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Chemistry & Drug Discovery

Supporting Information

A Novel Synthetic Route for the Anti-HIV Drug MC-1220 and its Analogues

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Contents

Materials and Methods

General

NMR spectra were recorded on a Varian Gemini 2000 NMR spectrophotometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C with TMS as an internal standard. EI mass spectra were recorded on a Finnigan MAT SSQ 710. MALDI spectra were recorded on a 4.7 T Ultima Fourier transform Mass spectrometer (IonSpec, Irvine, CA). Melting points were determined in a Büchi melting point apparatus. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from Merck. Microanalyses were carried out at Chemical Laboratory II at University of Copenhagen, Denmark.

Cell-based assays

Compounds, Cells and Viruses

Compounds were dissolved in DMSO at 100 mM and then diluted in culture medium.

Cell lines were purchased from American Type Culture Collection (ATCC). The absence of mycoplasma contamination was checked periodically by the Hoechst staining method. Cell lines supporting the multiplication of RNA viruses were the $CD4^+$ human T-cells containing an integrated HTLV-1 genome (MT-4).

Cytotoxicity Assays

For cytotoxicity evaluations, exponentially growing cells derived from human haematological tumors [$CD4^+$ human T-cells containing an integrated HTLV-1 genome (MT-4)] were seeded at an initial density of 1×10^5 cells/mL in 96 well plates in RPMI-1640 medium supplemented with 10% fetal calf serum (FCS), 100 units/mL penicillin G and 100 µg/mL streptomycin. Cell cultures were then incubated at 37°C in a humidified, 5% CO_2 atmosphere in the absence or presence of serial dilutions of test compounds. Cell viability was determined after 96 h at 37°C by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) method .[21]

Antiviral assays

Activity of compounds against Human Immunodeficiency virus type-1 (HIV-1) was based on inhibition of virus-induced cytopathogenicity in MT-4 cells acutely infected with a multiplicity of

infection (m.o.i.) of 0.01. Briefly, 50 μL of RPMI containing $1x10^4$ MT-4 were added to each well of flat-bottom microtitre trays containing 50 μL of RPMI, without or with serial dilutions of test compounds. Then, 20 μL of an HIV-1 suspension containing 100 $CCID_{50}$ were added. After 4-day incubation, cell viability was determined by the MTT method.

Synthetic Procedures

General procedure for the synthesis of 2-(6-chloro-2-(dimethylamino)-5-methylpyrimidin-4-yl)-2-(aryl)acetonitriles 2a-c: To a mixture of compound **1** (1.0 g, 5.0 mmol) and the appropriate benzyl cyanide derivative (5.5 mmol) in dry dimethylformamide (20 mL) was added sodium hydride (55% suspension in paraffin oil, 0.655 g, 15.0 mmol) portionwise at room temperature. After stirring for 1 h under dry conditions, the reaction mixture was quenched by addition of water (2 mL) dropwise. Then the solution was poured on cold water (50 mL) and neutralized with 4M hydrochloric acid. Then ether (40 mL) was added to the mixture and the two layers were separated. The ether layer was dried (magnesium sulfate) and evaporated under reduced pressure to afford compounds **2a-c** as pure solids.

[6-Chloro-2-(dimethylamino)-5-methylpyrimidin-4-yl](2,6-difluoro-phenyl) acetonitrile (2a): Yield: 1.56 g, 97%; m.p.: 120–122°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3H, CH_3), 3.08 (s, 6H, $(CH_3)_2N$)), 5.54 (s, 1H, CH-CN), 6.96 (t, 2H, *J* = 8.3 Hz, H_{arom}), 7.31–7.41 (m, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.21 (CH_3), 32.17 (*C*H-CN), 36.71 ($(CH_3)_2N$), 109.75 (t, *J* = 17.2 Hz, C_{arom}), 111.79 (dd, *J* = 3.0, 22.5 Hz, C_{arom}), 112.04 (C5), 115.67 (CN), 130.96 (t, *J* = 40.5 Hz, C_{arom}), 159.46 (C6), 159.60 (C4), 162.31 (C2), 160.74 (dd, *J* = 6.6, 252.2 Hz, C_{arom}); HR-MALDI MS *m/z* calcd for $C_{15}H_{14}ClF_2N_4$: 323.0875 $[M+H]^+$, found 323.0863. Anal. calcd for $C_{15}H_{14}ClF_2N_4$ (322.74): C 55.82, H 4.06, N 17.36, found: C 55.97, H 4.00, N 17.11.

