Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

A High-Quality Photoswitchable Probe that Selectively and Potently Regulates the Transcription Factor RORγ

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Supporting Information to

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Author Contributions: M.R. performed all synthesis, photocharacterisation, and assisted in cellular studies. S.W. and J.A.M. performed cellular studies. T.W. performed docking studies. D.M. and O.T.-S. supervised the project. D.M., O.T-S. and M.R. conceived the study, and wrote the manuscript with contributions from all authors. All authors have given approval to the final version of the manuscript.

Supporting Figures

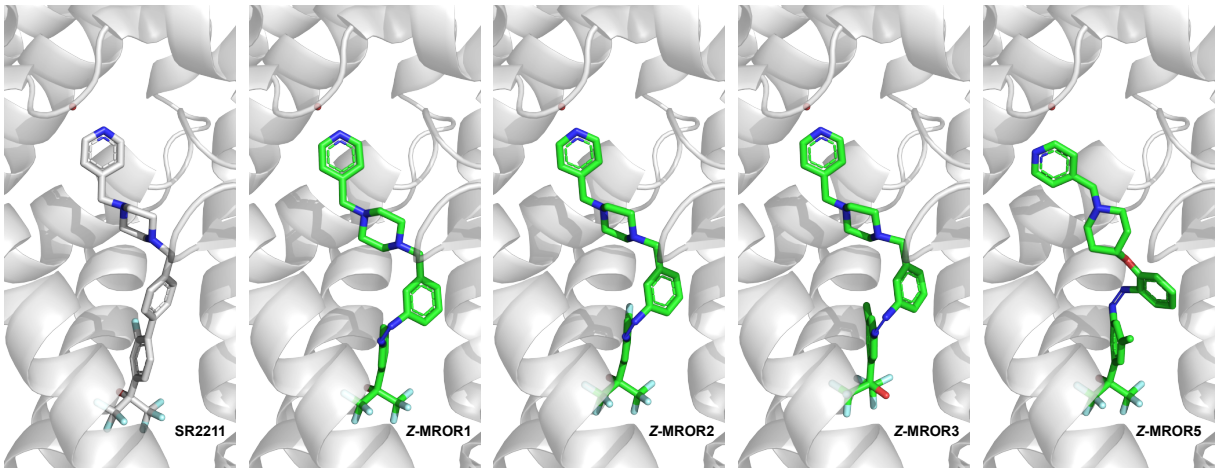


Figure S1. Docking poses of SR2211 and of *Z*-**MROR1,2,3,5** in the RORγ ligand binding domain (PDB: 6NWT[1]).

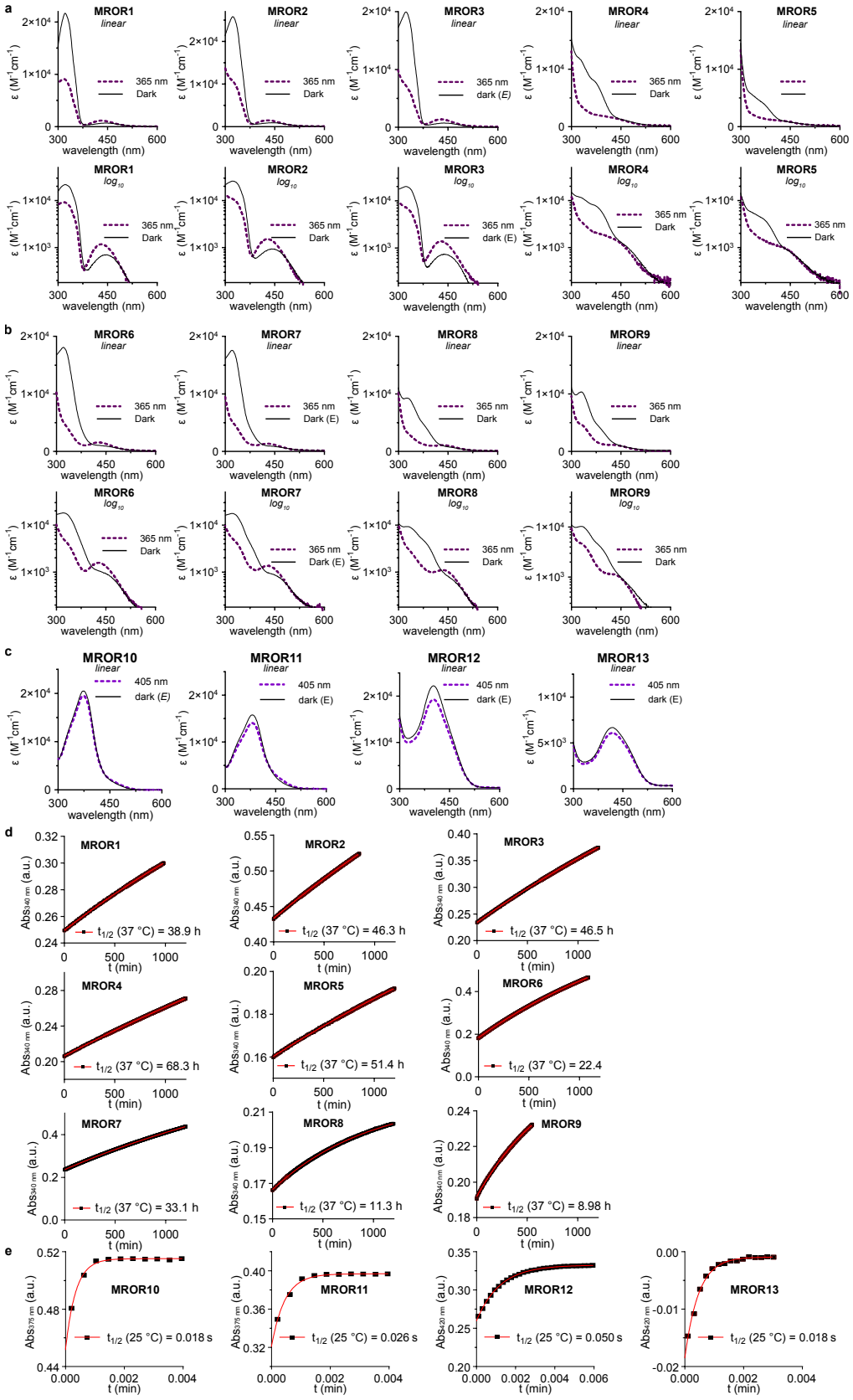


Figure S2. UV-Vis absorption spectra and thermal *Z*→*E* isomerization of MROR1-13. (a-b) UV-Vis spectra in the dark (all-*E*) and at 365 nm PSS (mostly-*Z*), on linear scale (typical presentation), and on logarithmic scale which is more useful for estimating PSS(λ) from $Abs_E(\lambda)/Abs_Z(\lambda)$ (e.g. by the method of lower bounds[2], **MROR6-9** have 365 nm PSS with >70% *Z*, while **MROR1-5** have >50% *Z*). **(c)** UV-Vis spectra of **MROR10-13** in the dark and under ongoing 405 nm LED irradiation ("*partial*-PSS" in **Figure 3** since it is not a true PSS), showing an *E*-rich state as expected for compounds where fast *Z*→*E* relaxation counteracts *E*→*Z* photoisomerisation. **(d-e)** Thermal relaxation of **MROR1-13** in DMSO; in our cell settings, PSS is typically reached in ca. 3 hours (see discussion at **Fig 1** of ref[2]).

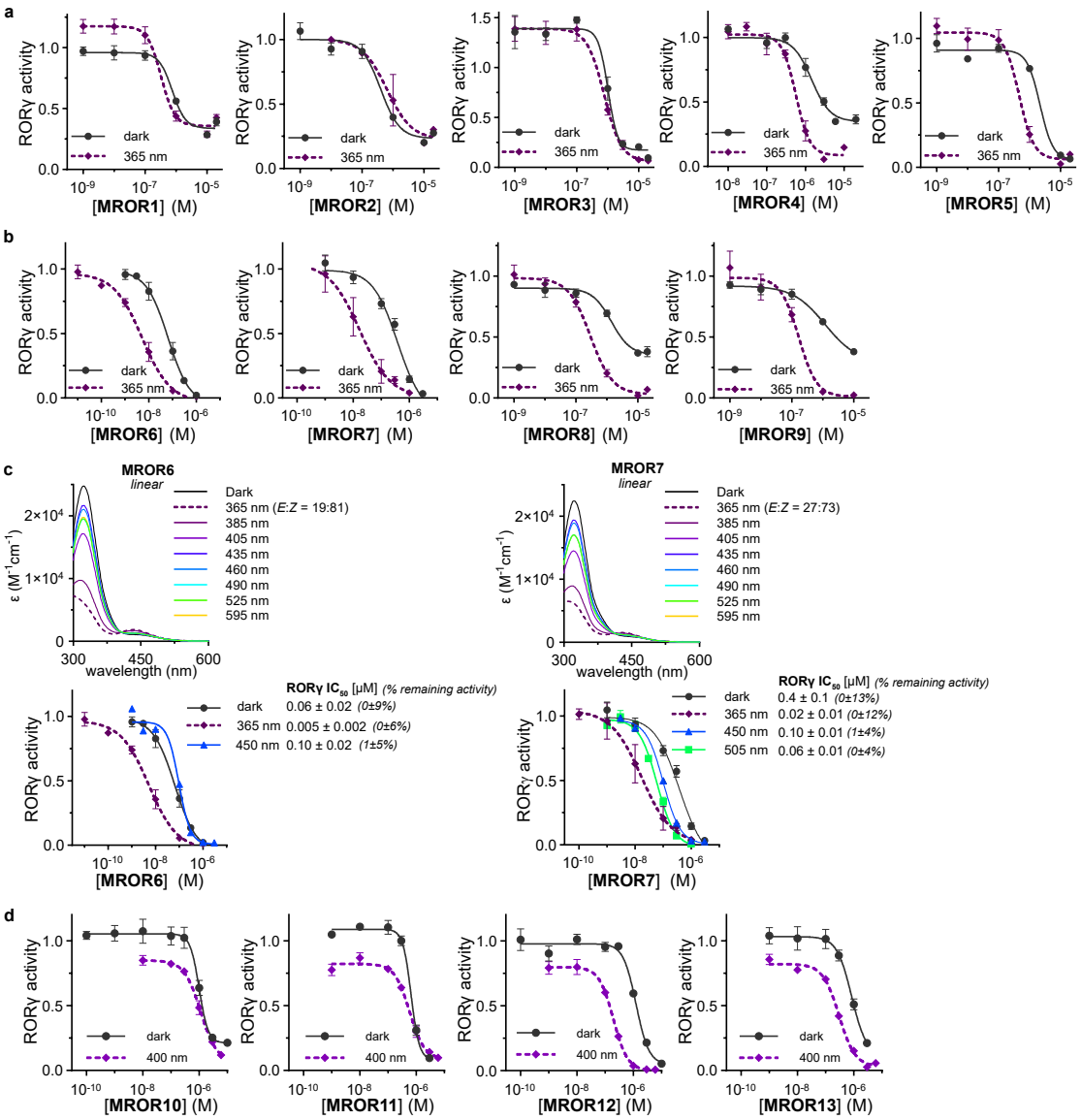


Figure S3. Cellular reporter gene assay of RORγ activity. (a-b) Activity of RORγ after treatment in the dark or under pulsed 365 nm irradiation (100 ms every 20 s) with slow-relaxing **MROR1-9**. **(c)** Photostationary states of **MROR6-7** and RORγ activity at different wavelengths (450 nm irradiation pulsed 100 ms every 20 s, 505 nm irradiation pulsed 10 ms every 100 ms). **(d)** Activity of RORγ after treatment with fast-relaxing **MROR10-13** in the dark or under pulsed 400 nm irradiation (10 ms every 100 ms). Although the half-life of **MROR12-13** is very short, a sizeable difference in activity can be seen; and although as compared to **MROR6-7** these compounds had lower absolute potency and *Z/E* bioactivity differential (**Figure 3jk**), the best of them (**MROR12**) has an acceptable 6-fold *Z/E* activity ratio. We imagine the source of this is, that the *Z*-isomer is stabilised against thermal relaxation in the cellular lipid environments where it will preferentially partition into, and potentially also in the RORγ binding pocket, a behavior that has been reported for photoswitchable estrogen receptor ligands.[3] Data shown as mean ± S.E.M. from at least three independent experiments each with two technical replicates.

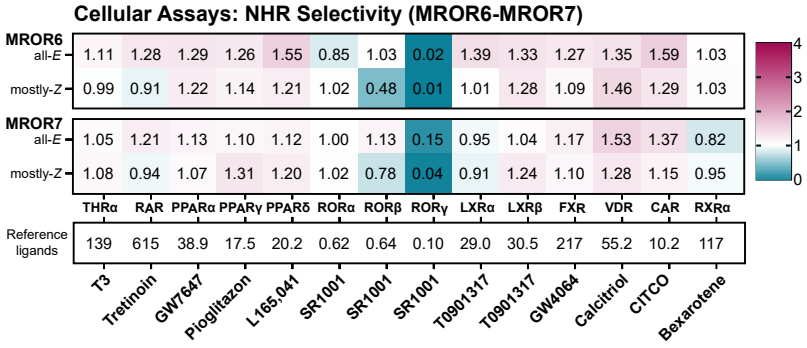


Figure S4. NHR selectivity profile. Cellular NHR activity reporter assay results of *E/Z*-**MROR6**/**7** at 1 μM show their NHR selectivity profiles. (*Z*)-**MROR6/7** refers to the PSS of 365 nm pulse-irradiated samples, (*E*)-**MROR6/7** refers to samples kept in the dark. Data shown as mean fold/remaining activity from at least two independent experiments each with two technical replicates. Reference agonists / inverse agonist were all also applied at 1 μM.

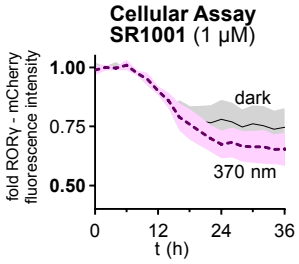


Figure S5. Timecourse control using reference inhibitor SR1001 at 1 μM (compare to **Fig 4bc**), Data shown as mean ± S.E.M. from four independent experiments each with two technical replicates..

Synthetic Methods - General

Reagents and Procedures: Reactions were carried out by default using commercially available chemicals (BLDPharm, Sigma, TCI, Enamine, ThermoScientific) and unpurified solvents under air; or if indicated, under nitrogen atmosphere, using heat-dried glassware and dry solvents. The procedures are mostly unoptimized and the yields refer to isolated dried materials. The hexane used for chromatography was distilled from commercial hexane fraction. Flash column chromatography was performed on a Biotage Isolera One using Biotage silica gel cartiges (20 or 60 µm particles) as stationary phase. The solvent mixtures are given as volume ratios. Thin-layer chromatography (TLC) was performed using 0.25 mm Merck silica gel plates (60, F-254). UV light (254 nm, 366 nm) and substance colour was used for visualization. R_f values were determined in the specified solvent mixtures.

NMR Spectroscopy: ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Ascend 400 NMR spectrometer (400 MHz & 100 MHz for ^{1}H and ^{13}C respectively) in deuterated solvents. Chemical shifts (δ) are reported in ppm standardized to the used solvent as reference. The peaks are described by as: singlet (s), doublet (d), triplet (t), quartet (q), heptet (hept), multiplet (m), broad (br) and combinations thereof. The multiplets are reported as observed.

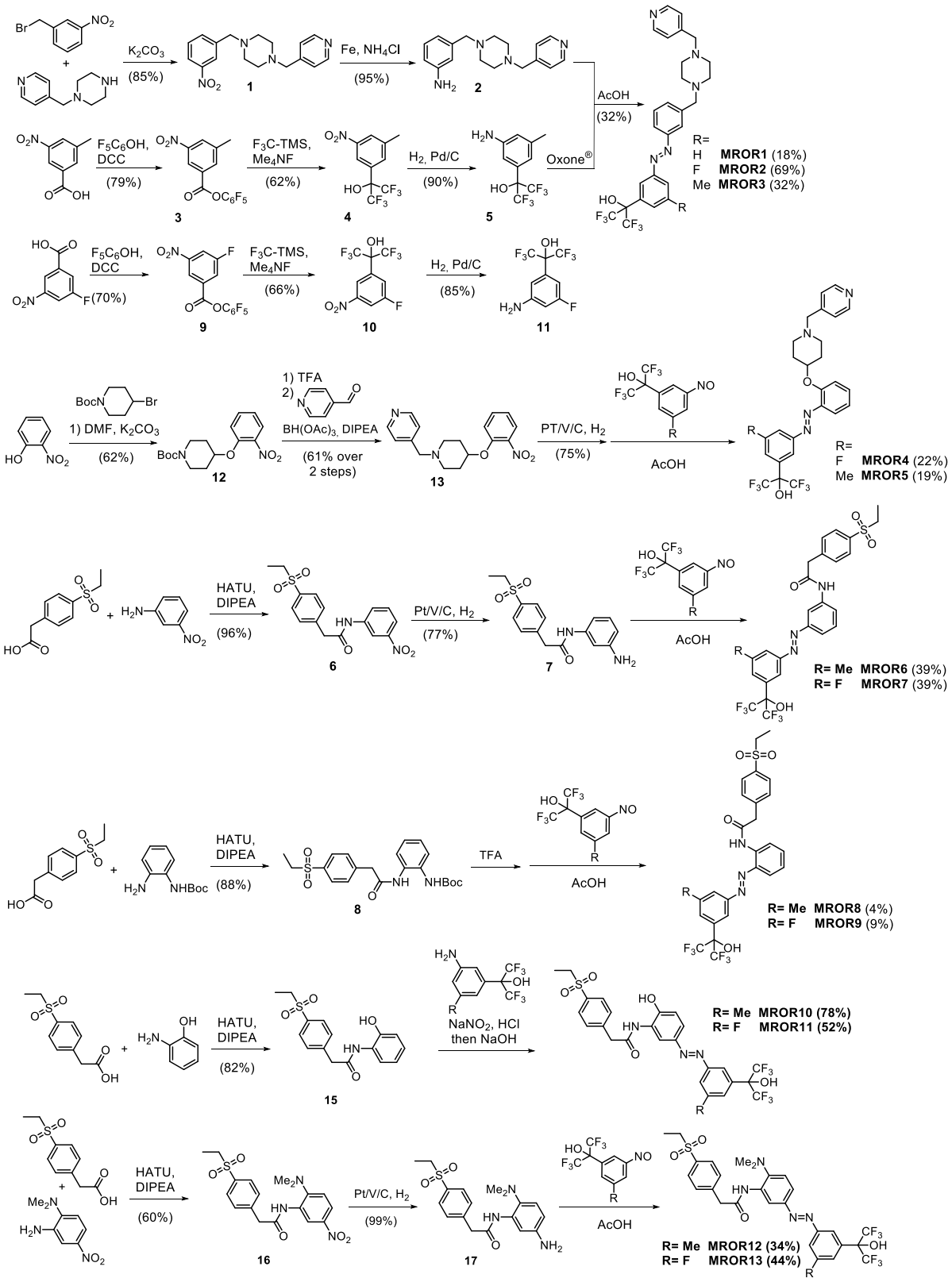
Mass Spectrometry: High resolution mass spectrometry (HRMS) was performed on a Thermo Q Exactive GC Orbitrap mass spectrometer for **EI** spectra or a Thermo Finnigan LTQ FT Ultra Fourier Transform Ion Cyclotron Resonance mass spectrometer for **ESI** spectra. **EI** samples were separated on a Thermo Trace 1300 gas chromatograph (Machery-Nagel 5%-phenyl-95%-methyl-silphenylene phase column) and injected into the mass spectrometer at 300 °C. For **ESI** samples, the aerosol was formed using a IonMax ESI-probe head at 4 kV and 250 °C.

LCMS measurements were performed on an Agilent 1100 SL coupled LCMS system using an Agilent LC/MSD iQ mass spectrometer (ESI). The eluent was a gradually increasing mixture of acetonitrile in water, both containing 0.1 % formic acid, at a 0.4 mL/min flow rate. For LCMS a YMC-Triart C18 column (3.0 µm; 50 mm × 3 mm) maintained at 40 °C was used. The standard method starts with a 0.5 min of a 10:90 acetonitrile:water mix followed by a constant increase to 100:0 over 5 min. 100% acetonitrile was maintained for 2 min, before switching back to a 10:90 mix over 0.5 min and equilibrated at this eluent mixture for 2 min.

UV-Vis Spectrometry: Absorption spectra were acquired on a Varian CaryScan 50 in *d*=1 cm cuvettes at room temperature. Photoisomerization studies by UV-Vis spectroscopy were performed using a pE-4000 illumination system (CoolLED) set to 10 mW/cm^2 *for all wavelengths*, at light guide exit (power in the sample plane for UV-Vis measurement ca. half of this; power spectra and geometric optics as reported previously[4,5]).

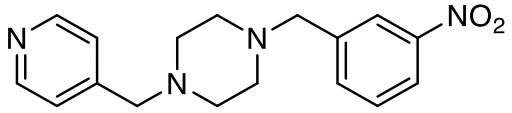
Although azobenzenes are mostly depicted in their *E* form, both *E* & *Z* form can be present in a sample, depending on its exposure to light. Therefore E/Z nomenclature is not applied.

Compound Syntheses



Scheme S1: Overview of syntheses for **MROR1-9**.

1-(3-nitrobenzyl)-4-(pyridin-4-ylmethyl)piperazine (1)



1-(pyridin-4-ylmethyl)piperazine (250 mg, 1.41 mmol, 1.00 eq.) and 3-nitrobenzyl bromide (305 mg, 1.41 mmol 1.00 eq.) were dissolved in DMF (3 mL) and potassium carbonate (292 mg, 2.12 mmol, 1.50 eq.) was added. The reaction was stirred for 24 h, concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography (CH_2Cl_2:MeOH gradient, 0→10% MeOH) gave **1** (374 mg, 1.20 mmol, 85%) as a yellow solid.

R_f = 0.25 [CH_2Cl_2:MeOH, 9:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.51 – 8.46 (m, 2H), 8.15 – 8.09 (m, 2H), 7.75 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.31 – 7.27 (m, 2H), 3.60 (s, 2H), 3.49 (s, 2H), 2.41 (s, br, 8H) ppm.

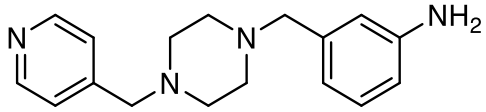
^{13}C NMR (101 MHz, DMSO-d_6) δ = 149.55, 147.83, 147.43, 140.86, 135.44, 129.75, 123.74, 123.04, 122.01, 60.75, 60.61, 52.66, 52.48 ppm.

HRMS (ESI): calcd. for $C_{17}H_{21}N_4O_2^+$: 313.16590 m/z $[M+H]^+$

found: 313.16649 m/z $[M+H]^+$.

LCMS (ESI): t_{ret} = 3.97 min. 313 m/z $[M+H]^+$.

3-((4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)aniline (2)



1 (156 mg, 0.500 mmol, 1.00 eq.), iron powder (197 mg, 2.5 mmol, 5.00 eq.) and ammonium chloride (134 mg, 2.50 mmol, 5.00 eq.) were suspended in a MeOH:water mixture (1:1, 15 mL) and the reaction was heated to 65 °C for 3 h. The mixture was concentrated under reduced pressure and the resulting aqueous mixture was extracted with EtOAc (3×20 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude white solid **2** (134 mg, 0.475 mmol, 95%) was used without further purification.

R_f = 0.08 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.52 – 8.45 (m, 2H), 7.33 – 7.27 (m, 2H), 6.92 (t, *J* = 7.7 Hz, 1H), 6.51 (t, *J* = 1.9 Hz, 1H), 6.44 – 6.36 (m, 2H), 4.99 (s, 2H), 3.48 (s, 2H), 3.28 (s, 2H), 2.37 (s, br, 8H) ppm.

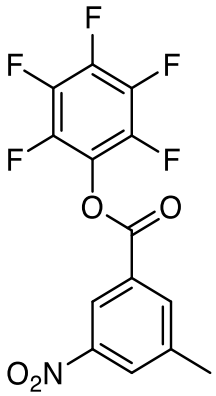
^{13}C NMR (101 MHz, DMSO-d_6) δ = 149.54, 148.55, 147.50, 138.73, 128.56, 123.75, 116.43, 114.30, 112.64, 62.60, 60.69, 52.72, 52.69 ppm.

HRMS (ESI): calcd. for $C_{17}H_{23}N_4^+$: 283.19172 m/z $[M+H]^+$

found: 283.19222 m/z $[M+H]^+$.

LCMS (ESI): t_{ret} = 1.39 min. 283+ m/z $[M+H]^+$.

perfluorophenyl 3-methyl-5-nitrobenzoate (3)



3-Methyl-5-nitrobenzoic acid (1.00 g, 5.52 mmol, 1.0 eq.) and pentafluorophenol (1.12 g, 6.07 mmol, 1.1 eq.) and *N*,*N*'-dicyclohexylcarbodiimide (1.25 g, 6.07 mmol, 1.1 eq.) were dissolved in 1,4-dioxane (20 mL) and stirred for 60 h. The reaction was filtered, concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (Hx/EA gradient, 0→10% EA) gave **3** (1.52 g, 4.38 mmol, 79%) as a faint yellow solid.

R$_f$ = 0.45 [Hx:EA, 9:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.84 (ddd, *J* = 2.3, 1.5, 0.7 Hz, 1H), 8.37 (ddd, *J* = 2.3, 1.6, 0.8 Hz, 1H), 8.33 (td, *J* = 1.7, 0.8 Hz, 1H), 2.60 (s, 3H) ppm.

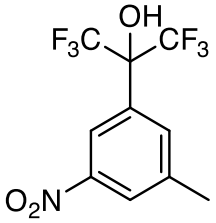
^{13}C NMR (101 MHz, Chloroform-*d*) δ = 161.08, 148.62, 141.44, 141.34 (dm, *J* = 252.1 Hz), 140.01 (dm, *J* = 254.3 Hz), 138.10 (dm, *J* = 251.3 Hz), 136.91, 129.63, 128.54, 125.37 – 124.69 (m), 123.03, 21.44 ppm.

HRMS (EI): calcd. for $C_8H_6NO_3^+$: 164.0348 m/z [M-$C_6F_5O^-$]$^+$

found: 164.0341 m/z [M-$C_6F_5O^-$]$^+$

LCMS (ESI): t_{ret} = 7.80 min. (no ions observed).

1,1,1,3,3,3-hexafluoro-2-(3-methyl-5-nitrophenyl)propan-2-ol (4)



3 (694 mg, 2.00 mmol, 1.0 eq.) was dissolved in DME (4 mL) under nitrogen atmosphere and cooled to -50 °C before adding $TMSCF_3$ (0.614 mL, 4.10 mmol, 2.05 eq.). The reaction was stirred for 5 min and then tetramethylammonium fluoride (186 mg, 2.00 mmol, 1.0 eq.) was added and the reaction mixture was allowed to reach r.t. slowly over night (16 h). The reaction was diluted with EtOAc (25 mL) and acidified water (29 mL water + 1 mL 2M HCl), water (30 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (Hx/EA gradient, 0→100% EA) gave **4** (378 mg, 1.25 mmol, 62%) as a pale-yellow solid.

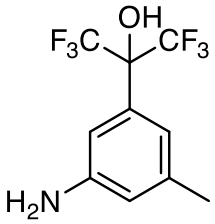
$\mathbf{R}_f$ = 0.32 [Hx:EA, 9:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.44 (s, 1H), 8.18 (ddd, *J* = 2.2, 1.5, 0.7 Hz, 1H), 7.85 (dd, *J* = 1.7, 0.8 Hz, 1H), 3.62 (s, 1H), 2.55 (s, 3H) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ = 148.59, 140.86, 133.23 (hept, *J* = 1.4 Hz), 131.06, 125.92, 122.37 (q, *J* = 287.2), 119.62 (p, *J* = 1.4 Hz), 77.69 – 76.07 (m), 21.72 ppm.

HRMS (ESI):	calcd. for $C_{10}H_6F_6NO_3^-$:	302.02574 m/z $[M-H]^-$
	found:	302.02607 m/z $[M-H]^-$.
LCMS (ESI):	t_{ret} = 6.96 min.	302 m/z $[M-H]^-$.

2-(3-amino-5-methylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5)



4 (304 mg, 1.00 mmol) and Pd/C (10% Pd, 59.4 mg) were dissolved in methanol (10 mL). The reaction was vigorously stirred under a hydrogen atmosphere until completion. After 60 h, the mixture was filtered through celite, and the filtrate concentrated under reduced pressure. The resulting faint yellow solid **5** (245 mg, 0.897 mmol, 90%) was used without further purification.

$\mathbf{R}_f$ = 0.57 [Hx:EA, 1:1].

^{1}H NMR 1H NMR (400 MHz, Chloroform-*d*) δ = 6.90 – 6.88 (m, 1H), 6.82 (s, 1H), 6.61 (dd, J = 1.4, 0.7 Hz, 1H), 3.69 (s, br, 3H), 2.31 (s, 3H) ppm.

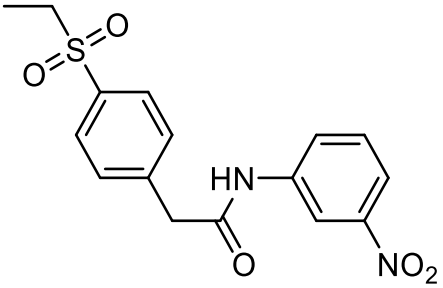
^{13}C NMR (101 MHz, Chloroform-*d*) δ = 146.40, 139.75, 130.58, 122.77 (q, J = 288.1 Hz), 117.86, 117.70 – 117.47 (m), 110.69 – 110.62 (m), 77.85 – 76.59 (m), 21.77.

HRMS (ESI): calcd. for $C_{10}H_8F_6NO^-$: 272.05156 m/z $[M-H]^-$

found: 272.05169 m/z $[M-H]^-$.

LCMS (ESI): t_{ret} = 5.89 min. 274 m/z $[M+H]^+$.

2-(4-(ethylsulfonyl)phenyl)-N-(3-nitrophenyl)acetamide (6)



3-Nitroaniline (166 mg, 1.20 mmol, 1.1 eq), 2-(4-(ethylsulfonyl)phenyl)acetic acid (250 mg, 1.10 mmol, 1 eq), and HATU (458 mg, 1.20 mmol, 1.1 eq) were dissolved in DMF (2 mL) and DIPEA (0.572 mL, 2.66 mmol) were added. The reaction was stirred for 14 h, diluted with ethyl acetate (30 mL) and washed with saturated aqueous $NaHCO_3$ solution (10 mL), LiCl solution (10%, 2×30 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (Hx/EA gradient, 0→100% EA) gave **6** (366 mg, 1.05 mmol, 96%) as a light-yellow solid.

R_f = 0.33 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.77 (s, 1H), 8.63 (t, *J* = 2.2 Hz, 1H), 7.92 (t, *J* = 1.9 Hz, 1H), 7.90 (t, *J* = 2.0 Hz, 1H), 7.88 – 7.81 (m, 2H), 7.66 – 7.57 (m, 3H), 3.86 (s, 2H), 3.28 (q, *J* = 7.4 Hz, 2H), 1.09 (t, *J* = 7.4 Hz, 3H) ppm.

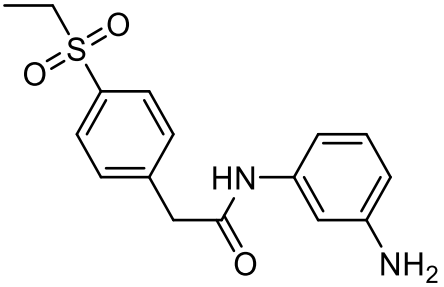
^{13}C NMR (101 MHz, DMSO-d_6) δ = 169.07, 147.96, 141.61, 140.12, 136.92, 130.38, 130.32, 127.91, 125.11, 117.98, 113.24, 49.21, 42.88, 7.21 ppm.

HRMS (ESI): calcd. for $C_{16}H_{15}N_2O_5S^-$: 347.07072 m/z $[M-H]^-$

found: 347.07102 m/z $[M-H]^-$.

LCMS (ESI): t_{ret} = 6.12 min. 347 m/z $[M-H]^-$.

N-(3-aminophenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide (7)



6 (200 mg, 0.574 mmol) and Pt/V/C (1% Pt/ 2% V, 70.6 mg) were dissolved in methanol (10 mL). The reaction was vigorously stirred under a hydrogen atmosphere until full conversion was observed by LCMS. After 60 h, the mixture was filtered through celite, and the filtrate concentrated under reduced pressure. The resulting off-white solid **7** (141 mg, 0.443 mmol, 77%) was used without further purification.

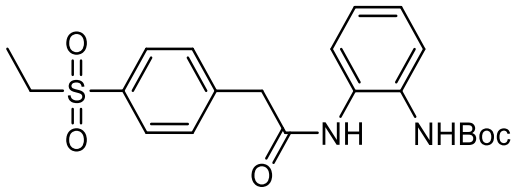
$\mathbf{R}_f$ = 0.23 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.96 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 6.95 – 6.86 (m, 2H), 6.73 – 6.65 (m, 1H), 6.32 – 6.22 (m, 1H), 5.12 (s, br, 2H), 3.75 (s, 2H), 3.28 (q, *J* = 7.3 Hz, 2H), 1.10 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.22, 149.51, 142.91, 140.08, 137.12, 130.56, 129.41, 128.29, 109.89, 107.47, 105.24, 49.67, 43.52, 7.65 ppm.

HRMS (ESI):	calcd. for $C_{16}H_{19}N_2O_3S^+$:	319.11109 m/z $[M+H]^+$
	found:	319.11166 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 4.03 min.	319 m/z $[M+H]^+$.

tert-butyl (2-(2-(4-(ethylsulfonyl)phenyl)acetamido)phenyl)carbamate (8)



tert-butyl (2-aminophenyl)carbamate (212 mg, 1.02 mmol, 1.15 eq), 2-(4-(ethylsulfonyl)phenyl)acetic acid (202 mg, 0.885 mmol, 1.00 eq.), and HATU (370 mg, 0.974 mmol, 1.10 eq.) were dissolved in DMF (2 mL) and DIPEA (0.463 mL, 2.66 mmol, 3.00 eq.) were added. The reaction was stirred for 6 h, diluted with ethyl acetate (30 mL) and washed with saturated aqueous $NaHCO_3$ solution (10 mL), LiCl solution (10%, 2×30 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (Hx/EA gradient, 0→100% EA) gave **8** (324 mg, 0.774 mmol, 88%) as a colourless solid.

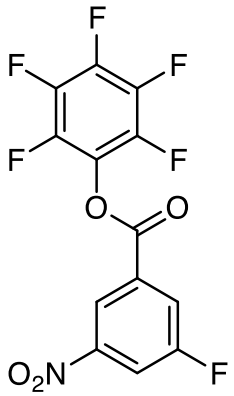
$\mathbf{R}_f$ = 0.14 [Hx:EA, 1:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.72 (s, 1H), 8.39 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.43 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.14 (td, *J* = 7.7, 1.7 Hz, 1H), 7.06 (td, *J* = 7.6, 1.6 Hz, 1H), 3.85 (s, 2H), 3.28 (q, *J* = 7.3 Hz, 2H), 1.45 (s, 9H), 1.10 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.80, 153.08, 142.26, 136.76, 131.28, 130.24, 129.39, 127.84, 125.30, 125.05, 123.88, 123.69, 79.39, 49.22, 42.49, 28.10, 7.24 ppm.

HRMS (ESI):	calcd. for $C_{21}H_{25}N_2O_5S^-$:	417.14897 m/z $[M-H]^-$
	found:	417.14919 m/z $[M-H]^-$.
LCMS (ESI):	t_{ret} = 6.58 min.	417 m/z $[M-H]^-$.

perfluorophenyl 3-fluoro-5-nitrobenzoate (9)



3-fluoro-5-nitrobenzoic acid (1.00 g, 5.40 mmol, 1.0 eq.) and pentafluorophenol (1.04 g, 5.67 mmol, 1.1 eq.) and *N*,*N*'-dicyclohexylcarbodiimide (1.17 g, 5.67 mmol, 1.1 eq.) were dissolved in 1,4-dioxane (20 mL) and stirred for 20 h. The reaction was filtered, concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (Hx/EA gradient, 0→10% EA) gave **9** (1.33 g, 3.79 mmol, 70%) as a faint yellow solid.

