

## Supporting Information

### Discovery of 9-(6-aminopyridin-3-yl)-1-(3-

(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (Torin2) as a potent, selective and orally available mTOR inhibitor for treatment of cancer

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**NMR spectra of compound 2, 9-31.**

**1-(4-fluoro-3-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (2):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 9.20 (s, 1H), 8.79 (d, *J* = 2.4 Hz, 1H),

8.35 (d,  $J = 10.2$  Hz, 1H), 8.20 – 8.24 (m, 3H), 8.06 (d,  $J = 8.4$  Hz, 1H), 8.00 – 8.02 (m, 2H), 7.90 – 7.93 (m, 2H), 7.80 (dd,  $J = 7.8, 7.2$  Hz, 1H), 7.70 (dd,  $J = 7.8, 6.6$  Hz, 1H), 7.18 (d,  $J = 1.2$  Hz, 1H), 6.96 (d,  $J = 10.2$  Hz, 1H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 486.22.

**1-(4-fluoro-3-(trifluoromethyl)phenyl)-9-(1H-pyrazol-4-**

**yl)benzo[h][1,6]naphthyridin-2(1H)-one (9):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  13.08 (s, 1H), 9.07 (s, 1H), 8.30 (d,  $J = 9.6$  Hz, 1H), 8.20 (dd,  $J = 6.0, 2.4$  Hz, 1H), 8.01 (d,  $J = 8.4$  Hz, 1H), 7.97 (dd,  $J = 8.4, 1.8$  Hz, 1H), 7.93 (m, 1H), 7.89 (dd,  $J = 10.2, 9.0$  Hz, 1H), 6.91 (d,  $J = 9.0$  Hz, 1H), 6.88 (d,  $J = 1.8$  Hz, 1H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 425.22.

**1-(4-fluoro-3-(trifluoromethyl)phenyl)-9-(1-methyl-1H-pyrazol-4-**

**yl)benzo[h][1,6]naphthyridin-2(1H)-one (10):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.07 (s, 1H), 8.29 (d,  $J = 9.6$  Hz, 1H), 8.21 (d,  $J = 10.2$  Hz, 1H), 8.02 (d,  $J = 8.4$  Hz, 1H), 7.86 – 7.91 (m, 3H), 7.78 (s, 1H), 7.11 (s, 1H), 6.91 (d,  $J = 9.0$  Hz, 1H), 6.83 (s, 1H), 3.81 (s, 3H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 439.26

**9-(6-aminopyridin-3-yl)-1-(4-fluoro-3-**

**(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (11):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.09 (s, 1H), 8.31 (d,  $J = 9.6$  Hz, 1H), 8.21 (d,  $J = 4.8$  Hz, 1H), 8.05 (d,  $J = 8.4$  Hz, 1H), 7.91 -7.94 (m, 2H), 7.84 -7.86 (m, 2H), 7.08 (d,  $J = 8.4$  Hz, 1H), 6.92 (d,  $J = 9.6$  Hz, 1H), 6.90 (s, 1H), 6.42 (d,  $J = 9.0$  Hz, 1H), 6.23 (s, 2H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 451.14.

**9-(2-aminopyrimidin-5-yl)-1-(4-fluoro-3-**

**(trifluoromethyl)phenyl)benzo[h][1,6]naphthyridin-2(1H)-one (12):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 9.13 (s, 1H), 8.32 (d, *J* = 9.6 Hz, 1H), 8.17 (d, *J* = 6.0 Hz, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 8.06 (s, 2H), 7.98 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.95 (m, 1H), 7.86 (dd, *J* = 9.6, 9.6 Hz, 1H), 6.96 (s, 2H), 6.93 (d, *J* = 9.6 Hz, 1H), 6.89 (s, 1H). MS (ESI): *m/z* (M+H)<sup>+</sup> 452.10.

**1-(4-fluoro-3-(trifluoromethyl)phenyl)-9-(1H-indazol-5-**

**yl)benzo[h][1,6]naphthyridin-2(1H)-one (13):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 13.17 (s, 1H), 9.14 (s, 1H), 8.33 (d, *J* = 9.6 Hz, 1H), 8.26 (d, *J* = 4.2 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 9.0 Hz, 1H), 8.02 (s, 1H), 7.93 (m, 1H), 7.85 (dd, *J* = 9.6, 9.0 Hz, 1H), 7.50 -7.51 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.06 (s, 1H), 6.94 (d, *J* = 9.6 Hz, 1H). MS (ESI): *m/z* (M+H)<sup>+</sup> 475.14.

