AN UNEXPECTED DIMER FORMATION FROM A 4-(2-AMINOETHYLAMINO)-5-FORMYL-PYRIMIDINE INTERMEDIATE

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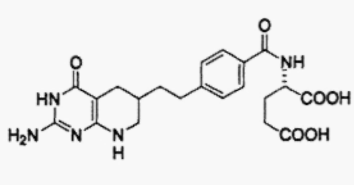
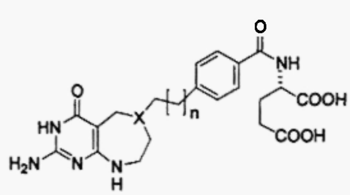
Abstract: Reaction of {2-[2-(2,2-dimethylpropionylamino)-5-formyl-6-methoxypyrimidin-4-ylamino]ethyl}-carbamic acid *tert*-butyl ester (**12**) with TFA followed by treatment with triethylamine in chloroform was expected to provide *N*-(4-methoxy-8,9-dihydro-7*H*-pyrimido[4,5-*e*][1,4]diazepin-2-yl)-2,2-dimethylpropionamide (**6**) via an intramolecular condensation. Surprisingly, the above reaction led to the formation of the dimer, *N*-[11-(2,2-dimethylpropionylamino)-4,13-dimethoxy-7,8,9,16,17,18-hexahydro-1,3,6,9,10,12,15,18-octaazadibenzo[*a,h*]-cyclotetradecen-2-yl]-2,2-dimethylpropionamide (**14**), via an initial intermolecular reaction followed by cyclization.

Introduction

The discovery of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF, **1**) as a potent anti-tumor agent, [1] which operates by shutting down *de novo* purine biosynthesis via inhibiting the enzyme glycinamide ribonucleotide formyltransferase (GARFT), has led to much research in this area of medicinal chemistry. [2-20] Interestingly, both diastereomers of DDATHF are equipotent as inhibitors of GARFT. In fact, the (6R)-diasteromer, lometrexol, (LTX, **2**), is currently in clinical trials for the treatment of human neoplastic diseases. However, the drug is known to be severely toxic to the liver, and is apparently better tolerated when it is co-administered with folic acid. [21] The overall potency of the drug is, however, somewhat lowered. Thus, it is a worthwhile goal to prepare structurally modified analogs of DDATHF with the aim of discovering a more selective, less toxic agent than lometrexol.



1: DDATHF (6RS)
2: LTX (6R)



3: X = CH, n = 0
4: X = CH, n = 1
5: X = N, n = 1

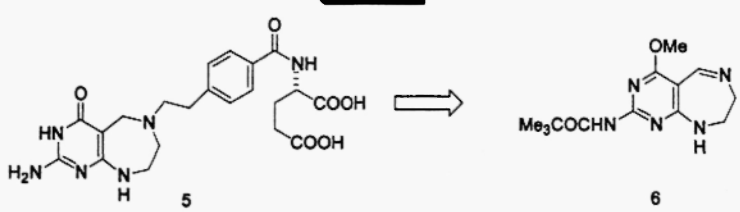
We have recently reported the synthesis of the ring expanded azepine analog **3**, which was found to be weakly active in a human colon carcinoma cell culture assay (GC3cl). [20] Taylor and Dowling have reported the preparation of a diastereomeric mixture of the one carbon extended side chain homologue **4**, which was reported to be essentially as active as DDATHF against trifunctional GRAFT isolated from murine L1210 leukemia cells. [14]

In order for a mixture of diastereomers to progress to a drug candidate, the Food and Drug Administration requires that, when possible, they be separated and tested individually. Such separations are typically laborious and expensive, adding to the overall cost of the drug. We have recently initiated a program aimed at the synthesis of the diazepine analog **5**, where the heterocyclic stereogenic carbon atom in **4** is replaced with a nitrogen atom. Since sp^3 hybridized nitrogen atoms undergo rapid pyramidal inversion at room temperature, the resulting isomers of **5** will not be separable, which alleviates the need for a potentially costly separation step. Also, it will be interesting to compare the biological properties of **5** with **4**, **1**, and LTX (**2**). Our hope is that the pyrimidodiazepine **5** will have a better therapeutic index than LTX.

Results and Discussion

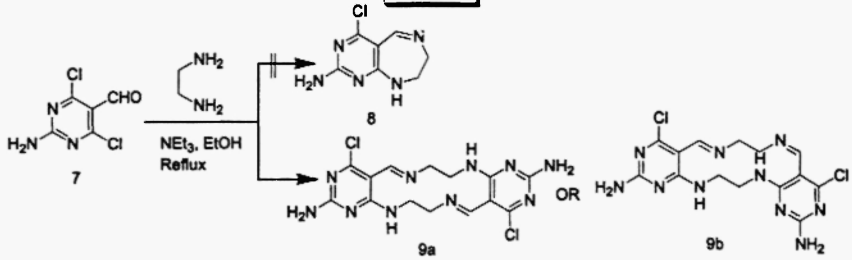
One of our synthetic strategies to target **5** relies on the preparation of intermediate **6** (Scheme 1), which contains the pyrimido[4,5-*e*][1,4]diazepine heterocyclic system. The N^6-oxide of this ring system has recently been reported by Heaney et. al.[22]