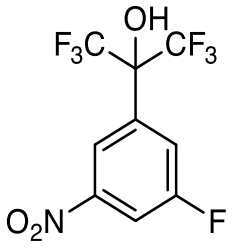
$\mathbf{R}_f$ = 0.62 [Hx:EA, 9:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.87 (ddd, *J* = 2.1, 1.4, 0.8 Hz, 1H), 8.29 (ddd, *J* = 7.7, 2.1 Hz, 1H), 8.24 (ddd, *J* = 7.7, 2.5, 1.4 Hz, 1H) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ = 162.50 (d, *J* = 255.0 Hz), 159.89 (d, *J* = 2.5 Hz), 149.55 (d, *J* = 8.3 Hz), 141.29 (dm, *J* = 253.4 Hz), 140.21 (dm, *J* = 254.8 Hz), 138.16 (dm, *J* = 256.4 Hz), 130.44 (d, *J* = 7.8 Hz), 124.99 – 124.42 (m), 123.72 (d, *J* = 23.7 Hz), 121.53 (d, *J* = 3.6 Hz), 117.22 (d, *J* = 26.2 Hz) ppm.

HRMS (EI):	calcd. for $C_7H_3FNO_3^+$:	168.0097 m/z $[M\text{-}C_6F_5O^-]^+$
	found:	168.0091 m/z $[M\text{-}C_6F_5O^-]^+$
LCMS (ESI):	t_{ret} = 8.18 min.	(no ions observed).

1,1,1,3,3,3-hexafluoro-2-(3-fluoro-5-nitrophenyl)propan-2-ol (10)



9 (878 mg, 2.50 mmol, 1.0 eq.) was dissolved in DME (4 mL) under nitrogen atmosphere and cooled to -50 °C before adding $TMSCF_3$ (0.767 mL, 5.13 mmol, 2.05 eq.). The reaction was stirred for 5 min and then tetramethylammonium fluoride (233 mg, 2.50 mmol, 1.0 eq.) was added and the reaction mixture was allowed to reach r.t. slowly over night (19 h). The reaction was diluted with EtOAc (25 mL) and acidified water (29 mL water + 1 mL 2M HCl), water (30 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (Hx/EA gradient, 0→100% EA) gave **10** (505 mg, 1.64 mmol, 66%) as a volatile oil.

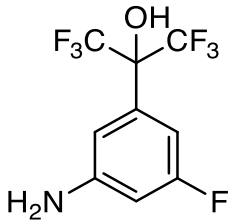
$\mathbf{R}_f$ = 0.36 [Hx:EA, 9:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.46 (t, *J* = 1.8 Hz, 1H), 8.09 (dt, *J* = 7.7, 2.2 Hz, 1H), 7.83 (dt, *J* = 8.9, 2.1 Hz, 1H), 4.21 (s, 1H) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ = 162.38 (d, *J* = 253.0 Hz), 149.41 (d, *J* = 9.0 Hz), 133.34 (d, *J* = 8.0 Hz), 121.93 (q, *J* = 287.8 Hz), 120.88 (dm, *J* = 25.0 Hz), 118.24 (hept, *J* = 1.5 Hz), 113.50 (d, *J* = 26.3 Hz), 77.58 – 75.92 (m) ppm.

HRMS (ESI):	calcd. for $C_9H_3F_7NO_3^-$:	306.00066 m/z $[M-H]^-$
	found:	306.00098 m/z $[M-H]^-$.
LCMS (ESI):	t_{ret} = 6.89 min.	306 m/z $[M-H]^-$.

2-(3-amino-5-fluorophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (11)



10 (400 mg, 1.30 mmol) and Pd/C (10% Pd, 78.1 mg) were dissolved in methanol (12 mL). The reaction was vigorously stirred under a hydrogen atmosphere until completion. After 60 h, the mixture was filtered through celite, and the filtrate concentrated under reduced pressure. The resulting faint yellow solid **11** (305 mg, 1.10 mmol, 85%) was used without further purification.

$\mathbf{R}_f$ = 0.37 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR 400 MHz, Chloroform-*d*) δ = 6.82 – 6.78 (m, 2H), 6.48 (dt, *J* = 10.1, 2.2 Hz, 1H), 3.91 (s, br, 2H), 3.58 (s, br, 1H) ppm.

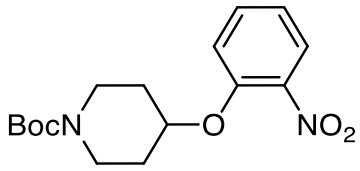
^{13}C NMR (101 MHz, Chloroform-*d*) δ = 163.75 (d, *J* = 243.9 Hz), 148.26 (d, *J* = 11.3 Hz), 132.08 (d, *J* = 10.2 Hz), 122.52 (q, *J* = 287.6 Hz), 109.21 – 108.99 (m), 104.25 (d, *J* = 25.4 Hz), 103.88 (d, *J* = 24.7 Hz), 77.67 – 76.55 (m).

HRMS (ESI): calcd. for $C_9H_5F_7NO^-$: 276.02648 m/z $[M-H]^-$

found: 276.02676 m/z $[M-H]^-$.

LCMS (ESI): t_{ret} = 6.06 min. 278 m/z $[M+H]^+$.

4-(2-nitrophenoxy)piperidine (12)



tert-butyl 4-bromopiperidine-1-carboxylate (528 mg, 2.00 mmol, 1.00 eq.) and 2-nitrophenol (278 mg, 2.00 mmol, 1.00 eq.) were dissolved in DMF (3 mL) and potassium carbonate (415 mg, 3.00 mmol, 1.50 eq.) was added. The reaction was heated to 90 °C for 60 h. The reaction was diluted with EtOAc (30 mL) and water (40 mL) and extracted. The organic phase was washed with LiCl solution (10%, 2×30 mL) and brine (50 mL) to remove all yellow coloured nitrophenol. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (Hx/EA gradient, 0→100% EA) gave **12** (401 mg, 1.24 mmol, 62%) as a faint-yellow oil.

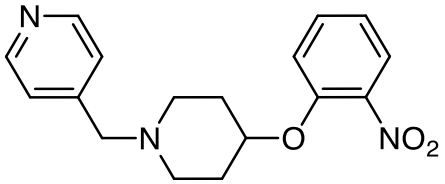
$\mathbf{R}_f$ = 0.67 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.85 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.63 (ddd, *J* = 8.9, 7.4, 1.7 Hz, 1H), 7.45 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.11 (ddd, *J* = 8.3, 7.4, 1.1 Hz, 1H), 4.86 (tt, *J* = 7.0, 3.4 Hz, 1H), 3.50 – 3.45 (m, 2H), 3.40 – 3.35 (m, 2H), 1.88 – 1.79 (m, 2H), 1.64 – 1.57 (m, 2H), 1.40 (s, 9H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 153.90, 149.52, 140.53, 134.24, 125.08, 120.79, 116.49, 73.16, 39.98, 29.81 (br), 28.08 ppm.

HRMS (EI):	calcd. for $C_{12}H_{13}N_2O_5^+$:	265.0819 m/z $[M\text{-}C_4H_9^-]^+$
	found:	265.0815 m/z $[M\text{-}C_4H_9^-]^+$.
LCMS (ESI):	t_{ret} = 7.38 min.	345 m/z $[M+Na]^+$.

4-((4-(2-nitrophenoxy)piperidin-1-yl)methyl)pyridine (13)



12 (288 mg, 0.892 mmol, 1.00 eq) was dissolved in a 2:1 CH_2Cl_2:TFA mixture (2 mL), stirred for 3 min and concentrated under reduced pressure and triturated with diethyl ether (3×2 mL). The resulting crude was dissolved in CH_2Cl_2 (10 mL) and 4-pyridinecarboxaldehyde (95.6 mg, 0.892 mmol, 0.084 mL, 1.00 eq.) sodium triacetoxyborohydride (473 mg, 2.23 mmol, 2.50eq.) and DIPEA (0.154 mL, 0.892 mmol, 1.00 eq.) were added. The suspension was stirred for 18 h, diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (Hx/EA gradient, 0→100% EA) gave **13** (171 mg, 0.545 mmol, 61%) as a faint-yellow oil.

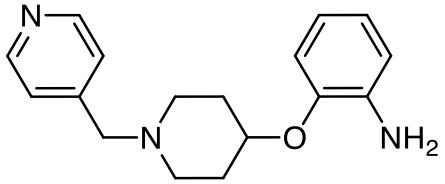
$\mathbf{R}_f$ = 0.23 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.51 – 8.49 (m, 2H), 7.83 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.60 (ddd, *J* = 8.9, 7.4, 1.7 Hz, 1H), 7.42 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.33 (m, 2H), 7.09 (ddd, *J* = 8.3, 7.4, 1.1 Hz, 1H), 4.71 (tt, *J* = 7.4, 3.6 Hz, 1H), 3.52 (s, 2H), 2.61 – 2.53 (m, 2H), 2.37 – 2.28 (m, 2H), 1.96 – 1.88 (m, 2H), 1.76 – 1.65 (m, 2H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 149.62, 149.56, 147.74, 140.65, 134.11, 124.87, 123.68, 120.58, 116.48, 73.35 (br), 60.62, 49.50, 30.08 ppm.

HRMS (ESI):	calcd. for $C_{17}H_{20}N_3O_3^+$:	314.14992 m/z $[M+H]^+$
	found:	314.15041 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 4.01 min.	314 m/z $[M+H]^+$.

2-((1-(pyridin-4-ylmethyl)piperidin-4-yl)oxy)aniline (14)



13 (120 mg, 0.383 mmol) and Pt/V/C (1% Pt/ 2% V, 47.1 mg) were dissolved in methanol (10 mL). The reaction was vigorously stirred under a hydrogen atmosphere until completed. After 60 h, the mixture was filtered through celite, and the filtrate concentrated under reduced pressure. The resulting off-white solid **14** (86.6 mg, 0.332 mmol, 87%) was directly used in the next step without further purification (product slowly decomposes at room temperature).

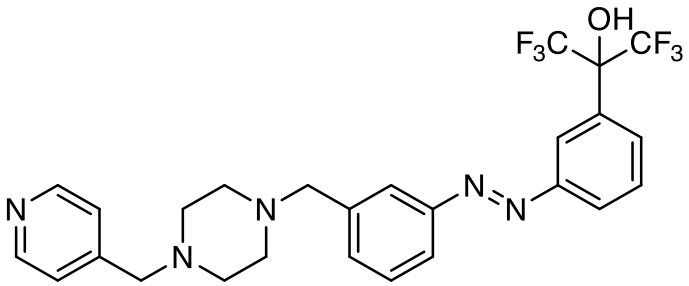
R_f = 0.18 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6): n.d.

^{13}C NMR (100 MHz, DMSO-d_6): n.d.

HRMS (EI):	calcd. for $C_{17}H_{21}N_3O^+$:	283.1685 m/z $[M]^+$
	found:	283.1679 m/z $[M]^+$.
LCMS (ESI):	t_{ret} = 1.10 min.	284 m/z $[M+H]^+$.

1,1,1,3,3,3-hexafluoro-2-(3-((3-((4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)phenyl)diazenyl)phenyl)propan-2-ol (MROR1)



2-(3-Aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (50 mg, 0.193 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (10 mL) and Oxone® (119 mg, 0.386 mmol, 2.00 eq.) dissolved in water (1 mL) was added. The reaction was stirred vigorously for 18 h before adding CH_2Cl_2 (20 mL) and extracting the mixture with aqueous HCl (1 M, 20 mL). The organic phase was extracted with brine (30 mL) and dried over Na_2SO_4. Next, **2** (21.8 mg, 0.0772 mmol, 0.40 eq.) and acetic acid (5 mL) were added. The mixture was concentrated under reduced pressure to remove most of the CH_2Cl_2 and then stirred for 24 h. Then, the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4 and concentrated. The crude product was first purified by normal phase flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH), followed by reverse phase column chromatography (H_2O:MeCN+0.1% FA, 0→100% MeCN) to yield **MROR1** as a yellow solid (7.6 mg, 0.014 mmol, 18%).

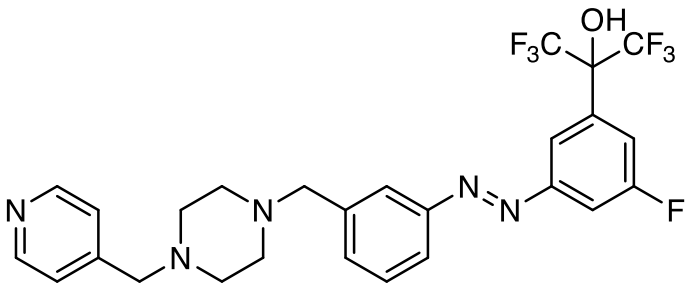
R_f = 0.24 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.09 (s, 1H), 8.49 (d, *J* = 5.3 Hz, 2H), 8.20 (d, *J* = 2.3 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.90 – 7.81 (m, 3H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.31 (d, *J* = 5.5 Hz, 2H), 3.60 (s, 2H), 3.50 (s, 2H), 2.44 (s, 8H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 151.87, 151.85, 149.58, 147.53, 140.02, 132.52, 132.32, 130.27, 129.51, 129.49, 124.55, 123.81, 122.92 (q, *J* = 286.8 Hz), 122.87, 121.81, 120.87, 76.82 (m), 61.56, 60.67, 52.71, 52.62 ppm.

HRMS (ESI):	calcd. for $C_{26}H_{24}F_6N_5O^-$:	536.18905 m/z $[M-H]^-$
	found:	536.18958 m/z $[M-H]^-$.
LCMS (ESI):	t_{ret} = 5.63 min.	538 m/z $[M+H]^+$.

1,1,1,3,3,3-hexafluoro-2-(3-fluoro-5-((3-((4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)phenyl)diazenyl)phenyl)propan-2-ol (MROR2)



11 (50 mg, 0.180 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (20 mL) and Oxone® (227 mg, 0.740 mmol, 4.11 eq.) dissolved in water (1 mL) was added. The reaction was stirred vigorously for 18 h before adding CH_2Cl_2 (20 mL) and extracting the mixture with aqueous HCl (1 M, 20 mL). The organic phase was extracted with brine (30 mL) and dried over Na_2SO_4. Next, **2** (40.7 mg, 0.144 mmol, 0.80 eq) and acetic acid (5 mL) were added. The mixture was concentrated under reduced pressure to remove most of the CH_2Cl_2 and then stirred for 24 h. Then, the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, concentrated, and purified by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) to yield **MROR2** as a yellow solid (55.6 mg, 0.100 mmol, 70%).

R_f = 0.13 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.32 (s, 1H), 8.48 (d, *J* = 5.0 Hz, 2H), 8.07 (s, 1H), 7.91 – 7.80 (m, 3H), 7.67 (d, *J* = 9.4 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.29 (d, *J* = 5.2 Hz, 2H), 3.58 (s, 2H), 3.48 (s, 2H), 2.45 – 2.37 (m, 8H) ppm.

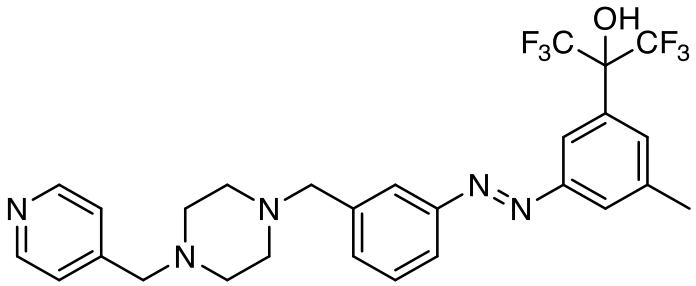
^{13}C NMR (101 MHz, DMSO-d_6) δ = 162.52 (d, *J* = 247.4 Hz), 153.42 (d, *J* = 7.7 Hz), 151.58, 149.54, 147.48, 140.11, 134.32 (d, *J* = 8.1 Hz), 133.00, 129.49, 123.75, 123.06, 122.64 (q, *J* = 288.5 Hz), 122.04, 118.33, 116.62 (d, *J* = 25.2 Hz), 110.31 (d, *J* = 23.0 Hz), 76.62 (m), 61.50, 60.64, 52.68 ppm.

HRMS (ESI): calcd. for $C_{26}H_{23}F_7N_5O^-$: 554.17963 m/z $[M-H]^-$

found: 554.18030 m/z $[M-H]^-$.

LCMS (ESI): t_{ret} = 6.08 min. 556 m/z $[M+H]^+$.

1,1,1,3,3,3-hexafluoro-2-(3-methyl-5-((3-((4-(pyridin-4-ylmethyl)piperazin-1-yl)methyl)phenyl)diazenyl)phenyl)propan-2-ol (MROR3)



5 (50 mg, 0.183 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (10 mL) and Oxone® (113 mg, 0.366 mmol, 2.00 eq.) dissolved in water (1 mL) was added. The reaction was stirred vigorously for 18 h before adding CH_2Cl_2 (20 mL) and extracting the mixture with aqueous HCl (1 M, 20 mL). The organic phase was extracted with brine (30 mL) and dried over Na_2SO_4. Next, **2** (41.3 mg, 0.146 mmol, 0.80 eq.) and acetic acid (5 mL) were added. The mixture was concentrated under reduced pressure to remove most of the CH_2Cl_2 and then stirred for 24 h. Then, the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, concentrated, and purified by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) to yield **MROR3** as a yellow solid (26 mg, 0.0471 mmol, 32%).

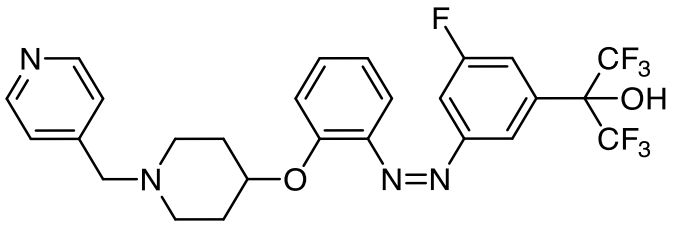
R_f = 0.25 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.01 (s, 1H), 8.48 (s, br 2H), 8.01 (s, 1H), 7.89 – 7.79 (m, 3H), 7.68 (s, 1H), 7.58 – 7.49 (m, 2H), 7.30 (d, *J* = 6.0 Hz, 2H), 3.59 (s, 2H), 3.49 (s, 2H), 2.50 (s, 3H), 2.42 (s, br, 8H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 152.29, 152.24, 149.96, 147.90, 140.40, 140.35, 132.80, 132.58, 130.32, 129.84, 125.01, 124.18, 123.30 (q, *J* = 288.6 Hz), 123.21, 122.11, 118.97, 77.18 (m), 61.96, 61.06, 53.11, 53.01, 21.51 ppm.

HRMS (ESI):	calcd. for $C_{27}H_{26}F_6N_5O^-$:	550.20470 m/z $[M-H]^-$
	found:	550.20520 m/z $[M-H]^-$.
LCMS (ESI):	t_{ret} = 5.96 min.	552 m/z $[M+H]^+$.

1,1,1,3,3,3-hexafluoro-2-(3-fluoro-5-((2-((1-(pyridin-4-ylmethyl)piperidin-4-yl)oxy)phenyl)diazenyl)phenyl)propan-2-ol (MROR4)



11 (50 mg, 0.180 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (20 mL) and Oxone® (227 mg, 0.740 mmol, 4.11 eq.) dissolved in water (1 mL) was added. The reaction was stirred vigorously for 18 h before adding CH_2Cl_2 (20 mL) and extracting the mixture with aqueous HCl (1 M, 20 mL). The organic phase was extracted with brine (30 mL) and dried over Na_2SO_4. Next, **14** (35.7 mg, 0.126 mmol, 0.70 eq.) and acetic acid (5 mL) were added. The mixture was concentrated under reduced pressure to remove most of the CH_2Cl_2 and then stirred for 24 h. Then, the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, concentrated, and purified by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) to yield **MROR4** as a yellow solid (15.7 mg, 0.0282 mmol, 22%).

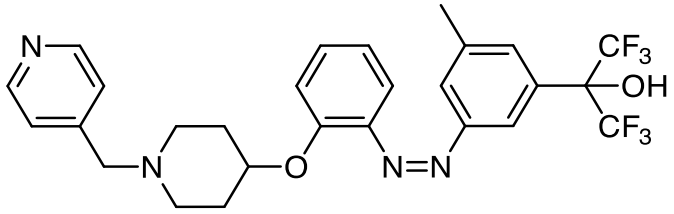
R_f = 0.16 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.55 – 8.44 (m, 2H), 8.21 (s, 1H), 8.06 (s, 1H), 7.89 (dt, *J* = 9.0, 2.1 Hz, 1H), 7.68 (dt, *J* = 9.6, 2.1 Hz, 1H), 7.63 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.56 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.37 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.08 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 4.77 – 4.66 (m, 1H), 3.50 (s, 2H), 2.69 – 2.57 (m, 2H), 2.41 – 2.29 (m, 2H), 2.03 – 1.91 (m, 2H), 1.88 – 1.76 (m, 2H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 162.53 (d, *J* = 246.9 Hz), 155.59, 153.85 (d, *J* = 7.6 Hz), 149.53, 147.96, 142.31, 134.33 (d, *J* = 8.5 Hz), 134.24, 123.70, 123.63, 122.68 (q, *J* = 289.1 Hz), 121.36, 117.92, 116.67, 116.36 (d, *J* = 32.8 Hz), 111.92 (d, *J* = 23.2 Hz), 76.65 (m), 73.73, 60.74, 49.61, 30.40 ppm.

HRMS (ESI):	calcd. for $C_{27}H_{22}F_7N_4O_2^-$:	555.16365 m/z $[M-H]^-$
	found:	555.16403 m/z $[M-H]^-$.
LCMS (ESI):	t_{ret} = 6.86 min.	557 m/z $[M+H]^+$.

1,1,1,3,3,3-hexafluoro-2-(3-methyl-5-((2-((1-(pyridin-4-ylmethyl)piperidin-4-yl)oxy)phenyl)diazenyl)phenyl)propan-2-ol (MROR5)



5 (50 mg, 0.183 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (10 mL) and Oxone® (113 mg, 0.366 mmol, 2.00 eq.) dissolved in water (1 mL) was added. The reaction was stirred vigorously for 18 h before adding CH_2Cl_2 (20 mL) and extracting the mixture with aqueous HCl (1 M, 20 mL). The organic phase was extracted with brine (30 mL) and dried over Na_2SO_4. Next, **14** (35.7 mg, 0.126 mmol, 0.69 eq.) and acetic acid (5 mL) were added. The mixture was concentrated under reduced pressure to remove most of the CH_2Cl_2 and then stirred for 24 h. Then, the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, concentrated, and purified by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) to yield **MROR5** as a yellow solid (13.2 mg, 0.0239 mmol, 19%).

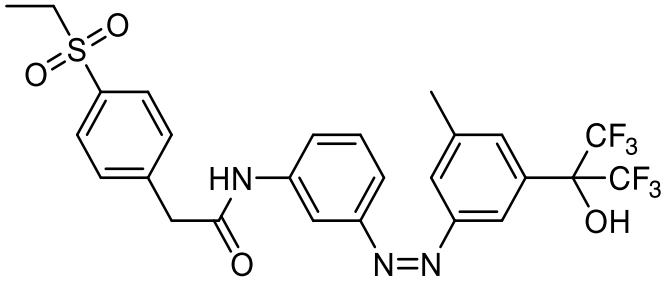
$\mathbf{R}_f$ = 0.17 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.55 – 8.43 (m, 2H), 8.21 (s, 1H), 8.01 (s, 1H), 7.90 (s, 1H), 7.69 (s, 1H), 7.60 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.52 (ddd, *J* = 8.8, 7.2, 1.7 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.08 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 4.73 – 4.65 (m, 1H), 3.50 (s, 2H), 2.68 – 2.60 (m, 2H), 2.52 (s, 3H), 2.36 – 2.30 (m, 2H), 2.03 – 1.91 (m, 2H), 1.87 – 1.76 (m, 2H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 155.19, 152.36, 149.55, 147.92, 142.74, 139.80, 133.41, 132.14, 129.65, 126.35, 123.59, 122.93 (q, *J* = 289.1 Hz), 121.47, 118.18, 116.87, 116.57, 77.10, 73.55, 60.74, 49.63, 30.43, 21.16 ppm.

HRMS (ESI):	calcd. for $C_{27}H_{25}F_6N_4O_2^-$:	551.18872 m/z $[M-H]^-$
	found:	551.18910 m/z $[M-H]^-$.
LCMS (ESI):	t_{ret} = 6.98 min.	553 m/z $[M+H]^+$.

2-(4-(ethylsulfonyl)phenyl)-N-(3-((3-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-5-methylphenyl)diazenyl)phenyl)acetamide (MROR6)



5 (50 mg, 0.183 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (10 mL) and Oxone® (113 mg, 0.366 mmol, 2.00 eq.) dissolved in water (1 mL) was added. The reaction was stirred vigorously for 18 h before adding CH_2Cl_2 (20 mL) and extracting the mixture with aqueous HCl (1 M, 20 mL). The organic phase was extracted with brine (30 mL) and dried over Na_2SO_4. Next, **7** (45.8 mg, 0.144 mmol, 0.79 eq.) and acetic acid (5 mL) were added. The mixture was concentrated under reduced pressure to remove most of the CH_2Cl_2 and then stirred for 8 days. Then, the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, concentrated, and purified by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) to yield **MROR6** as a yellow solid (33.1 mg, 0.0563 mmol, 39%).

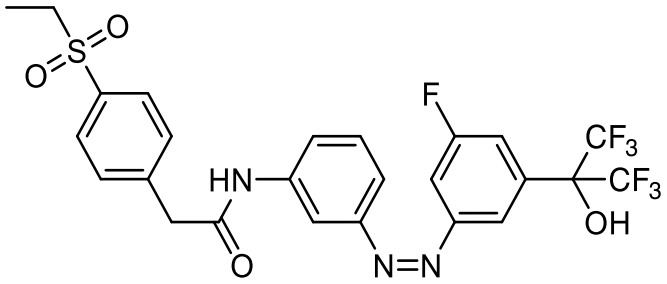
$\mathbf{R}_f$ = 0.31 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.59 (s, 1H), 9.03 (s, 1H), 8.26 (t, *J* = 2.0 Hz, 1H), 7.99 (s, 1H), 7.88 – 7.83 (m, 3H), 7.74 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.70 – 7.61 (m, 4H), 7.56 (t, *J* = 8.0 Hz, 1H), 3.85 (s, 2H), 3.28 (q, *J* = 7.4 Hz, 2H), 2.50 (s, 3H), 1.09 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.75, 152.17, 151.80, 141.99, 140.16, 140.06, 136.89, 132.24, 130.37, 130.09, 130.03, 127.96, 124.51, 122.93 (q, *J* = 289.1 Hz), 122.37, 119.57, 118.74, 111.59, 76.51 (m), 49.28, 43.02, 21.13, 7.26 ppm.

HRMS (ESI):	calcd. for $C_{26}H_{22}F_6N_3O_4S^-$:	586.12407 m/z $[M-H]^-$
	found:	586.12468 m/z $[M-H]^-$.
LCMS (ESI):	t_{ret} = 6.65 min.	588 m/z $[M+H]^+$.

2-(4-(ethylsulfonyl)phenyl)-N-(3-((3-fluoro-5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)diazenyl)phenyl)acetamide (MROR7)



11 (50 mg, 0.180 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (20 mL) and Oxone® (227 mg, 0.740 mmol, 4.11 eq.) dissolved in water (1 mL) was added. The reaction was stirred vigorously for 18 h before adding CH_2Cl_2 (20 mL) and extracting the mixture with aqueous HCl (1 M, 20 mL). The organic phase was extracted with brine (30 mL) and dried over Na_2SO_4. Next, **7** (45.8 mg, 0.144 mmol, 0.80 eq.) and acetic acid (5 mL) were added. The mixture was concentrated under reduced pressure to remove most of the CH_2Cl_2 and then stirred for 8 days. Then, the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, concentrated, and purified by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) to yield **MROR7** as a yellow solid (33.4 mg, 0.0565 mmol, 39%; *this yield is real and is not a copy-paste error from procedure **MROR6***).

$\mathbf{R}_f$ = 0.21 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.61 (s, 1H), 9.35 (s, 1H), 8.28 (t, *J* = 2.0 Hz, 1H), 8.05 (s, 1H), 7.89 – 7.84 (m, 3H), 7.78 (ddd, *J* = 8.1, 2.2, 1.1 Hz, 1H), 7.71 – 7.61 (m, 4H), 7.58 (t, *J* = 8.0 Hz, 1H), 3.85 (s, 2H), 3.27 (q, *J* = 7.3 Hz, 2H), 1.09 (t, *J* = 7.4 Hz, 3H) ppm.

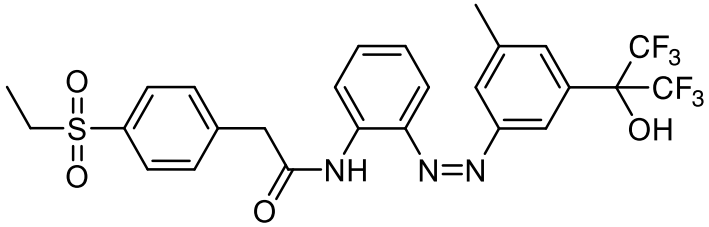
^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.81, 162.59 (d, *J* = 247.6 Hz), 153.35 (d, *J* = 7.3 Hz), 151.90, 141.96, 140.21, 136.91, 134.39 (d, *J* = 8.4 Hz), 130.39, 130.13, 127.97, 122.98, 122.67 (q, *J* = 288.7 Hz), 119.86, 118.43, 116.82 (d, *J* = 24.8 Hz), 111.86, 110.34 (d, *J* = 23.1 Hz), 76.38 (m), 49.29, 43.02, 7.26 ppm.

HRMS (ESI): calcd. for $C_{25}H_{19}F_7N_3O_4S^-$: 590.09900 m/z $[M-H]^-$

found: 590.09971 m/z $[M-H]^-$.

LCMS (ESI): t_{ret} = 7.38 min. 592 m/z $[M+H]^+$.

2-(4-(ethylsulfonyl)phenyl)-N-(2-((3-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-5-methylphenyl)diazenyl)phenyl)acetamide (MROR8)



8 (60.3 mg, 0.144 mmol, 0.79 eq.) was dissolved in a 2:1 CH_2Cl_2:TFA mixture (2 mL), stirred for 2 h, concentrated under reduced pressure and triturated with diethyl ether (3×2 mL).

In parallel, **5** (50 mg, 0.183 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (10 mL) and Oxone® (113 mg, 0.366 mmol, 2.00 eq.) dissolved in water (1 mL) was added. The reaction was stirred vigorously for 18 h before adding CH_2Cl_2 (20 mL) and extracting the mixture with aqueous HCl (1 M, 20 mL). The organic phase was extracted with brine (30 mL) and dried over Na_2SO_4.

Next, deprotected **8**, the crude nitroso compound and acetic acid (5 mL) were combined. The mixture was concentrated under reduced pressure to remove most of the CH_2Cl_2 and then stirred for 48 h. Then, the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, concentrated. The crude product was first purified by normal phase flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH), followed by a second column chromatography (Hx:EA, 0→100% EA) to yield **MROR8** as a yellow solid (3.1 mg, 0.0053 mmol, 3.7%).

$\mathbf{R}_f$ = 0.51 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.38 (s, 1H), 9.02 (s, 1H), 8.15 – 8.09 (m, 2H), 7.93 (td, *J* = 1.7, 0.8 Hz, 1H), 7.85 – 7.79 (m, 2H), 7.74 – 7.63 (m, 4H), 7.56 (ddd, *J* = 8.5, 7.3, 1.6 Hz, 1H), 7.26 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 3.99 (s, 2H), 3.24 (q, *J* = 7.3 Hz, 2H), 2.52 (s, 3H), 1.04 (t, *J* = 7.3 Hz, 3H) ppm.

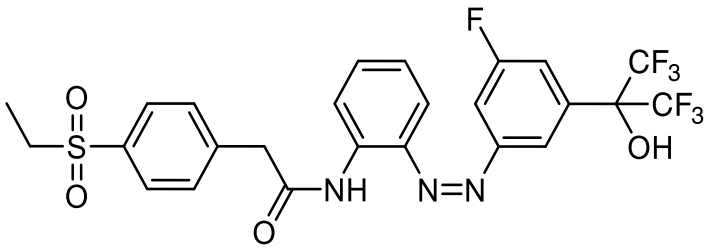
^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.73, 152.23, 142.09, 141.86, 139.74, 136.88, 136.84, 132.73, 132.14, 130.27, 130.10, 127.94, 124.73, 123.37, 123.01, 122.90 (q, J = 290.5 Hz), 121.12, 116.38, 76.80 (m), 49.23, 42.93, 21.27, 7.19 ppm.

HRMS (ESI): calcd. for $C_{26}H_{22}F_6N_3O_4S^-$: 586.12407 m/z $[M-H]^-$

found: 586.12471 m/z $[M-H]^-$.

LCMS (ESI): t_{ret} = 6.82 min. 588 m/z $[M+H]^+$.

2-(4-(ethylsulfonyl)phenyl)-N-(2-((3-fluoro-5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)diazenyl)phenyl)acetamide (MROR9)



8 (60.3 mg, 0.144 mmol, 0.80 eq.) was dissolved in a 2:1 CH_2Cl_2:TFA mixture (2 mL), stirred for 2 h, concentrated under reduced pressure and triturated with diethyl ether (3×2 mL).

In parallel, **11** (50 mg, 0.180 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (20 mL) and Oxone® (227 mg, 0.740 mmol, 4.11 eq.) dissolved in water (1 mL) was added. The reaction was stirred vigorously for 18 h before adding CH_2Cl_2 (20 mL) and extracting the mixture with aqueous HCl (1 M, 20 mL). The organic phase was extracted with brine (30 mL) and dried over Na_2SO_4.

Next, deprotected **8**, the crude nitroso compound and acetic acid (5 mL) were combined. The mixture was concentrated under reduced pressure to remove most of the CH_2Cl_2 and then stirred for 50 h. Subsequently, the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, concentrated, and purified by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) to yield **MROR9** as a yellow solid (7.6 mg, 0.0128 mmol, 8.9%).

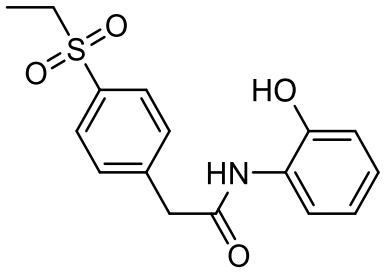
$\mathbf{R}_f$ = 0.58 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.38 (s, 1H), 9.02 (s, 1H), 8.15 – 8.09 (m, 2H), 7.93 (td, *J* = 1.7, 0.8 Hz, 1H), 7.85 – 7.79 (m, 2H), 7.74 – 7.63 (m, 4H), 7.56 (ddd, *J* = 8.5, 7.3, 1.6 Hz, 1H), 7.26 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 3.99 (s, 2H), 3.24 (q, *J* = 7.3 Hz, 2H), 2.52 (s, 3H), 1.04 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (201 MHz, DMSO-d_6) δ = 168.75, 162.53 (d, *J* = 247.0 Hz), 153.76 (d, *J* = 7.1 Hz), 142.01, 141.37, 137.50, 136.85, 134.28 (d, *J* = 8.4 Hz), 133.45, 130.26, 127.89, 124.60, 123.25, 122.62 (q, *J* = 288.4 Hz), 121.68, 116.72 (d, *J* = 26.2 Hz), 116.05, 108.06 (d, *J* = 23.3 Hz), 76.60 (m), 49.23, 42.91, 7.13 ppm.

HRMS (ESI):	calcd. for $C_{25}H_{19}F_7N_3O_4S^-$:	590.09900 m/z $[M-H]^-$
	found:	590.09955 m/z $[M-H]^-$.
LCMS (ESI):	t_{ret} = 6.87 min.	592 m/z $[M+H]^+$.

2-(4-(ethylsulfonyl)phenyl)-N-(2-hydroxyphenyl)acetamide (15)



2-Aminophenol (78.9 mg, 0.723 mmol, 1.1 eq), 2-(4-(ethylsulfonyl)phenyl)acetic acid (150 mg, 0.657 mmol, 1.0 eq), and HATU (275 mg, 0.723 mmol, 1.1 eq) were dissolved in DMF (2 mL) and DIPEA (0.343 mL, 1.97 mmol, 3.0 eq) were added. The reaction was stirred for 70 h, diluted with ethyl acetate (20 mL) and washed with saturated aqueous $NaHCO_3$ solution (20 mL), LiCl solution (10%, 20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) gave **15** (173 mg, 0.542 mmol, 82%) as a faint-yellow solid.