2-(6-Chloro-2-(dimethylamino)-5-methylpyrimidin-4-yl)-2-(3,5-dimethylphenyl)acetonitrile 2b: Yield: 1.54 g, 98%; m.p.: 108–109°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10 (s, 3H, CH_3), 2.30 (s, 6H, $(CH_3)_2Ar$), 3.21 (s, 6H, $(CH_3)_2N$), 5.16 (s, 1H, CHCN), 6.95 (s, 1H, H_{arom}), 6.98 (s, 2H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.53 (CH_3), 21.24 ($(CH_3)_2Ar$), 36.94 ($(CH_3)_2N$), 43.24 (HCCN), 112.11 (C-5), 118.18 (CN), 125.54, 130.29, 132.66, 138.90 (C_{arom}), 159.68 (C-6), 162.32 (C-4), 162.42 (C-2); EI-MS *m/z* (%) 313.90 $[M]^+$ (100). Anal. calcd for $C_{17}H_{19}N_4Cl$: (313.90): C 64.86, H 6.08, N 17.80, found: C 64.75, H 6.14, N 17.98.

[6-Chloro-2-(dimethylamino)-5-methylpyrimidin-4-yl](mesityl)acetonitrile 2c: Yield: 1.41 g, 86%; m.p.: 140–142°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80 (s, 3H, CH_3-C5), 2.26 (s, 9H, 3 $(CH_3)_3$Ar), 3.18 (s, 6H, $(CH_3)_2$N), 5.50 (s, 1H, CH), 6.87 (s, 2H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.83 (CH_3-C5), 20.82 (CH_3Ar), 20.93 (($CH_3)_2$Ar), 36.84 (CH-CN), 40.13 (($CH_3)_2$N), 112.23 (C5), 117.08 (CN), 127.02, 130.34, 137.01, 138.41 (C_{arom}), 159.28 (C2), 162.28 (C4), 162.43 (C6); HR-MALDI MS *m/z* calcd for $C_{18}H_{22}ClN_4$ (329.1528) $[M+H]^+$, found 329.1525.

General procedure for the synthesis of 6-aryl-2-(dimethylamino)-5-methylpyrimidin-4(3H)-ones 3a-c: A solution of **2a-c** (2.5 mmol) in concentrated hydrochloric acid (20 mL), acetic acid (10 mL) and water (10 mL) was refluxed at 115°C for 40 h. The solvent was evaporated under reduced pressure, and the residual material was treated with water (20 mL) and neutralized with 10% sodium hydroxide. The solid product formed was filtered and dried to afford the pure compounds **3a-c**.

6-(2,6-Difluorobenzyl)-2-(dimethylamino)-5-methylpyrimidin-4(3H)-one 3a: Yield: 0.59 g, 84%; m.p.: 208–210°C [237–238°C (CH_3CN)] [20]; ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.94 (s, 3H, CH_3), 2.82 (s, 6H, $(CH_3)_2$N), 3.78 (s, 2H, C*H*$_2$Ar), 7.03 (t, 2H, *J* = 7.7 Hz, H_{arom}), 7.25–7.35 (m, 1H, H_{arom}); ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 9.66 (CH_3), 27.04 (*C*H_2Ph), 36.33 (($CH_3)_2$N), 110.62–110.95 (m, C_{arom}), 128.30 (t, *J* = 10.0 Hz, C_{arom}), 161.61 (dd, *J* = 8.3, 245.0 Hz, C_{arom}); HR-MALDI MS *m/z* calcd for $C_{14}H_{16}F_2N_3O$ (280.1256) $[M+H]^+$, found 280.1247. Anal. calcd for $C_{14}H_{15}F_2N_3O$ (279.29): C 60.21, H 5.41, N 15.05, found: C 59.93, H 5.32, N 14.71.

2-(Dimethylamino)-6-(3,5-dimethylbenzyl)-5-methylpyrimidin-4(3H)-one 3b: Yield: 0.60 g, 89% as a white solid; m.p.: 163–164°C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.83 (s, 3H, C*H*$_3$), 2.21 (s, 6H, (C*H*$_3)_2$Ar), 2.99 (s, 6H, (C*H*$_3)_2$N), 3.64 (s, 2H, C*H*$_2$), 6.79 (s, 1H, H_{arom}), 6.85 (s, 2H, H_{arom}), 10.89 (s, 1H, NH); ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 10.13 (CH_3), 20.88 ((*C*$H_3)_2$Ar), 36.82 (($CH_3)_2$N), 40.68 (CH_2), 126.29, 127.37, 136.95, 138.41 (C_{arom}); HR-MALDI MS *m/z* calcd for $C_{16}H_{22}N_3O$ (272.1757) $[M+H]^+$, found 272.1745.

