SYNTHESIS AND BRIDGEHEAD REACTIONS OF 9-SUBSTITUTED 5,6,7,8,9,10-HEXAHYDRO-5,9-METHANOPYRIMIDO[4,5-b]AZOCIN-4(3H)-ONES

Edward C. Taylor* and Beena Bhatia[§]

Department of Chemistry, Princeton University
Princeton, New Jersey 08544, USA
e-mail: etaylor@princeton.edu

Abstract - The condensation of a variety of 6-amino-4(3H)-pyrimidinones with 2-cyclohexen-1-one in water, and replacement of the bridgehead 9-hydroxy group in the resulting Michael/cyclization adducts with carbon nucleophiles, are described. These reactions have been exploited for the preparation of a novel bridged tricyclic analog of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF).

6-Amino-4(3H)-pyrimidinones behave as enaminones, with electrophilic reactions such as nitrosation, nitration, acylation and diazo coupling taking place at C-5.[1] Michael reactions have also been observed to take place at C-5. α,β-Unsaturated carbonyl compounds lead directly to condensed pyrimidines such as pyrido[2,3-d]pyrimidines and quinolino[2,3-d]pyrimidines (or their dihydro derivatives) by intramolecular cyclization of the initial Michael adducts through participation of the pyrimidine 6-amino grouping.[2] Activated azo compounds (diethyl azodicarboxylate, 4-phenyl-1,2,4-triazoline-3,5-dione) can also react as Michael acceptors to give 5-hydrazino derivatives that serve as versatile intermediates for the synthesis of purines, isoalloxazines, alloxazines, toxoflavins, and fervenulins.[3] Michael addition of nitrosoolefins (prepared *in situ* by dehydrohalogenation of α-halo oximes)[4] and of nitro olefins[5] are also known, and lead through subsequent transformations of the initial Michael adducts to pyrrolo[2,3-d]pyrimidines, following the above mentioned intramolecular participation of the pyrimidine-6-amino group.
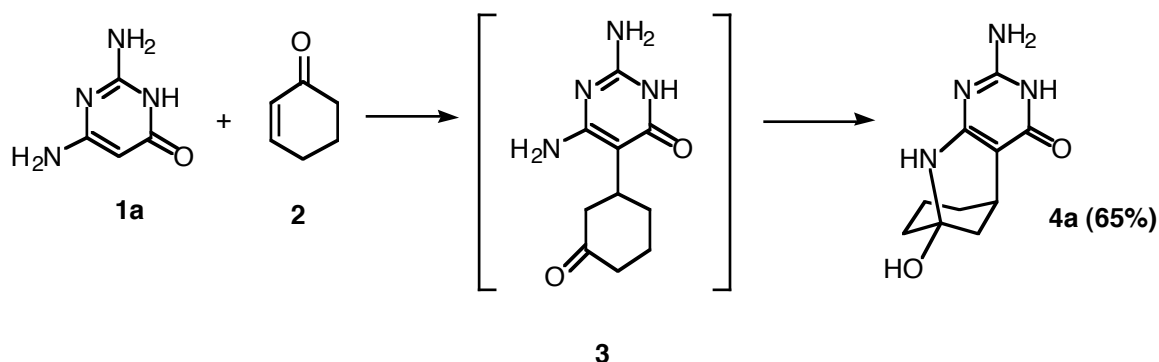
We recently reported an extension of this Michael addition/cyclization concept to the sodium methoxide-promoted reaction of 2,6-diamino-4(3H)-pyrimidinone (**1a**) with 2-cyclohexen-1-one (**2**).[6] The initially formed Michael adduct (**3**) undergoes irreversible hemiaminal formation through intramolecular cyclization of the cyclohexanone carbonyl group with the 6-amino pyrimidine substituent to give the novel tricyclic azabicyclo[3.3.1]nonane structure (**4a**). We have also described a number of subsequent transformations of **4a** involving conversion to (**5**),[7] and replacement of the hemiaminal –OH group by –SR, -OR, and -NR$_2$ *via* a 2-azabicyclo[3.3.1]non-1-ene anti-Bredt bridgehead imine intermediate.[6,7] In view of the overall structural resemblance between these
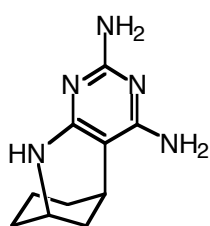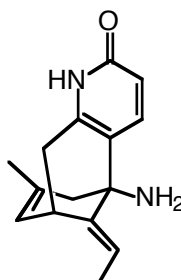
5   **6**

derivatives of **4a** (such as **5**) and Huperazine A (**6**) as well as initial molecular modeling studies indicating that **5** appears to match trimethoprim reasonably well as a ligand for the active site of *P. carinii* DHFR,[8] we have studied several additional aspects of the chemistry of these readily available tricyclic compounds, with the results reported herein.

