Supporting Information

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Selective N-terminal BET bromodomain inhibitors by targeting non-conserved residues and structured water displacement

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DOI: 10.1002/anie.2016XXXXX

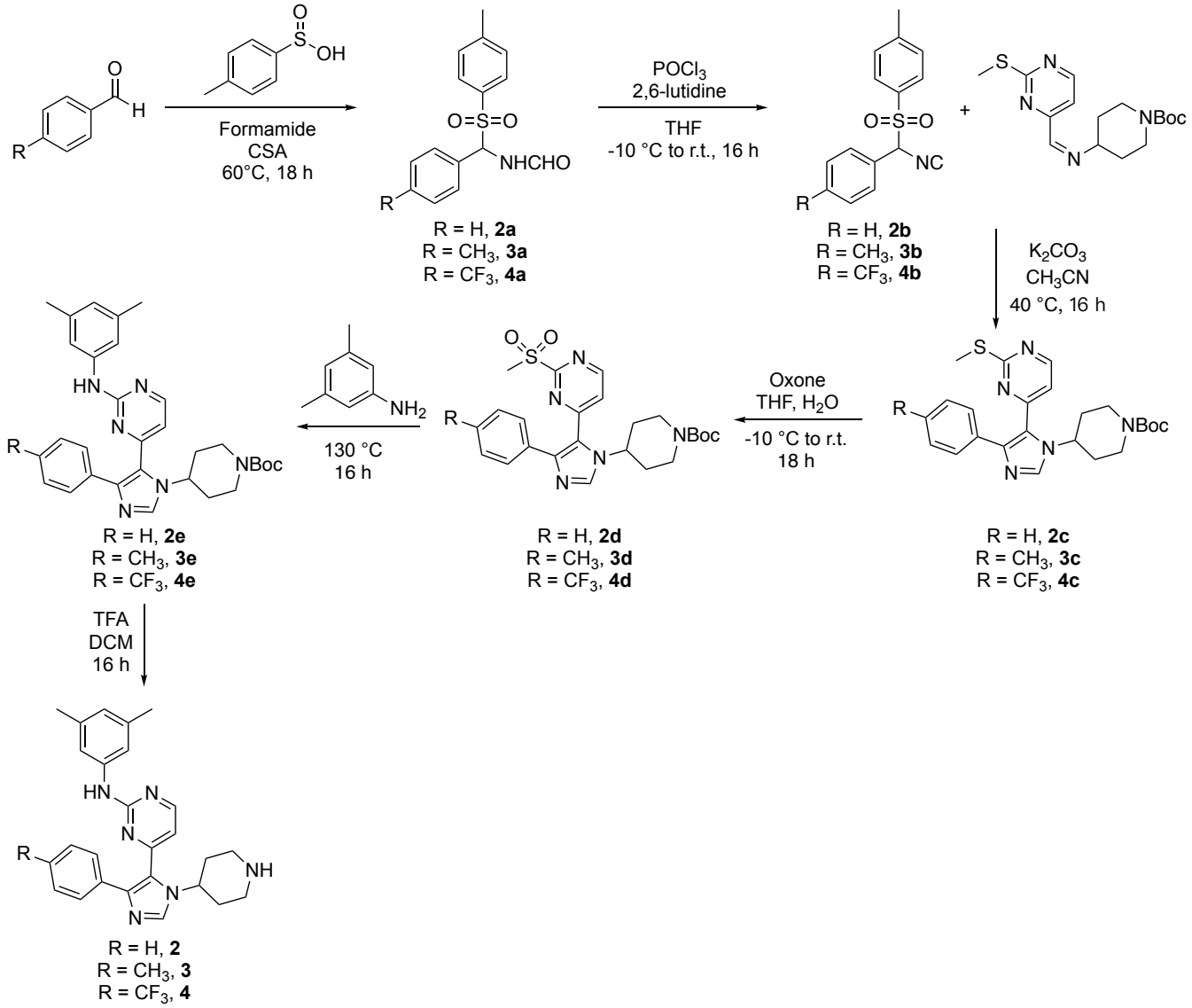
SUPPORTING INFORMATION

Table of Contents

SUPPORTING INFORMATION

General Synthetic Methods:

All chemicals were commercially available and used without further purification. Flash column chromatography was performed on a Teledyne-Isco Rf-plus CombiFlash instrument with RediSep columns. Spectra were collected on a Bruker Avance III HD 500 or a Bruker Avance III HD 400. Chemical shift (δ) are reported in parts per million (ppm) and referenced to residual solvent signal, ^{1}H 7.26 ppm, ^{13}C 77.0 ppm in $CDCl_3$; ^{1}H 3.32 ppm, ^{13}C 49.2 ppm in MeOD; ^{1}H 2.50 ppm, ^{13}C 39.5 ppm in DMSO-d_6. Coupling constants (J) are in Hz. Splitting patterns are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). High resolution mass spectrometry was used with positive-mode electrospray-ionization methods (ESI-MS) by a Bruker BioTOF II. Purities of compound **2-10** were checked by reverse-phase high-performance liquid chromatography (RP-HPLC) with a C-18 column and 10-60% 0.1% TFA water and acetonitrile over 60 min.



Scheme S1. Synthesis of compounds 2-4.

General procedure for preparation of *N*-((4-substituted-phenyl)(tosyl)methyl)formamide (2a-4a).
A mixture of a para-substituted benzaldehyde (8.3 mmol, 1.5 equiv.); p-methylbenzenesulfinic acid (5.7 mmol, 1.0 equiv.); camphorsulfonic acid (0.68 mmol, 0.12 equiv.) and formamide (20 mmol, 3.5 equiv.) was stirred at 60 ˚C for 18 h. The resulting solid was resuspended in hexane/methanol (4:1, 20 mL) for 30 min. The suspension was filtered and dried to give compound **2a-4a**.

2a (0.60 g, 2.1 mmol) was isolated as a white solid. The crude product was carried on without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.77 (dd, J = 10.5, 1.5 Hz, 1H), 7.97 (d, J = 1.4 Hz, 1H), 7.77 – 7.68 (m, 2H), 7.57 – 7.53 (m, 2H), 7.45 – 7.42 (m, 5H), 6.39 (d, J = 10.5 Hz, 1H), 2.42 (s, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.3, 144.8, 133.4, 130.3, 129.6, 129.5, 129.2, 128.3, 70.2, 21.2.

3a (1.2 g, 4.0 mmol) was isolated as a white solid. The crude product was carried on without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.72 (dd, J = 10.4, 1.6 Hz, 1H), 7.95 (d, J = 1.4Hz 1H), 7.74 – 7.68 (m, 2H), 7.43 (d, J = 8.0 Hz, 4H), 7.24 (d, J = 7.9 Hz, 2H), 6.33 (d, J = 10.5 Hz, 1H), 2.41 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.2, 144.7, 139.0, 133.5, 129.6, 129.3, 129.1, 128.8, 127.3, 70.0, 21.1, 20.8.

4a (0.79 g, 2.2 mmol) was isolated as a white solid. The crude product was carried on without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.89 (dd, J = 10.4, 1.5 Hz, 1H), 8.03 – 7.94 (m, 2H), 7.84 (s, 4H), 7.79 – 7.76 (m, 2H), 7.46 (d, J = 8.0 Hz, 3H), 6.61 (d, J = 10.5 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.9, 160.4, 145.1, 135.0, 133.2, 130.4, 129.7, 129.3, 125.4 – 125.1 (m), 69.6, 21.2.
^{19}F NMR (470 MHz, DMSO-d_6O) δ -61.18.

General procedure for preparation of 1-substituted-4-(isocyano(tosyl)methyl)benzene.(2b-4b)
$POCl_3$ (6.6 mmol, 2.0 equiv.) was added drop-wise to a solution of **2a-4a**, (3.3 mmol, 1.0 equiv.) in anhydrous THF at -10 °C, followed by 2,6-lutidine (20 mmol, 6.0 equiv.). The reaction was warmed to room temperature and stirred for 16 h. The reaction was quenched by saturated NH_4Cl. The aqueous phase was extracted with ethyl acetate (3 x 40 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel chromatography using hexane and ethyl acetate (0-100%) as eluent to give the desired products **2b-4b**.

2b (0.75 g, 2.8 mmol, 85%) was isolated as a brown solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.68 – 7.56 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.23 – 7.16 (m, 4H), 5.56 (s, 1H), 2.47 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 165.9, 146.6, 141.2, 130.7, 130.3, 129.88, 129.6, 128.5, 123.6, 76.5, 21.9, 21.5.

3b (0.76 g, 2.7 mmol, 81%) was isolated as a brown solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.68 – 7.56 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.23 – 7.16 (m, 4H), 5.56 (s, 1H), 2.47 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 165.9, 146.6, 141.2, 130.7, 130.3, 129.9, 129.6, 128.5, 123.6, 76.5, 21.9, 21.5.

4b (0.89 g, 2.6 mmol, 79 %) was isolated as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.73 – 7.65 (m, 4H), 7.53 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 5.68 (s, 1H), 2.51 (s, 3H). ^{13}C NMR (125 MHz, Chloroform-d) δ 167.2, 147.3, 130.6, 130.1, 129.9, 129.1, 125.9 (q, J = 3.7 Hz), 75.9, 22.0. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.95.

General procedure for preparation of *tert*-butyl 4-(4-(4-substituted-phenyl)-5-(2-(methylthio)pyrimidin-4-yl)-1*H*-imidazol-1-yl)piperidine-1-carboxylate.(2c-4c)
A mixture of **2b-4b** (1.2 mmol, 1.0 equiv.), tert-butyl 4-(((2-(methylthio)pyrimidin-4-yl)methylene)-amino)piperidine-1-carboxylate (1.2 mmol, 1.0 equiv.) and potassium carbonate (4.8 mmol, 4.0 equiv.) in acetonitrile (3.9 mL) was stirred at 40 °C for 16 h. The reaction mixture was quenched by addition of brine and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel chromatography using hexane and ethyl acetate (0-100%) as eluent to give the desired product **2c-4c**.

2c (0.30 g, 0.66 mmol, 60 %) was isolated as a yellow solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.34 (d, J = 5.3 Hz, 1H), 7.80 (s, 1H), 7.50 – 7.46 (m, 2H), 7.37 – 7.33 (m, 3H), 6.84 (d, J = 5.2 Hz, 1H), 4.95 – 4.84 (m, 1H), 4.33 (s, 2H), 2.89 – 2.78 (m, 2H), 2.62 (s, 3H), 2.20 (dq, J = 12.0, 2.3 Hz, 2H), 1.90 (tt, J = 12.3, 6.1 Hz, 2H), 1.51 (s, 10H). ^{13}C NMR (125 MHz, Chloroform-d) δ 172.8, 158.0, 157.1, 154.6, 144.7, 136.6, 134.3, 128.7, 128.7, 128.1, 124.1, 117.2, 80.2, 54.4, 43.4(br), 33.6, 28.5, 14.2. HRMS (ESI-TOF) m/z [M + Na]+ calcd. for $C_{24}H_{29}N_5NaO_2S^+$ 474.1934, found 474.1933.

3c (0.22 g, 0.48 mmol, 40 %) was isolated as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.31 (d, J = 5.2 Hz, 1H), 7.75 (s, 1H), 7.37 – 7.32 (m, 2H), 7.14 (d, J = 7.8 Hz, 2H), 6.84 (d, J = 5.2 Hz, 1H), 4.88 (tt, J = 12.0, 3.7 Hz, 1H), 4.30 (s, 2H), 2.85 – 2.73 (m, 1H), 2.59 (s, 3H), 2.36 (s, 3H), 2.17 (dt, J = 12.5, 2.6 Hz, 2H), 1.86 (qd, J = 12.3, 4.3 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR (125 MHz, Chloroform-d) δ 172.7, 158.1, 157.0, 154.7, 144.9, 137.9, 136.5, 131.4, 129.4, 128.6, 117.1, 80.2, 54.4, 43.4, 33.6, 28.5, 21.4, 14.2. HRMS (ESI-TOF) m/z [M + Na]+ calcd. for $C_{25}H_{31}N_5NaO_2S^+$ 488.2091, found 488.2102.

4c (0.49 g, 0.94 mmol, 79 %) was isolated as a yellow solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.34 (d, J = 5.3 Hz, 1H), 7.80 (s, 1H), 7.50 – 7.46 (m, 2H), 7.37 – 7.33 (m, 3H), 6.84 (d, J = 5.2 Hz, 1H), 4.95 – 4.84 (m, 1H), 4.33 (s, 2H), 2.89 – 2.78 (m, 2H), 2.62 (s, 3H), 2.20 (dq, J = 12.0, 2.3 Hz, 2H), 1.90 (tt, J = 12.3, 6.1 Hz, 2H), 1.51 (s, 10H). ^{13}C NMR (125 MHz, Chloroform-d) δ 172.8, 158.0, 157.1, 154.6, 144.7, 136.6, 134.3, 128.7, 128.7, 128.1, 124.1, 117.2, 80.2, 54.4, 43.4(br), 33.6, 28.5, 14.2. ^{19}F NMR (470 MHz, CDCl3) δ -62.52. HRMS (ESI-TOF) m/z [M + Na]+ calcd. for $C_{25}H_{28}F_3N_5NaO_2S^+$ 542.1808, found 542.1818.

General procedure for preparation of *tert*-butyl 4-(4-(4-substituted-phenyl)-5-(2-(methylsulfonyl)pyrimidin-4-yl)-1*H*-imidazol-1-yl)piperidine-1-carboxylate. (2d-4d)
A solution of oxone (1.1 mmol, 2.4 equiv.) in water (8.5 mL) was added dropwise to a solution of **2c-4c** (0.45 mmol, 1.0 equiv.) in THF (6.0 mL) at -10 °C. The reaction mixture was stirred at room temperature for 16 h and then quenched by water and extracted with DCM (3 x 30 mL). The combined organic phase was washed with brine and concentrated under reduced pressure to give the product.

2d (0.21 g, 0.43 mmol, 95 %) was isolated as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.54 (d, J = 5.4 Hz, 1H), 7.86 (s, 1H), 7.49 – 7.45 (m, 2H), 7.40 (ddt, J = 4.2, 3.0, 1.6 Hz, 3H), 7.31 (d, J = 5.4 Hz, 1H), 5.09 (tt, J = 12.0, 3.7 Hz, 1H), 4.37 – 4.24 (m, 2H), 3.38 (s, 3H), 2.95 (s, 2H), 2.32 – 2.21 (m, 2H), 1.88 – 1.82 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-d) δ 166.1, 159.6, 157.2, 154.7, 147.6, 138.2, 134.0, 129.1, 128.8, 122.8, 80.0, 55.5, 43.3(br), 39.2, 33.7(br), 28.5.

3d (0.20 g, 0.41 mmol, 90 %) was isolated as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.53 (d, J = 5.4 Hz, 1H), 7.85 (s, 1H), 7.37 – 7.33 (m, 3H), 7.20 (d, J = 7.8 Hz, 2H), 5.09 (tt, J = 11.9, 3.7 Hz, 1H), 4.31 (s, 2H), 3.38 (s, 3H), 2.95 (s, 2H), 2.39 (s, 3H), 1.96

– 1.81 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-d) δ 166.0, 159.7, 157.1, 154.7, 147.8, 138.8, 138.2, 131.1, 129.8, 128.7, 122.8, 80.0, 68.1, 55.5, 43.3 (br), 39.2, 33.8 (br), 28.5, 21.4.

4d (0.24 g, 0.44 mmol, 98 %) was isolated as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.63 (d, J = 5.4 Hz, 1H), 7.89 (s, 1H), 7.63 (q, J = 8.4 Hz, 5H), 7.31 (d, J = 5.4 Hz, 1H), 5.02 (tt, J = 12.2, 3.7 Hz, 1H), 3.40 (s, 3H), 2.94 (s, 2H), 2.25 (s, 2H)1.87 (d, J = 13.4 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR (125 MHz, Chloroform-d) δ 166.4, 159.3, 157.7, 154.7, 145.4, 138.4, 137.6, 129.1, 126.0 (q, J = 3.7 Hz), 123.0, 80.1, 55.6, 43.1(br), 39.1, 33.9(br), 28.5. ^{19}F NMR (470 MHz, CDCl3) δ -62.63.

General procedure for preparation of *tert*-butyl 4-(5-(2-((3,5-dimethylphenyl)amino)pyrimidin-4-yl)-4-(4-substituted-phenyl)-1*H*-imidazol-1-yl)piperidine-1-carboxylate.
A mixture of **2d-4d** (0.26 mmol, 1.0 equiv.) and 3,5-dimethylaniline (1.3 mmol, 5.0 equiv.) were heated in a sealed tube at 130 °C for 16 h behind a blast shield. The crude product was obtained as a brown oil, which was purified by silica gel chromatography using hexane and ethyl acetate (0-100%) as eluent to give the desired products **2e-4e**.

2e (68 mg, 0.13 mmol, 50%) was isolated as a brown solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.24 (d, J = 5.1 Hz, 1H), 7.73 (s, 1H), 7.55 – 7.51 (m, 2H), 7.34 – 7.30 (m, 3H), 7.22 – 7.18 (m, 2H), 7.09 (s, 1H), 6.75 (d, J = 2.1 Hz, 1H), 6.59 (d, J = 5.1 Hz, 1H), 4.83 (tt, J = 12.1, 3.7 Hz, 1H), 2.44 (t, J = 12.5 Hz, 2H), 2.32 (s, 6H), 2.07(s, 2H), 1.79 (tt, J = 12.8, 6.4 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, Chloroform-d) δ 160.5, 158.7, 158.3, 154.6, 143.5, 138.9, 138.6, 136.0, 134.4, 128.6, 128.5, 127.8, 125.3, 118.4, 113.7, 80.1, 53.8, 43.1(br), 33.5, 28.5, 21.5.

3e (64 mg, 0.12 mmol, 46%) was isolated as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.23 (d, J = 5.1 Hz, 1H), 7.72 (s, 1H), 7.43 – 7.39 (m, 2H), 7.31 (s, 1H), 7.21 – 7.18 (m, 2H), 7.15 – 7.11 (m, 2H), 6.75 – 6.72 (m, 1H), 6.60 (d, J = 5.1 Hz, 1H), 4.84 (tt, J = 12.0, 3.7 Hz, 1H), 2.48 – 2.38 (m, 2H), 2.36 (s, 3H), 2.31 (s, 6H), 2.03 (d, J = 6.6 Hz, 2H), 1.78 (td, J = 12.3, 4.3 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-d) δ 160.5, 158.8, 158.2, 154.6, 143.7, 139.0, 138.7, 137.6, 135.9, 131.5, 129.3, 128.5, 125.3, 118.4, 113.7, 80.1, 53.8, 43.1(br), 33.5, 28.5, 21.6, 21.4.

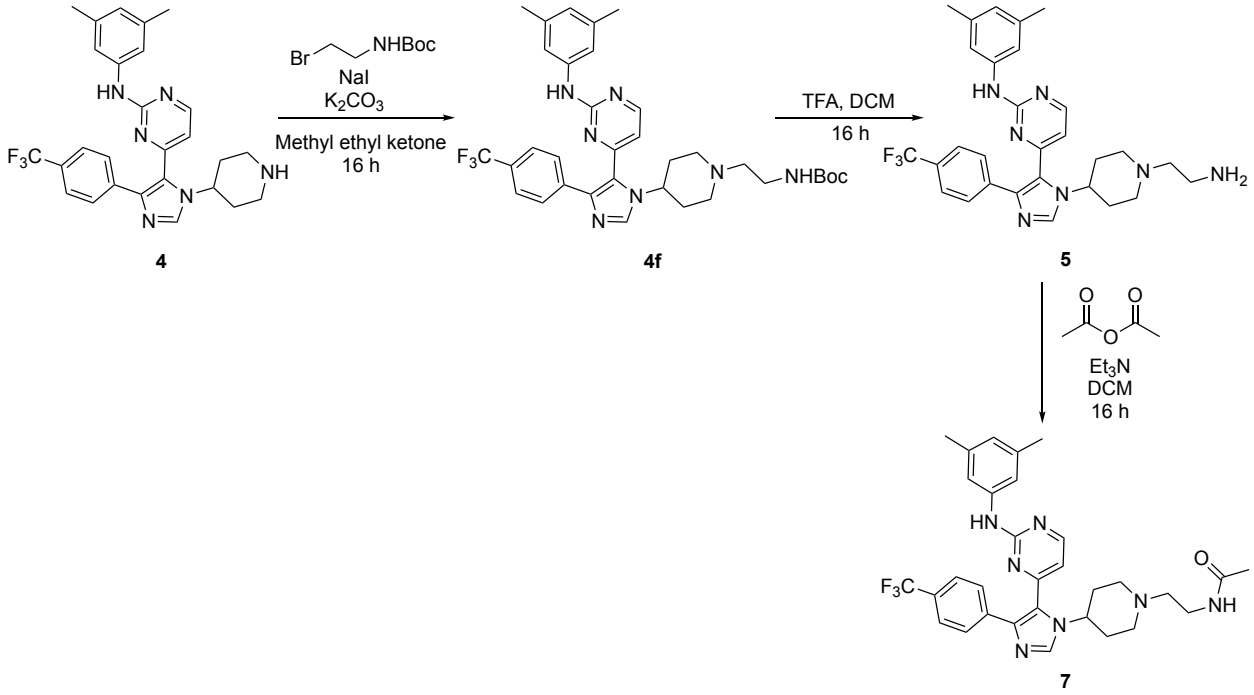
4e (69 mg, 0.12 mmol, 45%) was isolated as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 5.0 Hz, 1H), 7.75 (s, 1H), 7.68 – 7.63 (m, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.22 – 7.18 (m, 2H), 7.09 (s, 1H), 6.78 – 6.74 (m, 1H), 6.58 (d, *J* = 5.0 Hz, 1H), 4.75 (tt, *J* = 12.1, 3.8 Hz, 1H), 2.45 (d, *J* = 9.2 Hz, 2H), 2.32 (s, 5H), 2.07 (s, 1H), 1.87 – 1.71 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, Chloroform-d) δ 160.7, 158.8, 158.3, 154.6, 141.5, 138.8, 138.7, 138.0, 136.2, 128.6, 125.5 (q, J = 4.5 Hz), 118.5, 113.7, 80.2, 53.9, 43.1(br), 33.5, 28.50, 21.54. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.46.

General procedure for preparation of *N*-(3,5-dimethylphenyl)-4-(1-(piperidin-4-yl)-4-(4-substituted-phenyl)-1*H*-imidazol-5-yl)pyrimidin-2-amine.
Trifluoroacetic acid (TFA) (0.50 mL) was added to a solution of **2e-4e** (0.13 mmol) in DCM (0.50 mL). After 16 h, the reaction was concentrated under reduced pressure. Cold ether (4.0 mL) was used to precipitate out the desired product **2-4**.

2 (92 mg, 0.12 mmol, 95%) was isolated as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 8.97 (s, 1H), 8.35 (d, *J* = 5.1 Hz, 1H), 7.50 (s, 5H), 7.27 – 7.19 (m, 2H), 6.79 (tt, *J* = 1.5, 0.8 Hz, 1H), 6.57 (d, *J* = 5.1 Hz, 1H), 5.08 (ddt, *J* = 12.2, 8.5, 3.8 Hz, 1H), 3.46 – 3.38 (m, 2H), 2.77 (t, *J* = 13.0 Hz, 2H), 2.48 (d, *J* = 13.3 Hz, 2H), 2.34 – 2.29 (m, 6H), 2.27 – 2.18 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ 162.1, 160.3, 156.5, 140.3, 139.6, 137.3, 136.4, 131.2, 130.4, 130.0, 129.3, 126.4, 120.5, 114.1, 54.5, 44.3, 30.7, 21.5. HRMS (ESI-TOF) m/z [M + Na]+ calcd. for $C_{26}H_{29}N_6^+$ 425.2448, found 425.2449.

3 (94 mg, 0.12 mmol, 96%) was isolated as a white solid. ^{1}H NMR (500 MHz, MeOD) δ 9.17 (d, *J* = 5.0 Hz, 1H), 8.35 (d, *J* = 5.0 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 3H), 7.32 (d, *J* = 8.0 Hz, 3H), 7.21 (s, 2H), 6.78 (s, 1H), 6.57 (d, *J* = 5.1 Hz, 1H), 5.08 (tt, *J* = 12.3, 3.8 Hz, 1H), 3.42 – 3.37 (m, 2H), 2.75 (t, *J* = 13.0 Hz, 2H), 2.47 (dt, *J* = 14.0, 2.8 Hz, 2H), 2.40 (s, 3H), 2.29 (s, 6H), 2.27 – 2.19 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ 162.2, 160.5, 156.3, 142.1, 140.4, 139.6, 136.2, 131.1, 129.9, 126.4, 120.5, 114.1, 54.8 (d, *J* = 40.0 Hz), 44.3, 30.7, 21.5, 21.4. HRMS (ESI-TOF) m/z [M + Na]+ calcd. for $C_{27}H_{31}N_6^+$ 439.2605, found 439.2605.

4 (86 mg, 0.12 mmol, 96%) was isolated as a white solid. ^{1}H NMR (500 MHz, MeOD) δ 8.87 (s, 1H), 8.36 (d, *J* = 5.1 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 1.6 Hz, 2H), 6.78 (s, 1H), 6.60 (d, *J* = 5.1 Hz, 1H), 4.99 (ddt, *J* = 12.1, 8.3, 3.8 Hz, 1H), 3.44 – 3.37 (m, 2H), 2.82 – 2.74 (m, 2H), 2.49 – 2.41 (m, 2H), 2.29 (s, 6H), 2.24 (td, *J* = 13.0, 3.9 Hz, 2H). ^{13}C NMR (125 MHz, MeOD) δ 161.9, 160.0, 157.2, 140.2, 139.6, 137.6, 137.4, 130.5, 127.1, 127.1, 127.0, 127.0, 126.4, 120.5, 114.1, 54.0, 44.3, 30.9, 30.8, 21.5.^{19}F NMR (376 MHz, MeOD) δ -64.28, -77.09. HRMS (ESI-TOF) m/z [M + Na]+ calcd. for $C_{27}H_{28}F_3N_6^+$ 493.2322, found 493.2348.

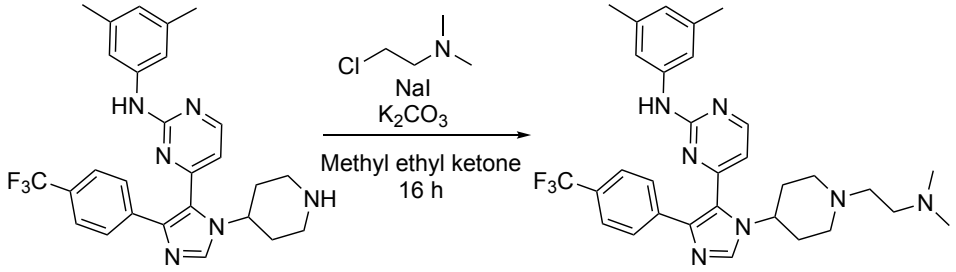


Scheme S2. Synthesis of compounds 5 and 7.

Procedure for preparation of *tert*-butyl (2-(4-(5-(2-((3,5-dimethylphenyl)amino)pyrimidin-4-yl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-1-yl)piperidin-1-yl)ethyl)carbamate(4f).
Compound **4** (0.11 mmol, 1.0 equiv.), 2-(Boc-amino)ethyl bromide (0.14 mmol, 1.3 equiv.), NaI (0.14 mmol, 1.3 equiv.) and K_2CO_3 (0.77 mmol, 7.0 equiv.) were dissolved in methyl ethyl ketone (0.37 mL). The reaction was stirred at room temperature for 16 h then quenched by water and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product, which was purified by silica gel chromatography using DCM and methanol (0-20%) as eluent to give the desired product **4f** (47 mg, 0.074 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 5.3 Hz, 1H), 7.80 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.21 (s, 2H), 7.07 (s, 1H), 6.75 (s, 1H), 6.58 (d, *J* = 5.0 Hz, 1H), 4.90 (s, 1H), 4.59 (tt, *J* = 11.9, 4.1 Hz, 1H), 3.19 (q, *J* = 5.9 Hz, 2H), 2.89 (d, *J* = 11.3 Hz, 2H), 2.38 (t, *J* = 6.1 Hz, 2H), 2.32 (s, 6H), 2.04 (d, *J* = 10.9 Hz, 2H), 1.95 (qd, *J* = 12.0, 3.6 Hz, 2H), 1.80 (t, *J* = 11.6 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 158.7, 158.5, 156.1, 141.3, 138.9, 138.7, 138.0, 136.3, 128.5, 125.5 – 125.3 (m), 118.4, 113.7, 57.1, 53.9, 52.6, 37.5, 33.6, 28.6, 21.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.45.

Procedure for preparation of 4-(1-(1-(2-aminoethyl)piperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)-*N*-(3,5-dimethylphenyl)pyrimidin-2-amine(5). TFA (0.30 mL) was added to a solution of **4f** (0.074 mmol) in DCM (0.30 mL). After 16 h, the reaction was concentrated under reduced pressure. Cold ether (3 mL) was used to precipitate out the desired product **5** (70 mg, 0.071 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 5.1 Hz, 1H), 7.80 (s, 1H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.22 (s, 1H), 7.20 (s, 2H), 6.75 (s, 1H), 6.57 (d, *J* = 5.0 Hz, 1H), 5.95 (s, 1H), 4.60 (tt, *J* = 11.8, 4.0 Hz, 1H), 3.30 (q, *J* = 5.6 Hz, 2H), 2.88 (d, *J* = 11.2 Hz, 2H), 2.39 (t, *J* = 6.0 Hz, 2H), 2.31 (s, 6H), 2.09 – 2.03 (m, 2H), 2.00 (s, 3H), 1.93 (qd, *J* = 12.2, 3.5 Hz, 2H), 1.79 (td, *J* = 11.8, 2.2 Hz, 2H). ^{13}C NMR (100 MHz, MeOD) δ 161.8, 160.0, 156.7, 140.2, 139.7, 137.2, 130.6, 127.2 (d, *J* = 3.8 Hz), 126.5, 120.3, 114.0, 54.3, 54.1, 53.2, 35.4, 31.0, 21.5. ^{19}F NMR (376 MHz, MeOD) δ -64.33, -77.27. HRMS (ESI-TOF) m/z [M + H]+ calcd. for $C_{29}H_{33}F_3N_7^+$ 536.2744, found 536.2749.

Procedure for preparation of *N*-(2-(4-(5-(2-((3,5-dimethylphenyl)amino)pyrimidin-4-yl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-1-yl)piperidin-1-yl)ethyl)acetamide(7).
5 (0.071mmol, 1.0 equiv.) was dissolved in DCM (0.70 mL), triethylamine (0.14mmol, 2.0 equiv.) was added dropwise followed by acetic anhydride (0.35 mmol, 5.0 equiv.). The reaction was stirred at room temperature for 16 h and then quenched by water and extracted by ethyl acetate (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product, which was purified by silica gel chromatography using DCM and methanol (0-20%) as eluent to give the desired product **7** (40 mg, 0.070 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 5.0 Hz, 1H), 7.80 (s, 1H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.20 (s, 2H), 6.74 (s, 1H), 6.57 (d, *J* = 5.2 Hz, 1H), 5.94 (d, *J* = 5.3 Hz, 1H), 4.60 (tt, *J* = 12.2, 4.1 Hz, 1H), 3.30 (q, *J* = 5.7 Hz, 2H), 2.90 – 2.84 (m, 2H), 2.39 (t, *J* = 6.1 Hz, 2H), 2.30 (s, 5H), 2.08 – 2.01 (m, 2H), 2.00 (s, 3H), 1.92 (qd, *J* = 12.1, 3.5 Hz, 2H), 1.79 (t, *J* = 11.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 160.7, 158.8, 158.4, 141.4, 138.8, 138.7, 138.0, 136.2, 128.5, 126.1, 125.5 (dd, *J* = 8.6, 4.5 Hz), 118.4, 113.7, 56.5, 53.9, 52.6, 36.4, 33.6, 23.5, 21.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.45. Final compound failed to ionize by ESI-MS.

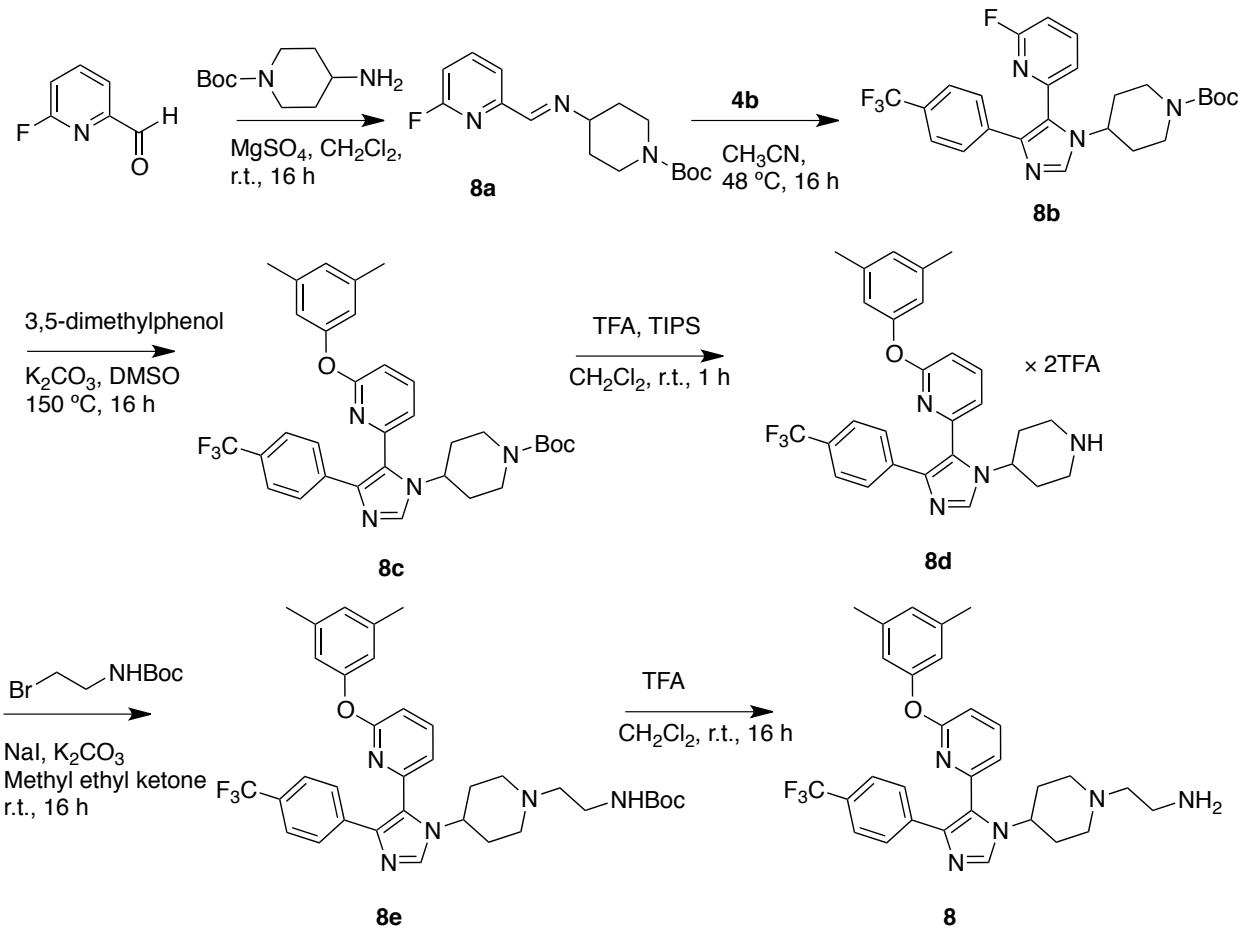


4 **6**

Scheme S3. Synthesis of compound 6.

Procedure for preparation of 4-(1-(1-(2-(dimethylamino)ethyl)piperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)-*N*-(3,5-dimethylphenyl)pyrimidin-2-amine (6).

Compound **4** (0.11 mmol, 1.0 equiv.), 2-Chloro-*N,N*-dimethylethylamine hydrochloride (0.17 mmol, 1.5 equiv.), NaI (0.17 mmol, 1.5 equiv.) and K_2CO_3 (0.77 mmol, 7.0 equiv.) were dissolved in methyl ethyl ketone (0.37 mL). The reaction was stirred at room temperature for 16 h then quenched by water and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product, which was purified by neutral alumina chromatography using ethyl acetate and methanol (0-20%) as eluent to give the desired product **6** (25 mg, 0.044 mmol, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 5.4 Hz, 1H), 7.79 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.22 (s, 2H), 7.07 (s, 1H), 6.75 (s, 1H), 6.58 (d, *J* = 4.9 Hz, 1H), 4.57 (tt, *J* = 10.6, 4.9 Hz, 1H), 2.95 (d, *J* = 11.4 Hz, 2H), 2.39 (h, *J* = 7.1 Hz, 4H), 2.32 (s, 6H), 2.24 (s, 6H), 2.02 (q, *J* = 6.1, 3.4 Hz, 4H), 1.82 (td, *J* = 11.6, 3.0 Hz, 2H). ^{13}C NMR (125 MHz, MeOD) δ 162.2, 160.0, 159.1, 140.8, 139.3, 138.0, 129.9, 126.5, 126.5, 125.8, 119.9, 114.1, 57.4, 56.4, 55.3, 54.0, 45.8, 45.7, 33.8, 21.6. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.45. HRMS (ESI-TOF) m/z [M + H]+ calcd. for $C_{31}H_{37}F_3N_7^+$ 564.3057, found 564.3047.



Scheme S4. Synthesis of compound 8.

(*E*)-*tert*-butyl 4-(((6-fluoropyridin-2-yl)methylene)amino)piperidine-1-carboxylate (**8a**): Commercially available 6-fluoropicolinaldehyde (1.0 g, 8.0 mmol) and *tert*-butyl 4-aminopiperidine-1-carboxylate (1.6 g, 8.0 mmol) were dissolved in anhydrous CH_2Cl_2 (50 mL). $MgSO_4$ (1.9 g, 16 mmol) was added to the reaction mixture and was allowed to stir at room temperature for 18 h.

$MgSO_4$ was filtered out and the solvent was removed under reduced pressure. The crude compound thus obtained was purified via combiflash, 0-100% ethyl acetate in hexanes over 20 min to obtain the pure product as white solid (1.29 g, 53%).^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 7.93 – 7.89 (m, 2H), 7.85 (q, *J* = 7.8 Hz, 1H), 7.01 – 6.96 (m, 2H), 4.09 (s, 2H), 3.49 (p, *J* = 7.1, 6.6 Hz, 1H), 3.02 (s, 2H), 1.75 (dt, *J* = 9.4, 5.8 Hz, 4H), 1.49 (s, 9H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 164.2, 162.3, 159.0, 154.9, 153.2 (d, *J* = 12.4 Hz), 141.4 (d, *J* = 7.6 Hz), 118.5 (d, *J* = 4.0 Hz), 110.9, 110.6, 79.5, 66.9, 32.9, 28.4; ^{19}F NMR (470 MHz, Chloroform-*d*) δ -67.71 (d, *J* = 7.7 Hz).

***tert*-butyl 4-(5-(6-fluoropyridin-2-yl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-1-yl)piperidine-1-carboxylate (8b):** To a solution of isonitrile (**4b**) (400 mg, 1.18 mmol) and imine (**8a**) (362 mg, 1.18 mmol) in CH_3CN (10 mL) was added K_2CO_3 (652 mg, 4.72 mmol). The resulting reaction mixture was heated to 48 ºC in an oil-bath with stirring for 16 h. Reaction was diluted with 25 mL H_2O and the crude compound was extracted with ethyl acetate (10 mL × 3). The combine organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude compound was purified via combiflash, 0-100% ethyl acetate in hexanes over 20 min to obtain the pure product as pale yellow solid (466 mg, 61%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (s, 1H), 7.77 (q, *J* = 7.9 Hz, 1H), 7.58 – 7.52 (m, 5H), 7.14 (d, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 4.55 (t, *J* = 12.0 Hz, 1H), 4.28 (s, 2H), 2.76 (s, 2H), 2.14 (d, *J* = 11.7 Hz, 2H), 1.85 (qd, *J* = 12.3, 4.0 Hz, 3H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 164.2, 162.3, 154.5, 141.9 (d, *J* = 7.9 Hz), 135.3, 128.1, 125.4 (d, *J* = 3.7 Hz), 123.6 (d, *J* = 4.2 Hz), 109.1, 108.8, 80.1, 54.2, 33.3, 28.4. ^{19}F NMR (470 MHz, Chloroform-*d*) δ -62.59, -64.97 (d, *J* = 5.7 Hz).

***tert*-butyl 4-(5-(6-(3,5-dimethylphenoxy)pyridin-2-yl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-1-yl)piperidine-1-carboxylate (8c):** To a solution of **8b** (450 mg, 0.92 mmol) and 2,6-dimethylphenol (225 mg, 1.84 mmol) in DMSO (4 mL) in a vacuum dried sealed tube was added K_2CO_3 (509 mg, 3.68 mmol). The resulting reaction mixture was heated to 150 ºC in an oil-bath with stirring for 24 h. After cooling, the crude reaction mixture was diluted with H_2O (20 mL) and brine (10 mL). The crude compound was extracted with ethyl acetate (10 mL × 3) and the combined organic layers were dried over MgSO4 and the solvent was removed in vacuo. The crude compound was purified via combiflash, 0-100% ethyl acetate in hexanes over 20 min to obtain the pure product as white solid (501 mg, 92%).^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.94 (s, 1H), 7.68 – 7.54 (m, 6H), 6.94 (t, *J* = 6.6 Hz, 2H), 6.87 (s, 1H), 6.78 (s, 2H), 4.34 (t, *J* = 11.9 Hz, 1H), 4.07 (brs, 1H), 2.43 (d, *J* = 12.2 Hz, 2H), 2.32 (s, 6H), 1.84 (d, *J* = 11.9 Hz, 2H), 1.66 (q, *J* = 11.7 Hz, 2H), 1.47 (s, 9H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 154.4, 153.5, 140.2, 139.5, 134.3, 128.3, 126.9, 125.5, 125.4, 120.6, 119.4, 111.3, 80.1, 54.3, 28.4, 21.3.

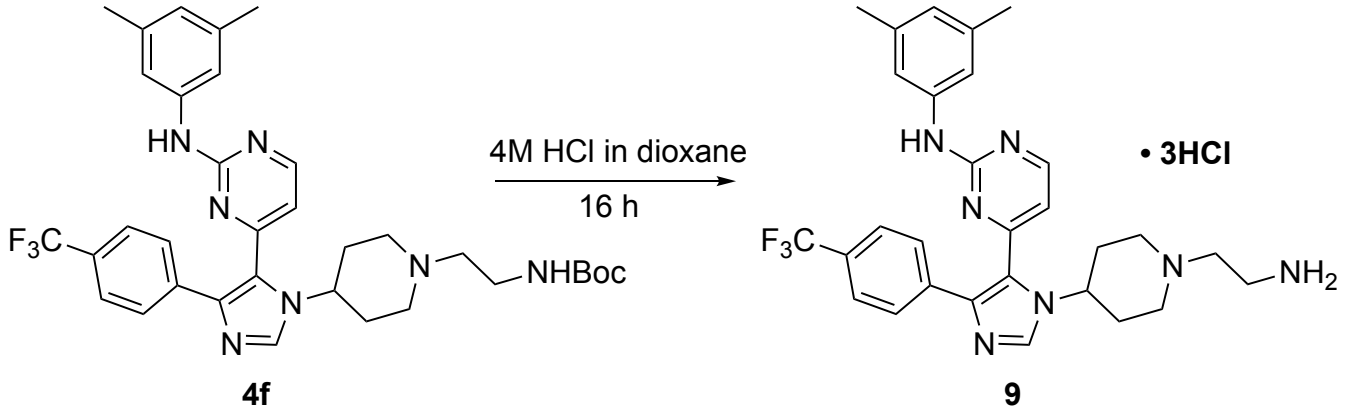
2-(3,5-dimethylphenoxy)-6-(1-(piperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)pyridine (8d): Compound **8c** (480 mg, 0.81 mmol) was dissolved in CH_2Cl_2 (5 mL) and trifluoroacetic acid (5 mL) was added to it. The resulting reaction mixture was stirred at room temperature for 1h. The solvent was evaporated, and the crude compound was triturated with diethyl ether. The desired product was obtained as a white solid (510 mg, 87%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.80 (d, *J* = 10.3 Hz, 1H), 8.42 (d, *J* = 10.4 Hz, 1H), 8.18 (s, 1H), 7.98 – 7.91 (m, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.18 (dd, *J* = 7.7, 2.1 Hz, 2H), 6.84 (s, 1H), 6.80 (s, 2H), 4.18 (tt, *J* = 10.8, 4.8 Hz, 1H), 3.27 (d, *J* = 12.6 Hz, 2H), 2.80 (q, *J* = 10.9 Hz, 2H), 2.22 (s, 6H), 2.07 – 1.93 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.3, 153.4, 146.2, 141.3, 139.0, 135.4, 127.9, 127.3, 126.3, 125.4, 121.3, 118.9, 112.0, 50.6, 42.5, 39.5, 29.5, 20.8. ^{19}F NMR (470 MHz, DMSO-d_6) δ -63.07, -76.55.

Procedure for preparation of *tert*-butyl (2-(4-(5-(6-(3,5-dimethylphenoxy)pyridin-2-yl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-1-yl)piperidin-1-yl)ethyl)carbamate(8e).

