Supporting Information

Method of Cell-Based Assay

Human embryonic rhabdomyosarcoma (RD) cells were seeded in a 96-well cell culture plate (8000 cells/well) in Dulbecco's Modified Eagle's Medium (DMEM) with 2% fetal bovine serum (FBS). Cells were pre-incubated overnight in a 5% CO_2 incubator at 37 °C. The virus (EV71/Shenzhen/120F1/09 at 100×TCID50) and the chemical compounds in DMSO were added to the cells and incubated at 37 °C for 72 hours. The final concentration of DMSO in each well was 1%. CCK-8 was added to each well in the end of incubation to determine the cell viability. The optical density in each well was measured at 450 nm. The compound concentration required to reduce the virus-induced cell death by 50% was defined as EC_{50}.

Cytotoxicity Assay

The influence of antiviral drugs on the viability of RD cells during 72 hours incubation period was evaluated using the CCK-8 viability assay. Briefly, 96-well cell culture plates were seeded with 8000 cells/well and incubated overnight. The chemical compounds were added to the wells in 3-fold serial dilutions starting from 100 mM (the DMSO concentration was kept constant at 1% throughout the whole plate). After 72 hours incubation period, CCK-8 solution was added to each well and the optical density in each well was measured. The compound concentration reducing cell viability by 50% was defined as CC_{50}.

EV71 infected model study

Mice were inoculated with EV71 at $1x10^6$ PFU in 30 μl medium via intraperitoneal (i.p.) injection route. They were i.p. administrated with vehicle or compounds at 10 ml/kg before or after infection, daily for seven days. During the in life period, mice were observed, recorded with body weight, mortality and clinical score daily for two weeks. The sickness of mice were evaluated using a graded score: 0 (healthy), 1 (slow movement), 2 (weakness in hind limbs), 3 (paralysis in single limb), 4 (paralysis in two limbs), and 5 (death). At the end of the study, all surviving mice were euthanized.

hERG test on QPatch

Stable CHO-K1 cells expressing hERG channels were used. Test compounds are dissolved in 100% DMSO to make stock solutions for each concentration, transferred into compound

plates, and then diluted into extracellular solution to achieve final concentration for testing. Visual check for precipitation will be conducted before testing. Final DMSO concentration is not more than 0.3% for all concentrations of compounds, vehicle (negative) control, and positive control Amitriptyline.

Three additions of 5 µl of the vehicle are applied, followed by 30 runs of voltage protocol for a baseline period. Then the ascending doses of each compound are added with three repetitions (5 µl*3). The exposure of test compound at each concentration is no less than 5 minutes. The recording for the whole process has to pass the quality control or the cell will be abandoned and the compound will be retested, all automatically set by QPatch Assay Software.

NLD overlay with compound 12, 14 and 16

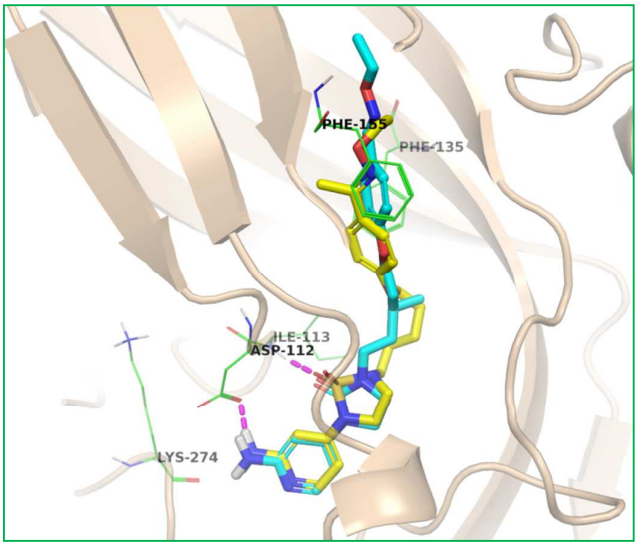


Figure S1. Predicted binding mode of compound **12** overlay with NLD on EV71 capsid.

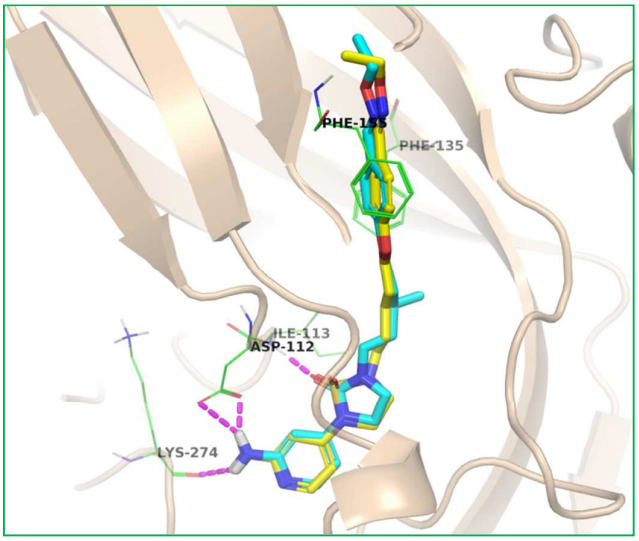


Figure S2. Predicted binding mode of compound **14** overlay with NLD on EV71 capsid.

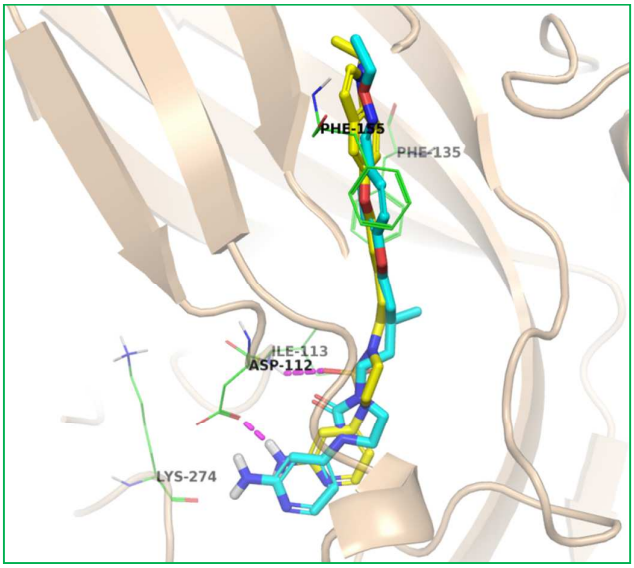


Figure S3. Predicted binding mode of compound **16** overlay with NLD on EV71 capsid.

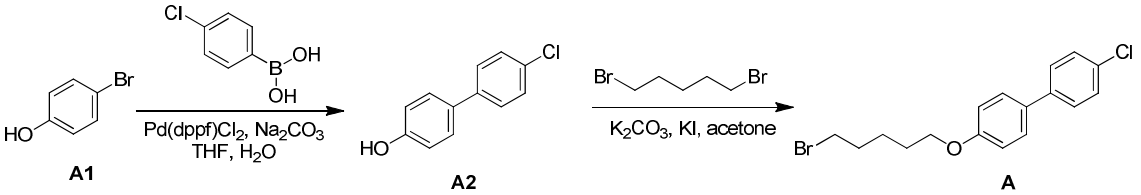
Chemistry Part

General Information.

Reagents and solvents were obtained from commercial suppliers and were used without further purification. 1H NMR measurements were recorded at 400 MHz using a Bruker AMX400 instrument. Preparative HPLC separations were performed on a Boston Green ODS 150*30*5u column using gradient mixtures of water/0.1% TFA and water (10%)/acetonitrile (90%)/0.1% TFA. Chromatographic purifications were performed on silica gel (300-400 mesh). All of the compounds were established by a variety of LC/MS, and NMR analytical

techniques, with >95% purity for all final products.

