Activation of Cell-Penetrating Peptides with Ionpair-π Interactions and Fluorophiles

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Supplementary Information

Table of Content

1. Materials and Methods

As in ref. S1, Supporting Information. Briefly, reagents for synthesis were purchased from Fluka, Sigma-Aldrich, Apollo Scientific and Bachem, buffers and salts of the best grade available from Fluka or Sigma-Aldrich and used as received. Egg yolk phosphatidylcholine (EYPC) was purchased from Avanti Polar Lipids. Cy5-NHS was purchased from Lumiprobe. Poly-L-arginine (MW = 5-15 kDa) was purchased from Sigma-Aldrich.

Unless stated otherwise, column chromatography was carried out on silica gel (SiliaFlash® P60, SILICYCLE, 230–400 mesh). Analytical (TLC) and preparative thin layer chromatography (PTLC) were performed on TLC Silica gel 60 F_{254} (Merck) and SilicaPlate TLC (SILICYCLE, 1000 µm), respectively. Reverse phase flash chromatography was performed on Biotage Isolera^{TM} Four (column: SNAP Cartridge, KP-C18-HS-12g or -60g, eluents: MeCN or MeOH and H_2O with 0.1% TFA). Semi-preparative HPLC was performed using a Jupiter Proteo 90A Column (Phenomenex) 4 µm, 250 x 10 mm with MeCN and H_2O with TFA 0.1% as eluents. The microwave (µW) reactions were performed using Biotage® Initiator^{+} Microwave Synthesizer. Melting points (Mp) were measured on a Melting Point M-565 (BUCHI). IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer (ATR, Golden Gate, unless stated) and are reported as wavenumbers ν in cm^{-1} with band intensities indicated as s (strong), m (medium), w (weak), br (broad). ^{1}H and ^{13}C spectra were recorded (as indicated) either on a Bruker 300 MHz, 400 MHz or 500 MHz spectrometer and are reported as chemical shifts (δ) in ppm relative to TMS ($\delta = 0$). Spin multiplicities are reported as a singlet (s), doublet (d), triplet (t), quartet (q) and quintet (quint) with coupling constants (J) given in Hz, or multiplet (m). Broad peaks are marked as br. ^{1}H and ^{13}C resonances were assigned with the aid of additional information from 1D & 2D NMR spectra (H,H-COSY, DEPT 135, HSQC and HMBC). ESI-MS were performed on

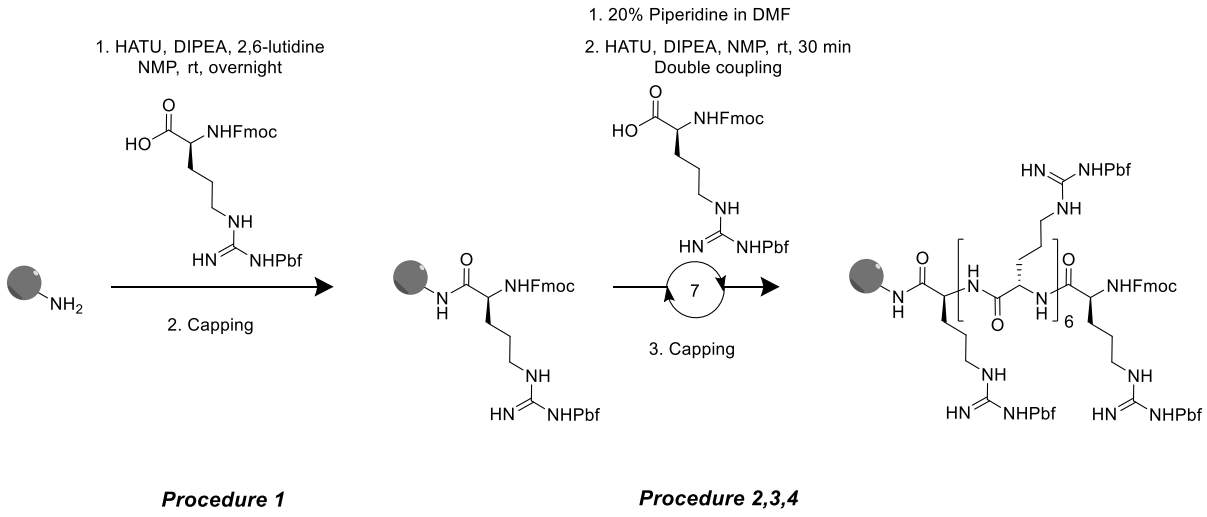
a ESI API 150EX and are reported as *m/z* (%). Accurate mass determinations using ESI (HR ESI-MS) were performed on a Sciex QSTAR Pulsar mass spectrometer. LC-MS (ESI) were recorded using a Thermo Scientific Accela HPLC with a LCQ Fleet three-dimensional ion trap mass spectrometer (both ESI, thermo scientific) and a diode array detector. The chromatographic column used was a Thermo C18 Hypersil gold column 1.9 μm, 5 cm x 2.1 mm, using an eluent gradient MeCN and H_2O with TFA 0.01% at a flow rate 0.75 mL/min. MALDI-TOF MS were measured using a Bruker Daltonics Autoflex speed spectrometer. Fluorescence measurements were performed with a FluoroMax-4 spectrofluorometer (Horiba Scientific) equipped with a stirrer and a temperature controller (25 ± 1 ºC). Fluorescence spectra were corrected using instrument-supplied correction factors. UV-Vis spectra were recorded on a JASCO V-650 spectrophotometer equipped with a stirrer and a temperature controller (25 ± 1 ºC) and are reported as maximal absorption wavelength λ in nm (extinction coefficient ε in $M^{-1}cm^{-1}$). Vesicles were prepared with a Mini-Extruder from Avanti Polar Lipids (pore size 100 nm). NovaPEG Rink Amide Resin was purchased from Novabiochem®, and was swollen in CH_2Cl_2 before each reaction. Solid phase reactions were carried in SPE tubes fitted with a frit and a tap. Automated solid phase synthesis was carried out on an Intavis AG Multipep RS instrument.

Abbreviations. ANI: Aminonaphthalimide; CF: 5(6)-Carboxyfluorescein; CLSM: Confocal laser scanning microscopy; CPP: Cell-penetrating peptides; Cy5: Cyanine 5; d: Days; Dba: Dibenzylidenacetone; DHB: 2,5-Dihydroxybenzoic acid; DIPEA: *N,N*-Diisopropylethylamine DMF: *N,N*-Dimethylformamide; DMSO: Dimethyl sulfoxide; Dppf: 1,1'-Bis(diphenylphophine)-ferrocene; EYPC: Egg yolk phosphatidylcholine; Fmoc: Fluorenylmethyloxycarbonyl; HATU: *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-

tetramethyluronium-hexafluorophosphate); LUVs: Large unilamellar vesicles; NHS: *N*-Hydroxysuccinimide; NMP: *N*-Methyl-2-pyrrolidone; Pbf: 2,2,4,6,7-Pentamethyldihydrobenzofuran-5-sulfonyl; pR: Poly-L-arginine; R_8: Octaarginine; rt: Room temperature; TEA: Triethylamine; TFA: Trifluoroacetic acid; THF: Tetrahydrofuran, µW: Microwave.

2. Synthesis

2.1. Cy5-CPP 1



Scheme S1. Solid-phase synthesis of octaarginine.

Preparation of Solutions. Capping Mixture: 0.9 mL of acetic anhydride, 1.3 mL of 2,6-lutidine and 18 mL of DMF. **Fmoc Deprotection Solution*:*** 20% vol. piperidine in DMF. **Base Solution**: 1.96 mL DIPEA, 2.05 mL 2,6-lutidine were added to 5.54 mL NMP.

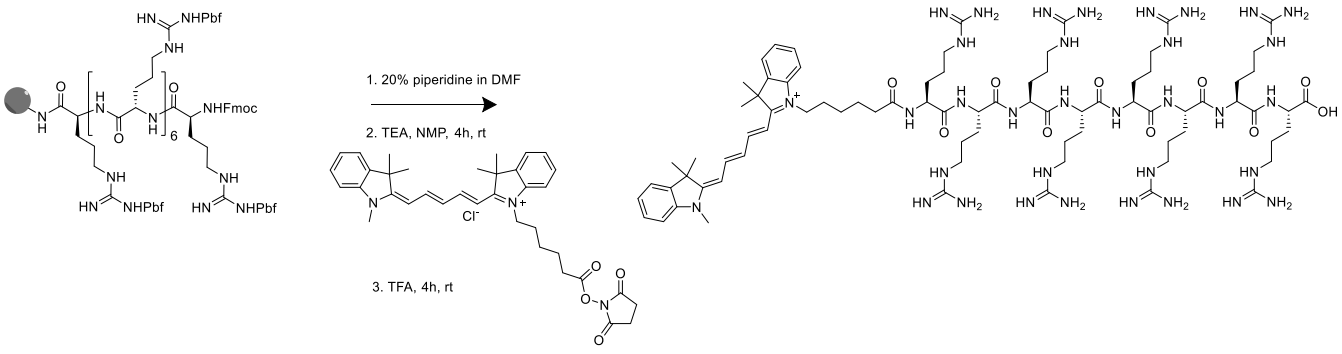
Procedure 1. To a solution of Fmoc-Arg(Pbf)-OH (97 mg, 0.15 mmol) in NMP (1.0 mL) were added HATU (56 mg, 0.26 mmol) followed by DIPEA (21 μL, 0.12 mmol) and 2,6-lutidine (7 μL, 0.06 mmol). The mixture was shaken for 5 min at rt, and then added to NovaPEG Rink amide resin (30 mg, initial loading 0.5 mmol/g). The reaction mixture was shaken for 13 h at rt and the resin was subsequently washed with DMF (3 x 5 mL) and CH_2Cl_2 (3 x 5 mL). The remaining free amino groups were capped by adding **Capping Mixture** (1 mL), the reaction was shaken for 45 min at rt. Subsequently, the resin was

washed with DMF (3 x 5 mL) and CH_2Cl_2 (3 x 5 mL). The loaded resin obtained was used in the next steps of synthesis with a loading of 0.2 mmol/g.

Procedure 2. To NovaPEG Rink amide resin (5 mg) were added of **Fmoc Deprotection Solution** (200 μL). After 2 min, the resin was washed with DMF (1.8 mL) and the sequence was repeated a second time for 4 min. Finally, the resin was washed with DMF (2 x 1.8 mL) and CH_2Cl_2 (3 x 1.6 μL) and DMF (3 x 1.8 mL).

Procedure 3. To a solution of Fmoc-Arg(Pbf)-OH (6 μmol) in NMP (30 μL) were added HATU (5 μmol) in NMP (10 μL), followed by **Base Solution** (5 μL). The mixture was then added to the corresponding resin (5 mg). After 20 min the resin was filtered and washed with DMF (3 x 1.8 mL) and the sequence was repeated, then, the resin was washed with DMF (3 x 1.8 mL) and CH_2Cl_2 (3 x 1.8 mL).

Procedure 4. To NovaPEG Rink amide resin (5 mg) were added **Capping Mixture** (200 μL***)***. After 5 min, the resin was washed with DMF (3 x 1.8 mL). Finally, procedures 2-4 were repeated 6 more times.



Scheme S2. Coupling of Cy5-NHS to octaarginine on solid-phase and cleavage of **1** from the resin.

Procedure 5. To the resin (7.9 mg) was added a solution of 20% piperidine in DMF and the mixture was shaken for 4 h at 25 °C. The resin was washed with DMF (3 x 5 mL) and CH_2Cl_2 (3 x 5 mL). To the resin, Cy5-NHS (4 mg, 0.007 mmol) dissolved in NMP (300 μL) and TEA (10 μL) was added. The mixture was shaken for 4 h at 25 °C. The resin was washed with DMF (3 x 5 mL) and CH_2Cl_2 (3 x 5 mL). 150 μL of TFA was added to the resin and the mixture was shaken for 4 h at 25 °C. The resulting mixture was added to 1.5 mL of Et_2O and centrifuged. The supernatant was removed and the pellet was washed with 2 x 1.5 mL of Et_2O. The pellet was suspended in H_2O/ACN 1:1 mixture, the resin was filtered off and the filtrate was purified by reverse-phase chromatography (SNAP C18 12 g, ACN/H_2O/TFA 5:95:0.1 to 100:0:0.1) to give product **1**. MALDI-MS (+ve, DHB matrix): 1732 ([M^+]).

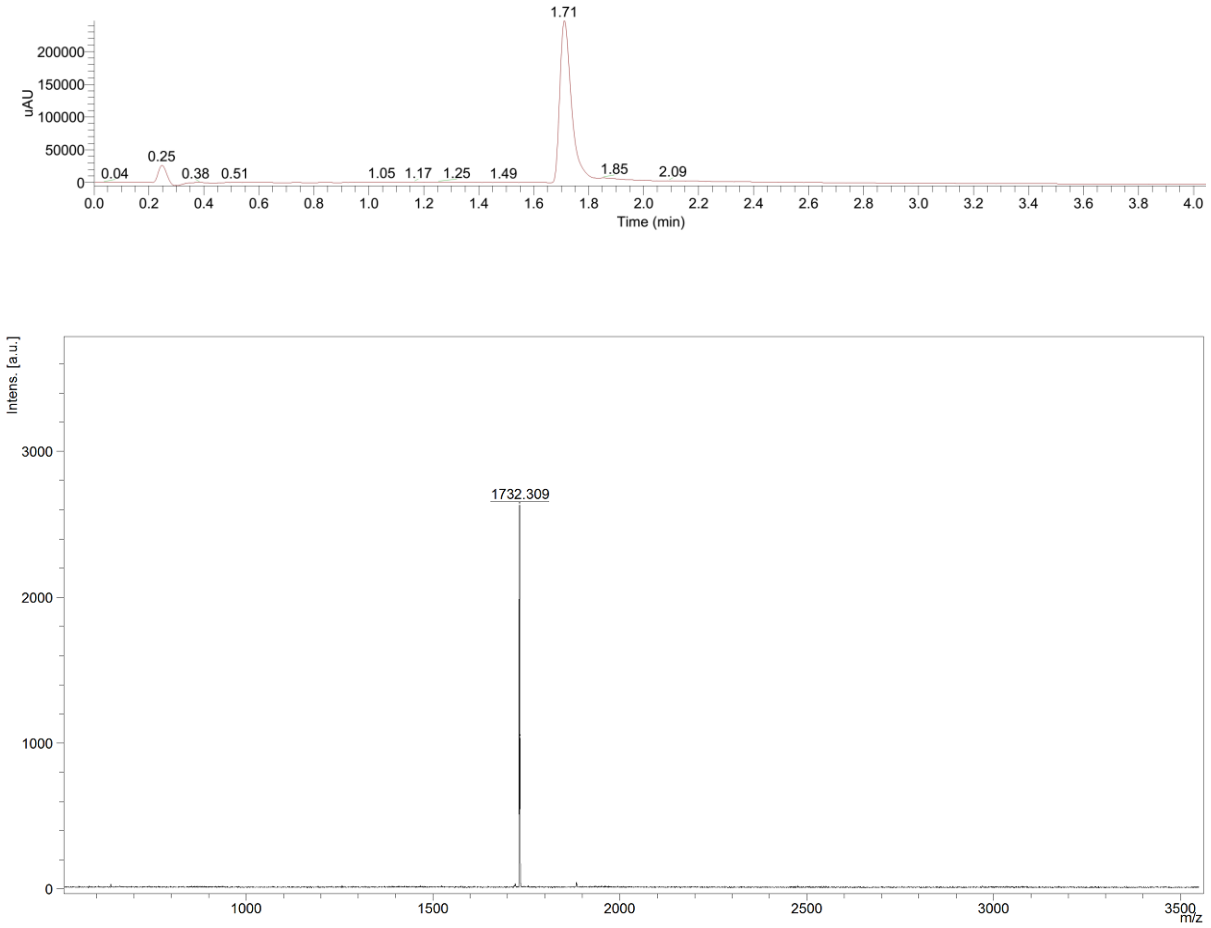
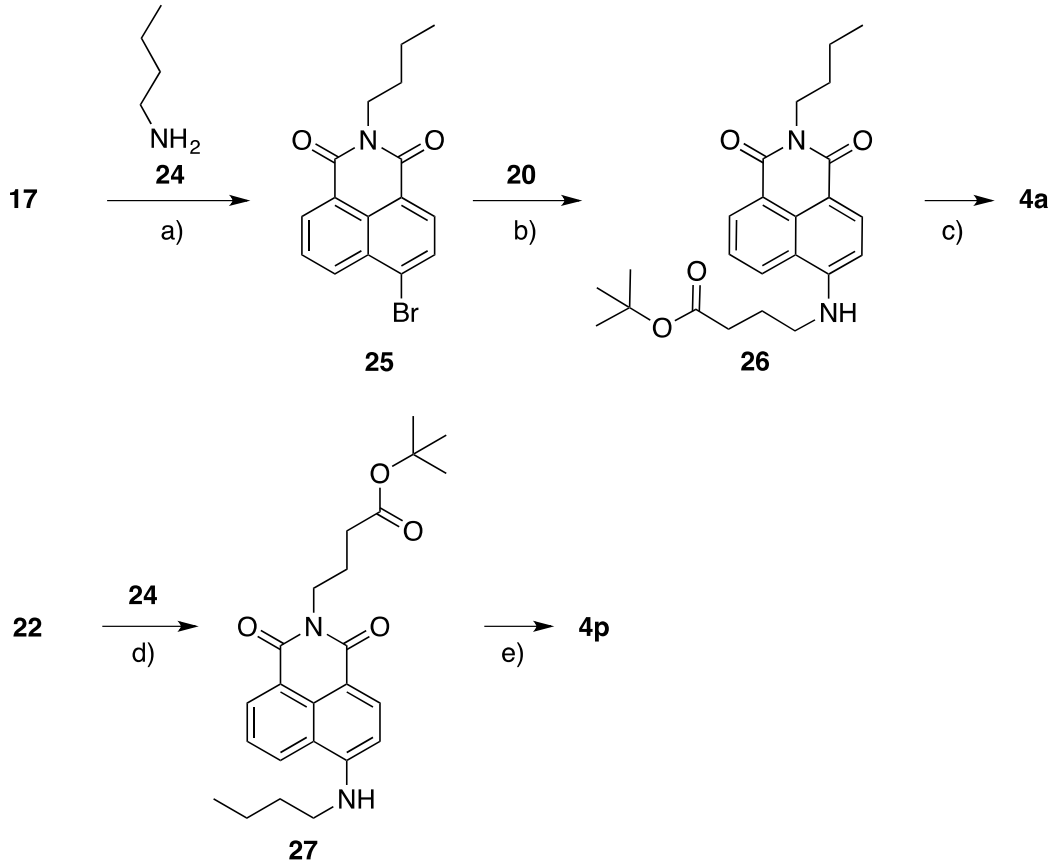
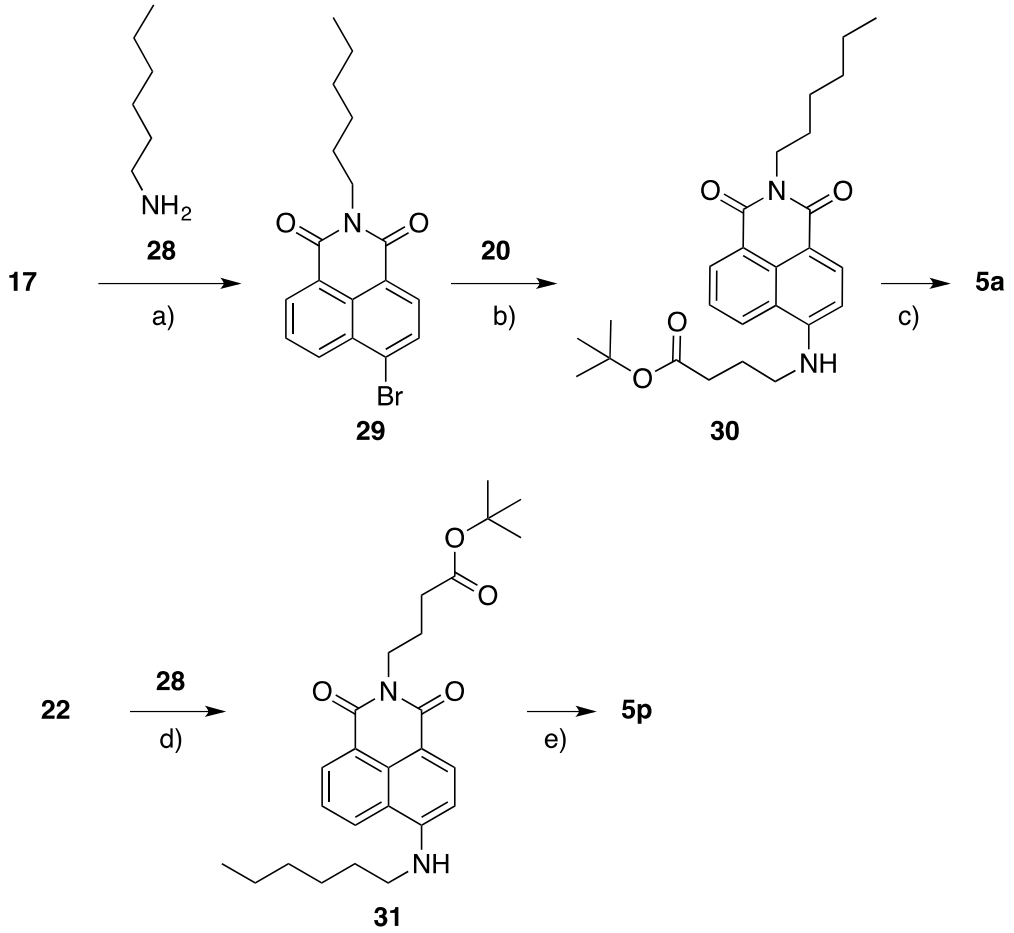


Figure S1. Characterization of Cy5-CPP **1**: HPLC profile (top); Thermo C18 Hypersil gold column 1.9 μm, 5 cm x 2.1 mm, using an eluent gradient MeCN and H_2O with TFA 0.01% at a flow rate 0.75 mL/min. MALDI-TOF MS (bottom).

