Supporting Information

Discovery of 1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one as a highly potent, selective Mammalian Target of Rapamycin (mTOR) inhibitor for the treatment of cancer

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NMR spectra of compound 16-17, 19-36, 38-47

1-(4-(4-([3,6'-biquinolin]-4'-ylamino)-2-(trifluoromethyl)phenyl)piperazin-1-yl)-3-methoxypropan-1-one (16): ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.15 (s, 1H), 9.49 (d, J = 2.4 Hz, 1H), 9.06 (d, J = 1.8 Hz, 1H), 8.84 (d, J = 2.4 Hz, 1H), 8.68 (s, 1H), 8.43 (dd, J = 9.0, 1.8 Hz, 1H), 8.25 (dd, J = 8.4, 2.4 Hz, 1H), 8.19 (d, J = 3.0 Hz, 1H), 8.10 – 8.12 (m, 2H), 7.96 (d, J = 9.0 Hz, 1H), 7.82 (ddd, J = 7.2, 6.6, 1.2 Hz, 1H), 7.69 (ddd, J = 7.2, 6.6, 1.2 Hz, 1H), 7.63 (d, J = 9.0 Hz, 1H), 3.57 (s, 3H), 3.30 - 3.32 (m, 6H), 2.86 (t, J = 4.8 Hz, 2H), 2.82 (t, J = 4.8 Hz, 2H), 2.61 (t, J = 7.2 Hz, 2H).MS (ESI): m/z $(M+H)^+$ 586.94.

1-(4-(4-([3,6'-biquinolin]-4'-ylamino)-2-(trifluoromethyl)phenyl)piperazin-1-yl)-3-(dimethylamino)propan-1-one (17): ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.12 (s, 1H), 9.49 (s, 1H), 9.05 (s, 1H), 8.84 (s, 1H), 8.67 (s, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 8.09 – 8.11 (m, 3H), 7.96 (d, J = 8.4 Hz, 1H), 7.81 (dd, J = 7.8, 7.2 Hz, 1H), 7.69 (dd, J = 7.8, 7.2 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 3.58 (s, 4H), 2.87 (s, 2H), 2.81 (s, 2H), 2.48 – 2.53 (m, 4H), 2.19 (s, 6H). MS (ESI): m/z $(M+H)^+$ 599.93.

1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (19): ^{1}H NMR 600 MHz (DMSO-d_6) δ 9.18 (s, 1H), 8.45 (d, J = 9.0 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.88 (m, 3H), 7.74 (m, 4H), 7.60 (d, J = 6.4 Hz, 1H), 7.04 (m, 2H), 6.96 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 3.31(m, 4H), 3.00 (m, 4H), MS (ESI): m/z $(M+H)^+$552.21.

9-(4-methoxyphenyl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (20): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.30 (d, J = 9.6 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.01 (s, 1H), 7.94 (dd, J = 8.4, 1.8 Hz, 1H), 7.65 – 7.72 (m, 2H), 7.09 (d, J = 9.0 Hz, 2H), 7.00 (s, 1H), 6.91 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 9.0 Hz, 2H), 3.77 (s, 3H), 2.98 – 3.10 (m, 4H), 2.78 – 2.85 (m, 4H). MS (ESI): m/z$(M+H)^+$ 531.28.

9-(benzo[b]thiophen-3-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (21): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.34 (d, J = 9.6 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.88 (dd, J = 8.4, 1.8 Hz, 1H), 7.78 (dd, J = 7.8, 1.8 Hz, 1H), 7.49 (m, 2H), 7.43 (s, 1H), 7.38 – 7.42 (m, 2H), 6.94 (d, J = 9.6 Hz, 1H), 6.79 (d, J = 1.2 Hz, 1H), 3.00 – 3.10 (m, 4H), 2.62 – 2.68 (m, 2H), 2.29 - 2.36 (m, 2H). MS (ESI): m/z $(M+H)^+$ 557.47.

1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(thianthren-1-yl)benzo[h][1,6]naphthyridin-2(1H)-one (22): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.35 (d, J = 9.6 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.95 (m, 1H), 7.78 – 7.84 (m, 2H), 7.69 – 7.73 (m, 1H), 7.58 – 7.60 (m, 2H), 7.42 (d, J = 9.0 Hz, 1H), 7.35 (dd, J = 7.8, 7.2 Hz, 2H), 7.28 -7.32(m, 2H), 6.94 (d, J = 9.6 Hz, 1H), 6.48 (d, J = 1.2 Hz, 1H), 3.06 – 3.10 (m, 4H), 2.90 – 2.93 (m, 2H), 2.75 – 2.79 (m, 2H). MS (ESI): m/z $(M+H)^+$ 638.79.

