*Supplementary Information*

# Discovery of Isoquinolinoquinazolinones as a Novel Class of Potent PPARγ Antagonists with Anti-adipogenic Effects

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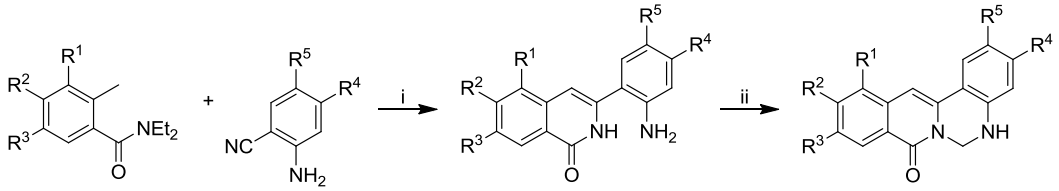
**Scheme S1. Synthesis of isoquinolinoquinazolinones 8**[a]

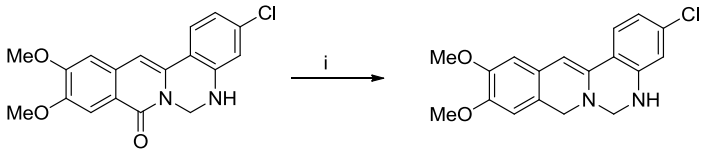



5 6 7a-o 8a-o

| | $R^1$ | $R^2$ | $R^3$ | | $R^4$ | $R^5$ |
|---|---|---|---|---|---|---|
| **5a** | H | H | H | **6a** | H | H |
| **5b** | $CH_3$ | H | H | **6b** | H | Cl |
| **5c** | H | $CH_3$ | H | **6c** | Cl | H |
| **5d** | H | H | $CH_3$ | | | |
| **5e** | H | $CH_3$ | $CH_3$ | | | |
| **5f** | H | $OCH_3$ | H | | | |
| **5g** | H | $OCH_3$ | $OCH_3$ | | | |

[a]Reagents and conditions: (i) *n*-BuLi, dry THF, −78 °C; (ii) $CH_2I_2$, $K_2CO_3$, DMF, 100 °C.

**Scheme S2. Synthesis of 5,8-dihydro-6*H*-isoquino[*2,3-c*]quinazoline 9.**[a]




**8o** **9**

[a]Reagents and conditions: (i) $LiAlH_4$, dry THF, MeOH.

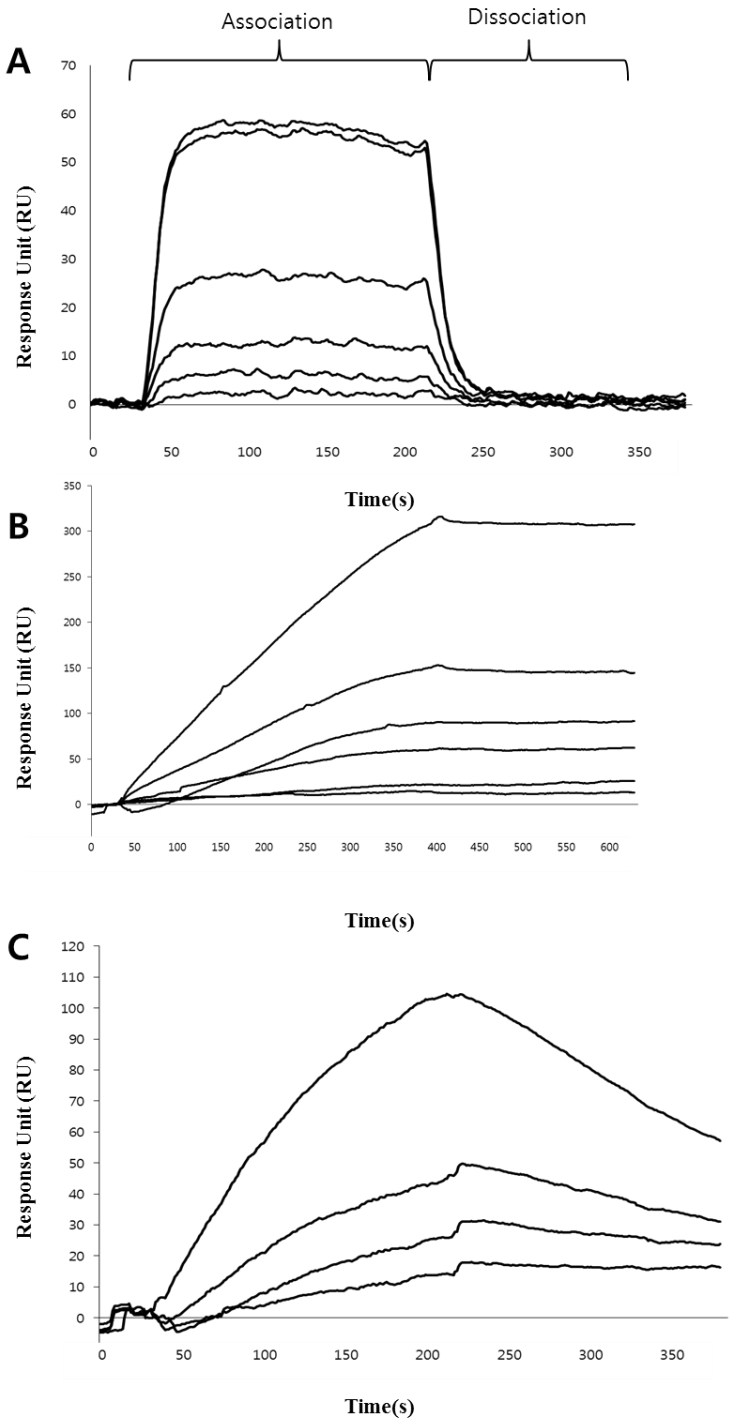



**Figure S1. SPR analysis.** Representative sensorgrams were obtained by immobilizing PPARγ protein on the sensor chip and treating with (**A**) rosiglitazone at concentrations of 2.5, 5, 10, 20, 40, and 80 μM; (**B**) GW9662 at concentrations of 3.125, 6.25, 12.5, 25, 50, and 100 μM; (**C**) **8o** at concentrations of 7.5, 15, 30, and 60 μM.

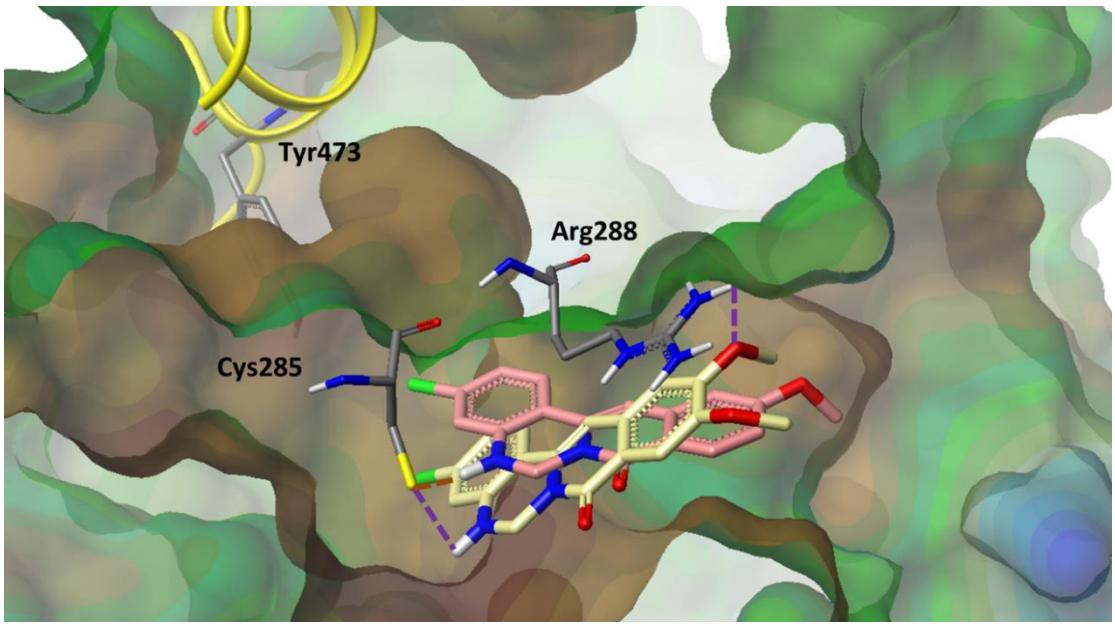



**Figure S2. Molecular docking mode of 8l (pink), 8o (yellow) and PPARγ (PDB: 3E00).** H-bonds are shown as brown (for **8l**) and purple (for **8o**) discontinuous lines. Compound **8l** lacks H-bond interaction with Arg288.

