Methods S2

(A) Synthetic Methods

GENERAL ANALYTICAL INFORMATION

KB63, **BPK-5**, **BPK-7 — BPK-11**, **BPK-16**, **BPK-18 — BPK-22**, **BPK-25**, **BPK-29 — BPK-31**, **BPK-34**, **HS58A-C2**, **HS77**, **HS81C**, **HS81E**, **HS92**, **HS95 — HS98**, **HS125**, **HS126**, **HS145**, **HS175**, **HS177**, **HS178**, and **RS004** were previously characterized (Backus et al., 2016; Bar-Peled et al., 2017; Lee et al., 2018). All novel compounds were characterized using ^{1}H NMR and HRMS. ^{1}H NMR spectra can be found at the end of the Supporting Information. NMR spectra were recorded on a Bruker 400 MHz instrument. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) and are listed relative to residual signals for DMSO (2.50 ppm), $CHCl_3$ (7.26 ppm), MeOH (3.31 ppm), CH_3CN (1.94 ppm), or H_2O (4.87 ppm) in the deuterated solvent. Reactions were monitored by LCMS. HRMS analyses were performed using an Agilent ESI-TOF instrument and were required to be within 5 ppm error.

List of Abbreviations

TEA	triethylamine
DIPEA	*N*,*N*-diisopropylethylamine
HATU	*N*-[(Dimethylamino)-1H-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
HOBt	1-Hydroxybenzotriazole hydrate
EDCI	*N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
TMSCl	chlorotrimethylsilane
Boc_2O	Di-*tert*-butyl dicarbonate
MsCl	methanesulfonyl chloride
NBS	*N*-bromosuccinimide
DCDMH	1,3-Dichloro-5,5-dimethylhydantoin
Ac_2O	acetic anhydride
DAST	diethylaminosulfur trifluoride
HOAc	glacial acetic acid
TFA	trifluoroacetic acid
HCl	hydrochloric acid
FA	formic acid
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
EtOAc	ethyl acetate
MeCN	acetonitrile
MeOH	methanol
THF	tetrahydrofuran
PE	petroleum ether
EtOH	ethanol
DCE	1,2-dichloroethane
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$Pd(dppf)Cl_2$	1,1′-Bis(diphenylphosphino)ferrocenedichloropalladium(II)
$Ni(dppp)Cl_2$	[1,3-Bis(diphenylphosphino)propane]dichloronickel(II)
TLC	thin-layer chromatography

General conditions for preparative HPLC (prep-HPLC)

HCl conditions
Column: Phenomenex Synergi C18 150x25 mm,10 µm
Mobile Phase: solvent A – water (0.05% HCl), solvent B – MeCN
Gradient: 36-56% solvent B, 7.8 min

FA conditions
Column: Phenomenex Synergi C18 150x30 mm, 4 µm
Mobile Phase: solvent A – water (0.225% FA), solvent B – MeCN
Gradient: 40-70% solvent B, 12 min

OR

Column: Waters BEH C18 160x19 mm, 5 µm
Mobile Phase: solvent A – water (0.1% FA), solvent B – MeCN
Gradient: 45-65% solvent B, 8 min

TFA conditions
Column: Phenomenex Synergi C18 150x25 mm,10 µm
Mobile Phase: solvent A – water (0.1% TFA), solvent B – MeCN
Gradient: 40-70% solvent B, 10 min

Basic

Column: Phenomenex Gemini C18 150x25 mm,10 µm
Mobile Phase: solvent A – water (0.05% NH_4OH v/v), solvent B – MeCN
Gradient: 58-80% solvent B, 10 min

OR

Column: Agela Durashell C18 150x25 mm, 5 µm
Mobile Phase: solvent A – water (0.05% NH_4OH v/v), solvent B – MeCN
Gradient: 30-60% solvent B, 10 min

SYNTHETIC PROCEDURES

General Procedures

General Procedure 1: Chloroacetyl chloride (varying eq) was added to a solution of amine (1.0 eq) and TEA (varying eq) in anhydrous DCM (0.1 M) at 0 °C. The reaction was warmed to room temperature and stirred until the starting material could not be detected via TLC, generally 2-4 h. Water was added to the reaction (2x the volume of DCM) and the reaction was extracted with DCM (2x). The combined organic layers were washed with brine (1x), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified as indicated.

General Procedure 2: Acryloyl chloride (varying eq) was added to a solution of amine (1.0 eq) and TEA (varying eq) in anhydrous DCM (0.1 M) at 0 °C. The reaction was warmed to 15 °C and stirred for 1 h. Water was added to the reaction (2x the volume of DCM) and the reaction was extracted with DCM. The combined

organic layers were washed with brine (1x), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified as indicated.

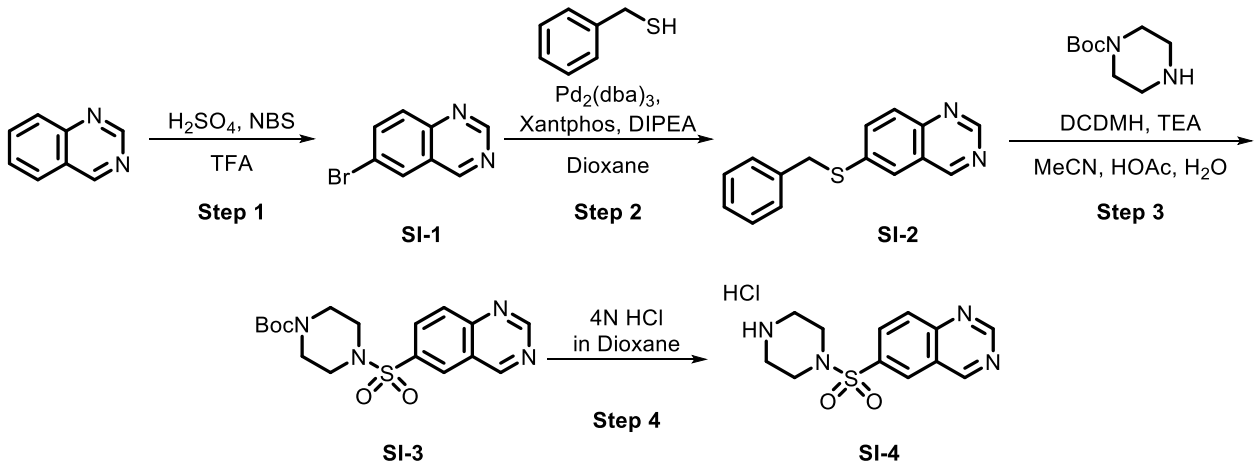
General Procedure 3: HATU (1.5 eq) and DIPEA (3.0 eq) were added to a solution of the carboxylic acid (1.1 eq) in DMF (0.1 M) and the mixture was stirred for 10 min. The amine (1.0 eq*)* was added to the mixture at 0 °C. The reaction was warmed to room temperature and stirred for 3 h. The reaction was quenched with water (equal volume to DMF) and extracted with EtOAc (3x). The combined organic phases were washed with brine (2x), dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified as indicated.

General Procedure 4: A solution of acid chloride (2.0 eq) in DCM (0.1 M) was added dropwise to a solution of amine (1.0 eq) and DIPEA (3.0 eq) in DCM (0.1 M) at 0 °C. The reaction was then stirred for 3 h at 0 °C. Water (equal volume to DCM) was added to the reaction mixture and the aqueous layer was extracted with DCM (2x). The combined organic phases were washed with brine (1x), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified as indicated.

General Procedure 5: HOAc (2.0 eq) and $NaBH_3CN$ (4.0 eq) were added to a stirred solution of ketone or aldehyde (1.0 eq) and amine (1.0 eq) in anhydrous MeCN (0.9 M) at 15 °C. The reaction mixture was heated to 50 °C and stirred for 8 h. The reaction was then cooled, water (equal volume to MeCN) was added and the mixture was extracted with EtOAc (3x). The organic layers were washed with brine (1x), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was used in the next step or purified as indicated.

General procedure 6: Acryloyl chloride (0.45 mM solution in DCM, 1.5 eq) was slowly added to a mixture of the amine (1.0 eq) and K_2CO_3 (3.0 eq) in EtOAc (0.05 M) at 0 °C. The reaction was allowed to warm to room temperature and stirred until complete disappearance of starting material (as monitored by TLC). The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography as indicated.

Synthesis of SI-4 as a precursor for EV-1 and EV-2



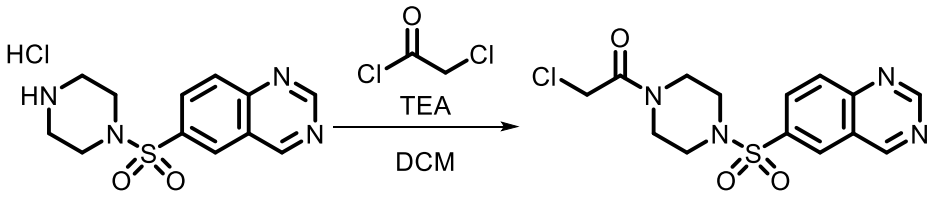
Step 1: Under an atmosphere of nitrogen, H_2SO_4 (8 mL) was added to a solution of quinazoline (5.0 g, 38.4 mmol, 1.0 eq) in anhydrous TFA (20 mL) at 15 °C. NBS (9.2 g, 51.9 mmol, 1.4 eq) was then added to the reaction mixture. The reaction was stirred at 15 °C for 8 h. The reaction mixture was poured into water (100

mL) and aqueous Na_2CO_3 was added until pH 8. The resulting solution was extracted with EtOAc (40 mL x 2). The combined organic extracts were washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (PE:EtOAc = 20:1) to afford **SI-1** (3.3 g, 41%) as a yellow solid.

Step 2: A two-neck round-bottom flask was charged with **SI-1** (2.0 g, 9.6 mmol, 1.0 eq), Xantphos (277 mg, 0.48 mmol, 0.05 eq), $Pd_2(dba)_3$ (263 mg, 0.29 mmol, 0.03 eq), DIPEA (3.3 mL, 19.1 mmol, 2.0 eq), and 1,4-dioxane (30 mL) under a nitrogen atmosphere. The flask was fitted with a reflux condenser and placed in an 80 °C heating bath. After 10 min, benzyl mercaptan (1.14 mL, 9.8 mmol, 1.0 eq) was added dropwise to the mixture. After an additional 20 min, the mixture was cooled and the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by flash chromatography (PE:EtOAc = 20:1 to 5:1) to afford **SI-2** (2.0 g, 83%) as a yellow solid.

Step 3: DCDMH (1.6 g, 7.9 mmol, 2.0 eq) was added to a solution of **SI-2** (1.0 g, 4.0 mmol, 1.0 eq) in H_2O (33 µL), AcOH (66 µL) and MeCN (10 mL) at 0 °C. After 30 min, TEA (2.2 mL, 15.8 mmol, 4.0 eq) was added to the reaction mixture and then stirred for 30 min at 0 °C. *Tert*-butyl piperazine-1-carboxylate (738 mg, 3.96 mmol, 1.00 eq) was then added and the mixture was stirred at 15 °C for 1h. The mixture was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (PE:EtOAc = 10:1 to 1:1) to afford **SI-3** (1.0 g, 66%) as a yellow solid.

Step 4: HCl/dioxane (4 N, 1.7 mL, 5.0 eq) was added to a solution of **SI-3** (500 mg, 1.3 mmol, 1.0 eq) in dioxane (3 mL) at 15 °C. The mixture was stirred for 1 h and then concentrated under reduced pressure to afford **SI-4** (400 mg, crude) as a yellow solid. **SI-4** was used in the next step without purification.

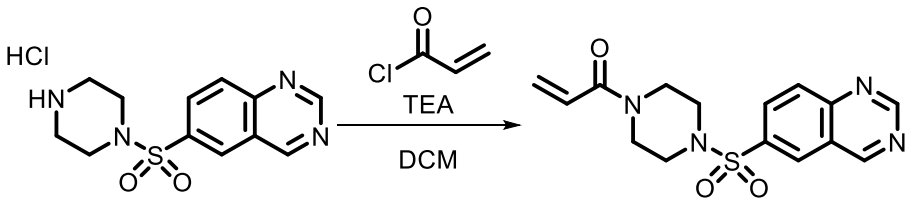


SI-4 **EV-1**

Following **General Procedure 1**, starting from **SI-4** (200 mg, 0.64 mmol, 1.0 eq), chloroacetyl chloride (1.0 eq), and TEA (4.0 eq), **EV-1** was obtained after prep-HPLC (HCl) as an off-white solid (30 mg, 13%).

^{1}H NMR (400 MHz, MeOD) δ 8.73 (s, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.97 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 6.27 (s, 1H), 4.24 – 4.18 (m, 2H), 3.74-3.62 (m, 4H), 3.23 – 3.02 (m, 4H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{14}H_{16}ClN_4O_3S$ 355.0626, found 355.0629.



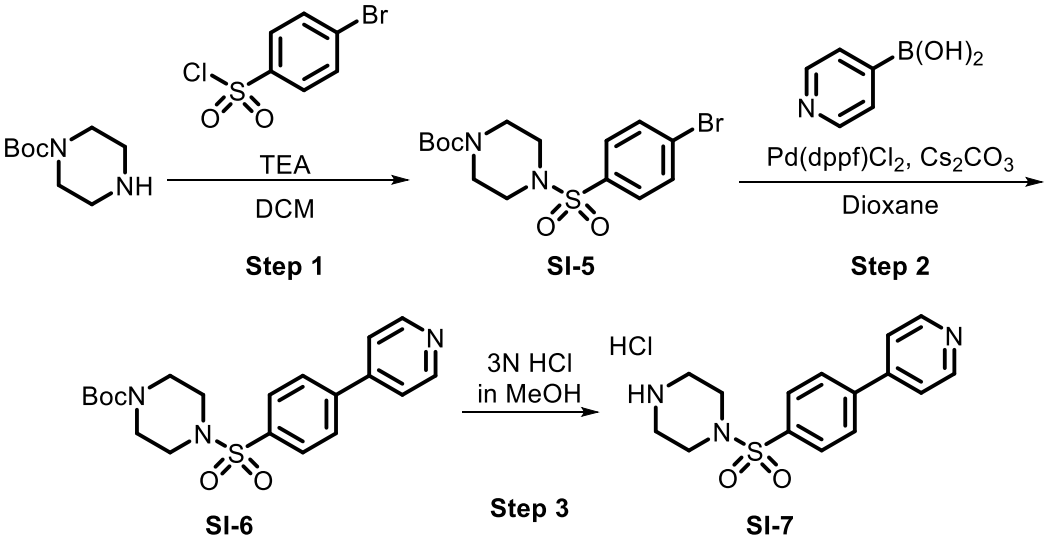
SI-4 **EV-2**

Following **General Procedure 2**, starting from **SI-4** (200 mg, 0.64 mmol, 1.0 eq), acryloyl chloride (1.0 eq), and TEA (4.0 eq), **EV-2** was obtained after prep-HPLC (HCl) as an off-white solid (20 mg, 9%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 9.49 (s, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 8.25 – 8.15 (m, 2H), 6.44 (dd, *J* = 16.8, 10.5 Hz, 1H), 6.23 (dd, *J* = 16.8, 1.8 Hz, 1H), 5.69 (dd, *J* = 10.5, 1.8 Hz, 1H), 3.74 (d, *J* = 45.3 Hz, 4H), 3.14 (t, *J* = 5.1 Hz, 4H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{15}H_{17}N_4O_3S$ 333.1016, found 333.1021.

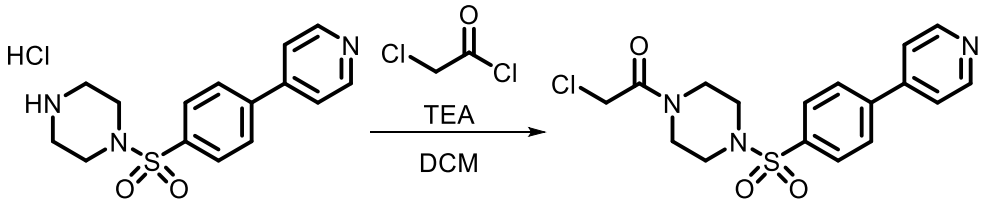
Synthesis of SI-7 as a precursor for EV-3 and EV-4



Step 1: TEA (1.5 mL, 10.7 mmol, 2.0 eq) was added to a mixture of *tert*-butyl piperazine-1-carboxylate (1.0 g, 5.4 mmol, 1.0 eq) and 4-bromobenzenesulfonyl chloride (1.4 g, 5.4 mmol, 1.0 eq) in DCM (30 mL) at 15 °C under a nitrogen atmosphere and stirred for 3 h. The reaction mixture was concentrated under reduced pressure to afford **SI-5** as a white solid (2.1 g, crude) which was used without purification.

Step 2: Under an atmosphere of nitrogen, $Pd(dppf)Cl_2$ (180 mg, 0.25 mmol, 0.1 eq) was added to a mixture of **SI-5** (1.0 g, 2.5 mmol, 1.0 eq), Cs_2CO_3 (1.6 g, 4.9 mmol, 2.0 eq) and 4-pyridylboronic acid (455 mg, 3.7 mmol, 1.5 eq) in dioxane (10 mL) at 15 °C. The reaction mixture was then heated to 110 °C and stirred for 4 h. After cooling, the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (40 mL x 2). The combined organic phases were washed with brine (10 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (PE:EtOAc = 50:1 to 2:1) to afford **SI-6** (800 mg, 80%) as white solid.

Step 3: 3N HCl in MeOH (20 mL) was added to **SI-6** (800 mg, 2.0 mmol, 1.0 eq) and the reaction mixture was stirred at 15 °C for 2 h. The reaction mixture was concentrated under reduced pressure to provide **SI-7** (600 mg, crude) as a white solid which was used without purification.

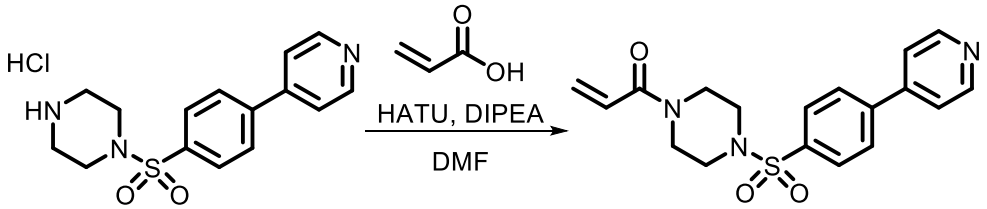


SI-7 **EV-3**

Following **General Procedure 1**, starting from **SI-7** (200 mg, 0.59 mmol, 1.0 eq), chloroacetyl chloride (3.0 eq) and TEA (2.0 eq), **EV-3** was obtained after prep-HPLC (HCl) as a white solid (43 mg, 17%).

^{1}H NMR (400 MHz, D_2O) δ 8.87 – 8.82 (m, 2H), 8.37 – 8.32 (m, 2H), 8.11 (d, *J* = 8.6 Hz, 2H), 7.99 (d, *J* = 8.6 Hz, 2H), 4.25 (s, 2H), 3.66 (t, *J* = 5.2 Hz, 4H), 3.17 (dt, *J* = 21.5, 5.2 Hz, 4H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{17}H_{19}ClN_3O_3S$ 380.0830, found 380.0833.



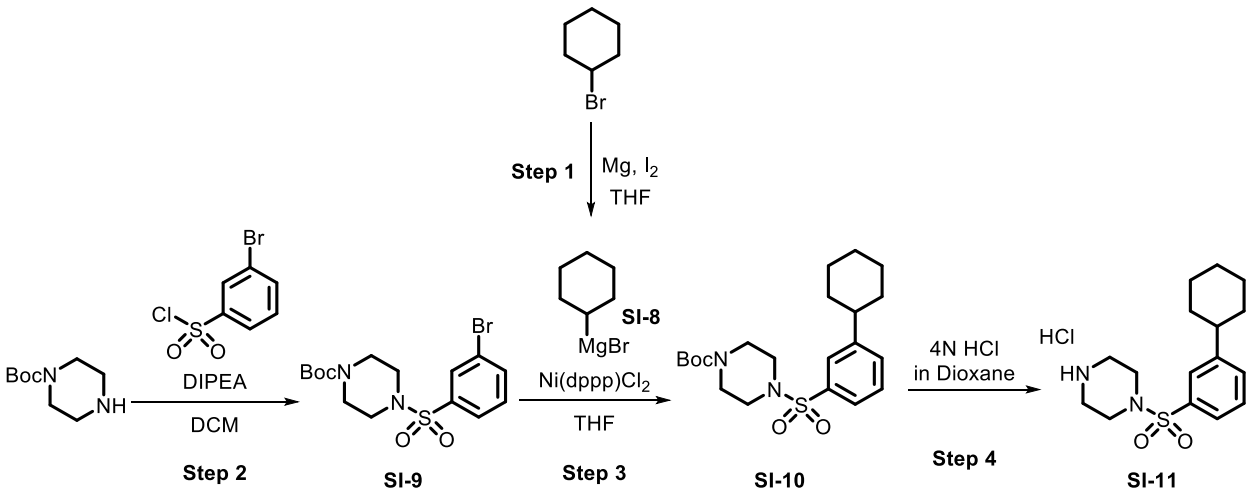
SI-7 **EV-4**

Following **General Procedure 3**, starting with **SI-7** (200 mg, 0.66 mmol, 1.0 eq) and acrylic acid (4.0 eq), **EV-4** was obtained after prep-HPLC (basic) as a white solid (13 mg, 5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 5.7 Hz, 2H), 7.89 – 7.75 (m, 4H), 7.54 – 7.47 (m, 2H), 6.47 (dd, *J* = 16.7, 10.5 Hz, 1H), 6.26 (dd, *J* = 16.8, 1.8 Hz, 1H), 5.70 (dd, *J* = 10.5, 1.8 Hz, 1H), 3.74 (d, *J* = 48.4 Hz, 4H), 3.08 (t, *J* = 5.1 Hz, 4H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{18}H_{20}N_3O_3S$ 358.1220, found 358.1224.

Synthesis of SI-11 as a precursor for EV-5 and EV-6

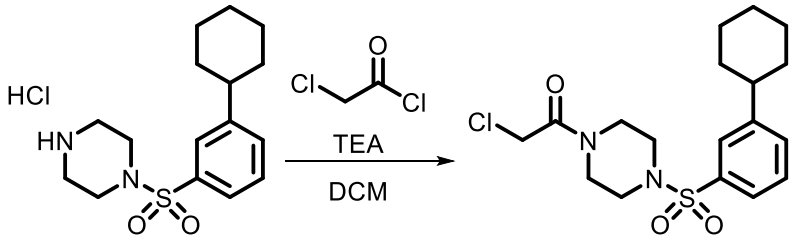


Step 1: A suspension of Mg (447 mg, 18 mmol, 1.5 eq) in THF (20 mL) was treated with I_2 (31 mg, 0.12 mmol, 0.01 eq) and heated to 80 °C. A solution of bromocyclohexane (2.0 g, 12.3 mmol, 1.0 eq) in THF (15 mL) was added dropwise over 30 min. After addition, the resulting mixture was cooled to 20 °C and stirred for an additional 2 h. **SI-8** was used in the **Step 3** without purification.

Step 2: 2-bromopheylsulfonyl chloride (2.5 g, 9.8 mmol, 1.0 eq) was added to a solution of *tert*-butyl piperazine-1-carboxylate (1.7 g, 9.3 mmol, 0.95 eq) and DIPEA (2.1 mL, 11.7 mmol, 1.2 eq) in DCM (25 mL) at 0 °C. The mixture was warmed to 20 °C and stirred for 1 h. The mixture was poured into water (5 mL) and DCM (5 mL). The aqueous solution was extracted with DCM (5 mL x 2). The organic phases were combined, dried over anhydrous Na_2SO_4, and concentrated to obtain **SI-9** as a light yellow oil. **SI-9** was used in the next step without purification.

Step 3: SI-8 (0.5 M, 20 mL, 4.0 eq) was added to a solution of **SI-9** (1.0 g, 2.5 mmol, 1.0 eq) and Ni(dppp)Cl_2 (134 mg, 0.25 mmol, 0.1 eq) in THF (20 mL) at 0 °C. After addition, the reaction mixture was warmed to 20 °C and stirred for an additional 2 h. The reaction was poured into water (5 mL) and EtOAc (5 mL). The aqueous solution was extracted with EtOAc (5 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (PE:EtOAc = 25:1 to 5:1) to provide **SI-10** (340 mg, 0.7 mmol, 28%) as a white solid.

Step 4: HCl/dioxane (4N, 5.0 mL, 24 eq) was added to a solution of **SI-10** (340 mg, 0.82 mmol, 1.0 eq) in dioxane (5 mL) at 20 °C and stirred for 2 h. The reaction mixture was concentrated to provide **SI-11** (250 mg, crude) as a light yellow oil. **SI-11** was used for the synthesis of **EV-5** and **EV-6** without purification.

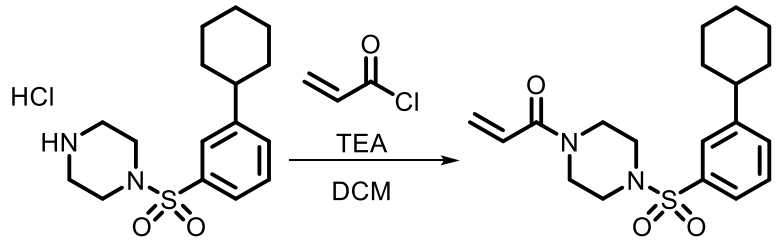


SI-11 **EV-5**

Following **General Procedure 1**, starting with **SI-11** (50 mg, 0.14 mmol, 1.0 eq), chloroacetyl chloride (1.5 eq), and TEA (3.0 eq), **EV-5** was obtained after prep-HPLC (FA) as a white solid (15 mg, 24%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2H), 7.49 – 7.43 (m, 2H), 4.00 (s, 2H), 3.66 (dt, *J* = 39.6, 5.1 Hz, 4H), 3.04 (dt, *J* = 23.0, 5.1 Hz, 4H), 2.64 – 2.54 (m, 1H), 1.93 – 1.81 (m, 4H), 1.81 – 1.74 (m, 1H), 1.49 – 1.33 (m, 4H), 1.32 – 1.19 (m, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{18}H_{26}ClN_2O_3S$ 385.1347, found 385.1348.



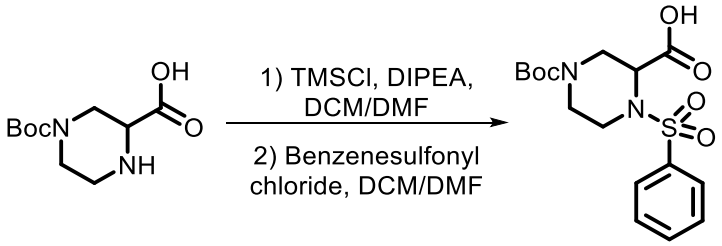
SI-11 **EV-6**

Following **General Procedure 2**, starting with **SI-11** (150 mg, 0.43 mmol, 1.0 eq), acryloyl chloride (1.5 eq), and TEA (3.0 eq), **EV-6** was obtained after prep-TLC (PE:EtOAc = 1:1) as a white solid (49 mg, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 2H), 7.49 – 7.40 (m, 2H), 6.46 (dd, *J* = 16.8, 10.6 Hz, 1H), 6.25 (dd, *J* = 16.9, 1.9 Hz, 1H), 5.69 (dd, *J* = 10.5, 1.8 Hz, 1H), 3.71 (d, *J* = 48.6 Hz, 4H), 3.02 (t, *J* = 5.1 Hz, 4H), 2.58 (t, *J* = 10.2 Hz, 1H), 1.97 – 1.72 (m, 5H), 1.49 – 1.20 (m, 5H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{19}H_{27}N_2O_3S$ 363.1737, found 363.1738.

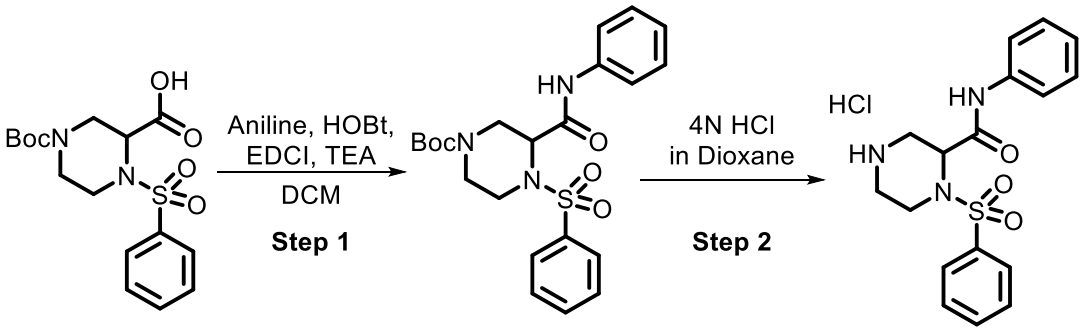
Synthesis of SI-12 as a precursor for EV-7 – EV-10



SI-12

Under an atmosphere of nitrogen, TMSCl (4.4 mL, 34.7 mmol, 1.6 eq) was added to a stirred solution of 4-Boc-piperazine-2-carboxylic acid (5.0 g, 21.7 mmol, 1.0 eq) and DIPEA (13.2 mL, 76.0 mmol, 3.5 eq) in anhydrous DCM (50 mL) and DMF (20 mL) at 15 °C. The reaction was stirred for 2 h followed by the addition of benzenesulfonyl chloride (3.0 mL, 23.9 mmol, 1.1 eq) and stirred for an additional 2 h. The reaction mixture was diluted with water (50 mL) and extracted with DCM (100 mL x 3). The combined organic phases were washed with 0.5 M HCl (50 mL x 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give **SI-12** (3.5 g, crude) as a yellow oil which was used without purification.

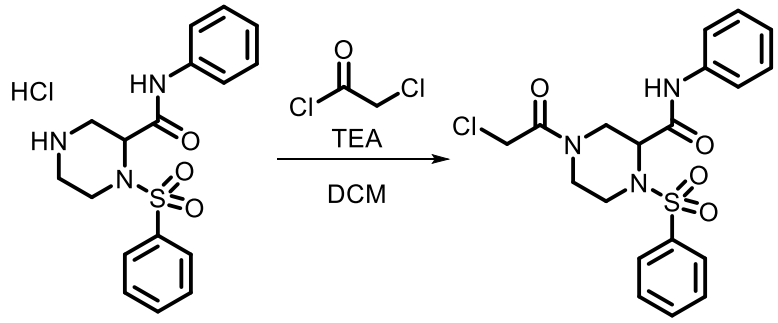
Synthesis of SI-14 as a precursor for EV-7 and EV-8



SI-12 **SI-13** **SI-14**

Step 1: HOBt (87 mg, 0.65 mmol, 1.2 eq), EDCI (124 mg, 0.65 mmol, 1.2 eq), and aniline (49 µL, 0.54 mmol, 1.0 eq) were added to a solution of **SI-12** (200 mg, 0.54 mmol, 1.0 eq), and TEA (0.23 mL, 1.62 mmol, 3.0 eq) in anhydrous DCM (1 mL) and stirred for 8 h. Upon completion, 50 mL of water was added to the reaction mixture and then extracted with DCM (75 mL x 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford **SI-13** (200 mg, crude) as yellow oil. **SI-13** was used in the next step without purification.

Step 2: HCl/dioxane (4 N, 0.84 mL, 10.0 eq) was added to a solution of **SI-13** (150 mg, 0.34 mmol, 1.0 eq) in anhydrous dioxane (1 mL) and stirred for 1h. Upon consumption of the starting material, the reaction was concentrated under reduced pressure to afford **SI-14** (110 mg, crude) as yellow oil which was used without purification.

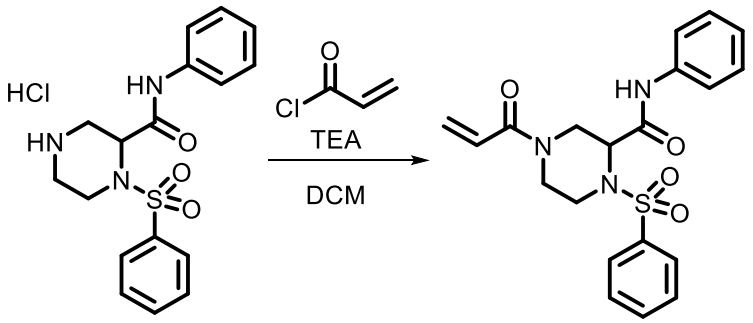


SI-14 **EV-7**

Following **General Procedure 1**, starting with **SI-14** (50 mg, 0.13 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (4.0 eq), **EV-7** was obtained after prep-HPLC (HCl) as a yellow solid (17 mg, 28%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.94 (d, *J* = 7.3 Hz, 2H), 7.73 (t, *J* = 7.4 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 4.57 (d, *J* = 12.7 Hz, 1H), 4.51 (d, *J* = 13.9 Hz, 1H), 4.35 (d, *J* = 13.6 Hz, 1H), 4.11 (d, *J* = 12.6 Hz, 1H), 4.02 (d, *J* = 14.5 Hz, 1H), 3.24 (ddd, *J* = 15.0, 12.4, 3.4 Hz, 2H), 2.87 (dd, *J* = 14.0, 4.1 Hz, 1H), 2.46 (td, *J* = 12.8, 3.3 Hz, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{19}H_{21}ClN_3O_4S$ 422.0936, found 422.0939.



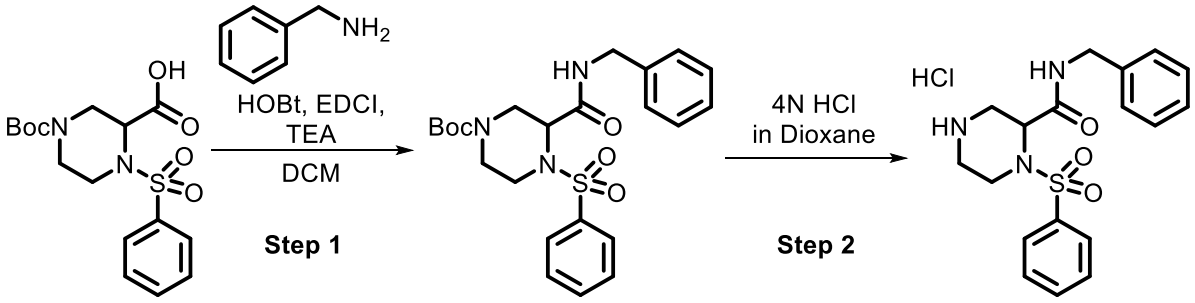
SI-14 **EV-8**

Following **General Procedure 2**, starting with **SI-14** (50 mg, 0.13 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (4.0 eq), **EV-8** was obtained after prep-HPLC (FA) as an off-white solid (21 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.96 – 7.90 (m, 2H), 7.74 – 7.56 (m, 3H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.86 – 6.74 (m, 1H), 6.25 (d, *J* = 16.7 Hz, 1H), 5.71 (dd, *J* = 10.5, 1.9 Hz, 1H), 4.73 – 4.55 (m, 2H), 4.37 (d, *J* = 13.6 Hz, 1H), 4.01 (d, *J* = 14.4 Hz, 1H), 3.31 (t, *J* = 13.1 Hz, 1H), 2.80 (d, *J* = 13.8 Hz, 1H), 2.49 (m, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{22}N_3O_4S$ 400.1326, found 400.1329.

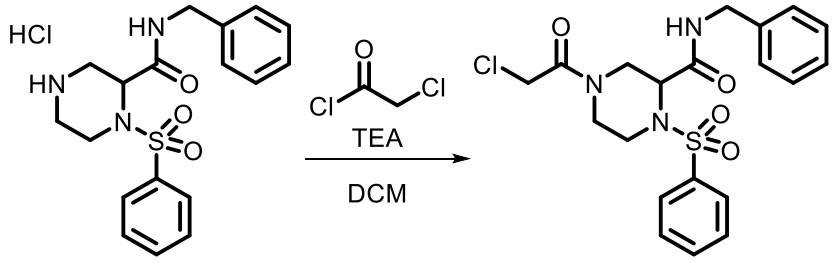
Synthesis of SI-16 as a precursor for EV-9 and EV-10



SI-12 **SI-15** **SI-16**

Step 1: HOBt (88 mg, 0.65 mmol, 1.2 eq), EDCI (124 mg, 0.65 mmol, 1.2 eq) and benzylamine (59 µL, 0.54 mmol, 1.0 eq) were added to a solution of **SI-12** (200 mg, 0.54 mmol, 1.0 eq) and TEA (226 µL, 1.6 mmol, 3.0 eq) in anhydrous DCM (1.0 mL) at 15 °C and then stirred for 8 h. 50 mL of water was added to the reaction mixture and then extracted with DCM (75 mL x 3). The combined organic phases were washed with brine (25 mL x 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **SI-15** (250 mg, crude) as a yellow oil which was used without purification.

Step 2: HCl/dioxane (4 M, 1.4 mL, 10.0 eq) was added to a solution of **SI-15** (250 mg, 0.54 mmol, 1.0 eq) in anhydrous dioxane (1.0 mL) at 15 °C. The reaction was stirred for 1h. The reaction was then concentrated under reduced pressure to afford **SI-16** (200 mg, crude) as a yellow oil which was used without purification.

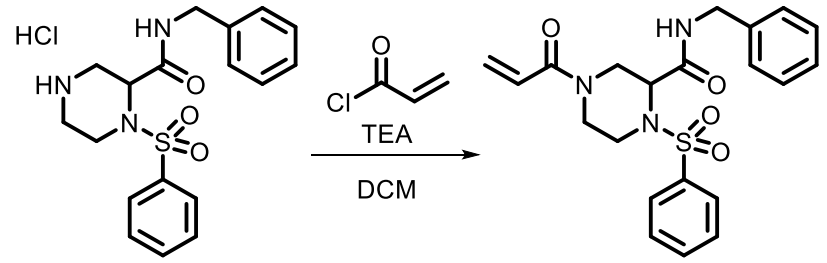


SI-16 **EV-9**

Following **General Procedure 1**, starting with **SI-16** (100 mg, 0.25 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (4.0 eq), **EV-9** was obtained after prep-HPLC (HCl) as an off-white solid (21 mg, 19%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.83 (m, 2H), 7.70 – 7.64 (m, 1H), 7.57 (t, *J* = 7.7 Hz, 2H), 7.38 – 7.27 (m, 3H), 7.23 – 7.17 (m, 2H), 6.95 (br s, 1H), 4.53 – 4.42 (m, 5H), 4.28 (d, *J* = 14.4 Hz, 1H), 4.08 (d, *J* = 12.7 Hz, 1H), 3.90 (d, *J* = 14.5 Hz, 1H), 3.14 (ddd, *J* = 14.8, 12.1, 3.5 Hz, 1H), 2.83 (dd, *J* = 13.8, 4.0 Hz, 1H), 2.46 – 2.34 (m, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{23}ClN_3O_4S$ 436.1093, found 436.1093.



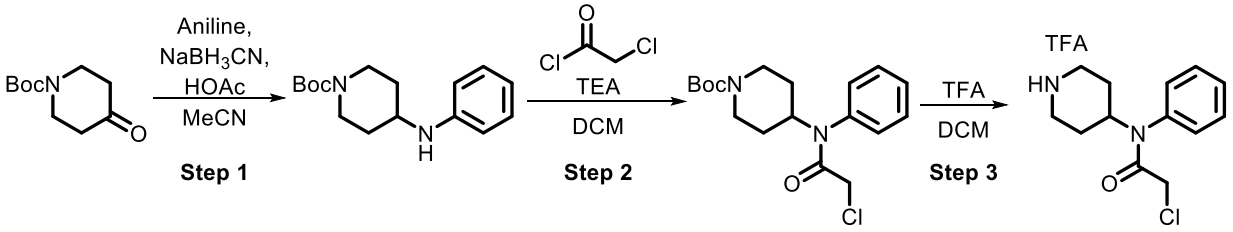
SI-16 **EV-10**

Following **General Procedure 2**, starting with **SI-16** (100 mg, 0.26 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (4.0 eq), **EV-10** was obtained after prep-HPLC (FA) as an off white solid (19 mg, 18%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.25 (m, 3H), 7.23 – 7.16 (m, 2H), 6.90 (br s, 1H), 6.76 (dd, *J* = 16.7, 10.8 Hz, 1H), 6.25 (dd, *J* = 16.6, 1.8 Hz, 1H), 5.69 (dd, *J* = 10.5, 1.9 Hz, 1H), 4.64 (d, *J* = 13.8 Hz, 1H), 4.51 (s, 1H), 4.43 (dd, *J* = 5.9, 3.7 Hz, 2H), 4.32 (d, *J* = 13.7 Hz, 1H), 3.89 (d, *J* = 14.5 Hz, 1H), 3.20 (t, *J* = 13.3 Hz, 1H), 2.78 (d, *J* = 13.6 Hz, 1H), 2.44 (t, *J* = 12.6 Hz, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{24}N_3O_4S$ 414.1482, found 414.1486.

Synthesis of SI-19 as a precursor for EV-11 – EV-31

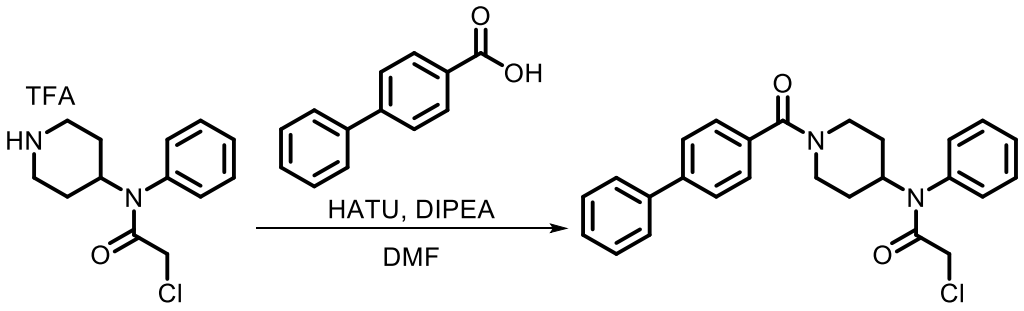


SI-17 **SI-18** **SI-19**

Step 1: Following **General Procedure 5**, starting with 1-Boc-4-piperidone (19 g, 95 mmol, 1.0 eq) and aniline (8.7 mL, 95.4 mmol, 1.0 eq), **SI-17** (13.0 g, 49%) was obtained as a white solid after purification via prep-HPLC (basic).

Step 2: Following General Procedure 1, starting with **SI-17** (13.5 g, 48.9 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (2.0 eq), **SI-18** (12.8 g, 74%) was obtained as a yellow solid after purification by prep-HPLC (basic).

Step 3: TFA (34.7 mL, 454 mmol, 10.0 eq) was added to a solution of **SI-18** (16.0 g, 45.4 mmol, 1.0 eq) in DCM (20 mL) at 18 °C and stirred for 3 h. Upon completion, the mixture was concentrated under reduced pressure to provide **SI-19** (23.0 g, crude) as a yellow oil which was used without purifiaction.

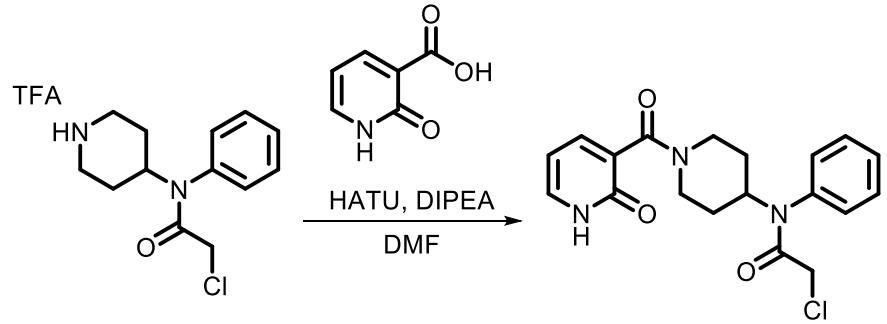


SI-19 **EV-11**

Following **General Procedure 3**, starting with **SI-19** (100 mg, 0.27 mmol, 1.0 eq*)* and 4-phenylbenzoic acid (1.1 eq), **EV-11** was obtained after prep-HPLC (HCl) as a white solid (41 mg, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 4H), 7.51 – 7.41 (m, 5H), 7.41 – 7.33 (m, 3H), 7.14 (br s, 2H), 4.87 (m, 2H), 3.90 (br s, 1H), 3.71 (s, 2H), 3.18 (br s, 1H), 2.87 (br s, 1H), 2.03 – 1.78 (m, 2H), 1.49 – 1.19 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{26}H_{26}ClN_2O_2$ 433.1678, found 433.1677.

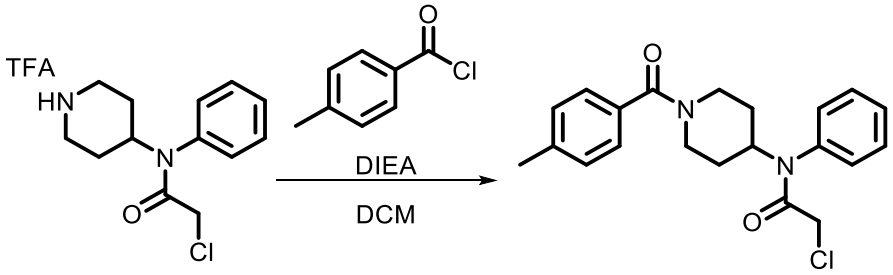


SI-19 **EV-12**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 2-hydroxynicotinic acid (1.1 eq), **EV-12** was obtained after prep-HPLC (HCl) as a solid (3 mg, 2%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.59 (br s, 1H), 7.46 (br s, 3H), 7.15 (br s, 2H), 6.60 (br s, 1H), 4.77 (br s, 1H), 3.71 (s, 2H), 2.95 (br s, 2H), 1.91 (br s, 2H), 1.48 (br s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{19}H_{21}ClN_3O_2$ 374.1266, found 374.1266.

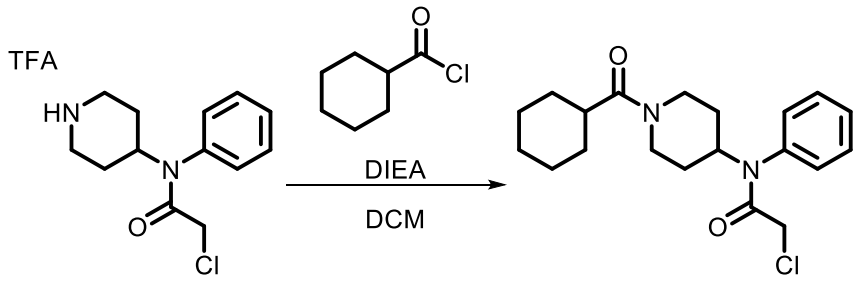


SI-19 **EV-13**

Following **General Procedure 4**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 4-methylbenzoyl chloride (2.0 eq), **EV-13** was obtained after prep-HPLC (HCl) as an off-white solid (66 mg, 44%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 3H), 7.22 – 7.10 (m, 6H), 4.90-4.78 (m, 1H), 3.71 (s, 2H), 2.99 (br s, 2H), 2.35 (s, 3H), 1.95 – 1.77 (m, 4H), 1.37 – 1.25 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{24}ClN_2O_2$ 371.1521, found 371.1522.

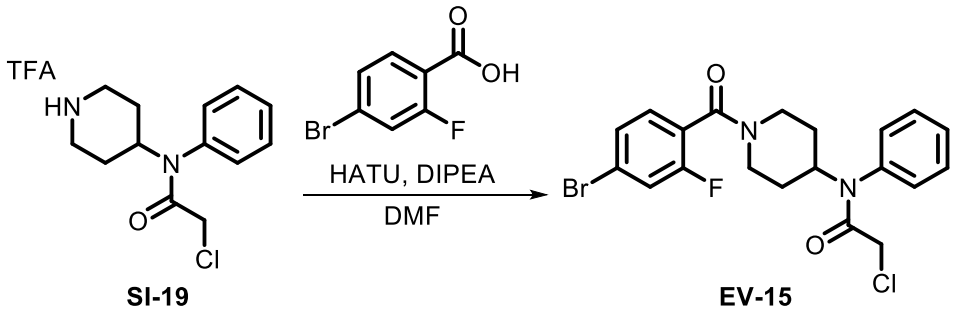


SI-19 **EV-14**

Following **General Procedure 4**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and cyclohexylcarbonyl chloride (2.0 eq), **EV-14** was obtained after prep-HPLC (HCl) as an off-white solid (57 mg, 38%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 3H), 7.12 (dd, *J* = 6.3, 3.0 Hz, 2H), 4.82 (t, *J* = 12.2 Hz, 1H), 4.32 (br s, 2H), 3.71 (s, 2H), 2.85 (br s, 2H), 2.38 (t, *J* = 11.9 Hz, 1H), 1.89 (d, *J* = 12.0 Hz, 2H), 1.77 (s, 3H), 1.69 – 1.56 (m, 1H), 1.51 – 1.34 (m, 2H), 1.29 – 1.10 (m, 4H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{28}ClN_2O_2$ 363.1834, found 363.1833.

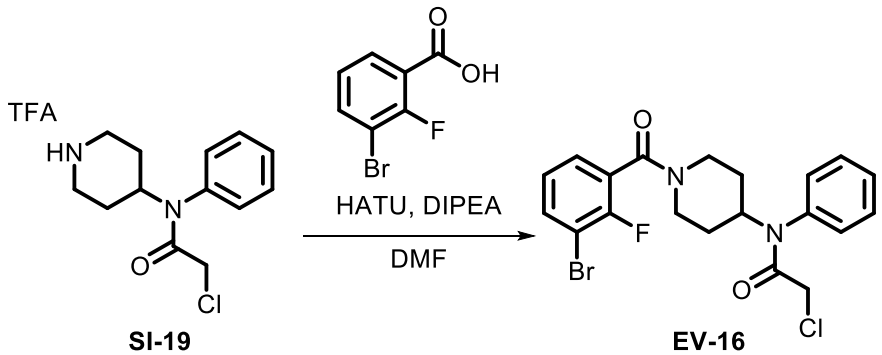


SI-19 **EV-15**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 4-bromo-2-fluorobenzoic acid (2.0 eq), **EV-15** (9 mg, 5%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 3H), 7.31 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.24 (dd, *J* = 8.9, 1.7 Hz, 1H), 7.20 – 7.13 (m, 2H), 7.09 (br s, 1H), 4.93 – 4.72 (m, 2H), 3.71 (s, 2H), 3.59 – 3.43 (m, 1H), 3.18 (br s, 1H), 2.83 (t, *J* = 12.5 Hz, 1H), 1.89 (dd, *J* = 39.4, 12.6 Hz, 2H), 1.46 – 1.15 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{20}BrClFN_2O_2$ 453.0375, found 453.0374.

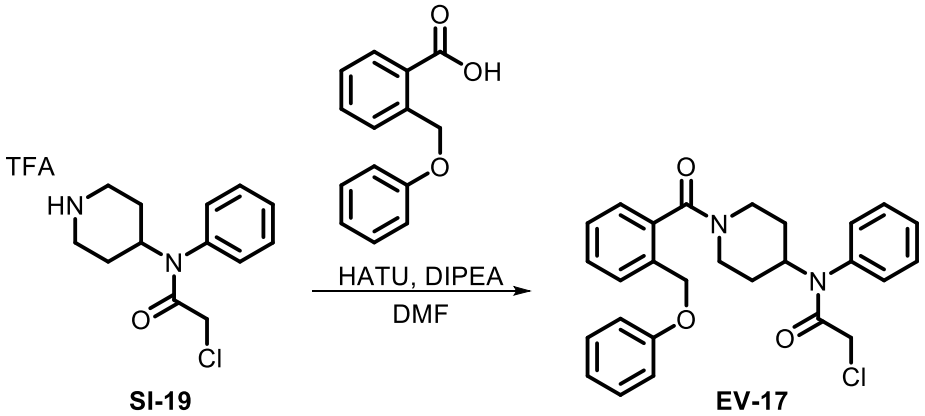


SI-19 **EV-16**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 3-bromo-2-fluorobenzoic acid (2.0 eq), **EV-16** (27 mg, 15%) was obtained after prep-HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.44 (m, 3H), 7.25 – 7.09 (m, 3H), 7.05 (t, *J* = 7.7 Hz, 1H), 4.91 – 4.72 (m, 2H), 3.71 (s, 2H), 3.60 – 3.45 (m, 1H), 3.18 (br s, 1H), 2.85 (s, 1H), 1.98 – 1.77 (m, 3H), 1.37 (qd, *J* = 12.8, 11.9, 3.9 Hz, 1H), 1.22 (br s, 1H).

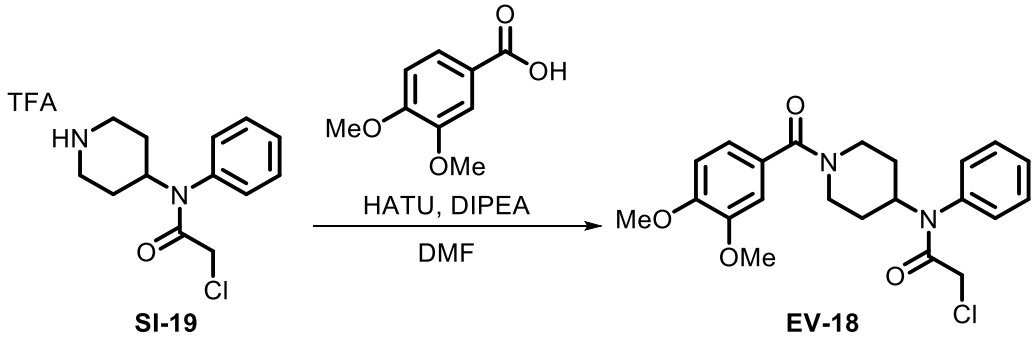
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{20}BrClFN_2O_2$ 453.0375, found 453.0377.



Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 2-(phenoxymethyl)benzoic acid (2.0 eq), **EV-17** (37 mg, 19%) was obtained after prep-HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 2H), 7.46 – 7.23 (m, 6H), 7.21 – 6.94 (m, 4H), 6.89 (s, 1H), 6.79 (s, 1H), 5.16 – 4.86 (m, 2H), 4.80 (s, 2H), 3.80 – 3.46 (m, 3H), 3.07 (d, *J* = 63.3 Hz, 1H), 2.76 (d, *J* = 50.2 Hz, 1H), 1.80 (s, 2H), 1.55 – 1.05 (m, 2H).

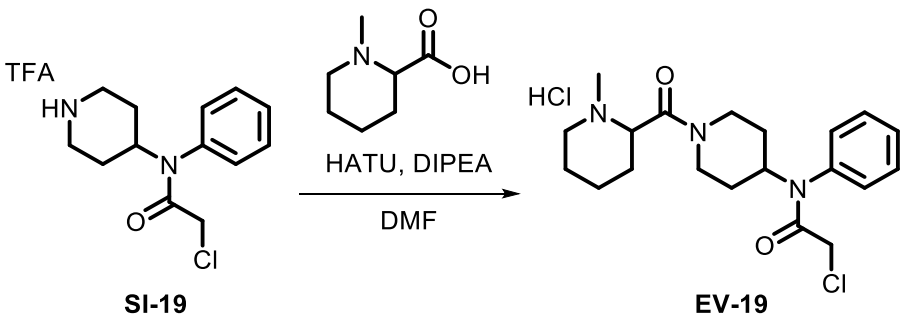
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{27}H_{28}ClN_2O_3$ 463.1783, found 463.1785.



Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 3,4-dimethoxybenzoic acid (2.0 eq), **EV-18** (44 mg, 26%) was obtained after prep-HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (br s, 3H), 7.14 (br s, 2H), 6.86 (dd, *J* = 24.0, 9.5 Hz, 3H), 4.87 (br s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.71 (s, 2H), 2.03 – 1.90 (m, 6H), 1.33 (br s, 2H).

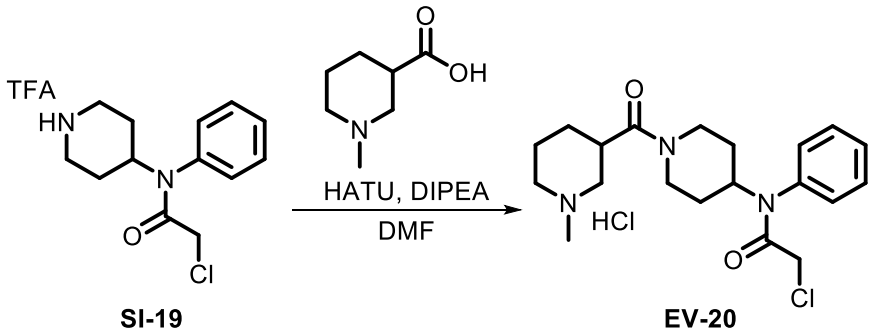
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{22}H_{26}ClN_2O_4$ 417.1576, found 417.1577.



Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 1-methylpiperidine-2-carboxylic acid (2.0 eq), **EV-19** (20 mg, 13%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.03 (br s, 0.5H), 9.77 (d, *J* = 38.5 Hz, 0.5H), 7.46 (s, 3H), 7.13 (s, 2H), 4.89 – 4.49 (m, 2H), 4.41 – 3.95 (m, 1H), 3.71 (s, 3H), 3.35 – 3.06 (m, 2H), 2.87 – 2.61 (m, 4H), 2.56 – 2.30 (m, 2H), 2.22 – 1.90 (m, 3H), 1.92 – 1.59 (m, 3H), 1.52 – 1.35 (m, 1H), 1.36 – 1.14 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{29}ClN_3O_2$ 378.1943, found 378.1950.

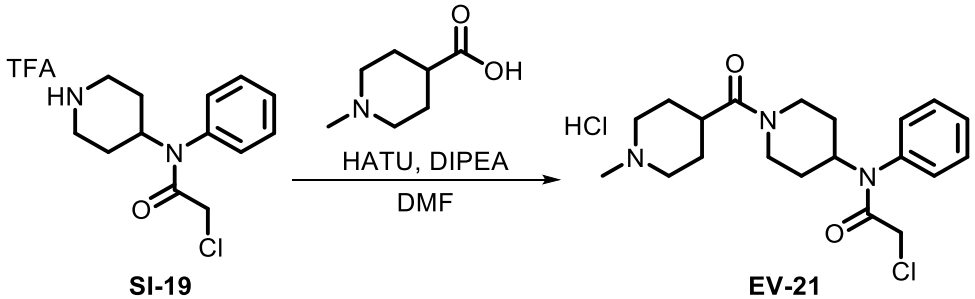


SI-19 **EV-20**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 1-methylpiperidine-3-carboxylic acid (2.0 eq), **EV-20** (12 mg, 8%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.34 (br s, 0.8H), 9.44 (d, *J* = 46.2 Hz, 0.2H), 7.46 (br s, 3H), 7.12 (br s, 2H), 4.87 – 4.72 (m, 1H), 4.61 (d, *J* = 13.4 Hz, 1H), 4.04 (dd, *J* = 45.2, 13.8 Hz, 1H), 3.70 (d, *J* = 4.4 Hz, 2H), 3.68 – 3.51 (m, 1H), 3.49 – 3.42 (m, 1H), 3.35 – 3.10 (m, 2H), 3.02 – 2.81 (m, 1H), 2.74 (t, *J* = 5.0 Hz, 3H), 2.70 – 2.57 (m, 1H), 2.41 – 2.22 (m, 1H), 2.06 – 1.85 (m, 5H), 1.61 – 1.39 (m, 1H), 1.37 – 1.08 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{29}ClN_3O_2$ 378.1943, found 378.1949.



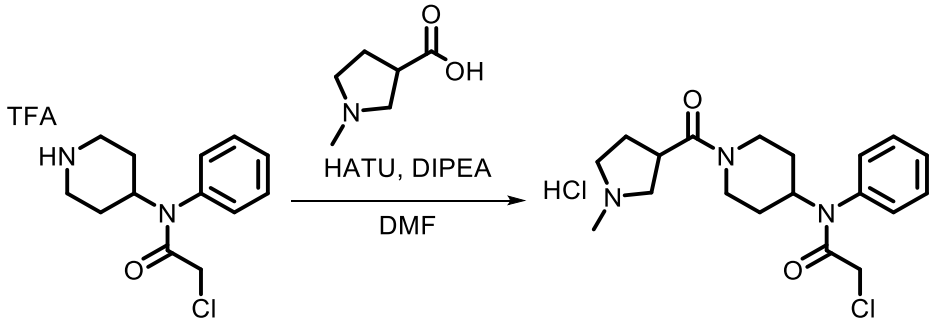
SI-19 **EV-21**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 1-methylpiperidine-4-carboxylic acid (2.0 eq), **EV-21** (16 mg, 10%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.57 (s, 0.4H), 10.76 (s, 0.6H), 7.46 (br s, 3H), 7.13 (br s, 2H), 4.82 – 4.70 (m, 1H), 4.59 (br s, 2H), 4.09 – 3.79 (m, 1H), 3.70 (s, 2H), 3.48 (br s, 1H), 3.41 – 3.25 (m, 1H), 3.22 – 2.95 (m, 2H),

2.94 – 2.84 (m, 1H), 2.85 – 2.69 (m, 3H), 2.61 (t, *J* = 12.8 Hz, 1H), 2.51 – 2.26 (m, 1H), 2.17 (s, 1H), 2.06 – 1.70 (m, 4H), 1.36 – 1.13 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{29}ClN_3O_2$ 378.1943, found 378.1950.

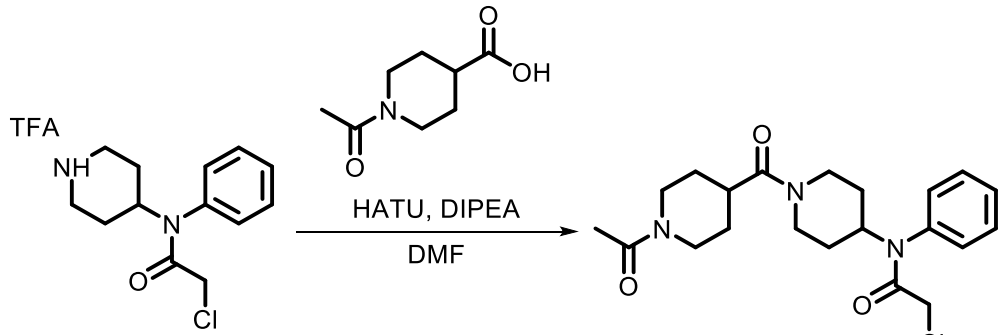


SI-19 **EV-22**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 1-methylpyrrolidine-3-carboxylic acid (2.0 eq), **EV-22** (17 mg, 11%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, D_2O) δ 7.54 – 7.48 (m, 3H), 7.28 (br s, 2H), 4.72 (t, *J* = 12.1 Hz, 1H), 4.49 – 4.34 (m, 1H), 3.98 (d, *J* = 14.0 Hz, 1H), 3.88 (s, 2H), 3.85 – 3.56 (m, 3H), 3.39 – 3.02 (m, 3H), 2.95 – 2.88 (m, 3H), 2.84 – 2.71 (m, 1H), 2.63 – 2.22 (m, 1H), 2.18 – 1.77 (m, 3H), 1.39 – 1.14 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{19}H_{27}ClN_3O_2$ 364.1787, found 364.1794.

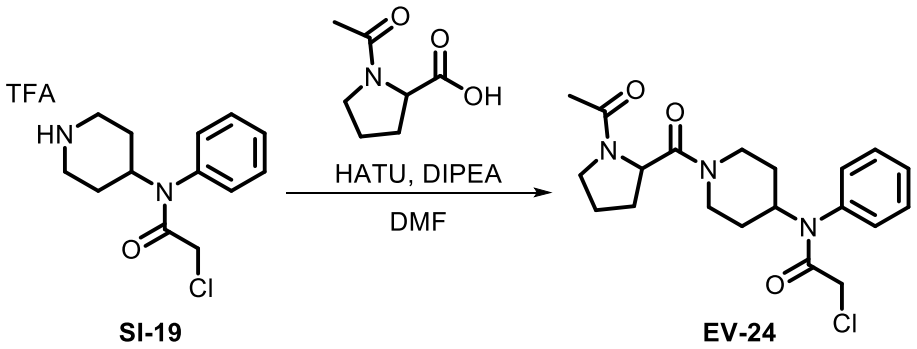


SI-19 **EV-23**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and *N*-acetylpiperidine-4-carboxylic acid (2.0 eq), **EV-23** (37 mg, 22%) was obtained after prep-HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 3H), 7.14 – 7.10 (m, 2H), 4.82 (t, *J* = 12.2 Hz, 1H), 4.74 – 4.25 (m, 2H), 3.90 (br s, 1H), 3.71 (s, 2H), 3.29 – 2.74 (m, 3H), 2.63 (br s, 4H), 2.13 (s, 3H), 1.96 (br s, 1H), 1.88 (br s, 1H), 1.68 (br s, 3H), 1.23 (d, *J* = 13.1 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{29}ClN_3O_3$ 406.1892, found 406.1893.

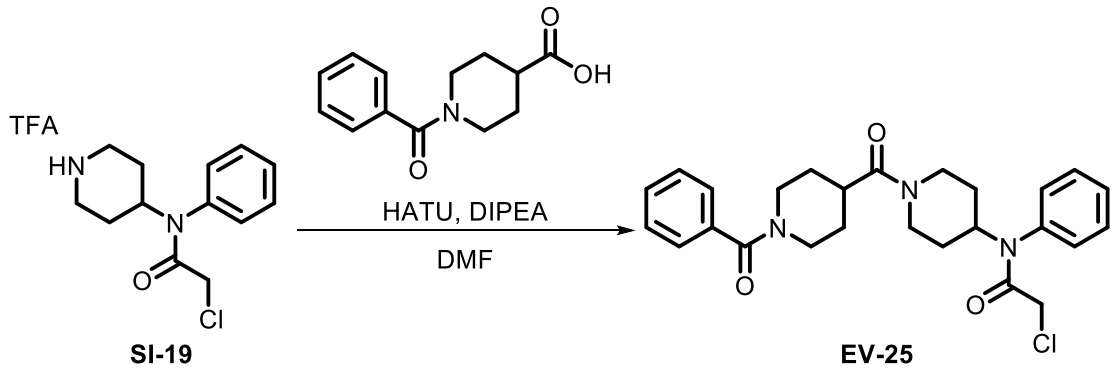


SI-19 **EV-24**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and *N*-acetylpyrrolidine-2-carboxylic acid (2.0 eq), **EV-24** (28 mg, 17%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (br s, 3H), 7.14 (br s, 2H), 6.22 (br s, 1H), 4.89 (br s, 1H), 4.75 (br s, 1H), 4.58 (d, *J* = 12.1 Hz, 1H), 3.92 (br s, 1H), 3.76 – 3.55 (m, 4H), 3.21 (d, *J* = 41.3 Hz, 1H), 2.81 – 2.58 (m, 1H), 2.28 – 2.14 (m, 3H), 2.15 – 1.69 (m, 5H), 1.60 – 1.16 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{27}ClN_3O_3$ 392.1736, found 392.1737.

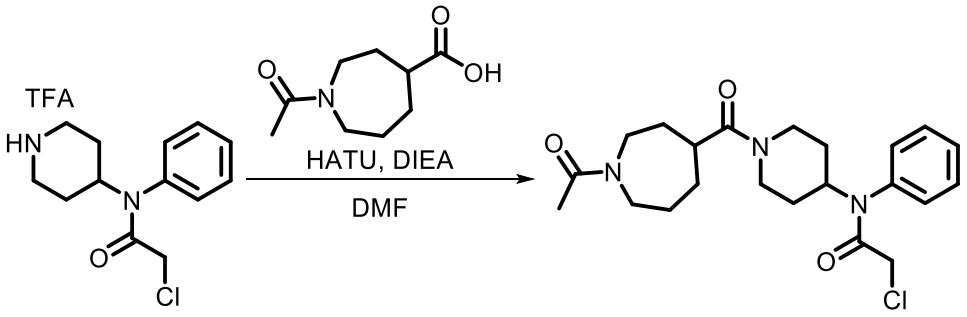


SI-19 **EV-25**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and *N*-benzoylpiperidine-4-carboxylic acid (2.0 eq), **EV-25** (24 mg, 12%) was obtained after prep-HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (br s, 3H), 7.38 (br s, 5H), 7.12 (br s, 2H), 4.82 (t, *J* = 12.0 Hz, 1H), 4.68 (br s, 1H), 3.92 (br s, 1H), 3.71 (s, 2H), 3.17 (br s, 1H), 2.94 (br s, 2H), 2.69 (br s, 2H), 2.32 – 2.10 (m, 3H), 1.92 (br s, 2H), 1.74 (br s, 3H), 1.25 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{26}H_{31}ClN_3O_3$ 468.2049, found 468.2051.

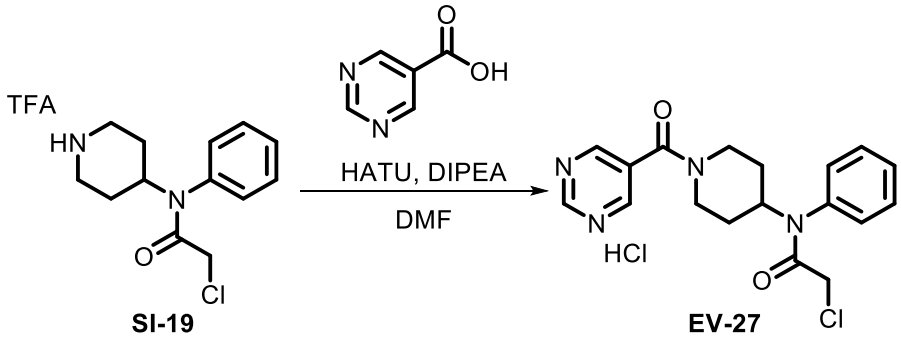


SI-19 **EV-26**

Following **General Procedure 3**, starting with **SI-19** (100 mg, 0.27 mmol, 1.0 eq) and 1-acetylazepane-4-carboxylic acid (1.1 eq), **EV-26** was obtained after prep-HPLC (HCl) as a white solid (12 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 3H), 7.19 – 7.07 (m, 2H), 4.78 (t, *J* = 10.8 Hz, 1H), 4.64 (br s, 1H), 3.93 (m, 1H), 3.70 (m, 3H), 3.58 (m, 1H), 3.36 (m, 1H), 3.14 (m, 1H), 2.67 (m, 2H), 2.41 (br s, 3H), 1.97 (m, 5H), 1.67 (m, 3H), 1.25 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{22}H_{31}ClN_3O_3$ 420.2049, found 420.2049.

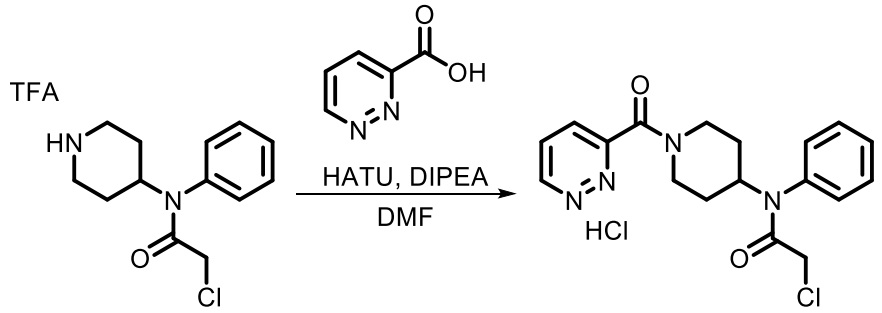


SI-19 **EV-27**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and pyrimidine-5-carboxylic acid (2.0 eq), **EV-27** (13 mg, 9%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.70 (s, 2H), 7.49 (s, 3H), 7.13 (br s, 2H), 4.88 (tt, *J* = 12.2, 3.8 Hz, 1H), 4.76 (br s, 1H), 3.75 – 3.63 (m, 3H), 3.28 (br s, 1H), 2.89 (br s, 1H), 1.99 (br s, 1H), 1.91 (br s, 1H), 1.39 (br s, 1H), 1.31 (dd, *J* = 10.5, 6.8 Hz, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{19}H_{20}ClN_4O_2$ 359.1270, found 359.1270.