8d (0.14 mmol, 1.0 equiv.), 2-(Boc-amino)ethyl bromide (0.18 mmol, 1.3 equiv.), NaI (0.18 mmol, 1.3 equiv.) and K_2CO_3 (0.70 mmol, 5.0 equiv) were dissolved in methyl ethyl ketone (0.40 mL). The reaction was stirred at room temperature for 16 h then quenched by water and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the crude product, which was purified by silica gel chromatography using DCM and methanol (0-20%) as eluent to give the desired product **8e** (65 mg, 0.074 mmol, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.83 (s, 1H), 6.78 (s, 2H), 4.93 (s, 1H), 4.20 – 4.08 (m, 1H), 3.20 (t, *J* = 6.0 Hz, 2H), 2.80 (d, *J* = 11.1 Hz, 2H), 2.40 (t, *J* = 6.1 Hz, 2H), 2.31 (s, 6H), 1.86 – 1.81 (m, 4H), 1.73 (td, *J* = 11.1, 5.9 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 156.1, 153.9, 148.1, 140.0, 139.4, 139.2, 138.5, 135.2, 128.1, 126.8, 125.3 (q, *J* = 3.7 Hz), 120.8, 119.5, 110.7, 57.2, 53.6, 52.8, 37.6, 33.5, 28.6, 21.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.44.

Procedure for preparation of 2-(4-(5-(6-(3,5-dimethylphenoxy)pyridin-2-yl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-1-yl)piperidin-1-yl)ethan-1-amine(8).

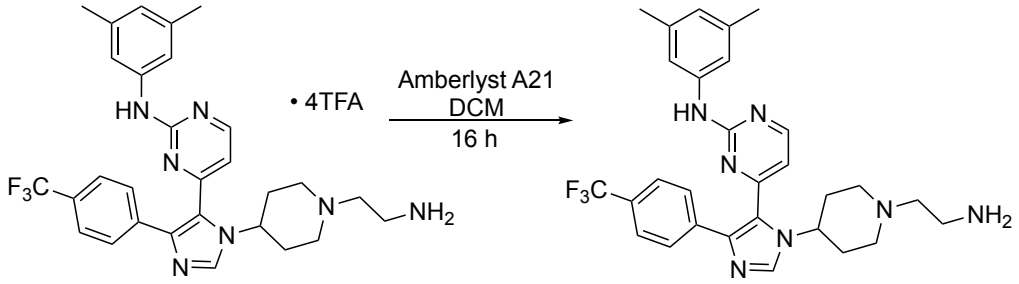
TFA (0.50 mL) was added to a solution **8e** (0.10 mmol) in DCM (0.50 mL). After 16 h, the reaction was concentrated under reduced pressure. Cold ether (3 mL) was used to precipitate out the desired product **8 (**99 mg, 0.10 mmol, 96%**)**. ^{1}H NMR (500 MHz, MeOD) δ 9.04 (s, 1H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.91 (s, 1H), 6.83 (s, 2H), 4.53 (tt, *J* = 12.0, 4.2 Hz, 1H), 3.43 (d, *J* = 12.4 Hz, 2H), 3.34 (t, *J* = 6.5 Hz, 2H), 3.24 (t, *J* = 6.6 Hz, 2H), 2.68 (t, *J* = 12.4 Hz, 2H), 2.35 (dd, *J* = 13.4, 9.6 Hz, 2H), 2.30 (s, 6H), 2.18 (dd, *J* = 13.9, 3.8 Hz, 2H). ^{13}C NMR (100 MHz, MeOD) δ 165.6, 154.9, 144.5, 142.5, 141.0, 130.4, 128.0, 127.2 (d, *J* = 3.9 Hz), 122.5, 120.5, 114.2, 54.3, 53.1, 35.6, 30.9, 21.4. ^{19}F NMR (470 MHz, MeOD) δ -64.40, -77.20. HRMS (ESI-TOF) m/z [M + H]+ calcd. for $C_{30}H_{32}F_3N_5O^+$ 536.2632, found 536.2627.



4f **9**

Scheme S5. Synthesis of compound 9.

Procedure for preparation of 4-(1-(1-(2-aminoethyl)piperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)-N-(3,5-dimethylphenyl)pyrimidin-2-amine(9, HCl salt). 4f (0.030 mmol) was added in 4M anhydrous HCl in dioxane (0.5 mL) and dioxane (0.5 mL). After 16 h, the solvent was removed and cold ether was used to precipitate out the desired product (16 mg, 0.025 mmol, 83%). ^{1}H NMR (500 MHz, MeOD) δ 8.80 – 8.75 (m, 1H), 8.38 (d, *J* = 5.2 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.24 (s, 2H), 6.76 (s, 1H), 6.61 (d, *J* = 5.3 Hz, 1H), 4.94 (td, *J* = 10.7, 4.9 Hz, 1H), 3.40 (d, *J* = 12.0 Hz, 2H), 3.26 (dd, *J* = 6.4, 2.3 Hz, 2H), 3.08 (d, *J* = 6.6 Hz, 2H), 2.58 (d, *J* = 15.1 Hz, 2H), 2.36 (d, *J* = 6.7 Hz, 4H), 2.29 (s, 6H). ^{19}F NMR (470 MHz, MeOD) δ -64.47.



4 **10**

Scheme S6. Synthesis of compound 10.

Procedure for preparation of 4-(1-(1-(2-aminoethyl)piperidin-4-yl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)-N-(3,5-dimethylphenyl)pyrimidin-2-amine(10, free base). DCM (0.5 mL) was added to **4** (0.030 mmol) and Amberlyst A21 resin (0.20 g). After 16 h, the resin was filtered out and DCM was removed under reduced pressure to give the desired product **10** (11 mg). ^{1}H NMR (500 MHz, MeOD) δ 8.93 (s, 1H), 8.39 (d, *J* = 5.1 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 1.6 Hz, 2H), 6.77 (s, 1H), 6.61 (d, *J* = 5.0 Hz, 1H), 5.02 – 4.96 (m, 1H), 3.55 (d, *J* = 12.3 Hz, 2H), 3.36 (t, *J* = 6.3 Hz, 2H), 3.26 (t, *J* = 6.5 Hz, 2H), 2.78 (s, 2H), 2.46 (h, *J* = 3.6 Hz, 4H), 2.29 (s, 6H). ^{19}F NMR (470 MHz, MeOD) δ -64.50.

Protein expression:

His_6 BRD4 D1 were expressed and purified as previously reported.[1]

His_9 BRD4 D1 expression.

The His_6 BRD4 D1 insert was modified by addition of three histidines to the hexahistidine tag via site-directed mutagenesis by standard procedures.[1] The resulting gene was co-transformed with pRARE (Novagen) into BL21(DE3) *E. coli*.[2] Cells were grown on Luria-Bertani (LB) agar plates containing kanamycin (100 mg/mL) at 37 °C for 12 h. Individual colonies were picked and grown for 12 hours in 5 mL of LB containing kanamycin (100mg/mL). The primary culture was used to inoculated 1 L of LB media containing kanamycin (100mg/mL) and the culture was grown by shaking at 220 RPM at 37 °C until an OD600 of 0.6-0.8 was reached.

BRD4 D2 expression.

The pET-28a(+) plasmid containing the second bromodomain of BRD4 (residues 333-460) was purchased from GenScript. The *E.coli* strain BL21 Star (DE3) was transformed with the plasmid containing the desired insert and plated onto an agar plate containing the appropriate antibiotics. The plate was incubated overnight at 37°C. A 5 mL LB culture containing antibiotics, chloramphenicol (35 mg/L) and kanamycin (100 mg/L), was inoculated using a single colony form this plate and grown overnight at 37°C and shaking at 215 rpm. The primary culture was used to inoculate 1 L of LB media containing chloramphenicol (35 mg/L) and kanamycin (100 mg/L) at 37°C at 215 rpm until the optical density at 600 nm had reached 0.6-0.8. An equilibration time of 30 minutes at 20°C and 215

rpm was followed by the addition of 1 mM IPTG to induce protein expression. The culture was shaken for 16-20 hours at 20°C and 220 rpm. Cells were pelleted by centrifugation at 8,000 g and stored at -20°C until purification.

BRD2 D1 Expression.

The pET28a(+) plasmid containing the first bromodomain of BRD2 (Residues 71-194) was purchased from GenScript. The *E.coli* strain BL21(DE3)-RIL were transformed with the BRD2 D1 plasmid and plated onto an agar plates containing kanamycin(100mg/L) and chloramphenicol (35mg/L). The plate was incubated overnight at 37°C. A 5 mL LB culture containing kanamycin(100mg/L) and chloramphenicol (35mg/L) was inoculated using a single colony from this plate and grown overnight at 25°C and shaking at 220 rpm. The primary culture was used to inoculate 1 L of LB media containing chloramphenicol (35 mg/L) and kanamycin (100 mg/L) until the optical density at 600 nm had reached 0.6-0.8. At this point, an equilibration time of 30 minutes at 20°C and 220 rpm was followed by the addition of 1 mM IPTG to induce protein expression. The culture was shaken for 16-20 hours at 20°C and 220 rpm. Cells were pelleted by centrifugation at 8,000 g and stored at -20°C until purification.

Fluorescence Anisotropy.

Fluorescence-anisotropy experiments were carried out in 50 mM HEPES, 100 mM NaCl, and 4 mM CHAPS at pH = 7.4 in 384-well plates (Corning 4511). 10 μM Fl-JQ1 stock in DMSO were diluted to 15 nM.[3] A Tecan Infinity 500 was used with an excitation wavelength at 485 nm and emission at 535 nm. Protein was serially diluted across the plate, after 30 min, anisotropy values were measured and fit using *equation 1* in GraphPad Prism for direct binding experiment. B and c are the maximum and minimum anisotropy values; a is the concentration of Fl-JQ1(15 nM); x is the concentration of protein; and y is the observed anisotropy value in *equation 1*.

$$y = c + (b - c)\frac{(Kd+a+x)-\sqrt{(Kd+a+x)^2-4ax}}{2a} \qquad \textit{equation 1}$$

The protein concentrations of the competition experiments were determined from the direct-binding experiments at which the Fl-JQ1 is 80% bound. Using a 10 mM stock solution in DMSO, inhibitors were serially diluted from 50 μM to subnanomolar concentrations. The concentrations of protein, tracer, and other components were kept constant. Anisotropy values were fit using GraphPad Prism's [inhibitor] versus response (four parameters) function. The IC_{50} values are reported as the mean ± SEM, as determined from three independent experiments. Direct binding with Fl-JQ1 and self-competition experiments with (+)-JQ1 were carried out before competition experiments to check protein quality and assay stability.

General procedure for AlphaScreen assay with His_9-BRD4 D1:

AlphaScreen assay procedure for BRD4 D1 was adapted from the manufacturers protocol (PerkinElmer, USA). Nickel chelate (Ni-NTA) acceptor beads and streptavidin donor beads were purchased from PerkinElmer (Cat.#: 6760619M). The biotinylated histone H4 KAc5,8,12,16 peptide was purchased from EpiCypher, with the sequence:
Ac-SGRGK(Ac)GGK(Ac)GLGK(Ac)GGAK(Ac)RHRKVLR-Peg (Biot)
All reagents were diluted in the assay buffer (50 mM HEPES-Na^+ (ChemImpex), 100 mM NaCl (SigmaAldrich), 0.05% CHAPS (RPI), 0.1% BSA (SigmaAldrich), pH = 7.4). Final assay concentrations (after the addition of all assay components) of 7.5-60 nM for His_9-tagged BRD4 D1 and 25-100 nM for the biotinylated peptide were used. 3-fold serial dilutions were prepared with varying concentrations of the compounds and a fixed protein concentration, keeping the final DMSO concentration at 0.1%. For each plate, (+)-JQ1 was run in duplicate as a positive control. 5 μL of these solutions were added to a 384-well plate (ProxiPlate-384, PerkinElmer). The plate was sealed and kept at room temperature for 30 minutes, followed by the addition of 5 μL of the biotinylated peptide. 5 μL of nickel chelate acceptor beads was added to each well under low light conditions (<100 lux), to a final concentration of 20 μg/mL, and the plate was incubated at room temperature in the dark for 30 minutes. This was followed by the addition of 5 μL (20 μg/mL final concentration) of streptavidin donor beads in low light conditions. After incubation for 30 minutes in the dark, the plate was read in AlphaScreen mode using a PerkinElmer EnSpire plate reader. Each compound was run in duplicate. The data was normalized against DMSO negative control signal to obtain the % normalized AlphaScreen signal and IC_{50} values were calculated in GraphPad Prism 5 using [inhibitor] versus response (four parameters) function.

Crystallization conditions and X-ray data collection methods.

6 (20 μM) was co-crystalized with BRD D1 (300-400 μM, in 10 mM HEPES, 100 mM NaCl, pH 7.4) in 200 mM NaI, 100 mM Bis-Tris propane, 20% (v/v) PEG 3350, 10% (v/v) ethylene glycol at pH 8.5 using the hanging drop method. Harvestable crystals grew in 1-2 days at ambient temperature. Crystals were harvested, cryoprotected in ethylene glycol and flash frozen. Data was collected at Advanced Photon Source with the NECAT 24-IDE beamline. Phaser-MR17[4] was used to solve the structure via molecular replacement using PDB ID 3MXF as a reference. Phenix18 and Coot[5] were used for structure refinement.

Cell Culture.

MM.1S cells were grown in a humidified 5% CO_2 environment at 37 °C. Cells were cultured in standard tissue culture flasks using RPMI 1640 media (Corning) supplemented with 10% fetal-bovine serum (FBS, Cellgro), penicillin/streptomycin (50 μg/mL each, Cellgro). The mixed suspension/adherent cells were sub-cultured at a 1:8 dilution by decanting suspended cells and dissociating adherent cells from

plates in 0.25% trypsin/ EDTA (Gibco) with 2 min incubation times. Cell-line authenticity was verified using the short-tandem-repeat (STR)-profiling service provided by ATCC.

Thermal Stability Profiling.[3,6]

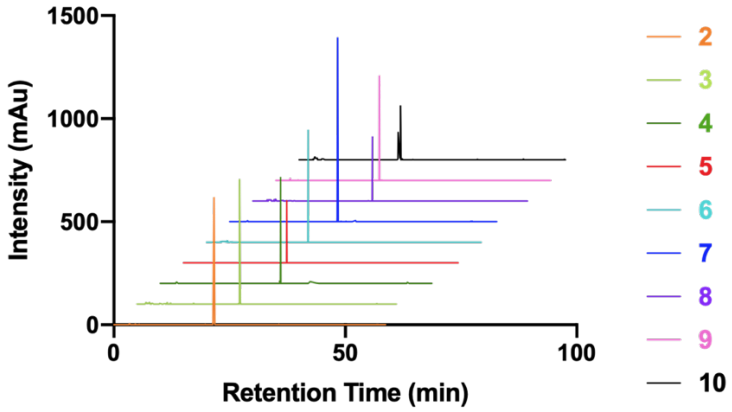
Approximately 3 × 10^6 MM.1S cells were treated with the desired amounts of compound in serum supplemented RPMI-1640 media, with DMSO concentrations normalized to 0.05% for all samples. Dosed cells in microcentrifuge tubes were incubated at 37 °C for 1 h. with mild intermittent agitation. Upon completion of the incubation period, cells were pelleted at 300 X *g.* and rinsed in PBS, before being re-suspended in 100 µL PBS supplemented with 1× cOmplete Mini Protease (Roche). Re-suspended cells were thermally denatured at 48 °C for 3 min in a heat block and subsequently equilibrated at room temperature for a further 3 min. Cells were lysed over three freeze-thaw cycles and centrifuged (15 min at 15,000 X *g.*), before soluble protein concentrations of supernatants were determined using the BCA protein assay kit (Pierce). Samples were normalized to the lowest total soluble-protein concentration and analyzed by western blot.

Western Blotting.

MM.1S cells were seeded in 24-well plates at a density of 2 X 10^6 cells per well and treated with compounds for 8 h, with DMSO concentrations normalized to 0.05%. Cells were harvested by low-speed centrifugation at 500 X *g.* for 5 min. and washed twice with ice-cold PBS. Cells were lysed in 100 µL of RIPA buffer (ThermoFisher Scientific) supplemented with 1x cOmplete Mini Protease (Roche). After high-speed centrifugation (15 min at 15,000 X *g.*), protein concentrations were determined by a Bradford assay (ThermoFisher Scientific) and normalized by total protein content. Normalized samples were mixed with 4× NuPAGE LDS loading buffer (Invitrogen) and 10x reducing agent (Invitrogen), and heated at 95 °C for 5 minutes. This was followed by separation on 8-12% SDS-PAGE using Tris/Glycine/SDS buffer (BioRad). Proteins were transferred to PVDF membranes for 7 minutes on a BioRad Trans-Blot Turbo. Membranes were incubated subsequently with TBS-TWEEN20 (TBS-T) containing 5% nonfat dry milk for 16 h. at 4 °C with primary antibodies (c-Myc, Cell Signaling Technology, #5605, diluted 1:500 in TBS-T containing 5% nonfat dry milk; BRD4, Cell Signaling Technology, # 13440, diluted 1:1000 in TBS-T containing 5% nonfat dry milk; β-actin, Invitrogen # MA5-11869, diluted 1:1000 in TBS-T containing 5% nonfat dry milk). After the membranes were washed five times with TBS-T, they were incubated with 1000-fold-diluted HRP-, or Alexa Fluor 680-conjugated secondary antibodies from Invitrogen (goat anti-rabbit-IgG, #G-31460 and goat anti-mouse-IgG, #G-21040/A-21057; in TBS-T containing 5% nonfat dry milk) for 4 h at room temperature. Membranes were washed three times in TBS-T and treated with SuperSignal West Dura substrates (ThermoFisher Scientific) for 1 min. and imaged using a LiCor Odessey Fc. Experiments were performed in biological triplicate and densitometry was processed using ImageJ.

Viability Assays.

MM.1S cells were seeded in 96-well plates at approximately 20 000 cells per well (0.05 mL) and dosed with increasing compound concentrations in the presence of 0.05% DMSO with three technical replicates per concentration (100 µL final volume). After incubation for 69 hours at 37 °C, 10 µL of Alamar Blue reagent (Invitrogen) was added to each well and the plates were incubated a further 3 h at 37 °C. Fluorescence was determined using a Synergy plate reader (BioTek, Ex.: 560 nm, Em.: 590 nm) and dose-response data were normalized to untreated and blank wells containing 0.05% DMSO in cell culture media. Data analysis was performed using GraphPad Prism as previously reported.[3]



Compound	2	3	4	5	6	7	8	9
% Purity	95%	96%	99%	99%	99%	97%	98%	99%

10 had more than 1 peak on HPLC since it can form TFA salts from the mobile phase during separation. ^{19}F NMR was used to determine the purity after separation.

Figure S1. Purity analysis of compounds in **Table 1**, HCl salt of **5** (**9**) and free base of **5** (**10**) at 254 nm.

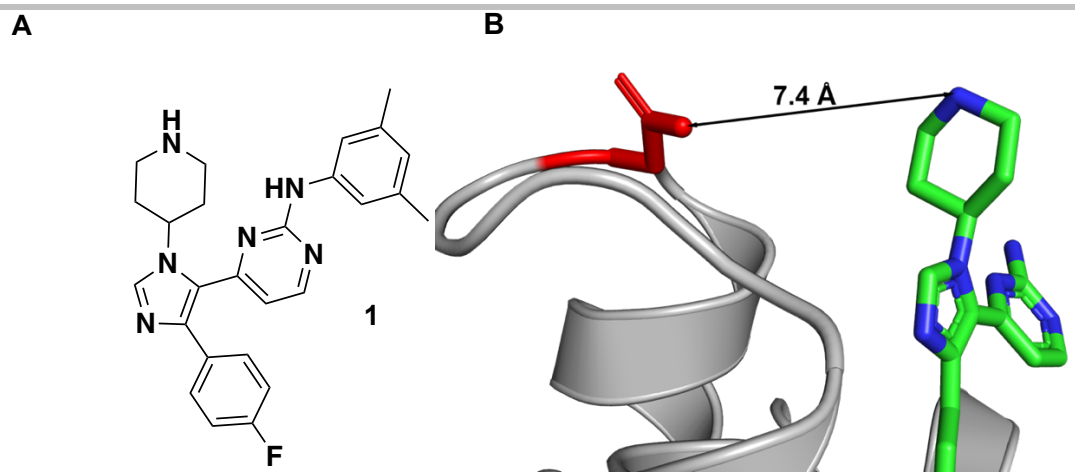


Figure S2. A) Structure of **1**. B) Co-crystal structure of **1** against BRD4 D1, the distance between piperidyl group and surface-exposed Asp144 is 7.4 Å (PDB: 6MH1).

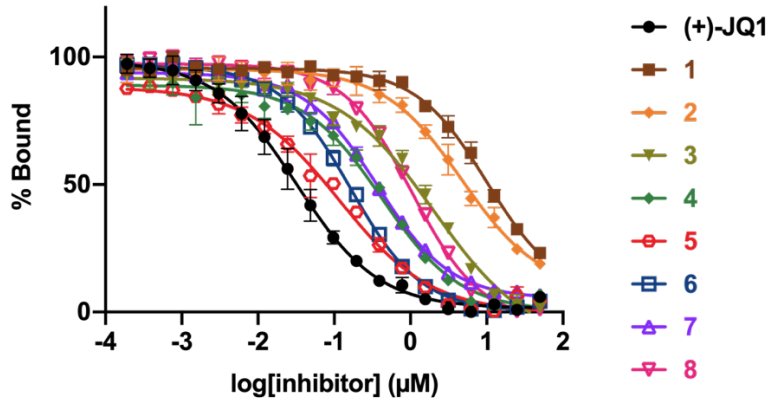


Figure S3. Fluorescence anisotropy assays of BRD4 D1, with competition of Fl-JQ1 against compounds in **Table 1**.

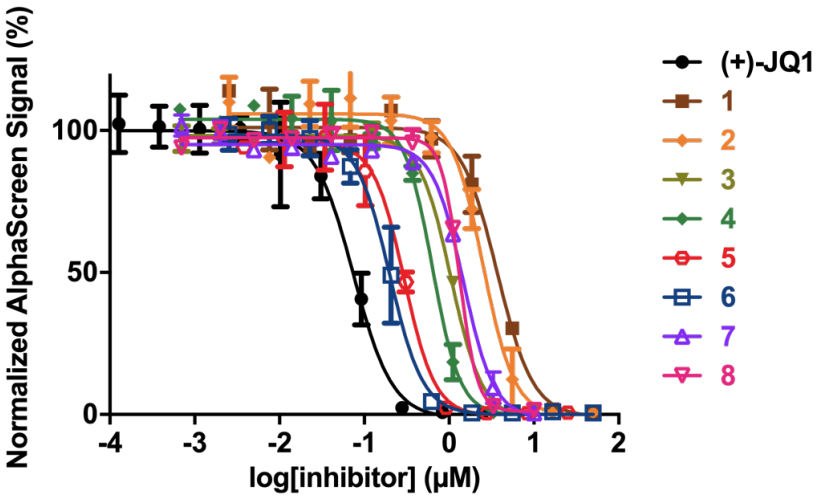


Figure S4. AlphaScreen assay of BRD4 D1, with competition of biotinylated histone H4 peptide against compounds in **Table 1.**

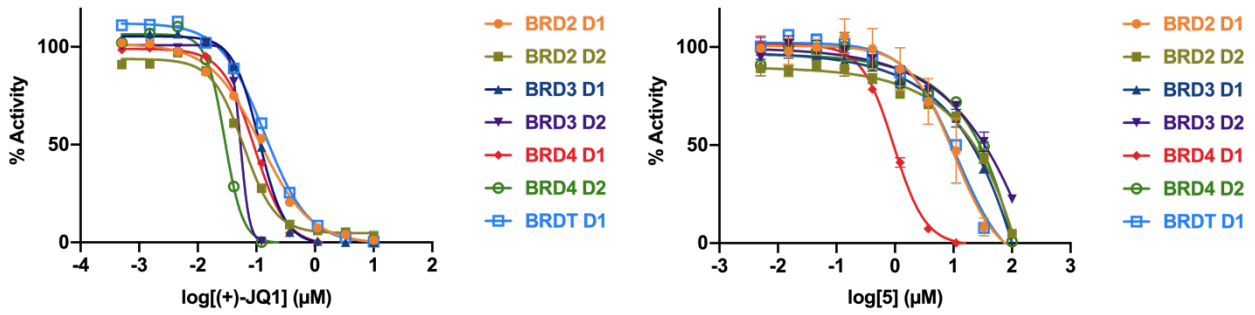


Figure S5. AlphaScreen assay of (+)-JQ1 (Left) and compound **5** (Right) against BET bromodomains (except BRDT D2) by ReactionBiology (N=2) in Figure 2B.

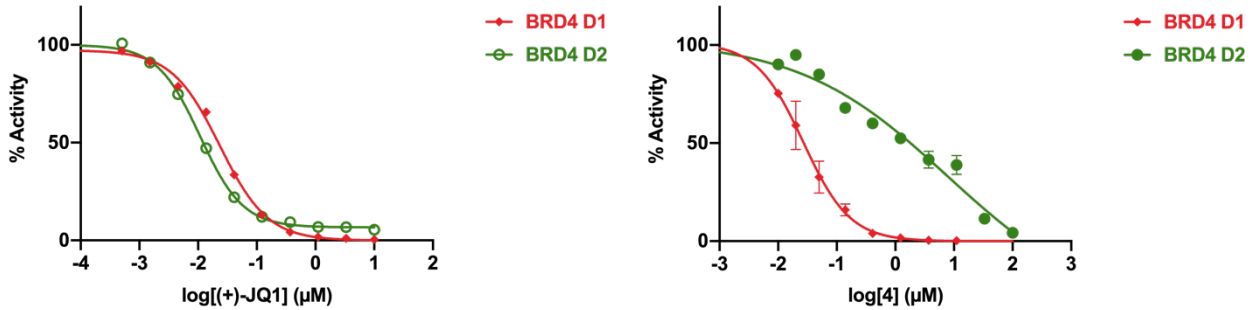


Figure S6. AlphaScreen assay of (+)-JQ1 (Left, N=1) and compound **4** (Right, N=2) against BRD4 D2 by ReactionBiology. (+)-JQ1: IC_{50} = 23.3 nM and 12.6 nM respectively. **4**: IC_{50} = 21.7 nM and 1.58 μM respectively. The IC_{50} value for BRD4 D2 is considered an estimate due to the shallow hill slope and poor fitting of the data.

Table S1. Affinity of compound **5** against bromodomains as determined by DiscoverX Bromoscan.

Bromodomain	K_d (nM)[a]
BRD4 D1	3000 ± 1208[b]
BRD2 D1	17000 ± 2000
BRD1	> 50000
EP300	> 50000
PBRM1(5)	> 50000
PCAF	> 50000
SMARCA2	> 50000
SMARCA4	> 50000

[a] Data represents the mean and standard deviation of two biological replicates.
[b] Data represents the mean and standard deviation of four biological replicates.

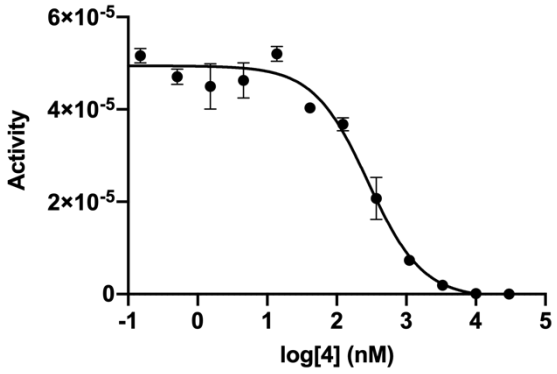


Figure S7. Affinity of **4** for p38α (K_d = 260 nM) as determined by DiscoverX KINOMEscan (N=2) in **Table 1.**

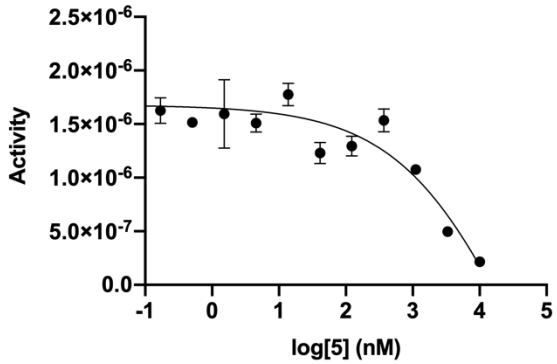


Figure S8. Affinity of **5** for p38α (K_d = 1900 nM) as determined by DiscoverX KINOMEscan (N=2) in **Table 1**.

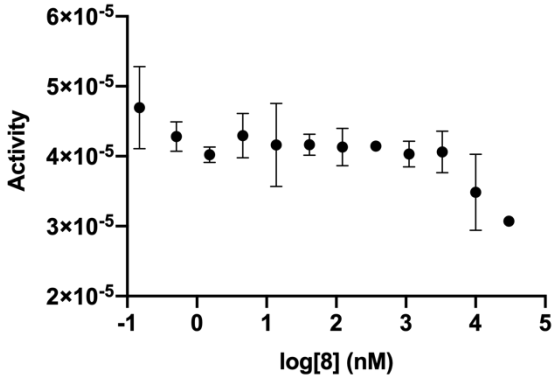


Figure S9. Affinity of **8** for p38α (K_d > 30,000 nM) as determined by DiscoverX KINOMEscan (N=2) in **Table 1**.

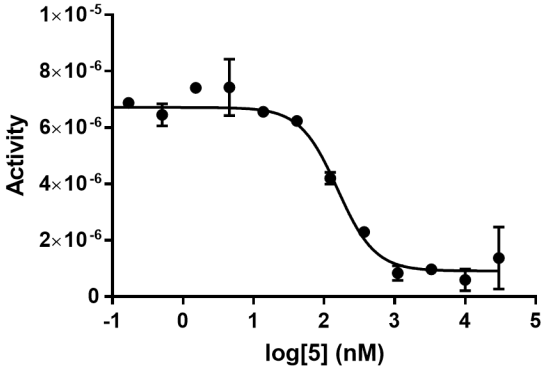


Figure S10. Affinity of 5 for CK1 (K_d = 220 nM) as determined by DiscoverX KINOMEscan (N=2) in **Table 1.**

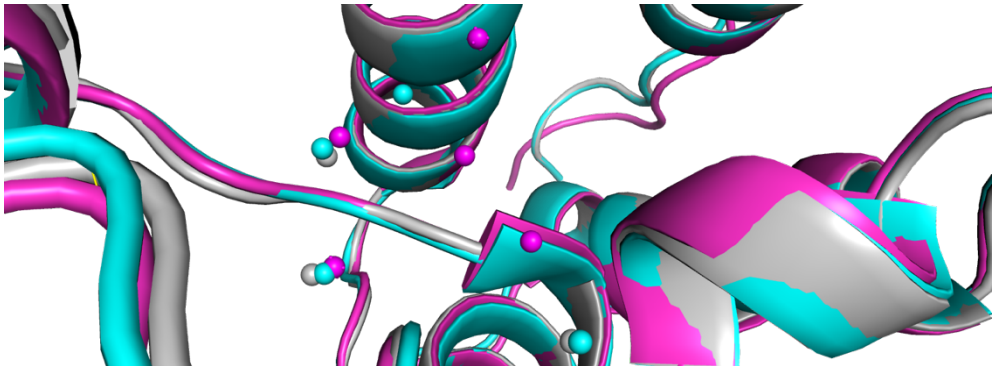


Figure S11: Overlay of BRD4 D1 co-crystal structures of **6** (PDB ID = 6WGX, Gray), **1** (PDB ID = 6mh1, teal), and H4K5acK8ac (PDB ID = 3UVW, pink) showing the displacement and reorganization of the waters in the binding site.

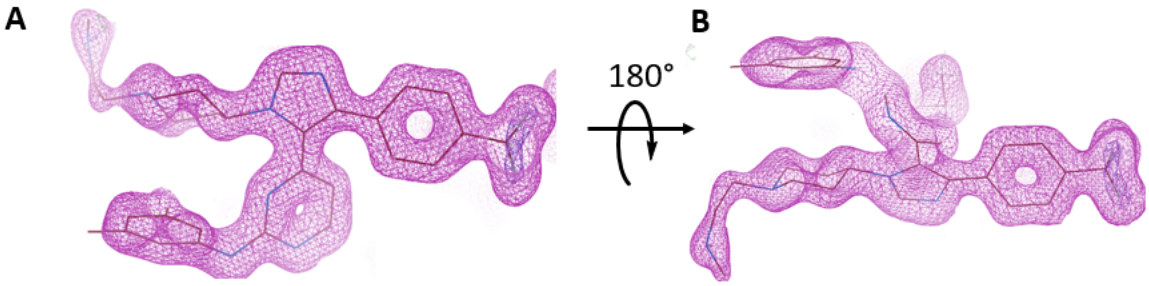


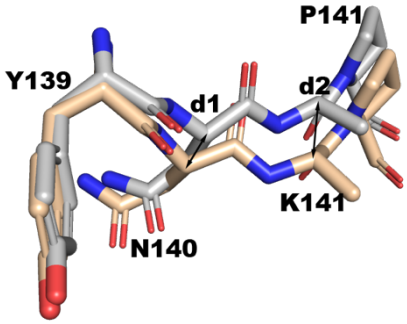
Figure S12: A) and B) The electron density map is shown in pink for two views of **6**. C) Unmodeled electron density (green) that the dimethylamine of 6 could be modeled into illustrating the flexibility of this.

Table S2. Data collection and refinement statistics for **6** (PDB: 6WGX)

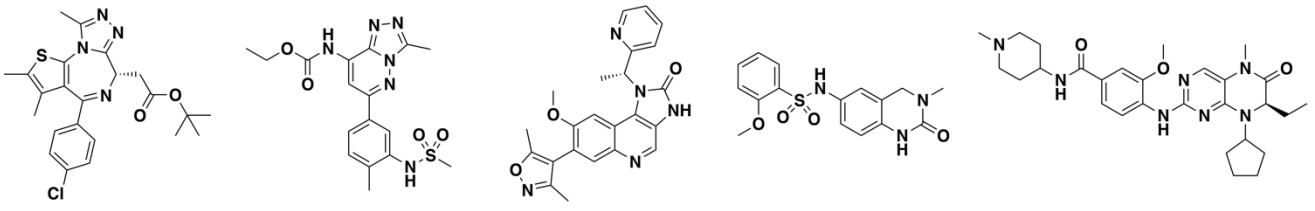
Data Collection	
Wavelength	0.979
Resolution range	52.4 - 1.53 (1.585 - 1.53)
Space group	P 21 21 21
Unit cell	41.909 59.198 112.604 90 90 90
Total reflections	195958 (9095)
Unique reflections	42053 (3449)
Multiplicity	4.7 (2.6)
Completeness (%)	97.26 (81.44)
Mean I/sigma(I)	12.34 (1.27)
Wilson B-factor	20.93
R-merge	0.06728 (0.578)
R-meas	0.07513 (0.7074)
R-pim	0.03255 (0.3989)
CC1/2	0.998 (0.628)
CC*	1 (0.878)
Refinement	
Reflections used in refinement	41968 (3448)
Reflections used for R-free	2063 (177)
R-work	0.1443 (0.2617)
R-free	0.1810 (0.2956)
CC(work)	0.967 (0.849)
CC(free)	0.951 (0.821)
Number of non-hydrogen atoms	2513
macromolecules	2123
ligands	99
solvent	291
Protein residues	252
RMS(bonds)	0.016
RMS(angles)	1.18
Ramachandran favored (%)	99.19
Ramachandran allowed (%)	0.81
Ramachandran outliers (%)	0
Rotamer outliers (%)	0
Clashscore	2.52
Average B-factor	27.01
macromolecules	25.26
ligands	28.43
solvent	39.29

Statistics for the highest-resolution shell are shown in parentheses.

Table S3. Backbone differences between BRD4 D1 bound to acetylated H4K5acK8ac (3UVW, wheat) and BRD4 D1 with pan-BET inhibitors, pan-BD1 inhibitors and selective BRD4 BD1 inhibitor(grey).



	PDB	Molecule	d1(Å)	d2(Å)
Pan-BET inhibitors	3MXF	(+)-JQ1	0.83	1.4
	6V0U	Bromosporine	0.64	0.79
	3ZYU	i-BET151	0.69	1.3
	4E96	PFi-1	0.87	0.94
	4O74	BI 2536	0.36	0.25
	Pending[7]	**27**	0.77	1.2
	Average	-	0.69	0.98
Pan-BD1	6MH1	**1**	0.89	0.99
	6MH7	**IV**	0.93	1.7
	6SWN	iBET-BD1	0.79	1.4
Selective BRD4 BD1	6WGX	**6**	0.94	1.7



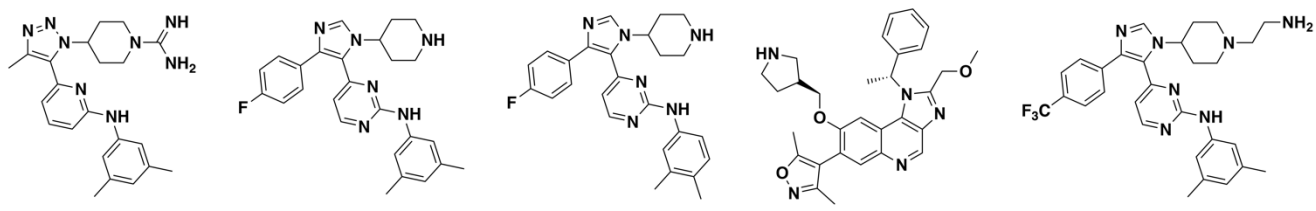


Figure S13. Structures of inhibitors in **Table S2.**

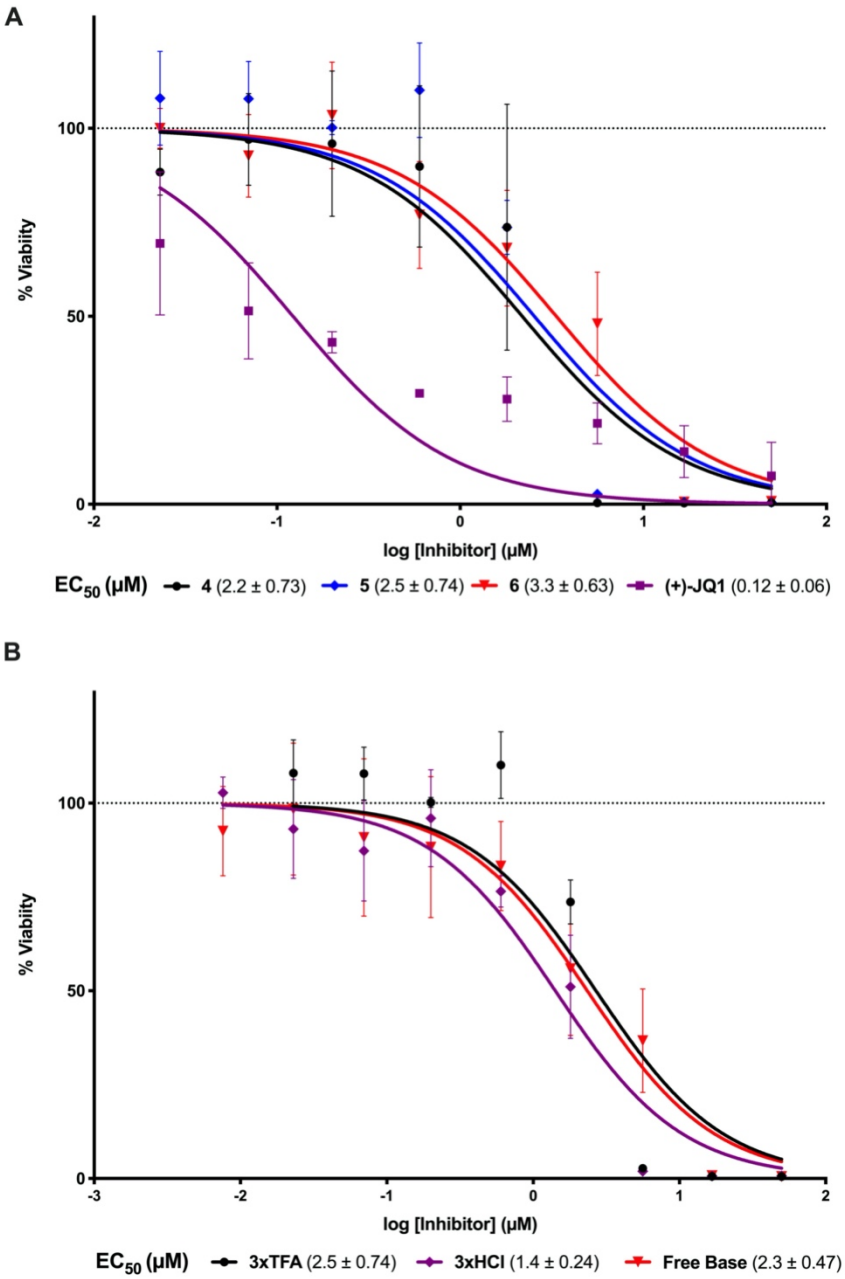


Figure S14: Viability of MM.1S Cells upon 72 h. treatment with compounds. A) Treatment with compounds **4**, **5**, **6** and (+)-JQ1. B) Comparison of viability with trifluoroacetate, chloride (**9**) and free-base (**10**) forms of compound **5**. Data is represented as mean ± S.E.M of three biological replicates, each with at least three technical replicates.

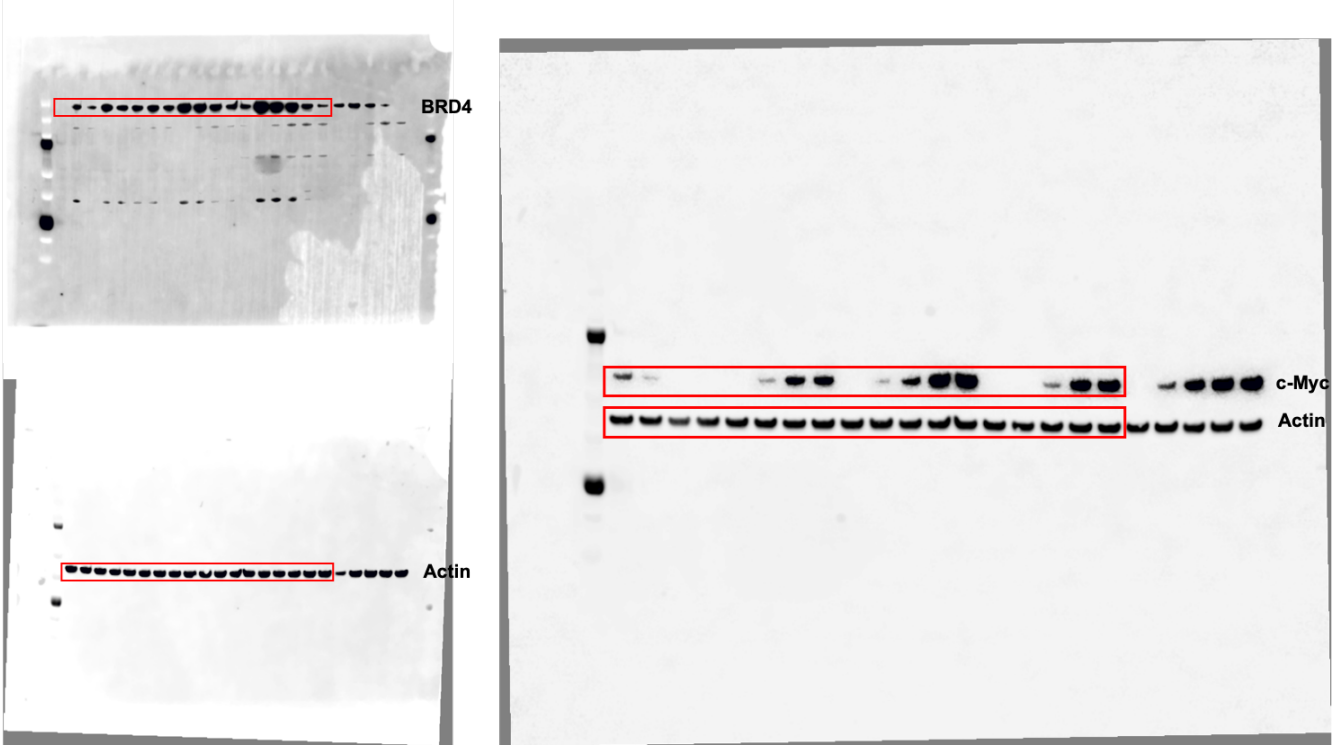


Figure S15: Full images of highlighted panels shown in western blots from **Figure 4**. Gels included Precision Plus Dual Color ladder.

References

[1] A. K. Urick, L. M. L. Hawk, M. K. Cassel, N. K. Mishra, S. Liu, N. Adhikari, W. Zhang, C. O. Dos Santos, J. L. Hall, W. C. K. Pomerantz, *ACS Chem. Biol.* **2015**, *10*, 2246–2256.

[2] N. K. Mishra, A. K. Urick, S. W. J. Ember, E. Schonbrunn, W. C. Pomerantz, *ACS Chem. Biol.* **2014**, *9*, 2755–2760.

[3] A. Divakaran, S. K. Talluri, A. M. Ayoub, N. K. Mishra, H. Cui, J. C. Widen, N. Berndt, J. Y. Zhu, A. S. Carlson, J. J. Topczewski, et al., *J. Med. Chem.* **2018**, *61*, 9316–9334.

[4] P. Emsley, B. Lohkamp, W. G. Scott, K. Cowtan, *Acta Crystallogr. Sect. D Biol. Crystallogr.* **2010**, *66*, 486–501.