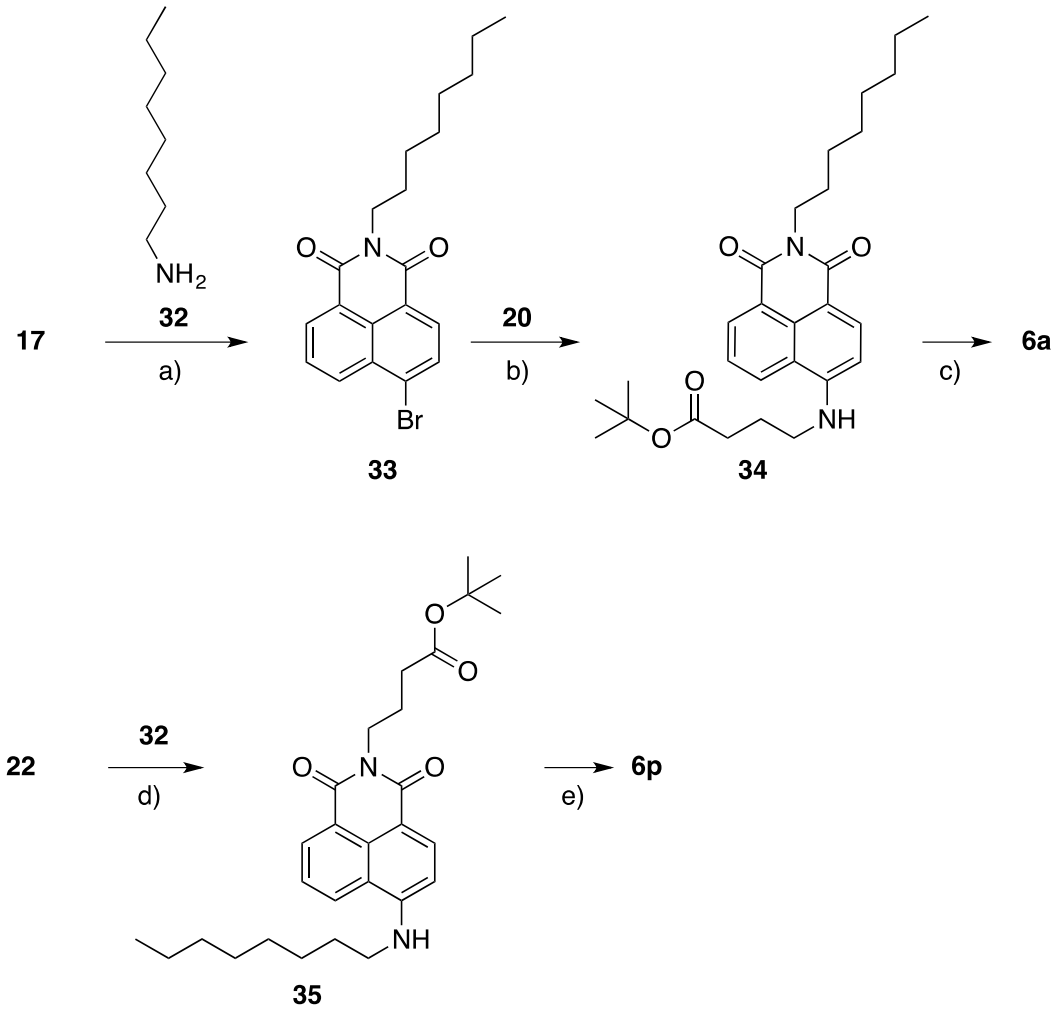
2.2. Activators



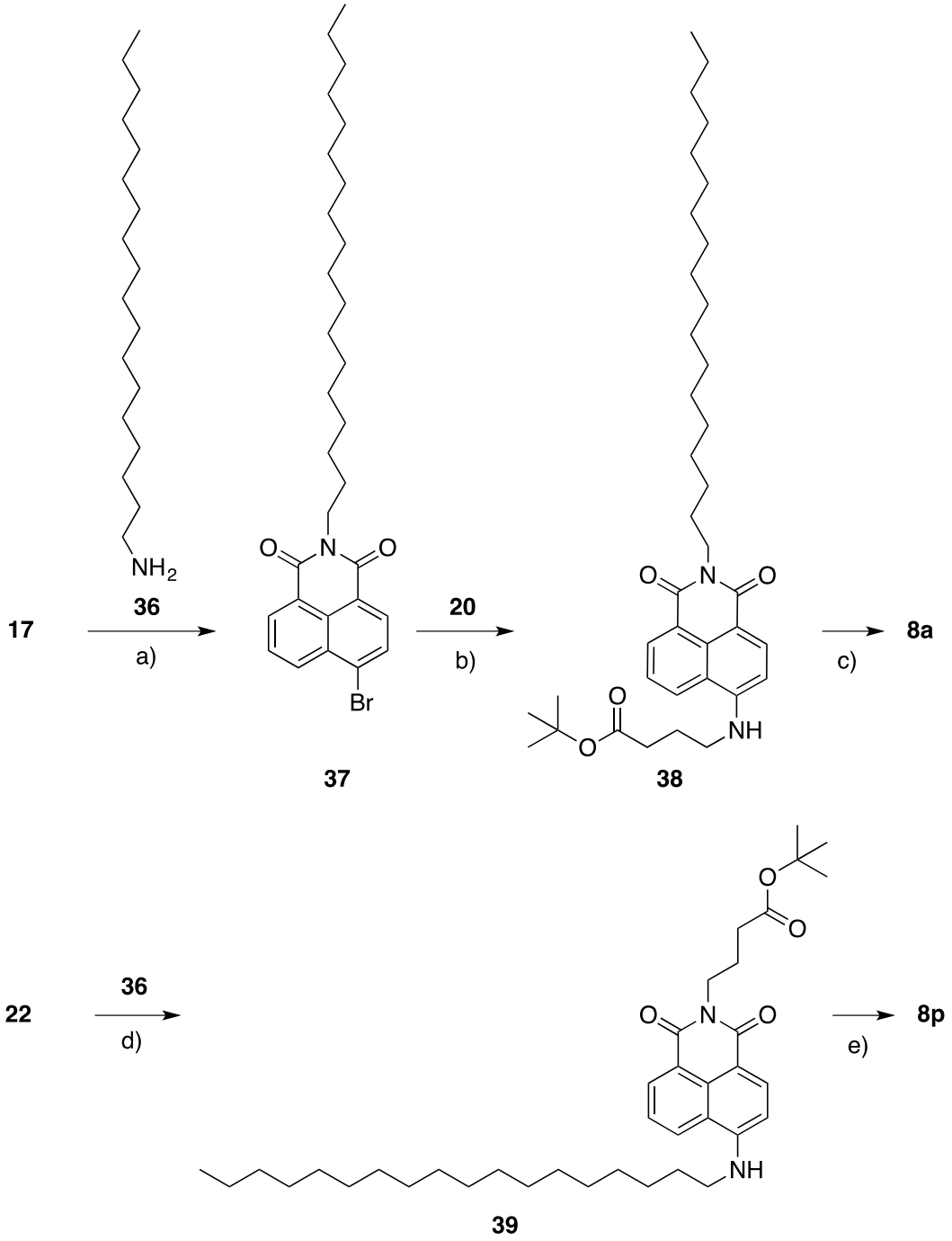
Scheme S3. Synthesis of **4a** and **4p**. (a) EtOH, 90 °C, 15 h, 36%; (b) DMSO, TEA, 90 °C, 3 d, 72%; (c) TFA, CH_2Cl_2, rt, 2 h, 96%; (d) 90 ºC, 15 h, 93%; (e) TFA, CH_2Cl_2, rt, 2 h, 75%.



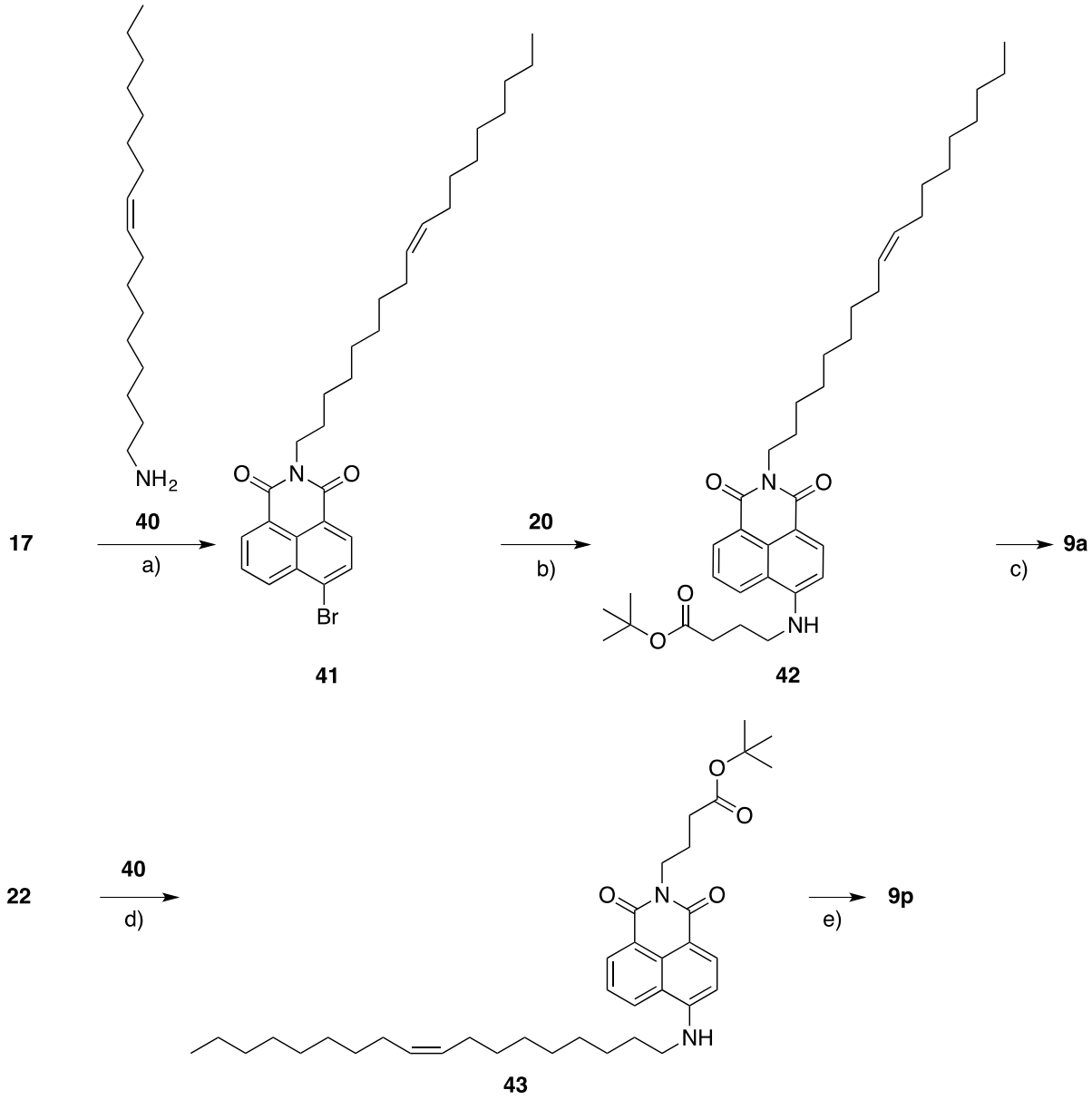
Scheme S4. Synthesis of **5a** and **5p**. (a) EtOH, 90 °C, 15 h, 92%; (b) DMSO, TEA, 90 °C, 3 d, 24%; (c) TFA, CH_2Cl_2, rt, 2 h, 95%; (d) 90 ºC, 15 h, 70%; (e) TFA, CH_2Cl_2, rt, 2 h, 93%.



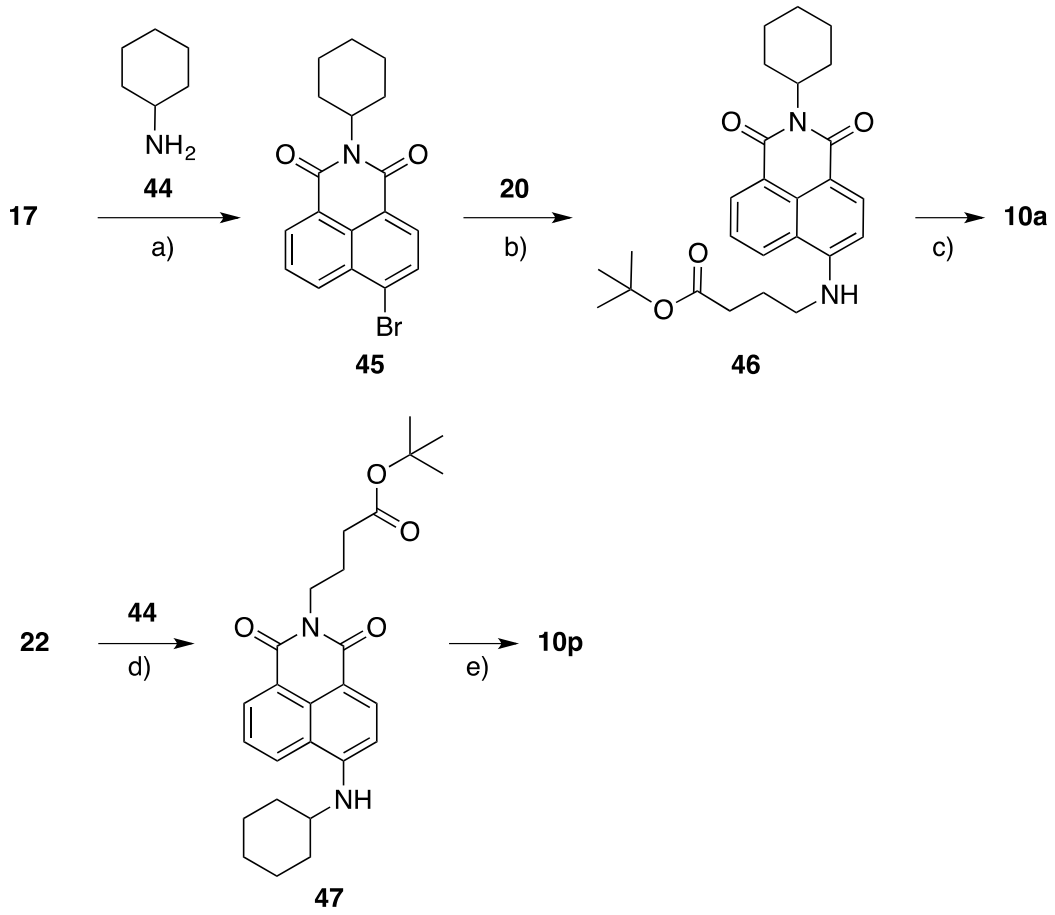
Scheme S5. Synthesis of **6a** and **6p**. (a) EtOH, 90 °C, 15 h, 71%; (b) DMSO, TEA, 90 °C, 3 d, 36%; (c) TFA, CH_2Cl_2, rt, 2 h, 90%; (d) 90 ºC, 2 d, 80%; (e) TFA, CH_2Cl_2, rt, 2 h, 86%.



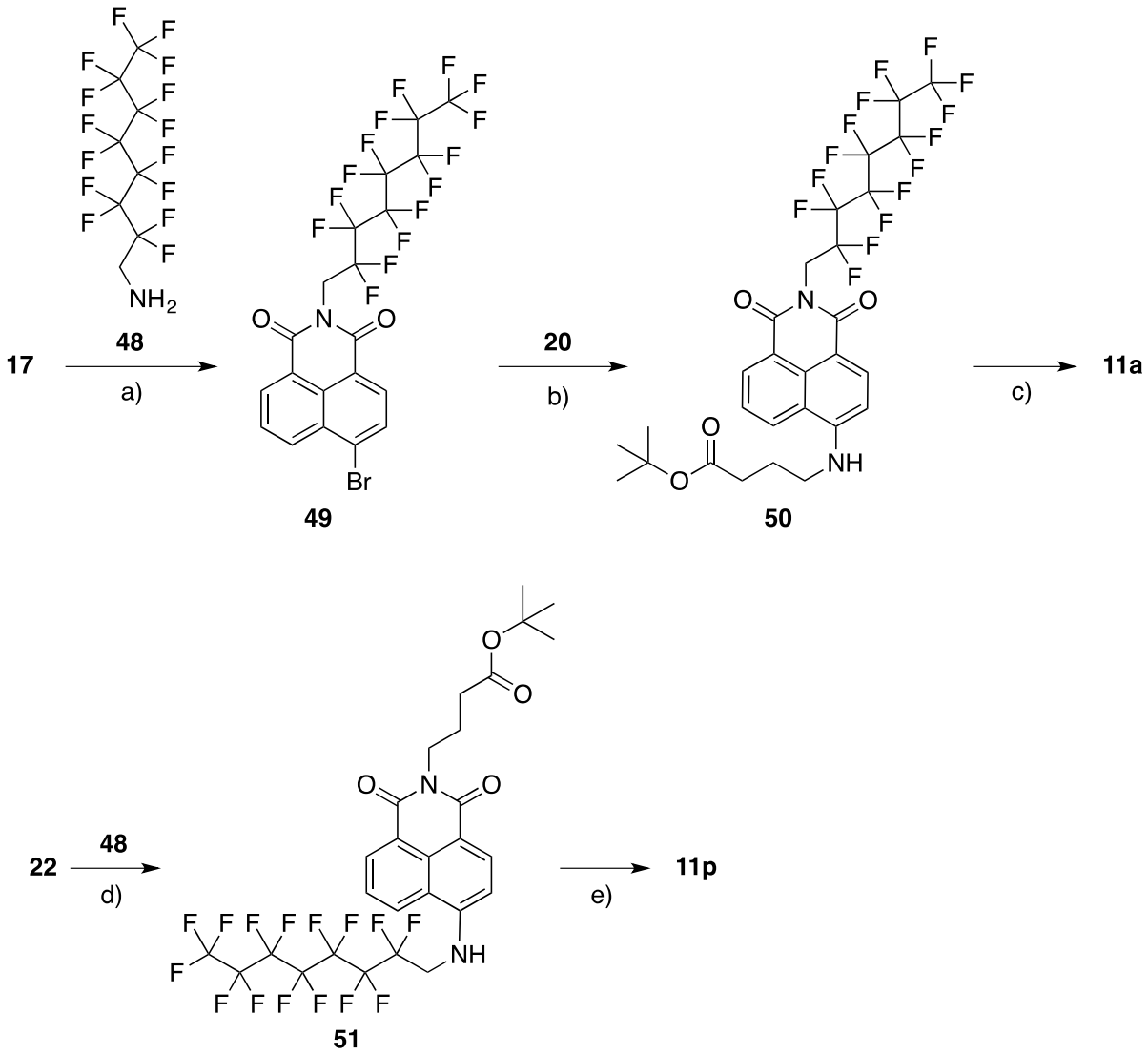
Scheme S6. Synthesis of **8a** and **8p**. (a) EtOH, 90 °C, 15 h, 34%; (b) DMSO, TEA, 90 °C, 3 d, 61%; (c) TFA, CH_2Cl_2, rt, 2 h, 92%; (d) 90 ºC, 3 d, quant.; (e) TFA, CH_2Cl_2, rt, 2 h, 79%.



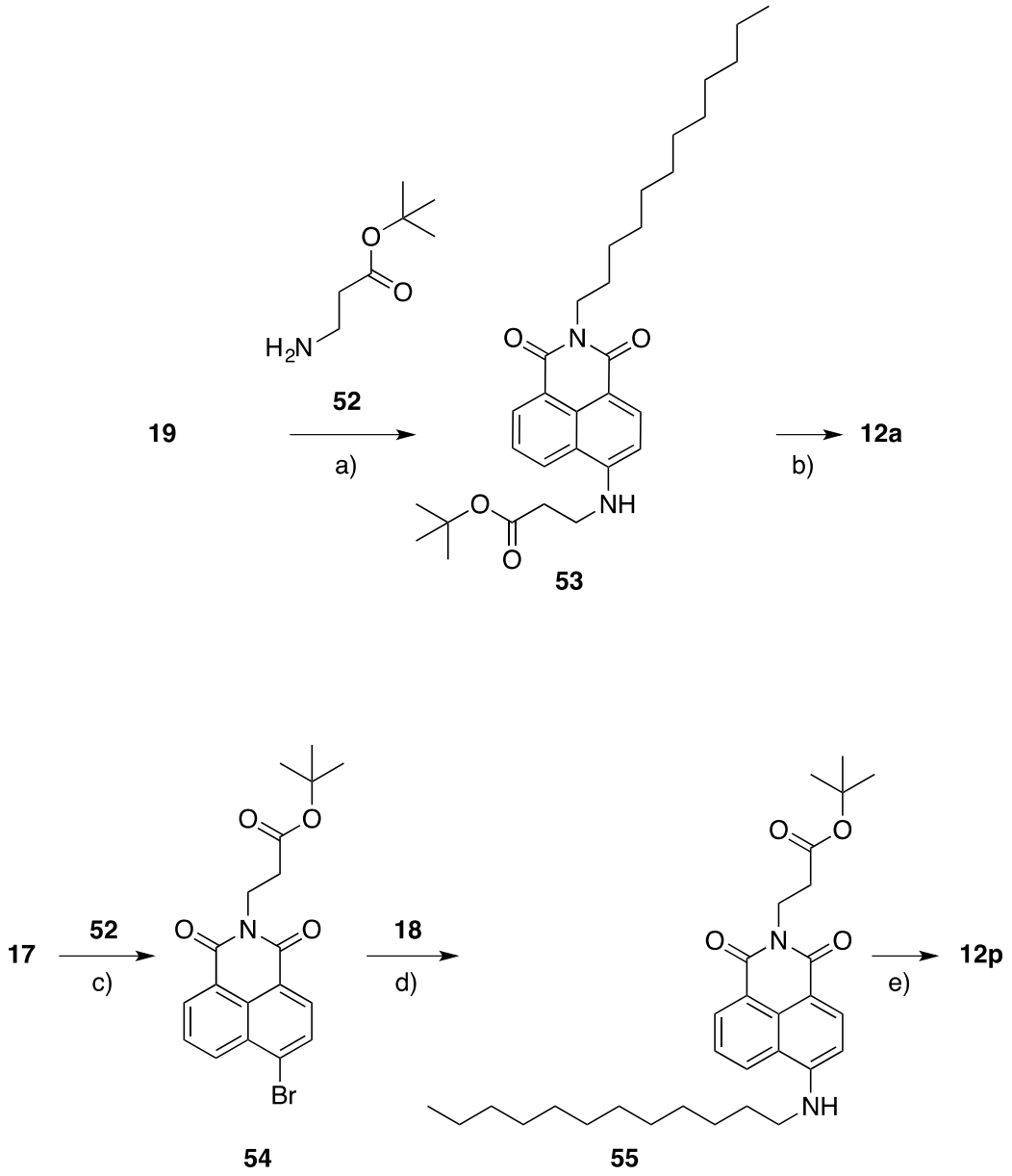
Scheme S7. Synthesis of **9a** and **9p**. (a) EtOH, 90 °C, 15 h, 77%; (b) DMSO, TEA, 90 °C, 3 d, 78%; (c) TFA, CH_2Cl_2, rt, 2 h, 75%; (d) 90 ºC, 15 h, 81%; (e) TFA, CH_2Cl_2, rt, 2 h, 86%.



Scheme S8. Synthesis of **10a** and **10p**. (a) EtOH, 90 °C, 15 h, 80%; (b) DMSO, TEA, 90 °C, 3 d, 34%; (c) TFA, CH_2Cl_2, rt, 2 h, 61%; (d) 90 ºC, 15 h, 83%; (e) TFA, CH_2Cl_2, rt, 2 h, 95%.



Scheme S9. Synthesis of **11a** and **11p**. (a) EtOH, 90 °C, 24 h, 79%; (b) DMSO, TEA, 110 °C, 2 d, 83%; (c) TFA, CH_2Cl_2, rt, 2 h, 37%; (d) NaO*t*Bu, Dppf, $Pd_2(dba)_3$, toluene, 90 ºC, 18 h, 5%; (e) TFA, CH_2Cl_2, rt, 2 h, 25%.



Scheme S10. Synthesis of **12a** and **12p**. (a) DMF, TEA, 90 °C, 15 h, 83%; (b) TFA, CH_2Cl_2, rt, 2 h, 62%; (c) DMF, 100 °C, μW, 2 h, 67%; (d) 90 ºC, 15 h, 83%; (e) TFA, CH_2Cl_2, rt, 2 h, 55%.

Compounds 3a,[S1] **3p,**[S1] **19,**[S2] **22**,[S3] **25,**[S2] **29,**[S2] **33,**[S2] **37,**[S4] **45.**[S2] These compounds were prepared following the literature procedures.

Method A. To a stirred solution of **40** or **48** (0.4 M, 1.2 eq.) in EtOH was added **17** (1.0 eq.) and the mixture was stirred overnight at 90 °C. The resulting mixture was diluted with AcOEt and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatographic purifications of the crude mixture afforded products **41**, **49**.

Method B. To a stirred solution of **19**, **25**, **29**, **33**, **37**, **41**, **45**, **49** (1.0 eq., 0.4 M in DMSO) was added **20** (5.0 eq. with 1.0 eq. TEA) and the mixture was stirred for 3 d at 110 °C. The resulting mixture was diluted with AcOEt and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatographic purifications of the crude mixture afforded products **21**, **26**, **30**, **34**, **38**, **42**, **46**, **50**.

Method C. A mixture of **18**, **24**, **28**, **32**, **36**, **40**, **44** (5 eq.) and **22** or **54** (1.0 eq.) was stirred for 1-3 d at 110 °C. The resulting mixture was diluted with AcOEt and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatographic purifications of the crude mixture afforded products **23**, **27**, **31**, **35**, **39**, **43**, **47**, **55**.

Method D. To a stirred solution of **21**, **23**, **26**, **27**, **30**, **31**, **34**, **35**, **38**, **39**, **42**, **43**, **46**, **47**, **50**, **51**, **53** or **55** (1 eq, 0.03 M in CH_2Cl_2) was added TFA (20%) and the mixture was stirred for 2 h at rt. The resulting mixture was diluted with AcOEt and washed with 1 M $KHSO_4$ and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure.

Pure products **4-12a**, **4-12p** were obtained as precipitates upon addition of hexane to the solution of the crude mixture in CH_2Cl_2.

Compound 21. This compound was prepared by **Method B**. Purification of the crude product by column chromatography (pentane/AcOEt 9:1, R_f: 0.5) and precipitation from CH_2Cl_2 upon addition of hexane afforded **21** as a yellow solid (72%). Mp: 75 – 76 °C; IR (neat): 3384 (w), 2923 (w), 2853 (w), 1730 (m), 1684 (m), 1638 (m), 1575 (s), 1545 (s), 1450 (w), 1427 (w), 1393 (m), 1350 (s), 1298 (w), 1244 (m), 1147 (s), 1116 (m), 1073 (w), 961 (w), 845 (w), 821 (w), 772 (s), 757 (m), 722 (w), 666 (w), 582 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.52 (dd, ^3J (H,H) = 7.3 Hz, ^4J (H,H) = 0.8 Hz, 1H), 8.40 (d, ^3J (H,H) = 8.5 Hz, 1H), 8.28 – 8.14 (m, 1H), 7.70 – 7.54 (m, 1H), 6.69 (d, ^3J (H,H) = 8.5 Hz, 1H), 6.23 (br s, 1H), 4.17 – 4.01 (m, 2H), 3.43 (q, ^3J (H,H) = 6.4 Hz, 2H), 2.58 – 2.42 (m, 2H), 2.20 – 2.02 (m, 2H), 1.74 – 1.59 (m, 2H), 1.46 (s, 9H), 1.41 – 1.15 (m, 18H), 0.96 – 0.79 (m, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 174.4 (C), 164.9 (C), 164.3 (C), 150.2 (C), 134.5 (CH), 131.1 (CH), 130.2 (C), 126.8 (C), 125.0 (CH), 123.6 (C), 120.8 (C), 110.5 (C), 104.1 (CH), 81.5 (C), 44.5 (CH_2), 40.4 (CH_2), 34.1 (CH_2), 32.3 (CH_2), 30.1 (CH_2), 30.1 (2×CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 28.6 (CH_2), 28.3 (3×CH_3), 27.6 (CH_2), 23.6 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 524 (100, $[M+H]^+$), 467 (80, $[M–t\text{Bu}+H]^+$).

