Supporting Information

Design, synthesis and biological evaluation of small molecule inhibitors of CD4-gp120 binding based on virtual screening

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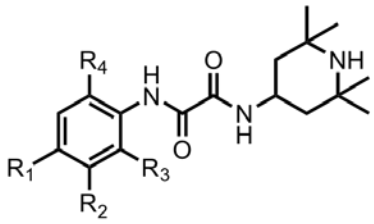
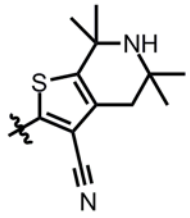
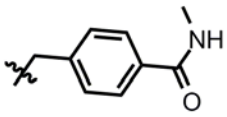
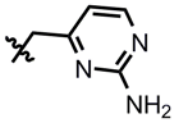
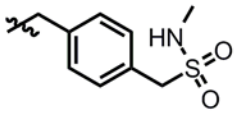
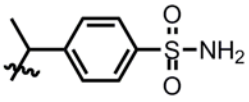
Supplemental Table 1. Ortho-substituted analogues of NBD-566



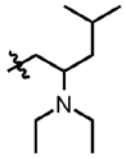
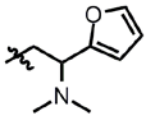
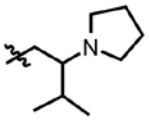
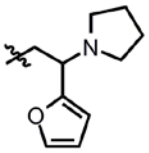
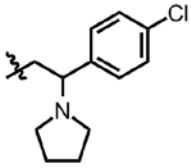
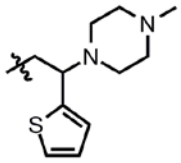
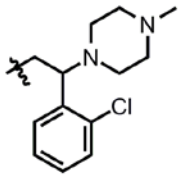
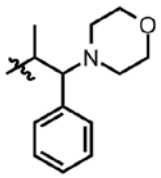
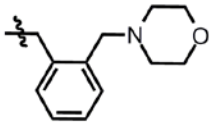
Cmpd	R_1	R_2	R_3	R_4	n[a]	IC_{50} μM[b]	K_d μM[c]	Activation of Viral Infectivity[d]
55	Cl	H	F	H	1	>100	N.D.	0.0
56	Cl	H	Cl	H	1	>100	N.D.	0.0
57	Cl	H	CH_3	H	1	>100	N.D.	0.0
58	Cl	H	CF_3	H	1	>100	N.D.	0.0
59	Cl	H	OCH_3	H	1	>100	N.D.	0.0
60	Cl	H	OCH_2CH_3	H	1	>100	N.D.	0.0
61	Cl	H	OBn	H	1	>100	N.D.	0.0

[a]Each compound was assayed in triplicate and is reported as a mean for one experiment. For multiple experiments, the means and standard deviations are reported. The number of times independent experiments were performed is indicated by n. [b]The compound concentrations that inhibited 50% of virus infection (IC_{50}) were determined by infecting Cf2Th-CD4/CCR5 cells with 10,000 RT units of wild-type virus expressing luciferase in the presence of increasing concentrations of the compound. Compounds labeled non-specific in the supplemental tables were found to have comparable IC_{50}'s when assayed against recombinant HIV-1_{YU2} pseudotyped with the A-MLV envelop glycoproteins. [c]Kd's were measured by isothermal titration calorimetry once, unless indicated otherwise in parentheses. [d]Activation of viral infectivity was determined by infecting Cf2Th-CCR5 cells with wild-type recombinant HIV-1_{YU2} expressing luciferase in the presence of NBD analogues. The luciferase activity in the target cells incubated with each compound was divided by that in the cells incubated with JRC-II-191 to obtain the relative activation of infectivity. N.D. indicates not determined. N.B. indicates no detectable binding.

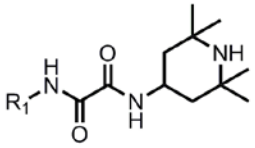
Supplemental Table 2. Inactive analogues based on screening by docking

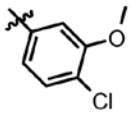
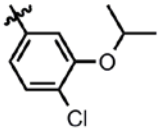
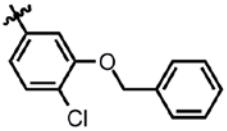
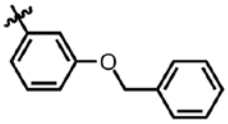
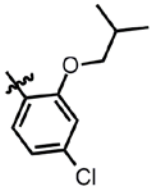
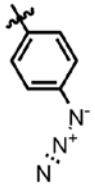
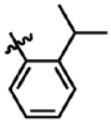
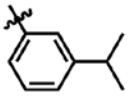
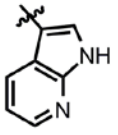
Cmpd	R_1	R_2	Ring	n	IC_{50} μM	K_d μM	Activiation of Viral Infectivity
62	Cl	F		1	>100	N.D.	0.0
63	Cl	F		1	>100	N.D.	N.D.
64	Cl	F		1	>100	N.D.	0.0
65	Cl	F		1	>100	N.D.	0.0
66	Cl	F		1	>100	N.D.	0.0

Supplemental Table 3. Inactive analogues based on screening by docking

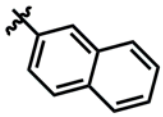
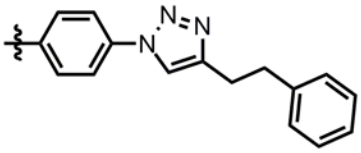
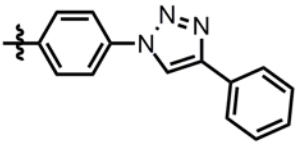
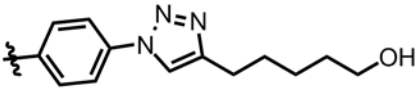
Cmpd	R_1	R_2	Ring	n[a]	IC_{50} μM[b]	K_d μM[c]	Activation of Viral Infectivity[d]
67	Cl	F		1	>100	N.D.	0.0
68	Cl	F		1	>100	N.D.	0.0
69	Cl	F		1	>100	N.D.	0.0
70	Cl	F		1	>100	N.D.	0.0
71	Cl	F		1	61.4 Non-Specific	N.D.	0.4
72	Cl	F		1	>100	N.D.	0.0
73	Cl	F		1	73.6 Non-Specific	N.D.	0.11
74	Cl	F		1	>100	N.D.	0.0
75	Cl	F		1	20.5 non-specific	N.D.	0.5

Supplemental Table 4. Various ortho- and meta-substituted analogues of NBD-566

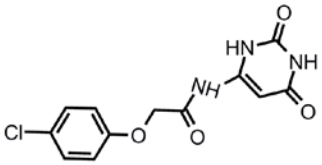
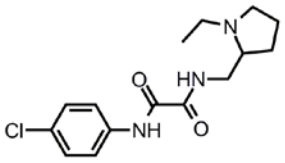
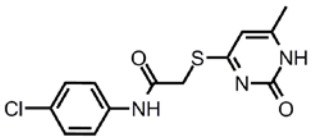
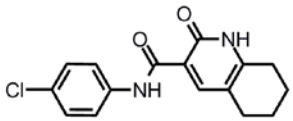
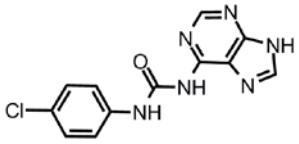
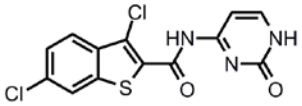
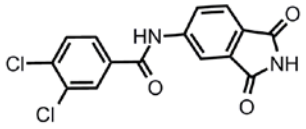
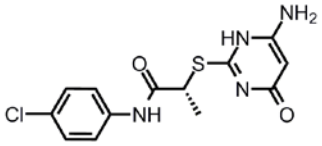
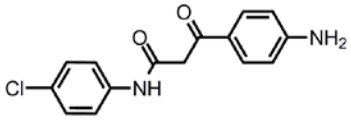
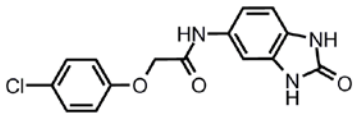


Cmpd	R_1	n[a]	IC_{50} μM[b]	K_d μM[c]	Activation of Viral Infectivity[d]
76		1	>100	N.D.	0.0
77		1	>100	N.D.	0.0
78		1	>100	N.D.	0.0
79		1	>100	N.D.	0.0
80		1	>100	N.D.	0.0
81		1	>100	N.D.	0.0
82		1	>100	N.D.	0.0
83		1	>100	N.D.	0.0
84		1	>100	N.D.	0.0

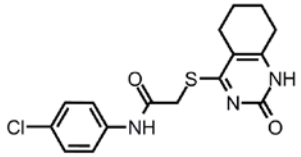
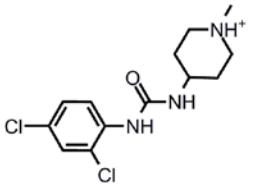
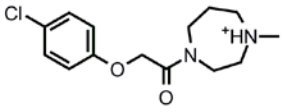
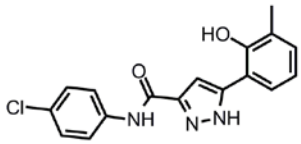
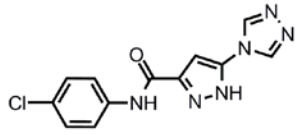
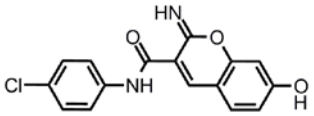
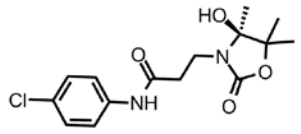
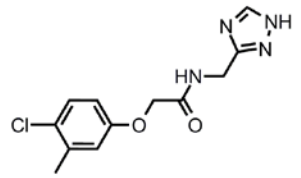
Supplemental Table 4. Various ortho- and meta-substituted analogues of NBD-566

Cmpd	R_1	n[a]	IC_{50} μM[b]	K_d μM[c]	Activation of Viral Infectivity[d]
85		1	>100	N.D.	0.0
86		1	>100	N.D.	0.0
87		1	>100	N.D.	0.0
88		1	>100	N.D.	0.0

Supplemental Table 5. Inactive analogues based on Rocs shaped based virtual screening using the docked conformation of NBD-556.

Cmpd	Compound	Combo Score	Suppler	Catalog Num.	n[a]	IC_{50} μM[b]	K_d μM[c]	Activation of Viral Infectivity[d]
89		1.397	Life Chemicals	F1803-0015	1	>100	N.D.	0.0
90		1.350	Chem Bridge	7783517	1	>100	N.D.	0.0
91		1.304	Life Chemicals	F2585-0240	1	>100	N.D.	0.0
92		1.292	ChemDiv	8016-7621	1	>100	N.D.	0.0
93		1.286	Enamine	T5280327	1	>100	N.D.	0.0
94		1.275	Enamine	T0509-5123	1	>100	N.D.	0.0
95		1.268	Chem Bridge	7953778	1	>100	N.D.	0.0
96		1.263	Chem Bridge	7677145	1	>100	N.D.	0.0
97		1.260	ChemDiv	0104-0055	1	>100	N.D.	0.0
98		1.260	Chem Bridge	9011769	1	>100	N.D.	0.0

Supplemental Table 5. Inactive analogues based on Rocs shaped based virtual screening using the docked conformation of NBD-556.

Cmpd	Compound	Combo Score	Suppler	Catalog Num.	n[a]	IC_{50} μM[b]	K_d μM[c]	Activation of Viral Infectivity[d]
99		1.259	Life Chemicals	F2684-0055	1	>100	N.D.	0.0
100		1.270	Chem Bridge	9051669	1	>100	N.D.	0.0
101		1.256	Chem Bridge	9046833	1	>100	N.D.	0.0
102		1.254	IBScreen	6S-02785	1	>100	N.D.	0.0
103		1.252	Chem Block	A411/0175316	1	>100	N.D.	0.0
104		1.249	Asinex	BAS01020667	1	>100	N.D.	0.0
106		1.247	Chem Block	A4024/0171636	1	>100	N.D.	0.0
106		1.244	Asinex	BAS03451297	1	>100	N.D.	0.0

Supplemental Table 5. Inactive analogues based on Rocs shaped based virtual screening using the docked conformation of NBD-556.

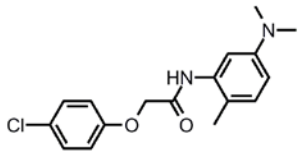
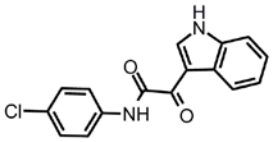
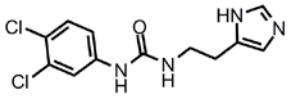
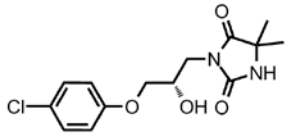
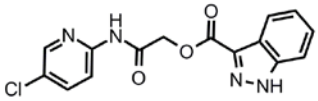
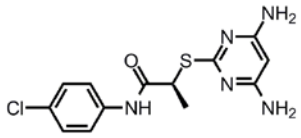
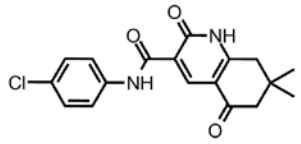
Cmpd	Compound	Combo Score	Suppler	Catalog Num.	n[a]	IC_{50} μM[b]	K_d μM[c]	Activation of Viral Infectivity[d]
107		1.243	Chem Bridge	5403628	1	>100	N.D.	0.0
108		1.241	Asinex	BAS11404615	1	>100	N.D.	0.0
109		1.240	ChemBlock	A3862/0164059	1	>100	N.D.	0.0
110		1.235	Chem Bridge	6024390	1	>100	N.D.	0.0
111		1.233	Enamine	ZT6938267	1	>100	N.D.	0.0
112		1.232	Chem Bridge	7650527	1	>100	N.D.	0.0
113		1.230	Chemdiv	C202-2200	1	>100	N.D.	0.0

Table 6. Inactive analogues based on Rocs shaped based virtual screening using the crystal structure of NBD-557 bound to gp120.

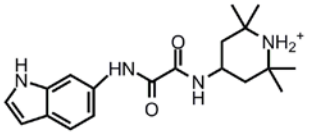
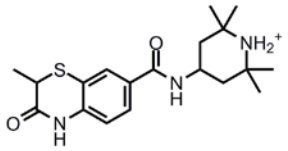
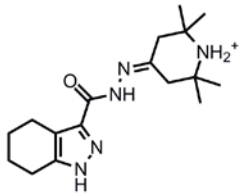
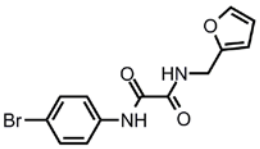
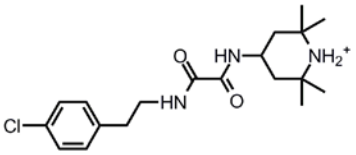
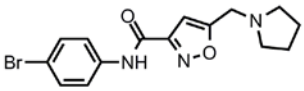
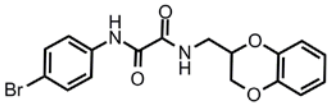
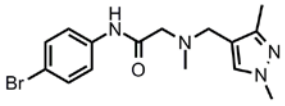
Cmpd	Compound	Combo Score	Suppler	Catalog Num.	n[a]	IC_{50} μM[b]	K_d μM[c]	Activation of Viral Infectivity[d]
114		1.706	VitasM	STK617731		>100	N.D.	0.0
115		1.5290	Enamine	T5743242		>100	N.D.	0.0
117		1.433	Asinex	BAS00589002	1	>100	N.D.	0.0
118		1.405	Princeton BioMolecular	OSSK 522395	1	>100	N.D.	0.0
119		1.391	Chem Bridge	5620165	1	>100	N.D.	0.0
120		1.337	Chem Div	C700-1767	1	>100	N.D.	0.0
121		1.337	Princeton BioMolecular	OSSK 917592	1	>100	N.D.	0.0
122		1.332	VitasM	STK628694	1	>100	N.D.	0.0

Table 6. Inactive analogues based on Rocs shaped based virtual screening using the crystal structure of NBD-557 bound to gp120.

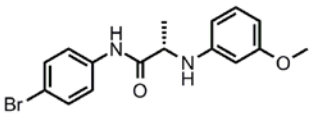
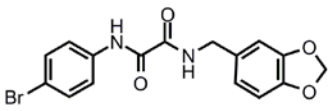
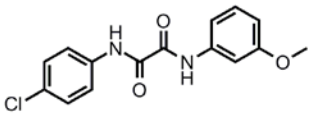
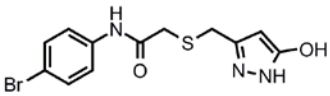
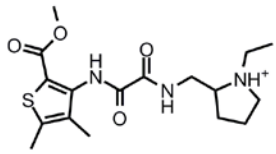
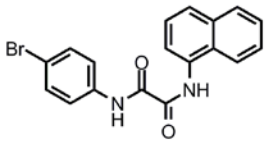
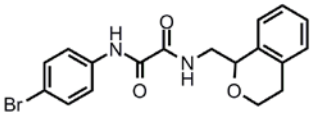
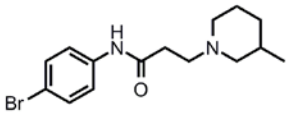
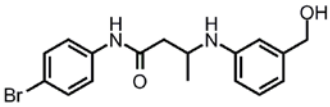
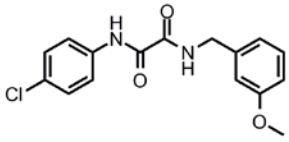
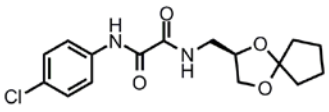
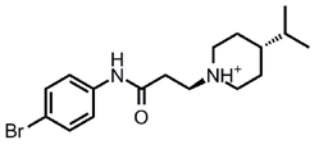
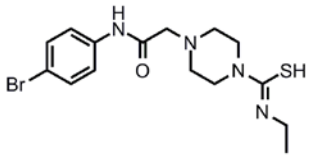
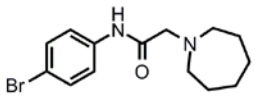
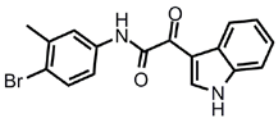
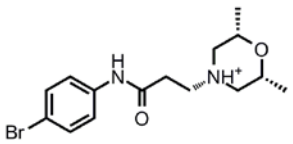
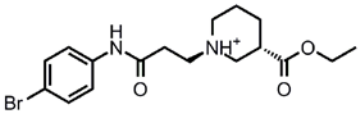
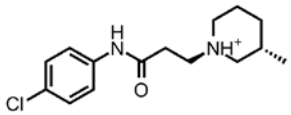
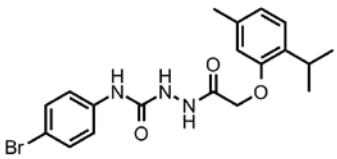
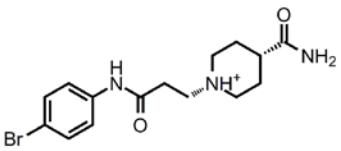
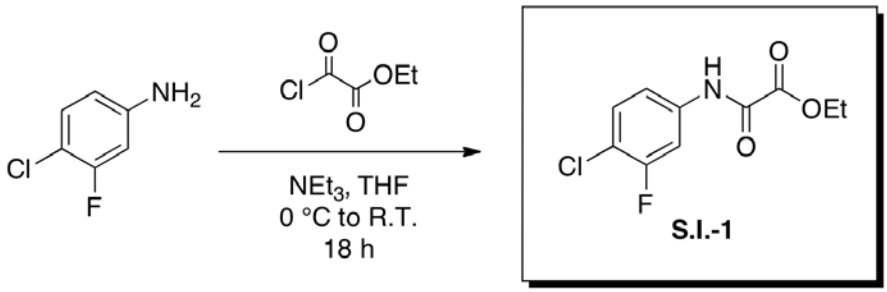
Cmpd	Compound	Combo Score	Suppler	Catalog Num.	n[a]	IC_{50} μM[b]	K_d μM[c]	Activation of Viral Infectivity[d]
123		1.330	Chem Bridge	7747030	1	>100	N.D.	0.0
124		1.330	Life Chemicals	F2764-0221	1	>100	N.D.	0.0
125		1.330	Life Chemicals	F2659-0130	1	>100	N.D.	0.0
126		1.310	Princeton BioMolecular	OSK558096	1	>100	N.D.	0.0
127		1.310	VitasM	STK628694	1	>100	N.D.	0.0
128		1.306	Asinex	ASN06415394	1	>100	N.D.	0.0
129		1.301	Princeton BioMolecular	OSSK56247	1	>100	N.D.	0.0
130		1.288	Princeton BioMolecular	OSSk59870	1	>100	N.D.	0.0
131		1.284	Enamine	T6085799	1	>100	N.D.	0.0
132		1.284	Chem Bridge	7747030	1	>100	N.D.	0.0

Table 6. Inactive analogues based on Rocs shaped based virtual screening using the crystal structure of NBD-557 bound to gp120.

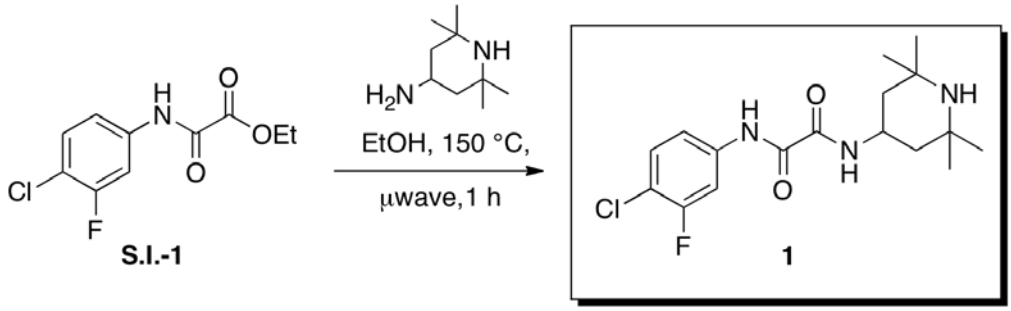
Cmpd	Compound	Combo Score	Suppler	Catalog Num.	n[a]	IC_{50} μM[b]	K_d μM[c]	Activation of Viral Infectivity[d]
133		1.272	Life Chemicals	F2764-0221	1	>100	N.D.	0.0
134		1.267	VitasM	STK145981	1	>100	N.D.	0.0
135		1.265	Chem Bridge	7847948	1	>100	N.D.	0.0
136		1.263	Chem Bridge	7873060	1	>100	N.D.	0.0
137		1.254	Life Chemicals	F0676-0176	1	>100	N.D.	0.0
138		1.253	Chem Bridge	6513612	1	>100	N.D.	0.0
139		1.247	Chem Bridge	6516605	1	>100	N.D.	0.0
140		1.245	Chem Bridge	6516605	1	>100	N.D.	0.0
141		1.244	Chem Bridge	7784659	1	>100	N.D.	0.0
142		1.239	VitasM	STK145981	1	>100	N.D.	0.0

Materials and Methods: All solvents employed during synthesis were reagent grade; solvents used during purification were HPLC grade. Anhydrous CH_2Cl_2 and THF were obtained from the Pure Solve™ PS-400 system under an argon atmosphere. All reagents were purchased from commercially available sources and used as received. Many of the amine coupling partners were identified and vendors identified through searching the ZINC database, as noted in the text. Unless specifically noted, all compounds were obtained as racemic mixtures. Microwave heating was conducted with a Biotage Initiator system equipped with an autosampling arm, in either 0.5-2.0 mL or 2.0-5.0 mL sealed reaction vials. Reactions were magnetically stirred under an argon atmosphere, unless otherwise noted and reactions were monitored by either thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates or analytical high performance liquid chromatography (HPLC). Yields refer to chromatographically and spectroscopically pure compounds. FT-IR spectra were acquired with a JASCO-480Plus (thin film layer on a NaCl plate by evaporation of a CH_2Cl_2 solution). Optical rotations were measured on a JASCO P-2000 polarimeter. Melting points were measured with a Thomas-Hoover oil submersion capillary melting point apparatus and are reported uncorrected. Proton and carbon-13 NMR spectra were recorded on a Bruker Avance III equipped with either a 5 mm dual inverse probe or 5 mm DCH CryoProbe at the University of Pennsylvania. Chemical shifts are reported relative to chloroform (δ 7.26), methanol (δ 3.31), acetonitrile (δ 1.94), or dimethyl sulfoxide (δ 2.50) for ^{1}H NMR and either chloroform (δ 77.2), methanol (δ 49.2), acetonitrile (δ 1.39), or dimethyl sulfoxide (δ 39.5). The NMR data was processed with a combination of TOPSPIN (Ver. 1.3, Bruker BioSpin) and/or MestReNova (Ver. 5.3.0, Mestrelab Research S.L.) High-resolution mass spectra (HRMS) were recorded at the University of Pennsylvania Mass Spectroscopy Service Center on either a VG Micromass 70/70H or VG ZAB-E spectrometer. Analytical HPLC was preformed with a Waters HPLC-MS system, consisting of a 515 pump and Sunfire C18 reverse phase column (20 μL injection volume, 5 μm packing material, 4.5 x 50 mm column dimensions) with detection accomplished by a Micromass ZQ mass spectrometer and 2996 PDA detector. Preparative scale HPLC was preformed with a Gilson 333/334 preparative pump system equipped with a 5 mL injection loop, Sunfire C18 OBD column (5 μm packing material, 19 x 100 mm column dimensions) equipped with a UV-Vis dual wavelength (210 and 254 nm) detector and 215 liquid handling module. Solvent systems employed were based on the following buffers: Buffer A: H_2O containing 0.05% formic acid; Buffer B: MeCN containing 0.05% formic acid; Buffer C: H_2O containing 0.5% trifluoroacetic acid; Buffer D: MeCN containing 0.5% trifluoroaetic acid. The purity of new compounds was judged by ^{1}NMR (see pp. S.I.-44 – S.I.-117) and LCMS.

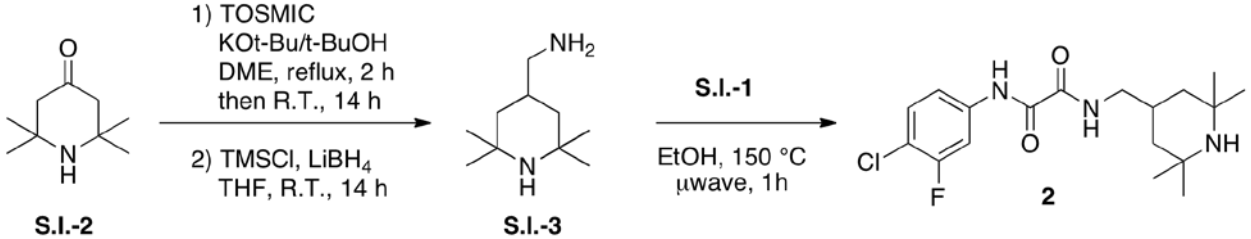


Ethyl 2-(4-chloro-3-fluorophenylamino)-2-oxoacetate (S.I.-1). To a solution containing *para*-chloro-*meta*-fluoroaniline (10.0 g, 70.1 mmol) in 600 mL THF at 0 °C was added Et_3N (9.11 mL, 70.1 mmol) followed by ethyl oxalylchloride (7.70 mL, 70.1 mmol) dropwise over 15 minutes. The reaction mixture was warmed to room temperature and stirred for 18 hrs. The reaction

mixture was filtered and the filter cake was washed with one-300 mL portion of ethyl acetate. The organic phase was washed with two-100 mL portions of 1M HCl, dried over $MgSO_4$, filtered, and concentrated to give the product. Recrystallization from hot Et_2O gave 14.4 g (84%) of **27** as a colorless crystalline solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (br, 1H), 7.72 (dd, *J* = 2.5, 10.5 Hz, 1H), 7.37 (t, *J* = 8.5 Hz, 1H), 7.25 (dq, *J* = 1.0, 8.5 Hz, 1H), 4.42 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.86 (dd, *J* = 2.5, 11.5 Hz, 1H), 7.63 (dd, *J* = 1.5, 8.5 Hz, 1H), 7.57 (t, *J* = 8.5 Hz, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.1, 156.8 (d, J_{CF} = 234.9 Hz), 155.6, 138.1 (d, J_{CF} = 9.9 Hz), 117.4 (d, J_{CF} = 3.3 Hz), 114.6 (d, J_{CF} = 17.6 Hz), 108.6 (d, J_{CF} = 25.8 Hz), 62.6, 13.8; HRMS (ES+) *m/z* 246.0336 [(M+H)$^+$; calcd for $C_{10}H_{10}ClFNO_3$: 246.0334].



1. ***N*^{1}-(4-Chloro-3-fluorophenyl)-*N*^{2}-(2,2,6,6-tetramethylpiperidin-4-yl)oxalamide.** To a solution containing **S.I.-1** (0.20 g, 0.81 mmol) in 2 mL EtOH in a microwave reaction vial which could be sealed with a Teflon® cap was added 4-amino-2,2,6,6-tetramethylpiperidine (0.13 g, 0.81 mmol). The tube was briefly flushed with an Argon stream (approximately 30 s) and sealed. The reaction was heated to 150 °C for 1 hr in microwave and then allowed to cool to room temperature and stand for 12 hours, during which time a glassy solid formed. The solid was collected by filtration, washed with cold hexanes, and dried to give 140 mg (48%) of the product as a colorless crystalline solid; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.07 (t, *J* = 12 Hz, 2 H), 1.16 (s, 6 H), 1.28 (s, 6 H), 1.57 (br, 1 H), 1.92 (dd, *J* = 12.7, 4 Hz, 2 H), 4.26 (m, 1 H), 7.23 (dd, *J* = 14 Hz, 1.5 Hz, 1 H), 7.38 (m, 1H), 7.70 (dd, *J* = 10.5, 2.5 Hz, 1H), 9.31 (br, 1H) Note: 1 N*H* proton was not observed in $CDCl_3$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 8.83 (d, *J* = 8.5 Hz, 1H), 7.93 (dd, *J* = 2.0, 11.5 Hz, 1H), 7.70 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.58 (t, *J* = 8.5 Hz, 1H), 4.18-4.11 (m, 1H), 1.58 (dd, *J* = 3.5, 12.0 Hz, 2H), 1.23 (app. t, *J* = 12.0 Hz, 2H), 1.15 (s, 6H), 1.03 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.2, 158.8, 156.8 (d, J_{CF} = 243.0 Hz), 138.3 (d, J_{CF} = 10.0 Hz), 130.3, 117.3 (d, J_{CF} = 3.3 Hz), 114.3 (d, J_{CF} = 17.3 Hz), 108.4 (d, J_{CF} = 25.5 Hz), 50.4, 43.4, 42.8, 34.4, 28.6; HRMS (ES+) *m/z* 356.1546 [(M+H)$^+$; calcd for $C_{17}H_{24}ClFN_3O_2$: 356.1542].

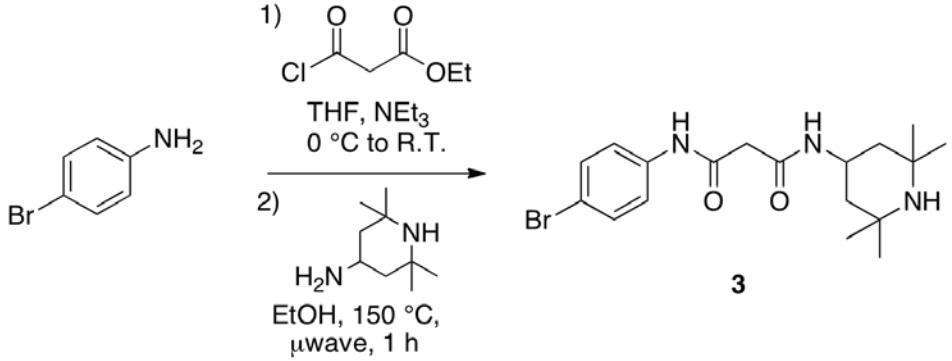


Compound 2. A solution of KOt-Bu (5190 mg, 46.3 mmol, 10 eq.) in 30 mL of t-BuOH was added to a solution of 2,2,6,6-Tetramethylpiperid-4-one (**S.I.-2**, 717 mg, 4.63 mmol) in 5 mL of DME and this solution was stirred for 1 h. Then a solution of TOSMIC (1806 mg, 9.25 mmol, 2

eq) in 5 mL of DME was added in one portion. The reaction was stirred at reflux for 2 h, after which time it was cooled to room temperature and allowed to stir for 14 h. The resulting solution was poured into 100 mL of ice water and extracted 3x with 50 mL of Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to afford the intermediate nitrile 2,2,6,6-tetramethyl-4-cyanopiperidine in greater than 90% yield. This product was used without further purification.

A 25 mL over-dried round bottom flask was charged with $LiBH_4$ (60 mg, 2.77 mmol, 2 eq.) and suspended in 3 mL of THF. To this solution TMSCl (0.70 mL, 5.53 mmol, 4 eq.) was added added drop-wise over 5 min., during which the solution became cloudy. After stirring for 5 min, 2,2,6,6-tetramethyl-4-cyanopiperidine from above (230 mg, 1.38 mmol), dissolved in 1 mL of THF was added and the reaction was stirred at room temperature for 14 h. The reaction was then quenched by the addition of 10 mL of MeOH over 30 min., followed by removal of volatile products and solvent in vacuo. The resulting solid was suspended in 20 mL of 2 N KOH followed by extraction 3x with 20 mL of CH_2Cl_2, and the combined organic fractions were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*, to obtain 216 mg of **S.I.-3** as a waxy solid in greater than 90% yield and this product was used without further purification.

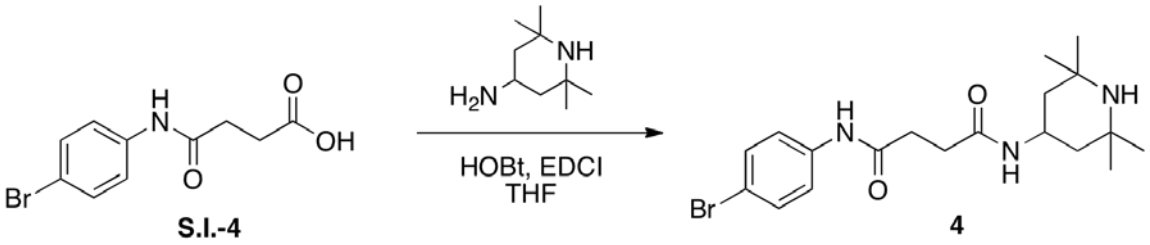
Amine **S.I.-3** (200 mg, 1.17 mmol) and ester **S.I.-1** (288 mg, 1.17 mmol, 1 eq.) were coupled using the microwave procedure described in the synthesis of **1** to afford 229 mg of **2** (53 %) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.0 (bs, 1H), 9.01 (t, J = 6.1 Hz, 1H), 7.95 (dd, J = 11.8, 2.1 Hz, 1H), 7.73 (dd, J = 8.9, 1.8 Hz, 1H), 7.56 (t, J = 8.9 Hz, 1H), 3.06 (t, J = 6.1 Hz, 2H), 2.07 (bs, 1H), 1.48 (d, J = 11.5 Hz, 2H), 1.09 (s, 6H), 1.01 (s, 6H), 0.76 (t, J = 12.0, 2H); HRMS (ES+) *m/z* 370.1702 [(M+H)$^+$; calcd for $C_{18}H_{26}ClFN_3O_2$: 370.1698].



Compound 3. Ethyl malonyl chloride (1.0 mL, 7.90 mmol, 1 eq.) was added drop-wise to an ice bath cooled solution of *p*-bromoaniline (1359 mg, 7.90 mmol) and NEt_3 (0.98 mL, 7.90 mL, 1 eq.) in 10 mL of THF. The reaction was stirred for 14 h, after which the solvent was removed *in vacuo*. The resulting solid was suspended in 50 mL of EtOAc and was 3x 30 mL of 0.1 M HCl, 1x 20 mL H_2O, and 20 mL of brine. The organic layer was then dried over Na_2SO_4, filtered, and the solvent was removed in vacuo to obtain ethyl 3-((4-bromophenyl)amino)-3-oxopropanoate (1750 mg, 77%) that was used without further purification.

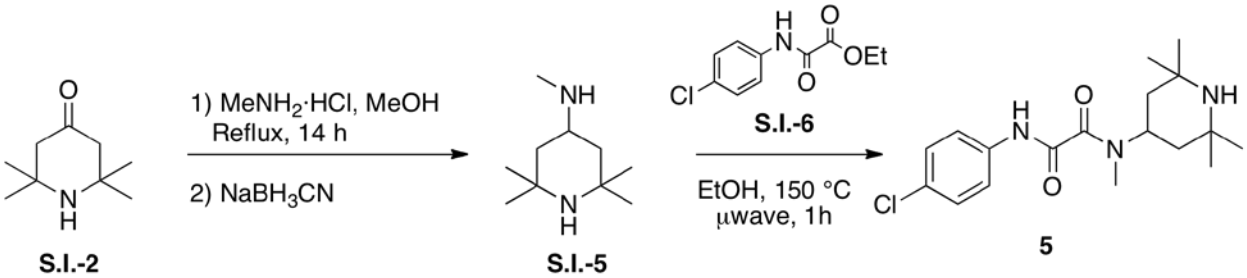
In a microwave reaction tube ethyl 3-((4-bromophenyl)amino)-3-oxopropanoate (131 mg, 0.46 mmol) and 4-amino-2,2,6,6-tetramethylpiperidine (0.08 mL, 0.46 mmol) were dissolved in 1.5 mL of EtOH and heated to 150 °C for 1 h. After standing overnight the white precipitate formed was collected by filtration to obtain **3** (46 mg, 28%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.4 (s, 1H), 8.02 (d, J = 10.8 Hz, 1H), 7.59 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 9.0 Hz, 2H), 4.00 (m, 1H), 3.23 (s, 2H), 1.63 (dd, J = 12.6, 3.6 Hz, 2H), 1.12 (s, 6H), 1.01 (s, 6H); HRMS (ES+) *m/z* 396.1285 [(M+H)$^+$; calcd for $C_{18}H_{27}BrN_3O_2$:

396.1287]



S.I.-4 4

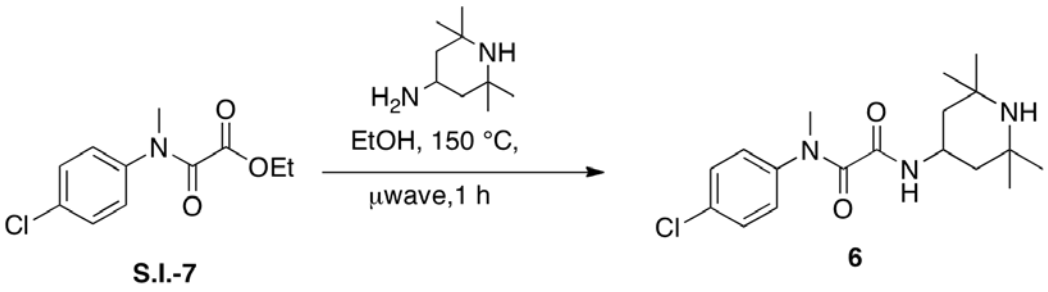
Compound 4. A round bottom flask was charged with HOBt (108.2 mg, 0.41 mmol, 1.1 eq.) and EDCI (153.5 mg, 0.41 mmol, 1.1 eq.) and **S.I.-4** (102.1 mg, 0.38 mmol). The solids were suspended in 5 mL of THF with vigorous stirring and 4-amino-2,2,6,6-tetramethylpiperidine was added in one portion. The reaction was stirred for 14 h. The solvent was removed in vaccuo and the resulting solid was suspended in 50 mL of EtOAc, washed 3x 0.1 M HCl, 1x H_2O, 1x brine and the organic layer was dried over Na_2SO_4, filtered, and the solvent was removed in vaccuo. The resulting solid was recrystallized from hot EtOH to obtain **4** as a white solid (111 mg, 66%). ^{1}H NMR (500 MHz, CD_3OD): δ 7.49 (d, *J* = 8.9 Hz, 2H), 7.43 (d, *J* = 8.9 Hz, 2H), 4.24 (tt, *J* = 12.5, 3.4 Hz, 1H), 2.68 (d, *J* = 7.1 Hz, 2H), 2.54 (d, *J* = 7.1 Hz, 2H), 1.98 (d, *J* = 12.5 Hz, 2H), 1.44 (s, 6H), 1.36 (m, 8H); note in CD_3OD the NH peaks were not observed due to exchange with the solvent.; HRMS (ES+) *m/z* 410.1444 [$(M+H)^+$; calcd for $C_{19}H_{29}BrN_3O_2$: 410.1443]



S.I.-2 S.I.-5 S.I.-6 5

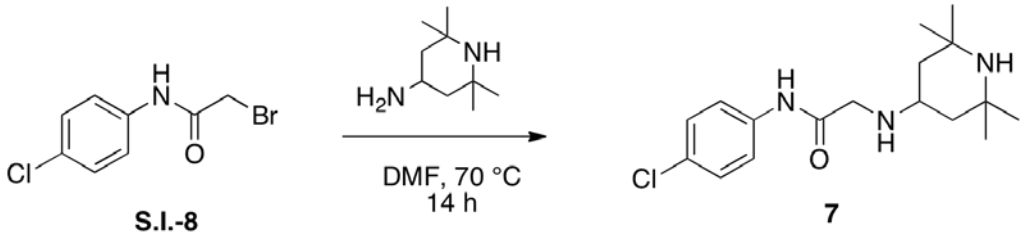
Compound 5. 2,2,6,6-tetramethylpiperidin-4-one (**S.I.-2**, 2400 mg, 15.6 mmol) and $MeNH_2$·HCl (1600 mg, 23.4 mmol, 1.5 eq) were weighed into an oven-dried 100 mL round bottom flask, dissolved in 30 mL of anhydrous MeOH, and stirred for 14 h under argon, during which time the solution turned from yellow to brown. Then a solution of $NaBH_3CN$ (2941 mg, 46.8 mmol, 3 eq.) in 30 mL of MeOH was added dropwise over 1 h. followed by stirring for 14 h. The resulting red solution was poured in to 50 mL of sat. NH_4Cl, stirred for 15 min, then the pH was adjusted to 12 with 1 N NaOH. This cloudy suspension was extracted 4x 50 mL of Et_2O, the combined organic layers were washed with brine and dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to afford **S.I.-5** as a yellow oil (535 mg, ~20%) which was used directly in the next reaction without further purification.

S.I.-6 (prepared analogously to **S.I.-1**, 200 mg, 0.88 mmol) and **S.I.-5** (150 mg, 0.88 mmol) were placed in a microwave reaction vial, dissolved in 1 mL of EtOH, and heated to 150 °C for 1 h. After cooling **5** was obtained as a white powder (96 mg, 31%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.3 (s, 1H), 7.83 (m, 2H), 7.34 (m, 2H), 3.63 (tt, *J* = 12.4, 3.2 Hz, 1H), 2.62 (s, 3H), 2.13 (dd, *J* = 12.9, 2.8 Hz, 2H), 1.70 (t, *J* = 12.9 Hz, 2H), 1.42 (s, 6H), 1.41 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.7, 163.2, 137.9, 128.4, 126.8, 120.9, 55.7, 49.2, 36.9, 29.9, 29.7, 24.3; HRMS (ES+) *m/z* 352.1786 [$(M+H)^+$; calcd for $C_{18}H_{27}ClN_3O_2$: 352.1792].



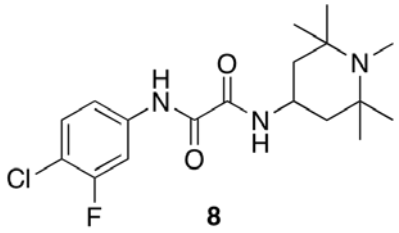
S.I.-7 6

Compound 6. S.I.-7 was prepared in an analogous manner to **S.I.-1** and **S.I.-7** (197 mg, 0.82 mmol) was coupled to 4-amino-2,2,6,6-tetramethylpiperidine (0.14 mL, 0.82 mL) using the microwave procedure described for the synthesis of **1** to afford **6** (205 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.31 (bs, 1H), 8.78 (d, *J* = 2.6 Hz, 1H), 8.15 (ddd, *J* = 8.7, 2.7, 1.5 Hz, 1H), 7.33 (dd, *J* = 8.3, 4.9 Hz), 4.27 (dtt, *J* = 12.5, 8.5, 3.5 Hz, 1H), 1.93 (dd, *J* = 12.5, 3.5 Hz, 2H), 1.30 (s, 6H), 1.18 (s, 6H), 1.11 (m, 2H); HRMS (ES+) *m/z* 352.1793 [$(M+H)^+$; calcd for $C_{18}H_{27}ClN_3O_2$: 352.1792].



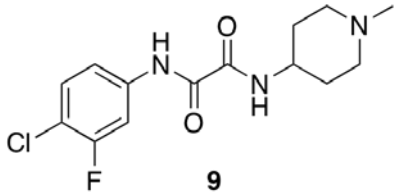
S.I.-8 7

Compound 7. A solution of **S.I.-8** (151 mg, 0.60 mmol) in 1 mL of DMF was treated with 4-amino-2,2,6,6-tetramethylpiperidine (0.11 mL, 0.62 mmol) at 70 °C for 14 h. The solution was poured into 10 mL of H_2O and 10 mL of sat $NaHCO_3$, extracted 3x 10 mL EtOAc, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The resulting residue was recrystallized from warm EtOH to afford **7** as a white powder (81 mg, 42%).^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (bs, 1H), 7.55 (dd, *J* = 6.6, 2.0 Hz, 2H), 7.29 (dd, *J* = 6.6, 2.0 Hz, 2H), 2.12 (s, 2H), 2.96 – 2.88 (m, 2H), 1.89 (dd, *J* = 12.5, 3.5 Hz, 2H), 1.27 – 1.15 (m, 12H). HRMS (ES+) *m/z* 324.1846 [$(M+H)^+$; calcd for $C_{17}H_{27}ClN_3O$: 324.1843].



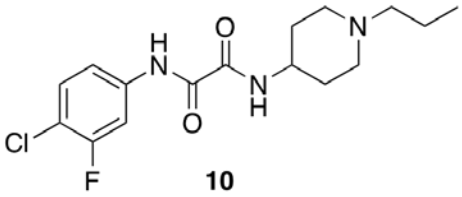
8

Compound 8. Prepared in an analogous manner to **1** to give **8**. ^{1}H-NMR (DMSO, 500 MHz), δ 1.01 (s, 6H), 1.07 (s, 6H), 1.54 (m, 4H), 2.16 (s, 3H), 4.06 (m, 1H), 7.57 (dd, *J* =8.5, 8.5 Hz, 1H), 7.70 (dd, *J* =8.5, 2.0 Hz, 1H), 7.92 (dd, *J* =11.5, 2.0 Hz, 1H), 8.86 (d, *J* =8.6 Hz, 1H), 10.9 (s, 1H). HRMS (ES+) *m/z* 370.1695 [$(M+H)^+$; calcd for $C_{18}H_{26}ClFN_3O_2$: 370.1698].



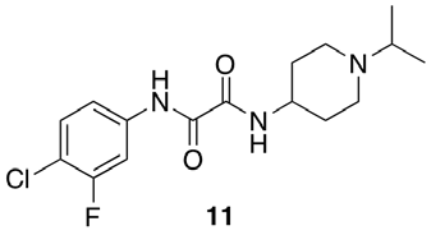
9

Compound 9. Prepared in an analogous manner to **1** to give **9.** ^{1}H-NMR (DMSO, 500 MHz), δ97m, 2H), 1.52 (m, 2H), 1.60 (m, 1H), 2.35 (t, *J* =6.0 Hz, 2H), 2.88 (d, *J* =11.5 Hz, 2H), 3.05 (t, *J* =6.0 Hz, 2H), 4.35 (m, 2H), 7.57 (dd, *J* =9.0, 9.0 Hz, 1H), 7.72 (dd, *J* =9.0, 2.0 Hz, 1H), 7.93 (dd, *J* =11.5, 2.0 Hz, 1H), 9.03 (t, *J* =6.0 Hz, 1H). HRMS (ES+) *m/z* 314.1071 [(M+H)$^+$; calcd for $C_{14}H_{18}ClFN_3O_2$: 314.1072]



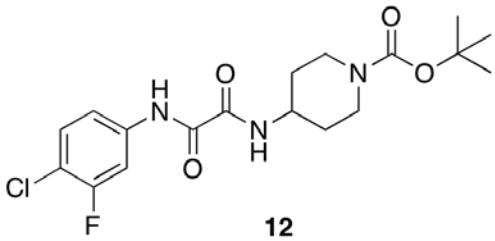
10

Compound 10. Prepared in an analogous manner to **1** to give **10**. ^{1}H-NMR (DMSO, 500 MHz), δ0.98 (t, *J* =7.0 Hz, 3H), 1.65 (m, 4H), 1.89 (t, *J* =8.5 Hz, 2H), 2.28 (q, *J* =7.0 Hz, 2H), 2.83 (d, *J* =8.5 Hz, 2H), 3.32 (m, 2H), 3.60 (m, 1H), 7.57 (dd, *J* =9.0, 9.0 Hz, 1H), 7.72 (d, *J* =8.0 Hz, 1H), 7.93 (dd, *J* =11.5, 2.0 Hz, 1H), 8.92 (d, *J* =8.0 Hz, 1H), 10.9 (s, 1H). HRMS (ES+) *m/z* 342.1387 [(M+H)$^+$; calcd for $C_{16}H_{22}ClFN_3O_2$: 342.1385].



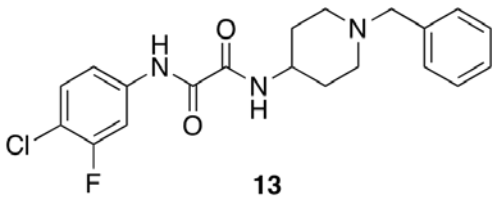
11

Compound 11. Prepared in an analogous manner to **1** to give **11** in 23% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.93 (br, 1H), 7.93 (dd, *J* = 12.0, 2.5 Hz, 1H), 7.73 (m, 1H), 7.57 (t, *J* = 9.0 Hz, 1H), 3.62 (m, 1H), 2.79 (m, 4H), 2.15 (m, 1H), 1.70 (m, 4H), 0.97 (m, 6H); high resolution mass spectrum (ES+) *m/z* 342.1381 [(M + H)$^+$; calcd for $C_{16}H_{22}N_3O_2FCl$: 342.1385].



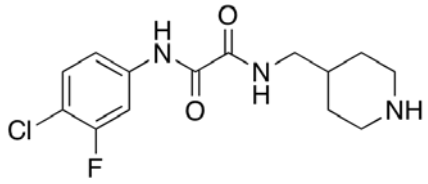
12

Compound 12. Prepared in an analogous manner to **1** above from **S.I.-1** to give **12** in 38% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.98 (d, *J* = 8.5 Hz, 1H), 7.93 (dd, *J* = 11.5, 2.0 Hz, 1H), 7.72 (m, 1H), 7.57 (t, *J* = 8.5 Hz, 1H), 3.93 (m, 2H), 3.84 (m, 1H), 2.80 (m, 2H), 1.69 (m, 2H), 1.51 (m, 2H), 1.40 (s, 9H); high resolution mass spectrum (ES–) *m/z* 398.1288 [(M – H)$^-$; calcd for $C_{18}H_{22}N_3O_4FCl$: 398.1283].



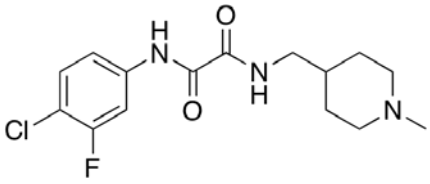
13

Compound 13. Prepared in an analogous manner to **1** above from **S.I.-1** to give **13** as a white powder. ^{1}H-NMR (DMSO, 500 MHz), δ 1.66 (m, 4H), 1.98 (m, 2H), 2.79 (d, *J* =11.5 Hz, 2H), 3.44 (s, 2H), 3.63 (m, 1H), 7.26 (m, 5H), 7.57 (dd, *J* =9.0, 9.0 Hz, 1H), 7.72 (d, *J* =8.5 Hz, 1H), 7.93 (dd, *J* =11.5, 2.0 Hz, 1H), 8.92 (d, *J* =8.5 Hz, 1H). HRMS (ES+) *m/z* 390.1385 [(M+H)$^+$; calcd for $C_{20}H_{22}ClFN_3O_2$: 390.1385].



