Supplementary Information

Triazine-pyrimidine based molecular hybrids: Synthesis, docking studies and antimalarial activity evaluation

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Experimental Protocols

All the chemicals were purchased from Sigma-Aldrich. Solvents used for the chemical synthesis were of analytical grade and used without further purification. Thin layer chromatography (Merck Kiesel 60 F254, 0.2 mm thickness) was used to monitor the progress of the reactions and the compounds were purified by silica gel (60-120 mesh) column chromatography.IR spectra were recorded on Perkin-elmer FT-IR spectrophotometer using KBr pellets or as film in chloroform and the values were expressed in cm^{-1}.^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Jeol ECX spectrospin instrument using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal reference. The chemical shift values were expressed on δ scale and the coupling constant (*J*) in Hz. Melting points were recorded on EZ-Melt automated melting point apparatus, Stanford Research Systems and are uncorrected. Mass data were recorded in Jeol-Accu TOF JMS-T100LC mass spectrometer.

Typical procedure for the synthesis of 4-(2-chloropyrimidin-4-yl)morpholine (2) and related compounds 3 and 4: To a solution of 2,4-dichloropyrimidine (**1**, 2.0 g, 0.013 mol) and triethylamine (1.63 g, 0.016 mol) in ethanol at 0 °C, morpholine (1.13 g, 0.013 mol) was added. The reaction mixture was stirred overnight at room temperature. After completion of the reaction as observed by TLC, excess ethanol was evaporated. The compound was extracted with chloroform and washed with cold water. The $CHCl_3$ layer was dried over Na_2SO_4 and excess solvent removed under reduced pressure. The crude product was purified by column chromatography using EtOAc/Hexane as eluent to afford pure compound **2**.

4-(2-Chloropyrimidin-4-yl)morpholine (2): Yield 85%; mp 115-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (brs, 4H), 3.77 (t, *J* = 5.13 Hz, 4H), 6.38 (d, *J* = 6.59 Hz, 1H), 8.07 (d, *J* = 6.59 Hz, 1H); ESI-HRMS (*m/z*) calculated for $C_8H_{10}ClN_3O$: 199.0512, found: 200. 0732 $(M + H)^+$.

2-Chloro-4-(4-methylpiperazin-1-yl)pyrimidine (3): Yield 82%; mp 94-96 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H, N*CH*$_3$), 2.44 (t, *J* = 5.13 Hz, 4H), 3.64 (brs, 4H), 6.35 (d, *J* = 6.59 Hz, 1H), 7.99 (d, *J* = 6.59 Hz, 1H); ESI-HRMS (*m/z*) calculated for $C_9H_{13}ClN_4$: 212.0829, found: 213.1031 (M + H)$^{+}$.

2-Chloro-4-(4-ethylpiperazin-1-yl)pyrimidine (4): Yield 75%; mp 68-70 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09-1.13 (m, 3H), 2.42-2.47 (m, 2H), 2.48-2.52 (m, 4H), 3.67 (brs, 4H), 6.38 (dd, *J* = 1.46, 6.59Hz, 1H), 8.02 (dd, *J* = 2.20, 5.86 Hz, 1H); ESI-HRMS (*m/z*) calculated for $C_{10}H_{15}ClN_4$: 226.0985, found: 227.1280 (M + H)$^{+}$.

Typical procedure for the synthesis of 4,4'-(6-chloro-1,3,5-triazine-2,4-diyl)dimorpholine (6) and related compound 7: Morpholine (4.70 g, 0.054 mol) was added to a mixture of cyanuric chloride (**5**, 5g, 0.027 mol) and K_2CO_3 (11.25 g, 0.081 mol) in THF at 0 ^{o}C. The reaction mixture was allowed to stir at 25 ^{o}C for 4-6 h. After completion of reaction as observed by TLC, K_2CO_3 was removed by filtration and excess solvent was removed under vacuum. The crude productthus obtained was dissolved in chloroform and washed with water (3 x 50 mL). The organic layer was dried over Na_2SO_4 and excess solvent was removed. The crude product thus obtained was purified by column chromatography to yield pure compound **6**.

4,4'-(6-Chloro-1,3,5-triazine-2,4-diyl)dimorpholine (6): Yield 85%; mp 172-174 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (br, 8H), 3.69-3.72 (m, 8H); ESI-HRMS (*m/z*) calculated for $C_{11}H_{16}ClN_5O_2$: 285.0993, found: 286.1156 (M + H)$^{+}$.

