Synthesis of 2,4-Diamino-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine

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We have initiated a program aimed at the synthesis of derivatives of 2,4-diamino-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (**3**) as potential selective inhibitors of *Pneumocystis carinii* DHFR. The present paper describes a simple synthesis of **3** from 2,4,6-triaminopyrimidine and 2-cyclohexen-1-one as well as methodology for the introduction of a variety of substituents at bridgehead position C-9.

The maintenance of a steady cellular supply of tetrahydrofolate is critical to a number of biochemical processes. Inhibition of dihydrofolate reductase (DHFR) results in an impaired regeneration of tetrahydrofolate and represents an effective method for arresting cellular metabolism and growth. This strategy forms the basis for the activity of several clinically employed antibacterial, antiprotozoal, and antineoplastic agents.[1]

Among the most potent inhibitors of DHFR are derivatives of 2,4-diaminopyrimidine bearing lipophilic substituents at the C-5 position. Members of this structural class, such as trimethoprim (**1**)[2] and the 5-adamantyl derivatives (**2**),[3] are inhibitors of DHFR that exhibit pronounced selectivity for DHFR from bacterial and mammalian sources, respectively.

The structures of a number of apo and inhibitor-containing DHFRs from various eukaryotic and prokaryotic sources have been determined by X-ray crystallography.[4,5] The conformations adopted by the inhibitor in complexes of *Escherichia coli* and avian DHFR containing cocrystallized **1** indicate that the orientation of the side chain varies dramatically between the two species.[6] The tighter, more complementary binding mode of **1** in *E. coli* DHFR and the narrowness of the binding pocket have been implicated as sources of the higher specificity of that agent for the bacterial enzyme. Conversely, the increased steric bulk of the adamantyl substituent in **2a** is not well accommodated by the narrow hydrophobic cleft adjoining the pyrimidine binding pocket of the bacterial enzyme; a more favorable interaction is established in the wider cavity common to mammalian DHFRs.[7]

The structural and functional diversities of DHFRs which exist among organisms have proven to be exploitable features of the enzyme. The species-specific properties of several known inhibitors suggest that the goal of developing agents specific for other pathogens is an attainable one. The most common opportunistic infection in AIDS patients is the pneumonia brought on by *Pneumocystis carinii*, a fungus whose virulence is manifested almost exclusively in individuals with an impaired immune system.[8] Existing inhibitors of DHFR with proven clinical efficacy have been evaluated against *P. carinii*. With an IC_{50} of 20 μm, trimethoprim (**1**) is a weak inhibitor of the fungal enzyme, and it displays only moderate species specificity. Examination, in the crystallographic complex, of the inter-residue distances between *P. carinii* DHFR and **1** indicates that the active site in this enzyme consists of an unoccupied volume that is intermediate between that of the *E. coli* and those of the mammalian proteins.[9] These data suggested that a diaminopyrimidine derivative with steric bulk lying between that of **1** and the 5-adamantyl derivatives (**2**) might exhibit selectivity for the fungal enzyme. The presence of structural elements of the tight-binding 6-ethyl derivative **2c** that are common with those found in 2,4-diamino-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (**3**) suggested that the latter may represent the prototype of a series of less sterically encumbered and conformationally constrained derivatives of the former (Figure 1). We have recently described the synthesis and reactivity of bridgehead hemiaminal **4**.[10] The present paper details our efforts to apply the results of our earlier studies toward the synthesis of **3**, with a view toward the evolution of a method for the rapid preparation of a potential library of derivatives based on this structural class.

Our initial efforts focused on conversion of the lactam portion of the previously prepared **6** into the amidine component of the desired **3**, a reaction whose conditions we hoped to develop using the protected derivative **5** (see Scheme 1).[10] A variety of methods exists for effecting this transformation in pyrimidines and their fused-ring derivatives. Among them, thionation followed by S-alkylation, sulfonylation, and chlorination are frequently relied

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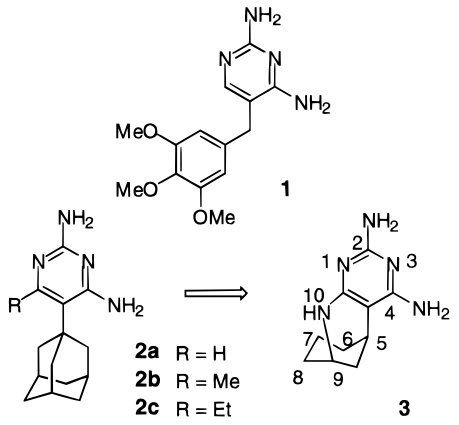
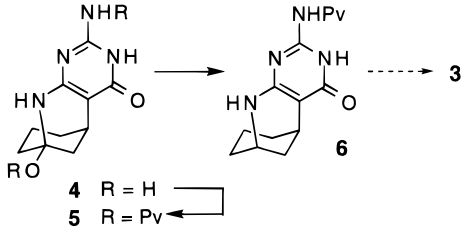


Figure 1.