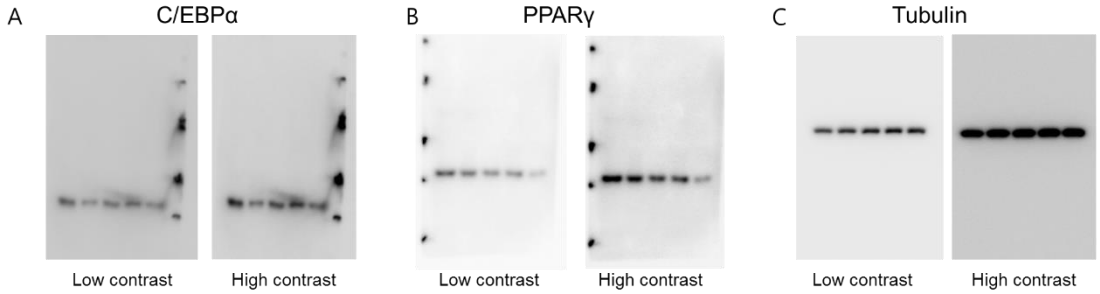



**Figure S3. Full-length membrane blots corresponding to Fig 2D (C/EBPα, PPARγ, and Tubulin).**

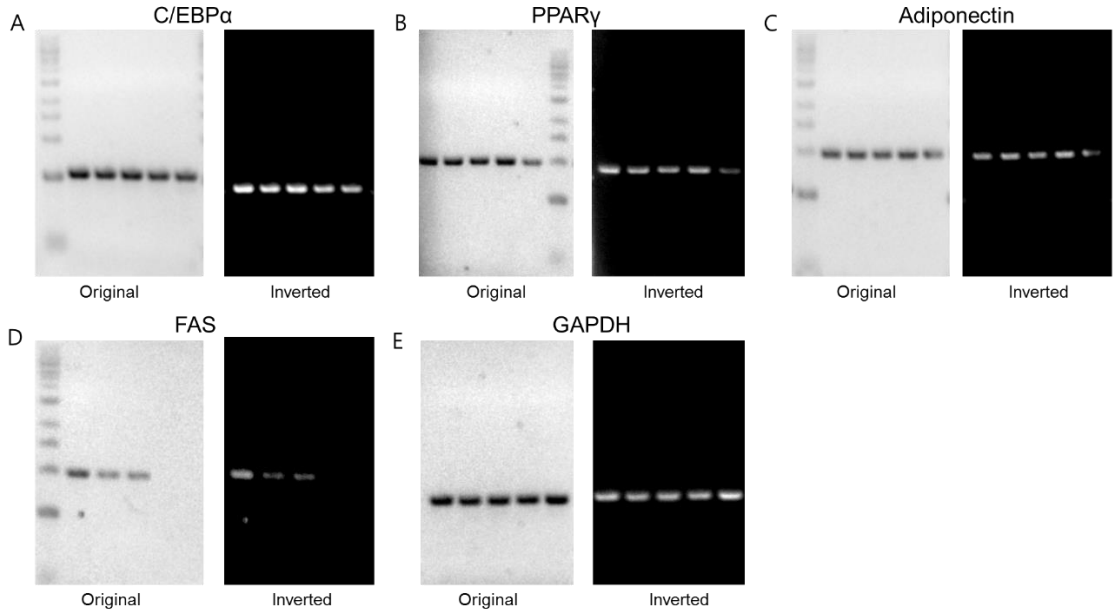



**Figure S4. Full-length gel images corresponding to Fig 2E (C/EBPα, PPARγ, Adiponectin, FAS, and GAPDH).**

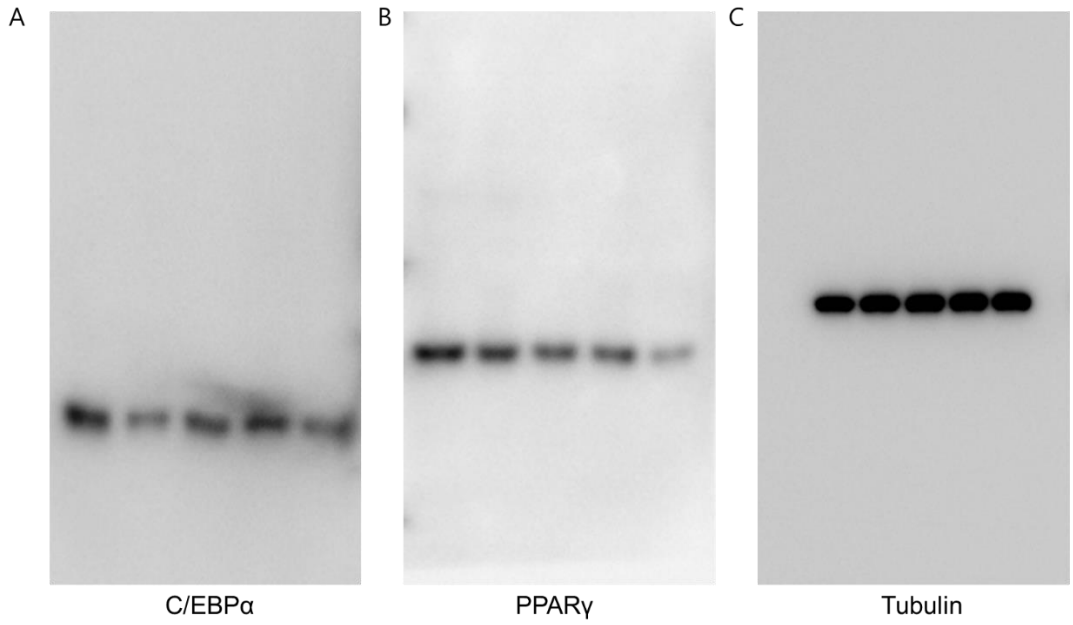



**Figure S5. High resolution of full-length membrane blots corresponding to Fig 2D (C/EBPα, PPARγ, and Tubulin).**

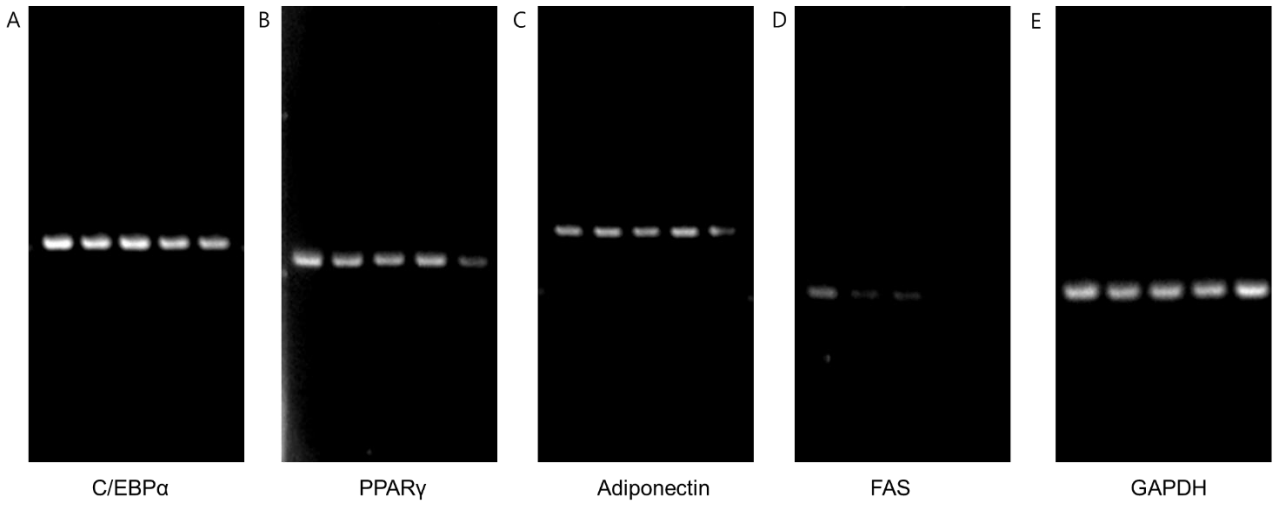
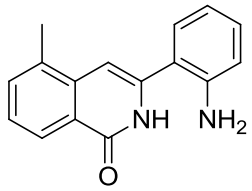
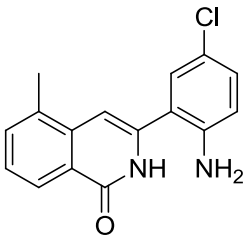



