Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Electronic supplementary Information

Synthesis of hybrid 4-anilinoquinoline triazine as potent antimalarial agents, their *in silico* modeling and bioevaluation as *Plasmodium falciparum* transketolase and *β*-hematin inhibitors

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General Chemistry

Commercially available reagent grade chemicals were used as received. TLC was carried out with E. Merck Kieselgel 60 F_{254}, Spots were visualized under UV light and I_2 vapors. Column chromatography was performed on silica gel (60-120 and 100-200 mesh, E. Merck). IR spectra were recorded as thin films or in KBr solution with a Perkin–Elmer Spectrum RX-1 (4000–450 cm^{-1}) spectrophotometer. The ^{1}H (200 and 300 MHz) and ^{13}C NMR (50 MHz and 75 MHz) spectra were recorded on a Avance-200 and Brucker DRX-300 NMR spectrometer in duterated NMR solvent. Chemical shift values are reported in ppm relative to TMS as internal reference, unless otherwise stated; s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet); *J* in hertz. FAB mass spectra were performed using a mass Spectrometer Jeol SX-102 and ESI mass spectra with Quattro II (Micromass). Elemental analyses were performed on a Perkin–Elmer 2400 II elemental analyzer.

General Method for the preparation of hybrid anilinoquinoline-triazine (16-52)

A solution of 6-chloro-N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N4-(3-fluorophenyl)-1,3,5-triazine-2,4-diamine (**13a**, 1.0 equiv.), N-methylpiperazine (1.5 equiv.) and K_2CO_3 (1.5 equiv.) in dry THF was refluxed for 5 hrs. After completion of reaction as confirmed by TLC the reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was dissolved in $CHCl_3$, washed with water and dried over Na_2SO_4. The dried solution was concentrated under reduced pressure. The resulting crude mass was purified by column chromatography using 2% MeOH/$CHCl_3$ as eluents to obtain the titled compound **16.** The compounds **17-52** were also obtained by the similar procedure.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N4-(3-fluorophenyl)-6-(4-methylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine (16)

Yellow solid, 73%; mp 160-162 °C; Anal. Calcd. for $C_{29}H_{27}ClFN_9$: C, 62.64; H, 4.89; N, 22.67; Found: C, 62.69; H, 4.83; N, 22.69. IR (KBr): ν 3266, 2936, 1575, 1501 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.54 (d, *J* = 5.4 Hz, 1H), 8.03 (d, *J* = 2.1 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.73-7.63 (m, 3H), 7.48 (dd, *J* = 2.1 Hz, *J* = 8.7 Hz, 1H), 7.29-7.21 (m, 3H), 7.08-7.05 (m, 1H), 6.95-6.93 (m, 1H), 6.86 (d, *J* = 5.3 Hz, 1H), 6.76-6.69 (m, 1H), 6.60 (s, 1H), 3.88-3.85 (m, 4H), 2.49-2.45 (m, 4H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 168.7, 168.0, 155.1, 153.3, 152.8, 140.2, 139.4, 138.1, 133.6, 131.4, 129.6, 128.2, 126.1, 125.4, 121.7, 119.0, 113.1, 112.8, 105.3, 58.5, 49.7, 46.8; MS (ESMS): *m/z* 556 $[M+H]^+$.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-6-(4-ethylpiperazin-1-yl)-N4-(3-fluorophenyl)-1,3,5-triazine-2,4-diamine (17)

Yellow solid, 71%; mp 210-212 °C; Anal. Calcd. for $C_{30}H_{29}ClFN_9$: C, 63.21; H, 5.13; N, 22.11; Found: C, 63.28; H, 5.09; N, 22.19. IR (KBr): ν 3270, 2932, 1568, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.51 (s, 1H), 8.03 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.68-7.60 (m, 3H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.25-7.23 (m, 3H), 7.07 (s, 1H), 6.92-6.82 (m,3H), 6.71 (s, 1H), 6.58 (s,1H), 3.86 (bs, 4H), 2.49 (bs, 6H), 1.14 (t, *J* = 7.2 Hz, 1H); MS (ESMS): *m/z* 570 $[M+H]^+$.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N4-(3-fluorophenyl)-N6-(2-morpholinoethyl)-1,3,5-triazine-2,4,6-triamine (18)

Yellow solid, yield 69 %; mp 148-150 °C; Anal. Calcd. for $C_{30}H_{29}ClFN_9O$: C, 61.48; H, 4.99; N, 21.51; Found: C, 61.41; H, 4.93; N, 21.56. IR (KBr): ν 3285, 2941, 1579, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.52 (d, *J* = 4.9 Hz, 1H), 8.02 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.73-7.62

(m, 3H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.25-7.07 (m, 5H), 6.84 (d, *J* = 5.0 Hz, 1H), 6.75-6.70 (m, 1H), 5.66 (s, 1H), 3.71 (bs, 4H), 3.57-3.52 (m, 2H), 2.60-2.48 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 165.9, 164.3, 151.7, 149.4, 148.4, 140.5, 135.3, 134.3, 129.8, 128.7, 125.9, 124.2, 121.8, 117.8, 109.2, 101.9, 66.9, 57.2, 53.4, 37.2; MS (ESMS): *m*/*z* 586 $[M+H]^+$.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N4-(3-fluorophenyl)-N6-(3-morpholinopropyl)-1,3,5-triazine-2,4,6-triamine (19)

Yellow solid, yield 67 %; mp 120-122 °C; Anal. Calcd. for $C_{31}H_{31}ClFN_9O$: C, 62.05; H, 5.21; N, 21.09; Found: C, 62.09; H, 5.29; N, 21.02. IR (KBr): ν 3298, 2935, 1565, 1509 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.52 (d, *J* = 5.4 Hz, 1H), 8.03 (d, *J* = 1.9 Hz, 1H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.79-7.76 (m, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.46 (dd, *J* = 8.7 Hz, *J* = 1.8 Hz, 1H), 7.26-7.23 (m, 3H), 7.08-7.05 (m, 3H), 6.84 (d, *J* = 5.2 Hz, 1H), 6.75-6.70 (m, 1H), 6.34 (bs, 1H), 3.77-3.74 (m, 4H), 3.57-3.51 (m, 2H), 2.53-2.49 (m, 6H), 1.85-1.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 165.3, 164.7, 152.8, 150.7, 148.5, 136.5, 135.3, 132.9, 128.5, 126.2, 124.2, 122.7, 121.7, 118.2, 115.7, 113.5, 106.8, 67.2, 56.2, 53.6, 40.3, 29.3; MS (ESMS): *m*/*z* 600 $[M+H]^+$.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N4-(3-fluorophenyl)-6-(piperidin-1-yl)-1,3,5-triazine-2,4-diamine (20)