**1-(4-fluoro-3-(trifluoromethyl)phenyl)-9-(1H-pyrrolo[2,3-b]pyridin-5-**

**yl)benzo[h][1,6]naphthyridin-2(1H)-one (14):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 11.82 (s, 1H), 9.15 (s, 1H), 8.33 (d, *J* = 9.0 Hz, 1H), 8.25 (d, *J* = 4.2 Hz, 1H), 8.09 – 8.13 (m, 3H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.85 (dd, *J* = 10.2, 9.0 Hz, 1H), 7.60 (s, 1H), 7.53 (s, 1H), 7.08 (s, 1H), 6.93 (d, *J* = 9.6 Hz, 1H), 6.41 (s, 1H). MS (ESI): *m/z* (M+H)<sup>+</sup> 475.11.

**1-(4-fluoro-3-methylphenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one**

**(15):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 9.17 (s, 1H), 8.82 (d, *J* = 1.8 Hz, 1H), 8.32 (d, *J* = 9.6 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H),

8.03 (s, 1H), 7.96 (d,  $J = 8.4$  Hz, 1H), 7.80 (dd,  $J = 8.4, 6.6$  Hz, 1H), 7.70 (dd,  $J = 7.8, 7.2$  Hz, 1H), 7.56 (d,  $J = 4.8$  Hz, 1H), 7.48 (dd,  $J = 9.0, 9.0$  Hz, 1H), 7.39 (m, 1H), 7.35 (s, 1H), 6.93 (d,  $J = 9.6$  Hz, 1H), 2.32 (s, 3H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 432.20.

**1-(4-fluoro-3-methylphenyl)-9-(1H-pyrazol-4-yl)benzo[h][1,6]naphthyridin-2(1H)-one (16):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  13.05 (s, 1H), 9.04 (s, 1H), 8.26 (d,  $J = 10.2$  Hz, 1H), 7.99 (d,  $J = 9.0$  Hz, 1H), 7.94 (dd,  $J = 9.0, 1.8$  Hz, 1H), 7.79 (s, 1H), 7.47 – 7.51 (m, 2H), 7.25 – 7.37 (m, 2H), 7.02 (s, 1H), 6.88 (d,  $J = 9.6$  Hz, 1H), 2.32 (s, 3H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 371.15.

**1-(4-fluoro-3-methylphenyl)-9-(1-methyl-1H-pyrazol-4-yl)benzo[h][1,6]naphthyridin-2(1H)-one (17):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.03 (s, 1H), 8.26 (d,  $J = 9.6$  Hz, 1H), 7.98 (d,  $J = 8.4$  Hz, 1H), 7.87 (dd,  $J = 8.4, 1.8$  Hz, 1H), 7.78 (s, 1H), 7.47 – 7.51 (m, 2H), 7.33 – 7.36 (m, 1H), 7.16 (s, 1H), 6.96 (d,  $J = 1.8$  Hz, 1H), 6.88 (d,  $J = 9.0$  Hz, 1H), 3.83 (s, 3H), 2.32 (s, 3H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 385.27.

**1-(4-fluoro-3-methylphenyl)-9-(6-methoxypyridin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (18):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.12 (s, 1H), 8.29 (d,  $J = 9.6$  Hz, 1H), 8.08 (m, 2H), 7.99 (d,  $J = 8.4$  Hz, 1H), 7.53 (d,  $J = 6.0$  Hz, 1H), 7.40 – 7.44 (m, 2H), 7.32 (s, 1H), 7.05 (s, 1H), 6.91 (d,  $J = 9.0$  Hz, 1H), 6.83 (d,  $J = 8.4$  Hz, 1H), 3.88 (s, 3H), 2.31 (s, 3H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 412.25.

**5-(1-(4-fluoro-3-methylphenyl)-2-oxo-1,2-dihydrobenzo[h][1,6]naphthyridin-9-yl)picolinonitrile (19):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 9.19 (s, 1H), 8.51 (d, *J* = 2.4 Hz, 1H), 8.32 (d, *J* = 9.6 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.11 – 8.14 (m, 2H), 7.89 (dd, *J* = 7.8, 2.4 Hz, 1H), 7.54 (dd, *J* = 6.6, 2.4 Hz, 1H), 7.41 (dd, *J* = 9.0, 9.0 Hz, 1H), 7.34 (m, 1H), 7.18 (d, *J* = 1.8 Hz, 1H), 6.93 (d, *J* = 9.6 Hz, 1H), 2.31 (s, 3H). MS (ESI): *m/z* (M+H)<sup>+</sup> 407.26.

