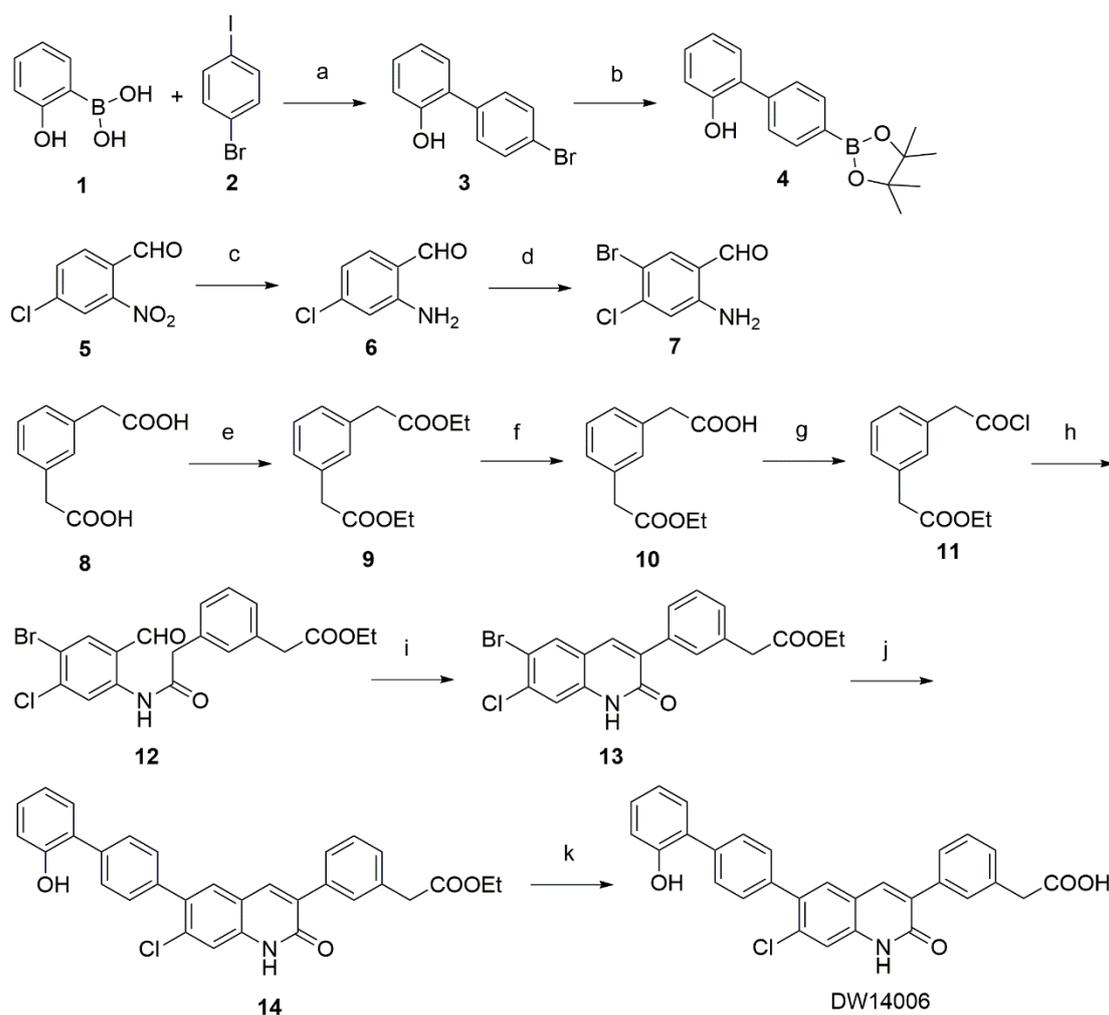


Preparation of DW14006

DW14006 was prepared according to Scheme 1. Detailed information is provided in supplementary materials. The crude product of DW14006 was purified by silica gel chromatography (dichloromethane/methanol, v/v, 98:2) to afford the desired product as a white powder. Yield: 89%. ^1H NMR (300 MHz, DMSO- d_6) δ 12.37 (s, 1H), 12.10 (s, 1H), 9.64 (s, 1H), 8.16 (s, 1H), 7.87 (s, 1H), 7.71–7.59 (m, 4H), 7.53–7.47 (m, 3H), 7.39 (t, $J = 7.9$ Hz, 1H), 7.35–7.26 (m, 2H), 7.24–7.14 (m, 1H), 6.97 (d, $J = 8.1$ Hz, 1H), 6.90 (t, $J = 7.4$ Hz, 1H), 3.63 (s, 2H). ^{13}C NMR (126 MHz, DMSO- d_6) δ 172.72, 160.86, 154.42, 138.17, 137.96, 136.94, 136.25, 135.91, 134.85, 133.40, 133.11, 132.21, 130.53, 130.28, 129.57, 129.15, 129.03 (2C), 128.86 (2C), 128.67, 127.89, 127.10, 127.03, 119.51, 118.86, 116.12, 115.18, 40.86. HRMS (ESI $^+$) m/z $\text{C}_{29}\text{H}_{21}\text{ClNO}_4$: calcd 482.1159, found 482.1154 [M + H] $^+$.

Scheme 1. Synthesis of the Target Compound DW14006^a



^aReagents and conditions: (a) Na₂CO₃, Pd(PPh₃)₄, 1,4-dioxane/H₂O, 90 °C; (b) bis(pinacolato)diboron, AcOK, PdCl₂(dppf), 1,4-dioxane, 90 °C; (c) iron powder, NH₄Cl, EtOH/H₂O, 60 °C; (d) 1-bromopyrrolidine-2,5-dione, DMF, rt; (e) sulfoxide chloride, EtOH, 0 °C to rt; (f) 1 N NaOH in H₂O, EtOH, rt; (g) sulfoxide chloride, DMF, DCM, 0 °C to rt; (h) 7, pyridine, toluene, rt; (i) K₂CO₃, DMF, 60 °C; (j) 4, PdCl₂(dppf), K₂CO₃, toluene/EtOH/H₂O, 110 °C; (k) 1 N NaOH in H₂O, THF/EtOH, rt.

Supplementary Materials

Synthesis of DW14006

