Synthesis and *In Vitro* Evaluation of Fluorine-18 Benzimidazole Sulfones as CB2 PET-Radioligands

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Supporting information

Chemistry

General

All reactions were performed under an atmosphere of nitrogen unless otherwise specified. Anhydrous *N,N*-dimethylformamide, dichloromethane, tetrahydrofuran and toluene were obtained from a PureSolv MD 7 solvent purification system (Innovative Technology, Inc.). All other solvents and reagents were used as received from commercial sources. Analytical thin-layer chromatography (TLC) was performed using Merck aluminium backed silica gel 60 F_{254} (0.2 mm) plates that were visualised with shortwave (254 nm) and/or longwave (365 nm) ultraviolet light. Products were also visualised with potassium permanganate, vanillin, cerium molybdate, bromocresol green or ninhydrin stains. Flash column chromatography was performed using Grace Davisil 60 (230-400 mesh) silica gel, with the eluent mixture reported as the volume:volume ratio, unless otherwise stated. Melting points were measured in open capillaries using a Stanford Research System Optimelt Automated melting point apparatus and are uncorrected. Infrared absorption spectra were recorded on a Bruker ALPHA FT-IR spectrometer as a solid or a thin film from ethanol, and the data are reported as vibrational frequencies (cm^{-1}). Nuclear magnetic resonance spectra were recorded at 300 K using a Bruker AVANCE DRX300, 400 or 500 (300 MHz, 400 MHz, 500 MHz) spectrometer. ^{1}H chemical shifts are expressed as parts per million (ppm) with residual chloroform (δ 7.26) and dimethyl sulfoxide (δ 2.50) as reference and are reported as chemical shift (δ); relative integral; multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, t= triplet, q = quartet, m = multiplet); coupling constants (*J*) reported in Hz. ^{13}C chemical shifts

are expressed as parts per million (ppm) with residual chloroform (δ 77.16) and dimethyl sulfoxide (δ 39.52) as reference and reported as chemical shift (δ); multiplicity, coupling constants (*J*) reported in Hz. Proton coupled or decoupled ^{19}F chemical shifts are reported as parts per million (ppm). Low-resolution mass spectra (LRMS) were recorded using electrospray ionisation (ESI) recorded on a Bruker AmaZon SL ion trap spectrometer. High-resolution mass spectrometry was performed on a Bruker Apex Qe 7T Fourier Transform Ion Cyclotron Resonance mass spectrometer equipped with an Apollo II ESI/MALDI dual source. Samples were run with syringe infusion at 150 μL/hr on a Cole Palmer syringe pump into the electrospray ionisation (ESI) source. High performance liquid chromatography (HPLC) analysis of organic purity was conducted on a Waters Alliance 2695 instrument using a SunFire™ C18 column (5 μm, 2.1 x 150 mm) or an X-Bridge™ C18 column (5 μm, 2.1 x 150 mm) and detected using a Waters 2996 photodiode array (PDA) detector set at 254 nm. Separation was achieved using water (solvent A) and acetonitrile (solvent B) at a flow rate of 0.2 mL/min and a gradient of 0 % B to 100 % B over 30 minutes. HPLC data is reported as percentage purity and retention time (RT) in minutes.

N-(5-((4-methoxybenzyl)thio)-2-(pentylamino)phenyl)pivalamide **(6b)**

Was prepared according to the general method ***iv*** from *N*-(2-amino-5-((4-methoxybenzyl)thio)phenyl)pivalamide **5** (0.90 g, 2.6 mmol) and n-pentanal (0.28 mL, 2.6 mmol). Purification on basic alumina using Hex → EtOAc:Hex (1:10) → (1:5) → (1:2) gradient, which gave the title compound as an orange oil (0.76 g, 55%). ^{1}H NMR (200 MHz): δ 0.91 (3H, t, *J* = 5 Hz), 1.33 (9H, s), 1.37 (4H, m), 1.62 (2H, m), 3.04 (2H, t, *J* = 7.0 Hz), 3.77 (3H, s), 3.92 (2H, s), 6.65 (1H, d, *J* = 8.4 Hz), 6.79 (2H, d, *J* = 8.8 Hz), 7.08 (1H, m), 7.11 (2H, d, *J* = 8.6 Hz), 7.23 (1H, s), 7.26 (1H, bs); ^{13}C NMR (75 MHz): δ 14.2, 22.6, 27.9 (3xC), 29.3, 29.4, 39.6, 41.1, 44.5, 55.4, 113.9 (2xC), 114.2, 123.4, 124.9, 130.0, 130.3 (2xC), 130.5, 132.2, 142.4, 158.9, 177.5; HRMS (ESI-TOF) *m/z*: calculated for $C_{24}H_{34}N_2O_2S$ $[M+Na]^+$ 437.2233; found 437.2234.

N-(2-((cyclobutylmethyl)amino)-5-((4-methoxybenzyl)thio)phenyl)pivalamide **(6c)**

Was prepared according to the general method ***iv*** from *N*-(2-amino-5-((4-methoxybenzyl)thio)phenyl)pivalamide **5** (0.40 g, 1.17 mmol) and cyclobutane carbaldehyde (0.11 g, 1.29 mmol). Purification on basic alumina EtOAc:Hex (1:5) → (1:4) gave the title product as dark orange solid (0.40 g, 82%).

m.p. 105.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (9H, s), 1.71-1.84 (2H, m), 1-84-1.99 (2H, m), 2.02-2.14 (2H, m), 2.58 (1H, m, *J* = 7.5 Hz), 3.06 (2H, d, *J* = 7.2 Hz), 3.77 (3H, s), 3.92 (2H, s), 6.64 (1H, d, *J* = 8.4 Hz), 6.79 (2H, d, *J* = 8.7 Hz), 7.10 (2H, d, *J* = 8.7 Hz), 7.10 (1H, m), 7.23 (1H, s), 7.24 (1H, bs); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 26.1 (2xC), 27.8 (3xC), 35.2, 39.5, 41.1, 49.9, 55.3, 113.8 (3xC), 123.0, 124.7, 130.0, 130.2 (2xC), 130.4, 132.2, 142.7, 158.7, 177.3; HRMS (ESI-TOF) *m/z*: calculated for $C_{24}H_{32}N_2O_2S$ $[M+H]^+$ 435.2077, found 435.2077.

2-(tert-butyl)-5-((4-methoxybenzyl)thio)-1-pentyl-1H-benzo[d]imidazole **(7b)**

Was prepared from *N*-(5-((4-methoxybenzyl)thio)-2-(pentylamino)phenyl)pivalamide (0.74 g, 1.78 mmol) and *p*-TsOH monohydrate (0.30 g, 0.9 equiv.) according to general method ***v***. The crude product was purified on silica chromatography (EtOAc:Hex (1:6) → (1:4) → (1:2) to give the title product as a light orange solid (0.56 g, 79%).

m.p. 96.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (3H, t, *J* = 6.6 Hz), 1.43 (4H, m), 1.54 (9H, s), 1.84 (2H, m), 3.77 (3H, s), 4.05 (2H, s), 4.23 (2H, m), 6.78 (2H, d, *J* = 7.8 Hz), 7.2 (4H, m), 7.83 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.5, 29.3, 29.5, 29.8 (3xC), 34.3, 40.7, 45.9, 55.4, 109.7, 113.9, 123.0, 126.4, 128.6, 130.07 (2xC), 130.13, 135.9, 142.5, 158.7, 161.3; HRMS (ESI-TOF) *m/z*: calculated for $C_{24}H_{32}N_2OS$ $[M+Na]^+$ 419.2128, found 419.2129.

2-(tert-butyl)-1-(cyclobutylmethyl)-5-((4-methoxybenzyl)thio)-1H-benzo[d]imidazole **(7c)**

Was prepared from *N*-(2-((cyclobutylmethyl)amino)-5-((4-methoxybenzyl)thio)phenyl)pivalamide (0.34 g, 0.83 mmol) using *p*-TsOH monohydrate (0.18 g, 0.96 mmol) according to the general method ***v***. Purification on silica gel using EtOAc:Hex (1:6) afforded the product as light orange solid (0.245 g, 75%).

m.p. 91.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (9H, s), 1.88 - 2.05 (4H, m), 2.09 - 2.20 (2H, m), 2.76 - 2.91 (1H, m), 3.85 (3H, s), 4.13 (2H, s), 4.37 (2H, d, *J* = 6.6 Hz), 6.86 (2H, d, *J* = 8.4 Hz), 7.20 - 7.34 (4H, m), 7.88 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5, 28.2 (2xC), 30.2 (3xC), 34.4, 37.4, 40.7, 50.9, 55.4, 110.2, 113.9 (2xC), 122.8, 126.2, 128.3, 130.1 (2xC), 130.2, 136.2, 142.4, 158.7, 161.4; HRMS (ESI-TOF) *m/z*: calculated for $C_{24}H_{30}N_2OS$ $[M+H]^+$ 395.2152, found 395.2151.

N-(5-bromo-2-((3-methoxypropyl)amino)phenyl)pivalamide **(12d)**

General method xi: 2,5-dibromonitrobenzene (6.00 g, 90%, 19.2 mmol) was dissolved in ethanol (80 mL) in a pressure flask and and 3-methoxypropan-1-amine (2.20 mL, 21.1 mmol) and di-isopropylethylamine (6.6 mL, 38 mmol) were added. The flask was sealed and the solution was heated to 100 °C. After 48 h, reaction mixture was cooled down to room temperature and solution was concentrated. Residue was dissolved in EtOAc (60 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). Aqueous phase was extracted with EtOAc (2 x 10 mL), and the combined organic phase was dried over anhydrous $MgSO_4$. Concentrated crude product was purified on silica gel chromatography using EtOAc:Hex gradient (1:8 → 1:6 → 1:4), which gave 4-bromo-*N*-(3-methoxypropyl)-2-nitroaniline as orange oil (4.35 g, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97 (2H, m, *J* = 6.6 Hz), 3.37 (3H, s), 3.40 (2H, m), 3.53 (2H, t, *J* = 5.7 Hz), 6.77 (1H, d, *J* = 9.3 Hz), 7.47 (1H, dd, J_1 = 9.3 Hz, J_2 = 2.4 Hz), 8.25 (1H, bs), 8.29 (1H, d, *J* = 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.0, 41.2, 58.9, 70.5, 106.2, 115.6, 129.0, 132.3, 138.9, 144.6; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{10}H_{13}N_2O_3Br$ 311.0002 and 312.9981, found 311.0005 and 312.9985.

4-bromo-*N*-(3-methoxypropyl)-2-nitroaniline (3.50 g, 12.2 mmol) was treated with iron powder (6.8 g, 10 equiv) according to the general method ***iii***. Purification on silica gel using EtOAc:Hex gradient (1:2 → 1:1) gave 4-bromo-*N1*-(3-methoxypropyl)benzene-1,2-diamine as light brown solid (2.59 g, 82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92 (2H, m, *J* = 6 Hz), 3.18 (2H, t, *J* = 6.3 Hz), 3.36 (s, 3H), 3.43 (2H, bs), 3.53 (2H, t, *J* = 5.7 Hz), 6.50 (1H, d, *J* = 8.4 Hz), 6.82 (1H, d, *J*

= 2.4 Hz), 6.89 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.5, 42.5, 58.9, 71.7, 110.4, 113.0, 118.8, 123.0, 135.9, 137.1; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{10}H_{15}BrN_2O$ 281.0260 and 283.0240, found 281.0264 and 283.0244.

4-bromo-*N1*-(3-methoxypropyl)benzene-1,2-diamine (2.50 g, 9.69 mmol) was reacted with pivaloyl chloride (1.19 mL, 9.70 mmol) according to the general method ***ii***. Purification on silica gel using EtOAc:Hex (1:6 → 1:5 → 1:2) gave the title product (**12d**) as white solid (2.26 g, 68%).
m.p. 96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (9H, s), 1.90 (2H, pentet, J = 6 Hz), 3.15 (2H, t, J = 6 Hz), 3.33 (3H, s), 3.52 (2H, t, J = 5.7 Hz), 4.02 (1H, bs), 6.63 (1H, d, J = 8.7 Hz), 7.18 (1H, dd, J_1= 8.7 Hz, J_2 = 2.1 Hz), 7.62 (1H, d, J = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.8 (3xC), 39.8, 43.1, 59.0, 72.1, 110.1, 114.8, 126.3, 127.2, 129.3, 141.1, 177.3; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{15}H_{23}BrN_2O_2$ 365.0835 and 367.0818, found 365.0838 and 367.0818.

N-(5-bromo-2-(((tetrahydro-2H-pyran-4-yl)methyl)amino)phenyl)pivalamide **(12e)**

Was prepared in three steps following methods ***xi***, ***iii*** and ***ii***. 2,5-dibromonitrobenzene (8.0 g, 90%, 25.6 mmol) and 4-aminomethyl tetrahydropyran (6.24 mL, 2 equiv) were reacted according to the general method ***xi***. Purification on silica gel using EtOAc:Hex (1:4 → 1:2) gave 4-bromo-2-nitro-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)aniline as red solid (3.10 g, 38%).
m.p. 106.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (2H, m), 1.76 (2H, m), 1.95 (1H, m), 3.20 (2H, t), 3.41 (2H, td, J_1 = 11.8 Hz, J_2 = 1.8 Hz), 4.04 (2H, dd, J_1 = 11 Hz, J_2 = 3.8 Hz), 6.78 (1H, d, J = 9.2 Hz), 7.50 (1H, dd, J_1 = 9.2 Hz, J_2 = 2.4 Hz), 8.13 (1H, bs), 8.32 (1H, d, J= 2.4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.0 (2xC), 34.9, 49.2 (2xC), 67.6, 106.5, 115.6, 129.2, 132.4, 139.1, 144.7; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{12}H_{15}BrN_2O_3$ 337.0158 and 339.0138, found 337.0155 and 339.0135.

4-bromo-2-nitro-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)aniline (3.04 g, 9.66 mmol) was treated with iron powder (5.40 g, 10 equiv) according to the general method ***iii***.

Purification on silica gel using EtOAc:Hex (1:2) gave 4-bromo-*N1*-((tetrahydro-2*H*-pyran-4-yl)methyl)benzene-1,2-diamine as light brown solid (2.62 g, 95%).
m.p. 93°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (2H, m), 1.73 (2H, d, *J* = 13.5 Hz), 1.86 (1H, m), 2.98 (2H, d, *J* = 6.3 Hz), 3.32 (2H, bs), 3.40 (2H, t, *J* = 10.8 Hz), 4.00 (2H, d, *J* = 10.5 Hz), 6.50 (1H, d, *J* = 8.4 Hz), 6.84 (1H, s), 6.90 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.3 (2xC) 35.0, 50.4, 67.9 (2xC), 110.5, 113.1, 119.2, 123.3, 135.9, 137.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{12}H_{17}BrN_2O$ 285.0597 and 287.0577, found 285.0595 and 287.0574.

4-bromo-*N1*-((tetrahydro-2*H*-pyran-4-yl)methyl)benzene-1,2-diamine (2.62 g, 9.20 mmol) was treated with pivaloyl chloride (1.25 mL, 10.1 mmol) according to the general method ***ii***. Purification on silica gel using EtOAc:Hex (1:2) afforded the title product (**12e**) as light pink solid (3.35 g, 98%).
m.p. 188.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (9H, s), 1.40 (2H, m), 1.70 (2H, d, *J* =12.9 Hz), 1.83 (1H, m), 2.96 (2H, d, *J* = 6.3 Hz), 3.40 (2H, t, *J* = 11.7 Hz), 4.00 (2H, d, *J* = 10.2 Hz), 6.65 (1H, d, *J* = 8.7 Hz), 7.22 (1H, d, *J*= 8.7 Hz), 7.41 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.9 (3xC), 31.2 (2xC), 35.1, 39.6, 50.5, 67.8 (2xC), 109.7, 115.1, 126.2, 127.8, 129.9, 141.8, 177.9; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{17}H_{25}BrN_2O_2$ 391.0992 and 393.0971; found 391.0988 and 393.0968.

N-(5-bromo-2-((3-(dimethylamino)propyl)amino)phenyl)pivalamide **(12f)**

Was prepared in three steps following the general methods ***xi, iii*** and ***ii***. 2,5-dibromonitrobenzene (90%, 8.03 g, 25.7 mmol) and dimethylamino propylamine (3.56 mL, 28.3 mmol) were reacted according to the general method ***xi***. Crude product was purified on silica gel chromatography using 1%→5% MeOH saturated with NH_3 in DCM to give *N1*-(4-bromo-2-nitrophenyl)-N^3,N^3-dimethylpropane-1,3-diamine as bright red oil (4.81 g, 61%).
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84 (2H, m, *J* = 6.6 Hz), 2.24 (6H, s), 2.41 (2H, t, *J* = 6.6 Hz), 3.35 (2H, q, *J* = 6.6 Hz), 6.77 (1H, d, *J* = 9.3 Hz), 7.44 (1H, dd, J_1 = 9.3 Hz, J_2 = 2.4 Hz), 8.28 (1H, d, *J* = 2.4 Hz), 8.54 (1H, bs); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 42.4, 45.7 (2xC), 57.8, 106.2, 115.9, 129.2, 132.4, 139.0, 144.8; HRMS (ESI-

TOF) *m/z*: $[M+Na]^+$ calculated for $C_{11}H_{16}BrN_3O_2$ 324.0318 and 326.0318, found 324.0321 and 326.0321.

N1-(4-bromo-2-nitrophenyl)-N^3,N^3-dimethylpropane-1,3-diamine (3.02 g, 10.0 mmol) was treated with iron powder (5.6 g, 10 equiv) according to the general method ***iii***. Purification of the crude material on silica gel using MeOH (sat. with NH_3) in DCM (2% → 5% → 10%) afforded 4-bromo-*N1*-(3-(dimethylamino)propyl)benzene-1,2-diamine as a purple solid (2.71 g, >99%).
m.p. 68 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82 (2H, m, J = 6.3 Hz), 2.25 (6H, s), 2.42 (2H, t, J = 6.6 Hz), 3.13 (2H, t, J = 6.6 Hz), 3.38 (2H, bs), 4.16 (1H, bs), 6.46 (1H, d, J = 8.4 Hz), 6.80 (1H, d, J = 2.1 Hz), 6.87 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.0, 44.0, 45.8 (2xC), 58.8, 110.3, 112.9, 118.6, 123.0, 136.1, 137.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{11}H_{18}BrN_3$ 272.0757 and 274.0736, found 272.0757 and 274.0737.

4-bromo-*N1*-(3-(dimethylamino)propyl)benzene-1,2-diamine (2.71 g, 9.97 mmol) was treated with pivaloyl chloride (1.90 mL, 15.4 mmol) according to the general method ***ii***. Purification on silica gel using MeOH (sat. with NH_3) in DCM (3% → 5%) afforded the title product (**12f**) as a light pink solid (2.42 g, 68%).
m.p. 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (9H, s), 1.80 (2H, pentet, J = 6.6 Hz), 2.24 (6H, s), 2.42 (2H, t, J = 6.6 Hz), 3.12 (2H, t, J = 6.6 Hz), 4.42 (1H, bs), 6.63 (1H, d, J = 8.7 Hz), 7.18 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.2 Hz), 7.29 (1H, bs), 7.66 (1H, d, J_1 = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.8, 28.0 (3xC), 39.9, 44.4, 46.1 (2xC), 59.1, 110.3, 114.9, 126.8, 127.2, 129.3, 141.3, 177.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{26}BrN_3O$ 356.1332 and 358.1312, found 356.1332 and 358.1313.

Methyl 4-((4-bromo-2-pivalamidophenyl)amino)butanoate (**12h**)

Was synthesised in three steps following the methods ***xi***, ***iii*** and ***ii***: 2-nitro-4-bromofluorobenzene (10 g, 5.6 mL, 45 mmol) and gamma-amino butyric acid (5.1 g, 50 mmol) were reacted according to the general method ***xi***. After completion of the reaction, solution was cooled down and ethanol was evaporated off. The residue was treated with warm MeOH and $CHCl_3$ and a small amount of hexane to form an orange precipitate which was filtered and dried under vacuum to give 4-((4-bromo-2-

nitrophenyl)amino)butanoic acid as orange crystalline solid (12.3 g, 89%). 4-((4-bromo-2-nitrophenyl)amino)butanoic acid (6.0 g) was dissolved in methanol (60 mL) and refluxed in the presence of acid (20 mol-% H_2SO_4) for overnight. The crude product methyl 4-((4-bromo-2-nitrophenyl)amino)butanoate was carried over directly to the next step. Orange solid (6.25 g, >99%)

m.p. 72.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02 (2H, pentet, J = 7.2 Hz), 2.46 (2H, t, J = 7.2 Hz), 3.35 (2H, dt, J_1 = 5.7 Hz, J_2 = 6.9 Hz), 3.68 (3H, s), 6.80 (1H, d, J = 9 Hz), 7.47 (1H, dd, J_1 = 9.3 Hz, J_2 = 2.4 Hz), 8.03 (1H, bt), 8.27 (1H, d, J = 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 31.2, 42.4, 51.9, 106.6, 115.6, 129.0, 132.4, 139.0, 144.4, 173.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{11}H_{13}BrN_2O_4$ 338.9951 and 340.9930, found 338.9956 and 340.9935.

Methyl 4-((4-bromo-2-nitrophenyl)amino)butanoate (6.25 g, 19.9 mmol) was treated with iron powder (11.1 g, 10 equiv) according to the general method ***iii***. The crude product methyl 4-((2-amino-4-bromophenyl)amino)butanoate was obtained as a light brown solid (5.1 g, 89%) and was used directly to the next step.

m.p. 83.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99 (2H, pentet, J = 6.9 Hz), 2.47 (2H, t, J = 7.2 Hz), 3.13 (2H, t, J = 6.6 Hz), 3.30 (2H, bs), 3.68 (3H, s), 6.49 (1H, d, J = 8.4 Hz), 6.82 (1H, d, J = 2.4 Hz), 6.88 (1H, dd, J_1 = 8.1 Hz, J_2 = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 32.0, 43.8, 51.8, 110.4, 113.1, 119.0, 123.1, 136.1, 136.6, 174.1; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{16}H_{21}BrN_2O_2$ 375.0679 and 377.0658, found 375.0684 and 377.0664

Methyl 4-((2-amino-4-bromophenyl)amino)butanoate (5.03 g, 17.6 mmol) was treated with pivaloyl chloride (2.33 g, 19.4 mmol) according to the general method ***ii***. Purification on silica gel using EtOAc:Hex (1:5) → (1:3) → (1:1) afforded the title compound (**12h**) as a white solid (5.38 g, 82%).

m.p. 116.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (9H, s), 1.95 (2H, pentet, J = 6.9 Hz), 2.44 (2H, t, J = 7.2 Hz), 3.10 (2H, t, J = 6.9 Hz), 3.67 (3H, s), 3.86 (1H, bs), 6.61 (1H, d, J = 8.7 Hz), 7.19 (1H, dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz), 7.33 (1H, bs), 7.50 (1H, d, J = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 27.9 (3xC), 32.0, 39.8, 44.1, 52.0, 110.0, 115.0, 126.3, 127.9, 129.7, 141.3, 174.2, 177.7; HRMS (ESI-TOF) m/z:

$[M+Na]^+$ calculated for $C_{16}H_{21}BrN_2O_2$ 393.0784 and 395.0764, found 393.0790 and 395.0770.

5-bromo-2-(tert-butyl)-1-(3-methoxypropyl)-1H-benzo[d]imidazole **(13d)**

Was prepared from *N*-(5-bromo-2-((3-methoxypropyl)amino)phenyl)pivalamide (2.26 g, 6.60 mmol) using *p*-TsOH monohydrate (1.25 g, 6.60 mmol) in DMF according to the general method ***v***. Purification on silica gel using EtOAc:Hex gradient (1:6 → 1:4) afforded the product as off-white crystalline solid (1.94 g, 90%).
m.p. 109 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (9H, s), 2.07 (2H, m), 3.39 (3H, s), 3.49 (2H, t, J = 5.4 Hz), 4.39 (2H, m), 7.18 (1H, d, J = 8.7 Hz), 7.31 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.86 (1H, d, J = 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.8, 30.2, 34.3, 43.2, 59.1, 69.7, 110.8, 114.7, 122.5, 125.1, 135.5, 143.3, 162.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{21}BrN_2O$ 325.0910 and 327.0890, found 325.0914 and 327.0892.

5-bromo-2-(tert-butyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazole **(13e)**

Was prepared from *N*-(5-bromo-2-(((tetrahydro-2*H*-pyran-4-yl)methyl)amino)phenyl)pivalamide (2.01 g, 5.43 mmol) using *p*-TsOH monohydrate (1.03 g, 4.08 mmol) in DMF according to the general method ***v***. Purification on silica gel using eluent mixture Hex:DCM:MeOH (9:9:0.25) afforded the product as off-white solid (1.01 g, 58%).
Melting range 78-80°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (4H, m), 1.56 (9H, s), 2.26 (1H, m), 3.31 (2H, m), 3.96 (2H, d, J = 11.4 Hz), 4.18 (2H, d, J = 7.5 Hz), 7.19 (1H, d, J = 8.7 Hz), 7.33 (1H, d, J = 8.4 Hz), 7.87 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4 (3xC), 31.2 (2xC), 34.7, 36.8, 51.0, 67.6 (2xC), 111.5, 114.7, 122.5, 125.0, 135.9, 143.1, 162.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{23}BrN_2O$ 351.1067 and 353.1046, found 351.1063 and 353.1043.

2-(5-bromo-2-(tert-butyl)-1H-benzo[d]imidazol-1-yl)-N,N-dimethylethan-1-amine **(13f)**

Was prepared from *N*-(5-bromo-2-((3-(dimethylamino)propyl)amino)phenyl)-pivalamide (2.40 g, 6.72 mmol) using *p*-TsOH monohydrate (2.57 g, 13.5 mmol) according to the general method ***v*** with DMF as solvent. Purification on silica gel using MeOH (sat. with NH_3) in DCM (2%) afforded the title compound as light brown crystalline solid (1.35 g, 60%).

m.p. 90.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (9H, s), 1.95 (2H, m), 2.25 (6H, s), 2.39 (2H, t, J = 6.6 Hz), 4.31 (2H, m), 7.17 (1H, d, J = 8.7 Hz), 7.30 (1H, d, J = 8.4 Hz), 7.86 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2, 30.0 (3xC), 34.5, 44.3, 45.9 (2xC), 57.2, 110.9, 114.9, 122.7, 125.3, 135.7, 143.5, 162.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{16}H_{24}BrN_3$ 338.1226 and 340.1206, found 338.1226 and 340.1206.

Methyl 4-(5-bromo-2-(tert-butyl)-1H-benzo[d]imidazol-1-yl)butanoate **(13h)**

Was prepared from methyl 4-((4-bromo-2-pivalamidophenyl)amino)butanoate (5.07 g, 13.7 mmol) using *p*-TsOH monohydrate (1.3 g, 6.9 mmol) in DMF according to the general method ***v***. The crude product was recrystallized from Et_2O/hexane, which afforded the product as colourless crystalline solid (2.93 g, 60%).

m.p. 113.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (9H, s), 2.14 (2H, m), 2.51 (2H, t, J = 6.6 Hz), 3.75 (3H, s), 4.34 (2H, m), 7.26 (1H, d, J = 8.4 Hz), 7.34 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.87 (1H, d, J = 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 29.8 (3xC), 31.0, 34.3, 45.0, 52.0, 110.8, 114.8, 122.6, 125.3, 135.4, 143.3, 161.8, 173.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{16}H_{21}BrN_2O_2$ 375.0679 and 377.0658, found 375.0684 and 377.0664.

2-(tert-butyl)-5-((4-methoxybenzyl)thio)-1-(3-methoxypropyl)-1H-benzo[d]imidazole **(7d)**

General method xii: A two-necked flask and a condenser were dried under vacuum with a heatgun and the system was left to cool down to room temperature under N_2 atmosphere. Dioxane (10 mL, dry) was added to the flask and degassed. Xantphos® (0.23 g, 14 mol-%) and $Pd_2(dba)_3$ (0.23 g, 9 mol-%) were added to the flask and the mixture was degassed. 5-bromo-2-(*tert*-butyl)-1-(3-methoxypropyl)-1*H*-

benzo[d]imidazole (0.90 g, 2.78 mmol) was dissolved in dioxane (10 mL) and added to the reaction flask, after which (4-methoxyphenyl)methanethiol (90%, 0.87 mL, 5.60 mmol) and di-isopropylethylamine (0.95 mL, 5.6 mmol) were added at room temperature. The reaction mixture was heated to reflux at 100 °C for 18 h. After completion of the reaction, the mixture was diluted with MeOH and filtered through a pad of silica and Celite® with MeOH. Purification on silica gel using EtOAc:Hex (1:6) afforded the title compound (**7d**) as light yellow solid (0.96 g, 86%).

m.p. 95.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (9H, s), 2.08 (2H, m), 3.39 (3H, s), 3.50 (2H, t, *J* = 5.4 Hz), 3.77 (3H, s), 4.05 (2H, s), 4.39 (2H, m), 6.78 (2H, d, *J* = 8.7 Hz), 7.16 - 7.19 (4H, m), 7.82 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.9 (3xC), 30.2, 34.3, 40.8, 43.2, 55.4, 59.0, 69.8, 109.7, 114.0 (2xC), 123.0, 126.5, 128.5, 130.1 (2xC), 130.3, 136.0, 142.5, 158.8, 161.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{23}H_{30}N_2O_2S$ 399.2101, found 399.2096.

2-(tert-butyl)-5-((4-methoxybenzyl)thio)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazole **(7e)**

Was synthesised from 5-bromo-2-(*tert*-butyl)-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1H-benzo[d]imidazole (0.96 g, 2.73 mmol) and (4-methoxyphenyl)methanethiol (90%, 0.85 mL, 5.47 mmol) according to the general method ***xii***. Purification on silica gel using EtOAc:Hex gradient (1:4 → 1:3 → 1:2) gave the title compound (**7e**) as light yellow solid (0.51 g, 44%).

m.p. 104.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 - 1.51 (4H, m), 1.55 (9H, s), 2.18 - 2.31 (1H, m), 3.25 - 3.34 (2H, m), 3.76 (3H, s), 3.95-3.98 (2H, m), 4.06 (2H, s), 4.16 (2H, d, *J* = 7.5 Hz), 6.77 (2H, d, *J* = 8.7 Hz), 7.07 - 7.24 (4H, m), 7.80 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.5 (3xC), 31.3, 34.7, 36.8, 40.5, 51.0, 55.3, 67.7, 110.5, 113.9 (2xC), 122.7, 126.1, 128.6, 130.0 (2xC), 130.3, 136.3, 142.3, 158.7, 161.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{25}H_{32}N_2O_2S$ 425.2257, found 425.2252.

3-(2-(tert-butyl)-5-((4-methoxybenzyl)thio)-1H-benzo[d]imidazol-1-yl)-N,N-dimethylpropan-1-amine **(7f)**

Was synthesised from 2-(5-bromo-2-(*tert*-butyl)-1*H*-benzo[d]imidazol-1-yl)-*N*,*N*-dimethylethan-1-amine (1.02 g, 3.04 mmol) and (4-methoxyphenyl)methanethiol (90%, 0.94 mL, 6.07 mmol) according to the general method ***xii***. Purification of the crude material on silica gel using gradient from DCM → MeOH (saturated with NH_3) in DCM (2% → 4%) gave the title compound **7f** as yellow solid (1.20 g, >99%).
m.p. 105 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.54 (9H, s), 2.09 (2H, m), 2.41 (6H, s), 2.63 (2H, t, *J* = 6.9 Hz), 3.77 (3H, s), 4.05 (2H, s), 4.36 (2H, m), 6.79 (2H, d, *J* = 8.7 Hz), 7.16 (2H, d, *J* = 8.6 Hz), 7.21 (2H, m), 7.80 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1, 29.9 (3xC), 34.3 ($\underline{C}(CH_3)_3$), 40.9, 44.0, 45.8 (2xC), 55.3, 57.0, 109.6, 114.0 (2xC), 122.9, 126.3, 128.4, 130.1 (2xC), 130.3, 136.1, 142.8, 158.6, 161.2; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{24}H_{33}N_3OS$ 434.2237, found 434.2239.

Methyl 4-(2-(tert-butyl)-5-((4-methoxybenzyl)thio)-1H-benzo[d]imidazol-1-yl)butanoate **(7h)**

Was prepared from methyl 4-(5-bromo-2-(*tert*-butyl)-1*H*-benzo[d]imidazol-1-yl)butanoate (2.0 g, 5.7 mmol) and and 4-methoxytoluene thiol (90%, 1.3 mL, 8.5 mmol) using the general method ***xii***. Purification on silica gel chromatography using EtOAc:Hex (1:4) afforded the title product **7h** as light yellow solid (2.2 g, 91%).

m.p. 98.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (9H, s), 2.16 (2H, m), 2.51 (2H, t, *J* = 6.6 Hz), 3.74 (3H, s), 3.77 (3H, s), 4.05 (2H, s), 4.32 (2H, m), 6.78 (2H, d, *J* = 8.7 Hz), 7.16 - 7.27 (4H, m), 7.81 (1H, d, *J* = 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 29.8 (3xC), 31.1, 34.3, 40.7, 44.9, 52.0, 55.4, 109.7, 114.0 (2xC), 123.0, 126.6, 128.6, 130.0 (2xC), 130.2, 135.8, 142.5, 158.7, 161.3, 173.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{24}H_{30}N_2O_3S$ 449.1869, found 449.1875.

4-(2-(tert-butyl)-5-((4-methoxybenzyl)thio)-1H-benzo[d]imidazol-1-yl)butanoic acid **(7k)**

General method ***xvii***: Methyl 4-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazol-1-yl)-butanoate **7h** (0.78 g, 1.83 mmol) was dissolved in THF/MeOH/H_2O (3:1:1, 20 mL) at room temperature. Solution was treated with LiOH (4.0 M, 0.91 mL) and stirred at room temperature for 1 h. Reaction mixture was

concentrated, pH was adjusted to 7 (1 M HCl) and the residue was extracted with EtOAc. Organic phase was dried over $MgSO_4$ and concentrated to give title product **7k** as yellow solid (0.73 g, 96%).

m.p. 140.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (9H, s), 2.11 (2H, m), 2.59 (2H, t, *J* = 6.3 Hz), 3.70 (3H, s), 4.07 (2H, s), 4.43 (2H, m), 6.73 (2H, d, *J* = 8.4 Hz), 7.11 (2H, d, *J* = 8.4 Hz), 7.25 (1H, d, *J* = 8.4 Hz), 7.45 (2H, d, *J* = 8.4 Hz), 8.04 (1H, s), 10.3 (1H, bs); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 29.4 (3xC), 31.2, 34.5, 39.3, 45.5, 55.3, 111.3, 114.0 (2xC), 118.4, 127.3, 129.1, 130.1 (2xC), 133.0, 133.1, 136.0, 158.8, 159.3, 174.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{23}ClN_4OS$ 403.1354, found 403.1349.

***4-(2-(tert-butyl)-5-((4-methoxybenzyl)thio)-1H-benzo[d]imidazol-1-yl)butanamide* (7j)**

General procedure xiv: 4-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazol-1-yl)butanoic acid (0.41 g, 1.0 mmol) was dissolved in anhydrous DMF (4 mL) under N_2 atmosphere at RT and DIPEA (0.15 mL, 1.0 mmol) was added to the solution. 1,1'-carbonyldimidazole (0.32 g, 2.0 mmol) was dissolved in DMF (2 mL) and added to the stirring solution gradually at RT. After 1 hour, NH_4Cl (0.16 g, 3.0 mmol) and DIPEA (0.55 mL, 3.0 mmol) were added to the solution, and the reaction was left to stir at RT over 24 h. Reaction was quenched by diluting with EtOAc (10 mL) and adding 5% $KHSO_4$ (5 mL). The organic phase was washed with 5% LiCl (2x10 mL) and dried over $MgSO_4$. Purification of the crude material on silica gel using 1% MeOH in DCM with 0.1% AcOH afforded the title product **7j** as off-white solid (0.21 g, 50%).

m.p. 183.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (9H, s), 2.10 (2H, m), 2.35 (2H, t, *J* = 6.6 Hz), 3.75 (3H, s), 4.04 (2H, s), 4.32 (2H, m), 5.83 (1H, bs), 5.96 (1H, bs), 6.77 (2H, d, *J* = 8.7 Hz), 7.15 (2H, d, *J* = 8.7 Hz), 7.21 (1H, m), 7.29 (1H, m), 7.81 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 29.8 (3xC), 32.2, 34.3, 40.7, 45.0, 55.4, 109.9, 114.0 (2xC), 122.8, 126.6, 128.6, 130.1 (2xC)**,** 130.2, 135.8**,** 142.3, 158.7, 161.4, 173.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{29}N_3O_2S$ 412.2053, found 412.2057.

***2-(tert-butyl)-5-((2-fluoropyridin-4-yl)thio)-1-pentyl-1H-benzo[d]imidazole* (8b)**

Was prepared from 2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1-pentyl-1*H*-benzo[d]-imidazole (0.14 g, 3.57 mmol) and 4-bromo-2-fluoropyridine (40 μL, 0.36 mmol) according to the general methods ***vi*** and ***vii***. The crude material was purified on silica gel using EtOAc:Hex (1:8 → 1:6) to give the title product **8b** as colourless oil (82 mg, 62% over two steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, J = 6.9 Hz), 1.46 (4H, m), 1.58 (9H, s), 1.90 (2H, m), 4.30 (2H, m), 6.39 (1H, t, J = 1.5 Hz), 6.82 (1H, dt, J_1 = 5.4 Hz, J_2 = 1.8 Hz), 7.36 (1H, dd, J_1 = 8.1 Hz, J_2 = 0.9 Hz), 7.40 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 7.91 (1H, d, J_1 = 5.4 Hz), 7.99 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.5, 29.3, 29.6, 29.8 (3xC), 34.4, 46.1, 105.3 (1C, d, J = 40.5 Hz), 111.2, 118.1 (1C, d, J = 3.8 Hz), 120.1, 127.7, 129.5, 137.8, 142.9, 146.8 (1C, d, J = 16.1 Hz), 157.8 (1C, d, J = 8.5 Hz), 164.3 (1C, d, J = 237 Hz), 162.4; ^{19}F NMR (258 Hz): -68.8 (s); HRMS (ESI-TOF) *m/z*: calculated for $C_{21}H_{26}FN_3S$ $[M+H]^+$ 372.1904, found 372.1905.

2-(tert-butyl)-1-(cyclobutylmethyl)-5-((2-fluoropyridin-4-yl)thio)-1H-benzo[d]imidazole **(8c)**

Was synthesised from 2-(*tert*-butyl)-1-(cyclobutylmethyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazole (0.11 g, 0.28 mmol) and 4-bromo-2-fluoropyridine (30 μL, 0.28 mmol) following the general methods ***vi*** and ***vii***. Purification of the crude material on silica gel using EtOAc:Hex gradient (1:6 → 1:4 → 1:2) afforded the product **8c** as light yellow oil (70 mg, 66% over two steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (9H, s), 1.83 - 2.04 (4H, m), 2.06 - 2.17 (2H, m), 2.75 - 2.83 (1H, m), 4.36 (2H, d, J = 6.3 Hz), 6.40 (1H, s), 6.81 (1H, d, J = 5.4 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.41 (1H, d, J = 8.4 Hz), 7.90 (1H, d, J = 5.4 Hz), 7.95 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5, 28.3 (2xC), 30.1 (3xC), 34.6, 37.4, 51.1, 105.3 (1C, d, J = 40.7 Hz), 111.7, 118.1 (1C, d J = 3.5 Hz), 119.9, 127.6, 129.2, 138.2, 143.0, 146.8 (1C, d, J = 16.1 Hz), 157.8 (1C, d, J = 8.5 Hz), 162.6, 164.2 (1C, d, J = 236.9 Hz); ^{19}F NMR (282 MHz): -68.8 (s); HRMS (ESI-TOF) *m/z*: calculated for $C_{21}H_{24}FN_3S$ $[M+H]^+$ 370.1748, found 370.1748.

2-(tert-butyl)-5-((2-fluoropyridin-4-yl)thio)-1-(3-methoxypropyl)-1H-benzo[d]imidazole **(8d)**

Was prepared from 2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1-(3-methoxypropyl)-1*H*-benzo[d]imidazole (0.50 g, 1.26 mmol) and 2-fluoro-4-bromopyridine (0.14 mL, 1.40 mmol) according to the general methods ***vi*** and ***vii***. Purification on silica gel using EtOAc:Hex (1:4) afforded the title product **8d** as light yellow solid (0.43 g, 92% over two steps).

m.p. 85.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (9H, s), 2.15 (2H, m), 3.42 (3H, s), 3.54 (2H, t, *J* = 5.4 Hz), 4.48 (2H, m), 6.40 (1H, s), 6.82 (1H, d, *J* = 5.4 Hz), 7.40 (1H, d, *J* = 8.4 Hz), 7.44 (1H, d, *J* = 8.4 Hz), 7.91 (1H, d, *J* = 5.7 Hz), 7.98 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 30.3, 34.4, 43.4, 59.1, 69.7, 105.2 (1C, d, *J* = 40.7 Hz), 111.2, 118.1 (1C, d, *J* = 3.6 Hz), 120.0, 127.6, 129.4, 137.9, 143.0, 146.8 (1C, d, *J* = 16.1 Hz), 157.8 (1C, d, *J* = 8.3 Hz), 162.7, 164.2 (1C, d, *J* = 237 Hz); ^{19}F NMR (282 MHz): -68.8 (s); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{20}H_{24}FN_3OS$ 374.1697, found 374.1704.

2-(tert-butyl)-5-((2-fluoropyridin-4-yl)thio)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazole **(8e)**

Was prepared from 2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazole (0.20 g, 0.47 mmol) and 2-fluoro-4-bromopyridine (60 μL, 0.58 mmol) according to the general procedures ***vi*** and ***vii***. Purification on silica gel using EtOAc:Hex gradient (1:4 → 1:3 → 1:2) yielded the product **8e** as light orange oil (0.12 g, 65%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (4H, m), 1.59 (9H, s), 2.31 (1H, m), 3.34 (2H, m), 4.00 (2H, d, *J* = 11.1 Hz), 4.25 (2H, d, *J* = 7.2 Hz), 6.41 (1H, s), 6.84 (1H, d, *J* = 5.4 Hz), 7.38 (1H, d, *J* = 8.7 Hz), 7.42 (1H, d, *J* = 8.4 Hz), 7.92 (1H, d, *J* = 5.4 Hz), 7.98 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4 (3xC), 31.3 (2xC), 34.9, 36.9, 51.3, 67.7 (2xC), 105.3 (1C, d, *J* = 40.7 Hz), 111.9, 118.2 (1C, d, *J* = 3.7 Hz), 120.2, 127.7, 129.3, 138.4, 142.9, 146.9 (1C, d, *J* = 16.1 Hz), 157.6 (1C, d, *J* = 7.9 Hz), 164.2 (1C, d, *J* = 251.0 Hz), 163.0; ^{19}F NMR (282 MHz, $CDCl_3$): δ -68.8 (s); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{27}FN_2OS$ 351.1901, found 351.1897.

3-(2-(tert-butyl)-5-((2-fluoropyridin-4-yl)thio)-1H-benzo[d]imidazol-1-yl)-N,N-dimethylpropan-1-amine **(8f)**

Was prepared from 3-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazol-1-yl)-*N*,*N*-dimethylpropan-1-amine (0.50 g, 1.22 mmol) and 2-fluoro-4-bromopyridine (0.13 mL, 1.22 mmol) according to the general methods ***vi*** and ***vii***. Purification of the crude material on silica gel using MeOH (saturated with NH_3) in DCM (1% → 2% → 5%) afforded the product **8f** as light yellow solid (0.12 g, 26% over two steps).

m.p. 107.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (9H, s), 2.03 (2H, m), 2.29 (6H, s), 2.45 (2H, t, J = 6.8 Hz), 4.40 (2H, m), 6.39 (1H, s), 6.81 (1H, dt, J_1 = 5.4 Hz; J_2 = 1.6 Hz), 7.38 (1H, m), 7.42 (1H, m), 7.90 (1H, d, J = 5.4 Hz), 7.97 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1, 29.8 (3xC), 34.5, 44.3, 45.8 (2xC), 57.0, 105.2 (1C, d, J = 40.6 Hz), 111.2, 118.1 (1C, d, J = 3.8 Hz), 120.1, 127.7, 129.4, 137.9, 143.0, 146.8 (1C, d, J = 16.1 Hz), 157.8 (1C, d, J = 12.5 Hz), 163.4 (1C, d, J_{CF} = 240.7 Hz), 165.9; ^{19}F NMR (282 MHz, $CDCl_3$): -68.8 (s); LRMS (ESI) m/z: estimated 387.20 $[M+H]^+$, found 387.21; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{21}H_{27}FN_4S$ 387.2013, found 387.2016.

Methyl 4-(2-(tert-butyl)-5-((2-fluoropyridin-4-yl)thio)-1H-benzo[d]imidazol-1-yl)butanoate **(8h)**

Was prepared from methyl 4-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazol-1-yl)butanoate (2.00 g, 4.69 mmol) and 2-fluoro-4-bromopyridine (0.48 mL, 4.69 mmol) using the general methods ***vi*** and ***vii***. Purification on silica gel using EtOAc:Hex (1:1 → 2:1) afforded the title product **8h** as yellow solid (1.79 g, 86%).

m.p. 104.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (9H, s), 2.21 (2H, m), 2.56 (2H, t, J = 6.6 Hz)**,** 3.76 (3H, s), 4.42 (2H, m), 6.41 (1H, s), 6.82 (1H, d, J = 5.4 Hz), 7.42 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 7.53 (1H, d, J = 8.1 Hz), 7.91 (1H, d, J = 5.4 Hz), 7.99 (1H, d, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 29.7 (3xC), 30.9, 34.4, 45.1, 52.1, 105.3 (1C, d, J = 40.7 Hz), 111.3, 118.1 (1C, d, J = 3.6 Hz), 120.4, 127.6, 129.6, 137.8, 142.9, 146.8 (1xC, d, J_{CF} = 16.2 Hz), 157.8 (1C, d, J = 8.5 Hz), 162.5,

164.2 (1C, d, J = 236.9 Hz), 172.9; ^{19}F NMR (282 MHz): -68.8 (s); HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{21}H_{24}FN_3O_2S$ 402.1646, found 402.1651.

***4-(2-(tert-butyl)-5-((2-fluoropyridin-4-yl)thio)-1H-benzo[d]imidazol-1-yl)butan-1-ol* (8i)**

General procedure xvi: Methyl 4-(2-(*tert*-butyl)-5-((2-fluoropyridin-4-yl)thio)-1*H*-benzo[d]imidazol-1-yl)butanoate **8h** (0.10 g, 0.25 mmol) was dissolved in anhydrous THF (5 mL) under N_2 atmosphere and cooled down to -78 °C. Di-isobutyl aluminium hydride (1.0 mL, 1.00 mmol, 1M in THF) was added dropwise to the stirring solution over 20 min at -78 °C, after which the reaction was left to stir at room temperature over night. Once the reaction was complete, the mixture was cooled to 0 °C and 0.5 mL EtOAc was added. Then, 40 μL of water was added dropwise, followed by addition of 40 μL of 15% NaOH, and finally 100 μL of water. The solution was taken to room temperature and stirred for 15 min, after which small amount of $MgSO_4$ was added. The resulting gel was filtered through a pad of silica and Celite® and washed with EtOAc. Concentration gave the title product **8i** as opaque oil (90 mg, >99%), which was used without purification for the next step.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (9H, s), 1.77 (2H, m), 2.02 (2H, m), 2.18 (1H, bs), 3.79 (2H, t, J = 6 Hz), 4.39 (2H, m), 6.40 (1H, s), 6.82 (1H, d, J = 5.4 Hz), 7.40 (2H, m), 7.90 (1H, d, J = 6 Hz), 7.97 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.7, 29.8 (3xC), 29.8, 34.4, 45.9, 62.1, 105.3 (1C, d, J = 40.6 Hz), 111.3, 118.2 (1C, d, J = 3.5 Hz), 120.1, 127.7, 129.5, 137.8, 143.0, 146.8 (1C, d, J_{CF} = 16.0 Hz), 157.9 (1C, d, J = 7.4 Hz), 162.5, 164.3 (1C, d, J = 237 Hz); ^{19}F NMR (282 MHz): -68.8 (s); HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{24}FN_3OS$ 374.1697, found 374.1702.

***Rac-2-(tert-butyl)-5-((2-fluoroethyl)thio)-1-(2-methylpentyl)-1H-benzo[d]imidazole* (9a)**

***General procedure vi*:** *rac*-2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1-(2-methylpentyl)-1*H*-benzo[d]imidazole (0.17 g, 0.41 mmol) was dissolved in trifluoroacetic acid (5 mL) and was refluxed at 80 °C for over night under N_2 atmosphere. The mixture was cooled down to room temperature and concentrated under N_2 flow to give the crude thiol that was used directly for the next step.

General method viii: Cs_2CO_3 (0.20 g, 0.62 mmol) was weighed into a two-necked flask and degassed dioxane (4 mL) was added under N_2 atmosphere. Crude thiol was dissolved in dioxane (4 mL, degassed) and added to the reaction flask. 2-fluoro-1-bromoethane (34 μL, 0.45 mmol) was added at room temperature, after which the reaction mixture was heated to 65 °C for 18 h. Reaction mixture was cooled down to room temperature, diluted with EtOAc and washed with saturated NH_4Cl and brine (2 x 10 mL). Organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated. Purification of the crude material on silica gel using EtOAc:Hex gradient (1:10 → 1:8) gave the product **9a** as a colourless viscous oil (89 mg, 64% over two steps).
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (3H, d, J = 6.6 Hz), 0.90 (3H, t, J = 6.3 Hz), 1.21 - 1.50 (4H, m), 1.57 (9H, s), 2.27 - 2.38 (1H, m), 3.17 (2H, dt, J_1 = 16.8 Hz, J_2 = 6.9 Hz), 4.10 (1H, dd, J_1 = 14.4 Hz, J_2 = 8.7 Hz), 4.21 (1H, dd, J_1 = 14.7 Hz, J_2 = 6.9 Hz), 4.44 – 4.60 (1H, dt, J_1 = 47.1 Hz; J_2 = 6.9 Hz), 7.24 - 7.34 (m, 2H), 7.87 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 17.6, 20.2, 30.5 (3xC), 33.6, 34.7, 35.55 (1C, d, J = 20.9 Hz), 37.1, 51.8, 81.8 (1C, d, J = 171 Hz), 111.2, 123.3, 126.3, 126.4, 136.7, 142.5, 162.4; ^{19}F NMR (282 MHz): δ -212.6 (tt, J_1 = 47 Hz, J_2 = 17 Hz); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{29}FN_2S$ 337.2108, found 337.2108.