**9-(2-aminopyrimidin-5-yl)-1-(4-fluoro-3-methylphenyl)benzo[h][1,6]naphthyridin-2(1H)-one (20):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 9.09 (s, 1H), 8.28 (d, *J* = 10.2 Hz, 1H), 8.08 (s, 2H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.97 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.51 (d, *J* = 4.8 Hz, 1H), 7.42 (dd, *J* = 9.6, 8.4 Hz, 1H), 7.33 (m, 1H), 7.04 (d, *J* = 1.8 Hz, 1H), 6.95 (s, 2H), 6.90 (d, *J* = 9.6 Hz, 1H), 2.30 (s, 3H). MS (ESI): *m/z* (M+H)<sup>+</sup> 398.25.

**1-(4-fluoro-3-methylphenyl)-9-(1H-pyrrolo[2,3-b]pyridin-5-yl)benzo[h][1,6]naphthyridin-2(1H)-one (21):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 11.80 (s, 1H), 9.11 (s, 1H), 8.30 (d, *J* = 9.6 Hz, 1H), 8.07 – 8.12 (m, 3H), 7.65 (s, 1H), 7.57 (d, *J* = 5.4 Hz, 1H), 7.54 (s, 1H), 7.42 (dd, *J* = 9.0, 8.4 Hz, 1H), 7.32 (m, 1H), 7.23 (s, 1H), 6.91 (d, *J* = 9.6 Hz, 1H), 6.45 (s, 1H), 2.34 (s, 3H). MS (ESI): *m/z* (M+H)<sup>+</sup> 420.20.

**1-(3-chloro-4-fluorophenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (22):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 9.19 (s, 1H), 8.86 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 9.6 Hz, 1H), 8.25 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 8.07 (m, 2H), 8.02

(d,  $J = 1.8$  Hz, 1H), 7.98 (d,  $J = 8.4$  Hz, 1H), 7.80 (m, 2H), 7.71 (t,  $J = 8.4$  Hz, 1H), 7.63 (m, 1H), 7.29 (d,  $J = 1.8$  Hz, 1H), 6.96 (d,  $J = 9$  Hz, 1H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 452.19.

**1-(3-chloro-4-fluorophenyl)-9-(1-methyl-1H-pyrazol-4-**

**yl)benzo[h][1,6]naphthyridin-2(1H)-one (23):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.05 (s, 1H), 8.29 (d,  $J = 9.6$  Hz, 1H), 8.0 (m, 2H), 7.89 (dd,  $J = 8.4, 1.8$  Hz, 1H), 7.85 (s, 1H), 7.78 (t,  $J = 9$  Hz, 1H), 7.58 (m, 1H), 7.14 (s, 1H), 6.95 (s, 1H), 6.91 (d,  $J = 9$  Hz, 1H), 3.83 (s, 3H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 405.17.

**1-(3-chloro-4-fluorophenyl)-9-(1H-pyrrolo[2,3-b]pyridin-5-**

**yl)benzo[h][1,6]naphthyridin-2(1H)-one (24):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  11.82 (s, 1H), 9.13 (s, 1H), 8.32 (d,  $J = 8.4$  Hz, 1H), 8.11 – 8.13 (m, 3H), 8.05 (dd,  $J = 7.2, 3.0$  Hz, 1H), 7.74 (dd,  $J = 9.6, 8.4$  Hz, 1H), 7.67 (d,  $J = 2.4$  Hz, 1H), 7.58 (m, 1H), 7.54 (dd,  $J = 9.0, 8.4$  Hz, 1H), 7.18 (d,  $J = 1.2$  Hz, 1H), 6.93 (d,  $J = 9.0$  Hz, 1H), 6.46 (m, 1H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 441.18.

**9-(2-aminopyrimidin-5-yl)-1-(3-chloro-4-fluorophenyl)benzo[h][1,6]naphthyridin-**

**2(1H)-one (25):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.11 (s, 1H), 8.31 (d,  $J = 9$  Hz, 1H), 8.09 (s, 2H), 8.08 (d,  $J = 9$  Hz, 1H), 7.99 (m, 2H), 7.73 (t,  $J = 9$  Hz, 1H), 7.57 (m, 1H), 7.0 (m, 3H), 6.92 (d,  $J = 9.6$  Hz, 1H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 418.29.