**Figure S6. High resolution of full-length gel images corresponding to Fig 2E (C/EBPα, PPARγ, Adiponectin, FAS, and GAPDH).**

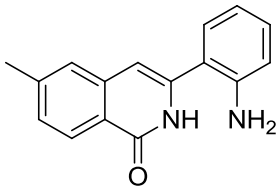
**Synthesis of isoquinolinoquinazolinones**



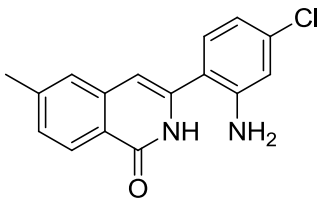
3-(2-aminophenyl)-5-methylisoquinolin-1(*2H*)-one (**7b**). The procedure used to prepare compound **7a** was carried out using compound *N,N*-diethyl-2,3-dimethyl-benzamide **5b** (2 g, 9.74 mmol), **6a** (1.76 g, 14.6 mmol), and *n*-BuLi (2.5 M solution in hexane; 12 mL) to afford compound **7b** as a yellow solid (515 mg, 21%). Mp: 216.9–218.1 °C. $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$: 11.21 (bs, 1H), 8.05 (d, $J$ = 7.5 Hz, 1H), 7.52 (d, $J$ = 6.0 Hz, 1H), 7.34 (t, $J$ = 7.5 Hz, 1H), 7.14–7.09 (m, 2H), 6.76 (d, $J$ = 7.5 Hz, 1H), 6.62 (t, $J$ = 7.5 Hz, 1H), 6.59 (s, 1H), 5.20 (bs, 2H), 2.48 (s, 3H). MS (ESI) *m/z* = 251 $(M + H)^+$. Anal. Calcd. for $C_{16}H_{14}N_2O$•1.85 $CH_2Cl_2$•0.2 $C_3H_7NO$: C, 52.51; H, 4.56; N, 7.30. Found: C, 52.43; H, 4.45; N, 7.43.



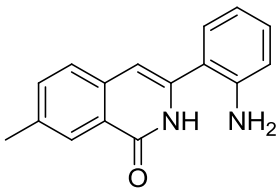
3-(2-amino-5-chlorophenyl)-5-methylisoquinolin-1(*2H*)-one (**7c**). The procedure used to prepare compound **7a** was used with compound **5b** (750 mg, 3.65 mmol), **6b** (557 mg, 3.65 mmol), and *n*-BuLi (2.5 M solution in hexane; 5 mL) to afford compound **7c** as a yellow solid (305 mg, 29%). Mp: 193.7–194.3 °C. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$: 11.25 (bs, 1H), 8.05 (d, $J$ = 8.1 Hz, 1H), 7.53 (d, $J$ = 6.6 Hz, 1H), 7.55 (t, $J$ = 7.8 Hz, 1H), 7.15–7.12 (m, 2H), 6.77–6.74 (m, 1H), 6.60 (s, 1H), 5.38 (bs, 2H), 2.48 (s, 3H). MS (ESI) *m/z* = 285 $(M + H)^+$. Anal. Calcd. for $C_{15}H_{12}N_2O$•0.15 $C_4H_8O_2$: C, 66.92; H, 4.80; N, 9.40. Found: C, 67.00; H, 4.92; N, 9.33.



3-(2-aminophenyl)-6-methylisoquinolin-1(*2H*)-one (**7d**). The procedure used to prepare compound **7a** was carried out using compound *N,N*-diethyl-2,4-dimethyl-benzamide **5c** (1 g, 4.88 mmol), **6a** (472 mg, 4.0 mmol), and *n*-BuLi (2.5 M solution in hexane; 5 mL) to afford compound **7d** as a yellow solid (241 mg, 20%). Mp: 238.7–239.6 °C. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$: 11.06 (bs, 1H), 8.06 (d, $J$ = 8.1 Hz, 1H), 7.43 (s, 1H), 7.28 (dd, $J$ = 8.1, 1.2 Hz, 1H), 7.12–7.07 (m, 2H), 6.77–6.74 (m, 1H), 6.61 (td, $J$ = 7.8, 1.2 Hz, 1H), 6.49 (s, 1H), 5.13 (bs, 2H), 2.43 (s, 3H). MS (ESI) $m/z$ = 251 $(M + H)^+$. Anal. Calcd. for $C_{16}H_{14}N_2O$•0.05 $C_4H_8O_2$: C, 75.37; H, 5.64; N, 10.82. Found: C, 75.49; H, 5.79; N, 10.62.

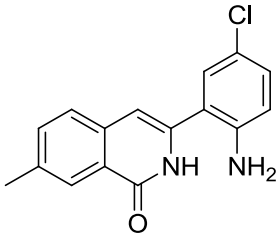


3-(2-amino-4-chlorophenyl)-6-methylisoquinolin-1(*2H*)-one (**7e**). The procedure used to prepare compound **7a** was carried out using compound **5c** (1 g, 4.88 mmol), **6c** (610 mg, 4.0 mmol), and *n*-BuLi (2.5 M solution in hexane; 5 mL) to afford compound **7e** as a yellow solid (237 mg, 17%). Mp: 236.5–237.8 °C. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$: 11.11 (bs, 1H), 8.07 (d, $J$ = 8.1 Hz, 1H), 7.43 (s, 1H), 7.29 (dd, $J$ = 8.1, 1.2 Hz, 1H), 7.09 (d, $J$ = 8.4 Hz, 1H), 6.79 (d, $J$ = 2.4 Hz, 1H), 6.60 (dd, $J$ = 8.4, 2.1 Hz, 1H), 6.47 (s, 1H), 5.47 (bs, 2H), 2.43 (s, 3H). MS (ESI) $m/z$ = 285 $(M + H)^+$. Anal. Calcd. for $C_{16}H_{13}ClN_2O$•1.05 $H_2O$: C, 66.29; H, 5.30; N, 8.27. Found: C, 66.38; H, 5.44; N, 8.36.

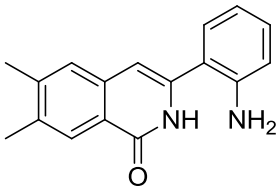


3-(2-aminophenyl)-7-methylisoquinolin-1(*2H*)-one (**7f**). The procedure used to prepare compound **7a** was carried out using compound *N,N*-diethyl-2,5-dimethyl-benzamide **5d** (1 g, 4.88 mmol), **6a** (472 mg, 4.0 mmol), and *n*-BuLi (2.5 M solution in hexane; 5 mL) to afford compound **7f** as an orange solid

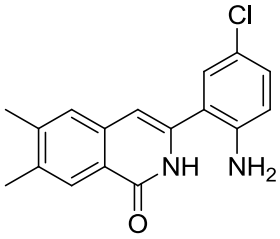
(502 mg, 40%). Mp: 218.8–219.7 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 11.08 (bs, 1H), 7.99 (s, 1H), 7.56–7.49 (m, 2H), 7.12–7.07 (m, 2H), 6.77–6.74 (m, 1H), 6.61 (td, $J$ = 7.5, 1.2 Hz, 1H), 6.53 (s, 1H), 5.12 (bs, 2H), 2.44 (s, 3H). Anal. MS (ESI) $m/z$ = 251 $(M + H)^+$. Calcd. for $C_{16}H_{14}N_2O$•0.1 $C_6H_{14}$•0.05 $CH_2Cl_2$: C, 75.99; H, 5.94; N, 10.64. Found: C, 76.09; H, 5.76; N, 10.66.