2-(tert-butyl)-5-((2-fluoroethyl)thio)-1-pentyl-1H-benzo[d]imidazole **(9b)**

Was prepared from 2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1-pentyl-1*H*-benzo[d]imidazole (0.15 g, 0.39 mmol) and 2-fluoro-1-bromoethane (30 μL, 0.39 mmol) according to the general methods ***vi*** and ***viii***. The crude product was purified on silica gel using EtOAc:Hex gradient (1:8 → 1:6) to give the title product **9b** as a colourless oil (82 mg, 65% over two steps).
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (3H, t, J = 6.9 Hz), 1.44 (4H, m), 1.55 (9H, s), 1.85 (2H, m), 3.14 (2H, dt, J_1 = 16.5 Hz, J_2 = 6.9 Hz), 4.24 (2H, m), 4.41 - 4.57 (2H, dt, J_1 = 46.8 Hz; J_2 = 6.9 Hz), 7.20 (1H, d, J = 8.1 Hz), 7.34 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.88 (1H, d, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.4, 29.3, 29.5, 29.8 (3xC), 34.3, 35.7 (1C, d, J = 20.9 Hz), 45.9, 81.7 (1C, d, J = 171.1 Hz), 110.1, 123.4, 126.7, 126.9, 136.1, 142.2, 161.5; ^{19}F NMR (282 MHz): δ -212.8 (tt, J_1 = 47 Hz, J_2 = 34 Hz); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{18}H_{27}FN_2SH$ 323.1952, found 323.1953.

***2-(tert-butyl)-1-(cyclobutylmethyl)-5-((2-fluoroethyl)thio)-1H-benzo[d]imidazole* (9c)**

Was prepared from 2-(*tert*-butyl)-1-(cyclobutylmethyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazole (0.11 g, 0.28 mmol) and 2-fluoro-1-bromoethane (23 μL, 0.30 mmol) according to the general methods ***vi*** and ***viii***. Purification on silica gel using EtOAc:Hex (1:8 → 1:6) afforded the product **9c** as a colourless oil (56 mg, 61% over two steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (9H, s), 1.83 - 2.00 (4H, m), 2.06 - 2.15 (2H, m), 2.72 -2.84 (1H, m), 3.16 (2H, dt, J_1 = 16.5 Hz, J_2 = 6.9 Hz), 4.33 (2H, d, J = 6.3 Hz), 4.44 – 4.59 (2H, dt, J_1 = 47.1 Hz, J_2 = 6.9 Hz), 7.27 (1H, d, J = 8.1 Hz), 7.33 (1H, d, J = 8.4 Hz), 7.86 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5, 28.2 (2xC), 30.2 (3xC), 34.5, 35.6 (1C, d, J = 21 Hz), 37.4, 51.0, 81.8 (1C, d, J = 171.2 Hz), 110.6, 123.3, 126.4, 126.6, 136.6, 142.5, 161.8; ^{19}F NMR (282 MHz): δ -212.7 (tt, J_1 = 47 Hz, J_2 = 16 Hz); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{18}H_{25}FN_2S$ 321.1795, found 321.1796.

***2-(tert-butyl)-5-((2-fluoroethyl)thio)-1-(3-methoxypropyl)-1H-benzo[d]imidazole* (9d)**

Was prepared from 2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1-(3-methoxypropyl)-1*H*-benzo[*d*]imidazole (0.25 g, 0.63 mmol) and 2-fluoro-1-bromoethane (52 μL, 0.69 mmol) using the general methods ***vi*** and ***viii***. Purification on silica gel using EtOAc:Hex (1:5) gave the product **9d** as colourless oil (0.11 g, 55% over two steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (9H, s), 2.09 (2H, m), 3.14 (2H, dt, J_1 = 16.5 Hz, J_2 = 6.9 Hz), 3.41 (3H, s), 3.51 (2H, t, J = 5.4 Hz), 4.39 (2H, m), 4.42 - 4.57 (2H, dt, J_1 = 47 Hz, J_2 = 6.9 Hz), 7.27 (1H, d, J = 8.1 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.89 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.8 (3xC), 30.2, 34.3, 35.7 (1C, d, J = 20.9 Hz), 43.2, 59.0, 69.8, 81.7 (1C, d, J = 171.2 Hz), 110.1, 123.5, 126.6, 126.9, 136.3, 142.6, 161.9; ^{19}F NMR (282 MHz, $CDCl_3$): -212.8 (tt, J_1 = 43.0 Hz, J_2 = 15.2 Hz); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{17}H_{25}FN_2OS$ 325.1744, found 325.1741.

***2-(tert-butyl)-5-((2-fluoroethyl)thio)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazole* (9e)**

Was prepared from 2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazole (0.31 g, 0.73 mmol) and 2-fluoro-1-bromoethane (60 μL, 0.73 mmol) according to the general procedures ***vi*** and ***viii***. Purification on silica gel using EtOAc:Hex (1:3 → 1:2) yielded the product **9e** as colourless oil (99 mg, 38%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (4H, m), 1.56 (9H, s), 2.28 (1H, m), 3.13 – 3.19 (2H, dt, J_1 = 16.5 Hz, J_2 = 7.2 Hz), 3.31 (2H, m), 3.98 (2H, m), 4.19 (2H, d, J = 7.2 Hz), 4.43 – 4.59 (2H, dt, J = 47.1 Hz), 7.19 (1H, m), 7.33 (1H, m), 7.86 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.5 (3xC), 31.3 (2xC), 34.7, 35.5 (1C, d, J = 21.2 Hz), 36.9, 51.1, 67.7 (2xC), 81.8 (1C, d, J = 172.9 Hz), 110.8, 123.3, 126.6, 130.2, 136.5, 142.6, 162.1; ^{19}F NMR (282 MHz, $CDCl_3$): δ -212.6 (tt, J_1 = 46.8 Hz, J_2 = 16.6 Hz); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{19}H_{27}FN_2OS$ 351.1901, found 351.1897.

Methyl 4-(2-(tert-butyl)-5-((2-fluoroethyl)thio)-1H-benzo[d]imidazol-1-yl)butanoate **(9h)**

Was prepared from methyl 4-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazol-1-yl)butanoate (1.8 g, 4.2 mmol) and 2-fluoro-1-bromoethane (0.35 mL, 4.6 mmol) according to the general procedures ***vi*** and ***viii***. Purification on silica gel using EtOAc:Hex (1:4 → 1:3) afforded the title compound **9h** as light yellow oil (1.12 g, 75% over 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (9H, s), 2.15 (2H, m), 2.50 (2H, t, J = 6.6 Hz), 3.13 (2H, t, J = 6.9 Hz, J = 16.5 Hz), 3.73 (3H, s), 4.33 (2H, m), 4.50 (2H, t, J = 6.9 Hz, J = 47.1 Hz), 7.31 (1H, m), 7.34 (1H, m), 7.85 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 29.7 (3xC), 31.0, 34.3, 35.7 (1C, d, J = 21 Hz), 45.0, 52.0, 81.7 (1C, d, J = 171.3 Hz), 110.1, 123.6, 126.8, 127.0, 136.2, 142.6, 161.7, 172.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ -212.8 (tt, J_1 = 63.5 Hz, J_2 = 16.6 Hz); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{18}H_{25}FN_2O_2S$ 375.1513, found 375.1518.

4-(2-(tert-butyl)-5-((2-fluoroethyl)thio)-1H-benzo[d]imidazol-1-yl)butan-1-ol **(9i)**

Was prepared from methyl 4-(2-(*tert*-butyl)-5-((2-fluoroethyl)thio)-1*H*-benzo[d]imidazol-1-yl)butanoate **9h** (0.30 g, 0.85 mmol) using DIBAL-H (3.42 mL, 3.4 mmol, 1M in THF) according to the general method ***xvi***. Purification of the crude material on silica gel using EtOAc:Hex (1:1) as eluent afforded the title product **9i** as clear oil (94 mg, 34%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (9H, s), 1.71 (2H, m), 1.93 (2H, m), 2.72 (1H, br s), 3.10 (2H, dt, J_1 = 17.1 Hz, J_2 = 6.9 Hz), 3.73 (2H, t, J = 6.3 Hz), 4.29 (2H, m), 4.45 (2H, dt, J_1 = 47.1 Hz, J_2 = 6.9 Hz), 7.22 (1H, d, J = 8.1 Hz), 7.34 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 7.85 (1H, d, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 29.7 (3xC), 29.8, 34.3, 35.7 (1C, d, J = 21 Hz), 45.7, 61.9, 81.7 (1C, d, J = 171.0), 110.2, 123.4, 126.6, 126.9, 136.1, 142.4, 161.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ -212.8 (tt, J_1 = 47.1 Hz, J_2 = 16.6 Hz); LRMS (ESI) *m/z*: estimated 325.17 $[M+H]^+$, found 325.18; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{17}H_{25}FN_2OS$ 347.1564, found 347.1568.

4-(2-(tert-butyl)-5-((2-fluoroethyl)thio)-1H-benzo[d]imidazol-1-yl)butanamide **(9j)**

Was prepared from 4-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazol-1-yl)butanamide **7j** (0.31 g, 0.74 mmol) and 2-fluoro-1-bromoethane (0.14 mL, 1.9 mmol) following the general procedures ***vi*** and ***viii***. Purification on silica gel using MeOH in DCM (2.5% → 5%) afforded the product **9j** as colourless oil (0.2 g, 80% over 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (9H, s), 2.15 (2H, m)**,** 2.39 (2H, t, J = 6.6 Hz), 3.12 (2H, dt, J_1 = 17.1 Hz, J_2 = 6.9 Hz)**,** 4.35 (2H, m), 4.40 (2H, dt, J_1 = 47.1 Hz, J_2 = 6.9 Hz), 5.70 (2H, br s)**,** 7.32 (1H, d, J = 8.7 Hz), 7.36 (1H, d, J = 8.7 Hz), 7.84 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 29.8 (3xC), 32.1, 34.3, 35.7 (1C, d, J = 20.8 Hz), 45.0, 81.7 (1C, d, J = 171 Hz) 110.3, 123.4, 126.7, 127.0, 136.2, 142.5, 161.8, 173.7; ^{19}F NMR (282 MHz): δ -212.8 (tt, J_1 = 46.8 Hz, J_2 = 16.9 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{17}H_{24}FN_3OS$ 338.1697, found 338.1696.

4-(2-(tert-butyl)-5-((2-fluoroethyl)thio)-1H-benzo[d]imidazol-1-yl)butanenitrile **(9g)**

General procedure xv: 4-(2-(*tert*-butyl)-5-((2-fluoroethyl)thio)-1*H*-benzo[d]imidazol-1-yl)butanamide (0.19 g, 0.55 mmol) was dissolved in dry DCM (8 mL) under N_2 atmosphere and cooled down to 0 °C. Triethyl amine (0.61 mL, 8 equiv) was added to the solution, after which trifluoroacetic anhydride (0.39 mL, 5 equiv) was added dropwise. The solution was stirred at room temperature for 12 h. The reaction mixture was diluted with DCM and washed with water (5 mL) and sat. $NaHCO_3$ (5 mL). The organic phase was dried over anhydrous $MgSO_4$. Filtered and concentrated crude product was purified on silica gel using EtOAc:Hex gradient (1:4 → 1:2), which afforded the title product **9g** as clear oil (0.17 g, 94%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (9H, s), 2.18 (2H, m), 2.54 (2H, t, J = 6.9 Hz), 3.12 (2H, dt, J_1 = 17.1 Hz, J_2 = 6.9 Hz), 4.42 (2H, m), 4.37 - 4-58 (2H, dt, J_1 = 47.1 Hz, J2 = 6.9 Hz), 7.20 (1H, d, J = 8.4 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.85 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 25.3, 29.8 (3xC), 34.3, 35.6 (1C, d, J = 21.1 Hz), 44.1, 81.6 (1C, d, J = 171.1 Hz), 109.7, 118.3, 123.5, 127.1, 127.3, 137.5, 142.4, 161.5; ^{19}F NMR (282 MHz): -212.9 (tt, J_1 = 47.1 Hz, J_2 = 16.9 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{17}H_{22}FN_3S$ 320.1591, found 320.1586.

2-(tert-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1-pentyl-1H-benzo[d]imidazole **(1b)**

Was prepared from 2-(*tert*-butyl)-5-((2-fluoropyridin-4-yl)thio)-1-pentyl-1*H*-benzo[d]imidazole (70 mg, 0.19 mmol) according to the general method ***x***. Purification on silica gel using EtOAc:Hex gradient (1:4 → 1:2) gave the title product **1b** as colourless oil (58 mg, 76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 6.9 Hz), 1.41 (4H, m), 1.53 (9H, s), 1.82 (2H, m), 4.28 (2H, m), 7.38 (1H, m), 7.40 (1H, m), 7.63 (1H, dt, J_1 = 5.1 Hz, J_2 = 1.5 Hz), 7.79 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz), 8.32 (1H, d, J = 5.1 Hz), 8.36 (1H, d, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.4, 29.2, 29.6, 29.59 (3xC), 34.6, 46.2, 107.9 (1C, d, J = 40.1 Hz), 110.8, 118.7 (1C, d, J = 5 Hz), 121.0, 121.8, 132.0, 140.5, 141.7, 149.5 (1C, d, J= 14.4 Hz), 156.1 (1C, d, J = 6.7 Hz), 163.9 (1C, d, J = 239 Hz), 164.3; ^{19}F NMR (282 Hz): -221.7 (tt, J_1 = 46.5 Hz, J_2 = 20.9 Hz); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{18}H_{27}FN_2O_2S$ 355.1850, found 355.1850; HPLC-purity: >98%, RT = 21.8 min.

2-(tert-butyl)-1-(cyclobutylmethyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1H-benzo[d]imidazole **(1c)**

Was prepared from 2-(*tert*-butyl)-1-(cyclobutylmethyl)-5-((2-fluoropyridin-4-yl)thio)-1H-benzo[d]imidazole (70 mg, 0.19 mmol) according to the general method ***x***. Purification on silica gel using EtOAc:Hex (1:6 → 1:3 → 1:2) afforded the product **1c** as colourless viscous oil (60 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (9H, s), 1.83 - 1.95 (4H, m), 2.04 - 2.13 (2H, m), 2.68 - 2.78 (1H, m), 4.35 (2H, d, *J* = 6.3 Hz), 7.41 (1H, s), 7.45 (1H, d, *J* = 8.4 Hz), 7.65 (1H, d, *J* = 5.1 Hz), 7.78 (1H, d, *J* = 8.7 Hz), 8.34 (1H, s), 8.36 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5, 28.3 (2xC), 30.0 (3xC), 34.8, 37.3, 51.2, 108.0 (1C, d, *J* = 40.3 Hz), 111.3, 118.7 (1C, d, *J* = 5 Hz), 121.0, 121.7, 131.9, 140.9, 141.8, 149.5 (1C, d, *J* = 14.4 Hz), 156.1 (1C, d, *J* = 6.5 Hz), 163.9 (1C, d, *J* = 242 Hz), 164.4; ^{19}F NMR (376 MHz): δ -63.4 (s); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{21}H_{24}FN_3O_2S$ 424.1466, found 424.1465; HPLC-purity: >99%, RT = 25.8 min.

2-(tert-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1-(3-methoxypropyl)-1H-benzo[d]imidazole **(1d)**

Was prepared from 2-(*tert*-butyl)-5-((2-fluoropyridin-4-yl)thio)-1-(3-methoxypropyl)-1*H*-benzo[d]imidazole (0.11 g, 0.30 mmol) according to the general method ***x***. Purification on silica gel using EtOAc:Hex gradient (1:5 → 1:3 → 1:2) afforded the product **1d** as light yellow thick oil (0.10 g, 0.26 mmol, 87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (9H, s), 2.08 (2H, m), 3.41 (3H, s), 3.51 (2H, t, *J* = 5.4 Hz), 4.46 (2H, m), 7.41 (1H, s), 7.49 (1H, d, *J* = 8.4 Hz), 7.64 (1H, d, *J* = 3.9 Hz), 7.82 (1H, d, *J* = 8.4 Hz), 8.35 (1H, d, *J* = 5.4 Hz), 8.38 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.6, 30.3, 34.6, 43.5, 59.1, 69.4, 108.0 (1C, d, *J* = 40.1 Hz), 110.8, 118.7 (1C, d, *J* = 5.3 Hz), 121.1, 121.9, 132.0, 140.7, 141.9, 149.5 (1C, d, *J* = 6.5 Hz), 156.2 (1C, d, *J* = 25.8 Hz) 163.9 (1C, d, *J* = 244 Hz), 164.5; ^{19}F NMR (282 MHz): δ -63.5 (s); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{20}H_{24}FN_3O_3S$ 428.1415, found 428.1409; HPLC purity >95%, RT = 18.9 min.

2-(tert-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazole **(1e)**

Was prepared from 2-(*tert*-butyl)-5-((2-fluoropyridin-4-yl)thio)-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazole (0.12 g, 0.31 mmol) according to the general method ***x***. Purification on silica gel using EtOAc:Hex (1:1) gave the title product **1e** as white solid (73 mg, 55%).

m.p. 171.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (4H, m), 1.57 (9H, s), 2.26 (1H, m), 3.30 (2H, m), 3.96 (2H, m), 4.25 (2H, d, J = 7.5 Hz), 7.43 (1H, d, J = 1.8 Hz), 7.49 (1H, d, J = 8.7 Hz), 7.67 (1H, d, J = 5.1 Hz), 7.80 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 8.36 (1H, m), 8.38 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.2 (3xC), 31.1 (2xC), 35.0, 36.9, 51.3, 67.5 (2xC), 108.0 (1C, d, J = 40.1 Hz), 111.5, 118.7 (1C, d, J = 4.8 Hz), 121.0, 121.6, 132.0, 141.0, 141.6, 149.5 (1C, d, J = 14.5 Hz), 155.9 (1C, d, J = 6.7 Hz), 163.9 (1C, d, J = 233.6 Hz), 164.8; ^{19}F NMR (282 MHz): δ -63.4 (s); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{22}H_{26}FN_3O_3S$ 454.1571, found 454.1566. HPLC purity >98%, RT = 18.3 min.

3-(2-(tert-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1H-benzo[d]imidazol-1-yl)-N,N-dimethylpropan-1-amine **(1f)**

3-(2-(*tert*-butyl)-5-((2-fluoropyridin-4-yl)thio)-1H-benzo[d]imidazol-1-yl)-*N*,*N*-dimethylpropan-1-amine (0.10 g, 0.26 mmol) was dissolved in 7 mL of methanol in a round bottom flask and solution was cooled to 0 °C. Oxone® (0.24 g, 0.78 mmol) was dissolved in 4 mL of H_2O, cooled to 0 °C, and added dropwise to a stirring solution of the starting material over 20 min. Suspension was left to stir at 0 °C for an hour, after which the reaction was left to warm to room temperature. The formation and disappearance of the sulfoxide intermediate was monitored on TLC, after which the reaction mixture was concentrated, diluted with water and the pH was adjusted to 9. The water phase was extracted with EtOAc (3 x 10 mL) and combined organic phase was dried over $MgSO_4$. Concentrated crude product was purified on silica gel with MeOH (sat. with NH_3) in DCM (2% → 5%), which gave the product **1f** as clear sticky oil (58 mg, 54%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (9H, s), 1.95 (2H, m), 2.26 (6H, s), 2.40 (2H, t, *J* = 6.6 Hz), 4.39 (2H, m), 7.40 (1H, d, *J* = 2.4 Hz), 7.47 (1H, d, *J* = 8.7 Hz), 7.64 (1H, d, *J* = 5.1 Hz), 7.81 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz), 8.34 (1H, d, *J* = 5.1 Hz), 8.36 (1H, d, *J* = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1, 29.6 (3xC), 34.6, 44.4, 45.7 (2xC), 56.8, 108.0 (1C, d, *J* = 40.1 Hz), 110.8, 118.7 (1C, d, *J* = 5 Hz), 121.1, 121.9, 132.0, 140.7, 141.9, 149.5 (1C, d, *J* = 14.5 Hz), 156.1 (1C, d, *J* = 6.8 Hz), 163.9 (1C, d, J_{CF} = 242.4 Hz), 164.5; ^{19}F NMR (282 MHz): -63.4 (s); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{21}H_{27}FN_4O_2S$ 441.1730, found 441.1733; HPLC-purity: >98%, RT = 19.1 min.

***4-(2-(tert-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol* (1i)**

Was prepared from 4-(2-(*tert*-butyl)-5-((2-fluoropyridin-4-yl)thio)-1*H*-benzo[*d*]imidazol-1-yl)butan-1-ol (0.19 g, 0.51 mmol) using the general method ***x***. The crude product was purified on silica gel using MeOH in DCM (2.5%), which gave the title product **1i** as white solid (0.17 g, 81%).

m.p. 145.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (9H, s), 1.63 (1H, bs), 1.74 (2H, m), 1.96 (2H, m), 3.77 (2H, t, *J* = 6 Hz), 4.38 (2H, m), 7.40 (1H, d, *J* = 2.7 Hz), 7.45 (1H, d, *J* = 8.7 Hz), 7.64 (1H, d, *J* = 5.1 Hz), 7.81 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz), 8.34 (1H, d, *J* = 5.4 Hz), 8.37 (1H, d, *J* = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.7, 29.61, 29.67 (3xC), 34.7, 46.1, 62.1, 108.1 (1C, d, *J* = 37.5 Hz), 110.8, 118.7 (1C, d, *J* = 6.2 Hz), 121.2, 121.9, 132.1, 140.6, 141.9, 149.5 (1C, d, *J* = 15 Hz), 156.2 (1C, d, *J* = 6.1 Hz), 164.0 (1C, d, *J* = 242.6 Hz), 164.4; ^{19}F NMR (282 MHz): -63.4 (s); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{20}H_{24}FN_3O_3S$ 428.1415, found 428.1420; HPLC-purity >98%, RT = 15.7 min.

***Methyl 4-(2-(tert-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1H-benzo[d]imidazol-1-yl)butanoate* (1h)**

Was prepared from methyl 4-(2-(*tert*-butyl)-5-((2-fluoropyridin-4-yl)thio)-1*H*-benzo[d]imidazol-1-yl)butanoate (0.51 g, 1.26 mmol) according to the general method ***x***. The purification on silica gel using EtOAc:Hex (1:2) gave the product **1h** as white solid (0.53 g, 98%).

m.p. 93.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (9H, s), 2.14 (2H, m), 2.53 (2H, t, *J* = 6.6 Hz), 3.75 (3H, s), 4.40 (2H, m), 7.41 (1H, d, *J* = 3.0 Hz), 7.60 (1H, d, *J* = 8.7

Hz), 7.65 (1H, dt, J_1 = 5.4 Hz, J_2 = 1.2 Hz), 7.85 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 8.35 (1H, d, J = 5.1 Hz), 8.38 (1H, d, J = 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 29.6 (3xC), 30.7, 34.6, 45.3, 52.1, 108.0 (1C, d, J = 40.1 Hz), 110.9, 118.7 (1C, d, J = 4.9 Hz), 121.2, 122.1, 132.3, 140.6, 141.9, 149.5 (1C, d, J = 14.6 Hz), 156.1 (1C, d, J = 6.5 Hz), 164.3, 164.0 (1C, d, J = 242.7 Hz), 172.9; ^{19}F NMR (282 MHz): -63.4 (s); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{21}H_{24}FN_3O_4S$ 456.1364, found 456.1369; HPLC-purity >98%, RT = 18.7 min.

4-(2-(tert-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1H-benzo[d]imidazol-1-yl)butanoic acid **(1k)**

General procedure xiii. Methyl 4-(2-(*tert*-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1*H*-benzo[*d*]imidazol-1-yl)butanoate **1h** (0.25 g, 0.58 mmol) was dissolved in 1,2-dichloroethane (15 mL) under N_2 atmosphere and trimethyltin hydroxide (0.40 g, 3.8 equiv.) was added to the stirring solution. Reaction mixture was heated to 100 °C for overnight. After completion, the reaction mixture was cooled down to RT and 1,2-dichloroethane was evaporated off under N_2 flow. Residue was redissolved in EtOAc and washed with 5% $KHSO_4$ several times, dried over Na_2SO_4 and concentrated under reduced pressure to give crude product that was purified on silica gel using EtOAc:Hex gradient (1:2 → 1:1) to get the title compound **1k** as white amorphous solid (0.22 g, 91%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (9H, s), 2.17 (2H, m), 2.61 (2H, t, J = 6.6 Hz), 4.44 (2H, m), 7.42 (1H, d, J = 2.4 Hz), 7.62 (1H, m), 7.65 (1H, m), 7.45 (1H, d, J = 8.7 Hz), 8.34 (1H, d, J = 5.1 Hz), 8.44 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 29.6 (3xC), 30.7, 34.7, 45.3, 108.0 (1C, d, J = 40.1 Hz), 111.2, 118.7 (1C, d, J = 5.0 Hz), 121.0, 122.4, 132.5, 140.3, 141.3, 149.5 (1C, d, J = 14.3 Hz), 156.0 (1C, d, J = 6.7 Hz), 164.4, 163.9 (1C, d, J = 242.7 Hz), 176.0; ^{19}F NMR (282 MHz): -63.4 (s); LRMS (ESI) *m/z*: Estimated 418.12 $[M-H]^-$, found 418.11; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{22}FN_3O_4S$ 420.1388, found 420.1392; HPLC-purity >99%, RT = 16.4 min.

4-(2-(tert-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1H-benzo[d]imidazol-1-yl)butanamide **(1j)**

Was prepared from 4-(2-(*tert*-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1*H*-benzo[*d*]imidazol-1-yl)butanoic acid **1k** (0.14 g, 0.33 mmol) using the general method

xiv. Purification of the crude material on silica gel using MeOH in DCM (1%) and AcOH (0.1%) afforded the title product **1j** as white solid (0.10 g, 70%).

m.p. 85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 (9H, s), 2.09 (2H, m), 2.41 (2H, t, *J* = 6.3 Hz), 4.38 (2H, m), 5.97 (1H, bs), 6.19 (1H, bs), 7.40 (1H, d, *J* = 2.1 Hz), 7.60 (1H, d, *J* = 5.1 Hz), 7.64 (1H, d, *J* = 8.7 Hz), 7.77 (1H, d, *J* = 8.4 Hz), 8.31 (1H, d, *J* = 5.1 Hz), 8.33 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 29.7, 31.8 (3xC), 34.7, 45.4, 108.0 (1C, d, *J* = 40.3 Hz), 111.2, 118.7 (1C, d, *J* = 4.95 Hz), 121.1, 122.1, 132.2, 140.7, 141.9, 149.5 (1C, d, *J* = 14.3 Hz), 156.1 (1C, d, *J* = 6.7 Hz), 164.0 (1C, d, *J* = 242.9 Hz), 164.4, 173.4; ^{19}F NMR (282 MHz): -63.5; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{20}H_{23}FN_4O_3S$ 441.1367, found 441.1372; HPLC-purity >97%, RT = 15.0 min.

***4-(2-(tert-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1H-benzo[d]imidazol-1-yl)butanenitrile* (1g)**

Was prepared from 4-(2-(*tert*-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1*H*-benzo[*d*]imidazol-1-yl)butanamide **1j** (81 mg, 0.19 mmol) according to the general procedure ***xv***. Purification of the crude product on silica gel using EtOAc:Hex (1:2 → 1:1) as eluent gave the title product **1g** as white amorphous solid (67 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (9H, s), 2.19 (2H, m), 2.41 (2H, t, *J* = 6.6 Hz), 4.50 (2H, m), 7.40 (1H, s), 7.44 (1H, d, *J* = 8.7 Hz), 7.65 (1H, d, *J* = 5.1 Hz), 7.70 (1H, d, *J* = 8.7 Hz), 8.36 (1H, d, *J* = 5.1 Hz), 8.39 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1, 25.3, 29.7 (3xC), 34.7, 44.4, 108.1 (1C, d, *J* = 40.1 Hz), 110.2, 118.1, 118.7 (1C, d, *J* = 5.0 Hz), 121.4, 122.4, 132.7, 140.2, 141.9, 149.6 (1C, d, *J* = 14.6 Hz), 155.9 (1C, d, *J* = 6.7 Hz), 163.9 (1C, d, *J* = 242.8 Hz), 164.2; ^{19}F NMR (282 MHz): -63.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{21}FN_4O_2S$ 401.1442, found 401.1436; HPLC-purity >99%, RT = 18.0 min.

***Rac*-2-(*tert*-butyl)-5-((2-fluoroethyl)sulfonyl)-1-(2-methylpentyl)-1H-benzo[d]imidazole (2a)**

Was prepared from *rac*-2-(*tert*-butyl)-5-((2-fluoroethyl)thio)-1-(2-methylpentyl)-1*H*-benzo[d]imidazole (89 mg, 0.26 mmol) according to the general method ***x***. Purification on silica gel using EtOAc:Hex gradient (1:6 → 1:4 → 1:2) afforded the product **2a** as colourless oil (80 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (3H, m), 0.89 (3H, m), 1.17 - 1.50 (4H, m, 2xCH_2), 1.57 (9H, s), 2.24 - 2.38 (1H, m), 3.51 (2H, dt, J_1 = 20.7 Hz, J_2 = 6 Hz), 4.19 (2H, 2xdd, J_1 = 8.7 Hz, J_2 = 14.7 Hz), 4.69 – 4.84 (2H, dt, J_1 = 46.5 Hz, J_2 = 6 Hz), 7.44 (1H, d, J = 8.7 Hz), 7.75 (1H, d, J = 9 Hz), 8.32 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 17.6, 20.2, 30.4 (3xC), 33.7, 35.0, 37.1, 52.0, 57.2 (1C, d, J = 21.3 Hz), 76.4 (1C, d, J = 172 Hz), 111.3, 120.8, 121.5, 132.4, 140.7, 141.6, 164.7; ^{19}F NMR (282 Hz): δ -221.8 (tt, J_1 = 20.6 Hz, J_2 = 46.2 Hz); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{19}H_{29}FN_2O_2S$ 391.1826, found 391.1826; HPLC-purity: 98%, RT = 25.0 min.

2-(tert-butyl)-5-((2-fluoroethyl)sulfonyl)-1-pentyl-1H-benzo[d]imidazole **(2b)**

Was prepared from 2-(*tert*-butyl)-5-((2-fluoroethyl)thio)-1-pentyl-1*H*-benzo[d]imidazole (81 mg, 0.25 mmol) using the general method ***x***. Purification on silica gel using EtOAc:Hex (1:4 → 1:2) afforded the product **2b** as colourless solid (48 mg, 54%).

m.p. 93.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (3H, t, J = 6.9 Hz), 1.43 (4H, m), 1.54 (9H, s), 1.85 (2H, m), 3.47 – 3.54 (2H, dt, J_1 = 21 Hz, J_2 = 5.7 Hz), 4.29 (2H, m), 4.66 – 4.81 (2H, t, J_1 = 46.5 Hz, J_2 = 6.0 Hz), 7.40 (1H, d, J = 8.4 Hz), 7.76 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 8.30 (1H, d, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.4, 29.2, 29.5, 29.6 (3xC), 34.5, 46.1, 57.2 (1C, d, J = 21.5 Hz), 77.3 (1C, d, J = 172 Hz), 110.2, 120.7, 121.7, 132.4, 140.2, 141.6, 163.9; ^{19}F NMR (282 Hz): δ -221.7 (tt, J_1 = 46.5 Hz, J_2 = 20.9 Hz); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_{18}H_{27}FN_2O_2S$ 355.1850, found 355.1850; HPLC-purity: >98%, RT = 19.4 min.

2-(tert-butyl)-1-(cyclobutylmethyl)-5-((2-fluoroethyl)sulfonyl)-1H-benzo[d]imidazole **(2c)**

Was prepared from 2-(*tert*-butyl)-1-(cyclobutylmethyl)-5-((2-fluoroethyl)thio)-1*H*-benzo[d]imidazole (56 mg, 0.17 mmol) according to the general method ***x***. Purification on silica gel using EtOAc:Hex (1:6 → 1:4 → 1:2) gave the product **2c** as white powder (45 mg, 74%).

m.p. 100.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (9H, s), 1.87 - 2.00 (4H, m), 2.03 - 2.14 (2H, m), 2.69 - 2.84 (1H, m), 3.52 (2H, dt, J_1 = 21 Hz, J_2 = 6 Hz), 4.37 (2H, d, J = 6.3 Hz), 4.68 – 4.84 (2H, dt, J_1 = 46.5 Hz, J_2 = 6.0 Hz), 7.46 (1H, d, J = 8.4 Hz),

7.77 (1H, d, J = 6 Hz), 8.31 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5, 28.3 (2xC), 30.0 (3xC), 34.8, 37.4, 51.2, 57.2 (1C, d, J_{CF} = 21.3 Hz), 77.4 (1C, d, J = 171.9 Hz), 110.8, 120.7, 121.6, 132.4, 140.6, 141.6, 164.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.4 (s); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{18}H_{25}FN_2O_2S$ 375.1513, found 375.1513; HPLC-purity >99%, RT = 23.1 min.

***2-(tert-butyl)-5-((2-fluoroethyl)sulfonyl)-1-(3-methoxypropyl)-1H-benzo[d]imidazole* (2d)**

Was prepared from 3-(2-(*tert*-butyl)-5-((2-fluoroethyl)thio)-1*H*-benzo[d]imidazol-1-yl)-*N*,*N*-dimethylpropan-1-amine (92 mg, 2.8 mmol) according to the general method ***x***. Purification on silica gel using EtOAc:Hex (1:2 → 1:1) afforded the product **2d** as white solid (0.11 g, >99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (9H, s), 2.11 (2H, m), 3.41 (3H, s), 3.51 (2H, m), 3.53 (2H, m), 4.49 (2H, m), 4.69 (2H, dt, J_1 = 46.5 Hz, J_2 = 6 Hz), 7.49 (1H, d, J = 8.7 Hz), 7.79 (1H, d, J = 8.4 Hz), 8.33 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): 29.7 (3xC), 30.3, 43.5, 57.2 (1C, d, J = 21.3 Hz), 59.1, 69.5, 77.3 (1C, d, J = 172.5 Hz), 110.3, 120.7, 121.8, 132.5, 140.3, 141.6, 164.1; ^{19}F NMR (282 MHz): δ -221.7 (tt, J_1 = 46.8 Hz, J_2 = 20.9 Hz); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{17}H_{25}FN_2O_3S$ 379.1462, found 379.1458; HPLC purity > 95%, RT = 16.7 min.

***2-(tert-butyl)-5-((2-fluoroethyl)sulfonyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazole* (2e)**

Was prepared from 2-(*tert*-butyl)-5-((2-fluoroethyl)thio)-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1H-benzo[d]imidazole (99 mg, 0.28 mmol) using the general method ***x***. Purification on silica gel using EtOAc:Hex (1:1) afforded the title compound **2e** as amorphous white solid (80 mg, 74%).

Melting range 40 - 58 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (4H, m), 1.59 (9H, s), 2.28 (1H, m), 3.31 (2H, m), 3.55 (2H, dt, J_1 = 21 Hz, J_2 = 5.7 Hz), 3.99 (2H, m), 4.26 (2H, d, J = 7.5 Hz), 4.80 (2H, dt, J_1 = 46.5 Hz, J_2 = 5.7 Hz), 7.48 (1H, d, J = 8.4 Hz), 7.79 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 8.33 (1H, d, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 30.3 (3xC), 31.3 (2xC), 35.0, 37.0, 51.3, 57.2 (1C, d, J = 15.0 Hz), 67.6 (2xC), 77.5 (1C, d, J = 180.0 Hz), 111.0, 120.9, 121.7, 132.8, 140.8, 141.6, 164.6; ^{19}F NMR (282 MHz): δ -221.7 (tt, J_1 = 46.5 Hz, J_2 = 20.9 Hz); HRMS (ESI-TOF) m/z:

$[M+Na]^+$ calculated for $C_{19}H_{27}FN_2O_3S$ 405.1619, found 405.1614; HPLC-purity >97%, RT = 14.9 min.

***4-(2-(tert-butyl)-5-((2-fluoroethyl)sulfonyl)-1H-benzo[d]imidazol-1-yl)butanenitrile* (2g)**

Was prepared from 4-(2-(*tert*-butyl)-5-((2-fluoroethyl)thio)-1*H*-benzo[d]imidazol-1-yl)butanenitrile (0.17 g, 0.52 mmol) according to the general method ***x***. The crude product was purified on silica gel using EtOAc:Hex (1:1) and recrystallised from DCM and hexane to give the title product **2g** as white solid (90 mg, 47%).

m.p. 116.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (9H, s), 2.20 (2H, m)**,** 2.59 (2H, t, J = 6.6 Hz), 3.50 (2H, dt, J_1 = 21.9 Hz, J_2 = 4.8 Hz), 4.49 (2H, m), 4.64 - 4.84 (2H, dt, J_1 = 46.5 Hz, J_2 = 5.7 Hz), 7.44 (1H, d, J = 8.4 Hz), 7.75 (1H, d, J = 8.7 Hz), 8.30 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 25.2, 29.6 (3xC), 34.5, 44.3, 57.2 (1C, d, J = 21.3 Hz), 77.2 (1C, d, J = 67.5 Hz), 109.9, 118.3, 120.9, 122.2, 133.0, 139.8, 141.5, 163.8; ^{19}F NMR (282 MHz): -221.4 (tt, J_1 = 46.5 Hz, J_2 = 21.4 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{17}H_{22}FN_3O_2S$ 352.1490, found 352.1485; HPLC-purity >97%, RT = 15.9 min.

***Methyl 4-(2-(tert-butyl)-5-((2-fluoroethyl)sulfonyl)-1H-benzo[d]imidazol-1-yl)butanoate* (2h)**

Was prepared from methyl 4-(2-(*tert*-butyl)-5-((2-fluoroethyl)thio)-1H-benzo[d]imidazol-1-yl)butanoate (0.40 g, 1.14 mmol) using the general method ***x***. Purification of the crude material on silica gel using EtOAc:Hex gradient (1:3 → 1:2) afforded the title product **2h** as light yellow oil (0.35 g, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (9H, s,), 2.16 (2H, m), 2.54 (2H, t, J = 6.6 Hz), 3.52 (2H, t, J_1 = 21 Hz, J_2 = 6 Hz), 3.75 (3H, s), 4.41 (2H, m), 4.75 (2H, t, J_1 = 6.9 Hz, J_2 = 46.5 Hz), 7.57 (1H, d, J = 8.4 Hz), 7.34 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 8.32 (1H, d, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 29.7 (3xC), 30.8, 34.6, 45.2, 52.1, 57.3 (1C, d, J = 21.4 Hz), 77.4 (1C, d, J = 172.5 Hz), 110.4, 120.8, 122.0, 132.6, 140.2, 141.6, 163.9, 172.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ -221.7 (tt, J_1 = 46.5 Hz; J_2 = 20.9 Hz); HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{18}H_{25}FN_2O_4S$ 407.1411, found 407.1416; HPLC-purity >95%, RT = 17.7 min.

***4-(2-(tert-butyl)-5-((2-fluoroethyl)sulfonyl)-1H-benzo[d]imidazol-1-yl)butan-1-ol* (2i)**

Was prepared from 4-(2-(*tert*-butyl)-5-((2-fluoroethyl)thio)-1*H*-benzo[d]imidazol-1-yl)butan-1-ol (91 mg, 0.28 mmol) according to the general method ***x***. Purification on silica gel using EtOAc:Hex (1:1) → EtOAc as eluent afforded the title product **2i** as opaque oil (71 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (9H, s), 1.72 (2H, m), 1.94 (2H, m), 2.66 (1H, br s), 3.47 (2H, dt, J_1 = 21.3 Hz, J_2 = 5.7 Hz), 3.73 (2H, t, J = 6.0 Hz), 4.36 (2H, m), 4.71 (2H, dt, J_1 = 46.5 Hz, J_2 = 5.7 Hz), 7.44 (1H, d, J = 8.4 Hz), 7.71 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 8.27 (1H, d, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.6, 29.6 (3xC), 29.8, 34.5, 45.9, 57.2 (1C, d, J = 21.3 Hz) 61.8, 77.2 and 78.3 (1C, d, J = 172.0), 110.5, 120.5, 121.7, 132.3, 140.1, 141.4, 163.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ - 221.6 (tt, J_1 = 46.8 Hz, J_2 = 21.2 Hz); HRMS (ESI-TOF) m/z: $[2M+Na]^+$ calculated for $C_{17}H_{25}FN_2O_3S$ 735.3032, found 735.3044; HPLC-purity >97%, RT = 12.7 min.

***4-(2-(tert-butyl)-5-((2-fluoroethyl)sulfonyl)-1H-benzo[d]imidazol-1-yl)butanamide* (2j)**

Was prepared from 4-(2-(*tert*-butyl)-5-((2-fluoroethyl)thio)-1*H*-benzo[d]imidazol-1-yl)butanamide (30 mg, 0.09 mmol) according to the general procedure ***x***. Purification on silica gel using MeOH in DCM (4% → 5%) afforded the title product **2j** as white solid (28 mg, 84%).

m.p. 175.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (9H, s), 2.16 (2H, m), 2.43 (2H, t, J = 6.6 Hz)**,** 3.52 (2H, dt, J_1 = 21 Hz, J_2 = 5.7 Hz), 4.43 (2H, m), 4.40 (2H, dt, J_1 = 46.5 Hz, J_2 = 5.7 Hz)**,** 5.60 (2H, br s), 7.62 (1H, d, J = 8.4 Hz), 7.78 (1H, d, J = 8.4 Hz), 8.32 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 29.7 (3xC), 31.9, 34.6, 45.3, 57.3 (1C, d, J = 21.3 Hz), 77.3 and 78.4 (1C, d, J = 172 Hz), 110.7, 120.7, 121.9, 132.5, 140.4, 141.6, 164.0, 173.4; ^{19}F NMR (282 MHz): δ -221.6 (tt, J_1 = 46.5 Hz, J_2 = 20.9 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{17}H_{24}FN_3O_3S$ 370.1595, found 370.1591; HPLC purity >95%, RT = 12.9 min.

***4-(2-(tert-butyl)-5-((2-fluoroethyl)sulfonyl)-1H-benzo[d]imidazol-1-yl)butanoic acid* (2k)**

Was prepared from methyl 4-(2-(*tert*-butyl)-5-((2-fluoroethyl)sulfonyl)-1*H*-benzo[d]imidazol-1-yl)butanoate (0.25 g, 0.65 mmol) using trimethyltin hydroxide (0.58 g, 3.23 mmol) according to the general method ***xiii***. Purification of the crude

material was done on silica gel using EtOAc:Hex (1:1) with 0.1% acetic acid as eluent, which gave the title compound **2k** as white crystalline solid.

m.p. 97.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (9H, s), 2.13 (2H, m), 2.58 (2H, t, J = 6.6 Hz), 3.65 (2H, t, J_1 = 24 Hz, J_2 = 5.4 Hz), 4.55 (2H, m), 4.75 (2H, t, J_1 = 5.1 Hz, J_2 = 46.8 Hz), 7.81 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.5 Hz), 7.90 (1H, d, J = 8.7 Hz), 8.18 (1H, d, J = 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.8, 29.6 (3xC), 31.5, 35.5, 46.5, 59.0 (1C, d, J = 20.9 Hz), 78.5 (1C, d, J = 169.8 Hz), 112.9, 119.9, 123.6, 135.0, 140.4, 140.7, 165.2, 177.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ -222.17 (tt, J_1 = 46.8 Hz; J_2 = 24 Hz); LRMS (ESI) *m/z*: estimated 393.13 $[M+Na]^+$, found 393.11; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{17}H_{23}FN_2O_4S$ 371.1435, found 371.1440; HPLC purity >95%, RT = 14.6 min.

Isopropyl (4-bromo-2-pivalamidophenyl)glycinate **(12m)**

Was prepared in three steps in a telescoped process from the starting material **(11b)**.

4-bromo-1-fluoro-2-nitrobenzene **(11b)** (3.36 mL, 27.2 mmol) and glycine (2.25 g, 1.1 equiv) were reacted according to the general procedure ***xi***. After completion of the reaction, ethanol was evaporated off and the residue was dissolved in EtOAc (100 mL) and water (30 mL). HCl (1M) was added until all the carboxylic acid was free of the di-isopropylamine salt. The organic layer was separated and dried over anhydrous $MgSO_4$. Filtration and concentration under reduced pressure gave yellow solid (7.6 g, >99%) that was used without purification in the next step. (4-bromo-2-nitrophenyl)glycine (4.21 g, 15.3 mmol) was dissolved in isopropanol (60 mL) and treated with H_2SO_4 (0.16 mL, 20 mol%). After refluxing the solution overnight, the solution was concentrated to get isopropyl (4-bromo-2-nitrophenyl)glycinate as bright orange solids. The crude material was dissolved in ethanol (80 mL), treated with Fe powder (5 equiv, 4.27 g) and aqueous NH_4Cl (5 equiv, 4.09 g/20 mL H_2O) and placed in a sonicator for 2 hours. The resulting mixture containing isopropyl (2-amino-4-bromophenyl)glycinate was neutralised with saturated $NaHCO_3$ and filtered through a pad of basic alumina and Celite®. The organic layer was separated from the aqueous phase, washed with brine and dried over anhydrous $MgSO_4$. Concentration of the filtered solution gave the crude aniline as brown solid that was dissolved in dry DCM under N_2 atmosphere and cooled down to 0 °C. Pyridine (1.2 equiv., 1.48 mL) and

DMAP (5 mol%, 93 mg) were added to the solution. Pivaloyl chloride (1.1 equiv, 2.07 mL) was added dropwise to the solution at 0°C. The reaction was stirred at room temperature for 1 hour, after which it was diluted with DCM. The organic phase was washed with saturated NH_4Cl, $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. The solution was filtered and concentrated to give crude product that was purified on silica gel using hexane → EtOAc:Hex (1:8 → 1:4). The title product **(12m)** was collected as white solid (3.36 g, 61% over three steps).

m.p. 112.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (6H, d, J = 6.3 Hz), 1.35 (9H, s), 3.79 (2H, s), 4.22 (1H, bs), 5.10 (1H, m), 6.51 (1H, d, J = 8.4 Hz), 7.50 (1H, dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz), 7.44 (1H, bs), 7.56 (1H, d, J = 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9 (2xC), 27.8 (3xC), 39.7, 47.0, 69.5, 111.2, 115.6, 126.7, 128.3, 129.7, 140.3, 170.5, 177.6; LRMS (ESI) *m/z*: Estimated 393.08 and 395.08, found 393.05 and 395.04.

***2-(2-(tert-butyl)-5-((4-methoxybenzyl)thio)-1H-benzo[d]imidazol-1-yl)ethan-1-ol* (7n)**

Was prepared from isopropyl (4-bromo-2-pivalamidophenyl)glycinate **(12m)** in three steps ***v***, ***xii*** and ***xvi***: Intermediate **12m** (1.87 g, 5.06 mmol) was treated with *p*-TsOH monohydrate in DMSO according to the general method ***v***. Purification of the crude material on silica gel using EtOAc:Hex (1:10) as the eluent afforded isopropyl 2-(5-bromo-2-(*tert*-butyl)-1*H*-benzo[d]imidazol-1-yl)acetate **13m** as yellow oil (1.78 g, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (6H, d, J = 6.3 Hz), 1.49 (9H, s), 4.97 (2H, s), 4.22 (1H, bs), 5.07 (1H, m), 7.00 (1H, d, J = 8.4 Hz), 7.31 (1H, d, J = 8.4 Hz), 7.88 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7 (2xC), 29.5 (3xC), 34.1, 47.2, 70.3, 110.0, 115.1, 122.7, 125.7, 136.0, 142.9, 161.8, 166.9; LRMS (ESI) *m/z*: estimated 375.07 and 377.07 $[M+H]^+$, found 375.04 and 377.02.

Isopropyl 2-(5-bromo-2-(*tert*-butyl)-1*H*-benzo[d]imidazol-1-yl)acetate **13m** (0.42 g, 1.23 mmol) was reacted with 4-methoxy-α-toluenethiol (90%, 0.29 mL, 1.85 mmol) according to the general procedure ***xii***. Purification of the crude material on silica gel using EtOAc:Hex (1:6) gave isopropyl 2-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazol-1-yl)acetate **7m** as light yellow solid (0.45 g, 85%).

m.p. 101.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (6H, d, *J* = 6.3 Hz), 1.51 (9H, s), 3.75 (3H, s), 4.04 (2H, s), 4.97 (2H, s), 5.07 (1H, m), 6.76 (2H, d, *J* = 8.4 Hz), 7.00 (1H, d, *J* = 8.4 Hz), 7.15 (2H, d, *J* = 8.1 Hz), 7.19 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 7.82 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7 (2xC), 29.5 (3xC), 34.0, 40.6, 47.2, 55.3, 70.1, 109.0, 113.9 (2xC), 123.1, 127.0, 128.9, 130.0 (2xC), 130.1, 136.3, 142.1, 158.7, 161.3, 167.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{24}H_{30}N_2O_3S$ 427.2050, found 427.2044.

Isopropyl 2-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazol-1-yl)acetate **7m** (0.45 g, 1.05 mmol) was treated with DIBAL-H (4.2 mL, 1M, 4.2 mmol) according to the general procedure ***xvi***. Purification of the crude material on silica gel using EtOAc:Hex (1:2 → 1:1) gave the title compound **7n** as white solid (0.34 g, 86%).

m.p. 114.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (9H, s), 3.71 (3H, s), 3.95 (2H, s), 3.95 (2H, t, *J* = 6.6 Hz), 4.02 (2H, s), 4.43 (2H, t, *J* = 6.6 Hz), 4.97 (2H, s), 5.07 (1H, m), 6.73 (2H, d, *J* = 8.1 Hz), 7.14 (2H, d, *J* = 8.1 Hz), 7.15 (1H, m), 7.20 (1H, d, *J* = 8.4 Hz), 7.75 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.9 (3xC), 34.3, 40.6, 47.4, 55.3, 60.8, 110.2, 114.0 (2xC), 122.4, 126.5, 128.9, 130.0 (3xC), 136.0, 142.0, 158.7, 161.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{21}H_{26}N_2O_2S$ 371.1788, found 371.1781.