9-(isoquinolin-4-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (23): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.29 (s, 1H), 9.22 (s, 1H), 8.35 (d, J = 9.6 Hz, 1H), 8.18 – 8.20 (m, 2H), 8.03 (s, 1H), 7.83 (dd, J = 8.4, 1.8 Hz, 1H), 7.77 (s, 1H), 7.67 – 7.75 (m, 4H), 7.49 (dd, J = 9.0, 4.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 1.8 Hz, 1H), 2.95 – 2.99 (m, 4H), 2.63 -2.66 (m, 4H). MS (ESI): m/z $(M+H)^+$ 552.87.

9-(2,4-dimethoxypyrimidin-5-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (24): ^{1}H NMR 600 MHz (DMSO-d_6) δ 9.14 (s, 1H), 8.31 (d, J = 9.4 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.82 (m, 2H), 7.75 (dd, J = 2.3, 6.2 Hz, 1H), 7.71 (s, 1H), 7.68 (d, J= 8.5 Hz, 1H), 6.91 (d, J = 9.4 Hz, 1H), 6.68 (d, J = 1.8 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 2.96 (m, 4H), 2.80 (m, 4H), MS (ESI): m/z $(M+H)^+$ 563.95.

9-(naphthalen-2-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (25): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.35 (d, J = 9.6 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.77 (dd, J = 8.4, 1.8 Hz, 1H), 7.75 (d, J = 9.6 Hz, 1H), 7.53 (m, 1H), 7.46 (dd, J = 8.4, 7.2 Hz, 1H), 7.40 – 7.43 (m, 3H), 7.03 (d, J = 6.6 Hz, 1H), 6.93 (d, J = 9.6 Hz, 1H), 6.58 (s, 1H), 2.97 – 3.03 (m, 4H), 2.54 – 2.62 (m, 4H). MS (ESI): m/z $(M+H)^+$ 550.85.

9-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (26): ^{1}H NMR 600 MHz (DMSO-d_6) δ 9.10 (s, 1H), 8.29 (d, J = 9.4 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 2.3, 1H), 7.89 (dd, J= 2.0, 6.4 Hz, 1H), 7.70 (dd, J = 2.3, 5.9 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.02 (d, J = 1.8 Hz, 1H), 6.89 (d, J = 9.4 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.67 (d, J = 2.1 Hz, 1H), 6.55 (dd, J = 2.3, 6.2 Hz, 1H), 4.23 (m, 4H), 3.02 (m, 4H), 2.96 (m, 2H), 2.88 (m, 2H), MS (ESI): m/z $(M+H)^+$ 559.07.

9-(benzo[d][1,3]dioxol-5-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (27): ^{1}H NMR 600 MHz (DMSO-d_6) δ 9.11 (s, 1H), 8.30 (d, J = 9.4 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 2.3, 1H), 7.90 (dd, J= 2.1, 6.7, 1H), 7.72 (m, 2H), 6.99 (s, 1H), 6.90 (d, J = 9.4 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 1.8, 6.2 Hz, 1H), 6.62 (s, 1H), 6.04 (d, J = 0.9 Hz, 1H), 6.02 (d, J = 1.2 Hz, 1H), 3.22 (m, 4H), 3.02 (m, 2H), 2.90 (m, 2H), MS (ESI): m/z$(M+H)^+$ 545.01.

N-(4-(2-oxo-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1,2-dihydrobenzo[h][1,6]naphthyridin-9-yl)phenyl)methanesulfonamide(28): ^{1}H NMR 600 MHz (DMSO-d_6) δ 9.11 (s, 1H), 8.30 (d, J = 9.4 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 8.00 (s, 1H), 7.95 (dd, J = 1.8, 6.7 Hz, 1H), 7.68 (m, 2H), 7.31 (t, J = 7.3 Hz, 1H), 7.18 (m, 2H), 7.09 (m, 2H), 6.91 (d, J = 9.4 Hz, 1H), 3.02 (m, 6H), 2.95 (s, 3H), 2.85 (m, 2H), MS (ESI): m/z $(M+H)^+$ 594.84.