Scheme 1

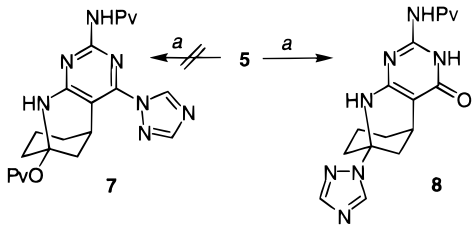


upon to furnish intermediates for the preparation of the desired amidine.[11]

Similarly, an approach originally developed for use in nucleoside chemistry achieves the desired conversion through the intermediacy of 4-[1′-(1,2,4-triazolyl)] derivatives.[12] This methodology has been successfully applied to pteridines and deazapterins, and its extension to the 5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine system appeared straightforward.[13] However, attempts to implement this protocol using the model system **5** in pyridine at rt resulted only in the recovery of starting material; none of the desired **7** could be detected. When the reaction was conducted in refluxing pyridine for 8 h, the starting material was consumed, but the spectral data of the isolated product indicated the absence of the pivaloyl ester together with the presence of a 1,2,4-triazolyl substituent. On the basis of the previously noted propensity of **5** to react with nucleophiles in basic media to afford products of bridgehead substitution,[10] the new material was assigned structure **8** (see Scheme 2).

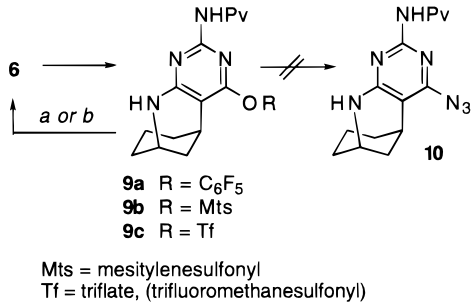
To avoid the complication introduced by the high lability of the bridgehead ester, the above reaction was attempted with **6**; however, no reaction was observed even after prolonged reflux in pyridine. Attempts to prepare the 4-*O*-pentafluorophenyl derivative **9a** by treatment of **6** with trifluoroacetic anhydride in pyridine followed by treatment with pentafluorophenol were unsuccessful.[14] Conversion to either the mesitylenesulfonyl derivative **9b** or triflate **9c**, followed by treatment with

Scheme 2[a]



[a] Reagents and conditions: (a) 4-chlorophenyldichlorophosphate, 1,2,4-triazole, pyridine, 110 °C, 8 h, 52%.

Scheme 3[a]



[a] Reagents and conditions: (a) NaN_3, DMF; (b) $TMSN_3$, DMF.

NaN_3 or $TMSN_3$ in DMF, which was intended to furnish azide **10**, led to cleavage of the sulfonate and regeneration of the precursor **6** (see Scheme 3).

Despite the steric congestion present in **9b**, attack on sulfur is preferred to substitution at the pyrimidine C-4 carbon atom. Examination of a molecular model of **9b** suggested that the three-carbon bridge of the bicyclic system could partially impede the approach of nucleophiles from one face of the pyrimidine ring. Reaction at the opposite face is potentially retarded by the steric congestion likely to result when rehybridization of the ipso carbon atom from sp^2 to sp^3 causes the sulfonate group to occupy the already-crowded region on the other side. To eliminate this unanticipated mode of reactivity and ensure that only the pyrimidine ring was susceptible to nucleophilic attack, conversion of the lactam to the corresponding imidoyl chloride was undertaken. In anticipation of the need to reduce the yet-to-be introduced azido group to a primary amine, ethyl sulfide **11**,[10] the precursor to **6**, was employed as a substrate; subsequent simultaneous azide reduction and desulfurization would lead directly to **3**. Heating a neat mixture of **11** in $POCl_3$ at 120 °C for 4 h cleanly effected conversion to the desired chloro derivative **12**. Although displacement of the newly introduced halogen with NaN_3 in ethanol was unsuccessful, even when the reaction was conducted in a screw-capped pressure tube at 150 °C, the use of elevated temperature (110 °C) and DMF as solvent afforded the desired azide **13**, albeit in low yield due to competing displacement of the halogen by adventitious dimethylamine. In light of this complication, the use of a polar, aprotic solvent not prone to decomposition at elevated temperature seemed warranted, and the reaction was instead conducted in *N*-methylpyrrolidinone to give **13** in 90% yield. Reduction of the newly installed azido group was readily accomplished by hydrogenation in EtOH using 1 weight equiv of 5% Pd/C catalyst in order to overcome catalyst poisoning by the thioether moiety. Radical-induced desulfurization of amine **14** was effected

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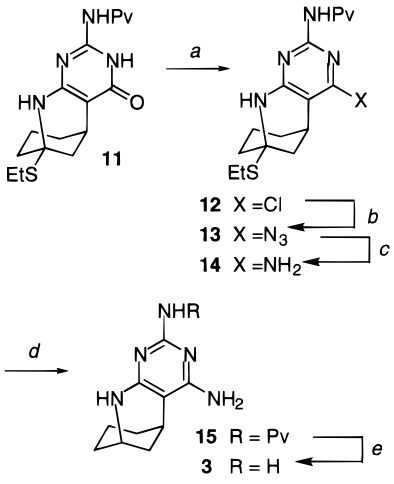
Scheme 4[a]

