Supporting Information

Structure-Based Design of 1,4-Dibenzoylpiperazines as *β*-catenin/B-Cell Lymphoma 9 Protein–Protein Interaction Inhibitors

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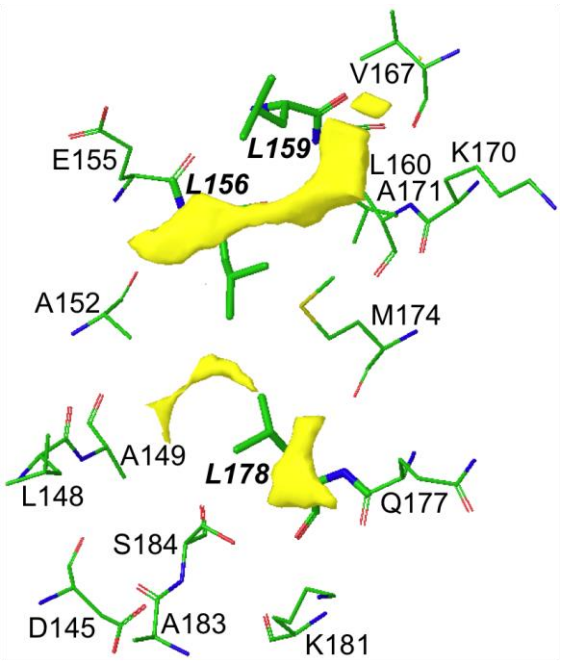


Figure S1. Stick model for the results of the hydrophobic SiteMap analysis (PDB id, 2GL7[1]). The threshold of the SiteMap contour was set to –0.5 kcal/mol. The *β*-catenin residues are colored green.

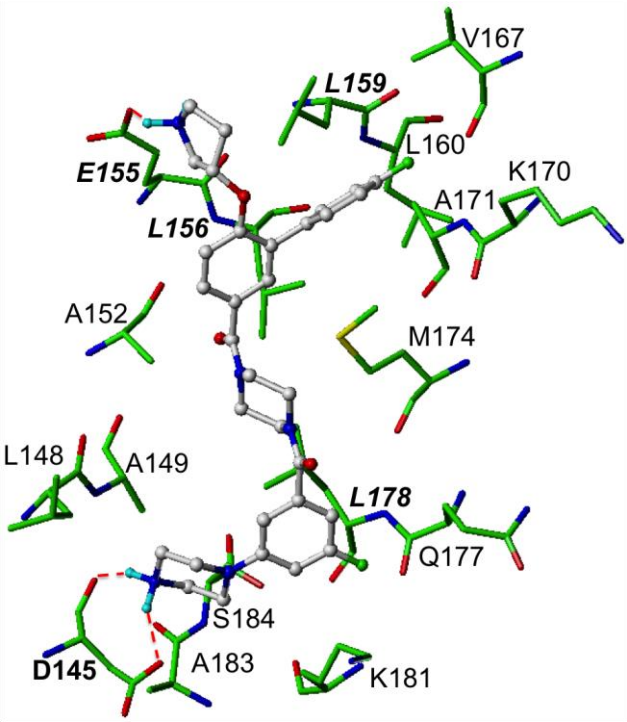


Figure S2. Stick model of the AutoDock predicted binding conformation of **3** in *β*-catenin (PDB id, 2GL7[1]). The *β*-catenin residues are colored green. Compound **3** is colored gray.

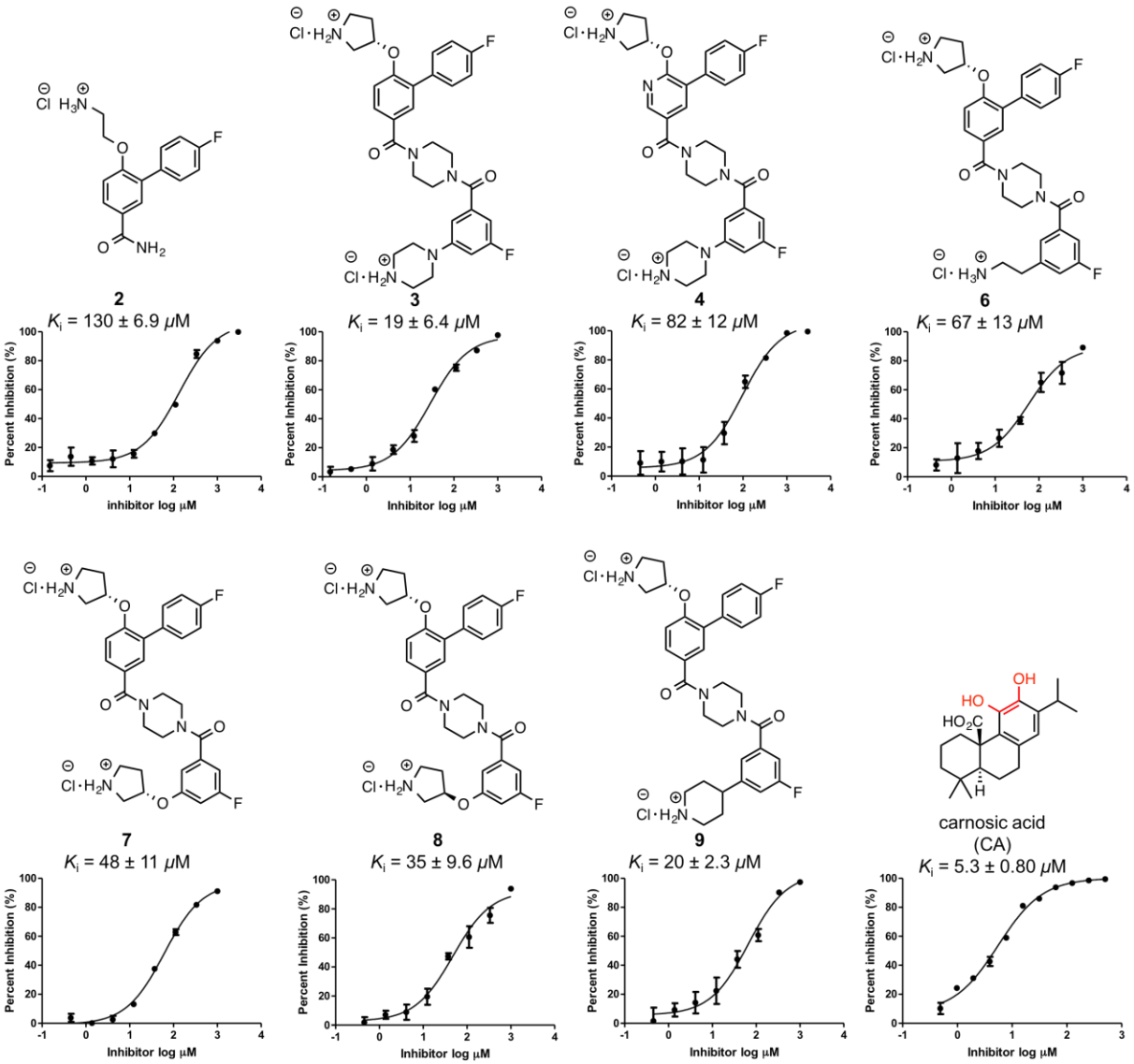


Figure S3. AlphaScreen competitive inhibition assay results of **2**–**4**, **5**–**9** and carnosic acid for the inhibition of the *β*-catenin/BCL9 PPI. Each set of data is expressed as mean ± standard deviation (n =3). The substructure of pan assay interference compounds (PAINS[2,3]) in carnosic acid is colored red.

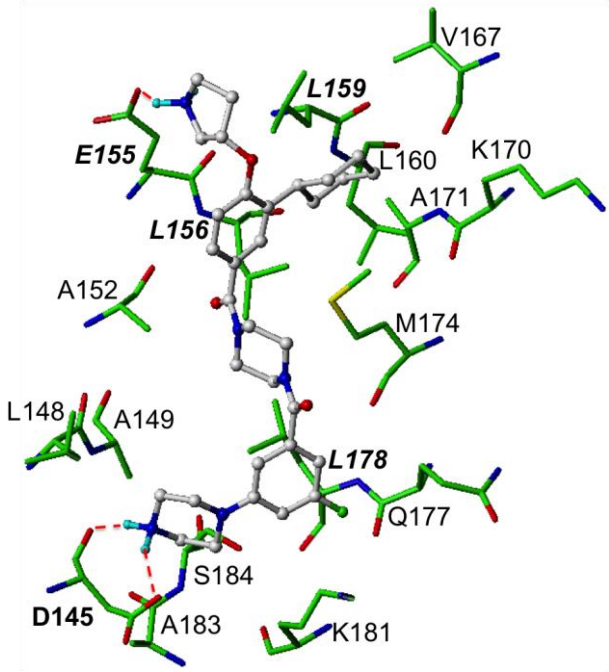


Figure S4. Stick model of the AutoDock predicted binding conformation of **3** in *β*-catenin (PDB id, 2GL7[1]). The *β*-catenin residues are colored green. Compound **3** is colored gray.

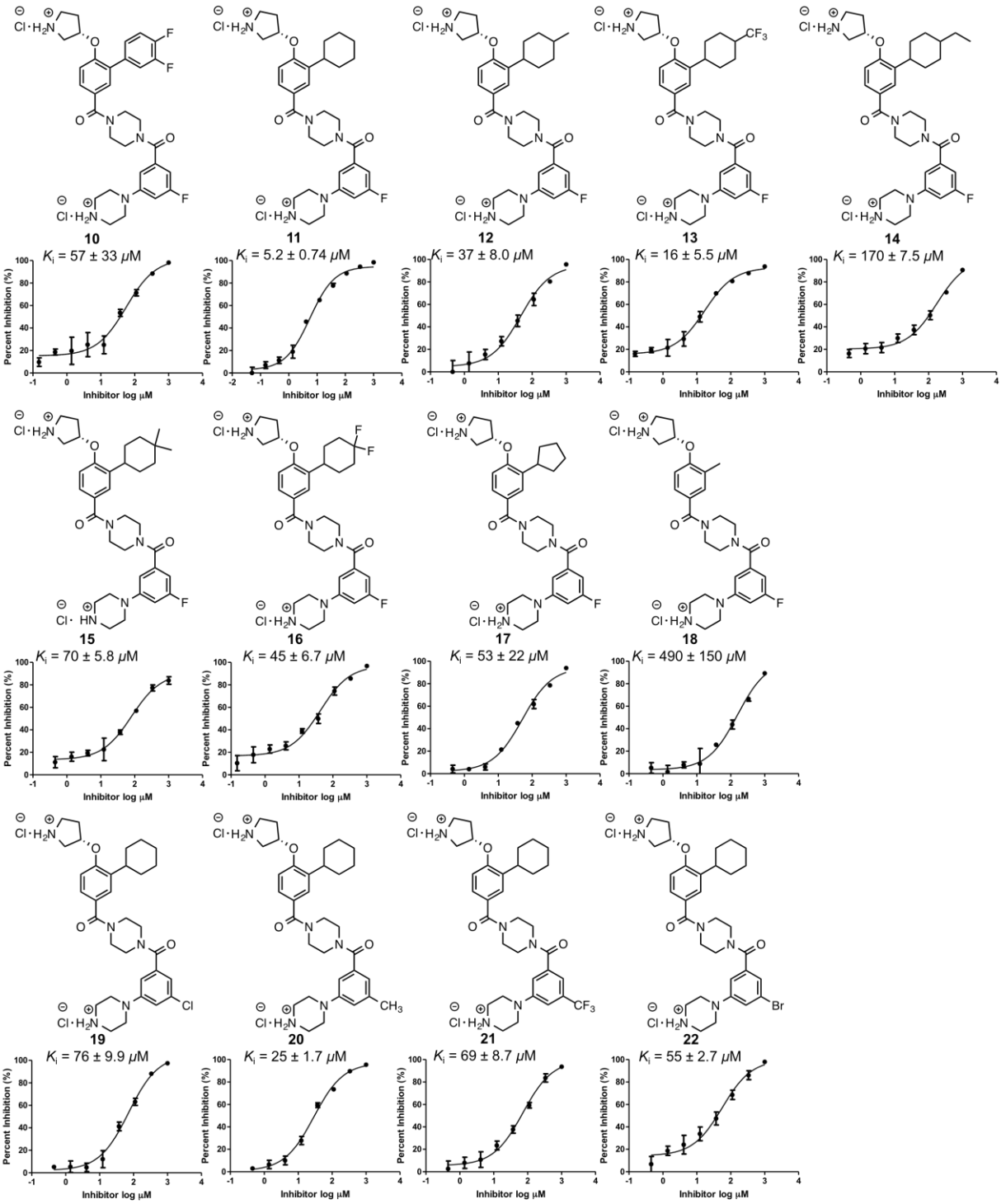


Figure S5. AlphaScreen competitive inhibition assay results of **10**–**22** for the inhibition of the *β*-catenin/BCL9 PPI. Each set of data is expressed as mean ± standard deviation (n =3).

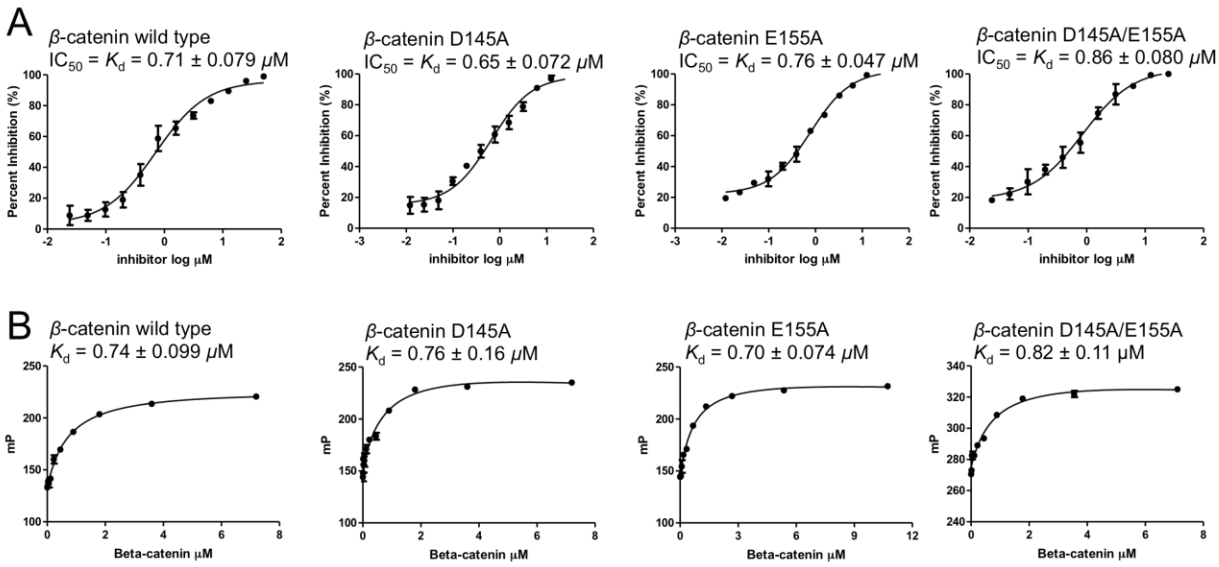


Figure S6. (A)AlphaScreen competitive binding assay to determine the apparent K_d values for the wild-type *β*-catenin/wild-type BCL9 PPI and the mutant *β*-catenin/wild-type BCL9 PPIs. (B) Fluorescence polarization saturation binding experiments to determine the K_d values for the wild-type *β*-catenin/wild-type BCL9 PPI and the mutant *β*-catenin/wild-type BCL9 PPIs. Each set of data is expressed as mean ± standard deviation (n =3). The concentrations of mutant *β*-catenin proteins used in the assays were the same as that of wild-type *β*-catenin protein.

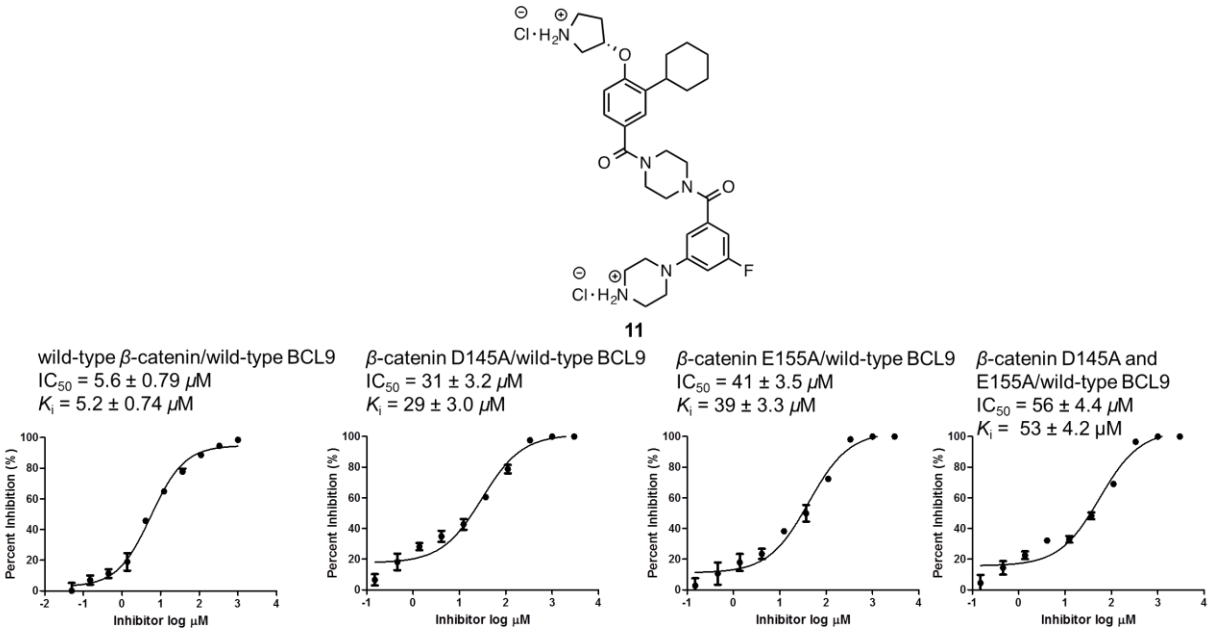


Figure S7. AlphaScreen competitive inhibition assay results of **11** with wild-type and mutant *β*-catenin proteins. Each set of data is expressed as mean ± standard deviation (n = 3). The experimental detail for the AlphaScreen competitive inhibition assay has been described previously.

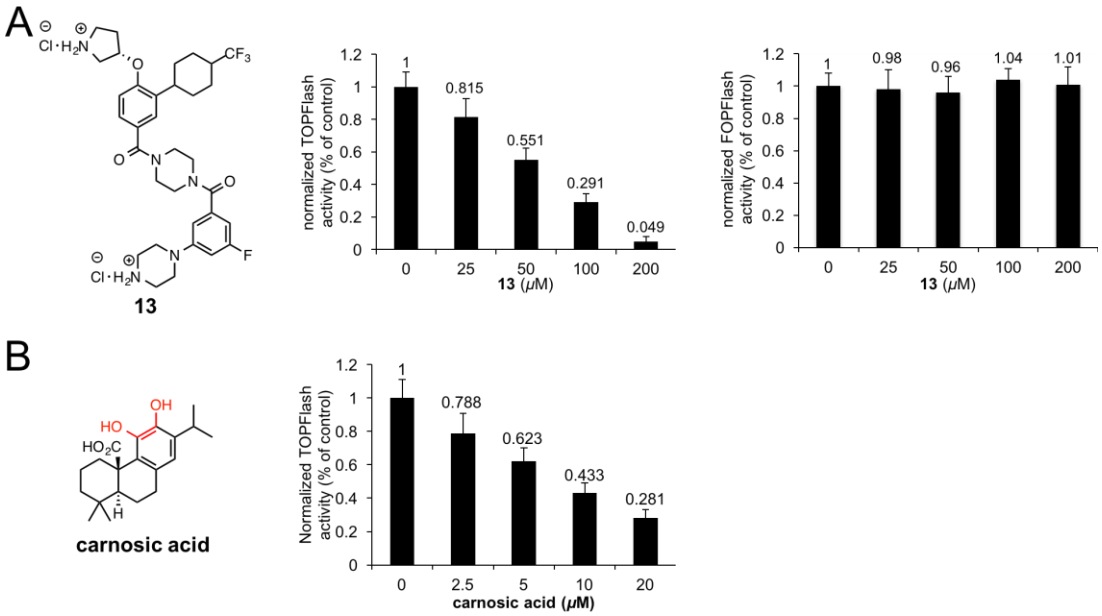
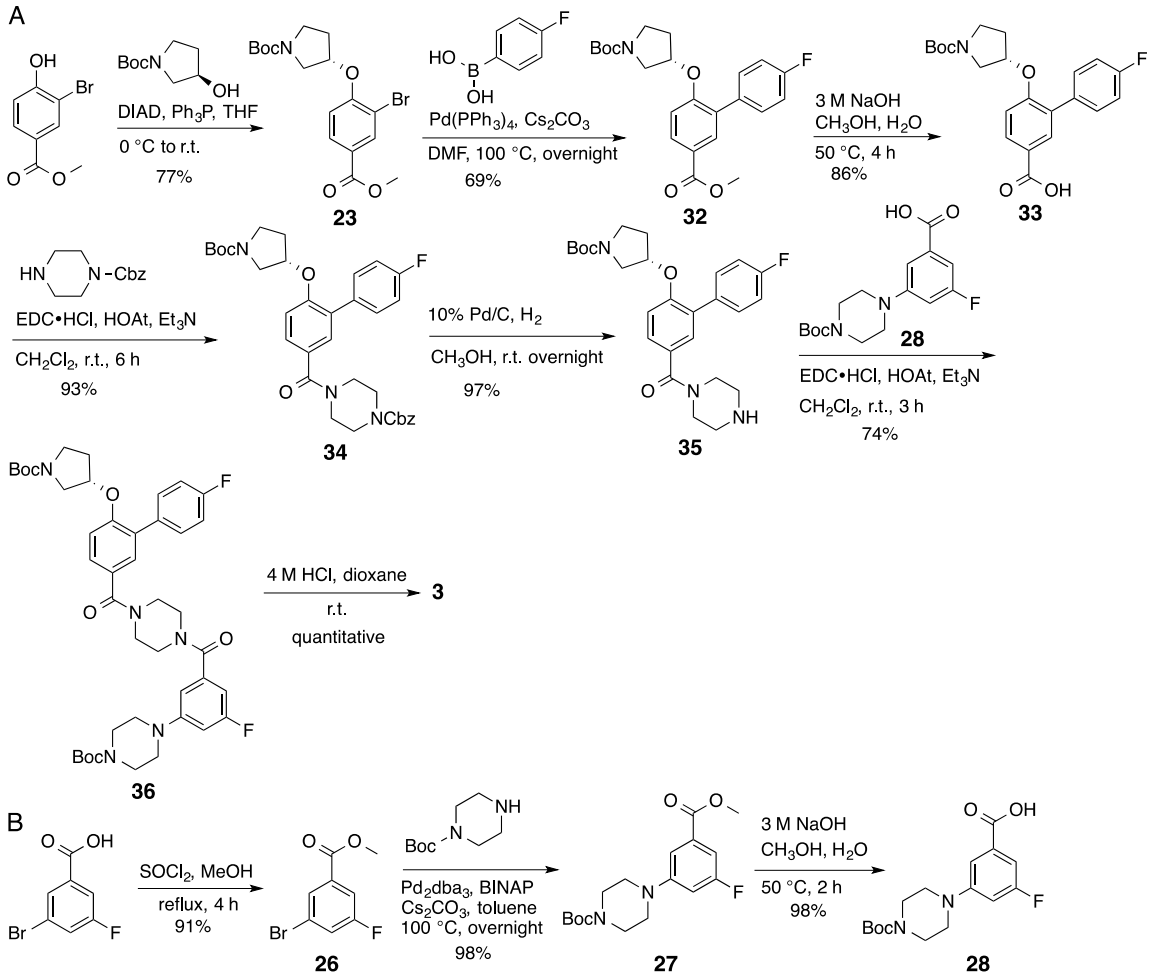


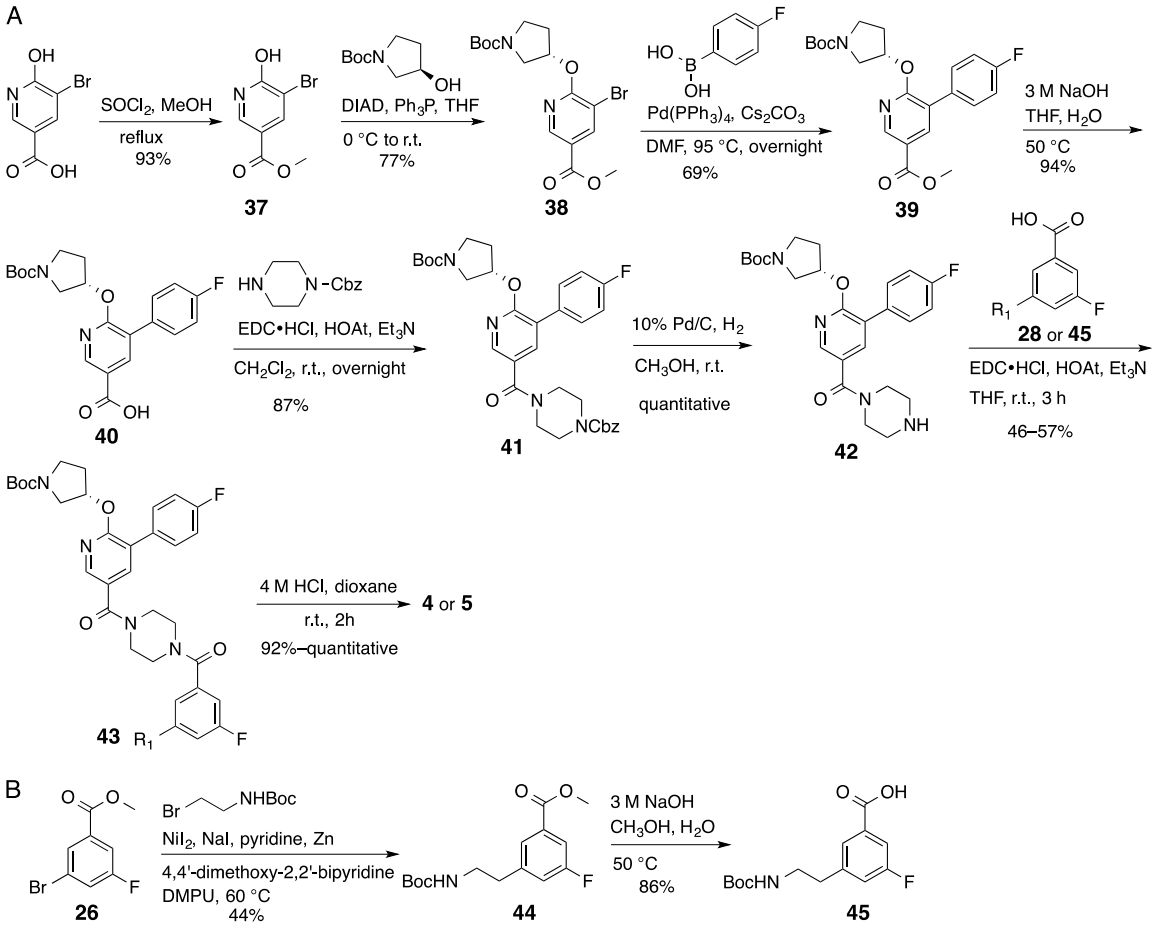
Figure S8. Effects of **13** and carnosic acid on the transactivation of the canonical Wnt signaling pathway determined by the luciferase reporter assay. (A) TOPFlash and FOPFlash luciferase reporter assay results of **13**. (B) TOPFlash luciferase reporter assay result of carnosic acid. Each set of data is expressed as mean ± standard deviation (n = 3).

Scheme S1.

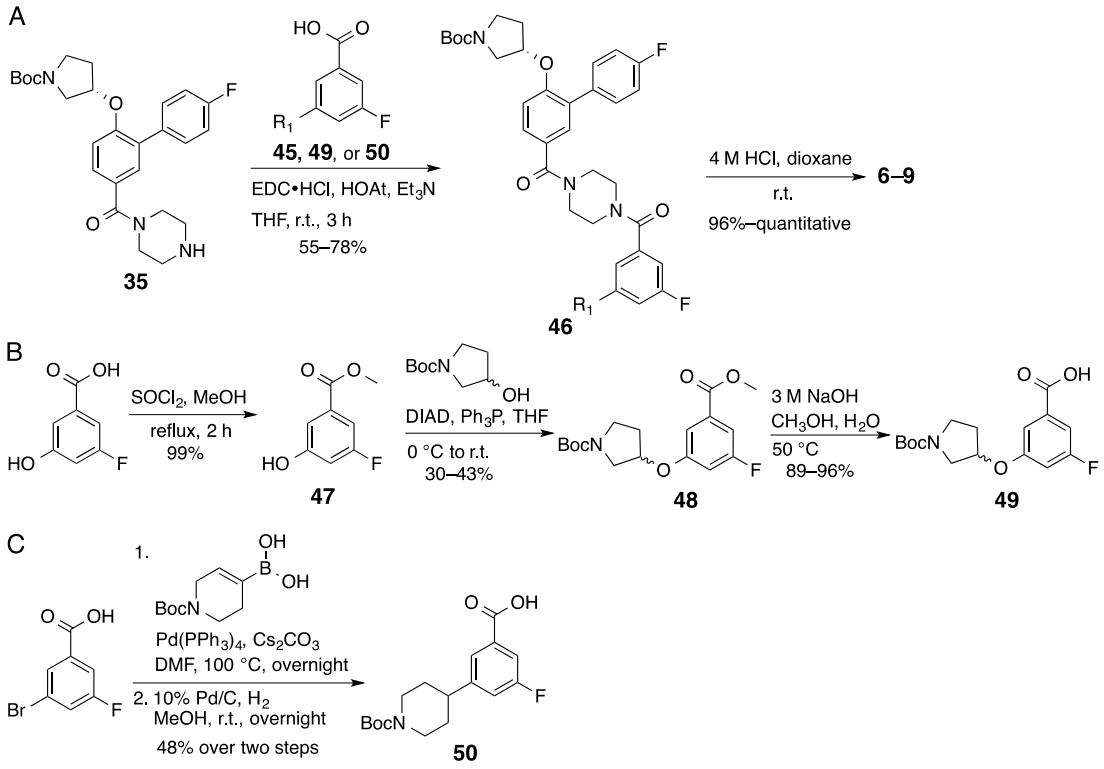

A
DIAD, Ph3P, THF
0 °C to r.t.
77%
23
Pd(PPh3)4, Cs2CO3
DMF, 100 °C, overnight
69%
32
3 M NaOH
CH3OH, H2O
50 °C, 4 h
86%
33
EDC•HCl, HOAt, Et3N
CH2Cl2, r.t., 6 h
93%
34
10% Pd/C, H2
CH3OH, r.t. overnight
97%
35
28
EDC•HCl, HOAt, Et3N
CH2Cl2, r.t., 3 h
74%
36
4 M HCl, dioxane
r.t.
quantitative
3
B
SOCl2, MeOH
reflux, 4 h
91%
26
Pd2dba3, BINAP
Cs2CO3, toluene
100 °C, overnight
98%
27
3 M NaOH
CH3OH, H2O
50 °C, 2 h
98%
28

Scheme S2.

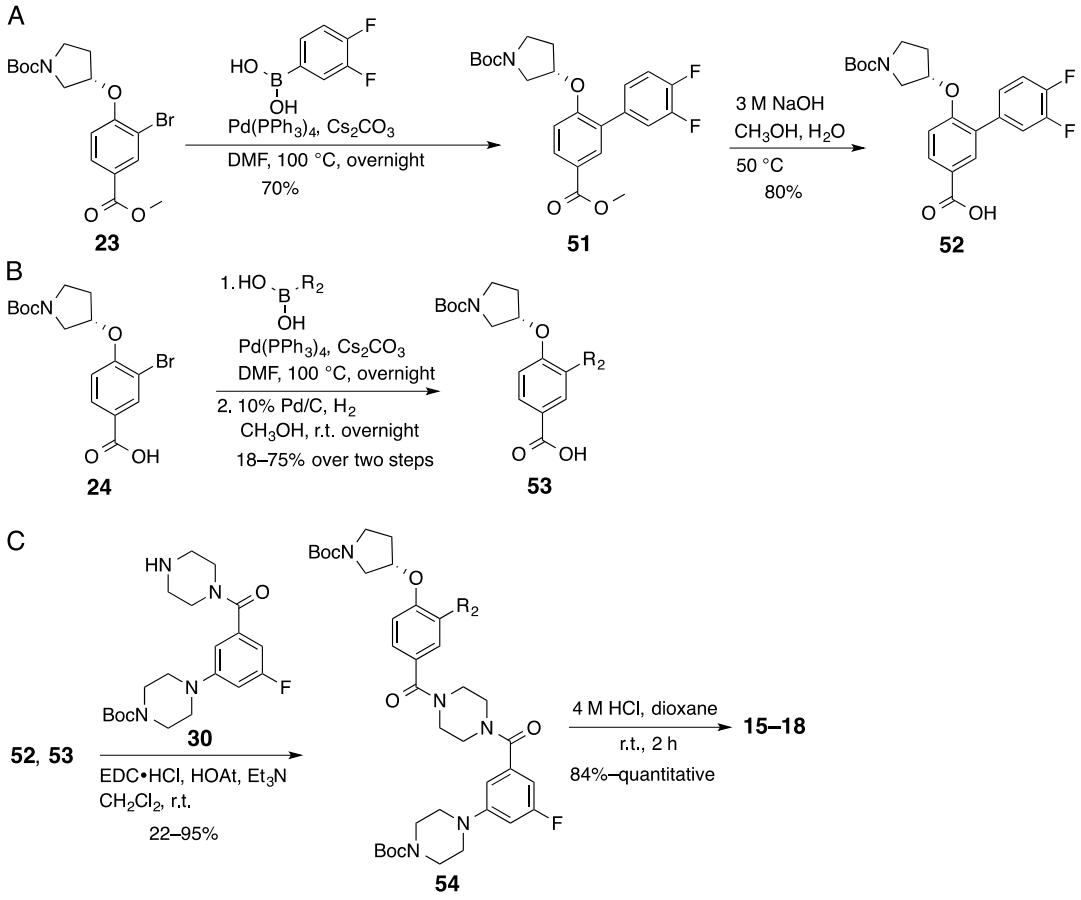
Boc protected aminoethyl group was conveniently installed to **25** by the nickel-catalyzed reductive alkylation reaction developed by Weix and co-workers.[4]



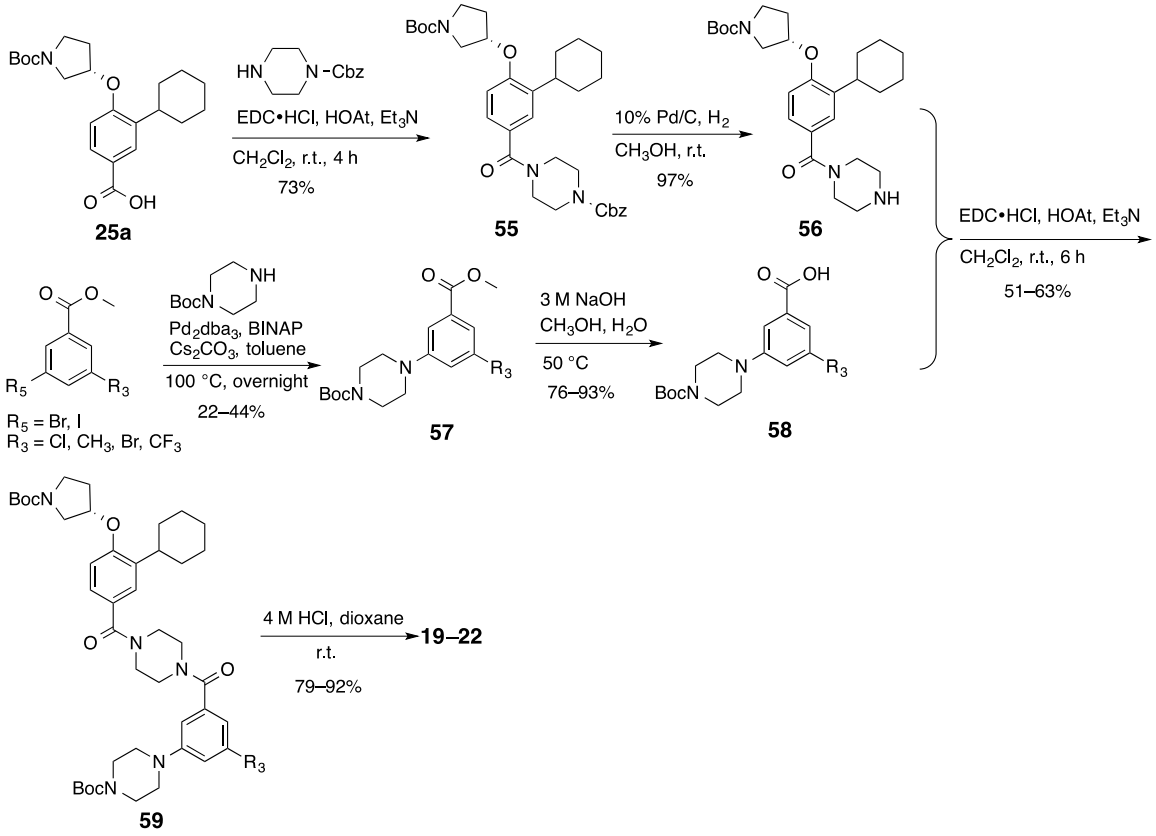
Scheme S3.


A
BocN
O
F
O
N
NH
35
HO
O
R1
F
45, 49, or 50
EDC•HCl, HOAt, Et3N
THF, r.t., 3 h
55–78%
BocN
O
F
O
N
N
O
R1
F
46
4 M HCl, dioxane
r.t.
96%–quantitative
6–9
B
O
OH
HO
F
SOCl2, MeOH
reflux, 2 h
99%
O
O
HO
F
47
BocN
OH
DIAD, Ph3P, THF
0 °C to r.t.
30–43%
O
O
BocN
O
F
48
3 M NaOH
CH3OH, H2O
50 °C
89–96%
O
OH
BocN
O
F
49
C
1.
OH
B
OH
BocN
Pd(PPh3)4, Cs2CO3
DMF, 100 °C, overnight
2. 10% Pd/C, H2
MeOH, r.t., overnight
48% over two steps
O
OH
Br
F
O
OH
BocN
F
50

Scheme S4.


A
BocN
O
Br
O
O
23
HO
B
OH
F
F
Pd(PPh3)4, Cs2CO3
DMF, 100 °C, overnight
70%
51
3 M NaOH
CH3OH, H2O
50 °C
80%
OH
52
B
1. HO
R2
2. 10% Pd/C, H2
CH3OH, r.t. overnight
18–75% over two steps
24
53
C
HN
N
F
30
52, 53
EDC•HCl, HOAt, Et3N
CH2Cl2, r.t.
22–95%
54
4 M HCl, dioxane
r.t., 2 h
84%–quantitative
15–18

Scheme S5.


BocN
O
O
OH
25a
HN
N
Cbz
EDC•HCl, HOAt, Et3N
CH2Cl2, r.t., 4 h
73%
55
10% Pd/C, H2
CH3OH, r.t.
97%
56
NH
EDC•HCl, HOAt, Et3N
CH2Cl2, r.t., 6 h
51–63%
R5 = Br, I
R3 = Cl, CH3, Br, CF3
Pd2dba3, BINAP
Cs2CO3, toluene
100 °C, overnight
22–44%
57
3 M NaOH
CH3OH, H2O
50 °C
76–93%
58
4 M HCl, dioxane
r.t.
79–92%
19–22
59

Protein structure for computer modeling. The crystallographic coordinates for human *β*-catenin (PDB id, 2GL7[1], 2.60 Å resolution, R_{cryst} = 0.223) were obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) protein data bank. The preparation of the crystal structure and molecular modeling were achieved with the commercially available Schrodinger (http://www.schrodinger.com/), Accelrys Discovery Studio 3.0 (http://accelrys.com/), and SYBYL X2.0 (http://www.tripos.com/) software packages. The missing side chains of *β*-catenin were added in SYBYL X2.0. The protonation states of the residues were set to pH 7.0 when adding hydrogen. The AMBER 7 force field 99 and the AMBER FF99 charges within SYBYL X2.0 were used to optimize the orientation of hydrogen atoms and the missing side chains of the protein. After the protein complex was optimized. Chains B (Tcf4), C (BCL9), D (the second monomer of *β*-catenin), E (the second monomer of Tcf4), F (the second monomer of BCL9), and solvent molecules were removed, leaving only one monomer of *β*-catenin for further calculation. The residues in the BCL9 L366/I369/L373 binding site of *β*-catenin include D144–A146, L148, A149, A152, I153, E155–L160, D162–A171, M174, V175, Q177, L178, K180, K181, A183, S184, A187, I188, M194, and I198.

SiteMap calculation. This calculation was performed with SiteMap 2.6 in Schrodinger. The evaluation on a single binding site region was selected, and all residues of the BCL9 L366/I369/L373 binding site were included. At least 15 site points per reported site were required to initiate the SiteMap calculation. The more restrictive definition for hydrophobicity was used. The grid spacing was set to 0.35 Å. The site maps were cropped at 4 Å from nearest site point, and the OPLS-2005 force field was used to map the hydrophobic, H-bond donor and H-bond acceptor regions.

Ligand docking using AutoDock 4.2. The three-dimensional (3D) structures of the ligands were built, and the partial atomic charges were calculated using the Gasteiger–Marsili method. The rotatable bonds in the ligands were defined using AutoTors, which also united the nonpolar hydrogens and partial atomic charges to the bonded carbon atoms. The grid maps were calculated using AutoGrid. The AutoDock area was defined to include all of the residues in the BCL9 L366/I369/L373 binding site, and the grid spacing was set to 0.375 Å. Docking was performed using the Lamarckian genetic algorithm, and the pseudo-Solis and Wets method was applied for the local search. Each docking experiment was performed 100 times, yielding 100 docked conformations. The other settings were the default parameters. All of the ligands followed the same docking protocol. The results of the docking experiments were evaluated by the auxiliary clustering analysis and the visual inspection to match the proposed *critical binding elements*.

Protein expression and purification. *β*-Catenin mutants D145A, E155A, D145A/E155A have been made previously.[5] Wild-type *β*-catenin and its mutants (residues 138–686) were cloned into a pET-28b vector carrying a *C*-terminal 6 × histidine (Novagen), and transformed into *Escherichia coli* BL21 DE3 (Novagen). Cells were cultured in LB medium with 30 *μ*g/mL kanamycin until the OD_{600} was approximately 0.8, and then protein expression was induced with 400 *μ*M of IPTG at 20 °C overnight. Cells were lysed by sonication. The proteins were purified by Ni-NTA affinity chromatography (30210, Qiagen) and dialyzed against a buffer containing 20 mM of Tris (pH 8.5), 100 mM NaCl, 10% glycerol, and 3 mM DTT. The purity of *β*-catenin was greater than 95% as determined by SDS-PAGE gel analysis. Native non-denaturing gel electrophoresis was performed to confirm the homogeneity of the purified proteins. Thermal-shift assay was performed on an iCycler iQ Real Time Detection System (Bio-Rad) to monitor protein stability and detect protein aggregation. Protein unfolding was evaluated through measuring the

fluorescence changes of fluorescent dye Sypro Orange when interacting with wild-type or mutant β-catenin proteins. A temperature increment of 1°/min was applied. CD spectra were measured on a J-815 spectropolarimeter (Jasco). All spectra were recorded at room temperature, and the baseline control containing all of the substances except protein. Sample were prepared at a concentration around 1–5 μM in a buffer of 10 mM potassium phosphate and 100 mM potassium fluoride at pH 7.0 to ensure that the transmission of light through the sample was not restricted. All proteins were stable and no aggregation was observed under storage or assay conditions. Proteins were aliquoted and stored at –80 °C.

BCL9 peptide synthesis and purification. Human BCL9 (residues 350–375), *N*-terminally biotinylated human BCL9 (residues 350–375), *N*-terminally fluorescein-labeled human BCL9 (residues 350–375), and *N*-terminally biotinylated human E-cadherin (residues 824–877) were synthesized by InnoPep Inc. (www.innopep.com) and HPLC purified by HPLC with purity > 95%. The structures were validated by LC/MS. The sequences of these peptides have been described previously.[6]

AlphaScreen assays to determine the apparent K_d values for wild-type and mutant β-catenin/BCL9 interactions. The experimental detail using AlphaScreen to determine the apparent K_d values for β-catenin/BCL9 and β-catenin/E-cadherin PPIs has been described previously.[6] The concentrations of mutant β-catenin proteins used in the assays were the same as that of wild-type β-catenin.

