**Supplemental data**

**Synthesis of LEDGIN-6**

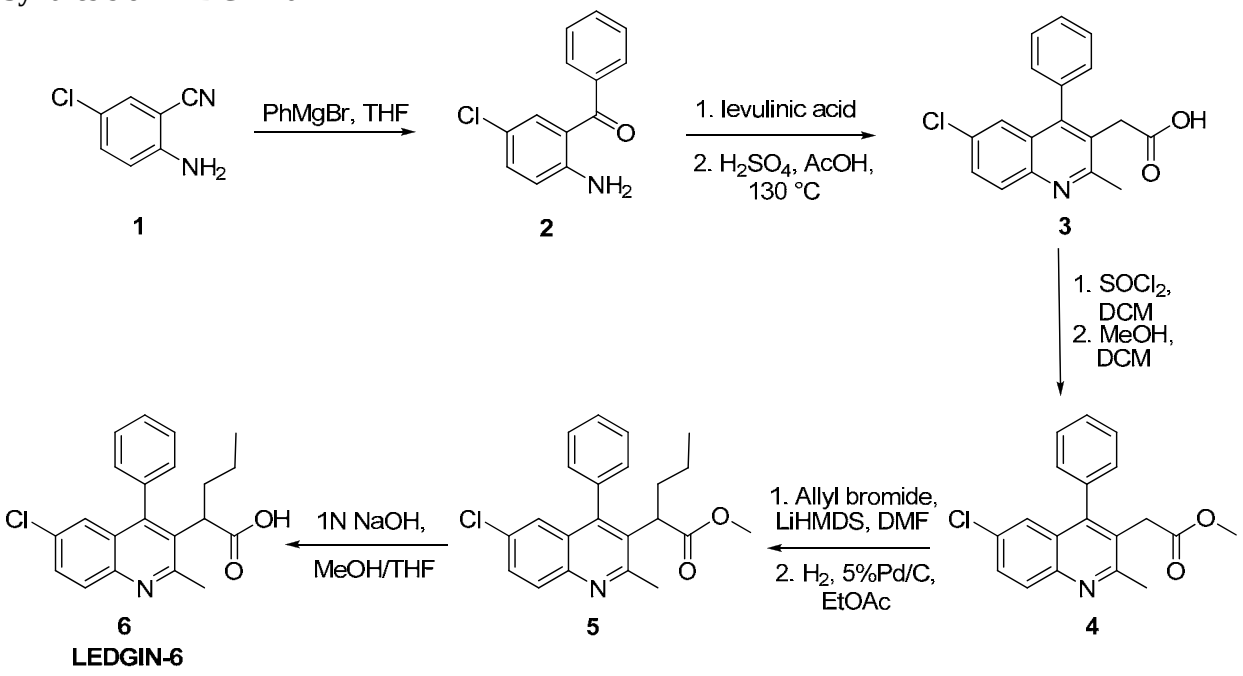


**Figure S1.** Synthetic scheme for the preparation of LEDGIN-6.

**(2-amino-5-chlorophenyl)(phenyl)methanone (2).** Phenyl magnesium bromide (1 M in THF, 13.2 mL, 13.2 mmol) was added dropwise over 5 min to a solution of 2-amino-5-chloro-benzonitrile **1** (500 mg, 3.28 mmol) in anhydrous THF (10 mL) at 0 °C. The yellow reaction mixture was allowed to stir at room temperature for 15 min. and then heated to 70 °C overnight. The resulting orange reaction mixture was cooled to 0 °C and acidified with 2 M HCl to pH 1, stirred for 2 h extracted with ethyl acetate (3 x 10 mL) washed with sat. $NaHCO_3$ followed by brine and water. The combined organic layer were dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography to provide **2** (646 mg, 85%) as a yellow solid: mp 95-96 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, $J$ = 7.5 Hz, 2H), 7.61–7.46 (m, 3H), 7.43 (d, $J$ = 2.3 Hz, 1H), 7.25 (dd, $J$ = 8.7, 2.3 Hz, 1H), 6.70 (d, $J$ = 8.8 Hz, 1H), 6.10 (s, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 197.9, 149.3, 139.2, 134.1, 133.2, 131.5, 129.0, 128.3, 119.9, 118.7, 118.4.