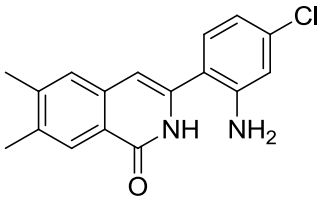

3-(2-amino-5-chlorophenyl)-7-methylisoquinolin-1(*2H*)-one (**7g**). The procedure used to prepare compound **7a** was carried out using compound **5d** (1 g, 4.88 mmol), **6b** (610 mg, 4.0 mmol), and *n*-BuLi (2.5 M solution in hexane; 5 mL) to afford compound **7g** as a yellow solid (550 mg, 25%). Mp: 232.1–233.0 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 11.15 (bs, 1H), 7.79 (s, 1H), 7.57–7.50 (m, 2H), 7.15–7.10 (m, 2H), 6.77–6.74 (m, 1H), 6.56 (s, 1H), 5.32 (bs, 2H), 2.45 (s, 3H). MS (ESI) $m/z$ = 285 $(M + H)^+$.



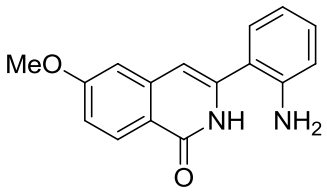

3-(2-aminophenyl)-6,7-dimethylisoquinolin-1(*2H*)-one (**7h**). The procedure used to prepare compound **7a** was carried out using compound *N,N*-diethyl-2,4,5-trimethyl-benzamide **5e** (1 g, 4.56 mmol), **6a** (539 mg, 4.56 mmol), and *n*-BuLi (2.5 M solution in hexane; 5 mL) to afford compound **7h** as a yellow solid (308 mg, 25%). Mp: 253.6–255.8 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 10.98 (bs, 1H), 7.94 (s, 1H), 7.41 (s, 1H), 7.12–7.07 (m, 2H), 6.77–6.74 (m, 1H), 6.61 (td, $J$ = 7.5, 0.9 Hz, 1H), 6.46 (s, 1H), 5.10 (bs, 2H), 2.36 (s, 3H), 2.35 (s, 3H). MS (ESI) $m/z$ = 265 $(M + H)^+$. Anal. Calcd. for $C_{17}H_{16}N_2O$•0.05 $C_4H_8O_2$•0.1 $CH_2Cl_2$: C, 76.95; H, 6.04; N, 10.10. Found: C, 76.95; H, 6.12; N, 10.19.




3-(2-amino-5-chlorophenyl)-6,7-dimethylisoquinolin-1(*2H*)-one (**7i**). The procedure used to prepare compound **7a** was carried out using compound **5e** (1 g, 4.56 mmol), **6b** (696 mg, 4.56 mmol), and *n*-BuLi (2.5 M solution in hexane; 5 mL) to afford compound **7i** as a yellow solid (660 mg, 48%). Mp: 272.8–273.7 °C. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$: 11.04 (bs, 1H), 7.94 (s, 1H), 7.41 (s, 1H), 7.14–7.10 (m, 2H), 6.77–6.74 (m, 1H), 6.49 (s, 1H), 5.30 (bs, 2H), 2.36 (s, 3H), 2.35 (s, 3H). MS (ESI) *m/z* = 299 (M + H)$^+$. Anal. Calcd. for $C_{17}H_{15}ClN_2O$•0.6 $H_2O$: C, 65.96; H, 5.27; N, 9.05. Found: C, 65.90; H, 5.25; N, 9.00.

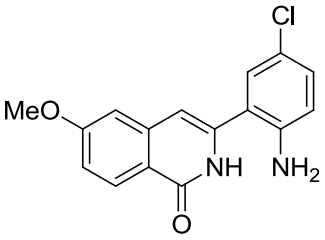



3-(2-amino-4-chlorophenyl)-6,7-dimethylisoquinolin-1(*2H*)-one (**7j**). The procedure used to prepare compound **7a** was carried out using compound **5e** (1 g, 4.56 mmol), **6c** (696 mg, 4.56 mmol), and *n*-BuLi (2.5 M solution in hexane; 5 mL) to afford compound **7j** as a yellow solid (320 mg, 23%). Mp: 273.6–274.7 °C. $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$: 11.03 (bs, 1H), 7.94 (s, 1H), 7.41 (s, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 2.1 Hz, 1H), 6.60 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.45 (s, 1H), 5.44 (bs, 1H), 2.36 (s, 3H), 2.35 (s, 3H). MS (ESI) *m/z* = 299 (M + H)$^+$. Anal. Calcd. for $C_{17}H_{15}ClN_2O$•0.1 $C_4H_8O_2$•0.15 H2O: C, 67.35; H, 5.23; N, 9.03. Found: C, 67.35; H, 5.27; N, 8.99.

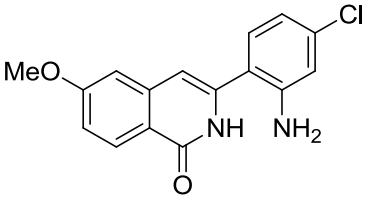



3-(2-aminophenyl)-6-methoxyisoquinolin-1(*2H*)-one (**7k**). The procedure used to prepare compound **7a** was carried out using compound *N,N*-diethyl-4-dimethoxy-2-methyl-benzamide **5f** (1 g, 4.52 mmol), **6a** (534 mg, 4.52 mmol), and *n*-BuLi (2.5 M solution in hexane; 5 mL) to afford compound **7k** as a yellow solid (296 mg, 24%). Mp: 209.1–209.9 °C. $^1$H NMR (300 MHz, DMSO-d$_6$)

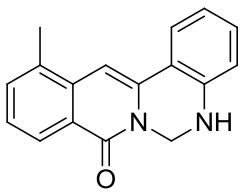
$\delta$: 11.00 (bs, 1H), 8.09 (d, $J$ = 9.0 Hz, 1H), 7.13–7.01 (m, 4H), 6.76 (dd, $J$ = 9.0, 3.0 Hz, 1H), 6.64–6.39 (m, 1H), 6.50 (s, 1H), 5.13 (bs, 2H), 3.88 (s, 3H). MS (ESI) $m/z$ = 267 $(M + H)^+$. Anal. Calcd. for $C_{16}H_{14}N_2O_2 \bullet 0.2\ C_4H_8O_2 \bullet 0.35\ CH_2Cl_2$: C, 67.29; H, 5.63; N, 8.94. Found: C, 67.31; H, 5.42; N, 8.96.




3-(2-amino-5-chlorophenyl)-6-methoxyisoquinolin-1(*2H*)-one (**7l**). The procedure used to prepare compound **7a** was carried out using compound **5f** (1 g, 4.52 mmol), **6b** (690 mg, 4.52 mmol), and *n*-BuLi (2.5 M solution in hexane; 5 mL) to afford compound **7l** as a yellow solid (275 mg, 20%). Mp: 238.4–239.9 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.09 (d, $J$ = 9.0 Hz, 1H), 7.15–7.11 (m, 3H), 7.06–7.02 (m, 1H), 6.78–6.75 (m, 1H), 6.53 (s, 1H), 5.33 (bs, 2H), 3.86 (s, 3H). MS (ESI) $m/z$ = 301 $(M + H)^+$.

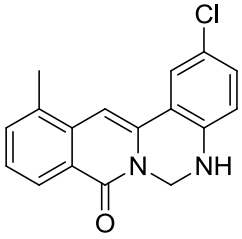



3-(2-amino-4-chlorophenyl)-6-methoxyisoquinolin-1(*2H*)-one (**7m**). The procedure used to prepare compound **7a** was carried out using compound **5f** (1 g, 4.52 mmol), **6c** (690 mg, 4.52 mmol), and *n*-BuLi (2.5 M solution in hexane; 5 mL) to afford compound **7m** as a yellow solid (380 mg, 28%). Mp: 252.2–253.0 °C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 11.02 (bs, 1H), 8.09 (d, $J$ = 9.0 Hz, 1H), 7.13–7.02 (m, 3H), 6.79 (s, 1H), 6.61 (d, $J$ = 6.0 Hz, 1H), 6.49 (s, 1H), 5.47 (bs, 2H), 3.86 (s, 3H). Anal. MS (ESI) $m/z$ = 301 $(M + H)^+$. Calcd. for $C_{16}H_{13}ClN_2O_2 \bullet 0.35\ C_4H_8O_2 \bullet 0.15\ CH_2Cl_2$: C, 61.22; H, 4.71 N, 8.31. Found: C, 61.17; H, 4.94; N, 8.31.