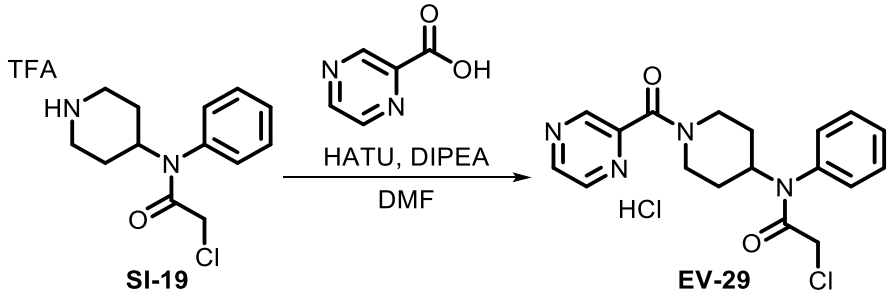


SI-19 **EV-28**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and pyridazine-3-carboxylic acid (2.0 eq), **EV-28** (14 mg, 9%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (br s, 1H), 8.36 (br s, 2H), 7.46 (br s, 3H), 7.16 (br s, 2H), 4.94 – 4.66 (m, 2H), 4.08 (br s, 1H), 3.71 (s, 2H), 3.30 (br s, 1H), 2.97 (t, *J* = 11.4 Hz, 1H), 2.26 – 1.79 (m, 2H), 1.66 – 1.17 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{19}H_{20}ClN_4O_2$ 359.1270, found 359.1273.

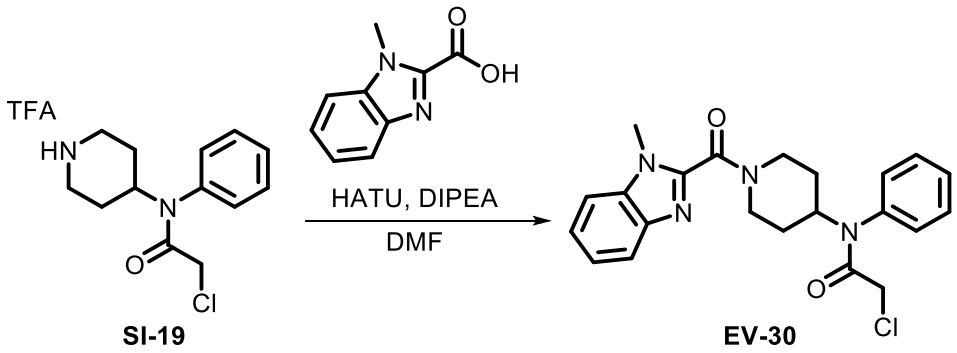


SI-19 **EV-29**

Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and pyrazine-2-carboxylic acid (2.0 eq), **EV-29** (24 mg, 16%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.58 (d, *J* = 21.5 Hz, 2H), 7.47 (s, 3H), 7.13 (dd, *J* = 17.3, 5.6 Hz, 2H), 4.95 – 4.85 (m, 1H), 4.81 (d, *J* = 12.9 Hz, 1H), 4.06 (d, *J* = 13.4 Hz, 1H), 3.71 (s, 2H), 3.23 (t, *J* = 12.9 Hz, 1H), 2.90 (t, *J* = 13.0 Hz, 1H), 1.99 (d, *J* = 12.6 Hz, 1H), 1.88 (d, *J* = 12.2 Hz, 1H), 1.50 – 1.34 (m, 2H).

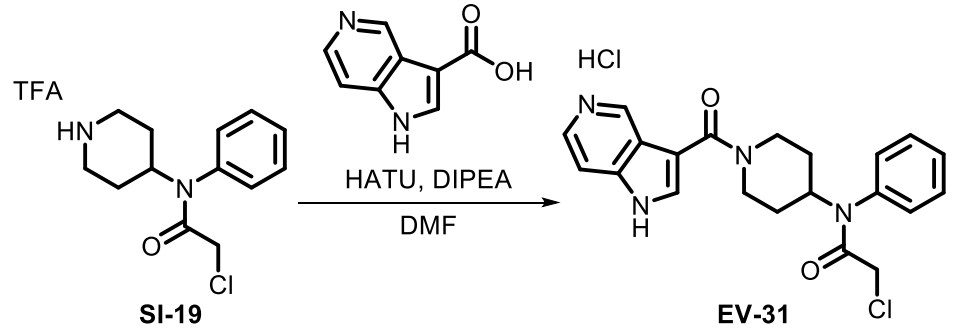
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{19}H_{20}ClN_4O_2$ 359.1270, found 359.1270.



Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 1-methyl-1*H*-benzimidazole-2-carboxylic acid (2.0 eq), **EV-30** (12 mg, 7%) was obtained after prep-HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.63 (s, 3H), 7.46 (s, 3H), 7.26 (br s, 1H), 7.16 (br s, 1H), 4.72 (d, *J* = 12.1 Hz, 2H), 4.01 (s, 3H), 3.72 (s, 4H), 3.05 (t, *J* = 12.6 Hz, 1H), 1.98 (d, *J* = 12.7 Hz, 3H), 1.57 (d, *J* = 12.4 Hz, 1H).

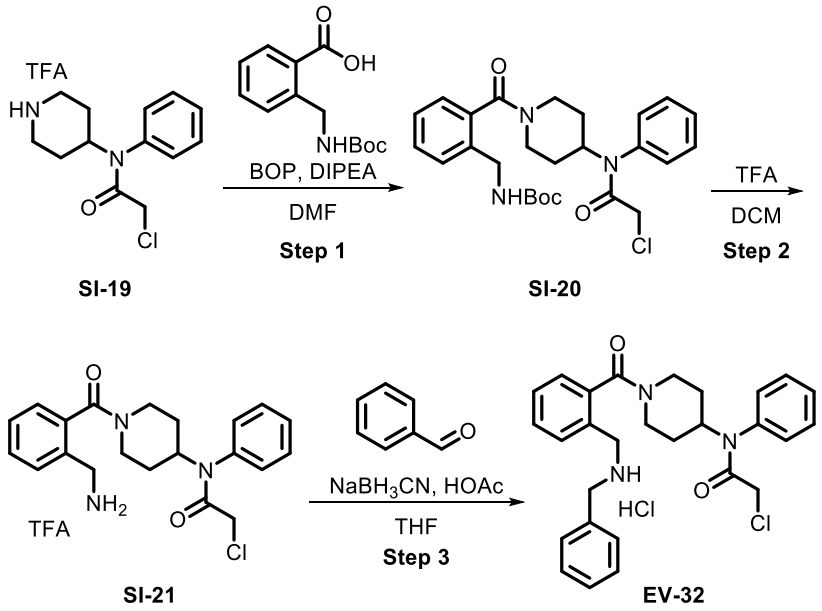
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{22}H_{24}ClN_4O_2$ 411.1583, found 411.1588.



Following **General Procedure 3**, starting with **SI-19** (150 mg, 0.41 mmol, 1.0 eq) and 1*H*-pyrrolo[3,2-*c*]pyridine-3-caroxylic acid (2.0 eq), **EV-31** (3 mg, 2%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, CD_3CN) δ 12.53 (br s, 1H), 10.91 (br s, 1H), 9.07 (d, *J* = 6.7 Hz, 1H), 8.26 (t, *J* = 6.3 Hz, 1H), 7.94 (d, *J* = 6.6 Hz, 1H), 7.89 (d, *J* = 2.5 Hz, 1H), 7.50 – 7.45 (m, 3H), 7.27 – 7.20 (m, 2H), 4.84 – 4.71 (m, 1H), 4.43 (s, 2H), 3.77 (s, 2H), 3.21 – 3.03 (m, 2H), 1.91 (br s, 2H), 1.33 (dd, *J* = 12.5, 4.3 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{22}ClN_4O_2$ 397.1426, found 397.1428.



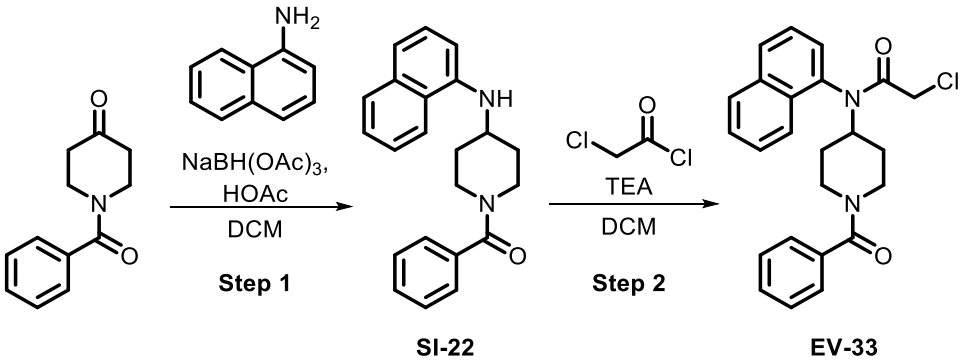
Step 1: BOP (880 mg, 2.0 mmol, 1.0 eq) and DIPEA (1.0 mL, 6.0 mmol, 3.0 eq) were added to a solution of 2-(Boc-aminomethyl)benzoic acid (500 mg, 2.0 mmol, 1.0 eq) and **SI-19** (730 mg, 2.0 mmol, 1.0 eq) in DMF (2 mL). The mixture was stirred at 25 °C for 10 h. The mixture was diluted with DCM (30 mL) and washed with brine (30 mL x 3). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography to afford **SI-20** (500 mg, 11%) as a white solid.

Step 2: TFA (0.32 mL, 4.1 mmol, 5.0 eq) was added to a solution of **SI-20** (400 mg, 0.82 mmol, 1.0 eq) in DCM (3 mL) and the mixture was stirred at 25 °C for 10 h. The reaction was diluted with H_2O (20 mL) and extracted with DCM (30 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by prep-HPLC (HCl) to provide **SI-21** (130 mg, 35%) as a white solid.

Step 3: HOAc (7.4 µL, 0.13 mmol, 1.0 eq) was added to a solution of **SI-21** (50 mg, 0.13 mmol, 1.0 eq) and benzaldehyde (13 µL, 0.13 mmol, 1.0 eq) in THF (1 mL) and the mixture was stirred at 25 °C for 1 h. $NaBH_3CN$ (8 mg, 0.13 mmol, 1.0 eq) was then added and the mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by the addition of 1 M HCl (10 mL) and then diluted with H_2O (10 mL). The mixture was extracted with DCM (20 mL x 2) and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The resulting residue was purified by prep-HPLC (HCl) to afford **EV-32** (11 mg, 18%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (br s, 1H), 7.73 (br s, 1H), 7.61 – 7.38 (m, 7H), 7.33 (br s, 3H), 7.23 – 7.05 (m, 3H), 4.89 – 4.66 (m, 2H), 4.02 (br s, 3H), 3.79 – 3.66 (m, 3H), 3.19 (br s, 1H), 2.84 (t, *J* = 13.8 Hz, 1H), 2.07 – 1.95 (m, 1H), 1.86 (br s, 1H), 1.69 (br s, 1H), 1.48 – 1.16 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{28}H_{31}ClN_3O_2$ 476.2100, 476.2104.

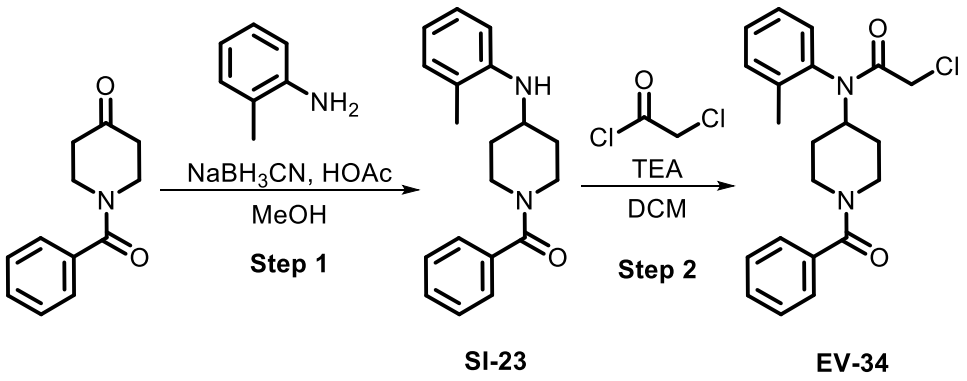


Step 1: Following **General Procedure 5**, starting with 1-benzoylpiperidin-4-one (300 mg, 1.5 mmol, 1.0 eq) and naphthalen-1-amine (1.2 eq) in DCM (2 mL), **SI-22** was obtained as a yellow oil and used without purification.

Step 2: Following **General Procedure 1**, starting with **SI-22** (425 mg, 1.2 mmol, 1.0 eq), chloroacetyl chloride (3.0 eq), and TEA (6.0 eq). **EV-33** was obtained after prep-HPLC (FA) as a yellow oil (68 mg, 13%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.90 (m, 2H), 7.82 (br s, 1H), 7.63 – 7.48 (m, 3H), 7.43 – 7.12 (br s, 6H), 4.95 (tt, *J* = 12.2, 3.9 Hz, 1H), 4.73 (br , 1H), 3.82 (br s, 1H), 3.70 – 3.55 (m, 2H), 3.09 (br s, 1H), 2.88 (br s, 1H), 2.32 – 2.04 (m, 1H), 1.78 – 1.43 (m, 2H), 1.04 (br, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{24}H_{24}ClN_2O_2$ 407.1521, found 407.1523.

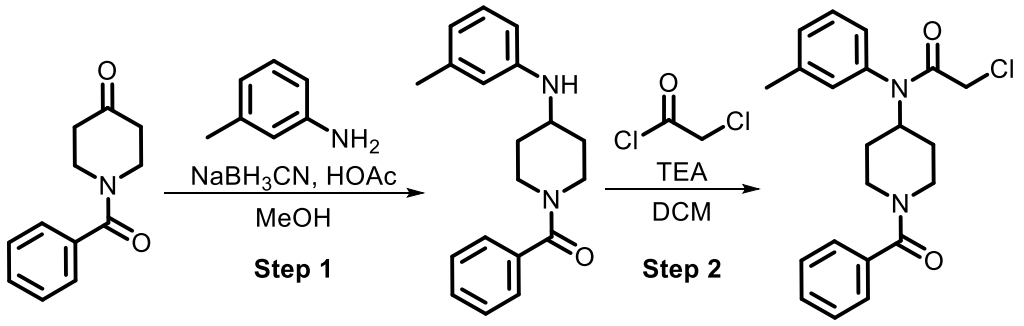


Step 1: Following **General Procedure 5**, starting with 1-benzoylpiperidin-4-one (300 mg, 1.5 mmol, 1.0 eq) and 2-methylaniline (1.2 eq) in MeOH, **SI-23** was obtained as a yellow oil and used without purification.

Step 2: Following **General Procedure 1**, starting with **SI-23** (1.0 eq), chloroacetyl chloride (3.0 eq), and TEA (6.0 eq), **EV-34** (43 mg, 10%) was obtained after prep-HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 5H), 7.32 – 7.23 (m, 3H), 7.05 (s, 1H), 4.71 (tt, *J* = 12.1, 3.9 Hz, 2H), 3.80 (br s, 1H), 3.64 (s, 2H), 3.10 (br s, 1H), 2.82 (br s, 1H), 2.24 (br s, 3H), 2.15 – 1.98 (m, 1H), 1.83 (br s, 1H), 1.64 – 1.42 (m, 1H), 1.35 – 1.11 (m, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{24}ClN_2O_2$ 371.1521, found 371.1520.

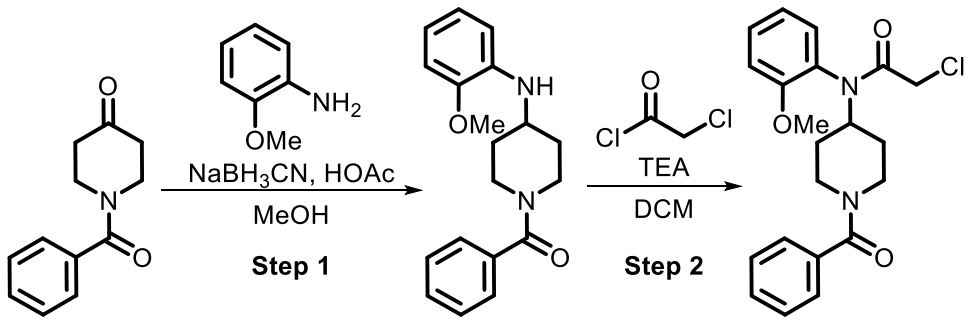


Step 1: Following **General Procedure 5**, starting with 1-benzoylpiperidin-4-one (300 mg, 1.5 mmol, 1.0 eq) and 3-methylaniline (1.2 eq) in MeOH, **SI-24** was obtained as a yellow oil and used without purification.

Step 2: Following **General Procedure 1**, starting with **SI-24** (1.0 eq), chloroacetyl chloride (3.0 eq), and TEA (6.0 eq), **EV-35** (71 mg, 16%) was obtained after prep-HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.15 (m, 7H), 6.83 (s, 2H), 4.79 – 4.66 (m, 2H), 3.70 (br s, 1H), 3.62 (s, 2H), 3.04 (br s, 1H), 2.79 (br s, 1H), 2.31 (s, 3H), 1.87 (br s, 1H), 1.73 (br s, 1H), 1.31 (br s, 1H), 1.18 – 1.09 (m, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{24}ClN_2O_2$ 371.1521, found 371.1522.

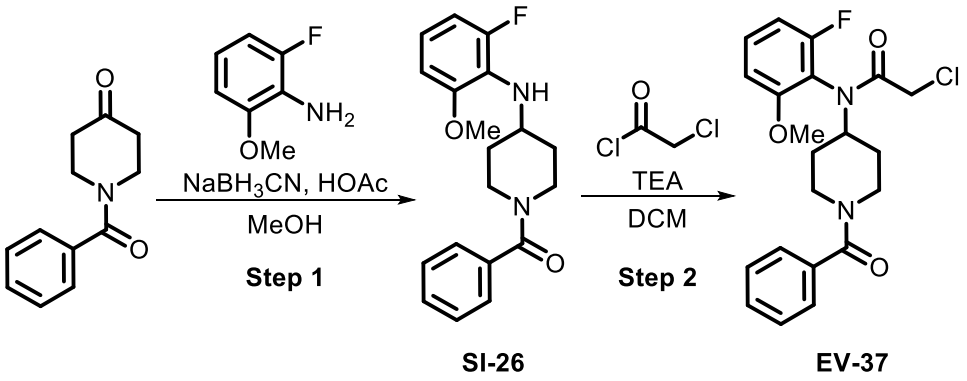


Step 1: Following **General Procedure 5**, starting with 1-benzoylpiperidin-4-one (300 mg, 1.5 mmol, 1.0 eq) and 2-methoxyaniline (1.2 eq) in MeOH, **SI-25** was obtained as a yellow oil and used without purification.

Step 2: Following **General Procedure 1**, starting with **SI-25** (1.0 eq), chloroacetyl chloride (3.0 eq), and TEA (6.0 eq), **EV-36** (400 mg, 86%) was obtained after prep-HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.34 (m, 4H), 7.33 – 7.28 (m, 2H), 7.07 (m, 3H), 4.86 – 4.74 (m, 2H), 3.82 (d, *J* = 17.1 Hz, 4H), 3.73 (d, *J* = 4.2 Hz, 2H), 3.15 (d, *J* = 13.7 Hz, 1H), 2.85 (d, *J* = 15.7 Hz, 1H), 2.11 – 1.79 (m, 2H), 1.60 – 1.00 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{24}ClN_2O_3$ 387.1470, found 387.1472.

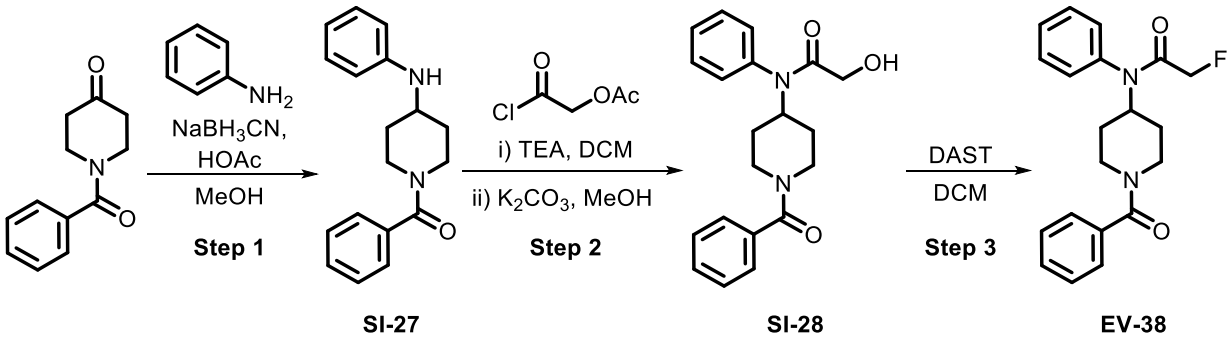


Step 1: Following **General Procedure 5**, starting with 1-benzoylpiperidin-4-one (300 mg, 1.5 mmol, 1.0 eq) and 2-fluoro-6-methoxyaniline (1.2 eq) in MeOH, **SI-26** was obtained as a yellow oil and used without purification.

Step 2: Following **General Procedure 1**, starting with **SI-26** (1.0 eq), chloroacetyl chloride (3.0 eq), and TEA (6.0 eq), **EV-37** (71 mg, 15%) was obtained after prep-HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 4H), 7.35 – 7.30 (m, 2H), 6.89 – 6.77 (m, 2H), 4.75 (br s, 2H), 3.90 – 3.78 (m, 4H), 3.73 (s, 2H), 3.14 (br s, 1H), 2.84 (br s, 1H), 1.98 (d, *J* = 12.7 Hz, 2H), 1.54 – 1.20 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{23}ClFN_2O_3$ 405.1376, found 405.1381.



Step 1: Following **General Procedure 5**, starting with 1-benzoylpiperidin-4-one (300 mg, 1.5 mmol, 1.0 eq) and aniline (1.2 eq) in MeOH, **SI-27** was obtained as a yellow oil and used without purification.

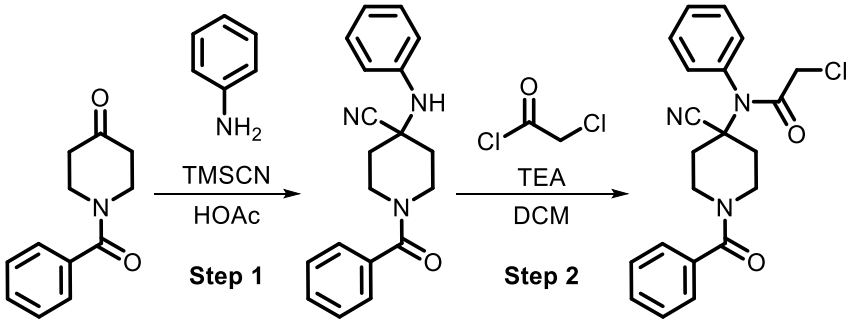
Step 2: Acetoxyacetyl chloride (115 µL, 1.1 mmol, 1.5 eq) was added to a solution of **SI-27** (200 mg, 0.71 mmol, 1.0 eq) and TEA (297 µL, 2.1 mmol, 3.0 eq) in DCM (3 mL). The reaction was stirred for 1 h before being diluted with DCM (15 mL). The mixture was washed with water (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting residue was dissolved in MeOH (5 mL), K_2CO_3 (196 mg, 1.4 mmol, 2.0 eq) was added, and the reaction was stirred for 1 h. The reaction was concentrated under reduced pressure and the residue was dissolved in water (10 mL) and DCM (15 mL). The aqueous phase was extracted with DCM (2 x 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to provide **SI-28** which was used without purification.

Step 3: DAST (47 µL, 0.35 mmol, 1.2 eq) was added to a solution of **SI-28** (100 mg, 0.30 mmol, 1.0 eq) in DCM (2 mL) at 0 °C. The reaction was warmed to 25 °C and stirred for 2 h. Upon completion, the reaction

mixture was diluted with DCM (15 mL) and washed with H_2O (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting residue was purified by prep-TLC (PE:EtOAc = 1:2) to provide **EV-38** (30 mg, 29%) as a white solid.

^{1}H NMR (400 MHz, MeOD) δ 7.55 – 7.50 (m, 3H), 7.46 – 7.39 (m, 3H), 7.32 – 7.25 (m, 4H), 4.80 (tt, *J* = 12.1, 3.9 Hz, 1H), 4.69 (br s, 1H), 4.60 (s, 1H), 4.48 (s, 1H), 3.74 (br s, 1H), 3.24 (br s, 1H), 2.93 (br s, 1H), 2.00 (br s, 1H), 1.86 (br s, 1H), 1.50 – 1.07 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{22}FN_2O_2$ 341.1660, found 341.1663.

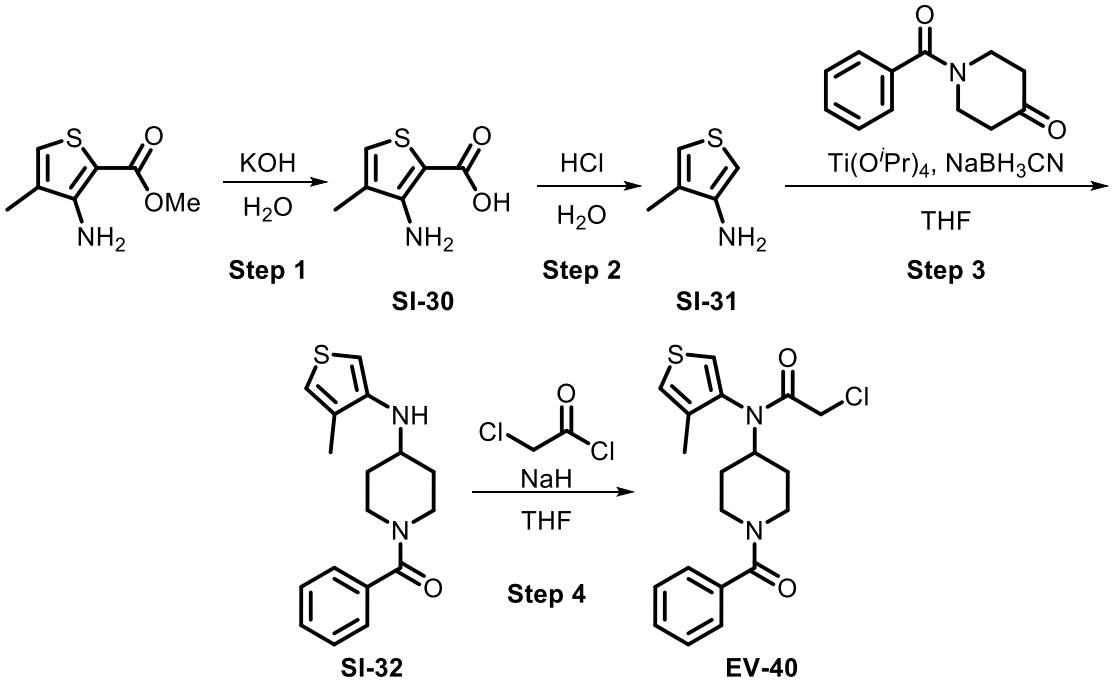


Step 1: TMSCN (107 mg, 1.1 mmol, 1.1 eq) was added dropwise to a solution of 1-benzoylpiperidin-4-one (200 mg, 0.98 mmol, 1.0 eq) and aniline (90 µL, 0.98 mmol, 1.0 eq) at 0 °C. The reaction was warmed to 25 °C and stirred for 3 h. The reaction was cooled to 0 °C and aqueous NH_4OH was added to the reaction until pH 10 and then extracted with DCM (3 x 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by flash chromatography (PE:EtOAc = 50:1-2:1) to provide **SI-29** (260 mg, 74%) as a yellow oil.

Step 2: Following **General Procedure 1**, starting with **SI-29** (260 mg, 0.85 mmol, 1.0 eq), chloroacetyl chloride (1.5 eq), and TEA (3.0 eq), **EV-39** was obtained after prep-TLC (PE:EtOAc = 1:1) as a light yellow solid (70 mg, 23%).

^{1}H NMR (400 MHz, MeOD) δ 7.59 – 7.54 (m, 3H), 7.48 – 7.37 (m, 7H), 4.71 (br s, 1H), 3.85 (s, 3H), 3.46 (br s, 1H), 3.15 (br s, 1H), 2.41 (dd, *J* = 13.4, 2.6 Hz, 2H), 1.68 (t, *J* = 12.2 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{21}ClN_3O_2$ 382.1317, found 382.1316.



Step 1: Methyl 3-amino-4-methylthiophene-2-carboxylate (1.0 g, 5.8 mmol, 1.0 eq) was added to a solution of KOH (459 mg, 8.2 mmol, 1.4 eq) in H_2O (3 mL) at 28 °C. The mixture was heated to 80 °C and stirred for 30 min. The mixture was not worked up and used directly in the next step.

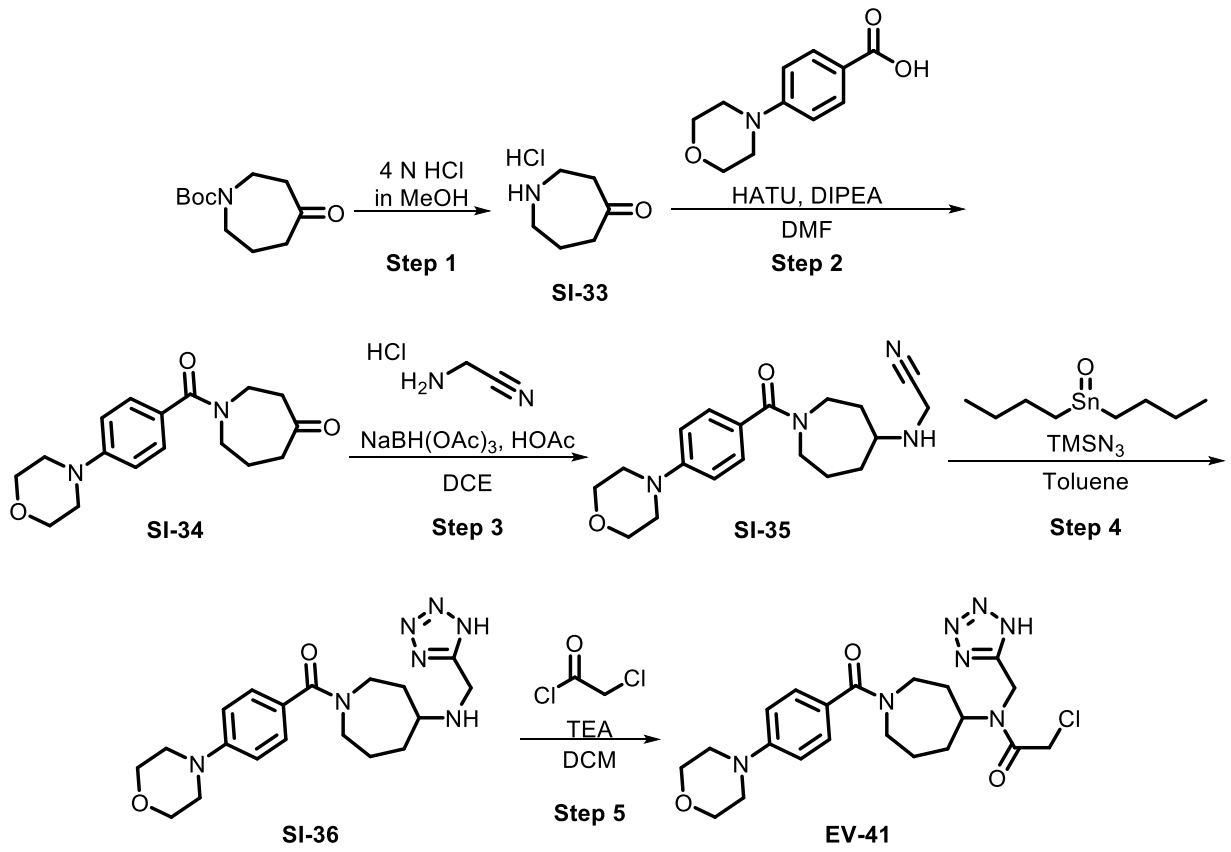
Step 2: The solution of **SI-30** (1.0 g, 5.1 mmol, 1.0 eq) in H_2O (3 mL) and HCl (6 M, 2.8 mL, 3.3 eq) was stirred at 50 °C for 16 h. The mixture was slowly poured into aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (10 mL x 2). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. **SI-31** (500 mg, crude) was obtained as brown liquid and used without purification.

Step 3: $Ti(O^iPr)_4$ (786 µL, 2.7 mmol, 1.5 eq) was added to a solution of 1-benzoylpiperidin-4-one (468 mg, 2.3 mmol, 1.3 eq) and **SI-31** (200 mg, 1.8 mmol, 1.0 eq) in THF (5 mL) and the mixture was stirred at 70 °C for 16 h. The reaction was cooled to 0 °C and $NaBH_3CN$ (167 mg, 2.7 mmol, 1.5 eq) was added. The mixture was stirred for an additional 1 h and then poured into aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (15 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by flash chromatography (PE:EtOAc = 15:1-3:1) to provide **SI-32** (200 mg, 25%) as yellow oil.

Step 4: NaH (68 mg, 1.7 mmol, 60% dispersion in mineral oil, 3.0 eq) was added to a solution of **SI-32** (170 mg, 0.57 mmol, 1.0 eq) in THF (3 mL) at 0 °C. The mixture was warmed to 28 °C and stirred for 0.5 h. The reaction was cooled to 0 °C and chloroacetyl chloride (90 µL, 1.1 mmol, 2.0 eq) was added. The mixture was warmed to 28 °C and stirred for an additional 1.5 h. The reaction was cooled to 0 °C and water (5 mL) was added. The mixture was extracted with EtOAc (5 mL x 3) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by prep-TLC (PE:EtOAc = 1:1) and then by prep-HPLC (HCl) to provide **EV-40** (24 mg, 11%) as a light yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.28 (m, 5H), 7.11 (br s, 2H), 4.76 (tt, *J* = 12.1, 4.0 Hz, 2H), 3.78 (br s, 1H), 3.76 – 3.62 (m, 2H), 3.13 (br s, 1H), 2.84 (br s, 1H), 2.10 (br s, 3H), 1.97 – 1.68 (m, 2H), 1.60 – 1.05 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{19}H_{22}ClN_2O_2S$ 377.1085, found 377.1086.



Step 1: A mixture of *tert*-butyl 4-oxoazepane-1-carboxylate (1.0 g, 4.7 mmol, 1.0 eq) in 4N HCl/MeOH (5.0 mL, 4.3 eq) was stirred at 15 °C for 2 h. The reaction mixture was concentrated under reduced pressure to afford **SI-33** (700 mg, crude) as a white solid which was used in the next step without purification.

Step 2: Following **General Procedure 3**, starting with **SI-33** (51 mg, 0.34 mmol, 1.0 eq) and 4-morpholinobenzoic acid (1.0 eq), **SI-34** was obtained as a yellow oil and used in the next step without purification.

Step 3: HOAc (642 µL, 11.2 mmol, 2.0 eq) and 2-aminoacetonitrile hydrochloride (2.9 g, 22.5 mmol, 4.0 eq) were added to a solution of **SI-34** (1.70 g, 5.6 mmol, 1.0 eq) in DCE (4 mL) and the mixture was stirred at 30 °C for 30 min. The reaction was cooled to 0 °C and $NaBH(OAc)_3$ (1.79 g, 8.4 mmol, 1.5 eq) was added portion-wise. The reaction was heated to 20 °C and stirred for 16 h. The mixture was quenched with H_2O (20 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by prep HPLC (TFA) to provide **SI-35** (560 mg, 1.6 mmol, 29%) as a colorless oil.

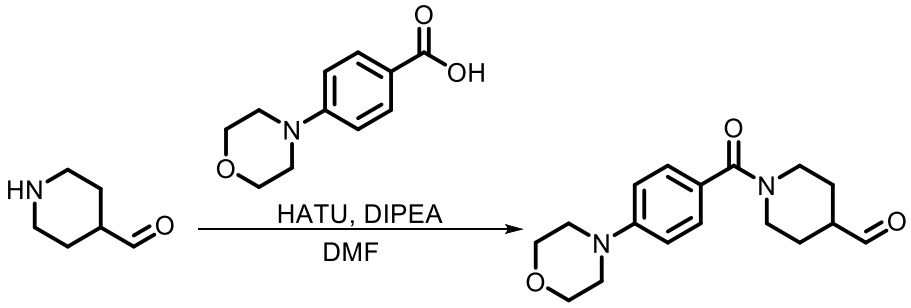
Step 4: Dibutyltin oxide (22 mg, 0.09 mmol, 0.2 eq) and azido(trimethyl)silane (233 µL, 1.8 mmol, 4.0 eq) were added to a solution of **SI-35** (150 mg, 0.44 mmol, 1.0 eq) in toluene (3 mL). The reaction mixture was stirred at 110 °C for 16 h. Toluene was removed and 1N NaOH (10 mL) was added to the resulting residue. The mixture was washed with DCM (10 mL). The aqueous phase was concentrated and the remaining residue was purified by prep-HPLC (basic) to provide **SI-36** (50 mg, 30%) as a light yellow solid.

Step 5: Following **General Procedure 1**, starting with **SI-36** (20 mg, 0.06 mmol, 1.0 eq), chloroacetyl chloride (1.0 eq), and TEA (3.0 eq), **EV-41** was obtained after prep-HPLC (HCl) as a colorless oil (7 mg, 56%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 – 7.20 (m, 2H), 7.00 (d, *J* = 8.2 Hz, 2H), 4.93 – 4.62 (m, 2H), 4.59 – 4.33 (m, 2H), 4.13 (s, 1H), 3.73 (t, *J* = 4.8 Hz, 5H), 3.58 – 3.42 (m, 1H), 3.38 – 3.21 (m, 2H), 3.17 (t, *J* = 4.8 Hz, 4H), 2.09 – 1.81 (m, 3H), 1.79 – 1.45 (m, 3H).

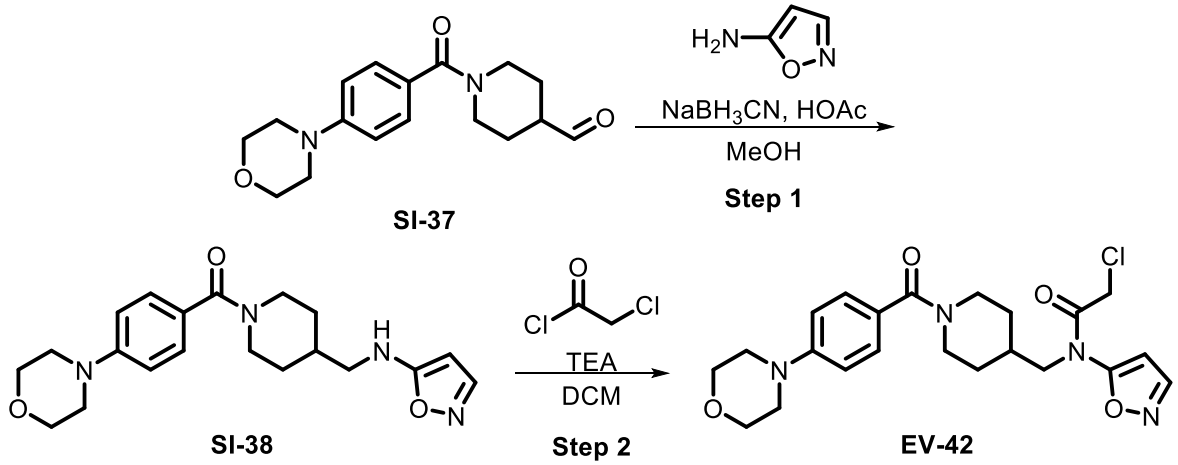
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{29}ClN_7O_3$ 462.2015, found 462.2017.

Synthesis of SI-37 as a precursor for EV-42 and EV-43



SI-37

Following **General Procedure 3**, starting with piperidine-4-carboxaldehyde (2.0 g, 13.4 mmol, 1.0 eq) and 4-morpholinobenzoic acid (1.1 eq), **SI-37** was obtained after prep-HPLC (TFA) as a yellow oil (1.15 g, 20%).



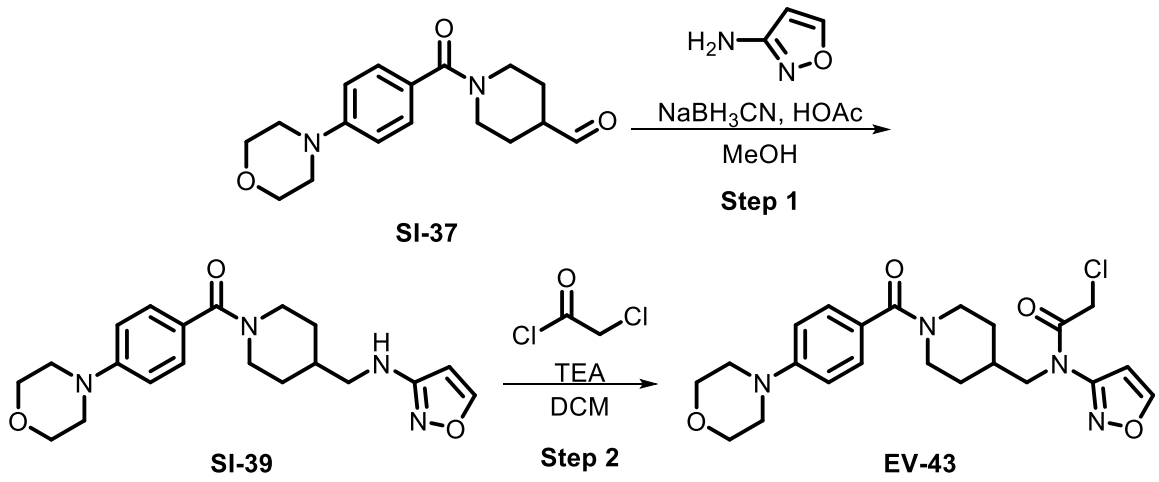
SI-37 **SI-38** **EV-42**

Step 1: Following **General Procedure 5**, starting with **SI-37** (40 mg, 0.13 mmol, 1.0 eq) and isoxazol-5-amine (1.1 eq), **SI-38** (30 mg, 45%) was obtained after purification by prep-TLC (EtOAc:MeOH = 10:1).

Step 2: Following **General Procedure 1**, starting with **SI-38** (30 mg, 0.08 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (4.0 eq), **EV-42** was obtained after prep-HPLC (HCl) as a colorless oil (13 mg, 29%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, *J* = 1.9 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.04 – 6.94 (m, 2H), 6.57 (d, *J* = 1.9 Hz, 1H), 4.47 (br s, 2H), 3.76 – 3.71 (m, 5H), 3.68 (d, *J* = 7.3 Hz, 2H), 3.21 – 3.13 (m, 5H), 2.82 (br s, 2H), 1.90 – 1.80 (m, 1H), 1.61 (d, *J* = 12.5 Hz, 2H), 1.26 – 0.96 (m, 3H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{22}H_{28}ClN_4O_4$ 447.1794, found 447.1796.



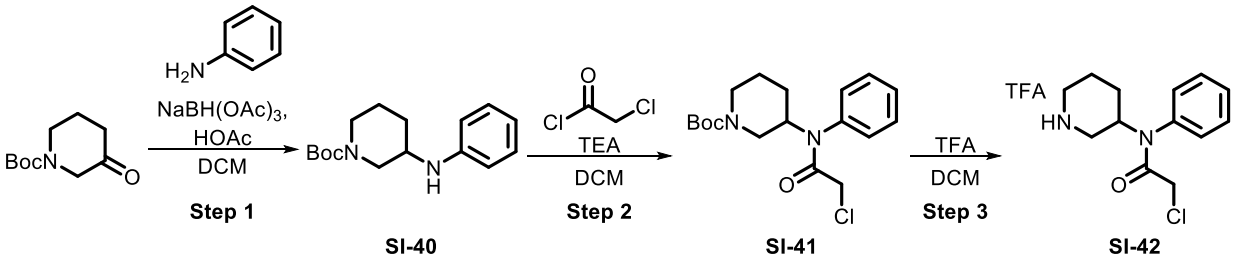
Step 1: Following **General Procedure 5**, starting with **SI-37** (30 mg, 0.1 mmol, 1.0 eq) and isoxazol-5-amine (1.1 eq), **SI-39** (13 mg, 29%) was obtained after purification by flash chromatography (DCM:MeOH = 100:1 – 10:1).

Step 2: Following **General Procedure 1**, starting with **SI-39** (30 mg, 0.08 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (4.0 eq), **EV-43** was obtained after prep-HPLC (HCl) as a colorless oil (13 mg, 29%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 1.7 Hz, 1H), 4.52 (s, 2H), 3.77 (t, *J* = 4.8 Hz, 6H), 3.71 (d, *J* = 7.3 Hz, 2H), 3.21 (t, *J* = 4.8 Hz, 4H), 2.80 (br s, 2H), 1.87 (br s, 1H), 1.59 (d, *J* = 12.6 Hz, 2H), 1.28-1.02 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{22}H_{28}ClN_4O_4$ 447.1794, found 447.1796.

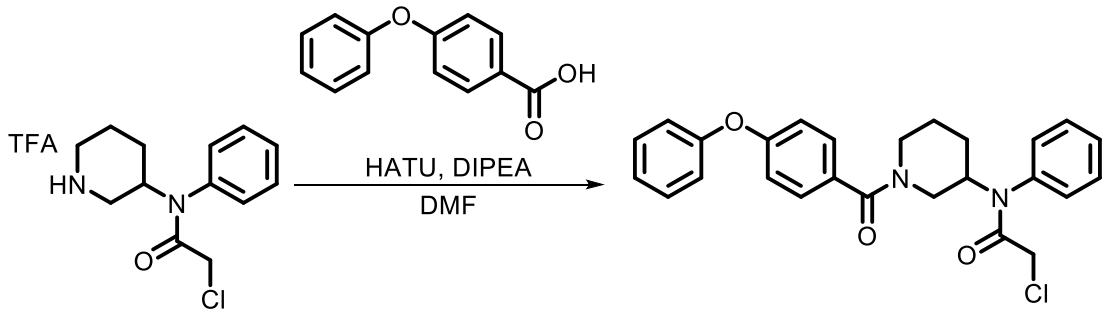
Synthesis of SI-42 as a precursor for EV-44 and EV-45



Step 1: A solution of HOAc (2.9 mL, 50.2 mmol, 1.0 eq) , aniline (4.6 mL, 50.2 mmol, 1.0 eq) and 1-Boc-3-piperidone (10.0 g, 50.2 mmol, 1.0 eq) in anhydrous DCM (150 mL) was stirred at 25 °C for 16 h. $NaBH(OAc)_3$ (21.3 g, 100 mmol, 2.0 eq) was then added and the reaction was stirred for an additional 3 h. The reaction mixture was quenched with aq. $NaHCO_3$ (50 mL), washed with saturated brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. **SI-40** was obtained as yellow oil which was used without purification.

Step 2: Following **General Procedure 1**, starting with **SI-40** (1.0 eq), chloroacetyl chloride (1.5 eq), and TEA (3.0 eq), **SI-41** was obtained and used in the next step without additional purification.

Step 3: TFA (1.5 mL, 20.4 mmol, 3.0 eq) was added dropwise to a solution of **SI-41** (2.4 g, 6.80 mmol, 1.0 eq) in DCM (2 mL) at 0 °C. The mixture was then warmed to 25 °C and stirred for 2 h. The solution was quenched with H_2O (2 mL) and extracted with DCM (2 mL x 3), the combined organic layers were washed with brine (2 mL x 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to provide **SI-42** (1.3 g, crude) as a yellow oil which was used without purification.

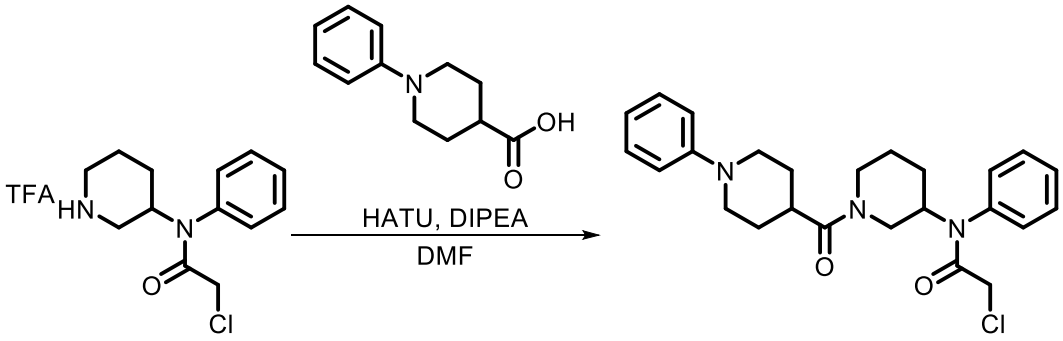


SI-42 **EV-44**

Following **General Procedure 3**, starting with **SI-42** (248 mg, 0.98 mmol, 1.2 eq) and 4-phenoxybenzoic acid (1.0 eq), **EV-44** (29 mg, 29%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (s, 3H), 7.43 (t, *J* = 7.8 Hz, 4H), 7.40 – 7.24 (m, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 4.43 (s, 2H), 3.83 (s, 2H), 3.55 (br s, 1H), 2.89 – 2.53 (m, 2H), 1.88 (br s, 1H), 1.74 – 1.42 (m, 2H), 1.31 – 1.00 (m, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{26}H_{26}ClN_2O_3$ 449.1627, found 449.1626.

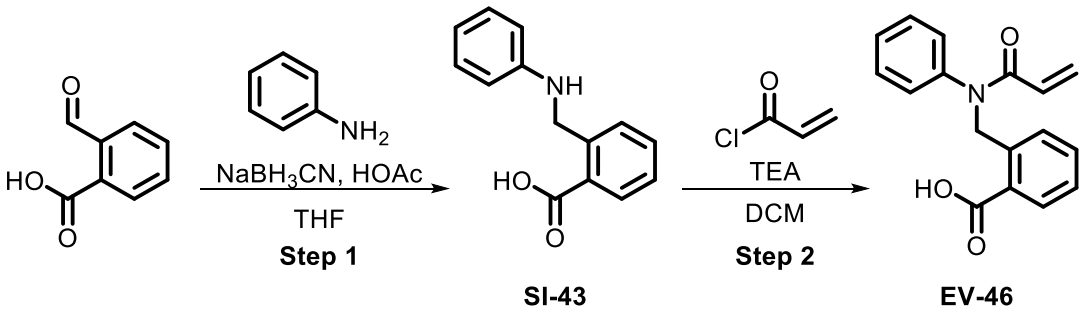


SI-42 **EV-45**

Following **General Procedure 3**, starting with **SI-42** (248 mg, 0.98 mmol, 1.2 eq) and 1-phenylpiperidine-4-carboxylic acid (1.0 eq), **EV-45** (71 mg, 17%) was obtained after prep-HPLC (HCl).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 – 7.46 (m, 3H), 7.44 – 7.31 (m, 2H), 7.19 (q, *J* = 7.2 Hz, 2H), 6.93 (dd, *J* = 14.5, 8.1 Hz, 2H), 6.74 (q, *J* = 6.8 Hz, 1H), 4.38 – 4.18 (m, 2H), 3.96 – 3.60 (m, 5H), 2.88 – 2.63 (m, 4H), 2.21 (t, *J* = 11.9 Hz, 1H), 2.00 – 1.77 (m, 2H), 1.74 – 1.56 (m, 4H), 1.53 – 1.25 (m, 1H), 1.23 – 0.95 (m, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{25}C_{31}ClN_3O_2$ 440.2100, found 440.2104.

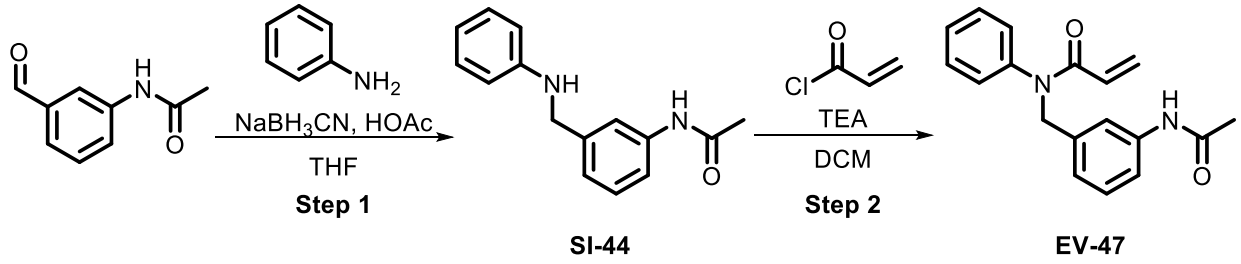


Step 1: Following **General Procedure 5**, starting with 2-formylbenzoic acid (100 mg, 0.67 mmol, 1.0 eq) and aniline (1.0 eq), **SI-43** was obtained as a crude product and used in the next step without purification.

Step 2: Following **General Procedure 2**, starting with **SI-43** (190 mg, 0.66 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (3.0 eq), **EV-46** was obtained after prep-HPLC (FA) as a yellow solid (49 mg, 26%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.45 (m, 2H), 7.39 – 7.24 (m, 4H), 7.19 – 7.13 (m, 2H), 6.44 (dd, *J* = 16.8, 2.0 Hz, 1H), 6.14 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.59 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.42 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{17}H_{16}NO_3$ 282.1125, found 282.1127.

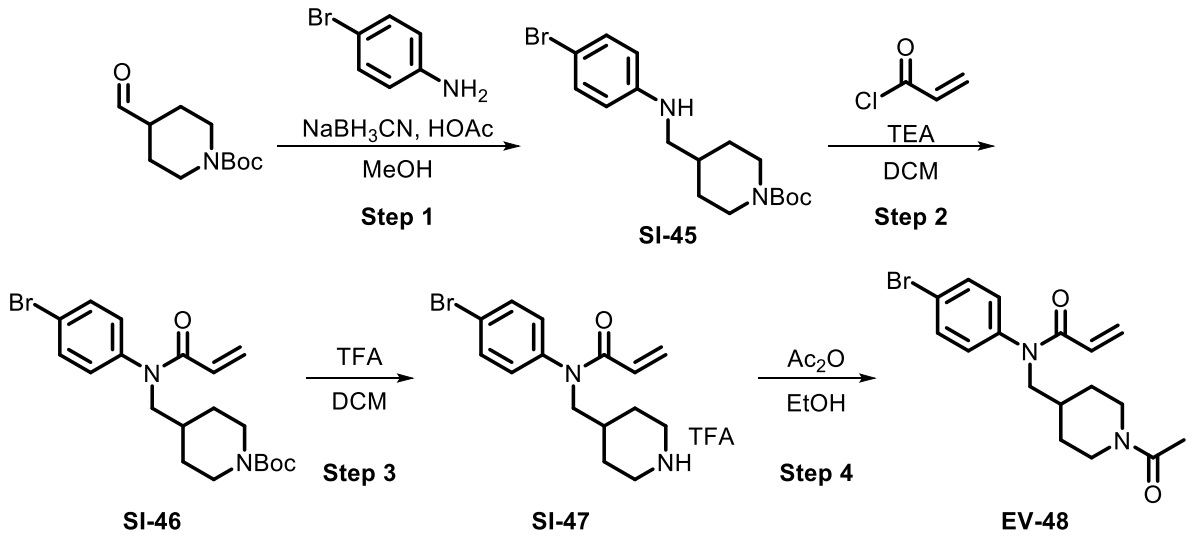


Step 1: Following **General Procedure 5**, starting with *N*-(3-formylphenyl)acetamide (100 mg, 0.61 mmol, 1.0 eq), and aniline (1.0 eq), **SI-44** was obtained as a crude product and used in the next step without purification.

Step 2: Following **General Procedure 2**, starting with **SI-44** (1.0 eq), acryloyl chloride (2.0 eq), and TEA (3.0 eq), **EV-47** (86 mg, 48%) was obtained after prep-HPLC (FA).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.40 (br s, 1H), 7.36 – 7.28 (m, 4H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 6.4 Hz, 2H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.41 (dd, *J* = 16.8, 2.0 Hz, 1H), 6.05 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.55 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.94 (s, 2H), 2.13 (s, 3H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{18}H_{19}N_2O_2$ 295.1441, found 295.1442.



Step 1: Following **General Procedure 5**, starting with *tert*-butyl 4-formylpiperidine-1-carboxylate (130 mg, 0.61 mmol, 1.0 eq) and 4-bromoaniline (1.0 eq), **SI-45** (220 mg, crude) was obtained as a crude product and used in the next step without purification

Step 2: Following **General Procedure 2**, starting with **SI-45** (220 mg, 0.60 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (3.0 eq), **SI-46** (250 mg, crude) was obtained as a crude product and used in the next step without purification.

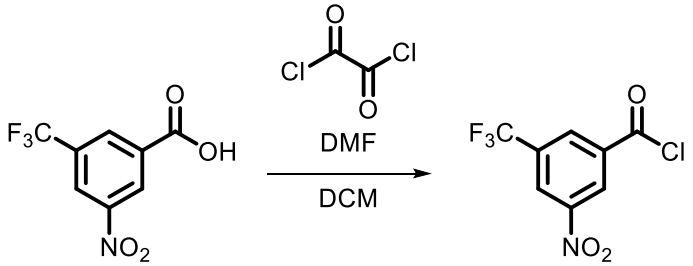
Step 3: TFA (452 µL, 5.9 mmol, 10.0 eq) was added to a solution of **SI-46** (250 mg, 0.59 mmol, 1.0 eq) in DCM (2 mL). The mixture was stirred at 15 °C for 16 h. The reaction mixture was concentrated under reduced pressure to afford **SI-47** (250 mg, crude) as a yellow oil which was used without purification.

Step 4: Ac_2O (108 µL, 1.1 mmol, 2.0 eq) was added to a solution of **SI-47** (250 mg, 0.57 mmol, 1.00 eq) in EtOH (4 mL) at room temperature. The mixture was heated to 60 °C and stirred for 3 h. The reaction mixture was purified by prep. HPLC (basic). The eluent was evaporated to remove organic solvents followed by lyophilization to afford **EV-48** (25 mg, 12%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2H), 7.09 – 7.00 (m, 2H), 6.37 (dd, *J* = 16.7, 1.9 Hz, 1H), 6.00 (dd, *J* = 16.7, 10.3 Hz, 1H), 5.56 (dd, *J* = 10.3, 1.9 Hz, 1H), 4.60 – 4.49 (m, 1H), 3.88 – 3.74 (m, 2H), 3.55 (dd, *J* = 13.5, 6.6 Hz, 1H), 3.03 – 2.91 (m, 1H), 2.51 (td, *J* = 12.8, 3.0 Hz, 1H), 2.05 (s, 3H), 1.92 – 1.78 (m, 1H), 1.77 – 1.70 (m, 1H), 1.65 – 1.60 (m, 1H), 1.33 – 1.08 (m, 2H).

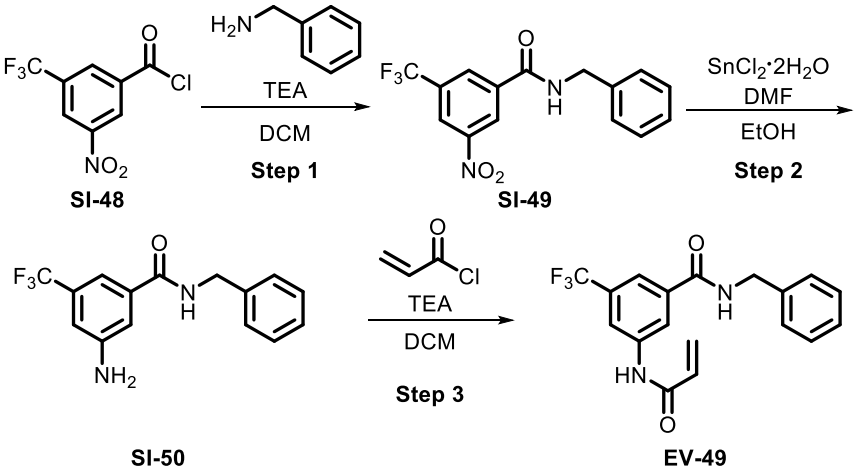
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{17}H_{22}BrN_2O_2$ 365.0859, found 365.0861.

Synthesis of SI-48 as a precursor for EV-49 – EV-52



SI-48

Oxalyl chloride (93 µL, 1.1 mmol, 1.3 eq) and DMF (50 µL) were added to a solution of 3-nitro-5-(trifluoromethyl)benzoic acid (200 mg, 0.85 mmol, 1.0 eq) in DCM (2 mL). The mixture was stirred at 40 °C for 3 h. The reaction mixture was concentrated under reduced pressure to afford **SI-48** (250 mg, crude) as a light yellow oil, which was used without purification.



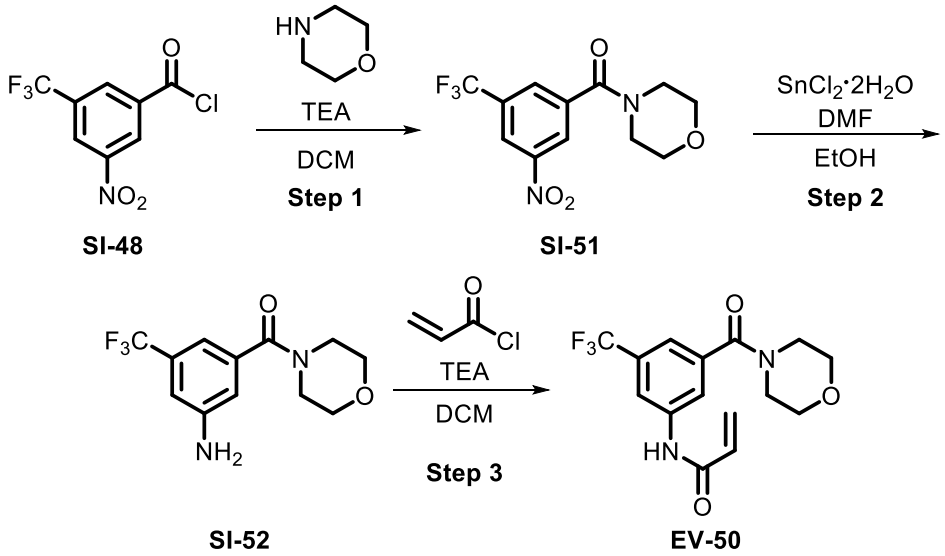
Step 1: Following **General Procedure 4**, starting with **SI-48** (60 mg, 0.24 mmol, 1.0 eq), benzylamine (1.0 eq), and TEA (3.0 eq), **SI-49** (80 mg, crude) was obtained as crude product and used without purification.

Step 2: $SnCl_2 \cdot 2H_2O$ (223 mg, 1.0 mmol, 4.0 eq) and DMF (1 mol %) were added to a solution of **SI-49** (80 mg, 0.25 mmol, 1.0 eq) in EtOH (1 mL). The mixture was heated to 80 °C and stirred for 2 h. The reaction was then cooled, sat. aqueous $NaHCO_3$ (2 mL) was added, and the reaction was stirred for 5 min. The mixture was extracted with DCM (2 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to afford **SI-50** (90 mg, crude) as light yellow oil.

Step 3: Following **General Procedure 2**, starting with **SI-50** (90 mg, 0.31 mmol, 1.0 eq), acryloyl chloride (0.8 eq), and DMF (1 mol %), **EV-49** was obtained as a white solid (22 mg, 21%) after prep-HPLC (FA).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 9.31 (t, *J* = 5.9 Hz, 1H), 8.35 (d, *J* = 10.8 Hz, 2H), 7.96 (s, 1H), 7.37 – 7.31 (m, 4H), 7.31 – 7.21 (m, 1H), 6.50 – 6.26 (m, 2H), 5.84 (dd, *J* = 9.9, 2.1 Hz, 1H), 4.50 (d, *J* = 5.8 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{18}H_{16}F_3N_2O_2$ 349.1159, found 349.1161.



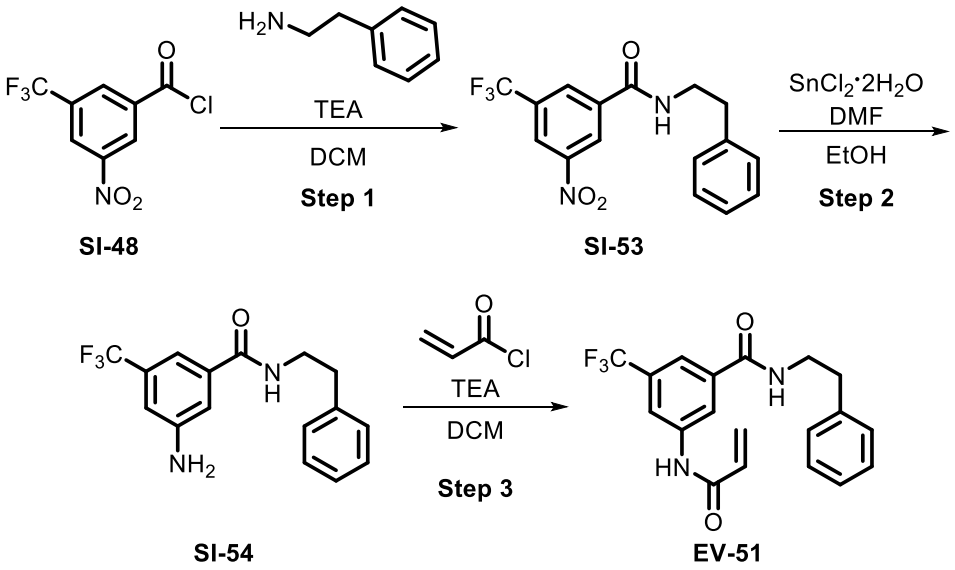
Step 1: Following **General Procedure 4**, starting with **SI-48** (60 mg, 0.24 mmol, 1.0 eq), benzylamine (1.0 eq), and TEA (3.0 eq), **SI-51** (80 mg, crude) was obtained as crude product and used without purification.

Step 2: $SnCl_2 \cdot 2H_2O$ (237 mg, 1.1 mmol, 4.0 eq) and DMF (1 mol %) were added to a solution of **SI-51** (80 mg, 0.26 mmol, 1.0 eq) in EtOH (1 mL). The mixture was stirred at 80 °C for 2 h. The reaction was cooled, sat. aqueous $NaHCO_3$ (2 mL) was added, and the mixture was stirred for 5 min. The reaction mixture was extracted with DCM (2 mL x 3) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to afford **SI-52** (90 mg, crude) as a light yellow oil.

Step 3: Following **General Procedure 2**, starting with **SI-52** (90 mg, 0.31 mmol, 1.0 eq), acryloyl chloride (0.8 eq), and DMF (1 mol %), **EV-50** was obtained as a white solid (22 mg, 25%) after prep-HPLC (FA)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.85 (s, 1H), 7.43 (s, 1H), 6.44 – 6.26 (m, 2H), 5.83 (dd, *J* = 9.7, 2.0 Hz, 1H), 3.65 – 3.59 (m, 4H), 3.52 (br s, 2H), 3.30 (br s, 2H)

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{15}H_{16}F_3N_2O_3$ 329.1108, found 329.1107.



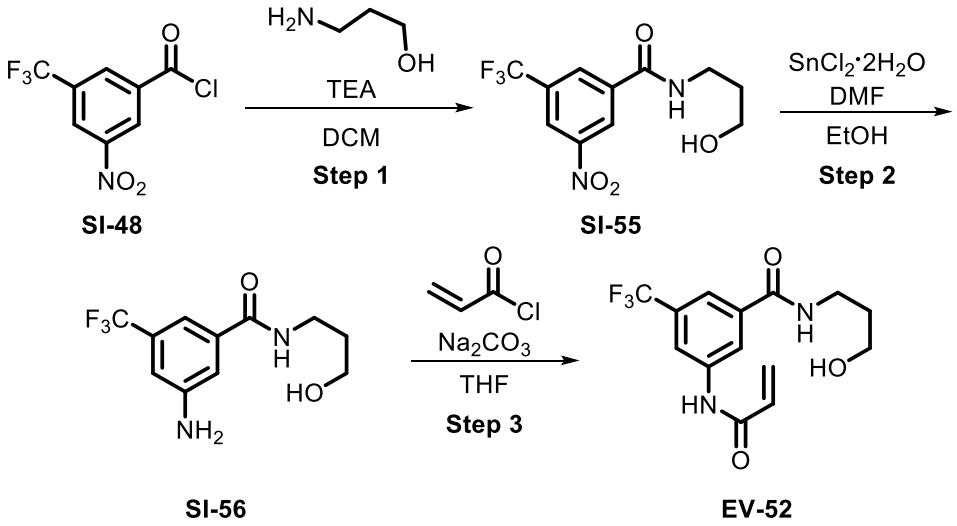
Step 1: Following **General Procedure 4**, starting with **SI-48** (60 mg, 0.24 mmol, 1.0 eq), phenethylamine (1.0 eq), and TEA (3.0 eq), **SI-53** (80 mg, crude) was obtained as crude product and used without purification.

Step 2: $SnCl_2 \cdot 2H_2O$ (213 mg, 0.95 mmol, 4.0 eq) and DMF (1 mol %) were added to a solution of **SI-53** (80 mg, 0.24 mmol, 1.0 eq) in EtOH (1 mL). The mixture was stirred at 80 °C for 2 h. The reaction was cooled to rt, sat. aqueous $NaHCO_3$ (2 mL) was added, and the mixture was stirred for 5 min. The mixture was extracted with DCM (2 mL x 3), the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to afford **SI-54** (90 mg, crude) as light yellow oil.

Step 3: Following **General Procedure 2**, starting with **SI-54** (90 mg, 0.31 mmol, 1.0 eq), acryloyl chloride (0.8 eq), and DMF (1 mol %), **EV-51** was obtained after prep-HPLC (FA) as a white solid (22 mg, 17%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 8.84 (t, *J* = 5.6 Hz, 1H), 8.31 (d, *J* = 20.2 Hz, 2H), 7.86 (s, 1H), 7.34 – 7.15 (m, 5H), 6.50 – 6.28 (m, 2H), 5.84 (dd, *J* = 9.9, 2.1 Hz, 1H), 3.50 (q, *J* = 6.8 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{19}H_{18}F_3N_2O_2$ 363.1315, found 363.1317.



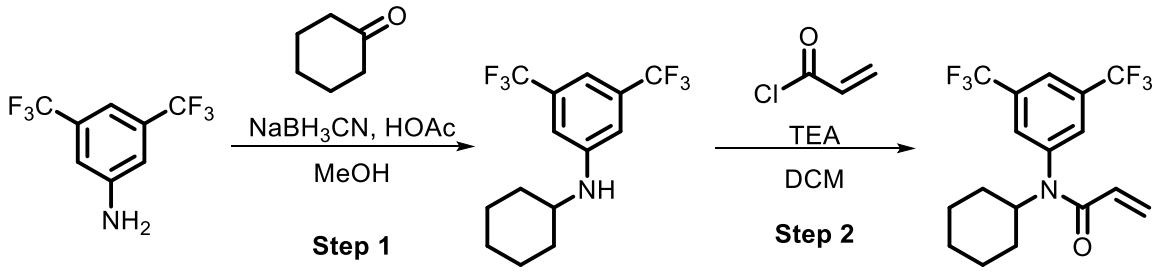
Step 1: Following **General Procedure 4**, starting with **SI-48** (215 mg, 0.85 mmol, 1.0 eq), phenethylamine (1.0 eq), and TEA (3.0 eq), **SI-55** (200 mg, crude) was obtained as crude product and used without purification.

