Discovery of 3-substituted 1*H*-indole-2-carboxylic Acid Derivatives as a Novel Class of $CysLT_1$ Selective Antagonists

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Chemistry

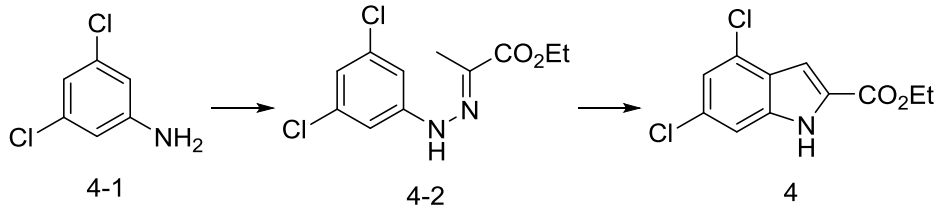
General Experimental

Starting materials, reagents and solvents were purchased from commercial suppliers and used without further purification. Anhydrous toluene and DCE were obtained from a distillation over sodium wire or CaH_2. All non-aqueous reactions were performed under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and all reaction flasks were oven-dried. TLC was carried out on pre-coated TLC plates with silica gel HSGF 254. Spots were visualized under UV at 254 nm. ^{1}H-NMR and ^{13}C-NMR spectra were measured on a Varian Mercury-VX 300, Varian MR 400, AVANCE Ⅲ 500 or AVANCE Ⅲ 600 spectrometer using deuterated chloroform ($CDCl_3$), deuterated methanol (CD_3OD), deuterated acetone (acetone-d_6) and deuterated dimethyl sulfoxide (DMSO-d_6) as the solvent. Chemical shifts are expressed in δ (ppm). Abbreviations for signal coupling are as follows: s, singlet; brs, broad singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; m, multiplet. Coupling constants (*J*) are given in Hz. MS data were obtained with a Micromass Q-Tof UltimaTM spectrometer. HRMS were measured on a Micromass Ultra Q-Tof. Purity was evaluated by analytical HPLC chromatograms using Agilent 1200 series LC system equipped with Zorbax SB C18 column, 4.6 ×150 mm, 5mm par-1

tical size, at room temperature. Mobile phase: MeOH: 0.1% TFA in H_2O (75:25). Flow rate: 1.0 mL/min. UV detection: 368 nm. The following abbreviations for solvents and reagents are used: N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), sodium hydroxide (NaOH), 1,2-dichloroethane (DCE), tetrahydrofuran (THF), dichloromethane (DCM), ethyl acetate (EtOAc), petroleum ether (PE), 1-ethyl-3-(3-dimethylaminopropylcarbodiimide hydrochloride (EDCI), N,N-4-dimethylaminopyridine (DMAP), diisopropylethylamine (DIPEA), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), dicyclohexylcarbodiimide (DCC), tetra-n-butylammonium fluoride (TBAF).

Experimental procedure

Ethyl 4,6-dichloro-1*H*-indole-2-carboxylate (4)



Step 1: **ethyl (*E*)-2-(2-(3,5-dichlorophenyl)hydrazono)propanoate (4-2)**

To a suspension of 3,5-dichloroaniline (5.00 g, 30.9 mmol) in water (20.0 mL) concentrated hydrochloric acid (20.0 mL) was added, the suspension was cooled to 0 ^{0}C. A solution of sodium nitrite (2.34 g, 33.9 mmol) in water (11.0 mL) was added dropwise and the mixture was stirred for 20 min (solution 1). In a separate round-bottom flask, a solution of potassium hydroxide (15.5 g, 276 mmol) in water (30.0 mL) was added dropwise at 0 ^{0}C to a solution of ethyl 2-methylacetoacetate (6.60 g, 45.8 mmol) in ethanol (25.0 mL) and the mixture was stirred for 10 min (solution 2). Solution 1 was cooled to 0 ^{0}C and ice was added, then solution 2 was added slowly. The resulting mixture was warmed to 40 ^{0}C for 15 min, the reaction mixture was cooled and extracted three times with diethyl ether, the combined extracts were dried ($MgSO_4$), the solvent was evaporated, the crude residue was purified by column chromatography on silica gel (PE/EtOAc = 100:1 to 50:1 to 20:1) to give **4-2** (2.88 g, 33.9%) as a yellow solid.

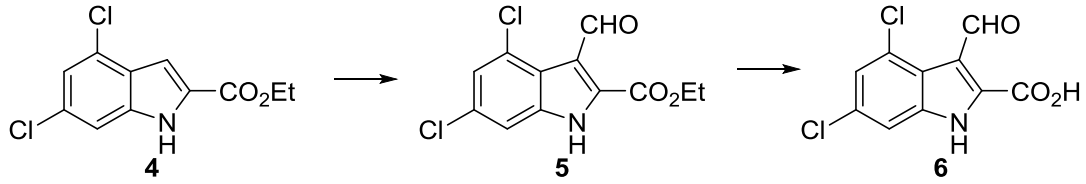
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (s, 1H), 7.11 (d, J = 1.8 Hz, 2H), 6.94 (d, J = 1.8 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.10 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H).

Step 2: **Ethyl 4,6-dichloro-1*H*-indole-2-carboxylate (4)**

A mixture of compound **4-2** (780 mg, 2.84 mmol), polyphosphoric acid (9.60 g) and toluene (10.0 mL) was stirred overnight at 45 ^{0}C. The solvent was subsequently evaporated and ice was added to the residue, the resulting precipitate was filtered and washed twice with DCM to give **4** (707 mg, 96.5%) as a white solid. 1.88 g of compound **4** was prepared again by this method.

^{1}H NMR (300 MHz, DMSO-d_6): δ 7. 43 (s, 1H), 7.25 (s, 1H), 7.09 (s, 1H), 4.34 (q, J = 6.6 Hz, 2H), 1.33 (t, J = 6.6 Hz, 3H).

4,6-dichloro-3-formyl-1*H*-indole-2-carboxylic acid (6)



Step 1: **ethyl 4,6-dichloro-3-formyl-1*H*-indole-2-carboxylate (5)**

$POCl_3$ (3.65 mL, 39.9 mmol) was added dropwise to DMF (3.26 mL, 42.3 mmol) under stirring at 0 ^{0}C, the mixture was stirred at room temperature for 15 min, a solution of compound **4** (2.06 g, 7.98 mmol) in DCE (40.0 mL) was added, the mixture was refluxed for 7 hours, cooled to room temperature and poured onto a solution of NaOAc (50.0 g) in water (100 mL), the mixture was stirred overnight, the resulting precipitate was filtered and washed with water, DCM to give **5** (1.10 g, 48.2%) as a grey solid.

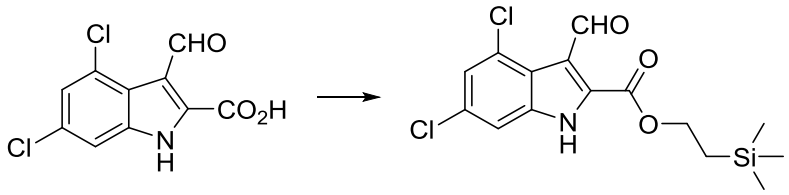
^{1}H NMR (300 MHz, DMSO-d_6): δ 10.63 (s, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.42 (d, J = 1.8 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H).

Step 2: **4,6-dichloro-3-formyl-1*H*-indole-2-carboxylic acid (6)**

Compound **5** (1.10 g, 3.86 mmol) was dissolved in ethanol (60.0 mL) and lithium hydroxide monohydrate (616 mg, 14.7 mmol) was added, the reaction mixture was stirred at 50 ^{0}C for 2 hours, the solvent was evaporated, the resulting residue was diluted with water and adjusted pH to 2 with 1 N HCl, the resulting precipitate was filtered and washed with water to afford **6** (920 mg, 92.4%) as a yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.76 (s, 1H), 7.50 (d, J = 1.5 Hz, 1H), 7.34 (d, J = 1.5 Hz, 1H).

2-(Trimethylsilyl)ethyl 4,6-dichloro-3-formyl-1*H*-indole-2-carboxylate (7)

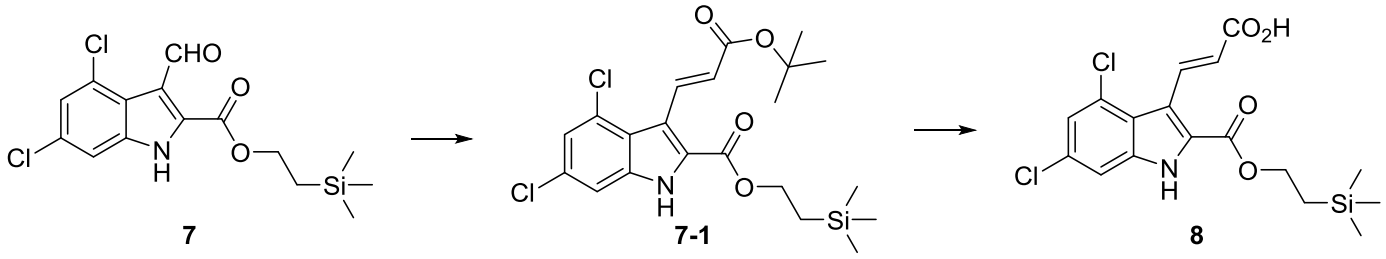


6 **7**

To a solution of compound **6** (600 mg, 2.33 mmol) in dry DCE (20.0 mL) was added 2-(trimethylsilyl)ethan-1-ol (332 mg, 2.79 mmol), EDCI (671 mg, 3.50 mmol) and DMAP (340 mg, 2.79 mmol). The mixture was stirred overnight at room temperature, filtered and the filtrate was concentrated, the residue was dissolved in EtOAc (30.0 mL), the organic phase was washed with 0.5 N HCl (40.0 mL×3) and brine (20.0 mL), dried by $MgSO_4$, the solvent was evaporated, the crude residue was purified by column chromatography on silica gel (PE/EtOAc = 20:1) to give **7** (200 mg, 24.0%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.81 (s, 1H), 9.47 (brs, NH), 7.38 (d, *J* = 1.5 Hz, 1H), 7.34 (d, *J* = 1.5 Hz, 1H), 4.56-4.51 (m, 2H), 1.24-1.18 (m, 2H), 0.11 (s, 9H).

(*E*)-3-(4,6-dichloro-2-((2-(trimethylsilyl)ethoxy)carbonyl)-1*H*-indol-3-yl)acrylic acid (8)



7 **7-1** **8**

Step 1: **2-(trimethylsilyl)ethyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-4,6-dichloro-1*H*-indole-2-carboxylate (7-1)**

Compound **7** (200 mg, 0.558 mmol) and tert-butyl (triphenylphosphoranylidene)acetate (315 mg, 0.837 mmol), toluene (20.0 mL) were mixed in a flask under argon atmosphere, the mixture was heated at reflux overnight, then the solvent was evaporated and the crude product was purified by column chromatography on silica gel (PE/EtOAc = 30:1) to give **7-1** (203 mg, 79.7%) as a yellow solid.

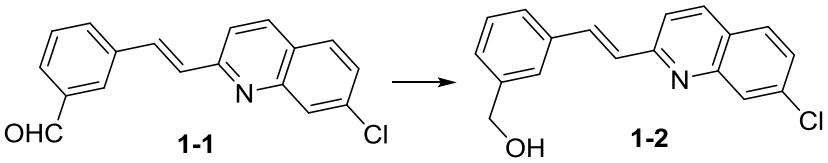
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.15 (brs, NH), 8.32 (d, *J* = 16.5 Hz, 1H), 7.32 (d, *J* = 1.5 Hz, 1H), 7.20 (d, *J* = 1.5 Hz, 1H), 6.48 (d, *J* = 16.5 Hz, 1H), 4.49-4.43 (m, 2H), 1.26-1.15 (m, 2H), 0.08 (s, 9H).

Step 2: **(*E*)-3-(4,6-dichloro-2-((2-(trimethylsilyl)ethoxy)carbonyl)-1*H*-indol-3-yl)acrylic acid (8)**

A solution of compound **7-1** (190 mg, 0.416 mmol) in 98% formic acid (50.0 mL) was stirred overnight at room temperature, the solvent was evaporated and the residue was purified by column chromatography on silica gel (PE/EtOAc = 20:1) to give **7-1** (62.0 mg), (PE/EtOAc = 4:1) to give **8** (78.0 mg, 46.8%) as a white solid.

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.63 (brs, 1H), 10.69 (brs, 1H), 8.50 (d, J = 16.5 Hz, 1H), 7.59 (s, 1H), 7.27 (s, 1H), 6.64 (d, J = 16.5 Hz, 1H), 4.48 (t, J = 9.0 Hz, 2H), 1.19 (t, J = 9.0 Hz, 2H), 0.09 (s, 9H).

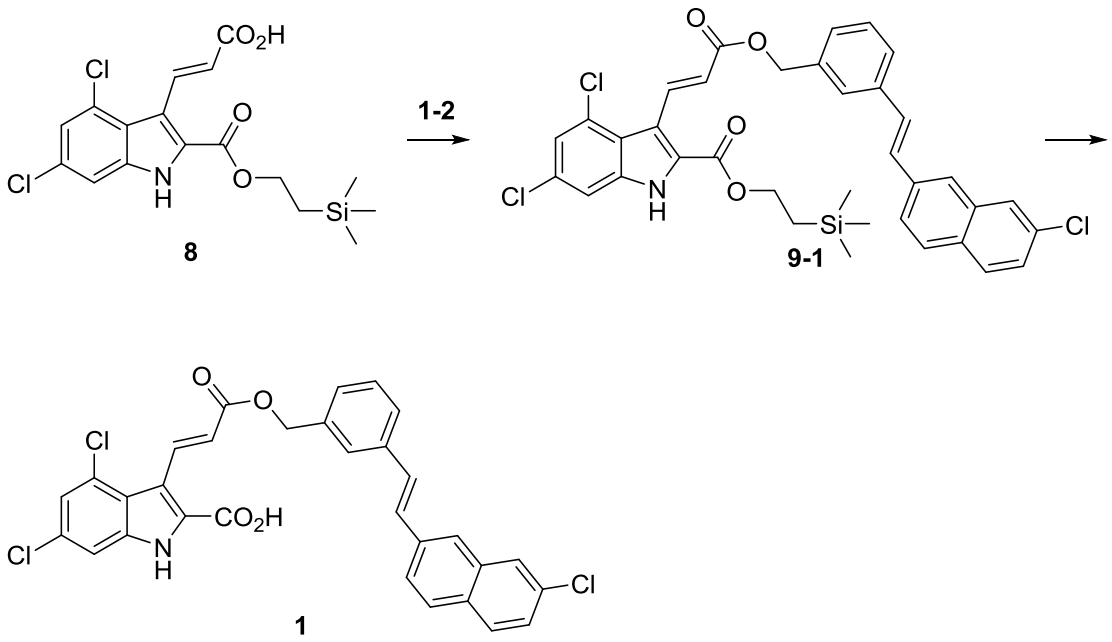
(*E*)-(3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)methanol (1-2)



To a suspension of compound **1-1** (100 mg, 0.340 mmol) in methanol (5.00 mL) was added $NaBH_4$ (28.0 mg, 0.740 mmol) at 0 ^{0}C, then the mixture was stirred for 8 hours at room temperature, TLC showed that compound **1-1** remained, another 50.0 mg of $NaBH_4$ was added and the mixture was stirred overnight at room temperature, the reaction was completed, the solvent was evaporated and the residue was diluted with water (10.0 mL), filtered and dried to give **1-2** (100 mg, 100%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.40 (d, J = 9.0 Hz, 1H), 8.03-7.31 (m, 10H), 5.26 (s, 1H), 4.56 (s, 2H).

4,6-Dichloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)benzyl)oxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (1)



Step 1: **2-(trimethylsilyl)ethyl 4,6-dichloro-3-((*E*)-3-((3-((*E*)-2-(7-chloronaphthalen-2-yl)vinyl)benzyl)oxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylate (9-1)**

To a solution of compound **8** (20.0 mg, 50.0 μmol) in dry DMF (1.00 mL) was added compound **1-2** (16.0 mg, 54.1 μmol), DCC (16.0 mg, 77.6 μmol) and DMAP (4.00 mg, 32.7 μmol). The mixture was stirred overnight at room temperature and diluted with EtOAc (5.00 mL) followed by washing with water (5.00 mL×2) and brine, respectively, the organic phase was dried by $MgSO_4$ and concentrated, the crude residue was purified by column chromatography on silica gel (PE/EtOAc =10:1) to give **9-1** (25.0 mg, 73.9%) as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.20 (brs, NH), 8.54 (d, *J* = 15.9 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 8.07 (s, 1H), 7.77-7.22 (m, 11H), 6.69 (d, *J* = 15.9 Hz, 1H), 5.33 (s, 2H), 4.46 (m, 2H), 1.15 (m, 2H), 0.06 (s, 9H).

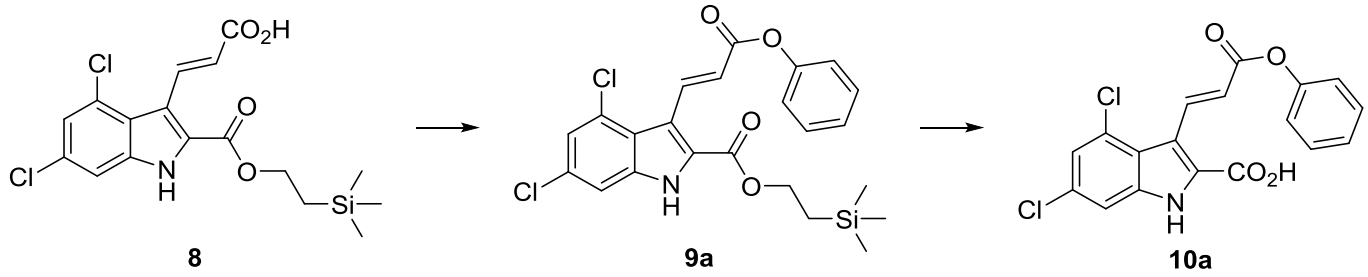
Step 2: **4,6-dichloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)benzyl)oxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (1)**

To a solution of compound **9-1** (25.0 mg, 36.9 μmol) in THF (1.00 mL) was added dropwise TBAF (300 μL, 300 μmol, 1M in THF), the mixture was stirred for 2 hours at room temperature, TLC monitored that the reaction was completed, the solvent was evaporated, the resulting residue was diluted with water (2.00 mL) and adjusted pH to 2 with 1 N HCl, the resulting precipitate was filtered and washed with water. Overnight drying in vacuo to afford **1**, which was recrystallized with acetone to give 10.0

mg of product (47.0%) as a yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.63 (d, J = 7.8 Hz, 1H), 8.54 (d, J = 15.9 Hz, 1H), 8.17-8.06 (m, 5H), 7.81 (s, 1H), 7.75-7.50 (m, 5H), 7.32 (s, 1H), 6.74 (d, J = 15.9Hz, 1H), 5.31 (s, 2H). HRMS (ESI, Neg.) $C_{30}H_{19}N_2O_4Cl_3$ $(M - H)^-$ calc. mass 575.0332, found 575.0343.

(*E*)-4,6-dichloro-3-(3-oxo-3-phenoxyprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10a)



Step 1: **2-(trimethylsilyl)ethyl (*E*)-4,6-dichloro-3-(3-oxo-3-phenoxyprop-1-en-1-yl)-1*H*-indole-2-carboxylate (9a)**

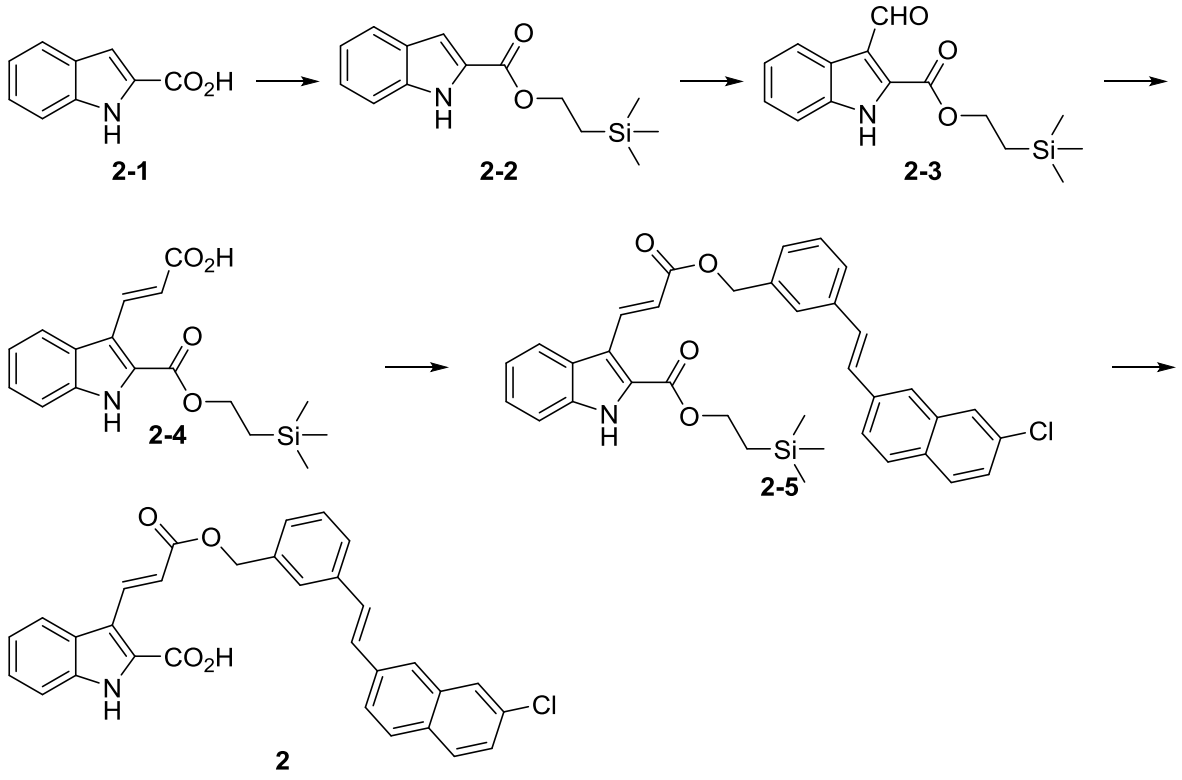
To a solution of compound **8** (20.0 mg, 50.0 μmol) in dry DMF (2.00 mL) was added phenol (6.00 mg, 63.8 μmol), EDCI (12.0 mg, 62.6 μmol) and DMAP (5.00 mg, 40.9 μmol). The mixture was stirred overnight at room temperature and diluted with EtOAc (5.00 mL) followed by washing with 0.1 N HCl, water and brine, respectively, the organic phase was dried by $MgSO_4$ and concentrated, the crude residue was purified by column chromatography on silica gel (PE/EtOAc =10:1) to give **9a** (13.0 mg, 54.6%) as a white solid.