**9-(6-aminopyridin-3-yl)-1-(3-chloro-4-fluorophenyl)benzo[h][1,6]naphthyridin-**

**2(1H)-one (26):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.08 (s, 1H), 8.29 (d,  $J = 9.6$  Hz, 1H),

8.04 (d,  $J = 9.0$  Hz, 1H), 8.00 (d,  $J = 5.4$  Hz, 1H), 7.93 (d,  $J = 9.0$  Hz, 1H), 7.81 (s, 1H), 7.73 (dd,  $J = 9.0, 8.4$  Hz, 1H), 7.55 – 7.57 (m, 1H), 7.19 (d,  $J = 8.4$  Hz, 1H), 7.01 (s, 1H), 6.90 (d,  $J = 8.4$  Hz, 1H), 6.44 (d,  $J = 8.4$  Hz, 1H), 6.24 (s, 2H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 417.24.

**1-(3,4-difluorophenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-2(1H)-one (27):**

<sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.19 (s, 1H), 8.82 (d,  $J = 2.4$  Hz, 1H), 8.34 (d,  $J = 9.0$  Hz, 1H), 8.25 (dd,  $J = 9.0, 2.4$  Hz, 1H), 8.20 (d,  $J = 8.4$  Hz, 1H), 8.09 (d,  $J = 1.8$  Hz, 1H), 8.07 (d,  $J = 7.8$  Hz, 1H), 7.96 (d,  $J = 7.2$  Hz, 1H), 7.93 (m, 1H), 7.79 - 7.87 (m, 2H), 7.70 (ddd,  $J = 7.8, 7.2, 1.2$  Hz, 1H), 7.50 (m, 1H), 7.29 (d,  $J = 1.8$  Hz, 1H), 6.95 (d,  $J = 9.0$  Hz, 1H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 436.23.

**1-(3,4-difluorophenyl)-9-(1-methyl-1H-pyrazol-4-yl)benzo[h][1,6]naphthyridin-**

**2(1H)-one (28):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.06 (s, 1H), 8.28 (d,  $J = 9.6$  Hz, 1H), 8.01 (d,  $J = 9.0$  Hz, 1H), 7.88 (dd,  $J = 9.0, 1.8$  Hz, 1H), 7.80 – 7.86 (m, 3H), 7.46 (m, 1H), 7.15 (s, 1H), 6.93 (d,  $J = 1.8$  Hz, 1H), 6.89 (d,  $J = 9.6$  Hz, 1H), 3.83 (s, 3H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 389.15.

**1-(4-fluoro-2-(trifluoromethyl)phenyl)-9-(quinolin-3-yl)benzo[h][1,6]naphthyridin-**

**2(1H)-one (29):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.22 (s, 1H), 8.81 (d,  $J = 2.4$  Hz, 1H), 8.40 (d,  $J = 9.6$  Hz, 1H), 8.27 (dd,  $J = 8.4, 1.8$  Hz, 1H), 8.23 (d,  $J = 8.4$  Hz, 1H), 8.19 (d,  $J = 9.0$  Hz, 1H), 8.07 (d,  $J = 8.4$  Hz, 1H), 8.03 – 8.06 (m, 4H), 7.82 (m, 1H), 7.71 (dd,  $J =$

8.4, 7.8 Hz, 1H), 7.04 (d,  $J = 1.8$  Hz, 1H), 6.98 (d,  $J = 9.6$  Hz, 1H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 485.68.

**1-(4-fluoro-2-(trifluoromethyl)phenyl)-9-(1-methyl-1H-pyrazol-4-**

**yl)benzo[h][1,6]naphthyridin-2(1H)-one (30):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  9.09 (s, 1H), 8.33 (d,  $J = 9.6$  Hz, 1H), 8.18 (dd,  $J = 8.4, 2.4$  Hz, 1H), 8.03 (d,  $J = 9.0$  Hz, 1H), 8.00 (dd,  $J = 8.4, 3.0$  Hz, 1H), 7.95 (dd,  $J = 8.4, 5.4$  Hz, 1H), 7.89 (dd,  $J = 9.0, 1.8$  Hz, 1H), 7.80 (s, 1H), 7.18 (s, 1H), 6.93 (d,  $J = 9.0$  Hz, 1H), 6.72 (d,  $J = 1.2$  Hz, 1H), 3.83 (s, 3H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 439.18.

**1-(4-fluoro-2-(trifluoromethyl)phenyl)-9-(1H-pyrazol-4-**

**yl)benzo[h][1,6]naphthyridin-2(1H)-one (31):** <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  13.10 (s, 1H), 9.08 (s, 1H), 8.33 (d,  $J = 9.6$  Hz, 1H), 8.18 (d,  $J = 6.0$  Hz, 1H), 7.94 - 8.03 (m, 4H), 7.82 (br, 1H), 7.23 (br, 1H), 6.93 (d,  $J = 9.0$  Hz, 1H), 6.80 (s, 1H). MS (ESI):  $m/z$  (M+H)<sup>+</sup> 425.09.