2-(Dimethylamino)-6-(mesitylmethyl)-5-methylpyrimidin-4(3H)-one 3c: Yield: 0.58 g, 82%; m.p.: 223–225°C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.96 (s, 3H, CH_3-C5), 2.16 (s, 3H, C*H*$_3$Ar), 2.19 (s, 6H, (C*H*$_3)_2$Ar), 2.80 (s, 6H, $(CH_3)_2$N), 3.66 (s, 2H, C*H*$_2$Ar); ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 9.75 (*C*H_3-C5), 20.02 ((*C*$H_3)_2$Ar), 20.39 (*C*H_3Ar), 33.23 (*C*H_2Ar), 36.47 (($CH_3)_2$N), 127.82, 133.12, 133.96, 136.37 (C_{arom}), EI-MS *m/z* (%) 285 [M^+] (60), 270 (100).

Anal. calcd for $C_{17}H_{23}N_3O \times 0.2\ H_2O$ (289): C 70.65, H 8.16, N 14.54, found: C 70.55, H 8.23, N 14.21.

Synthesis of [6-chloro-2-(dimethylamino)-5-methylpyrimidin-4-yl](2,6-difluorophenyl) methanone 4a: Sodium (0.08 g, 3.7 mmol) was dissolved in methanol (3 mL) and added to a stirred solution of compound **2a** (1.00 g, 3.0 mmol) in dry toluene (40 mL). A stream of oxygen was bubbled through the reaction mixture with refluxing at 120°C for 12 h. The solvent was removed under reduced pressure. The residual material was treated with a mixture of petroleum ether/ether (5:1, v/v, 15 mL). The precipitated material was filtered and dried to afford 0.49 g of compound **4a**, yield: 52%; as greenish yellow crystals; m.p.: 118–120°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3H, CH_3), 3.00 (s, 6H, $(CH_3)_2N$), 6.94 (t, 2H, *J* = 8.1 Hz, H_{arom}), 7.38–7.47 (m, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.36 (CH_3), 36.76 ($(CH_3)_2N$), 111.41–111.75 (m, C_{arom}), 113.85 (C5), 132.65 (t, *J* = 10.4 Hz, C_{arom}), 159.55 (C4), 160.03 (C2), 160.59 (dd, *J* = 7.2, 254.2 Hz, C_{arom}), 163.62 (C6); EI-MS *m/z* (%): 311 [M^+] (100). Anal. calcd for $C_{14}H_{12}ClF_2N_3O$ (311.71): C 53.94, H 3.88, N 13.48, found: C 54.30, H 3.61, N 13.42.

Synthesis of (6-chloro-2-(dimethylamino)-5-methylpyrimidin-4-yl)(3,5-dimethylphenyl)-methanone 4b: To a mixture of compound **1** (2.06 g, 10 mmol) and (3,5-dimethylphenyl)acetonitrile (1.60 g, 11 mmol) in dimethylformamide (50 mL) was added sodium hydride (55% suspension in paraffin oil, 1.09 g, 25 mmol) portionwise. After stirring for 2 h at room temperature, the reaction mixture was stirred for another 4 h under a stream of oxygen. The mixture was quenched by addition of water (2 mL) dropwise followed by addition of water (25 mL) and ether (30 mL) for separation of the two layers. The ether layer was dried (magnesium sulfate), and evaporated under reduced pressure. The resulting solid was purified by addition of methanol (5 mL), filtered and dried to afford compound **4b** as a pure solid. The filtrate was evaporated under reduced pressure, methanol (5 mL) was added to the residual material and stirred. The pure solid product was filtered off, washed with methanol and dried to afford 3.00 g of **4b**, yield: 99% as a pale yellow solid; m.p.: 108–110°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3H, CH_3), 2.36 (s, 6H, (CH_3)$_2$Ar), 3.14 (s, 6H, (CH_3)$_2$N), 7.26 (s, 1H, H_{arom}), 7.48 (s, 2H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.53 (CH_3), 21.15 ((CH_3)$_2$Ar), 37.03 ($(CH_3)_2N$), 111.91 (C-5), 127.86, 134.82, 135.97, 138.42 (C_{arom}), 159.74 (C-6), 162.29 (C-4), 164.65 (C-2), 194.12 (CO); HR-MALDI MS *m/z* calcd for $C_{16}H_{19}N_3OCl$ (304.1211) $[M+H]^+$, found 304.1215.

Synthesis of 6-aroyl-2-(dimethylamino)-5-methylpyrimidin-4(3H)-ones 5a,b: A solution of compound **4a,b** (3 mmol) in concentrated hydrochloric acid (20 mL), acetic acid (10 mL) and water (10 mL) was refluxed at 115°C for 40 h. The solvent was evaporated under reduced pressure, the residual material was treated with water (20 mL) and neutralized with 10% sodium hydroxide. The solid product formed was filtered and dried to afford compounds **5a,b** as pure solids.