***2-(tert-butyl)-5-(ethylsulfonyl)-1-(2-(2-fluoroethoxy)ethyl)-1H-benzo[d]imidazole* (3l)**

Was prepared in four steps ***xvii***, ***vi***, ***ix*** and ***x*** from the intermediate **7n**:

Compound **7n** (0.33 g, 0.90 mmol) was reacted with 2-fluoroethylbromide (0.34 mL, 4.50 mmol) according to the general procedure ***xvii.*** The crude product was purified on silica gel using EtOAc:Hex (1:3) as eluent, which afforded 2-(*tert*-butyl)-1-(2-(2-fluoroethoxy)ethyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazole **7l** as light yellow oil (0.35 g, 94%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (9H, s), 3.62 – 3.72 (2H, dt, J_1 = 29.7 Hz, J_2 = 3.6 Hz), 3.78 (3H, s), 3.88 (2H, t, *J* = 6.3 Hz), 4.07 (2H, s), 4.44 - 4.59 (2H, dt, J_1 = 47.7 Hz, J_2 = 3.9 Hz), 4.56 (2H, t, *J* = 6.3 Hz), 6.79 (2H, d, *J* = 8.4 Hz), 7.19 (2H, d, *J* = 8.4 Hz), 7.22 - 7.29 (2H, m), 7.84 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.8

(3xC), 34.2, 40.4, 45.1, 55.2, 69.6, 70.6 (1C, d, J = 19.5 Hz), 83.0 (1C, d, J = 169 Hz), 110.0, 113.8 (2xC), 122.6, 126.3, 128.6, 129.9 (2xC), 130.0, 135.9, 142.2, 158.6, 161.4; ^{19}F NMR (282 MHz): δ -223.0 (tt, J_1 = 47.7 Hz, J_2 = 29.3 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{29}FN_2O_2S$ 417.2007, found 417.2001.

Intermediate **7l** (0.19 g, 0.45 mmol) was deprotected and the free thiol was substituted with ethyl bromide (0.08 mL, 1.13 mmol) according to the general methods ***vi*** and ***ix.*** The crude material was purified on silica gel with EtOAc:Hex (1:2) to afford 2-(*tert*-butyl)-5-(ethylthio)-1-(2-(2-fluoroethoxy)ethyl)-1*H*-benzo[d]imidazole **10l** as light yellow oil (0.15 g, >99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (3H, t, J = 7.5 Hz), 1.41 (9H, s), 2.76 (2H, q, J = 7.5 Hz), 3.47 - 3.57 (dt, J_1 = 29.7 Hz, J_2 = 4.2 Hz), 3.73 (2H, t, J = 6.3 Hz), 4.28 - 4.44 (dt, J_1 = 47.7 Hz, J_2 = 3.9 Hz), 4.39 (2H, t, J = 6.6 Hz), 7.15 (2H, m), 7.66 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): 14.6, 29.6, 29.9, 34.2, 45.1, 69.6, 70.6 (1C, d, J = 19.5 Hz), 83.0 (1C, d, J = 168.7 Hz), 110.1, 121.9, 125.9, 128.6, 135.7, 142.3, 161.4; ^{19}F NMR (282 MHz): δ -223.0 (tt, J_1 = 47.7 Hz, J_2 = 29.6 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{17}H_{25}FN_2OS$ 325.1744, found 325.1739.

Sulfide **10l** (0.15 g, 0.45 mmol) was oxidised according to the general method ***x***. Purification of the crude material on silica gel using EtOAc:Hex gradient (1:3 → 1:2 → 1:1) afforded the title product **3l** as white crystalline solid (0.12 g, 72%).

m.p. 133.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, t, J = 7.5 Hz), 1.59 (9H, s), 3.12 (2H, q, J = 7.5 Hz), 3.63 - 3.73 (2H, dt, J_1 = 29.7 Hz, J_2 = 4.2 Hz), 3.92 (2H, t, J = 6.3 Hz), 4.44 - 4.54 (2H, dt, J_1 = 47.4 Hz, J_2 = 3.9 Hz), 4.62 (H, t, J = 6.0 Hz), 7.55 (1H, d, J = 8.4 Hz), 7.76 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz), 8.30 (1H, d, J = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 7.86, 29.9 (3xC), 34.7, 45.7, 51.2, 70.0, 70.8 (1C, d, J = 19.4 Hz), 83.1 (1C, d, J = 168.9 Hz), 110.9, 120.8, 122.1, 132.1, 140.3, 141.4, 163.9; ^{19}F NMR (282 MHz): δ -222.9 (tt, J_1 = 47.4 Hz, J_2 = 29.6 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{17}H_{25}FN_2O_3S$ 357.1643, found 357.1638; HPLC-purity 98%, RT = 17.5 min.

Radiolabelling precursors:

4-((2-(tert-butyl)-1-(3-methoxypropyl)-1H-benzo[d]imidazol-5-yl)sulfonyl)-N,N,N-trimethylpyridin-2-aminium iodide **(14d)**

Was prepared in two steps: 2-(*tert*-butyl)-5-((2-fluoropyridin-4-yl)sulfonyl)-1-(3-methoxypropyl)-1*H*-benzo[d]imidazole (0.23 g, 0.57 mmol) and dimethylamine (2M in THF, 0.43 mL, 1.5 equiv) were first reacted using the general method ***xi***. The crude material was purified on silica gel using EtOAc:Hex (1:1.5) → (1:1), which afforded 4-((2-(*tert*-butyl)-1-(3-methoxypropyl)-1*H*-benzo[d]imidazol-5-yl)sulfonyl)-*N*,*N*-dimethylpyridin-2-amine as white solid (0.21 g, 84%).

m.p. 161.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (9H, s), 2.08 (2H, m), 3.10 (6H, s), 3.39 (3H, s), 3.49 (2H, t, J = 5.4 Hz), 4.43 (2H, m), 6.86 (1H, d, J = 5.1 Hz), 7.02 (1H, s), 7.42 (1H, d, J = 8.7 Hz), 7.82 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz), 8.19 (1H, d, J = 5.1 Hz), 8.33 (1H, d, J = 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 30.3, 34.6, 38.2 (2xC), 43.5, 59.1, 69.6, 102.8, 107.8, 110.3, 120.7, 121.7, 133.8, 140.1, 142.0, 149.5, 151.5, 159.6, 164.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{22}H_{30}N_4O_3S$ 453.1931, found 453.1935; HPLC-purity >97%, RT = 17.9 min.

Procedure ***xix***: 4-((2-(*tert*-butyl)-1-(3-methoxypropyl)-1H-benzo[d]imidazol-5-yl)sulfonyl)-N,N-dimethylpyridin-2-amine (40 mg, 0.093 mmol) was dissolved in methanol (2 mL) and methyl iodide (1.5 mL) and heated to 40 °C in a sealed pressure tube. After 27 h, the reaction mixture was evaporated to dryness and the solid residue was dried under high vacuum. The dried residue was triturated with DCM and hexane several times to give the product **14d** as orange solid (41 mg, 77%).

m.p. 139.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.78 (9H, s), 2.22 (2H, m), 3.41 (3H, s), 3.58 (11H, s and t) 4.72 (2H, m), 7.05 (1H, dd, J_1 = 6.9 Hz, J_2 = 1.2 Hz), 7.65 (1H, s), 8.00 (1H, d, J = 9.0 Hz), 8.18 (1H, dd, J_1 = 8.7 Hz; J_2 = 1.8 Hz), 8.28 (1H, d, J = 6.6 Hz), 9.23 (1H, s); HRMS (ESI-TOF) m/z: [M]+ calculated for $C_{23}H_{33}N_4O_3S$ 445.2268, found 445.2263.

2-(tert-butyl)-5-((2-chloropyridin-4-yl)sulfonyl)-1-(3-methoxypropyl)-1H-benzo[d]imidazole **(15d)**

Was prepared in three steps following the general methods ***vi***, ***vii*** and ***x***: 2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1-(3-methoxypropyl)-1*H*-benzo[d]imidazole (0.26 g, 0.65 mmol) was deprotected and then reacted with 4-bromo-2-chloropyridine (80 μL, 0.71 mmol) according to the general methods ***vi*** and ***vii***. Purification of the crude material on silica gel using EtOAc:Hex (1:4 → 1:3) gave 2-(*tert*-butyl)-5-((2-chloropyridin-4-

yl)thio)-1-(3-methoxypropyl)-1*H*-benzo[d]imidazole as light yellow solid (0.22 g, 87%).

m.p. 102.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (9H, s), 2.15 (2H, m), 3.41 (3H, s), 3.54 (2H, t, *J* = 5.4 Hz), 4.47 (2H, m), 6.83 (1H, m), 6.84 (1H, m), 7.37 (1H, d, *J* = 8.4 Hz), 7.43 (1H, d, *J* = 8.4 Hz), 7.97 (1H, s), 8.05 (1H, d, *J* = 5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.8, 30.3, 34.5, 43.4, 59.1, 69.7, 111.3, 119.1, 119.88, 119.96, 127.7, 129.4, 138.0, 143.1, 148.8, 151.9, 155.5, 162.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{24}ClN_3OS$ 390.1401, found 390.1405.

2-(*tert*-butyl)-5-((2-chloropyridin-4-yl)thio)-1-(3-methoxypropyl)-1H-benzo[d]imidazole was oxidised to give **(15d)** according to the general method ***x***. Purification of the crude material on silica gel using the eluent EtOAc:Hex (1:3) gave the title product as clear viscous oil (0.20 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (9H, s), 2.07 (2H, m), 3.40 (3H, s), 3.50 (2H, t, *J* = 5.4 Hz), 4.46 (2H, m), 7.49 (1H, d, *J* = 8.4 Hz), 7.67 (1H, d, *J* = 5.1 Hz), 7.78 (1H, s), 7.81 (1H, d, *J* = 8.7 Hz), 8.37 (1H, s), 8.51 (1H, d, *J* = 5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 30.3, 34.7, 43.5, 59.1, 69.5, 110.8, 119.4, 121.1, 121.8, 121.9, 132.2, 140.7, 142.0, 153.7, 164.6; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{20}H_{24}ClN_3O_3S$ 444.1119, found 444.1124; HPLC-purity >99%, RT = 18.9 min.

2-(tert-butyl)-5-((2-chloropyridin-4-yl)sulfonyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazole **(15e)**

Was prepared in three steps following the general methods ***vi***, ***vii*** and ***x***: 2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]-imidazole (0.20 g, 0.47 mmol) was deprotected, followed by a coupling reaction with 2-chloro-4-bromopyridine (60 μL, 0.51 mmol) according to the methods ***vi*** and ***vii***. Purification of the crude material on silica gel using EtOAc:Hex (1:3 → 1:2) afforded 2-(*tert*-butyl)-5-((2-chloropyridin-4-yl)thio)-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazole as light yellow solid (0.15 g, 79% over two steps).

m.p. 146.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (4H, m), 1.59 (9H, s), 2.31 (1H, m**)**, 3.33 (2H, m), 4.00 (2H, m), 4.24 (2H, d, *J* = 7.2 Hz), 6.84 (2H, m), 7.37 (1H, d, *J* = 8.4 Hz), 7.41 (1H, d, *J* = 8.4 Hz), 7.96 (1H, s), 8.06 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4 (3xC), 31.4 (2xC), 34.9, 37.0, 51.3, 67.7 (2xC), 112.0, 119.1, 119.9,

121.0, 127.7, 129.3, 138.4, 142.9, 148.8, 151.8, 155.3, 163.1; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{22}H_{26}ClN_3OS$ 416.1558, found 416.1552.

2-(*tert*-butyl)-5-((2-chloropyridin-4-yl)thio)-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazole (0.18 g, 0.44 mmol) was oxidised using the general method ***x***. Purification of the crude material on silica gel using EtOAc:Hex (1:2 → 1:1) gave **(15e)** as off-white solid (0.15 g, 74%).

m.p. 202.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (4H, m), 1.56 (9H, s), 2.24 (1H, m), 3.29 (2H, m), 3.98 (2H, m), 4.25 (2H, d, *J* = 7.5 Hz), 7.46 (2H, d, *J* = 8.7 Hz), 7.68 (1H, d, *J* = 5.1 Hz), 7.78 (2H, m), 8.37 (1H, s), 8.53 (1H, d, *J* = 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.3 (3xC), 31.2 (2xC), 35.1, 37.0, 51.4, 67.6 (2xC), 111.5, 119.5, 121.2, 121.7, 121.9, 132.3, 141.0, 141.7, 151.2, 152.9, 153.5, 164.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{26}ClN_3O_3S$ 448.1456, found 448.1453; HPLC-purity >99%, RT = 19.8 min.

4-(2-(tert-butyl)-5-((2-chloropyridin-4-yl)sulfonyl)-1H-benzo[d]imidazol-1-yl)butanenitrile **(15g)**

Was prepared in four steps following the general methods ***vi***, ***vii***, ***xv*** and ***v***: 4-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[d]imidazol-1-yl)butanamide (0.26 g, 0.62 mmol) was deprotected and reacted with 4-bromo-2-chloropyridine (76 μL, 0.68 mmol) according to the general methods ***vi*** and ***vii***. Purification of the crude material on silica gel using MeOH in DCM (2% → 3%) gave 4-(2-(*tert*-butyl)-5-((2-chloropyridin-4-yl)thio)-1*H*-benzo[*d*]imidazol-1-yl)butanamide as opaque oil (0.11 g, 43%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (9H, s), 2.16 (2H, m), 2.41 (2H, t, *J* = 6.6 Hz), 4.38 (2H, m), 6.08 (2H, bs), 6.76 - 6.79 (2H, m), 7.33 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz), 7.53 (1H, d, *J* = 8.4 Hz), 7.90 (1H, d, *J* = 1.2 Hz), 7.98 (1H, d, *J* = 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 29.6 (3xC), 32.0, 34.3, 45.2, 111.6, 119.0, 119.7 (2xC), 127.3, 129.4, 137.8, 142.8, 148.6, 151.6, 155.6, 162.4, 173.9; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{23}ClN_4OS$ 403.1354, found 403.1349.

4-(2-(*tert*-butyl)-5-((2-chloropyridin-4-yl)thio)-1*H*-benzo[*d*]imidazol-1-yl)butanamide (100 mg, 0.27 mmol) was treated with trifluoroacetic anhydride and triethylamine according to the general method ***xv***. Purification of the crude material on silica gel using the gradient EtOAc:Hex (1:2 → 1:1 → EtOAc) gave 4-(2-(*tert*-butyl)-5-((2-chloropyridin-4-yl)thio)-1*H*-benzo[d]imidazol-1-yl)butanenitrile as opaque viscous oil (85 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58 (9H, s), 2.25 (2H, m), 2.59 (2H, t, J = 6.9 Hz), 4.50 (2H, m), 6.81 (2H, m), 7.38 (1H, m), 7.39 (1H, m), 7.97 (1H, m), 8.04 (1H, d, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1, 25.3, 29.8 (3xC), 34.4, 44.3, 110.6, 118.2, 119.1, 119.8, 120.6, 127.9, 129.8, 137.5, 143.0, 148.8, 151.7, 155.1, 162.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{21}ClN_4O_2S$ 417.1147, found 417.1141.

4-(2-(*tert*-butyl)-5-((2-chloropyridin-4-yl)thio)-1H-benzo[d]imidazol-1-yl)butanenitrile (85 mg, 0.22 mmol) was oxidised to give **(15g)** according to the general method ***x***. Purification of the crude material on silica gel using EtOAc:Hex (1:1 → 2:1) as an eluent afforded the product as sticky oil (88 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (9H, s), 2.18 (2H, m), 2.57 (2H, t, J = 6.9 Hz), 4.49 (2H, m), 7.44 (1H, d, J = 8.4 Hz), 7.66 (1H, dd, J_1 = 1.5 Hz, J_2 = 5.1 Hz), 7.76 (1H, m), 7.80 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz), 8.35 (1H, d, J = 1.2 Hz), 8.51 (1H, dd, J_1 = 5.1 Hz, J_2 = 0.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1, 25.3, 29.6, 34.6, 44.4, 110.3, 118.1, 119.3, 121.3, 121.8, 122.3, 132.6, 140.2, 141.9, 151.2, 152.9, 153.4, 164.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{20}H_{21}ClN_4O_2S$ 417.1147, found 417.1141; HPLC-purity: >98%, RT = 21.2 min.

2-((2-(tert-butyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)sulfonyl)ethyl 4-methylbenzenesulfonate **(16e)**

Was prepared in four steps ***vi***, ***ix***, ***x*** and ***xx*** from the intermediate **(7e)**:

2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1-((tetrahydro-2*H*-pyran-4-yl)methyl)-1*H*-benzo[d]imidazole **(7e)** (0.19 g, 0.45 mmol) was first deprotected according to the general method ***vi***.

General procedure ix: The crude material was evaporated to dryness under N_2 flow. The residue was dissolved in MeOH (10 mL) under N_2 atmosphere and cooled to 0

°C. 2-bromoethanol (56 μL, 0.68 mmol) and aqueous NaOH (1M, 1.35 mL, 3 equiv) were added at 0 °C, after which the solution was heated to 40 °C for overnight. Reaction mixture was cooled to RT, diluted with EtOAc (20 mL) and brine (5 mL). Organic phase was separated and aqueous phase extracted with EtOAc (2x10 mL). The combined organic phase was dried over anhydrous $MgSO_4$. Filtration and concentration under reduced pressure afforded the crude product that was purified on silica gel using EtOAc:Hex (1:2) → (1:1), which gave 2-((2-(*tert*-butyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1H-benzo[d]imidazol-5-yl)thio)ethan-1-ol as clear viscous oil (0.14 g, 88% over two steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (4H), 1.54 (9H, s), 2.25 (1H, m), 3.06 (2H, t, *J* = 5.7 Hz), 3.29 (2H, m), 3.69 (2H, t, *J* = 5.7 Hz), 3.95 (2H, d, *J* = 11.4 Hz)**,** 4.16 (2H, d, *J* = 7.5 Hz), 7.22 (1H, d, *J* = 9 Hz), 7.28 (1H, d, *J* = 8.4 Hz), 7.82 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4 (3xC), 31.2 (2xC), 34.7, 36.8, 38.9, 51.0, 60.3, 67.6 (2xC), 110.8, 122.6, 126.4, 127.2, 136.3, 142.0, 162.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{19}H_{28}NO_2S$ 349.1944, found 349.1940.

2-((2-(*tert*-butyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1*H*-benzo[d]imidazol-5-yl)thio)ethan-1-ol (70 mg, 0.2 mmol) was oxidised to 2-((2-(*tert*-butyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1*H*-benzo[d]imidazol-5-yl)sulfonyl)ethan-1-ol according to the general method ***x***. The product was isolated as light yellow solid (86 mg, >99%) and used without purification for the next step.

General procedure xx: 2-((2-(*tert*-butyl)-1-((tetrahydro-2H-pyran-4-yl)methyl)-1*H*-benzo[d]imidazol-5-yl)sulfonyl)ethan-1-ol (80 mg) was dissolved in DCM (6 mL) under N_2 atmosphere. Tosyl chloride (62 mg, 0.33 mmol, in 2 mL of DCM) and pyridine (30 μL, 2 equiv) were added dropwise to a stirring solution of alcohol. The reaction mixture was heated to mild reflux. After the reaction was complete, the solution was diluted with DCM, washed with 5% $CuSO_4$ (2 x 5 mL) and dried over $MgSO_4$. Purification on silica gel using EtOAc:Hex (1:3 → 1:1 → EtOAc) afforded the product (**16e)** as opaque viscous oil (65 mg, 56%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (4H, m), 1.57 (9H, s), 2.27 (1H, m), 2.44 (3H, s), 3.29 (2H, m), 3.45 (2H, t, *J* = 6.9 Hz), 3.96 (2H, d), 4.25 (2H, d, *J* = 7.5 Hz), 4.28 (2H, t, *J* = 6.9 Hz), 7.32 (1H, d, *J* = 8.1 Hz), 7.47 (1H, d, *J* = 8.4 Hz), 7.64 (1H, d, *J* =

8.1 Hz), 7.70 (1H, dd, *J* = 8.4 Hz, *J* = 1.5 Hz), 8.18 (1H, d, *J* = 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8, 30.3 (3xC), 31.2 (2xC), 35.0, 36.9, 51.3, 55.6, 63.8, 67.6 (2xC), 111.3, 120.7, 121.6, 128.1 (2xC), 130.1 (2xC), 132.0, 132.2, 140.8, 141.4, 164.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{26}H_{34}N_2O_6S_2$ 535.1931, found 535.1923; HPLC-purity >99%, RT = 20.0 min.

2-(2-(2-(tert-butyl)-5-((4-methoxybenzyl)thio)-1H-benzo[d]imidazol-1-yl)ethoxy)ethan-1-ol **(17)**

General procedure xxi. NaH dispersion (60%, 0.25 g, 6.2 mmol) was weighed in a two-necked flask and placed under N_2 atmosphere. Dry THF (10 mL) was added to the flask, followed by 2-bromoacetic acid (0.29 g, 2.1 mmol) and TBAI (51 mg, 10 mol-%). The solution was warmed to 50 °C and 2-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1H-benzo[d]imidazol-1-yl)ethan-1-ol **(7n)** (0.51 g, 1.4 mmol) in dry THF (10 mL) was added gradually to the warm solution. The reaction was left to proceed at 50 °C for overnight. The solution was cooled down, and EtOAc (2 mL) and water (2 mL) were added. The pH of the aqueous layer was adjusted to ~5 and was extracted with EtOAc. The combined organic phases were dried over anhydrous $MgSO_4$. After filtration, the concentrated crude material was dissolved in DCM and filtered through a silica plug with DCM/MeOH. The baseline fraction was collected and evaporated to dryness under reduced pressure. The collected material was dissolved in MeOH (10 mL) and H_2SO_4 (15 μL, 20 mol%) was added. The solution was refluxed at 60 °C for overnight. Once complete, the reaction mixture was cooled down to RT and concentrated. The residue was dissolved in EtOAc and washed with sat. $NaHCO_3$ and brine, and was dried over anhydrous $MgSO_4$. Filtration and concentration gave methyl 2-(2-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[*d*]imidazol-1-yl)ethoxy)acetate as colourless oil (0.53g, 87% over two steps).
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (9H, s), 3.70 (3H, s), 3.75 (3H, s), 3.88 (2H, t, *J* = 6.6 Hz), 4.04 (2H, s), 4.05 (2H, s), 4.55 (2H, t, *J* = 6.9 Hz), 6.76 (2H, d, *J* = 8.7 Hz), 7.15 (2H, d, *J* = 8.7 Hz), 7.20 (1H, d, *J* = 1.8 Hz), 7.26 (1H, d, *J* = 8.4 Hz), 7.79 (1H, d, *J* = 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.9 (3xC), 34.3, 40.6, 45.0, 52.0, 53.3, 68.5, 69.6, 109.9, 113.9 (2xC), 122.8, 126.5, 128.7, 130.0 (2xC), 130.1, 136.0, 142.4,

158.7, 161.5; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{24}H_{30}N_2O_4S$ 443.1999, found 443.1993.

Methyl 2-(2-(2-(*tert*-butyl)-5-((4-methoxybenzyl)thio)-1*H*-benzo[*d*]imidazol-1-yl)ethoxy)acetate (0.36 g, 0.82 mmol) was treated with DIBAL-H (3.3 mL, 1.0 M in hexane, 3.3 mmol) according to the general procedure ***xvi***. The crude product **17** (light yellow oil, 0.31 g, 91%) was carried over to the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (9H, s), 2.32 (1H, bs), 3.52 (2H, t, J = 4.8 Hz), 3.68 (2H, t, J = 4.8 Hz), 3.74 (3H, s), 3.82 (2H, t, J = 6.3 Hz), 4.03 (2H, s), 6.75 (2H, d, J = 8.7 Hz), 7.14 (2H, dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz), 7.18 (1H, d, J = 1.8 Hz), 7.24 (1H, d, J = 8.4 Hz), 7.79 (1H, d, J = 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 29.9 (3xC), 34.3, 40.6, 45.2, 55.3, 61.7, 69.6, 72.8, 110.0, 113.9 (2xC), 122.8, 126.4, 128.8, 130.0 (2xC), 130.1, 136.0, 142.2, 158.7, 161.4; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{23}H_{30}N_2O_3S$ 415.2050, found 415.2043.

2-(2-(2-(tert-butyl)-5-(ethylsulfonyl)-1H-benzo[d]imidazol-1-yl)ethoxy)ethyl 4-methylbenzenesulfonate **(18)**

Intermediate **17** (0.25 g, 0.61 mmol) was deprotected and reacted with ethyl bromide (0.11 mL, 1.5 mmol) according to the general methods ***vi*** and ***ix***. Purification of the crude material on silica gel using EtOAc:Hex (1:1) afforded 2-(2-(2-(*tert*-butyl)-5-(ethylthio)-1*H*-benzo[*d*]imidazol-1-yl)ethoxy)ethan-1-ol as yellow oil (0.19 g, 97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, t, J = 7.5 Hz), 1.55 (9H, s), 2.90 (2H, q, J = 7.2 Hz), 3.54 (2H, m), 3.71 (2H, m), 3.85 (2H, t, J = 6.3 Hz), 4.52 (2H, t, J = 6.6 Hz), 7.28 (2H, m), 7.79 (1H, d); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 29.8, 30.1 (3xC), 34.4, 45.3, 61.9, 69.8, 72.9, 110.1, 122.5, 126.1, 128.9, 136.1, 142.6, 162.0; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{17}H_{26}N_2O_2S$ 323.1788, found 323.1784.

2-(2-(2-(*tert*-butyl)-5-(ethylthio)-1*H*-benzo[*d*]imidazol-1-yl)ethoxy)ethan-1-ol (0.17 g, 0.53 mmol) was oxidised to the corresponding sulfone using the general procedure ***x***. The product was isolated as a crude material (light yellow oil 0.16 g, 86%) and carried over to the next step without purification. 2-(2-(2-(*tert*-butyl)-5-(ethylsulfonyl)-1*H*-benzo[d]imidazol-1-yl)ethoxy)ethan-1-ol (0.15 g, 0.42 mmol) was reacted with tosyl chloride (0.13 g, 0.68 mmol) according to the general method ***xx***.

The crude material was purified on silica gel using EtOAc:Hex (1:2 → 1:1) to give the product **18** as clear, viscous oil (0.13 g, 54%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (3H, t, *J* = 7.5 Hz), 1.56 (9H, s), 2.45 (3H, s), 3.11 (2H, q, *J* = 7.5 Hz), 3.62 (2H, m), 3.84 (2H, t, *J* = 6.0 Hz), 4.08 (2H, m), 4.55 (2H, t, *J* = 6.0 Hz), 7.35 (2H, d, *J* = 8.1 Hz), 7.53 (1H, d, *J* = 8.7 Hz), 7.74 (1H, d, *J* = 8.1 Hz), 7.74 (1H, dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 8.30 (1H, d, *J* = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.8, 21.8, 29.9 (3xC), 34.6, 45.6, 51.1, 69.0 (2xC), 70.0, 111.1, 120.6, 122.0, 127.9 (2xC), 130.1 (2xC), 132.0, 132.9, 140.3, 141.1, 145.2, 163.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{24}H_{32}N_2O_6S$ 509.1775, found 509.1771; HPLC-purity >97%, RT = 21.5 min.

Radiochemistry

General

^{18}F isotope was produced from [^{18}O]H_2O using (p,n) reaction on a medical cyclotron (18 MeV, IBA, Netherlands) by running a current of 14 μA for the required time (0.25 - 0.5 h). The target water was then transferred into a hot-cell and trapped in an anion exchange cartridge (Light QMA carb, 45 mg or 130 mg, Waters, unless otherwise stated). The radiolabelling was either conducted manually on a heater block or on an automated synthesis module (Synthra RN_{plus}, Synthra GmbH, Hamburg, Germany). Quantification of radioactivity measurements was done using CRC-25PET (Capintec Inc., USA) or VDC-505 (Veenstra, Netherlands) dose calibrators. Radioactive yields are reported as non-decay corrected, isolated yields at the end of synthesis and are based on the starting activity that was measured with the dose calibrator at the end of transfer from cyclotron to the hot cell. High-performance liquid chromatography (HPLC) analysis was performed on a LabSolutions system (Shimadzu, LC-20AD and CTO-20A) connected to a PDA ultraviolet spectrometer (λ = 254 nm). The eluate was directed after passage of UV-detector through a scintillation detector (Bioscan, Eckert&Ziegler, Germany) connected to a (single or multi)channel analyser for the analysis of radioactive compounds.

Radiosynthesis

The [^{18}F]fluoride was eluted from the QMA cartridge with a solution of Kryptofix® $K_{2.2.2.}$ (4 mg) and K_2CO_3 (0.69 mg, 5 μmol) dissolved in 500 μL of water and 500 μL of acetonitrile. The mixture was dried under flow of helium and reduced pressure at 68 °C for 5 min and at 95 °C for 7 min. The required 2-Cl-pyridine precursor (1.5 mg/mL, DMSO) or tosylate precursor (1.5 mg/mL, MeCN) was added to the dried [^{18}F]-[K($K_{2.2.2}$)]F complex. The reaction was carried out at 130 °C for 15 min (2-Cl-pyridine precursors) or at 100 °C for 10 min, after which the reaction mixture was cooled to RT, diluted with water (1 mL) and loaded onto a 5 mL HPLC-loop. The purification of the product was performed on preparative HPLC (Agilent Zorbax Eclipse XDB-C18 (9.4 × 250 mm, 5 μm) using the eluent conditions described in the supplementary information. The desired radioactive product was collected in a

reformulation vessel containing 40 mL of H_2O. The product solution was then trapped in Sep-pak Light C18 (Waters) that was preconditioned with ethanol (10 mL), H_2O (10 mL) and air (2 × 10 mL). The cartridge was washed with H_2O (10 mL), and the product was eluted out with ethanol (1 mL) to a sterile vial containing saline (0.9%, 9 mL). Na-ascorbate (5 mg/mL) was added to the formulation of the final product (**[^{18}F]-1e,** (**[^{18}F]-1g** and **[^{18}F]-3l**), or additionally, in HPLC-eluent (0.5% w/v), reformulation vessel (5 mg/mL) and C18-SPE cartridge washing solution (5 mg/mL) (**[^{18}F]-3l)**. Non-decay corrected, isolated radioactive yields were 24 ± 5% **[^{18}F]-1d** (n = 8), 26 ± 6% **[^{18}F]-1e** (n = 3**)**, 28% (**[^{18}F]-1g**, n = 1) and 43 ± 4% (**[^{18}F]-3l**, n = 4) at the end of synthesis. The molar activities were measured by using linear UV-calibration curves prepared from the ^{19}F-standards. The average molar activities were 263 ± 56 GBq/μmol (**[^{18}F]-1d**), 158 ± 32 GBq/μmol (**[^{18}F]-1e**), 128 GBq/μmol (**[^{18}F]-1g**) and 115 ± 64 GBq/μmol (**[^{18}F]-3l**). Radiochemical purity was confirmed to be over 95% for all the radioligands produced.

Radiolabelling of tosylate precursor 16e

Analytical UV- and HPLC-chromatograms of the reaction mixtures highlighted significant degradation of the precursor. Attempts to improve radiolabelling by decreasing the quantities of base in the labelling reactions (entries 4 – 7) also failed to produce any of the desired product. In a few of these reactions, formation of some [^{18}F]tosylfluoride was observed. The side product was identified by labelling a prosthetic group methyl bistosylate with [^{18}F]F$^-$, which is known to result in a mixture of product [^{18}F]fluoromethyltosylate and [^{18}F]tosylfluoride.[1]

Table 1. Conditions tested in the [^{18}F]fluorination of tosylate precursor **16e**.

Entry[a]	Cartridge	Base[b]	$K_{2.2.2.}$/μmol	Solvent	T / °C	RCY/%
1	QMA-carb	K_2CO_3	10	MeCN	150	0
2	QMA-carb	K_2CO_3	10	DMSO	150	0
3	QMA-carb	K_2CO_3	10	DMF	150	0
4	QMA-carb	$KHCO_3$	5	MeCN	86	0
5[c]	PS-HCO_3^-	$KHCO_3$	40	*t*-BuOH	86	0
6	not used	$KHCO_3$	5	MeCN	86	0[d]
7	not used	$KHCO_3$	5	*t*-BuOH	86	0[d]

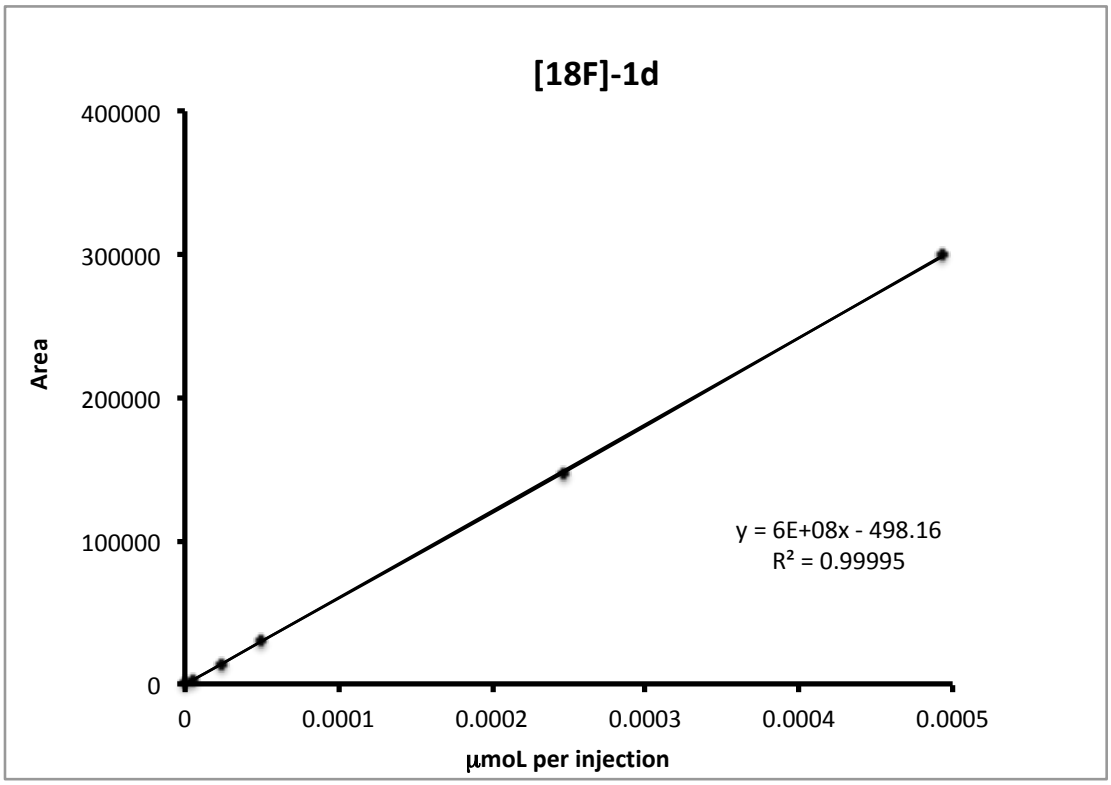
[a] Reaction time 5 min; [b] 5 μmol of base; [c] Elution of [^{18}F]F^- from PS-HCO_3^- (45 mg) cartridge with KOMs (0.2 M, 0.1 mL) in MeOH (0.8 mL) and azeotropic drying with MeCN; [d] [^{18}F]tosylfluoride by-product observed.

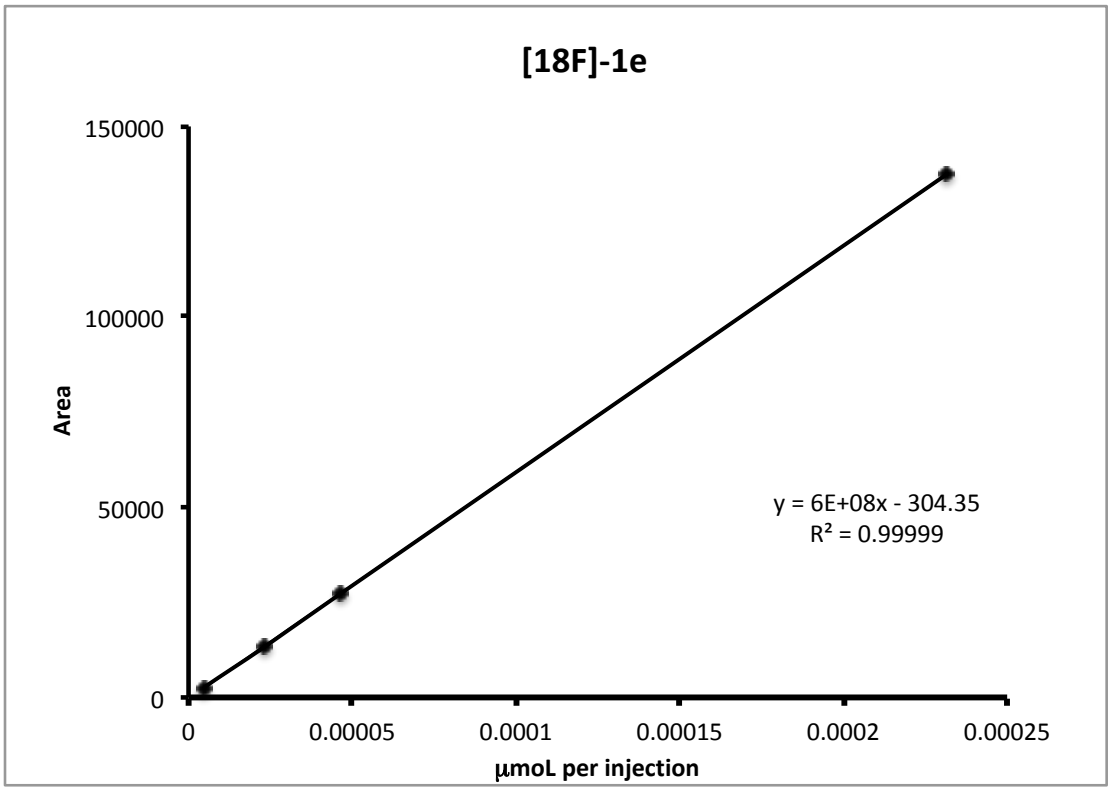
HPLC conditions

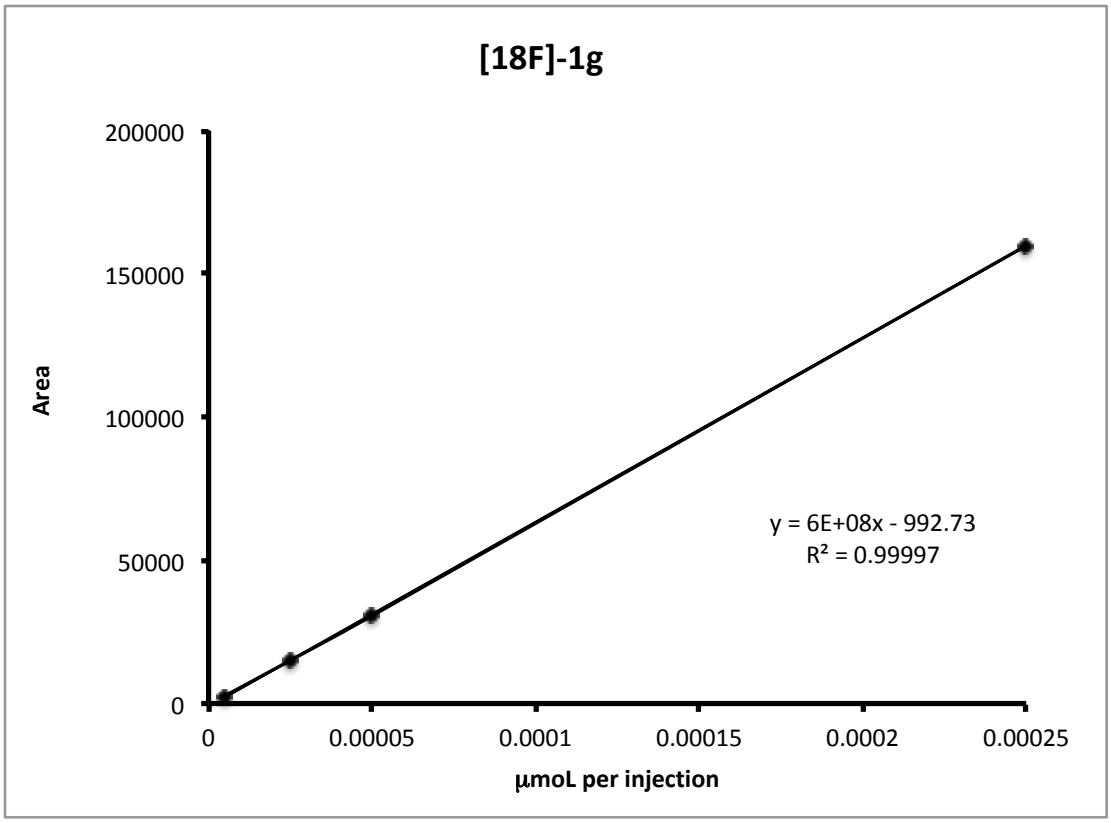
The chemical and radiochemical purity of the products were analysed on analytical HPLC (Agilent Eclipse Plus, C18, 4.6 × 150 mm), and the purification of the radiotracers was carried out on a preparative scale column Zorbax Eclipse XDB-C18 (9.4 × 250 mm, 5 μm). The HPLC conditions used and the retention times of radioligands were the following:

Radioligand	Analytical HPLC	T_r (min)	Preparative HPLC	T_r (min)
[^{18}F]-1d	MeCN:H_2O (50:50), 1 mL/min	7.5	MeCN:H_2O (50:50), 4 mL/min	14.5
[^{18}F]-1e	MeCN:H_2O (50:50), 1 mL/min	5.8	MeCN:H_2O (40:60), 4 mL/min	21.5
[^{18}F]-1g	MeCN:H_2O (50:50), 1 mL/min	5.8	MeCN:H_2O (50:50), 4 mL/min	12.0
[^{18}F]-3l	MeCN: 0.1 M NH_4OAc (40:60), 1 mL/min	6.1	MeCN:NH_4OAc (30:70), 0.5% Na-ascorbate (w/v), 4 mL/min	25.5

The molar activites were determined from the following calibration curves:



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150000
100000
50000
0
Area
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R² = 0.99997
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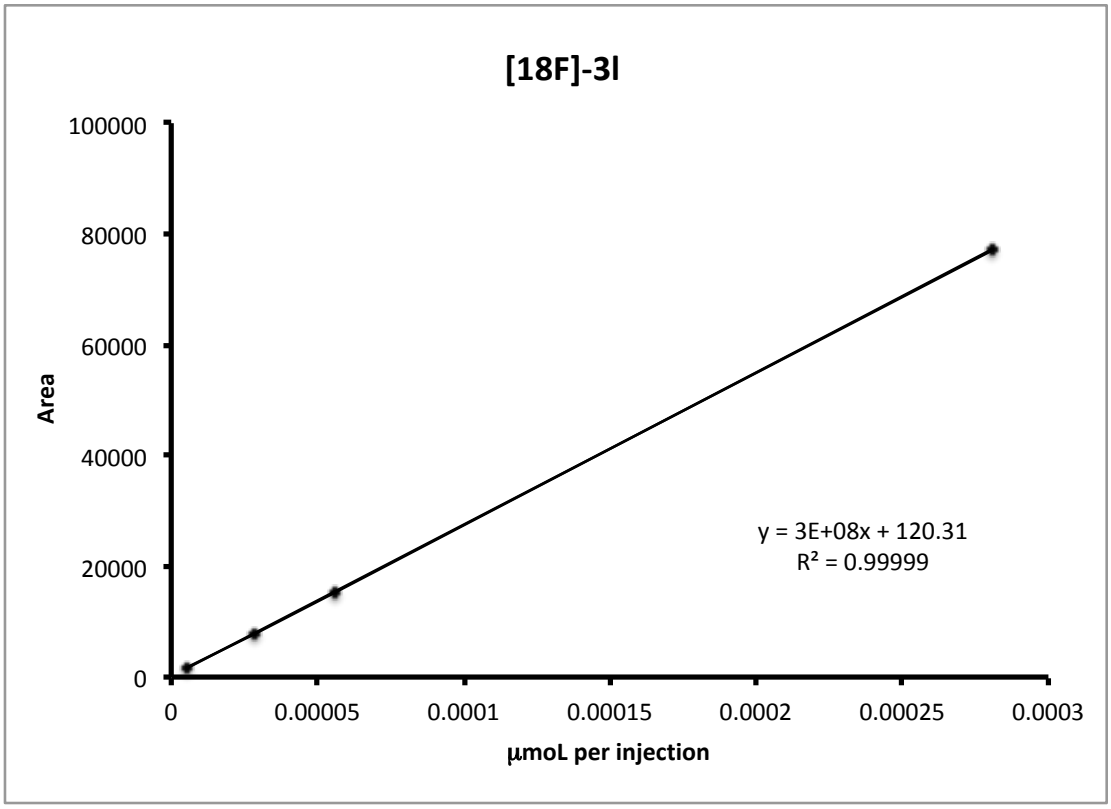
0.0001
0.00015
0.0002
0.00025
µmoL per injection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R² = 0.99999
0
0.00005
0.0001
0.00015
0.0002
0.00025
0.0003
µmoL per injection

Functional activity in fluorometric membrane potential assay

AtT20 neuroblastoma cells expressing CB1 or CB2 were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS), 100 U penicillin/streptomycin, 80 μg/mL of hygromycin, as described previously.[2] Cells were plated for assay in black-walled, clear bottomed 96-well microplates (Corning) in a volume of 90 μL of Leibovitz's L-15 media supplemented with 1% FBS, 100 U penicillin/streptomycin and 15 mM glucose and incubated overnight at 37 °C in ambient CO_2.

Membrane potential was measured using a FLIPR Membrane Potential Assay kit (blue) from Molecular Devices, as described previously.[3] The dye was reconstituted with assay buffer (145 mM NaCl, 22 mM HEPES, 0.338 mM Na_2HPO_4, 4.17 mM $NaHCO_3$, 0.441 mM KH_2PO_4, 0.407 mM $MgSO_4$, 0.493 mM $MgCl_2$, 1.26 mM $CaCl_2$, 5.56 mM glucose (pH 7.4, osmolarity 315 ± 5 mOsm). Dye solution (90 μL/well) was added to the plates without removal of the L-15. Plates were then incubated at 37 °C at ambient CO_2 for 60 min. Fluorescence was measured using a FlexStation 3 (Molecular Devices) microplate reader with cells excited at a wavelength of 530 nm and emission measured at 565 nm. Baseline readings were taken every 2 s for at least 60s, at which time either drug or vehicle was added in a volume of 20 μL. The background fluorescence of cells without dye or dye without cells was negligible. Changes in fluorescence were expressed as a percentage of predrug fluorescence after subtraction of the changes produced by vehicle (DMSO, 0.1% final concentration) addition.

Data were analyzed with Prism, using four-parameter nonlinear regression to fit concentration-response curves. A full CP-55940 concentration response curve was done every day, and a maximally effective concentration of CP-55940 (1 μM) was included in each column of each plate to facilitate comparisons between experiments.

Binding affinity measurement

Cell culture & compounds

CHO cells stably transfected with human CB1 and CB2 receptors (as in Grimsey *et al*., 2010) were cultured in Dulbecco Modified Earl's Medium: Ham's F-12 Nutrient Mixture (Invitrogen, CA, U.S.A.) supplemented with 10% FBS (Invitrogen), penicillin-streptomycin (100U, 0.1mg/mL) and geneticin (0.5 mg/mL).[4] All chemicals and solvents were obtained from Sigma-Aldrich (St Louis, MO, U.S.A) or Perkin Elmer (Beaconsfield, UK) unless indicated otherwise.

Radioligand binding assay

CHO cells were harvested by incubation in 0.04% EDTA in PBS, then by being scraped from flasks. After centrifugation, the supernatant was aspirated, and resulting cells homogenised in homogenisation buffer (15 mM Hepes, 0.3 mM EDTA, 1 mM EGTA, 2 mM $MgCl_2$, pH 7.4) using a hand-held Ultra-Turrax homogeniser (IKA Werke, Staufen, Germany) (3 x 10 second pulses). The homogenate was centrifuged three times (48,000 *g*) using an Avanti J-E centrifuge and resuspended in cold storage buffer (75 mM Tris, 0.3 mM EDTA, 1 mM EGTA, 12.5 mM $MgCl_2$, 250 mM sucrose, pH 7.4). A bicinchoninic acid assay (BCA) was performed (Thermo Scientific, IL, U.S.A.) according to the manufacturer's protocol, and the membrane was stored at -80°C. For saturation binding, 20 μg/well of membrane solution was diluted in binding buffer (50 mM Tris-HCl, 12 mM $MgCl_2$, 2.5 mM EGTA, and 2% fatty acid-free BSA, pH 7.4) and incubated with 0.06 - 2.6 nM of [^{3}H]CP-55940 (Perkin Elmer, M.A., U.S.A.), in the presence of 0.1% DMSO control solution, or 25μM unlabelled CP-55940 to index non-specific binding. The reaction was incubated for 3 h at room temperature to achieve equilibrium. Termination of the reaction was achieved by washing eight times with wash buffer (50 mM Tris-HCl, 5 mM $MgCl_2$, 2.5 mM EGTA, pH 7.4) via rapid filtration using a Brandel 96-sample vacuum harvester (Gaithersburg, MD, U.S.A.) through a glass-fibre filter (GF/B; Millipore, Carrigtwonhill, Ireland) pre-soaked in 0.3% polyethylenimine. The filters were dried overnight, Microscint-0 scintillation liquid added, and radioactivity measured using a Microbeta^2 2450 Microplate Counter (Perkin-Elmer). For competition binding, increasing concentrations of compounds were incubated with 20 μg of CB1 or CB2 membrane and ~K_d concentration of [^{3}H]CP-55940 (3 nM and 2 nM respectively). Non-specific binding was measured at an unlabelled CP-55,940

concentration of 25 μM. Incubation, harvesting and reading protocol follow that used in saturation binding.

Statistical Analysis

GraphPad Prism 7 (San Diego, CA, U.S.A.) was used for statistical analysis. Competition binding data were calculated by subtracting non-specific binding from total binding to give specific binding, and were expressed as a percentage of vehicle control. K_i values were calculated by comparing one- and two-site four-parameter non-linear regression fits, and are expressed as mean ± SEM from at least three independent experiments.

In vitro Autoradiography

In Vitro Autoradiography with **[^{18}F]-1d** and **[^{18}F]-3l** was performed on 20 μm rat spleen sections. The tissue sections were adsorbed to SuperFrost Plus slides. The tissue slices were pre-incubated with cold incubation buffer (50mM TRIS/HCL, pH 7.4 containing 5% BSA) for 10 min. Some slides were incubated with 5 nM of **[^{18}F]-1d** or 20 nM of **[^{18}F]-3l** alone. Adjacent slides were incubated with a mixture of 5 nM of **[^{18}F]-1d** or 20 nM of **[^{18}F]-3l** together with specific CB2 agonist (GW-405833, 10 μM) or respective ^{19}F-standards of **1d** (10 μM) and **3l** (10 μM) in incubation buffer. After incubation for 30 minutes at room temperature, slides were washed three times with ice cold washing buffer (50mM TRIS/HCL, pH 7.4 containing 1% BSA) for 1 min each. The tissue sections were then washed in distilled water for three successive washes to remove excess of buffer salts. Dried slices were exposed to a phosphor imager plate overnight and the plate was scanned in an AmershamTyphoon Biomolecular Imager (GE Healthcare, USA).

