid: mp 105-108 °C ^{1}H NMR (DMSO-d_6): δ 1.17 (two overlapping t, and one s, 15 H, J = 7.2 Hz), 1.87 (m, 1 H), 1.99 (m, 1 H), 2.08 (m, 1 H), 2.35 (m, 1 H), 2.42 (t, 2 H, J = 7.5 Hz), 3.17 (m, 1 H), 3.45 (m, 1 H), 3.59 (q, 1 H, J = 7.2 Hz), 3.87 (s, 3 H), 4.03 (q, 2 H, J = 7.0 Hz), 4.09 (q, 2 H, J = 7.3 Hz), 4.42 (m, 1 H), 5.32 (d, 1 H, J = 7.1 Hz), 7.46 (d, with overlapping m, 3 H, J = 8.2 Hz), 7.87 (d, 2 H, J = 8.2 Hz), 8.72 (d, 1 H, J = 7.5 Hz), 9.50 (br s, 1 H); ^{13}C NMR (DMSO-d_6): δ 14.00, 25.63, 26.72, 30.10, 32.72, 40.72, 51.94, 54.03, 58.02, 59.86, 60.51, 85.52, 86.47, 125.76, 127.71, 133.31, 143.45, 153.15, 155.86, 164.66, 166.21, 167.62, 171.64, 172.12, 175.81. HRMS (FAB) calcd. for $C_{31}H_{40}N_6O_8$ *m/z*: 625.2907 (MH^+). Found : 625.2985.

Diethyl 4-[(10(9*H*)-oxo-8-pivaloylamino)-3,4,5,6-tetrahydro-(6*H*)-isoxazolino[3,4-*d*]pyrimido[4,5-*b*]-azepin-3-yl] benzoyl-L-glutamate (24b). To a solution of **23** (381 mg, 0.61 mmoles) in 6 mL anhydrous methylene chloride was added iodotrimethylsilane (0.173 mL, 1.22 mmoles) and the resulting mixture was refluxed under nitrogen for 1.5 h. The reaction was cooled to rt and quenched with 5 mL of methanol and stirred for 0.5 h. The solution was then passed through a pad of celite and the solvents were removed by evaporation under reduced pressure. The residue was chromatographed on silica gel, eluting with 7% methanol in methylene chloride, to give 0.302 g (82%) of a pale orange solid: mp 163-167 °C. ^{1}H NMR (CD_3OD): δ 1.25 (two overlapping t, and one s, 15 H, J = 7.0 Hz), 2.05 (m, 2 H), 2.26 (m, 1 H), 2.47 (m, 3 H), 2.75-3.30 (m, 3 H), 4.09 (q, 2 H, J = 7.0 Hz), 4.19 (q, 2 H, J = 7.0 Hz), 4.60 (m, 1 H), 5.26 (two overlapping d, 1 H, J = 6.8 Hz), 7.42 (two overlapping d, 2 H, J = 7.8 Hz), 7.76 (two overlapping d, 2 H, J = 7.5 Hz). HRMS (FAB) calcd. for $C_{30}H_{38}N_6O_8$ *m/z*: 611.2751 (MH^+). Found : 611.2849.

4-[(8-Amino-10(9*H*)-oxo)-3,4,5,6-tetrahydro-(6*H*)-isoxazolino[3,4-*d*]pyrimido[4,5-*b*]azepin-3-yl] benzoyl-L-glutamic Acid (7a). A suspension of **24b** (100 mg, 0.164 mmoles) in 3 mL of 1% NaOH was stirred at rt for 14 days. The solution was filtered and cooled in an ice bath. The filtrate was acidified by the dropwise addition of conc. HCl. The precipitate was collected by filtration at the pump, washed with a small portion of ice cold water, and dried under vacuum to yield 35 mg (46%) of a colorless solid: mp >230 °C. ^{1}H NMR (DMSO-d_6): δ 1.92 (m, 2 H), 2.06 (m, 1 H), 2.33 (m, 3 H), 3.23 (m, 1 H), 3.36 (m, 1 H), 3.52 (m, 1 H), 4.38 (m, 1 H), 5.21 (two overlapping d, 1 H, J = 6.5 Hz), 7.02 (br s, 2 H), 7.30 (two overlapping d, 2 H, J = 7.5 Hz), 7.86 (two overlapping d, 2 H, J = 7.4 Hz), 8.61 (br d, 1 H, J = 7.4 Hz), 10.75 (br s, 1 H). HRMS (FAB) calcd. for $C_{21}H_{22}N_6O_7$ *m/z*: 471.1550 (MH^+). Found: 471.1624.