Condensation of **1a** with 2-cyclohexen-1-one (**2**) to give **4a**, as carried out in our initial studies, was promoted by sodium methoxide in methanol, but other 6-aminopyrimidines failed to react under these conditions. We have now found that this reaction can be carried out very effectively simply by heating the reactants *in water*, and that these conditions are successful with a variety of 6-aminopyrimidines (see Table 1). Yields are generally good, and the products are readily obtained by cooling and filtering the aqueous reaction mixture. Although 2,4,6-triaminopyrimidine (**1g**) failed to react with **2** in aqueous solution, the reaction proceeded successfully in glacial acetic acid to give **4g**, as noted previously.[7]

We have now extended to carbon nucleophiles the protocol previously employed for replacement of the tertiary hemiaminal –OH grouping in **4a** with –SH, -OR, -NR$_2$ and –H. Reaction of the N,O-dipivaloyl derivative(**7**)[6] with Grignard reagents (ethynylmagnesium bromide, ethylmagnesium bromide, benzylmagnesium bromide, allylmagnesium bromide) resulted in smooth introduction of the corresponding carbon nucleophile into the tertiary position to give **8a-d**. A similar series of

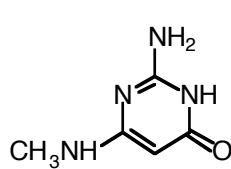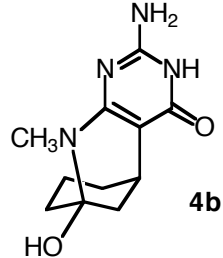## Table 1. Reaction of 6-Aminopyrimidines (1b-g) with 2-Cyclohexen-1-one
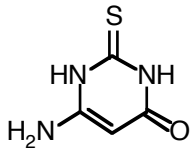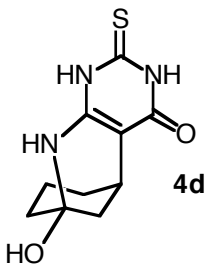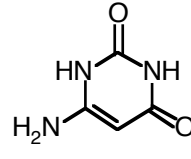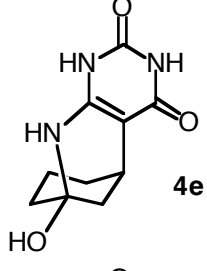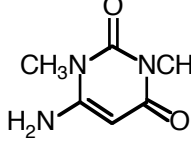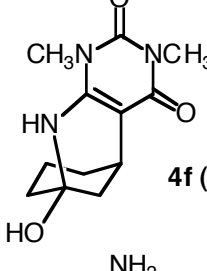
Substrate

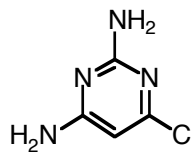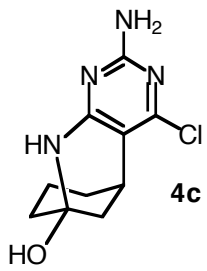**Product (yield)**

1b

4b (56%)

1c

4c (34%)

1d

4d (73%)

1e

4e (62%)

1f

4f (58%)

1g

4g (41%)
(in HOAc)

