Bromine-Mediated Addition of Nucleophiles to the Electron-Rich Pyrimidine Subunit of Tirilazad

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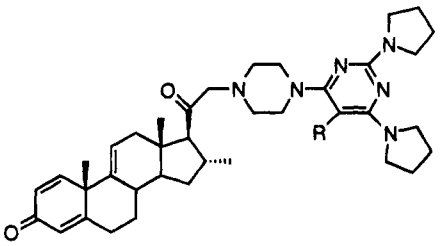
Tirilazad (**1a**) is a 21-amino steroid first synthesized by Jacobsen and co-workers.[1] The mesylate salt is currently in phase III clinical trials for the treatment of traumatic central nervous system injuries. While trying to synthesize two suspected impurities formed in the plant scale synthesis, we have discovered a mild, bromine-mediated addition of nucleophiles to the pyrimidine subunit.[2]



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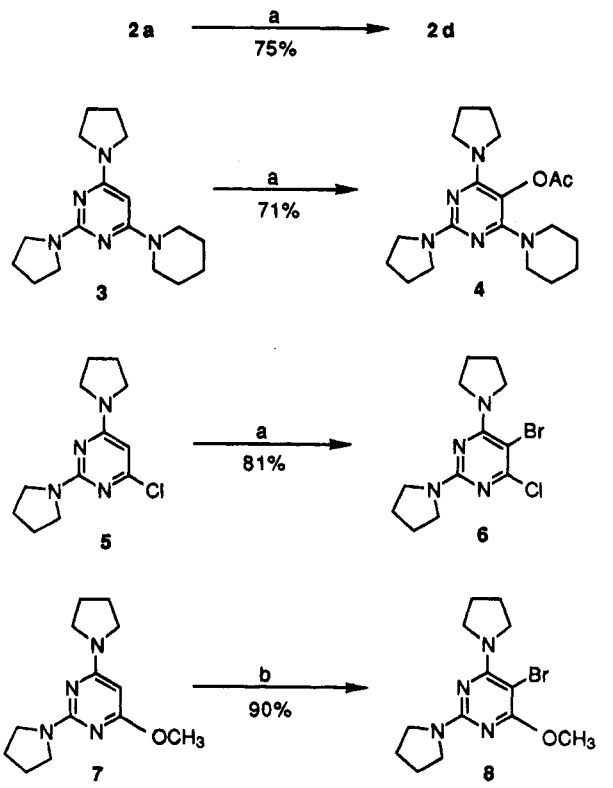
a: R = H, Tirilazad
b: R = CH_2COCH_3, U-96,970
c: R = OH, U-97,945

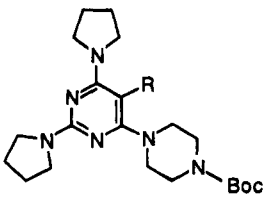
The two impurities, which were needed for toxicology studies, are designated as U-96,760 (**1b**) and U-97,945 (**1c**).[3] Our initial goal was to halogenate the C-5 position, with the hope that we could perform a transition-metal-mediated coupling reaction with an appropriate nucleophile. However, attempted iodination of **2a** with KI_3 (I_2, KI, K_2CO_3, CH_3CN, H_2O, 70 °C) unexpectedly produced the dimer **2b** in 77% yield after chromatography. Chlorination[4] ($Ca(OCl)_2$, CH_2Cl_2, H_2O, 0 °C to rt) was successful and cleanly produced the moderately stable chloride **2c** in 78% yield after recrystallization.[5] Attempted Pd(0)- and Cu(I)-mediated couplings of **2c** with various nucleophiles resulted in dechlorination to give **2a**. Radical-mediated couplings gave a complicated mixture of products.

