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An Intramolecular 1,3-Dipolar Cycloaddition Approach to a Pyrimidoazepinone Derivative. A Potentially Useful Intermediate Towards the Synthesis of Pyrimidoazepine Based Folic Acid Derivatives

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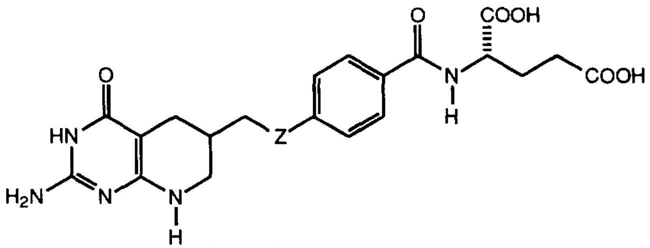
Abstract: An intramolecular nitrile oxide cycloaddition route to the isoxazolinopyrimidoazepine derivative **21** is described. This was transformed to the pyrimidoazepinone derivative **22**, a potentially useful intermediate for the synthesis of pyrimidoazepine based folic acid derivatives.

The design and synthesis of folic acid based antimetabolites as potential antitumor agents has received much enthusiasm over the past decade.[1] This renewed interest is at least in part due to the discovery of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid[2] (DDATHF, **1**) and 5-deaza-5,6,7,8-tetrahydrofolic acid[3] (DATHF, **2**) by E. C. Taylor and associates. Both DDATHF and DATHF exert their cytostatic effects by inhibition of the enzyme glycinamide ribonucleotide formyltransferase (GARFT) which catalyzes the transfer of the formyl group from 10-formyl-5,6,7,8-tetrahydrofolic acid to the amino group of glycinamide ribonucleotide during *de novo* purine biosynthesis. Both DDATHF and DATHF exhibit potent growth inhibition against leukemic cells in culture as well against transplantable solid tumors *in vivo*. There have been several reports documenting the structure-activity relationships for DDATHF type analogs.[4] The excellent selectivity exhibited by DDATHF, against a broad spectrum of tumors, in experimental animals was unfortunately not apparent in clinical trials.[5] It is therefore important to prepare structurally modified analogs of DDATHF with the goal of providing a more selective antitumor agent.

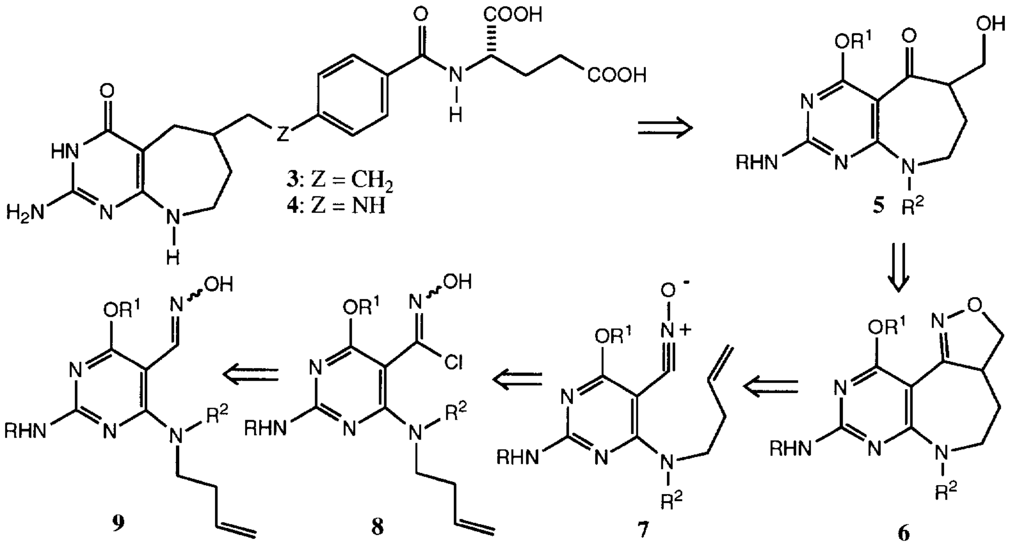


1: Z = CH_2 (DDATHF)
2: Z = NH (DATHF)

We have initiated a program aimed at the synthesis of novel, pyrimidoazepine analogs of DDATHF and DATHF such as **3** and **4**. We envisioned that these compounds could be obtained from the pyrimidoazepine β-hydroxy ketone **5** (Scheme 1). We reasoned that this intermediate could arise from the reductive cleavage of the N-O bond of the corresponding isoxazoline moiety of **6**. We wanted to approach the synthesis of this isoxazolinopyrimidoazepine using an intramolecular 1,3-dipolar cycloaddition reaction between an appropriately substituted pyrimidine 5-nitrile oxide and an appropriate alkene dipolarophile tethered to the 6-position of the pyrimidine ring (**7**).[6] The nitrile oxide would be generated *in situ* from the corresponding oxime (**9**) via the alpha-chloro oxime (**8**). Our approach is shown in a retrosynthetic format in Scheme 1.