**2-(6-chloro-2-methyl-4-phenylquinolin-3-yl)acetic acid (3).** (2-amino-5-chlorophenyl)-(phenyl)methanone (**2**) (646 mg, 2.78 mmol) was dissolved in a mixture of acetic acid and sulfuric acid (100 : 1, 5.55 mL). Levulinic acid (323.8 mg 2.78 mmol) was then added and the reaction mixture was heated to 90 °C overnight. After heating for 16 h, the mixture was cooled to room temperature and allowed to sit for 2 h before cold water was added. The precipitate which formed was filtered and dried to provide **3** (638 mg; 73%) as a yellow solid: mp 125-128 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.02 (d, $J$ = 8.9 Hz, 1H), 7.73 (dd, $J$ = 9.0, 2.4 Hz, 1H), 7.59 (m, 3H), 7.28–7.22 (m, 2H), 7.13 (d, $J$ = 2.3 Hz, 1H), 2.67 (s, 3H);. $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.8, 160.5, 136.4, 131.5, 131.3, 130.6, 129.9, 129.8, 129.6, 127.9, 127.7, 125.3, 72.4, 36.9, 24.5.

**Methyl 2-(6-chloro-2-methyl-4-phenylquinolin-3-yl)acetate (4).** Thionyl chloride (1.1 mL, 15.3 mmol) was added dropwise to a suspension of 2-(6-chloro-2-methyl-4-phenylquinolin-3-yl)acetic acid (**3**) (350 mg, 1.07 mmol) in dichloromethane (12 mL) under argon. After stirring for 16 h the reaction mixture was

concentrated under reduced pressure. The crude acid chloride was dissolved in DCM (10 mL) and methanol (3 mL) and stirred at room temperature. After 2 h, the mixture was concentrated and the crude methyl ester was dissolved in dichloromethane and stirred with triethylamine (1 mL) for 30 min before being quenched with water and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Flash chromatography gave **4** (269 mg, 73.8%) as an off-white solid: mp 178-180 °C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.9 Hz, 1H), 7.57 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.51 (d, *J* = 4.5 Hz, 3H), 7.30–7.18 (m, 3H), 3.65 (s, 3H), 3.61 (s, 2H), 2.71 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 171.2, 158.8, 147.3, 145.2, 135.9, 131.6, 130.3, 129.9, 129.1, 128.8, 128.5, 127.5, 125.5, 125.2, 52.2, 36.2, 24.1.

**Methyl 2-(6-chloro-2-methyl-4-phenylquinolin-3-yl)pentanoate (5).** A stirred solution of methyl 2-(6-chloro-2-methyl-4-phenylquinolin-3-yl)acetate (**4**) (200 mg, 0.61 mmol) in anhydrous THF under argon at 0 °C was treated with ally bromide (1.11 g, 9.19 mmol) followed by LiHMDS (1.53 mL, 1.53 mmol). After completion of the addition, the ice bath was removed and stirring continued for 45 min. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Flash chromatography afforded methyl 2-(6-chloro-2-methyl-4-phenylquinolin-3-yl)pent-4-enoate (162.2 mg, 72.5%) as a light yellow solid: mp 108-110 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 1H), 7.56–7.50 (m, 1H), 7.47 (dd, *J* = 11.7, 6.7 Hz, 3H), 7.30–7.22 (m, 1H), 7.17 (d, *J* = 2.1 Hz, 2H), 5.43 (dt, *J* = 16.9, 7.8 Hz, 1H), 4.82 (d, *J* = 6.3 Hz, 1H), 4.79 (s, 1H), 3.91 (t, *J* = 7.4 Hz, 1H), 3.62 (s, 3H), 2.96–2.86 (m, 1H), 2.65 (s, 3H), 2.49–2.37 (m, 1H).$^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.4, 158.0, 147.6, 144.8, 136.2, 135.2, 131.7, 130.2, 130.1, 129.9, 129.8, 129.5, 128.9, 128.5, 128.5, 127.5, 125.5, 121.3, 117.1, 71.8, 52.4, 46.5, 34.8, 24.4.