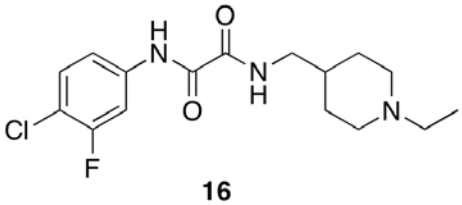
14

Compound 14. Prepared in an analogous manner to **1** above from **S.I.-1** to give **14** as an off white powder. ^{1}H-NMR (DMSO, 500 MHz), δ0982m, 2H), 1.52 (m, 2H), 1.60 (m, 1H), 2.38 (m, 2H), 2.88 (m, 2H), 3.05 (t, *J* =6.5 Hz, 2H), 3.44 (m, 2H), 7.57 (dd, *J* =8.5, 9.0 Hz, 1H), 7.72 (dd, *J* =8.5, 1.5 Hz, 1H), 7.93 (dd, *J* =7.3, 1.5 Hz, 1H), 9.08 (m, 1H). HRMS (ES+) *m/z* 314.1075 [(M+H)$^+$; calcd for $C_{14}H_{18}ClFN_3O_2$: 314.1071].



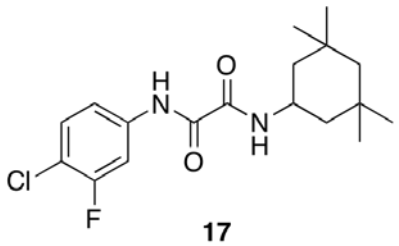
15

Compound 15. Prepared in an analogous manner to **1** above from **S.I.-1** to give **15** as an off white powder. ^{1}H-NMR (DMSO, 500 MHz), δ113m, 2H), 1.49 (m, 1H), 1.56 (d, *J* =12.0 Hz, 2H), 1.76 (t, *J* =12.0 Hz, 2H), 2.11 (s, 3H), 2.71 (d, *J* =12.0 Hz, 2H), 3.07 (t, *J* =6.5 Hz, 2H), 7.57 (dd, *J* =9.0, 9.0 Hz, 1H), 7.72 (dd, *J* =9.0, 2.0 Hz, 1H), 7.93 (dd, *J* =11.5, 2.0 Hz, 1H), 9.04 (m, 1H), 10.9 (s, 1H). HRMS (ES+) *m/z* 328.1225 [(M+H)$^+$; calcd for $C_{15}H_{20}ClFN_3O_2$: 328.1228].



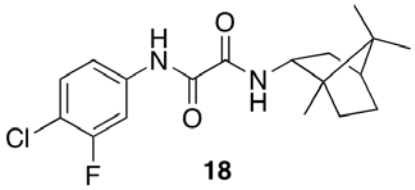
16

Compound 16. Prepared in an analogous manner to **1** above from **S.I.-1** to give **16** as an off white powder. ^{1}H-NMR (DMSO, 500 MHz), δ 97t, *J* =7.0 Hz, 3H), 1.13 (m, 2H), 1.51 (m, 1H), 1.58 (d, *J* =12.5 Hz, 2H), 1.76 (t, *J* =11.5 Hz, 2H), 2.26 (m, 2H), 2.81 (d, *J* =11.5 Hz, 2H), 3.08 (t, *J* =6.5 Hz, 2H), 7.57 (dd, *J* =9.0, 9.0 Hz, 1H), 7.72 (dd, *J* =9.0, 2.0 Hz, 1H), 7.93 (dd, *J* =11.5, 2.0 Hz, 1H), 9.03 (t, *J* =6.0 Hz, 1H), 10.9 (s, 1H). HRMS (ES+) *m/z* 342.1384 [(M+H)$^+$; calcd for $C_{16}H_{22}ClFN_3O_2$: 342.1385].



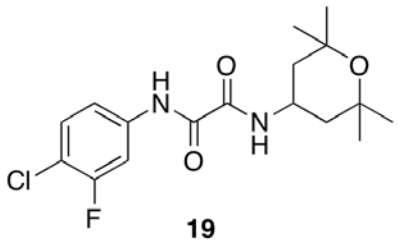
17

Compound 17. Prepared in an analogous manner to **1** above from **S.I.-1** to give **17** in 48% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.77 (d, J = 8.5 Hz, 1H), 7.92 (dd, J = 12.0, 3.0 Hz, 1H), 7.70 (m, 1H), 7.57 (t, J = 9.0 Hz, 1H), 4.02 (m, 1H), 1.47 (m, 2H), 1.22 (M, 3H), 1.04 (m, 1H), 1.03 (s, 6H); high resolution mass spectrum (ES–) *m/z* 353.1421 [(M – H)$^-$; calcd for $C_{18}H_{23}N_2O_2FCl$: 353.1432].



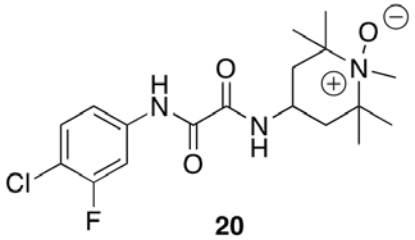
18

Compound 18. Prepared in an analogous manner to **18** above from **S.I-1** to give **18** in 63% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.67 (d, J = 9.0 Hz, 1H), 7.95 (dd, J = 12.0, 2.5 Hz, 1H), 7.30 (m, 1H), 7.58 (t, J = 8.5 Hz, 1H), 4.18 (m, 1H), 2.13 (m, 1H), 1.63 (m, 3H), 1.46 (m, 1H), 1.27 (m, 2H), 0.94 (s, 3H), 0.85 (s, 3H), 0.75 (s, 3H); high resolution mass spectrum (ES–) *m/z* 351.1280 [(M – H)$^-$; calcd for $C_{18}H_{21}N_2O_2FCl$: 351.1276].



19

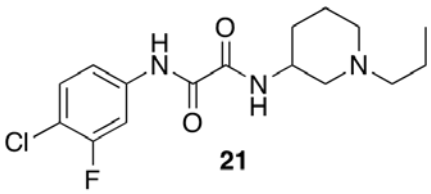
Compound 19. Prepared in an analogous manner to **1** above from **S.I.-1** to give **19** in 24% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.92 (d, J = 8.5 Hz, 1H), 7.92 (dd, J = 12.0, 2.0 Hz, 1H), 7.70 (m, 1H), 7.58 (t, J = 8.5 Hz, 1H), 4.22 (m, 1H), 1.66 (dd, J = 12.5, 4.0 Hz, 2H), 1.41 (dd, J = 12.5, 12.5 Hz, 1H), 1.24 (s, 6H), 1.13 (s, 6H); high resolution mass spectrum (ES–) *m/z* 355.1215 [(M – H)$^-$; calcd for $C_{17}H_{21}N_2O_3FCl$: 355.1225].



20

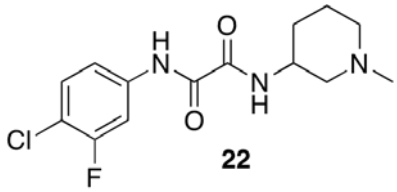
Compound 20. To a solution of **8** (80.5 mg, 0.218 mmol) in DCM (2.2 mL) was added *m*-CPBA (75.2 mg, 0.327 mmol) at room temperature. After being stirred for 1h the resulting precipitate was filtered and washed with DCM and hexanes and dried to give 41.1 mg of **20** as a white solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.95 (s, 1H), 9.05 (d, J = 7.6 Hz, 1H), 7.92 (dd, J = 2.1, 11.7 Hz, 1H), 7.71-7.69 (m, 1H), 7.58 (t, J = 8.7 Hz, 1H), 4.26-4.22 (m, 1H), 2.98 (s, 3H), 2.48-2.43

(m, 4H), 1.57 (s, 6H), 1.46 (s, 6H); HRMS (ES+) *m/z* 386.1642 [(M+H)$^+$; calcd for $C_{18}H_{26}N_3O_3ClF$: 386.1647].



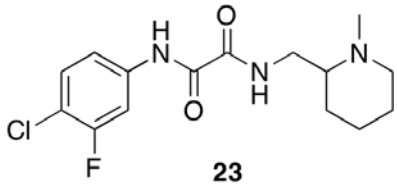
21

Compound 21. Prepared in an analogous manner to **1** above from **S.I.-1** to give **21** in 47% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.69 (d, J = 8.5 Hz, 1H), 7.93 (dd, J = 11.0, 2.5 Hz, 1H), 7.72 (m, 1H), 7.58 (t, J = 8.5 Hz, 1H), 3.82 (m, 1H), 2.65-2.50 (m, 2H), 2.24 (t, J = 7.5 Hz, 1H), 2.04 (m, 2H), 1.65 (m, 2H), 1.48 (m, 2H), 1.42 (m, 2H), 0.85 (t, J = 7.5 Hz, 1H); high resolution mass spectrum (ES+) *m/z* 342.1371 [(M + H)$^+$; calcd for $C_{16}H_{22}N_3O_2FCl$: 342.1385].



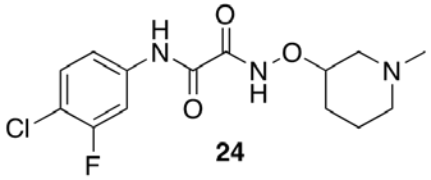
22

Compound 22. Prepared in a manner analogous to **1** to give 75.6 mg (0.241 mmol, 29%) of **22** as a white solid by recrystallization from EtOH; IR (neat) 3275, 2933, 2781, 1663, 1592, 1519, 1426, 809 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.70 (d, J = 5.5 Hz, 1H), 7.93 (d, J = 12.0 Hz, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.57 (app t, J = 8.5 Hz, 1H), 3.85-3.84 (m, 1H), 2.62-2.61 (m, 1H), 2.18 (s, 3H), 2.05-2.03 (m, 1H), 1.65-1.64 (m, 2H), 1.50-1.44 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.0, 158.7, 156.8 (J_{CF} = 243.0 Hz), 138.2 (J_{CF} = 10.0 Hz), 130.5, 117.4 (J_{CF} = 3.8 Hz), 114.4 (J_{CF} = 17.6 Hz), 108.5 (J_{CF} = 25.4 Hz), 67.0, 59.2, 54.7, 46.2, 28.3, 23.1. HRMS (ES+) m/z 314.1065 [(M+H)$^+$; calcd for $C_{14}H_{18}N_3O_2ClF$: 314.1072].



23

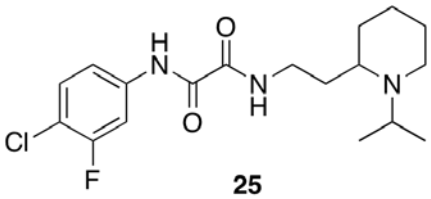
Compound 23. Prepared in an analogous manner to **1** above from **S.I.-1** to give **23** in 42% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 8.64 (d, J = 6.0 Hz, 1H), 7.94 (dd, J = 12.0, 3.0 Hz, 1H), 7.72 (m, 1H), 7.58 (t, J = 8.5 Hz, 1H), 3.40 (m, 1H), 3.25 (m, 1H), 3.25 (m, 1H), 2.74 (m, 1H), 2.22 (ms, 3H), 2.06 (m, 1H), 2.10 (m, 1H), 2.01 (m, 1H), 1.64 (m, 1H), 1.53 (m, 2H), 1.40 (m, 1H), 1.21 (m, 2H); high resolution mass spectrum (ES–) *m/z* 326.1082 [(M – H)$^-$; calcd for $C_{15}H_{18}N_3O_2FCl$: 326.1072].



24

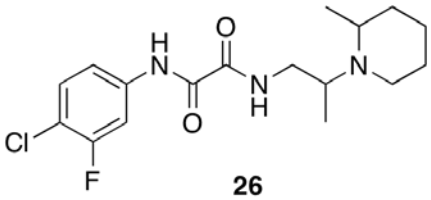
Compound 24. Prepared in an analogous manner to **1** above from **S.I.-1** to give **24** in 13% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.92 (dd, J = 12.0, 2.5 Hz, 1H), 7.70 (m, 1H), 7.58 (t, J = 9.0 Hz, 1H), 3.90 (m, 1H), 2.81 (m, 1H), 2.47 (m,

1H), 2.17 (s, 3H), 1.97 (m, 2H), 1.83 (m, 1H), 1.72 (m, 1H), 1.41 (m, 1H), 1.30 (m, 1H); high resolution mass spectrum (ES+) *m/z* 330.1010 [(M + H)$^+$; calcd for $C_{14}H_{18}N_3O_3FCl$: 330.1021].



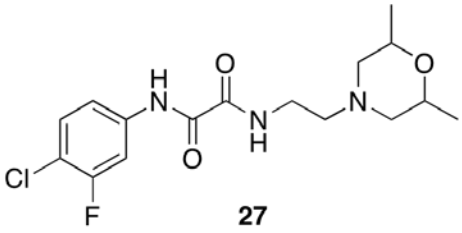
25

Compound 25. Prepared in an analogous manner to **1** above from **S.I.-1** to give **25** in 42% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 8.84 (d, *J* = 6.0 Hz, 1H), 7.94 (dd, *J* = 12.0, 2.5 Hz, 1H), 7.73 (m, 1H), 7.57 (t, *J* = 9.0 Hz, 1H), 3.30 (q, *J* = 9.0 Hz, 1H), 2.56 (m, 1H), 2.41 (m, 9H), 0.94 (d, *J* = 6.5 Hz, 6H); high resolution mass spectrum (ES+) *m/z* 370.1694 [(M + H)$^+$; calcd for $C_{18}H_{26}N_3O_2FCl$: 370.1698].



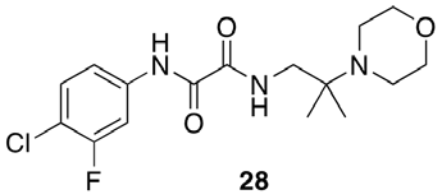
26

Compounds 26a and 26b. Prepared in an analogous manner to **1** above from **S.I.-1** to give **26a** in 21% yield and **26b** in 30% yield, both as a colorless crystalline solid; **26a.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.34 (br, 1H), 7.78 (m, 1H), 7.34 (m ,2H), 3.47 (m, 1H), 3.30 (m, 1H), 3.04 (t, *J* = 12.0 Hz, 1H), 2.67 (m, 1H), 2.50 (m, 1H), 2.11 (t, *J* = 11.0 Hz, 1H), 1.71 (m, 1H), 1.63 (m, 2H), 1.50-1.23 (m,3H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H); high resolution mass spectrum (ES+) *m/z* 356.1534 [(M + H)$^+$; calcd for $C_{17}H_{24}N_3O_2FCl$: 356.1541].
26b. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.13 (br, 1H), 7.74 (dd, *J* = 11.0, 2.5 Hz, 1H), 7.33 (m, 2H), 3.35 (m, 1H), 3.20 (m, 1H), 3.04 (m, 1H), 2.86 (m, 1H), 2.75 (m, 1H), 2.36 (m, 1H), 1.78 (m, 1H), 1.58 (m, 3H), 1.41 (m, 2H), 1.13 (m, 6H); high resolution mass spectrum (ES+) *m/z* 356.1536 [(M + H)$^+$; calcd for $C_{17}H_{24}N_3O_2FCl$: 356.1541].



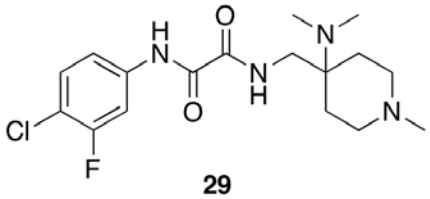
27

Compound 27. Prepared in an analogous manner to **1** above from **S.I.-1** to give **27** in 79% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.88 (t, *J* = 6.0 Hz, 1H), 7.94 (dd, *J* = 12.0, 2.5 Hz, 1H), 7.73 (m, 1H), 7.57 (t, *J* = 8.5 Hz, 1H), 3.52 (m, 2H), 3.30 (m, 2H), 2.76 (d, *J* = 10.0 Hz, 2H), 2.42 (t, *J* = 6.5 Hz, 2H), 1.62 (t, *J* = 10.5 Hz, 2H), 1.03 (d, *J* = 6.0 Hz, 6H); high resolution mass spectrum (ES+) *m/z* 358.1339 [(M + H)$^+$; calcd for $C_{16}H_{22}N_3O_3FCl$: 358.1334].



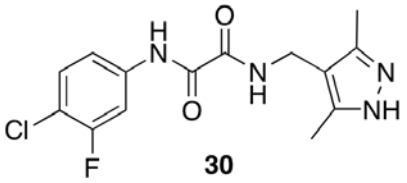
28

Compound 28. Prepared in an analogous manner to **1** above from **S.I.-1** to give **28** in 63% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 8.33 (t, J = 5.5 Hz, 1H), 7.96 (dd, J = 11.5, 2.0 Hz, 1H), 7.75 (m, 1H), 7.58 (t, J = 8.5 Hz, 1H), 3.57 (t, J = 4.0 Hz, 1H), 3.21 (t, J = 6.0 Hz, 1H), 2.49 (m, 4H), 0.98 (s, 6H); high resolution mass spectrum (ES+) *m/z* 358.1329 [(M + H)$^+$; calcd for $C_{16}H_{22}N_3O_3FCl$: 358.1334].



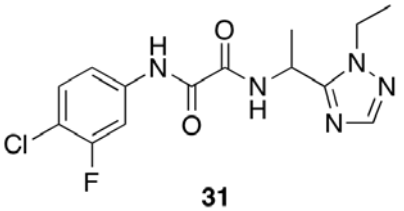
29

Compound 29. Prepared in an analogous manner to **1** above from **S.I.-1** to give **29** in 87% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.50 (t, J = 6.0 Hz, 1H), 7.94 (dd, J = 11.5, 2.0 Hz, 1H), 7.72 (m, 1H), 7.57 (t, J = 8.5 Hz, 1H), 3.30 (d, J = 6.5 Hz, 2H), 2.34 (m, 2H), 2.24 (s, 6H), 2.22 (m, 2H), 2.12 (s, 3H), 1.70 (m, 2H), 1.40 (m, 2H); high resolution mass spectrum (ES+) *m/z* 371.1666 [(M + H)$^+$; calcd for $C_{17}H_{25}N_4O_2FCl$: 371.1650].



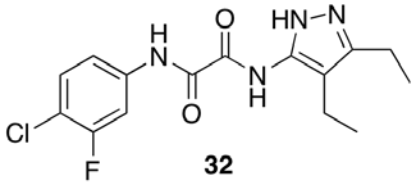
30

Compound 30. Prepared in a manner analogous to **1** to give 213.1 mg (0.656 mmol, 63%) of **30** as a white solid by recrystallization from EtOH; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.22 (t, J = 5.8 Hz, 1H), 7.92 (dd, J = 2.5, 12.0 Hz, 1H), 7.73-7.70 (m, 1H), 7.56 (app t, J = 8.8 Hz, 1H), 4.13 (d, J = 7.0 Hz, 3H), 1.33 (d, J = 6.0 Hz, 2H), 2.19 (br. s, 3H), 2.14 (br. s, 3H). HRMS (ES+) *m/z* 325.0872 [(M+H)$^+$; calcd for $C_{14}H_{15}N_4O_2ClF$: 325.0868].



31

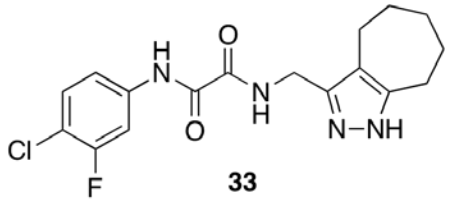
Compound 31. Prepared in a manner analogous to **1** to give 223.4 mg (0.658 mmol, 45%) of **31** as a white solid by recrystallization from EtOH; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.12 (s, 1H), 9.50 (d, J = 7.7 Hz, 1H), 7.91 (dd, J = 2.4, 11.8 Hz, 1H), 7.86 (s, 1H), 7.72-7.69 (m, 1H), 7.57 (app t, J = 8.7 Hz, 1H), 5.29-5.24 (m, 1H), 4.24-4.16 (m, 1H), 1.55 (d, J = 7.0 Hz, 3H), 1.33 (t, J = 7.3 Hz, 3H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 159.2, 158.5, 156.8 (d, J_{CF} = 242.7 Hz), 154.7, 149.9, 138.1 (d, J_{CF} = 10.0 Hz), 130.5, 117.3 (d, J_{CF} = 3.0 Hz), 114.4 (d, J_{CF} = 17.5 Hz), 108.5 (d, J_{CF} = 25.5 Hz), 42.7, 41.0, 18.8, 14.9. HRMS (ES-) m/z 338.0814 [(M-H)$^-$; calcd for $C_{14}H_{14}N_5O_2ClF$: 338.0820].



32

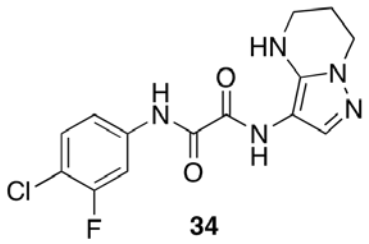
Compound 32. Prepared in a manner analogous to **1** to give 242.2 mg (0.715 mmol, 44%) of **32** as a white solid by recrystallization from EtOH; IR (neat) 3270, 2969, 1671, 1596, 1513, 1426,

1065, 871 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 11.10 (s, 1H), 10.37 (s, 1H), 7.98 (dd, *J* = 2.3, 11.9 Hz, 1H), 7.76 (dd, *J* = 1.5, 8.9 Hz, 1H), 7.59 (app t, *J* = 8.7 Hz, 1H), 2.56 (q, *J* = 7.5 Hz, 2H), 2.29 (q, *J* = 7.5 Hz, 2H), 1.18 (t, *J* = 7.5 Hz, 3H), 1.00 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.1, 158.8, 156.8 (J_{CF} = 242.2 Hz), 142.5, 141.6, 138.2 (J_{CF} = 10.1 Hz), 130.5, 117.4 (J_{CF} = 3.1 Hz), 114.4 (J_{CF} = 17.4 Hz), 112.7, 108.6 (J_{CF} = 25.4 Hz), 17.4, 15.4, 14.9, 13.7. HRMS (ES-) m/z 337.0870 [$(M-H)^+$; calcd for $C_{15}H_{15}N_4O_2ClF$: 337.0868].



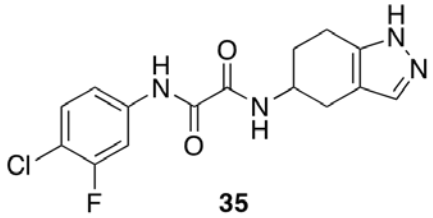
33

Compound 33. Prepared in a manner analogous to **1** to give 221.0 mg (0.606 mmol, 71%) of **33** as a white solid by recrystallization from EtOH; IR (neat) 3232, 2920, 1659, 1591, 1509, 1407, 1210, 1151, 1068, 867, 813 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 11.81 (s, 1/2H, NH), 11.01 (s, 1H), 9.25 (s, 1/2H, NH), 8.96 (s, 1H), 7.93 (dd, *J* = 2.1, 11.9 Hz, 1H), 7.73-7.72 (m, 1H), 7.57 (app t, *J* = 8.7 Hz, 1H), 4.29 (br. s, 2H), 2.63 (br. s, 2H), 2.47 (br. s, 2H, the peak overlaps with the peak of DMSO), 1.76 (br. s, 2H), 1.55 (br. s, 4H). HRMS (ES-) *m/z* 363.1030 [$(M-H)^-$; calcd for $C_{17}H_{17}N_4O_2ClF$: 363.1024].



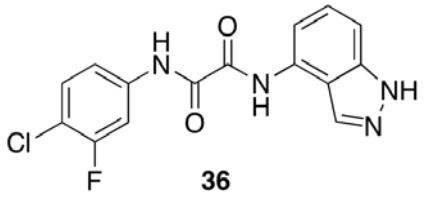
34

Compound 34. Prepared in a manner analogous to **1** to give 211.6 mg (0.625 mmol, 65%) of **34** as a brown solid by recrystallization from EtOH; ^1H NMR (500 MHz, DMSO-d_6) δ 11.06 (s, 1H), 10.37 (s, 1H), 7.97 (dd, *J* = 2.3, 11.8 Hz, 1H), 7.76-7.74 (m, 1H), 7.59 (app t, *J* = 8.7 Hz, 1H), 7.49 (s, 1H), 6.06 (s, 1H), 3.97 (t, *J* = 6.1 Hz, 2H). 3.24-3.21 (m, 2H), 2.01-1.97 (m, 2H). HRMS (ES+) *m/z* 338.0817 [$(M+H)^+$; calcd for $C_{14}H_{14}N_5O_2ClF$: 338.0820].



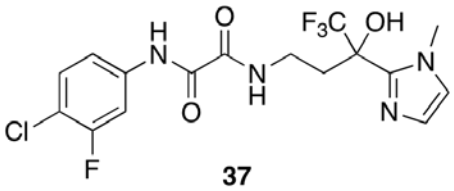
35

Compound 35. Prepared in an analogous manner to **1** above from **S.I.-1** to give **35** in 51% yield as a colorless crystalline solid; ^1H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.01 (d, *J* = 8.5 Hz, 1H), 7.94 (dd, *J* = 11.5, 2.0 Hz, 1H), 7.73 (m, 1H), 7.58 (t, *J* = 8.5 Hz, 1H), 7.30 (br, 1H), 4.01 (m, 1H), 2.69 (m, 4H), 1.88 (m, 2H); high resolution mass spectrum (ES–) *m/z* 335.0706 [$(M - H)^-$; calcd for $C_{15}H_{13}N_4O_2FCl$: 335.0711].



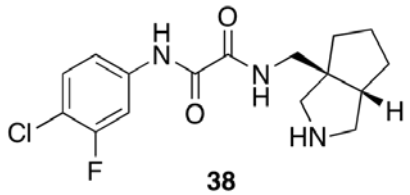
36

Compound 36. Prepared in an analogous manner to **61** (see below) from the free acid of **S.I.-1** to give **36** in 12% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.15 (s, 1H), 11.26 (s, 1H), 10.98 (s, 1H), 8.19 (s, 1H), 8.03 (dd, J = 12.0, 2.5 Hz, 1H), 7.78 (m, 1H), 7.63 (t, J = 9.0 Hz, 1H), 7.39 (m, 3H); high resolution mass spectrum (ES–) *m/z* 331.0395 [(M – H)$^-$; calcd for $C_{15}H_9N_4O_2FCl$: 331.0398].



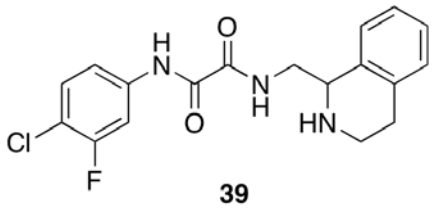
37

Compound 37. Prepared in an analogous manner to **1** above from **S.I.-1** to give **37** in 17% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 9.00 (t, J = 5.5 Hz, 1H), 7.92 (dd, J = 11.5, 2.0 Hz, 1H), 7.72 (m, 1H), 7.57 (t, J = 8.5 Hz, 1H), 7.17 (d, J = 1.0 Hz, 1H), 7.01 (s, 1H), 6.88 (d, J = 1.0 Hz, 1H), 3.81 (s, 3H), 3.29 (m, 2H), 2.72 (m, 1H), 2.20 (m, 1H); high resolution mass spectrum (ES–) *m/z* 421.0707 [(M – H)$^-$; calcd for $C_{16}H_{14}N_4O_3F_4Cl$: 421.0691].



38

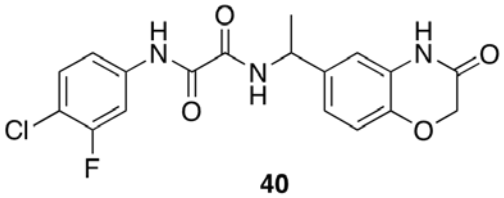
Compound 38. Prepared in an analogous manner to **1** above from **S.I.-1** to give **38** in 29% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.02 (t, J = 6.0 Hz, 1H), 7.94 (dd, J = 12.0, 2.5 Hz, 1H), 7.72 (m, 1H), 7.57 (t, J = 8.5 Hz, 1H), 3.23 (d, J = 6.5 Hz, 1H), 2.96 (dd, J = 10.5, 8.0 Hz, 1H), 2.82 (d, J = 11.0 Hz, 1H), 2.40 (d, J = 11.0 Hz, 1H), 2.33 (dd, J = 10.5, 5.5 Hz, 1H), 2.17 (m, 1H), 1.55 (m, 4H), 1.38 (m, 1H), 1.28 (m, 1H); high resolution mass spectrum (ES+) *m/z* 340.1233 [(M + H)$^+$; calcd for $C_{16}H_{20}N_3O_2FCl$: 340.1228].



39

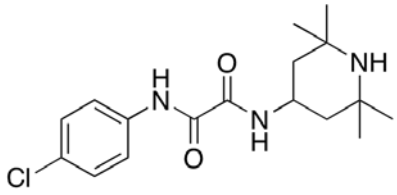
Compound 39. Prepared in a manner analogous to **1** to give 57.0 mg (0.158 mmol, 36%) of **39** as a white solid by silica gel column chromatography (DCM/MeOH/NH_4OH 100/1/0.1 to 10/1/0.1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.80 (t, J = 5.9 Hz, 1H), 7.95 (dd, J = 2.3, 11.8 Hz, 1H), 7.75-7.73 (m, 1H), 7.58 (t, J = 8.7 Hz, 1H), 7.18-7.08 (m, 4H), 4.07-4.05 (m, 1H), 3.50-3.47 (m, 2H), 3.08-3.03 (m, 1H), 2.87-2.82 (m, 1H), 2.73-2.64 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.4, 158.9, 156.8 (d, J_{CF} = 242.3 Hz), 138.2 (d, J_{CF} = 9.9

Hz), 136.6, 135.8, 130.5, 129.1, 126.4, 126.1, 125.6, 117.3 (d, J_{CF} = 3.2 Hz), 114.3 (d, J_{CF} = 17.7 Hz), 108.5 (d, J_{CF} = 25.6 Hz), 54.0, 436., 38.7, 29.1. HRMS (ES+) *m/z* 362.1061 [$(M+H)^+$; calcd for $C_{18}H_{18}N_3O_2ClF$: 362.1072].



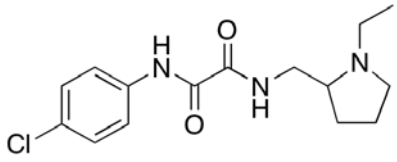
40

Compound 40. Prepared in an analogous manner to **1** above from **S.I.-1** to give **40** in 53% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.97 (s, 1H), 10.69(s, 1H), 9.44 (d, *J* = 8.0 Hz, 1H), 7.92 (dd, *J* = 12.0, 2.5 Hz, 1H), 7.71 (m, 1H), 7.57 (t, *J* = 8.5 Hz, 1H), 6.97-6.89 (m, 3H), 4.92 (m, 1H), 4.52 (s, 2H), 1.45 (d, *J* = 7.0 Hz, 3H); high resolution mass spectrum (ES–) *m/z* 390.0670 [$(M - H)^-$; calcd for $C_{18}H_{14}N_3O_4FCl$: 390.0657].



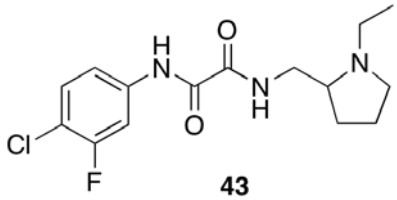
41

Compound 41 (aka **NBD-556**). **NBD-556** was prepared by the previously reported synthesis (see Smith, A.B., III; Sodroski, J.; Freire, E. *et. al. Biochemistry* **2006**, *45*, 10973).



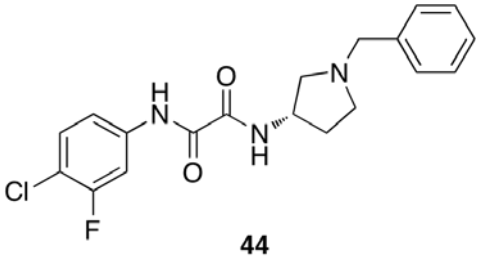
42

Compound 42. Analogue **42** was purchased from commercially a available source identified by searching the ZINC database and used directly in antiviral assays.



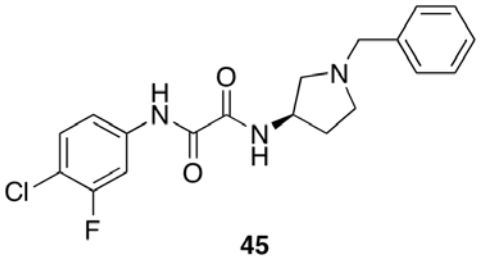
43

Compound 43. Prepared in an analogous manner to **1** above from **S.I.-1** to give **43** in 84% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.76 (t, *J* = 5.5 Hz, 1H), 7.94 (dd, *J* = 11.5, 2.0 Hz, 1H), 7.72 (m, 1H), 7.57 (t, *J* = 8.5 Hz, 1H), 3.29 (m, 1H), 3.07 (m, 1H), 3.02 (m, 1H), 2.80 (m, 1H), 2.58 (m, 1H), 2.24 (m, 1H), 2.12 (m, 1H), 1.75 (m, 1H), 1.63 (m, 2H), 1.52 (m, 1H), 1.04 (t, *J* = 7.5 Hz, 3H); high resolution mass spectrum (ES–) *m/z* 326.1085 [$(M - H)^-$; calcd for $C_{15}H_{18}N_3O_2FCl$: 326.1072].



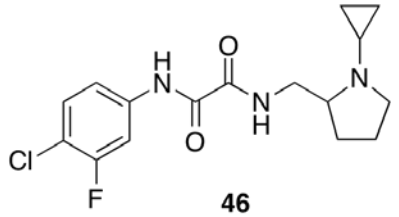
44

Compound 44. Prepared in a manner analogous to **1** to give 100.5 mg (0.267 mmol, 44%) of **44** as a light brown solid by recrystallization from EtOH; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.95 (d, J = 7.7 Hz, 1H), 7.92 (dd, J = 2.3, 11.8 Hz, 1H), 7.72-7.69 (m, 1H), 7.57 (t, J = 8.7 Hz, 1H), 7.32-7.31 (m, 4H), 7.26-7.22 (m, 1H), 4.29-4.23 (m, 1H), 3.58 (s, 2H), 2.76 (dd, J = 7.1, 9.3 Hz, 1H), 2.63-2.58 (m, 1H), 2.51-2.47 (m, 1H), 2.43 (dd, J = 5.5, 9.4 Hz, 1H), 2.15-2.07 (m, 1H), 1.86-1.80 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.3, 158.9, 156.8 (d, J_{CF} = 242.7 Hz), 138.9, 138.2 (d, J_{CF} = 10.0 Hz), 130.5, 128.5, 128.1, 126.8, 117.3 (d, J_{CF} = 2.9 Hz), 114.3 (d, J_{CF} = 17.5 Hz), 108.5 (d, J_{CF} = 25.5 Hz), 59.2, 59.0, 52.1, 48.7, 30.2. HRMS (ES+) *m/z* 376.1227 [(M+H)$^{+}$; calcd for $C_{19}H_{20}N_3O_2ClF$: 376.1228].



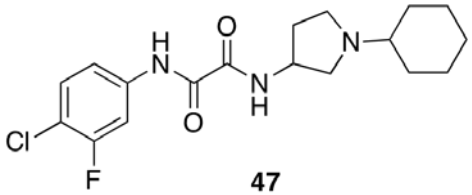
45

Compound 45. Prepared in a manner analogous to **1** to give 129.0 mg (0.343 mmol, 58%) of **45** as a light yellow solid by recrystallization from EtOH; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.95 (d, J = 7.5 Hz, 1H), 7.92 (dd, J = 2.3, 11.8 Hz, 1H), 7.71-7.69 (m, 1H), 7.57 (t, J = 8.8 Hz, 1H), 7.32-7.31 (m, 4H), 7.26-7.22 (m, 1H), 4.29-4.22 (m, 1H), 3.58 (s, 2H), 2.76 (dd, J = 7.0, 9.5 Hz, 1H), 2.63-2.58 (m, 1H), 2.50-2.47 (m, 1H), 2.43 (dd, J = 5.8, 9.3 Hz, 1H), 2.16-2.07 (m, 1H), 1.86-1.80 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.3, 158.9, 156.8 (d, J_{CF} = 242.6 Hz), 138.9, 138.2 (d, J_{CF} = 10.0 Hz), 130.5, 128.5, 128.1, 126.8, 117.3 (d, J_{CF} = 3.3 Hz), 114.3 (d, J_{CF} = 17.5 Hz), 108.5 (d, J_{CF} = 25.6 Hz), 59.2, 59.0, 52.1, 48.7, 30.2. HRMS (ES+) *m/z* 376.1228 [(M+H)$^{+}$; calcd for $C_{19}H_{20}N_3O_2ClF$: 376.1228].



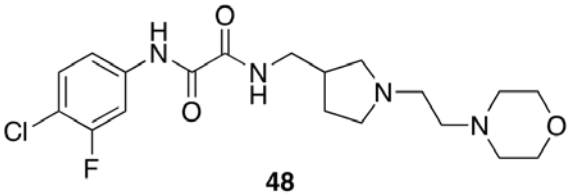
46

Compound 46. Prepared in an analogous manner to **1** above from **S.I.-1** to give **46** in 58% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.10 (t, J = 5.5 Hz, 1H), 7.93 (dd, J = 11.5, 2.0 Hz, 1H), 7.73 (m, 1H), 7.57 (t, J = 8.5 Hz, 1H), 3.17 (m, 2H), 2.64 (m, 1H), 2.53 (m, 1H), 2.44 (m, 1H), 2.36 (m, 1H), 1.82 (m, 1H), 1.59 (m, 1H), 1.42 (m, 1H), 0.37 (m, 2H), 0.31 (m, 2H); high resolution mass spectrum (ES+) *m/z* 340.1233 [(M + H)$^{+}$; calcd for $C_{16}H_{20}N_3O_2FCl$: 340.1228].



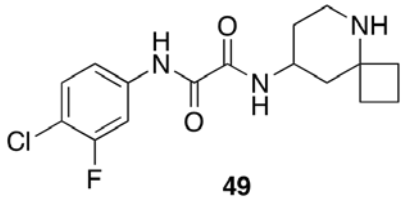
47

Compound 47. Prepared in a manner analogous to **1** to give 94.2 mg (0.256 mmol, 59%) of **47** as a white solid by recrystallization from EtOH; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.91 (s, 1H), 7.92 (dd, J = 2.3, 11.8 Hz, 1H), 7.72-7.70 (m, 1H), 7.57 (t, J = 8.6 Hz, 1H), 4.26 (m, 1H), 2.86-2.56 (m, 4H), 2.12-2.06 (m, 2H), 1.84-1.82 (m, 3H), 1.69-1.68 (m, 2H), 1.55-1.53 (m, 1H), 1.25-1.11 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.2, 158.9, 156.8 (d, J_{CF} = 242.7 Hz), 138.2 (d, J_{CF} = 10.1 Hz), 130.5, 117.3 (d, J_{CF} = 3.2 Hz), 114.3 (d, J_{CF} = 17.5 Hz), 108.5 (d, J_{CF} = 25.6 Hz), 62.0, 56.2, 49.4, 48.4, 30.8 (2C), 29.9, 25.6, 24.2 (2C). HRMS (ES+) *m/z* 368.1536 [(M+H)$^+$; calcd for $C_{18}H_{24}N_3O_2ClF$: 368.1541].



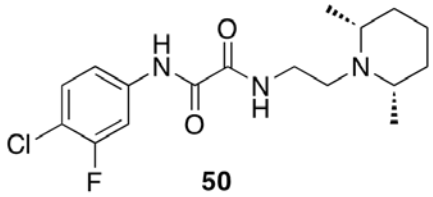
48

Compound 48. Prepared in an analogous manner to **1** above from **S.I.-1** to give **48** in 52% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 9.09 (t, J = 6.0 Hz, 1H), 7.93 (dd, J = 12.0, 2.5 Hz, 1H), 7.72 (m, 1H), 7.56 (t, J = 9.0 Hz, 1H), 3.53 (t, J = 4.5 Hz, 4H), 3.15 (m, 1H), 2.48 (m, 4H), 2.32 (m, 9H), 1.81 (m, 1H), 1.39 (m, 1H); high resolution mass spectrum (ES+) *m/z* 413.1752 [(M + H)$^+$; calcd for $C_{19}H_{27}N_4O_3FCl$: 413.1756].



49

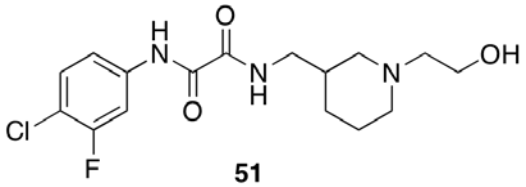
Compound 49. Prepared in an analogous manner to **1** above from **S.I.-1** to give **49** in 71% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.91 (d, J = 7.0 Hz, 1H), 7.93 (dd, J = 12.0, 2.5 Hz, 1H), 7.71 (m, 1H), 7.58 (t, J = 8.5 Hz, 1H), 3.74 (m, 1H), 2.72 (m, 1H), 2.55 (m, 1H), 2.10 (br, 1H), 1.95 (m, 1H), 1.90-1.65 (m, 6H), 1.58 (m, 1H), 1.41 (m, 2H); high resolution mass spectrum (ES+) *m/z* 340.1217 [(M + H)$^+$; calcd for $C_{16}H_{20}N_3O_2FCl$: 340.1228].



50

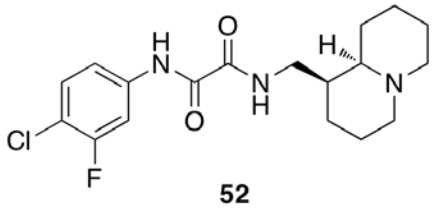
Compound 50. Prepared in an analogous manner to **1** above from **S.I.-1** to give **50** in 70% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.05 (t, J = 6.5 Hz, 1H), 7.93 (dd, J = 12.0, 2.5 Hz, 1H), 7.72 (m, 1H), 7.57 (t, J = 9.0 Hz, 1H), 3.20 (m, 2H), 2.67 (m, 2H), 2.42 (m, 2H), 1.57 (m, 1H), 1.51 (m, 2H), 1.23 (m, 2H), 1.13 (m, 1H), 1.09 (d, J =

6.0 Hz, 6H); high resolution mass spectrum (ES+) *m/z* 356.1530 [(M + H)$^+$; calcd for $C_{17}H_{24}N_3O_2FCl$: 356.1541].



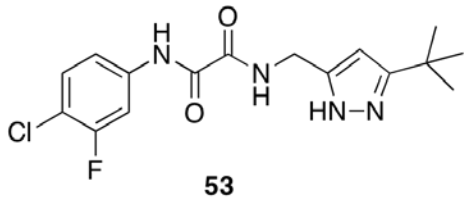
51

Compound 51. Prepared in a manner analogous to **1** to give 264.7 mg (0.740 mmol, 56%) of **51** as a light pink powder by recrystallization from EtOH; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.96 (s, 1H), 9.04 (t, J = 6.2 Hz, 1H), 7.94 (dd, J = 2.4, 11.9 Hz, 1H), 7.74-7.71 (m, 1H), 7.57 (t, J = 8.7 Hz, 1H), 4.30 (t, J = 5.1 Hz, 1H), 3.46 (dd, J = 6.1, 11.5 Hz, 2H), 3.13-3.05 (m, 2H), 2.73-2.68 (m, 2H), 2.34 (t, J = 6.3 Hz, 1H), 1.95 (t, J = 10.3 Hz, 1H), 1.81-1.72 (m, 2H), 1.61-1.59 (m, 2H), 1.61-1.59 (m, 2H), 1.43-1.36 (m, 1H), 0.95-0.89 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.6, 159.0, 156.8 (d, J_{CF} = 242.7 Hz), 138.3 (d, J_{CF} = 10.0 Hz), 130.5, 117.3 (d, J_{CF} = 3.3 Hz), 114.3 (d, J_{CF} = 17.5 Hz), 108.5 (d, J_{CF} = 25.7 Hz), 60.8, 58.5, 58.0, 54.1, 42.8, 35.8, 28.0, 24.3. HRMS (ES+) *m/z* 358.1331 [(M+H)$^+$; calcd for $C_{16}H_{22}N_3O_3ClF$: 358.1334].



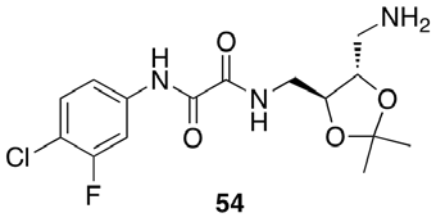
52

Compound 52. Prepared in a manner analogous to **1** to give 250.3 mg (0.680 mmol, 83%) of **52** as a light pink powder by recrystallization from EtOH; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.06 (t, J = 5.8 Hz, 1H), 7.94 (dd, J = 2.0, 12.0 Hz, 1H), 7.74-7.72 (m, 1H), 7.57 (t, J = 8.8 Hz, 1H), 3.50-3.44 (m, 1H), 2.73 (br. s, 2H), 1.92-1.16 (m, 15H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.4, 159.0, 156.8 (d, J_{CF} = 242.6 Hz), 138.3 (d, J_{CF} = 10.0 Hz), 130.5, 117.3 (d, J_{CF} = 2.9 Hz), 114.2 (d, J_{CF} = 17.5 Hz), 108.4 (d, J_{CF} = 25.4 Hz), 64.2, 56.7, 37.9, 37.0, 29.0, 26.9, 25.2, 24.6, 20.5. HRMS (ES+) *m/z* 368.1548 [(M+H)$^+$; calcd for $C_{18}H_{24}N_3O_2ClF$: 368.1541].



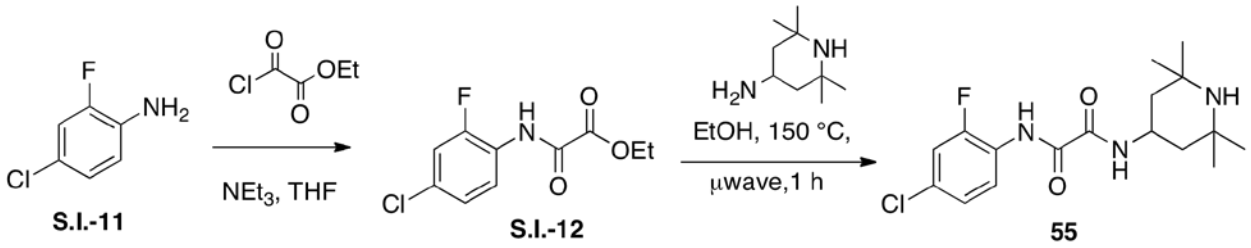
53

Compound 53. Prepared in a manner analogous to **1** to give 226.1 mg (0.641 mmol, 58%) of **53** as a white solid by flash column chromatography (DCM/MeOH 50/1-20/1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.28 (br. s, 1H), 7.95 (dd, J = 2.3, 11.8 Hz, 1H), 7.74-7.72 (m, 1H), 7.58 (t, J = 8.7 Hz, 1H), 5.92 (br. s, 1H), 4.32 (br. s, 1H), 1.23 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.4, 158.9, 156.8 (d, J_{CF} = 242.5 Hz), 153.1, 148.0, 138.2 (d, J_{CF} = 10.0 Hz), 130.5, 117.3 (d, J_{CF} = 2.9 Hz), 114.3 (d, J_{CF} = 17.5 Hz), 108.5 (d, J_{CF} = 25.6 Hz), 99.2, 37.2, 30.5, 30.1. HRMS (ES+) *m/z* 353.1184 [(M+H)$^+$; calcd for $C_{16}H_{19}N_4O_2ClF$: 353.1181].



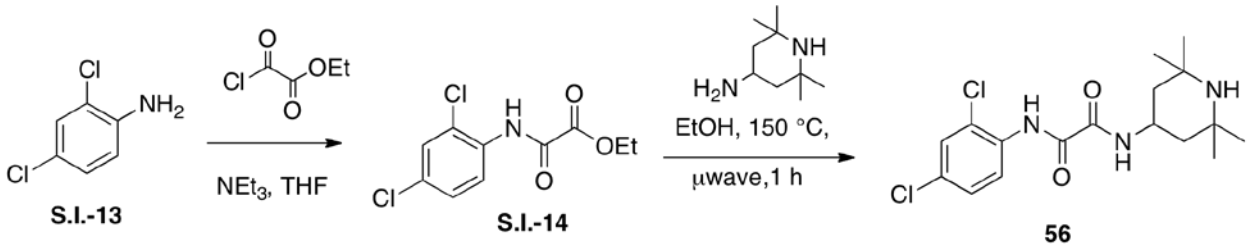
54

Compound 54. Prepared in a manner analogous to **1** to give 151.6 mg (0.421 mmol, 29%) of **54** as a yellow solid by silica gel column chromatography (DCM/MeOH/NH_4OH 100/1/0.1 to 10/1/0.1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 (dd, J = 2.4, 11.8 Hz, 1H), 7.74-7.72 (m, 1H), 7.57 (t, J = 8.7 Hz, 1H), 3.92-3.88 (m, 1H), 3.75-3.72 (m, 1H), 3.51 (dd, J = 5.5, 13.6 Hz, 1H), 3.35 (dd, J = 5.8, 13.6 Hz, 1H), 3.31 (br. S, 2H), 1.31 (s, 6H). *NOTE; the corresponding protons of the amide bonds were not observed.* ^{13}C NMR (500 MHz, DMSO-d_6) δ 159.6, 158.8, 156.8 (d, J_{CF} = 242.5 Hz), 138.2 (d, J_{CF} = 9.9 Hz), 130.5, 117.3 (d, J_{CF} = 2.9 Hz), 114.3 (d, J_{CF} = 17.7 Hz), 108.5 (d, J_{CF} = 25.7 Hz), 107.9, 80.4, 77.0, 43.5, 41.6, 27.1, 27.0. HRMS (ES+) *m/z* 360.1123 [$(M+H)^+$; calcd for $C_{15}H_{20}N_3O_4ClF$: 360.1126].



S.I.-11 S.I.-12 55

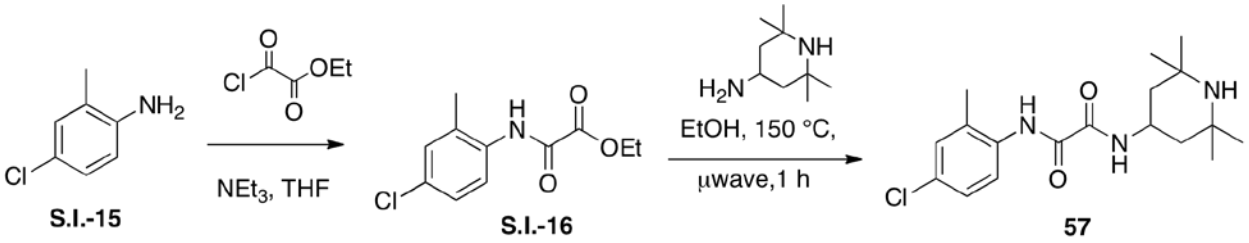
Compound 55. Analogue **55** was synthesized in 2 steps from **S.I.-11.** First, **S.I.-12** was prepared from **S.I.-11** employing the method described in the synthesis of **S.I.-1** in >90% yield and used directly without further purification. **S.I.-12** (140 mg, 0.58 mmol) was coupled to 4-amino-2,2,6,6-tetramethylpiperidine using the method described in the synthesis of **1** to afford **55** after recrystallization from EtOH (117 mg, 57%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.2 (bs, 1H), 8.83 (d, J = 8.5 Hz, 1H), 7.73 (t, J = 8.5 Hz, 1H), 7.55 (dd, J = 10.5, 2.5 Hz, 1H), 7.33 (dd, J = 8.5, 0.9 Hz, 1H), 4.14 (tt, J = 8.5, 3.5 Hz, 1H), 1.58 (dd, J = 12.0, 3.5 Hz, 2H), 1.24 (t, J = 12.5 Hz, 2H), 1.15 (s, 6H), 1.03 (s, 6H);. HRMS (ES+) *m/z* 356.1547 [$(M + H)^+$ calc. for $C_{17}H_{24}ClFN_3O_2^+$: 356.1543].