Yellow solid, Yield 65 %; mp 158-160 °C; Anal. Calcd. for $C_{29}H_{26}ClFN_8$: C, 64.38; H, 4.84; N, 20.71; Found: C, 64.32; H, 4.89; N, 20.68. IR (KBr): ν 3329, 2935, 1572, 1501 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.43 (d, *J* = 5.3 Hz, 1H), 7.98-7.95 (m, 2H), 7.72-7.63 (m, 3H),), 7.45 (d, *J* = 8.9 Hz, 1H), 7.30-7.19 (m, 3H), 7.12-7.09 (m, 1H), 6.84 (d, *J* = 5.3 Hz, 1H), 6.74-6.69 (m, 1H), 3.79 (bs, 4H), 2.71 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD): δ_C 168.5, 168.1, 168.0,

155.0, 153.6, 152.7, 140.5, 139.4, 137.9, 133.6, 131.1, 129.6, 128.3, 126.3, 125.4, 121.8, 119.0, 112.9, 111.4, 48.5, 29.6, 28.6; MS (ESMS): *m*/*z* 541 $[M+H]^+$.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N4-(4-fluorophenyl)-6-(4-methylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine (21)

Brown solid, Yield 71 %; mp 170-172 °C; Anal. Calcd. for Chemical Formula: $C_{29}H_{27}ClFN_9$: C, 62.64; H, 4.89; N, 22.67; Found: C, 62.69; H, 4.81; N, 22.62. IR (KBr): ν 3171, 2923, 1572, 1492 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.53 (d, *J* = 5.2 Hz, 1H), 8.04 (s, 1H), 7.87 (d, J = 9.0, 1H), 7.63 (d, J = 8.7, 2H), 7.52-7.44 (m, 3H), 7.26-7.22 (m, 2H), 7.04 (t, *J* = 8.4 Hz, 2H), 6.92 (s, 1H), 6.83-6.81 (m, 2H), 6.60 (s, 1H), 3.85 (bs, 4H), 2.46 (bs, 4H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD): δ_C 165.2, 164.6, 164.5, 151.4, 149.9, 149.1, 136.9, 135.9, 135.3, 134.4, 127.7, 126.1, 124.7, 122.6, 121.7, 118.2, 115.7, 115.3, 101.7, 55.04, 46.2, 43.2; MS (ESMS): *m*/*z* 556 $[M+H]^+$.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-6-(4-ethylpiperazin-1-yl)-N4-(4-fluorophenyl)-1,3,5-triazine-2,4-diamine (22)

Brown solid, Yield 62 %; mp 200-202 °C; Anal. Calcd. for $C_{30}H_{29}ClFN_9$: C, 63.21; H, 5.13; N, 22.11; Found: C, 63.28; H, 5.18; N, 22.18. IR (KBr): ν 3172, 2923, 1572, 1492 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.53 (d, *J* = 5.3 Hz, 1H), 8.03 (d, *J* = 2.0, 1H), 7.87 (d, *J* = 8.9, 1H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.57-7.44 (m, 3H), 7.25 (bs, 2H), 7.04 (t, *J* = 8.6 Hz, 2H), 6.87 (s, 1H), 6.84 (d, *J* = 5.3 Hz, 1H), 6.78 (s, 1H), 6.57 (s, 1H), 3.88-3.85 (m, 4H), 2.53-2.48 (m, 6H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD): δ_C 168.0, 167.4, 167.3, 154.0, 153.0, 151.8, 139.7, 138.7, 138.2, 137.1, 130.1, 128.7, 127.5, 125.8, 124.4, 121.0, 118.3, 104.3, 55.5, 55.4, 45.9,14; MS (ESMS): *m*/*z* 570 $[M+H]^+$.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N4-(4-fluorophenyl)-N6-(2-morpholinoethyl)-1,3,5-triazine-2,4,6-triamine (23)

Yellow solid, Yield 64 %; mp 155-157 °C; Anal. Calcd. for $C_{30}H_{29}ClFN_9O$: C, 61.48; H, 4.99; N, 21.51;. Found: C, 61.41; H, 4.93; N, 21.58. IR (KBr): ν 3398, 2923, 1574, 1513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CD_3OD): δ_H 8.42 (d, *J* = 5.4 Hz, 1H), 8.01-7.97 (m, 2H), 7.65-7.63 (m, 2H), 7.52 (bs, 2H), 7.47 (dd, *J* = 8.8 Hz, *J* = 1.7 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.04 (t, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 5.3 Hz, 1H), 3.75-3.72 (m, 4H), 3.55 (t, *J* = 5.8 Hz, 2H), 2.62 (t, *J* = 6.0 Hz, 2H), 2.51 (bs, 4H); ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD): δ_C 169.6, 167.2 155.7, 151.9, 144.2, 137.4, 133.5, 129.2, 128.6, 125.2, 121.0, 119.9, 117.2, 106.4, 69.2, 61.7, 56.2, 45.2; MS (ESMS): *m*/*z* 586 $[M+H]^+$.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N4-(4-fluorophenyl)-N6-(3-morpholinopropyl)-1,3,5-triazine-2,4,6-triamine (24)

Yellow solid, Yield 70 %; mp 128-130 °C; Anal. Calcd. for $C_{31}H_{31}ClFN_9O$: C, 62.05; H, 5.21; N, 21.01;. Found: C, 62.08; H, 5.29; N, 21.08. IR (KBr): ν 3286, 2925, 1576, 1508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.53 (d, *J* = 5.3 Hz, 1H), 8.05 (d, *J* = 1.9 Hz, 1H), 7.90 (d, *J* = 8.9 Hz, 1H) 7.67 (d, *J* = 8.1 Hz, 2H), 7.53 (bs, 2H), 7.47 (dd, *J* = 8.9 Hz, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.04-6.99 (m, 4H), 6.83 (d, *J* = 5.3 Hz, 1H), 6.70 (s,1H), 6.28 (s,1H), 3.78-3.75 (m, 4H), 3.54-3.52 (m, 2H), 2.53-2.49 (m, 6H), 1.84-1.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 165.9, 151.6, 149.3, 148.5, 136.5, 135.3, 133.9, 128.6, 125.9, 124.2, 122.2, 121.3, 117.7, 115.4, 114.0, 101.8, 66.9, 57.4, 53.7, 40.4, 29.6; MS (ESMS): *m*/*z* 600 $[M+H]^+$.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N4-(4-fluorophenyl)-6-(piperidin-1-yl)-1,3,5-triazine-2,4-diamine (25)

Yellow solid, Yield 65 %; mp 160-162 °C; Anal. Calcd. for Chemical Formula: $C_{29}H_{26}ClFN_8$: C, 64.38; H, 4.84; N, 20.71; Found: C, 64.32; H, 4.89; N, 20.77. IR (KBr): ν 3316, 2930, 1569, 1502 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.36 (d, *J* = 5.3 Hz, 1H), 8.15 (d, J = 9.1, 1H), 7.90

(s, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.57-7.53 (m, 2H), 7.44 (bs, 1H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.04 (t, J = 8.4 Hz, 2H), 6.83 (d, *J* = 5.3 Hz, 1H), 3.79 (bs, 4H), 1.63 (bs, 6H); ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD): δ_C 164.7, 164.5, 164.4, 152.1, 149.8, 142.4, 141.1, 135.3, 130.9, 127.9, 125.1, 124.7, 121.9, 118.3, 115.3, 44.2, 29.4, 25.9; MS (ESMS): *m*/*z* 541 $[M+H]^+$.