6-Chloro-*N*^{2},*N*^{2},*N*^{4},*N*^{4}-tetraethyl-1,3,5-triazine-2,4-diamine (7): Yield 90%; mp 50-52^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, *J* = 6.59 Hz, 12H), 3.52 (q, *J* = 6.59 Hz, 8H); ESI-HRMS (*m/z*) calculated for $C_{11}H_{20}ClN_5$: 257.1407, found: 258.1787 (M + H)$^{+}$.

Typical procedure for the synthesis of *N*^{1}-(4,6-dimorpholino-1,3,5-triazin-2-yl)ethane-1,2-diamine (8) and related compounds (9-13): To a mixture of 4,4'-(6-chloro-1,3,5-triazine-2,4-diyl)dimorpholine (**6**, 5.0 g, 0.017 mol) and K_2CO_3 (3.63 g, 0.026 mol) in THF, 1,2-diaminoethane (5.2 g, 0.87 mol) was added. The reaction mixture was refluxed at 80^{0}C for 8-10 h. After completion of the reaction, excess solvent was removed under vacuum and water was added to the reaction mixture. The product was extracted with chloroform (3 x 50 mL) and washed with excess of water. The organic layer was dried over Na_2SO_4 and excess solvent was removed. The crude product thus obtained was purified by column chromatography using $CHCl_3$/MeOH as eluent to yield pure compound **8**.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)ethane-1,2-diamine (8):** Yield 48%; mp 126-128 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (br, 2H, *NH*$_2$), 2.87 (t, *J* = 5.86 Hz, 2H), 3.43 (q, *J* = 5.86 Hz, 2H), 3.69-3.70 (m, 8H), 3.70 (br, 8H), 5.06 (t, *J* = 5.86 Hz, 1H, *NH*); ESI-HRMS (*m/z*) calculated for $C_{13}H_{23}N_7O_2$: 309.1913, found: 310.2132 (M + H)$^{+}$.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)propane-1,3-diamine (9):** Yield 45%; mp 116-118 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (br, 2H, *NH*$_2$), 1.68 (quintet, *J* = 6.59 Hz, 2H), 2.78 (t, *J* = 6.59 Hz, 2H), 3.47 (q, *J* = 6.59 Hz, 2H), 3.70 (br, 8H), 3.72 (br, 8H), 5.04 (t, *J* = 5.86 Hz, 1H, *NH*); ESI-HRMS (*m/z*) calculated for $C_{14}H_{25}N_7O_2$: 323.2070, found: 324.2577 $(M + H)^+$.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)butane-1,4-diamine (10):** Yield 40%; mp 112-114 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (br, 2H, *NH*$_2$), 1.46-1.53 (m, 2H), 1.55-1.62 (m, 2H), 2.71 (t, *J* = 6.59 Hz, 2H), 3.37 (q, *J* = 6.59 Hz, 2H), 3.70 (br, 8H), 3.72 (br, 8H), 4.88 (t, *J* = 5.86 Hz, 1H, *NH*); ESI-HRMS (*m/z*) calculated for $C_{15}H_{27}N_7O_2$: 337.2226, found: 337.1989 $(M + H)^+$.

***N*^{2}-(2-Aminoethyl)-*N*^{4},*N*^{4},*N*^{6},*N*^{6}-tetraethyl-1,3,5-triazine-2,4,6-triamine (11):** Yield 40%; mp 76-77 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 7.32 Hz, 12H), 1.33 (br, 2H, *NH*), 2.86 (t, *J* = 5.86 Hz, 2H), 3.42 (q, *J* = 5.86 Hz, 2H), 3.52 (q, *J* = 7.32 Hz, 8H), 4.83 (t, *J* = 5.86 Hz, 1H, *NH*); ESI-HRMS (*m/z*) calculated for $C_{13}H_{27}N_7$: 281.2328, found: 281.2576 $(M + H)^+$.