Diethyl 4-[(5-imino-4-methoxy-2-pivaloylamino-5,6,7,8-tetrahydropyrimido[4,5-*b*]azepin-6-yl)-hydroxymethyl-benzoyl]-L-glutamate (25). A mixture of the isoxazoline **23** (100 mg, 0.16 mmoles), 20% palladium hydroxide on carbon (100 mg), and acetic acid (10 ml) was shaken in a Parr apparatus with 50 psi of hydrogen for 10 days. The reaction mixture was filtered through a pad of Celite which was washed well with methanol. The filtrate was evaporated under reduced pressure and the residue was partitioned between methylene chloride and saturated solution of sodium bicarbonate. The organic layer was dried with anhydrous sodium sulfate, filtered and the solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with 10% methanol in methylene chloride. The fractions containing the pure product were combined and the solvent was removed in vacuo to give 30 mg (34%) of a colorless solid; mp 106-108 °C; ^{1}H NMR (DMSO-d_6) δ 1.16 (two overlapping t, and one s, 15 H, J = 7.1 Hz), 1.55 (m, 1 H), 1.83 (m, 1 H), 2.08 (m, 2 H), 2.42 (m, 2 H), 2.60 (m, 1 H), 2.80 (m, 1 H), 3.09 (m, 2 H), 3.72 (s, 3 H), 4.03 (q, 2 H, J = 7.1 Hz, with overlapping proton), 4.09 (q, 2 H, J = 7.1 Hz), 4.22 (m, 1 H), 7.16 (m, 1 H), 7.25 (d, 2 H, J = 8.1 Hz), 7.76 (d, 2 H, J = 8.1 Hz), 8.64 (d, 1 H, J = 6.7 Hz), 9.31 (br s, 1 H), 11.0 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 14.11, 14.13, 27.18, 27.39, 30.51, 31.90, 38.64, 39.42, 40.22, 41.54, 52.30, 54.13, 60.73, 61.68, 90.83, 127.05, 129.04, 131.46, 143.80, 155.19, 155.42, 163.69, 167.07, 168.84, 172.20, 173.15, 176.05. LRMS (electrospray) m/z: 627 (MH^+).

4-Methoxy-9-(4-methoxybenzyl)-2-pivaloylamino-6,7,8,9-tetrahydropyrimido-[4,5-*b*]azepine-5-one (29) and Diethyl 4-formylbenzoylglutamate (30). A mixture of the isoxazoline **22b** (50 mg, 0.067 mmol), molybdenum hexacarbonyl (10 mg, 0.0335 mmol), water (5 drops), and acetonitrile (2.5 mL) was heated at reflux for 1 h. The solvents were removed by evaporation under reduced pressure, and the residue was chromatographed on silica gel eluting with 50% ethyl acetate in hexane to give 7 mg of **29**: ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 9 H), 2.03 (m, 2 H), 2.62 (t, *J* = 7.3 Hz, 2 H), 3.35 (t, *J* = 6.4 Hz, 2 H), 3.81 (s, 3 H), 4.0 (s, 3 H), 5.0 (s, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 7.8 (s, 1 H); HRMS (EI) calcd. for $C_{22}H_{28}N_4O_4$: 412.2110 (M^+). Found: 412.2117; and 5 mg of **30**: ^{1}H NMR ($CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 3 H), 1.31 (t, *J* = 7.2 Hz, 3 H), 2.17 (m, 1 H), 2.31 (m, 1 H), 2.49 (m, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 4.78 (m, 1 H), 7.29 (d, *J* = 7.2 Hz, 1 H), 7.95 (d, *J* = 8.8 Hz, 2 H), 7.99 (d, *J* = 8.8 Hz, 2 H), 10.08 (s, 1 H); HRMS (EI) calcd. for $C_{17}H_{21}NO_6$: 335.1369 (M^+). Found: 335.1351.