N2-(3-chlorophenyl)-N4-(4-(7-chloroquinolin-4-ylamino)phenyl)-6-(4-methylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine (26)

Yellow solid, Yield 62%; mp 158-160 °C; Anal. Calcd. for $C_{29}H_{27}Cl_2N_9$: C, 60.84; H, 4.75; N, 22.02; Found: C, 60.86; H, 4.73; N, 22.07. IR (KBr): ν 3229, 2924, 1569, 1492 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD): δ_H 8.26 (d, *J* = 5.5 Hz, 1H), 8.11 (d, *J* = 9.3 Hz, 1H), 7.88 (s, 1H) 7.59-7.56 (m, 2H), 7.47-7.39 (m, 3H), 7.28-7.18 (m, 4H), 6.74 (d, *J* = 5.7 Hz, 1H), 3.87 (bs, 4H), 2.54 (bs, 4H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD): δ_C 169.8, 152.9, 151.2, 143.4, 140.6, 135.6, 130.7, 128.5, 124.3, 122.3, 118.8, 114.4, 54.5, 45.8, 42.8; MS (ESMS): *m*/*z* 572 $[M+H]^+$.

N2-(3-chlorophenyl)-N4-(4-(7-chloroquinolin-4-ylamino)phenyl)-6-(4-ethylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine (27)

Yellow solid, Yield 65 %; mp 230-232 °C; Anal. Calcd. for $C_{30}H_{29}Cl_2N_9$: C, 61.43; H, 4.98; N, 21.49; Found: C, 61.49; H, 4.92; N, 21.44. IR (KBr): ν 3229, 2924, 1569, 1492 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.45 (d, *J* = 5.3 Hz, 1H), 7.95 (d, *J* = 1.8 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 1H) 7.63-7.59 (m, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.38 (dd, *J* = 8.8 Hz, *J* = 1.9 Hz, 1H), 7.18-7.11 (m, 3H), 7.00-6.94 (m, 3H), 6.77 (d, *J* = 5.3 Hz, 1H), 6.67 (s, 1H), 6.59 (s, 1H), 3.80 (bs, 4H), 2.43-2.35 (m, 6H), 1.07 (t, *J* = 7.1Hz, 3H); MS (ESMS): *m*/*z* 586 $[M+H]^+$.

N^2-(3-chlorophenyl)-N^4-(4-(7-chloroquinolin-4-ylamino)phenyl)-N6-(2-morpholinoethyl)-1,3,5-triazine-2,4,6-triamine (28)

Orange solid, Yield 68 %; mp 190-192 °C; Anal. Calcd. for $C_{30}H_{29}Cl_2N_9O$: C, 59.80; H, 4.85; N, 20.92; Found: C, 59.74; H, 4.80; N, 20.98. IR (KBr): ν 3263, 2967, 1578, 1503 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CD_3OD): δ_H 8.24 (d, *J* = 5.9 Hz, 1H), 8.12 (d, *J* = 8.9 Hz, 1H), 7.89 (d, *J* = 1.5 Hz, 1H), 7.60 (bs, 2H), 7.48 (s,1H), 7.41 (dd, *J* = 9.0 Hz, *J* = 1.8 Hz, 1H), 7.25-7.20 (m, 3H), 7.16 (t, *J* = 7.7 Hz, 1H), 6.95-6.92 (m, 1H), 6.73 (d, *J* = 5.9 Hz, 1H), 3.68-3.66 (m, 4H), 3.50 (t, J = 5.7 Hz, 2H), 2.58 (t, *J* = 6.1 Hz, 2H), 2.47 (bs, 4H); ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD): δ_C 168.6, 153.1, 150.0, 140.6, 134.6, 130.0, 126.5, 124.9, 122.9, 117.8, 114.4, 101.6, 67.1, 57.1, 53.7, 50.1; MS (ESMS): *m/z* 602 $[M+H]^+$.

N2-(3-chlorophenyl)-N4-(4-(7-chloroquinolin-4-ylamino)phenyl)-N6-(3-morpholinopropyl)-1,3,5-triazine-2,4,6-triamine (29)

Yellow solid, Yield 70 %; mp 125-127 °C; Anal. Calcd. for $C_{31}H_{31}Cl_2N_9O$: C, 60.39; H, 5.07; N, 20.45 Found: C, 60.31; H, 5.01; N, 20.48. IR (KBr): ν 3278, 2924, 1575, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.52 (d, *J* = 5.1 Hz, 1H), 8.05 (d, *J* = 1.9 Hz, 1H), 8.00-7.92 (m, 2H), 7.69- 7.66 (m, 2H), 7.49 (dd, *J* = 8.9 Hz, *J* = 1.8 Hz, 1H), 7.29-7.22 (m, 4H), 7.10(s, 1H),7.04-7.02 (m, 1H), 6.85 (d, *J* = 5.2 Hz, 1H), 3.79-3.72 (m, 6H), 3.59-3.54 (m, 2H), 2.57-2.52 (m, 4H), 2.47-2.43 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 166.2, 150.6, 148.1, 140.7, 136.8, 134.7, 130.0, 126.4, 124.7, 123.0, 121.8, 120.5, 118.0, 102.1, 67.3, 54.1, 40.9, 30.1; MS (ESMS): *m/z* 616 $[M+H]^+$.

N2-(4-chlorophenyl)-N4-(4-(7-chloroquinolin-4-ylamino)phenyl)-6-(4-methylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine (30)

Yellow solid, Yield 69%; mp 180-182 °C; Anal. Calcd. for Chemical Formula: $C_{29}H_{27}Cl_2N_9$: C,60.84; H, 4.98; N, 21.49; Found: C, 60.88; H, 4.92; N, 21.42. IR (KBr): ν 3428, 2930, 1547, 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ_H 8.47 (d, *J* = 5.4 Hz, 1H), 8.19 (d, *J* = 9.0, 1H), 7.99 (s, 1H), 7.95 (d, *J* = 1.9 Hz, 1H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.61-7.58 (m, 3H), 7.39 (s, 2H), 7.30-7.24 (t, *J* = 8.5 Hz, 4H), 6.83 (d, *J* = 5.4 Hz, 1H), 3.86 (bs, 4H), 2.46 (bs, 4H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ_C 169.0, 169.7, 156.3, 154.1, 152.2, 143.3, 141.5, 139.5 133.3, 131.4, 129.8, 129.0, 128.2, 126.1, 122.9, 106.0, 59.5, 50.9, 47.9; MS (ESMS): *m/z* 572 $[M+H]^+$.