^{1}H NMR (300 MHz, Acetone-d_6): δ 9.32 (brs, 1H), 8.65 (d, J = 15.9 Hz, 1H), 7.44-7.35 (m, 4H), 7.24-7.19 (m, 3H), 6.81 (d, J = 15.9 Hz, 1H), 4.53-4.47 (m, 2H), 1.26-1.15 (m, 2H), 0.09 (s, 9H).

Step 2: **(*E*)-4,6-dichloro-3-(3-oxo-3-phenoxyprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10a)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.73 (brs, 1H), 8.77 (d, J = 15.9 Hz, 1H), 7.65 (s, 1H), 7.45-7.22 (m, 6H), 6.99 (d, J = 15.9 Hz, 1H). HRMS (ESI, Neg.) $C_{18}H_{11}NO_4Cl_2$ $(M - H)^-$ calc. mass 373.9987, found 373.9977.

3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)benzyl)oxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (2)



Step 1: **2-(trimethylsilyl)ethyl 1*H*-indole-2-carboxylate (2-2)**

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.03 (brs, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.33 (m, 1H), 7.22 (s, 1H), 7.15 (m, 1H), 4.48 (m, 2H), 1.17 (m, 2H), 0.11 (s, 9H).

Step 2: **2-(trimethylsilyl)ethyl 3-formyl-1*H*-indole-2-carboxylate (2-3)**

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.77 (s, 1H), 9.33 (brs, 1H), 8.48 (d, *J* = 8.1 Hz, 1H), 7.48-7.33 (m, 3H), 4.55 (m, 2H), 0.88 (m, 2H), 0.11 (s, 9H).

Step 3: **(*E*)-3-(2-((2-(trimethylsilyl)ethoxy)carbonyl)-1*H*-indol-3-yl)acrylic acid (2-4)**

To a solution of compound **2-3** (52.0 mg, 180 μmol) in pyridine (1.00 mL) was added malonic acid (37.0 mg, 356 μmol) and piperidine (153 mg, 1.80 mmol), the mixture was stirred 6 h at 50 ^{0}C. The reaction mixture was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (PE/EtOAc = 1:1+ 1% HCOOH) to obtain **2-4** (12.0 mg, 20.1%) as a white solid.

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.36 (brs, 1H), 8.76 (d, *J* = 16.5 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.40 (m, 1H), 7.30 (m, 1H), 6.69 (d, *J* = 16.5 Hz, 1H), 4.51 (m, 2H), 1.22 (m, 2H), 0.11 (s, 9H).

Step 4: **2-(trimethylsilyl)ethyl 3-((*E*)-3-((3-((*E*)-2-(7-chloronaphthalen-2-yl)vinyl)benzyl)oxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylate (2-5)**

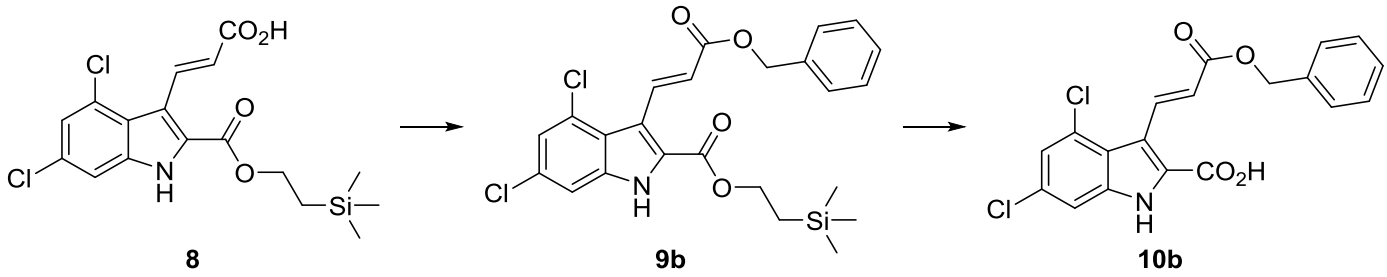
Compound **2-5** was prepared by the previously described for compound **9a** using compounds **2-4** and **1-2.**

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.72 (d, *J* = 16.2 Hz, 1H), 8.14-8.02 (m, 3H), 7.77-7.63 (m, 5H), 7.46-7.36 (s, 6H), 7.27 (m, 1H), 6.77 (d, *J* = 16.2 Hz, 1H), 5.34 (s, 2H), 4.50 (m, 2H), 1.22 (m, 2H), 0.07 (s, 9H).

Step 5: **3-((*E*)-3-((3-((E)-2-(7-chloroquinolin-2-yl)vinyl)benzyl)oxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (2)**

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.53 (s, 1H), 9.19 (s, 1H), 8.83 (d, *J* = 16.5 Hz, 1H), 8.36 (s, 1H), 8.18 (d, *J* = 8.7 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.82-7.70 (m, 2H), 7.59 (s, 1H), 7.53-7.21 (m, 8H), 6.78 (d, *J* = 16.5 Hz, 1H), 5.35 (s, 2H). HRMS (ESI, Neg.) $C_{30}H_{21}N_2O_4Cl$ $(M - H)^-$ calc. mass 507.1112, found 507.1106.

(*E*)-3-(3-(benzyloxy)-3-oxoprop-1-en-1-yl)-4,6-dichloro-1*H*-indole-2-carboxylic acid (10b)



Step 1: **2-(trimethylsilyl)ethyl(*E*)-3-(3-(benzyloxy)-3-oxoprop-1-en-1-yl)-4,6-dichloro-1*H*-indole-2-carboxylate (9b)**

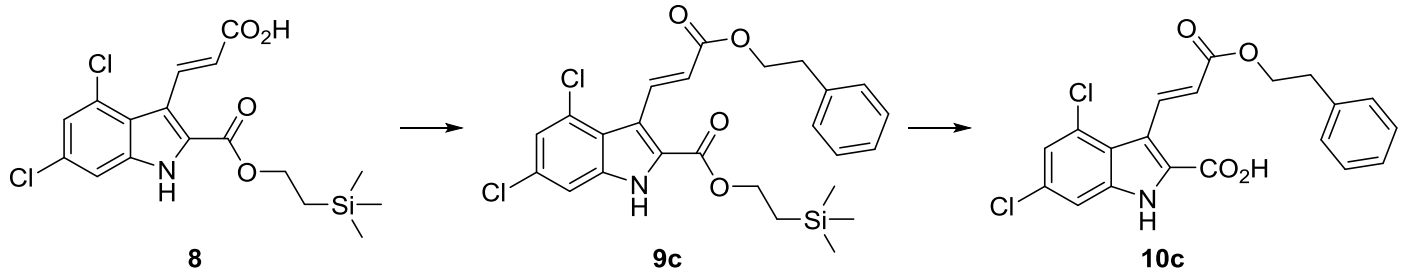
To a solution of compound **8** (10.0 mg, 25.0 μmol) in dry DMF (500 μL) was added cesium carbonate (12.0 mg, 36.8 μmol) at 0 ^{0}C, then a solution of benzyl bromide (4.70 mg, 27.5 μmol) in dry DMF (200 μL) was added, the mixture was stirred for 4 hours at room temperature. The solution was diluted with water (5.00 mL) and extracted with EtOAc (5.00 mL), the organic phase was dried by $MgSO_4$ and concentrated, the crude residue was purified by column chromatography on silica gel (PE/EtOAc =20:1) to give **9b** (10.0 mg, 81.6%) as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.20 (brs, NH), 8.49 (d, *J* = 16.2 Hz, 1H), 7.44-7.21 (m, 7H), 6.64 (d, *J* = 16.2 Hz, 1H), 5.28 (s, 2H), 4.48-4.42 (m, 2H), 1.17-1.11 (m, 2H), 0.09 (s, 9H).

Step 2: **(*E*)-3-(3-(benzyloxy)-3-oxoprop-1-en-1-yl)-4,6-dichloro-1*H*-indole-2-carboxylic acid (10b)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.66 (brs, 1H), 8.62 (d, *J* = 16.2 Hz, 1H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.49-7.33 (m, 5H), 7.27 (d, *J* = 1.5 Hz, 1H), 6.79 (d, *J* = 16.2 Hz, 1H), 5.27 (s, 2H). HRMS (ESI, Neg.) $C_{19}H_{13}N_2O_4Cl_2$ $(M - H)^-$ calc. mass 388.0143, found 388.0132.

(*E*)-4,6-dichloro-3-(3-oxo-3-phenethoxyprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10c)



Step 1: **2-(trimethylsilyl)ethyl (*E*)-4,6-dichloro-3-(3-oxo-3-phenethoxyprop-1-en-1-yl)-1*H*-indole-2-carboxylate (9c)**

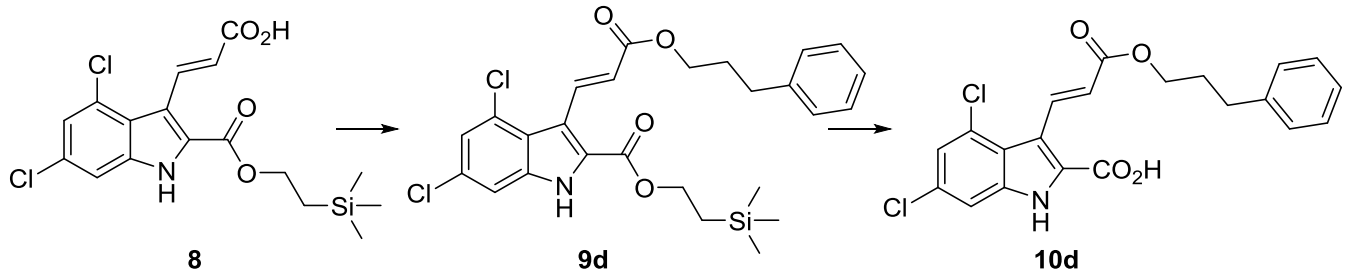
Compound **9c** was prepared by the previously described for compound **9b** using (2-bromoethyl)benzene.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.20 (brs, NH), 8.41 (d, *J* = 15.9 Hz, 1H), 7.33-7.21 (m, 7H), 6.56 (d, *J* = 15.9 Hz, 1H), 4.45 (m, 2H), 3.03 (t, 2H),1.16 (m, 2H), 0.85 (t, 2H), 0.08 (s, 9H).

Step 2: **(*E*)-4,6-dichloro-3-(3-oxo-3-phenethoxyprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10c)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.62 (brs, 1H), 8.53 (d, *J* = 16.2 Hz, 1H), 7.61 (s, 1H), 7.33-7.17 (m, 6H), 6.69 (d, *J* = 16.2 Hz, 1H), 4.41 (t, *J* = 6.9 Hz, 2H), 3.03 (t, *J* = 6.9 Hz, 2H). MS (ESI, Neg.) m/z 402.1 $(M-H)^-$. HRMS (ESI, Neg.) $C_{20}H_{15}NO_4Cl_2$ $(M - H)^-$ calc. mass 402.0300, found 402.0295.

(*E*)-4,6-dichloro-3-(3-oxo-3-(3-phenylpropoxy)prop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10d)



Step 1: **2-(trimethylsilyl)ethyl (*E*)-4,6-dichloro-3-(3-oxo-3-(3-phenylpropoxy)prop-1-en-1-yl)-1*H*-indole-2-carboxylate (9d)**

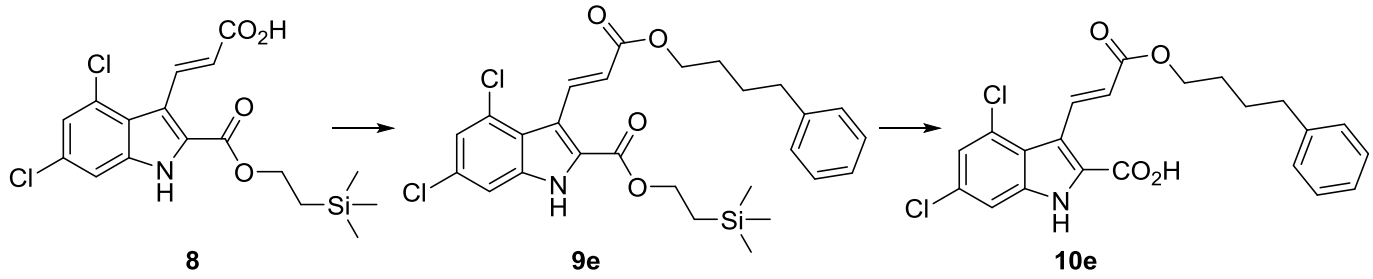
Compound **9d** was prepared by the previously described for compound **9b** using (3-bromopropyl)benzene.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.32 (brs, NH), 8.46 (d, *J* = 16.2 Hz, 1H), 7.34-7.21 (m, 7H), 6.60 (d, *J* = 16.2 Hz, 1H), 4.47 (m, 2H), 4.26 (t, 2H), 2.76 (m, 2H), 2.06 (m, 2H), 1.16 (m, 2H), 0.08 (s, 9H).

Step 2: **(*E*)-4,6-dichloro-3-(3-oxo-3-(3-phenylpropoxy)prop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10d)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.65 (brs, 1H), 8.57 (d, *J* = 15.9 Hz, 1H), 7.62 (d, *J* = 1.5 Hz, 1H), 7.30-7.11 (m, 6H), 6.74 (d, *J* = 15.9 Hz, 1H), 4.21 (t, *J* = 6.6 Hz, 2H), 3.78 (t, *J* = 7.8 Hz, 2H), 2.04 (m, 2H). MS (ESI, Neg.) m/z 416.0 $(M-H)^-$. HRMS (ESI, Neg.) $C_{21}H_{17}NO_4Cl$ $(M - H)^-$ calc. mass 416.0456, found 416.0448.

(*E*)-4,6-dichloro-3-(3-oxo-3-(4-phenylbutoxy)prop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10e)



Step 1: **2-(trimethylsilyl)ethyl (*E*)-4,6-dichloro-3-(3-oxo-3-(4-phenylbutoxy)prop-1-en-1-yl)-1*H*-indole-2-carboxylate (9e)**

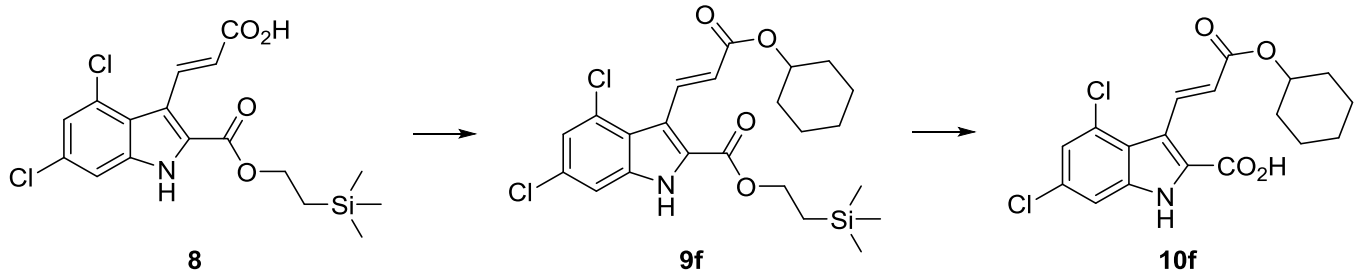
Compound **9e** was prepared by the previously described for compound **9b** using (4-bromobutyl)benzene.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.28 (brs, NH), 8.43 (d, *J* = 16.2 Hz, 1H), 7.33-7.09 (m, 7H), 6.57 (d, *J* = 16.2 Hz, 1H), 4.45 (m, 2H), 4.25 (s, 2H), 2.69 (s, 2H), 1.76 (m, 4H), 1.17 (m, 2H), 0.08 (s, 9H).

Step 2: **(*E*)-4,6-dichloro-3-(3-oxo-3-(4-phenylbutoxy)prop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10e)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.62 (brs, 1H), 8.54 (d, J = 15.9 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 7.29-7.10 (m, 6H), 6.72 (d, J = 15.9 Hz, 1H), 4.23 (t, J = 6.0 Hz, 2H), 2.69 (t, J = 7.2 Hz, 2H), 1.77-1.73 (m, 4H). HRMS (ESI, Neg.) $C_{22}H_{19}NO_4Cl_2$ (M - H)$^-$ calc. mass 430.0613, found 430.0607.

(*E*)-4,6-dichloro-3-(3-(cyclohexyloxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10f)



Step 1: **2-(trimethylsilyl)ethyl (*E*)-4,6-dichloro-3-(3-(cyclohexyloxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylate (9f)**

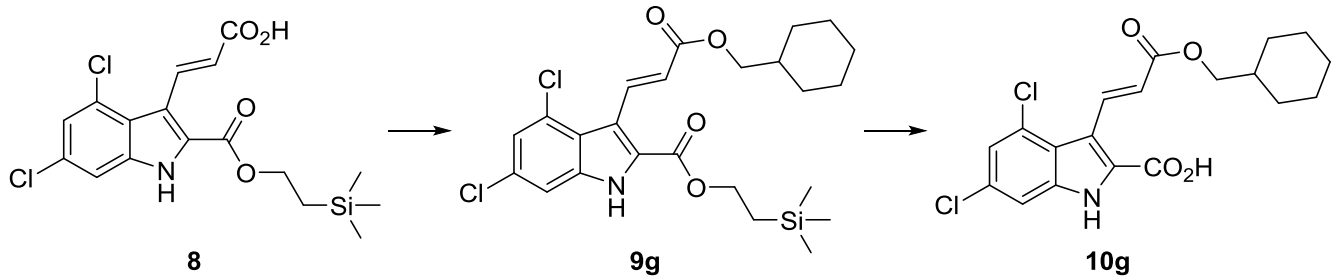
Compound **9f** was prepared by the previously described for compound **9-1** using cyclohexanol.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.32 (brs, NH), 8.40 (d, J = 16.2 Hz, 1H), 7.33 (s, 1H), 7.20 (s, 1H), 6.54 (d, J = 16.2 Hz, 1H), 4.82 (m, 1H), 4.45 (m, 2H), 1.90-1.25 (s, 10H), 1.18 (m, 2H), 0.08 (s, 9H).

Step 2: **(*E*)-4,6-dichloro-3-(3-(cyclohexyloxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10f)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.62 (brs, 1H), 8.55 (d, J = 16.2 Hz, 1H), 7.61 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 1.8 Hz, 1H), 6.71 (d, J = 16.2 Hz, 1H), 4.86 (m, 1H), 1.96-1.20 (m, 10H). HRMS (ESI, Neg.) $C_{18}H_{17}NO_4Cl_2$ (M - H)$^-$ calc. mass 380.0456, found 380.0460.

(*E*)-4,6-dichloro-3-(3-(cyclohexylmethoxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10g)



Step 1: **2-(trimethylsilyl)ethyl (*E*)-4,6-dichloro-3-(3-(cyclohexylmethoxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylate (9g)**

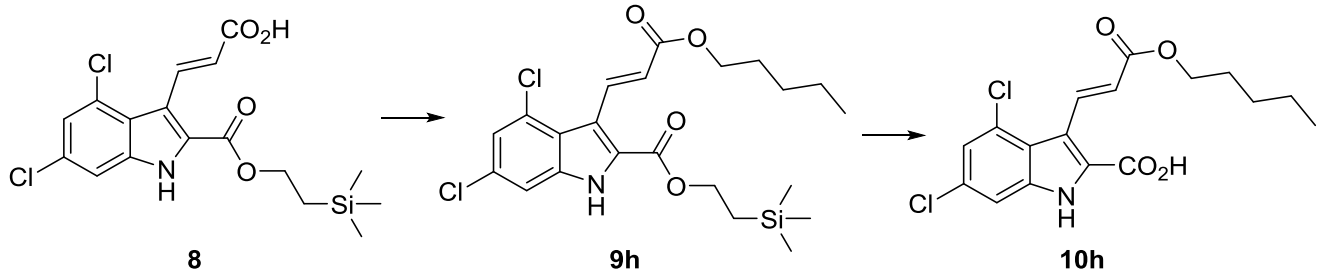
Compound **9g** was prepared by the previously described for compound **9b** using (bromomethyl)cyclohexane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.16 (brs, NH), 8.43 (d, *J* = 16.2 Hz, 1H), 7.33 (s, 1H), 7.21 (s, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 4.46 (m, 2H), 4.04 (d, *J* = 6.3 Hz, 2H), 1.82-1.73 (m, 5H), 1.33-1.01 (m, 8H), 0.09 (s, 9H).

Step 2: **(*E*)-4,6-dichloro-3-(3-(cyclohexylmethoxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10g)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.63 (brs, 1H), 8.55 (d, *J* = 15.9 Hz, 1H), 7.61 (d, *J* = 0.9 Hz, 1H), 7.27 (d, *J* = 1.2 Hz, 1H), 6.72 (d, *J* = 15.9 Hz, 1H), 4.01 (d, *J* = 6.3 Hz, 2H), 1.96-1.05 (m, 11H). HRMS (ESI, Neg.) $C_{19}H_{19}NO_4Cl_2$ $(M - H)^-$ calc. mass 394.0613, found 394.0607.

(*E*)-4,6-dichloro-3-(3-oxo-3-(pentyloxy)prop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10h)



Step 1: **2-(trimethylsilyl)ethyl (*E*)-4,6-dichloro-3-(3-oxo-3-(pentyloxy)prop-1-en-1-yl)-1*H*-indole-2-carboxylate (9h)**

Compound **9h** was prepared by the previously described for compound **9b** using 1-bromopentane.