Table 2. Introduction of Bridgehead Carbon Substituents

a, R = -CH₂CH=CH₂
b, R = —C≡CH
c, R = -C₂H₅
d, R = -CH₂C₆H₅
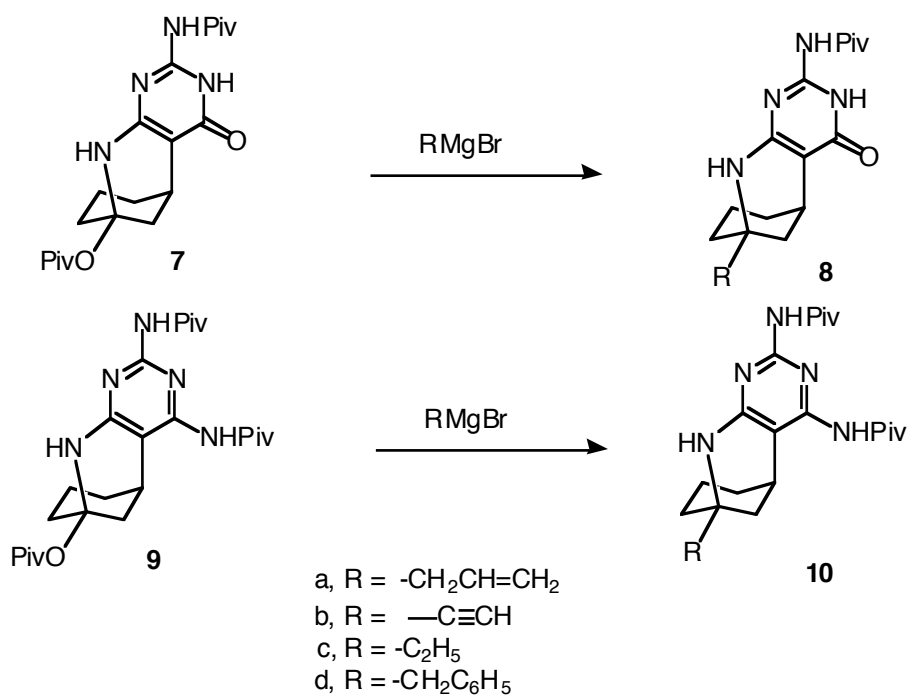
Scheme 1
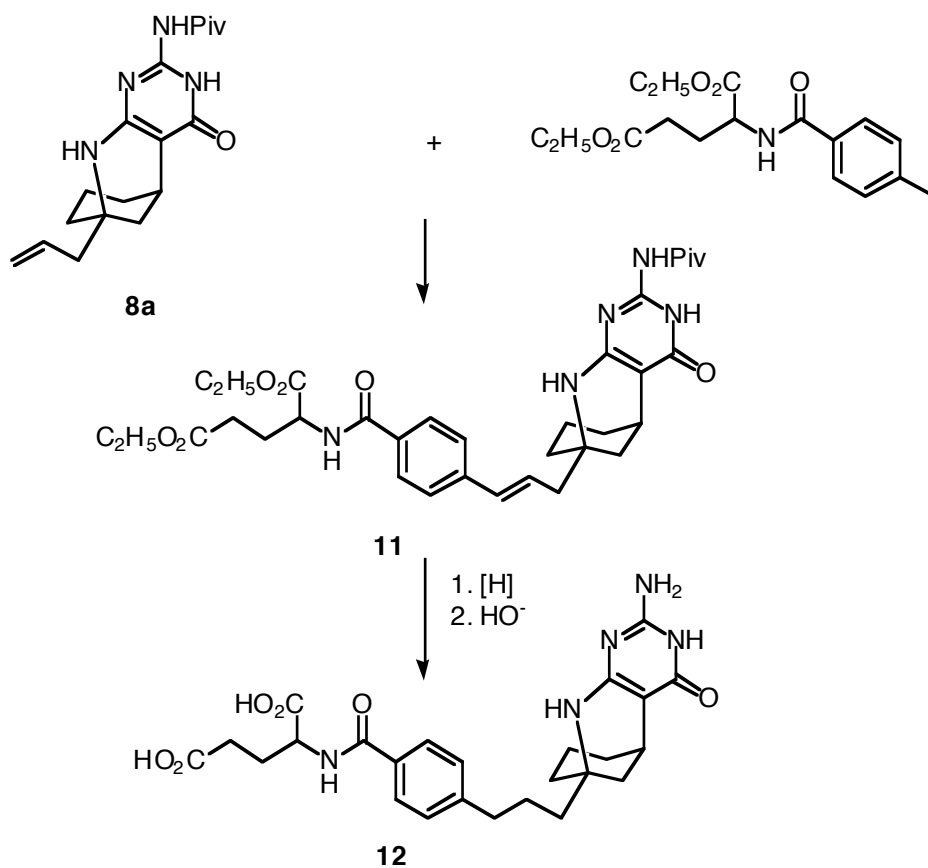
derivatives (**10a-d**) was prepared from **9**, the tripivaloyl derivative of **4g**[7] (see Table 2). The bridgehead allyl derivative (**8a**) was subjected to a palladium-catalyzed Heck coupling with diethyl 4-iodobenzoyl-L-glutamate to give **11**. Hydrogenation of **11** followed by hydrolysis of the pivaloyl and ester groups gave the intriguing lipophilic analog (**12**) of DDATHF.[9]

EXPERIMENTAL

2-Amino-5,6,7,8,9,10-hexahydro-9-hydroxy-5,9-methanopyrimido[4,5-*b*]azocin-4(3*H*)-one (4a).