While examining the bromination of **2a** with bromine (Br_2, NaOAc, HOAc),[6] we discovered, to our surprise, that the acetate **2d** was produced in 75% yield after aqueous bicarbonate workup and recrystallization (Scheme 1). We subsequently determined that the acetate addition was probably occurring during the bicarbonate workup. When **2a** was treated with 1.0 equiv of Br_2 and 3.3 equiv of NaOAc in CH_2Cl_2/H_2O at a pH of 9, **2d** was isolated in 82% yield after chromatography. This reaction can be extended to pyrimidine **3** to give the acetate **4**. However, the chloropyrimidine **5**[1] and the C-6 methoxypyrimidine **7** afforded the bromides **6** and **8**, respectively. Acetate **2d** and other C-5 esters of **2a** have been made previously using peracids.[7] Treatment of **2d** with anhydrous KOH under Gassman conditions[8] yields the unstable 5-hydroxy compound. This compound can be observed by chromatography (HPLC and TLC) and can be isolated in impure form as a solid, but it has very limited stability in solution. The 5-hydroxy compound was trapped with methyl iodide to give the 5-methoxy compound **2g**. Standard basic hydrolysis, transesterification, as well as

Scheme 1[a]



[a] Key: (a) Br_2, NaOAc, HOAc, rt, then $NaHCO_3$, H_2O; (b) Br_2, NaOAc, CH_2Cl_2, H_2O, rt.



2

a: R = H
b: R = **2a**
c: R = Cl
d: R = OAc
e: R = CN
f: R = succinimide
g: R = OCH_3

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(1) Jacobsen, E. J.; McCall, J. M.; Ayer, D. E.; VanDoornick, F. J.; Palmer, J. R.; Belonga, K. L.; Braughler, J. M.; Hall, E. D.; Houser, D. J.; Krook, M. A.; Runge, T. A. *J. Med. Chem.* **1990**, *33*, 1145 and references therein.

(2) For a comprehensive review of pyrimidine chemistry, see: Brown, D. J.; *The Pyrimidines*; Wiley Interscience: New York, 1962. Brown, D. J.; *The Pyrimidines*; Wiley Interscience: New York, 1970; Suppl. 1. Brown, D. J.; *The Pyrimidines*; Wiley Interscience: New York, 1985; Suppl. 2.

(3) Compound **1c** was tentatively assigned based on uv and mass spectral evidence.

(4) Lampilas, M.; Lett, R. *Tetrahedron Lett.* **1992**, *33*, 777.

(5) Fluorination of **2a** with 1-chloro-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) was also successful and produced the moderately stable C-5 fluoropyrimidine in 95% yield (crude).

(6) Wriede, U.; Fernandez, M.; West, K. F.; Harcourt, D.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 4485.

(7) McCall, J. M.; Jacobsen, E. J. (The Upjohn Company) WO 91/11453, 1991.

(8) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918.

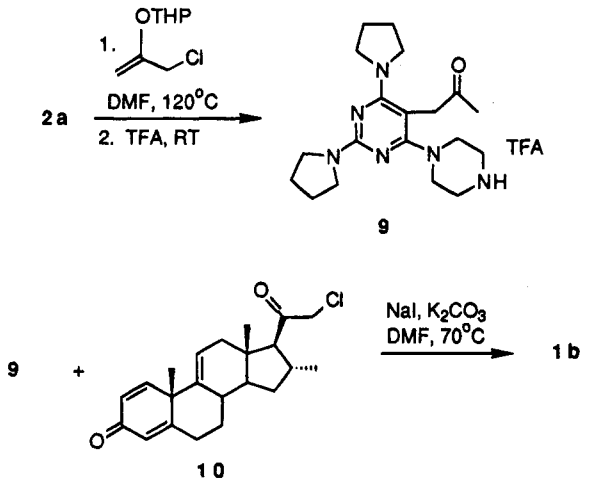
0022-3263/94/1959-5090$04.50/0

Table 1. Bromine-Mediated Additions to Pyrimidine 2a

entry	conditions	product	yield (%)[a]
1	Br_2, NaOAc, CH_2Cl_2, H_2O, rt	**2d**	82
2	Br_2, NaCN, CH_2Cl_2, $NaHCO_3$, rt	**2e**	72
3	Br_2, succinimide, CH_2Cl_2, $NaHCO_3$, rt	**2f**	65

[a] Isolated yields.