Synthesis of Intermediate A



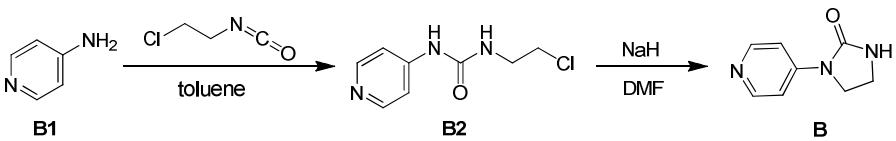
A2

To a solution of **A1** (62.0 g, 360 mmol) in THF/H_2O (600/100 mL) were added (4-chlorophenyl) boronic acid (56.0 g, 360 mmol), Pd(dppf)Cl_2 (7.31 g, 10 mmol) and Na_2CO_3 (76.0 g, 720 mmol) at room temperature. The mixture was stirred at 70^{o}C for 6 hr under N_2 atmosphere, and then poured into water (1 L) and extracted with EtOAc (500 mL x 3). Organic layers were washed with water (1 L) and brine (1 L), dried over Na_2SO_4, filtered and concentrated. The crude product **A2** (60.0 g) was obtained by silica gel chromatography (petroleum ether:EtOAc = 20:1) and used in the next step without chemical characterization.

A

To a solution of **A2** (20.0 g, 97.70 mmol) in acetone (200 mL) were added 1,5-dibromopentane (67.0 g, 293 mmol), K_2CO_3 (27.0 g, 195.40 mmol) and KI (1.62 g, 9.77 mmol). The mixture was stirred at 80^{o}C for 12 hr, and then filtrated. The filtrate was concentrated under reduced pressure. Petroleum ether (200 mL) was added to the residue and stirred at 0^{o}C for 2 hr, filtered to give Intermediate **A** (25.0 g, 75%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.5, 2.0 Hz, 4H), 7.35-7.41 (m, 2H), 6.91-7.00 (m, 2H), 3.96-4.06 (m, 2H), 3.41-3.50 (m, 2H), 1.96 (quin, *J* = 7.2 Hz, 2H), 1.80-1.90 (m, 2H), 1.60-1.71 (m, 2H). **^{13}C NMR** (101MHz, $CDCl_3$) δ 158.82, 139.30, 132.67, 132.42, 128.88, 128.03, 127.94, 114.91, 67.72, 33.64, 32.54, 28.49, 24.89.

Synthesis of Intermediate B



B2

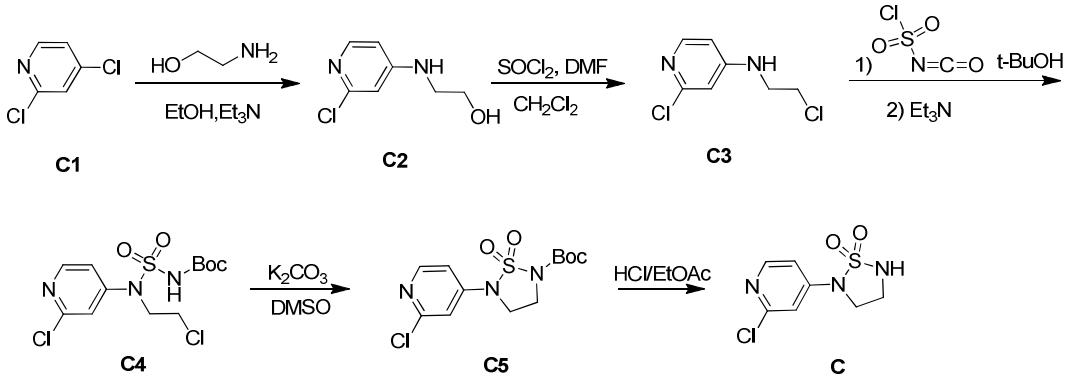
To a solution of **B1** (25.0 g, 265.63 mmol) in toluene (1.0 L) was added

1-chloro-2-isocyanatoethane (42.05 g, 398.45 mmol) at 0°C, then the mixture was stirred at 25°C for 12 hr. Filtered and the filter cake was washed with toluene (200 mL) to give **B2** (50.0 g, 94%) as a white solid. LCMS (ESI) calc'd for $C_8H_{10}ClN_3O$ $[M+H]^+$: 200, found: 200. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.34-8.41 (m, 2H), 7.34-7.39 (m, 2H), 3.61-3.70 (m, 4H).

B

To a solution of **B2** (50.0 g, 269.38 mmol) in DMF (200 mL) was added NaH (12.93 g, 60% in oil, 323.26 mmol) at 0°C in portions, then the mixture was stirred at 25°C for 10 hr. The mixture was poured into water (500 mL), and extracted with EtOAc (500 mL x 3). Organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Petroleum ether (500 mL) and EtOAc (25 mL) was added to the residue, after stirred for 2 hr, filtrated and the filter cake was washed with petroleum ether (20 mL) to give intermediate **B** (43.0 g, 98%) as a yellow solid. LCMS (ESI) calc'd for $C_8H_9N_3O$ $[M+H]^+$: 164, found: 164, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42-8.50 (m, 2H), 7.43-7.51 (m, 2H), 3.86-4.01 (m, 2H), 3.58-3.71 (m, 2H).

Synthesis of Intermediate C



C2

To a solution of **C1** (100.0 g, 0.68 mol) and Et_3N (137 g, 1.35 mol) in EtOH (500 mL) was added a solution of 2-aminoethanol (41.27 g, 0.68 mol), the resulting mixture was stirred at 110°C for 48 hr. The mixture was concentrated and the residue was washed with EtOAc (500 mL x 10). The organic layers were concentrated and purified by flash column chromatography (petroleum ether:EtOAc = 10:1, 2:1, 2:1.5, EtOAc:MeOH = 10:1) to obtain **C2** (25.0 g, 21%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 6.0 Hz, 1H), 6.60 (dd, *J* =5.5, 1.5 Hz, 1H), 6.46 (d, *J* = 1.0 Hz, 1H), 4.91 (br. s. 1H), 3.77-3.85 (m, 2H), 3.47-3.56 (m, 2H).

C3

To a solution of **C2** (25.0 g, 144.84 mmol) in CH_2Cl_2 (100 mL) and DMF (2 mL) was added $SOCl_2$ (86.16 g, 724.20 mmol) dropwise at 0°C. After addition, the solution was stirred at 15°C for 16 hr and then stirred at 40°C for another 13 hr. The mixture was cooled to 25°C and poured into ice-water and basified with NaOH (aq, 2N) to pH = 9. The aqueous phase was extracted with EtOAc (400 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (petroleum ethe:EtOAc = 2:1 to 1:1) to give **C3** (23.0 g, 83%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.81 (d, J = 5.8 Hz, 1H), 7.14 (t, J = 5.5 Hz, 1H), 6.50-6.63 (m, 2H), 3.70 (t, J = 5.9 Hz, 2H), 3.46 (q, J = 5.9 Hz, 2H).

C4

To a solution of **C3** (35.50 g, 478.91 mmol) in CH_2Cl_2 (365 mL) was added N-(oxomethylene)sulfamoyl chloride (59.98 g, 423.81 mmol) dropwise at 0°C. After addition, the mixture was warmed up to 10°C and stirred for 30 min. The resulting solution and Et_3N (114.14 g, 1.13 mol) were added dropwise together to a solution of **C3** (23.0 g, 120.38 mmol) in CH_2Cl_2 (47 mL) at 0°C over 30 min, then stirred at 12°C for another 96 hr. The residue was poured into water (500 mL) and extracted with CH_2Cl_2 (500 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Crude product **C4** (44.50 g, 99%) was obtained as a yellow oil and used in the next step without chemical characterization.

C5

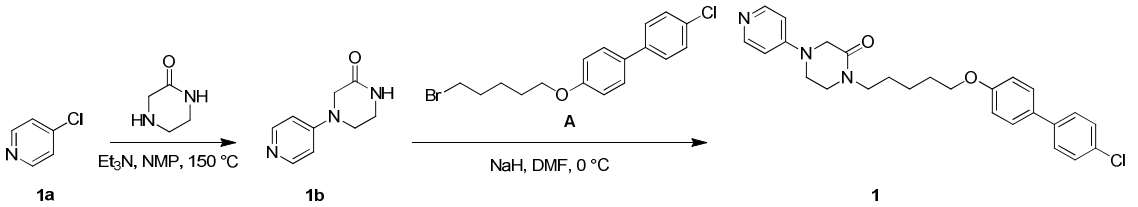
To a solution of **C4** (44.50 g, 120.19 mmol) in DMSO (500 mL) was added K_2CO_3 (46.35 g, 335.33 mmol) in one portion at 25°C. After was stirred at 15°C for 8 hr, the mixture was poured into water (1000 mL) to obtain a white solid which was dissolved in EtOAc (1000 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **C5** (40.0 g, 99%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.35 (d, J = 5.8 Hz, 1H), 7.20-7.33 (m, 2H), 3.99 (s, 4H), 1.48 (s, 9H).