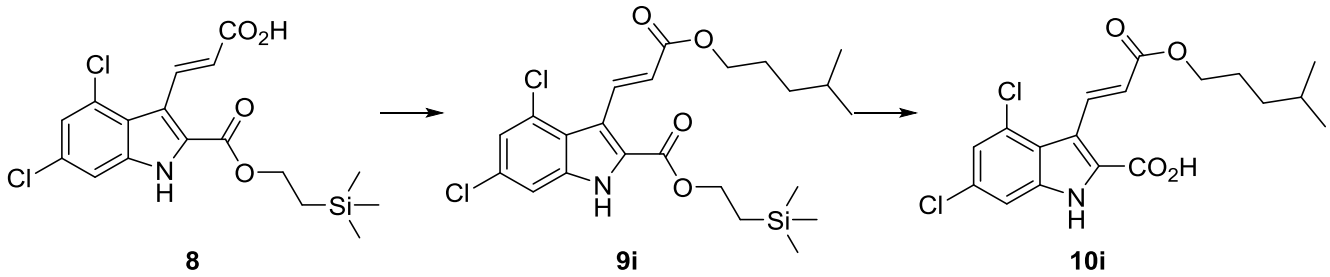
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.18 (brs, NH), 8.42 (d, *J* = 15.9 Hz, 1H), 7.33 (s, 1H), 7.21 (s, 1H),

6.56 (d, *J* = 15.9 Hz, 1H), 4.46 (m, 2H), 4.22 (t, *J* = 6.6 Hz, 2H), 1.71 (m, 2H), 1.38 (m, 4H), 1.17 (m, 2H), 0.93 (t, *J* = 6.6 Hz, 3H), 0.08 (s, 9H).

Step 2: **(*E*)-4,6-dichloro-3-(3-oxo-3-(pentyloxy)prop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10h)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.62 (brs, 1H), 8.54 (d, *J* = 16.2 Hz, 1H), 7.62 (d, *J* = 1.8 Hz, 1H), 7.27 (d, *J* = 1.8 Hz, 1H), 6.72 (d, *J* = 16.2 Hz, 1H), 4.19 (t, *J* = 6.6 Hz, 2H), 1.73-1.53 (m, 2H), 1.42-1.29 (m, 4H), 0.82 (t, *J* = 7.2 Hz, 3H). HRMS (ESI, Neg.) $C_{17}H_{17}NO_4Cl_2$ (M - H)$^-$ calc. mass 368.0456, found 368.0450.

(*E*)-4,6-dichloro-3-(3-((4-methylpentyl)oxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10i)



Step 1: **2-(trimethylsilyl)ethyl (*E*)-4,6-dichloro-3-(3-((4-methylpentyl)oxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylate (9i)**

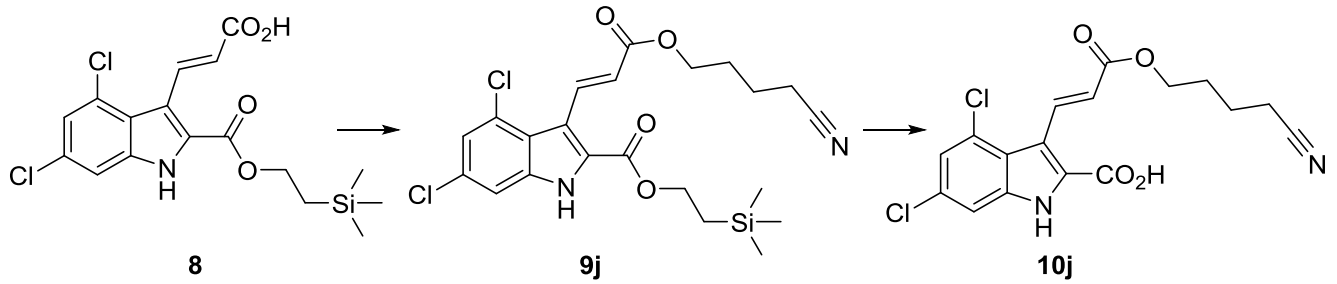
Compound **9i** was prepared by the previously described for compound **9b** using 1-bromo-4-methylpentane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.27 (brs, NH), 8.42 (d, *J* = 16.2 Hz, 1H), 7.33 (s, 1H), 7.21 (s, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 4.46 (m, 2H), 4.21 (t, *J* = 6.6 Hz, 2H), 1.77-1.67 (m, 2H), 1.33-1.25 (m, 3H), 1.17 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 6H), 0.08 (s, 9H).

Step 2: **(*E*)-4,6-dichloro-3-(3-((4-methylpentyl)oxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10i)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.63 (brs, 1H), 8.54 (d, *J* = 15.9 Hz, 1H), 7.61 (s, 1H), 7.27 (s, 1H), 6.71 (d, *J* = 15.9 Hz, 1H), 4.18 (t, *J* = 6.6 Hz, 2H), 1.74-1.67 (m, 2H), 1.37-1.28 (m, 3H), 0.92 (d, *J* = 6.6 Hz, 6H). HRMS (ESI, Neg.) $C_{18}H_{19}NO_4Cl_2$ (M - H)$^-$ calc. mass 382.0613, found 382.0606.

(*E*)-4,6-dichloro-3-(3-(4-cyanobutoxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10j)



Step 1: **2-(trimethylsilyl)ethyl (E)-4,6-dichloro-3-(3-(4-cyanobutoxy)-3-oxoprop-1-en-1-yl)-1H-indole-2-carboxylate (9j)**

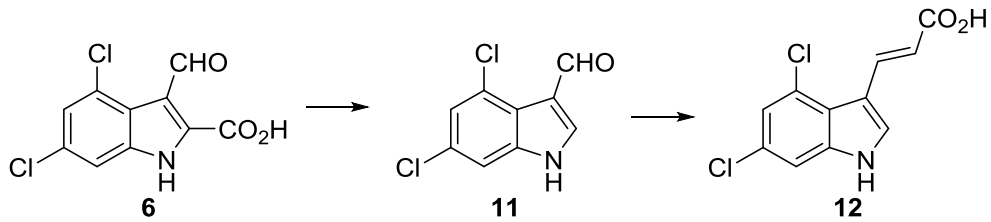
Compound **9j** was prepared by the previously described for compound **9b** using 5-bromopentanenitrile.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.34 (brs, NH), 8.45 (d, *J* = 16.2 Hz, 1H), 7.34 (s, 1H), 7.21 (s, 1H), 6.59 (d, *J* = 16.2 Hz, 1H), 4.47 (m, 2H), 4.28 (t, *J* = 6.0 Hz, 2H), 2.44 (t, *J* = 6.6 Hz, 2H),1.89-1.79 (m, 4H), 1.17 (m, 2H), 0.09 (s, 9H).

Step 2: **(*E*)-4,6-dichloro-3-(3-(4-cyanobutoxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (10j)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.65 (brs, 1H), 8.56 (d, *J* = 15.9 Hz, 1H), 7.61 (s, 1H), 7.27 (s, 1H), 6.73 (d, *J* = 15.9 Hz, 1H), 4.26 (t, *J* = 6.0 Hz, 2H), 2.57 (t, *J* = 6.6 Hz, 2H), 1.53-1.46 (m, 4H). HRMS (ESI, Neg.) $C_{17}H_{14}N_2O_4Cl_2$ $(M - H)^-$ calc. mass 379.0252, found 379.0250.

(*E*)-3-(4,6-dichloro-1*H*-indol-3-yl)acrylic acid (12)



Step 1: **4,6-dichloro-1*H*-indole-3-carbaldehyde (11)**

A suspension of compound **6** (300 mg, 1.16 mmol) and cuprous chloride (53.0 mg, 0.535 mmol) in quinolone (2.00 mL) was subjected to microwave heating for 10 min at 220 ^{0}C, upon cooling, the entire contents were diluted with EtOAc (15.0 mL). The solution was washed twice with 1 N HCl, the emulsified solution was filtered and the filtrate was washed with brine, the organic phase was dried by $MgSO_4$ and concentrated, the crude residue was purified by column chromatography on silica gel (PE/EtOAc = 1:1) to give **11** (120 mg, 48.3%) as a grey solid.

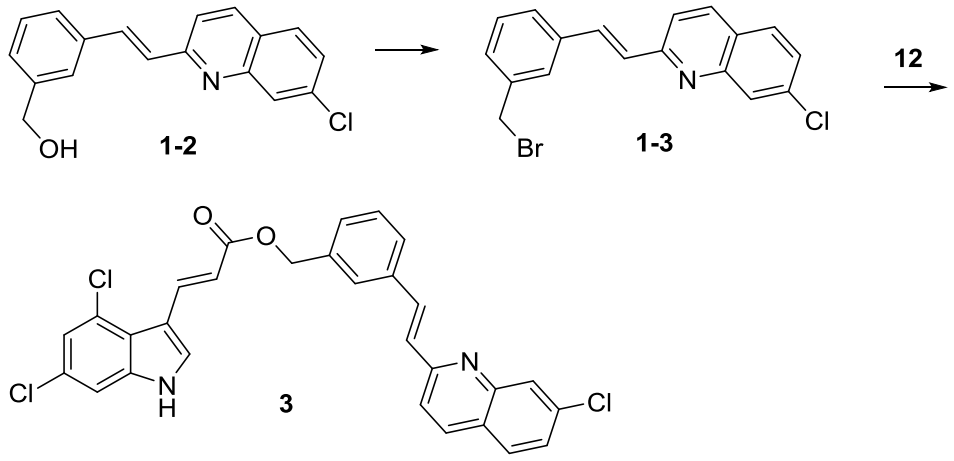
^{1}H NMR (300 MHz, DMSO-d_6): δ 10.42 (s, 1H), 8.34 (s, 1H), 7.59 (s, 1H), 7.41 (s, 1H).

Step 2: **(*E*)-3-(4,6-dichloro-1*H*-indol-3-yl)acrylic acid (12)**

The mixture of compound **11** (63.0 mg, 0.294 mmol), malonic acid (59.0 mg, 0.567 mmol), pyridine (1.70 mL) and piperidine (246 mg, 2.89 mmol) was stirred overnight at 50 ^{0}C. The reaction mixture was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (PE/EtOAc = 1:1+ 1% HCOOH) to obtain **12** (50.0 mg, 78.4%) as a grey solid.

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.21 (brs, 1H), 10.46 (brs, 1H), 8.57 (d, J = 15.9 Hz, 1H), 8.16 (s, 1H), 7.53 (s, 1H), 7.21 (s, 1H), 6.36 (d, J = 15.9 Hz, 1H).

3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)benzyl (*E*)-3-(4,6-dichloro-1*H*-indol-3-yl)acrylate (3)



Step 1: **(*E*)-2-(3-(bromomethyl)styryl)-7-chloroquinoline (1-3)**

To a solution of compound **1-2** (100 mg, 0.338 mmol) in dry DMF (2.50 mL) was added triphenylphosphine (108 mg, 0.412 mmol) and N-bromosuccinimide (73.3 mg, 0.412 mmol) at 0 ^{0}C, then the mixture was stirred for 3 hours at room temperature. The reaction mixture was diluted with EtOAc (10.0 mL) and washed with aqueous lithium hydroxide (0.5 M, 10.0 mL), water (10.0 mL) and brine (10.0 mL), respectively, the organic phase was dried by $MgSO_4$ and concentrated, the crude residue was purified by column chromatography on silica gel PE/EtOAc = 20:1) to give **1-3** (66.0 mg, 54.5%) as a light yellow solid.

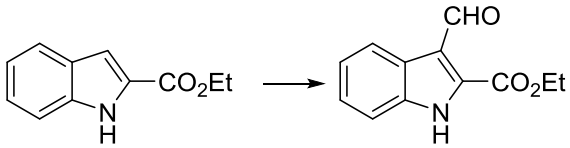
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13-8.08 (m, 2H), 7.74-7.56 (m, 6H), 7.47-7.35 (m, 3H), 4.54 (s, 2H). MS (ESI, Pos.) m/z 357.1 $(M+H)^+$, 359.1 $(M+2+H)^+$.

Step 2: **3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)benzyl(*E*)-3-(4,6-dichloro-1*H*-indol-3-yl)acrylate (3)**

To a solution of compound **12** (35.0 mg, 0.137 mmol) in dry DMF (3.00 mL) was added potassium carbonate (39.0 mg, 0.282 mmol) at 0 ^{0}C, after stirring for 15 min at the same temperature, compound **1-3** (50.0 mg, 0.139 mmol) was added, the resulting solution was stirred overnight at room temperature. The solution became yellow suspension which was diluted with EtOAc (10.0 mL) and water (10.0 mL), the precipitated white solid was filtered and dried in vacuo to give **3** (20.0 mg, 27.4%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.51 (d, *J* = 15.9 Hz, 1H), 8.41 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 8.02 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.94-7.87 (m, 3H), 7.80 (s, 1H), 7.73 (d, *J* = 6.9 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.54 (s, 1H), 7.50-7.48 (m, 2H), 7.43 (t, *J* = 6.3 Hz, 1H), 7.24 (s, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 5.26 (s, 2H). HRMS (ESI, Neg.) $C_{29}H_{19}N_2O_2Cl_3$ $(M - H)^-$ calc. mass 531.0434, found 531.0449.

Ethyl 3-formyl-1*H*-indole-2-carboxylate (14b)

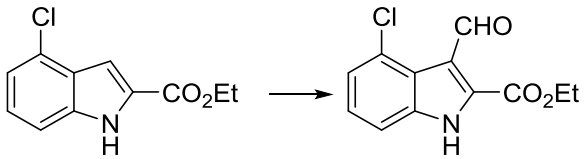


13b **14b**

Compound **14b** was prepared by the previously described for compound **5** using Compound **13b**.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.60 (s, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H).

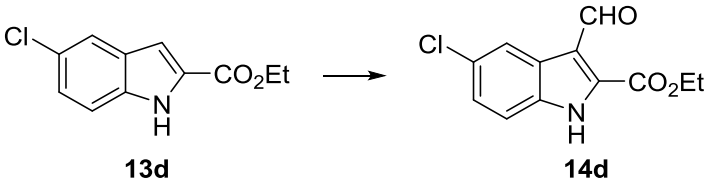
Ethyl 4-chloro-3-formyl-1*H*-indole-2-carboxylate (14c)



13c **14c**

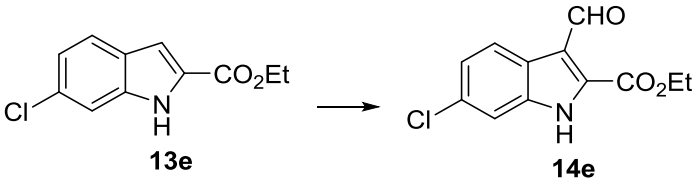
^{1}H NMR (300 MHz, DMSO-d_6): δ 10.66 (s, 1H), 7.55 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.35-7.33 (m, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H).

Ethyl 5-chloro-3-formyl-1*H*-indole-2-carboxylate (14d)



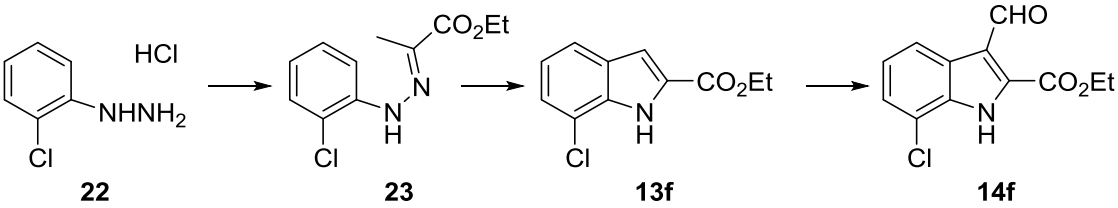
^{1}H NMR (300 MHz, DMSO-d_6): δ 10.54 (s, 1H), 8.19 (s, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.39-7.36 (m, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H).

Ethyl 6-chloro-3-formyl-1*H*-indole-2-carboxylate (14e)



^{1}H NMR (300 MHz, DMSO-d_6): δ 10.53 (s, 1H), 8.18 (d, *J* = 8.7 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.24 (dd, *J* = 8.7, 1.8 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

Ethyl 7-chloro-3-formyl-1*H*-indole-2-carboxylate (14f)



Step 1: **ethyl (*E*)-2-(2-(2-chlorophenyl)hydrazono)propanoate (23)**

To a solution of ethyl pyruvate (3.10 g, 26.7 mmol) in ethanol (60.0 mL) was added glacial acetic acid (498 mg, 8.29 mmol) and 2-chlorophenylhydrazine hydrochloride (3.00 g, 16.8 mmol), the mixture was stirred for 2 hours at 80 ^{0}C. After the mixture was cooled at room temperature, the solid was filtered and recrystallized from ethanol to afford **23** (2.02 g, 50.0%).[1]

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.30 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.13 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

Step 2: **ethyl 7-chloro-1*H*-indole-2-carboxylate (13f)**

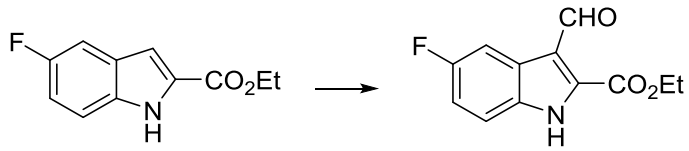
A mixture of **23** (1.00 g, 4.15 mmol) and polyphosphoric acid (10.0 g) was stirred at 45 ^{0}C for 1 hour, then ice-water was added and extracted with ethyl ether (50.0 mL), the organic phase was dried by $MgSO_4$ and concentrated, the crude residue was purified by column chromatography on silica gel (PE/EtOAc =50:1) to give **13f** (300 mg, 32.3%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.13 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.26 (s, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 4.35 (q, *J* = 6.9 Hz, 2H), 1.34 (t, *J* = 6.9 Hz, 3H).

Step 3: **Ethyl 7-chloro-3-formyl-1*H*-indole-2-carboxylate (14f)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 10.74 (s, 1H), 8.33 (d, *J* = 9.0 Hz, 1H), 7.48 (d, *J* = 9.6 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 4.50 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H).

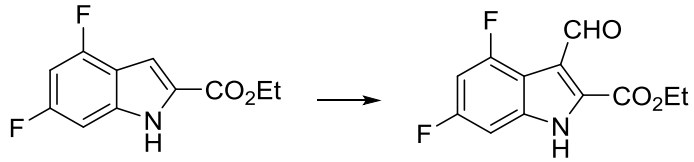
Ethyl 5-fluoro-3-formyl-1*H*-indole-2-carboxylate (14g)



13g **14g**

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.57 (s, 1H), 7.89 (dd, *J* = 9.6, 2.4 Hz, 1H), 7.59 (m, 1H), 7.28 (m, 1H), 4.46 (q, *J* = 6.9 Hz, 2H), 1.37 (t, *J* = 6.9 Hz, 3H).

Ethyl 4,6-difluoro-3-formyl-1*H*-indole-2-carboxylate (14h)



13h **14h**

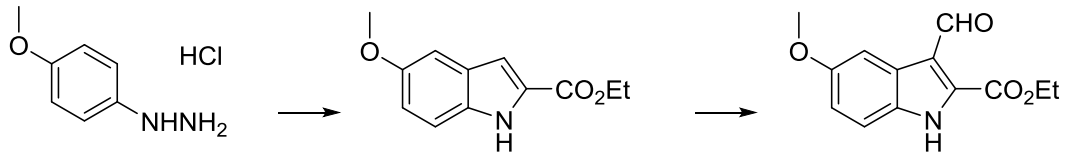
Step 1: **ethyl 4,6-difluoro-1*H*-indole-2-carboxylate (13h)**

Compound **13h** was prepared by the previously described for compound **4** starting from 3,5-difluoroaniline. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.34 (s, 1H), 7.16 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.96 (t, *J* = 8.4 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H).

Step 2: **ethyl 4,6-difluoro-3-formyl-1*H*-indole-2-carboxylate (14h)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 11.09 (d, J = 5.4 Hz, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.55 (t, J = 9.9 Hz, 1H), 5.00 (q, J = 7.2 Hz, 2H), 1.96 (t, J = 7.2 Hz, 3H).

Ethyl 3-formyl-5-methoxy-1*H*-indole-2-carboxylate (14i)



24 **13i** **14i**

Step 1: **ethyl 5-methoxy-1*H*-indole-2-carboxylate (13i)**

A mixture of 4-Methoxyphenylhydrazine hydrochloride (3.00 g, 17.2 mmol), glacial acetic acid (517 mg, 8.61 mmol) and ethyl pyruvate (3.19 g, 27.5 mmol) in ethanol (50.0 mL) was stirred for 5 hours at 80 ^{0}C. After the mixture was cooled at room temperature, the solid was filtered and the filtrate was concentrated, the crude residue was purified by column chromatography on silica gel (PE/EtOAc =10:1) to give **13i** (456 mg, 12.1%) as a white solid.

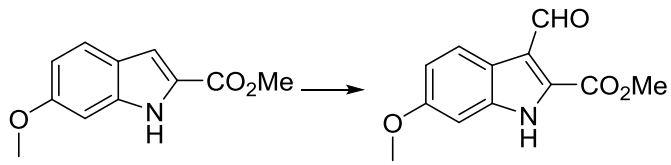
^{1}H NMR (300 MHz, DMSO-d_6): δ 11.72 (brs, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.07 (d, J = 2.1 Hz, 1H), 7.02 (s, 1H), 6.89 (dd, J = 9.0, 2.1 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.73 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H).

Step 2: **ethyl 3-formyl-5-methoxy-1*H*-indole-2-carboxylate (14i)**

To a solution of compound **13i** (456 mg, 2.08 mmol) in DMF (4.00 mL) was added dropwise $POCl_3$ (0.500 mg, 5.21 mmol) at room temperature, then the mixture was stirred for 3 hours at room temperature. Ice was added and the solution was neutralized with 2 N NaOH, the resulting precipitate was filtered and washed with water, dried in vacuo to give **14i** (435 mg, 84.6%) as a yellow solid.[2]

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.59 (s, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 9.0 Hz, 1H), 7.04 (dd, J = 9.0, 2.4 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 3.80 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H).

Methyl 3-formyl-6-methoxy-1*H*-indole-2-carboxylate (14j)



13j **14j**

Step 1: **methyl 6-methoxy-1*H*-indole-2-carboxylate (13j)**

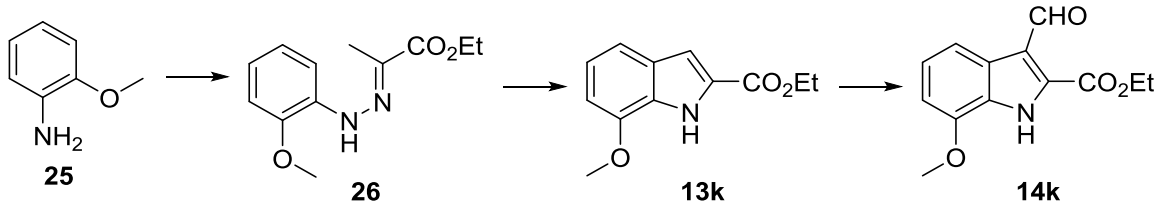
Compound **13j** was prepared according to the literature procedure[3] starting from ethyl 2-bromoacetate and 4-methoxybenzaldehyde. ^{1}H NMR (300 MHz, Acetone-d_6): δ 10.70 (brs, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.11 (s, 1H), 7.00 (s, 1H), 6.77 (dd, J = 9.0, 2.1 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H). MS (ESI, Pos.) m/z 228.1 $(M+Na)^+$.