All starting materials and reagents were either purchased from commercial sources or prepared according to known procedures. All purchased chemicals and solvents were used as received without further purification. All reactions were monitored by thin-layer chromatography (TLC) on silica gel plates and visualized under UV light. Flash chromatography was performed using silica gel (300–400 mesh). NMR spectral data were generated in DMSO-*d*₆ on Varian Mercury NMR spectrometers (300 MHz for ¹H, 126 MHz for ¹³C). Chemical shifts (δ) were reported in parts per million, coupling constants (*J*) values were in hertz, and the splitting patterns were abbreviated as follows: s for singlet; d for doublet; t for triplet; q for quartet and m for multiplet. Low resolution mass spectrometry was conducted using an Agilent 6110 Quadrupole LC/MS spectrometer (ESI-MS mode). High resolution mass spectrometry was conducted using an Agilent G6530-Q-TOF spectrometer (ESI-MS mode). DW14006 was purified to \geq 95% purity for each test as determined by the Agilent Infinity 1260 HPLC system.

Synthesis of 4'-bromo-[1,1'-biphenyl]-2-ol (3). (2-Hydroxyphenyl)boronic acid (**1**) (6.9 g, 50.0 mmol, 1.0 eq), 1-bromo-4-iodobenzene (**2**) (28.3 g, 100.0 mmol, 2.0 eq), sodium carbonate (10.6 g, 100.0 mmol, 2.0 eq) and tetrakis(triphenylphosphine)palladium (2.89 g, 2.50 mmol, 0.05 eq) were suspended in the mixed solvent of 1,4-dioxane (200 mL) and water (50 mL) under argon atmosphere and the reaction mixture was heated to 90 °C for 12 h. After cooling to room temperature, the mixture was distributed in water and ethyl acetate. The organic layer

was separated and washed with water and brine, dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, v/v, 95:5) to afford the compound **3**. Yield: 76%. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.65 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.22–7.11 (m, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.91–6.82 (m, 1H). MS (ESI⁻) *m/z*: 247.0 [M - H]⁻.

