Supporting Information

Cytosine analogs from substituted acetonitriles via Thorpe condensation

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General Information. Unless otherwise noted, all reactions were carried out under an atmosphere of nitrogen in flame-dried glassware with magnetic stirring. Tetrahydrofuran and dichloromethane, were filtered through a column of activated alumina under an atmosphere of argon. Benzene (A.C.S. reagent grade), and acetone (Optima grade) were purchased from Fisher and used without further purification. Ethyl alcohol, USP grade, was purchased from Pharmco and used without further purification. Benzoyl isocyanate (95%) was purchased from Alfa and used without further purification. Purification of reaction products was carried out by column chromatography using EM Reagents silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 250 μ m silica gel 60-F₂₅₄ plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution or anisaldehyde followed by heating.

Melting points were measured with a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer.

¹H NMR spectra were recorded on Bruker Avance 300 (300 MHz) or Avance 400 (400 MHz) spectrometers and are reported in ppm using solvent as the internal standard (CDCl₃ at 7.26 ppm, (CD₃)₂CO at 2.05 ppm, (CD₃)₂SO at 2.50 ppm). Data are reported as: (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz, integration). ¹³C NMR spectra were recorded on Avance 300 (75 MHz) or Avance 400 (100 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent resonance employed as the internal standard (CDCl₃ at 77.1 ppm, (CD₃)₂CO at 29.8 ppm, (CD₃)₂SO at 39.5 ppm). High resolution mass spectra were obtained on Jeol HMS 600-H spectrometers in the Brown University Mass Spectrometry Laboratory. Exact mass measurements were obtained by internal calibration with an appropriate lock mass compound.

General Procedure A.

(4-*tert*-Butyl-phenoxy)-acetonitrile (1a): Anhydrous K₂CO₃ (10.3 g, 74.7 mmol) was added to a solution of 4-*tert*-butylphenol (5.76 g, 36.8 mmol) in acetone (70 mL) followed by

chloroacetonitrile (9.30 mL, 147 mmol). The mixture was heated to reflux overnight. After being allowed to cool to rt, the reaction mixture was diluted with EtOAc (140 mL) and H₂O (100 mL). The organic layer was separated, washed with H₂O (2 × 100 mL), 2.0 N NaOH (2 × 100 mL), H₂O (100 mL), brine (100 mL), dried (Na₂SO₄), and concentrated to afford a brown oil. Column chromatography (SiO₂, 12.5% EtOAc/hexanes) provided 6.47 g (93%) of **1a** as a colorless oil: *R*_f = 0.26 (12.5 % EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.45–7.37 (m, 2H), 6.99–6.94 (m, 2H), 4.76 (s, 2H), 1.35 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 154.3, 145.9, 126.6, 115.3, 114.5, 53.7, 34.2, 31.3; IR (film) 2966, 2907, 2870, 1608, 1586, 1513, 1464, 1448, 1365, 1300, 1266, 1222, 1187, 1114, 1050, 897, 830, 789, 728 cm⁻¹; HRMS (TOF/electrospray) *m/z* 212.1044 (212.1051 calc. for C₁₂H₁₅N₁O₁Na₁, M + Na⁺).

***o*-Tolyloxy-acetonitrile (1b)**: Using general procedure A, *o*-cresol (2.17 g, 20.4 mmol) was converted into 2.88 g (96%) of **1b** as a colorless oil: *R*_f = 0.45 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.29–7.20 (m, 2H), 7.05–6.99 (m, 1H), 6.94–6.89 (m, 1H), 4.80 (s, 2H), 2.29 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.2, 131.9, 128.1, 127.5, 123.3, 115.8, 112.1, 54.2, 16.4; IR (film) 3029, 2928, 1590, 1549, 1494, 1462, 1445, 1368, 1307, 1293, 1266, 1240, 1225, 1187, 1164, 1124, 1057, 1044, 894, 753, 712 cm⁻¹; HRMS (EI⁻) *m/z* 147.0689 (147.0684 calc. for C₉H₉N₁O₁, M⁻).

(Naphthalen-2-yloxy)-acetonitrile (1c): Using general procedure A, 2-naphthol (1.01 g, 7.02 mmol) was converted into 1.28 g (99%) after column chromatography (25% EtOAc/hexanes), of **1c** as a white solid: mp 74–76 °C; *R*_f = 0.35 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.86–7.78 (m, 3H), 7.55–7.39 (m, 2H), 7.28–7.17 (m, 2H), 4.90 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 154.8, 134.4, 130.6, 130.3, 128.2, 127.5, 127.3, 125.2, 118.5, 115.5, 108.2, 53.9; IR (KBr) 3057, 2067, 1949, 1925, 1631, 1600, 1507, 1472, 1446, 1392, 1259, 1217, 1185, 1040, 962, 840, 742, 624, 477 cm⁻¹; HRMS (EI⁻) *m/z* 183.0680 (183.0684 calc. for C₁₂H₉N₁O₁, M⁻).

(Naphthalen-1-yloxy)-acetonitrile (1d): Using general procedure A, 1-naphthol (5.01 g, 34.8 mmol) was converted into 6.35 g (99%) of **1d** as a colorless oil: *R*_f = 0.28 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.27–8.19 (m, 1H), 7.90–7.83 (m, 1H), 7.62–7.51 (m, 3H), 7.47–7.38 (m, 1H), 6.96–6.90 (m, 1H), 4.97 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 152.8, 135.0, 128.1, 127.4, 126.5, 125.8, 125.7, 123.2, 122.0, 115.6, 106.1, 54.0; IR (film) 3060, 2926, 2860, 1925, 1631, 1600, 1507, 1472, 1446, 1392, 1259, 1217, 1185, 1040, 962, 840, 742, 624, 477 cm⁻¹; HRMS (EI⁻) *m/z* 183.0679 (183.0684 calc. for C₁₂H₉N₁O₁, M⁻).

(2,6-Dimethyl-phenoxy)-acetonitrile (1e): Using general procedure A, 2,6-dimethylphenol (1.79 g, 14.7 mmol) was converted into 2.28 g (96%) of **1e** as a colorless oil: *R*_f = 0.49 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.09–6.99 (m, 4H), 4.62 (s, 2H), 2.35 (s,

6H); ^{13}C NMR (100 MHz, CDCl_3) δ 154.9, 131.1, 129.7, 125.9, 116.2, 57.5, 16.8; IR (film) 3025, 2919, 2038, 1584, 1475, 1379, 1266, 1185, 1093, 1029, 894, 806, 773 cm^{-1} ; HRMS (EI^+) m/z 161.0848 (161.0841 calc. for $\text{C}_{10}\text{H}_{11}\text{N}_1\text{O}_1$, M^+).

(2-*tert*-Butylphenoxy)-acetonitrile (1f): Using general procedure A, 2-*tert*-butylphenol (2.39 g, 15.9 mmol) was converted into 2.94 g (98%) of **1f** as an orange oil: R_f = 0.39 (25% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.40–7.36 (m, 1H), 7.29–7.24 (m, 1H), 7.09–7.04 (m, 1H), 6.96–6.91 (m, 1H), 4.84 (s, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.0, 139.5, 127.8, 127.7, 123.2, 115.7, 112.7, 53.6, 35.2, 30.3; IR (film) 2959, 2871, 1601, 1580, 1549, 1488, 1444, 1392, 1361, 1295, 1261, 1211, 1199, 1138, 1096, 1042, 894, 753 cm^{-1} ; HRMS (EI^-) m/z 189.1149 (189.1154 calc. for $\text{C}_{12}\text{H}_{15}\text{N}_1\text{O}_1$, M^-).