To a suspension of 2,6-diamino-4(3*H*)-pyrimidinone (**1a**) (0.63 g, 5 mmol) in 10 mL of distilled water, 2-cyclohexen-1-one (**2**) (0.48 g, 5 mmol) was added and the mixture was heated at 80 ˚C for 20 h. The resulting solid was collected by filtration, washed with water (2x10 mL) followed by methanol (2x10 mL) and dried under vacuum to give 0.72 g (65%) of **4a** as a white powder, mp 310-312 ˚C (from methanol/ether). This compound was identical in all respects (mp, NMR, MS, IR) with an authentic sample of **4a**.[6]

2-Amino-5,6,7,8,9,10-hexahydro-9-hydroxy-10-methyl-5,9-methanopyrimido[4,5-*b*]azocin-4(3*H*)-one (4b).
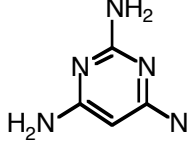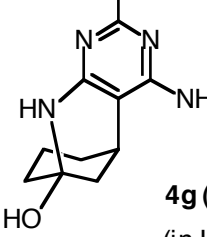
To a suspension of 2-amino-6-methylamino-4(3*H*)-pyrimidinone (**1b**) (0.32 g, 2.5 mmol) in 10 ml of H_2O, 2-cyclohexen-1-one (**2**) (0.48 g, 5 mmol) was added. After heating the reaction mixture at 90 ˚C for 25 h, a light brown solid precipitated. The solid was absorbed on silica gel and purified by column chromatography using 10% MeOH/CH_2Cl_2 as eluent to give 0.33 g (56%) of **4b** as a pale brown solid, mp 261-262 ˚C (from methanol/ether). This compound was identical in all respects (mp, NMR, MS, IR) with an authentic sample of **4b**.[6]

2-Amino-4-chloro-5,6,7,8,9,10-hexahydro-9-hydroxy-5,9-methanopyrimido(4,5-*b*)azocine (4c).

A solution of 4-chloro-2,6-diaminopyrimidine (**1c**) (0.65 g, 5 mmol) was heated with 2-cyclohexen-1-one (**2**) (0.96 g, 10 mmol) in 10 mL of H_2O for 23 h. The suspended solid was collected by filtration and subjected to column chromatography on silica using 2% MeOH/CH_2Cl_2 as eluent. Evaporation of the fractions corresponding to an R_f value of 0.5 on TLC, using 10% MeOH/CH_2Cl_2, gave 0.41 g (34%) of **4c** as a white solid, mp 183-185 ˚C (from methanol/ether); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.60 (m, 2H), 1.95 (m, 2H), 2.21 (m, 1H), 2.32 (dd, 2H, *J* =1.6 and 11.6 Hz), 2.52 (m, 1H), 4.18 (br s, 1H), 5.68 (s, 1H),) 6.41 (s, 2H), 7.20 (d, 1H, *J* = 1.6 Hz); ^{13}C NMR(DMSO-d_6, 500 MHz): δ 208.82, 163.05, 162.93, 48.65, 47.32, 40.28, 40.01, 30.19, 21.61; MS m/z (relative intensity) 240(4), 197(22), 144(71), 109(1); HRMS calcd for $C_{10}H_{13}N_4OCl$: 240.0778; Found: 240.0779; Anal Calcd for $C_{10}H_{13}N_4OCl$: C, 49.90; H, 5.44; N, 23.27. Found: C, 49.60; H, 5.38; N, 23.17.

5,6,7,8,9,10-Hexahydro-9-hydroxy-2-mercapto-5,9-methanopyrimido[4,5-*b*]azocin-4(3*H*)-one (4d).

To a suspension of 6-amino-2-mercapto-4(3H)-pyrimidinone (**1d**) (0.71 g, 5 mmol) in 10 mL of H_2O, 2-cyclohexen-1-one (**2**) (0.72 g, 7.5mmol) was added. The reaction mixture was heated at 80 °C for 26 h. The white suspension was collected by filtration, washed with H_2O (20 mL) followed by methanol (20 mL) and dried under vacuum to give **4d** (0.88 g, 73%) as a white powder, mp 298 °C (decomp, after recrystallization from water); ^{1}H NMR(DMSO-d_6, 500 MHz): δ 1.30 (m, 2H), 1.48 (m, 2H), 1.56 (m, 2H), 1.74 (m, 2H), 2.97 (s, 1H), 6.04 (s, 1H), 6.17 (s, 1H), 11.33 (s, 1H), 11.62 (s, 1H). ^{13}C NMR (DMSO-d$_6$, 125 MHz); δ 173.1, 159.3, 149.5, 88.3, 80.3, 40.7, 37.1, 29.6, 27.3, 19.3. MS m/z (relative intensity) 239(67), 196(100), 137(19); HRMS calcd for $C_{10}H_{13}N_3O_2S$: 239.0728; Found: 239.0735; Anal Calcd for $C_{10}H_{13}N_3O_2S$: C, 50.19; H, 5.47; N, 17.56. Found: C, 50.05; H, 5.33; N, 17.60.

5,6,7,8,9,10-Hexahydro-9-hydroxy-5,9-methanopyrimido[4,5-b]azocin-2,4(1H,3H)-dione (4e).