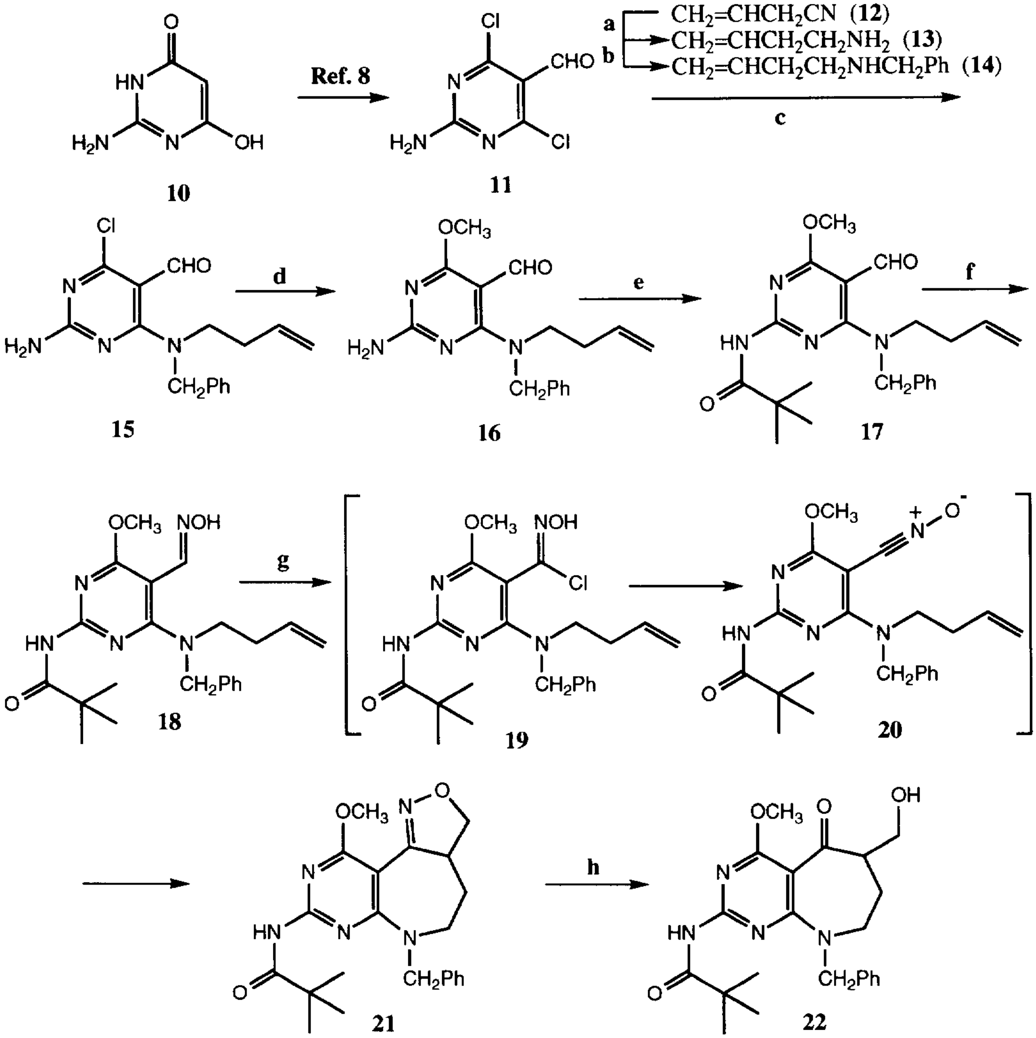
In this paper we describe the execution of the above strategy and report the synthesis of the tetrahydropyrimidoazepinone derivative **22**, a pivotal intermediate, with which we intend to prepare several pyrimidoazepine based antifolates including **3** and **4**.