C

To a mixture of **C5** (20.0 g, 59.92 mmol) in EtOAc (100 mL) was added HCl/EtOAc (4N, 100 mL) at 15°C under N_2. The mixture was stirred at 60°C for 5 hr, then concentrated to give **C**

(12.0 g, 86%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.03-8.19 (m, 1H), 6.89-7.02 (m, 2H), 3.67 (t, J = 6.2 Hz, 2H), 3.36-3.50 (m, 2H).

Synthesis of 1



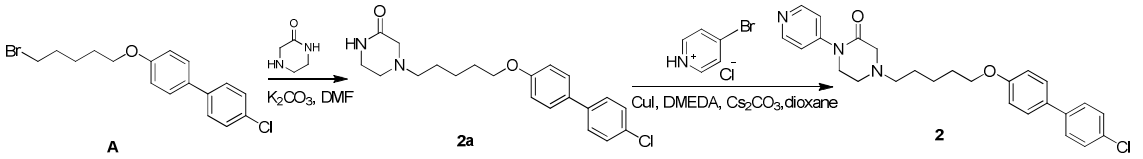
1b

To a solution of 4-chloropyridine **1a** (500 mg, 4.4 mmol) in N-Methyl Pyrrolidone (10 mL) were added piperazin-2-one (441 mg, 4.4 mmol) and Et_3N (1.84 mL, 13.2 mmol). After stirred at 150^{o}C for 4 hr, the mixture was cooled and diluted with CH_2Cl_2 (50 mL). The insoluble solid was filtered and washed with CH_2Cl_2 (10 mL x 2). The solid was dried under reduced pressure to afford **1b** (900 mg, 92%) as a yellow solid. **^{1}H NMR** (400 MHz, MeOD) δ 8.25 (d, J = 7.0 Hz, 2H), 7.20 (d, J = 5.0 Hz, 2H), 4.27 (s, 2H), 3.88-3.93 (m, 2H), 3.54-3.58 (m, 2H).

1

To a solution of **1b** (100 mg, 0.56 mmol) in anhydrous DMF (10 mL) was added NaH (34 mg, 60% in oil, 0.85 mmol) in one portion. The mixture was stirred at 0^{o}C for 0.5 hr under N_2. Then **A** (220 mg, 0.62 mmol) was added to the mixture, and the resulting mixture was stirred at 0^{o}C for additional 2 hr. The reaction was quenched by an aqueous saturated solution of NH_4Cl (10 mL), and diluted with water (100 mL).The mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to give a residue which was purified by prep-HPLC affording **1** (100 mg, 40%) as a yellow solid. LCMS (ESI) calc'd for $C_{26}H_{28}ClN_3O_2$ $[M+H]^+$: 450, found: 450, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (d, J = 6.2 Hz, 2H), 7.46 (dd, J = 8.5, 1.2 Hz, 4 H), 7.34-7.40 (m, 2H), 6.94 (d, J = 8.5 Hz, 2H), 6.61 (d, J = 6.5 Hz, 2H), 3.97-4.03 (m, 4H), 3.57-3.62 (m, 2H), 3.48-3.55 (m, 4H), 1.83-1.88 (m, 2H), 1.67-1.71 (m, 2H), 1.54 (d, J = 7.0 Hz, 2H). **^{13}C NMR** (101MHz, $CDCl_3$) δ 165.21, 158.77, 152.80, 150.25 x 2, 139.24, 132.67, 132.42, 128.85 x 2, 128.01 x 2, 127.90 x 2, 114.85 x 2, 107.48 x 2, 67.64, 49.90, 46.80, 45.70, 42.77, 28.91, 26.86, 23.41.

Synthesis of 2



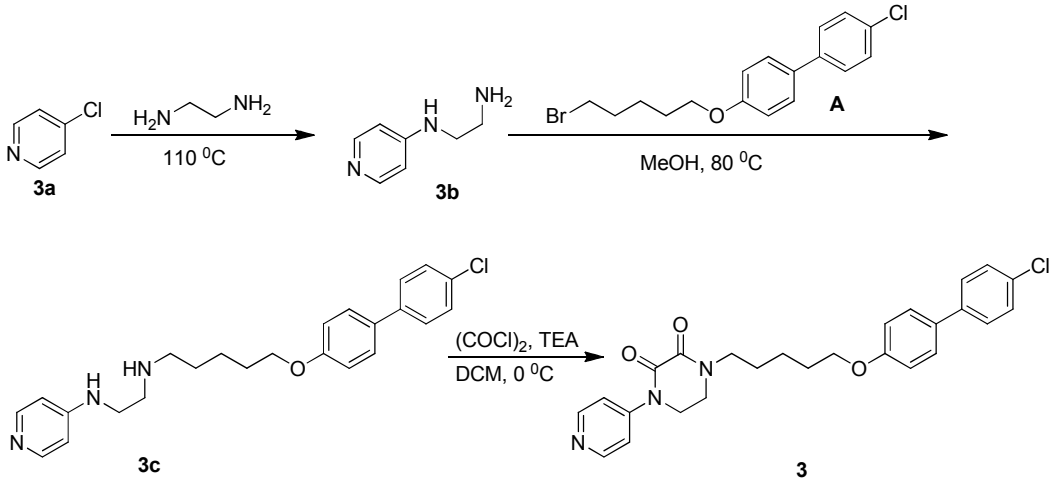
2a

To a solution of **A** (250 mg, 0.71 mmol) in DMF (3 mL) were added piperazin-2-one (70 mg, 0.71 mmol) and K_2CO_3 (200 mg, 1.41 mmol) at 10°C. After stirred at 50°C for 8 hr, the mixture was diluted with EtOAc (10 mL) and concentrated under reduced pressure to give a residue. The residue let stand for 8 hr and the white precipitates were filtered. The precipitates was washed with petroleum ether (5 mL x 2) and dried *in vacuo*. **2a** (200 mg, 76%) was obtained as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.5 Hz, 4H), 7.37 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 4.00 (t, *J* = 6.2 Hz, 2H), 3.34-3.41 (m, 2H), 3.14 (s, 2H), 2.66 (t, *J* = 5.2 Hz, 2H), 2.46 (t, *J* = 7.0 Hz, 2H), 1.83 (quin, *J* = 6.8 Hz, 2H), 1.49-1.62 (m, 4H).

2

To a solution of **2a** (50 mg, 134 umol) in dioxane (2 mL) were added 4-bromopyridine hydrochloride salt (52 mg, 269 umol), DMEDA (4.7 mg, 54 umol), Cs_2CO_3 (131 mg, 402 umol) and CuI (5 mg, 27 umol). The mixture was stirred at 100°C under N_2 for 12 hr. Then the mixture was filtered and concentrated. The residue was purified by prep-HPLC to afford **2** (30 mg, 50%) as a white solid. LCMS (ESI) calc'd for $C_{26}H_{28}ClN_3O_2$ $[M+H]^+$: 450, found: 450, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 6.0 Hz, 2H), 7.48 (dd, *J* = 8.5, 3.5 Hz, 4H), 7.34-7.43 (m, 4H), 6.96 (d, *J* = 8.5 Hz, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.76 (t, *J* = 5.3 Hz, 2H), 3.35 (s, 2H), 2.84 (t, *J* = 5.3 Hz, 2H), 2.50 (t, *J* = 7.0 Hz, 2H), 1.86 (quin, *J* = 6.8 Hz, 2H), 1.52-1.67 (m, 4H). **^{13}C NMR** (101MHz, CDCl3) δ 167.20, 158.82, 150.59, 148.90, 139.27, 132.68, 132.44, 128.85, 128.01, 127.91, 118.08, 114.87, 67.81, 58.44, 57.45, 49.98, 48.39, 29.11, 26.50, 23.85.

Synthesis of 3



3b

3a (14.0 g, 123.3 mmol) in ethylenediamine (20 mL) was stirred at 110°C in seal tube for 20 hr. After concentrated, the residue was purified by column chromatography on silica gel (CH_2Cl_2:MeOH = 10:1) to give compound **3b** (14.0 g, 83%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.99 (d, J = 6.4 Hz, 2H), 6.50 (d, J = 5.6 Hz, 1H), 6.47 (d, J = 6.0 Hz, 2H), 3.01-3.05 (m, 2H), 2.68-2.71 (m, 2H).