6-(2,6-Difluorobenzoyl)-2-(dimethylamino)-5-methylpyrimidin-4(3H)-one 5a: Yield: 0.70 g, 80%; as a pale yellow solid; m.p.: 202–204°C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.05 (s, 3H, CH_3), 2.85 (s, 6H, $(CH_3)_2N$), 7.19 (t, 2H, *J* = 8.3 Hz, H_{arom}), 7.56–7.65 (m, 1H, H_{arom}), 11.41 (bs, 1H, NH); ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 9.77 (CH_3), 36.59 ($(CH_3)_2N$), 111.57–111.90 (m, C_{arom}), 132.99 (t, *J* = 10.5 Hz, C_{arom}), 159.12 (dd, *J* = 7.7, 249.9 Hz, C_{arom}), 190.94 (C=O); EI-MS *m/z* (%) 293 [M^+] (100). Anal. calcd for $C_{14}H_{13}F_2N_3O_2$ (293.27): C 57.34, H 4.47, N 14.33, found: C 57.45, H 4.38, N 14.05.

2-(Dimethylamino)-6-(3,5-dimethylbenzoyl)-5-methylpyrimidin-4(3H)-one 5b: Yield: 0.80 g, 94%; m.p.: 200–202ºC; ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.66 (s, 3H, CH_3-C5), 2.32 [s, 6H, $(CH_3)_2$Ar], 2.30 [s, 6H, $(CH_3)_2N$], 7.32 (s, 1H, H_{arom}), 7.47 (s, 2H, H_{arom}), 11.27 (bs, 1H, NH); ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 10.00 (CH_3-C5), 20.63 ($(CH_3)_2$Ar), 37.02 ($(CH_3)_2N$), 127.05, 134.69, 135.53, 138.19 (C_{arom}), 194.70 (C=O); EI-MS *m/z* (%) 285 [M^+] (35), 270 (100). Anal. calcd for $C_{16}H_{19}N_3O_2$×0.25 H_2O (289.85): C 66.30, H 6.78, N 14.50, found: C 66.45, H 6.65, N 14.41.

Synthesis of 1-[6-chloro-2-(dimethylamino)-5-methylpyrimidin-4-yl]-1-(aryl)-ethanol 6a,b: To a solution of **4a,b** (16.5 mmol) in ether (70 mL) was added methyl magnesium bromide (3M in ether, 11 mL, 33.0 mmol) and the reaction mixture was stirred for 14 h under nitrogen at room temperature. The reaction was quenched by addition of saturated ammonium chloride (5 mL) followed by addition of water (15 mL) and ether (15 mL). The ether layer was separated, dried (magnesium sulfate) and evaporated under reduced pressure. The resulting solid was purified by addition of petroleum ether (5 mL) and **6a,b** was obtained by filtration and drying. The filtrate was evaporated under reduced pressure and petroleum ether (5 mL) was added to the residual material, filtered, and repeated two times to give pure compounds **6a,b**.

1-[6-Chloro-2-(dimethylamino)-5-methylpyrimidin-4-yl]-1-(2,6-difluorophenyl)-ethanol 6a*:* Yield: 4.42 g, 82%; m.p.: 92–94°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 3H, CH_3-C5), 1.92

(t, 3H, J_{HF} = 3.9 Hz, C*H*$_3$-C-OH), 3.22 (s, 6H, $(CH_3)_2N$), 6.69 (s, 1H, OH), 6.83 (t, 2H, *J* = 8.2 Hz, H_{arom}), 7.18–7.27 (m, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.59 (CH_3), 28.25 (t, *J* = 22.6 Hz, *C*H_3-C-OH), 37.19 ($(CH_3)_2N$), 72.96 (C-OH), 99.97 (t, *J* = 17.8 Hz, C_{arom}), 110.27 (C5), 112.13–112.50 (m, C_{arom}), 129.59 (t, *J* = 45.5 Hz, C_{arom}), 158.03 (C2), 161.45 (dd, *J* = 8.5, 251.5 Hz, C_{arom}), 163.34 (C4), 171.13 (C6); HR-MALDI MS *m/z* calcd for $C_{15}H_{17}ClF_2N_3O$ (328.1023) $[M+H]^+$, found 328.1018. Anal. calcd for $C_{15}H_{16}ClF_2N_3O$ (327.76): C 54.97, H 4.92, N 12.82, found: C 55.23, H 4.69, N 12.80.