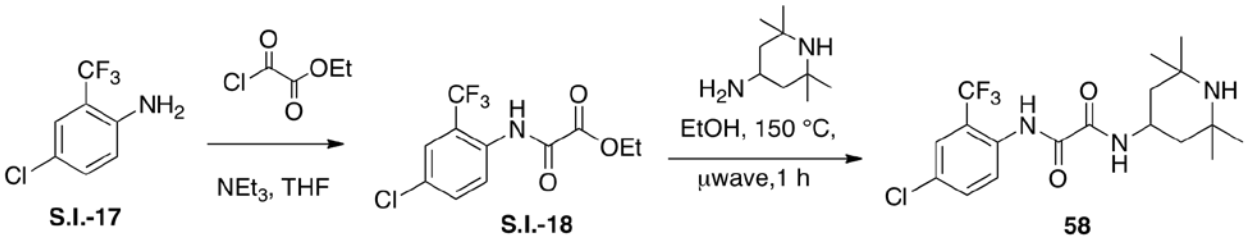
S.I.-13 S.I.-14 56

Compound 56. Analogue **56** was synthesized in 2 steps from **S.I.-13.** First, **S.I.-14** was prepared from **S.I.-13** employing the method described in the synthesis of **S.I.-1** in >90% yield and used directly without further purification. **S.I.-14** (152 mg, 0.58 mmol) was coupled to 4-amino-2,2,6,6-tetramethylpiperidine using the method described in the synthesis of **1** to afford **56** after recrystallization from EtOH (169 mg, 78%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.1 (bs, 1H), 8.95 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.51 (dd, J = 9.0, 2.0 Hz, 1H), 4.16 (tt, J = 8.5, 4.5 Hz, 1H), 1.59 (dd, J = 12.0, 3.5 Hz, 2H), 1.25 (t, J = 12.5 Hz, 2H), 1.16 (s, 6H), 1.04 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.4, 158.2, 132.8, 129.8, 129.0,

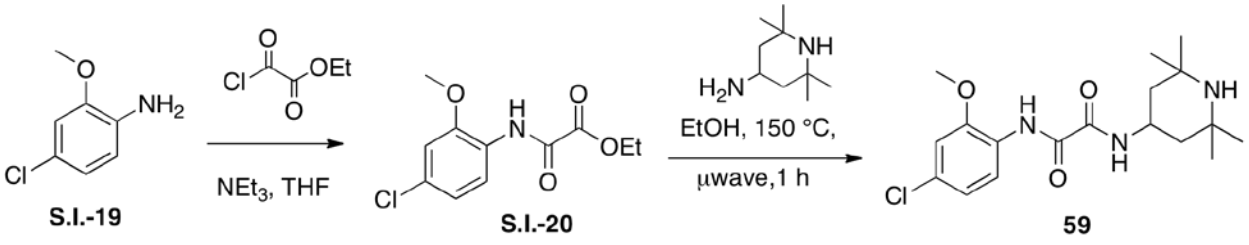
128.0, 126.5, 124.6, 50.3, 43.3, 43.0, 34.4, 28.6. HRMS (ES+) *m/z* 372.1243 [(M + H)$^+$ calc. for $C_{17}H_{24}Cl_2N_3O_2^+$: 372.1245].



Compond 57. Analogue **57** was synthesized in 2 steps from **S.I.-15.** First, **S.I.-16** was prepared from **S.I.-15** employing the method described in the synthesis of **S.I.-1** in >90% yield and used directly without further purification. **S.I.-16** (140 mg, 0.58 mmol) was coupled to 4-amino-2,2,6,6-tetramethylpiperidine using the method described in the synthesis of **1** to afford **57** after recrystallization from EtOH (88 mg, 43%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.1 (bs, 1H), 8.78 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 9.0, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.29 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.16 (tt, *J* = 9.0, 3.5 Hz, 1H), 2.26 (s, 3H), 1.59 (dd, *J* = 12.0, 3.5 Hz, 2H), 1.24 (t, *J* = 12.0 Hz, 2H), 1.16 (s, 6H), 1.04 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.9, 158.6, 134.3, 129.8, 125.9, 50.3, 43.4, 42.7, 34.5, 28.6, 17.2; HRMS (ES+) *m/z* 352.1805 [(M + H)$^+$ calc. for $C_{18}H_{27}ClN_3O_2^+$: 352.1792].

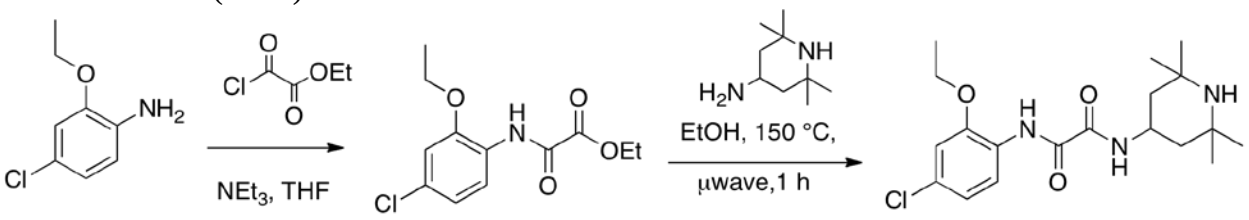


Compound 58. Analogue **58** was synthesized in 2 steps from **S.I.-17.** First, **S.I.-18** was prepared from **S.I.-17** employing the method described in the synthesis of **S.I.-1** in >90% yield and used directly without further purification. **S.I.-18** (171 mg, 0.58 mmol) was coupled to 4-amino-2,2,6,6-tetramethylpiperidine using the method described in the synthesis of **1** to afford **58** after recrystallization from EtOH (143 mg, 61%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.94 (bs, 1H), 8.95 (d, *J* = 8.3 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.88 (bs, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 4.16 (tt, *J* = 8.6, 4.3 Hz, 1H), 1.60 (dd, *J* = 12.2, 3.4 Hz, 2H), 1.27 (t, *J* = 12.2 Hz, 2H), 1.17 (s, 6H), 1.05 (s, 6H); HRMS (ES+) *m/z* 406.1508 [(M + H)$^+$ calc. for $C_{18}H_{24}ClF_3N_3O_2^+$: 406.1510].



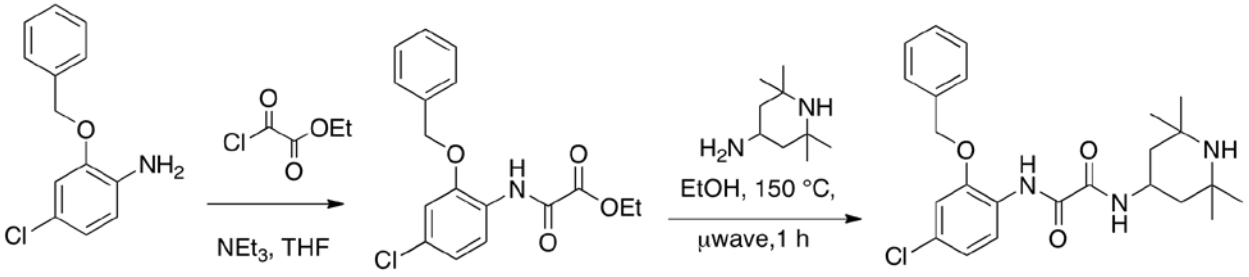
Compound 59. Analogue **59** was synthesized in 2 steps from **S.I.-19.** First, **S.I.-20** was prepared from **S.I.-19** employing the method described in the synthesis of **S.I.-1** in >90% yield and used directly without further purification. **S.I.-20** was coupled to 4-amino-2,2,6,6-tetramethylpiperidine using the method described in the synthesis of **1** to afford **59** after purification. ^{1}H NMR (DMSO, 500 MHz) δ 1.24-1.31 (m, 12H), 1.51 (m, 2H), 1.73 (m, 2H), 1.90 (s, 1H), 3.91 (s, 3H), 4.16 (m, 1H), 7.07 (dd, *J*=8.5, 2.0 Hz, 1H), 7.22 (d, *J*=2.0 Hz, 1H),

8.12 (d, *J*=8.5 Hz, 1H), 9.14 (brs, 1H), 9.84 (s, 1H). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 21.8, 27.1, 29.6, 33.0, 42.6, 43.1, 53.3, 53.4, 72.1, 113.3, 120.2, 120.7, 125.7, 129.9, 147.5, 156.9, 159.1. LCMS *m/z*: 367 $(M+H)^+$.



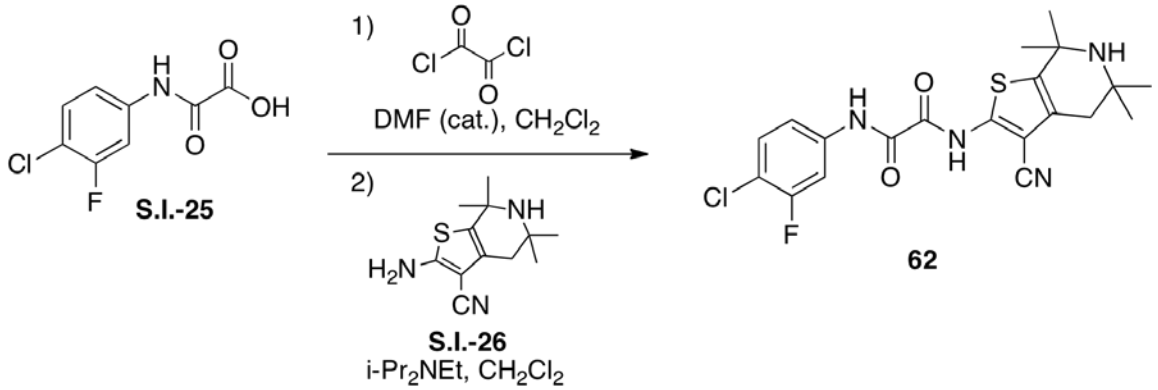
S.I.-21 S.I.-22 60

Compound 60. Analogue **60** was synthesized in 2 steps from **S.I.-21.** First, **S.I.-22** was prepared from **S.I.-21** employing the method described in the synthesis of **S.I.-1** in >90% yield and used directly without further purification. **S.I.-22** was coupled to 4-amino-2,2,6,6-tetramethylpiperidine using the method described in the synthesis of **1** to afford **60** after purification. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.85 (m, 2H), 0.97-1.26 (m, 12H), 1.29-1.55 (m, 4H), 1.92 (m, 2H), 3.72 (m, 1H), 4.13 (m, 2H), 4.25 (m, 1H), 7.01 (d, *J*=6.7 Hz, 1H), 7.34 (m, 1H), 7.47 (s, 1H), 9.23 (s, 1H). LCMS *m/z*: 382 (M^++H).



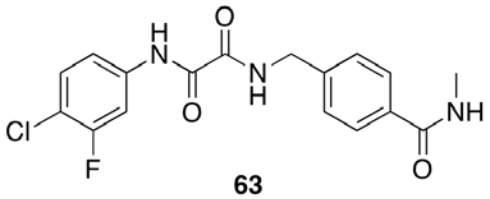
S.I.-23 S.I.-24 61

Compound 61. Analogue **61** was synthesized in 2 steps from **S.I.-23.** First, **S.I.-24** was prepared from **S.I.-23** employing the method described in the synthesis of **S.I.-1** in >90% yield and used directly without further purification. **S.I.-24** was coupled to 4-amino-2,2,6,6-tetramethylpiperidine using the method described in the synthesis of **1** to afford **61** after purification.^{1}H-NMR (DMSO, 500 MHz) δ 1.37 (s, 6H), 1.41 (s, 6H), 1.69 (m, 2H), 1.82 (m, 2H), 4.18 (m, 1H), 5.26 (s, 2H), 7.09 (d, *J*=2.0 Hz, 1H), 7.35-7.49 (m, 5H), 7.84 (d, *J*=11.0 Hz, 1H), 8.17 (d, *J*=9.0 Hz, 1H), 8.96 (d, *J*=11.0 Hz, 1H), 9.34 (d, *J*=9.0 Hz, 1H), 9,84 (s, 1H). LCMS *m/z*: 444 (M^++H).



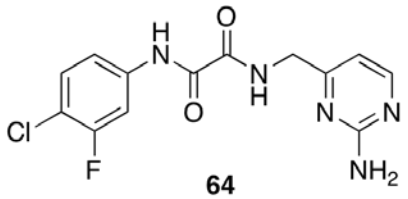
S.I.-25 S.I.-26 62

Compound 62. To a solution containing the free acid of **S.I.-25**, prepared by basic hydrolysis of **S.I.-1** (0.100 g, 45.9 mmol) in 5 mL of CH_2Cl_2 at room temperature was added oxalyl chloride (0.12 mL, 1.38 mmol) and 1 drop of DMF. Reaction was stirred until gas evolution ceased and the solution cleared (~2 hr). Excess solvent was removed under reduced pressure followed by addition of **S.I.-26** in 10 mL of CH_2Cl_2 followed by iPr_2Net (0.24 mL, 1.38 mmol). The reaction was stirred for 18 hr and quenched with $NaHCO_{3(aq)}$. The aqueous phase was then extracted with dichloromethane (1X) and ethyl acetate (1X). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (MeOH in CH_2Cl_2 1% → 3%) gave 0.07 g (35% yield) of **62** as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.61 (s, 1H), 8.80 (br, 1H), 7.95 (dd, *J* = 12.0, 2.5 Hz, 1H), 7.62 (m, 1H), 7.53 (t, *J* = 8.5 Hz, 1H), 2.68 (m, 2H), 1.62 (s, 6H), 1.39 (s, 6H); high resolution mass spectrum (ES–) *m/z* 433.0894 [(M – H)$^-$; calcd for $C_{20}H_{19}N_4O_2FClS$: 433.0901].



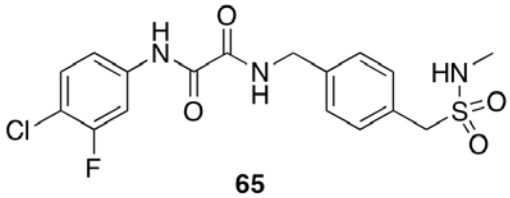
63

Compound 63. Prepared in an analogous manner to **1** above from **S.I.-1** to give **63** in 81% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 9.65 (t, *J* = 6.5 Hz, 1H), 8.39 (d, *J* = 7.0 Hz, 1H), 7.94 (dd, *J* = 11.5, 2.0 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.73 (m, 1H), 7.58 (t, *J* = 8.5 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.43 (d, *J* = 6.5 Hz, 2H), 2.77 (d, *J* = 8.5 Hz, 3H); high resolution mass spectrum (ES–) *m/z* 362.0698 [(M – H)$^-$; calcd for $C_{17}H_{14}N_3O_3FCl$: 362.0708].



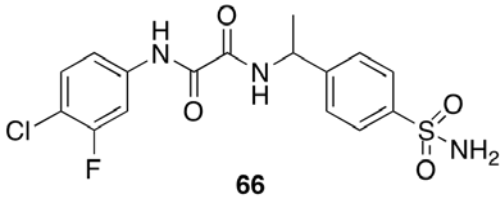
64

Compound 64. Prepared in an analogous manner to **1** above from **S.I.-1** to give **64** in 55% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.06 (s, 1H), 9.47 (t, *J* = 6.0 Hz, 1H), 8.16 (d, *J* = 5.0 Hz, 1H), 7.95 (dd, *J* = 12.0, 2.5 Hz, 1H), 7.74 (m, 1H), 7.59 (t, *J* = 9.0 Hz, 1H), 6.62 (s, 2H), 6.46 (d, *J* = 5.5 Hz, 1H), 4.24 (d, *J* = 6.0 Hz, 2H); high resolution mass spectrum (ES+) *m/z* 324.0653 [(M + H)$^+$; calcd for $C_{13}H_{12}N_5O_2FCl$: 324.0664].



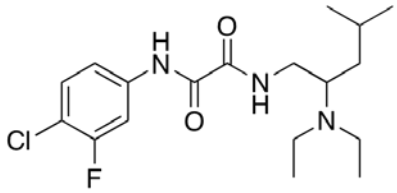
65

Compound 65. Prepared in an analogous manner to **1** above from **S.I.-1** to give **65** in 80% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 9.62 (t, *J* = 6.0 Hz, 1H), 7.93 (dd, *J* = 12.0, 2.5 Hz, 1H), 7.72 (m, 1H), 7.57 (t, *J* = 6.5 Hz, 1H), 7.31 (m, 4H), 6.89 (q, *J* = 5.0 Hz, 2H), 4.39 (d, *J* = 6.5 Hz, 2H), 4.29 (s, 2H), 2.56 (d, *J* = 4.5 Hz, 3H); high resolution mass spectrum (ES–) *m/z* 412.0549 [(M – H)$^-$; calcd for $C_{17}H_{16}N_3O_4FCl$: 412.0534].



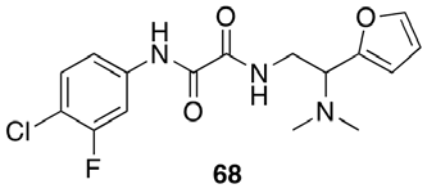
66

Compound 66. Prepared in an analogous manner to **1** above from **S.I.-1** to give **66** in 49% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.97 (s, 1H), 9.59 (t, J = 8.0 Hz, 1H), 7.92 (dd, J = 11.5, 2.0 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.70 (m, 1H), 7.56 (m, 3H), 7.31 (s, 2H), 5.07 (m, 1H), 1.50 (d, J = 7.0 Hz, 1H); high resolution mass spectrum (ES–) m/z 398.0396 [(M – H)$^-$; calcd for $C_{16}H_{14}N_3O_4FClS$: 398.0378].



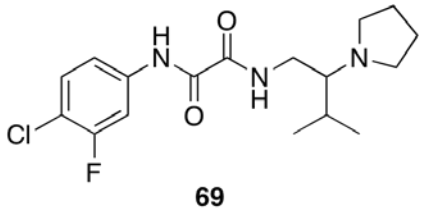
67

Compound 67. Prepared in an analogous manner to **1** above from **S.I.-1** to give **66** in 61% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.79 (t, J = 6.0 Hz, 1H), 7.95 (dd, J = 12.0, 2.5 Hz, 1H), 7.74 (m, 1H), 7.57 (t, J = 8.5 Hz, 1H), 3.12 (m, 1H), 2.87 (m, 1H), 2.46 (m, 4H), 1.65 (m, 1H), 1.30 (m, 1H), 0.97 (t, J = 7.0 Hz, 6H), 0.05 (dd, J = 12.5, 6.5 Hz, 6H); high resolution mass spectrum (ES–) m/z 370.1711 [(M – H)$^-$; calcd for $C_{18}H_{26}N_3O_2FCl$: 370.1698].



68

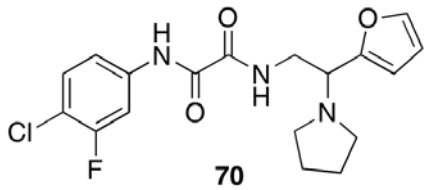
Compound 68. Prepared in an analogous manner to **1** above from **S.I.-1** to give **68** in 41% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 8.83 (d, J = 5.5 Hz, 1H), 7.94 (dd, J = 12.0, 2.5 Hz, 1H), 7.72 (m, 1H), 7.63 (m, 1H), 7.57 (t, J = 8.5 Hz, 1H), 6.43 (dd, J = 3.0, 2.0 Hz, 1H), 6.34 (d, J = 3.5 Hz, 1H), 3.96 (dd, J = 8.5, 6.5 Hz, 1H), 3.65 (m, 1H), 3.49 (m, 1H), 2.11 (s, 6H); high resolution mass spectrum (ES+) m/z 354.1006 [(M + H)$^+$; calcd for $C_{16}H_{18}N_3O_3FCl$: 354.1021].



69

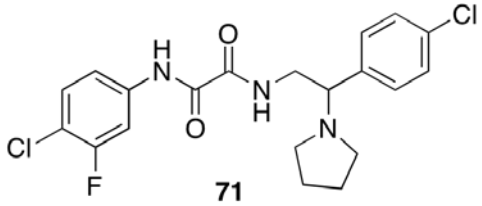
Compound 69. Prepared in an analogous manner to **1** above from **S.I.-1** to give **69** in 83% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 8.70 (t, J = 6.0 Hz, 1H), 7.94 (dd, J = 12.0, 2.5 Hz, 1H), 7.73 (m, 1H), 7.59 (t, J = 8.5 Hz, 1H), 3.29 (m, 2H), 2.58 (m, 4H), 2.38 (q, J = 5.0 Hz, 1H), 1.89 (m, 1H), 1.65 (m, 4H), 0.94 (d, J = 6.5 Hz, 3H), 0.87

(d, J = 6.5 Hz, 3H); high resolution mass spectrum (ES+) *m/z* 356.1536 [(M + H)$^+$; calcd for $C_{17}H_{21}N_3O_2FCl$: 356.1541].



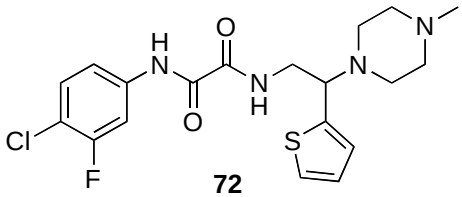
70

Compound 70. Prepared in an analogous manner to **1** above from **S.I.-1** to give **70** in 24% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 8.82 (br, 1H), 7.92 (dd, J = 12.0, 2.5 Hz, 1H), 7.71 (m, 1H), 7.60-7.55 (m, 2H), 6.40 (s, 1H), 6.31 (s, 1H), 3.99 (m, 1H), 3.59 (m, 2H), 2.50 (m, 4H), 1.60 (s, 4H); high resolution mass spectrum (ES–) *m/z* 378.1022 [(M – H)$^-$; calcd for $C_{18}H_{18}N_3O_3FCl$: 378.1021].



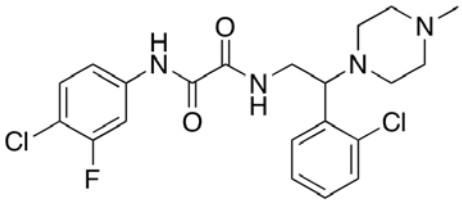
71

Compound 71. Prepared in an analogous manner to **1** above from **S.I.-1** to give **71** in 48% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 8.69 (t, J = 6.0 Hz, 1H), 7.90 (dd, J = 11.5, 2.0 Hz, 1H), 7.69 (m, 1H), 7.55 (t, J = 8.5 Hz, 1H), 7.36-7.29 (m, 4H), 3.67 (m, 1H), 3.47 (m, 2H), 2.50 (m, 2H), 2.34 (m, 2H), 1.65 (m, 4H); high resolution mass spectrum (ES+) *m/z* 424.0978 [(M + H)$^+$; calcd for $C_{20}H_{21}N_3O_2FCl_2$: 424.0995].



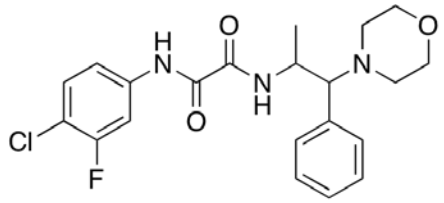
72

Compound 72. Prepared in an analogous manner to **1** above from **S.I.-1** to give **72** in 67% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 8.82 (t, J = 6.0 Hz, 1H), 7.94 (dd, J = 11.5, 2.0 Hz, 1H), 7.73 (m, 1H), 7.57 (t, J = 9.0 Hz, 1H), 7.45 (dd, J = 5.0, 1.0 Hz, 1H), 7.02 (m, 2H), 4.17 (t, J = 7.5 Hz, 1H), 3.70 (m, 1H), 3.55 (m, 1H), 2.51 (m, 2H), 2.30 (m, 6H), 2.10 (s, 3H); high resolution mass spectrum (ES+) *m/z* 425.1215 [(M + H)$^+$; calcd for $C_{19}H_{22}N_4O_2SFCl$: 425.1214].

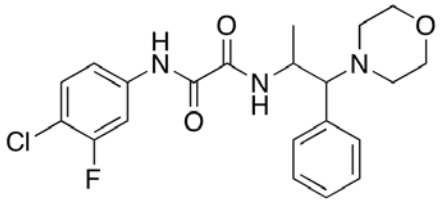


73

Compound 73. Prepared in an analogous manner to **1** above from **S.I.-1** to give **73** in 60% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.75 (t, J = 5.5 Hz, 1H), 7.92 (dd, J = 11.5, 2.0 Hz, 1H), 7.70 (m, 1H), 7.56 (t, J = 9.0 Hz, 1H), 7.45 (m, 2H), 7.35 (m, 2H), 4.34 (t, J = 7.0 Hz, 1H), 3.77 (m, 1H), 3.49 (m, 1H), 2.44 (m, 4H), 2.27 (m, 4H), 2.10 (s, 3H); high resolution mass spectrum (ES+) *m/z* 453.1247 [(M + H)$^+$; calcd for $C_{21}H_{24}N_4O_2FCl_2$: 453.1260].

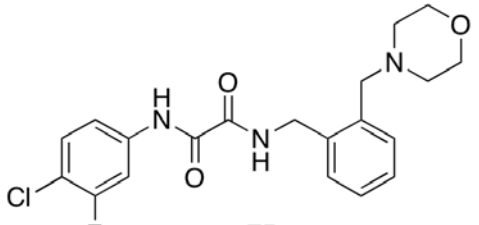


74a



74b

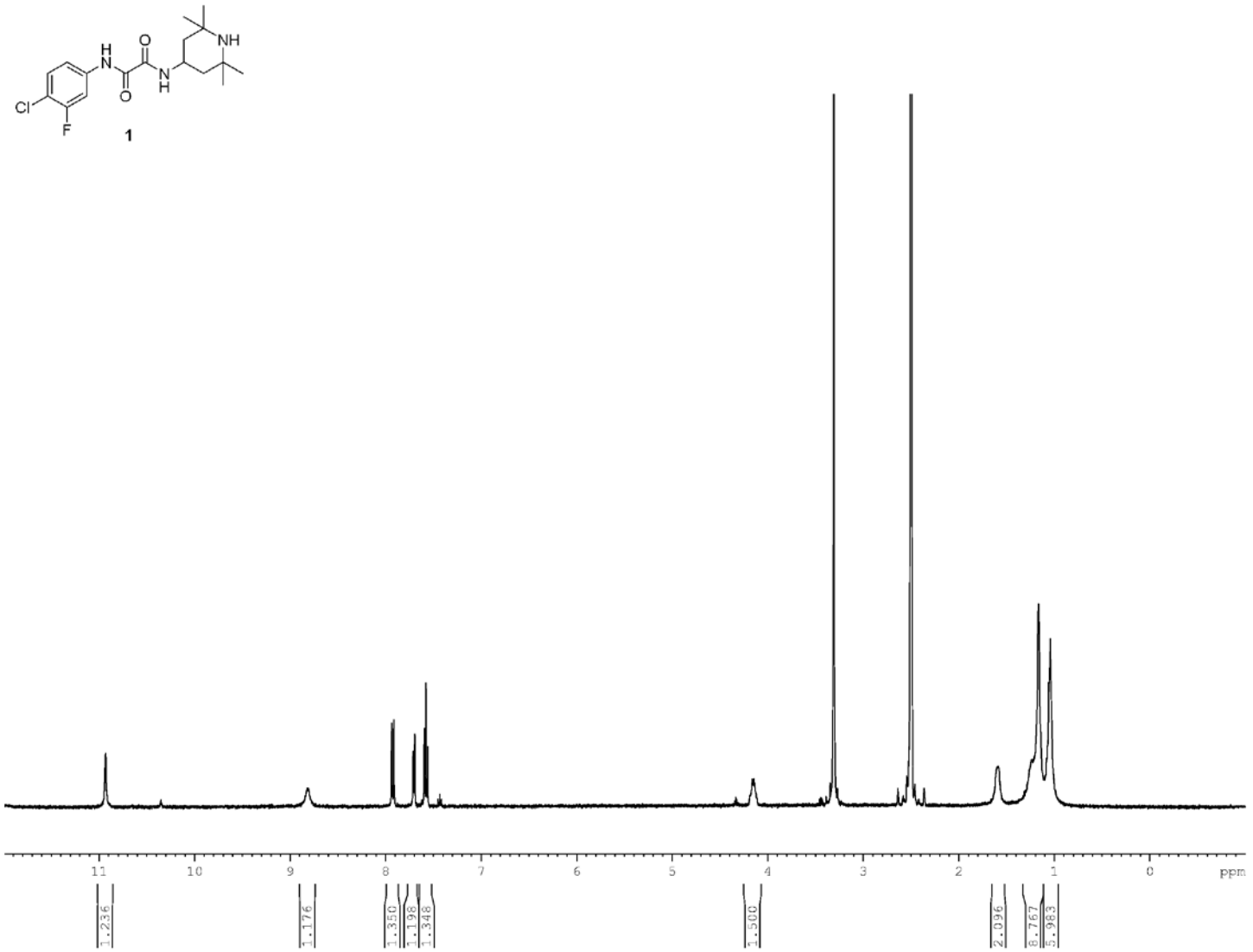
Compounds 74a and 74b. Prepared in an analogous manner to **1** above from **S.I.-1**. Purification by flash chromatography on silica gel (hexanes:ethyl acetate 4:1 → 3:1) gave **74a** in 18% yield as a colorless crystalline solid (mixture of enantiomers); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.76 (d, *J* = 7.5 Hz, 1H), 7.98 (dd, *J* = 12.0, 2.5 Hz, 1H), 7.78 (m, 1H), 7.59 (t, *J* = 8.5 Hz, 1H), 7.40 (t, *J* = 7.0 Hz, 2H), 7.35 (m, 1H), 7.21 (d, *J* = 7.0 Hz, 2H), 4.47 (m, 1H), 3.62 (d, *J* = 10.5 Hz, 1H), 3.49 (m, 4H), 2.36 (m, 2H), 2.19 (m, 2H), 0.96 (d, *J* = 6.5 Hz, 3H); high resolution mass spectrum (ES+) *m/z* 420.1487 [(M + H)$^+$; calcd for $C_{21}H_{24}N_3O_3FCl$: 420.1490]; and **74b** in 25% yield as a colorless crystalline solid (mixture of enantiomers); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.65 (d, *J* = 9.5 Hz, 1H), 7.86 (dd, *J* = 11.5, 2.0 Hz, 1H), 7.65 (m, 1H), 7.53 (t, *J* = 9.0 Hz, 1H), 7.31 (t, *J* = 7.0 Hz, 2H), 7.25 (m, 1H), 7.15 (d, *J* = 7.0 Hz, 2H), 4.59 (m, 1H), 3.70 (d, *J* = 10.0 Hz, 1H), 3.54 (m, 4H), 2.32 (m, 2H), 2.19 (m, 2H), 1.29 (d, *J* = 6.5 Hz, 3H); high resolution mass spectrum (ES+) *m/z* 420.1497 [(M + H)$^+$; calcd for $C_{21}H_{24}N_3O_3FCl$: 420.1490]. Note, although separable, the relative stereochemistry in **74a** and **74b** could not be unambiguously determined. Neither diastereomer displayed biological activity so further efforts to determine the relative stereochemistry were not pursued.



75

Compound 75. Prepared in an analogous manner to **1** above from **S.I.-1** to give **75** in 73% yield as a colorless crystalline solid; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 9.60 (t, *J* = 6.5 Hz, 1H), 7.91 (dd, *J* = 12.0, 2.5 Hz, 1H), 7.74 (m, 1H), 7.58 (t, *J* = 8.5 Hz, 1H), 7.34-7.25 (m, 4H), 4.55 (d, *J* = 6.5 Hz, 1H), 3.64 (t, *J* = 4.5 Hz, 1H), 3.57 (s, 2H), 2.40 (br, 4H); high resolution mass spectrum (ES+) *m/z* 406.1320 [(M + H)$^+$; calcd for $C_{20}H_{22}N_3O_3FCl$: 406.1334].

Compounds 76 – 88. Standard procedures were employed to synthesize compounds **76 – 88** (Table 4, p. S.I.-5), following the general procedures outlined in the syntheses of **S.I.-1** and **1**. The identity and purity of **76 – 88** was established by LC-MS analysis before the compounds were employed in viral entry assays. Given that these compounds were inactive, further characterization was not conducted.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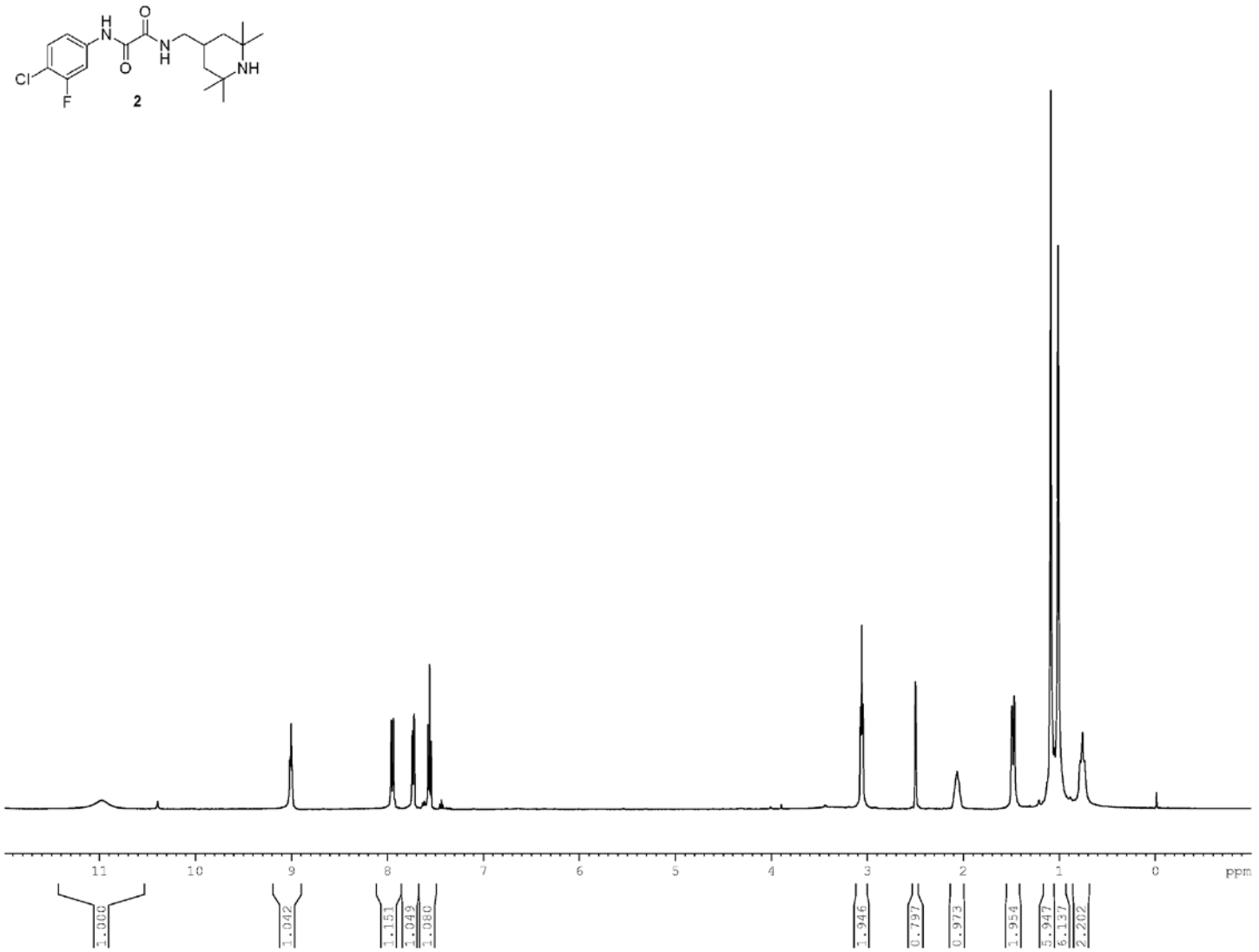
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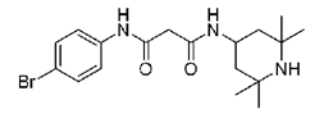
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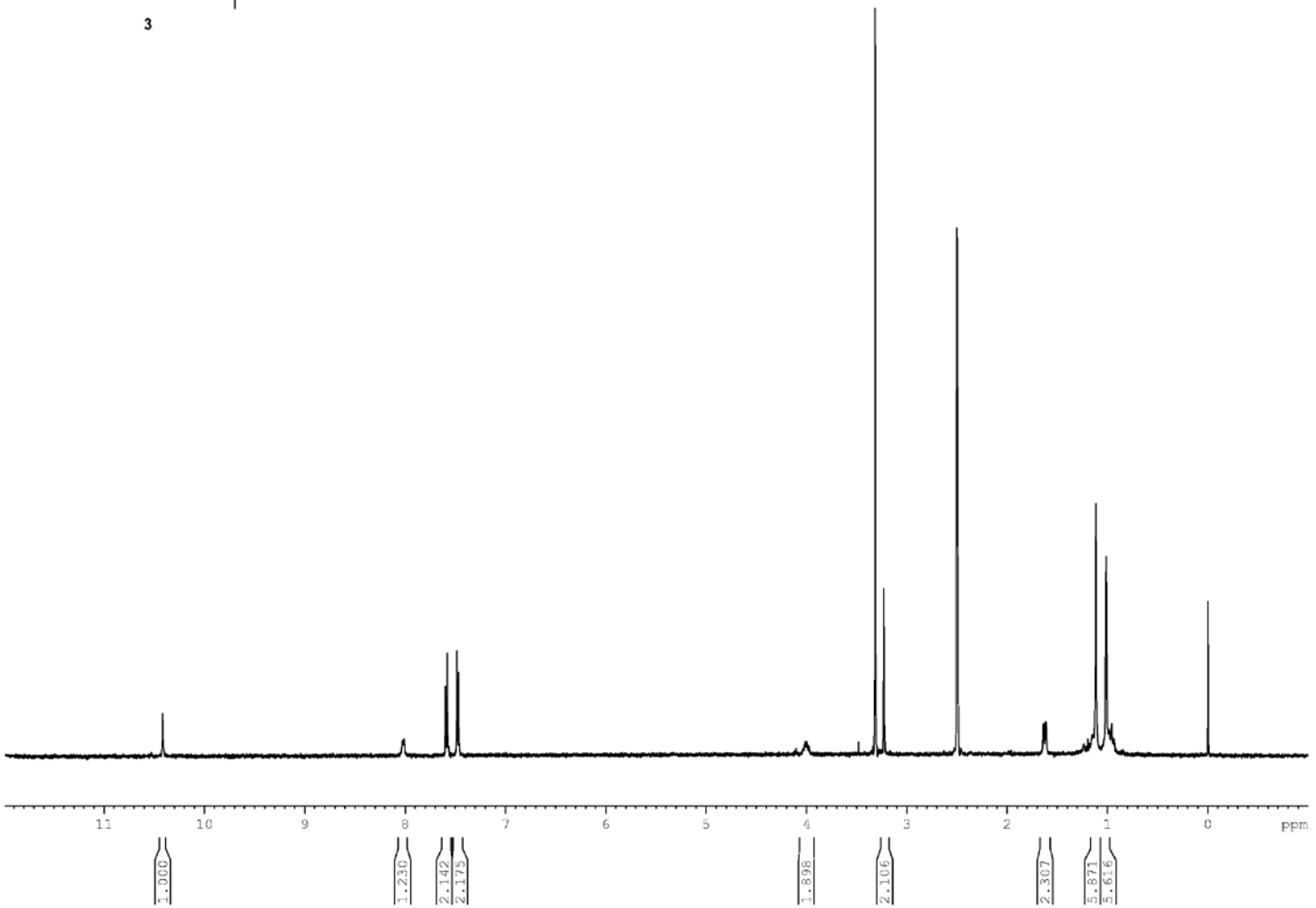
NH