3c

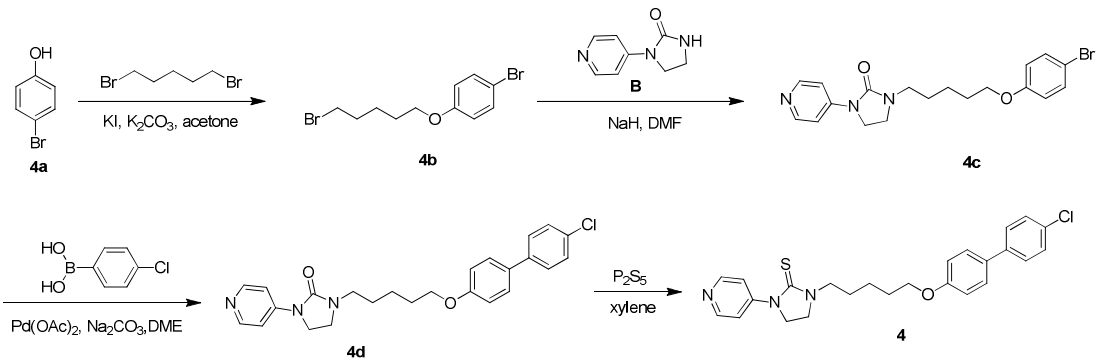
To a solution of **A** (1.0 g, 2.83 mmol) in MeOH (50 mL) was added compound **3b** (3.1 g, 22.62 mmol). The reaction mixture was refluxed for 20 hr. After concentrated, the residue was purified by column flash chromatography (CH_2Cl_2:MeOH = 10:1) to give the **3c** (0.26 g, 22%). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.00 (d, J = 6.8 Hz, 2H), 7.58-7.65 (m, 4H), 7.47 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 9.2 Hz, 2H), 6.48 (d, J = 6.4 Hz, 2H), 6.43-6.45 (m, 2H), 2.20 (brs, 1H), 4.01 (t, J = 6.0 Hz, 2H), 3.10-3.15 (m, 2H), 2.69 (t, J = 6.0 Hz,2H), 2.57-2.54 (m, 2H), 1.72-1.75 (m, 2H), 1.47 (d, J = 3.6 Hz, 1H).

3

To a solution of **3c** (200 mg, 0.49 mmol) in CH_2Cl_2 (5 mL) were added triethylamine (148 mg, 1.47 mmol) and $(COCl)_2$ (124 mg, 0.98 mmol) at 0°C. After stirred at 0°C for 2 hr, the reaction mixture was concentrated and the residue was purified by prep-HPLC to give **3** (30 mg, 13%) as a yellow solid. LCMS (ESI) calc'd for $C_{26}H_{26}ClN_3O_3$ $[M+H]^+$: 464, found: 464, **^{1}H NMR:** (400 MHz, DMSO-d_6) δ 8.58 (d, J = 6.4 Hz, 2H), 7.66-7.59 (m, 4H), 7.52-7.47 (m, 4H), 7.03 (d, J = 8.4 Hz, 2H), 4.05-4.02 (m, 4H), 3.68-3.71 (m, 2H), 3.46-3.48 (m, 2H),

1.75-1.80 (m, 2H), 1.63-1.66 (m, 2H), 1.46-1.50 (m, 2H). **^{13}C NMR** (101MHz, $CDCl_3$) δ 158.73, 156.68, 150.87 x 2, 147.53, 139.21, 132.72, 132.50, 128.86 x 2, 128.11 x 2, 128.04 x 2, 127.91 x 2, 117.07, 114.85 x 2, 67.56, 47.69, 46.13, 44.46, 28.84, 26.84, 23.42.

Synthesis of 4



4b

To a solution of 4-bromophenol (5.0 g, 28.9 mmol) in acetone (50 mL) were added 1,5-dibromopentane (19.95 g, 86.7 mmol), K_2CO_3 (8.0 g, 57.8 mmol) and KI (0.4 g, 2.89 mmol), the mixture was stirred at 80°C for 12 hr. The mixture was filtrated and the filter cake washed with acetone (50 mL). The filtrate was concentrated under reduced pressure, the residue was stirred in petroleum ether (100 mL) at 0°C for 1 hr and filtered to give **4b** (4 g, 43%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37-7.39 (m, 1H), 7.34-7.36 (m, 1H), 6.77-6.79 (m, 1H), 6.75-6.77 (m, 1H), 3.93 (t, *J* = 6.4 Hz, 2H), 3.44 (t, *J* = 6.8 Hz, 2H), 1.90-1.99 (m, 2H), 1.75-1.84 (m, 2H), 1.58-1.67 (m, 2H).

4c

To a solution of **B** (500 mg, 3.06 mmol) in DMF (5 mL) was added NaH (123 mg, 60% in oil, 3.06 mmol) at 0°C in portions. The mixture was stirred at 25°C for 1 hr, and then **4b** (1.48 g, 4.6 mmol) in DMF (1mL) was added dropwise to the mixture. After stirred at 25°C for 10 h, the mixture was poured into water (10 mL), and extracted with EtOAc (10 mL x 3). Organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **4c** (10 mg, 16%) as a yellow soild. LCMS (ESI) calc'd for $C_{19}H_{22}BrN_3O_2$ $[M+H]^+$: 404, found: 404, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43-8.48 (m, 2H), 7.46-7.50 (m, 2H), 7.33-.38 (m, 2H), 6.73-6.78 (m, 2H), 3.93 (t, *J* = 6.4 Hz, 2H), 3.78-3.85 (m, 2H), 3.54 (dd, *J* = 9.2, 6.8 Hz, 2H),

3.35 (t, *J* = 7.2 Hz, 2H), 1.78-1.89 (m, 2H), 1.63-1.71 (m, 2H), 1.46-1.57 (m, 2H).

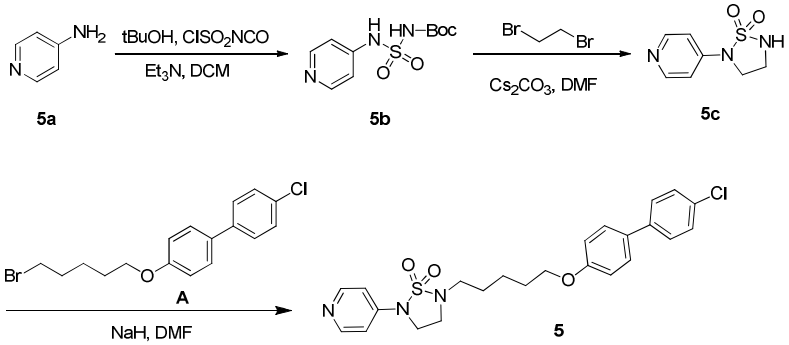
4d

To a solution of **4c** (100 mg, 0.25 mmol) in DME (2 ml) were added (4-chlorophenyl) boronic acid (39 mg, 0.25 mmol), Na_2CO_3 (53 mg, 0.5 mmol) and $Pd(OAc)_2$ (5 mg, 0.03 mmol) under N_2. After stirred at 100°C for 4 hr, the mixture was poured into water (50 mL), and extracted with EtOAc (10 mL x 3). Organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC to give **4d** (30 mg, 28%) as a white solid. LCMS (ESI) calc'd for $C_{25}H_{26}ClN_3O_2$ $[M+H]^+$: 436, found: 436, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.6 Hz, 2H), 7.45-7.51 (m, 6H), 7.34-7.39 (m, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.01 (t, *J* = 6.4 Hz, 2H), 3.82 (dd, *J* = 9.6, 6.4 Hz, 2H), 3.47-3.62 (m, 2H), 3.36 (t, *J* = 7.2 Hz, 2H), 1.82-1.91 (m, 2H), 1.63-1.73 (m, 2H), 0.86 (m, 2H).

4

A mixture of **4d** (100 mg, 0.23 mmol), P_2S_5 (51 mg, 0.23 mmol) in xylene (3 mL) was stirred at 140°C for 12 hr. The mixture was diluted with EtOAc (20 mL), washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by prep-HPLC to give **4** (15 mg, 15%) as a white solid. LCMS (ESI) calc'd for $C_{25}H_{26}ClN_3OS$ $[M+H]^+$: 452, found: 452. **^{1}H NMR** (400MHz, $CDCl_3$) δ 8.55 (d, *J* = 6.3 Hz, 2H), 7.92 (d, *J* = 6.0 Hz, 2H), 7.43-7.53 (m, 4H), 7.33-7.42 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.97-4.15 (m, 4H), 3.69-3.85 (m, 4H), 1.85-1.95 (m, 2H), 1.78 (quin, *J* = 7.5 Hz, 2H), 1.54-1.64 (m, 2H).