Synthesis of 1-[6-chloro-2-(dimethylamino)-5-methylpyrimidin-4-yl]-1-(3,5-dimethylphenyl)-ethanol 6b: Yield: 3.11 g (59%) as a white solid; m.p.: 109–110°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76 (s, 3H, CC*H*$_3$), 1.85 (s, 3H, C*H*$_3$), 2.28 (s, 6H, $(CH_3)_2$Ar), 3.24 (s, 6H, $(CH_3)_2$N), 6.42 (s, 1H, OH), 6.89 (s, 3H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.55 (CH_3), 21.40 ($(CH_3)_2$Ar), 25.69 (C*C*H$_3$), 37.21 ($(CH_3)_2$N), 74.63 (*C*-OH), 111.83 (C-5), 124.03, 129.22, 137.86, 144.03 (C_{arom}), 157.89 (C-6), 163.43 (C-4), 171.77 (C-2); HR-MALDI MS *m/z* calcd for $C_{17}H_{22}ClNaN_3O$ (342.1344) $[M+Na]^+$, found 342.1347.

Synthesis of 4-Chloro-6-[1-(aryl)vinyl]-N,N,5-trimethylpyrimidin-2-amine 7a,b: Method A**:** A solution of **6a,b** (6.26 mmol) and phosphorus pentoxide (5.0 g, 35.2 mmol) in dichloromethane (50 mL) was stirred for 20 h at room temperature, followed by slowly addition of water (200 mL). The two layers were separated and the organic layer was evaporated under reduced pressure to afford compound **7a** as a pure solid. For compound **7b**, the residual material from evaporation of the organic layer was purified by a silica gel column using petroleum ether/ether (5:1, v/v) as eluent.

Method B: A solution of **6b** (3.00 g, 9.40 mmol) and phosphorus oxychloride (4 mL, 21.20 mmol) in dichloromethane (50 mL) was refluxed at 45°C for 20 h. Then the solvent was evaporated under reduced pressure followed by addition of water (70 mL). After addition of ether, the two layers were separated. The ether layer was dried (magnesium sulfate) then the solvent was evaporated under reduced pressure and the residual material was chromatographed on a silica gel column using petroleum ether / ether (2:1, v/v) to afford compound **7b**.

Method C: To a suspension of magnesium (0.19 g, 8 mmol) and titanium tetrachloride (0.38 g, 0.21 mL, 2 mmol) in dichloromethane (4 mL) was added dry THF (2 mL) over a 2 min period. After being stirred for 20 minutes at 0°C, a solution of **4b** in dichloromethane (3 mL) was added

dropwise. After stirring for 30 min at 0°C, the reaction mixture was stirred for an additional 30 min at room temperature and cooled to 0°C. Saturated potassium carbonate solution (10 mL) was added and the mixture was diluted with ether (20 mL). The organic layer was separated, dried and removed under reduced pressure. The residual material was chromatographed on a silica gel column using petroleum ether / ether (2:1, v/v) to afford compounds **7b** and **8**.

4-Chloro-6-[1-(2,6-difluorophenyl)vinyl]-N,N,5-trimethylpyrimidin-2-amine 7a: Yield: 1.26 g, 65%; m.p.: 88–90°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 3H, CH_3), 3.06 (s, 6H, $(CH_3)_2N$), 5.88 (s, 1H, *H*CH=C), 5.92 (s, 1H, HC*H*=C), 6.88 (t, 2H, *J* = 8.1 Hz, H_{arom}), 7.18–7.28 (m, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.85 (CH_3), 36.81 ($(CH_3)_2N$), 111.13–111.47 (m, C_{arom}), 112.27 (C5), 125.92 (CH_2=C), 129.12 (t, *J* = 10.3 Hz, C_{arom}), 135.81 (CH_2=*C*), 160.33 (dd, *J* = 7.2, 249.4 Hz, C_{arom}), 159.73 (C4), 162.60 (C2), 166.59 (C6); HR-MALDI MS *m/z* calcd for $C_{15}H_{15}ClF_2N_3$ (310.0917) $[M+H]^+$, found 310.0917. Anal. calcd for $C_{15}H_{14}ClF_2N_3$ (309.74): C 58.16, H 4.56, N 13.57, found: C 58.50, H 4.44, N 13.58.

6-Chloro-4-[1-(3,5-dimethylphenyl)vinyl]-N,N,5-trimethylpyrimidin-2-amine 7b: Yield: 43% (method A), 74% (method B), 7% (method C) as a white solid; m.p.: 65–67°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (s, 3H, C*H*$_3$), 2.28 (s, 6H, (C*H*$_3$)$_2$Ar), 3.17 (s, 6H, (C*H*$_3$)$_2$N), 5.30 (s, 1H, C*H*$_2$), 5.81 (s, 1H, C*H*$_2$), 6.91 (s, 3H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.79 (CH_3), 21.30 [(CH_3)$_2$Ar], 37.08 ($(CH_3)_2N$), 113.34 (C-5), 115.89 (CH_2=C), 124.03, 129.77, 137.92 (C_{arom}),147.42 (CH_2=*C* and C_{arom}), 160.15 (C-6), 161.60 (C-4), 168.60 (C-2); HR-MALDI MS *m/z* calcd for $C_{17}H_{21}ClN_3$ (302.1419) $[M+H]^+$, found 302.1418.