The analysis of the autoradiograms was done using the ImageQuant TL image analysis software from GE HealthCare. For the quantification, regions-of-interest (ROI) were drawn on the spleen images (n=10 spleen sections for each group) using an irregular shaped drawing tool, to measure the amount of radioactivity in the whole spleen section. Similar ROIs were drawn in a background region (n=10 regions) to enable background subtraction.

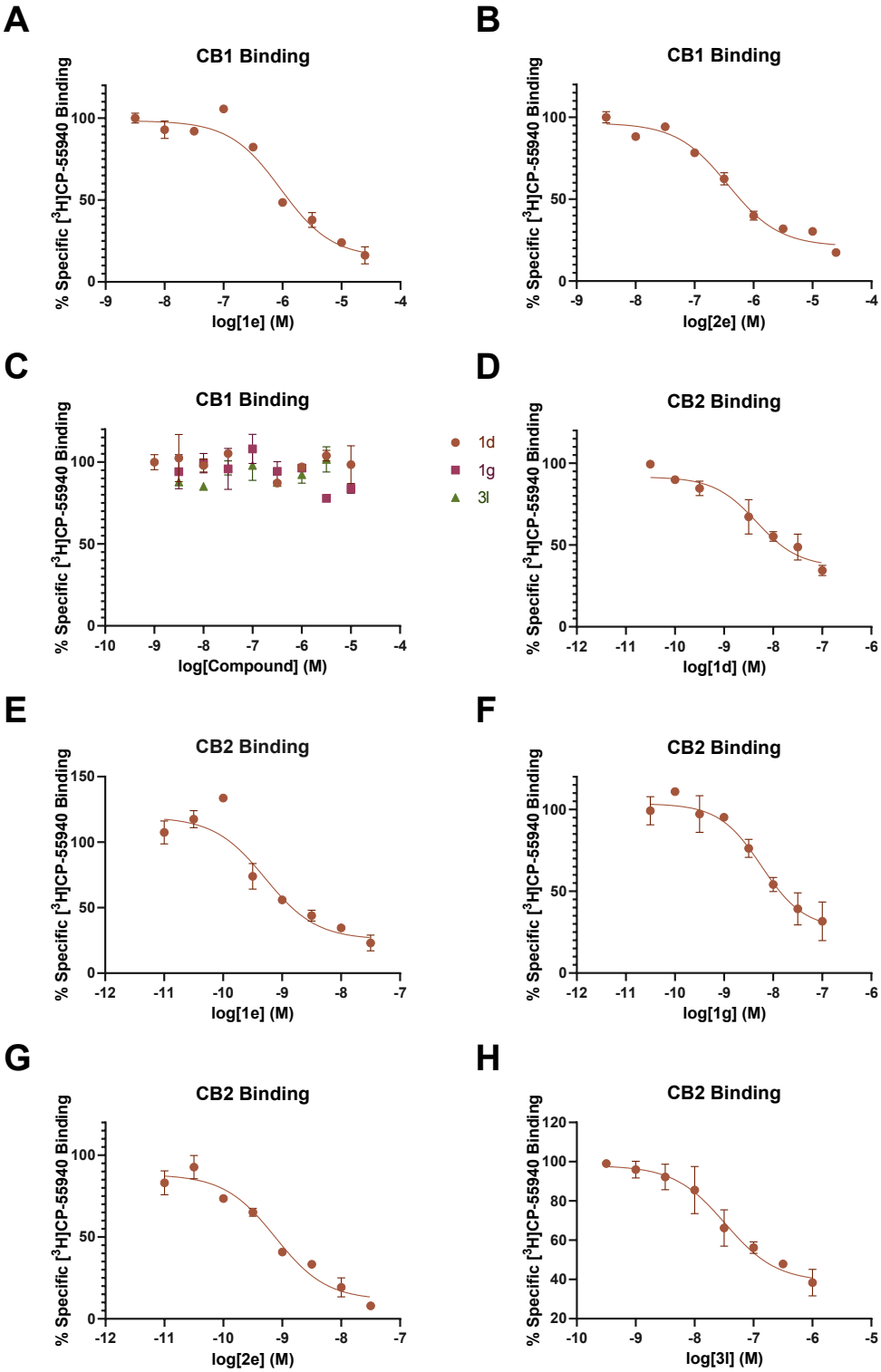

Figure 1: Displacement of [3H]-CP55940 by fluorinated benzimidazole sulfones at CHO cell membranes expressing CB1 or CB2 receptors. Displacement of 2 nM [3H]-CP55940 at (A) 1e, (B) 2e and (C) 1d, 1g and 3l at CB1-transfected CHO cell membranes. Displacement of 3 nM [3H]-CP55940 (D) 1d, (E) 1e, (F) 1g, (G) 2e and (H) 3l at CB2-transfected CHO cell membranes. Data are represented as mean ± S.E.M. of one experiment performed in duplicate that are representative of overall data from at least 3 experiments All compounds preferred a 1-site fit with a Hill slope of -1.

SHIMADZU LabSolutions

Analysis Report

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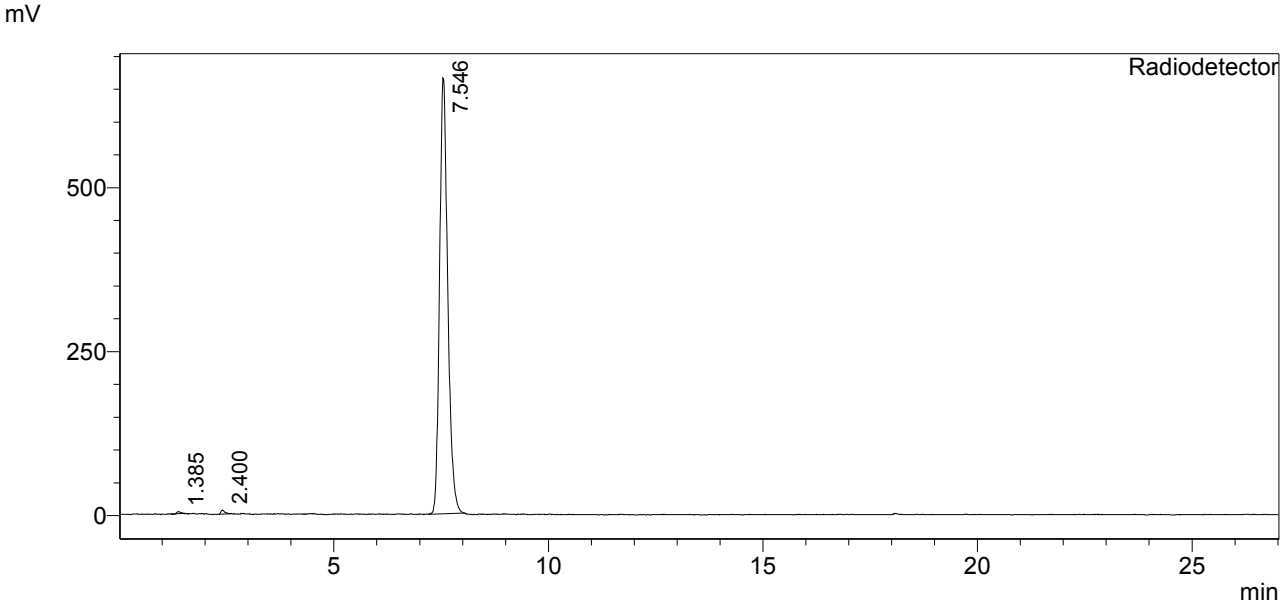

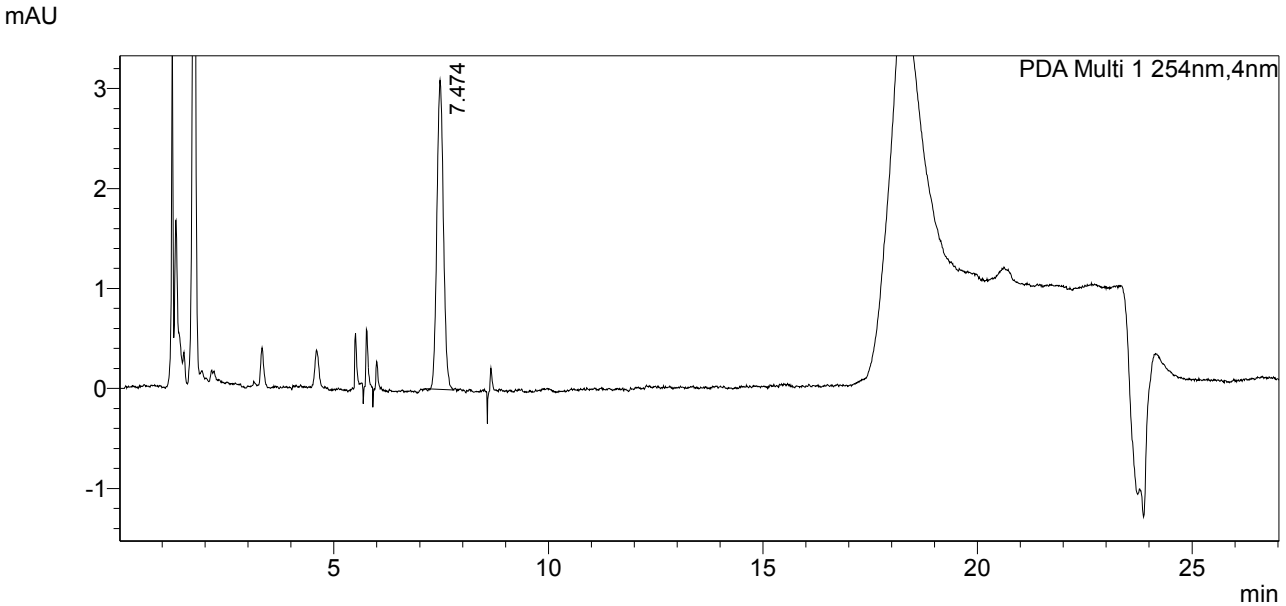

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2	2.400	36515	5808	0.413		M	
3	7.546	8786279	664212	99.391		M	
Total		8840115	673209				

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
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SHIMADZU LabSolutions

Analysis Report

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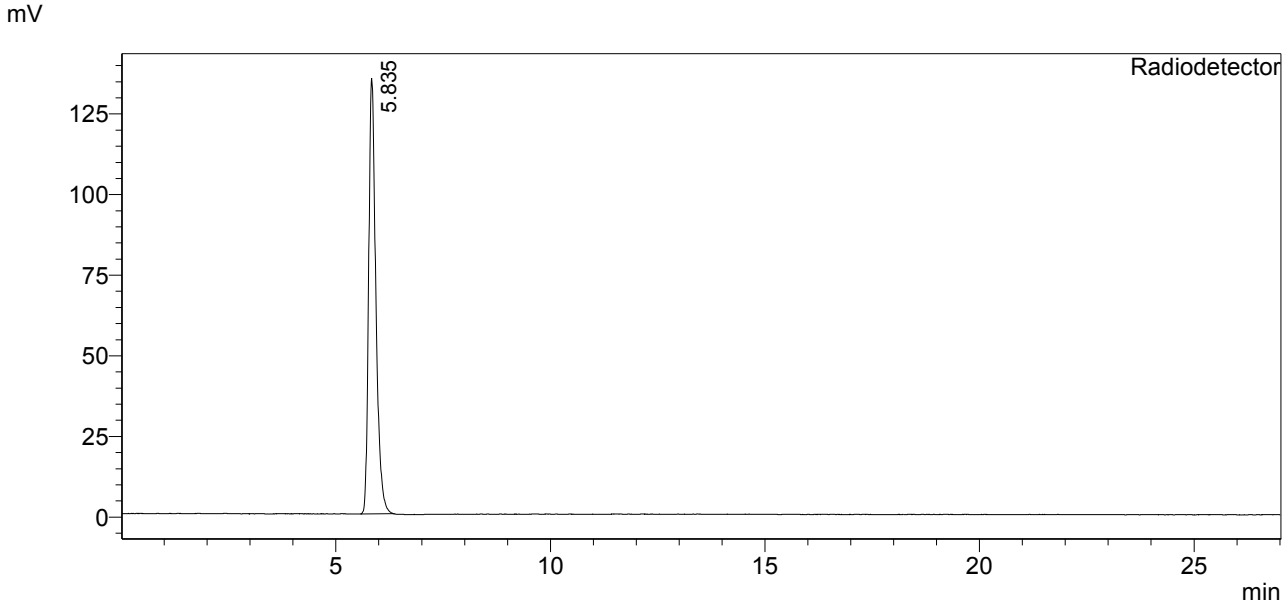

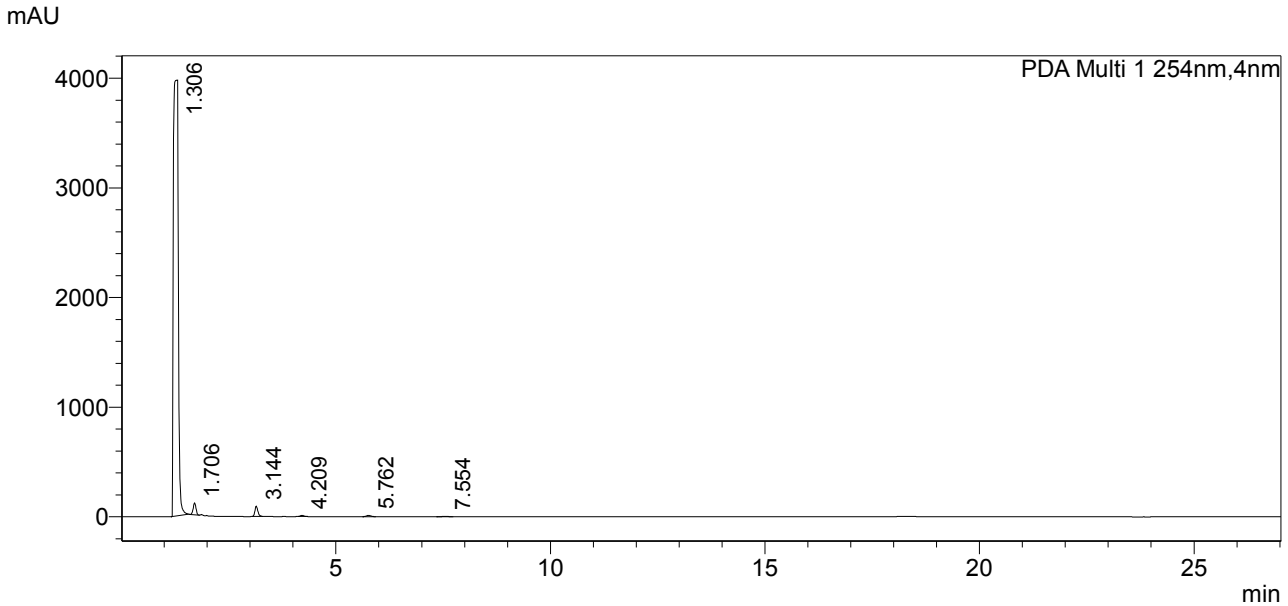

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PDA Ch1 254nm

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1	1.306	31645945	3972701	0.000		M	
2	1.706	487401	106448	0.000		M	
3	3.144	436528	92325	0.000		M	
4	4.209	55505	10105	0.000		M	
5	5.762	88043	11214	0.000		M	
6	7.554	29599	2997	0.000		M	
Total		32743021	4195791				

SHIMADZU LabSolutions

Analysis Report

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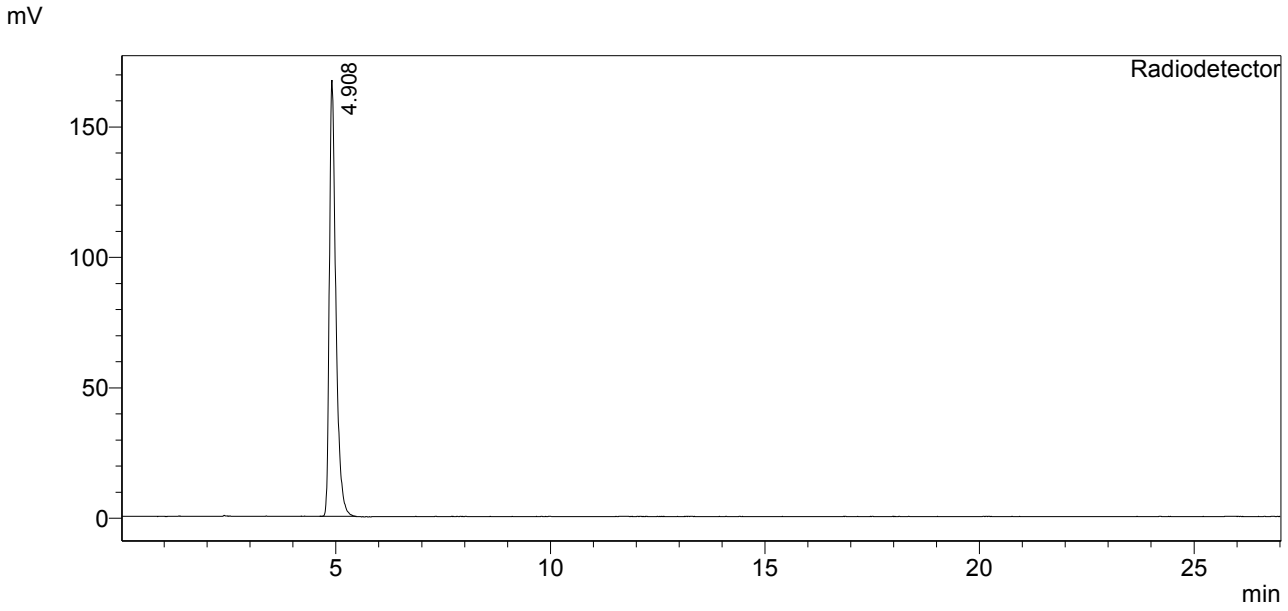

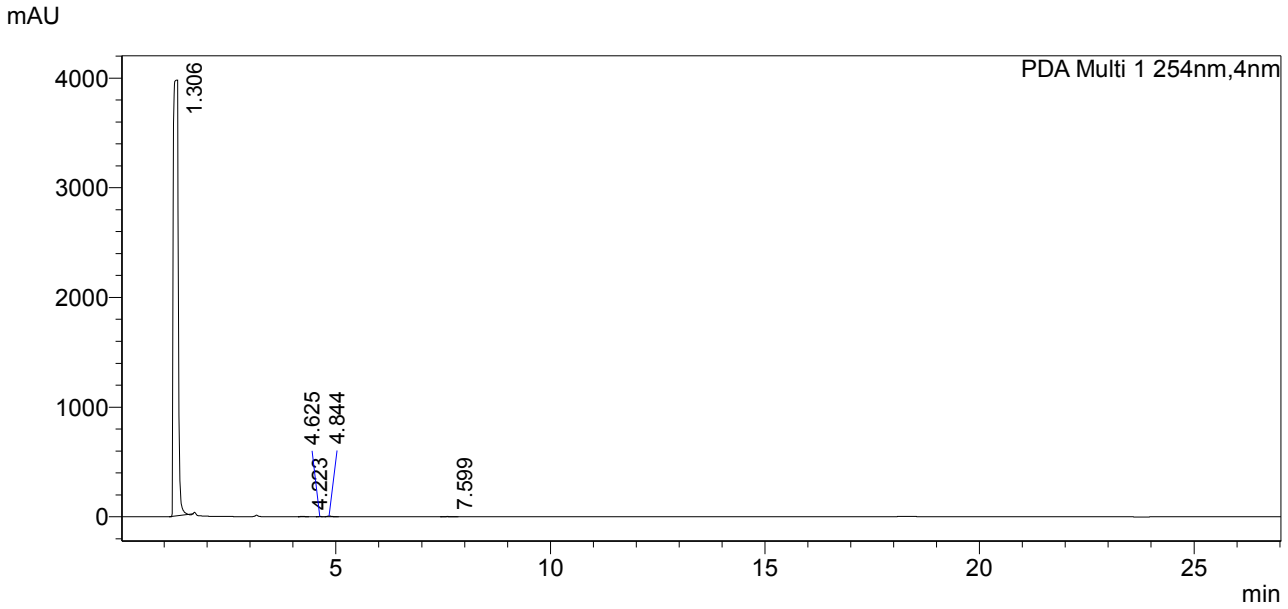

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PDA Ch1 254nm

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1	1.306	31959393	3971156	0.000		M	
2	4.223	20074	3425	0.000		M	
3	4.625	7392	1472	0.000		M	
4	4.844	39104	5673	0.000		M	
5	7.599	21765	2096	0.000		M	
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SHIMADZU LabSolutions

Analysis Report

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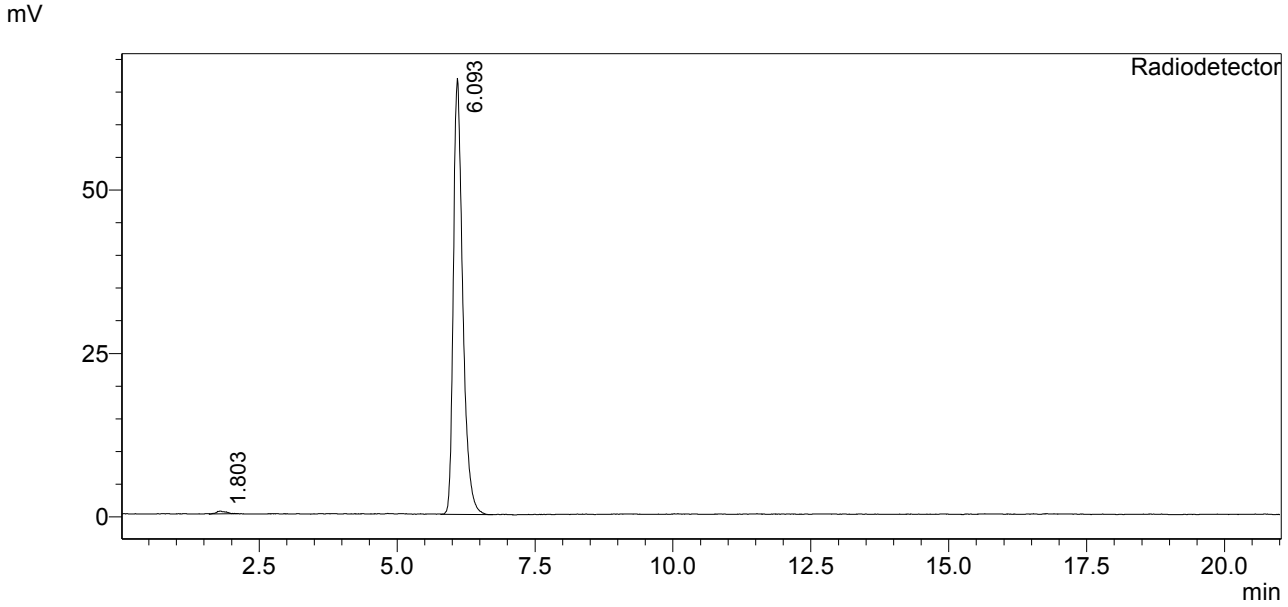