***N*^{2}-(3-Aminopropyl)-*N*^{4},*N*^{4},*N*^{6},*N*^{6}-tetraethyl-1,3,5-triazine-2,4,6-triamine (12):** Yield 41%; mp 72-74 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (t, *J* = 7.32 Hz, 12H), 1.44 (br, 2H, *NH*), 1.65 (quintet, *J* = 6.59 Hz, 2H), 2.74 (t, *J* = 6.59 Hz, 2H), 3.43 (q, *J* = 6.59 Hz, 2H), 3.49 (q, *J* = 7.32 Hz, 8H), 4.71 (t, *J* = 5.86 Hz, 1H, *NH*); ESI-HRMS (*m/z*) calculated for $C_{14}H_{29}N_7$: 295.2484, found: 295.2911 $(M + H)^+$.

Typical procedure for the synthesis of *N*^{1}-(4,6-dimorpholino-1,3,5-triazin-2-yl)-*N*^{2}-(4-morpholinopyrimidin-2-yl)ethane-1,2-diamine (14) and related compounds (15-31): To a mixture of *N*^{1}-(4,6-dimorpholino-1,3,5-triazin-2-yl)ethane-1,2-diamine (**8**, 200 mg, 0.65 mmol) and 4-(2-chloropyrimidin-4-yl)morpholine (**2**, 130 mg, 0.65 mmol) in *N*-methyl pyrrolidone (NMP), K_2CO_3 (135 mg, 0.98 mmol) was added and the reaction mixture was stirred at 140 ^{0}C for 10-12 h. After completion of the reaction, water was added to the reaction mixture and the product was extracted with chloroform (3 x 20mL). The combined organic layer was dried over sodium sulphate and the excess solvent was evaporated under reduced pressure. Crude product was purified through column using MeOH/$CHCl_3$ as eluent to afford pure compound **15** in quantitative yield.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-*N*^{2}-(4-morpholinopyrimidin-2-yl)ethane-1,2-diamine (14)**: Yield 65%; mp 140-142 ^{o}C; IR (film, cm^{-1}): 2921, 2851, 1584, 1552, 1535, 1500, 1482, 1439, 1359, 1289, 1259, 1129, 1114, 1084, 1003, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.54-3.55 (m, 4H), 3.70 (brs, 12H), 3.73-3.75 (m, 12H), 5.25 (brs, 1H, *NH*), 5.39 (brs, 1H, *NH*), 5.85 (d, *J* = 6.5 Hz, 1H), 7.88 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.73, 41.78, 43.49, 43.99, 66.49, 66.77, 93.12, 156.78, 162.08, 162.68, 165.13, 166.47; ESI-HRMS (*m/z*) calculated for $C_{21}H_{32}N_{10}O_3$: 472.2659, found: 473.2871 $(M + H)^+$; Anal. calcd. for $C_{21}H_{32}N_{10}O_3$: C, 53.38; H, 6.83; N, 29.64; O, 10.16, found: C, 53.32; H, 6.86; N, 29.62; O, 10.20.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-*N*^{3}-(4-morpholinopyrimidin-2-yl)propane-1,3-diamine (15)**: Yield 65%; mp 138-140 ^{o}C; IR (film, cm^{-1}): 2960, 2919, 2852, 1587, 1555, 1534, 1499, 1438,