4-(*N*-2,4-Dimethoxybenzyl)aminobutanal diethylacetal (35). A mixture of 4-aminobutanal diethylacetal (10 mL, 0.0579 mol), 2,4-dimethoxybenzaldehyde (9.710 g, 0.0584 mol) and benzene (150 mL) was heated at reflux for 3 h, using a Dean-Stark trap. The solvent was removed by evaporation under reduced pressure and the residue was dissolved in anhydrous methanol (100 mL). Sodium borohydride (2.909 g, 0.0769 mol) was added in portions to the stirred solution at 10 °C. The reaction was warmed to rt, stirred for a further 0.5 h, and quenched with saturated ammonium chloride solution. The solvents were removed by evaporation under reduced pressure and the residue was partitioned between water (50 mL) and ethyl acetate (100 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 100 ml). The combined organic layer was dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give 13.49 g (75%) of a pale yellow liquid, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 1.15 (t, *J* = 7.3 Hz, 6 H), 1.59 (m, 4 H), 2.58 (t, *J* = 7.3 Hz, 2 H), 3.05 (br s, 1 H), 3.46 (two overlapping q, *J* = 7.3 Hz, 2 H), 3.58 (two overlapping q, *J* = 7.3 Hz, 2 H), 3.71 (s, 2 H), 3.75 (s, 3 H), 3.77 (s, 3 H), 4.43 (t, *J* = 5.4 Hz, 1 H), 6.39 (m, with overlapping s, 2 H), 7.11 (d, *J* = 8.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 15.19, 24.70, 31.28, 48.25, 48.36, 55.14, 55.20, 60.90, 98.36, 102.69, 103.63, 119.73, 130.55, 158.51, 160.12. HRMS (FAB) calcd. for $C_{17}H_{29}NO_4$ m/z: 312.2096 (MH^+). Found: 312.2166.

Ethyl ester of [*N*-2,4-dimethoxy-*N*-(4,4-diethoxy)butyl malonamide (36). Ethylmalonyl chloride (5.40 mL, 0.0422 mol) was added dropwise to a stirred mixture of **35** (13.108 g , 0.0421 mol), triethylamine (7.0 ml, 0.0502 mol), and anhydrous THF (200 mL) cooled to 10°C. The reaction was stirred at rt overnight, and then quenched with saturated ammonium chloride solution, and extracted with ethyl acetate (3 x 200 ml). The combined organic layer was dried over anhydrous magnesium sulfate and the solvent was removed by evaporation under reduced pressure. The residual oil was purified by chromatography on silica gel, eluting with 50% ethyl acetate in hexanes, to give 17.06g (98%) of an orange oil. ^{1}H NMR ($CDCl_3$): 1.17 (two overlapping t, *J* = 7.2 Hz, 6 H), 1.25 (two overlapping t, *J* = 7.2 Hz, 3 H), 1.60 (m, 4 H), 3.15-3.70 (m, 7 H),

3.8 (m, 6 H) 4.20 (two overlapping q, J = 7.3 Hz, 2 H), 4.40 (s, 1.4H), 4.45 (br t, J = 5.4 Hz, 1 H), 4.60 (s, 0.6 H), 6.45 (m, with overlapping s, 2 H), 6.98 (d, J = 8.6 Hz, 0.6 H), 7.21 (d, J = 8.6 Hz, 0.4 H). LRMS (FAB) calcd. for $C_{22}H_{35}NO_7$ m/z: 426 (MH^+). Found: 426. Anal. Calcd. for $C_{22}H_{35}NO_7$: C, 62.12; H, 8.23; N, 3.30. Found: C, 62.04; H, 7.96; N, 3.17.