Fluorescence polarization (FP) assays to determine the apparent K_d values for wild-type and mutant β-catenin/BCL9 interactions. The FP experiments were performed in 96-well Microfluor 2 black plates (Waltham, MA), and the sample signals were read by a Synergy 2 plate reader (Biotek, Winooski, VT). The polarization was measured at room temperature with an excitation wavelength at 485 nm and an emission wavelength at 535 nm. All of the FP experiments were performed in an assay buffer of 137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, 2 mM KH_2PO_4, 100 μg/mL of bovine γ-globulin, and 0.01% Triton X-100. The final reaction volume was set to 100 μL. In the FP saturation binding experiments, the concentration of human BCL9 fluorescent tracer was fixed at 5 nM. The concentrations of β-catenin were ranged from 0 to 10 μM in the assay buffer giving a final volume of 100 μL. After the addition, each assay plate was covered black and gently mixed on an orbital shaker for 3 h before the polarization signals were recorded. The data were analyzed by nonlinear least-square analyses using GraphPad Prism 5.0 to derive the apparent K_d value. Each experiment was repeated three times, and the results were expressed as mean ± standard deviation.

AlphaScreen competitive inhibition assays using wild-type and mutant β-catenin proteins. The experimental details of the AlphaScreen competitive inhibition assays for the β-catenin/BCL9 and β-catenin/E-cadherin PPIs have been described previously.[5] The concentrations of mutant β-catenin proteins used in the AlphaScreen competitive inhibition assays were the same as that of wild-type β-catenin protein.

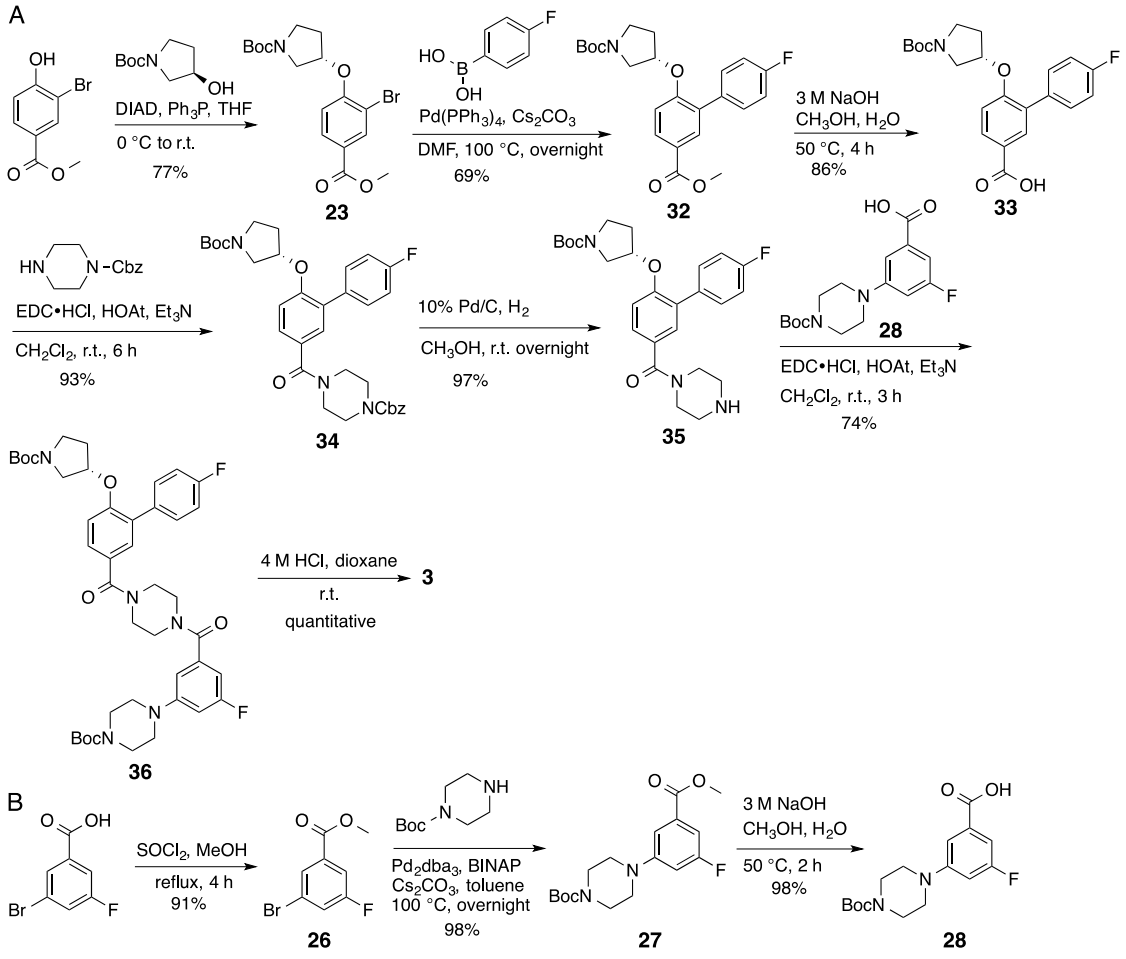
MTs Cell Viability Assay. Colorectal cancer cell lines, SW480 and HCT116, lung adenocarcinoma cell line A549, and human embryonic kidney 293 cell line (HEK293) were seeded in 96-well plates at 4×10^3 cells/well, maintained overnight at 37 °C, and incubated with the tested compounds at various concentrations in 5 mL Dulbecco's modified Eagle's media (DMEM, Sigma-Aldrich catalogue # D5523) with 1% fetal bovine serum (FBS, Thermo Fisher Scientific catalogue # 16140071). Cell viability was monitored after 72 h using a freshly prepared mixture of 1 part phenazine methosulfate (PMS, Sigma) solution (0.92 mg/mL) and 19 parts 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTs,

Promega) solution (2 mg/mL). Cells were incubated in 10 μL of this solution at 37 °C for 3 h, and A_{490} was measured. The effect of each compound is expressed as the concentration required to reduce A_{490} by 50% (IC_{50}) relative to DMSO-treated cells. Experiments were performed in triplicate.

Cell Transfection and Luciferase Assay. FuGENE 6 (E2962, Promega) in a 96-well plate format was used for the transfection of HEK293 cells according to the manufacturer's instructions. HEK293 cells were co-transfected with 45 ng of the TOPFlash (with three wild-type Tcf binding sites) or FOPFlash (with three mutant Tcf binding sites) reporter gene, 135 ng pcDNA3.1–β-catenin and 20 ng pCMV-RL normalization reporter gene. Cells were cultured at 37 °C for 24 h, and different concentrations of inhibitors were then added. After 24 h, the luciferase reporter activity was measured using the Dual-Glo system (E2940, Promega). Normalized luciferase activity in response to the treatment with the inhibitors was compared with that obtained from the cells treated with DMSO. Experiments were performed in triplicate.

Chemical synthesis.

General Methods, Reagents, and Materials. All reagents were purchased from Aldrich and Acros Organics and used without further purification unless stated otherwise. Organic solution was concentrated under reduced pressure on a Büchi rotary evaporator using an isopropyl alcohol-dry ice bath. Thin-layer chromatography (TLC) was carried out on 0.25 mm pre-coated silica gel 60 F254 plates (SiliCycle Inc. Candida), and the compounds were visualized with a UV–visible lamp at 254 nM. Further visualization was achieved by staining with iodine. Column chromatography was performed with SilicaFlash@ F60 (230–400 mesh) and commercial solvents. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VXR-500 (500 MHz), a Varian Inova-400 (400 MHz), or a Varian Unity-300 (300 MHz) spectrometer (125.7 MHz, 100 MHz, and 75 MHz for ^{13}C NMR spectra, respectively) in $CDCl_3$, d^4-methanol and D_2O. Chemical shifts were reported as values in parts per million (ppm), and the reference resonance peaks were set at 7.26 ppm ($CHCl_3$), 3.31 ppm (CD_2HOD), and 4.80 ppm (HOD) for the ^{1}H NMR spectra and 77.23 ppm ($CDCl_3$) and 49.00 ppm (CD_3OD) for the ^{13}C NMR spectra. Low-resolution (LRMS) were determined on a Micromass Quattro II mass spectrometer with an ESI source. High-resolution mass spectra (HRMS) was recorded on Waters LCT Premier XE TOF with Acquity Classic UPLC.



***tert*-Butyl (*S*)-3-(2-bromo-4-(methoxycarbonyl) phenoxy) pyrrolidine-1-carboxylate (23).** To a solution of methyl 3-bromo-4-hydroxybenzoate (0.626 g, 2.70 mmol) in dry THF (35 mL)

under anhydrous conditions was added (*R*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (0.505 g, 2.70 mmol) and triphenyl phosphine (1.43 g, 5.39 mmol). The reaction mixture was then cooled in an ice bath, and DIAD (1.12 g, 5.56 mmol) dissolved in THF (10 mL) was added dropwise. The reaction mixture was stirred for 1 h at room temperature under argon. Upon completion the reaction was diluted with ethyl acetate (100 mL). The organic layer was washed with water (2 × 50 mL), brine (50 mL), dried over $MgSO_4$, solids filtered, and the solvent removed under reduced pressure. The residue was then purified by column chromatography (silica gel, hexanes:EtOAc = 5:1) to yield **23** (0.837g, 77% yield) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.22 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 5.00–4.98 (m, 1H), 3.88 (s, 3H), 3.63–3.56 (m, 4H), 2.23–2.13 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 165.67, 157.47, 143.72, 135.31, 130.41, 124.36, 113.33, 79.76, 79.74, 78.32, 52.29, 51.57, 51.22, 44.25, 43.84, 31.85, 31.02, 28.60. MS (ESI) m/z = 400.6 $[M + H]^+$.

***tert*-Butyl (*S*)-3-((4'-fluoro-5-(methoxycarbonyl)-[1,1'-biphenyl]-2-yl) oxy) pyrrolidine-1-carboxylate (32).** To a solution of **23** (1.00 g, 2.50 mmol) in dry DMF (50 mL) under anhydrous conditions was added (4-fluorophenyl) boronic acid (0.574 g, 4.10 mmol), $Pd(PPh_3)_4$ (0.254 g, 0.220 mmol), and Cs_2CO_3 (2.41 g, 7.40 mmol). The mixture was heated to 100 °C under argon and stirred for 20 h. The solvent was then removed under reduced pressure, and the residue was taken into EtOAc (100 mL). The organic solution was washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, solids filtered, and solvent removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes:EtOAc = 5:1) to yield **32** (0.71 g, 69% yield) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.00 (d, 2H, J = 6.8 Hz), 7.43 (dd, 2H, J = 5.6, 8.2 Hz), 7.08 (t, 2H, J = 8.5 Hz), 6.94 (d, 1H, J = 9.0 Hz), 4.97–4.95 (m, 1H), 3.90 (s, 3H), 3.66–3.29 (m, 4H), 2.11–2.08 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 166.77, 163.29, 161.33, 157.67, 154.61, 132.81, 131.17, 131.11, 130.69, 123.46, 115.15, 115.02, 113.14, 112.85, 79.77, 52.16, 51.60, 51.24, 51.23, 51.21, 44.23, 44.21, 44.20, 43.92, 43.89, 31.70, 30.98, 30.97, 28.61. MS (ESI) m/z = 416.7 $[M + H]^+$.

(*S*)-6-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-4'-fluoro-[1,1'-biphenyl]-3-carboxylic acid (33). To a solution of **32** (1.12 g, 2.70 mmol) in MeOH (10 mL) was added 6 M NaOH (10 mL), and the reaction was allowed to stir at room temperature for 6 h. MeOH was then removed under reduced pressure. The remaining aqueous solution was acidified with 12 M HCl to pH = 2. The product was extracted with CH_2Cl_2 (50 mL) and the organics washed with water (2 × 50 mL), brine (50 mL), dried over $MgSO_4$, solids filtered, and solvent removed under reduced pressure to yield **33** (0.94 g, 86% yield) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.07–8.04 (m, 2H), 7.46–7.42 (m, 2H), 7.09 (t, J = 8.3 Hz, 2H), 6.97 (d, J = 9.5 Hz, 1H), 5.00–4.97 (m, 1H), 3.69–3.30 (m, 4H), 2.14–2.12 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.39, 171.24, 163.33, 161.35, 158.29, 158.22, 154.83, 154.62, 133.41, 133.32, 131.38, 131.17, 131.14, 130.93, 130.87, 122.65, 115.23, 115.09, 114.92, 113.09, 112.75, 79.98, 77.26, 76.48, 51.63, 51.19, 44.26, 43.91, 31.67, 30.92, 28.59.

Benzyl (*S*)-4-(6-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-4'-fluoro-[1,1'-biphenyl]-3-carbonyl) piperazine-1-carboxylate (34). To a solution of **33** (0.681 g, 1.70 mmol) in anhydrous CH_2Cl_2 (50 mL) was added benzyl piperazine-1-carboxylate (0.374 g, 1.70 mmol), triethylamine (0.8 mL, 6 mmol), EDC-HCl (0.644 g, 3.36 mmol), and HOAt (0.230 g, 1.70 mmol). The mixture was then stirred at room temperature for 4 h. The mixture was diluted with CH_2Cl_2 (50 mL) and the organic solution was washed with water (2 × 50 mL), brine (50 mL), dried over $MgSO_4$, solids filtered, and solvent removed under reduced pressure. The residue was then purified by column chromatography (silica gel, hexanes:EtOAc = 3:1) to yield white solid

(0.930 g, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.41–7.29 (m, 9H), 7.08–7.04 (m, 2H), 6.94 (d, 1H, J = 6.9 Hz), 5.14 (s, 2H), 4.90–4.88 (m, 1H), 3.65–3.20 (m, 12H), 2.09–2.03 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 173.10, 171.02, 170.10, 162.08 (d, J = 245.6 Hz), 155.10, 155.02, 154.99, 154.45, 154.27, 136.19, 133.11, 133.01, 131.11, 130.89, 130.86, 130.22, 128.43, 128.20 (d, J = 4.8 Hz), 128.08, 127.89, 114.93 (d, J = 20.9 Hz), 114.80 (d, J = 20.9 Hz), 113.74, 113.46, 79.53, 79.46, 77.14, 76.26, 67.38, 60.26, 51.34, 50.85, 44.05, 43.64, 31.41, 30.64, 28.36, 20.92, 20.57, 14.08.

***tert*-Butyl (*S*)-3-((4'-fluoro-5-(piperazine-1-carbonyl)-[1,1'-biphenyl]-2-yl) oxy) pyrrolidine-1-carboxylate (35).** To a solution of **34** (0.927 g, 0.154 mmol) in MeOH (20 mL) under argon was added 10% Pd on activated carbon (0.012 g). The argon was evacuated and exchanged with H_2 gas three times and the reaction was allowed to stir under H_2 for 3 h. The reaction mixture was filtered through celite, and the solvent removed under reduced pressure to yield **35** (0.699 g, 97% yield) as off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.38–7.30 (m, 4H), 7.01 (t, 2H, J = 8.4 Hz), 6.90 (d, 1H, J = 8.1 Hz), 4.86–4.83 (m, 1H), 3.61-3.17 (m, 8H), 2.85–2.79 (m, 4H), 2.02–1.98 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 169.77, 161.78 (d, J = 247.3 Hz), 154.64, 154.54, 154.32, 154.17, 132.98 (d, J = 9.3 Hz), 130.80, 130.70, 130.65, 129.90, 129.86, 128.46, 127.59, 114.64 (d, J = 21.7 Hz), 114.53 (d, J = 21.3 Hz), 113.61, 113.33, 79.37, 79.30, 76.89, 76.09, 51.16, 50.66, 49.69, 45.72, 43.81, 43.42, 31.12, 30.39, 28.11.

Methyl 3-bromo-5-fluorobenzoate (26). To an ice cold stirred solution of 3-bromo-5-fluorobenzoic acid (4.13 g, 18.9 mmol) in anhydrous methanol (40 mL) was added thionyl chloride (2.05 mL, 28.2 mmol) dropwise. The reaction mixture was allowed to stir for 15 min and then heated to reflux. Upon completion (1 h) the solvent was removed under reduced pressure, and the residue was taken into EtOAc (150 mL). The organic solution was washed with water (2 × 150 mL), brine (150 mL) and dried over $MgSO_4$. The solids were filtered, and solvent removed under reduced pressure to yield compound **26** (4.00 g, 91% yield) as brown liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.95–7.93 (m, 1H), 7.64 (ddd, 1H, J = 1.4, 2.4, 8.8 Hz), 7.41 (td, 1H, J = 2.1, 7.8 Hz), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 164.59 (d, J = 3.1Hz), 162.25 (d, J = 251.9 Hz), 133.36 (d, J = 8.0 Hz), 128.54 (d, J = 3.3 Hz), 123.38 (d, J = 24.5 Hz), 122.60 (d, J = 9.2 Hz), 115.48 (d, J = 23.1 Hz), 52.66.

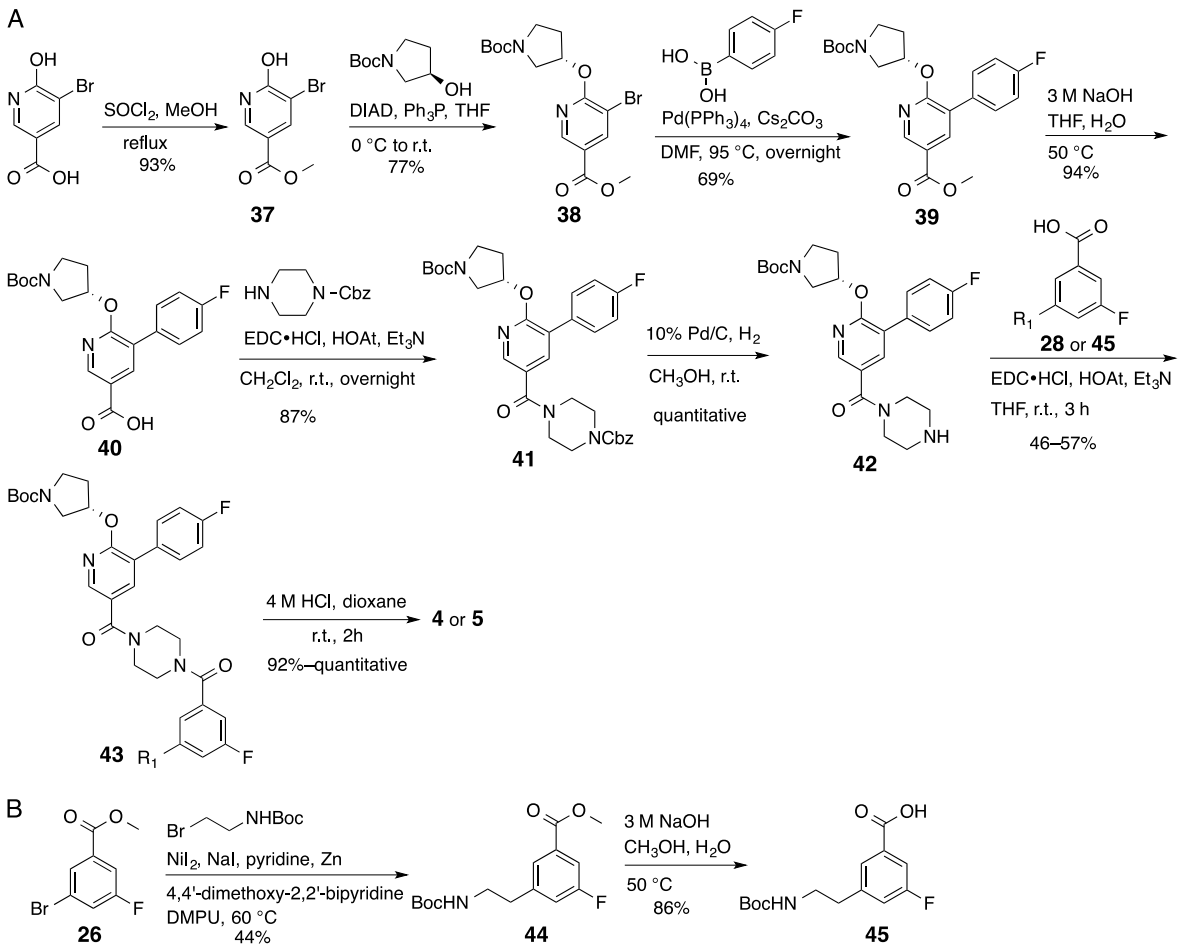
***tert*-Butyl 4-(3-fluoro-5-(methoxycarbonyl) phenyl) piperazine-1-carboxylate (27).** To a solution of **26** (0.117 g, 0.432 mmol) in dry toluene (25 mL) under anhydrous conditions was added *N*-Boc-piperazine (0.109 g, 0.585 mmol), tris (dibenzylideneacetone) dipalladium (0) ($Pd_2(dba)_3$) (0.0217g, 0.0237 mmol), 2,2'-bis (diphenylphosphino)-1,1'-binapthyl (BINAP) (0.0551 g, 0.0886 mmol) and Cs_2CO_3 (0.1981 g, 0.608 mmol). The mixture was heated to 90 °C in a pressurized flask and stirred for 20 h. The solvent was then removed under reduced pressure, and the residue was taken into EtOAc (100 mL). The organic solution was washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, solids filtered, and solvent removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes:EtOAc = 9:1) to yield **27** (0.143 g, 98% yield) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.37 (dd, 1H, J = 1.3, 2.3 Hz), 7.18 (ddd, 1H, J = 1.3, 2.3, 8.6 Hz), 6.75 (td, 1H, J = 2.4, 11.6 Hz), 3.90 (s, 3H), 3.58 (t, 4H, J = 5.1 Hz), 3.19 (t, 4H, J = 5.1 Hz), 1.48 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 166.27 (d, J = 3.71 Hz), 163.44 (d, J = 244.5 Hz), 154.60, 152.50 (d, J = 9.8 Hz), 132.40 (d, J = 9.6 Hz), 112.62 (d, J = 2.3 Hz), 107.17 (d, J = 23.8 Hz), 107.04 (d, J = 25.3 Hz), 80.12, 52.35, 48.51, 28.39.

3-(4-(*tert*-Butoxycarbonyl) piperazin-1-yl)-5-fluorobenzoic acid (28). The synthesis of compound **28** followed the same procedure as for compound **33** to afford white solid (0.0779 g,

98% yield). ^{1}H NMR (300 MHz, CD_3OD): δ ppm 7.41 (s, 1H), 7.12 (d, 1H, J = 8.6 Hz), 6.92 (td, 1H, J = 2.1, 11.9 Hz), 3.57 (t, 4H, J = 5.0 Hz), 3.21 (t, 4H, J = 5.1 Hz), 1.48 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.67, 163.43 (d, J = 245.0 Hz), 154.71, 152.47 (d, J = 9.8 Hz), 131.68 (d, J = 10.0 Hz), 113.08 (d, J = 2.1 Hz), 107.79 (d, J = 25.6 Hz), 107.72 (d, J = 23.9 Hz), 80.34, 48.48, 28.38.

***tert*-Butyl (*S*)-4-(3-(4-(6-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-4'-fluoro-[1,1'-biphenyl]-3-carbonyl) piperazine-1-carbonyl)-5-fluorophenyl) piperazine-1-carboxylate (36).** To a solution of **35** (0.066 g, 0.14 mmol) in anhydrous CH_2Cl_2 (50 mL) was added **28** (0.046 g, 0.14 mmol), triethylamine (0.066 mL, 0.494 mmol), EDC-HCl (0.053 g, 0.28 mmol), and HOAt (0.019 g, 0.14 mmol). The mixture was then stirred at room temperature for 4 h. The mixture was diluted with CH_2Cl_2 (50 mL), and the organic solution was washed with water (2 × 50 mL), brine (50 mL), dried over $MgSO_4$, solids filtered, and solvent removed under reduced pressure. The residue was then purified by column chromatography (silica gel, CH_2Cl_2:MeOH = 98:2) to yield **36** as white solid (0.0811 g, 74% yield). ^{1}H NMR (500 MHz, CD_3OD): δ ppm 7.46–7.44 (m, 4H), 7.18 (t, 1H, J = 6.5 Hz), 7.11 (t, 2H, J = 8.8 Hz), 6.91–6.79 (m, 2H), 5.08–5.06 (m, 1H), 3.78–3.40 (m, 16H), 3.21 (t, 4H, J = 4.5 Hz), 2.12–2.09 (m, 2H), 1.48 (s, 9H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 172.37, 171.71 (d, J = 2.9 Hz), 165.02 (d, J = 244.3 Hz), 163.61 (d, J = 245.6 Hz), 156.73, 156.44, 156.38 156.32, 154.59 (d, J = 10.3 Hz), 138.9 (d, J = 9.3 Hz), 134.92, 132.71, 132.46, 132.40, 132.34, 131.40 (d, J = 6.7 Hz), 129.44, 129.31 (d, J = 15.9 Hz), 115.92 (d, J = 21.7 Hz), 115.87 (d, J = 21.7 Hz), 115.56, 115.41, 110.89 (d, J = 2.2 Hz), 105.16 (d, J = 24.1 Hz), 104.95 (d, J = 25.7 Hz), 81.48, 81.14, 81.05, 78.59, 78.05, 52.70, 52.20, 49.33, 45.34, 44.98, 40.23, 34.79, 32.22, 31.64, 31.49, 30.13, 28.80, 28.71.

(*S*)-(4-(3-Fluoro-5-(piperazin-1-yl) benzoyl) piperazin-1-yl) (4'-fluoro-6-(pyrrolidin-3-yloxy)-[1,1'-biphenyl]-3-yl) methanone hydrochloride (3). To compound **36** (0.080 g, 0.103 mmol) under anhydrous conditions was added 4 M HCl in dioxane (10 mL), and the mixture was stirred at room temperature for 1 h. The solvent was then removed under reduced pressure. The product was dissolved in DI water (20 mL) and the aqueous layer was washed with ethyl acetate (3 × 20 mL). The resulting aqueous solution was frozen and lyophilized to yield **3** (0.0664 g, quantitative yield) as white solid. ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.20 (brs, 2H), 8.99 (brs, 2H), 7.61 – 7.57 (m, 2H), 7.43 (dd, 1H, J = 1.5, 8.5 Hz), 7.37 (s, 1H), 7.24 – 7.18 (m, 3H), 6.90 (d, 1H, J = 12.0 Hz), 6.80 (s, 1H), 6.65 (d, 1H, J = 8.0 Hz), 5.18 – 5.12 (m, 1H), 3.66 – 3.06 (m, 20H), 2.21 – 2.13 (m, 1H), 2.07 – 2.02 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ ppm 171.03, 170.27, 163.79 (d, J = 244.4 Hz), 162.55 (d, J = 243.5 Hz), 155.06, 152.41, 152.33, 138.06, 137.98, 133.58, 131.38, 131.26, 130.48, 128.74, 128.37, 114.95 (d, J = 21.3 Hz), 114.10, 110.23, 105.18 (d, J = 23.5 Hz), 104.39 (d, J = 25.8 Hz), 76.85, 50.62, 48.38-47.36 (m, 4C), 45.58, 44.42, 43.31, 30.95; HRMS (ESI) m/z calculated for $C_{32}H_{35}F_2N_5O_3$ $(M+H)^+$ = 576.2781, found 576.2786.



Methyl 5-bromo-6-hydroxynicotinate (37). To an ice cold stirred solution of 5-bromo-6-hydroxy nicotinic acid (2.03 g, 9.31 mmol) in anhydrous methanol (40 mL) was added thionyl chloride (1.01 mL, 13.9 mmol) dropwise. The reaction mixture was allowed to stir for 15 min and then heated to reflux. Upon completion (1 h) the solvent was removed under reduced pressure, and the residue was taken into EtOAc (150 mL). The organic solution was washed with water (2 × 150 mL), brine (150 mL), and dried over $MgSO_4$. The solids were filtered, and solvent removed under reduced pressure to yield compound **37** (2.01 g, 93% yield) as off-white solid. ^{1}H NMR (500 MHz, CD_3OD): δ ppm 12.65 (s, 1H), 8.11 (d, 1H, J = 2.3 Hz), 8.04 (d, 1H, J = 2.3 Hz), 3.73 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 172.94, 168.07, 150.22, 149.46, 124.33, 118.41, 61.60.

Methyl (*S*)-5-bromo-6-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy) nicotinate (38). To a solution of **37** (0.626 g, 2.70 mmol) in dry THF (35 mL) under anhydrous conditions was added (*R*)-*tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (0.505 g, 2.70 mmol) and triphenyl phosphine (1.43 g, 5.39 mmol). The reaction mixture was then cooled in an ice bath, and DIAD (1.12 g, 5.56 mmol) dissolved in THF (10 mL) was added dropwise. The reaction mixture was stirred for 1 h at room temperature under argon. Upon completion the reaction was diluted with ethyl acetate (100 mL). The organic layer was washed with water (2 × 50 ml), brine (50 mL), dried over $MgSO_4$, solids filtered, and the solvent removed under reduced pressure. The residue was then purified by column chromatography (silica gel, hexanes:EtOAc = 7:1) to yield **38** (0.837g, 77% yield) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.70 (d, 1H, J = 2.0 Hz), 8.38 (d,

1H, *J* = 2.1 Hz), 5.64–5.62 (m, 1H), 3.91 (s, 3H), 3.72–3.69 (m, 1H), 3.59–3.52 (m, 3H), 2.21–2.17 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 164.65, 161.64, 154.51, 147.88, 142.55, 121.08, 107.19, 79.47, 72.19, 52.30, 51.65, 44.02, 28.49.

Methyl (*S*)-6-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-5-(4-fluorophenyl) nicotinate (39). The synthesis of compound **39** followed the same procedure as for compound **32**. Column chromatography (silica gel, hexanes:EtOAc = 5:1) afforded white solid (0.147 g, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.74 (s, 1H), 8.16 (s, 1H), 7.48–7.45 (m, 2H), 7.09–7.06 (m, 2H), 5.69–5.66 (m, 1H), 3.90 (s, 3H), 3.68–3.30 (m, 4H), 2.13–2.11 (m, 2H), 1.42 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 165.76, 162.49 (d, *J* = 247.9 Hz), 162.06, 154.56, 142.28, 139.46, 130.72 (d, *J* = 8.2 Hz), 123.57, 120.34, 115.27 (d, *J* = 22.0 Hz), 79.46, 52.15, 28.47.

(*S*)-6-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-5-(4-fluorophenyl) nicotinic acid (40). The synthesis of compound **40** followed the same procedure as for compound **33** (except solvent CH_3OH was replaced by THF) to afford white solid (0.130 g, 94% yield). ^{1}H NMR (500 MHz, CD_3OD): δ ppm 8.74 (d, 1H, *J* = 2.2 Hz), 8.18 (s, 1H), 7.52 (dd, 2H, *J* = 5.6 Hz, *J* = 8.0 Hz), 7.13 (t, 2H, *J* = 8.7 Hz), 5.72–5.69 (m, 1H), 3.65–3.48 (m, 3H), 3.40–3.35 (m, 1H), 2.23–2.13 (m, 2H), 1.44 (s, 4.5H), 1.42 (s, 4.5H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 168.20, 163.95 (d, *J* = 246.4 Hz), 163.36, 156.56, 156.54, 149.60, 140.79, 133.02, 132.13 (d, *J* = 8.2 Hz), 124.97, 122.32, 116.20 (d, *J* = 21.8 Hz), 116.17 (d, *J* = 21.9 Hz), 81.66, 81.11, 77.31, 76.61, 53.28, 52.81, 45.53, 45.10, 32.39, 31.17, 28.79.

Benzyl (*S*)-4-(6-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-5-(4-fluorophenyl) nicotinoyl) piperazine-1-carboxylate (41). The synthesis of compound **41** followed the same procedure as for compound **34**. Column chromatography (silica gel, hexanes:EtOAc = 1:1) afforded white solid (0.168 g, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.19 (d, 1H, *J* = 7.8 Hz), 7.68 (s, 1H), 7.46–7.44 (m, 2H), 7.34–7.28 (m, 5H), 7.09–7.05 (m, 2H), 5.64–5.61 (m, 1H), 5.13 (s, 2H), 3.64–3.33 (m, 12H), 2.14–2.11 (m, 2H), 1.44 (s, 4.5H), 1.43 (s, 4.5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 167.97, 162.39 (d, *J* = 250.0 Hz), 160.16, 154.94, 154.52, 154.40, 144.59, 138.04, 136.15, 131.24, 131.13, 130.57 (d, *J* = 8.15 Hz), 128.42, 128.06, 127.88, 124.80, 123.88, 115.23 (d, *J* = 20.6 Hz), 115.12 (d, *J* = 21.4 Hz), 79.30, 75.55, 74.69, 67.39, 60.21, 51.84, 51.23, 44.24, 43.80, 31.82, 30.72, 28.36.

***tert*-Butyl (*S*)-3-((3-(4-fluorophenyl)-5-(piperazine-1-carbonyl) pyridin-2-yl) oxy) pyrrolidine-1-carboxylate (42).** To a solution of **41** (0.119 g, 0.197 mmol) in MeOH (20 mL) under argon was added 10% Pd on activated carbon (0.0132 g). The argon was evacuated and exchanged with H_2 gas three times, and the reaction was allowed to stir under H_2 for 3 h. The reaction mixture was filtered through celite, and the solvent removed under reduced pressure to yield **42** (0.0994 g, quantitative yield) as off-white solid. ^{1}H NMR (500 MHz, CD_3OD): δ ppm 8.24 (s, 1H), 7.79 (s, 1H), 7.56 (dd, 2H, *J* = 5.6, 8.1 Hz), 7.15 (t, 2H, *J* = 8.6 Hz), 5.69–5.67 (m, 1H), 3.71–3.35 (m, 8H), 2.88–2.83 (m, 4H), 2.21–2.14 (m, 2H), 1.45 (s, 4H), 1.43 (s, 5H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 169.82, 163.06 (d, *J* = 246.50 Hz), 161.50, 156.53, 156.51, 145.98, 139.30, 133.04, 132.21 (d, *J* = 8.2 Hz), 126.75, 125.22, 116.19 (d, *J* = 21.9 Hz), 116.16 (d, *J* = 21.6 Hz), 81.10, 81.04, 77.01, 76.30, 53.28, 52.81, 46.53, 45.54, 45.11, 44.33, 32.38, 31.66, 28.80.

Methyl 3-(2-((*tert*-butoxycarbonyl) amino) ethyl)-5-fluorobenzoate (44). To a solution of **26** (1.52 g, 6.52 mmol) in dry DMPU (22 mL) was added NiI_2, (0.176 g, 0.563 mmol), 4,4'-dimethoxy-2,2'-bipyridine (0.125 g, 0.578 mmol), NaI (0.212 g, 1.41 mmol), pyridine (0.06 mL, 0.7 mmol), *tert*-butyl (2-bromoethyl) carbamate (2.49 g, 11.1 mmol), and zinc (0.734 g, 11.2 mmol). The reaction mixture was stirred and heated to 60 °C for 6 h, then allowed to cool. The

reaction mixture was purified directly by column chromatography (silica gel, hexane: EtOAc = 4:1) to afford **44** (0.844 g, 44% yield) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.66 (t, 1H, J = 1.4 Hz), 7.56 (ddd, 1H, J = 1.5, 2.5, 9.0 Hz), 7.12–7.07 (m, 1H), 4.61 (bs, 1H), 3.91 (s, 3H), 3.38 (q, 2H, J = 6.6 Hz), 2.84 (t, 2H, J = 7.0 Hz), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 165.92 (d, J = 3.1 Hz), 162.54 (d, J = 247.1 Hz), 155.74, 141.88 (d, J = 7.2 Hz), 132.21 (d, J = 8.0 Hz), 125.67 (d, J = 2.7 Hz), 120.33 (d, J = 21.23 Hz), 114.52 (d, J = 23.2 Hz), 79.46, 52.35, 41.41, 35.86, 28.31.

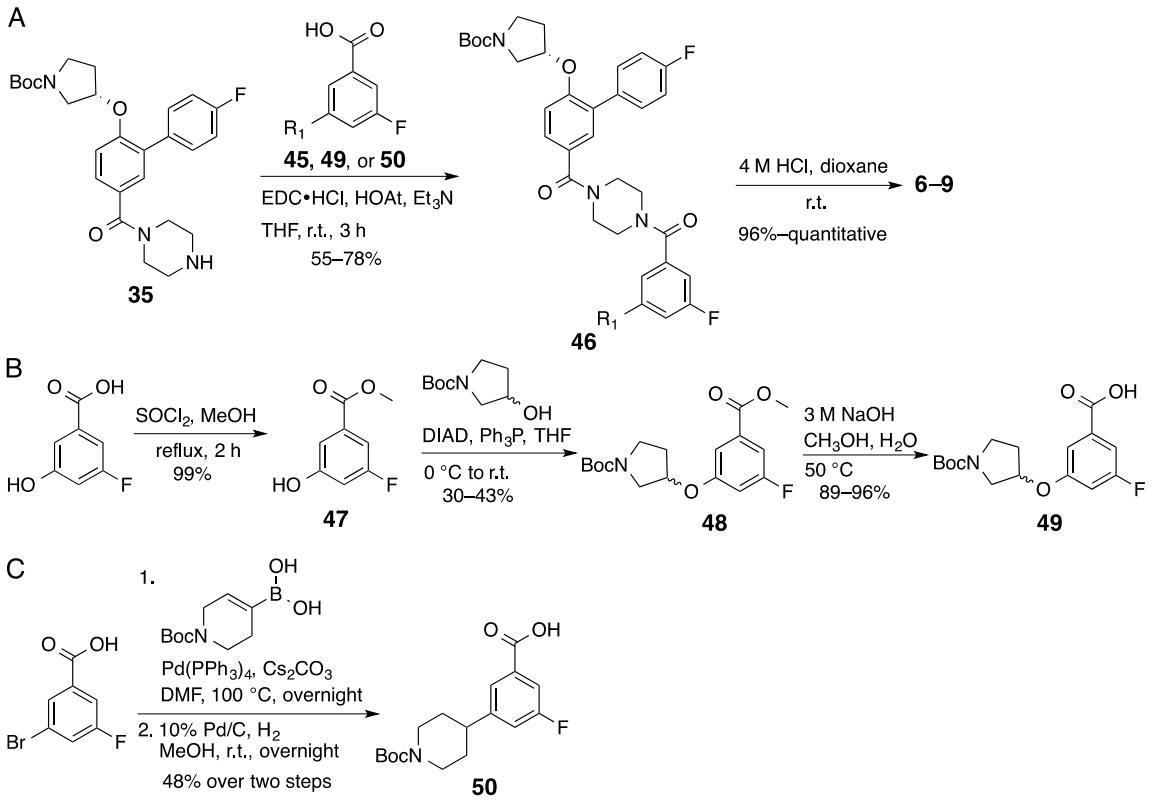
3-(2-((*tert*-Butoxycarbonyl) amino) ethyl)-5-fluorobenzoic acid (45). To a solution of **44** (0.144 g, 0.484 mmol) in MeOH (10 mL) was added 6 M NaOH (10 mL) and the reaction stirred at room temperature for 6 h. MeOH was then removed under reduced pressure. The remaining aqueous solution was acidified with 12 M HCl to pH = 2. The product was then extracted with CH_2Cl_2 (50 mL) and the organics washed with water (2 × 50 mL), brine (50 mL), dried over $MgSO_4$, solids filtered, and solvent removed under reduced pressure to yield **45** (0.118 g, 86% yield) as white solid. ^{1}H NMR (500 MHz, CD_3OD): δ ppm 7.71 (s, 1H), 7.52 (d, 1H, J = 9.0 Hz), 7.21 (d, 1H, J = 9.2 Hz), 3.39 (t, 2H, J = 7.0 Hz), 2.83 (t, 2H, J = 7.0 Hz), 1.39 (s, 9H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 168.54 (d, J = 2.5 Hz), 163.99 (d, J = 245.2 Hz), 158.42, 144.04 (d, J = 7.5 Hz), 134.22 (d, J = 8.1 Hz), 127.31 (d, J = 2.4 Hz), 121.27 (d, J = 21.5 Hz), 115.12 (d, J = 23.2 Hz), 80.08, 42.45, 36.75, 28.76.

***tert*-Butyl (*S*)-4-(3-(4-(6-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-5-(4-fluorophenyl) nicotinoyl) piperazine-1-carbonyl)-5-fluorophenyl) piperazine-1-carboxylate (43a)** The synthesis of compound **43a** followed the same procedure as for compound **36** (except solvent anhydrous CH_2Cl_2 was replaced by anhydrous THF). Column chromatography (silica gel, CH_2Cl_2:MeOH = 99:1) afforded white solid (0.0497 g, 46% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 8.20 (d, 1H, J = 2.6 Hz), 7.69 (s, 1H), 7.45 (d, 2H, J = 5.5 Hz), 7.08 (t, 2H, J = 8.4 Hz), 6.68 (s, 1H), 6.60 (td, 1H, J = 2.1, 12.1 Hz), 6.51 (d, 1H, J = 7.8 Hz), 5.62 – 5.60 (m, 1H), 3.77–3.33 (m, 16H), 3.16 (t, 4H, J = 5.0 Hz), 2.17–2.10 (m, 2H), 1.46 (s, 9H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 169.59 (d, 1H, J = 2.0 Hz), 168.14, 163.38 (d, J = 246.2 Hz), 162.44 (d, J = 246.9 Hz), 160.33, 160.31, 154.61, 154.50, 152.95 (d, J = 10.1 Hz), 144.69, 138.11, 137.29 (d, J = 9.1 Hz), 131.21, 131.10, 130.62 (d, J = 8.15 Hz), 124.57, 124.04, 115.33 (d, J = 21.5 Hz), 115.22 (d, J = 21.4 Hz), 109.73 (d, J = 1.5 Hz), 104.30 (d, J = 23.3 Hz), 103.96 (d, J = 25.4 Hz), 80.12, 79.44, 79.41, 75.66, 74.81, 51.90, 51.85, 48.19, 44.29, 43.85, 31.44, 30.79, 28.42, 28.32.

***tert*-Butyl (*S*)-3-((5-(4-(3-(2-((*tert*-butoxycarbonyl) amino) ethyl)-5-fluorobenzoyl) piperazine-1-carbonyl)-3-(4-fluorophenyl) pyridin-2-yl) oxy) pyrrolidine-1-carboxylate (43b).** The synthesis of compound **43b** followed the same procedure as for compound **36** (except solvent anhydrous CH_2Cl_2 was replaced by anhydrous THF). Column chromatography (silica gel, hexanes:EtOAc = 1:4) afforded white solid (0.0877 g, 57% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.21 (s, 1H), 7.70 (s, 1H), 7.46 (dd, 2H, J = 5.5, 7.8 Hz), 7.09 (t, 2H, J = 8.3 Hz), 7.03 (s, 1H), 6.97 (d, 2H, J = 8.3 Hz), 5.65–5.62 (m, 1H), 4.60 (bs, 1H), 3.80–3.40 (m, 14H), 2.81 (t, 2H, J = 6.9 Hz), 2.15–2.12 (m, 2H), 1.44 (s, 9H), 1.40 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 169.12, 168.16, 162.56 (d, J = 249.0 Hz), 162.51 (d, J = 247.1 Hz), 160.38, 155.73, 154.63, 144.75, 142.57 (d, J = 7.7 Hz), 138.15, 137.08 (d, J = 6.6 Hz), 130.66 (d, J = 8.2 Hz), 124.62, 124.08, 123.03 (d, J = 1.5 Hz), 117.51 (d, J = 20.8 Hz), 115.37, 115.35 (d, J = 22.1 Hz), 112.31 (d, J = 22.9 Hz), 79.43, 75.70, 74.86, 51.94, 51.63, 47.47, 44.33, 44.32, 42.42, 41.29, 36.00, 31.48, 30.85, 28.46, 28.32.

(*S*)-(4-(3-Fluoro-5-(piperazin-1-yl) benzoyl) piperazin-1-yl) (5-(4-fluorophenyl)-6-(pyrrolidin-3-yloxy) pyridin-3-yl) methanone hydrochloride (4). The synthesis of compound **4** followed the same procedure as for compound **3** to afford white solid (0.0431 g, quantitative yield). ^{1}H NMR (500 MHz, d^{6}-DMSO): δ ppm 9.17 (brs, 2H), 8.94 (brs, 2H), 8.26 (s, 1H), 7.84 (s, 1H), 7.73 – 7.70 (m, 2H), 7.29 – 7.25 (m, 2H), 6.91 (d, 1H, J = 13.0 Hz), 6.81 (s, 1H), 6.66 (d, 1H, J = 8.5 Hz), 5.65 – 5.63 (m, 1H), 3.70 – 3.18 (m, 20H), 2.26 – 2.21 (m, 1H), 2.15 – 2.10 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ ppm 170.23, 168.81, 163.80 (d, J = 244.4 Hz), 162.89 (d, J = 245.1 Hz), 159.92, 152.42, 152.34, 144.85, 138.55, 138.04, 137.97, 131.59, 131.28, 125.86, 124.11, 115.18 (d, J = 21.3 Hz), 110.21, 105.16 (d, J = 23.5 Hz), 104.38 (d, J = 25.8 Hz), 74.99, 50.97, 48.39-47.37 (m, 4C), 45.55, 44.59, 43.28, 30.92. HRMS (ESI) m/z calculated for $C_{31}H_{34}F_2N_6O_3$ $(M+H)^+$ = 577.2733, found 577.2741.