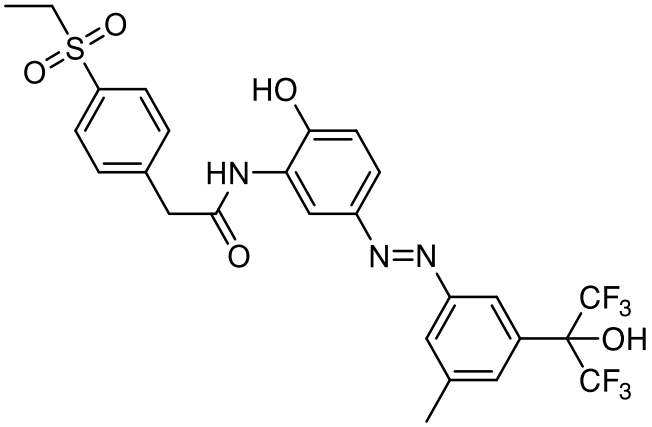
$\mathbf{R}_f$ = 0.52 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.81 (s, 1H), 9.47 (s, 1H), 7.84 (d, J = 8.3 Hz, 2H), 7.78 (dd, J = 8.0, 1.6 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 6.93 (ddd, J = 8.8, 7.3, 1.6 Hz, 1H), 6.86 (dd, J = 8.1, 1.6 Hz, 1H), 6.74 (ddd, J = 8.6, 7.3, 1.6 Hz, 1H), 3.90 (s, 2H), 3.27 (q, J = 7.4 Hz, 2H), 1.09 (t, J = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.52, 147.79, 142.46, 136.70, 130.21, 127.83, 126.13, 124.64, 122.15, 118.88, 115.40, 49.21, 42.50, 7.19 ppm.

HRMS (ESI):	calcd. for $C_{16}H_{18}NO_4S^+$:	320.09511 m/z $[M+H]^+$
	found:	320.09513 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 5.75 min.	320 m/z $[M+H]^+$.

2-(4-(ethylsulfonyl)phenyl)-N-(5-((3-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-5-methylphenyl)diazenyl)-2-hydroxyphenyl)acetamide (MROR10)



5 (27.3 mg, 0.1 mmol, 1.00 eq.) was dissolved in aq. HCl (2 M, 1 mL) and methanol (3 mL), and aq. $NaNO_2$ (2 M, 0.0525 mL, 0.105 mmol, 1.05 eq.) was added. The reaction was stirred 0.5 h before adding it dropwise into a solution of **15** (31.9 mg, 0.1 mmol, 1.00 eq.) in aq. NaOH (1 M, 2 mL) and methanol (3 mL) at 0 °C. The mixture was stirred for 1 h, saturated aq. NH_4Cl (20 mL) was added, and the mixture was extracted with EtOAc (25 mL). The organic phase was washed with brine (30 mL) and dried over Na_2SO_4 concentrated, and the crude material was purified by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) to yield **MROR10** as an orange solid (47.2 mg, 0.0782 mmol, 78%).

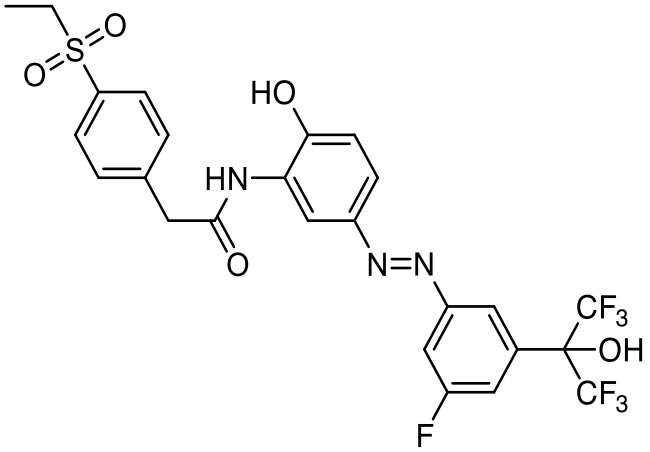
R_f = 0.32 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.01 (s, 1H), 9.65 (s, 1H), 8.91 (s, 1H), 8.59 (d, J = 2.4 Hz, 1H), 7.92 (s, 1H), 7.88 – 7.83 (m, 2H), 7.78 (d, J = 1.7 Hz, 1H), 7.68 – 7.62 (m, 3H), 7.60 (s, 1H), 7.08 (d, J = 8.6 Hz, 1H), 3.97 (s, 2H), 3.28 (q, J = 7.3 Hz, 2H), 2.47 (s, 3H), 1.10 (t, J = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.91, 151.98, 151.53, 144.67, 142.36, 139.68, 136.77, 132.02, 130.30, 128.94, 127.88, 127.08, 124.17, 122.89 (q, J = 287.2 Hz), 122.27, 118.16, 115.17, 114.49, 76.79 (p, J = 29.9 Hz), 49.25, 42.56, 21.08, 7.21 ppm.

HRMS (ESI):	calcd. for $C_{26}H_{24}F_6N_3O_5S^+$:	604.13354 m/z $[M+H]^+$
	found:	604.13221 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 6.70 min.	604 m/z $[M+H]^+$.

2-(4-(ethylsulfonyl)phenyl)-N-(5-((3-fluoro-5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)diazenyl)-2-hydroxyphenyl)acetamide (MROR11)



11 (27.7 mg, 0.1 mmol, 1.00 eq.) was dissolved in aq. HCl (2 M, 1 mL) and methanol (3 mL), and aq. $NaNO_2$ (2 M, 0.0525 mL, 0.105 mmol, 1.05 eq.) was added. The reaction was stirred 0.5 h before adding it dropwise into a solution of **15** (31.9 mg, 0.1 mmol, 1.00 eq.) in aq. NaOH (1 M, 2 mL) and methanol (3 mL) at 0 °C. The mixture was stirred for 1 h, saturated aq. NH_4Cl (20 mL) was added, and the mixture was extracted with EtOAc (25 mL). The organic phase was washed with brine (30 mL) and dried over Na_2SO_4 concentrated, and the crude material was purified by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) to yield **MROR11** as an orange solid (31.8 mg, 0.0523 mmol, 52%).

$\mathbf{R}_f$ = 0.32 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.15 (s, 1H), 9.67 (s, 1H), 9.22 (s, 1H), 8.61 (d, J = 2.4 Hz, 1H), 7.97 (s, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.78 (ddd, J = 9.2, 2.5, 1.6 Hz, 1H), 7.68 (dd, J = 8.6, 2.5 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.58 (dt, J = 9.5, 2.0 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 3.97 (s, 2H), 3.28 (q, J = 7.3 Hz, 2H), 1.10 (t, J = 7.3 Hz, 3H) ppm.

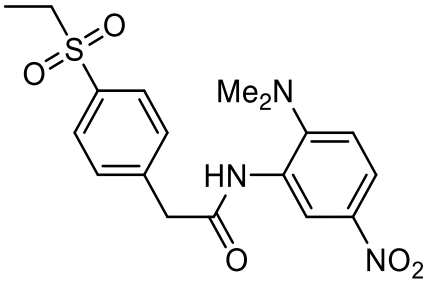
^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.95, 162.52 (d, J = 246.7 Hz), 153.65 (d, J = 7.3 Hz), 152.21, 144.44, 142.32, 136.78, 134.12 (d, J = 8.3 Hz), 130.31, 127.87, 127.19, 122.99, 122.63 (q, J = 287.0 Hz), 117.83, 115.56 (d, J = 25.3 Hz), 115.24, 114.61, 109.83 (d, J = 23.0 Hz), 76.63 (q, J = 29.5 Hz), 49.25, 42.54, 7.21 ppm.

HRMS (ESI): calcd. for $C_{25}H_{21}F_7N_3O_5S^+$: 608.10847 m/z $[M+H]^+$

found: 608.10724 m/z $[M+H]^+$.

LCMS (ESI): t_{ret} = 6.67 min. 608 m/z $[M+H]^+$.

N-(2-(dimethylamino)-5-nitrophenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide (16)



N[1],*N*[1]-dimethyl-4-nitrobenzene-1,2-diamine (131 mg, 0.723 mmol, 1.1 eq), 2-(4-(ethylsulfonyl)phenyl)acetic acid (150 mg, 0.657 mmol, 1.0 eq), and HATU (275 mg, 0.723 mmol, 1.1 eq) were dissolved in DMF (2 mL) and DIPEA (0.343 mL, 1.97 mmol, 3.0 eq) were added. The reaction was stirred for 70 h, diluted with ethyl acetate (20 mL) and washed with saturated aqueous $NaHCO_3$ solution (20 mL), LiCl solution (10%, 20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) gave **16** (154 mg, 0.392 mmol, 60%) as orange solid.

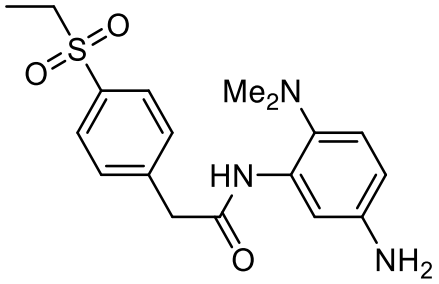
R$_f$ = 0.54 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.77 (s, 1H), 8.45 (d, J = 2.8 Hz, 1H), 7.95 (dd, J = 9.0, 2.8 Hz, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.66 – 7.62 (m, 2H), 7.13 (d, J = 9.1 Hz, 1H), 3.93 (s, 2H), 3.28 (q, J = 7.4 Hz, 2H), 2.79 (s, 6H), 1.09 (t, J = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.73, 151.75, 141.92, 139.71, 136.81, 130.90, 130.32, 127.88, 121.09, 120.32, 117.71, 49.21, 42.37, 42.21, 7.19 ppm.

HRMS (ESI):	calcd. for $C_{18}H_{22}N_3O_5S^+$:	392.12747 m/z $[M+H]^+$
	found:	392.12728 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 7.08 min.	392 m/z $[M+H]^+$.

N-(5-amino-2-(dimethylamino)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide (17)



16 (120 mg, 0.307 mmol) and Pt/V/C (1% Pt/ 2% V, 37.7 mg) were dissolved in methanol (10 mL). The reaction was vigorously stirred under a hydrogen atmosphere for 20 h. Next, the mixture was filtered through celite, and the filtrate concentrated under reduced pressure. The resulting yellow/brown oil **17** (122 mg, 0.304 mmol, 99%) slowly decomposes at room temperature and was directly used in the next step without further purification.

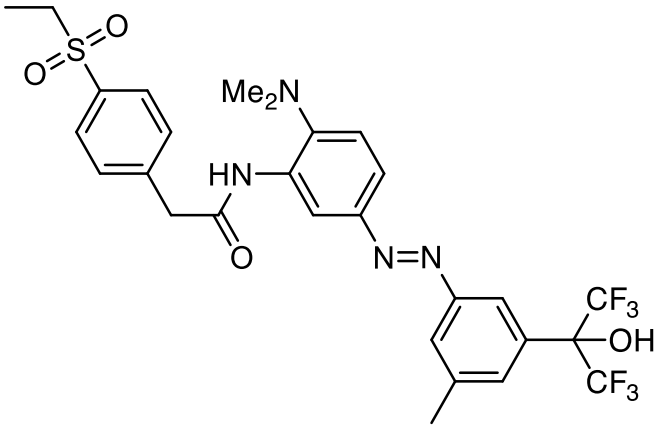
$\mathbf{R}_f$ = 0.39 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.97 (s, 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 2.6 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.23 (dd, J = 8.5, 2.6 Hz, 1H), 4.90 (s, br, 2H), 3.90 (s, 2H), 3.28 (q, J = 7.4 Hz, 2H), 2.37 (s, 6H), 1.09 (t, J = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 167.66, 145.38, 142.25, 136.89, 133.25, 132.68, 130.35, 127.98, 120.35, 109.26, 105.91, 49.17, 44.88, 43.34, 7.20 ppm.

HRMS (ESI):	calcd. for $C_{18}H_{24}N_3O_3S^+$:	362.15329 m/z $[M+H]^+$
	found:	362.15331 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 2.47 min.	362 m/z $[M+H]^+$.

N-(2-(dimethylamino)-5-((3-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)-5-methylphenyl)diazenyl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide (MROR12)



5 (40 mg, 0.146 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (15 mL) and Oxone® (185 mg, 0.600 mmol, 4.1 eq.) dissolved in water (1 mL) was added. The reaction was stirred vigorously for 18 h before adding CH_2Cl_2 (15 mL) and extracting the mixture with aqueous HCl (1 M, 20 mL). The organic phase was extracted with brine (30 mL) and dried over Na_2SO_4.

Next, **17** (41.6 mg, 0.115 mmol, 0.80 eq.), the crude nitroso compound and acetic acid (5 mL) were combined. The mixture was concentrated under reduced pressure to remove most of the CH_2Cl_2 and then stirred for 65 h. Subsequently, the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, concentrated, and purified by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) to yield **MROR12** as an orange solid (25,0 mg, 0.0396 mmol, 34%).

R_f = 0.48 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.57 (s, 1H), 8.93 (s, 1H), 8.31 (d, *J* = 2.4 Hz, 1H), 7.95 (s, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.83 – 7.80 (m, 1H), 7.72 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.61 (s, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 3.96 (s, 2H), 3.28 (q, *J* = 7.4 Hz, 2H), 2.72 (s, 6H), 2.48 (s, 3H), 1.10 (t, *J* = 7.4 Hz, 3H) ppm.

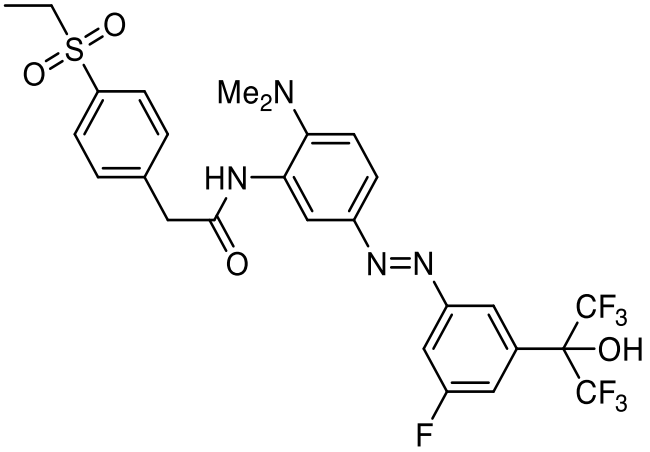
^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.55, 151.99, 148.87, 146.33, 142.19, 139.74, 136.81, 132.05, 130.65, 130.34, 129.14, 127.93, 124.25, 122.88 (q, J = 288.7 Hz), 121.84, 118.76, 118.28, 116.82, 76.78 (p, J = 29.8 Hz), 49.23, 42.80, 42.63, 21.06, 7.21 ppm.

HRMS (ESI): calcd. for $C_{28}H_{29}F_6N_4O_4S^+$: 631.18082 m/z $[M+H]^+$

found: 631.17979 m/z $[M+H]^+$.

LCMS (ESI): t_{ret} = 5.74 min. 631 m/z $[M+H]^+$.

N-(2-(dimethylamino)-5-((3-fluoro-5-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)diazenyl)phenyl)-2-(4-(ethylsulfonyl)phenyl)acetamide (MROR13)



11 (40 mg, 0.144 mmol, 1.00 eq.) was dissolved in CH_2Cl_2 (15 mL) and Oxone® (182 mg, 0.592 mmol, 4.1 eq.) dissolved in water (1 mL) was added. The reaction was stirred vigorously for 18 h before adding CH_2Cl_2 (15 mL) and extracting the mixture with aqueous HCl (1 M, 20 mL). The organic phase was extracted with brine (30 mL) and dried over Na_2SO_4.

Next, **17** (41.6 mg, 0.115 mmol, 0.80 eq.), the crude nitroso compound and acetic acid (5 mL) were combined. The mixture was concentrated under reduced pressure to remove most of the CH_2Cl_2 and then stirred for 64 h. Subsequently, the volatiles were removed under reduced pressure and the residue was dissolved in ethyl acetate (15 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic phase was dried over Na_2SO_4, concentrated, and purified by flash column chromatography (CH_2Cl_2:MeOH, 0→10% MeOH) to yield **MROR13** as an orange solid (43.8 mg, 0.0504 mmol, 44%).

$\mathbf{R}_f$ = 0.48 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.62 (s, 1H), 9.23 (s, 1H), 8.28 (d, J = 2.4 Hz, 1H), 7.99 (s, 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.80 (ddd, J = 9.3, 2.4, 1.6 Hz, 1H), 7.75 (dd, J = 8.6, 2.4 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.61 – 7.57 (m, 1H), 7.22 (d, J = 8.7 Hz, 1H), 3.95 (s, 2H), 3.28 (q, J = 7.4 Hz, 2H), 2.75 (s, 6H), 1.09 (t, J = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 168.56, 162.52 (d, *J* = 246.8 Hz), 153.66 (d, *J* = 7.4 Hz), 149.69, 145.82, 142.15, 136.81, 134.13 (d, *J* = 8.3 Hz), 130.34, 130.21, 127.92, 122.62 (q, *J* = 289.2 Hz), 122.54, 118.58, 117.92, 117.61, 115.68 (d, *J* = 27.1 Hz), 109.89 (d, *J* = 22.8 Hz), 76.77 (q, *J* = 29.3 Hz), 49.23, 42.65, 42.58, 7.20 ppm.

HRMS (ESI): calcd. for $C_{27}H_{26}F_7N_4O_4S^+$: 635.15575 m/z $[M+H]^+$

found: 635.15416 m/z $[M-H]^+$.

LCMS (ESI): t_{ret} = 5.84 min. 635 m/z $[M+H]^+$.

Docking

Docking of ligands into the RORγ ligand binding domain (PDB: 6NWT[1]) was performed using the Schrödinger software suite (version 2019–1; Schrödinger, LLC, New York, NY, 2019) with standard parameters.[6,7]

In general, docking suggested that our designs' *E*-isomers might be much worse binders than their corresponding *Z*-isomers (**Fig 2e**), which was encouraging since it ought to result in the ideal tool scenario[8] of a compound that is inactive in the applied, dark state (*E*-isomer), and only becomes active where and when illuminated (*Z*-isomer).

Biological evaluation

Illumination setup

For illumination of standard well-plates, we performed pulsed irradiation with the indicated wavelength using our previously developed arrays of 24 x 5 mm LEDs, pulsed at 100 ms "on" every 20 seconds[9] (LEDs were supplied by Roithner Lasertechnik). **MROR10-13** were pulse irradiated with 400 nm LEDs at 10 ms "on" every 100 ms.

Gal4 hybrid reporter gene assays

Reporter gene assays were performed in HEK293T cells (German Collection of Microorganisms and Cell Culture GmbH, DSMZ) as reported previously using the Gal4-fusion receptor plasmids pFA-CMV-hRORγ-LBD, pFA-CMV-hRORα-LBD, pFA-CMV-hRORβ-LBD, pFA-CMV-hTHRα-LBD, pFA-CMV-hRARα-LBD, pFA-CMV-hPPARα-LBD, pFA-CMV-hPPARγ-LBD, pFA-CMV-hPPARδ-LBD, pFA-CMV-hLXRα-LBD, pFA-CMV-hLXRβ-LBD, pFA-CMV-hFXR-LBD, pFA-CMV-hVDR-LBD, pFA-CMV-hCAR-LBD, and pFA-CMV-hRXRα-LBD, which code for the hinge region and LBD of the canonical isoform of the respective human nuclear receptor.[10–15] pFR-Luc (Stratagene, La Jolla, CA, USA) served as a reporter plasmid, and pRL-SV40 (Promega, Madison, WI, USA) was used for normalization of transfection efficiency and test compound toxicity. Cells were cultured in Dulbecco's modified Eagle's medium (DMEM), high glucose supplemented with 10% fetal calf serum (FCS), sodium pyruvate (1 mM), penicillin (100 U/mL), and streptomycin (100 µg/mL) at 37 °C and 5% CO_2 and seeded in 96-well plates (3×10^4 cells/well). After 24 h, the medium was changed to Opti-MEM without supplements, and cells were transiently transfected using Lipofectamine LTX reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. Five hours after transfection, cells were incubated with the test compounds in Opti-MEM supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), and 0.1% dimethyl sulfoxide (DMSO) for 14−16 h before luciferase activity was measured using the Dual-Glo Luciferase Assay System (Promega) according to the manufacturer's protocol on a Tecan Spark luminometer (Tecan Deutschland GmbH, Crailsheim, Germany). Each concentration was tested in duplicates, and each experiment was performed independently at least three times for dose−response characterization and at least two times for selectivity screening. Firefly luciferase data were divided by renilla luciferase data and multiplied by 1000 to obtain relative light units (RLU). Fold activation was obtained by dividing the mean RLU of a test compound at a respective concentration by the mean RLU of untreated control and used for dose−response curve fitting with the equation "[inhibitor] vs response − variable slope (four parameters)" in GraphPad Prism (version 7.00, GraphPad software, La Jolla, CA, USA). All hybrid assays were validated

with the respective reference agonists/inverse agonists (RORα/β/γ: SR1001; THRα: triiodothyronine; RARα: tretinoin; PPARα: GW7647; PPARγ: pioglitazone; PPARδ: L165,041; LXRα/β: T0901317; FXR: GW4064; VDR: calcitriol; CAR: CITCO; RXRα: bexarotene), which yielded IC_{50}/EC_{50} values in agreement with the literature. Characterization of the respective *Z*-counterparts was performed in the same way with preirradiated compounds (irradiation for 3 min at λ = 365 nm before incubation). To maintain the compound in the *Z*-adapted state, the Cell DISCO system[9] was used during incubation with 100 ms light pulses (λ = 365 nm) every 20 s. All luminescence reporter gene assay data are shown as mean ± S.E.M. from at least three independent experiments each with two technical replicates for the RORγ dose-response curves (**Fig 2gh**, **Fig 3ef**, **Fig S3**). For selectivity screening, mean fold/remaining activity ± S.E.M. from at least two independent experiments each with two technical replicates are shown (**Fig 4a**, **Fig S4**).

Fluorescence Reporter Gene Assay

The fluorescence reporter gene assay was performed in HEK293T cells (German Collection of Microorganisms and Cell Culture GmbH, DSMZ) using the Gal4-fusion receptor plasmid pFA-CMV-hRORγ-LBD[10], which codes for the hinge region and LBD of the canonical isoform of RORγ. The Gal4-responsive fluorescence reporter mCherry was expressed from plasmid pUAS-mCherry-NLS (Addgene, entry 87695, Watertown, MA, USA).[16] Cells were cultured in DMEM, high glucose with 10% FCS, sodium pyruvate (1 mM), penicillin (100 U/mL), and streptomycin (100 µg/mL) at 37 °C and 5% CO_2. 24 h before transfection, the cells were seeded in black cell culture 96-well microplates with clear flat bottom (3×10^4 cells/well; Corning Incorporated, Corning, NY, USA). Before transfection, the medium was changed to Opti-MEM without supplements. Transient transfection was carried out using Lipofectamine LTX reagent (Invitrogen) according to the manufacturer's protocol. Five hours after transfection, the medium was changed to Opti-MEM supplemented with penicillin (100 U/mL) and streptomycin (100 µg/mL) and additionally containing 0.1% DMSO and the respective test compound or 0.1% DMSO alone as the untreated control. Each concentration was tested in duplicate, and each experiment was repeated independently four times. After incubation, the live cells were assayed for fluorescence reporter intensity every second hour until 36 h. The fluorescence intensity (FI) was measured for excitation at 585/10 nm, emission 610/10 nm in bottom reading mode with a Tecan Spark Cyto (Tecan Deutschland GmbH). Fold FI was obtained by dividing the mean FI of the test compound by the mean FI of the untreated control. Hybrid fluorescence assay performance was monitored with the inverse agonist SR1001 (1 µM) as a reference. Characterization of the respective *Z*-counterparts was performed in the same way with preirradiated compounds (irradiation for 3 min at λ = 365 nm before incubation). To maintain the compound in the *Z*-rich state, the Cell DISCO system[9] was used during incubation of one study arm with 100 ms light pulses (λ = 365 nm) every 20 s. Due to the overall increase in fluorescence over the course of the experiment, the gain and threshold were readjusted for each measurement and thus only relative values are given for fluorescence intensity. All fluorescence reporter gene assay data are shown as mean ± S.E.M. from four independent experiments each with two technical replicates (**Fig 4bc**, **Fig S5**).

Adipocyte-derived mesenchymal stem cell differentiation

Cell culture and treatment: Differentiation experiments of ASC52telo, hTERT cells (ATCC® SCRC-4000™) were conducted according to a previously described procedure.[17] In brief, cells were grown in DMEM high glucose, supplemented with 10% fetal calf serum, sodium pyruvate

(1 mM), penicillin (100 U/mL), and streptomycin (100 µg/mL) at 37 °C and 5% CO_2. Cells were seeded in standard culture medium at a density of 5,000 cells per well in 96-well plates. After adherence overnight, cells were incubated with differentiation medium, composed of standard culture medium supplemented with human insulin (10 µg/mL, #I3536, Merck KgaA, Darmstadt, Germany), dexamethasone (1 µM, #D4902, Merck KgaA, Darmstadt, Germany,), isobutylmethylxanthine (IBMX, 0.5 mM, #I5879, Merck KgaA, Darmstadt, Germany), pioglitazone (1 µM, #AB451092, abcr GmbH, Karlsruhe, Germany) (medium A), additionally containing DMSO (final concentration 0.1%) and **MROR6** at the indicated concentrations, or DMSO alone as untreated control. Cells were cultured in differentiation medium for 48-72 h followed by medium exchange and 24 h cultivation in standard culture medium supplemented with human insulin (medium B) additionally containing DMSO (final concentration 0.1%) and **MROR6** at the indicated concentrations, or DMSO alone as untreated control. The sequence of consecutive cultivation in medium A and medium B represents one differentiation cycle (72-96 h), of which six consecutive sequences were completed within 21 days of culture. Cells were kept in the dark to determine the effects of the *E*-isomer. Characterisation of the respective *Z*-counterparts was performed in the same way with preirradiated compounds (irradiation for 3 min at λ = 365 nm before incubation). To maintain the compound in the *Z*-adapted state, the Cell DISCO system[9] was used during incubation with 100 ms light pulses (λ = 365 nm) every 8 s. **Oil Red O staining**: After the 21-day differentiation procedure and test compound treatment, cells were washed with phosphate buffered saline (PBS) once and fixed with formalin (10%, stabilized with methanol, 100 µL per well, #15071, Morphisto GmbH, Offenbach am Main, Germany) for 15 min at room temperature. The fixing solution was aspirated, and the fixed cells were washed twice with 40% 2-propanol with the second wash step incubating for 30 min at room temperature to equilibrate the specimen for staining. Oil Red O (#O0625, Merck KgaA, Darmstadt, Germany) was prepared at 10 mg/mL in 2-propanol, filtered with grade 595 Whatman® filter paper (#311611, Schleicher & Schuell GmbH, London, UK) and a 0.2 µm syringe filter (FP 30/0,2 CA-S, #10462200, Schleicher & Schuell GmbH, London, UK), and diluted with ddH_2O to a final concentration of 0.4% Oil Red O and 40% 2-propanol. Upon equilibration, specimen were incubated with 50 µL of 0.4% Oil Red O solution for 1 h at room temperature before the staining solution was aspirated and the wells were washed with ddH_2O 2-3 times to remove precipitated Oil Red O crystals. Specimen were kept in ddH_2O for subsequent analysis. For each well, multiple pictures were taken at a 20X magnification using a Motic®AE31E inverted microscope and a Moticam 1080 (Motic Hong Kong Ldt.). Images were dichromized and the red channel was extracted for analysis using ImageJ 1.53q. Oil Red O-positive stained area was evaluated by applying an appropriate color threshold to extract red image area only and was further normalized to its respective DMSO control. The experiment was conducted in five to six biologically independent iterations. **Statistical analysis**: Data were evaluated for normal distribution (Shapiro-Wilk-Test) and homoscedasticity (Levenes Test); differences between groups were analyzed by Welch Two Sample t-test.

Vectorial copies of the images in the main text

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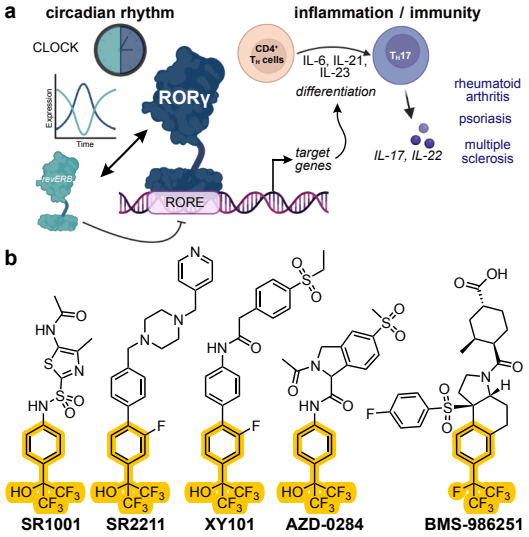
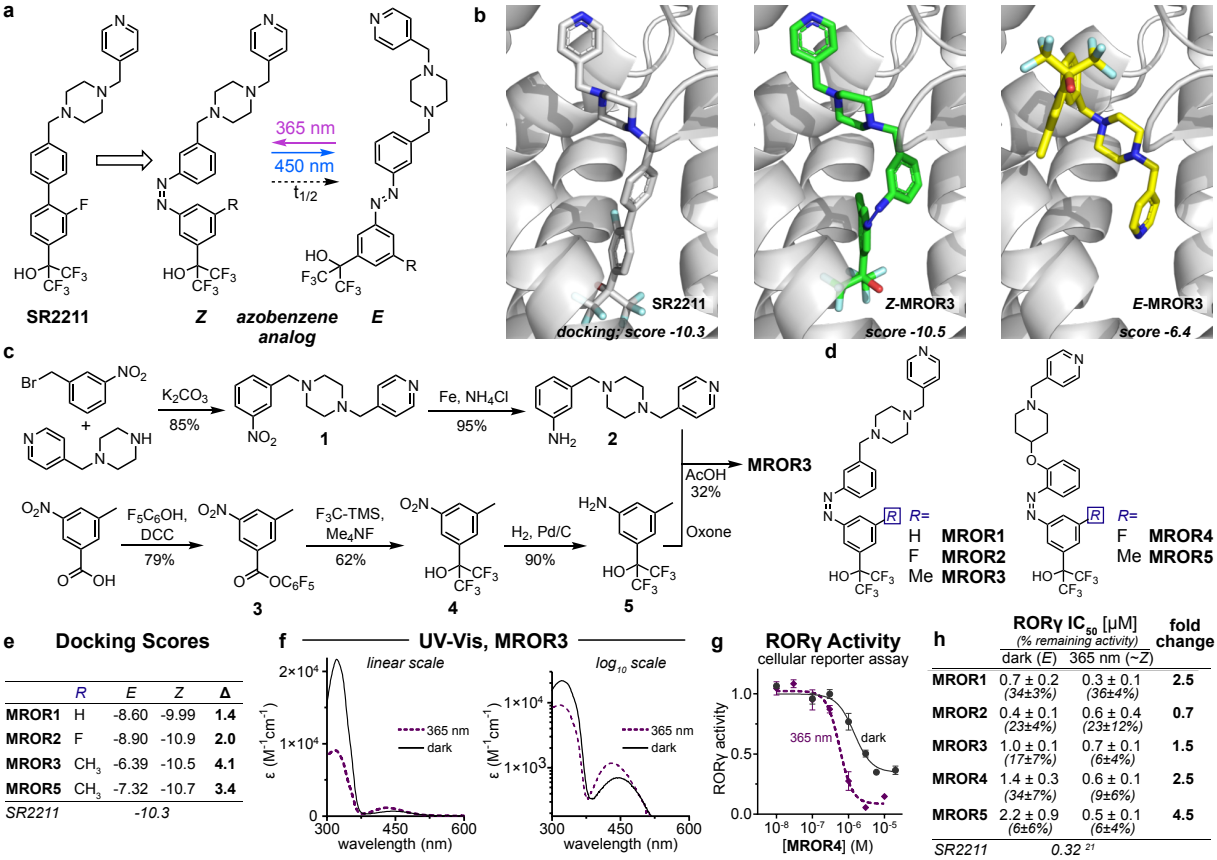


Figure S6 (reproduction of Figure 1). RORγ biology and pharmacology. a) Schematic of RORγ function and biological roles. b) Inverse RORγ agonists featuring a terminal (hexafluoroisopropyl)phenyl motif near a central aryl ring.



e Docking Scores

	R	E	Z	Δ
MROR1	H	-8.60	-9.99	**1.4**
MROR2	F	-8.90	-10.9	**2.0**
MROR3	CH_3	-6.39	-10.5	**4.1**
MROR5	CH_3	-7.32	-10.7	**3.4**
SR2211			*-10.3*	

h

	RORγ IC_{50} [μM] (% remaining activity) dark (*E*)	365 nm (~*Z*)	fold change
MROR1	0.7 ± 0.2 *(34±3%)*	0.3 ± 0.1 *(36±4%)*	**2.5**
MROR2	0.4 ± 0.1 *(23±4%)*	0.6 ± 0.4 *(23±12%)*	**0.7**
MROR3	1.0 ± 0.1 *(17±7%)*	0.7 ± 0.1 *(6±4%)*	**1.5**
MROR4	1.4 ± 0.3 *(34±7%)*	0.6 ± 0.1 *(9±6%)*	**2.5**
MROR5	2.2 ± 0.9 *(6±6%)*	0.5 ± 0.1 *(6±4%)*	**4.5**
SR2211	*0.32* [21]		

Figure S7 (reproduction of Figure 2). SR2211-based azologues **MROR1-5** as photoswitchable RORγ ligands. a) A SR2211 azologue. b) Docking of SR2211 and *E/Z*-**MROR3** into the RORγ LBD (PDB: 6NWT[1]; the low score for *E*-**MROR3**, and its unrealistic pose, are coherent with steric clash). c) Synthesis of **MROR3**. d) Structures of **MROR1-5**. e) Docking scores of *E/Z*-azologues. f) Representative UV-Vis spectra, as all-*E* (dark) or mostly-*Z* (PSS 365 nm) (**Figure S2a**). g-h) Mostly-*Z*-**MROR1-5** are submicromolar inverse RORγ agonists, similar to SR2211[18]; but their *E*-isomers are not weaker enough to qualify as *usefully-switchable* ligands (**Figure S3a**), data shown as mean ± S.E.M. from at least three independent experiments each with two technical replicates.

