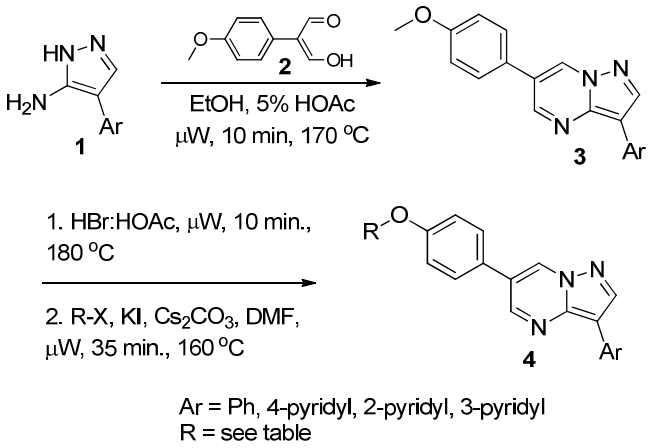
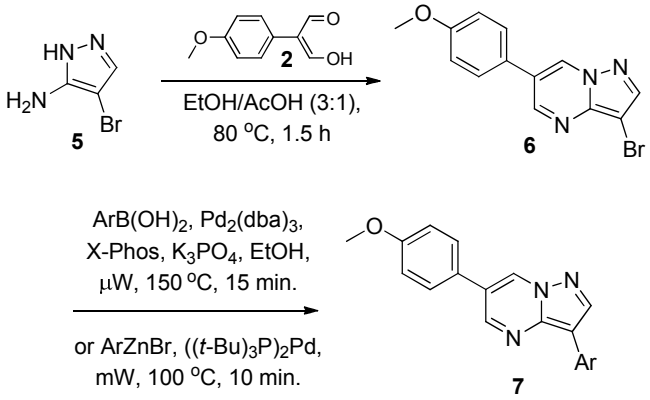
Supporting Information

Supplementary Methods for Synthesis of Dorsomorphin Analogs.



Scheme S1. Synthesis of pyrazolo[1,5-*a*]pyrimide compounds.



Scheme S2. Alternative cross-coupling strategy for the synthesis of pyrazolo[1,5-*a*]pyrimidine compounds.

Detailed Chemical Synthesis

***Chemical Synthesis*.** All NMR spectra were recorded on either a Varian Inova 400 (400 MHz) or Varian Inova 500 (500 MHz) spectrophotometer located in the Small Molecule NMR Facility at Vanderbilt University. ^{1}H chemical shifts are reported in δ values in ppm downfield from TMS as the internal standard in DMSO or $CDCl_3$. Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet), integration, coupling constant (Hz). ^{13}C chemical shifts are reported in δ values in ppm with the DMSO carbon peak set to 39.5 ppm (or $CDCl_3$ at 77.23 ppm). Low-resolution mass spectra were obtained on an Agilent 1200 LCMS with electrospray ionization. High-resolution mass spectra were recorded on a Waters Qtof-API-US plus Acquity system. Analytical thinlayer chromatography was performed on 250 mM silica gel 60 F254 plates. Analytical HPLC was performed on an Agilent 1200 analytical LCMS with UV detection at 214 nm and 254 nm along with ELSD detection. Preparative purification was performed on a custom Agilent 1200 preparative LCMS with collection triggered by mass detection. Solvents for extraction, washing, and chromatography were HPLC grade. All reagents were purchased from Aldrich Chemical Co. and were used without purification. All polymer-supported reagents were purchased from Biotage.

5-Amino-4-arylpyrazole[14] was reacted with malondialdehyde **2** in 5% AcOH/EtOH at 150 ^{o}C for 10 min. under microwave conditions to afford pyrazolo[1,5-*a*]pyrimidine **3** (Scheme 1). Compound **3** was deprotected in the microwave at 180 ^{o}C for 10 min. to

afford the phenol which was then alkylated with a diverse collection of functionalized alkyl halides in 35 min. at 160 ^{o}C under microwave conditions to yield the desired dorsomorphin analogs such as **4**. An additional synthetic sequence is outlined in Scheme 2 wherein 3-amino-4-bromopyrazole **5** was reacted with malondialdehyde **2** under reflux conditions yielding the brominated pyrazolo[1,5-*a*]pyrimidine **6**. The bromopyrazole was reacted under reflux conditions due to the fact that under microwave conditions there was substantial debromination products observed. The pyrazolo[1,5-*a*]pyrimidine **6** was subjected to transition metal-catalyzed cross coupling conditions to yield the desired intermediate **7**. The compound **6** was either reacted under Suzuki-Miyaura[17] conditions ($ArB(OH)_2$, $Pd_2(dba)_3$, X-Phos, K_3PO_4, EtOH, μW), or Negishi coupling conditions to yield the desired **7**. Compound **7** was then subjected to the demethylation/alkylation conditions as described above.