Step 2: **methyl 3-formyl-6-methoxy-1*H*-indole-2-carboxylate (14j)**

Compound **14j** was prepared by the previously described for compound **14i** using Compound **13j**.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.57 (s, 1H), 8.10 (d, J = 8.7 Hz, 1H), 6.96 (s, 1H), 6.95 (d, J = 7.8 Hz, 1H), 3.97 (s, 3H), 3.81 (s, 3H). MS (ESI, Pos.) m/z 256.1 $(M+Na)^+$.

Ethyl 3-formyl-7-methoxy-1*H*-indole-2-carboxylate (14k)



Step 1: **ethyl (*E*)-2-(2-(2-methoxyphenyl)hydrazono)propanoate (26)**

Compound **26** was prepared by the previously described for compound **4-2** using Compound **25**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.59 (d, J = 7.5 Hz, 1H), 6.70-6.85 (m, 3H), 4.32 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 2.35 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H).

Step 2: **ethyl 7-methoxy-1*H*-indole-2-carboxylate (13k)**

A mixture of **26** (760 mg, 3.22 mmol), glacial acetic acid (5.00 mL) and $ZnCl_2$ (1.09 g, 8.09 mmol) in toluene (5.00 mL) was stirred for 12 hours at 110 ^{0}C. After evaporation of the toluene, water (10.0 mL) and ethyl ether (10.0 mL) were added, the resulting solution was neutralized with 2 N NaOH, the organic phase was separated and the aqueous phase was extracted with ethyl ether (10.0 mL), the combined organic phase was washed with water and saturated brine, dried over $MgSO_4$ and concentrated, the crude residue was purified by column chromatography on silica gel (PE/EtOAc = 20:1) to give **13k** (200 mg, 28.3%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.04 (brs, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.20 (s, 1H), 7.06 (t, J = 8.1Hz,

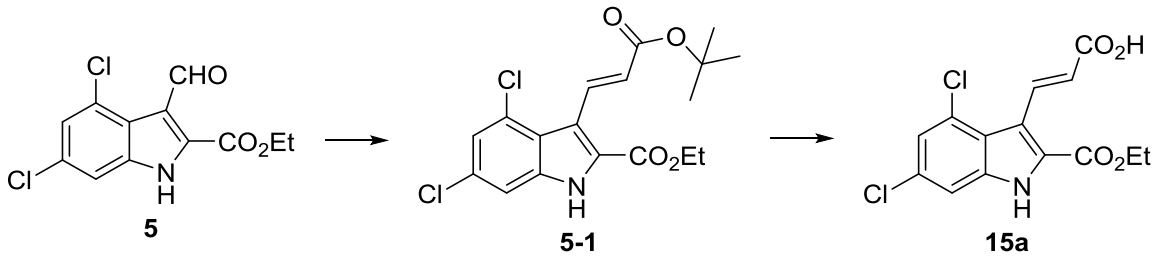
1H), 6.72 (d, *J* = 7.5 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.96 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).

Step 3: **ethyl 3-formyl-7-methoxy-1*H*-indole-2-carboxylate (14k)**

Compound **14k** was prepared by the previously described for compound **14i** using Compound **13k**.

^{1}H NMR (300 MHz, Acetone-d_6): δ 10.74 (brs, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.23 (t, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H).

(*E*)-3-(4,6-dichloro-2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15a)



Step 1: **ethyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-4,6-dichloro-1*H*-indole-2-carboxylate (5-1)**

Compound **5-1** was prepared according to the method used for **7-1**.

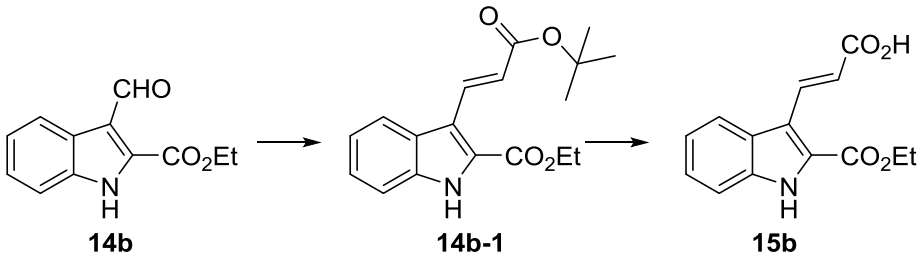
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.18 (brs, 1H), 8.33 (d, *J* = 16.2 Hz, 1H), 7.34 (s, 1H), 7.21 (s, 1H), 6.48 (d, *J* = 16.2 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.56 (s, 9H), 1.44 (t, *J* = 7.2 Hz, 3H).

Step 2: **(*E*)-3-(4,6-dichloro-2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15a)**

TFA (2.00 mL, 26.9 mmol) was added dropwise to a solution of **5-1** (417 mg, 1.09 mmol) in DCM (15.0 mL) at 0 ^{0}C, then the mixture was stirred for 1 hour at room temperature, TLC show that the reaction was completed. After evaporation of the solvent in vacuo, the crude product was purified by column chromatography on silica gel (chloroform/methanol = 30:1) to give **15a** (340 mg, 95.1%) as a yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.66 (s, 1H), 8.28 (d, *J* = 15.9 Hz, 1H), 7.51 (s, 1H), 7.33 (s, 1H), 6.45 (d, *J* = 15.9 Hz, 1H), 4.37 (q, *J* = 6.9 Hz, 2H), 1.35 (t, *J* = 6.9 Hz, 3H).

(*E*)-3-(2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15b)



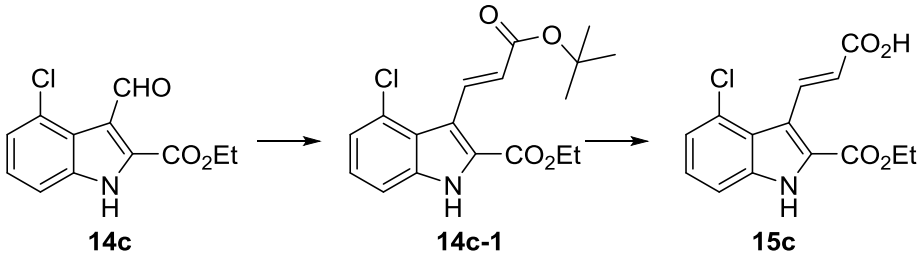
Step 1: **ethyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylate (14b-1)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.30 (brs, 1H), 8.64 (d, *J* = 16.5 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.39 (m, 1H), 7.29 (m, 1H), 6.61 (d, *J* = 16.5 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.55 (s, 9H), 1.43 (t, *J* = 7.2 Hz, 3H). The product contained a little Z-isomer.

Step 2: **(*E*)-3-(2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15b)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.34 (brs, 1H), 8.54 (d, *J* = 16.2 Hz, 1H), 8.99 (d, *J* = 8.1 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.37 (m, 1H), 7.24 (t, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H).

(*E*)-3-(4-chloro-2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15c)



Step 1: **ethyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-4-chloro-1*H*-indole-2-carboxylate (14c-1)**

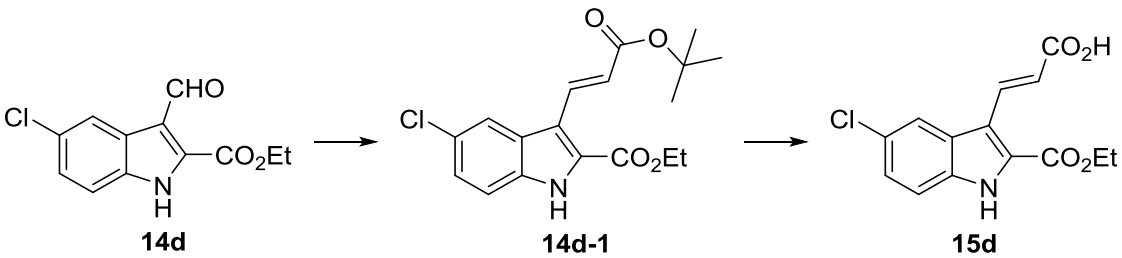
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.27 (s, 1H), 8.41 (d, *J* = 16.5 Hz, 1H), 7.33-7.17 (m, 3H), 6.50 (d, *J* = 16.5 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 1.55 (s, 9H), 1.43 (t, *J* = 7.2 Hz, 3H).

Step 2: **(*E*)-3-(4-chloro-2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15c)**

TFA (1.20 mL, 16.2 mmol) was added dropwise to a solution of **14c-1** (559 mg, 1.60 mmol) in DCM (10.0 mL) at 0 ^{0}C, then the mixture was stirred for 1 hour at room temperature, TLC showed that the reaction was completed. The precipitated solid was filtered and the filter cake was washed twice with DCM to give **15c** (500 mg, ＞100%) as a yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.57 (s, 1H), 8.38 (d, J = 15.9 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 8.1 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 6.48 (d, J = 15.9 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H).

(*E*)-3-(5-chloro-2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15d)



Step 1: **ethyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-5-chloro-1*H*-indole-2-carboxylate (14d-1)**

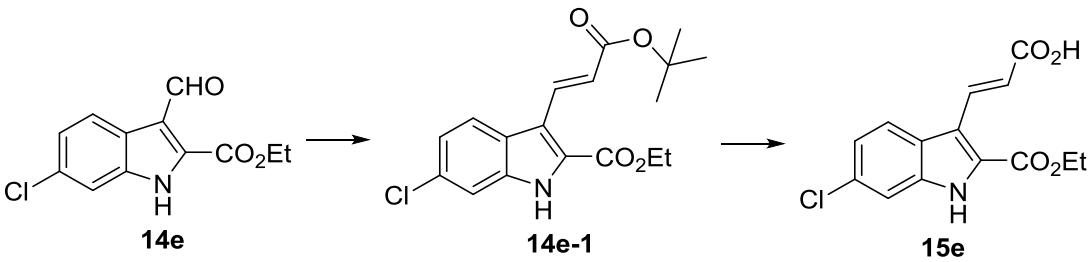
^{1}H NMR (300 MHz, DMSO-d_6): δ 8.43 (d, J = 16.5 Hz, 1H), 7.98 (s, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.38 (m, 1H), 6.48 (d, J = 16.5 Hz, 1H), 4.41 (q, J = 6.9 Hz, 2H), 1.51 (s, 9H), 1.39 (t, J = 6.9 Hz, 3H).

Step 2: **(*E*)-3-(5-chloro-2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15d)**

Compound **15d** was prepared according to the method used for **15c**.

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.53 (s, 1H), 8.46 (d, J = 16.5 Hz, 1H), 8.00 (s, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.39 (d, J = 9.0 Hz, 1H), 6.56 (d, J = 16.5 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H).

(*E*)-3-(6-chloro-2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15e)



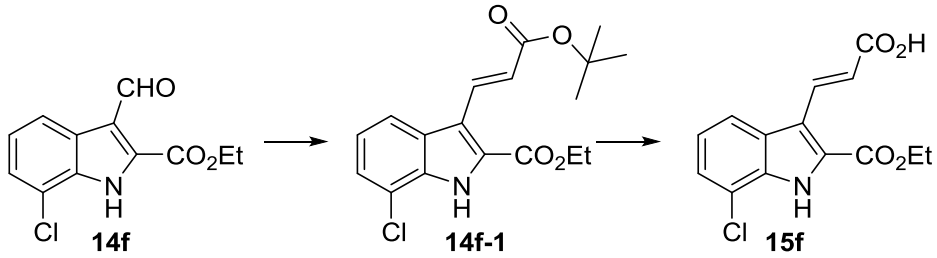
Step 1: **ethyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-6-chloro-1*H*-indole-2-carboxylate (14e-1)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.45 (d, J = 16.5 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.53 (s, 1H), 7.23 (d, J = 8.1 Hz, 1H), 6.51 (d, J = 16.5 Hz, 1H), 4.41 (q, J = 6.9 Hz, 2H), 1.50 (s, 9H), 1.40 (t, J = 6.9 Hz, 3H).

Step 2: **(*E*)-3-(6-chloro-2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15e)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.43 (s, 1H), 8.48 (d, *J* = 16.5 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.53 (s, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 6.56 (d, *J* = 16.5 Hz, 1H), 4.41 (q, *J* = 6.9 Hz, 2H), 1.38 (t, *J* = 6.9 Hz, 3H).

(*E*)-3-(7-chloro-2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15f)



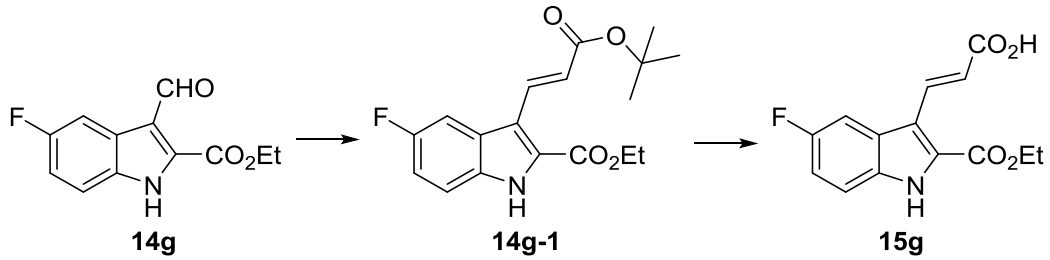
Step 1: **ethyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-7-chloro-1*H*-indole-2-carboxylate (14f-1)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.43 (d, *J* = 16.5 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.25 (t, *J* = 8.5 Hz, 1H), 6.53 (d, *J* = 16.5 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.50 (s, 9H), 1.39 (t, *J* = 7.2 Hz, 3H).

Step 2: **(*E*)-3-(7-chloro-2-(ethoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15f)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.43 (s, 1H), 12.35 (s, 1H), 8.46 (d, *J* = 16.5 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 6.58 (d, *J* = 16.5 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H).

(*E*)-3-(2-(ethoxycarbonyl)-5-fluoro-1*H*-indol-3-yl)acrylic acid (15g)



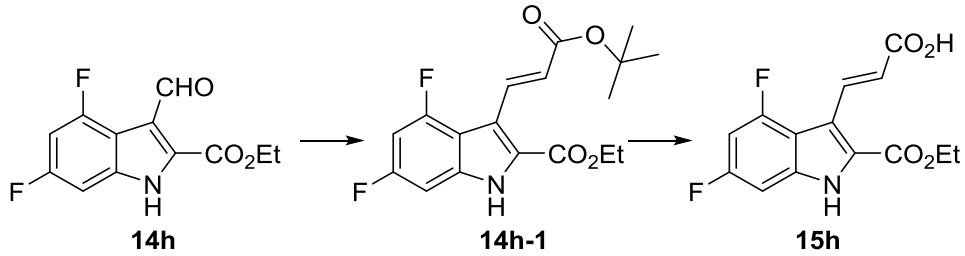
Step 1: **ethyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-5-fluoro-1*H*-indole-2-carboxylate (14g-1)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.43 (d, *J* = 16.5 Hz, 1H), 7.72 (m, 1H), 7.53 (m, 1H), 7.23 (m, 1H), 6.44 (d, *J* = 16.5 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 1.49 (s, 9H), 1.37 (t, *J* = 7.2 Hz, 3H). The product contained a little Z-isomer.

Step 2: **(*E*)-3-(2-(ethoxycarbonyl)-5-fluoro-1*H*-indol-3-yl)acrylic acid (15g)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.46 (s, 1H), 8.49 (d, *J* = 16.5 Hz, 1H), 7.75 (d, *J* = 10.2 Hz, 1H), 7.56 (m, 1H), 7.26 (t, *J* = 9.6 Hz, 1H), 6.53 (d, *J* = 16.5 Hz, 1H), 4.41 (q, *J* = 6.9 Hz, 2H), 1.38 (t, *J* = 6.9 Hz, 3H).

(*E*)-3-(2-(ethoxycarbonyl)-4,6-difluoro-1*H*-indol-3-yl)acrylic acid (15h)



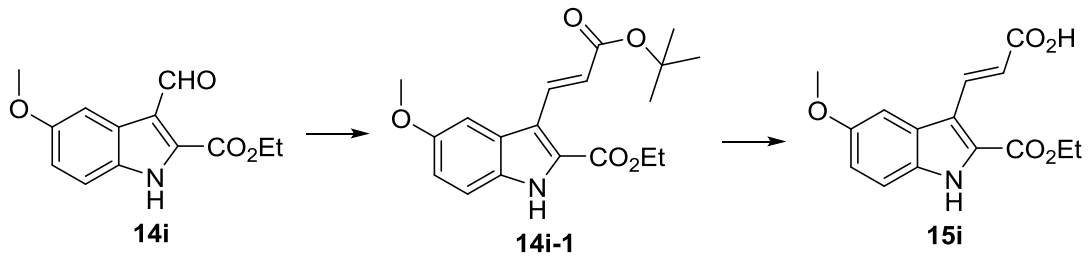
Step 1: **ethyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-4,6-difluoro-1*H*-indole-2-carboxylate (14h-1)**

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.40 (s, 1H), 8.42 (dd, *J* = 16.5, 2.1 Hz, 1H), 6.91 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.75-6.62 (m, 2H), 4.47 (q, *J* = 7.2 Hz, 2H), 1.55 (s, 9H), 1.47 (t, *J* = 7.2 Hz, 3H).

Step 2: **(*E*)-3-(2-(ethoxycarbonyl)-4,6-difluoro-1*H*-indol-3-yl)acrylic acid (15h)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.66 (s, 1H), 8.46 (dd, *J* = 16.2, 2.4 Hz, 1H), 7.14 -7.06 (m, 2H), 6.51 (d, *J* = 16.2, 1.2 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

(*E*)-3-(2-(ethoxycarbonyl)-5-methoxy-1*H*-indol-3-yl)acrylic acid (15i)



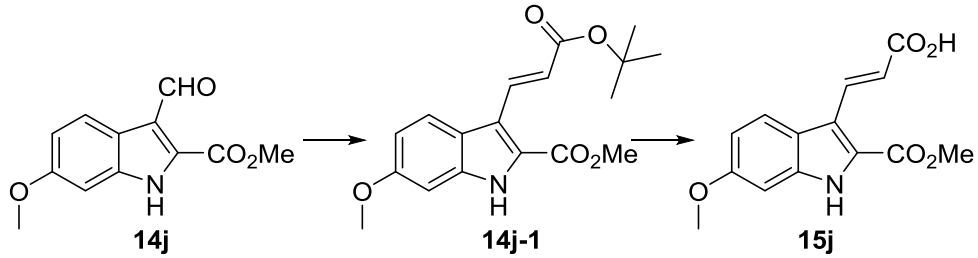
Step 1: **ethyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-5-methoxy-1*H*-indole-2-carboxylate (14i-1)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.28 (s, 1H), 8.50 (d, *J* = 16.2 Hz, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.27 (s, 1H), 7.08 (d, *J* = 9.0 Hz, 1H), 6.45 (d, *J* = 16.2 Hz, 1H), 4.39 (q, *J* = 6.9 Hz, 2H), 3.84 (s, 3H), 1.50 (s, 9H), 1.38 (t, *J* = 6.9 Hz, 3H).

Step 2: **(*E*)-3-(2-(ethoxycarbonyl)-5-methoxy-1*H*-indol-3-yl)acrylic acid (15i)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.26 (s, 1H), 8.54 (d, *J* = 16.2 Hz, 1H), 7.45 (d, *J* = 9.3 Hz, 1H), 7.30 (s, 1H), 7.04 (d, *J* = 9.3 Hz, 1H), 6.52 (d, *J* = 16.2 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H).

(*E*)-3-(6-methoxy-2-(methoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15j)



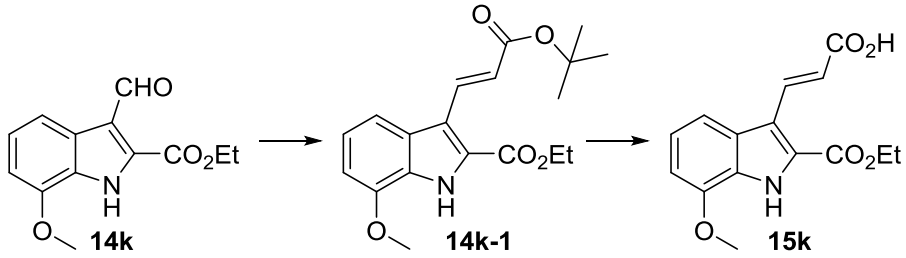
Step 1: **methyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-6-methoxy-1*H*-indole-2-carboxylate (14j-1)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.13 (s, 1H), 8.59 (d, *J* = 16.5 Hz, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 6.93 (dd, *J* = 9.0, 2.1 Hz, 1H), 6.57 (d, *J* = 16.5 Hz, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 1.54 (s, 9H).

Step 2: **(*E*)-3-(6-methoxy-2-(methoxycarbonyl)-1*H*-indol-3-yl)acrylic acid (15j)**

^{1}H NMR (300 MHz, Acetone-d_6): δ 11.15 (s, 1H), 8.68 (d, *J* = 16.2 Hz, 1H), 7.96 (d, *J* = 9.0 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 6.94 (dd, *J* = 9.0, 2.1 Hz, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 3.94 (s, 3H), 3.86 (s, 3H).

(*E*)-3-(2-(ethoxycarbonyl)-7-methoxy-1*H*-indol-3-yl)acrylic acid (15k)



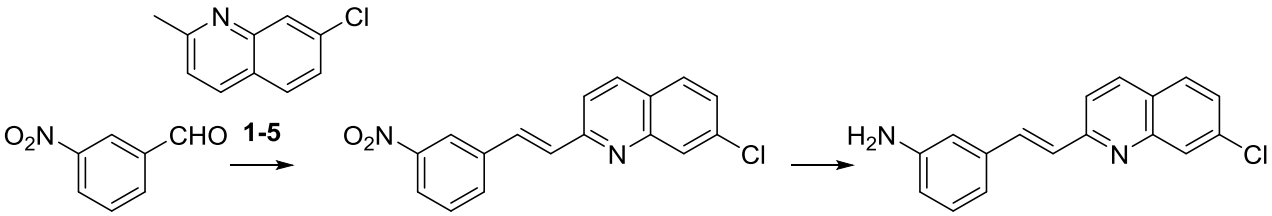
Step 1: **ethyl (*E*)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-7-methoxy-1*H*-indole-2-carboxylate (14k-1)**

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.27 (s, 1H), 8.50 (d, *J* = 16.2 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 16.2 Hz, 1H), 4.48 (q, *J* = 7.2 Hz, 2H), 3.98 (s, 3H), 1.56 (s, 9H), 1.48(t, *J* = 7.2 Hz, 3H). The product contained a little Z-isomer.