Compound 7a. This compound was obtained as a yellow solid following **Method D** (50%). Mp: 139 – 140 °C; IR (neat): 3382 (w), 2918 (m), 2850 (w), 1703 (m), 1686 (m), 1627 (s), 1609 (m), 1588 (s), 1553 (m), 1467 (w), 1429 (w), 1398 (m), 1356 (m), 1304 (m), 1245 (w), 1185 (m), 1117 (s), 947 (w), 883 (w), 827 (w), 771 (s), 757 (m), 722 (w), 662 (w), 581 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.48 (dd, ^3J (H,H) = 7.3 Hz, ^4J (H,H) = 0.8 Hz, 1H),

8.39 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.10 (dd, ^{3}J (H,H) = 8.4 Hz, ^{4}J (H,H) = 0.8 Hz, 1H), 7.54 (dd, ^{3}J (H,H) = 8.4 Hz, ^{3}J (H,H) = 7.3 Hz, 1H), 6.69 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 5.91 (br s, 1H), 4.16 – 4.00 (m, 2H), 3.47 (t, ^{3}J (H,H) = 6.5 Hz, 2H), 2.64 (t, ^{3}J (H,H) = 6.6 Hz, 2H), 2.25 – 2.06 (m, 2H), 1.76 – 1.57 (m, 2H), 1.51 – 1.15 (m, 18H), 0.87 (t, ^{3}J (H,H) = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 177.6 (C), 164.9 (C), 164.3 (C), 149.9 (C), 134.5 (CH), 131.2 (CH), 130.1 (C), 126.5 (C), 125.0 (CH), 123.5 (C), 120.7 (C), 110.7 (C), 104.4 (CH), 44.0 (CH_2), 40.5 (CH_2), 32.3 (CH_2), 32.1 (CH_2), 30.1 (CH_2), 30.1 (2×CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 28.6 (CH_2), 27.6 (CH_2), 23.6 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 490 (10, $[M+Na]^+$), 467 (100, $[M+H]^+$).

Compound 23. This compound was prepared by **Method C**. Purification of the crude product by a column chromatography (pentane/AcOEt 8:2, R_f: 0.2) and precipitation from CH_2Cl_2 upon addition of hexane afforded **23** as a yellow solid (79%). Mp: 90 – 91 °C; IR (neat): 3371 (w), 2923 (m), 2853 (w), 1728 (m), 1684 (m), 1638 (s), 1577 (s), 1546 (s), 1464 (w), 1430 (w), 1394 (m), 1349 (s), 1328 (m), 1298 (w), 1245 (m), 1152 (s), 1102 (w), 1054 (w), 958 (w), 899 (w), 845 (w), 821 (w), 774 (s), 758 (m),663 (w), 583 (w), 556 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.54 (d, ^{3}J (H,H) = 7.2 Hz, 1H), 8.41 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 8.13 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 7.63 (dd, ^{3}J (H,H) = 8.4 Hz, ^{3}J (H,H) = 7.2 Hz, 1H), 6.74 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 5.38 – 5.33 (m, 1H), 4.15 (t, ^{3}J (H,H) = 7.1 Hz, 2H), 3.41 (q, ^{3}J (H,H) = 6.7 Hz, 2H), 2.30 (t, ^{3}J (H,H) = 7.1 Hz, 2H), 2.03 – 1.88 (m, 2H), 1.88 – 1.71 (m, 2H), 1.56 (d, ^{3}J (H,H) = 7.5 Hz, 2H), 1.49 (q, ^{3}J (H,H) = 7.3 Hz, 2H), 1.41 (s, 9H), 1.37 – 1.20 (m, 16H), 0.88 (t, ^{3}J (H,H) = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 172.8 (C), 165.0 (C), 164.4 (C), 150.1 (C), 134.7 (CH), 131.4 (CH), 130.4 (C), 126.4 (CH), 125.1 (CH), 123.8 (C), 120.7 (C), 110.6 (C), 104.8 (CH), 80.4 (C), 44.3 (CH_2), 39.7 (CH_2), 33.7 (CH_2),

32.5 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 28.3 (3×CH_3), 27.7 (CH_2), 24.2 (CH_2), 23.3 (CH_2), 14.4 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 524 (70, $[M+H]^+$), 468 (100, $[M–t\text{Bu}+H]^+$).

Compound 7p. This compound was obtained as a yellow solid following **Method D** (79%). Mp: 134 – 135 °C; IR (neat): 3405 (w), 3127 (br), 2960 (w), 2927 (w), 2852 (w), 1715 (m), 1681 (s), 1639 (s), 1611 (m), 1580 (s), 1549 (s), 1467 (w), 1431 (w), 1395 (m), 1343 (s), 1301 (w), 1279 (w), 1211 (w), 1134 (w), 1056 (w), 924 (w), 893 (w), 820 (w), 772 (m), 758 (m), 722 (w), 657 (w), 627 (w), 581 (w), 553 (w); ^{1}H NMR (400 MHz, CD_2Cl_2 / DMSO-d_6 95:5): 8.53 (d, ^3J (H,H) = 6.6 Hz, 1H), 8.40 (d, ^3J (H,H) = 8.5 Hz, 1H), 8.25 (br d, ^3J (H,H) = 8.4 Hz, 1H), 7.70 – 7.54 (m, 1H), 6.73 (d, ^3J (H,H) = 8.5 Hz, 1H), 5.80 (br s, 1H), 4.17 (t, ^3J (H,H) = 7.1 Hz, 2H), 3.40 (q, ^3J (H,H) = 6.9 Hz, 2H), 2.35 (t, ^3J (H,H) = 7.5 Hz, 2H), 1.99 (quint, ^3J (H,H) = 7.5 Hz, 2H), 1.80 (quint, ^3J (H,H) = 7.1 Hz, 4H), 1.58 – 1.43 (m, 3H), 1.45 – 1.17 (m, 16H), 0.88 (t, ^3J (H,H) = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2 / DMSO-d_6 95:5): 175.1 (C), 165.0 (C), 164.3 (C), 150.3 (C), 134.7 (CH), 131.2 (CH), 126.9 (CH), 124.8 (CH), 123.5 (C), 120.7 (C), 112.3 (C), 104.5 (CH), 44.1 (CH_2), 39.6 (CH_2), 32.3 (CH_2), 32.1 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 27.6 (CH_2), 24.0 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 468 (100, $[M+H]^+$), 450 (80, $[M–O]^+$), 422 (50, $[M–COO]^+$).

Compound 26. This compound was prepared by **Method B**. Purification of the crude product by a column chromatography (pentane/AcOEt 8:2, R_f: 0.4) and precipitation from hexane afforded **26** as a yellow solid (72%). Mp: 113 – 114 °C; IR (neat): 3358 (w), 2967 (w), 2933 (w), 2861 (w), 1718 (m), 1681 (m), 1632 (s), 1571 (s), 1546 (s), 1472 (w), 1428

(w), 1386 (m), 1352 (s), 1299 (w), 1255 (m), 1160 (s), 1130 (m), 1115 (w), 1094 (w), 1057 (w), 976 (w), 834 (w), 774 (s), 759 (m), 669 (w), 609 (w), 580 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.52 (dd, ^{3}J (H,H) = 7.4 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 8.40 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 8.21 (dd, ^{3}J (H,H) = 8.3 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 7.62 (dd, ^{3}J (H,H) = 8.3 Hz, ^{3}J (H,H) = 7.4 Hz, 1H), 6.69 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 6.22 (br s, 1H), 4.19 – 4.02 (m, 2H), 3.43 (q, ^{3}J (H,H) = 6.4 Hz, 2H), 2.50 (t, ^{3}J (H,H) = 6.4 Hz, 3H), 2.11 (quint, ^{3}J (H,H) = 6.4 Hz, 2H), 1.73 – 1.60 (m, 2H), 1.46 (s, 9H), 1.47 – 1.32 (m, 2H), 0.96 (t, ^{3}J (H,H) = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 174.5 (C), 165.0 (C), 164.4 (C), 150.3 (C), 134.7 (CH), 131.3 (CH), 130.3 (C), 126.9 (CH), 125.1 (CH), 123.8 (C), 120.9 (C), 110.6 (C), 104.3 (CH), 81.6 (C), 44.6 (CH_2), 40.3 (CH_2), 34.2 (CH_2), 30.9 (CH_2), 28.4 (3×CH_3), 23.7 (CH_2), 21.0 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 442 (100, $[M+H]^+$), 356 (90, $[M-t\text{Bu}+H]^+$).

Compound 4a. This compound was obtained as a yellow solid following **Method D** (96%). Mp: 152 – 153 °C; IR (neat): 3336 (w), 2957 (w), 2934 (w), 2868 (w), 2868 (w), 1715 (w), 1673 (m), 1628 (m), 1611 (m), 1577 (s), 1548 (s), 1458 (w), 1433 (w), 1400 (m), 1373 (s), 1352 (s), 1305 (w), 1244 (m), 1203 (w), 1181 (s), 1158 (s), 1115 (m), 1078 (w), 1061 (w), 944 (w), 881 (w), 830 (w), 771 (s), 756 (m), 683 (w), 621 (w), 588 (w); ^{1}H NMR (400 MHz, CD_2Cl_2/DMSO-d_6 95:5): 8.58 – 8.46 (m, 1H), 8.39 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.27 (d, ^{3}J (H,H) = 7.8 Hz, 1H), 7.67 – 7.50 (m, 1H), 6.69 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 6.54 (br s, 1H), 4.18 – 4.01 (m, 2H), 3.44 (q, ^{3}J (H,H) = 6.2 Hz, 2H), 2.55 (t, ^{3}J (H,H) = 6.4 Hz, 2H), 2.12 (quint, ^{3}J (H,H) = 6.4 Hz, 2H), 1.66 (quint, ^{3}J (H,H) = 7.5 Hz, 2H), 1.41 (quint, ^{3}J (H,H) = 7.5 Hz, 2H), 0.96 (t, ^{3}J (H,H) = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2/DMSO-d_6 95:5): 176.8 (C), 165.0 (C), 164.4 (C), 150.5 (CH), 134.7 (CH), 131.2 (C), 130.4 (C),

127.3 (CH), 124.9 (CH), 123.6 (C), 121.0 (C), 110.3 (C), 104.3 (CH), 44.5 (CH_2), 40.2 (CH_2), 32.9 (CH_2), 30.8 (CH_2), 23.7 (CH_2), 21.0 (CH_2), 14.2 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 710 (20, $[2M+H]^+$), 356 (100, $[M+H]^+$).

Compound 27. This compound was prepared by **Method C**. Purification of the crude product by a column chromatography (pentane/AcOEt 9:1, R_f: 0.1) and precipitation from CH_2Cl_2 upon addition of hexane afforded **27** as a yellow solid (93%). Mp: 115 – 116 °C; IR (neat): 3403 (w), 2960 (w), 2930 (w), 2860 (w), 1725 (m), 1680 (m), 1634 (s), 1574 (s), 1544 (s), 1462 (w), 1430 (w), 1394 (m), 1366 (m), 1343 (s), 1299 (w), 1244 (w), 1216 (w), 1159 (s), 1145 (m), 1106 (w), 1076 (w), 1051 (w), 953 (w), 905 (w), 844 (w), 816 (w), 802 (w), 769 (m), 755 (m), 724 (w), 678 (w), 653 (w), 580 (w), 556 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.53 (dd, ^3J (H,H) = 7.3 Hz, ^4J (H,H) = 0.9 Hz, 1H), 8.41 (d, ^3J (H,H) = 8.5 Hz, 1H), 8.12 (dd, ^3J (H,H) = 7.8 Hz, ^4J (H,H) = 0.9 Hz, 1H), 7.63 (dd, ^3J (H,H) = 7.8 Hz, ^3J (H,H) = 7.3 Hz, 1H), 6.74 (d, ^3J (H,H) = 8.5 Hz, 1H), 5.34 – 5.32 (m, 1H), 4.15 (t, ^3J (H,H) = 7.5 Hz, 2H), 3.51 – 3.33 (m, 2H), 2.30 (t, ^3J (H,H) = 7.5 Hz, 2H), 1.96 (quint, ^3J (H,H) = 7.5 Hz, 2H), 1.80 (quint, ^3J (H,H) = 7.4 Hz, 2H), 1.62 – 1.47 (m, 2H), 1.41 (s, 9H), 1.02 (t, ^3J (H,H) = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 172.8 (C), 165.0 (C), 164.4 (C), 150.1 (C), 134.7 (CH), 131.4 (CH), 130.4 (C), 126.4 (CH), 125.1 (CH), 123.8 (C), 120.7 (C), 110.7 (C), 104.8 (CH), 80.4 (C), 44.0 (CH_2), 39.7 (CH_2), 33.8 (CH_2), 31.6 (CH_2), 28.4 (3×CH_3), 24.2 (CH_2), 20.9 (CH_2), 14.2 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 411 (100, $[M+H]^+$), 356 (80, $[M–t\text{Bu}]^+$), 338 (100, $[M–O t\text{Bu}]^+$), 310 (80, $[M–t\text{Bu}–C_4H_9N]^+$).

Compound 4p. This compound was obtained as a yellow solid following **Method D** (75%). Mp: 168 – 169 °C; IR (neat): 3347 (w), 2947 (w), 2864 (w), 2619 (w), 1734 (m),

1685 (m), 1623 (w), 1604 (s), 1581 (s), 1553 (s), 1468 (w), 1430 (w), 1357 (s), 1341 (s), 1247 (w), 1223 (w), 1184 (w), 1143 (m), 1119 (w), 1099 (w), 1057 (w), 962 (w), 893 (w), 819 (w), 773 (s), 756 (m), 658 (w), 600 (w); ^{1}H NMR (400 MHz, THF-d_8): 8.48 (dd, ^{3}J (H,H) = 7.4 Hz, ^{4}J (H,H) = 0.9 Hz, 2H), 8.39 (dd, ^{3}J (H,H) = 8.3 Hz, ^{4}J (H,H) = 0.9 Hz, 2H), 8.35 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 7.57 (dd, ^{3}J (H,H) = 8.3 Hz, ^{3}J (H,H) = 7.4 Hz, 1H), 6.76 (d, ^{3}J (H,H) = 8.5 Hz, 2H), 6.74 (br s, 1H), 4.15 (t, ^{3}J (H,H) = 7.0 Hz, 2H), 3.43 (q, ^{3}J (H,H) = 7.1 Hz, 2H), 2.30 (t, ^{3}J (H,H) = 7.7 Hz, 2H), 1.96 (quint, ^{3}J (H,H) = 7.2 Hz, 2H), 1.83 – 1.75 (m, 4H), 1.52 (quint, ^{3}J (H,H) = 7.4 Hz, 2H), 1.00 (t, ^{3}J (H,H) = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, THF-d_8): 174.3 (C), 165.0 (C), 164.2 (C), 151.3 (C), 135.0 (CH), 131.4 (CH), 131.1 (C), 127.9 (CH), 125.0 (CH), 124.3 (C), 121.8 (C), 110.7 (C), 104.7 (CH), 44.3 (CH_2), 39.8 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 25.6 (CH_2), 21.4 (CH_2), 14.4 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 710 (20, $[2M+H]^+$), 356 (100, $[M+H]^+$).

Compound 30. This compound was prepared by **Method B**. Purification of the crude product by a column chromatography (pentane/AcOEt 8:2, R_f: 0.4) and precipitation from hexane afforded **30** as a yellow solid (24%). Mp: 120 – 121 °C; IR (neat): 3338 (w), 2931 (w), 2865 (w), 1732 (m), 1683 (m), 1637 (s), 1575 (s), 1545 (s), 1449 (w), 1426 (w), 1393 (m), 1348 (s), 1317 (w), 1299 (w), 1245 (m), 1206 (w), 1147 (s), 1117 (m), 1087 (w), 1023 (w), 959 (w), 907 (w), 844 (w), 820 (w), 772 (m), 756 (m), 726 (w), 653 (w), 581 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.53 (dd, ^{3}J (H,H) = 7.3 Hz, ^{4}J (H,H) = 0.8 Hz, 1H), 8.40 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.22 – 8.20 (m, 1H), 7.62 (dd, ^{3}J (H,H) = 8.5 Hz, ^{3}J (H,H) = 7.3 Hz, 1H), 6.69 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 6.23 (br s, 1H), 4.09 (t, ^{3}J (H,H) = 7.4 Hz, 2H), 3.51 – 3.35 (m, 3H), 2.57 – 2.42 (m, 2H), 2.11 (quint, ^{3}J (H,H) = 6.3 Hz, 2H), 1.66 (d, ^{3}J (H,H) = 7.4 Hz, 2H), 1.46 (s, 9H), 1.44 – 1.23 (m, 6H), 0.97 – 0.81 (m, 3H); ^{13}C NMR (126 MHz,

CD_2Cl_2): 174.4 (C), 164.9 (C), 164.3 (C), 150.1 (C), 134.5 (CH), 131.1 (CH), 130.2 (C), 126.8 (CH), 125.0 (CH), 123.6 (C), 120.7 (C), 110.5 (C), 104.1 (CH), 81.5 (C), 44.5 (CH_2), 40.4 (CH_2), 34.1 (CH_2), 32.1 (CH_2), 28.5 (CH_2), 28.3 (3×CH_3), 27.3 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 439 (100, $[M+H]^+$), 383 (30, [M–*t*Bu+H]$^+$).

Compound 5a. This compound was obtained as a yellow solid following **Method D** (95%). Mp: 152 – 153 °C; IR (neat): 3346 (w), 2947 (w), 2864 (w), 2619 (br), 1734 (w), 1685 (m), 1624 (m), 1604 (m), 1581 (s), 1553 (s), 1467 (w), 1430 (w), 1400 (m), 1356 (s), 1341 (s), 1247 (s),1223 (m), 1198 (w), 1183 (w), 1142 (m), 1119 (w), 1099 (w), 1056 (w), 962 (w), 893 (w), 819 (w), 773 (s), 757 (m), 659 (w), 600 (w); ^{1}H NMR (400 MHz, CD_2Cl_2/DMSO-d_6 95:5): 8.51 (d, ^3J (H,H) = 7.3 Hz, 1H), 8.38 (d, ^3J (H,H) = 8.5 Hz, 1H), 8.34 (br d, ^3J (H,H) = 4.3 Hz, 1H), 7.66 – 7.51 (m, 1H), 6.70 (d, ^3J (H,H) = 8.5 Hz, 1H), 4.09 (t, ^3J (H,H) = 7.4 Hz, 2H), 3.45 (q, ^3J (H,H) = 6.2 Hz, 3H), 2.62 – 2.45 (m, 4H), 2.20 – 1.95 (m, 2H), 1.67 (quint, ^3J (H,H) = 7.4 Hz, 2H), 1.50 – 1.24 (m, 6H), 0.89 (t, ^3J (H,H) = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2/DMSO-d_6 95:5): 176.5 (C), 164.9 (C), 164.2 (C), 150.5 (C), 134.6 (CH), 131.0 (CH), 130.3 (C), 127.5 (C), 124.7 (CH), 123.4 (C), 120.9 (C), 110.0 (C), 104.1 (CH), 44.2 (CH_2), 40.3 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 28.5 (CH_2), 27.3 (CH_2), 23.6 (CH_2), 23.0 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 384 (100, $[M+H]^+$).

Compound 31. This compound was prepared by **Method C**. The crude product was purified twice by column chromatography (pentane/AcOEt 7:3, R_f: 0.5; CH_2Cl_2/MeOH 97:3, R_f: 0.2) and precipitation from CH_2Cl_2 upon addition of hexane to give **31** as a yellow solid (70%). Mp: 103 – 104 °C; IR (neat): 3403 (w), 2961 (w), 2930 (w), 2860 (w), 1725 (m),

1680 (m), 1634 (s), 1574 (s), 1544 (s), 1462 (w), 1431 (w), 1394 (m), 1365 (m), 1343 (s), 1299 (w), 1244 (w), 1216 (w), 1159 (s), 1145 (s), 1106 (w), 1051 (w), 953 (w), 905 (w), 844 (w), 817 (w), 769 (m), 755 (m), 724 (w), 678 (w), 653 (w), 580 (w), 557 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.54 (d, ^{3}J (H,H) = 7.2 Hz, 1H), 8.41 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 8.13 (d, ^{3}J (H,H) = 8.3 Hz, 1H), 7.63 (dd, ^{3}J (H,H) = 8.3 Hz, ^{3}J (H,H) = 7.2 Hz, 1H), 6.74 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 5.34 (br s, 1H), 4.15 (t, ^{3}J (H,H) = 7.3 Hz, 2H), 3.41 (q, ^{3}J (H,H) = 6.8 Hz, 2H), 2.30 (t, ^{3}J (H,H) = 7.3 Hz, 2H), 1.96 (quint, ^{3}J (H,H) = 7.3 Hz, 2H), 1.81 (quint, ^{3}J (H,H) = 7.4 Hz, 2H), 1.54 – 1.45 (m, 2H), 1.41 (s, 9H), 0.92 (t, ^{3}J (H,H) = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 172.6 (C), 164.9 (C), 164.3 (C), 150.0 (C), 134.6 (CH), 131.2 (CH), 130.2 (C), 126.3 (CH), 125.0 (CH), 123.6 (C), 120.6 (C), 110.5 (C), 104.6 (CH), 80.3 (C), 44.2 (CH_2), 39.6 (CH_2), 33.6 (CH_2), 32.0 (CH_2), 29.3 (CH_2), 28.2 (3×CH_2), 27.2 (CH_2), 24.1 (CH_2), 23.0 (CH_2), 14.2 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 493 (95, $[M+H]^+$), 383 (100, $[M–t\text{Bu}+H]^+$).

Compound 5p. This compound was obtained as a yellow solid following **Method D** (93%). Mp: 156 – 157 °C; IR (neat): 3392 (w), 2923 (w), 2856 (w), 1710 (m), 1680 (m), 1667 (m), 1626 (m), 1580 (s), 1546 (s), 1469 (w), 1432 (w), 1398 (m), 1380 (m), 1354 (m), 1334 (m), 1302 (w), 1254 (m), 1208 (m), 1135 (m), 1098 (w), 1057 (w), 943 (w), 894 (w), 853 (w), 816 (w), 771 (m), 757 (m), 736 (w), 677 (w), 664 (w), 578 (w); ^{1}H NMR (500 MHz, CD_2Cl_2/DMSO-d_6 95:5): 8.55 (dd, ^{3}J (H,H) = 7.4 Hz, ^{4}J (H,H) = 1.0 Hz, 1H), 8.42 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 8.18 (dd, ^{3}J (H,H) = 8.4 Hz, ^{4}J (H,H) = 1.0 Hz, 1H), 7.63 (dd, ^{3}J (H,H) = 8.4 Hz, ^{3}J (H,H) = 7.4 Hz, 1H), 6.74 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 5.52 (br s 1H), 4.18 (t, ^{3}J (H,H) = 7.0 Hz, 3H), 3.49 – 3.33 (m, 2H), 2.37 (t, ^{3}J (H,H) = 7.5 Hz, 2H), 2.00 (quint, ^{3}J (H,H) = 7.3 Hz, 4H), 1.87 – 1.62 (m, 2H), 1.58 – 1.44 (m, 2H), 1.44 – 1.31 (m, 4H), 0.99 –

0.86 (m, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2/DMSO-d_6 95:5): 175.0 (C), 165.0 (C), 164.4 (C), 150.2 (C), 134.7 (CH), 131.3 (CH), 130.3 (C), 126.6 (C), 124.9 (CH), 123.5 (CH), 120.6 (C), 110.2 (C), 104.6 (CH), 44.2 (CH_2), 39.5 (CH_2), 32.0 (2xCH_2), 29.3 (CH_2), 27.2 (CH_2), 24.0 (CH_2), 23.0 (CH_2), 14.2 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 406 (40, $[M+Na]^+$), 384 (100, $[M+H]^+$), 366 (50, $[M–OH]^+$).

Compound 34. This compound was prepared by **Method B**. The crude product was purified twice by column chromatography (pentane/AcOEt 8:2; CH_2Cl_2/MeOH 98:2, R_f: 0.1) and precipitation from hexane afforded **34** as a yellow solid (36%). Mp: 91 – 92 °C; IR (neat): 3384 (w), 2923 (w), 2853 (w), 1724 (m), 1685 (m), 1635 (s), 1578 (s), 1545 (s), 1464 (w), 1426 (w), 1397 (m), 1357 (s), 1297 (w), 1241 (w), 1210 (w), 1149 (s), 1115 (m), 1083 (w), 900 (w), 845 (w), 775 (m), 757 (m), 662 (w) 583 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.52 (d, ^3J (H,H) = 7.2 Hz, 1H), 8.39 (d, ^3J (H,H) = 8.4 Hz, 1H), 8.21 (d, ^3J (H,H) = 8.4 Hz, 1H), 7.61 (dd, ^3J (H,H) = 8.4 Hz, ^3J (H,H) = 7.2 Hz, 1H), 6.68 (d, ^3J (H,H) = 8.4 Hz, 1H), 6.24 (br s, 1H), 4.18 – 3.99 (m, 2H), 3.43 (q, ^3J (H,H) = 6.0 Hz, 2H), 2.50 (t, ^3J (H,H) = 6.3 Hz, 2H), 2.10 (quint, ^3J (H,H) = 6.2 Hz, 2H), 1.65 (quint, ^3J (H,H) = 8.4 Hz, 2H), 1.46 (s, 9H), 1.40 – 1.14 (m, 10H), 0.87 (t, ^3J (H,H) = 5.5 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 174.3 (C), 164.9 (C), 164.3 (C), 150.2 (C), 134.5 (CH), 131.1 (CH), 130.2 (C), 126.8 (C), 125.0 (CH), 123.6 (C), 120.8 (C), 110.5 (C), 104.1 (CH), 81.5 (C), 44.4 (CH_2), 40.4 (CH_2), 34.0 (CH_2), 32.3 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 28.6 (CH_2), 28.3 (3×CH_3), 27.6 (CH_2), 23.6 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 468 (100, $[M+H]^+$), 412 (50, $[M–t\text{Bu}+H]^+$).