Scheme 1



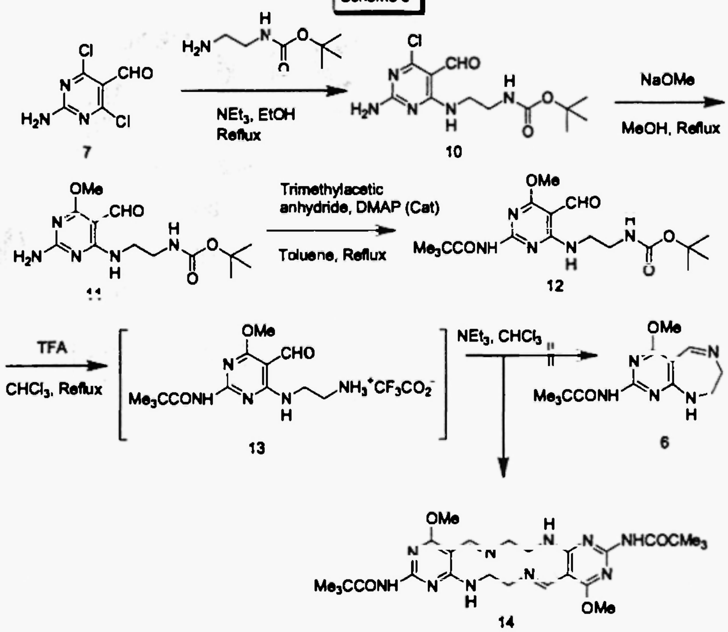
Our initial approach to **6** was to react 2-amino-4,6-dichloro-5-formylpyrimidine (**7**)[23] with ethylenediamine, with the anticipation that this would provide the pyrimidodiazepine **8** (Scheme 2). In the event, however, the above reaction led to the formation of the dimer **9a** or **9b**. A similar tetraazacyclotetradecadiene dimer has been reported from the reaction of ethylene diamine with 2-methylsulfinylquinoline-3-carbaldehyde. [24]

Scheme 2



Based on this observation we proposed an alternative route to **6** which was designed to prevent dimer formation and this is shown in Scheme 3. [25] Thus, reaction of **7** with *tert*-butyl *N*-(2-aminoethyl)carbamate [26] gave the pyrimidine **10** in 77 % yield, and reaction of **10** with sodium methoxide in refluxing methanol gave the corresponding methyl ether **11** in 93 % yield. Based on our previous experience with similar heterocyclic systems, we have found that conversion of the 2-amino group to the 2-pivaloylamino derivative results in beneficial solubility properties, which makes the manipulation of these materials less problematic.[27,28] Thus, the treatment of **11** with trimethylacetic anhydride and a catalytic amount 4-dimethylaminopyridine in refluxing toluene gave the 2-pivaloylamino derivative **12**[29] in 80 % yield after chromatography on silica gel. Removal of the BOC group from **12** was achieved by heating **12** in trifluoroacetic acid. Surprisingly, this reaction was slow and took several hours to go to completion. Treatment of the resulting ammonium trifluoroacetate salt (**13**, which was not isolated) with triethylamine in refluxing chloroform was expected to give the desired pyrimidodiazepine intermediate **6** via an intramolecular condensation reaction. However, spectral analysis revealed that the material isolated in near quantitative yield was in fact the dimer **14**.[30] The neutralization of the ammonium trifluoroacetate salt was repeated under high dilution conditions (0.001 molar solution in chloroform), and once again we were surprised to find the dimer **14** as the only isolated product. We are currently investigating a different approach to the desired pyrimidodiazepine system.

Scheme 3



Acknowledgments

We are grateful to Dr. David Bostwick at the School of Chemistry and Biochemistry, Georgia Institute of Technology for obtaining the MS data. We also thank the National Cancer Institute (Grant Number: 1R15CA093398-01), and the SARP and SOFREA programs at the State University of West Georgia for financial support.

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29. Compound **12**: mp 154-154.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.39 (s, 9H), 3.37 (m, 2H), 3.68 (m, 2H), 4.01 (s, 3H), 5.7 (br s, 1H), 7.9 (br s, 1H), 10.05 (s, 1H). HRMS (CI). Calcd for $C_{18}H_{30}N_5O_5$ m/z: 396.2169 (MH^+). Found: 396.2198.
30. Compound **14**: mp 276-277 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (s, 18H), 3.77 (br s, 8H), 3.99 (s, 6H), 7.91 (s, exchanges with D_2O, 2H), 8.71 (s, 2H), 11.3 (br s, exchanges with D_2O, 2H). HRMS (EI). Calcd. for $C_{26}H_{38}N_{10}O_4$ m/z: 554.3077 (M^+). Found: 554.3089. MS (EI) *m/e* (relative intensity) 554 (5), 206 (20), 165 (10), 57 (100).

Received on September 5, 2002