Scheme 1



Our synthesis began with the reduction of, commercially available, allyl cyanide (**12**) to but-3-enylamine (**13**) with lithium aluminum hydride as described in the literature.[7] Reductive alkylation of but-3-enylamine *via* reaction with benzaldehyde followed by treatment with sodium borohydride provided the benzyl derivative **14** in 57% yield. Reaction of **14** with 2-amino-4,6-dichloro-5-formylpyrimidine[8] (**11**; readily available from the reaction of 2-amino-4,6-dihydroxypyrimidine (**10**) with phosphorus oxychloride in DMF) in the presence of triethylamine in refluxing ethanol gave **15** in 84% yield (Scheme 2). Reaction of **15** with sodium methoxide in refluxing methanol gave the methoxy

Scheme 2



(a) $LiAlH_4$, THF, Δ (ref.7); (b) PhCHO, MeOH then $NaBH_4$ (57%); (c) **14**, Et_3N, EtOH, Δ (84%); (d) NaOMe, MeOH, Δ (94%); (e) $(Me_3CCO)_2O$, DMAP (cat.), $PhCH_3$, Δ (86%); (f) NH_2OH, EtOH, RT (87%); (g) NCS, CH_2Cl_2, RT then Et_3N (84%); (h) W-2 Raney-Ni, MeOH, AcOH, H_2O, H_2 (44%)

pyrimidine **16** in 94% yield. Treatment of **16** with pivalic anhydride in the presence of a catalytic amount of 4-dimethylaminopyridine in refluxing toluene gave the trimethylacetamide derivative **17** in 86% yield. Treatment of **17** with hydroxylamine provided the corresponding oxime **18** in 87% yield. With the alkene **18** in hand we were ready to attempt the intramolecular nitrile oxide cycloaddition reaction. Thus, we treated **18** with one equivalent of N-chlorosuccinimide in dry methylene chloride at 20 °C and after allowing the mixture to stir for 1.5 hours, triethylamine was added to the reaction mixture. After stirring at room temperature for a further one hour, the reaction was worked up by washing with water. The desired cycloadduct **21** was isolated in 84% yield after purification by chromatography on silica gel. At first we attempted to cleave the isoxazoline N-O bond of **21** by treatment with molybdenum hexacarbonyl in refluxing aqueous acetonitrile.[9] However, this resulted in the formation of a number of products as evidenced by the observation of, at least, five spots by TLC. We were unable to isolate the β-hydroxy ketone **22** from this reaction mixture. However, treatment of **21** with Raney-nickel and hydrogen in aqueous methanol in the presence of acetic acid finally provided the desired β-hydroxy ketone **22** in 44% yield. Interestingly, the ^{1}H nmr of the cycloadduct (**21**) showed that the diastereotopic benzylic protons appeared as a pair of doublets at δ 4.51 and δ 5.25 with a coupling constant of 14.6 Hz. These protons appeared at δ 4.76 and δ 5.10 in the proton nmr spectrum of the β-hydroxy ketone **22**. With the pyrimidoazepinone intermediate **22** in hand we are investigating different methods to convert it to our desired targets **3** and **4** and we will report this work in due course.

Experimental

Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are uncorrected. The proton (300 MHz) and carbon (75 MHz) nmr spectra were recorded on a Varian VXR-300 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. High resolution mass spectral data were obtained on a VG Analytical 7070 E-HF double focusing mass spectrometer by peak matching technique with known PFK peaks.

N-Benzyl-but-3-enylamine (14). A mixture of but-3-enylamine[7] (15.7 g, 0.224 mole), benzaldehyde (23.75 g, 0.224 mole) and methylene chloride (100 ml) were stirred at room temperature for 2 hours. The solvent was removed by evaporation under reduced pressure and the residue dissolved in methanol (100 ml). Sodium borohydride (16.95 g, 0.448 mole) was added portionwise over a period of 30 minutes and the mixture stirred at room temperature for an additional hour. Water (100 ml) was added and the mixture was extracted with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. Distillation of the residue (Kugelrohr, bulb to bulb) at 110-115 °C at 2 mmHg gave 20.5 g (57%) of a colorless oil. ^{1}H nmr ($CDCl_3$): δ 2.26 (q, 2H, J = 7.2 Hz), 2.67 (t, 2H, J = 7.2 Hz), 3.73 (s, 2H), 5.08 (m, 2H), 5.74 (m, 1H), 7.31 (m, 5H).