3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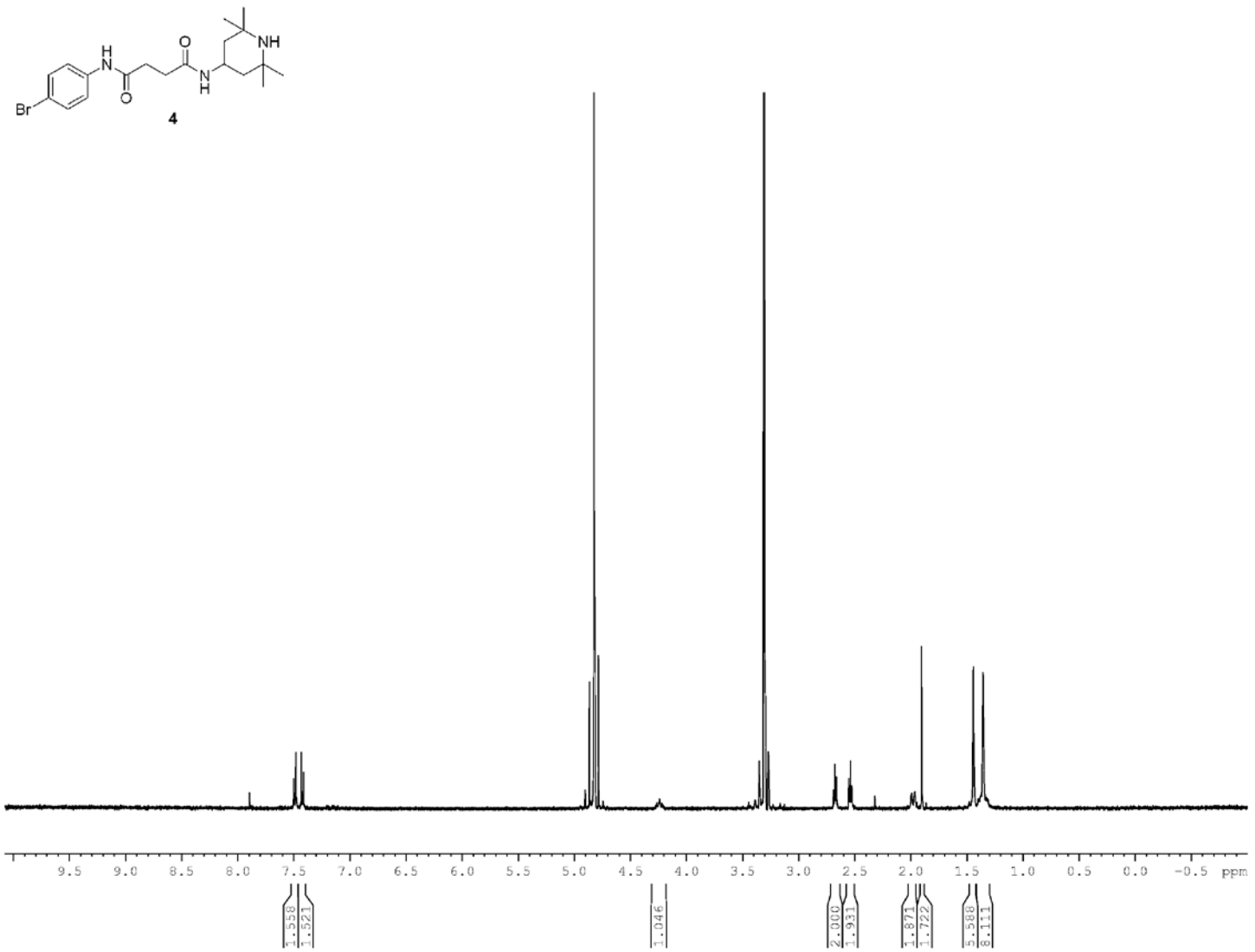
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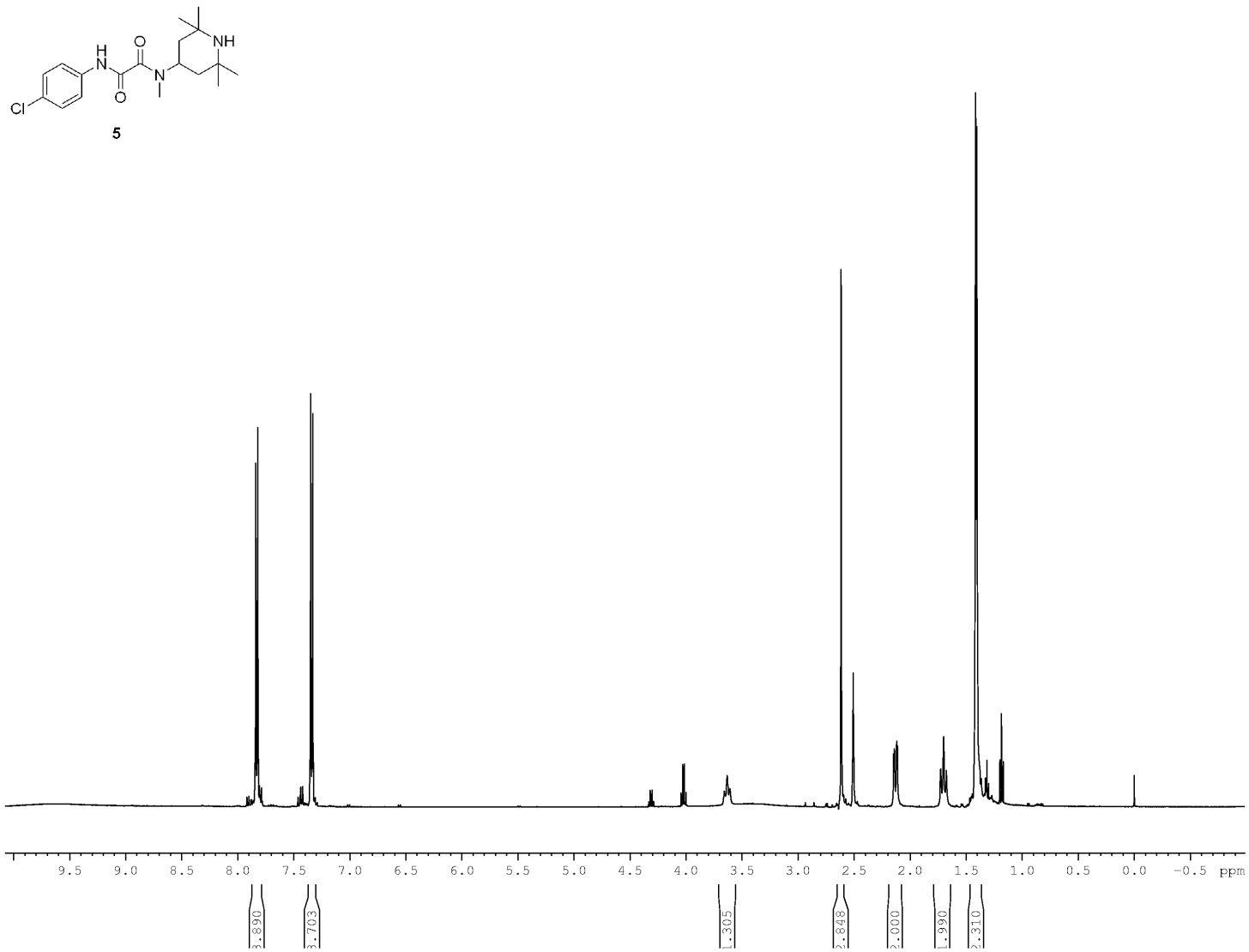
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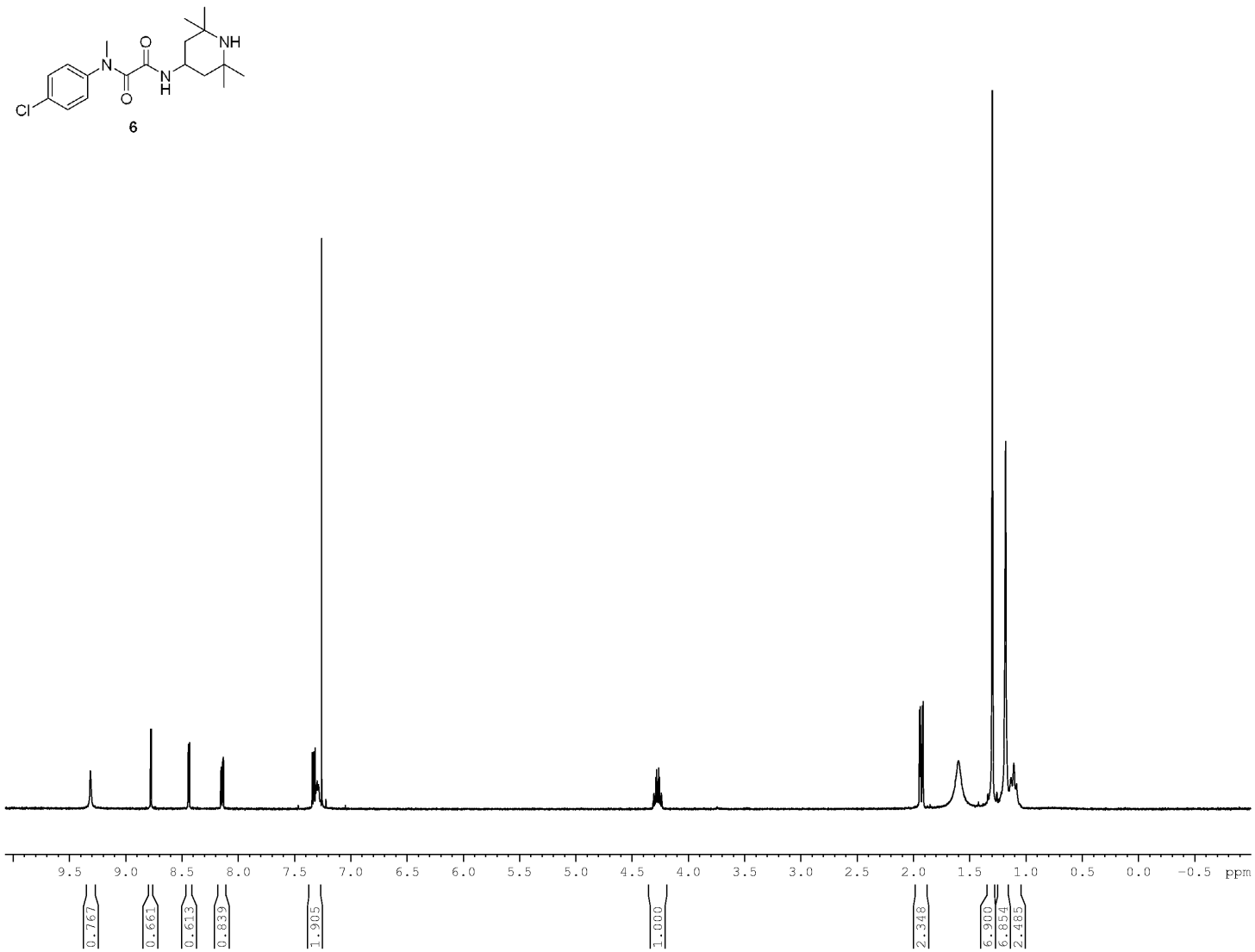
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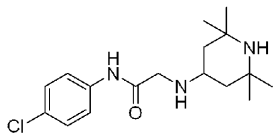
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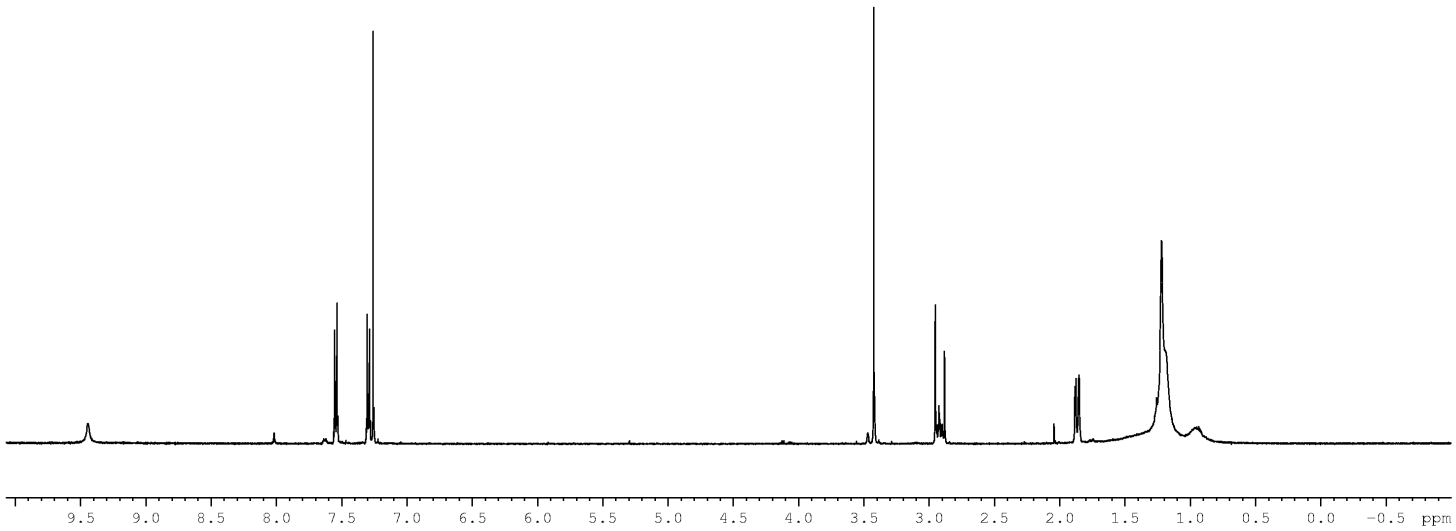
7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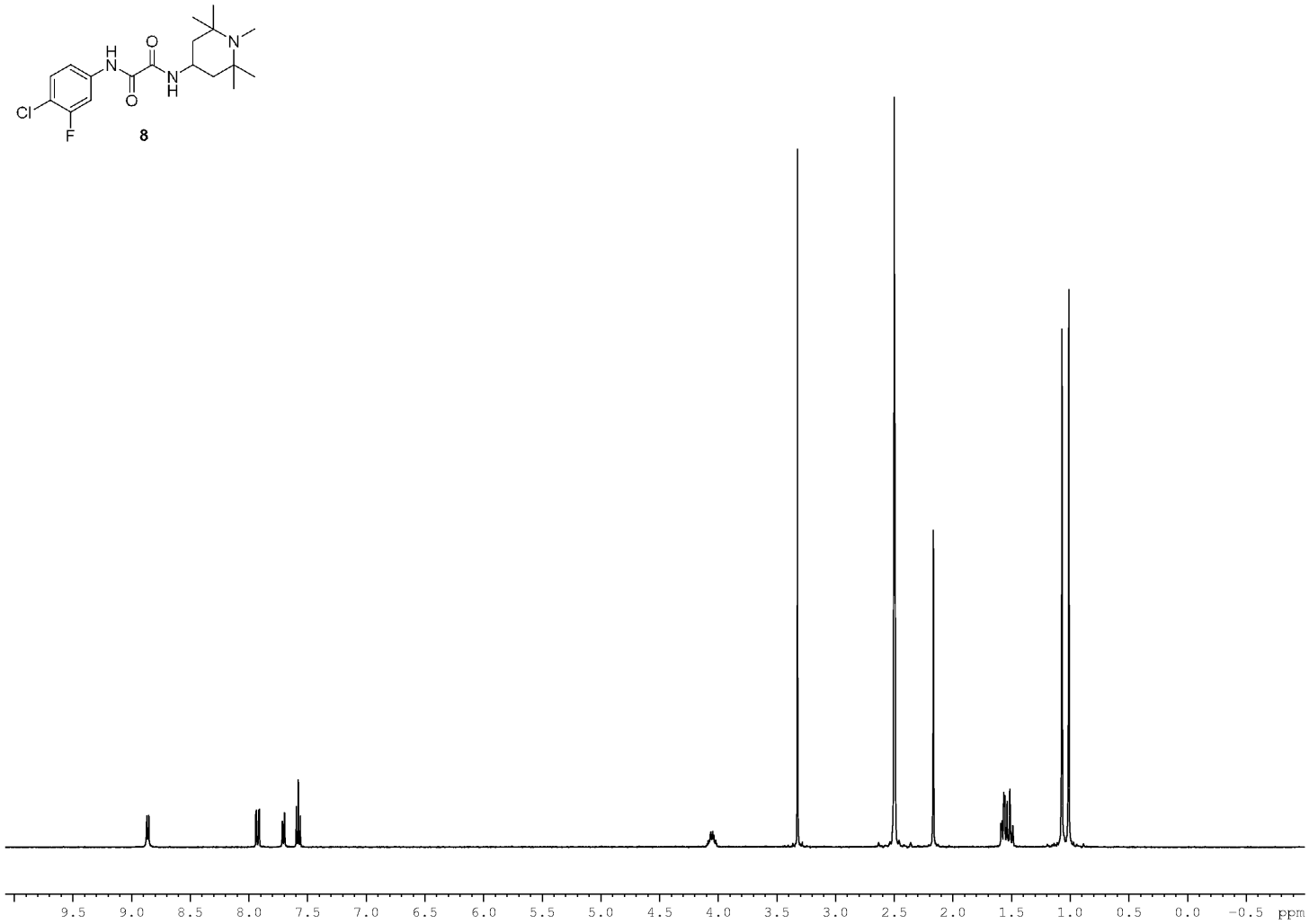
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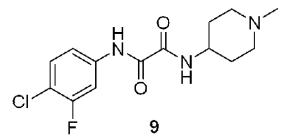
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Cl
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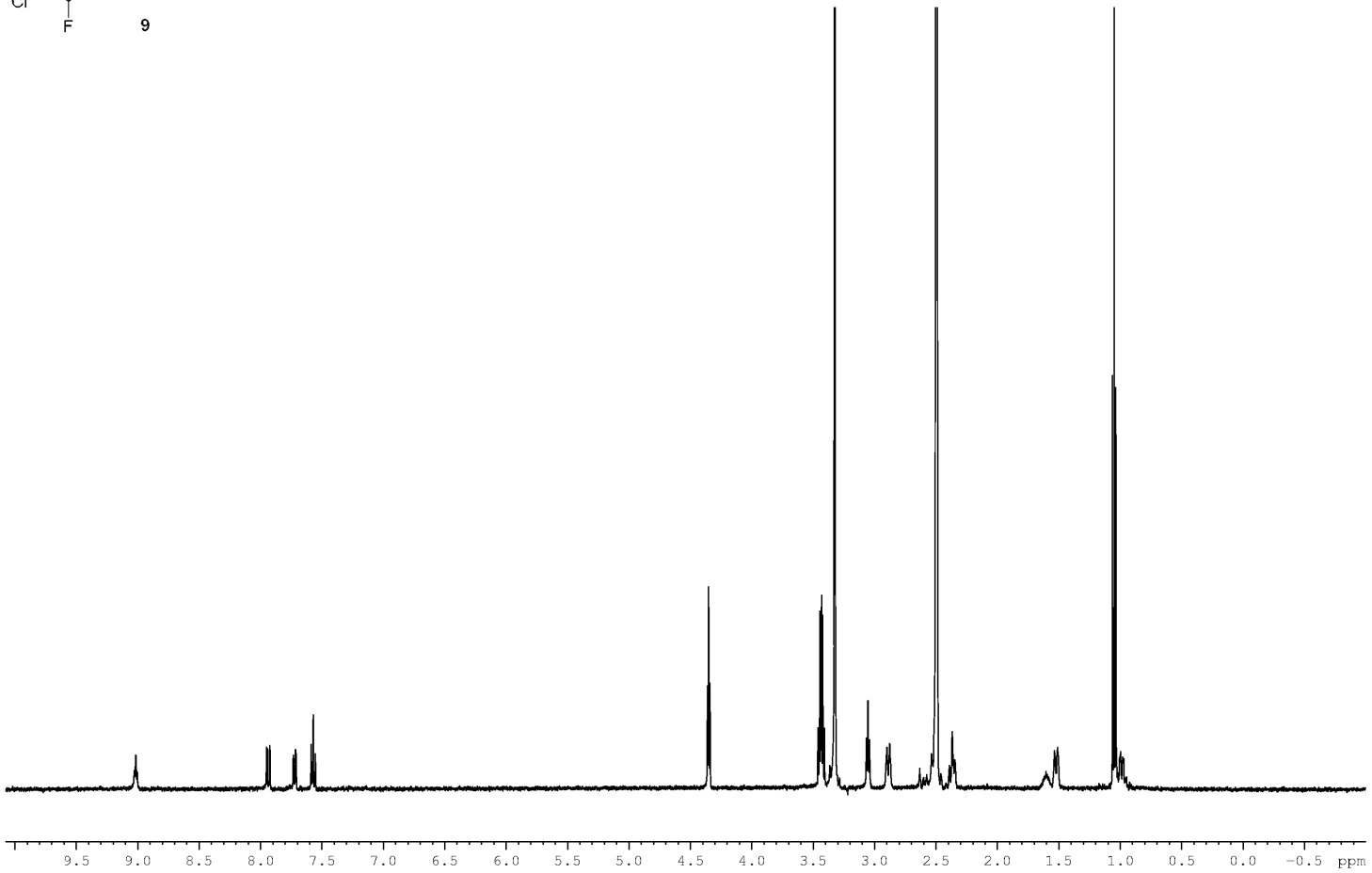
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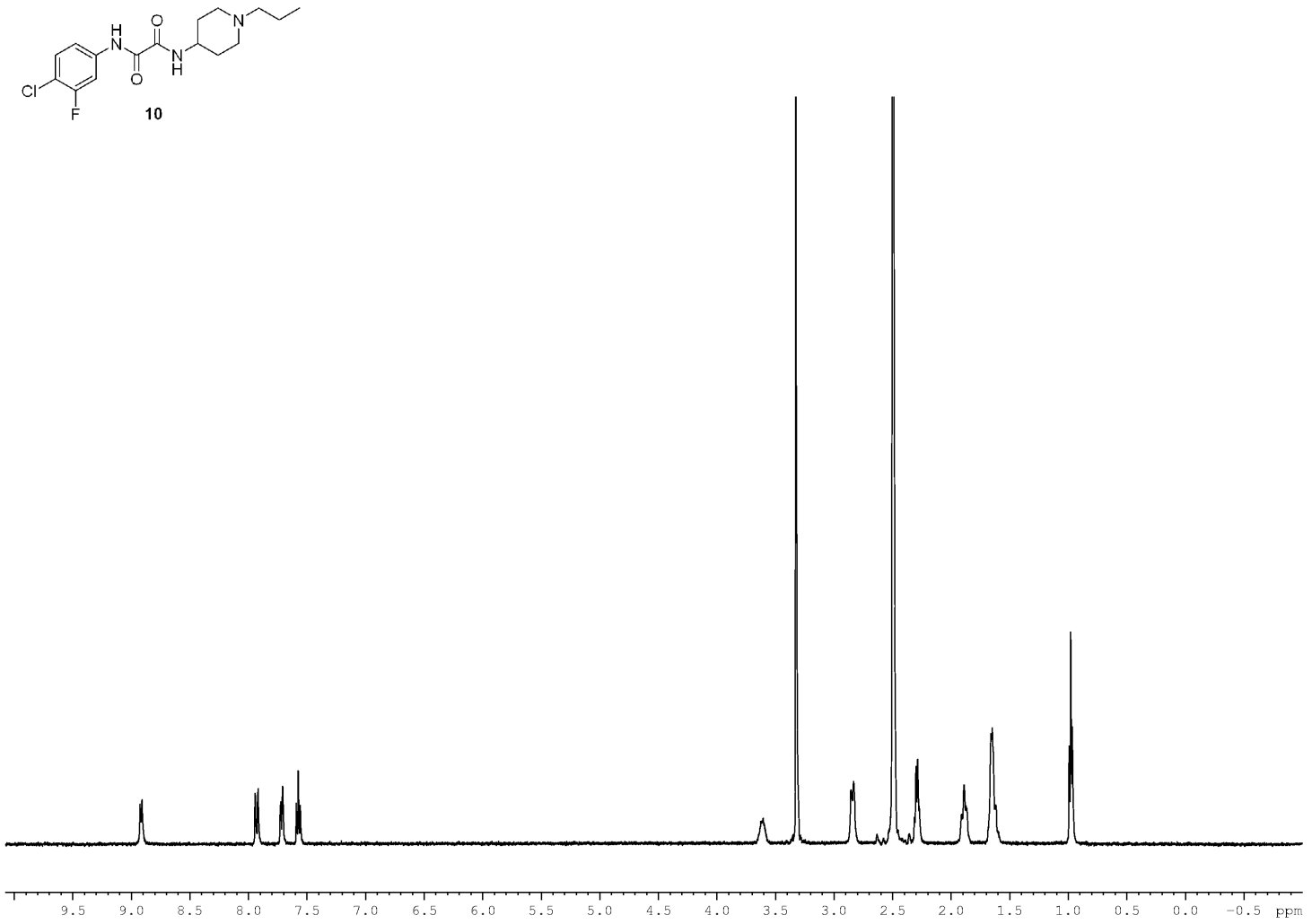
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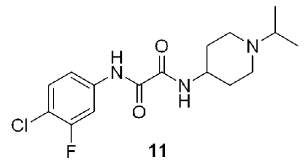

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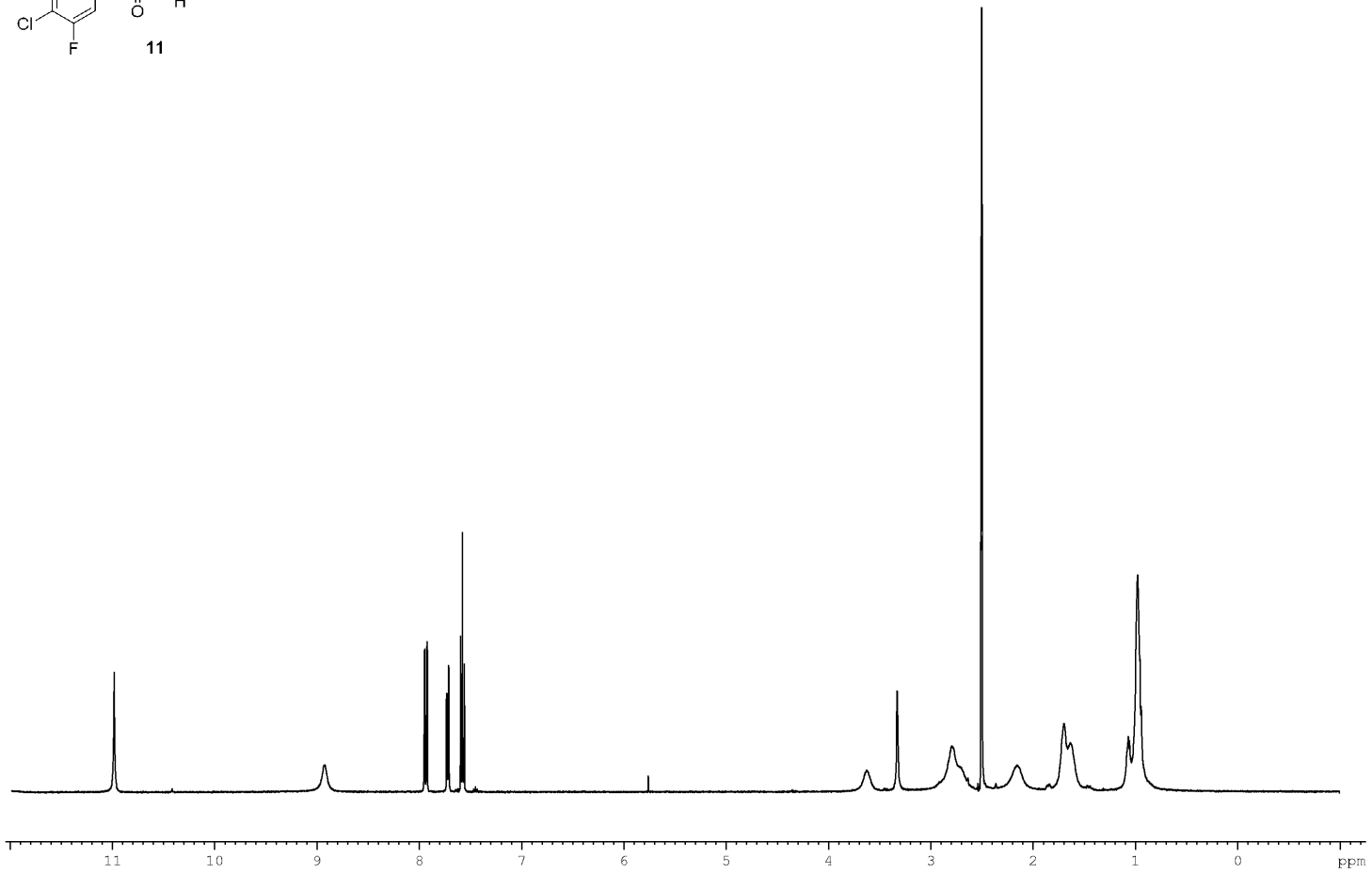

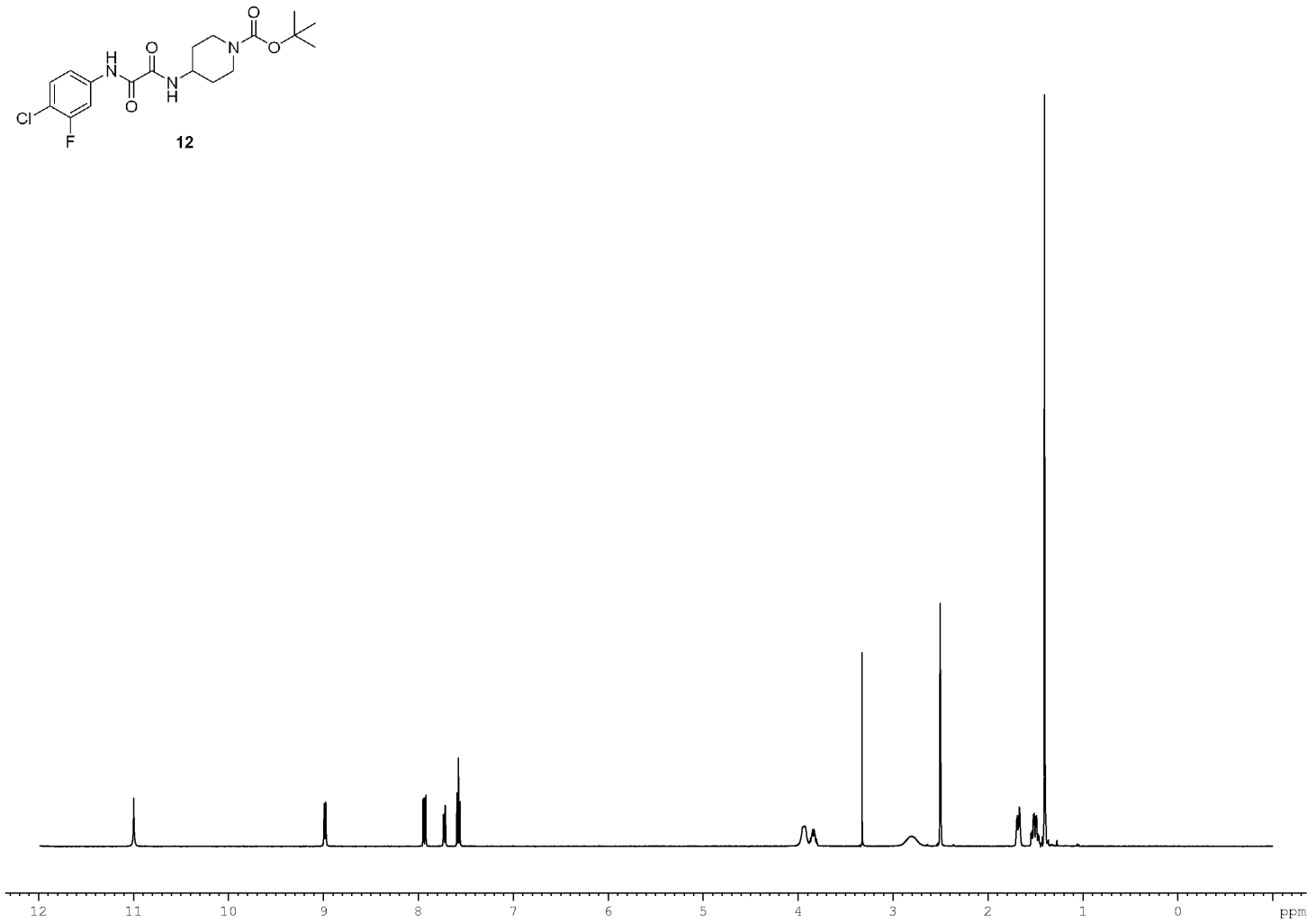
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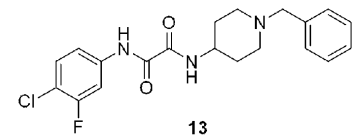
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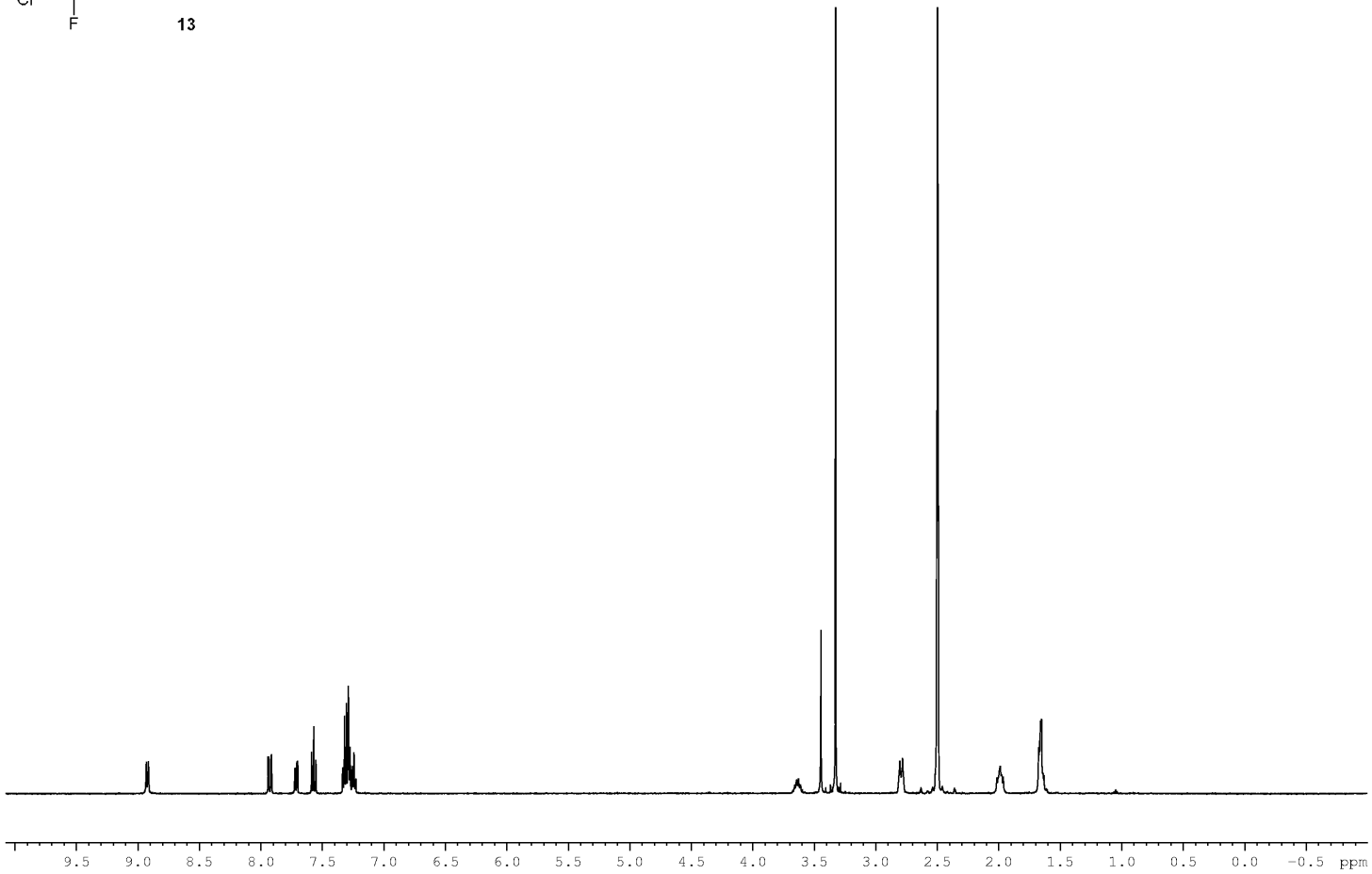
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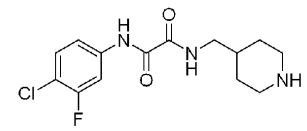
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NH
Cl
F

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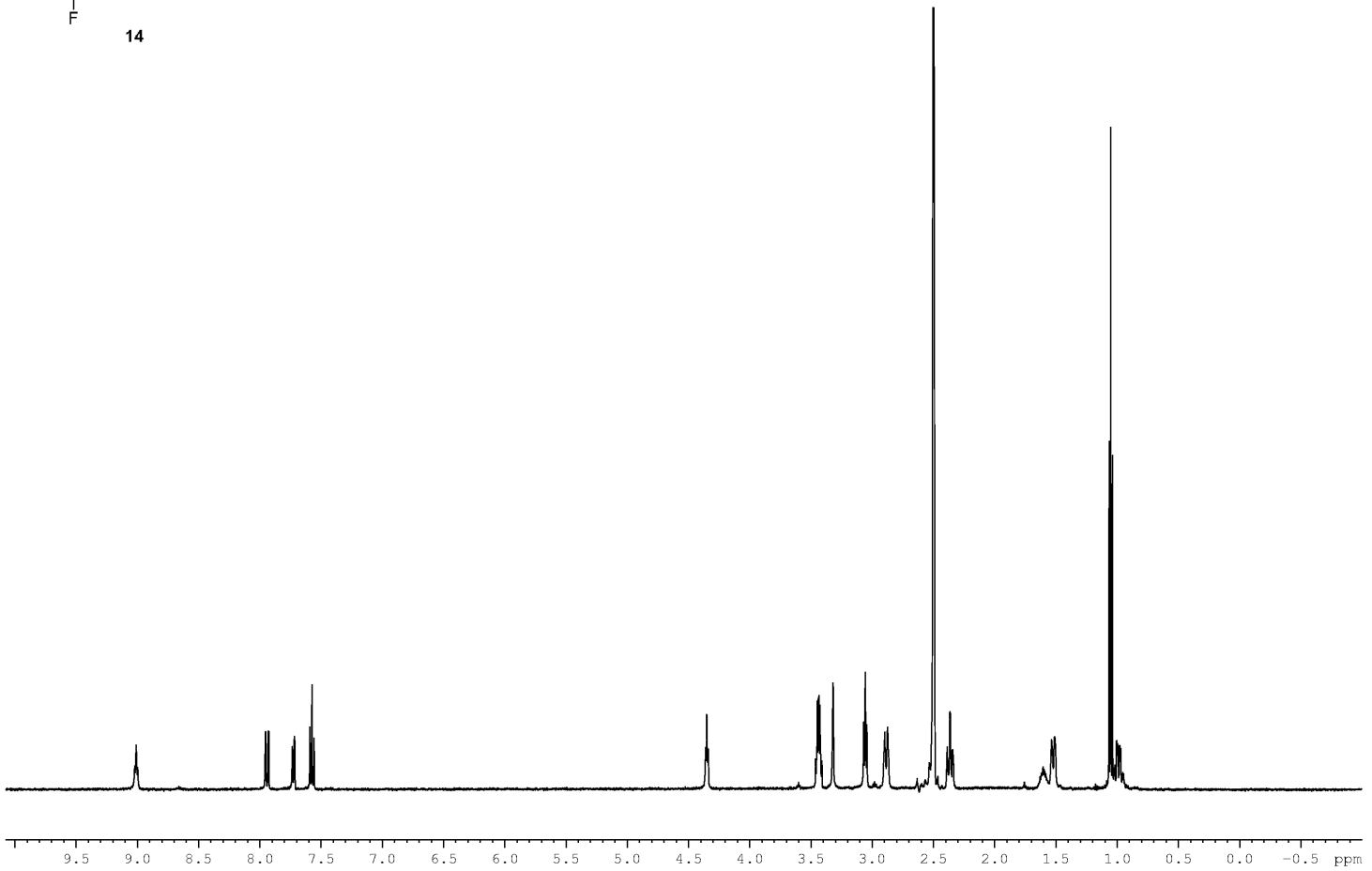
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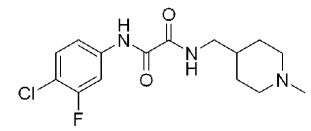
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Cl
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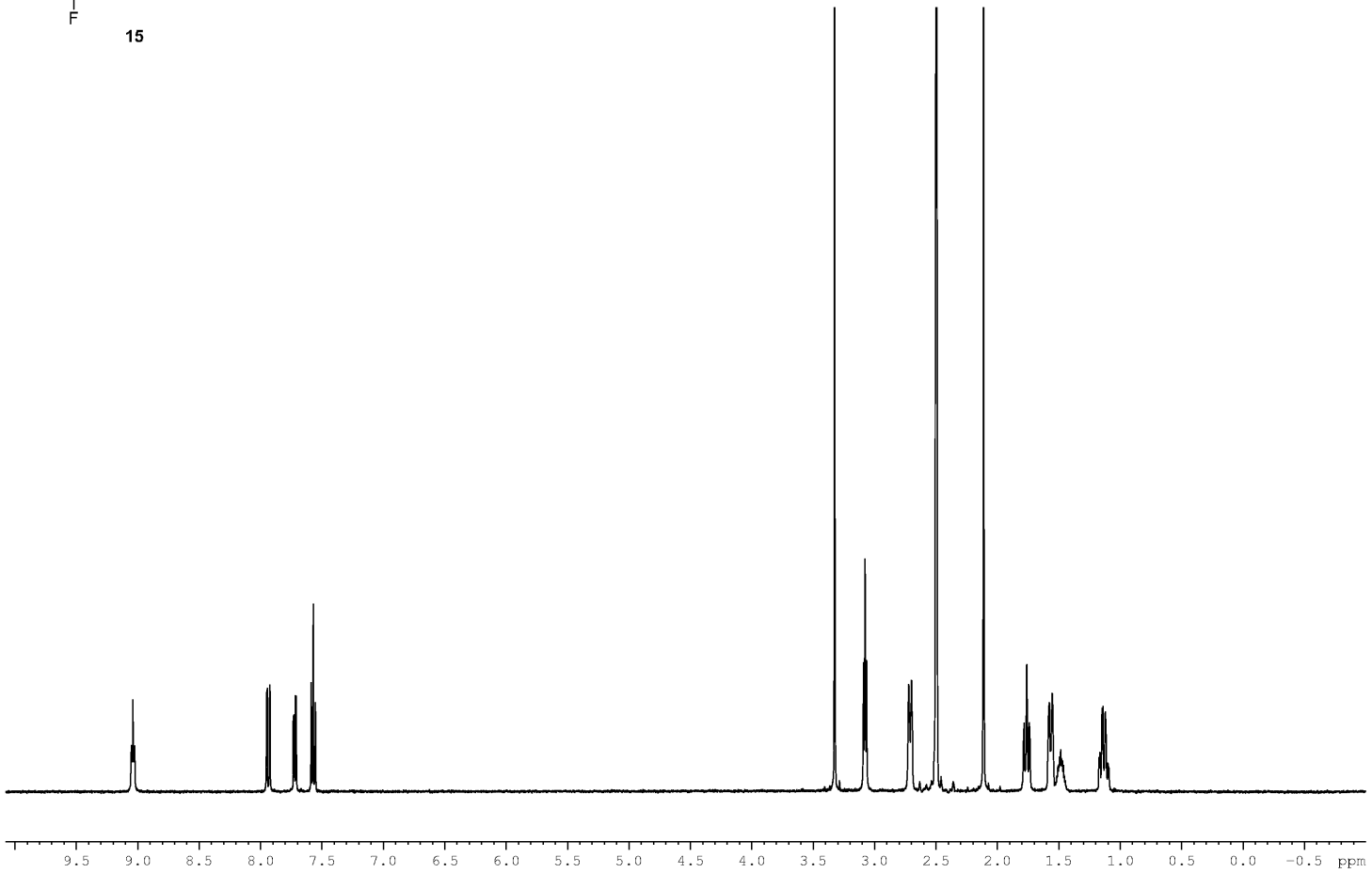
N

15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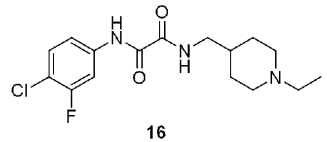
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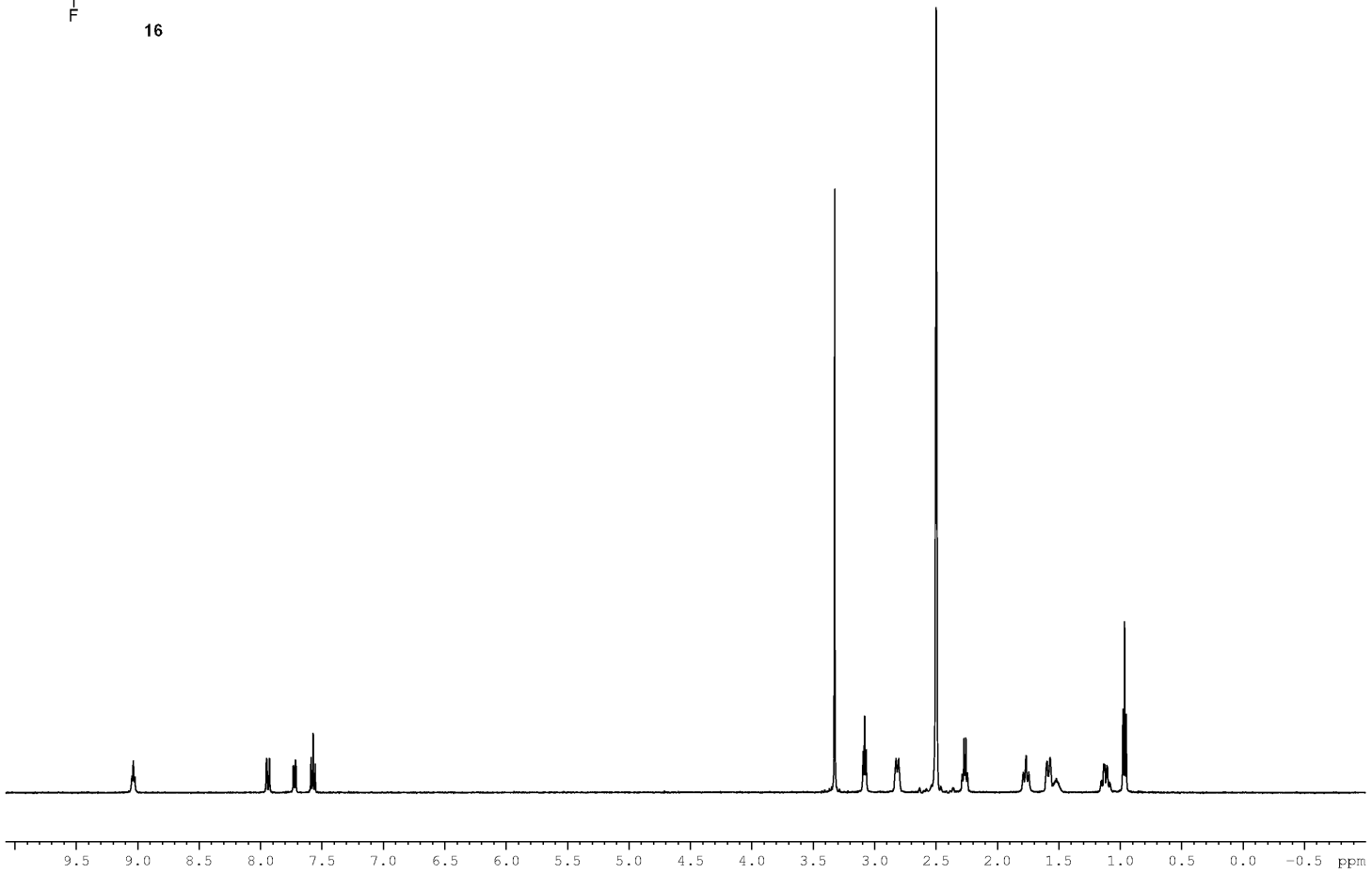
16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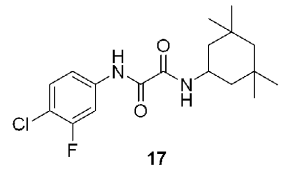
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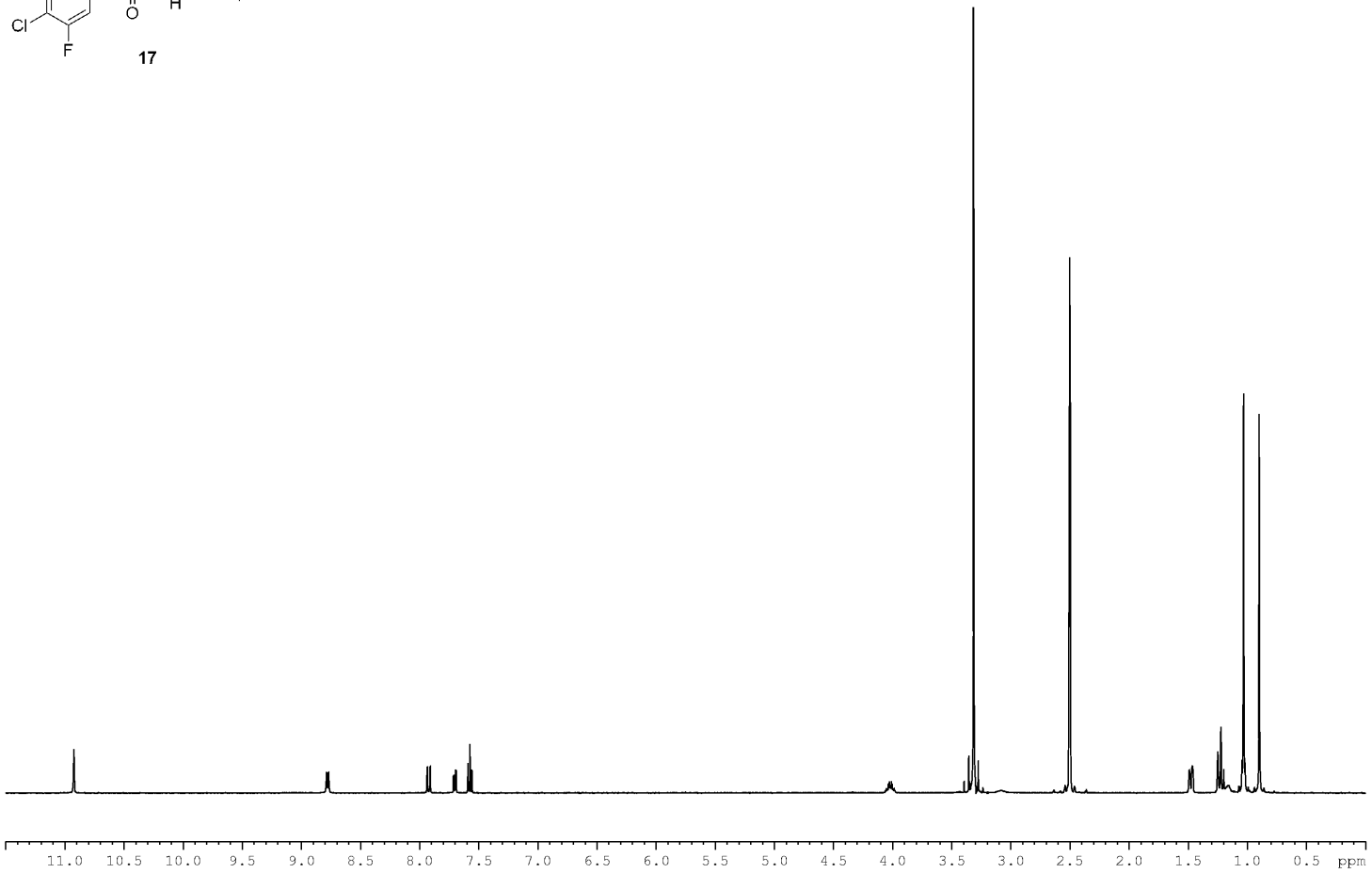
17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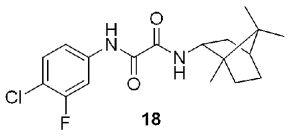
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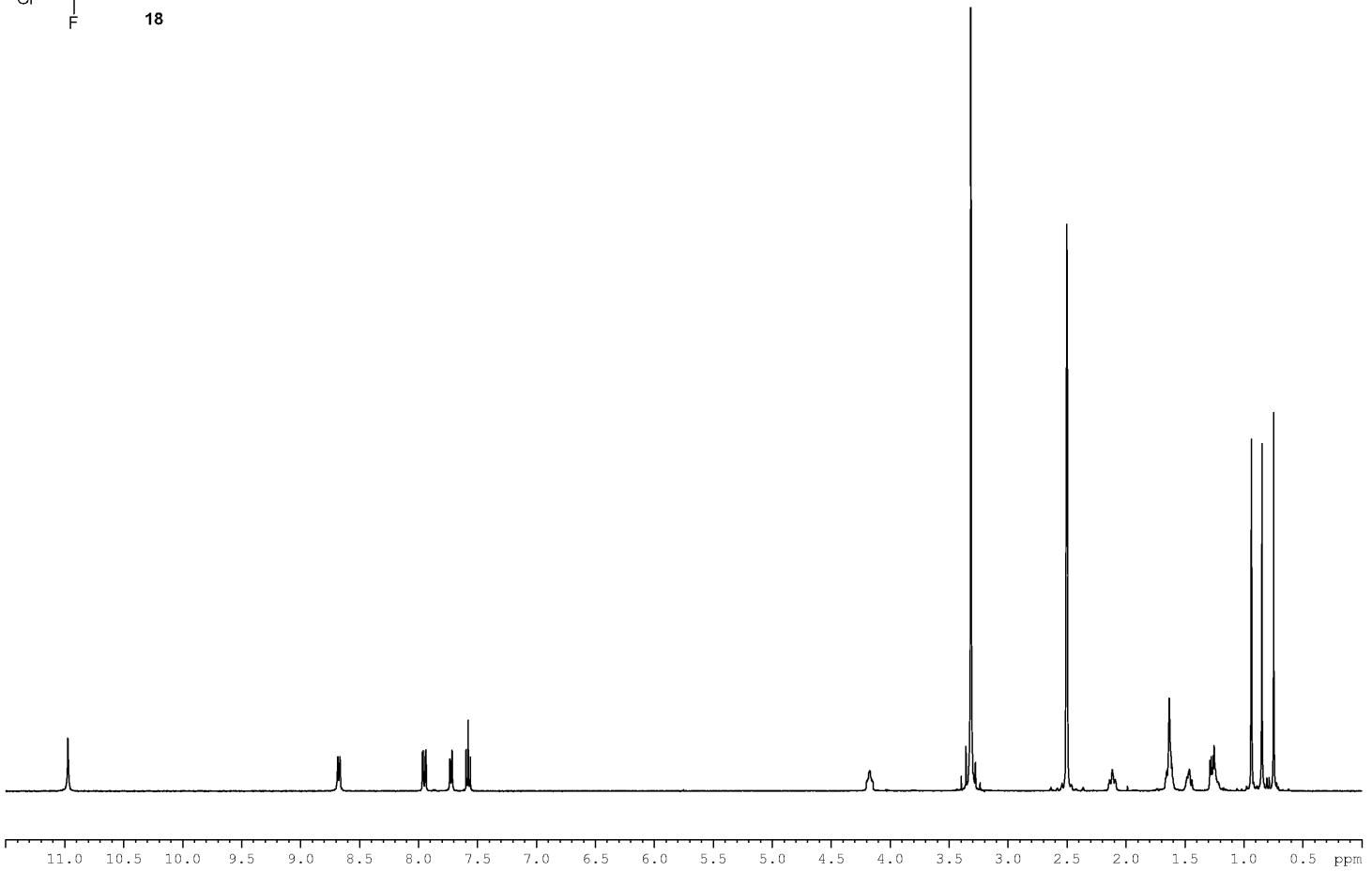
18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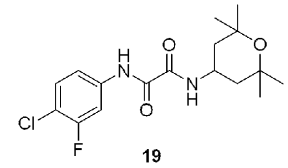

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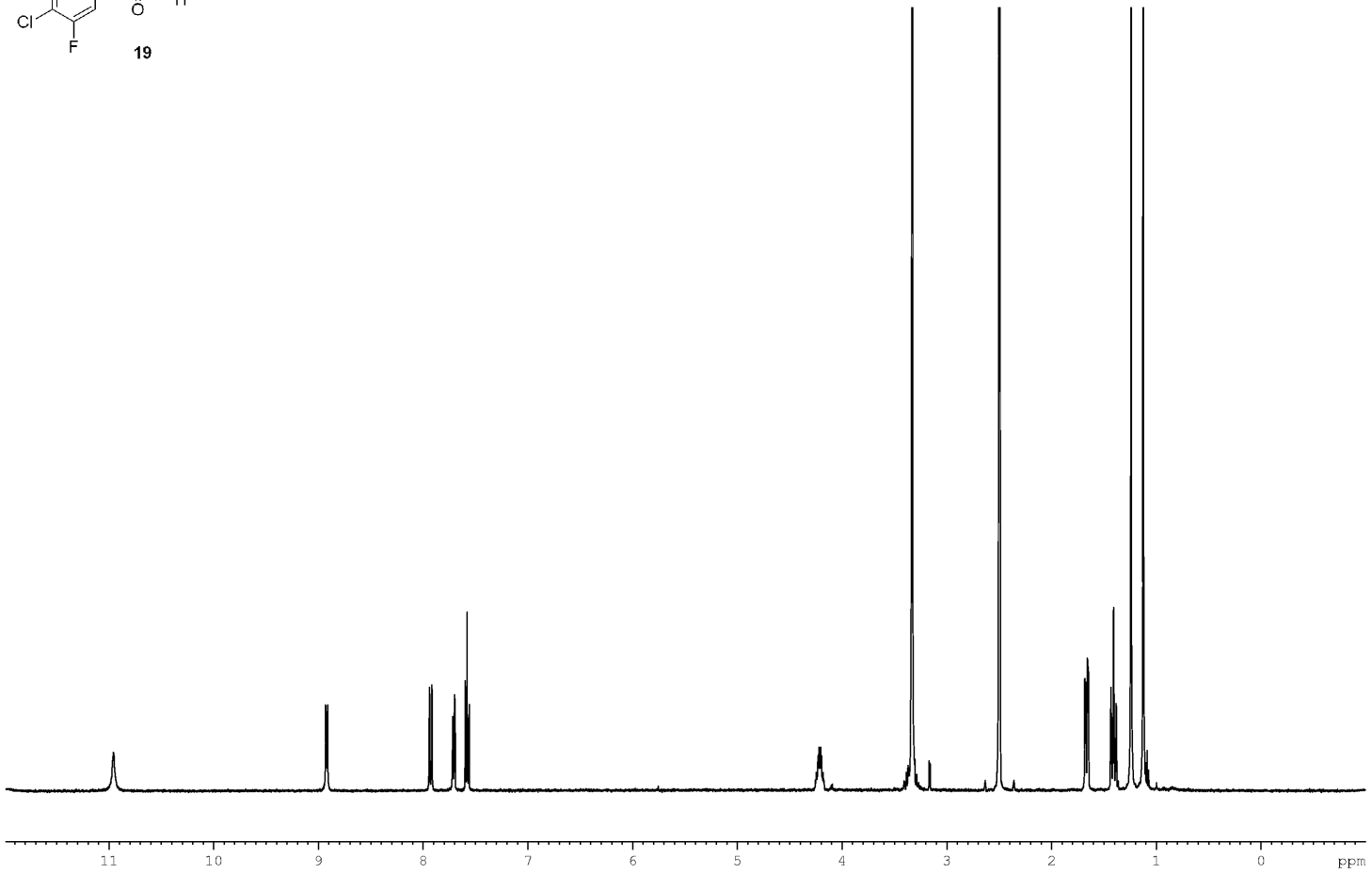