Step 2: **(*E*)-3-(2-(ethoxycarbonyl)-7-methoxy-1*H*-indol-3-yl)acrylic acid (15k)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.29 (s, 1H), 8.49 (d, *J* = 16.5 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.53 (d, *J* = 16.2 Hz, 1H), 4.36 (q, *J* = 6.9 Hz, 2H), 3.95 (s, 3H), 1.37 (t, *J* = 6.9 Hz, 3H). The product contained a little Z-isomer.

(*E*)-3-(2-(7-chloroquinolin-2-yl)vinyl)aniline (1-7)

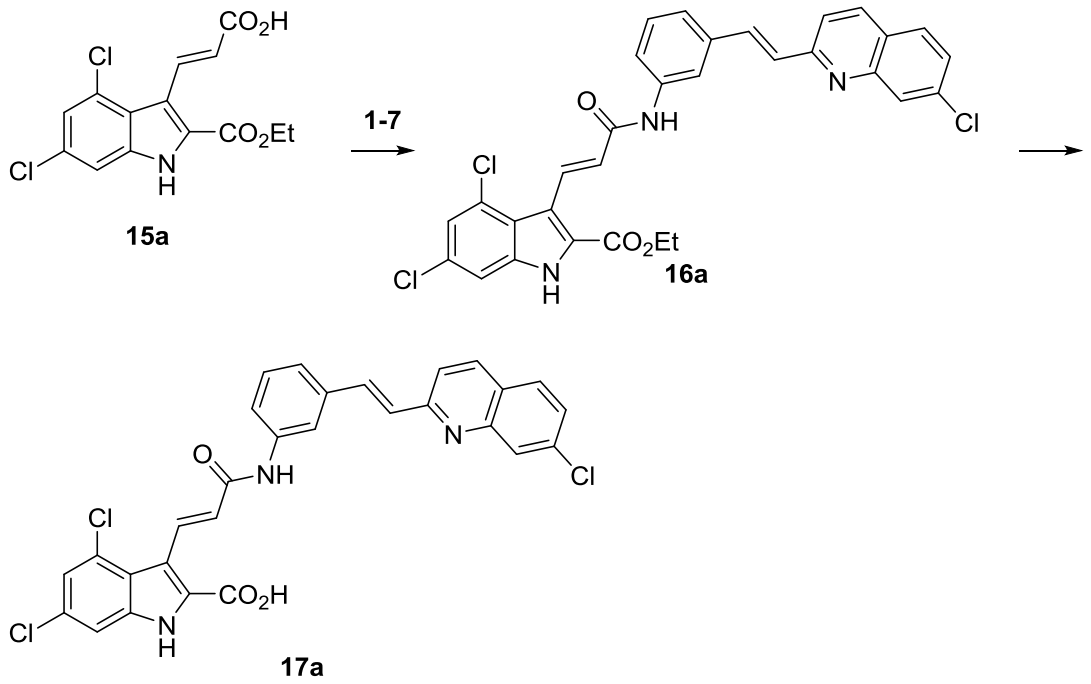


1-4 **1-6** **1-7**

Compound **1-7** was prepared according to the literature procedure[4] staring from 3-nitrobenzaldehyde and 7-chloro-2-methylquinoline.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.38 (d, *J* = 8.7 Hz, 1H), 8.02 (d, *J* = 1.8 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.71 (d, *J* = 16.2 Hz, 1H), 7.58 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.28 (d, *J* = 16.2 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.89 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 9.0 Hz, 1H), 5.17 (s, 2H). MS (ESI, Pos.) m/z 281.0 $(M+H)^+$.

4,6-dichloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17a)



Step 1: **ethyl 4,6-dichloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylate (16a)**

To a solution of compound **15a** (80.0 mg, 0.244 mmol) in DMF (1.00 mL) was added HATU (139 mg, 0.366 mmol) and DIPEA (74.0 mg, 0.573 mmol), the mixture was stirred at room temperature for 30 min, then compound **1-7** (68.0 mg, 0.242 mmol) in DCM (1.00 mL) was added, the resulting mixture was stirred overnight at room temperature. After evaporation of DCM, the residues were diluted with EtOAc (10.0 mL), sequentially washed with water (10.0 mL×2) and saturated brine, the organic phase was dried over $MgSO_4$ and concentrated to precipitated solid, the solid was filtered and washed twice with DCM to give compound **16a** (55.0 mg, 38.5%) as a grey solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.41 (s, 1H), 8.44 (d, J = 9.0 Hz, 1H), 8.33 (d, J = 15.6 Hz, 1H), 8.22 (s, 1H), 8.06 (s, 1H), 8.03-7.98 (m, 2H), 7.89 (d, J = 16.5 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.54 (s, 1H), 7.50-7.36 (m, 4H), 6.86 (d, J = 15.6 Hz, 1H), 4.41 (q, J = 6.9 Hz, 2H), 1.38 (t, J = 6.9 Hz, 3H).

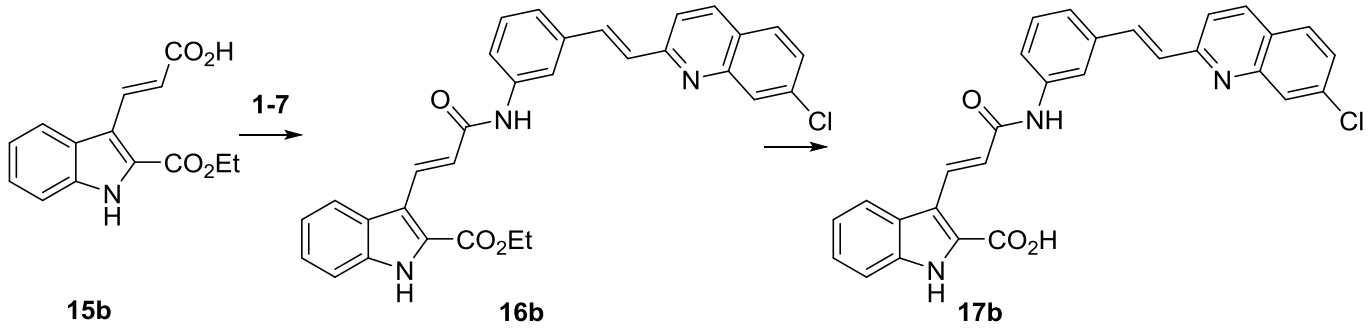
Step 2: **4,6-dichloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17a)**

Compound **16a** (50.0 mg, 84.6 μmol) was dissolved in ethanol (5.00 mL) and NaOH (22.0 mg, 0.550 mmol) was added, after adding several drops of water, the reaction mixture was stirred at 60 ^{0}C for 18 hours, the solvent was evaporated, the resulting residue was diluted with water (2.00 mL) and adjust-

ed pH to 2 with 1 N HCl, the resulting precipitate was filtered and washed with water, dried in vacuum to afford **17a** (24.0 mg, 50.4%) as a red solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.55 (d, J = 8.7 Hz, 1H), 8.36 (d, J = 15.6 Hz, 1H), 8.27 (s, 1H), 8.11 (s, 1H), 8.09-8.06 (m, 2H), 7.98 (d, J = 16.5 Hz, 1H), 7.69-7.64 (m, 2H), 7.51-7.34 (m, 5H), 6.97 (d, J = 15.6 Hz, 1H). HRMS (ESI, Neg.) $C_{29}H_{18}N_3O_3Cl_3$ (M - H)$^-$ calc. mass 560.0335, found 560.0348. ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.51, 162.49, 155.73, 140.61, 137.81, 136.49, 136.35, 132.04, 130.67, 129.96, 129.60, 128.44, 128.35, 128.12, 127.62, 126.18, 123.36, 122.61, 122.17, 121.27, 120.63, 118.62, 116.96, 112.13.

3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17b)



Step 1: **ethyl 3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylate (16b)**

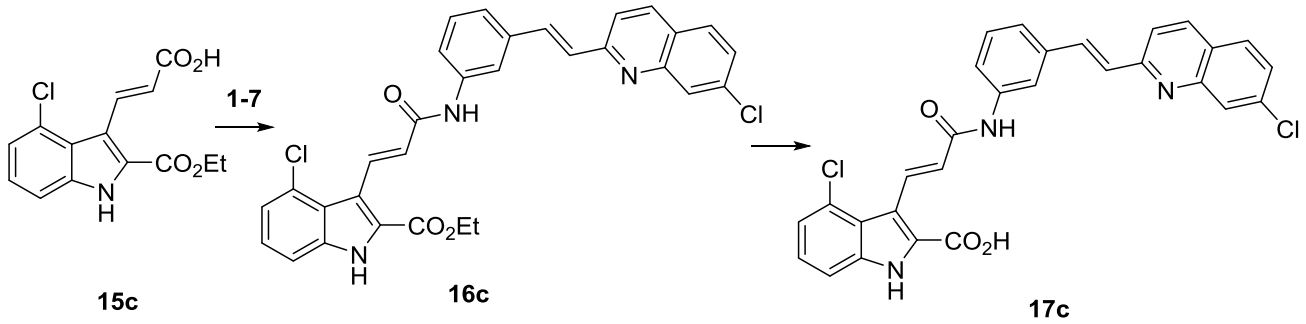
To a solution of compound **15b** (50.0 mg, 0.193 mmol) in DMF (2.00 mL) was added HATU (108 mg, 0.284 mmol) and DIPEA (49.0 mg, 0.379 mmol), the mixture was stirred at room temperature for 30 min, then compound **1-7** (57.0 mg, 0.203 mmol) was added, the resulting mixture was stirred overnight at room temperature. The solution was diluted with ethyl acetate (10 mL), sequentially washed with water (10.0 mL×2) and saturated brine, the organic phase was dried over $MgSO_4$ and concentrated, the crude residue was purified by column chromatography on silica gel (PE/EtOAc = 2:1) to give **16b** (80.0 mg, 79.4%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.26 (s, 1H), 10.29 (s, 1H), 8.55 (d, J = 15.9 Hz, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.18 (s, 1H), 8.14 (d, J = 8.1 Hz, 1H), 8.06 (s, 1H), 8.03-7.96 (m, 2H), 7.88 (d, J = 16.5 Hz, 1H), 7.65-7.57 (m, 3H), 7.49-7.39 (m, 4H), 7.31 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 15.9 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

Step 2: **3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17b)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.23 (s, 1H), 10.45 (s, 1H), 8.68 (d, J = 8.4 Hz, 1H), 8.60 (d, J = 15.9 Hz, 1H)8.31 (s, 1H), 8.17-8.08 (m, 4H), 7.73 (d, J = 8.7 Hz, 1H), 7.67 (s, 1H), 7.57 (s, 1H), 7.53 (d, J = 5.4 Hz, 1H), 7.46 (d, J = 3.6 Hz, 2H), 7.39 (t, J = 10.2 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 15.9 Hz, 1H). 99.8 % pure by HPLC. HRMS (ESI, Pos.) $C_{29}H_{20}N_3O_3Cl$ $(M + H)^+$ calc. mass 494.1271, found 494.1260. ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.38, 163.12, 154.90, 142.07, 140.98, 137.45, 137.07, 135.99, 134.18, 130.91, 130.04, 128.96, 128.45, 126.23, 125.59, 125.42, 123.25, 122.47, 122.00, 121.58, 120.59, 118.62, 116.48, 113.72.

4-chloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17c)



Step 1: **ethyl 4-chloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylate (16c)**

Compound **16c** was prepared by the previously described for compound **16a** using compound **15c**.

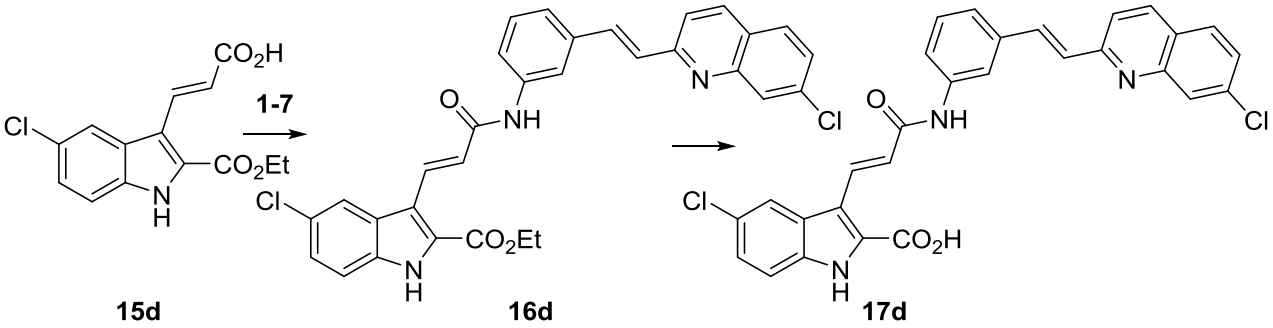
^{1}H NMR (300 MHz, DMSO-d_6): δ 10.32 (s, 1H), 8.43 (d, J = 8.7 Hz, 1H), 8.41 (d, J = 15.9 Hz, 1H), 8.22 (s, 1H), 8.06-7.97 (m, 3H), 7.88 (d, J = 16.5 Hz, 1H), 7.67-7.60 (m, 2H), 7.54-7.41 (m, 4H), 7.36-7.24 (m, 2H), 6.87 (d, J = 15.9 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H).

Step 2: **4-chloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17c)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.47 (s, 1H), 10.31 (s, 1H), 8.46-8.41 (m, 2H), 8.22 (s, 1H), 8.14 (s, 1H), 8.06-8.95 (m, 3H), 7.87 (d, J = 16.5 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.60 (dd, J = 8.7, 2.1 Hz, 1H), 7.51-7.40 (m, 3H), 7.31 (m, 1H), 7.23 (m, 1H), 6.88 (d, J = 15.6 Hz, 1H). HRMS (ESI, Neg.) $C_{29}H_{19}N_3O_3Cl_2$ $(M - H)^-$ calc. mass 526.0725, found 526.0729. ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.66, 162.79, 157.01, 148.07, 140.55, 137.99, 137.44, 136.93, 135.93, 135.00, 132.62, 130.30,

129.82, 128.53, 127.58, 127.54, 127.44, 127.34, 126.50, 126.13, 126.03, 123.20, 122.92, 122.84, 120.83, 120.43, 118.31, 116.78, 112.73.

5-chloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17d)



Step 1: **ethyl 5-chloro-3-((E)-3-((3-((E)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1H-indole-2-carboxylate (16d)**

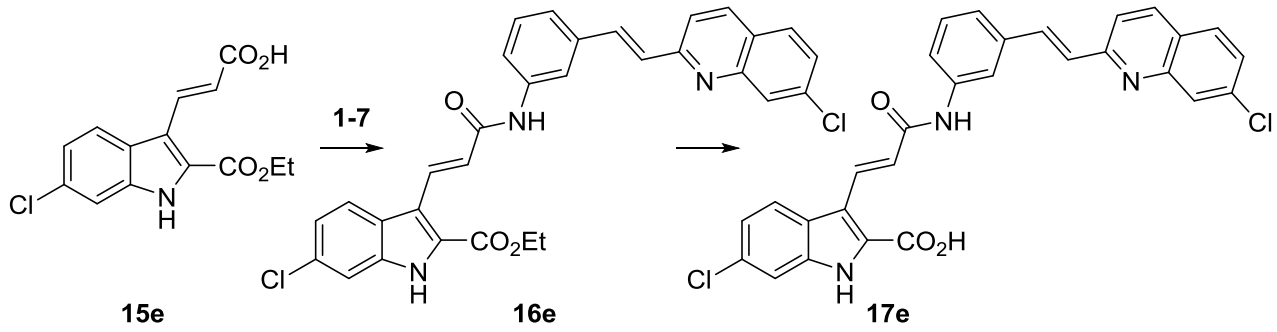
Compound **16d** was prepared by the previously described for compound **16b** using compound **15d**.

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.33 (s, 1H), 8.51 (d, J = 15.9 Hz, 1H), 8.43 (d, J = 9.0 Hz, 1H), 8.18 (s, 1H), 8.15 (s, 1H), 8.06 (s, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 16.5 Hz, 1H), 7.65-7.58 (m, 3H), 7.50-7.42 (m, 4H), 7.08 (d, J = 15.9 Hz, 1H), 4.45 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

Step 2: **5-chloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17d)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.43 (s, 1H), 10.49 (s, 1H), 8.72 (d, J = 8.7 Hz, 1H), 8.56 (d, J = 16.2 Hz, 1H), 7.28-8.24 (m, 3H), 8.18-8.14 (m, 3H), 7.76-7.71 (m, 2H), 7.62-7.55 (m, 2H), 7.48-7.39 (m, 3H), 7.09 (d, J = 15.9 Hz, 1H). HRMS (ESI, Neg.) $C_{29}H_{19}N_3O_3Cl_2$ (M - H)$^-$ calc. mass 526.0725, found 526.0723. ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.06, 162.84, 155.45, 140.72, 136.87, 136.29, 135.50, 133.74, 130.76, 130.10, 129.79, 128.58, 126.80, 126.21, 125.85, 123.46, 121.66, 121.23, 120.64, 118.32, 115.85, 115.44.

6-chloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17e)



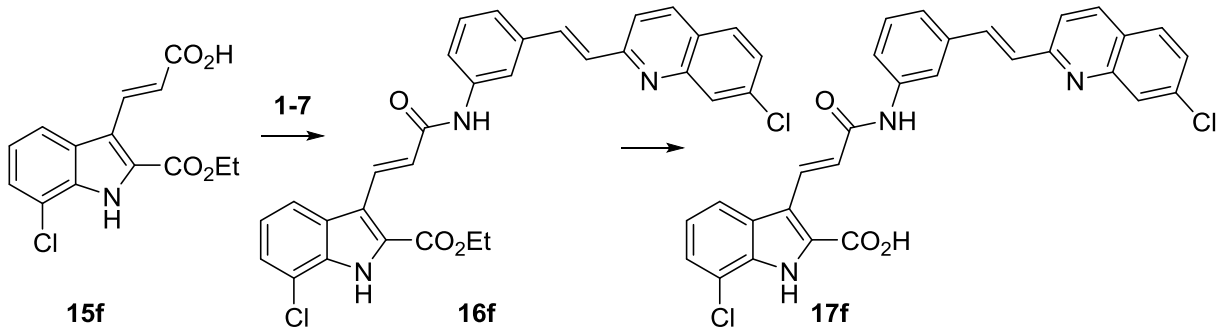
Step 1: **ethyl 6-chloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylate (16e)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.42 (s, 1H), 10.56 (s, 1H), 8.52-8.45 (m, 2H), 8.21-8.00 (m, 5H), 7.92 (d, *J* = 16.2 Hz, 1H), 7.69-7.58 (m, 3H), 7.51-7.40 (m, 3H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.22 (d, *J* = 16.2 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

Step 2: **6-chloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17e)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 11.58 (brs, 1H), 10.12 (s, 1H), 8.98 (d, *J* = 16.2 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.15 (s, 1H), 8.06-7.96 (m, 4H), 7.87 (d, *J* = 16.2 Hz, 1H), 7.69-7.59 (m, 2H), 7.46-7.40 (m, 4H), 7.16 (d, *J* = 8.1 Hz, 1H), 6.84 (d, *J* = 16.5 Hz, 1H). HRMS (ESI, Neg.) $C_{29}H_{19}N_3O_3Cl_2$ (M - H)$^-$ calc. mass 526.0725, found 526.0730. ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.95, 164.89, 157.17, 148.52, 141.05, 140.39, 137.47, 137.10, 136.96, 136.14, 135.60, 134.79, 130.25, 129.81, 128.85, 127.78, 127.52, 127.18, 126.13, 125.15, 122.85, 122.29, 120.95, 120.83, 120.00, 117.96, 117.54, 112.64, 111.45.

7-chloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17f)



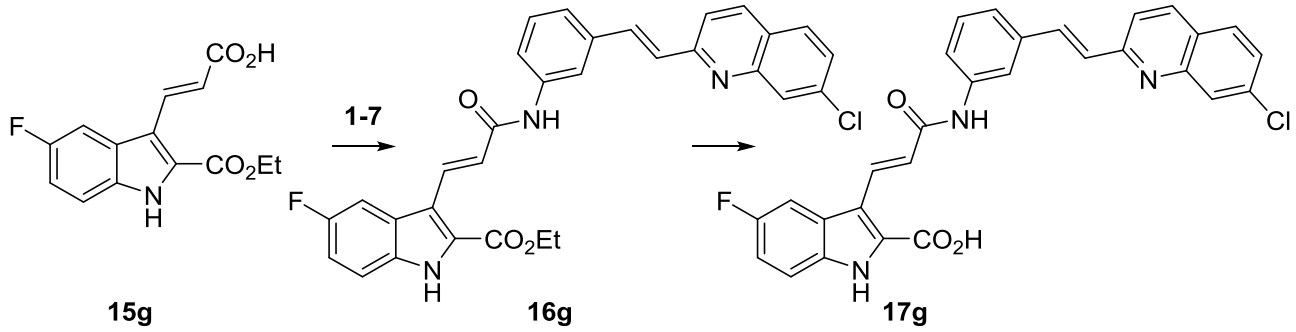
Step 1: **ethyl 7-chloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylate (16f)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.36 (s, 1H), 10.38 (s, 1H), 8.50-8.45 (m, 2H), 8.20 (s, 1H), 8.13-8.00 (m, 4H), 7.92 (d, *J* = 16.2 Hz, 1H), 7.63-7.43 (m, 6H), 7.33 (t, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 16.2 Hz, 1H), 4.45 (q, 2H), 1.43 (t, 3H).

