Supplementary Material:

The Synthesis of Pyrazolo[1,5- α]pyrimidinone Regioisomers

Lori K. Gavrin^{*1}, Arthur Lee¹, Brian A. Provencher¹, Walter W. Masefski², Stephen D. Huhn², Gregory M. Ciszewski³, Derek C. Cole³ and John C. McKew¹

Departments of ¹Exploratory Medicinal Chemistry and ²Chemical Technologies; Chemical and Screening Sciences; Wyeth Research, 200 CambridgePark Dr., Cambridge, MA 02140 & ³Department of Exploratory Medicinal Chemistry; Chemical and Screening Sciences, Wyeth Research, 401 N. Middletown Rd., Pearl River, NY 10965.

*Email: gavrinl@wyeth.com

Table of Contents:

Chemistry General Procedures	S3
Characterization of Ethyl 7-oxo-4,7-dihydropyrazolo[1,5- α]pyrimidine-6-carboxylate (6)	S3
Characterization of 7-Oxo-4,7-dihydropyrazolo[1,5- α]pyrimidine-6-carboxylic acid (7)	S3
Characterization of Pyrazolo[1,5- α]pyrimidin-7(4 <i>H</i>)-one (8)	S3
Characterization of 2-(3-Bromophenyl)pyrazolo[1,5- α]pyrimidin-7(4 <i>H</i>)-one (14)	S4
Characterization of 2-(3-Bromophenyl)pyrazolo[1,5- α]pyrimidin-5(4 <i>H</i>)-one (19)	S4
3-(3-Bromophenyl)-3-oxopropanenitrile (10)	S4
3-(3-Bromophenyl)-1 <i>H</i> -pyrazol-5-amine (11)	S5
Ethyl 2-(3-bromophenyl)-7-oxo-4,7-dihydropyrazolo[1,5- α]pyrimidine-6-carboxylate (12) via Method A	S5
2-(3-Bromophenyl)-7-oxo-4,7-dihydropyrazolo[1,5- α]pyrimidine-6-carboxylic acid (13) via Method A	S6

2-(3-Bromophenyl)pyrazolo[1,5- α]pyrimidin-7(4 <i>H</i>)-one (14) via Method A	S6
3-(3-bromophenyl)-4-methyl-1 <i>H</i> -pyrazol-5-amine (15)	S6
2-(3-bromophenyl)-3-methylpyrazolo[1,5- α]pyrimidin-7(4 <i>H</i>)-one (17) via Method B	S7
Pyrazolo[1,5- α]pyrimidin-7(4 <i>H</i>)-one (8) via Method B	S7
Ethyl 7-oxo-4,7-dihydropyrazolo[1,5- α]pyrimidine-3-carboxylate (18) via Method B	S7
2-(3-Bromophenyl)-3-methylpyrazolo[1,5- α]pyrimidin-5(4 <i>H</i>)-one (20) via Method C	S8
Pyrazolo[1,5- α]pyrimidin-5(4 <i>H</i>)-one (21) via Method C	S8
Ethyl 5-oxo-4,5-dihydropyrazolo[1,5- α]pyrimidine-3-carboxylate (22) via Method C	S8
4-Methylpyrazolo[1,5- α]pyrimidin-7(4 <i>H</i>)-one (23)	S9
4-Methylpyrazolo[1,5- α]pyrimidin-5(4 <i>H</i>)-one (24)	S9
Pyrazolo[1,5- α]pyrimidin-5(4 <i>H</i>)-one (21) via Method D	S10
Ethyl 3-[5-amino-3-(3-bromophenyl)-1 <i>H</i> -pyrazol-1-yl]-3-ethoxypropanoate (11A)	S10
2-(3-Bromophenyl)-7-ethoxy-6,7-dihydropyrazolo[1,5- α]pyrimidin-5(4 <i>H</i>)-one (11B)	S11
Table of chemical shifts for 8 and 21	S12
NOE data for 23	S13
NOE data for 24	S14
Table of HPLC purity in 2 solvent systems for Compounds 6, 7, 8, 10, 11, 11A, 11B, 12, 13, 14, 15, 17, 18, 19, 20, 21, 22, 23, and 24.	S15