A suspension of 6-aminouracil (**1e**) (0.68 g, 5 mmol) was refluxed with 2-cyclohexen-1-one (**2**) (1.92 g, 20 mmol) in H_2O (10 mL) for 36 h. The suspension was filtered to give a white powder. Recrystallization from aqueous DMF afforded 0.69 g (62%) of **4e**, mp 291°C decomp; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.32 (d, 2H, $J = 9.0$ Hz), 1.45 (m, 2H), 1.60 (m, 2H), 1.70 (m, 2H), 2.94 (s, 1H), 5.97 (s, 1H), 6.03 (s, 1H), 9.74 (s, 1H), 10.09 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 161.9, 150.3, 150.2, 83.4, 80.3, 40.7, 37.8, 29.9, 19.3; IR(KBr) 3499, 3238, 2957, 1675, 1604, 1520 cm^{-1}; MS m/z (relative intensity) 223(25), 180(77), 68(100); HRMS calcd for $C_{10}H_{13}N_3O_3$: 223.0957; Found: 223.0966; Anal Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.86; N, 18.82. Found: C, 53.48; H, 5.73; N, 18.80.

1,3-Dimethyl-5,6,7,8,9,10-hexahydro-9-hydroxy-5,9-methanopyrimido[4,5-b]azocin-2,4-dione (4f).

A solution of 6-amino-1,3-dimethyluracil (**1f**) (0.78 g, 5 mmol) was heated at 80 °C with 2-cyclohexen-1-one (**2**) (0.48 g, 5 mmol) in 10 mL of water for 19 h and the reaction mixture was then cooled to rt. The precipitated solid was collected by filtration and purified by chromatography on silica using 5% MeOH/CH_2Cl_2 as eluent. Evaporation of fractions with an R$_f$ value of 0.5 (on TLC using 20% MeOH/CH_2Cl_2) gave 0.73 g (58%) of **4f** as white flakes, mp 231-232 °C (from methanol/ether). ^{1}H NMR(DMSO-d_6, 500 MHz): δ 1.40 (m, 2H), 1.48 (m, 2H), 1.52 (m, 2H), 1.66 (d, 1H, $J = 11.6$ Hz), 1.74 (dd, 1H, $J = 1.6, 11.6$ Hz) 1.90 (d, 1H, $J = 12.8$ Hz), 3.10 (s, 1H), 3.15 (s, 3H), 3.33 (s, 3H), 6.03 (s, 1H), 6.98 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 159.7, 151.0, 150.0, 84.7, 81.2, 40.5, 37.6, 29.8, 29.1, 28.1, 27.2, 19.3; MS m/z (relative intensity) 251(55), 234(24), 208(100); HRMS calcd for $C_{12}H_{17}N_3O_3$: 251.1270. Found: 251.1275 ; Anal Calcd for $C_{12}H_{17}N_3O_3$: C, 57.34; H, 6.82; N, 16.73. Found: C, 57.16; H, 6.65; N, 16.58.

General Procedure for the Preparation of 8a-d and 10a-d:

The appropriate Grignard reagent (in THF or ether solution, 5 eq.) was added dropwise to the solid 9-pivaloyloxy derivatives (7)[6] and (9)[7] at 0 °C, and the resulting mixture was stirred for 1h. The reaction mixture was then partitioned between EtOAc (20 mL) and saturated aq. NH_4Cl solution (20 mL) and the aqueous phase was extracted with an additional 20 mL of EtOAc. The combined organic phases were washed with 20 mL of a saturated aq. NaCl solution, dried over $MgSO_4$ filtered and concentrated *in vacuo*. The C-9 alkylated products were obtained as colorless solids by purification of the residual solid by column chromatography using 2-5% MeOH/CH_2Cl_2 as eluent.

2-Pivaloylamino-9-allyl-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocin-4(3*H*)-one (8a).

^{1}H NMR(CDCl$_3$, 500 MHz): δ 1.29 (s, 9H), 1.38 (m, 2H), 1.43 (m, 2H), 1.1 (m, 2H), 1.67 (m, 1H), 1.80 (d, 1H, J = 10.5 Hz), 2.16 (dd, 1H, J = 8.8, 13.73), 2.30 (dd, 1H, J = 6.10, 12.73 Hz), 3.29 (s, 1H), 4.74 (s, 1H), 5.16 (m, 2H), 5.84 (m, 1H), 8.07 (s, 1H), 11.21 (s, 1H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 19.0, 26.6, 27.2, 31.1, 35.6, 39.7, 40.3, 46.6, 52.7, 94.2, 119.8, 132.5, 148.5, 159.6, 159.7, 179.7; IR (KBr) 3384, 3272, 2932, 1641, 1564 cm^{-1}; MS m/z (relative intensity) 330 (50), 289 (100), 287 (94); mp 209 °C. HRMS calcd for $C_{18}H_{26}N_4O_2$: 330.2055. Found: 330.2054.