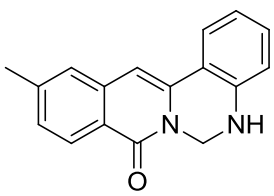



12-methyl-*5H*-isoquinolino[2,3-c]quinazolin-8(*6H*)-one (**8b**). The procedure used to prepare compound **8a** was carried out using compound **7b** (300 mg,

1.27 mmol), $K_2CO_3$ (438 mg, 3.17 mmol), and diiodomethane (1.36 g, 5.08 mmol) to afford compound **8b** as a yellow solid (185 mg, 55%). Mp: 226.5–228.1 °C. IR ($cm^{-1}$): 3296, 1588. $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$: 8.29 (d, $J$ = 8.0 Hz, 1H), 7.82 (d, $J$ = 8.0 Hz, 1H), 7.48 (d, $J$ = 7.0 Hz, 1H), 7.34 (t, $J$ = 8.0 Hz, 1H), 7.29–7.28 (m, 2H), 7.03–7.00 (m, 2H), 6.86 (d, $J$ = 8.0 Hz, 1H), 5.36 (d, $J$ = 3.0 Hz, 2H), 2.60 (s, 3H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$: 159.7, 144.5, 134.1, 134.1, 133.3, 130.1, 125.0, 123.3, 119.1, 117.5, 97.6, 52.2, 18.9. MS (ESI) $m/z$ = 263 $(M + H)^+$. Anal. Calcd. for $C_{17}H_{14}N_2O$•0.05 $C_4H_8O_2$: C, 77.46; H, 5.44; N, 10.50. Found: C, 77.43; H, 5.41; N, 10.32. HPLC: $t_r$ 2.28 min, purity 98.9%.

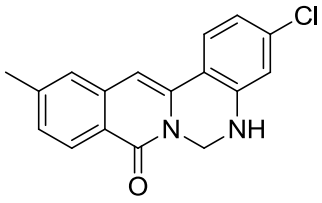



2-chloro-12-methyl-*5H*-isoquinolino[2,3-c]quinazolin-8(*6H*)-one (**8c**). The procedure used to prepare compound **8a** was carried out using compound **7c** (280 mg, 0.98 mmol), $K_2CO_3$ (387 mg, 2.80 mmol), and diiodomethane (1.20 g, 4.47 mmol) to afford compound **8c** as a yellow solid (60 mg, 21%). Mp: 240.5–242.1 °C. IR ($cm^{-1}$): 3263, 1592. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.12 (d, $J$ = 2.4 Hz, 1H), 8.08 (d, $J$ = 8.1 Hz, 1H), 7.56–7.54 (m, 1H), 7.36 (t, $J$ = 7.8 Hz, 1H), 7.27 (dd, $J$ = 8.4, 2.4 Hz, 1H), 7.18 (s, 1H), 6.99 (bs, 1H), 6.92 (d, $J$ = 8.7 Hz, 1H), 5.14 (d, $J$ = 2.1 Hz, 2H), 2.60 (s, 3H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$: 160.2, 144.9, 134.6, 134.5, 133.7, 130.5, 125.4, 123.7, 119.5, 117.9, 98.0, 52.6, 19.3. MS (ESI) $m/z$ = 297 $(M + H)^+$. Anal. Calcd. for $C_{17}H_{13}ClN_2O$•0.1 $H_2O$•0.1 $C_4H_8O_2$: C, 67.99; H, 4.59; N, 9.11. Found: C, 68.13; H, 4.41; N, 8.95. HPLC: $t_r$ 2.45 min, purity 95.4%.

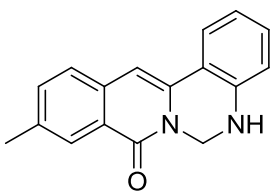



11-methyl-*5H*-isoquinolino[2,3-c]quinazolin-8(*6H*)-one (**8d**). The procedure used to prepare compound **8a** was carried out using compound **7d** (218 mg, 0.87 mmol), $K_2CO_3$ (301 mg, 2.18 mmol), and diiodomethane

(933 mg, 3.48 mmol) to afford compound **8d** as a yellow solid (97 mg, 42%). Mp: 119.1–120.4 °C. IR ($cm^{-1}$): 3300, 1598. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.09 (d, $J$ = 8.4 Hz, 1H), 7.84 (d, $J$ = 7.5 Hz, 1H), 7.47 (s, 1H), 7.29–7.22 (m, 2H), 7.08 (s, 1H), 6.92–6.86 (m, 2H), 6.82 (bs, 1H), 5.12 (d, $J$ = 2.1 Hz, 2H), 2.44 (s, 3H). $^{13}C$ NMR (125 MHz, CDCl3) $\delta$: 160.8, 144.1, 142.9, 137.0, 135.4, 130.3, 127.8, 124.6, 121.0, 119.3, 116.7, 100.9, 52.9, 21.8. MS (ESI) $m/z$ = 263 $(M + H)^+$. Anal. Calcd. for $C_{17}H_{14}N_2O$•0.1 $C_6H_{14}$•0.1 $CH_2Cl_2$: C, 76.08; H, 5.63; N, 10.03. Found: C, 76.33; H, 5.34; N, 10.09. HPLC: $t_r$ 2.19 min, purity 98.5%.

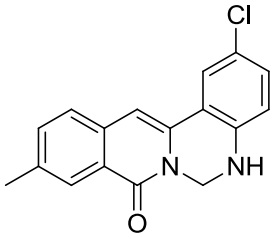



3-chloro-11-methyl-5*H*-isoquinolino[2,3-c]quinazolin-8(6*H*)-one (**8e**). The procedure used to prepare compound **8a** was carried out using compound **7e** (207 mg, 0.73 mmol), $K_2CO_3$ (251 mg, 1.82 mmol), and diiodomethane (779 mg, 2.91 mmol) to afford compound **8e** as a yellow solid (96 mg, 44%). Mp: 210.0–211.5 °C. IR ($cm^{-1}$): 3329, 1594. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.09 (d, $J$ = 8.1 Hz, 1H), 7.86 (d, $J$ = 8.4 Hz, 1H), 7.47 (s, 1H), 7.30 (d, $J$ = 8.4 Hz, 1H), 7.12 (s, 1H), 7.05 (s, 1H), 6.95–6.89 (m, 2H), 5.14 (d, $J$ = 2.1 Hz, 2H), 2.44 (s, 3H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$: 159.5, 146.7, 142.8, 136.8, 134.8, 134.7, 127.9, 127.1, 126.4, 126.0, 121.9, 119.2, 116.2, 115.0, 99.8, 52.0, 21.3. MS (ESI) $m/z$ = 297 $(M + H)^+$. Anal. Calcd. for $C_{17}H_{13}ClN_2O$•0.05 $C_6H_{14}$•0.1 $CH_2Cl_2$: C, 67.51; H, 4.53; N, 9.05. Found: C, 67.77; H, 4.40; N, 9.02. HPLC: $t_r$ 2.47 min, purity 95.6%.