Synthesis of 5



5b

To a solution of sulfurisocyanatidic chloride (1.50 g, 11 mmol) in CH_2Cl_2 (20 mL) was added tBuOH (788 mg, 11 mmol) at 0°C. After stirred at 15°C for 1 hr, Et_3N (2.15 g, 21 mmol) and

pyridin-4-amine (1.0 g, 11 mmol) were added, the resulting mixture was stirred at 15°C for 12 hr. Petroleum ether (30 mL) was added and filtered. The filter cake was collected to give **5b** (2.0 g, 69%) as a white solid. LCMS (ESI) calc'd for $C_{10}H_{15}N_3O_4S$ $[M+H]^+$: 274, found: 274. **^{1}H NMR** (400MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.5 Hz, 2H), 6.50 (d, *J* = 7.5 Hz, 2H), 1.15 (s, 9H).

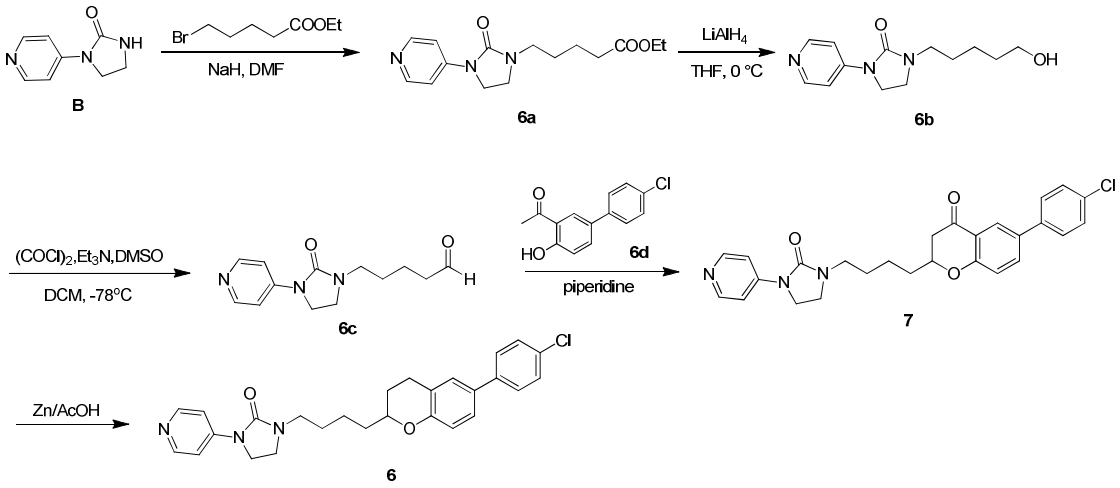
5c

To a mixture of Cs_2CO_3 (10.70 g, 33 mmol) and **5b** (3.00 g, 11 mmol) in DMF (150 mL) was added 1,2-dibromoethane (3.0 g, 16 mmol). After stirred at 80°C for 2 hr, water (500 mL) was added. The mixture was extracted with EtOAc (300 mL x 3), washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC to give **5c** (500 mg, 23 %) as a white solid. LCMS (ESI) calc'd for $C_7H_9N_3O_2S$ $[M+H]^+$: 200, found: 200.

5

To a mixture of **5c** (40 mg, 0.2 mmol) in DMF (10 mL) was added NaH (9.6 mg, 60% in oil, 0.4 mmol) at 0°C. After stirred for 30 min, **A** (71 mg, 0.2 mmol) in DMF (2 mL) was added and the result mixture was stirred at 15°C for 2 hr. The mixture was quenched with water (30 mL), and extracted with EtOAc (10 mL x 3). The combined extracts were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC to give **5** (10 mg, 11%) as a white solid. LCMS (ESI) calc'd for $C_{24}H_{26}ClN_3O_3S$ $[M+H]^+$: 472, found: 472. **^{1}H NMR** (400MHz, $CDCl_3$) δ 8.51 (d, *J* = 6.3 Hz, 2H), 7.44-7.50 (m, 4H), 7.34-7.41 (m, 2H), 7.04-7.10 (m, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.81-3.89 (m, 2H), 3.55 (t, *J* = 6.4 Hz, 2H), 3.19 (t, *J* = 7.2 Hz, 2H), 1.84-1.91 (m, 2H), 1.78-1.82 (m, 2H), 1.58-1.67 (m, 2H). **^{13}C NMR** (101MHz, $CDCl_3$) δ 158.75, 150.65, 144.78, 139.26, 132.69, 132.48, 128.85, 128.03, 127.92, 114.87, 110.27, 67.64, 47.40, 44.39, 43.03, 28.74, 27.21, 23.41.

Synthesis of 6 and 7



6a

To a solution of **B** (2.0 g, 12.26 mmol) in DMF (100 mL) was added NaH (588 mg, 60% in oil, 24.51 mmol) at 0°C. After stirred at 0°C for 1 hr. ethyl 5-bromopentanoate (3.08 g, 14.71 mmol) was added at 0°C, and the resulting mixture was stirred at 20°C for 2 hr. Water (200 mL) was added to the mixture, and the mixture was extracted with EtOAc (200 mL x 3), dried over Na_2SO_4, filtered and concentrated to give a residue which was purified by flash column chromatography (petroleum ether:EtOAc = 1:1 to CH_2Cl_2:MeOH = 10:1) affording **6a** (1.2 g, 34%) as a colorless oil. LCMS (ESI) calc'd for $C_{15}H_{21}N_3O_3$ $[M+H]^+$: 292, found: 292. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 6.0 Hz, 2H), 7.45 (d, *J* = 6.0 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.75-3.82 (m, 2H), 3.48-3.55 (m, 2H), 3.31 (t, *J* = 6.8 Hz, 2H), 2.30-2.35 (m, 2H), 1.57-1.67 (m, 4H), 1.21-1.25 (m, 3H).

6b

To a suspension of $LiAlH_4$ (208 mg, 5.49 mmol) in THF (10 mL) was added a solution of **6a** (800 mg, 2.75 mmol) in THF (8 mL) at 0°C. The resulting mixture was stirred at 20°C for 2 hr. An aqueous solution of 15% NaOH (1 mL) and water (3 mL) were added, and the mixture was filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (CH_2Cl_2:MeOH = 20:1 to 10:1) to afford **6b** (400 mg, 58%) as a white solid. **LCMS (ESI)** calc'd for $C_{13}H_{19}N_3O_2$ $[M+H]^+$: 250, found: 250. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40-8.46 (m, 2H), 7.44-7.51 (m, 2H), 3.81 (dd, *J* = 9.3, 6.8 Hz, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.54 (dd, *J* = 9.3, 6.8 Hz, 2H), 3.33 (t, *J* = 7.2 Hz, 2H), 1.59-1.65 (m, 4H), 1.39-1.46 (m, 2H).

6c

To a solution of oxalylchloride (712 mg, 5.6 mmol) in CH_2Cl_2 (10 mL) was added DMSO (790 mg, 10.1 mmol) at -78°C, and the mixture was stirred for 0.5 hr. Then **6b** (700 mg, 2.8 mmol) in CH_2Cl_2 (10 mL) was added and the reaction was stirred at -78°C for 0.5 hr. after Et_3N (336 mg, 3.33 mmol) was added, the resulting mixture was stirred for another 1.5 hr while allowing the mixture warmed to room temperature. The mixture was quenched by addition of an aqueous saturated solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were concentrated to give crude **6c** (800 mg, 86%) as a yellow solid. **LCMS (ESI)** calc'd for $C_{13}H_{17}N_3O_2$ $[M+H]^+$: 248, found: 248.