Compound 6a. This compound was obtained as a yellow solid following **Method D** (90%). Mp: 91 – 92 °C; IR (neat): 3371 (w), 2953 (w), 2924 (w), 2858 (w), 1703 (s), 1689 (s), 1626 (s), 1612 (m), 1585 (s), 1560 (m), 1466 (w), 1428 (w), 1397 (m), 1350 (s), 1244 (m), 1203 (m), 1118 (m), 1068 (w), 1046 (w), 990 (w), 887 (w), 828 (w), 771 (s), 757 (m), 722 (w), 655 (w), 586 (w), 566 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.47 (d, ^{3}J (H,H) = 7.3 Hz, 1H), 8.38 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 8.10 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 7.53 (dd, ^{3}J (H,H) = 8.4 Hz, ^{3}J (H,H) = 7.3 Hz, 1H), 6.69 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 5.91 (br s, 1H), 4.08 (t, ^{3}J (H,H) = 7.5 Hz, 2H), 3.46 (t, ^{3}J (H,H) = 6.5 Hz, 2H), 2.64 (t, ^{3}J (H,H) = 6.5 Hz, 2H), 2.15 (quint, ^{3}J (H,H) = 6.5 Hz, 2H), 1.67 (quint, ^{3}J (H,H) = 7.5 Hz, 2H), 1.48 – 1.15 (m, 10H), 0.87 (t, ^{3}J (H,H) = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 177.5 (C), 164.9 (C), 164.3 (C), 149.9 (C), 134.5 (CH), 131.2 (CH), 130.1 (C), 126.5 (CH), 125.0 (CH), 123.5 (C), 120.7 (C), 110.7 (C), 104.4 (CH), 44.0 (CH_2), 40.5 (CH_2), 32.3 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 28.6 (CH_2), 27.6 (CH_2), 23.6 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 412 (100, $[M+H]^+$), 300 (50, $[M–C_8H_{17}]^+$).

Compound 35. This compound was prepared by **Method C**. Purification of the crude product by a column chromatography (pentane/AcOEt 9:1, R_f: 0.3) and precipitation from CH_2Cl_2 upon addition of hexane afforded **35** as a yellow solid (80%). Mp: 110-112 °C; IR (neat): 3410 (w), 2925 (w), 2854 (w), 1724 (m), 1678 (m), 1641 (s), 1615 (w), 1574 (s), 1541 (s), 1461 (w), 1424 (w), 1395 (m), 1372 (m), 1346 (s), 1299 (w), 1246 (w), 1222 (w), 1142 (s), 1099 (m), 1049 (w), 957 (w), 844 (w), 794 (w), 769 (m), 755 (s), 655 (w), 580 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.54 (dd, ^{3}J (H,H) = 7.3 Hz, ^{4}J (H,H) = 0.8 Hz, 1H), 8.41 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.12 (d, ^{3}J (H,H) = 7.8 Hz, 1H), 7.63 (dd, ^{3}J (H,H) = 7.8 Hz, ^{3}J (H,H) = 7.3 Hz, 1H), 6.74 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 5.33 (br s, 1H), 4.23 – 4.06 (m, 2H), 3.49 – 3.32

(m, 2H), 2.30 (t, ^{3}J (H,H) = 7.6 Hz, 2H), 2.06 – 1.89 (m, 2H), 1.89 – 1.71 (m, 2H), 1.53 – 1.41 (m, 2H), 1.41 (s, 9H), 1.38 – 1.16 (m, 8H), 0.97 – 0.80 (m, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 172.6 (C), 164.9 (C), 164.3 (C), 150.0 (C), 134.6 (CH), 131.2 (CH), 130.2 (C), 126.2 (CH), 125.0 (CH), 123.6 (C), 120.6 (C), 110.5 (C), 104.6 (CH), 80.3 (C), 44.2 (CH_2), 39.6 (CH_2), 33.6 (CH_2), 32.2 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 28.2 (3×CH_3), 27.6 (CH_2), 24.1 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 468 (50, $[M+H]^+$), 412 (80, $[M–t\text{Bu}+H]^+$), 394 (100, $[M–O t\text{Bu}]^+$), 366 (80, $[M–\text{COO}t\text{Bu}]^+$), 338 (80, $[M–C_8H_{19}N]^+$).

Compound 6p. This compound was obtained as a yellow solid following **Method D** (86%). Mp: 129 – 130 °C; IR (neat): 3390 (w), 2923 (w), 2853 (w), 1707 (m), 1668 (m), 1625 (m), 1584 (s), 1547 (m), 1470 (w), 1432 (m), 1399 (w), 1381 (m), 1336 (m), 1259 (m), 1211 (w), 1138 (m), 1098 (w), 1056 (w), 944 (w), 898 (w), 770 (m), 756 (m), 678 (w), 583 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.55 (dd, ^{3}J (H,H) = 7.3 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 8.43 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.16 (dd, ^{3}J (H,H) = 8.4 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 7.63 (t, ^{3}J (H,H) = 8.4 Hz, ^{3}J (H,H) = 7.3 Hz, 1H), 6.75 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 5.46 (br s, 1H), 4.20 (t, ^{3}J (H,H) = 6.8 Hz, 2H), 3.41 (t, ^{3}J (H,H) = 7.0 Hz, 2H), 2.40 (t, ^{3}J (H,H) = 7.0 Hz, 2H), 2.02 (quint, ^{3}J (H,H) = 7.0 Hz, 2H), 1.81 (quint, ^{3}J (H,H) = 7.3 Hz, 2H), 1.59 – 1.43 (m, 2H), 1.43 – 1.20 (m, 8H), 0.97 – 0.80 (m, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 176.4 (C), 165.2 (C), 164.6 (C), 150.3 (C), 134.9 (CH), 131.5 (CH), 130.3 (C), 126.6 (CH), 125.0 (CH), 123.4 (C), 120.6 (C), 110.1 (C), 104.7 (CH), 44.2 (CH_2), 39.4 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 27.6 (CH_2), 23.9 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 412 (100, $[M+H]^+$), 394 (80, $[M–O]^+$), 365 (100, $[M–\text{COO}]^+$).

Compound 38. This compound was prepared by **Method B**. Purification of the crude product by column chromatography twice (pentane/AcOEt 9:1, R_f: 0.3) and precipitation from CH_2Cl_2 upon addition of hexane afforded **38** as a yellow solid (61%). Mp: 79 – 80 °C; IR (neat): 3386 (w), 2920 (w), 2851 (w), 1732 (m), 1684 (m), 1637 (s), 1675 (s), 1544 (s), 1461 (w), 1426 (w), 1393 (m), 1351 (s), 1298 (w), 1244 (m), 1148 (s), 1117 (m), 1069 (w), 965 (w), 846 (w), 771 (m), 756 (m), 720 (w), 666 (w), 582 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.52 (d, ^3J (H,H) = 7.3 Hz, 1H), 8.39 (d, ^3J (H,H) = 8.5 Hz, 1H), 8.21 (d, ^3J (H,H) = 8.4 Hz, 1H), 7.61 (dd, ^3J (H,H) = 8.4 Hz, ^3J (H,H) = 7.3 Hz, 1H), 6.68 (d, ^3J (H,H) = 8.5 Hz, 1H), 6.24 (br s, 1H), 4.18 – 4.00 (m, 2H), 3.43 (q, ^3J (H,H) = 6.4 Hz, 2H), 2.59 – 2.41 (m, 2H), 2.10 (quint, ^3J (H,H) = 6.4 Hz, 2H), 1.67 (quint, ^3J (H,H) = 7.5 Hz, 2H), 1.46 (s, 9H), 1.42 – 1.16 (m, 30H), 0.87 (t, ^3J (H,H) = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 174.5 (C), 165.0 (C), 164.4 (C), 150.3 (C), 134.7 (CH), 131.2 (CH), 130.3 (C), 126.9 (C), 125.1 (CH), 123.7 (C), 120.9 (C), 110.6 (C), 104.3 (CH), 81.6 (C), 44.6 (CH_2), 40.5 (CH_2), 34.2 (CH_2), 32.5 (CH_2), 30.3 (6×CH_2), 30.2 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 28.8 (CH_2), 28.4 (3×CH_3), 27.8 (CH_2), 23.7 (CH_2), 23.3 (CH_2), 14.5 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 607 (100, $[M+H]^+$), 552 (20, $[M–t\text{Bu}+H]^+$).

Compound 8a. This compound was obtained as a yellow solid following **Method D** (92%). Mp: 136 – 137 °C; IR (neat): 3380 (w), 3090 (br), 2953 (w), 2916 (s), 2850 (s), 1710 (m), 1687 (s), 1624 (m), 1590 (s), 1552 (m), 1470 (w), 1430 (w), 1399 (m), 1361 (m), 1301 (w), 1245 (w), 1224 (w), 1182 (m), 1112 (m), 1069 (w), 942 (w), 862 (w), 825 (w), 772 (m), 758 (m), 716 (m), 682 (w), 606 (w), 582 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.50 (d, ^3J (H,H) = 7.3 Hz, 1H), 8.39 (d, ^3J (H,H) = 8.5 Hz, 1H), 8.12 (d, ^3J (H,H) = 8.4 Hz, 1H), 7.57 (dd, ^3J (H,H) = 8.4 Hz, ^3J (H,H) = 7.3 Hz, 1H), 6.71 (d, ^3J (H,H) = 8.5 Hz, 1H), 5.91 (br s, 1H), 4.17

– 4.00 (m, 2H), 3.48 (t, ^{3}J (H,H) = 6.2 Hz, 2H), 2.64 (t, ^{3}J (H,H) = 6.6 Hz, 2H), 2.16 (quint, ^{3}J (H,H) = 6.6 Hz, 2H), 1.87 – 1.57 (m, 2H), 1.44 – 1.14 (m, 30H), 0.87 (t, ^{3}J (H,H) = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): 176.4 (C), 170.2 (C), 164.9 (C), 164.2 (C), 149.9 (C), 134.5 (CH), 131.1 (CH), 130.1 (C), 126.5 (CH), 125.1 (CH), 123.6 (C), 120.7 (C), 110.8 (C), 104.4 (CH), 44.0 (CH_2), 40.4 (CH_2), 32.3 (CH_2), 31.8 (CH_2), 30.1 (5×CH_2), 30.1 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 28.6 (CH_2), 27.6 (CH_2), 23.6 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 574 (10, $[M+Na]^+$), 552 (100, $[M+H]^+$).

Compound 39. This compound was prepared by **Method C**. Purification of the crude product by a gradient column chromatography (CH_2Cl_2/MeOH 99:1, R_f: 0.3) and precipitation from CH_2Cl_2 upon addition of hexane afforded **39** as a yellow solid (quant.); Mp: 66 – 67 °C; IR (neat): 3401 (w), 2919 (s), 2949 (s), 1707 (m), 1686 (m), 1644 (s), 1583 (s), 1543 (m), 1469 (w), 1428 (w), 1384 (m), 1355 (s), 1277 (m), 1244 (m), 1154 (s), 1129 (m), 1097 (w), 1053 (w), 1031 (w), 987 (w), 961 (w), 844 (w), 776 (s), 757 (m), 721 (m), 677 (w), 581 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.54 (dd, ^{3}J (H,H) = 7.3 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 8.41 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.12 (dd, ^{3}J (H,H) = 8.3 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 7.63 (dd, ^{3}J (H,H) = 8.3 Hz, ^{3}J (H,H) = 7.3 Hz, 1H), 6.74 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 5.34 (br s, 1H), 4.15 (d, ^{3}J (H,H) = 7.6 Hz, 2H), 3.49 – 3.32 (m, 2H), 2.30 (t, ^{3}J (H,H) = 7.6 Hz, 2H), 1.96 (quint, ^{3}J (H,H) = 7.6 Hz, 2H), 1.81 (quint, ^{3}J (H,H) = 7.3 Hz, 2H), 1.51 – 1.43 (m, 2H), 1.41 (s, 9H), 1.36 – 1.16 (m, 28H), 0.96 – 0.79 (m, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 172.6 (C), 164.9 (C), 164.3 (C), 150.0 (C), 134.6 (CH), 131.2 (CH), 130.2 (C), 126.2 (CH), 125.0 (CH), 123.6 (C), 120.6 (C), 110.5 (C), 104.6 (CH), 80.3 (C), 44.2 (CH_2), 39.6 (CH_2), 33.6 (CH_2), 32.3 (CH_2), 30.1 (8×CH_2), 30.1 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.3

(CH_2), 28.2 (3×CH_3), 27.6 (CH_2), 24.1 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 608 (80, $[M+H]^+$), 552 (100, $[M–t\text{Bu}]^+$).

Compound 8p. This compound was obtained as a yellow solid following **Method D** (79%). Mp: 124 – 125 °C; IR (neat): 3341 (w), 3371 (w), 3100 (br), 2917 (m), 2850 (w), 1716 (m), 1684 (m), 1639 (m), 1612 (m), 1584 (s), 1552 (m), 1468 (w), 1430 (w), 1397 (m), 1347 (s), 1303 (w), 1249 (m), 1203 (w), 1119 (m), 1058 (w), 893 (w), 829 (w), 771 (s), 758 (m), 721 (w), 657 (w), 627 (w), 586 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.55 (d, ^3J (H,H) = 7.3 Hz, 1H), 8.43 (d, ^3J (H,H) = 8.5 Hz, 1H), 8.16 (d, ^3J (H,H) = 8.4 Hz, 1H), 7.63 (dd, ^3J (H,H) = 8.4 Hz, ^3J (H,H) = 7.3 Hz, 1H), 6.75 (d, ^3J (H,H) = 8.5 Hz, 1H), 5.45 (br s, 1H), 4.20 (t, ^3J (H,H) = 6.7 Hz, 2H), 3.41 (t, ^3J (H,H) = 5.0 Hz, 2H), 2.40 (t, ^3J (H,H) = 7.2 Hz, 2H), 2.03 (quint, ^3J (H,H) = 7.1 Hz, 2H), 1.81 (quint, ^3J (H,H) = 7.3 Hz, 2H), 1.59 – 1.42 (m, 2H), 1.43 – 1.17 (m, 2H), 1.33 – 1.20 (m, 26H), 0.88 (t, ^3J (H,H) = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 176.1 (C), 165.2 (C), 164.6 (C), 150.3 (C), 134.9 (CH), 131.5 (CH), 130.3 (C), 126.6 (CH), 125.0 (CH), 123.4 (C), 120.6 (C), 110.1 (C), 104.7 (CH), 44.2 (CH_2), 39.4 (CH_2), 32.3 (CH_2), 31.8 (CH_2), 30.1 (7×CH_2), 30.1 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.8 (2×CH_2), 29.3 (CH_2), 27.6 (CH_2), 23.9 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 552 (100, $[M+H]^+$), 534 (50, $[M–O]^+$), 506 (20, $[M–COO]^+$).

Compound 41. This compound was prepared by **Method A**. Column chromatographic purifications of the crude mixture (pentane/AcOEt 8:2, R_f: 0.3) afforded **41** (77%). Mp: 42 – 44 °C; IR (neat): 3390 (w), 3354 (w), 3093 (br w), 2940 (w), 1703 (s), 1640 (s), 1592 (s), 1555 (w), 1402 (m), 1362 (m), 1237 (w), 1194 (s), 1142 (s), 1117 (m), 1090 (w), 1052 (w), 1017 (w), 990 (w), 859 (w), 827 (w), 795 (w), 770 (m), 754 (m), 701 (w), 646 (w), 591 (w),

569 (w); ^{1}H NMR (400 MHz, $CDCl_3$): 8.65 (d, ^{3}J (H,H) = 7.2 Hz, 1H), 8.56 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 8.41 (d, ^{3}J (H,H) = 7.6 Hz, 1H), 8.03 (d, ^{3}J (H,H) = 7.6 Hz, 1H), 7.84 (dd, ^{3}J (H,H) = 8.4 Hz, ^{3}J (H,H) = 7.2 Hz, 1H), 5.55 – 5.16 (m, 2H), 4.25 – 4.04 (m, 2H), 2.12 – 1.84 (m, 4H), 1.71 (q, ^{3}J (H,H) = 7.5 Hz, 2H), 1.48 – 1.00 (m, 22H), 0.87 (t, ^{3}J (H,H) = 6.1 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 164.0 (C), 164.0 (C), 133.5 (CH), 132.3 (CH), 131.7 (CH), 131.5 (CH), 131.2 (C), 130.4 (CH), 130.4 (CH), 129.5 (C), 128.6 (CH), 123.9 (C), 123.1 (C), 41.0 (CH_2), 33.2 (CH_2), 32.5 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (2×CH_2), 28.6 (CH_2), 27.7 (CH_2), 27.7 (CH_2), 23.3 (CH_2), 14.4 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 527 (100, $[M+H]^+$).

Compound 42. This compound was prepared by **Method B**. Purification of the crude product by a column chromatography (pentane/AcOEt 9:1; R_f: 0.4 with pentane/AcOEt 8:2) afforded **42** as a yellow liquid (78%). IR (neat): 3385 (w), 2923 (m), 2853 (m), 1729 (w), 1686 (m), 1641 (s), 1577 (s), 1545 (s), 1462 (w), 1430 (w), 1393 (m), 1350 (s), 1298 (w), 1151 (s), 1128 (m), 1053 (w), 964 (w), 899 (w), 844 (w), 774 (s), 758 (m), 661 (w), 583 (w); ^{1}H NMR (400 MHz, $CDCl_3$): 8.64 – 8.52 (m, 1H), 8.45 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 8.19 (d, ^{3}J (H,H) = 7.7 Hz, 1H), 7.67 – 7.57 (m, 1H), 6.66 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 5.44 – 5.24 (m, 2H), 4.22 – 4.06 (m, 2H), 3.43 (t, ^{3}J (H,H) = 6.3 Hz, 2H), 2.59 – 2.32 (m, 2H), 2.22 – 2.07 (m, 2H), 2.04 – 1.90 (m, 4H), 1.70 (d, ^{3}J (H,H) = 7.3 Hz, 2H), 1.48 (s, 9H), 1.40 – 1.15 (m, 22H), 0.87 (t, ^{3}J (H,H) = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): 174.3 (C), 164.9 (C), 164.3 (C), 149.8 (C), 134.6 (CH), 131.2 (CH), 130.1 (CH), 130.0 (CH), 130.0 (C), 126.5 (CH), 124.8 (CH), 123.3 (C), 120.5 (C), 110.4 (C), 104.0 (CH), 81.6 (C), 44.3 (CH_2), 40.4 (CH_2), 34.0 (CH_2), 32.8 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (2×CH_2), 28.4 (CH_2), 28.3 (3×CH_3), 27.4 (CH_2),

23.2 (CH_2), 22.8 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 606 (100, $[M+H]^+$), 549 (100, $[M–t\text{Bu}]^+$).

Compound 9a. This compound was obtained as a yellow solid following **Method D** (75%). Mp: 107 – 108 °C; IR (neat): 3377 (w), 3100 (br), 2922 (s), 2853 (m), 1704 (s), 1687 (m), 1627 (m), 1611 (m), 1589 (s), 1554 (m), 1462 (w), 1431 (m), 1398 (w), 1357 (m), 1305 (w), 1246 (m), 1185 (m), 1117 (m), 1072 (w), 968 (w), 881 (w), 828 (w), 772 (s), 758 (m), 722 (w), 662 (w), 584 (w); ^{1}H NMR (500 MHz, $CDCl_3$): 8.56 (d, ^3J (H,H) = 7.2 Hz, 1H), 8.45 (d, ^3J (H,H) = 8.4 Hz, 1H), 8.26 (d, ^3J (H,H) = 8.3 Hz, 1H), 7.57 (dd, ^3J (H,H) = 8.3 Hz, ^3J (H,H) = 7.2 Hz, 1H), 6.68 (d, ^3J (H,H) = 8.4 Hz, 1H), 6.56 (br s, 1H), 5.47 – 5.23 (m, 2H), 4.14 (t, ^3J (H,H) = 7.4 Hz, 2H), 3.57 – 3.35 (m, 2H), 2.66 – 2.48 (m, 2H), 2.36 – 1.85 (m, 6H), 1.80 – 1.61 (m, 2H), 1.51 – 1.13 (m, 22H), 0.86 (d, ^3J (H,H) = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): 176.8 (C), 165.0 (C), 164.3 (C), 150.5 (C), 134.7 (CH), 131.1 (2×CH), 130.3 (CH), 130.3 (C), 127.4 (CH), 124.8 (CH), 123.6 (C), 121.0 (C), 110.2 (C), 104.2 (CH), 40.3 (CH_2), 33.1 (CH_2), 32.8 (CH_2), 32.4 (CH_2), 30.3 (CH_2), 30.2 (2×CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.8 (2×CH_2), 28.7 (CH_2), 27.7 (2×CH_2), 27.7 (2×CH_2), 23.7 (CH_2), 23.2 (CH_2), 14.4 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 572 (100, $[M+Na]^+$), 550 (100, $[M+H]^+$).

Compound 43. This compound was prepared by **Method C**. Purification of the crude product by a gradient column chromatography (pentane/AcOEt 9:1 to 8:2; R_f: 0.5 with pentane/AcOEt 8:2) afforded **43** (81%) as a yellow oil. IR (neat): 3381 (w), 2923 (m), 2853 (m), 1723 (m), 1685 (m), 1641 (s), 1578 (s), 1545 (s), 1462 (w), 1429 (w), 1393 (m), 1354 (s), 1298 (w), 1243 (m), 1150 (s), 1112 (m), 1081 (w), 1047 (w), 947 (w), 884 (w), 844 (w), 774 (s), 758 (m), 722 (w), 670 (w), 585 (w); ^{1}H NMR (400 MHz, $CDCl_3$): 8.51 (d, ^3J (H,H) =

7.4 Hz, 1H), 8.39 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 8.00 (d, ^{3}J (H,H) = 8.3 Hz, 1H), 7.55 (dd, ^{3}J (H,H) = 8.4 Hz, ^{3}J (H,H) = 7.4 Hz, 1H), 6.65 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 5.39 – 5.18 (m, 2H), 4.23 – 4.05 (m, 2H), 3.33 (t, ^{3}J (H,H) = 7.2 Hz, 2H), 2.28 (t, ^{3}J (H,H) = 7.7 Hz, 2H), 2.15 – 1.64 (m, 6H), 1.81 – 1.64 (m, 2H), 1.57 – 1.40 (m, 2H), 1.36 (s, 9H), 1.30 – 1.08 (m, 20H), 0.89 – 0.70 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): 172.5 (C), 164.8 (C), 164.2 (C), 149.5 (C), 134.6 (CH), 131.3 (CH), 130.2 (CH), 130.0 (C), 129.8 (CH), 125.9 (CH), 124.8 (CH), 123.3 (C), 120.3 (C), 110.4 (C), 104.5 (CH), 80.3 (C), 43.9 (CH_2), 39.5 (CH_2), 33.5 (CH_2), 32.8 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.2 (3×CH_3), 27.4 (CH_2), 27.3 (CH_2), 23.9 (CH_2), 22.8 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 606 (50, $[M+H]^+$), 550 (100, [M–*t*Bu]$^+$), 532 (50, [M–O*t*Bu]$^+$).

Compound 9p. This compound was obtained as a yellow solid following **Method D** (86%). Mp: 87-89 °C; IR (neat): 3381 (w), 3195 (br), 2923 (m), 2852 (w), 1716 (m), 1681 (m), 1637 (m), 1612 (m), 1576 (s), 1546 (s), 1460 (w), 1433 (w), 1396 (m), 1347 (s), 1300 (w), 1248 (w), 1191 (w), 1131 (w), 1056 (w), 966 (w), 921 (w), 893 (w), 818 (w), 772 (s), 757 (m), 723 (w), 655 (w), 582 (w), 556 (w); ^{1}H NMR (400 MHz, $CDCl_3$): 8.57 (dd, ^{3}J (H,H) = 7.3 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 8.45 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.17 (dd, ^{3}J (H,H) = 8.3 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 7.61 (dd, ^{3}J (H,H) = 8.3 Hz, ^{3}J (H,H) = 7.3 Hz, 1H), 6.71 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 5.58 (br s, 1H), 5.48 – 5.26 (m, 2H), 4.24 (t, ^{3}J (H,H) = 7.1 Hz, 2H), 3.40 (q, ^{3}J (H,H) = 7.1 Hz, 2H), 2.42 (t, ^{3}J (H,H) = 7.6 Hz, 2H), 2.33 – 1.90 (m, 6H), 1.81 (quint, ^{3}J (H,H) = 7.4 Hz, 2H), 1.55 – 1.44 (m, 2H), 1.45 – 1.14 (m, 20H), 1.06 – 0.77 (m, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): 175.3 (C), 165.1 (C), 164.4 (C), 150.4 (C), 134.8 (CH), 131.3 (CH), 130.4 (CH), 130.4 (C), 130.2 (CH), 127.0 (CH), 124.9 (CH), 123.5 (C), 120.8

(C), 110.2 (C), 104.6 (CH), 44.3 (CH_2), 39.7 (CH_2), 32.2 (2×CH_2), 30.3 (CH_2), 30.2 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.3 (2×CH_2), 27.7 (3×CH_2), 24.1 (CH_2), 23.2 (CH_2), 14.4 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 550 (100, $[M+H]^+$), 532 (60, $[M–O]^+$).