2-Pivaloylamino-9-ethynyl-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocin-4(3*H*)-one (8b).

^{1}H NMR(DMSO-d_6, 500 MHz): δ 1.21 (s, 9H), 1.26 (m, 1H), 1.48 (m, 3H), 1.68 (m, 1H), 1.74 (m, 1H), 1.95 (d, 1H, J = 12.51 Hz), 1.98 (d, 1H, J = 3.66 Hz), 3.01(s, 1H), 3.39 (s, 1H), 6.91 (s, 1H), 10.55 (s, 1H), 11.27 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 181.1, 159.2, 158.4, 149.0, 118.9, 91.9, 87.3, 73.1, 47.8, 41.0, 36.1, 29.9, 26.3, 25.2, 17.9. IR (KBr) 3367, 3252, 2934, 1643, 1567, 1459 cm^{-1}; mp >237 °C decomp; MS m/z (relative intensity) 314(46), 271(100), 187(50); HRMS calcd for $C_{17}H_{22}N_4O_2$: 314.1742 Found: 314.1729.

2-Pivaloylamino-9-ethyl-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocin-4(3*H*)-one (8c).

^{1}H NMR(CDCl$_3$, 500 MHz): δ 0.89 (t, 3H, J = 6.63 Hz), 1.27 (s, 9H), 1.43 (m, 2H), 1.49 (m, 2H), 1.57 (m, 3H), 1.60 (m, 2H), 1.79 (d, 1H, J = 10.99 Hz), 3.25 (s, 1H), 4.60 (s, 1H), 8.26 (s, 1H), 11.22 (s, 1H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 179.8, 160.0, 159.6, 148.5, 94.1, 53.4, 40.3, 39.7, 34.7, 34.1, 31.2, 28.2, 27.1, 26.5, 26.4, 19.1; IR (KBr) 3389, 3265, 2931, 1644, 1565, 1458 cm^{-1}; MS m/z (relative intensity) 318(30), 289(35), 275(100); mp >210 °C; HRMS calcd for $C_{17}H_{26}N_4O_2$: 318.2055. Found: 318.2062.

2-Pivaloylamino-9-benzyl-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocin-4(3*H*)-one (8d).

^{1}H NMR(CDCl$_3$, 500 MHz): δ 1.27 (s, 9H), 1.50 (m, 3H), 1.69 (m, 2H), 1.78 (m, 2H), 1.91 (m, 1H), 2.73 (d, 1H, *J* = 13.43 Hz), 2.84 (d, 1H, *J* = 13.12 Hz), 2.97 (s, 1H), 4.63 (s, 1H), 7.19 (d, 2H, *J* = 7.02 Hz), 7.28 (m, 1H), 7.34 (t, 2H, *J* = 7.02 Hz), 7.87 (s, 1H), 11.17 (s, 1H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 179.6, 159.6, 142.3, 13.9, 130.7, 128.6, 127.1, 94.3, 53.2, 51.3, 48.7, 40.3, 39.4, 36.2, 31.0, 27.2, 26.6, 18.9; IR (KBr) 3409, 3262, 2933, 1651, 1567, 1457 cm^{-1}; MS m/z (relative intensity) 380(43), 290(38), 289(100); HRMS calcd for C$_{22}$H$_{28}$N$_4$O$_2$: 380.2212. Found: 380.2216.

2,4-Bis(pivaloylamino)-9-allyl-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (10a).

^{1}H NMR(CDCl$_3$, 500 MHz): δ 1.28 (s, 9H), 1.29 (s, 9H), 1.51 (m, 4H), 1.63 (m, 2H), 1.68 (m, 2H), 2.20 (dd, 1H, *J* = 8.85, 13.73 Hz), 2.31 (dd, 1H, *J* = 6.41, 13.74), 3.10 (s, 1H), 5.17 (dd, 2H, *J* = 6.41, 10.07 Hz), 5.45 (s, 1H), 5.82 (m, 1H), 7.41 (s, 1H), 7.82 (s, 1H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 176.8, 176.2, 163.9, 155.4, 152.7, 131.9, 120.3, 103.7, 52.6, 46.5, 40.3, 40.1, 38.5, 34.8, 31.5, 28.4, 27.7, 27.6, 18.6. IR (KBr) 3419, 3269, 2955, 2931, 1684, 1606, 1492 cm^{-1}; mp 205 °C; MS m/z (relative intensity) 413(15), 371(38), 356(100); HRMS calcd for C$_{23}$H$_{35}$N$_5$O$_2$: 413.2790. Found: 413.2806.