(4-Bromo-phenoxy)-acetonitrile (1g): Using general procedure A, 4-bromophenol (2.53 g, 14.6 mmol) was converted into 3.00 g (99%) of **1g** as a light yellow solid: mp 52–54 °C; R_f = 0.29 (25% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.50–7.45 (m, 2H), 6.92–6.85 (m, 2H), 4.76 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.0, 133.2, 117.2, 116.1, 115.1, 54.2; IR (KBr) 3425, 2061, 1878, 1581, 1487, 1444, 1381, 1366, 1304, 1286, 1234, 1179, 1116, 1071, 1046, 1006, 946, 828, 807, 656, 503 cm^{-1} ; HRMS (EI^+) m/z 210.9630 (210.9633 calc. for $\text{C}_8\text{H}_6\text{Br}_1\text{N}_1\text{O}_1$, M^+).

(3-Trifluoromethyl-phenoxy)acetonitrile (1h): Using general procedure A, 3,3,3-trifluoro-*m*-cresol (2.22 g, 13.7 mmol) was converted into 2.68 g (97%) of **1h** as a colorless oil: R_f = 0.35 (25% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.54–7.48 (m, 1H), 7.41–7.37 (m, 1H), 7.25–7.17 (m, 2H), 4.85 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.0, 131.4 (q, J = 130 Hz), 131.0, 123.9 (q, J = 1083 Hz), 120.3 (q, J = 15 Hz), 118.5, 114.9, 112.6 (q, J = 15 Hz), 54.1; IR (KBr) 3463, 1595, 1494, 1457, 1329, 1219, 1172, 1129, 1055, 891, 861, 791, 738, 697, 656 cm^{-1} ; HRMS (EI^-) m/z 201.0407 (201.0401 calc. for $\text{C}_9\text{H}_6\text{F}_3\text{N}_1\text{O}_1$, M^-).

(4-Methoxy-phenoxy)acetonitrile (1i): Using general procedure A, 4-methoxyphenol (2.26 g, 18.2 mmol) was converted into 2.69 g (87%) of **1i** as colorless oil: R_f = 0.30 (25% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.00–6.86 (m, 4H), 4.72 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.1, 151.1, 117.2, 115.8, 115.3, 56.1, 55.4; IR (film) 2960, 2095, 1595, 1505, 1445, 1294, 1244, 1204, 1109, 1048, 1025, 891, 823, 752, 712 cm^{-1} ; HRMS (EI^-) m/z 163.0632 (163.0633 calc. for $\text{C}_9\text{H}_9\text{N}_1\text{O}_2$, M^-).

General Procedure B.

3-Amino-2,4-bis-(4-*tert*-butylphenoxy)-but-2-enenitrile (2a): Potassium *tert*-pentylate (1.7M in

PhMe, 1.4 mL, 2.38 mmol) was added to a 0 °C solution of (4-*tert*-butyl-phenoxy)-acetonitrile (**1a**) (0.439 g, 2.33 mmol) and THF (10 mL). After 4h at 0 °C, the reaction mixture was diluted with sat'd NaHCO₃ (10 mL) and washed with H₂O (10 mL), brine (10 mL), dried over Na₂SO₄ and concentrated to afford a yellow oil. Column chromatography (SiO₂, 25% EtOAc/hexanes) provided 0.426 g (96%) of **2a** as a light yellow oil: *R*_f = 0.34 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.41–7.25 (m, 4H), 6.99–6.90 (m, 4H), 4.90 (s, 2H), 4.72 (bs, 2H), 1.34 (s, 9H), 1.32 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 155.3, 154.0, 146.6, 146.5, 145.6, 127.0, 127.0, 126.8, 116.5, 115.2, 115.1, 114.9, 102.6, 64.6, 31.9, 31.8; IR (film) 3486, 3359, 2962, 2868, 2194, 1648, 1606, 1509, 1462, 1393, 1364, 1293, 1267, 1222, 1177, 1112, 1012, 830, 780 cm⁻¹; HRMS (TOF/electrospray) *m/z* 379.2387 (379.2386 calc. for C₂₄H₃₁N₂O₂, M+H⁺).

3-Amino-2,4-bis-*o*-tolylloxy-but-2-enitrile (2b**):** Using general procedure B, *o*-tolylloxy-acetonitrile (**1b**) (0.43 g, 2.9 mmol) was converted into 0.41 g (94%) of **2b** as a colorless oil: *R*_f = 0.28 (12.5% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.30–7.11 (m, 4H), 7.04–6.90 (m, 4H), 4.94 (s, 2H), 4.72 (bs, 2H), 2.33 (s, 3H), 2.27 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.8, 154.3, 146.3, 131.9, 131.6, 127.6, 127.5, 127.5, 127.3, 123.6, 122.5, 116.4, 113.6, 112.1, 102.7, 64.6, 16.7, 16.4; IR (film) 3485, 3358, 3026, 2919, 2193, 1648, 1580, 1550, 1490, 1462, 1406, 1306, 1222, 1181, 1122, 1044, 859, 751 cm⁻¹; HRMS (TOF/electrospray) *m/z* 295.1443 (295.1447 calc. for C₁₈H₁₉N₂O₂, M+H⁺).

3-Amino-2,4-bis-(naphthalen-2-yloxy)-but-2-enitrile (2c**):** Using general procedure B, (naphthalen-2-yloxy)-acetonitrile (**1c**) (0.095 g, 0.52 mmol) was converted into 0.095 g (99%) of **2c** as an off-white solid: mp 131–133 °C; *R*_f = 0.19 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.89–7.77 (m, 5H), 7.58–7.51 (m, 2H), 7.49–7.36 (m, 4H), 7.30–7.22 (m, 3H), 5.11 (s, 2H), 4.82 (bs, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 155.3, 153.9, 146.5, 134.7, 134.5, 130.6, 130.4, 130.1, 128.1, 128.1, 127.6, 127.3, 127.2, 125.1, 125.0, 118.7, 117.9, 116.4, 110.0, 108.4, 102.8, 64.5; IR (film) 3485, 3382, 3057, 2193, 1648, 1631, 1600, 1511, 1464, 1390, 1358, 1246, 1214, 1171, 1120, 1037, 960, 906, 839, 810, 748 cm⁻¹; HRMS (TOF/electrospray) *m/z* 367.1444 (367.1447 calc. for C₂₄H₁₉N₂O₂, M+H⁺).

3-Amino-2,4-bis-(naphthalen-1-yloxy)-but-2-enitrile (2d**):** Using general procedure B, (naphthalen-1-yloxy)-acetonitrile (**1d**) (2.0 g, 11.0 mmol) was converted into 2.0 g (99%) of **2d** as an off-white solid: mp 153–155 °C; *R*_f = 0.28 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 8.34–8.22 (m, 2H), 7.92–7.84 (m, 2H), 7.64–7.38 (m, 8H), 7.11–7.02 (m, 2H), 5.19 (s, 2H), 4.84 (bs, 2H); ¹³C NMR

(100 MHz, CDCl₃) δ 153.3, 151.7, 146.6, 135.2, 135.1, 128.3, 128.2, 127.2, 127.2, 126.4, 126.2, 126.2, 126.0, 125.8, 125.5, 123.5, 122.5, 121.9, 121.8, 116.3, 107.8, 106.1, 102.5, 64.8; IR (film) 3483, 3368, 3054, 2193, 1648, 1597, 1579, 1509, 1462, 1390, 1268, 1225, 1176, 1156, 1101, 1078, 1019, 909, 880, 791, 770, 732 cm⁻¹; HRMS (TOF/electrospray) m/z 367.1445 (367.1447 calc. for C₂₄H₁₉N₂O₂, M+H⁺).