Compound 46. This compound was prepared by **Method B**. Purification of the crude product twice by column chromatography (pentane/AcOEt 8:2 and CH_2Cl_2/MeOH 98:2; R_f: 0.4 with pentane/AcOEt 8:2, R_f: 0.4 with CH_2Cl_2/MeOH 98:2) afforded **46** as a yellow solid (34%). Mp: 149 – 150 °C; IR (neat): 3434 (br w), 3385 (br w), 2972 (w), 2932 (w), 2852 (w), 1725 (m), 1691 (m), 1645 (s), 1581 (s), 1545 (m), 1474 (w), 1455 (w), 1395 (w), 1358 (s), 1299 (w), 1257 (w), 1240 (w), 1174 (w), 1153 (s), 1120 (s), 1101 (w), 1077 (w), 1048 (w), 1000 (w), 954 (w), 902 (w), 847 (w), 775 (m), 757 (w), 734 (m), 684 (w), 664 (w), 621 (w), 576 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.48 (d, ^3J (H,H) = 7.3 Hz, 1H), 8.36 (d, ^3J (H,H) = 8.4 Hz, 1H), 8.18 (d, ^3J (H,H) = 8.4 Hz, 1H), 7.58 (dd, ^3J (H,H) = 8.4 Hz, ^3J (H,H) = 7.3 Hz, 1H), 6.66 (d, ^3J (H,H) = 8.4 Hz, 1H), 6.19 (br s, 1H), 5.06 – 4.88 (m, 1H), 3.41 (q, ^3J (H,H) = 6.2 Hz, 2H), 2.64 – 2.51 (m, 2H), 2.49 (t, ^3J (H,H) = 6.4 Hz, 2H), 2.10 (quint, ^3J (H,H) = 6.5 Hz, 2H), 1.88 –1.84 (m, 2H), 1.75 – 1.52 (m, 3H), 1.46 (s, 9H), 1.45 – 1.16 (m, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 174.4 (C), 165.4 (C), 164.9 (C), 150.0 (C), 134.5 (CH), 131.1 (CH), 130.3 (C), 126.6 (CH), 125.1 (CH), 124.3 (C), 120.7 (C), 111.1 (C), 104.3 (CH), 81.6 (C), 53.6 (CH), 44.5 (CH_2), 34.2 (CH_2), 29.7 (2×CH_2), 28.4 (3×CH_3), 27.2 (2×CH_2), 26.2 (CH_2), 23.8 (CH_2); MS (ESI, CH_2Cl_2/MeOH 1:1): 438 (100, $[M+H]^+$), 382 (100, $[M–O$*t*$Bu+H]^+$).

Compound 10a. This compound was obtained as a yellow solid following **Method D** (61%). Mp: 225 – 226 °C; IR (neat): 3389 (w), 2927 (w), 2855 (w), 1703 (m), 1683 (m), 1627 (m), 1612 (m), 1586 (s), 1554 (m), 1450 (w), 1399 (m), 1364 (s), 1341 (m), 1258 (w), 1240 (m), 1183 (m), 1123 (m), 1071 (w), 1039 (w), 1010 (w), 958 (w), 940 (w), 914 (w), 890 (w), 826 (w), 798 (w), 771 (s), 758 (m), 685 (w), 617 (w), 583 (w); ^{1}H NMR (400 MHz, CD_2Cl_2/DMSO-d_6 95:5): 8.47 (d, ^{3}J (H,H) = 7.3 Hz, 1H), 8.41 – 8.27 (m, 2H), 7.65 – 7.48 (m, 1H), 6.84 (br s, 1H), 6.69 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 5.07 – 4.87 (m, 1H), 3.44 (br s, 2H), 2.74 – 2.36 (m, 4H), 2.09 (quint, ^{3}J (H,H) = 6.5 Hz, 2H), 1.95 – 1.76 (m, 2H), 1.76 – 1.57 (m, 3H), 1.53 – 1.22 (m, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 176.3 (C), 165.3 (C), 164.6 (C), 150.4 (C), 134.5 (CH), 130.9 (CH), 130.2 (C), 127.4 (C), 124.6 (CH), 123.9 (C), 120.7 (C), 110.3 (C), 104.0 (CH), 53.3 (CH), 43.9 (CH_2), 32.5 (CH_2), 29.5 (2xCH_2), 27.0 (2xCH_2), 26.0 (CH_2), 23.7 (CH_2); MS (ESI, CH_2Cl_2/MeOH 1:1): 382 (100, $[M+H]^+$).

Compound 47. This compound was prepared by **Method C**. Purification of the crude product by a column chromatography (pentane/AcOEt 8:2, R_f: 0.4) and precipitation from CH_2Cl_2 upon addition of hexane afforded **47** as a yellow solid (83%). Mp: 63 – 64 °C; IR (neat): 3375 (w), 2931 (w), 2856 (w), 1722 (m), 1682 (m), 1639 (s), 1578 (s), 1543 (s), 1464 (w), 1430 (w), 1391 (s), 1348 (s), 1278 (w), 1245 (m), 1144 (s), 1126 (m), 1105 (m), 1053 (w), 990 (w), 959 (w), 890 (w), 843 (w), 772 (s), 757 (m), 673 (w), 582 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.53 (dd, ^{3}J (H,H) = 7.3 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 8.39 (d, ^{3}J (H,H) = 8.6 Hz, 1H), 8.12 (dd, ^{3}J (H,H) = 7.8 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 7.62 (dd, ^{3}J (H,H) = 7.8 Hz, ^{3}J (H,H) = 7.3 Hz, 1H), 6.77 (d, ^{3}J (H,H) = 8.6 Hz, 1H), 5.33 – 5.18 (m, 1H), 4.23 – 4.06 (m, 2H), 3.72 – 3.54 (m, 1H), 2.30 (t, ^{3}J (H,H) = 7.6 Hz, 2H), 2.23 – 2.06 (m, 2H), 2.05 – 1.89 (m, 2H), 1.89 – 1.75 (m, 2H), 1.75 – 1.64 (m, 1H), 1.55 – 1.33 (m, 14H); ^{13}C NMR (101

MHz, CD_2Cl_2): 172.8 (C), 165.0 (C), 164.4 (C), 149.0 (C), 134.7 (CH), 131.4 (CH), 130.6 (C), 126.4 (CH), 125.0 (CH), 123.8 (C), 120.7 (C), 110.2 (C), 105.0 (CH), 80.4 (C), 52.4 (CH), 39.7 (CH_2), 33.7 (CH_2), 33.3 (2xCH_2), 28.3 (3×CH_3), 26.2 (CH_2), 25.4 (2xCH_2), 24.2 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 438 (30, $[M+H]^+$), 382 (50, $[M–t\text{Bu}+H]^+$), 364 (100, $[M–O t\text{Bu}+H]^+$), 336 (50, $[M–COO t\text{Bu}+H]^+$).

Compound 10p. This compound was obtained as a yellow solid following **Method D** (95%). Mp: 174 – 175 °C; IR (neat): 3361 (w), 2931 (w), 2856 (w), 1706 (w), 1678 (m), 1632 (s), 1574 (s), 1543 (s), 1431 (w), 1393 (s), 1349 (s), 1284 (w), 1244 (m), 1181 (w), 1130 (m), 1142 (m), 1105 (m), 1054 (w), 921 (w), 889 (w), 819 (w), 770 (m), 756 (m), 675 (w), 650 (w), 583 (w); ^{1}H NMR (400 MHz, CD_2Cl_2/DMSO-d_6 95:5): 8.54 (dd, ^3J (H,H) = 7.3 Hz, ^3J (H,H) = 0.9 Hz, 1H), 8.40 (d, ^3J (H,H) = 8.6 Hz, 1H), 8.16 (dd, ^3J (H,H) = 8.4 Hz, ^4J (H,H) = 0.9 Hz, 1H), 7.62 (dd, ^3J (H,H) = 8.4 Hz, ^3J (H,H) = 7.3 Hz, 1H), 6.77 (d, ^3J (H,H) = 8.6 Hz, 1H), 5.34 (s, 1H), 4.18 (t, ^3J (H,H) = 7.0 Hz, 2H), 3.73 – 3.58 (m, 1H), 2.36 (t, ^3J (H,H) = 7.4 Hz, 2H), 2.27 – 2.10 (m, 2H), 2.00 (quint, ^3J (H,H) = 7.3 Hz, 2H), 1.91 – 1.63 (m, 3H), 1.57 – 1.24 (m, 5H); ^{13}C NMR (101 MHz, CD_2Cl_2/DMSO-d_6 95:5): 175.1 (C), 165.0 (C), 164.3 (C), 149.1 (C), 134.7 (CH), 131.3 (CH), 130.5 (C), 126.5 (CH), 124.8 (CH), 123.5 (C), 120.6 (C), 109.9 (C), 104.9 (CH), 52.3 (CH), 39.5 (CH_2), 33.1 (2×CH_2), 32.0 (CH_2), 26.1 (CH_2), 25.3 (2×CH_2), 24.0 (CH_2); MS (ESI, CH_2Cl_2/MeOH 1:1): 382 (100, $[M+H]^+$), 363 (50, $[M–O]^+$).

Compound 49. This compound was prepared by **Method A**. Column chromatographic purifications of the crude mixture (pentane/AcOEt 9:1, R_f: 0.5) afforded **49** (79%). Mp: 142–143 °C; IR (neat): 1714 (m), 1667 (s), 1591 (m), 1571 (m), 1501 (w), 1402 (w), 1361 (m),

1324 (w), 1234 (m), 1202 (s), 1145 (s), 1104 (m), 1083 (s), 1045 (m), 1010 (w), 947 (m), 882 (w), 859 (w), 842 (w), 782 (m), 737 (w), 712 (w), 700 (w), 671 (w), 639 (m), 563 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.70 (d, ^{3}J (H,H) = 7.3 Hz, 1H), 8.65 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.46 (d, ^{3}J (H,H) = 7.9 Hz, 1H), 8.11 (d, ^{3}J (H,H) = 7.9 Hz, 1H), 7.91 (t, ^{3}J (H,H) = 7.9 Hz, 1H), 4.99 (t, ^{3}J (H,F) = 15.8 Hz, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2): 163.8 (C), 163.8 (C), 134.6 (CH), 133.2 (CH), 132.4 (CH), 131.9 (CH), 131.6 (C), 131.4 (C), 129.7 (C), 128.8 (CH), 123.9 (x, CF_2), 122.9 (C), 122.1 (C), 119.5 – 118.4 (m, CF_2), 116.6 – 116.0 (m, CF_2), 114.3 – 113.7 (m, 3×CF_2), 112.0 – 111.3 (m, 3×CF_2), 109.2 – 108.6 (m, CF_2), 39.1 (t, ^{2}J (C,F) = 22.1 Hz, CH_2); ^{19}F NMR (282 MHz, $CDCl_3$): –80.3 to –80.5 (m, 3F), –114.4 to –114.7 (m, 2F), –121.1 (br s, 2F), –121.4 (br s, 2F), –122.1 (br s, 2F), –123.0 (br s, 2F), –125.6 (br s, 2F); MS (ESI, CH_2Cl_2/MeOH 1:1): 661 (100, $[M+H]^+$).

Compound 50. This compound was prepared by **Method B**. Purification of the crude product by a column chromatography (pentane/AcOEt 8:2, R_f: 0.3) and reprecipitation from CH_2Cl_2 upon addition of hexane afforded **50** as a yellow solid (83%). Mp: 194 – 195 °C; IR (neat): 3398 (w), 2983 (w), 1700 (m), 1656 (m), 1585 (m), 1537 (w), 1396 (m), 1358 (m), 1236 (s), 1202 (s), 1142 (s), 1118 (m), 1079 (m), 1020 (w), 986 (w), 943 (w), 882 (w), 837 (w), 792 (m), 775 (s), 753 (m), 700 (w), 671 (w), 641 (m), 565 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.58 (d, ^{3}J (H,H) = 7.3 Hz, 1H), 8.46 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.29 (d, ^{3}J (H,H) = 8.3 Hz, 1H), 7.66 (dd, ^{3}J (H,H) = 8.3 Hz, ^{3}J (H,H) = 7.3 Hz, 1H), 6.72 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 6.50 (br s, 1H), 4.97 (t, ^{3}J (H,F) = 16.0 Hz, 2H), 3.45 (q, ^{3}J (H,H) = 6.2 Hz, 2H), 2.52 (t, ^{3}J (H,H) = 6.2 Hz, 2H), 2.21 – 2.03 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2): 174.6 (C), 164.8 (C), 163.7 (C), 150.9 (C), 135.5 (CH), 131.9 (CH), 130.5 (C), 127.8 (C), 125.1 (CH), 122.6 (C), 120.8 (C), 118.7– 118.5 (m, CF_3), 117.0 – 115.9 (m, CF_2), 114.7 –

112.4 (m, CF_2), 112.2 – 110.1 (m, CF_2), 110.1 – 108.0 (m, CF_2), 109.1 (C), 107.4 – 106.0 (m, CF_2), 104.3 (CH), 81.7 (CH), 44.6 (CH_2), 38.5 (t, ^3J (C,F) = 21.8 Hz, CH_2), 34.1 (CH_2), 28.3 (3×CH_3), 23.4 (CH_2); ^{19}F NMR (282 MHz, CD_2Cl_2): –80.3 to –80.5 (m, 3F), –114.37 to –114.64 (m, 2F), –120.9 to –121.2 (m, 2F), –121.2 to –121.6 (m, 2F), –122.0 to –122.3 (m, 2F), –122.9 to –123.2 (m, 2F), –125.4 to –125.7 (m, 2F); MS (ESI, CH_2Cl_2/MeOH 1:1): 738 (100, $[M+H]^+$), 682 (100, $[M–t\text{Bu}]^+$).

Compound 11a. This compound was obtained as a yellow solid following **Method D** (37%). Mp: 194 – 195 °C; IR (neat): 3390 (w), 3093 (br), 1703 (m), 1639 (m), 1592 (m), 1555 (w), 1402 (m), 1362 (m), 1324 (w), 1237 (m), 1194 (s), 1143 (s), 1117 (m), 1090 (m), 1052 (w), 1017 (w), 990 (w), 859 (w), 826 (w), 796 (m), 771 (s), 701 (m), 671 (m), 647 (m), 569 (w); ^{1}H NMR (400 MHz, CD_2Cl_2/DMSO-d_6 95:5): 8.64 (d, ^3J (H,H) = 8.4 Hz, 1H), 8.54 (d, ^3J (H,H) = 6.9 Hz, 1H), 8.40 (d, ^3J (H,H) = 8.6 Hz, 1H), 7.62 (dd, ^3J (H,H) = 8.4 Hz, ^3J (H,H) = 6.9 Hz, 1H), 7.54 (br s, 1H), 6.75 (d, ^3J (H,H) = 8.6 Hz, 1H), 4.96 (t, ^3J (H,F) = 16.0 Hz, 2H), 3.46 (br s, 2H), 2.48 (t, ^3J (H,H) = 6.9 Hz, 2H), 2.11 – 2.03 (m, 2H); ^{13}C NMR (126 MHz, CD_2Cl_2/DMSO-d_6 95:5): 175.7 (C), 164.7 (C), 163.5 (C), 151.7 (C), 135.5 (CH), 131.8 (CH), 130.6 (C), 129.4 (CH), 124.5 (CH), 122.1 (C), 121.0 (C), 119.0 – 118.1 (m, CF_2), 116.9 – 115.8 (m, CF_2), 114.8 – 113.4 (m, 2×CF_2), 112.0 – 109.9 (m, CF_2), 109.7 – 108.3 (m, CF_2, CF_3), 107.9 (C), 104.2 (CH), 43.5 (CH_2), 38.2 (t, ^3J (C,F) = 21.0 Hz, CH_2), 32.1 (CH_2), 23.6 (CH_2); ^{19}F NMR (282 MHz, CD_2Cl_2/DMSO-d_6 95:5): –81.1 (t, ^3J (F,F) = 10.1 Hz, 3F), –115.0 to –115.5 (m, 2F), –121.8 (br s, 2F), –122.2 (br s, 2F), –122.9 (br s, 2F), –123.8 (br s, 2F), –126.0 to –126.6 (m, 2F); MS (ESI, CH_2Cl_2/MeOH 1:1): 704 (10, $[M+Na]^+$), 682 (100, $[M+H]^+$).

Compound 51. A solution of compound **22** (200 mg, 0.48 mmol), **48** (570 mg, 0.34 mmol), tris(dibenzylidenacetone)dipalladium(0) (26 mg, 29 μmol), 1,1'-bis(diphenylphosphine)-ferrocene (5.3 mg, 9.6 μmol) and sodium *tert*-butoxide (140 mg, 1.4 mmol) in dry degassed toluene (10 mL) was heated at 90 °C for 18 h under Ar atmosphere. The resulting mixture was diluted with AcOEt and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatographic purifications (pentane/AcOEt 8:2 to 7:3 and CH_2Cl_2/MeOH 99/1; R_f: 0.3 with pentane/AcOEt 7:3, R_f: 0.2 with CH_2Cl_2/MeOH 99/1) then PTLC (CH_2Cl_2/MeOH 99:1) of the crude mixture afforded a desired product **50** (18 mg, 5%) as a yellow solid. Mp: 63 – 64 °C; IR (neat): 3530 (w), 3394 (w), 2982 (w), 1709 (m), 1689 (m), 1642 (m), 1615 (m), 1582 (s), 1453 (w), 1429 (w), 1393 (m), 1359 (m), 1305 (w), 1240 (s), 1203 (s), 1142 (s), 1057 (w), 1024 (w), 961 (w), 885 (w), 836 (w), 809 (w), 776 (m), 756 (w), 723 (w), 711 (w), 664 (w), 642 (w), 559 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.58 (d, ^3J (H,H) = 7.4 Hz, 1H), 8.47 (d, ^3J (H,H) = 8.4 Hz, 1H), 8.18 (d, ^3J (H,H) = 8.1 Hz, 1H), 7.71 (dd, ^3J (H,H) = 8.1 Hz, ^3J (H,H) = 7.4 Hz, 1H), 6.92 (d, ^3J (H,H) = 8.4 Hz, 1H), 5.48 (s, 1H), 4.26 – 4.20 (m, 2H), 4.16 (t, ^3J (H,H) = 7.6 Hz, 2H), 2.31 (t, ^3J (H,H) = 7.6 Hz, 2H), 1.97 (quint, ^3J (H,H) = 7.6 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2): 172.6 (C), 164.6 (C), 164.0 (C), 148.1 (C), 133.8 (CH), 131.6 (CH), 130.0 (C), 126.1 (CH), 126.0 (CH), 123.9 (C), 121.2 (C), 119.4 – 118.2 (m, CF_2), 116.9 – 115.8 (m, CF_2), 115.2 – 114.4 (m, CF_3), 114.4 – 112.5 (m, CF_2), 113.4 (C), 112.2 – 110.3 (m, 2×CF_2), 110.0 – 108.1 (m, CF_2), 105.6 (CH), 80.4 (C), 44.1 (t, ^3J (C,F) = 23 Hz, CH_2), 39.7 (CH_2), 33.5 (CH_2), 28.2 (3×CH_3), 24.0 (CH_2); ^{19}F NMR (282 MHz, CD_2Cl_2): –80.3 to –80.5 (m, 3F), –116.5 to –117.2 (m, 2F), –120.9 to –121.2 (m, 2F), –121.4 (br s, 2F), –122.1 (br s, 2F), –122.5 (br s, 2F), –125.3 to –125.9 (m, 2F); MS (ESI, CH_2Cl_2/MeOH 1:1): 738 (40, $[M+H]^+$), 682 (100, $[M–t\text{Bu}]^+$), 664 (30, $[M–O t\text{Bu}]^+$).

Compound 11p. This compound was obtained as a yellow solid following **Method D** (25%). Mp: 158 – 159 °C; IR (neat): 3378 (br), 2965 (w), 1719 (m), 1687 (m), 1638 (m), 1612 (w), 1582 (s), 1434 (w), 1497 (m), 1397 (m), 1361 (m), 1326 (w), 1299 (w), 1235 (m), 1198 (s), 1143 (s), 1088 (w), 1057 (w), 1017 (w), 939 (w), 885 (w), 835 (w), 774 (m), 736 (m), 720 (w), 701 (w), 658 (w), 583 (w); ^{1}H NMR (400 MHz, CD_2Cl_2/DMSO-d_6 90:10): 11.64 (s, 1H), 8.62 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.55 (d, ^{3}J (H,H) = 7.2 Hz, 1H), 8.41 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 7.67 (dd, ^{3}J (H,H) = 8.4 Hz, ^{3}J (H,H) = 7.2 Hz, 1H), 7.61 (d, ^{3}J (H,H) = 6.8 Hz, 1H), 6.88 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 4.32 – 4.09 (m, 4H), 2.34 (t, ^{3}J (H,H) = 7.4 Hz, 2H), 2.07 – 1.90 (m, 2H); ^{13}C NMR (126 MHz, CD_2Cl_2/DMSO-d_6 90:10): 174.9 (C), 164.7 (C), 164.0 (C), 150.1 (C), 134.0 (CH), 131.3 (CH), 130.0 (C), 128.4 (CH), 125.1 (CH), 123.1 (C), 121.4 (C), 119.0 – 118.1 (m, CF_2), 117.6 – 116.7 (m, CF_2), 116.6 – 115.8 (m, CF_3), 115.4 –114.6 (m, CF_2) 114.4 – 113.0 (m, CF_2), 111.4 – 110.4 (m, 2×CF_2), 111.6 (C), 104.9 (CH), 43.4 (t, ^{3}J (C,F) = 23 Hz, CH_2), 39.5 (CH_2), 32.0 (CH_2), 23.8 (CH_2); ^{19}F NMR (282 MHz, CD_2Cl_2/DMSO-d_6 90:10): –81.0 (t, ^{3}J (F,F) = 10.0 Hz, 3F), –117.0 (br s, 2F), –121.8 (br s, 2F), –122.2 (br s, 2F), –122.9 (br s, 2F), –123.4 (br s, 2F), –126.2 (br s, 2F); MS (ESI, CH_2Cl_2/MeOH 1:1): 682 (50, $[M+H]^+$), 664 (100, $[M–O]^+$), 636 (30, $[M–COO]^+$).

Compound 53. To a stirred solution of **19** (0.4 M, 1.0 eq.) in DMF was added **52** (1.0 eq. with 0.8 eq. of TEA) and the mixture was stirred overnight at 90 °C. The resulting mixture was diluted with AcOEt and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatographic purifications of the crude mixture (pentane/AcOEt 8:2, R_f: 0.3) afforded desired product **53** as a viscous yellow liquid (83%). IR (neat): 3383 (w), 2923 (w), 2853 (w), 1726 (m), 1686

(m), 1641 (s), 1578 (s), 1545 (s), 1462 (w), 1429 (w), 1391 (m), 1354 (s), 1297 (w), 1245 (w), 1151 (s), 1112 (m), 1073 (w), 952 (w), 893 (w), 845 (w), 774 (m), 758 (m), 724 (w), 665 (w), 584 (w), 556 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.54 (d, ^{3}J (H,H) = 7.2 Hz, 1H), 8.42 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 8.20 – 8.05 (m, 1H), 7.64 (dd, ^{3}J (H,H) = 8.4 Hz, ^{3}J (H,H) = 7.2 Hz, 1H), 6.76 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 5.97 (br t, ^{3}J (H,H) = 6.2 Hz, 1H), 4.18 – 4.01 (m, 2H), 3.68 (q, ^{3}J (H,H) = 6.2 Hz, 2H), 2.70 (t, ^{3}J (H,H) = 6.2 Hz, 2H), 1.77 – 1.61 (m, 2H), 1.46 (s, 9H), 1.42 – 1.17 (m, 18H), 0.87 (t, ^{3}J (H,H) = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 171.9 (C), 164.8 (C), 164.2 (C), 149.5 (C), 134.3 (CH), 131.2 (CH), 130.2 (C), 126.3 (CH), 125.2 (CH), 123.8 (C), 120.9 (C), 111.2 (C), 104.5 (CH), 81.8 (C), 40.4 (CH_2), 39.7 (CH_2), 34.7 (CH_2), 32.3 (CH_2), 30.1 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.8 (CH_2), 28.6 (2×CH_2), 28.2 (3×CH_3), 27.6 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 510 (100, $[M+H]^+$), 454 (80, $[M–t\text{Bu}]^+$).

Compound 12a. This compound was obtained as a yellow solid following **Method D** (62%). Mp: 157 – 158 °C; IR (neat): 3395 (w), 3100 (br), 2923 (m), 2951 (m), 2851 (w), 1727 (m), 1693 (m), 1635 (m), 1607 (m), 1579 (s), 1547 (s), 1464 (w), 1435 (w), 1395 (s), 1345 (s), 1246 (m), 1191 (m), 1114 (m), 1081 (w), 1033 (w), 898 (w), 828 (w), 774 (s), 756 (w), 722 (w), 666 (w), 611 (w), 583 (w); ^{1}H NMR (500 MHz, CD_2Cl_2): 8.50 (d, ^{3}J (H,H) = 7.3 Hz, 1H), 8.38 (dd, ^{3}J (H,H) = 8.5 Hz, ^{4}J (H,H) = 1.8 Hz, 1H), 8.32 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 7.71 – 7.48 (m, 1H), 6.73 (dd, ^{3}J (H,H) = 8.5 Hz, ^{4}J (H,H) = 1.8 Hz, 1H), 6.62 (br s, 1H), 4.08 (t, ^{3}J (H,H) = 7.5 Hz, 3H), 3.79 – 3.48 (m, 2H), 2.87 – 2.64 (m, 2H), 1.78 – 1.54 (m, 2H), 1.48 – 1.04 (m, 18H), 0.98 – 0.69 (m, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2/DMSO-d_6 95:5): 174.3 (C), 164.9 (C), 164.2 (C), 150.1 (C), 134.5 (CH), 131.2 (CH), 130.3 (C), 127.5 (C), 124.9 (CH), 123.5 (C), 121.1 (C), 110.5 (C), 104.3 (CH), 40.4 (CH_2), 39.6 (CH_2), 33.5

(CH_2), 32.4 (CH_2), 30.1 (4×CH_2), 29.9 (CH_2), 29.8 (CH_2), 28.6 (CH_2), 27.7 (CH_2), 23.1 (CH_2), 14.4 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 476 (10, $[M+Na]^+$), 454 (100, $[M+H]^+$).