1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(thiophen-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one(29):

^{1}H NMR (600 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.29 (d, J = 9.6 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H), 8.00 (s, 1H), 7.95 (dd, J = 8.4, 1.8 Hz, 1H), 7.93 (s, 1H), 7.79 (s, 2H), 7.74 (s, 1H), 7.00 (s, 1H), 6.91 (s, 1H), 6.51 (s, 1H), 3.16 – 3.21 (m, 4H), 2.85 -2.92 (m, 4H). MS (ESI): m/z $(M+H)^+$ 507.66.

1-(4-morpholino-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (30): ^{1}H NMR 600 MHz (DMSO-d_6) δ 9.08 (s, 1H), 8.45 (d, J = 9.0 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.99 (m, 3H), 7.64 (m, 4H), 7.58 (d, J = 5.8 Hz, 1H), 7.12 (m, 2H), 6.84 (d, J = 7.5 Hz, 1H), 6.62 (d, J = 6.8 Hz, 1H), 3.82 (m, 4H), 3.02 (m, 4H). MS (ESI): m/z $(M+H)^+$ 553.17.

1-(4-(piperazin-1-ylsulfonyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (31): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.77 (d, J = 2.4 Hz, 1H), 8.36 (d, J = 9.0 Hz, 1H), 8.22 (s, 2H), 8.11 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.90 (dd, J = 8.4, 2.4 Hz, 1H), 7.79 (m, 1H), 7.64 (m, 1H), 7.37 (s, 1H), 6.94 (d, J = 9.6 Hz, 1H), 3.15- 3.25 (m, 8H). MS (ESI): m/z $(M+H)^+$ 547.99.

1-(4-(4-aminopiperidin-1-yl)-2-methoxyphenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (32): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.89 (d, J = 2.4 Hz, 1H), 8.27 (d, J = 9.6 Hz, 1H), 8.25 (dd, J = 8.4, 1.8 Hz, 1H),

8.17 (d, J = 9.0 Hz, 1H), 8.12 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.98 (m, 2H), 7.80 (m, 1H), 7.76 (d, J = 1.8 Hz, 1H), 7.74 (m, 1H), 7.23 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 9.6 Hz, 1H), 6.79 (dd, J = 8.4, 2.4 Hz, 1H), 3.56 (s, 3H), 2.83 – 2.88 (m, 4H), 2.50 – 2.54 (m, 1H), 2.00 (m, 2H), 1.78 (m, 2H). MS (ESI): m/z $(M+H)^+$ 528.12.

1-(4-((4-methylpiperazin-1-yl)methyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (33): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.96 (d, J = 2.4 Hz, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.33 (d, J = 9.6 Hz, 1H), 8.30 (d, J = 2.4 Hz, 1H), 8.19 (m, 1H), 8.07 – 8.12 (m, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.80 – 7.83 (m, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 1.2 Hz, 1H), 6.94 (d, J = 9.6 Hz, 1H), 3.74 (s, 2H), 3.25 – 3.30 (m, 4H), 2.75 – 2.95 (m, 4H), 2.74 (s, 3H). MS (ESI): m/z $(M+H)^+$ 512.02.

1-(4-(4-(cyclopropanecarbonyl)piperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (34): ^{1}H NMR 600 MHz (DMSO-d_6) δ 9.18 (s, 1H), 8.57 (d, J = 2.3 Hz, 1H), 8.34 (d, J = 9.4 Hz, 1H), 8.26 (d, J = 2.3 Hz, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.15 (dd, J = 1.8, 6.7 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.97 (m, 2H), 7.79 (m, 2H), 7.72 (d, J = 8.5 Hz, 1H), 7.67 (t, J = 7.0 Hz, 1H), 7.10 (d, J = 1.8 Hz, 1H), 6.95 (d, J = 9.4 Hz, 1H), 3.68 (m, 2H), 3.52 (m, 4H), 3.38 (m, 2H), 1.90 (m, 1H), 1.21 (m, 2H), 0.83 (m, 2H), MS (ESI): m/z $(M+H)^+$ 620.18.

1-(4-(4-(3-(dimethylamino)propanoyl)piperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one(35): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.56 (d, J = 2.4 Hz, 1H), 8.34 (d, J = 9.6 Hz, 1H), 8.29 (d, J = 2.4 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.15 (dd, J = 8.4, 1.8 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.98- 8.00 (m, 2H), 7.80 (dd, J = 7.8, 7.2 Hz, 1H), 7.69 (dd, J = 7.8, 7.2 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 1.2 Hz, 1H), 7.12 (d, J = 1.8 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 3.46 -3.54 (m, 4H), 2.97 (s, 2H), 2.72 – 2.82 (m, 4H), 2.72 (s, 6H), 2.27 (s, 2H). MS (ESI): m/z $(M+H)^+$ 651.20 .