Step 2: $SnCl_2 \cdot 2H_2O$ (247 mg, 1.1 mmol, 4.0 eq) and DMF (1 mol %) were added to a solution of **SI-56** (80 mg, 0.27 mmol, 1.0 eq) in EtOH (1.00 mL) at 25 °C. Following the addition, the mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched with H_2O (1 mL) and saturated $NaHCO_3$ (2 mL). The mixture was then extracted with DCM (2 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to provide **SI-56** (70 mg, 85%) as a yellow oil.

Step 3: A solution of Na_2CO_3 (28 mg, 0.27 mmol, 2.0 eq) in H_2O (0.2 mL) was added to a solution of **SI-56** (35 mg, 0.13 mmol, 1.0 eq) in THF (0.4 mL) in one portion. The mixture was cooled to 10 °C and acryloyl chloride (12 µL, 0.15 mmol, 1.1 eq) was added. Following the addition, the mixture was warmed to 25 °C and stirred for 16 h. The reaction mixture was quenched with H_2O (2 mL) and extracted with DCM (2 ml x 4). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was diluted with MeCN (2 mL) and purified by prep-HPLC (FA) to afford **EV-52** (15 mg, 35%) as colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 8.72 (t, *J* = 5.5 Hz, 1H), 8.32 (d, *J* = 20.8 Hz, 2H), 7.89 (s, 1H), 6.50 – 6.28 (m, 2H), 5.83 (dd, *J* = 9.8, 2.0 Hz, 1H), 4.50 (br s, 1H), 3.47 (t, *J* = 6.3 Hz, 2H), 3.33 (d, *J* = 6.7 Hz, 2H), 1.69 (p, *J* = 6.7 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{14}H_{16}F_3N_2O_3$ 317.1108, found 317.1109.



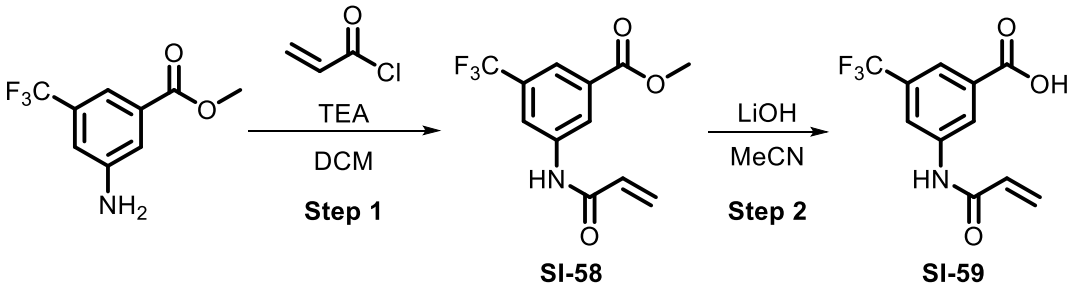
Step 1: Following **General Procedure 5**, starting with 3,5-bis(trifluoromethyl)aniline (200 mg, 0.87 mmol, 1.0 eq) and cyclohexanone (1.0 eq), **SI-57** (77 mg, 28%) was obtained as a white solid.

Step 2: Following **General Procedure 2**, starting with **SI-57** (77 mg, 0.25 mmol, 1.0 eq), acryloyl chloride (3.0 eq), and TEA (3.0 eq), **EV-53** was obtained after prep-HPLC (FA) as a white solid (45 mg, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.55 (s, 2H), 6.40 (dd, *J* = 16.5, 2.0 Hz, 1H), 5.69 (s, 1H), 5.56 (dd, *J* = 10.4, 2.1 Hz, 1H), 4.67 (s, 1H), 1.89 (d, *J* = 11.9 Hz, 2H), 1.79 (d, *J* = 13.6 Hz, 2H), 1.62 (d, *J* = 15.5 Hz, 1H), 1.43 (q, *J* = 14.0, 12.0 Hz, 2H), 1.08 – 0.86 (m, 3H).

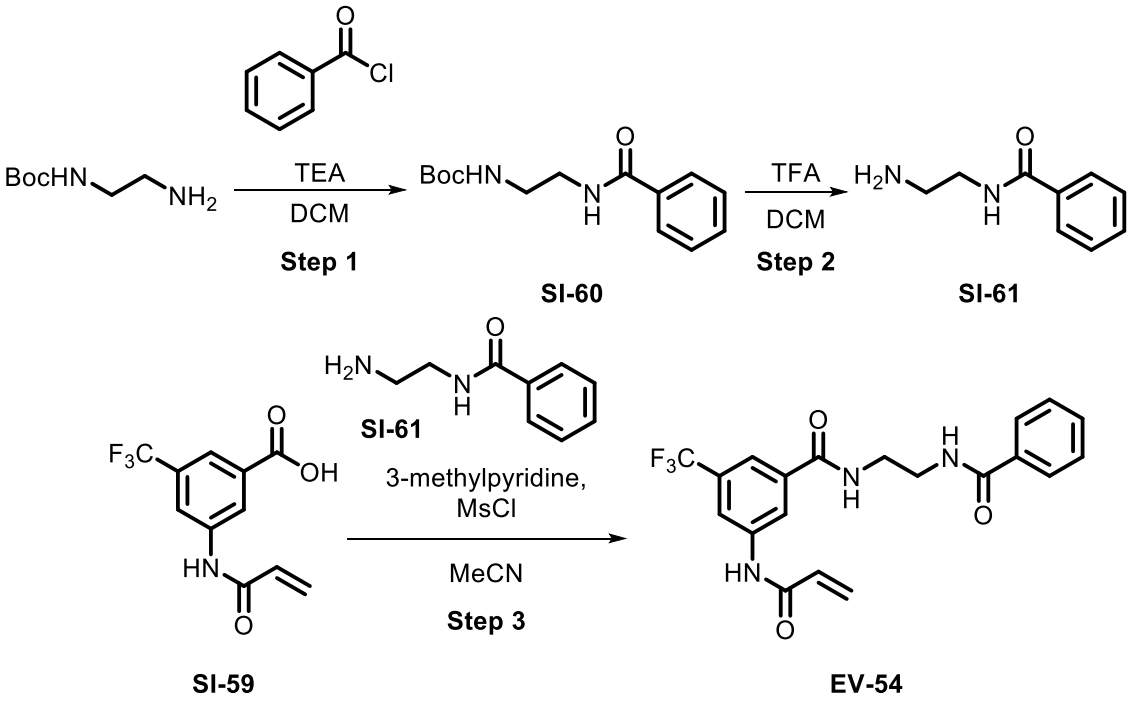
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{17}H_{18}F_6NO$ 366.1287, found 366.1288.

Synthesis of SI-58 as a precursor for EV-54 – EV-60



Step 1: Following **General Procedure 2**, starting with methyl 3-amino-5-(trifluoromethyl)benzoate (1.0 g, 4.6 mmol, 1.0 eq), acryloyl chloride (1.2 eq), and TEA (3.0 eq), **SI-58** was obtained after flash chromatography as a yellow oil (2.8 g, 56%).

Step 2: A solution of LiOH (210 mg, 8.8 mmol, 1.2 eq) in H_2O (5 mL) was added to a solution of **SI-58** (2.0 g, 7.3 mmol, 1.0 eq) in MeCN (15 mL) and stirred at 25 °C for 3 h. The reaction mixture was concentrated and the pH was adjusted to pH 3 with citric acid. The precipitate was collected by filtration to provide **SI-59** (1.0 g, 53%) as a light yellow solid. **SI-59** was used without purification.



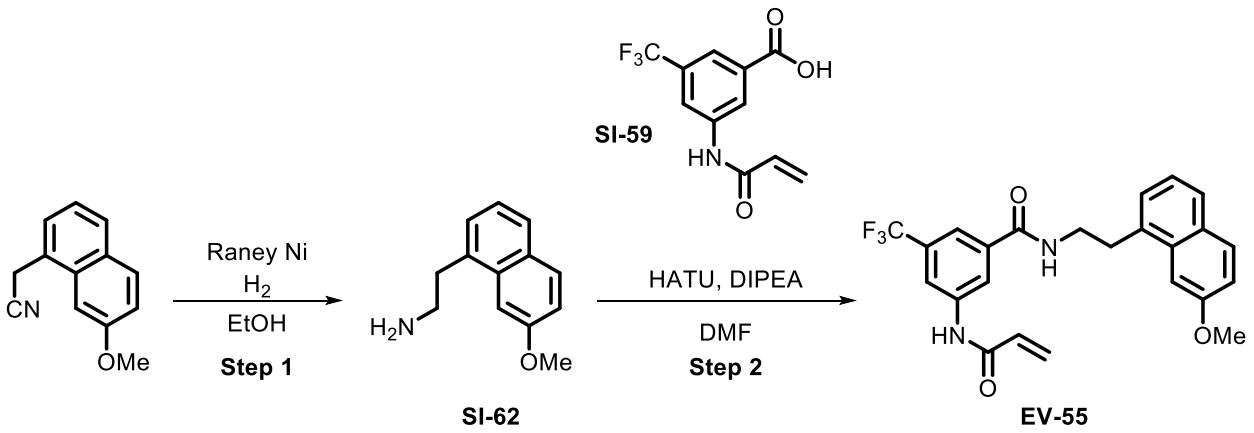
Step 1: Following **General Procedure 4**, starting with *tert*-butyl *N*-(2-aminoethyl)carbamate (2.0 g, 12.5 mmol, 1.0 eq) and benzoyl chloride (1.5 eq), **SI-60** was obtained as a crude product and used in the next step without purification.

Step 2: TFA (3.6 mL, 49.2 mmol, 5.0 eq) was added to a solution of **SI-60** (2.6 g, 9.8 mmol, 1.0 eq) in DCM (10 mL) and the reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with aqueous $NaHCO_3$ (20 mL) and extracted with DCM (5 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **SI-61** (1.20 g, crude) as a yellow oil which was used for the synthesis of **EV-54** without purification.

Step 3: MsCl (36 µL, 0.46 mmol, 1.2 eq) was added to a solution of **SI-59** (100 mg, 0.62 mmol, 1.0 eq), **SI-61** (70 mg, 0.42 mmol, 1.1 eq), and 3-methylpyridine (112 µL, 1.2 mmol, 3.0 eq) in MeCN (2 mL) and the resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with H_2O (5 mL) and extracted with DCM (5 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (basic) to provide **EV-54** (90 mg, 56%) as a white solid.

^{1}H NMR (400 MHz, MeOD) δ 8.25 (d, *J* = 1.6 Hz, 2H), 7.87 – 7.79 (m, 3H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.48 – 7.42 (m, 2H), 6.47 – 6.40 (m, 2H), 5.84 (dd, *J* = 6.7, 5.1 Hz, 1H), 4.59 (br s, 1H), 3.64 (s, 4H), 3.48 (t, *J* = 1.7 Hz, 1H), 3.13 (t, *J* = 1.7 Hz, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{19}F_3N_3O_3$ 406.1373, found 406.1375.

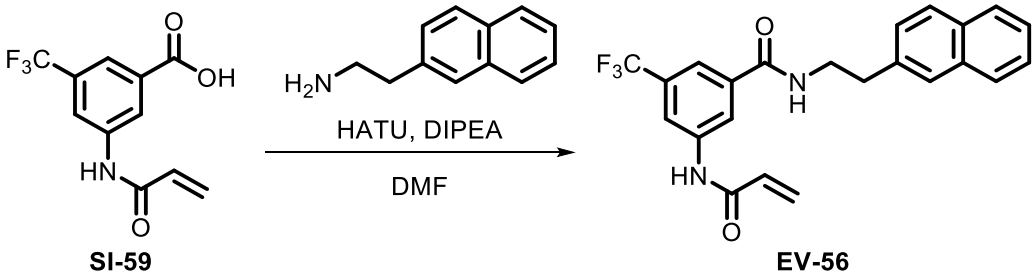


Step 1: Raney-Ni (20 mg, 0.23 mmol, 0.2 eq) was added to a solution of 7-methoxy-1-naphthylacetonitrile (200 mg, 1.0 mmol, 1.0 eq) and $NH_3 \cdot H_2O$ (500 µL) in EtOH (2 mL). The reaction vessel was evacuated and backfilled with H_2 (3x). The reaction was stirred for 16 h at 45 psi H_2 at 60 °C. The mixture was filtered and the filtrate was concentrated to provide **SI-62** (200 mg, crude) as a colorless oil. **SI-62** was used for the synthesis of **EV-55** without purification.

Step 2: Following **General Procedure 3**, starting with **SI-59** (100 mg, 0.39 mmol, 1.0 eq) and **SI-62** (1.1 eq), **EV-55** was obtained as a white solid (42 mg, 24%).

^{1}H NMR (400 MHz, MeOD) δ 8.24 (d, *J* = 7.2 Hz, 2H), 7.80 – 7.71 (m, 2H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.60 (s, 1H), 7.36 (d, *J* = 6.8 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.12 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.43 (d, *J* = 6.6 Hz, 2H), 5.88 – 5.80 (m, 1H), 3.95 (s, 3H), 3.72 (t, *J* = 7.9 Hz, 2H), 3.37 (t, *J* = 7.3 Hz, 2H).

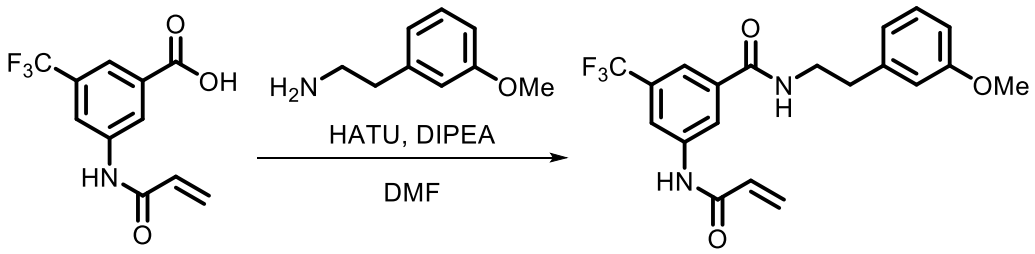
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{24}H_{22}F_3N_2O_3$ 443.1577, found 443.1579.



Following **General Procedure 3**, starting with **SI-59** (50 mg, 0.19 mmol, 1.0 eq) and 2-(naphthalen-2-yl)ethan-1-amine (1.0 eq), **EV-56** was obtained after prep-HPLC (basic) as a white solid (5 mg, 6%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.06 (s, 1H), 7.93 (s, 1H), 7.86 – 7.77 (m, 3H), 7.66 (d, *J* = 20.1 Hz, 2H), 7.52 – 7.42 (m, 2H), 7.38 (d, *J* = 8.1 Hz, 1H), 6.48 (d, *J* = 16.8 Hz, 1H), 6.41 – 6.33 (m, 1H), 6.30 (dd, *J* = 16.8, 10.2 Hz, 1H), 5.83 (d, *J* = 10.2 Hz, 1H), 3.80 (q, *J* = 6.7 Hz, 2H), 3.11 (t, *J* = 7.0 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{23}H_{19}F_3N_2O_2$ 413.1472, found 413.1470.

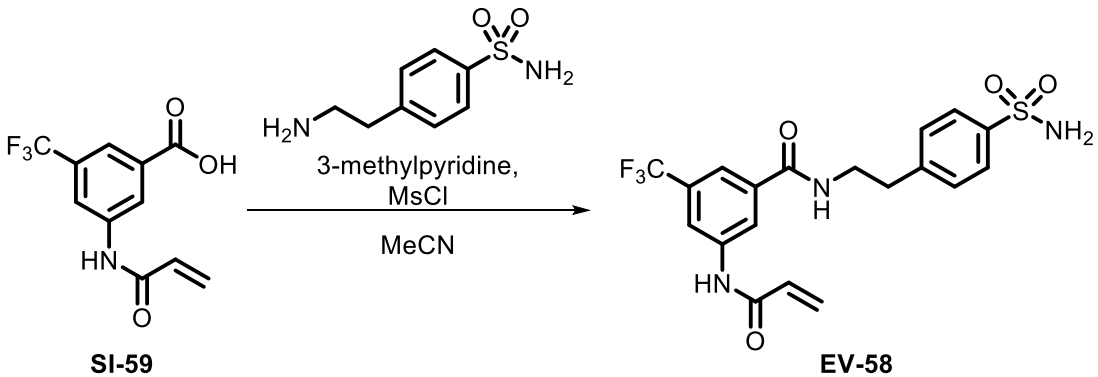


SI-59 **EV-57**

Following **General Procedure 3**, starting with **SI-59** (100 mg, 0.39 mmol, 1.0 eq) and 3-methoxyphenethylamine (1.2 eq), **EV-57** was obtained after prep-HPLC (basic) as a white solid (28 mg, 17%).

^{1}H NMR (400 MHz, MeOD) δ 8.24 (d, *J* = 8.1 Hz, 2H), 7.76 (s,10H), 7.20 (t, *J* = 8.2 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.77 (dd, *J* = 7.6, 2.1 Hz, 1H), 6.46 – 6.40 (m, 2H), 5.84 (dd, *J* = 7.0, 4.9 Hz, 1H), 3.76 (s, 3H), 3.61 (t, *J* = 7.4 Hz, 2H), 2.90 (t, *J* = 7.4 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{20}F_3N_2O_3$ 393.1421, found 393.1423.

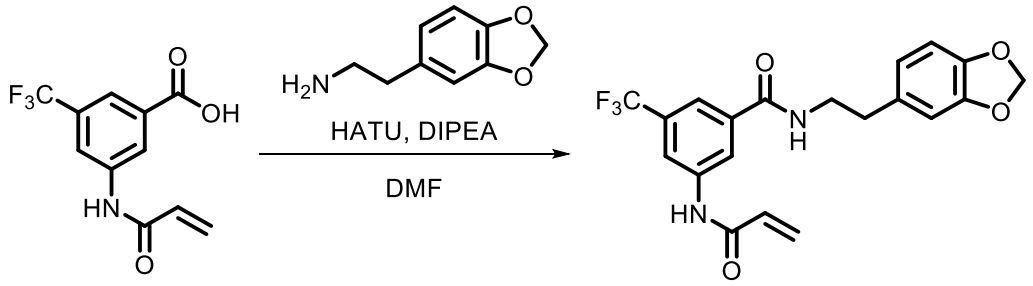


SI-59 **EV-58**

3-methylpyridine (108 mg, 1.2 mmol, 3.0 *eq*) and MsCl (30 µL, 0.39 mmol, 1.0 eq) were added to a solution of **SI-59** (100 mg, 0.39 mmol, 1.0 eq) and 4-(2-Aminoethyl)benzenesulfonamide (77 mg, 0.39 mmol, 1.0 eq) in MeCN (1 mL) at 0 °C. The reaction was warmed to 25 °C and stirred for 3 h. The reaction mixture was quenched with water (1 mL) and concentrated. The resulting residue was purified via prep-HPLC (basic) to provide **EV-58** (64 mg, 37%) as an off-white solid.

^{1}H NMR (400 MHz, MeOD) δ 8.23 (d, *J* = 22.5 Hz, 2H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.78 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 6.47 – 6.40 (m, 2H), 5.84 (t, *J* = 5.7 Hz, 1H), 4.60 (s, 2H), 3.66 (t, *J* = 7.2 Hz, 2H), 3.03 (t, *J* = 7.2 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{19}H_{19}F_3N_2O_4S$ 442.1043, found 442.1043.

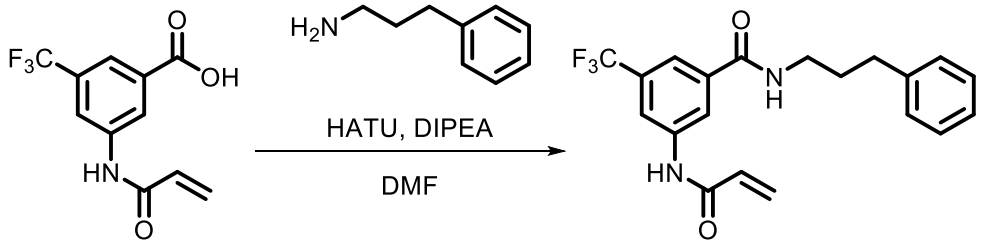


SI-59 **EV-59**

Following **General Procedure 3**, starting with **SI-59** (100 mg, 0.39 mmol, 1.0 eq) and homopiperonylamine (1.0 eq), **EV-59** was obtained after prep-HPLC (basic) as a white solid (8 mg, 5%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H), 8.79 (t, *J* = 5.6 Hz, 1H), 8.30 (d, *J* = 25.7 Hz, 2H), 7.85 (s, 1H), 6.86 – 6.80 (m, 2H), 6.69 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.43 (dd, *J* = 17.0, 9.9 Hz, 1H), 6.32 (dd, *J* = 17.0, 2.1 Hz, 1H), 5.96 (s, 2H), 5.84 (dd, *J* = 9.9, 2.1 Hz, 1H), 3.46 (q, *J* = 7.0 Hz, 2H), 2.77 (t, *J* = 7.3 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{18}F_3N_2O_4$ 407.1213, found 407.1213.



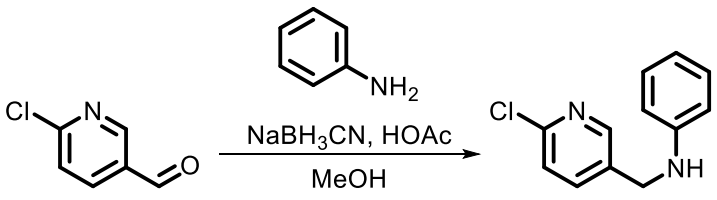
SI-59 **EV-60**

Following **General Procedure 3**, starting with **SI-59** (100 mg, 0.39 mmol, 1.0 eq) and 3-phenylpropylamine (1.2 eq), **EV-60** was obtained after prep-HPLC (basic) as a white solid (5 mg, 3%).

^{1}H NMR (400 MHz, MeOD) δ 8.25 (s, 2H), 7.80 (s, 1H), 7.29 – 7.19 (m, 4H), 7.19 – 7.10 (m, 1H), 6.48 – 6.38 (m, 2H), 5.84 (dd, *J* = 7.1, 4.7 Hz, 1H), 4.60 (br s, 1H), 3.42 (t, *J* = 7.1 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 1.96 (p, *J* = 7.5 Hz, 2H).

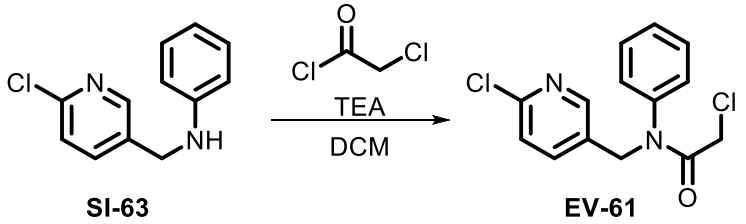
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{20}F_3N_2O_2$ 377.1472, found 377.1474.

Synthesis of SI-63 as a precursor for EV-61 and EV-62



SI-63

Following **General Procedure 5**, starting with 6-chloropyridine-3-carbaldehyde (100 mg, 0.71 mmol, 1.0 eq) and aniline (1.0 eq), **SI-63** was obtained as crude product and used without purification.

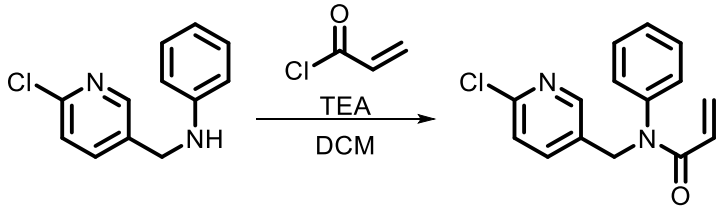


SI-63 **EV-61**

Following **General Procedure 1**, starting with **SI-63** (70 mg, 0.32 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (3.0 eq), **EV-61** was obtained after prep-HPLC (HCl) as a colorless oil (56 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.40 (s, 3H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.03 (s, 2H), 4.87 (s, 2H), 3.83 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{14}H_{13}Cl_2N_2O$ 295.0400, found 295.0404.

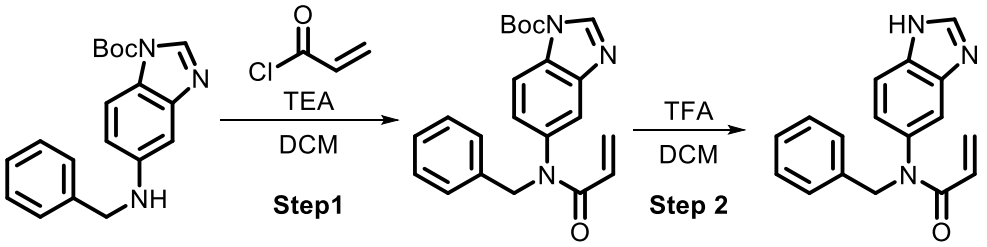


SI-63 **EV-62**

Following **General Procedure 2**, starting with **SI-63** (70 mg, 0.32 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (3.0 eq), **EV-62** (19 mg, 22%) was obtained after prep-HPLC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.5 Hz, 1H), 7.67 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.26 (d, *J* = 8.2 Hz, 1H), 6.99 (dd, *J* = 7.9, 1.8 Hz, 2H), 6.42 (dd, *J* = 16.8, 1.9 Hz, 1H), 6.01 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.57 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.94 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{15}H_{14}ClN_2O$ 273.0789, found 273.0791.



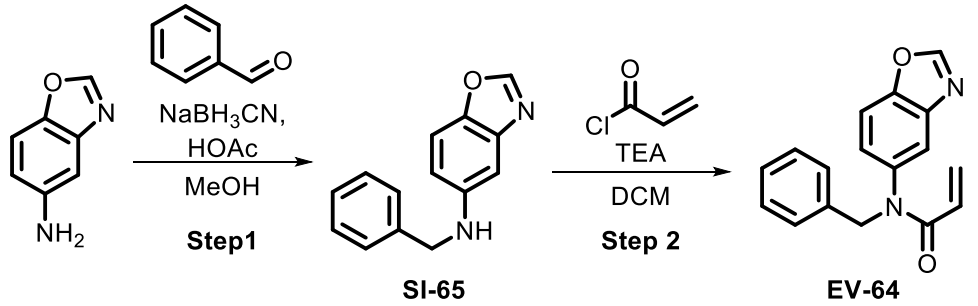
SI-64 **EV-63**

Step 1: Following **General Procedure 2**, starting with *tert*-butyl 5-(benzylamino)-1*H*-benzo[*d*]imidazole-1-carboxylate (100 mg, 0.3 mmol, 1.0 eq),(Bar-Peled et al., 2017) acryloyl chloride (2.0 eq), and TEA (3.0 eq), **SI-64** was obtained as crude product and used in the next step without purification.

Step 2: Following **General Procedure 6**, starting with **SI-64** (1.0 eq) and TFA (24 eq), **EV-63** (20 mg, 24% over 2 steps) after prep-HPLC (basic).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.30 – 7.25 (m, 3H), 7.24 – 7.18 (m, 3H), 6.93 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.22 (dd, *J* = 16.8, 2.5 Hz, 1H), 6.00 (dd, *J* = 16.8, 10.2 Hz, 1H), 5.56 (dd, *J* = 10.2, 2.5 Hz, 1H), 4.98 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{17}H_{16}N_3O$ 278.1288, found 278.1290.



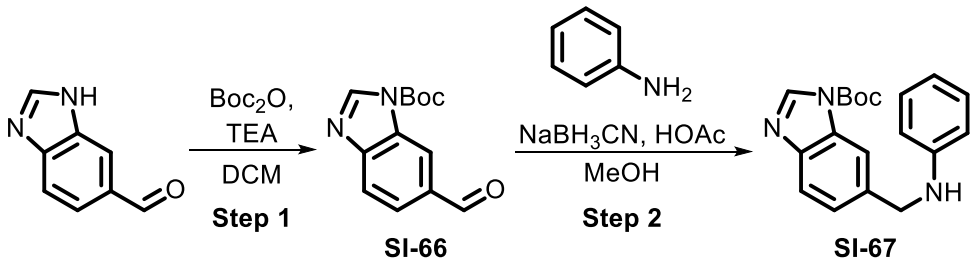
Step 1: Following **General Procedure 5**, starting with benzo[*d*]oxazol-5-amine (1.0 eq) and benzaldehyde (1.1 eq), **SI-65** (55 mg, crude) was obtained and used in the next step without purification.

Step 2: Following **General Procedure 2**, starting with **SI-65** (55 mg, 0.24 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (3.0 eq), **EV-64** (30 mg, 44%) was obtained after prep-HPLC (basic).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.46 (s, 1H), 7.31 – 7.20 (m, 5H), 7.04 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.46 (dd, *J* = 16.8, 2.0 Hz, 1H), 6.00 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.56 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.04 (s, 2H).

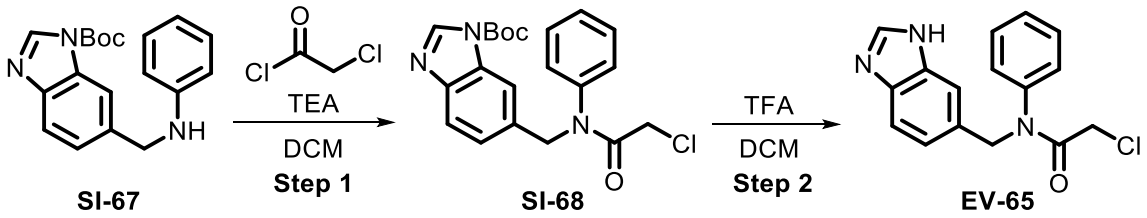
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{17}H_{15}N_2O_2$ 279.1128, found 279.1129.

Synthesis of SI-67 as a precursor for EV-65 and EV-66



Step 1: Boc_2O (1.57 mL, 6.8 mmol, 2.0 eq) was added in one portion to a mixture of 3H-benzimidazole-5-carbaldehyde (500 mg, 3.4 mmol, 1.0 eq) and TEA (948 µL, 6.8 mmol, 2.0 eq) in DCM (5 mL) at 25 °C and was stirred for 16 h. The reaction mixture was filtered and the filtrate was concentrated. The resulting residue was purified by flash chromatography to afford **SI-66** (800 mg, crude) as a yellow oil.

Step 2: Following **General Procedure 5**, starting with **SI-66** (180 mg, 0.73 mmol, 1.0 eq) and aniline (1.1 eq), **SI-67** was obtained as crude product and used without purification.

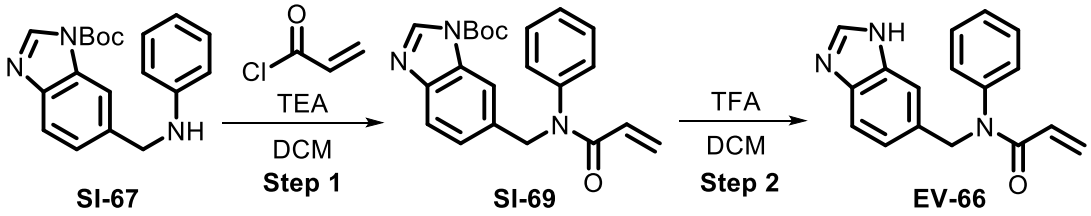


Step 1: Following **General Procedure 1**, starting with **SI-67** (200 mg, 0.62 mmol, 1.0 eq), chloroacetyl chloride (3.0 eq), and TEA (5.0 eq), **SI-68** was obtained as crude product and used in the next step without purification.

Step 2: Following **General Procedure 6**, starting with **SI-68** (1.0 eq) and TFA (24 eq), **EV-65** (46 mg, 13% over 2 steps) was obtained after prep-HPLC (basic).

NMR (400 MHz, DMSO-d_6) δ 9.58 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.65 (s, 1H), 7.45 – 7.31 (m, 4H), 7.23 (d, *J* = 7.3 Hz, 2H), 5.06 (s, 2H), 4.07 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{16}H_{15}ClN_3O$ 300.0898, found 300.0899.



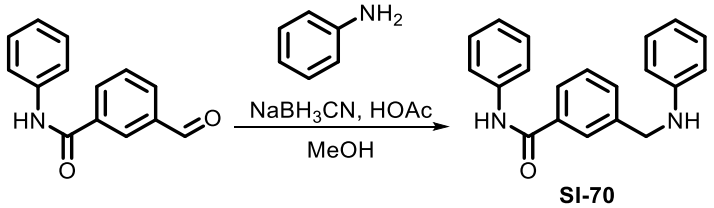
Step 1: Following **General Procedure 2**, starting with **SI-67** (200 mg, 0.62 mmol, 1.0 eq), acryloyl chloride (3.0 eq), and TEA (5.0 eq), **SI-69** was obtained as crude product and used in the next step without purification.

Step 2: Following **General Procedure 6**, starting with **SI-69** (1.0 eq) and TFA (24 eq), **EV-66** was obtained after prep-HPLC (basic) as a white solid (40 mg, 27% over 2 steps).

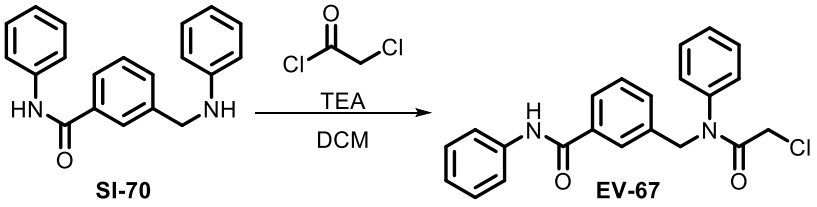
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.40 – 7.33 (m, 3H), 7.33 – 7.26 (m, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.26 (dd, *J* = 16.8, 2.4 Hz, 1H), 6.02 (br s, 1H), 5.62 (dd, *J* = 10.2, 2.4 Hz, 1H), 5.06 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{17}H_{16}N_3O$ 278.1288, found 278.1292.

Synthesis of SI-70 as a precursor for EV-67 and EV-68



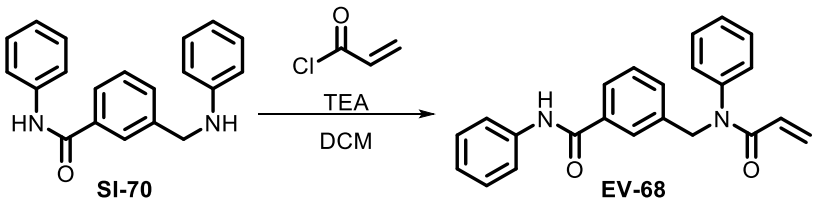
Following **General Procedure 5**, starting with 3-formyl-*N*-phenylbenzamide (750 mg, 3.3 mmol, 1.0 eq) and aniline (1.1 eq), **SI-70** was obtained and used in the next step without purification.



Following **General Procedure 1**, starting with **SI-70** (600 mg, 2.0 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (5.0 eq), **EV-67** was obtained after prep-HPLC (HCl) as a yellow oil (40 mg, 5%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.74 – 7.60 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.40 – 7.30 (m, 6H), 7.23 (d, *J* = 6.8 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 4.95 (s, 2H), 4.02 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{22}H_{19}ClN_2O_2$ 379.1208, found 379.1210.

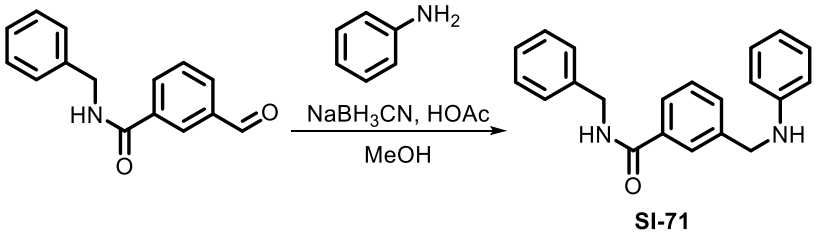


Following **General Procedure 2**, starting with **SI-70** (600 mg, 2.0 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (3.0 eq), **EV-68** (121 mg, 17%) was obtained after prep-HPLC (basic).

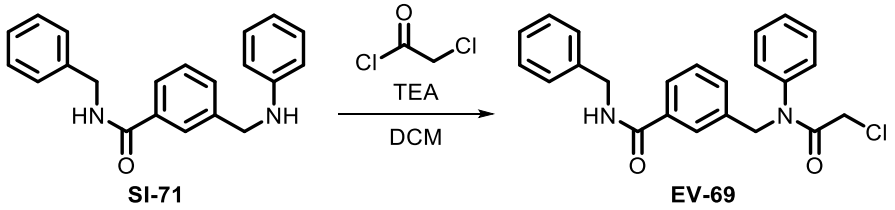
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, *J* = 7.7, 1.5 Hz, 1H), 7.74 – 7.65 (m, 3H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.39 – 7.27 (m, 6H), 7.16 – 7.12 (m, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.24 (dd, *J* = 16.8, 2.1 Hz, 1H), 6.09 – 5.95 (m, 1H), 5.62 (dd, *J* = 10.2, 2.1 Hz, 1H), 5.03 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{23}H_{21}N_2O_2$ 357.1598, found 357.1598.

Synthesis of SI-71 as a precursor for EV-69 and EV-70



Following **General Procedure 5**, starting with 3-formyl-*N*-benzylbenzamide (750 mg, 3.1 mmol, 1.0 eq) and aniline (1.1 eq), **SI-71** was obtained and used in the next step without purification.

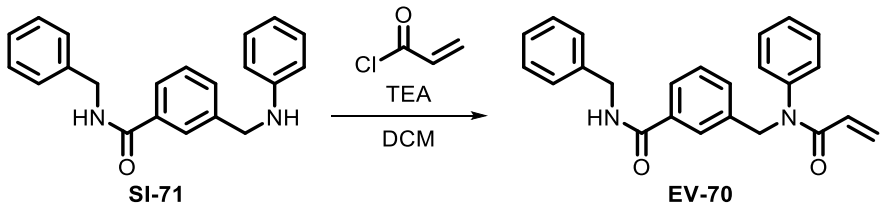


SI-71 **EV-69**

Following **General Procedure 1**, starting with **SI-71** (600 mg, 1.9 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (5.0 eq), **EV-69** (94 mg, 12%) was obtained after prep-HPLC (basic).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, *J* = 7.5 Hz, 1H), 7.68 (s, 1H), 7.42 – 7.31 (m, 4H), 7.32 – 7.24 (m, 3H), 7.22 (d, *J* = 6.9 Hz, 3H), 4.92 (s, 2H), 4.43 (s, 2H), 4.03 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{23}H_{22}ClN_2O_2$ 393.1365, found 393.1365.



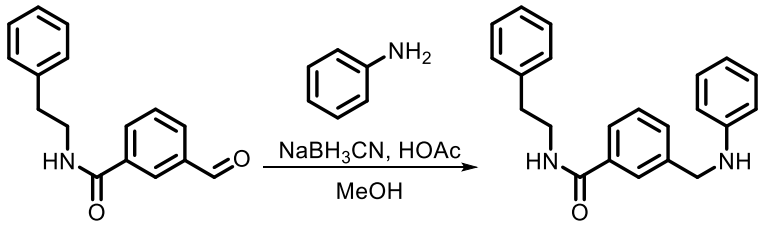
SI-71 **EV-70**

Following **General Procedure 2**, starting with **SI-71** (600 mg, 1.9 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (5.0 eq), **EV-70** (150 mg, 20%) was obtained after prep-HPLC (basic).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (t, *J* = 6.0 Hz, 0.3H), 8.38 (br s, 0.2H), 7.75 – 7.57 (m, 2H), 7.41 – 7.30 (m, 4H), 7.26 (br s, 5H), 7.20 (br s, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.33 – 6.18 (m, 1H), 6.08 – 5.92 (m, 1H), 5.60 (d, *J* = 10.3 Hz, 1H), 4.99 (s, 2H), 4.43 (s, 2H).

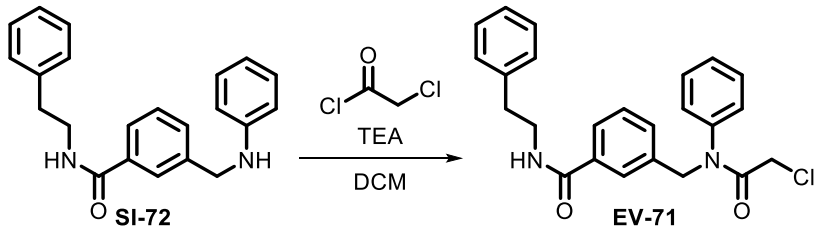
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{24}H_{23}N_2O_2$ 371.1754, found 371.1757.

Synthesis of SI-72 as a Precursor for EV-71 and EV-72



SI-72

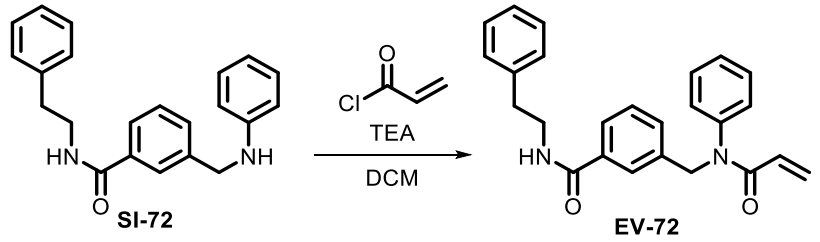
Following **General Procedure 5**, starting with 3-formyl-*N*-phenethylbenzamide (750 mg, 3.0 mmol, 1.0 eq) and aniline (1.1 eq), **SI-72** was obtained as crude product and used in the next step without purification.



Following **General Procedure 1**, starting with **SI-72** (600 mg, 1.8 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (5.0 eq), **EV-71** (203 mg, 25%) was obtained after prep-HPLC (basic).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 – 7.61 (m, 2H), 7.40 – 7.29 (m, 5H), 7.29 – 7.20 (m, 6H), 7.20 – 7.14 (m, 1H), 4.92 (s, 2H), 4.04 (s, 2H), 3.45 (t, *J* = 7.2 Hz, 2H), 2.81 (t, *J* = 7.6 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{24}H_{24}ClN_2O_2$ 407.1521, found 407.1521.

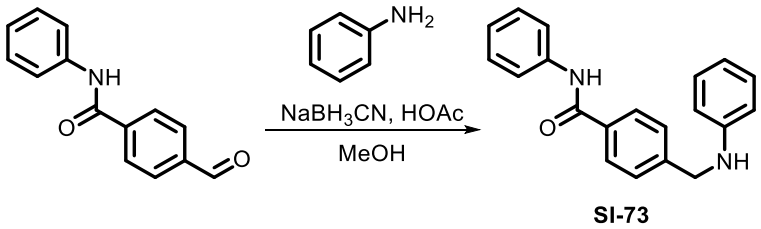


Following **General Procedure 2**, starting with **SI-72** (600 mg, 1.8 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (5.0 eq), **EV-72** (135 mg, 18%) was obtained after prep-HPLC (basic).

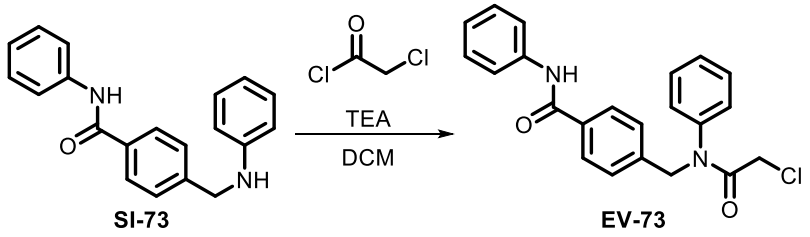
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (t, *J* = 5.6 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.37 – 7.27 (m, 5H), 7.27 – 7.18 (m, 4H), 7.15 (t, *J* = 7.0 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 2H), 6.24 (dd, *J* = 16.8, 2.2 Hz, 1H), 6.04 – 5.93 (m, 1H), 5.60 (dd, *J* = 10.1, 2.2 Hz, 1H), 4.98 (s, 2H), 3.50 – 3.37 (m, 2H), 2.80 (t, *J* = 7.4 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{25}H_{25}N_2O_2$ 385.1911, found 385.1910.

Synthesis of SI-73 as a precursor for EV-73 and EV-74



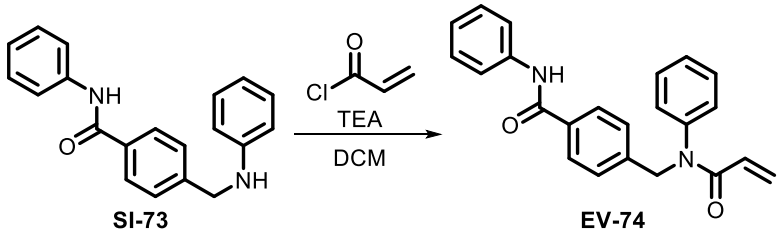
Following **General Procedure 5**, starting with 4-formyl-*N*-phenylbenzamide (750 mg, 3.3 mmol, 1.0 eq) and aniline (1.1 eq), **SI-73** was obtained as crude product and used without purification.



Following **General Procedure 1**, starting with **SI-73** (600 mg, 2.0 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (5.0 eq), **EV-73** (136 mg, 18%) was obtained after prep-HPLC (basic).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.28 (m, 9H), 7.09 (t, *J* = 7.4 Hz, 1H), 4.98 (s, 2H), 4.11 (s, 2H).

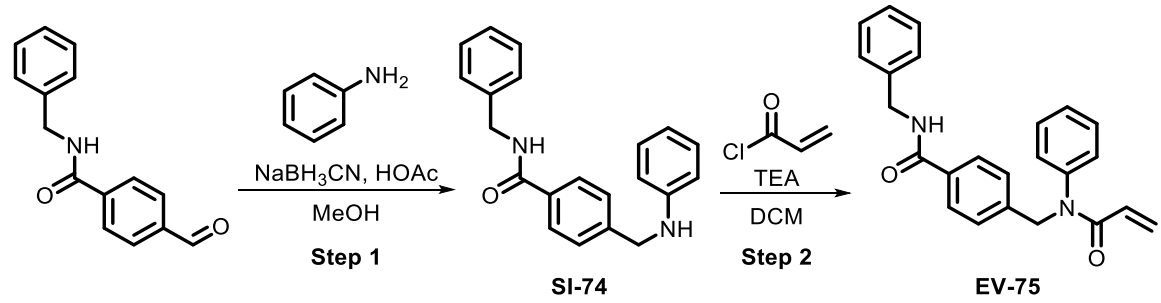
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{22}H_{20}ClN_2O_2$ 379.1208, found 379.1204.



Following **General Procedure 2**, starting with **SI-73** (600 mg, 2.0 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (5.0 eq), **EV-74** (72 mg, 10%) was obtained after prep-HPLC (basic).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.29 (m, 7H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.27 (dd, *J* = 16.8, 2.4 Hz, 1H), 6.15 – 6.00 (m, 1H), 5.65 (dd, *J* = 10.2, 2.4 Hz, 1H), 5.05 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{23}H_{21}N_2O_2$ 357.1598, found 357.1599.



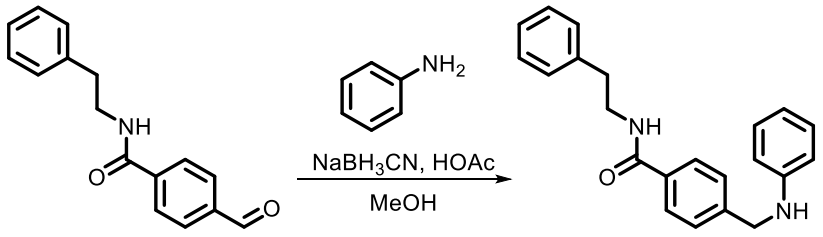
Step 1: Following **General Procedure 5**, starting with 4-formyl-*N*-benzylbenzamide (750 mg, 3.1 mmol, 1.0 eq) and aniline (1.1 eq), **SI-74** (600 mg, crude) was obtained and used in the next step without purification.

Step 2: Following **General Procedure 2**, starting with **SI-74** (600 mg, 1.9 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (5.0 eq), **EV-75** (233 mg, 31%) was obtained after prep-HPLC (basic).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (t, *J* = 6.1 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.32 – 7.24 (m, 7H), 7.23 – 7.18 (m, 1H), 7.13 (d, *J* = 7.2 Hz, 2H), 6.23 (dd, *J* = 16.8, 2.2 Hz, 1H), 6.13 – 5.91 (m, 1H), 5.63 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.99 (s, 2H), 4.43 (d, *J* = 6.0 Hz, 2H).

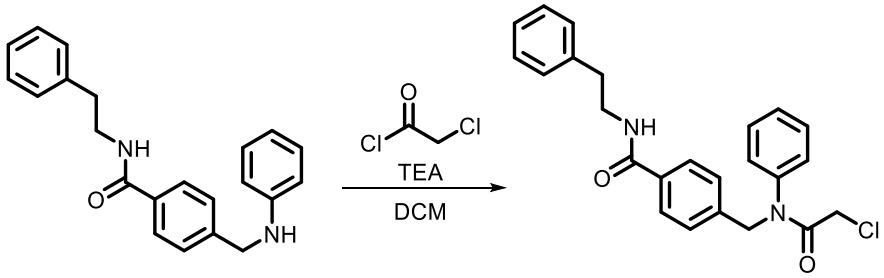
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{24}H_{23}N_2O_2$ 371.1754, found 371.1754.

Synthesis of SI-75 as a precursor for EV-76 and EV-77



SI-75

Following **General Procedure 5**, starting with 4-formyl-*N*-phenethylbenzamide (760 mg, 3.0 mmol, 1.0 eq) and aniline (1.1 eq), **SI-75** was obtained as crude product and used in the next step without purification.

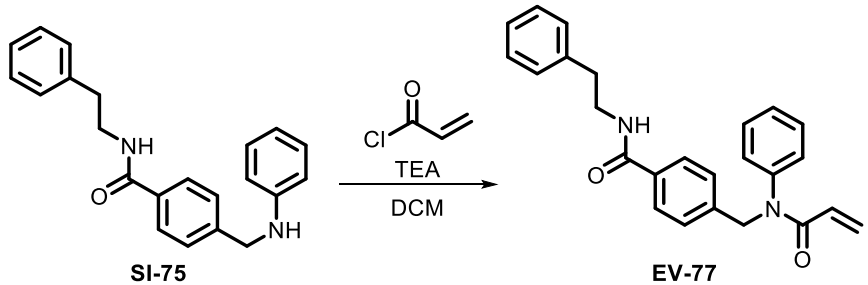


SI-75 **EV-76**

Following **General Procedure 1**, starting with **SI-75** (600 mg, 1.8 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (5.0 eq), **EV-76** (55 mg, 7%) was obtained after prep-HPLC (basic).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (t, *J* = 5.6 Hz, 0.1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.32 (m, 3H), 7.29 – 7.21 (m, 7H), 7.21 – 7.14 (m, 2H), 4.91 (s, 2H), 4.04 (s, 2H), 3.44 (t, *J* = 7.3 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{24}H_{24}ClN_2O_2$ 407.1521, found 407.1521.



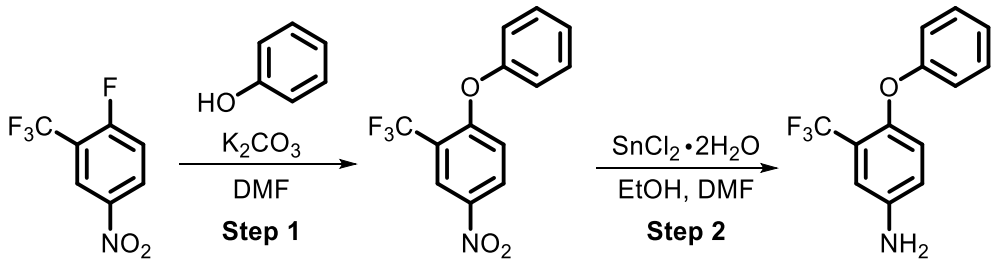
SI-75 **EV-77**

Following **General Procedure 1**, starting with **SI-75** (600 mg, 1.8 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (5.0 eq), **EV-77** (203 mg, 26%) was obtained after prep-HPLC (basic).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (t, *J* = 5.6 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 7.4 Hz, 2H), 7.33 – 7.26 (m, 2H), 7.27 – 7.16 (m, 6H), 7.16 – 7.09 (m, 2H), 6.23 (dd, *J* = 16.8, 2.2 Hz, 1H), 6.07 – 5.95 (m, 1H), 5.62 (dd, *J* = 10.2, 2.2 Hz, 1H), 4.98 (s, 2H), 3.45 (q, *J* = 6.5 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{25}H_{25}N_2O_2$ 385.1911, found 385.1913.

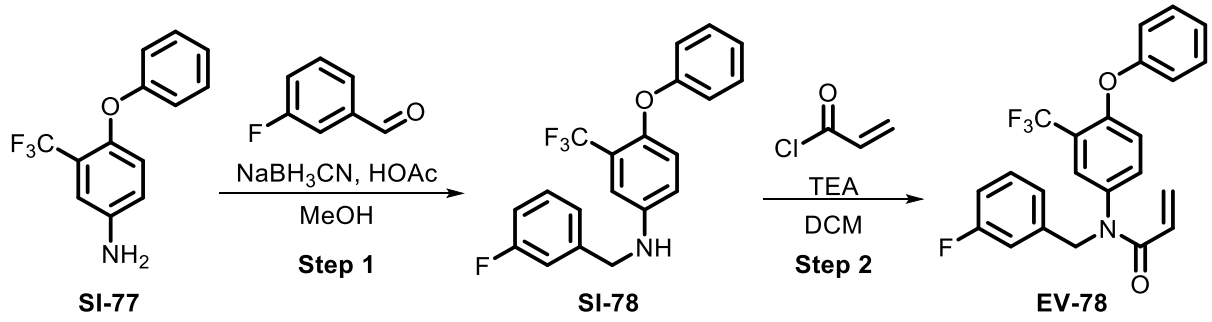
Synthesis of SI-77 as a precursor for EV-78 – EV-81



SI-76 **SI-77**

Step 1: K_2CO_3 (6.6 g, 48 mmol, 1.0 eq) was added in one portion to a solution of phenol (4.5 g, 48 mmol, 1.0 eq) in DMF (50 mL) at 25 °C and the mixture was stirred for 1 h. Fluoro-4-nitro-2-(trifluoromethyl)benzene (6.6 mL, 48 mmol, 1.0 eq) was then added and the reaction was heated to 80 °C and stirred for 16 h. Upon completion, the mixture was poured into H_2O (300 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give **SI-76** (13 g, 96%) as a yellow solid.

Step 2: DMF (35 µL, 0.46 mmol, 0.01 eq) and $SnCl_2 \cdot 2H_2O$ (41.4 g, 184 mmol, 4.0 eq) were added sequentially to a solution of **SI-76** (13.0 g, 46 mmol, 1.0 eq) in EtOH (130 mL) at 25 °C. The reaction mixture was heated to 80 °C and stirred for 2 h. The reaction was cooled and concentrated under reduced pressure and the resulting residue was diluted with H_2O (300 mL). The suspension was filtered and the filtrate was extracted with DCM (100 mL x 5). The combined layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to provide **SI-77** (11.0 g, 67%) as a yellow oil.



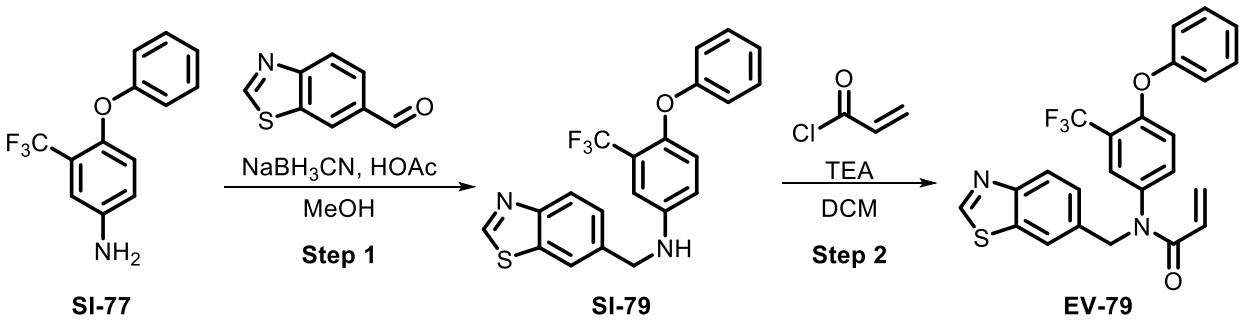
SI-77 **SI-78** **EV-78**

Step 1: Following **General Procedure 5**, starting with **SI-77** (200 mg, 0.79 mmol, 1.0 eq) and 3-fluorobenzaldehyde (1.1 eq), **SI-78** was obtained as crude product and used in the next step without purification.

Step 2: Following **General Procedure 2**, starting with **SI-78** (140 mg, 0.39 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (5.0 eq), **EV-78** was obtained after prep-HPLC (basic) as a colorless oil (30 mg, 18%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42(dd, *J* = 8.6, 7.4 Hz, 2H), 7.36 (d, *J* = 2.6 Hz, 1H), 7.31 – 7.19 (m, 2H), 7.12 – 7.06 (m, 2H), 7.06 – 6.94 (m, 4H), 6.84 (d, *J* = 8.8 Hz, 1H), 6.49 (dd, *J* = 16.7, 1.9 Hz, 1H), 6.05 (dd, *J* = 16.7, 10.3 Hz, 1H), 5.66 (dd, *J* = 10.3, 1.9 Hz, 1H), 4.97 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{23}H_{18}F_3NO_2$ 416.1268, found 416.1268.



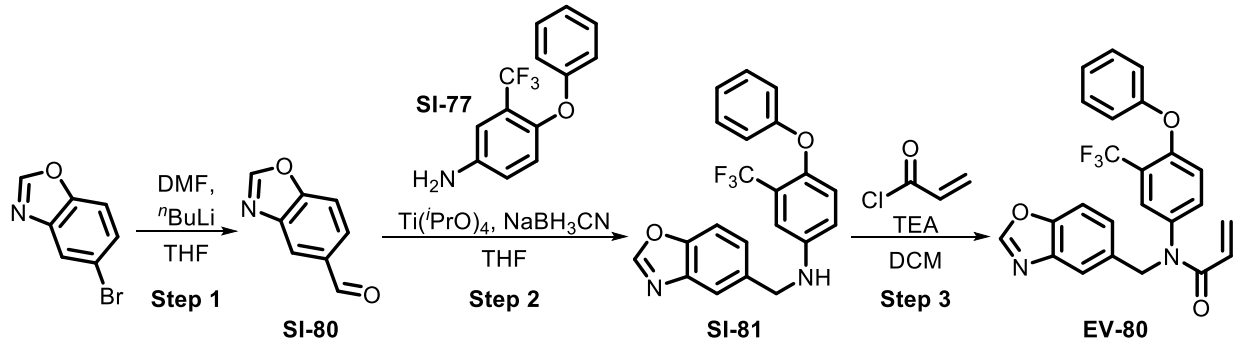
SI-77 **SI-79** **EV-79**

Step 1: Following **General Procedure 5**, starting with **SI-77** (300 mg, 1.2 mmol, 1.0 eq) and 1,3-benzothiazole-6-carbaldehyde (1.0 eq), **SI-79** was obtained as crude product and used without purification.

Step 2: Following **General Procedure 2**, starting with **SI-79** (125 mg, 0.31 mmol, 1.0 eq), acryoyl chloride (2.0 eq), and TEA (5.0 eq), **EV-79** was obtained after prep-HPLC (basic) as a light yellow oil (86 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 1.4 Hz, 1H), 7.44 – 7.32 (m, 4H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.05 (dd, *J* = 8.6, 1.1 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.49 (dd, *J* = 16.7, 1.9 Hz, 1H), 6.03 (dd, *J* = 16.5, 10.6 Hz, 1H), 5.65 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.10 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{24}H_{18}F_3N_2O_2S$ 455.1036, found 455.1037.



SI-80 **SI-81** **EV-80**

Step 1: ^{n}BuLi (2.5 M, 4.0 mL, 2.0 eq) was added to a solution of 5-bromobenzoxazole (1.0 g, 5.1 mmol, 1.0 eq) in THF (8 mL) at -78 °C under a nitrogen atmosphere. After stirring for 1 h at -78 °C, DMF (777 µL, 10.1 mmol, 2.0 eq) was added and the reaction mixture was stirred at -78 °C for an additional 2 h. The reaction mixture was warmed to 25 °C, quenched by the addition of aq. NH_4Cl (10 mL) and brine (20 mL) and then extracted with DCM (30 ml x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography to provide **SI-80** (100 mg, 11%) as a brown solid.

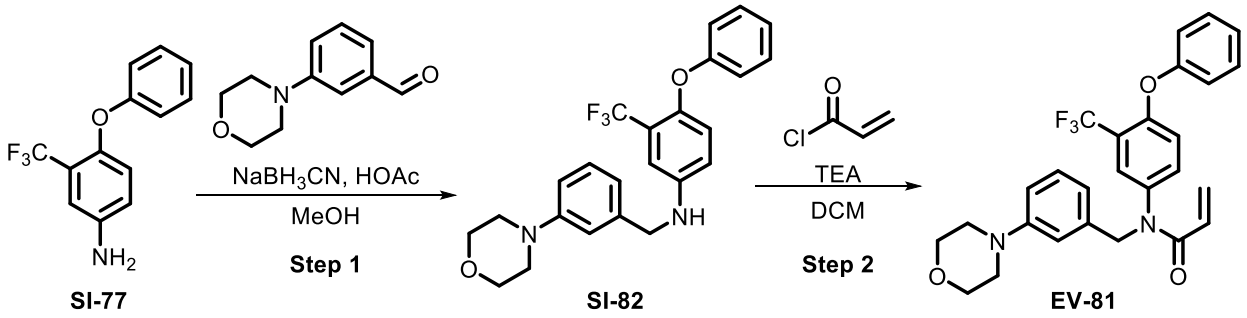
Step 2: $Ti(O^iPr)_4$ (201 µL, 0.68 mmol, 1.0 eq) was added to a solution of **SI-80** (100 mg, 0.68 mmol, 1.0 eq) and **SI-77** (207 mg, 0.82 mmol, 1.2 eq) in THF (2 mL) and stirred at 25 °C for 1 h. The reaction was cooled to 0 °C then $NaBH_3CN$ (85 mg, 1.4 mmol, 2.0 eq) and the reaction was stirred at 0 °C for 2 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (20 mL x 3). The combined organic layers were

washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated to provide **SI-81** (200 mg, crude) as a yellow oil which was used in the next step without purification.

Step 3: Following **General Procedure 2**, starting with **SI-81** (90 mg, 0.23 mmol, 1.0 eq), acryloyl chloride (1.5 eq), and TEA (5.0 eq), **EV-80** was obtained after prep-HPLC (basic) as a yellow solid (24 mg, 22%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.59 (d, *J* = 1.7 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.31 (m, 4H), 7.23 – 7.17 (m, 1H), 7.07 – 7.02 (m, 2H), 6.96 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 6.48 (dd, *J* = 16.7, 1.9 Hz, 1H), 6.02 (dd, *J* = 16.7, 10.2 Hz, 1H), 5.64 (dd, *J* = 10.3, 1.9 Hz, 1H), 5.08 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{24}H_{18}F_3N_2O_3$ 439.1264, found 439.1269.

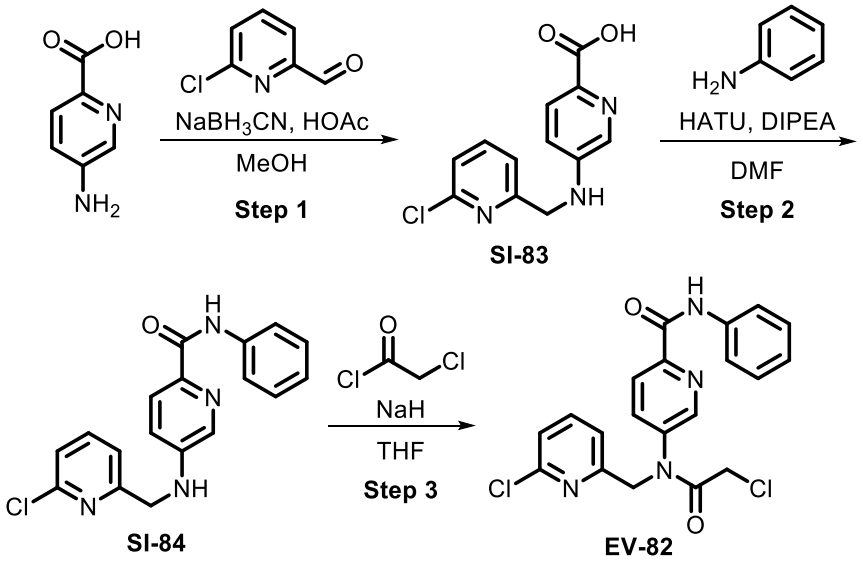


Step 1: Following **General Procedure 5**, **SI-77** (300 mg, 1.2 mmol, 1.0 eq) and 3-morpholinobenzaldehyde (1.0 eq), **SI-82** was obtained as a crude product and used without purification.

Step 2: Following **General Procedure 2**, starting with **SI-82** (125 mg, 0.29 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (5.0 eq), **EV-81** was obtained after prep-HPLC (HCl) as a light yellow oil (118 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.33 (m, 2H), 7.31 (br s, 1H), 7.24 – 7.14 (m, 2H), 7.09 – 6.98 (m, 3H), 6.83 – 6.76 (m, 3H), 6.69 (d, *J* = 7.5 Hz, 1H), 6.45 (dd, *J* = 16.7, 1.9 Hz, 1H), 6.10 – 5.96 (m, 1H), 5.62 (d, *J* = 10.3 Hz, 1H), 4.90 (s, 2H), 3.88 – 3.80 (m, 4H), 3.17 – 3.06 (m, 4H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{27}H_{26}F_3N_2O_3$ 483.1890, found 483.1901.



Step 1: Following **General Procedure 5**, starting with 6-chloropyridine-2-carbaldehyde (150 mg, 1.1 mmol, 1.0 eq) and 5-aminopicolinic acid (1.0 eq), **SI-83** was obtained as a crude product and used in the next step without purification.

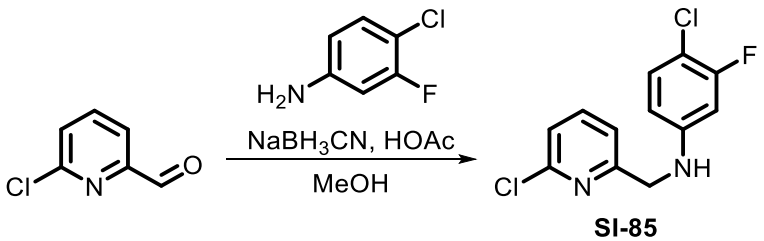
Step 2: Following **General Procedure 3**, starting with **SI-83** (1.0 eq) and aniline (1.0 eq), **SI-84** (150 mg, crude) was obtained as a crude product and used in the next step without purification.

Step 3: NaH (21 mg, 0.53 mmol, 60% dispersion in mineral oil, 2.0 eq) was added to a solution of **SI-84** (150 mg, 0.27 mmol, 1.0 eq) in anhydrous THF (2 mL) at 0 °C and then stirred for 1 h. Chloroacetyl chloride (127 µL, 1.6 mmol, 6.0 eq) was then added at 0 °C. The mixture was warmed to 25 °C and stirred for 15 h. The mixture was diluted with MeCN (3 mL) and the product was purified by prep-HPLC (HCl). The eluent was evaporated to remove organic solvents followed by lyophilization to provide **EV-82** (26 mg, 21%) as a yellow oil.

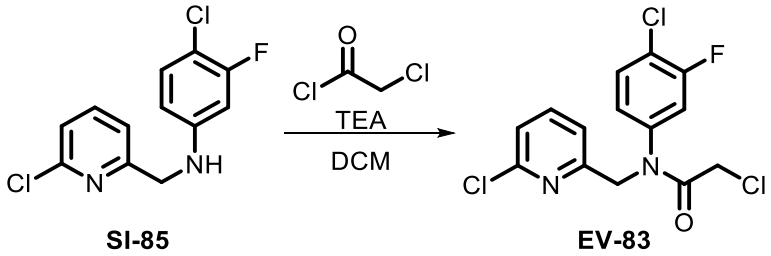
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.81 (br zs, 1H), 8.23 – 8.10 (m, 2H), 7.91 – 7.81 (m, 3H), 7.43 (dd, *J* = 15.4, 7.7 Hz, 2H), 7.35 (t, *J* = 7.9 Hz, 2H), 7.15 – 7.07 (m, 1H), 5.06 (s, 2H), 4.46 – 4.24 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{17}Cl_2N_4O_2$ 415.0723, found 415.0725.

Synthesis of SI-85 as a precursor for EV-83 and EV-84



Following **General Procedure 5**, starting with 6-chloropyridine-2-carbaldehyde (150 mg, 1.1 mmol, 1.0 eq) and 4-chloro-3-fluoro-aniline (1.0 eq), **SI-85** was obtained as a crude product and used in the next step without purification.

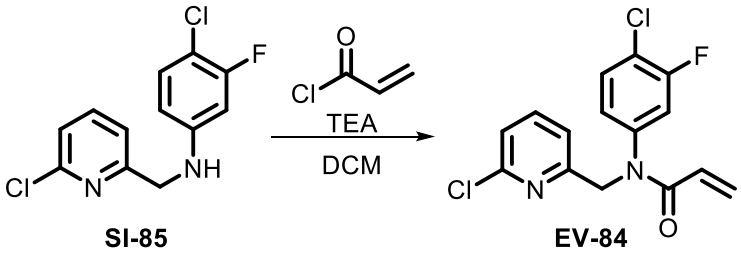


SI-85 **EV-83**

Following **General Procedure 1**, starting with **SI-85** (140 mg, 0.52 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (5.0 eq), **EV-83** was obtained after prep. HPLC (basic) as a colorless oil (25 mg, 12%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (t, *J* = 7.8 Hz, 1H), 7.71 – 7.57 (m, 2H), 7.40 (t, *J* = 7.1 Hz, 2H), 7.32 (br s, 1H), 4.94 (br s, 2H), 4.25 (br s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{14}H_{11}Cl_3FN_2O$ 346.9916, found 346.9916.



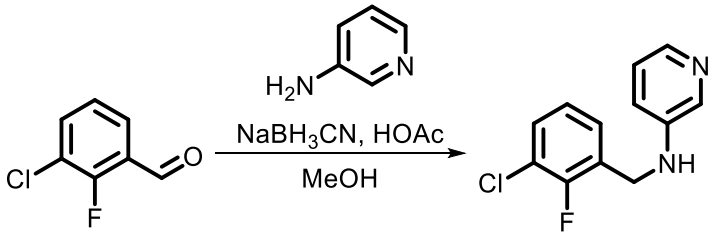
SI-85 **EV-84**

Following **General Procedure 2**, starting with **SI-85** (140 mg, 0.52 mmol, 1.0 eq), acryloyl chloride (2.0 eq), and TEA (5.0 eq), **EV-84** was obtained after prep. HPLC (basic) as a colorless oil (50 mg, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (t, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 6.8 Hz, 1H), 7.21 (d, *J* = 7.1 Hz, 1H), 7.14 (dd, *J* = 9.5, 2.4 Hz, 1H), 7.02 (ddd, *J* = 8.5, 2.4, 1.2 Hz, 1H), 6.42 (dd, *J* = 16.7, 1.8 Hz, 1H), 6.11 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.63 (dd, *J* = 10.3, 1.9 Hz, 1H), 4.99 (s, 2H).