Scheme 2



Dibal reduction of the acetate **2d**, gave only recovered starting material.

With pyrimidine **2a** as a test substrate, we examined the addition of other species to the pyrimidine ring, using Br_2 under mildly basic conditions (pH 9, Table 1). As can be seen from the table, acetate, cyanide, and succinimide can be added at room temperature. While C-5 bromination of pyrimidines and subsequent displacement with nucleophiles is known,[2] to our knowledge the mild *one-pot* addition described above is not. It is interesting to note that the major product isolated from treatment of **2a** with NBS was also the succinimide **2f**.

Compound **1b** was eventually synthesized by the route shown in Scheme 2. Heating **2a** with 3-chloro-2-(tetrahydropyranyloxy)propene[9] in DMF gave the ketone **9** upon Boc removal with TFA. Coupling of the resultant TFA salt with the 21-chloro steroid **10** produced U-96,760 in 3% overall yield from **2a**. To date, the 5'-hydroxy compound **1c** has been unattainable.

In conclusion, we have discovered a mild, bromine-mediated addition of acetate, cyanide, and succinimide to the C-5 position of the pyrimidine subunit of tirilazad. The mild conditions and one-pot procedure make this a viable route to other C-5 substituted triaminopyrimidines, as well.

Experimental Section

General Methods. Glassware and hypodermic needles were oven-dried and nitrogen-purged prior to use. THF was distilled from sodium benzophenone ketyl prior to use. Methylene chloride, DMF, and acetonitrile were purchased from EM Science or Burdick and Jackson and used as received. Acetic acid was purchased from Mallinkrodt and used as received. All reagents were purchased and used as received. TLC was performed using EM Science Kieselgel 60 F_{254} plates. EM Science 230–400 mesh silica gel was used for flash chromatography. ^1H and ^{13}C spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are reported in parts per million using TMS as an internal standard. Infrared spectra were run as KBr pellets or Nujol mulls by Upjohn PAC. Mass spectra were recorded by Upjohn PAC. Elemental analyses were also performed by Upjohn Physical and Analytical Chemistry. Melting points are uncorrected.

4-[4-(*tert*-Butoxycarbonyl)-1-piperazinyl]-2,6-bis(1-pyrrolidinyl)pyrimidine (2a). To 50.0 g (166 mmol) of 4-(1-piperazinyl)-2,6-bis(1-pyrrolidinyl)pyrimidine[1] in 150 mL of THF at 0 °C was added 36.1 g (166 mmol) of Boc_2O. After 2 h, 200 mL of heptane was added to the slurry. The slurry was then cooled to −20 °C for 2.5 h, filtered, washed with −20 °C heptane (3 × 6 mL), and dried via high vacuum to give 60.5 g (91%) of **2a** as a white solid. Mp: 164–165 °C, ^1H NMR ($CDCl_3$): 4.85 (s, 1H), 3.52 (m, 12H), 3.42 (bs, 4H), 1.90 (m, 8H), 1.52 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 163.94, 162.51, 160.21, 154.9, 79.73, 72.55, 46.20, 46.07, 44.34, 28.46, 25.58, 25.33 ppm. IR (KBr): 1700, 1560, 1438, 1350, 1225, 1150 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{34}N_6O_2$: 402.2743. Found: 402.2760. Anal. Calcd for $C_{21}H_{34}N_6O_2$: C, 62.50; H, 8.73; N, 20.83. Found: C, 62.70; H, 8.52; N, 20.89.