3-Amino-2,4-bis-(2,6-dimethyl-phenoxy)-but-2-enitrile (2e): Using general procedure B, (2,6-dimethyl-phenoxy)-acetonitrile (**1e**) (0.36 g, 2.3 mmol) was converted into 0.32 g (88%) of **2e** as a white crystalline solid: mp 110–112 °C; R_f = 0.58 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.09–6.94 (m, 6H), 4.82 (bs, 2H), 4.57 (s, 2H), 2.35 (s, 6H), 2.30 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 155.1, 152.3, 140.5, 131.4, 131.1, 129.6, 129.5, 125.9, 125.2, 115.1, 107.3, 68.5, 16.7, 16.6; IR (film) 3483, 3368, 3203, 3027, 2924, 2191, 1650, 1593, 1476, 1395, 1264, 1222, 1184, 1091, 999, 918, 860, 769 cm⁻¹; HRMS (TOF/electrospray) m/z 323.1770 (323.1760 calc. for C₂₀H₂₂N₂O₂Na, M+Na⁺).

3-Amino-2,4-bis-(2-tert-butyl-phenoxy)-but-2-enitrile (2f): Using general procedure B, (2-tert-butyl-phenoxy)-acetonitrile (**1f**) (0.90 g, 4.7 mmol) was converted into 0.77 g (86%) of **2f** as a colorless oil: R_f = 0.41 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.45–6.84 (m, 8H), 5.02 (s, 0.66H), 4.92 (s, 1.32H), 4.78 (bs, 0.66H), 4.72 (bs, 1.32H), 1.52 (s, 3H), 1.50 (s, 3H), 1.49 (s, 6H), 1.47 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 156.8, 156.0, 154.8, 149.9, 146.4, 139.3, 138.9, 138.8, 138.7, 127.9, 127.8, 127.8, 127.6, 127.6, 123.8, 123.4, 122.5, 122.4, 116.2, 115.8, 115.0, 114.1, 113.2, 113.1, 102.6, 100.2, 64.9, 63.6, 35.3, 35.3, 35.2, 30.6, 30.5; IR (film) 3487, 3384, 3222, 3059, 2995, 2958, 2912, 2670, 2196, 1648, 1599, 1579, 1486, 1442, 1392, 1360, 1293, 1212, 1137, 1094, 1055, 933, 910, 862, 833, 815, 752 cm⁻¹; HRMS (EI⁺) m/z 378.2309 (378.2307 calc. for C₂₄H₃₀N₂O₂, M⁺).

3-Amino-2,4-bis-(4-bromo-phenoxy)-but-2-enitrile (2g): Using general procedure B, (4-bromo-phenoxy)-acetonitrile (**1g**) (0.51 g, 2.4 mmol) was converted into 0.46 g (90%) of **2g** as a white solid: mp 130–133 °C; R_f = 0.24 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.50–7.45 (m, 4H), 6.91–6.76 (m, 4H), 4.87 (s, 2H), 4.75 (bs, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 156.6, 155.3, 146.1, 133.2, 133.1, 117.7, 117.1, 116.3, 115.8, 115.3, 102.6, 64.6; IR (film) 3480, 3369, 3069, 2946, 2193, 1646, 1580, 1482, 1412, 1283, 1225, 1206, 1169, 1100, 1070, 1039, 1006, 821 cm⁻¹; HRMS (FAB⁺) m/z 444.9152 (444.9163 calc. for C₁₆H₁₂N₂O₂Br₂Na, M + Na⁺).

3-Amino-2,4-bis-(3-trifluoromethyl-phenoxy)-but-2-enitrile (2h): Using general procedure B, (3-

trifluoromethyl-phenoxy)-acetonitrile (**1h**) (0.62 g, 3.1 mmol) was converted into 0.57 g (92%) of **2h** as a white solid: mp 82–85 °C; R_f = 0.14 (25% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.55–7.18 (m, 8H), 4.98 (s, 2H), 4.81 (bs, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 157.5, 156.3, 146.1, 132.9 (q, J = 130 Hz), 132.8 (q, J = 130 Hz), 131.0, 130.9, 124.0 (q, J = 1086 Hz), 123.9 (q, J = 1082 Hz), 120.7 (q, J = 14 Hz), 119.6 (q, J = 14 Hz), 119.0, 118.2, 115.6, 113.1 (q, J = 14 Hz), 112.6 (q, J = 14 Hz), 102.3, 64.6; IR (KBr) 3492, 3342, 2188, 1640, 1596, 1493, 1453, 1405, 1384, 1330, 1308, 1285, 1233, 1166, 1123, 1100, 1059, 885, 787, 751, 698, 658, 538 cm^{-1} ; HRMS (TOF/electrospray) m/z 425.0696 (425.0701 calc. for $\text{C}_{18}\text{H}_{12}\text{F}_6\text{N}_2\text{O}_2\text{Na}$, $\text{M}+\text{Na}^+$).

3-Amino-2,4-bis-(4-methoxy-phenoxy)-but-2-enitrile (2i): Using general procedure B, (4-methoxy-phenoxy)-acetonitrile (**1i**), (0.67 g, 4.1 mmol) was converted into 0.59 g (89%) of **2i** as a white solid: mp 71–73 °C; R_f = 0.11 (25%

EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 6.98–6.83 (m, 8H), 4.84 (s, 2H), 4.73 (bs, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.1, 155.3, 151.6, 150.1, 146.1, 117.0, 116.6, 116.4, 115.3, 115.3, 103.6, 65.3, 56.1; IR (film) 3472, 3354, 2951, 2836, 2192, 1648, 1504, 1464, 1403, 1296, 1197, 1106, 1034, 826, 717 cm^{-1} ; HRMS (TOF/electrospray) m/z 327.1348 (327.1345 calc. for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_4\text{Na}$, $\text{M}+\text{H}^+$).

General Procedure C.

1-Benzoyl-3-[2-(4-tert-butyl-phenoxy)-1-(4-tert-butyl-phenoxy)-2-cyano-vinyl]-urea (3a): Benzoyl isocyanate (0.053 g, 0.35 mmol) was added to a solution of 3-amino-2,4-bis-(4-tert-butyl-phenoxy)-but-2-enitrile (**2a**) (0.090 g, 0.24 mmol), CH_2Cl_2 (15 mL) and pyridine (0.08 mL,

0.98 mmol). The solution was stirred at rt for 2h, then diluted with CH_2Cl_2 (20 mL) and pH 7.0 buffer (20 mL). The organic layer was separated, washed with brine (20 mL), dried over Na_2SO_4 and concentrated to afford 0.12 g (92%) of **3a** as a white solid which required no further purification: mp 164–166 °C; R_f = 0.36 (25% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 11.29 (s, 1H), 8.64 (s, 1H), 7.95–6.84 (m, 13H), 5.37 (s, 0.9H), 5.03 (s, 0.1H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.3, 155.9, 152.9, 150.0, 147.9, 145.1, 136.9, 134.2, 131.9, 129.5, 129.4, 129.0, 128.1, 128.1, 128.0, 127.7, 127.3, 127.2, 126.8, 124.9, 121.0, 116.9, 116.5, 115.5, 115.0, 113.8, 64.0, 35.1, 34.8, 34.6, 31.9, 31.9; IR (film) 3247, 3141, 3038, 2963, 2215, 1710, 1643, 1603, 1508, 1468, 1393, 1364, 1264, 1237, 1210, 1175, 1112, 1014, 910, 830, 733, 705 cm^{-1} ; HRMS (TOF/electrospray) m/z 526.2707 (526.2706 calc. for $\text{C}_{32}\text{H}_{35}\text{N}_3\text{O}_4$, $\text{M}+\text{H}^+$).