[6-Chloro-2-(dimethylamino)-5-methylpyrimidin-4-yl](3,5-dimethylphenyl)methanol 8: Yield: 82 mg (27%) as a white solid; m.p.: 85–87°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (s, 3H, C*H*$_3$), 2.27 (s, 6H, (C*H*$_3$)$_2$Ar), 3.23 (s, 6H, (C*H*$_3$)$_2$N), 5.40 (d, 1H, HCO*H*), 5.53 (d, 1H, *H*COH), 6.85 (s, 2H, H_{arom}), 6.90 (s, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.96 (CH_3), 21.25 ((CH_3)$_2$Ar), 37.19 ($(CH_3)_2N$), 72.49 (CH-OH), 111.83 (C-5), 125.34, 129.81, 138.22, 140.74 (C_{arom}), 158.80 (C-6), 161.93 (C-4), 167.99 (C-2); HR-MALDI MS *m/z* calcd for $C_{16}H_{23}ClN_3O$ (308.1524) $[M+H]^+$, found 308.1520.

Reduction of 6-chloro-4-[1-(3,5-dimethylphenyl)vinyl]-N,N,5-trimethylpyrimidin-2-amine 7b: synthesis of 9 and 10: A suspension of **7b** (0.71 g, 2.35 mmol) and 10% Pd/C (0.41 mg) dissolved in ethanol (30 mL) was reduced in an autoclave under 3.5 bar of hydrogen for 4 h followed by filtration with boiling ethanol. The solvent was evaporated under reduced pressure.

After addition of water (25 mL) and a solution of potassium carbonate (2 mL) to appoint pH ≈ 7, the solvent was evaporated under reduced pressure again and the combined residual materials were chromatographed on a silica gel column using petroleum ether/ether (2:1, v/v) to afford compounds **9** and **10**.

4-Chloro-6-[1-(3,5-dimethylphenyl)ethyl]-N,N,5-trimethylpyrimidin-2-amine 9: Yield: 37 mg (5%) as a white solid; m.p.: 60–62°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (d, 3H, *J* = 6.9 Hz, C*H*$_3$CH), 2.10 (s, 3H, C*H*$_3$), 2.26 (s, 6H, (C*H*$_3$)$_2$Ar), 3.19 (s, 6H, (C*H*$_3$)$_2$N), 4.14 (q, 1H, *J* = 6.9 Hz, CH$_3$C*H*), 6.82 (s, 1H, H$_{arom}$), 6.87 (s, 2H, H$_{arom}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.55 (*C*H$_3$), 21.34 ((*C*H$_3$)$_2$Ar and CH*C*H$_3$), 36.94 ((CH$_3$)$_2$N), 43.92 (*C*HCH$_3$), 112.91 (C-5), 125.57, 128.11, 137.82, 143.75 (C$_{arom}$), 159.93 (C-6), 161.06 (C-4), 171.71 (C-2); HR-MALDI MS *m/z* calcd for $C_{17}H_{23}ClN_3$ (304.1575) $[M+H]^+$, found 304.1576.

4-[1-(3,5-Dimethylphenyl)ethyl]-N,N,5-trimethylpyrimidin-2-amine 10: Yield: 85 mg (13%) obtained as yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58 (d, 3H, *J* = 7.0 Hz , C*H*$_3$CH), 1.99 (s, 3H, C*H*$_3$), 2.26 (s, 6H, (C*H*$_3$)$_2$Ar), 3.20 (s, 6H, (C*H*$_3$)$_2$N), 4.07 (q, 1H, *J* = 7.0 Hz, CH$_3$C*H*), 6.81 (s, 1H, H$_{arom}$), 6.90 (s, 2H, H$_{arom}$), 7.95 (s, 1H, H-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.60 (CH$_3$), 20.95 (CH*C*H$_3$), 21.34 ((*C*H$_3$)$_2$Ar), 37.07 ((CH$_3$)$_2$N), 43.44 (*C*HCH$_3$), 115.12 (C-5), 125.71, 127.96, 137.69, 144.09 (C$_{arom}$), 157.76 (C-6), 161.41 (C-4), 170.01 (C-2); HR-MALDI MS *m/z* calcd for $C_{17}H_{24}N_3$ (270.1965) $[M+H]^+$, found 270.1972.