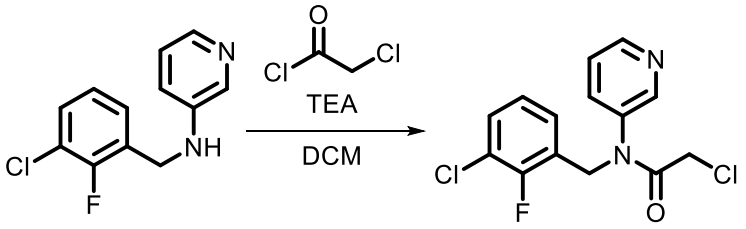
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{15}H_{12}Cl_2FN_2O$ 325.0305, found 325.0304.

Synthesis of SI-86 as a precursor for EV-85 and EV-86



SI-86

Following **General Procedure 5**, starting with 3-chloro-2-fluorobenzaldehyde (150 mg, 1.1 mmol, 1.0 eq) and 3-aminopyridine (1.0 eq), **SI-86** was obtained as a crude product and used without purification.

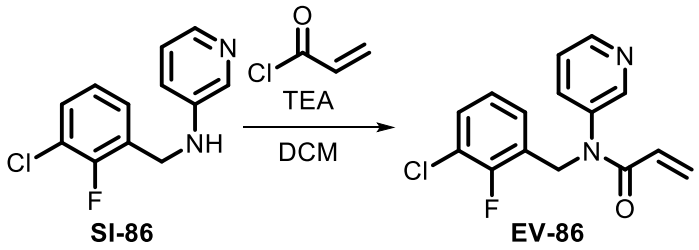


SI-86 **EV-85**

Following **General Procedure 1**, starting with **SI-86** (350 mg, 1.5 mmol, 1.0 eq), chloroacetyl chloride (1.5 eq), and TEA (4.0 eq), **EV-85** was obtained after prep. HPLC (FA) as a white solid (135 mg, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 53.0 Hz, 2H), 8.20 (s, 1H), 7.91 (s, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.29 (s, 1H), 7.11 (t, *J* = 7.3 Hz, 1H), 5.12 (s, 2H), 4.08 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{14}H_{12}Cl_2FN_2O$ 313.0305, found 313.0308.



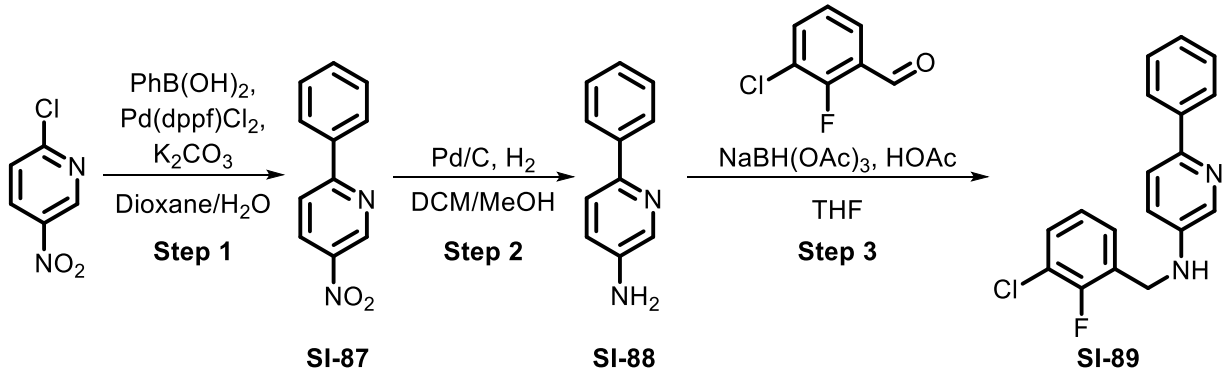
SI-86 **EV-86**

Following **General Procedure 1**, starting with **SI-86** (200 mg, 1.5 mmol, 1.0 eq), chloroacetyl chloride (1.5 eq), and TEA (3.0 eq), **EV-86** was obtained after prep. HPLC (FA) as a white solid (17 mg, 7%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.70 (dd, *J* = 5.3, 1.4 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.80 (dd, *J* = 8.3, 5.2 Hz, 1H), 7.48 (td, *J* = 7.6, 1.7 Hz, 1H), 7.34 (td, *J* = 7.3, 6.8, 1.6 Hz, 1H), 7.17 (td, *J* = 7.9, 1.1 Hz, 1H), 6.28 (dd, *J* = 16.5, 2.5 Hz, 2H), 5.80 – 5.61 (m, 1H), 5.13 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{15}H_{13}ClFN_2O$ 291.0695, found 391.0697.

Synthesis of SI-89 as a precursor for EV-87 and EV-88



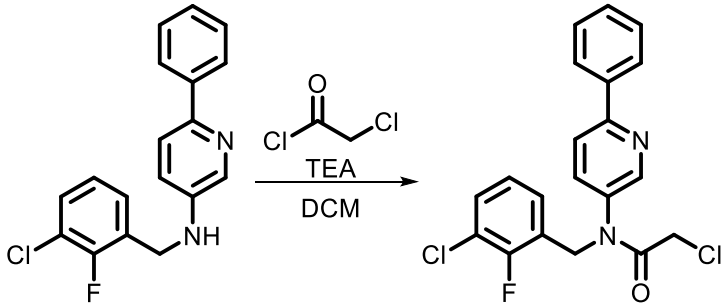
SI-87 **SI-88** **SI-89**

Step 1: Under an atmosphere of nitrogen, $Pd(dppf)Cl_2$ (462 mg, 0.63 mmol, 0.05 eq) and K_2CO_3 (3.5 g, 25 mmol, 2.0 eq) were added to a solution of 2-chloro-5-nitropyridine (2.0 g, 12.6 mmol, 1.0 eq) and

phenylboronic acid (1.7 g, 14 mmol, 1.1 eq) in dioxane (24 mL) and H_2O (8 mL). The mixture was stirred at 100 °C for 6 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash chromatography to give **SI-87** (2.4 g, 93%) as a yellow solid.

Step 2: A mixture of **SI-87** (1.0 g, 5.0 mmol, 1.0 eq), Pd/C (20 mg, 5.0 mmol, 1.0 eq) in DCM (3 mL) and MeOH (3 mL) was evacuated and backfilled with H_2 (3x). The reaction mixture was stirred at 25 °C for 6 h under H_2 atmosphere (15 psi). The reaction mixture was filtered and the filtrate was concentrated to provide **SI-88** (750 mg, 85%) as a light yellow solid.

Step 3: Following **General Procedure 5**, starting with **SI-88** (650 mg, 3.8 mmol, 1.0 eq) and 3-chloro-2-fluoro-benzaldehyde (606 mg, 3.8 mmol, 1.0 eq), **SI-89** (1.2 g, 71%) was obtained and used in the next step without purification.

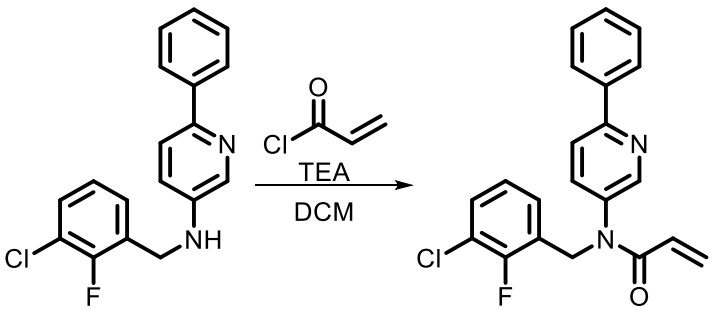


SI-89 **EV-87**

Following **General Procedure 1**, starting with **SI-89** (150 mg, 0.48 mmol, 1.0 eq), chloroacetyl chloride (1.5 *eq*), and TEA (5.0 eq), **EV-87** was obtained after prep-HPLC (HCl) as a yellow solid (15 mg, 8%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.00 (d, *J* = 6.4 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.60 – 7.42 (m, 4H), 7.41 – 7.30 (m, 2H), 7.07 (t, *J* = 7.8 Hz, 1H), 5.03 (s, 2H), 3.91 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{16}Cl_2FN_2O$ 389.0618, found 389.0623.



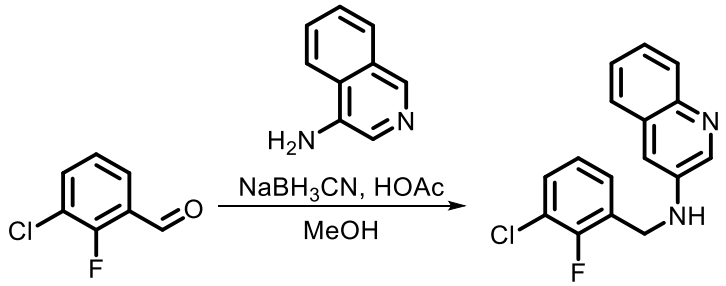
SI-89 **EV-88**

Following **General Procedure 2**, starting with **SI-89** (600 mg, 1.9 mmol, 1.0 eq), acryloyl chloride (1.5 eq), and TEA (5.0 eq), **EV-88** was obtained after prep-HPLC (HCl) as a yellow solid (212 mg, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.12 (dd, *J* = 6.6, 2.9 Hz, 2H), 8.04 – 7.87 (m, 2H), 7.64 – 7.52 (m, 3H), 7.43 – 7.31 (m, 2H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.52 (d, *J* = 16.6 Hz, 1H), 6.12 (dd, *J* = 16.5, 10.2 Hz, 1H), 5.77 (d, *J* = 10.1 Hz, 1H), 5.13 (s, 2H).

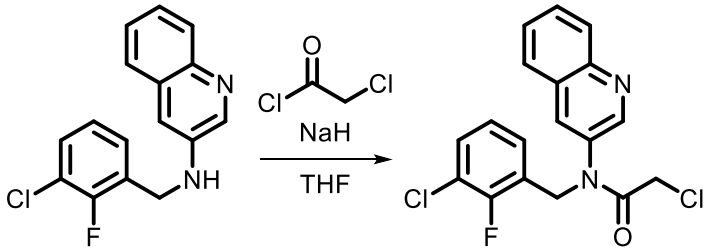
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{17}ClFN_2O$ 367.1008, found 367.1013.

Synthesis of SI-90 as a precursor for EV-89 and EV-90



SI-90

Following **General Procedure 5**, starting with 3-chloro-2-fluorobenzaldehyde (150 mg, 1.1 mmol, 1.0 eq) and 3-aminoquinoline (1.0 eq), **SI-90** was obtained as a crude product and used without purification.

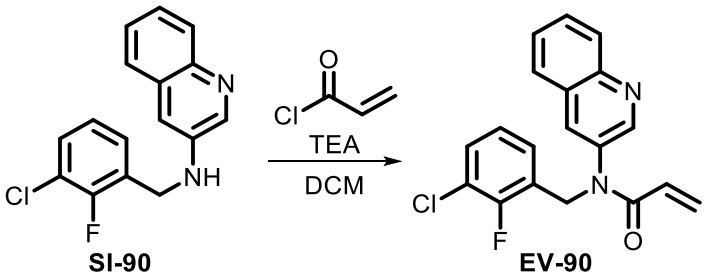


SI-90 **EV-89**

NaH (17 mg, 0.70 mmol, 2.0 eq) was added to a solution of **SI-90** (100 mg, 0.35 mmol, 1.0 eq) in THF (2 mL) at 0 °C. The reaction was warmed to 25 °C and stirred for 0.5 h. The reaction was cooled to 0 °C and chloroacetyl cloride (28 µL, 0.35 mmol, 1.0 eq) was added. The reaction was warmed to 25 °C and stirred for an additional 1.5 h. The reaction was quenched with H_2O (3 mL) and extracted with DCM (1 mL x 3). The combined organic layers were washed with brine (2 mL x 3), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (FA) to provide **EV-89** (17 mg, 13%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.46 (d, *J* = 31.6 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.77 (br s, 1H), 7.43 – 7.27 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 5.13 (s, 2H), 3.97 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{18}H_{14}Cl_2FN_2O$ 363.0462, found 363.0462.

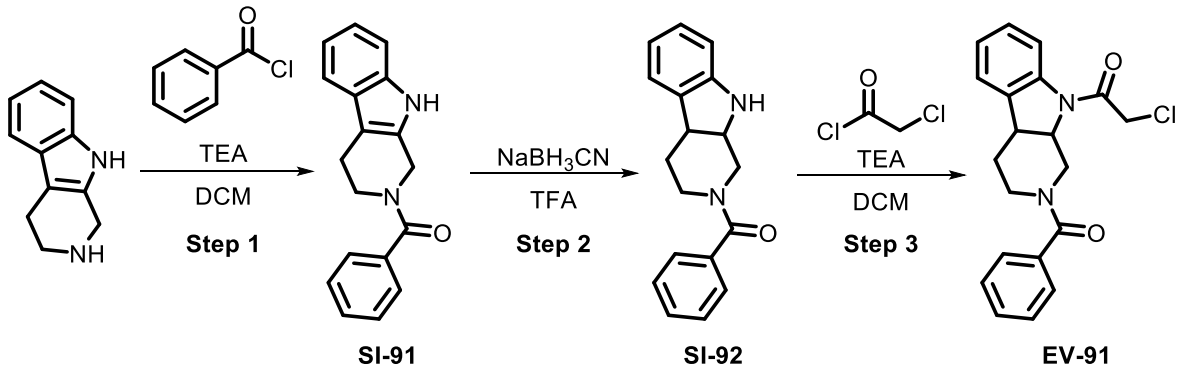


SI-90 **EV-90**

Following **General Procedure 2**, starting with **SI-90** (150 mg, 0.52 mmol, 1.0 eq), acryloyl chloride (1.0 eq), and TEA (3.0 eq), **EV-90** was obtained after prep-HPLC (basic) as a yellow oil (21 mg, 12%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 2.5 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 2.5 Hz, 1H), 7.81 – 7.71 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 6.6 Hz, 1H), 7.33 – 7.24 (m, 1H), 7.05 (t, *J* = 7.9 Hz, 1H), 6.49 (dd, *J* = 16.7, 1.8 Hz, 1H), 6.02 (dd, *J* = 16.8, 10.4 Hz, 1H), 5.62 (dd, *J* = 10.3, 1.8 Hz, 1H), 5.17 (s, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{19}H_{15}ClFN_2O$ 341.0852, found 341.0854.



SI-91 **SI-92** **EV-91**

Step 1: Following **General Procedure 4**, starting with 2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (100 mg, 0.58 mmol, 1.0 eq) and benzoyl chloride (1.0 eq), **SI-91** was obtained as crude product and used in the next step without purification.

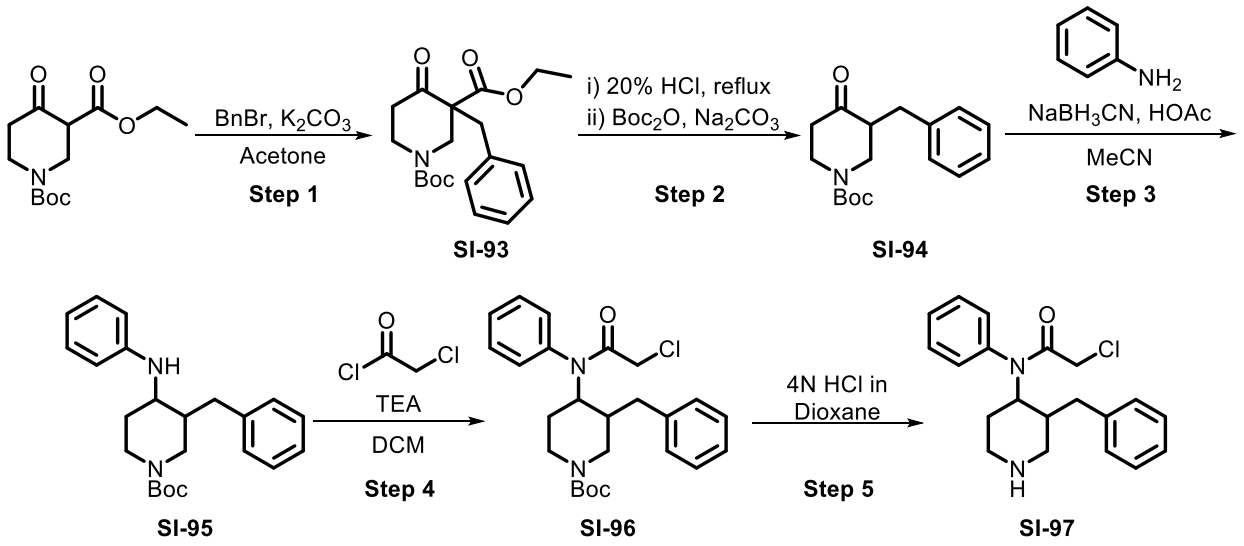
Step 2: $NaBH_3CN$ (73 mg, 1.2 mmol, 2.0 eq) was added to a solution of **SI-91** (160 mg, 0.58 mmol, 1.0 eq) in TFA (2 mL) at 0 °C. The reaction mixture was warmed to 20 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and the pH of the resulting residue was adjusted to pH 10 with aq. $NaHCO_3$ (30 mL). The aqueous phase was extracted with EtOAc (10 mL x 3) and the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **SI-92** (160 mg, crude) as a yellow oil which was used without purification.

Step 3: Following **General Procedure 1**, starting with **SI-92** (160 mg, 0.57 mmol, 1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (3.0 eq), **EV-91** was obtained after prep-HPLC (FA) as a yellow solid (63 mg, 31%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (br s, 1H), 7.39 (br s, 3H), 7.26 (t, *J* = 7.8 Hz, 2H), 7.22 (br s, 1H), 7.12 (br s, 1H), 7.03 (br s, 1H), 4.93 – 4.45 (m, 1H), 4.38 – 3.97 (m, 1H), 3.80 (br s, 1H), 3.67 (br s, 1H), 3.55 – 3.36 (m, 1H), 3.09 (br s, 1H), 2.91 (br s, 1H), 2.39 – 2.03 (m, 2H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{20}H_{20}ClN_2O_2$ 355.1208, found 355.1207.

Synthesis of SI-97 as a precursor for EV-94 and EV-95



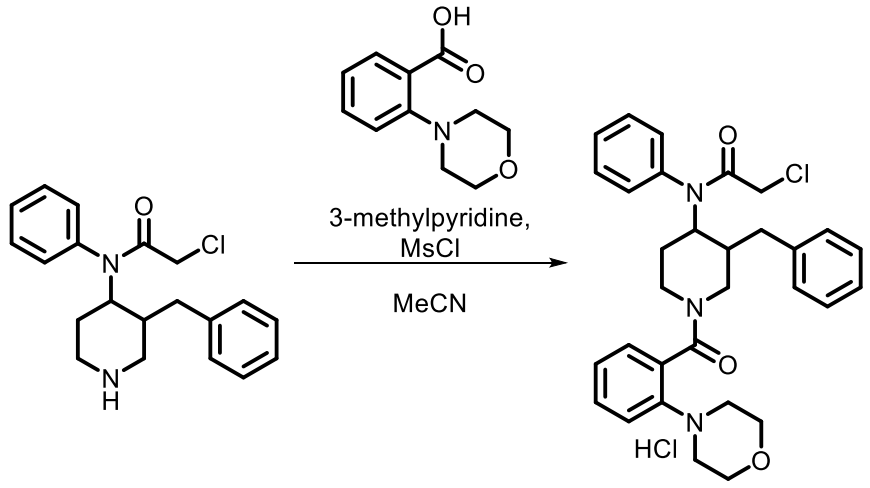
Step 1: Benzyl bromide (1.8 mL, 14.8 mmol, 2.0 eq) was added dropwise to a solution of *N*-Boc-3-carboethoxy-4-piperidone (2.0 g, 7.4 mmol, 1.0 eq) and K_2CO_3 (3.1 g, 22 mmol, 3.0 eq) in acetone (80 mL). The mixture was stirred at reflux for 12 h. The reaction was cooled and then filtered. The filtrate was concentrated and H_2O (50 mL) was added. The solution was extracted with EtOAc (40 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to provide **SI-93** (1.7 g, crude) which was used in the next step without purification.

Step 2: SI-93 (1.7 g, 4.7 mmol, 1.0 eq) was dissolved in 20% HCl (25 mL) and heated to reflux for 48 h. The solvent was removed and the resulting residue was dissolved in THF (50 mL). Boc_2O (2.0 g, 9.2 mmol, 2.0 eq) and Na_2CO_3 (1.5 g, 14.1 mmol, 3.0 eq) were added and the mixture was stirred for 12 h. H_2O (50 mL) was added the mixture was extracted with EtOAc (40 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated to provide **SI-94** as a crude product which was used without purification.(Hartman and Flores, 2013)

Step 3: Following **General Procedure 5**, starting with **SI-94** (1.0 eq) and aniline (1.0 eq), **SI-95** was obtained as a crude product and was used in the next step without purification.

Step 4: Following **General Procedure 1**, starting with **SI-95** (1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (5.0 eq), **SI-96** was obtained as crude product and used without purification.

Step 5: HCl/dioxane (4N, 1.1 mL, 5.0 eq) was added to a solution of **SI-95** (400 mg, 0.87 mmol, 1.0 eq) in dioxane (2 mL) at 0 °C. The reaction was warmed to 25 °C and stirred for 3 h. The reaction was concentrated under reduced pressure and partitioned between DCM (20 mL) and saturated $NaHCO_3$ (20 mL). The aqueous phase was extracted with DCM (20 mL x 2) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to provide **SI-96** (300 mg, crude) which was used without purification.

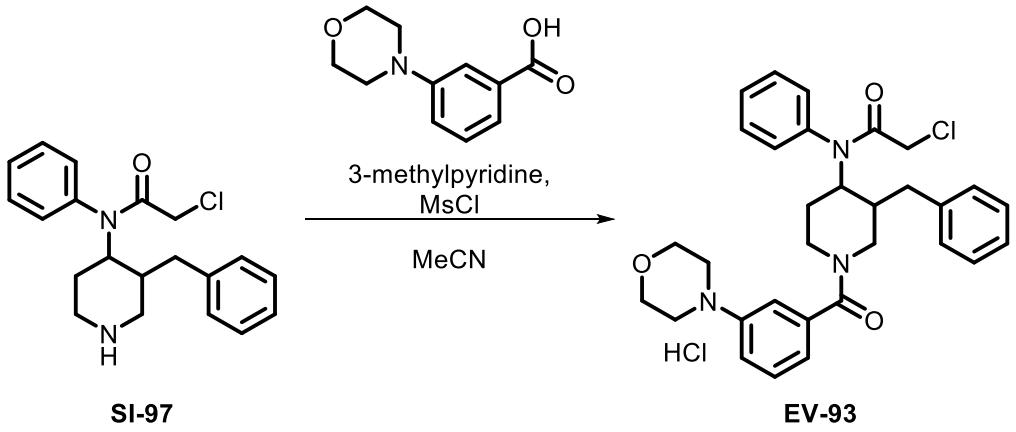


SI-97 **EV-92**

3-methylpyridine (85 µL, 0.87 mmol, 3.0 eq) and MsCl (34 µL, 0.44 mmol, 1.5 eq) were added to a solution of **SI-97** (100 mg, 0.29 mmol, 1.0 eq) and 2-morpholinobenzoic acid (60 mg, 0.29 mmol, 1.0 eq) in MeCN (1 mL) at 0 °C. The reaction was warmed to 25 °C and stirred for 3 h. The mixture was quenched with H_2O (1 mL) and extracted with EtOAc (0.5 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by prep. HPLC (HCl) to provide **EV-92** (9 mg, 5%) as a white solid.

^{1}H NMR (400 MHz, MeOD) δ 7.63 – 7.47 (m, 4H), 7.46 – 7.39 (m, 1H), 7.38 – 7.28 (m, 4H), 7.27 – 7.21 (m, 2H), 7.21 – 7.11 (m, 1H), 7.05 – 6.74 (m, 2H), 4.66 – 4.51 (m, 1H), 3.95 – 3.81 (m, 2H), 3.77 – 3.61 (m, 4H), 3.41 – 3.32 (m, 2H), 3.18 – 2.99 (m, 4H), 2.98 – 2.85 (m, 3H), 2.82 – 2.61 (m, 2H), 1.76 – 1.42 (m, 2H).

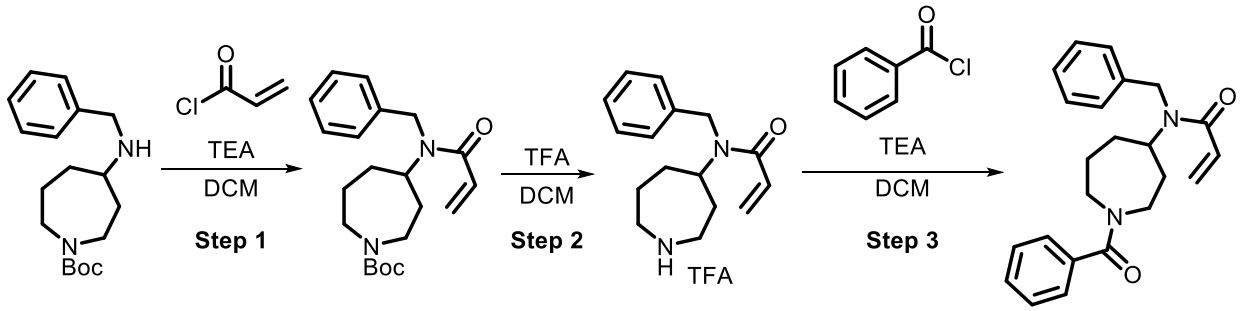
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{31}H_{34}ClN_3O_3$ 523.2362, found 532.2363.



SI-97 **EV-93**

3-methylpyridine (85 µL, 0.87 mmol, 3.0 eq) and MsCl (34 µL, 0.44 mmol, 1.5 eq) were added to a solution of **SI-97** (100 mg, 0.29 mmol, 1.0 eq) and 3-morpholinobenzoic acid (60 mg, 0.29 mmol, 1.0 eq) in MeCN (1 mL) at 0 °C. The reaction was warmed to 25 °C and stirred for 3 h. The mixture was quenched with H_2O (1 mL) and extracted with EtOAc (0.5 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by prep. HPLC (HCl) to provide **EV-93** (17 mg, 11%) as a white solid.

^{1}H NMR (400 MHz, MeOD) δ 7.50 (br s, 5H), 7.39 – 7.26 (m, 3H), 7.23 – 7.09 (m, 3H), 7.06 – 6.97 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 4.67 – 4.57 (m, 2H), 3.90 – 3.77 (m, 5H), 3.74 – 3.66 (m, 1H), 3.56 – 3.45 (m, 1H), 3.26 – 3.18 (m, 3H), 3.15 – 3.04 (m, 1H), 3.04 – 2.96 (m, 1H), 2.95 – 2.85 (m, 1H), 2.84 – 2.77 (m, 1H), 2.50 (br s, 1H), 1.73 – 1.51 (m, 2H).



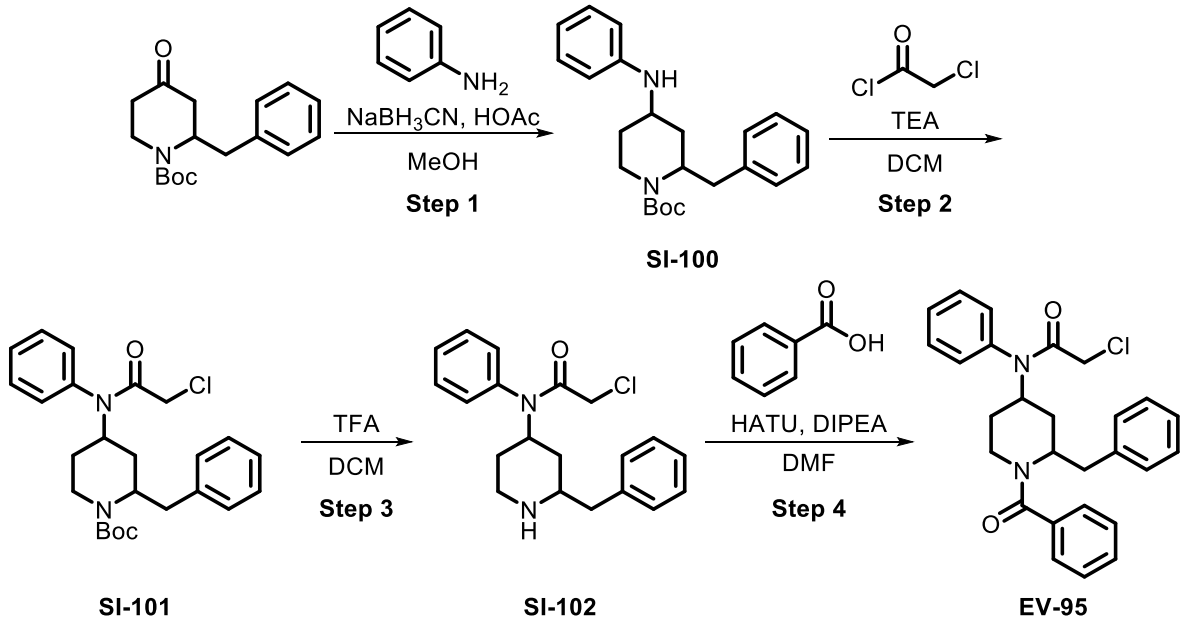
Step 1: Following **General Procedure 2**, starting with *tert*-butyl 4-(benzylamino)azepane-1-carboxylate (1.0 eq)[(Bar-Peled et al., 2017)], acryloyl chloride (1.0 eq), and TEA (3.0 eq), **SI-98** was obtained as crude product and used without purification.

Step 2: TFA (1.5 mL, 19.5 mmol, 5.0 eq) was added to a solution of **SI-98** (1.4 g, 3.9 mmol, 1.0 eq) in DCM (10 mL) and the resulting mixture was stirred for 0.5 h. The reaction was quenched by the addition of water (20 mL) and extracted with DCM (10 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to provide **SI-99** (800 mg, crude) as a yellow oil which was used without purification.

Step 3: Following **General Procedure 4**, starting with **SI-99** (1.0 eq) and benzoyl chloride (1.2 eq), **EV-94** (50 mg, 3%) was obtained after prep-HPLC (basic) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 8H), 7.21 (t, *J* = 8.1 Hz, 2H), 6.47 – 6.29 (m, 2H), 5.70 – 5.59 (m, 1H), 4.63 – 4.47 (m, 3H), 3.96 (dd, *J* = 89.1, 14.1 Hz, 1H), 3.60 – 3.37 (m, 2H), 3.36 – 3.17 (m, 2H), 2.14 – 1.89 (m, 2H), 1.85 – 1.70 (m, 3H), 1.70 – 1.59 (m, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{23}H_{27}N_2O_2$ 363.2067, found 363.2073.



Step 1: Following **General Procedure 5**, starting with 1-Boc-2-benzyl-4-piperidinone (1.0 eq) and aniline (1.0 eq), **SI-100** (300 mg, crude) was obtained as a crude product and used without purification.

Step 2: Following **General Procedure 1**, starting with **SI-100** (1.0 eq), chloroacetyl chloride (2.0 eq), and TEA (5.0 eq), **SI-101** (150 mg, crude) was obtained and used without purification.

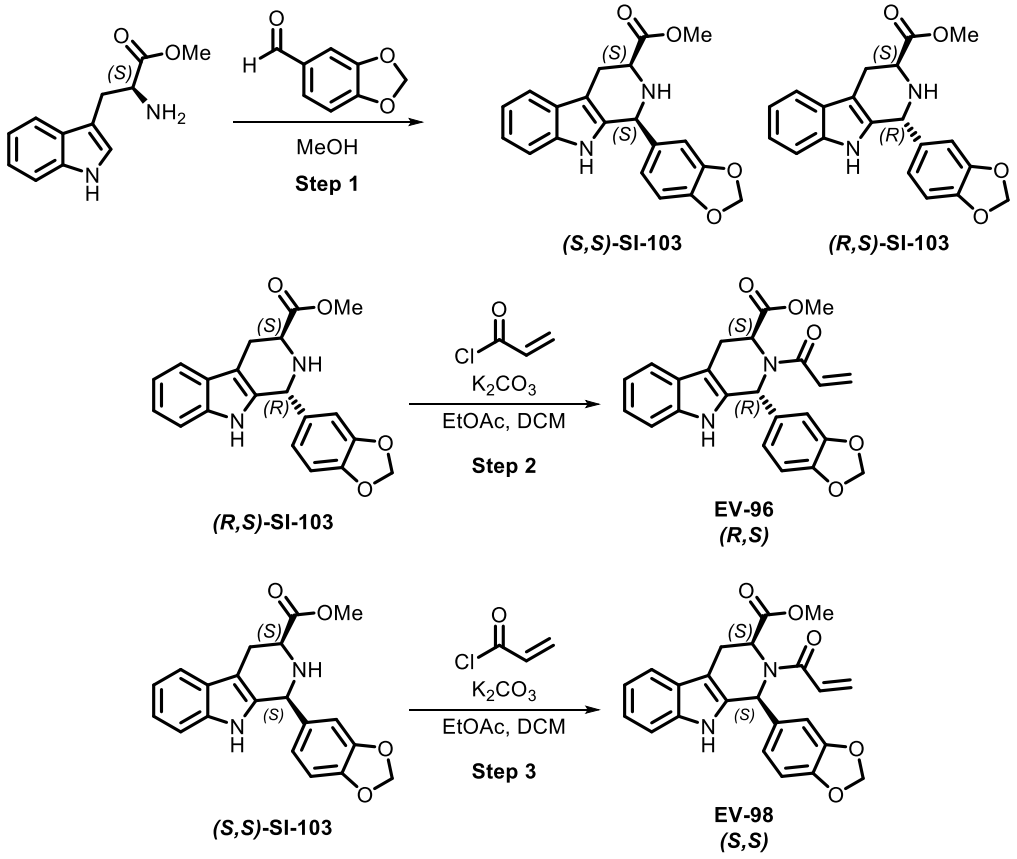
Step 3: TFA (25 µL, 0.34 mmol, 1.0 eq) was added to a solution of **SI-101** (150 mg, 0.34 mmol, 1.0 eq) in DCM (1 mL) at 0 °C. The mixture was then warmed to 25 °C and stirred for 2 h. The reaction was quenched with water (3 mL) and extracted with DCM (1 mL x 3). The combined organic layers were washed with brine (2 mL x 3), dried over anhydrous Na_2SO_4, and concentrated to provide **SI-102** (100 mg, crude) which was used in the next step without purification.

Step 4: Following **General Procedure 3**, starting with **SI-102** (1.0 eq) and benzoic acid (1.2 eq), **EV-95** (27 mg, 13%) was obtained after prep-HPLC (TFA) as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 – 7.44 (m, 3H), 7.43 – 7.36 (m, 3H), 7.28 – 7.15 (m, 7H), 7.06 (d, *J* = 7.2 Hz, 2H), 4.50 (d, *J* = 10.4 Hz, 1H), 4.21 (br s, 1H), 3.75 (s, 2H), 3.42 (d, *J* = 7.1 Hz, 1H), 3.07 – 2.97 (m, 1H), 2.91 (dd, *J* = 13.2, 5.4 Hz, 1H), 2.79 (dd, *J* = 13.1, 7.8 Hz, 1H), 2.06 – 1.90 (m, 1H), 1.81 (br s, 1H), 1.50 (q, *J* = 12.2 Hz, 1H), 1.34 (br s, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{27}H_{28}ClN_2O_2$ 447.1834, found 447.1836.

Synthesis of EV-96 and EV-98



Step 1: Following a procedure described in the literature (Xiao et al., 2009b) starting from *L*-tryptophan methyl ester hydrochloride (1.5 g, 5.9 mmol, 1.0 eq) and piperonal (1.2 eq) provided *(S,S)*-**SI-103** (1.1 g, 55%) and *(R,S)*-**SI-103** (532 mg, 26%) after recrystallisation as described in the literature (Xiao et al., 2009a).

Step 2: Following **General Procedure 6**, starting from (*R*,*S*)-**SI-103** (29 mg, 0.08 mmol,1.0 eq), acryloyl chloride (1.5 eq), and K_2CO_3 (3.0 eq) followed by purification by flash column chromatography (SiO_2, hexanes/EtOAc 9:1 to 1:1) afforded **EV-96** as a white foam (18 mg, 54%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.53 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.24 (s, 1H), 7.19 – 7.14 (m, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 6.80 (s, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.57 (dd, *J* = 16.7, 10.5 Hz, 1H), 6.29 (dd, *J* = 16.7, 1.7 Hz, 1H), 6.12 (s, 1H), 6.00 – 5.87 (m, 2H), 5.64 (d, *J* = 10.5 Hz, 1H), 5.14 (t, *J* = 5.2 Hz, 1H), 3.63 (s, 3H), 3.60 – 3.48 (m, 1H), 3.41 – 3.19 (m, 1H).

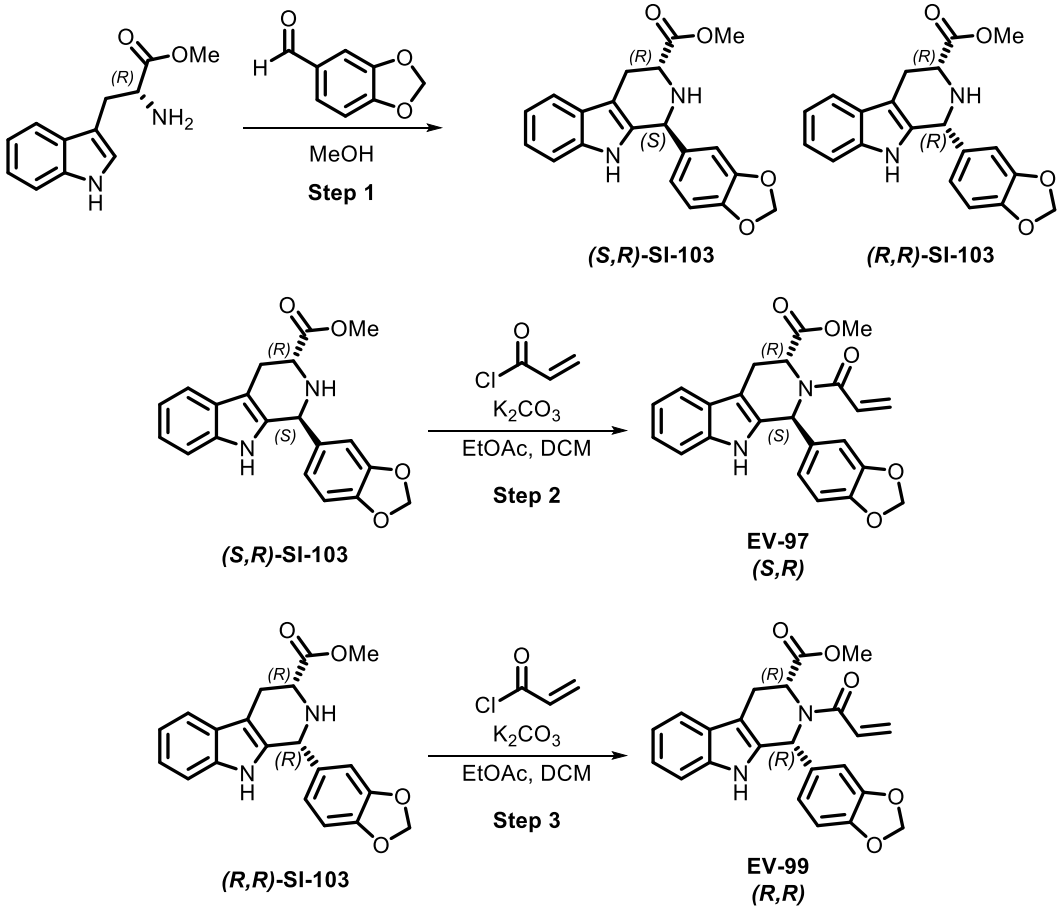
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{23}H_{20}N_2O_5$ 405.1445, found 405.1452.

Step 3: Following **General Procedure 6**, starting from (*S*,*S*)-**SI-103** (68 mg, 0.19 mmol, 1.0 eq), acryloyl chloride (1.5 eq), and K_2CO_3 (3.0 eq) followed by purification by flash column chromatography (SiO_2, hexanes/EtOAc 9:1 to 1:1) afforded **EV-98** as a white foam (22 mg, 28%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.59 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.29 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H), 7.15 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.98 (s, 1H), 6.93 (d, *J* = 1.4 Hz, 1H), 6.76 – 6.58 (m, 3H), 6.31 (s, 1H), 5.90 (d, *J* = 3.5 Hz, 2H), 5.77 (dd, *J* = 10.8, 1.6 Hz, 1H), 5.05 (s, 1H), 3.67 (d, *J* = 15.7 Hz, 1H), 3.36 – 3.14 (m, 3H), 3.06 (dd, *J* = 15.8, 6.8 Hz, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{23}H_{20}N_2O_5$ 405.1445, found 405.1453.

Synthesis of EV-97 and EV-99



Step 1: Following a procedure described in the literature (Xiao et al., 2009b) starting from *D*-tryptophan methyl ester hydrochloride (1.0 g, 3.9 mmol, 1.0 eq) and piperonal (1.2 eq) provided *(S,R)*-**SI-103** (162 g, 12%) and *(R,R)*-**SI-103** (413 mg, 30%) after recrystallisation as described in the literature (Xiao et al., 2009a).

Step 2: Following **General Procedure 6**, starting with (*S*,*R*)-**SI-103** (76 mg, 0.22 mmol, 1.0 eq), acryloyl chloride (1.5 eq), and K_2CO_3 (3.0 eq) followed by purification by flash column chromatography (SiO_2, hexanes/EtOAc 9:1 to 1:1) afforded **EV-97** as a white foam (30 mg, 34%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.53 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.25 (s, 1H), 7.19 – 7.13 (m, 1H), 7.12 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.86 (s, 1H), 6.80 (s, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.56 (dd, *J* = 16.7, 10.5 Hz, 1H), 6.29 (dd, *J* = 16.7, 1.7 Hz, 1H), 6.11 (s, 1H), 5.92 (d, *J* = 11.4 Hz, 2H), 5.64 (d, *J* = 10.6 Hz, 1H), 5.14 (t, *J* = 5.1 Hz, 1H), 3.64 (s, 3H), 3.57 (dd, *J* = 13.8, 9.1 Hz, 1H), 3.25 (s, 1H).

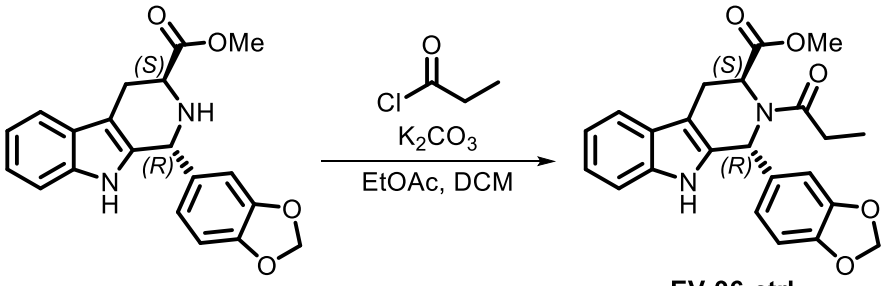
HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{23}H_{20}N_2O_5$ 405.1445, found 405.1449.

Step 3: Following **General Procedure 6**, starting with (*R*,*R*)-**SI-103** (87 mg, 0.3 mmol, 1.0 eq), acryloyl chloride (1.5 eq), and K_2CO_3 (3.0 eq) followed by purification by flash column chromatography (SiO_2, hexanes/EtOAc 9:1 to 1:1) afforded **EV-99** as a white foam (68 mg, 67%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.59 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.29 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H), 7.15 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.98 (s, 1H), 6.92 (s, 1H), 6.65 (s, 3H), 6.40 – 6.22 (m, 1H), 5.91 – 5.87 (m, 2H), 5.77 (dd, *J* = 10.8, 1.7 Hz, 1H), 5.17 – 4.96 (m, 1H), 3.67 (d, *J* = 15.7 Hz, 1H), 3.20 (s, 3H), 3.05 (dd, *J* = 16.3, 7.3 Hz, 1H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{23}H_{20}N_2O_5$ 405.1445, found 405.1449.

Synthesis of EV-96-ctrl



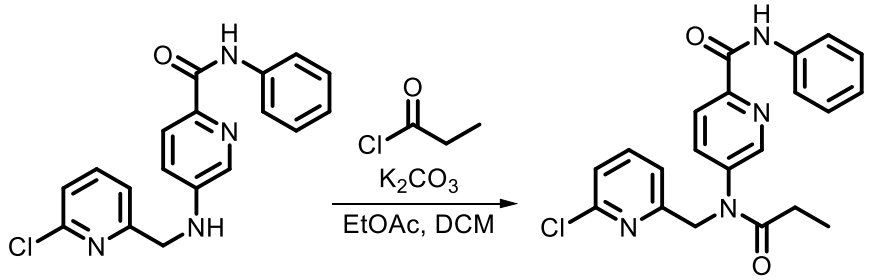
(R,S)*-SI-103** **EV-96-ctrl *(R,S)

Propanoyl chloride (186 µL, 0.45 mM solution in DCM, 1.3 eq) was slowly added to a mixture of the (*R*,*S*)-**SI-103** (35 mg, 0.1 mmol, 1.0 eq) and K_2CO_3 (42 mg, 0.3 mmol, 3.0 eq) in EtOAc (0.1 M) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 22 h. The reaction was quenched by the addition of half saturated NaCl (2 mL) and then extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by prep-HPLC (FA) to afford **EV-96-ctrl** (7.0 mg, 17%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (br, 1H), 7.52 (d, J = 7.3 Hz, 1H), 7.24 (br, 1H), 7.18 – 7.13 (m, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.90 – 6.65 (m, 3H), 6.01 (s, 1H), 5.92 (br, 2H), 5.27 – 5.03 (m, 1H), 3.62 (s, 3H), 3.56 – 3.11 (m, 2H), 2.45 (dq, J = 16.3, 7.3 Hz, 1H), 2.35 – 2.15 (br, 1H), 1.07 (br, 3H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{23}H_{23}N_2O_5$ 407.1601, found 407.1601

Synthesis of BPK-25-ctrl



SI-84 **BPK-25-ctrl**

Propanoyl chloride (0.45 mM solution in DCM, 1.5 eq) was slowly added to a mixture of the **SI-84** (10 mg, 0.03 mmol, 1.0 eq) and K_2CO_3 (3.0 eq) in EtOAc (0.05 M) at 0 °C. The reaction was allowed to warm to room temperature and stirred until complete disappearance of starting material (as monitored by TLC). The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, DCM/1M NH_3 in MeOH) to afford **BPK-25-ctrl** (7.0 mg, 59%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.58 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.35 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.86 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.80 – 7.73 (m, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.0, 0.8 Hz, 1H), 7.17 (tt, *J* = 7.5, 1.1 Hz, 1H), 5.16 – 4.86 (m, 2H), 2.19 (d, *J* = 8.1 Hz, 2H), 1.12 (t, *J* = 7.4 Hz, 3H).

HRMS ESI-TOF (*m/z*): $[M+H]^+$ for $C_{21}H_{20}ClN_4O_2$ 395.1270, found 395.1275

(B) References

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Bar-Peled, L., Kemper, E.K., Suciu, R.M., Vinogradova, E.V., Backus, K.M., Horning, B.D., Paul, T.A., Ichu, T.A., Svensson, R.U., Olucha, J.*, et al.* (2017). Chemical Proteomics Identifies Druggable Vulnerabilities in a Genetically Defined Cancer. Cell *171*, 696-709 e623.

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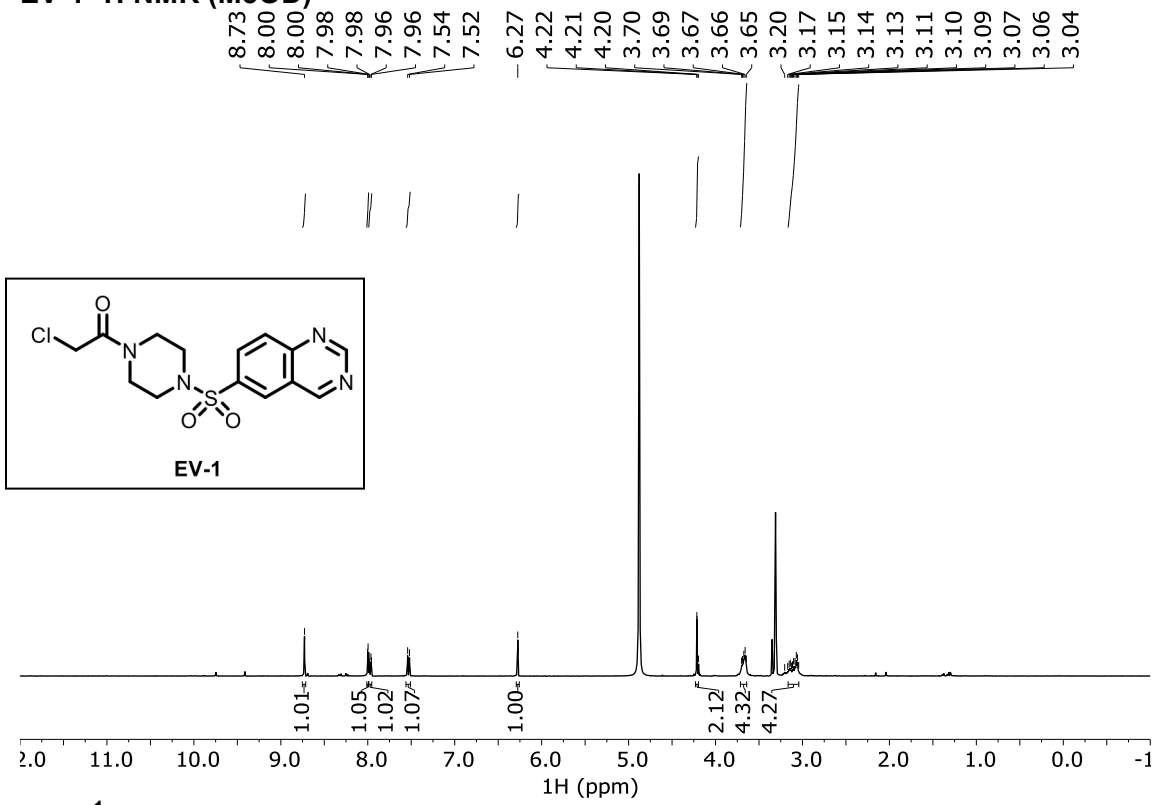
Xiao, S., Lu, X., Shi, X.-X., Sun, Y., Liang, L.-L., Yu, H.-H., and Dong, J. (2009a). Syntheses of chiral 1,3-disubstituted tetrahydro-β-carbolines via CIAT process: highly stereoselective Pictet–Spengler reaction of d-tryptophan ester hydrochlorides with various aldehydes. Tetrahedron: Asymmetry *20*, 430–439.

Xiao, S., Shi, X.-X., Xing, J., Yan, J.-J., Liu, S.-L., and Lu, W.-D. (2009b). Synthesis of tadalafil (Cialis) from L-tryptophan. . Tetrahedron: Asymmetry *20*, 2090–2096.

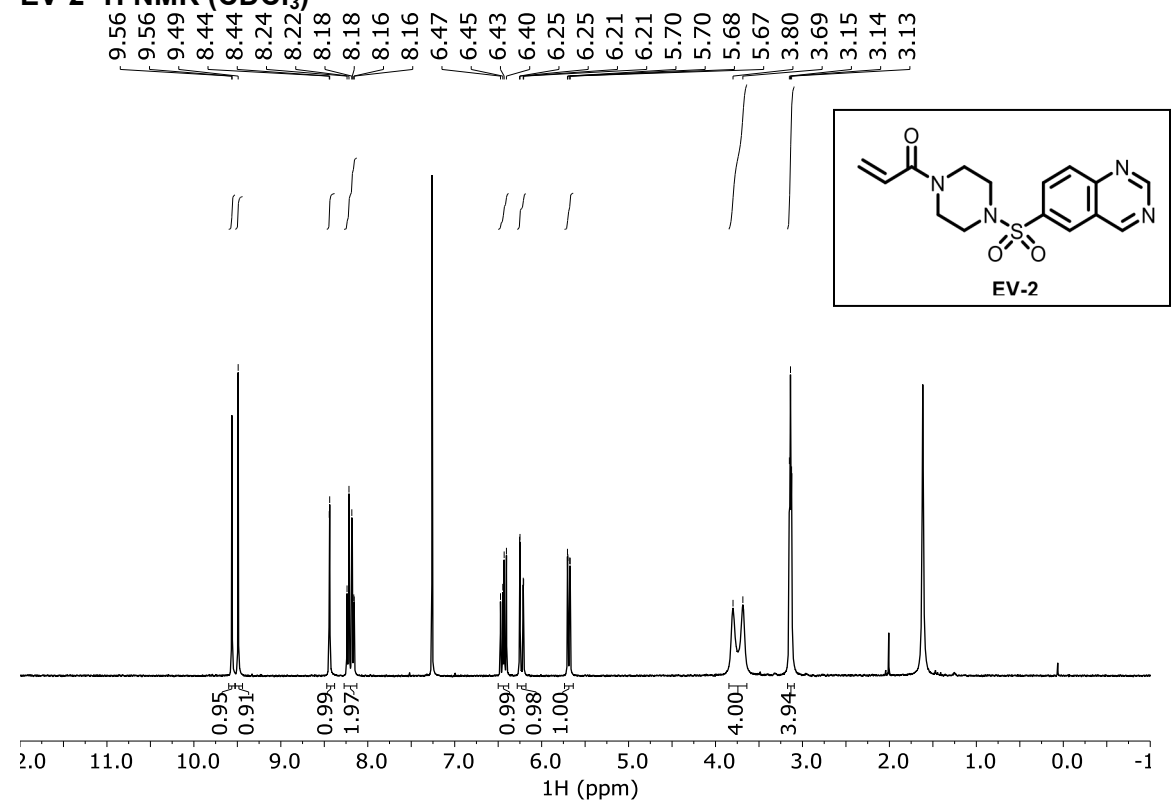
(C) NMR spectra

EV-1 ^{1}H NMR (MeOD)



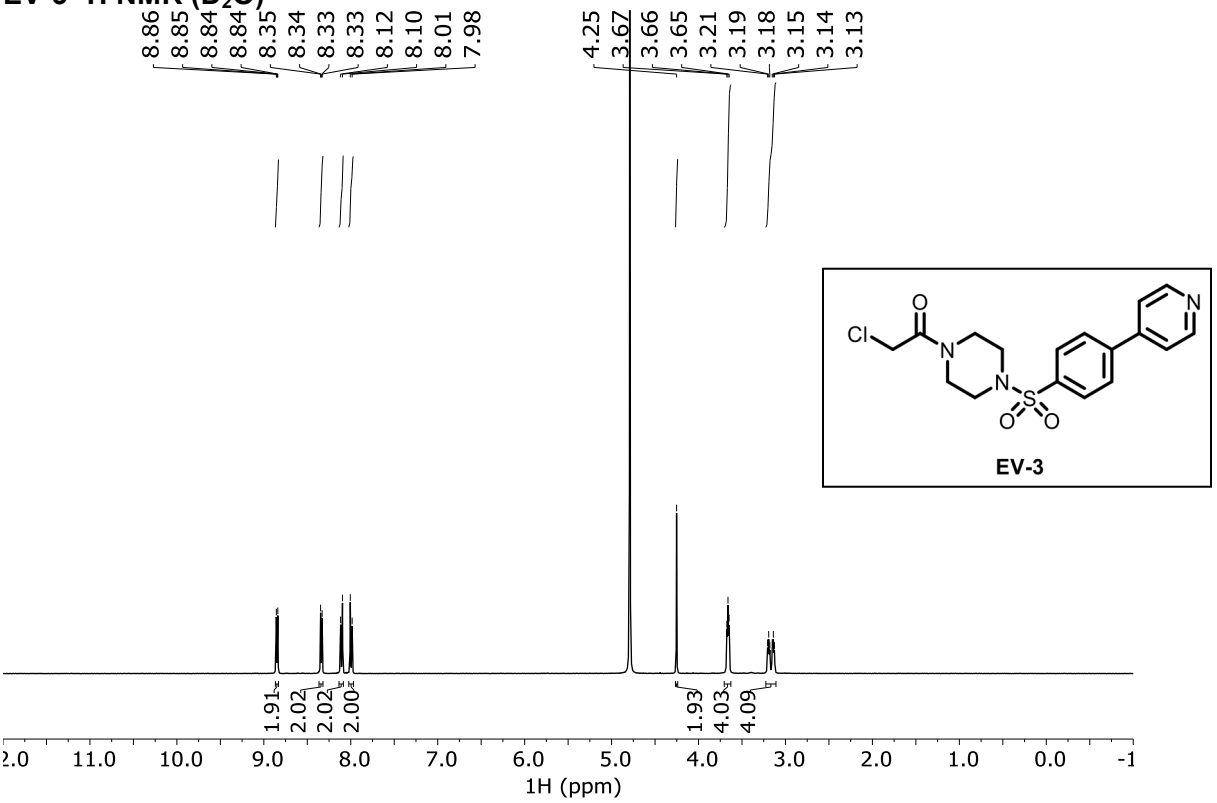
EV-1

EV-2 ^{1}H NMR ($CDCl_3$)



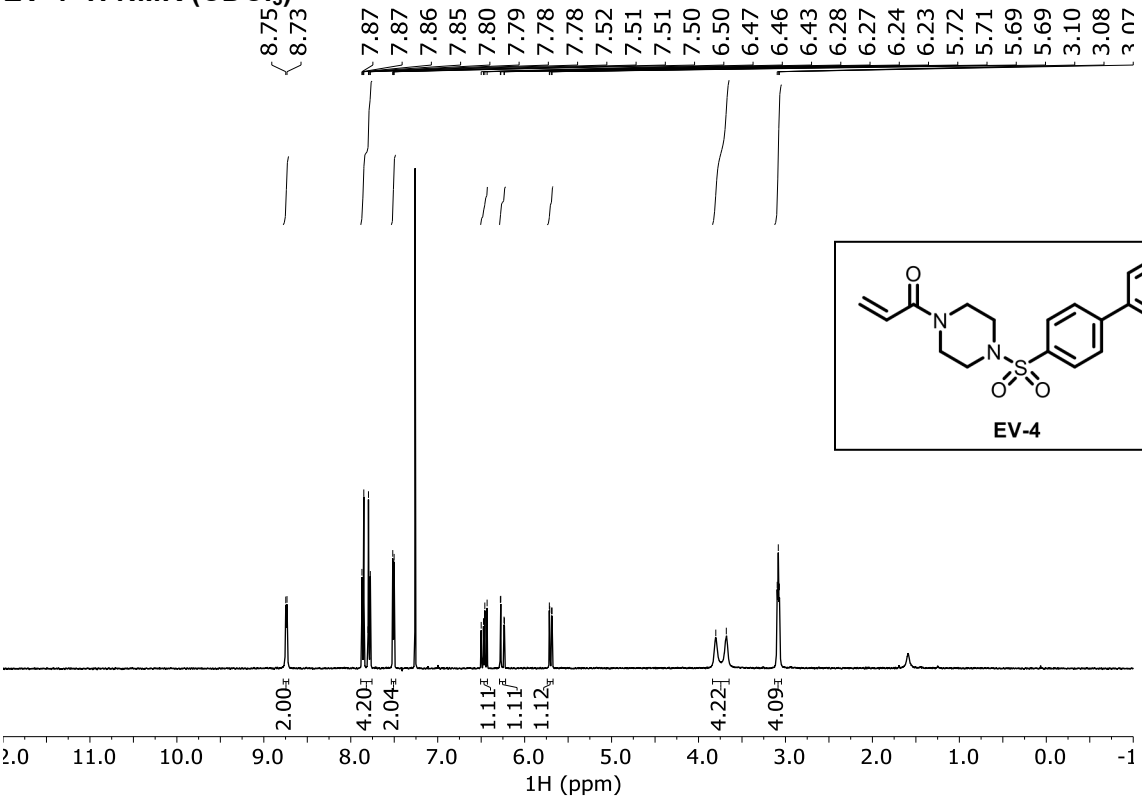
EV-2

EV-3 ^{1}H NMR (D_2O)



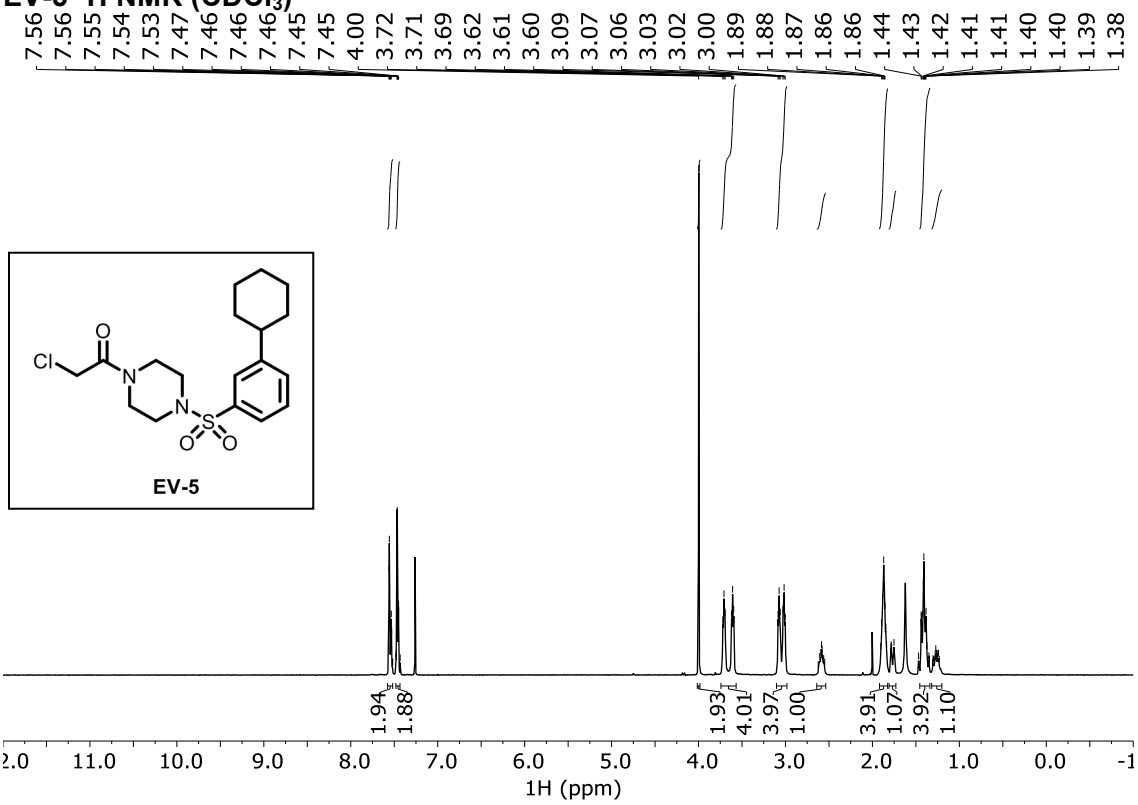
EV-3

EV-4 ^{1}H NMR ($CDCl_3$)

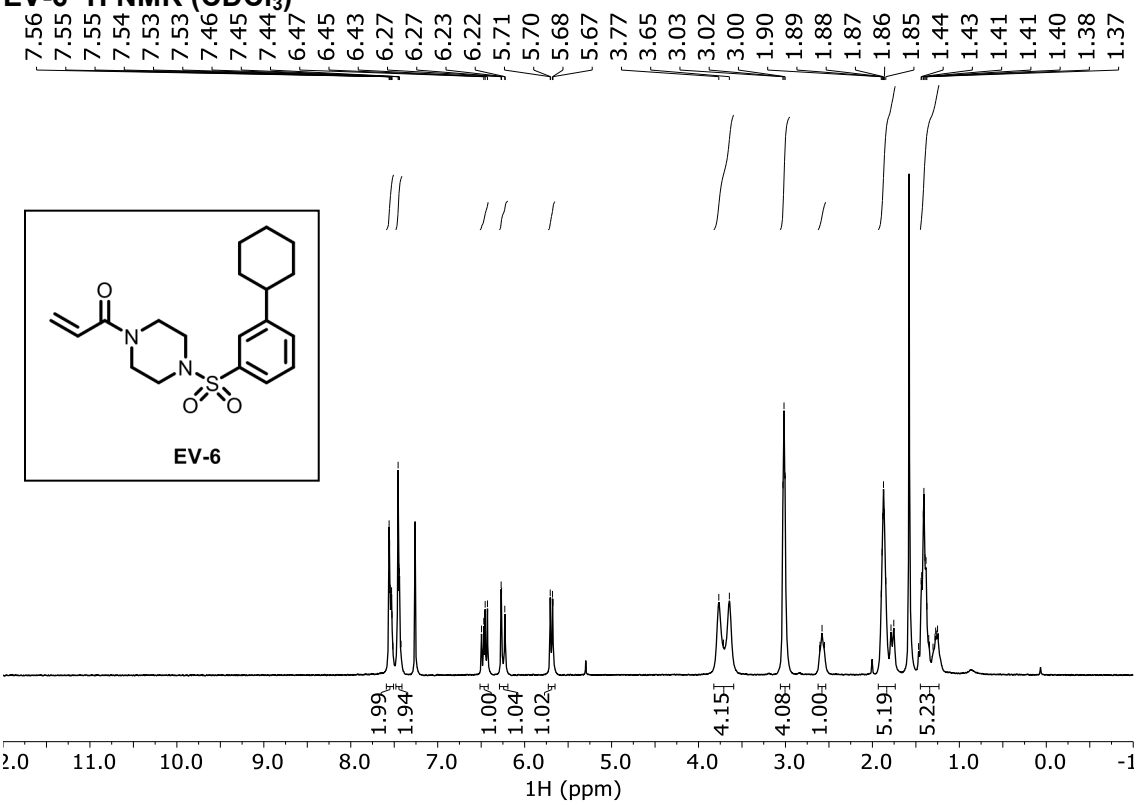


EV-4

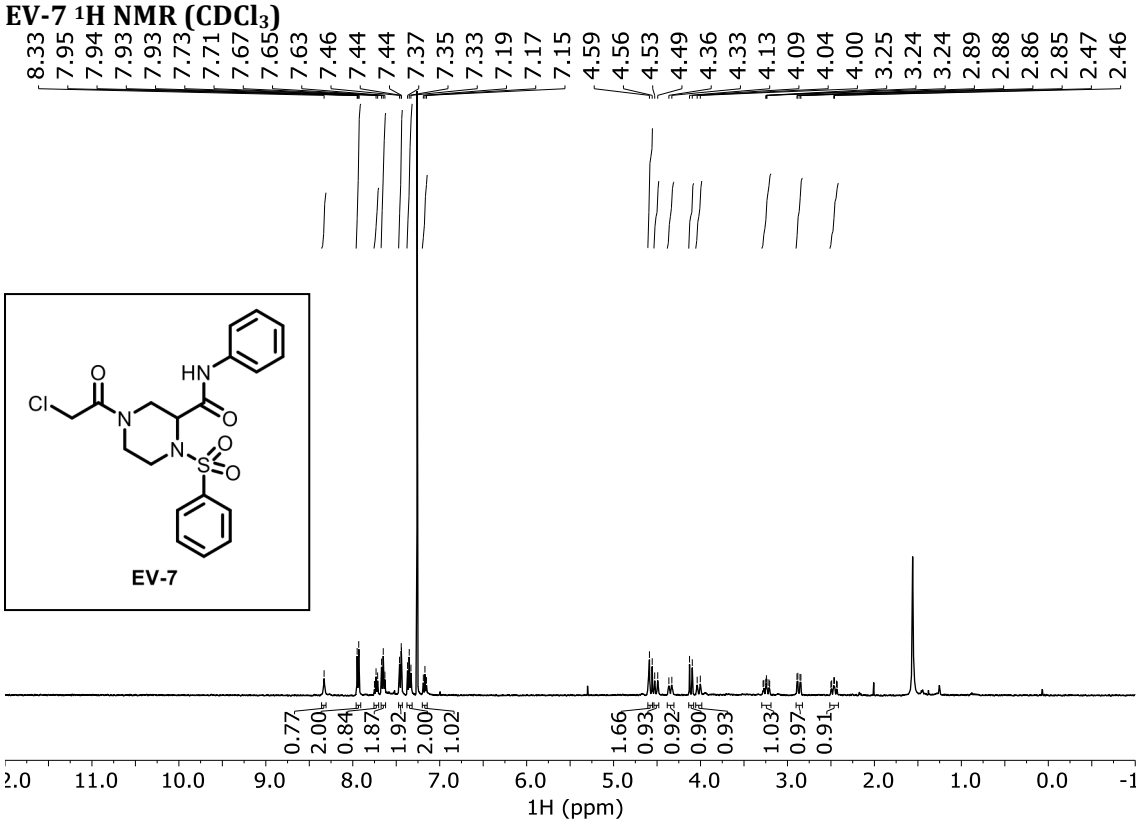
EV-5 ^{1}H NMR ($CDCl_3$)



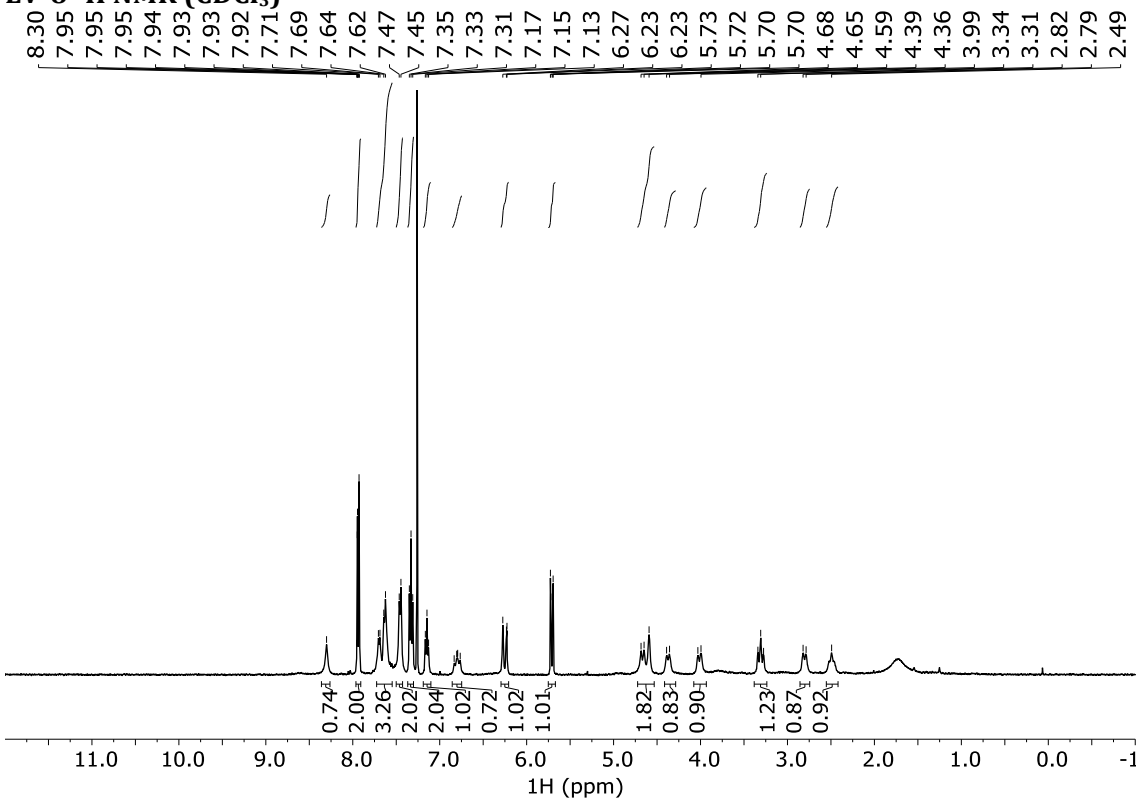
EV-6 ^{1}H NMR ($CDCl_3$)