2-Amino-6-(N-benzyl-but-3-enylamino)-4-chloro-5-formylpyrimidine (15). A mixture of 2-amino-4,6-dichloro-5-formylpyrimidine[8] (7.18 g, 0.0376 mole), N-Benzyl-but-3-enylamine (6.05 g, 0.0376 mole), triethylamine (3.8 g, 0.0376 mole) and ethanol (300 ml) was heated at reflux for 4 hours. The solvent was removed by evaporation under reduced pressure, the residue was partitioned between water (200 ml) and methylene chloride (400 ml). The organic layer was separated and dried with anhydrous magnesium sulfate and the solvent was removed by evaporation under reduced pressure to give 10.02 g (84%) of a cream colored solid. An analytical sample was obtained by chromatography on silica gel, eluting with 50% ethyl acetate in hexane which gave a colorless solid; mp 89-90 °C. ^{1}H nmr ($CDCl_3$): δ 2.33 (q, 2H, J = 7.2 Hz), 3.50 (t, 2H, J = 7.2 Hz), 4.71 (s, 2H), 5.01 (m, 2H), 5.39 (br s, 2H), 5.68 (m, 1H), 7.28 (m, 5H), 10.07 (s, 1H). ^{13}C nmr ($CDCl_3$): δ 31.76, 49.86, 54.29, 105.66, 116.96, 127.47, 127.58, 128.63, 134.79, 136.59, 160.68, 163.76, 167.43, 185.20. Anal. Calcd. for $C_{16}H_{17}ClN_4O$: C, 60.66; H, 5.37; N, 17.69. Found: C, 60.93; H, 5.21; N, 17.36.

2-Amino-6-(N-benzyl-but-3-enylamino)-5-formyl-4-methoxypyrimidine (16). To a freshly prepared solution of sodium methoxide (1.104 g, 0.048 mole of sodium in 300 ml of anhydrous methanol) was added **15** (15.00 g, 0.0475 mole) and the mixture was heated at reflux under nitrogen for 2.5 hours. The precipitated sodium chloride was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was partitioned between methylene chloride and water and the organic layer was separated, dried over anhydrous magnesium sulfate and the solvent was revoved by evaporation under reduced pressure to give 13.95 g (94 %) of a cream colored paste. An analytical sample was obtained by chromatography on silica gel, eluting with 50% ethyl acetate in hexane which gave a colorless film. ^{1}H nmr ($CDCl_3$): δ 2.32 (q, 2H, J = 7.2 Hz), 3.50 (t, 2H, J = 7.2 Hz), 3.94 (s, 3H), 4.75 (s, 2H), 4.98 (m, 2H), 5.07 (br s, 2H), 5.68 (m, 1H), 7.27 (m, 5H), 9.92 (s, 1H). ^{13}C nmr ($CDCl_3$): δ 32.02, 49.53, 54.14, 54.16, 95.90, 116.46, 127.02, 127.56, 128.46, 135.35, 137.67, 162.11, 164.83, 174.53, 183.65. Anal. Calcd. for $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.95. Found: C, 64.96; H, 6.14; N, 17.66.

6-(N-Benzyl-but-3-enylamino)-5-formyl-4-methoxy-2-pivaloylaminopyrimidine (17). A mixture of **16** (9.0 g, 0.0288 mole), trimethylacetic anhydride (37.5 g, 0.2016 mole), 4-dimethylaminopyridine (50 mg, 4.1 mmole) and toluene (300 ml) was heated at reflux for 18 hours. The solvent was removed by evaporation under reduced pressure and the residue was triturated with pentane and the pentane was decanted. 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 give 10.1 g (86 %) of a colorless solid; mp 92-94 °C. ^{1}H nmr ($CDCl_3$): δ 1.32 (s, 9H), 2.31 (q, 2H, J = 7.2 Hz), 3.58 (t, 2H, J = 7.2 Hz), 4.04 (s, 3H), 4.81 (s, 2H), 5.00 (m, 1H), 5.68 (m, 1H), 7.23 (m, 5H), 7.87 (br s, 1H), 10.02 (s, 1H). ^{13}C nmr ($CDCl_3$): δ 27.27, 31.75, 40.32, 49.79, 54.15, 54.63, 97.67, 116.72, 127.19, 127.59, 128.40, 134.92, 136.82, 156.58, 163.45, 174.24, 175.51, 184.55. Anal. Calcd. for $C_{22}H_{28}N_4O_3$: C, 66.65; H, 7.12; N, 14.13. Found: C, 66.45; H, 7.00; N, 13.93.