Chemistry General Procedures. All solvents and reagents were used as obtained. All reaction mixtures were stirred using a magnetic stir bar. Proton NMR spectra were recorded on a 400 MHz spectrometer using TMS (δ 0.0) as a reference. High resolution mass spectra were obtained using a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer equipped with an actively shielded 7 Tesla superconducting magnet and an electrospray ionization (ESI) source. Flash chromatography was performed using 230-400 mesh silica gel or flash columns packed with KP-SIL 60 Angstrom silica gel. Thin-layer chromatography (TLC) was performed using 250 μ m prescored silica gel 60 F₂₅₄ plates. Purity in two solvent systems (H₂O-CH₃CN and H₂O-MeOH) was determined using a HPLC instrument and all final compounds were >95 % pure (see below).

Characterization of Ethyl 7-oxo-4,7-dihydropyrazolo[1,5- α]pyrimidine-6-carboxylate (6)

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.28 (t, *J*=7.1 Hz, 3 H), 4.23 (q, *J*=7.1 Hz, 2 H), 6.31 (d, *J*=2.0 Hz, 1 H), 7.93 (d, *J*=2.0 Hz, 1 H), 8.59 (s, 1 H), 13.10 (s, 1 H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 14.3, 60.0, 91.2, 98.5, 140.9, 143.4, 145.3, 157.2, 163.6. HRMS: calcd for C₉H₉N₃O₃ + H⁺, 208.07167; found (ESI-FTMS, [M+H]¹⁺), 208.07203.

Characterization of 7-Oxo-4,7-dihydropyrazolo[1,5- α]pyrimidine-6-carboxylic acid (7)

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.41 (d, *J*=2.0 Hz, 1 H), 8.05 (d, *J*=2.0 Hz, 1 H), 8.72 (s, 1 H), 12.95 (s, 1 H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 91.9, 97.7, 141.0, 144.5, 145.7, 157.2, 164.7. HRMS: calcd for 2 C₇H₅N₃O₃ + H⁺, 359.07346; found (ESI-FTMS, [2M+H]¹⁺), 359.07197.

Characterization of Pyrazolo[1,5- α]pyrimidin-7(4*H*)-one (8)

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 5.68 (d, *J*=7.3 Hz, 1 H), 6.18 (dd, *J*=1.8, 0.6 Hz, 1 H), 7.86 - 7.89 (m, 2 H), 12.36 (s, 1 H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 86.9, 93.1, 137.5,

139.8, 140.5, 154.5. HRMS: calcd for 2 C₆H₅N₃O + H⁺, 271.09380; found (ESI-FTMS, [2M+H]¹⁺), 271.09415.

Characterization of 2-(3-Bromophenyl)pyrazolo[1,5- α]pyrimidin-7(4H)-one (14)

R_f (EtOAc) = 0.07; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 5.74 (d, *J*=7.3 Hz, 1 H), 6.76 (s, 1 H), 7.45 (t, *J*=8.0 Hz, 1 H), 7.61 (dq, *J*=8.0, 1.0, 0.9 Hz, 1 H), 7.88 (d, *J*=7.3 Hz, 1 H), 8.00 (dt, *J*=7.8, 1.3 Hz, 1 H), 8.18 (t, *J*=1.6 Hz, 1 H), 12.58 (s, 1 H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 86.7, 95.8, 122.2, 125.2, 128.5, 131.0, 131.5, 134.8, 140.0, 143.4, 151.2, 156.4. HRMS: calcd for C₁₂H₈BrN₃O + H⁺, 289.99235; found (ESI-FTMS, [M+H]¹⁺), 289.99295.

Characterization of 2-(3-Bromophenyl)pyrazolo[1,5- α]pyrimidin-5(4H)-one (19)

R_f (EtOAc) = 0.56; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.00 (d, *J*=7.8 Hz, 1 H), 6.40 (s, 1 H), 7.42 (t, *J*=8.0 Hz, 1 H), 7.56 - 7.61 (m, 1 H), 7.91 (d, *J*=7.6 Hz, 1 H), 8.09 (t, *J*=1.8 Hz, 1 H), 8.52 (d, *J*=7.8 Hz, 1 H), 12.27 (s, 1 H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 85.1, 106.4, 122.2, 124.8, 128.22, 131.0, 131.5, 134.4, 138.3, 142.0, 152.3, 159.6. HRMS: calcd for C₁₂H₈BrN₃O + H⁺, 289.99235; found (ESI-FTMS, [M+H]¹⁺), 289.99291.