(*S*)-(4-(3-(2-Aminoethyl)-5-fluorobenzoyl) piperazin-1-yl) (5-(4-fluorophenyl)-6-(pyrrolidin-3-yloxy) pyridin-3-yl) methanone hydrochloride (5). The synthesis of compound **5** followed the same procedure as for compound **3** to afford white solid (0.0667 g, 92% yield). ^{1}H NMR (500 MHz, d^{6}-DMSO) δ ppm 9.51 (brs, 3H), 8.27 (s, 1H), 8.08 (brs, 2H), 7.84 (s, 1H), 7.74 – 7.71 (m, 2H), 7.27 – 7.24 (m, 3H), 7.16 – 7.13 (m, 2H), 7.20–7.16 (m, 1H), 5.74–5.78 (m, 1H), 3.68 – 3.16 (m, 12H), 3.06 (t, 2H, J = 7.0 Hz), 2.93 (t, 2H, J = 7.0 Hz), 2.24 – 2.18 (m, 1H), 2.13 – 2.10 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ ppm 171.04, 169.68, 163.61, 161.65, 159.82, 144.55, 140.63, 140.57, 138.75, 136.56, 131.32, 131.27, 131.06, 124.98, 124.47, 123.31, 118.05 (d, J = 21.3 Hz), 115.62 (d, J = 22.0 Hz), 112.96 (d, J = 24.4 Hz), 75.21, 50.91, 47.78, 47.14, 44.58, 42.76, 42.13, 40.25, 32.58, 30.74. HRMS (ESI) m/z calculated for $C_{29}H_{31}F_2N_5O_3$ $(M + H)^+$ = 536.2468, found 536.2470.



Methyl 3-fluoro-5-hydroxybenzoate (47). The synthesis of compound **47** followed the same procedure as for compound **26** to afford brown liquid (2.35 g, 99% yield). ^{1}H NMR (500 MHz, CD_3OD): δ ppm 7.23 (s, 1H), 7.13 (ddd, 1H, J = 1.3, 2.1, 9.1 Hz), 6.73 (td, 1H, J = 2.3, 10.4 Hz), 3.39 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 167.43 (d, J = 3.7 Hz), 164.76 (d, J = 243.9 Hz), 160.57 (d, J = 11.5 Hz), 133.88 (d, J = 9.9 Hz), 113.48 (d, J = 2.7 Hz), 108.22 (d, J = 24.3 Hz), 107.92 (d, J = 24.0 Hz), 52.87.

***tert*-Butyl (*S*)-3-(3-fluoro-5-(methoxycarbonyl) phenoxy) pyrrolidine-1-carboxylate (48a).** The synthesis of compound **48a** followed the same procedure as for compound **23**. Column chromatography (silica gel, hexanes:EtOAc = 95:5) afforded white solid (0.141 g, 30%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.32–7.30 (m, 2H), 6.76 (td, 1H, J = 2.3, 10.0 Hz), 4.92–4.89 (m, 1H), 3.890 (s, 3H), 3.61–3.45 (m, 4H), 2.18–2.12 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): 165.66 (d, J = 3.6 Hz), 163.17 (d, J = 246.8 Hz), 158.31 (d, J = 11.0 Hz), 154.36, 132.73 (d, J = 9.5 Hz), 111.71 (d, J = 2.8 Hz), 109.30 (d, J = 23.6 Hz), 108.05 (d, J = 24.5 Hz), 79.54, 76.27, 52.39, 51.43, 51.21, 43.91, 43.63, 31.33, 30.61, 28.43.

***tert*-Butyl (*R*)-3-(3-fluoro-5-(methoxycarbonyl) phenoxy) pyrrolidine-1-carboxylate (48b).** The synthesis of compound **48b** followed the same procedure as for compound **23**. Column chromatography (silica gel, hexanes:EtOAc = 95:5) afforded yellow oil (0.254 g, 43% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.25-7.22 (m, 2H), 6.71 (d, 1H, J = 10.0 Hz), 4.87–4.84 (m, 1H), 3.83 (s, 3H), 3.57–3.39 (m, 4H), 2.11–2.03 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 165.45 (d, J = 3.4 Hz), 162.98 (d, J = 246.7 Hz), 158.15 (d, J = 10.9 Hz), 154.24, 154.15, 132.50 (d, J = 9.4 Hz), 111.57, 109.06 (d, J = 23.1 Hz), 107.83 (d, J = 24.8 Hz), 79.35, 79.32, 76.93, 76.07, 52.39, 51.31, 50.99, 43.78, 43.45, 31.16, 30.39, 28.25.

(*S*)-3-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-5-fluorobenzoic acid (49a). The synthesis of compound **49a** followed the same procedure as for compound **28** to afford white solid (0.125 g, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 11.33 (brs, 1H), 7.40–7.36 (m, 2H), 6.81 (d, 1H, J = 4.5 Hz), 4.94–4.92 (m, 1H), 3.68–3.48 (m, 4H), 2.17–2.12 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 169.50, 163.46 (d, J = 242.4 Hz), 158.35 (d, J = 10.9 Hz), 154.79, 154.67, 132.33 (d, J = 9.2 Hz), 112.07, 109.86 (d, J = 24.3 Hz), 108.73 (d, J = 24.9 Hz), 80.05, 77.10, 76.29, 51.55, 51.21, 44.05, 43.69, 31.36, 30.60, 28.70.

(*R*)-3-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-5-fluorobenzoic acid (49b). The synthesis of compound **49b** followed the same procedure as for compound **28** to afford white solid (0.419 g, 89% yield). ^{1}H NMR (300 MHz, CD_3OD): δ ppm 7.37 (s, 1H), 7.30 (d, 1H, J = 8.0 Hz), 6.96 (td, 1H, J = 2.4, 10.4 Hz), 5.07–5.04 (m, 1H), 3.66–3.43 (m, 4H), 2.19–2.17 (m, 2H), 1.46 (d, 9H, J = 4.1 Hz). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 168.10 (d, J = 3.4 Hz), 164.70 (d, J = 245.3 Hz), 159.93 (d, J = 11.0 Hz), 156.44, 156.36, 135.01 (d, J = 9.3 Hz), 113.48 (d, J = 2.6 Hz), 110.01 (d, J = 23.2 Hz), 108.62 (d, J = 24.6 Hz), 81.18, 81.16, 78.51, 77.73, 52.74, 52.36, 45.29, 44.86, 32.12, 31.39, 28.78.

3-(1-(*tert*-Butoxycarbonyl) piperidin-4-yl)-5-fluorobenzoic acid (50). To a solution of 3-bromo-5-fluoroboronic acid (0.410 g, 1.87 mmol), in dry DMF (40 mL) under anhydrous conditions was added *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (0.878 g, 2.84 mmol), $Pd(PPh_3)_4$ (0.325 g, 0.281 mmol), and K_2CO_3 (0.785 g, 5.68 mmol). The mixture was heated to 100 °C under argon and stirred for 20 h. The solvent was then removed under reduced pressure, and the residue was taken into EtOAc (100 mL). The organic solution was washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, solids filtered, and solvent removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexanes:EtOAc:acetic acid = 9:1:0.25) to yield

white solid (0.419 g, 1.30 mmol) . A portion of this solid (0.0845 g, 0.262 mmol) was dissolved in MeOH (20 mL). The air was evacuated and exchanged with argon three times and 10% Pd on activated carbon (0.017 g) was added. The argon was evacuated and exchanged with the H_2 gas three times and the reaction was allowed to stir under H_2 for 12 h. The mixture was filtered through celite and the solvent removed under reduced pressure to yield **50** (0.0584 g, 48% overall yield) as off-white solid. ^{1}H NMR (500 MHz, CD_3OD): δ ppm 7.72 – 7.70 (m, 1H), 7.52 (ddd, 1H, J = 1.4, 2.4, 9.0 Hz), 7.24 (td, 1H, J = 2.0, 9.7 Hz), 4.21 (m, 2 H), 2.87–2.78 (m, 3H) 1.84 (m, 2 H), 1.58 (dq, 2H, J = 4.3, 12.7 Hz), 1.47 (s, 9H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 168.51 (d, J = 3.1 Hz), 164.14 (d, J = 245.3 Hz), 156.51, 150.42 (d, J = 6.9 Hz), 134.43 (d, J = 7.8 Hz), 125.1 (d, J = 2.6 Hz), 119.28 (d, J = 21.8 Hz), 115.19 (d, J = 23.2 Hz), 81.14, 43.35, 43.34, 34.04, 28.76.

***tert*-Butyl (*S*)-3-((5-(4-(3-(2-((*tert*-butoxycarbonyl) amino) ethyl)-5-fluorobenzoyl) piperazine-1-carbonyl)-4'-fluoro-[1,1'-biphenyl]-2-yl) oxy) pyrrolidine-1-carboxylate (46a).** The synthesis of compound **46a** followed the same procedure as for compound **36**. Column chromatography (silica gel, 100% EtOAc) afforded white solid (0.0752 g, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.41–7.38 (m, 4H), 7.07 (t, 2H, J = 7.7 Hz), 7.02 (s, 1H), 6.98–6.94 (m, 3H), 4.91–4.89 (m, 1H), 4.58 (bs, 1H), 3.78–3.20 (m, 14H), 2.81, (t, 2H, J = 6.5 Hz), 2.11–2.07 (m, 2H), 1.44 (s, 9H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 172.91, 171.03 (d, J = 2.1 Hz), 170.12, 169.04, 163.45, 162.46 (d, J = 248.9 Hz), 162.05 (d, J = 247.5 Hz), 155.72, 155.22, 155.10, 154.44, 154.26, 142.50 (d, J = 7.5 Hz), 137.09 (d, J = 6.9 Hz), 133.00 (d, J = 11.7 Hz), 131,8, 131.00, 130.89, 130.83, 130.27, 127.92, 122.94, 117.35 (d, J = 21.03 Hz), 114.96 (d, J = 21.7 Hz), 114.83 (d, J = 21.3 Hz), 113.77, 113.47, 112.27 (d, J = 23.1 Hz), 79.53, 79.46, 79.31, 77.14, 76.28, 60.27, 51.35, 50.84, 44.00, 43.63, 41.21, 35.87, 31.41, 30.63, 28.36, 28.24.

***tert*-Butyl (*S*)-3-(3-(4-(6-(((*S*)-1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-4'-fluoro-[1,1'-biphenyl]-3-carbonyl) piperazine-1-carbonyl)-5-fluorophenoxy) pyrrolidine-1-carboxylate (46b).** The synthesis of compound **46b** followed the same procedure as for compound **36**. Column chromatography (silica gel, CH_2Cl_2:MeOH = 99:1) afforded white solid (0.0656 g, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.41–7.36 (m, 4H), 7.05, (t, 2H, J = 8.2Hz), 6.94 (d, 1H, J = 8.5 Hz), 6.69–6.67 (m, 2H), 6.62 (d, 1H, J = 10.8 Hz), 4.91–4.89 (m, 1H), 4.86–4.83 (m, 1H), 3.74–3.21 (m, 16H), 2.14–2.05 (m, 4H) 1.44 (s, 18H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 172.34, 170.89 (J = 2.8 Hz), 164.88 (d, J = 246.8 Hz), 163.60 (d, J = 245.6 Hz), 160.30 (d, J = 11.1 Hz), 156.72, 156.42, 156.41, 156.36, 156.29, 139.36 (d, J = 9.2 Hz), 134.91, 132.68, 132.45, 132.39, 132.33, 131.40 (d, J = 6.8 Hz), 129.44, 129.30 (d, J = 15.8 Hz), 115.91 (d, J = 21.6 Hz), 115.86 (d, J = 21.6 Hz), 115.54, 115.14, 111.26, 107.62 (d, J = 23.7 Hz), 105.61 (d, J = 25.1 Hz), 81.14, 81.03, 78.59, 78.52, 78.04, 77.76, 54.87, 52.76, 52.72, 52.36, 52.20, 45.34, 45.29, 44.97, 44.88, 32.22, 32.14, 31.49, 31.39, 28.80.

***tert*-Butyl (*R*)-3-(3-(4-(6-(((*S*)-1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-4'-fluoro-[1,1'-biphenyl]-3-carbonyl) piperazine-1-carbonyl)-5-fluorophenoxy) pyrrolidine-1-carboxylate (46c).** The synthesis of compound **46c** followed the same procedure as for compound **36**. Column chromatography (silica gel, CH_2Cl_2:MeOH = 99:1) afforded white solid (0.0788 g, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.39–7.36 (m, 4H), 7.06–7.02 (m, 2H), 6.94–6.93 (m, 1H), 6.69–6.67 (m, 2H), 6.62 (d, 1H, J = 10.0Hz), 4.90–4.88 (m, 1H), 4.85–4.83 (m, 1H), 3.74–3.21 (m, 16H), 2.14–2.02 (m, 4H), 1.44 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 174.10, 171.05, 170.19, 168.84 (d, J = 2.4 Hz), 163.19 (d, J = 249.2 Hz), 162.07 (d, J = 247.0 Hz), 158.70 (d, J = 10.7 Hz), 155.25, 155.13, 154.48, 154.42, 154.29, 137.63 (d, J = 10.7 Hz),

132.99 (d, *J* = 10.7 Hz), 131.21, 131.03, 130.83, 130.27, 127.94, 114.97 (d, *J* = 21.0 Hz), 114.84 (d, *J* = 21.3 Hz), 113.47, 110.00, 106.59 (d, *J* = 23.2 Hz), 104.39 (d, *J* = 24.29 Hz), 79.60, 79.52, 77.20, 77.15, 76.29, 76.17, 60.29, 51.42, 51.37, 51.06, 50.84, 44.02, 43.90, 43.65, 43.54, 31.42, 31.29, 30.64, 30.52, 28.38.

***tert*-Butyl (*S*)-4-(3-(4-(6-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-4'-fluoro-[1,1'-biphenyl]-3-carbonyl) piperazine-1-carbonyl)-5-fluorophenyl) piperidine-1-carboxylate (46d).** The synthesis of compound **46d** followed the same procedure as for compound **36**. Column chromatography (silica gel, CH_2Cl_2:MeOH = 99:1) afforded white solid (0.0848 g, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.39–7.36 (m, 4H), 7.08–7.04 (m, 2H), 7.02 (s, 1H), 6.97–6.93 (m, 3H), 4.91–4.88 (m, 1H), 4.27–4.17 (m, 2H), 3.76–3.21 (m, 12H), 2.79–2.76 (m, 2H), 2.65 (t, 1H, *J* = 12.1 Hz), 2.09–2.04 (m, 2H), 1.81–1.79 (m, 2H), 1.58–1.52 (m, 2H), 1.46 (s, 9H), 1.43 (s, 4.5H), 1.42 (s, 4.5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.17, 169.19, 162.56 (d, *J* = 248.4 Hz), 162.09 (d, *J* = 244.5 Hz), 155.26, 155.12, 154.62, 154.47, 154.27, 149.26 (d, *J* = 7.3 Hz), 137.07 (d, *J* = 6.9 Hz), 133.07, 132.96, 131.23, 132.05, 130.90, 130.84, 130.30, 127.95 (d, *J* = 5.3 Hz), 121.14, 115.39 (d, *J* = 22.3 Hz), 114.86 (d, *J* = 21.1 Hz), 113.76, 113.49, 112.07 (d, *J* = 22.9 Hz) 79.56, 79.49, 77.20, 76.27, 60.29, 51.37, 50.83, 44.03, 43.65, 42.34, 32.81, 31.46, 30.83, 30.67, 29.60, 28.37.

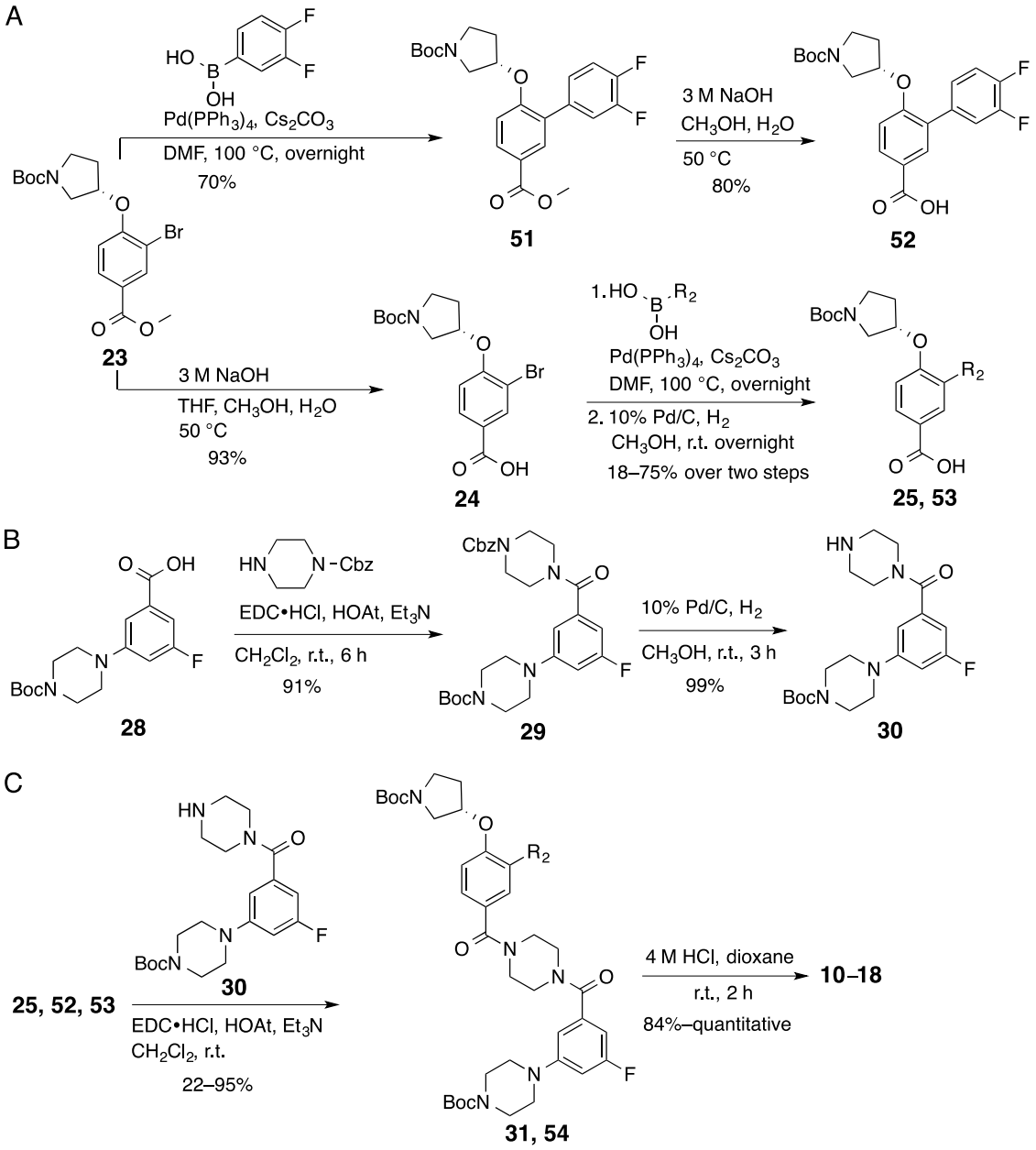
(*S*)-(4-(3-(2-Aminoethyl)-5-fluorobenzoyl) piperazin-1-yl) (4'-fluoro-6-(pyrrolidin-3-yloxy)-[1,1'-biphenyl]-3-yl) methanone hydrochloride (6). The synthesis of compound **6** followed the same procedure as for compound **3** to afford white solid (0.0593 g, 96% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.47 (brs, 2H), 8.03 (brs, 2H), 7.60 (d, 1H, *J* = 8.0 Hz), 7.59 (d, 1H, *J* = 8.0 Hz), 7.43 (d, 1H, *J* = 8.5 Hz), 7.37 (s, 1H), 7.26 – 7.15 (m, 6H), 5.18 – 5.13 (m, 1H), 3.65 – 3.26 (m, 12H), 3.07 (t, 2H, *J* = 7.2 Hz), 2.92 (t, 2H, *J* = 7.4 Hz), 2.17 – 2.12 (m, 2H), 2.06 – 2.02 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD): δ ppm 171.04, 169.77, 162.97 (d, *J* = 245.9 Hz), 162.56 (d, *J* = 244.3 Hz), 155.08, 140.71 (d, *J* = 7.5 Hz), 137.90 (d, *J* = 6.9 Hz), 133.59, 133.56, 131.43, 131.37, 131.28, 130.49, 128.73, 128.40, 123.45 (d, *J* = 2.4 Hz), 117.43 (d, *J* = 22.0 Hz), 114.96 (d, *J* = 21.3 Hz), 114.15, 112.92 (d, *J* = 22.8 Hz), 76.87, 50.63, 48.38 – 47.36 (m, 4C), 44.44, 40.28, 32.82, 30.97. HRMS (ESI) m/z calculated for $C_{30}H_{32}F_2N_4O_3$ $(M+H)^+$ = 535.2515, found 535.2522.

(4-(3-Fluoro-5-(((*S*)-pyrrolidin-3-yl) oxy) benzoyl) piperazin-1-yl) (4'-fluoro-6-(((*S*)-pyrrolidin-3-yl) oxy)-[1,1'-biphenyl]-3-yl) methanone hydrochloride (7). The synthesis of compound **7** followed the same procedure as for compound **3** to afford white solid (0.0531 g, 97% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.20 (brs, 4H), 7.61 – 7.57 (m, 2H), 7.43 (d, 1H, *J* = 8.5 Hz), 7.37 (s, 1H), 7.23 (t, 2H, *J* = 9.0 Hz), 7.19 (d, 1H, *J* = 8.5 Hz), 6.97 (d, 1H, *J* = 10.5 Hz), 6.89 (d, 1H, *J* = 8.5 Hz), 6.83 (s, 1H), 5.20 – 5.14 (m, 2H), 3.66 – 3.06 (m, 16H), 2.23 – 2.02 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 171.01, 169.54, 163.64 (d, *J* = 245.9 Hz), 162.54 (d, *J* = 244.3 Hz), 158.37, 158.28, 155.08, 138.38, 138.32, 133.58, 131.46, 131.32 (d, *J* =19 Hz), 130.50, 128.69, 128.42, 114.97 (d, *J* = 22.0 Hz), 114.14, 110.37, 107.18 (d, *J* = 23.5 Hz), 104.87 (d, *J* = 25.9 Hz), 76.86, 76.54, 50.71, 50.62, 48.40-47.38 (m, 4C), 44.45, 44.10, 31.00, 30.50. HRMS (ESI) m/z calculated for $C_{32}H_{34}F_2N_4O_4$ $(M+H)^+$ = 577.2621, found 577.2626.

(4-(3-Fluoro-5-(((*R*)-pyrrolidin-3-yl) oxy) benzoyl) piperazin-1-yl) (4'-fluoro-6-(((*S*)-pyrrolidin-3-yl) oxy)-[1,1'-biphenyl]-3-yl) methanone hydrochloride (8). The synthesis of compound **8** followed the same procedure as for compound **3** to afford white solid (0.0682 g, quantitative yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.43 (brs, 4H), 7.61 – 7.58 (m, 2H), 7.43 (d, 1H, *J* = 8.5 Hz), 7.37 (s, 1H), 7.23 (t, 2H, *J* = 9.0 Hz), 7.19 (d, 1H, *J* = 8.5 Hz), 6.98 (d,

1H, *J* = 10.5 Hz), 6.89 (d, 1H, *J* = 8.5 Hz), 6.83 (s, 1H), 5.21 – 5.14 (m, 2H), 3.69 – 3.08 (m, 16H), 2.23 – 2.02 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 171.00, 169.53, 163.64 (d, *J* = 245.9 Hz), 162.54 (d, *J* = 244.4 Hz), 158.37, 158.28, 155.07, 138.40, 138.32, 133.56, 131.45, 131.31 (d, *J* = 20.5 Hz), 130.48, 128.71, 128.40, 114.97 (d, *J* = 22.0 Hz), 114.12, 110.35, 107.16 (d, *J* = 22.8 Hz), 104.86 (d, *J* = 24.4 Hz), 76.85, 76.52, 51.68, 50.69, 48.41-47.39 (m, 4C), 44.44, 44.08, 30.98, 30.49. HRMS (ESI) m/z calculated for $C_{32}H_{34}F_2N_4O_4$ $(M+H)^+$ = 577.2621, found 577.2636.

(*S*)-(4-(3-Fluoro-5-(piperidin-4-yl) benzoyl) piperazin-1-yl) (4'-fluoro-6-(pyrrolidin-3-yloxy)-[1,1'-biphenyl]-3-yl) methanone hydrochloride (9). The synthesis of compound **9** followed the same procedure as for compound **3** to afford white solid (0.0685 g, 97% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.44 (brs, 2H), 8.93 (brs, 2H), 7.61–7.58 (m, 2H), 7.43 (d, 1H, *J* = 8.5 Hz), 7.37 (s, 1H), 7.22 (t, 2H, *J* = 9.0 Hz), 7.19 (d, 1H, *J* = 8.5 Hz), 7.17 – 7.14 (m, 2H), 7.11 (s, 1H), 5.17 – 5.13 (m, 1H), 3.66 – 2.83 (m, 16H), 2.19 – 1.80 (m, 6H). ^{13}C NMR (125 MHz, D_2O): δ ppm 171.87, 171.03, 162.60 (d, *J* = 242.9 Hz), 162.23 (d, *J* = 243.6 Hz), 154.74, 148.19, 136.34, 133.02, 131.44, 131.37, 130.00, 128.57, 127.75, 121.34, 115.95, (d, *J* = 22.0 Hz), 115.36 (d, *J* = 21.3 Hz), 114.56, 112.32 (d, *J* = 22 Hz), 76.79, 50.59, 47.82, 47.64, 47.25, 47.05, 44.38, 44.30, 42.60, 42.11, 39.02, 30.51, 29.20. HRMS (ESI) m/z calculated for $C_{33}H_{36}F_2N_4O_3$ $(M+H)^+$ = 575.2828, found 575.2842.



***tert*-Butyl (*S*)-3-((3',4'-difluoro-5-(methoxycarbonyl)-[1,1'-biphenyl]-2-yl) oxy) pyrrolidine-1-carboxylate (51).** The synthesis of compound **51** followed the same procedure as for compound **32**. Column chromatography (silica gel, hexanes:EtOAc = 5:1) afforded white solid (0.38 g, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.99 (d, 2H, J = 9.0 Hz), 7.29 (d, 1H, J = 8.1 Hz), 7.16 (d, 2H, J = 3.5 Hz), 6.94 (d, 1H, J = 8.4 Hz), 4.98–4.96 (m, 1H), 3.89 (s, 3H), 3.66–3.31 (m, 4H), 2.11–2.09 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 166.57, 157.44, 154.45, 150.84, 148.87, 132.64, 131.12, 129.65, 125.62, 125.59, 125.57, 125.54, 123.47, 118.63, 118.58, 118.56, 118.48, 118.45, 118.42, 117.00, 116.97, 116.89, 116.83, 113.01, 112.81, 79.86, 76.47, 52.18, 51.58, 51.12, 44.22, 43.83, 31.69, 30.88, 30.87, 28.53. MS (ESI) m/z = 434.6 $[M + H]^+$.

***(S)*-6-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-3',4'-difluoro-[1,1'-biphenyl]-3-carboxylic acid (52).** The synthesis of compound **52** followed the same procedure as for compound **33** to afford white solid (0.51 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 8.10–8.02 (m, 2H), 7.31–7.26 (m, 1H), 7.19–7.16 (m, 2H), 6.97 (d, 1H, J = 8.7 Hz), 5.03–5.00 (m, 1H), 3.71–3.33 (m, 4H), 2.16–2.12 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, d^6-DMSO/$CDCl_3$): δ ppm 171.12, 170.88, 158.18, 158.03, 154.96, 154.62, 150.92, 150.90, 148.96, 148.94, 148.93, 148.85, 148.83, 134.23, 133.19, 131.80, 129.74, 129.68, 125.60, 122.73, 118.65, 118.51, 117.00, 116.86, 112.98, 112.81, 80.18, 76.50, 51.63, 51.13, 44.29, 43.87, 31.69, 30.89, 28.55.

(*S*)-3-Bromo-4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy) benzoic acid (24). The synthesis of compound **24** followed the same procedure as for compound **33** to afford white solid (0.941 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 8.29 (d, 1H, J = 4.7 Hz), 8.01 (t, 1H, J = 8.9 Hz), 6.88 (d, 1H, J = 8.6 Hz), 5.03–5.01 (m, 1H), 3.70–3.56 (m, 4H), 2.30–2.13 (m, 2H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 169.84, 157.90, 154.76, 154.49, 135.77, 130.93, 123.49, 113.12, 112.98, 79.94, 78.18, 51.45, 51.07, 44.15, 43.72, 31.67, 30.87, 28.45.

(*S*)-4-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-cyclohexylbenzoic acid (25a). The synthesis of compound **25a** followed the same procedure as for compound **50.** Column chromatography (silica gel, hexanes:acetone:AcOH = 88:10:2) afforded off-white solid (0.173 g, 75% yield). ^{1}H NMR (500 MHz, CD_3OD): δ ppm 7.87–7.84 (m, 2H), 6.96 (d, 1H, J = 8.0 Hz), 5.10–5.08 (m, 1H), 3.61–3.45 (m, 4H), 2.85 (t, 1H, J = 9.8 Hz), 2.20–2.16 (m, 2H), 1.82–1.73 (m, 6H), 1.45 (s, 4.5H), 1.42, (s, 4.5H), 1.38–1.25 (m, 4H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 170.58, 159.11, 156.50, 156.39, 137.98, 137.89, 130.21, 129.73, 125.00, 124.90, 113.13, 113.10, 81.08, 81.04, 77.77, 76.94, 52.76, 52.28, 45.52, 45.12, 38.91, 38.85, 34.32, 34.29, 33.82, 33.72, 32.38, 31.69, 28.82, 28.29, 28.23, 28.19, 28.16, 27.43.

(*S*)-4-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-(4-(trifluoromethyl) cyclohexyl) benzoic acid (25b). The synthesis of compound **25b** followed the same procedure as for compound **50**. Column chromatography (silica gel, hexanes:acetone:AcOH = 88:10:2) afforded white solid (0.0983 g, 41% yield). ^{1}H NMR (300 MHz, CD_3OD): δ ppm 7.89–7.86 (m, 2H), 7.01–6.97 (m, 1H), 5.13–5.10 (m, 1H), 3.59–3.42 (m, 4H), 2.98–2.81 (m, 1H), 2.44–2.36 (m, 1H), 2.22–2.18 (m, 2H), 2.05–1.98 (m, 4H), 1.81–1.66 (m, 4H), 1.46 (m, 4.5H), 1.43 (m, 4.5H). ^{13}C NMR (75 MHz, CD_3OD): δ ppm 175.31, 169.94, 159.52, 159.35, 156.49, 156.44, 13662, 136.54, 136.51, 132.16, 130.69, 130.66, 130.12, 129.70, 129.63, 128.44, 124.50, 124.36, 124.30, 113.29, 113.15, 81.17, 81.13, 77.89, 77.82, 77.12, 52.76, 52.32, 45.52, 45.13, 38.37, 38.03, 37.43, 26.66, 25.08, 25.01, 20.88.

(*S*)-4-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-(4-methylcyclohexyl) benzoic acid (53a). The synthesis of compound **53a** followed the same procedure as for compound **50**. Column chromatography (silica gel, hexanes:acetone:AcOH = 88:10:2) afforded white solid (0.0763 g, 36% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.88–7.79 (m, 2H), 6.64–6.60 (m, 1H), 4.87–4.83 (m, 1H), 3.61–3.43 (m, 4H), 2.72–2.67 (m, 1H), 2.12–2.03 (m, 2H), 1.67–1.56 (m, 4H), 1.48–1.42 (m, 11H), 1.36–1.20 (m, 3H), 0.93 (d, 3H, J = 6.1 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ ppm 172.17, 158.67, 156.52, 156.46, 137.61, 137.53, 130.00, 129.68, 127.03, 126.85, 113.07, 113.04, 81.08, 81.05, 77.74, 76.92, 52.81, 52.33, 45.55, 45.16, 39.46, 39.42, 38.60, 37.02, 33.87, 33.46, 32.38, 31.69, 28.80, 28.56, 28.21, 27.73, 27.67, 23.19, 18.40.

(*S*)-4-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-(4-ethylcyclohexyl) benzoic acid (53b). The synthesis of compound **53b** followed the same procedure as for compound **50**. Column chromatography (silica gel, hexanes:acetone:AcOH = 88:10:2) afforded white solid (0.111 g, 45% yield). ^{1}H NMR (500 MHz, CD_3OD): δ ppm 7.90–7.86 (m, 1H), 7.85–7.82 (m,

1H), 6.96–6.93 (m, 1H), 5.10–5.08 (m, 1H), 3.61–3.48 (m, 4H), 2.88–2.79 (m, 1H), 2.20–2.16 (m, 2H), 1.87–1.62 (m, 6H), 1.56–1.48 (m, 2H), 1.46 (s, 4.5H), 1.43 (s, 4.5H), 1.29–1.17 (m, 2H), 1.07–1.00 (m, 1H), 0.93–0.89 (m, 3H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 172.26, 158.66, 158.62, 156.52, 156.50, 156.44, 156.42, 137.61, 137.53, 130.05, 129.99, 129.67, 129.64, 127.12, 127.09, 126.92, 113.06, 81.06, 81.01, 77.75, 76.91, 52.78, 52.32, 45.55, 45.15, 40.62, 39.49, 39.22, 39.13, 39.00, 36.07, 34.68, 34.60, 34.57, 34.54, 34.52, 34.16, 34.08, 33.65, 33.57, 32.40, 32.38, 31.72, 31.68, 31.40, 31.30, 31.21, 31.19, 31.16, 30.75, 29.60, 28.81, 28.56, 28.48, 28.05, 27.91, 25.14, 12.82, 11.93.

(*S*)-4-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-(4,4-dimethylcyclohexyl) benzoic acid (53c). The synthesis of compound **53c** followed the same procedure as for compound **50**. Column chromatography (silica gel, hexanes:acetone:AcOH = 85:15:2) afforded white solid (0.164 g, 58% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.88–7.81 (m, 2H), 6.64–6.64 (m, 1H), 4.88–4.85 (m, 1H), 3.64–3.41 (m, 4H), 2.63 (t, 1H, J = 10.3 Hz), 2.14–2.05 (m, 2H), 1.62–1.50 (m, 4H), 1.46 (s, 4.5H), 1.44 (s, 4.5H), 1.41 (m, 2H), 1.25 (t, 2H, J = 12.3 Hz), 0.90 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 172.35, 157.63, 154.48, 154.40, 135.87, 135.77, 129.25, 129.11, 124.58, 124.47, 110.98, 79.54, 79.44, 76.16, 75.30, 51.60, 51.29, 44.13, 43.78, 39.75, 38.36, 38.23, 33.05, 31.41, 30.75, 29.77, 28.40, 28.21, 28.07, 28.00, 24.25.

(*S*)-4-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-(4,4-difluorocyclohexyl) benzoic acid (53d). The synthesis of compound **53d** followed the same procedure as for compound **50**. Column chromatography (silica gel, hexanes:acetone:AcOH = 88:10:2) afforded white solid (0.0486 g, 18% yield). ^{1}H NMR (500 MHz, CD_3OD): δ ppm 7.88–7.87 (m, 1H), 7.84–7.81 (m, 1H), 6.95–6.92 (m, 1H), 5.12–5.10 (m, 1H), 3.60–3.50 (m, 4H), 2.98–2.94 (m, 1H), 2.24–2.20 (m, 2H), 2.15–2.10 (m, 2H), 1.86–1.81 (m, 6H), 1.47 (s, 4.5H), 1.43 (s, 4.5H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 180.27, 175.29, 157.42, 157.35, 156.56, 156.52, 134.67, 134.65, 134.54, 131.55, 130.03, 129.63, 129.59, 129.63, 129.59, 124.40, 112.95, 81.13, 81.09, 77.68, 76.99, 52.74, 52.34, 45.85, 45.18, 37.70, 37.57, 35.36, 32.44, 31.72, 30.05, 29.97, 29.90, 28.82, 28.76, 24.14.

(*S*)-4-((1-(*tert*-Butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-cyclopentylbenzoic acid (53e). The synthesis of compound **53e** followed the same procedure as for compound **50**. Column chromatography (silica gel, hexanes:acetone:AcOH = 88:10:2) afforded white solid (0.152 g, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.87–7.81 (m, 2H), 6.66–6.62 (m, 1H), 4.89–4.85 (m, 1H), 3.65–3.41 (m, 4H), 3.14–3.11 (m, 1H), 2.14–2.11 (m, 1H), 2.08–2.04 (m, 1H), 1.90–1.86 (m, 2H), 1.69–1.66 (m, 2H), 1.59–1.50 (m, 2H), 1.51–1.48 (m, 2H), 1.46 (s, 4.5H), 1.44 (s, 4.5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 172.32, 158.08, 154.54, 154.46, 134.73, 134.57, 129.23, 129.18, 124.40, 124.24, 110.88, 79.56, 79.47, 76.22, 75.36, 51.66, 51.40, 44.12, 43.78, 39.43, 32.49, 32.36, 32.30, 31.35, 30.84, 30.70, 28.40, 25.40, 24.75.

Benzyl 4-(3-(4-(*tert*-butoxycarbonyl) piperazin-1-yl)-5-fluorobenzoyl) piperazine-1-carboxylate (29). The synthesis of compound **29** followed the same procedure as for compound **34.** Column chromatography (silica gel, hexanes:acetone = 70:30) afforded yellow solid (0.873 g, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.29–7.24 (m, 5H), 6.63 (s, 1H), 6.57 (td, 1H, J = 2.0, 11.9 Hz), 6.46 (d, 1H, J = 7.7 Hz), 5.09 (s, 2H), 3.66–3.54 (m, 12H), 3.11 (t, 4H, J = 5.0 Hz), 1.42 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 169.26 (d, J = 2.8 Hz), 163.17 (d, J = 245.8 Hz), 154.79, 154.27, 152.70 (d, J = 10.1 Hz), 137.5 (d, J = 8.9 Hz), 136.07, 128.28, 127.92, 127.73, 109.51 (d, J = 2.1 Hz), 104.09 (d, J = 23.5 Hz), 103.59 (d, J = 25.1 Hz), 79.78, 67.19, 47.99, 28.12.

***tert*-Butyl 4-(3-fluoro-5-(piperazine-1-carbonyl) phenyl) piperazine-1-carboxylate (30).** The synthesis of compound **30** followed the same procedure as for compound **35** to afford off-white solid (0.644 g, 99% yield). ^{1}H NMR (500 MHz, CD_3OD): δ ppm 6.77–6.74 (m, 2H), 6.55 (d, J = 7.3 Hz), 3.77–3.71 (m, 2H), 3.52–3.43 (m, 6H), 3.18–3.16 (m, 4H), 2.96–2.88 (m, 4H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, CD_3OD): δ ppm 171.19, 164.87 (d, J = 244.1 Hz), 156.12, 154.43 (d, J = 10.3 Hz), 138.96 (d, J = 9.1 Hz), 110.73 (d, J = 1.6 Hz), 104.95 (d, J = 23.8 Hz), 104.67 (d, J = 25.5 Hz), 81.26, 49.20, 28.76.

***tert*-Butyl (*S*)-4-(3-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-cyclohexylbenzoyl) piperazine-1-carbonyl)-5-fluorophenyl) piperazine-1-carboxylate (31a).** The synthesis of compound **31a** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.0494 g, 21% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.25–7.20 (m, 2H), 6.78 (d, 1H, J = 7.8 Hz), 6.68 (s, 1H), 6.60 (d, 1H, J = 11.8 Hz), 6.52 (d, 1H, J = 7.2 Hz), 4.94–4.92 (m, 1H), 3.77–3.46 (m, 16H), 3.17–3.15 (m, 4H), 2.86–2.81 (m, 1H), 2.22–2.18 (m, 1H), 2.14–2.09 (m, 1H), 1.80–1.72 (m, 6H), 1.46 (s, 9H), 1.44 (s, 9H), 1.38–1.28 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.91, 169.58, 163.39 (d, J = 246.0 Hz), 155.64, 155.52, 154.53, 154.51, 154.37, 152.93 (d, J = 10.1 Hz), 137.52 (d, J = 8.3 Hz), 137.33 (d, J = 11.0 Hz), 127.22, 126.50,126.09, 126.0, 111.83, 109.75, 104.36 (d, J = 23.2 Hz), 103.9 (d, J = 23.2 Hz), 80.09, 79.50, 79.42, 76.46, 75.36, 53.77, 51.45, 50.96, 48.22, 44.18, 43.82, 37.31, 37.22, 33.08, 33.03, 32.80, 32.59, 31.68, 31.67, 31.63, 30.92, 29.21, 28.41, 28.33, 26.94, 26.88, 26.22.

***tert*-Butyl (*S*)-4-(3-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-(4-(trifluoromethyl) cyclohexyl) benzoyl) piperazine-1-carbonyl)-5-fluorophenyl) piperazine-1-carboxylate (31b).** The synthesis of compound **31b** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.0997 g, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.25–7.22 (m, 2H), 6.80–6.77 (m, 1H), 6.67–6.66 (m, 1H), 6.61–6.58 (m, 1H), 6.51–6.50 (m, 1H), 4.94–4.92 (m, 1H), 3.73–3.45 (m, 16H), 3.16–3.14 (m, 4H), 2.93–2.90 (m, 1H), 2.33–2.28 (m, 1H), 2.19–2.10 (m, 2H), 2.03–1.98 (m, 3H), 1.92–1.87 (m, 1H), 1.76–1.63 (m, 4H), 1.45 (s, 9H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.66, 169.50, 163.35 (d, J = 246.0 Hz), 155.61, 154.46, 154.32, 152.85 (d, J = 9.5 Hz), 137.46 (d, J = 8.9 Hz), 135.74, 135.59, 129.69, 127.46, 127.24, 126.78, 126.51, 126.44, 111.90, 111.83, 109.72, 104.37 (d, J = 22.9 Hz), 103.88 (d, J = 25.2 Hz), 80.05, 80.03, 79.53, 79.45, 76.48, 75.46, 51.41, 51.02, 48.21, 44.10, 43.75, 36.85, 36.63, 36.47, 35.57, 35.55, 31.50, 30.90, 30.81, 29.56, 29.16, 28.36, 28.27, 27.54, 27.35, 27.24, 25.25, 23.84, 20.92, 14.08.

***tert*-Butyl (*S*)-4-(3-(4-(6-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3',4'-difluoro-[1,1'-biphenyl]-3-carbonyl) piperazine-1-carbonyl)-5-fluorophenyl) piperazine-1-carboxylate (54a).** The synthesis of compound **54a** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.144 g, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.37–7.33 (m, 2H), 7.25–7.20 (m, 1H), 7.15–7.10 (m, 2H), 6.92 (d, 1H, J = 8.1 Hz), 6.64 (s, 1H), 6.57 (d, 1H, J = 11.5 Hz), 6.47 (d, 1H, J = 7.4 Hz), 4.91–4.88 (m, 1H), 3.77–3.24 (m, 16H), 3.14–3.11 (m, 4H), 2.08–2.04 (m, 2H), 1.42 (s, 9H), 1.40 (s, 5H), 1.39 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 169.84, 169.44 (d, J = 2.4 Hz), 163.26 (d, J = 246.11 Hz), 155.05, 154.86, 154.38, 154.12, 152.81 (d, J = 10.1 Hz), 150.62, 150.59, 150.49, 148.72, 148.62, 148.50, 137.31 (d, J = 8.6 Hz), 133.94, 133.79, 130.13, 129.87, 129.68, 128.32, 128.29, 127.92, 125.23, 118.30, 118.25, 118.23, 118.16, 118.11, 118.08, 116.81, 116.76, 116.67, 116.63, 113.44, 113.32, 109.58, 104.16 (d, J = 23.4 Hz), 103.77 (d, J = 25.5Hz),

79.96, 79.48, 77.20, 77.17, 76.13, 69.30, 53.72, 51.26, 50.67, 48.06, 43.95, 43.51, 31.58, 31.36, 30.73, 30.52, 29.09, 28.23, 28.20.