4-[4-(*tert*-Butoxycarbonyl)-1-piperazinyl]-2,6-bis(1-pyrrolidinyl)pyrimidine Dimer (2b). To 10.0 g (24.8 mmol) of **2a** were added 100 mL of CH_3CN, 3.40 g (25.0 mmol) of K_2CO_3, 8.22 g (49.0 mmol) of KI, 7.00 g (27.0 mmol) of I_2 and 20 mL of water. The reaction was heated to 70 °C for 2.5 h and then cooled to rt, at which point 25 mL of 38% $NaHSO_3$ was added. The CH_3CN was removed with a rotary evaporator and 150 mL of CH_2Cl_2 was added. Washing with water and drying with Na_2SO_4 gave the crude dimer as a brown foam, after concentration. Filtration followed by flash chromatography using 30% ethyl acetate/cyclohexane gave 7.68 g (77%) of the dimer **2b** as a white solid. Mp: 214–216 °C, ^1H NMR ($CDCl_3$): 3.51 (m, 8H), 3.42 (m, 8H), 3.20 (m, 16H), 1.92 (m, 8H), 1.75 (m, 8H), 1.47 (s, 18H) ppm. ^{13}C NMR ($CDCl_3$): 165.14, 161.79, 158.63, 154.86, 91.11, 79.44, 48.61, 47.85, 46.14, 28.47, 25.69, 25.56 ppm. IR (mull): 1700, 1530, 1420, 1240, 1160 cm^{-1}. HRMS (FAB) calcd for $C_{42}H_{66}N_{12}O_4$: 802.5330. Found: 802.5325.

4-[4-(*tert*-Butoxycarbonyl)-1-piperazinyl]-2,6-bis(1-pyrrolidinyl)-5-chloropyrimidine (2c). To the biphasic mixture of 28.32 g (70.45 mmol) of **2a** in 560 mL of CH_2Cl_2 and 280 mL of pH 4 buffer at 0 °C was added 10.12 g (70.77 mmol) of $Ca(OCl)_2$. After 0.5 h the reaction was warmed to rt and stirred for an additional 2 h. The layers were then separated, and the organic phase was washed with 100 mL of water and dried over Na_2SO_4. Heptane (100 mL) was then added, and the CH_2Cl_2 and most of the heptane were removed with a rotary evaporator to give an oily solid. An additional 100 mL of heptane and 30 mL of CH_2Cl_2 were added, and the solids were dissolved by gentle warming, allowed to cool to rt, and then were cooled to −20 °C. Filtration and washing of the solids with heptane (3 × 20 mL) gave 28.21 g (92%) of the chloride **2c** as a brown solid. Filtration of a CH_2Cl_2 solution of the crude chloride through magnesol and crystallization of the resultant oil from *tert*-butyl methyl ether gave 26.57 g (78%, two crops) of **2c** as a near white solid. Mp: 131–132 °C, ^1H NMR ($CDCl_3$): 3.62 (bt, J = 6.6 Hz, 4H), 3.50 (m, 8H), 3.40 (m, 4H), 1.86 (m, 8H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 164.20, 160.82, 157.01, 154.99, 87.72, 79.60, 49.69, 48.33, 46.40, 28.47, 25.68, 25.61 ppm. IR (mull): 1710, 1540, 1460, 1380, 1360, 1350, 1250, 1160 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{33}ClN_6O_2$: 436.2353. Found: 436.2345.

4-(1-Piperidinyl)-2,6-bis(1-pyrrolidinyl)pyrimidine (3). To 0.47 mL (4.7 mmol) of piperidine in 5 mL of THF at 0 °C was added 3.3 mL (4.3 mmol) of *n*-BuLi. After 45 min, 1.00 g (3.95 mmol) of **5** dissolved in 5 mL of THF was added. Stirring was continued for 1 h at which point the THF was removed with a rotary evaporator. The resultant brown solids were filtered, washed with water, and dried via high vacuum to give 1.15 g (97%) of crude **3**. Purification by flash chromatography using 20% ethyl acetate/cyclohexane as eluent gave 1.01 g (85%) of **3** as a white solid. Mp: 143–144 °C. ^1H NMR ($CDCl_3$): 4.87 (s, 1H), 3.50 (m, 8H), 3.42 (t, J = 6.6 Hz, 4H), 1.89 (m, 8H), 1.68 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$): 164.02, 162.59, 160.39, 72.73, 46.18, 46.03, 45.52, 25.61, 25.52, 25.35, 25.07 ppm. IR (mull): 1570, 1553, 1447, 1434, 1352, 1345, 1333, 1234 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{27}N_5$: 301.2266. Found: 301.2263. Anal. Calcd for $C_{17}H_{27}N_5$: C, 67.97; H, 8.72; N, 23.31. Found: C, 67.73; H, 9.11; N, 23.26.