2-(6-chloro-2-methyl-4-phenylquinolin-3-yl)pent-4-enoate in ethyl acetate and methanol (9:1 ratio, 10 mL) was stirred with 5% Pd/C under a balloon of hydrogen gas for 3 h. The reaction mixture was then filtered through celite and washed with ethyl acetate (3 x 10 mL). The filtrate was concentrated and taken to the next step without further purification: mp 104-105 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 1H), 7.60–7.55 (m, 1H), 7.55–7.48 (m, 3H), 7.30 (dd, *J* = 4.3, 3.0 Hz, 1H), 7.21 (dd, *J* = 5.7, 2.1 Hz, 2H), 3.83 (t, *J* = 7.0 Hz, 1H), 3.66 (s, 3H), 2.66 (d, *J* = 6.2 Hz, 3H), 2.19 (dt, *J* = 16.0, 5.9 Hz, 1H), 1.64 (dd, *J* = 24.1, 13.5 Hz, 1H), 1.11 (dd, *J* = 14.4, 9.2 Hz, 1H), 1.06–0.93 (m, 1H), 0.72 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.0, 158.2, 144.7, 136.4, 131.6, 131.2, 130.0, 129.8, 129.7, 129.5, 128.9, 128.5, 128.5, 127.5, 125.4, 93.5, 71.8, 71.8, 52.5, 46.4, 32.7, 24.4, 21.2, 13.9.

**2-(6-chloro-2-methyl-4-phenylquinolin-3-yl)pentanoic acid (6, LEDGIN-6).** Potassium hydroxide (52 mg, 0.93 mmol) in water (1 mL) was added to a solution of methyl 2-(6-chloro-2-methyl-4-phenylquinolin-3-yl)pentanoate (**5**) (170 mg, 0.46 mmol) in DMSO (3.4 mL). After heating for 1 h at 60 °C, the mixture was cooled to room temperature. Acetic acid (0.4 mL) was added and the resulting solution was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Residual DMSO was removed under vacuum at 50 °C. Recrystallization of the crude product in hexane/ dichloromethane provided compound **6** (70 mg, 42.6%) as an off-white crystalline solid: mp 215-217 °C; $^{1}$H NMR (300 MHz, DMSO-$d_6$) δ 12.69 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.61-7.59 (m, 3H), 7.32 (m, 2H), 7.08 (s, 1H), 3.69 (t, *J* = 6.8 Hz, 1H), 2.64 (s, 3H), 2.05 (m, 1H), 1.58 (s, 1H), 0.95 (s, 1H), 0.65 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 175.3, 159.4, 147.3, 145.0, 136.8, 132.6, 131.5, 131.4, 130.5, 130.4, 130.1, 129.9, 129.7, 129.5, 127.8, 125.5, 46.9, 32.9, 25.2, 21.7, 14.6.