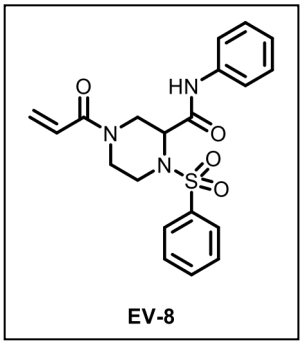


EV-7 ^{1}H NMR ($CDCl_3$)

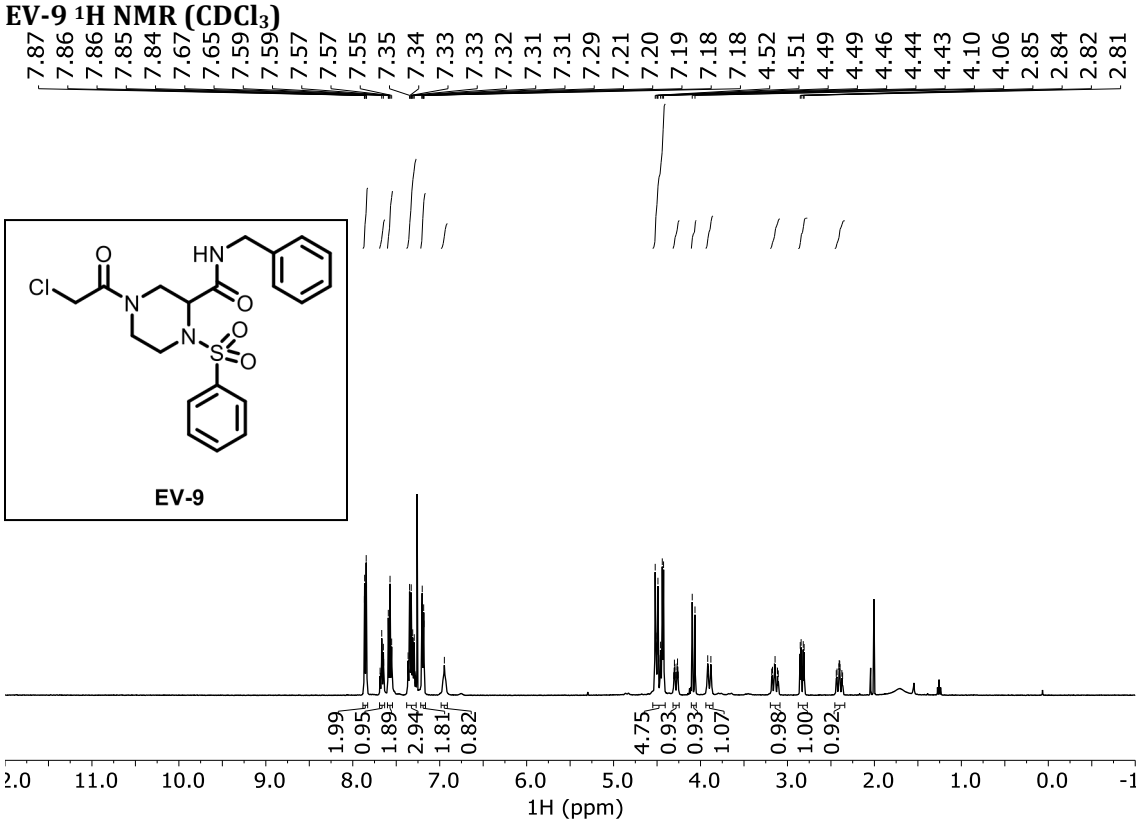


EV-8 ^{1}H NMR ($CDCl_3$)



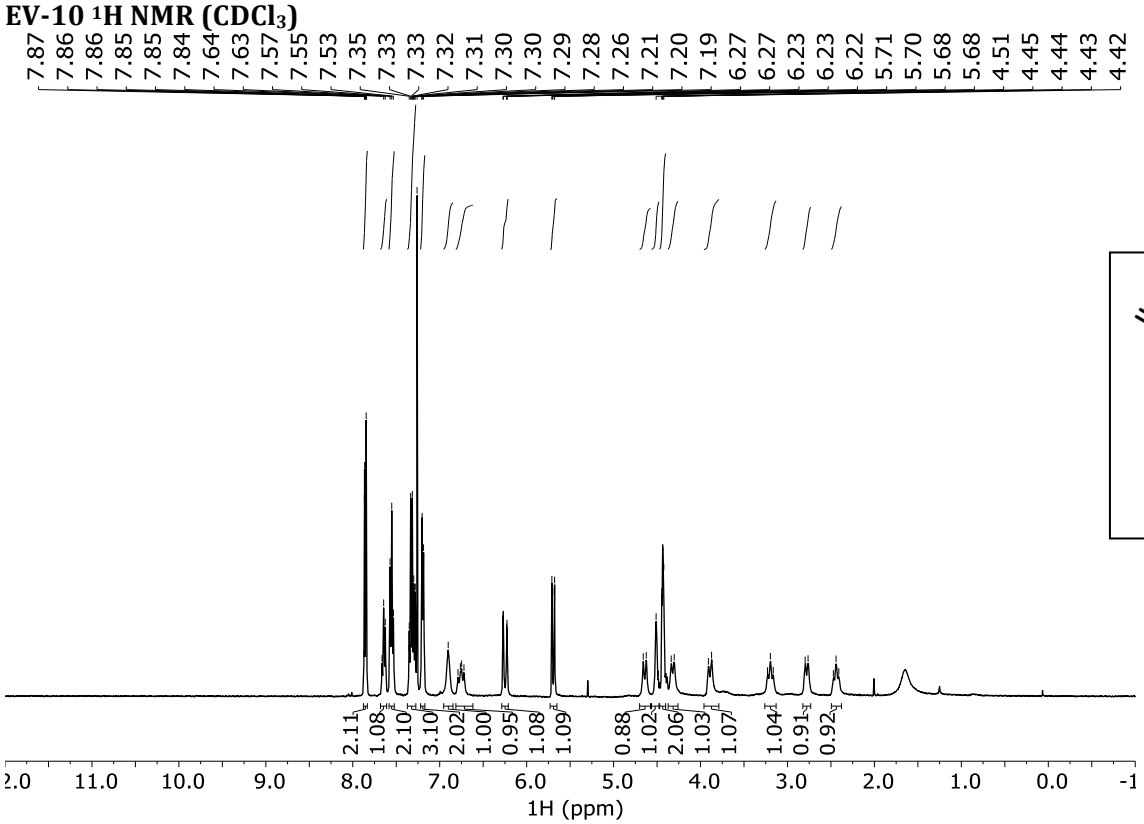


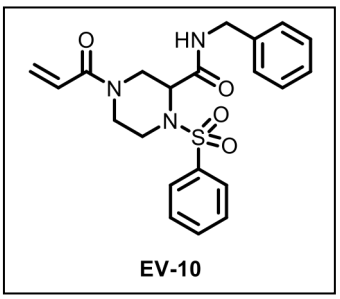
EV-9 ^{1}H NMR ($CDCl_3$)



EV-9

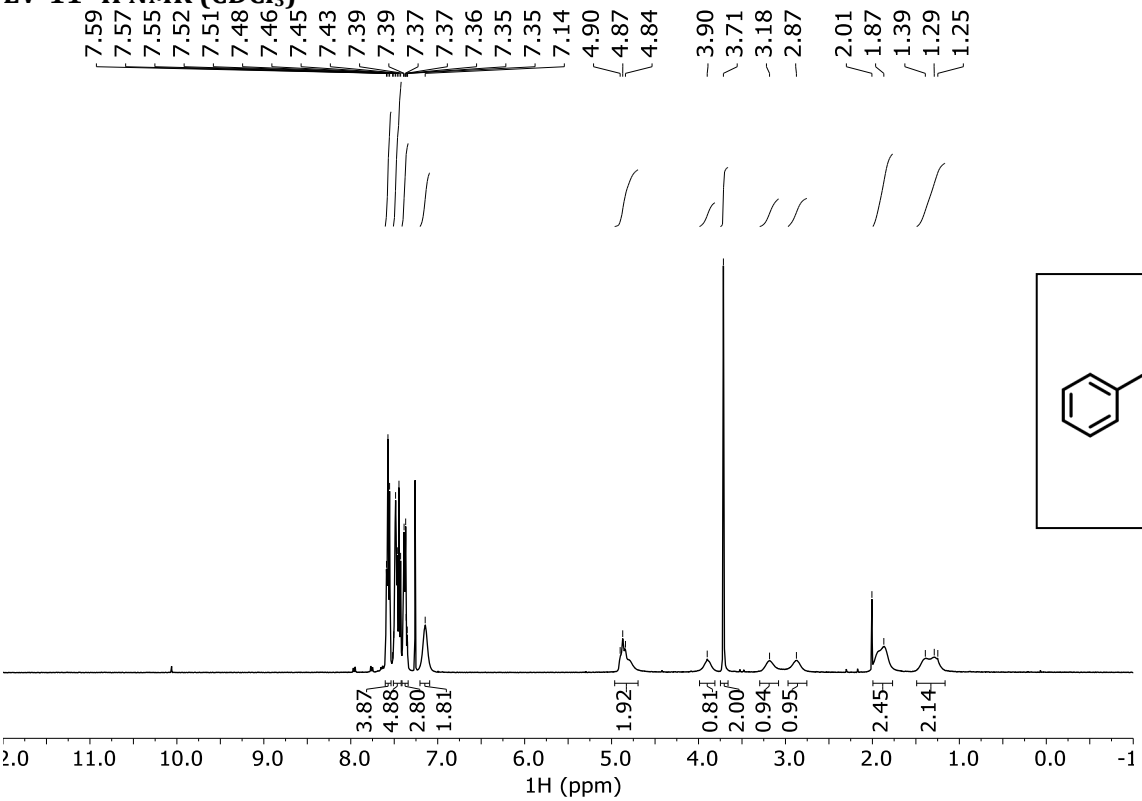
EV-10 ^{1}H NMR ($CDCl_3$)

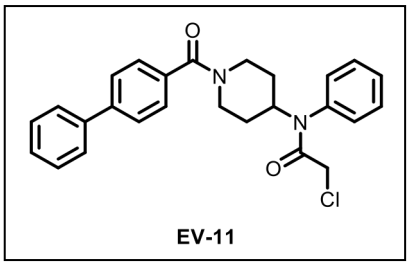




EV-10

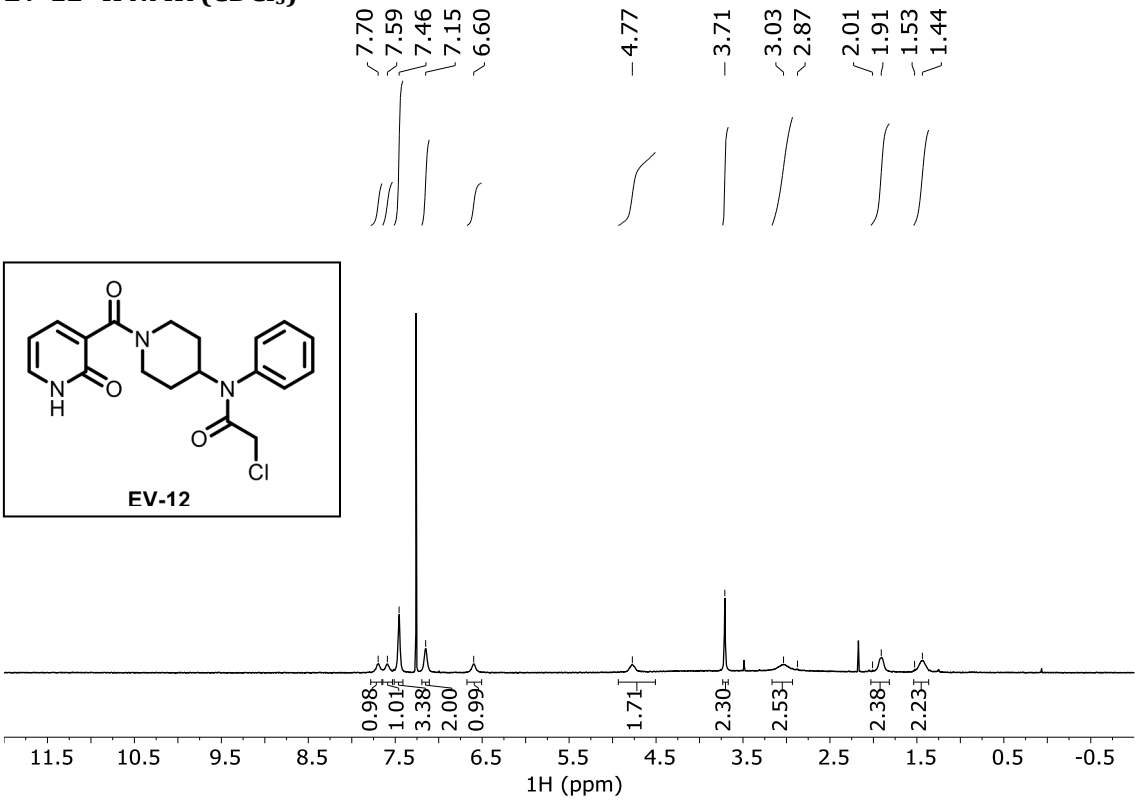
EV-11 ^{1}H NMR ($CDCl_3$)





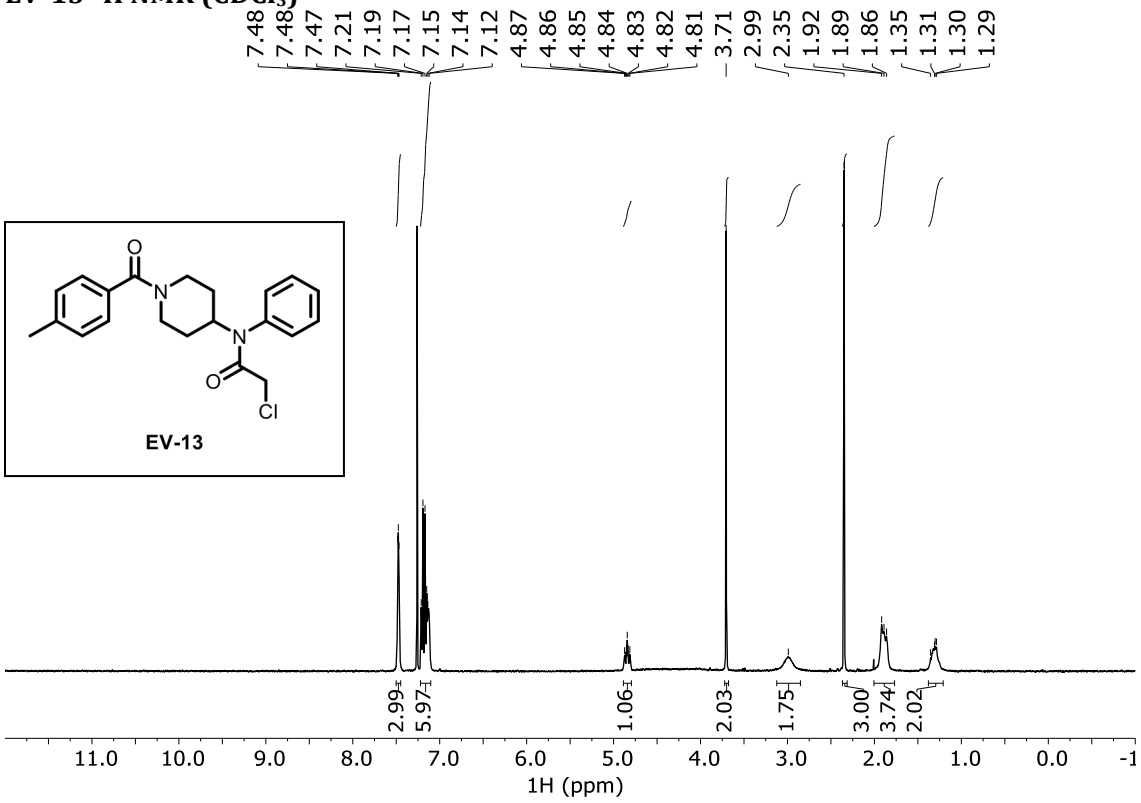
EV-11

EV-12 ^{1}H NMR ($CDCl_3$)

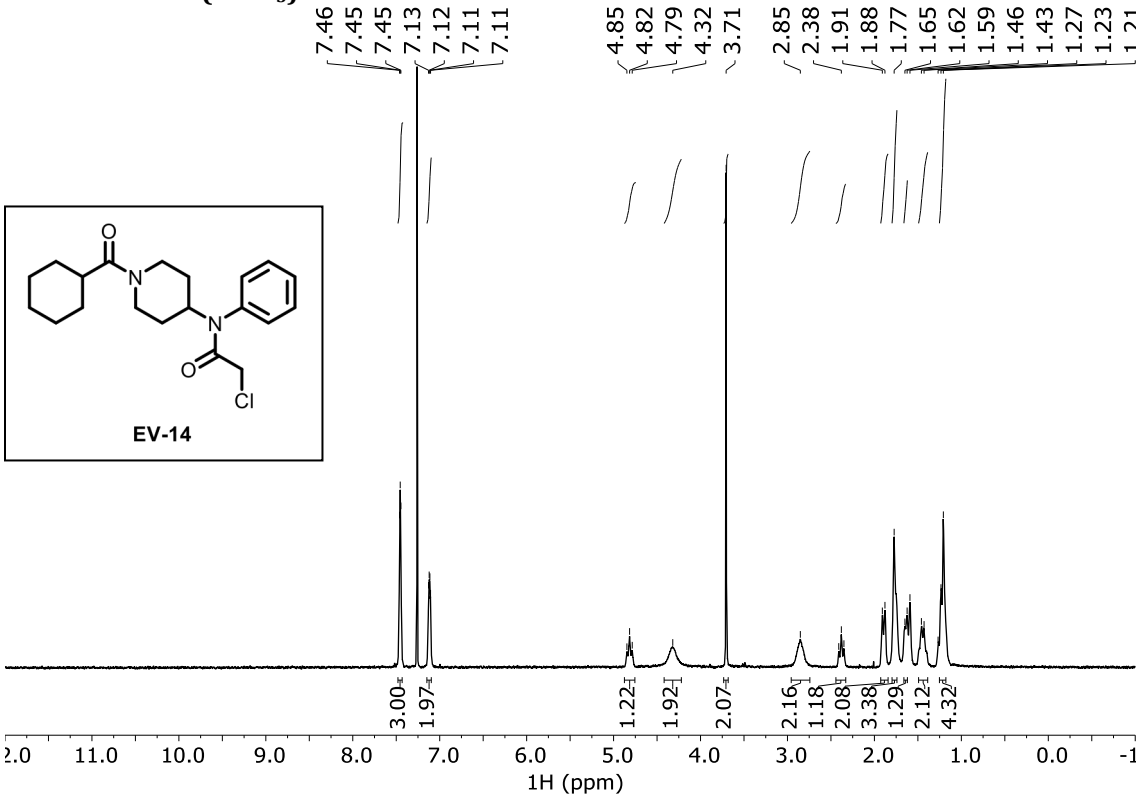


EV-12

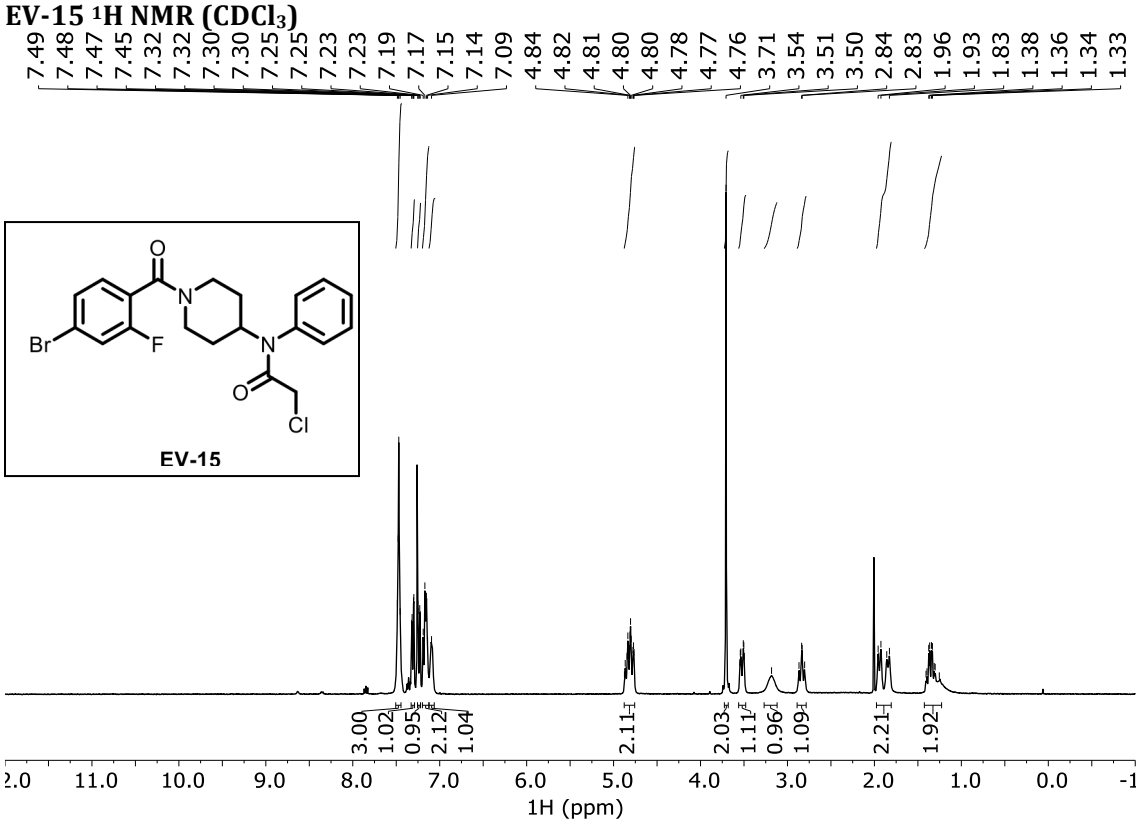
EV-13 ^{1}H NMR ($CDCl_3$)



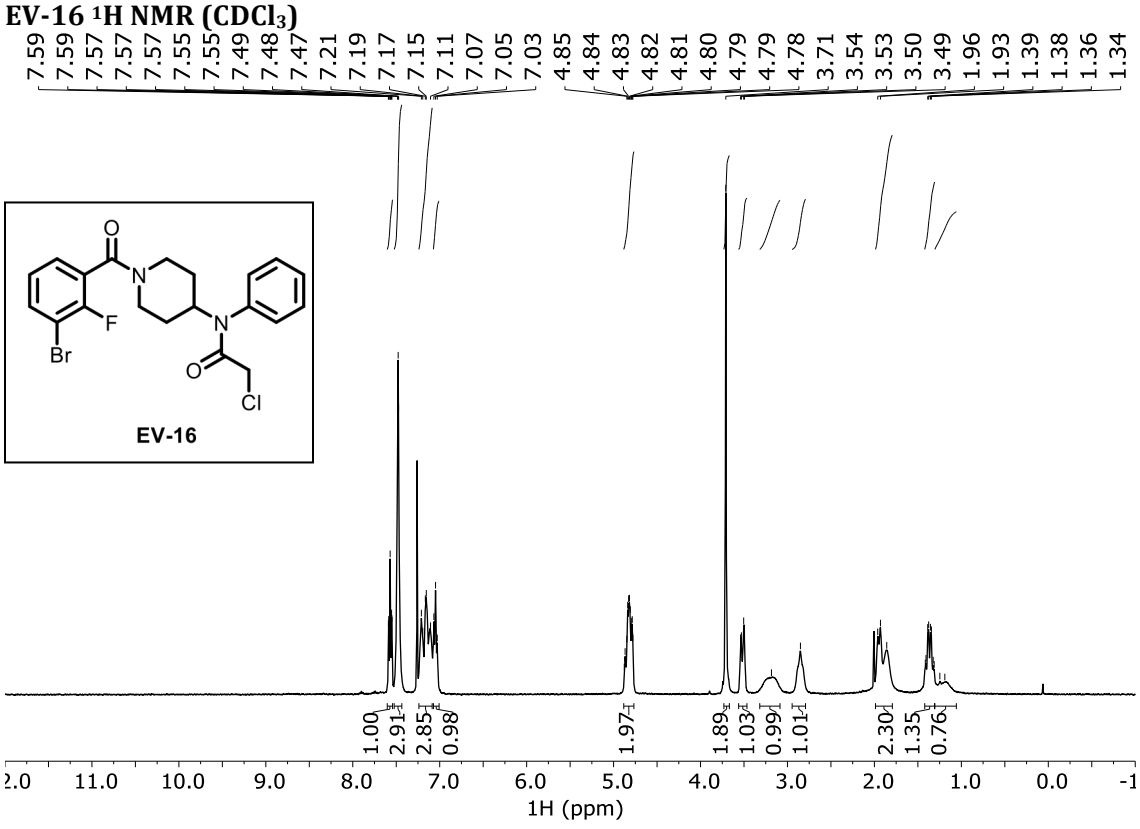
EV-14 ^{1}H NMR ($CDCl_3$)



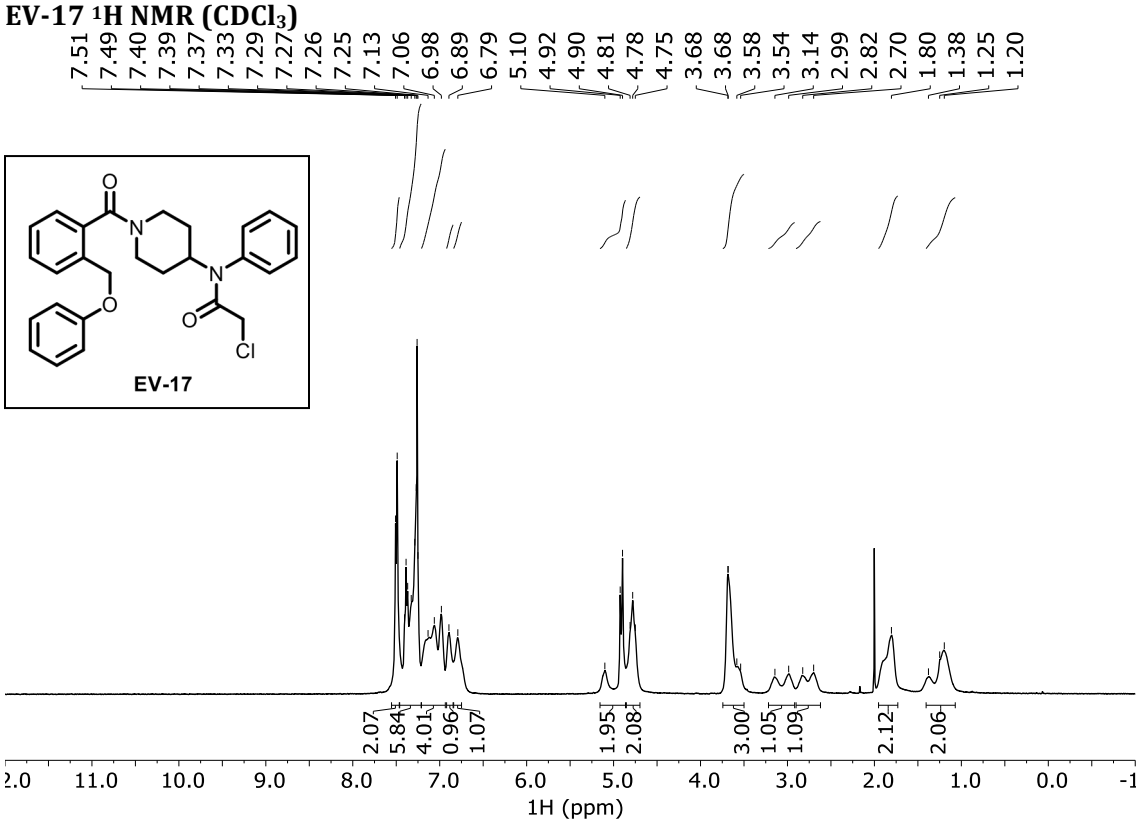
EV-15 ^{1}H NMR ($CDCl_3$)



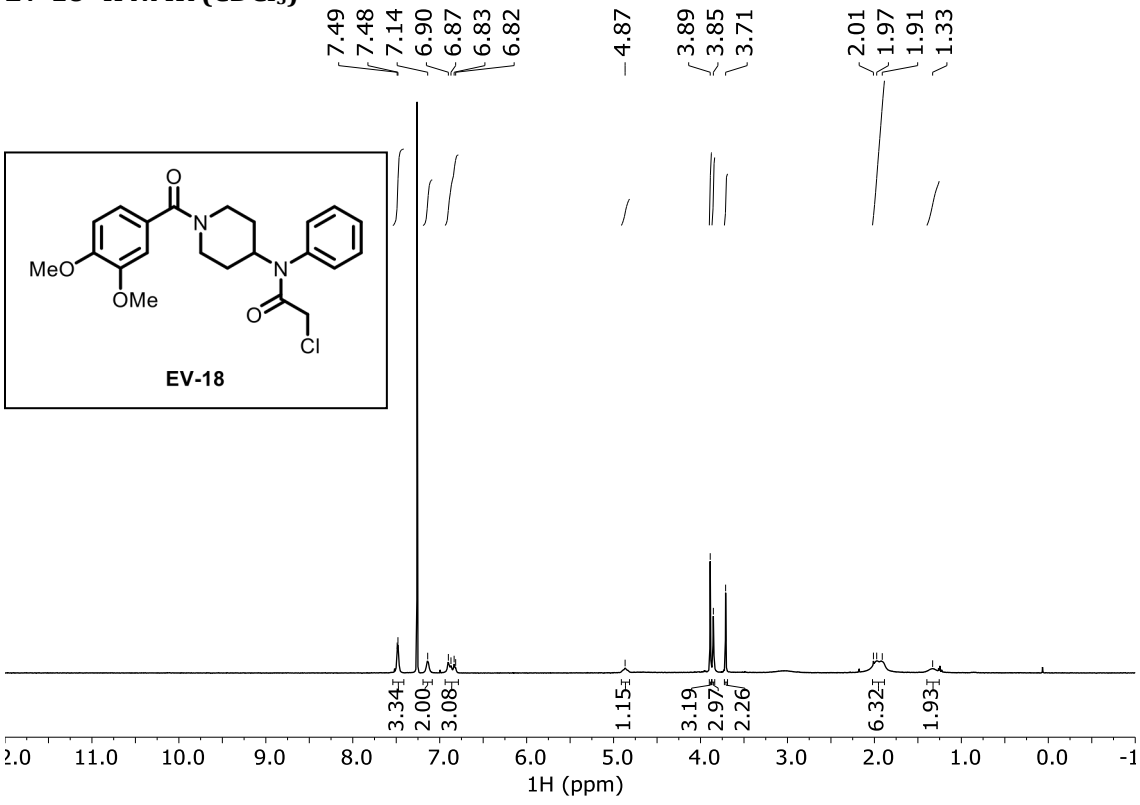
EV-16 ^{1}H NMR ($CDCl_3$)



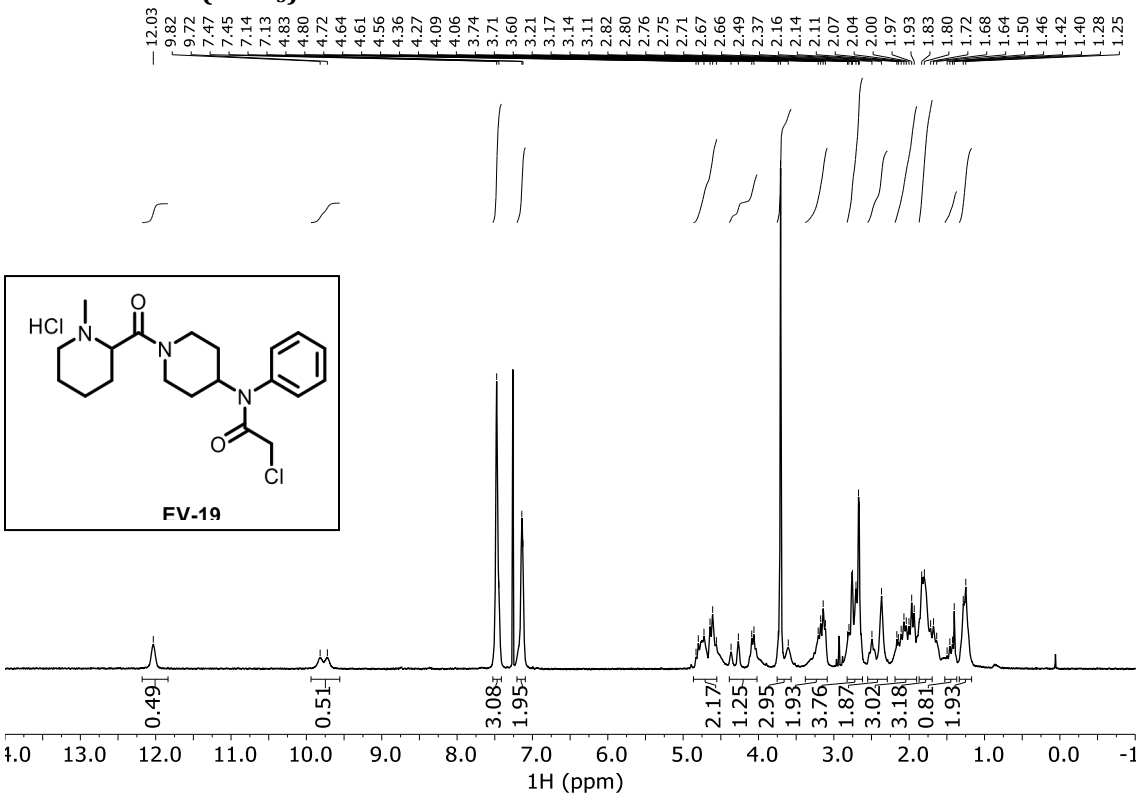
EV-17 ^{1}H NMR ($CDCl_3$)



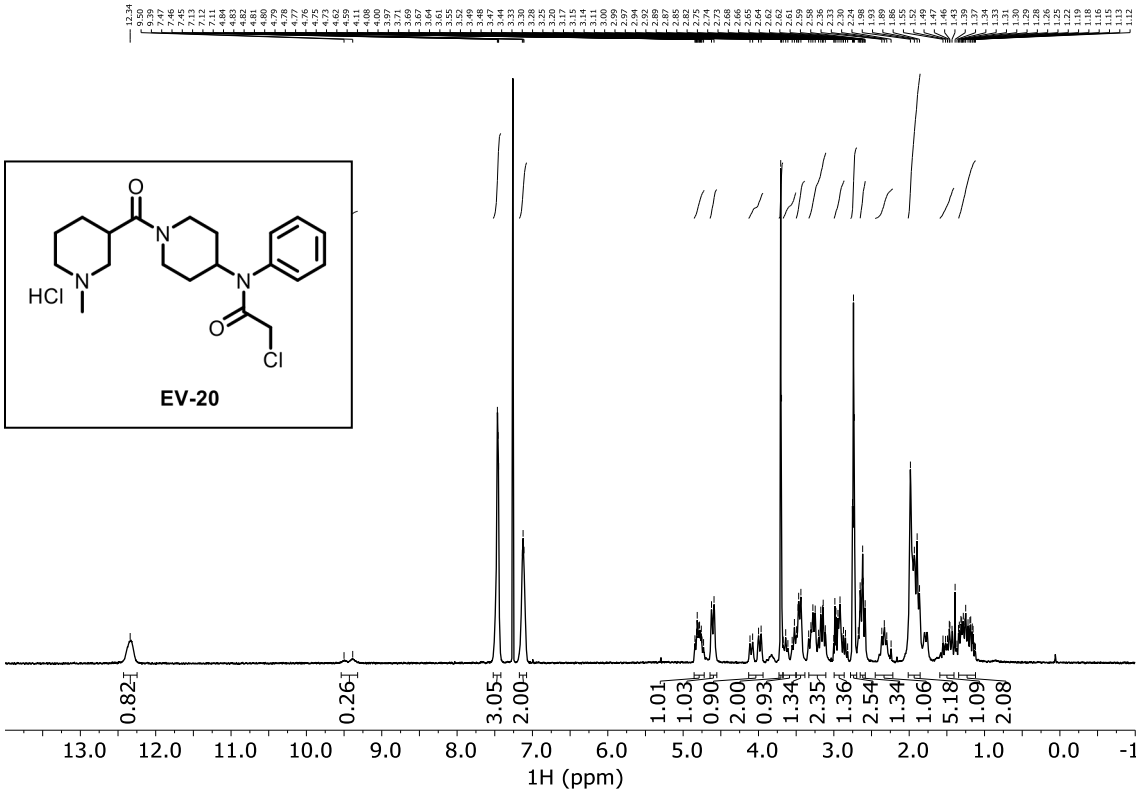
EV-18 ^{1}H NMR ($CDCl_3$)



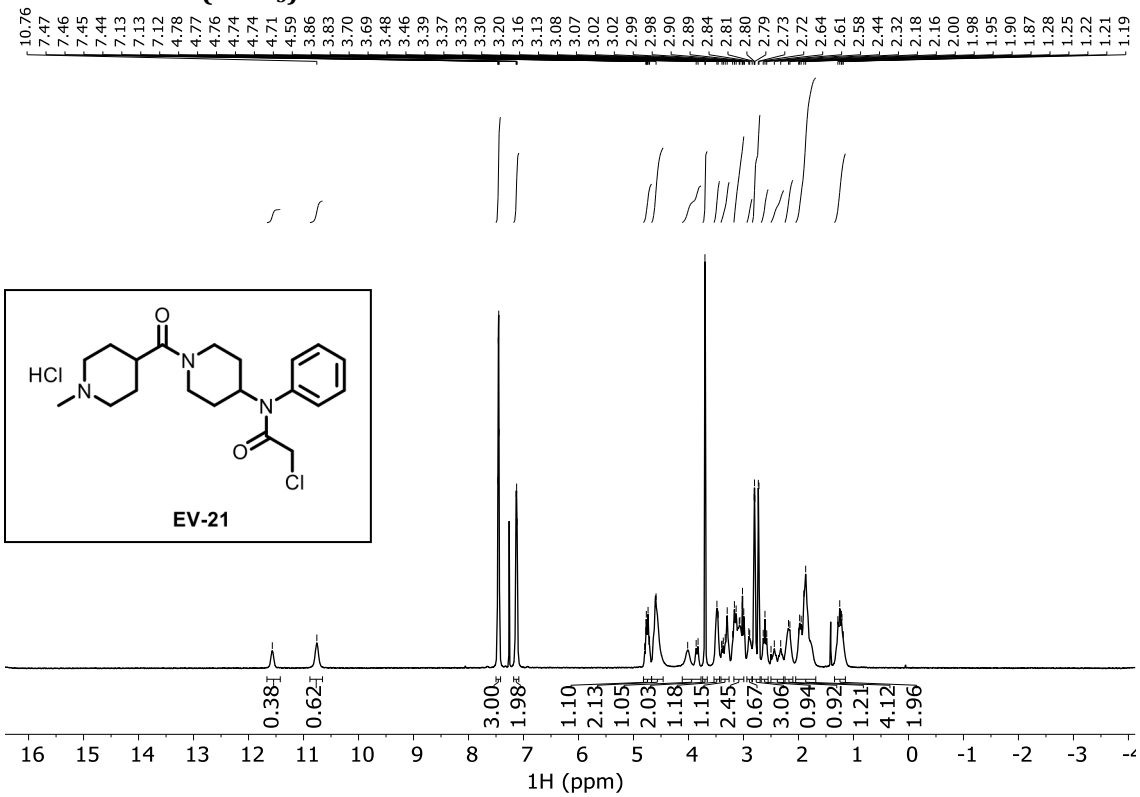
EV-19 ^{1}H NMR ($CDCl_3$)



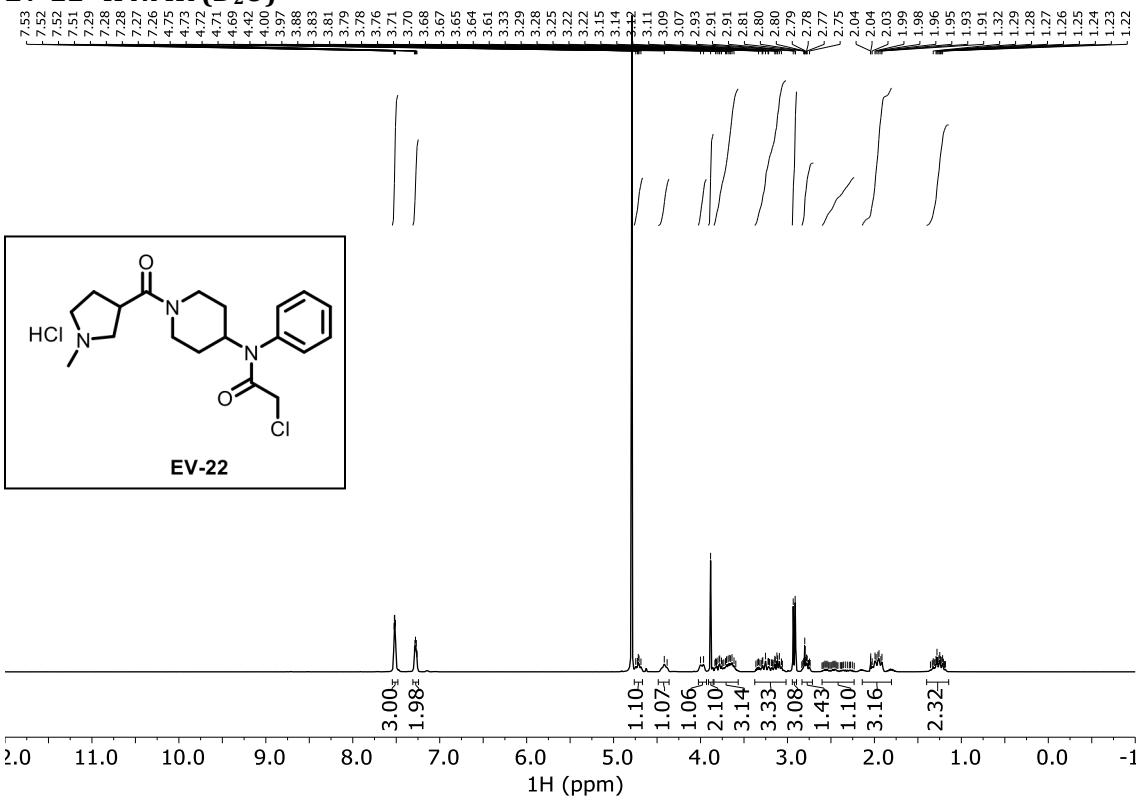
EV-20 ^{1}H NMR ($CDCl_3$)



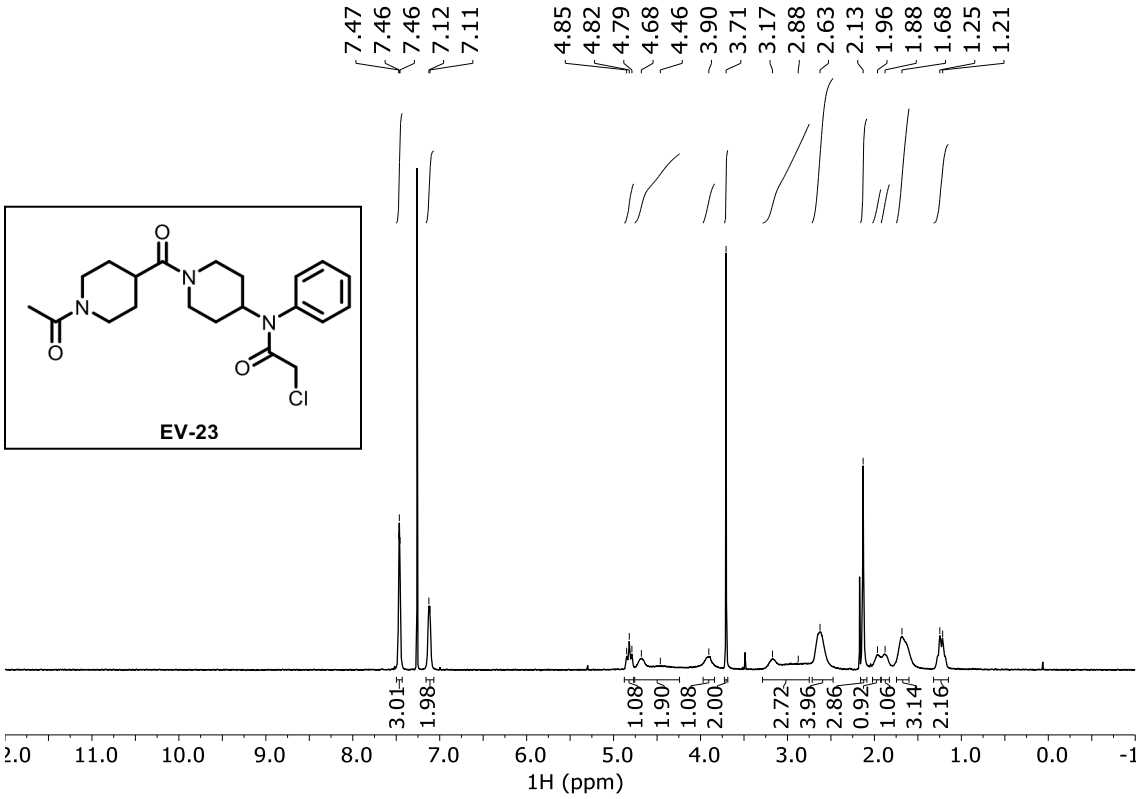
EV-21 ^{1}H NMR ($CDCl_3$)



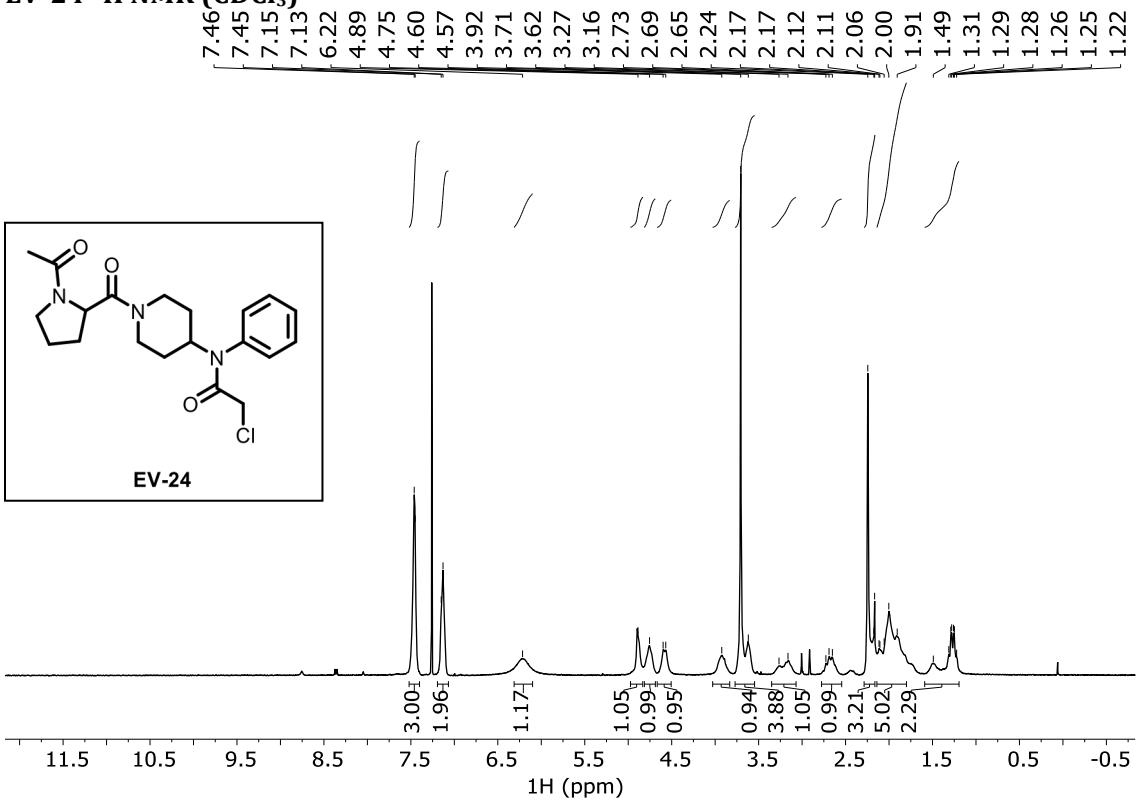
EV-22 ^{1}H NMR (D_2O)



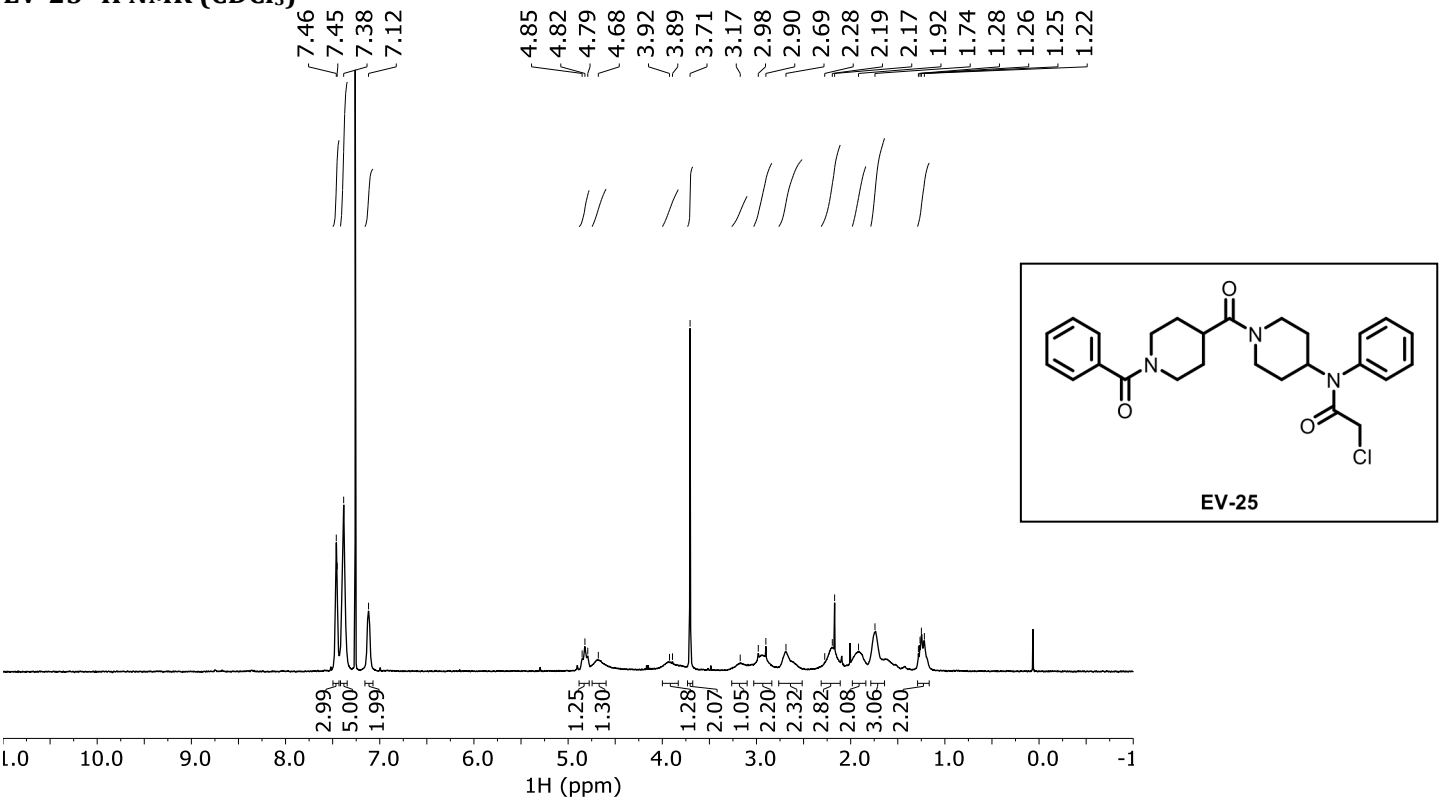
EV-23 ^{1}H NMR ($CDCl_3$)



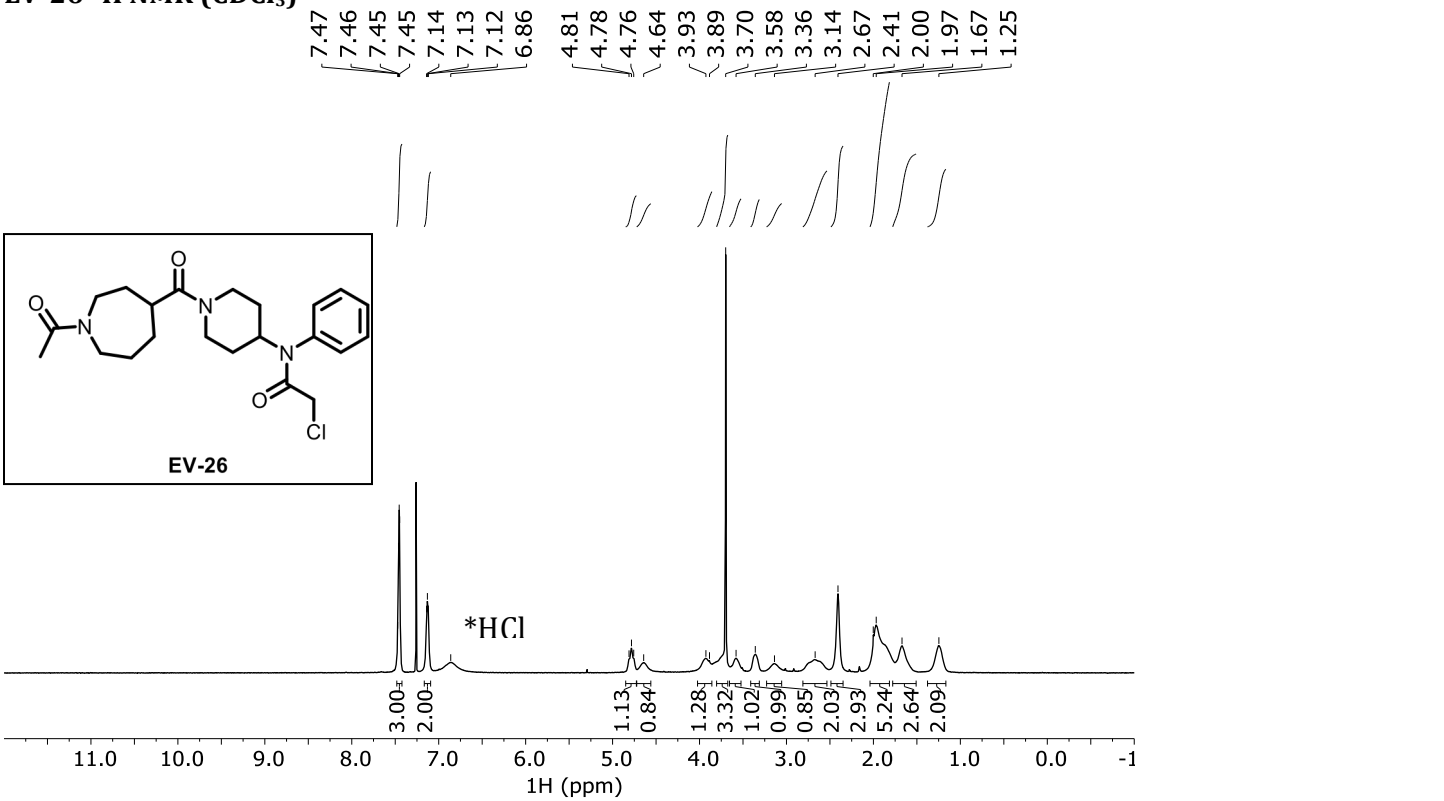
EV-24 ^{1}H NMR ($CDCl_3$)



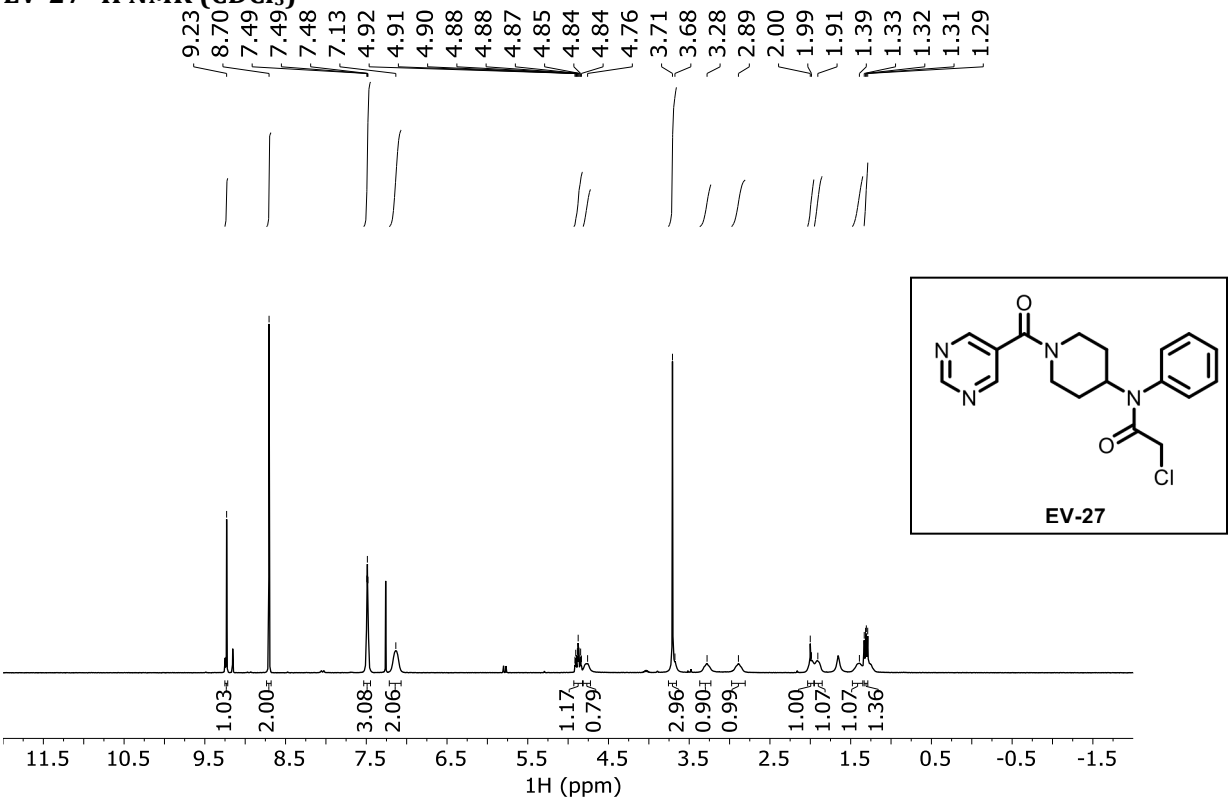
EV-25 ^{1}H NMR ($CDCl_3$)



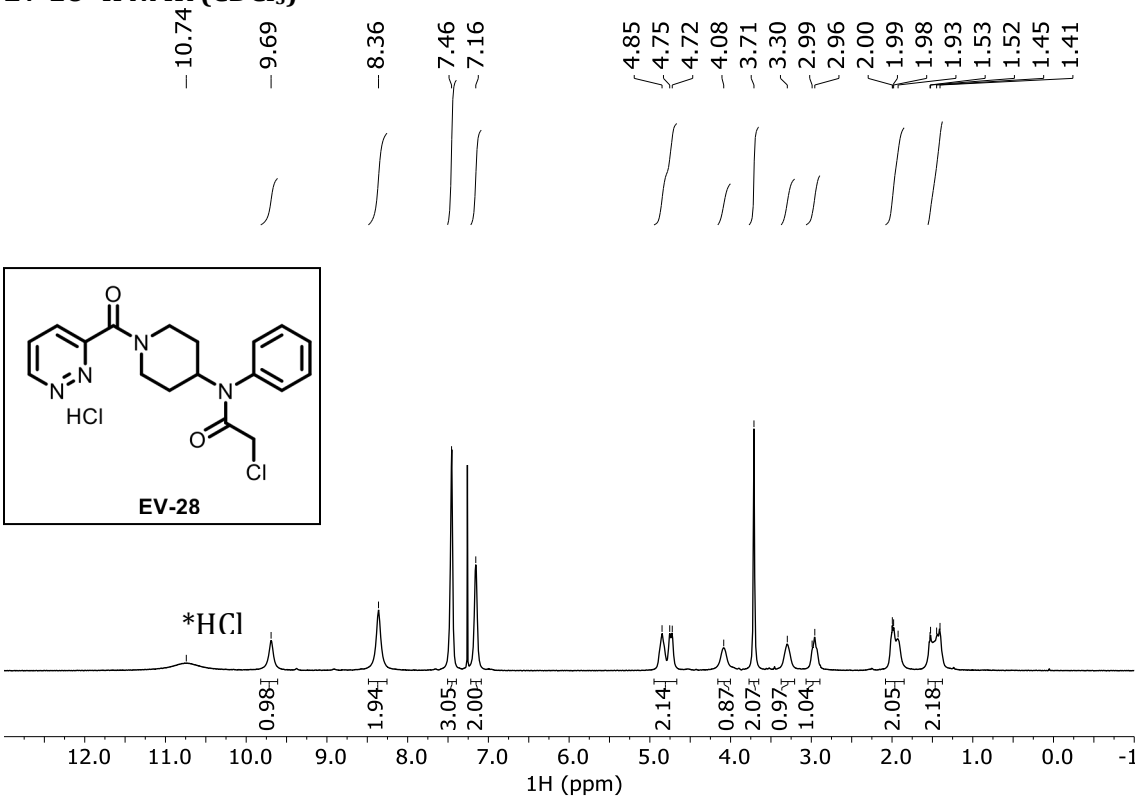
EV-26 ^{1}H NMR ($CDCl_3$)



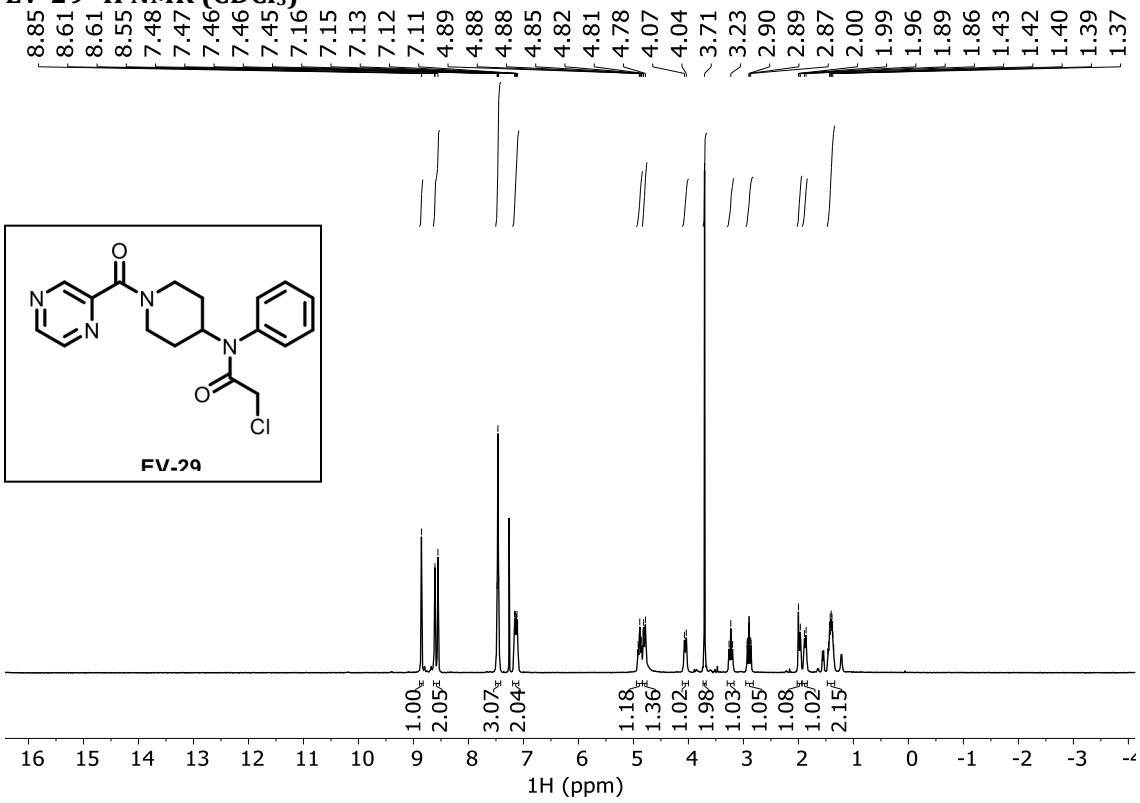
EV-27 ^{1}H NMR ($CDCl_3$)



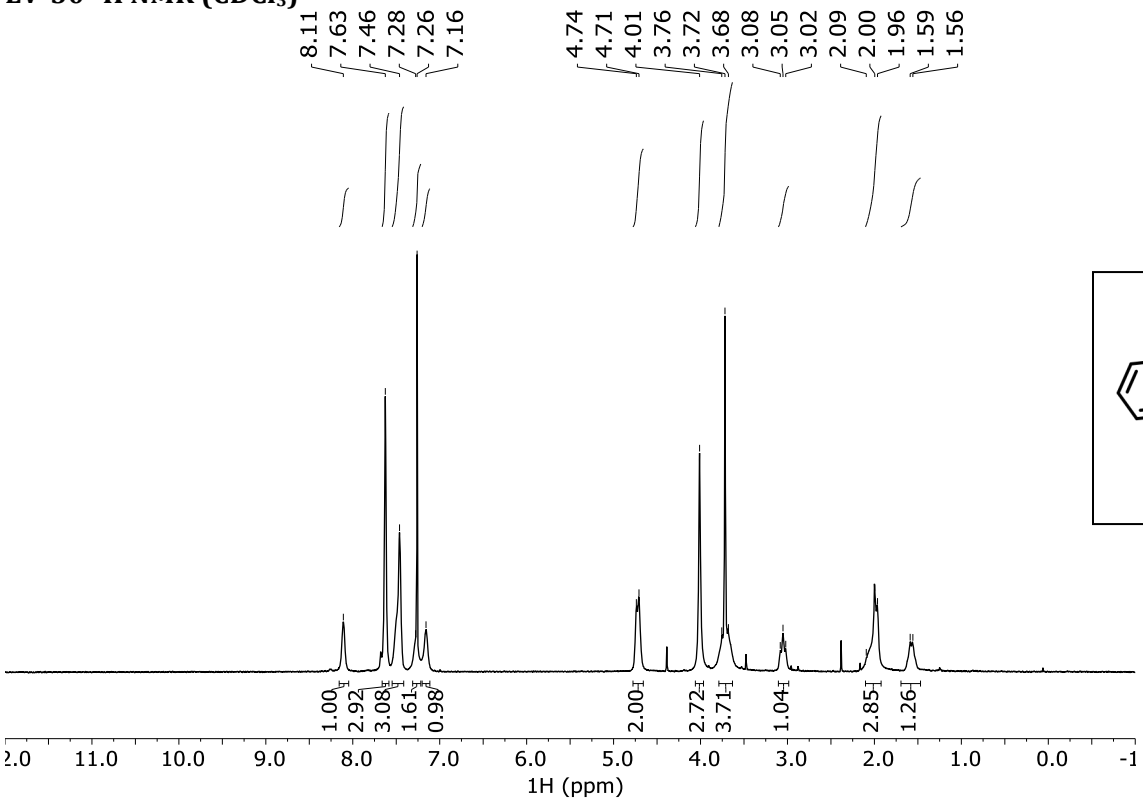
EV-28 ^{1}H NMR ($CDCl_3$)

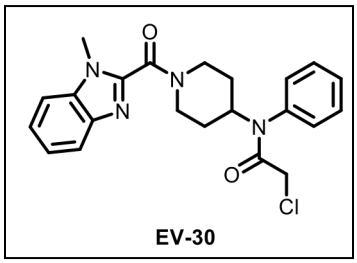


EV-29 ^{1}H NMR ($CDCl_3$)

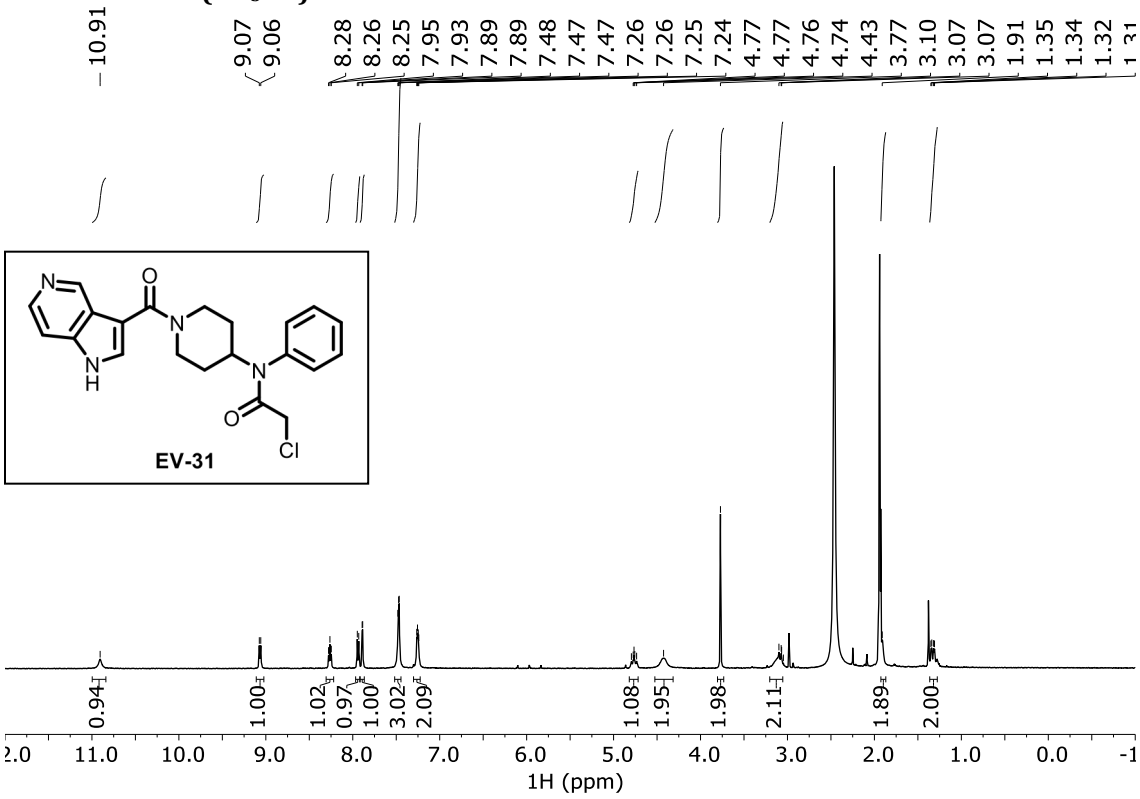


EV-30 ^{1}H NMR ($CDCl_3$)