1360, 1303, 1259, 1114, 1084, 1005, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80 (quintet, *J* = 6.59 Hz, 2H), 3.42-3.49 (m, 4H), 3.53-3.56 (m, 4H), 3.69-3.70 (m, 8H), 3.73-3.75 (m, 12H), 5.03 (brs, 1H, *NH*), 5.08 (brs, 1H, *NH*), 5.84 (d, *J* = 5.8 Hz, 1H), 7.88 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.08, 37.66, 38.19, 43.48, 43.95, 66.45, 66.76, 92.91, 156.66, 162.02, 162.69, 165.16, 166.33; ESI-HRMS (*m/z*) calculated for $C_{22}H_{34}N_{10}O_3$: 486.2815, found: 487.3019 $(M + H)^+$; $)^+$; Anal. calcd. for $C_{22}H_{34}N_{10}O_3$: C, 54.31; H, 7.04; N, 28.79; O, 9.86, found: C, 54.37; H, 7.11; N, 28.73; O, 9.91.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-*N*^{4}-(4-morpholinopyrimidin-2-yl)butane-1,4-diamine (16)**: Yield 60%; mp 154-156 ^{o}C; IR (film, cm^{-1}): 2960, 2919, 2854, 1588, 1557, 1536, 1500, 1440, 1361, 1304, 1260, 1114, 1069, 1007, 753; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (brs, 4H), 3.39 (t, *J* = 5.1 Hz, 4H), 3.54 (t, *J* = 5.1 Hz, 4H), 3.69 (brs, 8H), 3.73-3.75 (m, 12H), 4.82 (brs, 2H, 2*NH*), 5.84 (d, *J* = 5.8 Hz, 1H), 7.90 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.09, 27.21, 40.19, 40.87, 43.43, 43.91, 66.45, 66.74, 92.88, 156.82, 162.02, 162.67, 165.17, 166.23; ESI-HRMS (*m/z*) calculated for $C_{23}H_{36}N_{10}O_3$: 500.2972, found: 501.3051 $(M + H)^+$; Anal. calcd. for $C_{23}H_{36}N_{10}O_3$: C, 55.18; H, 7.25; N, 27.98; O, 9.59, found: C, 55.20; H, 7.23; N, 28.06; O, 9.62.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-*N*^{2}-(4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)ethane-1,2-diamine (17)**: Yield 65%; mp 150-154 ^{o}C; IR (film, cm^{-1}): 2959, 2919, 2851, 1587, 1557, 1537, 1505, 1438, 1361, 1303, 1259, 1114, 1084, 1007, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.43-2.44 (m, 4H), 3.59 (brs, 8H), 3.69 (brs, 16H), 5.27 (brs, 1H, *NH*), 5.45 (brs, 1H, *NH*), 5.87 (d, *J* = 5.8 Hz, 1H), 7.84 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.69, 41.75, 43.47, 43.96, 66.47, 66.75, 93.09, 156.68, 162.01, 162.65, 165.09, 166.44; ESI-HRMS (*m/z*) calculated for $C_{22}H_{35}N_{11}O_2$: 485.2975, found: 486. 3144 $(M + H)^+$; Anal. calcd. for $C_{22}H_{35}N_{11}O_2$: C, 54.42; H, 7.27; N, 31.73; O, 6.59, found: C, 54.47; H, 7.33; N, 31.74; O, 6.51.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-*N*^{3}-(4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)propane-1,3-diamine (18)**: Yield 62%; mp 140-142 ^{o}C; IR (film, cm^{-1}): 2920, 2851, 1587, 1554, 1535, 1500, 1483, 1439, 1359, 1303, 1260, 1114, 1084, 1002, 753; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.79 (quintet, *J* = 6.5 Hz, 2H), 2.32 (s, 3H), 2.43 (t, *J* = 5.1 Hz, 4H), 3.59 (t, *J* = 5.1 Hz, 4H), 3.42-3.49 (m, 4H), 3.70-3.71 (m, 8H), 3.73 (brs, 8H), 5.06 (brs, 2H, *NH*), 5.86 (d, *J* = 5.8 Hz, 1H), 7.86 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.17, 37.72, 38.25, 43.53, 46.11, 54.62, 66.81, 93.17, 156.46, 162.06, 162.45, 165.23, 166.38; ESI-HRMS (*m/z*) calculated for $C_{23}H_{37}N_{11}O_2$: 499.3132, found: 500.3376 $(M + H)^+$; Anal. calcd. for $C_{23}H_{37}N_{11}O_2$: C, 55.29; H, 7.46; N, 30.84; O, 6.40, found: C, 55.32; H, 7.41; N, 30.91; O, 6.51.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-*N*^{4}-(4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)butane-1,4-diamine (19)**: Yield 60%; mp 136-139 ^{o}C; IR (film, cm^{-1}): 2919, 2850, 1587, 1536, 1499, 1439, 1360, 1303, 1260, 1114, 1084, 1004, 750; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63-1.64 (m, 4H), 2.32 (s,