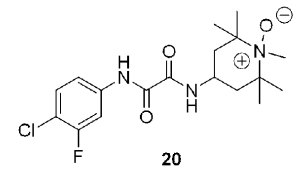
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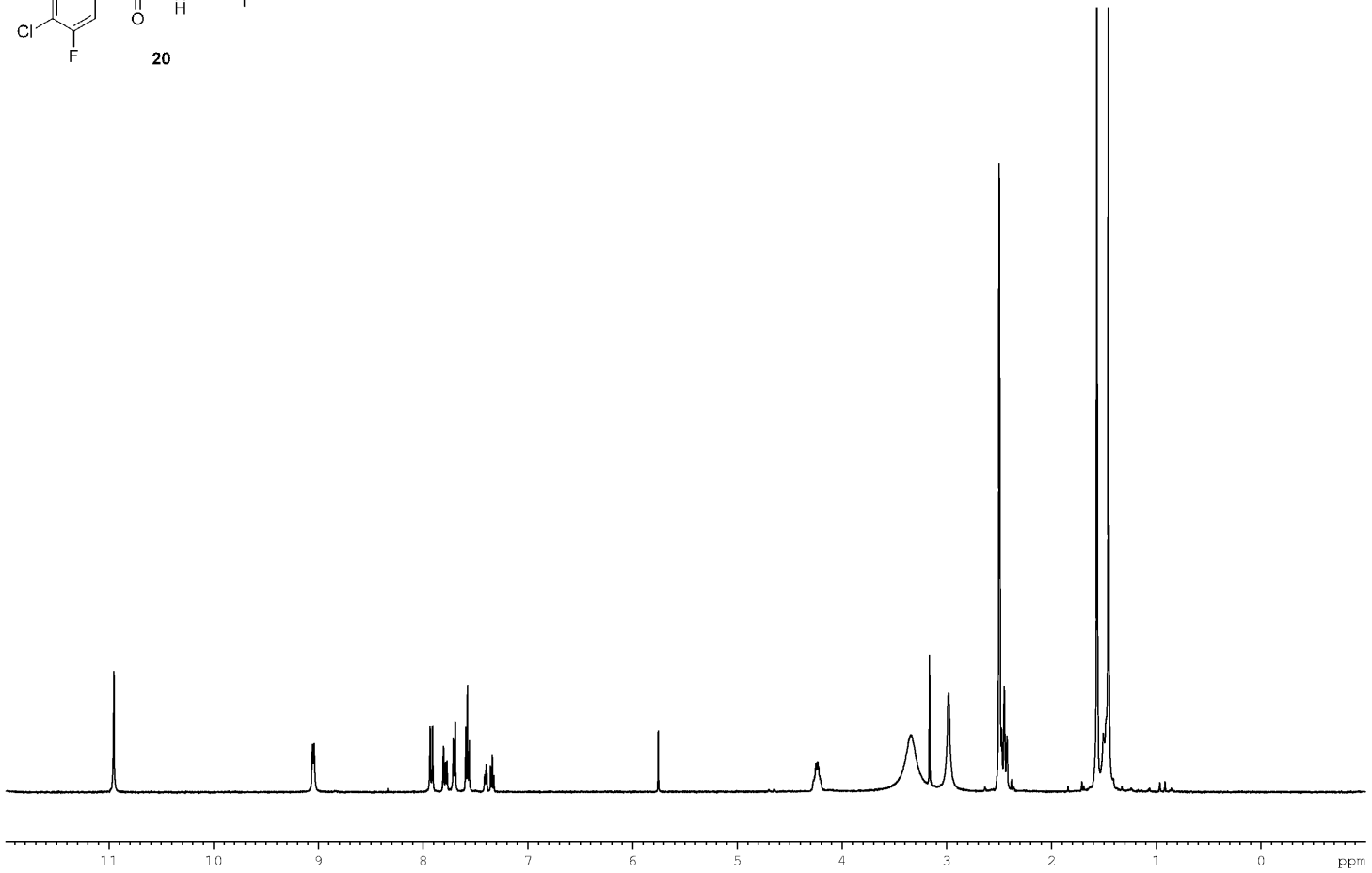
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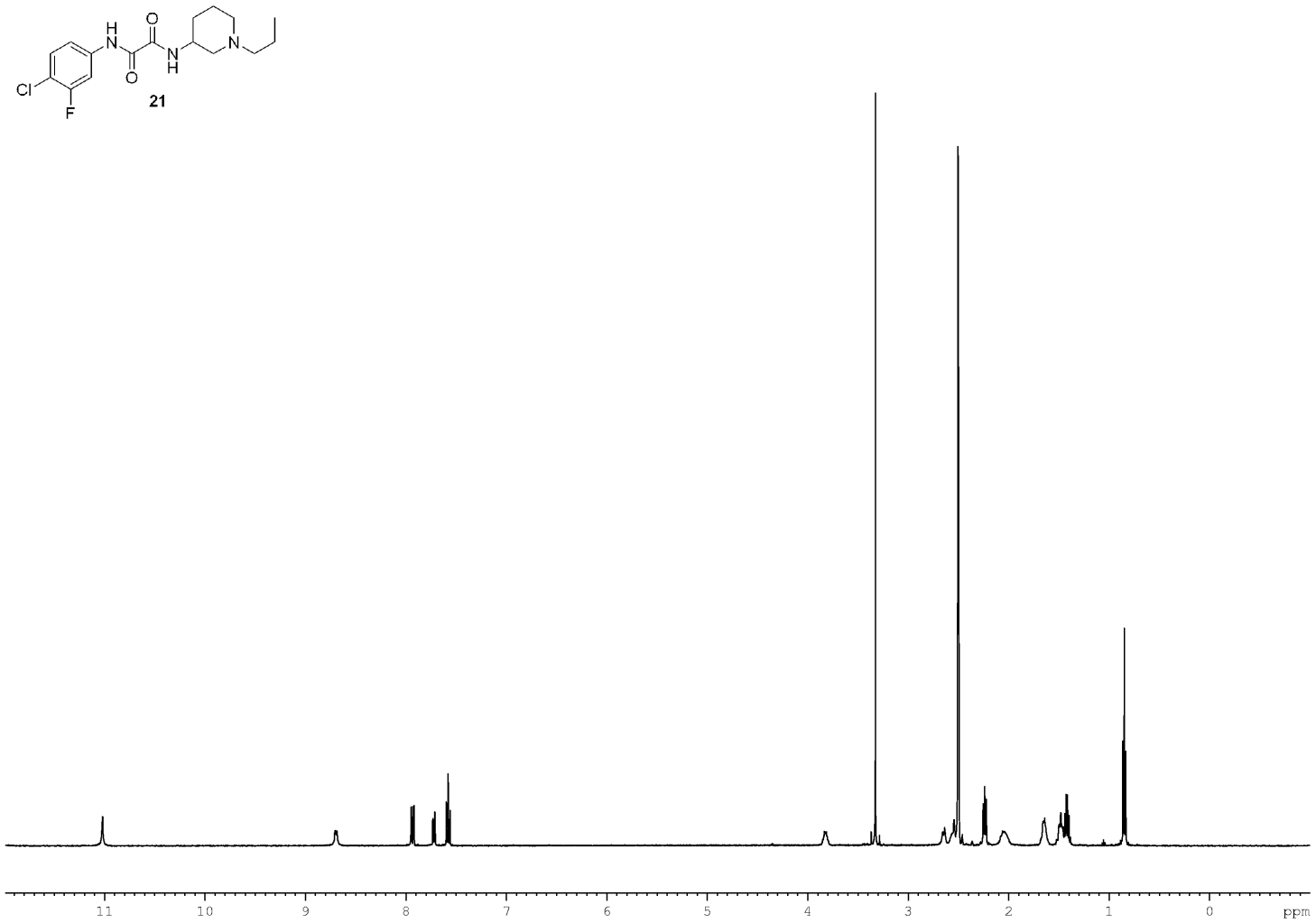
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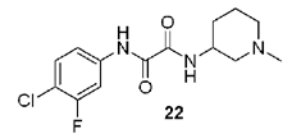

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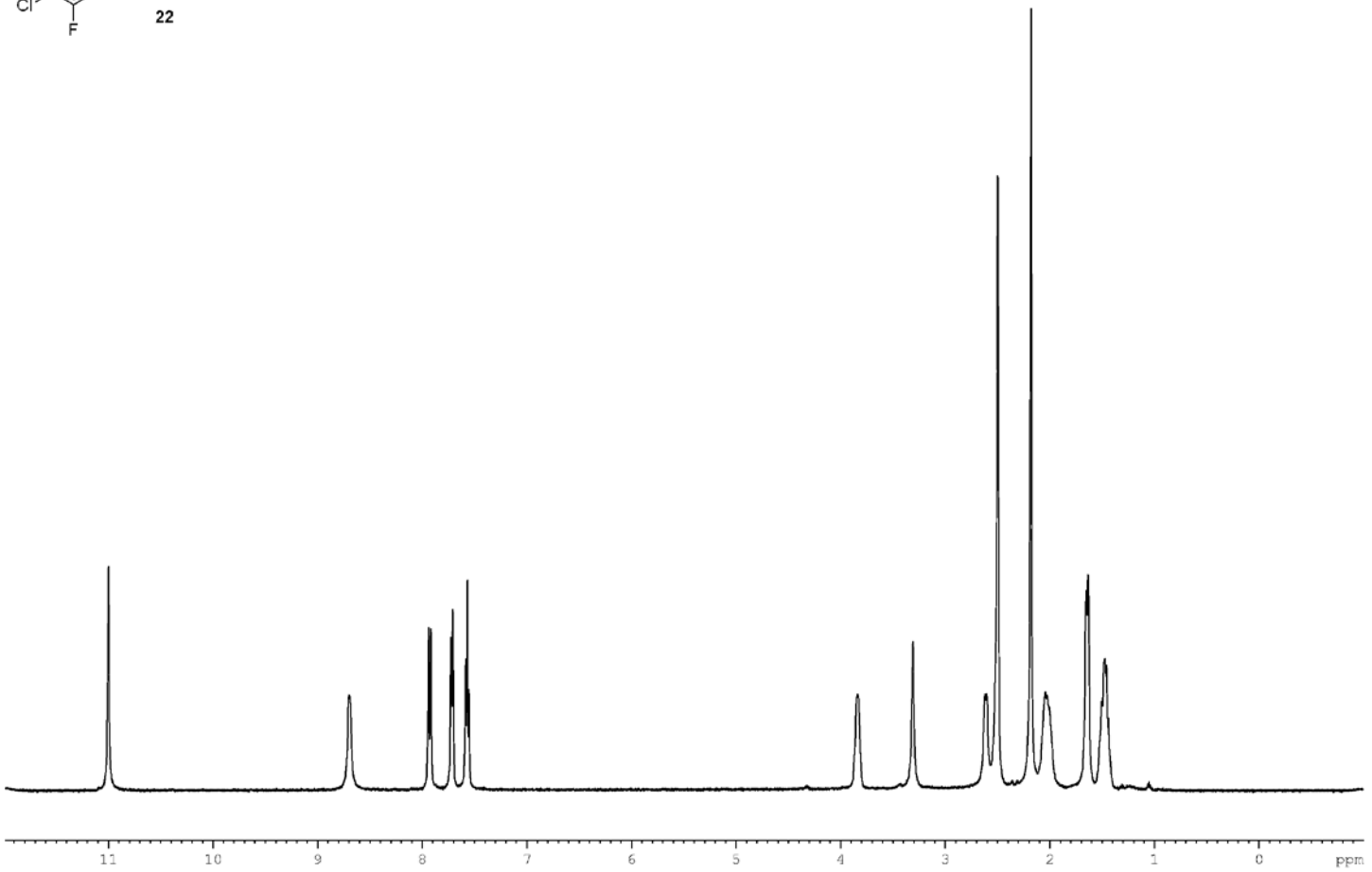

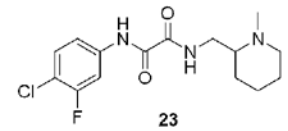

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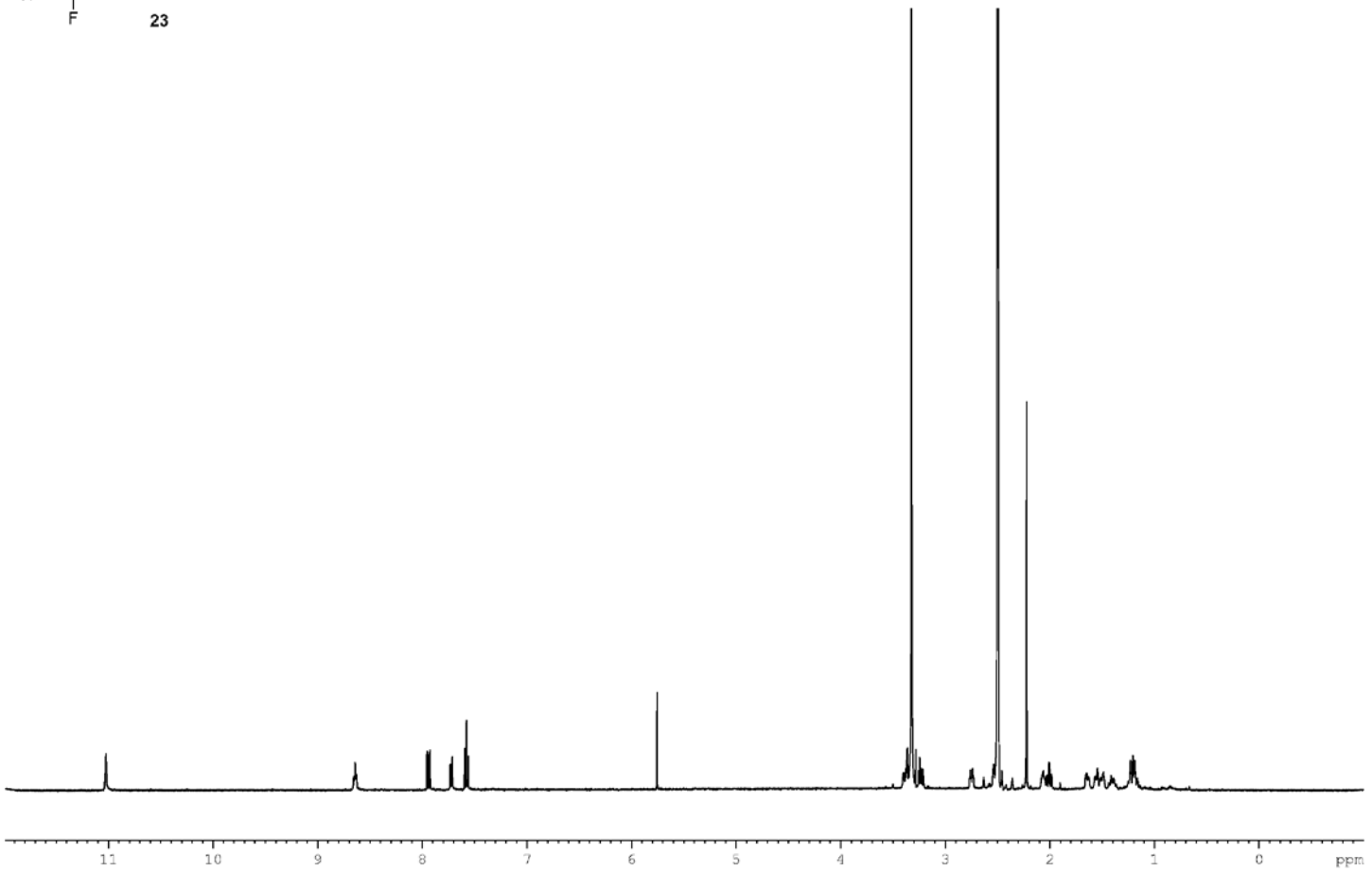

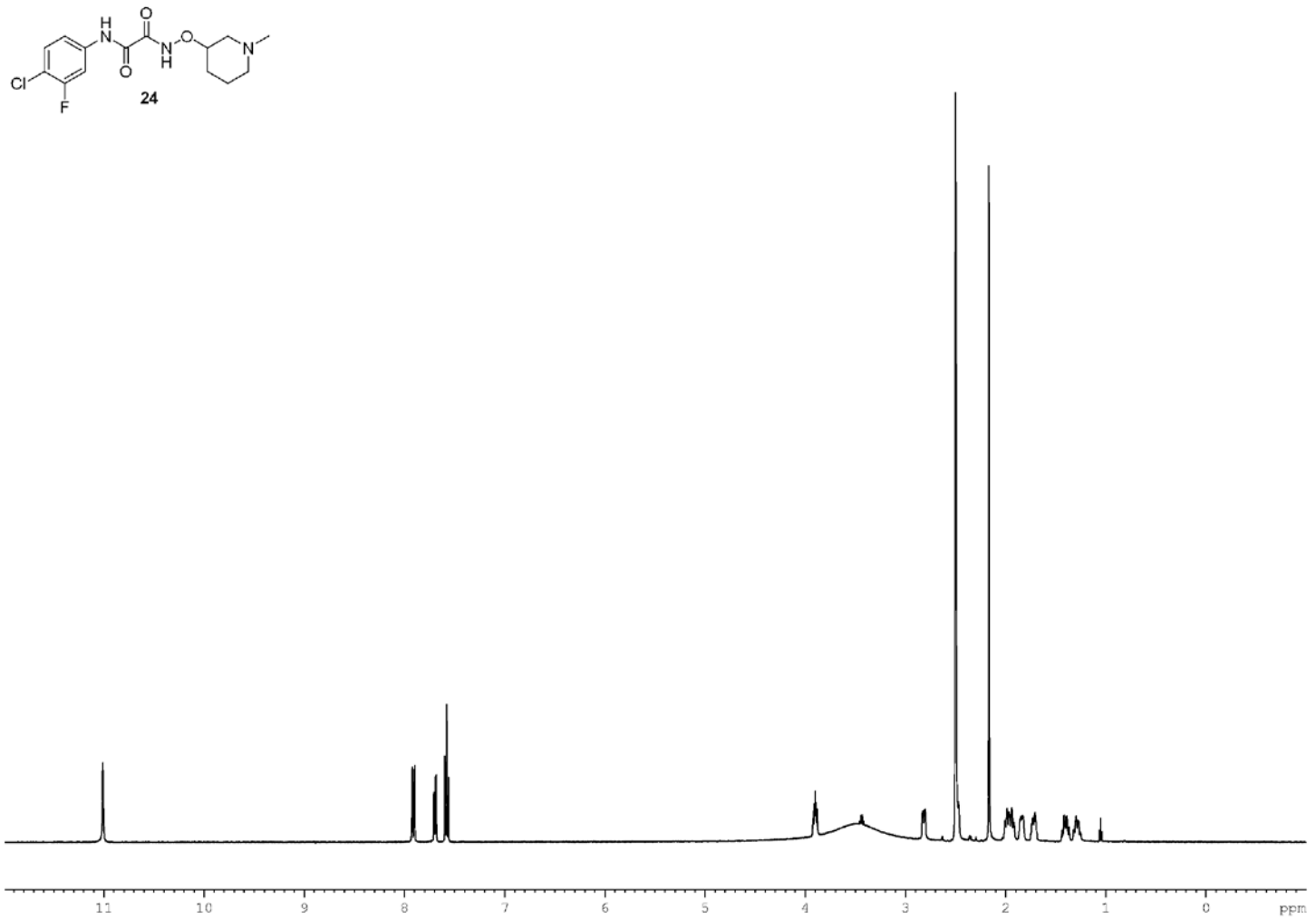
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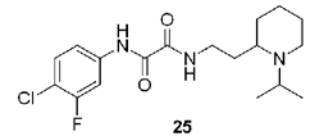

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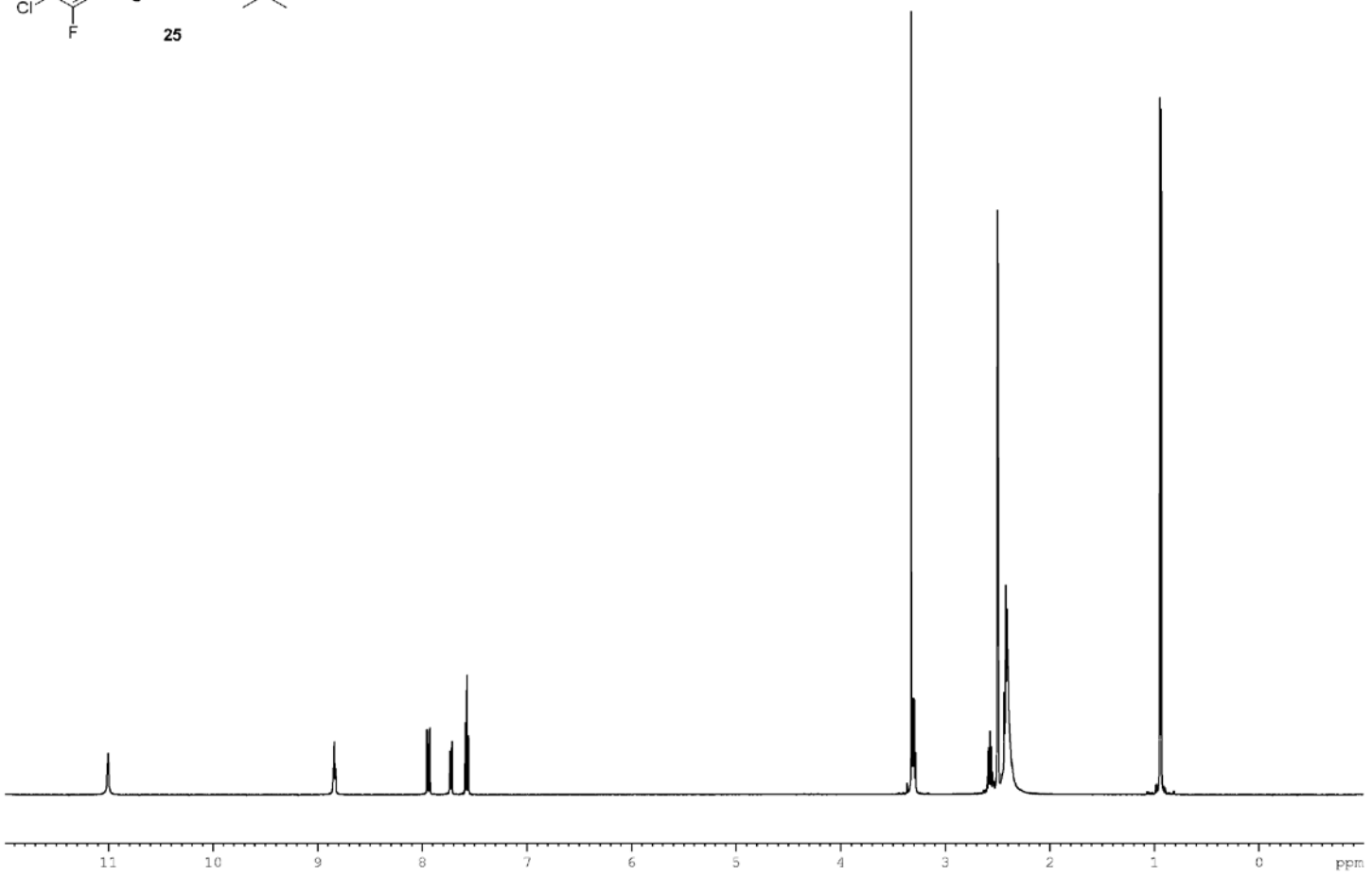

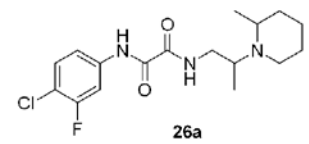

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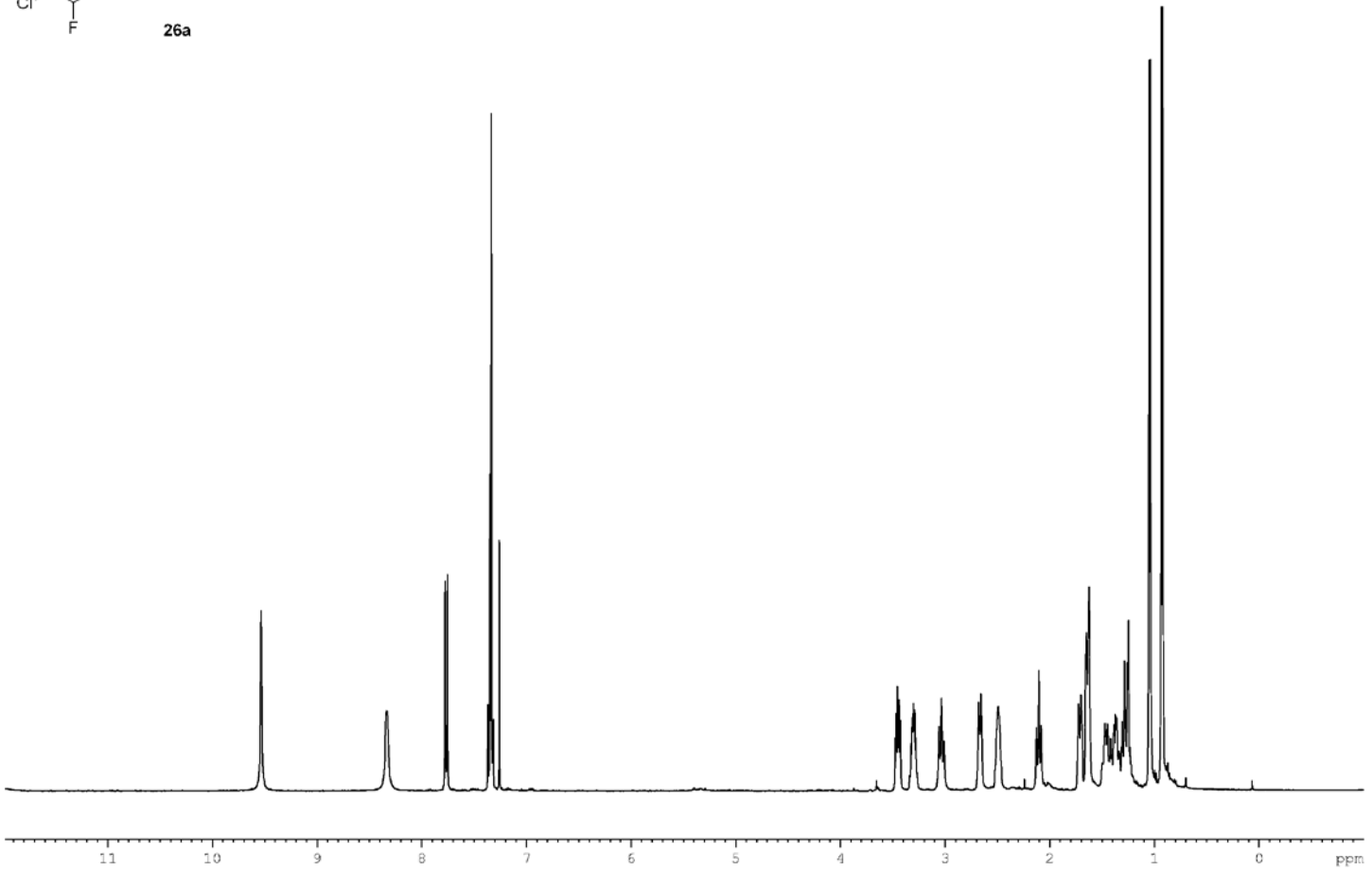

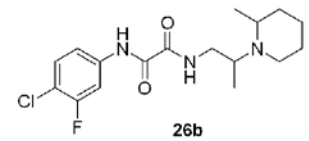

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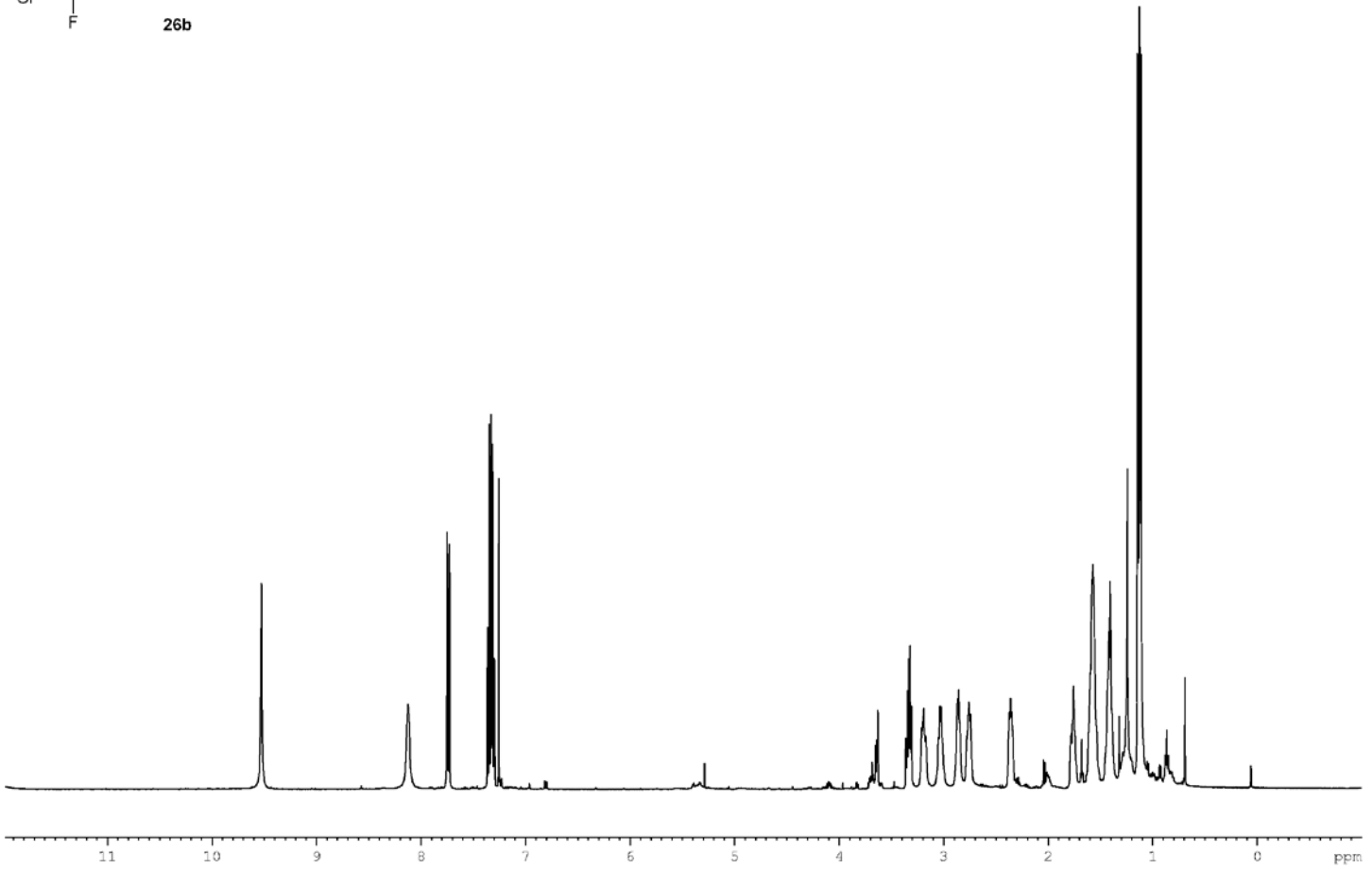

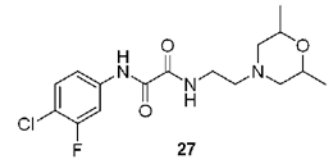
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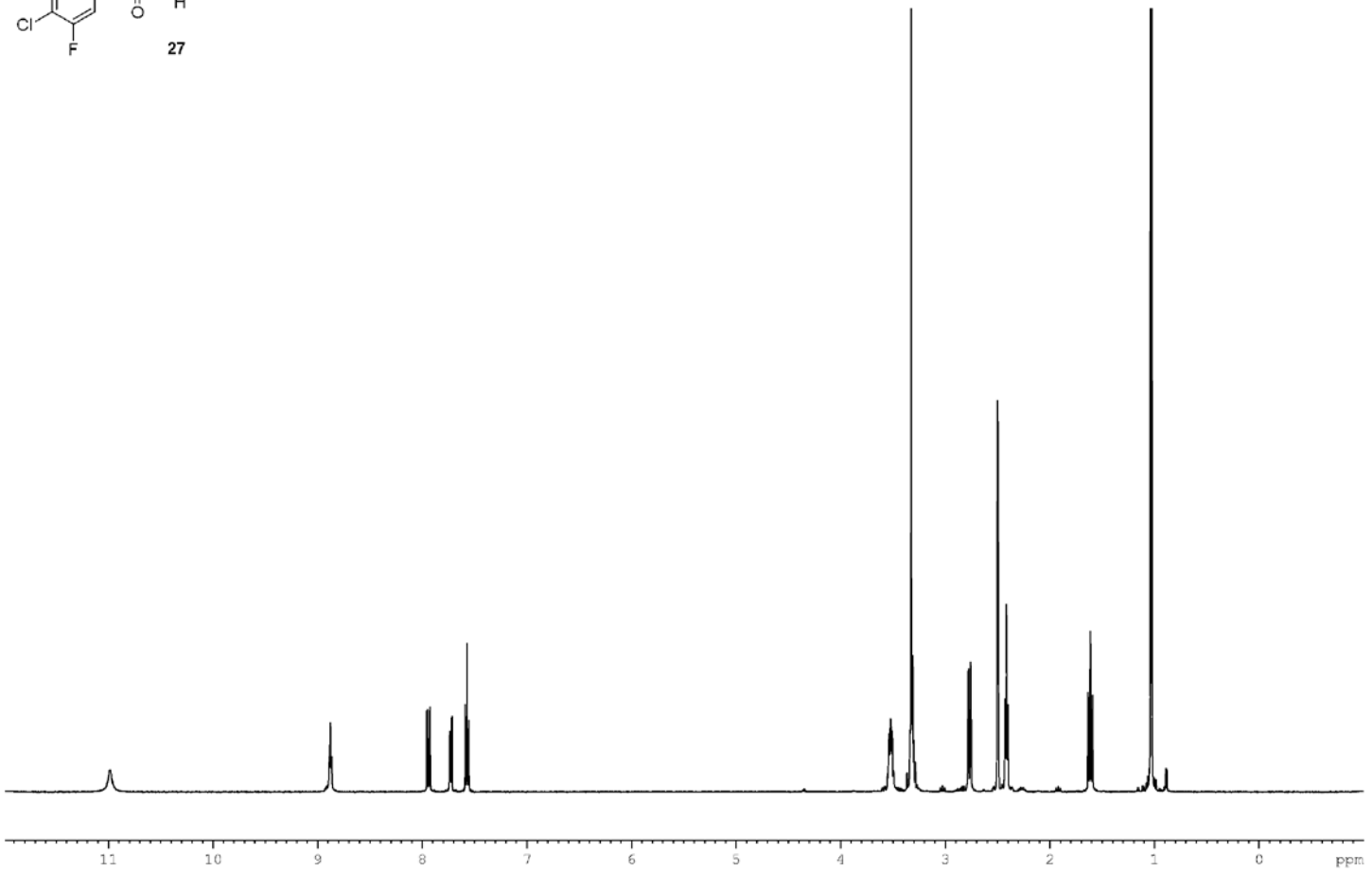
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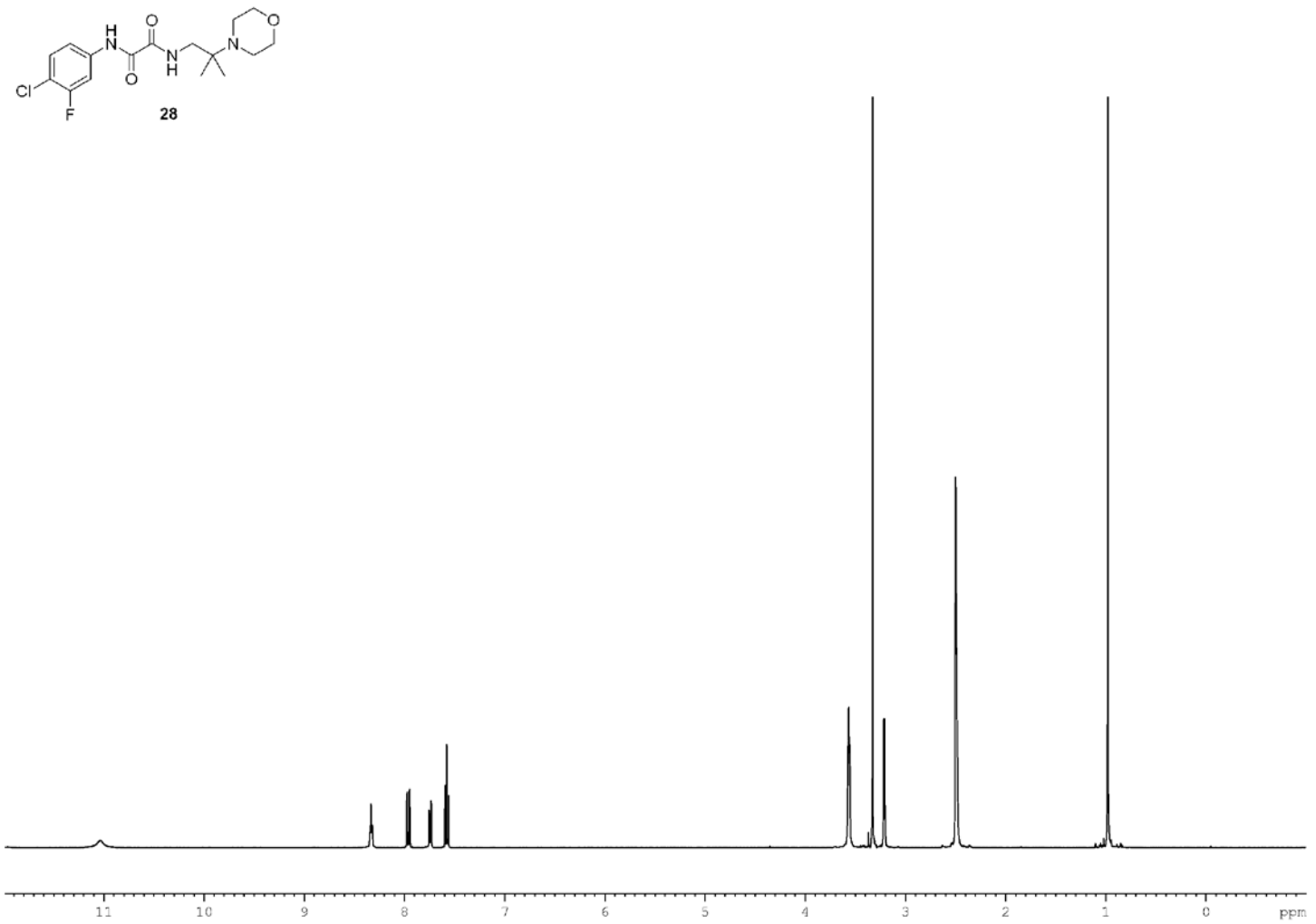
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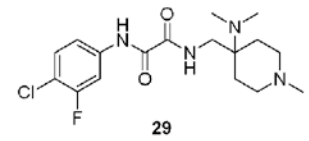

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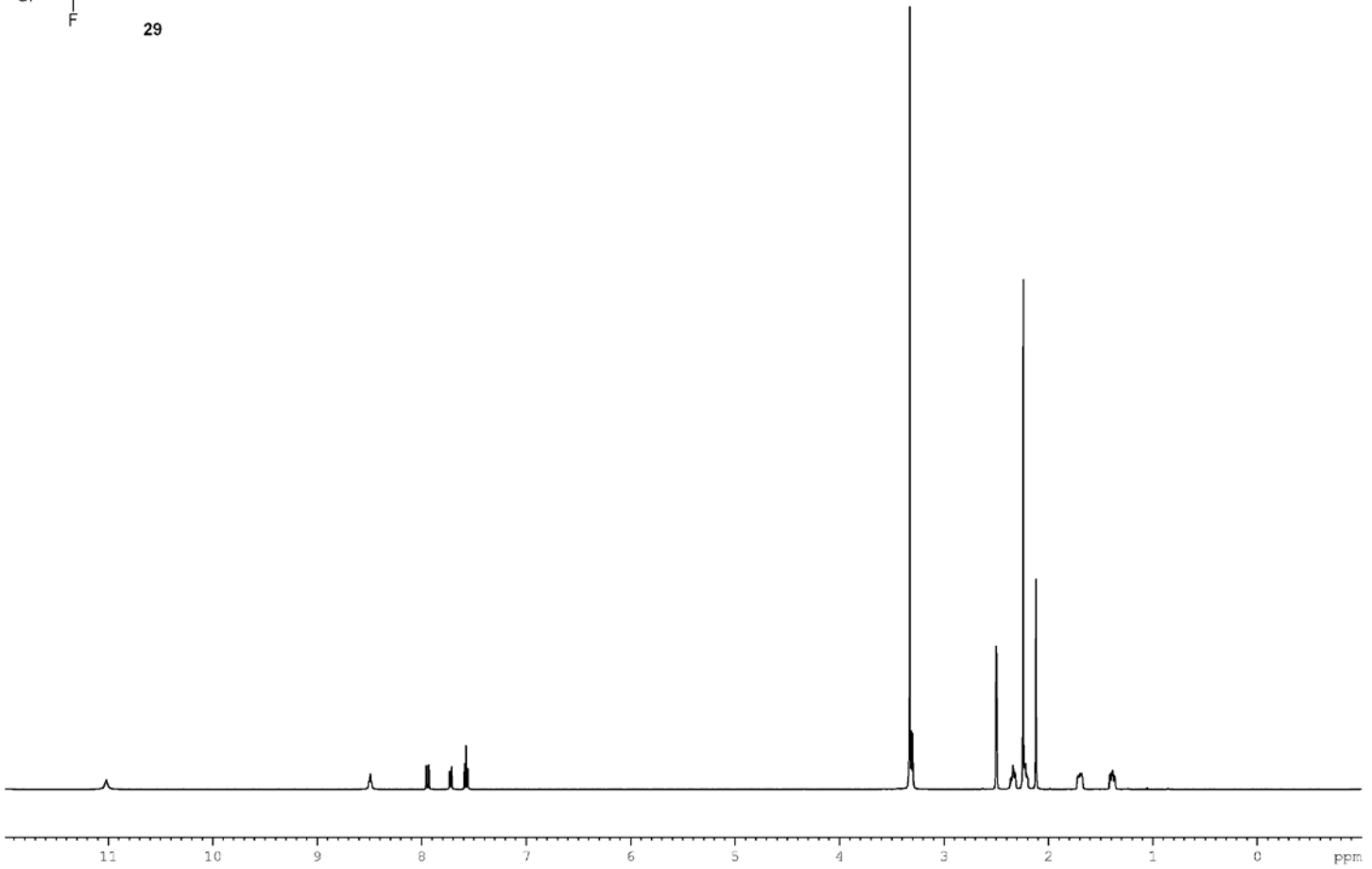

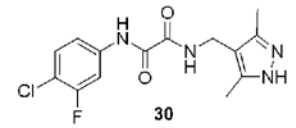

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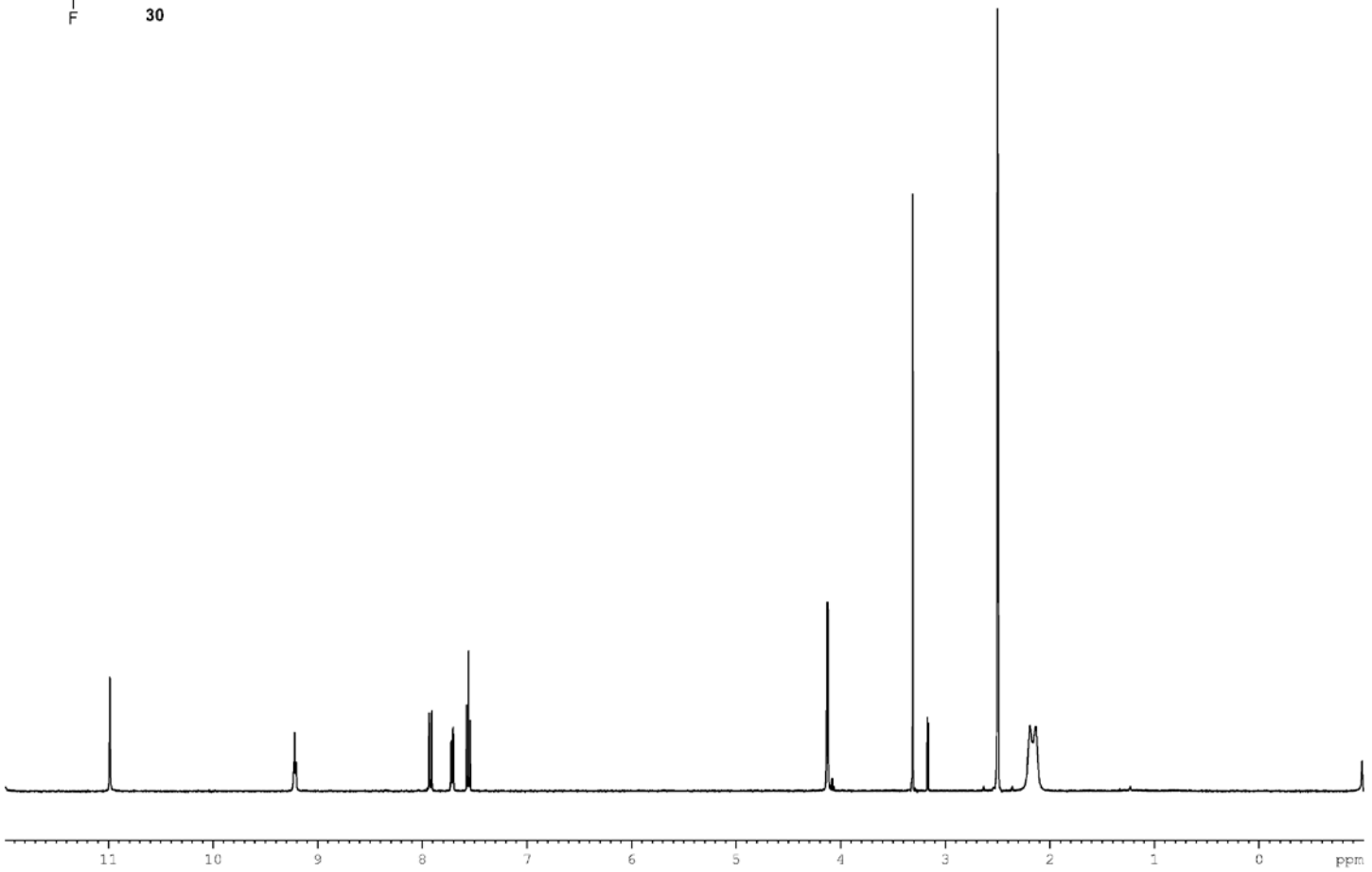

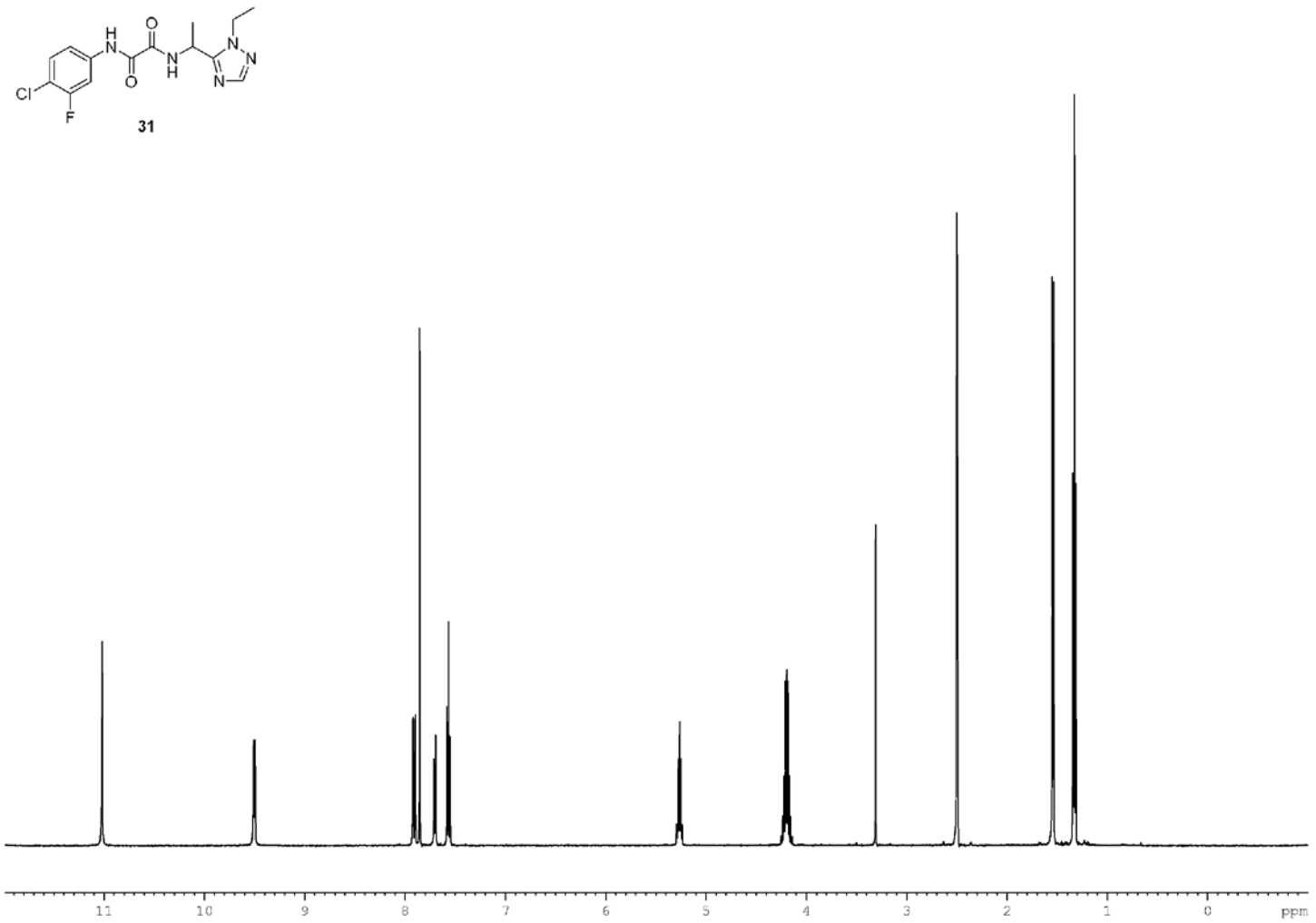
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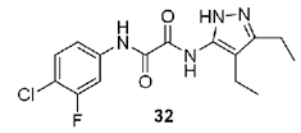

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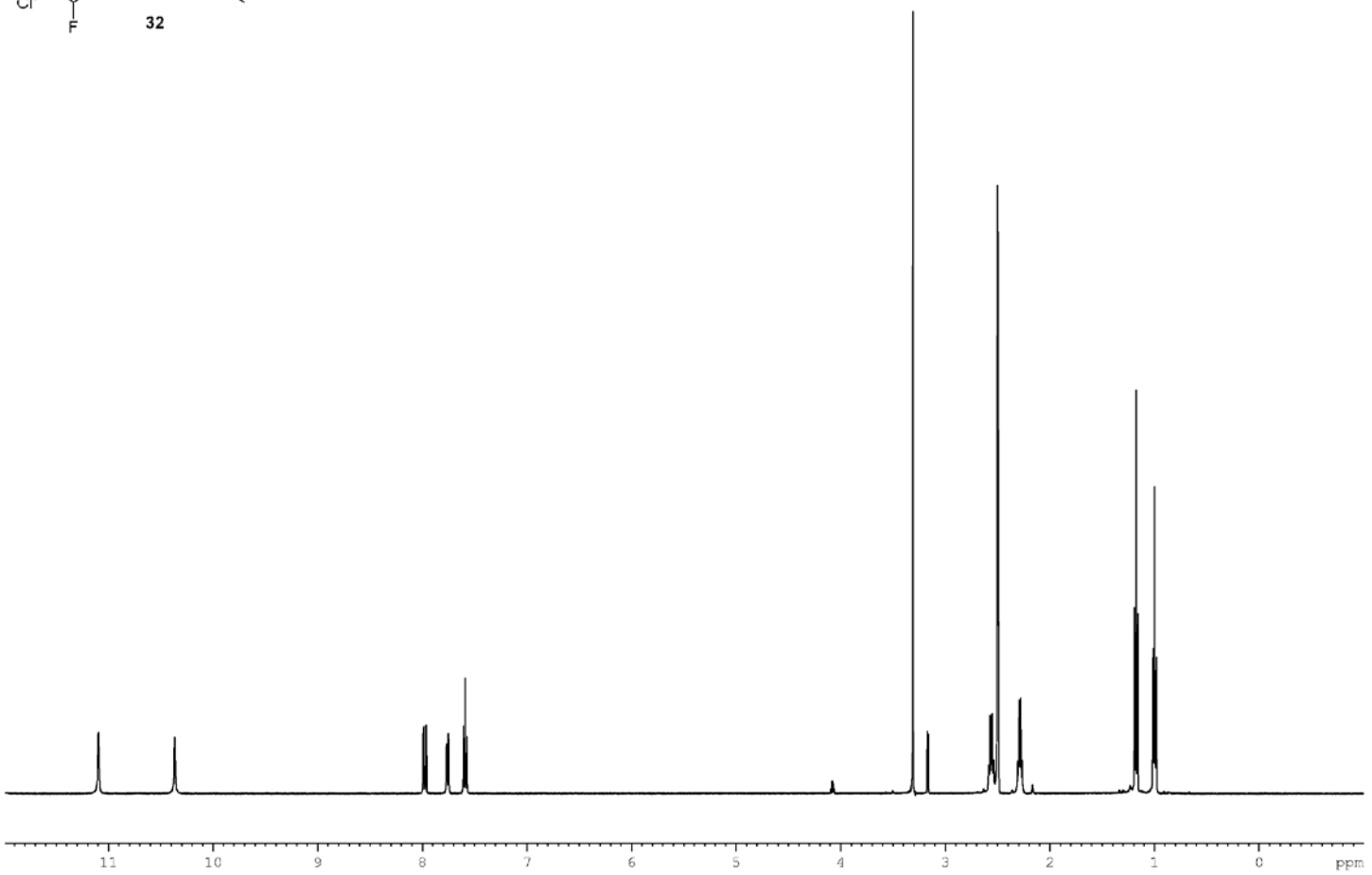