**Synthesis of Compound BI-1001**

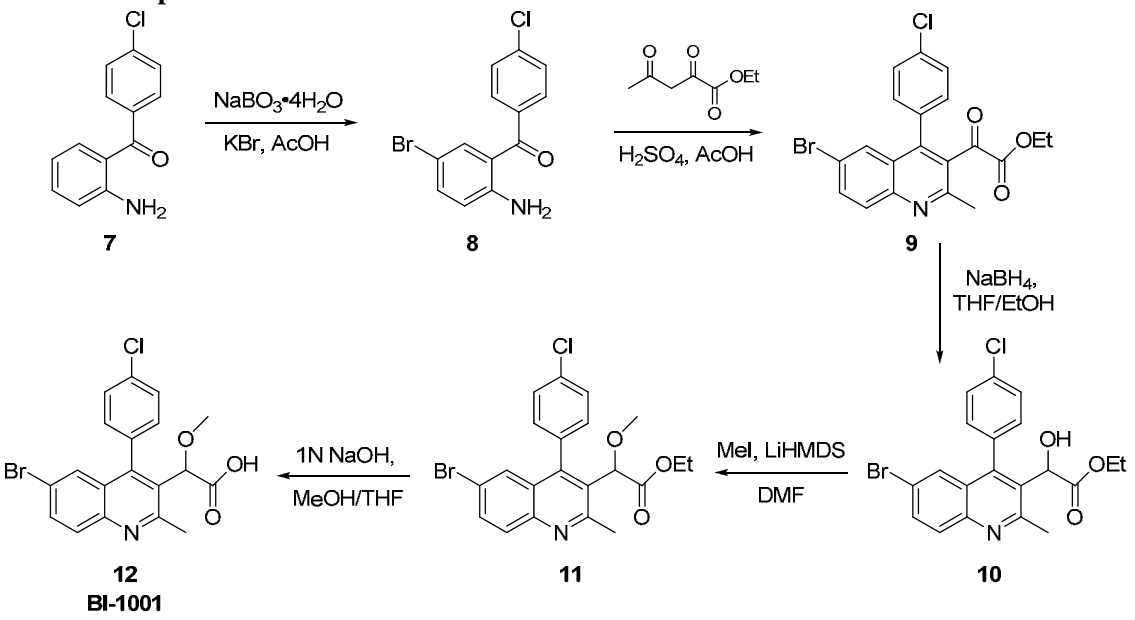


**Figure S2.** Synthetic scheme for the preparation of BI-1001.

**(2-amino-5-bromophenyl)(4-chlorophenyl)methanone (8).** Potassium bromide (615 mg, 5.17 mmol) and sodium perborate tetrahydrate (795 mg, 5.17 mmol) were added sequentially to a solution of **7** (1.0 g, 4.31 mmol) in acetic acid (7.5 mL) under argon. The mixture was allowed to stir at room temperature for 2 h. The precipitate which formed was filtered, washed with cold water, and dried under vacuum to provide **8** (934 mg, 69%) as a yellow solid: mp 100-102 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.6, 0.8 Hz, 2H), 7.52–7.41 (m, 3H), 7.40–7.32 (m, 1H), 6.64 (dd, *J* = 8.8, 0.9 Hz, 1H), 6.08 (br s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 196.5, 149.7, 137.9, 137.5, 137.0, 135.8, 130.6, 130.5, 128.7, 128.6, 119.0, 118.9, 106.6.

**Ethyl 2-(6-bromo-4-(4-chlorophenyl)-2-methylquinolin-3-yl)-2-oxoacetate (9).** Ethyl-acetopyruvate (0.36 mL, 2.50 mmol) was added dropwise to a solution of (2-amino-5-bromophenyl)(4-chlorophenyl)methanone (**8**) (600 mg, 1.93 mmol) in acetic acid (4.5 mL) and sulfuric acid (0.09 mL). The resulting mixture was heated to 130 °C for 16 h. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The crude residue was suspended in dichloromethane. The soluble material was subjected to column chromatography to provide **9** (81 mg, mmol). The insoluble portion (primarily composed of the corresponding carboxylic acid) was resuspended in acetone. The solid which precipitated out was filtered and dried to provide the acid (377.5 mg, 0.93 mmol) as a yellow solid. The acid was esterified by refluxing in ethanol (6 mL) in the presence of catalytic HCl (conc.) to give **9** as a yellow solid (399 mg, 98.9 %). The combined yield of **9** was 57% from compound **8**: $^1$H NMR (400 MHz, $CDCl_3$) δ $^1$H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 16 Hz, 1H), 7.85 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.70 (d, *J* = 10.0 Hz, 1H), 7.50 (d, *J* = 13.6 Hz, 2H), 7.32–7.18 (m, 2H), 3.97 (q, *J* = 7.2 Hz, 2H), 2.73 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 189.3, 161.5, 155.8, 146.6, 145.4, 136.0, 134.6, 132.0, 131.7, 130.8, 129.9, 129.1, 128.5, 127.8, 125.7, 121.1, 62.8, 23.9, 13.7.

**Ethyl 2-(6-bromo-4-(4-chlorophenyl)-2-methylquinolin-3-yl)-2-hydroxyacetate (10).** Sodium borohydride (32.5 mg, 0.86 mmol) was added portion wise over a period of 5 minutes to a solution of ethyl 2-(6-bromo-4-(4-chlorophenyl)-2-methylquinolin-3-yl)-2-oxoacetate (**9**) (410 mg, 0.94 mmol) in THF/EtOH (4:1 ratio, 8.5 mL) at 0 °C. After stirring for 3 h at 0 °C, the reaction was quenched by the

slow addition of water followed by addition of HCL (10% aq.). The solution was extracted with ethyl acetate (3 x 10 mL), washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Flash chromatography provided **10** (330 mg, 99%) as a yellow solid: mp 174-176 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.9 Hz, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.37 (s, 1H), 7.24 (t, *J* = 9.6 Hz, 2H), 5.15 (s, 1H), 4.25–4.11 (m, 2H), 3.58 (s, 1H), 2.67 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.5, 135.4, 134.1, 133.3, 131.5, 130.6, 130.4, 129.1, 128.9, 128.6, 128.3, 114.4, 69.6, 62.8, 48.3, 23.9, 14.0.