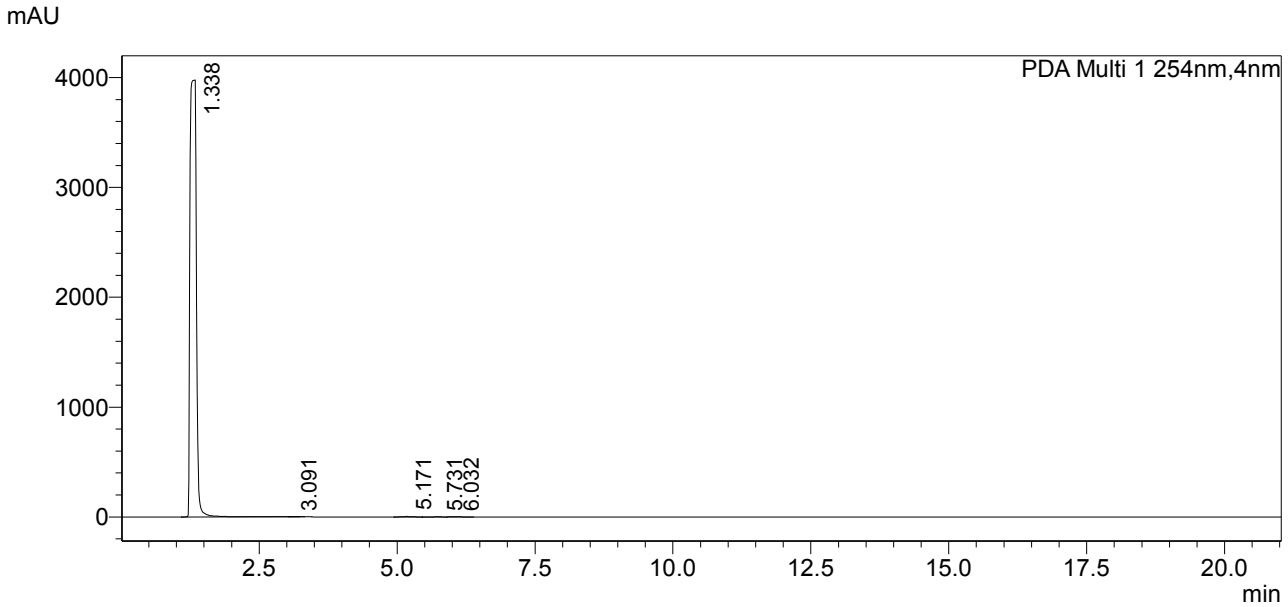

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Radiodetector

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PDA Ch1 254nm

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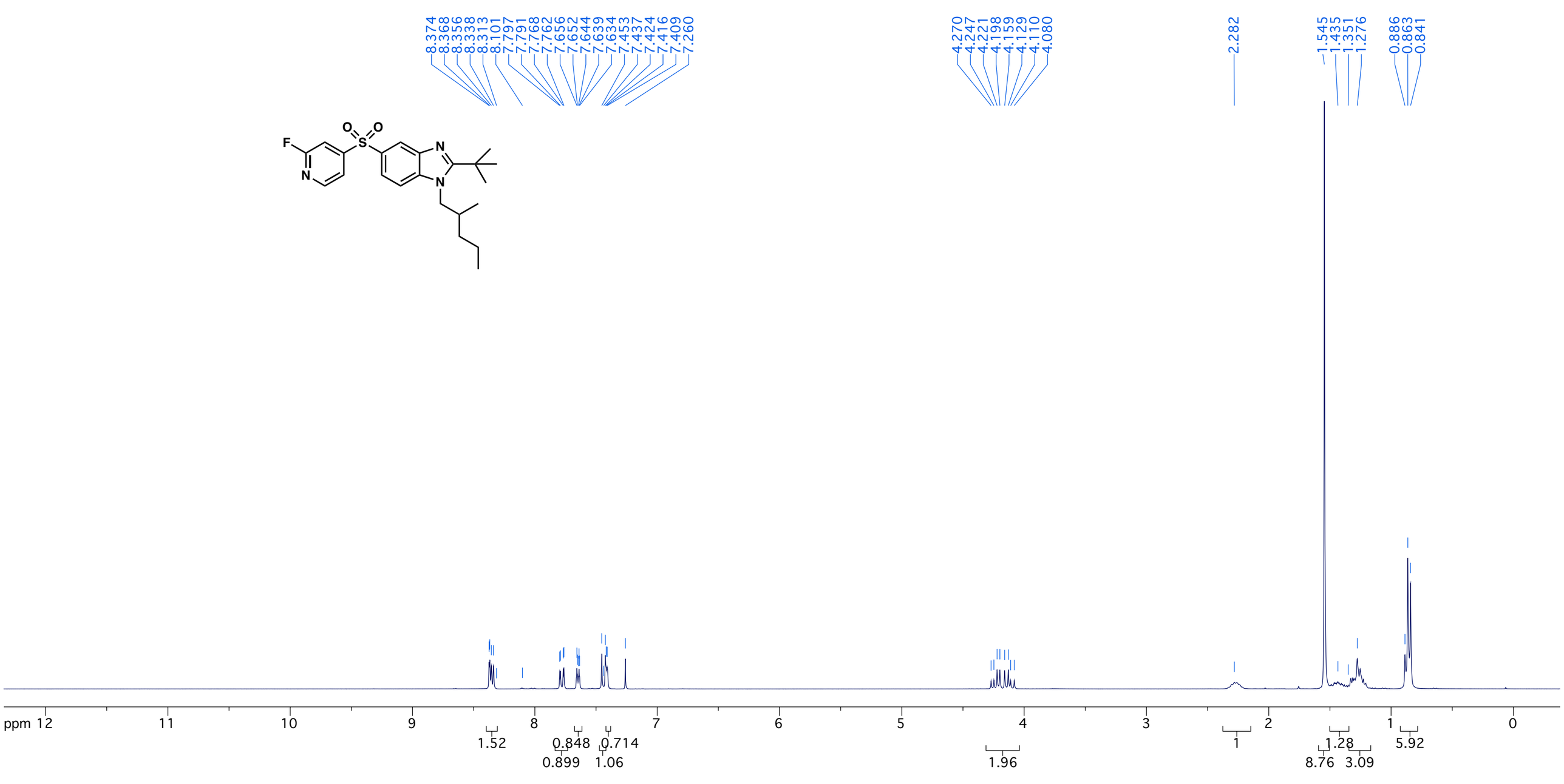
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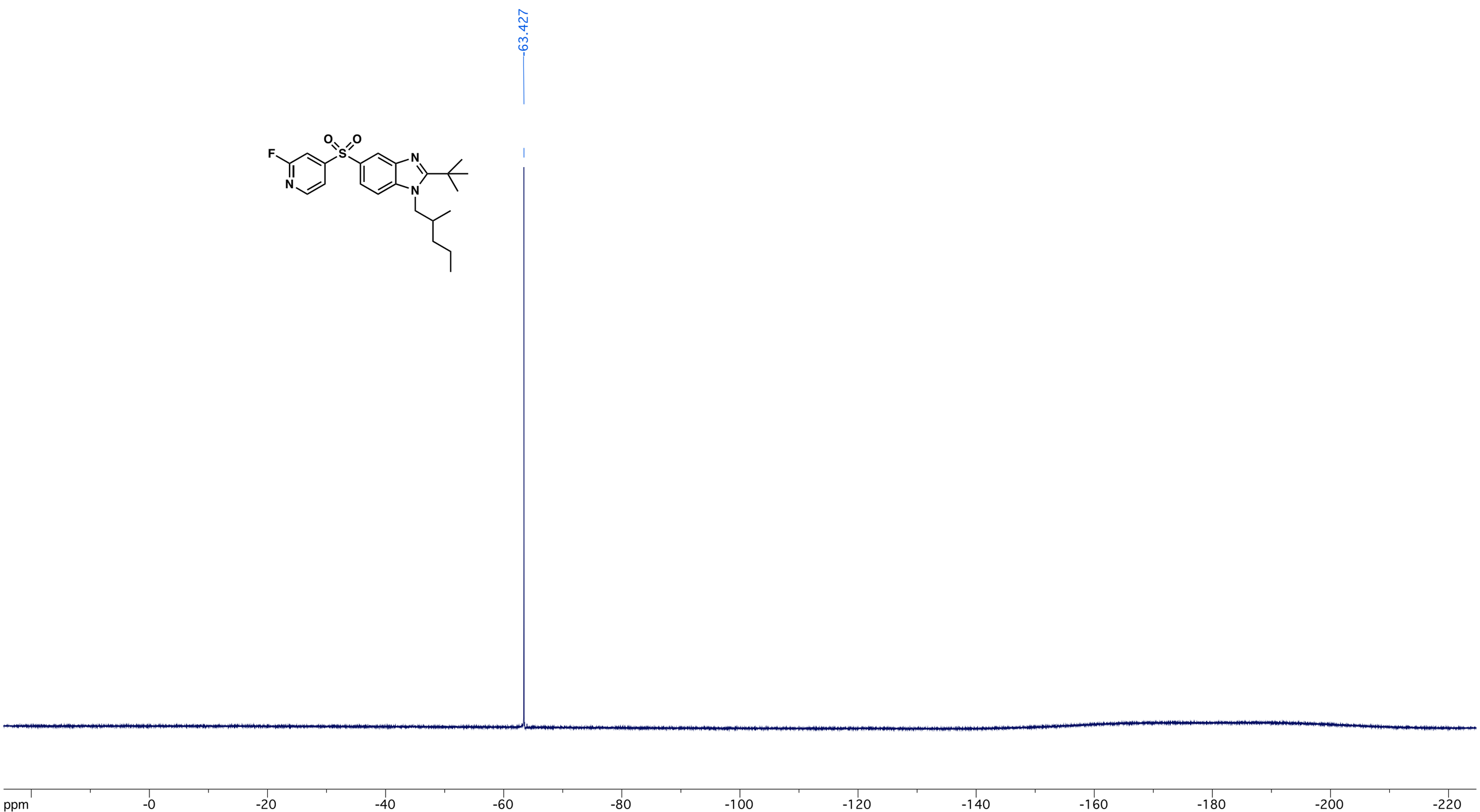
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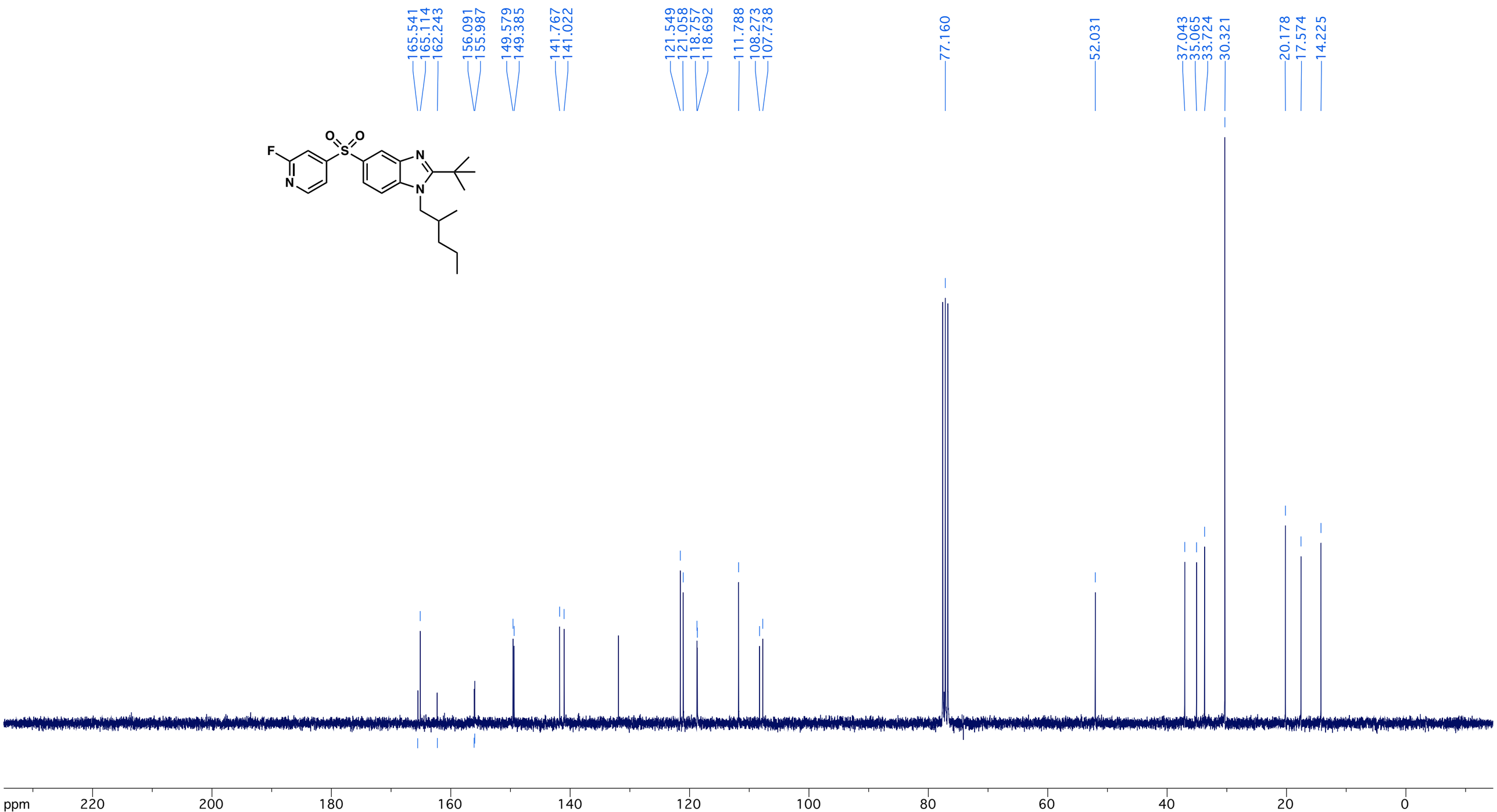
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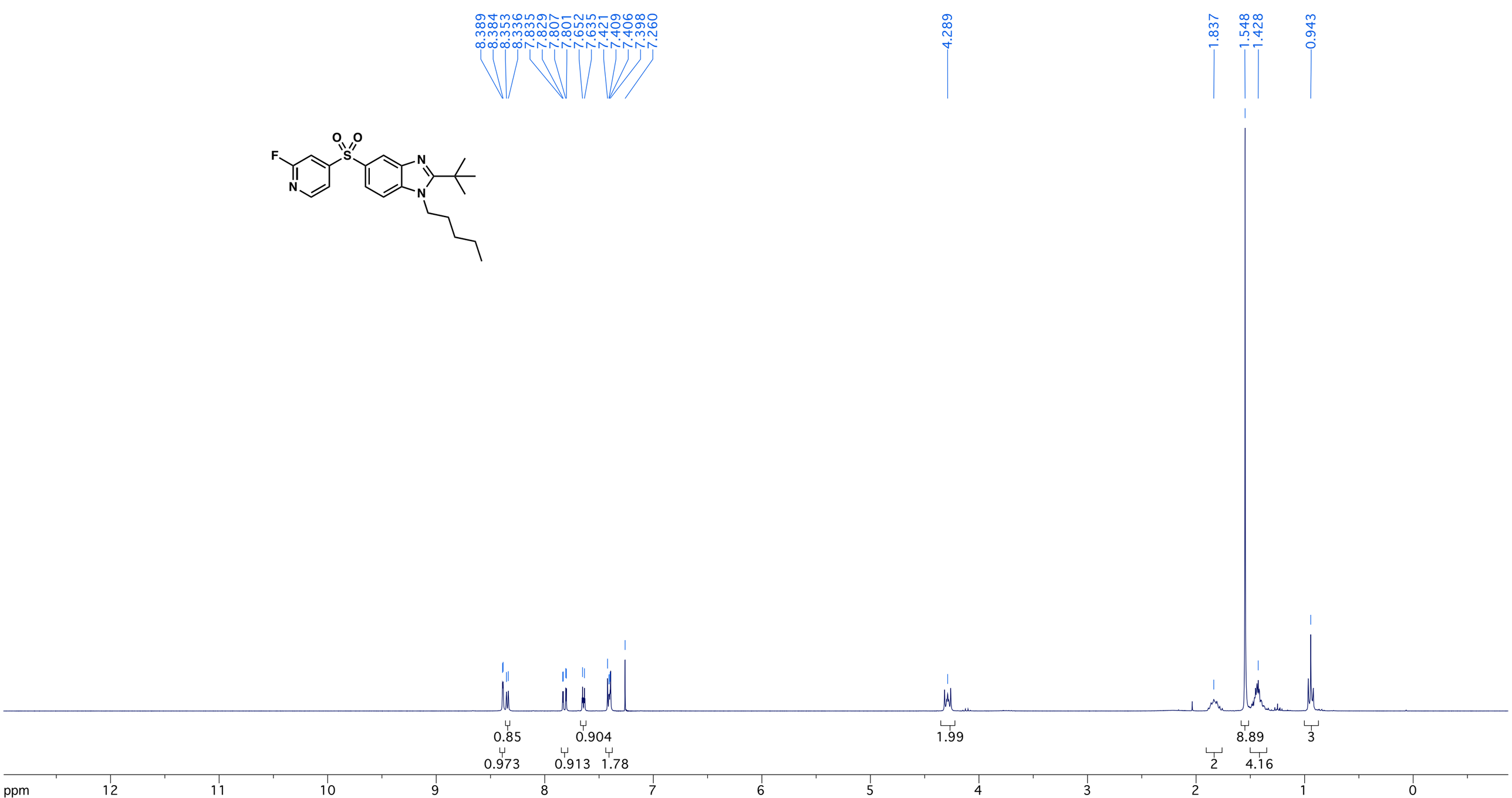
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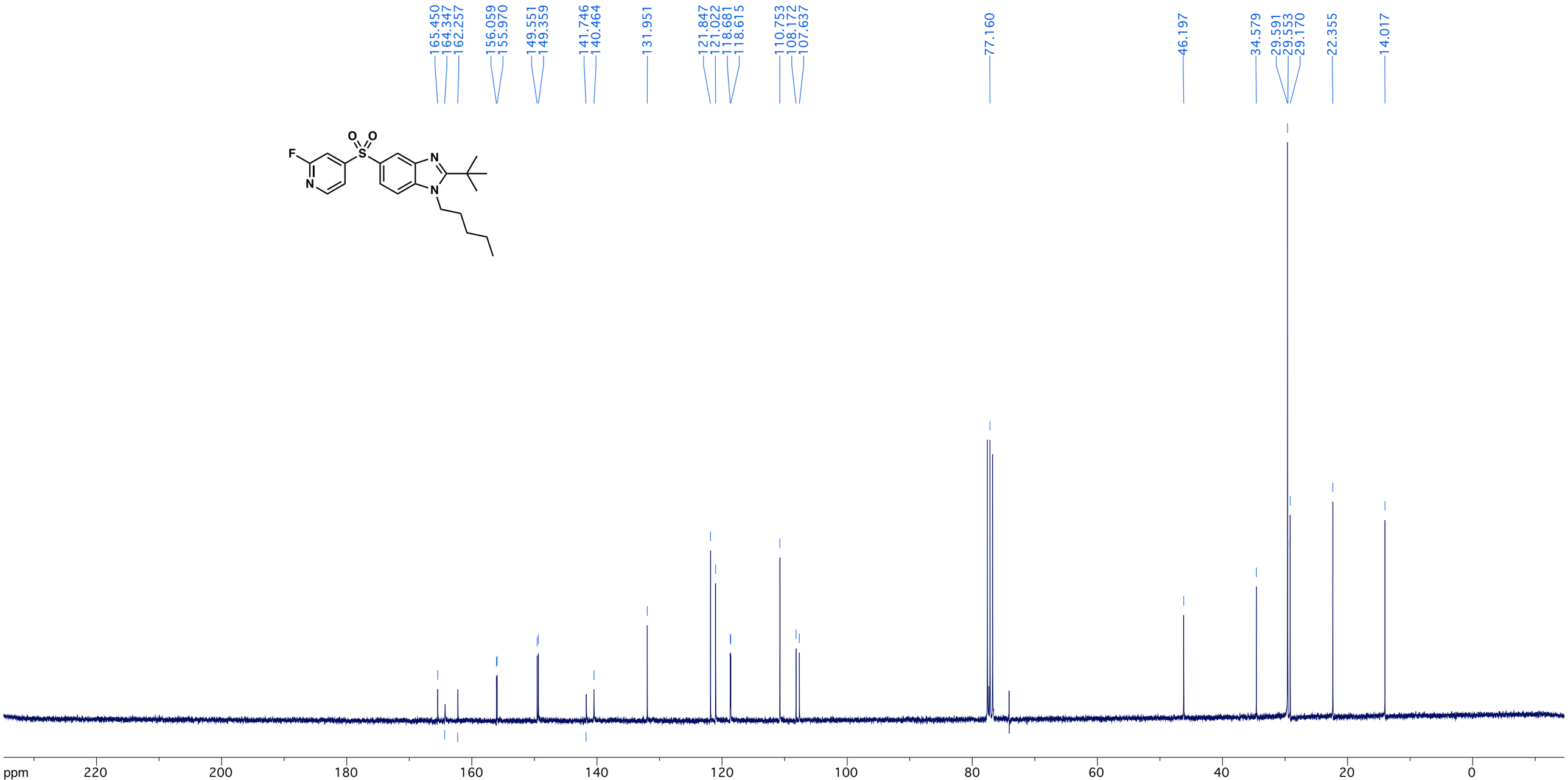
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141.746
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131.951
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121.022
118.681
118.615
110.753
108.172
107.637
77.160
46.197
34.579
29.591
29.553
29.170
22.355
14.017
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S
N
N
ppm
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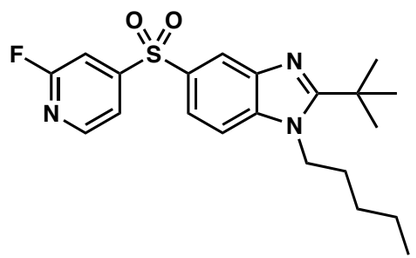
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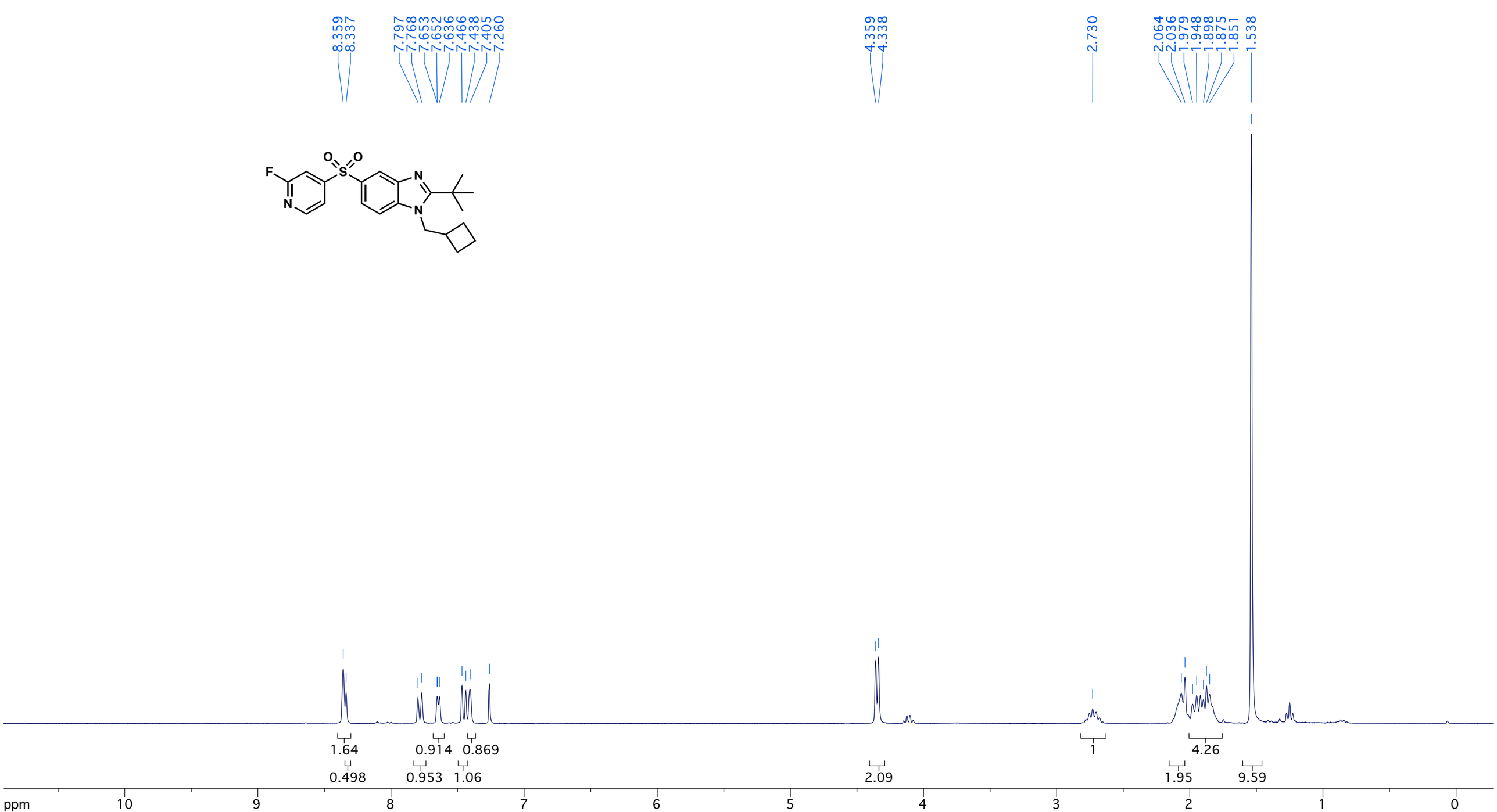
-150
-200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7.405
7.260
4.359
4.338
2.730
2.064
2.036
1.979
1.948
1.898
1.875
1.851
1.538
F
N
O
O
S
N
N
1.64
0.498
0.914
0.953
0.869
1.06
2.09
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1.95
4.26
9.59
ppm
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9
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7
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5
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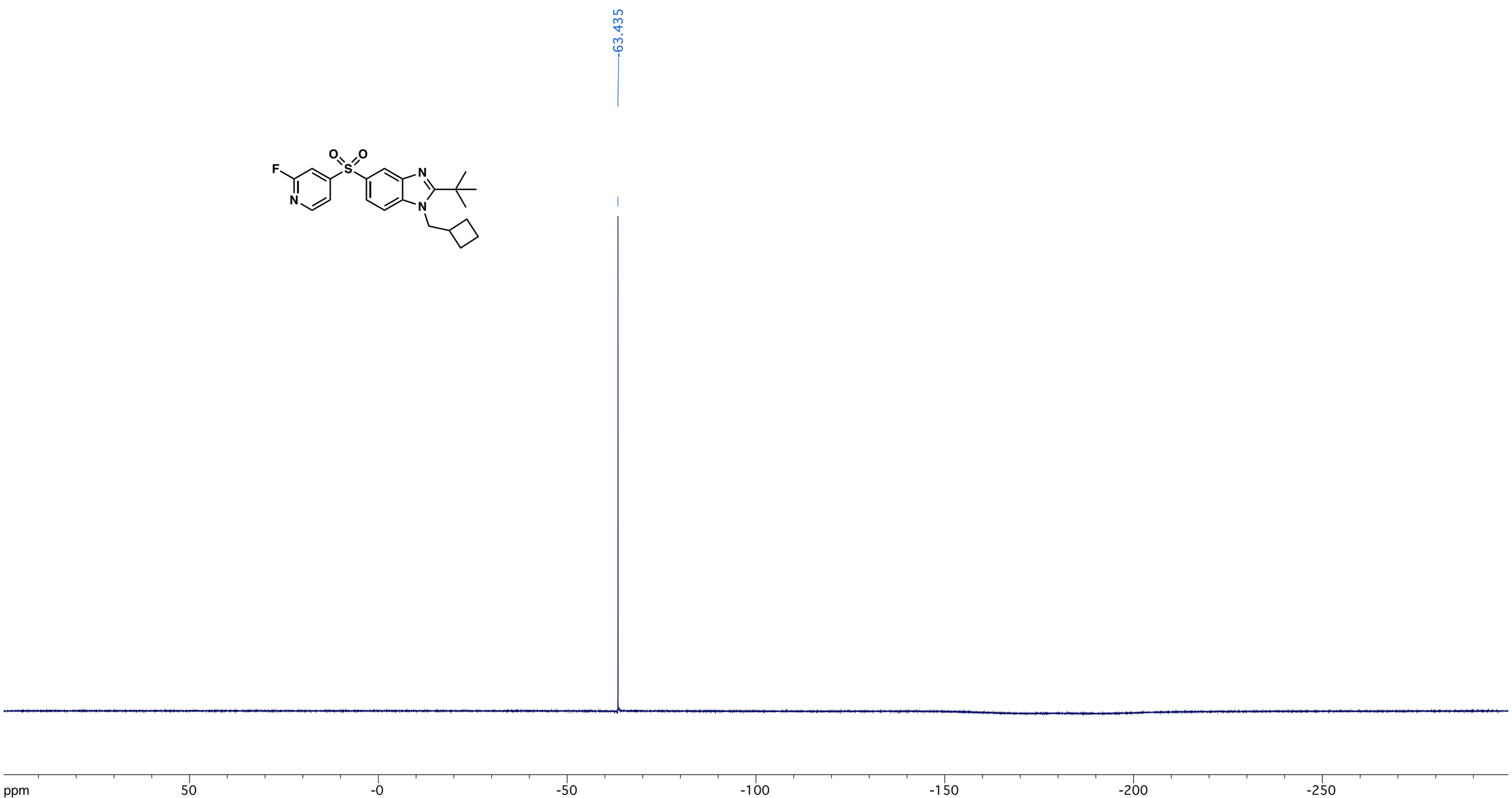
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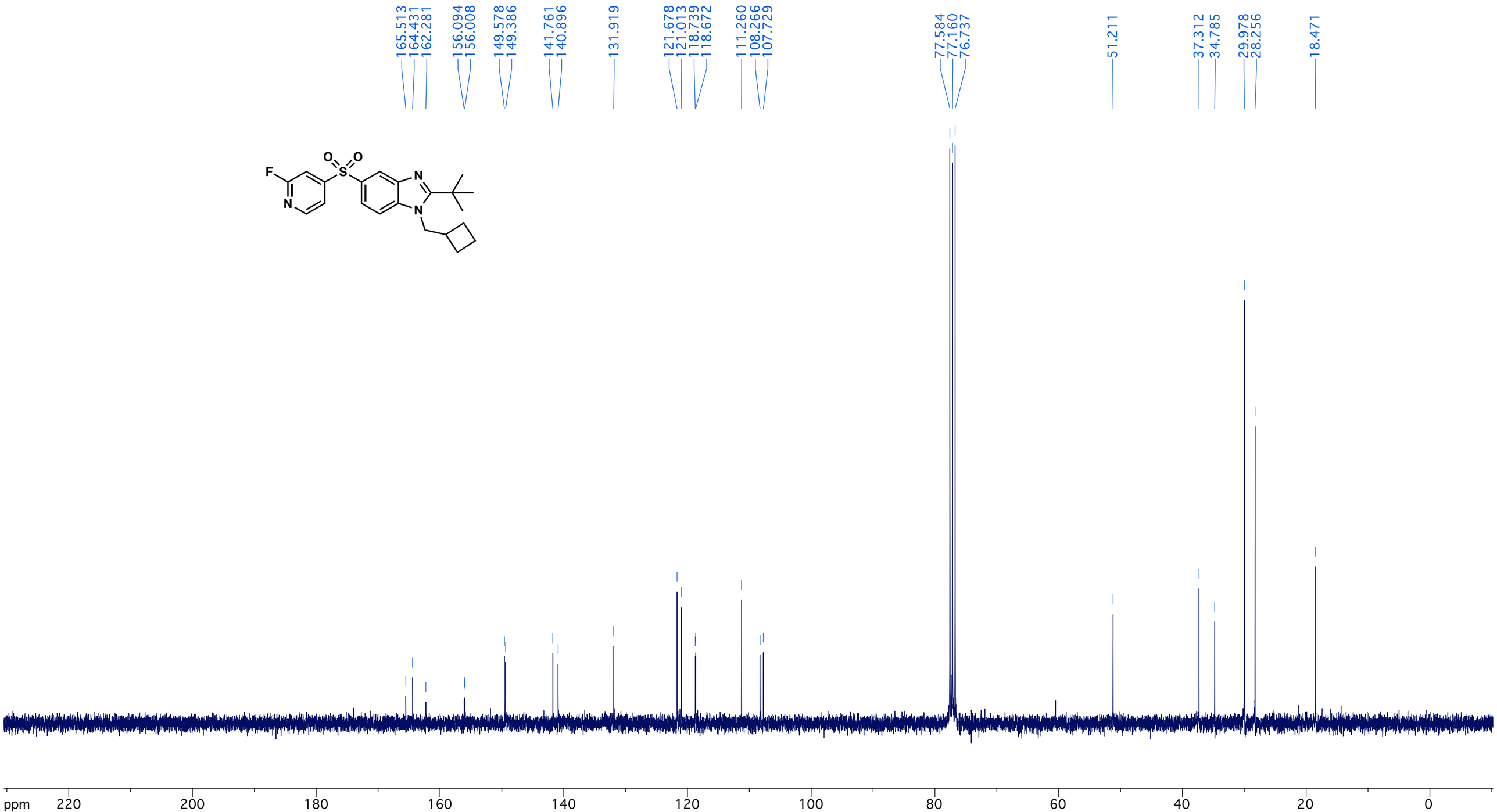
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108.266
107.729
77.584
77.160
76.737
51.211
37.312
34.785
29.978
28.256
18.471
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S
N
N
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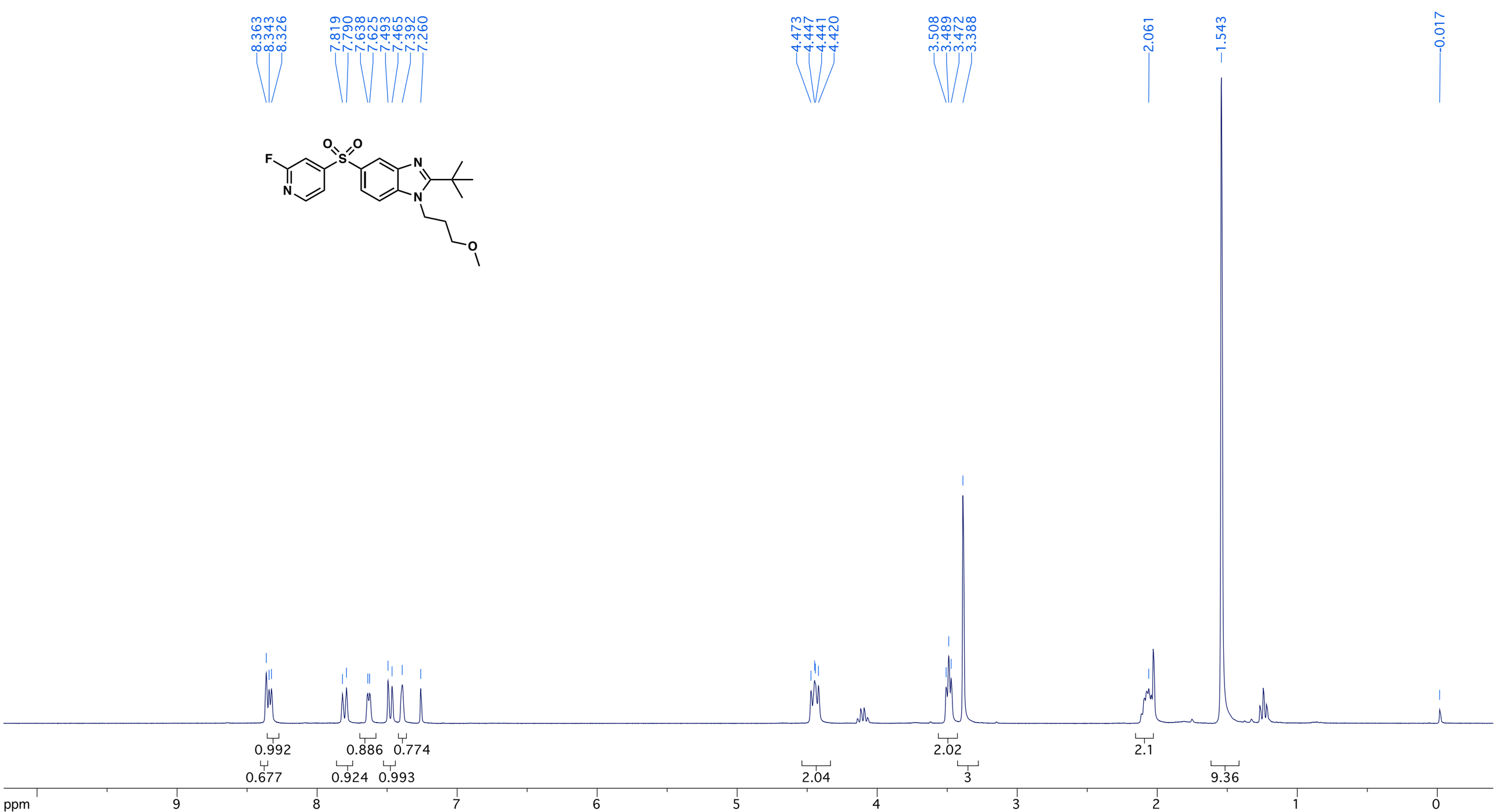
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7.638
7.625
7.493
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7.392
7.260
4.473
4.447
4.441
4.420
3.508
3.489
3.472
3.388
2.061
1.543
0.017
F
N
O
O
S
N
N
O
0.992
0.886
0.774
2.02
2.1
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0.924
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3
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ppm
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7
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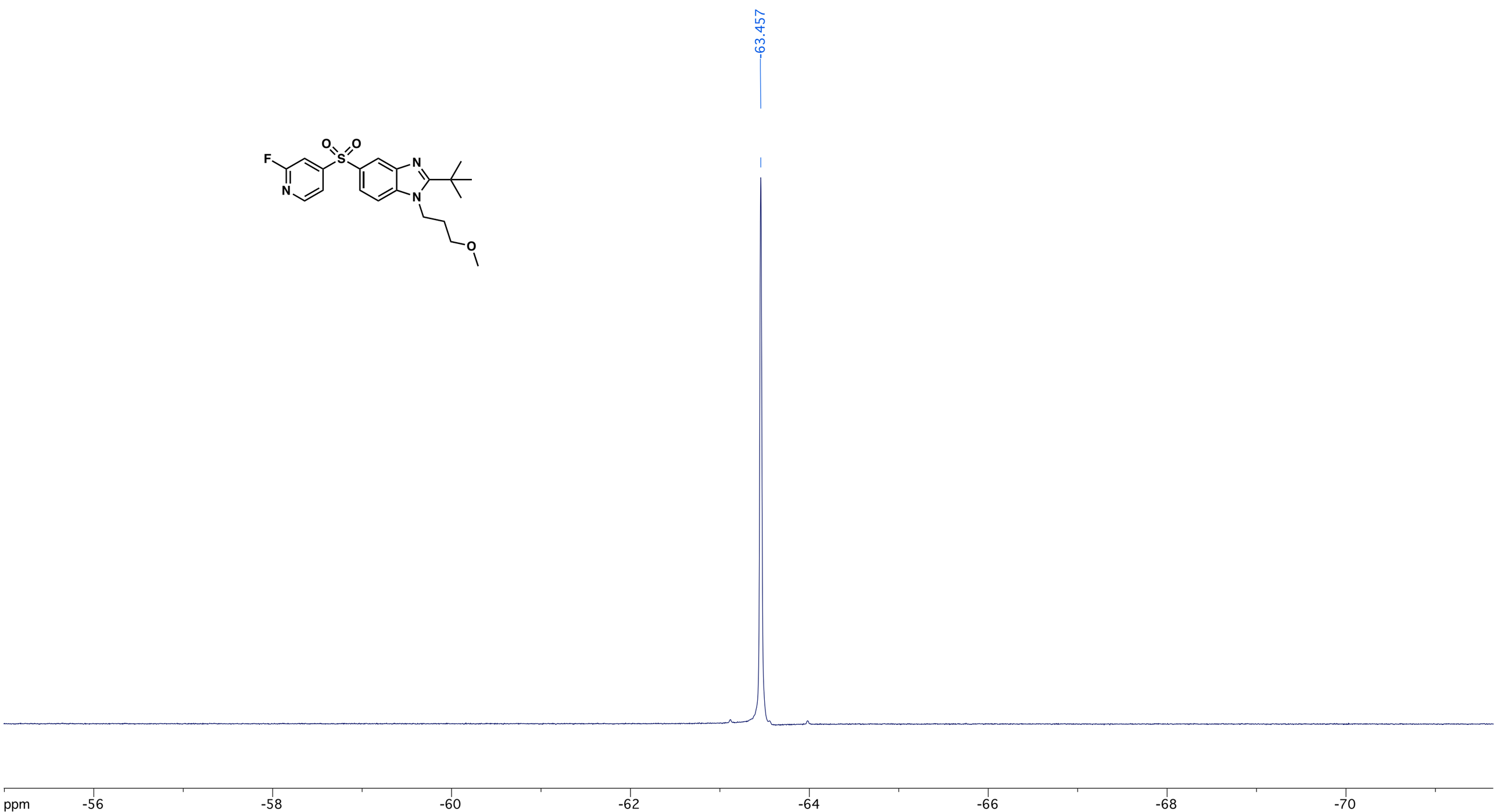
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O
ppm
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-58
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-62
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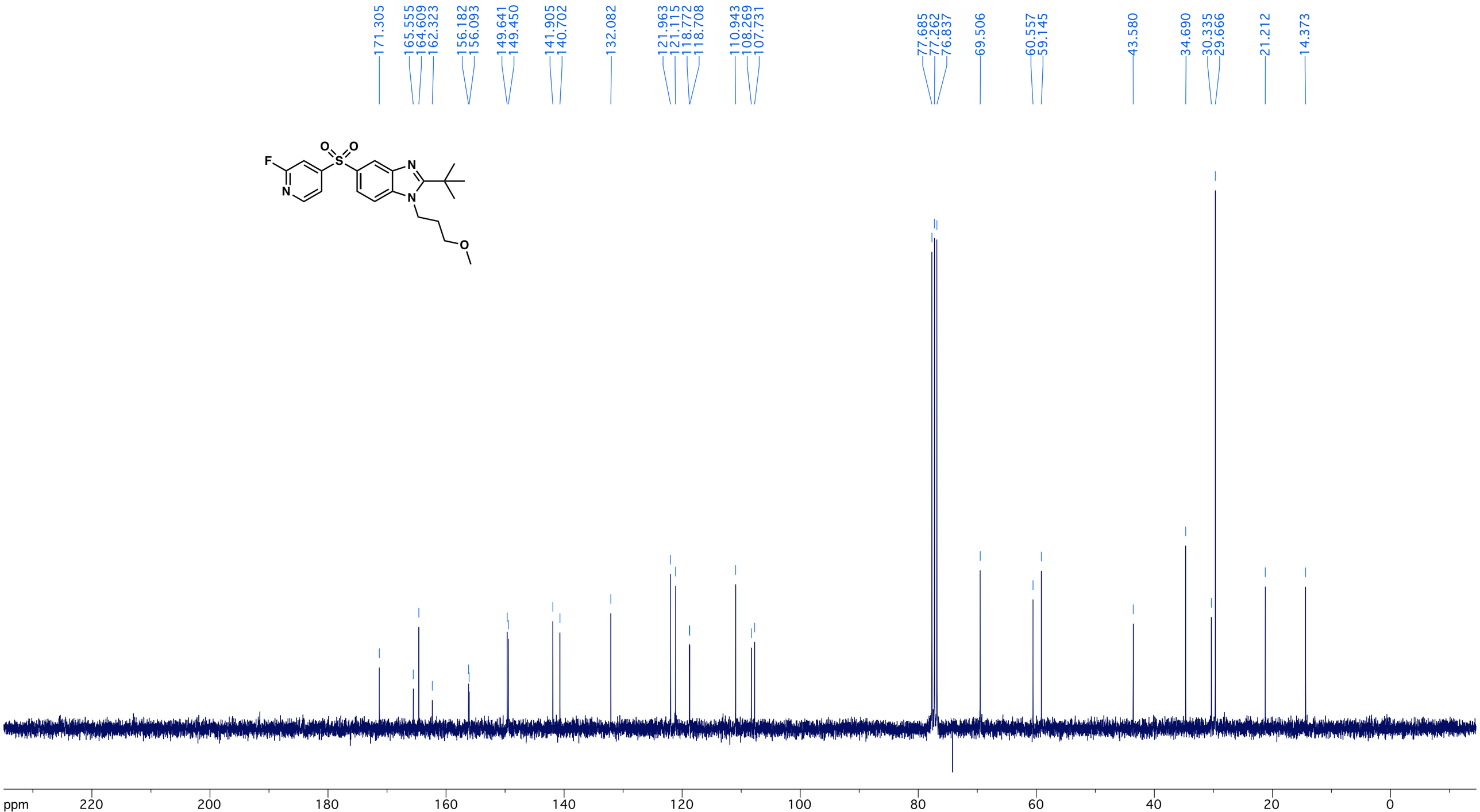
-66
-68
-70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121.963
121.115
118.772
118.708
110.943
108.269
107.731
77.685
77.262
76.837
69.506
60.557
59.145
43.580
34.690
30.335
29.666
21.212
14.373
F
N
O
O
S
N
N
O
ppm
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200
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140
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20
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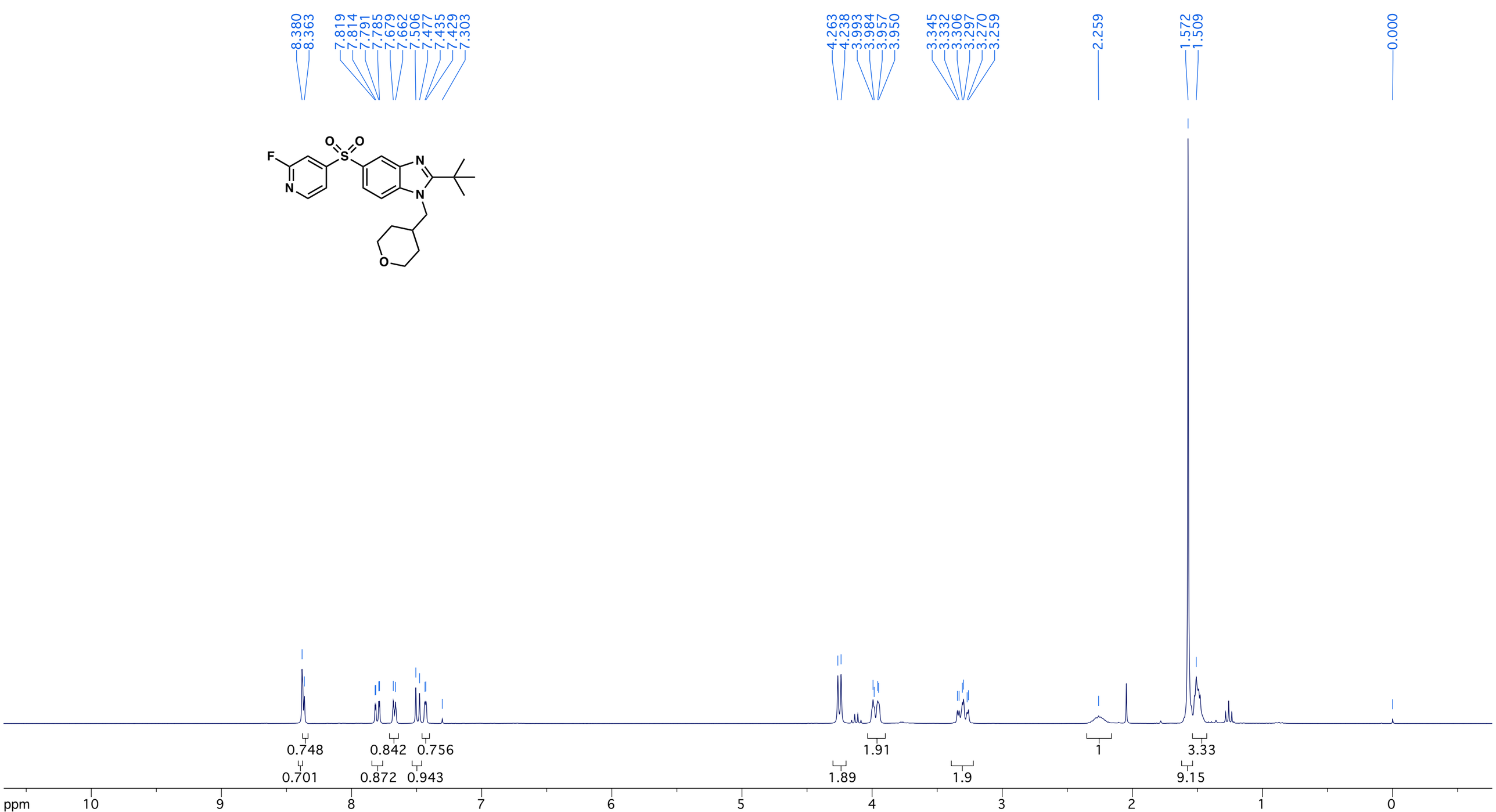
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7.785
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7.662
7.506
7.477
7.435
7.429
7.303
4.263
4.238
3.993
3.984
3.957
3.950
3.345
3.332
3.306
3.297
3.270
3.259
2.259
1.572
1.509
0.000
F
N
O
O
S
N
N
O
0.748
0.701
0.842
0.872
0.756
0.943
1.91
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ppm
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9
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7
6
5
4
3
2
1
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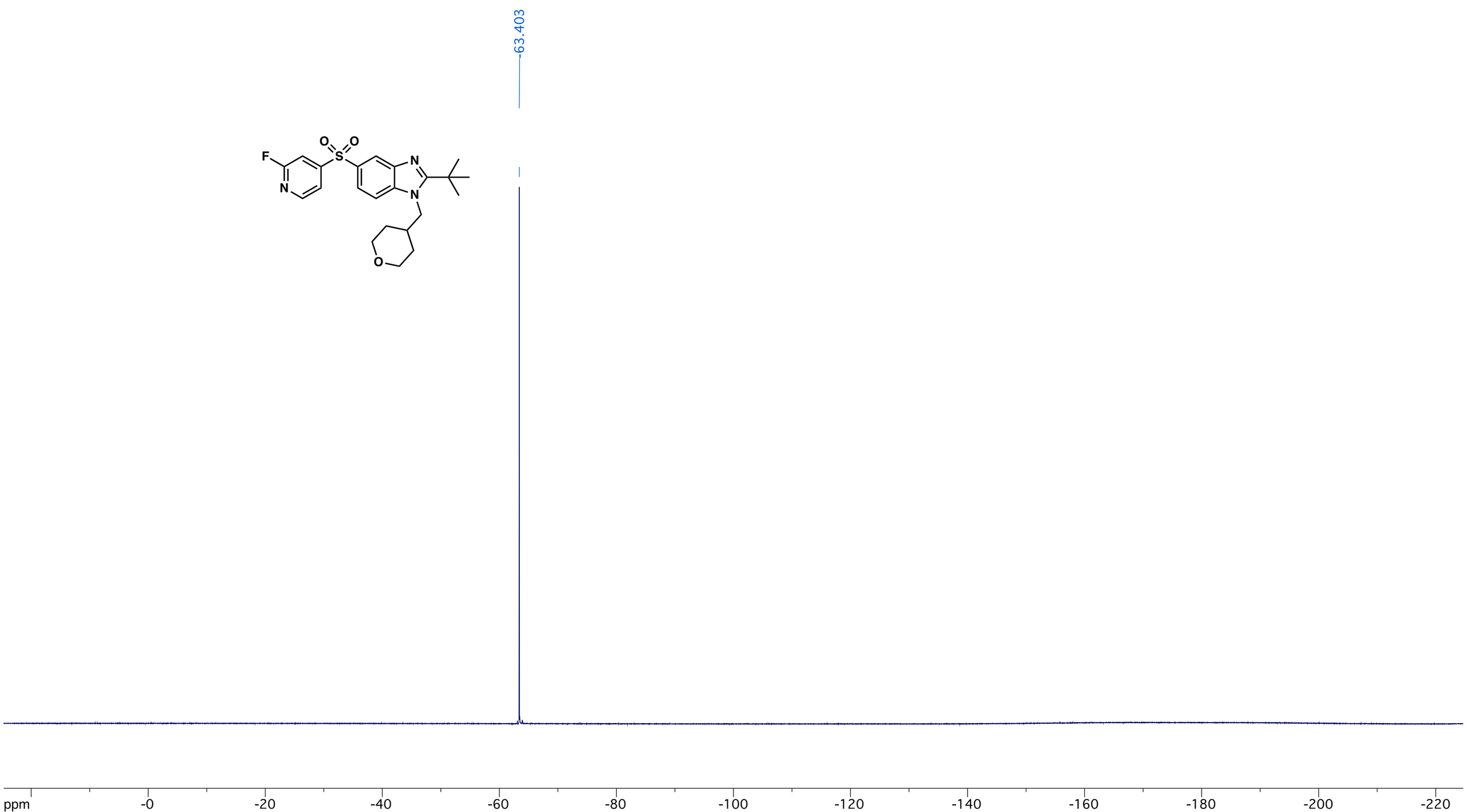
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O
O
S
N
N
O
ppm
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-100
-120
-140
-160
-180
-200
-220

165.420
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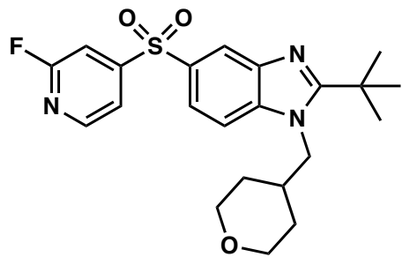

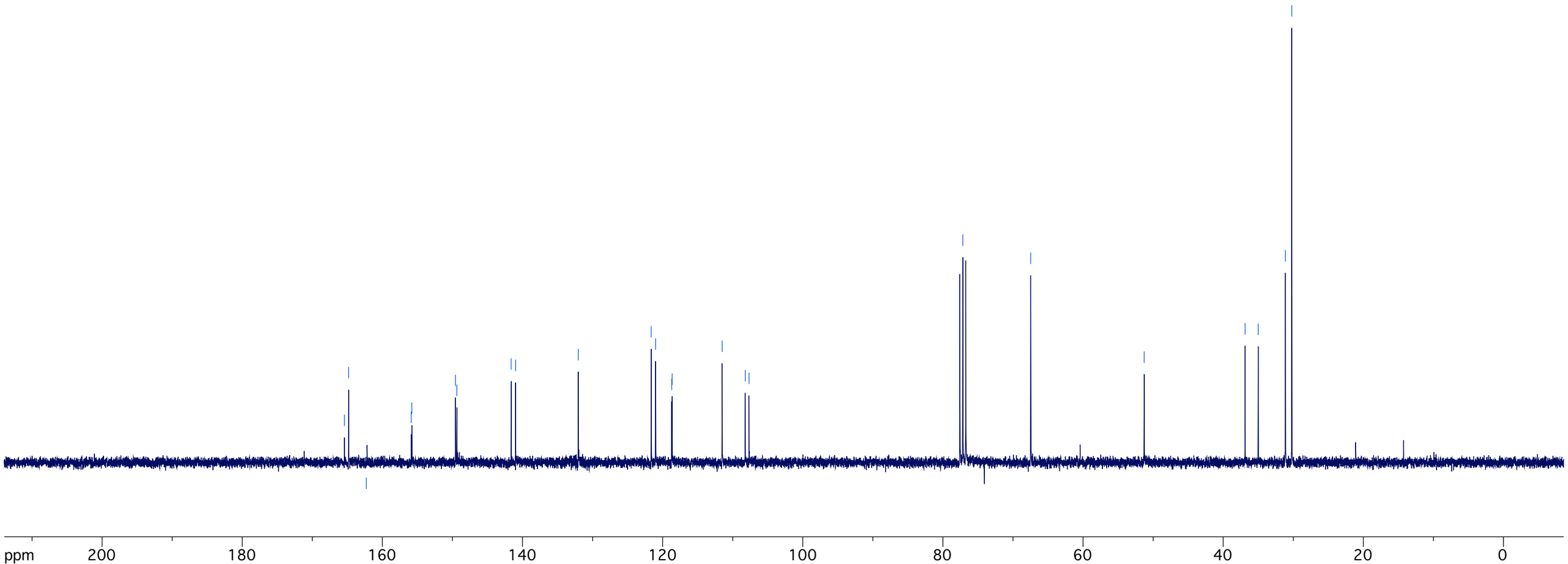

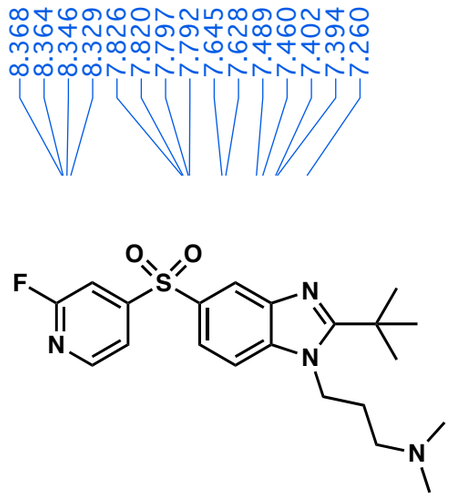
O
O
S
F
N
N
N
N

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7.797
7.792
7.645
7.628
7.489
7.460
7.402
7.394
7.260
4.415
4.388
4.361
2.426
2.404
2.383
2.257
1.946
1.545
1.53
0.915
0.891
1.01
0.81
1.96
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6
2.82
9.1
ppm
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9
8
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6
5
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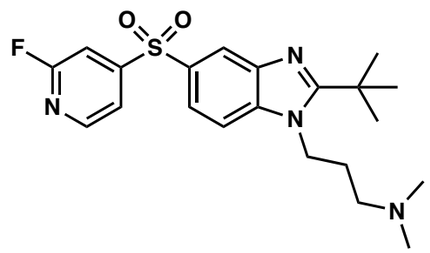
1
0
-1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N
N
N
N

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ppm-35
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-45
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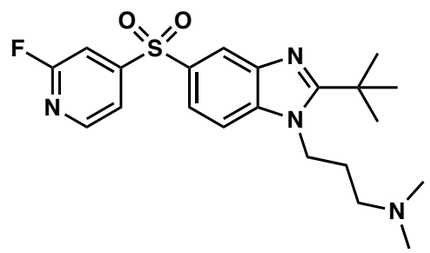
-65
-70
-75
-80
-85
-90



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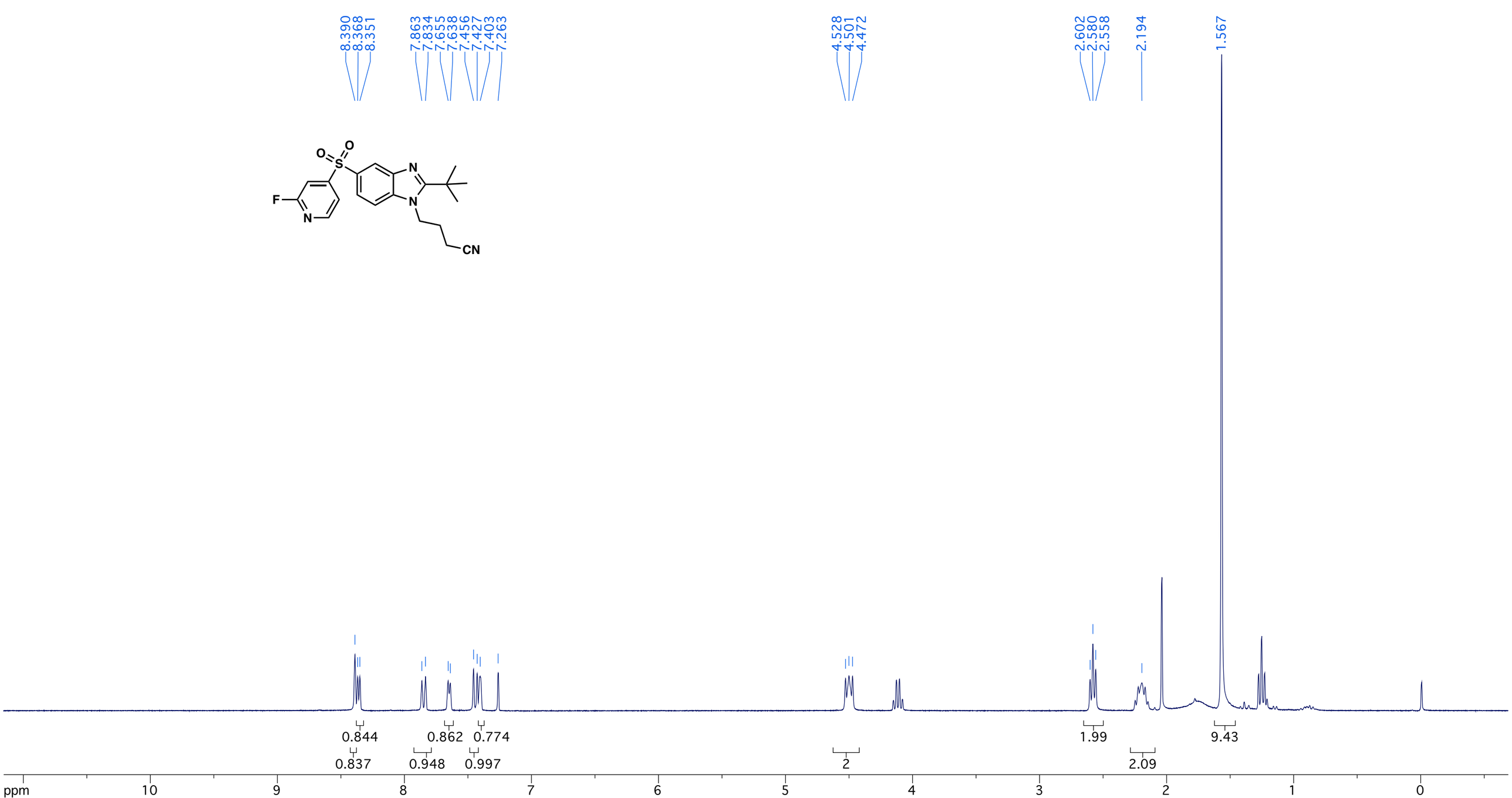
44.446
34.637
29.643
28.090

ppm 220 200 180 160 140 120 100 80 60 40 20 0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7.456
7.427
7.403
7.263
4.528
4.501
4.472
2.602
2.580
2.558
2.194
1.567
O
O
S
N
N
F
N
CN
0.844
0.862
0.774
1.99
9.43
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0.997
2
2.09
ppm
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9
8
7
6
5
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1
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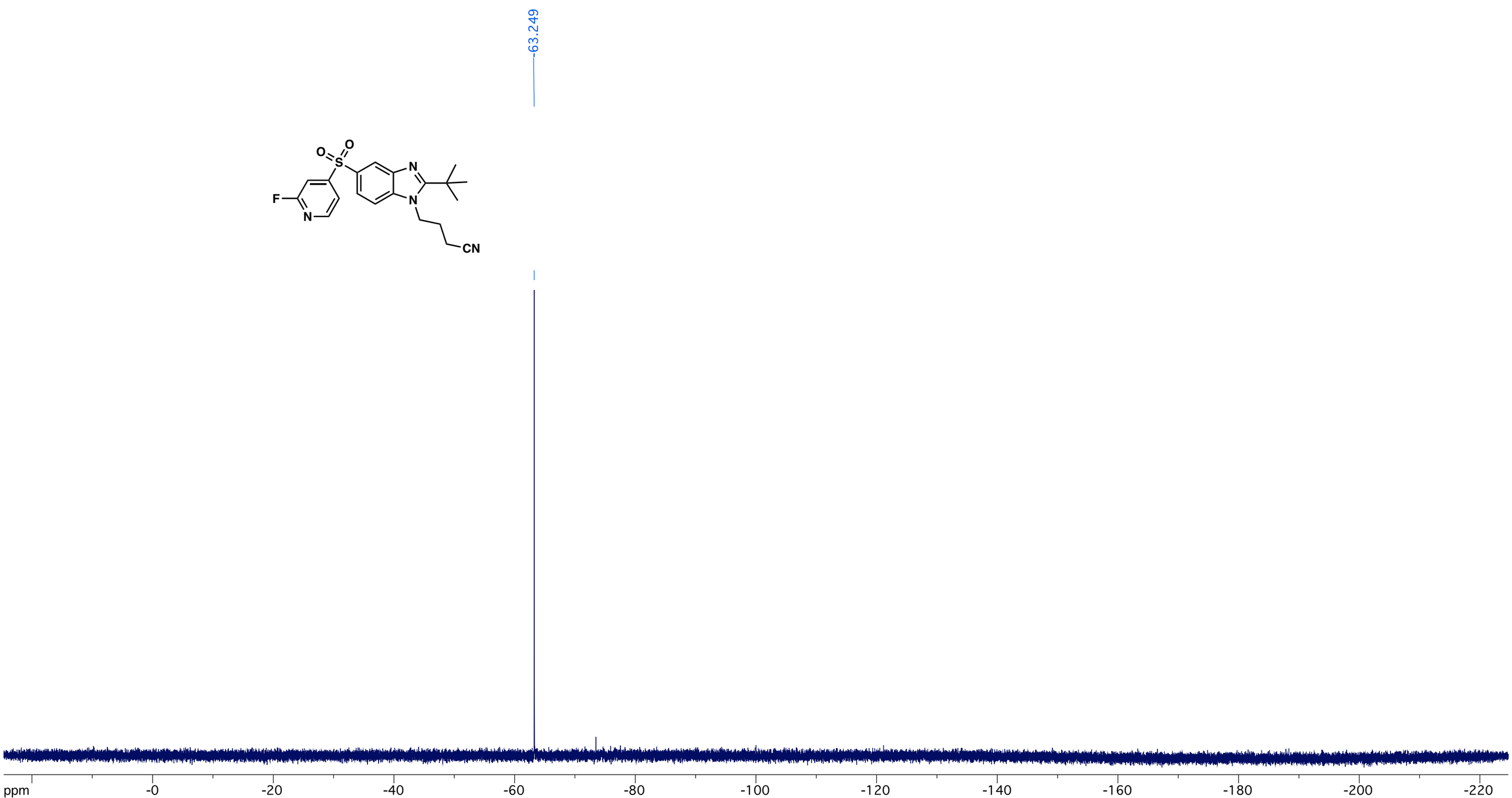
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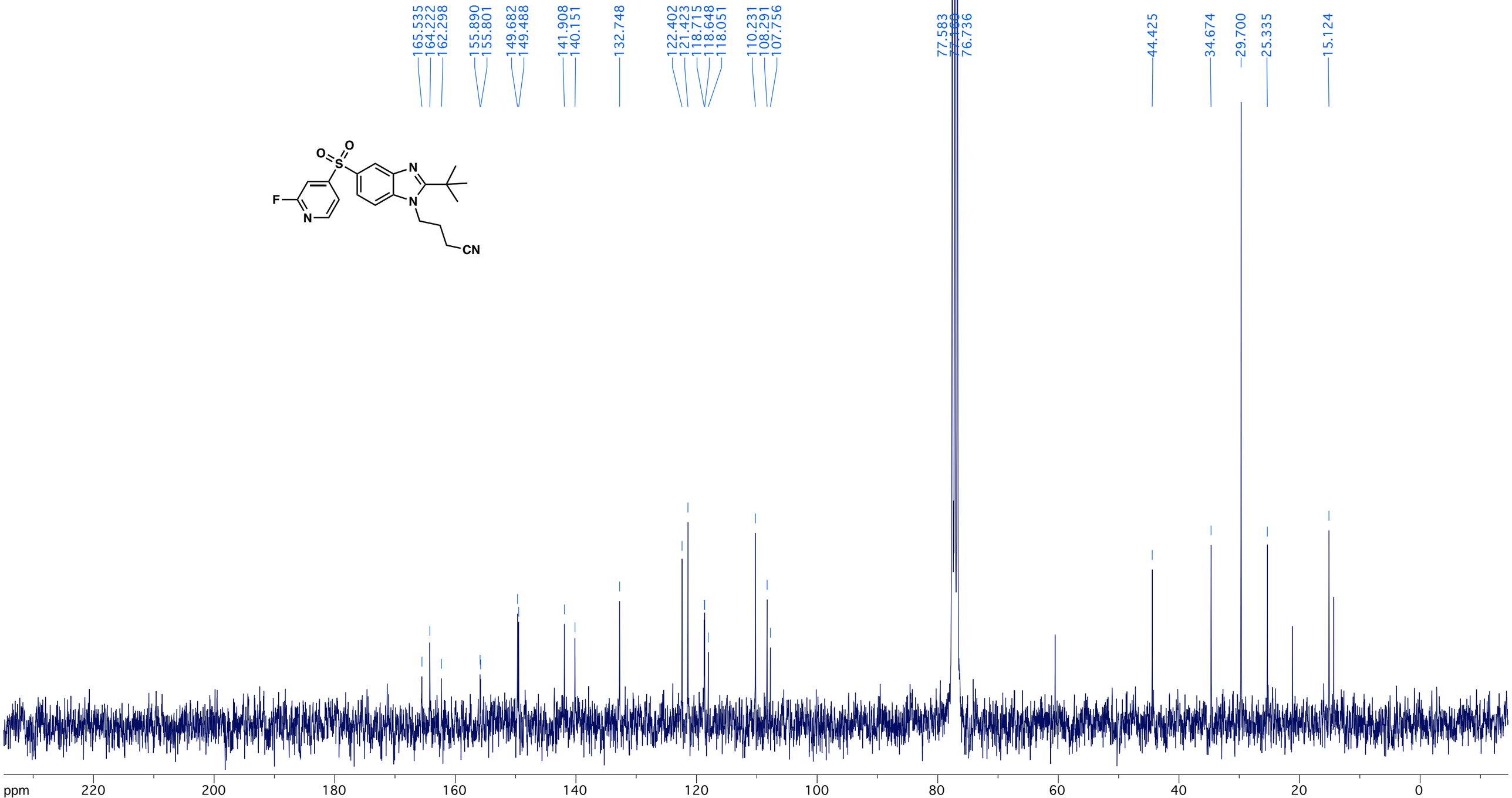
-200
-220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121.423
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77.268
76.736
44.425
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29.700
25.335
15.124
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N
CN
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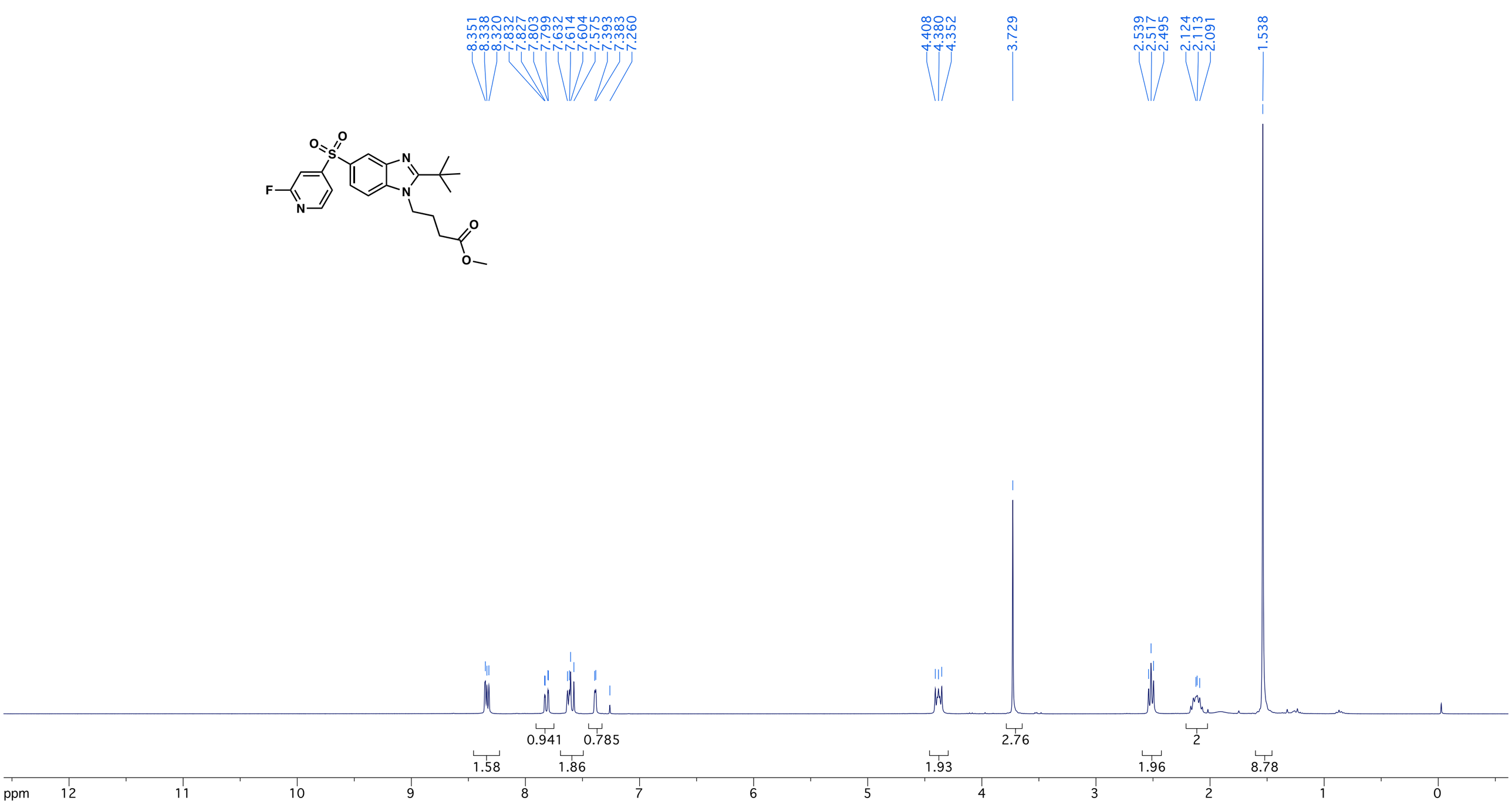
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7.383
7.260
4.408
4.380
4.352
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2.539
2.517
2.495
2.124
2.113
2.091
1.538
0.941
0.785
2.76
2
1.58
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11
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7
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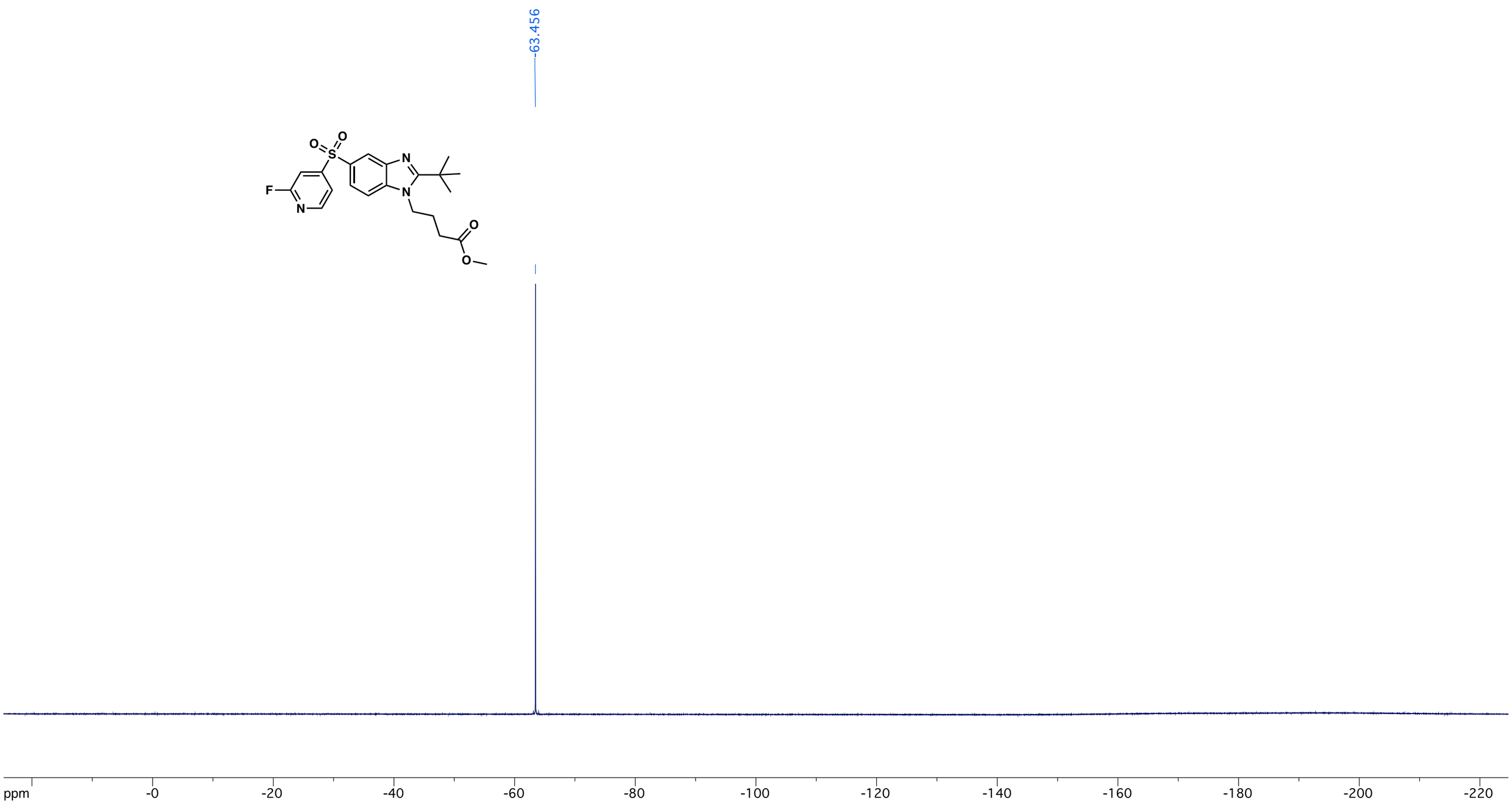
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-200
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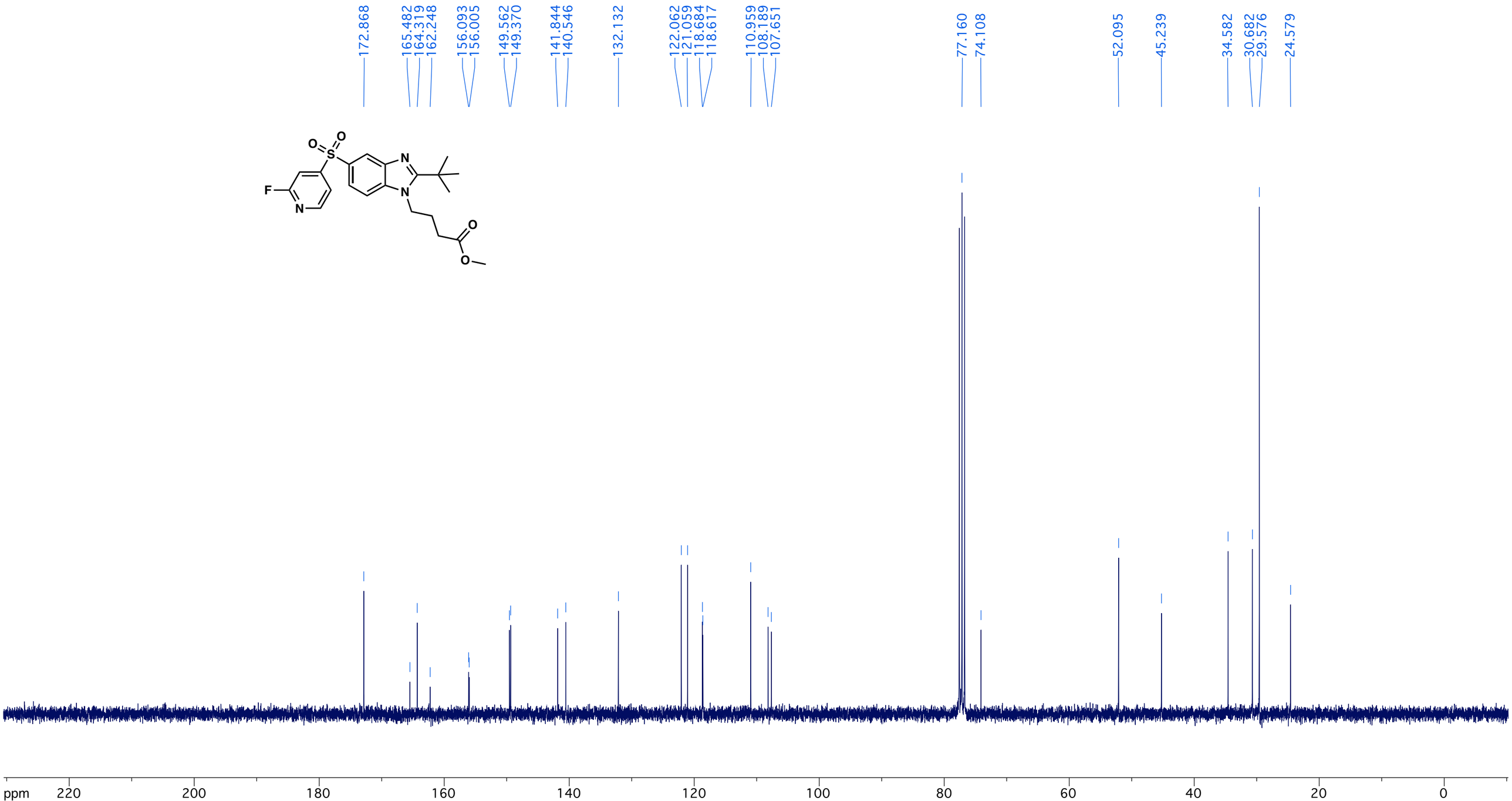
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110.959
108.189
107.651
77.160
74.108
52.095
45.239
34.582
30.682
29.576
24.579
O
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S
N
N
F
N
O
O
ppm
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140
120
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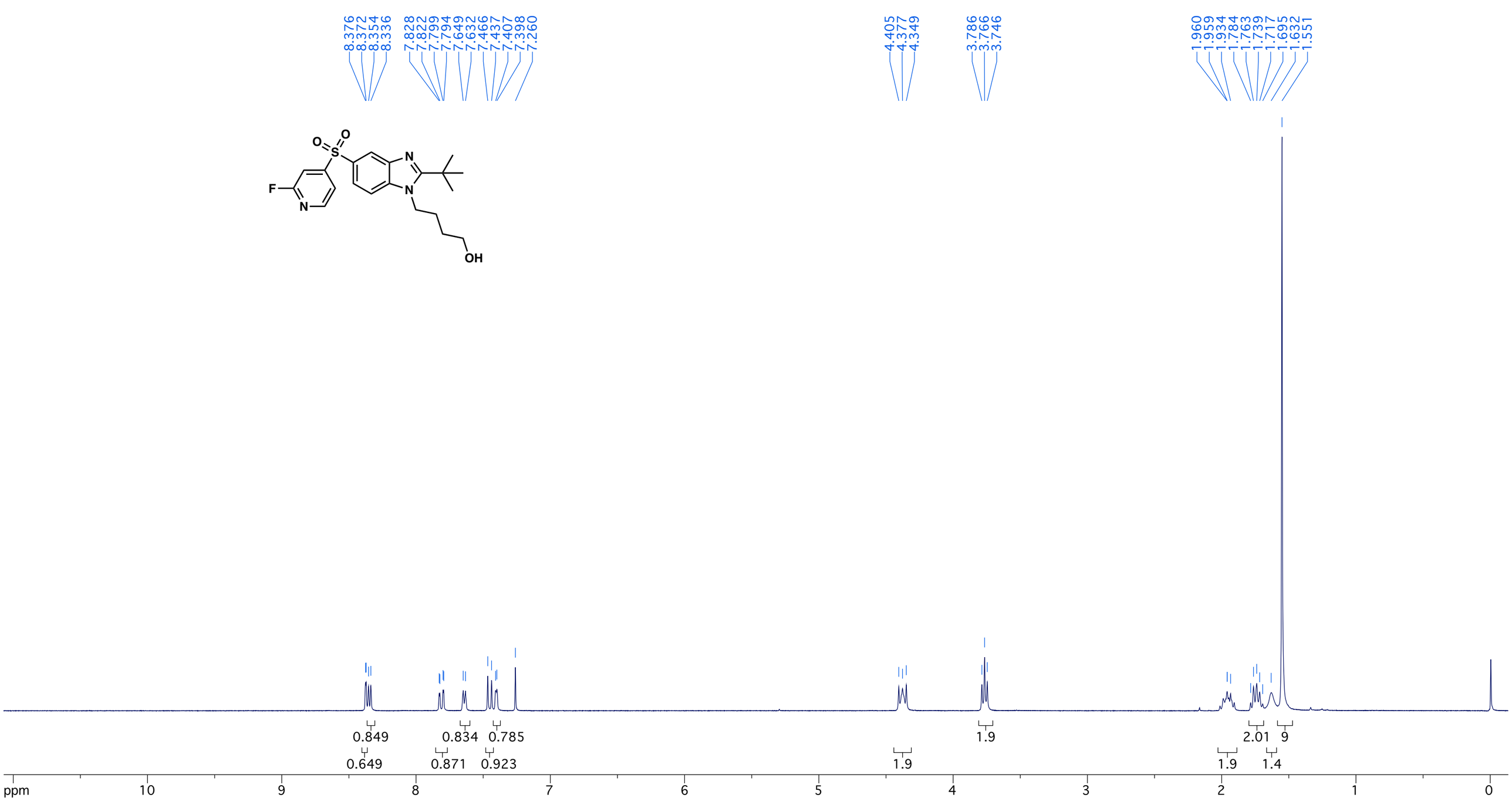
60
40
20
0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7.632
7.466
7.437
7.407
7.398
7.260
4.405
4.377
4.349
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3.766
3.746
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1.959
1.934
1.784
1.763
1.739
1.717
1.695
1.632
1.551
O
O
S
N
N
F
N
OH
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0.834
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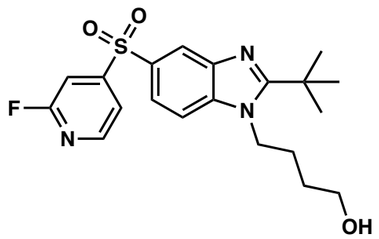
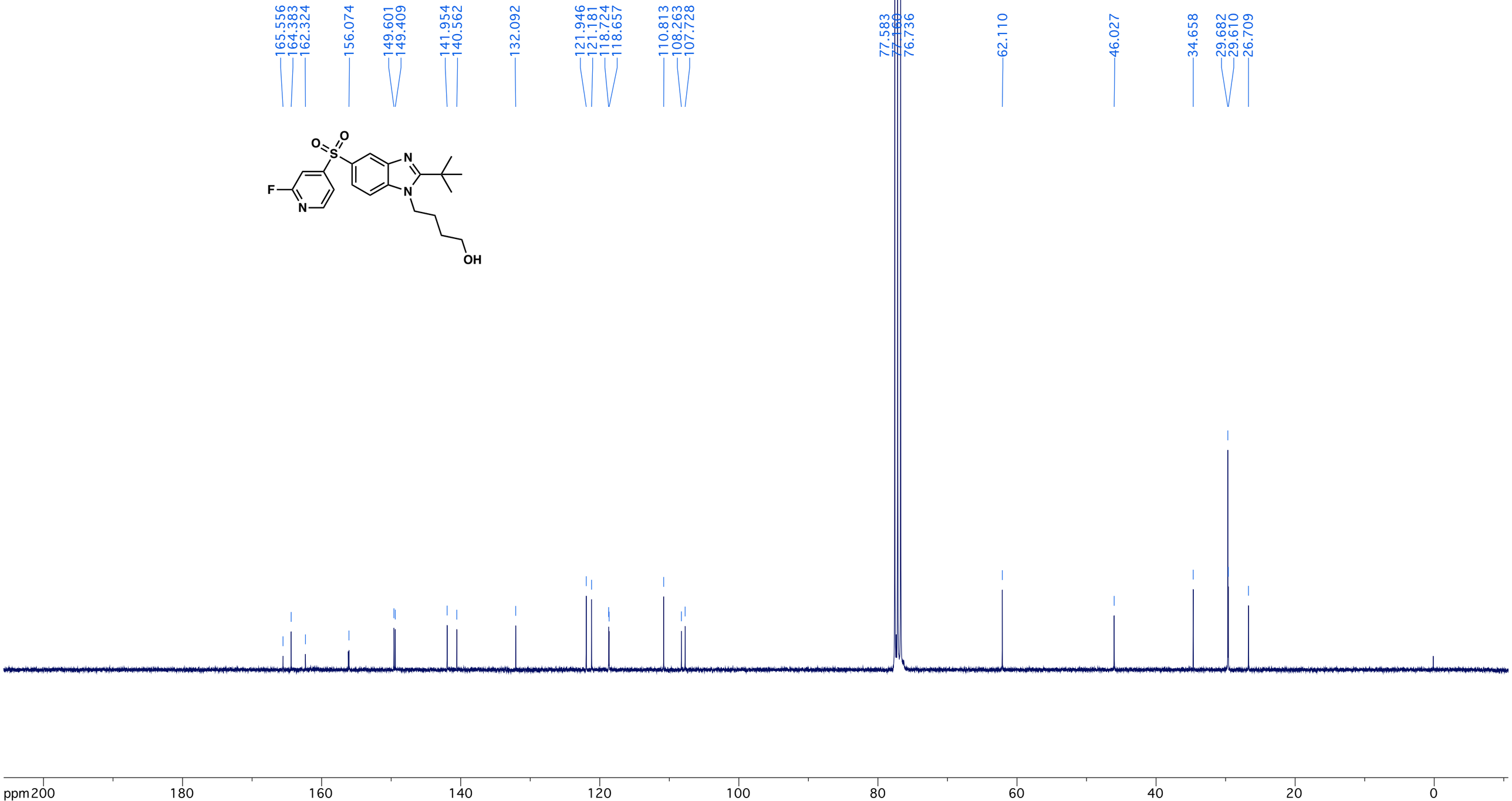