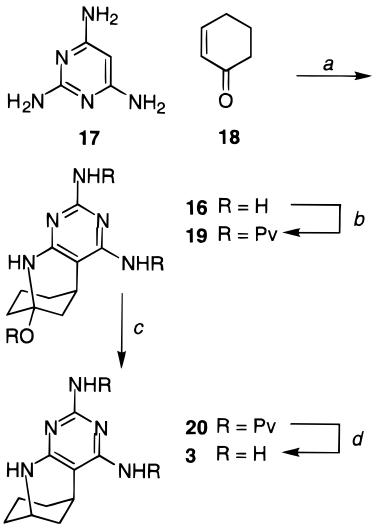


[a] Reagents and conditions: (a) $POCl_3$, 120 °C, 8 h, 90%; (b) $TMSN_3$, NMP, 120 °C, 8 h, 90%; (c) H_2, 5% Pd/C, EtOH, 3 h, 90%; (d) *n*-Bu_3SnH, AlBN, 120 °C, toluene, 80%; (e) LiOH, MeOH, 60 °C, 3 h, 80%.

with tributyltin hydride and AIBN in refluxing toluene.[15] Frequent reinitiation of the reaction was necessary and was accomplished by periodic addition of 10 mol % of the initiator. Purification of the reduction product was made difficult by the accompanying tributyltin thioether byproduct; however, repeated chromatography ultimately afforded pure **15** which was deprotected using LiOH in 10:1 MeOH/water to afford the desired **3** (see Scheme 4). Samples of this material also suffered from contamination by residual organotin, which was removed by purification using reversed-phase HPLC.

In an effort to improve the efficiency of the sequence detailed above, we sought to prepare adduct **16** by direct annulation of 2,4,6-triaminopyrimidine (**17**) with 2-cyclohexen-1-one (**18**) using the protocol developed for the synthesis of **3**.[10] However, under the standard conditions (NaOMe, MeOH) or after prolonged reaction periods, none of the desired material (**16**) was obtained. During the course of these studies a report appeared which described the condensation of *N*-alkyl-4-piperidinones at the C-5 position of various pyrimidines in acetic acid at elevated temperatures.[16] Encouraged by these results, the reaction of **17** with **18** was repeated using HOAc as solvent in a screw-capped pressure tube that was heated at 120 °C for 18 h. Gratifyingly, this approach afforded the expected heteroannulation product **16** which was then converted to the tripivaloyl derivative **19** by heating at 140 °C for 6 h in neat pivalic anhydride. Further streamlining of the sequence was achieved by direct deoxygenation of the bridgehead position with $NaCNBH_3$ in pyridine. Subsequent removal of both *N*-pivaloyl groups using LiOH in MeOH afforded the previously prepared **3** in four steps commencing with **17**. Aside from enabling a more rapid assembly of the target structure **3** and potential derivatives, the latter sequence eliminates the need to rely on toxic reagents such as Raney nickel and Bu_3SnH that were used previously to effect conversion of **11** to **6** and **14** to **15**, respectively.[10] The reductive removal of the pivaloyl ester in **19** is presumed

Scheme 5[a]



[a] Reagents and conditions: (a) HOAc, 160 °C, 18 h, 40%; (b) $(PvO)_2O$, 140 °C, 6 h, 85%; (c) $NaCNBH_3$, pyridine, 120 °C, 24 h, 88%; (d) LiOH, MeOH, 60 °C, 7 h, 68%.

to proceed by base-assisted removal of the annular N−H proton followed by generation of an intermediate bridgehead imine; reduction of this species in situ by cyanoborohydride ion then affords **20** (see Scheme 5).

Our earlier efforts at achieving this type of transformation have been described previously,[10] but other curious aspects germane to the present work are worthy of mention.

Hemiaminals are regarded as intermediates in the reduction of amides to methyleneamines and in the reductive amination of aldehydes and ketones, transformations for which a variety of reagents exists. A seemingly potential impediment to reduction in our system lies in the need to accommodate a bridgehead double bond at some intermediate stage in the sequence. This concern was alleviated by the demonstrated ease with which nucleophiles could be introduced in systems such as **5** *under basic conditions*, a process shown to likely proceed through the intermediacy of a bridgehead imine.

In light of these results it was surprising to us that a number of attempts to reduce **16** to **3** *under acidic conditions* ($NaCNBH_3$/TFA with or without added ZnI_2,[17] Et_3SiH/TFA,[18] or $NaBH_4$/TFA[19]) met with failure. Curiously, attempted reduction with $NaBH_4$/pyridine[20] or with BH_3/THF also led only to the recovery of **16**. Similarly, **19** was recovered unchanged when treated with $NaBH_4$/pyridine, $NaBH_4$/diglyme, or Ph_3SiH/TFA. The resistance of **16** and **19** to reduction under acidic conditions suggests that formation of a positive charge at the N-10 position may be disfavored as a result of the reduced ability of the fused pyrimidine ring to stabilize an adjacent positive charge when it, itself, is protonated (at N-1 or N-3). These results suggested consideration of a substrate whose hydrogenolytic lability might be optimum at a neutral or mildly acidic pH. Imidazole derivative **21**, prepared in the same manner as the corresponding triazole **8**, was

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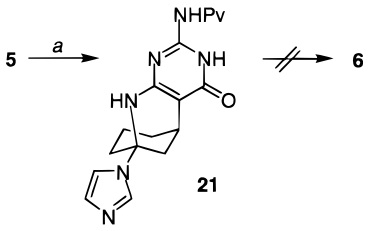
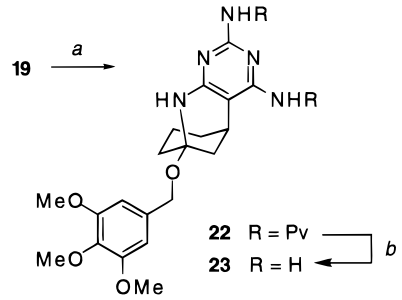
Scheme 6[a]



[a] Reagents and conditions: (a) imidazole, pyridine, 110 °C, 8 h, 78%.