Step 2: **7-chloro-3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-1*H*-indole-2-carboxylic acid (17f)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.27 (s, 1H), 10.42 (s, 1H), 8.58-8.51 (m, 2H), 8.27 (s, 1H), 8.13-8.07 (m, 4H), 8.01 (d, *J* = 15.9 Hz, 1H), 7.69-7.66 (m, 2H), 7.53-7.47 (m, 4H), 7.31 (t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 15.9 Hz, 1H). HRMS (ESI, Pos.) $C_{29}H_{19}N_3O_3Cl_2$ $(M + H)^+$ calc. mass 528.0882, found 528.0867. ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.99, 162.79, 155.56, 140.69, 136.69, 136.32, 134.23, 133.64, 130.68, 130.06, 128.44, 127.24, 126.17, 125.43, 124.21, 123.42, 122.89, 122.62, 121.11, 120.59, 118.26, 118.04, 117.49.

3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-5-fluoro-1*H*-indole-2-carboxylic acid (17g)



Step 1: **ethyl 3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-5-fluoro-1*H*-indole-2-carboxylate (16g)**

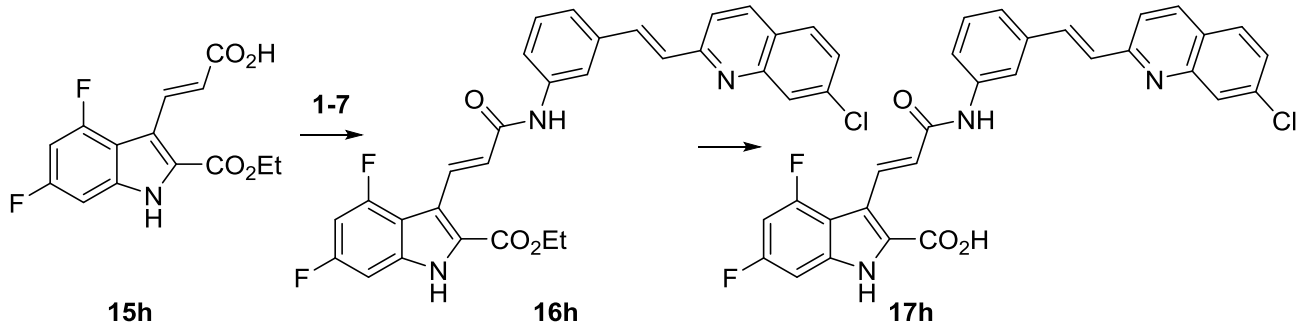
Compound **16g** was prepared by the previously described for compound **16b** using compound **15g**.

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.40 (s, 1H), 10.26 (s, 1H), 8.51 (d, *J* = 16.2 Hz, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 8.17 (s, 1H), 8.06-7.86 (m, 5H), 7.61 (m, 3H), 7.49-7.41 (m, 3H), 7.30 (t, *J* = 8.7 Hz, 1H), 7.07 (d, *J* = 16.2 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

Step 2: **3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-5-fluoro-1*H*-indole-2-carboxylic acid (17g)**

^{1}H NMR (300 MHz, DMSO-d_6): δ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.60 (brs, 1H), 10.06 (s, 1H), 8.99 (d, *J* = 16.2 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H), 8.06-7.96 (m, 3H), 7.87 (d, *J* = 16.5 Hz, 1H), 7.76 (d, *J* = 9.3 Hz, 1H), 7.67 (d, *J* = 6.6 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.48-7.38 (m, 4H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 16.2 Hz, 1H). HRMS (ESI, Pos.) $C_{29}H_{19}N_3O_3FCl$ $(M + H)^+$ calc. mass 512.1177, found 512.1176. ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.02, 164.50, 159.24, 157.40, 157.18, 148.53, 141.04, 137.92, 137.10, 136.99, 135.59, 134.80, 132.23, 130.26, 129.85, 128.86, 127.79, 127.19, 126.48, 126.40, 126.13, 122.25, 120.96, 119.89, 117.85, 116.54, 114.12, 111.27, 106.33

3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-4,6-difluoro-1*H*-indole-2-carboxylic acid (17h)



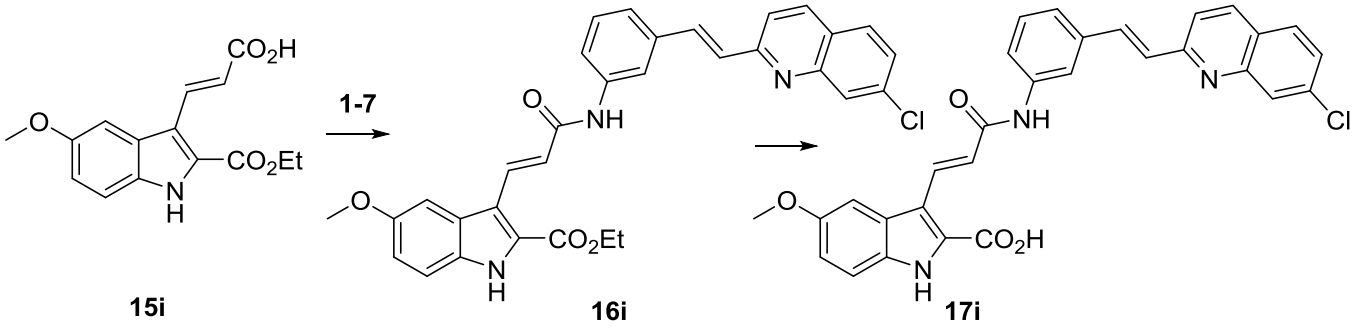
Step 1: **ethyl 3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-4,6-difluoro-1*H*-indole-2-carboxylate (16h)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 10.39 (s, 1H), 8.51 (d, *J* = 15.6 Hz, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 8.19 (s, 1H), 8.05 (d, *J* = 2.1 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.87 (d, *J* = 16.5 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.60 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.48-7.38 (m, 2H), 7.14 (d, *J* = 9.6 Hz, 1H), 6.98 (d, *J* = 16.2 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

Step 2: **3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-4,6-difluoro-1*H*-indole-2-carboxylic acid (17h)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.59 (s, 1H), 10.43 (s, 1H), 8.60-8.55 (m, 2H), 8.30 (s, 1H), 8.14-7.99 (m, 4H), 7.70-7.65 (m, 2H), 7.52-7.43 (m, 3H), 7.13-7.10 (m, 2H), 6.95 (d, *J* = 16.2 Hz, 1H). HRMS (ESI, Neg.) $C_{29}H_{18}N_3O_3F_2Cl$ $(M - H)^-$ calc. mass 528.0927, found 528.0925. ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.99, 162.77, 162.48, 161.60, 161.50, 159.68, 159.58, 157.74, 157.62, 155.93, 155.74, 155.62, 140.72, 138.74, 138.64, 138.52, 136.40, 132.63, 130.61, 129.93, 129.27, 128.19, 126.17, 124.60, 124.50, 123.33, 121.13, 120.66, 118.45, 116.00, 111.09, 110.94, 97.94, 97.71, 97.49, 95.78, 95.58.

3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-5-methoxy-1*H*-indole-2-carboxylic acid (17i)



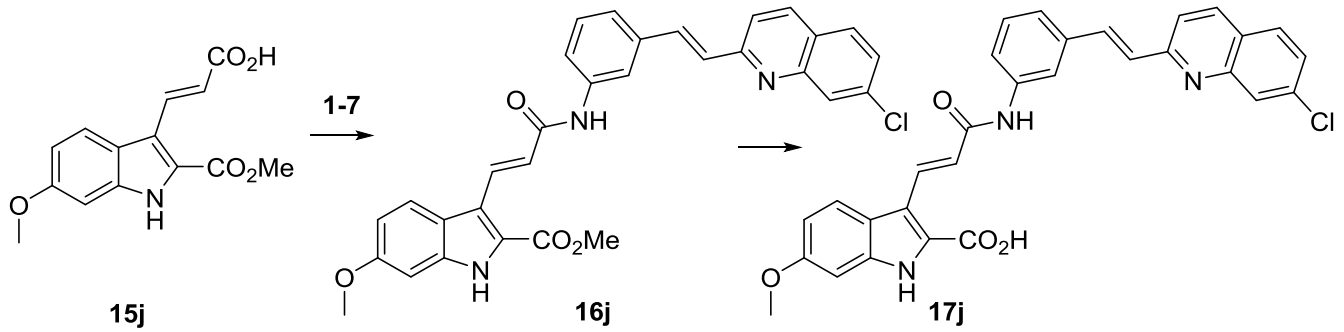
Step 1: **ethyl 3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-5-methoxy-1*H*-indole-2-carboxylate (16i)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.20 (s, 1H), 10.27 (s, 1H), 8.55 (d, J = 15.9 Hz, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.17 (s, 1H), 8.06 (s, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.95 (s, 1H), 7.89 (d, J = 15.9 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.61 (dd, J = 8.7, 2.1 Hz, 1H), 7.51 (s, 1H), 7.50-7.42 (m, 3H), 7.11 (dd, J = 9.0, 2.4 Hz, 1H), 7.03 (d, J = 15.9 Hz, 1H), 4.42 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H).

Step 2: **3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-5-methoxy-1*H*-indole-2-carboxylic acid (17i)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 11.36 (s, 1H), 10.07 (s, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.14 (s, 1H), 8.06-7.95 (m, 3H), 7.87 (d, J = 15.9 Hz, 1H), 7.69 (d, J = 6.0 Hz, 1H), 7.60 (d, J = 8.7 Hz, 1H), 7.46-7.42 (m, 4H), 7.36 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 9.0 Hz, 1H), 6.76 (d, J = 15.9 Hz, 1H), 3.87 (s, 3H). HRMS (ESI, Neg.) $C_{30}H_{22}N_3O_4Cl$ $(M - H)^-$ calc. mass 522.1221, found 522.1235. ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.22, 165.17, 162.78, 157.18, 154.97, 148.53, 141.08, 138.31, 137.09, 136.95, 135.60, 134.79, 130.87, 130.25, 129.79, 128.81, 127.78, 127.18, 126.82, 126.12, 122.25, 120.96, 120.08, 118.03, 116.23, 113.80, 112.54, 111.38, 104.60, 56.28.

3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-6-methoxy-1*H*-indole-2-carboxylic acid (17j)



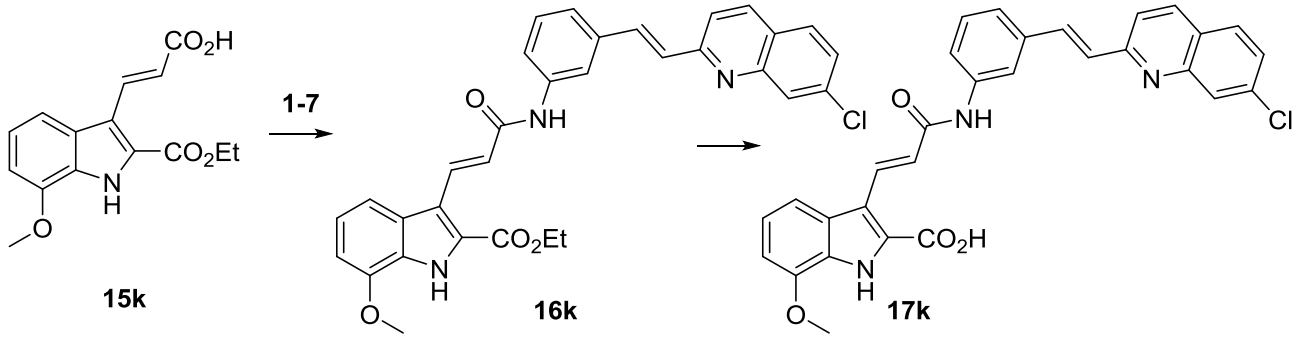
Step 1: **methyl 3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-6-methoxy-1*H*-indole-2-carboxylate (16j)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.16 (s, 1H), 10.29 (s, 1H), 8.48 (d, J = 15.9 Hz, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.20 (s, 1H), 8.06-7.96 (m, 4H), 7.88 (d, J = 16.5 Hz, 1H), 7.60 (m, 2H), 7.46-7.41 (m, 3H), 7.10 (d, J = 15.9 Hz, 1H), 6.97-6.93 (m, 2H), 3.95 (s, 3H), 3.84 (s, 3H).

Step 2: **3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-6-methoxy-1*H*-indole-2-carboxylic acid (17j)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.01 (s, 1H), 10.29 (s, 1H), 8.55 (d, J = 16.2 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 8.22 (s, 1H), 8.06 (d, J = 6.6 Hz, 1H), 8.02-7.98 (m, 3H), 7.91 (d, J = 16.5 Hz, 1H), 7.62 (d, J = 7.2 Hz, 2H), 7.47-7.43 (m, 3H), 7.07 (d, J = 16.2 Hz, 1H), 6.97 (s, 1H), 6.94 (d, J = 9.0 Hz, 1H), 3.83 (s, 3H). HRMS (ESI, Pos.) $C_{30}H_{22}N_3O_4Cl$ $(M + H)^+$ calc. mass 524.1377, found 524.1389. ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.18, 163.08, 158.48, 156.78, 147.51, 140.65, 138.34, 137.89, 136.90, 136.45, 135.25, 134.31, 130.36, 129.95, 128.03, 127.50, 127.39, 126.99, 126.14, 123.03, 122.94, 121.47, 120.83, 120.27, 119.67, 118.00, 116.91, 113.17, 95.18, 55.69.

3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-7-methoxy-1*H*-indole-2-carboxylic acid (17k)



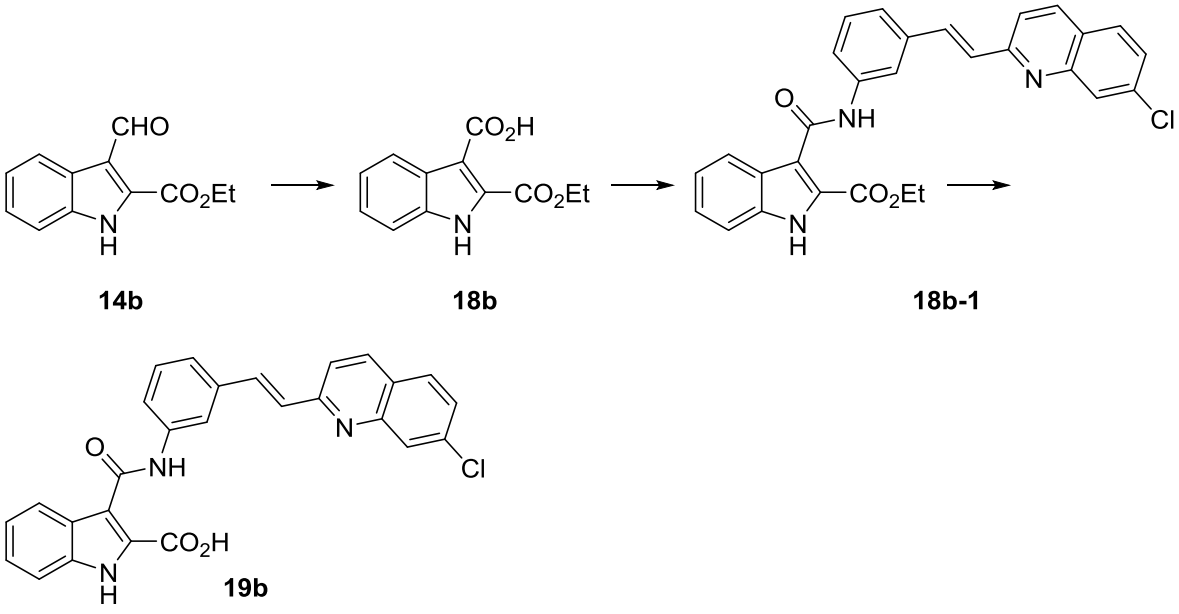
Step 1: **ethyl 3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-7-methoxy-1*H*-indole-2-carboxylate (16k)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.22 (s, 1H), 10.28 (s, 1H), 8.52 (d, *J* = 15.3 Hz, 1H), 8.42 (d, *J* = 9.3 Hz, 1H), 8.18 (s, 1H), 8.06 (s, 1H), 8.02 (d, *J* = 9.3 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.62 (m, 2H), 7.49-7.41 (m, 3H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 16.5 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 4.40 (q, *J* = 6.9 Hz, 2H), 3.98 (s, 3H), 1.41 (t, *J* = 6.9 Hz, 3H).

Step 2: **3-((*E*)-3-((3-((*E*)-2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxoprop-1-en-1-yl)-7-methoxy-1*H*-indole-2-carboxylic acid (17k)**

^{1}H NMR (300 MHz, DMSO-d_6): δ 11.57 (s, 1H), 10.26 (s, 1H), 8.69 (d, *J* = 15.9 Hz, 1H), 8.42 (d, *J* = 9.0 Hz, 1H), 8.19 (s, 1H), 8.06 (s, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.87 (d, *J* = 16.2 Hz, 1H), 7.69-7.59 (m, 3H), 7.46-7.41 (m, 3H),7.19 (t, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 15.9 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H). HRMS (ESI, Neg.) $C_{30}H_{22}N_3O_4Cl$ (M - H)$^-$ calc. mass 522.1221, found 522.1228. ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.04, 164.38, 157.18, 148.53, 146.92, 141.07, 137.99, 137.09, 136.96, 135.61, 134.79, 130.26, 129.82, 128.84, 127.83, 127.79, 127.18, 126.13, 125.50, 125.41, 122.26, 121.64, 120.95, 119.97, 117.92, 117.36, 117.23, 114.27, 103.93, 55.85.

(*E*)-3-((3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)carbamoyl)-1*H*-indole-2-carboxylic acid (19b)



Step 1: **2-(ethoxycarbonyl)-1*H*-indole-3-carboxylic acid (18b)**

To a suspension of compound **14b** (200 mg, 0.921 mmol) in water (2.00 mL) and acetonitrile (10.0 mL) was added sodium dihydrogen phosphate dihydrate (186 mg, 1.20 mmol) and hydrogen peroxide (125 mg, 1.10 mmol, 30% w/w aq. solution.), then a solution of sodium chlorite (116 mg, 1.29 mmol) in water (0.500 mL) was added dropwise at 0 ^{0}C, the mixture was stirred at room temperature for 7 hours, TLC showed that the reaction was not completed. Additional water (2.00 mL) and THF (10.0 mL) was added, after stirring overnight at room temperature, the pH of the solution was adjusted to 2 with 1 N HCl, the resulting solid was filtered and washed with water, dried in vacuo to give compound **18b** (177 mg, 82.4%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.71 (s, 1H), 12.48 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 7.2 Hz, 1H), 4.37 (q, J = 6.9 Hz, 1H), 1.33 (t, J = 6.9 Hz, 1H).

Step 2: **ethyl (*E*)-3-((3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)carbamoyl)-1*H*-indole-2-carboxylate (18b-1)**

Compound **18b-1** was prepared by the previously described for compound **16b** using compound **18b**.

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.33 (s, 1H), 10.77 (s, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.21 (s, 1H), 8.06-7.98 (m, 4H), 7.90 (d, J = 16.5 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.49-7.34 (m, 4H), 7.21 (t, J = 8.1 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H).

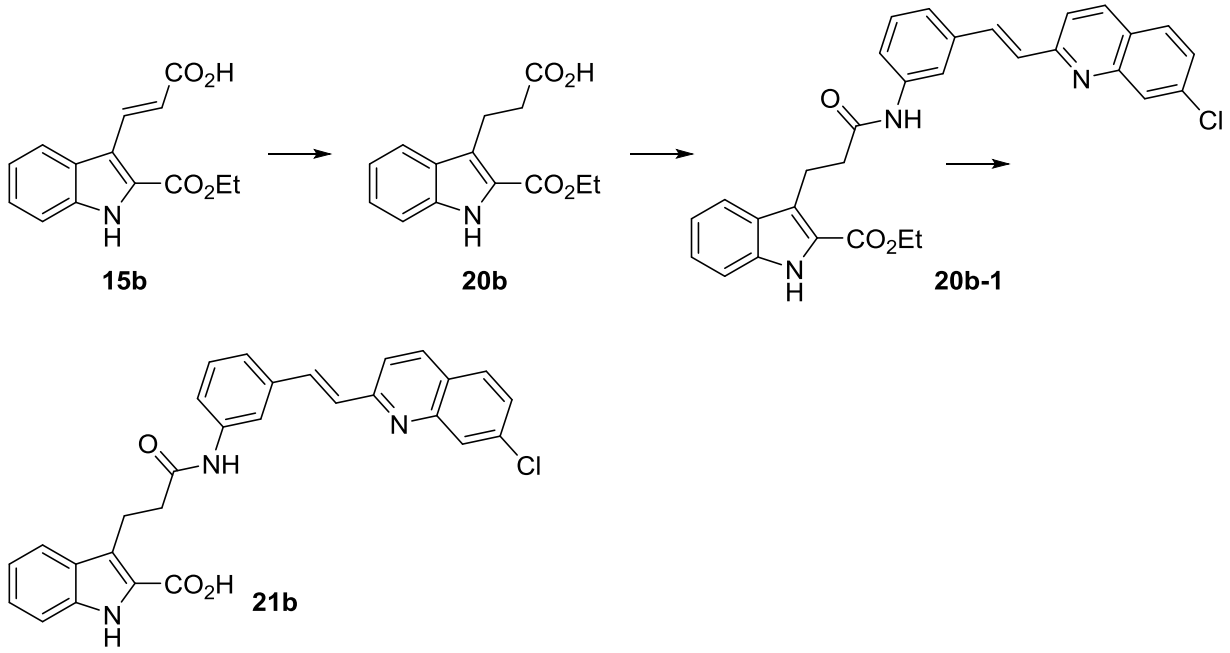
Step 3: **(*E*)-3-((3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)carbamoyl)-1*H*-indole-2-carboxylic acid (19b)**

Compound **19b** was prepared by the previously described for compound **17a** using compound **18b-1**.

^{1}H NMR (300 MHz, DMSO-d_6): δ 12.36 (s, 1H), 11.63 (s, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.1 Hz, 1H), 8.20 (s, 1H), 8.06-7.99 (m, 3H), 7.91 (d, J = 16.2 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.57-7.42 (m, 5H), 7.36 (t, J = 8.1 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H). HRMS (ESI, Neg.) $C_{27}H_{18}N_3O_3Cl$ (M - H)$^-$ calc. mass 466.0958, found 466.0970. ^{13}C NMR (125 MHz, DMSO-d_6) δ 164.19, 163.24, 157.14, 148.36, 140.38, 137.21, 137.09, 135.76, 135.67, 134.88, 130.26, 129.92, 128.88, 127.65, 127.26, 126.13, 125.68, 123.11, 122.90, 122.12, 120.74, 120.58, 118.55, 115.45, 113.27.