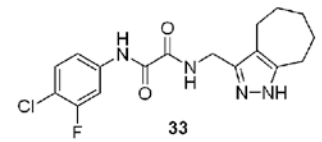

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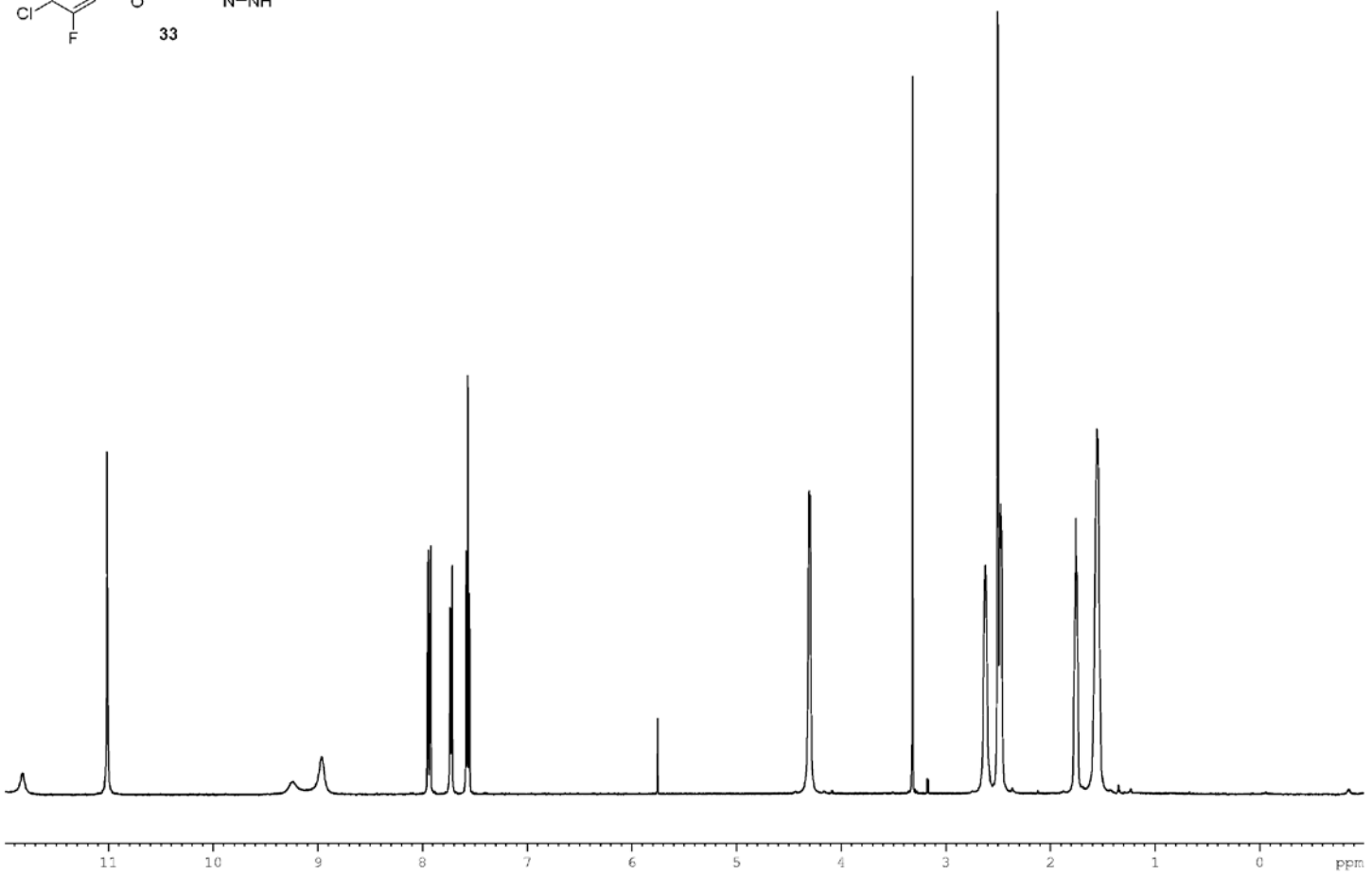

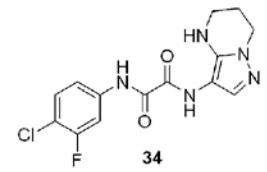

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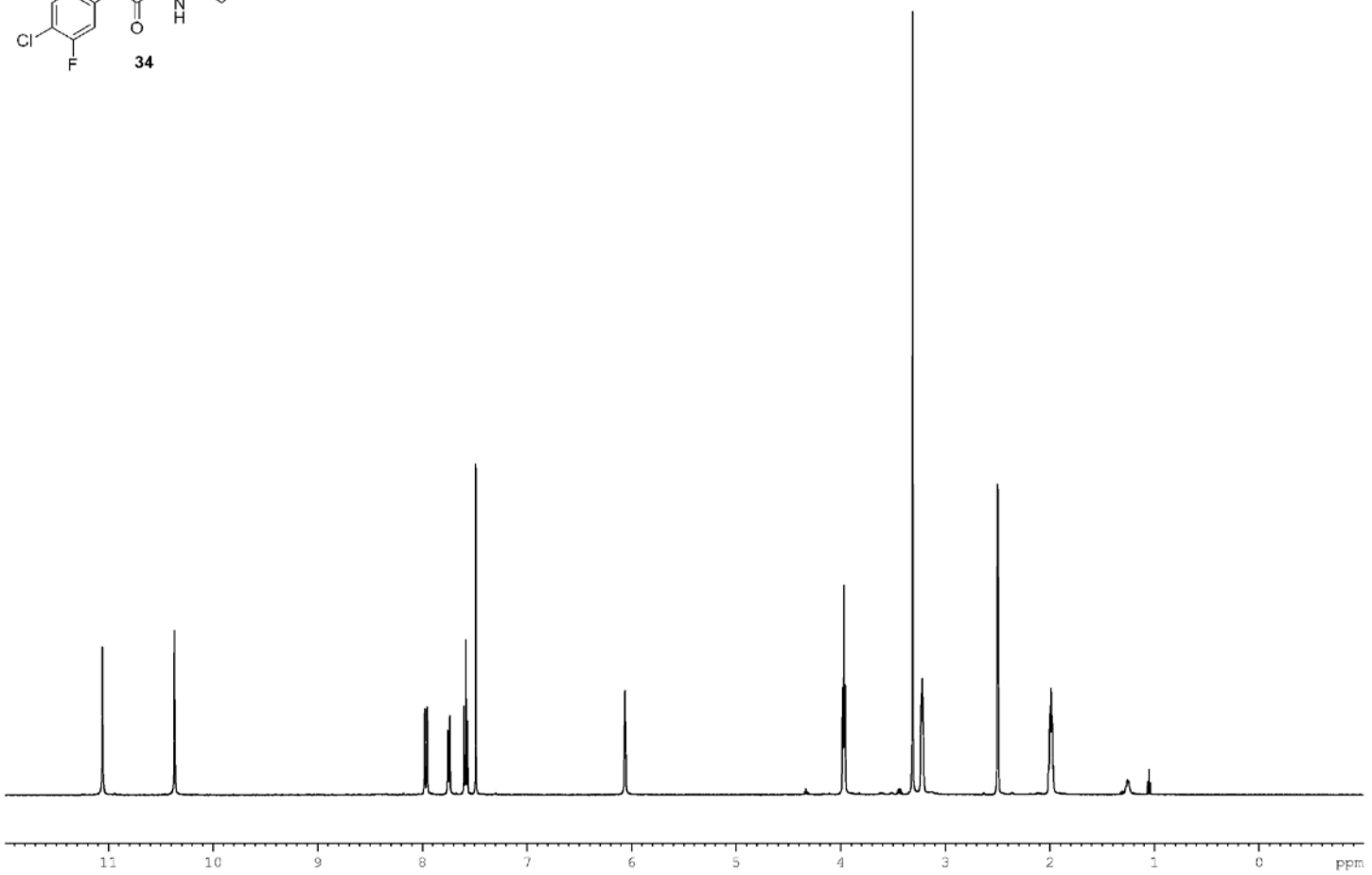

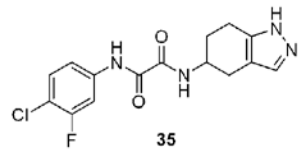
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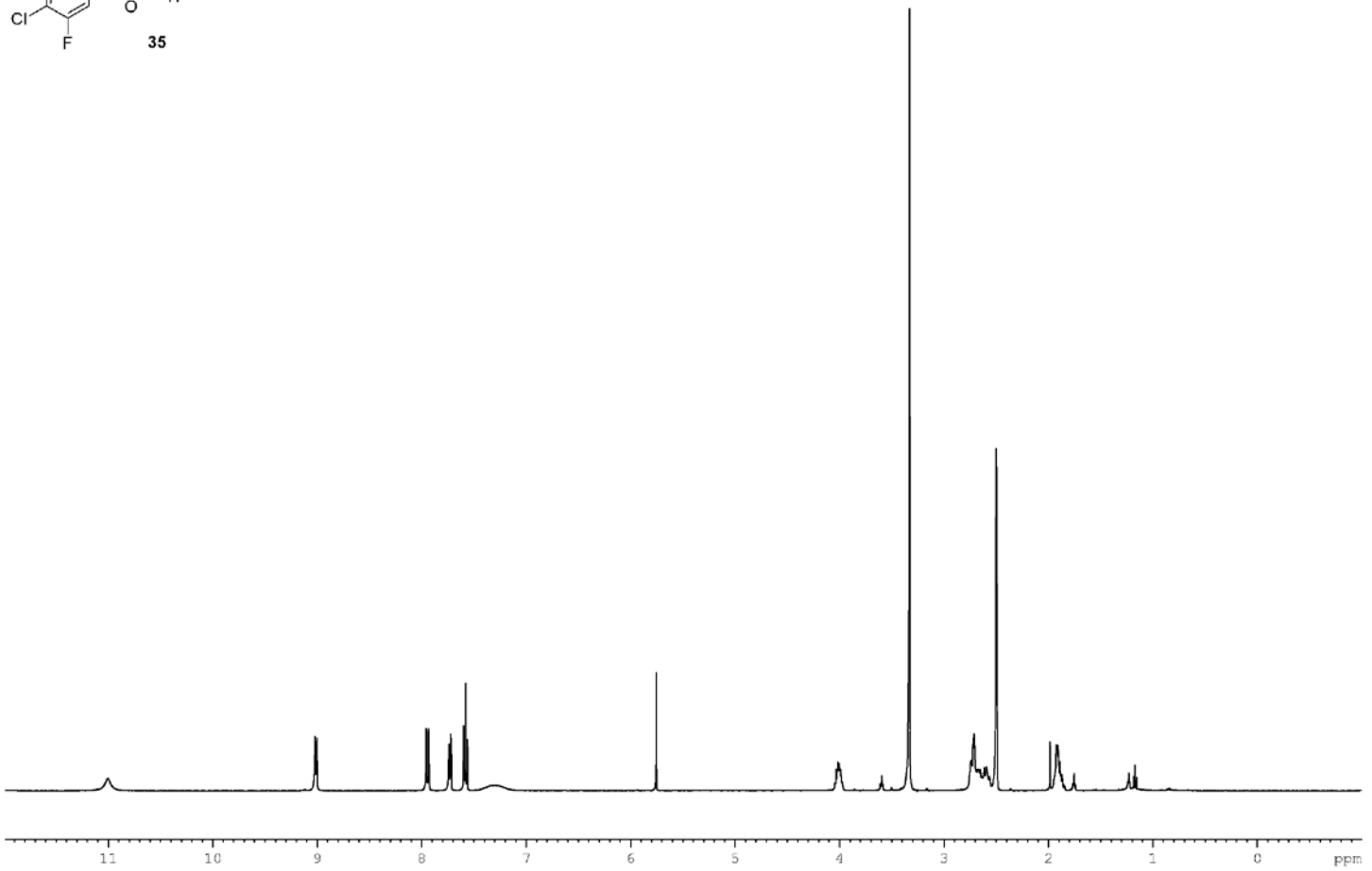
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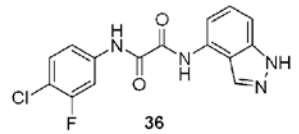

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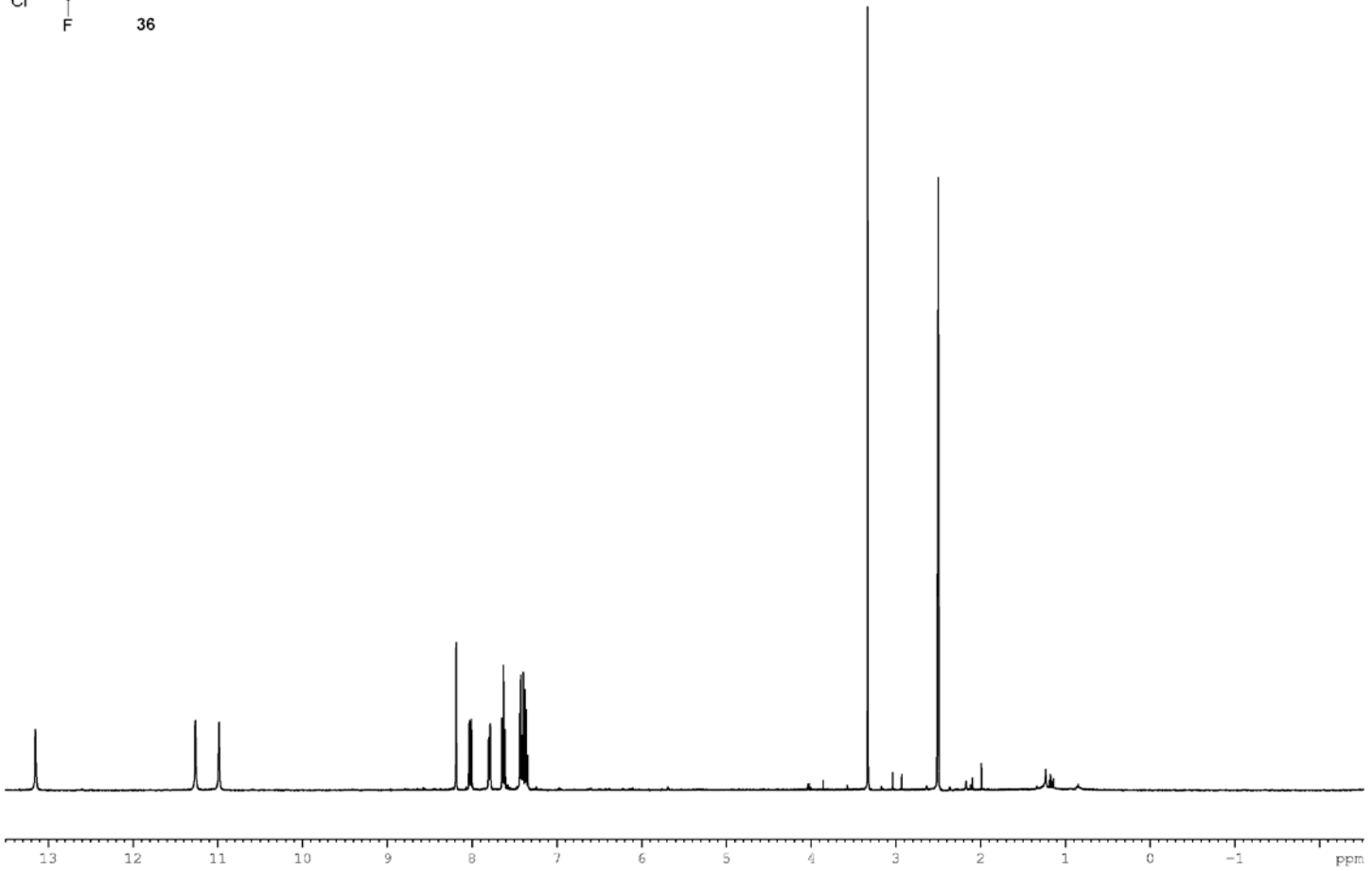

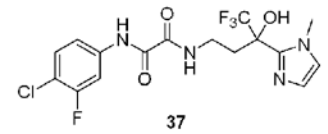

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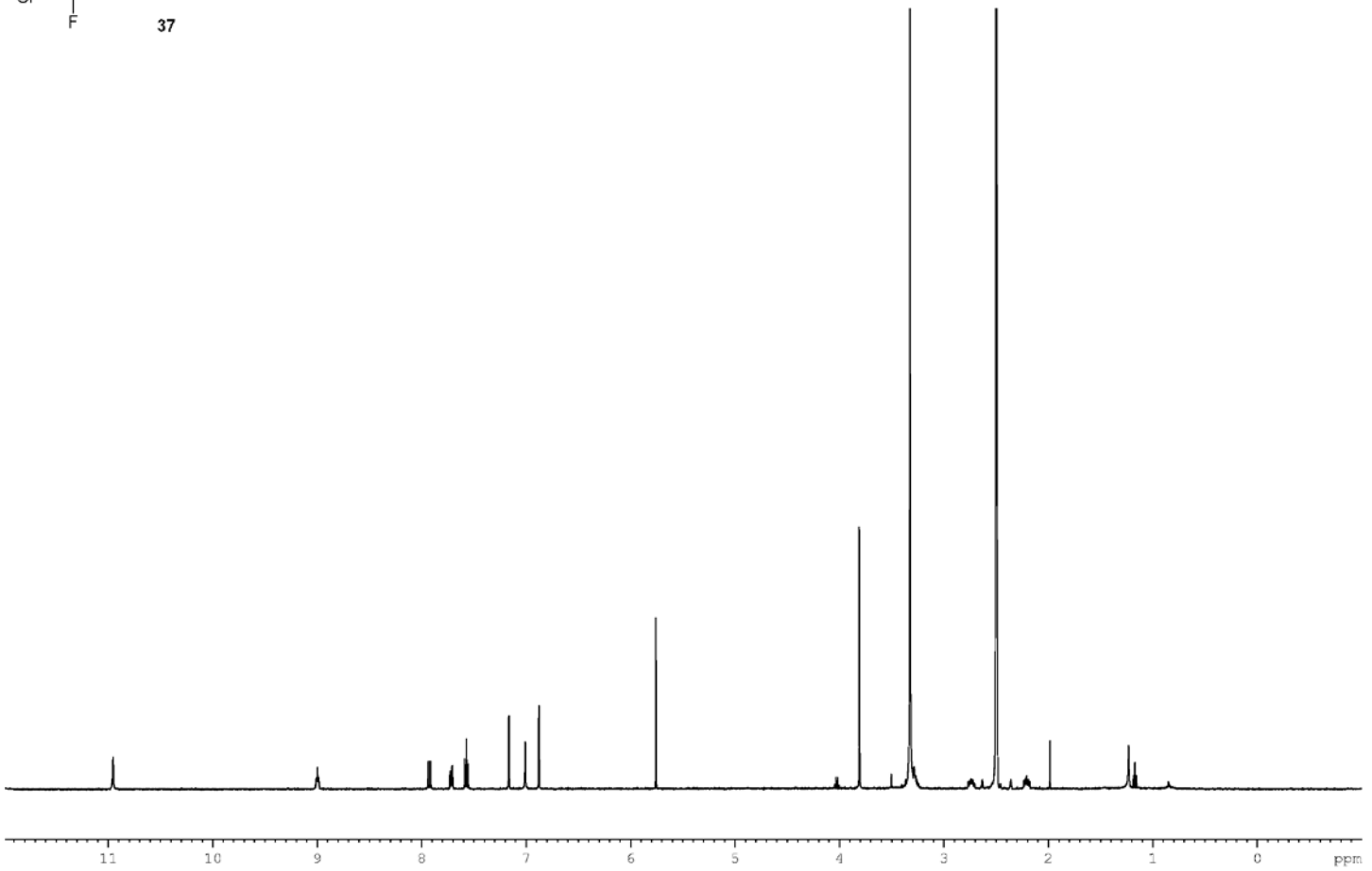

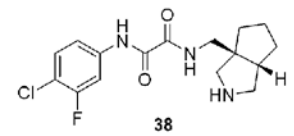

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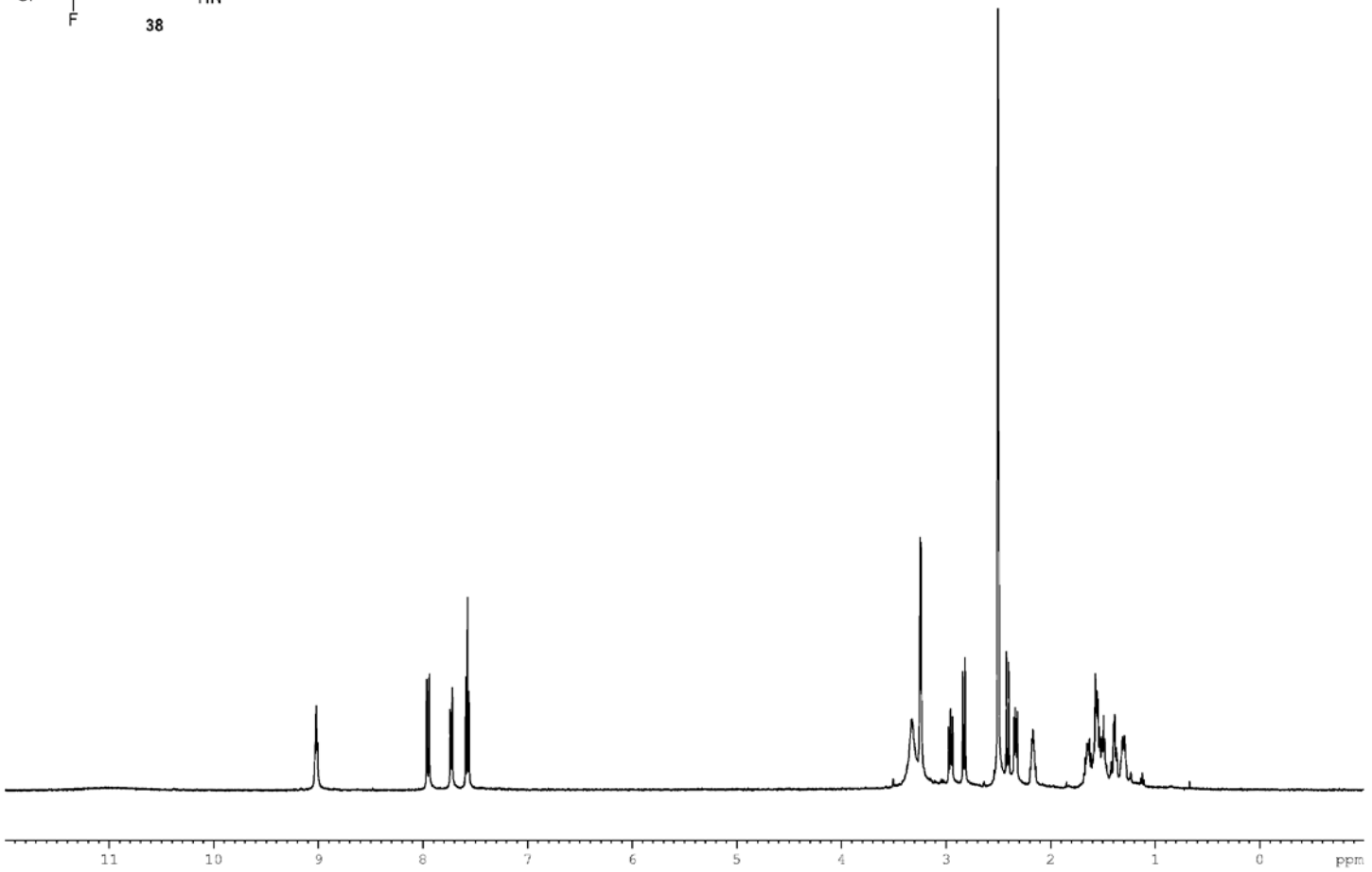

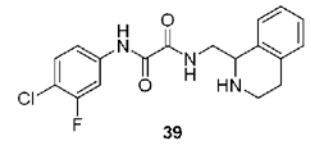

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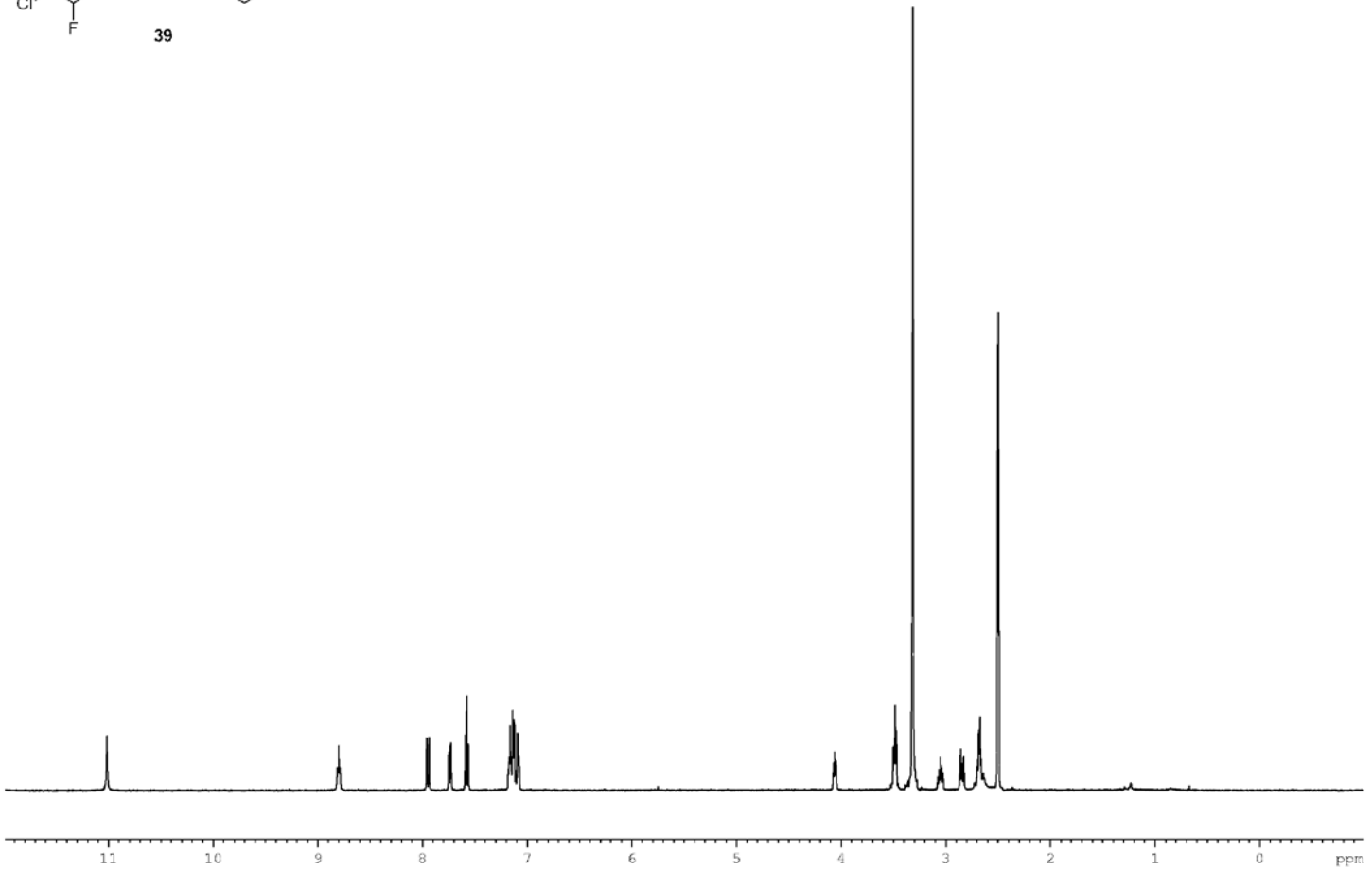

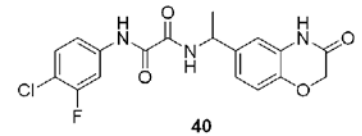

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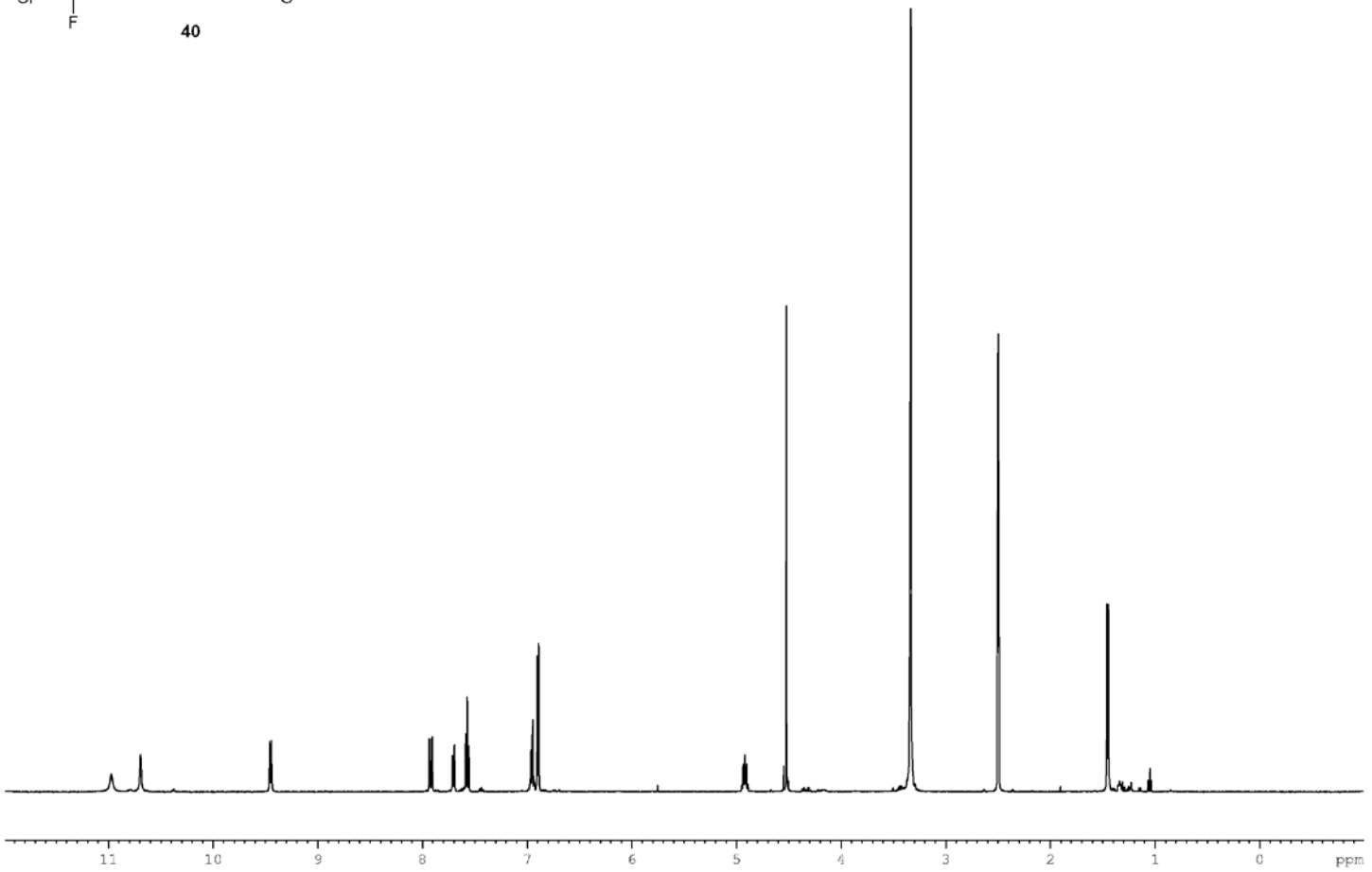

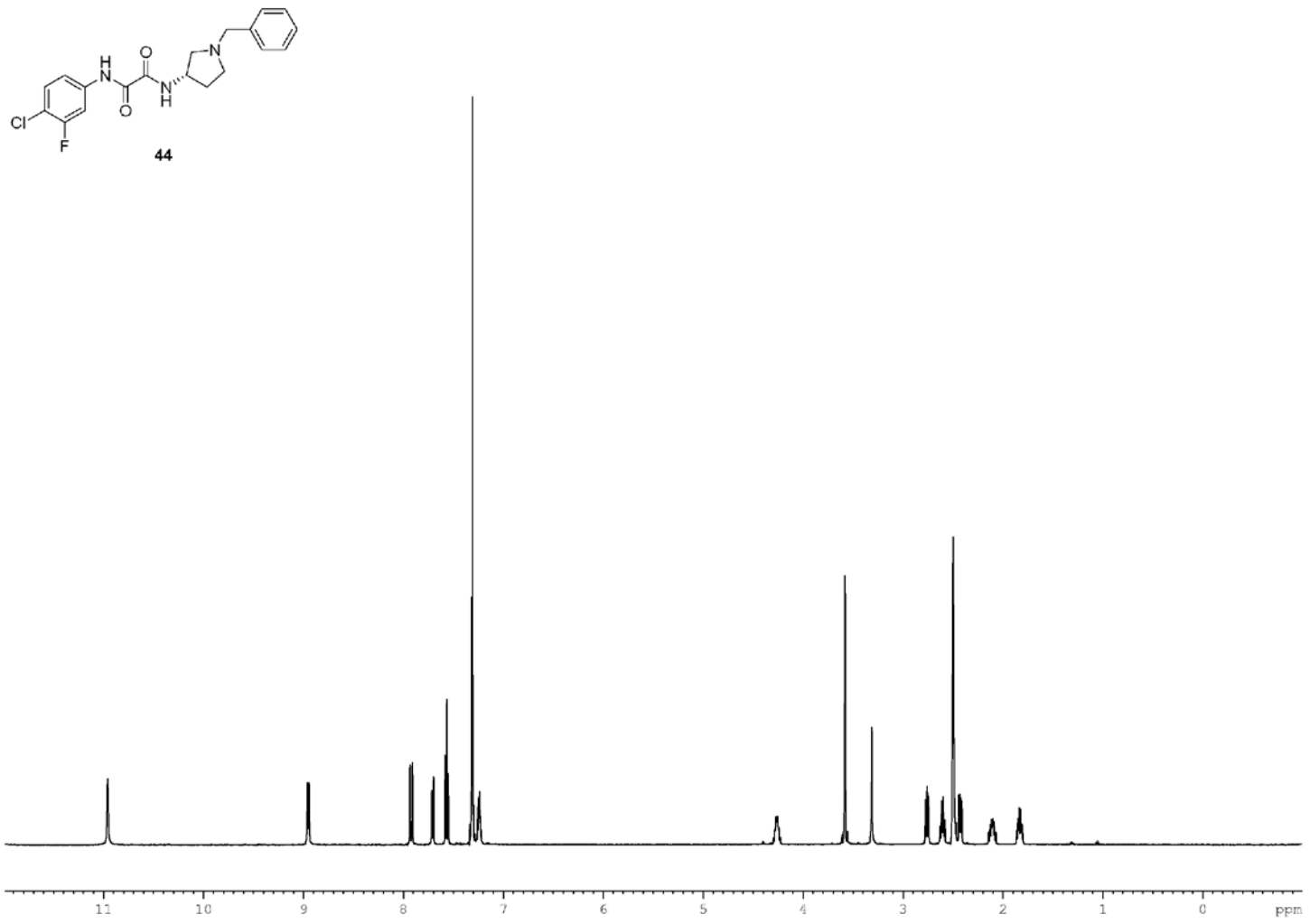
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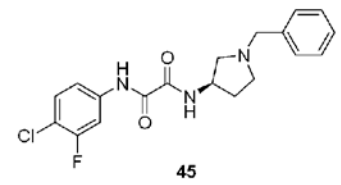

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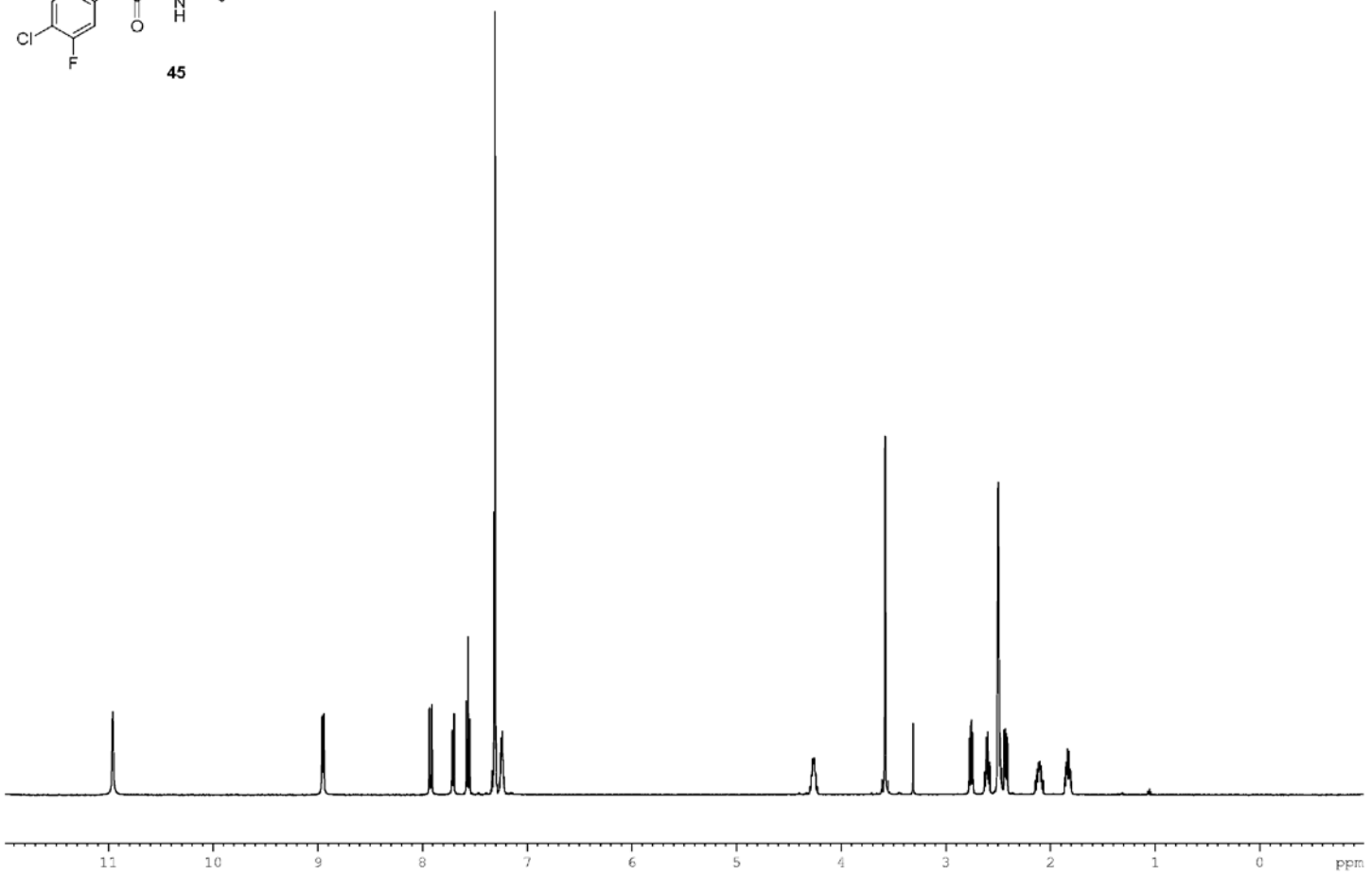

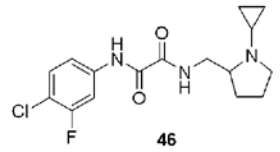

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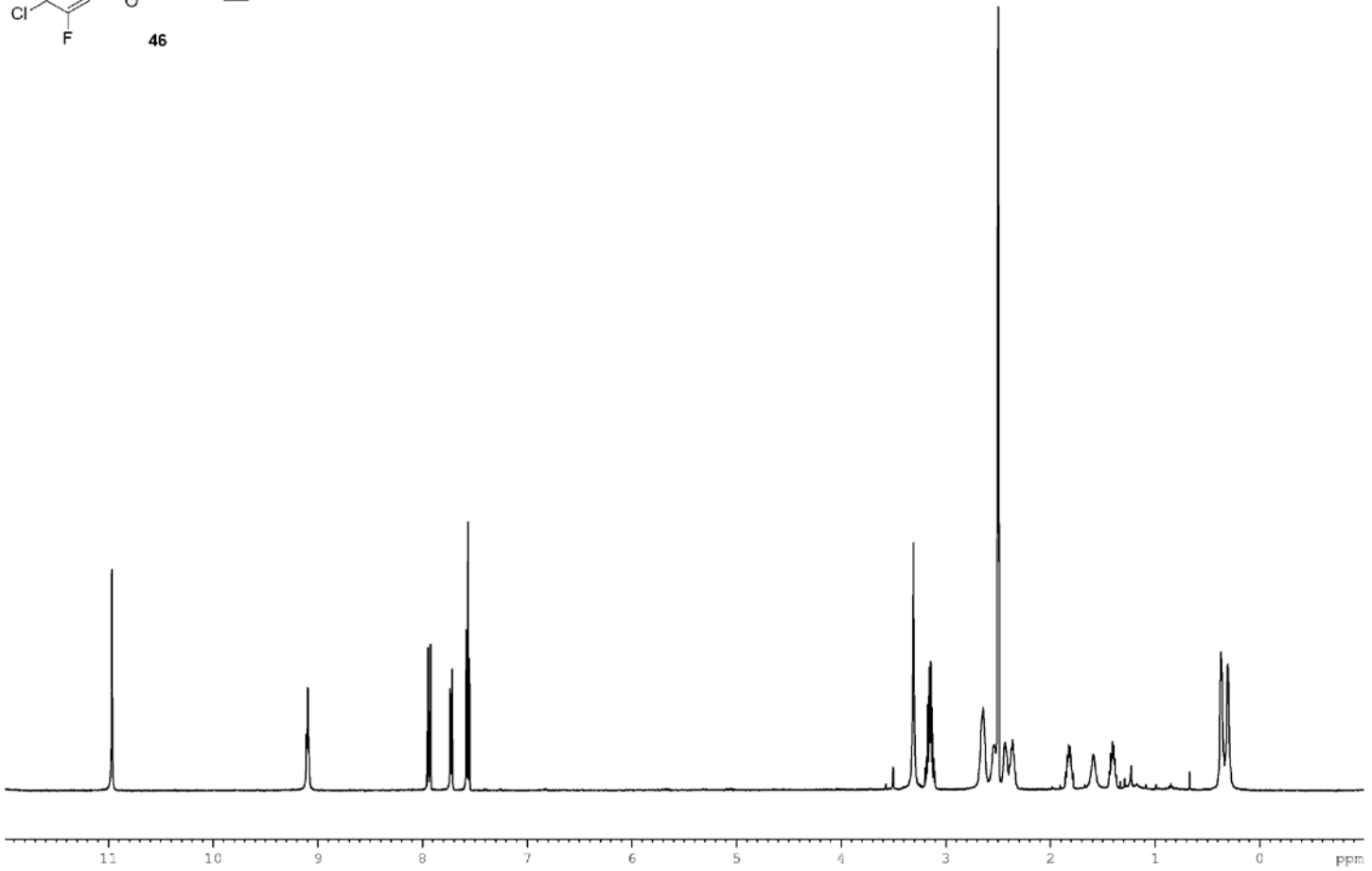

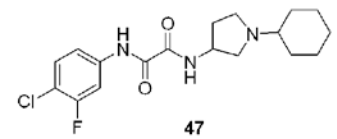

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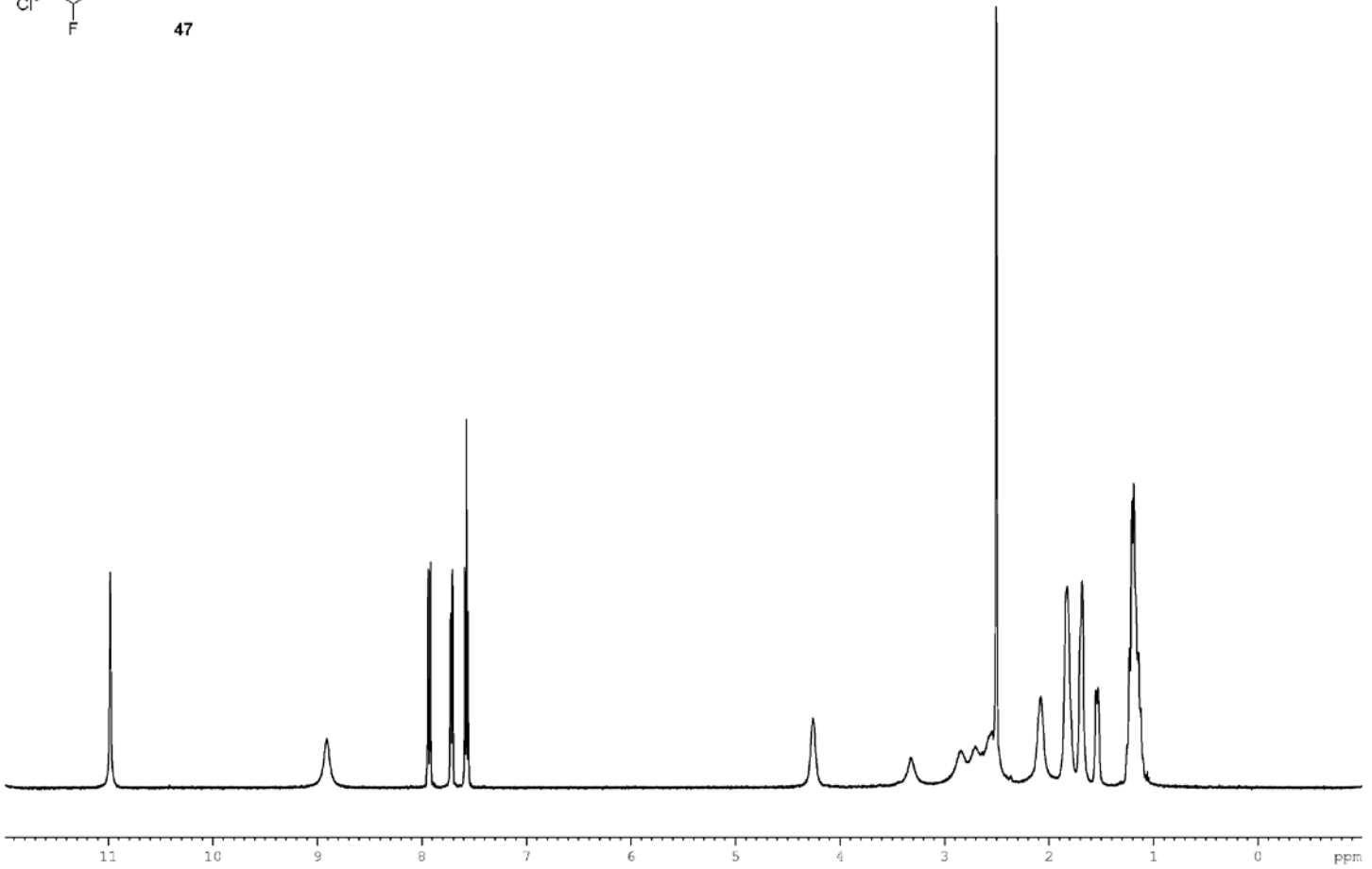

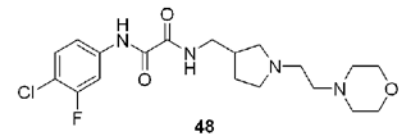

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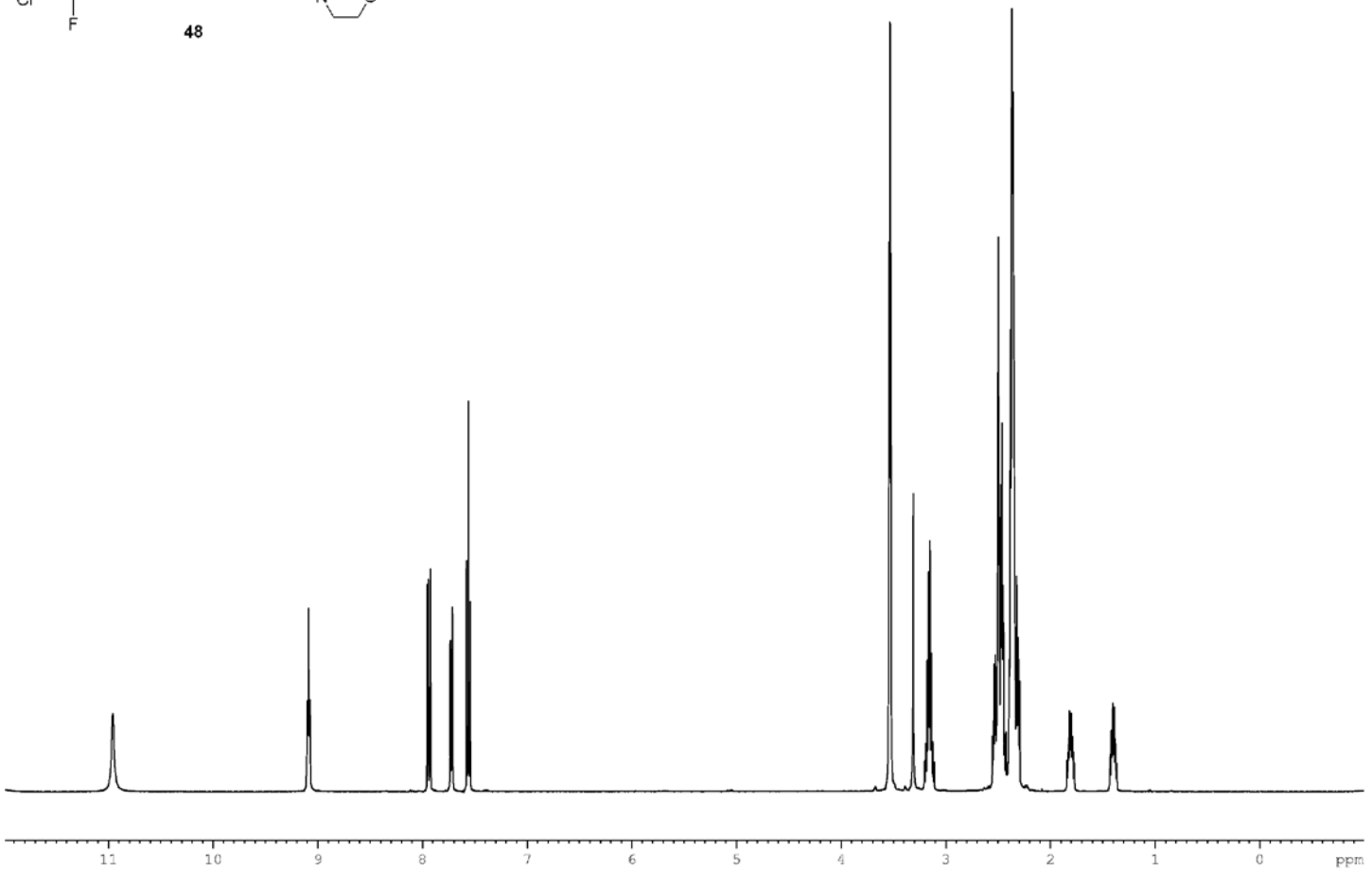