3-Carboethoxy-*N*-2,4-dimethoxybenzyl-1,5,6,7-tetrahydro-(1*H*)-azepin-2-one (33): A mixture of **36** (18.323 g, 0.0431 mol), acetic acid (80 mL), and water (20 mL) was heated to 40 °C for 6 h. Most of acetic acid was removed by evaporation under reduced pressure. The residue was partitioned between ethyl acetate and a saturated solution of sodium bicarbonate. The layers were seperated and the aqueous layer was extracted with ethyl acetate (3 x 200 ml). The combined organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel, eluting with 50% ethyl acetate in hexanes, to give 9.385 (65.4 %) of an orange oil. ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 7.3 Hz, 3 H), 1.58 (quintet, J = 7.3 Hz, 2 H), 2.12 (q, J = 7.3, 2 H), 3.23 (t, J = 6.6 Hz, 2 H), 3.70 (s, 3 H), 3.74 (s, 3 H), 4.19 (q, J = 7.3 Hz, 2 H), 4.61 (s, 2 H), 6.37 (m, 2 H), 7.17 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ14.08, 23.30, 27.92, 43.48, 45.02, 55.17, 55.22, 60.90, 98.18, 104.25, 118.24, 131.23, 132.82, 142.73, 158.40, 160.39, 164.43, 166.13. HRMS (EI) calcd. for $C_{18}H_{23}NO_5$ m/z: 333.1576 (M^+). Found: 333.1571.

3-Carboethoxy-5-(4-carbomethoxybenzylidenyl)-*N*-2,4-dimethoxybenzyl-6,7-dihydro-(1*H*)-azepin-2-one (38; Mixture of (*E*) and (*Z*) isomers): A 2M solution of lithium diisopropylamide (in heptane/THF/ethylbenzene; 12.0 mL, 24 mmol) was added dropwise to a mixture of **33** (7.082 g, 21.2 mmol), zinc chloride (1M, 43.0 mL, 43 mmol) and anhydrous THF (200 mL) cooled to -78 °C, kept under a nitrogen atmosphere. After stirring for 0.5 h, methyl 4-formylbenzoate (3.504 g, 21.3 mmol) dissolved in anhydrous THF (20 mL) was added dropwise. The solution was kept at -78 °C for a further 0.5 h, and then allowed to warmed to rt, and then heated at 40 °C for 6 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (3 x 250 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (eluting first with 20% then 50% ethyl acetate in hexanes) to give 4.1 g (40%) of a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.38 (two overlapping t, J = 7.3 Hz, 3 H), 2.65 (m, 2 H), 3.40 (m, 2 H), 3.72 (s, 3 H), 3.75 (s, 3 H), 3.87 (s, 3 H), 4.25 (two overlapping q, J = 7.3 Hz, 2 H), 4.63 (s, 2 H), 6.38 (m, 2 H), 6.62 (br s, 0.3 H), 6.80 (br. s, 0.7 H), 7.22 (m, 3 H), 7.32 (s, 0.7 H), 7.50 (s, 0.3 H), 7.95 (d, J = 8.6 Hz, 2 H). HRMS (EI) calcd. for $C_{27}H_{29}NO_7$ m/z: 479.1944 (M^+). Found: 479.1943.

3-Carboethoxy-5-(4-carbomethoxybenzyl)-*N*-2,4-dimethoxybenzylazepan-2-one (39; mixture of 2 pairs of enantiomers): A mixture of **38** (4.102g, 8.57 mmol), ethyl acetate (40 mL), and 10% palladium on carbon (0.200g) was shaken under 50 psi of hydrogen for 48 h. The mixture was filtered through a pad of celite and

concentrated under reduced pressure to give 4.057g (98 %) of a colorless gum. ^{1}H NMR ($CDCl_3$): δ 1.20 (two overlapping t, J = 7.3 Hz, 3 H), 1.5 (m, 2 H), 1.75 (m, 1 H), 2.0 (m, 2 H), 2.5 (m, 2 H), 3.21 (m, 2H), 3.50 (d, J = 10.6 Hz, 1 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 3.85 (s, 3 H), 4.15 (two overlapping q, J = 7.3 Hz, 2 H), 4.30-4.70 (m, 2 H), 6.33 (m, 2 H), 7.10 (m, 3 H), 7.85 (d, J = 8.6 Hz, 2 H). HRMS (EI) calcd. for $C_{27}H_{33}NO_7$ m/z: 483.2257 (M^+). Found: 483.2268.