(*E*)-3-(3-((3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxopropyl)-1*H*-indole-2-carboxylic

acid (21b)



Step 1: **3-(2-(ethoxycarbonyl)-1*H*-indol-3-yl)propanoic acid (20b)**

Compound **15b** (100 mg, 0.386 mmol) was dissolved in ethanol (5.00 mL) and THF(8.00 mL), the solution was degassed three times with nitrogen and Pd/C (29.0 mg, 10%) was added, after exchanging two times with hydrogen, the mixture was stirred for 7 hours at room temperature, Pd/C was filtered off with celite, the filtrate was concentrated to give compound **20b** (74.0 mg, 73.3%) as a white solid.

^{1}H NMR (300 MHz, Acetone-d_6): δ 10.69 (brs, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.28 (ddd, J = 8.1, 7.2, 1.2 Hz, 1H), 7.10 (ddd, J = 7.2, 6.9, 1.2 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 3.41 (t, J = 8.1 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H). MS (ESI, Neg.) m/z 260.1 $(M - H)^-$.

Step 2: **ethyl (*E*)-3-(3-((3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxopropyl)-1*H*-indole-2-carboxylate (20b-1)**

Compound **20b-1** was prepared by the previously described for compound **16a** using compound **20b**.

^{1}H NMR (300 MHz, DMSO-d_6): δ 11.55 (s, 1H), 9.93 (s, 1H), 8.41 (d, J = 8.7 Hz, 1H), 8.04-7.93 (m, 4H), 7.85-7.76 (m, 2H), 7.59 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.50-7.32 (m, 5H), 7.25 (t, J = 7.2 Hz, 1H), 7.07 (t, J = 8.1 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.40 (t, J = 7.5 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H).

Step 3: **(*E*)-3-(3-((3-(2-(7-chloroquinolin-2-yl)vinyl)phenyl)amino)-3-oxopropyl)-1*H*-indole-2-**

carboxylic acid (21b)

Compound **21b** was prepared by the previously described for compound **17a** using compound **20b-1**.

^{1}H NMR (300 MHz, DMSO-d_6): δ 11.39 (s, 1H), 10.01 (s, 1H), 8.40 (d, *J* = 8.7 Hz, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 8.02-7.92 (m, 3H), 7.82 (d, *J* = 16.5 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.59 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.40-7.32 (m, 5H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 3.40 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 7.5 Hz, 2H). MS (ESI, Neg.) *m/z* 494.1 $(M - H)^-$. HRMS (ESI, Neg.) $C_{29}H_{22}N_3O_3Cl$ $(M - H)^-$ calc. mass 494.1271, found 494.1268. ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.48, 164.12, 157.14, 148.51, 140.27, 137.07, 136.86, 136.42, 135.47, 134.80, 130.24, 129.67, 128.86, 127.77, 127.66, 127.20, 126.11, 125.03, 124.83, 122.59, 121.67, 120.92, 120.84, 120.31, 119.63, 118.34, 112.77, 38.35, 20.71.

Reference

(1)Regina G.L.; Coluccia A.; Piscitelli F.; Bergamini A.; Sinistro A.; Cavazza A. et al. Indolyl aryl sulfones as HIV-1 non-nucleoside reverse transcriptase inhibitors: role of two halogen atoms at the indole ring in developing new analogues with improved antiviral activity. *J. Med. Chem.* **2007**, *50*, 5034-8.

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Biology

Calcium mobilization assay

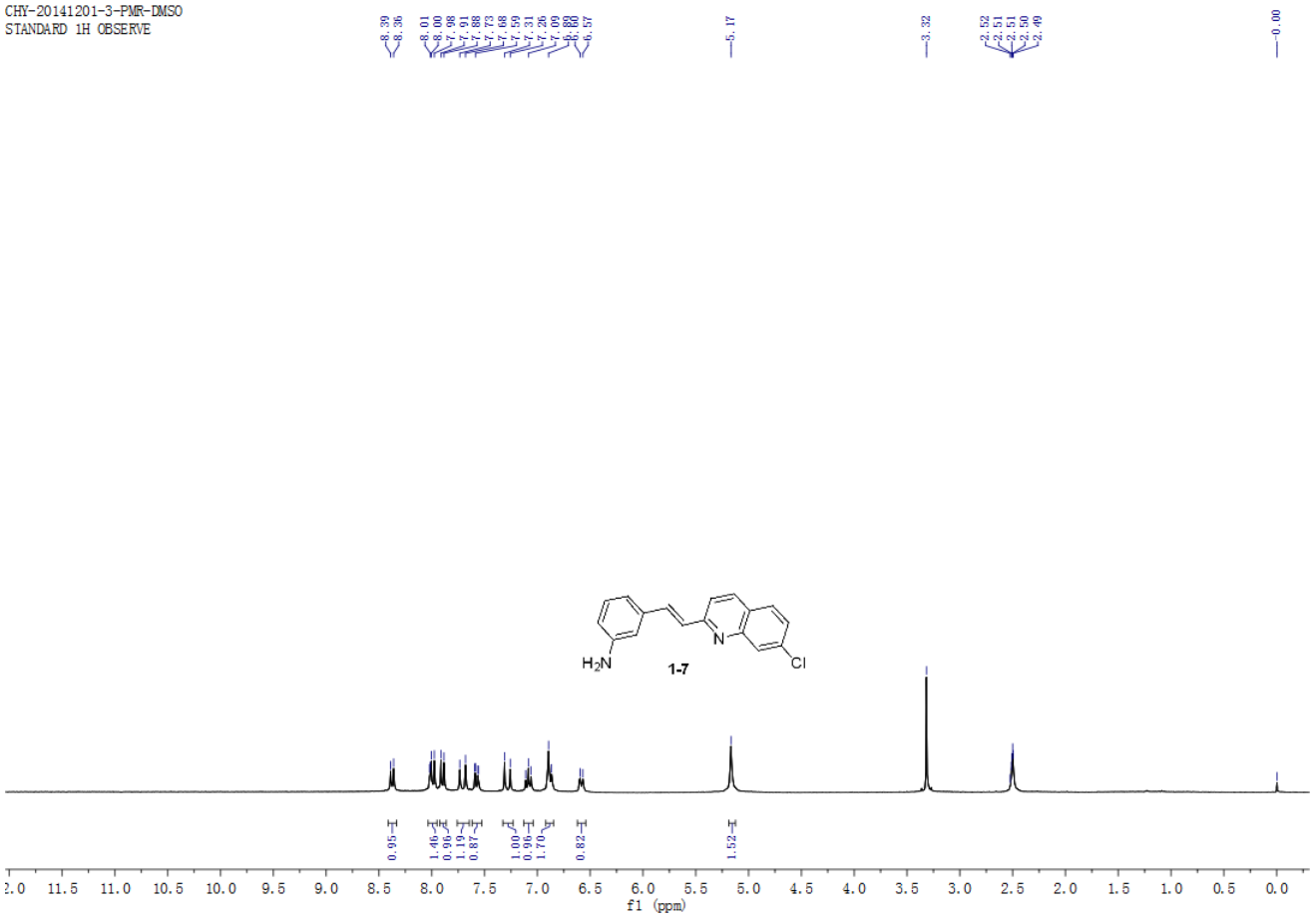
HEK 293 cells stably expressing $CysLT_1$ or $CysLT_2$ receptor and Gα16 protein were loaded with 2 μM Fluo-4 AM in Hanks balanced salt solution buffer (HBSS: 5.4 mM KCl, 0.3 mM Na_2HPO_4, 0.4 mM KH_2PO_4, 4.2 mM $NaHCO_3$, 1.3 mM $CaCl_2$, 0.5 mM $MgCl_2$, 0.6 mM Mg_2SO_4, 137 mM NaCl, pH 7.4) which contains 5 g/L BSA, 5.6 mM glucose and 250 μM sulfinpyrazone at 37 ^{0}C for 45 min. Using the reaction buffer to rinse the cells, and then add 50 μL HBSS containing montelukast (positive control) or compounds of interest into the 96 well plate. After 10 min's incubation at room temperatur, 25 μL LTD_4 (final concentration 1 nM) was dispensed into the well using a FlexStation II microplate reader (Molecular Devices, Sunnyvale, CA, USA) and intracellular calcium change was recorded with an excitation wavelength of 485 nm and emission wavelength of 525 nm. The half maximal inhibitory concentrations (IC_{50}) of compounds were determined with GraphPad Prism software by constructing their dose response curves.

Chemotaxis assay

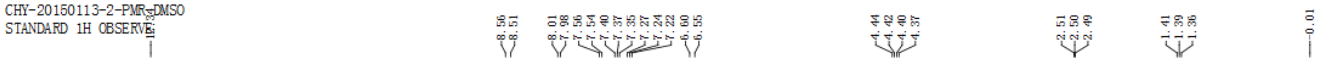
Female C57BL/6(8~10 wk age) mice obtained from Shanghai Laboratory Animal Center, Chinese Academy of Science were immunized s.c. with 200 μg myelin oligodendrocyte glycoprotein $(MOG)_{35-55}$ in CFA contaning heat-killed *Mycobacterium tuberculosis* (H37Ra strain, 5 mg/mL; BD Diagnostics). Pertusssis toxin (Calbiochem) were administered i.p. on day 0 and 2 at the concentration of 200 ng/mouse in PBS.

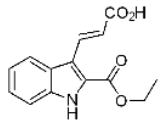
On day 10, splenocytes were isolated from EAE mice and preincubated for 0.5 h with RPMI 1640 supplemented with 1% BSA. In vitro chemotaxis assay was conducted with splenocytes in Transwell chambers with 5-μm polycarbonate filter pores (Corning Costar). Cells were washed and resuspended to a density of 1.0×10^7/mL in RPMI 1640 containg 20 mM HEPES and 0.5% BSA. LTD_4 was added into the lower chamber at various concentrations, and 100 μL cells were added into the upper chamber. For blocking assay, montelukast or other compounds at various concentrations was supplied in both upper and lower chambers, and 100 nM LTD_4 was added into the lower chamber. The chambers were then incubated for 1.5 h at normal culture condition, and the number of splenocytes that migrated to the low-

er chamber was counted using flow cytometry.

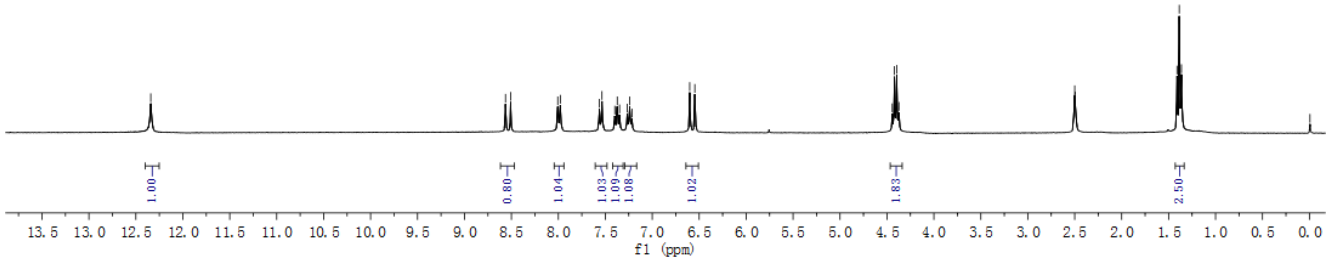


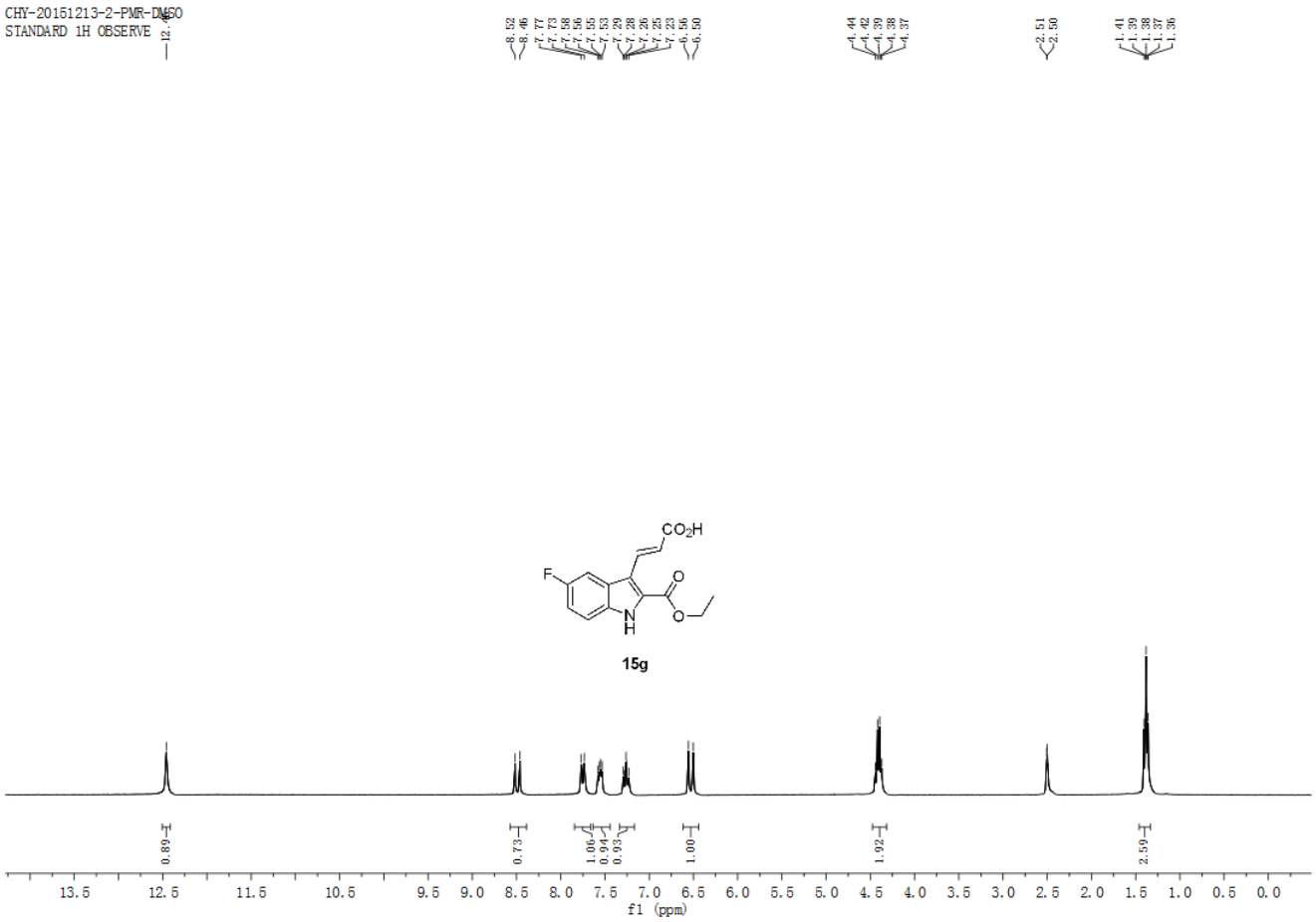
CHY-20150113-2-PMR-DMSO
STANDARD 1H OBSERVE