1-Benzoyl-3-(2-cyano-2-o-tolyloxy-1-o-tolyloxymethyl-vinyl)-urea (3b): Using general procedure C, 3-amino-2,4-bis-o-tolyloxy-but-2-enitrile (**2b**) (0.43 g, 1.5 mmol) was converted into 0.64 g (99%) of **3b** as a white solid without

further purification: mp 184–186 °C; R_f = 0.29 (25% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 11.38 (bs, 1H), 8.82–8.69 (m, 1H), 7.88–7.79 (m, 2H), 7.67–7.43 (m, 3H), 7.28–6.86 (m, 8H), 5.40 (s, 2H), 2.42 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.4, 156.3, 153.4, 150.2, 136.6, 134.2, 132.1, 131.8, 131.4, 129.5, 128.8, 128.2, 128.1, 127.5, 127.3, 125.0, 122.3, 116.4, 115.7, 113.6, 113.5, 64.1, 16.6, 16.4; IR (film) 3245, 3146, 2924, 2849, 2215, 1707, 1653, 1585, 1530, 1488, 1465, 1385, 1338, 1261, 1239, 1195, 1176, 1120, 1029, 908, 869, 749, 701, 672 cm^{-1} ; HRMS (TOF/electrospray) m/z 442.1780 (442.1767 calc. for $\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}_4$, $\text{M}+\text{H}^+$).

1-Benzoyl-3-[2-cyano-2-(naphthalen-2-yloxy)-1-(naphthalen-2-yloxymethyl)-vinyl]-urea (3c): Using general procedure C, 3-Amino-2,4-bis-(naphthalen-2-yloxy)-but-2-enenitrile (**2c**) (0.051 g, 0.14 mmol) was converted into 0.072 g (99%) of **3c** as a white solid following column chromatography (SiO_2 , 25% EtOAc/hexanes): mp 212–214 °C; R_f =

0.11 (25% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 11.46 (s, 1H), 8.51 (s, 1H), 7.90–7.76 (m, 7H), 7.64–7.25 (m, 12H), 5.58 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.2, 156.0, 152.9, 150.0, 137.7, 134.8, 134.3, 131.7, 131.1, 130.8, 130.2, 130.0, 129.5, 128.2, 128.1, 127.9, 127.8, 127.5, 127.3, 127.0, 125.7, 124.6, 119.3, 118.4, 115.8, 113.8, 112.1, 108.9, 63.9; IR (film) 3056, 2211, 1709, 1636, 1600, 1530, 1510, 1461, 1387, 1345, 1245, 1208, 1160, 1118, 1012, 954, 839, 743 cm^{-1} ; HRMS (TOF/electrospray) m/z 514.1765 (514.1767 calc. for $\text{C}_{32}\text{H}_{24}\text{N}_3\text{O}_4$, $\text{M}+\text{H}^+$).

1-Benzoyl-3-[2-cyano-2-(naphthalen-1-yloxy)-1-(2,6-dimethylphenoxy)-vinyl]-urea (3d): Using general procedure C, 3-Amino-2,4-bis-(naphthalen-1-yloxy)-but-2-enenitrile (**2d**) (0.22 g, 0.59 mmol) was converted into 0.30 g (99%) of **3d** as a white solid following column chromatography (SiO_2 , 25% EtOAc/hexanes) and recrystallization from EtOAc: mp 178–182 °C; R_f = 0.15 (25% EtOAc/hexanes); ^1H NMR (300 MHz, d_6 -DMSO) δ

11.64 (s, 1H), 11.30 (s, 1H), 8.28–8.19 (m, 2H), 8.08–7.72 (m, 5H), 7.71–7.30 (m, 10H), 7.25–7.13 (m, 2H), 5.61 (s, 2H); ^{13}C NMR (75 MHz, d_6 -DMSO) δ 170.1, 154.3, 150.9, 150.5, 139.5, 139.4, 135.3, 134.9, 134.2, 132.5, 129.5, 129.4, 129.3, 129.1, 128.7, 128.4, 128.3, 128.1, 127.6, 127.5, 127.0, 126.6, 126.4, 126.0, 125.5, 125.2, 122.5, 122.0, 121.8, 114.7, 114.5, 114.5, 111.0, 107.6, 64.9; IR (film) 2921, 2211, 1730, 1643, 1578, 1523, 1500, 1463, 1389, 1342, 1262, 1227, 1183, 1097, 1022, 771 cm^{-1} ; HRMS (TOF/electrospray) m/z 514.1770 (514.1767 calc. for $\text{C}_{32}\text{H}_{24}\text{N}_3\text{O}_4$, $\text{M}+\text{H}^+$).

1-Benzoyl-3-[2-cyano-2-(2,6-dimethylphenoxy)-1-(2,6-dimethylphenoxy)-vinyl]-urea (3e): Using general procedure C, 3-amino-2,4-bis-(2,6-dimethylphenoxy)-but-2-enenitrile (**2e**) (0.089 g, 0.28 mmol) was converted into 0.12 g (91%) of **3e** as a white solid following column chromatography

(SiO₂, 12.5% EtOAc/hexanes): mp 161–163 °C; *R_f* = 0.22 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 11.65 (bs, 1H), 10.00 (bs, 1H), 8.09–8.02 (m, 2H), 7.65–7.57 (m, 1H), 7.53–7.43 (m, 2H), 7.13–6.93 (m, 6H), 5.24 (s, 2H), 2.34 (s, 6H), 2.29 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 169.1, 155.0, 151.7, 151.4, 134.2, 132.0, 131.5, 131.4, 130.5, 129.6, 129.5, 129.4, 128.5, 126.9, 124.8, 120.0, 112.2, 67.1, 16.9, 16.5; IR (film) 3142, 2213, 1705, 1641, 1530, 1470, 1379, 1338, 1266, 1176, 1093, 990, 910, 770, 705 cm⁻¹; HRMS (TOF/electrospray) *m/z* 470.2071 (470.2080 calc. for C₂₈H₂₈N₃O₄, M+H⁺).