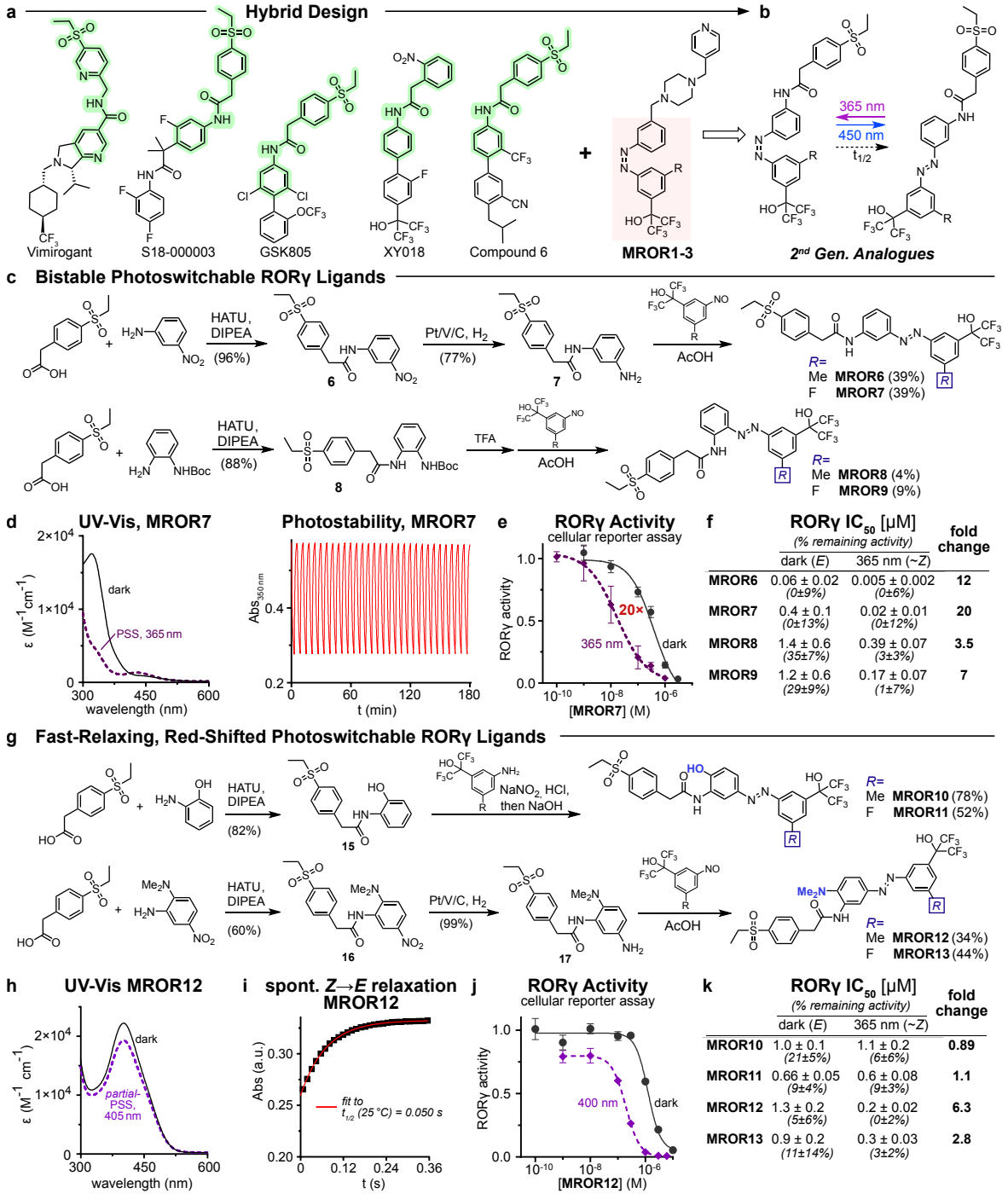


Figure S8 (reproduction of Figure 3). Hybrid photoswitchable RORγ ligands using *para*-(ethylsulfonyl)phenylacetamide, a common polar motif for inverse RORγ agonists. a-f) Bistable hybrids **MROR6-9**: a-b) design; c) syntheses; d) representative UV-Vis spectra and reversible *E*⇄*Z* photoswitching (365/450 nm) (**Figure S2bd**); e-f) **MROR6-9** have good light-dependency of cellular RORγ inhibition, and can reach high *Z*-potency (**Figure S3bc**), data shown as mean ± S.E.M. from at least three independent experiments each with two technical replicates. g-k) Fast-relaxing red-shifted **MROR10-13** (based on **MROR6-7**): g) synthesis; h-i) representative UV-Vis spectra and thermal *Z*→*E* isomerisation (**Figure S2ce**); j-k) light-dependent cellular RORγ inhibition (**Figure S3d**), data shown as mean ± S.E.M. from at least three independent experiments each with two technical replicates.

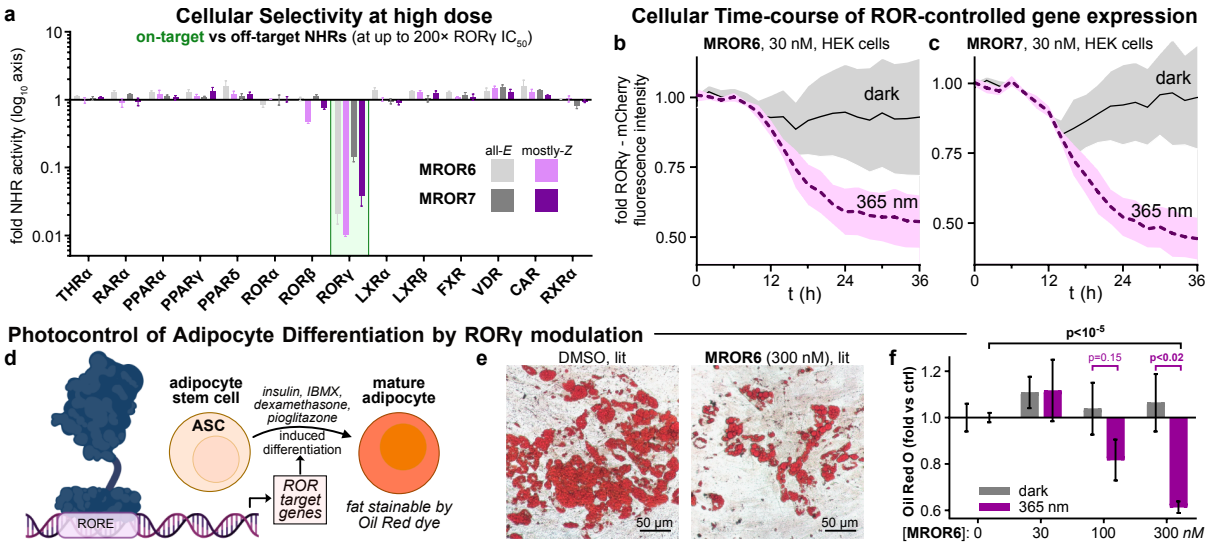


Figure S9 (reproduction of Figure 4, expanded legend). ***Figure 4.*** Cellular utility of **MROR6-7** as photopharmaceutical tools. a) Cellular NHR selectivity profiles of *E*/*Z*-**MROR6-7** at 1 µM (see also **Figure S4**), data shown as mean fold/remaining activity ± S.E.M. from at least two independent experiments each with two technical replicates. b-c) Time-course of RORγ-controlled protein expression depending on *E*/*Z*-**MROR6-7** (interpret: *Z* blocks RORγ-dependent transcription, so first target mRNA, and then target protein, levels drop relative to control; target here: mCherry; c.f. **Figure S5**); Data shown as mean ± S.E.M. from four independent experiments each with two technical replicates. d-f) *Z*-**MROR6** counteracts ASC differentiation, showing a role for RORγ in adipogenesis (*ASC52telo,hTERT* cells; 21 days' differentiation; e: representative micrographs, lipid stain: Oil Red O, scale bar 50 µm; f: data as mean±SEM; n=5; full legend at **Figure S9**), statistical significance was determined using a Welch Two Sample t-test.

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NMR Spectra

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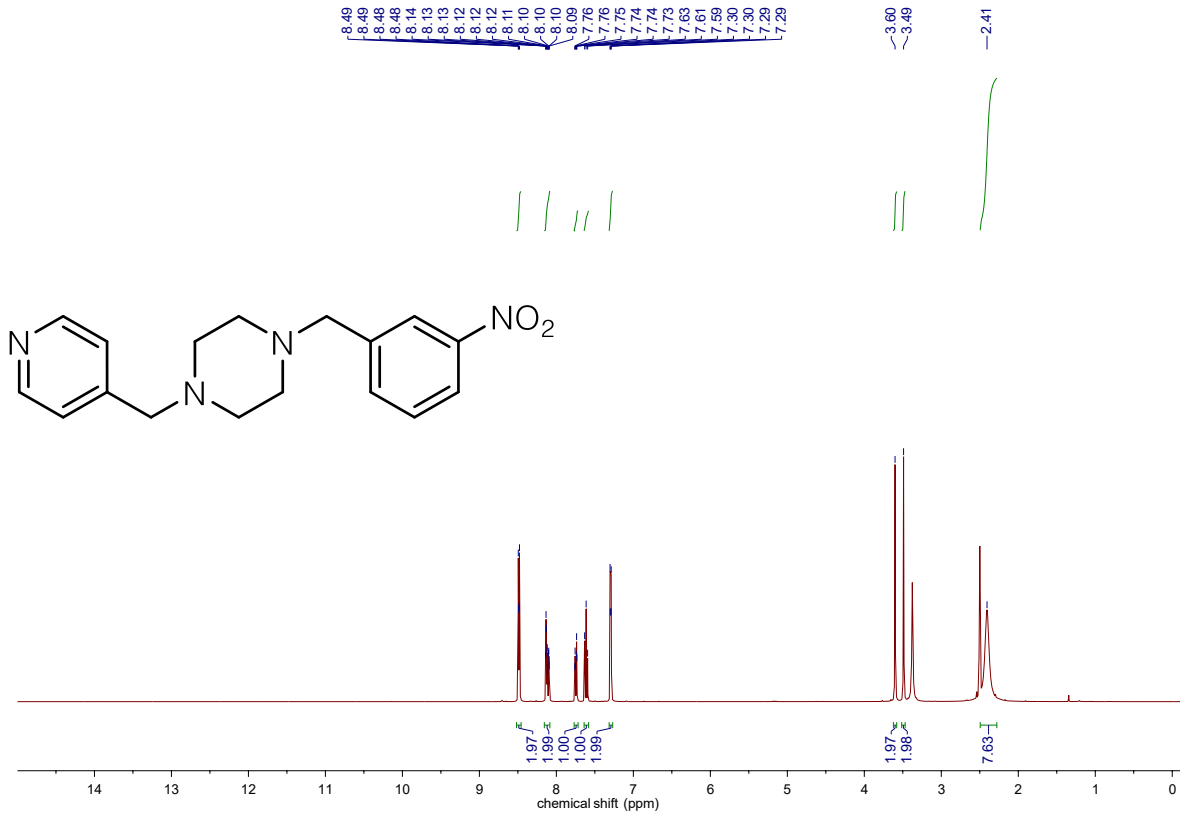

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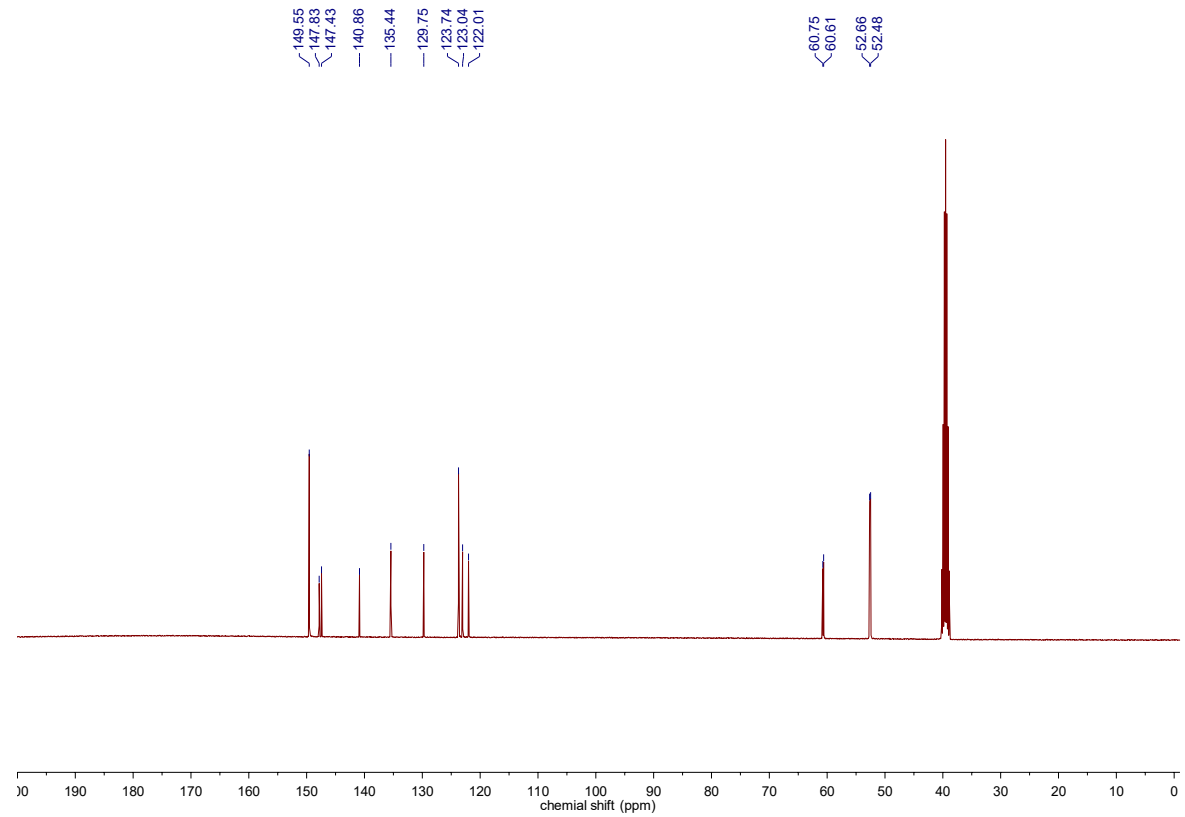

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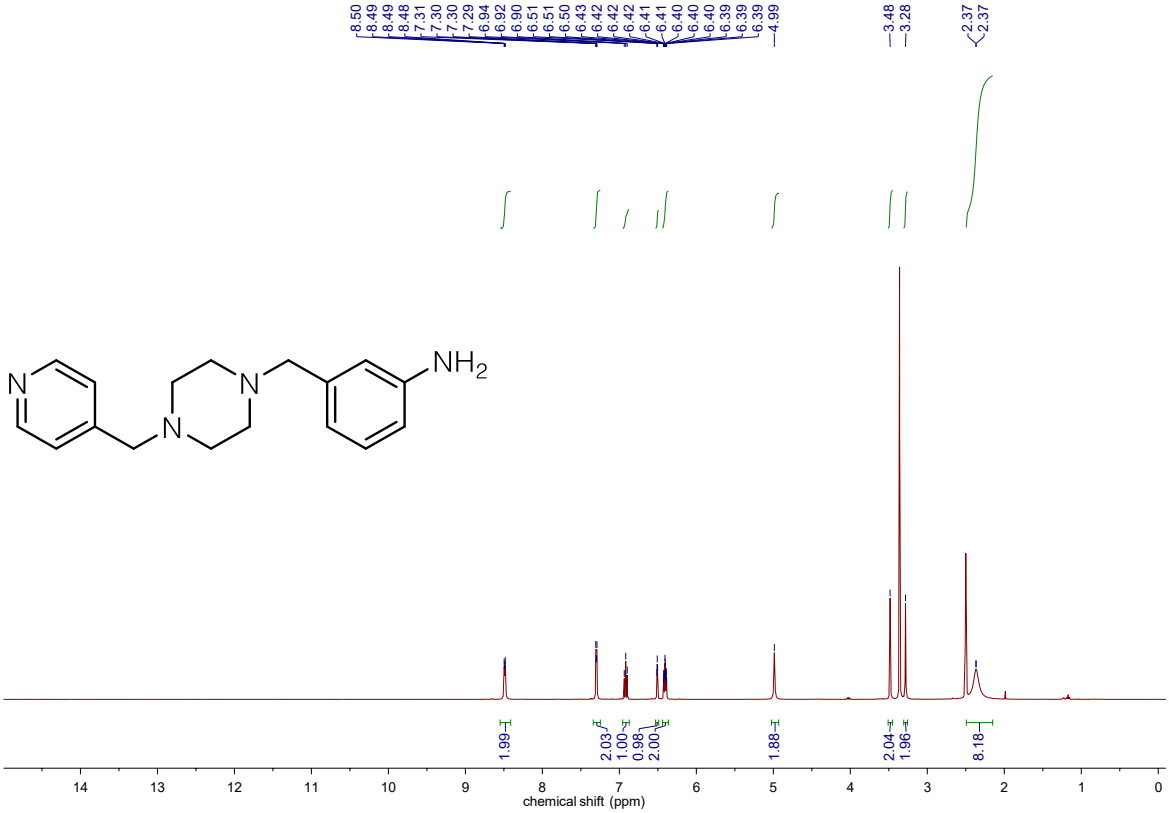

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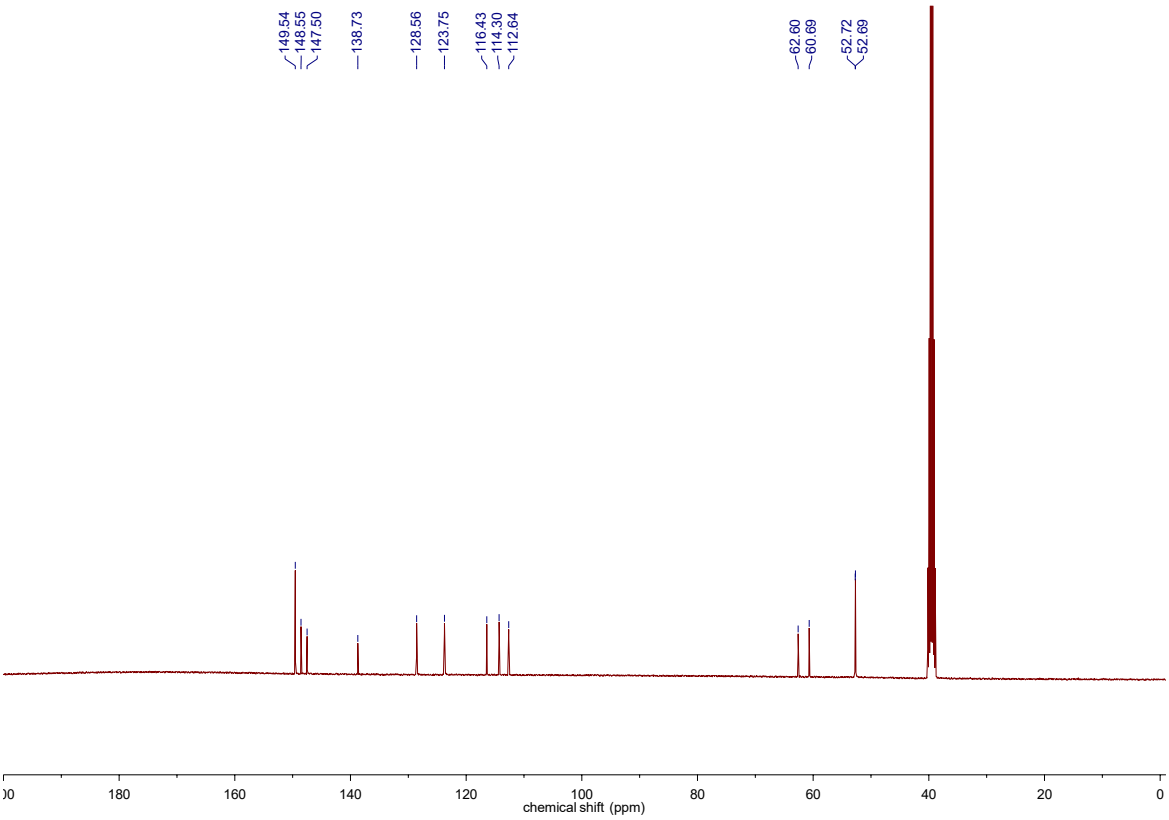

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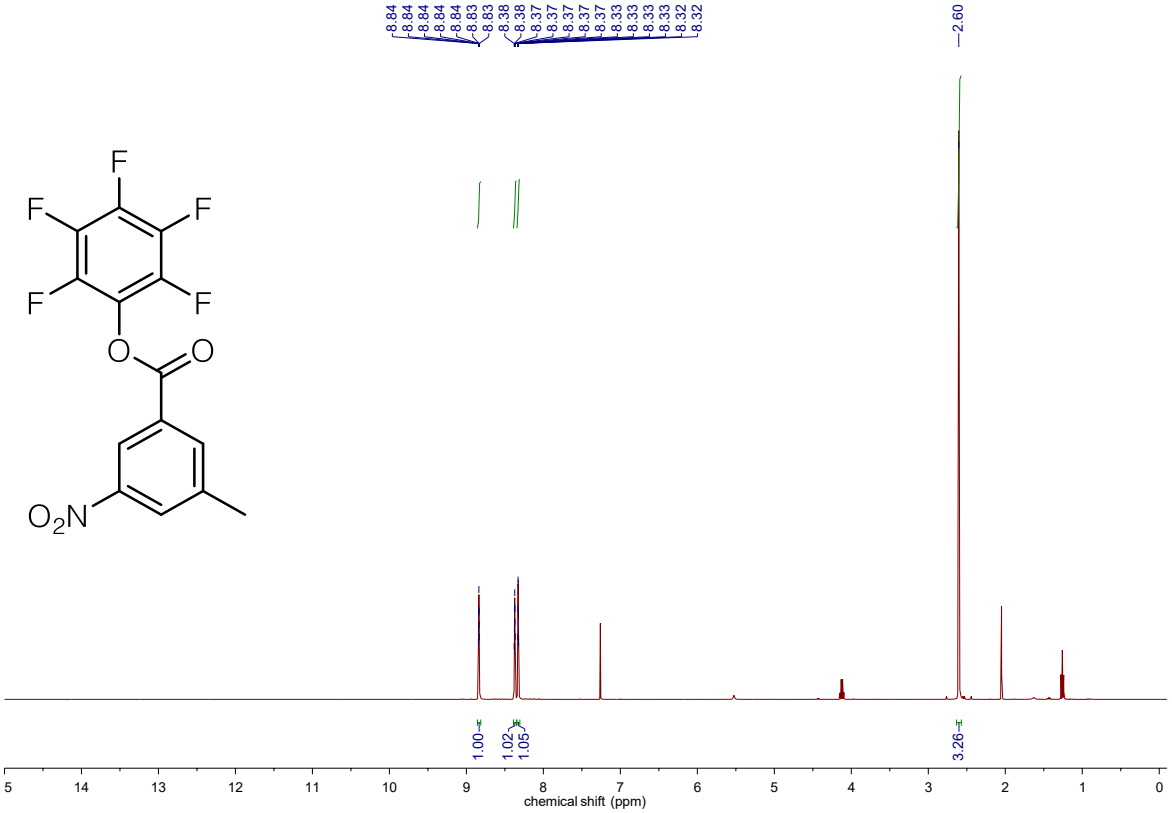

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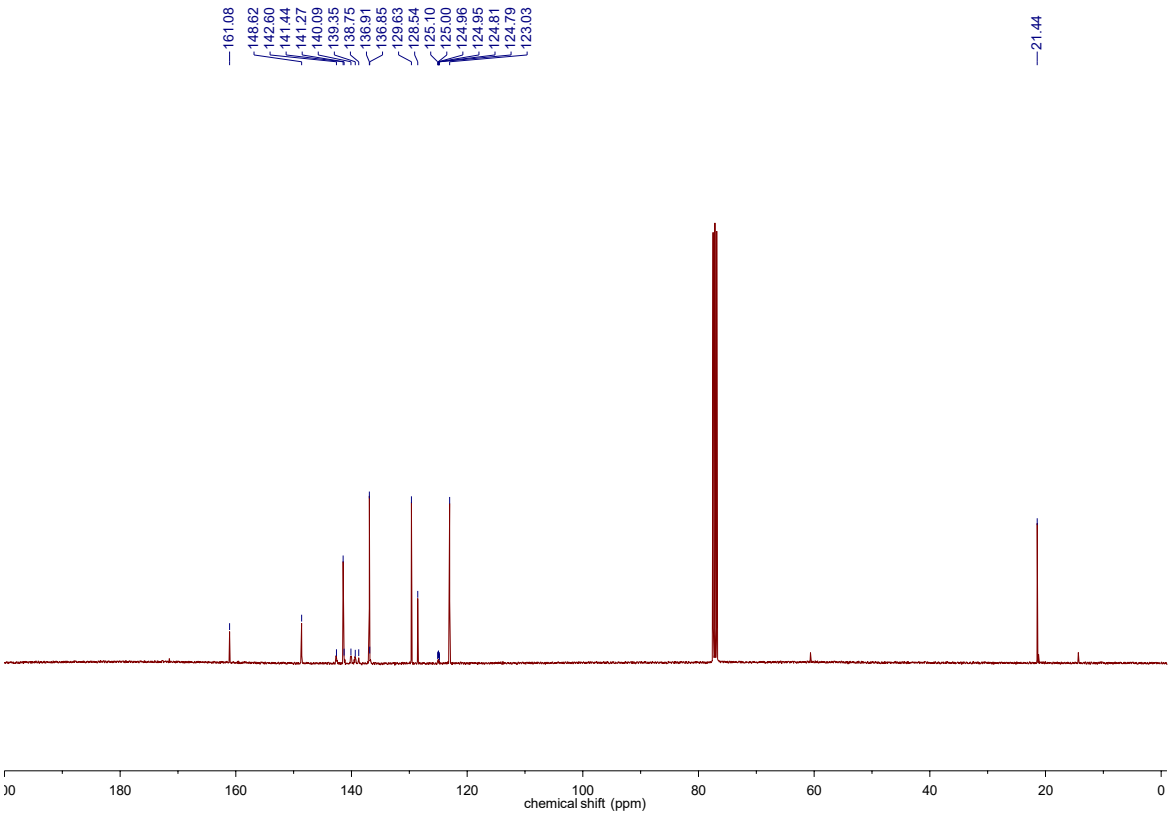

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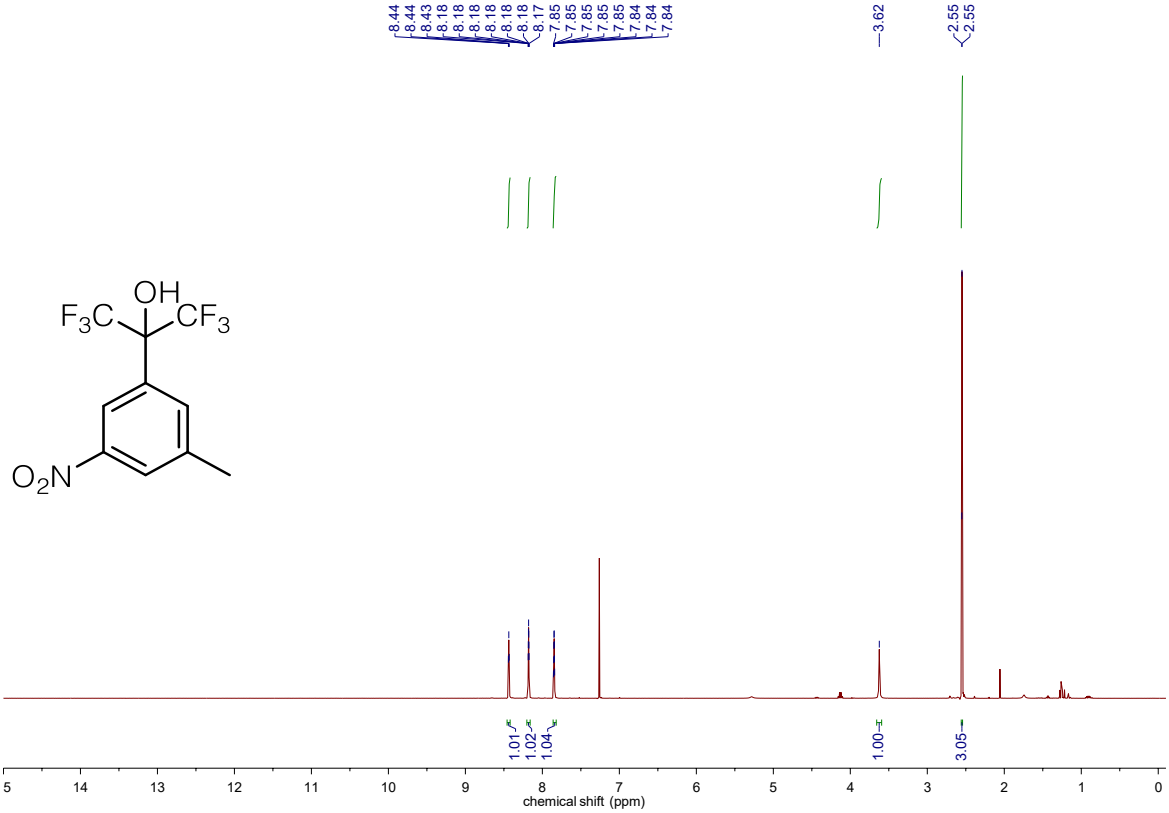

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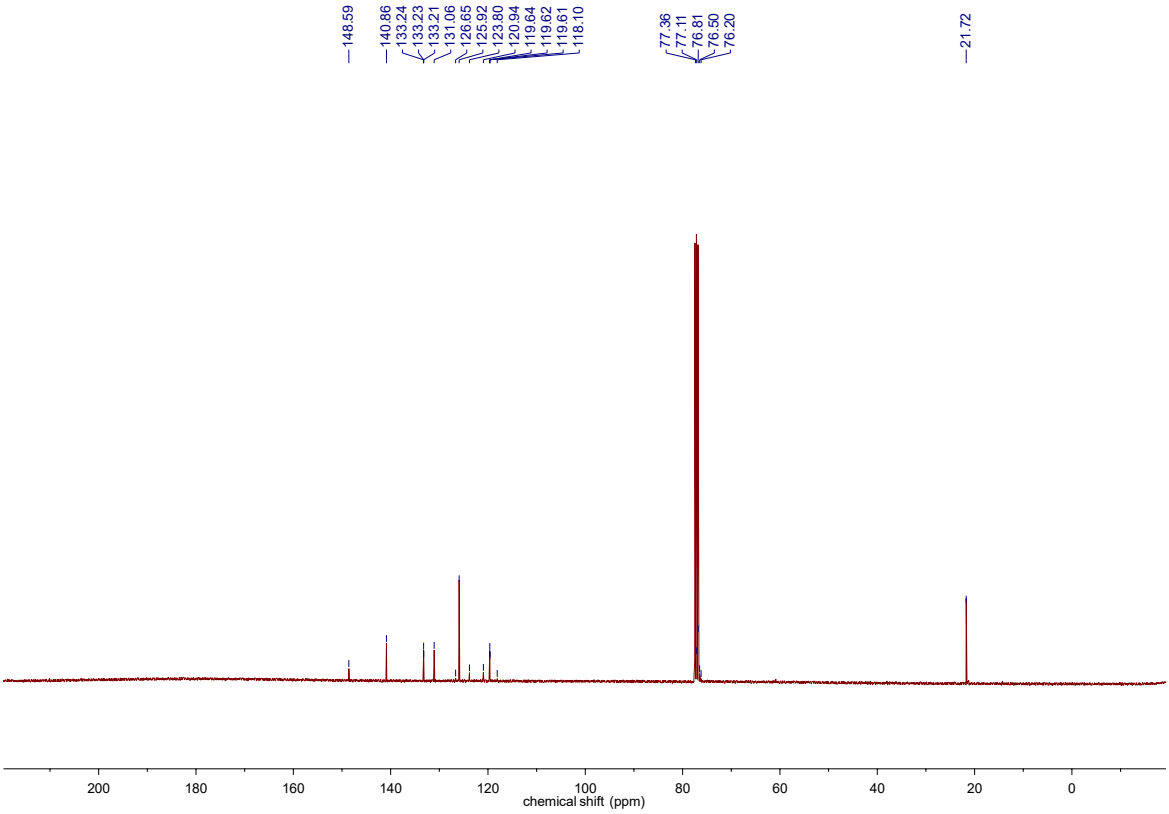

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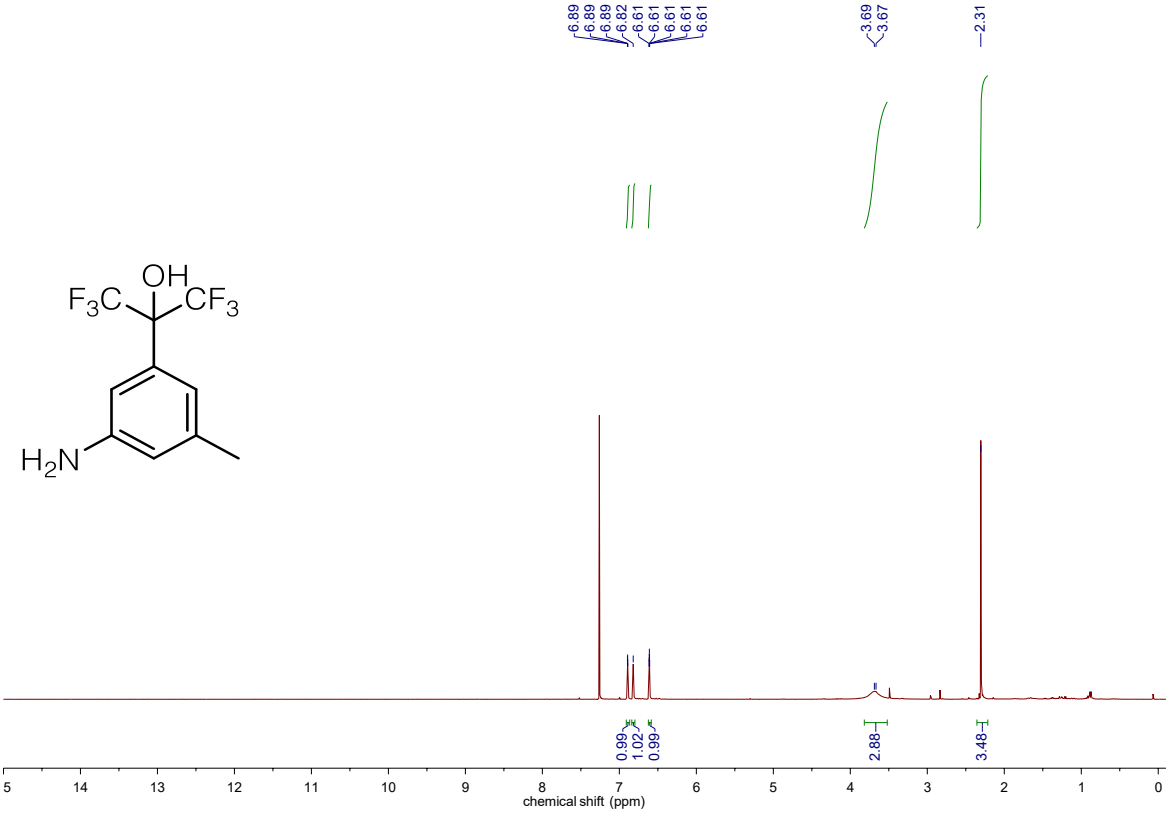

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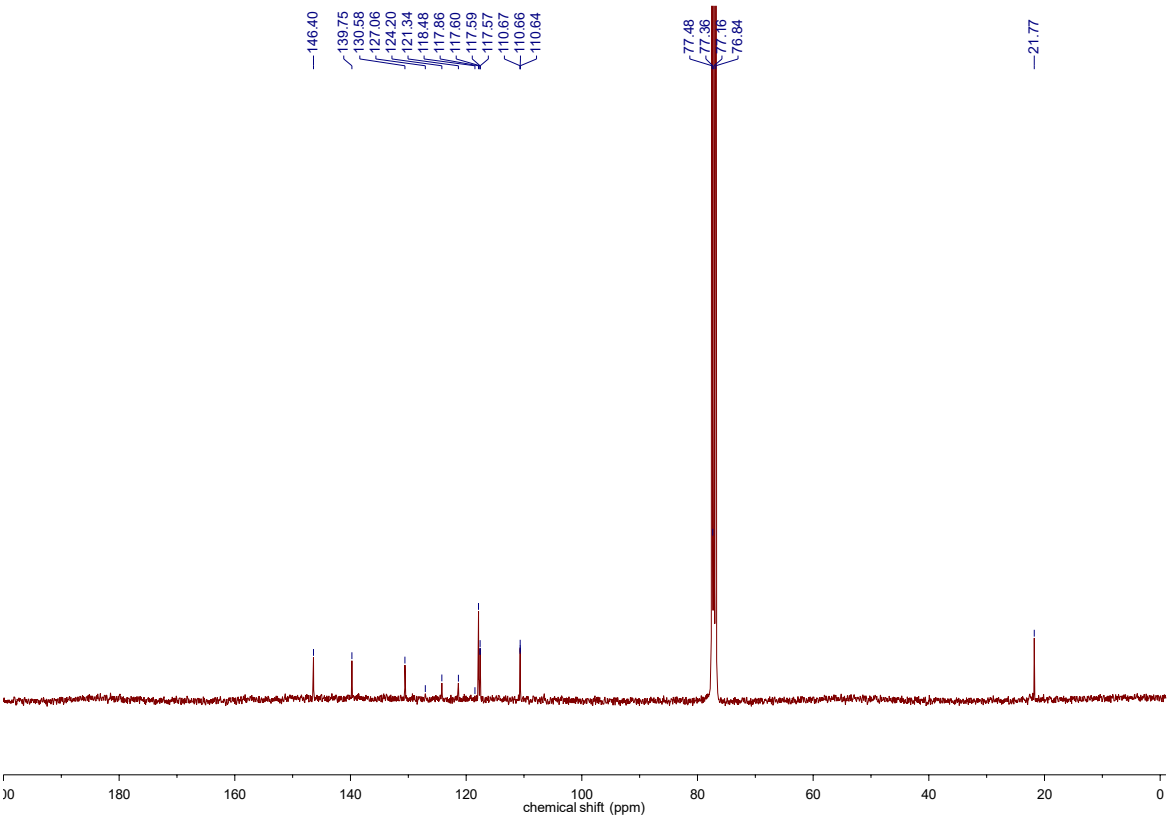