**Ethyl 2-(6-bromo-4-(4-chlorophenyl)-2-methylquinolin-3-yl)-2-methoxyacetate (11).** A solution of ethyl 2-(6-bromo-4-(4-chlorophenyl)-2-methylquinolin-3-yl)-2-hydroxyacetate (**10**) (63 mg, 0.14 mmol) in anhydrous DMF (1.2 mL) was treated with LiHMDS (1M in THF, 0.17 mL, 0.17 mmol) and then iodomethane (0.05 mL, 0.81 mmol) dropwise at room temperature. After stirring for 1 h, the reaction mixture was quenched with ice cold water and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. Flash chromatography gave **11** (60 mg, 65%) as a yellow solid: mp 148-150 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.74 (dd, *J* = 8.9, 1.6 Hz, 1H), 7.56–7.48 (m, 2H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.34–7.28 (m, 1H), 7.24–7.18 (m, 1H), 4.81 (s, 1H), 4.19 (q, *J* = 8.0 Hz, 2H), 3.22 (d, *J* = 0.5 Hz, 3H), 2.74 (s, 3H), 1.23–1.17 (t, *J* = 4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.1, 158.8, 146.9, 145.6, 135.0, 133.8, 133.2, 131.6, 130.4, 130.3, 129.2, 128.9, 128.5, 127.4, 127.2, 120.2, 78.3, 61.7, 57.6, 23.9, 14.1.

**2-(6-bromo-4-(4-chlorophenyl)-2-methylquinolin-3-yl)-2-methoxyacetic acid (12, BI-1001).** Ethyl 2-(6-bromo-4-(4-chlorophenyl)-2-methylquinolin-3-yl)-2-methoxyacetate (**11**) (180 mg, 0.40 mmol) was dissolved in MeOH/THF (1:1 ratio, 8 mL) and treated with 1 M aqueous NaOH (1 mL). After stirring for 1 h, the mixture was partitioned between water and ethyl acetate, the aqueous layer was acidified to pH 5, and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to yield **BI-1001** (100 mg, 59%) as a yellow solid: mp 232-234 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$) δ 13.23 (s, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.89 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.47–7.40 (m, 1H), 7.38–7.31 (m, 1H), 7.29 (d, *J* = 1.9 Hz, 1H), 4.67 (s, 1H), 3.15 (s, 3H), 2.67 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 172.3, 159.6, 147.1, 145.9, 134.7, 134.6, 133.8, 132.7, 131.9, 131.7, 129.9, 129.8, 129.2, 128.8, 127.8, 120.5, 78.7, 58.4, 24.6.

**Supplemental Table 1. Data-collection and structure-refinement statistics**

| **Data collection** | |
|---|---|
| Wavelength ( Å ) | 1.514 |
| Total reflection | 173125 |
| Unique reflection | 7155 |
| Space group | P3121 |
| Unit-cell parameters (Å º) | a=73.082, b=73.082, c=64.808<br>$\alpha = \beta = 90$, $\gamma = 120$ |
| Molecules per ASU | 1 |
| Resolution range (Å) | 2.45 |
| Completeness ( %) | 98.5 (100) |
| Redundancy | 6.9 ( 7.1) |
| I /σ | 51.36 (4.55) |
| $R_{merge}$ (%) | 4.4(56.3) |
| **Structure refinement** | |
| Resolution (Å) | 2.45 |
| $R_{cryst}$ / $R_{free}$ (%) | 0.2308/0.2763 |
| **R.m.s.d from ideal values** | |
| Bond length (Å) | 0.0193 |
| Bond angle( º) | 1.7932 |
| Average B factor | 69 |
| PDB # | 4DMN |