1-Benzoyl-3-[2-(2-*tert*-butyl-phenoxy)-1-(2-*tert*-butyl-phenoxy)-2-cyano-vinyl]-urea (3f): Using general procedure C, 3-amino-2,4-bis-(2-*tert*-butyl-phenoxy)-but-2-enenitrile (**2f**) (0.25 g, 0.69 mmol) was converted into 0.34 g (97%) of **3f** as a white solid following column chromatography (SiO₂, 25% EtOAc/hexanes): mp 81–84 °C; *R_f* = 0.13 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 11.40 (bs, 0.5

H), 10.84 (bs, 0.5H), 8.79 (bs, 0.5H), 8.61 (bs, 0.5H), 7.93–7.77 (m, 2H), 7.71–6.84 (m, 11H), 5.41 (s, 1H), 5.18 (s, 1H), 1.53 (s, 4.5H), 1.44 (s, 4.5H), 1.41 (s, 4.5H), 1.35 (s, 4.5H); ¹³C NMR (100 MHz, CDCl₃) δ 169.2, 168.9, 157.1, 156.9, 154.3, 153.9, 153.0, 151.6, 140.7, 140.0, 138.8, 138.7, 137.2, 136.4, 134.1, 132.0, 131.9, 131.0, 129.3, 129.3, 128.6, 128.5, 128.2, 128.2, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 125.4, 125.1, 121.9, 121.8, 121.7, 117.9, 117.3, 117.1, 113.4, 112.6, 112.4, 63.2, 61.6, 35.3, 35.2, 35.2, 35.0, 30.8, 30.7, 30.6, 30.3, 30.2; IR (film) 3233, 3144, 3067, 2995, 2959, 2912, 2670, 2253, 2217, 1789, 1709, 1648, 1600, 1579, 1529, 1500, 1485, 1442, 1393, 1362, 1336, 1263, 1209, 1135, 1092, 1056, 1023, 909, 866, 751, 707 cm⁻¹; HRMS (TOF/electrospray) *m/z* 526.2726 (526.2706 calc. for C₃₂H₃₇N₃O₄, M+H⁺).

1-Benzoyl-3-[2-(4-bromo-phenoxy)-1-(4-bromo-phenoxy)-2-cyano-vinyl]-urea (3g): Using general procedure C, 3-amino-2,4-bis-(4-bromo-phenoxy)-but-2-enenitrile (**2g**) (0.19 g, 0.46 mmol) was converted into 0.23 g (88%) of **3g** as a white solid following column chromatography (SiO₂, 25%

EtOAc/hexanes): mp 183–187 °C; *R_f* = 0.26 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 11.35 (bs, 1H), 8.23 (bs, 1H), 7.83–7.79 (m, 2H), 7.66–7.62 (m, 1H), 7.56–7.41 (m, 6H), 7.10–6.89 (m, 4H), 5.35 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 168.3, 157.3, 154.2, 149.7, 137.5, 134.4, 133.4, 132.9, 131.6, 129.6, 127.9, 119.0, 117.9, 117.7, 115.4, 114.9, 113.4, 64.1; IR (film) 2208, 1712, 1642, 1576, 1522, 1482, 1398, 1339, 1258, 1231, 1204, 1070, 1008, 817 cm⁻¹; HRMS (FAB⁺) *m/z* 487.9210 (487.9221 calc. for C₁₇H₁₃Br₂N₃O₃Na, M-Bz(C₆H₅C=O)+H+Na⁺).

1-Benzoyl-3-[2-cyano-2-(3-trifluoromethyl-phenoxy)-1-(3-trifluoromethyl-phenoxy)-vinyl]-urea (3h): Using general procedure C, 3-amino-2,4-bis-(3-trifluoromethyl-phenoxy)-but-2-enenitrile (**2h**) (0.25 g, 0.62 mmol) was converted into 0.32 g (94%) of **3h** as a

white solid following column chromatography (SiO₂, 25% EtOAc/hexanes): mp 134–137 °C; *R_f* = 0.13 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 11.56 (bs, 1H), 8.85 (bs, 1H), 7.97–7.80 (m, 2H), 7.67–7.06 (m, 11H), 5.42 (s, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 168.6, 158.2, 155.2, 150.2, 137.7, 134.5, 133.0 (q, *J* = 131 Hz), 132.5 (q, *J* = 130 Hz), 131.5, 131.2, 130.7, 129.5, 128.1, 124.2 (q, *J* = 1084 Hz), 123.8 (q, *J* = 1084 Hz), 122.0 (q, *J* = 141 Hz), 120.4, 119.3 (q, *J* = 135 Hz), 118.9, 115.2, 114.7 (q, *J* = 153 Hz), 113.2, 112.8 (q, *J* = 165 Hz), 63.9; IR (film) 3245, 3144, 2217, 1714, 1645, 1595, 1530, 1451, 1396, 1326, 1284, 1261, 1171, 1125, 1097, 1065, 1031, 886, 793, 752, 696, 655 cm⁻¹; HRMS (TOF/electrospray) *m/z* 550.1201 (550.1202 calc. for C₂₆H₁₈F₆N₃O₄, M+H⁺).

1-Benzoyl-3-[2-cyano-2-(4-methoxy-phenoxy)-1-(4-methoxy-phenoxy)methyl]-vinyl]-urea (3i):

Using general procedure C, 3-amino-2,4-bis-(4-methoxy-phenoxy)-but-2-enenitrile (**2i**) (0.25 g, 0.77 mmol) was converted into 0.36 g (98%) of **3i** as a white solid following column chromatography (SiO₂, 50% EtOAc/hexanes): mp 154–157 °C; *R_f* = 0.25 (50% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 11.27 (bs, 1H), 8.30 (bs, 1H), 7.87–7.81 (m, 2H), 7.68–7.47 (m, 3H), 7.06–6.84 (m, 8H), 5.32 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.9, 157.1, 155.4, 151.9, 151.1, 149.0, 136.1, 134.2, 131.9, 129.3, 128.4, 118.9, 118.1, 117.5, 115.3, 115.1, 113.7, 65.4, 56.1, 56.0; IR (film) 3233, 3144, 2950, 2836, 2215, 1707, 1646, 1598, 1532, 1504, 1467, 1341, 1242, 1195, 1103, 1071, 1032, 908, 825, 756 cm⁻¹; HRMS (TOF/electrospray) *m/z* 474.1679 (474.1665 calc. for C₂₆H₂₄N₃O₆, M+H⁺).

General Procedure D.

4-Amino-5-(4-tert-butyl-phenoxy)-6-(4-tert-butyl-phenoxy)methyl)-1H-pyrimidin-2-one (4a):

NaH (60% suspension, 0.030 mg, 0.75 mmol) was added to a solution of 1-benzoyl-3-[2-(4-tert-butyl-phenoxy)-1-(4-tert-butyl-phenoxy)methyl]-2-cyano-vinyl]-urea (**3a**) (0.041 g, 0.077 mmol), EtOH (4.0 mL) and benzene (4.0 mL). After stirring for 1/2h at rt, the mixture was heated to reflux for 1/2h, then cooled to rt and diluted with H₂O (10 mL) and CH₂Cl₂ (10 mL). The organic layer was separated, washed with sat'd NaCl (10 mL), dried over Na₂SO₄ and concentrated. Recrystallization from CH₃CN affords 0.023 g (70%) of the title compound **4a** as a white solid: mp 154–157 °C; *R_f* = 0.28 (90:9:1 CHCl₃/ MeOH/NH₄OH); ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.24 (m, 4H), 6.94–6.74 (m, 4H), 4.89 (s, 2H), 1.31 (s, 9H), 1.29 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 154.3, 127.1, 127.0, 126.5, 126.3, 114.2, 114.2, 114.0, 113.9, 34.3, 34.3, 34.1, 31.4; IR (film) 3482, 3296, 3051, 2961, 2867, 1665, 1612, 1550, 1511, 1364, 1294, 1244, 1217, 1185, 1169, 1113, 1080, 1013, 863, 829, 727 cm⁻¹; HRMS (TOF/electrospray) *m/z* 422.2457 (422.2444 calc. for C₂₅H₃₂N₃O₃, M+H⁺).