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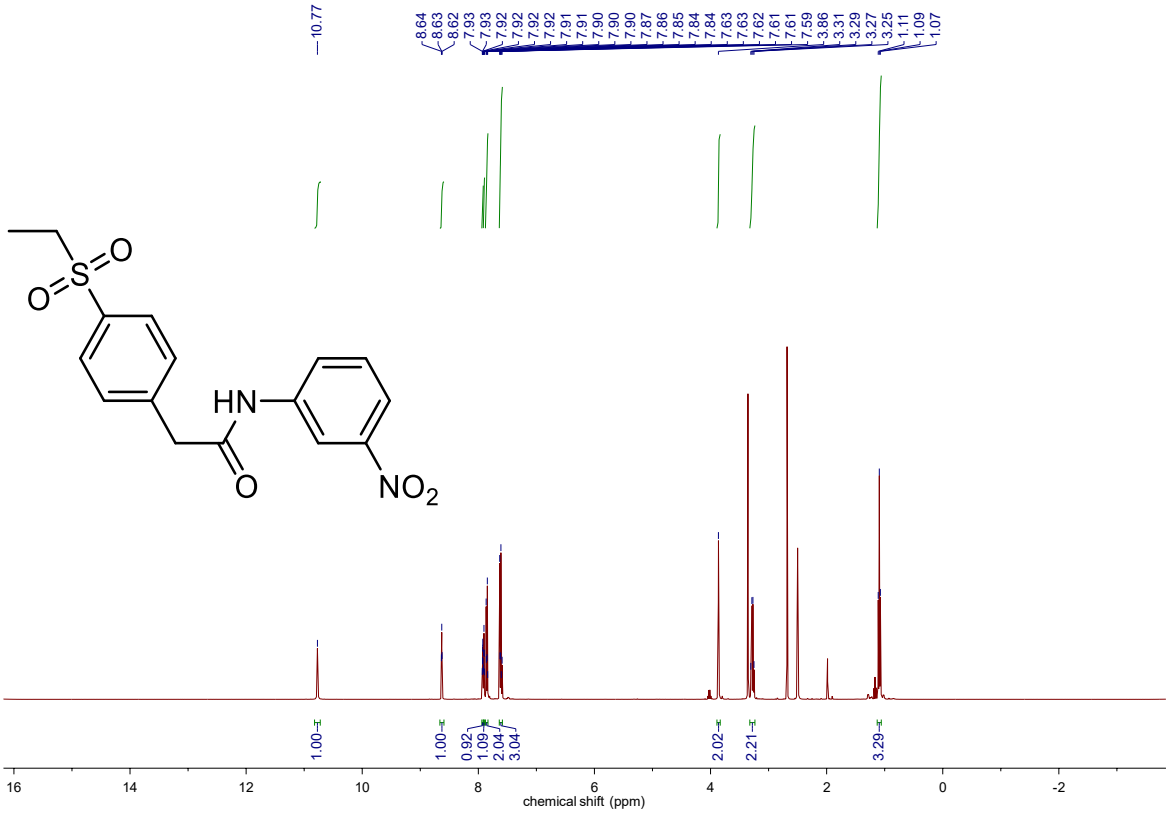

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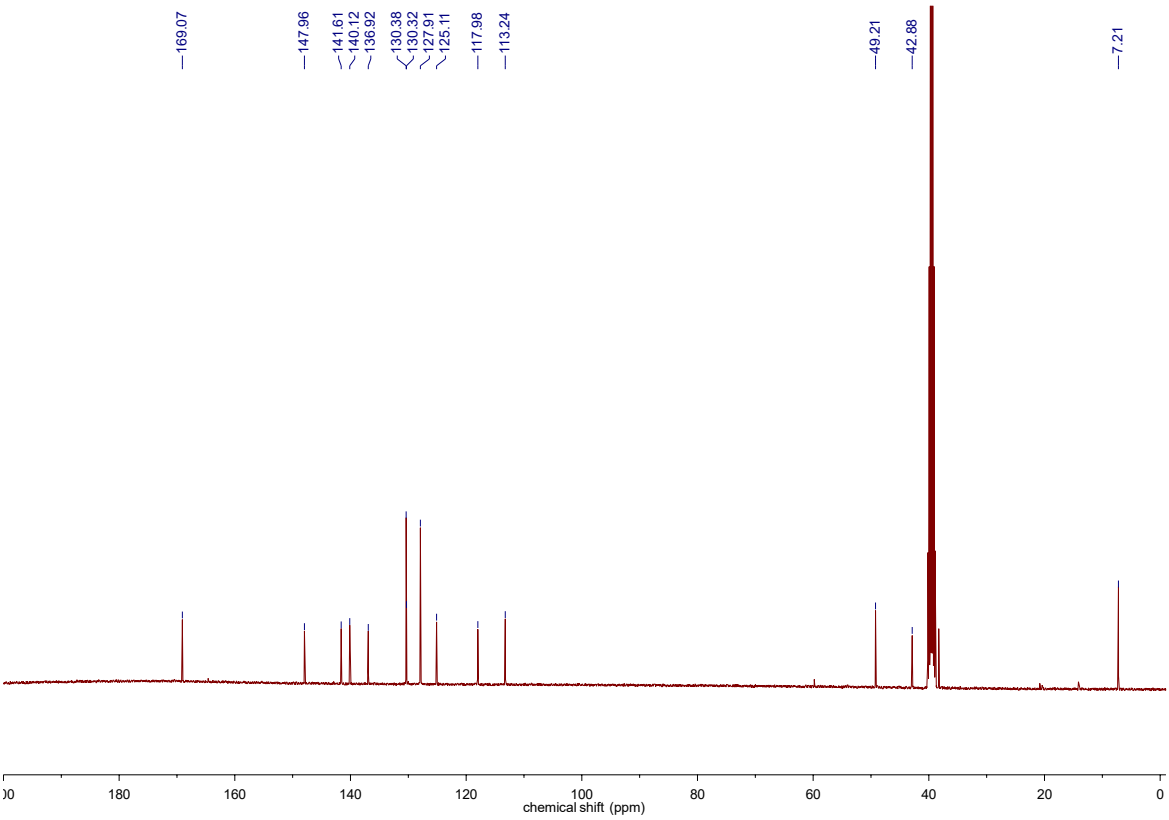

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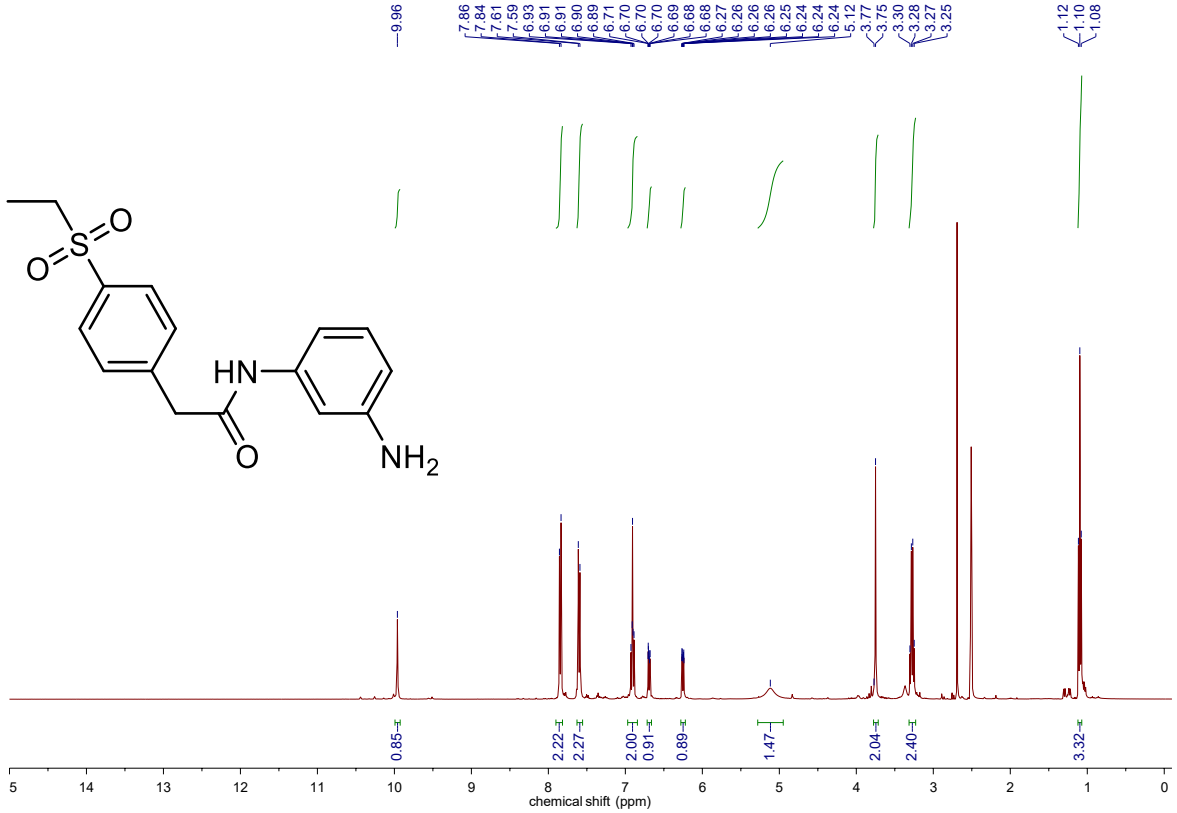

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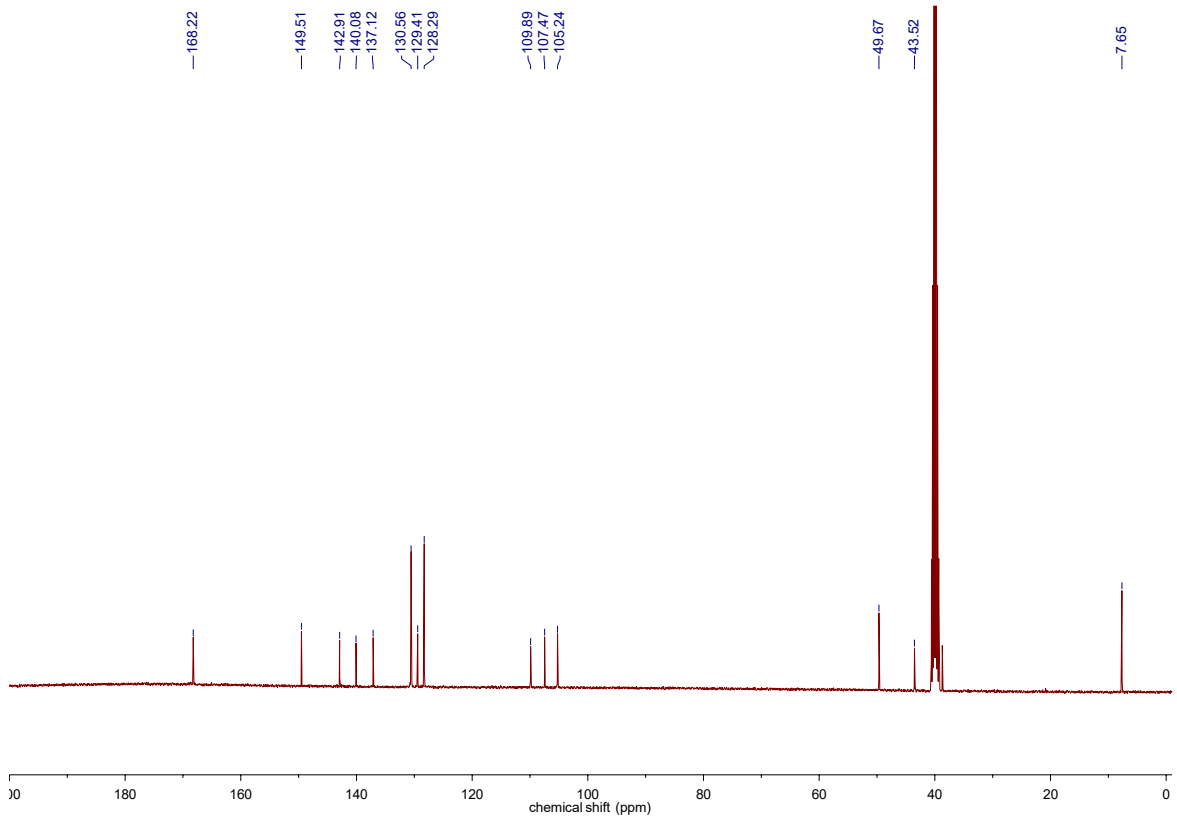

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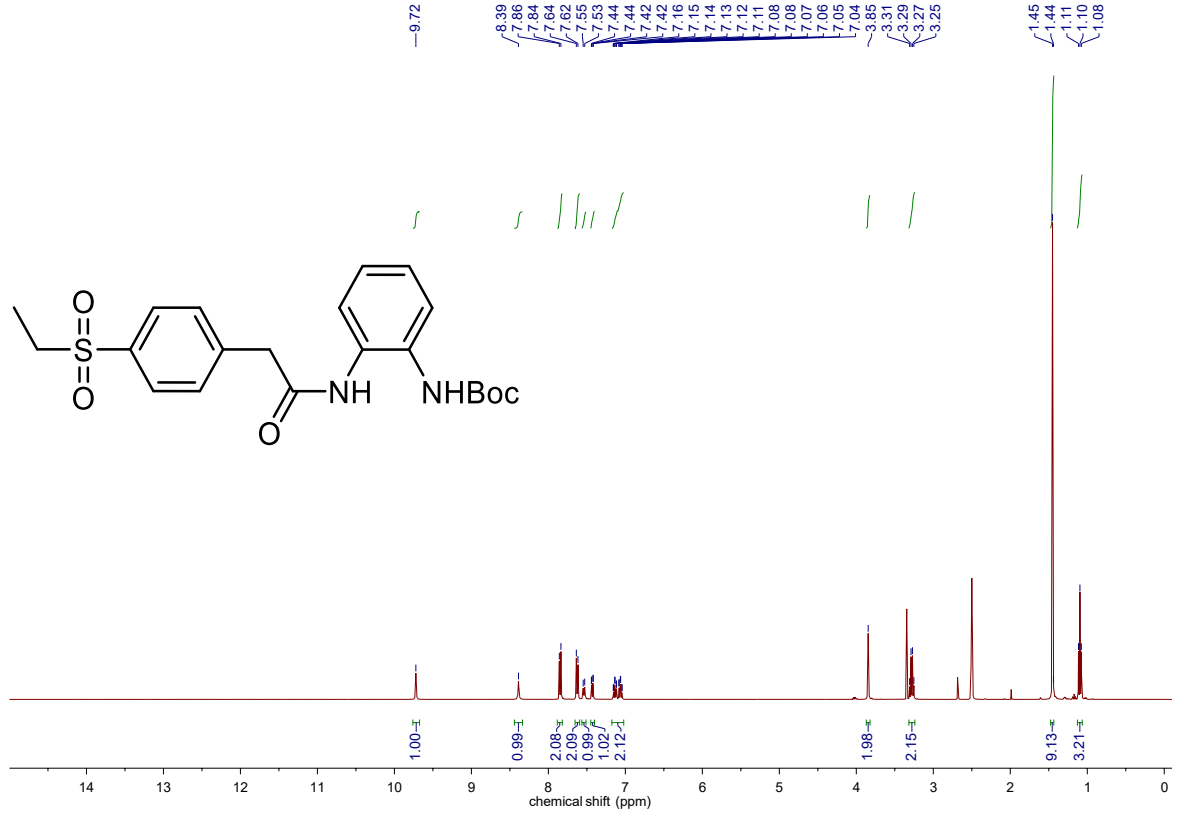

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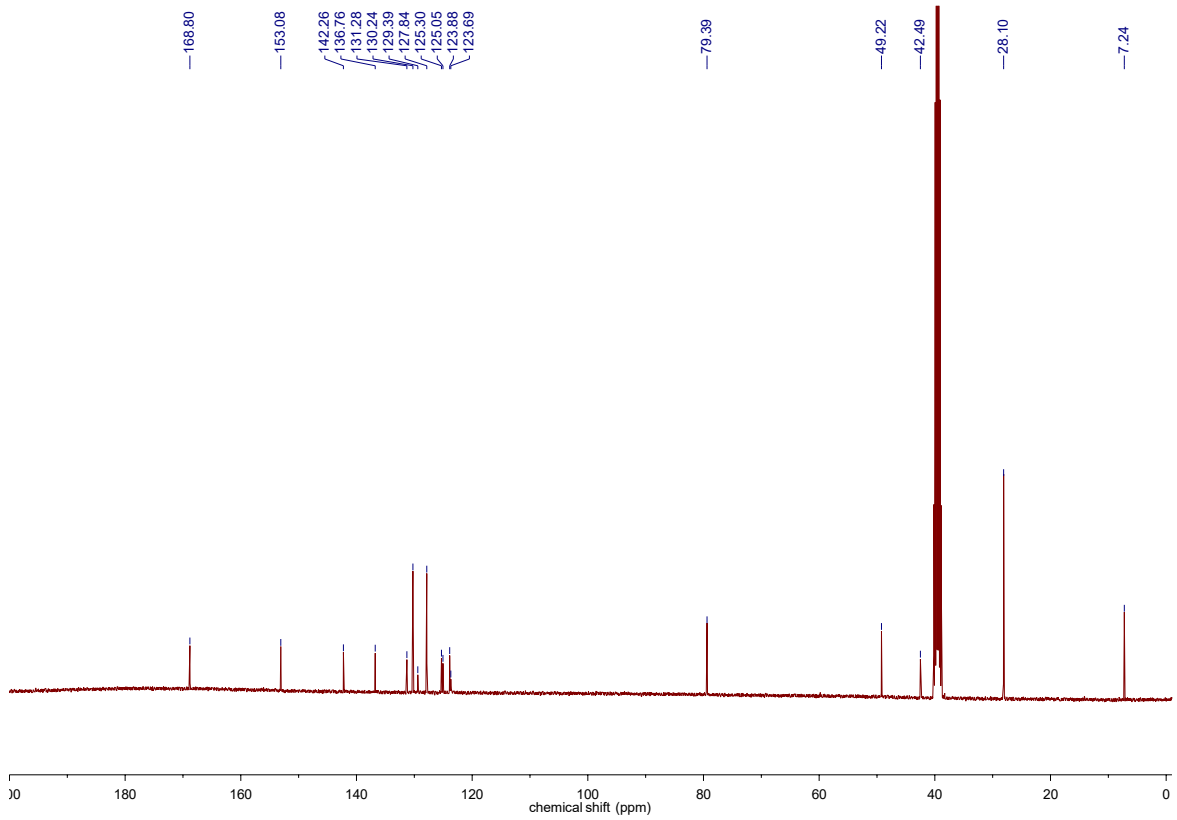

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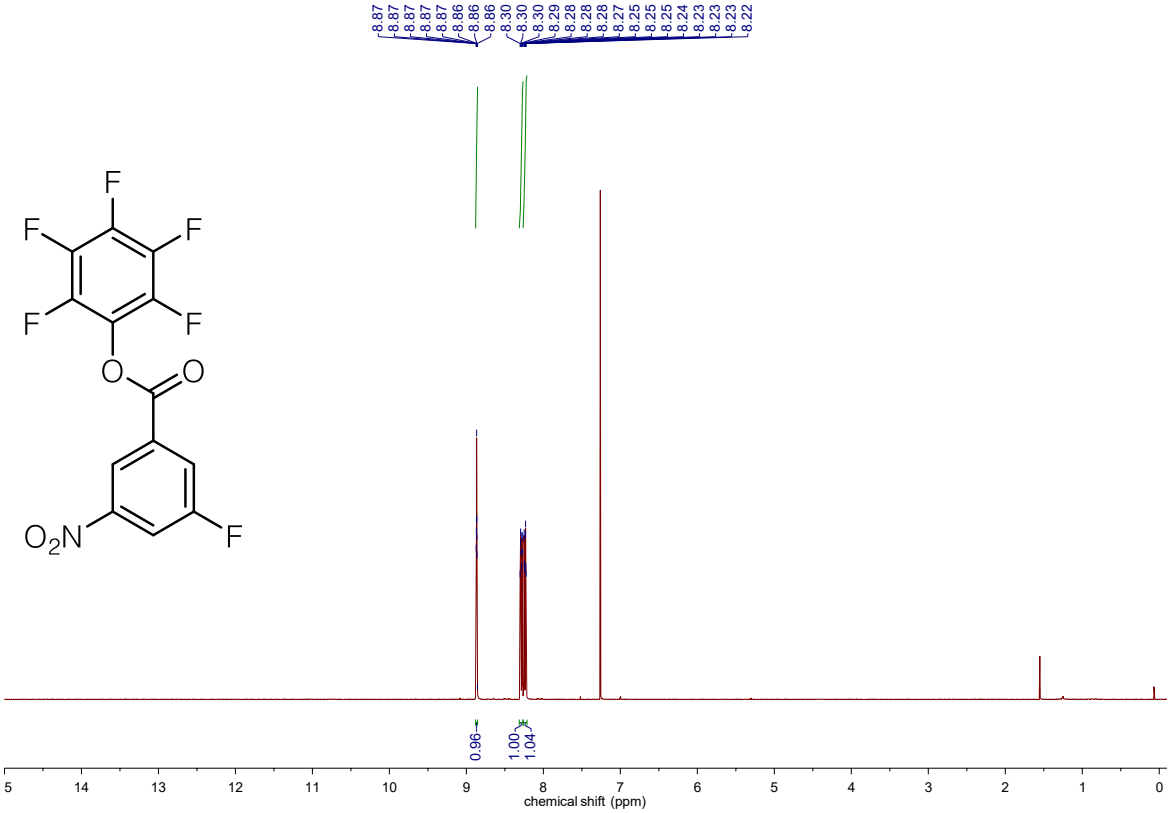

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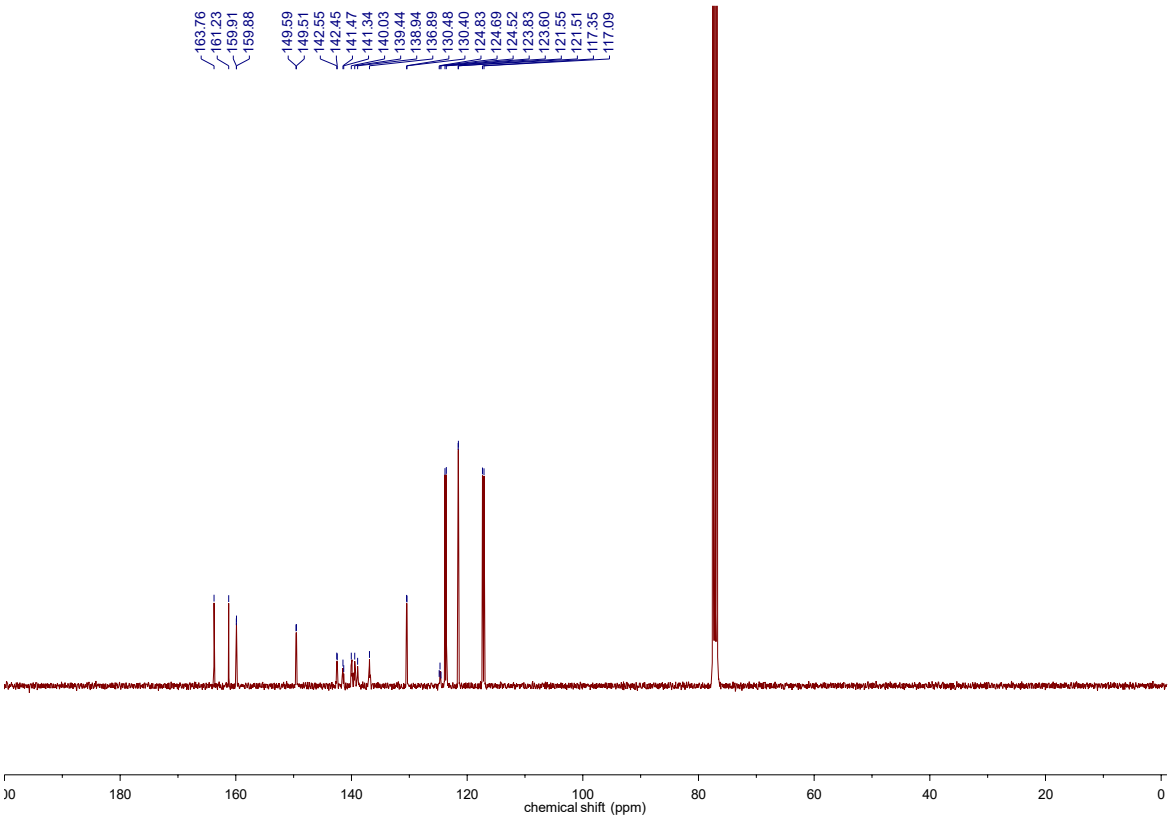

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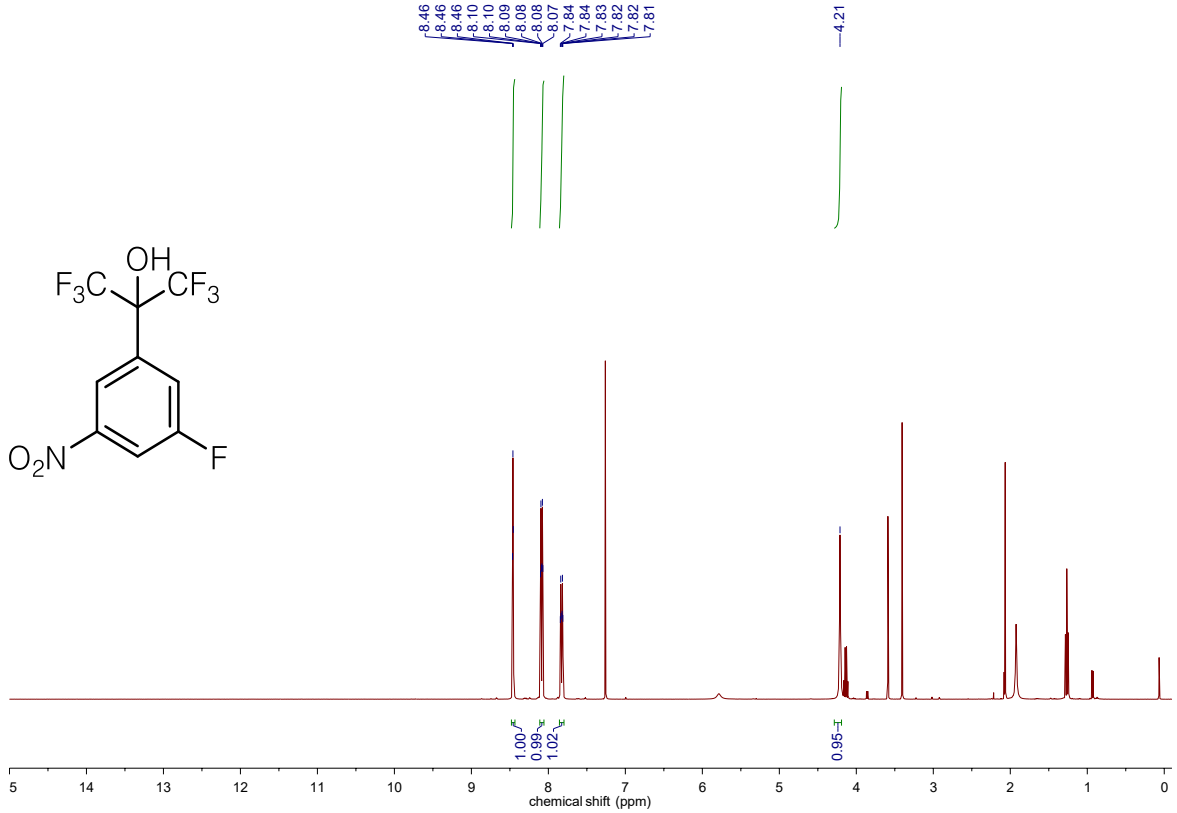

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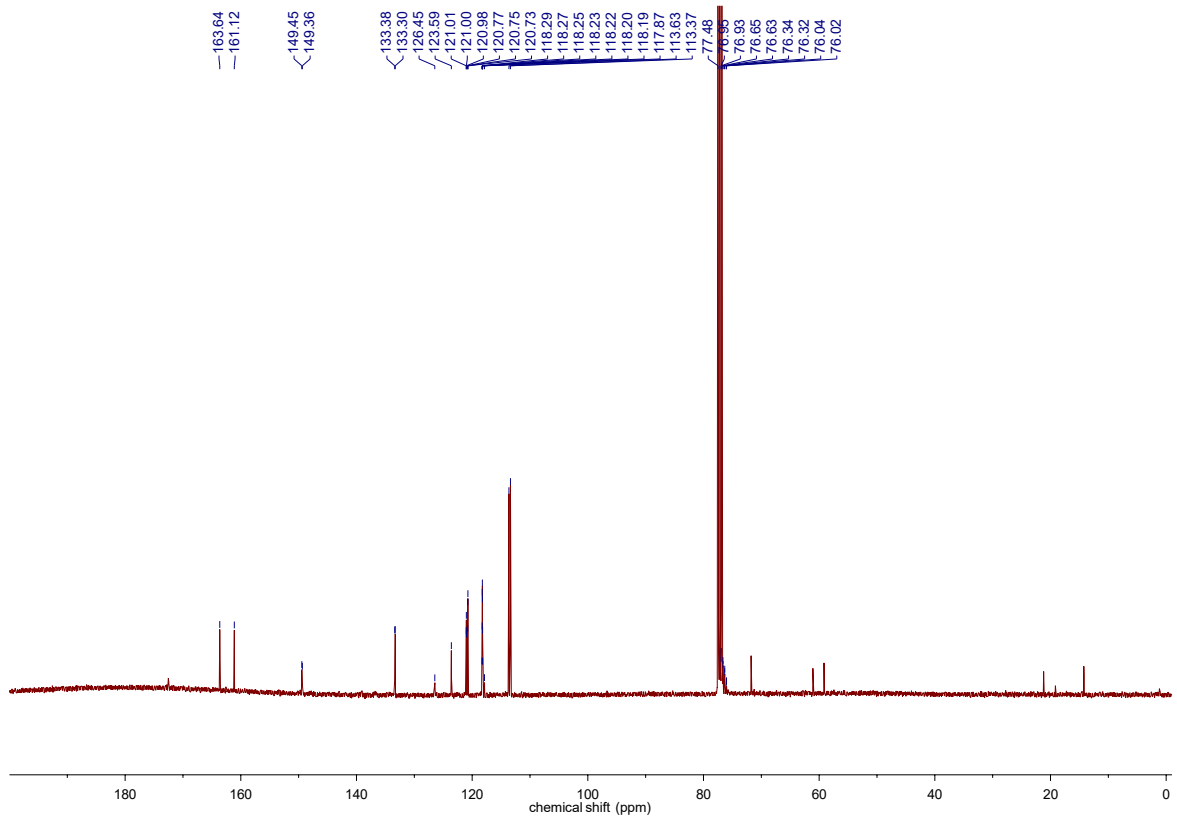

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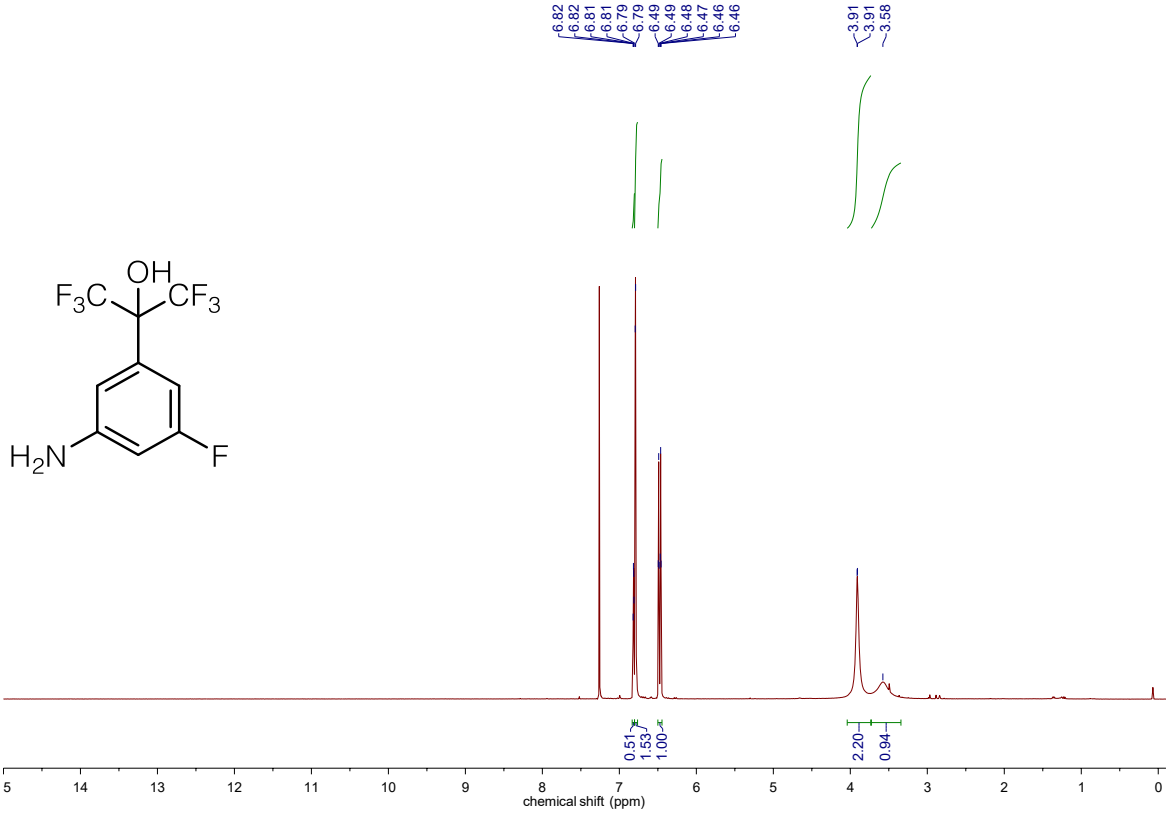

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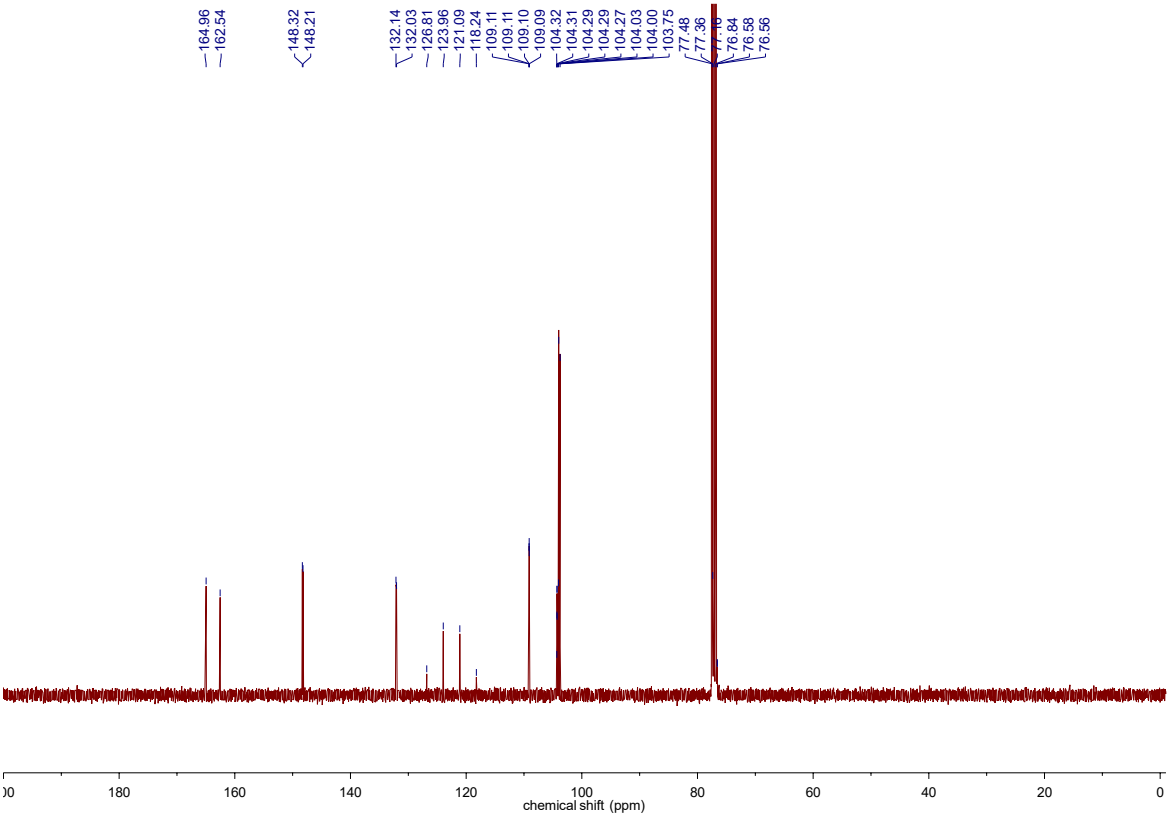