[5] P. D. Adams, P. V. Afonine, G. Bunkóczi, V. B. Chen, I. W. Davis, N. Echols, J. J. Headd, L. W. Hung, G. J. Kapral, R. W. Grosse-Kunstleve, et al., *Acta Crystallogr. Sect. D Biol. Crystallogr.* **2010**, *66*, 213–221.

[6] R. Jafari, H. Almqvist, H. Axelsson, M. Ignatushchenko, T. Lundbäck, P. Nordlund, D. M. Molina, *Nat. Protoc.* **2014**, *9*, 2100–2122.

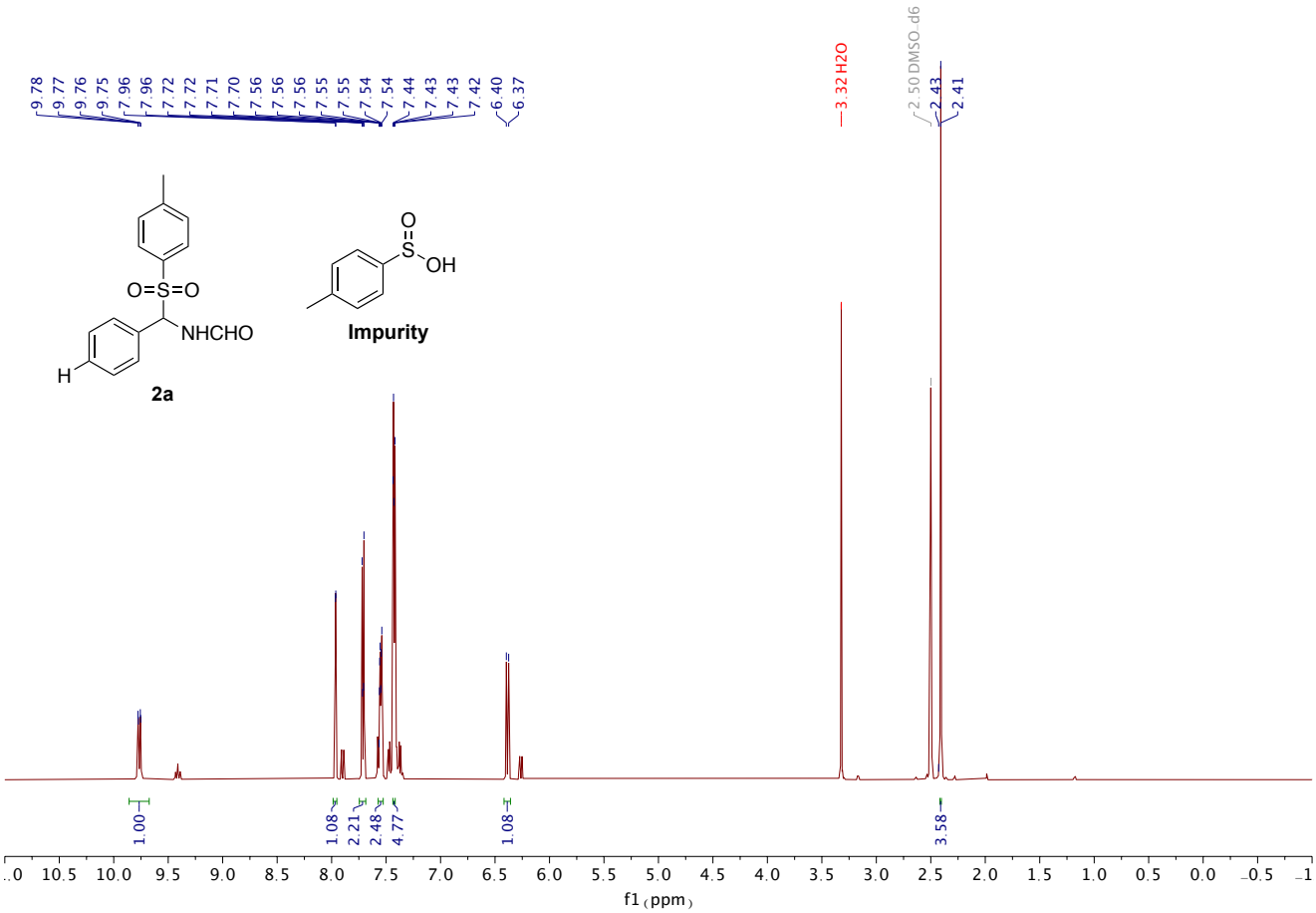
[7] A. S. Carlson, H. Cui, A. Divakaran, J. A. Johnson, R. M. Brunner, W. C. K. Pomerantz, J. J. Topczewski, *ACS Med. Chem. Lett.* **2019**, *10*, 1296–1301.

SUPPORTING INFORMATION

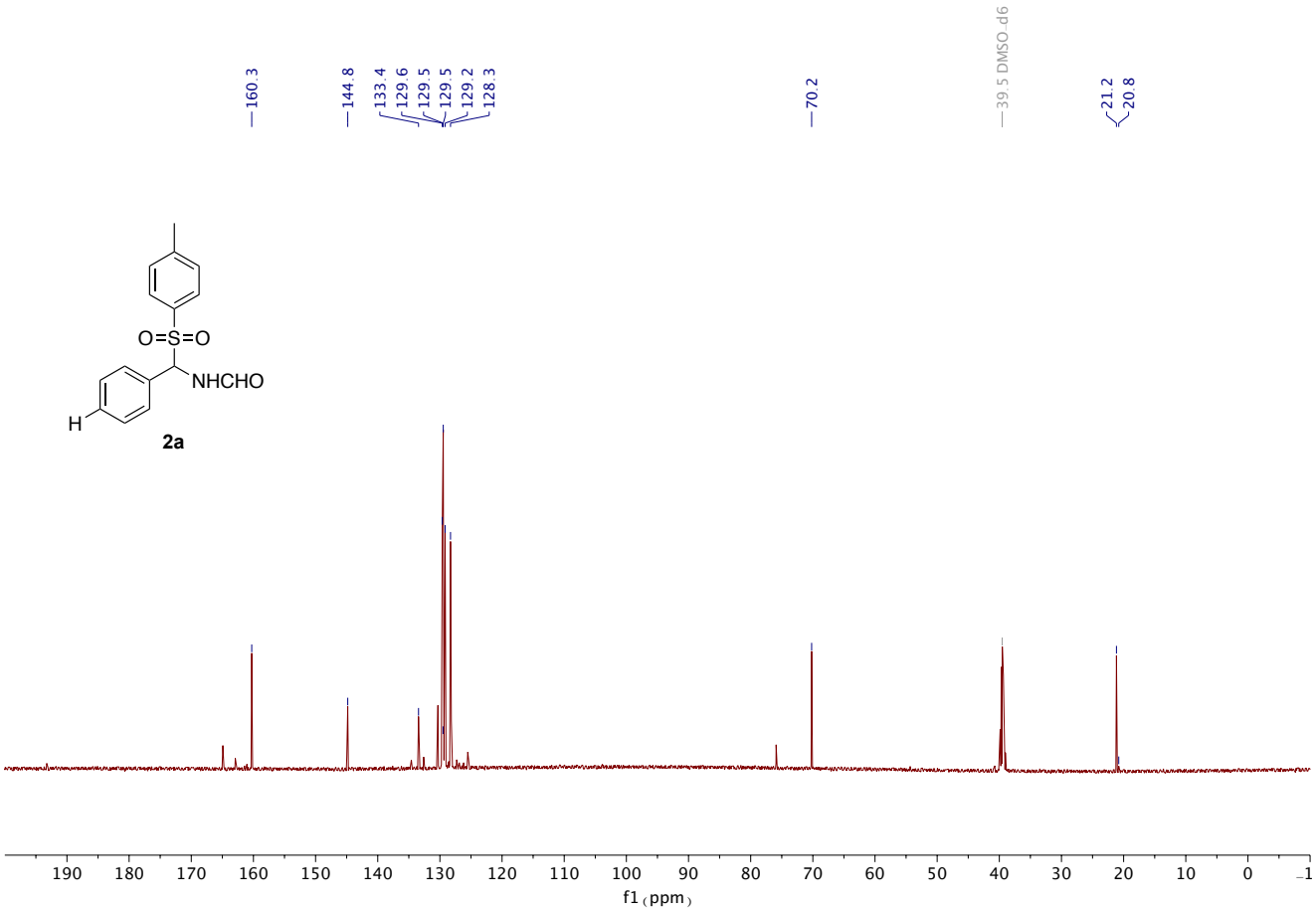
Author Contributions

H.C. designed and synthesized molecules along with A.D., A.K.P., Z.J.H., M.O.E..; H.C. and H.Z. performed biophysical experiments; A.D., D. H. designed and performed cellular experiments and/or interpretation of data; J.A.J., H.C., H.A. K.S. performed crystallography experiments and/or interpreted data; W.C.K.P oversaw all of the experimental and/or interpretation of data. H.C, A.D., and W. C. K. P. wrote the manuscript. All authors have given approval to the final version of the manuscript

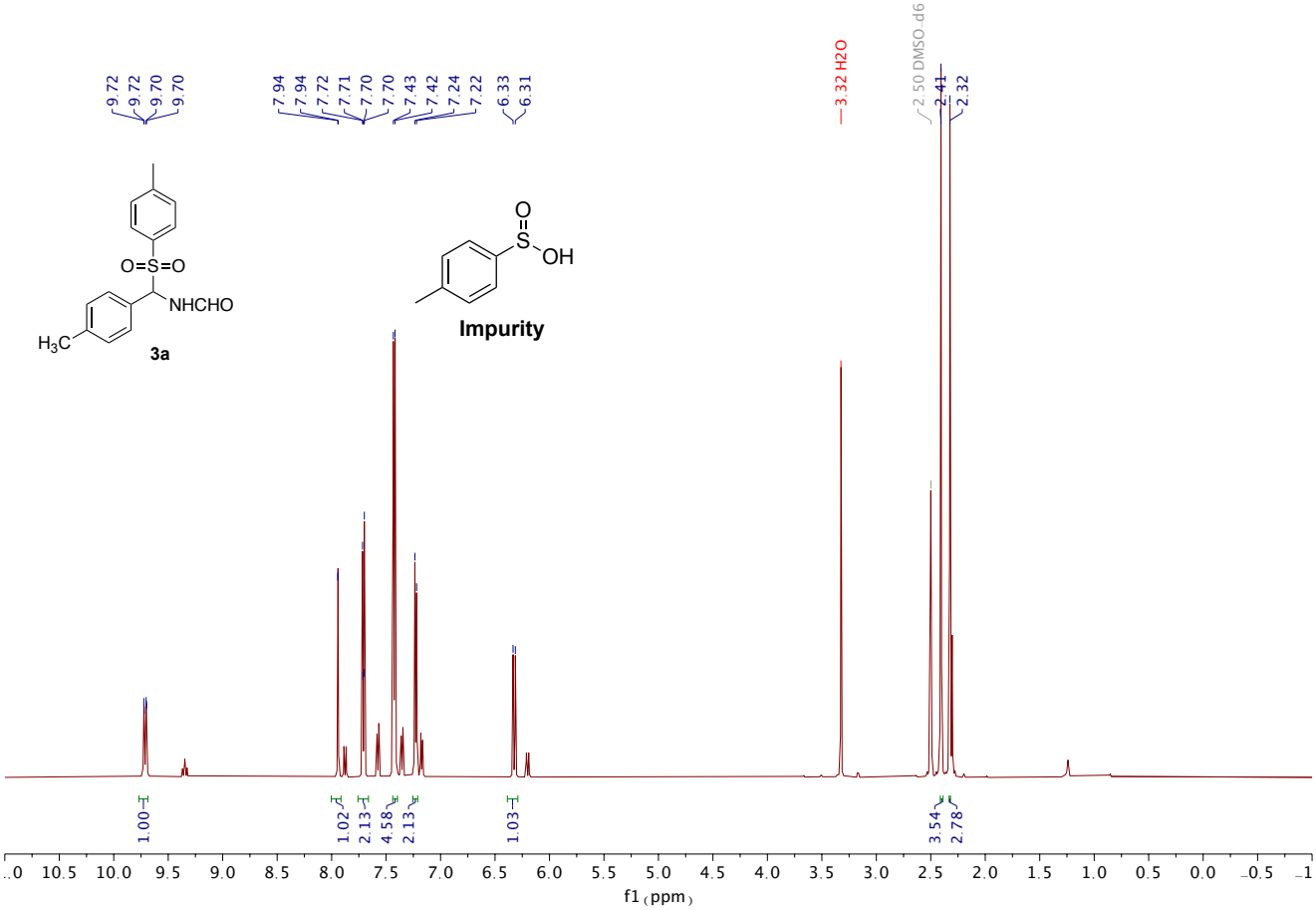
Spectra



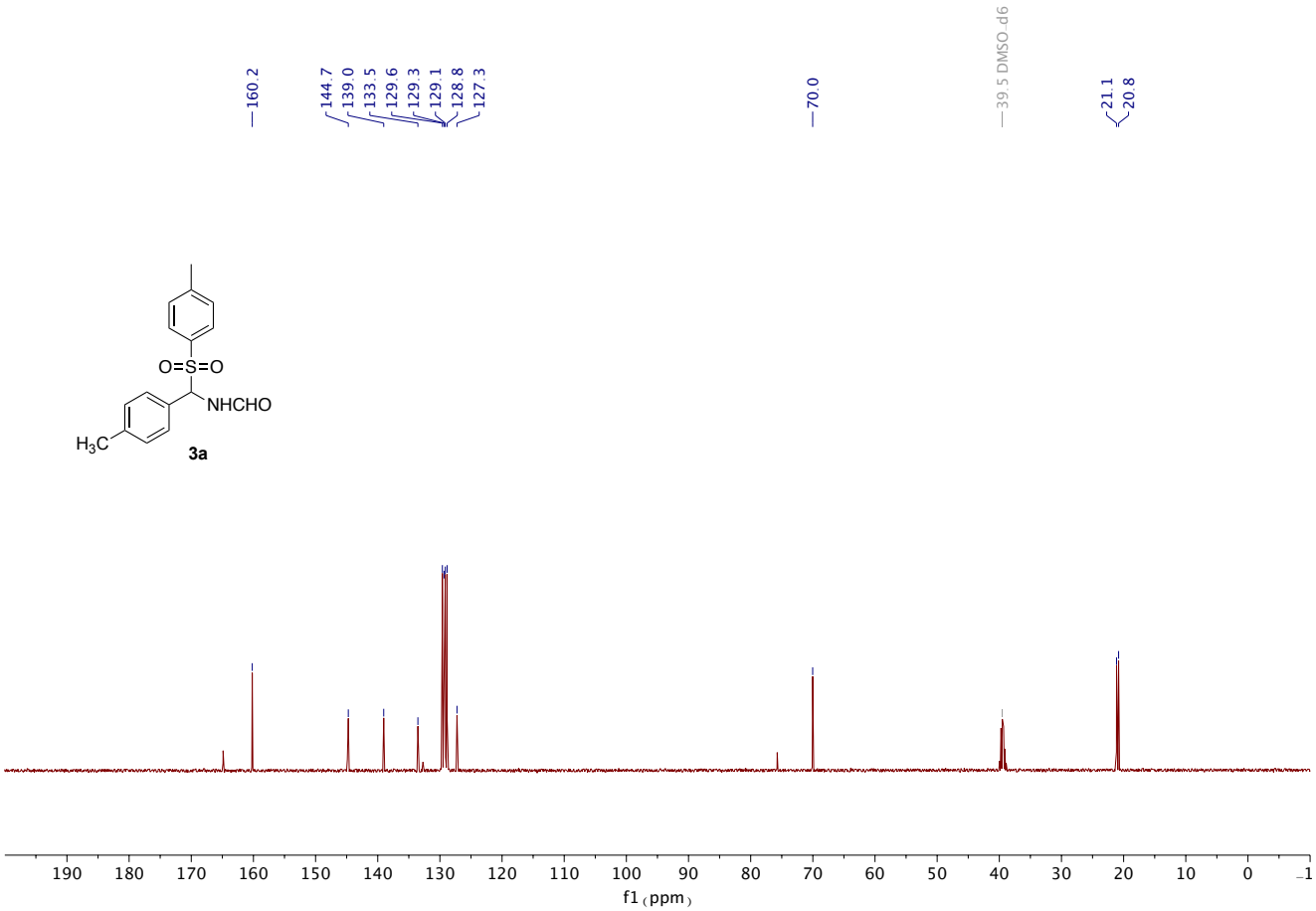
Compound **2a**: 500 MHz ^{1}H NMR spectrum in DMSO-d$_6$.



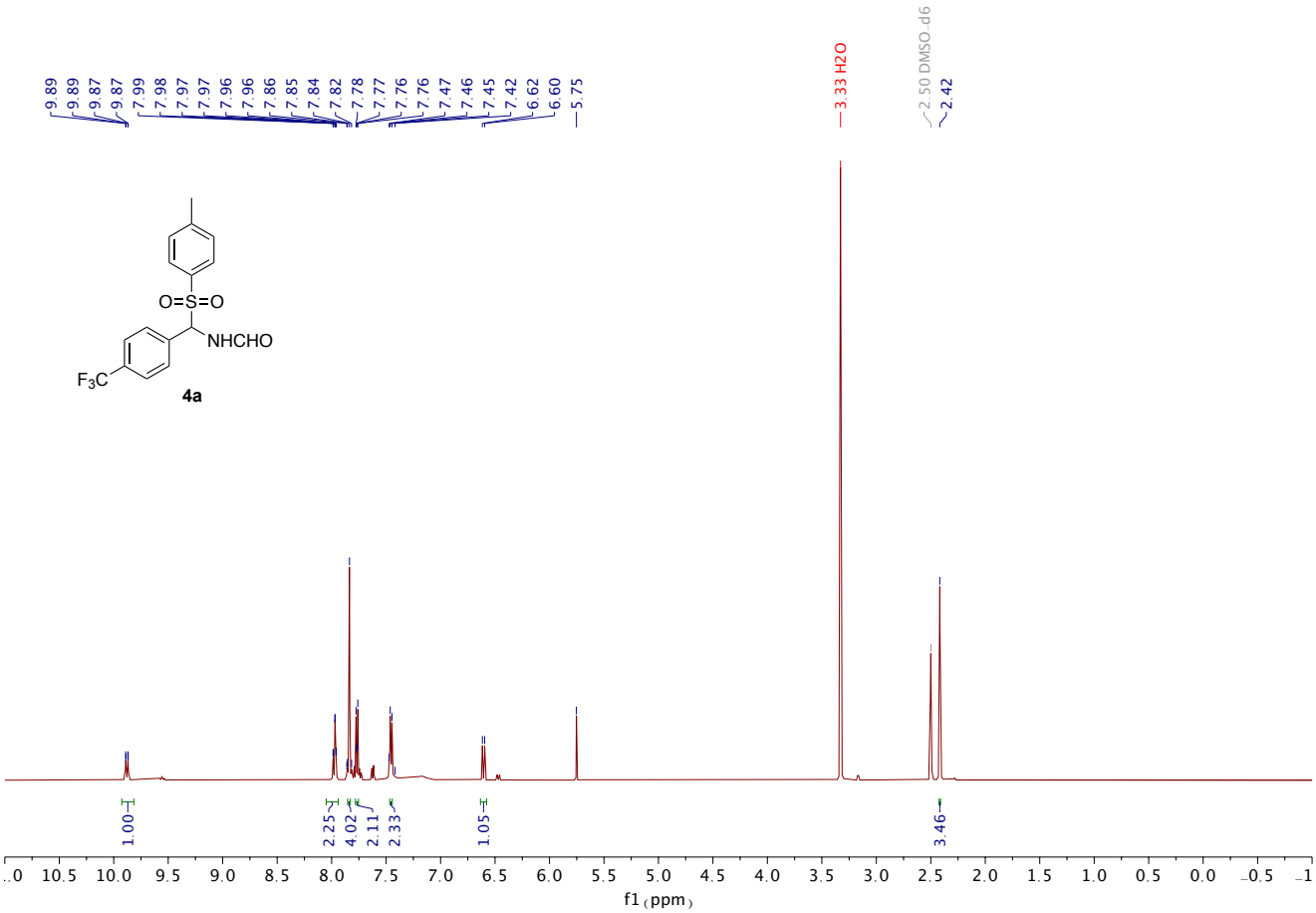
Compound **2a**: 125 MHz ^{13}C NMR spectrum in DMSO-d_6.



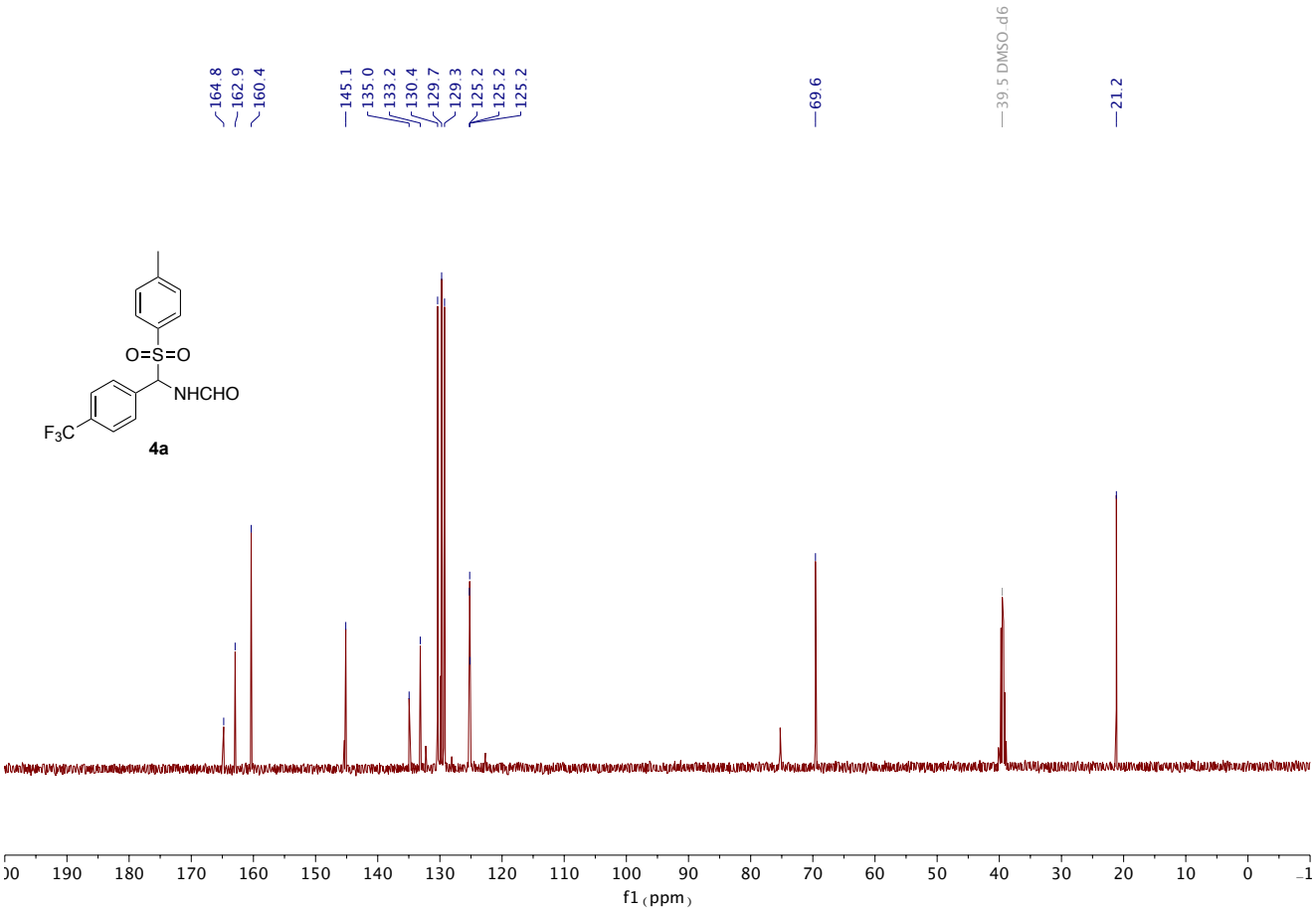
Compound **3a**: 500 MHz ^{1}H NMR spectrum in DMSO-d$_6$.



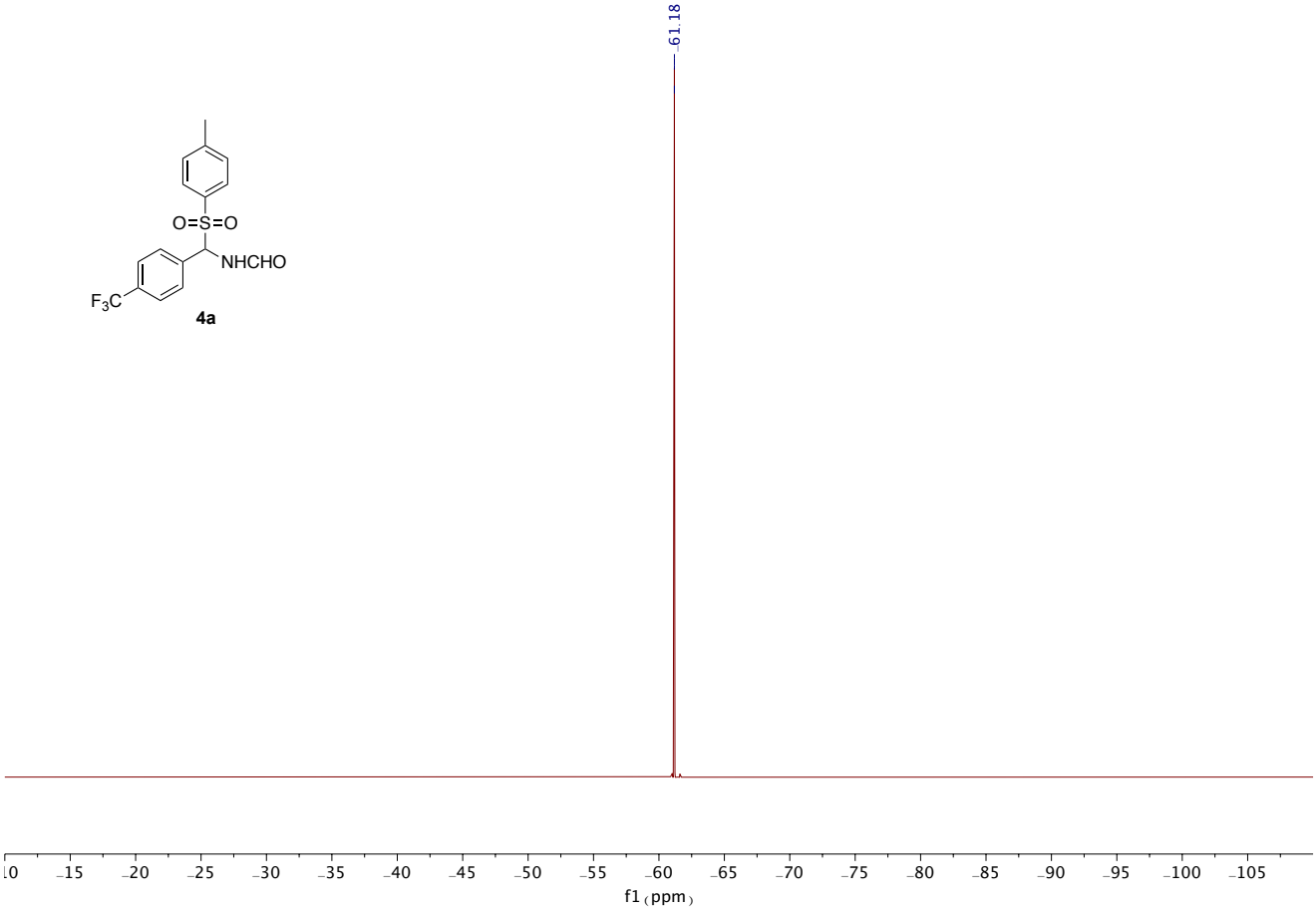
Compound **3a**: 100 MHz ^{13}C NMR spectrum in DMSO-d_6.



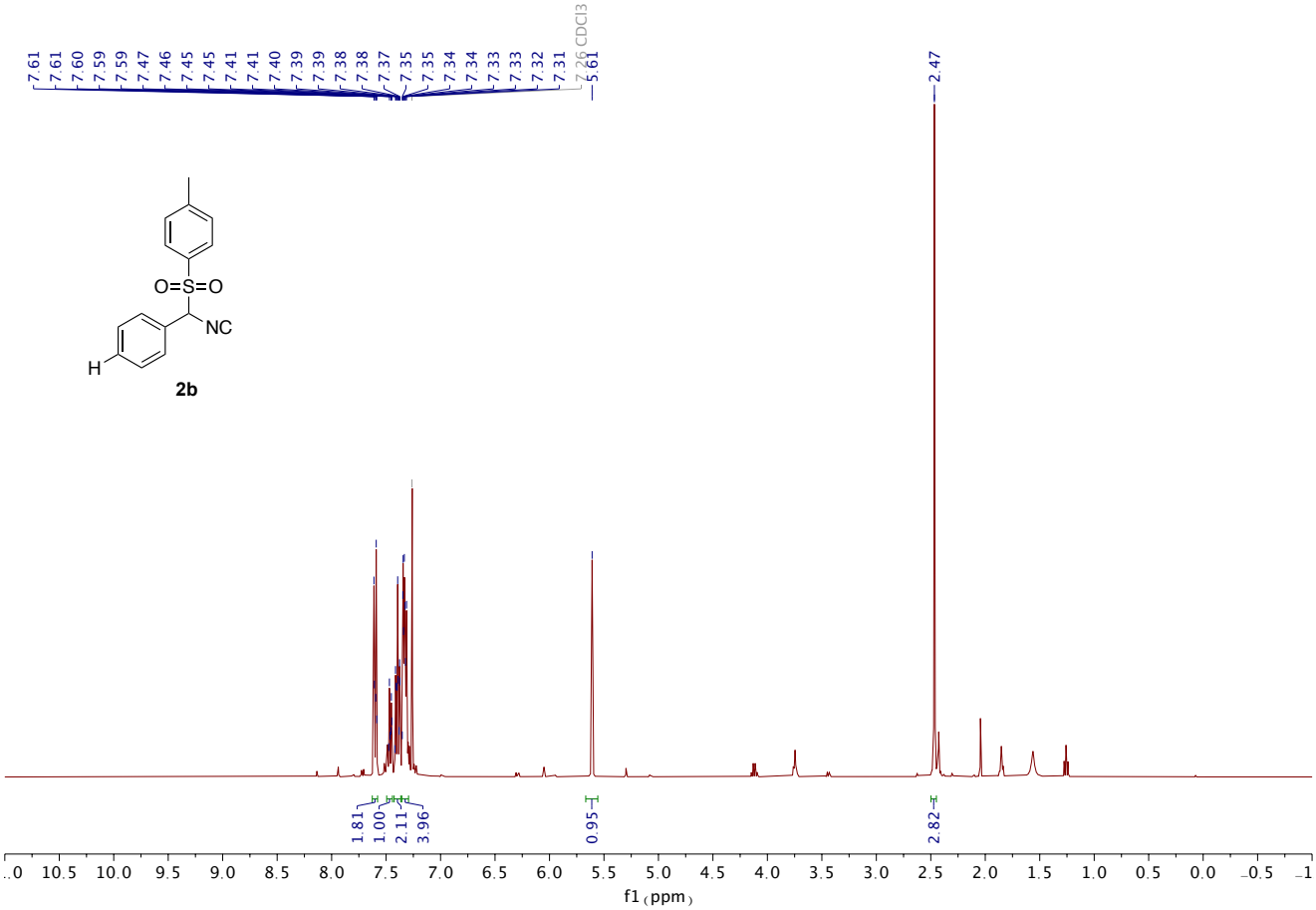
Compound **4a**: 500 MHz ^{1}H NMR spectrum in DMSO-d_6.



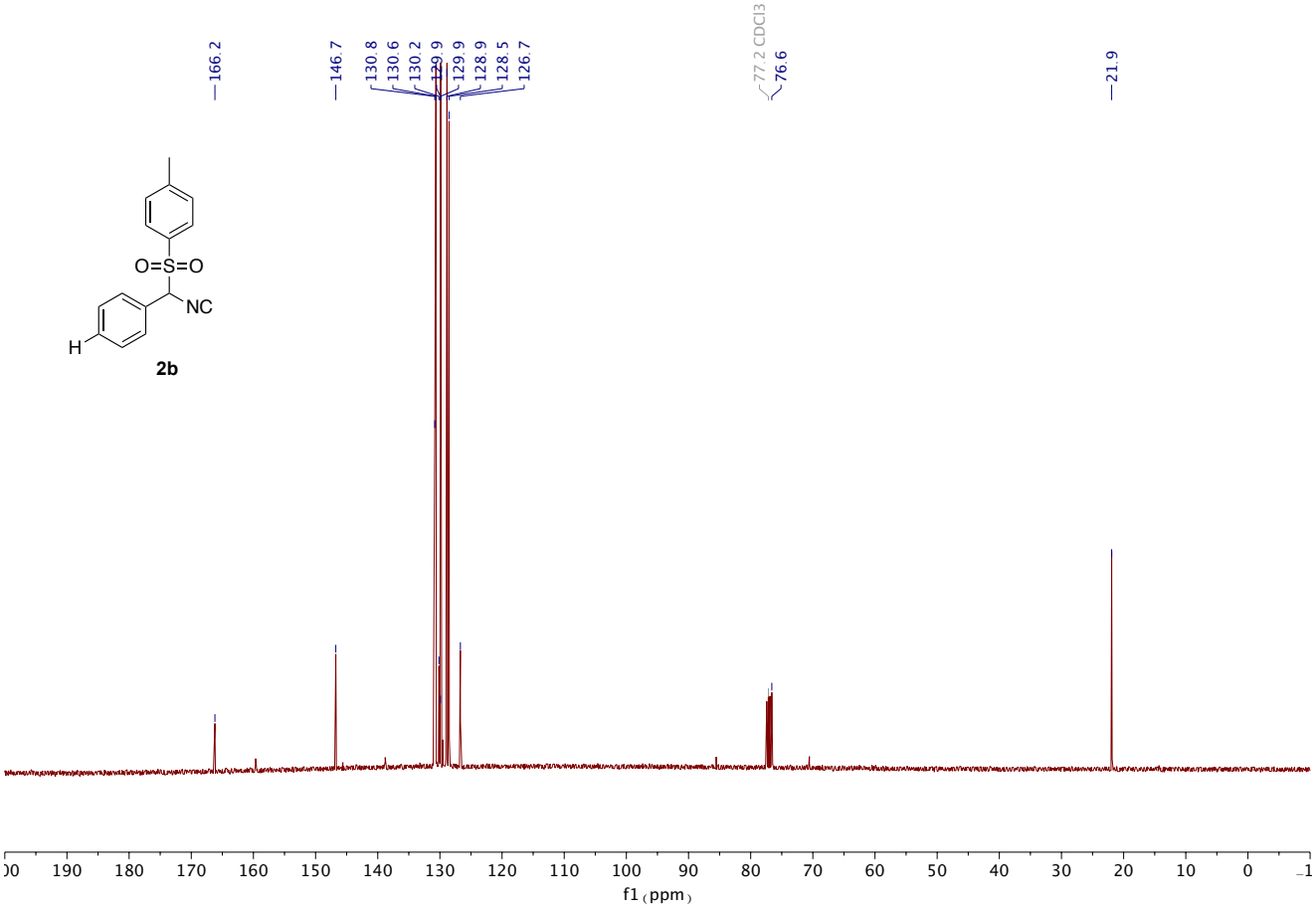
Compound **4a**: 100 MHz ^{13}C NMR spectrum in DMSO-d_6.



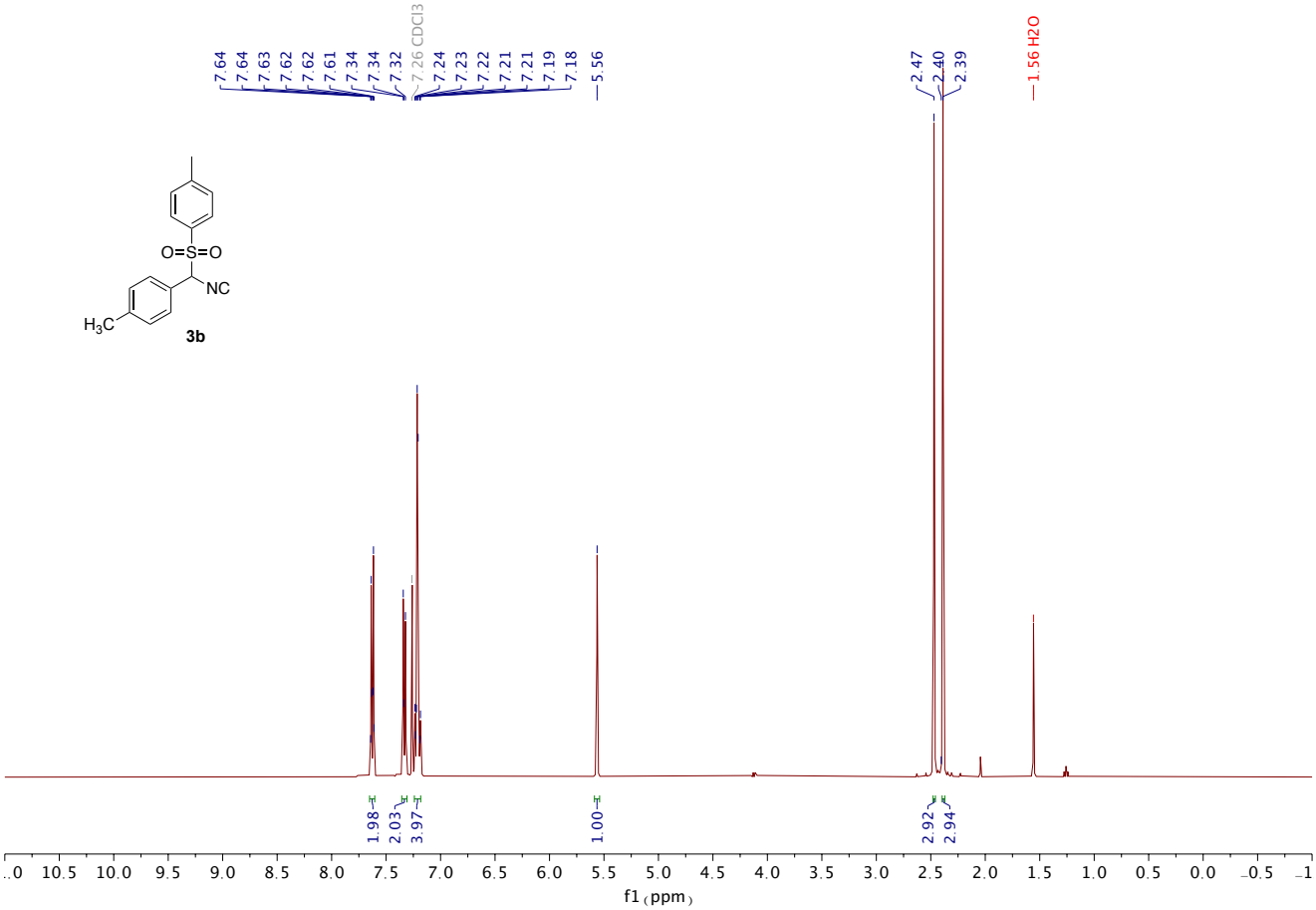
Compound **4a**: 470 MHz ^{19}F NMR spectrum in DMSO-d_6.



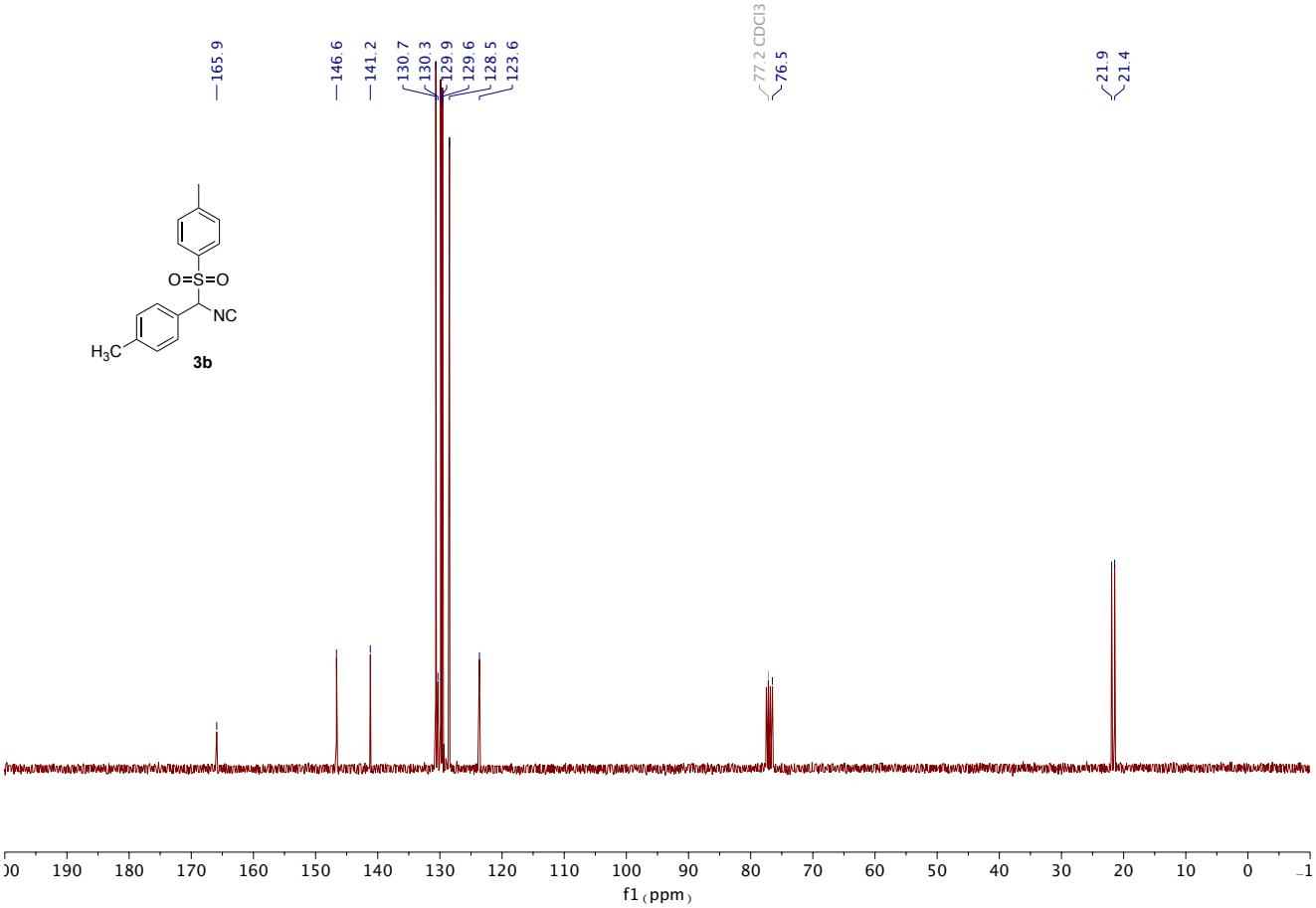
Compound **2b**: 400 MHz ^{1}H NMR spectrum in $CDCl_3$.



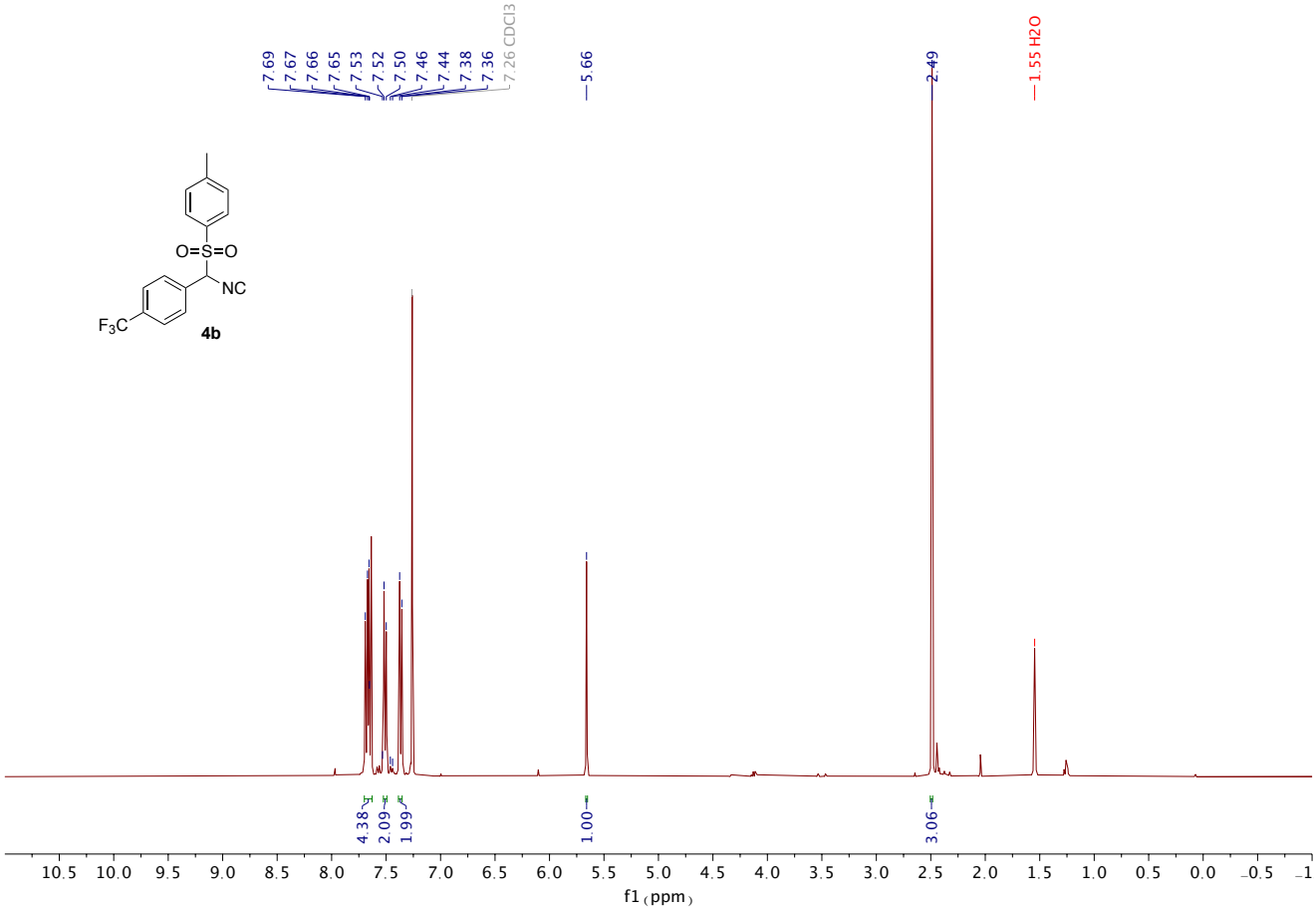
Compound **2b**: 125 MHz ^{1}C NMR spectrum in $CDCl_3$.