3-(3-Bromophenyl)-3-oxopropanenitrile (10)

To a solution of KCN (13.1 g, 200 mmol, 2 eq.) in H₂O (150 mL) was added MeOH (100 mL) at room temperature. To the rapidly stirring solution was added a solution of 2-bromo-1-(3-bromophenyl)-ethanone (27.8 g, 100 mmol) in MeOH (200 mL). After 20 minutes, ice (200 mL) and 1N HCl (130 mL) were added. The light yellow precipitate was filtered and washed with copious amounts of water. The wet solid was transferred to a beaker and triturated with 5% ethyl acetate in hexanes (100 mL). The solid was filtered and washed with hexanes (200 mL) to yield 3-(3-bromophenyl)-3-oxopropanenitrile (14.6 g, 65 mmol, 65%) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.07 (s, 2 H), 7.43 (t, *J*=7.8 Hz, 1 H), 7.78 - 7.82 (m, 1 H), 7.83 - 7.87

(m, 1 H), 8.06 (t, $J=1.9$ Hz, 1 H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 29.5, 113.3, 123.5, 127.0, 130.8, 131.5, 135.9, 137.7, 185.9. HRMS: calcd for $\text{C}_9\text{H}_6\text{BrNO} + \text{H}^+$, 223.97055; found (ESI-FTMS, $[\text{M}+\text{H}]^{1+}$), 223.9715.

3-(3-Bromophenyl)-1*H*-pyrazol-5-amine (11)

To a solution of 3-(3-bromophenyl)-3-oxopropanenitrile, **10**, (12.5 g, 56 mmol, 1 eq.) in 4:1 MeOH/ H_2O (100 mL) at room temperature was added hydrazine (5 mL, 160 mmol, 2.8 eq.). The mixture was heated to 100 °C for 2.25 hours. The solution was poured over ice (200 mL) and diluted with water (200 mL). The white precipitate was filtered. The wet solid was transferred to a round bottom flask equipped with a Dean-Stark trap and azeotroped to dryness by refluxing in toluene (250 mL). The suspension was cooled, filtered, washed with toluene (100 mL) and dried to yield 3-(3-bromophenyl)-1*H*-pyrazol-5-amine (9.2 g, 39 mmol, 69%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 3.23 (br. s, 3 H), 5.89 (s, 1 H), 7.27 (t, $J=7.8$ Hz, 1 H), 7.42 - 7.48 (m, $J=7.1$, 2.0 Hz, 1 H), 7.51 - 7.55 (m, 1 H), 7.76 (t, $J=1.8$ Hz, 1 H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 89.8, 122.9, 123.9, 128.3, 130.3, 131.0, 132.7, 144.9, 153.1. HRMS: calcd for $\text{C}_9\text{H}_8\text{BrN}_3 + \text{H}^+$, 237.99743; found (ESI-FTMS, $[\text{M}+\text{H}]^{1+}$), 237.99796.

Method A: Ethyl 2-(3-bromophenyl)-7-oxo-4,7-dihydropyrazolo[1,5- α]pyrimidine-6-carboxylate (12)

In an analogous fashion to Compound **6**, ethyl 2-(3-bromophenyl)-7-oxo-4,7-dihydropyrazolo[1,5- α]pyrimidine-6-carboxylate was prepared in 68% yield from 3-(3-bromophenyl)-1*H*-pyrazol-5-amine, **11**, and diethyl ethoxymethylenemalonate. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 1.30 (t, $J=7.1$ Hz, 3 H), 4.25 (q, $J=7.0$ Hz, 2 H), 6.90 (s, 1 H), 7.46 (t, $J=7.8$ Hz, 1 H), 7.62 - 7.65 (m, 1 H), 8.00 - 8.04 (m, 1 H), 8.19 (t, $J=1.8$ Hz, 1 H), 8.58 (s, 1 H), 13.29 (s, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm 14.6, 60.4, 89.1, 100.3, 122.6, 125.8,

129.3, 131.3, 132.2, 135.2, 142.4, 145.3, 152.8, 153.1, 163.9. HRMS: calcd for C₁₅H₁₂BrN₃O₃ + H⁺, 362.01348; found (ESI-FTMS, [M+H]¹⁺), 362.01374.