3-Carboethoxy-5-(4-carbomethoxybenzyl)azepan-2-one (40; mixture of 2 pairs of enantiomers): Compound **39** (4.210 g, 8.72 mmol) was dissolved in TFA (20 mL) and the mixture was heated to 40 °C for 30 min. The solvent was removed by evaporation under reduced pressure and the residue was coevaporated with absolute ethanol (4 x 50 mL). The residue was chromatographed on silica gel (eluting with 10% methanol in methylene chloride) to give 2.66g (91%) of an orange colored gum. ^{1}H NMR ($CDCl_3$): δ 1.24 (two overlapping t, J = 7.3 Hz, 3 H), 1.45-2.25 (m, 5 H), 2.63 (m, 2 H), 3.17 (m, 2 H), 3.47 (d, J = 10.6 Hz, 1 H), 3.90 (s, 3 H), 4.20 (two overlapping q, J = 7.3 Hz, 2 H), 6.12 (br s, 1 H), 7.29 (d, J = 8.6 Hz, 2 H), 7.94 (d, J = 8.0 Hz, 2 H). HRMS (EI) calcd. for $C_{18}H_{23}NO_5$ m/z: 333.1576 (M^+). Found: 333.1572.

3-Carboethoxy-5-(4-carbomethoxybenzyl)azepan-2-thione (41; mixture of 2 pairs of enantiomers): Phosphorous pentasulfide (3.914g, 8.80 mmol) was added in portions to a mixture of **40** (2.666 g, 8.0 mmol) and anhydrous THF (100 mL) heated to 40 °C. The slurry was stirred for 2 hours until a red colored solution was observed. The reaction mixture was cooled to rt, filtered at the pump, and the solvent was removed by evaporation under reduced pressure. The residue was partitioned between water (50 mL) and ethyl acetate (50 mL). After separation of the layers, the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed by evaporation under reduced pressure. The residue was chromatographed on silica gel (eluting with 80% ethyl acetate in hexanes) to give 2.68g (95 %) of a yellow gum. ^{1}H NMR ($CDCl_3$): δ 1.30 (two overlapping t, J = 7.3 Hz, 3 H), 1.45-2.1 (m, 5 H), 2.60 (m, 2 H), 3.35 (m, 2 H), 3.75 (m, 1 H), 3.90 (s, 3 H), 4.20 (two overlapping q, J = 7.3 Hz, 2 H), 7.19 (d, J = 8.0 Hz, 2 H), 7.95 (d, J = 8.0 Hz, 2 H), 8.52 (br s, 0.6 H), 8.65 (br s, 0.4 H). HRMS (EI) calcd. for $C_{18}H_{23}NO_4S$ m/z: 349.1348 (M^+). Found: 349.1345.

2-Amino-6-(4-carboxybenzyl)-4(3*H*)-oxo-5,6,7,8-tetrahydro-(9*H*)-pyrimido-[4,5-*b*]azepine (43; mixture of enantiomers): A solution of guanidine in ethanol was prepared by the addition of sodium ethoxide (1.77M, 21.8 mL, 38.6 mmol) to guanidine hydrochloride (3.677 g, 38.5 mmol) in absolute ethanol (10 mL). After stirring for 15 min, the mixture was filtered through a pad of celite and the guanidine/ethanol solution was added to **41** (2.682g, 7.67 mmol) dissolved in anhydrous ethanol (5 mL). After allowing the mixture to stir for 15 min, the solvent was removed under reduced pressure and the reaction mixture was heated to 90 °C under vacuum (4 mm Hg) for 3 h. After cooling to rt, the solid was ground to a fine powder which was suspended in water (25 mL). This mixture was boiled for 10 min, allowed to cool to rt, and acidified to pH 3 with conc. HCl and then filtered. The filtered solid was suspended in 1N sodium hydroxide solution (30 mL),

and the mixture was heated to 100° C for 18 h. The reaction mixture was cooled to rt and filtered at the pump. The filtrate was acidified to pH 3 with conc. HCl and the solid was filtered at the pump, and dried under vacuum at 70° C to give 1.23g (52 %) of a yellow solid: mp > 250 ° C. ^{1}H NMR (DMSO-d_6): δ 1.30 (m, 1 H), 1.78 (m, 1 H), 1.95 (m, 1 H), 2.20 (m, 1 H), 2.6 (m, 2 H), 3.0 (m, 1 H), 3.30 (m, 2 H), 5.80 (br s, 1 H), 5.95 (br s, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.90 (d, J = 8.6 Hz, 2 H). HRMS (FAB) calcd. for $C_{16}H_{18}N_4O_3$ m/z: 315.1379 (MH^+). Found: 315.1446.