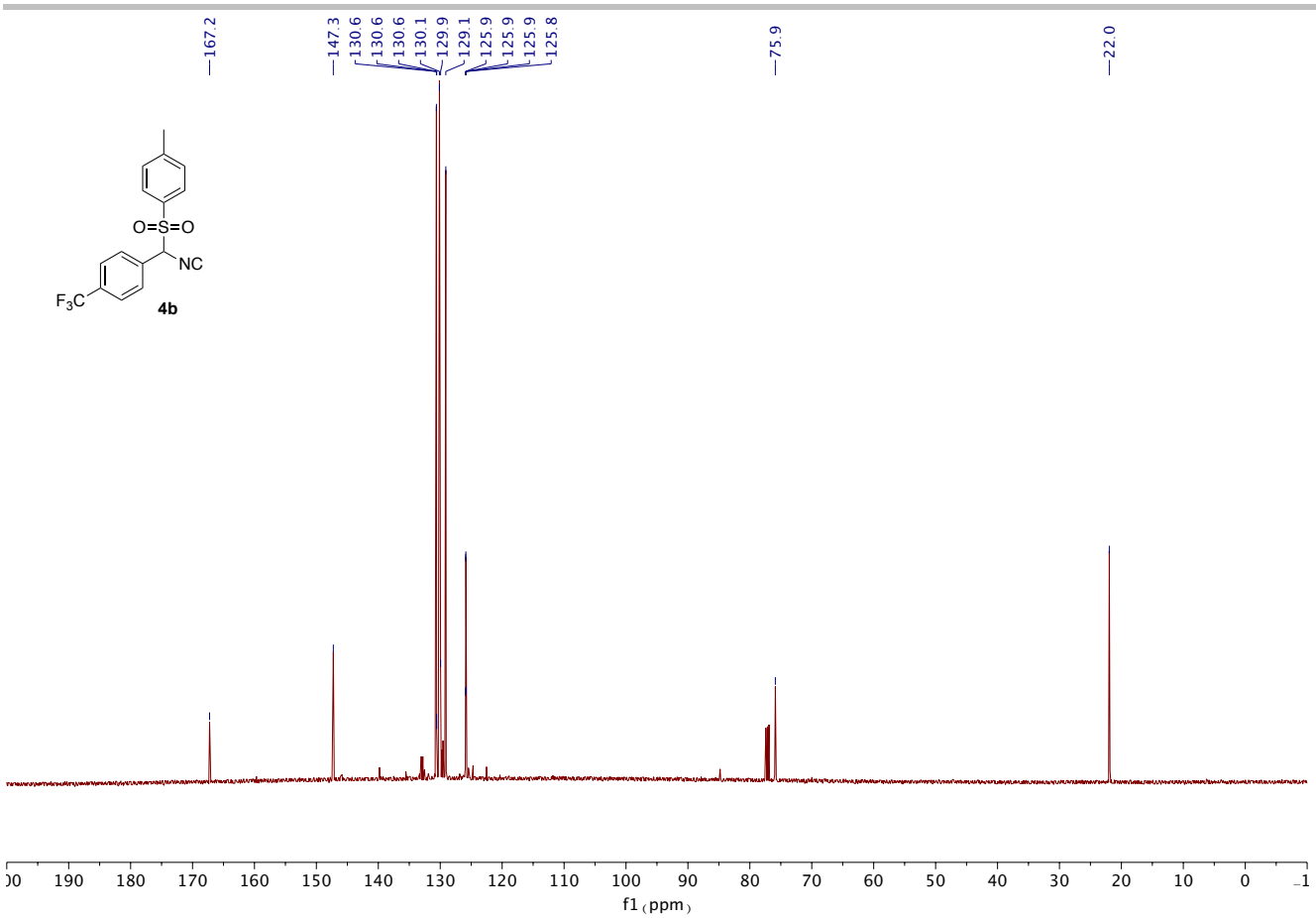
Compound **3b**: 500 MHz ^{1}H NMR spectrum in $CDCl_3$.



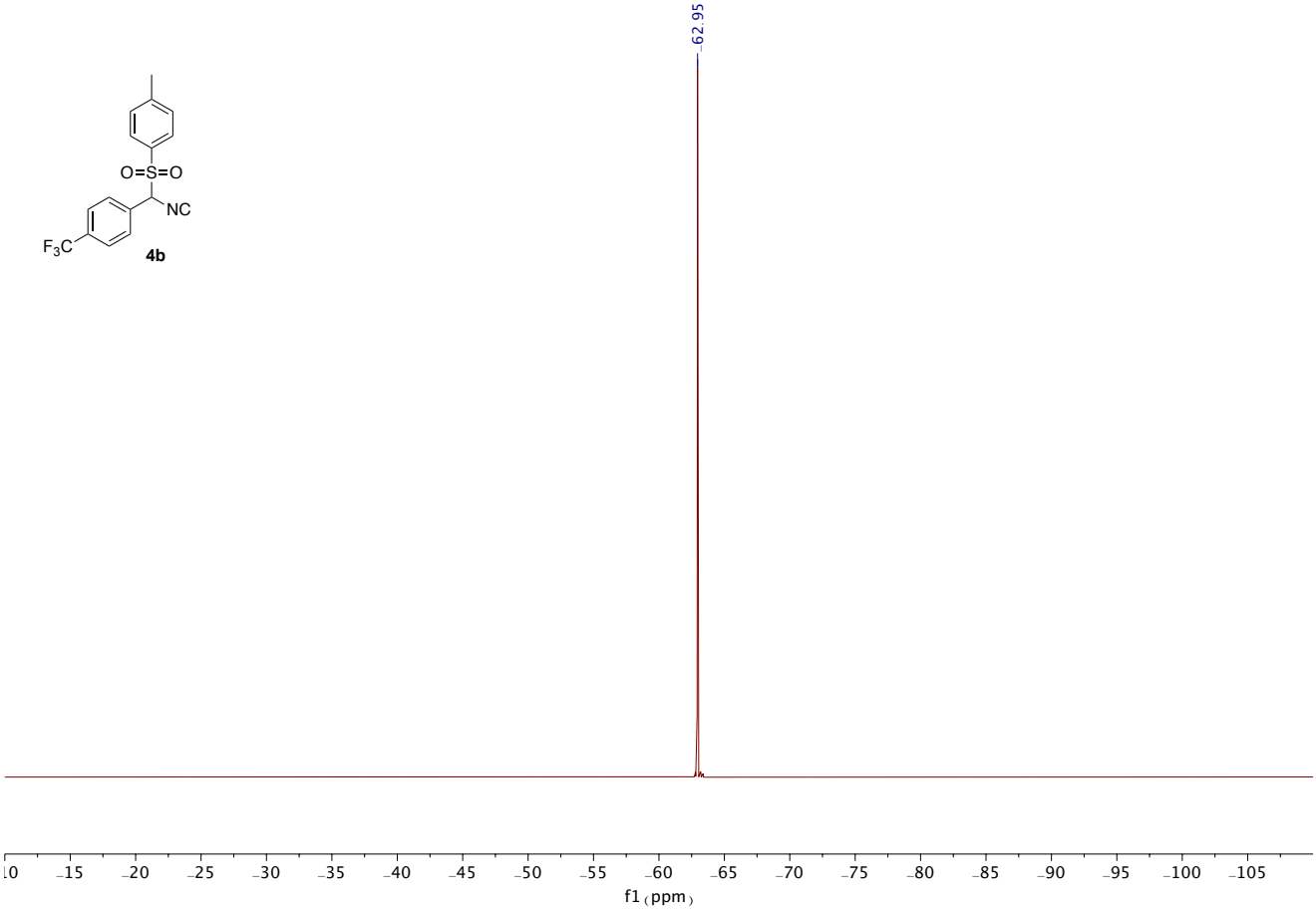
Compound **3b**: 100 MHz ^{13}C NMR spectrum in $CDCl_3$.



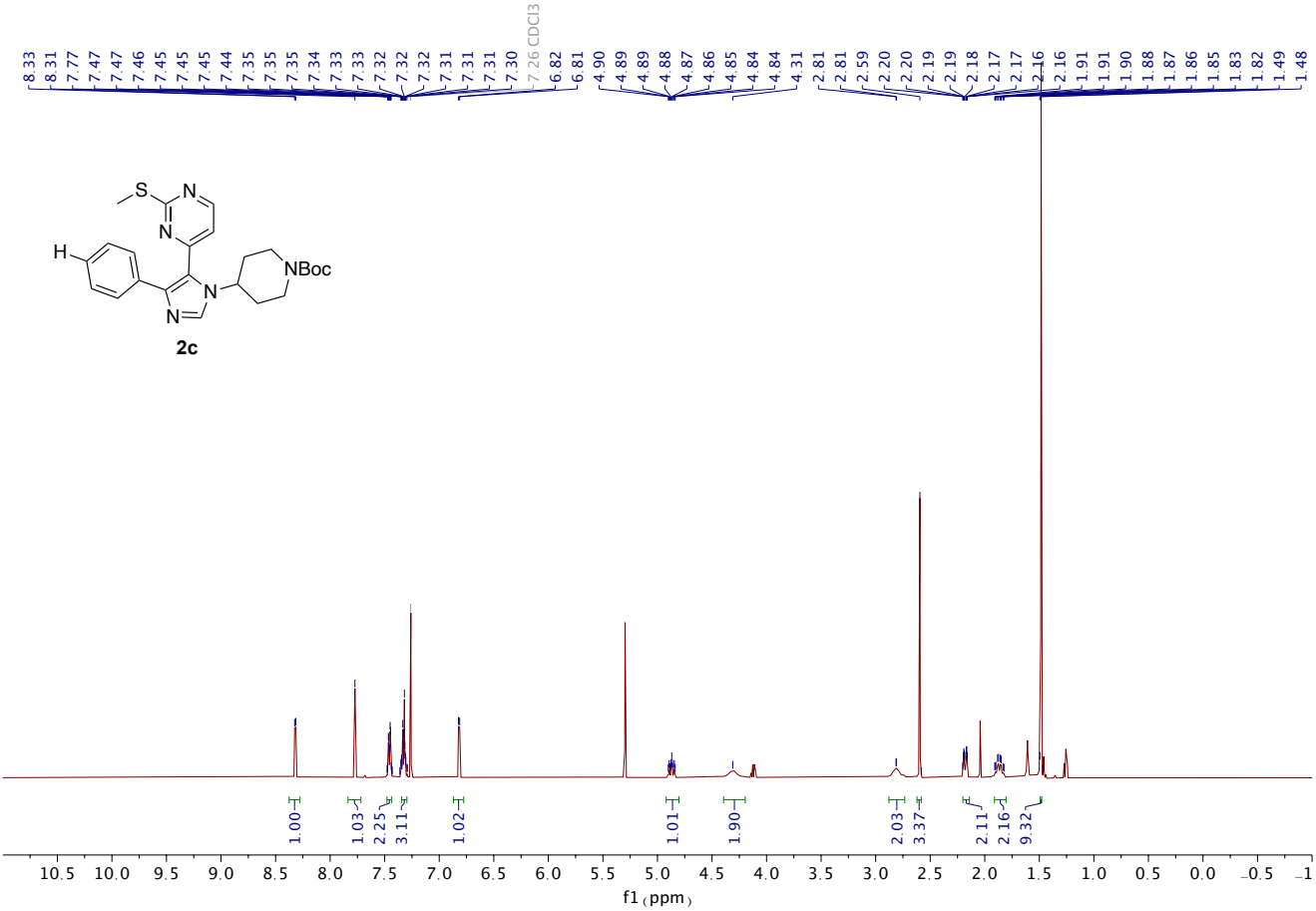
Compound **4b**: 400 MHz ^{1}H NMR spectrum in $CDCl_3$.



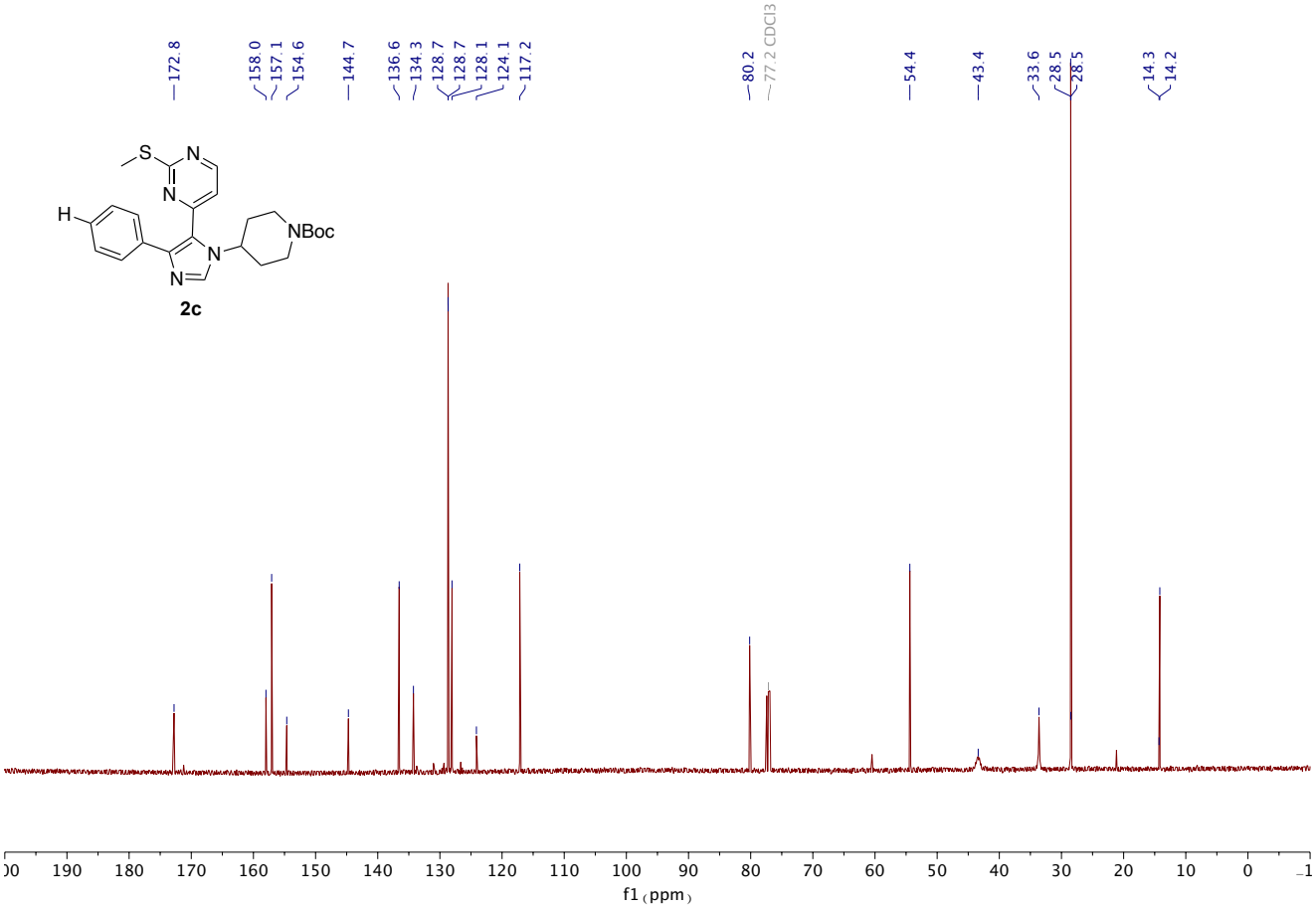
Compound **4b**: 125 MHz ^{13}C NMR spectrum in $CDCl_3$.



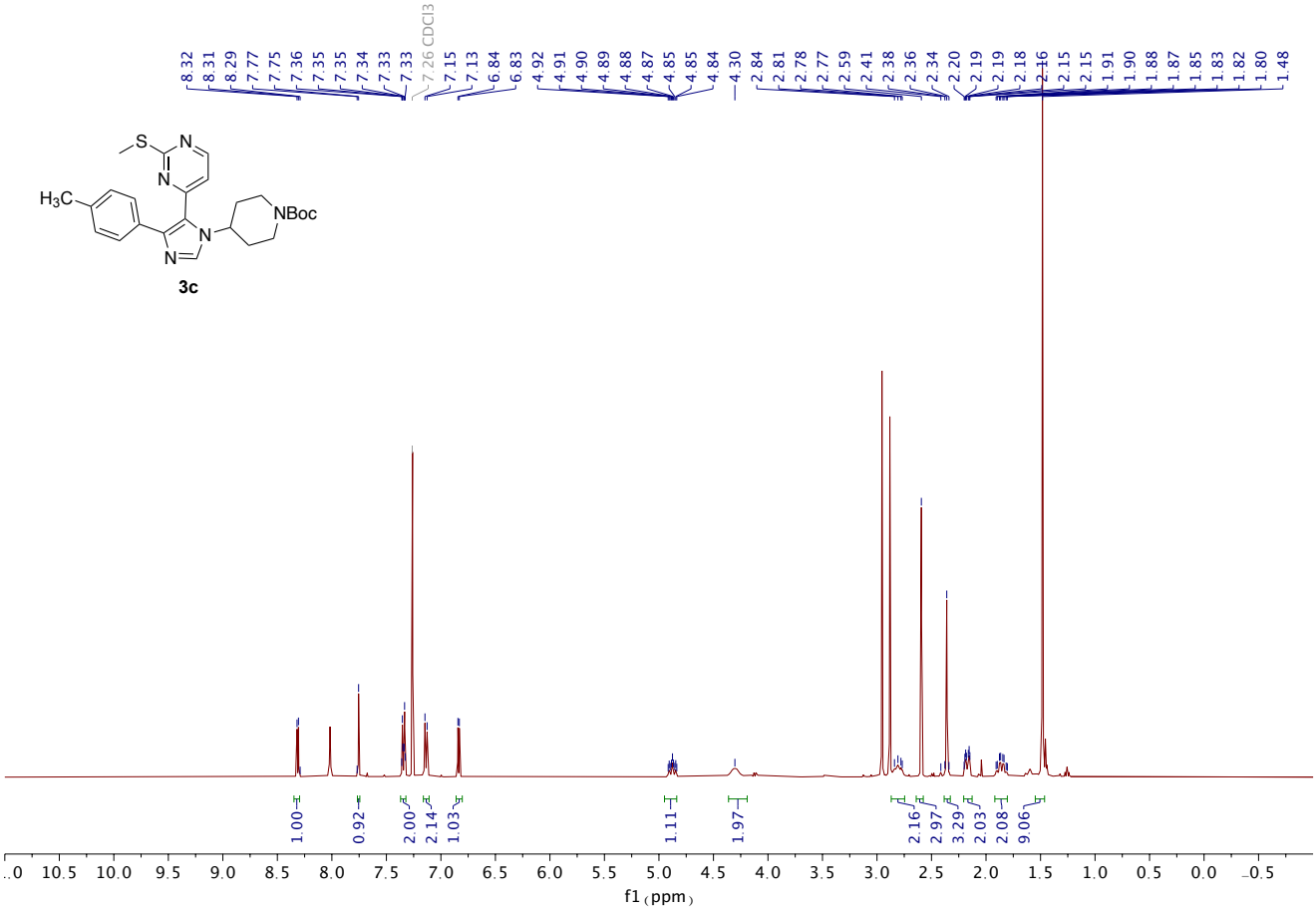
Compound **4b**: 470 MHz ^{19}F NMR spectrum in $CDCl_3$.



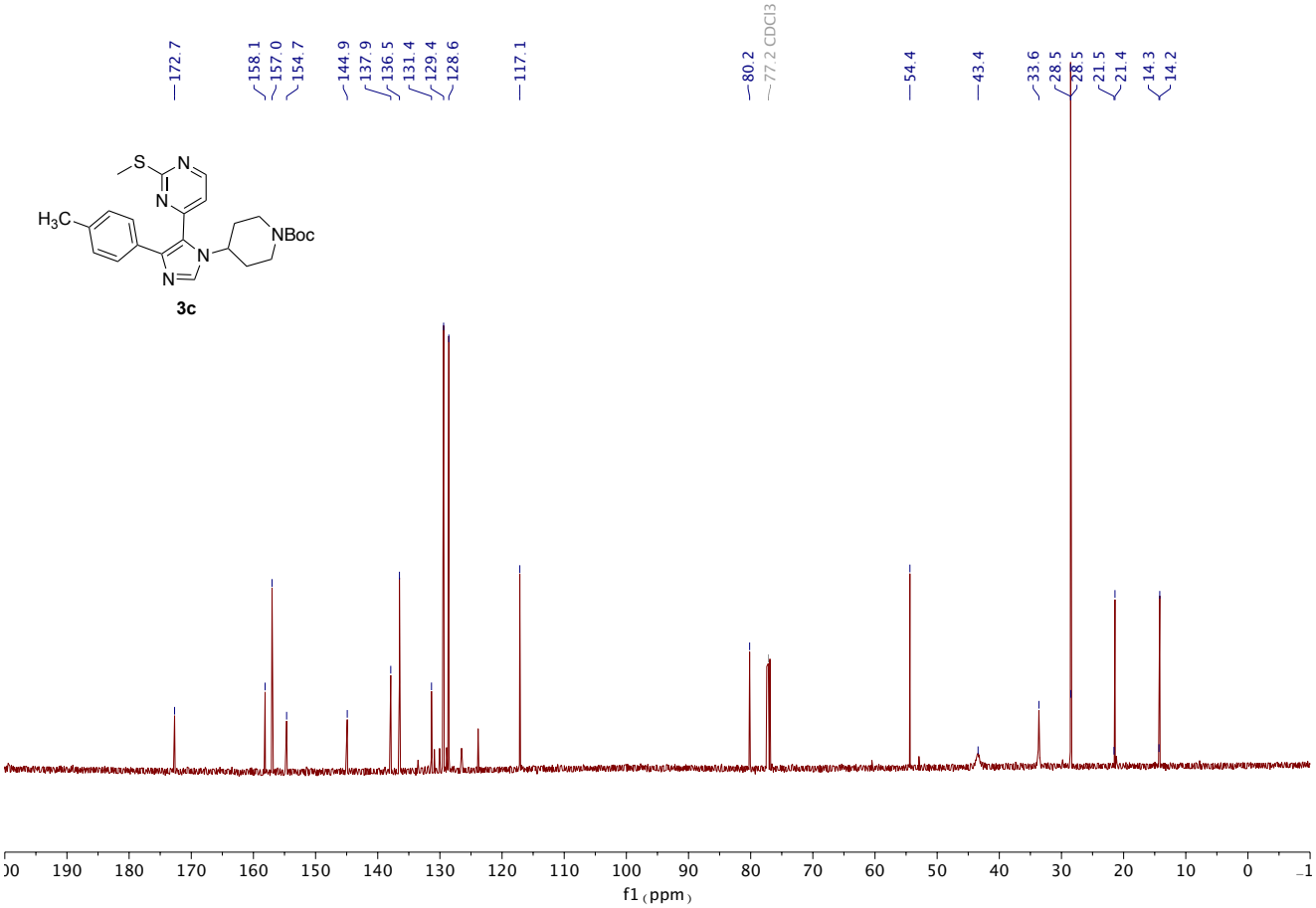
Compound **2c**: 500 MHz ^{1}H NMR spectrum in $CDCl_3$.



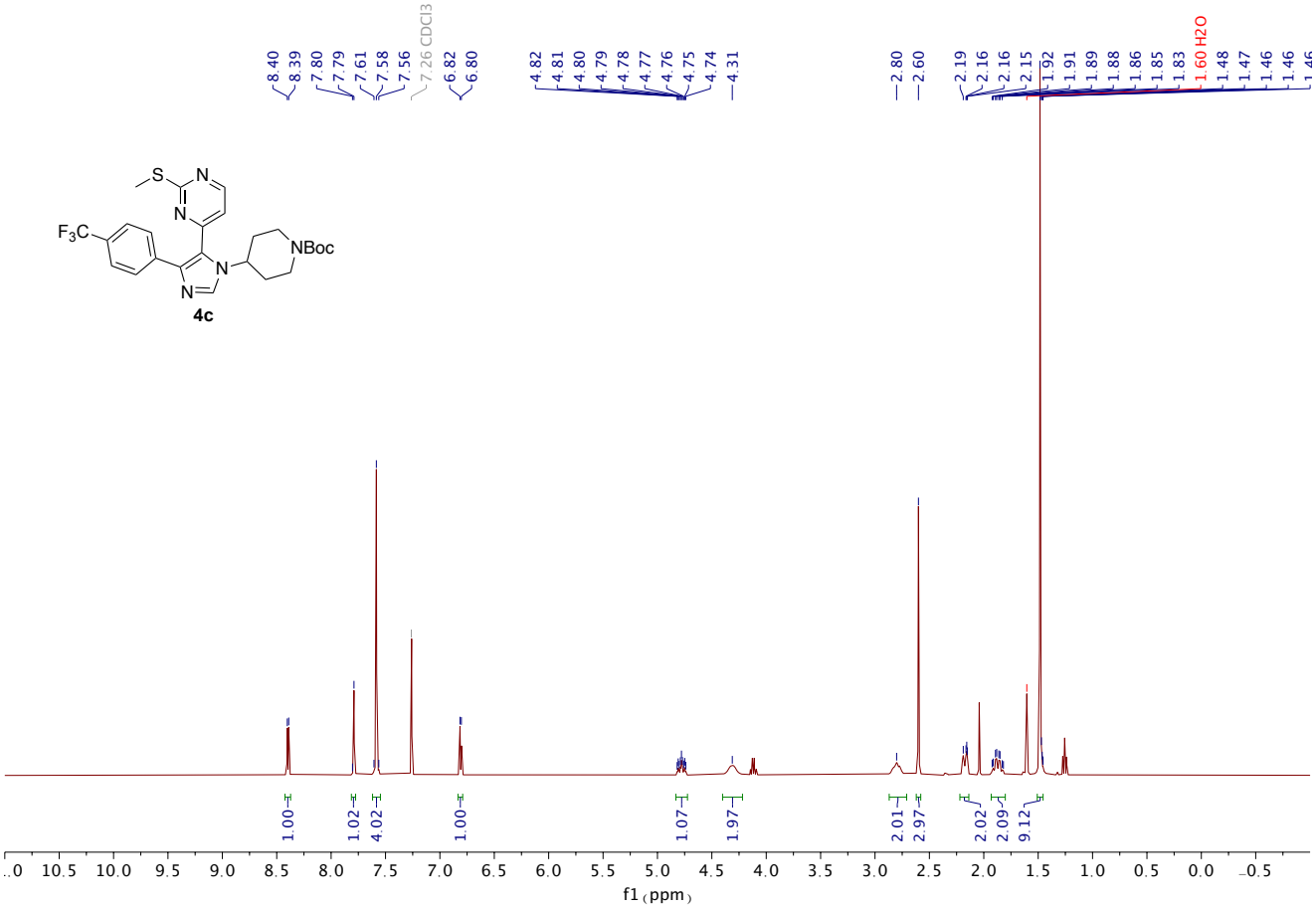
Compound **2c**: 125 MHz ^{13}C NMR spectrum in $CDCl_3$.



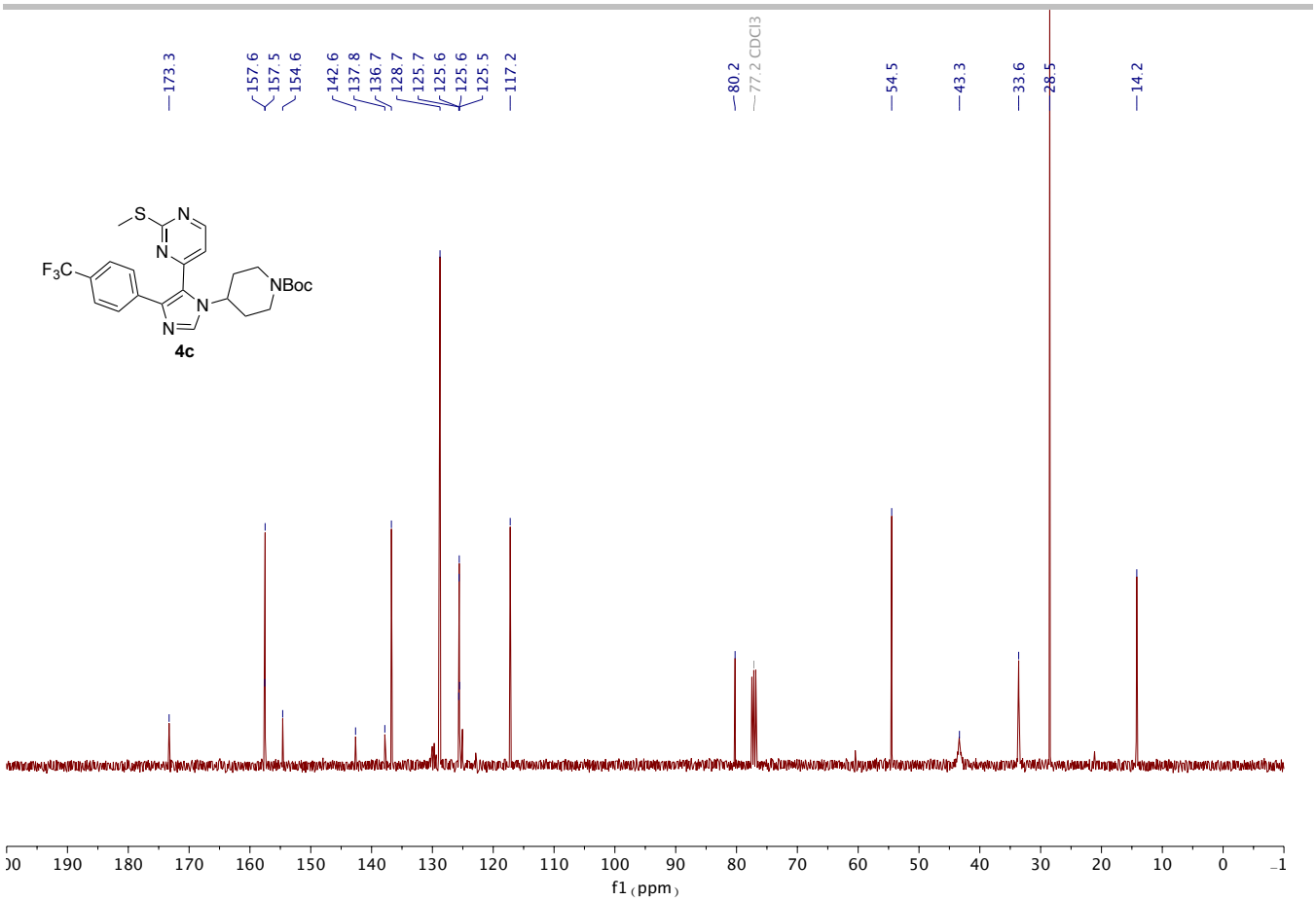
Compound **3c**: 400 MHz ^{1}H NMR spectrum in $CDCl_3$.



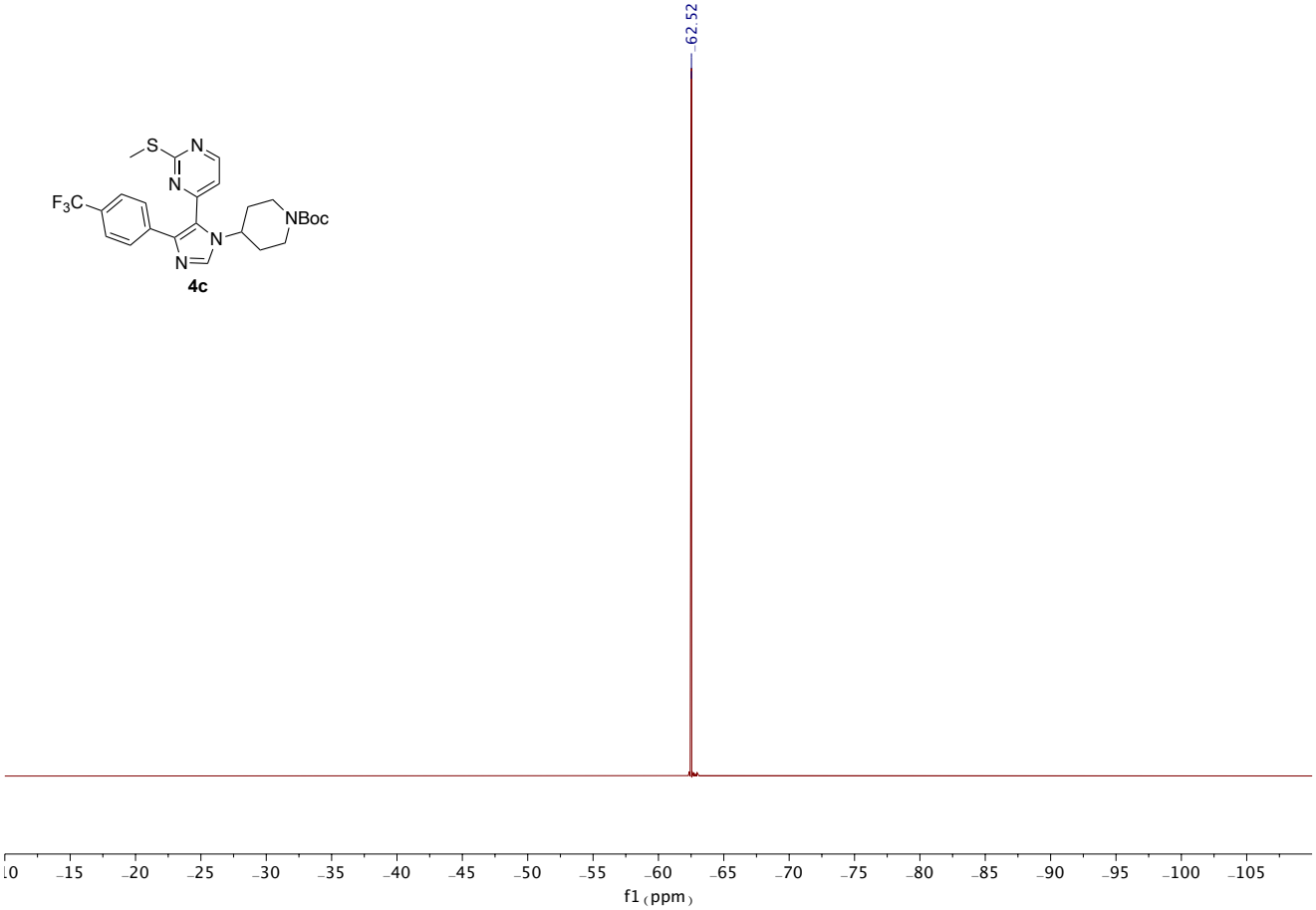
Compound **3c**: 100 MHz ^{13}C NMR spectrum in $CDCl_3$.



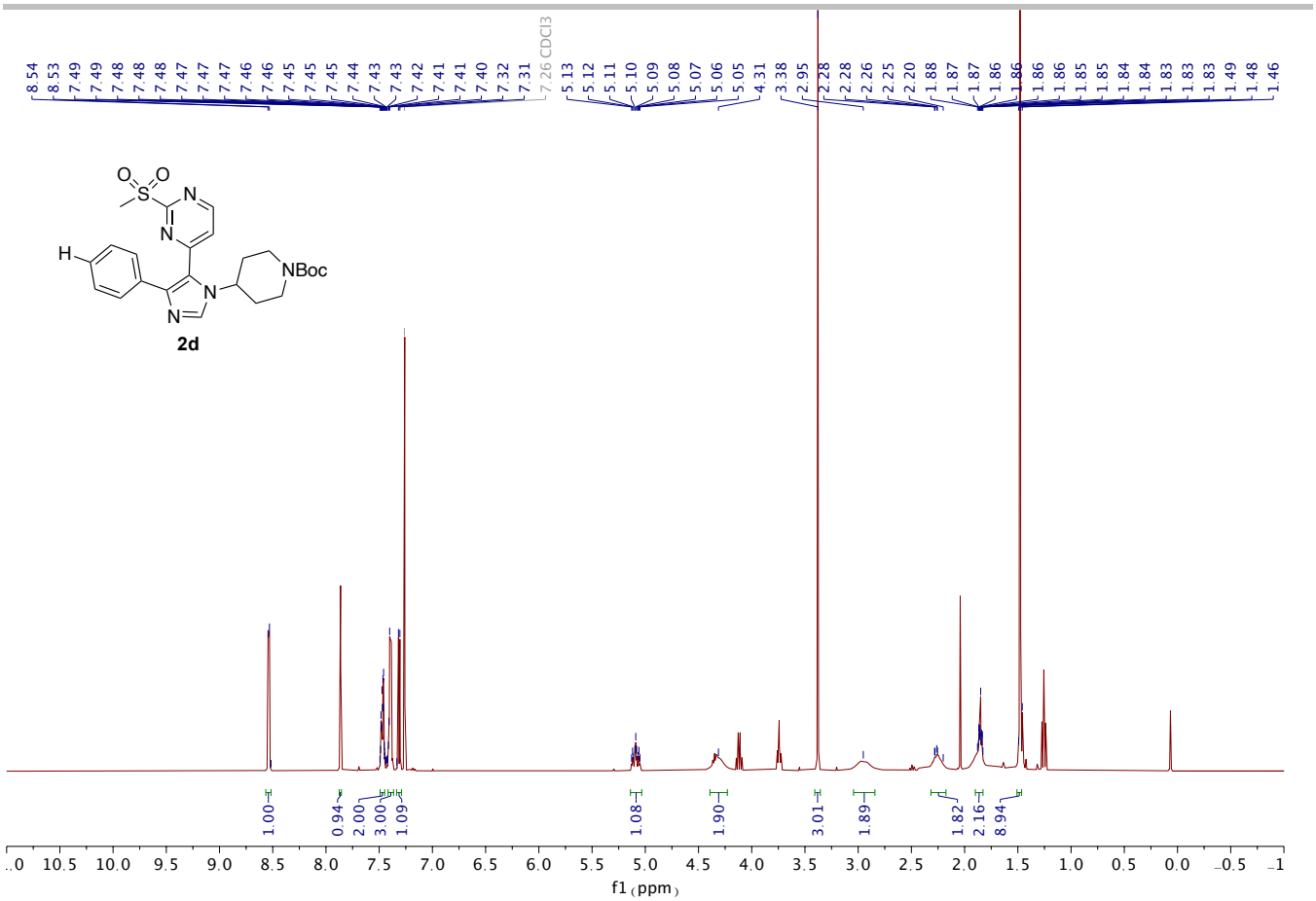
Compound **4c**: 400 MHz ^{1}H NMR spectrum in $CDCl_3$.



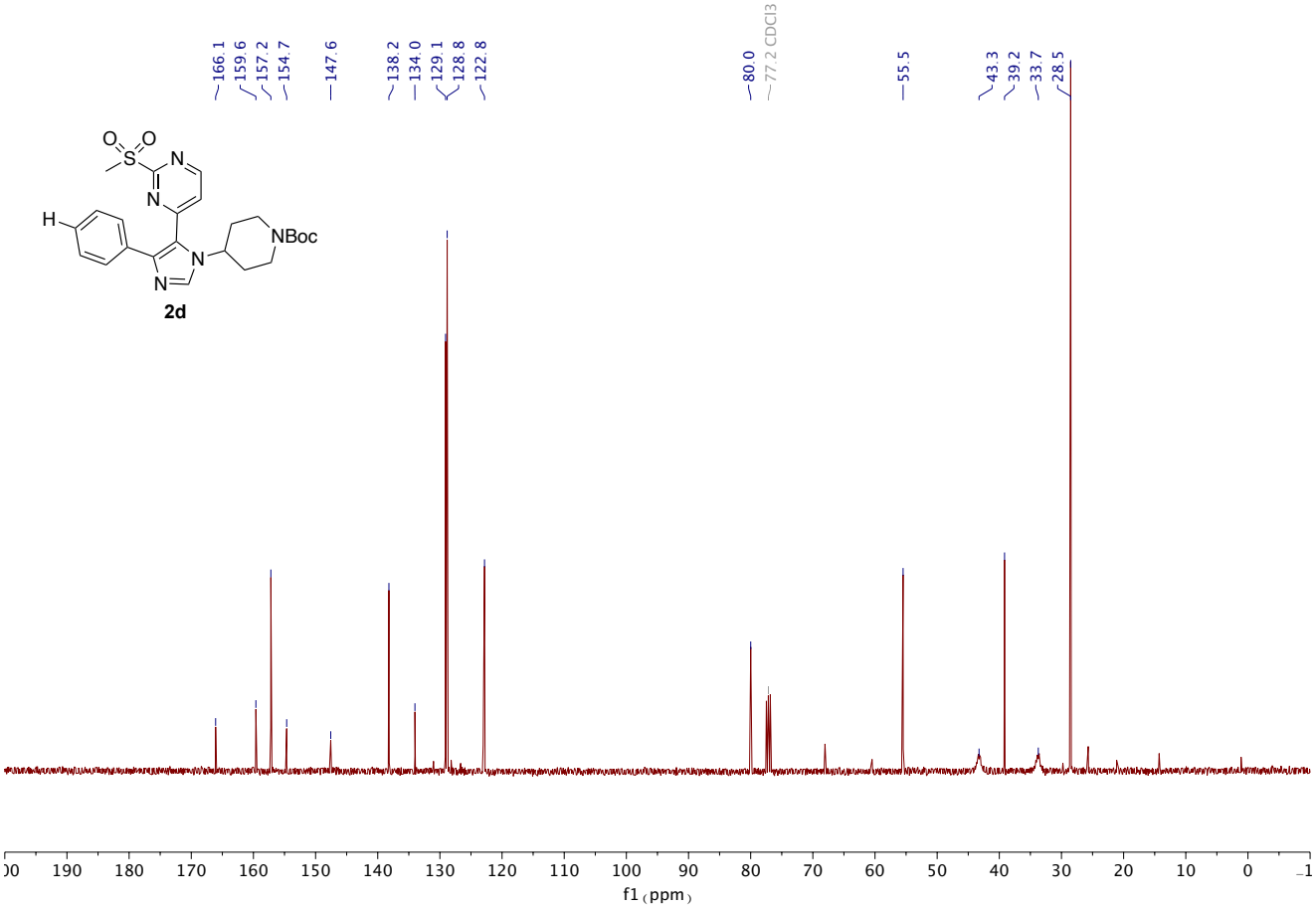
Compound **4c**: 100 MHz ^{13}C NMR spectrum in $CDCl_3$.