Method A: 2-(3-Bromophenyl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid (13)

In an analogous fashion to Compound **7**, 2-(3-bromophenyl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid was prepared in 90% yield from ethyl 2-(3-bromophenyl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate, **12**, and sodium hydroxide. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 6.98 (s, 1 H), 7.65 (dq, *J*=7.9, 0.9 Hz, 1 H), 8.04 (dd, *J*=6.6, 1.0 Hz, 1 H), 8.21 (t, *J*=1.8 Hz, 1 H), 8.68 (s, 1 H), 12.79 (br s, 2 H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 89.5, 98.2, 122.3, 125.3, 128.7, 131.1, 132.0, 134.2, 142.7, 146.0, 153.0, 156.8, 164.7. HRMS: calcd for C₁₃H₈BrN₃O₃ + H⁺, 333.98218; found (ESI-FTMS, [M+H]¹⁺), 333.9823.

Method A: 2-(3-Bromophenyl)pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one (14)

In an analogous fashion to Compound **8**, 2-(3-bromophenyl)pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one was prepared in 91% yield from 2-(3-bromophenyl)-7-oxo-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylic acid, **13**, and Dowtherm. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 5.74 (d, *J*=7.3 Hz, 1 H), 6.76 (s, 1 H), 7.45 (t, *J*=8.0 Hz, 1 H), 7.61 (dq, *J*=8.0, 1.0, 0.9 Hz, 1 H), 7.88 (d, *J*=7.3 Hz, 1 H), 8.00 (dt, *J*=7.8, 1.3 Hz, 1 H), 8.18 (t, *J*=1.6 Hz, 1 H), 12.58 (s, 1 H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 86.7, 95.8, 122.2, 125.2, 128.5, 131.0, 131.5, 134.8, 140.0, 143.4, 151.2, 156.4. HRMS: calcd for C₁₂H₈BrN₃O + H⁺, 289.99235; found (ESI-FTMS, [M+H]¹⁺), 289.99295.

3-(3-bromophenyl)-4-methyl-1*H*-pyrazol-5-amine (15)

In an analogous fashion to Compound **11**, 3-(3-bromophenyl)-4-methyl-1*H*-pyrazol-5-amine was prepared in 65% yield from 3-(3-bromophenyl)-2-methyl-3-oxopropanenitrile and hydrazine

hydrate. ^1H NMR (400 MHz, CDCl_3) δ ppm 2.04 (s, 3 H), 7.29 (t, $J=7.8$ Hz, 1 H), 7.29 (t, 1 H), 7.37 - 7.41 (m, 1 H), 7.46 - 7.49 (m, 1 H), 7.61 (t, $J=1.8$ Hz, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ ppm 7.8, 99.9, 122.9, 125.6, 129.9, 130.4, 131.0, 133.0, 140.4, 153.5. HRMS: calcd for $\text{C}_{10}\text{H}_{10}\text{BrN}_3 + \text{H}^+$, 252.01308; found (ESI-FTMS, $[\text{M}+\text{H}]^{1+}$), 252.01353.

Method B: 2-(3-bromophenyl)-3-methylpyrazolo[1,5- α]pyrimidin-7(4H)-one (17)

In an analogous fashion to Compound **14**, Method B, 2-(3-bromophenyl)-3-methylpyrazolo[1,5- α]pyrimidin-7(4H)-one was prepared in 42% yield from 3-(3-bromophenyl)-4-methyl-1H-pyrazol-5-amine, **15**, and the sodium salt of ethyl formylacetate. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 2.30 (s, 3 H), 5.71 (d, $J=7.3$ Hz, 1 H), 7.48 (t, $J=8.0$ Hz, 1 H), 7.63 - 7.67 (m, 1 H), 7.76 - 7.80 (m, 1 H), 7.89 (d, $J=7.3$ Hz, 1 H), 7.94 (t, $J=1.8$ Hz, 1 H), 12.38 (s, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ ppm 7.8, 95.2, 95.7, 121.8, 126.7, 130.0, 130.7, 131.1, 135.4, 139.3, 140.4, 150.3, 156.3. HRMS: calcd for $\text{C}_{13}\text{H}_{10}\text{BrN}_3\text{O} + \text{H}^+$, 304.00800; found (ESI-FTMS, $[\text{M}+\text{H}]^{1+}$), 304.00942.