1-(4-(4-(2-(4-methylpiperazin-1-yl)acetyl)piperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (36): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.58 (d, J = 2.4 Hz, 1H), 8.34 (d, J = 9.6 Hz, 1H), 8.27 (d, J = 2.4 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.16 (dd, J = 8.4, 1.8 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.77 – 7.81 (m, 2H), 7.66 – 7.69 (m, 2H), 7.12 (d, J = 1.8 Hz, 1H), 6.95 (d, J = 9.6 Hz, 1H), 3.58 (m, 2H), 3.43 (m, 4H), 3.38 (m, 2H), 3.22 (s, 2H), 2.65 – 2.75 (m, 8H), 2.12 (s, 3H). MS (ESI): m/z $(M+H)^+$ 692.26.

1-(2-(dimethylamino)ethyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one(38): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.50 (d, J = 3.0 Hz, 1H), 9.13 (d, J = 1.2 Hz, 1H), 9.07 (s, 1H), 8.91 (d, J = 2.4 Hz, 1H), 8.37 (dd, J = 9.0, 1.8 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.80 (ddd, J = 7.2, 6.6, 1.2 Hz, 1H), 7.68 (ddd, J = 7.2, 6.6, 1.2 Hz, 1H), 6.84 (d, J = 9.0 Hz,

1H), 4.66 (t, *J* = 7.2 Hz, 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.20(s, 6H). MS (ESI): m/z $(M+H)^+$ 395.28.

1-(4'-(4-methylpiperazine-1-carbonyl)-2-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one(39): ^{1}H NMR 600 MHz ($CDCl_3$) δ 9.07 (s, 1H), 8.73 (d, *J* = 1.8 Hz, 1H), 8.31 (d, *J* = 9 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 9.02 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.99 (d, *J* = 1.8 Hz, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.78 (m, 2H), 7.70 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.58 (m, 2H), 7.27 (m, 2H), 7.22 (d, *J* = 1.8 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 2H), 7.03 (d, *J* = 9.6 Hz, 1H), 3.84 (m, 2H), 3.49 (m, 2H), 3.35 (s, 3H), 2.53 (m, 2H), 2.40 (m, 2H). MS (ESI): m/z $(M+H)^+$ 670.31.

1-(4-(1-propionyl-1,2,3,6-tetrahydropyridin-4-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (40): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.52 (d, *J* = 7.2 Hz, 1H), 8.34 – 8.36 (m, 2H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.14 – 8.17 (m, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 8.03 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.80 – 7.83 (m, 2H), 7.66 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.08 – 7.11 (m, 1H), 6.96 (d, *J* = 9.0 Hz, 1H), 5.48 (d, *J* = 17.4 Hz, 1H), 3.83 – 3.93 (m, 2H), 3.43 – 3.51 (m, 2H), 2.31 (q, *J* = 6.6 Hz, 2H), 2.07 – 2.14 (m, 2H), 1.00 (t, *J* = 6.6 Hz, 3H). MS (ESI): m/z $(M+H)^+$ 605.33.

1-(4-(1-(2-morpholinoacetyl)piperidin-4-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (41): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.19

(s, 1H), 8.49 (dd, *J* = 6.0, 3.6 Hz, 1H), 8.34 (d, *J* = 10.8 Hz, 1H), 8.29 (d, *J* = 12.0 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.13 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.95 – 8.03 (m, 3H), 7.70 - 7.81 (m, 3H), 7.67 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.02 (d, *J* = 6.0 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 1H), 3.75 – 4.49 (m, 2H), 3.55 (s, 2H), 3.50 (s, 2H), 3.15 – 3.30 (m, 1H), 2.95 – 3.05 (m, 3H), 2.55 - 2.85 (m, 1H), 2.37 (m, 4H), 1.31 – 1.79 (m, 2H), 1.09 – 1.34 (m, 2H). MS (ESI): m/z $(M+H)^+$ 678.36.