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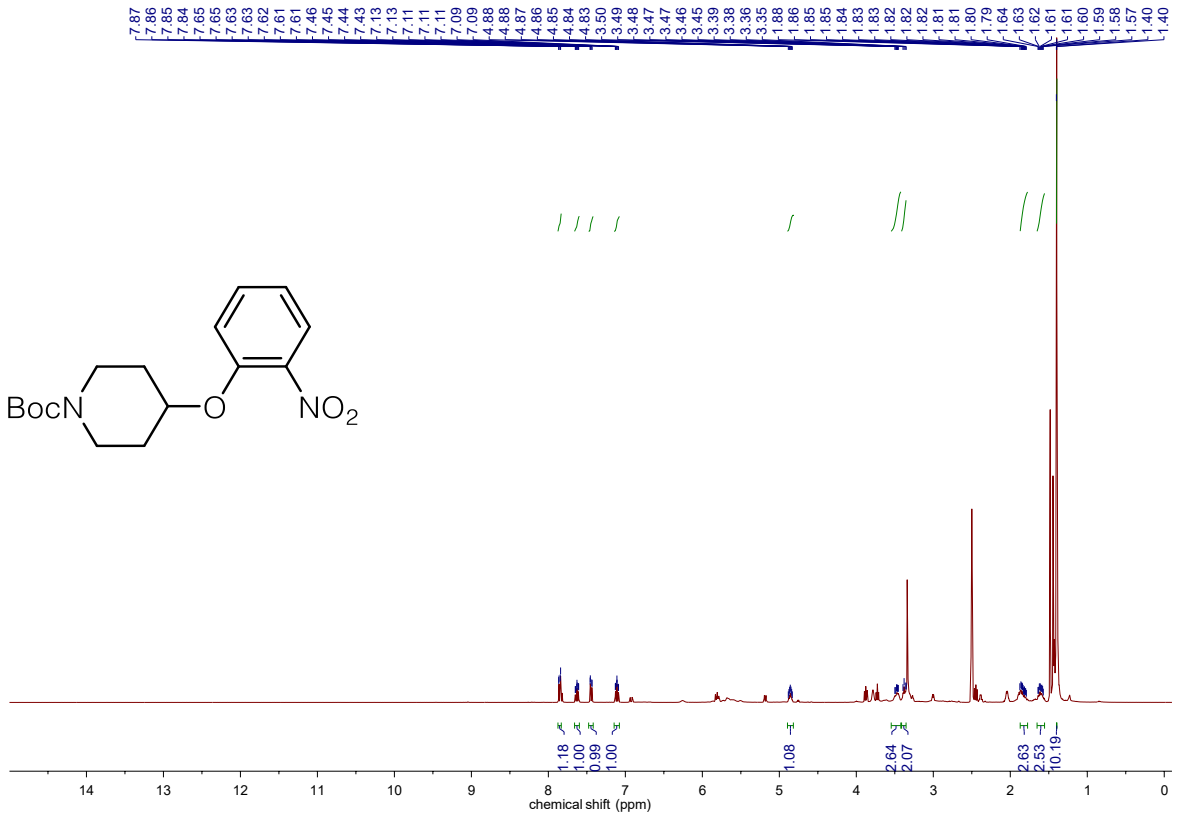

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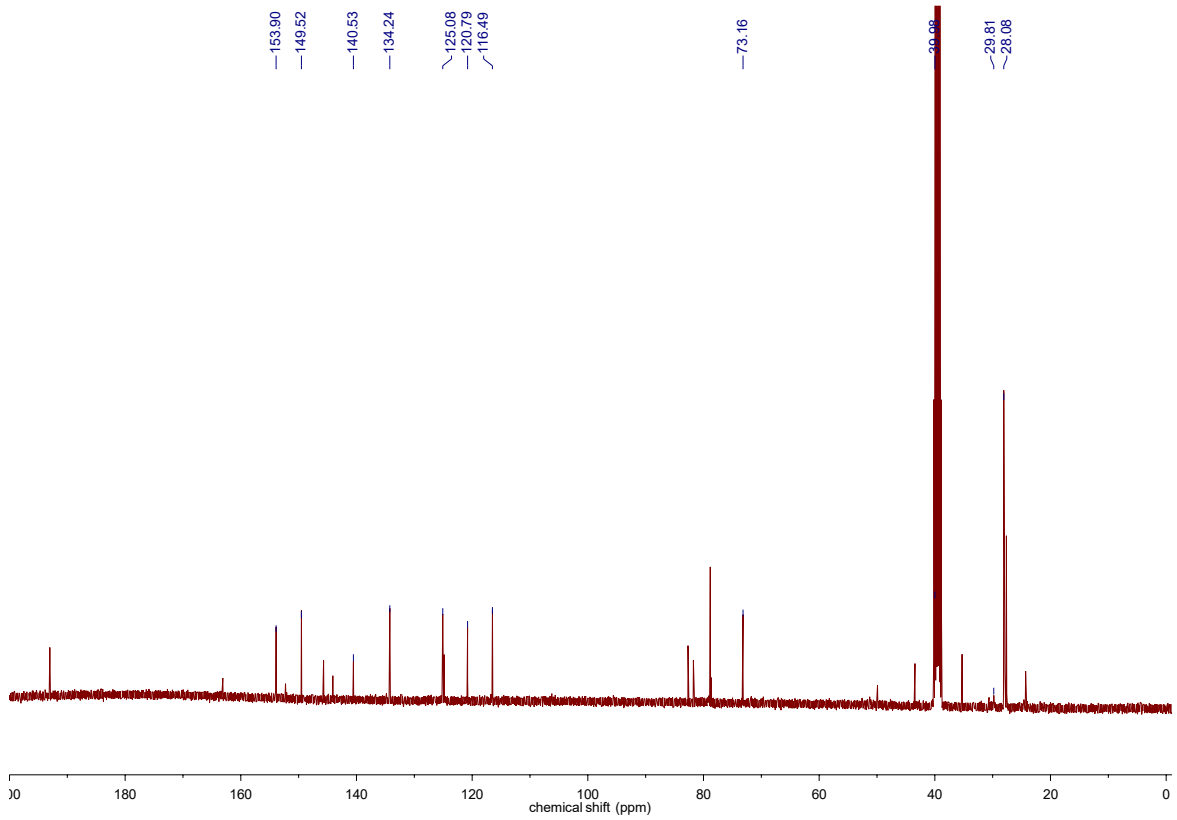

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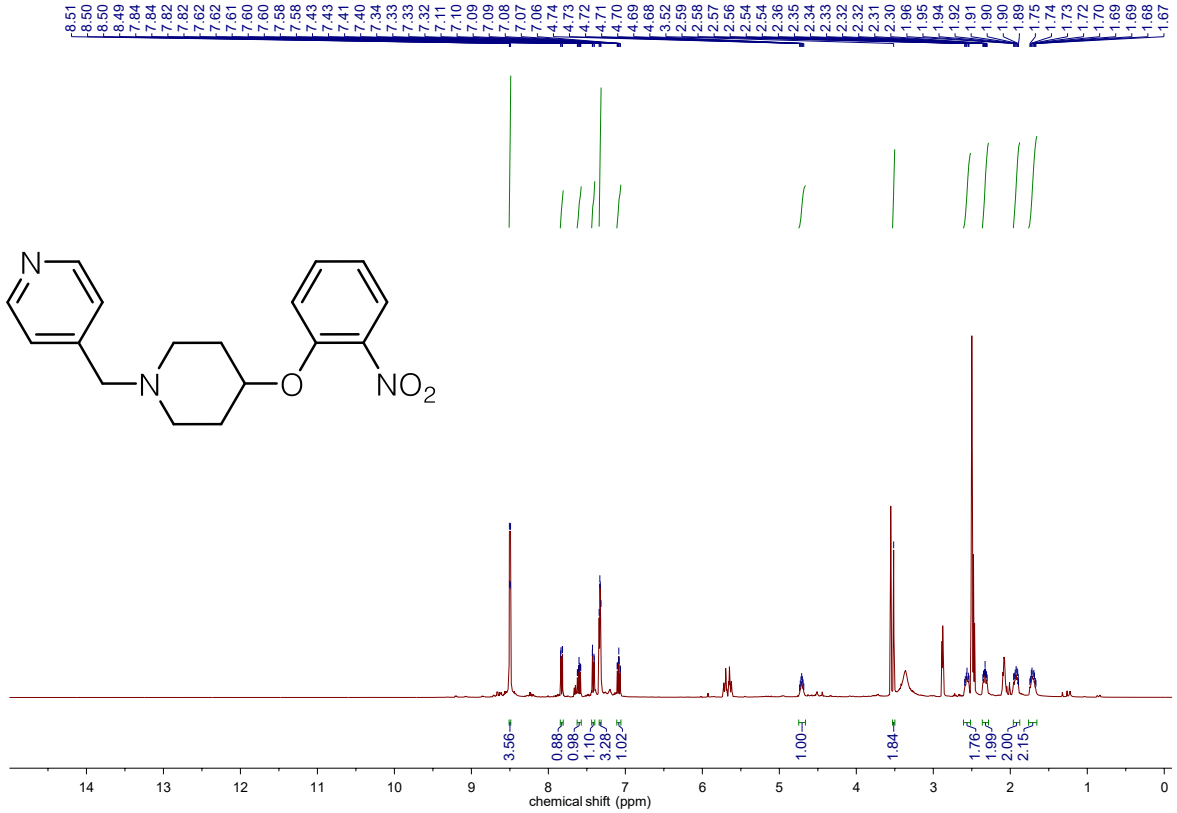

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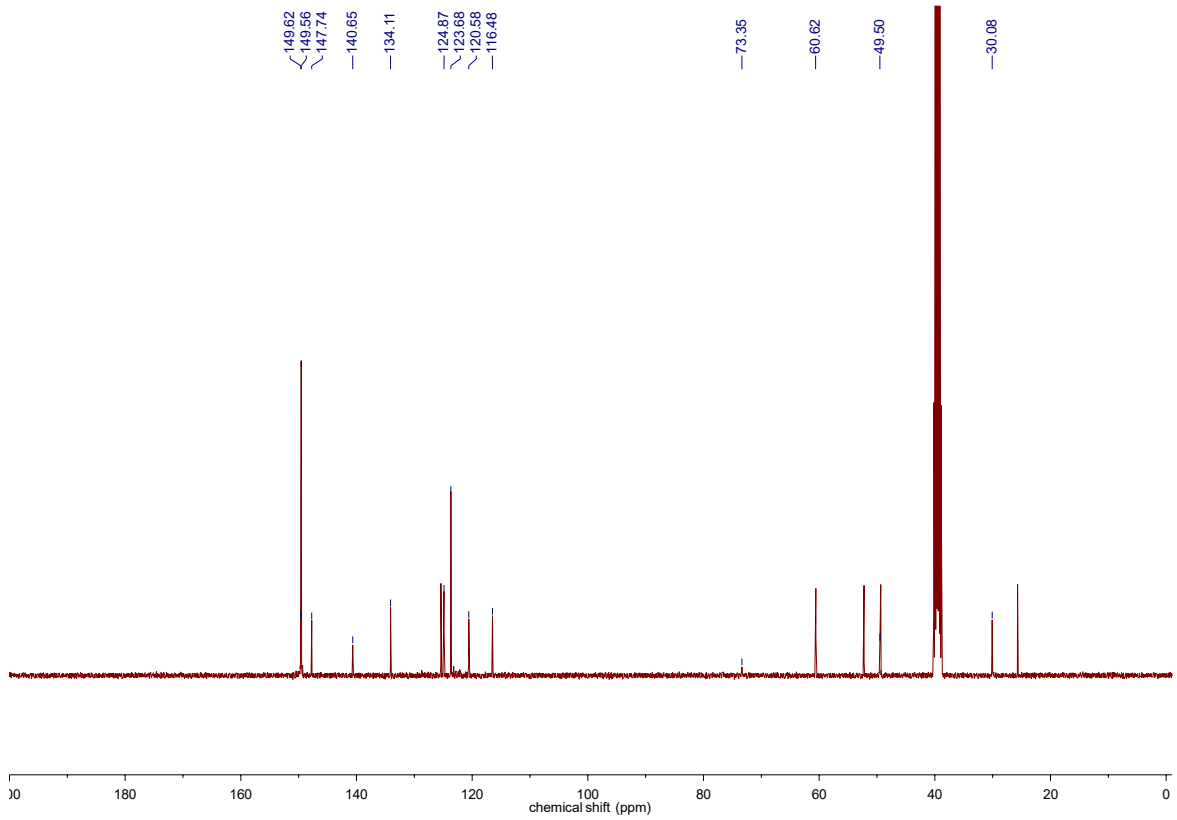

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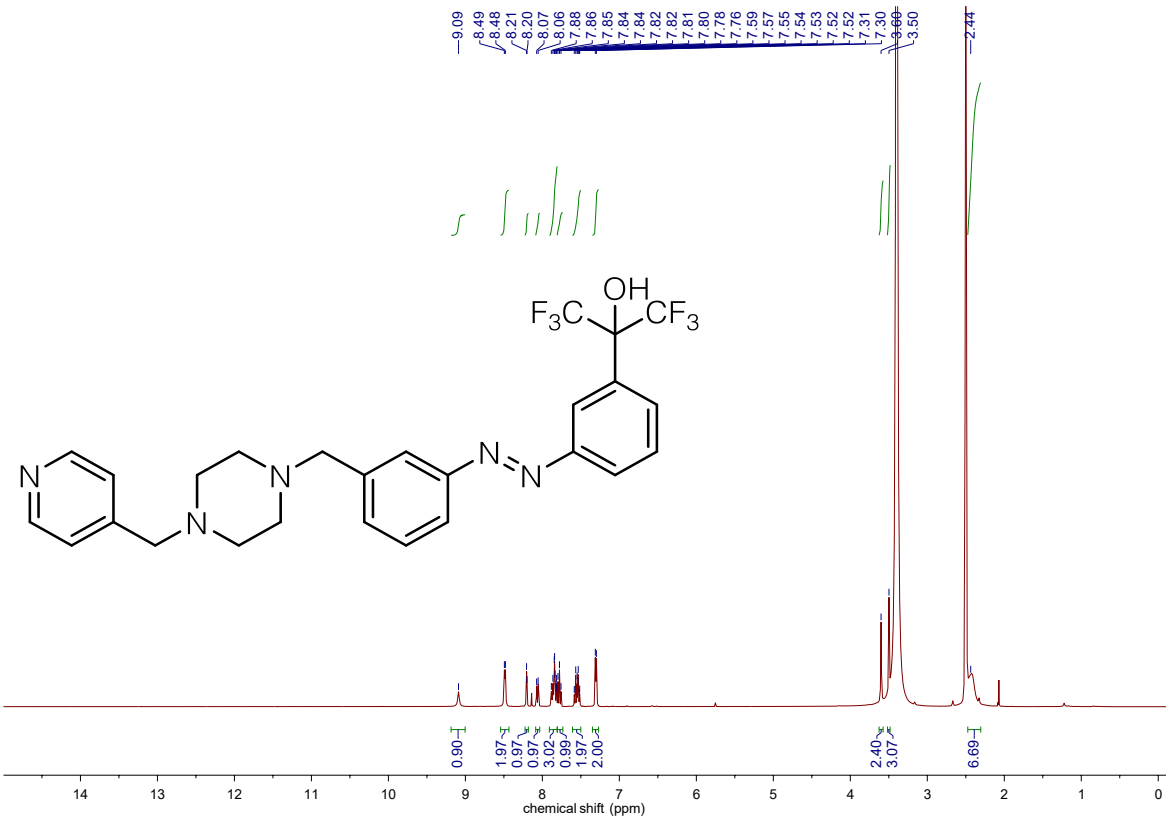

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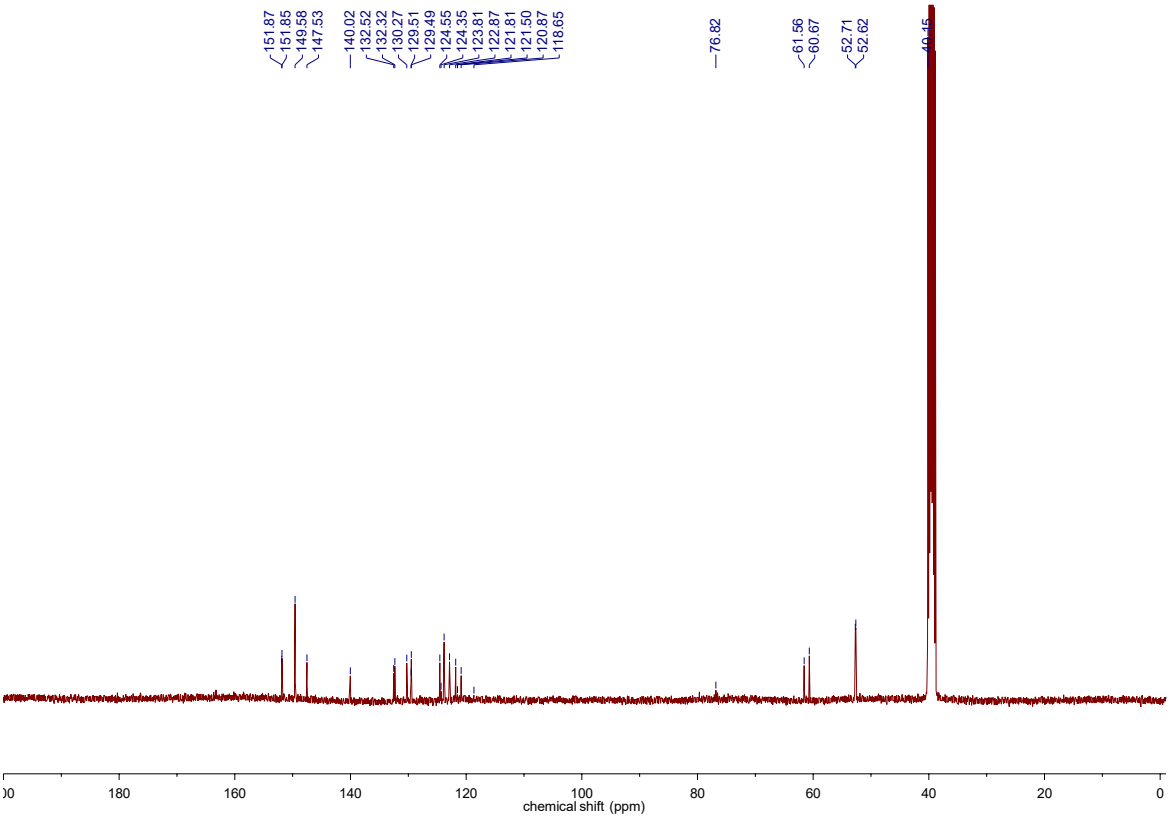

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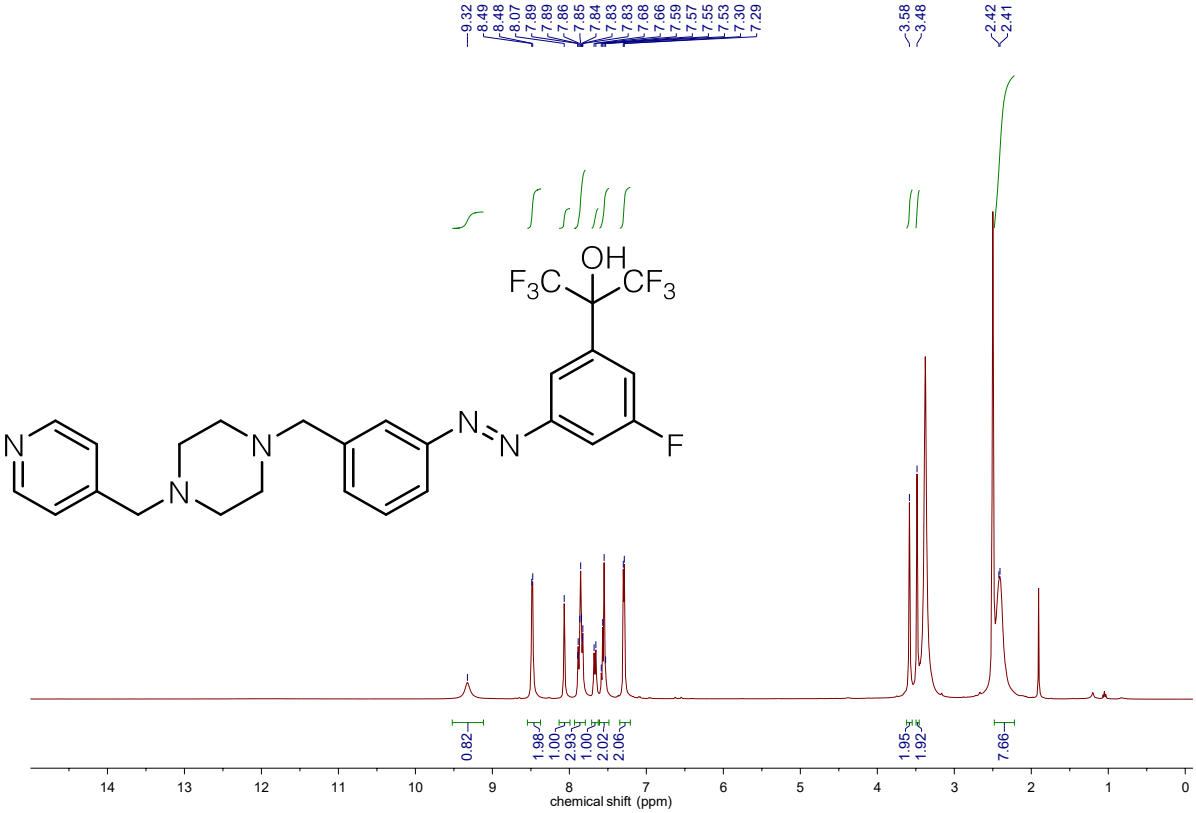

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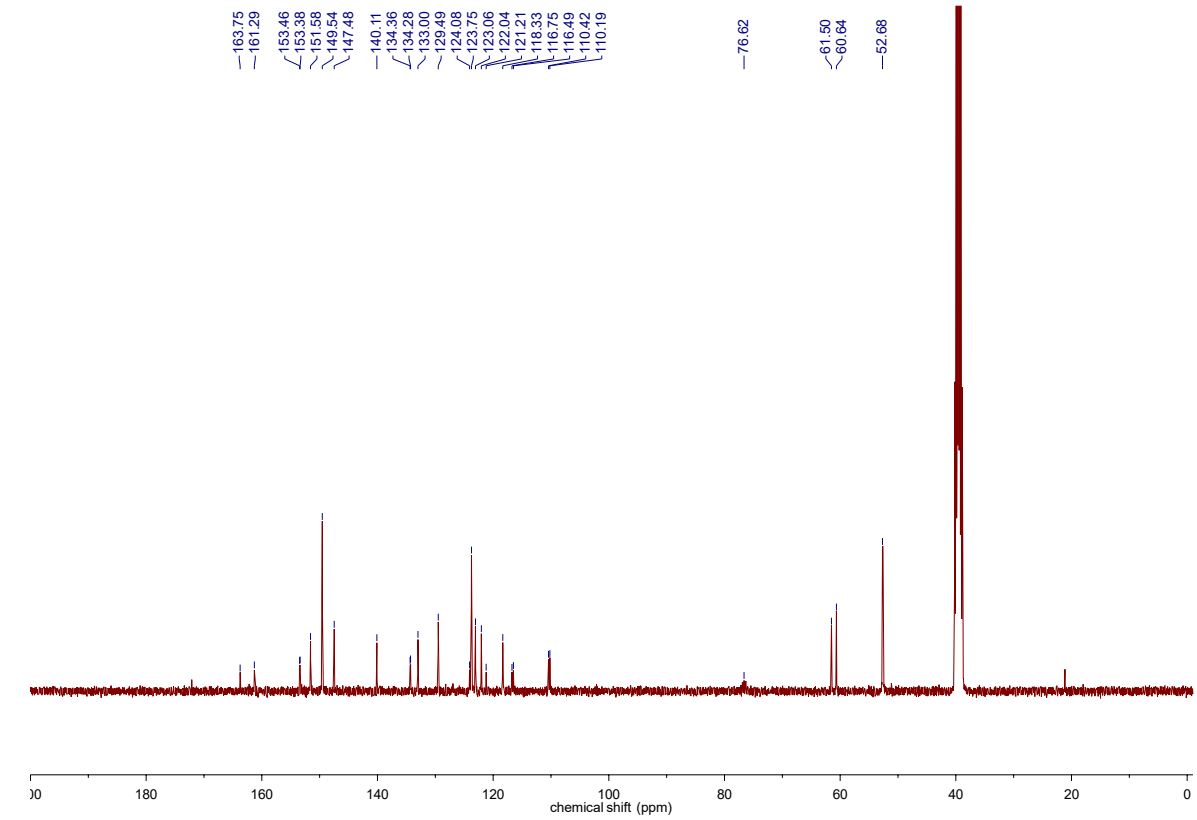

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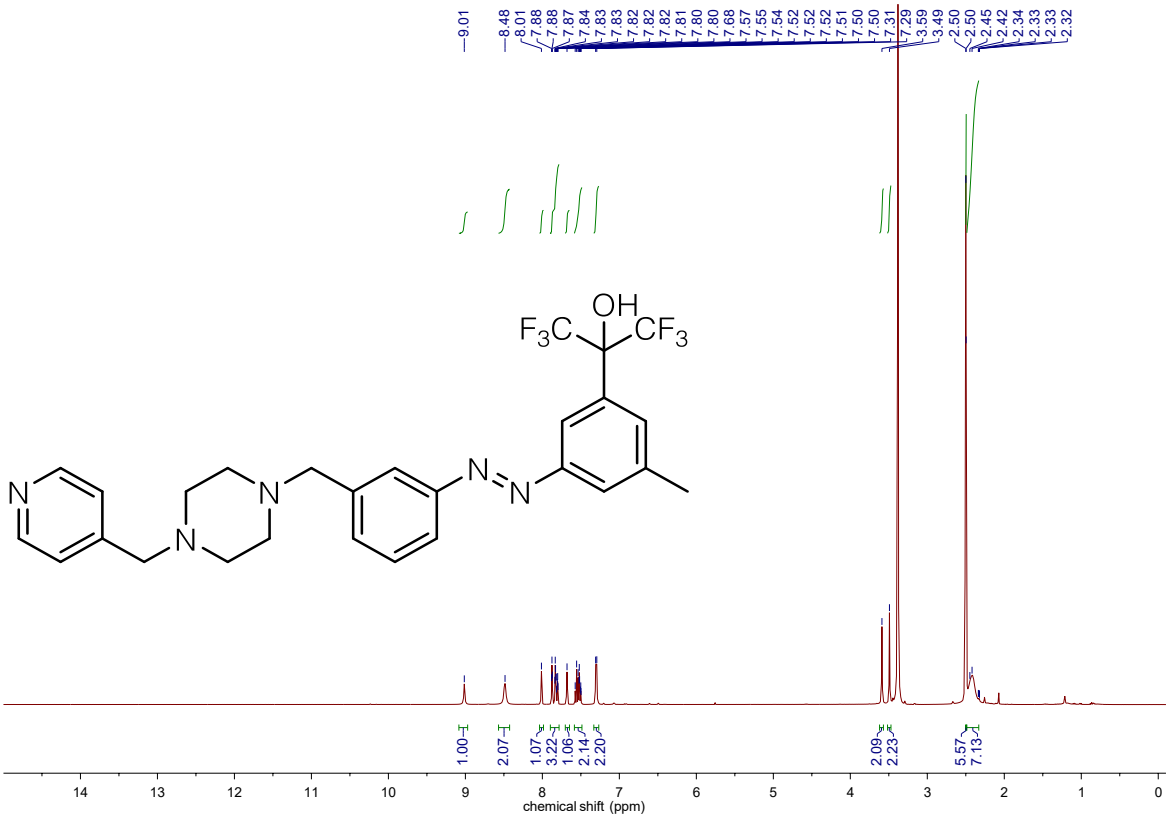

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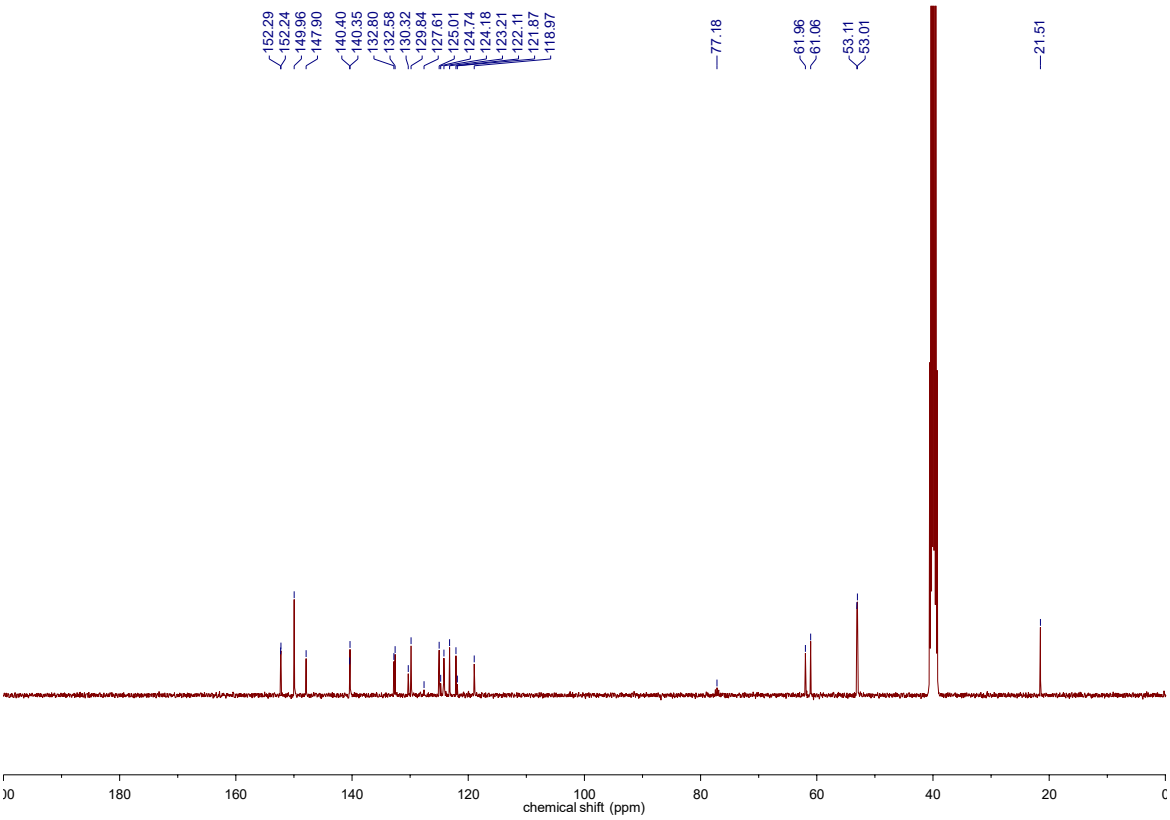

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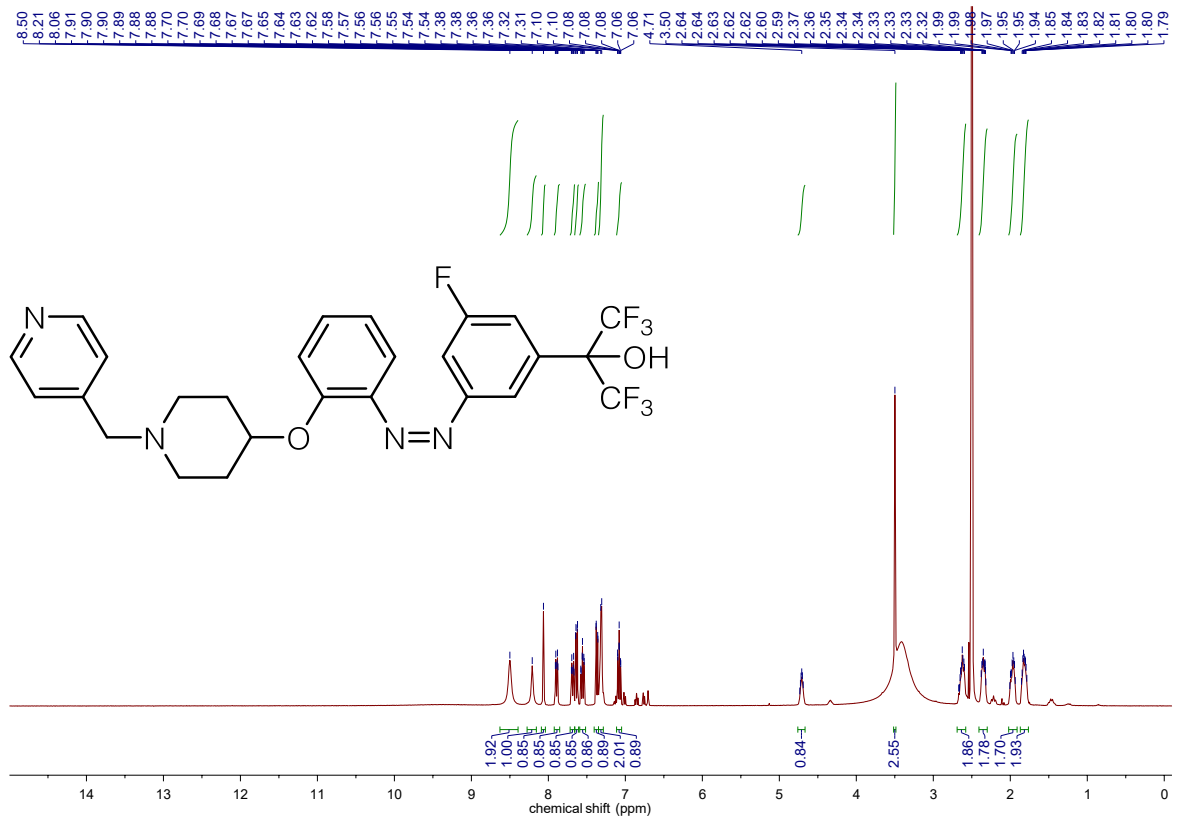