Method B: Pyrazolo[1,5- α]pyrimidin-7(4H)-one (8)

In an analogous fashion to Compound **14**, Method B, pyrazolo[1,5- α]pyrimidin-7(4H)-one was prepared in 60 % yield from 2H-pyrazol-3-ylamine and the sodium salt of ethyl formylacetate. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 5.68 (d, $J=7.3$ Hz, 1 H), 6.18 (dd, $J=1.9, 0.6$ Hz, 1 H), 7.86 - 7.89 (m, 2 H), 12.36 (s, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ ppm 86.9, 93.1, 137.5, 139.8, 140.5, 154.5. HRMS: calcd for $2 \text{ C}_6\text{H}_5\text{N}_3\text{O} + \text{H}^+$, 271.09380; found (ESI-FTMS, $[2\text{M}+\text{H}]^{1+}$), 271.09415.

Method B: Ethyl 7-oxo-4,7-dihydropyrazolo[1,5- α]pyrimidine-3-carboxylate (18)

In an analogous fashion to Compound **14**, Method B, ethyl 7-oxo-4,7-dihydropyrazolo[1,5- α]pyrimidine-3-carboxylate was prepared in 76% yield from ethyl 5-amino-1H-pyrazole-4-

carboxylate, **16**, and the sodium salt of ethyl formylacetate. ^1H NMR (400 MHz, CDCl_3) δ ppm 1.40 (t, $J=7.2$ Hz, 3 H), 4.36 (q, $J=7.1$ Hz, 2 H), 6.05 (d, $J=7.6$ Hz, 1 H), 7.62 (d, $J=7.6$ Hz, 1 H), 8.19 (s, 1 H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 14.4, 60.9, 97.9, 100.1, 138.7, 143.5, 144.0, 156.9, 163.1. HRMS: calcd for $\text{C}_9\text{H}_9\text{N}_3\text{O}_3 + \text{H}^+$, 208.07167; found (ESI-FTMS, $[\text{M}+\text{H}]^{1+}$), 208.07211.

Method C: 2-(3-Bromophenyl)-3-methylpyrazolo[1,5- α]pyrimidin-5(4H)-one (20)

In an analogous fashion to Compound **19**, Method C, 2-(3-bromophenyl)-3-methylpyrazolo[1,5- α]pyrimidin-5(4H)-one was prepared in 84 % yield from 3-(3-bromophenyl)-4-methyl-1H-pyrazol-5-amine, **15**, and 1,3-dimethyluracil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 2.20 (s, 3 H), 5.95 (d, $J=7.6$ Hz, 1 H), 7.45 (t, $J=8.0$ Hz, 1 H), 7.60 - 7.64 (m, 1 H), 7.72 (d, $J=7.8$ Hz, 1 H), 7.87 (t, $J=1.8$ Hz, 1 H), 8.47 (d, $J=7.6$ Hz, 1 H), 12.15 (s, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm 7.4, 94.3, 106.0, 121.9, 126.5, 129.8, 130.8, 131.1, 135.1, 138.2, 139.2, 151.3, 160.0. HRMS: calcd for $\text{C}_{13}\text{H}_{10}\text{BrN}_3\text{O} + \text{H}^+$, 304.00800; found (ESI-FTMS, $[\text{M}+\text{H}]^{1+}$), 304.00841.