4-Amino-5-*o*-tolylloxy-6-*o*-tolylloxymethyl-1*H*-pyrimidin-2-one (4b): Using general procedure D, 1-benzoyl-3-(2-cyano-2-*o*-tolylloxy-1-*o*-tolylloxymethyl-vinyl)-urea (**3b**) (0.15 g, 0.34 mmol) was converted into 0.11 g (92%) of **4b** as a white solid following column chromatography (SiO₂, 70:24:5:1 CH₂Cl₂/CHCl₃/MeOH/NH₄OH): mp 280 °C dec.; *R_f* = 0.19 (50:45:4.5:0.5 CH₂Cl₂/CHCl₃/MeOH/NH₄OH); ¹H NMR (300 MHz, d₆-DMSO) δ 10.75 (bs, 1H), 7.46 (bs, 1H), 7.21–7.03 (m, 4H), 6.95–6.78 (m, 4H), 6.64–6.57 (m, 1H), 4.61 (s, 2H), 2.25 (s, 3H), 1.98 (s, 3H); ¹³C NMR (100 MHz, d₆-DMSO) δ 162.7, 156.7, 156.4, 131.8, 131.3, 127.8, 127.7, 127.1, 126.9, 122.8, 121.9, 112.5, 112.3, 62.1, 16.8, 16.6; IR (KBr) 3468, 3022, 2919, 2850, 1670, 1625, 1542, 1491, 1414, 1384, 1330, 1290, 1242, 1224, 1208, 1177, 1113, 1088, 1037, 866, 744, 710, 659, 560, 508 cm⁻¹; HRMS (TOF/electrospray) *m/z* 338.1509 (338.1505 calc. for C₁₉H₂₀N₃O₃, M+H⁺).

4-Amino-5-(naphthalen-2-yloxy)-6-(naphthalen-2-yloxymethyl)-1*H*-pyrimidin-2-one (4c): Using general procedure D, 1-benzoyl-3-[2-cyano-2-(naphthalen-2-yloxy)-1-(naphthalen-2-yloxymethyl)-vinyl]-urea (**3c**) (0.036 g, 0.069 mmol) was converted into 0.027 g (94%) of **4c** as a white solid without any further purification: mp 235 °C dec.; *R_f* = 0.10 (5% MeOH/CH₂Cl₂); ¹H NMR (300 MHz, d₆-DMSO) δ 10.85 (bs, 1H), 7.93–7.60 (m, 6H), 7.54–7.21 (m, 8H), 7.10–6.85 (m, 2H), 4.82 (s, 2H); ¹³C NMR (100 MHz, d₆-DMSO) δ 162.6, 156.4, 156.4, 134.7, 134.6, 130.5, 130.3, 130.1, 129.6, 128.4, 128.3, 127.9, 127.5, 127.5, 127.3, 125.3, 124.8, 119.3, 118.9, 109.4, 107.8, 62.0; IR (film) 3462, 3058, 1651, 1601, 1508, 1469, 1385, 1359, 1324, 1273, 1246, 1216, 1177, 1071, 1029, 960, 910, 838, 813, 742, 533, 504, 474 cm⁻¹; HRMS (FAB⁺) *m/z* 432.1310 (432.1324 calc. for C₂₅H₂₀N₃O₃Na, M+Na⁺).

4-Amino-5-(naphthalen-1-yloxy)-6-(naphthalen-1-yloxymethyl)-1*H*-pyrimidin-2-one (4d): Using general procedure D, 1-benzoyl-3-[2-cyano-2-(naphthalen-1-yloxy)-1-(naphthalen-1-yloxymethyl)-vinyl]-urea (**3d**) (0.031 g, 0.16 mmol) was converted into 0.054 g (83%) of **4d** as a light red solid following flash chromatography (SiO₂, 90:9:1 CHCl₃/MeOH/NH₄OH) : mp 225 °C dec.; *R_f* = 0.10 (90:9:1 CHCl₃/MeOH/NH₄OH); ¹H NMR (300 MHz, d₆-DMSO) δ 10.97 (bs, 1H), 8.28–8.17 (m, 1H), 7.91–7.74 (m, 3H), 7.57–7.18 (m, 9H), 6.99 (bs, 2H), 6.85–6.76 (m, 3H), 4.85 (s, 2H); ¹³C NMR (100 MHz, d₆-DMSO) δ 162.6, 154.2, 154.0, 135.1, 134.8, 128.2, 128.1, 127.5, 127.4, 126.8, 126.7, 126.4, 126.1, 125.6, 125.2, 123.1, 122.7, 122.6, 122.6, 121.6, 107.5, 107.4, 106.4, 62.5; IR (film) 3474, 3056, 1651, 1578, 1485, 1462, 1394, 1269, 1226, 1153, 1100, 1044, 1017, 884, 789, 769, 558 cm⁻¹; HRMS (TOF/electrospray) *m/z* 410.1512 (410.1505 calc. for C₂₅H₂₀N₃O₃, M+H⁺).

4-Amino-5-(2,6-dimethyl-phenoxy)-6-(2,6-dimethyl-phenoxy-methyl)-1H-pyrimidin-2-one (4e): Using general procedure D, 1-benzoyl-3-[2-cyano-2-(2,6-dimethyl-phenoxy)-1-(2,6-dimethyl-phenoxy-methyl)-vinyl]-urea (**3e**) (0.12 g, 0.25 mmol) was converted into 0.036 g (40%) of **4e** as a white solid without further purification: mp 250 °C dec.; R_f = 0.10 (70:24:5.4:0.6 CH₂Cl₂/CHCl₃/MeOH/NH₄OH); ¹H NMR (300 MHz, CDCl₃/CD₃OD) δ 6.98–6.85 (m, 6H), 4.15 (s, 2H), 2.13 (s, 6H), 2.04 (s, 6H); ¹³C NMR (100 MHz, CDCl₃/CD₃OD) δ 154.5, 152.8, 130.7, 130.3, 129.5, 128.8, 125.5, 125.3, 63.8, 17.0, 16.4; IR (KBr) 3457, 3030, 2930, 2850, 1647, 1552, 1476, 1366, 1316, 1264, 1201, 1093, 1022, 992, 862, 793, 775, 662, 633, 535 cm⁻¹; HRMS (TOF/electrospray) m/z 366.1828 (366.1818 calc. for C₂₁H₂₄N₃O₃, M+H⁺).

4-Amino-5-(2-tert-butyl-phenoxy)-6-(2-tert-butyl-phenoxy-methyl)-1H-pyrimidin-2-one (4f): Using general procedure D, 1-benzoyl-3-[2-(2-tert-butyl-phenoxy)-1-(2-tert-butyl-phenoxy-methyl)-2-cyano-vinyl]-urea (**3f**) (0.14 g, 0.27 mmol) was converted into 0.086 g (75%) of **4f** as a white solid following column chromatography (SiO₂, 50:40:9:1 CH₂Cl₂/CHCl₃/MeOH/NH₄OH): mp 265 °C dec.; R_f = 0.36 (50:40:9:1 CH₂Cl₂/CHCl₃/MeOH/NH₄OH); ¹H NMR (300 MHz, d₆-DMSO) δ 10.80 (bs, 1H), 7.30–6.64 (m, 8H), 4.58 (d, 1H, J = 10.3 Hz), 4.49 (d, 1H, J = 10.3 Hz), 1.29 (s, 6H), 1.25 (s, 6H); ¹³C NMR (100 MHz, d₆-DMSO) δ 162.6, 157.6, 156.7, 137.9, 137.7, 128.3, 128.1, 127.9, 127.1, 123.2, 122.3, 121.6, 113.6, 112.8, 61.8, 35.3, 35.2, 30.6; IR (KBr) 3488, 2958, 2862, 1664, 1486, 1442, 1385, 1353, 1295, 1250, 1210, 1135, 1088, 1055, 1020, 866, 825, 749 cm⁻¹; HRMS (TOF/electrospray) m/z 422.2439 (422.2444 calc. for C₂₅H₃₂N₃O₃, M+H⁺).