Synthesis of 4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-2-ol (4). A mixture of the compound **3** (6.5 g, 26.1 mmol, 1.0 eq), bis(pinacolato)diboron (10.0 g, 39.2 mmol, 1.5 eq), potassium acetate (7.7 g, 78.3 mmol, 3.0 eq) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.9 g, 2.6 mmol, 0.1 eq) in 1,4-dioxane (130 mL) was heated to 90 °C under argon atmosphere for 12 h. After cooling, the crude mixture was filtered through a thin plug of celite. The celite plug was washed with ethyl acetate and the filtrate was concentrated. The resulting residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, v/v, 95:5 to 90:10) to afford the compound **4**. Yield: 95%. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.58 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.25 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.21–7.14 (m, 1H), 6.94 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.88 (td, *J* = 7.5, 0.9 Hz, 1H), 1.31 (s, 12H). MS (ESI⁺) *m/z*: 319.2 [M + Na]⁺.

Synthesis of 2-amino-4-chlorobenzaldehyde (6). 4-Chloro-2-nitrobenzaldehyde (**5**) (6.0 g, 32.3 mmol, 1.0 eq), iron powder (2.7 g, 48.5 mmol, 1.5 eq) and ammonium chloride (8.6 g, 161.5 mmol, 5.0 eq) were suspended in ethanol (128 mL)/water (32 mL). The reaction mixture was stirred at 60 °C for 2 h. After cooling, the residue was filtered through a thin plug of celite. The celite plug was washed with ethanol and the filtrate was concentrated. The resulting residue was extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and

concentrated in vacuum. The resulting residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, v/v, 98:2 to 95:5) to give the desired product. Yield: 40%. $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 9.80 (s, 1H), 7.57 (d, $J = 8.4$ Hz, 1H), 7.30 (s, 2H), 6.81 (d, $J = 1.8$ Hz, 1H), 6.65 (dd, $J = 8.4, 1.8$ Hz, 1H).

Synthesis of 2-amino-5-bromo-4-chlorobenzaldehyde (7). To a stirred solution of the compound **6** (2.0 g, 12.9 mmol, 1.0 eq) in *N,N*-dimethylformamide (65 mL) was added 1-bromopyrrolidine-2,5-dione (2.3 g, 12.9 mmol, 1.0 eq) at room temperature. The reaction mixture was allowed to stir for 2 h. The solution was poured into iced water and the precipitate was collected by filtration, washing with water and a small amount of ethanol successively. The precipitate was purified by silica gel chromatography (petroleum ether/ethyl acetate, v/v, 95:5) to afford the compound **7**. Yield: 91%. $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 9.78 (s, 1H), 7.94 (s, 1H), 7.33 (s, 2H), 7.02 (s, 1H). MS (ESI $^-$) m/z : 231.9 [M - H] $^-$.

Synthesis of diethyl 2,2'-(1,3-phenylene)diacetate (9). 2,2'-(1,3-Phenylene) diacetic acid (**8**) (10.0 g, 51.5 mmol, 1.0 eq) was dissolved in anhydrous ethanol (130 mL) and stirred at 0 °C under argon atmosphere. Sulfoxide chloride (7.5 mL, 103.0 mmol, 2.0 eq) was added dropwise. The resulting mixture was subsequently warmed up to room temperature and stirred for 3 h. The reaction mixture was concentrated and then diluted with ethyl acetate, washing with sodium bicarbonate solution and brine successively. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuum. The resulting residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, v/v, 95:5) to afford the compound **9**. Yield: 100%. $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 7.32–7.23 (m, 1H), 7.19–7.11 (m, 3H), 4.07 (q, $J = 7.1$ Hz, 4H), 3.64 (s, 4H), 1.18 (t, $J = 7.1$ Hz, 6H). MS (ESI $^+$) m/z : 273.2 [M + Na] $^+$.