63.414

ppm -0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220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121.181
118.724
118.657
110.813
108.263
107.728
77.583
77.160
76.736
62.110
46.027
34.658
29.682
29.610
26.709
O
O
S
N
N
F
N
OH
ppm 200
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140
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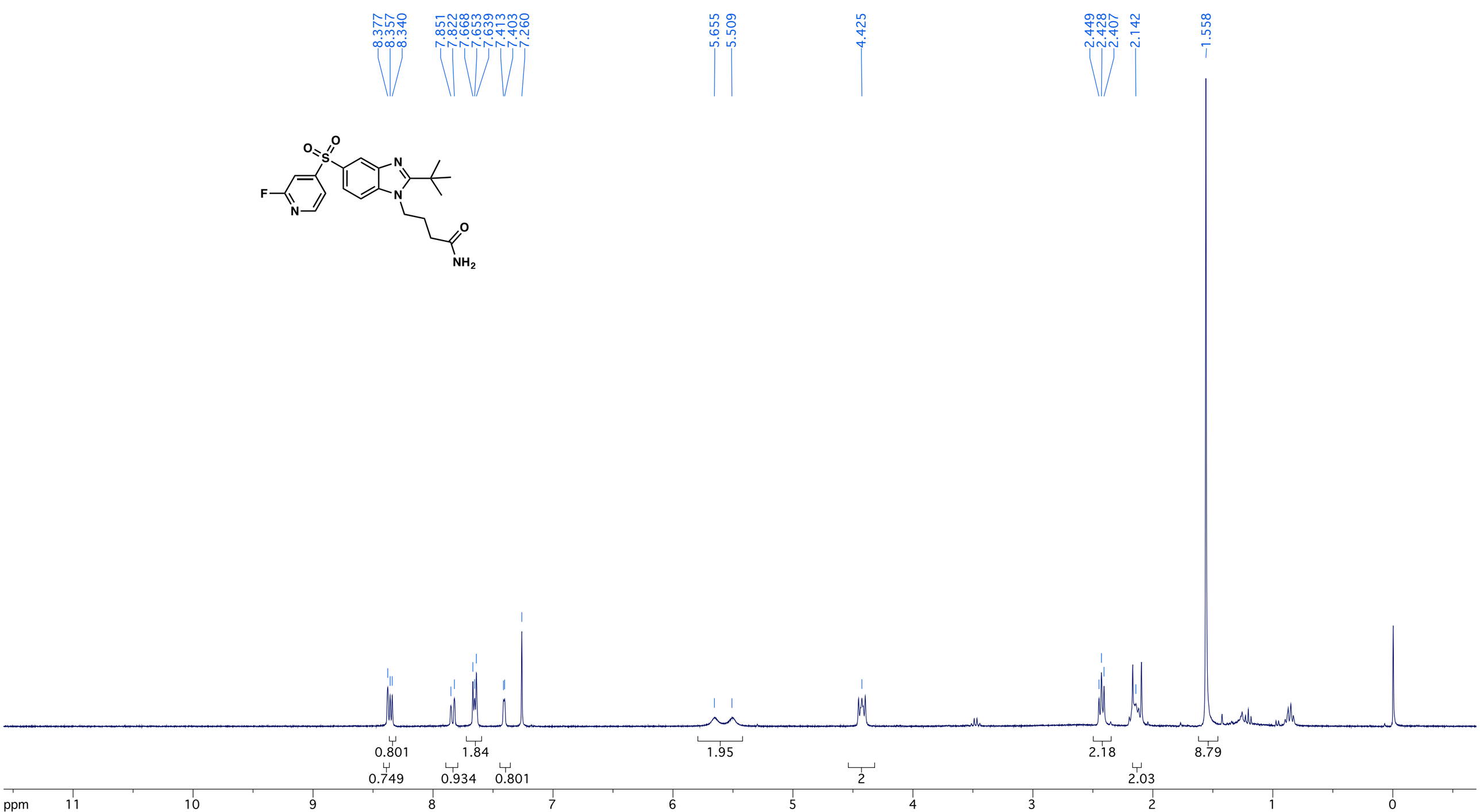
20
0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7.403
7.260
5.655
5.509
4.425
2.449
2.428
2.407
2.142
1.558
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S
F
N
N
N
O
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1.84
1.95
2
2.18
2.03
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9
8
7
6
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2
1
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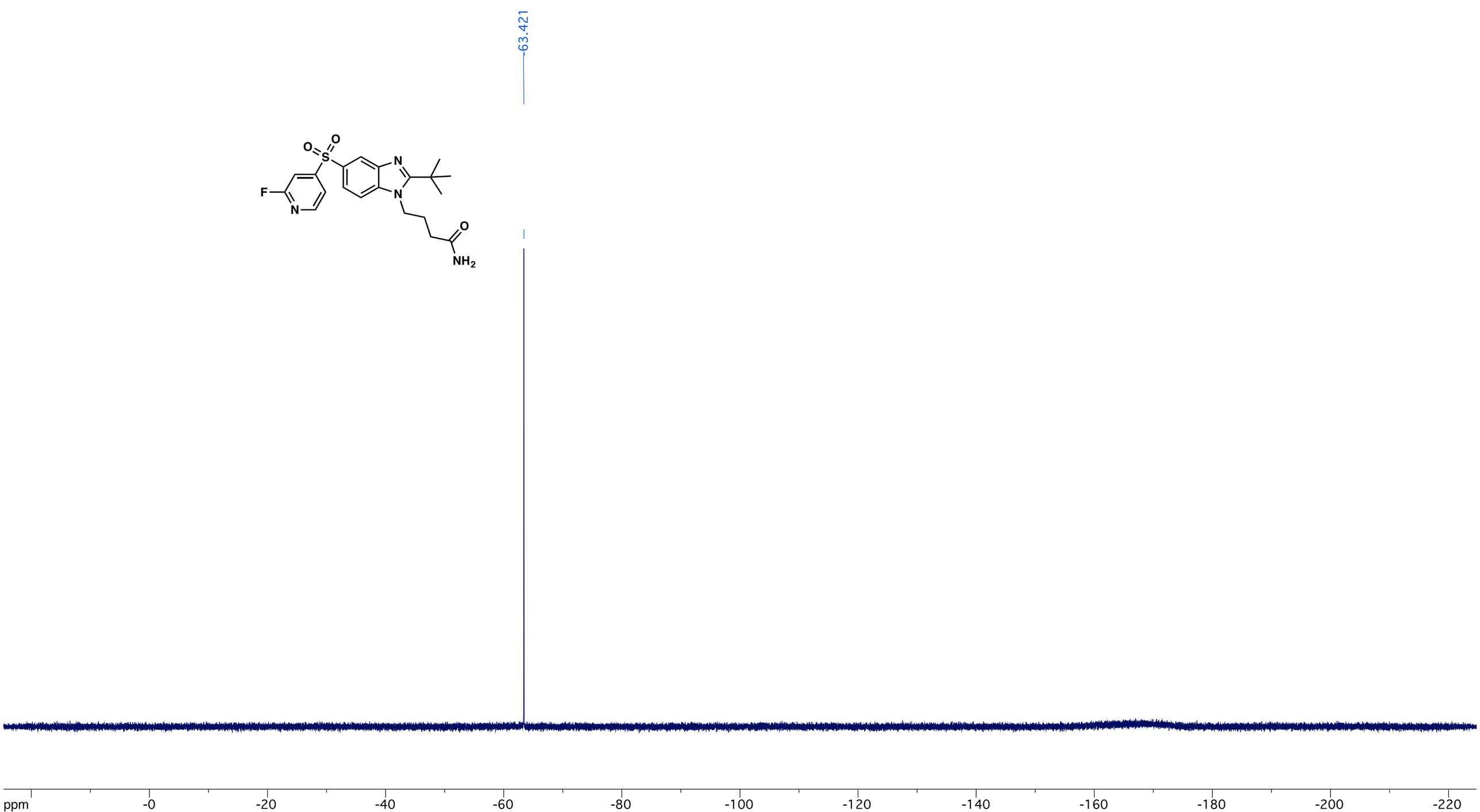
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-200
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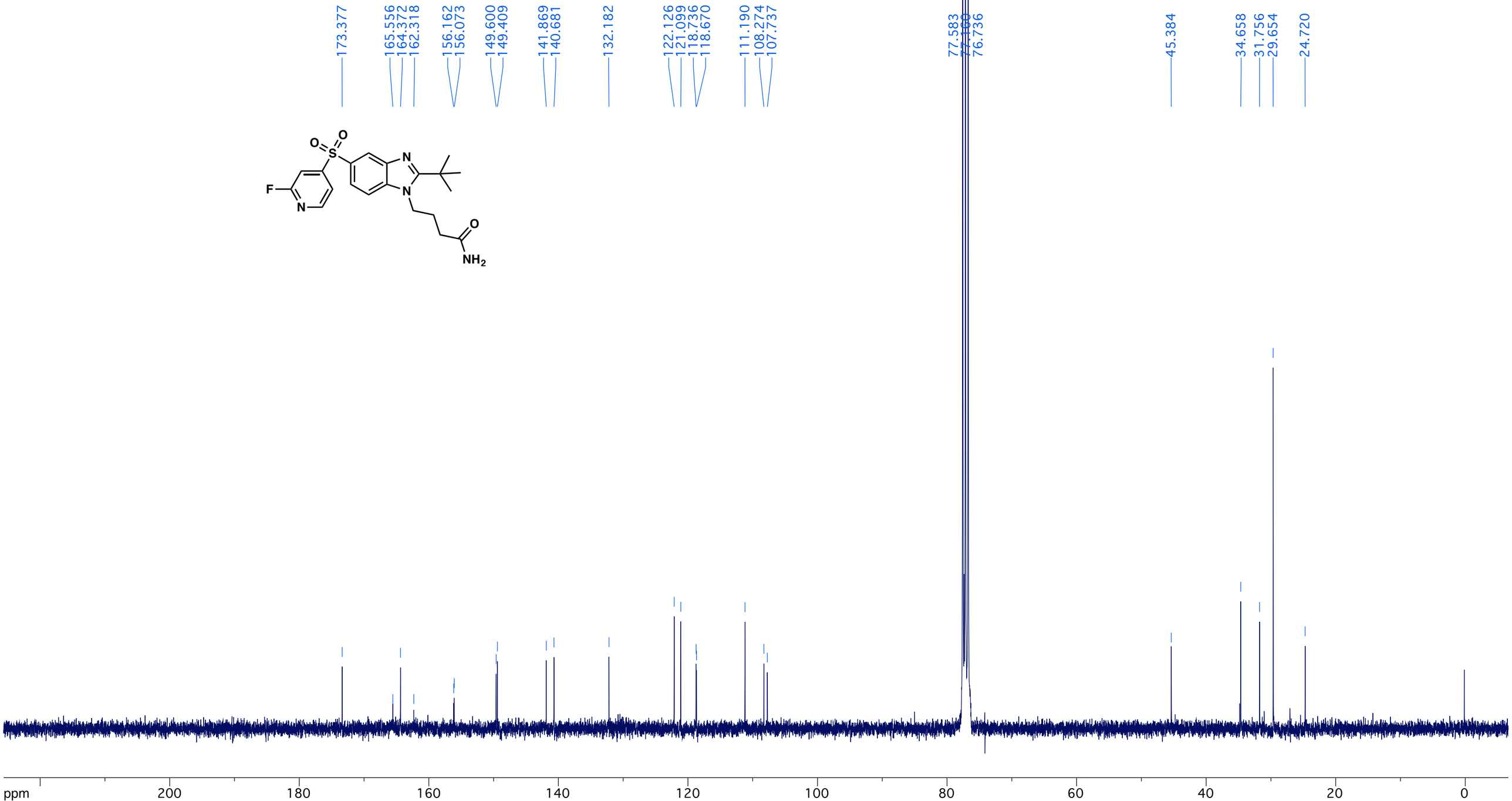
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164.372
162.318
156.162
156.073
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149.409
141.869
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132.182
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118.736
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111.190
108.274
107.737
77.583
77.160
76.736
45.384
34.658
31.756
29.654
24.720
O
O
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F
N
O
NH2
ppm
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60
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20
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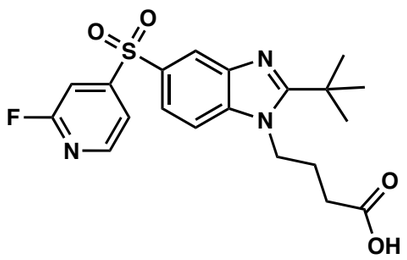
O
O
S
F
N
N
N
O
OH

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8.353
8.336
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7.635
7.619
7.415
7.407
7.260
4.473
4.446
4.436
4.418
2.612
2.590
2.172
1.571
0.884
1.9
2.12
2.02
0.893
0.97
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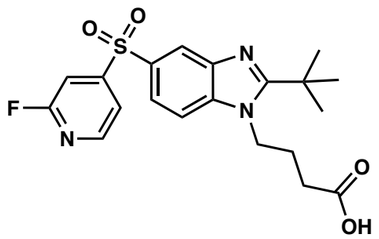

63.437

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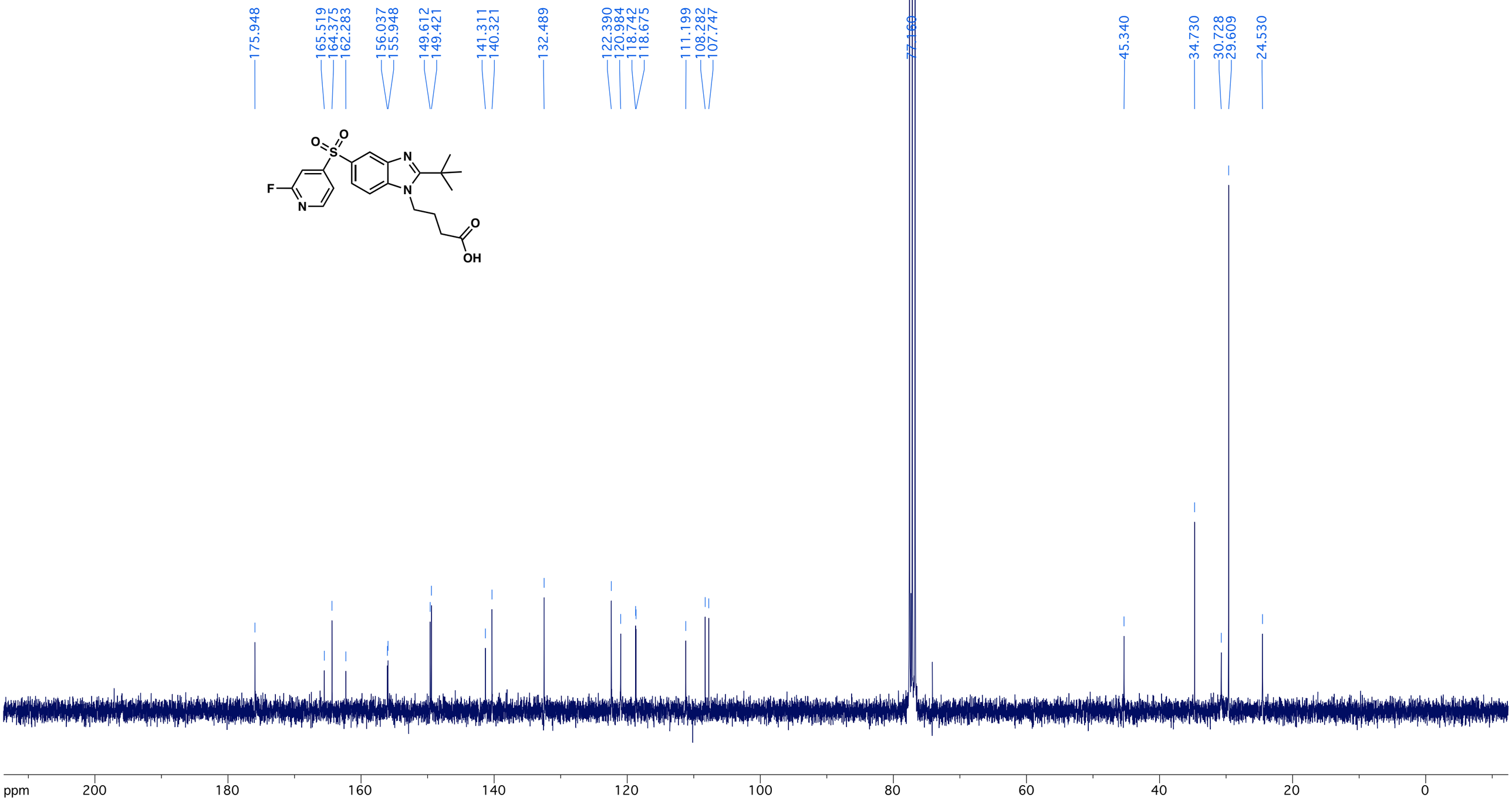
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149.421
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140.321
132.489
122.390
120.984
118.742
118.675
111.199
108.282
107.747
77.160
45.340
34.730
30.728
29.609
24.530
O
O
S
N
N
F
N
O
OH
ppm
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140
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20
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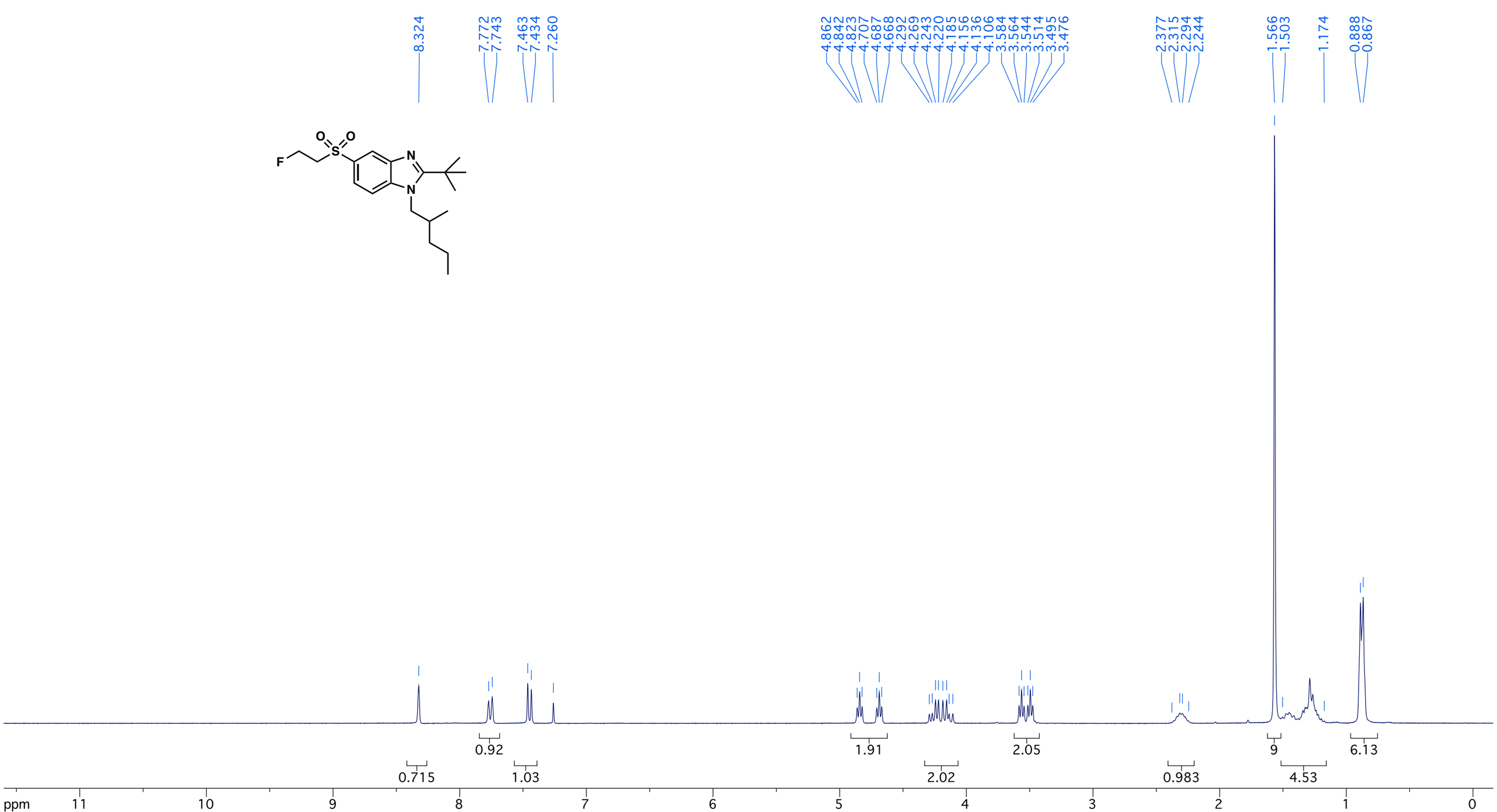
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4.842
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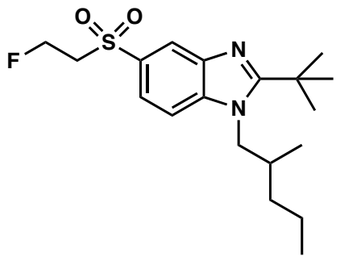
4.687
4.668
4.292
4.269
4.243
4.220
4.185
4.156
4.136
4.106
3.584
3.564
3.544
3.514
3.495
3.476
2.377
2.315
2.294
2.244
1.566
1.503
1.174
0.888
0.867
F
O
O
S
N
N
0.715
0.92
1.03
1.91
2.02
2.05
0.983
9
4.53
6.13
ppm
11
10
9
8
7
6
5
4
3
2
1
0



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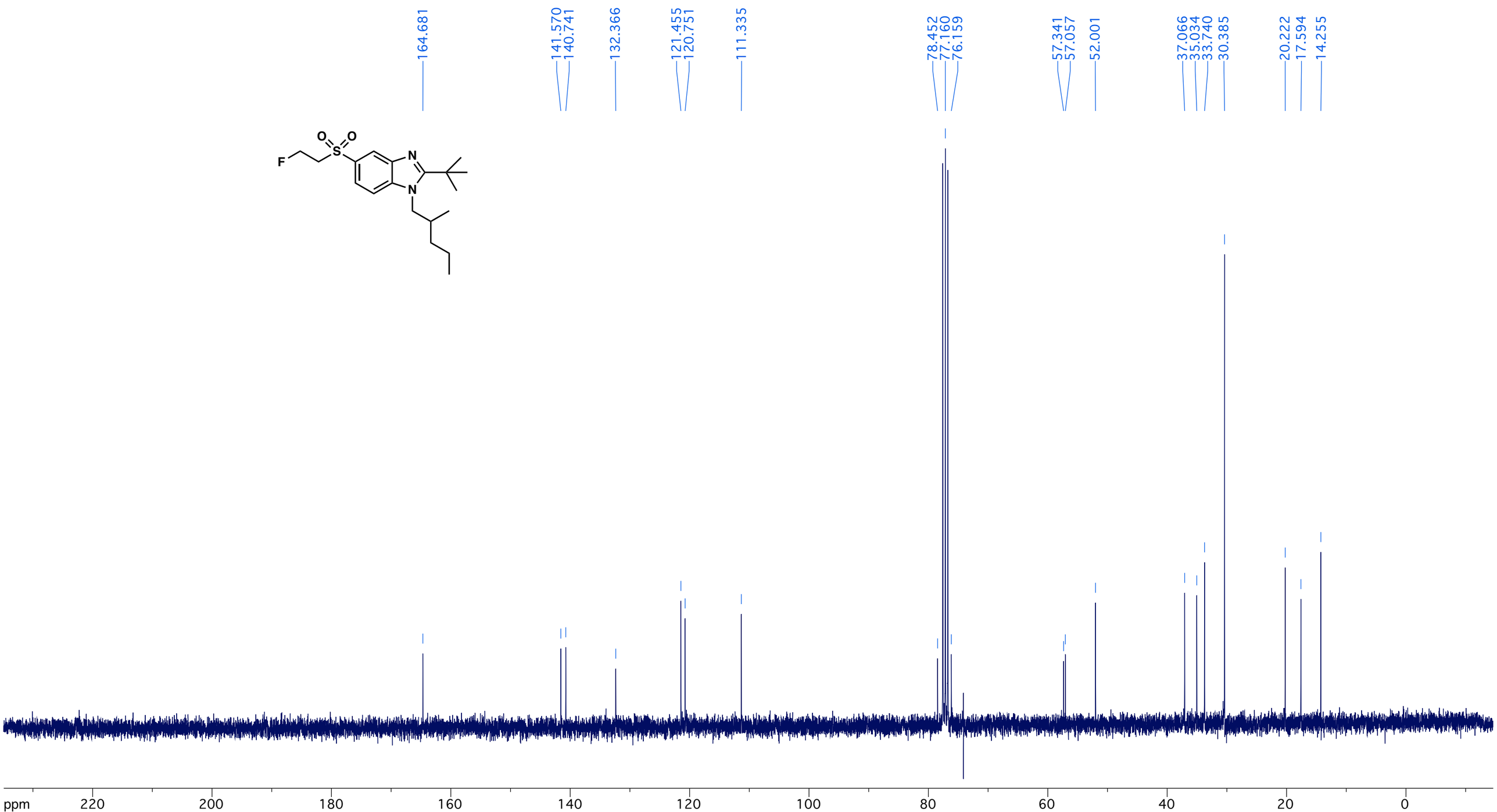
221.659
221.750
221.823
221.899
221.989
222.062

ppm -195 -200 -205 -210 -215 -220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140.741
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111.335
78.452
77.160
76.159
57.341
57.057
52.001
37.066
35.034
33.740
30.385
20.222
17.594
14.255
O
O
S
F
N
N
ppm
220
200
180
160
140
120
100
80
60
40
20
0

8.306
8.301
7.779
7.774
7.751
7.746
7.416
7.388
7.260
4.833
4.813
4.794
4.678
4.658
4.639
4.294
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3.486
3.467
3.447
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1.544
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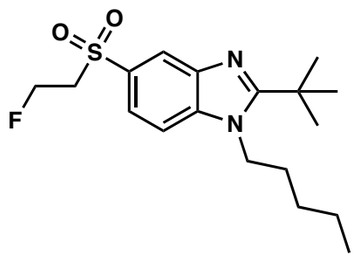
0.935
0.912



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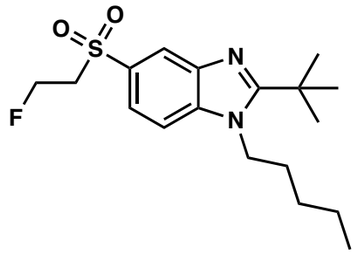
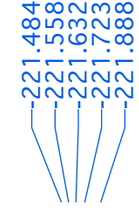
0.934
1.01
0.982
2.02
0.971
2.06
2.02
4.24
9.19
3

ppm 10 9 8 7 6 5 4 3 2 1 0


O
O
S
N
N
F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221.632
221.723
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ppm
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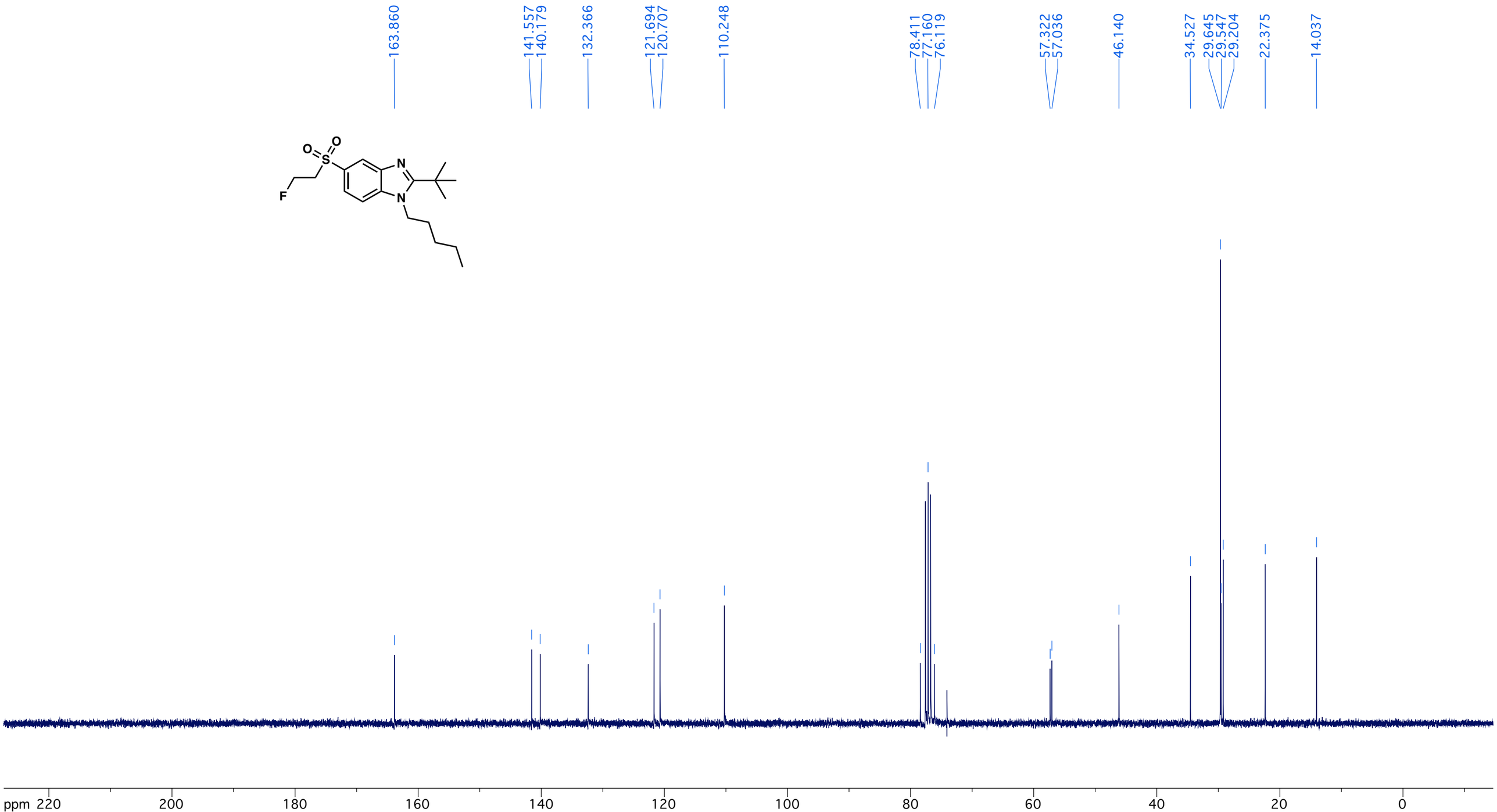
-205
-210
-215
-220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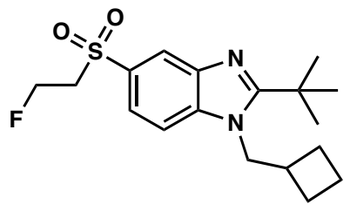
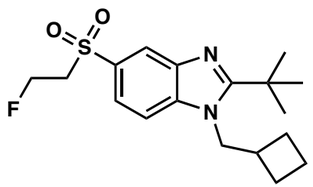
132.366
121.694
120.707
110.248
78.411
77.160
76.119
57.322
57.036
46.140
34.527
29.645
29.547
29.204
22.375
14.037
O
O
S
F
N
N
ppm 220
200
180
160
140
120
100
80
60
40
20
0


O
O
S
N
N
F

8.312
7.773
7.745
7.476
7.448
7.260
4.858
4.839
4.819
4.704
4.684
4.665
4.382
4.361
3.578
3.558
3.539
3.509
3.489
3.470
2.840
2.688
2.138
2.083
2.031
1.999
1.867
1.559
0.729
0.952
1.03
2.04
2.02
2.02
1.02
2.21
4.06
9
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0



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221.677
221.745
221.801
221.857
221.869
221.925
221.980

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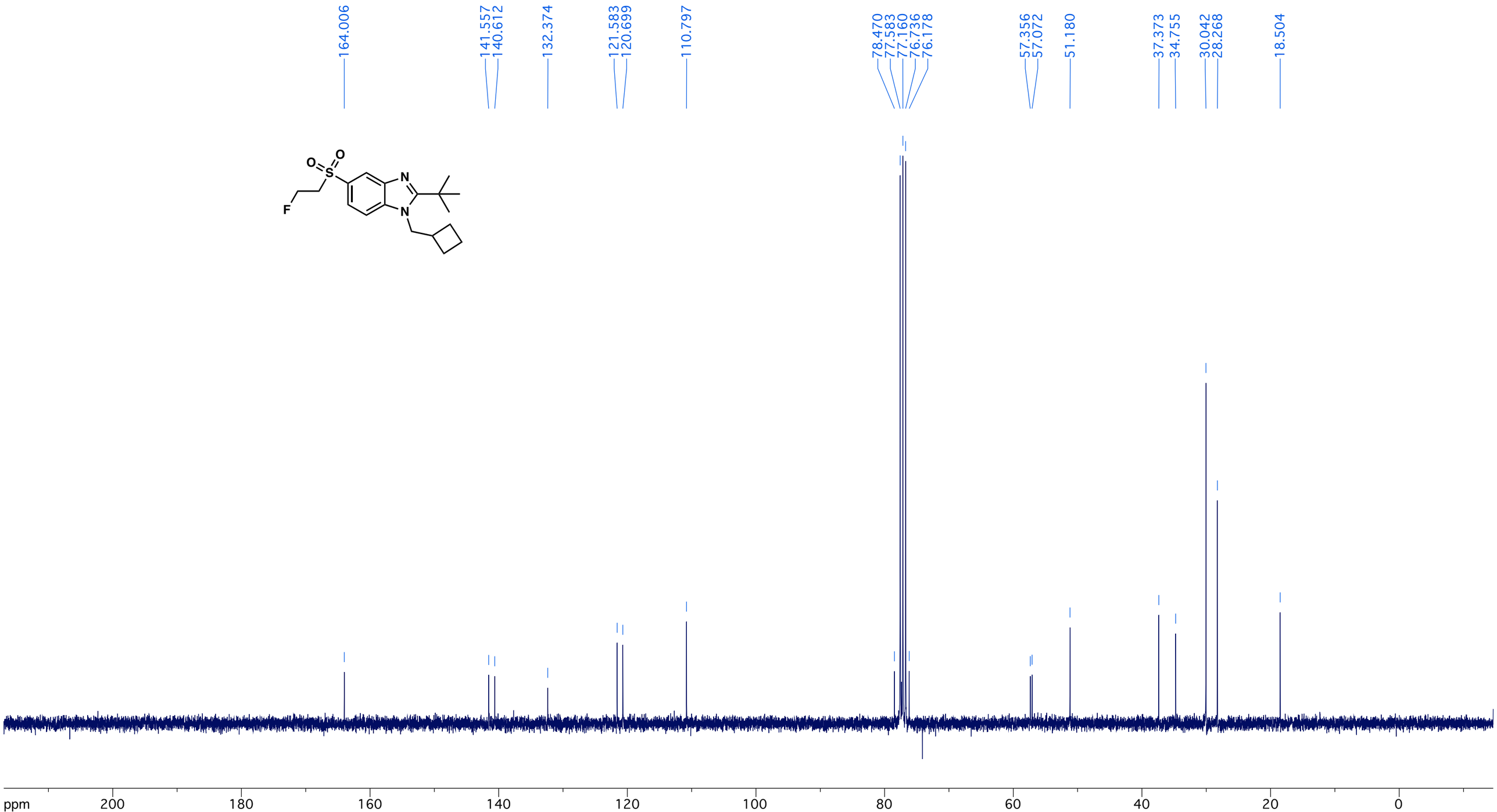
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110.797
78.470
77.583
77.160
76.736
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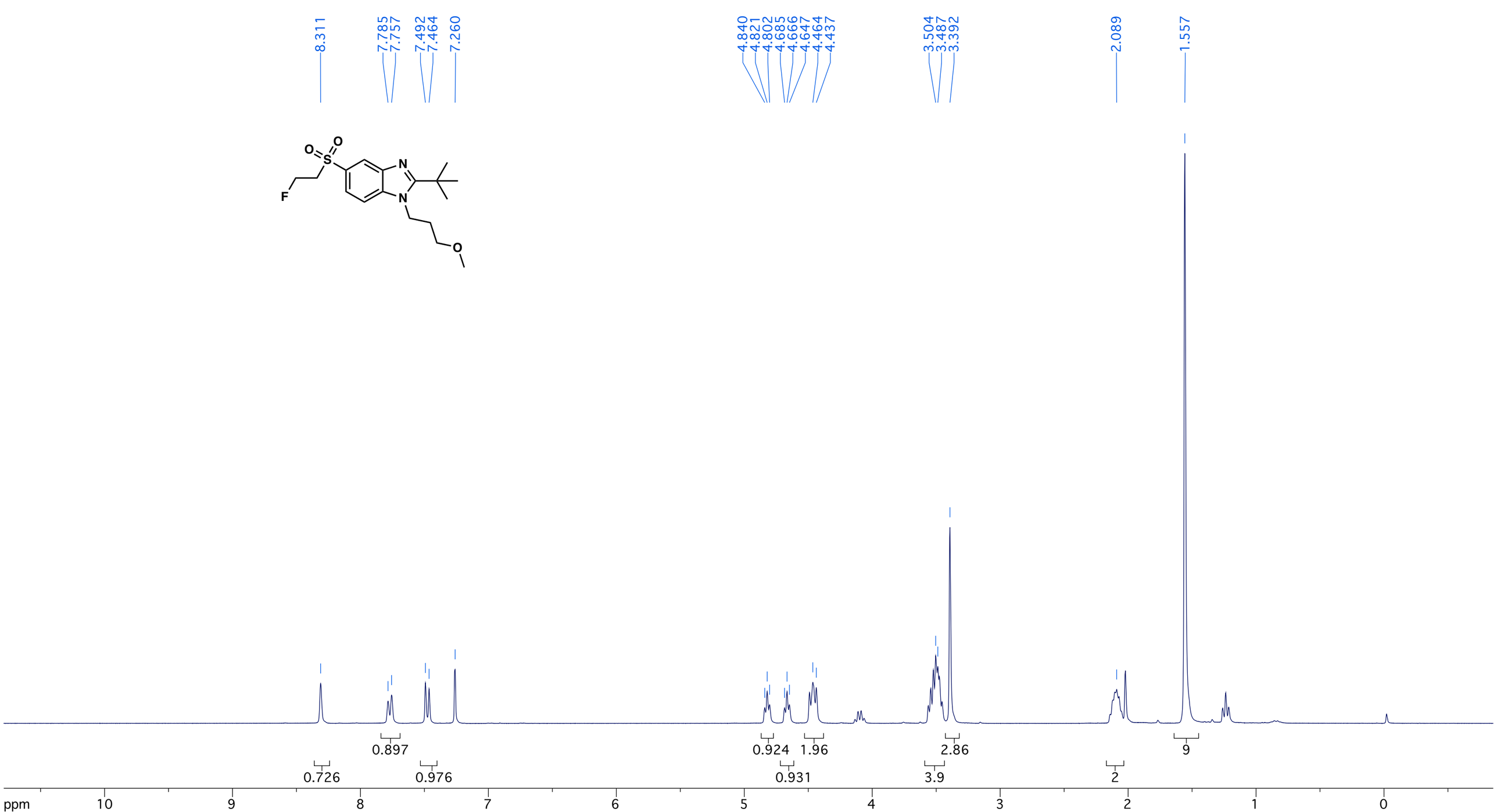
57.356
57.072
51.180
37.373
34.755
30.042
28.268
18.504
O
O
S
F
N
N
ppm
200
180
160
140
120
100
80
60
40
20
0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7.757
7.492
7.464
7.260
4.840
4.821
4.802
4.685
4.666
4.647
4.464
4.437
3.504
3.487
3.392
2.089
1.557
O
O
S
F
N
N
O
0.726
0.897
0.976
0.924
1.96
0.931
3.9
2.86
2
9
ppm
10
9
8
7
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5
4
3
2
1
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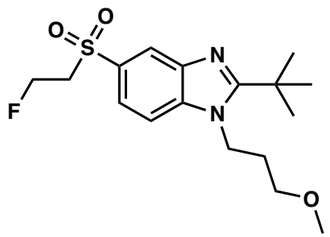
O
O
S
F
N
N
O