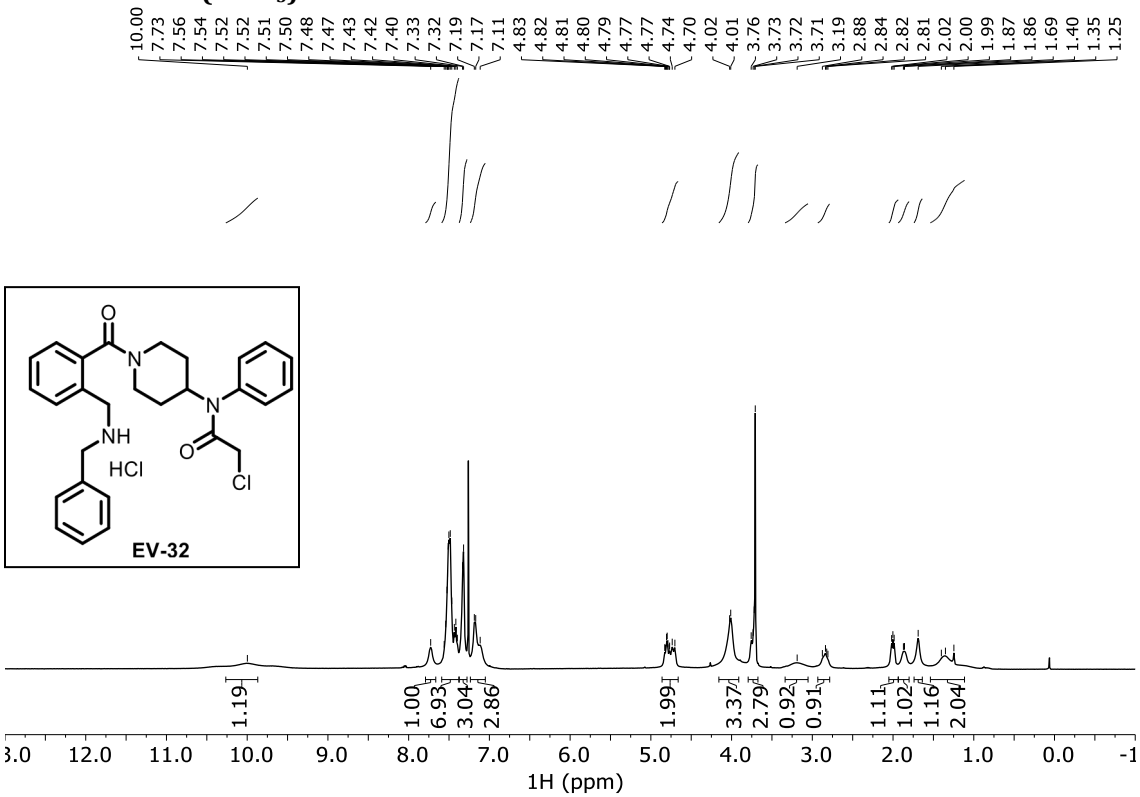




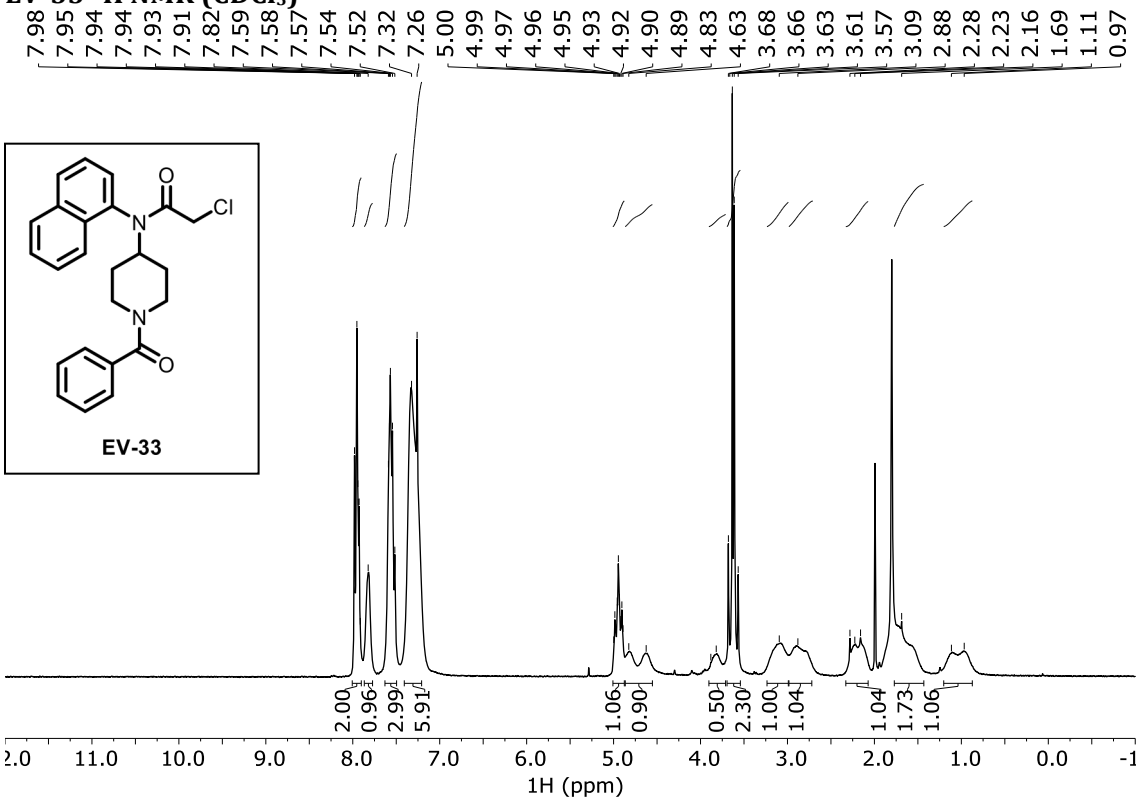
EV-31 ^{1}H NMR (CD_3CN)



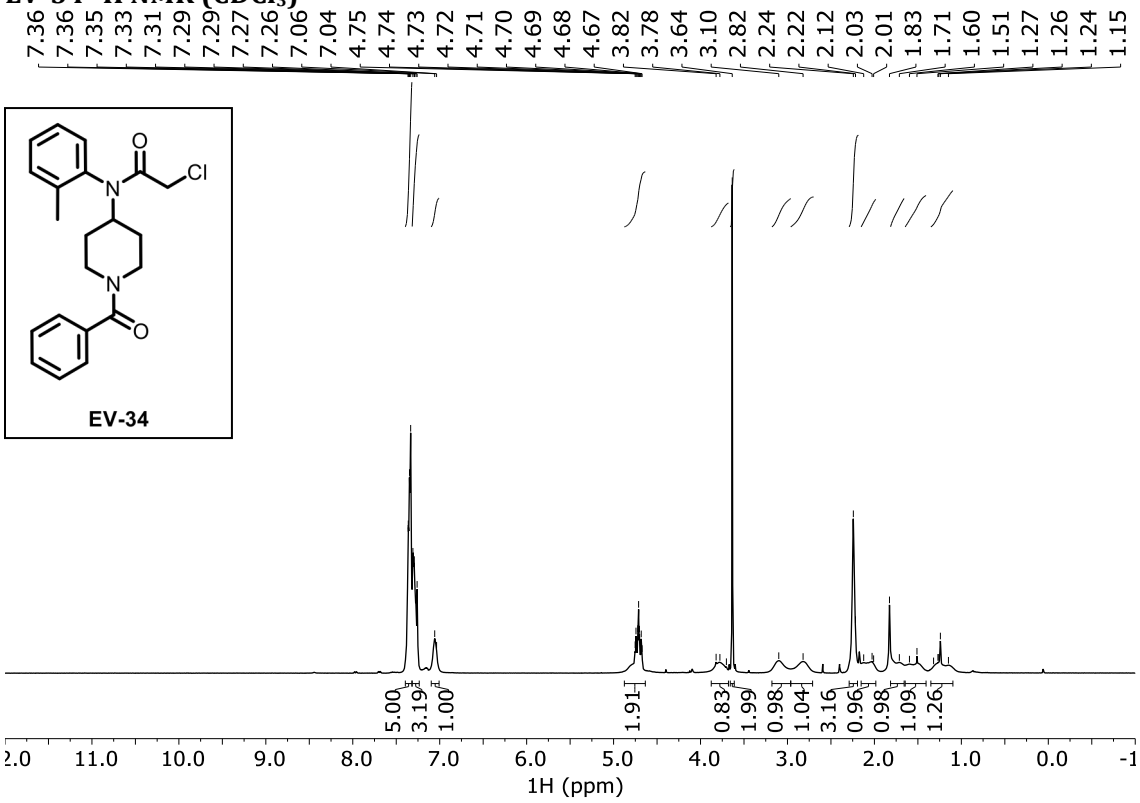
EV-32 ^{1}H NMR ($CDCl_3$)



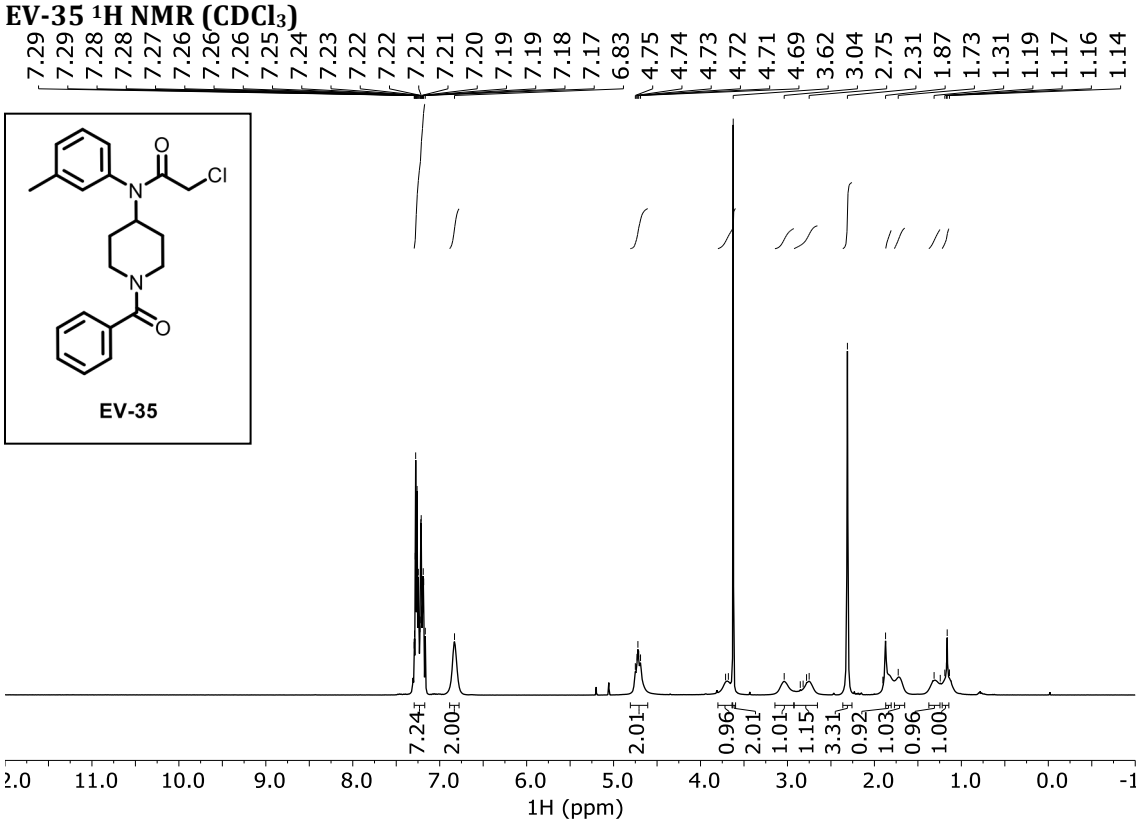
EV-33 ^{1}H NMR ($CDCl_3$)



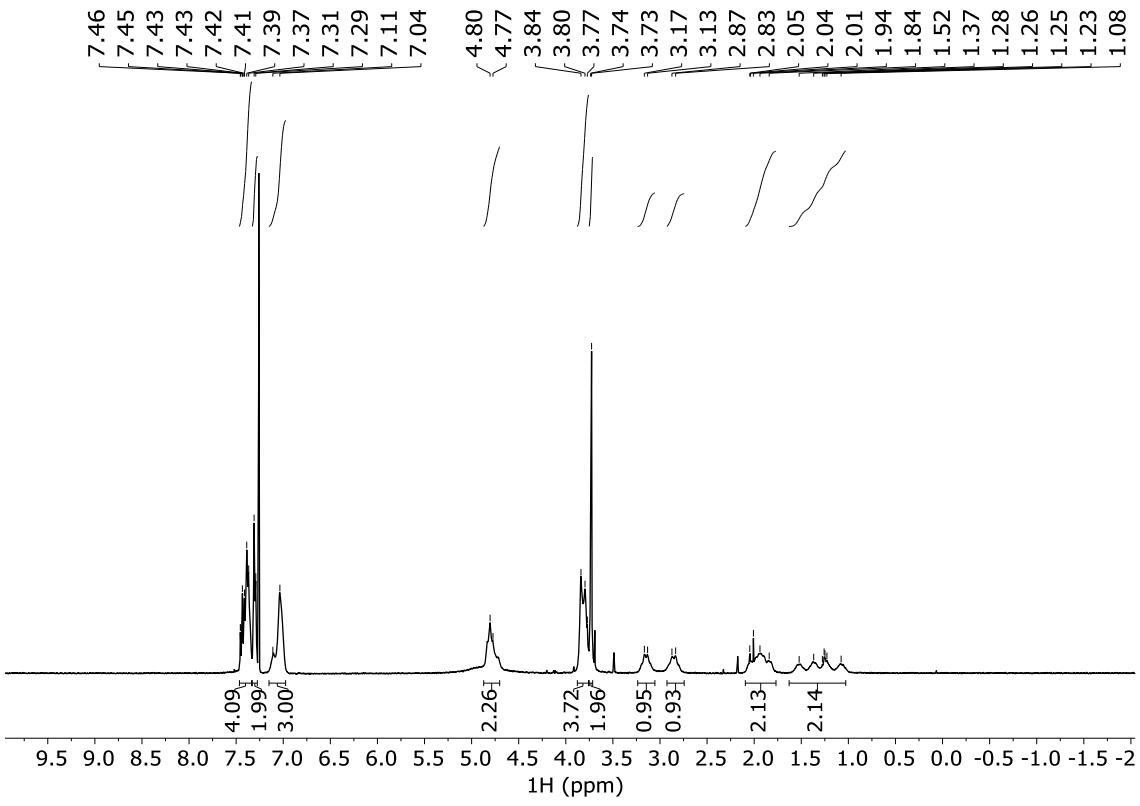
EV-34 ^{1}H NMR ($CDCl_3$)

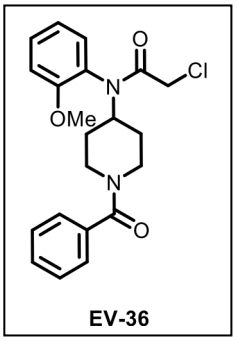


EV-35 ^{1}H NMR ($CDCl_3$)

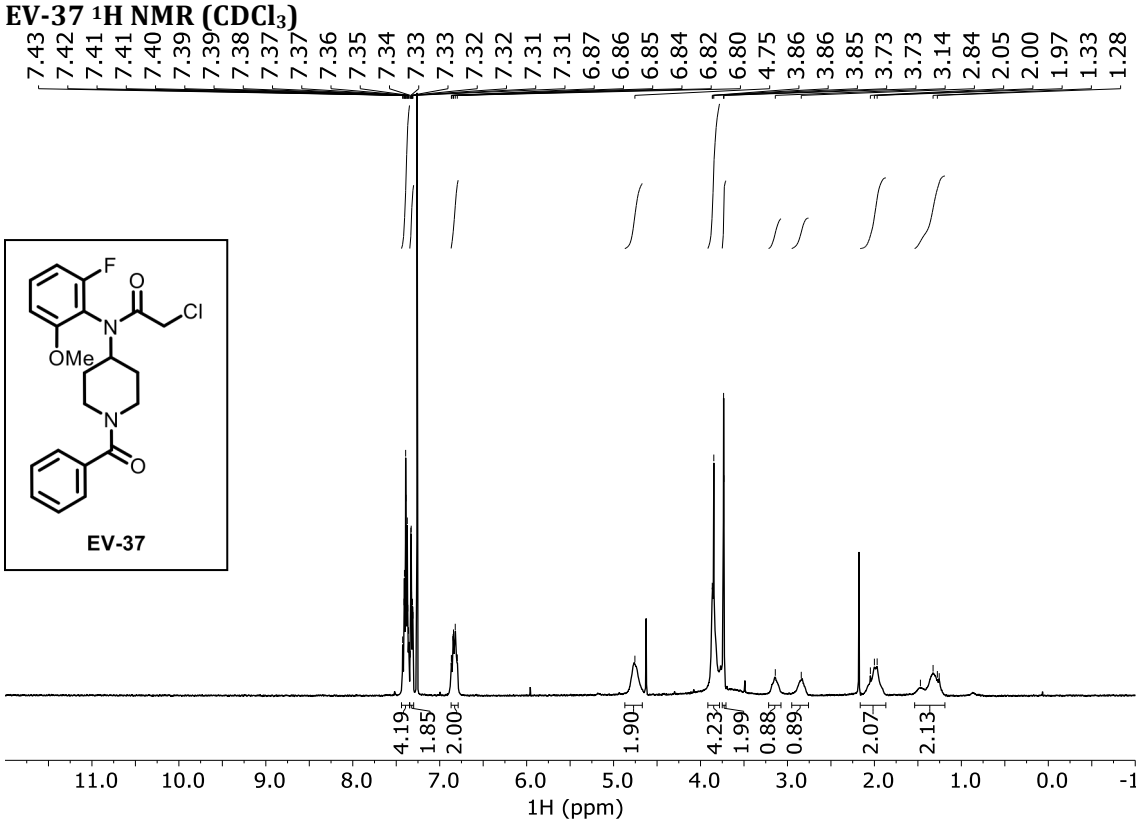


EV-36 ^{1}H NMR ($CDCl_3$)

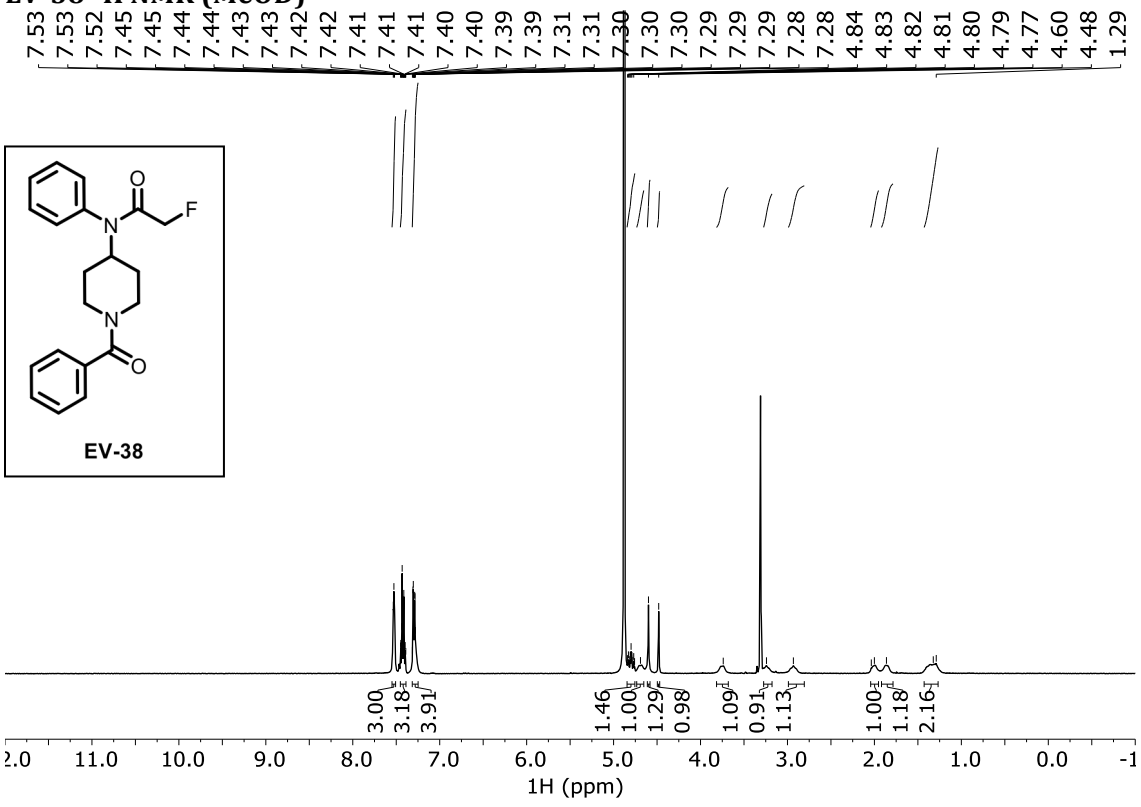




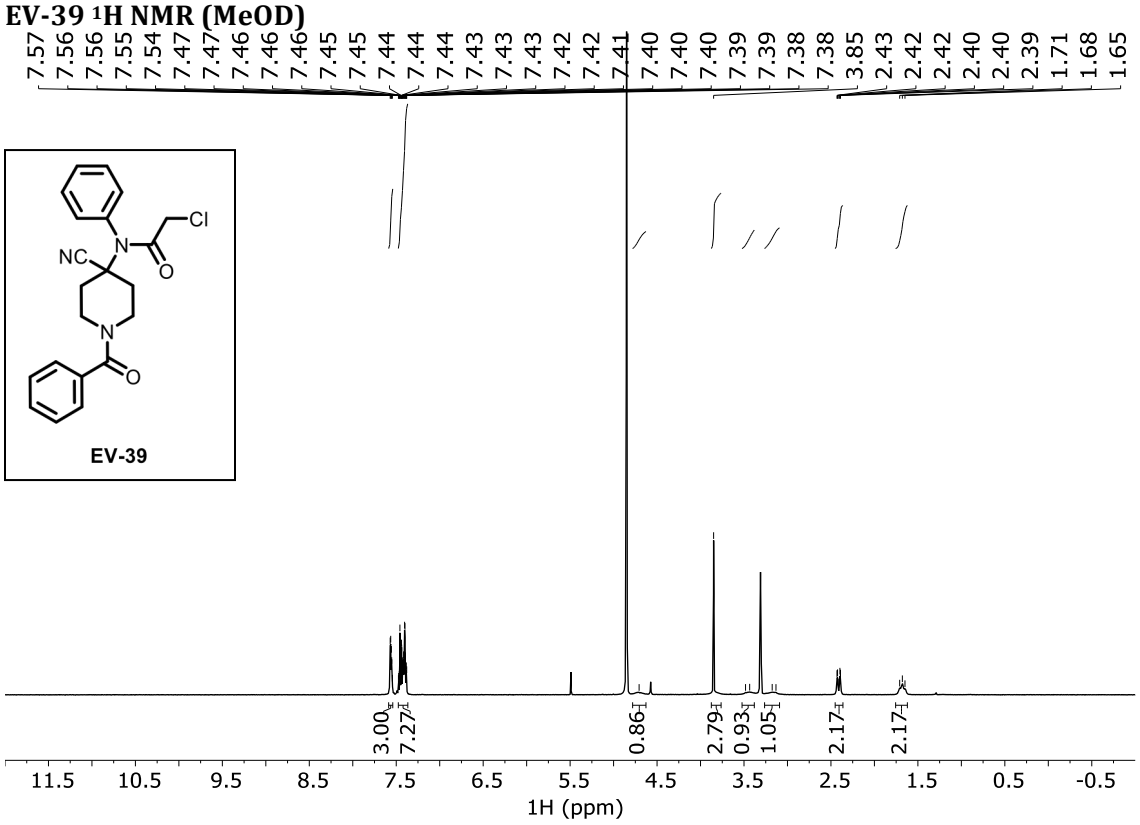
EV-37 ^{1}H NMR ($CDCl_3$)



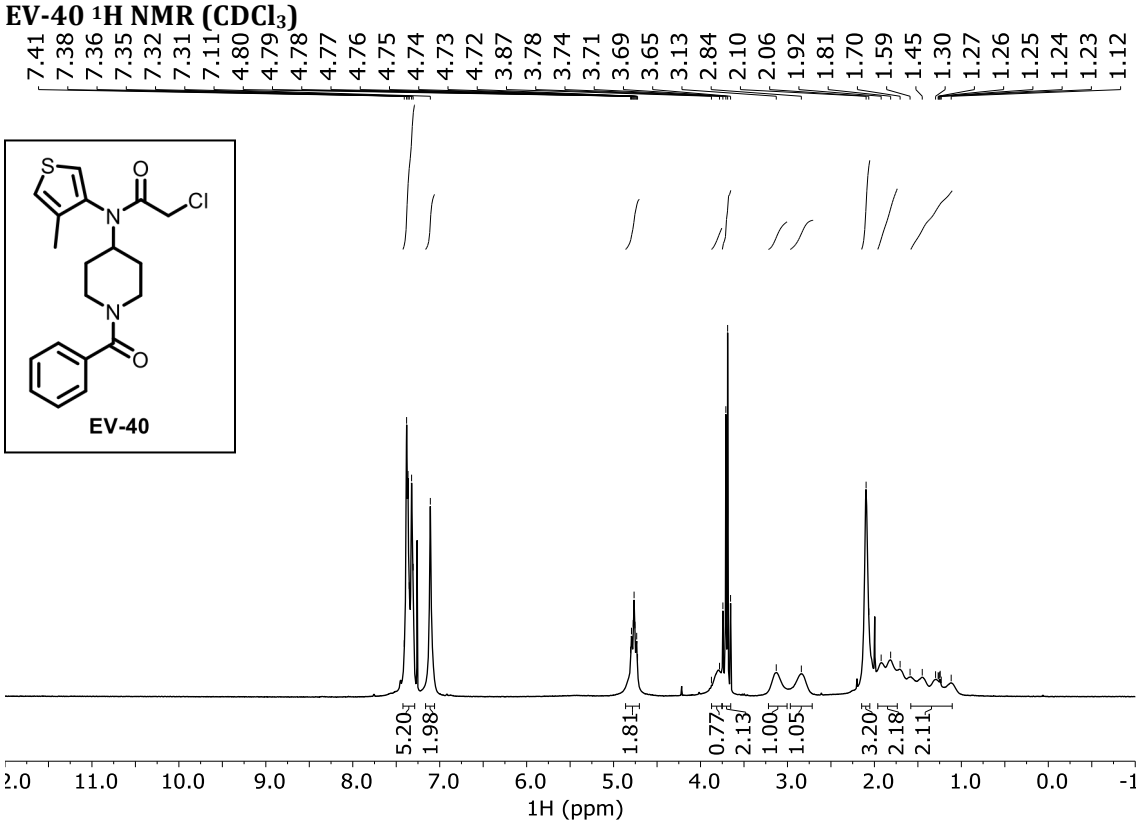
EV-38 ^{1}H NMR (MeOD)



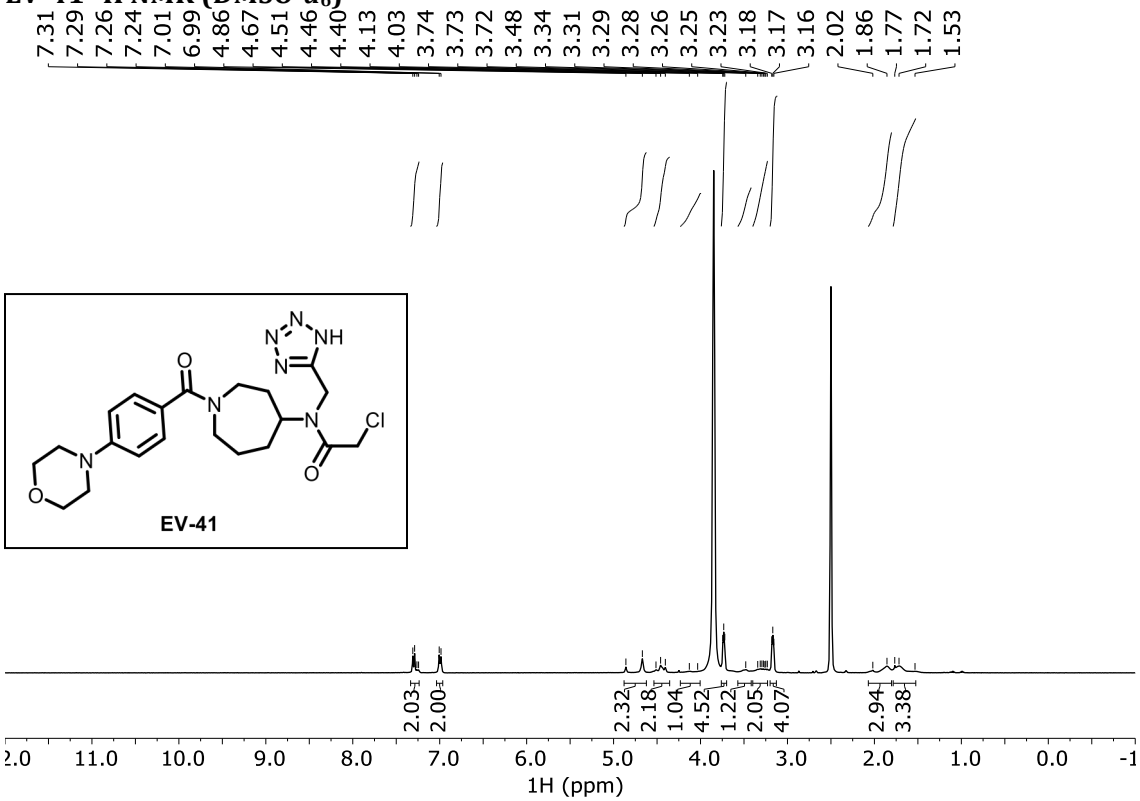
EV-39 ^{1}H NMR (MeOD)



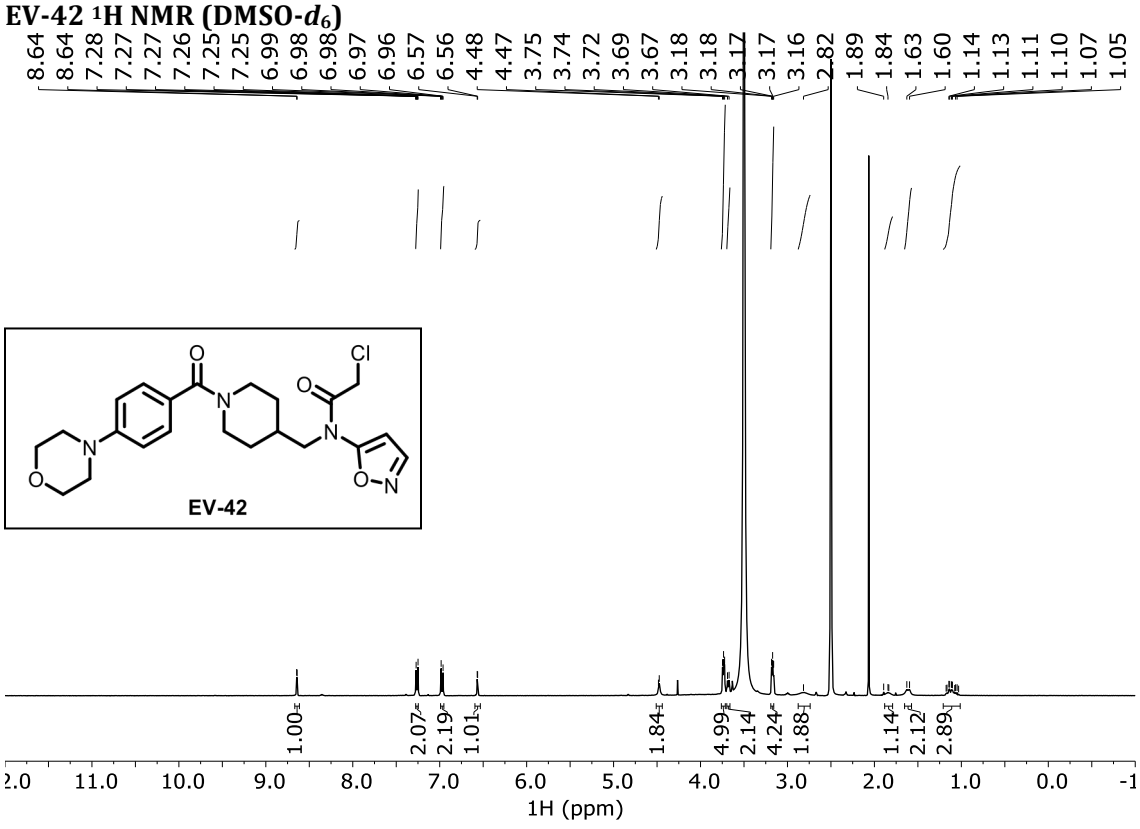
EV-40 ^{1}H NMR ($CDCl_3$)



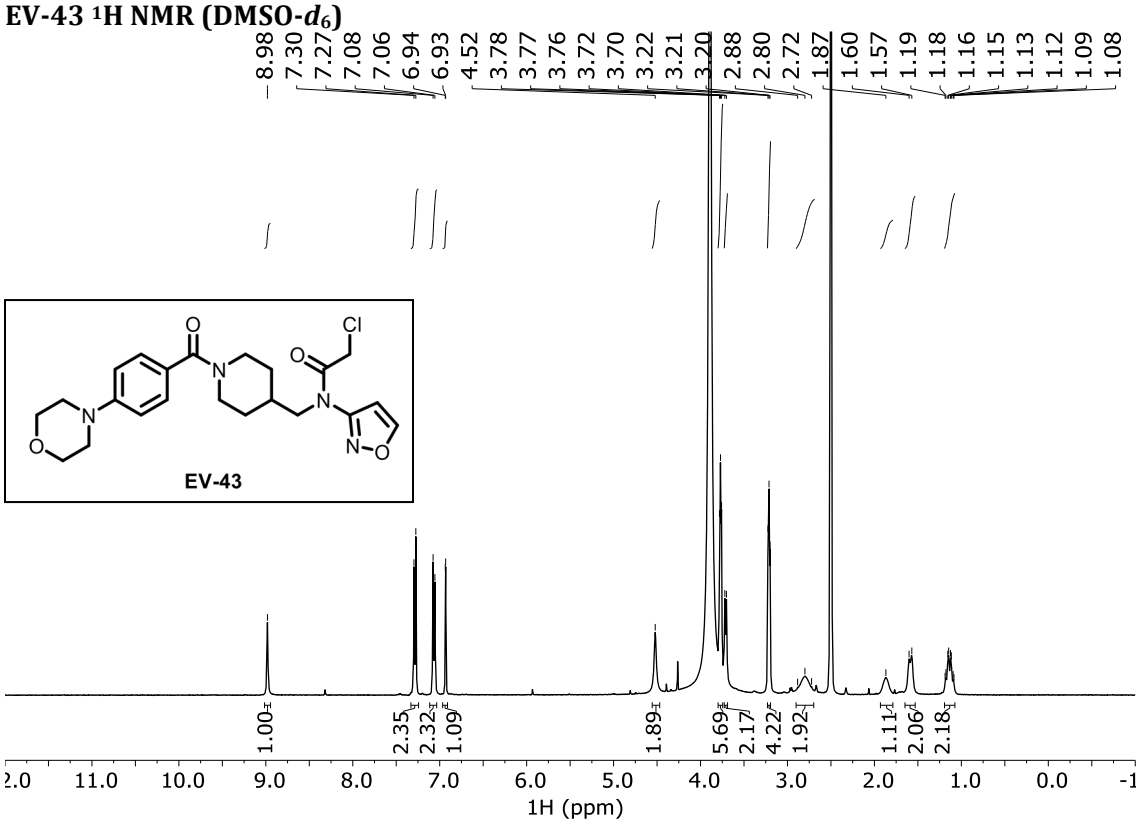
EV-41 ^{1}H NMR (DMSO-d_6)



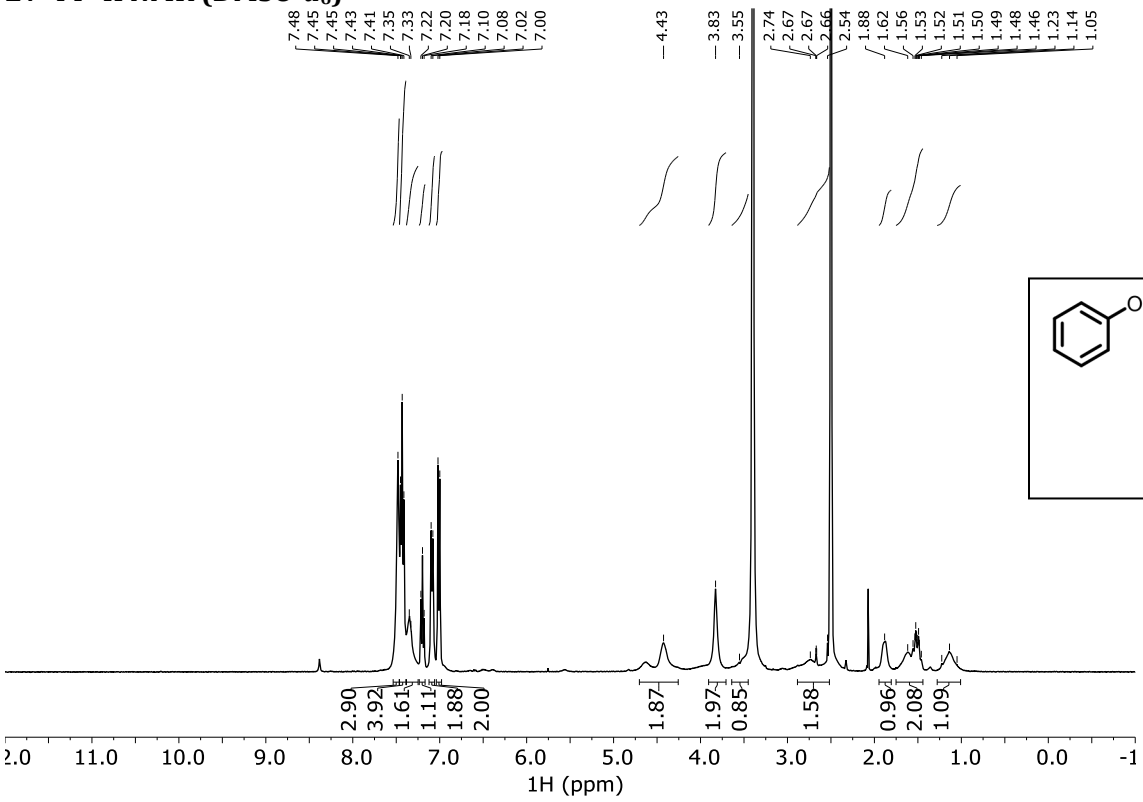
EV-42 ^{1}H NMR (DMSO-d_6)

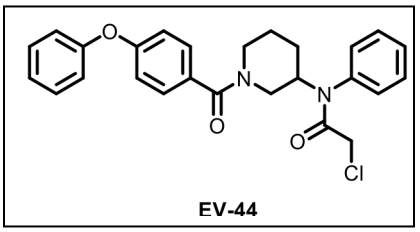


EV-43 ^{1}H NMR (DMSO-d_6)

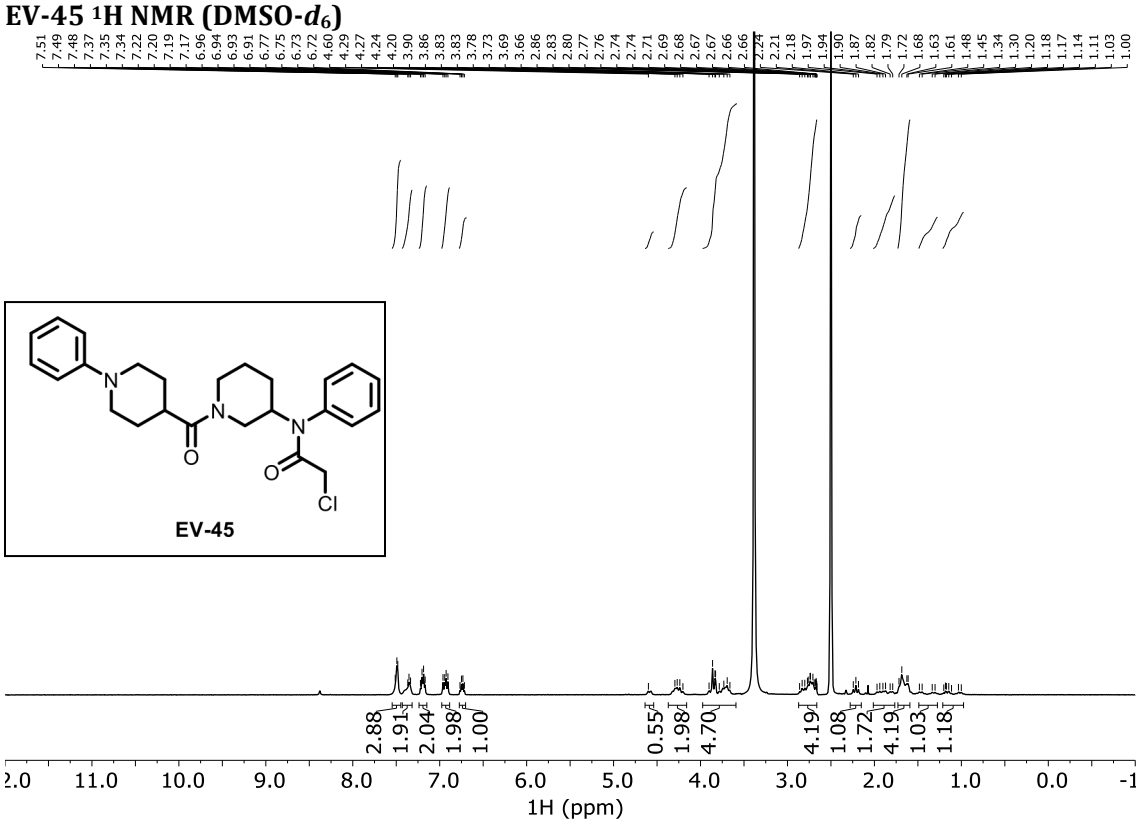


EV-44 ^{1}H NMR (DMSO-d_6)

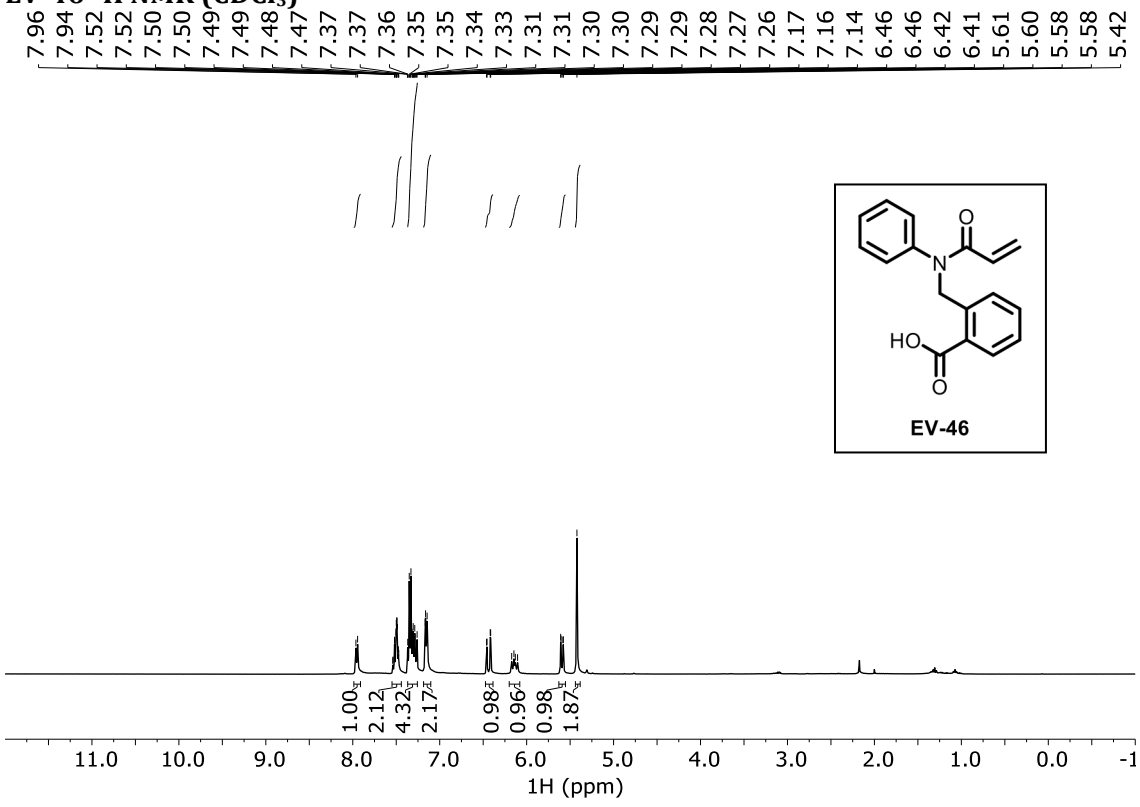




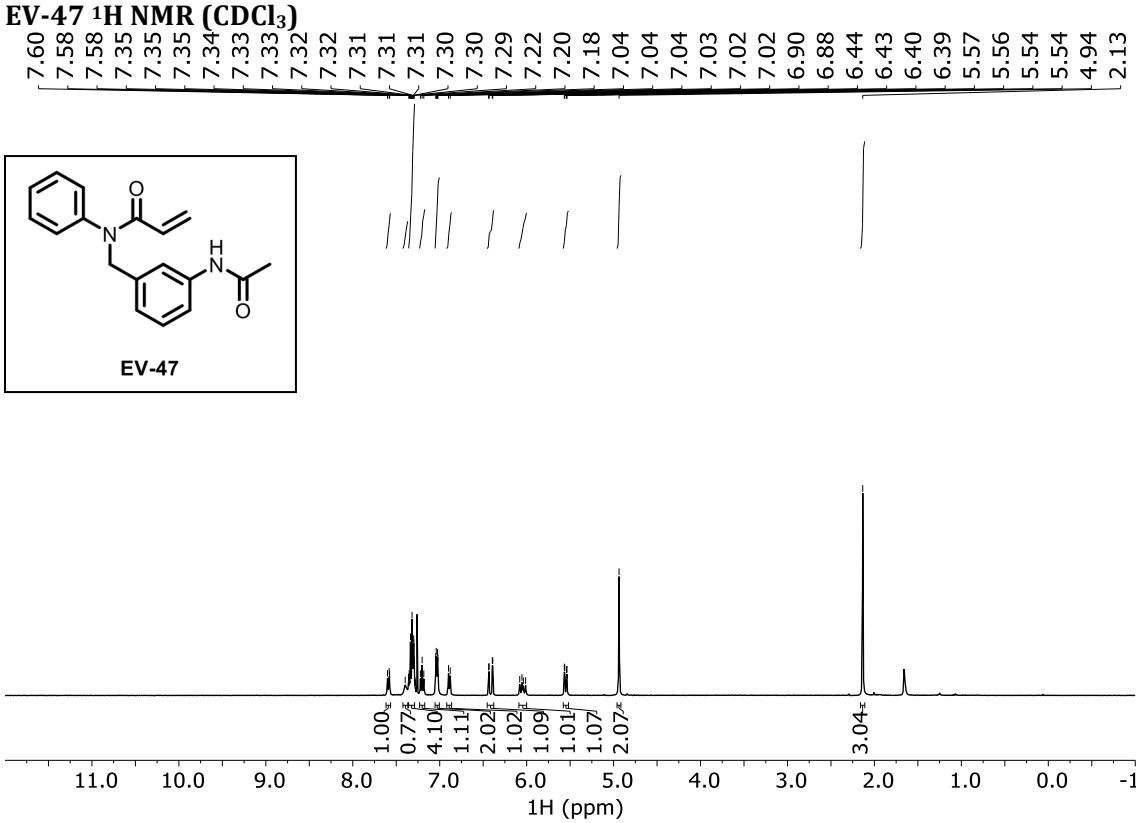
EV-45 ^{1}H NMR (DMSO-d_6)



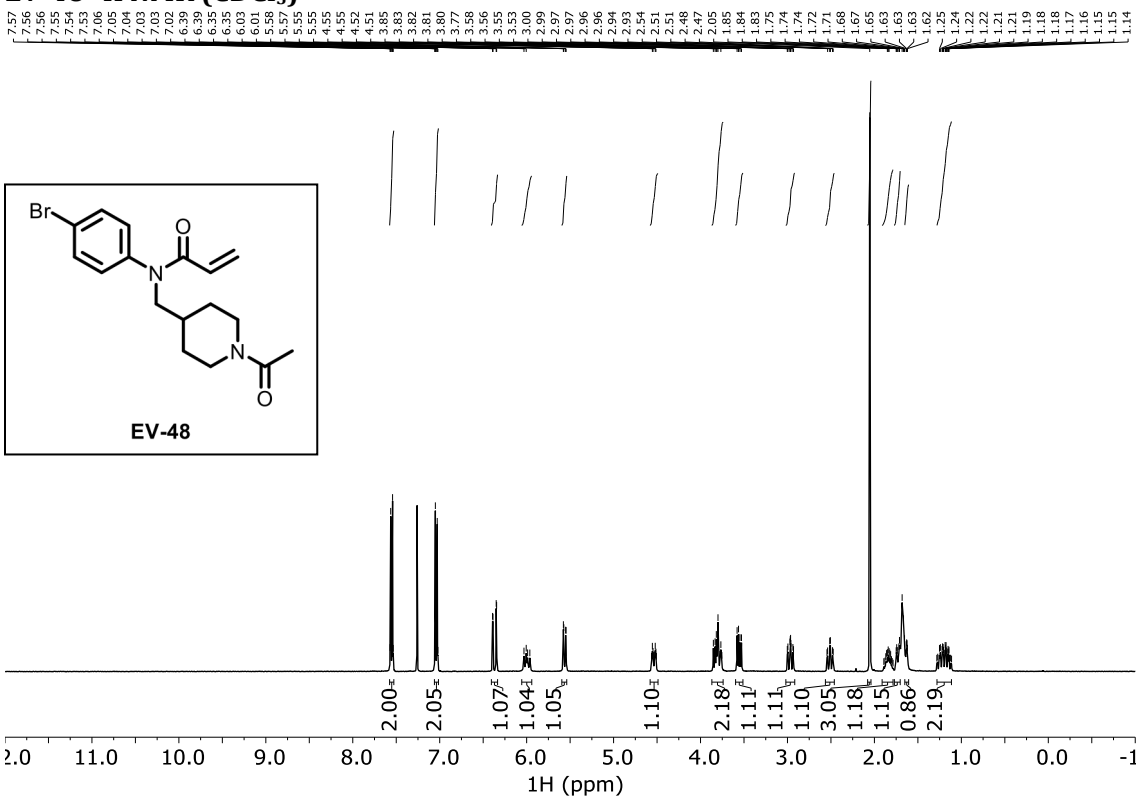
EV-46 ^{1}H NMR ($CDCl_3$)



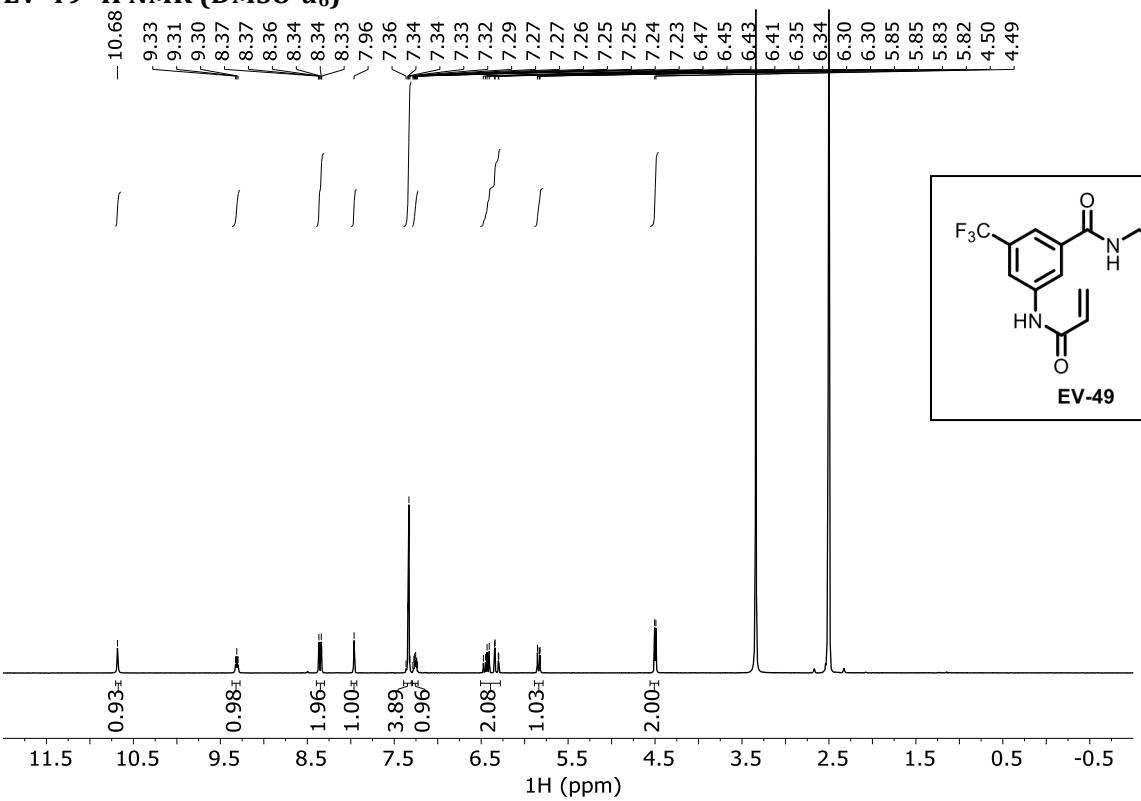
EV-47 ^{1}H NMR ($CDCl_3$)



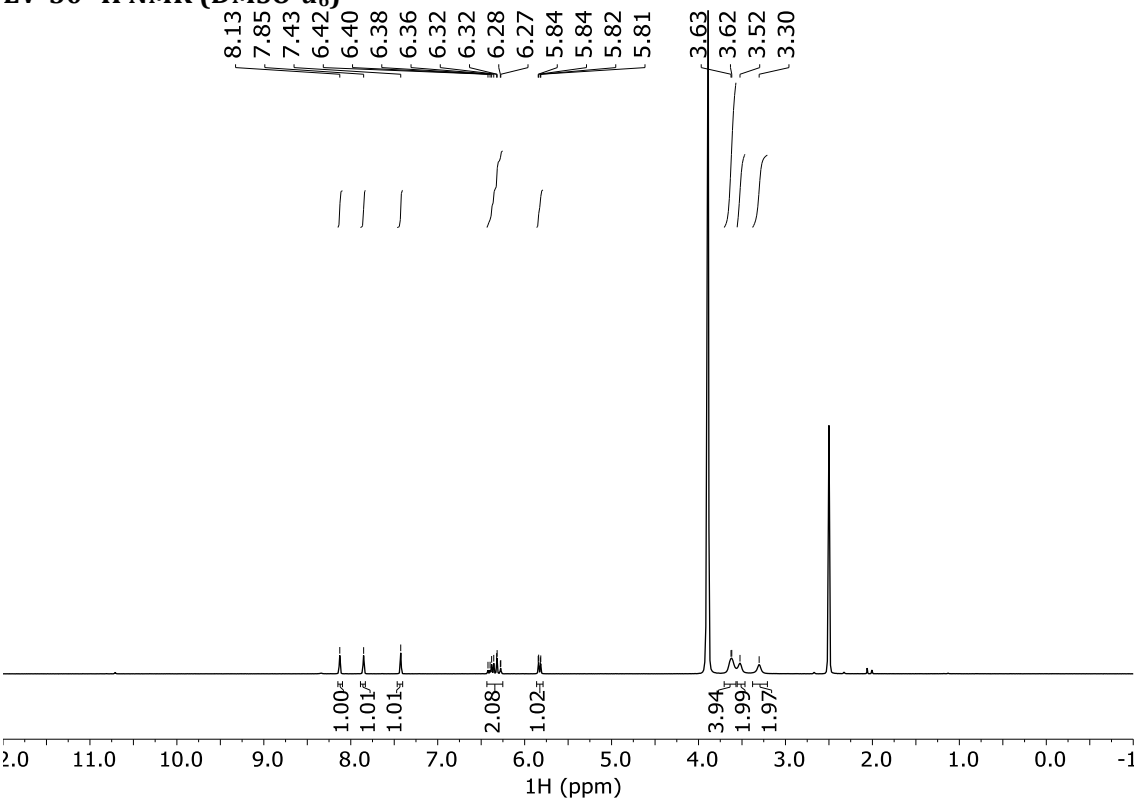
EV-48 ^{1}H NMR ($CDCl_3$)

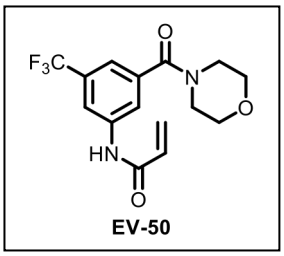


EV-49 ^{1}H NMR (DMSO-d_6)

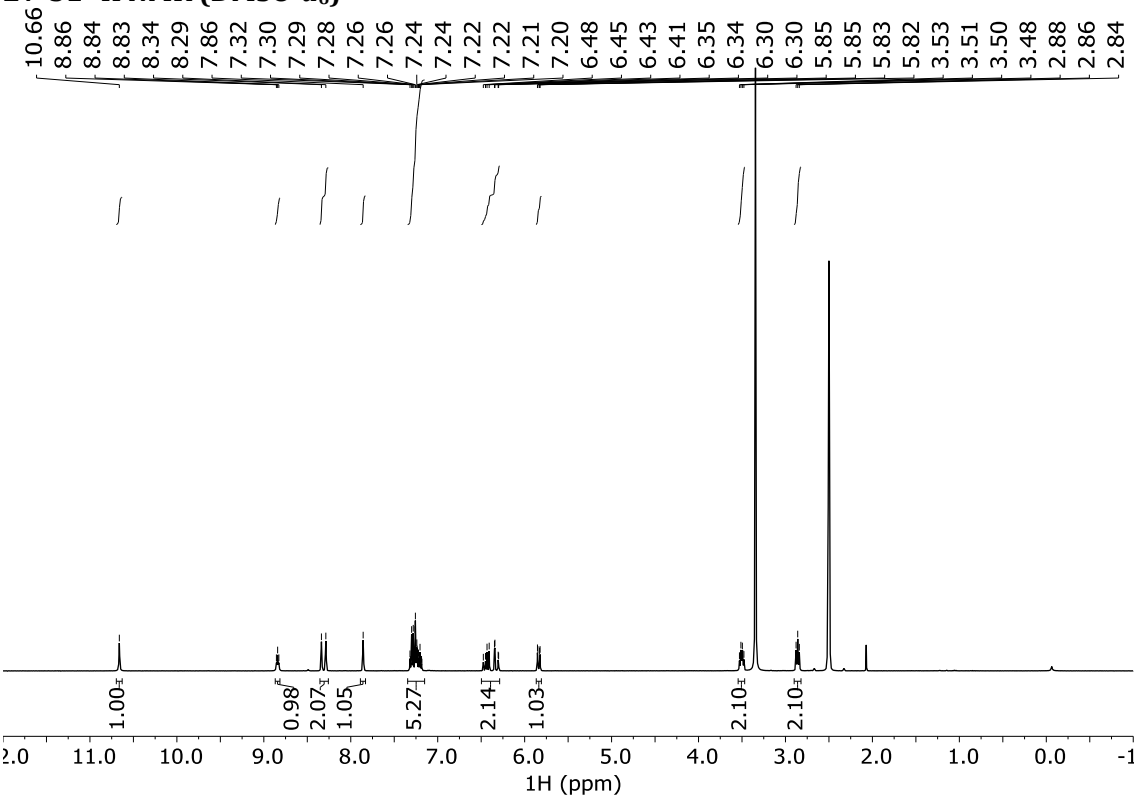


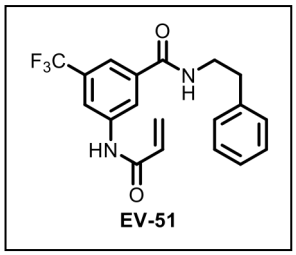
EV-50 ^{1}H NMR (DMSO-d_6)



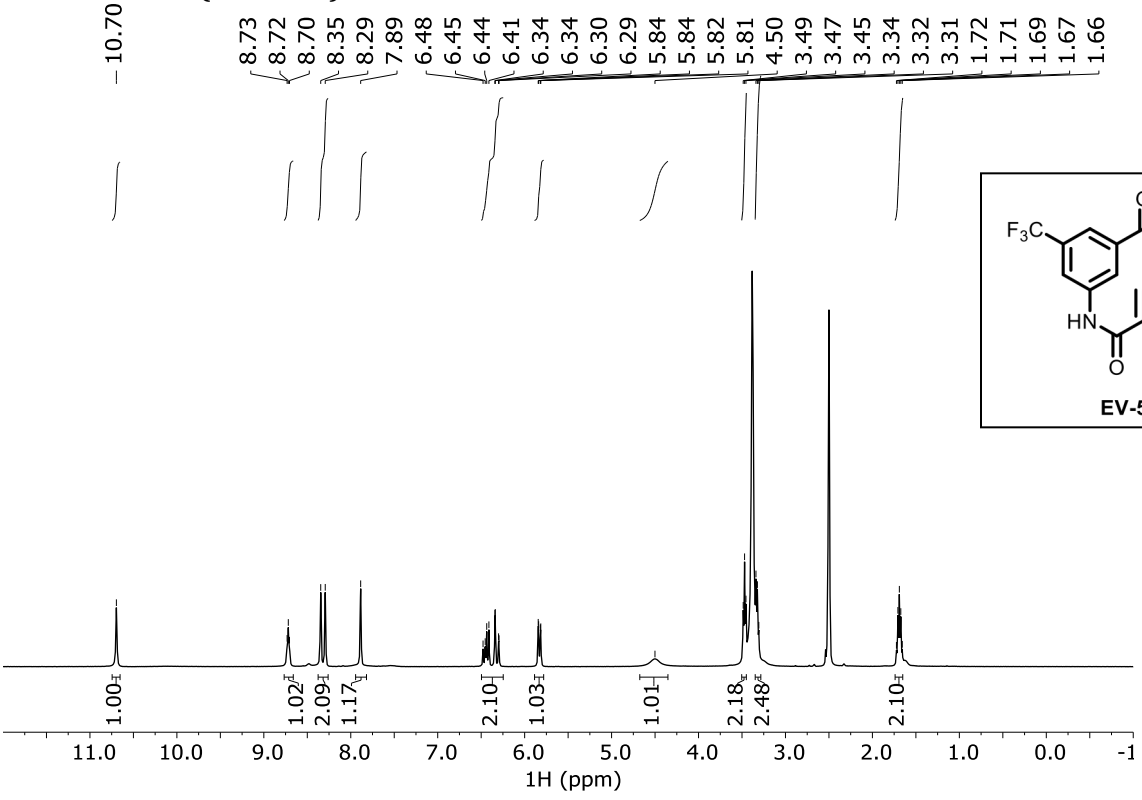


EV-51 ^{1}H NMR (DMSO-d_6)

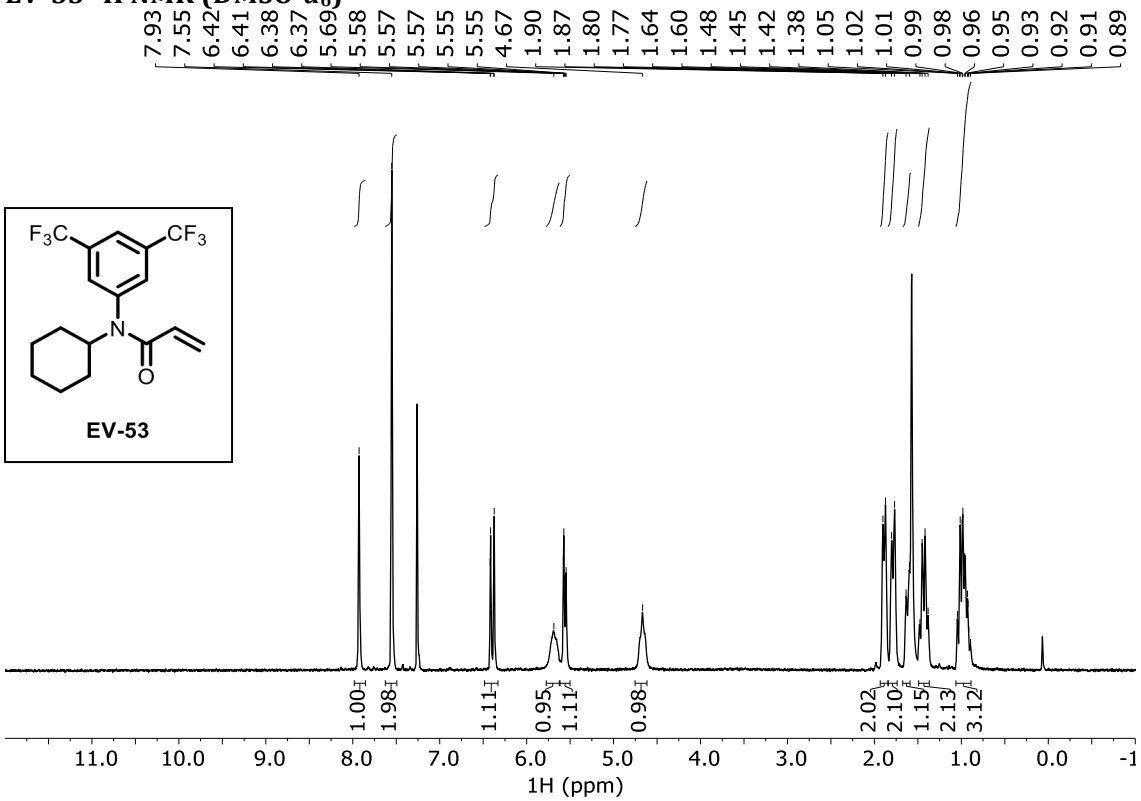




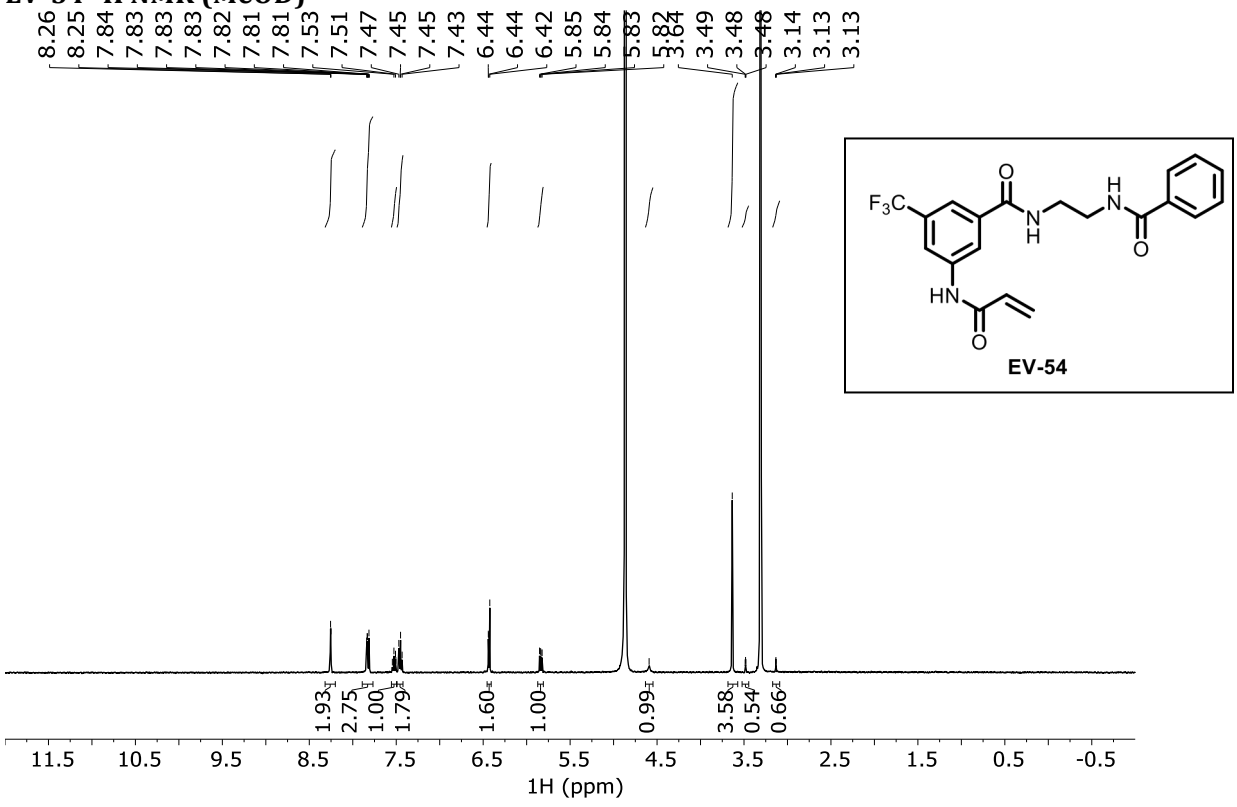
EV-52 ^{1}H NMR (DMSO-d_6)



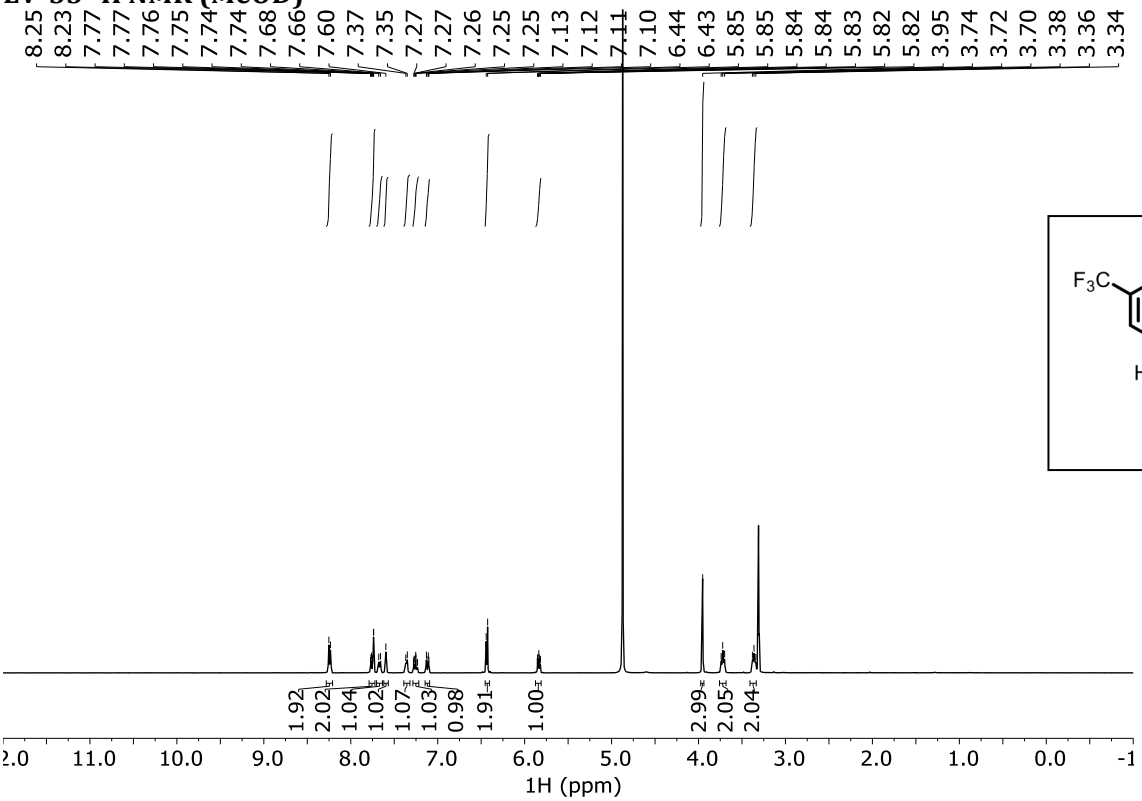
EV-53 ^{1}H NMR (DMSO-d_6)