2,6-Bis(1-pyrrolidinyl)-4-methoxypyrimidine (7). To 1.00 g (3.95 mmol) of **5** in 7 mL of DMSO was added 1.08 g (20.0

(9) Knapp, S.; Gibson, F. S. *J. Org. Chem.* **1992**, *57*, 4802. Capon, B.; Siddhanta, A. K.; Zucco, C. *J. Org. Chem.* **1985**, *50*, 3580.

mmol) of $NaOCH_3$. The brown slurry was heated at 115 °C for 16 h. The resultant solids were dissolved in 40 mL of CH_2Cl_2, washed with water (4 × 15 mL), dried over Na_2SO_4, and concentrated to give 1.03 g (100%) of **7** as a tan solid. Purification by flash chromatography using 20% ethyl acetate/cyclohexane as eluent gave 0.70 g (71%) of **7** as a white solid. Mp: 88–89 °C. ^1H NMR ($CDCl_3$): 5.00 (s, 1H), 3.81 (s, 3H), 3.52 (m, 4H), 3.42 (bs, 4H), 1.92 (m, 8H) ppm. ^{13}C NMR ($CDCl_3$): 170.65, 162.96, 160.15, 73.65, 52.88, 46.29, 46.12, 25.55, 25.30 ppm. IR (mull): 1566, 1523, 1451, 1396, 1346, 1349 cm^{-1}. HRMS (EI) calcd for $C_{13}H_{20}N_4O$: 248.1637. Found: 248.1638.

4-[4-(*tert*-Butoxycarbonyl)-1-piperazinyl]-2,6-bis(1-pyrrolidinyl)-5-acetylpyrimidine (2d). To a solution of 10.03 g (25.0 mmol) of **2a**, 7.03 g (85.0 mmol) of NaOAc, and 200 mL of acetic acid was added 1.3 mL (25 mmol) of Br_2. After stirring of the solution for 2 h, 200 mL of CH_2Cl_2 was added, and the brown solution was washed with water (4 × 100 mL) and saturated $NaHCO_3$ (2 × 200 mL), dried over Na_2SO_4, and concentrated to give 11.03 g (96%) of **2d** as a gold foam. Crystallization from MeOH gave a 75% yield of the acetate **2d** as a yellow solid. Mp: 176–177 °C. ^1H NMR ($CDCl_3$): 3.44 (m, 16H), 2.20 (s, 3H), 1.86 (m, 8H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 168.95, 158.65, 156.72, 156.00, 154.96, 110.96, 79.66, 48.25, 47.45, 46.39, 28.45, 25.65, 25.44, 20.68 ppm. IR (mull): 1780, 1710, 1550, 1450, 1370, 1340, 1160 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{36}N_6O_4$: 460.2798. Found: 460.2808.