Synthesis of 3-bromo-6-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine (6). To a mixture of 2-(4-methoxyphenyl)malondialdehyde **2** (1.5 g; 8.4 mmol) in 30 mL of 5% AcOH/EtOH was added 3-amino-4-bromopyrazole **5** (1.4 g; 8.4 mmol) and the mixture was heated at 80 ^{o}C for 1.5 h. The reaction mixture was concentrated and then the reaction mixture was purified by flash column chromatography on silica gel (hexanes/EtOAc = 1/1) to afford 3-bromo-6-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine (2.2 g; 7.2 mmol; 86%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.44 (d, 1 H, *J* = 2.4 Hz), 9.00 (d, 1 H, *J* = 2.0 Hz), 8.39 (s, 1 H), 7.80 (d, 2 H, *J* = 8.8 Hz), 7.09 (d, 2 H, *J* = 8.8 Hz), 3.82 (s, 3 H); LCMS, single peak, 3.21 min, m/e, 304.1 $[M]^{+}$.

Synthesis of 4-(6-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl)quinoline (7). To a mixture of 3-bromo-6-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine **6** (200 mg; 0.66 mmol), 4-quinoline boronic acid (171 mg; 0.986 mmol), $Pd_2(dba)_3$ (22.3 mg; 0.0243 mmol), X-Phos (22.9 mg; 0.0480 mmol), K_3PO_4 (303 mg; 1.43 mmol) was added EtOH (4 mL). The reaction solution was degassed by bubbling Ar through the system, and then the mixture was heated under microwave conditions (150 ^oC, 15 min.). The mixture was then filtered and the solids were washed with CH_2Cl_2 and the filtrate was concentrated and purified by flash column chromatography on silica gel (EtOAc) to afford 4-(6-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl)quinoline (142 mg; 0.403 mmol; 61%). ^1H NMR (DMSO-d_6, 400 MHz) δ 9.59 (d, 1 H, *J* = 2.0 Hz), 9.06 (d, 1 H, *J* = 2.0 Hz), 8.97 (d, 1 H, *J* = 4.8 Hz), 8.72 (s, 1 H), 8.21 (d, 1 H, *J* = 8.0 Hz), 8.11 (d, 1 H, *J* = 8.0 Hz), 7.86 (d, 2 H, *J* = 8.8 Hz), 7.80 (d, 2 H, *J* = 4.4 Hz), 7.62 (t, 1 H, *J* = 7.2 Hz), 7.12 (d, 2 H, *J* = 8.8 Hz), 3.84 (s, 3 H); LCMS, single peak, 2.63 min, m/e, 353.2 $[M + H]^+$.

Synthesis of 4-(6-(4-isopropoxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl)quinoline, DHM1 (4). A mixture of 4-(6-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl)quinoline (200 mg; 0.57 mmol) and 1:1 HBr:AcOH (3 mL) was heated under microwave conditions (180 ^oC, 10 min.). The mixture was neutralized with sat. aq. $NaHCO_3$ and the solids were filtered and dried to afford 4-(3-(quinolin-4-yl)pyrazolo[1,5-*a*]pyrimidin-6-yl)phenol which was carried on without further purification. A mixture of 4-(3-(quinolin-4-

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yl)pyrazolo [1,5-*a*]pyrimidin-6-yl)phenol (30 mg; 0.083 mmol), 2-bromopropane (17 mg; 0.092 mmol), KI (13.8 mg; 0.0832 mmol), cesium carbonate (54.2 mg; 0.166 mmol) and DMF was heated under microwave conditions (120^{o}C, 10 min.). The reaction mixture was diluted with water and extracted in CH_2Cl_2 and then purified by flash column chromatography on silica gel (EtOAc) to afford 4-(6-(4-isopropoxyphenyl) pyrazolo[1,5-*a*]pyrimidin-3-yl)quinoline (DMH1; 7.6 mg; 0.20 mmol; 24%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.01 (br. d., 1 H, *J* = 3.6 Hz), 8.91 (d, 1 H, *J* = 2.4 Hz), 8.85 (d, 1 H, *J* = 2.0 Hz), 8.49 (s, 1 H), 8.23-8.19 (m, 2 H), 7.77 (t, 2 H, *J* = 7.2 Hz), 7.60-7.53 (m, 3 H), 7.06 (d, 2 H, *J* = 6.8 Hz), 4.64 (hept., 1 H, *J* = 6.0 Hz), 1.40 (d, 6 H, *J* = 6.0 Hz); LCMS, single peak, 2.48 min, m/e, 381.2 $[M + H]^{+}$.

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