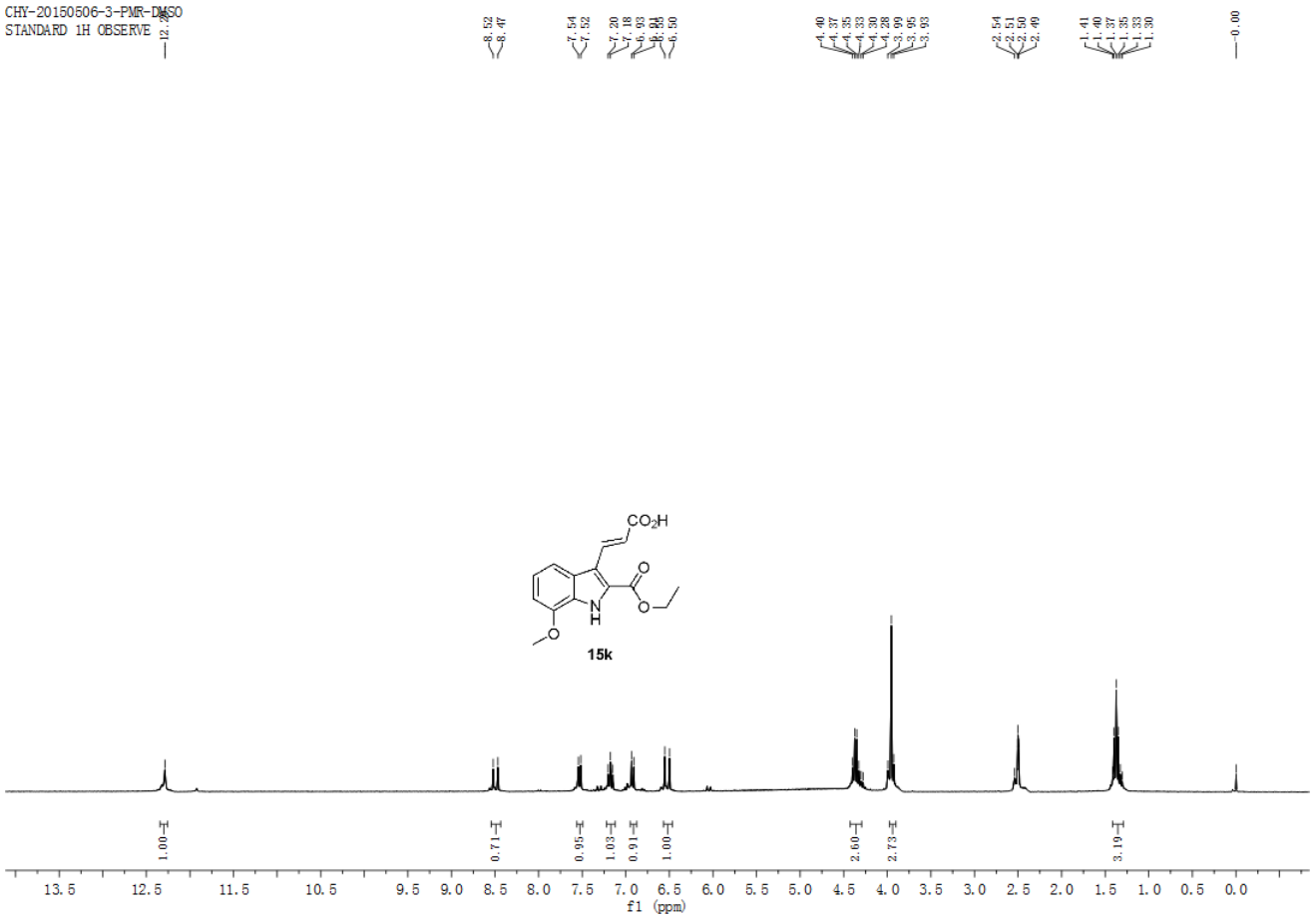


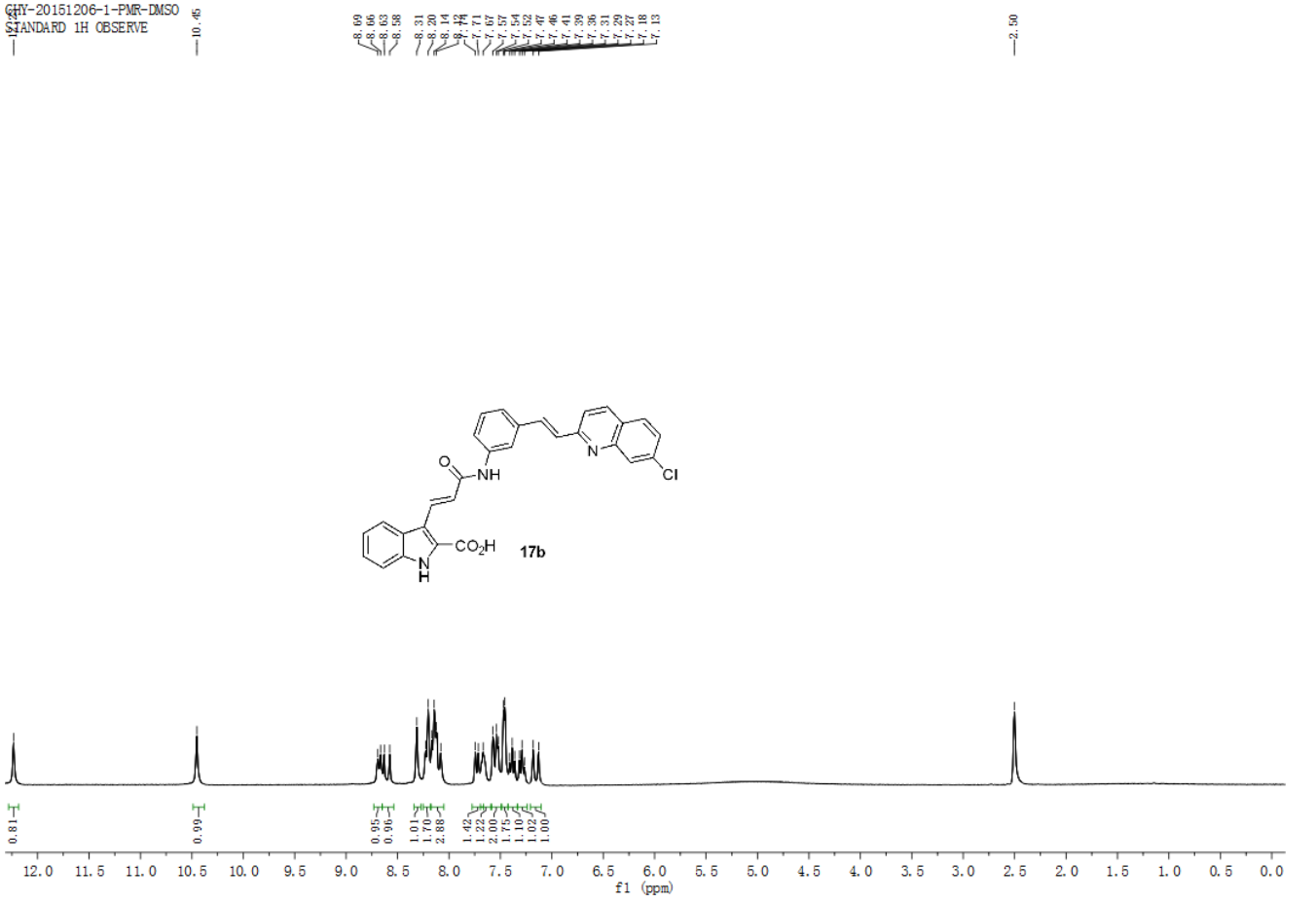


15b




CHY-20151213-2-PMR-DMSO
STANDARD 1H OBSERVE
12.
8.52
8.46
7.77
7.73
7.58
7.56
7.55
7.53
7.29
7.28
7.26
7.25
7.23
6.56
6.50
4.44
4.42
4.39
4.38
4.37
2.51
2.50
1.41
1.39
1.38
1.37
1.36
CO2H
F
O
O
N
H
15g
0.89
0.73
1.06
0.94
0.93
1.00
1.92
2.59
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CHY-20150506-3-PMR-DMSO
STANDARD 1H OBSERVE
12.29
8.52
8.47
7.54
7.52
7.20
7.18
6.93
6.88
6.50
4.40
4.37
4.35
4.33
4.30
4.28
3.99
3.95
3.93
2.54
2.51
2.50
2.49
1.41
1.40
1.37
1.35
1.33
1.30
0.00
CO2H
O
O
N
H
O
15k
1.00
0.71
0.95
1.03
0.91
1.00
2.60
2.73
3.19
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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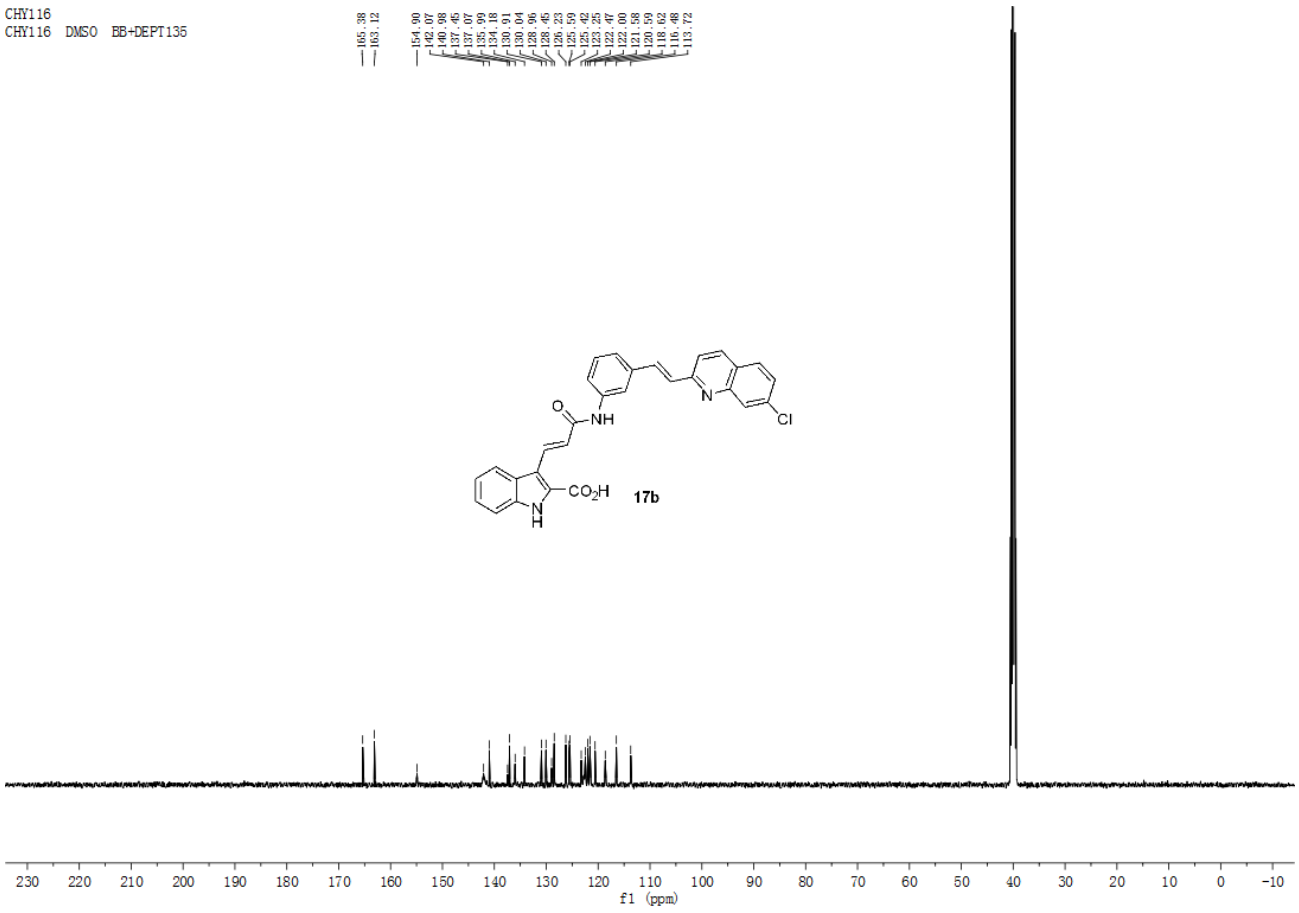
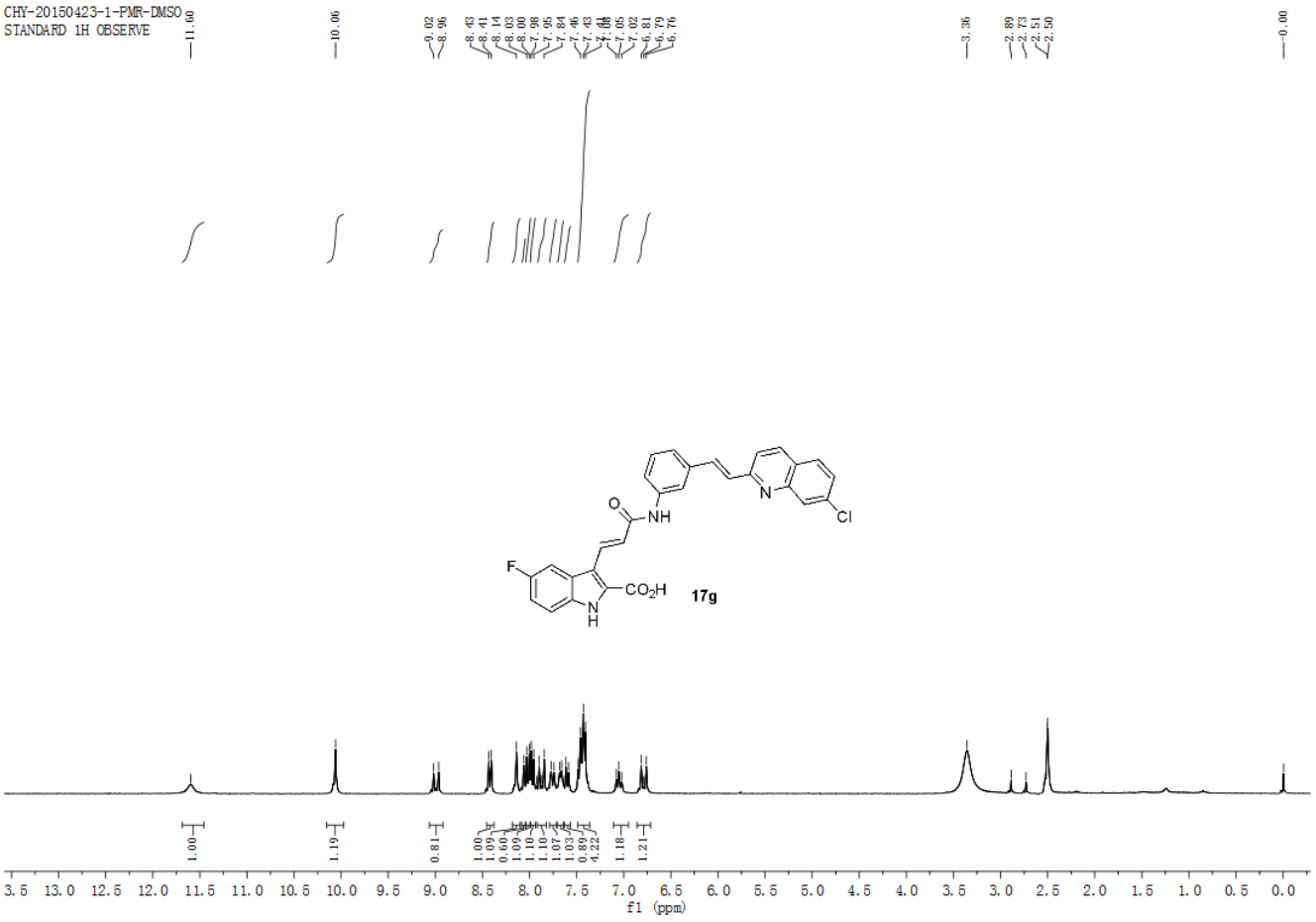
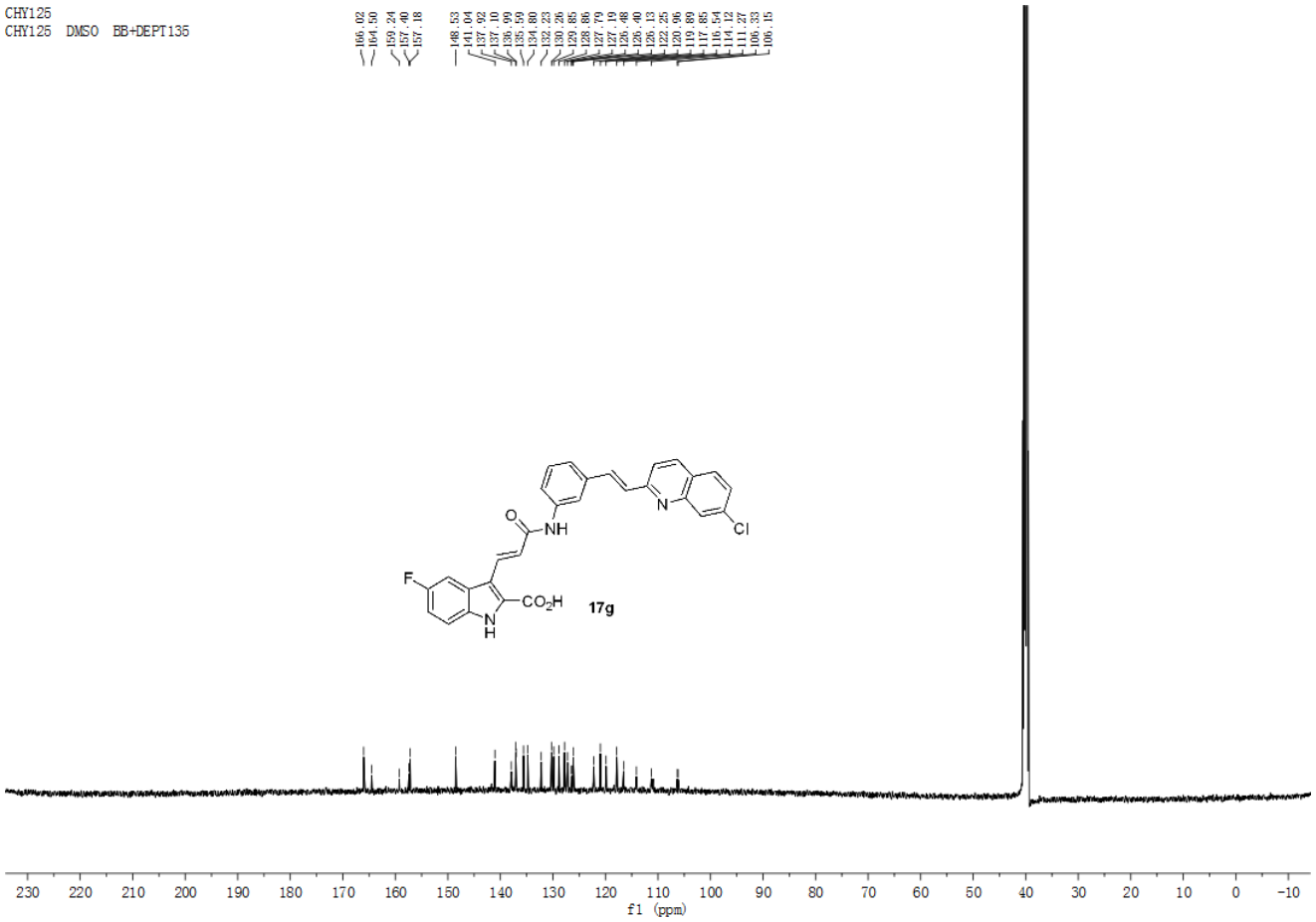
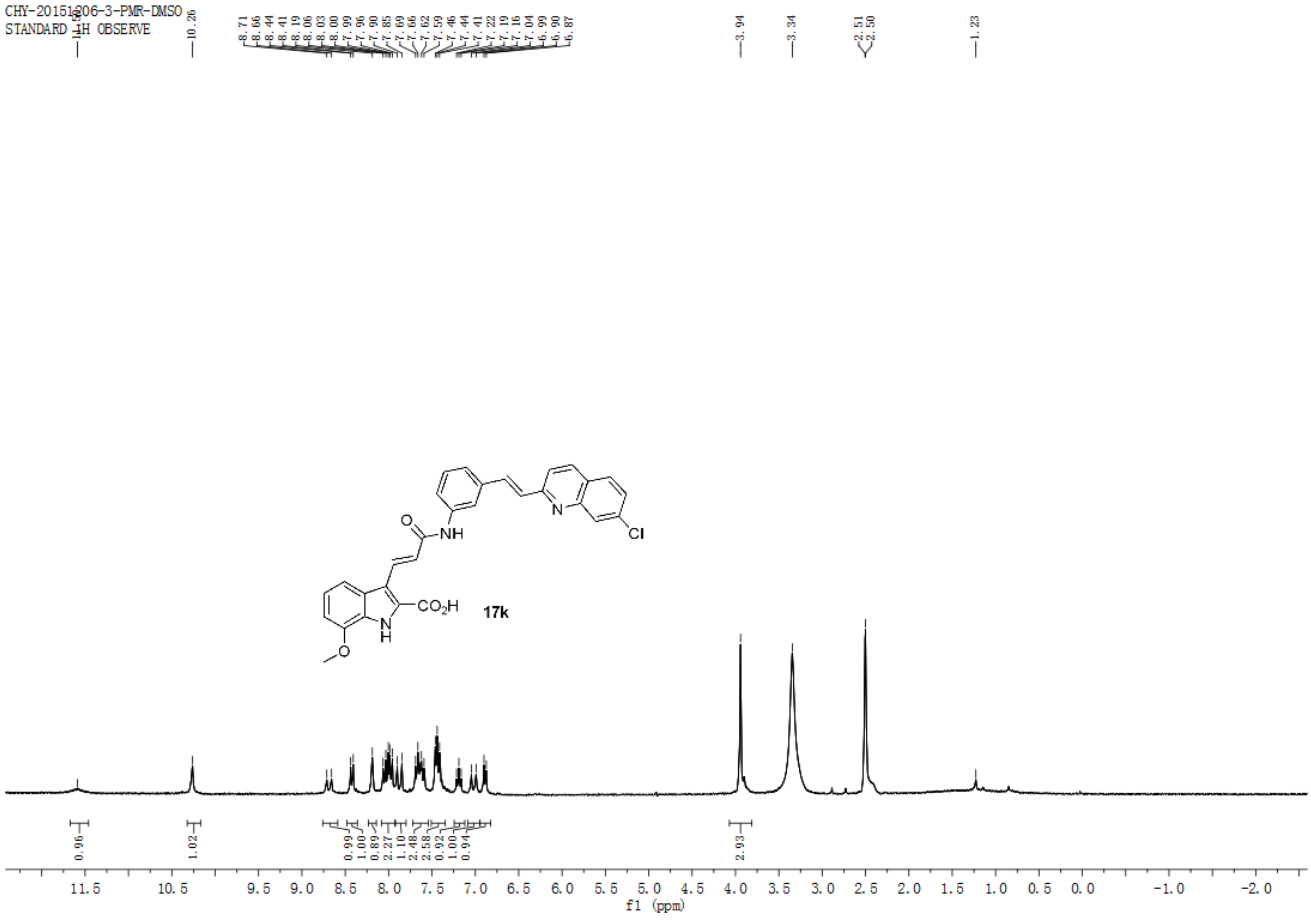
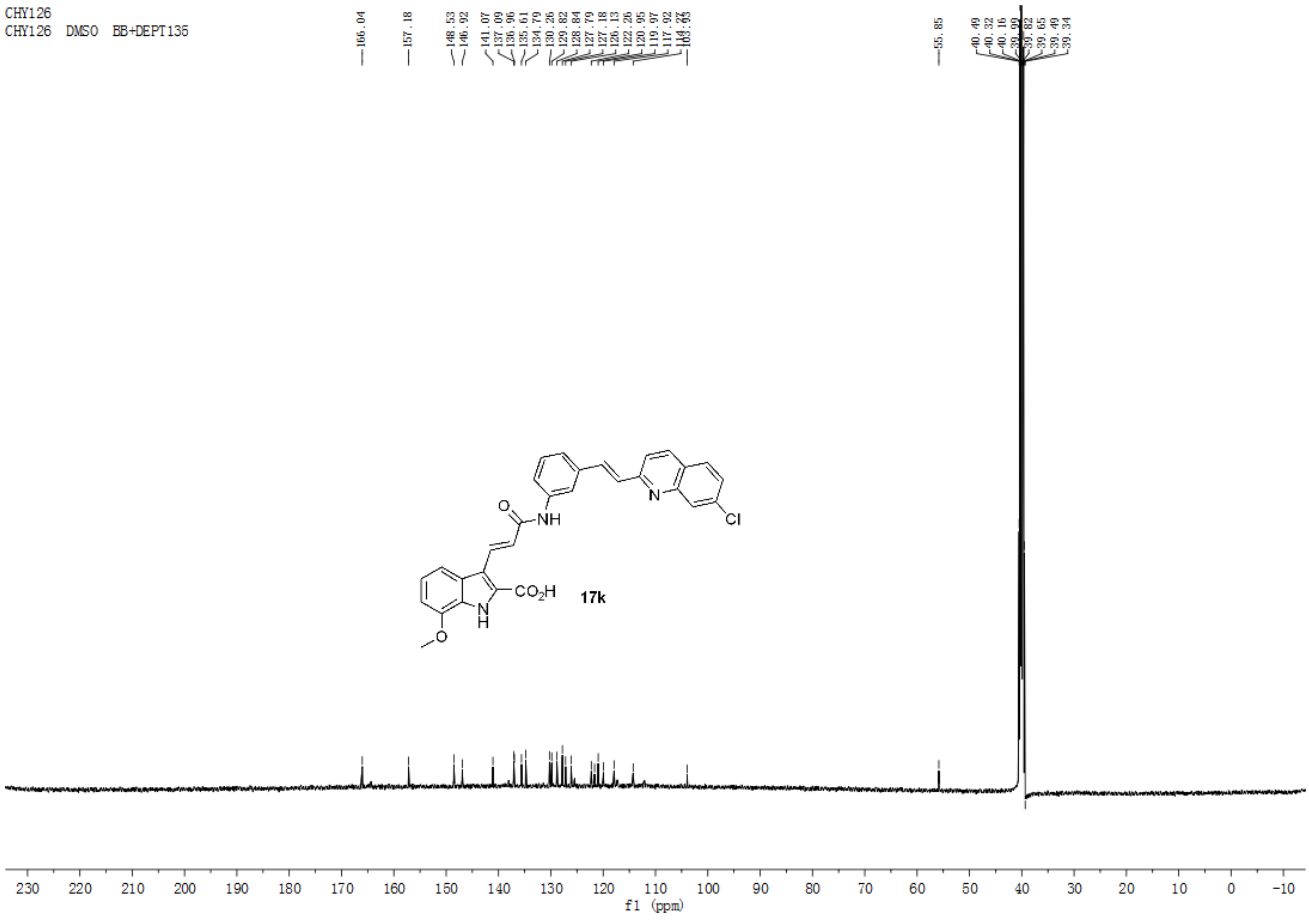
STANDARD 1H OBSERVE
10.45
8.69
8.66
8.63
8.58
8.31
8.20
8.14
8.12
7.71
7.67
7.57
7.54
7.52
7.47
7.46
7.41
7.39
7.36
7.31
7.29
7.27
7.18
7.13
2.50
O
NH
N
Cl
CO2H
N
H
17b
0.81
0.99
0.95
0.96
1.01
1.70
2.88
1.42
1.22
2.00
1.75
1.10
1.02
1.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


CHY116
CHY116 DMSO BB+DEPT135
165.38
163.12
154.90
142.07
140.98
137.45
137.07
135.99
134.18
130.91
130.04
128.96
128.45
126.23
125.59
125.42
123.25
122.47
122.00
121.58
120.59
118.62
116.48
113.72
O
NH
N
Cl
CO2H
N
H
17b
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CHY-20150423-1-PMR-DMSO
STANDARD 1H OBSERVE
11.60
10.06
9.02
8.96
8.43
8.41
8.14
8.03
8.00
7.98
7.95
7.84
7.46
7.43
7.05
7.02
6.81
6.79
6.76
3.36
2.89
2.73
2.51
2.50
0.00
O
NH
N
Cl
F
CO2H
N
H
17g
1.00
1.19
0.81
1.00
1.09
0.60
1.09
1.10
1.07
1.03
0.89
4.22
1.18
1.21
f1 (ppm)


CHY125
CHY125 DMSO BB+DEPT135
166.02
164.50
159.24
157.40
157.18
148.53
141.04
137.92
137.10
136.99
135.59
134.80
132.23
130.26
129.85
128.86
127.79
127.19
126.48
126.40
126.13
122.25
120.96
119.89
117.85
116.54
114.12
111.27
106.33
106.15
O
NH
N
Cl
F
CO2H
N
H
17g
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CHY-20151206-3-PMR-DMSO
STANDARD 1H OBSERVE
17k
f1 (ppm)


CHY126
CHY126 DMSO BB+DEPT135
166.04
157.18
148.53
146.92
141.07
137.09
136.96
135.61
134.79
130.26
129.82
128.84
127.79
127.18
122.13
122.26
120.95
119.97
117.92
104.47
103.93
55.85
40.49
40.32
40.16
39.99
39.82
39.65
39.49
39.34
O
NH
N
Cl
CO2H
N
H
O
17k
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)