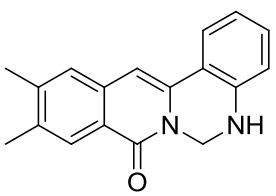



10-methyl-5H-isoquinolino[2,3-c]quinazolin-8(6H)-one (**8f**). The procedure used to prepare compound **8a** was carried out using compound **7f** (80 mg, 0.32 mmol), $K_2CO_3$ (110 mg, 0.80 mmol), and diiodomethane

(342 mg, 1.28 mmol) to afford compound **8f** as a yellow solid (56 mg, 67%). Mp: 213.2–214.5 °C. IR ($cm^{-1}$): 3290, 1593. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.01 (s, 1H), 7.83 (d, $J$ = 7.2 Hz, 1H), 7.60 (d, $J$ = 8.1 Hz, 1H), 7.53 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.23 (td, $J$ = 8.1, 1.2 Hz, 1H), 7.13 (s, 1H), 6.91–6.86 (m, 2H), 6.80 (bs, 1H), 5.13 (d, $J$ = 2.1 Hz, 2H), 2.44 (s, 3H). ). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$: 159.6, 145.5, 135.7, 134.8, 134.6, 134.0, 130.3, 126.6, 126.5, 124.6, 123.9, 119.5, 117.6, 115.9, 99.7, 52.3, 21.1. MS (ESI) $m/z$ = 263 $(M + H)^+$. Anal. Calcd. for $C_{17}H_{14}N_2O$•0.05 $H_2O$•0.05 $C_4H_8O_2$: C, 77.20; H, 5.46; N, 10.47. Found: C, 77.29; H, 5.38; N, 10.28. HPLC: $t_r$ 2.21 min, purity 99.0%.

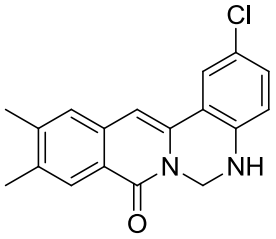



2-chloro-10-methyl-*5H*-isoquinolino[2,3-c]quinazolin-8(*6H*)-one (**8g**). The procedure used to prepare compound **8a** was carried out using compound **7g** (200 mg, 0.70 mmol), $K_2CO_3$ (242 mg, 1.75 mmol), and diiodomethane (752 mg, 2.81 mmol) to afford compound **8g** as a yellow solid (80 mg, 38%). Mp: 202.6–205.1 °C. IR ($cm^{-1}$): 3299, 1598. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.01 (d, $J$ = 0.9 Hz, 1H), 7.90 (d, $J$ = 2.4 Hz, 1H), 7.60 (d, $J$ = 8.1 Hz, 1H), 7.54 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.27–7.24 (m, 2H), 6.97 (bs, 1H), 6.90 (d, $J$ = 8.4 Hz, 1H), 5.13 (d, $J$ = 2.4 Hz, 2H), 2.44 (s, 3H). ). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$: 159.4, 144.2, 136.1, 134.1, 133.5, 129.8, 126.6, 124.2, 123.8, 123.2, 119.0, 117.5, 100.6, 52.2, 21.1. MS (ESI) $m/z$ = 297 $(M + H)^+$. Anal. Calcd. for $C_{17}H_{13}ClN_2O$•0.05 $C_4H_8O_2$•0.3 $CH_2Cl_2$: C, 64.35; H, 4.32; N, 8.58. Found: C, 64.22; H, 4.21; N, 8.47. HPLC: $t_r$ 2.52 min, purity 96.6%.

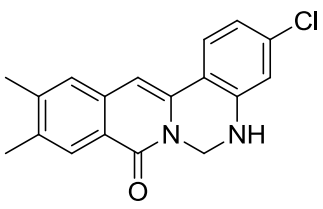



10,11-dimethyl-*5H*-isoquinolino[2,3-c]quinazolin-8(*6H*)-one (**8h**). The procedure used to prepare compound **8a** was carried out using compound **12h** (248 mg, 0.94 mmol), $K_2CO_3$ (324 mg, 2.34 mmol), and

diiodomethane (1 g, 3.76 mmol) to afford compound **8h** as a yellow solid (120 mg, 46%). Mp: 212.7–214.2 °C. IR ($cm^{-1}$): 3302, 1593. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.97 (s, 1H), 7.84–7.81 (m, 1H), 7.46 (s, 1H), 7.26–7.23 (m, 1H), 7.05 (s, 1H), 6.91–6.84 (m, 2H), 6.78 (bs, 1H), 5.12 (d, $J$ = 3.0 Hz, 2H), 2.36 (s, 3H), 2.34 (s, 3H). ). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$: 159.4, 145.4, 142.2, 135.3, 135.0, 134.9, 130.2, 127.0, 126.5, 124.5, 122.2, 119.5, 117.6, 115.9, 99.4, 52.2, 19.8, 19.5. MS (ESI) $m/z$ = 277 $(M + H)^+$. Anal. Calcd. for $C_{18}H_{16}N_2O$•0.1 $C_4H_8O_2$: C, 77.50; H, 5.94; N, 9.82. Found: C, 77.60; H, 5.82; N, 9.68. HPLC: $t_r$ 2.37 min, purity 97.0%.

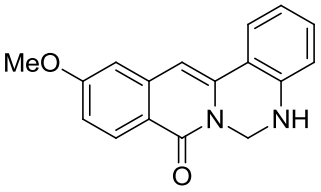



2-chloro-10,11-dimethyl-*5H*-isoquinolino[2,3-c]quinazolin-8(*6H*)-one (**8i**). The procedure used to prepare compound **8a** was carried out using compound **7i** (496 mg, 1.66 mmol), $K_2CO_3$ (573 mg, 4.15 mmol), and diiodomethane (1.78 g, 6.64 mmol) to afford compound **8i** as a yellow solid (94 mg, 18%). Mp: 268.7–270.6 °C. IR ($cm^{-1}$): 3259, 1592. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.97 (s, 1H), 7.90 (d, $J$ = 3.0 Hz, 1H), 7.45 (s, 1H), 7.25 (dd, $J$ = 9.0, 3.0 Hz, 1H), 7.18 (s, 1H), 6.95 (bs, 1H), 6.90 (d, $J$ = 9.0 Hz, 1H), 5.14 (d, $J$ = 3.0 Hz, 2H), 2.36 (s, 3H), 2.35 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$: 159.4, 144.3, 142.4, 135.9, 134.9, 133.6, 129.8, 126.8, 123.9, 122.5, 119.2, 117.6, 100.5, 52.2, 19.9, 19.6. MS (ESI) $m/z$ = 311 $(M+H)^+$. Anal. Calcd. for $C_{18}H_{15}N_2O$•0.1 $H_2O$•0.15 $C_4H_8O_2$: C, 68.57; H, 5.07; N, 8.60. Found: C, 68.66; H, 4.92; N, 8.46. HPLC: $t_r$ 2.72 min, purity 98.1%.

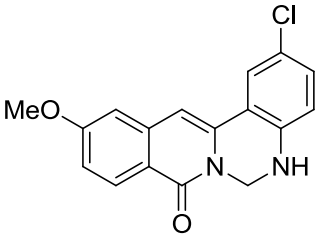



3-chloro-10,11-dimethyl-*5H*-isoquinolino[2,3-c]quinazolin-8(*6H*)-one (**8j**). The procedure used to prepare compound **8a** was carried out using compound **7j** (260 mg, 0.87 mmol), $K_2CO_3$ (300 mg, 2.17

mmol), and diiodomethane (932 mg, 3.48 mmol) to afford compound **8j** as a yellow solid (149 mg, 55%). Mp: 235.1–236.4 °C. IR ($cm^{-1}$): 3326, 1596. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 7.96 (s, 1H), 7.85 (d, $J$ = 9.0 Hz, 1H), 7.45 (s, 1H), 7.08 (s, 1H), 7.02 (bs, 1H), 6.94–6.88 (m, 2H), 5.14 (d, $J$ = 3.0 Hz, 2H), 2.36 (s, 3H), 2.35 (s, 3H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$: 159.4, 146.6, 142.3, 135.6, 134.9, 134.4, 134.0, 127.0, 126.6, 126.2, 122.2, 119.2, 116.6, 114.9, 99.7, 52.0, 19.8, 19.5. MS (ESI) $m/z$ = 311 $(M + H)^+$. Anal. Calcd. for $C_{18}H_{15}ClN_2O$•0.15 $C_4H_8O_2$: C, 68.95; H, 5.04; N, 8.65. Found: C, 69.10; H, 4.89; N, 8.58. HPLC: $t_r$ 2.75 min, purity 95.0%.