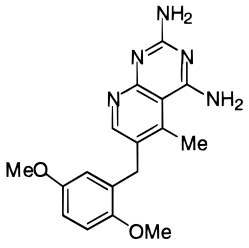
Scheme 7[a]



[a] Reagents and conditions: (a) 3,4,5-trimethoxy-benzyl alcohol, Na^0, 2 h, 92%; (b) LiOH, MeOH, 60 °C, 3 h, 80%.

expected to undergo protonation on the more basic imidazole ring and enable formation of an intermediate bridgehead imine. However, this substrate proved to be inert under a number of the conditions described above as well as with 2,6-lutidine/BH_3 or Me_3N/BH_3 in MeOH/H_2O (20:1) with or without added HOAc (see Scheme 6).

The majority of DHFR inhibitors are characterized by having not only a 2,4-diaminopyrimidine ring but often a tethered benzenoid ring bearing lipophilic groups such as chloro or methoxy substituents. Preliminary molecular modeling suggested that certain positions of the alicyclic portion of the tricyclic framework of **3** might serve as points of attachment for substituents that could impart additional binding affinity for DHFR and possibly species specificity through selective binding affinity. Incorporation of a trimethoxybenzyloxy substituent at the C-9 bridgehead would yield compound **23** in which the equatorial benzyl ether side chain is restricted from adopting an orientation seen in complexes of trimethoprim with mammalian DHFR, while the flanking axial hydrogens could serve to restrict this side chain to a "fungal" binding mode. The oxymethylene tether should allow the aromatic ring to project further into a remote binding pocket whose periphery is impinged upon by a similar side chain in the highly potent but nonselective agent piritrexim (**24**).[8] In a preliminary experiment,



compound **23** proved to be readily preparable by conversion of tripivaloyl derivative **19** into the 3,4,5-trimethoxybenzyl ether **22** followed by cleavage of the two amine protecting groups (see Scheme 7).

The synthesis of further derivatives of the intriguing tricyclic system found in **3**, including novel compounds resulting from bridgehead-carbon substitution, and their evaluation as potentially selective inhibitors of fungal DHFR are currently underway.

Experimental Section

2-Pivaloylamino-9-[1′-(1,2,4-triazolyl)]-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocin-4(3*H*)-one (8). To a stirred suspension of **5** (100 mg, 0.26 mmol) and 1,2,4-triazole (70 mg, 1.0 mmol, 4 equiv) in 5 mL of pyridine was added neat 4-chlorophenyldichlorophosphate (95 mg, 0.37 mmol) via syringe. The resulting solution was heated at 110 °C for 8 h and cooled to rt, and then the solvent was removed in vacuo. The solid residue was partially dissolved with CH_2Cl_2 (10 mL) and washed twice with a water/i-PrOH solution (10 mL, 8:1). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was filtered through a pad of silica gel, concentrated in vacuo, and purified by radial chromatography (1-mm plate) using a gradient of 10−20% MeOH in CH_2Cl_2, as eluent, to give 48 mg (52%) of a white powder which did not melt below 300 °C: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22 (s, 9 H), 1.52 (m, 1 H), 1.60 (m, 2 H), 1.72 (d, 1 H, J = 12.9 Hz), 2.07 (d, 1 H, J = 11.1 Hz), 2.16 (d, 1 H, J = 11.8 Hz), 2.30 (m, 2 H), 3.33 (br s, 1 H), 7.36 (s, 1 H), 8.03 (s, 1 H), 8.66 (s, 1 H), 10.64 (s, 1 H), 11.42 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 18.6, 26.2, 26.5, 29.7, 36.4, 38.5, 39.9, 71.7, 93.3, 141.8, 149.4, 150.9, 158.5, 159.2, 181.0; IR (KBr) 3196, 1633, 1569 cm^{-1}; MS *m/e* (relative intensity) 357 (10), 314 (5), 288 (23), 260 (50); HRMS calcd for $C_{17}H_{23}N_7O_2$ 357.1913, found 357.1906. Anal. Calcd for $C_{17}H_{23}N_7O_2$: C, 57.11; H, 6.49; N, 27.43. Found: C, 57.09; H, 6.76; N, 27.71.