General procedure for the synthesis of 6-[1-(aryl)vinyl]-2-(dimethylamino)-5-methylpyrimidin-4(3H)-ones 11a,b: A solution of **7a,b** (3.1 mmol) in concentrated hydrochloric acid (20 mL), acetic acid (10 mL) and water (10 mL) was refluxed at 115°C for 42 h. The solvent was evaporated under reduced pressure and the residue was dissolved in water (40 mL) and neutralized with 10% sodium hydroxide. The solid product formed was filtered and dried to afford **11a,b**.

6-[1-(2,6-Difluorophenyl)vinyl]-2-(dimethylamino)-5-methylpyrimidin-4(3H)-one 11a: Yield: 0.63 g, 70%; m.p.: 173–175°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.84 (s, 3H, CH$_3$), 2.88 (s, 6H, (CH$_3$)$_2$N), 5.74 (s, 1H, *H*CH=C), 5.89 (s, 1H, HC*H*=C), 7.08 (t, 2H, *J* = 8.1 Hz, H$_{arom}$), 7.34–7.44 (m, 1H, H$_{arom}$), 11.03 (bs, 1H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 11.30 (CH$_3$), 36.44 ((CH$_3$)$_2$N), 111.15–111.49 (m, C$_{arom}$), 124.61 (*C*H$_2$=C), 129.54 (t, *J* = 10.5 Hz, C$_{arom}$), 135.63 (CH$_2$=*C*), 159.69 (d, *J* = 7.3, 246.9 Hz, C$_{arom}$); EI-MS *m/z* (%) 291 $[M]^+$ (100). Anal. calcd for $C_{15}H_{15}F_2N_3O\times0.2H_2O$ (294.91): C 61.09, H 5.26, N 14.25, found: C 61.13, H 5.08, N 14.27.

2-(Dimethylamino)-6-[1-(3,5-dimethylphenyl)vinyl]-5-methylpyrimidin-4(3H)-one 11b: Yield: 0.78 g (89%) as a white solid; m.p.: 183–185°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.67 (s, 3H, C*H*$_3$), 2.26 (s, 6H, (C*H*$_3$)$_2$Ar), 2.99 (s, 6H, (C*H*$_3$)$_2$N), 5.18 (s, 1H, C=C*H*$_2$), 5.77 (s, 1H, C=C*H*$_2$), 6.93 (s, 1H, H$_{arom}$), 6.98 (s, 2H, H$_{arom}$), 11.08 (bs, 1H, N*H*); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 11.42 (CH$_3$), 20.93 ((*C*H$_3$)$_2$Ar), 36.97 ((CH$_3$)$_2$N), 105.86 (C-5), 114.69 (C=*C*H$_2$), 123.69, 129.28, 137.33, 138.03 (C$_{arom}$), 146.93 (*C*=CH$_2$); HR-MALDI MS *m/z* calcd for C$_{17}$H$_{21}$N$_3$NaO (306.1577) [M+Na]$^+$, found 306.1571.

General procedure for the synthesis of 6-[1-(aryl)ethyl]-2-(dimethylamino)-5-methylpyrimidin-4(3H)-ones 12a,b: A suspension of **11a,b** (2.3 mmol) and 10% Pd/C (0.40 g) in ethanol (40 mL) was reduced in an autoclave under 3.5 bar of hydrogen for 5 h. After filtration with boiling ethanol, the solvent was evaporated under reduced pressure to give **12a,b**.

6-[1-(2,6-Difluorophenyl)ethyl]-2-(dimethylamino)-5-methylpyrimidin-4(3H)-one (12a) [MC-1220]: Yield: 0.65 g, 97%; m.p.: 166–168°C [174–176°C].[12] ^{1}H-NMR (300 MHz, CDCl$_3$) δ = 1.61 (d, 3H, *J* = 7.2 Hz, C*H*$_3$CH), 1.89 (s, 3H, CH$_3$), 3.09 (s, 6H, (CH$_3$)$_2$N), 4.52 (s, 1H, *J* = 7.2 Hz, CH$_3$C*H*), 6.80 (t, 2H, *J* = 8.3 Hz, H$_{arom}$), 7.08–7.26 (m, 1H, H$_{arom}$), 11.66 (bs, 1H, NH); ^{13}C-NMR (75 MHz, CDCl$_3$) δ = 9.20 (*C*H$_3$CH), 17.54 (CH$_3$), 34.29 (CH), 37.06 ((CH$_3$)$_2$N), 105.14 (C5), 111.22 (dd, *J* = 8.2, 18.6 Hz, C$_{arom}$), 119.67 (t, *J* = 17.6 Hz, C$_{arom}$), 127.58 (t, *J* = 10.7 Hz, C$_{arom}$), 151.91 (C2), 161.76 (dd, *J* = 9.0, 248.1 Hz, C$_{arom}$), 166.01 (C4), 166.30 (C6); EI MS *m/z*: 293 (100%, M$^+$).