N2-(4-chlorophenyl)-N4-(4-(7-chloroquinolin-4-ylamino)phenyl)-6-(4-ethylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine (31)

Yellow solid, Yield 68 %; mp 208-210 °C; Anal. Calcd. for Chemical Formula: $C_{30}H_{29}Cl_2N_9$: C, 61.43; H, 4.98; N, 21.49; Found: C, 61.49; H, 4.92; N, 21.43. IR (KBr): ν 3428, 2930, 1547, 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.35 (d, *J* = 4.8 Hz, 1H), 8.12 (d, *J* = 8.5, 1H), 7.90 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.44-7.38 (m, 1H), 7.26 (bs, 4H), 6.80 (d, *J* = 5.0 Hz, 1H), 3.87 (bs, 4H), 2.54-2.48 (m, 6H), 1.16 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD): δ_C 168.7, 167.9,154.5, 152.2, 141.7,139.6, 137.8, 132.4, 131.5, 129.7, 125.3, 126.2, 125.3, 121.6, 118.3, 56.3, 46.8, 15.3; MS (ESMS): *m/z* 586 $[M+H]^+$.

N2-(4-chlorophenyl)-N4-(4-(7-chloroquinolin-4-ylamino)phenyl)-N6-(3-morpholinopropyl)-1,3,5-triazine-2,4,6-triamine (32)

Orange solid, Yield 75 %; mp 118-120 °C; Anal. Calcd. for $C_{31}H_{31}Cl_2N_9O$: C, 60.39; H, 5.07; N, 20.45; Found: C, 60.31; H, 5.10; N, 20.49. IR (KBr): ν 3280, 2930, 1575, 1510 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$+CD_3OD): δ_H 8.34 (d, *J* = 5.0 Hz, 1H), 7.97-7.92 (m, 2H), 7.59 (d, *J* = 8.0 Hz,

2H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.21- 7.16 (m, 4H), 6.74 (d, *J* = 5.6 Hz, 1H), 3.69 (bs, 4H), 3.45-3.39 (m, 2H), 2.43 (bs, 6H), 1.77-1.71 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$+CD_3OD): δ_C 166.2, 164.6, 150.1, 148.1, 142.6, 137.4, 133.7, 130.5, 128.6, 124.3, 123.0, 121.3, 120.5, 117.8, 66.9, 57.3, 53.6, 29.7; MS (ESMS): *m*/*z* 616 $[M+H]^+$.

N^2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(3-methoxyphenyl)-6-(4-methylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine (33)

Yellow solid; yield 70%; mp 157-159 °C; Anal.Calcd. for $C_{30}H_{30}ClN_9O$: C, 63.43; H, 5.32; N, 22.19;. Found: C, 63.32; H, 5.27; N, 22.28; IR (KBr) 3346, 2929, 1579, 1492 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.39 (d, *J* = 5.5 Hz, 1H), 8.07 (d, *J* = 9.2 Hz, 1H), 7.97 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.9 Hz, 1H), 7.35 (s, 1H), 7.28-7.19 (m, 3H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 5.6 Hz, 1H), 6.62-6.60 (m, 1H), 3.89 (bs, 4H), 3.80 (s, 3H), 2.52 (bs, 4H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 164.7, 164.0, 159.9, 155.5, 149.4, 147.0, 136.2, 133.3, 129.2, 125.8, 124.4, 121.2, 117.4, 114.2, 55.0, 54.4, 45.6, 42.7; MS (ESMS): *m*/*z* 568 $[M+H]^+$.

N^2-(4-(7-chloroquinolin-4-ylamino)phenyl)-6-(4-ethylpiperazin-1-yl)-N^4-(3-methoxyphenyl)-1,3,5-triazine-2,4-diamine (34)

Yellow solid; yield 68%; mp 156-158 °C; Anal.Calcd. for $C_{31}H_{32}ClN_9O$: C, 63.96; H, 5.54; N, 21.66;. Found: C, 63.91; H, 5.50; N, 20.59; IR (KBr) 3409, 2961, 1578, 1500 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.51 (d, *J* = 5.3 Hz, 1H), 8.02 (d, *J* = 1.8 Hz, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.45 (dd, J_1 = 2.0 Hz, J_2 = 8.9 Hz, 1H), 7.34 (bs, 1H), 7.25-7.17 (m, 3H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.96 (bs, 1H), 6.91 (bs, 1H),6.82 (d, *J* = 5.3 Hz, 1H), 6.61-6.58 (m, 1H), 3.87 (bs, 4H), 3.78 (s, 3H), 2.51-2.42 (m, 6H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 164.8, 164.1, 159.9, 151.4, 149.0, 148.8, 136.5, 135.4, 129.4, 128.1, 125.9,

124.3, 121.5, 121.2, 117.6, 112.5, 108.2, 101.6, 55.2, 52.4, 52.3, 43.1, 11.7; MS (ESMS): *m*/*z* 582 $[M+H]^+$.

N^2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(3-methoxyphenyl)-N^6-(3-morpholinopropyl)-1,3,5-triazine-2,4,6-triamine (35)

Brown solid; yield 71%; mp 142-144 °C; Anal.Calcd. for $C_{32}H_{34}ClN_9O_2$: C, 62.79; H, 5.60; N, 20.59;. Found: C, 62.71; H, 5.54; N, 20.52; IR (KBr) 3362, 2925, 1587, 1426 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CD_3OD): δ_H 8.35 (d, *J* = 5.5 Hz, 1H), 8.02 (d, *J* = 8.9 Hz, 1H), 7.90 (s, 1H), 7.62 (bs, 2H), 7.42 (dd, J_1 = 1.6 Hz, J_2 = 8.8 Hz, 1H), 7.28 (s, 1H), 7.23-7.14 (m, 3H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 5.6 Hz, 1H), 6.58-6.55 (m, 1H), 3.75 (s, 3H), 3.72 (t, *J* = 4.3 Hz, 4H), 3.46 (t, *J* = 5.5 Hz, 2H), 2.45 (bs, 6H), 1.79-1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 160.0, 157.8, 152.1, 150.4, 149.6, 139.2, 135.9, 129.4, 128.5, 126.0, 124.4, 122.1, 121.7, 117.5, 114.0, 110.8, 101.3, 66.7, 57.1, 55.2, 53.5, 29.6; MS (ESMS): *m*/*z* 612 $[M+H]^+$.

N^2-(4-(7-chloroquinolin-4-ylamino)phenyl)-6-(4-ethylpiperazin-1-yl)-N^4-(4-methoxyphenyl)-1,3,5-triazine-2,4-diamine (36)

Yellow solid; yield 69%; mp 126-128 °C; Anal.Calcd. for $C_{31}H_{32}ClN_9O$: C, 63.96; H, 5.54; N, 21.66;. Found: C, 64.88; H, 5.49; N, 21.61; IR (KBr) 3411, 2930, 1577, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.52 (d, *J* = 5.3 Hz, 1H), 8.02 (s, 1H), 7.86(d, *J* = 9.0 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 7.7 Hz, 3H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.90 (bs, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 5.3 Hz, 1H), 6.75 (bs, 1H), 6.58 (bs, 1H),3.90-3.86 (m, 4H), 3.82 (s, 3H), 2.54-2.45 (m, 6H), 1.17 (t, *J* = 7.2 Hz, 3H); MS (ESMS): *m*/*z* 582 $[M+H]^+$.