2-Pivaloylamino-4-(trifluoromethanesulfonyl)-5,6,7,8,-9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (9b). To a stirred suspension of **6** (200 mg, 0.69 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (212 mg, 1.03 mmol, 1.5 equiv) in 10 mL of CH_2Cl_2 at −78 °C was added neat Tf_2O (253 mg, 0.90 mmol, 1.3 equiv), via syringe. The reaction flask was held at this temperature for 1 h, removed from the cooling bath, and allowed to warm to rt over a period of 1 h. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and water (10 mL), and the organic phase was washed with a saturated aqueous solution of NaCl (10 mL) and dried over Na_2SO_4. The drying agent was removed by filtration, and the filtrate was concentrated in vacuo to afford a pale yellow oil which was purified by radial chromatography (2-mm plate) using 5% MeOH in CH_2Cl_2 as eluent. The pure product was obtained as a clear, colorless oil (247 mg, 85%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.29 (s, 9 H), 1.35 (m, 1 H), 1.60 (m, 2 H), 1.71 (m, 2 H), 1.79 (m, 2 H), 1.84 (d, 1 H, J = 12.8 Hz), 3.18 (s, 1 H), 3.81 (s, 1 H), 6.20 (s, 1 H), 7.72 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 17.1, 26.2, 27.5, 28.7, 31.9, 33.5, 40.4, 46.6, 100.2, 118.1 (d, J = 321 Hz), 154.7, 158.2, 165.1, 175.9; MS *m/e* (relative intensity) 422 (30), 379 (15), 338 (100), 295 (99); HRMS calcd for $C_{16}H_{21}N_4O_4SF_3$ 422.1235, found 422.1229. Anal. Calcd for $C_{16}H_{21}N_4O_4SF_3$: C, 45.49; H, 5.01; N, 13.26. Found: C, 46.06; H, 5.40; N, 12.86.

2-Pivaloylamino-4-chloro-9-ethylthio-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (12). A solution of **11**[10] (350 mg, 1.0 mmol) in 5 mL of phosphorus oxychloride was heated at 110 °C for 3 h. The solvent was removed in vacuo with the aid of a short-path distillation apparatus. The remaining viscous yellow oil was dissolved in $CHCl_3$ (15 mL) and concentrated to remove residual $POCl_3$. Purification of the resulting residue by radial chromatography (2-mm plate) using 1% Et_3N/5% MeOH in CH_2Cl_2 as eluent gave 370 mg (95%) of a white solid: mp 169−171 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22 (t, 3 H, J = 7.4 Hz), 1.28 (s, 9 H), 1.40 (m, 1 H), 1.64 (m, 2 H), 1.78 (dt, 1 H, J = 4.3, 13.1 Hz), 1.87 (m, 2 H), 2.01 (m, 2 H), 2.62 (m, 2 H), 3.35 (m, 1 H), 5.84 (s, 1 H), 7.78 (s, 1 H);

^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 14.7, 18.9, 21.5, 27.6, 30.6, 30.8, 35.4, 40.4, 40.5, 62.1, 108.4, 155.3, 156.0, 163.3, 176.1; MS *m/e* (relative intensity) 370 (11), 368 (28), 327 (16), 325 (43), 309 (54), 307 (100); HRMS calcd for $C_{17}H_{25}N_4OSCl$ 368.1437, found 368.1435. Anal. Calcd for $C_{17}H_{25}N_4OSCl$: C, 55.35; H, 6.83; N, 15.19. Found: C, 55.41; H, 6.56; N, 14.88.

2-Pivaloylamino-4-azido-9-ethylthio-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (13). A magnetically stirred suspension of **12** (280 mg, 0.76 mmol) and $TMSN_3$ (174 mg, 1.50 mmol, 2.0 equiv) in 5 mL of *N*-methylpyrrolidinone was heated at 110 °C for 6 h. After the reaction mixture was allowed to cool to rt, the solvent was removed by distillation under reduced pressure using a short-path apparatus. The resulting semisolid residue was purified by radial chromatography (2-mm plate) using a gradient of 2−5% MeOH in CH_2Cl_2 as eluent to afford 256 mg (90%) of a white foam: mp 45−60 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.21 (t, 3 H, J = 7.4 Hz), 1.31 (s, 9 H), 1.41 (m, 1 H), 1.56−2.04 (m, 7 H), 2.65 (m, 2 H), 3.14 (m, 1 H), 5.65 (s, 1 H), 7.71 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 14.6, 18.8, 21.4, 27.5, 28.2, 30.6, 35.3, 40.2, 40.5, 61.9, 108.3, 155.2, 156.6, 176.0; IR (NaCl) 3245, 2131, 1700, 1604, 1575 cm^{-1}; MS *m/e* (relative intensity) 375 (22), 332 (16), 314 (53), 288 (31); HRMS calcd for $C_{17}H_{25}N_7OS$ 375.1841, found 375.1829.