3H), 2.43 (t, *J* = 5.1 Hz, 4H), 3.38-3.40 (m, 4H), 3.58-3.60 (m, 4H), 3.69 (brs, 8H), 3.72 (brs, 8H), 4.84 (brs, 2H, 2*NH*), 5.86 (d, *J* = 6.5 Hz, 1H), 7.86 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 27.16, 27.26, 40.27, 40.92, 43.50, 46.09, 54.61, 66.79, 93.10, 156.36, 161.92, 162.41, 165.22, 166.28; ESI-HRMS (*m/z*) calculated for $C_{24}H_{39}N_{11}O_2$: 513.3288, found: 514.3622 $(M + H)^+$; Anal. calcd. for $C_{24}H_{39}N_{11}O_2$: C, 56.12; H, 7.65; N, 30.0; O, 6.23, found: C, 56.17; H, 7.70; N, 30.13; O, 6.31.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-*N*^{2}-(4-(4-ethylpiperazin-1-yl)pyrimidin-2-yl)ethane-1,2-diamine (20)**: Yield 65%; mp 144-147 ^{o}C; IR (film, cm^{-1}): 2962, 2922, 2852, 1589, 1536, 1500, 1484, 1439, 1359, 1303, 1259, 1114, 1006, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, *J* = 6.5 Hz, 3H), 2.41-2.45 (m, 2H), 2.46-2.48 (m, 4H), 3.54-3.60 (m, 8H), 3.70 (brs, 8H), 3.72 (brs, 8H), 5.25 (brs, 1H, *NH*), 5.35 (brs, 1H, *NH*), 5.87 (d, *J* = 5.8 Hz, 1H), 7.85 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.85, 40.67, 41.68, 43.46, 43.55, 52.25, 52.37, 66.75, 93.20, 156.43, 162.03, 162.32, 165.11, 166.43; ESI-HRMS (*m/z*) calculated for $C_{23}H_{37}N_{11}O_2$: 499.3132, found: 500. 3912 $(M + H)^+$; Anal. calcd. for $C_{23}H_{37}N_{11}O_2$: C, 55.29; H, 7.46; N, 30.84; O, 6.40, found: C, 55.35; H, 7.51; N, 30.93; O, 6.53.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-*N*^{3}-(4-(4-ethylpiperazin-1-yl)pyrimidin-2-yl)propane-1,3-diamine (21)**: Yield 60%; mp 120-123 ^{o}C; IR (film, cm^{-1}): 2921, 2852, 1589, 1536, 1498, 1438, 1359, 1304, 1259, 1114, 1084, 1005, 753; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, *J* = 7.3 Hz, 3H), 1.80 (quintet, *J* = 6.5 Hz, 2H), 2.43 (q, *J* = 7.3 Hz, 2H), 2.46-2.49 (m, 4H), 3.42-3.49 (m, 4H), 3.60-3.62 (m, 4H), 3.69-3.70 (m, 8H), 3.73 (brs, 8H), 5.04 (brs, 1H, *NH*), 5.23 (brs, 1H, *NH*), 5.87 (d, *J* = 5.8 Hz, 1H), 7.83 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.84, 29.97, 37.66, 38.19, 43.44, 43.55, 52.23, 52.32, 66.75, 93.03, 155.58, 161.53, 162.24, 165.11, 166.28; ESI-HRMS (*m/z*) calculated for $C_{24}H_{39}N_{11}O_2$: 513.3288, found: 514.3379 $(M + H)^+$; Anal. calcd. for $C_{24}H_{39}N_{11}O_2$: C, 56.12; H, 7.65; N, 30.0; O, 6.23, found: C, 56.19; H, 7.59; N, 30.14; O, 6.33.

***N*^{1}-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-*N*^{4}-(4-(4-ethylpiperazin-1-yl)pyrimidin-2-yl)butane-1,4-diamine (22)**: Yield 55%; mp 120-121 ^{o}C; IR (film, cm^{-1}): 2963, 2921, 2852, 1591, 1557, 1536, 1500, 1438, 1359, 1287, 1259, 1114, 1006, 751; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, *J* = 6.5 Hz, 3H), 1.83(brs, 4H), 2.42-2.45 (m, 2H), 2.46-2.49 (m, 4H), 3.38-3.40 (m, 4H), 3.59-3.61 (m, 4H), 3.70 (brs, 8H), 3.72 (brs, 8H), 4.82-4.84 (m, 2H, 2*NH*), 5.86 (d, *J* = 5.8 Hz, 1H), 7.85 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.83, 27.09, 27.20, 40.20, 40.85, 43.43, 43.50, 52.23, 52.33, 66.74, 93.01, 156.22, 161.84, 162.30, 165.14, 166.20; ESI-HRMS (*m/z*) calculated for $C_{25}H_{41}N_{11}O_2$: 527.3445, found: 528.3913 $(M + H)^+$; Anal. calcd. for $C_{25}H_{41}N_{11}O_2$: C, 56.90; H, 7.83; N, 29.20; O, 6.06, found: C, 56.97; H, 7.91; N, 29.26; O, 6.11.