7

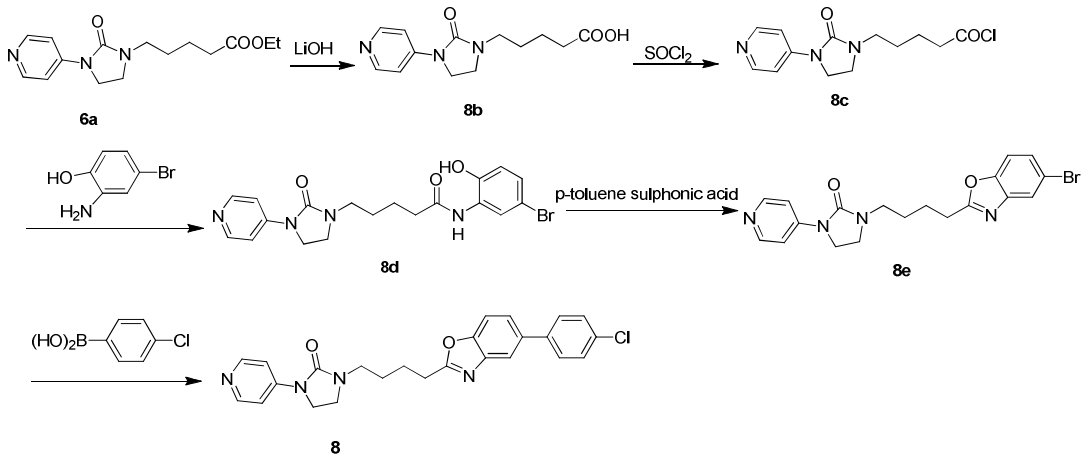
To a solution of **6c** (1.0 g, 4 mmol) and **6d** (998 mg, 4 mmol) in EtOH (10 mL) was added piperidine (700 mg, 8.1 mmol). The mixture was stirred at 85°C for 1 hr. CH_2Cl_2 (10 mL) and H_2O (10 mL) were added to the mixture. The mixture was adjusted to pH = 6 with 2 N aq. HCl, and then extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were concentrated to give a residue which was purified by flash column chromatography (CH_2Cl_2:EtOAc = 1:1 to CH_2Cl_2:MeOH = 30:1) affording **7** (650 mg, 34%) as a yellow solid. **LCMS (ESI)** calc'd for $C_{27}H_{26}ClN_3O_3$ $[M+H]^+$: 476, found: 476. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 6.0 Hz, 2H), 8.06 (d, *J* = 2.5 Hz, 1H), 7.68 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.45-7.52 (m, 4H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 1H), 4.43-4.54 (m, 1H), 3.77-3.88 (m, 2H), 3.49-3.63 (m, 2H), 3.37 (t, *J* = 6.8 Hz, 2H), 2.60-2.84 (m, 2H), 1.92-2.02 (m, 1H), 1.80 (td, *J* = 9.0, 4.5 Hz, 2H), 1.67 (d, *J* = 5.3 Hz, 2H), 1.49-1.61 (m, 1H). **^{13}C NMR** (101MHz, $CDCl_3$) δ 192.23, 161.07, 156.83, 150.16, 147.03, 138.05, 134.42 x 2, 133.42, 133.18, 129.01 x 2, 127.93 x 2, 124.92, 121.05, 118.61, 110.89 x 2, 77.78, 43.66, 42.94, 41.49, 41.39, 34.47, 27.18, 22.19.

6

To a suspension of Zn (3.0 g, 45.9 mmol) in AcOH (6 mL) was added a solution of **7** (250 mg, 0.52 mmol) in AcOH (3 mL). The mixture was stirred at 100°C for 18 hr. After cooled to room temperature, the mixture was adjusted to pH = 7 with an aqueous saturated solution of Na_2CO_3. The mixture was extracted with CH_2Cl_2:MeOH = 10:1 (10 mL x 3), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC (CH_2Cl_2:MeOH =

30:1) to afford **6** (100 mg, 40%) as a yellow solid. LCMS (ESI) calc'd for $C_{27}H_{28}ClN_3O_2$ $[M+H]^+$: 462, found: 462. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 5.8 Hz, 2H), 7.49 (d, *J* = 6.3 Hz, 2H), 7.42-7.46 (m, 2H), 7.34-7.37 (m, 2H), 7.25-7.28 (m, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 3.98-4.06 (m, 1H), 3.83 (dd, *J* = 9.3, 6.8 Hz, 2H), 3.52-3.59 (m, 2H), 3.36 (t, *J* = 6.5 Hz, 2H), 2.77-2.94 (m, 2H), 1.99-2.05 (m, 1H), 1.79 (dd, *J* = 9.9, 5.6 Hz, 2H), 1.63-1.70 (m, 4H), 1.52-1.56 (m, 1H). **^{13}C NMR** (101MHz, $CDCl_3$) δ 156.01, 154.82, 149.73, 147.26, 139.45, 132.48, 131.84, 128.78 x 2, 128.04 x 2, 127.85 x 2, 125.80, 122.38, 117.17, 111.43, 75.84, 43.83, 41.57, 41.28, 40.98, 34.92, 27.40, 27.22, 24.88, 22.52.

Synthesis of 8



8b

A solution of **6a** (265 mg, 0.91 mmol) and $LiOH.H_2O$ (153 mg, 3.6 mmol) in THF (6 mL) and H_2O (2 mL) were stirred at 15^{o}C for 12 hr. The mixture was adjusted to pH = 6 with HCl (1N), the solution was extracted with EtOAc (20 mL x 3), the combined organic layers were concentrated to give **8b** (300 mg, 99%) as a white solid. **LCMS (ESI)**: calc'd for $C_{13}H_{17}N_3O_3$ $[M+H]^+$: 264, found: 264. **^{1}H NMR** (400 MHz, MeOD) δ 8.36 (d, *J* = 6.0 Hz, 2H), 7.67 (d, *J* = 6.3 Hz, 2H), 3.86-4.00 (m, 2H), 3.53-3.71 (m, 2H), 3.36 (d, *J* = 5.8 Hz, 2H), 2.35 (br. s., 2H), 1.66 (br. s., 4H).

8c

A solution of **8b** (200 mg, 1.13 mmol) in $SOCl_2$ (5 mL) was stirred at 80 ^{o}C under N_2 for 2 hr. The reaction mixture was concentrated under reduced pressure to give **8c** (300 mg, crude), which was used for the next step without further purification.

8d

To a solution of **8c** (200 mg, 0.71 mmol) and 2-amino-4-bromophenol (200 mg, 3 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (212 mg, 2.12 mmol) at 0°C under N_2. After stirred at 10°C for 12 hr, the mixture was concentrated and the residue was purified by flash chromatography (CH_2Cl_2:MeOH = 20:1) to give **8d** (200 mg, 65%) as a yellow solid. **LCMS (ESI)**: calc'd for $C_{19}H_{21}BrN_4O_3$ $[M+H]^+$: 433, found: 433. **^{1}H NMR** (400 MHz, MeOD) δ 8.35 (d, *J* = 6.0 Hz, 2H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 6.5 Hz, 2H), 7.10 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 3.85-3.98 (m, 2H), 3.55-3.72 (m, 2H), 3.35-3.43 (m, 2H), 2.53 (t, *J* = 6.8 Hz, 2H), 1.70-1.78 (m, 4H).

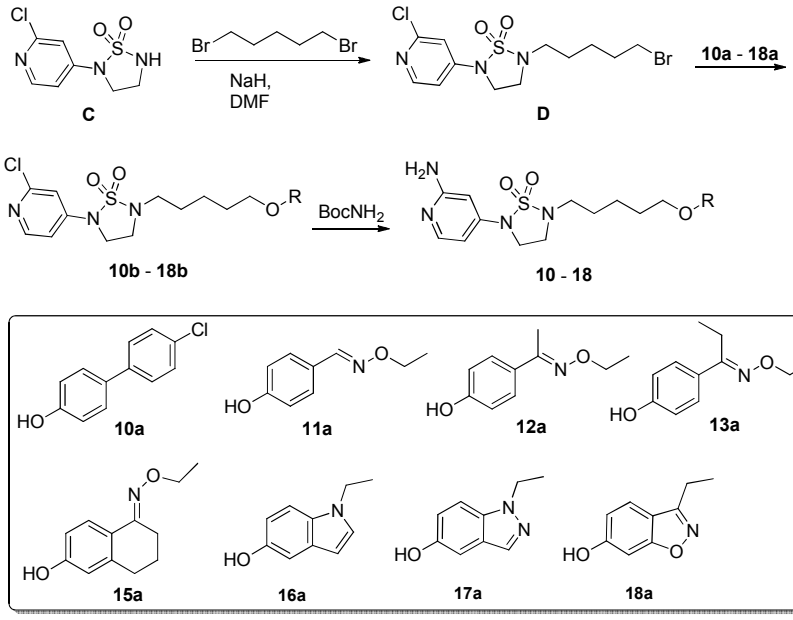
8e

A solution of **8d** (80 mg, 0.2 mmol) and p-toluene sulphonic acid (76 mg, 0.4 mmol) in toluene (8 mL) were stirred at 130°C for 12 hr. Aqueous $NaHCO_3$ was added to quench the reaction and the mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated, the residue was purified by prep-TLC (CH_2Cl_2:MeOH = 20:1) to give **8e** (30 mg, 36%) as a white solid. LCMS (ESI): calc'd for $C_{19}H_{19}BrN_4O_2$ $[M+H]^+$: 415, found: 415. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 6.5 Hz, 2H), 7.73 (s, 1H), 7.60 (d, *J* = 5.5 Hz, 2H), 7.29 -7. 42 (m, 2H), 3.84 (t, *J* = 8.0 Hz, 2H), 3.51-3.60 (m, 2H), 3.36 (br. s., 2H), 2.96 (t, *J* = 7.3 Hz, 2H), 1.82 -1. 95 (m, 2H), 1.59-1.75 (m, 2H).