2-Pivaloylamino-4-amino-9-ethylthio-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (14). A magnetically stirred suspension of **13** (256 mg, 0.68 mmol) and one weight equivalent of 5% Pd/C in 5 mL of EtOH was reduced under one atmosphere of H_2 for 3 h. The reaction mixture was filtered through Celite and the filter cake was washed with 15 mL of hot EtOH. Concentration of the filtrate in vacuo gave an oil which was purified by radial chromatography (1-mm plate) using 10% MeOH and 1% Et_3N in CH_2Cl_2 as eluent. The resulting clear, colorless oil (214 mg, 90%) solidified upon standing: mp 130 °C (dec); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.20 (t, 3 H, J = 7.4 Hz), 1.26 (s, 9 H), 1.27 (m, 1 H, obscured), 1.49 (m, 1 H), 1.56 (m, 3 H), 1.75 (m, 2 H), 1.85 (d, 1 H, J = 12.2 Hz), 2.62 (m, 2 H), 2.89 (m, 1 H), 4.68 (s, 2 H), 5.33 (s, 1 H), 7.63 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 14.7, 19.1, 21.3, 27.5, 28.2, 29.9, 36.1, 40.1, 41.1, 61.6, 90.2, 155.3, 159.4, 161.7, 175.9; MS *m/e* (relative intensity) 349 (19), 306 (19), 288 (100), 57 (40); HRMS calcd for $C_{17}H_{27}N_5OS$ 349.1936, found 349.1931.

2-Pivaloylamino-4-amino-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (15). A 50-mL, single-necked, pear-shaped flask fitted with a stoppered Claisen head, reflux condenser, and gas inlet and containing a solution of **14** (150 mg, 0.43 mmol), Bu_3SnH (150 mg, 0.52 mmol, 1.2 equiv), and AIBN (35 mg, 0.22 mmol, 0.5 equiv) in 10 mL of toluene, freshly distilled from CaH_2, was immersed in an oil bath heated to 125 °C. The flask was carefully evacuated and purged with Ar, a process that was repeated three times. Previous experiments indicated that periodic reinitiation of the reaction was required. At 6-h intervals, over a 36-h period, the reaction vessel was removed from the oil bath and additional AIBN (35 mg, 0.22 mmol, 0.5 equiv) was added to the reaction mixture. The evacuation and purging routine was repeated, and the reaction was allowed to continue until TLC analysis (1% Et_3N and 5% MeOH in CH_2Cl_2) indicated that the starting material had been consumed. Removal of the solvent in vacuo followed by Kugelrohr distillation of the oily residue afforded a semisolid material which was purified by radial chromatography using 1% Et_3N and 5% MeOH in CH_2Cl_2 as eluent. The desulfurized material was obtained as a white solid (100 mg, 80%): mp 220−221 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (m, 1 H, partially obscured), 1.27 (s, 9 H), 1.40 (dt, 1 H, J = 4.3, 12.9 Hz), 1.49 (d, 1 H, J = 11.7 Hz), 1.59 (m, 2 H), 1.72 (d, 2 H, J = 11.6 Hz), 1.84 (d, 1 H, J = 12.2 Hz), 2.79 (br s, 1 H), 3.69 (br s, 1 H), 4.58 (br s, 2 H), 5.46 (br s, 1 H), 7.62 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 17.8, 26.6, 27.7, 29.9, 30.7, 34.7, 40.2, 46.3, 91.2, 154.9, 159.1, 161.6, 176.1; MS *m/e* (relative intensity) 289 (10), 246 (13), 205 (27), 189 (9), 162 (41); HRMS calcd for $C_{15}H_{23}N_5O$ 289.1902, found 289.1916.

2,4-Diamino-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (3). Method A. A suspension of **15** (54 mg, 0.19 mmol) and LiOH (54 mg, 0.12 mmol, 7 equiv) in 5 mL of MeOH and 0.5 mL of water was heated to 50 °C. The resulting pale yellow solution was held at this temperature for 2.5 h, cooled to rt, and concentrated in vacuo. The resulting solid residue was purified by reversed-phase HPLC (C-18 preparative column) using a gradient of 1% MeCN/0.1% TFA in water and 90% MeCN/0.1% TFA in water. The resulting hygroscopic white solid was suspended in water and dissolved by slowly adjusting the pH to 9 with 0.1 M K_2CO_3 in water. The resulting solution (10 mL) was extracted with $CHCl_3$ (4 × 5 mL), and the combined organic extracts were dried by filtration through a pad of Na_2SO_4. The filtrate was concentrated in vacuo to afford a white microcrystalline solid (20 mg, 50%): mp 216−218 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28 (m, 1 H), 1.37 (br d, 1 H, J = 13.1 Hz), 1.45 (m, 3 H), 1.61 (m, 2 H), 1.73 (d, 1 H, J = 11.9 Hz), 2.84 (br s, 1 H), 3.48 (br s, 1 H), 5.10 (br s, 2 H), 5.38 (br s, 2 H), 6.35 (d, 1 H, J = 2.9 Hz); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 17.5, 25.2, 30.2, 30.9, 34.5, 44.7, 84.9, 159.6, 160.8, 161.4; MS *m/e* (relative intensity) 205 (24), 162 (100), 145 (11); HRMS calcd for $C_{10}H_{15}N_5$ 205.1327, found 205.1331. Anal. Calcd for $C_{10}H_{15}N_5$: C, 58.52; H, 7.37; N, 34.12. Found: C, 58.53; H, 7.22; N, 34.02.