2,4-Bis(pivaloylamino)-9-ethynyl-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (10b):

^{1}H NMR(DMSO-*d*$_6$, 500 MHz): δ 1.17 (s, 9H), 1.19 (s, 9H), 1.51(m, 4H), 1.69 (d, 1H, *J* = 12.2), 1.74 (m, 1H), 1.93 (d, 1H, *J* = 12.8 Hz), 2.02 (d, 1H, *J* = 11.9 Hz), 2.97 (br s, 1H), 3.37 (s, 1H), 7.93 (s, 1H), 9.24 (s, 1H), 9.41 (s, 1H). ^{13}C NMR (DMSO-*d*$_6$, 125 MHz): δ 176.7, 175.8, 162.8, 155.6, 153.9, 118.9, 107.2, 83.1, 73.1, 47.5, 38.7, 35.2, 27.1, 26.9; IR (KBr) 3440, 3285, 2959, 1701, 1606, 1482, 1418 cm^{-1}; mp 152 °C; MS m/z (relative intensity) 397(23), 358(57), 341(32), 340(100); HRMS calcd for C$_{22}$H$_{31}$N$_5$O$_2$: 397.2477. Found: 397.2475.

2,4-Bis(pivaloylamino)-9-ethyl-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (10c):

^{1}H NMR(CDCl$_3$, 500 MHz): δ 0.89 (t, 3H, *J* = 3.05 Hz), 1.23 (s, 9H), 1.24 (s, 9H), 1.40-1.26 (m, 2H), 1.48 (m, 4H), 1.58 (m, 4H), 3.03 (s, 1H), 5.55(s, 1H), 7.62 (s, 1H), 8.12 (s, 1H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 176.7, 176.3, 163.9, 155.3, 152.5, 102.9, 52.9, 40.2, 40.0, 38.5, 34.4, 33.5, 31.5, 28.1, 27.5, 18.6. IR (KBr) 3444, 3293, 2966, 1697, 1600, 1421 cm^{-1}; MS m/z (relative intensity) 401(14), 372(29), 344(100); HRMS calcd for C$_{22}$H$_{35}$N$_5$O$_2$: 401.2790. Found: 401.2771.

2,4-Bis(pivaloylamino)-9-benzyl-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocine (10d):

^{1}H NMR(CDCl$_3$, 500 MHz): δ 1.29 (s, 9H), 1.30(s, 9H), 1.51 (m, 4H), 1.62 (m, 1H), 1.72 (m, 3H), 2.75 (d, 1H, *J* = 13.12 Hz), 2.88 (d, 1H, *J* = 13.43 Hz), 3.12 (s, 1H), 5.46 (s, 1H), 7.21 (d, 2H, *J* = 8.62 Hz), 7.29 (m, 1H), 7.33 (t, 2H, *J* = 8.63 Hz), 7.52 (s, 1H), 7.90 (s, 1H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 176.5, 163.8, 155.2, 135.5, 130.7, 128.6, 127.1, 53.0, 48.6, 40.3, 40.1, 38.3, 35.0, 31.3, 28.3, 27.6, 18.5. IR (KBr) 3408, 2932, 1700, 1609, 1417 cm^{-1}; MS m/z (relative intensity) 463(18), 407(26), 406(100), 372(54); HRMS calcd for C$_{27}$H$_{37}$N$_5$O$_2$: 463.2947. Found: 463.2935.

***N*-{4-[3-(2-Amino-4(3*H*)-oxo-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocin-9-yl)propenyl]benzoyl}-L-glutamic Acid Diethyl Ester (11)**.