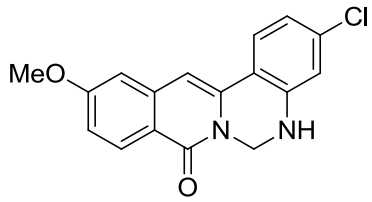



11-methoxy-*5H*-isoquinolino[2,3-c]quinazolin-8(*6H*)-one (**8k**). The procedure used to prepare compound **8a** was carried out using compound **7k** (220 mg, 0.83 mmol), $K_2CO_3$ (285 mg, 2.06 mmol), and diiodomethane (889 mg, 3.32 mmol) to afford compound **8k** as a yellow solid (120 mg, 52%). Mp: 145.4–148.0 °C. IR ($cm^{-1}$): 3265, 1577. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.10 (d, $J$ = 9.0 Hz, 1H), 7.82 (dd, $J$ = 9.0, 3.0 Hz, 1H), 7.28–7.22 (m, 1H), 7.13 (d, $J$ = 6.0 Hz, 1H), 7.09 (d, $J$ = 3.0 Hz, 1H), 6.92–6.87 (m, 2H), 6.82 (bs, 1H), 5.11 (d, $J$ = 3.0 Hz, 2H), 3.88 (s, 3H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$: 162.8, 159.7, 146.1, 139.4, 136.7, 130.9, 129.6, 125.0, 119.9, 117.8, 116.4, 116.1, 107.5, 99.9, 55.9, 55.9, 52.5. MS (ESI) $m/z$ = 279 $(M + H)^+$. Anal. Calcd. for $C_{17}H_{14}N_2O_2$•0.05 $C_4H_8O_2$•$CH_2Cl_2$: C, 72.20; H, 5.09; N, 9.76. Found: C, 72.19; H, 5.00; N, 9.67. HPLC: $t_r$ 2.02 min, purity 97.0%.




2-chloro-11-methoxy-*5H*-isoquinolino[2,3-c]quinazolin-8(*6H*)-one (**8l**). The procedure used to prepare compound **8a** was carried out

using compound **7l** (203 mg, 0.67 mmol), $K_2CO_3$ (233 mg, 1.69 mmol), and diiodomethane (718 mg, 2.68 mmol) to afford compound **8l** as a yellow solid (50 mg, 24%). Mp: 213.6–215.1 °C. IR ($cm^{-1}$): 3275, 1561. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.11 (d, $J$ = 6.0 Hz, 1H), 7.88 (s, 1H), 7.27 (dd, $J$ = 9.0, 3.0 Hz, 1H), 7.23 (s, 1H), 7.14 (d, $J$ = 3.0 Hz, 1H), 7.08–6.90 (m, 3H), 5.11 (d, $J$ = 3.0 Hz, 2H), 3.88 (s, 3H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$: 162.4, 159.2, 144.4, 138.7, 134.8, 130.0, 129.1, 123.9, 123.1, 118.7, 118.0, 117.6, 116.0, 107.3, 100.4, 55.4, 51.9. MS (ESI) $m/z$ = 313 $(M + H)^+$. Anal. Calcd. for $C_{17}H_{13}ClN_2O_2 \bullet 0.1\ C_4H_8O_2 \bullet 0.15\ CH_2Cl_2$: C, 63.05; H, 4.25; N, 8.38. Found: C, 63.14; H, 4.15; N, 8.21. HPLC: $t_r$ 2.15 min, purity 97.5%.




3-chloro-11-methoxy-*5H*-isoquinolino[2,3-c]quinazolin-8(*6H*)-one (**8m**). The procedure used to prepare compound **8a** was carried out using compound **7m** (215 mg, 0.71 mmol), $K_2CO_3$ (247 mg, 1.79 mmol), and diiodomethane (761 mg, 2.84 mmol) to afford compound **8m** as a yellow solid (97 mg, 44%). Mp: 203.9–205.2 °C. IR ($cm^{-1}$): 3321, 1591. $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.11 (d, $J$ = 9.0 Hz, 1H), 7.85–7.82 (m, 1H), 7.14–7.13 (m, 2H), 7.06–7.03 (m, 2H), 6.95–6.89 (m, 2H), 5.12 (d, $J$ = 3.0 Hz, 2H), 3.88 (s, 3H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$) $\delta$: 162.4, 159.2, 146.8, 138.7, 135.3, 134.8, 129.2, 126.3, 119.2, 117.9, 116.1, 115.9, 115.0, 107.2, 99.8, 55.4, 51.8. MS (ESI) $m/z$ = 313 $(M + H)^+$. Anal. Calcd. for $C_{17}H_{13}ClN_2O_2 \bullet 0.1\ C_4H_8O_2 \bullet 0.1\ CH_2Cl_2$: C, 63.68; H, 4.28; N, 8.49. Found: C, 63.82; H, 4.11; N, 8.43. HPLC: $t_r$ 2.17 min, purity 98.4%.