***tert*-Butyl (*S*)-4-(3-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-(4-methylcyclohexyl) benzoyl) piperazine-1-carbonyl)-5-fluorophenyl) piperazine-1-carboxylate (54b).** The synthesis of compound **54b** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.0313 g, 22% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.30–7.28 (m, 1H), 7.24–7.19 (m, 1H), 6.80–6.77 (m, 1H), 6.70–6.68 (m, 1H), 6.64–6.59 (m, 1H), 6.55–6.52 (m, 1H), 4.95–4.93 (m, 1H), 3.78–3.48 (m, 16H), 3.17 (t, 4H, J = 4.7 Hz), 2.83–2.78 (m, 1H), 2.21–2.10 (m, 2H), 1.99–1.95 (m, 1H), 1.80–1.52 (m, 6H), 1.47 (s, 9H), 1.45 (s, 9H), 1.32–1.25 (m, 2H), 1.01 (d, 3H, J = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 170.99, 169.64, 163.42 (d, J = 245.9 Hz), 155.81, 155.69, 154.56, 152.96 (d, J = 10.0 Hz), 137.53 (d, J = 8.5 Hz), 137.31, 127.15, 126.86, 126.11, 111.78, 109.82 (d, J = 2.3 Hz), 104.45 (d, J = 23.8 Hz), 103.98 (d, J = 25.7 Hz), 80.17, 79.56, 79.50, 53.73, 48.28, 37.69, 32.53, 32.15, 31.73, 30.93, 29.67, 29.23, 28.45, 28.37, 27.00, 26.56, 22.62, 17.90.

***tert*-Butyl (*S*)-4-(3-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-(4-ethylcyclohexyl) benzoyl) piperazine-1-carbonyl)-5-fluorophenyl) piperazine-1-carboxylate (54c).** The synthesis of compound **54c** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.120 g, 58% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.23–7.16 (m, 2H), 6.75–6.73 (m, 1H), 6.65–6.64 (m, 1H), 6.58–6.56 (m, 1H), 6.49–6.48 (m, 1H), 4.91–4.89 (m, 1H), 3.71–3.45 (m, 16H), 3.14–3.12 (m, 4H), 2.82–2.75 (m, 1H), 2.17–2.05 (m, 2H), 1.80–1.47 (m, 6H), 1.43 (s, 9H), 1.40 (s, 9H), 1.36–1.19 (m, 5H), 0.84 (t, 3H, J = 7.4Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.80, 169.45, 163.28 (d, J = 246.2 Hz), 155.63, 155.52, 154.39, 152.76 (d, J = 10.3 Hz), 137.44 (d, J = 9.1 Hz), 127.06, 126.68, 126.34, 125.94, 111.69, 109.68, 104.32 (d, J = 23.1 Hz), 103.83 (d, J = 25.2 Hz), 79.97, 79.37, 79.29, 76.34, 75.26, 53.73, 51.36, 50.87, 48.15, 44.09, 43.71, 39.05, 37.46, 37.31, 37.22, 34.30, 33.01, 32.69, 31.60, 31.51, 30.79, 30.76, 29.93, 29.81, 29.11, 28.31, 28.22, 27.16, 26.90, 26.71, 23.89, 12.20, 11.36.

***tert*-Butyl (*S*)-4-(3-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-(4,4-dimethylcyclohexyl) benzoyl) piperazine-1-carbonyl)-5-fluorophenyl) piperazine-1-carboxylate (54d).** The synthesis of compound **54d** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.0884 g, 44% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.27 (s, 1H), 7.23–7.18 (m, 1H), 6.76 (d, 1H, J = 8.3 Hz), 6.67 (s, 1H), 6.59 (d, 1H, 11.6 Hz), 6.51 (d, 1H, 7.5 Hz), 4.93–4.91 (m, 1H), 3.74–3.45 (m, 16H), 3.16–3.14 (m, 4H), 2.74–2.68 (m, 1H), 2.21–2.15 (m, 1H), 2.12–2.07 (m, 1H), 1.57–1.52 (m, 4H), 1.45 (s, 9H), 1.43 (s, 11H), 1.32–1.26 (m, 2H), 0.92 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.03, 169.65, 163.35 (d, J = 246.0 Hz), 155.82, 155.72, 154.58, 154.53, 154.42, 152.88 (d, J = 10.1 Hz), 137.34 (d, J = 8.7 Hz), 137.00, 126.96, 126.69, 126.08, 126.01, 111.69, 109.74 (d, J = 1.6 Hz), 104.33 (d, J = 23.7 Hz), 103.91 (d, J = 25.1 Hz), 80.16, 79.62, 79.54, 76.34, 75.36, 51.49, 50.99, 48.17, 44.18, 43.78, 39.71, 39.67, 39.62, 37.88, 37.82, 32.97, 31.55, 30.81, 29.80, 28.50, 28.44, 28.38, 28.29, 28.18, 28.13, 24.20.

***tert*-Butyl (*S*)-4-(3-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-(4,4-difluorocyclohexyl) benzoyl) piperazine-1-carbonyl)-5-fluorophenyl) piperazine-1-carboxylate (54e).** The synthesis of compound **54e** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.0530 g, 61% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.28–7.23 (m, 2H), 6.81–6.80

(m, 1H), 6.70–6.68 (m, 1H), 6.63–6.60 (m, 1H), 6.53–6.52 (m, 1H), 4.97–4.95 (m, 1H), 3.77–3.46 (m, 16H), 3.18–3.16 (m, 4H), 2.94–2.89 (m, 1H), 2.20–2.15 (m, 4H), 1.89–1.70 (m, 6H), 1.47 (s, 9H), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.56, 169.58, 163.40 (d, J = 246.2 Hz), 155.58, 154.52, 152.89 (d, J = 10.3 Hz), 137.49 (d, J = 8.2 Hz), 134.55, 127.44, 126.76, 126.74, 126.72, 126.68, 126.59, 126.57, 111.88, 109.82, 104.45 (d, J = 23.4 Hz), 103.99 (d, J = 24.8 Hz), 80.14, 79.68, 79.63, 53.75, 51.45, 50.97, 48.29, 44.17, 43.80, 35.92, 35.65, 34.31, 34.10, 33.93, 31.70, 31.64, 30.89, 29.22, 28.62, 28.53, 28.43, 28.35.

***tert*-Butyl (*S*)-4-(3-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-cyclopentylbenzoyl) piperazine-1-carbonyl)-5-fluorophenyl) piperazine-1-carboxylate (54f).** The synthesis of compound **54f** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.0742 g, 41% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.28 (s, 1H), 7.23–7.19 (m, 1H), 6.77 (d, 1H, J = 8.3 Hz), 6.68 (s, 1H), 6.60 (d, J = 11.8 Hz), 6.52 (d, J = 7.5 Hz), 4.95–4.93 (m, 1H), 3.75–3.45 (m, 16H), 3.23–3.19 (m, 1H), 3.17–3.15 (m, 4H), 2.23–2.16 (m, 1H), 2.13–2.09 (m, 1H), 1.98–1.93 (m, 2H), 1.75–1.71 (m, 2H), 1.66–1.62 (m, 2H), 1.55–1.49 (m, 2H), 1.46 (s, 9H), 1.44 (s, 9H). ^{13}C NMR (125 MHz, D_2O): δ ppm 170.89, 169.57 (d, J = 2.5 Hz), 163.39 (d, J = 246.0 Hz), 156.27, 156.21, 154.56, 154.51, 154.41, 152.93 (d, J = 10.1 Hz), 137.51 (d, J = 8.1 Hz), 135.90, 135.77, 127.00, 126.76, 126.06, 126.04, 126.02, 111.54, 109.75 (d, J = 1.9 Hz), 104.36 (d, J = 23.6 Hz), 103.91 (d, J = 25.3 Hz), 80.10, 79.53, 79.45, 76.39, 75.39, 51.59, 51.15, 48.23, 44.18, 43.79, 39.44, 39.35, 32.60, 32.54, 32.32, 31.51, 30.78, 28.42, 28.33, 25.46.

***tert*-Butyl (*S*)-4-(3-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-methylbenzoyl) piperazine-1-carbonyl)-5-fluorophenyl) piperazine-1-carboxylate (54g).** The synthesis of compound **54g** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.2507 g, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.15–7.11 (m, 2H), 6.70–6.68 (m, 1H), 6.61–6.59 (m, 1H), 6.54–6.51 (m, 1H), 6.45–6.43 (m, 1H), 4.85–4.83 (m, 1H), 3.66–3.44 (m, 16H), 3.10–3.07 (m, 4H), 2.09 (s, 3H), 1.38 (s, 9H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.34, 169.24 (d, J = 2.7 Hz), 163.15 (d, J = 246.0 Hz), 156.40, 154.23, 152.64 (d, J = 10.1 Hz), 137.36 (d, J = 8.8 Hz), 129.99, 127.78, 126.90, 126.02, 111.39, 109.44 (d, J = 1.5 Hz), 104.05 (d, J = 23.3 Hz), 103.57 (d, J = 25.1 Hz), 79.74, 79.14, 76.35, 75.47, 51.35, 50.95, 47.94, 43.88, 43.49, 31.35, 30.57, 28.18, 28.09.

(*S*)-(4-(3',4'-Difluoro-6-(pyrrolidin-3-yloxy)-[1,1'-biphenyl]-3-carbonyl) piperazin-1-yl) (3-fluoro-5-(piperazin-1-yl) phenyl) methanone hydrochloride (10). The synthesis of compound **10** followed the same procedure as for compound **3** to afford white solid (0.116 g, 97% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.45 (brs, 2H), 9.28 (brs, 2H), 7.68 – 7.64 (m, 2H), 7.48 – 7.39 (m, 3H), 7.20 (d, 1H, J = 8.5 Hz), 6.90 (d, 1H, J = 12.5 Hz), 6.80 (s, 1H), 6.65 (d, 1H, J = 8.0 Hz), 5.18 – 5.15 (m, 1H), 3.64 – 3.09 (m, 20H), 2.21 – 2.03 (m, 2H), 7.41 (d, 1H, J = 7.4 Hz), 7.13–7.10 (m, 4H), 7.00 (s, 1H), 6.76–6.72 (m, 2H), 6.44 (s, 1H), 5.15–5.11 (m, 1H), 3.69–3.12 (m, 20H), 2.24–2.16 (m, 1H), 2.09–2.04 (m, 1H). ^{13}C NMR (125 MHz, D_2O): δ ppm 171.43, 170.81, 163.60 (d, J = 244.4 Hz), 154.66, 150.45, 148.50, 136.92, 136.85, 134.06, 129.76, 129.16, 127.73, 126.25, 118.27, 118.13, 117.26, 117.13, 114.35, 110.56, 105.34, 76.63, 50.45, 45.64, 44.42, 43.05, 42.76, 30.45, 29.60. HRMS (ESI) m/z calculated for $C_{32}H_{34}F_3N_5O_3$ $(M+H)^+$ = 594.2687, found 594.2698.

(*S*)-(4-(3-Cyclohexyl-4-(pyrrolidin-3-yloxy) benzoyl) piperazin-1-yl) (3-fluoro-5-(piperazin-1-yl) phenyl) methanone hydrochloride (11). The synthesis of compound **11** followed the same procedure as for compound **3** to afford white solid (0.0392 g, 98% yield). ^{1}H NMR (500 MHz,

d^6-DMSO): δ ppm 9.34 (brs, 4H), 7.24 – 7.22 (m, 2H), 7.00 (d, 1H, *J* = 9.0 Hz), 6.90 (d, 1H, *J* = 12.5 Hz), 6.80 (s, 1H), 6.64 (d, 1H, *J* = 8.5 Hz), 5.18 – 5.14 (m, 1H), 3.62 – 2.85 (m, 20H), 2.90 – 2.85 (m, 1H), 2.19 – 1.20 (m, 12H). ^{13}C NMR (75 MHz, D_2O): δ ppm 172.71, 171.23, 163.38 (d, J = 243.2 Hz), 155.12 (d, *J* = 16.8 Hz), 151.97, 137.68, 136.77 (d, *J* = 15.0 Hz), 127.07, 126.46, 126.34, 112.69, 110.65, 105.80, 105.43, 75.91, 50.74, 47.76, 47.17,45.85, 44.47, 42.99, 42.69, 42.11, 36.56, 32.97, 30.66, 26.59, 25.94. HRMS (ESI) m/z calculated for $C_{32}H_{43}FN_5O_3$ $(M+H)^+$ = 564.3344, found 564.3348.

(*S*)-(4-(3-Cyclopentyl-4-(pyrrolidin-3-yloxy) benzoyl) piperazin-1-yl) (3-fluoro-5-(piperazin-1-yl) phenyl) methanone hydrochloride (12). The synthesis of compound **12** followed the same procedure as for compound **3** to afford white solid (0.0661 g, quantitative yield, *trans : cis* = 2:1). Major isomer: ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.47 (brs, 2H), 9.22 (brs, 2H), 7.28–7.22 (m 2H), 7.00 (d, 1H, *J* = 8.5 Hz), 6.90 (d, 1H, *J* = 12.5 Hz), 6.80 (s, 1H), 6.65 (d, 1H, *J* = 8.0 Hz), 5.18 – 5.15 (m, 1H), 3.72–3.16 (m, 20H), 2.90 – 2.82 (m, 1H) 2.20 – 1.07 (m, 11H), 1.00 (d, 1H, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, D_2O): δ ppm 172.67, 171.15, 163.23 (d, *J* = 244.9 Hz), 155.02, 151.79, 151.71, 137.44, 136.63, 136.56, 126.96, 126.89, 126.47, 116.24, 126.07, 112.53, 110.46, 75.73, 50.57, 47.74, 44.15, 46.89, 45.69, 44.31, 42.80, 42.58, 36.40, 36.09, 365.03, 32.62, 32.55, 31.88, 31.55, 30.47, 26.77, 26.70, 21.97. HRMS (ESI) m/z calculated for $C_{31}H_{40}FN_5O_3$ $(M+H)^+$ = 550.3188, found 550.3208.

(*S*)-(4-(3-Fluoro-5-(piperazin-1-yl) benzoyl) piperazin-1-yl) (3-(4-methylcyclohexyl)-4-(pyrrolidin-3-yloxy) phenyl) methanone hydrochloride (13). The synthesis of compound **13** followed the same procedure as for compound **3** to afford white solid (0.0252 g, quantitative yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.40 (brs, 2H), 9.06 (brs, 2H), 7.28 – 7.21 (m, 2H), 7.02 (d, 1H, *J* = 8.0 Hz), 6.91 (d, 1H, *J* = 12.5 Hz), 6.80 (s, 1H), 6.65 (d, 1H, *J* = 8.5 Hz), 5.21 – 5.16 (m 2H), 3.66 – 3.00 (m, 21H), 2.22 – 1.42 (m, 11H). ^{13}C NMR (125 MHz, D_2O): δ ppm 172.21, 170.73, 163.18 (d, *J* = 242.9 Hz), 155.19 (d, *J* = 12.4 Hz), 151.74 (d, *J* = 10.1 Hz), 151.94 (d, *J* = 10.5 Hz), 151.91 (d, *J* = 10.4 Hz), 136.80 (d, *J* = 9.5 Hz), 126.94 (d, *J* = 23.8 Hz), 126.86 (d, *J* = 15.1 Hz), 126.02, 112.66, 110.43, 105.13, 75.70, 50.58, 50.53, 47.75, 47.78, 45.50, 44.33, 42.89, 41.92, 35.61, 30.58, 27.46, 27.32, 24.83, 23.03. HRMS (ESI) m/z calculated for $C_{33}H_{44}FN_5O_3$ $(M+H)^+$ = 578.3547, found 578.3510.

(*S*)-(4-(3-Fluoro-5-(piperazin-1-yl) benzoyl) piperazin-1-yl) (4-(pyrrolidin-3-yloxy)-3-(4-(trifluoromethyl) cyclohexyl) phenyl) methanone hydrochloride (14). The synthesis of compound **14** followed the same procedure as for compound **3** to afford white solid (0.0767 g, 92% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.41 (brs, 2H), 9.18 (brs, 2H), 7.26–7.22 (m, 2H), 7.00 (d, 1H, *J* = 8.5 Hz), 6.90 (d, 1H, *J* = 12.0 Hz), 6.80 (s, 1H), 6.65 (d, 1H, *J* = 8.0 Hz), 5.18 – 5.15 (m, 1H), 3.70 – 2.81 (m, 21H), 2.21 – 1.10 (m, 13H); 0.86 (t, 3H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, D_2O): δ ppm 171.93, 170.44, 163.09 (d, *J* = 242.9 Hz), 155.17, 152.10, 152.02, 136.87, 136.32, 127.05, 126.98, 125.55, 112.76, 110.47, 104.79, 75.61, 50.41, 45.38, 44.28, 42.89, 39.24, 36.43, 36.21, 34.51, 32.86, 32.70, 30.68, 29.78, 29.63, 27.31, 27.14, 24.08, 12.13, 11.37. HRMS (ESI) m/z calculated for $C_{33}H_{41}F_4N_5O_3$ $(M+H)^+$ = 632.3224, found 632.3235.

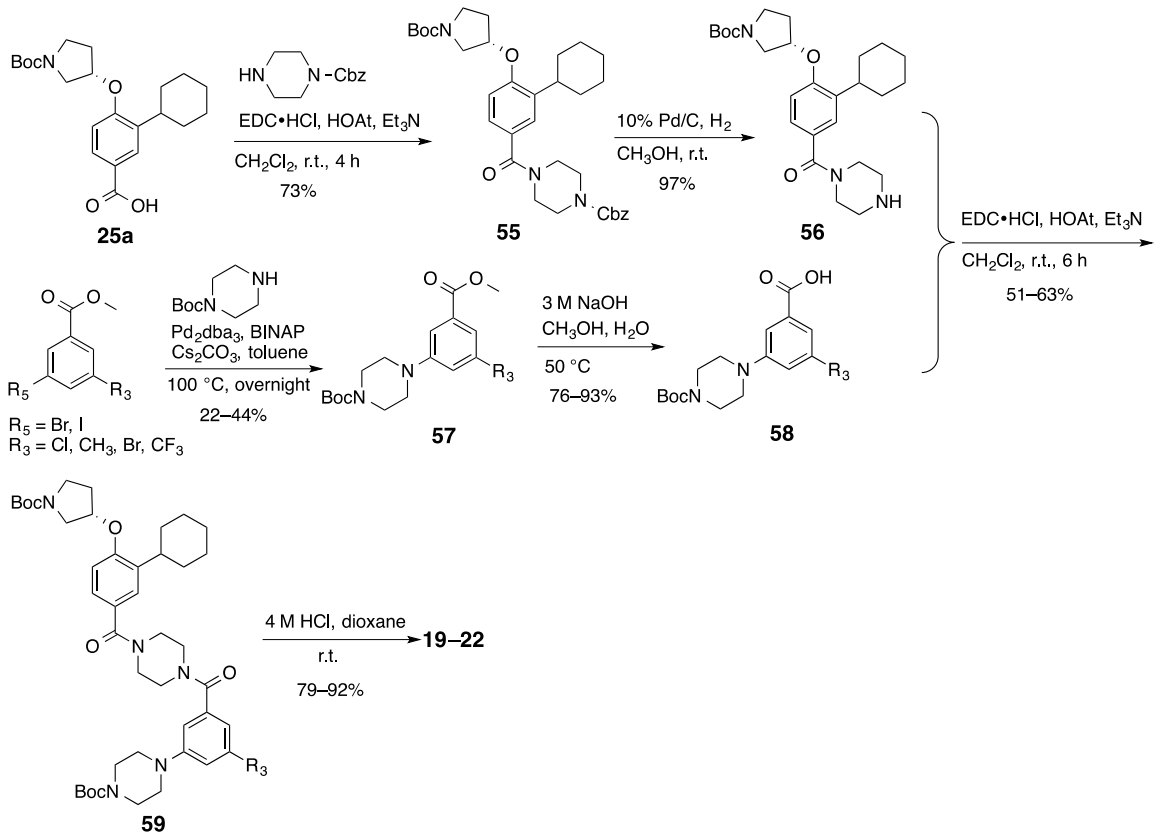
(*S*)-(4-(3-(4-Ethylcyclohexyl)-4-(pyrrolidin-3-yloxy) benzoyl) piperazin-1-yl) (3-fluoro-5-(piperazin-1-yl) phenyl) methanone hydrochloride (15). The synthesis of compound **15** followed the same procedure as for compound **3** to afford white solid (0.0836 g, 84% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.22 (brs, 2H), 8.89 (brs, 2H), 7.28 (s, 1H), 7.24 (d, 1H, *J* = 8.5 Hz), 7.00 (d, 1H, *J* = 8.5 Hz), 6.91 (d, 1H, *J* = 12.5 Hz), 6.80 (s, 1H), 6.65 (d, 1H, *J* = 8.5 Hz), 5.18 – 5.14 (m, 1H), 3.65 – 3.18 (m, 20H), 2.81 – 2.75 (m, 1H), 2.22 – 2.09 (m, 2H), 1.57 – 1.30 (m, 8H), 0.95 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (125 MHz, D_2O): δ ppm 172.23, 170.72

163.25, 155.33, 152.19, 152.06, 136.88, 136.76,136.54, 127.06, 126.89, 126.79, 112.78, 110.63, 105.03, 75.72, 50.55, 45.59, 44.41, 42.99, 36.37, 36.77, 32.93, 30.79, 30.40, 30.13, 29.88, 29.88, 29.54, 28.56, 24.24. HRMS (ESI) m/z calculated for $C_{33}H_{46}FN_5O_3$ $(M+H)^+$ = 592.3663, found 592.3667.

(*S*)-(4-(3-(4,4-Dimethylcyclohexyl)-4-(pyrrolidin-3-yloxy) benzoyl) piperazin-1-yl) (3-fluoro-5-(piperazin-1-yl) phenyl) methanone hydrochloride (16). The synthesis of compound **16** followed the same procedure as for compound **3** to afford white solid (0.0720 g, 97% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.72 (brs, 1H), 9.46 (brs, 1H), 9.18 (brs, 2H), 7.27 (d, 1H, *J* = 8.5 Hz), 7.23 (s, 1H), 7.04 (d, 1H, *J* = 8.5 Hz), 6.90 (d, 1H, *J* = 12.5 Hz), 6.80 (s, 1H), 6.64 (d, 1H, *J* = 8.0 Hz), 5.23 – 5.19 (m, 1H), 3,72 – 3.08 (m, 21 H), 2.49 – 1.54 (m, 10H). ^{13}C NMR (125 MHz, D_2O): δ ppm 172.58, 171.19, 163.30 (d, *J* = 243.9 Hz), 155.17, 151.81 (d, *J* = 10.5 Hz), 136.71 (d, *J* = 9.5 Hz), 134.92, 127.01, 126.64, 126.19, 112.48, 110.50, 105.93 (d, J = 21.9 Hz), 105.49 (d, *J* = 25.6 Hz), 75.79, 50.66, 45.74, 44.37, 42.87, 34.56, 33.50, 33.31 (t, *J* = 24.8 Hz), 33.12, 30.51, 28.35 (t, *J* = 10.4 Hz). HRMS (ESI) m/z calculated for $C_{34}H_{47}FN_5O_3$ $(M+H)^+$ = 592.3657, found 592.3674.

(*S*)-(4-(3-(4,4-Difluorocyclohexyl)-4-(pyrrolidin-3-yloxy) benzoyl) piperazin-1-yl) (3-fluoro-5-(piperazin-1-yl) phenyl) methanone hydrochloride (17). The synthesis of compound **17** followed the same procedure as for compound **3** to afford white solid (0.0512 g, 84% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.30 (brs, 2H), 9.02 (brs, 2H), 7.25 (s, 1H), 7.24 (d, 1H, *J* = 8.5 Hz), 7.00 (d, 1H, *J* = 8.5 Hz), 6.91 (d, 1H, *J* = 12.5 Hz), 6.80 (s, 1H), 6.65 (d, 1H, *J* = 8.5 Hz), 5.20 – 5.16 (m, 1H), 3.63 – 3.17 (m, 21H), 2.20 – 1.46 (m, 10H). ^{13}C NMR (125 MHz, D_2O): δ ppm 172.64, 171.16, 163.01 (d, J = 243.6 Hz), 155.74, 152.01, 151.87, 136.84, 136.29, 126.89, 126.42, 112.51, 110.63, 75.83, 50.75, 47.77, 47.19, 46.93, 45.78, 44.43, 42.99, 42.62, 42.08, 38.49, 32.77, 32.66, 30.59, 30.36, 25.15. HRMS (ESI) m/z calculated for $C_{32}H_{40}F_3N_5O_3$ $(M+H)^+$ = 600.3162, found 600.3168.

(*S*)-(4-(3-Fluoro-5-(piperazin-1-yl) benzoyl) piperazin-1-yl) (3-methyl-4-(pyrrolidin-3-yloxy) phenyl) methanone hydrochloride (18). The synthesis of compound **18** followed the same procedure as for compound **3** to afford white solid (0.189 g, 92% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.47 (brs, 2H), 9.23 (brs, 2H), 7.24 – 7.22 (m, 2H), 7.00 (d, 1H, *J* = 8.5 Hz), 6.90 (d, 1H, *J* = 8.5 Hz), 6.80 (s, 1H), 6.64 (d, 1H, *J* = 7.5 Hz), 5.20 – 5.17 (m, 1H), 3.61 – 3.16 (m, 20H), 2.19 – 2.09 (m, 5H). ^{13}C NMR (125 MHz, D_2O): δ ppm 172.29, 170.83, 163.15 (d, *J* = 242.9 Hz), 155.90, 155.54, 136.67, 129.84, 128.23, 126.60, 126.36, 112.26, 110.42, 105.77 (d, *J* = 20.7 Hz), 105.29 (d, *J* = 24.8 Hz), 75.62, 50.64, 47.56, 46.94, 45.62, 44.09, 42.80, 42.48, 41.85, 30.23, 15.39. HRMS (ESI) m/z calculated for $C_{27}H_{34}FN_5O_3$ $(M+H)^+$ = 496.2724, found 496.2731.



Benzyl (*S*)-4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-cyclohexylbenzoyl) piperazine-1-carboxylate (55). The synthesis of compound **55** followed the same procedure as for compound **34**. Column chromatography (silica gel, hexanes:EtOAc = 3:1) afforded white solid (0.800 g, 73% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.34–7.28 (m, 5H), 7.23–7.18 (m, 2H), 6.77 (d, 1H, J = 8.3 Hz), 5.13 (s, 2H), 4.93–4.91 (m, 1H), 3.66–3.48 (m, 12H), 2.83 (t, 1H, J = 9.4 Hz), 2.22–2.16 (m, 1H), 2.12–2.08 (m, 1H), 1.80–1.71 (m, 6H), 1.44 (s, 4.5H), 1.44 (s, 4.5H), 1.38–1.19 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.79, 155.43, 155.02, 154.46, 154.31, 137.22, 137.12, 136.23, 128.40, 128.04, 127.86, 127.44, 126.39, 125.97, 125.91, 111.80, 111.72, 79.40, 79.33, 76.37, 75.27, 67.30, 51.38, 50.94, 44.12, 43.77, 37.24, 37.14, 34.51, 32.96, 32.71, 32.53, 31.54, 31.43, 30.85, 28.34, 26.82, 26.15, 25.13, 22.50.

***tert*-Butyl (*S*)-3-(2-cyclohexyl-4-(piperazine-1-carbonyl) phenoxy) pyrrolidine-1-carboxylate (56).** The synthesis of compound **56** followed the same procedure as for compound **35** to afford off-white solid (0.58 g, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.23–7.21 (m, 2H), 6.79 (d, 1H, J = 8.4 Hz), 4.95–4.93 (m, 1H), 4.00–3.96 (m, 4H), 3.66–3.47 (m, 4H), 3.25–3.20 (m, 4H), 2.84 (t, 1H, J = 10.0 Hz), 2.23–2.18 (m, 1H), 2.15–2.11 (m, 1H), 1.81–1.72 (m, 6H), 1.45 (s, 9H), 1.39–1.21 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.90, 155.96, 154.60, 154.41, 137.66, 137.59, 126.57, 126.28, 126.21, 126.02, 125.97, 111.91, 79.61, 79.54, 76.53, 75.40, 51.51, 50.99, 44.21, 43.83, 43.51, 37.34, 37.27, 33.10, 33.02, 32.81, 32.56, 31.65, 30.94, 28.44, 26.94, 26.87, 26.19.

***tert*-Butyl 4-(3-chloro-5-(methoxycarbonyl) phenyl) piperazine-1-carboxylate (57a).** The synthesis of compound **57a** followed the same procedure as for compound **27** except using methyl 3-bromo-5-chlorobenzoate. Column chromatography (silica gel, hexanes:EtOAc = 9:1) afforded white solid (0.951 g, 41% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.46–7.45 (m,

1H), 7.44–7.43 (m, 1H), 7.02–7.00 (m, 1H), 3.89 (s, 3H), 3.57–3.54 (m, 4H), 3.19–3.17 (m, 4H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 166.12, 154.55, 151.93, 135.11, 132.14, 120.43, 120.37, 119.93, 115.24, 115.18, 80.06, 52.38, 52.30, 48.53, 28.36.

***tert*-Butyl 4-(3-(methoxycarbonyl)-5-methylphenyl) piperazine-1-carboxylate (57b).** The synthesis of compound **57b** followed the same procedure as for compound **27** using methyl 3-bromo-5-methylbenzoate. Column chromatography (silica gel, hexanes:EtOAc = 9:1) afforded white solid (0.246 g, 40% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.39–7.38 (m, 1H), 7.37–7.36 (m, 1H), 6.92–6.91 (m, 1H), 3.87 (s, 3H), 3.57 (t, 4H, J = 5.1 Hz), 3.15 (t, 4H, J = 5.0 Hz), 2.34 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 167.32, 154.60, 151.19, 138.95, 130.76, 121.98, 121.72, 114.49, 79.86, 51.99, 49.18, 28.33, 21.53.

***tert*-Butyl 4-(3-(methoxycarbonyl)-5-(trifluoromethyl) phenyl) piperazine-1-carboxylate (57c).** The synthesis of compound **57c** followed the same procedure as for compound **27** using methyl 3-bromo-5-trifluoromethylbenzoate. Column chromatography (silica gel, hexanes:EtOAc = 9:1) afforded white solid (0.680 g, 44% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.70–7.68 (m, 2H), 7.23–7.22 (m, 1H), 3.89 (s, 3H), 3.57 (t, 4H, J = 5.2 Hz), 3.21 (t, 4H, J = 5.1 Hz), 1.45 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 165.94, 154.46, 151.32, 131.72, 131.71 (q, J = 32.4 Hz), 123.67 (q, J = 272.8 Hz), 119.74, 119.68, 119.53, 116.95, 116.16, 80.01, 52.50, 52.38, 52.27, 52.16, 48.42, 28.28.

***tert*-Butyl 4-(3-bromo-5-(methoxycarbonyl) phenyl) piperazine-1-carboxylate (57d).** The synthesis of compound **57d** followed the same procedure as for compound **27** using methyl 3-bromo-5-iodobenzoate. Column chromatography (silica gel, hexanes:EtOAc = 9:1) afforded white solid (0.103 g, 22% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.63–7.62 (m, 1H), 7.49–7.48 (m, 1H), 7.18–7.17 (m, 1H), 3.90 (s, 3H), 3.57 (t, 4H, J = 5.0 Hz), 3.18 (m, 4H), 1.48 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 166.00, 154.57, 152.07, 132.35, 123.37, 123.11, 122.89, 115.72, 80.09, 52.37, 48.57, 28.38.

3-(4-(*tert*-Butoxycarbonyl) piperazin-1-yl)-5-chlorobenzoic acid (58a). The synthesis of compound **58a** followed the same procedure as for compound **33** to afford white solid (0.197 g, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 7.54–7.53 (m, 1H), 7.50–7.49 (m, 1H), 7.07–7.05 (m, 1H), 3.59 (t, 4H, J = 5.0 Hz), 3.21 (t, 4H, J = 4.9 Hz), 1.48 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.50, 154.71, 151.96, 135.27, 131.50, 120.99, 120.91, 120.66, 115.69, 115.61, 80.35, 48.50, 28.37.

3-(4-(*tert*-Butoxycarbonyl) piperazin-1-yl)-5-methylbenzoic acid (58b). The synthesis of compound **58b** followed the same procedure as for compound **33** to afford white solid (0.179 g, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.47–7.46 (m, 1H), 7.45–7.44 (m, 1H), 6.98–6.97 (m, 1H), 3.60–3.58 (m, 4H), 3.18–3.16 (m, 4H), 2.36 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 171.81, 154.73, 151.21, 139.11, 130.18, 122.65, 122.51, 115.02, 80.07, 49.21, 28.36, 21.53.

3-(4-(*tert*-Butoxycarbonyl) piperazin-1-yl)-5-(trifluoromethyl) benzoic acid (58c). The synthesis of compound **58c** followed the same procedure as for compound **33** to afford white solid (0.609 g, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.82–7.81 (m, 1H), 7.78–7.77 (m, 1H), 7.31–7.30 (m, 1H), 3.63 (t, 4H, J = 4.8 Hz), 3.28–3.26 (m, 4H), 1.49 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.16, 154.74, 151.42, 131.99 (q, J = 32.5 Hz), 131.20, 123.67 (q, J = 272.8 Hz), 120.11, 117.61, 116.91, 80.47, 48.45, 28.36.

3-Bromo-5-(4-(*tert*-butoxycarbonyl) piperazin-1-yl) benzoic acid (58d). The synthesis of compound **58d** followed the same procedure as for compound **33** to afford white solid (0.0816 g, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.70–7.69 (m, 1H), 7.55 (dd, 1H, J = 1.3, 2.3

Hz), 7.24–7.23 (m, 1H), 3.60 (t, 4H, J = 4.9 Hz), 3.22–3.20 (m, 4H), 1.49 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.41, 154.68, 152.12, 131.57, 123.90, 123.64, 123.23, 116.14, 80.31, 48.53, 28.40.

***tert*-Butyl (*S*)-4-(3-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-cyclohexylbenzoyl) piperazine-1-carbonyl)-5-chlorophenyl) piperazine-1-carboxylate (59a).** The synthesis of compound **59a** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.0998 g, 58% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.23–7.19 (m, 2H), 6.89–6.88 (m, 1H), 6.79–6.76 (m, 3H), 4.93–4.91 (m, 1H), 3.74–3.46 (m, 16H), 3.16–3.14 (m, 4H), 2.84–2.81 (m, 1H), 2.21–2.17 (m, 1H), 2.13–2.09 (m, 1H), 1.79–1.71 (m, 6H), 1.45 (s, 9H), 1.43 (s, 9H), 1.38–1.30 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.88, 169.33, 155.60, 155.48, 154.47, 154.32, 152.17, 137.37, 137.26, 135.27, 127.18, 127.14, 126.48, 126.04, 125.98, 117.33, 116.98, 112.45, 111.81, 80.07, 79.46, 79.38, 76.44, 75.34, 51.43, 50.95, 48.29, 44.17, 43.80, 37.29, 37.21, 34.56, 33.06, 32.78, 32.57, 31.61, 31.48, 30.90, 29.59, 28.39, 28.31, 26.86, 26.20, 25.18, 22.55, 20.61, 14.03.

***tert*-Butyl (*S*)-4-(3-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-cyclohexylbenzoyl) piperazine-1-carbonyl)-5-methylphenyl) piperazine-1-carboxylate (59b).** The synthesis of compound **59b** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.0880 g, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.25–7.19 (m, 2H), 6.79–6.76 (m, 2H), 6.73–6.72 (m, 1H), 6.68–6.67 (m, 1H), 4.94–4.92 (m, 1H), 3.76–3.46 (m, 16H), 3.14–3.11 (m, 4H), 2.86–2.81 (m, 1H), 2.31 (s, 3H), 2.22–2.18 (m, 1H), 2.13–2.09 (m, 1H), 1.86–1.72 (m, 6H), 1.46 (s, 9H), 1.44 (s, 9H), 1.38–1.28 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.90, 155.59, 155.47, 154.58, 154.53, 154.37, 151.29, 139.36, 137.35, 137.24, 136.11, 127.34, 126.50, 126.03, 118.97, 118.51, 111.92, 111.83, 79.93, 79.48, 79.41, 76.46, 75.37, 51.45, 50.99, 49.05, 44.18, 43.82, 37.31, 37.22, 34.58, 33.06, 32.80, 32.60, 31.63, 31.50, 30.93, 28.41, 28.34, 26.88, 26.22, 21.65.

***tert*-Butyl (*S*)-4-(3-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-cyclohexylbenzoyl) piperazine-1-carbonyl)-5-(trifluoromethyl) phenyl) piperazine-1-carboxylate (59c).** The synthesis of compound **59c** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.144 g, 65% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.23–7.17 (m, 2H), 7.11–7.10 (m, 1H), 7.05–7.03 (m, 2H), 6.77–6.74 (m, 2H), 4.92–4.90 (m, 1H), 3.74–3.42 (m, 16H), 3.20–3.18 (m, 4H), 2.84–2.79 (m, 1H), 2.20–2.15 (m, 1H), 2.12–2.07 (m, 1H), 1.77–1.69 (m, 6H), 1.44 (s, 9H), 1.42 (s, 9H), 1.37–1.31 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.84, 169.28, 155.59, 155.45, 154.45, 154.39, 154.28, 151.44, 137.30, 137.22, 136.94, 131.82, (q, J = 32.3 Hz), 127.09, 126.42, 126.00, 125.94, 123.55 (q, J = 272.8 Hz), 117.04, 113.87, 113.42, 111.76, 80.04, 79.38, 79.32, 76.39, 75.29, 51.38, 50.87, 48.17, 44.11, 43.73, 37.24, 37.17, 34.50, 34.35, 33.00, 32.96, 32.71, 32.48, 31.56, 31.41, 30.83, 29.13, 28.32, 28.23, 26.86, 26.80, 26.74, 26.14, 25.11.

***tert*-Butyl (*S*)-4-(3-bromo-5-(4-(4-((1-(*tert*-butoxycarbonyl) pyrrolidin-3-yl) oxy)-3-cyclohexylbenzoyl) piperazine-1-carbonyl) phenyl) piperazine-1-carboxylate (59d).** The synthesis of compound **59d** followed the same procedure as for compound **36**. Column chromatography (silica gel, hexanes:acetone = 70:30) afforded white solid (0.0845 g, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 7.19–7.14 (m, 2H), 7.00–6.98 (m, 1H), 6.89–6.87 (m, 1H), 6.77–6.76 (m, 1H), 6.73–6.71 (m, 1H), 4.88–4.86 (m, 1H), 3.68–3.43 (m, 16H), 3.11–3.08 (m, 4H), 2.79–2.75 (m, 1H), 2.16–2.11 (m, 1H), 2.09–2.04 (m, 1H), 1.75–1.66 (m, 6H), 1.40 (s, 9H),

1.38 (s, 9H), 1.33–1.21 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 170.92, 169.19, 155.63, 154.49, 152.26, 137.62, 137.35, 127.18, 126.51, 126.04, 123.33, 120.23, 119.96, 112.96, 111.84, 80.10, 79.45, 76.45, 75.36, 53.77, 51.44, 50.97, 48.31, 44.18, 43.80, 37.29, 37.24, 33.03, 32.77, 32.59, 31.65, 30.90, 29.19, 28.39, 28.30, 26.88, 26.19.

(*S*)-(4-(3-Chloro-5-(piperazin-1-yl) benzoyl) piperazin-1-yl) (3-cyclohexyl-4-(pyrrolidin-3-yloxy) phenyl) methanone hydrochloride (19). The synthesis of compound **19** followed the same procedure as for compound **3** to afford white solid (0.0752 g, 92% yield). ^{1}H NMR (300 MHz, d^6-DMSO): δ ppm 9.49 (brs, 2H), 9.23 (brs, 2H), 7.24 – 7.22 (m, 2H), 7.10 (s, 1H), 7.00 (d, 1H, J = 9.0 HZ), 6.92 (s, 1H), 6.85 (s, 1H), 5.19 – 5.15 (m, 1H), 3.68 – 3.16 (m, 20 H), 2.90 – 2.86 (m, 1H), 2.20 – 2.06 (m, 2H), 1.76 – 1.18 (m, 10H). ^{13}C NMR (125 MHz, D_2O): δ ppm 172.15, 170.37, 154.89, 151.11, 136.52, 134.80, 126.65, 126.34, 125.80, 117.83, 113.06, 112.41, 75.51, 50.36, 47.46, 47.05, 45.34, 44.09, 42.73, 42.28, 41.84, 36.21, 32.75, 32.69, 30.41, 26.32, 25.80. HRMS (ESI) m/z calculated for $C_{32}H_{42}ClN_5O_3$ $(M+H)^+$ = 580.3054, found 580.3060.

(*S*)-(4-(3-Cyclohexyl-4-(pyrrolidin-3-yloxy) benzoyl) piperazin-1-yl) (3-methyl-5-(piperazin-1-yl) phenyl) methanone hydrochloride (20). The synthesis of compound **20** followed the same procedure as for compound **3** to afford peach solid (0.0648 g, 90% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.44 (brs, 2H), 9.12 (brs, 2H), 7.24 – 7.22 (m, 2H), 7.00 (d, 1H, J = 9.0 Hz), 6.88 (s, 1H), 6.76 (s, 1H), 6.67 (s, 1H), 5.19 – 5.15 (m, 1H), 3.69 – 3.17 (m, 20H), 2.90 – 2.85 (m, 1H), 2.27 (s, 3H), 2.21 – 2.10 (m, 2H), 1.77 – 1.20 (m, 10H). ^{13}C NMR (125 MHz, D_2O): δ ppm 172.29, 172.09, 154.98, 149.27, 140.68, 137.28, 135.22, 126.87, 126.32, 126.07, 120.83, 119.95, 112.63, 112.53, 75.67, 50.52, 46.70, 44.28, 42.84, 36.40, 32.82, 32.75, 30.50, 26.42, 26.38, 25.81, 20.64, 13.22. HRMS (ESI) m/z calculated for $C_{32}H_{45}N_5O_3$ $(M+H)^+$ = 560.3601, found 560.3604.

(*S*)-(4-(3-Cyclohexyl-4-(pyrrolidin-3-yloxy) benzoyl) piperazin-1-yl) (3-(piperazin-1-yl)-5-(trifluoromethyl) phenyl) methanone hydrochloride (21). The synthesis of compound **21** followed the same procedure as for compound **3** to afford white solid (0.103 g, 85% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.49 (brs, 2H), 9.26 (brs, 2H), 7.31 (s, 1H), 7.25 – 7.23 (m, 3H), 7.12 (s, 1H), 7.00 (d, 1H, J = 9.0 Hz), 5.18 – 5.15 (m, 1H), 3.69 – 3.18 (m, 20H), 2.90 – 2.86 (m, 1H), 2.19 02.12 (m, 2H), 1.76 – 1.17 (m, 10H). ^{13}C NMR (125 MHz, D_2O): δ ppm 172.13, 170.34, 154.99, 150.67, 136.83, 136.42, 131.22 (d, J = 28.5 Hz), 126.90 (d, J = 8.5 Hz), 126.53, 125.65, 123.68 (d, J = 271.4 Hz), 120.42, 117.89, 114.43, 112.67, 75.61, 50.45, 47.56, 46.99, 45.32, 44.23, 42.88, 42.33, 41.88, 36.28, 32.81, 32.72, 30.51, 26.39, 26.36, 25.84. HRMS (ESI) m/z calculated for $C_{33}H_{42}F_3N_5O_3$ $(M+H)^+$ = 614.3318, found 614.3319.

(*S*)-(4-(3-Bromo-5-(piperazin-1-yl) benzoyl) piperazin-1-yl) (3-cyclohexyl-4-(pyrrolidin-3-yloxy) phenyl) methanone hydrochloride (22). The synthesis of compound **22** followed the same procedure as for compound **3** to afford white solid (0.0546 g, 79% yield). ^{1}H NMR (500 MHz, d^6-DMSO): δ ppm 9.58 (brs, 2H), 9.30 (brs, 2H), 7.24 – 7.22 (m, 3H), 7.00 (d, 1H, J = 9.0 Hz), 6.97 – 6.96 (m, 2H), 5.15 – 5.19 (m, 1H), 3.69 – 3.15 (m, 20H), 2.90 – 2.86 (m, 1H), 2.19 – 2.12 (m, 2H), 1.76 – 1.17 (m, 10H). ^{13}C NMR (125 MHz, D_2O): δ ppm 172.27, 170.32, 154.99, 151.27, 137.14, 136.87, 126.85, 126.42, 126.06, 122.98, 120.87, 113.58, 112.62, 75.69, 71.52, 70.66, 60.24, 50.52, 45.48, 44.28, 43.19, 42.84, 36.36, 32.88, 32.81, 30.52, 26.46, 26.41, 25.89. HRMS (ESI) m/z calculated for $C_{32}H_{42}BrN_5O_3$ $(M+H)^+$ = 624.2549, found 624.2551.

Supplementary References.