***N*^{2},*N*^{2},*N*^{4},*N*^{4}-Tetraethyl-*N*^{6}-(2-((4-morpholinopyrimidin-2-yl)amino)ethyl)-1,3,5-triazine-2,4,6-triamine (23):** Yield 60%; mp 120-121 ^{o}C; IR (film, cm^{-1}): 2968, 2926, 2853, 1587, 1561, 1529, 1507, 1429, 1373, 1302, 1233, 1118, 1084, 810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 6.5 Hz,

12H), 3.50-3.53 (m, 8H), 3.54-3.59 (m, 8H), 3.73 (t, *J* = 5.1 Hz, 4H), 5.01 (brs, 1H, *NH*), 5.52 (brs, 1H, *NH*), 5.83 (d, *J* = 5.8 Hz, 1H), 7.89 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.39, 40.65, 40.81, 42.19, 43.95, 66.50, 92.95, 156.84, 162.17, 162.65, 164.48, 166.57; ESI-HRMS (*m/z*) calculated for $C_{21}H_{36}N_{10}O$: 444.3074, found: 445. 3356 $(M + H)^+$; Anal. calcd. for $C_{21}H_{36}N_{10}O$: C, 56.73; H, 8.16; N, 31.51; O, 3.60, found: C, 56.67; H, 8.21; N, 31.58; O, 3.73.

***N*²,*N*²,*N*⁴,*N*⁴-Tetraethyl-*N*⁶-(3-((4-morpholinopyrimidin-2-yl)amino)propyl)-1,3,5-triazine-2,4,6-triamine (24):** Yield 55%; mp 86-88 °C; IR (film, cm^{-1}): 2969, 2928, 2855, 1586, 1562, 1530, 1504, 1430, 1372, 1325, 1302, 1235, 1118, 1084, 975, 810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 6.5 Hz, 12H), 1.82 (quintet, *J* = 6.5 Hz, 2H), 3.43-3.48 (m, 4H), 3.50-3.56 (m, 12H), 3.72-3.75 (m, 4H), 4.86 (brs, 1H, *NH*), 5.01 (brs, 1H, *NH*), 5.83 (d, *J* = 5.8 Hz, 1H), 7.89 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.43, 30.31, 37.86, 38.60, 40.82, 43.99, 66.53, 92.86, 156.84, 162.17, 162.73, 164.53, 166.38, ESI-HRMS (*m/z*) calculated for $C_{22}H_{38}N_{10}O$: 458.3230, found: 459.3546 $(M + H)^+$; Anal. calcd. for $C_{22}H_{38}N_{10}O$: C, 57.62; H, 8.35; N, 30.54; O, 3.49, found: C, 57.71; H, 8.38; N, 30.57; O, 3.53.

***N*²,*N*²,*N*⁴,*N*⁴-Tetraethyl-*N*⁶-(4-((4-morpholinopyrimidin-2-yl)amino)butyl)-1,3,5-triazine-2,4,6-triamine (25):** Yield 55%; mp 107-109 °C; IR (film, cm^{-1}): 2964, 2921, 2851, 1560, 1530, 1506, 1429, 1372, 1325, 1303, 1233, 1121, 1084, 810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 6.5 Hz, 12H), 1.63-1.65 (m, 4H), 3.36-3.41 (m, 4H), 3.49-3.56 (m, 12H), 3.73-3.75 (m, 4H), 4.67 (brs, 1H, *NH*), 4.80 (brs, 1H, *NH*), 5.83 (d, *J* = 5.8 Hz, 1H), 7.90 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.41, 27.24, 27.48, 40.28, 40.78, 41.06, 43.97, 66.51, 92.82, 156.84, 162.06, 162.73, 164.55, 166.33; ESI-HRMS (*m/z*) calculated for $C_{23}H_{40}N_{10}O$: 472.3387, found: 473.3791 $(M + H)^+$; Anal. calcd. for $C_{23}H_{40}N_{10}O$: C, 58.45; H, 8.53; N, 29.64; O, 3.39, found: C, 58.52; H, 8.61; N, 29.70; O, 3.43.