Compound 54. To a stirred solution of **52** (0.09 M, 1.0 eq.) in DMF was added **17** (1.0 eq.) and the mixture was stirred at 100 °C under microwave irradiations for 2 h. The resulting mixture was diluted with Et_2O and washed with water and 5% LiCl aq. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by column chromatography (pentane/AcOEt 8:2, R_f: 0.3) and precipitation from CH_2Cl_2 upon addition of hexane afforded **54** as a colorless solid (67%). Mp: 132 – 133 °C; IR (neat): 1721 (m), 1701 (m), 1661 (s), 1616 (w), 1590 (s), 1569 (w), 1503 (w), 1438 (w), 1402 (w), 1347 (m), 1320 (m), 1260 (w), 1230 (w), 1210 (w), 1155 (s), 1122 (m), 1046 (w), 1023 (w), 925 (w), 880 (w), 842 (w), 779 (s), 749 (m), 715 (w), 647 (w), 567 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.64 (dd, ^3J (H,H) = 7.3 Hz, ^4J (H,H) = 0.9 Hz, 1H), 8.59 (dd, ^3J (H,H) = 8.5 Hz, ^4J (H,H) = 0.9 Hz, 1H), 8.40 (d, ^3J (H,H) = 7.9 Hz, 1H), 8.07 (d, ^3J (H,H) = 7.9 Hz, 1H), 7.87 (dd, ^3J (H,H) = 8.5 Hz, ^3J (H,H) = 7.3 Hz, 1H), 4.47 – 4.30 (m, 2H), 2.73 – 2.56 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2): 170.8 (C), 163.9 (C), 163.8 (C), 133.8 (CH), 132.4 (CH), 131.7 (CH), 131.6 (CH), 131.2 (C), 130.7 (C), 129.5 (C), 128.7 (CH), 123.6 (C), 122.8 (C), 81.2 (C), 36.8 (CH_2), 34.3 (CH_2), 28.3 (3 × CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 407 (50, $[M+H]^+$), 351 (80, $[M–O\textit{t}Bu+Na]^+$), 331 (50, $[M–O\textit{t}Bu+H]^+$).

Compound 55. This compound was prepared by **Method C**. Purification of the crude product by a gradient column chromatography (pentane/AcOEt 9:1 to 8:2; R_f: 0.3 with pentane/AcOEt 8:2) and precipitation from CH_2Cl_2 upon addition of hexane afforded **55** as a

yellow solid (83%); Mp: 58-60 °C; IR (neat): 3390 (w), 2921 (m), 2852 (w), 1712 (w), 1687 (w), 1641 (s), 1578 (s), 1545 (m), 1465 (w), 1432 (w), 1395 (m), 1357 (s), 1298 (m), 1244 (m), 1215 (w),1156 (s), 1134 (m), 1104 (w), 1023 (w), 948 (w), 888 (w), 844 (w), 773 (m), 757 (m), 722 (m), 658 (w), 584 (w); ^{1}H NMR (400 MHz, CD_2Cl_2): 8.54 (dd, ^{3}J (H,H) = 7.4 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 8.41 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.13 (dd, ^{3}J (H,H) = 8.3 Hz, ^{4}J (H,H) = 0.9 Hz, 1H), 7.63 (dd, ^{3}J (H,H) = 8.3 Hz, ^{3}J (H,H) = 7.4 Hz, 1H), 6.74 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 5.43 – 5.24 (m, 1H), 4.43 – 4.26 (m, 2H), 3.49 – 3.32 (m, 2H), 2.69 – 2.53 (m, 2H), 1.80 (q, ^{3}J (H,H) = 7.5 Hz, 2H), 1.53 – 1.45 (m, 2H), 1.41 (s, 9H), 1.36 – 0.98 (m, 16H), 0.96 – 0.79 (m, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2): 171.0 (C), 164.7 (C), 164.0 (C), 150.1 (C), 134.6 (CH), 131.2 (CH), 130.2 (C), 126.4 (CH), 125.0 (CH), 123.5 (C), 120.6 (C), 110.3 (C), 104.6 (CH), 80.8 (C), 44.2 (CH_2), 36.3 (CH_2), 34.3 (CH_2), 32.3 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.3 (CH_2), 28.2 (3×CH_3), 27.6 (CH_2), 23.1 (CH_2), 14.3 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 510 (50, $[M+H]^+$), 454 (100, $[M–t\text{Bu}]^+$), 440 (90, $[M–O t\text{Bu}]^+$).

Compound 12p. This compound was obtained as a yellow solid following **Method D** (55%). Mp: 146 – 147 °C; IR (neat): 3416 (w), 3104 (br), 2923 (m), 2852 (m), 1721 (m), 1682 (m), 1635 (s), 1580 (s), 1544 (s), 1467 (w), 1437 (w), 1398 (w), 1370 (s), 1341 (s), 1261 (m), 1245 (w), 1175 (m), 1176 (m), 1132 (m), 1105 (w), 1017 (w), 909 (w), 884 (w), 821 (w), 775 (m), 757 (m), 723 (w), 692 (w), 652 (w), 588 (m), 555 (w); ^{1}H NMR (400 MHz, CD_2Cl_2/DMSO-d_6 95:5): 8.54 (d, ^{3}J (H,H) = 7.2 Hz, 1H), 8.41 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 8.22 (d, ^{3}J (H,H) = 8.4 Hz, 1H), 7.71 – 7.55 (m, 1H), 6.73 (d, ^{3}J (H,H) = 8.5 Hz, 1H), 5.68 (br s, 1H), 4.46 – 4.30 (m, 2H), 3.41 (q, ^{3}J (H,H) = 7.1 Hz, 2H), 2.75 – 2.59 (m, 2H), 2.04 – 1.71 (m, 2H), 1.58 – 1.17 (m, 18H), 0.88 (t, ^{3}J (H,H) = 6.8 Hz, 3H); ^{13}C NMR (101

MHz, CD_2Cl_2/DMSO-d_6 95:5): 173.7 (C), 164.9 (C), 164.2 (C), 150.5 (C), 134.8 (CH), 131.4 (CH), 130.4 (C), 127.0 (CH), 125.0 (CH), 123.5 (C), 120.8 (C), 110.1 (C), 104.7 (CH), 44.3 (CH_2), 36.4 (CH_2), 33.2 (CH_2), 32.5 (CH_2), 30.2 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 30.1 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 29.4 (CH_2), 27.7 (CH_2), 23.2 (CH_2), 14.4 (CH_3); MS (ESI, CH_2Cl_2/MeOH 1:1): 454 (100, $[M+H]^+$), 435 (100, $[M–t\text{Bu}]^+$).

3. Evaluation of CPP Activators in Vesicles

3.1. Vesicle Preparation

LUVs were prepared following the general procedures in refs. S5 and S7. A thin lipid film was obtained by evaporating a solution of 25 mg EYPC in 1 mL MeOH/$CHCl_3$ 1:1 on a rotary evaporator and then *in vacuo* overnight. The resulting film was hydrated with 1 mL buffer (50 mM CF, 10 mM sodium phosphate, 10 mM NaCl, pH 7.4) for 30 min, subjected to freeze-thaw cycles (5×) and extrusions (15×) through a polycarbonate membrane (pore size, 100 nm). Extravesicular components were removed by gel filtration (Sephadex G-50) with 10 mM sodium phosphate, 107 mM NaCl, pH 7.4 buffer as eluent. Final conditions: ~5 mM EYPC; inside: 50 mM CF, 10 mM sodium phosphate, 10 mM NaCl, pH 7.4; outside: 10 mM sodium phosphate, 107 mM NaCl, pH 7.4.

3.2. Transport Activity in Fluorogenic Vesicles

EYPC-LUV stock solutions (25 μL) were diluted with buffer solution (10 mM sodium phosphate, 107 mM NaCl, pH 7.4), placed in a thermostated fluorescence cuvette (25 °C) and gently stirred (total volume in the cuvette, 2000 μL; final lipid concentration, ~62.5 μM). CF efflux was monitored at λ_{em} 517 nm (λ_{ex} 492 nm) as a function of time after addition of activator (Na^+ salt, 20 μL of concentrated solution in DMSO) at t = 50 s, polyarginine (HCl salt, 20 μL of 25 μM aqueous solution, 250 nM final concentration in the cuvette) at t = 100 s and 1.2% aqueous triton X-100 (40 μL of 1,2% aqueous solution, 0.024% final concentration) at t = 500 s. Fluorescence intensities were normalized to fractional emission intensity I(t) using equation (Eq S1):

$$I(t) = (I_t - I_0) / (I_\infty - I_0) \qquad \text{(Eq S1)}$$

where $I_0 = I_t$ just before the addition of polyarginine, $I_\infty = I_t$ at saturation after lysis. Effective concentration EC_{50} and Hill coefficient n for activators were determined by plotting the fractional activity Y (= I(t) at saturation just before lysis, t = ~490 s) as a function of activators concentration c and fitting them to the Hill equation (Eq S2)

$$Y = Y_0 + (Y_{max} - Y_0) / \{1 + (EC_{50} / c)^n\} \qquad \text{(Eq S2)}$$

where Y_0 is Y without activators, Y_{max} is Y with an excess of activators at saturation, EC_{50} is the concentration of activators required to reach 50% activity and n is the Hill coefficient.

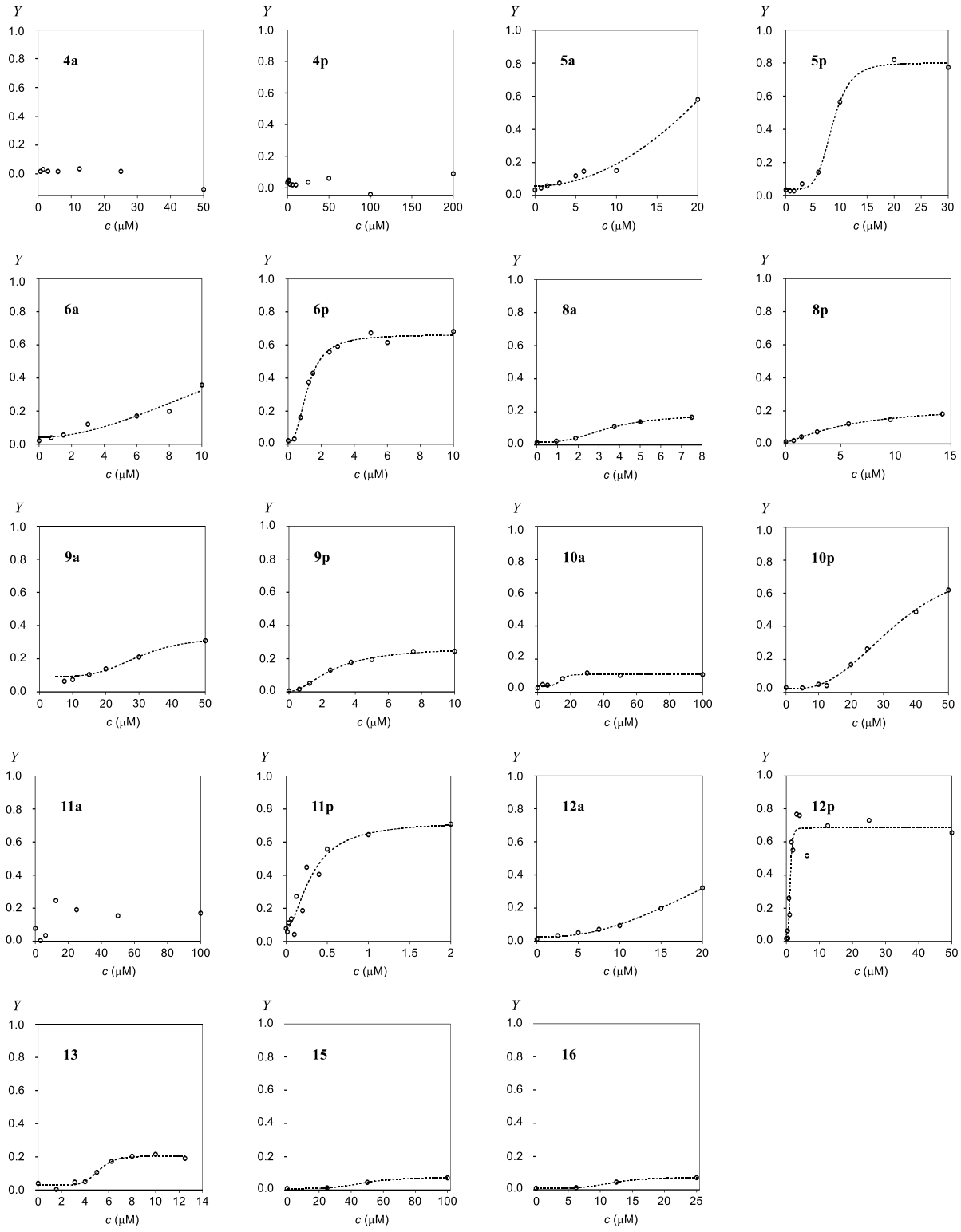


Figure S2. Transport activity *Y* in EYPC-LUVs⊃CF in function of the concentration of the compounds used in this study. The dashed lines correspond to the fit with the Hill equation S2.

3.3. Absorbance and Fluorescence of the Activators

EYPC-LUVs (without encapsulated CF) stock solutions (25 μL) were diluted with buffer solution (10 mM sodium phosphate, 107 mM NaCl, pH 7.4), placed in a thermostated fluorescence cuvette (25 °C) and gently stirred (total volume in the cuvette, 2000 μL; final lipid concentration, ~62.5 μM). The activators (3 μM final concentration) were added to the solution and the absorption spectra were measured. The fluorescence spectra were recorded upon excitation at the absorption maxima for every activator.

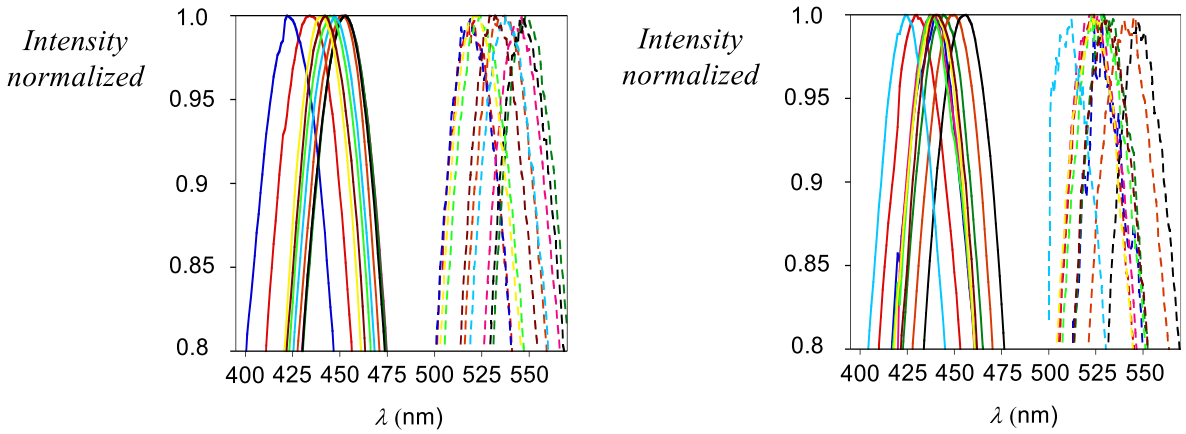


Figure S3. Absorbance and fluorescence (plain and dashed line respectively) spectra of all activators in LUVs. Left: **3a**: red; **3p**: blue; **4a**: purple; **4p**: dark green; **5a**: orange; **5p**: black; **6a**: light green; **6p**: cyan; **7a**: yellow; **7p**: brown. Right: **8a**: red; **8p**: blue; **9a**: purple; **9p**: dark green; **10a**: orange; **10p**: black; **11a**: light green; **11p**: cyan; **12a**: yellow; **12p**: brown.

4. Cellular Uptake Experiments

4.1. Cell Culture

Human cervical cancer-derived HeLa Kyoto cells were cultured in minimum essential medium (MEM) containing 10% fetal bovine serum (FBS), 1% Penicillin / Streptomycin

(PS) and 1% L-Glutamine. The cells were grown on a 25 cm^3 tissue culture flask (TPD corporation) at 37 °C under 5% CO_2.

4.2. Confocal Microscopy

HeLa-Kyoto cells were seeded at 5×10^4 cells/well on 35 mm glass-bottomed dishes (MatTek Corporation) and cultured overnight at 37 ºC. After removing the medium, the cells were washed twice with PBS and once with Leibovitz's medium. The cells were then incubated with activator solution (10 μM final concentration in the dish in Leibovitz's medium) for 5 min before the addition of Cy5-CPP **1** (1 μM final concentration in the dish in Leibovitz's medium). The cells were incubated for additional 15 min at 37 °C, then the medium was removed by aspiration. Cells were washed 3 times with PBS containing 0.1 mg/mL heparin and 3 times with Leibovitz's medium. The cells were kept in Leibovitz's medium and the distribution of Cy5-CPP **1** was analyzed without fixing using a confocal laser scanning microscope (Leica SP5) equipped with 63× oil immersion objective lens. HeNe 633 laser was used as light source (1-5% laser power) with excitation wavelength 633 nm and emission 650 – 700 nm (Leica HyD™ detector). During CLSM analysis the sample was kept at 37 °C. Ar laser was used to detect the ANI core of activators (5% laser power) with excitation wavelength 458 nm and emission 500 – 541 nm (Leica HyD™ detector).

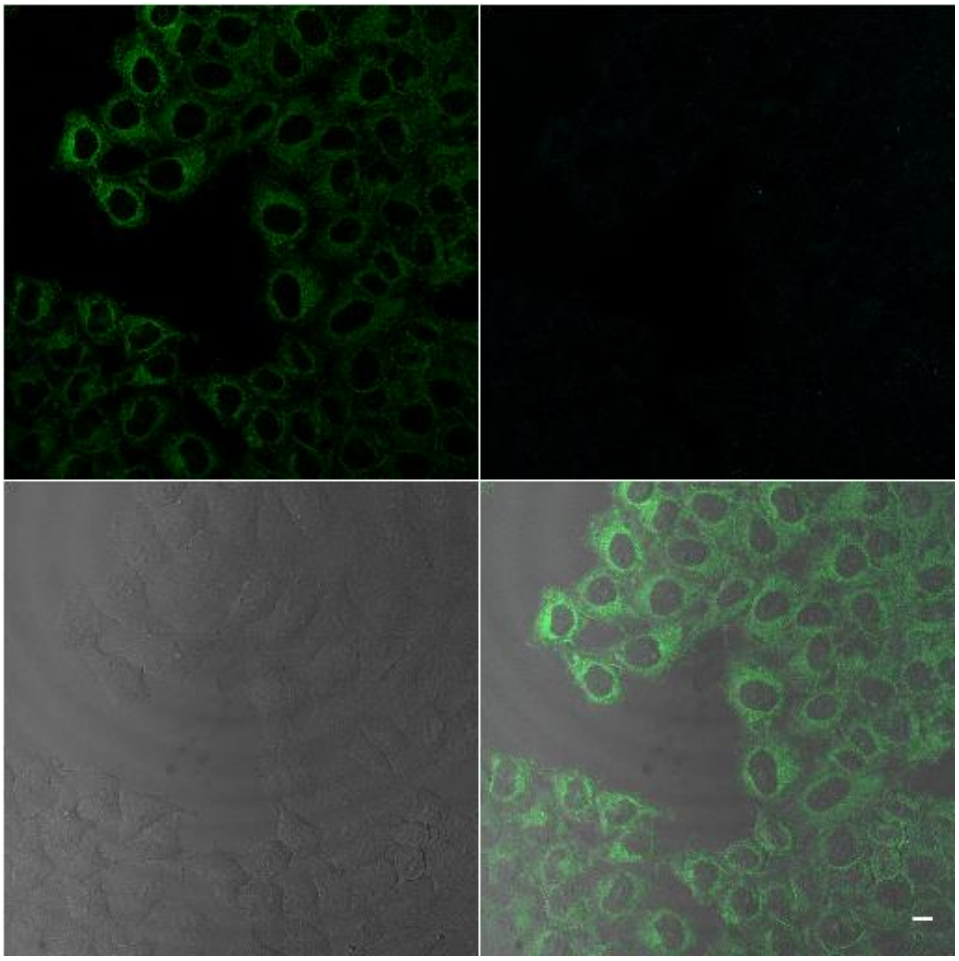


Figure S4. CLSM images of HeLa cells after 20 min incubation with activator **7a** (10 μM) in Leibovitz's medium at 37 °C. λ_{ex} 458 nm and λ_{em} 500 – 541 nm (top left), λ_{ex} 633 nm and λ_{em} 650 – 700 nm (top right), bright field (bottom left) and merge (bottom right). Scale bar: 10 μm.

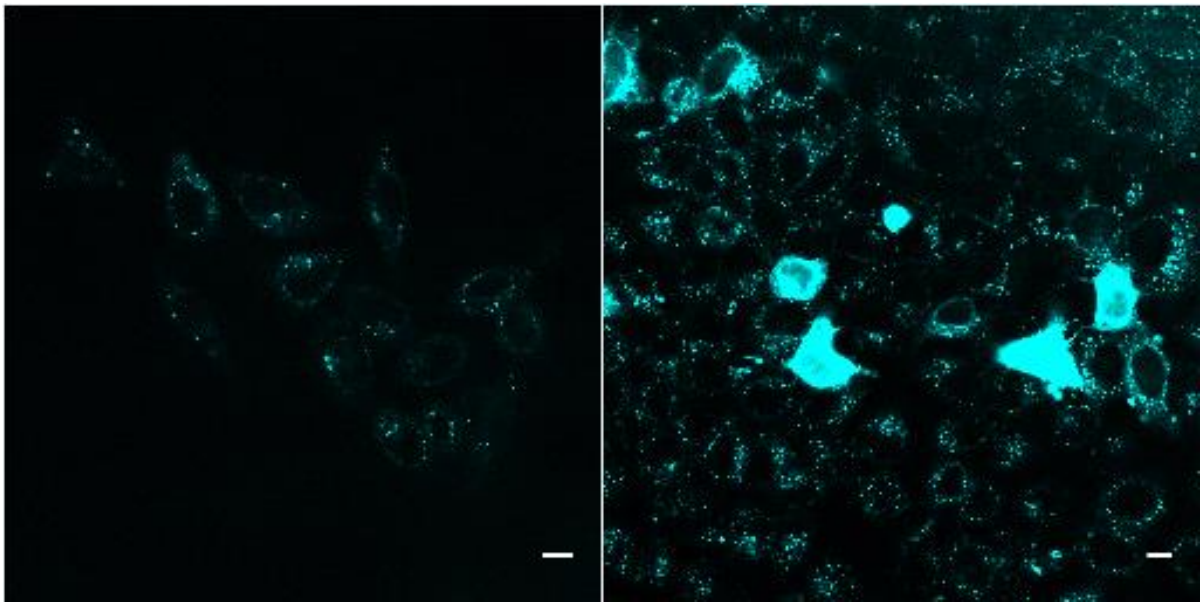


Figure S5. CLSM images of HeLa cells after 5 min incubation with activators (10 μM) **11a** (left), **11p** (right) and then 15 min with Cy5-CPP **1** (1 μM) in Leibovitz's medium at 37 °C. Scale bar: 10 μm.

5. Supplementary References

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(S4) Li, Y.; Xu, S.; Li, X.; Chen, K.; Tian, H. *Chem. Lett.* **2007**, *36*, 664-665.

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6. NMR Spectra

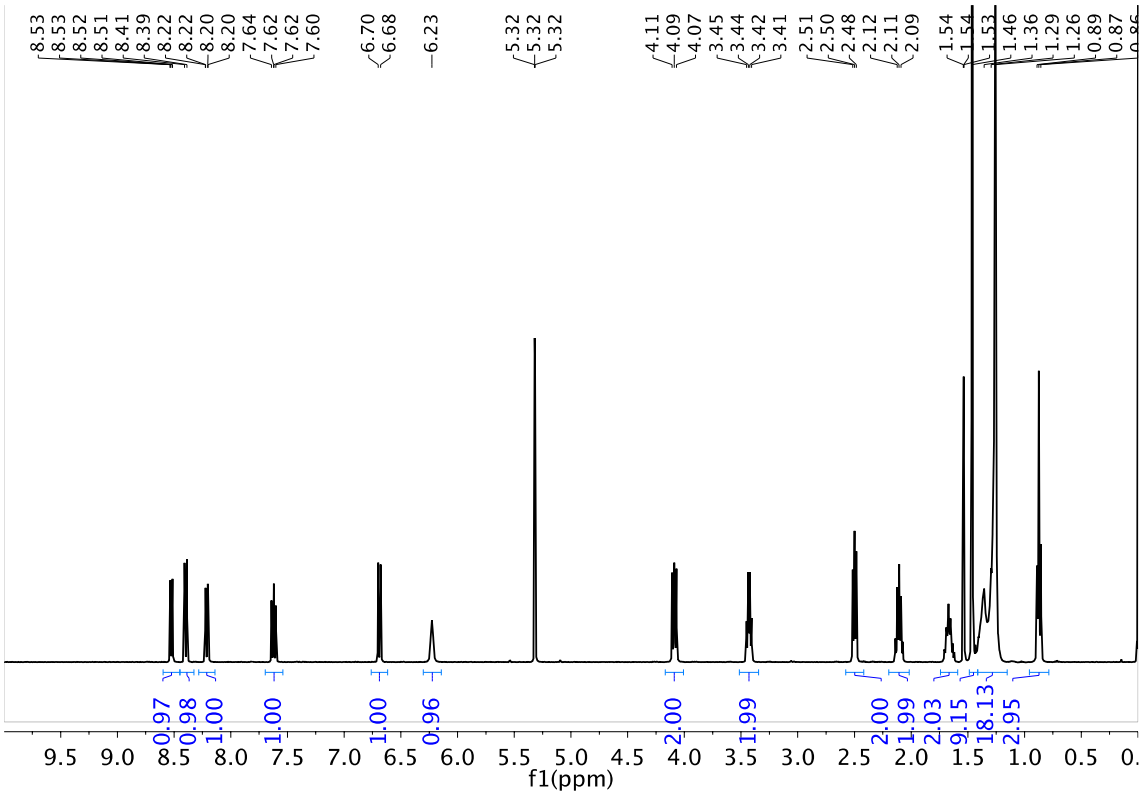

Figure S6. ^{1}H NMR spectrum of **21** in CD_2Cl_2.