1. Sampietro, J.; Dahlberg, C. L.; Cho, U. S.; Hinds, T. R.; Kimelman, D.; Xu, W. Crystal structure of a β-catenin/BCL9/Tcf4 complex. *Mol. Cell* **2006**, *24* (2), 293–300.
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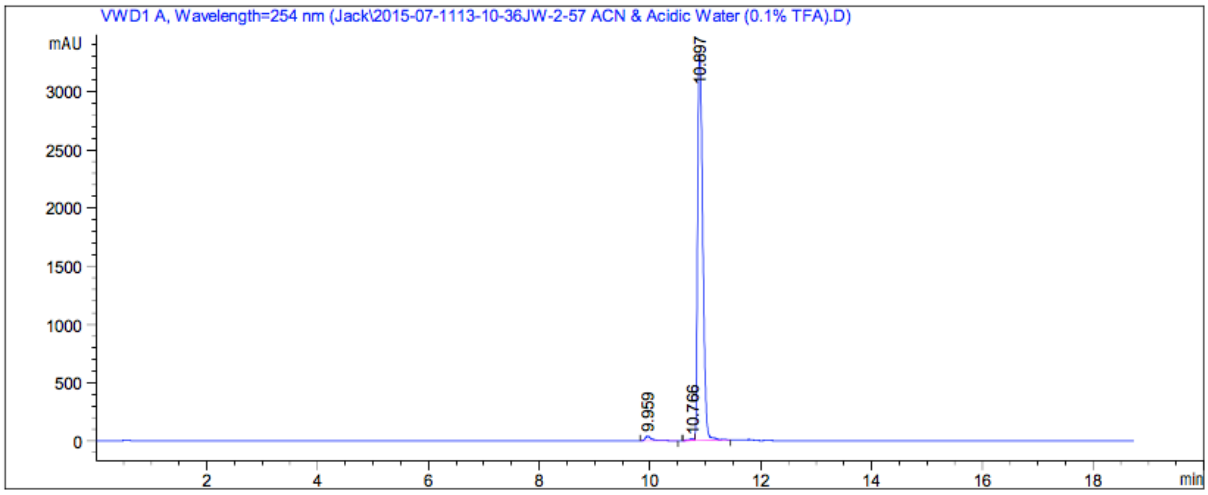
3. Baell, J.; Walters, M. A. Chemistry: Chemical con artists foil drug discovery. *Nature* **2014**, *513*, 481–483.
4. Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing conventional carbon nucleophiles with electrophiles: nickel-catalyzed reductive alkylation of aryl bromides and chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146–6159.
5. Hoggard, L. R.; Zhang, Y.; Zhang, M.; Panic, V.; Wisniewski, J. A.; Ji, H. Rational design of selective small-molecule inhibitors for catenin/B-cell lymphoma 9 protein–protein interactions. *J. Am. Chem. Soc.* **2015**, *137*, 12249–12260.
6. Zhang, M.; Wisniewski, J. A.; Ji, H. AlphaScreen selectivity assay for β-catenin/B-cell lymphoma 9 inhibitors. *Anal. Biochem.* **2015**, *469*, 43–53.

HPLC conditions

The purity of final compounds **2**–**22** was determined by HPLC analysis. The instrument was an Agilent 1260 Infinity Quaternary LC with an Agilent 1260 Infinity ELSD detector. The purity of all tested compounds was ≥ 90%. Some HPLC traces are shown below.

Compound 3, condition A. Elute with 0.1% TFA in water for first 5 minutes, and then change to a 5 minutes' gradient starting with 0.1% TFA in water and ending with 0.1% TFA in water and acetonitrile mixture (water with 0.1% TFA : acetonitrile = 1 : 1), and at last eluent with 0.1% TFA in water and acetonitrile 1 : 1 mixture for 10 minutes.

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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
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   1   9.959 BV R  0.1205  336.61703   40.71381   1.5455
   2  10.766 BV E  0.0987  104.32155   14.71576   0.4790
   3  10.897 VV R  0.1010 2.13390e4  3319.21606  97.9755

Totals :                  2.17799e4  3374.64563
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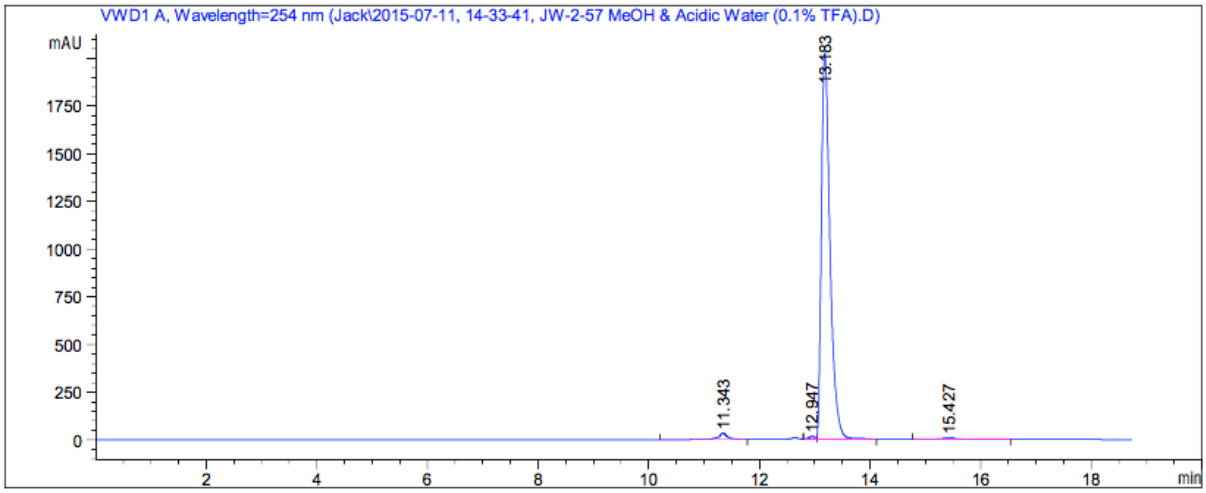
Compound 3, condition B. Elute with 0.1% TFA in water for first 5 minutes, and then change to a 5 minutes' gradient starting with 0.1% TFA in water and ending with 0.1% TFA in water and acetonitrile mixture (water with 0.1% TFA : methanol = 1 : 1), and at last eluent with 0.1% TFA in water and methanol 1 : 1 mixture for 10 minutes.

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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

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   2  12.947 BV E  0.1104   98.32527   13.92175   0.4347
   3  13.183 VV R  0.1643 2.18855e4  2021.41760  96.7519
   4  15.427 VV R  0.2950  200.57608    9.47480   0.8867

Totals :                  2.26202e4  2078.90404
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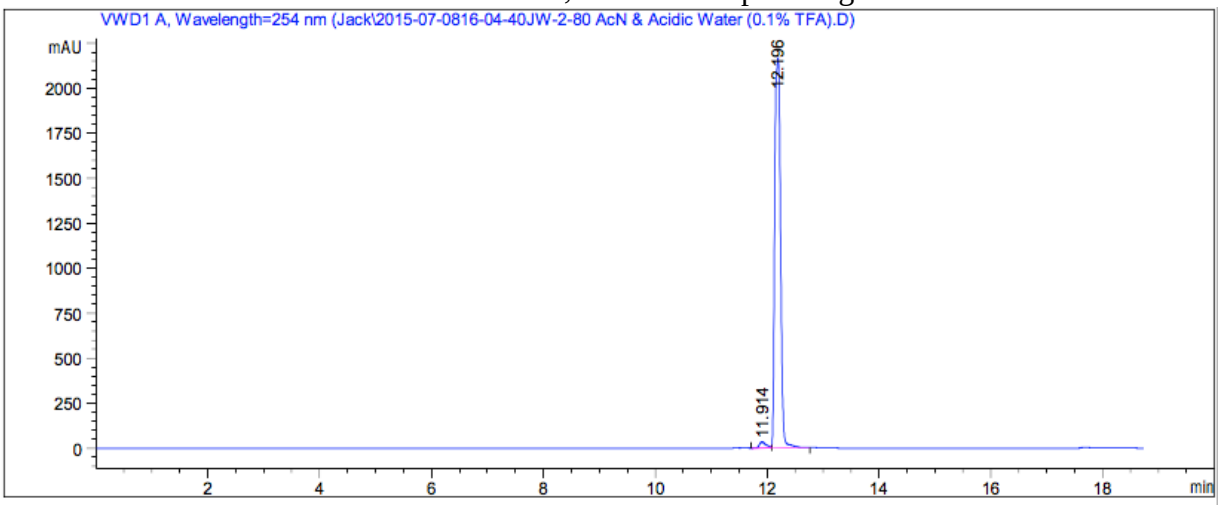
Compound 11, condition A. Elute with 0.1% TFA in water for first 8 minutes, and then change to a 2 minutes' gradient starting with 0.1% TFA in water and ending with 0.1% TFA in water and acetonitrile mixture (water with 0.1% TFA : acetonitrile = 1 : 1), and later eluent with 0.1% TFA in water and acetonitrile 1 : 1 mixture for 5 minutes. Then change mobile phase from the above mixture to 100% acetonitrile in 1 minute, and then keep eluting for 4 minutes.

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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


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Totals :                  1.58085e4  2199.72575
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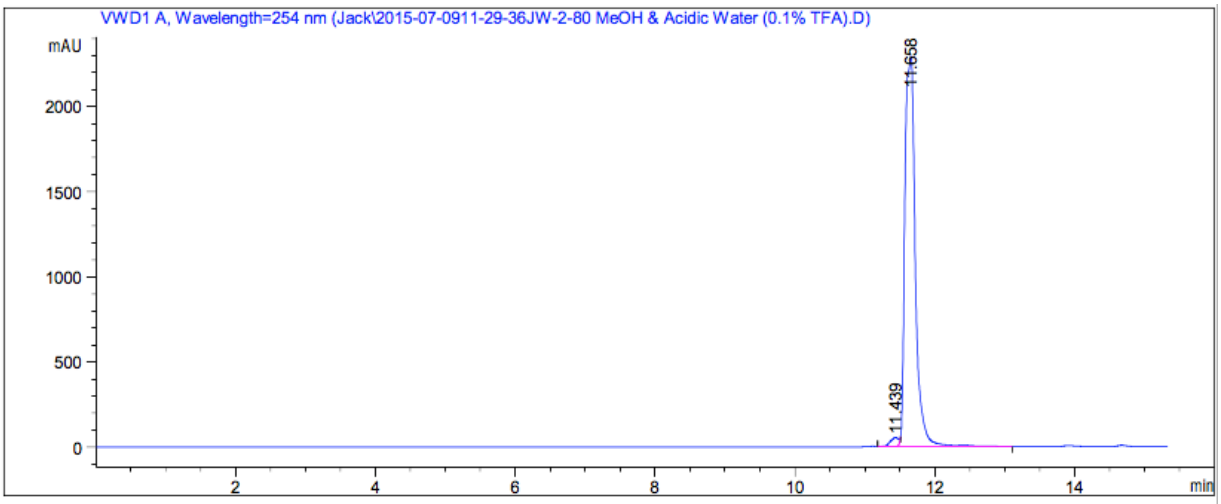
Compound 11, condition B. Elute with 0.1% TFA in water for first 8 minutes, and then change to a 3 minutes' gradient starting with 0.1% TFA in water and ending with 0.1% TFA in water and methanol mixture (water with 0.1% TFA:methanol = 1:1), and later eluent with 0.1% TFA in water and methanol 1 : 1 mixture for 4 minutes. Then change mobile phase from the above mixture to 100% methanol in 1 minute.

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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


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Totals :                  2.42199e4  2344.13500
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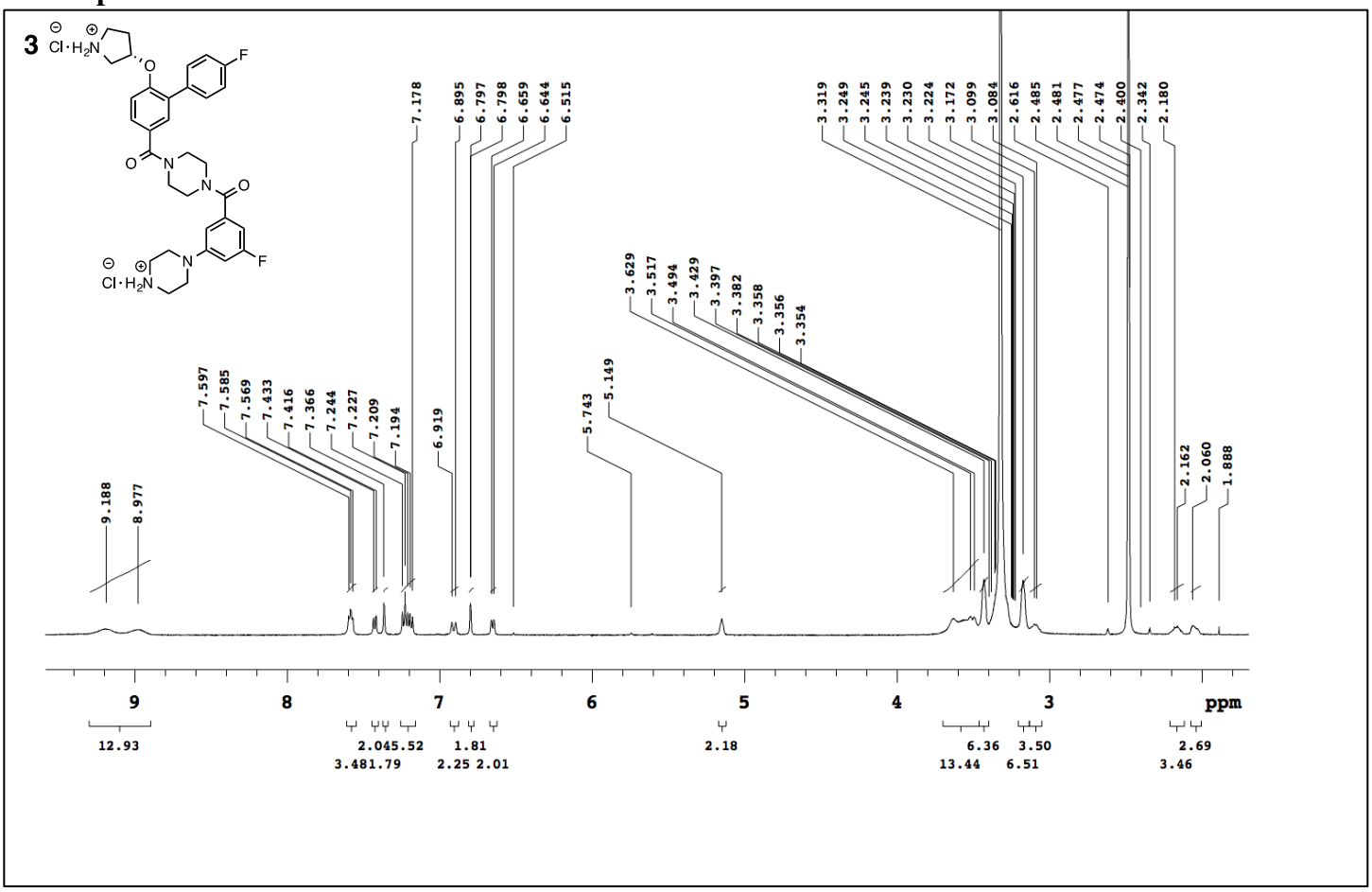
NMR Spectra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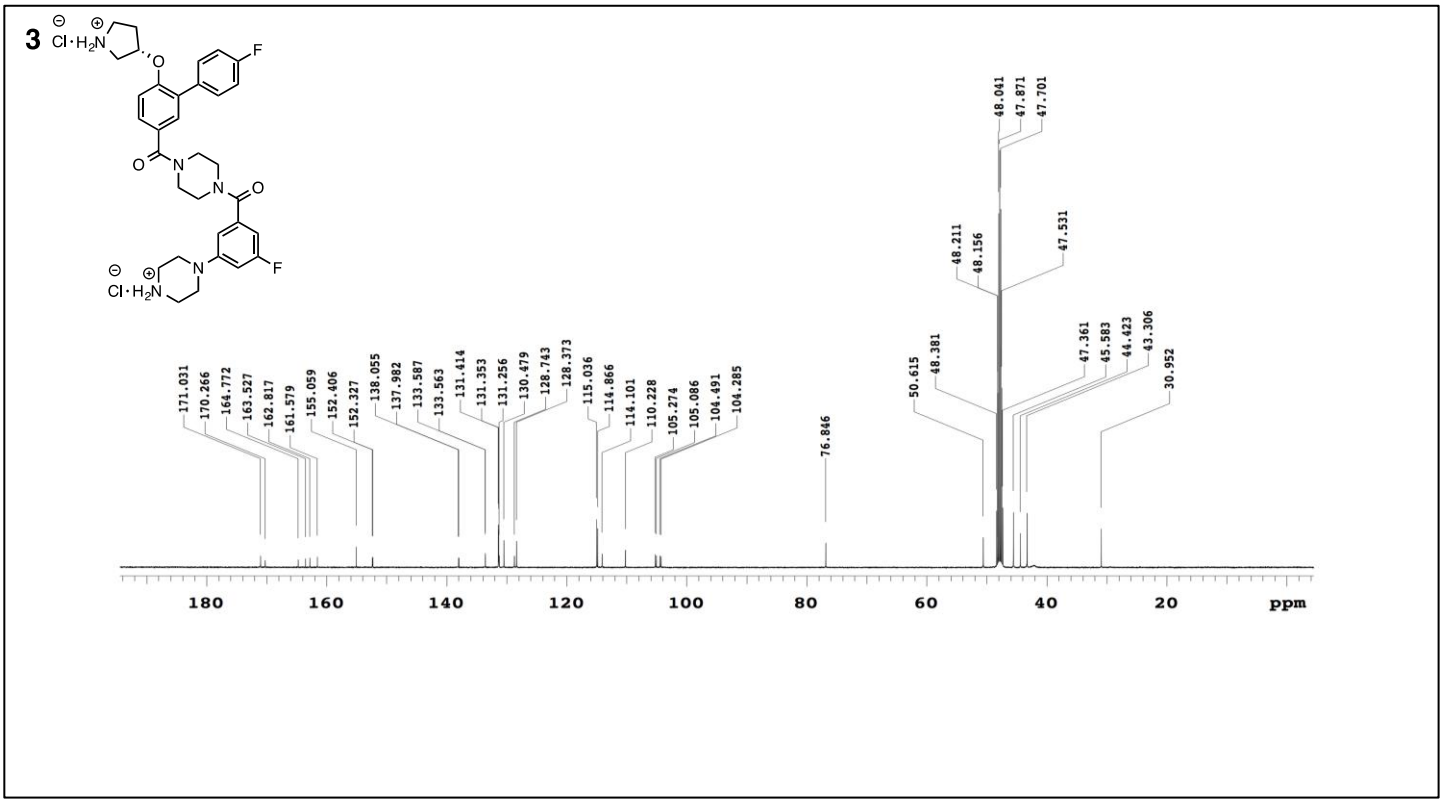
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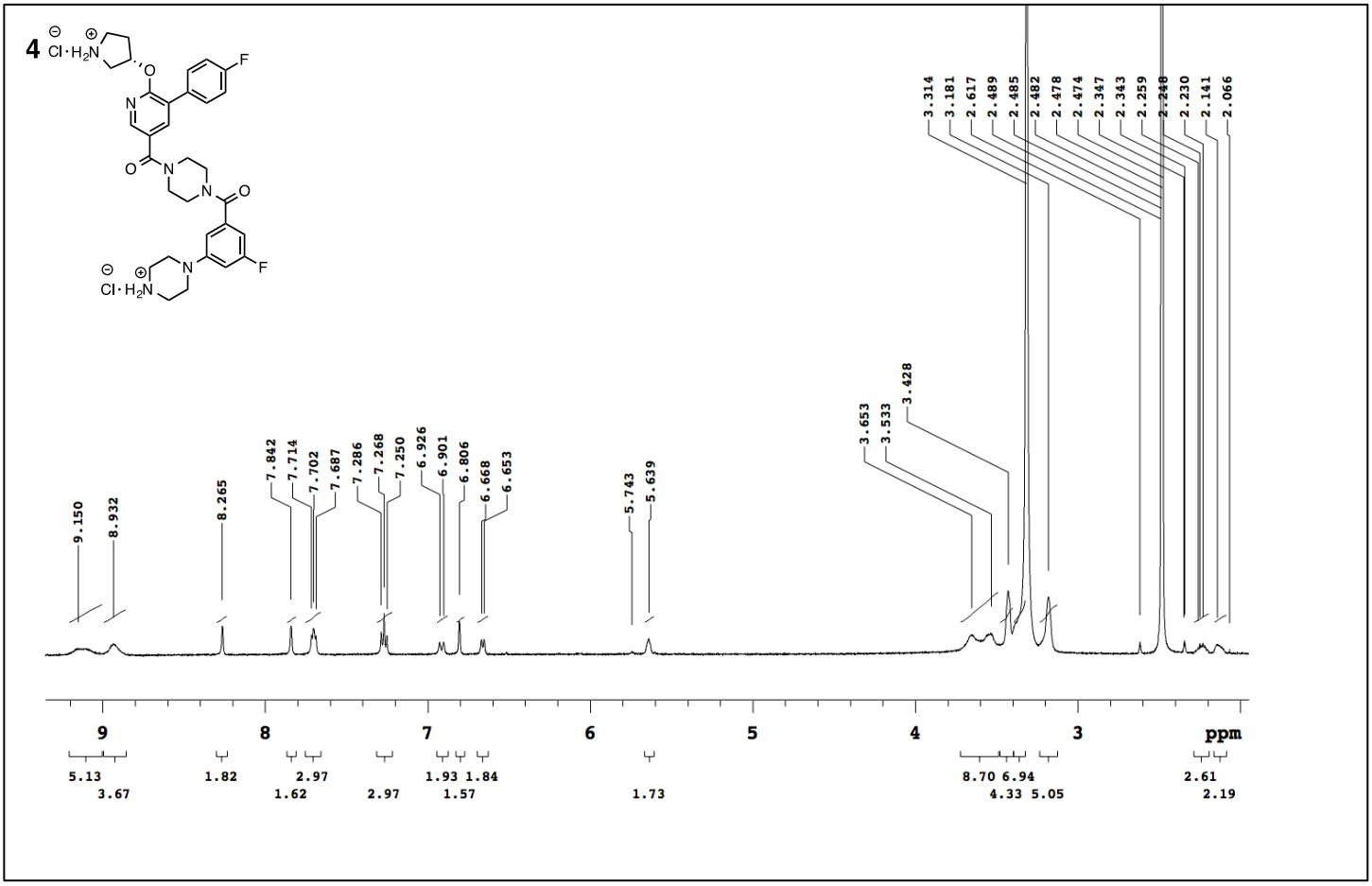
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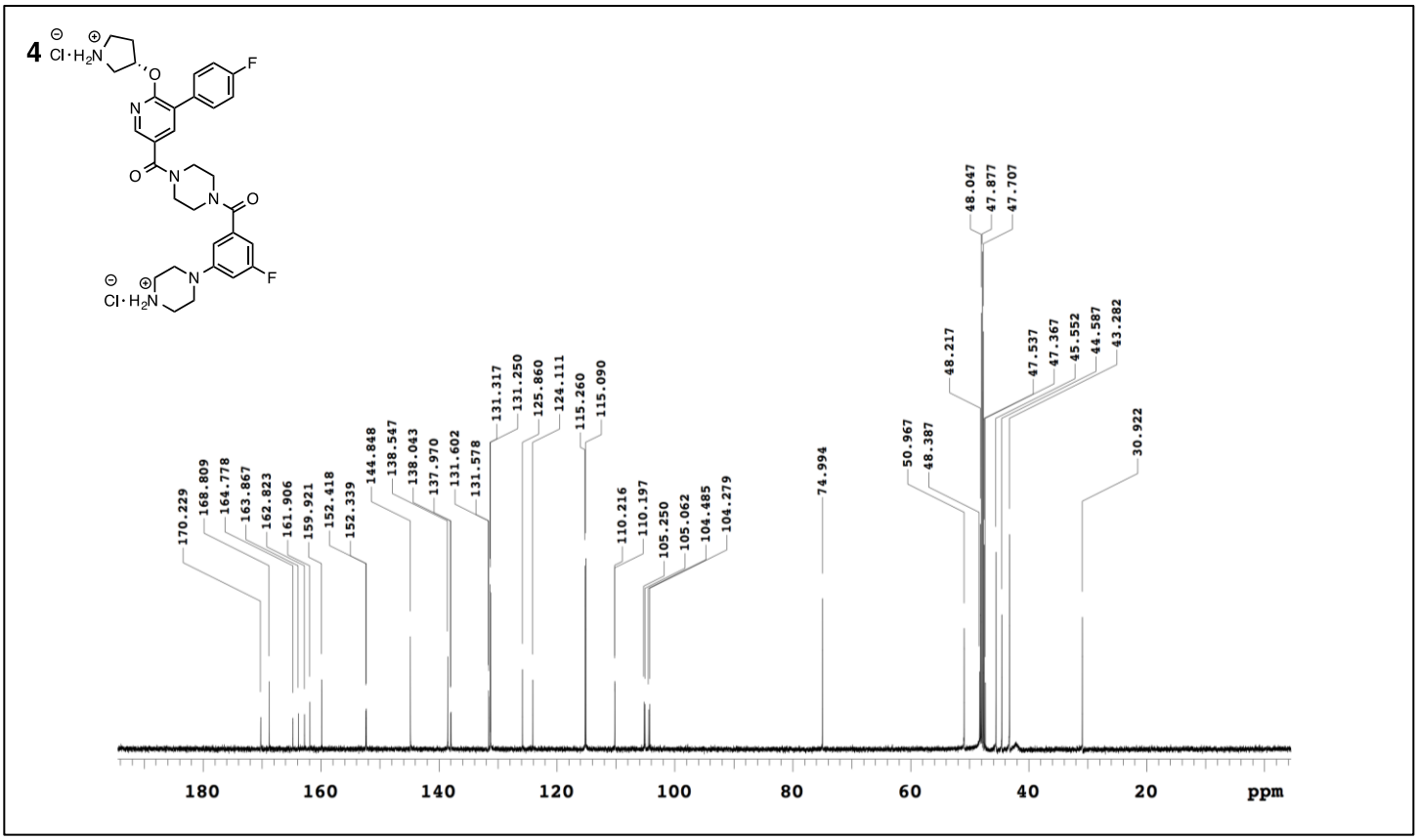
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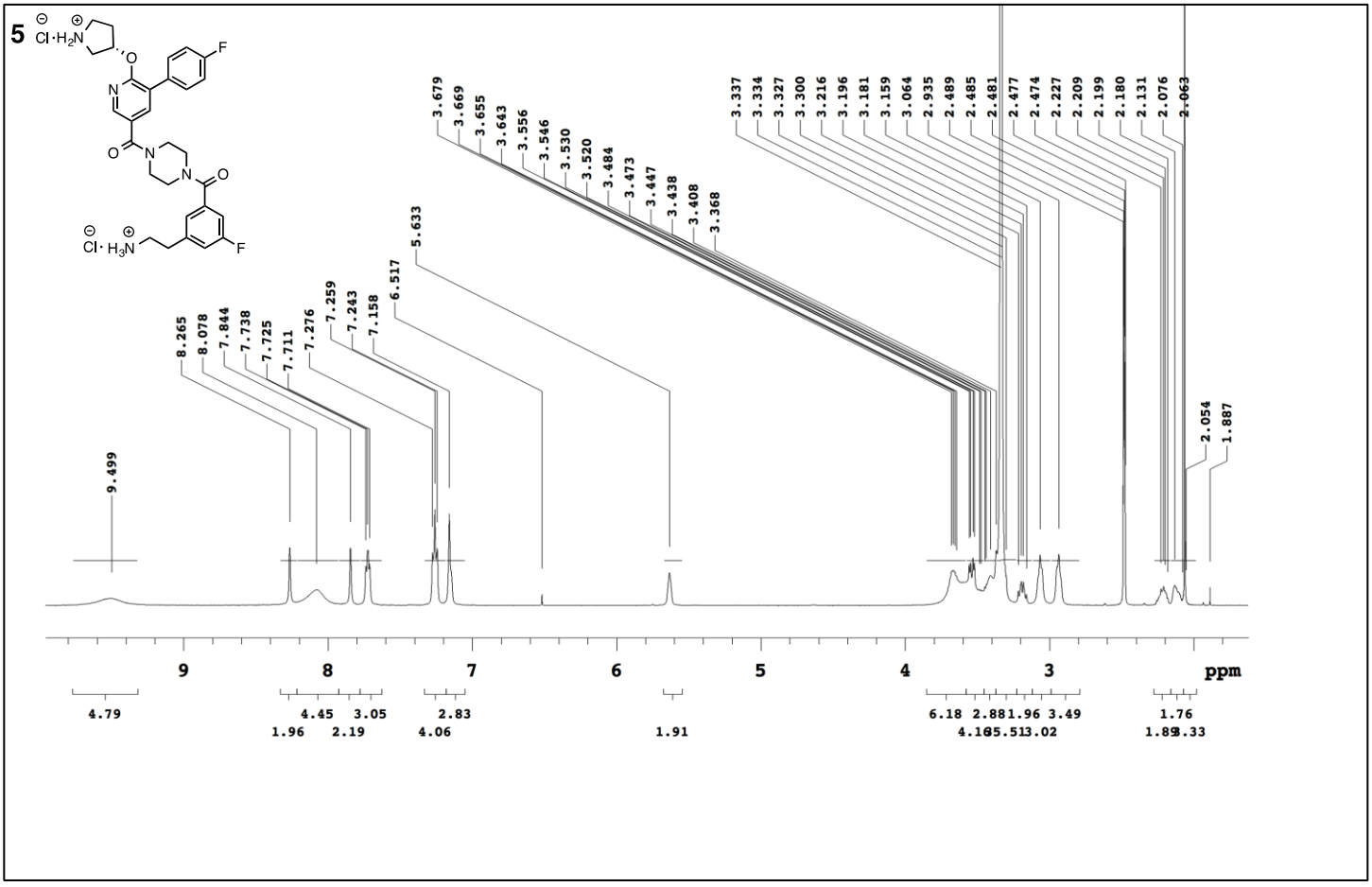
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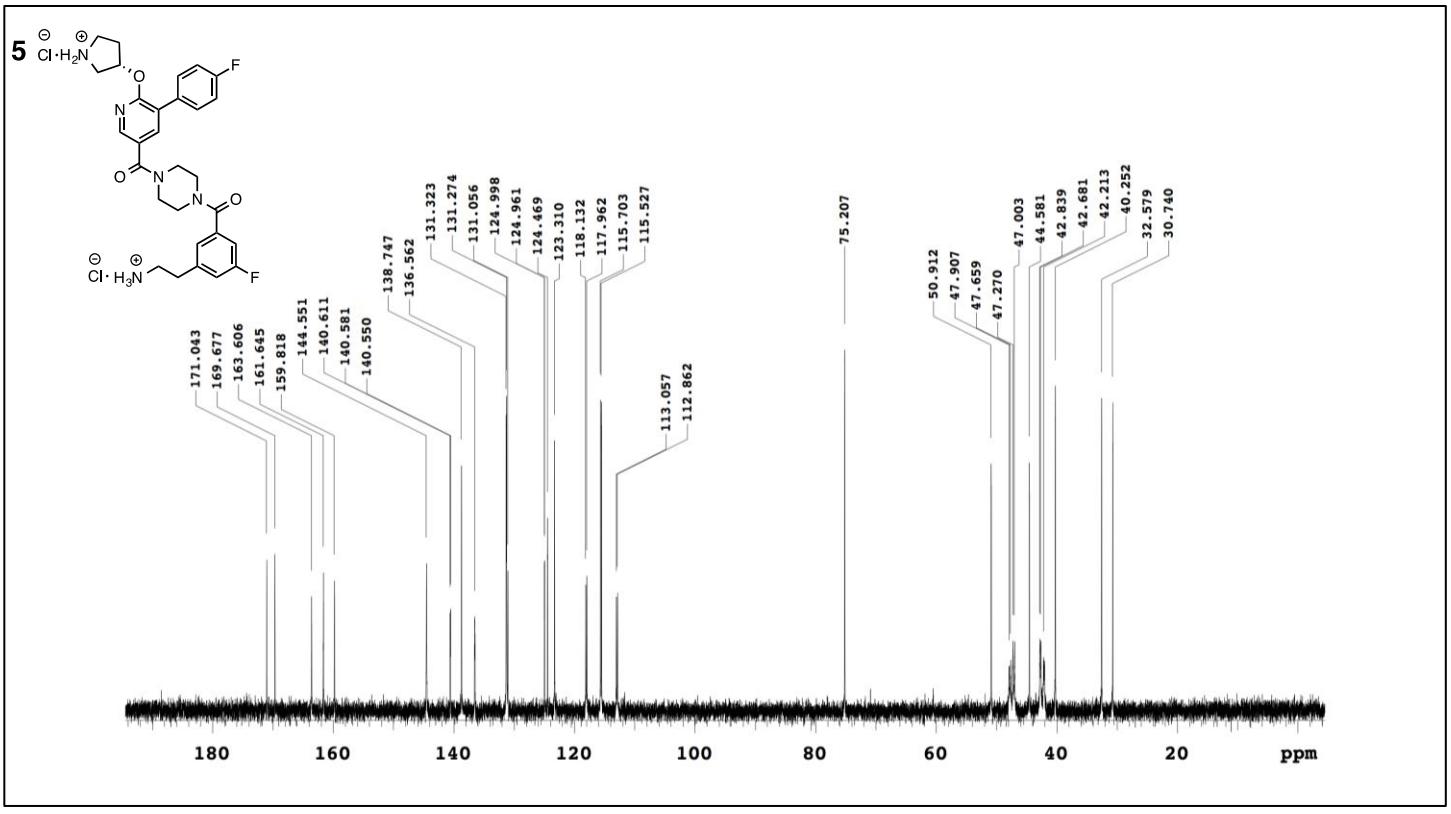
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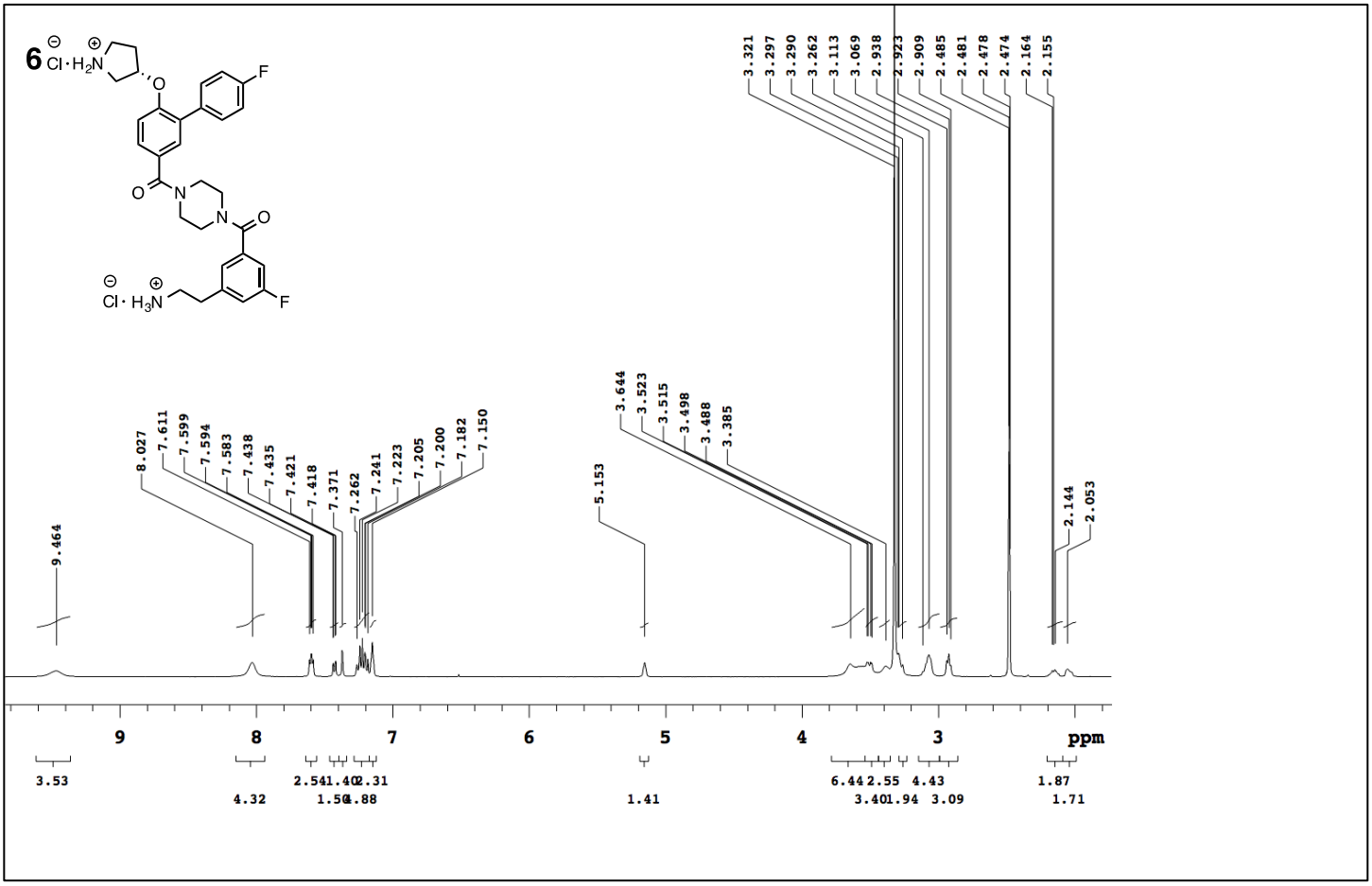
6
Cl·H2N
O
F
O
N
N
O
Cl· H3N
F
3.321
3.297
3.290
3.262
3.113
3.069
2.938
2.923
2.909
2.485
2.481
2.478
2.474
2.164
2.155
3.644
3.523
3.515
3.498
3.488
3.385
8.027
7.611
7.599
7.594
7.583
7.438
7.435
7.421
7.418
7.371
7.262
7.241
7.223
7.205
7.200
7.182
7.150
9.464
5.153
2.144
2.053
9
8
7
6
5
4
3
ppm
3.53
4.32
2.54
1.56
1.40
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2.31
1.41
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2.55
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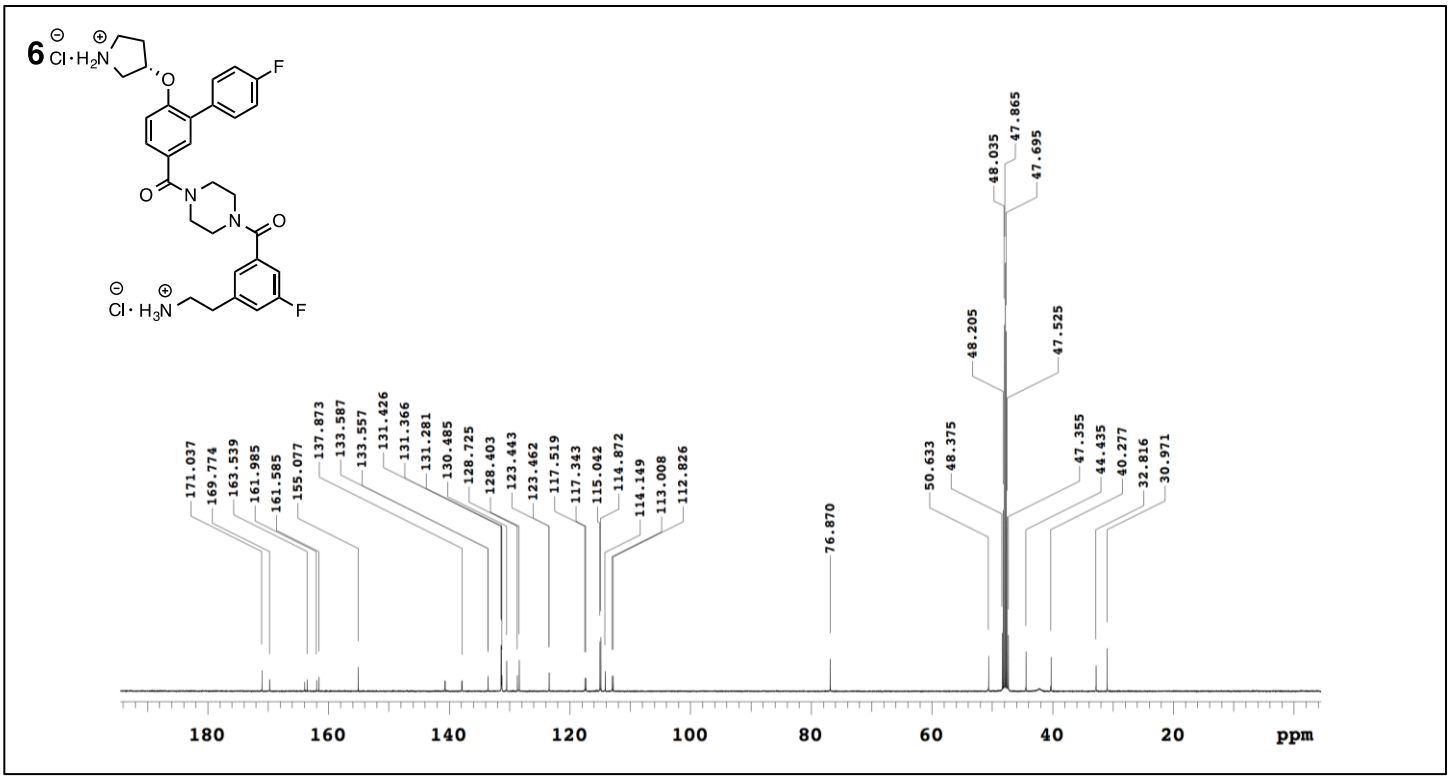
3.09
1.87
1.71