***N*²,*N*²,*N*⁴,*N*⁴-Tetraethyl-*N*⁶-(2-((4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)amino)ethyl)-1,3,5-triazine-2,4,6-triamine (26):** Yield 55%; mp 123-125 °C; IR (film, cm^{-1}): 2969, 2927, 2852, 1588, 1562, 1529, 1509, 1429, 1373, 1302, 1229, 1142, 1083, 771; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 6.5 Hz, 12H), 2.32 (s, 3H), 2.42 (t, *J* = 5.1 Hz, 4H), 3.53 (q, *J* = 6.5 Hz, 8H), 3.57-3.61 (m, 8H), 5.02 (brs, 1H, *NH*), 5.50 (brs, 1H, *NH*), 5.85 (d, *J* = 6.5 Hz, 1H), 7.86 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.38, 40.52, 40.84, 42.19, 43.48, 46.06, 54.59, 93.10, 156.36, 162.01, 162.32, 164.36, 166.44; ESI-HRMS (*m/z*) calculated for $C_{22}H_{39}N_{11}$: 457.3390, found: 458.3973 $(M + H)^+$; Anal. calcd. for $C_{22}H_{39}N_{11}$: C, 57.74; H, 8.59; N, 33.67, found: C, 57.77; H, 8.61; N, 33.81.

***N*²,*N*²,*N*⁴,*N*⁴-Tetraethyl-*N*⁶-(3-((4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)amino)propyl)-1,3,5-triazine-2,4,6-triamine (27):** Yield 52%; mp 134-136 °C; IR (film, cm^{-1}): 2969, 2928, 2852, 1587, 1561, 1530, 1505, 1429, 1372, 1302, 1230, 1142, 1083, 1002, 975; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 6.5 Hz, 12H), 1.82 (quintet, *J* = 6.5 Hz, 2H), 2.32 (s, 3H), 2.43 (t, *J* = 5.1 Hz, 4H), 3.45 (q,

J = 6.5 Hz, 4H), 3.53 (q, *J* = 6.5 Hz, 8H), 3.60 (t, *J* = 5.1 Hz, 4H), 4.81 (brs, 1H, *NH*), 4.95 (t, *J* = 5.8 Hz, 1H, *NH*), 5.85 (d, *J* = 5.8 Hz, 1H), 7.87 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.39, 30.23, 37.81, 38.52, 40.76, 43.44, 46.06, 54.57, 92.93, 156.59, 162.12, 162.35, 164.47, 166.33; ESI-HRMS (*m/z*) calculated for $C_{23}H_{41}N_{11}$: 471.3546, found: 472.3781 $(M + H)^+$; Anal. calcd. for $C_{23}H_{41}N_{11}$: C, 58.57; H, 8.76; N, 32.67, found: C, 58.67; H, 8.82; N, 32.70.

***N*²,*N*²,*N*⁴,*N*⁴-Tetraethyl-*N*⁶-(4-((4-(4-methylpiperazin-1-yl)pyrimidin-2-yl)amino)butyl)-1,3,5-triazine-2,4,6-triamine (28):** Yield 50%; mp 60-62 °C; IR (film, cm^{-1}): 2969, 2927, 2852, 1586, 1562, 1531, 1504, 1429, 1372, 1325, 1302, 1230, 1143, 1084, 1002, 810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 6.5 Hz, 12H), 1.64 (brs, 4H), 2.32 (s, 3H), 2.43(t, *J* = 5.1 Hz, 4H), 3.38-3.39 (m, 4H), 3.52 (q, *J* = 6.5 Hz, 8H), 3.59 (t, *J* = 5.1 Hz, 4H), 4.71 (brs, 1H, *NH*), 4.81 (brs, 1H, *NH*), 5.85 (d, *J* = 5.8 Hz, 1H), 7.86 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.40, 27.23, 27.44, 40.29, 40.79, 41.02, 43.48, 46.06, 54.58, 92.95, 156.40, 161.93, 162.37, 164.42, 166.18; ESI-HRMS (*m/z*) calculated for $C_{24}H_{43}N_{11}$: 485.3703, found: 486.3861 $(M + H)^+$; Anal. calcd. for $C_{24}H_{43}N_{11}$: C, 59.35; H, 8.92; N, 31.72, found: C, 59.33; H, 8.95; N, 31.69.