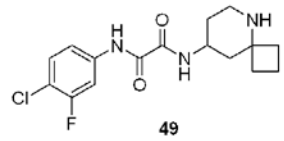

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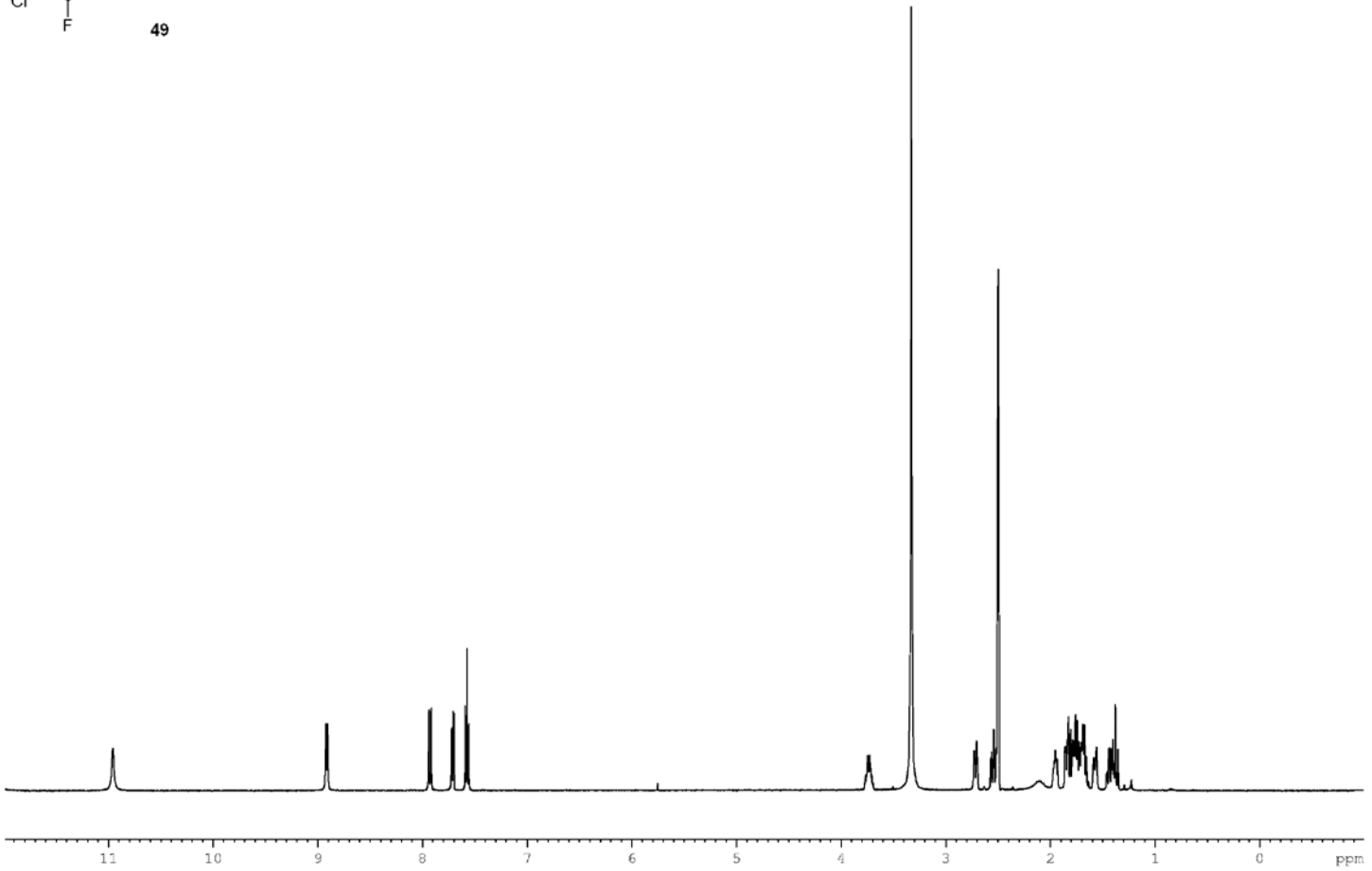

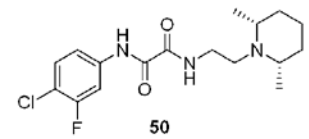

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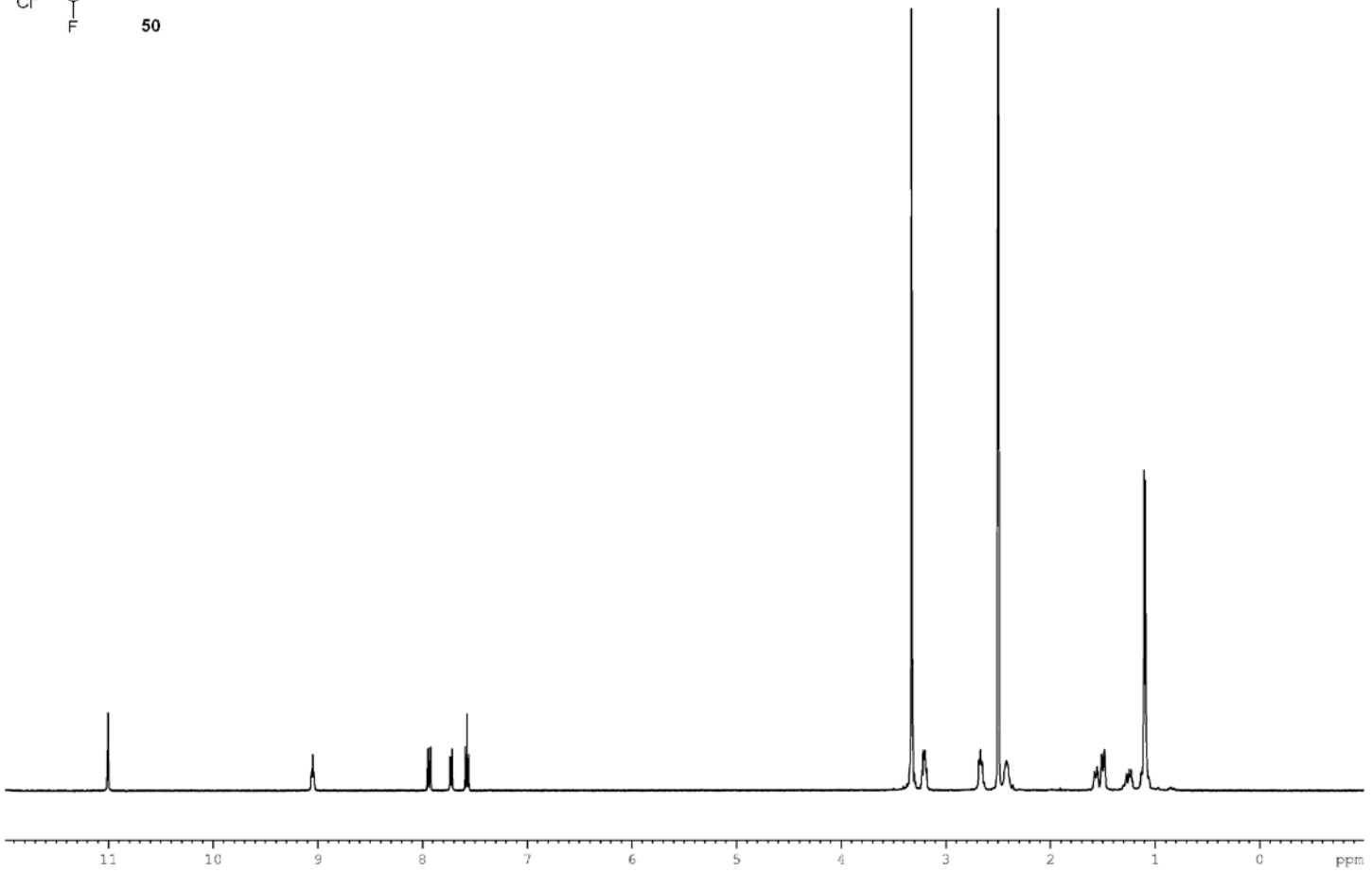

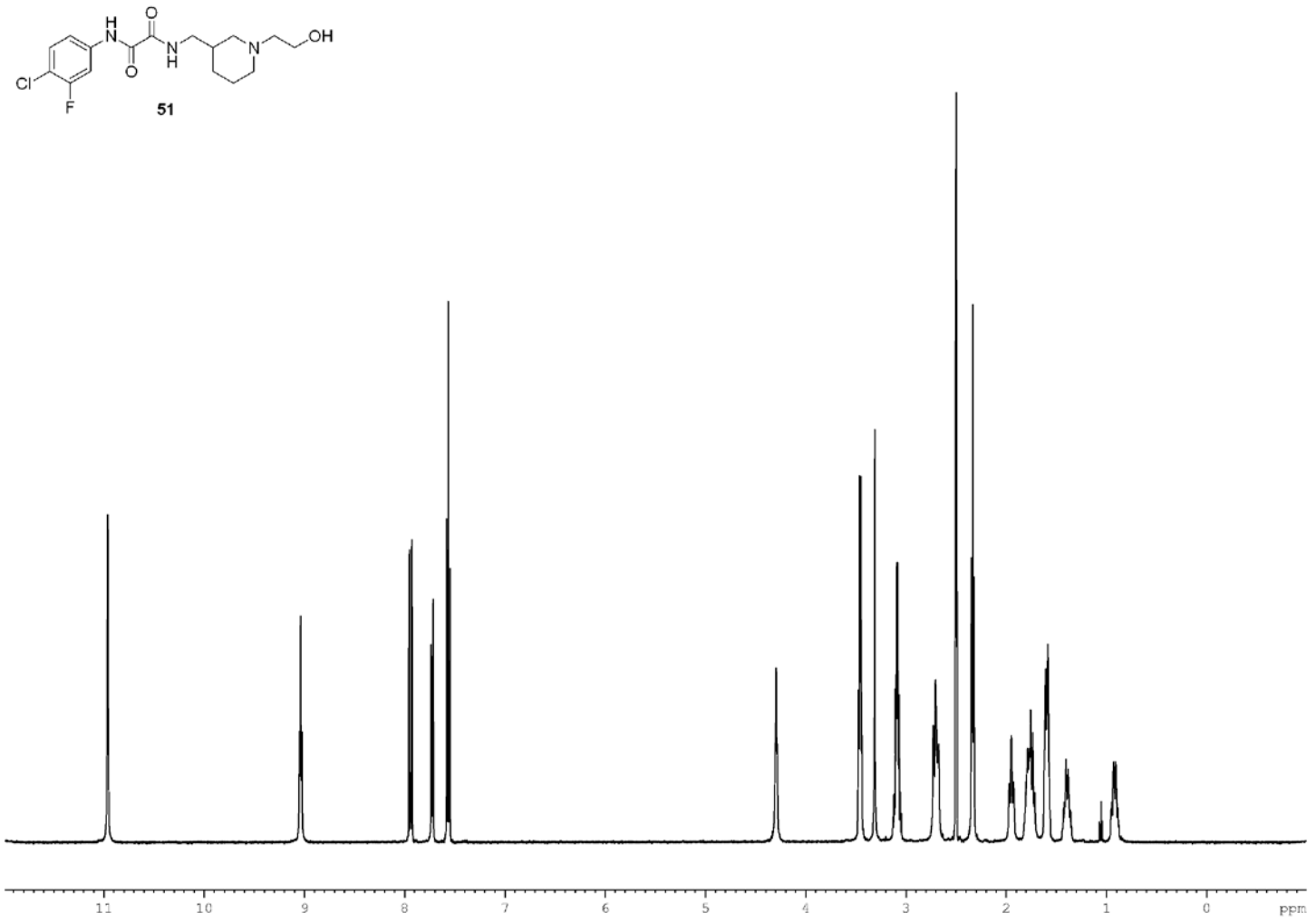
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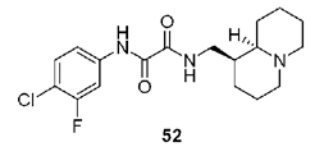

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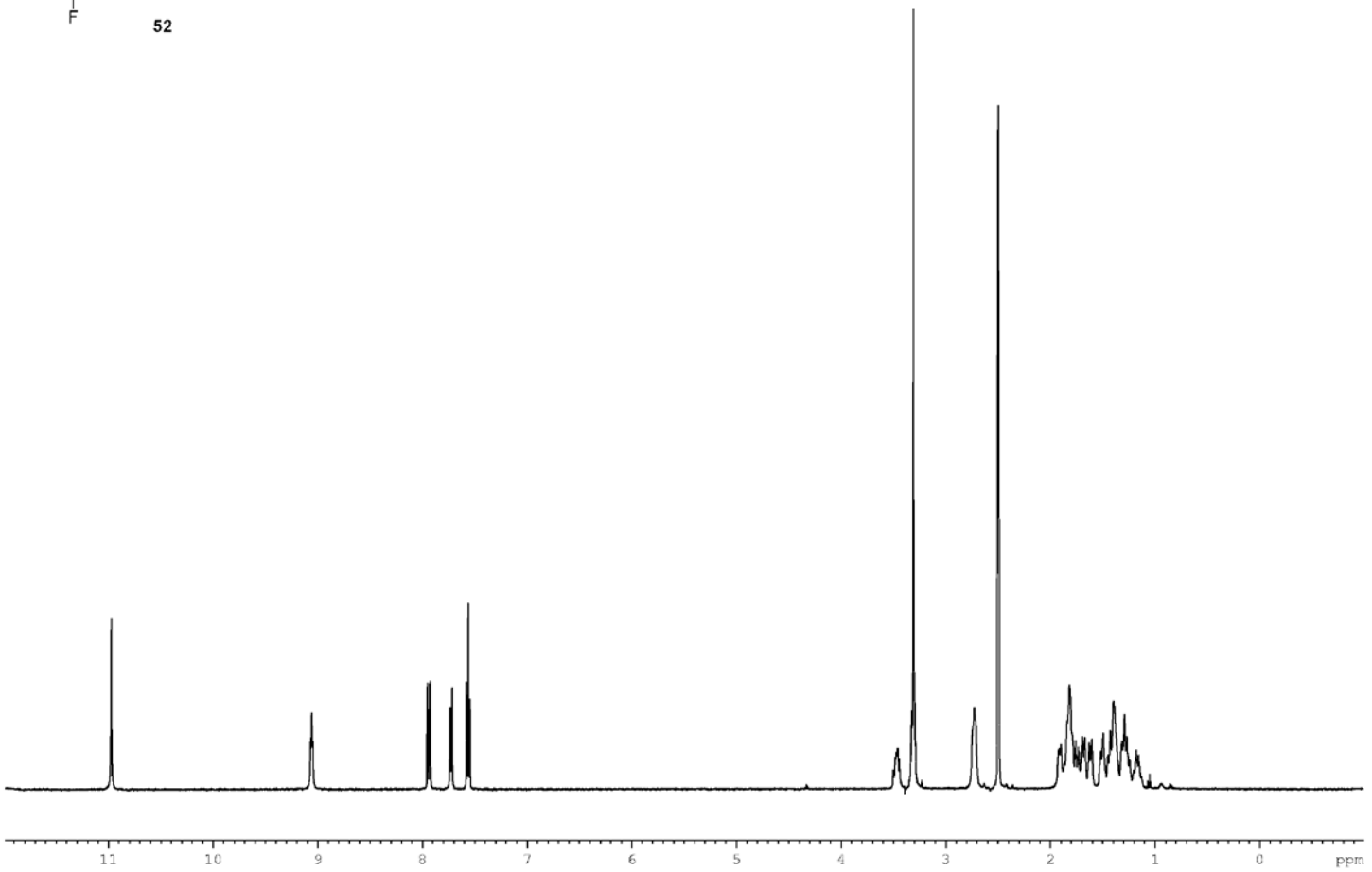

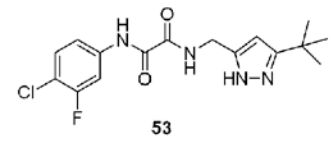

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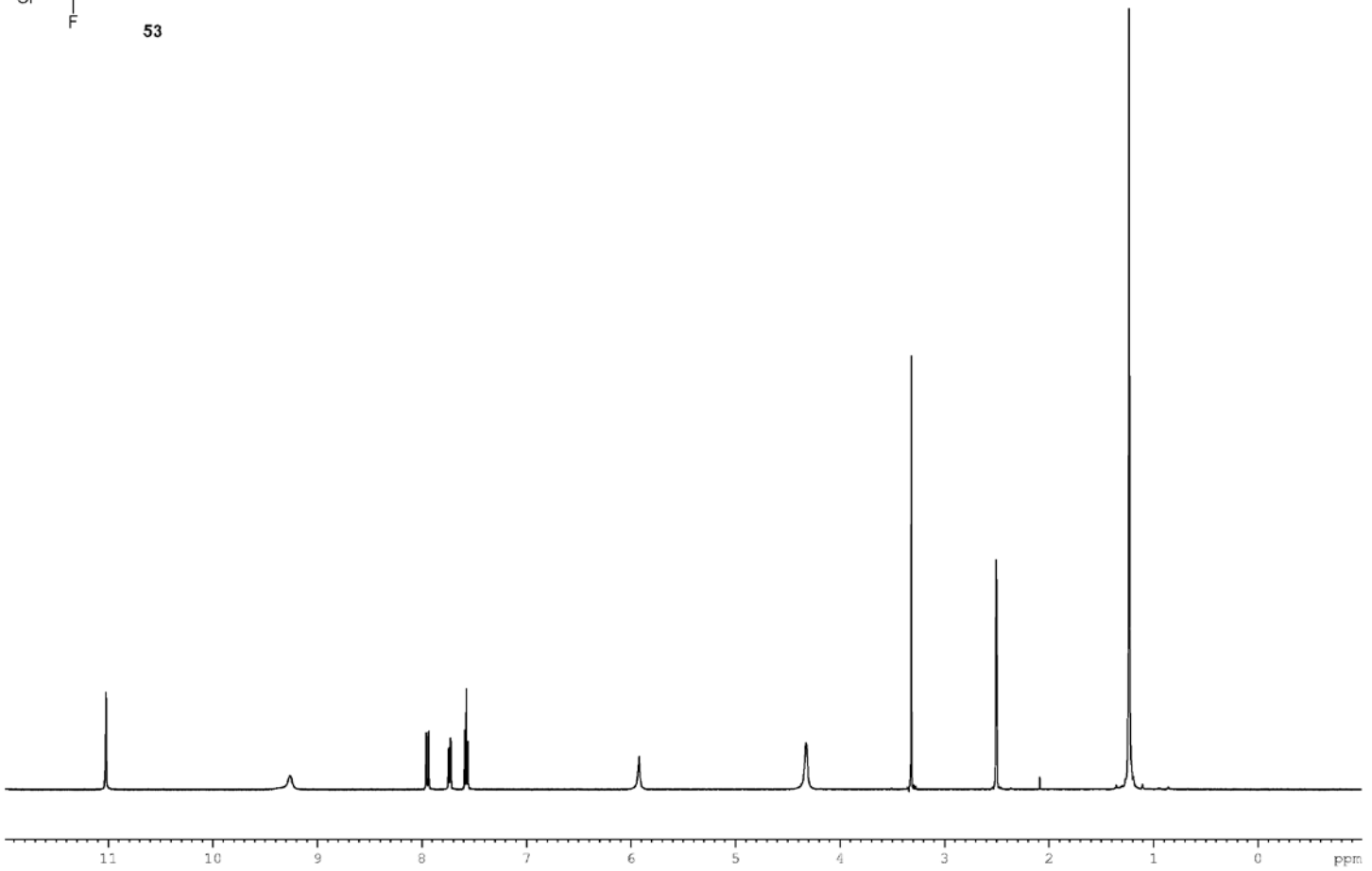

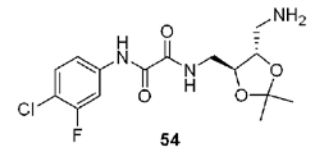

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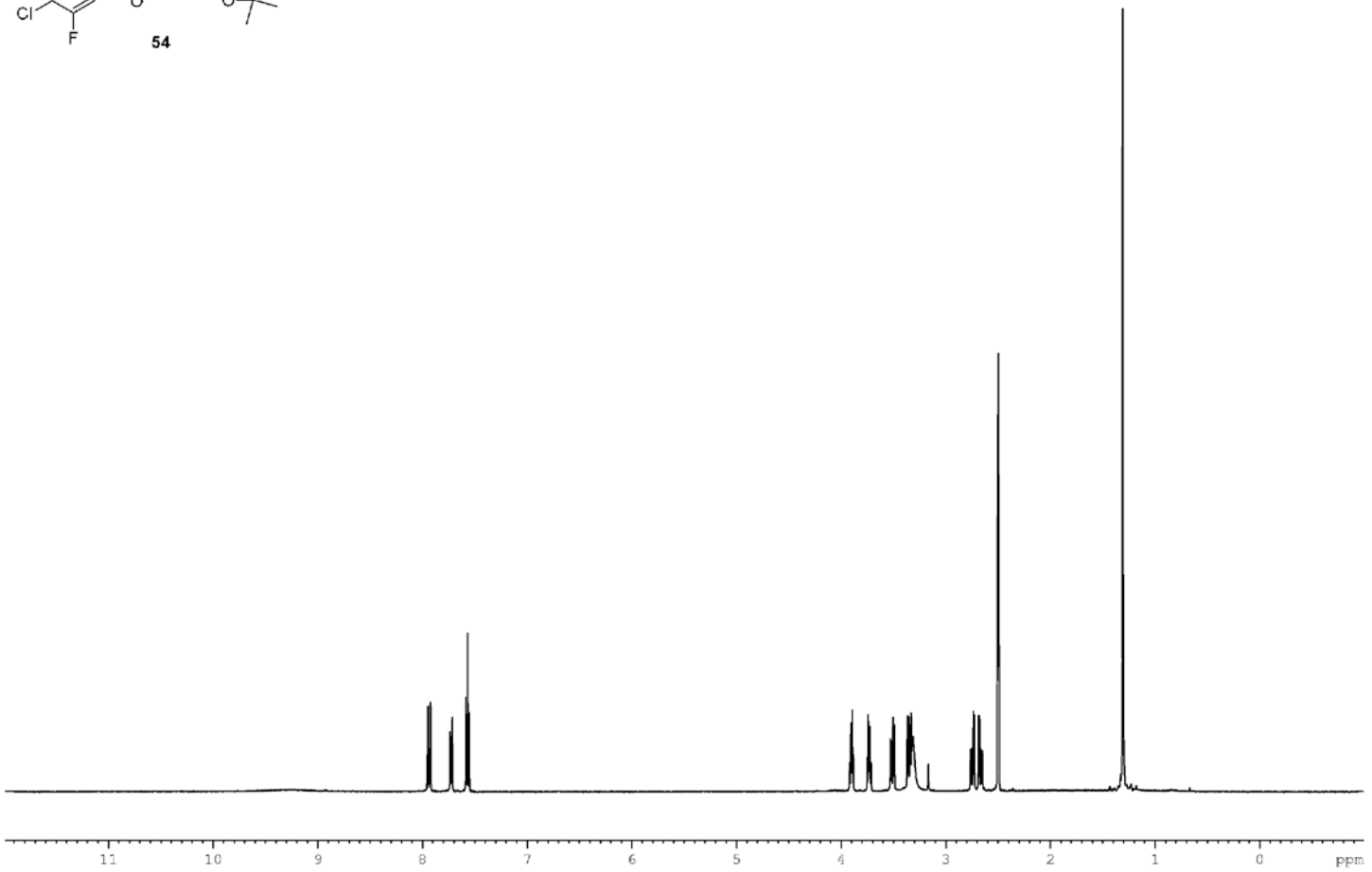

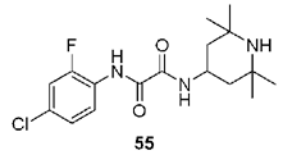

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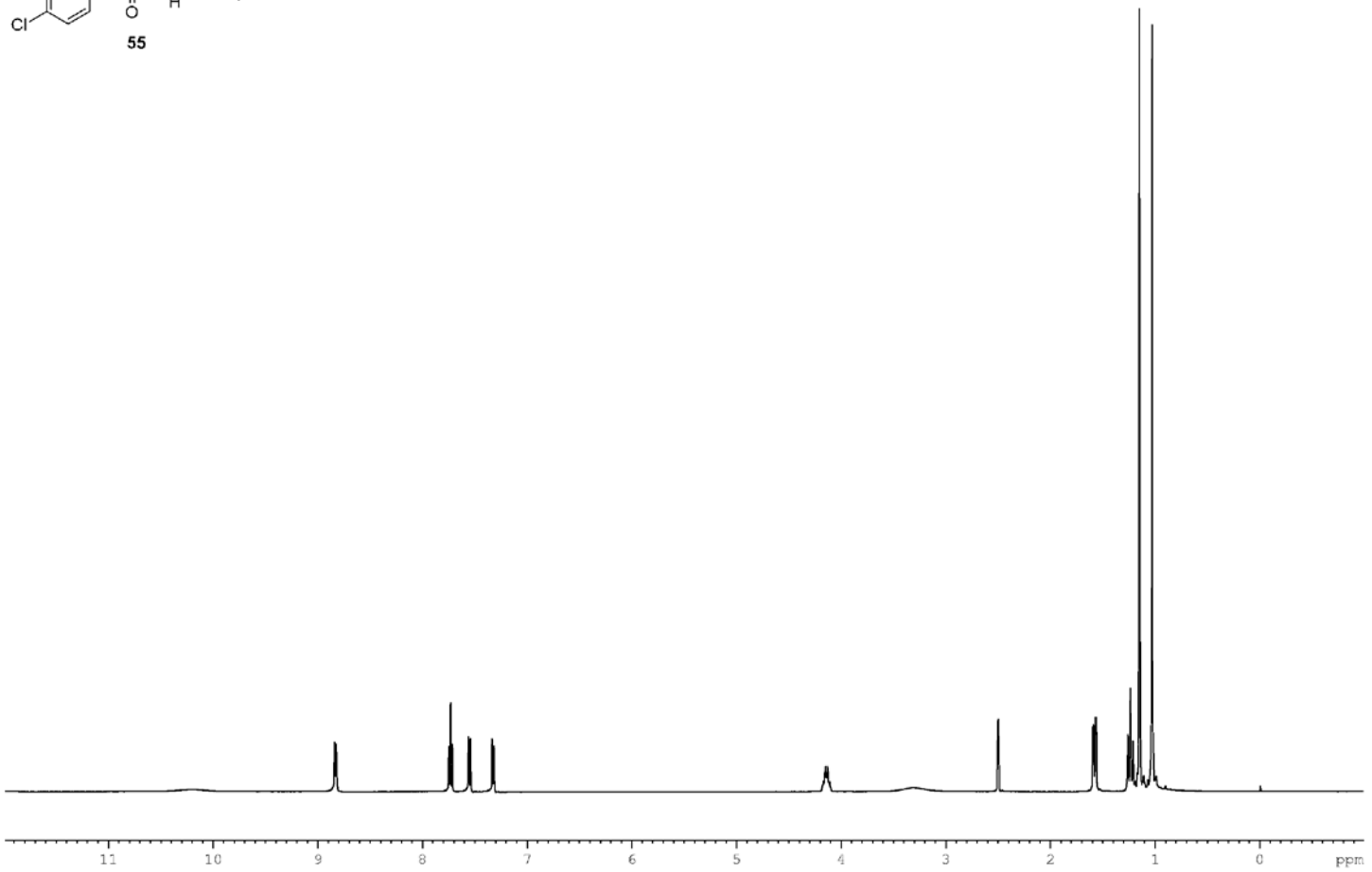

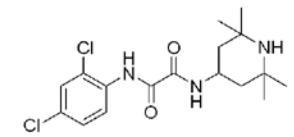

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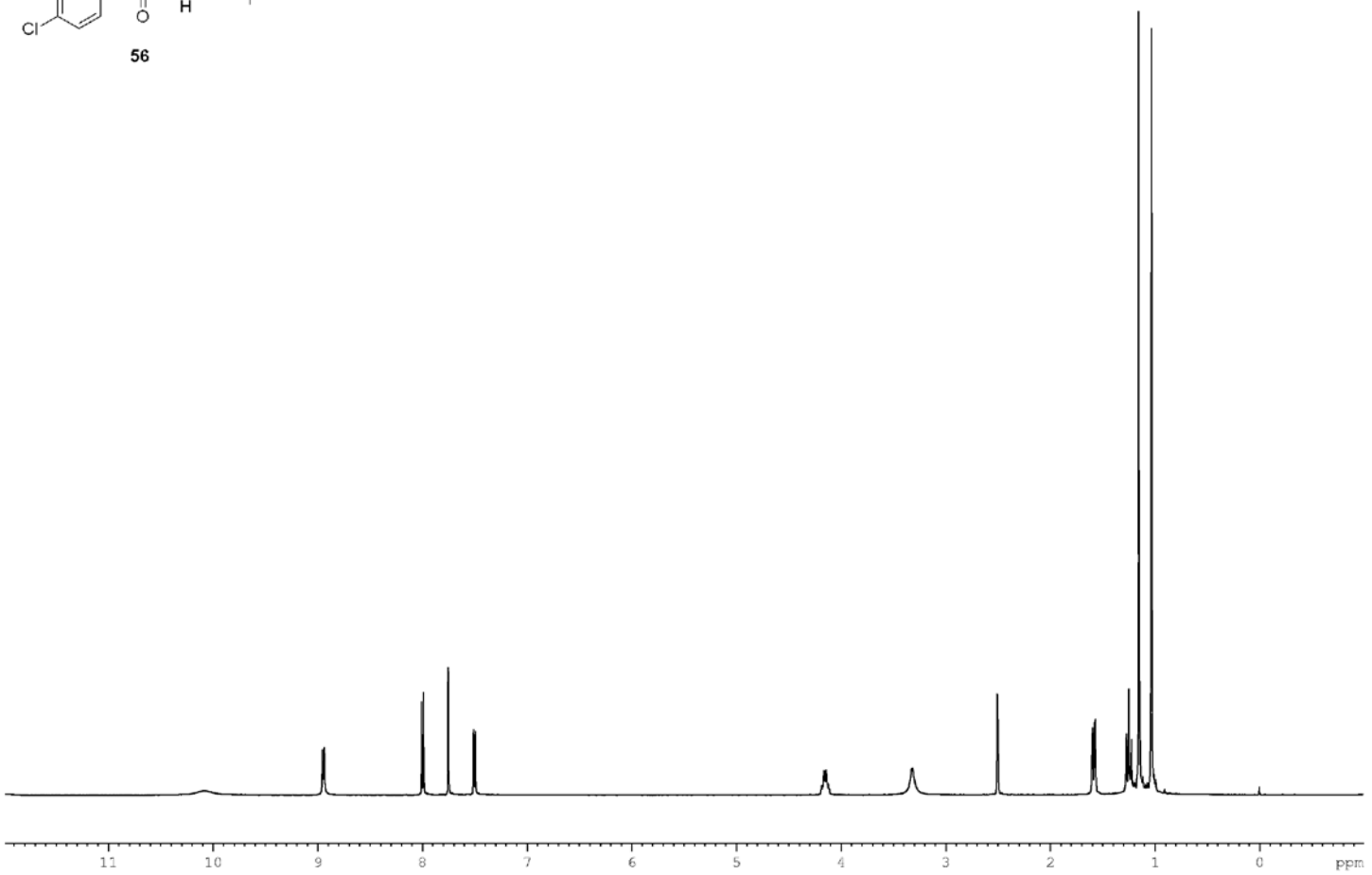

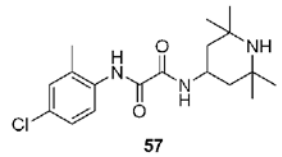

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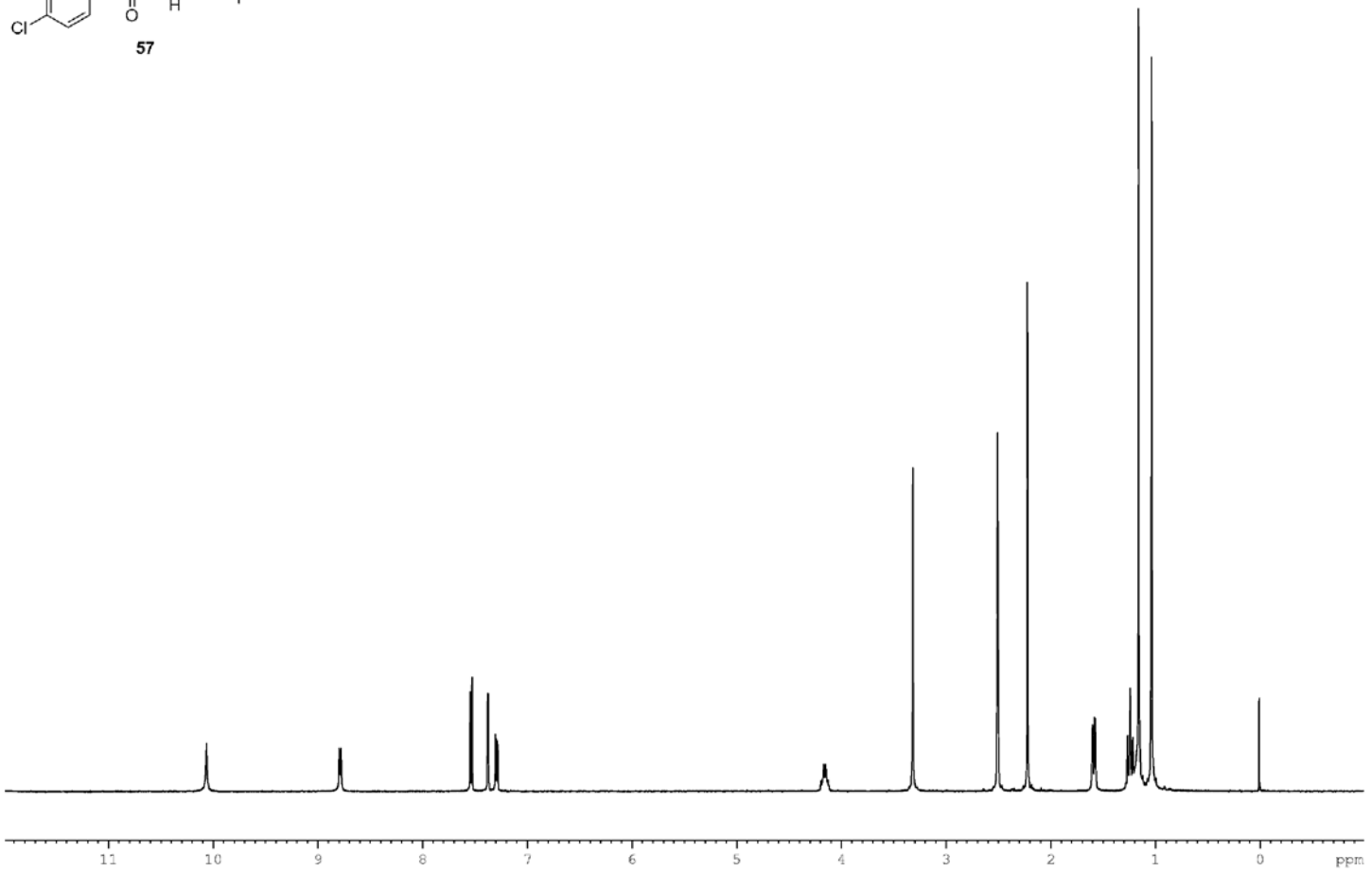

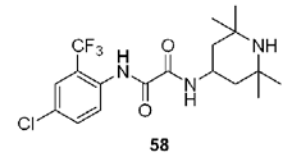

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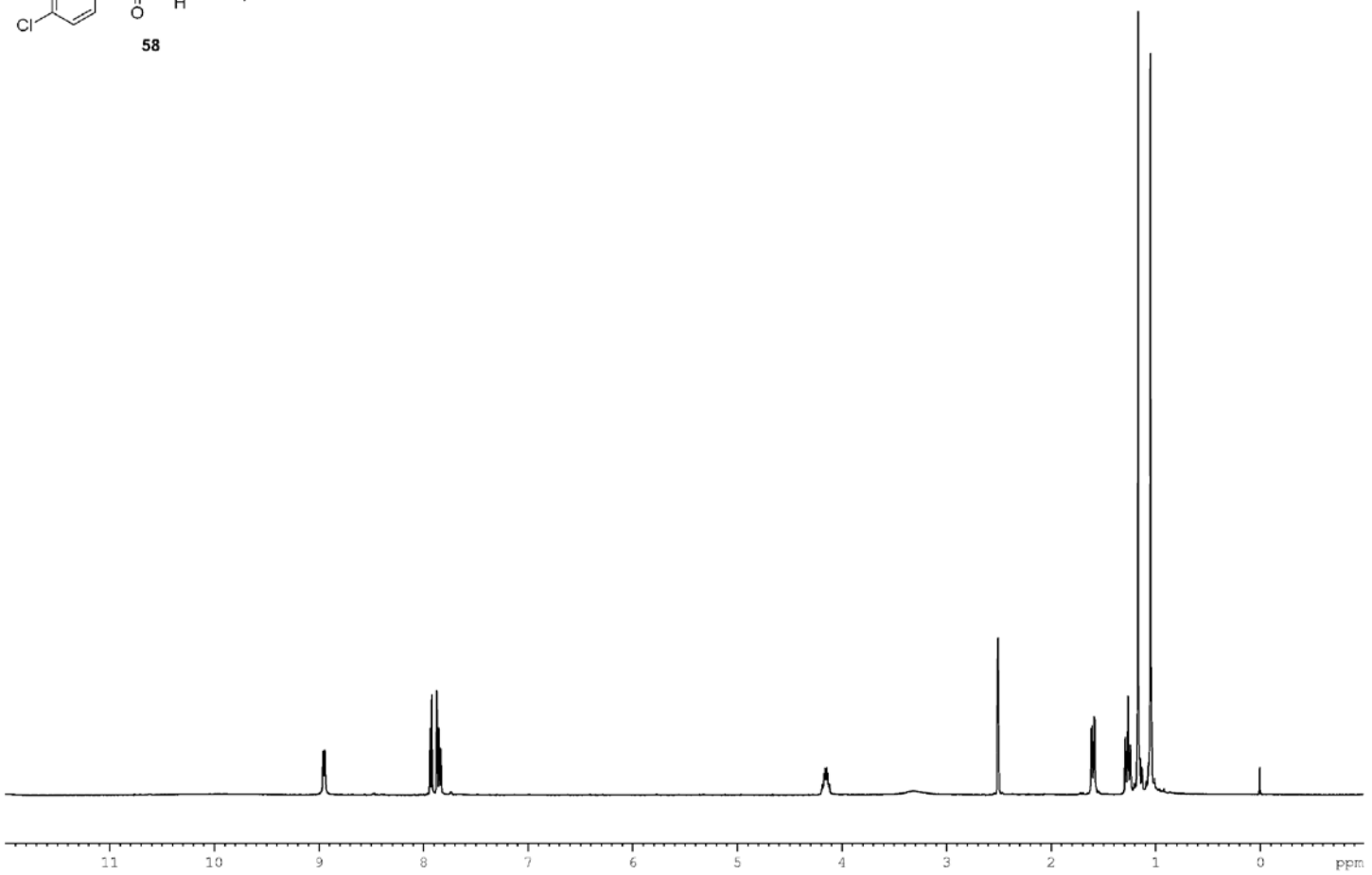

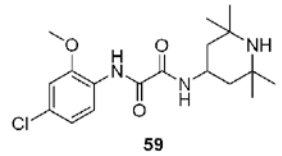

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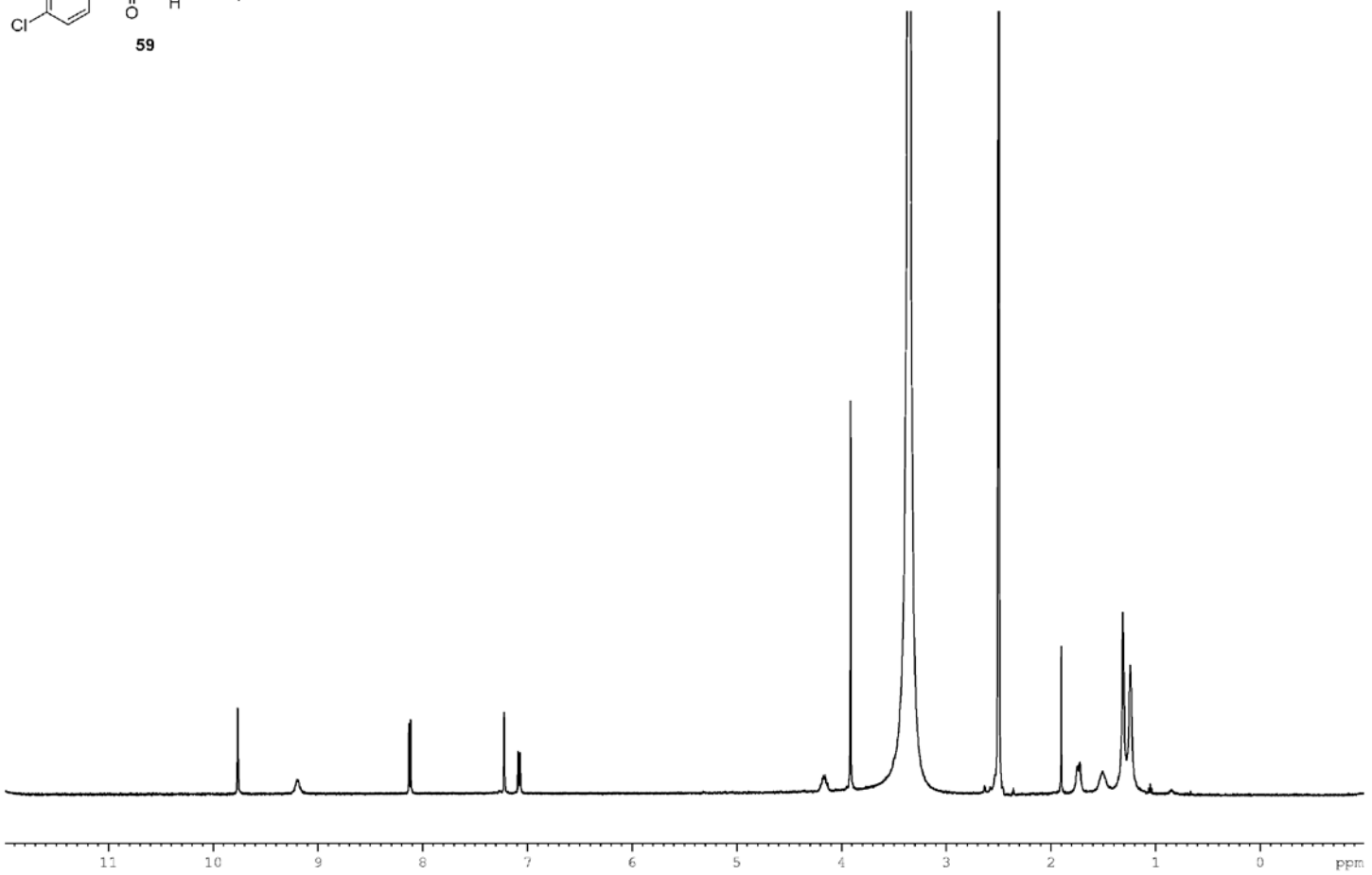

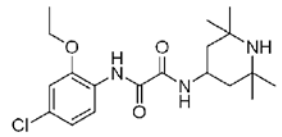
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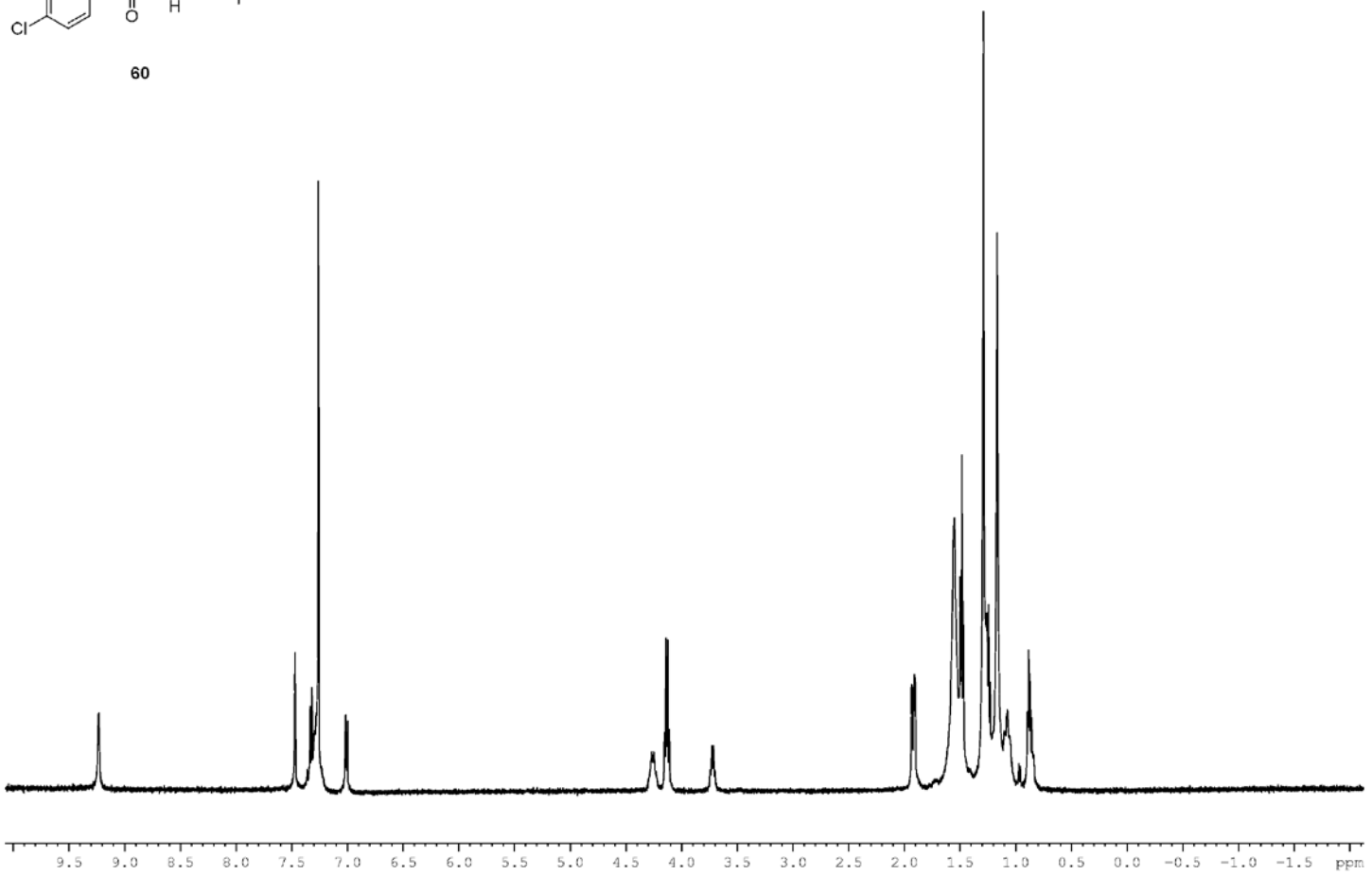
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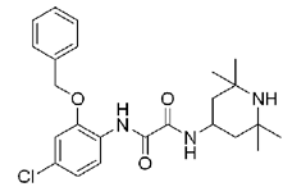
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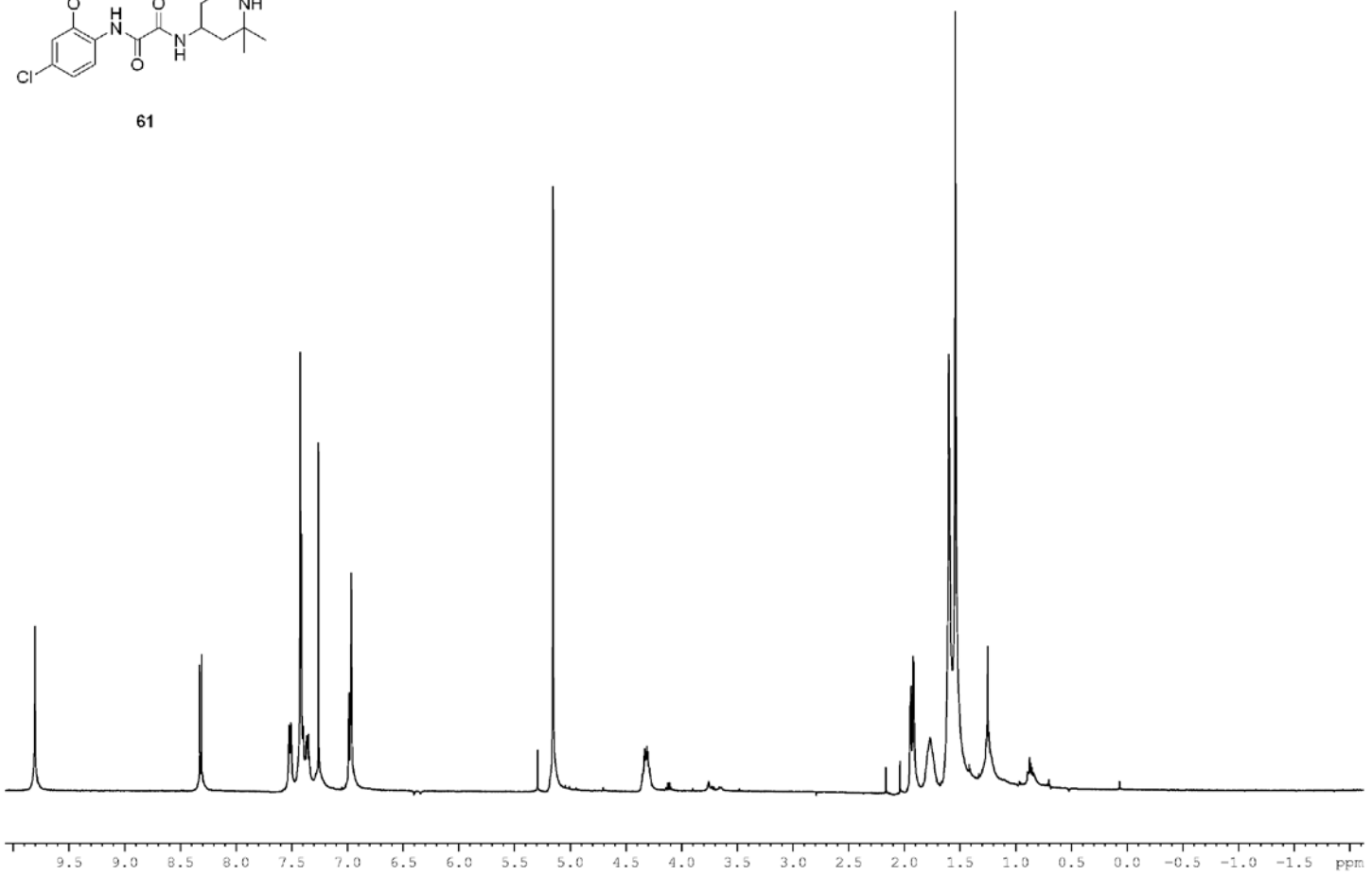
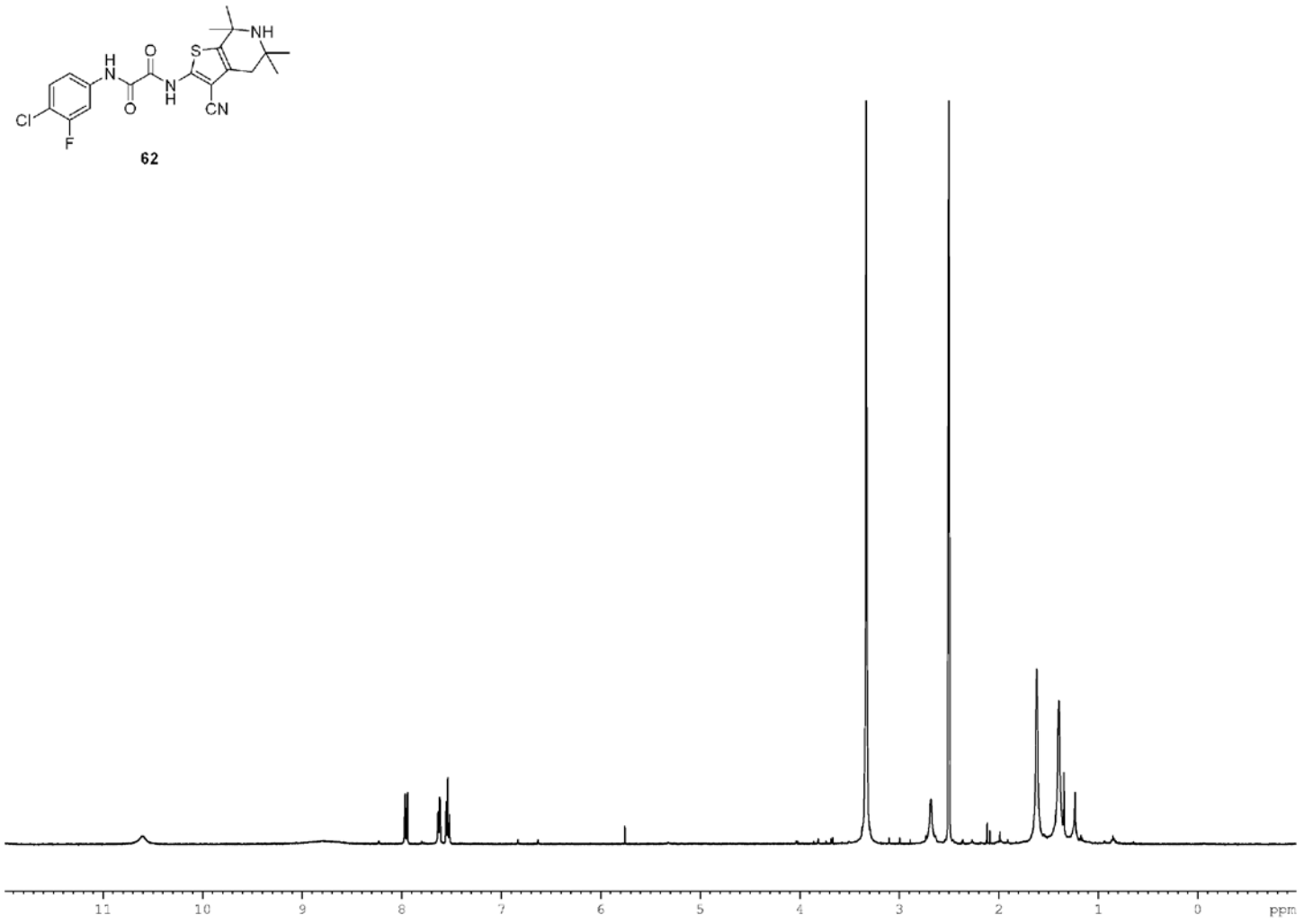