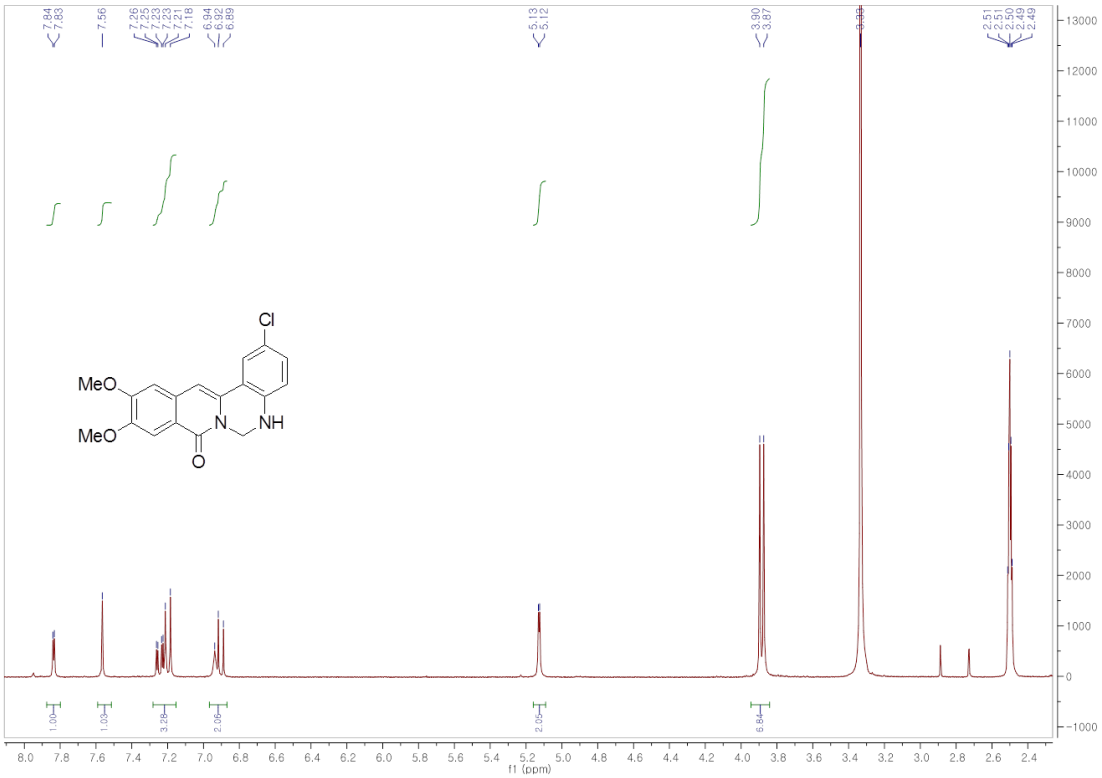



**Figure S3. $^{1}$H NMR (300 MHz, DMSO-$d_6$) spectrum of 8n.**

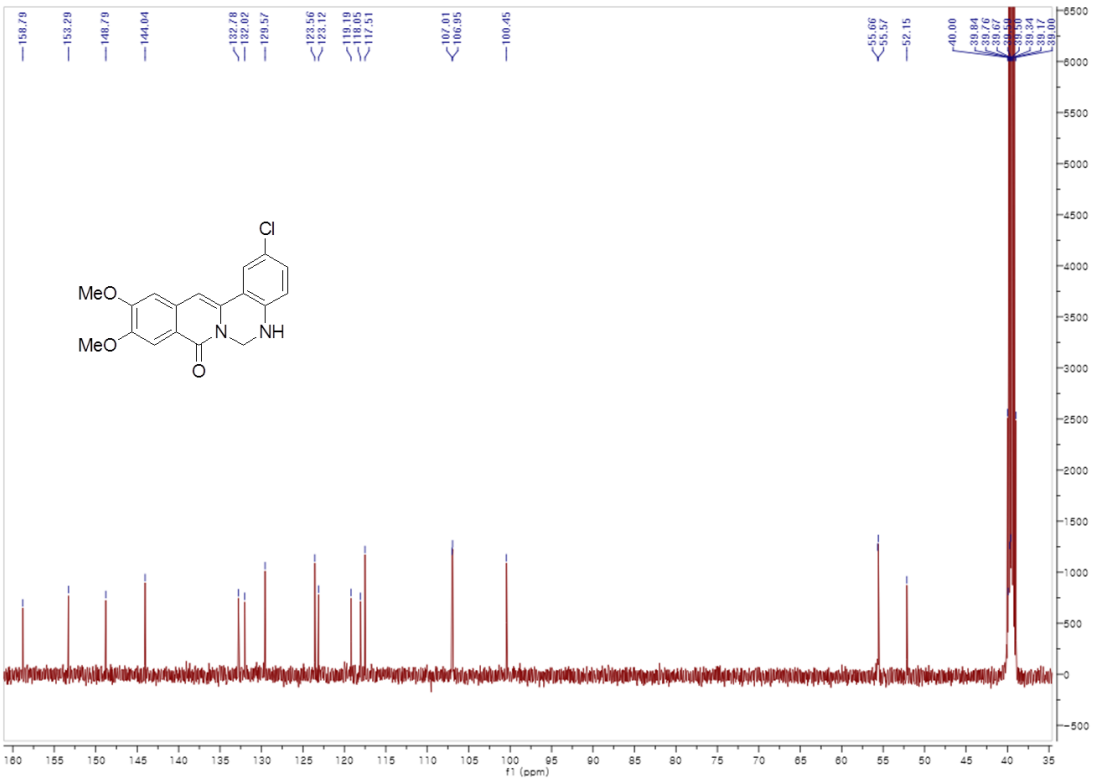



**Figure S4. $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectrum of 8n.**

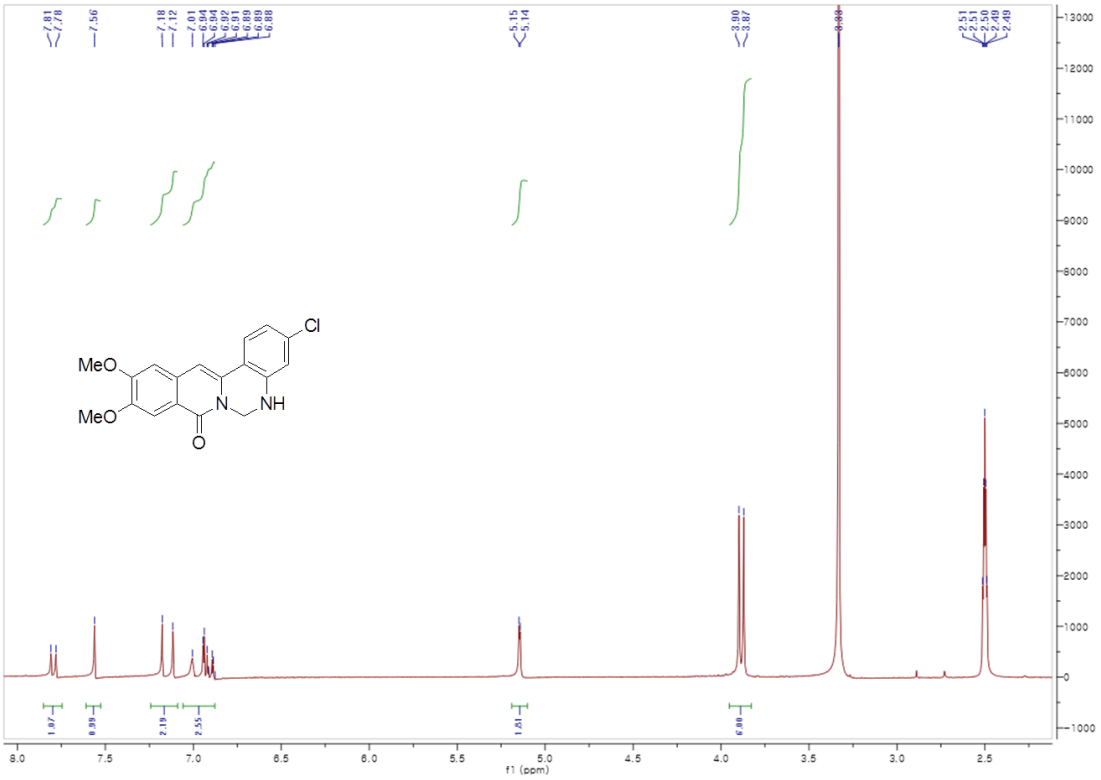



**Figure S5. $^{1}$H NMR (300 MHz, DMSO-$d_6$) spectrum of 8o.**

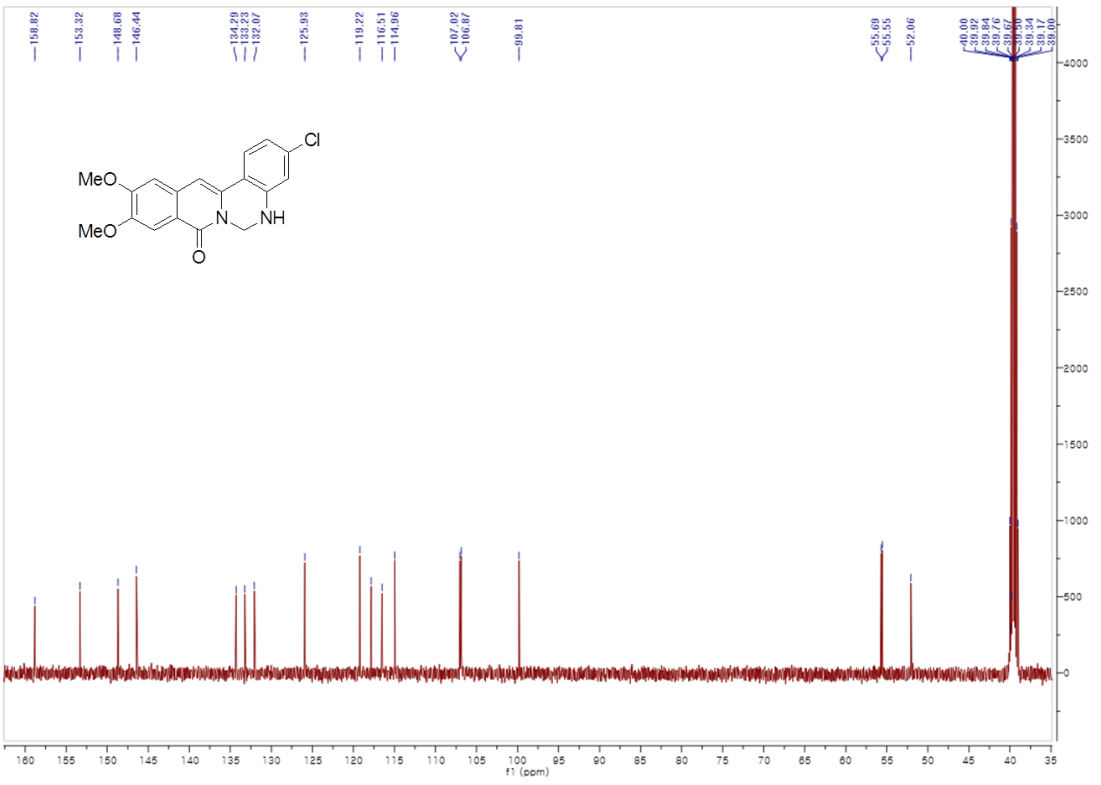



**Figure S6. $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectrum of 8o.**