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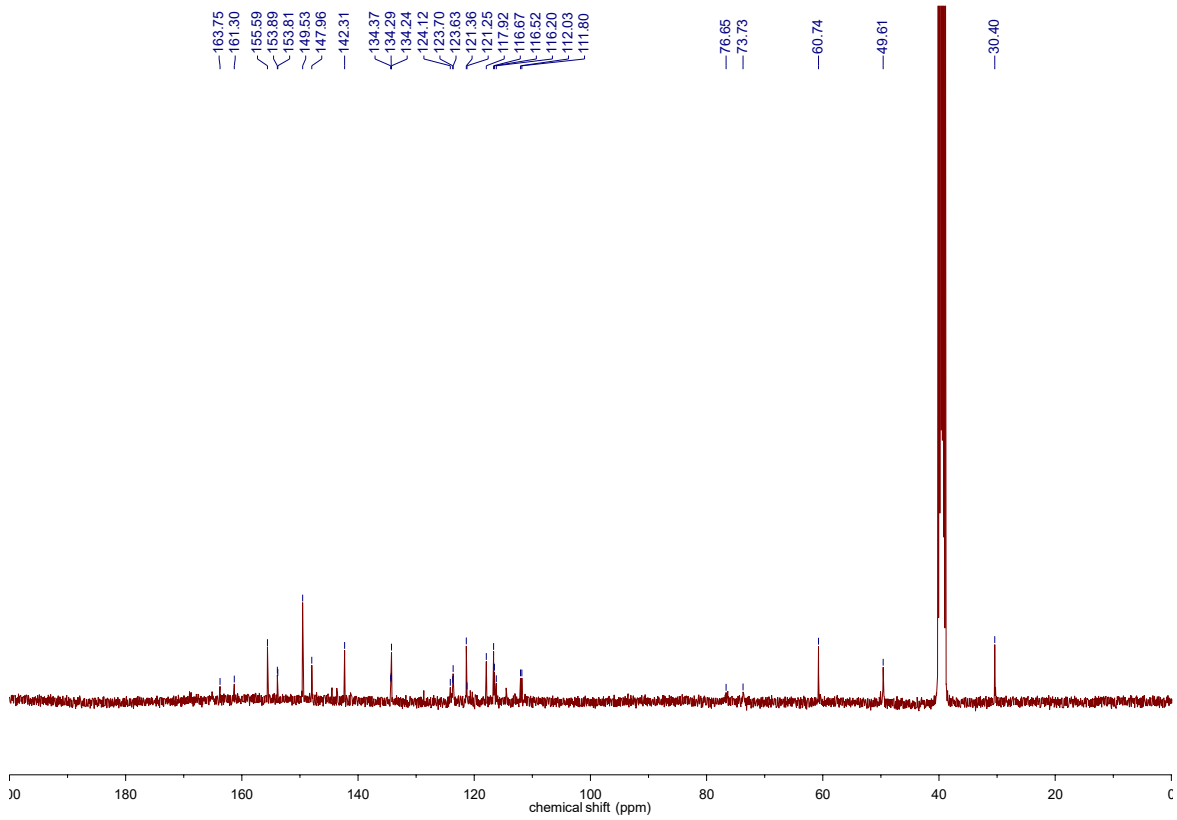

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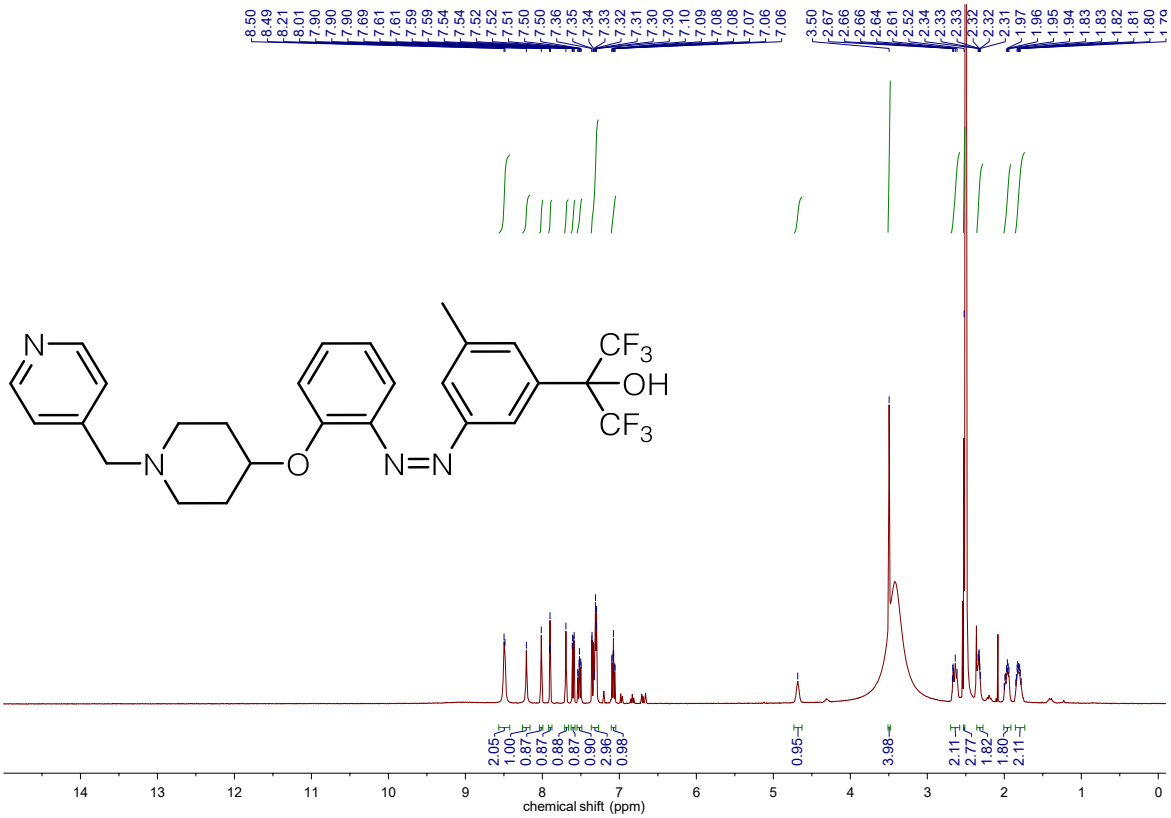

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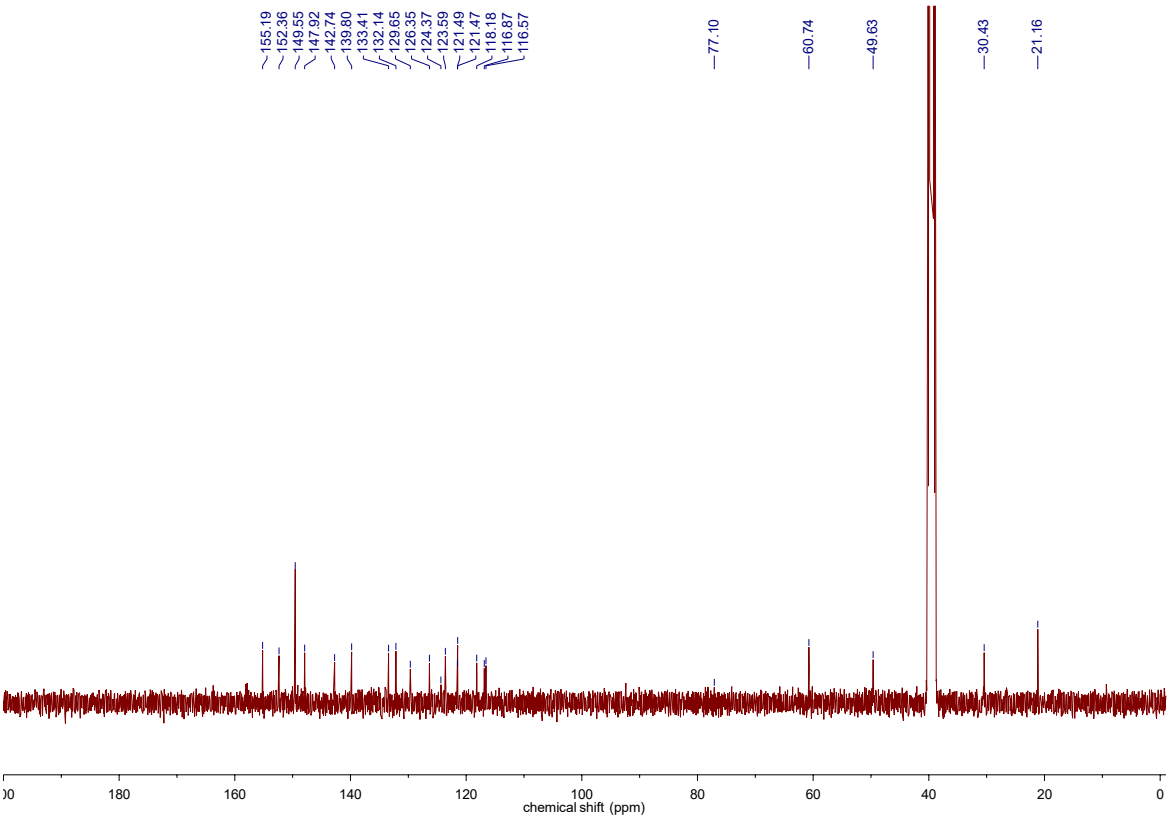

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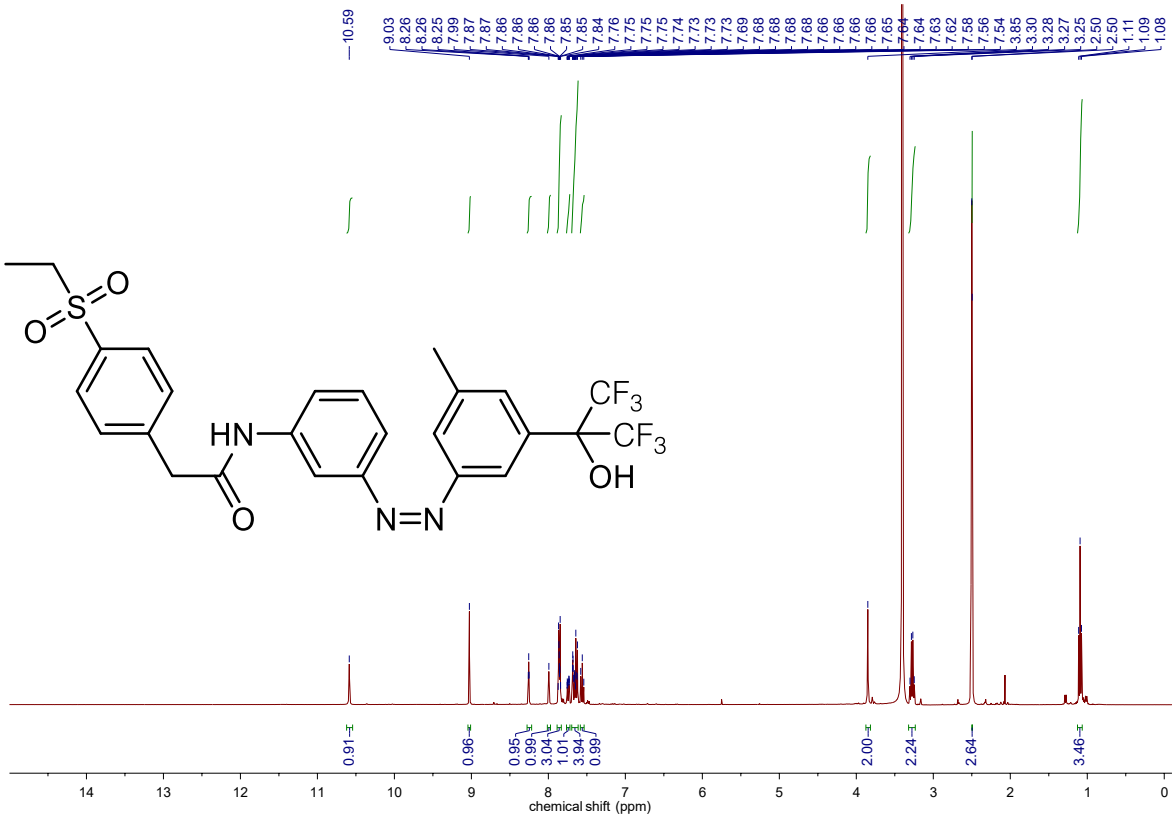

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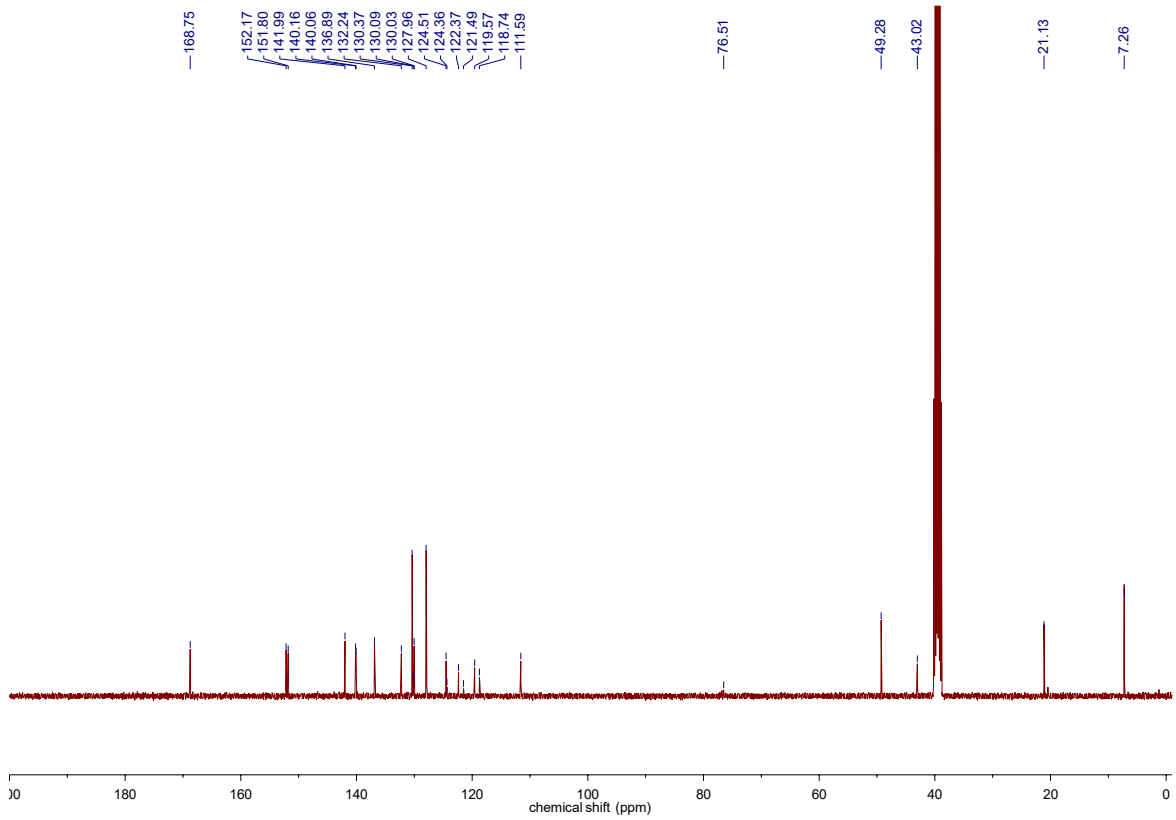

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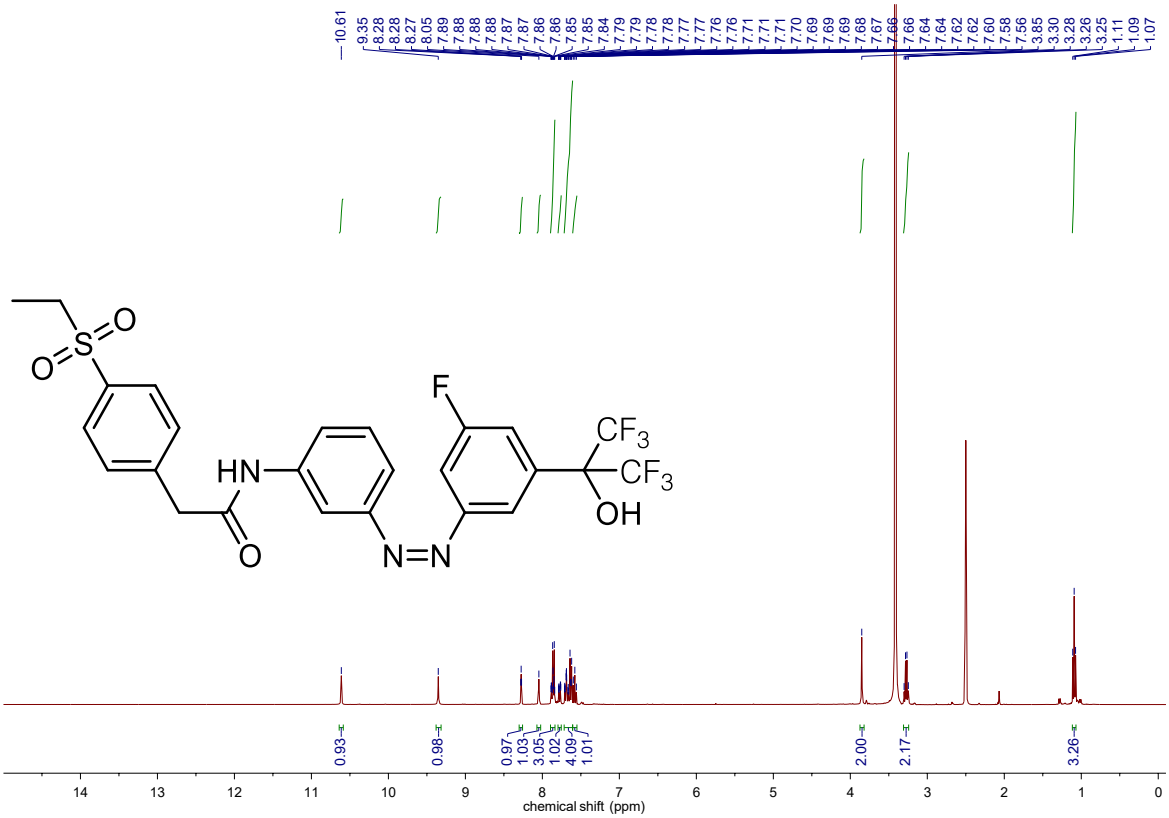

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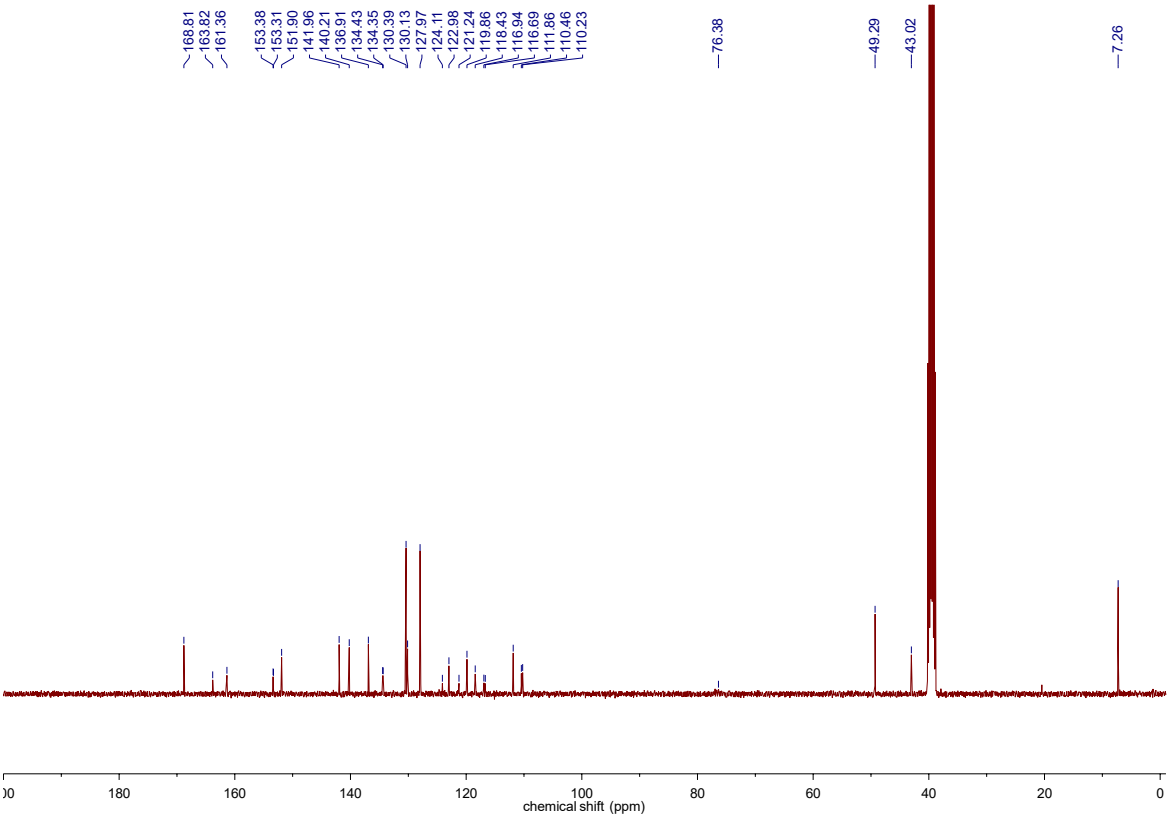

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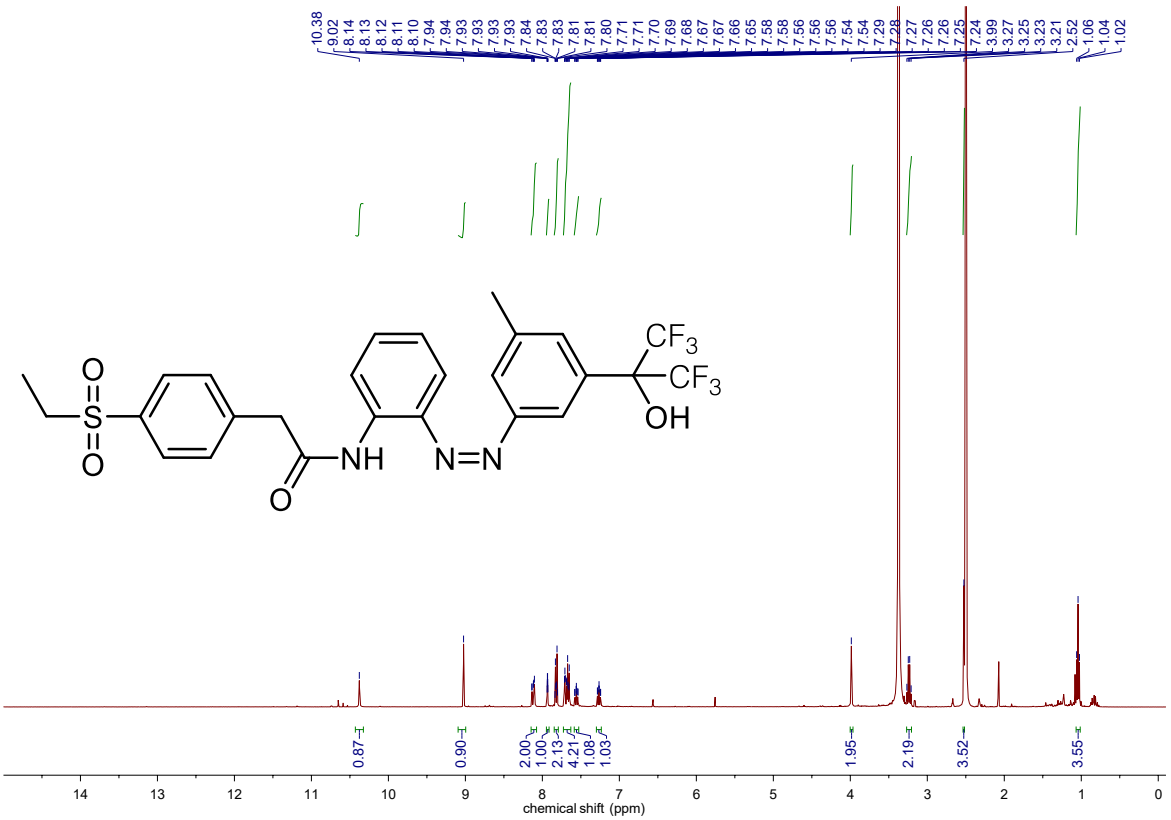
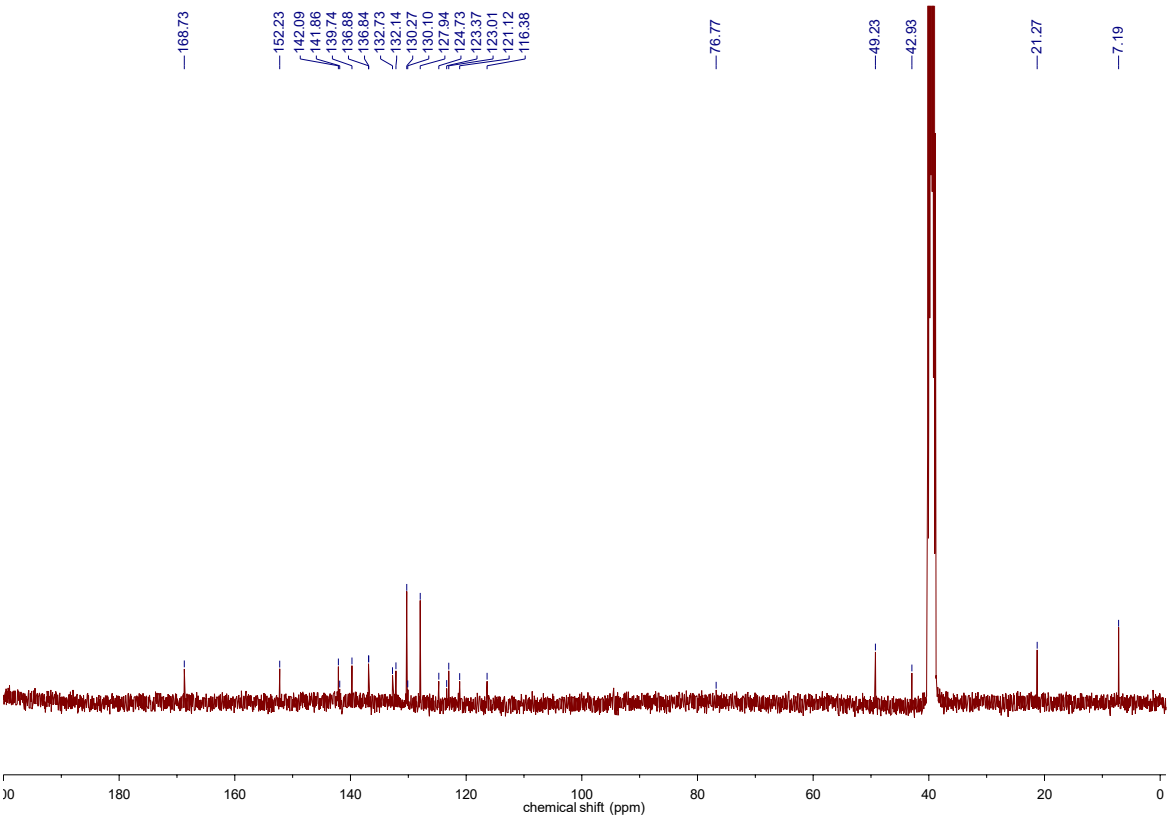
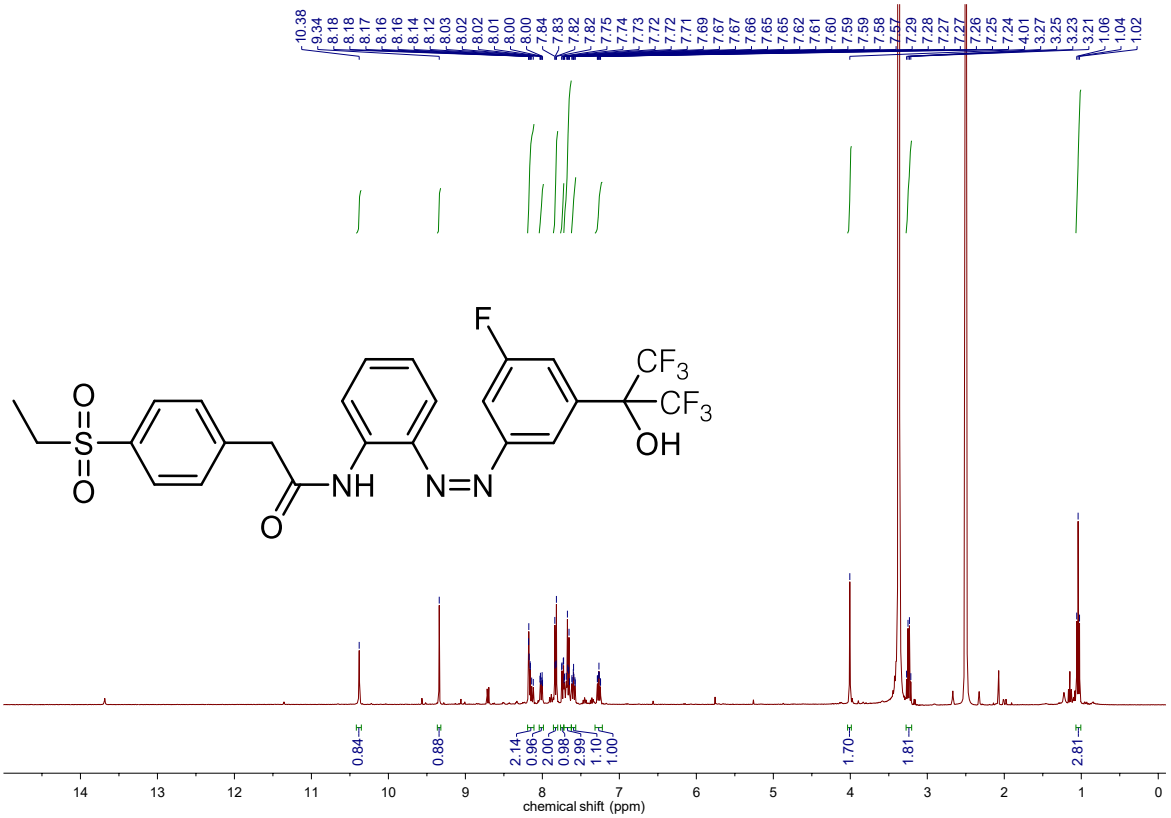