3-methyl-1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (42): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.58 (d, *J* = 2.4 Hz, 1H), 8.26 (d, *J* = 1.8 Hz, 1H), 8.22 (d, *J* = 1.2 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.13 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 2.4 Hz, 1H), 7.80 (ddd, *J* = 7.8, 7.2, 1.8 Hz, 1H), 7.77 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.67 – 7.70 (m, 2H), 7.08 (d, *J* = 1.8 Hz, 1H), 3.44 – 3.48 (m, 4H), 2.60 – 2.70 (m, 4H), 2.27 (q, *J* = 7.2 Hz, 2H), 2.23(s, 3H), 0.98 (t, *J* = 7.2 Hz, 3H). MS (ESI): m/z $(M+H)^+$ 622.38.

4-methyl-1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (43): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.30 (s, 1H), 8.57 (d, *J* = 1.8 Hz, 1H), 8.26 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 1.8 Hz, 1H), 7.80 (dd, *J* = 8.4, 6.6 Hz, 1H), 7.66 – 7.71 (m, 3H), 7.19 (s, 1H), 6.83 (s, 1H), 3.41 – 3.49 (m, 4H), 2.71 (s, 3H), 2.56 – 2.70 (m, 4H), 2.26 (q, *J* = 7.2 Hz, 2H), 0.99 (t, *J* = 7.2 Hz, 3H). MS (ESI): m/z $(M+H)^+$ 622.14.

3-methyl-1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)pyrimido[5,4-c]quinoline-2,4(1H,3H)-dione (44): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.55 (d, J = 2.4 Hz, 1H), 8.28 (d, J = 2.4 Hz, 1H), 8.24 (dd, J = 8.4, 1.8 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H),7.87 (dd, J = 6.6, 2.4 Hz, 1H), 7.81 (ddd, J = 7.2, 6.6, 1.8 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.68 (dd, J = 7.8, 7.2 Hz, 1H), 7.06 (d, J = 1.2 Hz, 1H), 3.45 – 3.48 (m, 4H), 3.39 (s, 3H), 2.63 – 2.72 (m, 4H), 2.28 (q, J = 7.2 Hz, 2H), 0.99 (t, J = 7.2 Hz, 3H). MS (ESI): m/z $(M+H)^+$ 639.49.

1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)-3,4-dihydropyrimido[5,4-c]quinolin-2(1H)-one (45): ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.54 (d, J = 2.4 Hz, 1H), 8.27 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 7.2 Hz, 1H), 8.01 (m, 1H), 7.95 (d, J = 6.6 Hz, 1H), 7.88 (d, J = 2.4 Hz, 1H), 7.77 (m, 1H), 7.67 (dd, J = 8.4, 7.8 Hz, 1H), 7.52 – 7.60 (m, 2H), 7.43 (m, 1H), 7.16 (d, J = 1.8 Hz, 1H), 5.00 (s, 2H), 3.39 – 3.48 (m, 4H), 2.62 – 2.68 (m, 4H), 2.28 (q, J = 7.8 Hz, 2H), 0.98 (t, J = 7.8 Hz, 3H). MS (ESI): m/z $(M+H)^+$ 611.12.

3-methyl-1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)-3,4-dihydropyrimido[5,4-c]quinolin-2(1H)-one (46): ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H), 8.06 – 8.09 (m, 2H), 8.03 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 6.6 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.76 (m, 1H), 7.66 (m, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 1.2 Hz, 1H), 4.75 (s,

2H), 3.46 – 3.50 (m, 4H), 3.01 (s, 3H), 2.64 – 2.69 (m, 4H), 2.28 (q, *J* = 7.8 Hz, 2H), 0.97 (t, *J* = 7.2 Hz, 3H). MS (ESI): m/z $(M+H)^+$ 625.22.

1-(4-(4-propionylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)-1H-[1,3]oxazino[5,4-c]quinolin-2(4H)-one (47): ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.55 (d, *J* = 2.4 Hz, 1H), 8.30 (d, *J* = 2.4 Hz, 1H), 8.14- 8.15 (m, 2H), 8.02 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 3.0 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.84 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.77 – 7.80 (m, 1H), 7.58 – 7.61 (m, 1H), 7.53 – 7.55 (m, 1H), 7.10 (d, *J* = 1.8 Hz, 1H), 5.70 (s, 2H), 3.46 – 3.49 (m, 4H), 2.71 – 2.73 (m, 4H), 2.29 (q, *J* = 7.2 Hz, 2H), 0.99 (t, *J* = 7.2 Hz, 3H). MS (ESI): m/z $(M+H)^+$ 612.22.