N^2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(4-methoxyphenyl)-N^6-(3-morpholinopropyl)-1,3,5-triazine-2,4,6-triamine(37)

Yellow solid; yield 68%; mp 107-109 °C; Anal.Calcd. for $C_{32}H_{34}ClN_9O_2$: C, 62.79; H, 5.60; N, 20.59;. Found: C, 62.71; H, 5.53; N, 20.60; IR (KBr) 3421, 2926, 1575, 1507 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.52 (d, *J* = 5.3 Hz, 1H), 8.03 (d, *J* = 1.8 Hz, 1H), 7.87(d, *J* = 8.9 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.46-7.42 (m, 3H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.93 (bs, 1H),6.88 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 5.3 Hz, 1H), 6.59 (bs, 1H), 3.79 (s, 3H) ,3.76 (t, *J* = 4.5 Hz, 4H), 3.54-3.48 (m, 2H), 2.51-2.47 (m, 6H) 1.82-1.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 166.0, 155.8, 151.7, 149.4, 148.5, 136.7, 135.3, 133.7, 128.6, 125.9, 124.3, 121.3, 117.7, 113.9, 67.0, 57.3, 55.5, 53.7, 40.3, 29.6; MS (ESMS): *m/z* 612 $[M+H]^+$.

N^2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(3,4-dimethoxyphenyl)-6-(4-methylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine (38)

Yellow solid; yield 70%; mp 132-134 °C; Anal.Calcd. for $C_{31}H_{32}ClN_9O_2$: C, 62.25; H, 5.39; N, 21.08;. Found: C, 62.31; H, 5.28; N, 21.17; IR (KBr) 3468, 2926, 1579, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+CD_3OD): δ_H 8.50 (d, *J* = 5.1 Hz, 1H), 8.02 (s, 1H), 7.89(d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.95-6.93 (m, 2H), 6.85-6.79 (m, 3H), 3.88-3.85 (m, 10H), 2.45 (bs, 4H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 164.9, 150.1, 149.5, 148.8, 136.7, 135.7, 133.7, 125.9, 124.3, 122.1, 121.8, 121.2, 117.6, 115.7, 111.5, 101.4, 56.1, 54.6, 45.9, 43.0; MS (ESMS): *m/z* 598 $[M+H]^+$.

N^2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(3,4-dimethoxyphenyl)-6-(4-ethylpiperazin-1-yl)-1,3,5-triazine-2,4-diamine (39)

Yellow solid; yield 71%; mp 121-123°C; Anal.Calcd. for $C_{32}H_{34}ClN_9O_2$: C, 62.79; H, 5.60; N, 20.59;. Found: C, 62.84; H, 5.53; N, 20.63; IR (KBr) 3422, 2929, 1578, 1499 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.51 (d, *J* = 5.3 Hz, 1H), 8.03 (d, *J* = 1.7 Hz, 1H), 7.88(d, *J* = 8.9 Hz,

1H), 7.64 (d, J = 8.7 Hz, 2H), 7.46 (dd, J_1 = 1.9 Hz, J_2 = 8.9 Hz, 1H), 7.24 (d, J = 8.6 Hz, 2H), 6.96-6.93 (m, 2H),6.83-6.80 (m, 3H), 3.89-3.85 (m, 10H), 2.52-2.44 (m, 6H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD): δ_C 164.7, 164.0, 162.3, 150.8, 149.5, 148.7, 136.5, 135.6, 133.7, 127.2, 125.8, 124.3, 122.0, 121.2, 117.6, 115.1, 111.4, 101.3, 56.0, 55.7, 52.3, 42.8, 11.3; MS (ESMS): m/z 612 $[M+H]^+$.

N^2-(4-(7-chloroquinolin-4-ylamino)phenyl)-N^4-(3,4-dimethoxyphenyl)-N^6-(3-morpholinopropyl)-1,3,5-triazine-2,4,6-triamine (40):

Yellow solid; yield 67%; mp 120-122 °C; Anal.Calcd. for $C_{33}H_{36}ClN_9O_3$: C, 61.72; H, 5.65; N, 19.63;. Found: C, 61.79; H, 5.72; N, 19.56; IR (KBr) 3294, 2941, 1577, 1510 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.51 (d, J = 4.6 Hz, 1H), 8.04 (s, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.47 (d, J_1 = 8.9 Hz, 1H), 7.25 (d, J = 8.2 Hz, 2H), 6.98 (bs, 2H), 6.85-6.82 (m, 3H), 3.87 (s, 6H), 3.76 (bs, 4H), 3.57-3.52 (m, 2H), 2.49 (bs, 6H), 1.81-1.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$+CD_3OD): δ_C 166.0, 164.4, 152.2, 151.3, 148.9, 136.7, 135.6, 132.3, 127.9, 125.9, 124.3, 121.8, 121.3, 117.6, 116.6, 111.4, 101.5, 66.9, 57.3, 56.1, 53.6, 40.3, 25.5; MS (ESMS): m/z 642 $[M+H]^+$.

N1-(7-chloroquinolin-4-yl)-N4-(4-(3,4-dihydroquinolin-1(2H)-yl)-6-(4-methylpiperazin-1-yl)- 1,3,5-triazine-2-yl)benzene-1,4,-diamine (41)

Yield 71%; mp 195-197 °C; Anal. Calcd. for $C_{32}H_{32}ClN_9$: C, 66.48; H, 5.58; N, 21.81;. Found: C, 66.44; H, 5.53 ; N, 21.74. IR (KBr): ν 3435, 2923, 1573, 1542 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.44 (d, J = 5.3 Hz, 1H), 7.95 (d J =1.7 Hz, 1H), 7.79-7.75 (m, 2H), 7.57 (d, J = 8.6 Hz 2H), 7.38 (dd, J = 1.8 Hz, J = 8.8Hz, 1H), 7.18-7.04 (m, 4H), 6.96(t, J = 7.2 Hz, 1H), 6.81 (s, 1H), 6.72 (d J =5.3 Hz, 1H),3.99(t, J = 6.0 Hz 2H), 3.77(s, 4H), 2.75 (t, J = 6.5 Hz 2H), 2.39(bs,4H), 2.27(s,3H) 1.97-1.88(m,2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 164.9, 164.2, 151.7,

149.4, 148.6, 139.2, 137.2, 131.6, 129.2, 128.9, 126.4, 125.3, 123.8, 121.6, 118.1, 114.4, 102.2, 53.1, 52.8, 44.8, 43.6, 34.2, 32.0, 30.1, 14.5; MS (ESMS): *m*/*z* 578 $[M+H]^+$.