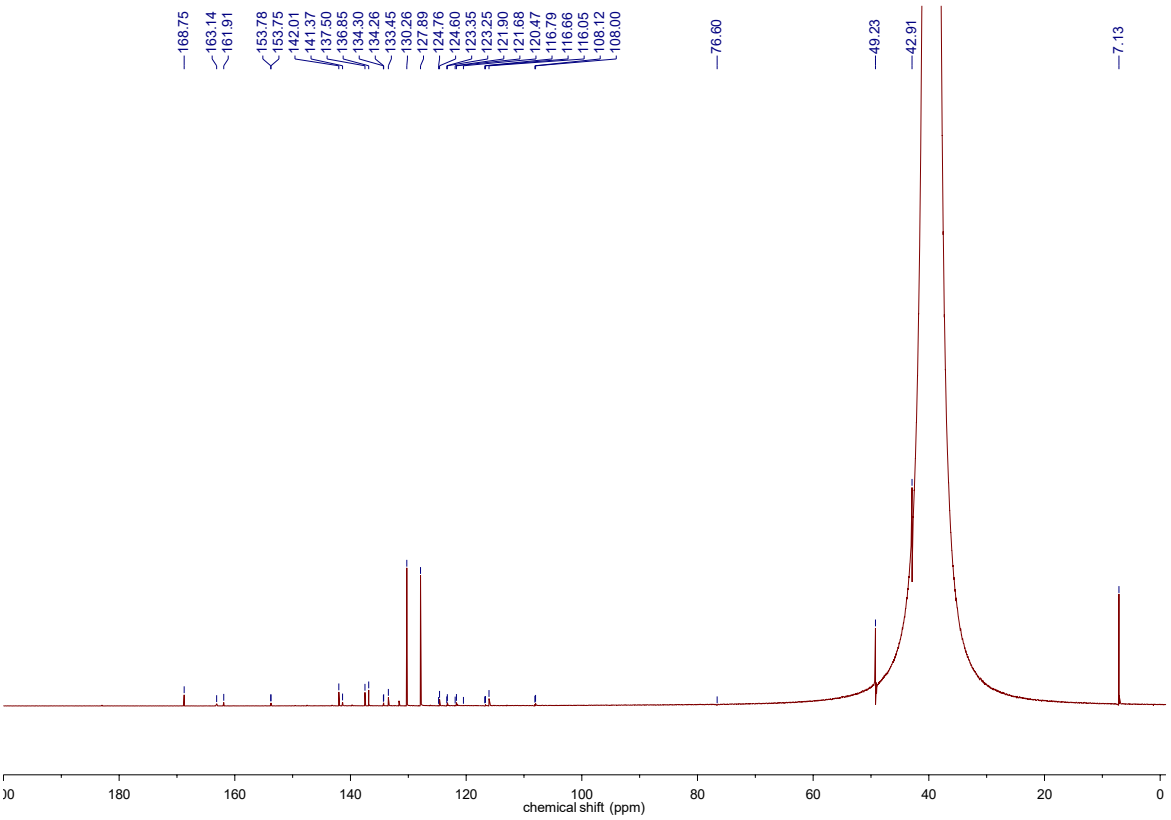
(MROR8) ^{13}C-NMR



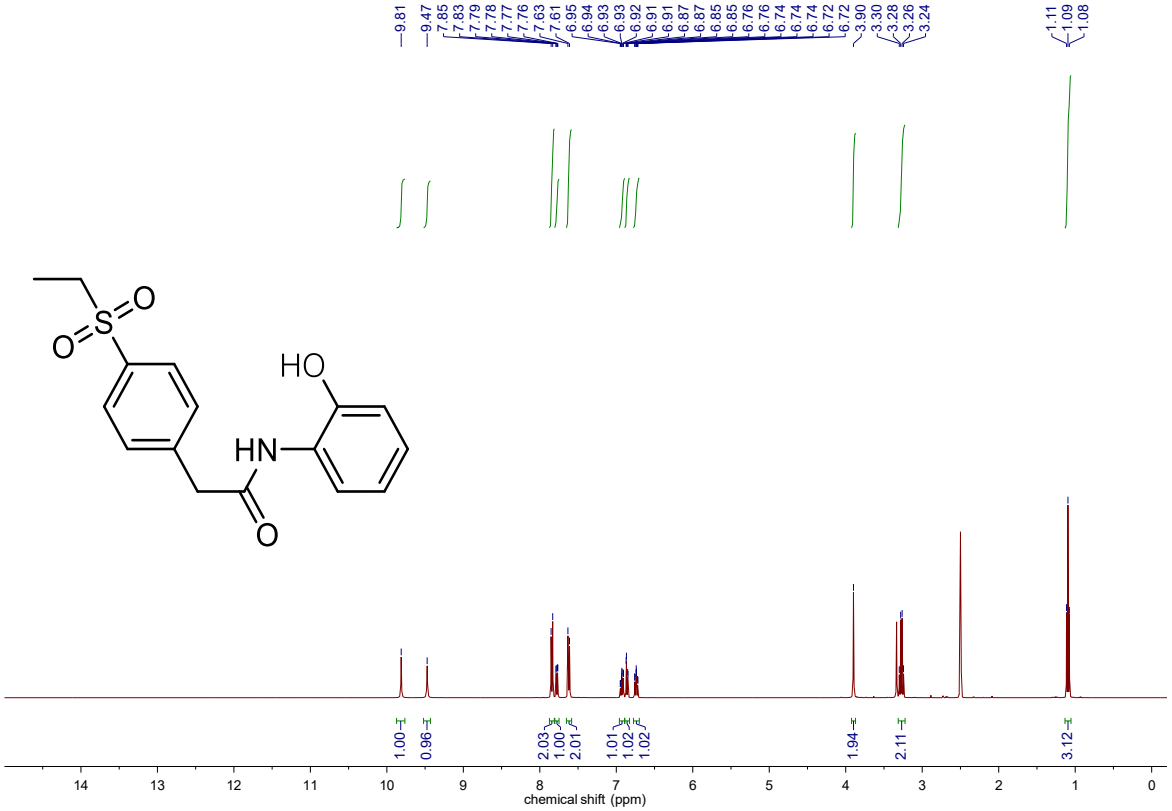
(MROR9) ^{1}H-NMR



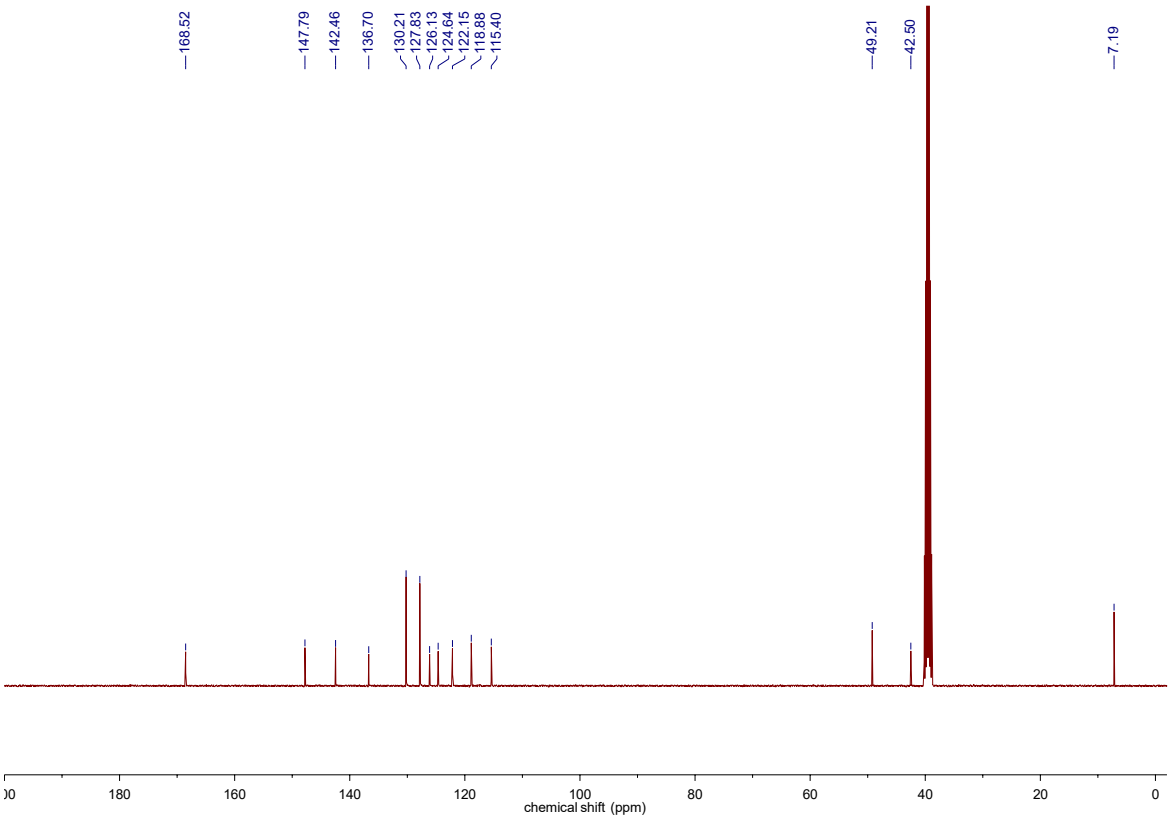
(MROR9) ^{13}C-NMR



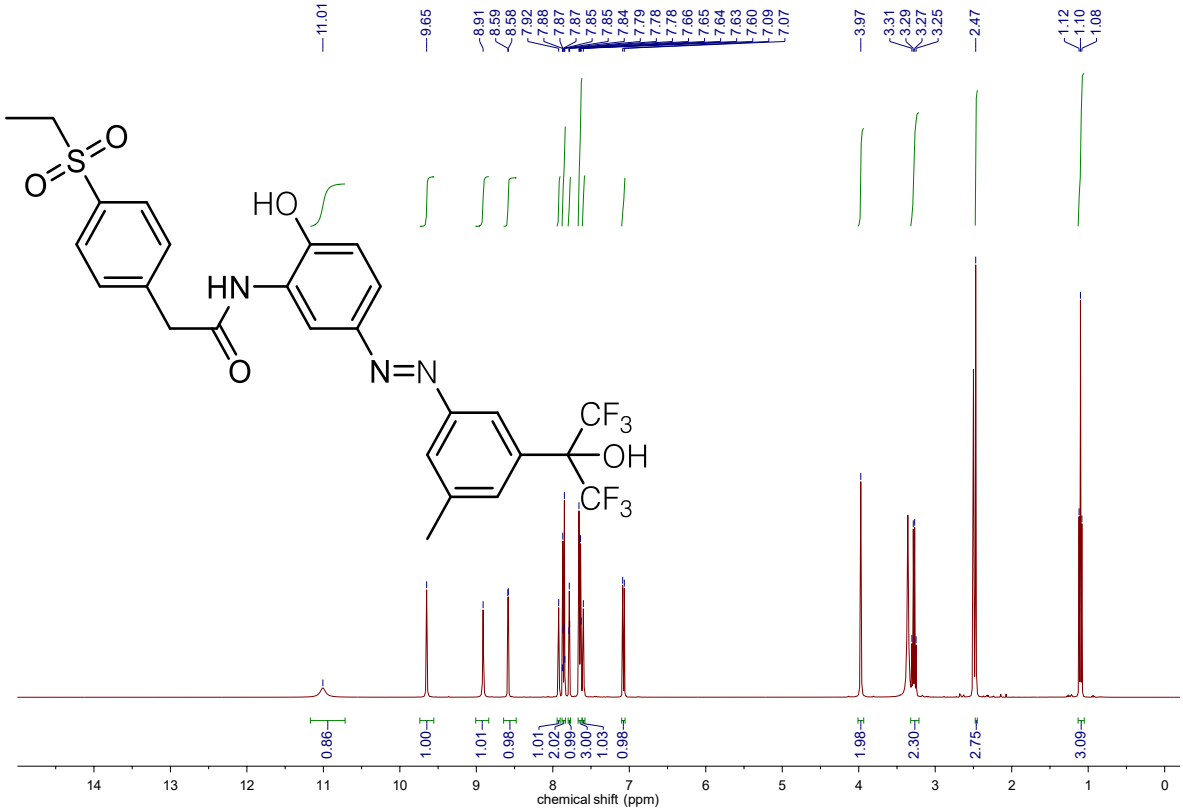
(15) ^{1}H-NMR



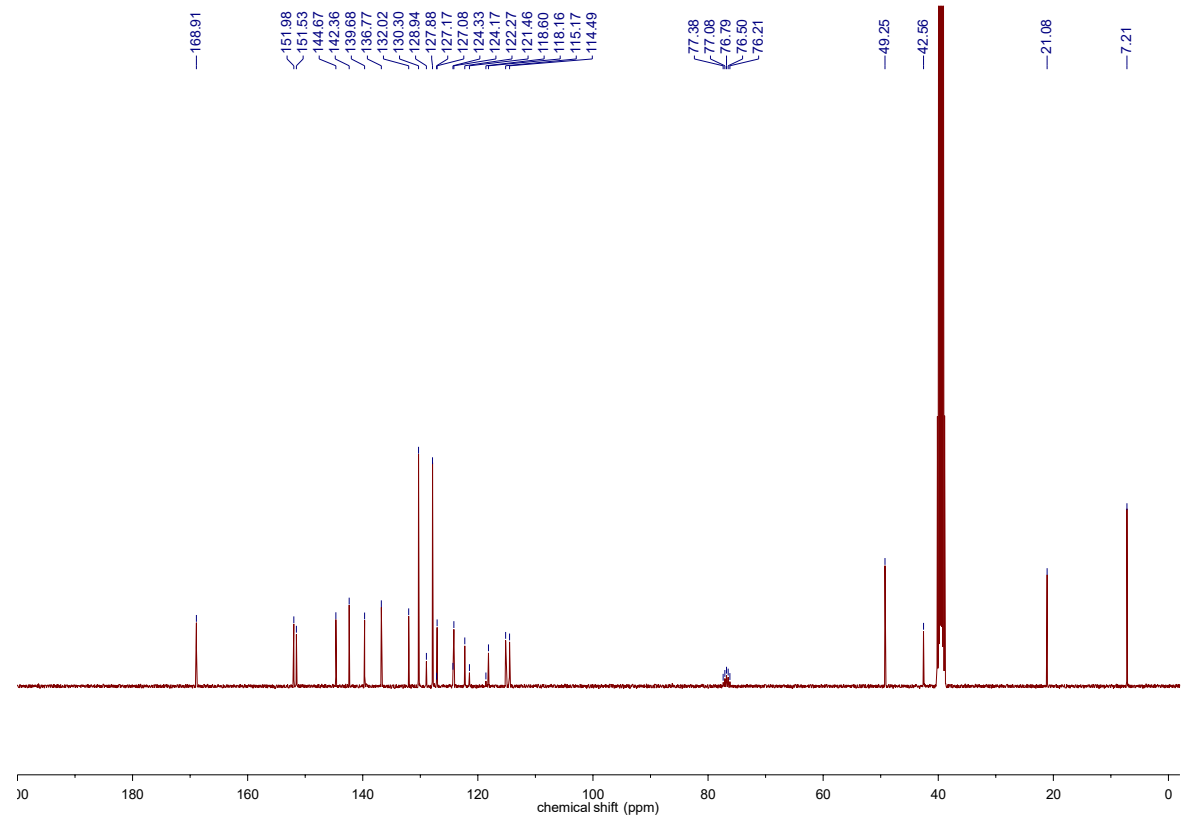
(15) ^{13}C-NMR



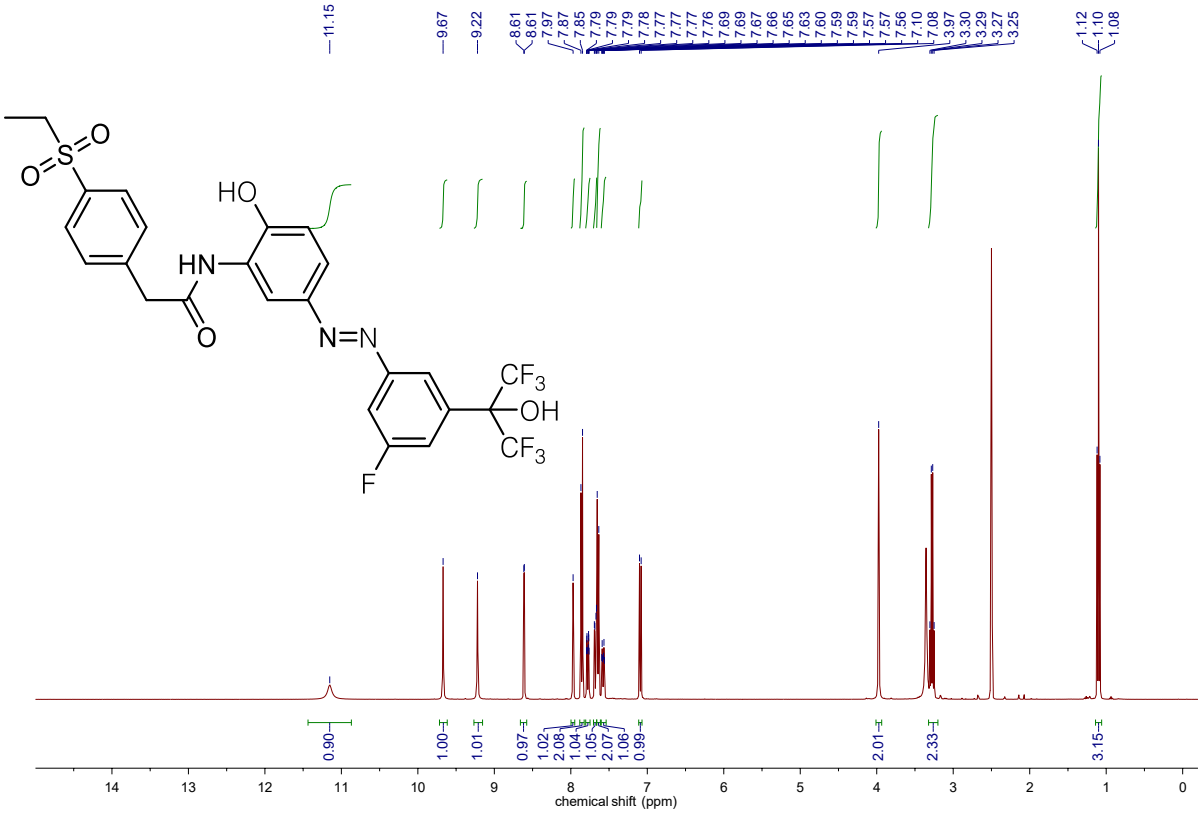
(MROR10) ^{1}H-NMR



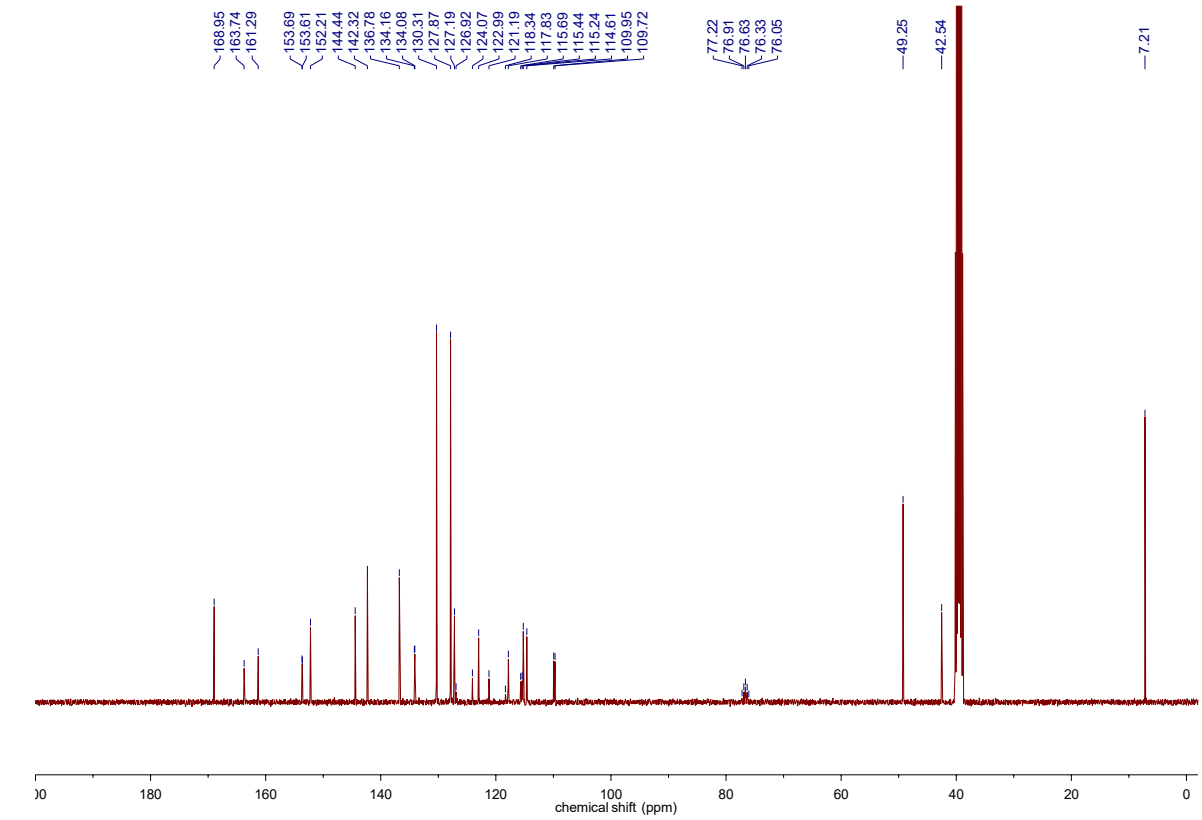
(MROR10) ^{13}C-NMR



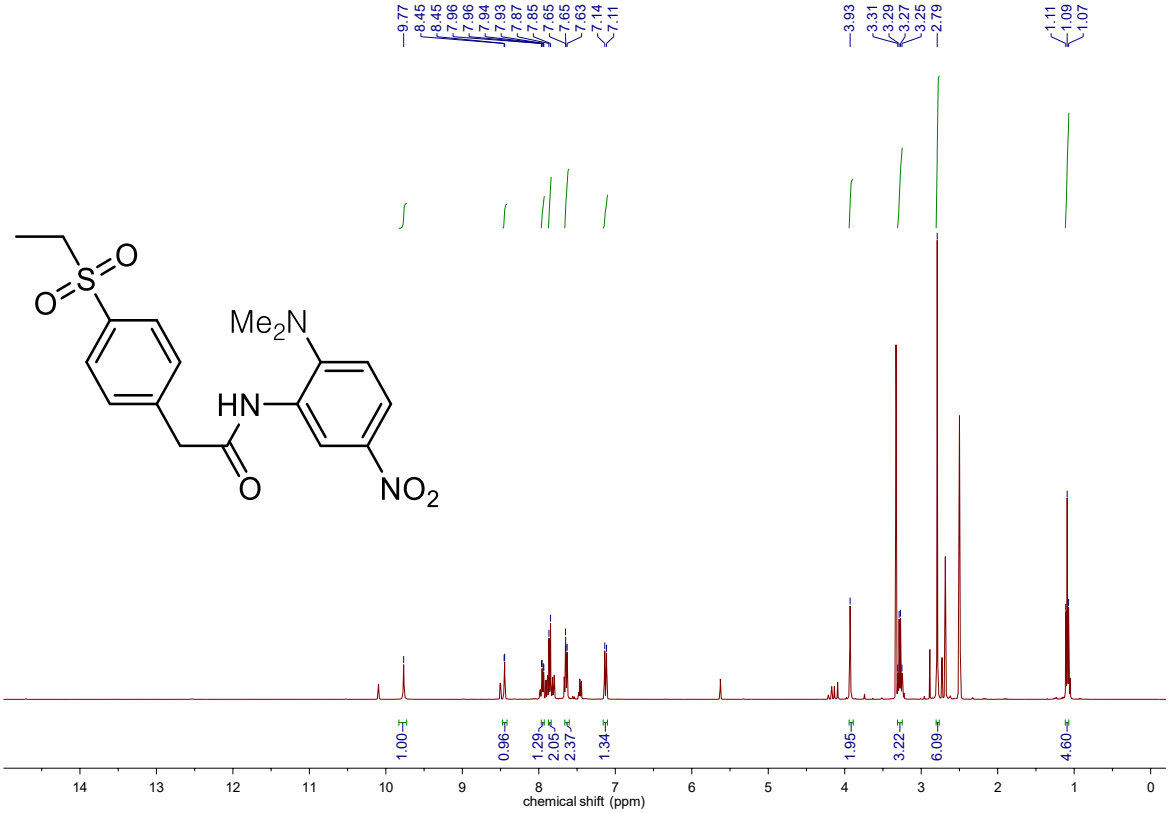
(MROR11) ^{1}H-NMR



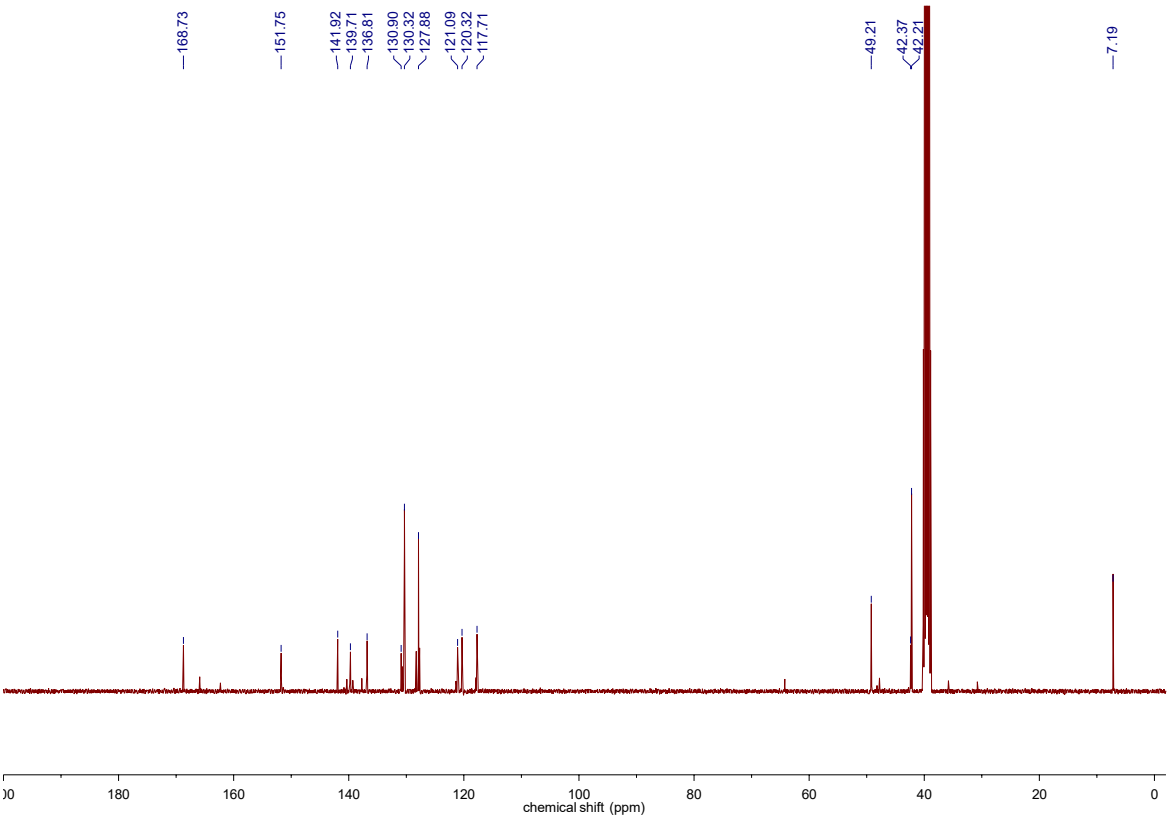
(MROR11) ^{13}C-NMR



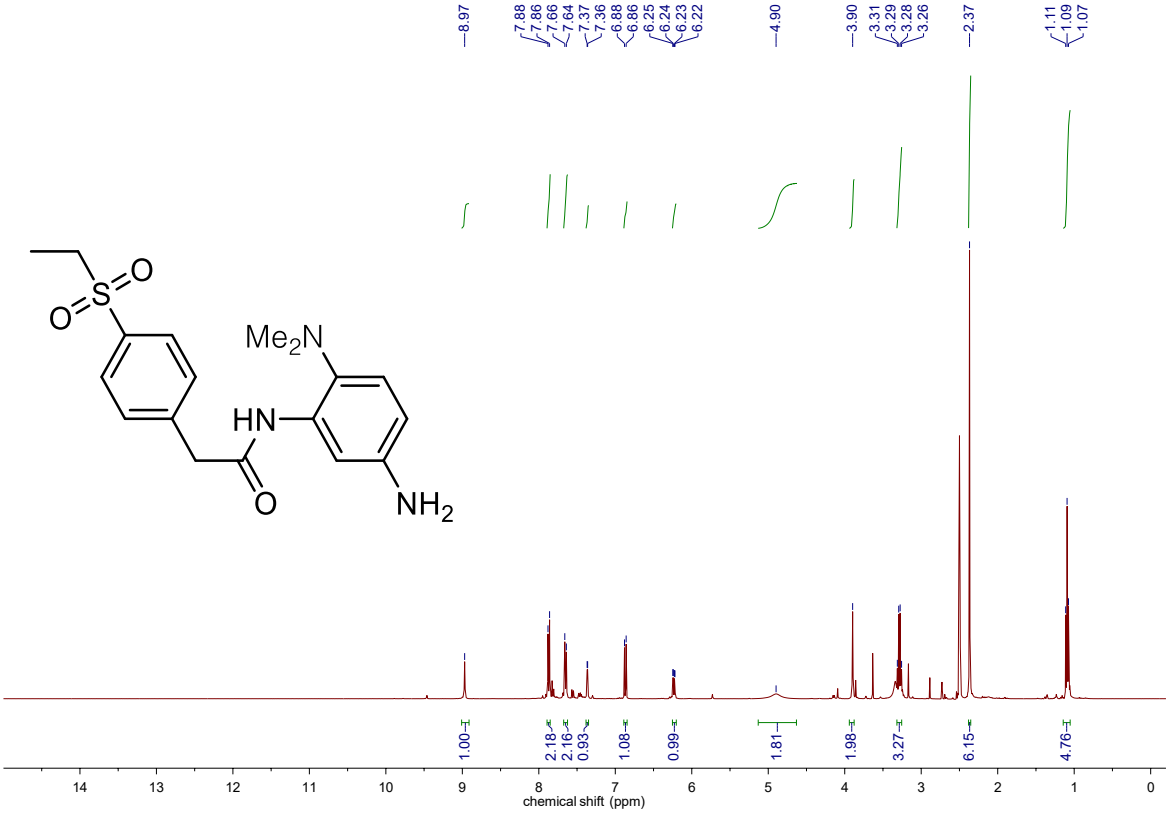
(16) ^{1}H-NMR



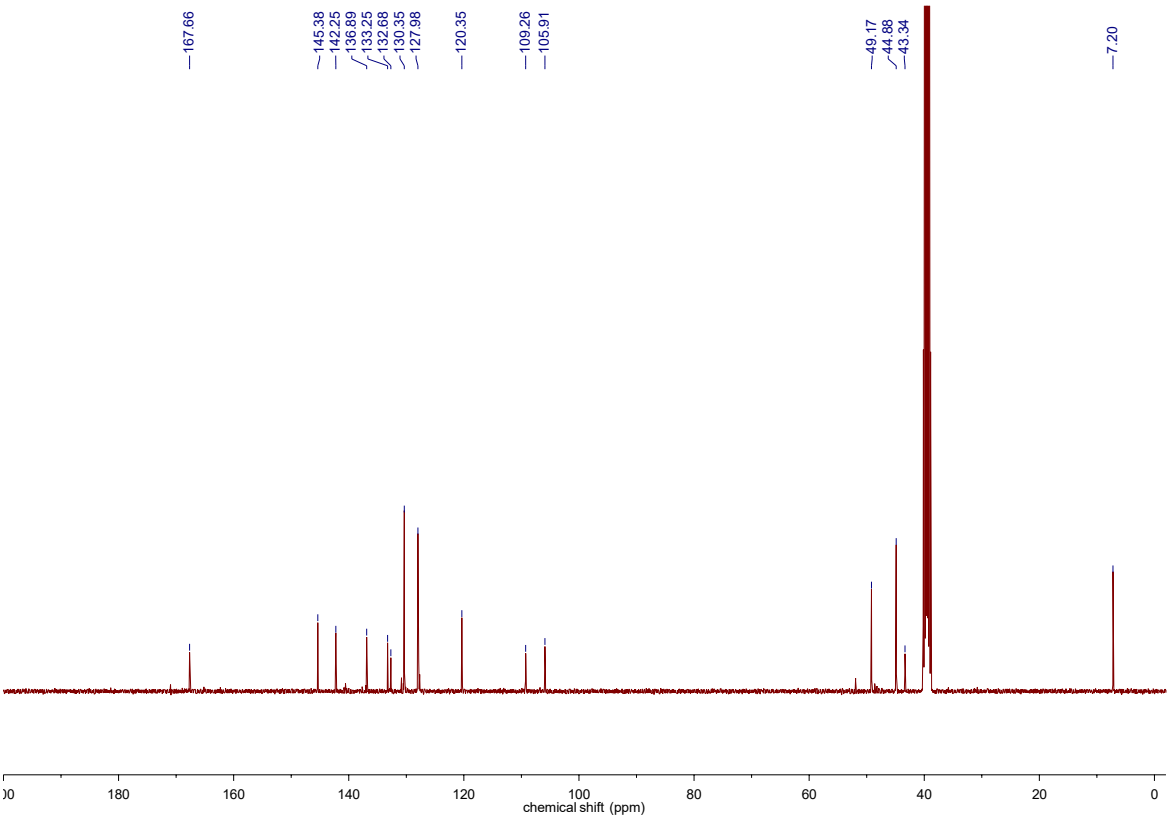
(16) ^{13}C-NMR



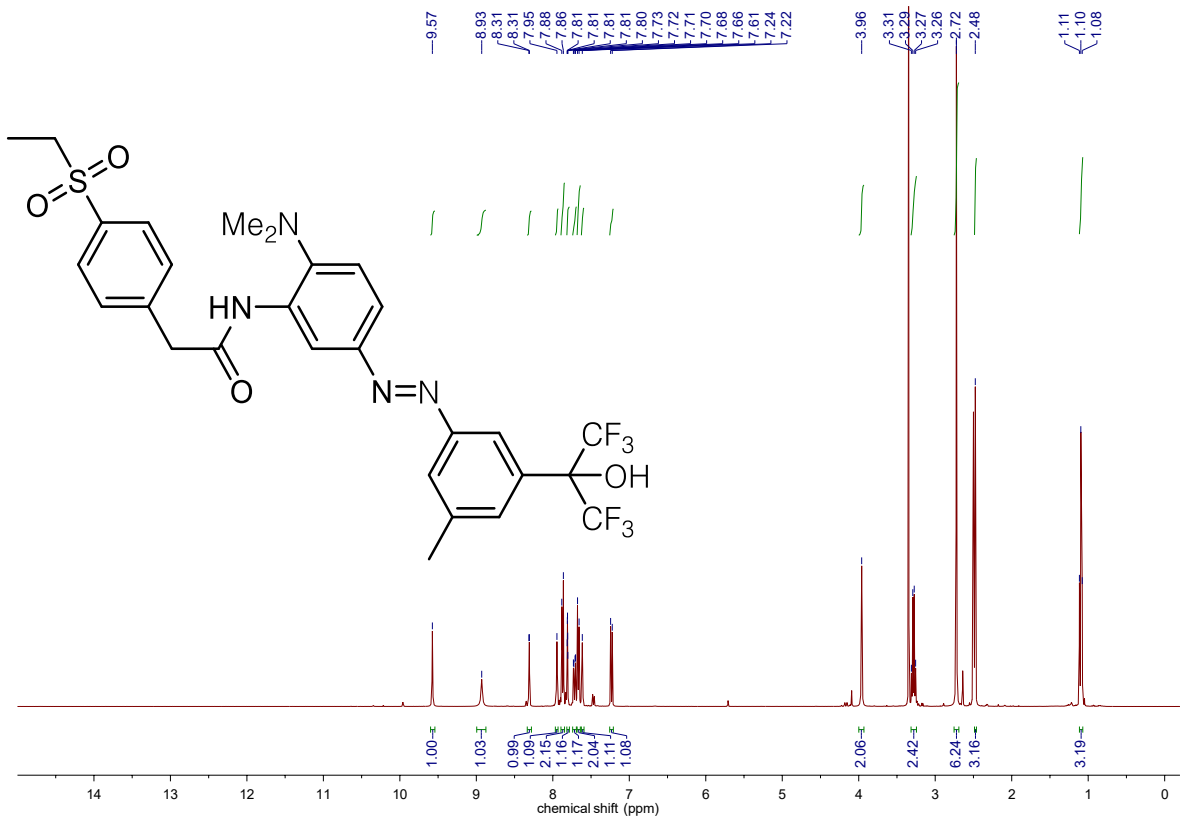
(17) ^{1}H-NMR



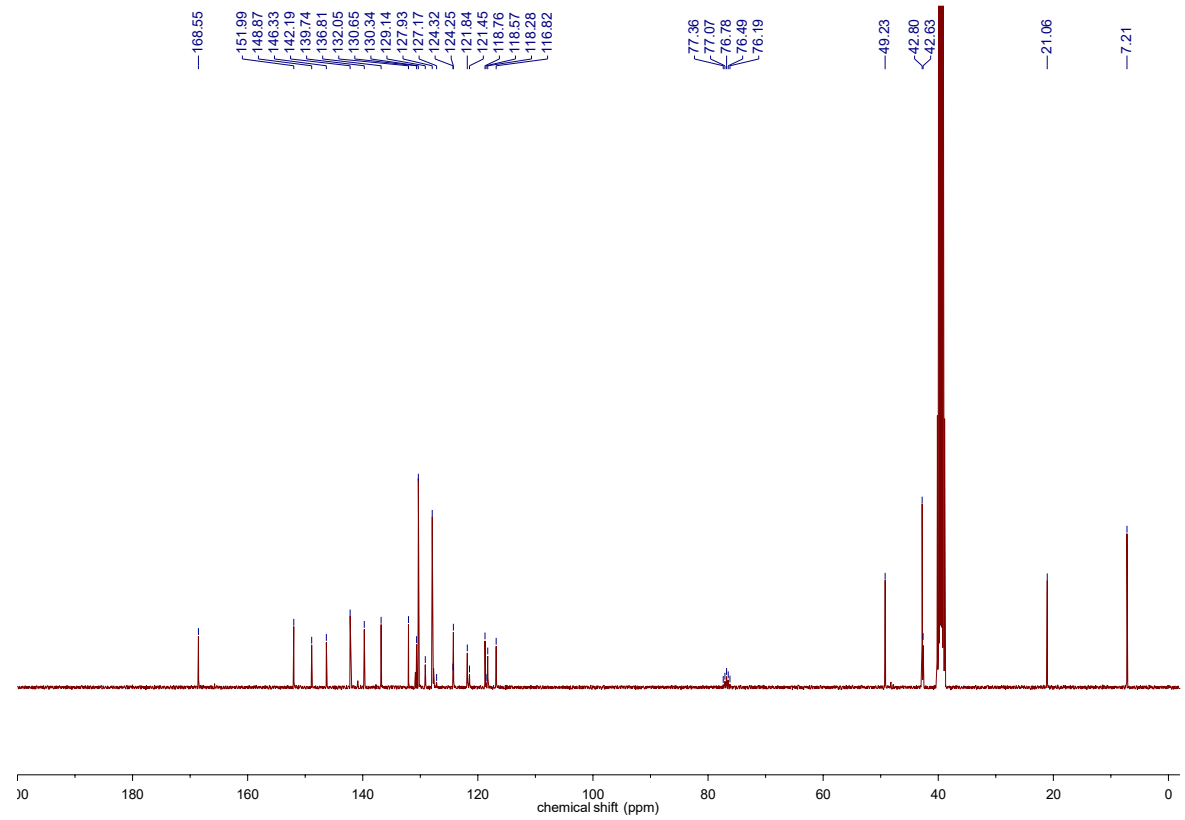
(17) ^{13}C-NMR



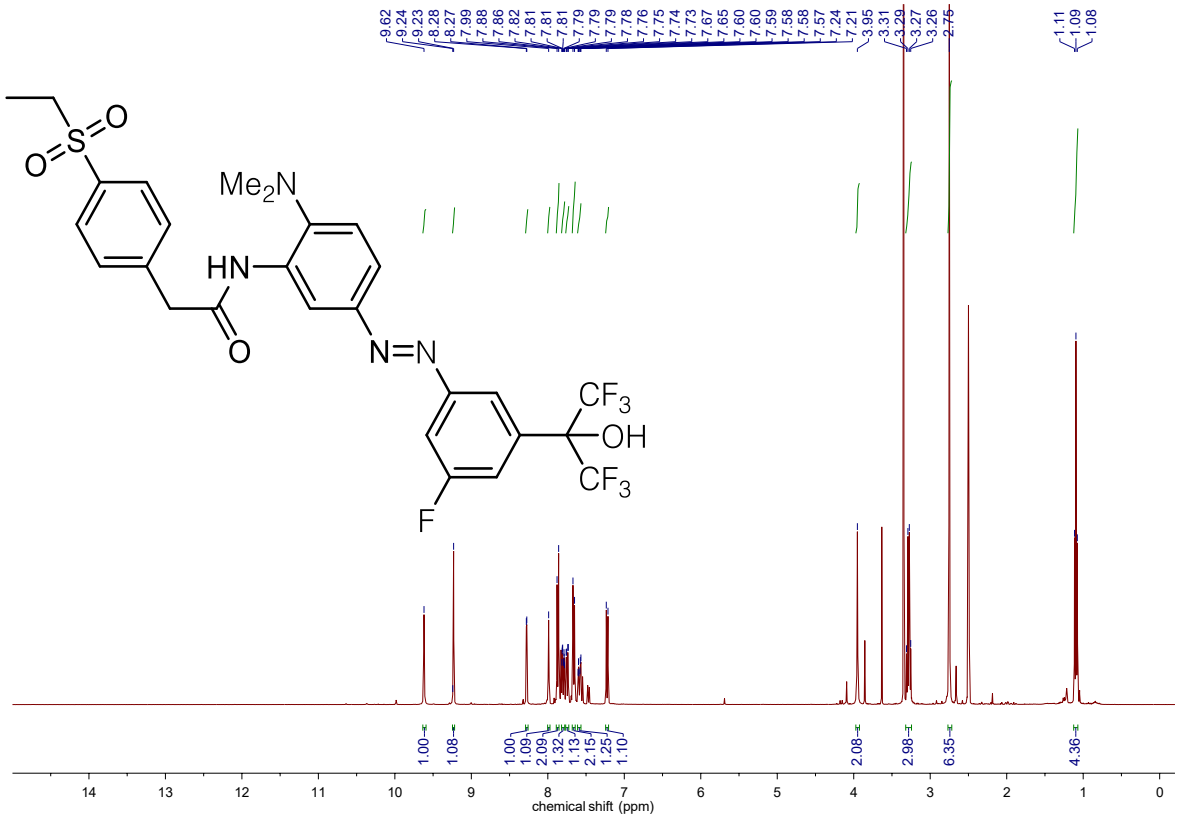
(MROR12) ^{1}H-NMR



(MROR12) ^{13}C-NMR



(MROR13) ^{1}H-NMR



(MROR13) ^{13}C-NMR