Method C: Pyrazolo[1,5- α]pyrimidin-5(4H)-one (21)

In an analogous fashion to Compound **19**, Method C, pyrazolo[1,5- α]pyrimidin-5(4H)-one was prepared in 11% yield from 2H-pyrazol-3-ylamine and 1,3-dimethyluracil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 5.81 (d, $J=1.3$ Hz, 1 H), 5.93 (d, $J=8.1$ Hz, 1 H), 7.75 (d, $J=2.0$ Hz, 1 H), 8.47 (dd, $J=8.1, 0.8$ Hz, 1 H), 12.09 (s, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm 87.2, 105.9, 138.4, 140.7, 143.5, 159.7. HRMS: calcd for $2 \text{C}_6\text{H}_5\text{N}_3\text{O} + \text{Na}^+$, 293.07574; found (ESI-FTMS, $[2\text{M}+\text{Na}]^{1+}$), 293.07449.

Method C: Ethyl 5-oxo-4,5-dihydropyrazolo[1,5- α]pyrimidine-3-carboxylate (22)

In an analogous fashion to Compound **19**, Method C, ethyl 5-oxo-4,5-dihydropyrazolo[1,5- α]pyrimidine-3-carboxylate was prepared in 57% yield from ethyl 5-amino-1H-pyrazole-4-

carboxylate, **16**, and 1,3-dimethyluracil. ^1H NMR (400 MHz, CDCl_3) δ ppm 1.39 (t, $J=7.2$ Hz, 3 H), 4.37 (q, $J=7.2$ Hz, 2 H), 6.16 (d, $J=8.1$ Hz, 1 H), 8.04 (s, 1 H), 8.11 (d, $J=7.8$ Hz, 1 H), 9.56 (s, 1 H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm 14.5, 60.9, 96.9, 108.1, 138.1, 142.6, 144.0, 159.1, 162.4. HRMS: calcd for $\text{C}_9\text{H}_9\text{N}_3\text{O}_3 + \text{H}^+$, 208.07167; found (ESI-FTMS, $[\text{M}+\text{H}]^{1+}$), 208.07257.

4-Methylpyrazolo[1,5- α]pyrimidin-7(4H)-one (**23**)

To vinylogous amide pyrazolo[1,5- α]pyrimidin-7(4H)-one, **8**, (0.25 g, 1.85 mmol) in N,N-DMF (7 mL) at 0°C , was added 60% NaH (0.088 g, 2.22 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 15 min. At this point, iodomethane was added and the reaction had gone to completion after 30 minutes at room temperature. The reaction mixture was diluted with saturated ammonium chloride solution and extracted with methylene chloride. The organic layer was washed with water and brine and dried over MgSO_4 , filtered and evaporated to give pure 4-methylpyrazolo[1,5- α]pyrimidin-7(4H)-one (0.245 g, 1.64 mmol, 89%) as a tan solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 3.70 (s, 3 H), 5.74 (d, $J=7.6$ Hz, 1 H), 6.36 (d, $J=2.0$ Hz, 1 H), 7.89 (d, $J=7.6$ Hz, 1 H), 7.93 (d, $J=2.0$ Hz, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm 39.6, 89.6, 95.6, 142.6, 143.5, 143.6, 155.9. HRMS: calcd for $2 \text{ C}_7\text{H}_7\text{N}_3\text{O} + \text{H}^+$, 299.12510; found (ESI-FTMS, $[2\text{M}+\text{H}]^{1+}$), 299.12523.

4-Methylpyrazolo[1,5- α]pyrimidin-5(4H)-one (**24**)

In an analogous fashion to Compound **23**, 4-methylpyrazolo[1,5- α]pyrimidin-5(4H)-one was prepared in 84% yield from pyrazolo[1,5- α]pyrimidin-5(4H)-one, **21**, and iodomethane. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 3.41 (s, 3 H), 6.06 (d, $J=7.8$ Hz, 1 H), 6.16 (dd, $J=2.0, 0.8$ Hz, 1 H), 7.85 (d, $J=2.0$ Hz, 1 H), 8.52 (dd, $J=7.8, 0.8$ Hz, 1 H); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ ppm 30.6, 88.6, 105.0, 137.6, 142.7, 143.7, 158.6. HRMS: calcd for $2 \text{ C}_7\text{H}_7\text{N}_3\text{O} + \text{H}^+$, 299.12510; found (ESI-FTMS, $[2\text{M}+\text{H}]^{1+}$), 299.12546.