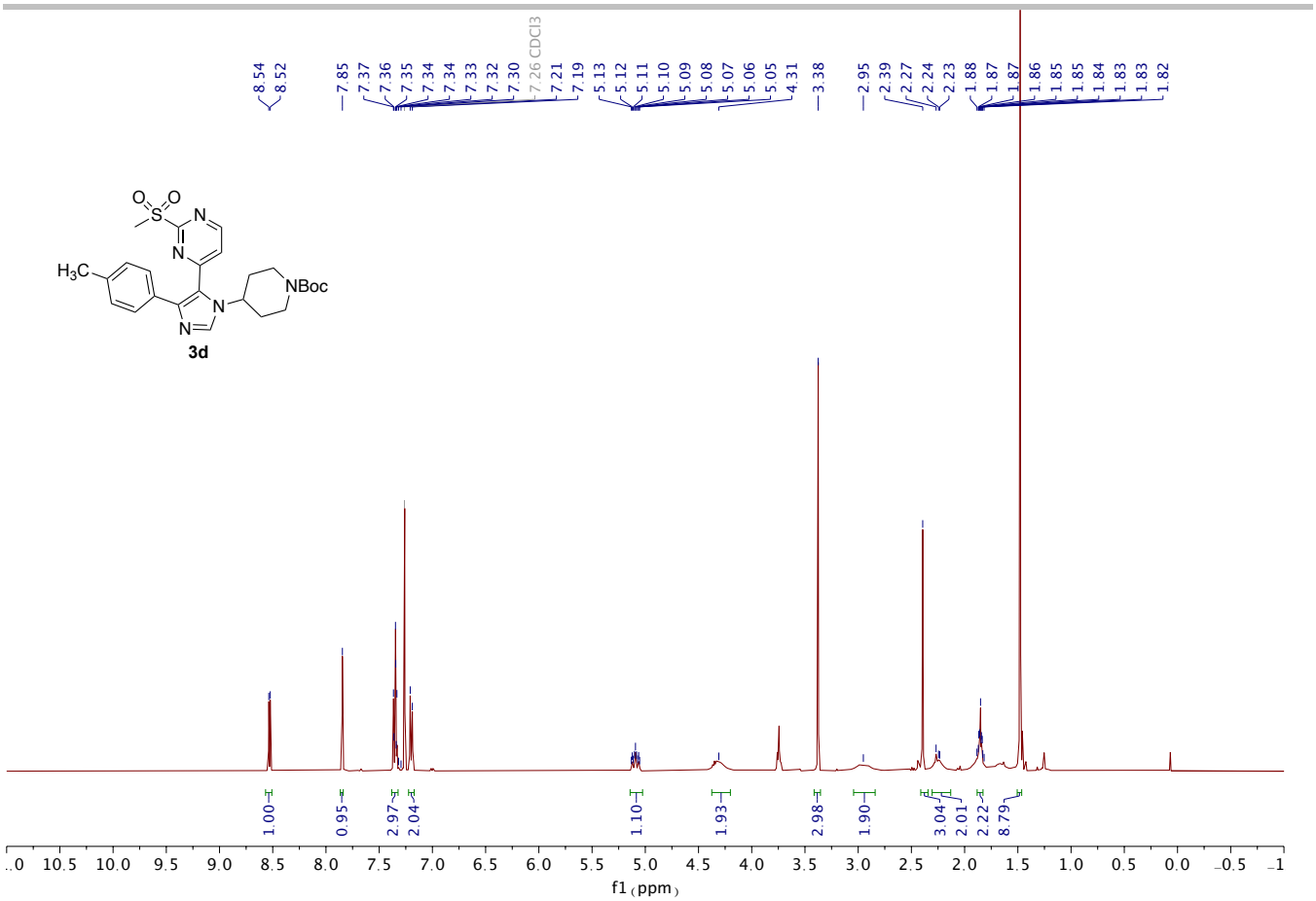
Compound **4c**: 470 MHz ^{19}F NMR spectrum in $CDCl_3$.



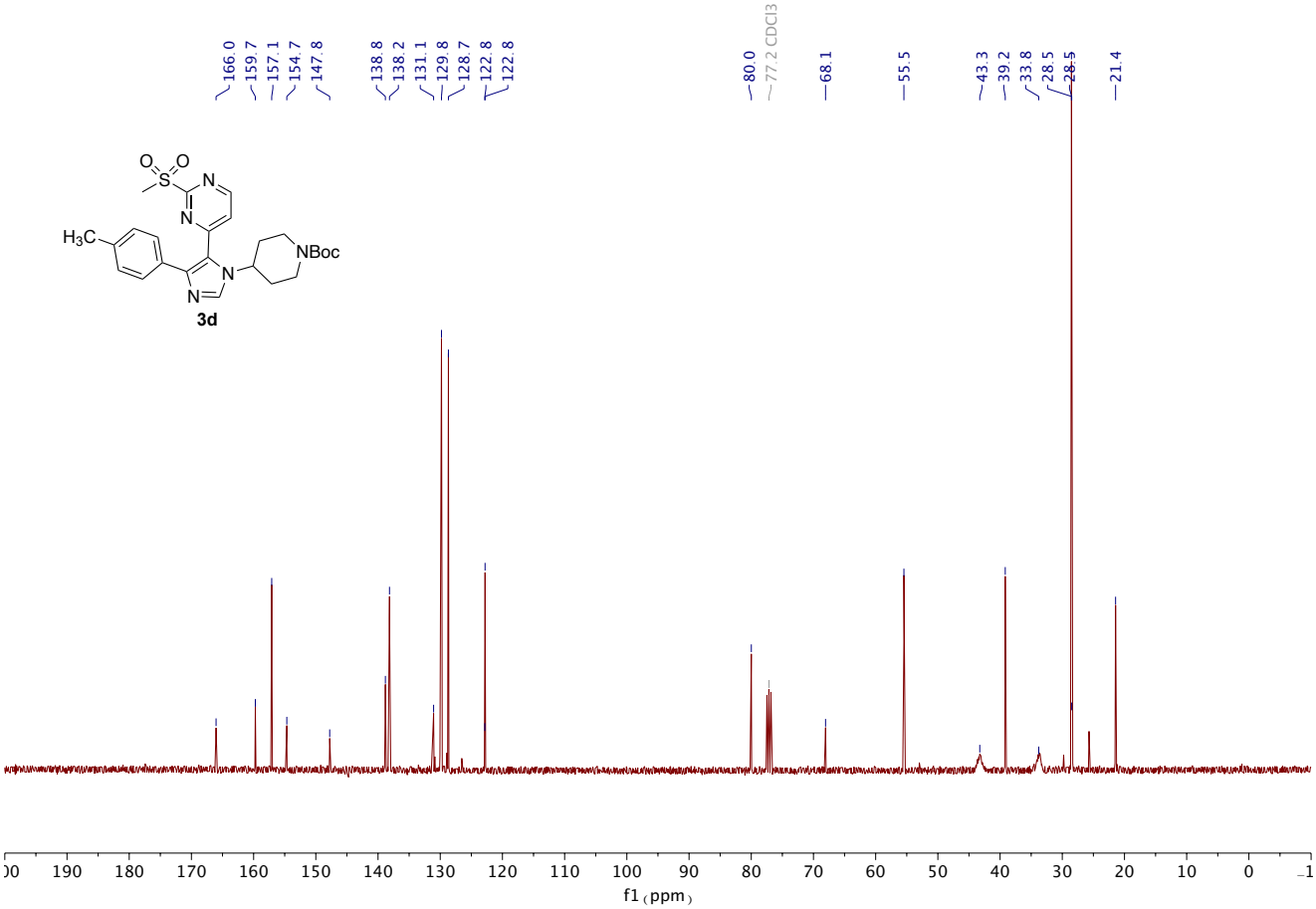
Compound **2d**: 400 MHz ^{1}H NMR spectrum in $CDCl_3$.



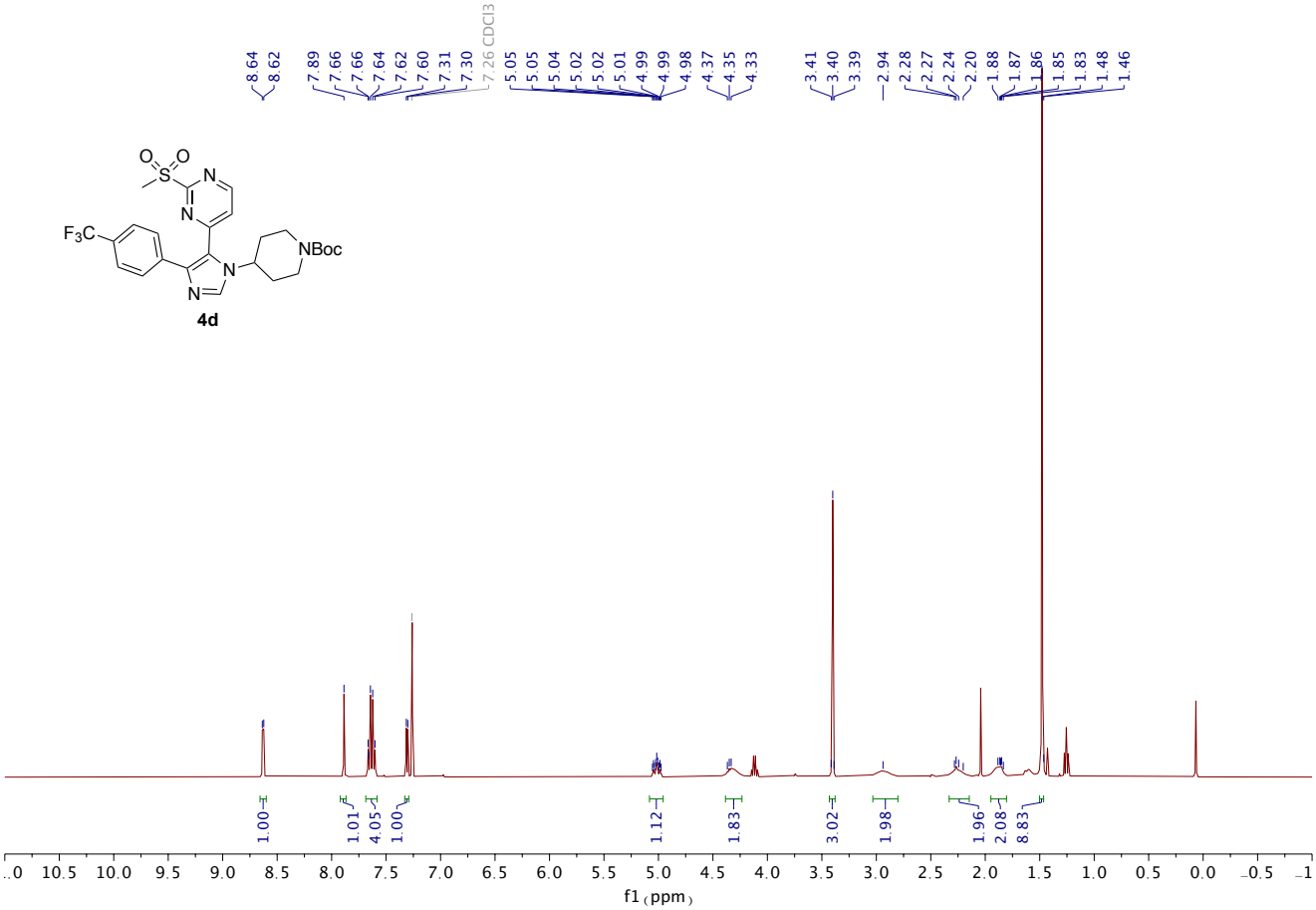
Compound **2d**: 100 MHz ^{13}C NMR spectrum in $CDCl_3$.



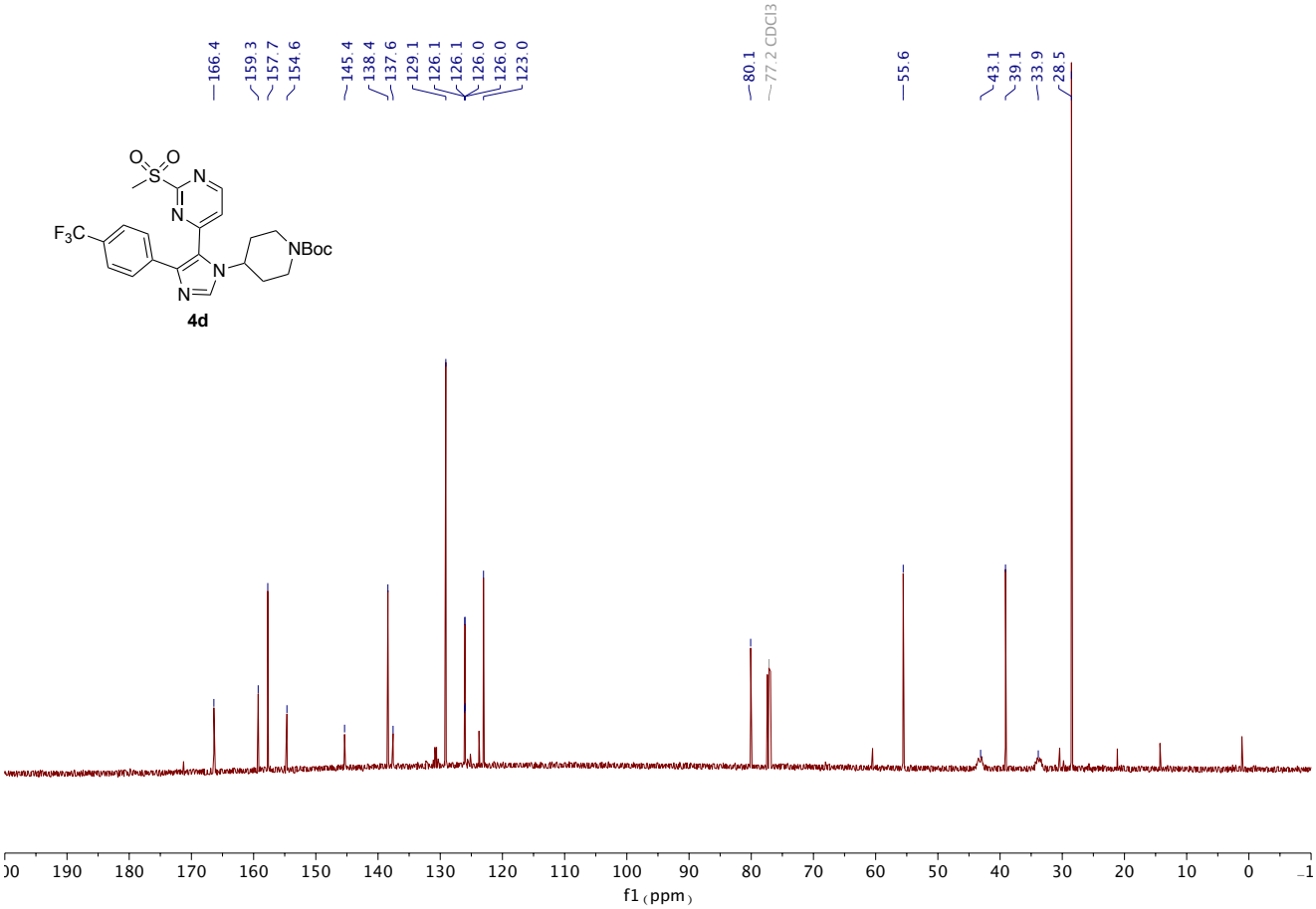
Compound **3d**: 400 MHz ^{1}H NMR spectrum in $CDCl_3$.



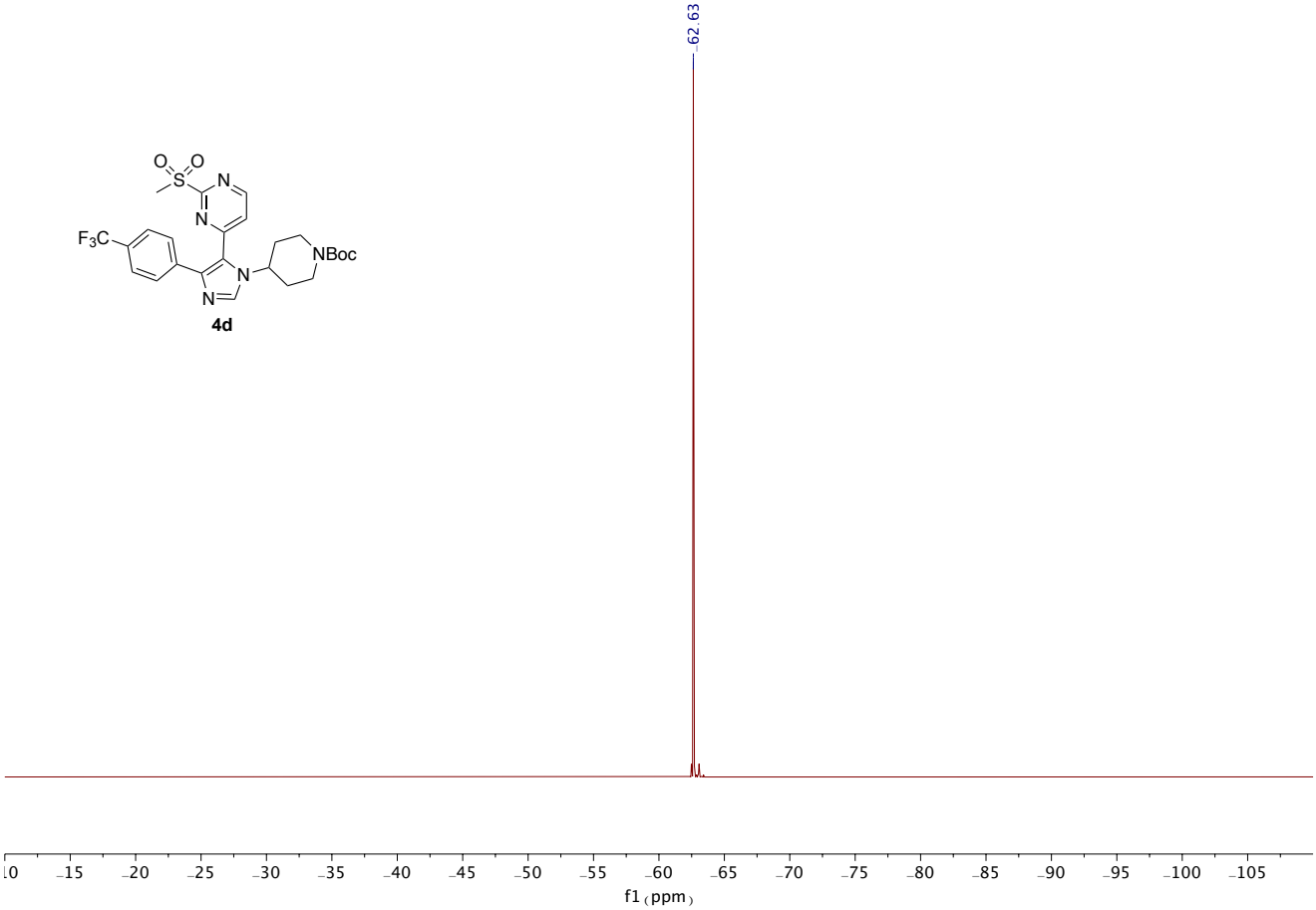
Compound **3d**: 100 MHz ^{13}C NMR spectrum in $CDCl_3$.



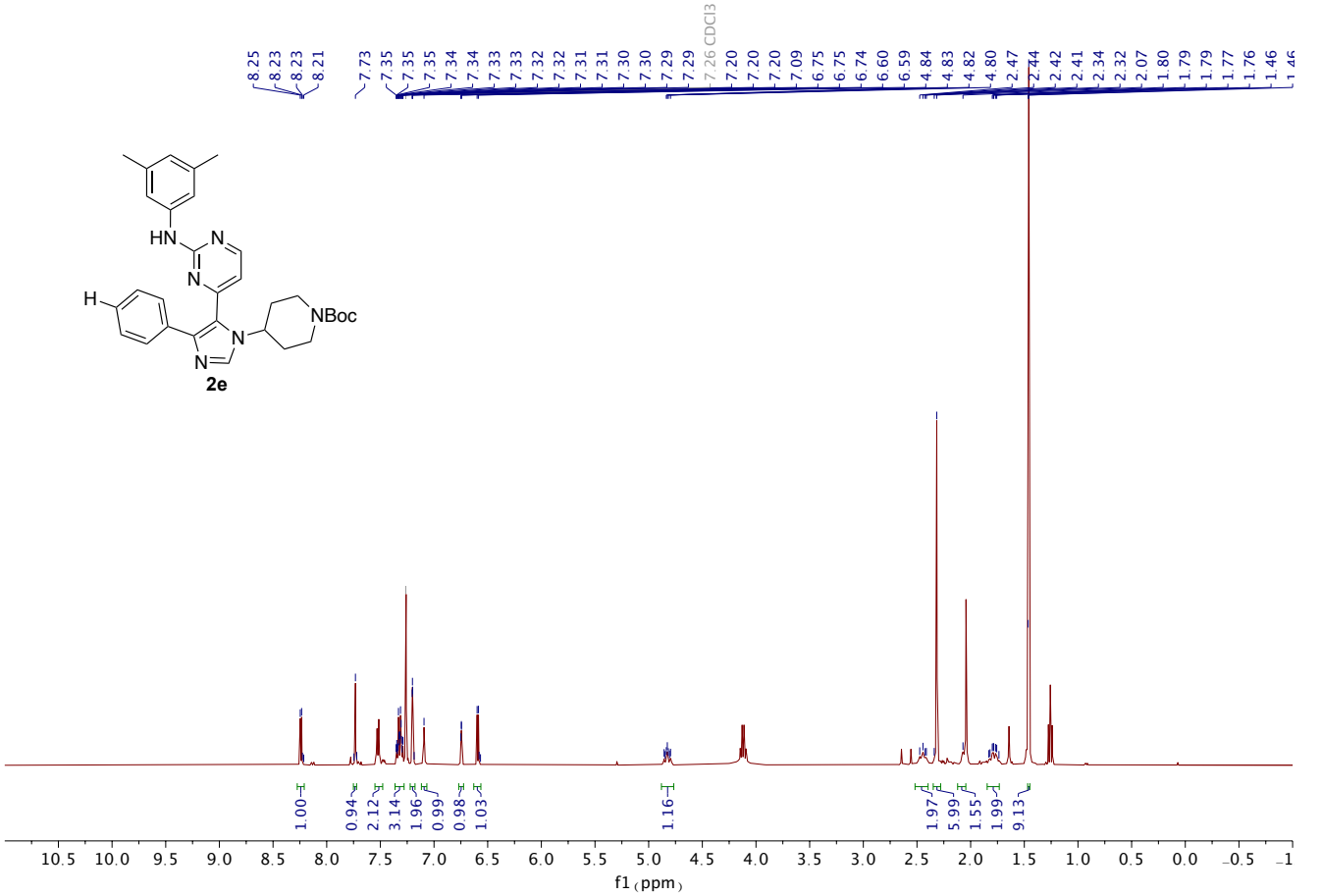
Compound **4d**: 400 MHz ^{1}H NMR spectrum in $CDCl_3$.



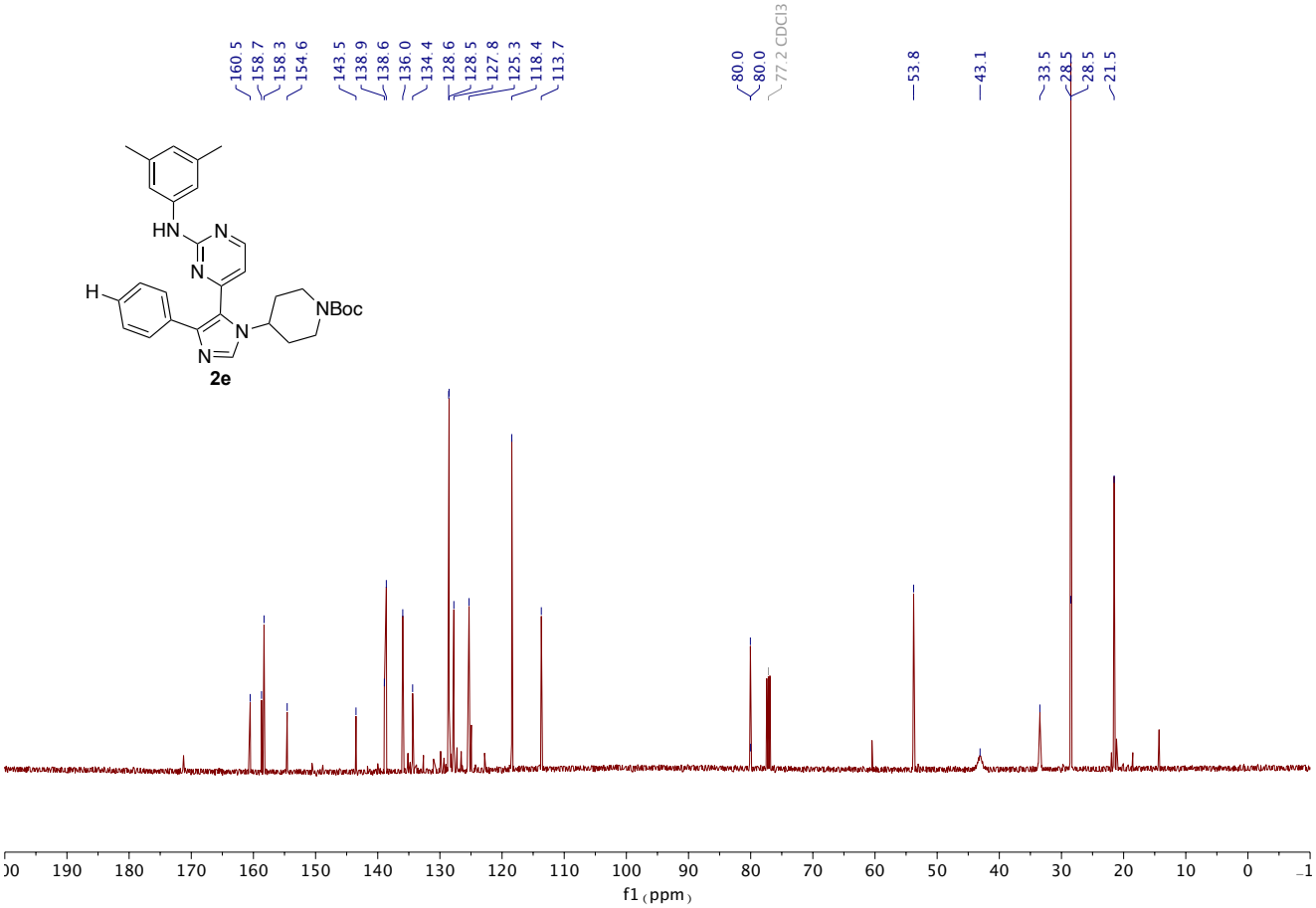
Compound **4d**: 100 MHz ^{13}C NMR spectrum in $CDCl_3$.



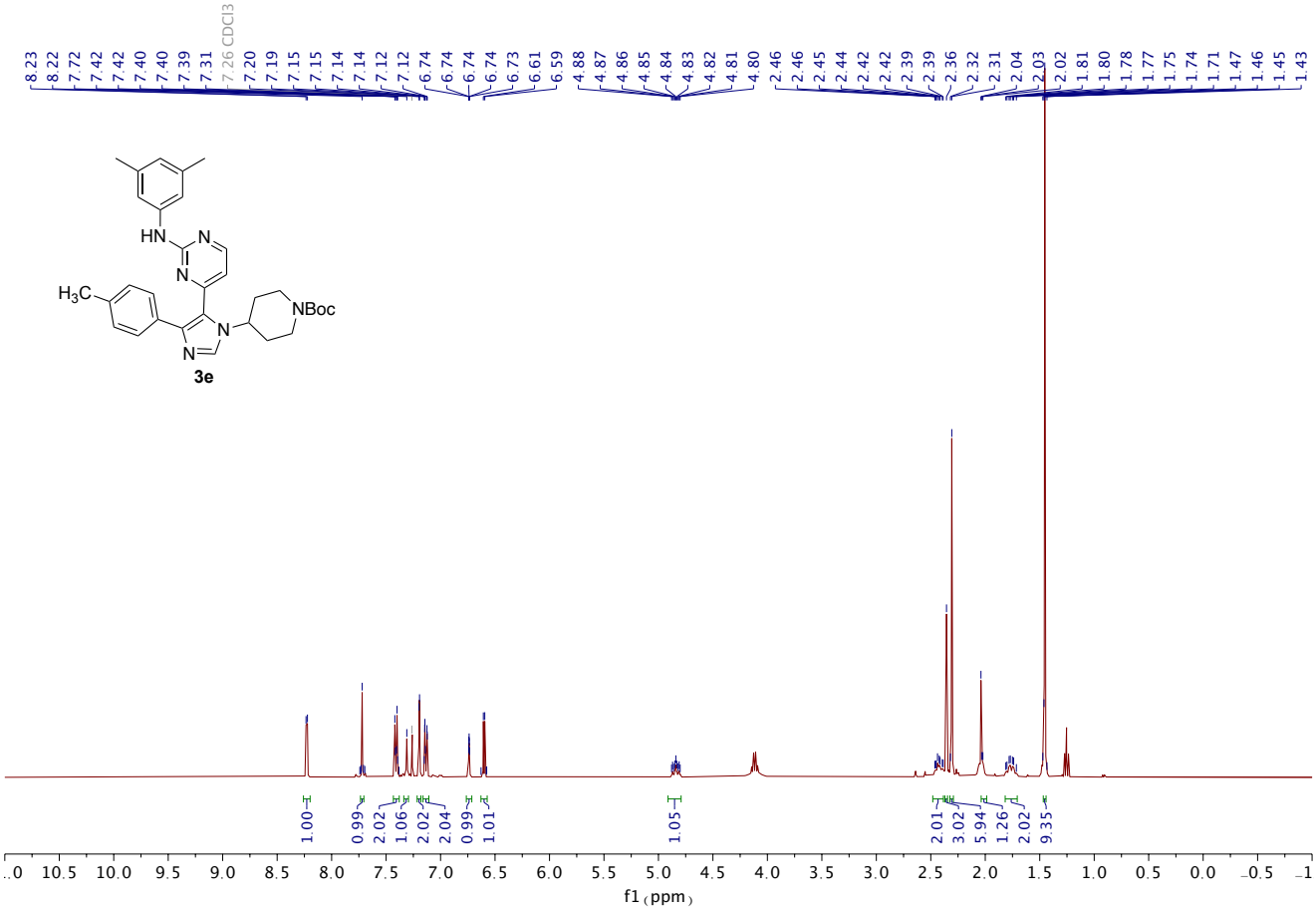
Compound **4d**: 470 MHz ^{19}F NMR spectrum in $CDCl_3$.



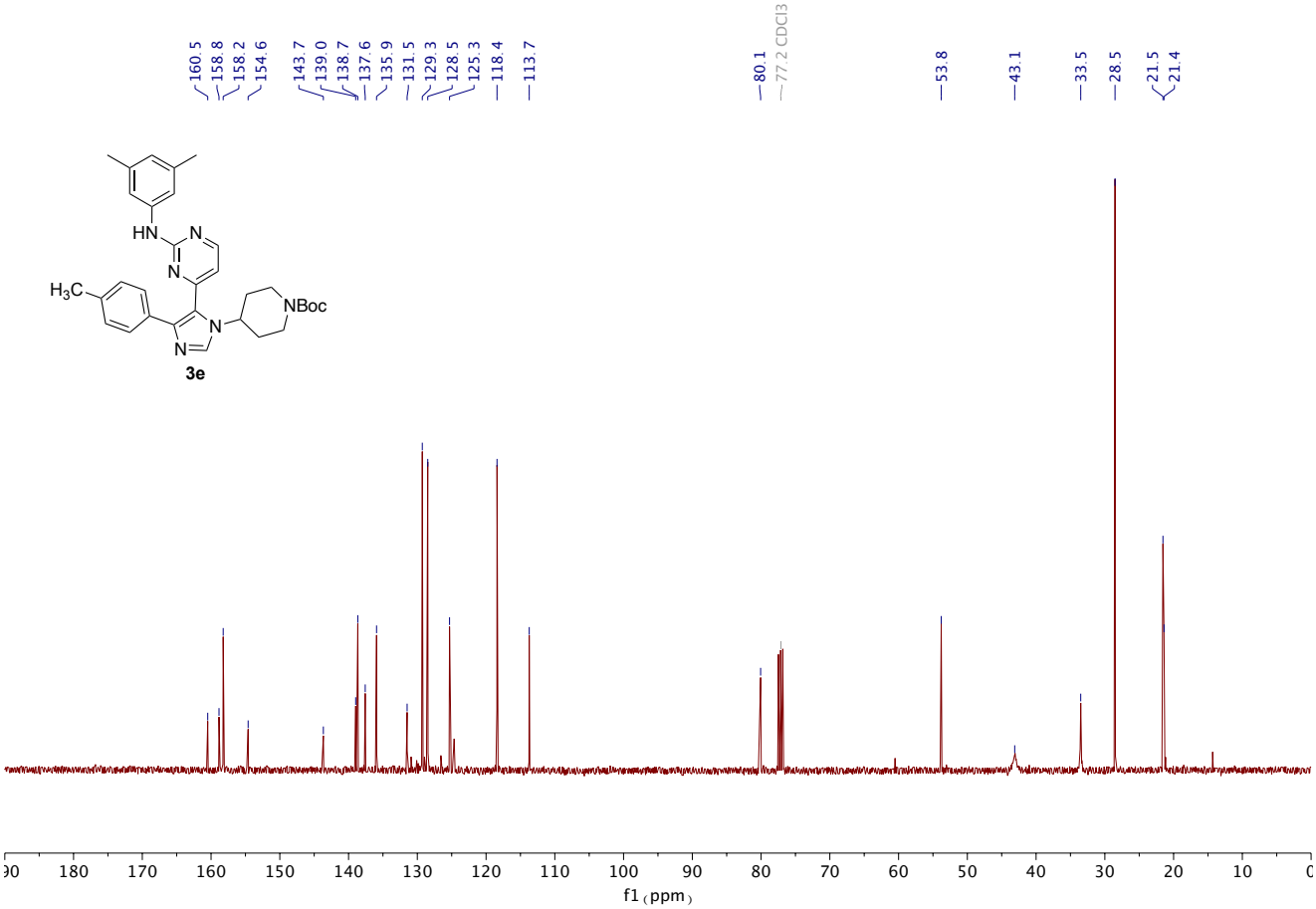
Compound **2e**: 400 MHz ^{1}H NMR spectrum in $CDCl_3$.



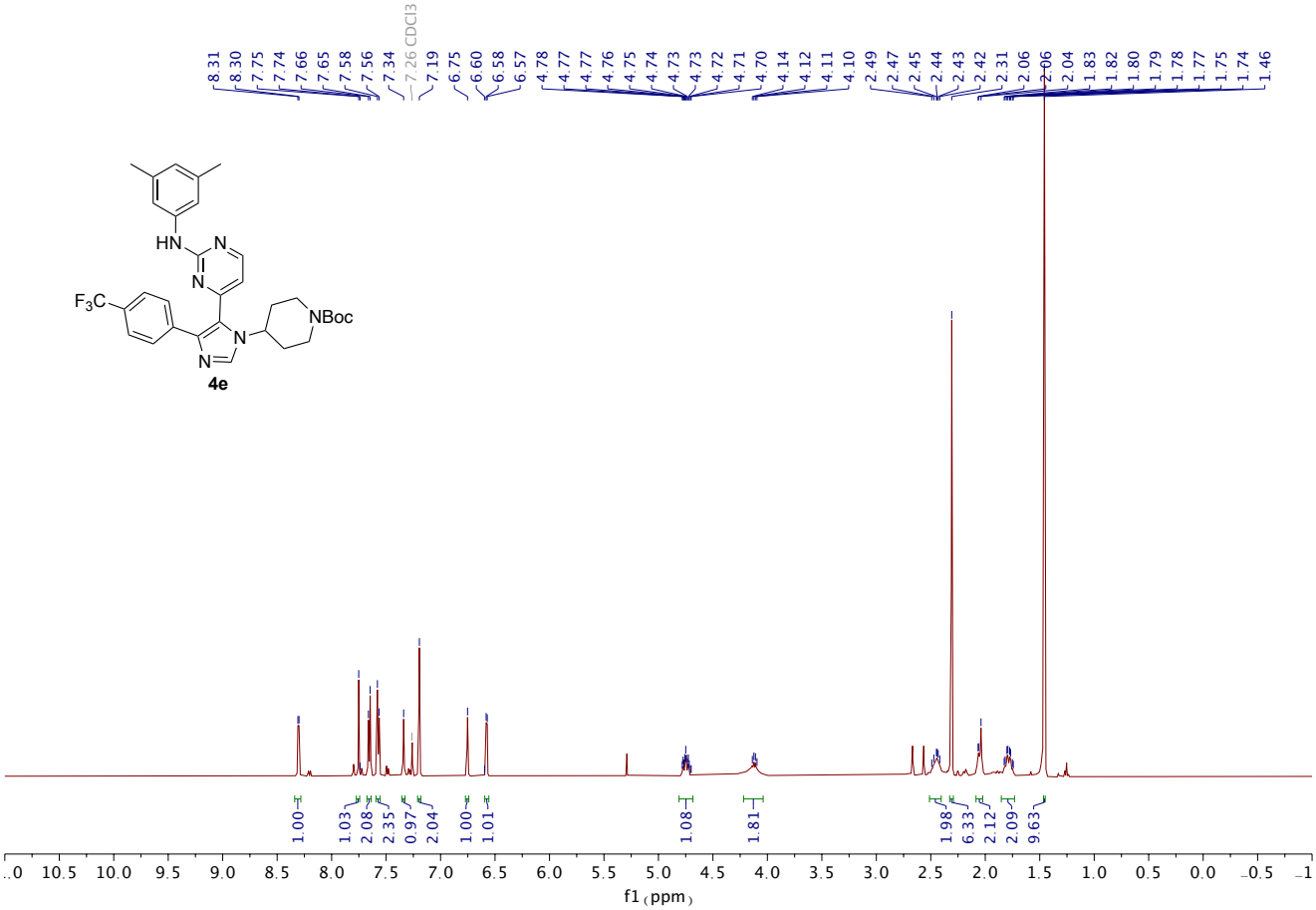
Compound **2e**: 125 MHz ^{1}C NMR spectrum in $CDCl_3$.



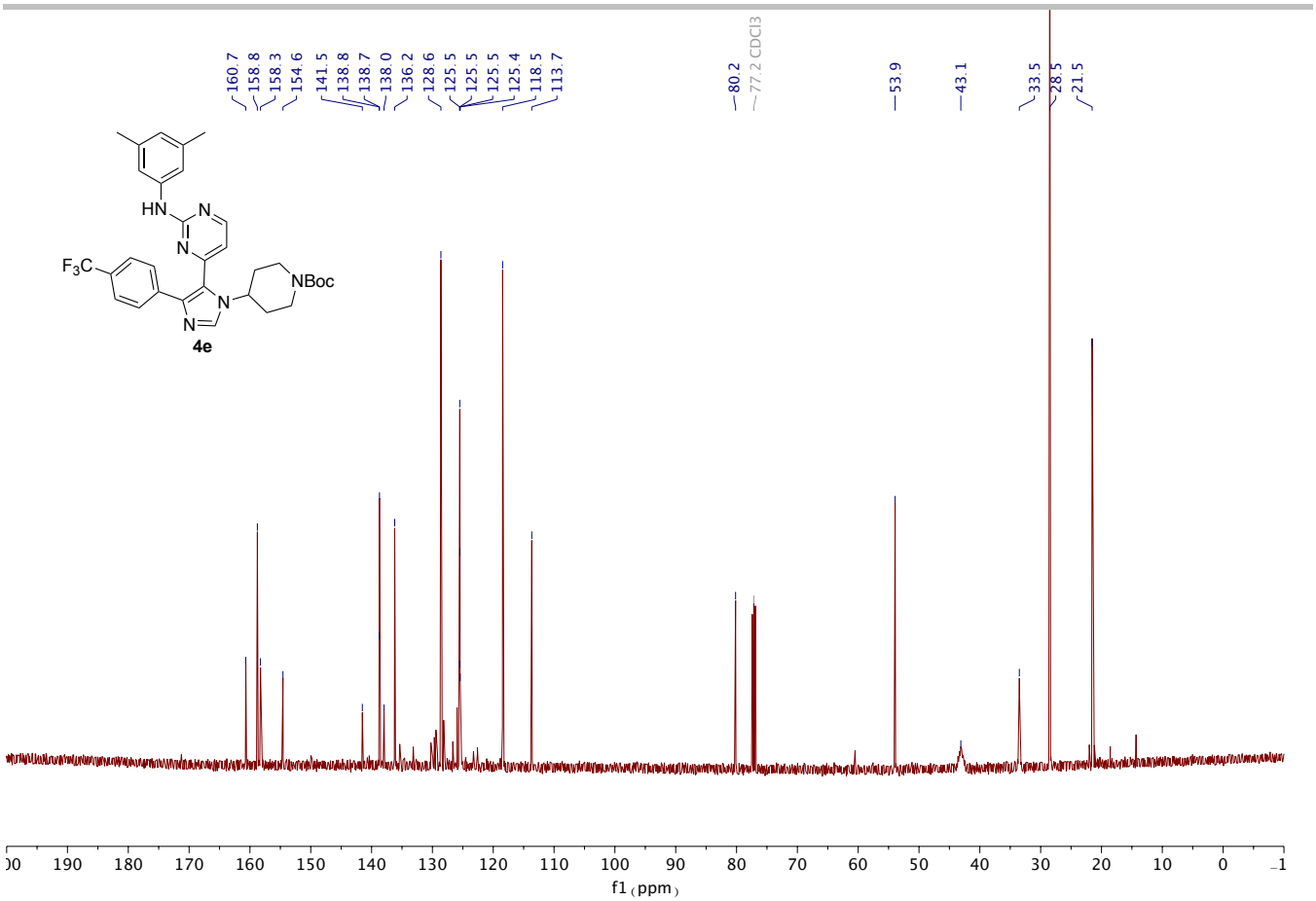
Compound **3e**: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



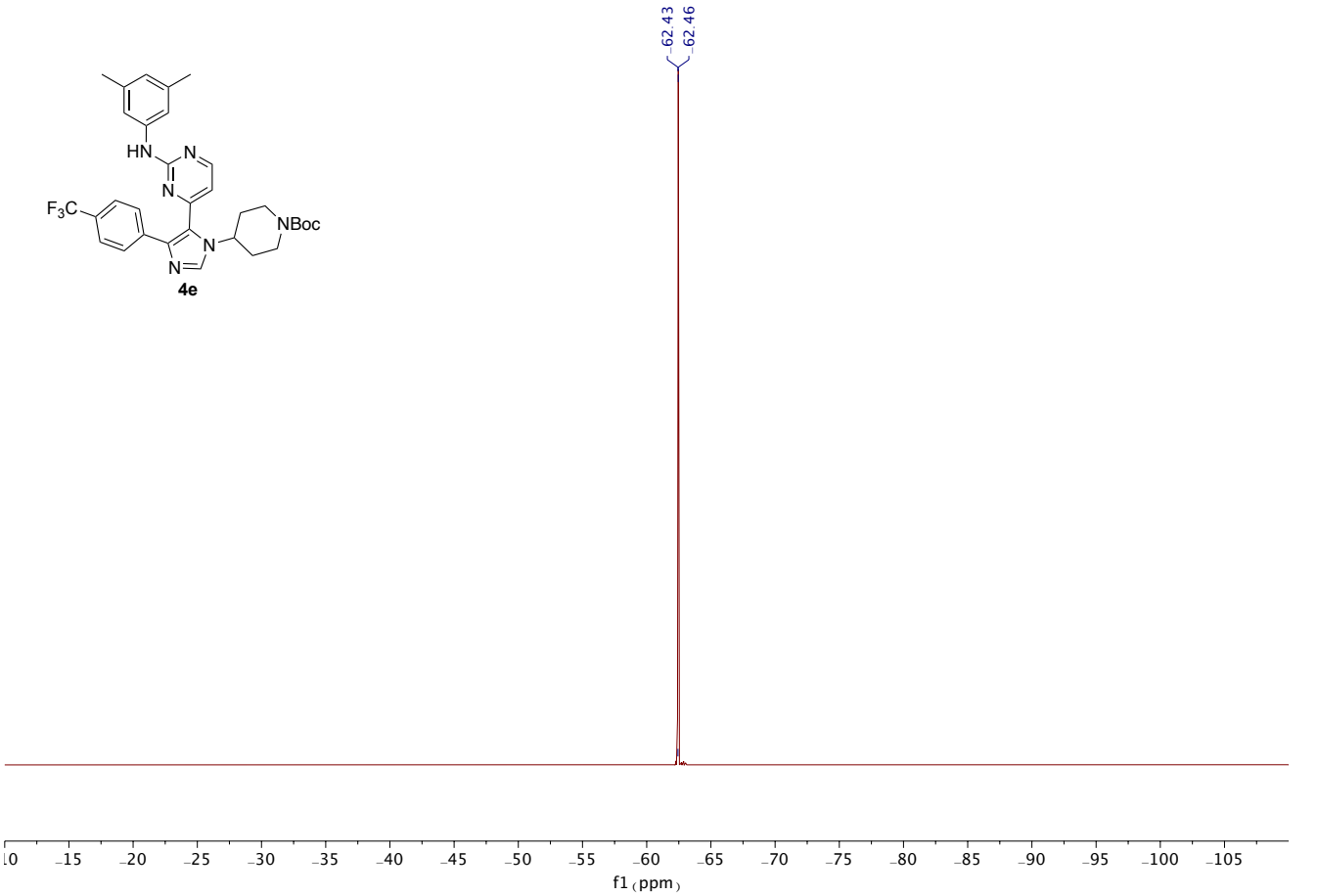
Compound **3e**: 125 MHz ^{13}C NMR spectrum in $CDCl_3$.