4-Amino-5-(4-bromo-phenoxy)-6-(4-bromo-phenoxy-methyl)-1H-pyrimidin-2-one (4g): Using general procedure D, 1-benzoyl-3-[2-(4-bromo-phenoxy)-1-(4-bromo-phenoxy-methyl)-2-cyano-vinyl]-urea (**3g**) (0.23 g, 0.40 mmol) was converted into 0.13 g (69%) of **4g** as a white solid following column chromatography (SiO₂, 90:9:1 CHCl₃/MeOH/NH₄OH) and reduced pressure (20 mTorr) sublimation at 60 °C: mp 260 °C dec.; R_f = 0.45 (80:18:2 CHCl₃/MeOH/NH₄OH); ¹H NMR (300 MHz, d₆-DMSO) δ 7.47–7.34 (m, 4H), 6.90–6.77 (m, 4H), 4.64 (s, 2H); ¹³C NMR (100 MHz, d₆-DMSO) δ 157.8, 133.1, 132.9, 118.3, 117.8, 114.8, 113.7; IR (KBr) 3390, 3064, 1869, 1630, 1482, 1462, 1433, 1393, 1328, 1286, 1227, 1207, 1161, 1072, 1008, 822, 794, 748, 724, 590, 550, 507 cm⁻¹; HRMS (FAB⁺) m/z 487.9235 (487.9221 calc. for C₁₇H₁₃Br₂N₃O₃Na, M+Na⁺).

An improved overall yield of **4g** was obtained by submission of compound **2g** (0.19 g, 0.46 mmol) to general procedure C then, after concentration of the reaction

mixture, the residue was reacted directly using general procedure D to afford 0.16 g (76% overall from **2g**) of compound **4g**.

4-Amino-5-(3-trifluoromethyl-phenoxy)-6-(3-trifluoromethyl-phenoxy)-1H-pyrimidin-2-one (4h):

Using general procedure D, 1-benzoyl-3-[2-cyano-2-(3-trifluoromethyl-phenoxy)-1-(3-trifluoromethyl-phenoxy)-vinyl]-urea (**3h**) (0.09 g, 0.17 mmol) was converted into 0.08 g (99%) of **4h** as a white solid following column chromatography (SiO₂, 50:40:9:1 CH₂Cl₂/CHCl₃/MeOH/NH₄OH): mp 245 °C dec.; R_f = 0.17 (50:45:4.5:0.5 CH₂Cl₂/CHCl₃/MeOH/NH₄OH); ¹H NMR (300 MHz, d₆-DMSO) δ 10.86 (bs, 1H), 7.56–6.97 (m, 8H), 4.81 (s, 2H); ¹³C NMR (100 MHz, d₆-DMSO) δ 162.3, 158.8, 158.6, 131.7, 131.5, 131.2, 131.2, 130.8, 130.7, 126.5, 122.9, 122.8, 122.5, 119.8, 119.2, 118.7, 113.1, 112.3, 62.7; IR (KBr) 3475, 3071, 1697, 1667, 1617, 1492, 1452, 1387, 1329, 1215, 1173, 1126, 1066, 906, 883, 789, 697, 656 cm⁻¹; HRMS (TOF/electrospray) *m/z* 446.0937 (446.0939 calc. for C₁₉H₁₄F₆N₃O₃, M+H⁺).

4-Amino-5-(4-methoxy-phenoxy)-6-(4-methoxy-phenoxy)-1H-pyrimidin-2-one (4i):

Using general procedure D, 1-benzoyl-3-[2-cyano-2-(4-methoxy-phenoxy)-1-(4-methoxy-phenoxy)-vinyl]-urea (**3i**) (0.11 g, 0.24 mmol) was converted into 0.068 g (78%) of **4i** as a white solid following column chromatography (SiO₂, 50:40:9:1 CH₂Cl₂/CHCl₃/MeOH/NH₄OH): mp 255 °C dec.; R_f = 0.23 (50:45:4.5:0.5 CH₂Cl₂/CHCl₃/MeOH/NH₄OH); ¹H NMR (300 MHz, d₆-DMSO) δ 10.71 (bs, 1H), 7.50 (bs, 1H), 6.86–6.80 (m, 8H), 6.80 (bs, 1H), 4.60 (s, 2H), 3.69 (s, 3H), 3.67 (s, 3H); ¹³C NMR (100 MHz, d₆-DMSO) δ 162.8, 156.3, 155.5, 154.8, 152.5, 152.3, 143.2, 123.2, 116.7, 116.7, 115.5, 115.3, 62.5, 56.3, 55.8; IR (KBr) 3400, 3104, 2942, 2839, 1639, 1506, 1462, 1439, 1385, 1327, 1238, 1214, 1186, 1106, 1035, 828, 717, 533 cm⁻¹; HRMS (TOF/electrospray) *m/z* 370.1410 (370.1403 calc. for C₁₉H₂₀N₃O₅, M+H⁺).

(2-Cyanomethoxy-phenoxy)-acetonitrile (5):

Using general procedure A, catechol (0.99 g, 8.95 mmol) was converted into 1.55 g (92%) of **5** as a white solid without further purification: mp 82–84°C; R_f = 0.14 (25% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.20–7.10 (m, 4H), 4.84 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 147.5, 125.1, 117.3, 115.3, 55.7; IR (film) 3003, 1596, 1502, 1459, 1442, 1359, 1329, 1294, 1263, 1240, 1197, 1135, 1064, 1043, 900, 742 cm⁻¹; HRMS (EI⁺) *m/z* 188.0581 (188.0586 calc. for C₁₀H₈N₂O₂, M⁺).

3-Amino-4H-benzo[b][1,4]dioxepine-2-carbonitrile (6):

Using general procedure B, (2-cyanomethoxy-phenoxy)-acetonitrile (**5**) (0.11 g, 0.58 mmol) was converted into 0.08 g (73%) of **6** as a tan solid following flash chromatography (25% EtOAc/hexanes): mp

160–162 °C; R_f = 0.13 (25% EtOAc/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.08–6.98 (m, 2H), 6.94–6.87 (m, 2H), 4.87 (s, 2H), 4.07 (bs, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.5, 148.4, 147.5, 125.8, 123.1, 122.2, 120.8, 115.0, 110.2, 68.0; IR (film) 3458, 3350, 2189, 1651, 1549, 1494, 1450, 1415, 1301, 1265, 1246, 1174, 1106, 1047, 1013, 962, 930, 850, 776, 740 cm^{-1} ; HRMS (EI) m/z 188.0578 (188.0586 calc. for $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2$, M^+).

1-Benzoyl-3-(4-cyano-2H-benzo[b][1,4]dioxepin-3-yl)-urea (7):

Using general procedure C, 3-amino-4H-benzo[b][1,4]dioxepine-2-carbonitrile (**6**) (0.052 g, 0.28 mmol) was converted into 0.090 g (96%) of **7** as a white solid following column chromatography (SiO_2 , 75:20:4.5:0.5 $\text{CH}_2\text{Cl}_2/\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$): 204 °C dec.; R_f = 0.67 (95:4.5:0.5 $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$); ^1H NMR (300 MHz, d_6 -DMSO) δ 11.29 (bs, 1H), 10.39 (bs, 1H), 8.03–7.96 (m, 2H), 7.70–7.09 (m, 7H), 5.03 (s, 2H); ^{13}C NMR (100 MHz, d_6 -DMSO) δ 169.4, 152.4, 149.9, 149.5, 136.3, 134.2, 132.7, 129.5, 129.2, 127.5, 125.7, 125.6, 123.1, 122.1, 114.3, 70.6; IR (KBr) 3441, 3264, 2219, 1695, 1603, 1535, 1495, 1463, 1384, 1311, 1264, 1247, 1199, 1108, 1070, 1038, 903, 801, 761, 703 cm^{-1} ; HRMS (TOF/electrospray) m/z 336.0993 (336.0984 calc. for $\text{C}_{18}\text{H}_{14}\text{N}_3\text{O}_4$, $\text{M}+\text{H}^+$).