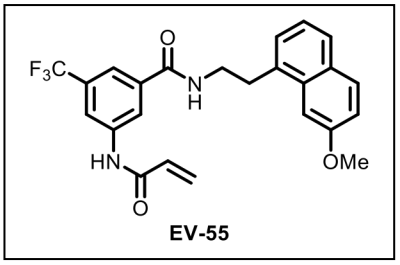


EV-54 ^{1}H NMR (MeOD)

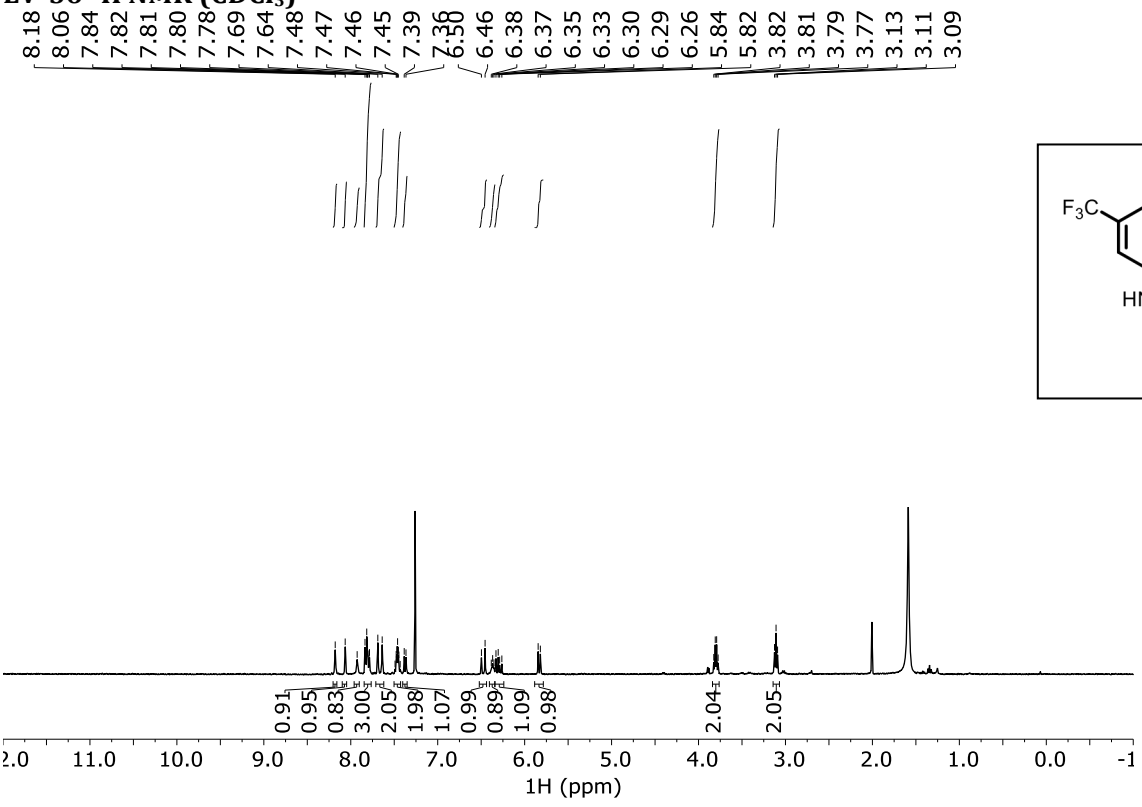


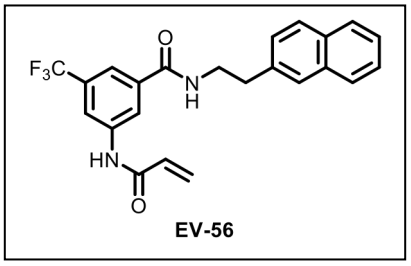
EV-55 ^{1}H NMR (MeOD)



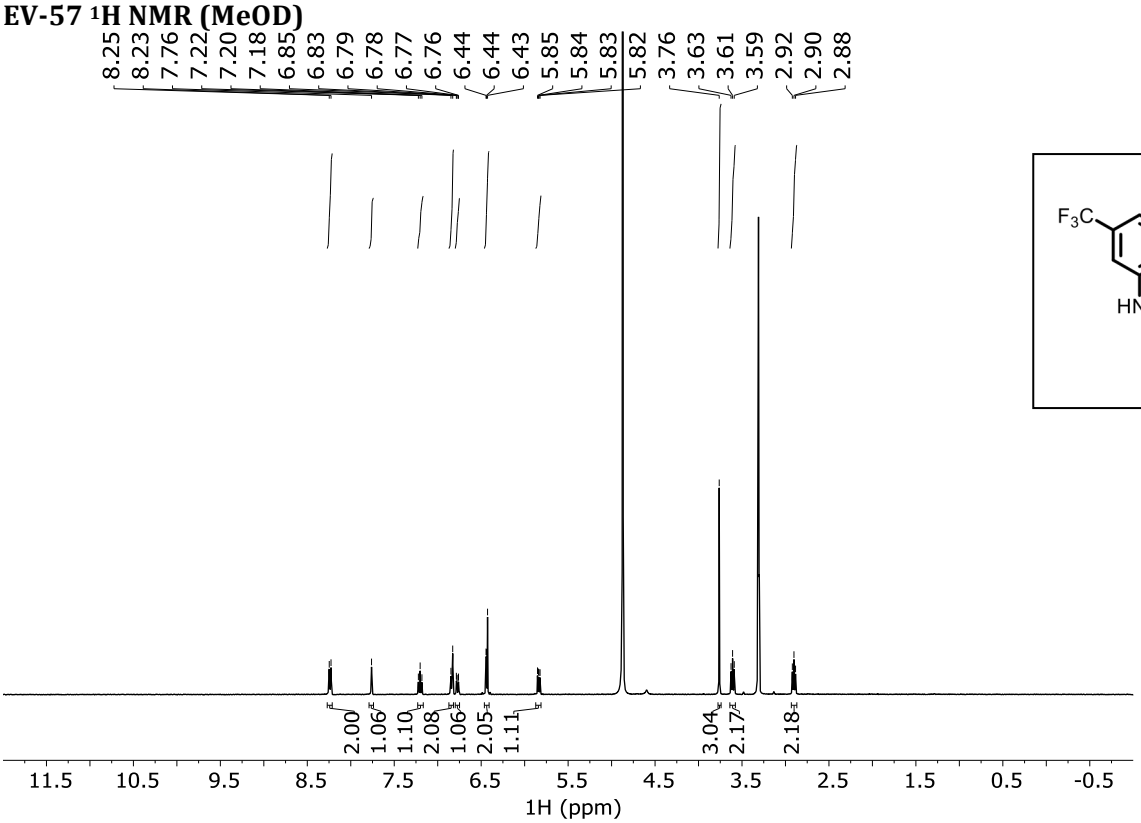


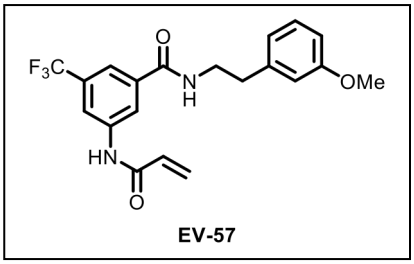
EV-56 ^{1}H NMR ($CDCl_3$)



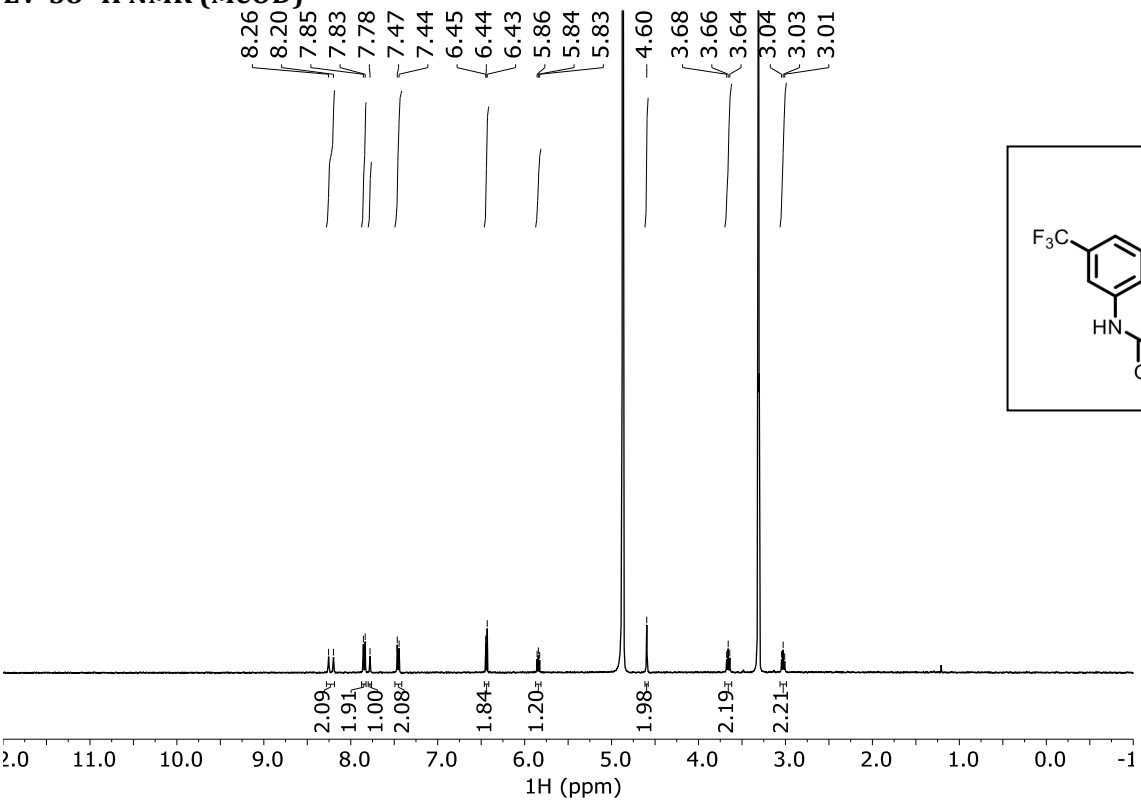


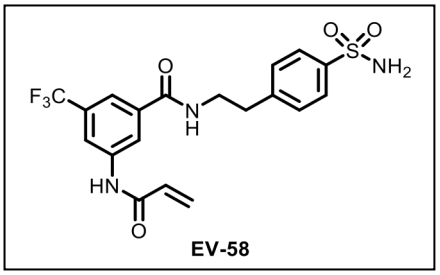
EV-57 ^{1}H NMR (MeOD)



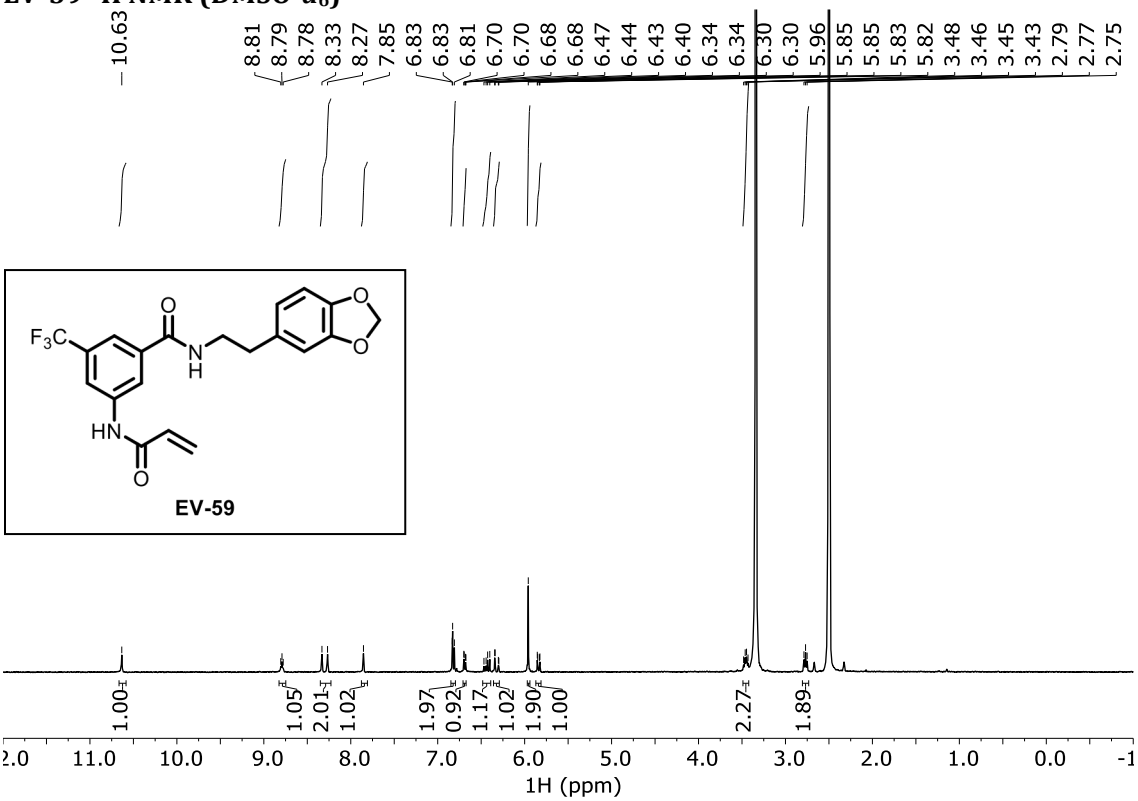


EV-58 ^{1}H NMR (MeOD)

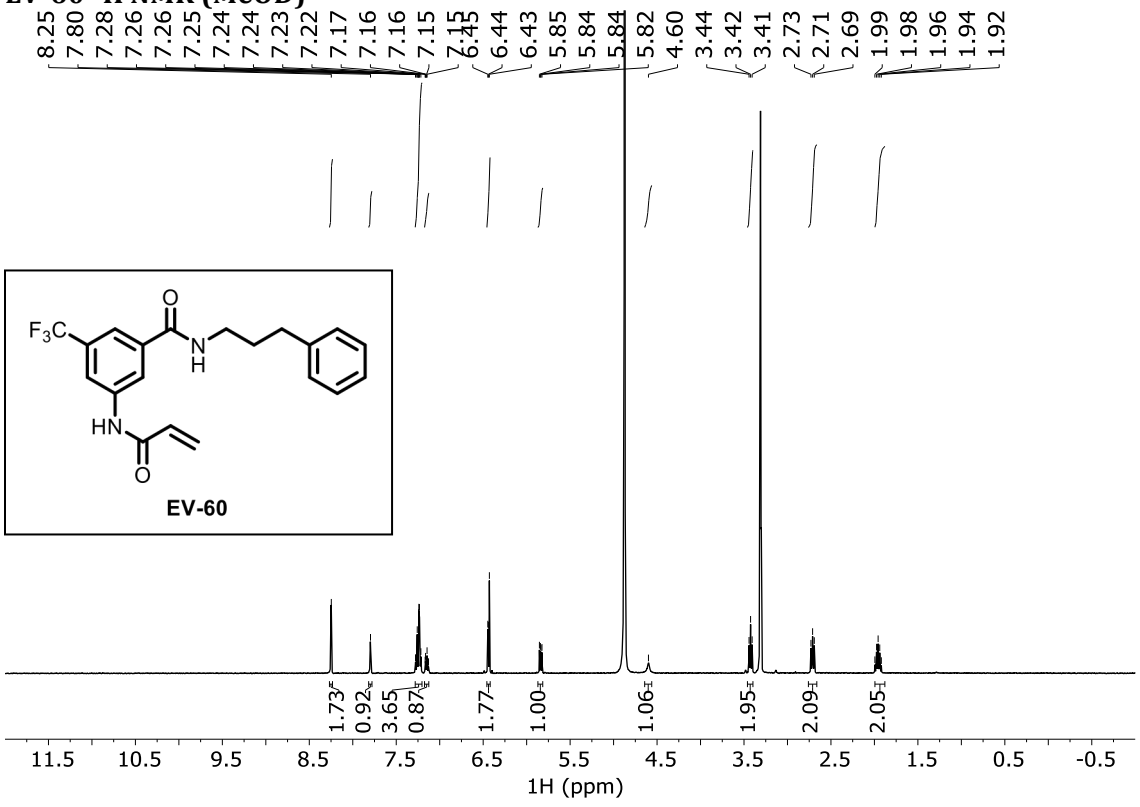




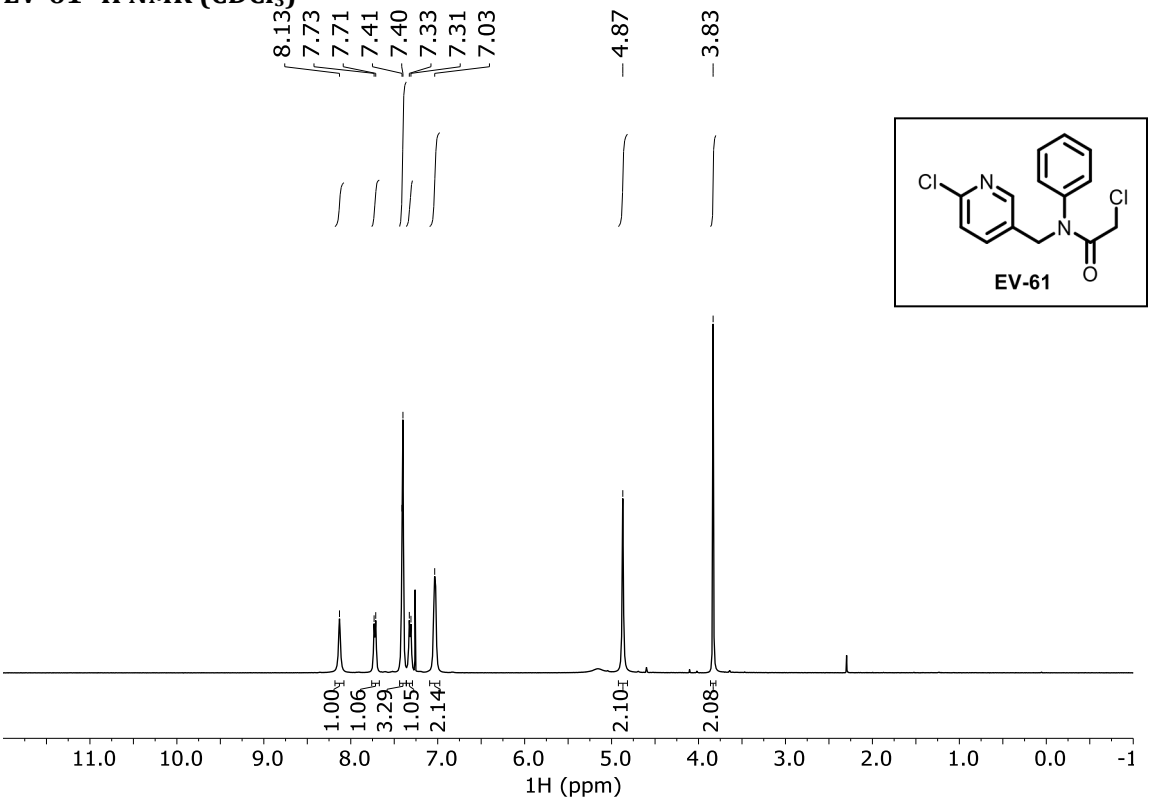
EV-59 ^{1}H NMR (DMSO-d_6)



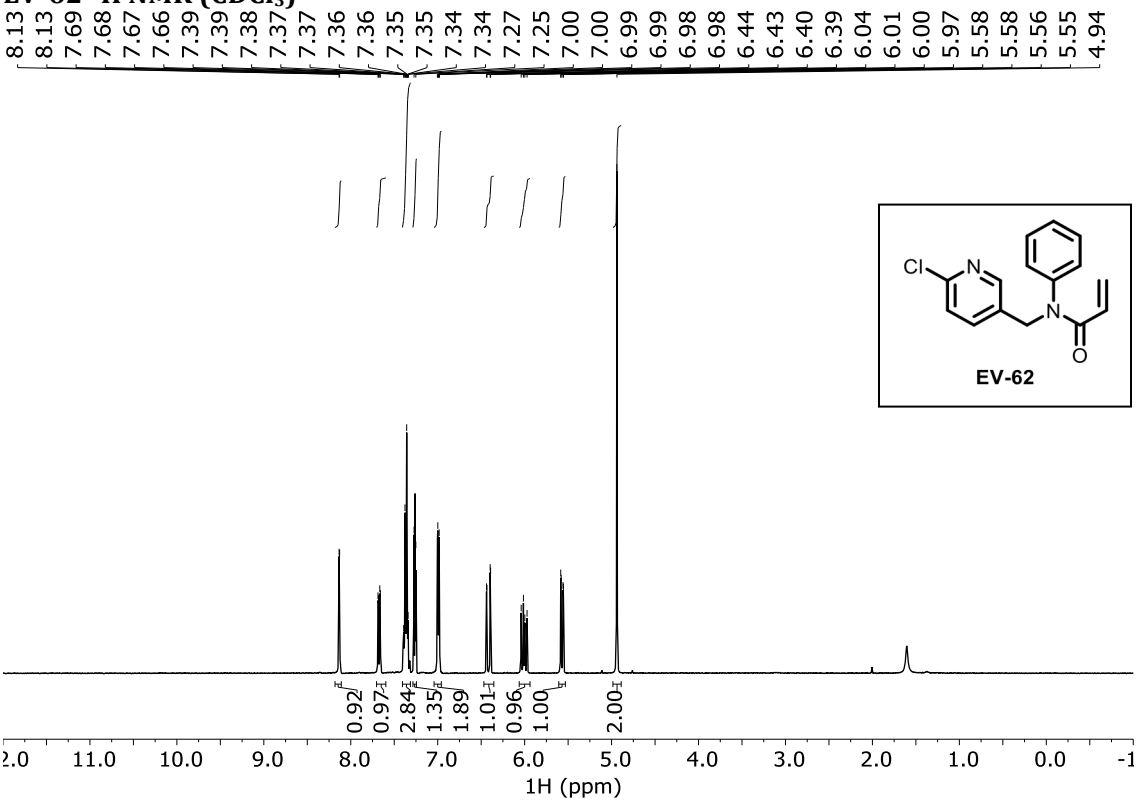
EV-60 ^{1}H NMR (MeOD)



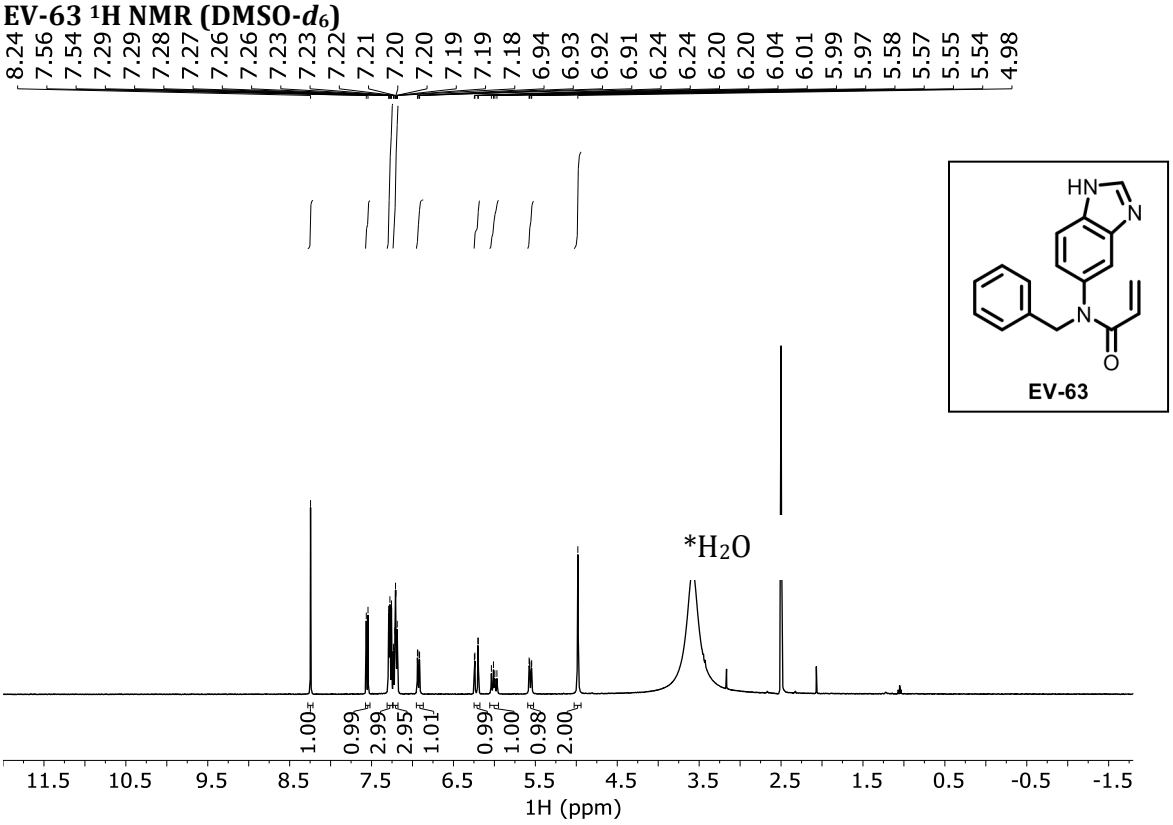
EV-61 ^{1}H NMR ($CDCl_3$)



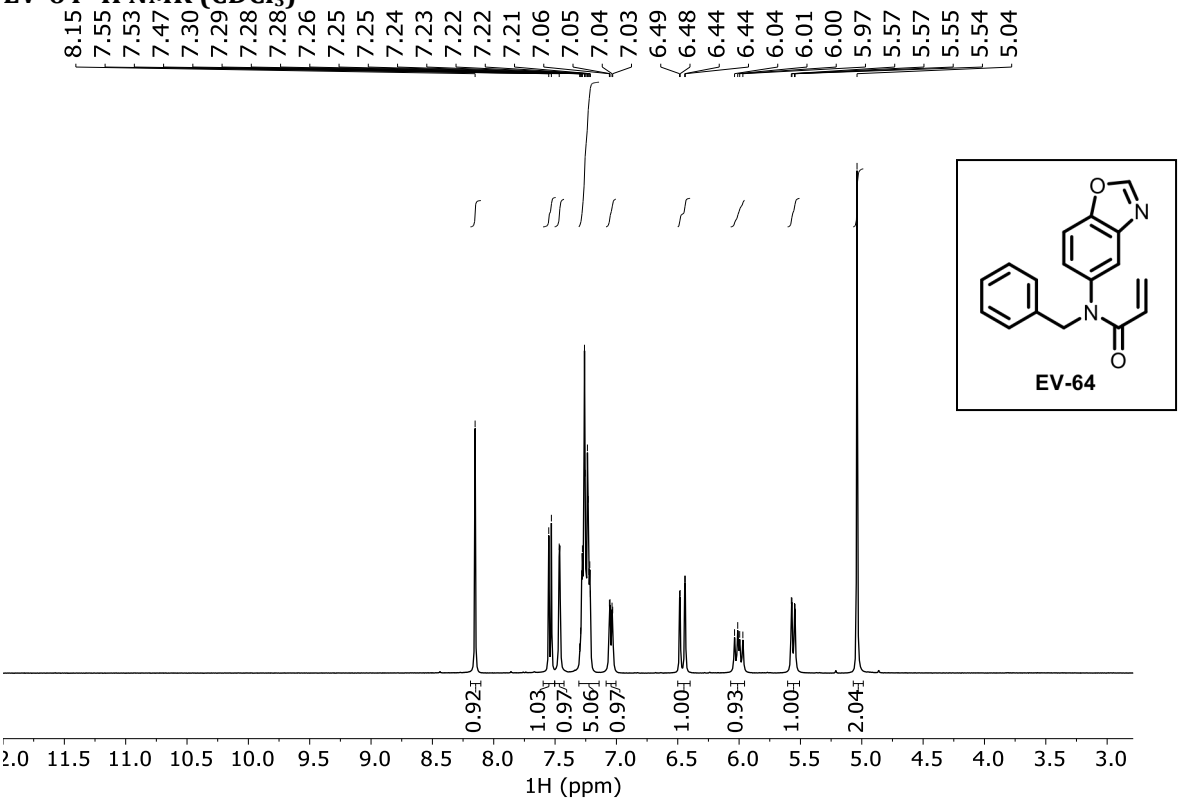
EV-62 ^{1}H NMR ($CDCl_3$)



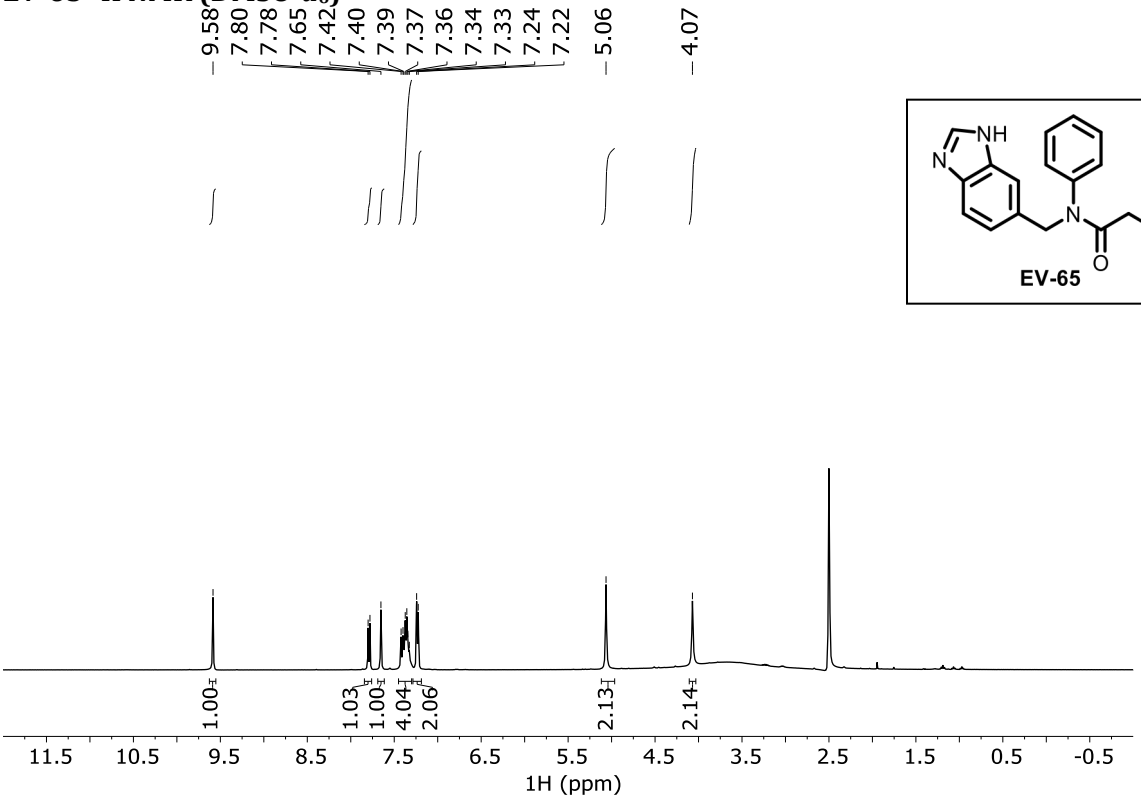
EV-63 ^{1}H NMR (DMSO-d_6)



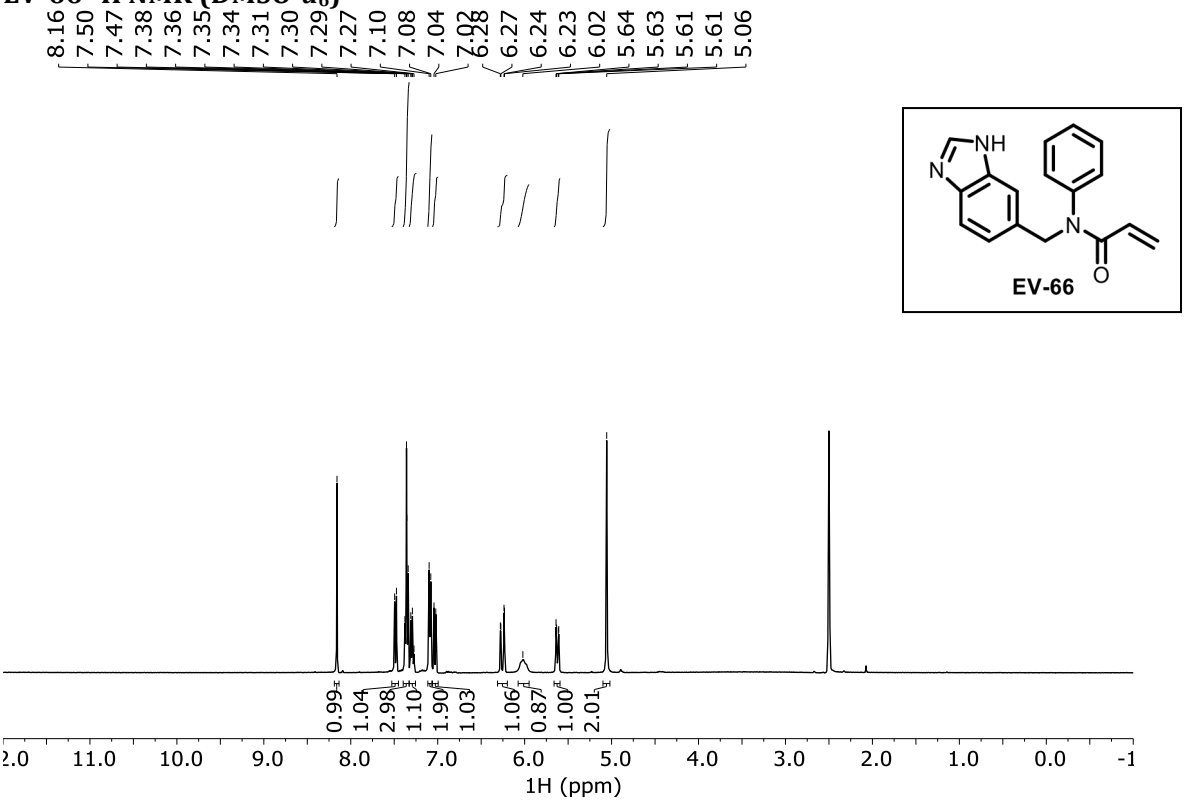
EV-64 ^{1}H NMR ($CDCl_3$)



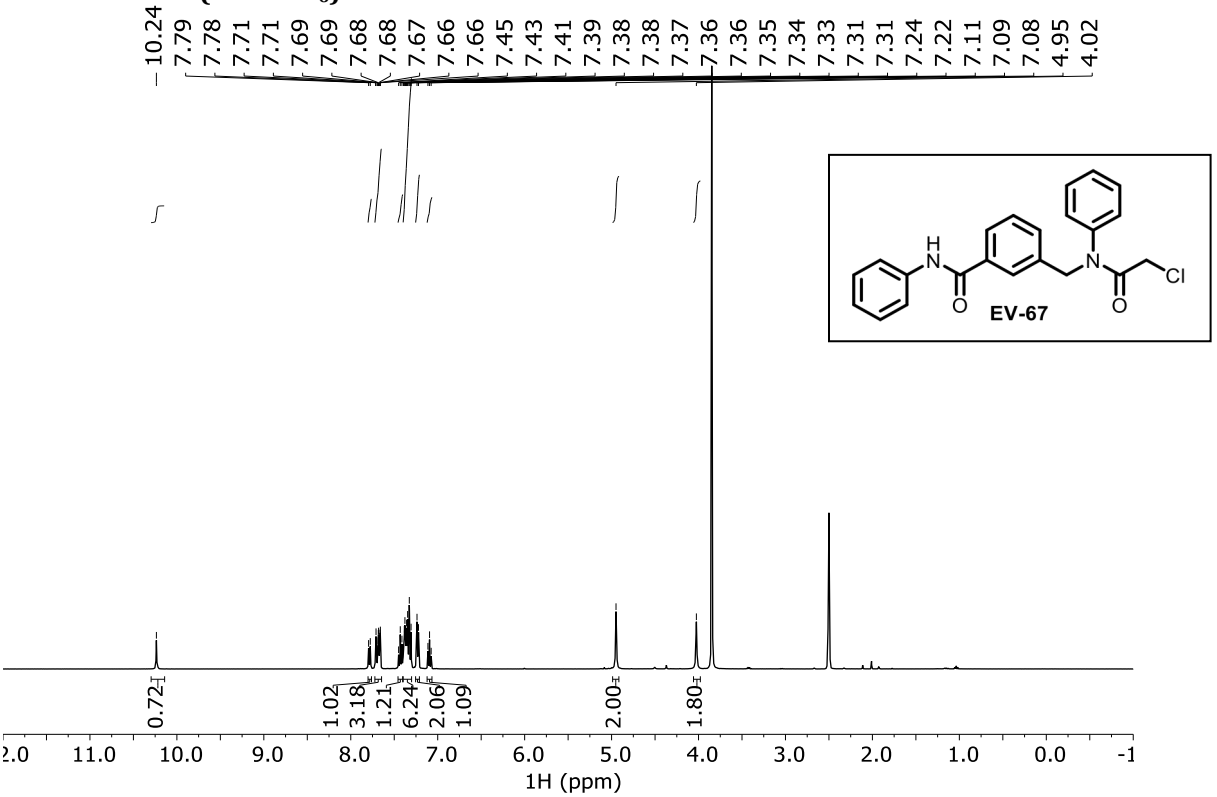
EV-65 ^{1}H NMR (DMSO-d_6)



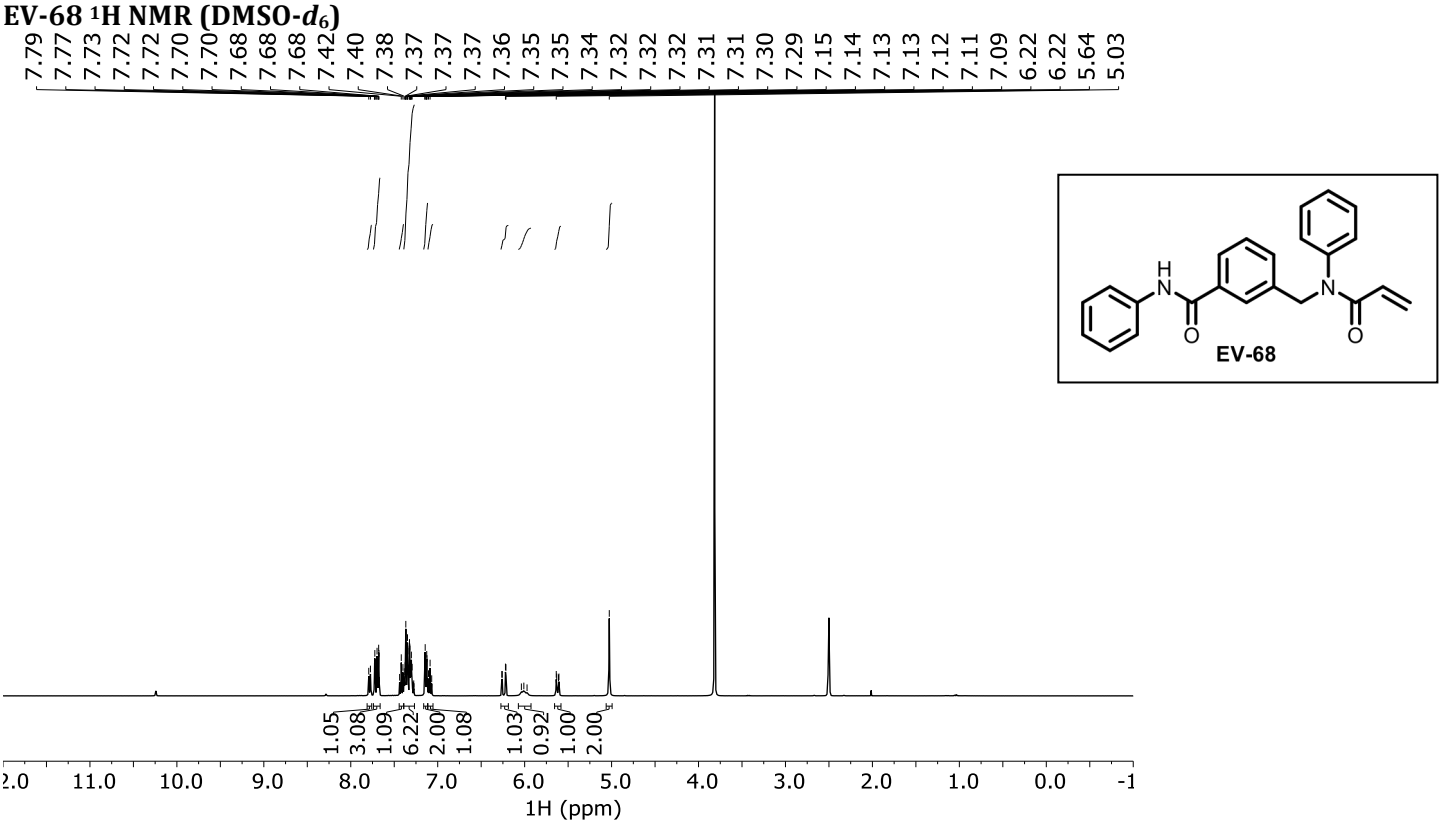
EV-66 ^{1}H NMR (DMSO-d_6)



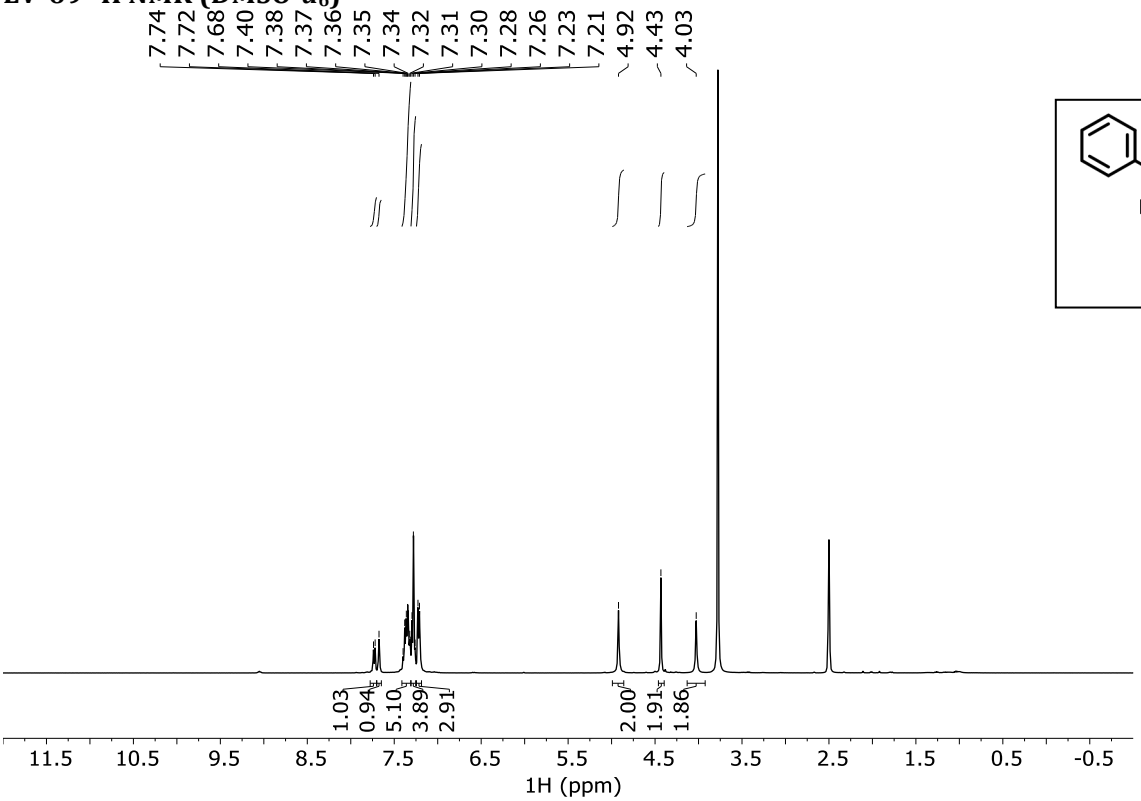
EV-67 ^{1}H NMR (DMSO-d_6)

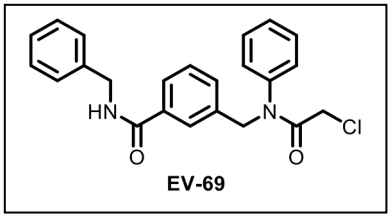


EV-68 ^{1}H NMR (DMSO-d_6)

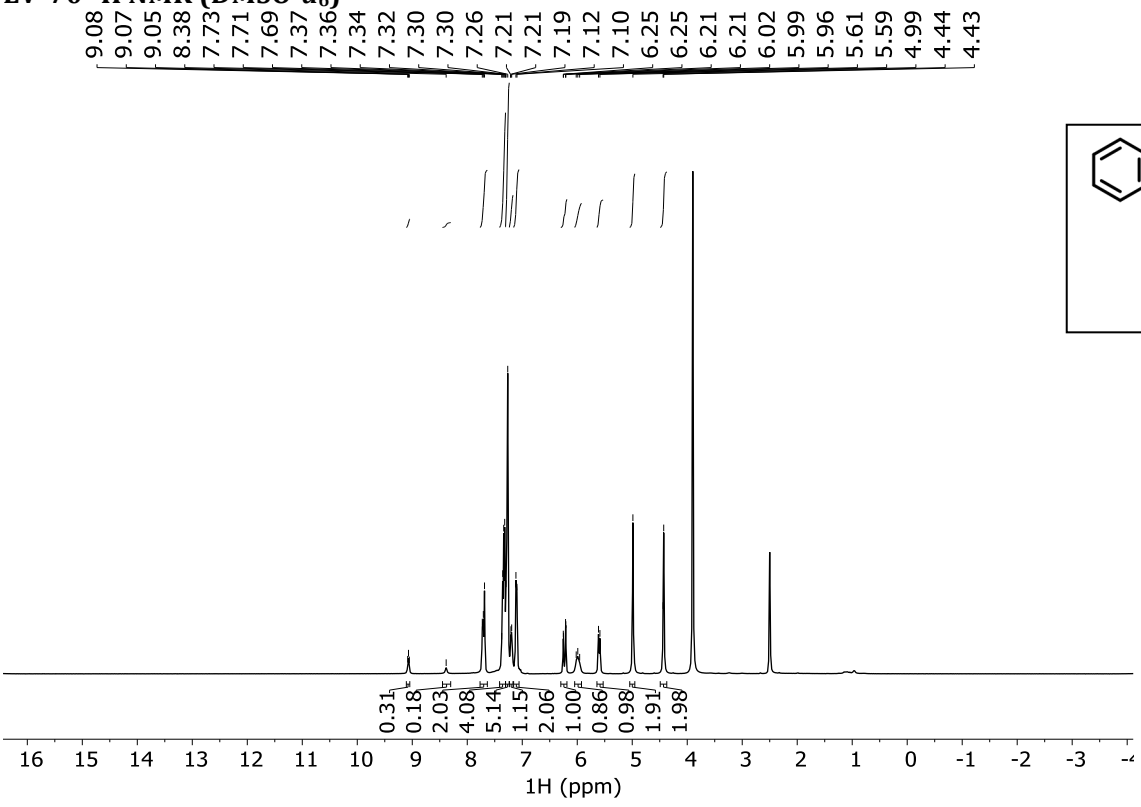


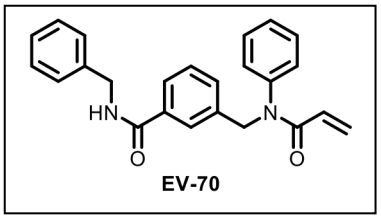
EV-69 ^{1}H NMR (DMSO-d_6)



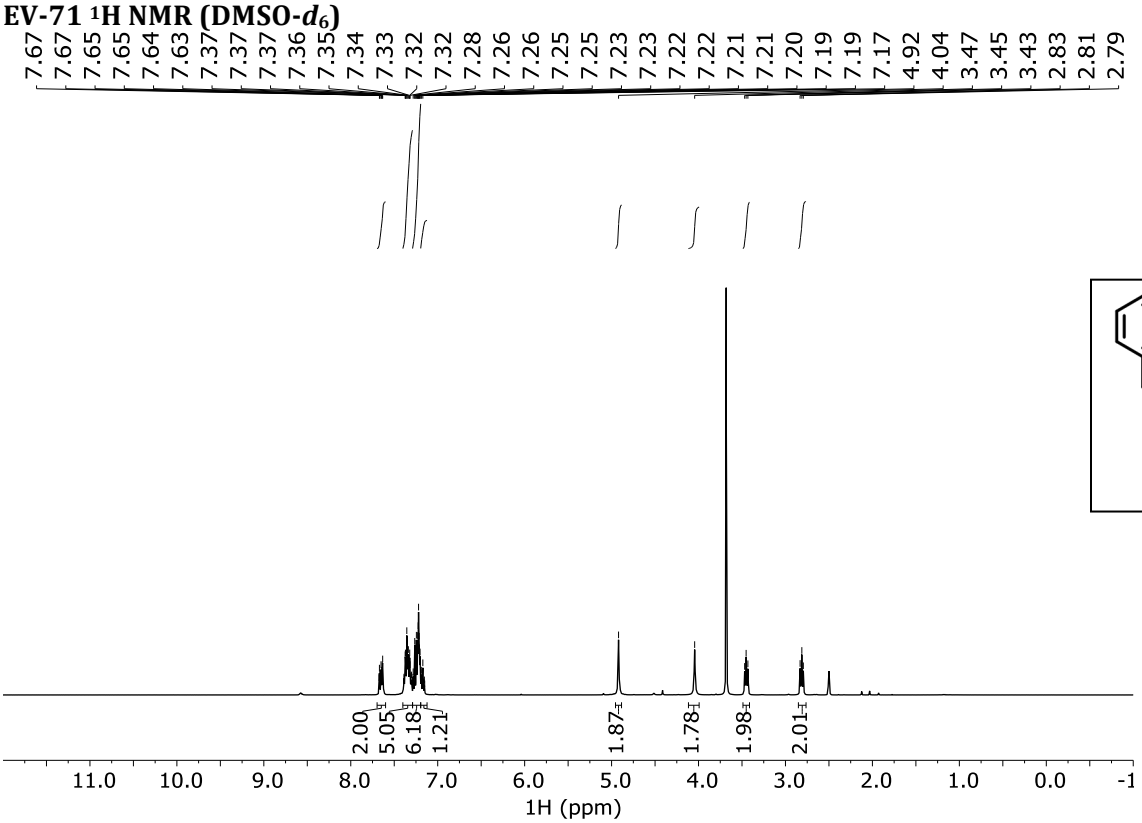


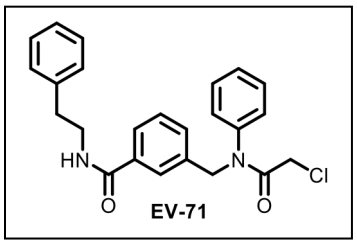
EV-70 ^{1}H NMR (DMSO-d_6)



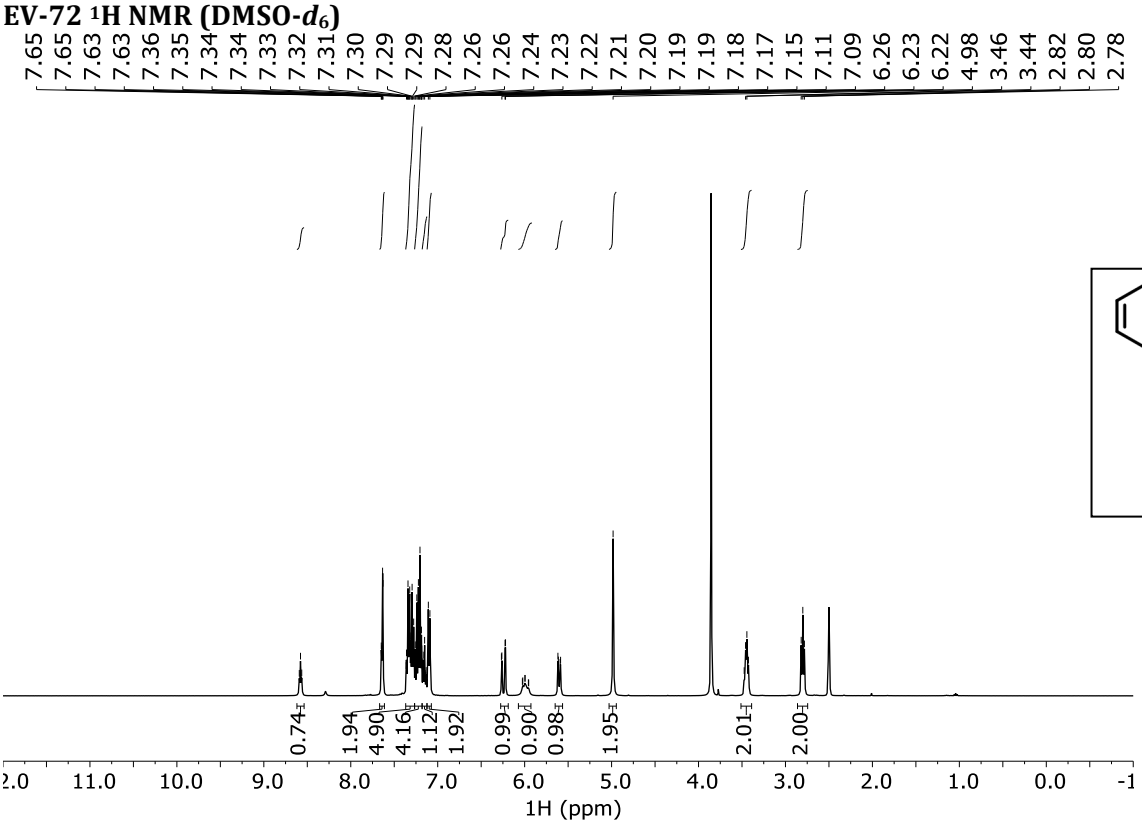


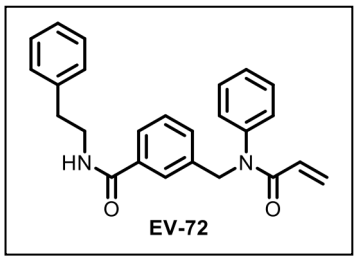
EV-71 ^{1}H NMR (DMSO-d_6)



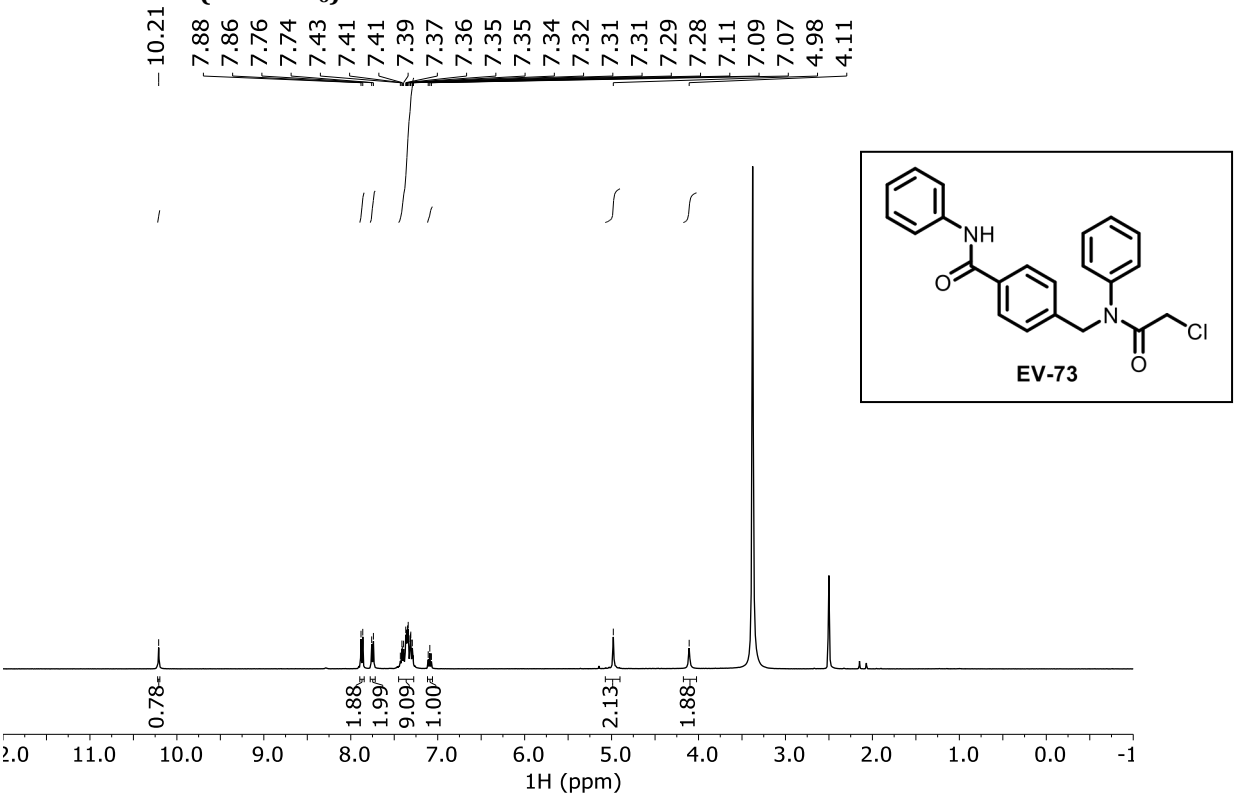


EV-72 ^{1}H NMR (DMSO-d_6)

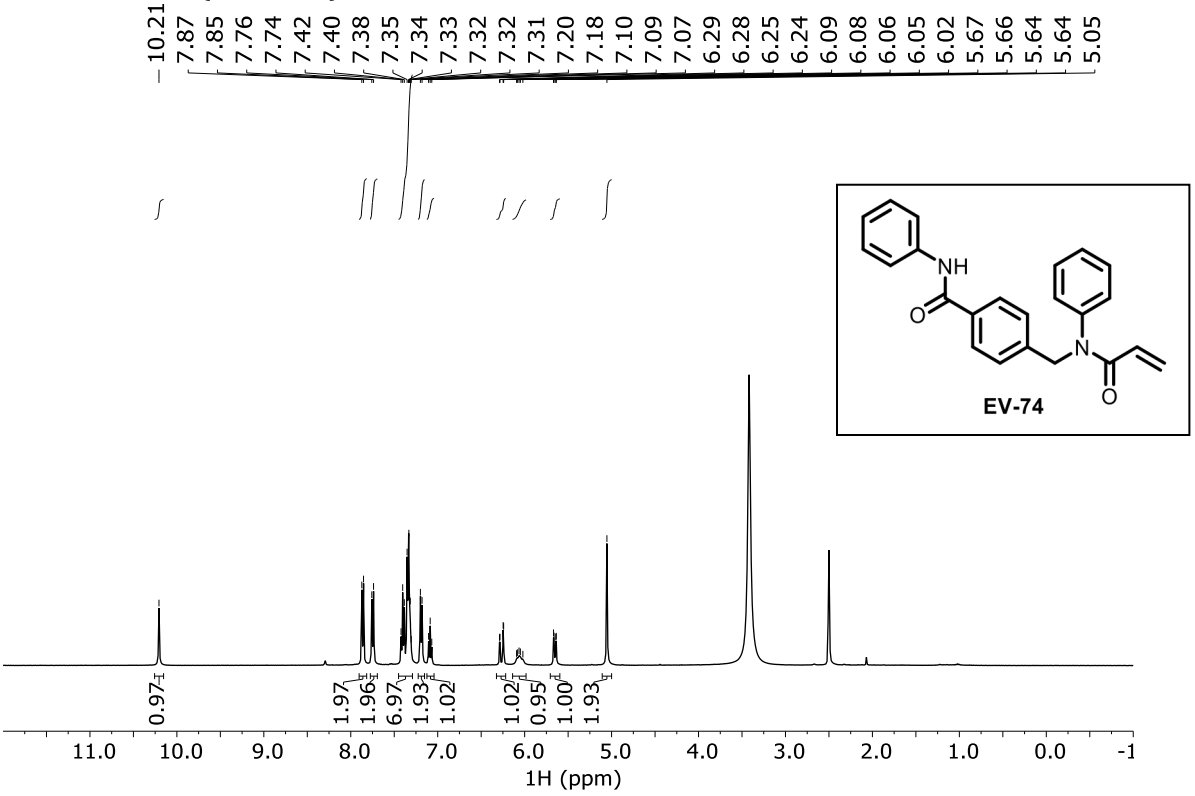




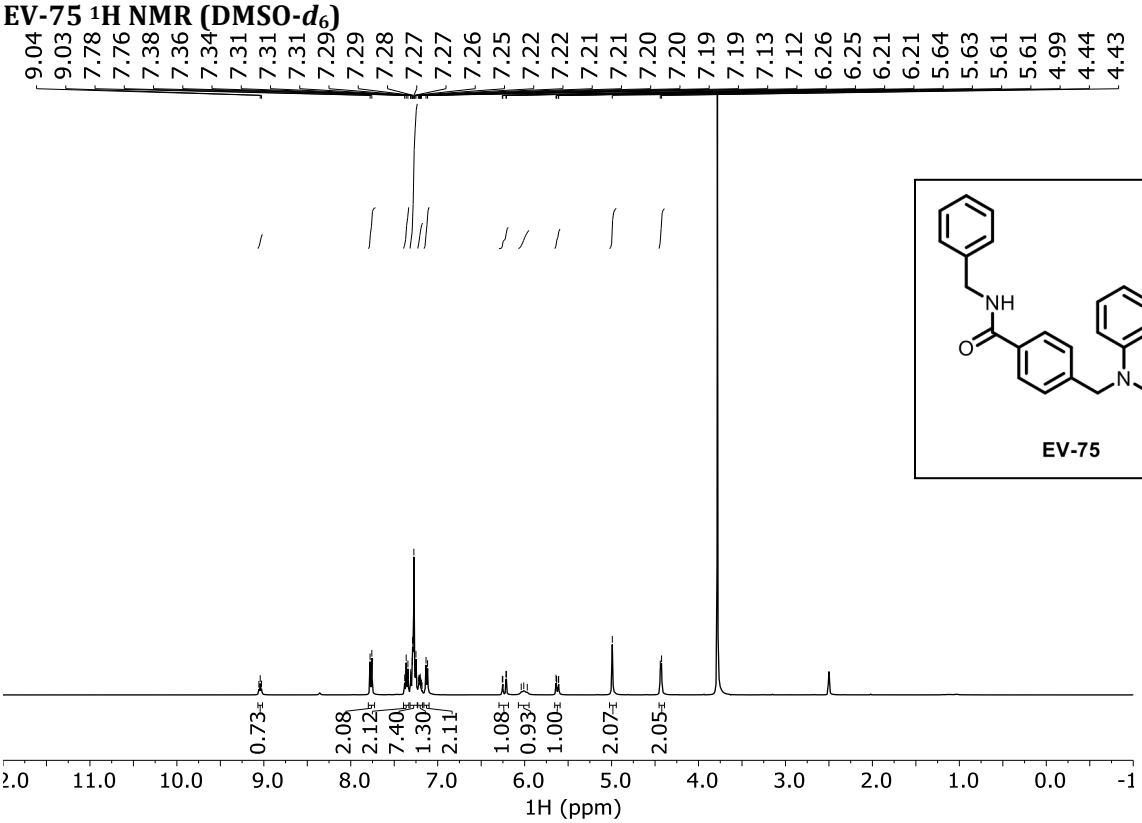
EV-73 ^{1}H NMR (DMSO-d_6)



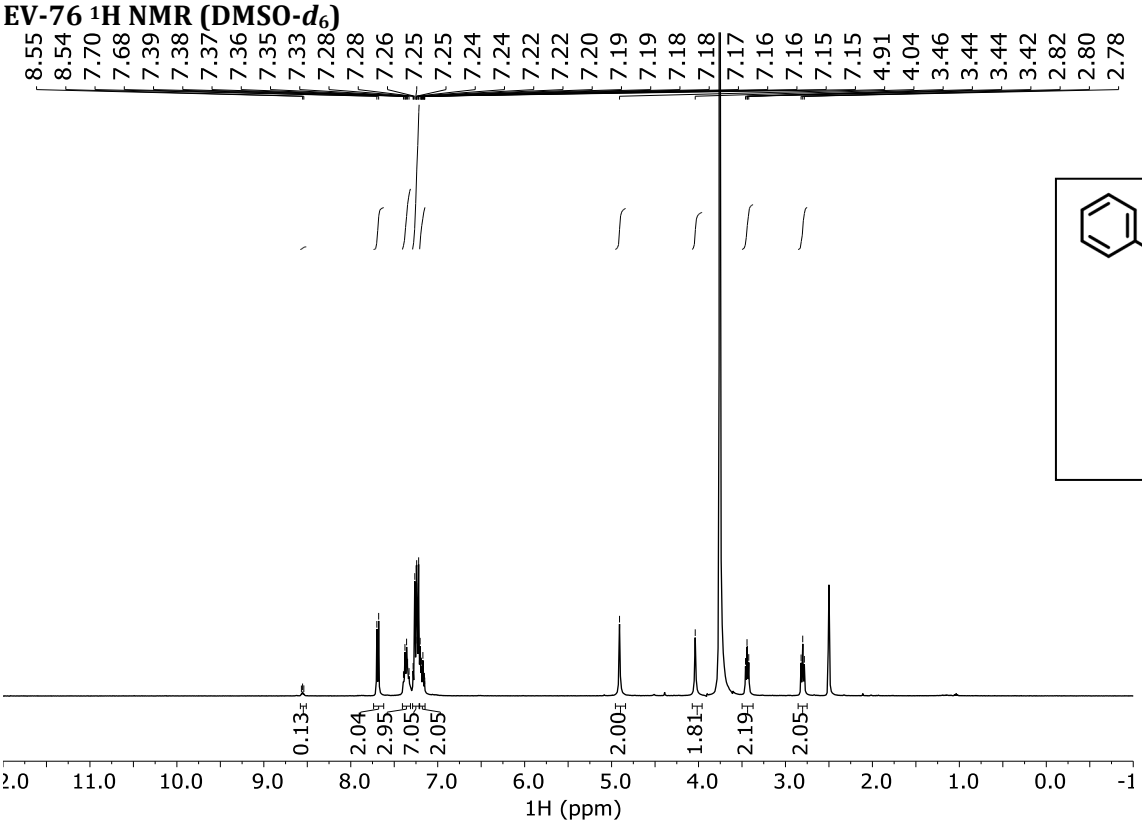
EV-74 ^{1}H NMR (DMSO-d_6)



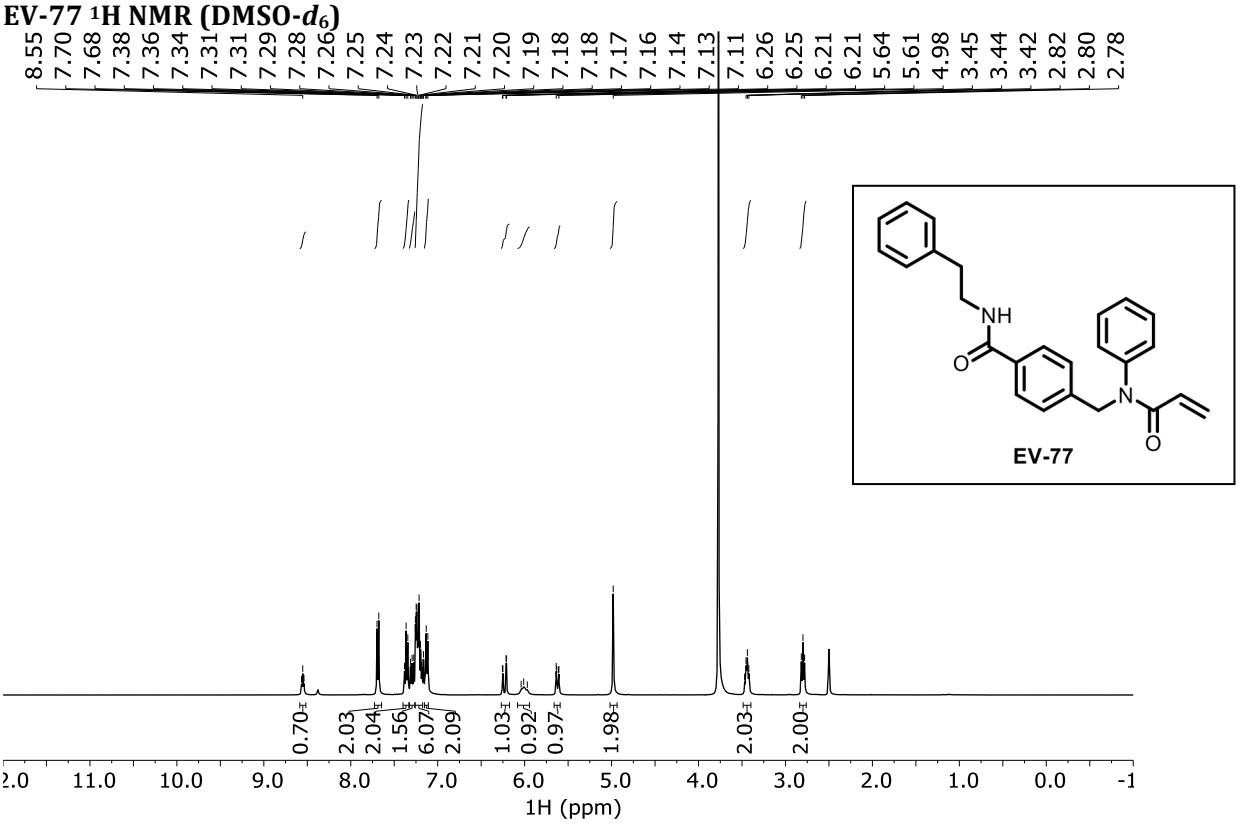
EV-75 ^{1}H NMR (DMSO-d_6)