6
Cl·H2N
O
F
O
N
N
O
Cl· H3N
F
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47.695
48.205
47.525
171.037
169.774
163.539
161.985
161.585
155.077
137.873
133.587
133.557
131.426
131.366
131.281
130.485
128.725
128.403
123.443
123.462
117.519
117.343
115.042
114.872
114.149
113.008
112.826
76.870
50.633
48.375
47.355
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32.816
30.971
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140
120
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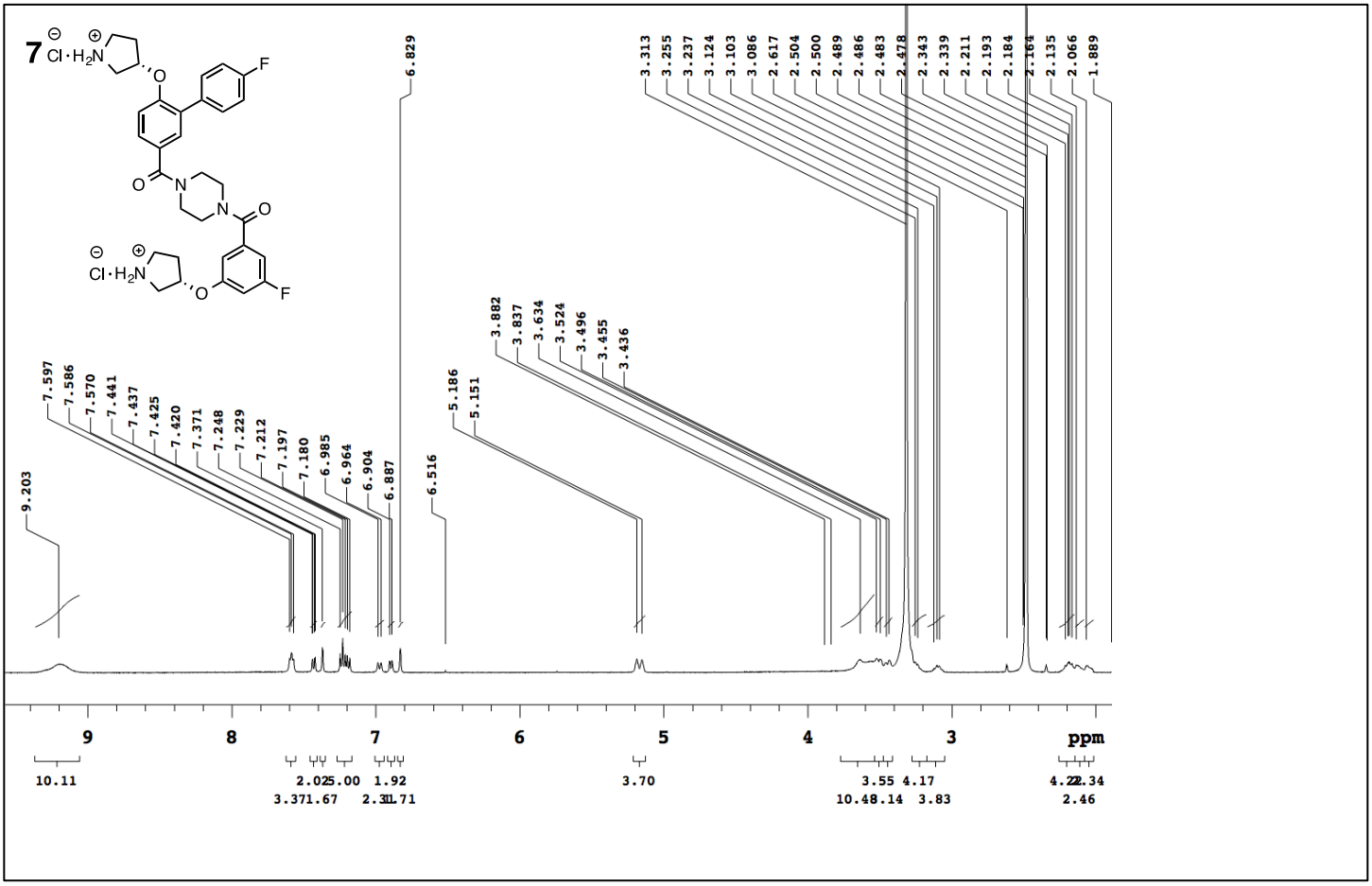
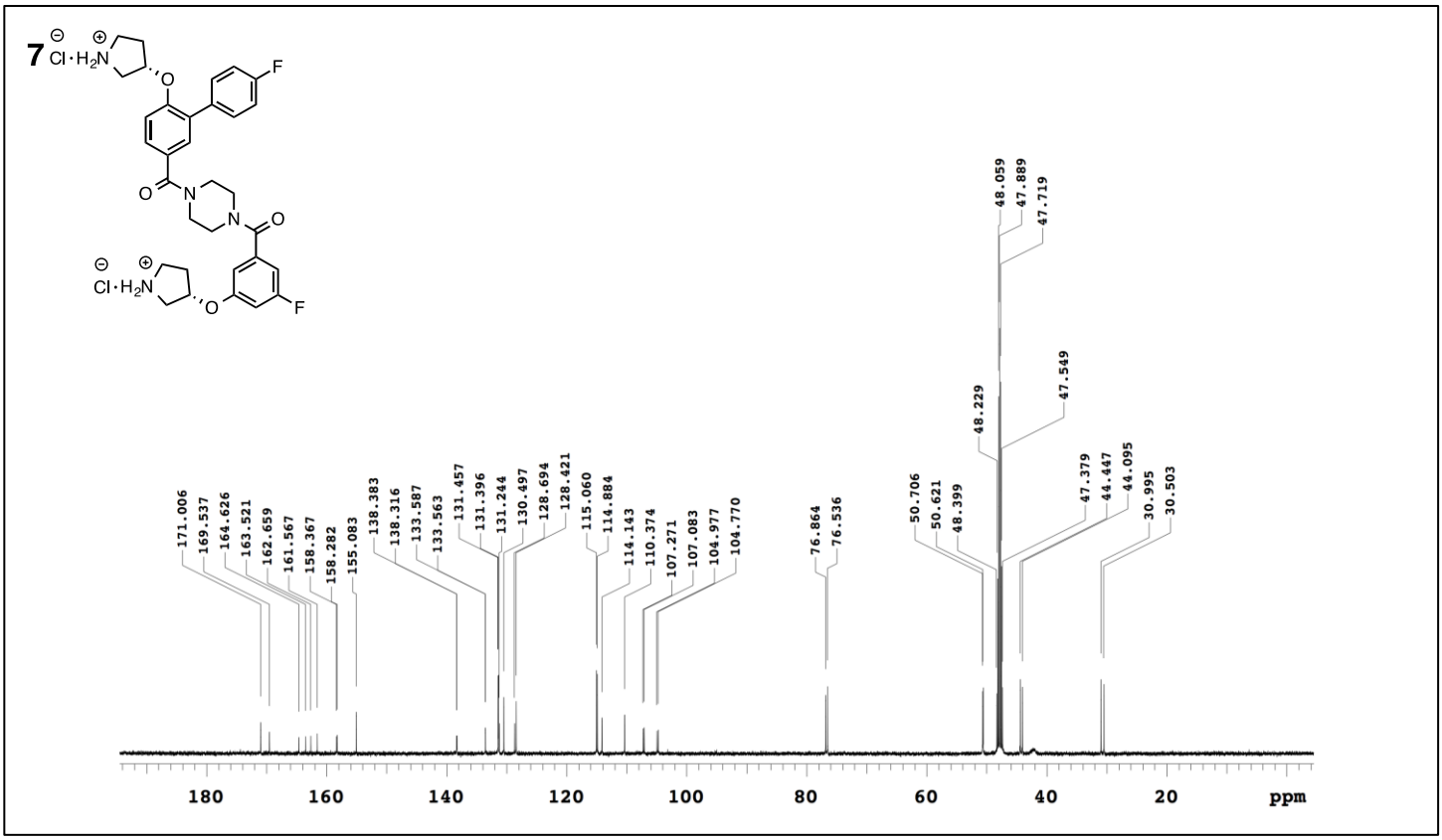
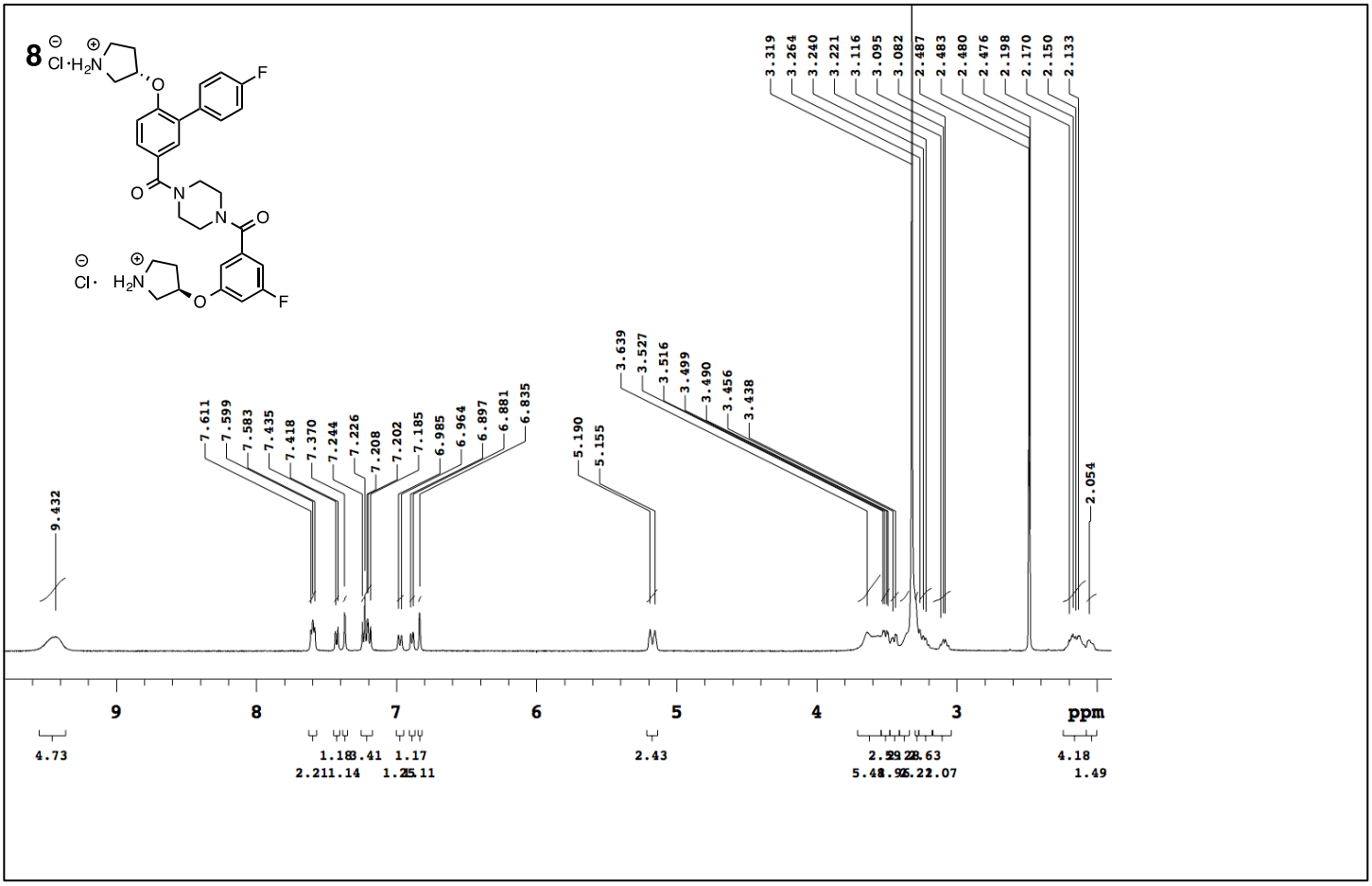
80
60
40
20
ppm


7
Cl·H2N
F
O
N
O
9.203
7.597
7.586
7.570
7.441
7.437
7.425
7.420
7.371
7.248
7.229
7.212
7.197
7.180
6.985
6.964
6.904
6.887
6.829
6.516
5.186
5.151
3.882
3.837
3.634
3.524
3.496
3.455
3.436
3.313
3.255
3.237
3.124
3.103
3.086
2.617
2.504
2.500
2.489
2.486
2.483
2.478
2.343
2.339
2.211
2.193
2.184
2.164
2.135
2.066
1.889
9
8
7
6
5
4
3
ppm
10.11
2.02
5.00
1.92
3.37
1.67
2.31
1.71
3.70
3.55
4.17
10.48.14
3.83
4.22
2.34
2.46


7
Cl·H2N
F
O
N
O
171.006
169.537
164.626
163.521
162.659
161.567
158.367
158.282
155.083
138.383
138.316
133.587
133.563
131.457
131.396
131.244
130.497
128.694
128.421
115.060
114.884
114.143
110.374
107.271
107.083
104.977
104.770
76.864
76.536
50.706
50.621
48.399
48.229
48.059
47.889
47.719
47.549
47.379
44.447
44.095
30.995
30.503
180
160
140
120
100
80
60
40
20
ppm


8
Cl· H2N
F
O
N
O
Cl· H2N
F
9.432
7.611
7.599
7.583
7.435
7.418
7.370
7.244
7.226
7.208
7.202
7.185
6.985
6.964
6.897
6.881
6.835
5.190
5.155
3.639
3.527
3.516
3.499
3.490
3.456
3.438
3.319
3.264
3.240
3.221
3.116
3.095
3.082
2.487
2.483
2.480
2.476
2.198
2.170
2.150
2.133
2.054
9
8
7
6
5
4
3
ppm
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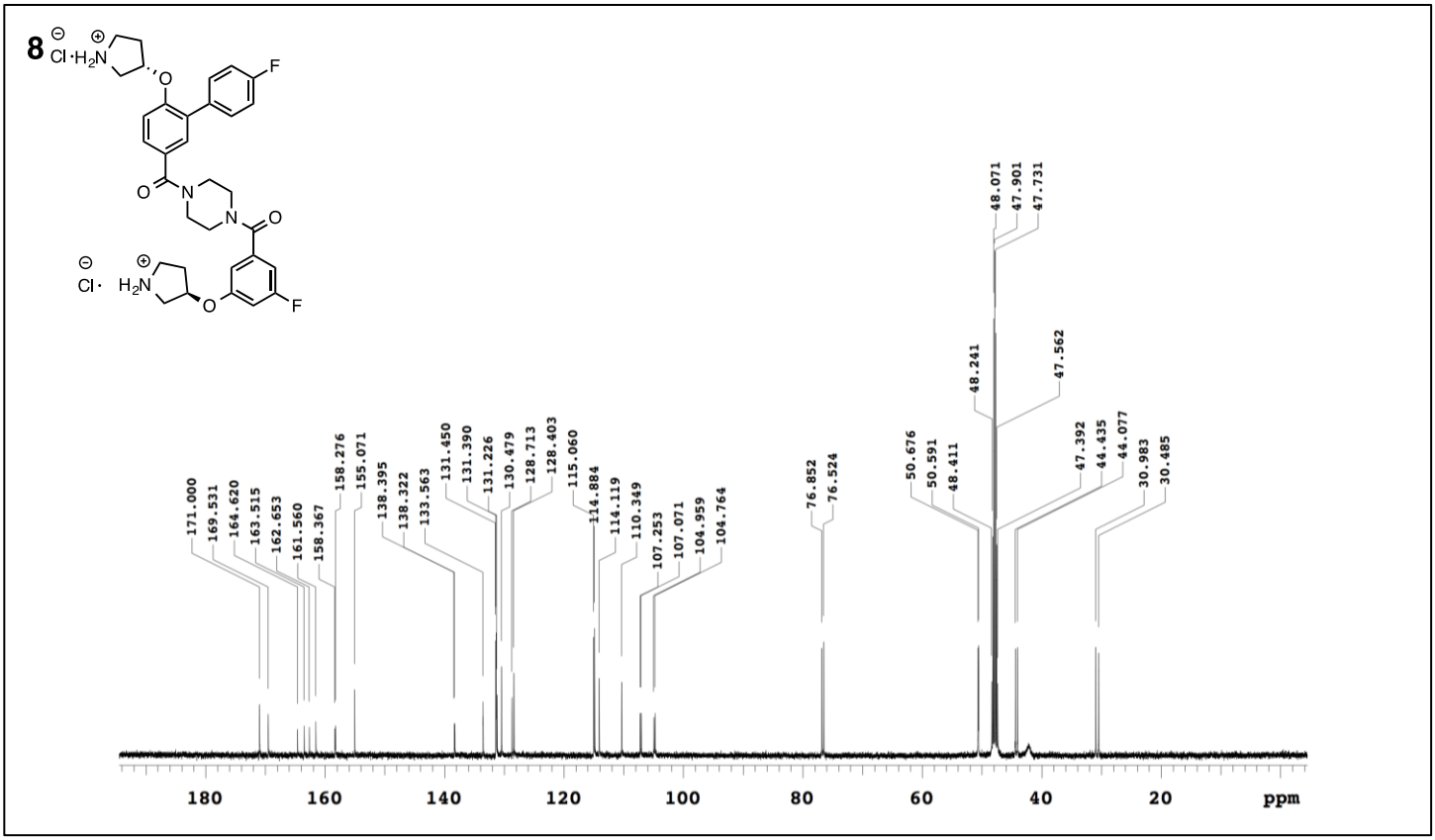
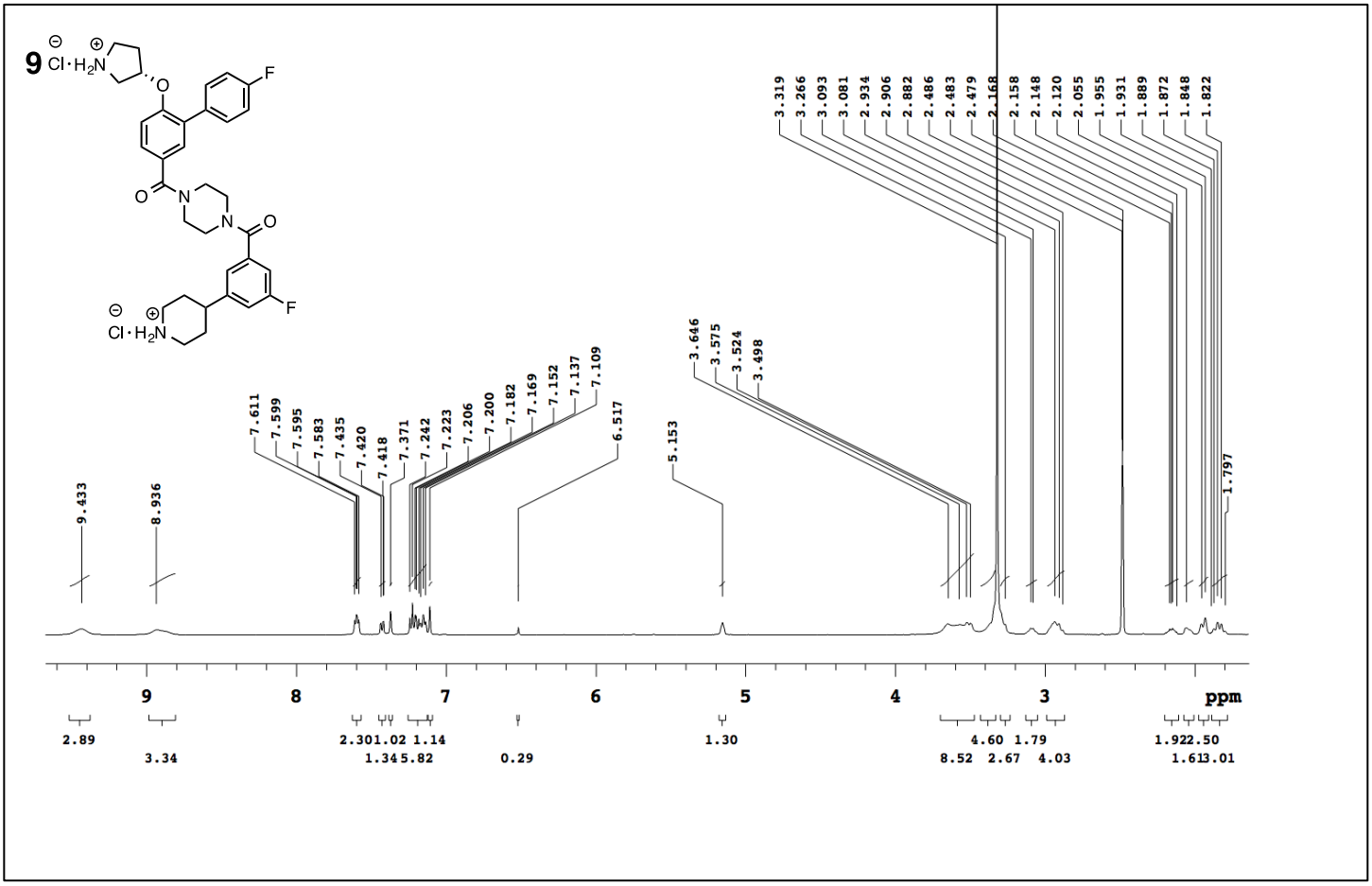
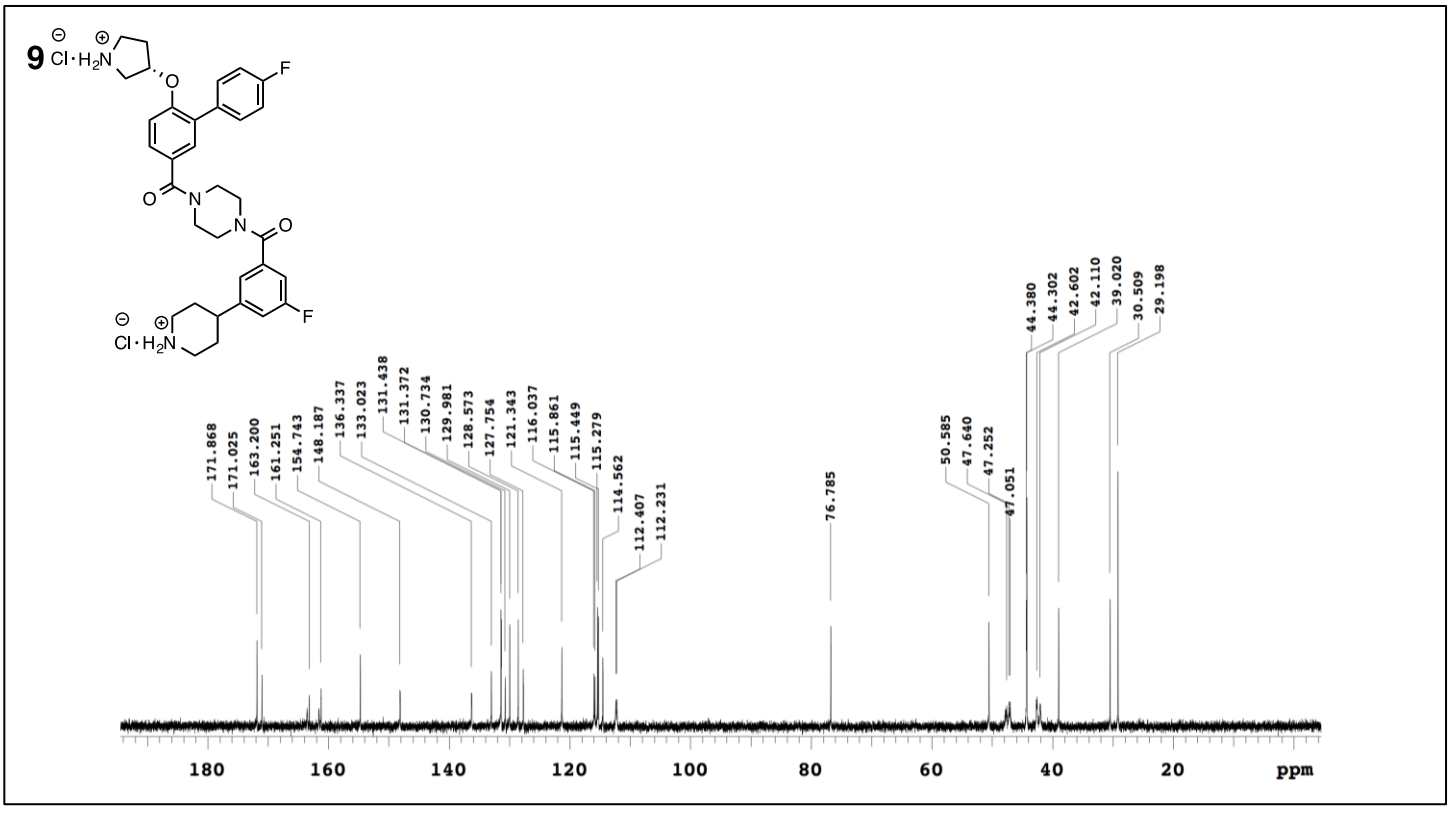
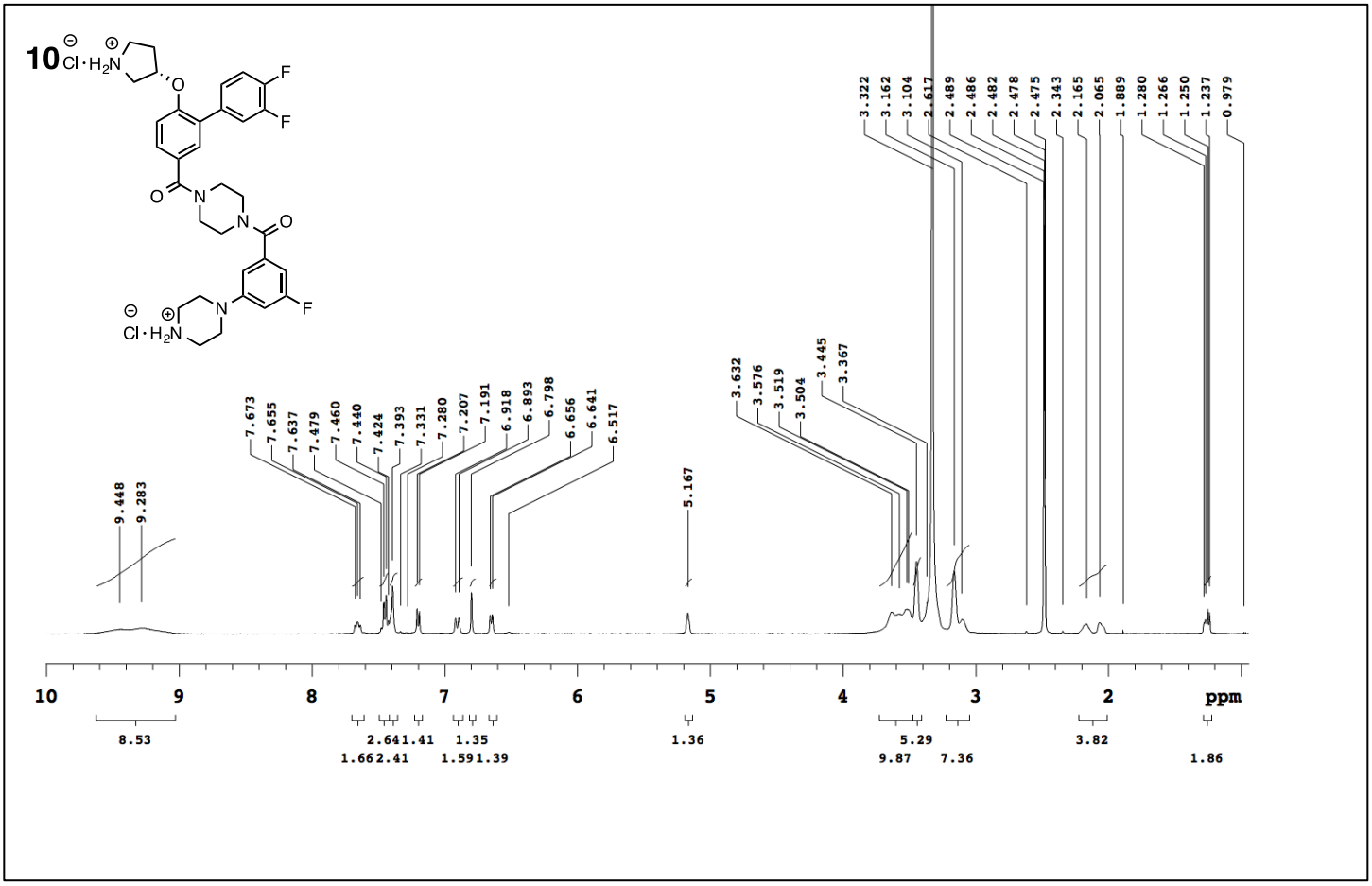
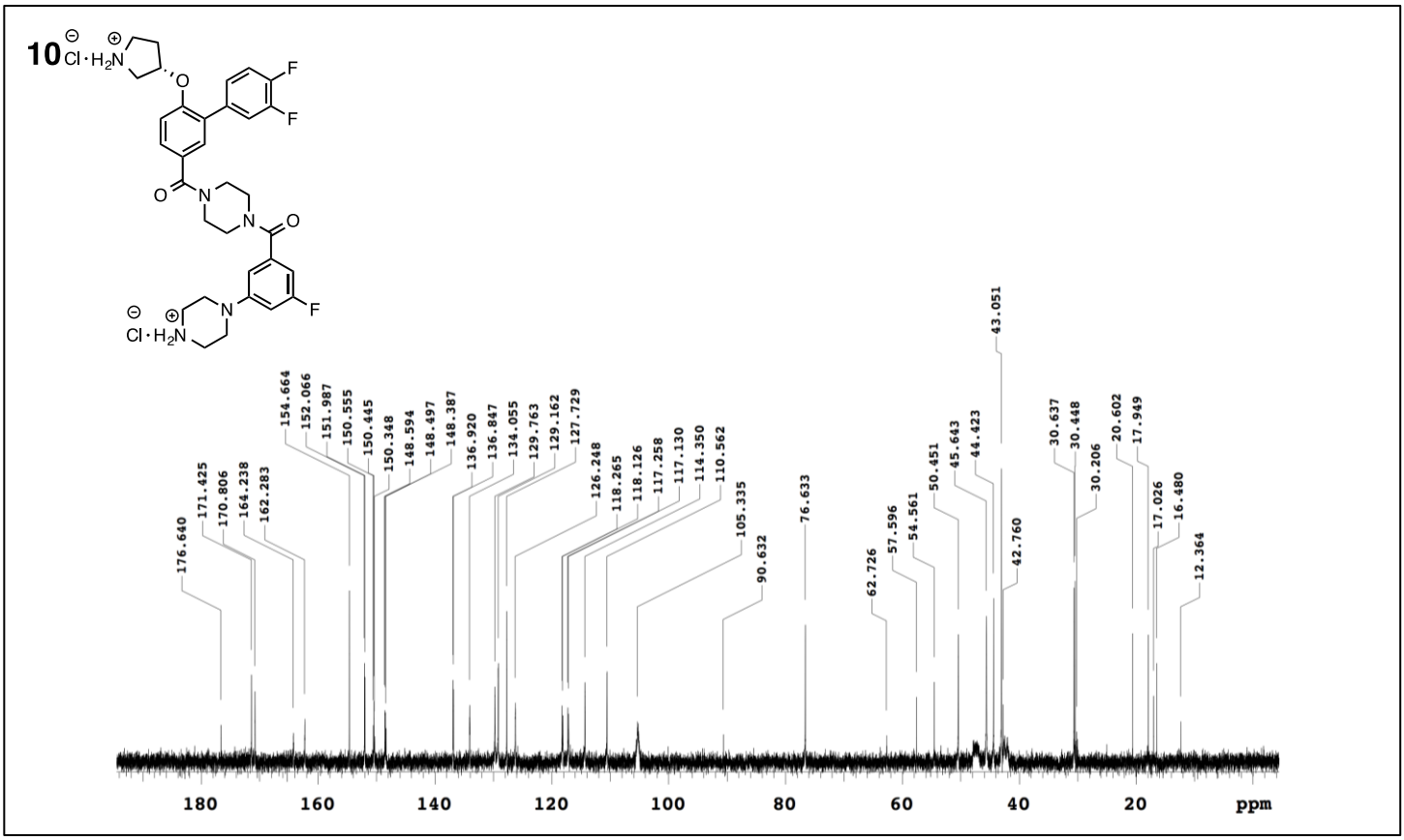
2.43
4.18
1.49

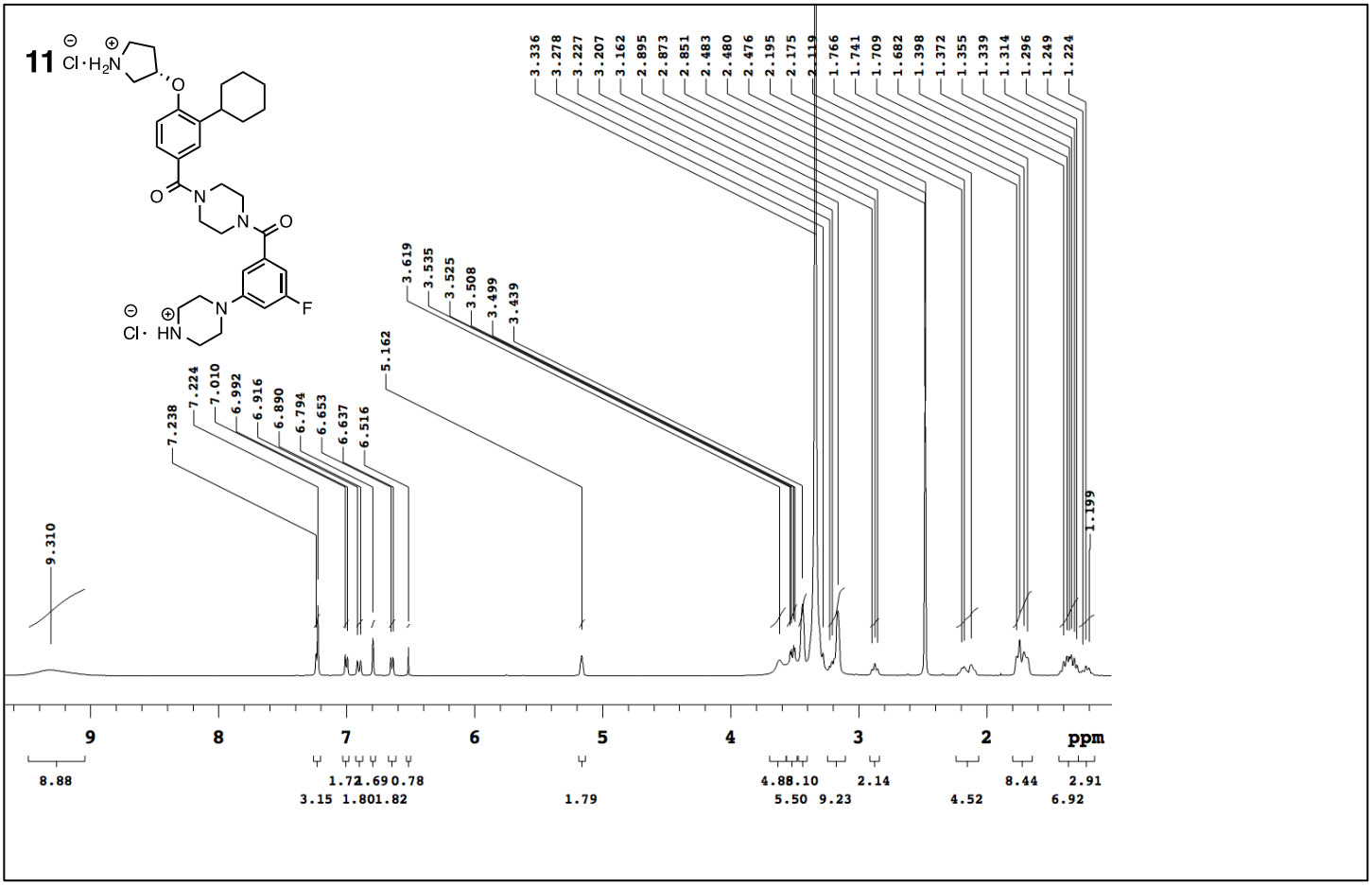

8
Cl· H2N
F
O
N
O
Cl· H2N
F
171.000
169.531
164.620
163.515
162.653
161.560
158.367
158.276
155.071
138.395
138.322
133.563
131.450
131.390
131.226
130.479
128.713
128.403
115.060
114.884
114.119
110.349
107.253
107.071
104.959
104.764
76.852
76.524
50.676
50.591
48.411
48.241
48.071
47.901
47.731
47.562
47.392
44.435
44.077
30.983
30.485
180
160
140
120
100
80
60
40
20
ppm

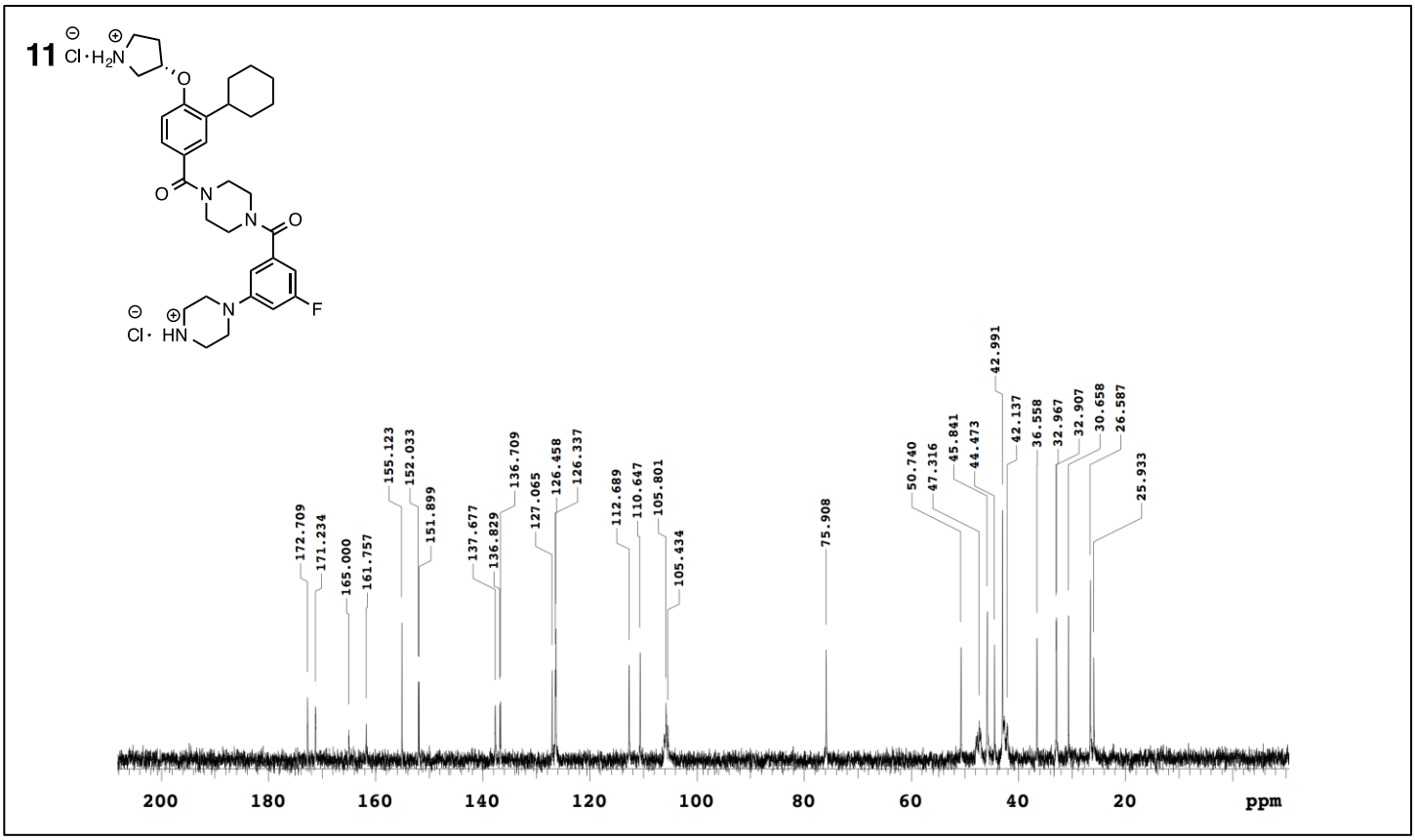

9
Cl·H2N
F
O
N
O
F
Cl·H2N
9.433
8.936
7.611
7.599
7.595
7.583
7.435
7.420
7.418
7.371
7.242
7.223
7.206
7.200
7.182
7.169
7.152
7.137
7.109
6.517
5.153
3.646
3.575
3.524
3.498
3.319
3.266
3.093
3.081
2.934
2.906
2.882
2.486
2.483
2.479
2.168
2.158
2.148
2.120
2.055
1.955
1.931
1.889
1.872
1.848
1.822
1.797
9
8
7
6
5
4
3
ppm
2.89
3.34
2.30
1.02
1.34
1.14
5.82
0.29
1.30
4.60
8.52
1.79
2.67
4.03
1.92
2.50
1.61
3.01

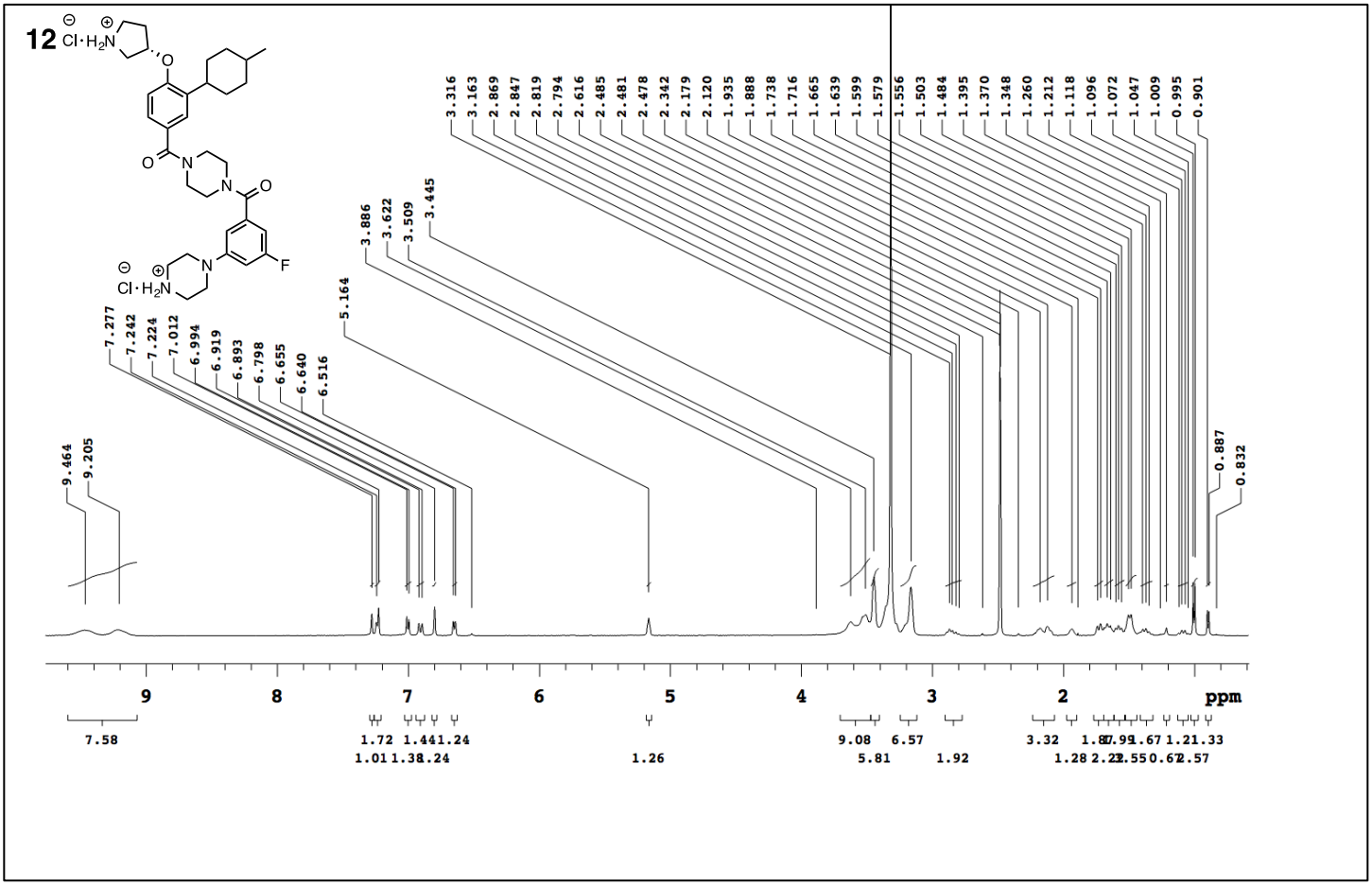

9
Cl·H2N
F
O
N
O
F
Cl·H2N
171.868
171.025
163.200
161.251
154.743
148.187
136.337
133.023
131.438
131.372
130.734
129.981
128.573
127.754
121.343
116.037
115.861
115.449
115.279
114.562
112.407
112.231
76.785
50.585
47.640
47.252
47.051
44.380
44.302
42.602
42.110
39.020
30.509
29.198
180
160
140
120
100
80
60
40
20
ppm

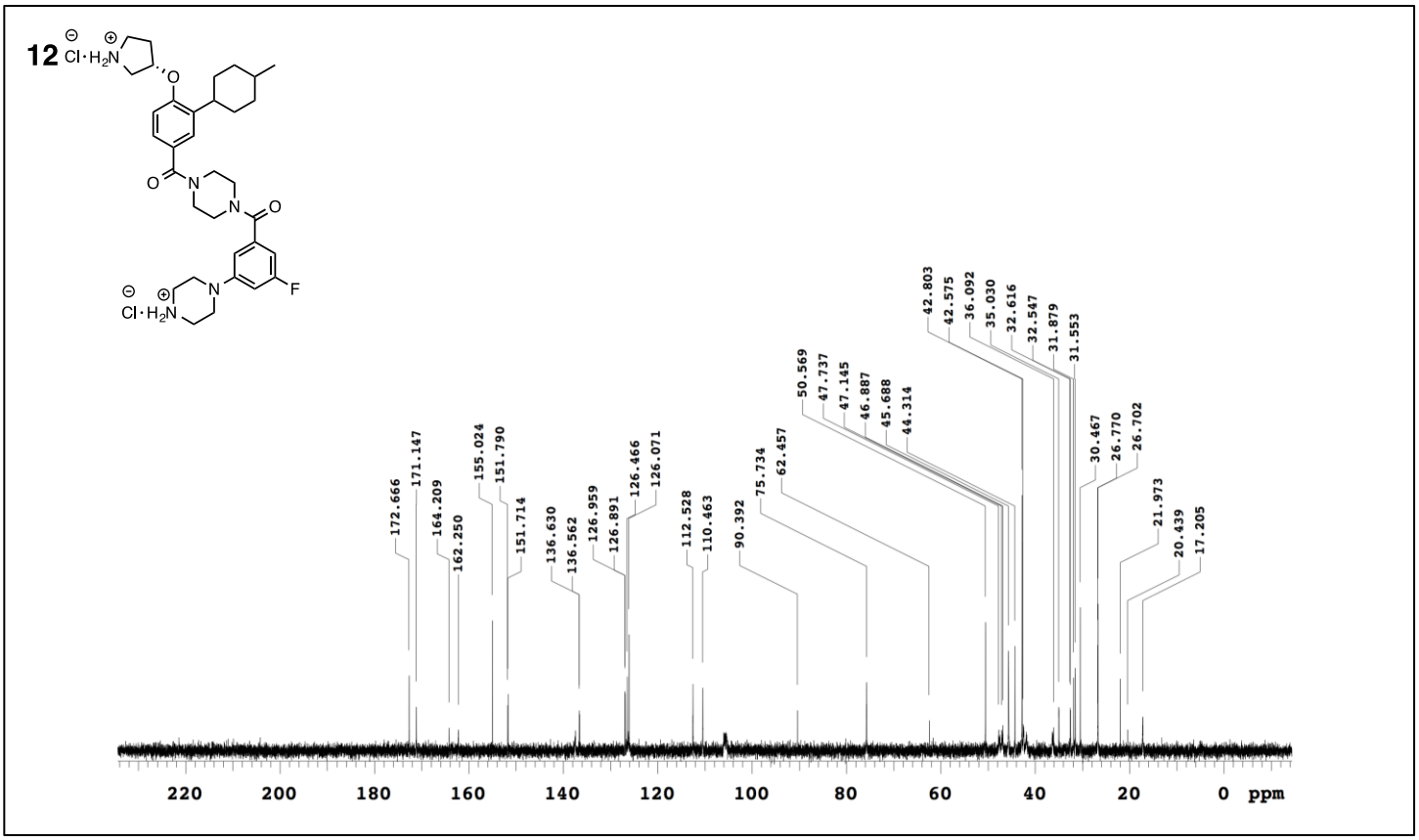

10
9.448
9.283
7.673
7.655
7.637
7.479
7.460
7.440
7.424
7.393
7.331
7.280
7.207
7.191
6.918
6.893
6.798
6.656
6.641
6.517
5.167
3.632
3.576
3.519
3.504
3.445
3.367
3.322
3.162
3.104
2.617
2.489
2.486
2.482
2.478
2.475
2.343
2.165
2.065
1.889
1.280
1.266
1.250
1.237
0.979
10
9
8
7
6
5
4
3
2
ppm
8.53
2.64
1.41
1.35
1.36
5.29
3.82
1.66
2.41
1.59
1.39
9.87
7.36
1.86