***N*²,*N*²,*N*⁴,*N*⁴-Tetraethyl-*N*⁶-(2-((4-(4-ethylpiperazin-1-yl)pyrimidin-2-yl)amino)ethyl)-1,3,5-triazine-2,4,6-triamine (29):** Yield 55%; mp 114-117 °C; IR (film, cm^{-1}): 2969, 2927, 2852, 1588, 1561, 1530, 1506, 1429, 1374, 1304, 1235, 1125, 1084, 810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09-1.15 (m, 15H), 2.41-2.43 (m, 2H), 2.45-2.47 (m, 4H), 3.52-3.56 (m, 8H), 3.57-3.60 (m, 8H), 4.96 (t, *J* = 5.8 Hz, 1H, *NH*), 5.45 (brs, 1H, *NH*), 5.85 (d, *J* = 5.8 Hz, 1H), 7.86 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.86, 13.98, 40.56, 40.80, 42.22, 43.54, 52.27, 52.40, 93.10, 156.61, 162.17, 162.34, 164.49, 166.58; ESI-HRMS (*m/z*) calculated for $C_{23}H_{41}N_{11}$: 471.3546, found: 472.3733 $(M + H)^+$; Anal. calcd. for $C_{23}H_{41}N_{11}$: C, 58.57; H, 8.76; N, 32.67, found: C, 58.62; H, 8.51; N, 32.63.

***N*²,*N*²,*N*⁴,*N*⁴-Tetraethyl-*N*⁶-(3-((4-(4-ethylpiperazin-1-yl)pyrimidin-2-yl)amino)propyl)-1,3,5-triazine-2,4,6-triamine (30):** Yield 50%; mp 97-98 °C; IR (film, cm^{-1}): 2969, 2927, 1587, 1561, 1530, 1507, 1429, 1372, 1325, 1304, 1237, 1125, 1084, 975, 810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09-1.15 (m, 15H), 1.82 (quintet, *J* = 6.5 Hz, 2H), 2.41-2.45 (m, 2H), 2.46-2.48 (m, 4H), 3.45 (q, *J* = 6.5 Hz, 4H), 3.53 (q, *J* = 6.5 Hz, 8H), 3.60 (t, *J* = 5.1 Hz, 4H), 4.82 (brs, 1H, *NH*), 4.94 (brs, 1H, *NH*), 5.85 (d, *J* = 5.8 Hz, 1H), 7.87 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.89, 13.46, 30.36, 37.93, 38.65, 40.84, 43.60, 52.33, 52.44, 93.05, 156.65, 162.22, 162.43, 164.59, 166.44; ESI-HRMS (*m/z*) calculated for $C_{24}H_{43}N_{11}$: 485.3703, found: 486.3916 $(M + H)^+$; Anal. calcd. for $C_{24}H_{43}N_{11}$: C, 59.35; H, 8.92; N, 31.72, found: C, 59.42; H, 8.89; N, 31.80.

***N*²,*N*²,*N*⁴,*N*⁴-Tetraethyl-*N*⁶-(4-((4-(4-ethylpiperazin-1-yl)pyrimidin-2-yl)amino)butyl)-1,3,5-triazine-2,4,6-triamine (31):** Yield 50%; mp 73-75 °C; IR (film, cm^{-1}): 2969, 2925, 2853, 1586, 1561, 1531, 1506, 1428, 1372, 1325, 1304, 1235, 1125, 1084, 810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09-1.14 (m, 15H), 1.63-1.65 (m, 4H), 2.44 (q, *J* = 7.3 Hz, 2H), 2.46-2.48 (m, 4H), 3.38-3.39 (m,

4H), 3.52 (q, *J* = 7.3 Hz, 8H), 3.59-3.61 (m, 4H), 4.67 (brs, 1H, *NH*), 4.76 (brs, 1H, *NH*), 5.85 (d, *J* = 5.8 Hz, 1H), 7.86 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.86, 13.42, 27.28, 27.49, 40.31, 40.78, 41.05, 43.53, 52.30, 52.41, 92.98, 156.60, 162.07, 162.39, 164.53, 166.31; ESI-HRMS (*m/z*) calculated for $C_{25}H_{45}N_{11}$: 499.3859, found: 500.4388 $(M + H)^+$; Anal. calcd. for $C_{25}H_{45}N_{11}$: C, 60.09; H, 9.08; N, 30.83, found: C, 60.16; H, 9.13; N, 30.77.