2,4-Diamino-9-hydroxy-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (16). A suspension of 2,4,6-triaminopyrimidine (0.31 g, 2.5 mmol) and 2-cyclohexen-1-one in glacial acetic acid (10 mL) was placed in a sealed tube which, upon heating at 120 °C for 20 min, gave a clear solution. The reaction mixture was heated for another 17 h at 120 °C. The solvent was removed in vacuo to give a white solid that was purified by column chromatography on silica gel using 50% MeOH/CH_2Cl_2 as eluent to give 0.23 g (41%) of **16**: mp 230 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.30 (m, 2 H), 1.46 (m, 1 H), 1.49 (m, 2 H), 1.56 (m, 1 H), 1.63 (d, 1 H, J = 11.6 Hz), 1.69 (d, 1 H, J = 11.6 Hz), 2.93 (s, 1 H), 5.18 (s, 2 H), 5.43 (s, 2 H), 5.52 (s, 1 H), 5.93 (s, 1 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 19.9, 28.2, 30.4, 41.2, 79.6, 84.7, 159.8, 161.1, 161.2; IR (KBr) 3371, 3189, 2971, 2858, 1611 cm^{-1}; MS *m/e* (relative intensity) 221 (36), 178 (100); HRMS calcd for $C_{10}H_{15}N_5O$ 221.1276, found 221.1284.

2,4-Bis(pivaloylamino)-9-(pivaloyloxy)-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (19). A suspension of **16** (1.0 g, 0.46 mmol) in 4 mL of pivalic anhydride was heated at 140 °C for 6 h. The solvent was removed in vacuo with the aid of a short-path distillation apparatus. The resulting solid residue was purified by column chromatography using 50% EtOAc in hexane as eluent to give 1.84 g (85%) of **19**: mp 145−147 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.15 (s, 9 H), 1.17 (s, 9 H), 1.18 (s, 9 H), 1.54 (m, 2 H), 1.60 (m, 2 H), 1.93 (m, 1 H), 2.05 (m, 1 H), 2.10 (d, 1 H, J = 11.3 Hz), 2.16 (d, 1 H, J = 11.3 Hz), 3.09 (s, 1 H), 7.92 (s, 1 H), 9.31 (s, 1 H), 9.50 (s, 1 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 19.1, 26.7, 26.8, 27.1, 28.9, 30.0, 32.5, 37.1, 38.7, 40.0, 87.7, 107.6, 154.2, 155.9, 162.4, 174.8, 175.7, 176.5, 176.7; IR (KBr) 3414, 3273, 2956, 1710, 1590 cm^{-1}; MS *m/e* (relative intensity) 473 (50), 372 (36), 314 (100), 286 (59); HRMS calcd for $C_{25}H_{39}N_5O_4$ 473.3002, found 473.3017. Anal. Calcd for $C_{25}H_{39}N_5O_4$: C, 63.40; H, 8.30; N, 14.79. Found: C, 63.56; H, 8.34; N, 14.26.

2,4-Bis(pivaloylamino)-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (20). To a solution of **19** (0.95 g, 2.0 mmol) in 10 mL of pyridine was added sodium cyanoborohydride (0.50 g, 8.0 mmol) in one portion, and the reaction mixture was heated at 110 °C for 24 h. The solvent was removed under reduced pressure followed by the addition of water. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue obtained was purified by column chromatography using 5% MeOH in CH_2Cl_2 as eluent to give **19** (0.66 g, 88%) as a white powder: mp 160−161 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.17 (s, 9 H), 1.18 (s, 9 H), 1.42 (m, 3 H), 1.50 (m, 2 H), 1.67 (m, 2 H), 1.80 (d, 1 H, J = 12.5 Hz), 2.91 (s, 1 H), 3.61 (s, 1 H), 7.64 (d, 1 H, J = 4.2 Hz), 9.18 (s, 1 H), 9.33 (s, 1 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 17.0, 26.6, 26.9, 27.1, 28.3, 31.1, 33.4, 38.6, 40.0, 44.8, 107.9, 153.5. 155.3.

163.4, 175.6; MS *m/e* (relative intensity) 373 (18), 316 (100), 289 (28); HRMS calcd for $C_{20}H_{31}N_5O_2$ 373.2477, found 373.2468.

2-Pivaloylamino-9-(1′-imidazolyl)-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocin-4(3*H*)-one (21). A stirred suspension of **5** (120 mg, 0.29 mmol) and imidazole (80 mg, 1.2 mmol, 4 equiv) in 3 mL of pyridine was heated at 110 °C for 8 h and cooled to rt. Then the solvent was removed in vacuo. The solid white residue was partially dissolved with CH_2Cl_2 (10 mL) and washed twice with a water/*i*-PrOH solution (10 mL, 8:1). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was filtered through a pad of silica gel, concentrated in vacuo, and purified by radial chromatography (1-mm plate) using a gradient of 10−20% MeOH in CH_2Cl_2 as eluent to give 81 mg (78%) of a white powder: mp 322−324 °C dec; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22 (s, 9 H), 1.54 (m, 1 H), 1.60 (m, 2 H), 1.70 (d, 1 H, J = 12.6 Hz), 2.00 (d, 1 H, J = 10.2 Hz), 2.09 (d, 1 H, J = 11.7 Hz), 2.25 (m, 2 H), 3.13 (br s, 1 H), 6.93 (s, 1 H), 7.37 (s, 1 H), 7.38 (s, 1 H), 7.84 (s, 1 H), 10.65 (s, 1 H), 11.40 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) δ 18.6, 26.2, 26.5, 29.7, 36.4, 38.5, 39.9, 71.7, 93.3, 141.8, 149.4, 150.9, 158.5, 159.2, 181.0; IR (KBr) 3196, 1633, 1569 cm^{-1}; MS *m/e* (relative intensity) 356 (28), 313 (12), 289 (81); HRMS calcd for $C_{18}H_{24}N_6O_2$ 356.1960, found 356.1963. Anal. Calcd for $C_{18}H_{24}N_6O_2$: C, 60.64; H, 6.79; N, 23.59. Found: C, 60.41; H, 6.64; N, 23.58.