10
176.640
171.425
170.806
164.238
162.283
154.664
152.066
151.987
150.555
150.445
150.348
148.594
148.497
148.387
136.920
136.847
134.055
129.763
129.162
127.729
126.248
118.265
118.126
117.258
117.130
114.350
110.562
105.335
90.632
76.633
62.726
57.596
54.561
50.451
45.643
44.423
43.051
42.760
30.637
30.448
30.206
20.602
17.949
17.026
16.480
12.364
180
160
140
120
100
80
60
40
20
ppm


11
Cl·H2N
O
N
N
O
F
Cl· HN
3.336
3.278
3.227
3.207
3.162
2.895
2.873
2.851
2.483
2.480
2.476
2.195
2.175
2.119
1.766
1.741
1.709
1.682
1.398
1.372
1.355
1.339
1.314
1.296
1.249
1.224
3.619
3.535
3.525
3.508
3.499
3.439
5.162
7.238
7.224
7.010
6.992
6.916
6.890
6.794
6.653
6.637
6.516
9.310
1.199
9
8
7
6
5
4
3
2
ppm
8.88
1.72
1.69
0.78
3.15
1.80
1.82
1.79
4.88
8.10
2.14
5.50
9.23
4.52
8.44
2.91
6.92


11
Cl·H2N
O
N
N
O
F
Cl· HN
172.709
171.234
165.000
161.757
155.123
152.033
151.899
137.677
136.829
136.709
127.065
126.458
126.337
112.689
110.647
105.801
105.434
75.908
50.740
47.316
45.841
44.473
42.991
42.137
36.558
32.967
32.907
30.658
26.587
25.933
200
180
160
140
120
100
80
60
40
20
ppm


12
Cl·H2N
O
N
F
3.316
3.163
2.869
2.847
2.819
2.794
2.616
2.485
2.481
2.478
2.342
2.179
2.120
1.935
1.888
1.738
1.716
1.665
1.639
1.599
1.579
1.556
1.503
1.484
1.395
1.370
1.348
1.260
1.212
1.118
1.096
1.072
1.047
1.009
0.995
0.901
3.886
3.622
3.509
3.445
5.164
7.277
7.242
7.224
7.012
6.994
6.919
6.893
6.798
6.655
6.640
6.516
9.464
9.205
0.887
0.832
9
8
7
6
5
4
3
2
ppm
7.58
1.72
1.44
1.24
1.01
1.38
1.24
1.26
9.08
6.57
5.81
1.92
3.32
1.28
1.67
1.21
1.33
2.57


12
Cl·H2N
O
N
F
42.803
42.575
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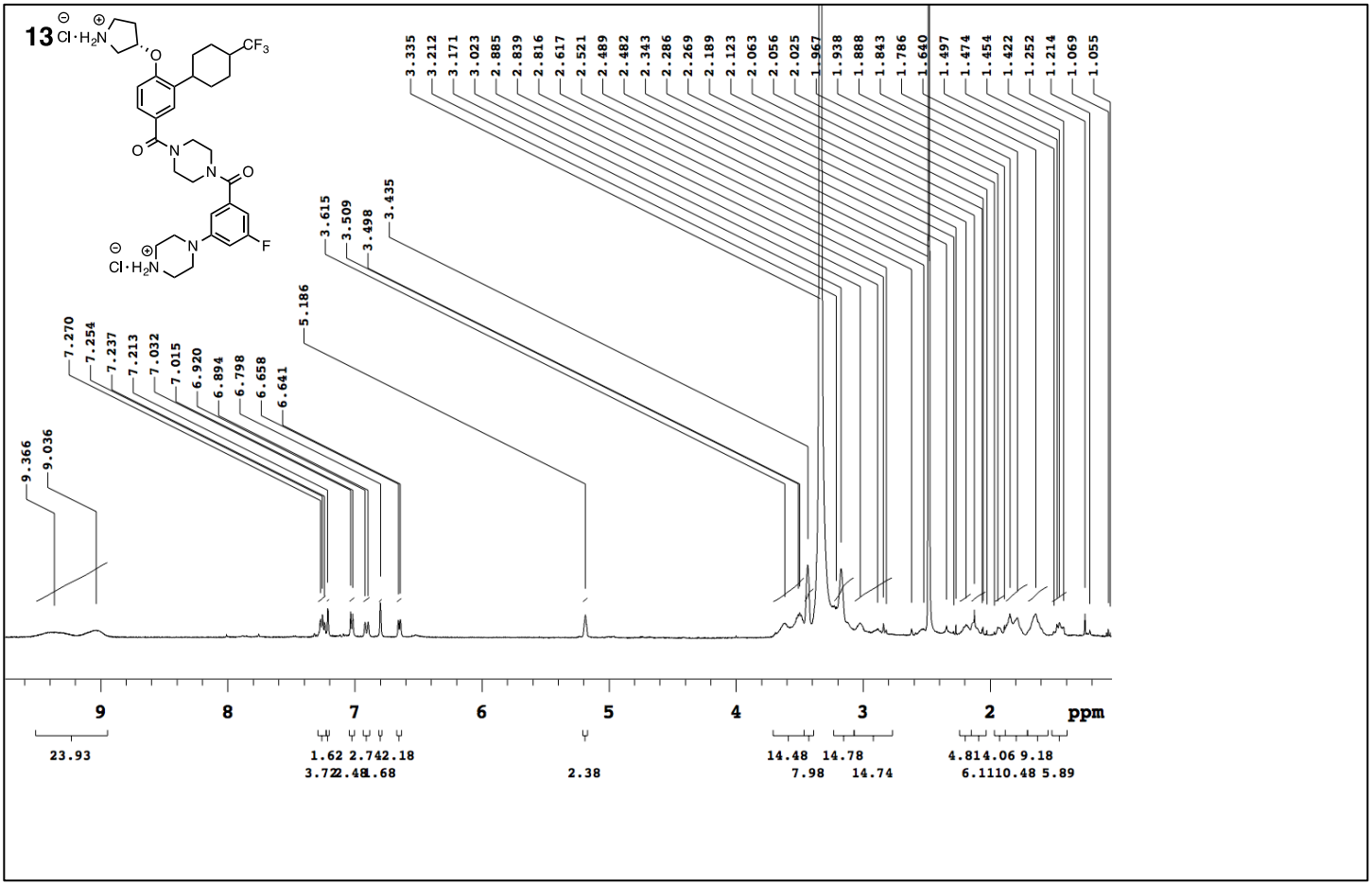
35.030
32.616
32.547
31.879
31.553
50.569
47.737
47.145
46.887
45.688
44.314
30.467
26.770
26.702
172.666
171.147
164.209
162.250
155.024
151.790
151.714
136.630
136.562
126.959
126.891
126.466
126.071
112.528
110.463
90.392
75.734
62.457
21.973
20.439
17.205
220
200
180
160
140
120
100
80
60
40
20
0
ppm


13
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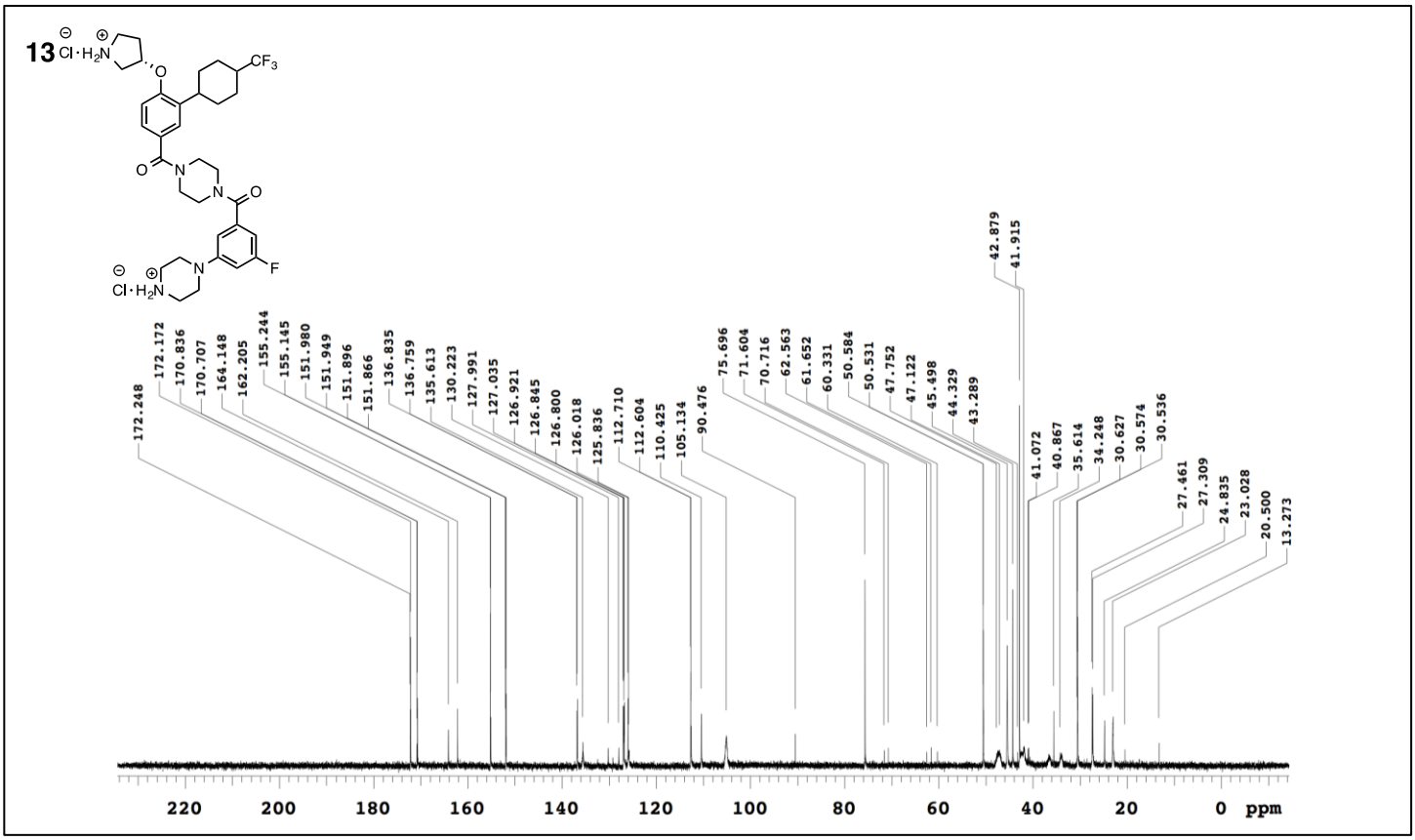
3.171
3.023
2.885
2.839
2.816
2.617
2.521
2.489
2.482
2.343
2.286
2.269
2.189
2.123
2.063
2.056
2.025
1.967
1.938
1.888
1.843
1.786
1.640
1.497
1.474
1.454
1.422
1.252
1.214
1.069
1.055
3.615
3.509
3.498
3.435
5.186
7.270
7.254
7.237
7.213
7.032
7.015
6.920
6.894
6.798
6.658
6.641
9.366
9.036
9
8
7
6
5
4
3
2
ppm
23.93
1.62
2.74
2.18
3.72
2.48
1.68
2.38
14.48
14.78
7.98
14.74
4.81
4.06
9.18
6.11
10.48
5.89


13
42.879
41.915
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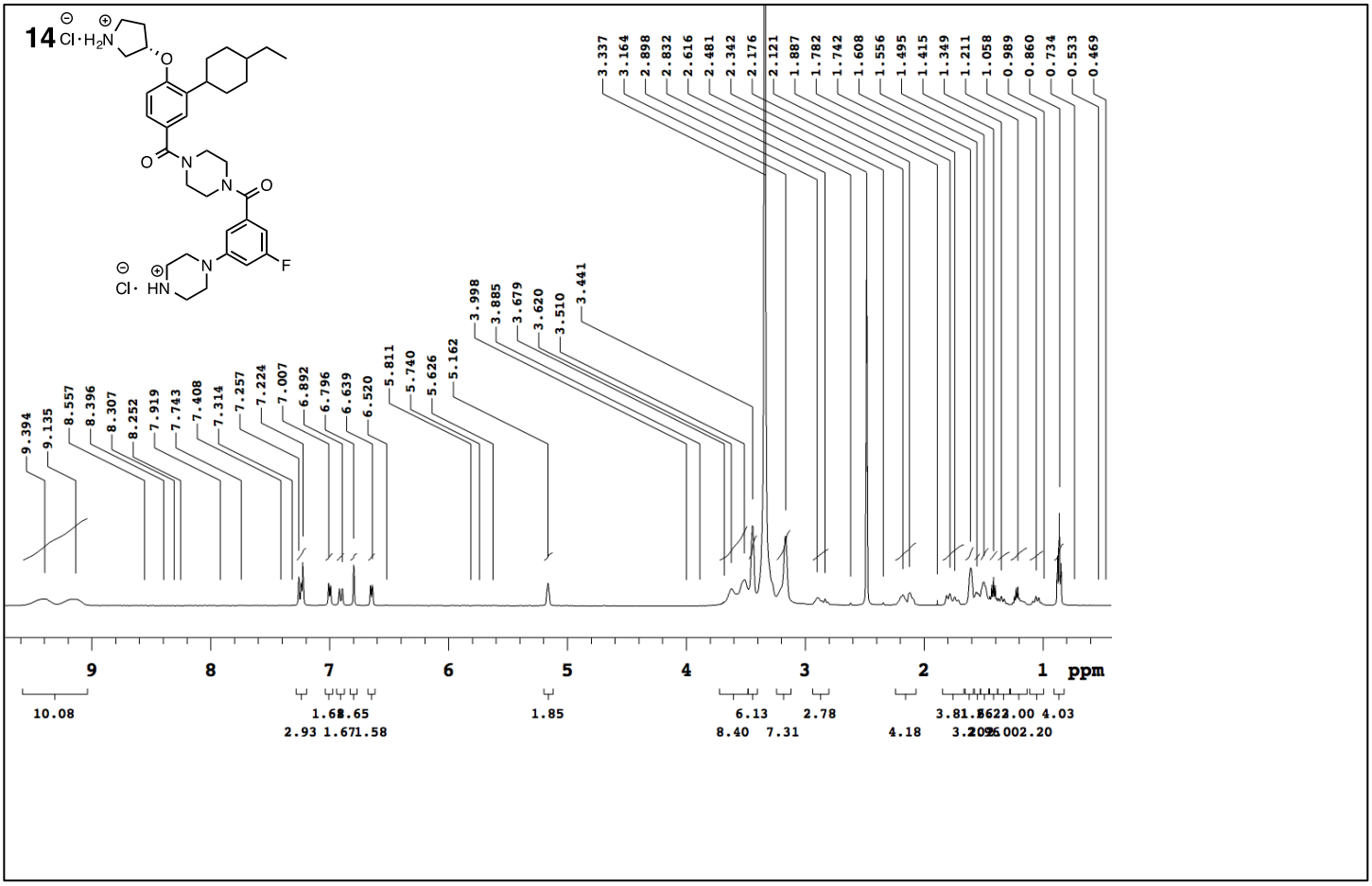
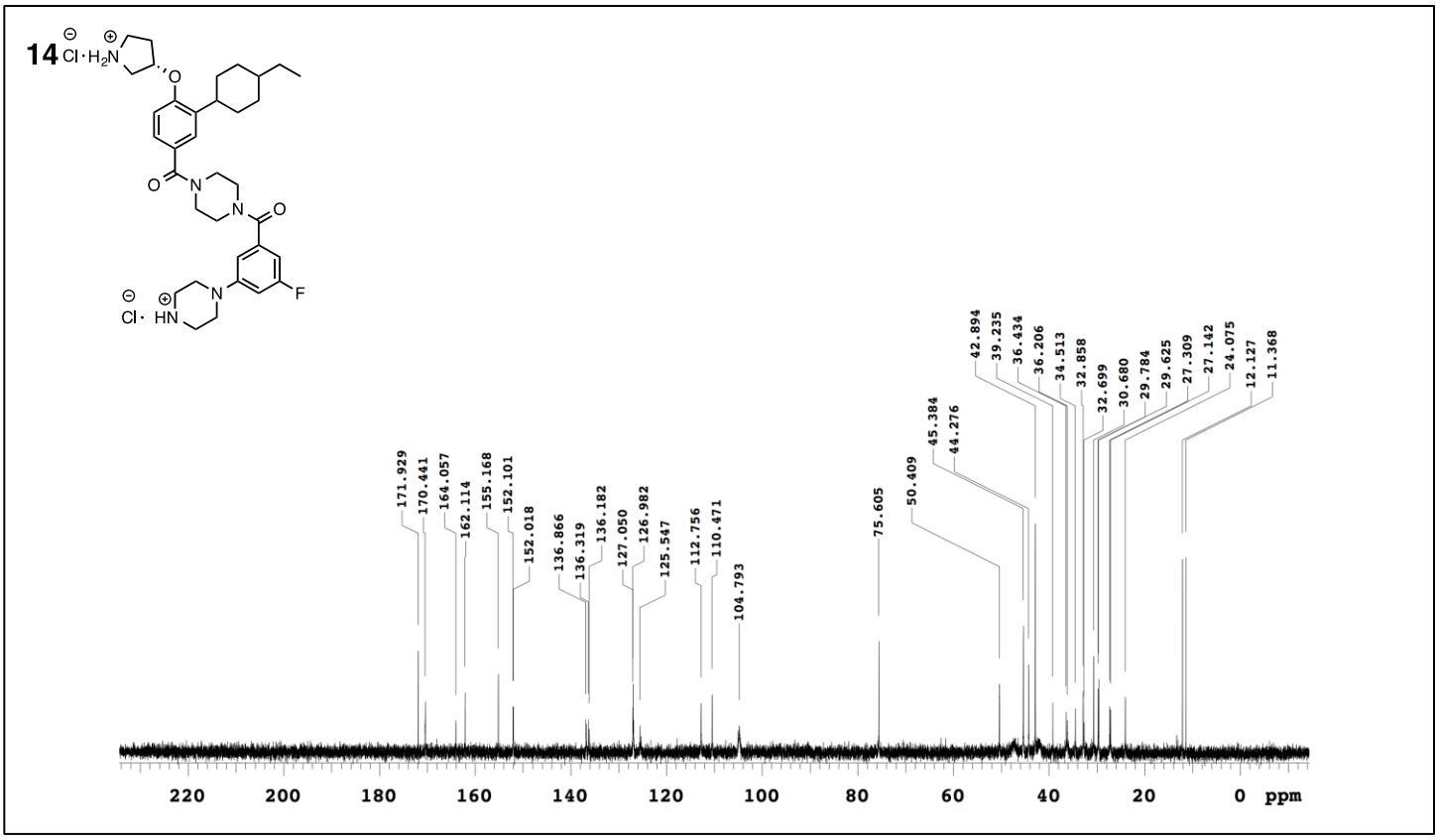
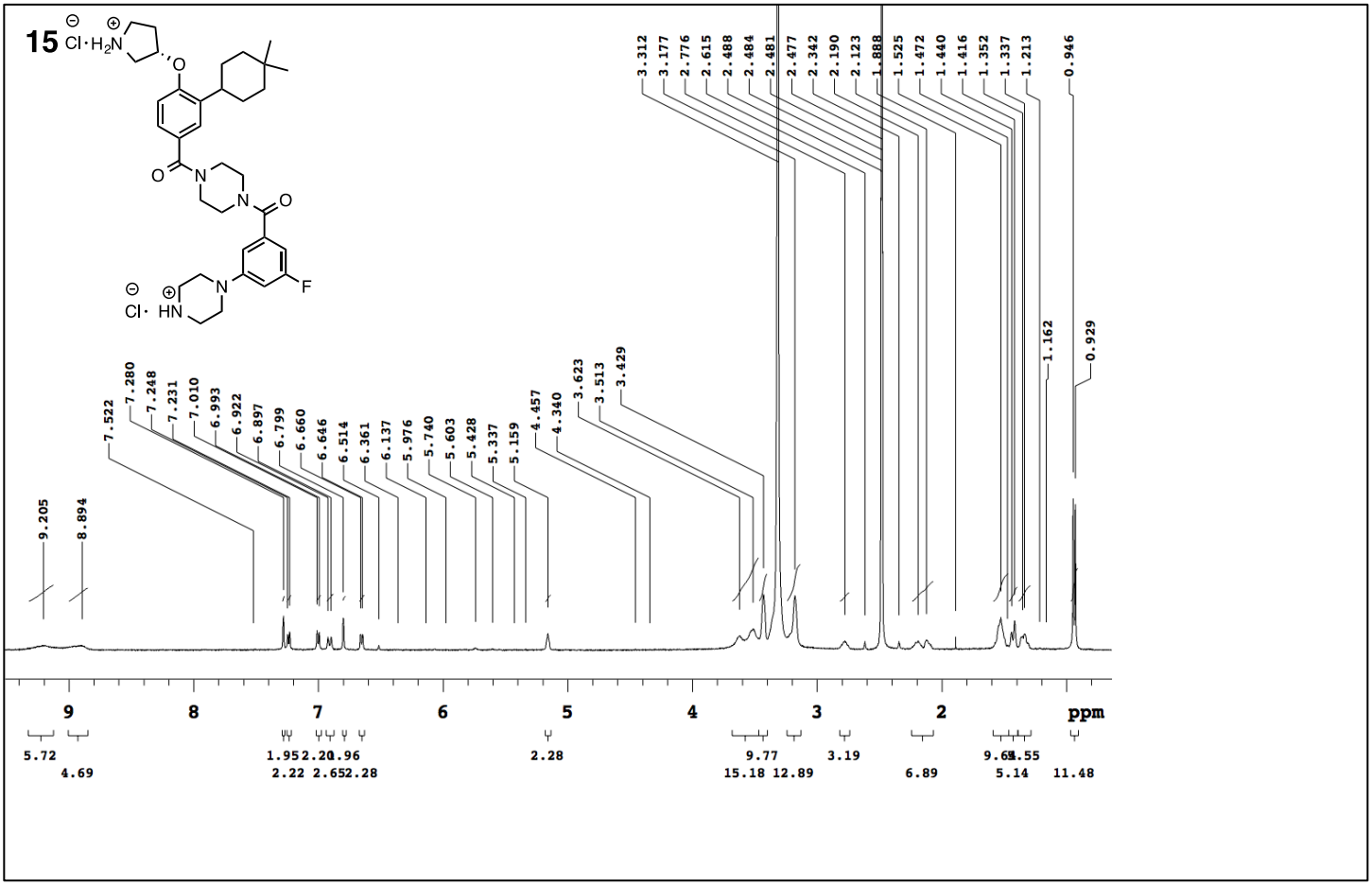
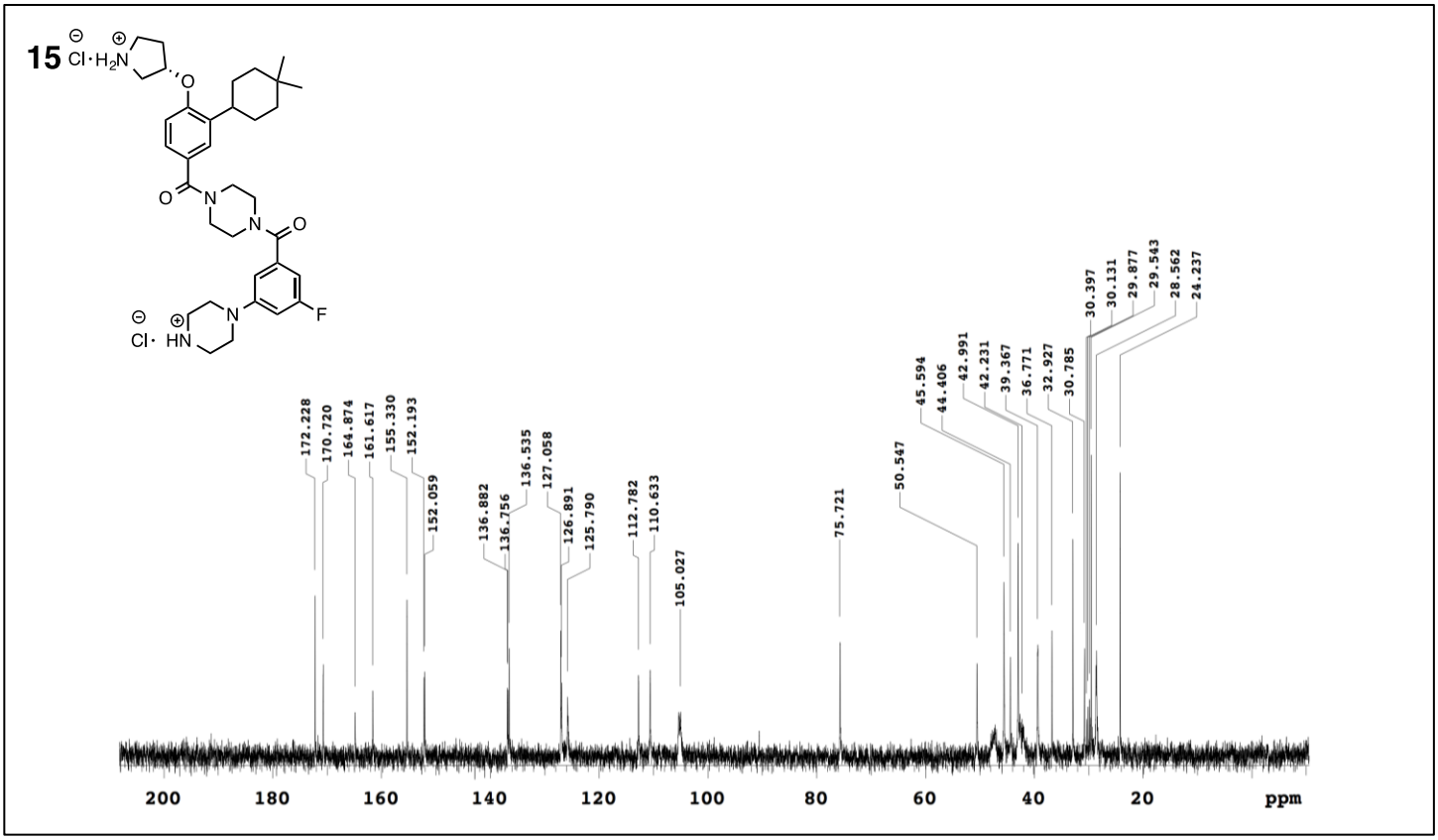
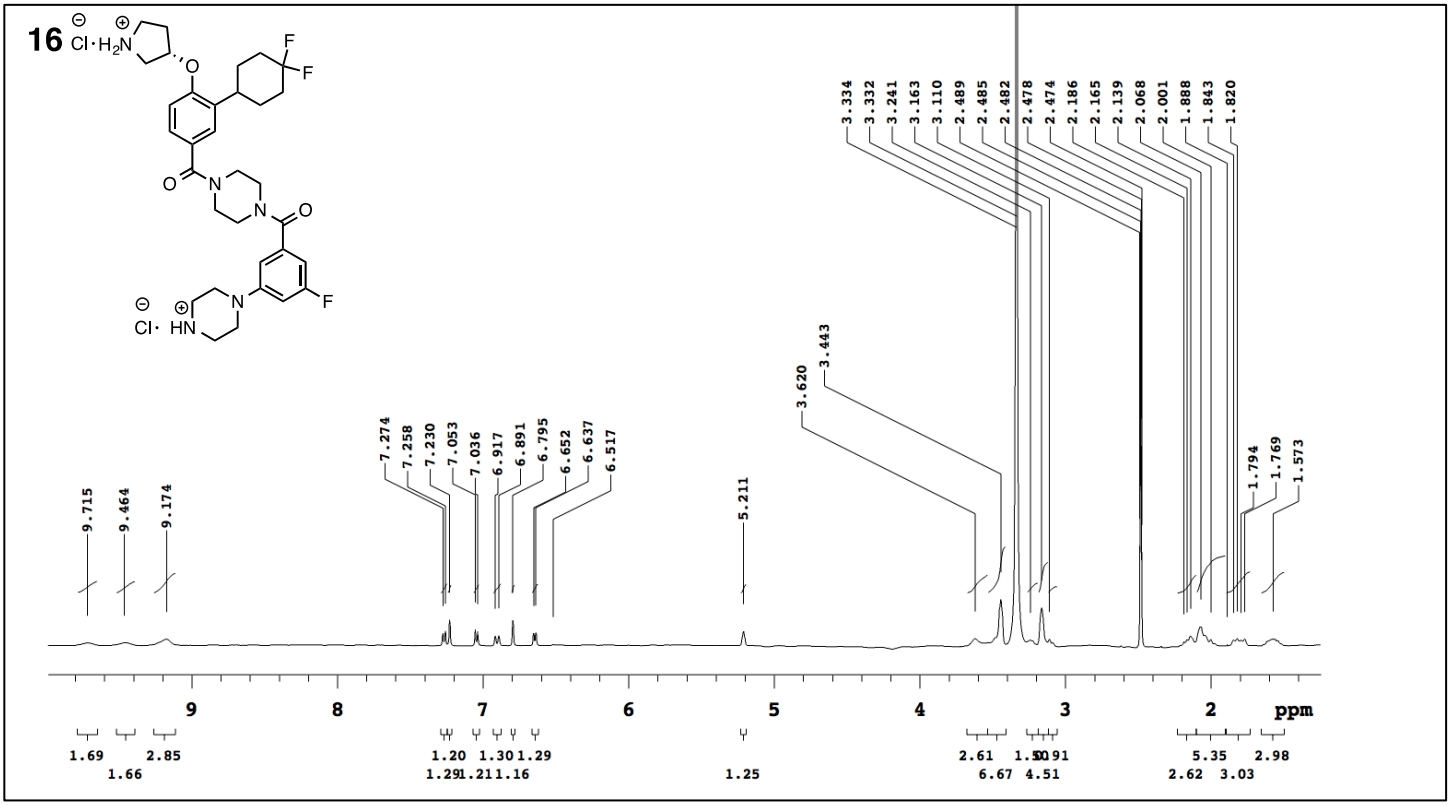
170.836
170.707
164.148
162.205
155.244
155.145
151.980
151.949
151.896
151.866
136.835
136.759
135.613
130.223
127.991
127.035
126.921
126.845
126.800
126.018
125.836
112.710
112.604
110.425
105.134
90.476
75.696
71.604
70.716
62.563
61.652
60.331
50.584
50.531
47.752
47.122
45.498
44.329
43.289
172.248
41.072
40.867
35.614
34.248
30.627
30.574
30.536
27.461
27.309
24.835
23.028
20.500
13.273
220
200
180
160
140
120
100
80
60
40
20
0
ppm

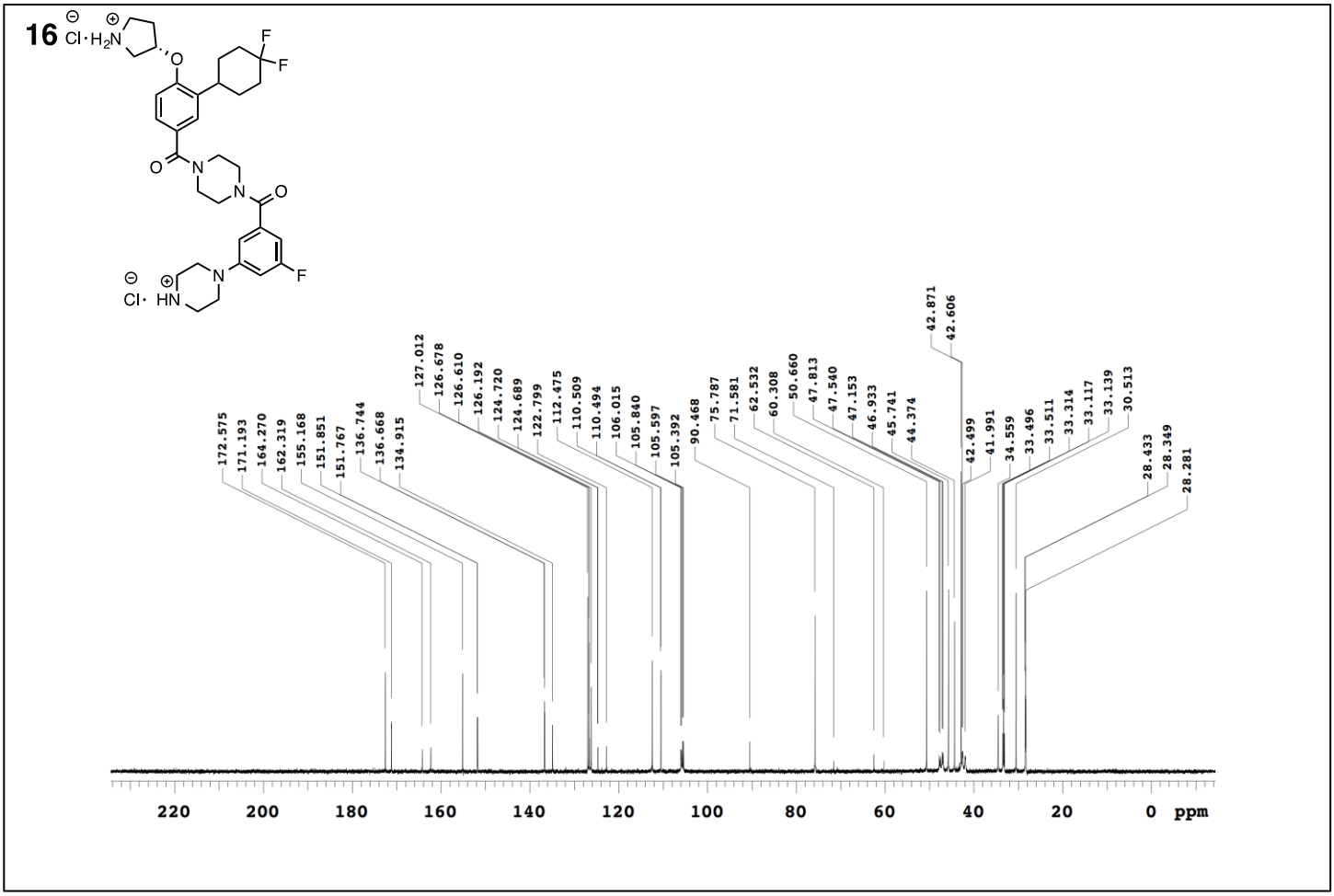

14
Cl· H2N
O
N
N
O
F
Cl· HN
3.337
3.164
2.898
2.832
2.616
2.481
2.342
2.176
2.121
1.887
1.782
1.742
1.608
1.556
1.495
1.415
1.349
1.211
1.058
0.989
0.860
0.734
0.533
0.469
3.998
3.885
3.679
3.620
3.510
3.441
9.394
9.135
8.557
8.396
8.307
8.252
7.919
7.743
7.408
7.314
7.257
7.224
7.007
6.892
6.796
6.639
6.520
5.811
5.740
5.626
5.162
9 8 7 6 5 4 3 2 1 ppm
10.08
1.68
1.65
2.93
1.67
1.58
1.85
6.13
2.78
8.40
7.31
4.18
4.03
2.00
2.20

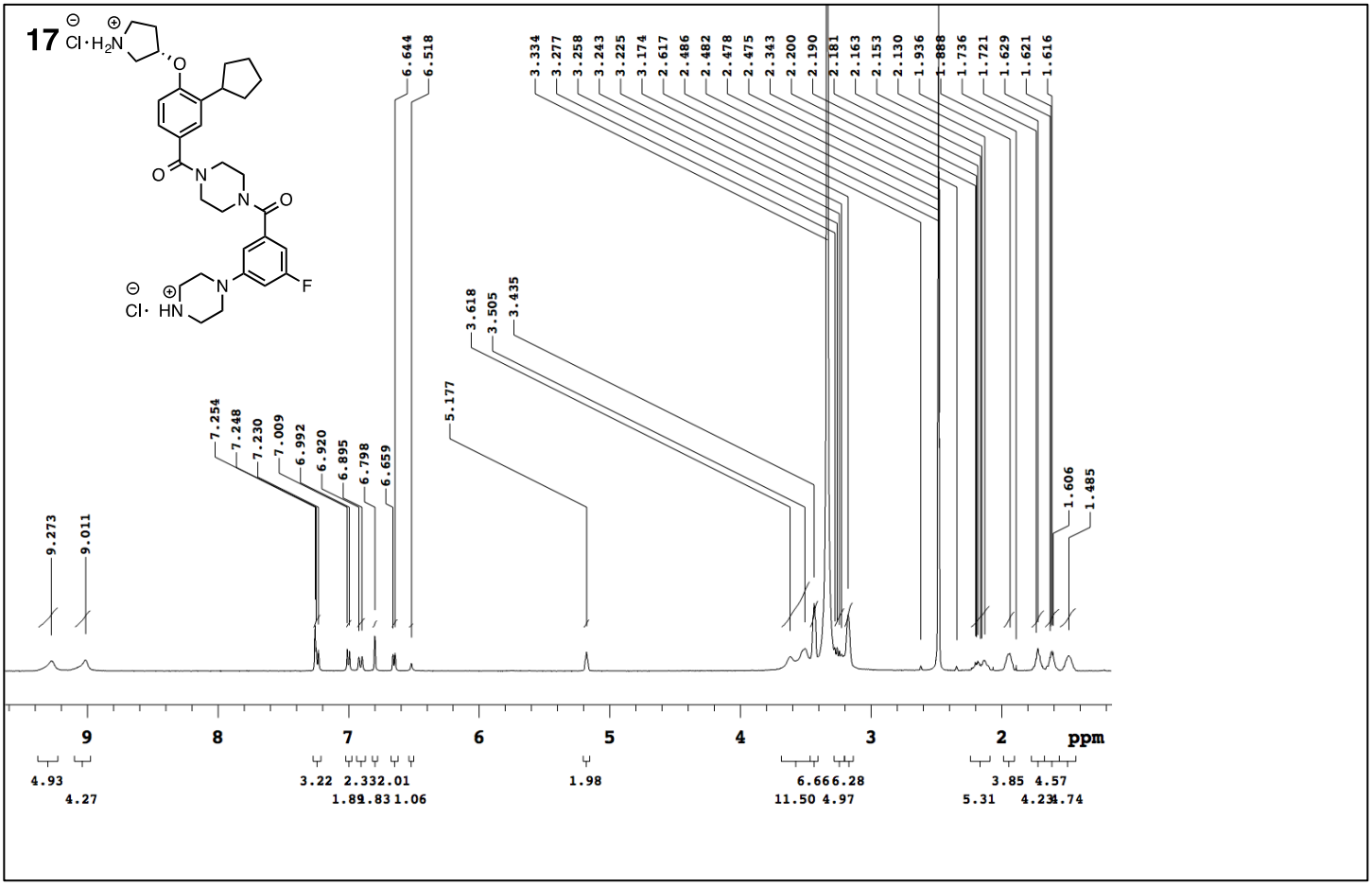

14
Cl· H2N
O
N
N
O
F
Cl· HN
171.929
170.441
164.057
162.114
155.168
152.101
152.018
136.866
136.319
136.182
127.050
126.982
125.547
112.756
110.471
104.793
75.605
50.409
45.384
44.276
42.894
39.235
36.434
36.206
34.513
32.858
32.699
30.680
29.784
29.625
27.309
27.142
24.075
12.127
11.368
220 200 180 160 140 120 100 80 60 40 20 0 ppm

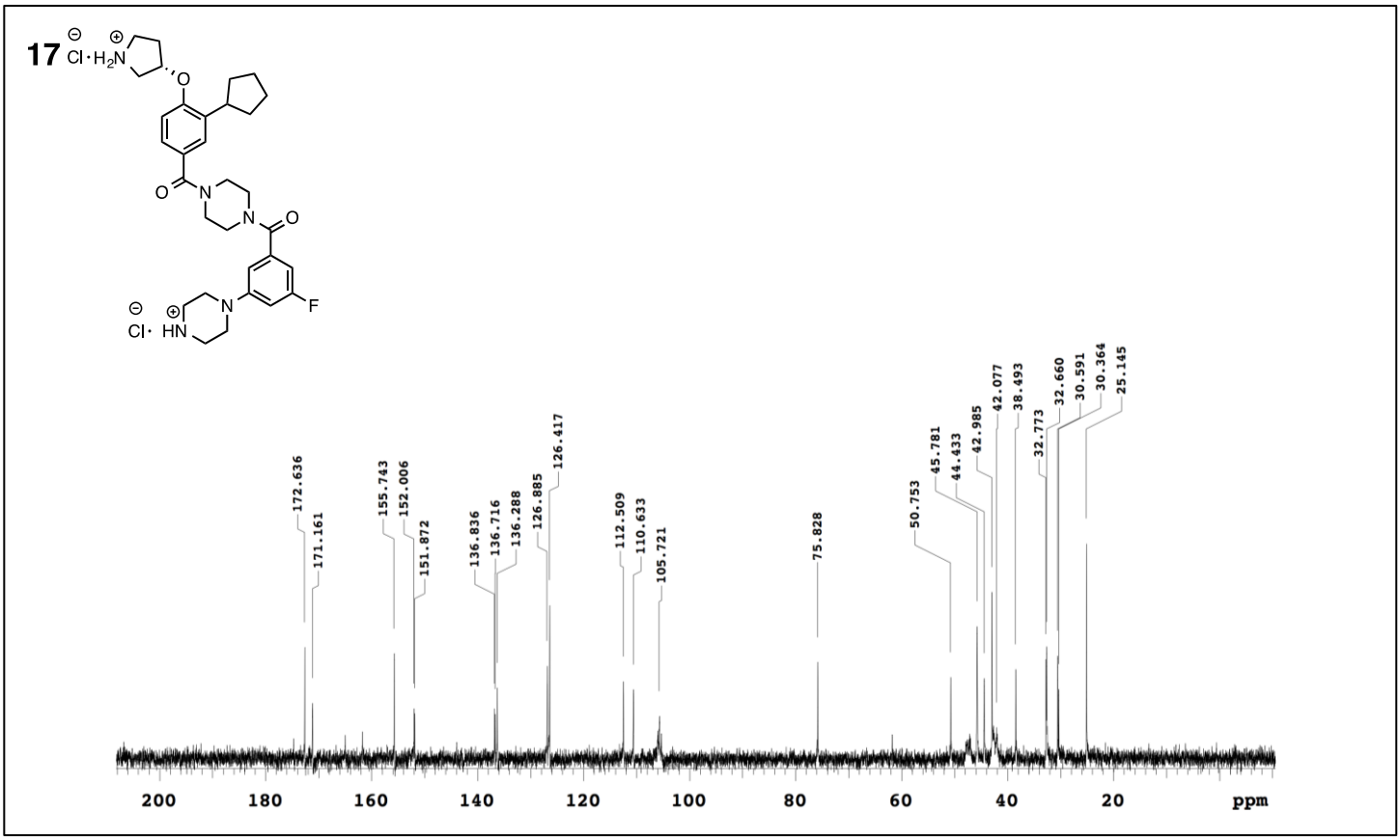

15
Cl·H2N
O
N
N
O
F
Cl· HN
3.312
3.177
2.776
2.615
2.488
2.484
2.481
2.477
2.342
2.190
2.123
1.888
1.525
1.472
1.440
1.416
1.352
1.337
1.213
0.946
1.162
0.929
7.522
7.280
7.248
7.231
7.010
6.993
6.922
6.897
6.799
6.660
6.646
6.514
6.361
6.137
5.976
5.740
5.603
5.428
5.337
5.159
4.457
4.340
3.623
3.513
3.429
9.205
8.894
9
8
7
6
5
4
3
2
ppm
5.72
4.69
1.95
2.22
2.20
2.65
0.96
2.52
2.28
9.77
15.18
12.89
3.19
6.89
9.68
5.14
4.55
11.48