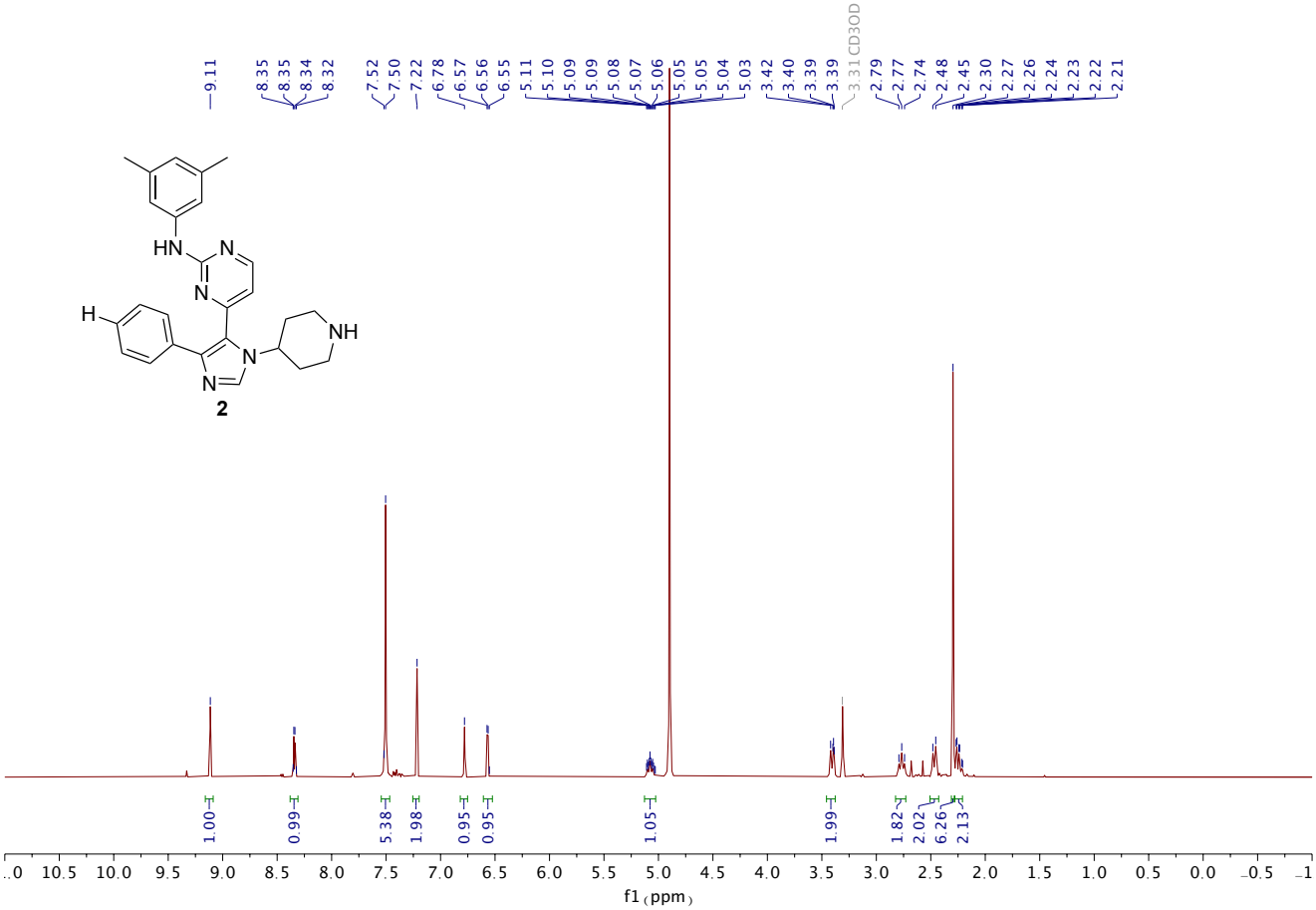
Compound **4e**: 500 MHz ^{1}H NMR spectrum in $CDCl_3$.



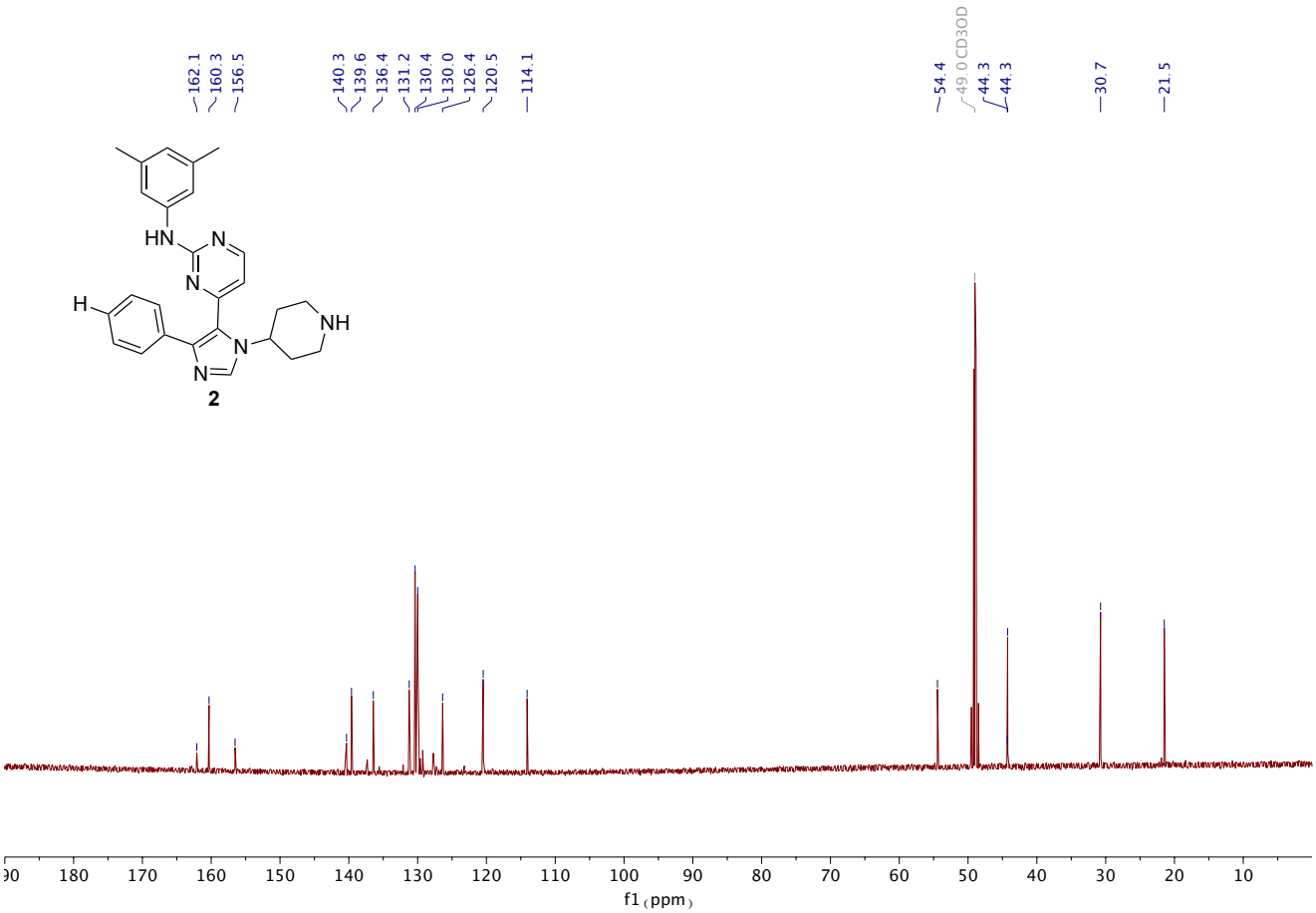
Compound **4e**: 125 MHz ^{13}C NMR spectrum in $CDCl_3$.



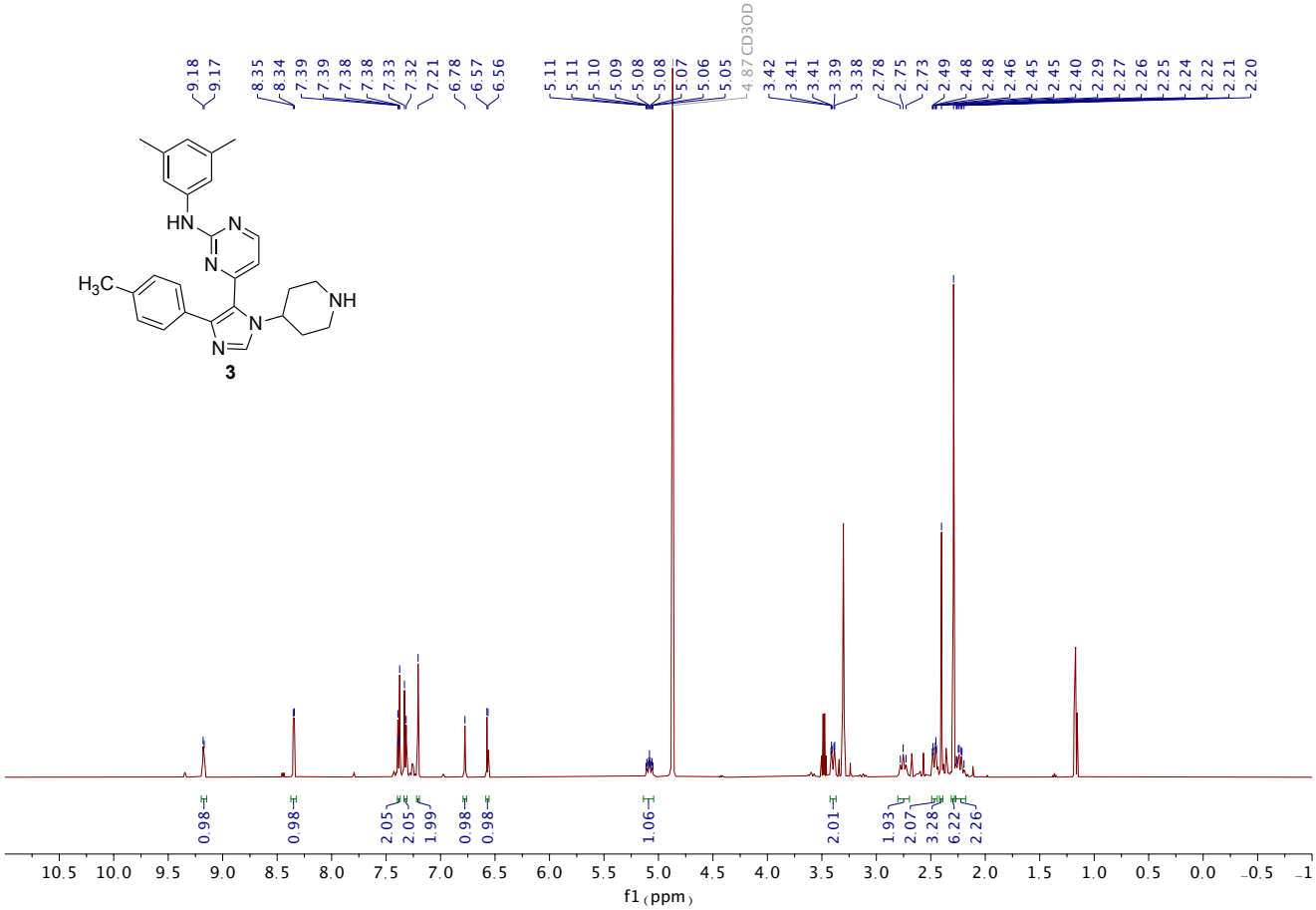
Compound **4e**: 470 MHz ^{19}F NMR spectrum in $CDCl_3$.



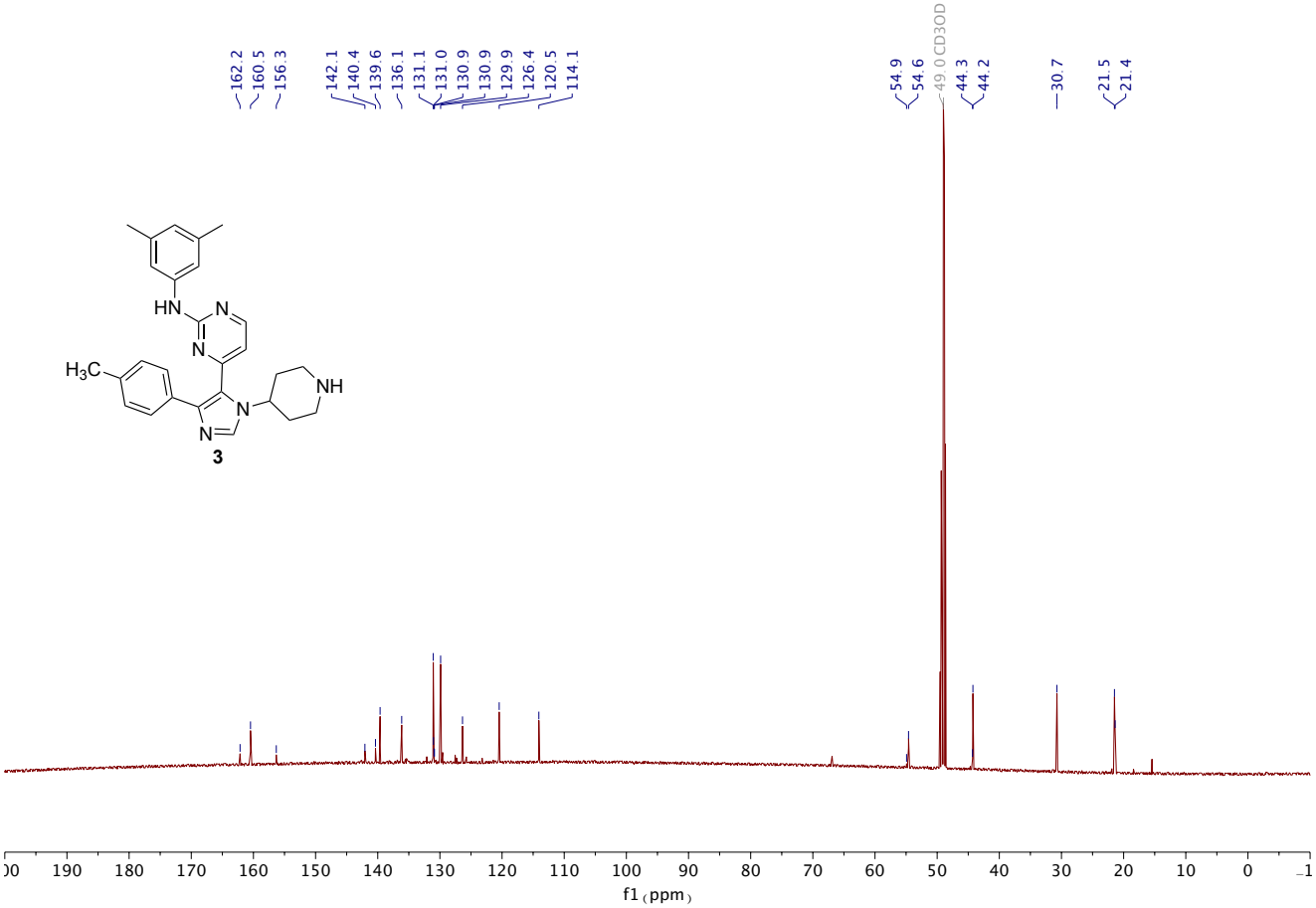
Compound **2**: 500 MHz ^{1}H NMR spectrum in MeOD.



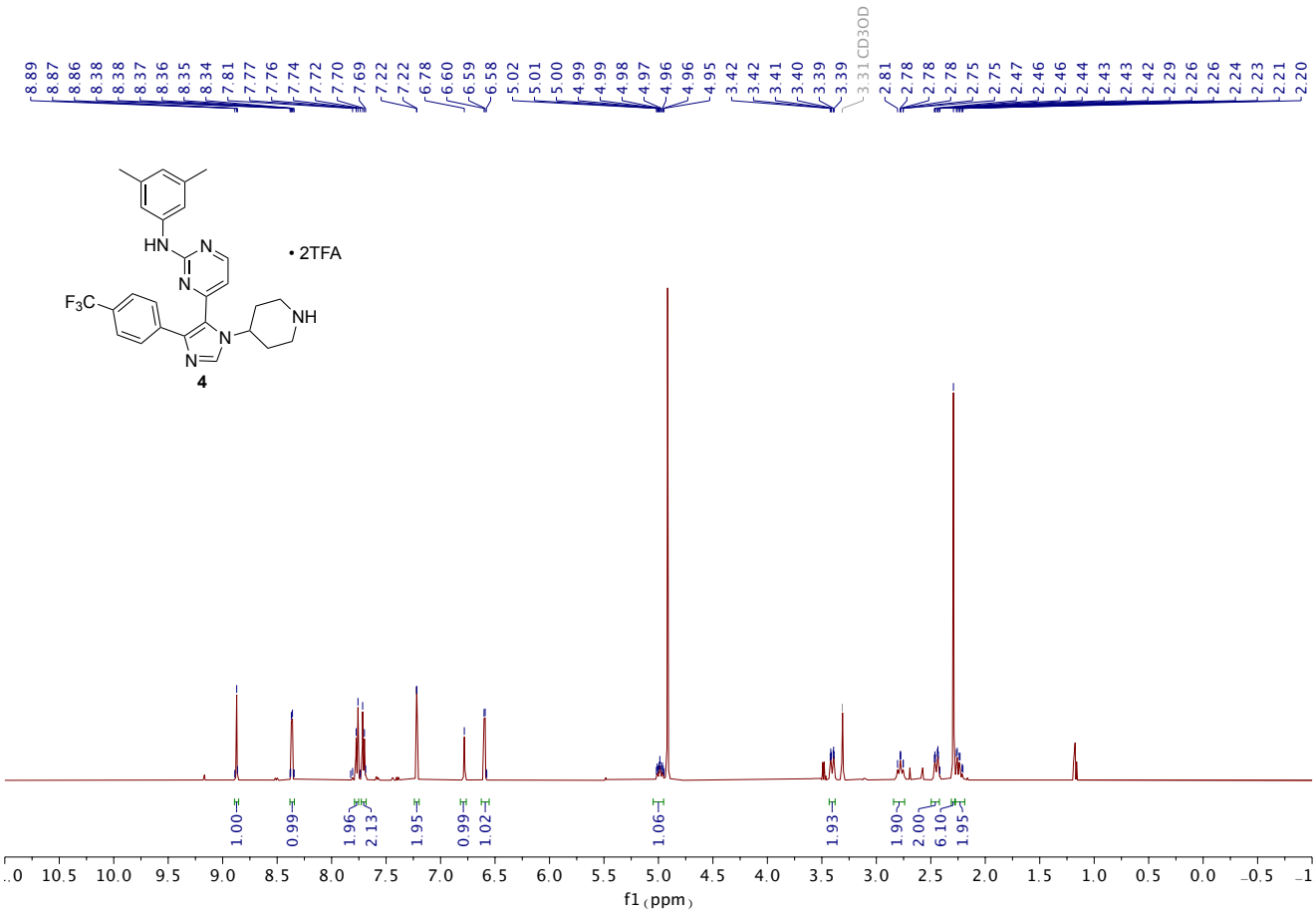
Compound **2**: 125 MHz ^{13}C NMR spectrum in MeOD.



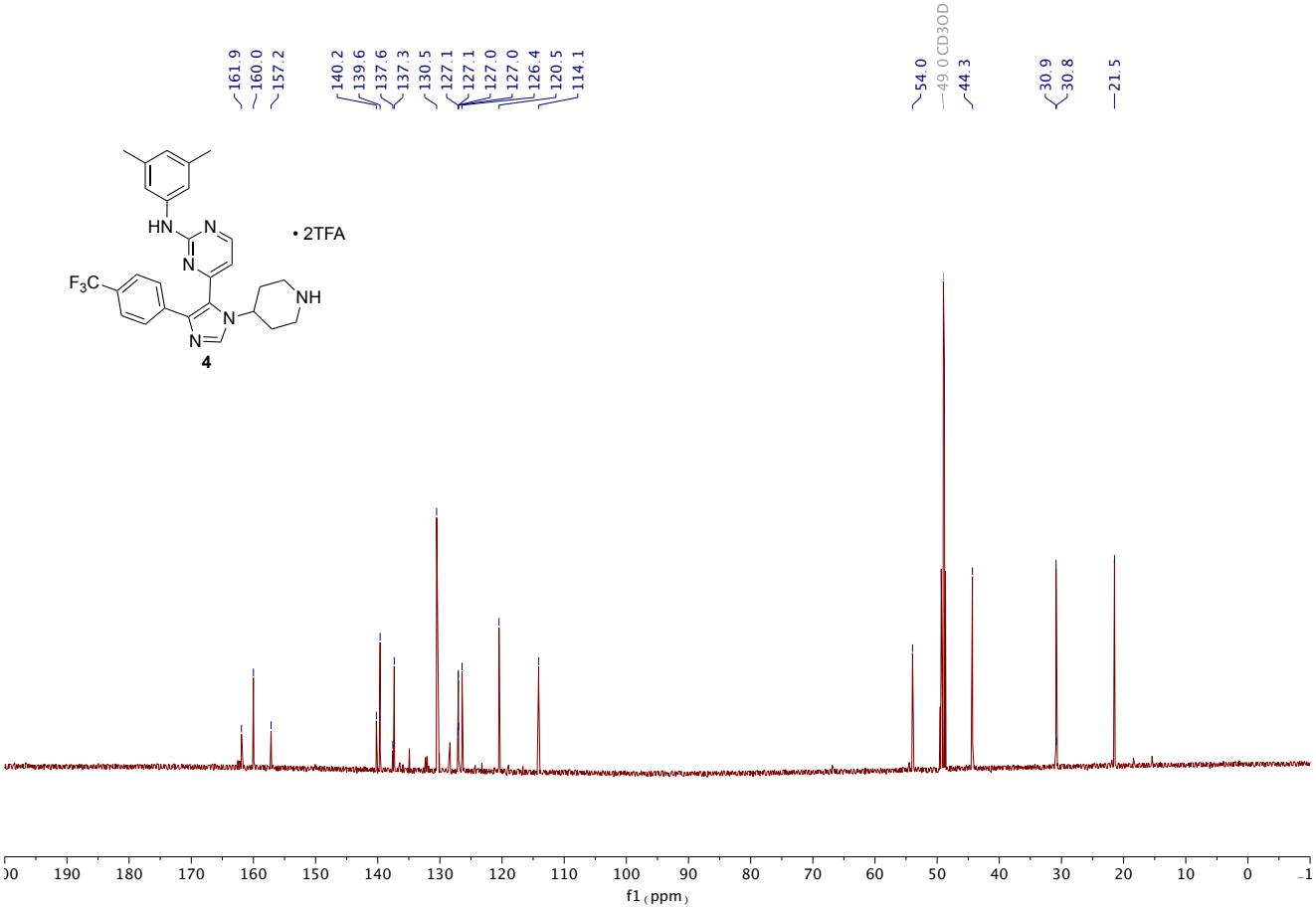
Compound **3**: 500 MHz ^{1}H NMR spectrum in MeOD.



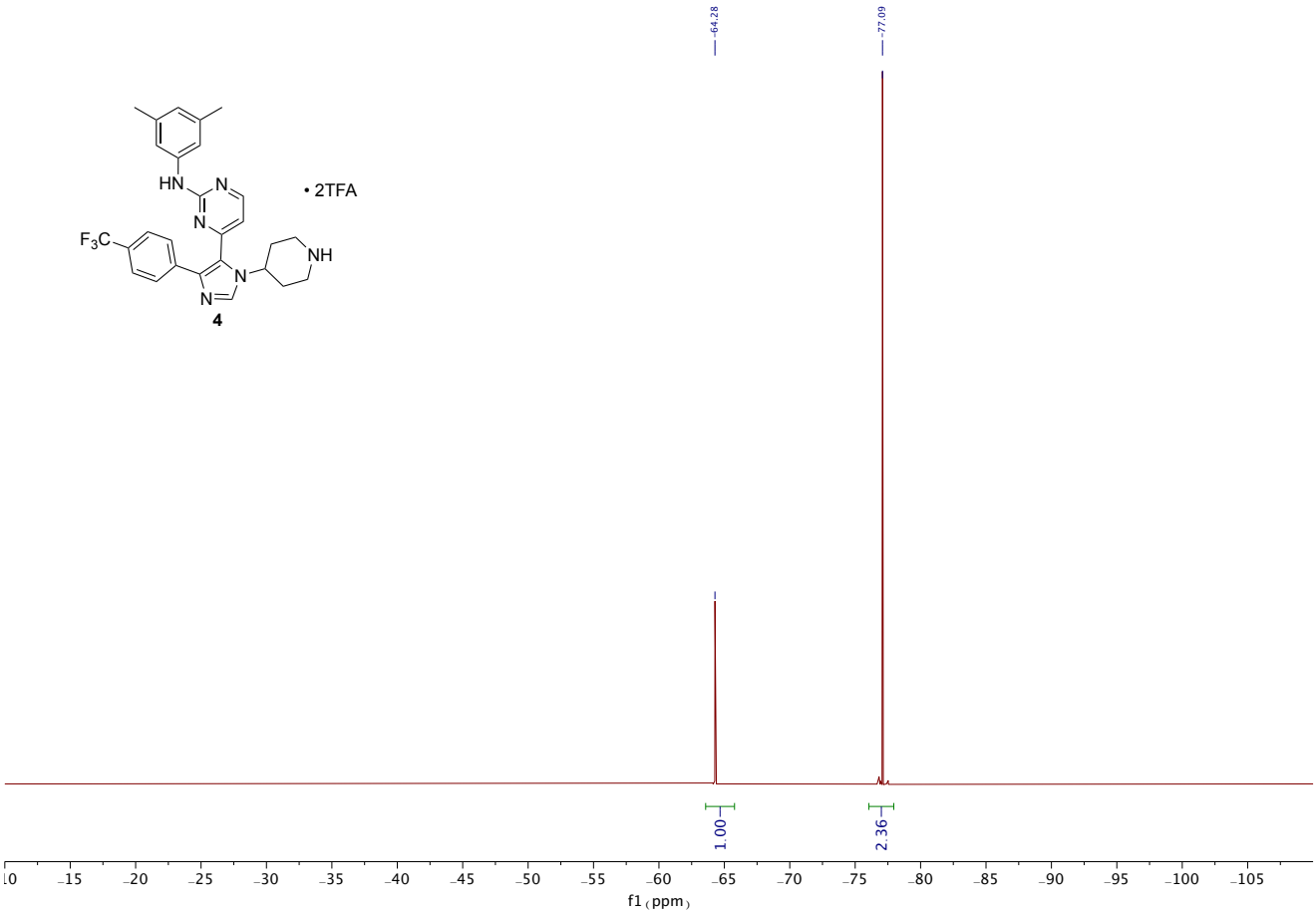
Compound **3**: 125 MHz ^{13}C NMR spectrum in MeOD.



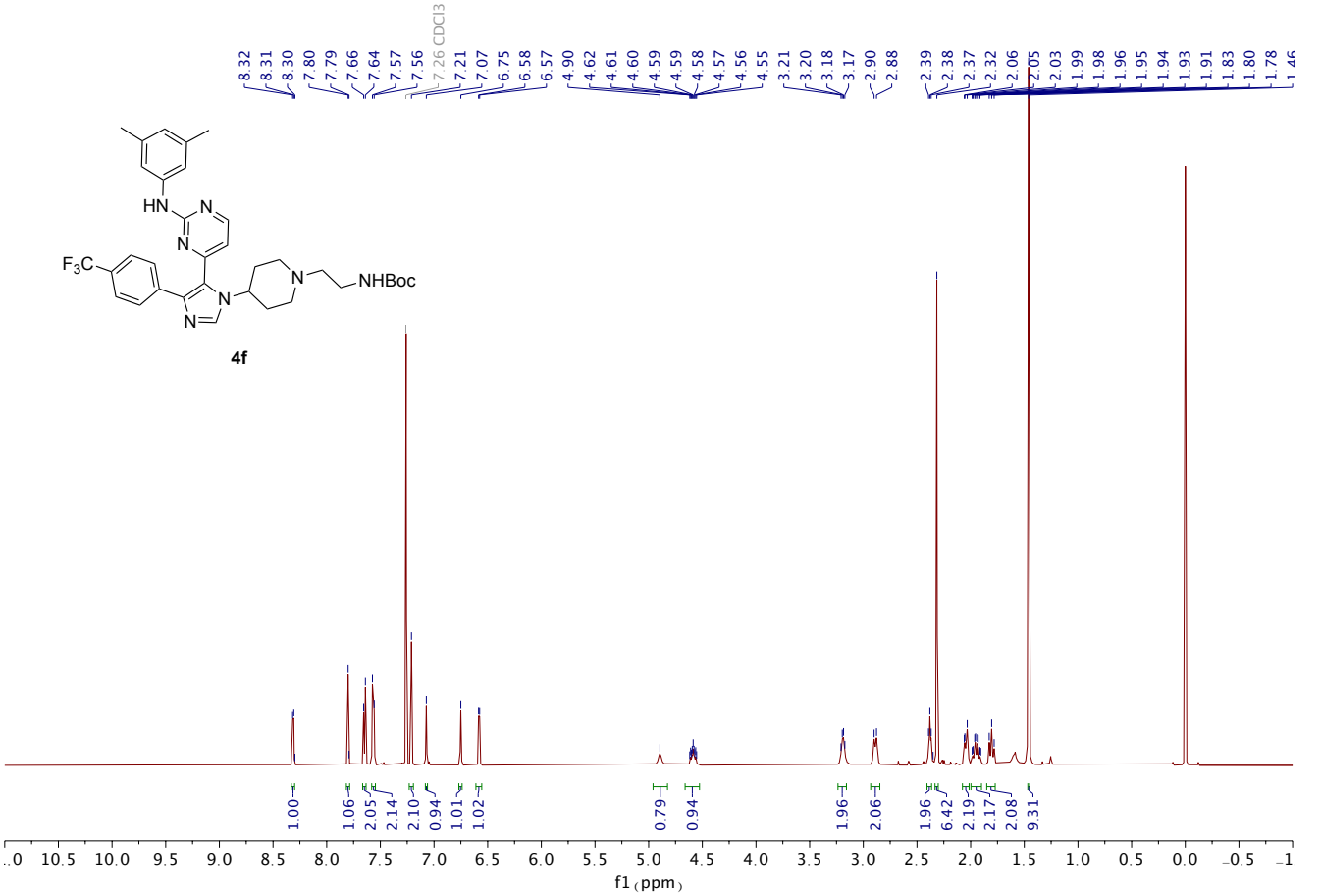
Compound **4**: 500 MHz ^{1}H NMR spectrum in MeOD.



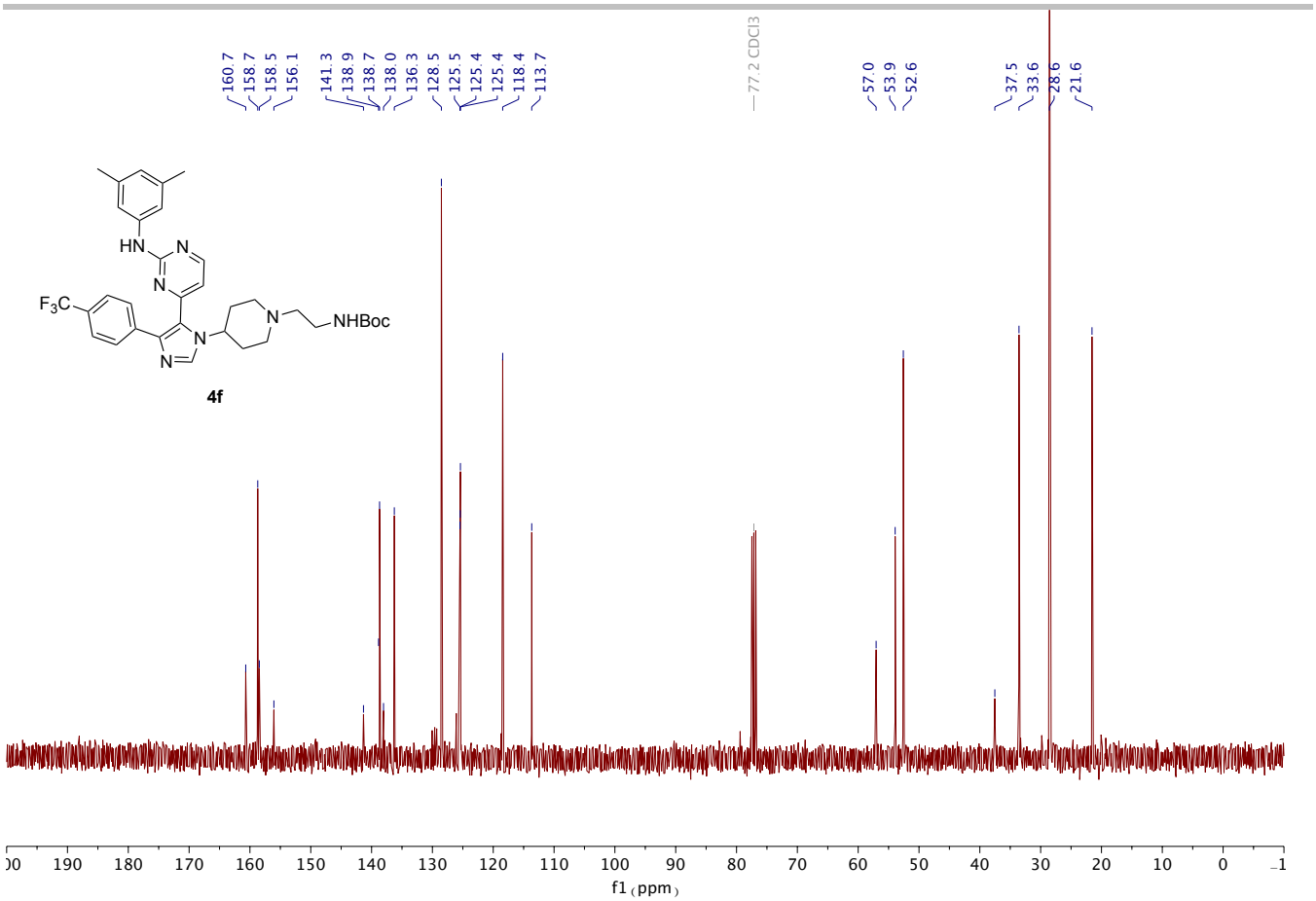
Compound **4**: 125 MHz ^{13}C NMR spectrum in MeOD.



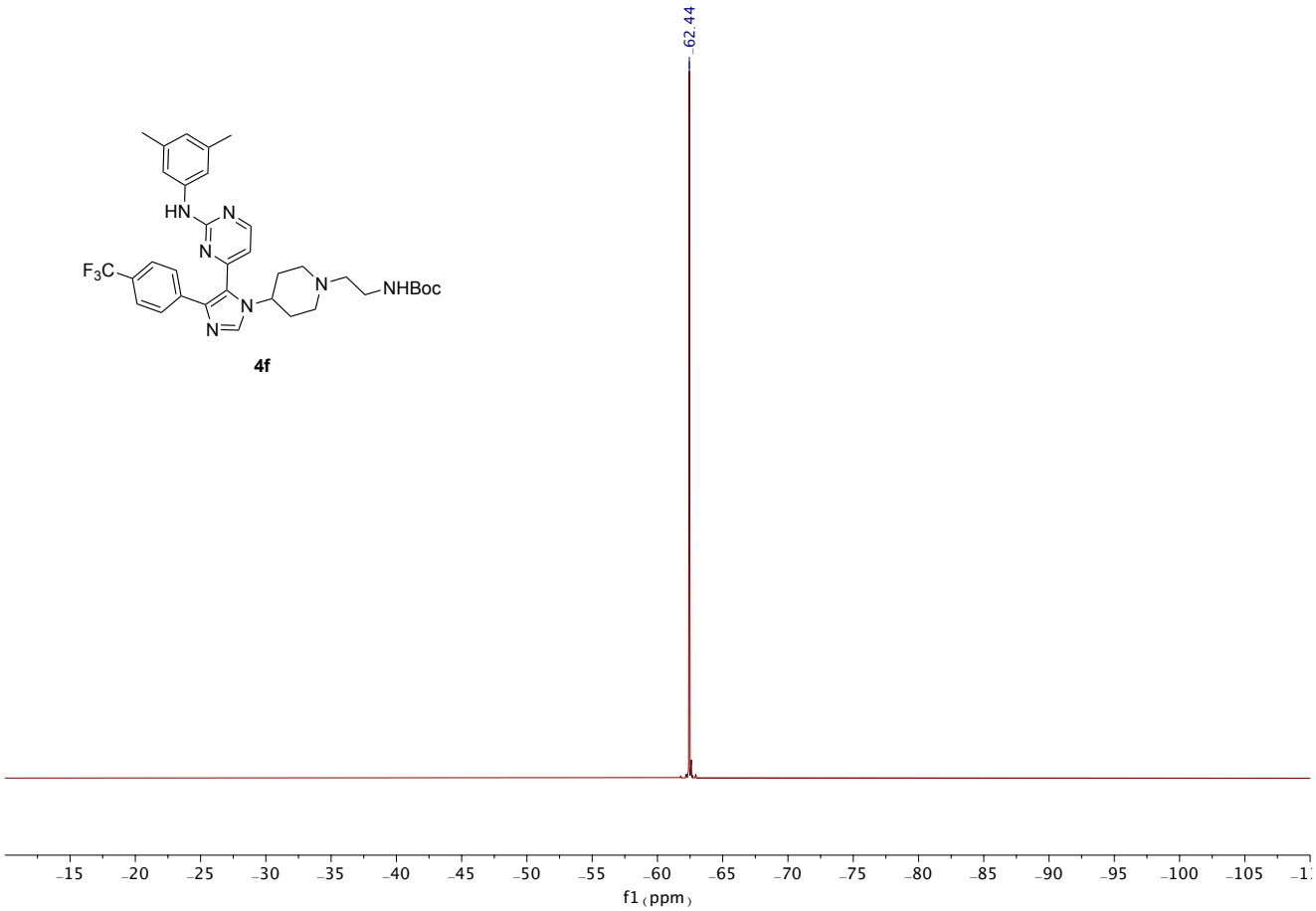
Compound **4**: 376 MHz ^{19}F NMR spectrum in MeOD.



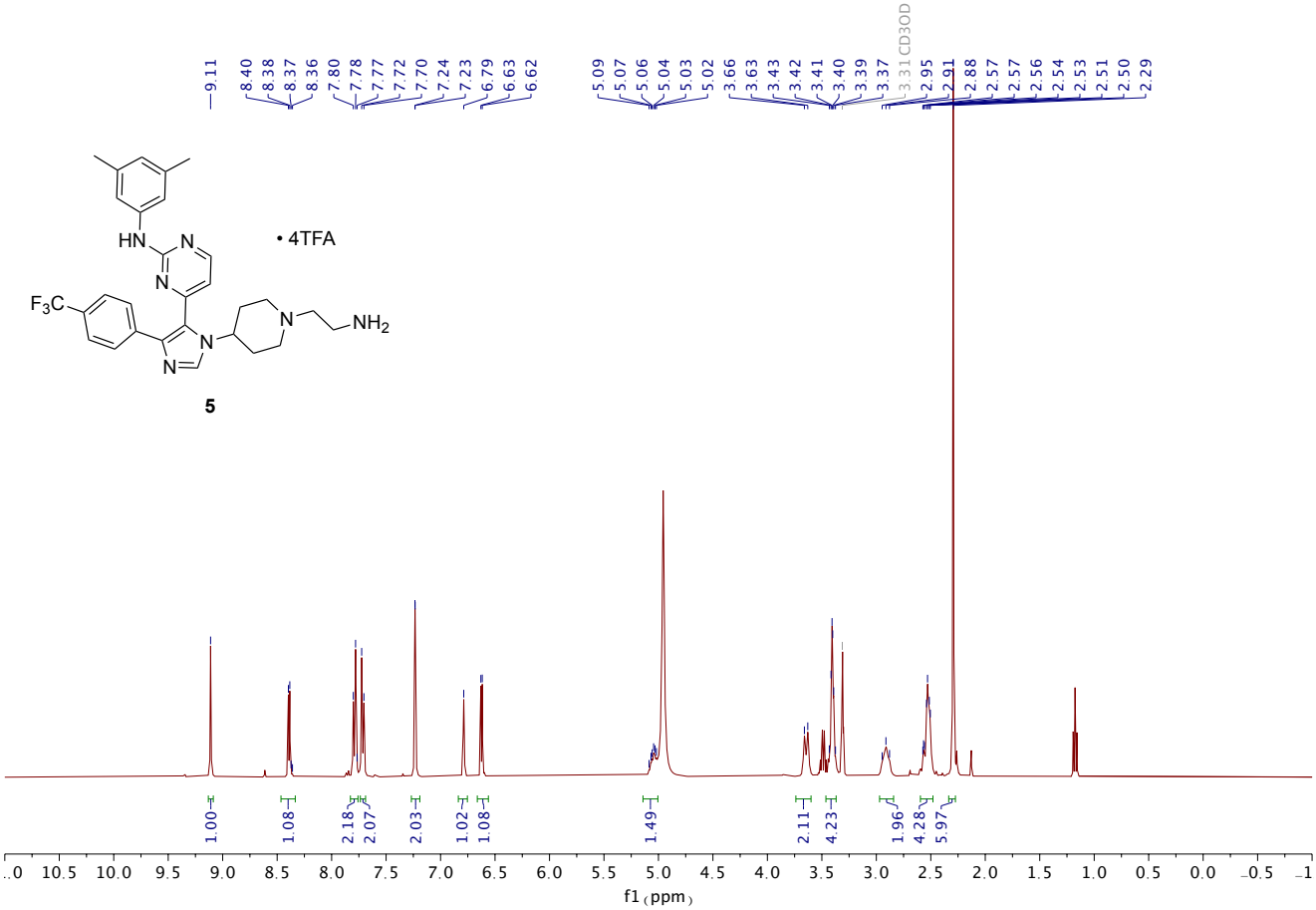
Compound **4f**: 500 MHz ^{1}H NMR spectrum in $CDCl_3$.



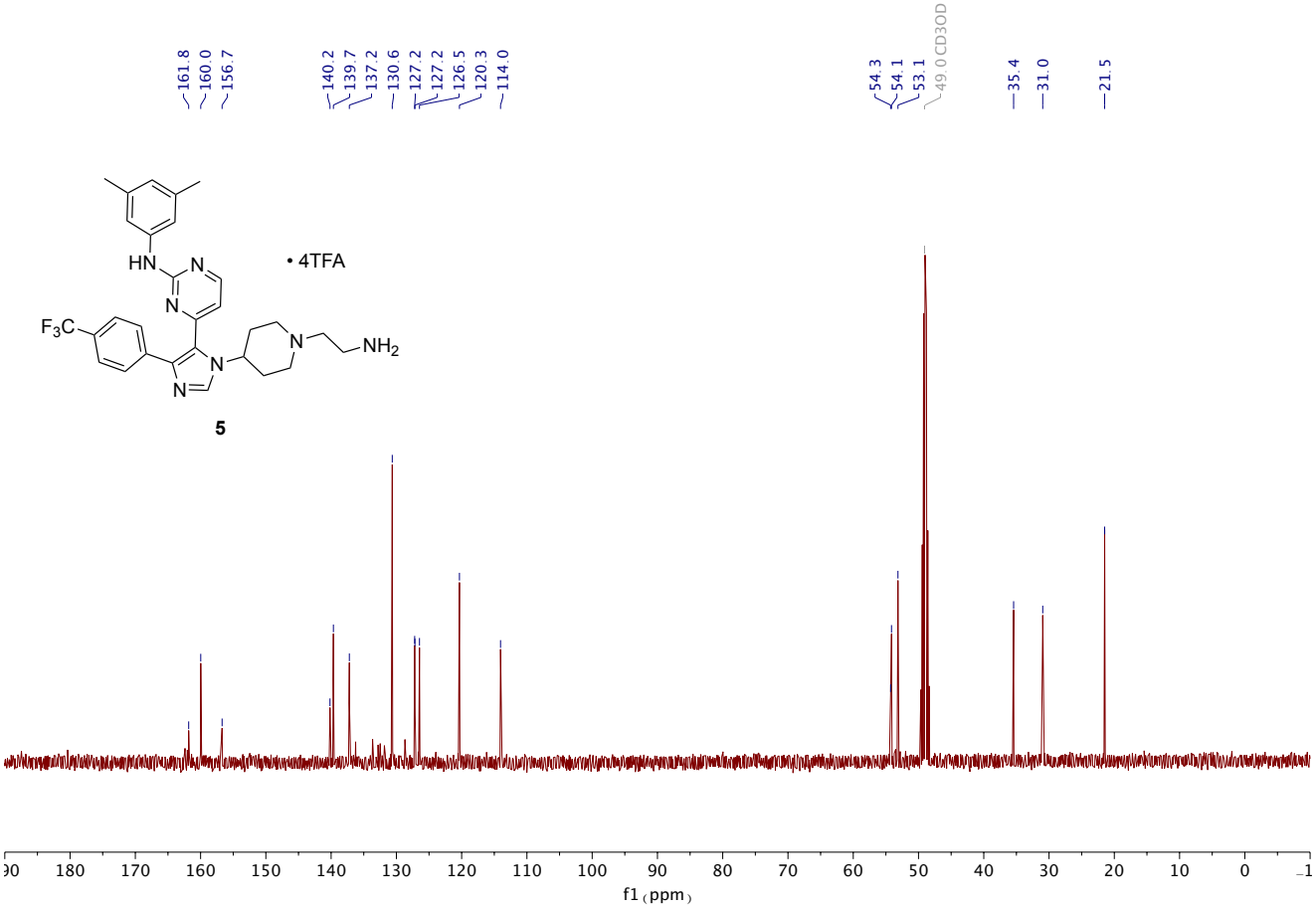
Compound **4f**: 100 MHz ^{13}C NMR spectrum in $CDCl_3$.