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-221.571
-221.661
-221.737
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-221.901
-221.975
ppm
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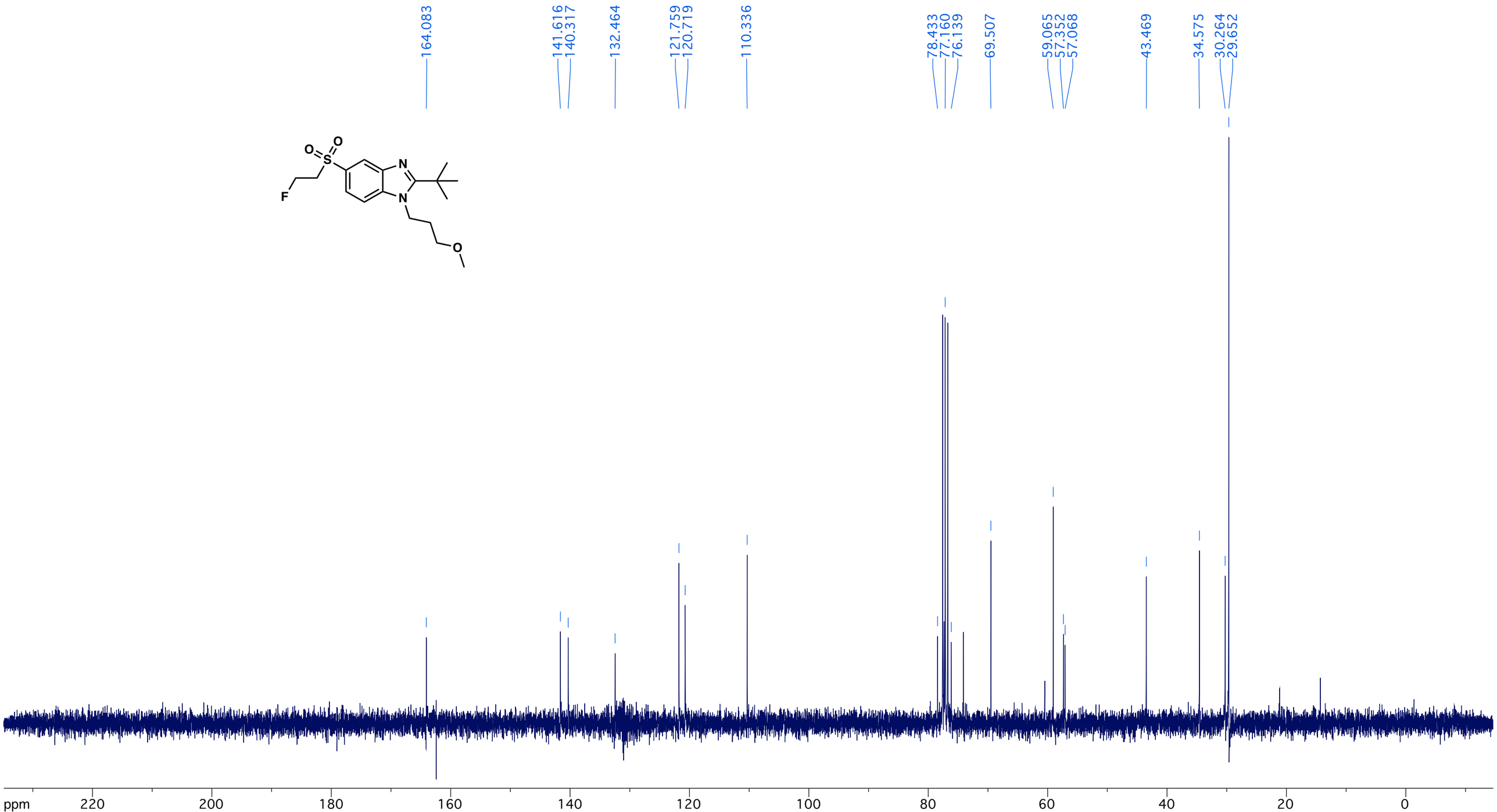
-204
-206
-208
-210
-212
-214
-216
-218
-220
-222
-224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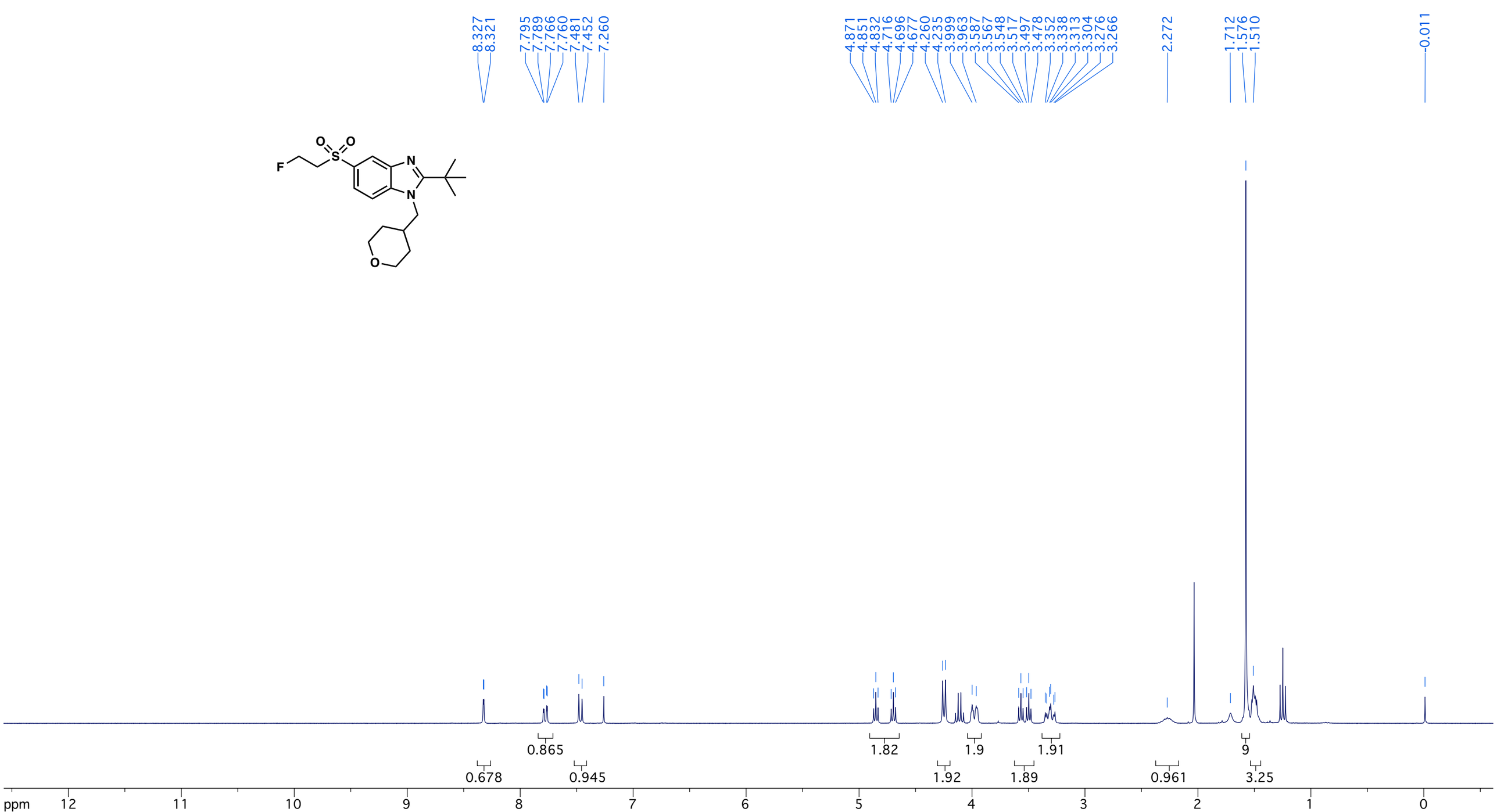
78.433
77.160
76.139
69.507
59.065
57.352
57.068
43.469
34.575
30.264
29.652
O
O
S
F
N
N
O
ppm
220
200
180
160
140
120
100
80
60
40
20
0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7.760
7.481
7.452
7.260
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4.851
4.832
4.716
4.696
4.677
4.260
4.235
3.999
3.963
3.587
3.567
3.548
3.517
3.497
3.478
3.352
3.338
3.313
3.304
3.276
3.266
2.272
1.712
1.576
1.510
0.011
F
O
O
S
N
N
O
0.678
0.865
0.945
1.82
1.92
1.9
1.89
1.91
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3.25
ppm
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7
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4
3
2
1
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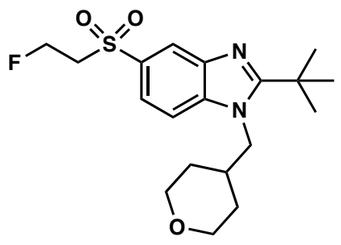
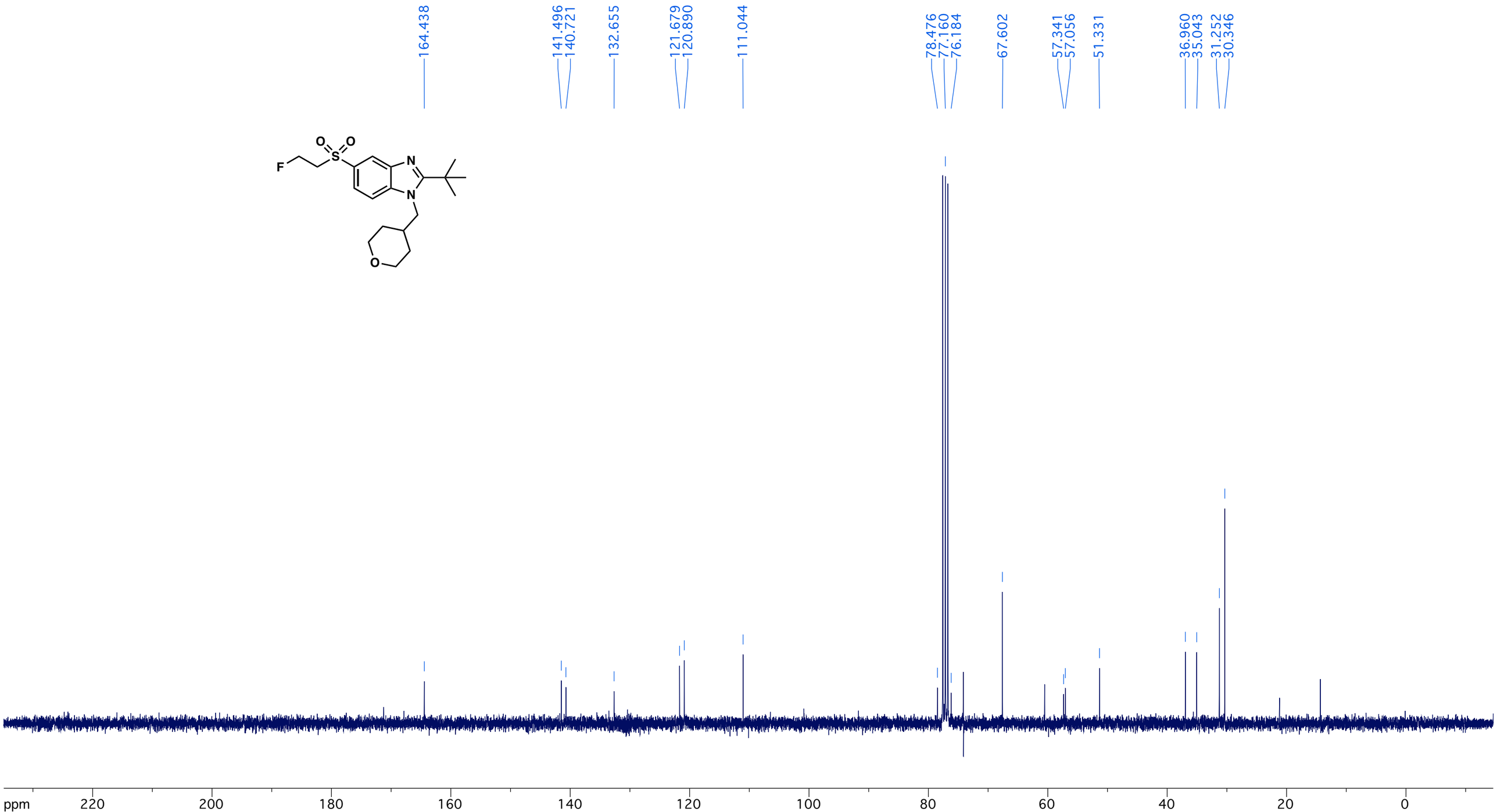


-221.457
-221.531
-221.606
-221.622
-221.696
-221.770
-221.786
-221.861
-221.935

ppm -204 -206 -208 -210 -212 -214 -216 -218 -220 -222 -224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76.184
67.602
57.341
57.056
51.331
36.960
35.043
31.252
30.346
O
O
S
F
N
N
O
ppm
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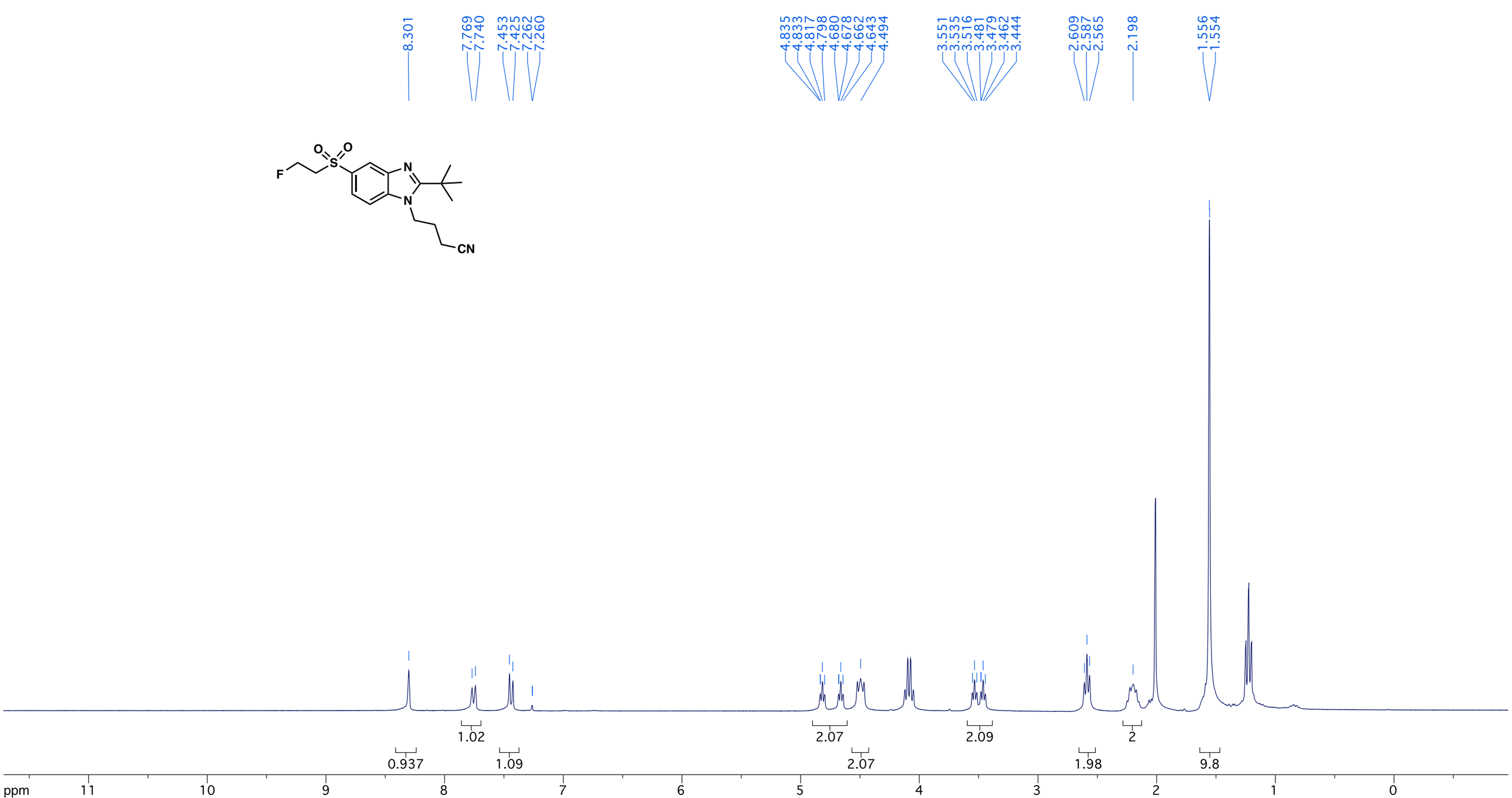
200
180
160
140
120
100
80
60
40
20
0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7.260
4.835
4.833
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4.798
4.680
4.678
4.662
4.643
4.494
3.551
3.535
3.516
3.481
3.479
3.462
3.444
2.609
2.587
2.565
2.198
1.556
1.554
O
O
S
F
N
N
CN
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1.02
1.09
2.07
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2.09
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2
9.8
ppm
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7
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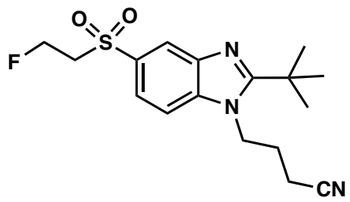
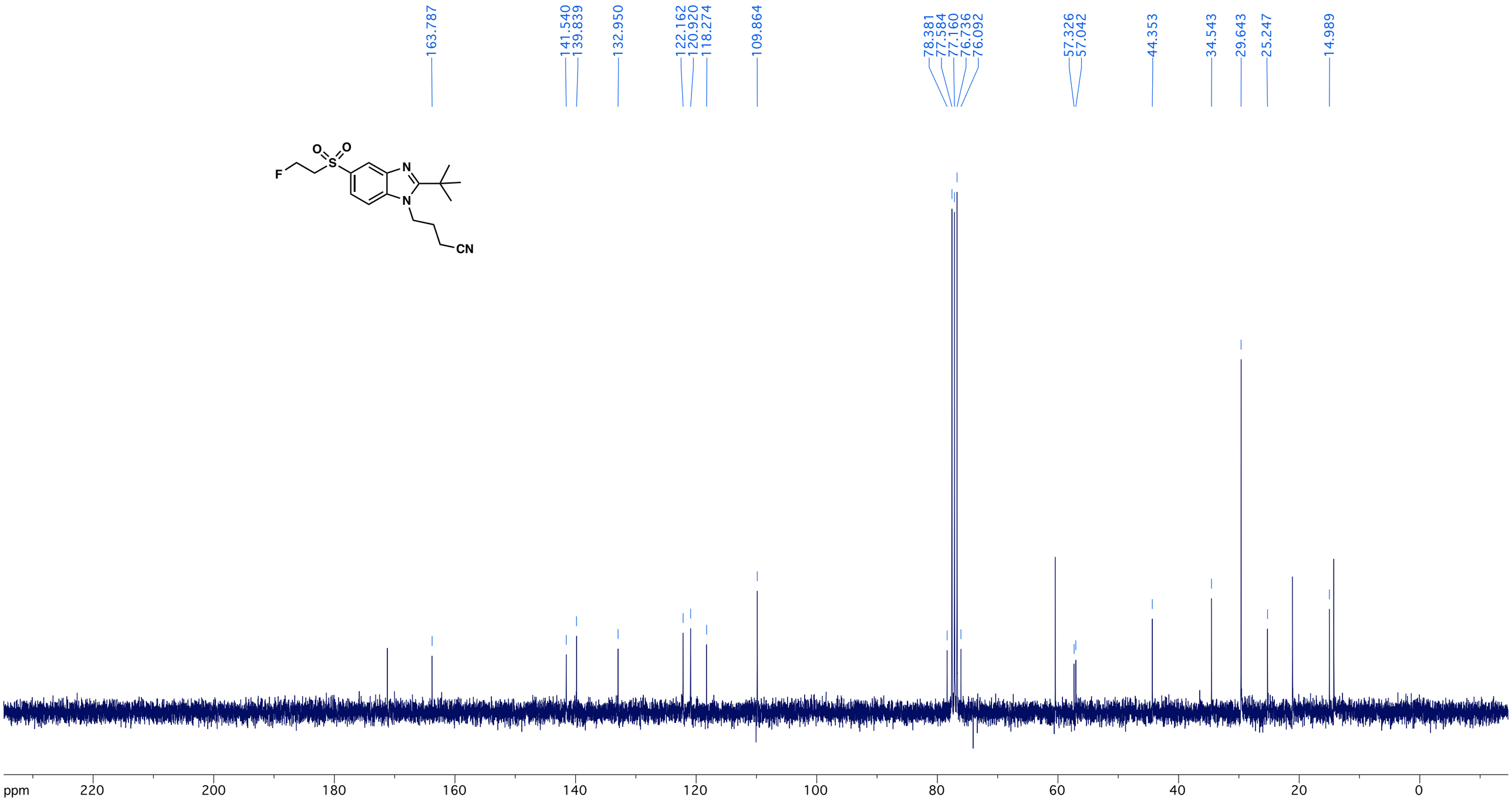


-221.198
-221.274
-221.362
-221.439
-221.516
-221.524
-221.604
-221.681

ppm -210 -211 -212 -213 -214 -215 -216 -217 -218 -219 -220 -221 -222 -223 -224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77.584
77.160
76.736
76.092
57.326
57.042
44.353
34.543
29.643
25.247
14.989
O
O
S
F
N
N
CN
ppm
220
200
180
160
140
120
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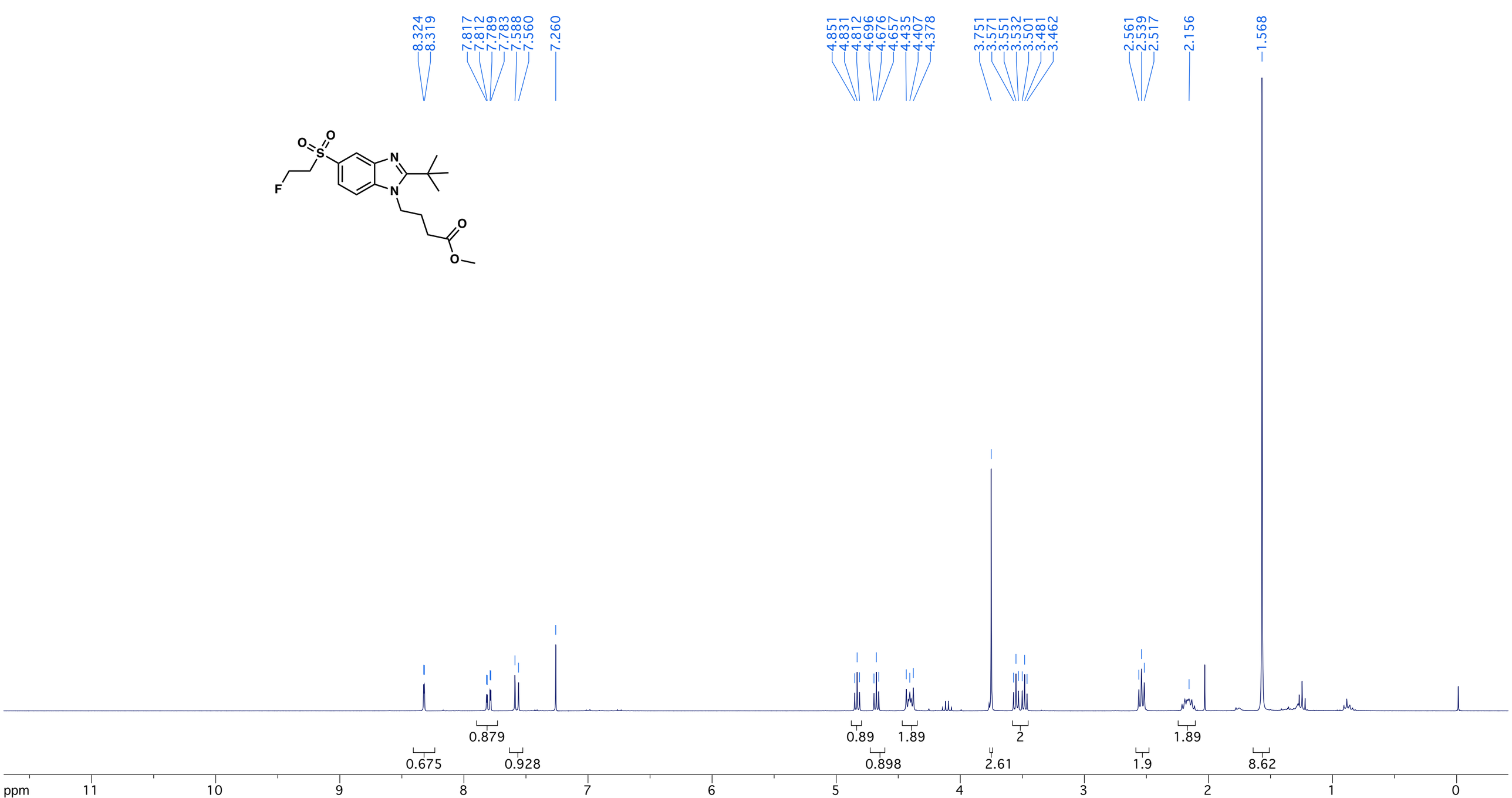
80
60
40
20
0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8.319
7.817
7.812
7.789
7.783
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7.560
7.260
4.851
4.831
4.812
4.696
4.676
4.657
4.435
4.407
4.378
3.751
3.571
3.551
3.532
3.501
3.481
3.462
2.561
2.539
2.517
2.156
1.568
O
O
S
F
N
N
O
O
0.675
0.879
0.928
0.89
0.898
1.89
2
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8.62
ppm
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9
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7
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4
3
2
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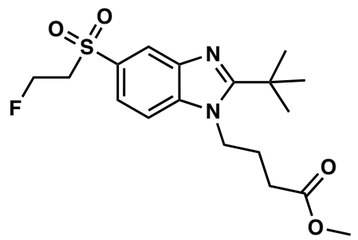

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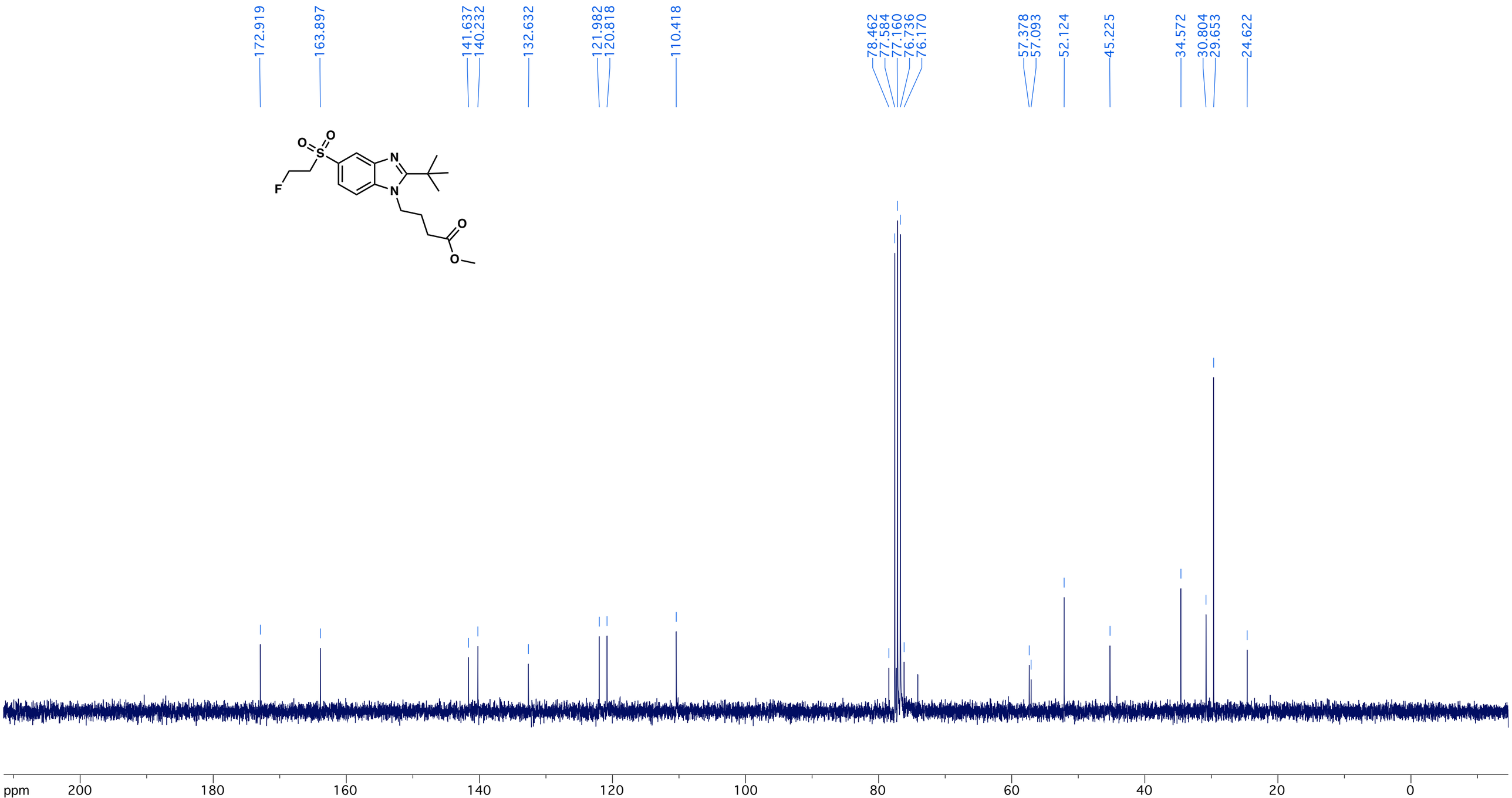
221.812
221.886
221.960

ppm -211 -212 -213 -214 -215 -216 -217 -218 -219 -220 -221 -222 -223 -224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77.584
77.160
76.736
76.170
57.378
57.093
52.124
45.225
34.572
30.804
29.653
24.622
O
O
S
F
N
N
O
O
ppm
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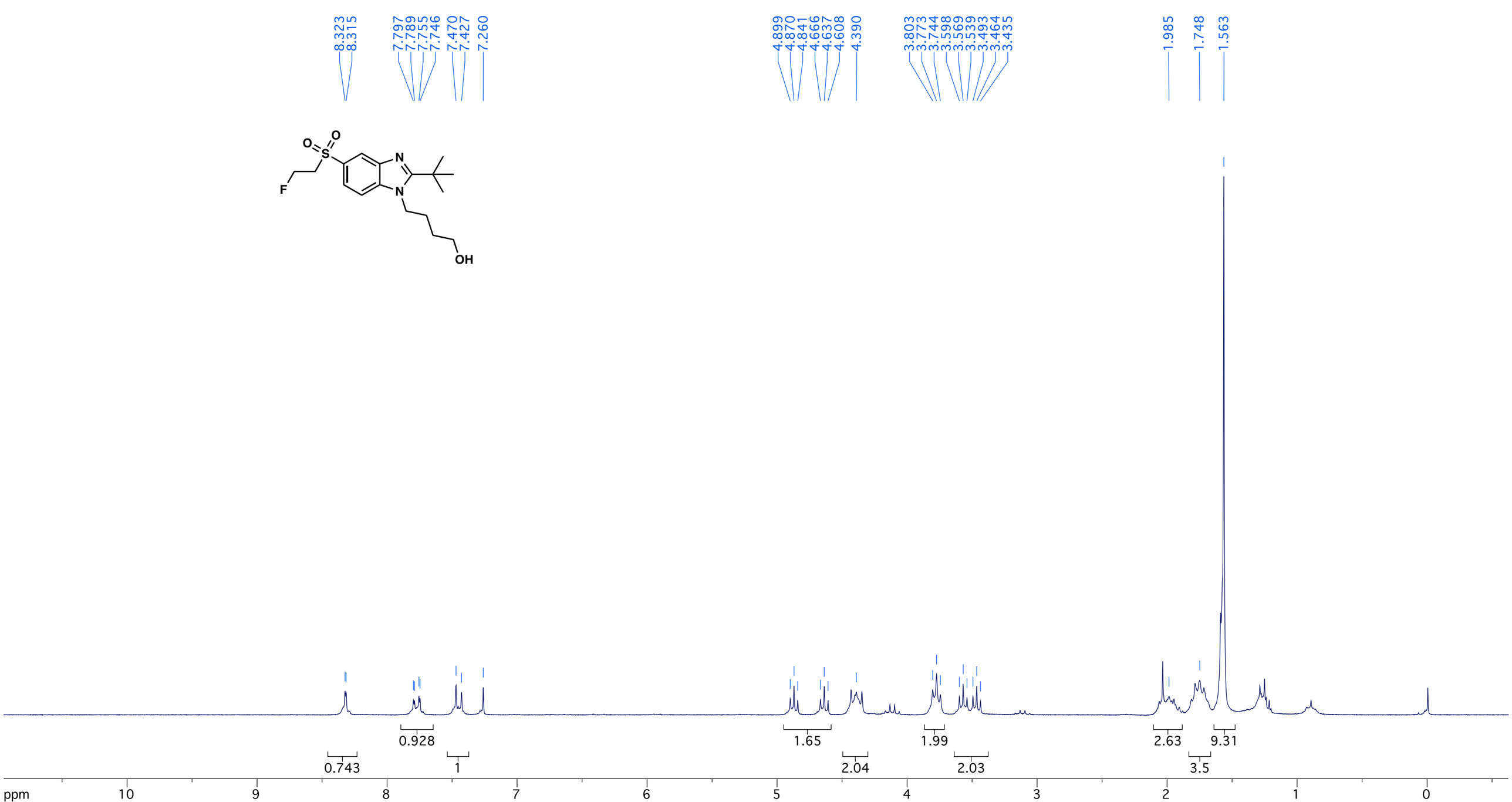
180
160
140
120
100
80
60
40
20
0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7.789
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7.746
7.470
7.427
7.260
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4.870
4.841
4.666
4.637
4.608
4.390
3.803
3.773
3.744
3.598
3.569
3.539
3.493
3.464
3.435
1.985
1.748
1.563
O
O
S
F
N
N
OH
0.743
0.928
1
1.65
2.04
1.99
2.03
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3.5
9.31
ppm
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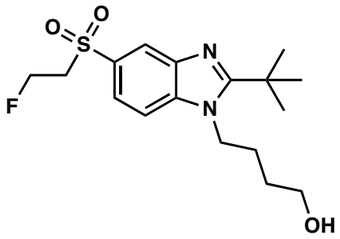
9
8
7
6
5
4
3
2
1
0



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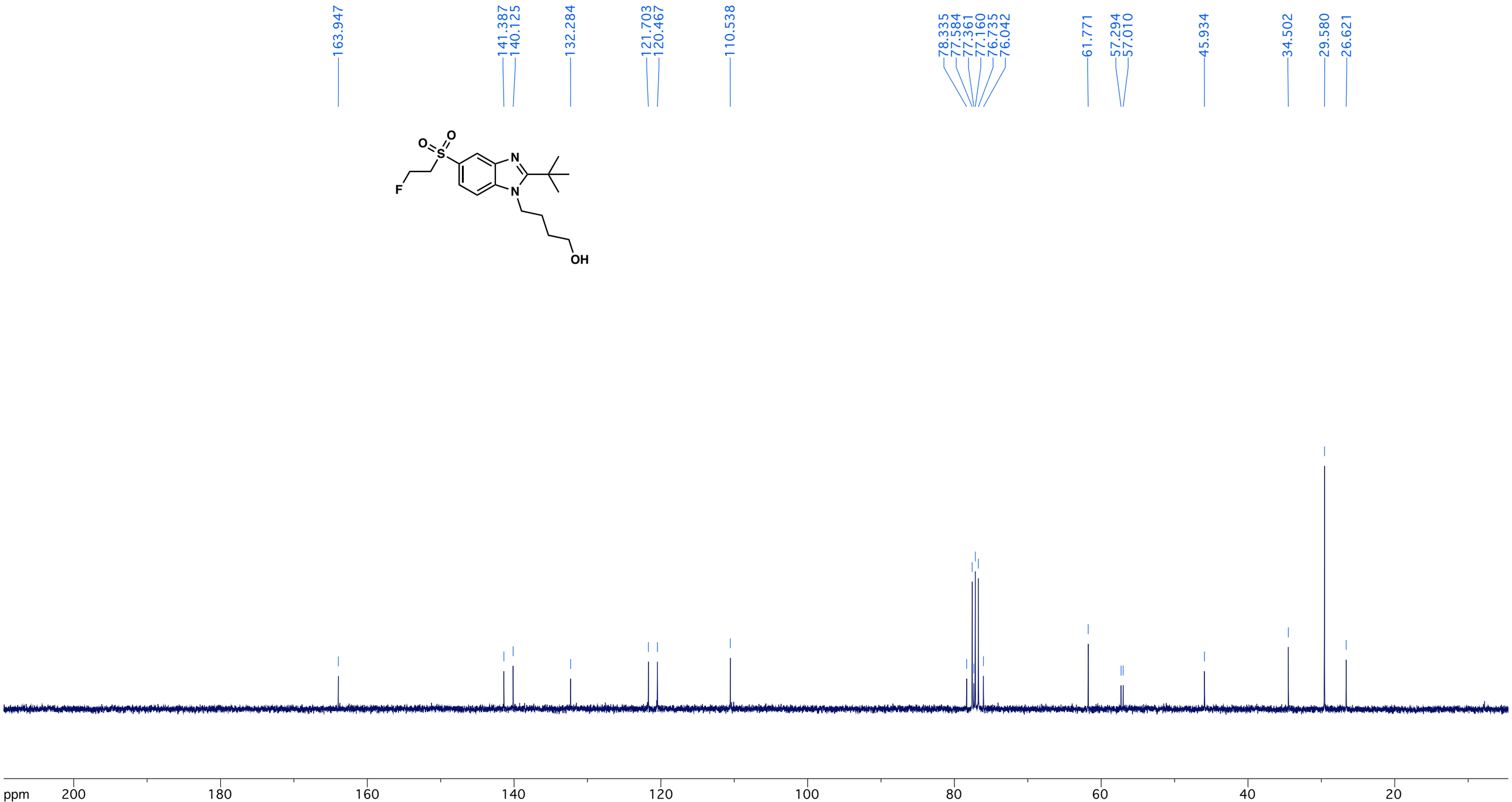
221.720
221.796

ppm
-208
-210
-212
-214
-216
-218
-220
-222
-224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78.335
77.584
77.361
77.160
76.735
76.042
61.771
57.294
57.010
45.934
34.502
29.580
26.621
O
O
S
F
N
N
OH
ppm
200
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160
140
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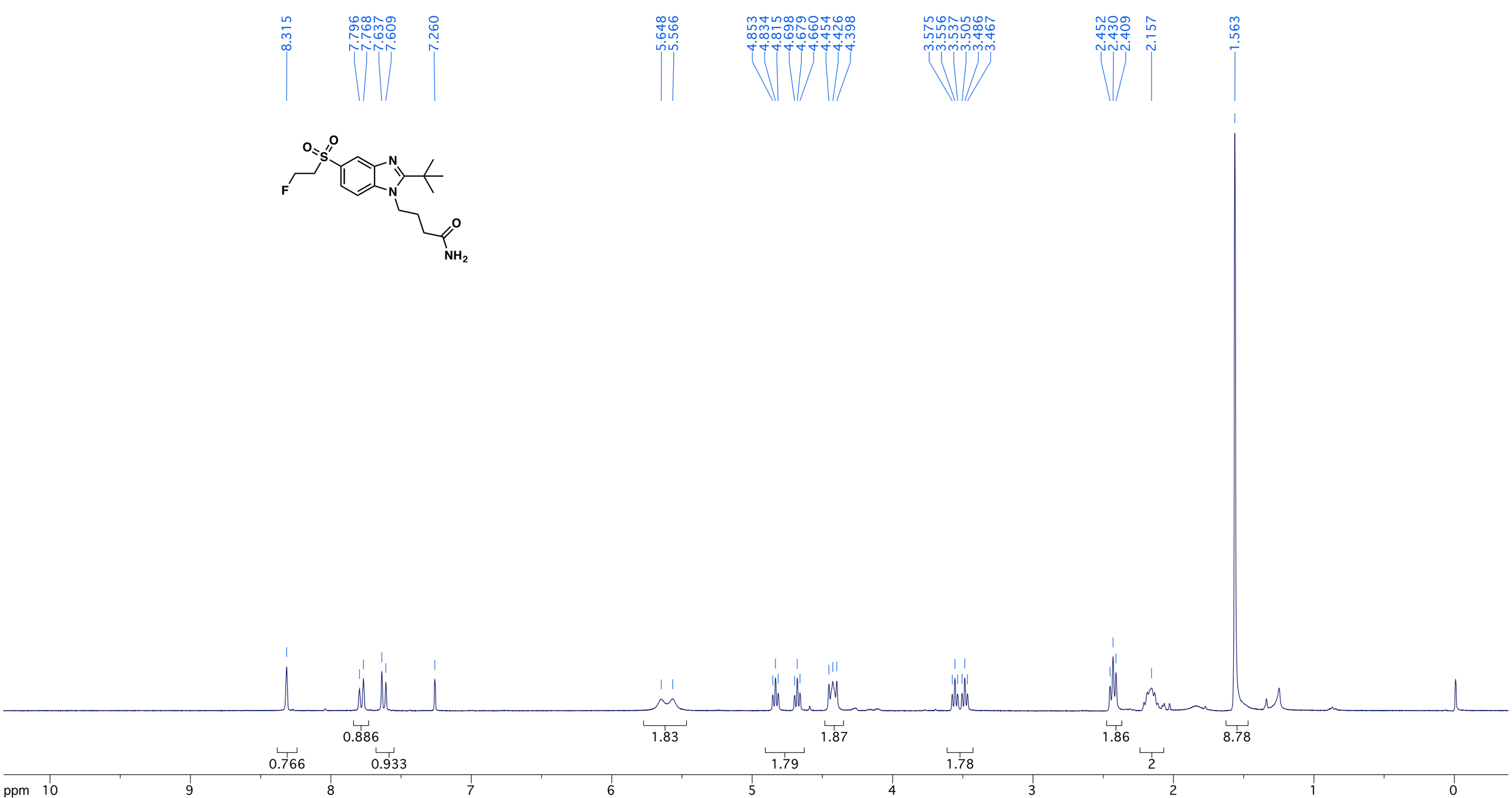
40
20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7.637
7.609
7.260
5.648
5.566
4.853
4.834
4.815
4.698
4.679
4.660
4.454
4.426
4.398
3.575
3.556
3.537
3.505
3.486
3.467
2.452
2.430
2.409
2.157
1.563
O
O
S
N
N
F
O
NH2
0.766
0.886
0.933
1.83
1.79
1.87
1.78
1.86
2
8.78
ppm
10
9
8
7
6
5
4
3
2
1
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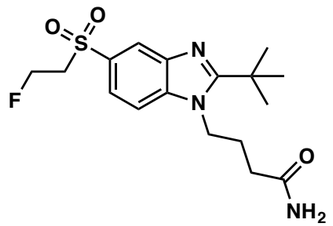

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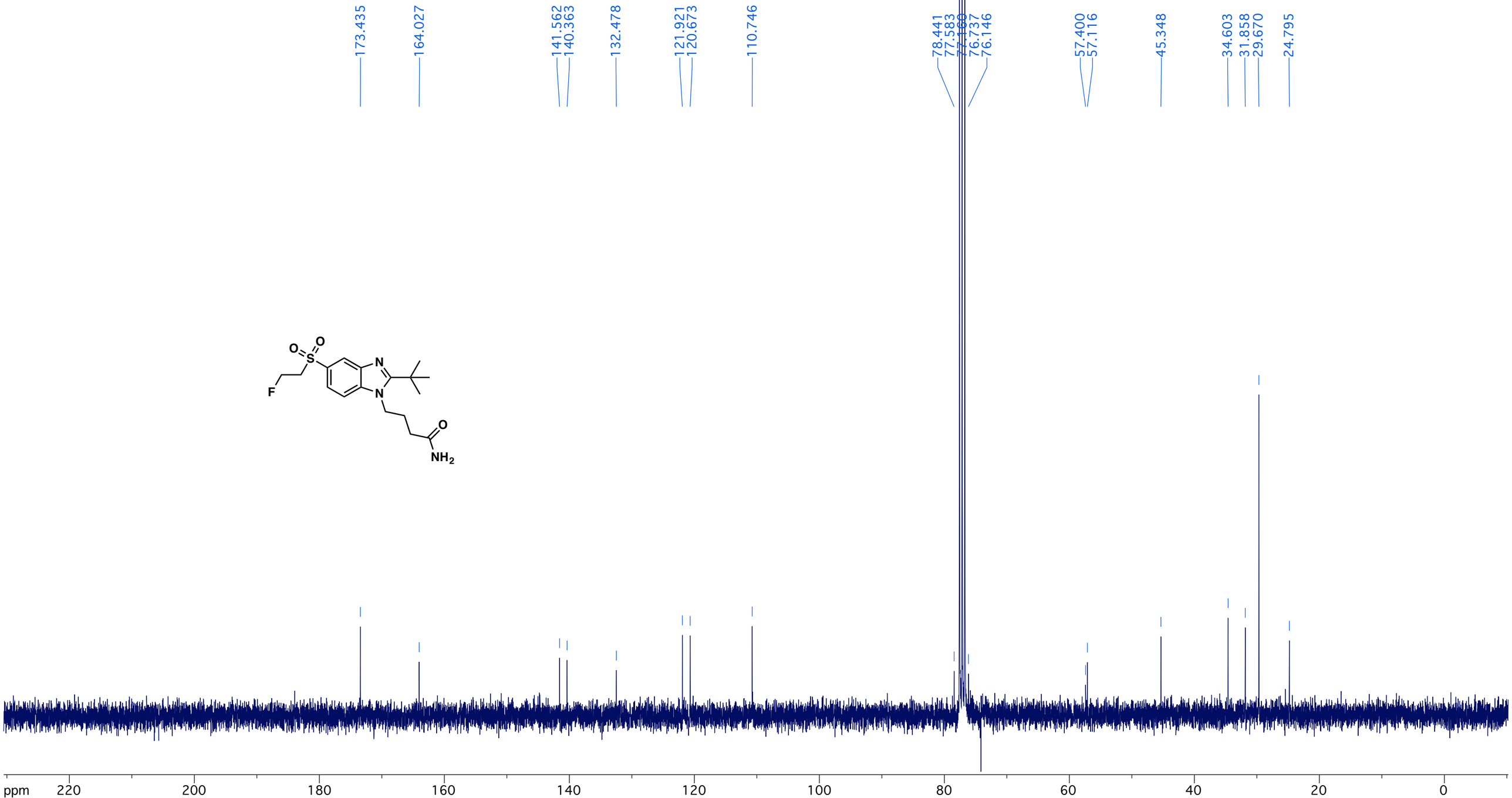
-221.484
-221.559
-221.574
-221.649
-221.724
-221.738
-221.814
-221.888

ppm
-206
-208
-210
-212
-214
-216
-218
-220
-222
-224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141.562
140.363
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121.921
120.673
110.746
78.441
77.583
77.160
76.737
76.146
57.400
57.116
45.348
34.603
31.858
29.670
24.795
O
O
S
F
N
N
O
NH2
ppm
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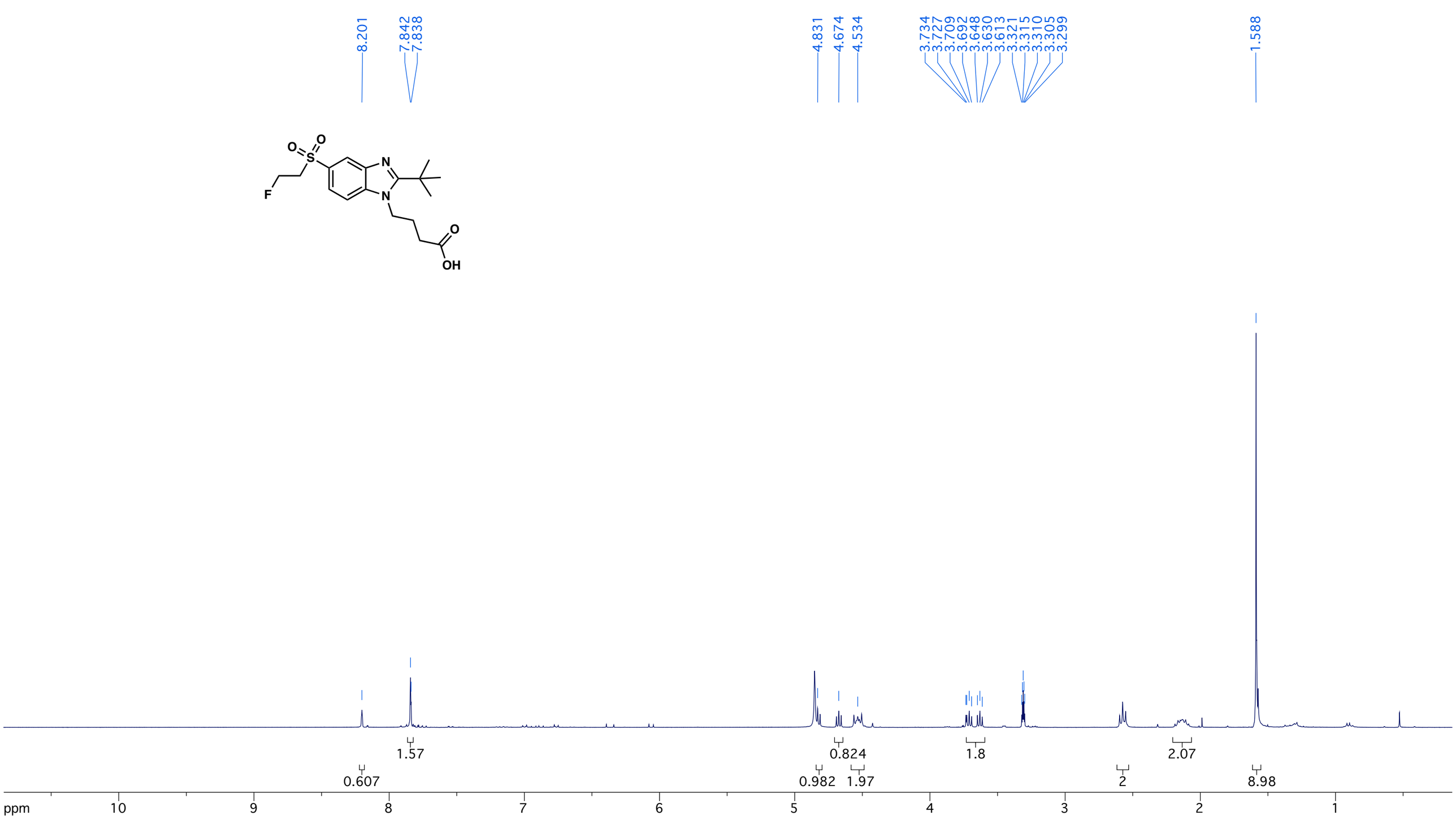
200
180
160
140
120
100
80
60
40
20
0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7.842
7.838
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4.674
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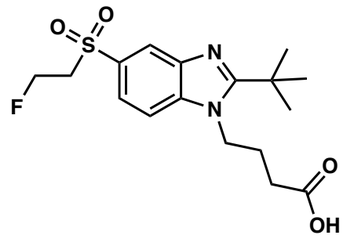
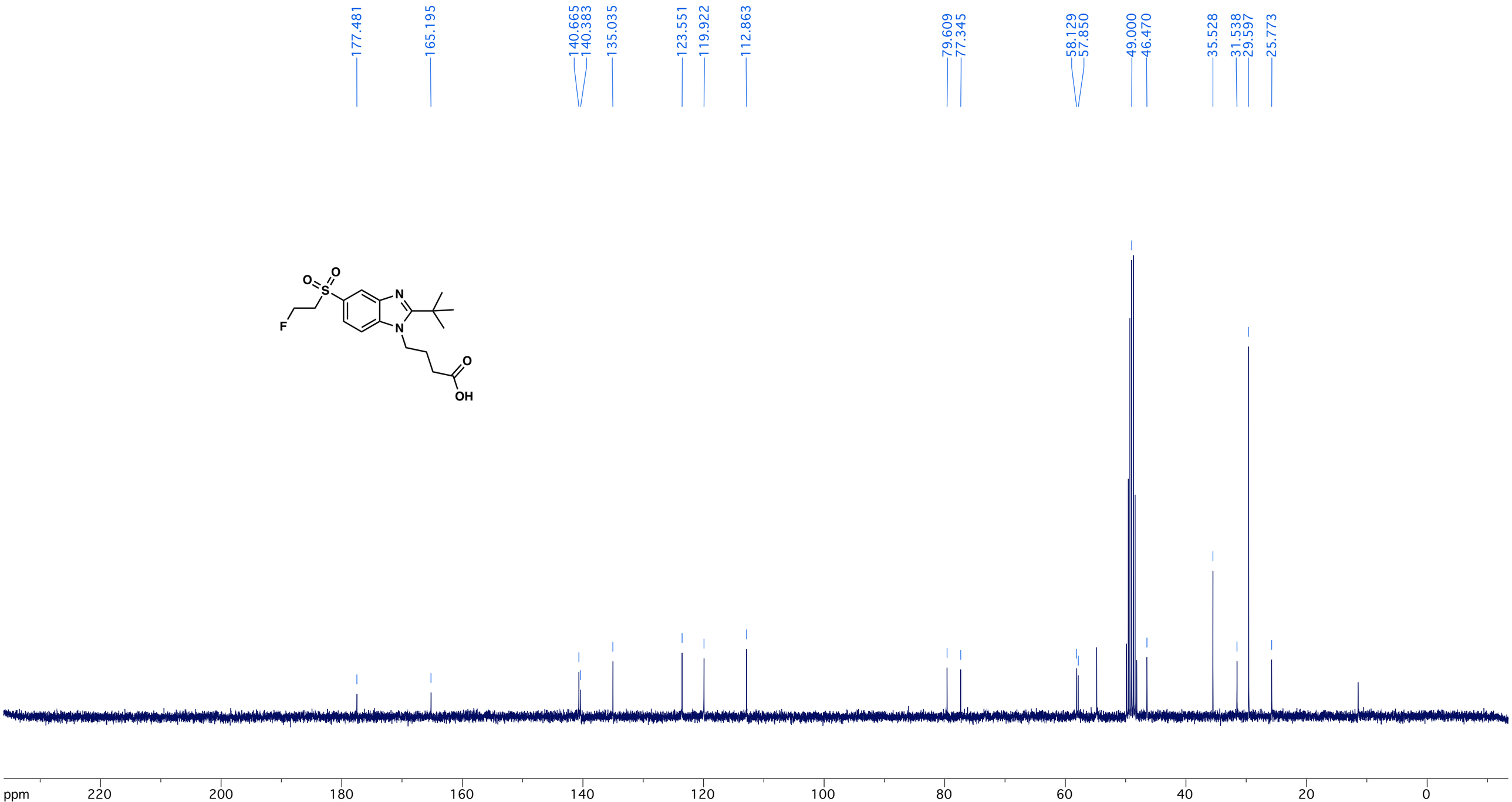
3.734
3.727
3.709
3.692
3.648
3.630
3.613
3.321
3.315
3.310
3.305
3.299
1.588
O
O
S
F
N
N
O
OH
1.57
0.824
1.8
2.07
0.607
0.982
1.97
2
8.98
ppm
10
9
8
7
6
5
4
3
2
1