Synthesis of 2-(3-(2-ethoxy-2-oxoethyl)phenyl)acetic acid (10). The compound **9** (12.0 g, 48.0 mmol, 1.0 eq) was dissolved in ethanol (72 mL) and stirred at room temperature. 1 N NaOH (57.6 mL, 57.6 mmol, 1.2 eq) was added dropwise and the solution was stirred for additional 1 h. The reaction mixture was concentrated and the resulting residue was cooled in ice bath, acidified with concentrated hydrochloric acid and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuum. The resulting residue was purified by silica gel chromatography (dichloromethane/methanol, v/v, 98:2) to afford the compound **10**. Yield: 48%. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.33 (s, 1H), 7.31–7.20 (m, 1H), 7.19–7.10 (m, 3H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.63 (s, 2H), 3.54 (s, 2H), 1.18 (t, *J* = 7.1 Hz, 3H). MS (ESI⁺) *m/z*: 245.1 [M + Na]⁺.

Synthesis of ethyl 2-(3-(2-chloro-2-oxoethyl)phenyl)acetate (11). To a stirred solution of the compound **10** (2.8 g, 12.6 mmol, 1.0 eq) in anhydrous dichloromethane (63 mL)/ *N,N*-dimethylformamide (0.1 mL) was slowly added sulfoxide chloride (1.4 mL, 18.9 mmol, 1.5 eq) at 0 °C under argon atmosphere. The resulting mixture was subsequently warmed up to room temperature and stirred for 12 h. The reaction mixture was concentrated in vacuum. The crude product (**11**) was used directly in the next step without further purification.

Synthesis of ethyl 2-(3-(2-((4-bromo-5-chloro-2-formylphenyl)amino)-2-oxoethyl)phenyl)acetate (12). The compound **7** (2.7 g, 11.5 mmol, 1.0 eq) and pyridine (1.4 mL, 17.3 mmol, 1.5 eq) were dissolved in toluene (23 mL) under argon. A solution of the acyl chloride **11** (3.0 g, 12.7 mmol, 1.1 eq) in toluene (23 mL) was added dropwise to the above mixture at room temperature. The reaction mixture was stirred for 5 h and concentrated in vacuum. The resulting residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, v/v, 95:5 to 90:10) to afford the

compound **12**. Yield: 92%. ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.89 (s, 1H), 9.86 (s, 1H), 8.47 (s, 1H), 8.23 (s, 1H), 7.42–6.90 (m, 4H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 3.65 (s, 2H), 1.16 (t, *J* = 7.1 Hz, 3H). MS (ESI⁻) *m/z*: 436.0 [M - H]⁻.

Synthesis of ethyl 2-(3-(6-bromo-7-chloro-2-oxo-1,2-dihydroquinolin-3-yl)phenyl)acetate (13). The compound **12** (4.5 g, 10.3 mmol, 1.0 eq) was dissolved in *N,N*-dimethylformamide (20 mL) and stirred at room temperature. Potassium carbonate (2.8 g, 20.6 mmol, 2.0 eq) was added, and the mixture was stirred at 60 °C for 3 h. After cooling, the mixture was distributed in water and ethyl acetate. The organic layer was separated and washed with water and brine successively, dried over anhydrous sodium sulfate and concentrated in vacuum. The resulting residue was purified by silica gel chromatography (dichloromethane/methanol, v/v, 98:2 to 96:4) to afford the compound **13**. Yield: 86%. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.12 (s, 1H), 8.18 (s, 1H), 8.07 (s, 1H), 7.73–7.54 (m, 2H), 7.49 (s, 1H), 7.46–7.35 (m, 1H), 7.30 (d, *J* = 6.7 Hz, 1H), 4.09 (q, *J* = 6.6 Hz, 2H), 3.71 (s, 2H), 1.19 (t, *J* = 6.6 Hz, 3H). MS (ESI⁻) *m/z*: 418.0 [M - H]⁻.