N1-(7-chloroquinolin-4-yl)-N4-(4-(3,4-dihydroquinolin-1(2H)-yl)-6-(4-ethylpiperazin-1-yl)-1,3,5-triazine-2-yl)benzene-1,4,-diamine (42)

Yellow solid; yield 72%; mp 204-206°C; Anal. Calcd. for $C_{33}H_{34}ClN_9$: C, 66.94; H, 5.79; N, 21.29;. Found: C, 66.91; H, 5.74; N, 21.26. IR (KBr): ν 3432, 2923, 1573, 1542 cm, 760,$^{-1}$; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 8.52 (d, *J* = 4.0 Hz, 1H), 8.02 (s, 1H), 7.86-7.82 (m, 2H) 7.66 (d, *J* = 7.6 Hz 2H), 7.46 (d, J = 8.6Hz, 1H), 7.21-7.11 (m, 4H), 6.87 (s, 1H), 6.80(d, *J* = 4.7 Hz, 1H), 6.57 (s, 1H), 4.08 (t, J = 5.5Hz, 2H), 3.85 (bs, 4H), 2.83 (t, *J* = 5.7 Hz 2H), 2.49(bs,6H), 2.05-1.96 (m,2H), 1.16(t, *J*=7.1Hz,3H), ; ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 165.4, 165.3, 164.6, 152.2, 149.9, 149.0, 135.6, 133.6, 131.6, 129.2, 128.9, 126.4, 125.3, 125.0, 123.8, 121.6, 121.0, 118.1, 114.4, 53.1, 52.8, 44.8, 27.7, 14.5; MS (ESMS): *m*/*z* 592 $[M+H]^+$.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-6-(3,4-dihydroquinolin-1(2H)-yl)-N4-(2-morpholinoethyl)-1,3,5-triazine-2,4,-diamine (43)

Yellow solid; yield 71%; mp 194-196 °C; Anal. Calcd. for $C_{33}H_{34}ClN_9O$: C, 65.18; H, 5.64; N, 20.73;. Found: C, 65.13; H, 5.61; N, 20.71. IR (KBr): ν 3273, 2944, 1574, 1506 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 8.51 (d, *J* = 5.3 Hz, 1H), 8.02 (d *J* = 2.0 Hz,, 1H), 7.87 (d, *J* = 8.9 Hz, 2H), 7.68 (d, *J* = 8.8 Hz 2H), 7.46 (dd, *J* = 2.1 Hz, J = 8.9Hz, 1H), 7.20-7.02 (m, 4H), 6.78(d, *J* = 5.3 Hz, 1H), 6.64 (bs, 1H), 5.84 (bs, 1H), 4.05 (bs, 2H), 3.73-3.69 (m, 4H), 3.54-3.52 (m, 2H), 2.83 (t, *J* = 6.5 Hz 2H), 2.60-2.46 (m, 6H), 2.06-1.97 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 164.5, 150.0, 147.9, 136.6, 135.2, 133.1, 131.1, 127.9, 126.0, 125.1, 124.4, 122.5, 120.5, 117.4, 66.1, 57.1, 52.9, 47.9, 43.9, 29.0, 26.5; MS (ESMS): *m*/*z* 608 $[M+H]^+$.

N2-(4-(7-chloroquinolin-4-ylamino)phenyl)-6-(3,4-dihydroquinolin-1(2H)-yl)-N4-(3-morpholinopropyl)-1,3,5-triazine-2,4,-diamine (44)

Cream solid; yield 69%; mp 198-200°C; Anal. Calcd. for $C_{34}H_{36}ClN_9O$: C, 65.64; H, 5.83; N, 20.26;. Found: C, 65.60; H, 5.81; N, 20.24. IR (KBr): ν 3378, 2936, 1577, 1506 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 8.43 (d, *J* = 5.3 Hz, 1H), 7.94 (d, *J* = 2.0 Hz,, 1H), 7.80-7.75 (m, 2H), 7.60 (d, *J* = 8.7 Hz 2H), 7.37 (dd, *J* = 2.0 Hz, J = 8.8 Hz, 1H), 7.11-7.01 (m, 4H), 6.96-6.92(m, 1H), 6.88 (bs, 1H), 6.71 (d, J=5.3Hz,1H), 6.51(bs, 2H),3.96 (bs, 2H), 3.68-3.64 (m, 4H), 3.47-3.38 (m, 2H), 2.77 (t, *J* = 6.5 Hz 2H), 2.44-2.39 (m, 6H), 2.00-1.87 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 164.9, 164.0, 151.7, 149.4, 148.6, 135.1, 133.2, 131.2, 128.6, 126.1, 125.7, 124.8, 124.4, 123.5, 121.2, 120.6, 117.6, 66.9, 57.3, 53.6, 44.2, 29.6, 27.2, 22.6 ; MS (ESMS): *m*/*z* 622 $[M+H]^+$.

N1-(7-chloroquinolin-4-yl)-N-(4-(3,4-dihydro-1H-isoquinolin-2-yl)-(4methylpiperazin-1-yl)-1,3,5-triazine-2-yl)benzene-1,4,-diamine (45)

Yellow solid; yield 66%; mp 194-196°C; Anal. Calcd. for $C_{32}H_{32}ClN_9$: C, 66.48; H, 5.58; N, 21.81;. Found: C, 66.43; H, 5.55 ; N, 21.80. IR (KBr): ν 3435, 2923, 1573, 1542 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 8.45 (d, *J* = 5.3 Hz, 1H), 7.96 (d *J* = 2.0 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.40 (dd, *J* = 2.1 Hz, *J* = 8.9Hz, 1H), 7.21-7.08 (m, 6H), 6.76-6.73(m, 2H), 6.58 (bs,1H), 4.84 (s, 2H), 3.99 (t, *J* = *5.7* Hz, 2H), 3.82-3.78 (m, 4H), 2.87 (t, *J* = 5.8 Hz, 2H), 2.43-2.38(m, 4H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 165.0, 164.2, 151.7, 149.3, 148.7, 139.2, 137.4, 135.7, 134.0, 133.1, 128.6, 125.9, 124.6, 121.3, 120.6, 117.6, 54.9, 46.2, 45.6, 43.1, 41.0, 28.9; MS (ESMS): *m*/*z* 578 $[M+H]^+$.

N1-(7-chloroquinolin-4-yl)-N´-(4-(3,4-dihydro-1H-isoquinolin-2-yl)-6-(4-ethylpiperazin-1-yl)- 1,3,5-triazine-2-yl)benzene-1,4,-diamine (46)

Yellow solid; yield 73%; mp 201-203 °C; Anal. Calcd. for $C_{33}H_{34}ClN_9$: C, 66.94; H, 5.79; N, 21.29;. Found: C, 66.90; H, 5.74; N, 21.24. IR (KBr): ν 3436, 2924, 1574, 1541 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 8.45 (s, 1H), 7.95 (s ,1H), 7.81 (d, *J* = 8.7 Hz, 1H) 7.62 (d, *J* = 8.3 Hz 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.19-7.10 (m, 6H), 6.74 (bs, 1H), 6.54 (bs, 1H), 4.84 (bs, 2H), 3.96 (bs, 4H), 2.84 (bs, 2H), 2.43 (bs, 6H), 1.10 (t, *J* = 6.4 Hz, 3H) ; ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 165.4, 152.2, 149.9, 139.6, 137.7, 135.6, 133.6, 131.6, 128.9, 126.4, 125.3, 123.8, 121.6, 118.1, 114.4, 102.2, 53.1, 52.8, 44.8, 30.1, 14.5; MS (ESMS): *m*/*z* 592 $[M+H]^+$.