-221.918
-222.003
-222.086
-222.169
-222.253
-222.335
-222.420

ppm
-210
-212
-214
-216
-218
-220
-222
-224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165.195
140.665
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123.551
119.922
112.863
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77.345
58.129
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49.000
46.470
35.528
31.538
29.597
25.773
O
O
S
F
N
N
O
OH
ppm
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200
180
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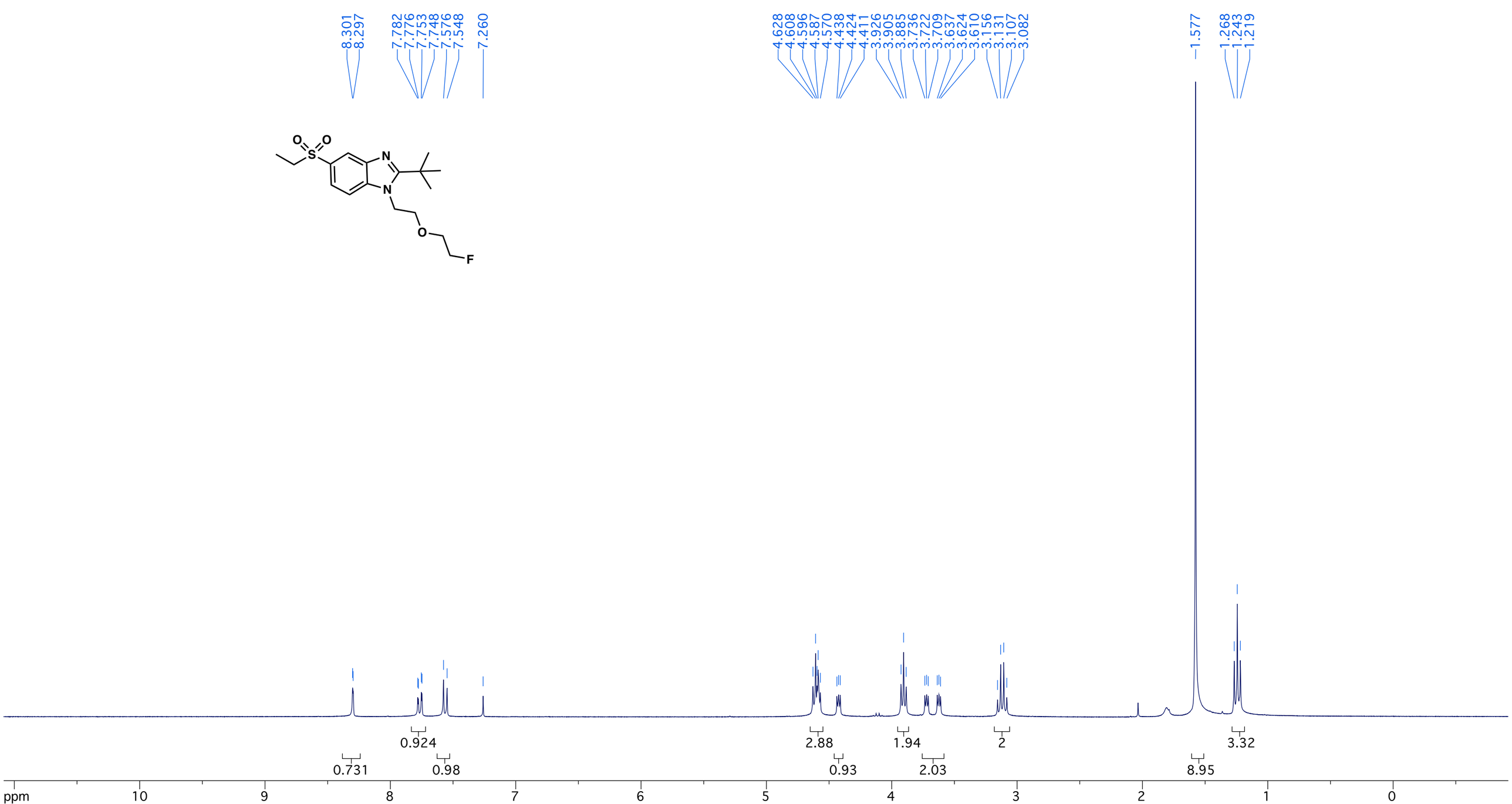
140
120
100
80
60
40
20
0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8.297
7.782
7.776
7.753
7.748
7.576
7.548
7.260
4.628
4.608
4.596
4.587
4.570
4.438
4.424
4.411
3.926
3.905
3.885
3.736
3.722
3.709
3.637
3.624
3.610
3.156
3.131
3.107
3.082
1.577
1.268
1.243
1.219
O
O
S
N
N
O
F
0.731
0.924
0.98
2.88
0.93
1.94
2.03
2
8.95
3.32
ppm
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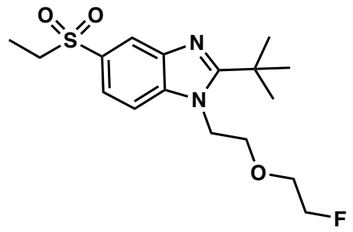
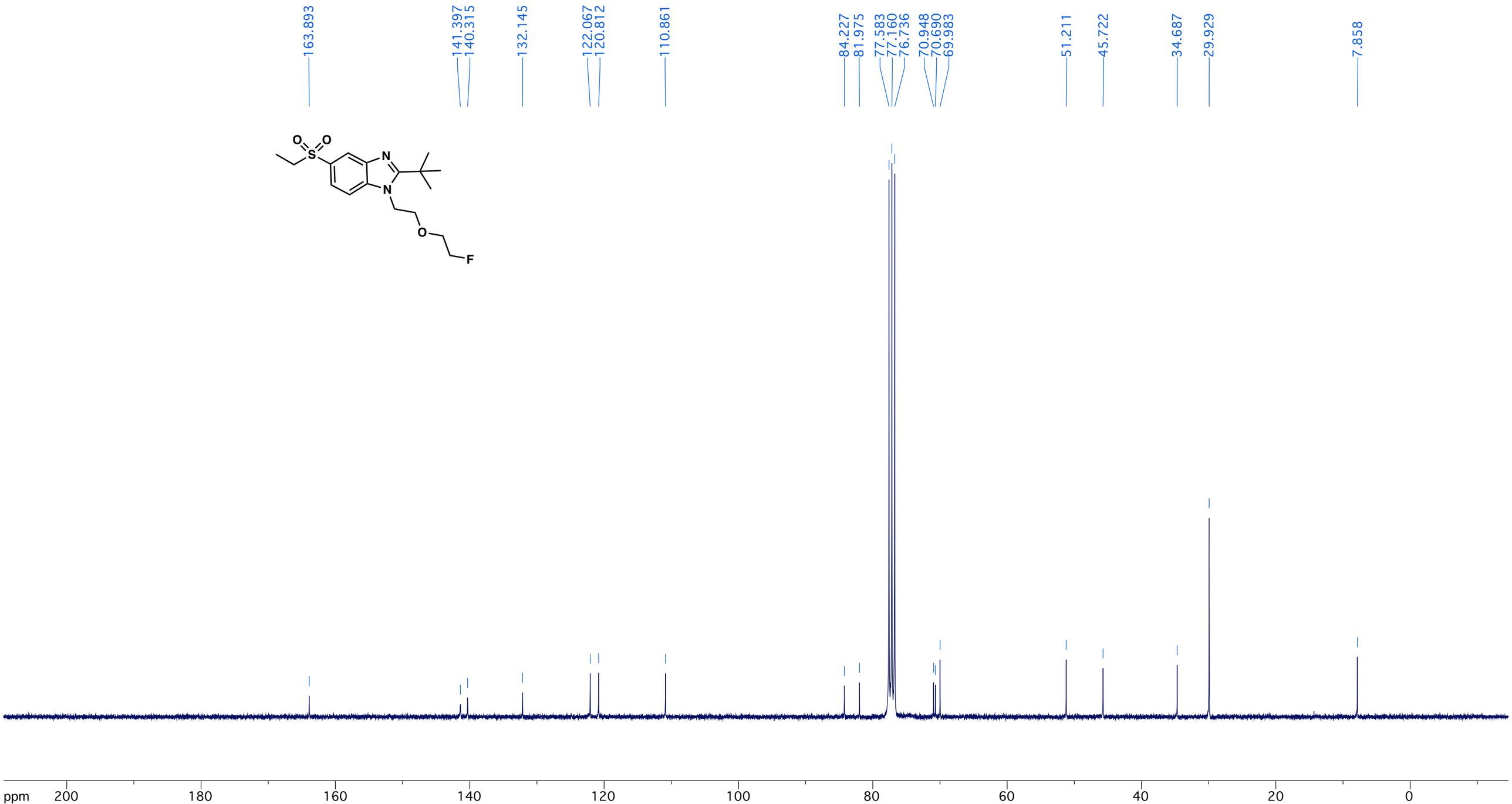
9
8
7
6
5
4
3
2
1
0



-222.658
-222.763
-222.827
-222.868
-222.931
-222.995
-223.037
-223.101
-223.205

ppm -210 -211 -212 -213 -214 -215 -216 -217 -218 -219 -220 -221 -222 -223 -224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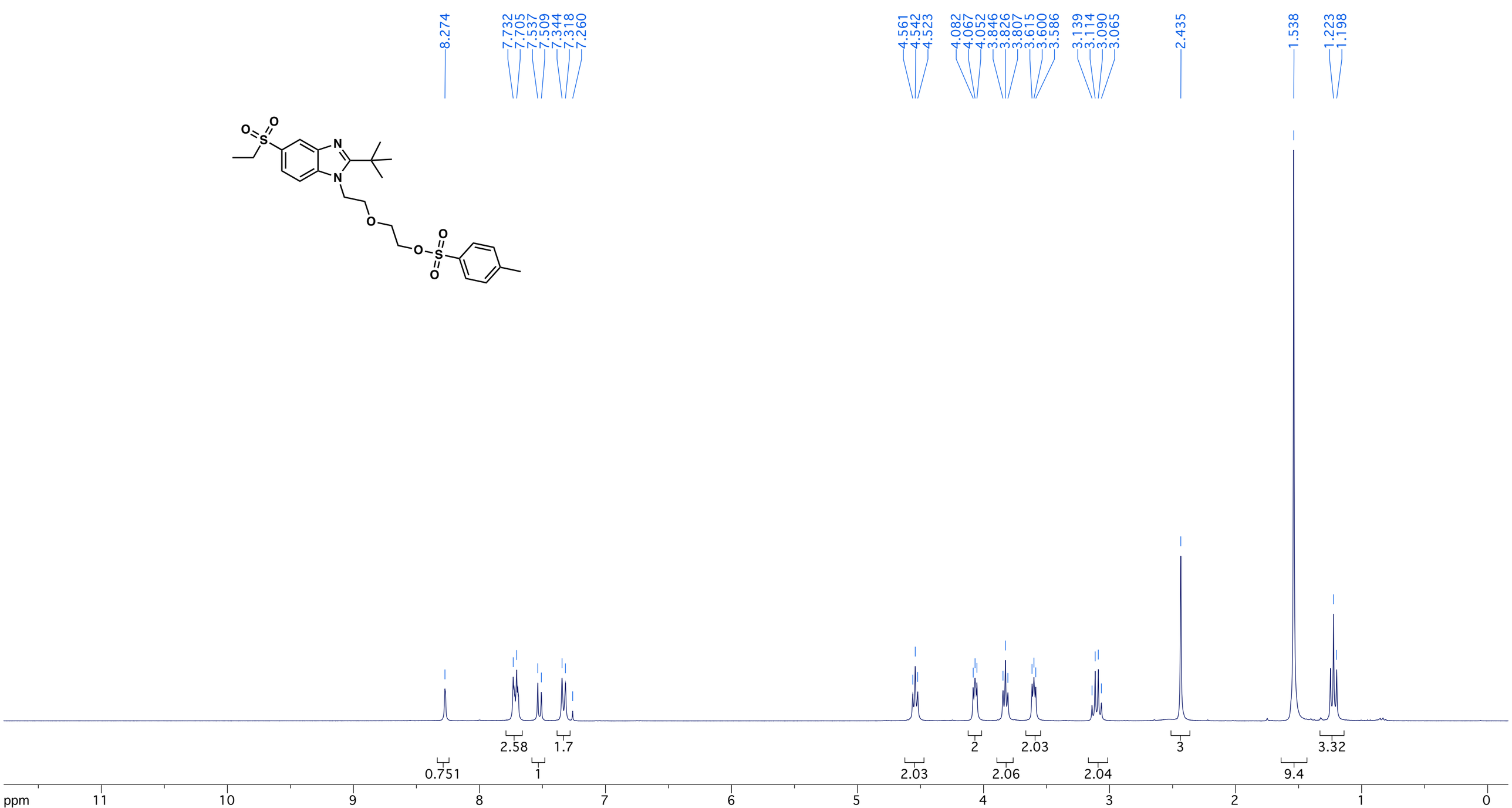
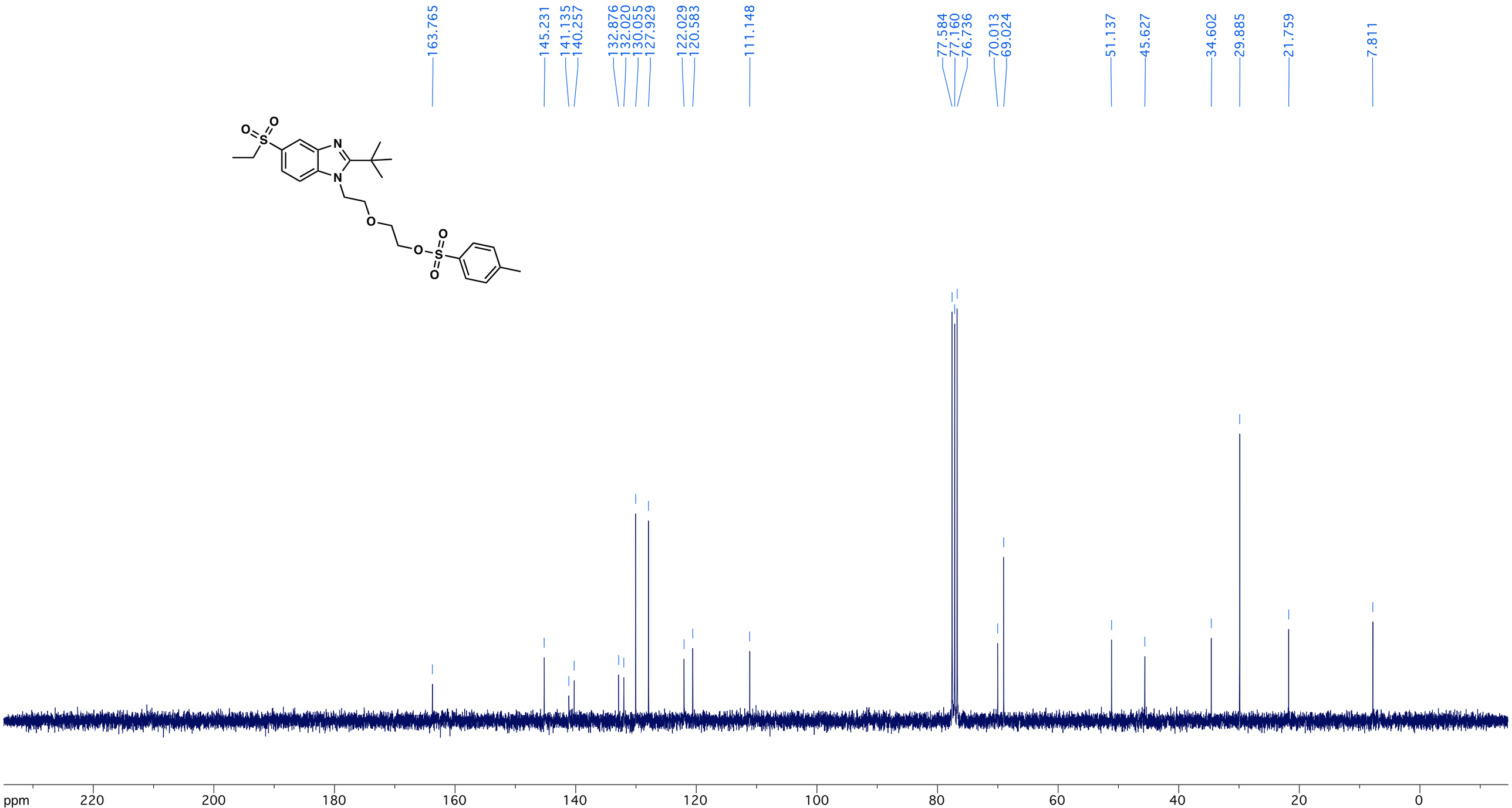
141.397
140.315
132.145
122.067
120.812
110.861
84.227
81.975
77.583
77.160
76.736
70.948
70.690
69.983
51.211
45.722
34.687
29.929
7.858
O
O
S
N
N
O
F
ppm
200
180
160
140
120
100
80
60
40
20
0


8.274
7.732
7.705
7.537
7.509
7.344
7.318
7.260
4.561
4.542
4.523
4.082
4.067
4.052
3.846
3.826
3.807
3.615
3.600
3.586
3.139
3.114
3.090
3.065
2.435
1.538
1.223
1.198
2.58
1.7
2
2.03
3
3.32
0.751
1
2.03
2.06
2.04
9.4
ppm
11
10
9
8
7
6
5
4
3
2
1
0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145.231
141.135
140.257
132.876
132.020
130.055
127.929
122.029
120.583
111.148
77.584
77.160
76.736
70.013
69.024
51.137
45.627
34.602
29.885
21.759
7.811
ppm
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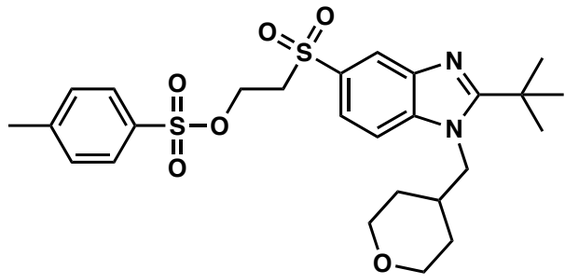
200
180
160
140
120
100
80
60
40
20
0



8.186
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7.718
7.713
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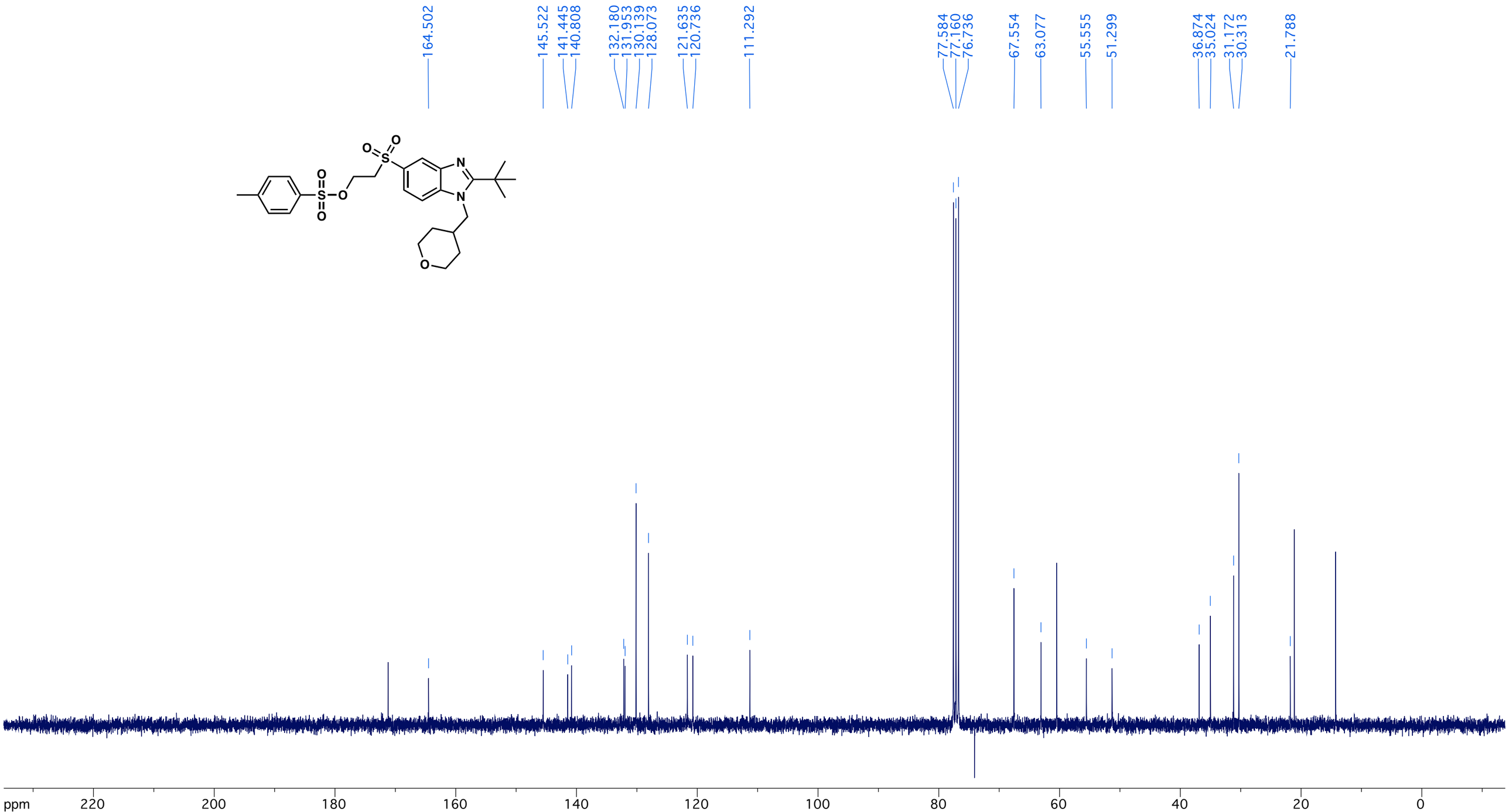
7.684
7.661
7.634
7.484
7.456
7.333
7.306
7.260

4.306
4.283
4.261
4.236
3.978
3.941
3.474
3.451
3.429
3.291
2.439
2.269
1.573
1.551
1.538
1.507
1.494
1.477
1.466

1.04 1.06 2.03 2.41 2.36 1.22 2.23
0.82 1.86 1.78 2.01 2.03 2.87 9 3.94

ppm 11 10 9 8 7 6 5 4 3 2 1 0


164.502
145.522
141.445
140.808
132.180
131.953
130.139
128.073
121.635
120.736
111.292
77.584
77.160
76.736
67.554
63.077
55.555
51.299
36.874
35.024
31.172
30.313
21.788
O
O
S
O
O
S
O
O
N
N
O
ppm
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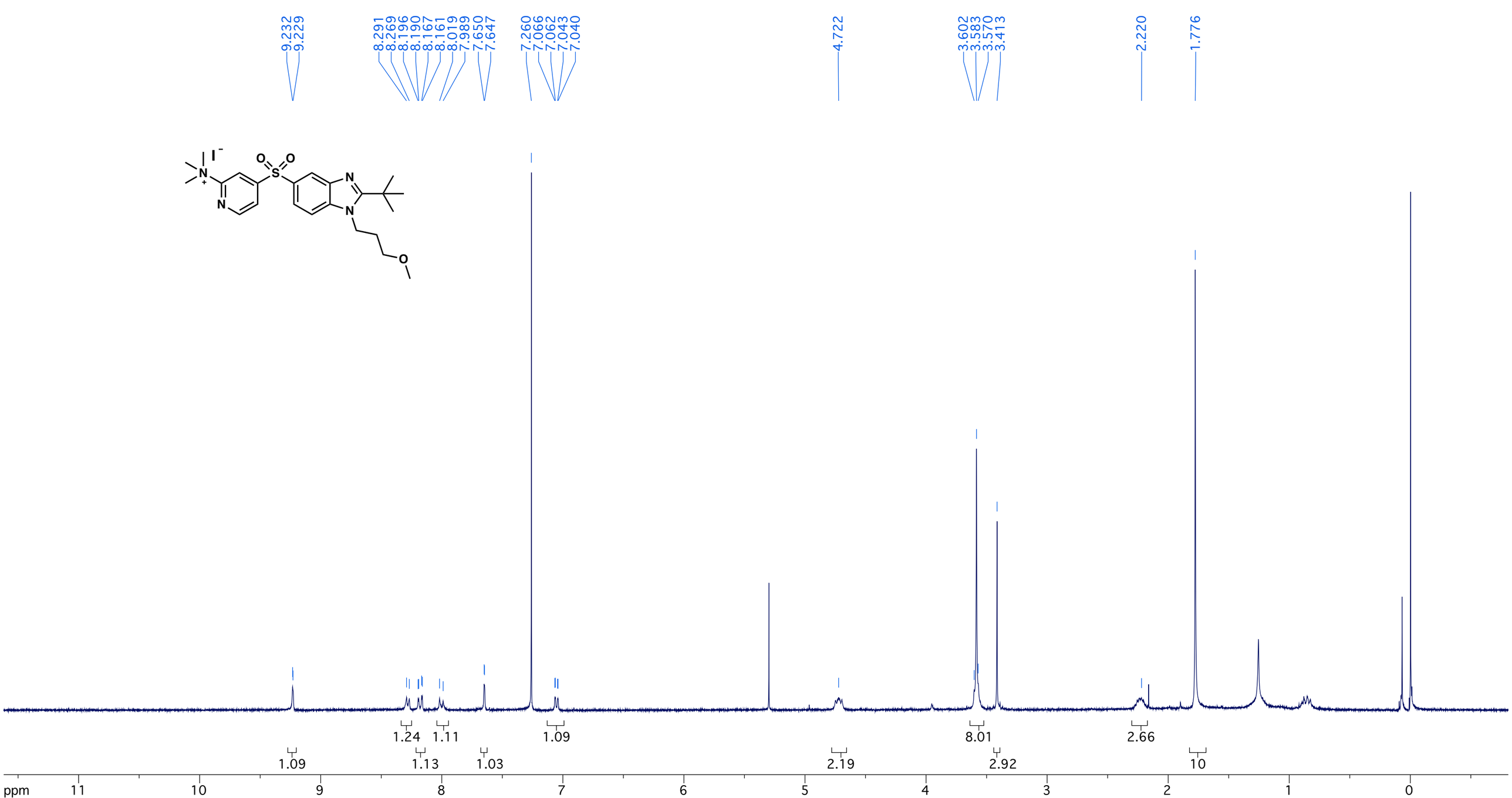
200
180
160
140
120
100
80
60
40
20
0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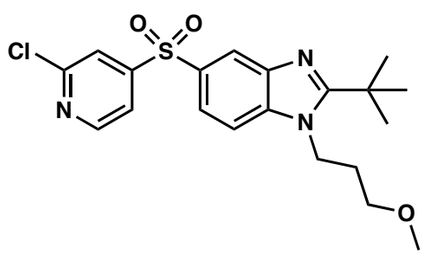
8.269
8.196
8.190
8.167
8.161
8.019
7.989
7.650
7.647
7.260
7.066
7.062
7.043
7.040
4.722
3.602
3.583
3.570
3.413
2.220
1.776
1.24
1.11
1.09
8.01
2.66
1.09
1.13
1.03
2.19
2.92
10
ppm
11
10
9
8
7
6
5
4
3
2
1
0


O
O
S
Cl
N
N
N
O

8.520
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8.366
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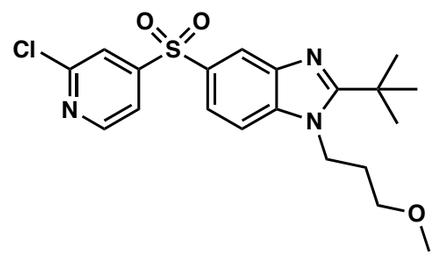
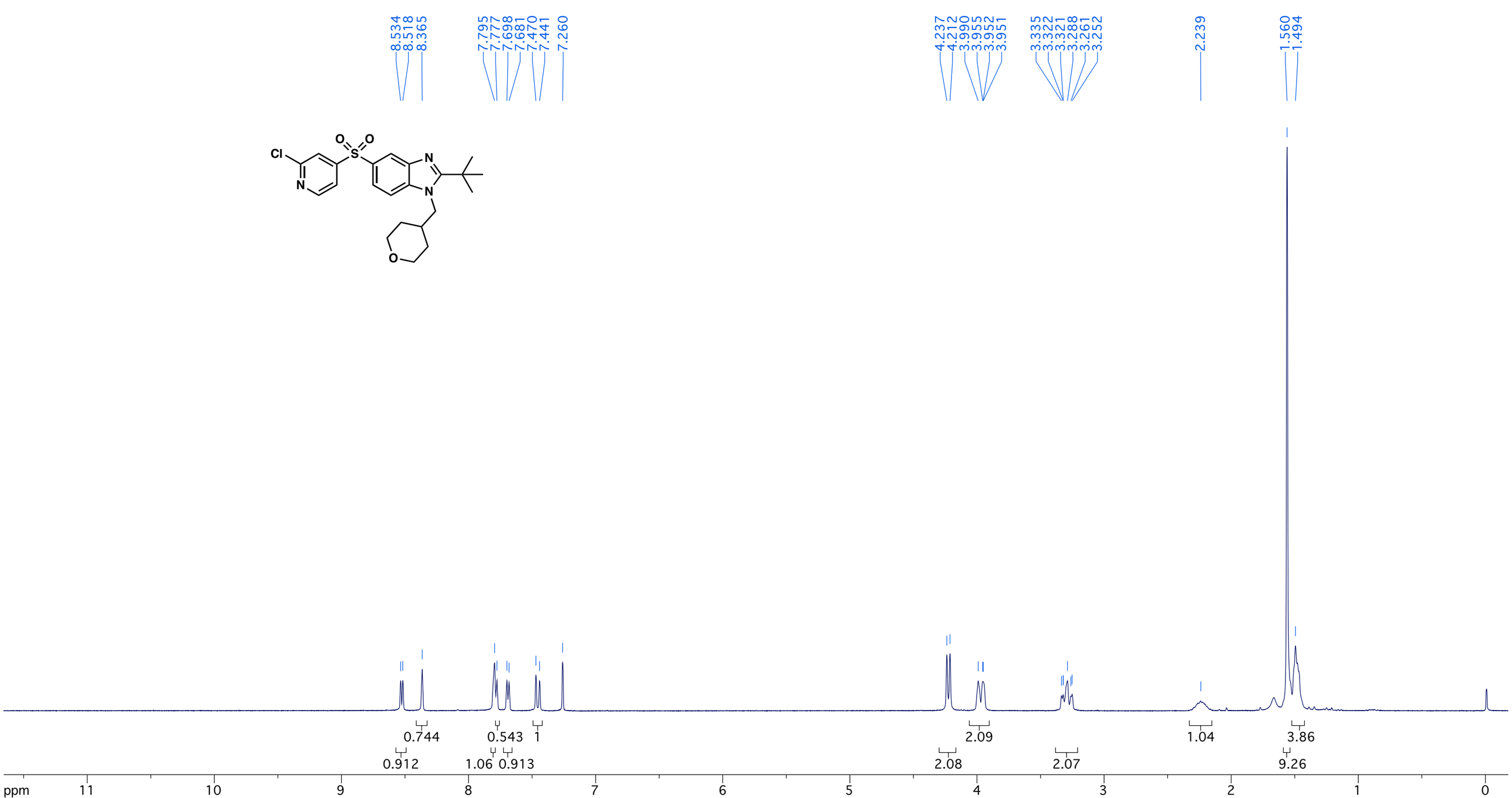
7.796
7.780
7.682
7.665
7.498
7.470
7.260
4.455
3.517
3.499
3.481
3.398
2.107
2.088
2.073
2.055
1.554
0.702
0.702
0.994
0.921
0.939
0.871
2.08
2.21
2.1
2.83
9.17
ppm
9
8
7
6
5
4
3
2
1
0

164.574
153.737
152.948
151.129
141.966
140.697
132.180
121.909
121.847
121.125
119.405
110.847
77.160
69.492
59.115
43.548
34.670
30.330
29.661

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7.698
7.681
7.470
7.441
7.260
4.237
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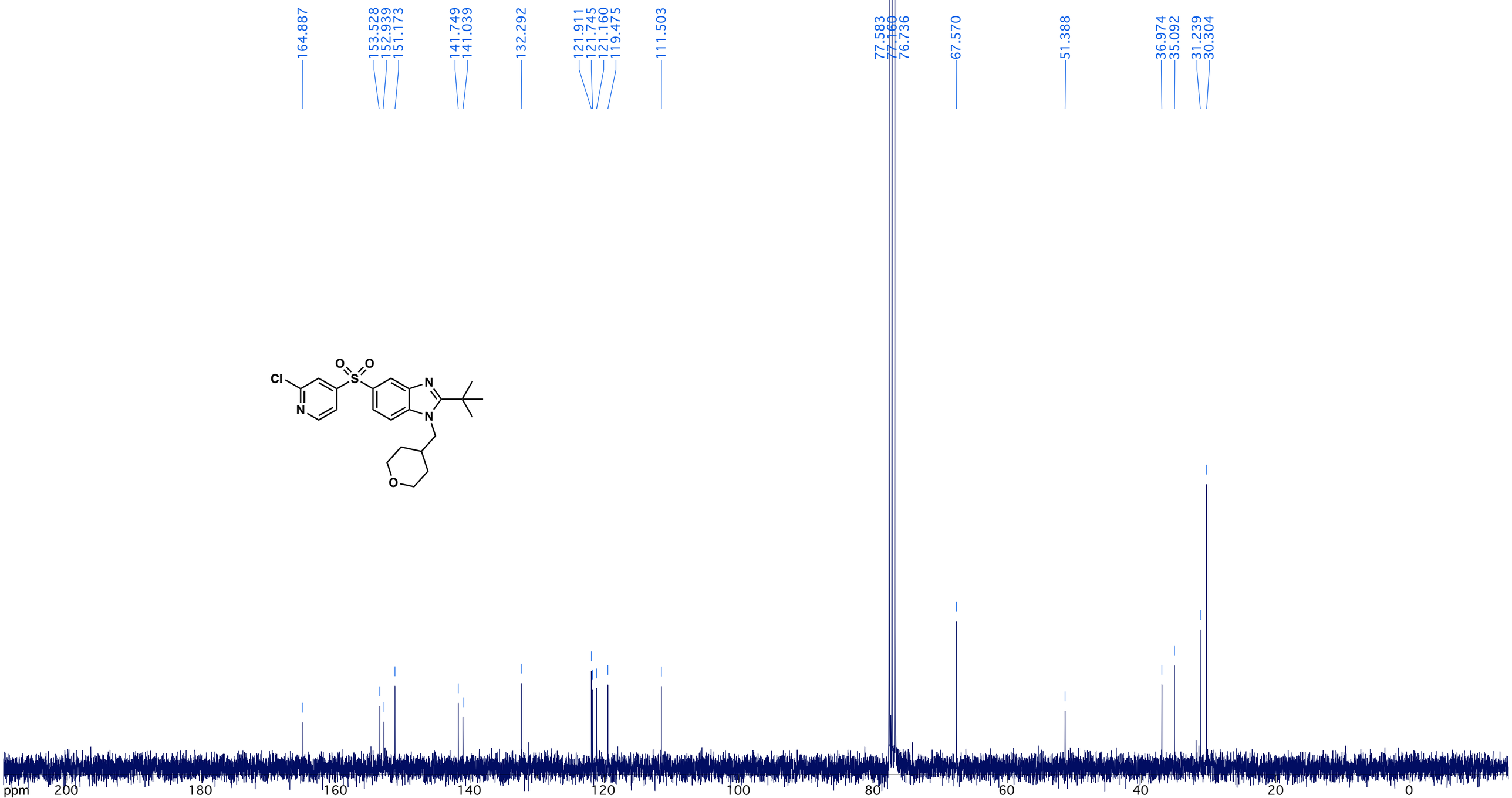
3.955
3.952
3.951
3.335
3.322
3.321
3.288
3.261
3.252
2.239
1.560
1.494
Cl
N
O
S
O
N
N
O
0.744
0.543
1
2.09
1.04
3.86
0.912
1.06
0.913
2.08
2.07
9.26
ppm
11
10
9
8
7
6
5
4
3
2
1
0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151.173
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141.039
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121.745
121.160
119.475
111.503
77.583
77.160
76.736
67.570
51.388
36.974
35.092
31.239
30.304
Cl
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O
S
O
N
N
O
ppm
200
180
160
140
120
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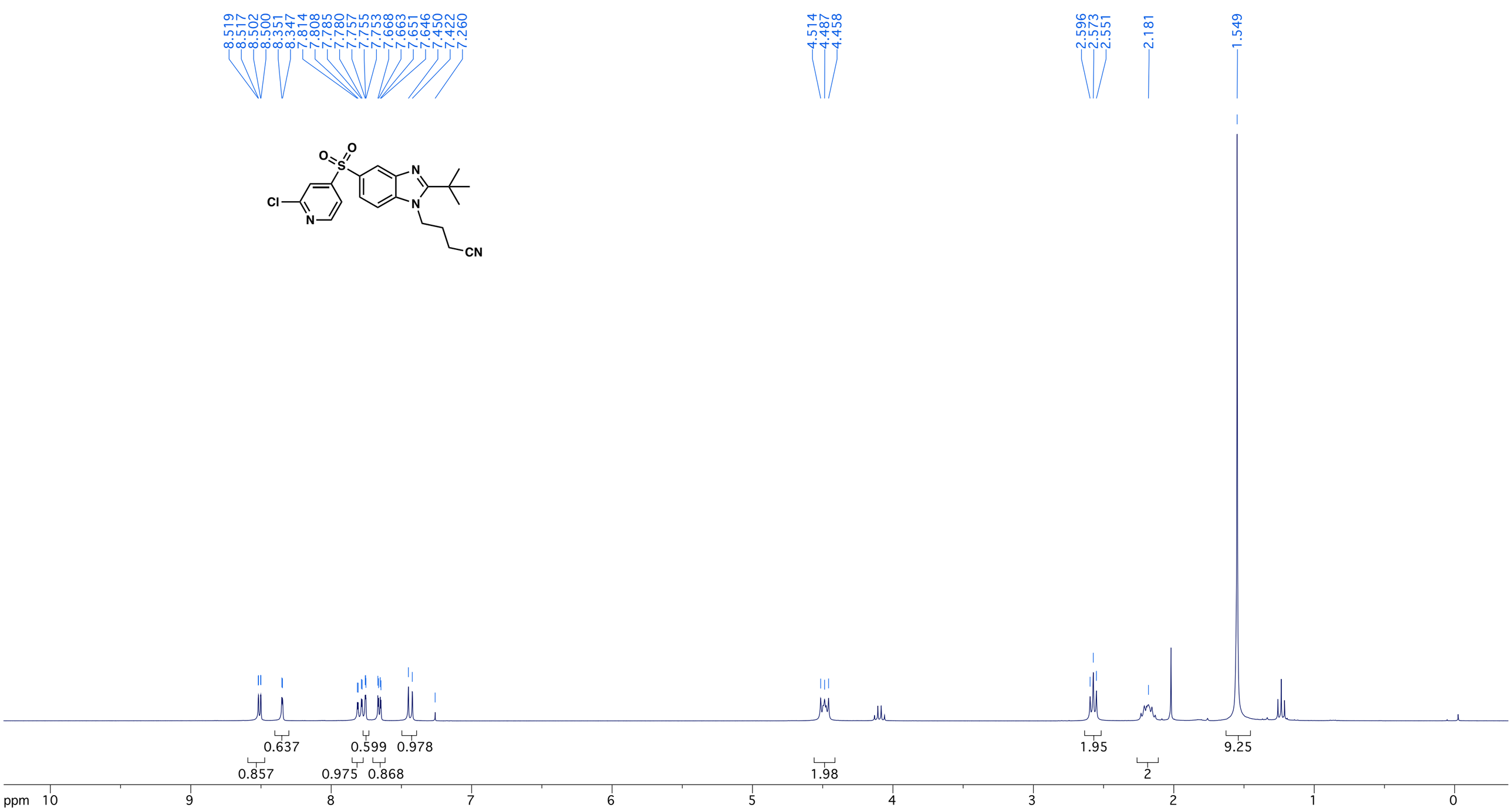
80
60
40
20
0


8.519
8.517
8.502
8.500
8.351
8.347
7.814
7.808
7.785
7.780
7.757
7.755
7.753
7.668
7.663
7.651
7.646
7.450
7.422
7.260
4.514
4.487
4.458
2.596
2.573
2.551
2.181
1.549
O
O
S
N
N
Cl
N
CN
0.857
0.637
0.975
0.599
0.868
0.978
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1.95
2
9.25
ppm
10
9
8
7
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5
4
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2
1
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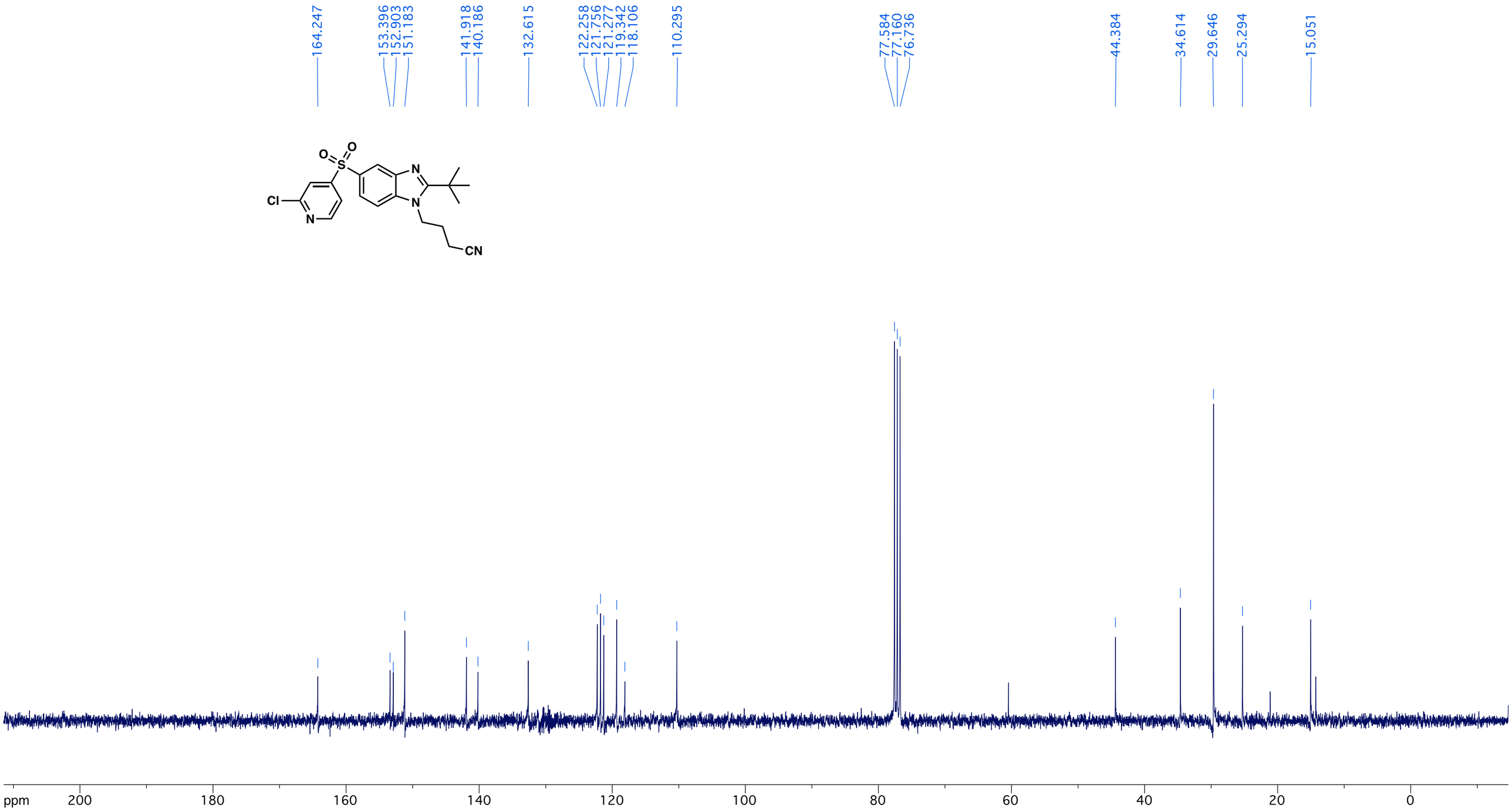
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151.183
141.918
140.186
132.615
122.258
121.756
121.277
119.342
118.106
110.295
77.584
77.160
76.736
44.384
34.614
29.646
25.294
15.051
O
O
S
N
N
Cl
N
CN
ppm
200
180
160
140
120
100
80
60
40
20
0

References

1. T.R. Neal, S. Apana, M.S. Berridge, *J. Labelled Compd. Radiopharm.* 2005, **48**, 557-568.
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3. A. Knapman, M. Santiago, Y.P. Du, P.R. Bennallack, M.J. Christie and M. Connor, *J. Biomol. Screen.* 2013, **18**, 269-276.
4. N.L. Grimsey, E.S. Graham, M. Dragunow, M. Glass *Biochem. Pharmacol.* 2010, **80**, 1050–1062.