8

A solution of **8e** (80 mg, 0.19 mmol), (4-chlorophenyl)boronic acid (45 mg, 0.29mmol) Pd(dppf)Cl_2 (15 mg, 0.02 mmol) and K_2CO_3 (78 mg, 0.57 mmol) in DMF (5 mL) and H_2O (1 mL) were stirred at 80°C for 2 hr. After Water was added and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-TLC to give **8** (10 mg, 12%) as a white solid. **LCMS (ESI)**: calc'd for $C_{25}H_{23}ClN_4O_2$ $[M+H]^+$: 447, found: 447. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 6.5 Hz, 2H), 7.84 (s, 1H), 7.74-7.59 (m, 6H), 7.48 (d, *J* = 8.5 Hz, 2H), 3.89-3.97 (m, 2H), 3.59-3.68 (m, 2H), 3.43 (t, *J* = 6.9 Hz, 2H), 3.09 (t, *J* = 7.3 Hz, 2H), 1.93-2.05 (m, 2H), 1.74-1.83 (m, 2H).

Synthesis of 10-18



General Procedure (**13** as an example)

D

To a solution of **C** (4.00 g, 17.12 mmol) in DMF (140 mL) was added NaH (1.03 g, 60% in oil, 25.68 mmol) in one portion at 10°C under N_2 for 1 hr. A solution of 1,5-dibromopentane (3.94 g, 17.12 mmol) in DMF (40 mL) was added dropwise at 10°C. After stirred at 10°C for 1 hr, the reaction was quenched with water (500 mL) and extract with EtOAc (200 mL), the organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (petroleum ether:EtOAc = 2:1) to give **D** (2.70 g, 41%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 5.5 Hz, 1H), 7.07 (dd, *J* = 6.0, 2.0 Hz, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 3.85 (t, *J* = 6.5 Hz, 2H), 3.56 (t, *J* = 6.3 Hz, 2H), 3.44 (t, *J* = 6.5 Hz, 2H), 3.17 (t, *J* = 7.0 Hz, 2H), 1.88-1.98 (m, 2H), 1.74 (quin, *J* = 7.4 Hz, 2H), 1.58-1.64 (m, 2H).

13b

KI (4 mg, 23.29 umol) was added to a mixture of K_2CO_3 (64 mg, 465.74 umol), **13a** (45 mg, 232.87 umol) and **D** (115 mg, 232.87 umol) in DMF (0.5 mL) and acetone (3 mL). The mixture was stirred at 70°C for 16 hr. Water (5 mL) and EtOAc (10 mL) were added to the mixture. The mixture was extracted with EtOAc (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC

(petroleum ether:EtOAc = 1:1) to give **13b** (80 mg, 69%) as a colorless oil. LCMS (ESI) calc'd for $C_{23}H_{31}ClN_4O_4S$ $[M+H]^+$: 495, found: 495. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.8 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.06 (dd, *J* = 5.8, 2.0 Hz, 1H), 6.99 (d, *J* = 1.8 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.99 (t, *J* = 6.1 Hz, 2H), 3.83 (t, *J* = 6.4 Hz, 2H), 3.54 (t, *J* = 6.4 Hz, 2H), 3.17 (t, *J* = 7.3 Hz, 2H), 2.72 (q, *J* = 7.5 Hz, 2H), 1.74-1.88 (m, 4H), 1.61 (d, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.5 Hz, 3H).

13

To a solution of **13b** (80 mg, 0.16 mmol), tert-butyl carbamate (114 mg, 0.97 mmol) and Cs_2CO_3 (105 mg, 0.32 mmol) in dioxane (3 mL) and DMF (0.5 mL) were added XPhos (8 mg, 0.02 mmol) and $Pd_2(dba)_3$ (9 mg, 0.02 mmol) under N_2, then the mixture was stirred at 110^{o}C for 16 hr. After the solvent was removed under reduced pressure, water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC to give **13** (30 mg, 39%) as a brown solid. **LCMS (ESI)** calc'd for $C_{23}H_{33}N_5O_4S$ $[M+H]^+$: 476, found: 476. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 6.0 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.52 (d, *J* = 6.5 Hz, 1H), 6.29 (s, 1H), 5.58 (br. s., 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.99 (t, *J* = 6.0 Hz, 2H), 3.80-3.85 (m, 2H), 3.52 (t, *J* = 6.3 Hz, 2H), 3.17 (t, *J* = 7.3 Hz, 2H), 2.69-2.75 (m, 2H), 1.85 (d, *J* = 7.0 Hz, 2H), 1.75 (br. s., 2H), 1.61 (d, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (101MHz, $CDCl_3$) δ 159.59, 158.97, 147.70, 128.38, 127.55, 114.36, 113.88, 102.00, 94.31, 69.39, 67.56, 47.39, 44.25, 43.55, 29.71, 28.69, 28.65, 27.18, 23.34, 20.02, 14.80, 14.67, 11.22.

10

LCMS (ESI) calc'd for $C_{24}H_{27}ClN_4O_3S$ $[M+H]^+$: 487, found: 487. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (br. s., 1H), 7.48 (dd, *J* = 8.8, 3.3Hz, 4H), 7.35-7.41 (m, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.58 (br. s., 1H), 6.33 (br. s., 1H), 4.02 (t, *J* = 6.02 Hz, 2H), 3.87 (br. s., 2H), 3.55 (t, *J* = 6.27 Hz, 2H), 3.19 (t, *J* = 7.3 Hz, 2H), 1.85-1.90 (m, 2H), 1.76-1.82 (m, 2H), 1.63 (d, *J* = 6.5 Hz, 2H). **^{13}C NMR** (101MHz, $CDCl_3$) δ 158.74, 139.24, 132.69, 132.48, 128.85 x 2, 128.03 x 2, 127.91 x 2, 114.87 x 2, 102.06, 94.27, 77.65, 77.54, 76.70, 67.64, 47.40, 44.28, 43.41, 28.74, 27.19, 23.38.

11

LCMS (ESI) calc'd for $C_{21}H_{29}N_5O_4S$ $[M+H]^+$: 448, found: 448. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95-8.07 (m, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.42 (dd, *J* = 5.5, 2.0 Hz, 1H), 6.29 (d, *J* = 2.0 Hz, 1H), 4.52 (br. s., 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.00 (t, *J* = 6.3 Hz, 2H), 3.80 (t, *J* = 6.5 Hz, 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 3.16 (t, *J* = 7.3 Hz, 2H), 1.73-1.90 (m, 4H), 1.62-1.65 (m, 2H), 1.32 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101MHz, $CDCl_3$) δ 160.22, 157.97, 147.58, 148.14, 144.53, 128.43, 124.97, 114.64 x 2, 101.89, 94.19, 69.54, 67.58, , 47.31, 44.22, 43.42, 28.61, 27.12, 23.28, 14.54.

12

LCMS (ESI) calc'd for $C_{22}H_{31}N_5O_4S$ $[M+H]^+$: 462, found: 462. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 5.8 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.46 (d, *J*=4.5 Hz, 1H), 6.30 (s, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 4.02 (t, *J* = 6.4 Hz, 2H), 3.82 (t, J = 6.4 Hz, 2H), 3.49-3.55 (m, 2H), 3.18 (t, *J* = 7.3 Hz, 2H), 2.23 (s, 3H), 1.72-1.93 (m, 6H), 1.64 (t, *J* = 6.8 Hz, 3H).