N1-(7-chloroquinolin-4-yl)-N´-(4-(3,4-dihydro-1H-isoquinolin-2-yl)morpholinoethyl)-1,3,5-triazine-2-yl)benzene-1,4,-diamine (47)

Cream solid; yield 76%; mp 205-207 °C; Anal. Calcd. for $C_{33}H_{34}ClN_9O$: C, 66.82; H, 5.61; N, 18.89;. Found: C, 66.79; H, 5.60; N, 18.83. IR (KBr): ν 3426, 2925, 1577, 1506 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 8.53 (d, *J* = 5.4 Hz, 1H), 8.03 (d, *J* = 2.0 Hz,1H), 7.88 (d, *J* = 8.8 Hz, 1H) 7.71 (d, *J* = 8.6 Hz, 2H), 7.47 (dd, *J* = 2.0 Hz, J = 8.9Hz, 1H), 7.22-7.18 (m, 6H), 6.95(bs, 1H), 6.83 (d, *J* = 5.3 Hz, 2 H), 6.64 (bs, 1H), 4.92 (bs, 2H), 4.06 (t, J = 5.5 Hz, 2H),3.75-3.71 (m, 4H), 3.56-3.53 (m, 2H),2.95 (t, J = 5.9 Hz, 2H), 2.61-2.50 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 164.9, 151.4, 149.0, 139.2, 137.3, 135.4, 133.9, 133.3, 128.6, 126.4, 125.9, 124.5, 121.5, 120.8, 114.0, 66.9, 57.4, 56.0, 54.1, 53.4, 37.1, 33.8; MS (ESMS): *m*/*z* 608 $[M+H]^+$.

N1-(7-chloroquinolin-4-yl)-N´-(4-(3,4-dihydro-1H-isoquinolin-2-yl)morpholinopropyl)-1,3,5-triazine-2-yl)benzene-1,4,-diamine (48).

Cream solid; yield 74%; mp 194-196°C; Anal. Calcd. for $C_{34}H_{36}ClN_9O$: C, 67.26; H, 5.81; N, 18.46;. Found: C, 67.24; H, 5.78; N, 18.43. IR (KBr): ν 3426, 2954, 1572, 1536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 8.50 (d, *J* = 5.3Hz, 1H), 8.03 (s ,1H), 7.91 (d, *J* = 8.7 Hz, 1H) 7.70 (d, *J* = 8.1 Hz, 2H), 7.46 (dd, *J* = 1.8 Hz, J = 8.8Hz, 1H), 7.11-7.8 (m, 6H), 6.94(bs, 1H), 6.81 (d, *J* =

5.3 Hz, 1H), 4.91 (s, 2H), 4.02 (bs, 2H), 3.71 (t, *J* = 4.4Hz, 4H), 3.53-3.51 (m, 2H), 2.93(t, *J* = 5.4 Hz, 2H), 2.51-2.47(m, 6H), 2.07(t, *J* = 7.8Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 164.9, 164.0 151.7, 149.4, 139.0, 137.1, 135.1, 133.2, 128.6, 126.1, 125.7, 124.8, 123.5, 121.6, 117.6, 114.4, 66.9, 57.3, 44.2, 40.0, 31.8, 31.6, 29.6; MS (ESMS): *m/z* 622 $[M+H]^+$.

N1-(7-chloroquinolin-4-yl)-N´-(4-methylpiperazin-1-yl)-6-morpholino-1,3,5-triazine-2-yl)benzene-1,4,-diamine (49).

Yellow solid; yield 69%; mp 205-207 °C; Anal. Calcd. for $C_{27}H_{30}ClN_9O$: C, 60.95; H, 5.68; N, 23.69;. Found: C, 60.02; H, 5.63; N, 22.42. IR (KBr): ν 3430, 3022, 1578, 1531 cm^{-1}; ^{1}H NMR (200 MHz,$CDCl_3$+CD_3OD): δ_H 8.32 (d, *J* = 5.8 Hz, 1H), 8.29 (d , *J* = 9.2 Hz, 1H), 7.91 (s, 1H) 7.70 (d, *J* = 8.2Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 5.4Hz ,1H), 3.85-3.78(m, 12H), 2.53 (bs, 4H), 2.37 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$+CD_3OD): δ_C 169.5, 169.2, 168.6, 154.8, 154.6, 141.6, 140.2, 137.7, 130.7, 130.1, 128.9, 127.2, 105.4, 51.6, 50.0, 48.0, 47.0, 33.9 ; MS (ESMS): *m/z* 532 $[M+H]^+$.

N1-(7-chloroquinolin-4-yl)-N´-(4-ethylpiperazin-1-yl)-6-morpholino-1,3,5-triazine-2-yl)benzene-1,4,-diamine (50).

Yellow solid; yield 68%; mp 195-197 °C; Anal. Calcd. for $C_{28}H_{32}ClN_9O$: C, 61.59; H, 5.91; N, 23.09;. Found: C, 61.53; H, 5.90; N, 23.04. IR (KBr): ν 3330, 2924, 1574, 1533 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 8.53 (d, , *J* = 4.7 Hz, 1H), 8.02 (s ,1H), 7.87 (d, *J* = 8.9 Hz, 1H) 7.64 (d, *J* = 7.9 Hz 2H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.21 (bs, 2H), 6.80 (d, 2H), 6.60 (s, 1H), 3.81-3.75 (m, 12H), 2.48 (bs, 6H), 1.16(t, *J* = 6.9 Hz,3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 164.8, 164.5, 163.9, 150.6, 149.7, 148.4, 136.8, 135.1, 133.2, 126.6, 125.2, 124.1, 122.4, 120.3, 117.5, 113.5, 66.4, 52.1, 48.2, 47.9, 47.6, 13.4; MS (ESMS): *m/z* 546 $[M+H]^+$.

N1-(7-chloroquinolin-4-yl)-N´-(4-morpholino-6-(3-morpholinoethyl)-1,3,5-triazine-2-yl)benzene-1,4,-diamine (51).

Cream solid; yield 69%; mp 215-217 °C; Anal. Calcd. for $C_{28}H_{32}ClN_9O_2$: C, 61.47; H, 5.71; N, 20.48;. Found: C, 61.44; H, 5.69; N, 20.43. IR (KBr): ν 3427, 2925, 1575, 1504 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 8.52 (d, *J* = 8.0 Hz, 1H), 8.03 (d , *J* = 3.0 Hz, 1H), 7.88 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 8.4 Hz 2H), 7.47 (dd, *J* = 2.1 Hz, J = 8.9Hz, 1H), 7.25 (bs, 2H), 6.87(bs, 1H), 6.82 (d, *J* = 5.4 Hz, 1H), 6.64 (bs, 1H),3.78-3.70 (m, 12H), 3.55-3.47 (m, 2H), 2.59-2.46(m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 165.1, 151.6, 149.3, 148.6, 139.2, 137.0, 135.3, 133.5, 128.7, 125.9, 124.4, 121.2, 120.9, 117.7, 114.0, 66.9, 66.8, 54.1, 53.4; MS (ESMS): *m/z* 562 $[M+H]^+$.