Method D: Pyrazolo[1,5- α]pyrimidin-5(4*H*)-one (21)

In an analogous fashion to Compound 19, Method D, pyrazolo[1,5- α]pyrimidin-5(4*H*)-one was prepared in 60% yield from ethyl 3-ethoxyacrylate and 2*H*-pyrazol-3-ylamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 5.81 (d, *J*=1.3 Hz, 1 H), 5.93 (d, *J*=8.1 Hz, 1 H), 7.75 (d, *J*=2.0 Hz, 1 H), 8.47 (dd, *J*=8.1, 0.8 Hz, 1 H), 12.09 (s, 1 H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 87.3, 105.9, 138.4, 140.7, 143.5, 159.7. HRMS: calcd for 2 C₆H₅N₃O + Na⁺, 293.07574; found (ESI-FTMS, [2M+Na]¹⁺), 293.07449.

Method D: Ethyl 3-[5-amino-3-(3-bromophenyl)-1*H*-pyrazol-1-yl]-3-ethoxypropanoate (11A)

To a solution of 3-(3-bromophenyl)-1*H*-pyrazol-5-amine, **11**, (915 mg, 3.6 mmol), ethyl 3-ethoxyacrylate 830 μ L, 5.7 mmol) in DMF (60 mL), was added cesium carbonate (1.8 g, 5.5 mmol). The reaction mixture was allowed to stir at room temperature for two hours. At this point, the reaction then was cooled and acetic acid (3ml) was added to neutralize the base. The product was then extracted into ethyl acetate three times, washed with brine and dried over sodium sulfate. The ethyl acetate was then removed *in vacuo*. The oil was then dissolved in methylene chloride and separated by column chromatography using 10-50% ethyl acetate in hexanes as the eluent to give ethyl 3-[5-amino-3-(3-bromophenyl)-1*H*-pyrazol-1-yl]-3-ethoxypropanoate (0.066 g, 0.17 mmol, 17%) as peak 1. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.04 (t, *J*=7.1 Hz, 3 H), 1.15 (t, *J*=7.1 Hz, 3 H), 2.97 - 3.21 (m, 2 H), 3.26 - 3.54 (m, 2 H), 4.05 (q, *J*=7.1 Hz, 2 H), 5.53 (s, 2 H), 5.74 (s, 1 H), 5.79 (dd, *J*=7.2, 5.9 Hz, 1 H), 7.32 (t, *J*=7.8 Hz, 1 H), 7.42 - 7.49 (m, 1 H), 7.68 (d, *J*=7.8 Hz, 1 H), 7.86 (t, *J*=1.6 Hz, 1 H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ ppm 14.5, 15.2, 29.5, 60.5, 63.2, 81.7,

85.9, 122.4, 124.4, 127.7, 130.4, 131.1, 136.8, 148.3, 149.9, 169.6. HRMS: calcd for $C_{16}H_{20}BrN_3O_3 + H^+$, 382.07608; found (ESI-FTMS, $[M+H]^+$), 382.07599.

Method D: 2-(3-Bromophenyl)-7-ethoxy-6,7-dihydropyrazolo[1,5- α]pyrimidin-5(4H)-one (11B)

To a solution of 3-(3-bromophenyl)-1H-pyrazol-5-amine, **11**, (238 mg, 1 mmol), ethyl 3-ethoxyacrylate (220 μ l, 1.5 mmol) in DMF (15 ml), was added cesium carbonate (490 mg, 1.5 mmol). The reaction mixture was allowed to stir at room temperature for two hours. At this point, the reaction then was cooled and acetic acid (3ml) was added to neutralize the base. The product was then extracted into ethyl acetate three times, washed with brine and dried over sodium sulfate. The ethyl acetate was then removed *in vacuo*. The oil was then dissolved in methylene chloride and separated by column chromatography using 10-50% ethyl acetate in hexanes as the eluent to give 2-(3-bromophenyl)-7-ethoxy-6,7-dihydropyrazolo[1,5- α]pyrimidin-5(4H)-one (0.48 g, 0.14 mmol, 14%) as peak 2. 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.05 (t, $J=7.1$ Hz, 3 H), 2.67 (d, $J=16.7$ Hz, 1 H), 3.26 - 3.36 (m, 1 H), 3.51 - 3.71 (m, 2 H), 5.63 (dd, $J=4.6, 1.5$ Hz, 1 H), 6.19 (s, 1 H), 7.34 - 7.40 (m, 1 H), 7.49 - 7.55 (m, 1 H), 7.78 - 7.84 (m, 1 H), 7.98 (t, $J=1.6$ Hz, 1 H), 11.04 (s, 1 H); ^{13}C NMR (101 MHz, DMSO- d_6) δ ppm 15.2, 29.5, 64.3, 82.5, 88.0, 122.6, 124.7, 128.0, 131.2, 131.5, 135.6, 140.4, 149.6, 160.1. HRMS: calcd for $C_{14}H_{14}BrN_3O_2 + H^+$, 336.03422; found (ESI-FTMS, $[M+H]^+$), 336.03398.