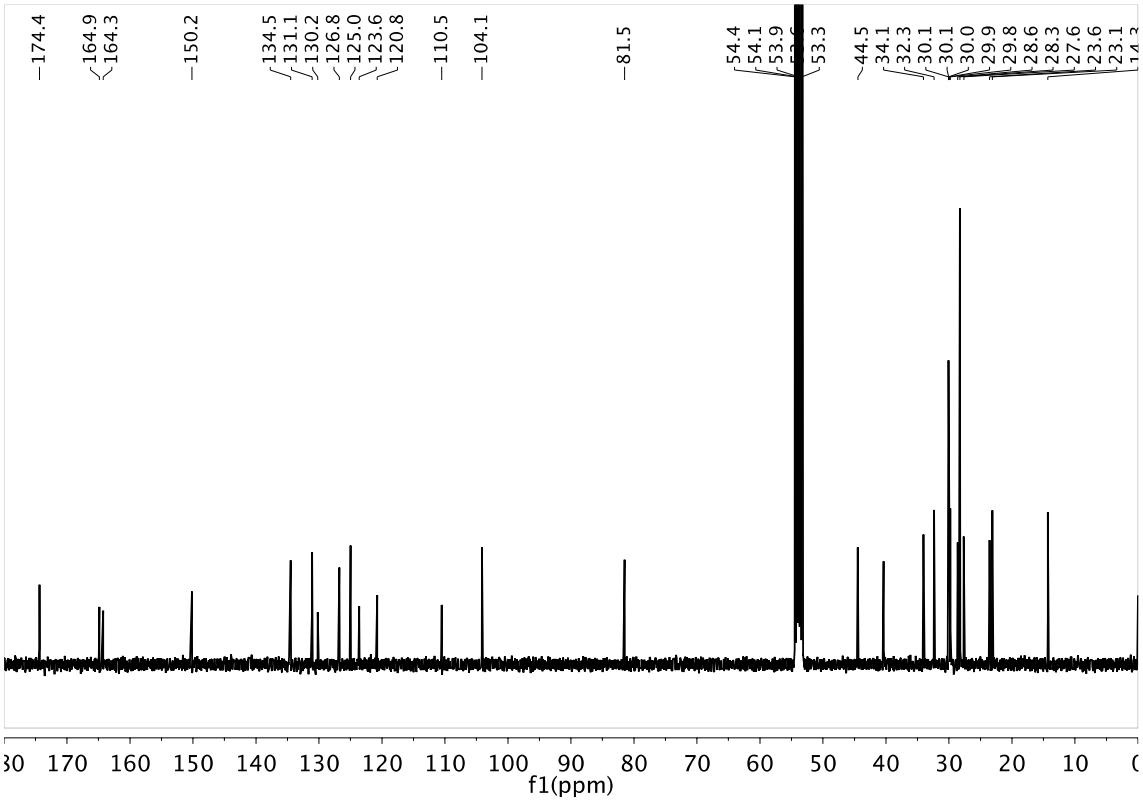

Figure S7. ^{13}C NMR spectrum of **21** in CD_2Cl_2.

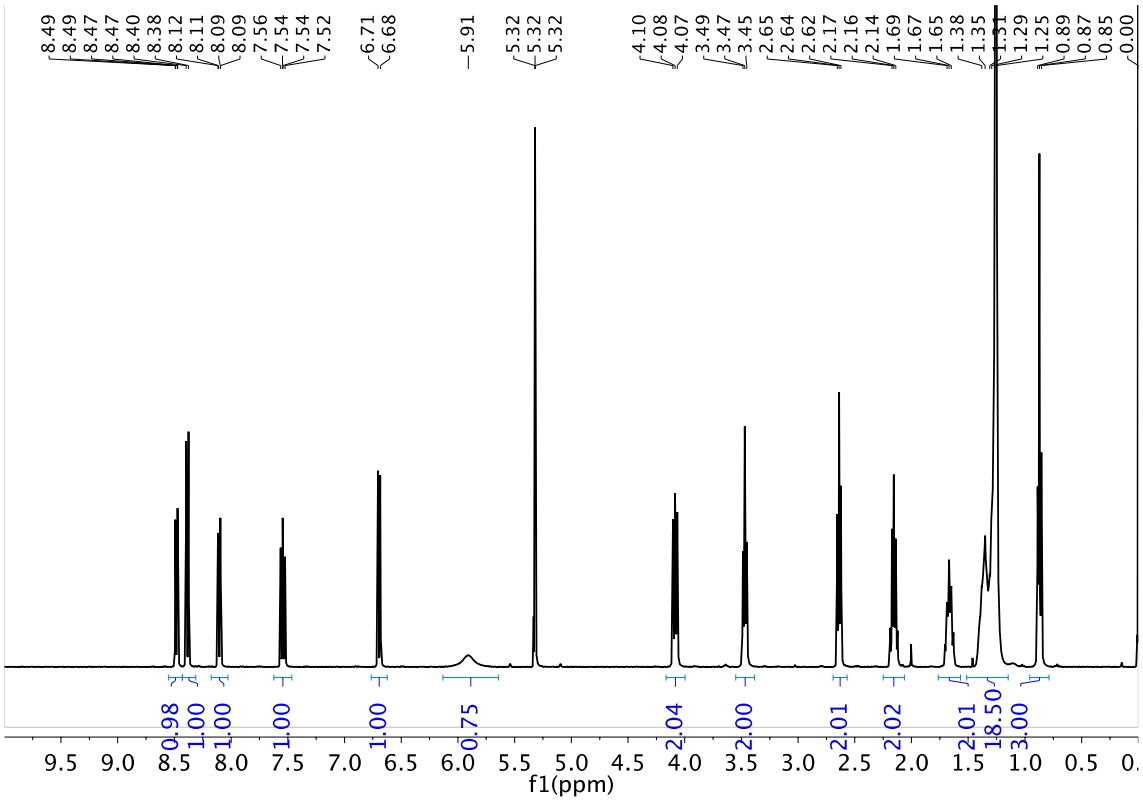

Figure S8. ^{1}H NMR spectrum of **7a** in CD_2Cl_2.

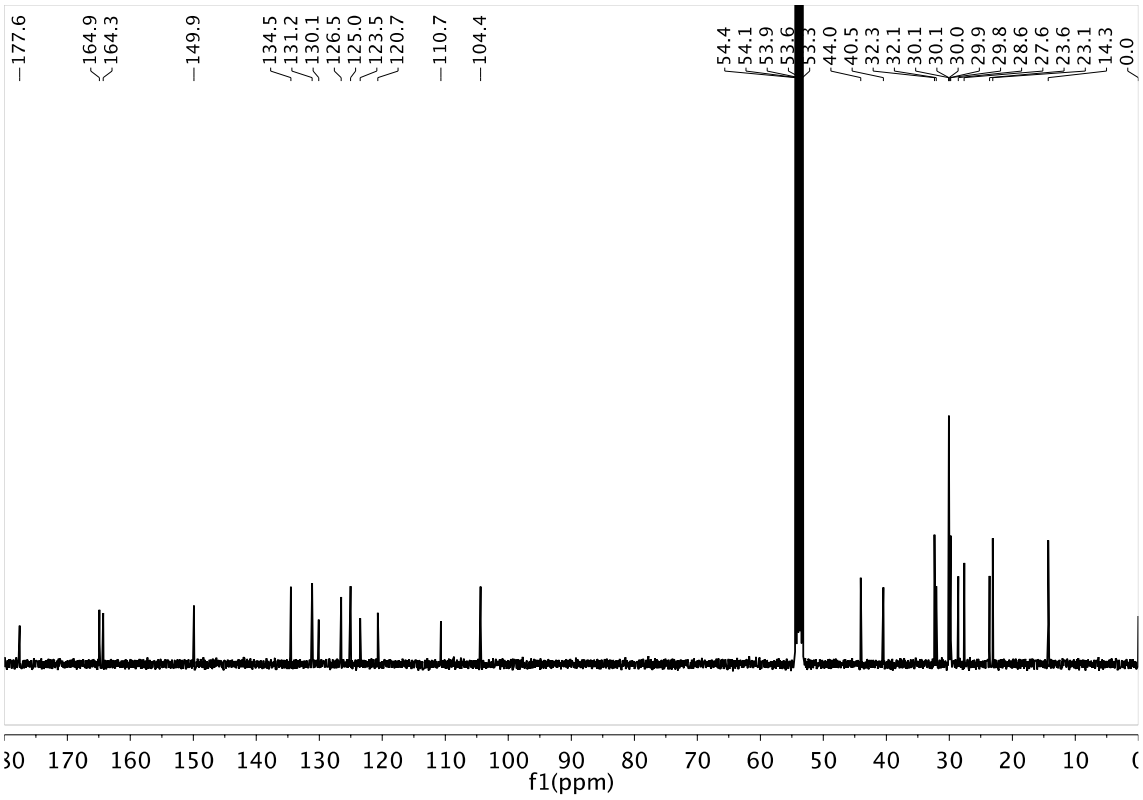

Figure S9. ^{13}C NMR spectrum of **7a** in CD_2Cl_2.

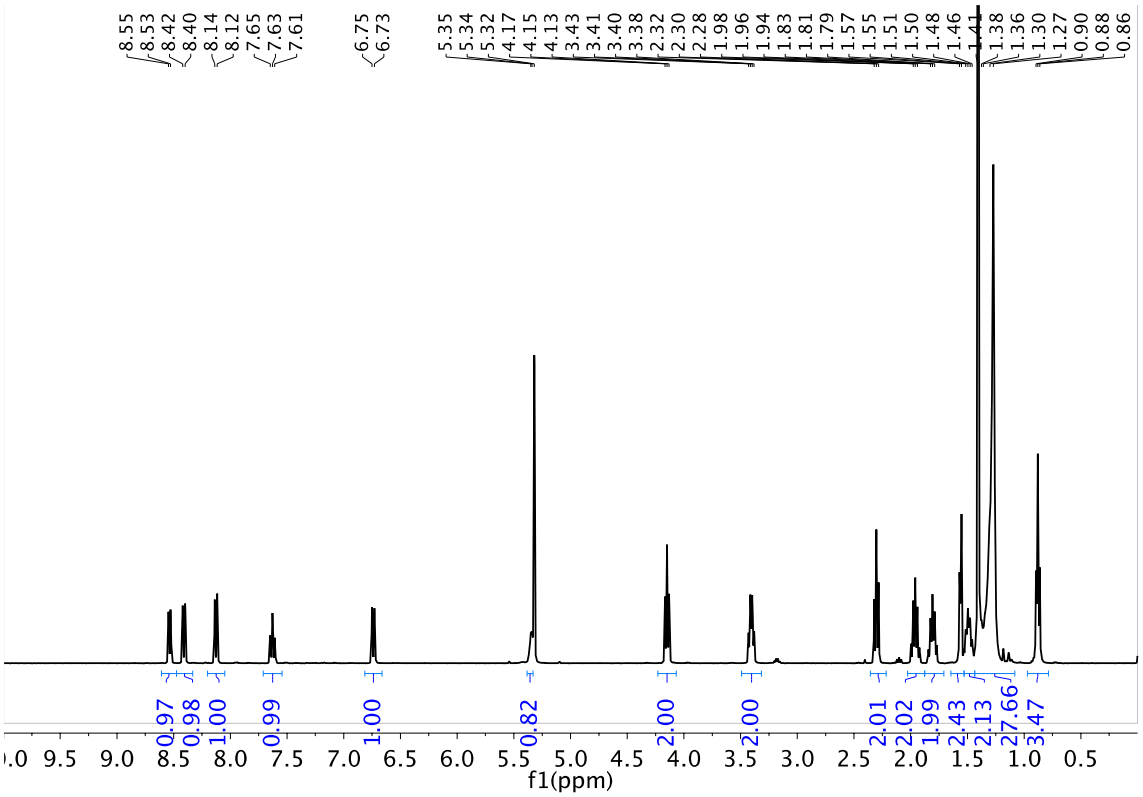

Figure S10. ^{1}H NMR spectrum of **23** in CD_2Cl_2.

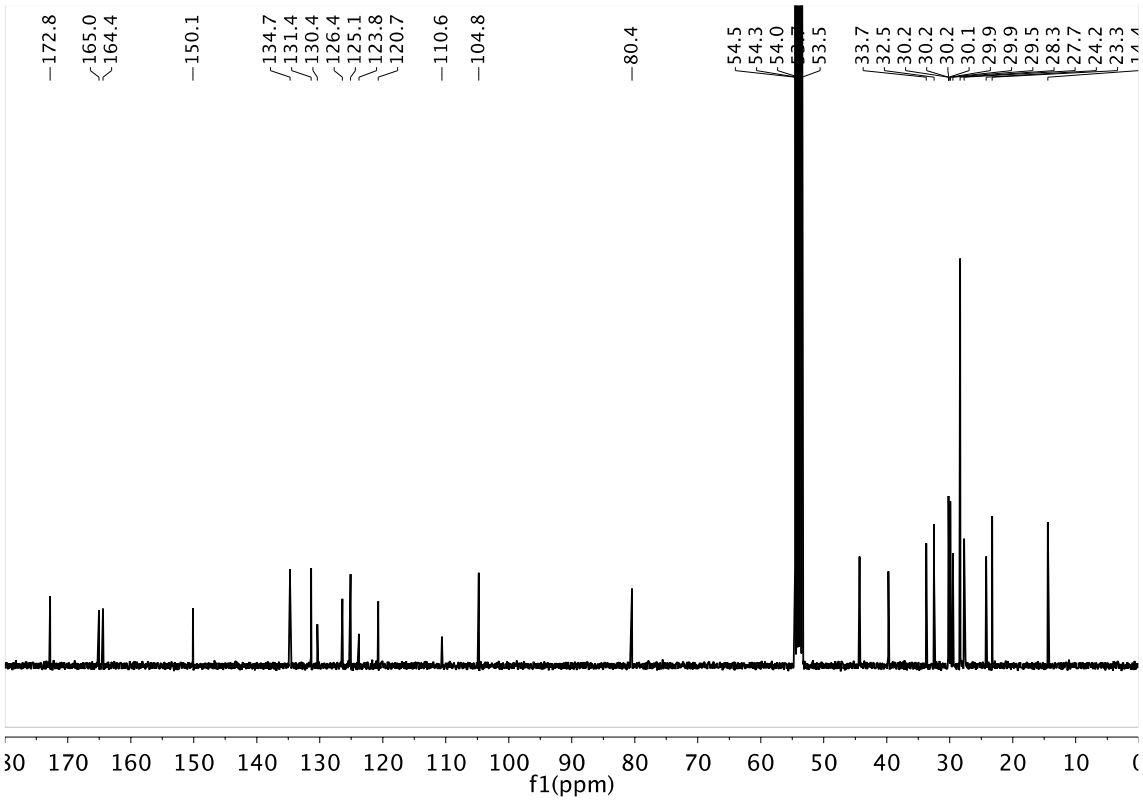

Figure S11. ^{13}C NMR spectrum of **23** in CD_2Cl_2.

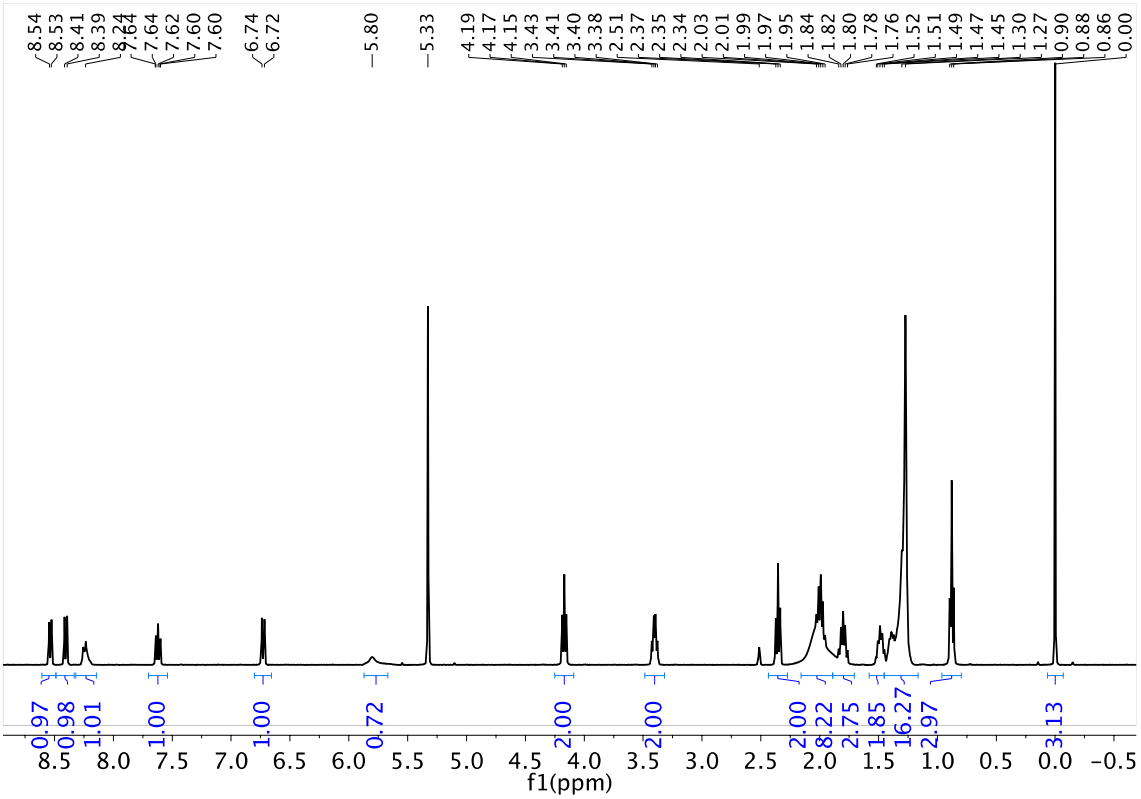

Figure S12. ^{1}H NMR spectrum of **7p** in CD_2Cl_2/DMSO-d_6 95:5.

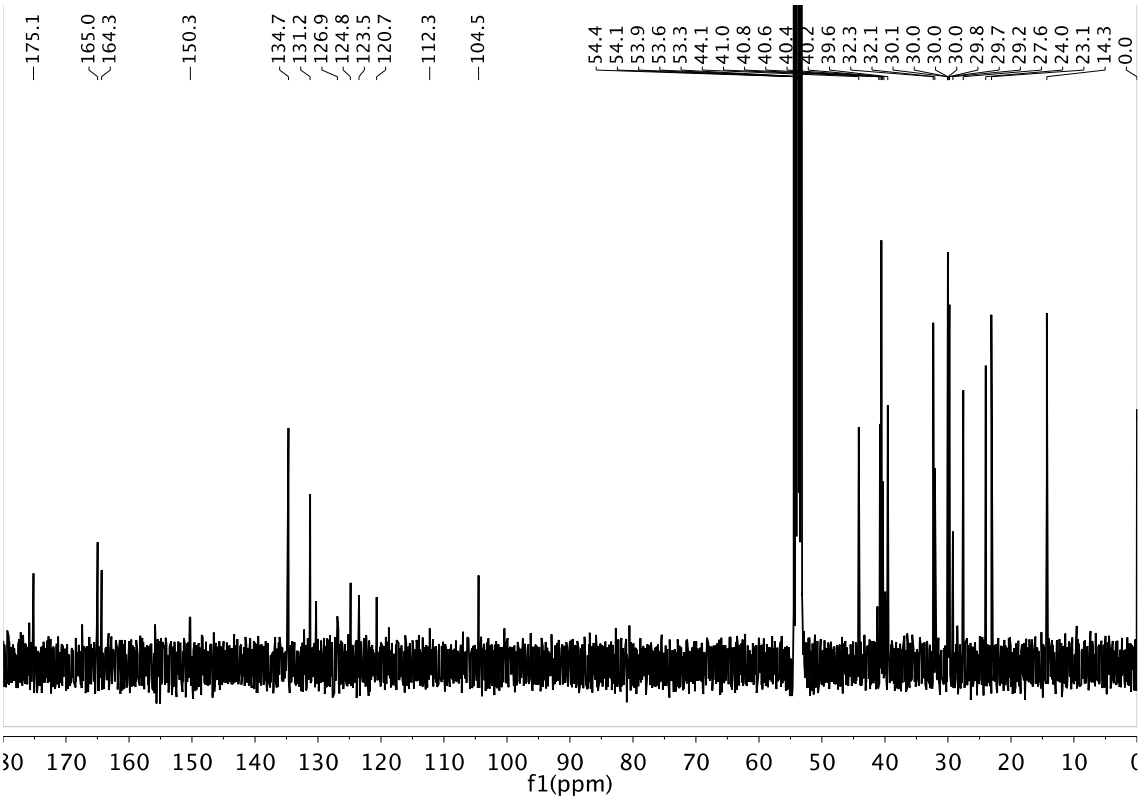

Figure S13. ^{13}C NMR spectrum of **7p** in CD_2Cl_2/DMSO-d_6 95:5.

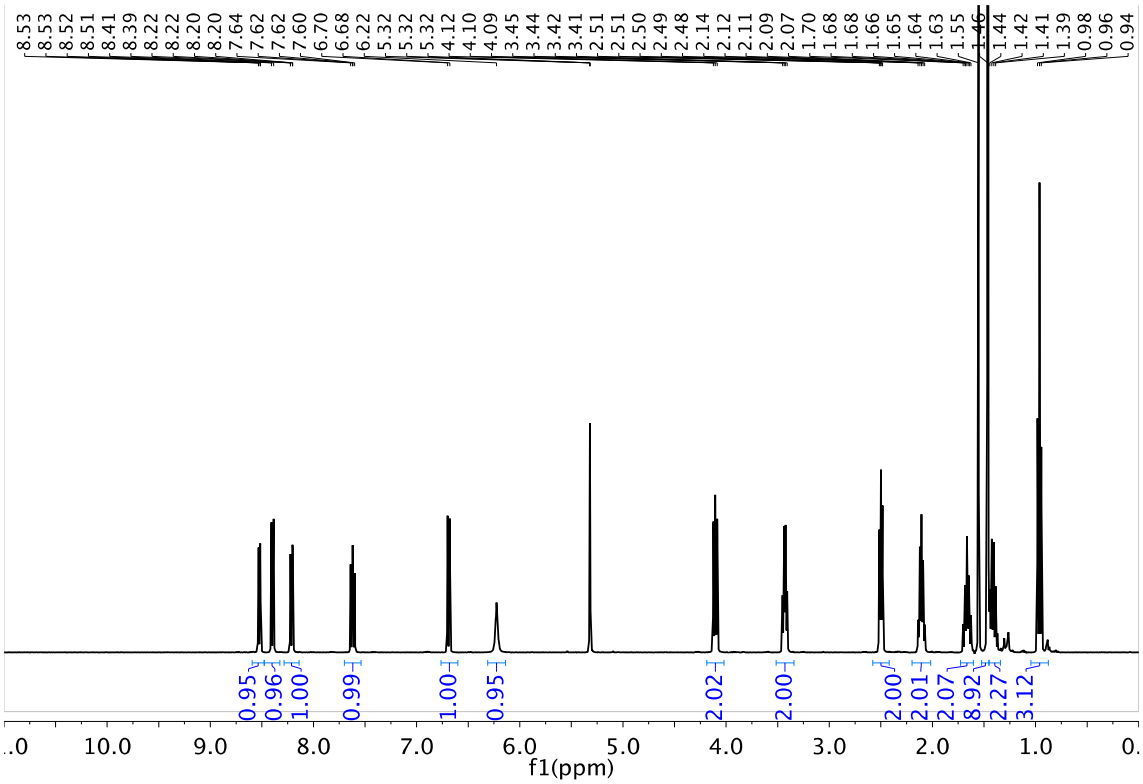

Figure S14. ^{1}H NMR spectrum of **26** in CD_2Cl_2.