Synthesis of ethyl 2-(3-(7-chloro-6-(2'-hydroxy-[1,1'-biphenyl]-4-yl)-2-oxo-1,2-dihydroquinolin-3-yl)phenyl)acetate (14). The compound **13** (2.0 g, 4.8 mmol, 1.0 eq), the intermediate **4** (1.7 g, 5.8 mmol, 1.2 eq), potassium carbonate (2.0 g, 14.4 mmol, 3.0 eq), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.7 g, 1.0 mmol, 0.2 eq) were suspended in toluene (25 mL)/ethanol (5 mL)/water (10 mL) under argon atmosphere. The reaction mixture was stirred at 110 °C for 5 h. After cooling, the reaction solution was concentrated and the resulting residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, v/v, 70:30 to 40:60) to afford the compound **14**. Yield: 70%. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.10 (s, 1H), 9.63 (s, 1H), 8.16 (s, 1H), 7.87 (s, 1H), 7.71–7.61 (m, 4H), 7.56–7.46 (m, 3H), 7.44–

7.36 (m, 1H), 7.36–7.26 (m, 2H), 7.24–7.12 (m, 1H), 6.97 (d, $J = 8.2$ Hz, 1H), 6.95–6.86 (m, 1H), 4.10 (q, $J = 7.1$ Hz, 2H), 3.72 (s, 2H), 1.20 (t, $J = 7.1$ Hz, 3H). MS (ESI) m/z : 508.1 [M - H]⁻.

Synthesis of 2-(3-(7-chloro-6-(2'-hydroxy-[1,1'-biphenyl]-4-yl)-2-oxo-1,2-dihydroquinolin-3-yl)phenyl)acetic acid (DW14006). The compound **14** (1.6 g, 3.1 mmol, 1.0 eq) was dissolved in tetrahydrofuran (15 mL)/ethanol (15 mL) and stirred at room temperature. 1 N NaOH (9.3 mL, 9.3 mmol, 3.0 eq) was added and the solution was stirred for additional 1 h. The reaction mixture was concentrated and the resulting residue was cooled in ice bath, acidified with 1 N HCl and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuum. The resulting residue was purified by silica gel chromatography (dichloromethane/methanol, v/v, 98:2) to give the desired product as a white powder. Yield: 89%. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.37 (s, 1H), 12.10 (s, 1H), 9.64 (s, 1H), 8.16 (s, 1H), 7.87 (s, 1H), 7.71–7.59 (m, 4H), 7.53–7.47 (m, 3H), 7.39 (t, $J = 7.9$ Hz, 1H), 7.35–7.26 (m, 2H), 7.24–7.14 (m, 1H), 6.97 (d, $J = 8.1$ Hz, 1H), 6.90 (t, $J = 7.4$ Hz, 1H), 3.63 (s, 2H). ¹³C NMR (126 MHz, DMSO-*d*₆) δ 172.72, 160.86, 154.42, 138.17, 137.96, 136.94, 136.25, 135.91, 134.85, 133.40, 133.11, 132.21, 130.53, 130.28, 129.57, 129.15, 129.03 (2C), 128.86 (2C), 128.67, 127.89, 127.10, 127.03, 119.51, 118.86, 116.12, 115.18, 40.86. HRMS (ESI⁺) m/z C₂₉H₂₁ClNO₄: calcd 482.1159, found 482.1154 [M + H]⁺.

General method for HPLC analysis.

HPLC conditions were as follows: column, Agilent Eclipse Plus C18 (4.6 × 150 mm, 5 μm); column temperature, 35 °C; solvent system, methanol/water (0.1% volume of

trifluoroacetic acid) = 75/25 (v/v); UV detection, 254 nm/360 nm; injection volume, 15 μ L; flow rate, 1.0 mL/min; retention time, $t_R = 5.7$ min.

Copies of ^1H NMR and ^{13}C NMR spectra