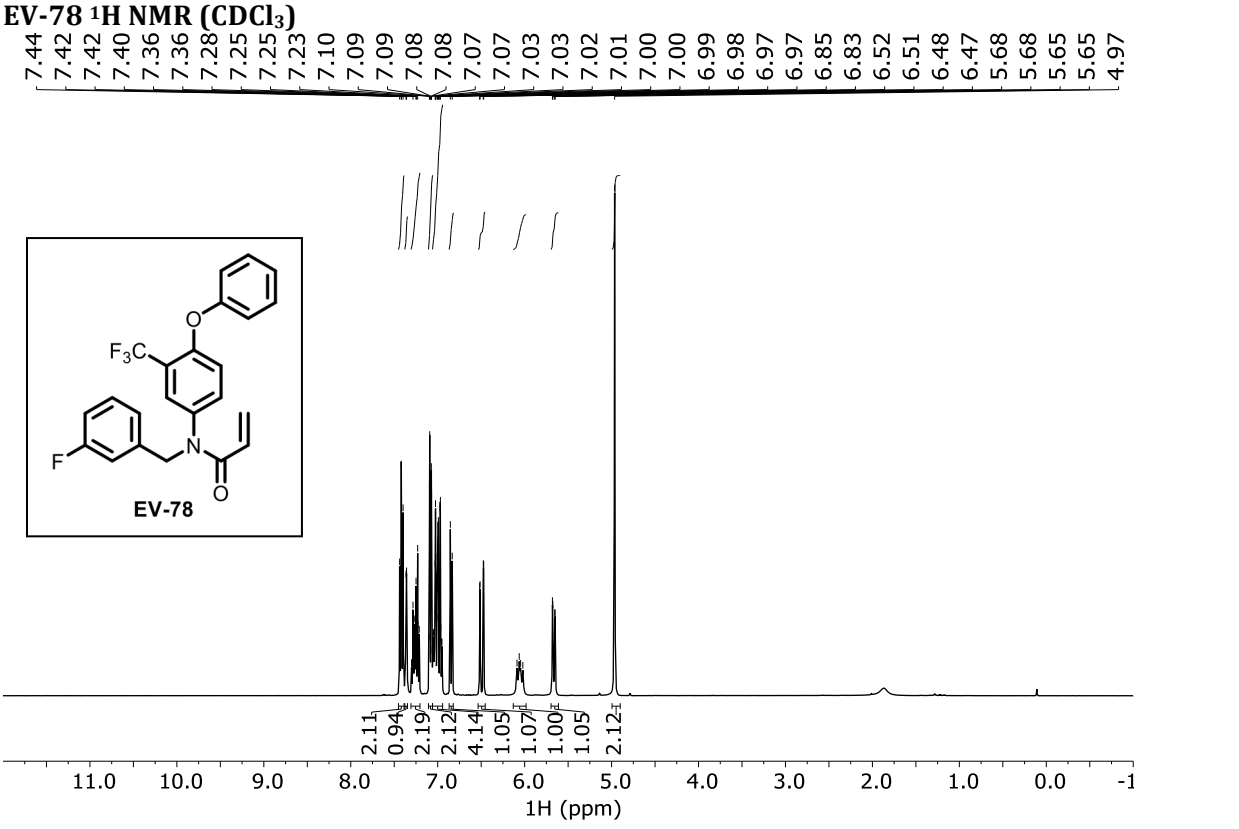
EV-76 ^{1}H NMR (DMSO-d_6)



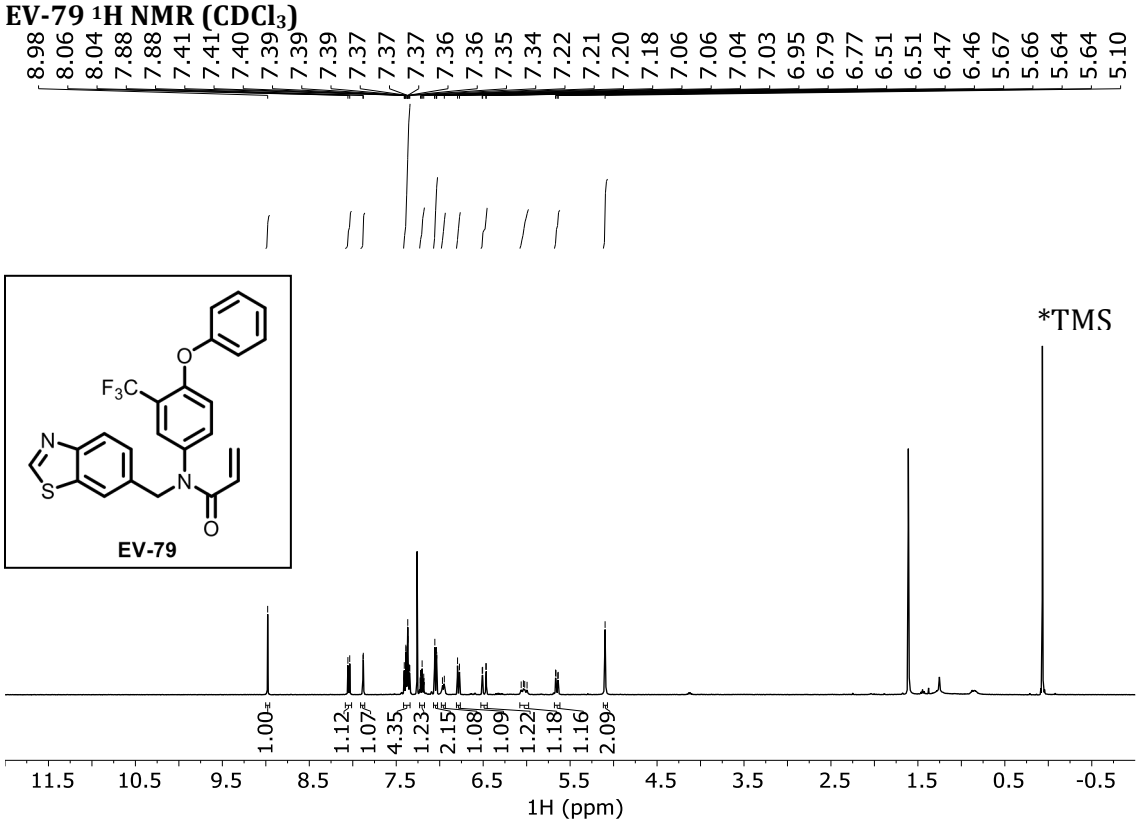
EV-77 ^{1}H NMR (DMSO-d_6)



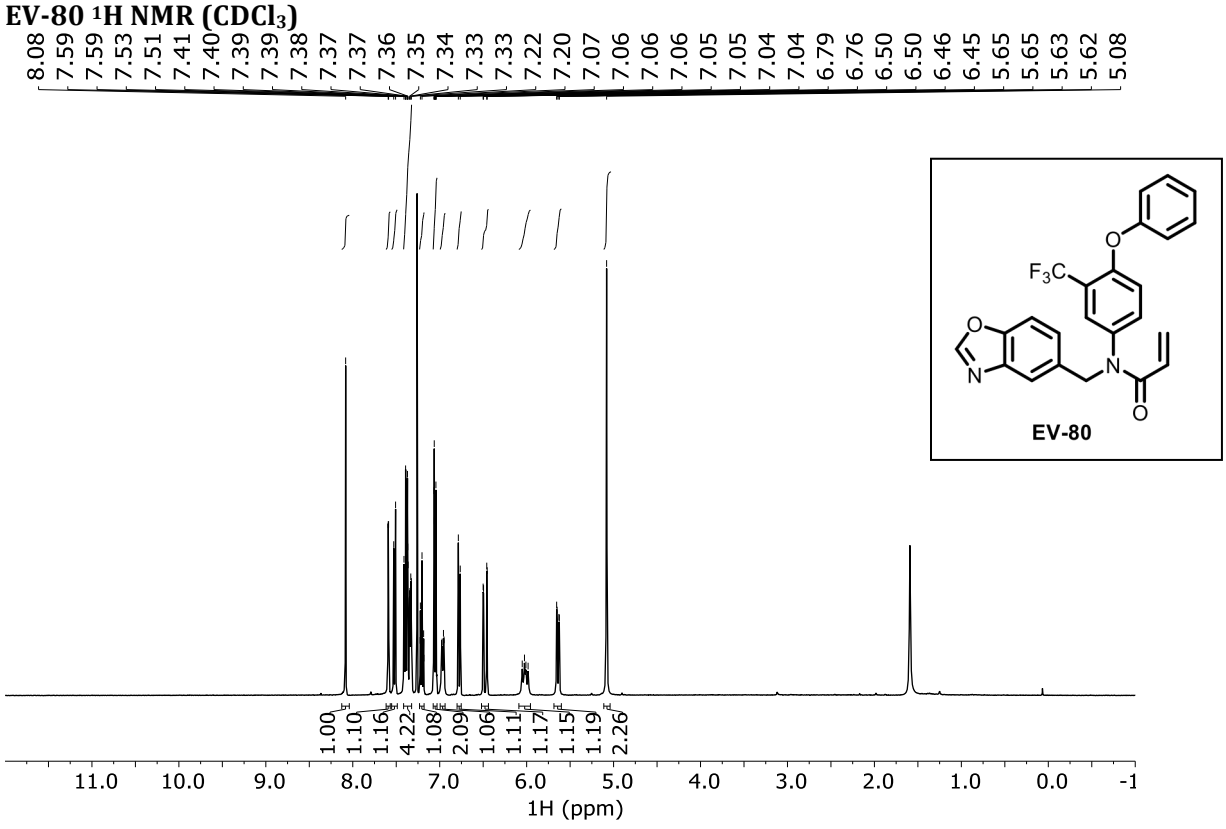
EV-78 ^{1}H NMR ($CDCl_3$)



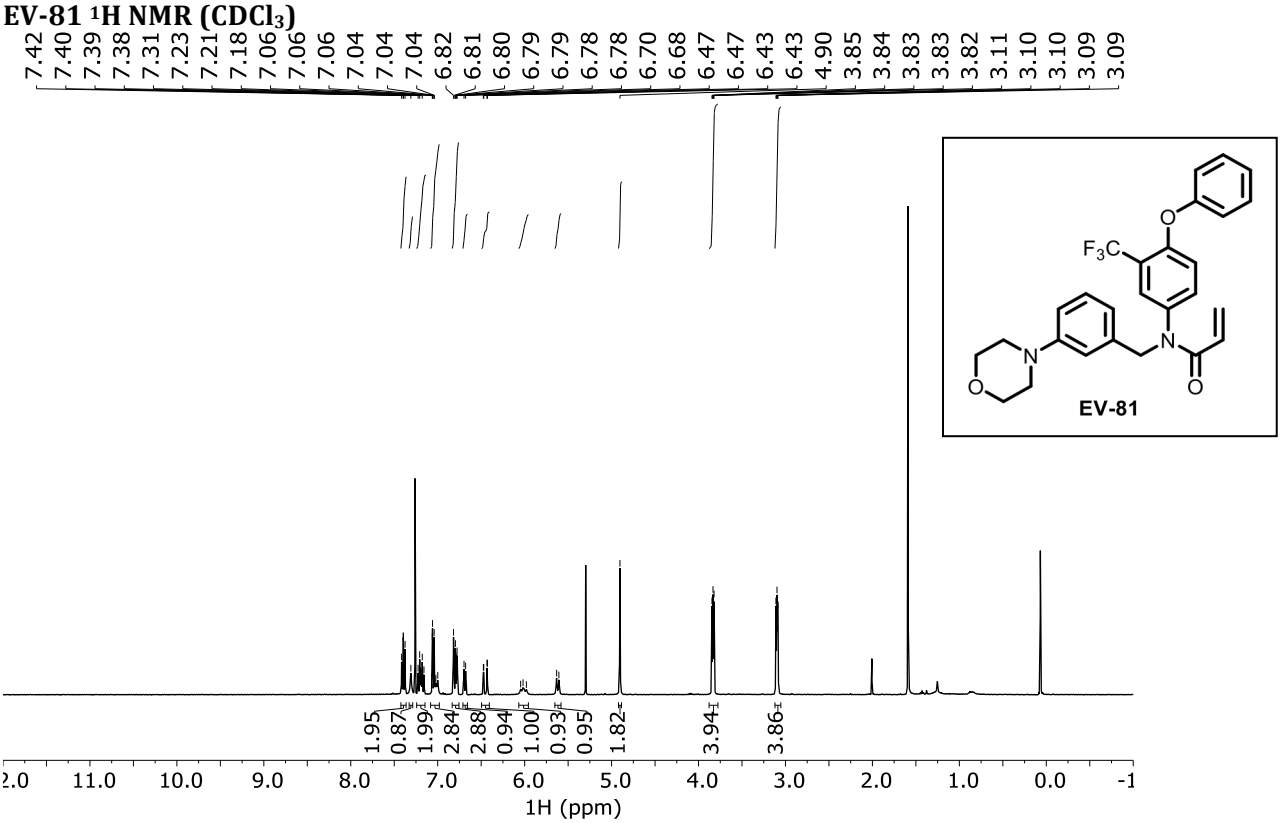
EV-79 ^{1}H NMR ($CDCl_3$)



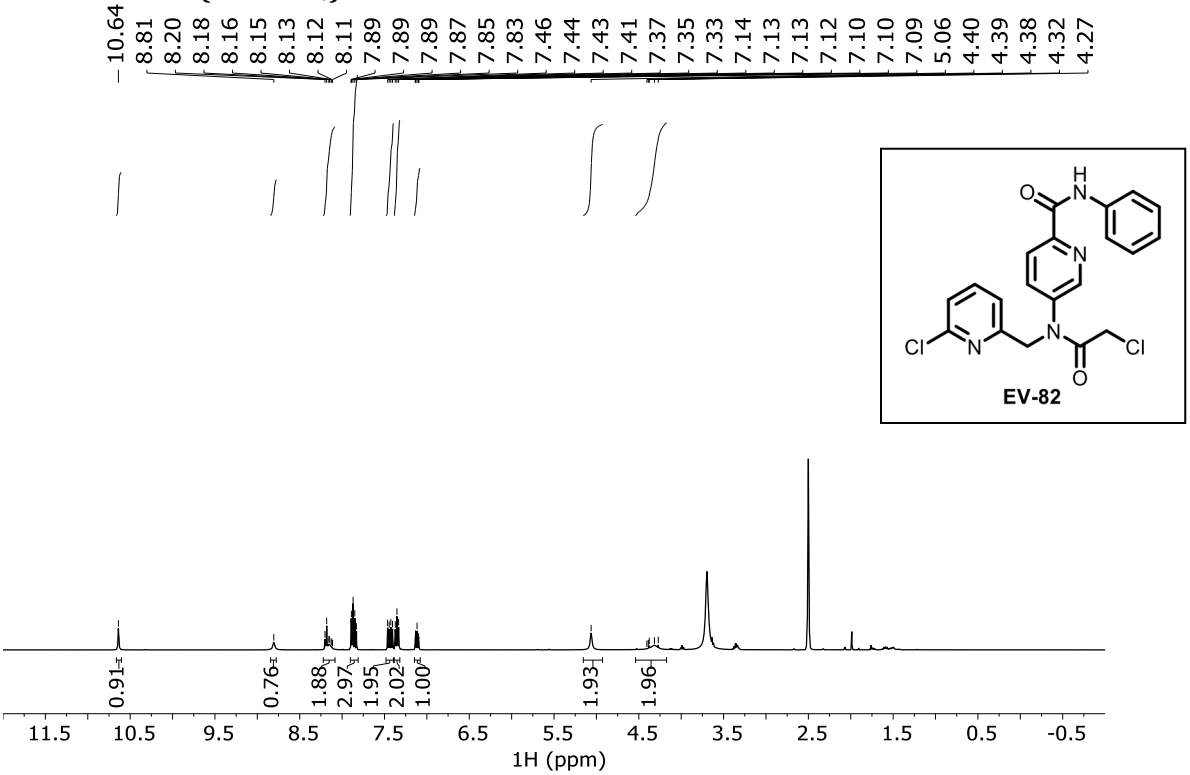
EV-80 ^{1}H NMR ($CDCl_3$)



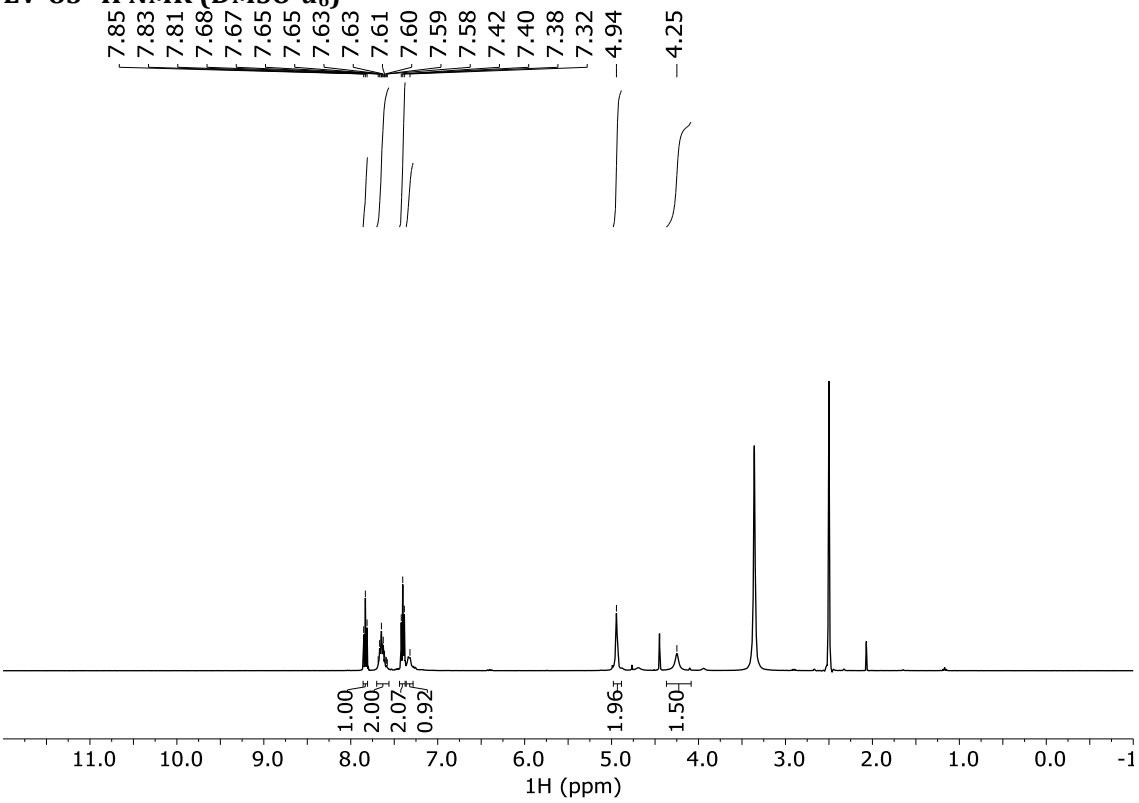
EV-81 ^{1}H NMR ($CDCl_3$)

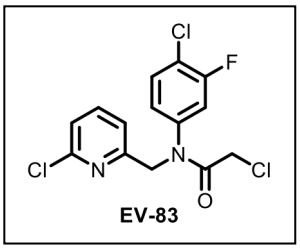


EV-82 ^{1}H NMR (DMSO-d_6)

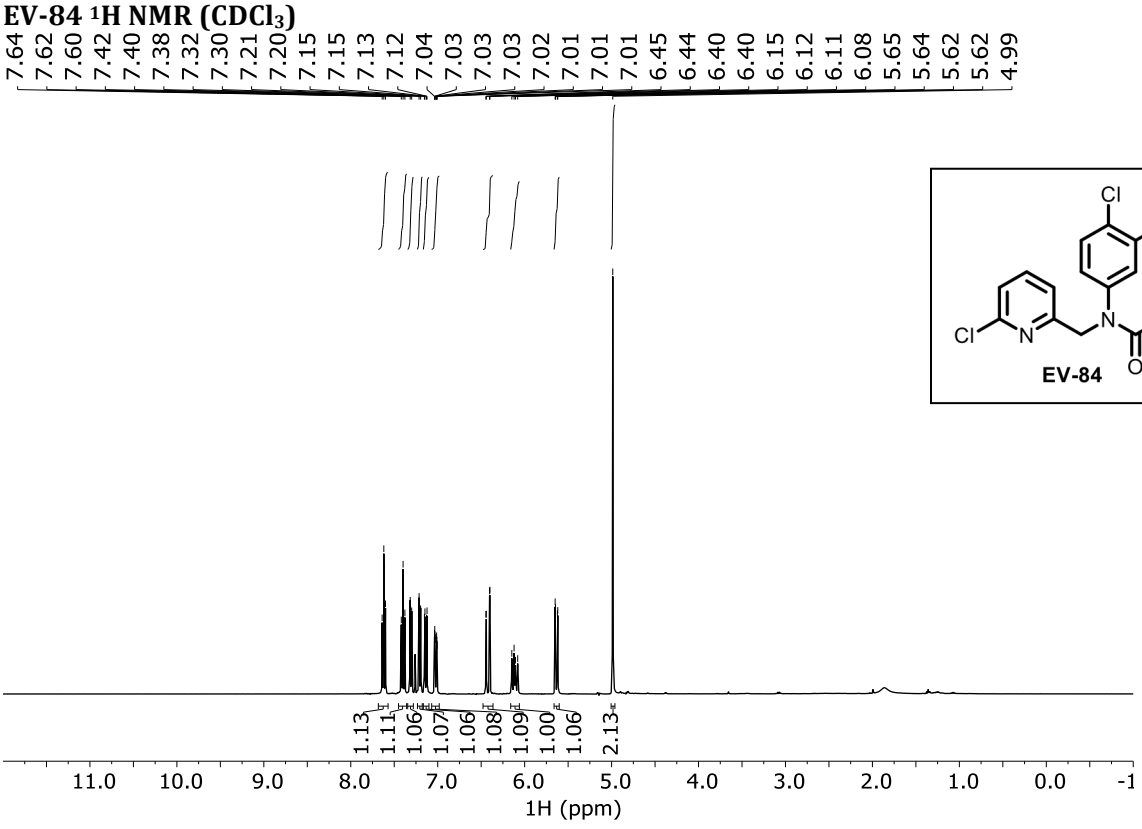


EV-83 ^{1}H NMR (DMSO-d_6)

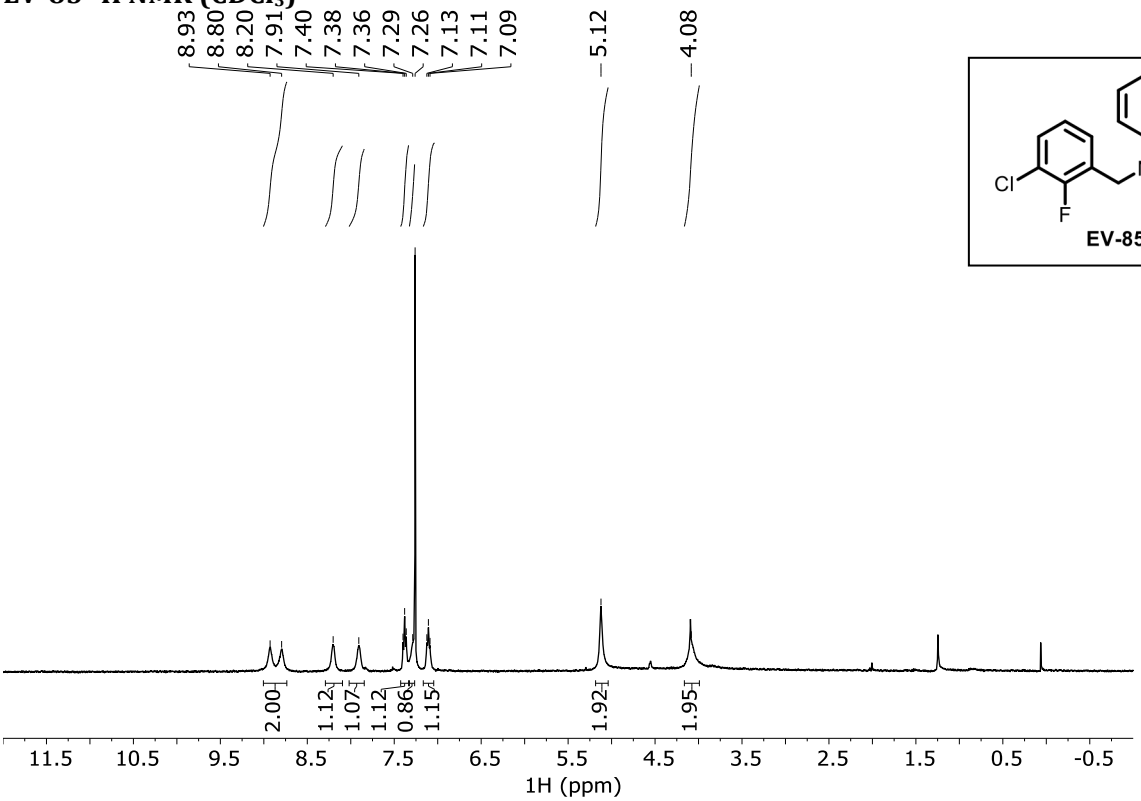




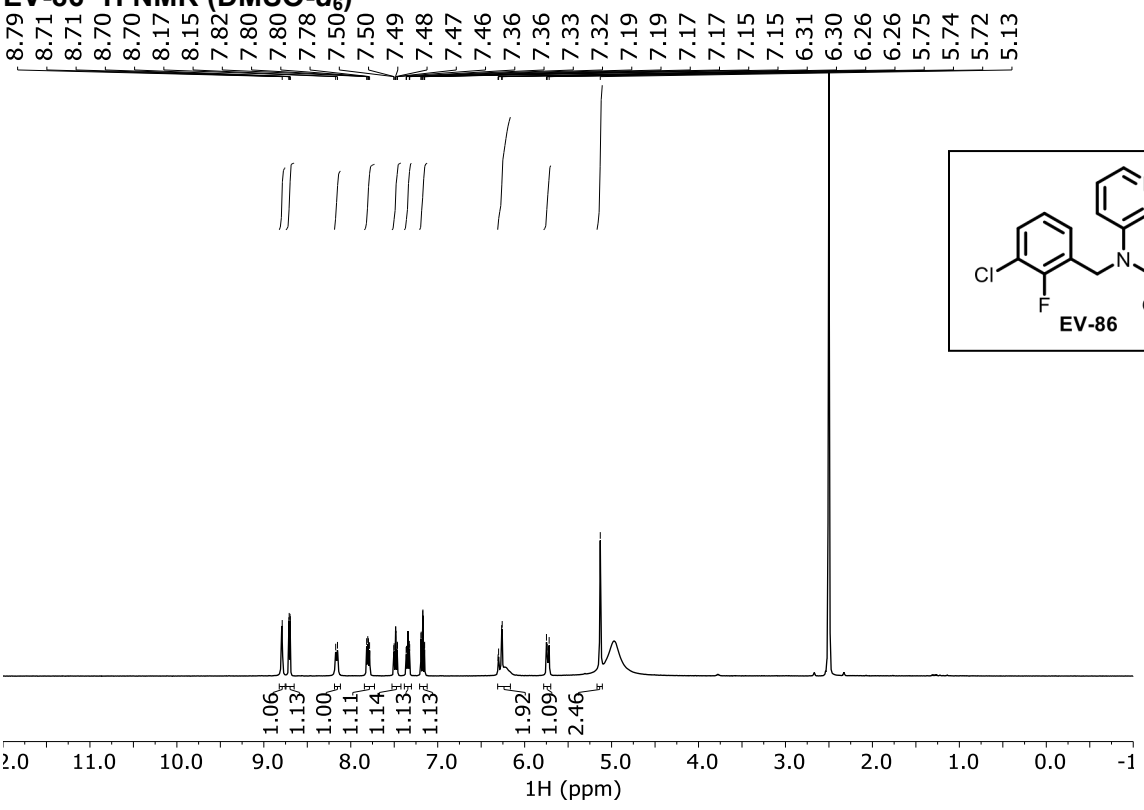
EV-84 ^{1}H NMR ($CDCl_3$)



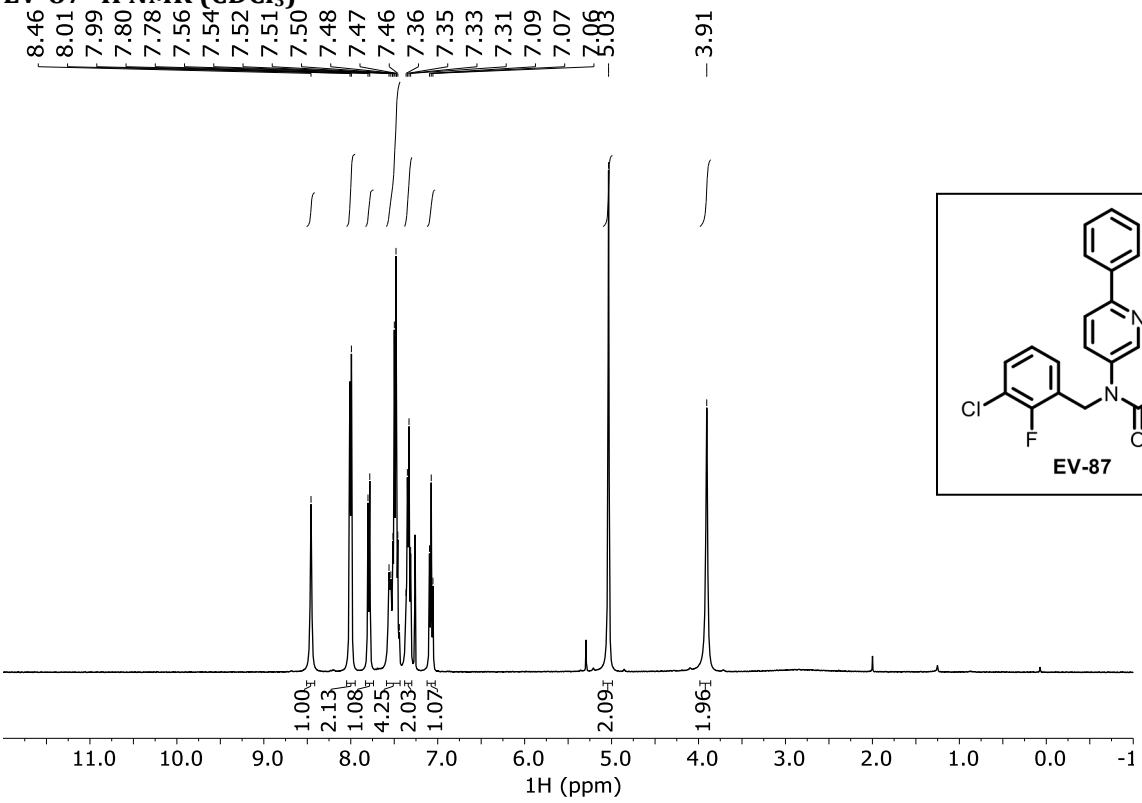
EV-85 ^{1}H NMR ($CDCl_3$)



EV-86 ^{1}H NMR (DMSO-d_6)

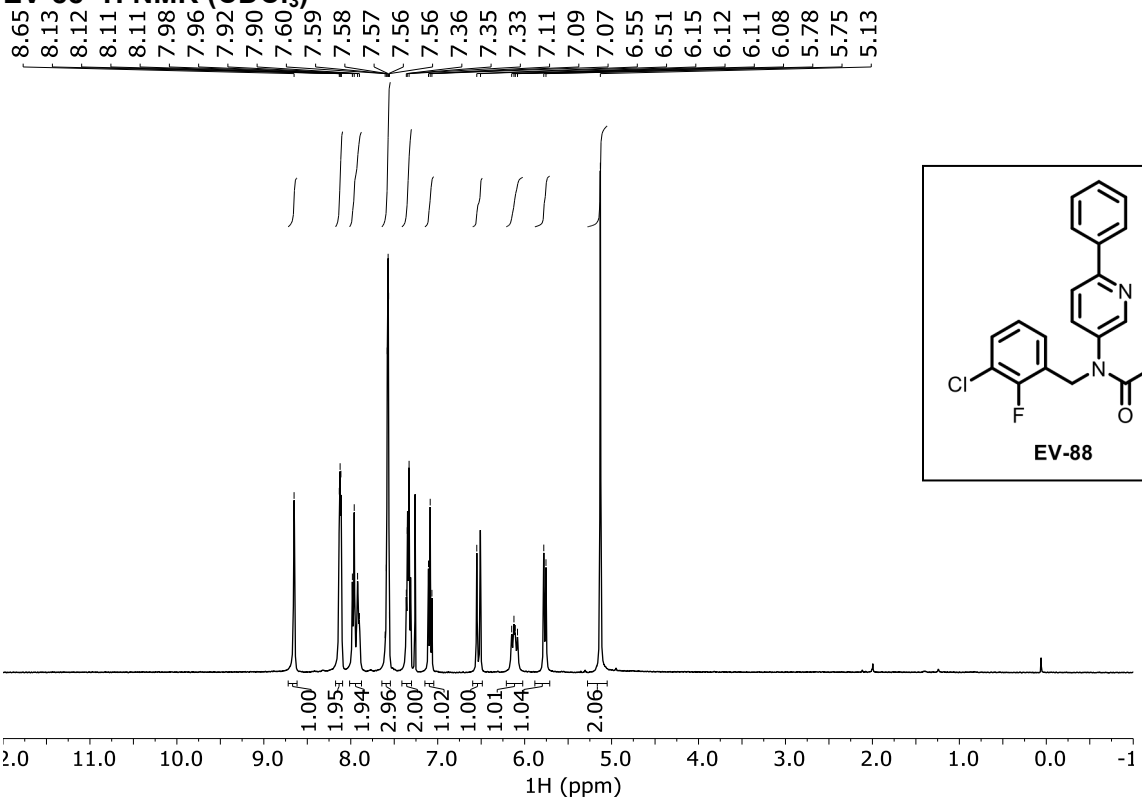


EV-87 ^{1}H NMR ($CDCl_3$)



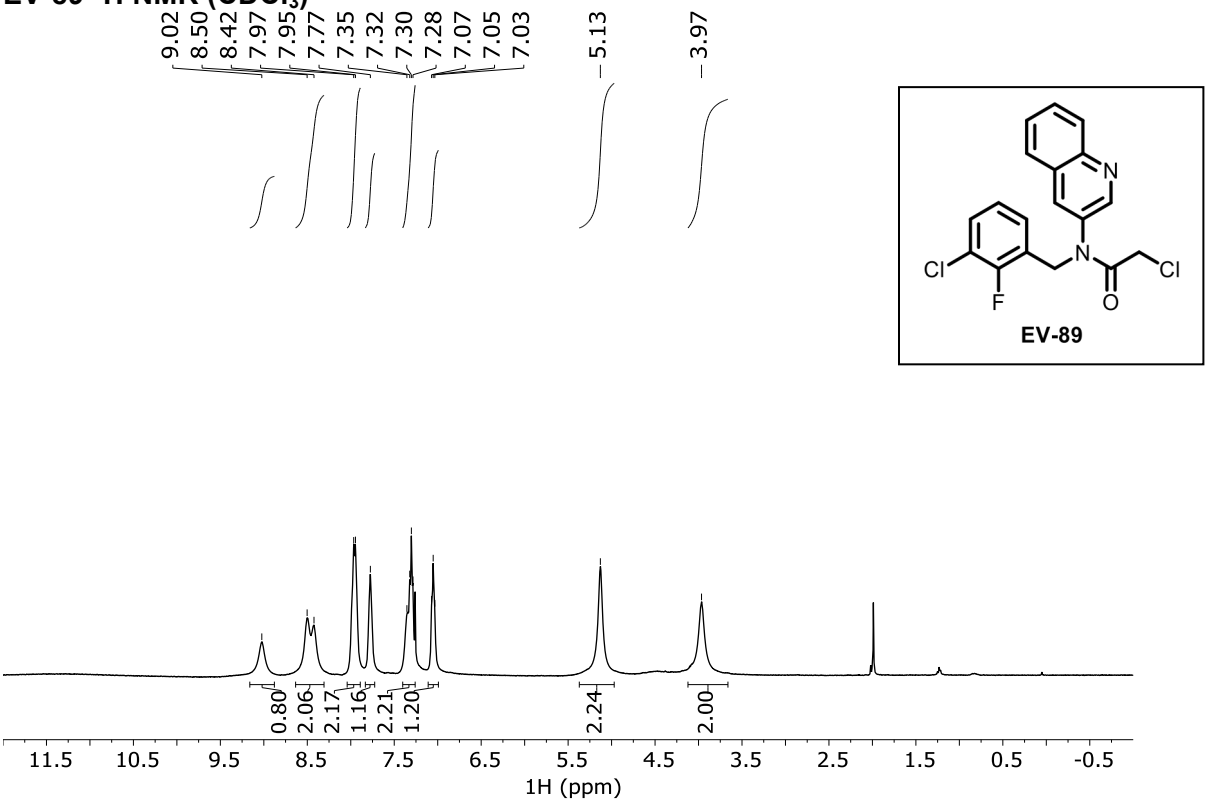
EV-87

EV-88 ^{1}H NMR ($CDCl_3$)

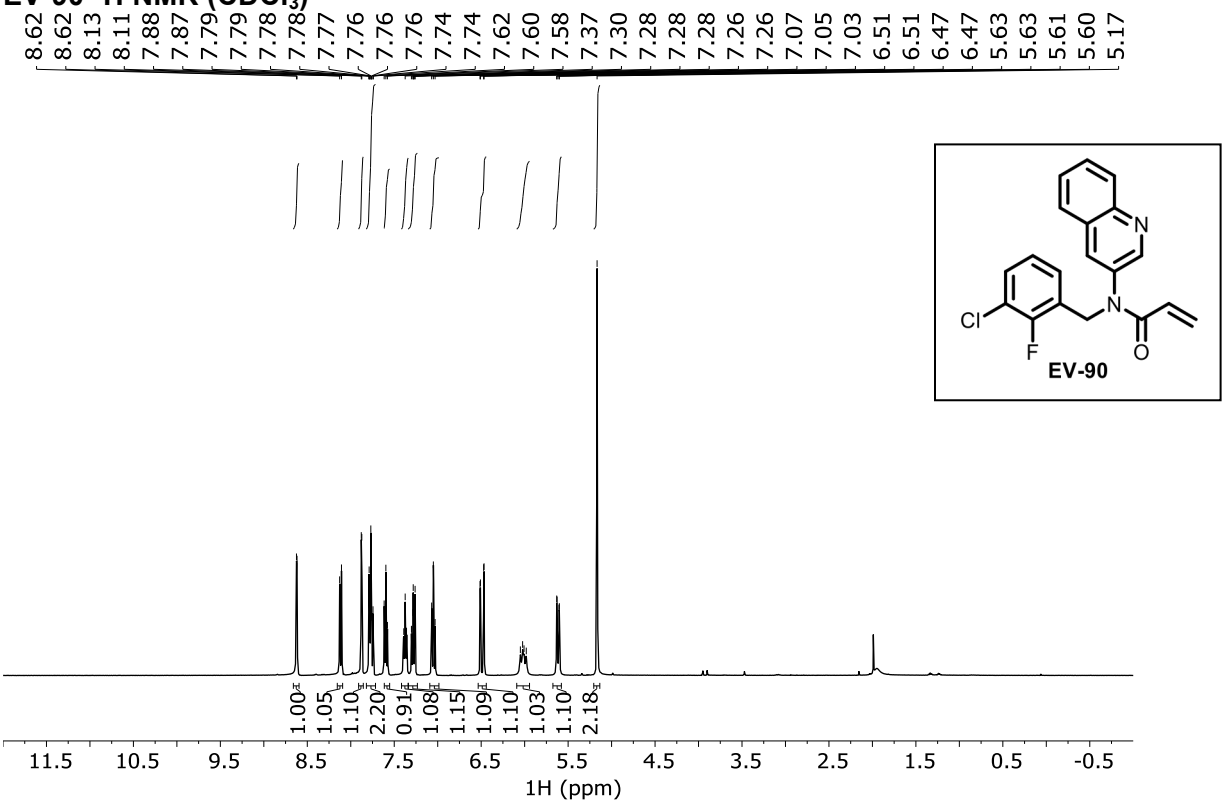


EV-88

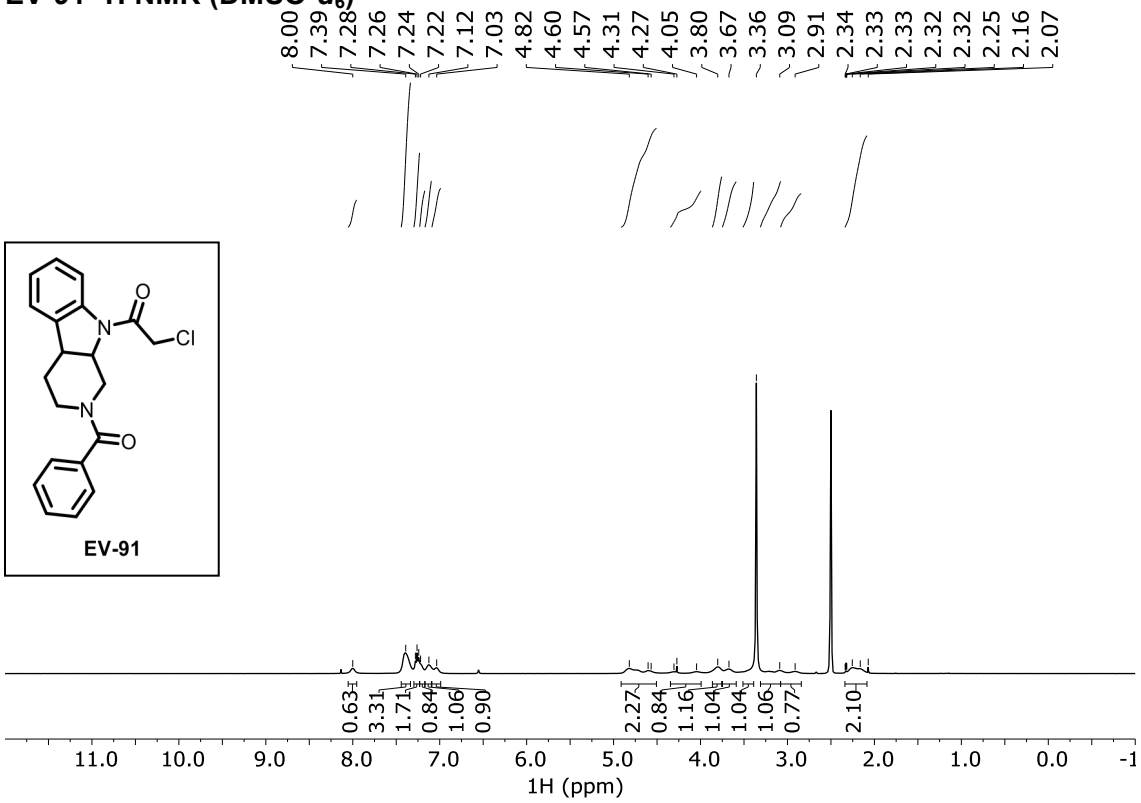
EV-89 ^{1}H NMR ($CDCl_3$)



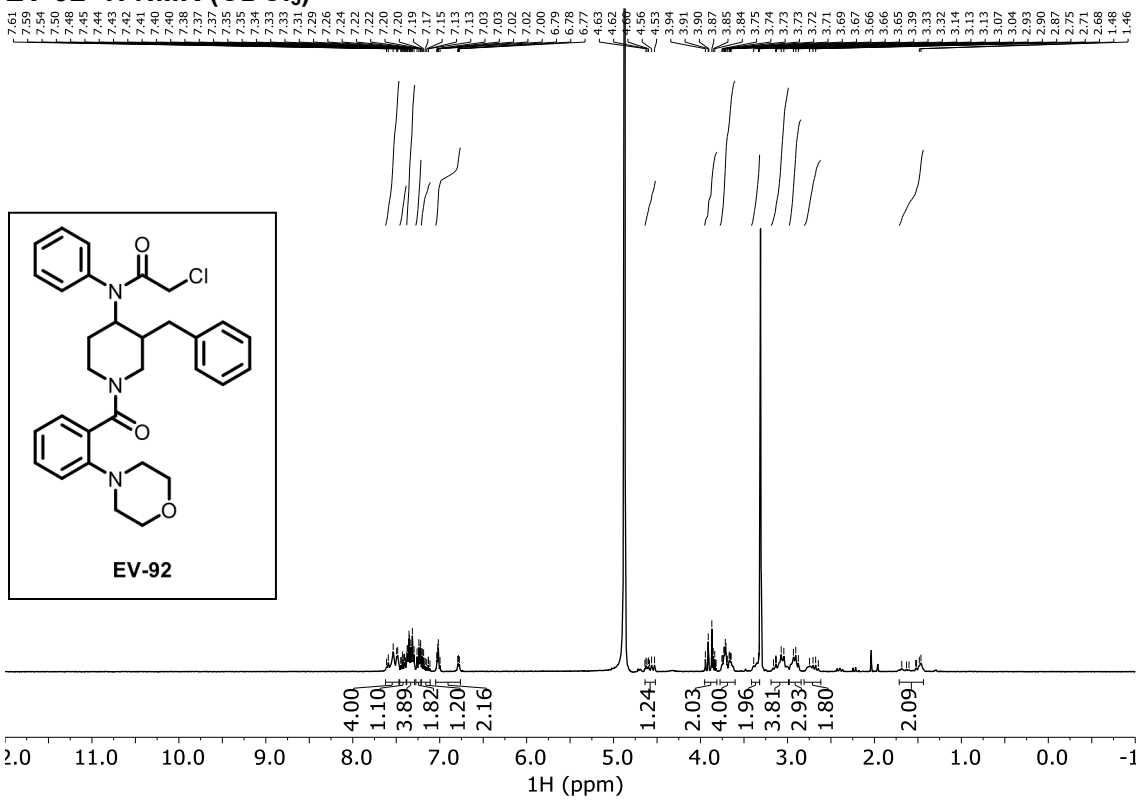
EV-90 ^{1}H NMR ($CDCl_3$)



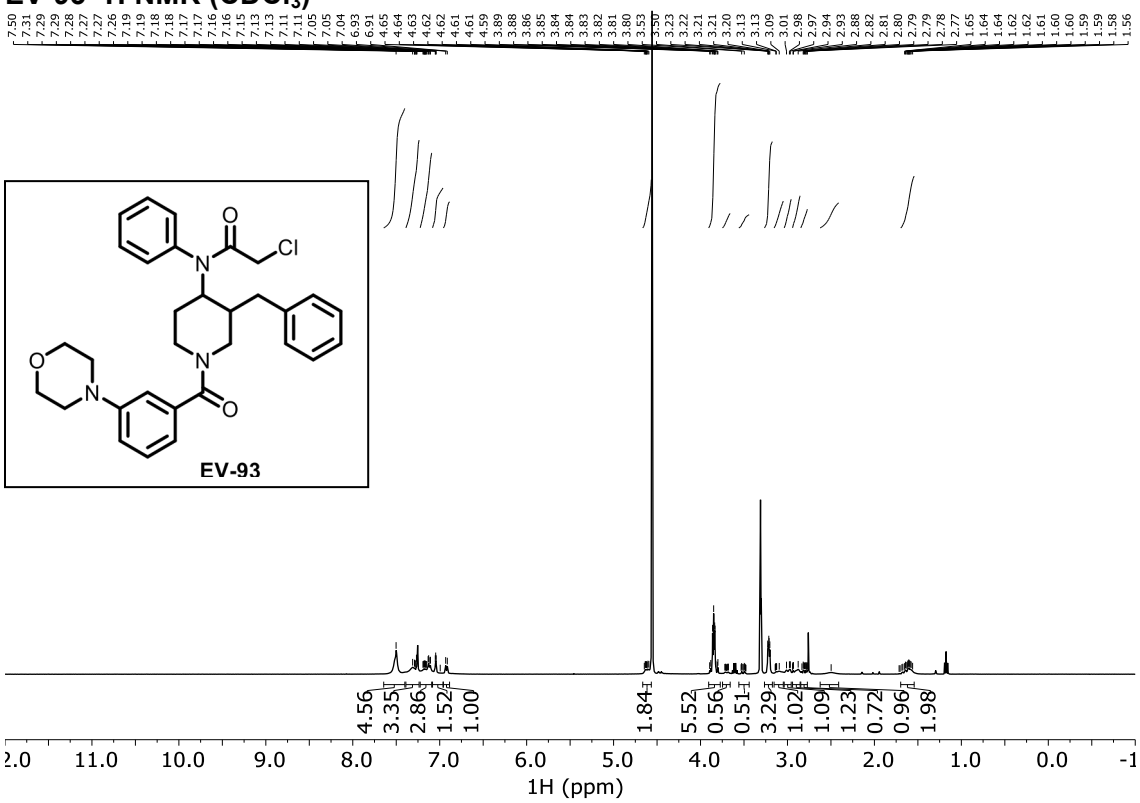
EV-91 ^{1}H NMR (DMSO-d_6)



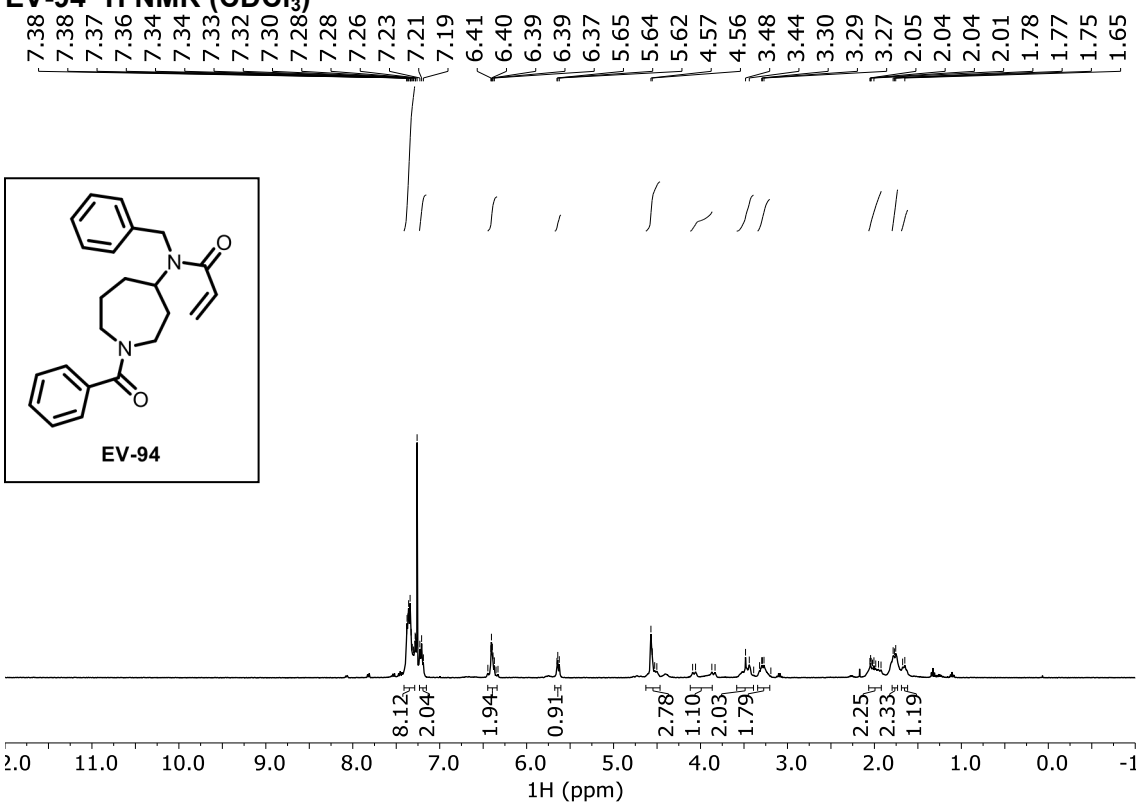
EV-92 ^{1}H NMR ($CDCl_3$)



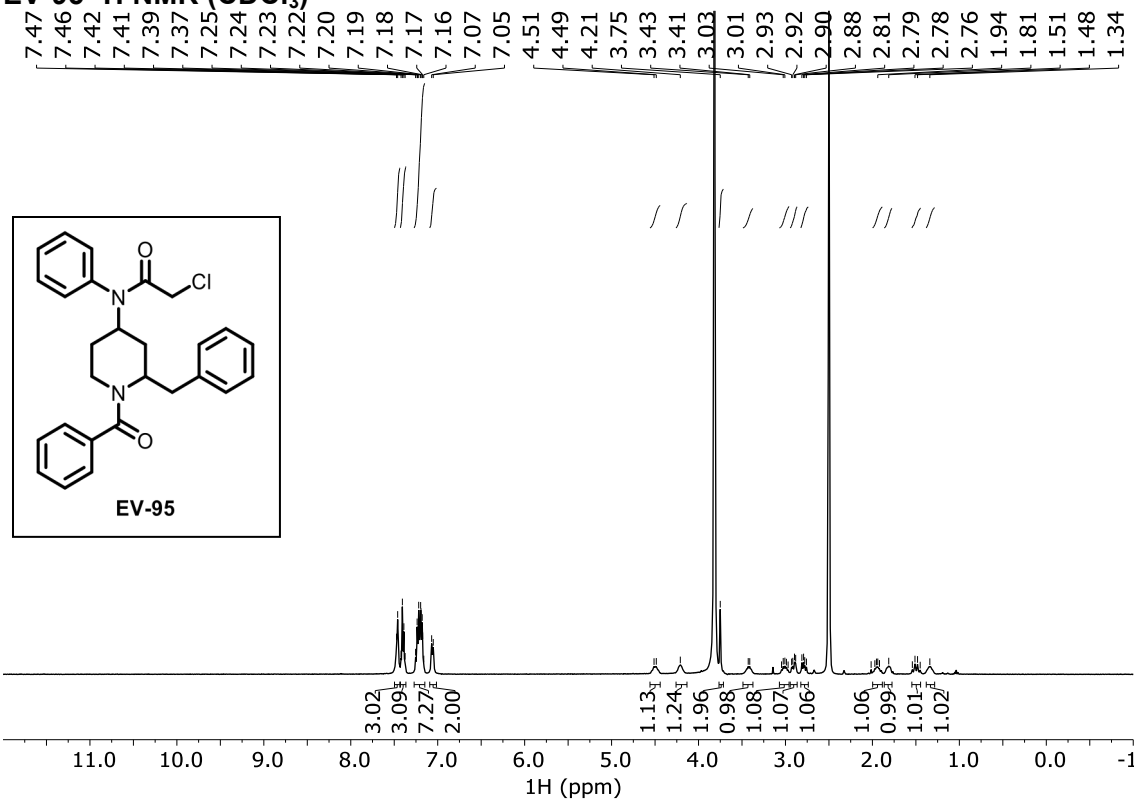
EV-93 ^{1}H NMR ($CDCl_3$)



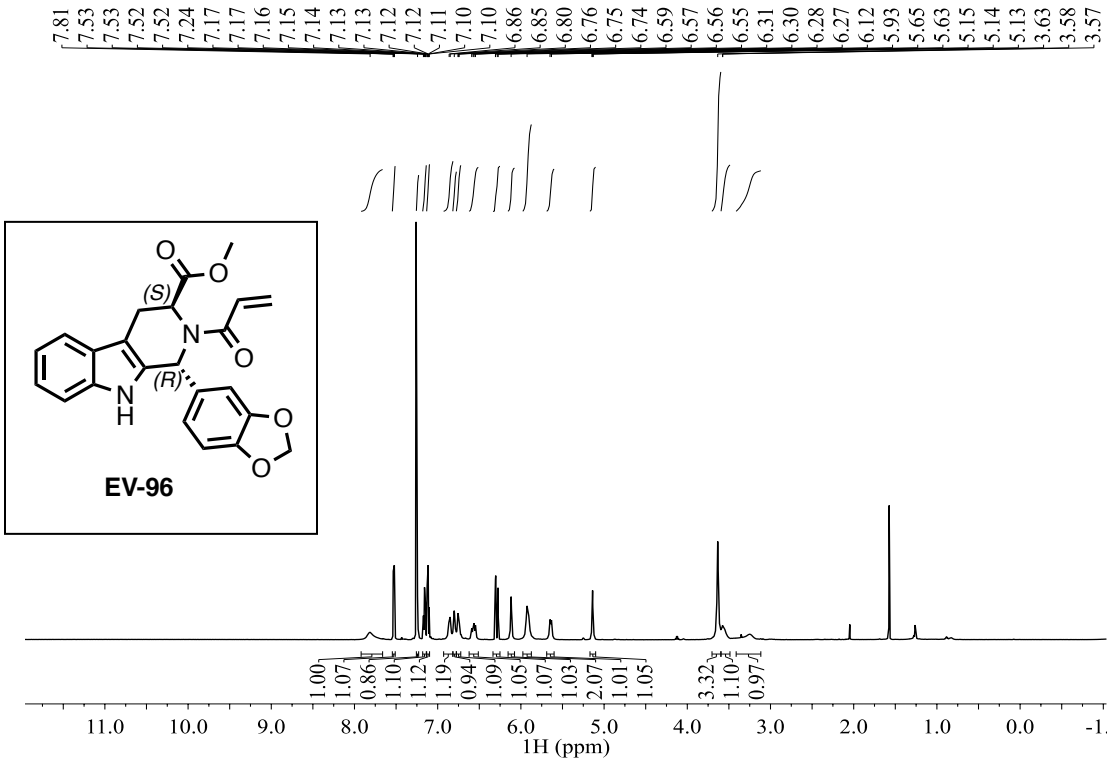
EV-94 ^{1}H NMR ($CDCl_3$)



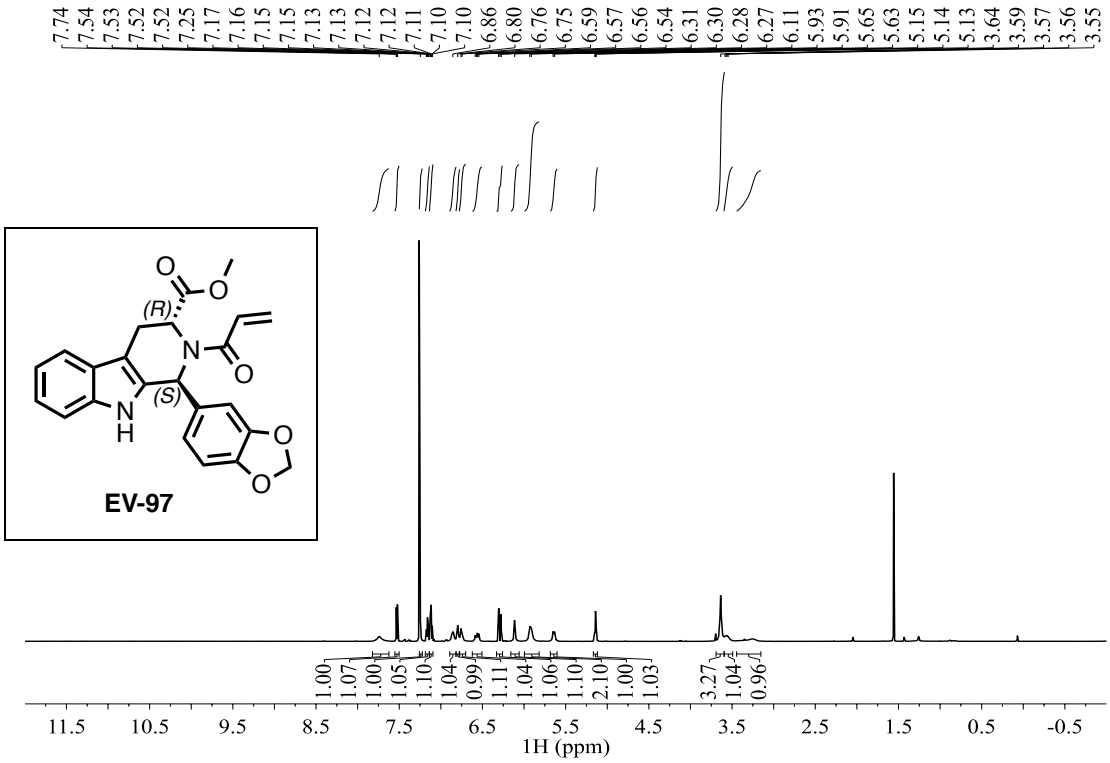
EV-95 ^{1}H NMR ($CDCl_3$)



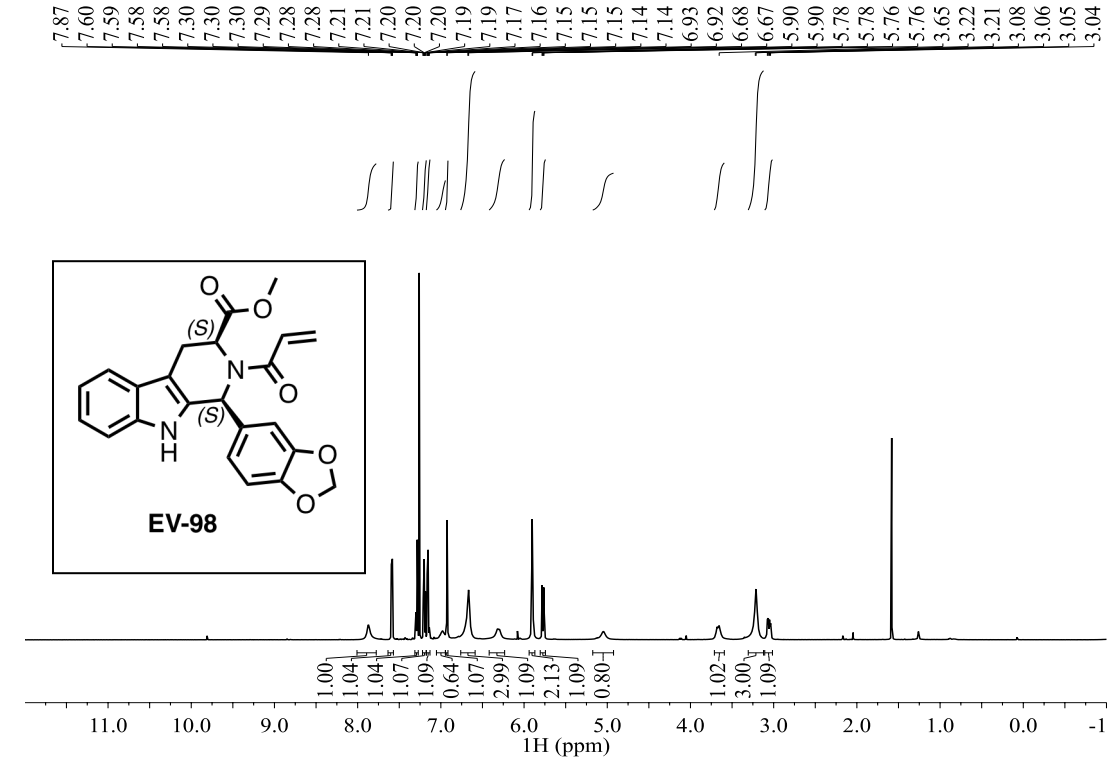
EV-96 ^{1}H NMR ($CDCl_3$)



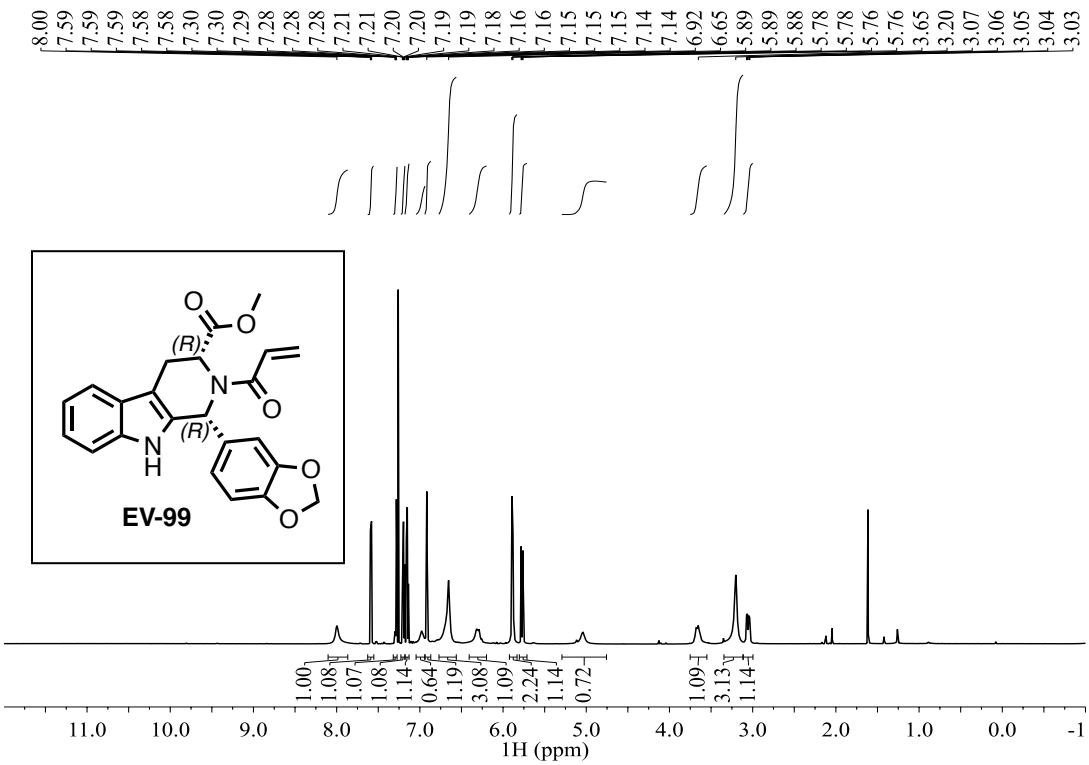
EV-97 ^{1}H NMR ($CDCl_3$)



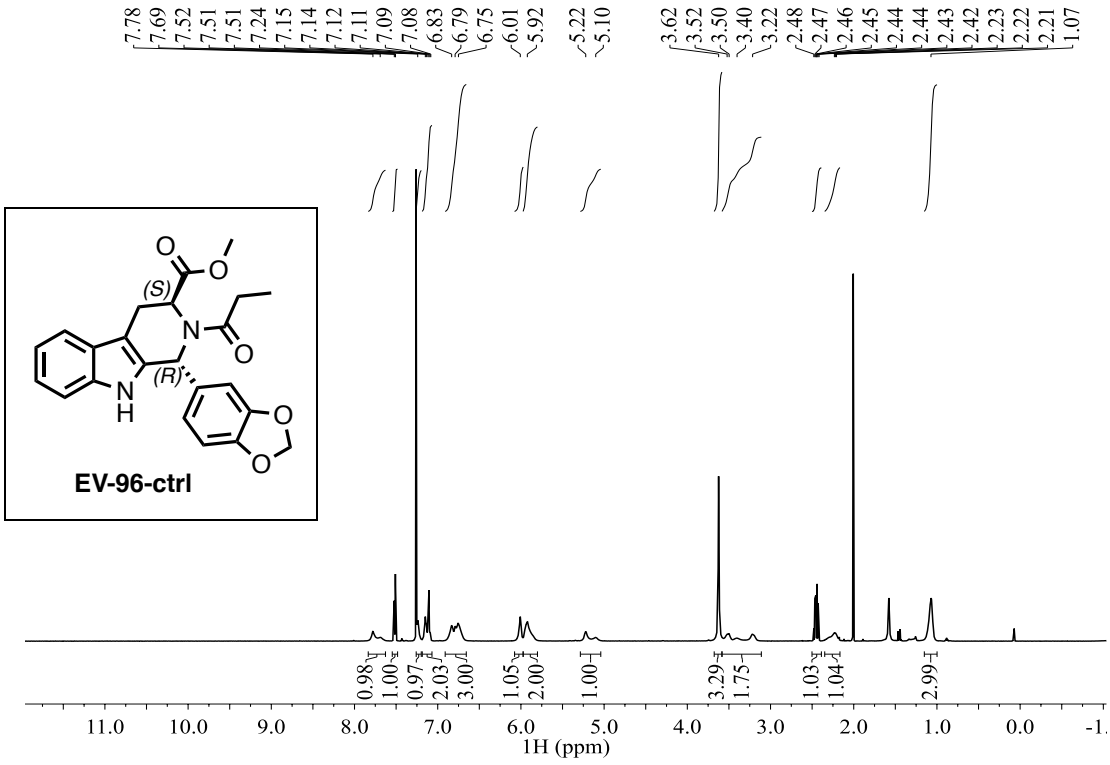
EV-98 ^{1}H NMR ($CDCl_3$)



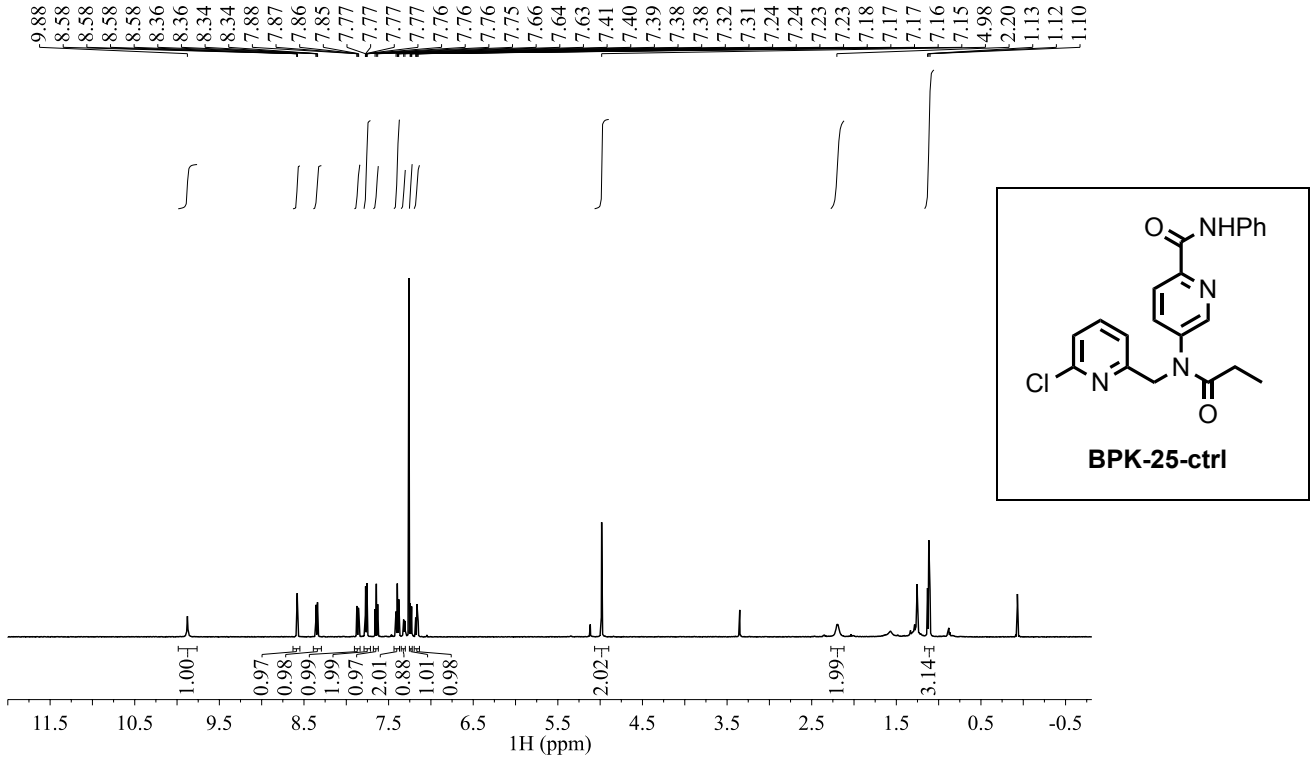
EV-99 ^{1}H NMR ($CDCl_3$)



EV-96-ctrl ^{1}H NMR ($CDCl_3$)



BPK-25-ctrl ^{1}H NMR ($CDCl_3$)



BPK-25-ctrl