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 ppm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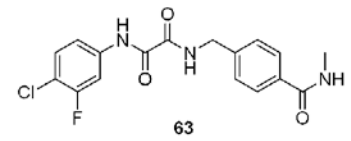

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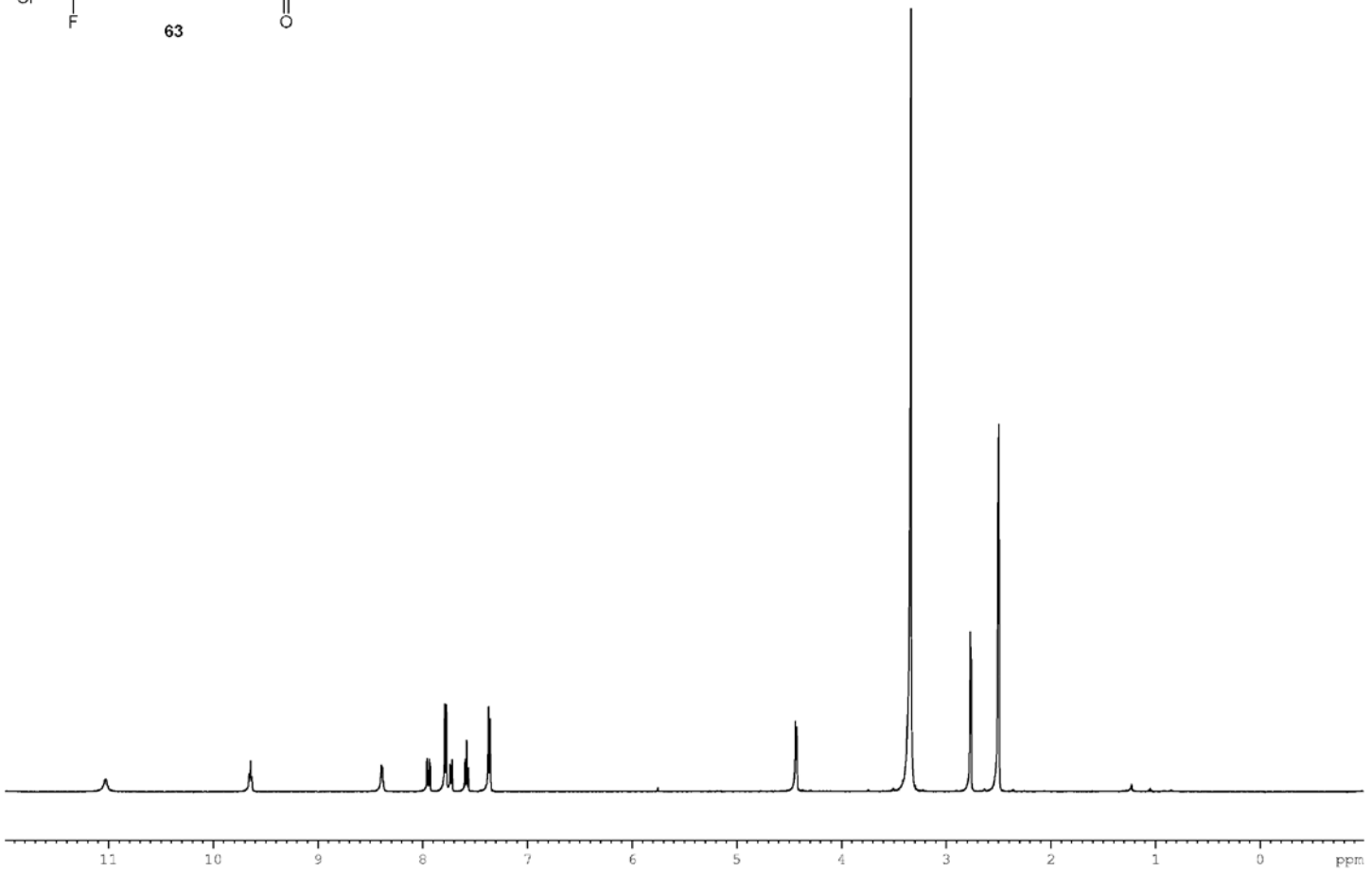

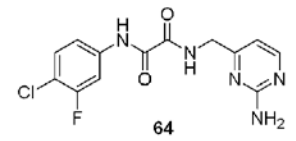

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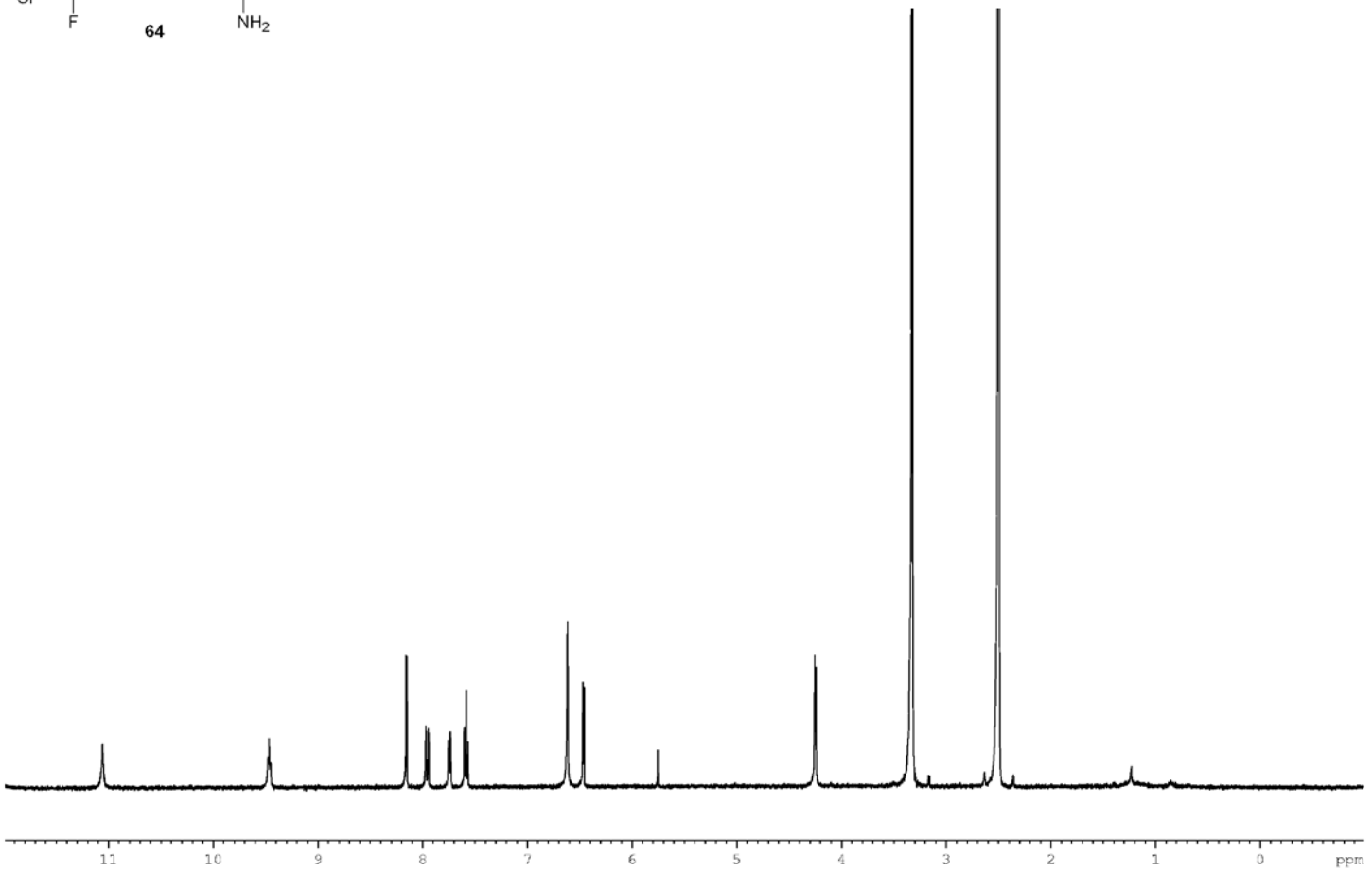

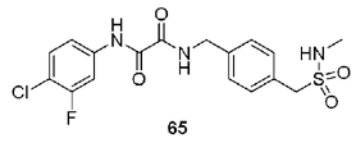

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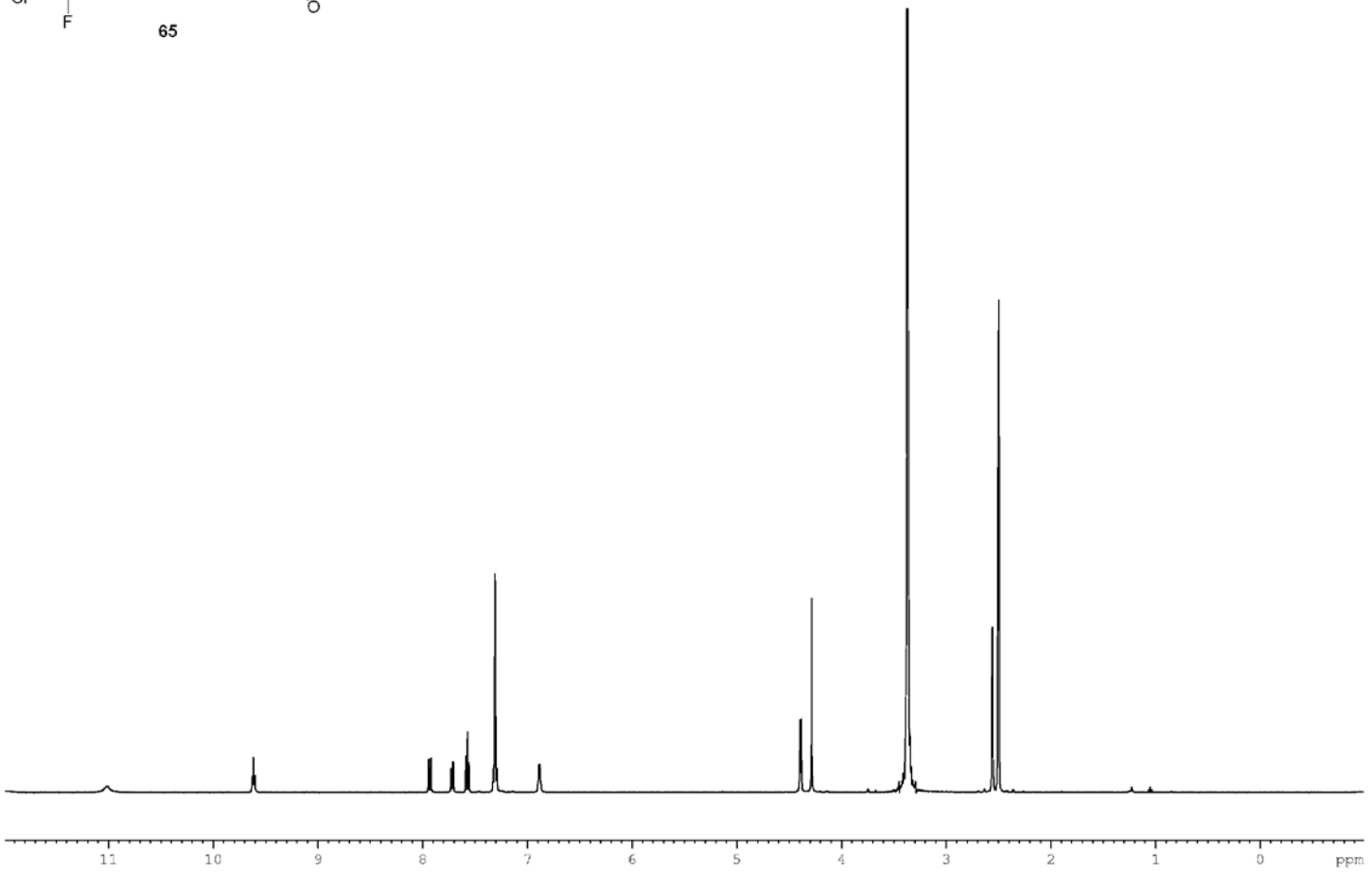

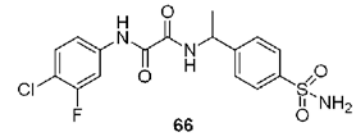

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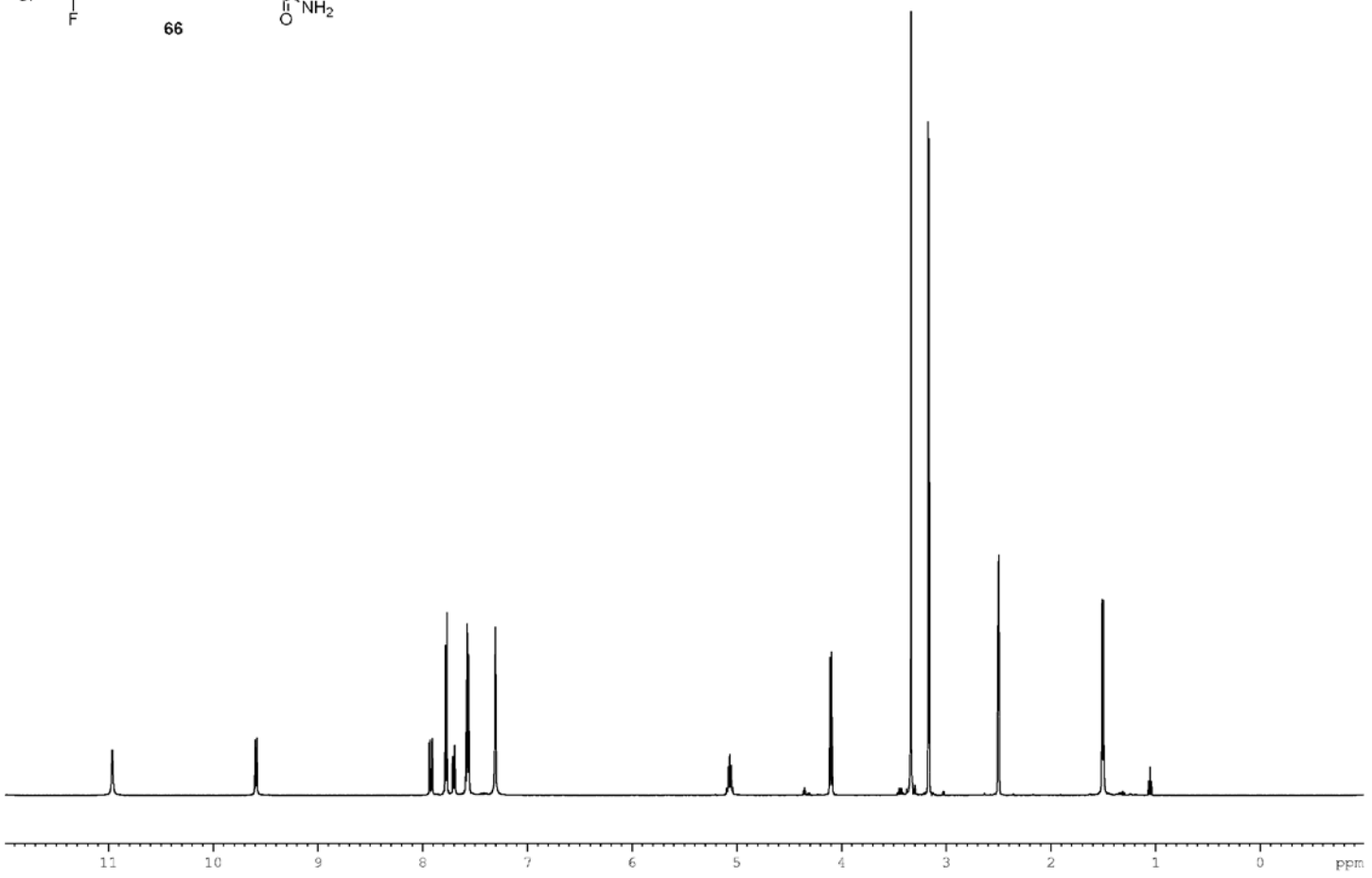

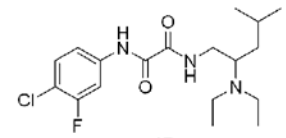

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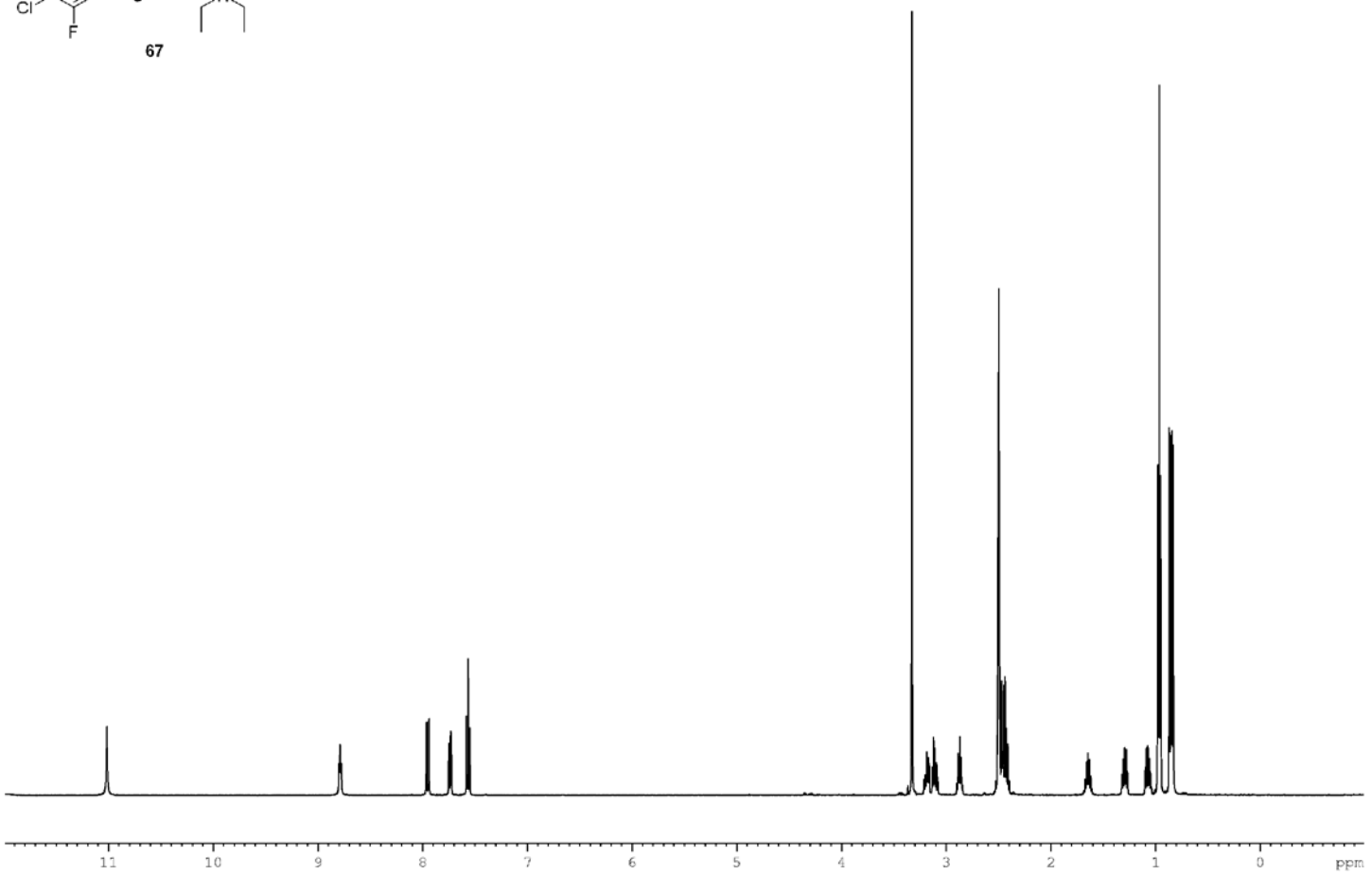

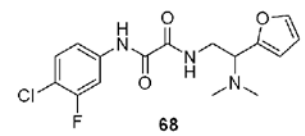

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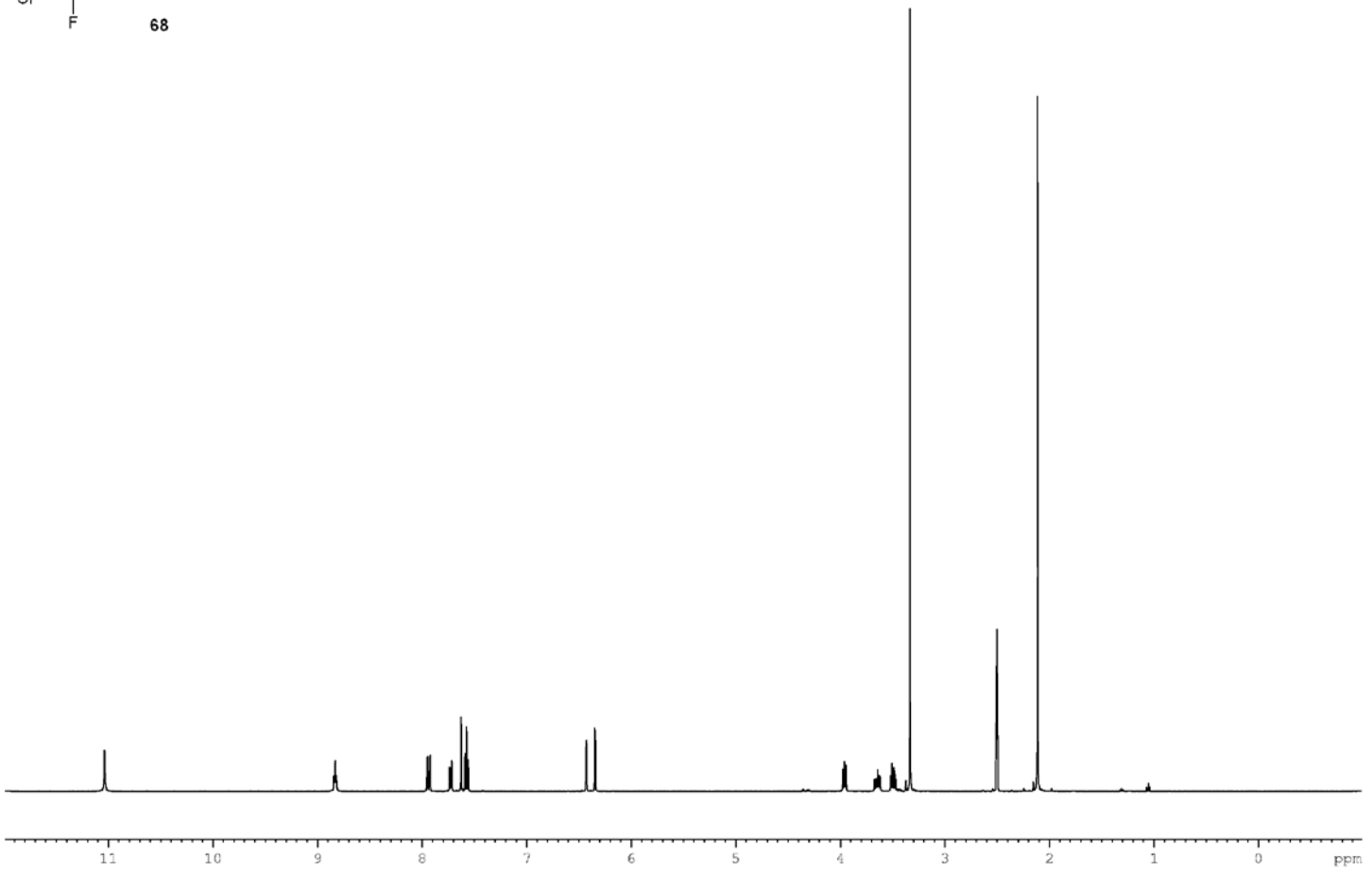

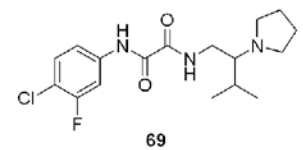

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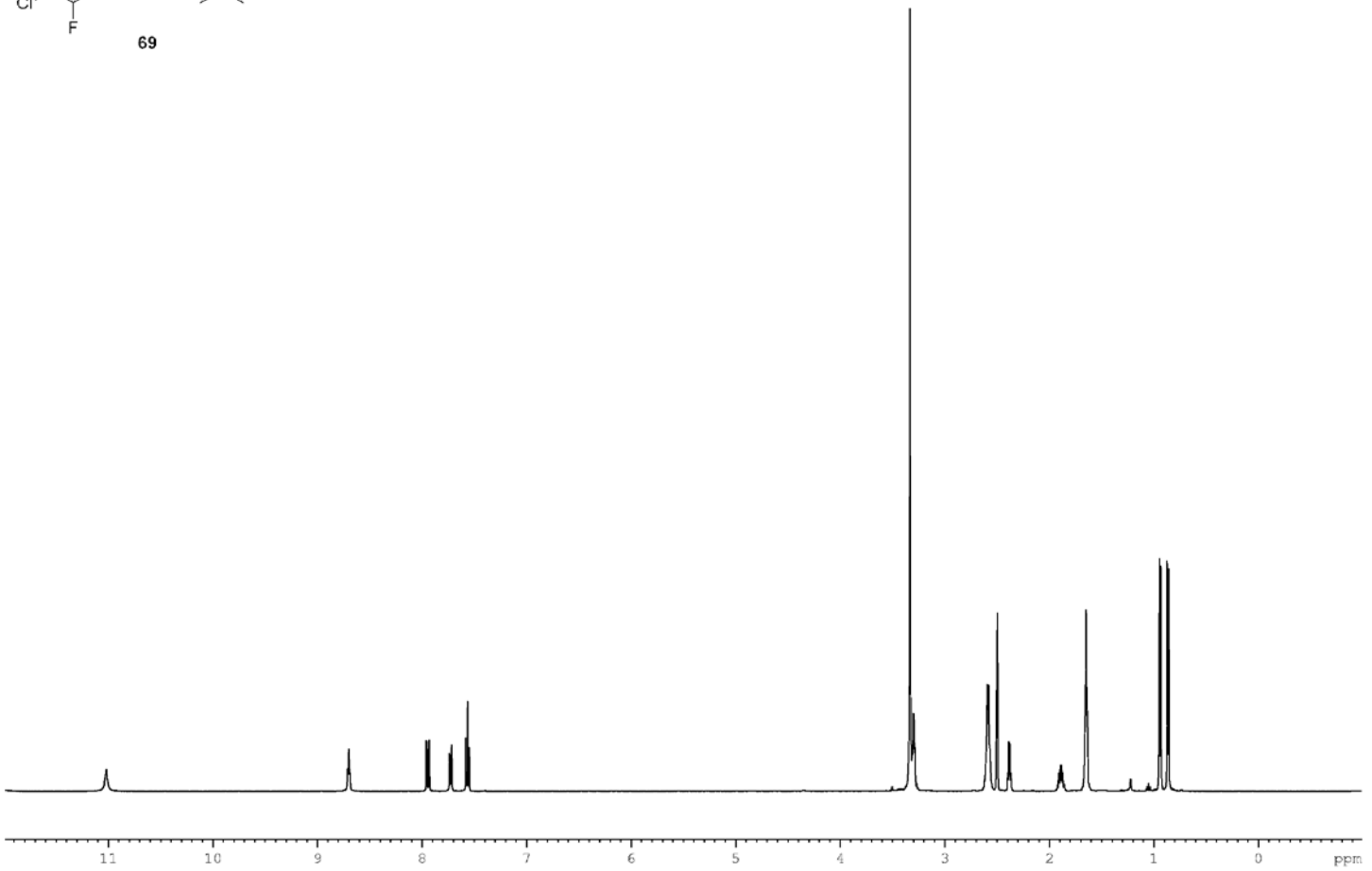

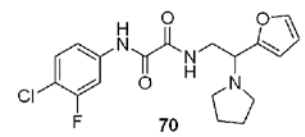

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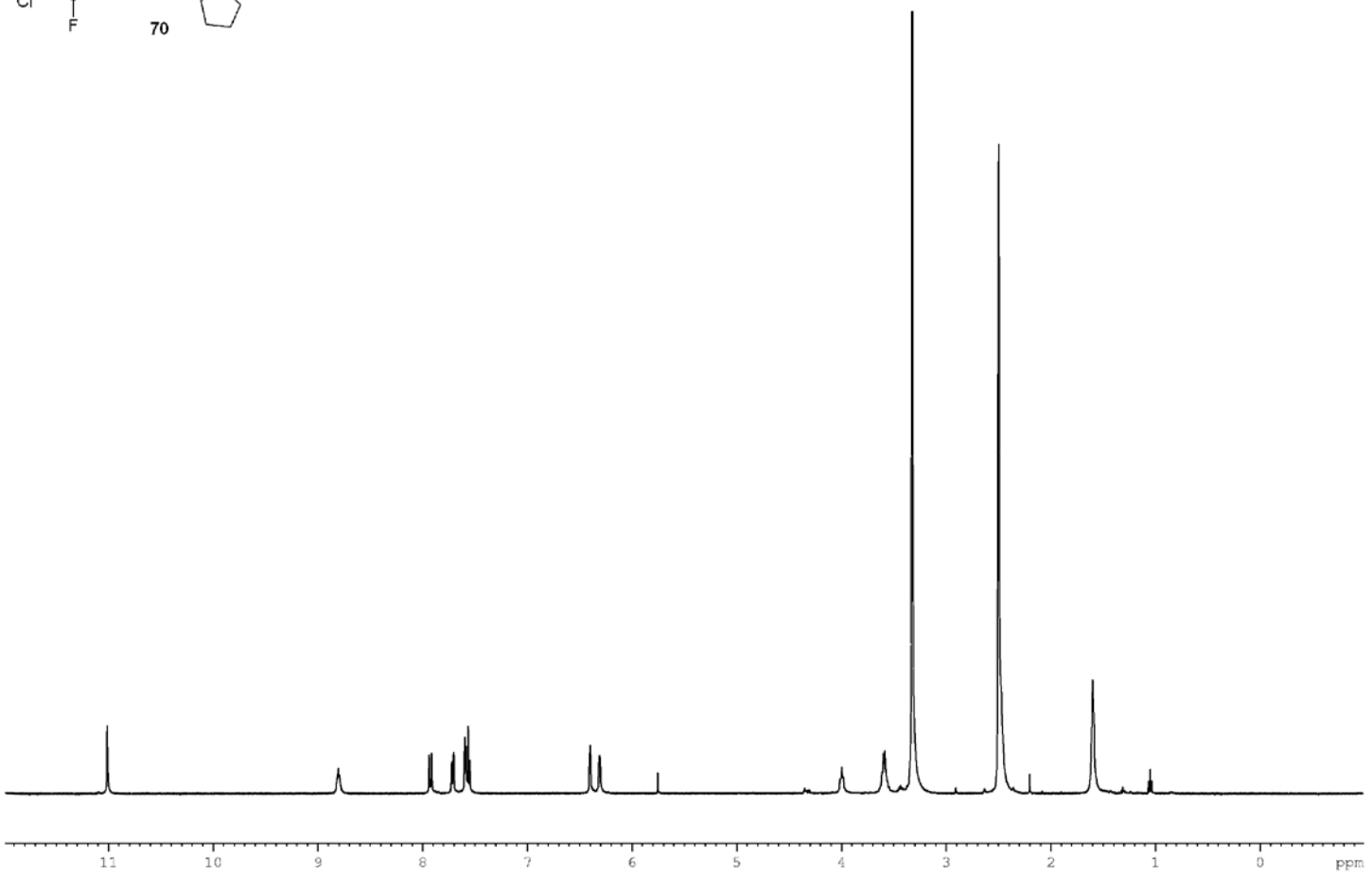

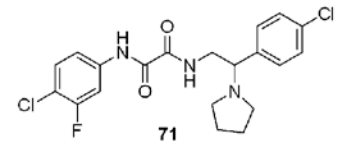

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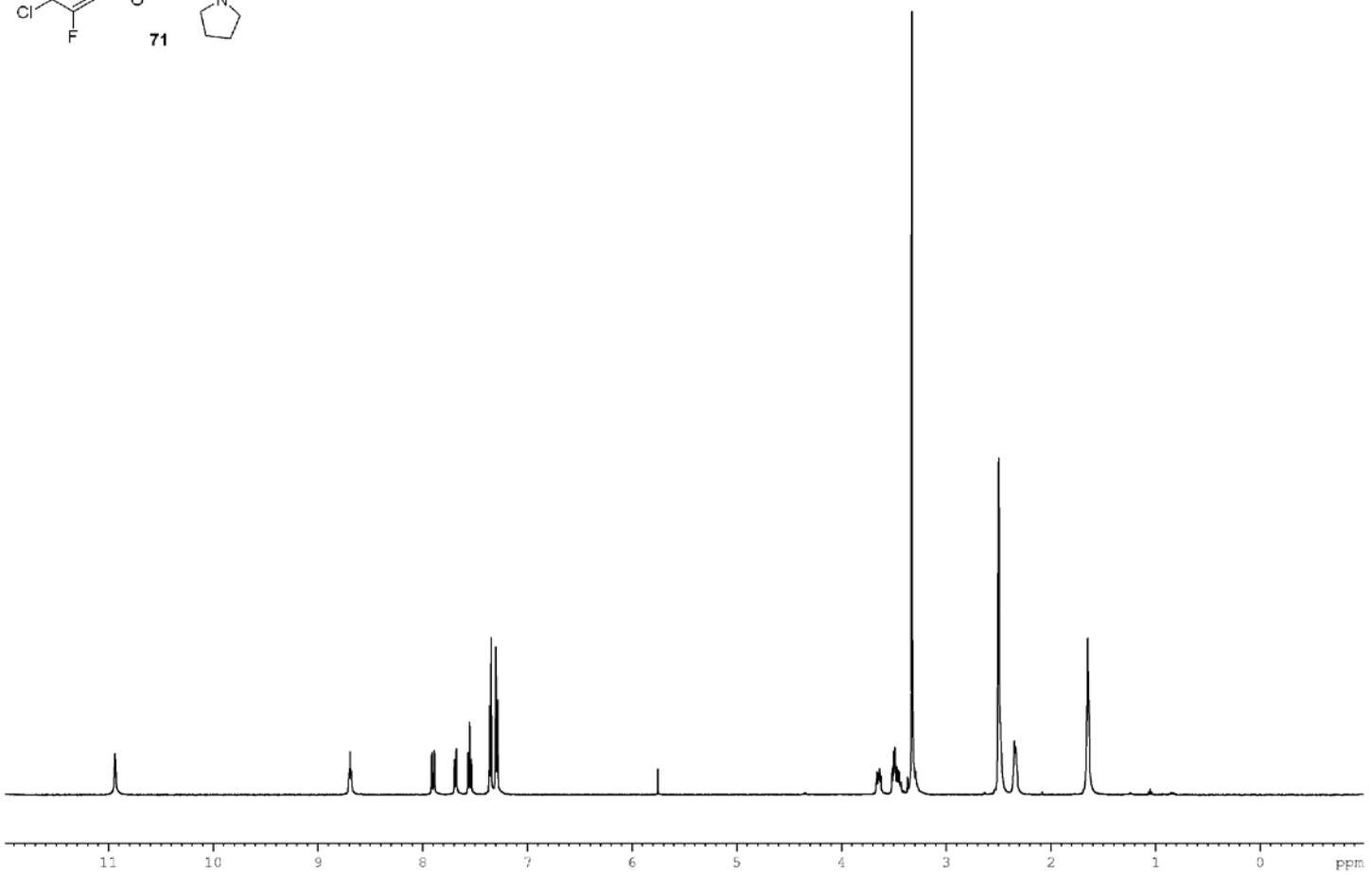

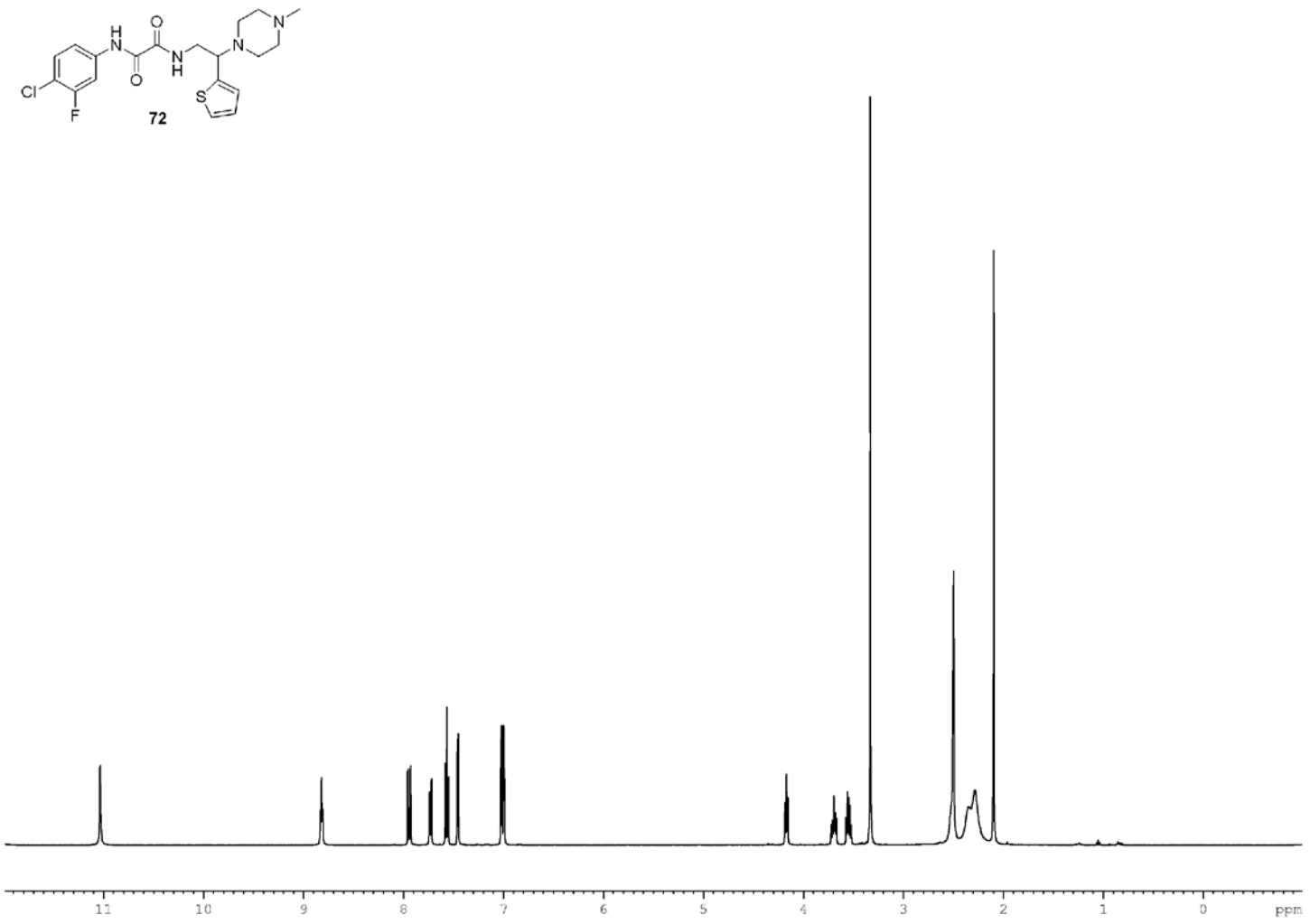
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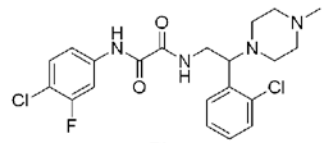

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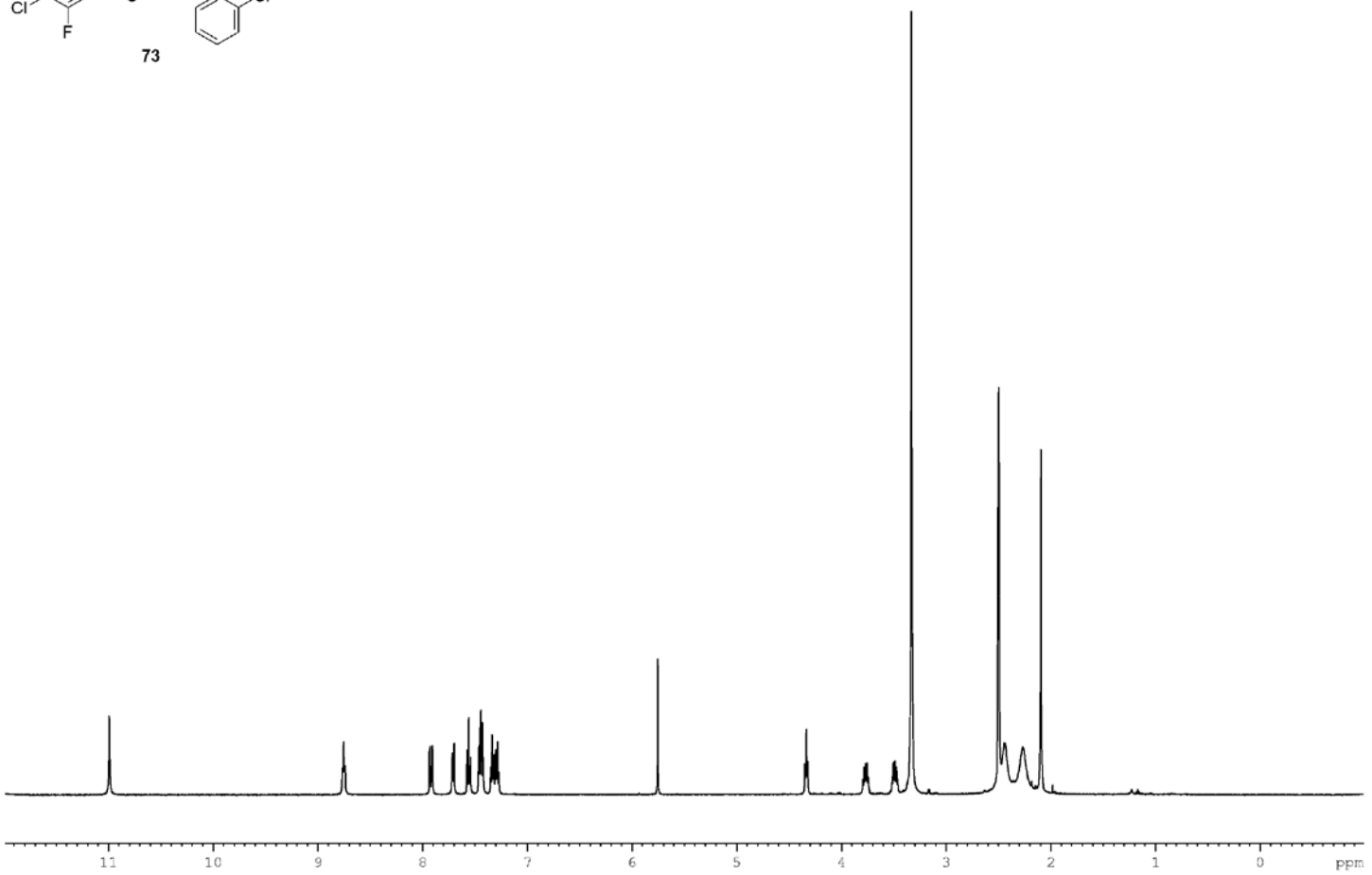

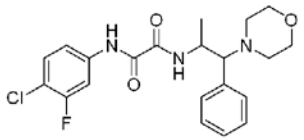

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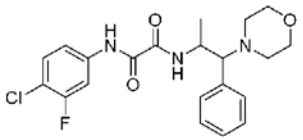

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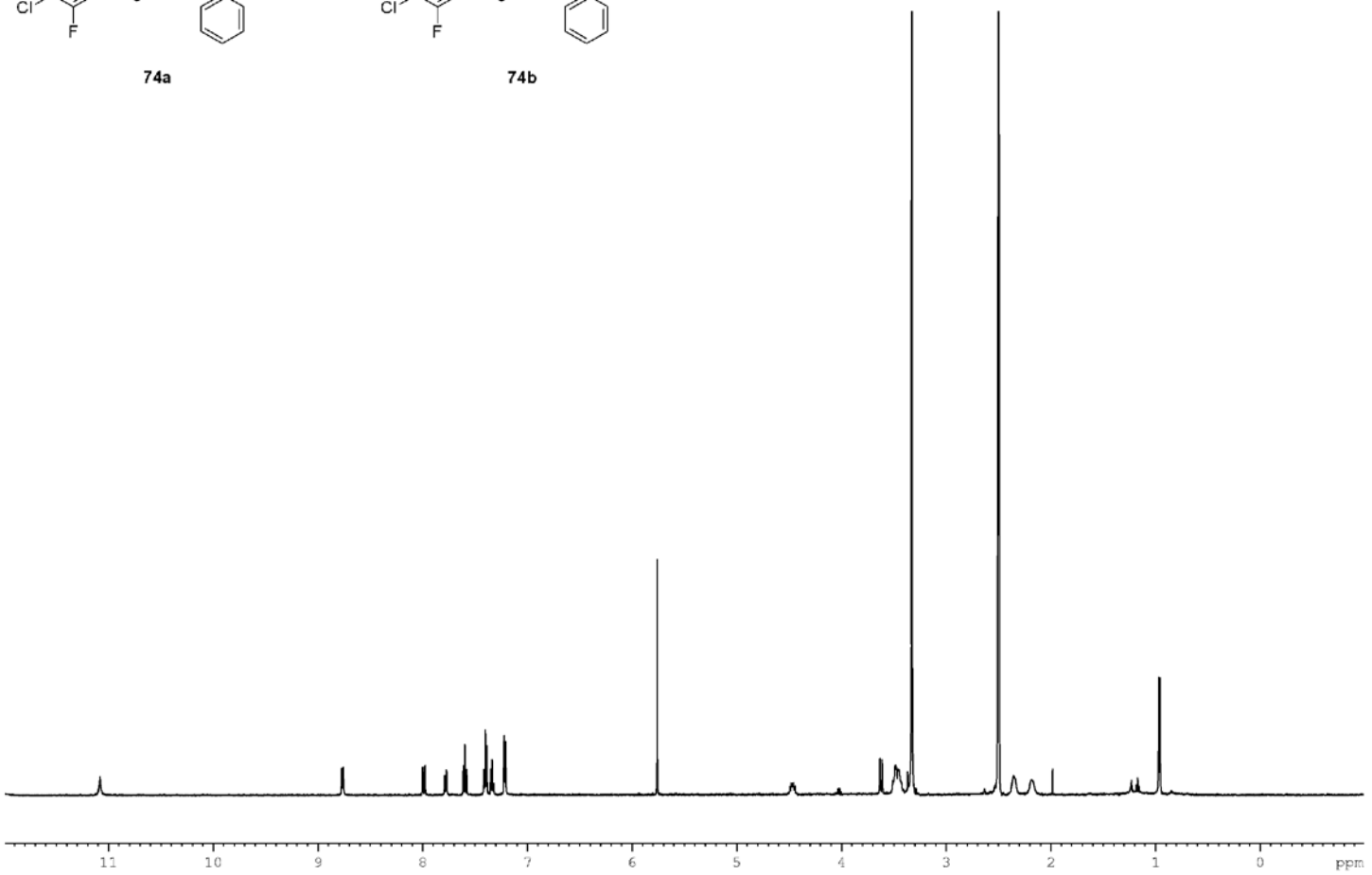

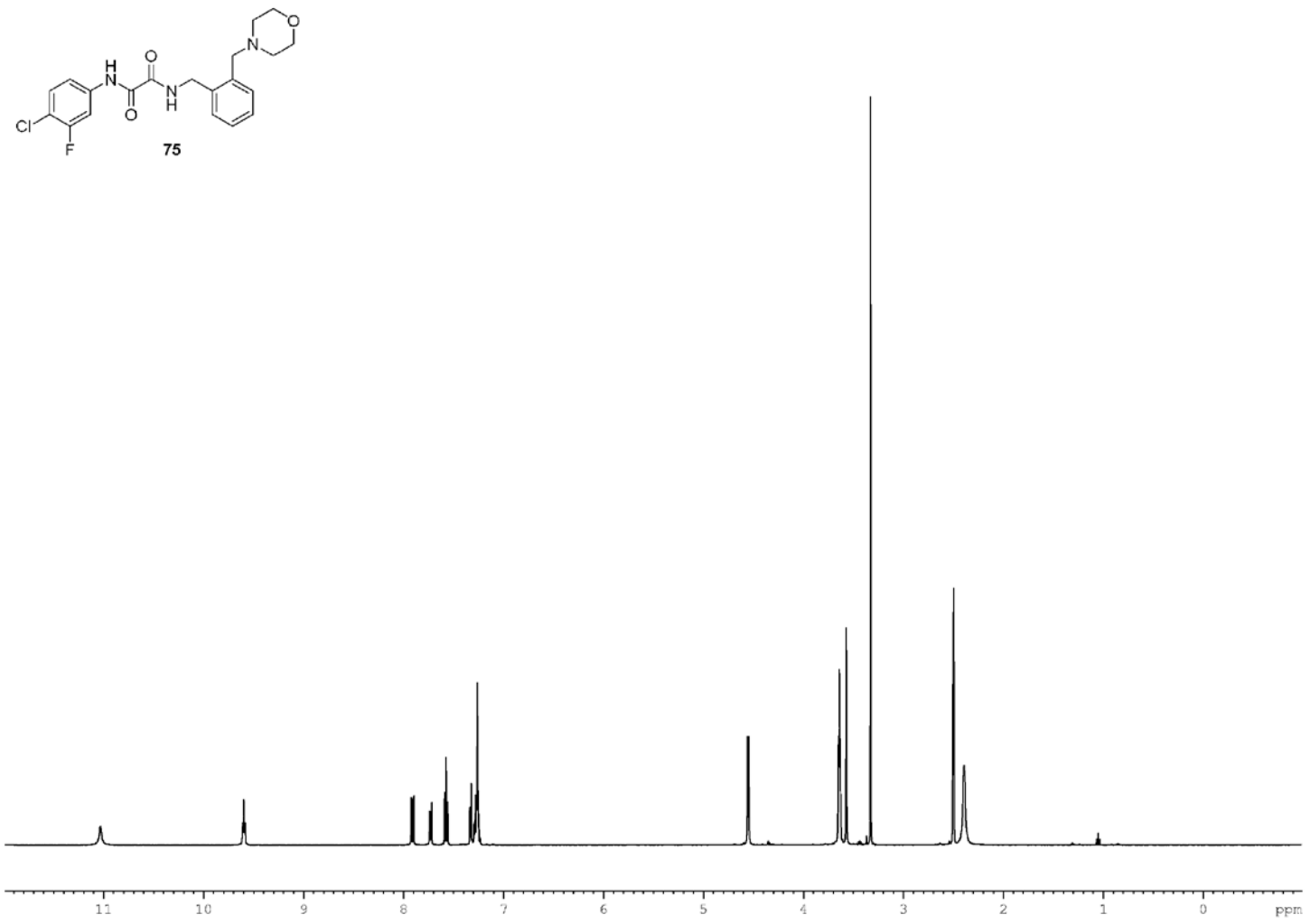
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