N1-(7-chloroquinolin-4-yl)-N´-(4-morpholino-6-(3-morpholinopropyl)-1,3,5-triazine-2-yl)benzene-1,4,-diamine (52).

Yellow solid; yield 75%; mp 190-192 °C; Anal. Calcd. for $C_{29}H_{34}ClN_9O_2$: C, 62.08; H, 5.93; N, 19.97;. Found: C, 62.02; H, 5.91; N, 19.94. IR (KBr): ν 3418, 2926, 1577, 1504 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 8.52 (d, *J* = 5.3 Hz, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.46 (dd, *J* = 2.1Hz, J = 8.9 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.89 (bs, 1H), 6.81 (d, J = 5.3 Hz, 1H), 6.63 (bs, 1H), 5.88 (bs, 1H), 3.76-3.74 (m, 12H), 3.53-3.44 (m, 2H), 2.51-2.44 (m, 6H), 1.76-1.63 (m,2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 163.4, 154.2, 146.9, 145.6, 135.7, 132.6, 131.8, 131.6, 129.2, 128.9, 126.4, 125.3, 123.8, 121.6, 118.1, 114.4, 67.8, 65.4, 53.1, 52.8, 44.8, 43.6, 34.2, 32.0, 30.1; MS (ESMS): *m/z* 576 $[M+H]^+$.

Bioevaluation methods

***In vitro* antimalarial assay:**

The compounds were evaluated for antimalarial activity against both 3D7 (CQ- sensitive) and K1 (CQ-resistant) strains of *Plasmodium falciparum* using Malaria SYBR Green I nucleic acid

staining dye based fluorescence (MSF) assay as mentioned by Singh *et al* (2011)[1]. The stock (5mg/ml) solution was prepared in DMSO and test dilutions were prepared in culture medium (RPMI-1640-FBS). Chloroquine was used as reference drug. The compounds were tested in 96well plate (in duplicate wells). 1.0% parasitized cell suspension containing 0.8% parasitaemia was used. The plates were incubated at 37 ºC in CO_2 incubator in an atmosphere of 5% CO_2 and air mixture. After 72 hours 100 µl of lysis buffer containing 1x concentration of SYBR Green-I (Invitrogen) was added to each well and incubated for another one hour at 37 ºC. The plates were examined at 485±20nm of excitation and 530±20nm of emission for relative fluorescence units (RFUs) per well using the fluorescence plate reader (FLUO star, BMG lab technologies). Data was transferred into a graphic programme (EXCEL) and IC_{50} values were obtained by Logit regression analysis using pre-programmed Excel spreadsheet.

***In vitro* cytotoxicity evaluation assay:**

Cytotoxicity of the compounds was carried out using Vero cell line (C1008; Monkey kidney fibroblast) following the method of Mosmann (1983) with certain modifications. The cells were incubated with compound dilutions for 72h and MTT was used as reagent for the detection of cytotoxicity [2]. 50% cytotoxic concentration (CC_{50}) was determined using nonlinear regression analysis using pre-programmed Excel spreadsheet. Selectivity Index was calculated as SI = CC_{50}/IC_{50}.

***β*-Hematin inhibitory (BHIA) assay:**

Male swiss mice, weighing 15—20 g were inoculated with 1 x 10^5 *p. yoelii* infected RBCs. Blood of infected animal at 50% parasitemia was collected by cardiac puncture in 2.0% citrate buffer and centrifuged at 5000 rpm for 10 min at 4 °C. The plasma was used in assay of β-hematin formation. The assay mixture

contained 100 mM sodium acetate buffer pH (5.1), 50 µL plasma, 100 µM hemin as the substrate and 1—20 µg compound/drug in a total volume of 1.0 mL. The control tube contained all reagents except compound. The reaction mixture in triplicate was incubated at 37 °C for 16 h in a rotary shaker. The reaction was stopped by centrifugation at 10,000 rpm for 10 min at 30 °C. The pellet was suspended in 100 mM Tris—HCl buffer pH (7.4) containing 2.5% SDS. The pellet obtained after centrifugation was washed thrice with distilled water (TDW) to remove free hemin attached to β-hematin. The pellet was solubilized in 50 L of 2 N NaOH and volume was made up to 1.0 mL with TDW. Absorbance was measured at 400 nm[3]. The 50% inhibitory concentration (IC_{50}) was determined using non-linear regression analysis dose response curves.

***In silico* modeling against *P. falciparum* transketolase:**

Three dimensional structures of all the molecules involved in docking studies were modeled with the SYBYL 7.1[4] molecular modeling program (Tripos Associates, Saint Louis, MO) using the FlexX module. Each structure was energy minimized using the standard Tripos force field (Powell method and 0.05 kcal/ (mol Å) energy gradient convergence criteria). FlexX module was used for molecular docking studies to understand the interaction mechanism of these compounds with *P. falciparum* transketolase active site[5]. Modeling of Three dimensional structure of *Plasmodium falciparum* transketolase used in this docking study and characterization of its active site has been reported earlier by our group[6,7], same active site was selected as determined earlier for binding of *p*-hydroxyphenylpyruvate. All the parameters were kept default for docking

studies. Resulting conformation of compounds were ranked on the basis of C-score ranking followed by Chem Score as a tie breaker.

***In vitro* enzymatic activity assay:**

The seven compounds selected on the basis of docking score were further biologically screened. For the screening of compounds, the reaction mixture in 1 ml contained, 50 mM glycyl-glycine buffer (pH 7.6), 2 mM magnesium chloride ($MgCl_2$), 0.1 mM thiamine pyrophosphate (TPP), 0.5 mM potassium ferricyanide (K_3FeCN_6), 3 mM fructose-6-phosphate (F6P) and 0.24 mg enzyme protein in the absence and presence of different concentration of compounds to be screened was added and initial activities were measured spectrophotometrically[7].

***In vivo* antimalarial activity assay:**

The in vivo drug response was evaluated in Swiss mice infected with *P. yoelii* (N-67 strain) which is innately resistant to CQ. The mice (22±2g) were inoculated with 1x106 parasitized RBC on day 0 and treatment was administered to a group of five mice from day 0 to 3, once daily. The aqueous suspensions of compounds were prepared with a few drops of Tween 80. Initially, the efficacy of test compounds was evaluated at 50.0 mg/kg/day and required daily dose was administered in 0.2 mL volume via intraperitoneal route. The efficacy of test compounds was evaluated at 100 mg/kg/day and required daily dose was administered in 0.1 mL volume via oral route. Parasitaemia levels were recorded from thin blood smears between days 4 and 6. The mean value determined for a group of 5 mice was used to calculate the percent suppression of parasitaemia with respect to the untreated control group. Mice treated with CQ served as reference controls[8].

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