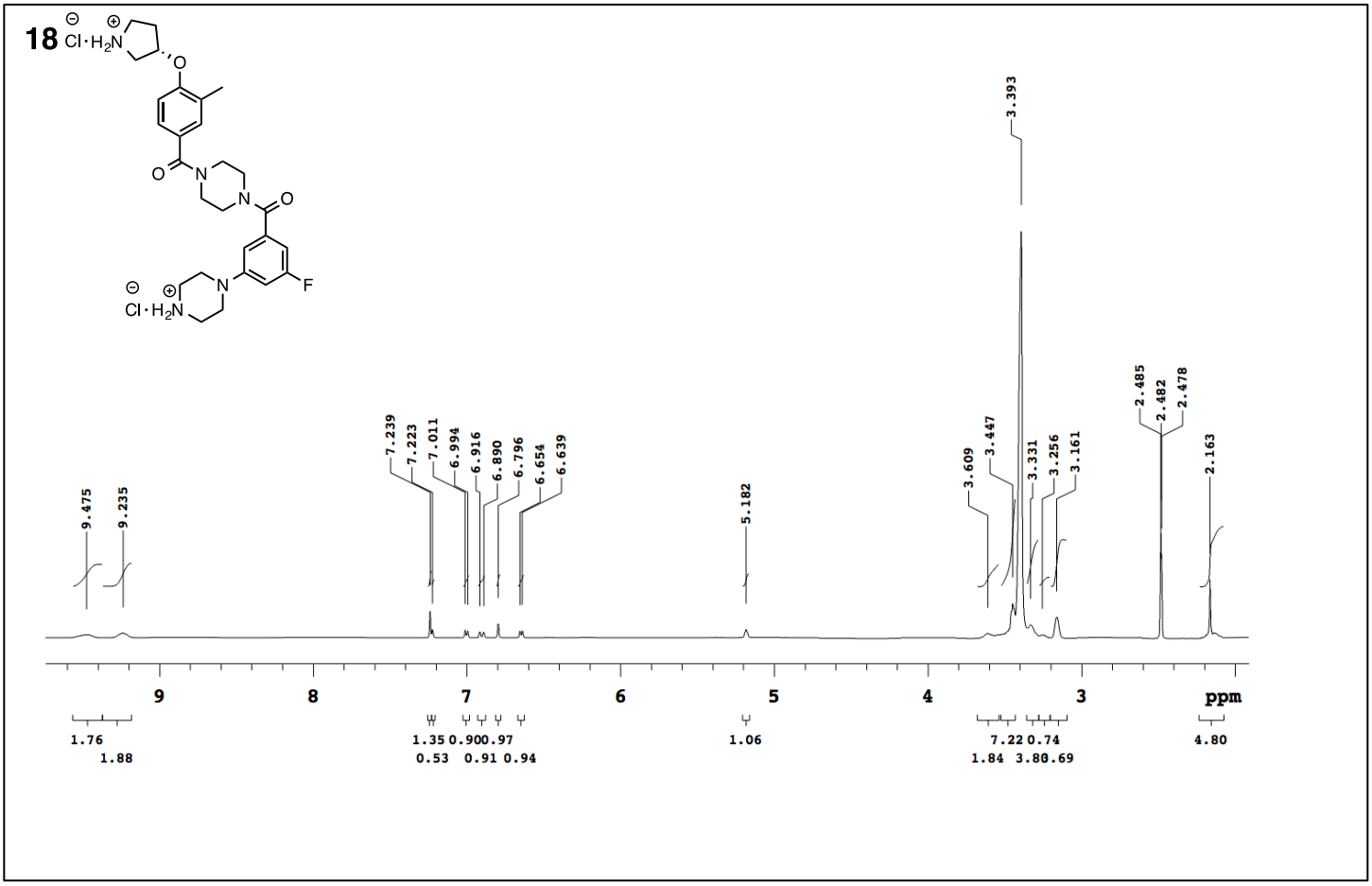

15
Cl·H2N
O
N
N
O
F
Cl· HN
172.228
170.720
164.874
161.617
155.330
152.193
152.059
136.882
136.756
136.535
127.058
126.891
125.790
112.782
110.633
105.027
75.721
50.547
45.594
44.406
42.991
42.231
39.367
36.771
32.927
30.785
30.397
30.131
29.877
29.543
28.562
24.237
200
180
160
140
120
100
80
60
40
20
ppm

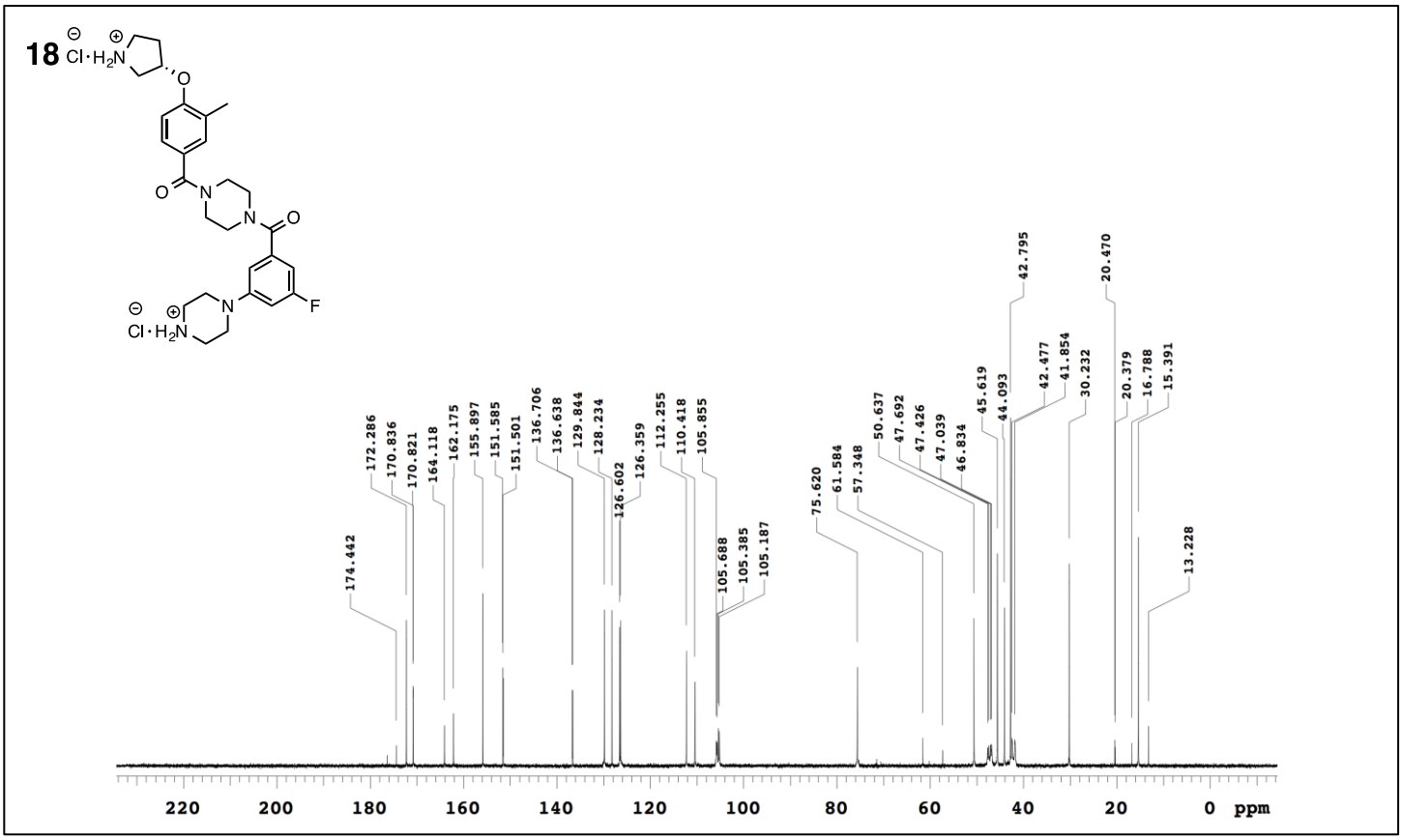

16
9.715
9.464
9.174
7.274
7.258
7.230
7.053
7.036
6.917
6.891
6.795
6.652
6.637
6.517
5.211
3.620
3.443
3.334
3.332
3.241
3.163
3.110
2.489
2.485
2.482
2.478
2.474
2.186
2.165
2.139
2.068
2.001
1.888
1.843
1.820
1.794
1.769
1.573
9
8
7
6
5
4
3
2
ppm
1.69
2.85
1.66
1.20
1.30
1.29
1.29
1.21
1.16
1.25
2.61
6.67
4.51
5.35
2.98
2.62
3.03

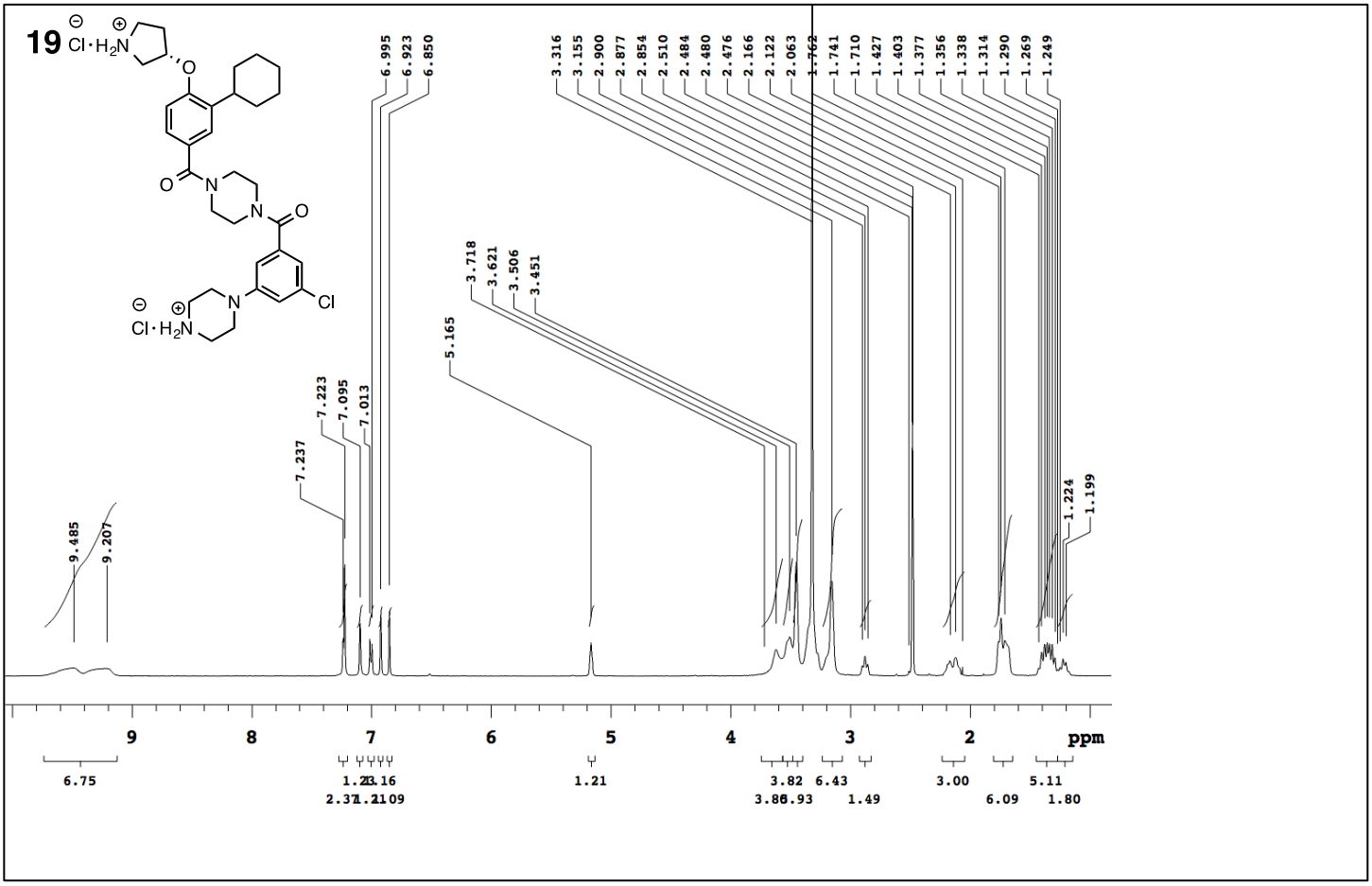

16
172.575
171.193
164.270
162.319
155.168
151.851
151.767
136.744
136.668
134.915
127.012
126.678
126.610
126.192
124.720
124.689
122.799
112.475
110.509
110.494
106.015
105.840
105.597
105.392
90.468
75.787
71.581
62.532
60.308
50.660
47.813
47.540
47.153
46.933
45.741
44.374
42.871
42.606
42.499
41.991
34.559
33.496
33.511
33.314
33.117
33.139
30.513
28.433
28.349
28.281
220
200
180
160
140
120
100
80
60
40
20
0
ppm

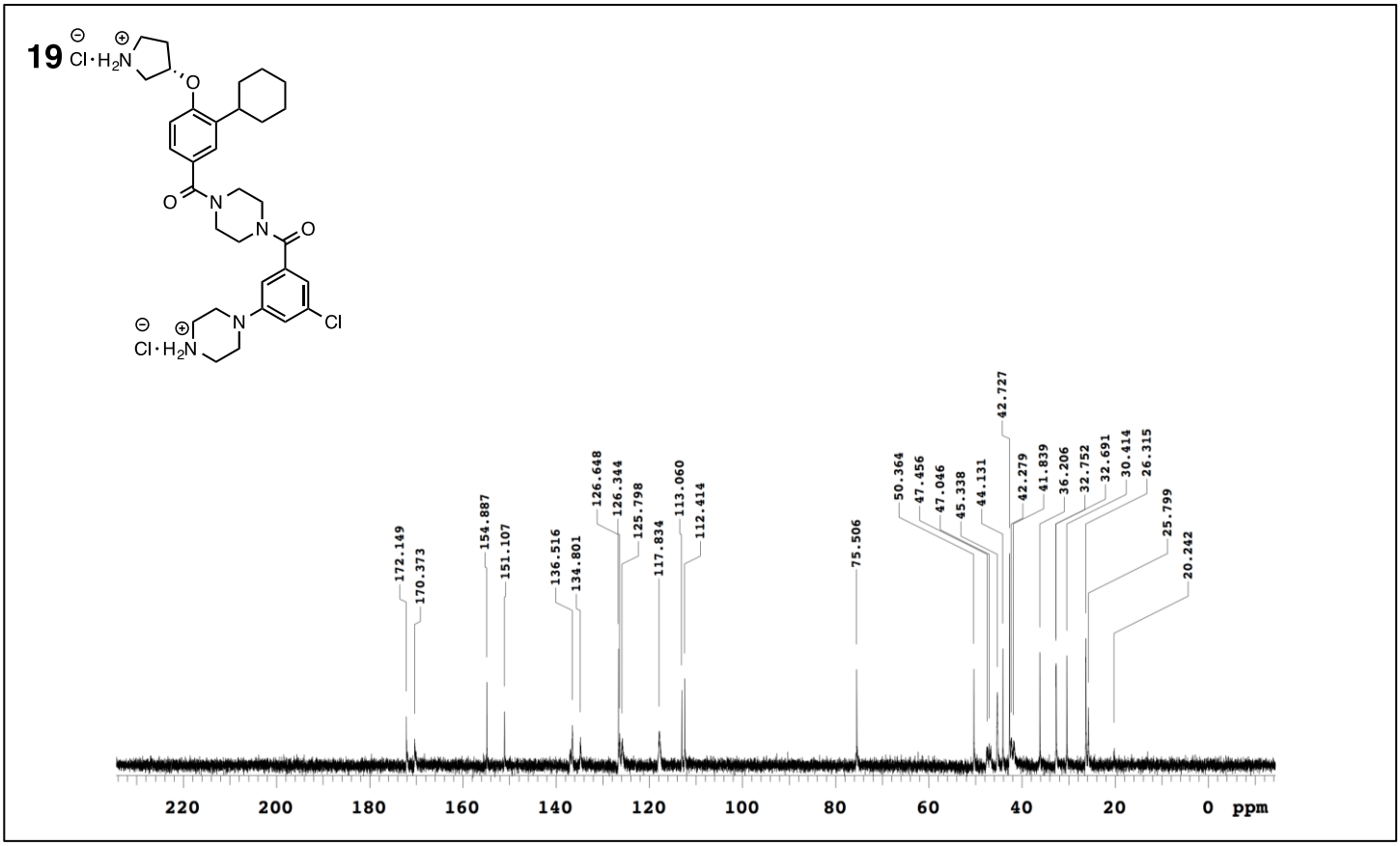

17
Cl·H2N
O
N
O
N
O
F
Cl· HN
9.273
9.011
7.254
7.248
7.230
7.009
6.992
6.920
6.895
6.798
6.659
6.644
6.518
5.177
3.618
3.505
3.435
3.334
3.277
3.258
3.243
3.225
3.174
2.617
2.486
2.482
2.478
2.475
2.343
2.200
2.190
2.181
2.163
2.153
2.130
1.936
1.888
1.736
1.721
1.629
1.621
1.616
1.606
1.485
9
8
7
6
5
4
3
2
ppm
4.93
4.27
3.22
2.33
2.01
1.89
1.83
1.06
1.98
6.66
6.28
11.50
4.97
3.85
4.57
5.31
4.23
1.74

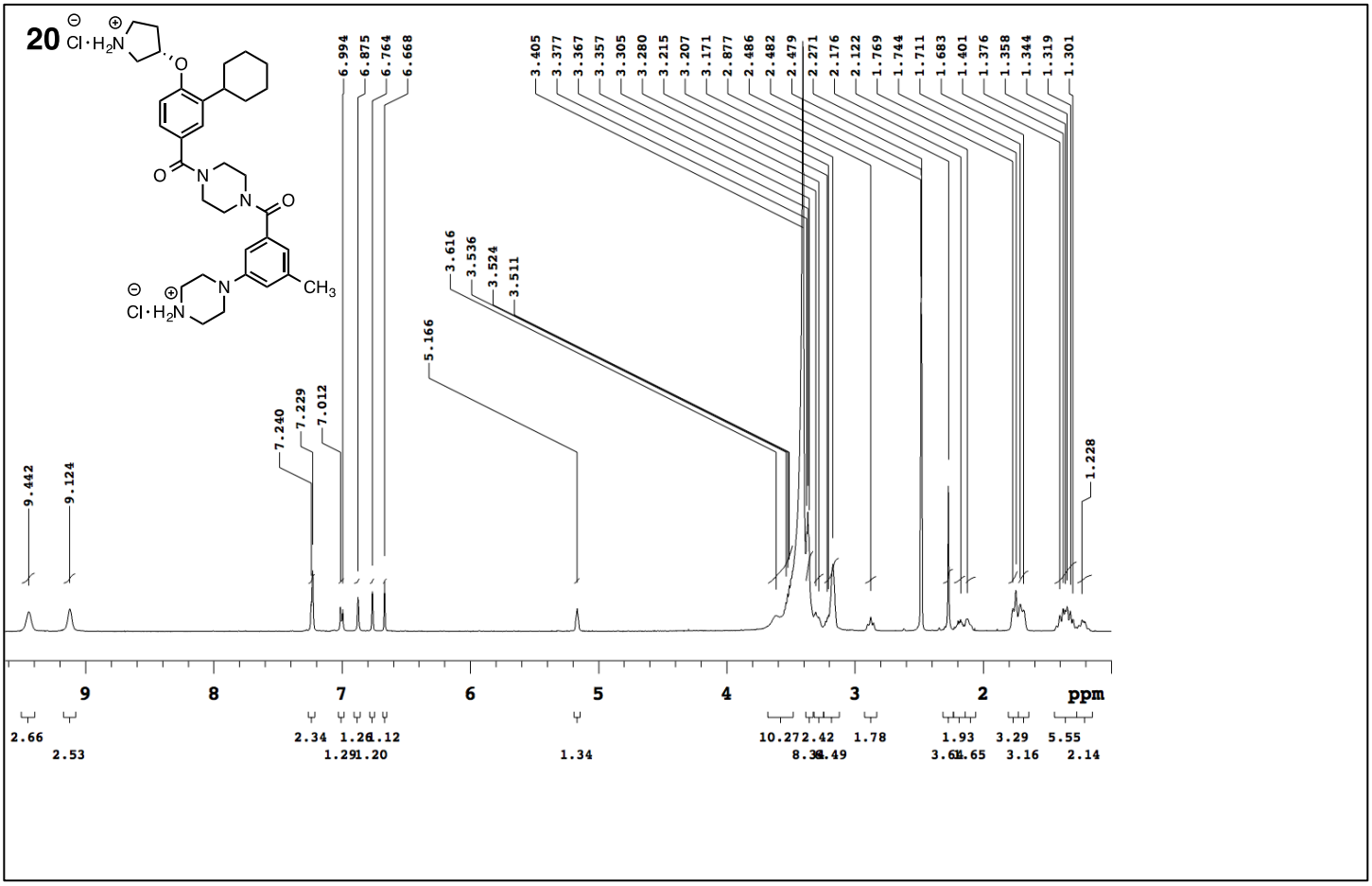

17
Cl·H2N
O
N
O
N
O
F
Cl· HN
172.636
171.161
155.743
152.006
151.872
136.836
136.716
136.288
126.885
126.417
112.509
110.633
105.721
75.828
50.753
45.781
44.433
42.985
42.077
38.493
32.773
32.660
30.591
30.364
25.145
200
180
160
140
120
100
80
60
40
20
ppm

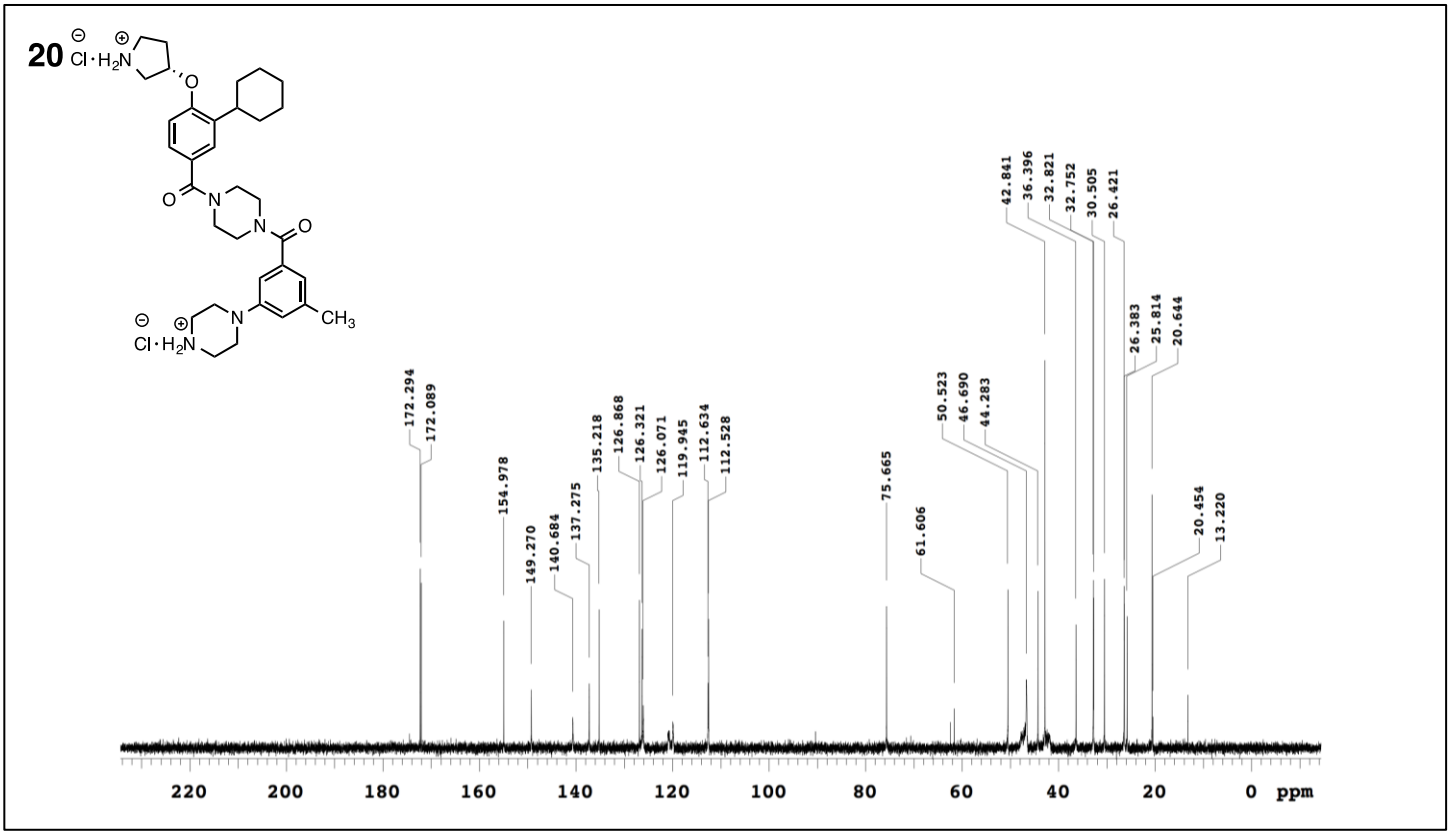

18
9.475
9.235
7.239
7.223
7.011
6.994
6.916
6.890
6.796
6.654
6.639
5.182
3.609
3.447
3.393
3.331
3.256
3.161
2.485
2.482
2.478
2.163
9
8
7
6
5
4
3
ppm
1.76
1.88
1.35
0.53
0.90
0.91
0.97
0.94
1.06
7.22
1.84
0.74
3.80
0.69
4.80

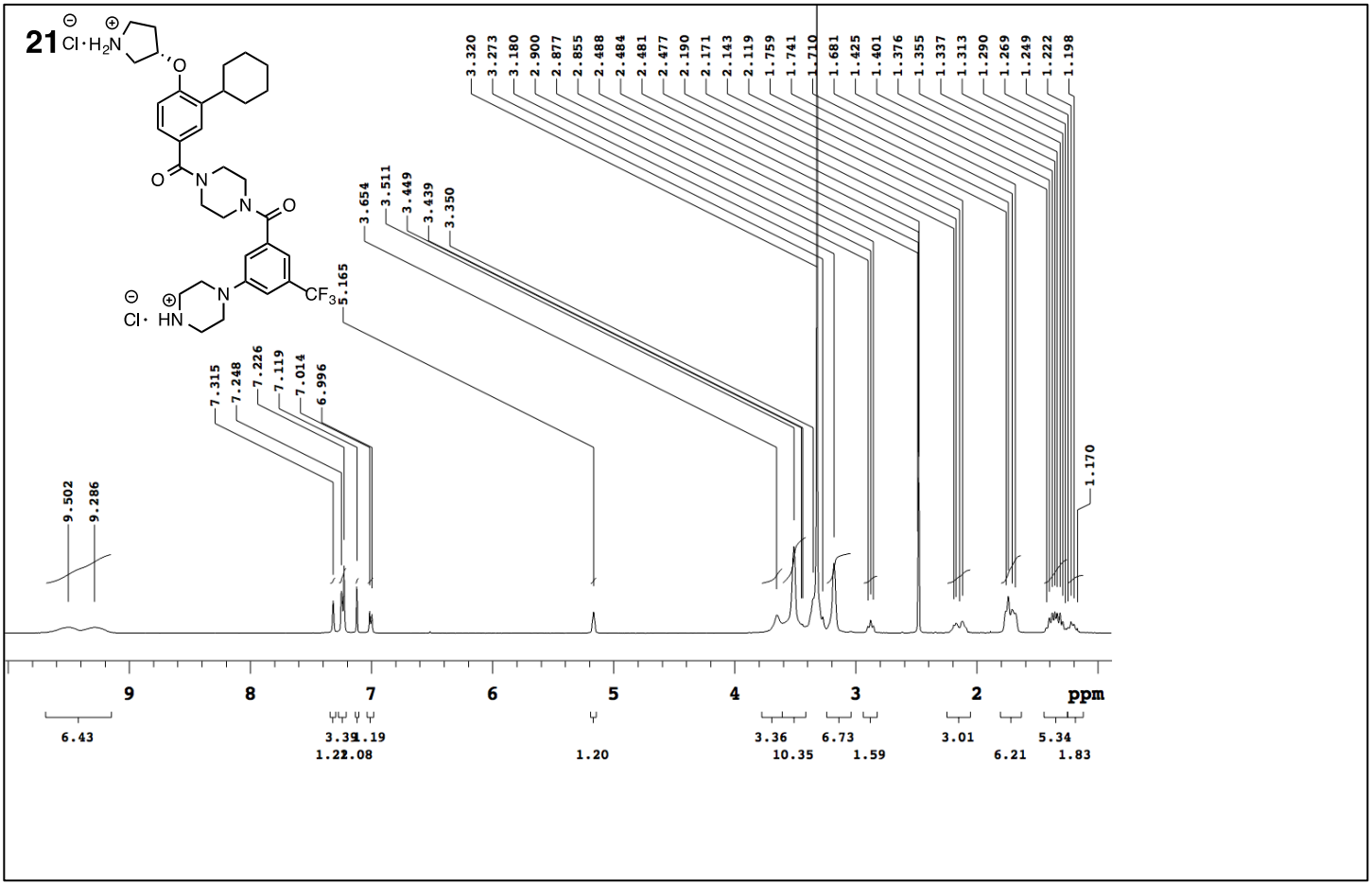

18
174.442
172.286
170.836
170.821
164.118
162.175
155.897
151.585
151.501
136.706
136.638
129.844
128.234
126.602
126.359
112.255
110.418
105.855
105.688
105.385
105.187
75.620
61.584
57.348
50.637
47.692
47.426
47.039
46.834
45.619
44.093
42.795
42.477
41.854
30.232
20.470
20.379
16.788
15.391
13.228
220
200
180
160
140
120
100
80
60
40
20
0
ppm


19
Cl·H2N
O
N
Cl
6.995
6.923
6.850
3.316
3.155
2.900
2.877
2.854
2.510
2.484
2.480
2.476
2.166
2.122
2.063
1.762
1.741
1.710
1.427
1.403
1.377
1.356
1.338
1.314
1.290
1.269
1.249
3.718
3.621
3.506
3.451
5.165
7.223
7.095
7.013
7.237
9.485
9.207
1.224
1.199
9
8
7
6
5
4
3
2
ppm
6.75
1.23
3.16
2.37
1.21
1.09
1.21
3.82
6.43
3.86
6.93
1.49
3.00
6.09
5.11
1.80


19
Cl·H2N
O
N
Cl
172.149
170.373
154.887
151.107
136.516
134.801
126.648
126.344
125.798
117.834
113.060
112.414
75.506
50.364
47.456
47.046
45.338
44.131
42.727
42.279
41.839
36.206
32.752
32.691
30.414
26.315
25.799
20.242
220
200
180
160
140
120
100
80
60
40
20
0
ppm


20
6.994
6.875
6.764
6.668
3.405
3.377
3.367
3.357
3.305
3.280
3.215
3.207
3.171
2.877
2.486
2.482
2.479
2.271
2.176
2.122
1.769
1.744
1.711
1.683
1.401
1.376
1.358
1.344
1.319
1.301
3.616
3.536
3.524
3.511
5.166
7.240
7.229
7.012
9.442
9.124
1.228
9
8
7
6
5
4
3
2
ppm
2.66
2.53
2.34
1.26
1.12
1.29
1.20
1.34
10.27
2.42
1.78
1.93
3.29
5.55
3.16
2.14


20
172.294
172.089
154.978
149.270
140.684
137.275
135.218
126.868
126.321
126.071
119.945
112.634
112.528
75.665
61.606
50.523
46.690
44.283
42.841
36.396
32.821
32.752
30.505
26.421
26.383
25.814
20.644
20.454
13.220
220
200
180
160
140
120
100
80
60
40
20
0
ppm


21
Cl·H2N
O
N
O
N
O
CF3
Cl· HN
3.320
3.273
3.180
2.900
2.877
2.855
2.488
2.484
2.481
2.477
2.190
2.171
2.143
2.119
1.759
1.741
1.710
1.681
1.425
1.401
1.376
1.355
1.337
1.313
1.290
1.269
1.249
1.222
1.198
3.654
3.511
3.449
3.439
3.350
5.165
7.315
7.248
7.226
7.119
7.014
6.996
9.502
9.286
1.170
9
8
7
6
5
4
3
2
ppm
6.43
3.39
1.19
1.22
2.08
1.20
3.36
6.73
3.01
5.34
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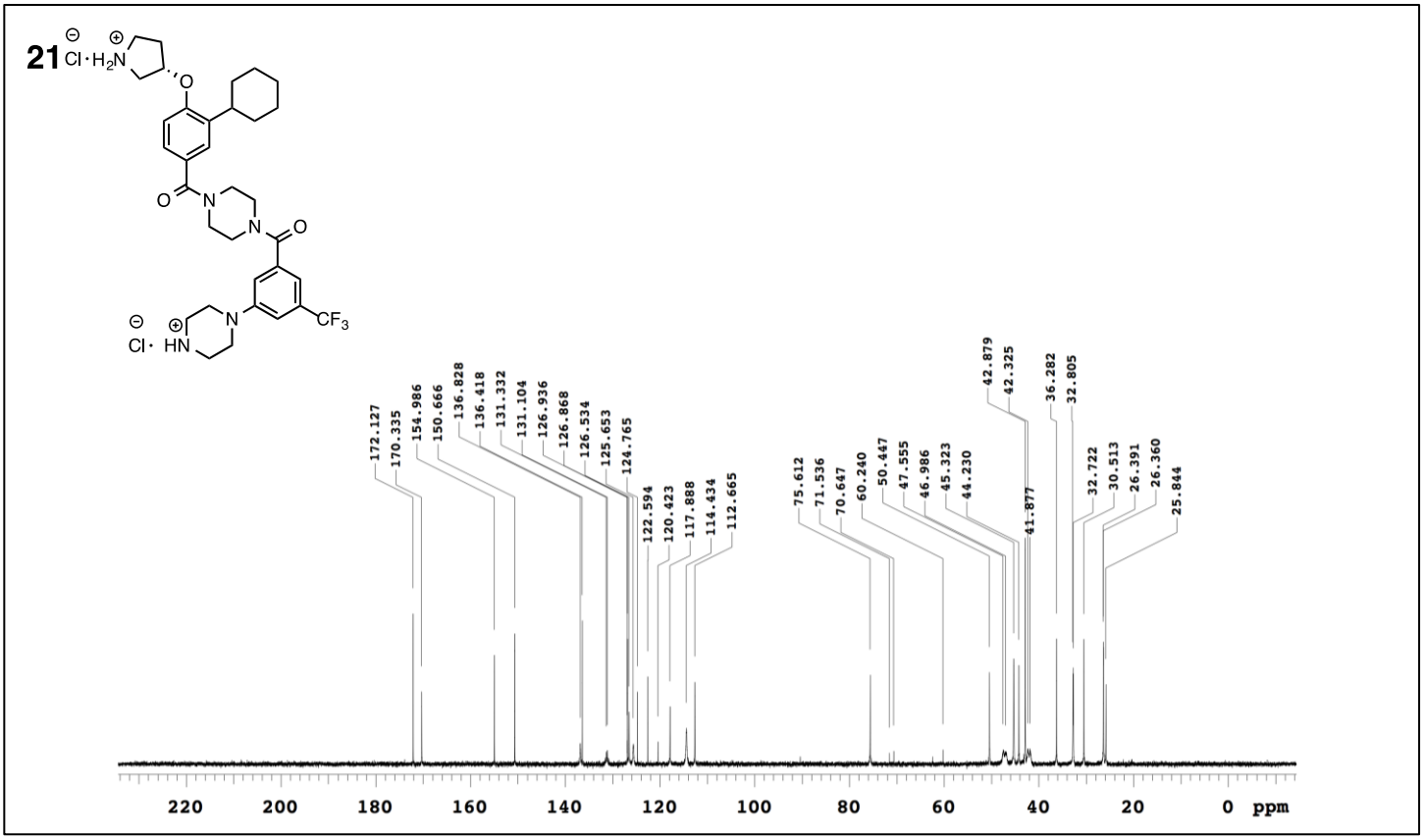
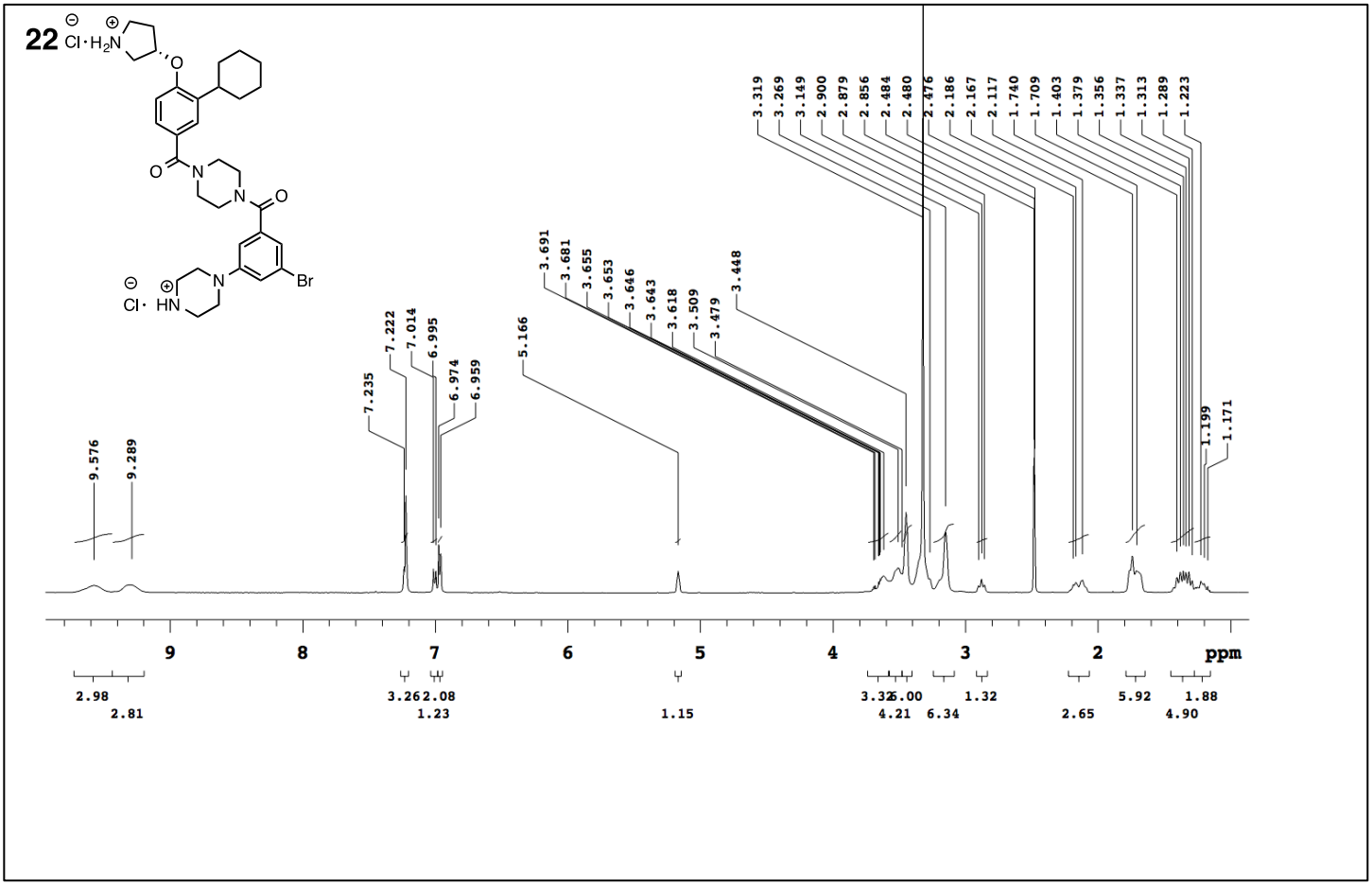
1.59
6.21
1.83


21
Cl·H2N
O
N
O
N
O
CF3
Cl· HN
172.127
170.335
154.986
150.666
136.828
136.418
131.332
131.104
126.936
126.868
126.534
125.653
124.765
122.594
120.423
117.888
114.434
112.665
75.612
71.536
70.647
60.240
50.447
47.555
46.986
45.323
44.230
42.879
42.325
41.877
36.282
32.805
32.722
30.513
26.391
26.360
25.844
220
200
180
160
140
120
100
80
60
40
20
0
ppm


22
Cl·H2N
O
N
O
Br
Cl· HN
3.319
3.269
3.149
2.900
2.879
2.856
2.484
2.480
2.476
2.186
2.167
2.117
1.740
1.709
1.403
1.379
1.356
1.337
1.313
1.289
1.223
3.691
3.681
3.655
3.653
3.646
3.643
3.618
3.509
3.479
3.448
7.235
7.222
7.014
6.995
6.974
6.959
5.166
9.576
9.289
1.199
1.171
9
8
7
6
5
4
3
2
ppm
2.98
2.81
3.26
2.08
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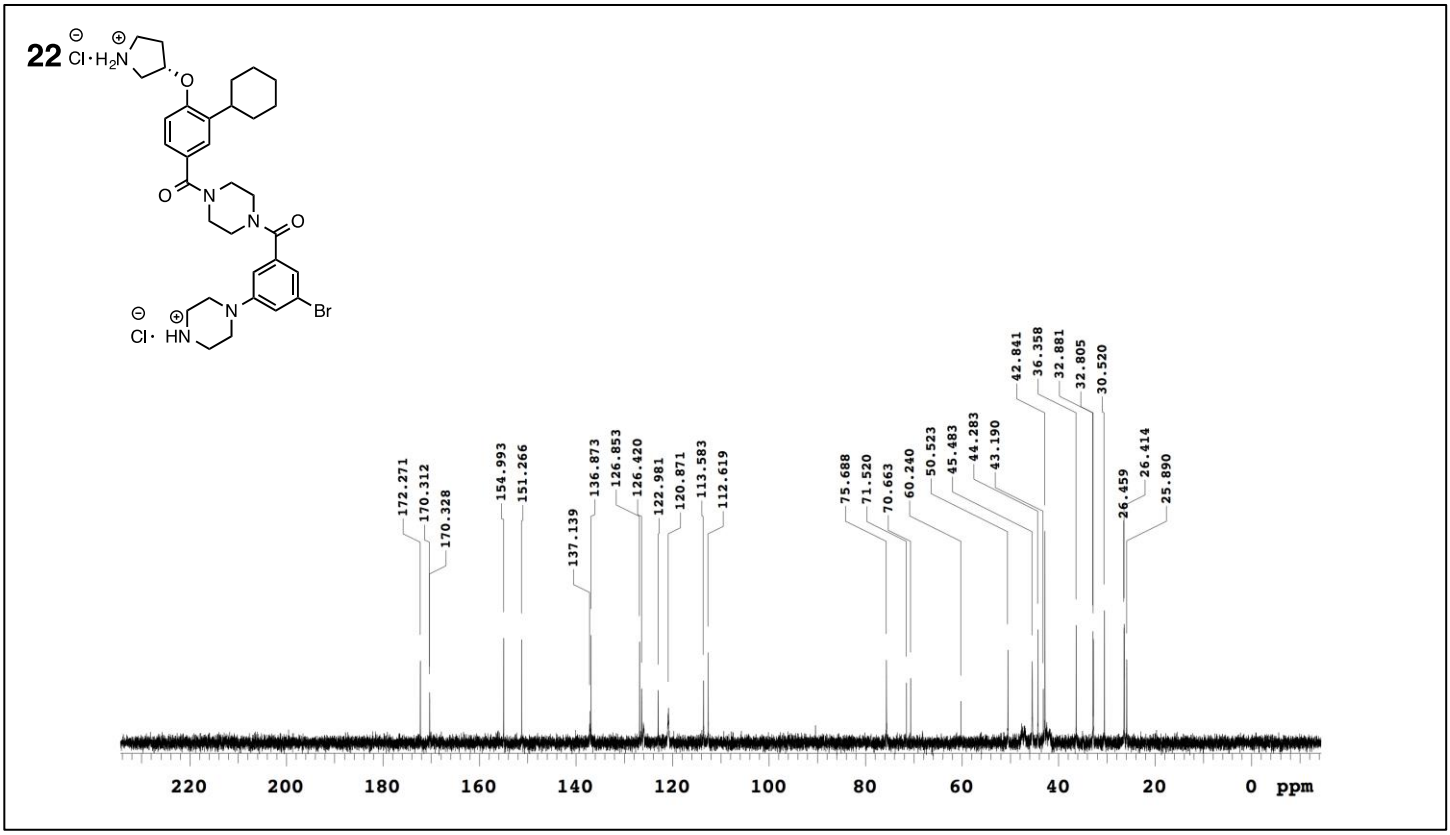
1.15
3.32
6.00
4.21
6.34
1.32
2.65
5.92
1.88
4.90


22
Cl·H2N
O
N
O
Br
Cl· HN
42.841
36.358
32.881
32.805
30.520
26.459
26.414
25.890
50.523
45.483
44.283
43.190
75.688
71.520
70.663
60.240
172.271
170.312
170.328
154.993
151.266
137.139
136.873
126.853
126.420
122.981
120.871
113.583
112.619
220
200
180
160
140
120
100
80
60
40
20
0
ppm