4-(1-Piperidinyl)-2,6-bis(1-pyrrolidinyl)-5-acetylpyrimidine (4). Compound **4** was generated with 1.00 g of **3** as the starting material and the same procedure as that for the synthesis of **2d**. Flash chromatography of the crude product gives 0.85 g (71%) of **4** as a colorless glass. Mp: 104–105 °C. ^1H NMR ($CDCl_3$): 3.49 (bt, J = 6.1 Hz, 8H), 3.36 (bs, 4H), 2.19 (s, 3H), 1.86 (m, 8H), 1.57 (bs, 6H) ppm. ^{13}C NMR ($CDCl_3$): 169.13, 159.13, 156.83, 156.03, 110.82, 48.62, 48.29, 46.37, 26.94, 26.27, 25.69, 25.47, 20.67 ppm. IR (mull): 1749, 1564, 1446, 1346, 1300, 1212, 1201 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{29}N_5O_2$: 359.2321. Found: 359.2324. Anal. Calcd for $C_{19}H_{29}N_5O_2$: C, 63.48; H, 8.13; N, 19.48. Found: C, 63.53; H, 8.17; N, 19.52.

2,4-Bis(1-pyrrolidinyl)-5-bromo-6-chloropyrimidine (6). Compound **6** was generated with 1.00 g of **5** as starting material and the same procedure as that for the synthesis of **2d**. Flash chromatography gave 1.01 g (81%) of **6** as a white solid. Mp: 102–103 °C. ^1H NMR ($CDCl_3$): 3.75 (bt, J = 6.7 Hz, 4H), 3.48 (bt, J = 6.7 Hz, 4H), 1.90 (m, 8H) ppm. ^{13}C NMR ($CDCl_3$): 159.87, 159.82, 156.98, 86.38, 50.23, 46.63, 25.71, 25.51 ppm. IR (mull): 1566, 1553, 1538, 1527, 1489, 1476, 1451, 1443, 1343, 1333, 1302 cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_4BrCl$: C, 43.46; H, 4.86; N, 16.89. Found: C, 43.55; H, 4.90; N, 16.90.

2,4-Bis(1-pyrrolidinyl)-5-bromo-6-methoxypyrimidine (8). To 0.66 g (2.7 mmol) of **7**, 0.73 g (8.9 mmol) of NaOAc, 20 mL of CH_2Cl_2, and 7 mL of water was added 0.14 mL (2.7 mmol) of Br_2. After 1.5 h, the mixture was worked up by washing with water (2 × 7 mL), drying over Na_2SO_4, and concentrating to give 0.92 g of **8** as a gold oily solid. Flash chromatography using 5% ethyl acetate/cyclohexane as eluent gave 0.79 g (91%) of **8** as a white solid. This compound is extremely unstable. Mp: 78–79 °C. ^1H NMR ($CDCl_3$): 3.90 (s, 3H), 3.74 (m, 4H), 3.50 (m, 4H), 1.88 (m, 8H) ppm. ^{13}C NMR ($CDCl_3$): 166.41, 160.46, 157.39, 72.24, 53.87, 49.85, 46.41, 25.71, 25.58 ppm. IR (mull): 1577, 1564, 1549, 1542, 1516, 1450, 1434, 1344 cm^{-1}. HRMS (EI) calcd for $C_{13}H_{19}BrN_4O$: 326.0743. Found: 326.0740. Anal. Calcd for $C_{13}H_{19}BrN_4O$: C, 47.72; H, 5.83; N, 17.12. Found: C, 47.67; H, 5.87; N, 17.27. The same procedure was used for the formation of the acetate **2d** using **2a** as the starting material.

4-[4-(*tert*-Butoxycarbonyl)-1-piperazinyl]-2,6-bis(1-pyrrolidinyl)-5-methoxypyrimidine (2g). Potassium *tert*-butoxide was dissolved in 5 mL of THF and the solution was degassed with nitrogen. Water (0.045 mL, 2.5 mmol) was added and the resulting suspension was stirred at room temperature for 1 min. A solution of **2d** in 5 mL of degassed THF was added and the mixture was stirred at room temperature for 15 min. Methyl iodide (0.62 mL, 10 mmol) was added and the mixture was stirred for 10 min. The reaction mixture was partitioned between ether and sat. NaCl solution. The organic layer was washed once with sat. NaCl, dried over sodium sulfate, and evaporated to yield 0.397 g (92%) of **2g** as a colorless foam. ^1H NMR ($CDCl_3$): 3.7 (m, 16H), 3.39 (s, 3H), 1.75 (m, 8H), 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$): 157.73, 156.93, 155.64, 155.15, 120.28, 79.63, 59.25, 48.51, 47.06, 46.56, 28.62, 25.86, 25.66. IR (mull): 2954, 2866, 2856, 1696, 1569, 1560, 1544, 1445, 1247, 1169 cm^{-1}. MS (EI) *m/z* 432 (M), 417, 375, 361 (100%), 331, 317, 276, 57. Anal. Calcd for $C_{22}H_{36}N_6O_3$: C, 61.09; H, 8.39; N, 19.43. Found: C, 60.72; H, 8.27; N, 19.19.