Supplementary NMR Material

Samples of **8**, **21**, **23**, and **24** for NMR analysis were typically 10-30 mg dissolved in deuterated DMSO. We used the DPGFSE NOE technique (Excitation Sculpting in High-Resolution Nuclear Magnetic Resonance Spectroscopy: Application to Selective NOE Experiments Katherine Stott, Jonathan Stonehouse, James Keeler, Tsang-Lin Hwang, A. J. Shaka

J. Am. Chem. Soc.; **1995**; *117*(14); 4199-4200) with a 800ms mixing time to measure NOEs in **23** and **24**. Chemical shift assignments for **8** and **21** were made using ^1H and ^{13}C 1D NMR experiments, and standard ^1H , ^{13}C , and ^{15}N heteronuclear correlation experiments (HSQC, HMBC). HMBC experiments were normally recorded optimized for 5-10 Hz couplings. ^{13}C and ^{15}N chemical shifts were confirmed using Advanced Chemistry Development ^{13}C and ^{15}N chemical shift prediction software (version 9.0).

Table of chemical shifts for **8** and **21**^a.

	^1H	^{13}C	^{15}N		^1H	^{13}C	^{15}N
1		157.2				160.3	
2	7.879	143.1		7.752	144.1		
3		142.6			141.2		
4	7.884	140.3		8.468	139.0		
5	5.695	95.7		5.942	106.4		
6	6.194	89.6		5.814	87.8		
a			275				279
b			228				204
c			124				139

^a All values are in parts per million (ppm) using the deuterium of d6-DMSO and an internal chemical shift standard.

NOE data for **23**:

NOE data for **24**:

Supporting Information

Purity of Final Compounds

Compound Number (Paper)	Method 1 HPLC% purity	Method 2 HPLC% purity	Method 3 HPLC% purity
6	99.0	99.2	
7	99.6	100	
8	97.1	100	
10	99.7	100	
11		95.4	100
11A	97.2	97.1	
11B	99.7	99.4	
12	100	100	
13	99.8	99.8	
14; M1	98.6	97.2	
15	98.5	99.7	
17	96.9	96.9	
18	96.6	97.6	
19; M1	99.2	100	
20	97.2	98.6	
21	99.1	99.2	
22		73*	100
23	100	98.5	
24	100	97.7	

Purity in two different solvent systems was determined using Methods 1, 2 and/or 3 and compounds were found to be >95 % pure.

* Due to protonation states of the compound in acid, not an impurity.

Method 1:

Solvent A is H₂O with 0.1% formic acid, solvent B is CH₃CN with 0.1% formic acid

Column: Agilent Zorbax SB-C18 2.1x30 mm

Flow rate: 0.8 mL/min

Gradient: A% B%

0 min 95 5

7 0 100

9 0 100

Method 2:

Solvent A is H₂O with 0.1% formic acid, solvent B is CH₃OH with 0.1% formic acid

Column: Agilent Zorbax SB-C18 2.1x30 mm

Flow rate: 0.8 mL/min

Gradient: A% B%

0 min 95 5

7 0 100

9 0 100

Method 3:

Solvent A is H₂O with 0.1% TEA, solvent B is CH₃CN with 0.1% TEA

Column: Waters xTerra MS C18 4.6x100 mm

Flow rate: 1 mL/min

Gradient: A% B%

0 min 95 5

18 5 95

20 5 95