2,4-Diamino-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (3). Method B. A solution of **20** (0.56 g, 1.5 mmol) and LiOH (0.26 g, 6.0 mmol) in 10 mL of MeOH was heated at 60 °C for 6 h. The reaction mixture was allowed to cool to rt, and the solvent was removed in vacuo to give a white solid. The crude material was purified by column chromatography using 30% MeOH in CH_2Cl_2 as eluent to afford 0.21 g (68%) of **3** as a white solid, mp 216−218 °C, whose spectral characteristics were identical in all respects with those of the material obtained by the earlier method.

2,4-Bis(pivaloylamino)-9-(3′,4′,5′-trimethoxybenzyloxy)-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (22). Sodium metal (46 μg, 2.0 mmol) was added to neat 3,4,5-trimethoxybenzyl alcohol (0.39 g, 2.0 mmol) at rt, and the resulting mixture was stirred for 1 h. In one portion, **19** (0.71 g, 1.5 mmol) was added, followed by the addition of 10 mL of dry THF to give a homogeneous mixture. The reaction mixture was stirred for an additional 2 h, during which time a voluminous precipitate was deposited. After the white suspension was refrigerated for 1 h, the white solid was collected by filtration and washed successively with water (10 mL) and diethyl ether (15 mL). Recystallization of the crude material from MeOH/CH_2Cl_2 gave 0.79 g (93%) of **22** as a white solid: mp 261−262 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.18 (s, 9 H), 1.19 (s, 9 H), 1.50 (m, 1 H), 1.57 (m, 2 H), 1.67 (m, 1 H), 1.71 (m, 1 H), 1.74 (d, 1 H, J = 11.3 Hz), 1.85 (d, 1 H, J = 11.9 Hz), 1.97 (d, 1 H, J = 11.0 Hz), 3.08 (s, 1 H), 3.63 (s, 3 H), 3.77 (s, 6 H), 4.43 (d, 1 H, J = 11.0 Hz), 4.52 (d, 1 H, J = 11.3 Hz), 6.74 (s, 2 H), 7.98 (s, 1 H), 9.28 (s, 1 H), 9.45 (s, 1 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 19.2, 26.9, 27.1, 29.0, 30.4, 31.9, 38.6, 40.0, 55.8, 59.9, 62.8, 84.0, 105.2, 107.9, 134.5, 136.5, 152.6, 153.8, 155.8, 162.8, 164.2, 175.7, 176.6; MS *m/e* (relative intensity) 569 (21), 512 (81), 372 (53), 198 (100); HRMS calcd for $C_{30}H_{43}N_5O_6$ 569.3213, found 569.3230. Anal. Calcd for $C_{30}H_{43}N_5O_6$: C, 63.25; H, 7.61; N, 12.29. Found: C, 63.12; H, 7.61; N, 12.00.

2,4-Diamino-9-(3′,4′,5′-trimethoxybenzyloxy)-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (23). A solution of **22** (0.57 g, 1.0 mmol) and LiOH (0.17 g, 4.0 mmol) in 10 mL of MeOH was heated at 60 °C for 4 h. The white solid formed was cooled to rt, filtered, and washed with water (15 mL), methanol (10 mL), and diethyl ether (10 mL). The solid compound was dried in vacuo to afford 0.27 g (67%) of **11** as a white powder: mp 200−201 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.39 (m, 2 H), 1.53 (m, 2 H), 1.65 (m, 2 H), 1.80 (d, 1 H, J = 12.6 Hz), 1.97 (d, 1 H, J = 11.3 Hz), 3.02 (s, 1 H), 3.62 (s, 3 H), 3.76 (s, 6 H), 4.37 (d, 1 H, J = 11.3 Hz), 4.51 (d, 1 H, J = 11.3 Hz), 5.19 (s, 2 H), 5.53 (s, 2 H), 6.48 (s, 1 H), 6.69 (s, 2 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 19.4, 27.6, 30.2, 33.9, 40.0, 55.7, 59.9, 62.4, 83.8, 85.0, 105.1, 135.0, 136.4, 152.6, 159.8, 161.3, 161.9; IR (KBr) 3351, 3196, 2921, 1597, 1442 cm^{-1}; MS *m/e* (relative intensity) 401 (34), 204 (100), 198 (29); HRMS calcd for $C_{20}H_{27}N_5O_4$ 401.2062, found 401.2056. Anal. Calcd for $C_{20}H_{27}N_5O_4$: C, 59.82; H, 6.78; N, 17.45. Found: C, 60.04; H, 6.59; N, 17.23.

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