4-[4-(*tert*-Butoxycarbonyl)-1-piperazinyl]-2,6-bis(1-pyrrolidinyl)-5-cyanopyrimidine (2e). To 0.50 g (1.2 mmol) of **2a**, 0.18 g (3.7 mmol) of NaCN, 10 mL of CH_2Cl_2, and 2.0 mL of saturated $NaHCO_3$ was added 0.062 mL (1.2 mmol) of Br_2. After 2 h, the reaction mixture was diluted with 15 mL of CH_2Cl_2, washed with 5 mL of water, dried over Na_2SO_4, and concentrated to give 0.50 g of **2e** as a yellow foam. Flash chromatography using 25% ethyl acetate/cyclohexane as eluent provided 0.38 g (72%) of **2e** as a gold oil which eventually crystallized. Mp: 163–164 °C. ^1H NMR ($CDCl_3$): 3.66 (m, 8H), 3.52 (m, 8H), 1.91 (m, 8H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 167.97, 163.29, 158.69, 154.88, 121.17, 79.87, 62.09, 48.77, 47.40, 46.38, 28.43, 26.93, 25.37 ppm. IR (mull): 2190, 1699, 1552, 1533, 1517, 1480, 1450, 1420, 1345 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{33}N_7O_2$: 427.2696. Found: 427.2700. Anal. Calcd for $C_{22}H_{33}N_7O_2$: C, 61.80; H, 7.78; N, 22.93. Found: C, 61.76; H, 7.62; N, 22.81.

4-[4-(*tert*-Butoxycarbonyl)-1-piperazinyl]-5-succinimido-2,6-bis(pyrrolidinyl)pyrimidine (2f). To 1.00 g (2.49 mmol) of **2a**, 0.50 g (5.0 mmol) of succinimide, 20 mL of CH_2Cl_2, and 4.0 mL of saturated $NaHCO_3$ was added 0.13 mL (5.0 mmol) of Br_2. After 1.5 h, the reaction mixture was diluted with 15 mL of CH_2Cl_2, washed with 10 mL of water, dried over Na_2SO_4, and concentrated to give 1.42 g of **2f** as a gold foam. Flash chromatography using 50% ethyl acetate/cyclohexane as eluent provided 0.80 g (65%) of **2f** as a white solid. Mp: 199–200 °C. ^1H NMR ($CDCl_3$): 3.50 (bt, J = 6.6 Hz, 4H), 3.37 (m, 8H), 3.00 (m, 4H), 2.82 (s, 4H), 1.88 (m, 4H), 1.83 (m, 4H), 1.45 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$): 178.38, 167.03, 159.97, 158.77, 154.86, 90.27, 79.66, 49.33, 47.83, 46.32, 28.42, 25.55, 25.42 ppm. IR (mull): 1774, 1712, 1688, 1564, 1539, 1521, 1492, 1475, 1444, 1427 cm^{-1}. HRMS (EI) calcd for $C_{25}H_{37}N_7O_4$: 499.2907. Found: 499.2919. Anal. Calcd for $C_{25}H_{37}N_7O_4$: C, 60.10; H, 7.46; N, 19.62. Found: C, 59.74; H, 7.41; N, 19.44.

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