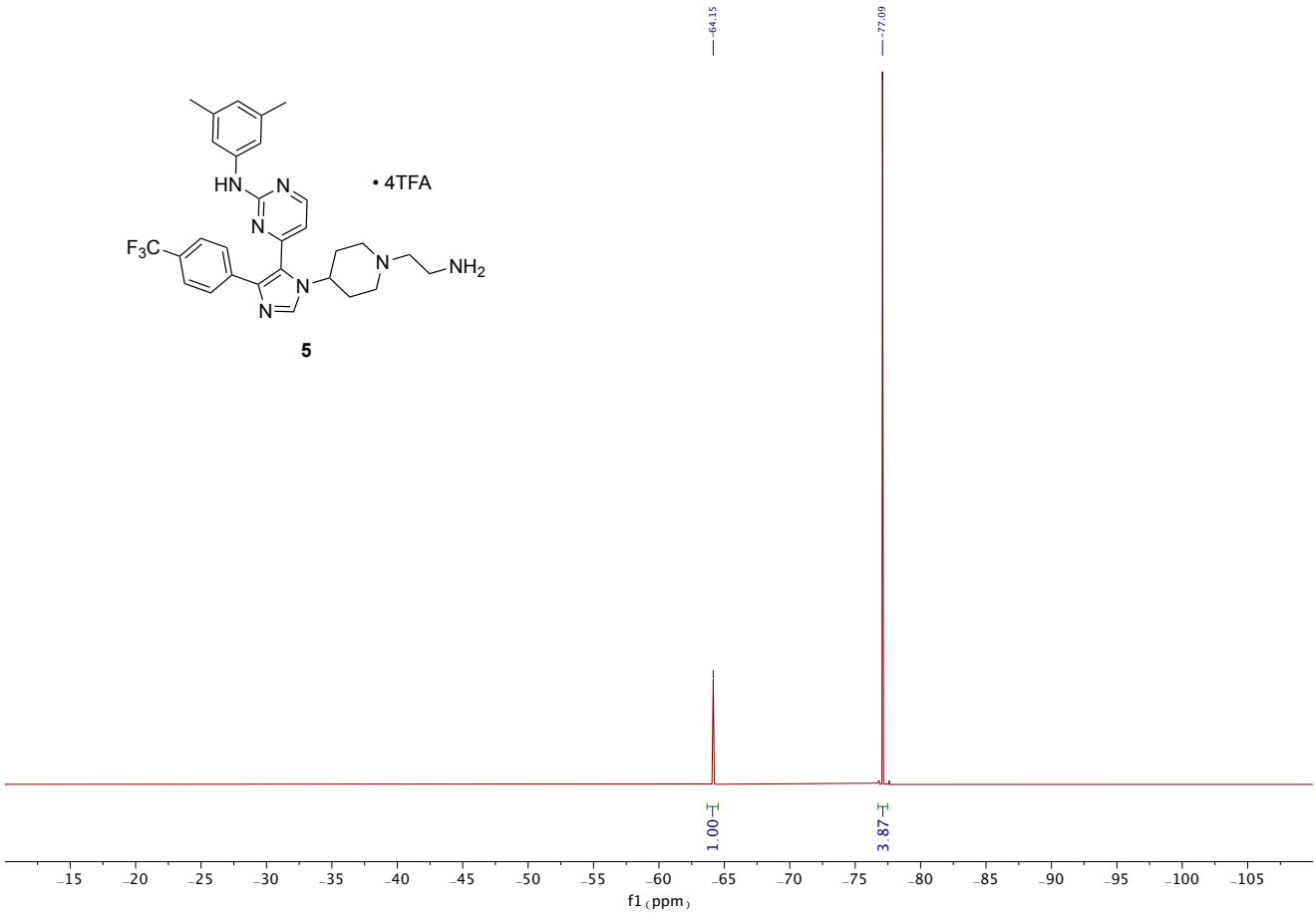
Compound **4f**: 470 MHz ^{19}F NMR spectrum in $CDCl_3$.



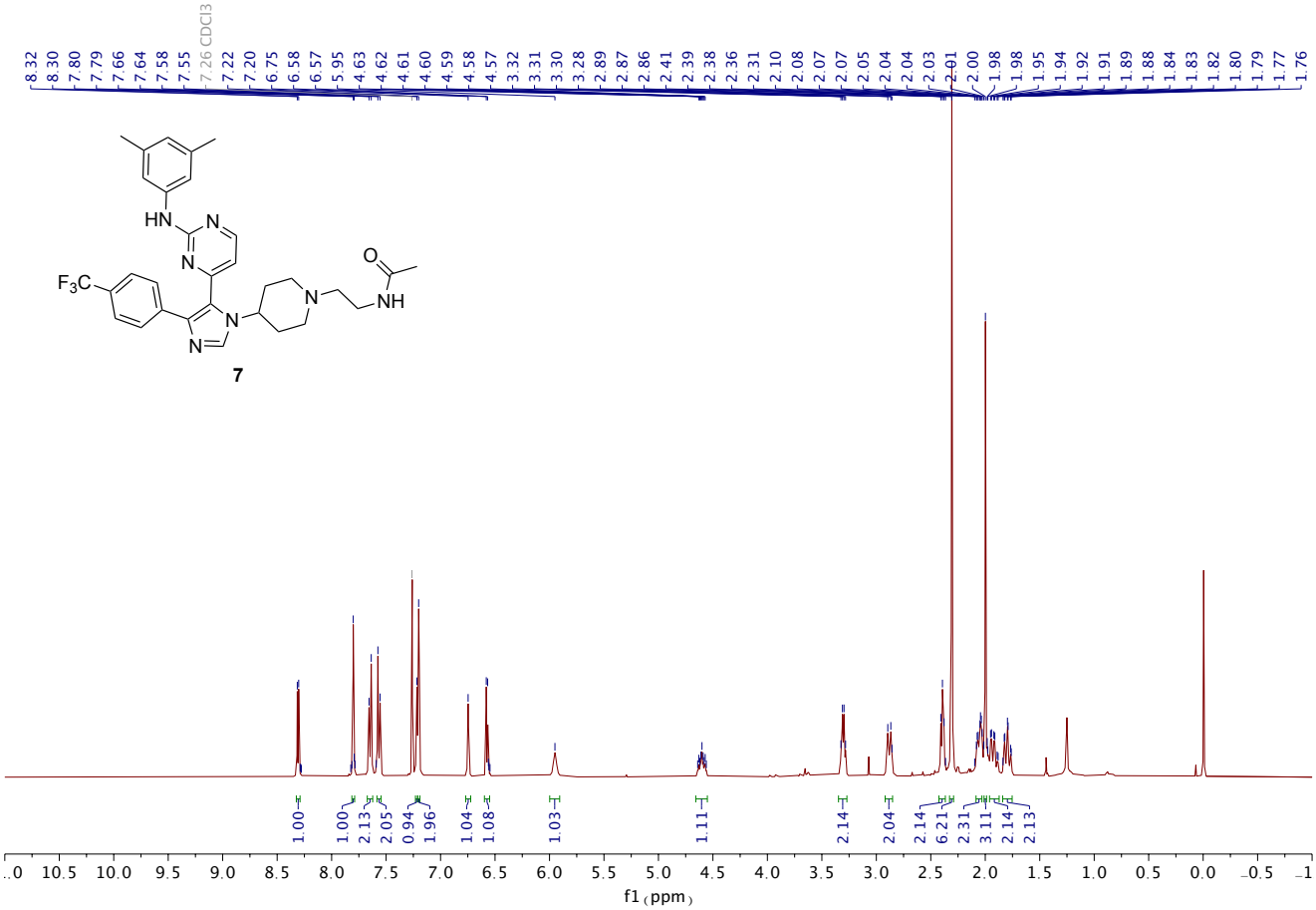
Compound **5**: 400 MHz ^{1}H NMR spectrum in MeOD.



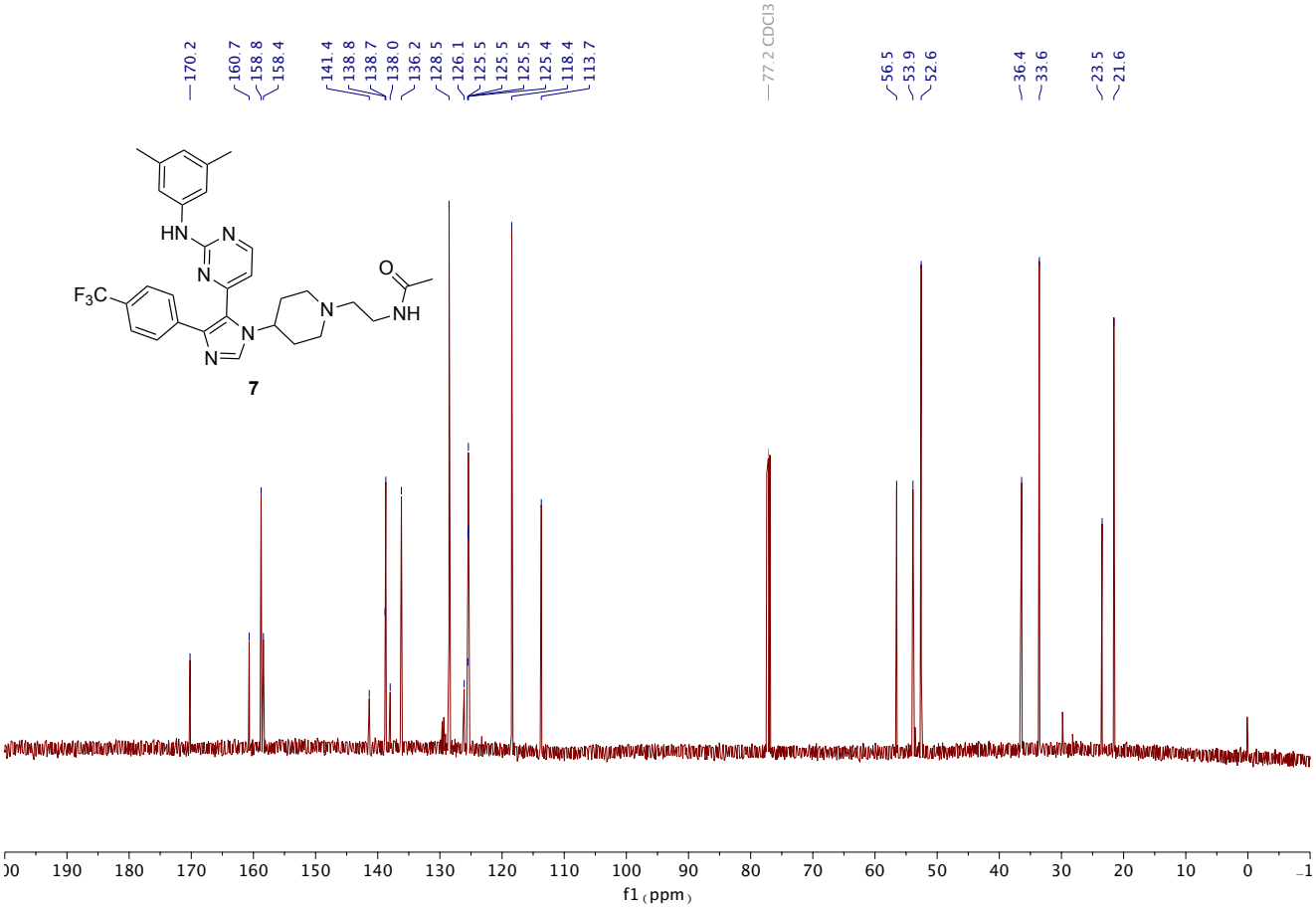
Compound **5**: 100 MHz ^{13}C NMR spectrum in MeOD.



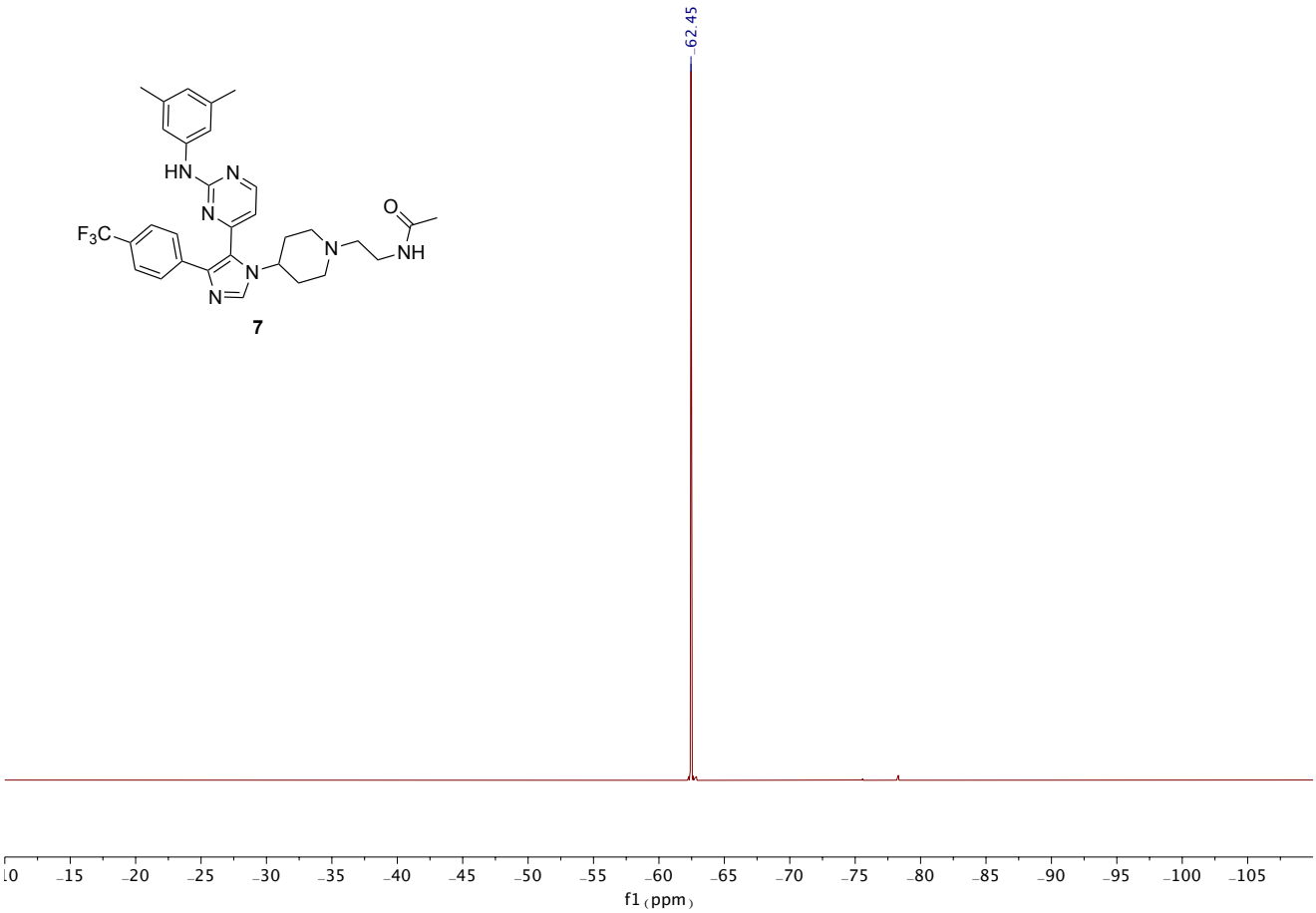
Compound **5**: 376 MHz ^{19}F NMR spectrum in MeOD



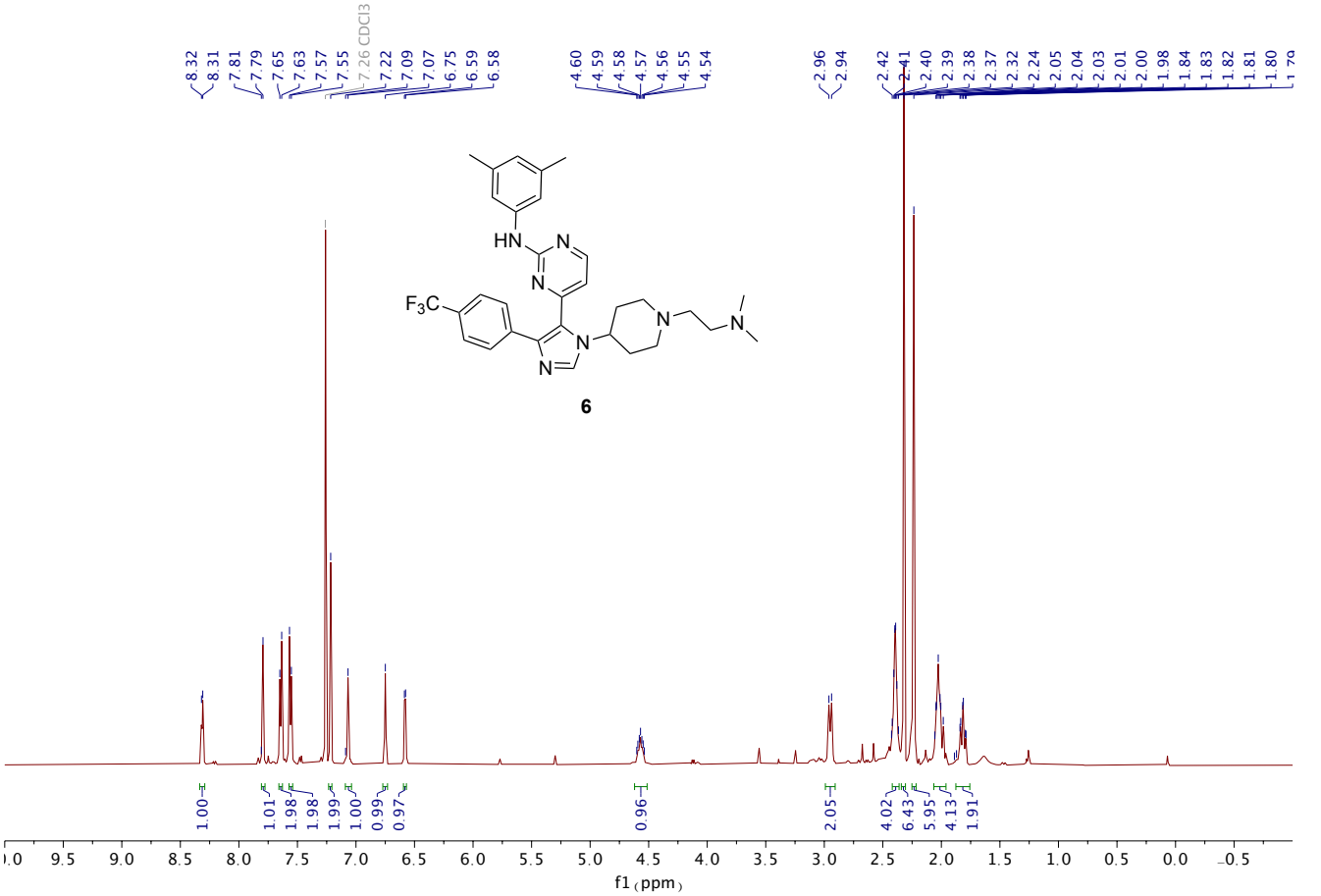
Compound **7**: 500 MHz ^{1}H NMR spectrum in $CDCl_3$.



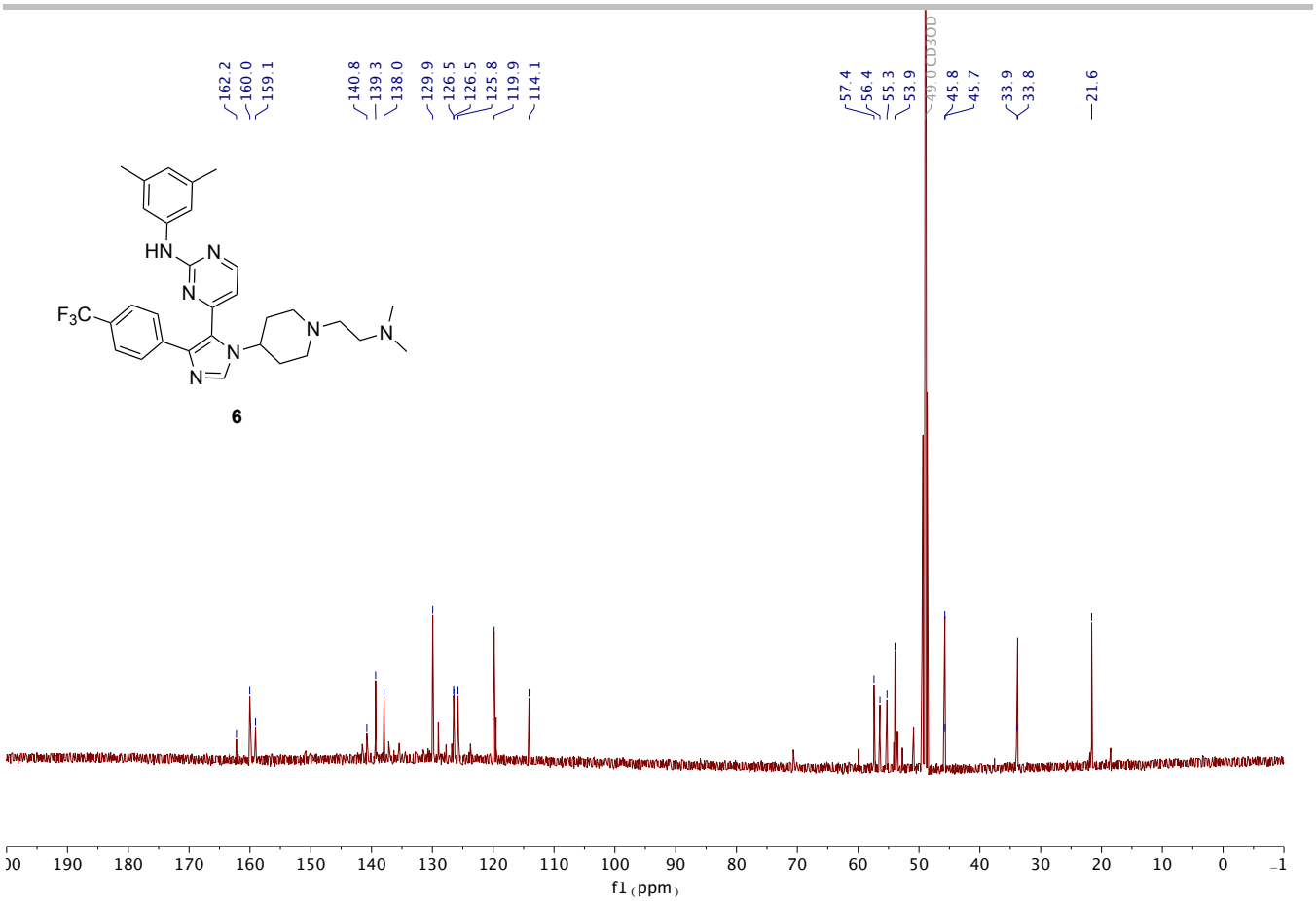
Compound **7**: 125 MHz ^{13}C NMR spectrum in $CDCl_3$.



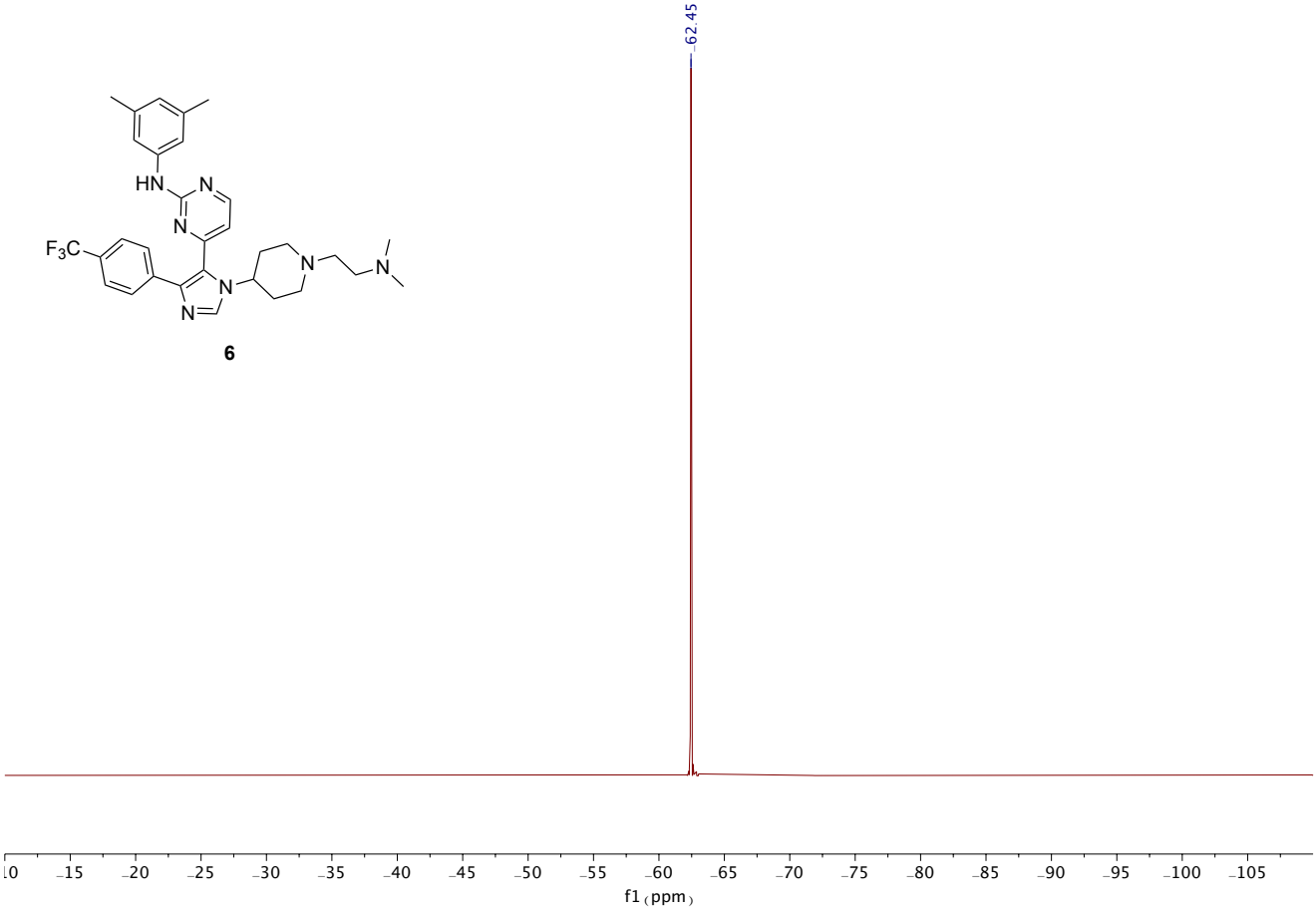
Compound **7**: 470 MHz ^{19}F NMR spectrum in $CDCl_3$.



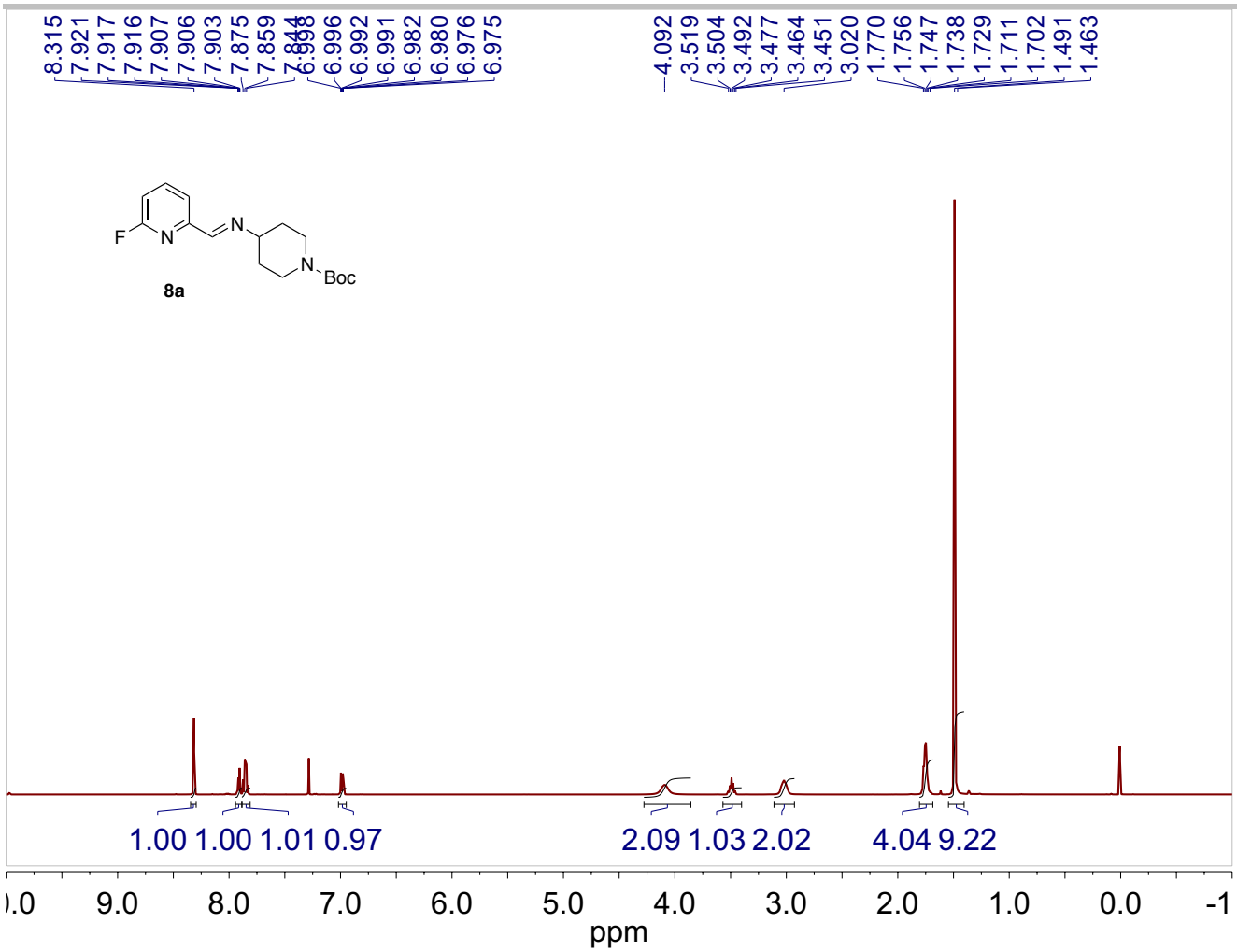
Compound **6**: 500 MHz ^{1}H NMR spectrum in $CDCl_3$.



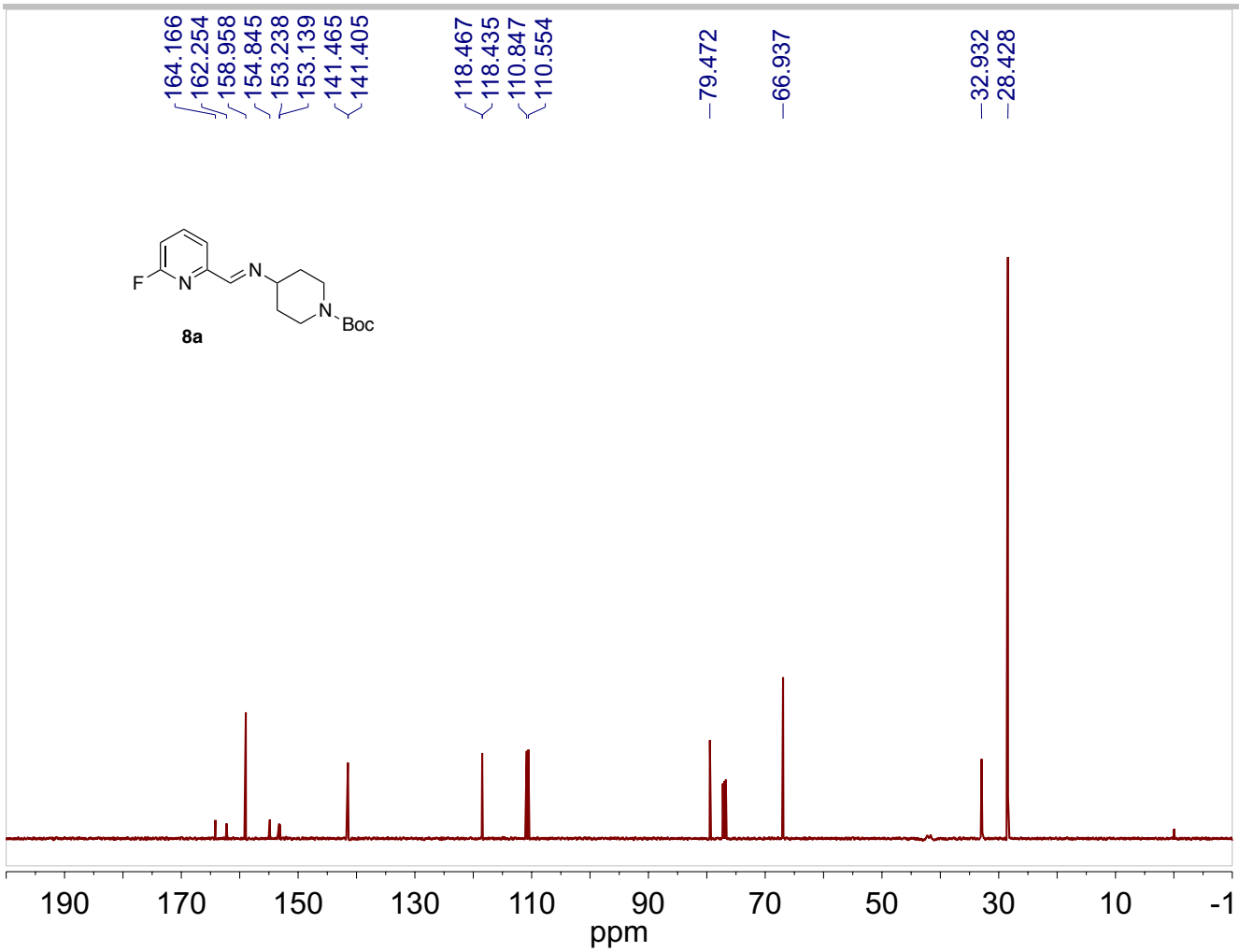
Compound **6**: 125 MHz ^{13}C NMR spectrum in MeOD.



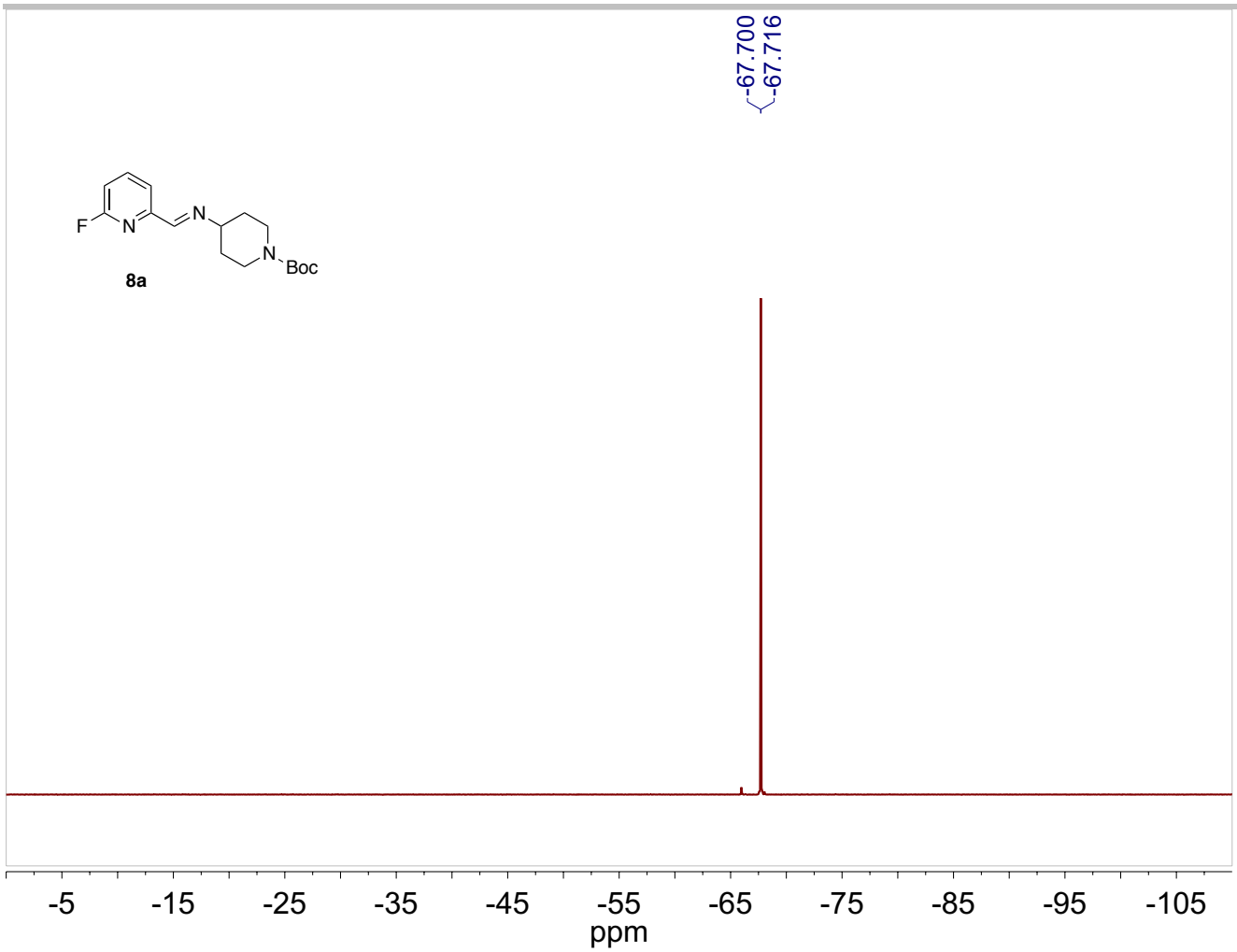
Compound **6**: 470 MHz ^{19}F NMR spectrum in $CDCl_3$.



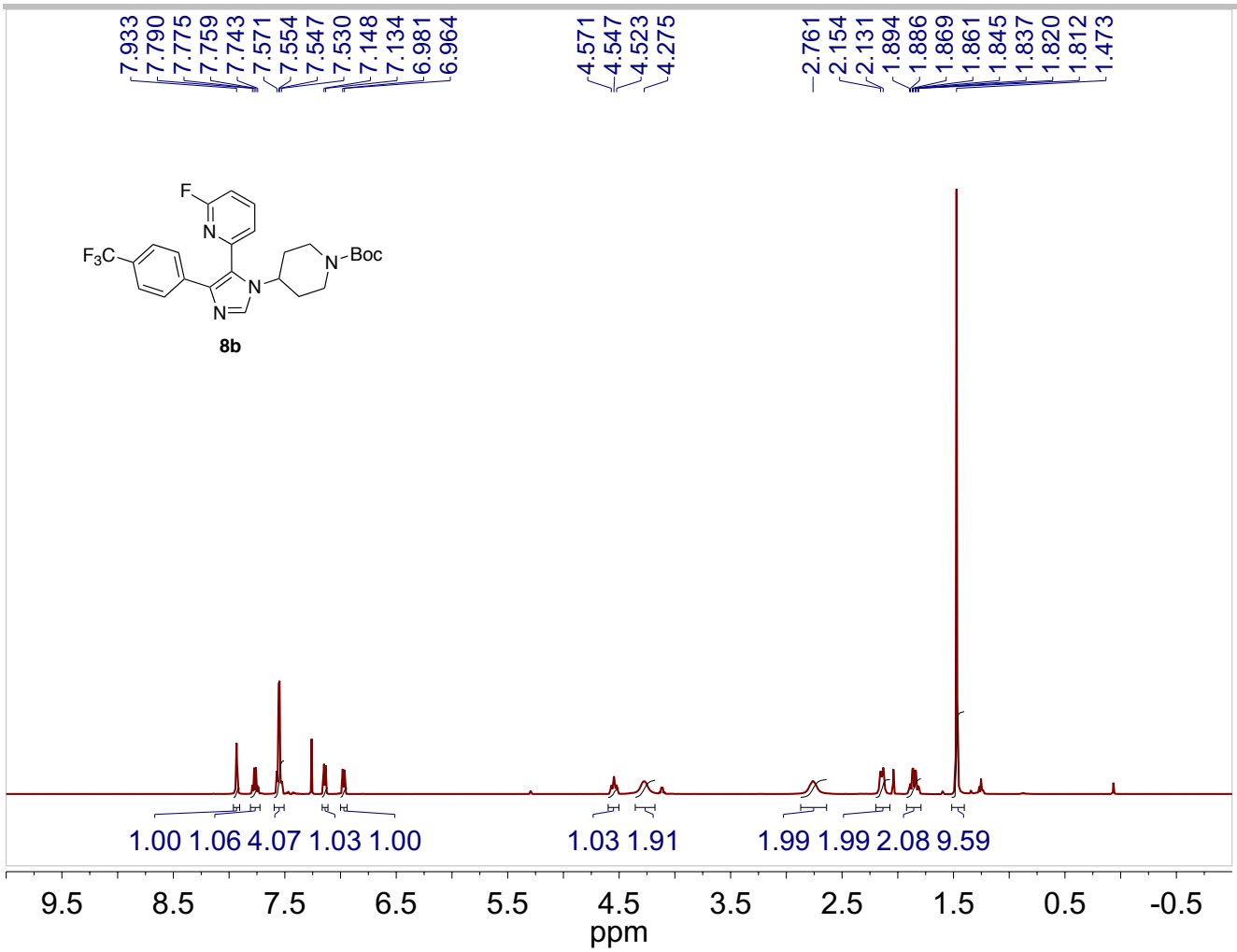
Compound **8a**: 500 MHz ^{1}H Spectrum in $CDCl_3$.



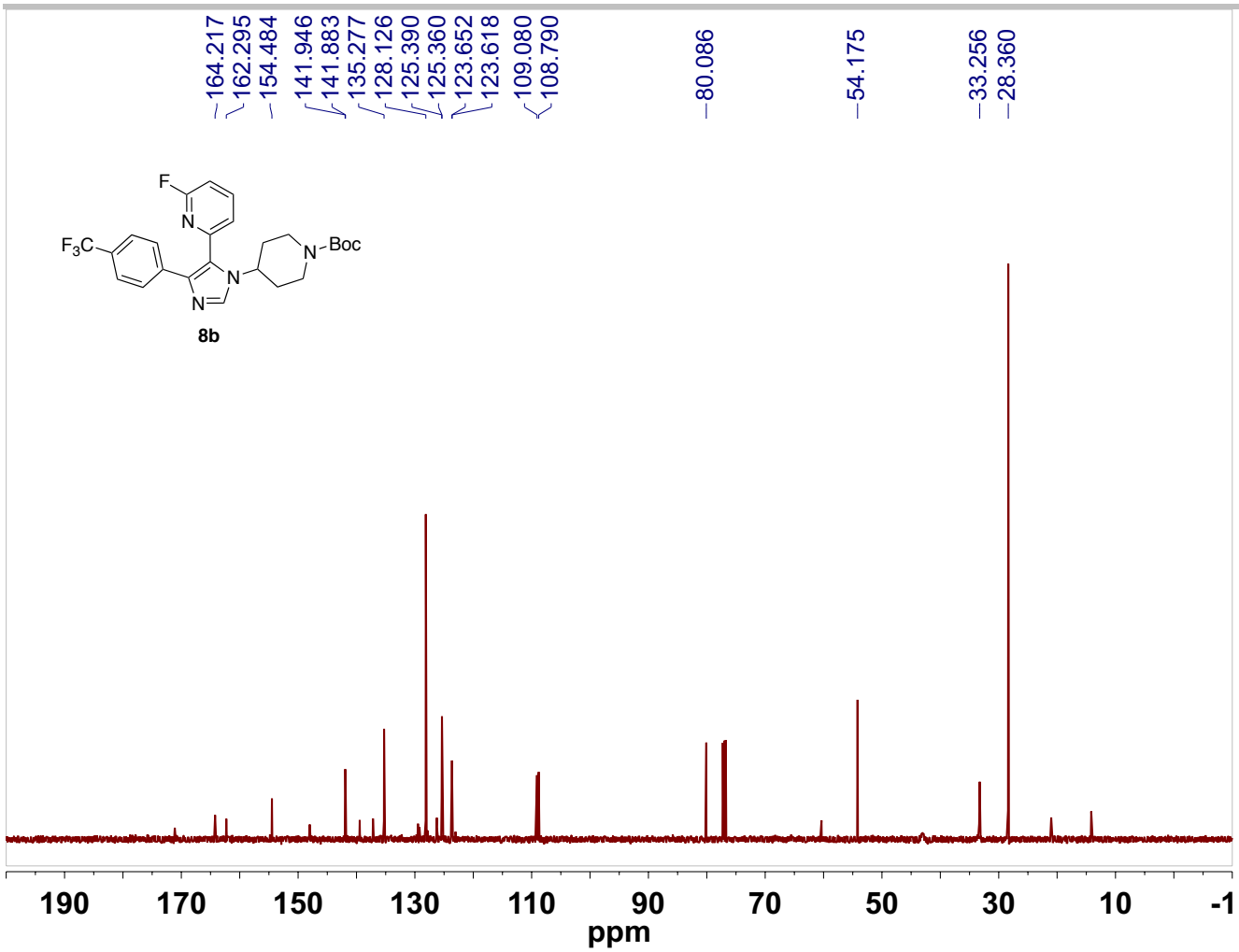
Compound **8a**: 125 MHz ^{13}C spectrum in $CDCl_3$.