2-(Dimethylamino)-6-[1-(3,5-dimethylphenyl)ethyl]-5-methylpyrimidin-4(3H)-one 12b: Yield: 0.55 g, 84% as a white solid; m.p.: 172–174°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.42 (d, 3H, *J* = 6.9 Hz, C*H*$_3$CH), 1.84 (s, 3H, C*H*$_3$), 2.21 (s, 6H, (C*H*$_3$)$_2$Ar), 3.03 (s, 6H, (C*H*$_3$)$_2$N), 4.05 (q, 1H, *J* = 6.9 Hz, CH$_3$C*H*), 5.18 (s, 1H, C=C*H*$_2$), 6.78 (s, 1H, H$_{arom}$), 6.95 (s, 2H, H$_{arom}$), 10.89 (bs, 1H, N*H*); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 9.58 (CH$_3$), 20.31 (*C*H$_3$CH), 20.97 ((*C*H$_3$)$_2$Ar), 36.75 ((CH$_3$)$_2$N), 41.68 (CH$_3$*C*H), 125.31, 127.42, 136.75, 144.26 (C$_{arom}$); HR-MALDI MS *m/z* calcd for C$_{17}$H$_{24}$N$_3$O (286.1914) [M+H]$^+$, found 286.1903.

General procedure for the synthesis of 4-(1-(aryl)ethyl)-6-methoxy-N,N,5-trimethylpyrimidin-2-amines 13a,b: Sodium hydride (0.05 g, 55% suspension in paraffin oil, 1.2 mmol) was added portionwise to a solution of **12a,b** (1.0 mmol) in dry dimethylformamide (5 mL) at room temperature, stirred for 0.5 h followed by addition of methyl iodide (0.07 mL, 1.1 mmol). The reaction mixture was stirred for 2 h then poured on cold water (25 mL) and stirred for 0.5 h. Compound **13a** was precipitated, filtered and dried. For compound **13b**, ether (30 mL)

was added to the reaction mixture and extracted and the ether layer was dried (magnesium sulfate). The solvent was removed under reduced pressure to afford compound **13b** as pure oil

4-(1-(2,6-Difluorophenyl)ethyl)-6-methoxy-N,N,5-trimethylpyrimidin-2-amine 13a: Yield: 0.28 g, 91% as a white solid; m.p.: 65–66°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65 (d, 3H, *J* = 7.1 Hz, C*H*$_3$CH), 1.90 (s, 3H, CH_3), 3.09 (s, 6H, $(CH_3)_2$N], 3.87 (s, 3H, OCH_3), 4.58 (s, 1H, *J* = 7.1 Hz, CH_3C*H*), 6.78 (t, 2H, *J* = 8.2 Hz, H_{arom}), 7.05–7.14 (m, 1H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.93 (*C*H_3CH), 17.81 (*C*H_3-C5), 33.83 (CH), 36.55 ($(CH_3)_2$N), 52.99 (OCH_3), 100.61 (C5), 111.23 (dd, *J* = 8.2, 18.6 Hz, C_{arom}), 120.18 (t, *J* = 17.5 Hz, C_{arom}), 127.50 (t, *J* = 10.5 Hz, C_{arom}), 159.94 (C2), 161.68 (dd, *J* = 8.9, 248.2 Hz, C_{arom}), 167.67 (C4), 168.14 (C6); HR-MALDI MS *m/z* calcd for $C_{16}H_{20}F_2N_3O$ (308.1569) $[M+H]^+$, found 308.1575.

4-(1-(3,5-Dimethylphenyl)ethyl)-6-methoxy-N,N,5-trimethylpyrimidin-2-amine 13b: Yield: 0.18 g (86%) obtained as yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56 (d, 3H, *J* = 6.9 Hz, C*H*$_3$CH), 1.94 (s, 3H, C*H*$_3$), 2.26 (s, 6H, (C*H*$_3$)$_2$Ar), 3.17 (s, 6H, (C*H*$_3$)$_2$N), 3.86 (s, 3H, OCH_3), 4.13 (q, 1H, *J* = 6.9 Hz, CH_3C*H*),), 6.79 (s, 1H, H_{arom}), 6.95 (s, 2H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.30 (CH_3), 21.16 ((*C*H_3)$_2$Ar), 21.36 (*C*H_3CH), 36.74 ((*C*H_3)$_2$N), 42.54 (CH_3*C*H), 52.95 (OCH_3), 100.92 (C-5), 125.66, 127.72, 137.47, 144.94 (C_{arom}), 160.12 (C-4), 168.16 (C-2), 169.31 (C-6); EI MS *m/z*: 299.3 (100%, M^+); HR-MALDI MS *m/z* calcd for $C_{18}H_{26}N_3O$ (300.2070) $[M+H]^+$, found 300.2078.