6-(N-benzyl-but-3-enylamino)-4-methoxy-5-oximinomethyl-2-pivaloylaminopyrimidine (18). A mixture of **17** (2.6 g, 0.0066 mole), hydroxylamine hydrochloride (0.502 g, 0.0072 mole), pyridine (0.57 g, 0.0072 mole) and ethanol (75 ml) was stirred at room temperature under nitrogn for 2 hours. The solvent and excess pyridine was removed by evaporation under reduced pressure and the residue was partitioned between methylene chloride and 0.1 N hydrochloric acid. The organic layer was separated, dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo* to give 2.38 g (87 %) of a cream colored solid. An analytical sample was obtained by chromatography on silica gel, eluting with 50% ethyl acetate in hexane to give a colorless solid; mp 120-121 °C. ^{1}H nmr ($CDCl_3$): δ 1.32 (s, 9H), 2.32 (q, 2H, J = 7.2 Hz), 3.48 (t, 2H, J = 7.2 Hz), 3.99 (s, 3H), 4.74 (s, 2H), 5.00 (m, 2H), 5.71 (m, 1H), 7.27 (m, 5H), 7.78 (br s, 1H), 8.04 (s, 1H), 9.12 (br s, 1H). ^{13}C nmr ($CDCl_3$): δ 27.50, 31.96, 40.31, 50.08, 53.86, 54.54, 90.89, 116.84, 127.20, 127.67, 128.50, 135.18, 137.83, 144.56, 154.92, 164.54, 169.35, 175.63. Anal. Calcd. for $C_{22}H_{29}N_5O_3$: C, 64.21; H, 7.10; N, 17.02. Found: C, 64.26; H, 6.89; N, 16.71.

6-Benzyl-10-methoxy-8-pivaloylamino-6,7,8,9-tetrahydroisoxazolino[3,4-*d*]pyrimido[4,5-*b*]azepine (21). A mixture of **18** (2.13 g, 0.0052 mole), N-chlorosuccinimide (0.69 g, 0.0052 mole), and anhydrous methylene chloride (200 ml) was stirred at room temperature, under nitrogen, for 1.5 hours. Triethylamine (0.945 g, 1.0936 mmole) was then added and the mixture was stirred for a further 2 hours. Water (50 ml) was added and the organic layer seperated, 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 to give 1.8 g (84%) of a cream colored solid; mp 149-151 °C. ^{1}H nmr ($CDCl_3$):

δ 1.27 (s, 9H), 1.67 (m, 1H), 1.91 (m, 1H), 3.09 (m, 1H), 3.43 (m, 2H), 3.97 (s, 3H), 4.11 (m, 2H), 4.51 (d, 1H, J = 14.6 Hz), 5.25 (d, 1H, J = 14.6 Hz), 7.24 (m, 5H), 7.76 (br s, 1H). ^{13}C nmr ($CDCl_3$): δ 27.37, 33.53, 40.25, 49.27, 49.42, 53.28, 54.75, 74.11, 87.51, 127.45, 128.37, 128.50, 138.12, 154.84, 165.76, 167.99, 175.78, 177.76. Anal. Calcd. for $C_{22}H_{27}N_5O_3$: C, 64.53; H, 6.65; N, 17.10. Found: C, 64.37; H, 6.50; N, 16.91.

9-Benzyl-6-hydroxymethyl-4-methoxy-2-pivaloylamino-6,7,8,9-tetrahydropyrimido[4,5-*b*]azepine-5-one (22). A mixture of W-2 Raney nickel (washed well with water and then with methanol; approx. 150 mg) the cycloadduct **21** (250 mg, 0.608 mmole), methanol (25 ml), acetic acid (1 ml) and water (3 ml) was stirred vigorously at room temperature under a hydrohen-filled ballon for 4 hours. The mixture was filtered through a pad of Celite and the filtrate was evaporated under reduced pressure. The residue was partitioned between methylene chloride and saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was chromatographed using a short pad of silica gel, eluting with 10% methanol in methylene chloride to give 110 mg (44%) of a colorless solid; mp 84-85 °C. ^{1}H nmr ($CDCl_3$): δ 1.25 (s, 9H), 1.92 (m, 1H), 2.08 (m, 2H), 2.77 (m, 1H), 3.29 (m, 2H), 3.55 (m, 1H), 3.87 (m, 1H), 3.98 (s, 3H), 4.76 (d, 1H, J = 14.6 Hz), 5.10 (d, 1H, J = 14.6 Hz), 7.24 (m, 5H), 7.73 (s, 1H). ^{13}C nmr ($CDCl_3$): δ 27.37, 33.27, 40.25, 46.25, 49.42, 52.96, 54.57, 63.63, 95.33, 127.48, 128.19, 128.51, 137.87, 154.32, 164.27, 168.37, 175.69, 176.58. EI-HRMS *m/z* calcd for $C_{22}H_{28}N_4O_4$: 412.211056. Found: 412.216195. Anal. Calcd. for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.73; H, 7.18; N, 13.75.

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