Diethyl *N*-{[4-(2-amino-4(3*H*)-oxo-5,6,7,8-tetrahydro-(9*H*)-pyrimido[4,5-*b*]azepin-6-yl) methyl]benzoyl}-L-glutamate (44; mixture of 2 diastereomers): The carboxylic acid **43** (0.200g, 0.636 mmol) was added to a mixture of 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.117g, 6.36 mmol), triethylamine (1.77 mL, 12.7 mmol), and anhydrous DMF (4 mL). After stirring at rt for 12 h, L-glutamic acid diethyl ester hydrochloride (0.183g, 0.763 mmol) was added. The reaction mixture was stirred at rt for a further 12 h, and then filtered at the pump. The filtrate was concentrated under reduced pressure, and the residue was triturated with saturated $NaHCO_3$ solution followed by water and the resulting solid was filtered at the pump. This material was chromatographed on silica gel (eluting with 10% methanol in methylene chloride) to give 0.128g (40%) of a colorless solid: mp > 250 ° C. ^{1}H nmr (DMSO-d_6): δ 1.15 (two overlapping t, J = 7.3 Hz, 6 H), 1.30 (m, 1 H), 1.72 (m, 1 H), 2.02 (m, 4 H), 2.30-2.78 (m, 5 H), 2.98 (m, 1 H), 3.30 (m, with overlapping H_2O, 1 H), 4.02 (two overlapping q, J = 7.3 Hz, 4 H), 4.40 (m, 1 H), 5.70 (br t, 1H), 5.88 (br s, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.78 (d, J = 8.6 Hz, 2 H), 8.62 (d, J = 8.0 Hz, 1 H), 9.80 (br s, 1 H). HRMS (FAB) calcd. for $C_{25}H_{33}N_5O_6$ m/z: 500.2431 (MH^+). Found: 500.2496. Anal. Calcd. for $C_{25}H_{33}N_5O_6$: C, 60.12; H, 6.61; N, 14.03. Found: C, 59.83; H, 6.52; N, 13.88.

***N*-{[4-(2-Amino-4(3*H*)-oxo-5,6,7,8-tetrahydro-(9*H*)-pyrimido[4,5-*b*]azepin-6-yl)-methyl]benzoyl}-L-glutamic Acid (6a; mixture of 2 diastereomers).** The diester **44** (0.114 g, 0.228 mmol) was suspended in 1N sodium hydroxide solution (1 mL), and the mixture was stirred at rt for 3 days. The resulting solution was acidified to pH 4 with 1N HCl, and the precipitate was collected by filtration at the pump. The solid was washed well with water and dried under vacuum at 70 °C to give 0.062 g (61%) of a colorless solid: mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ 1.30 (m, 1 H), 1.74 (m, 1 H), 1.82-2.18 (m, 4 H), 2.30 (m, 2 H), 2.58-2.80 (m, 3 H), 2.95 (m, 1 H), 3.40 (m, 1 H), 4.35 (m, 1 H), 5.72 (br t, 1 H), 5.88 (br s, 2 H), 7.28 (d, J = 8.0 Hz, 2 H), 7.78 (d, J = 8.6 Hz, 2 H), 8.5 (d, J = 8.0 Hz, 1 H), 9.82 (br s, 1 H), 12.4 (br s, 2 H). HRMS (FAB) calcd. for $C_{21}H_{25}N_5O_6$ m/z: 444.1805 (MH^+). Found: 444.1889. Anal. Calcd. for $C_{21}H_{25}N_5O_6$: C, 56.88; H, 5.64; N, 15.80. Found: C, 56.57; H, 5.87; N, 15.63.

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References and Notes

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