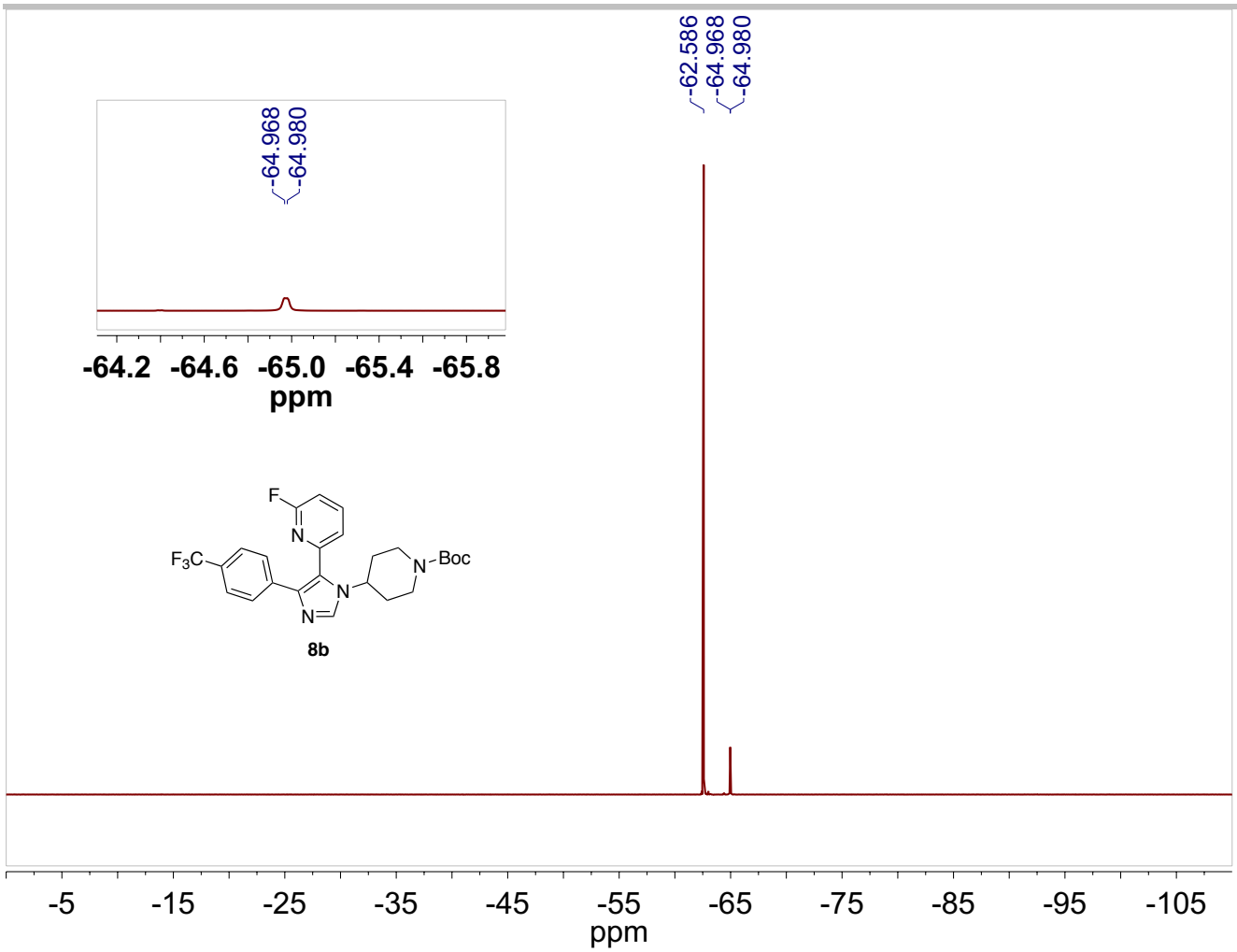
Compound **8a**: 470 MHz ^{19}F spectrum in $CDCl_3$.



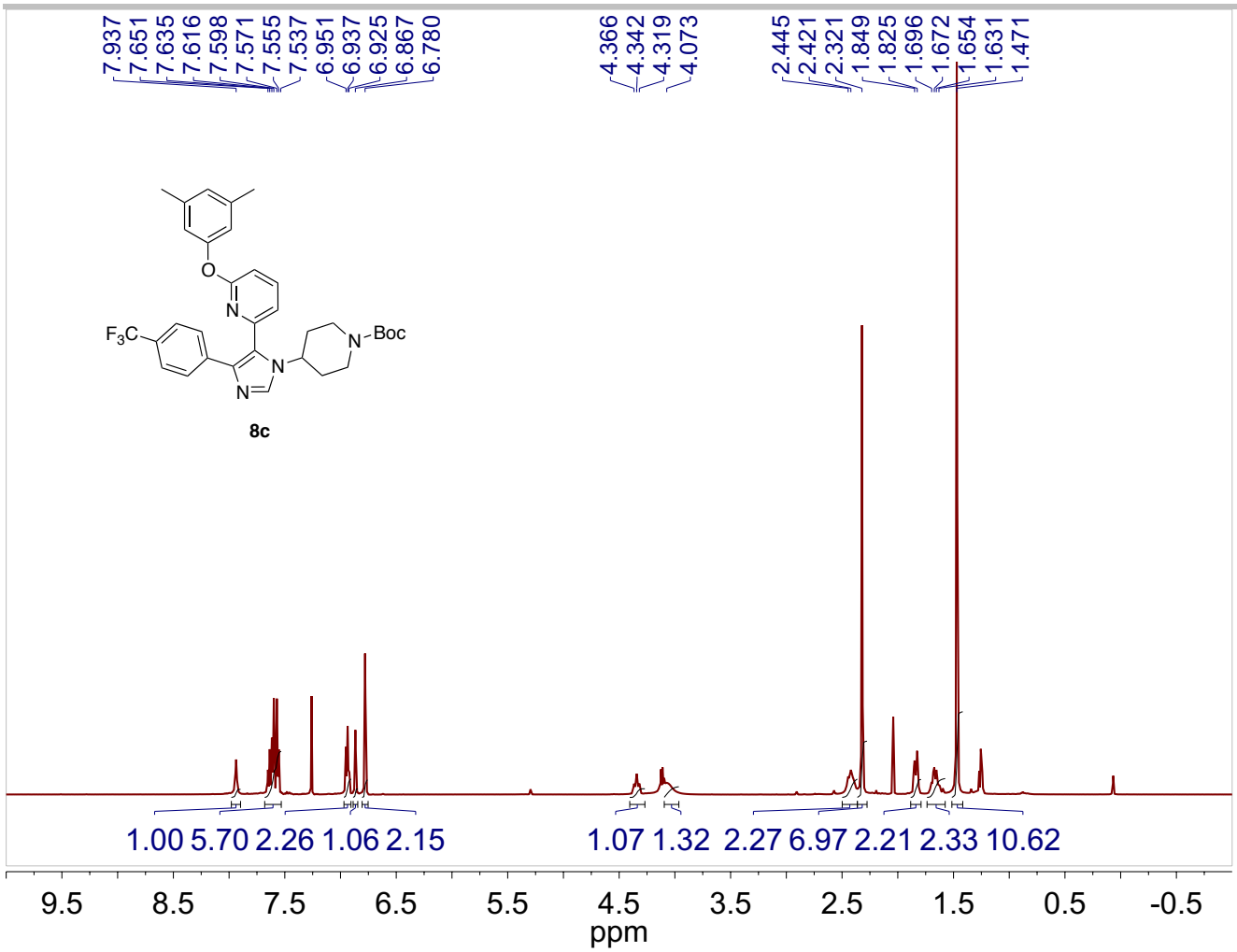
Compound **8b**: 500 MHz ^{1}H Spectrum in $CDCl_3$.



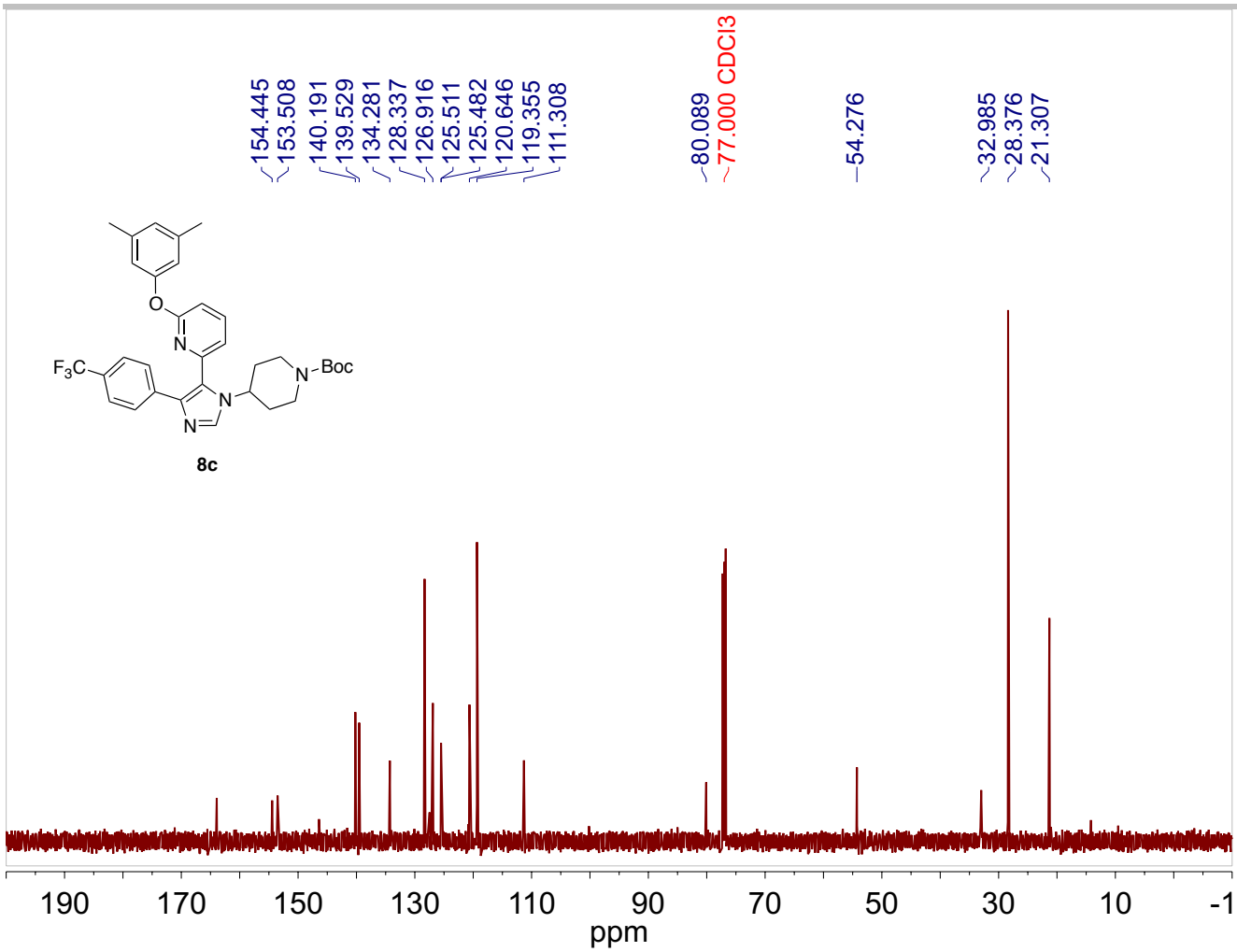
Compound **8b**: 125 MHz ^{13}C spectrum in $CDCl_3$ (Note: contains residual EtOAc) resonances).



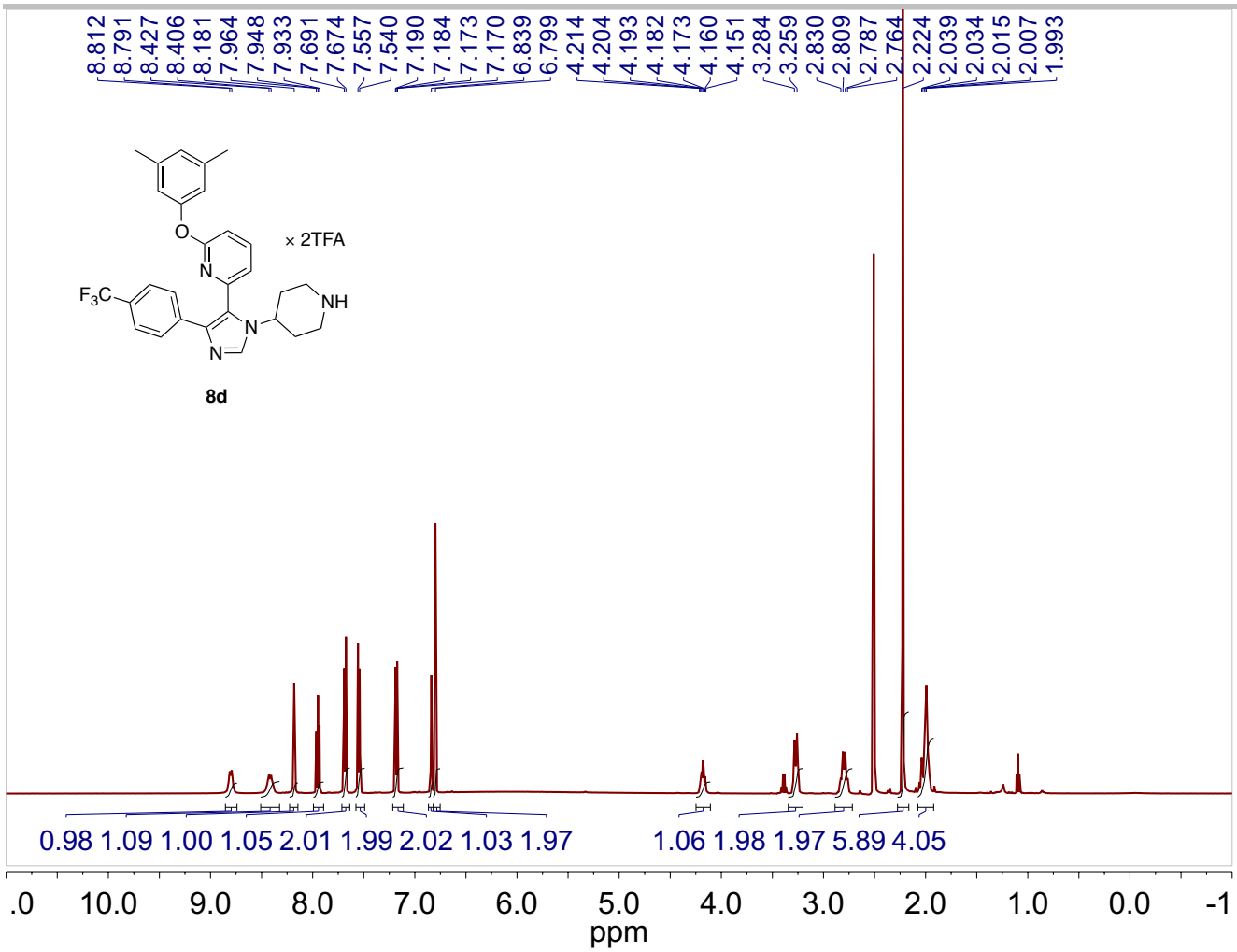
Compound **8b**: 470 MHz ^{19}F spectrum in $CDCl_3$.



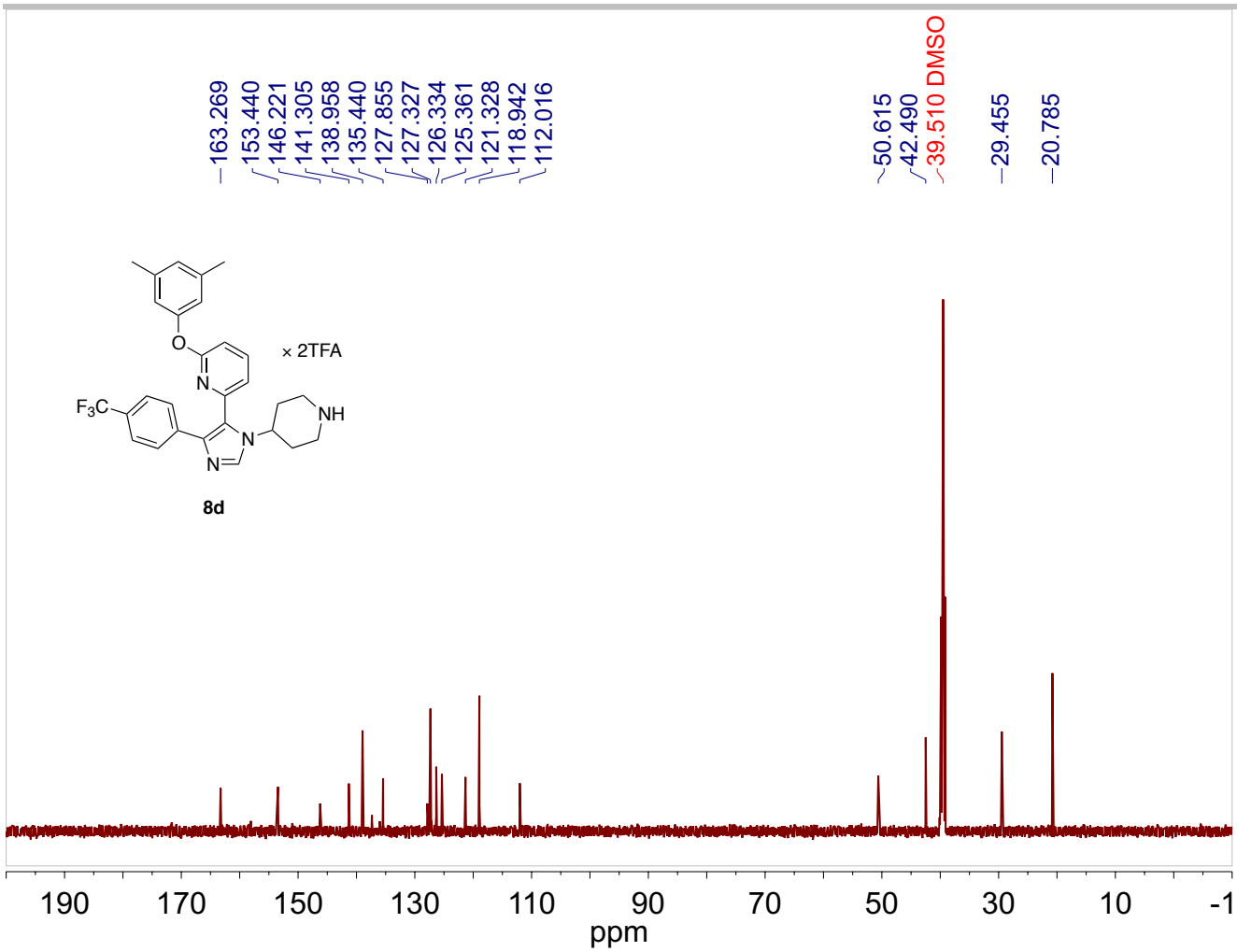
Compound **8c**: 500 MHz ^{1}H Spectrum in $CDCl_3$ (Note: contains residual EtOAc) resonances).



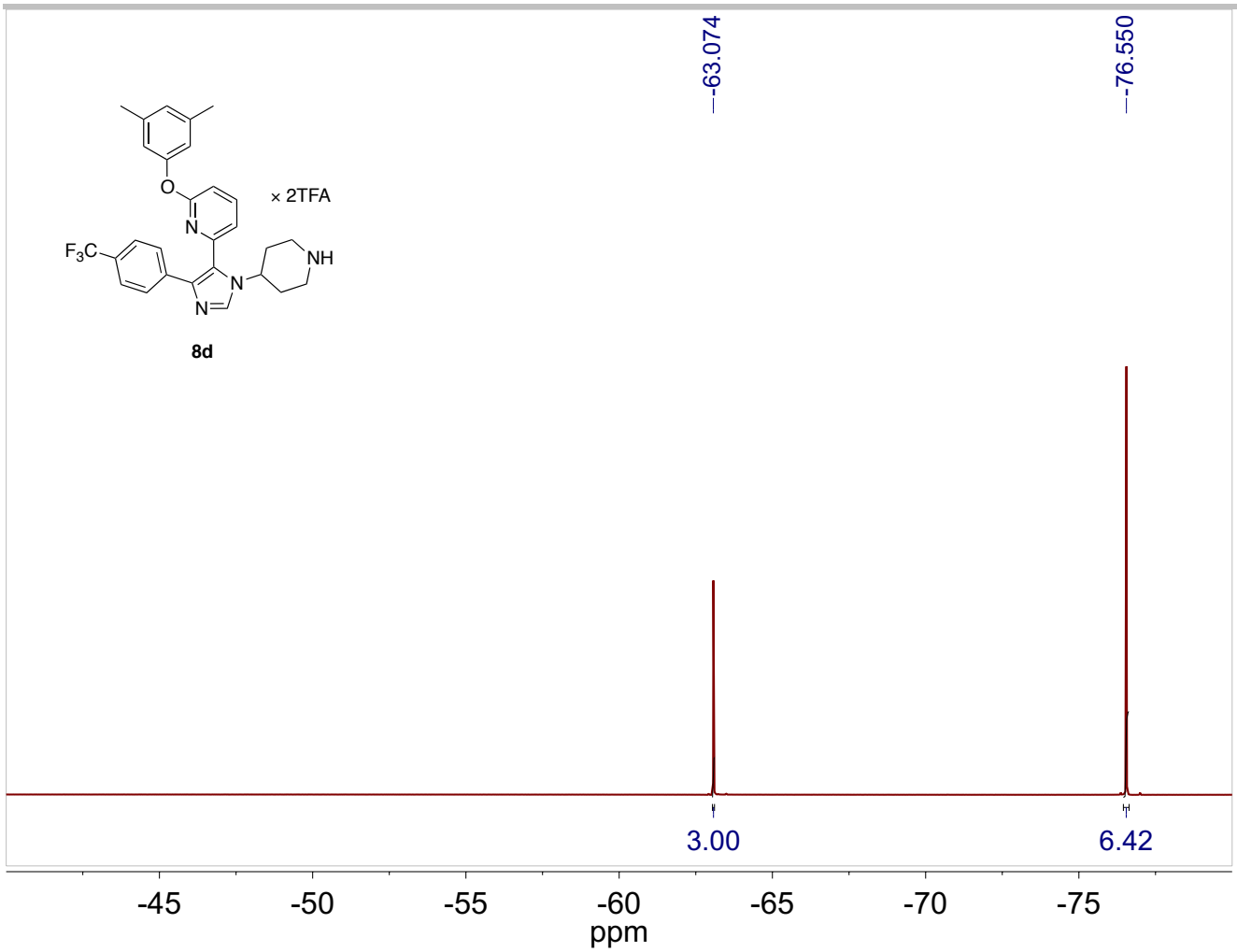
Compound **8c**: 125 MHz, ^{13}C spectrum in $CDCl_3$ (Note: contains residual EtOAc) resonances).



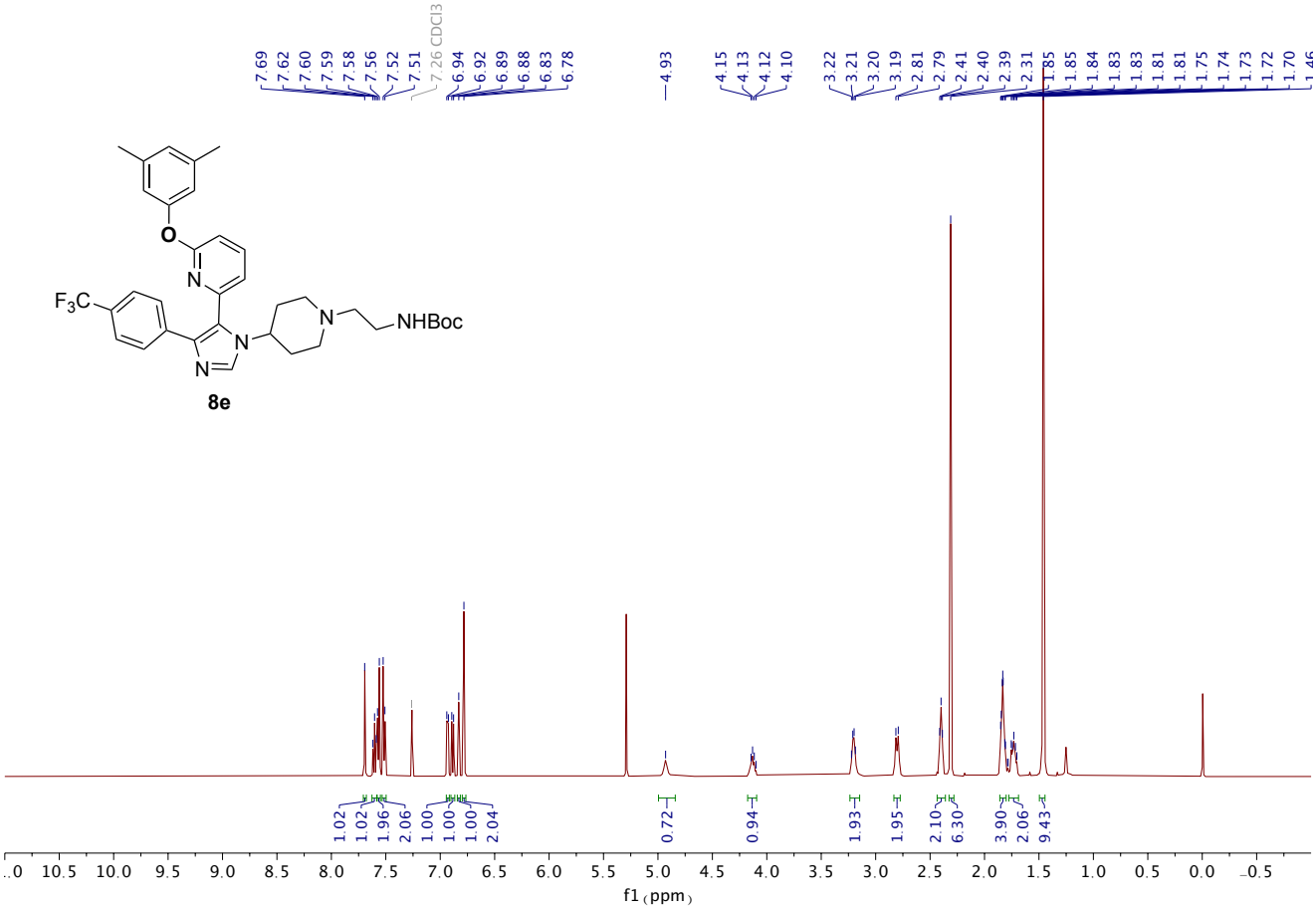
Compound **8d**: 500 MHz ^{1}H Spectrum in DMSO-d$_6$.



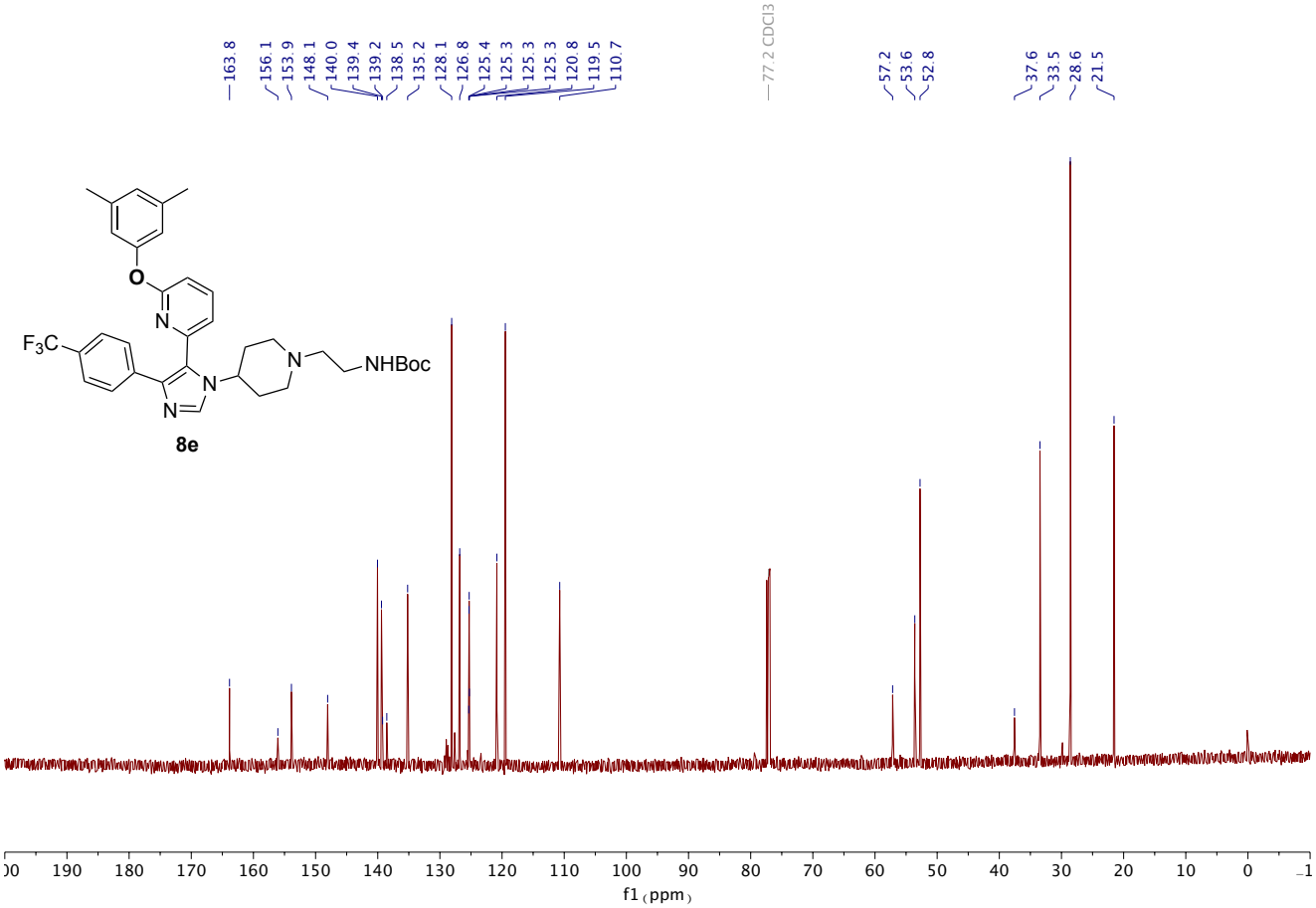
Compound **8d**: 125 MHz ^{13}C spectrum in DMSO-d_6.



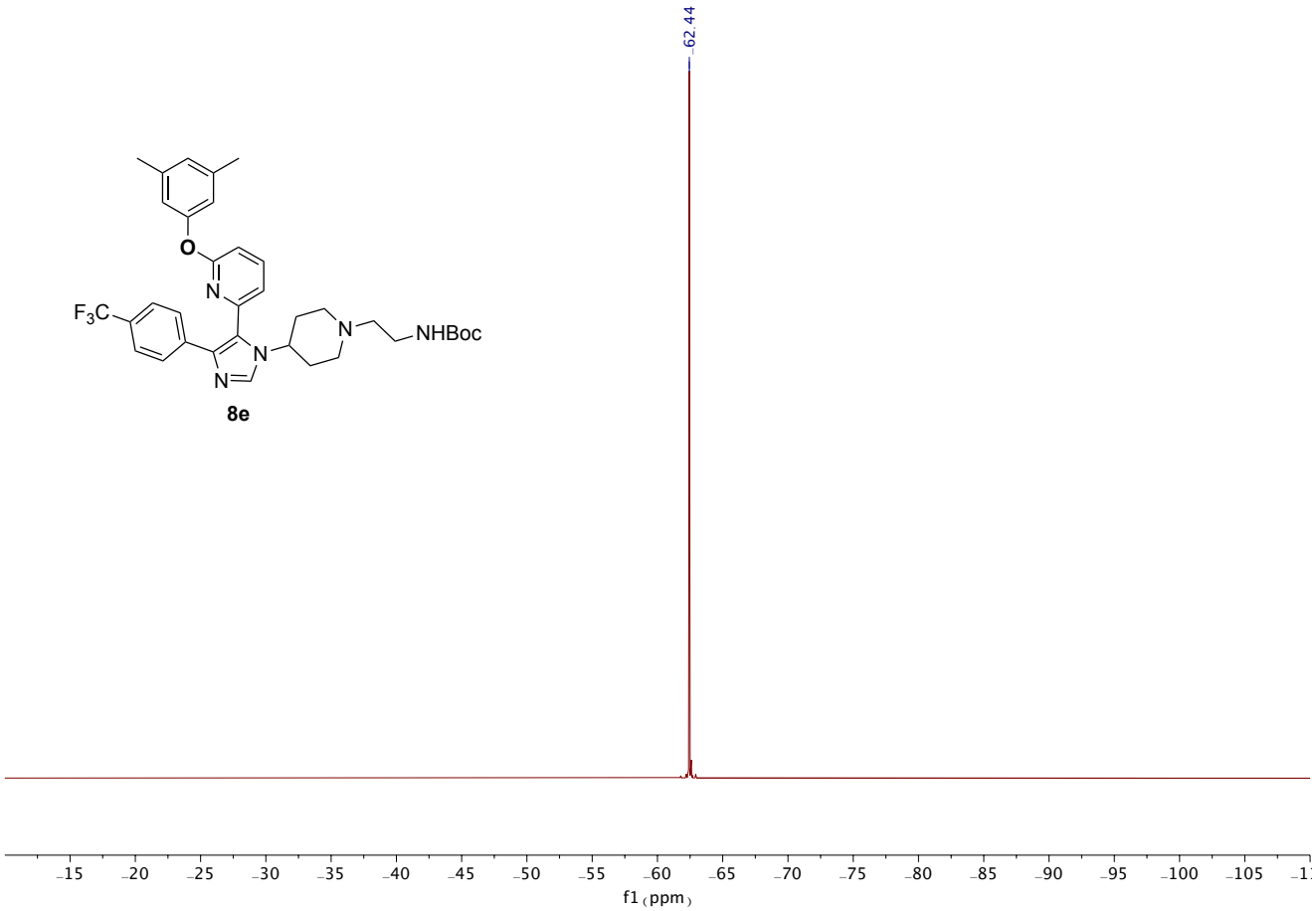
Compound **8d**: 475 MHz ^{19}F NMR spectrum in DMSO-d_6.



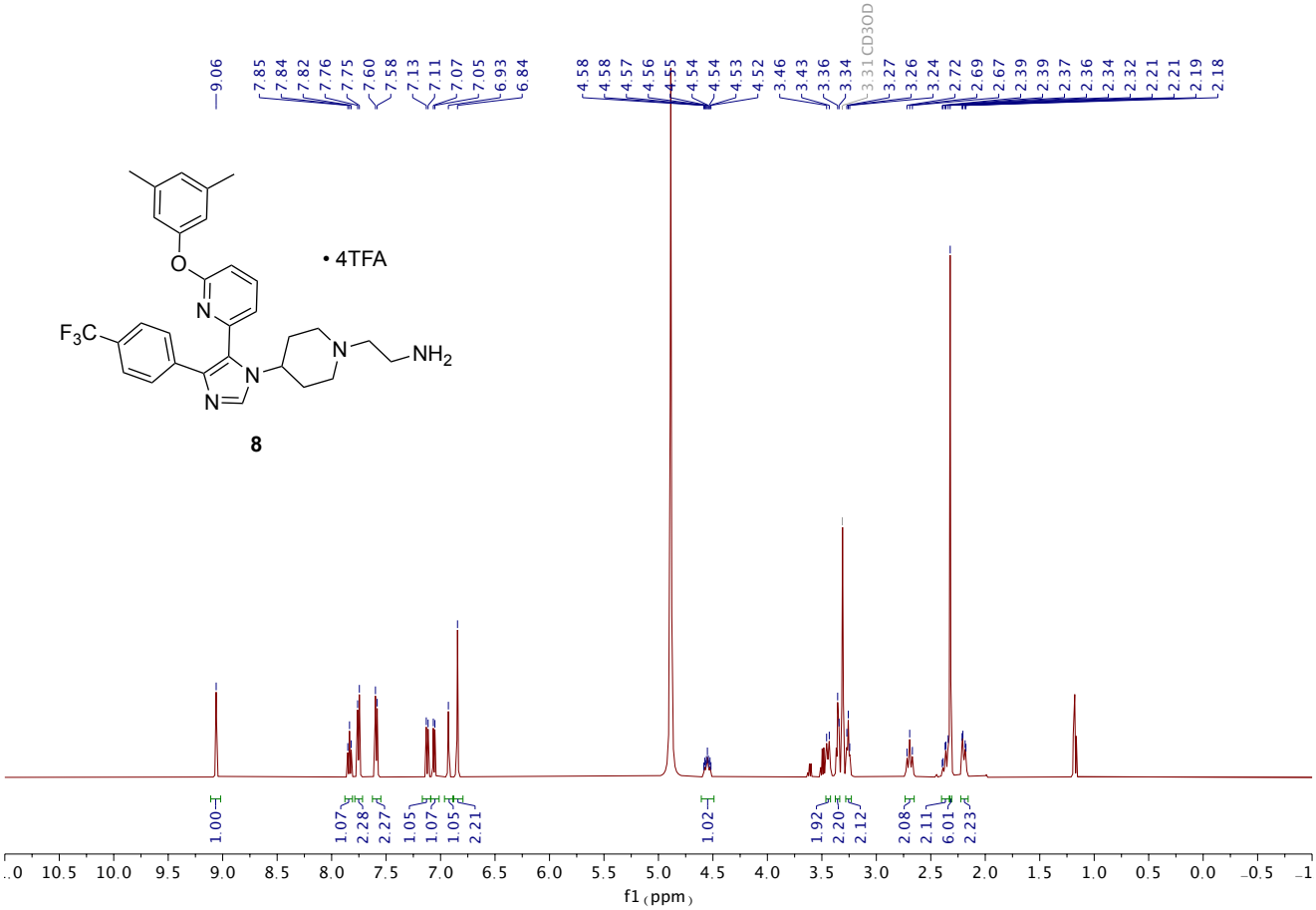
Compound **8e**: 500 MHz ^{1}H NMR spectrum in $CDCl_3$.



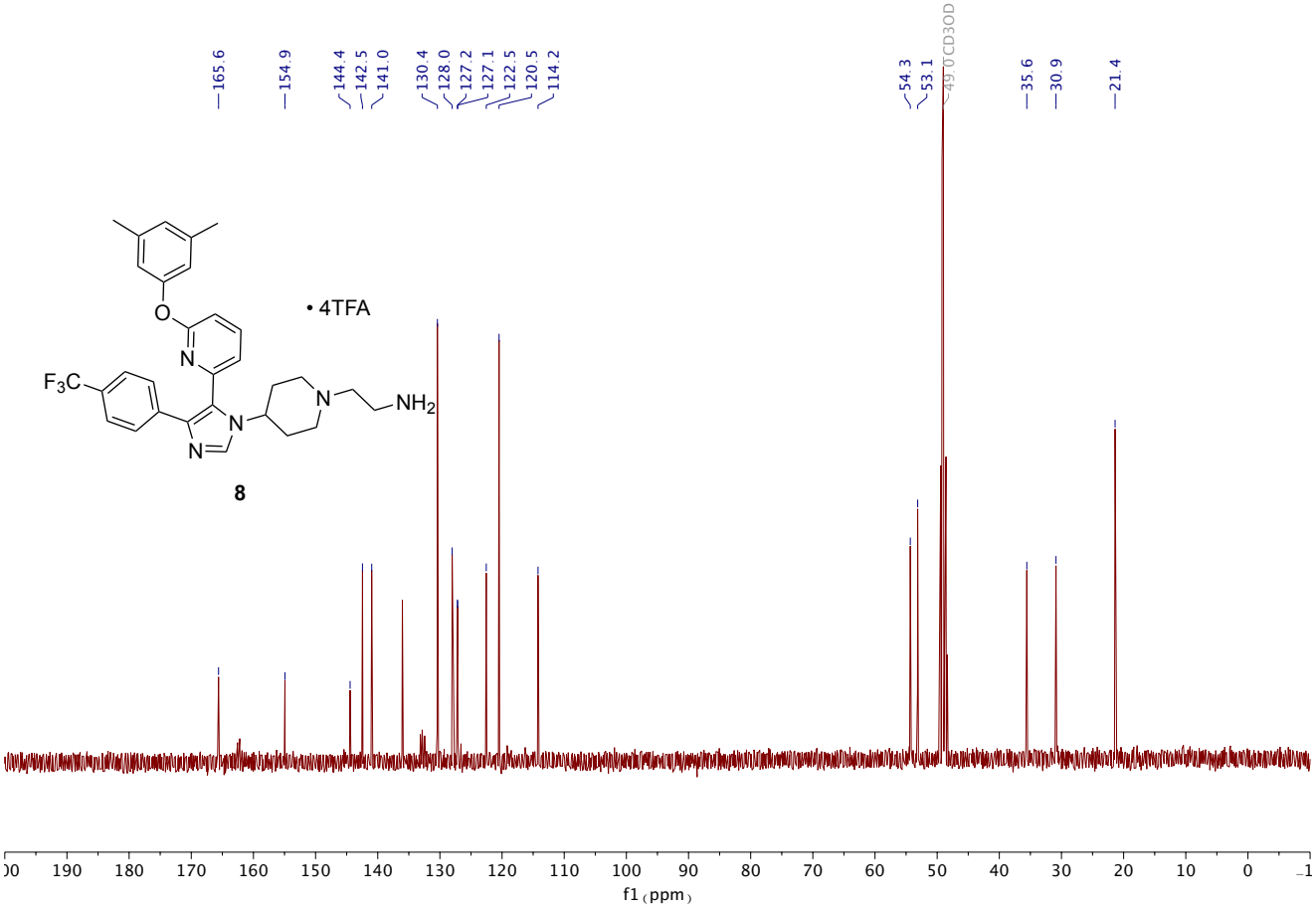
Compound **8e**: 125 MHz ^{13}C NMR spectrum in $CDCl_3$.



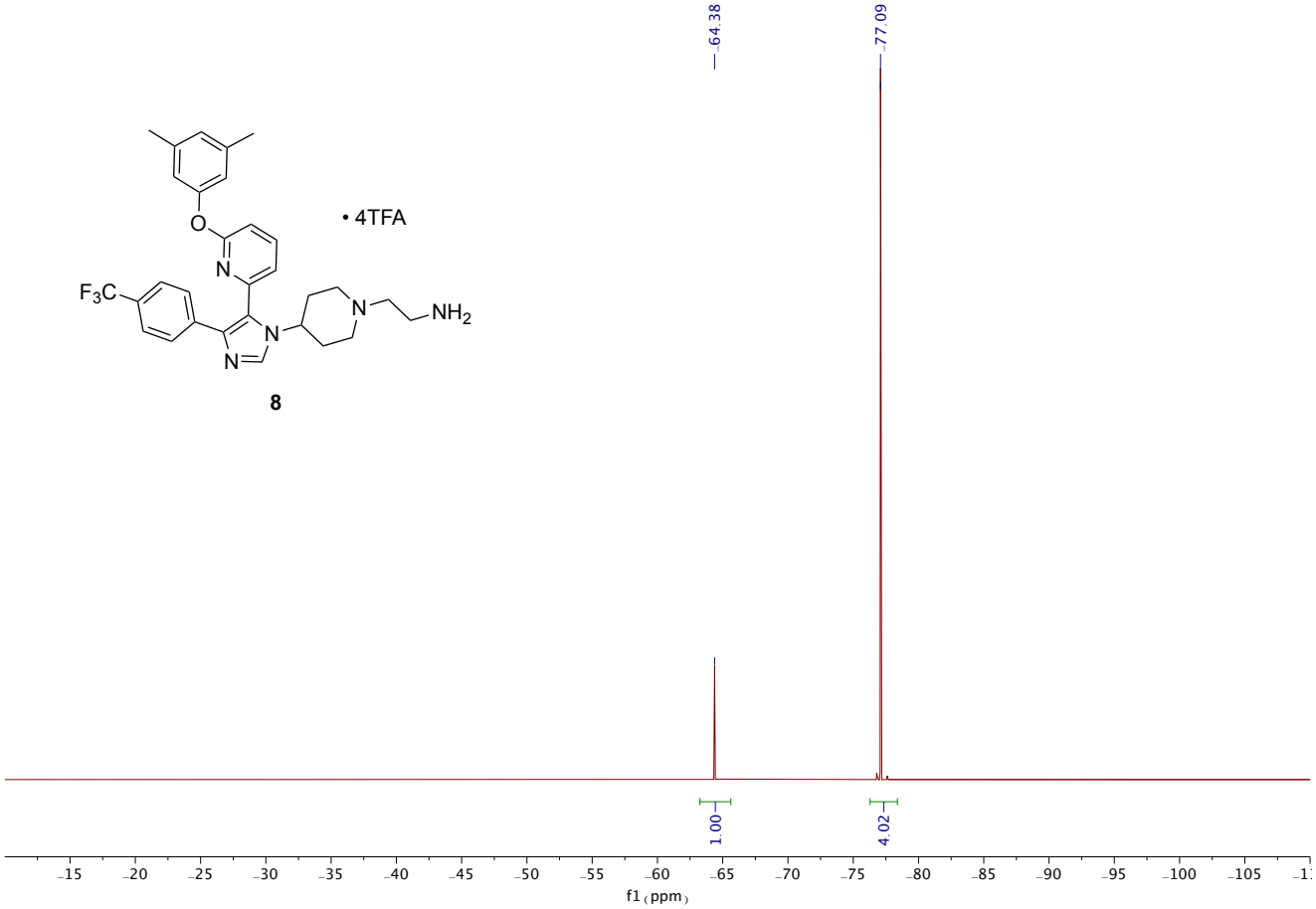
Compound **8e**: 470 MHz ^{19}F NMR spectrum in $CDCl_3$.



Compound **8**: 500 MHz ^{1}H NMR spectrum in MeOD.



Compound **8**: 100 MHz ^{13}C NMR spectrum in MeOD.



Compound **8**: 470 MHz ^{19}F NMR spectrum in MeOD.