4-Amino-1H,11H-5,10-dioxo-1,3-diazadibenzo[a,d]cyclohepten-2-one (8):

Using general procedure D, 1-benzoyl-3-(4-cyano-2H-benzo[b][1,4]dioxepin-3-yl)-urea (**7**) (0.08 g, 0.24 mmol) was converted into 0.04 g (70%) of **8** as a white solid following column chromatography (SiO_2 , 90:9:1 $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$): mp 265 °C dec.; R_f = 0.10 (90:9:1 $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$); ^1H NMR (300 MHz, d_6 -DMSO) δ 9.45 (bs, 1H), 7.95–7.00 (m, 4H), 4.93 (s, 2H); ^{13}C NMR (100 MHz, d_6 -DMSO) δ 161.1, 155.7, 149.6, 149.4, 130.1, 129.2, 126.6, 126.1, 125.1, 122.8, 122.6, 67.7; IR (KBr) 3474, 3062, 1678, 1495, 1458, 1385, 1330, 1307, 1247, 1203, 1104, 1049, 874, 812, 769, 698, 548 cm^{-1} ; HRMS (TOF/electrospray) m/z 232.0720 (232.0722 calc. for $\text{C}_{11}\text{H}_{10}\text{N}_3\text{O}_3$, $\text{M}+\text{H}^+$).

1-Benzoyl-3-(2'-cyano-2'-fluoro-1'-fluoromethyl-vinyl)-urea (11):

Potassium *t*-pentylate (3.80 ml, 6.47 mmol, 1.70 M in toluene) was slowly added along the wall of the reaction vessel to a 0 °C solution of fluoroacetonitrile (**9**) (0.30 ml, 5.39 mmol) and anhydrous THF (33.0 ml). The reaction mixture was stirred at 0 °C for 2 h then diluted with Et_2O (100 ml). The organic layer was washed sequentially with water (2 $\times$ 100 ml) and brine (100 ml), then dried (Na_2SO_4). Concentration under reduced pressure gave 1.58 grams of a mixture of 2-amino-1-cyano-1,3-difluoropropene (**10**) and solvent as a yellow oil. The mixture was acylated without further purification. Residual solvent can be removed by fractional distillation to allow isolation of pure 2-amino-1-cyano-1,3-difluoropropene (**10**).

Benzoyl isocyanate (0.347 mmol, 0.51 g) was added to a solution of unpurified **10**, pyridine (10.5 mmol, 0.89 ml) and CH_2Cl_2 (15.0 ml) at room temperature. The reaction

mixture was stirred at room temperature for 3 hours, then diluted with CHCl_3 (100 ml). The organic layer was washed sequentially with water (2 $\times$ 100 ml) and brine (100 ml) and dried (Na_2SO_4). Concentration under reduced pressure provided 0.638 g of yellow crystals. Purification via silica gel chromatography (90% CHCl_3 , 9% MeOH and 1% NH_4OH) provided 556 mg of 1-Benzoyl-3-(2'-cyano-2'-fluoro-1'-fluoromethyl-vinyl)-urea (**11**) (78% yield from **9**) as white crystals: mp: 193–195 °C; R_f 0.25 (25% EtOAc/hexanes); ^1H NMR (300 MHz, d_6 -DMSO) δ 11.47 (s, 1H), 11.27 (s, 1H), 8.03–7.94 (m, 2H), 7.71–7.47 (m, 3H), 7.53 (t, 1H, $J = 7.92$ Hz) 5.57 (dd, 2H, $J_{\text{HF}} = 46.12$, 3.71 Hz); ^{13}C (75 MHz, d_6 -DMSO) δ 170.1, 150.2, 134.4, 133.7 (dd, $J_{\text{CF}} = 37.5$, 27.8 Hz), 132.5, 129.5, 129.4, 123.8 (dd, $J_{\text{CF}} = 232.7$, 11.1 Hz), 112.4 (dd, $J_{\text{CF}} = 39.5$, 3.4 Hz), 77.5 (d, $J_{\text{CF}} = 171$ Hz); IR (KBr pellet) 3274, 3114, 3034, 2975, 2226, 1716, 1660, 1600, 1555, 1524, 1472, 1392, 1347, 1260, 1199; HRMS (EI^+) m/z 265.0662 (265.0662 calc. for $\text{C}_{12}\text{H}_9\text{F}_2\text{N}_3\text{O}_2$, M^+).

Characterization data for **2-Amino-1-cyano-1,3-difluoropropene (10)**: R_f 0.25 (25% EtOAc/hexanes); ^1H NMR (300 MHz, d_6 -DMSO) δ 6.14 (s, 2H), 5.05 (dd, 2H, $J_{\text{HF}} = 47.2$, 2.6 Hz); ^{13}C (100 MHz, d_6 -DMSO) δ 140.0, 118.1, 116.1, 114.3, 79.9; IR (film) 3409, 3370, 3228, 2966, 2925, 2852, 2206, 1671, 1618, 1464, 1406, 1365, 1239, 1182, 1025; HRMS (EI^+) m/z 118.0340 (118.0343 calc. for $\text{C}_4\text{H}_4\text{F}_2\text{N}_2$, M^+).

5-Fluoro-6-fluoromethyl-cytosine (12): NaH (60%, 18.6 mg, 0.465 mmol) was added to a solution of **11** (102 mg, 0.397 mmol), EtOH (25 ml) and benzene (15 ml). The reaction mixture was heated to reflux for 20 h, cooled to room temperature, mixed with SiO_2 gel (4 ml), and concentrated under reduced pressure. The mixture of **12** and SiO_2 was then dry-loaded onto a column and eluted (80% CHCl_3 , 18% MeOH and 2% NH_4OH) to give 501 mg (78%) of the desired product as white crystals: mp 203–205 °C (dec.); R_f 0.10 (80% CHCl_3 , 18% MeOH, 2% NH_4OH); ^1H (300 MHz, d_6 -DMSO) δ 7.55 (s, 1H), 5.21 (dd, 2H, $J_{\text{HF}} = 47.06$, 2.21 Hz); ^{13}C (75 MHz, d_6 -DMSO) δ 158.7 (d, $J_{\text{CF}} = 13.3$ Hz), 156.1, 136.9–133.6 (dd, $J_{\text{CF}} = 243.5$, 5.8 Hz), 135.2–134.6 (m), 129.8 (d, $J_{\text{CF}} = 51.9$ Hz), 75.8 (d, $J_{\text{CF}} = 165.4$ Hz); IR (KBr pellet) 3450, 3040, 2983, 2854, 2775, 1693, 1648, 1552, 1490, 1472, 1397, 1339, 1260, 1215, 1096; HRMS (EI^+) m/z 161.0400 (161.0401 calc. for $\text{C}_5\text{H}_5\text{F}_2\text{N}_3\text{O}$, M^+).