SYNTHESIS OF 2-AMINO-4-CHLORO-6,9-BIS-(2,4-DIMETHOXYBENZYL)-6,7,8,9-TETRAHYDRO-5*H*-PYRIMIDO[4,5-*e*][1,4]DIAZEPINE: A POTENTIALLY USEFUL INTERMEDIATE TO PYRIMIDO-[4,5-*e*][1,4]DIAZEPINE-BASED FOLATES

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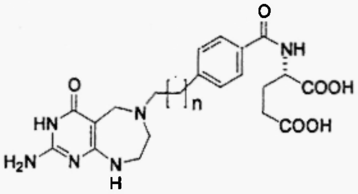
Abstract: Reaction of 2-amino-4,6-dichloro-5-chloromethylpyrimidine with *N,N'*-bis-(2,4-dimethoxybenzyl)-ethane-1,2-diamine gave the title compound 7 which is potentially a useful intermediate to pyrimido[4,5-*e*][1,4]-diazepine-based folates **1**.

Introduction

In an earlier paper[1] we described our rationale for the design of the pyrimido[4,5-*e*][1,4]diazepine-based folates **1** as potential antitumor agents via inhibition of the enzyme glycinamide ribonucleotide formyl transferase.[2-5] We reported our attempts at preparing the pyrimido[4,5-*e*][1,4]diazepine heterocyclic system, which led to the unexpected formation of dimers. Here we report our successful approach to the title compound **7**, a potentially useful intermediate to the target folates **1**.



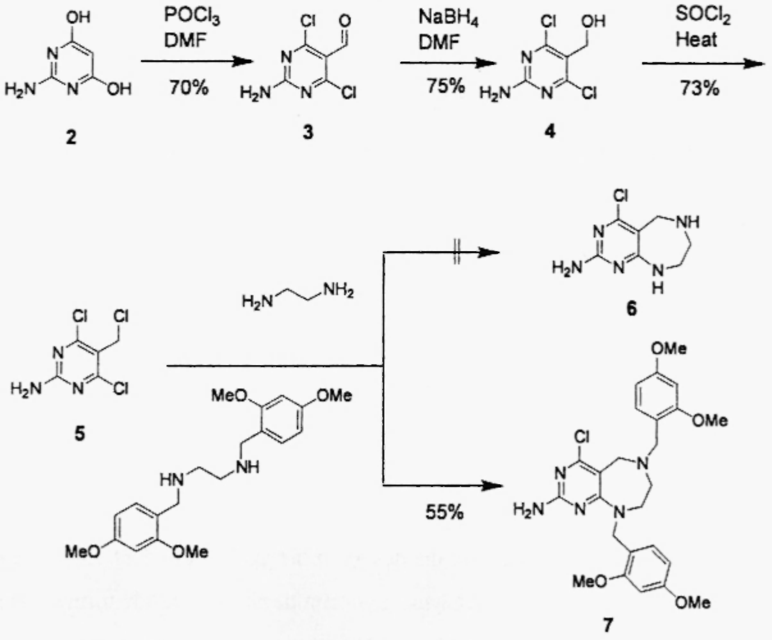
1: n = 0,1, or 2

Results and Discussion

Our synthesis of **7** starts with the conversion of commercially available 2-amino-4,6-dihydroxypyrimidine (**2**) to 2-amino-4,6-dichloro-5-formylpyrimidine (**3**) via a Vilsmeier-Haack reaction as reported by Bell[6] (Scheme). Treatment of **3**, suspended in cold anhydrous DMF, with sodium borohydride gave the corresponding alcohol **4** in 75% yield.[7] The alcohol **4** was heated at reflux with thionyl chloride and this resulted in the formation of the trichloropyrimidine **5** in 73% yield.[8] We had hoped that reaction of **5** with ethylenediamine would provide the pyrimidodiazepine **6**. However, this reaction led to the formation of a mixture of highly insoluble products (as evidenced by nmr) from which we were unable to isolate **6**. Consequently, we attempted the above reaction with *N,N'*-bis-(2,4-dimethoxybenzyl)-ethane-1,2-diamine (obtained via the reductive alkylation of ethylenediamine with 2,4-dimethoxybenzaldehyde) in the hope that the desired product would be soluble and thus would be easy to purify.

We were gratified to find that the above reaction did indeed lead to the formation of the pyrimidodiazepine 7 which was obtained in 55% yield after purification by chromatography on silica gel.[9] Compound 7 should be a useful intermediate to the desired pyrimido[4,5-*e*][1,4]diazepine-based folate targets **1**, and we are currently in the process of developing this chemistry.

Scheme



Acknowledgments

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References and Notes

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7. 2-Amino-4,6-dichloro-5-hydroxymethylpyrimidine (**4**): mp 185-200 °C (decomp.); ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.45 (d, J = 4.8 Hz, 2H), 5.07 (t, J = 4.8 Hz, 1H), 7.50 (br s, 2H)
8. B.K. Ayida, Ph.D. dissertation, The University of Memphis, 2001; 2-Amino-4,6-dichloro-5-chloromethylpyrimidine (**5**): mp 200-202 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.72 (s, 2H), 5.43 (br s, 2H)
9. Title Compound 7: mp 86-88 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.86 (br s, 2H), 3.49 (br s, 2H), 3.67 (s, 2H), 3.78 (s, 12H), 3.96 (s, 2H), 4.69 (s, 2H), 4.96 (s, exchangeable with D_2O, 2H), 6.43 (br s, 4H), 7.14 (m, 2H). HRMS (FAB) calcd. for $C_{25}H_{31}ClN_5O_4$ m/z 500.20646 (M^+), found m/z 500.20190

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