15

LCMS (ESI) calc'd for $C_{24}H_{33}N_5O_4S[M+H]^+$: 488, found: 488. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 1 H), 7.62 (d, *J* = 7.0 Hz, 1 H), 6.68-6.75 (m, 2 H), 6.62 (d, *J* = 2.0 Hz, 1 H), 6.18 (s, 1 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 3.98 (t, *J* = 6.3 Hz, 2 H), 3.84 (t, *J* = 6.3 Hz, 2 H), 3.57 (t, *J* = 6.3 Hz, 2 H), 3.19 (t, *J* = 7.0 Hz, 2 H), 2.65-2.76 (m, 4 H), 1.81-1.87 (m, 4 H), 1.76 (d, *J* = 7.0 Hz, 2 H), 1.57-1.63 (m, 2 H), 1.32 (t, *J* = 7.0 Hz, 3 H).

16

LCMS (ESI) calc'd for $C_{22}H_{29}N_5O_3S$ [M+H]+: 444, found: 444. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.18 (s,1H), 7.05-7.07 (m, 1H), 6.80-6.84 (m, 3H), 6.48 (d, *J* = 8.0 Hz, 1H), 4.17 (q, *J* = 7.6 Hz, 2H), 4.03 (t, *J* = 7.6 Hz, 2H), 3.97 (t, *J* = 6.0 Hz, 2H), 3.65 (t, *J* = 7.4 Hz, 2H), 3.22 (t, *J* = 6.8 Hz, 2H), 1.79-1.88 (m, 4H), 1.64-1.68 (m, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

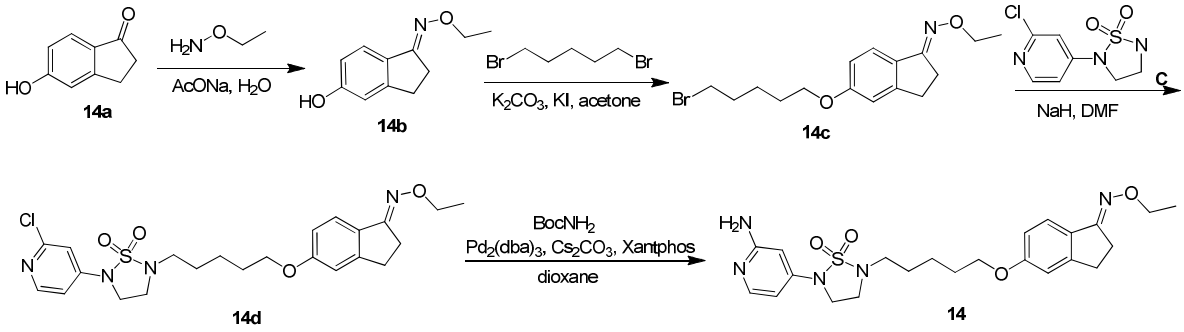
17

LCMS (ESI) calc'd for $C_{21}H_{28}N_6O_3S$ [M+H]+: 445, found: 445. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.67 (d, *J* = 7.0 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.04-7.11 (m, 2H), 6.66 (d, *J* = 6.3 Hz, 1H), 6.21 (br. s., 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.04 (t, *J* = 6.2 Hz, 2H), 3.88 (br. s., 2H), 3.60 (t, *J* = 6.0 Hz, 2H), 3.23 (t, *J* = 7.2 Hz, 2H), 1.88-1.96 (m, 2H), 1.71-1.88 (m, 2H), 1.67-1.69 (m, 2H), 1.52 (t, *J* = 7.3 Hz, 3H).

18

LCMS (ESI) calc'd for $C_{21}H_{27}N_5O_4S$ $[M+H]^+$: 446, found: 446. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 5.5 Hz, 1H), 7.50-7.56 (m, 1H), 7.00 (d, *J* = 2.0 Hz, 1H), 6.85-6.90 (m, 1H), 6.42 (d, *J* = 6.0 Hz, 1H), 6.30 (s, 1H), 4.01 (t, *J* = 6.3 Hz, 2H), 3.76-3.84 (m, 2H), 3.51 (t, *J*=6.3 Hz, 2H), 3.17 (t, *J* = 7.3 Hz, 2H), 2.93 (d, *J* = 7.5 Hz, 2H), 1.84-1.97 (m, 2H), 1.79 (t, *J* = 7.5 Hz, 2H), 1.64 (d, *J* = 7.0 Hz, 2H), 1.43 (t, *J*=7.8 Hz, 3H).

Synthesis of 14



14b

To a solution of **14a** (50 mg, 0.30 mmol) in water (5.0 mL) were added NH_2OEt (65 mg, 0.67 mmol) and NaOAc (55 mg, 0.67 mmol). After stirred at 80°C for 1 hr, the mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The obtained crude product was used in the next step directly. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.3 Hz, 1H), 6.80-6.69 (m, 2H), 4.15-4.24 (m, 2H), 23.94-3.01 (m, 2H), 2.82-2.92 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H).

14c

To a solution of **14b** (80 mg, 0.40 mmol) and 1,5-dibromopentane (288 mg, 1.26 mmol) in acetone (5.0 ml) were added K_2CO_3 (578 mg, 4.18 mmol) and KI (7.0 mg, 0.04 mmol), and then the solution was heated at 80°C for 5 hr. After filtration, the filtrate was concentrated and purified by prep-TLC to give **14c** (140 mg, 98%) as a yellow oil. **LCMS (ESI)** calc'd for

$C_{16}H_{22}BrNO_2$ $[M+H]^+$: 340, found: 340.

14d

To a solution of **C** (20 mg, 0.10 mmol) in dry DMF (1.0 mL) was added NaH (8 mg, 60% in oil, 0.2 mmol) under N_2, and the reaction was stirred at 0°C for 30 min. Then **14c** (34 mg, 0.10 mmol) in dry DMF (1.0 mL) was added to the above solution. The resulting mixture was stirred at 15°C overnight. Water (0.5 mL) was added. After filtration, the filtrate was concentrated and purified by prep-HPLC to give **14d** (17 mg, 37%) as a white solid. **LCMS (ESI)** calc'd for $C_{23}H_{29}ClN_4O_4S$ $[M+H]^+$: 493, found: 493. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 6.0 Hz, 1H), 7.57-7.64 (m, 1H), 7.06 (dd, *J* = 5.8, 2.3 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.75-6.83 (m, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.99 (t, *J* = 6.0 Hz, 2H), 3.84 (t, *J* = 6.3 Hz, 2H), 3.73 (q, *J* = 7.0 Hz, 1H), 3.55 (t, *J* = 6.3 Hz, 2H), 3.18 (t, *J* = 7.0 Hz, 2H), 1.72-1.91 (m, 4H), 1.59-1.67 (m, 3H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 2H).

14

A mixture of **14d** (50 mg, 0.10 mmol), Xantphos (12 mg, 0.02 mmol), $Pd_2(dba)_3$ (9.3 mg, 0.01 mmol), Cs_2CO_3 (66 mg, 0.2 mmol) and $BocNH_2$ (70 mg, 0.60 mmol) in dioxane (1 mL) and DMF (0.3 mL) was stirred at 110°C under N_2 overnight. The mixture was concentrated under reduced pressure and purified by prep-HPLC to give **14** (12 mg, 25%) as a white solid. **LCMS (ESI)** calc'd for $C_{23}H_{31}N_5O_4S$ $[M+H]^+$: 474, found: 474. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 5.5 Hz, 1H), 7.60 (d, *J* = 9.5 Hz, 1H), 6.75-6.83 (m, 2H), 6.42 (dd, *J* = 6.0, 2.0 Hz, 1H), 6.29 (d, *J* = 2.0 Hz, 1H), 4.56 (br. s., 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.95-4.03 (m, 2H), 3.80 (t, *J* = 6.3 Hz, 2H), 3.50 (t, *J* = 6.3 Hz, 2H), 3.16 (t, *J* = 7.0 Hz, 2H), 2.94-3.02 (m, 2H), 2.83-2.92 (m, 2H), 1.72-1.93 (m, 4H), 1.58-1.70 (m, 2H), 1.32 (t, *J* = 7.0 Hz, 3H).