To a solution of **7a** (0.66 g, 2 mmol) in 10 mL of anhydrous DMF were added diethyl 4-iodobenzoyl-L-glutamate (0.95 g, 2.2 mmol), Pd(OAc)$_2$ (0.03 g, 0.014 mmol), PPh$_3$ (0.073 g, 0.28 mmol), CuI (0.026 mg, 0.014 mmol), and triethylamine (1.39 mL, 10 mmol) in 30 mL of anhydrous acetonitrile. The reaction mixture was stirred at 60 ˚C for 10 h under a nitrogen atmosphere. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on a silica gel column using 2% MeOH/CH$_2$Cl$_2$ as eluent to give **11**, 0.85 g (68%) as a white solid. ^{1}H NMR(CDCl$_3$, 500 MHz): δ 1.24 (t, 3H, *J* = 7.02 Hz), 1.27 (s, 9H), 1.31(t, 3H, *J* = 7.02 Hz), 1.30 (m, 4H), 1.75 (d, 2H, *J* = 15.26 Hz), 1.79 (d, 2H, *J* = 8.86 Hz), 2.16 (m, 1H), 2.34 (m, 2H), 2.47 (m, 3H), 3.30 (s, 1H), 4.12 (dd, 2H, *J* = 7.02, 14.03 Hz), 4.24 (dd, 2H, *J* = 7.02, 14.2 Hz), 4.69 (br s, 1H), 4.79 (m, 1H), 6.35 (m, 1H), 6.52 (d, 1H, *J* = 15.87 Hz), 7.08 (d, 1H, *J* = 6.63 Hz), 7.41 (d, 2H, *J* = 8.55 Hz), 7.77 (d, 2H, *J* = 8.20 Hz), 7.85 (s, 1H), 11.19 (s, 1H). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 179.6, 173.5, 172.3, 166.8, 159.6, 159.5, 148.5, 140.5, 133.8, 132.7, 127.7, 126.5, 126.4, 94.4, 62.0, 61.1, 53.4, 52.6, 45.9, 40.3, 40.1, 35.9, 31.1, 30.8, 27.4, 27.2, 26.7, 19.1; MS m/z (relative intensity) 635(20), 290(36), 289(98), 287(100); HRMS calcd for C$_{34}$H$_{45}$N$_5$O$_7$: 635.3318. Found: 635.3303.

***N*-{4-[3-(2-Amino-4(3*H*)-oxo-5,6,7,8,9,10-hexahydro-5,9-methanopyrimido[4,5-*b*]azocin-9-yl)propyl]benzoyl}-L-glutamic Acid (12):**

To a solution of **11** (0.64 g, 1 mmol) in MeOH (50 mL) was added 5% Pd-C (0.20 g). The reaction mixture was hydrogenated on a Parr shaker for 5 h at 40 psi. The catalyst was filtered off through Celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography by using 2% MeOH/CH$_2$Cl$_2$ as eluent to give the bridged reduced derivative of **11**, 0.59 g (92%) as a white solid. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 1.23 (t, 3H, *J* = 7.34 Hz), 1.30 (s, 9H), 1.33 (t, 3H, *J* = 7.44 Hz), 1.69-1.40 (m, 12H), 1.80 (d, 1H, *J* = 10.60 Hz), 2.15 (m, 1H), 2.31 (m, 1H), 2.45 (m, 2H), 2.67 (m, 2H), 3.25 (s, 1H), 4.12 (dd, 2H, *J* = 7.02, 14.0 Hz), 4.24 (dd,

2H, J = 7.0, 14.01 Hz), 4.35 (d, 1H, J = 5.19 Hz), 4.80 (m, 1H), 7.03 (t, 1H, J = 7.94 Hz), 7.25 (d, 2H, J = 8.24 Hz), 7.75 (d, 2H, J = 7.93 Hz), 7.94 (d, 1H, J = 9.76 Hz), 11.18 (s, 1H). ^{13}C NMR (CDCl$_3$, 125 MHz): 179.6, 173.5, 172.3, 167.3, 159.8, 159.6, 148.5, 146.3, 131.7, 128.8, 127.6, 94.3, 61.9, 61.0, 53.3, 52.6, 41.4, 40.5, 40.3, 36.2, 34.6, 31.2, 30.7, 27.5, 27.2, 26.5, 24.7, 19.1; MS m/z (relative intensity) 637(14), 332(19), 289(100); HRMS calcd for C$_{34}$H$_{47}$N$_5$O$_7$: 637.3475. Found: 637.3449.

A solution of 0.30 g, 0.30 g of this reduced derivative of **11** in 1N NaOH (10 mL) was stirred at room temperature for 30 h. The reaction mixture was then acidified with excess glacial acetic acid and filtered. The residue was washed with diethyl ether (20 mL), and water (50 mL) and dried in vacuo to give 0.19 g (81%) of **12** as a white solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.53-1.35 (m, 9H), 1.61 (m, 2H), 1.95 (m, 1H), 2.08 (m, 1H), 2.35 (t, 2H, J = 7.63 Hz), 2.61 (m, 2H), 2.92 (s, 1H), 4.40 (m, 1H), 6.27 (br s, 2H), 7.30 (d, 2H, J = 8.20 Hz), 7.81 (d, 2H, J = 8.24 Hz), 8.53 (d, 1H, J = 7.63 Hz), 9.81 (s, 1H), 10.36 (s, 1H), 12.22 (s, 2H). HRFABMS calcd for C$_{25}$H$_{32}$N$_5$O$_6$: (MH$^+$) 498.2353. Found: 498.2363.

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§ Present address: Paratek Pharmaceuticals, Inc., 75 Kneeland St., Boston, MA 02111 (USA)

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