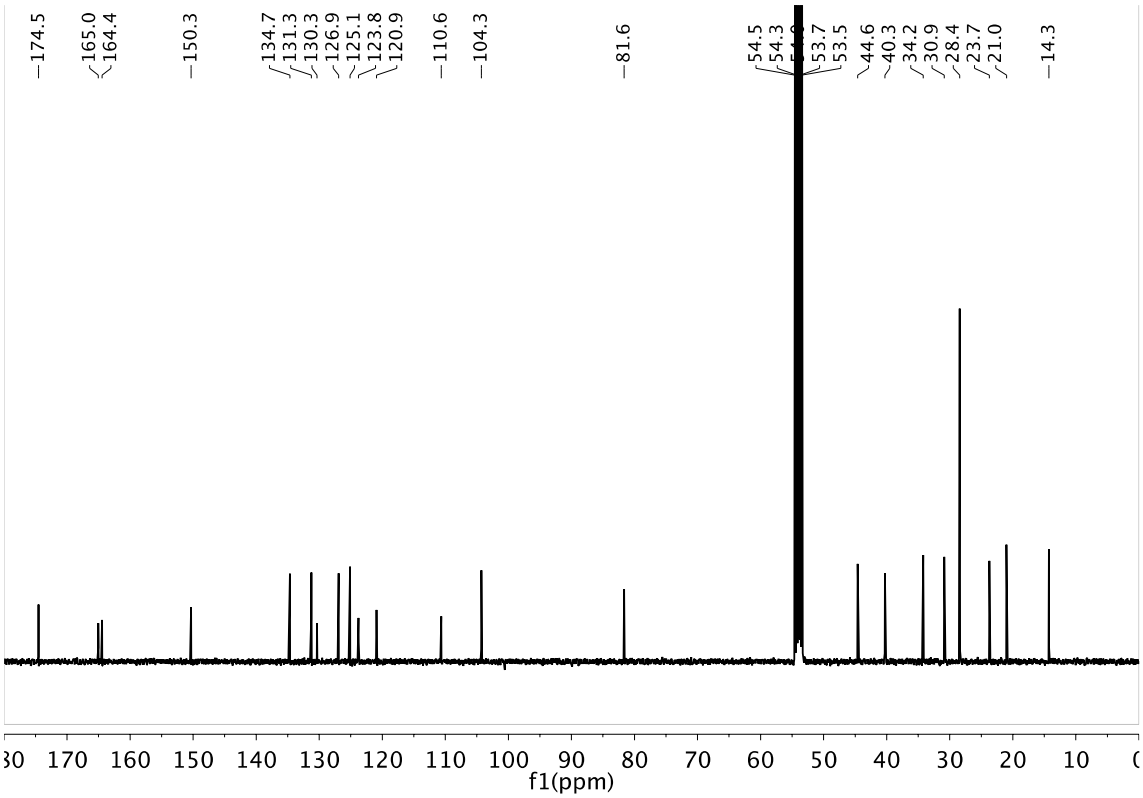

Figure S15. ^{13}C NMR spectrum of **26** in CD_2Cl_2.

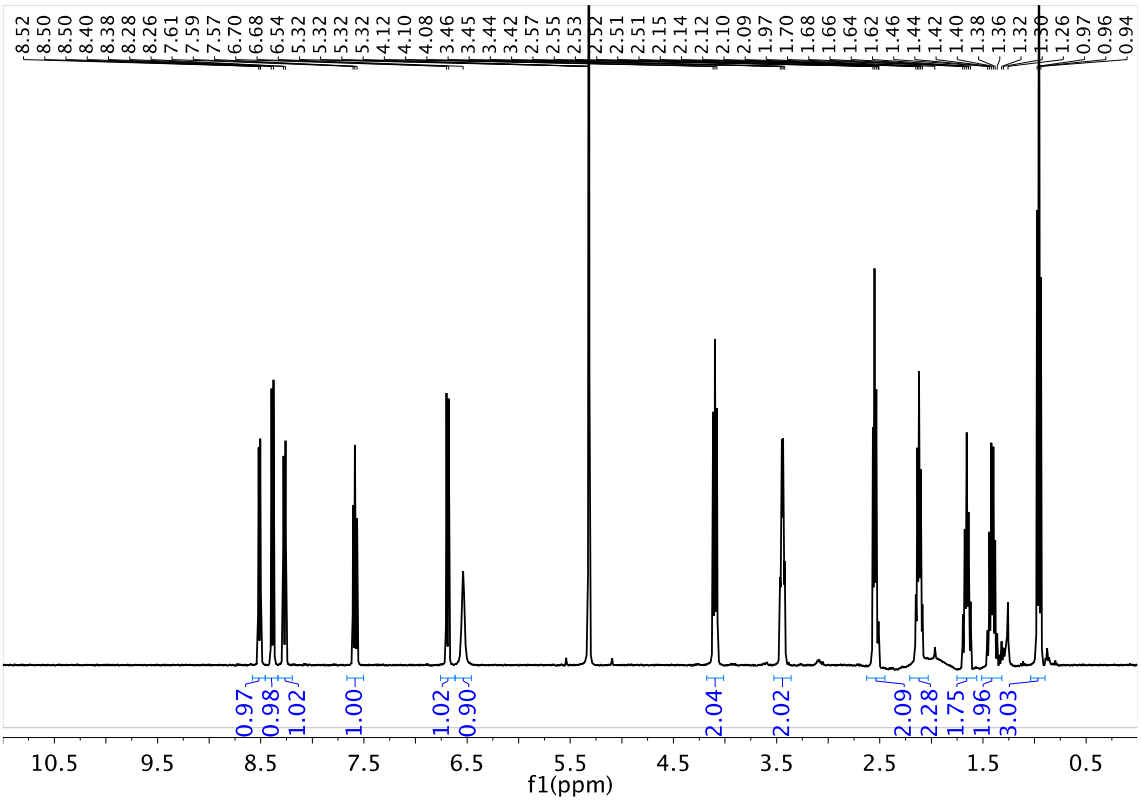

Figure S16. ^{1}H NMR spectrum of **4a** in CD_2Cl_2/DMSO-d_6 95:5.

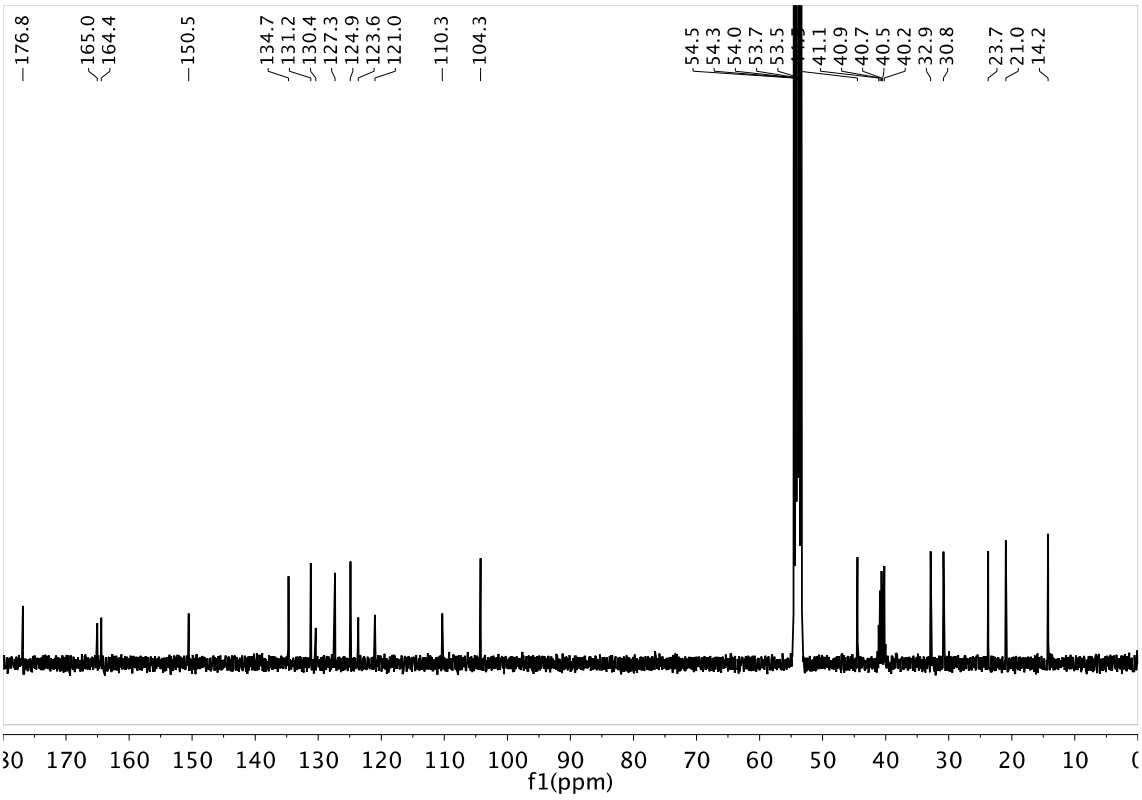

Figure S17. ^{13}C NMR spectrum of **4a** in CD_2Cl_2/DMSO-d_6 95:5.

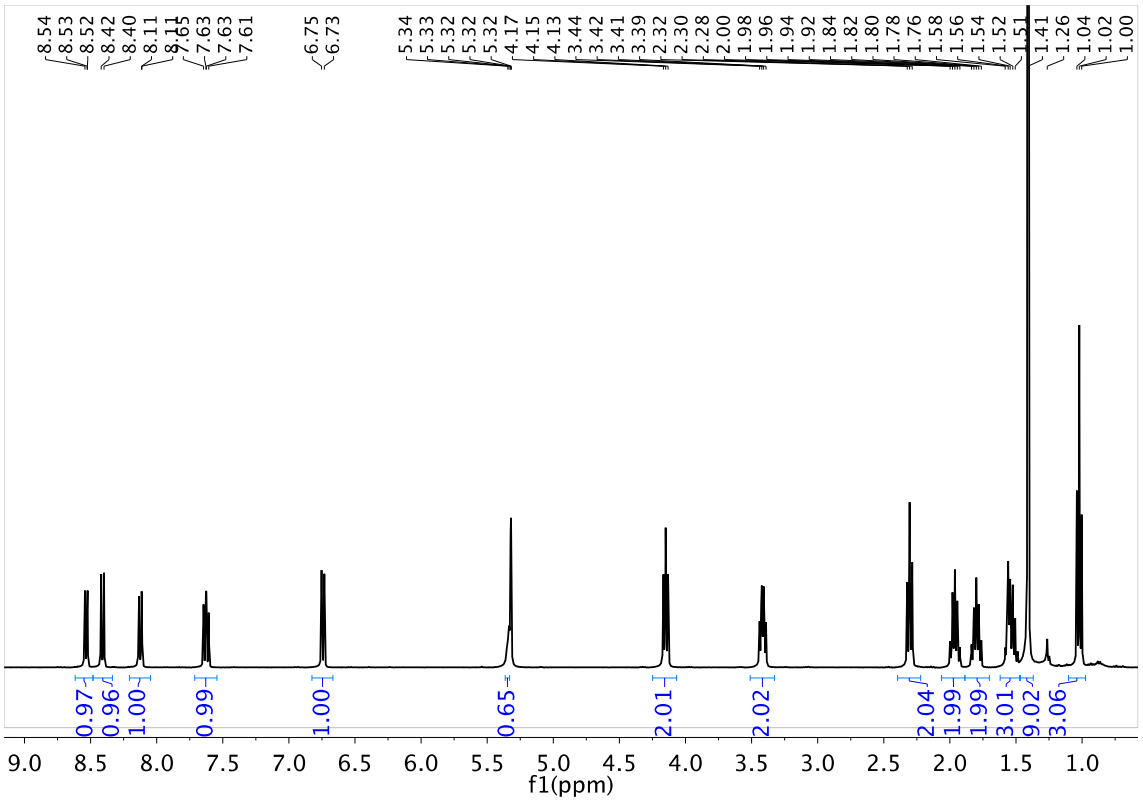

Figure S18. ^{1}H NMR spectrum of **27** in CD_2Cl_2.

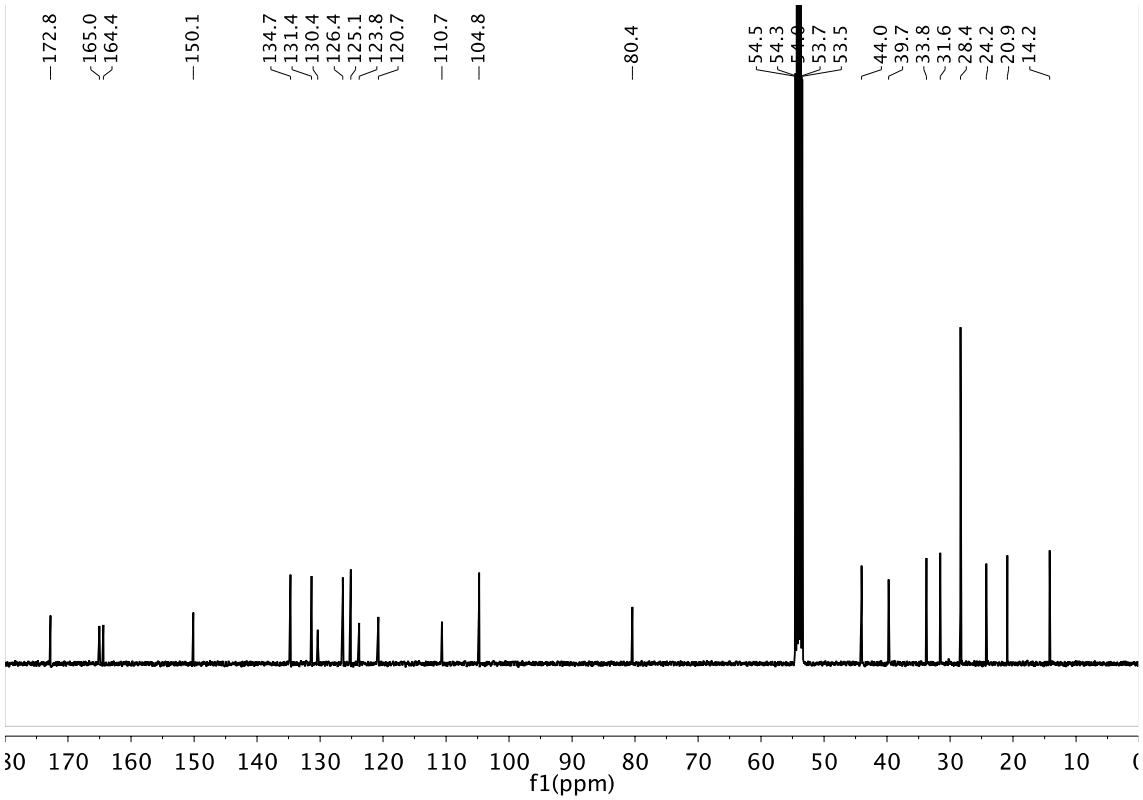

Figure S19. ^{13}C NMR spectrum of **27** in CD_2Cl_2.

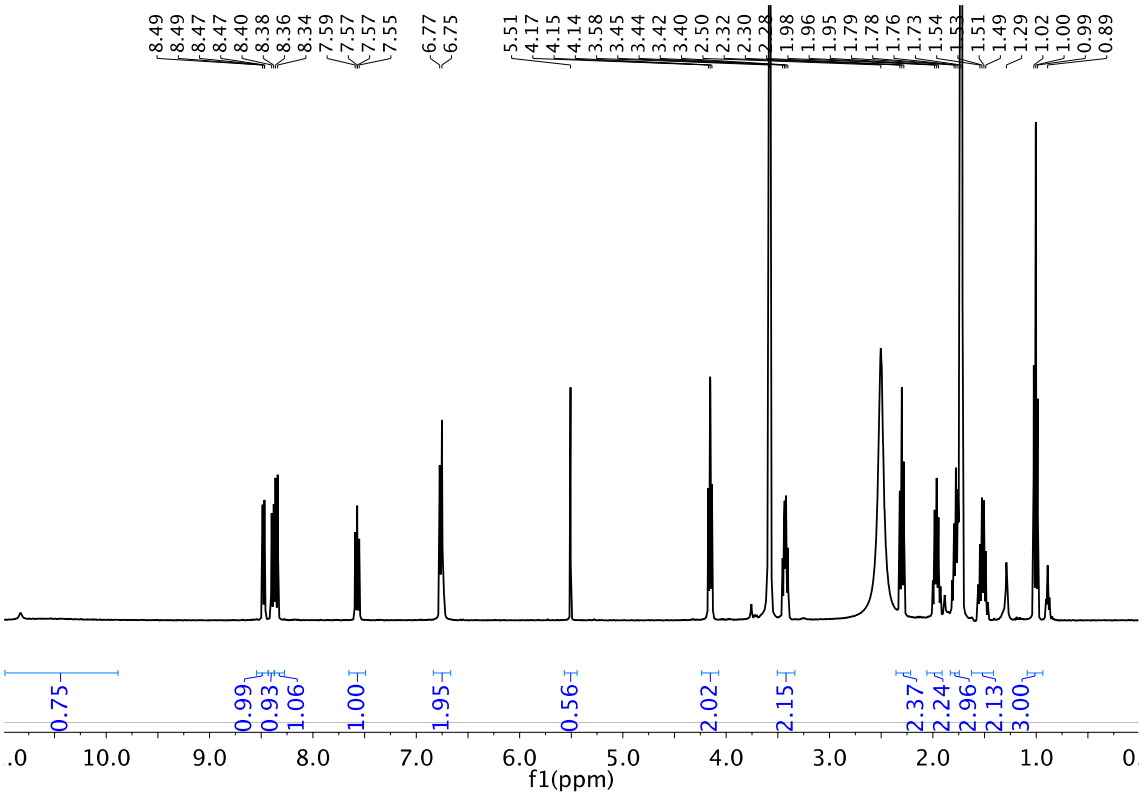

Figure S20. ^{1}H NMR spectrum of **4p** in THF-d_8.

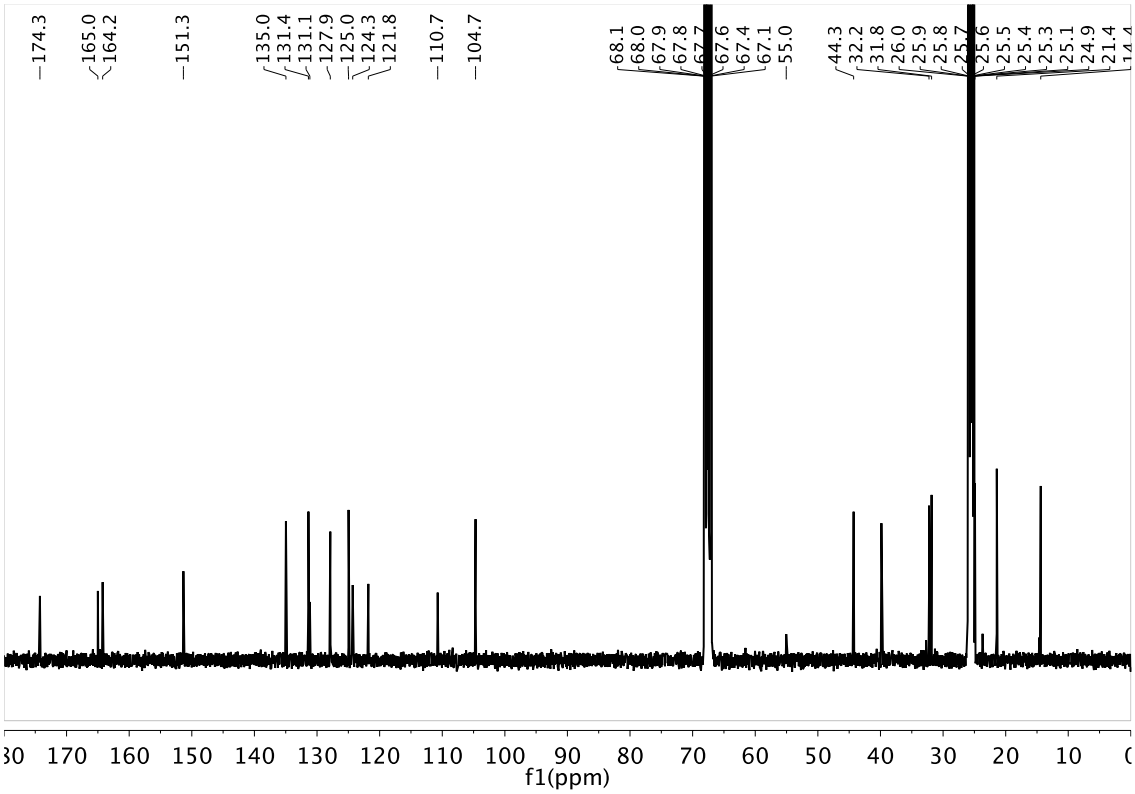

Figure S21. ^{13}C NMR spectrum of **4p** in THF-d_8.

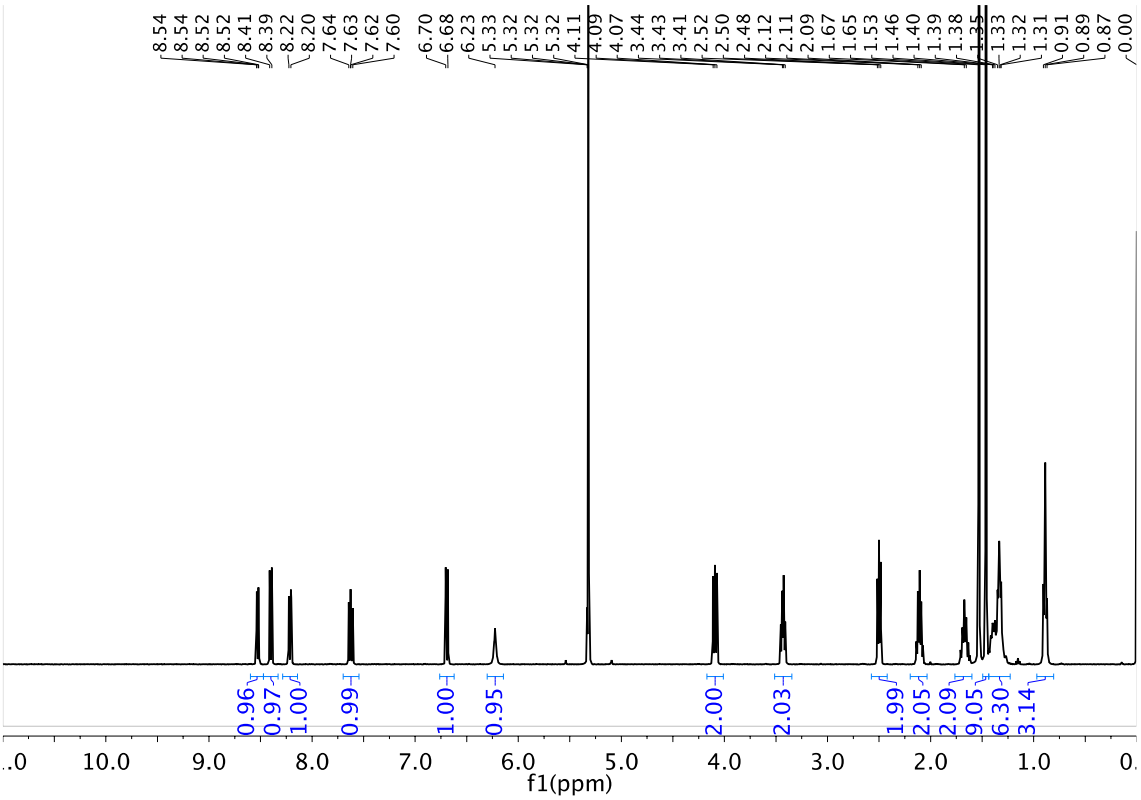

Figure S22. ^{1}H NMR spectrum of **30** in CD_2Cl_2.

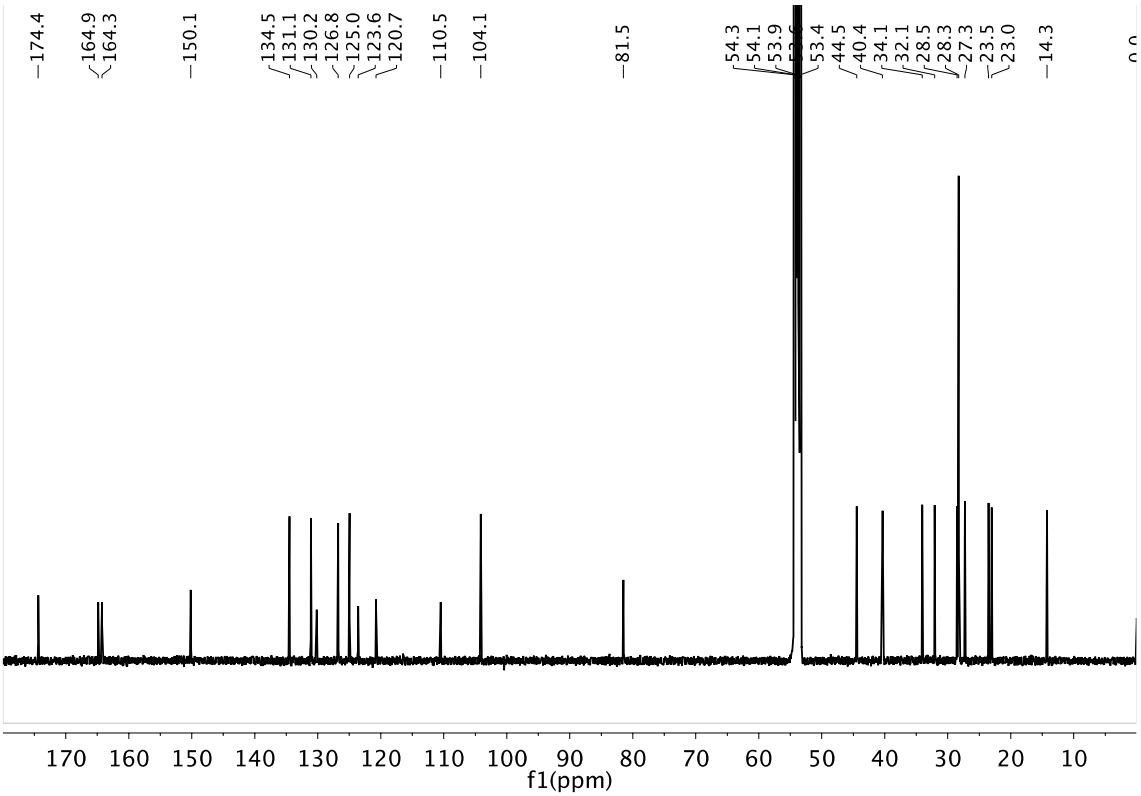

Figure S23. ^{13}C NMR spectrum of **30** in CD_2Cl_2.

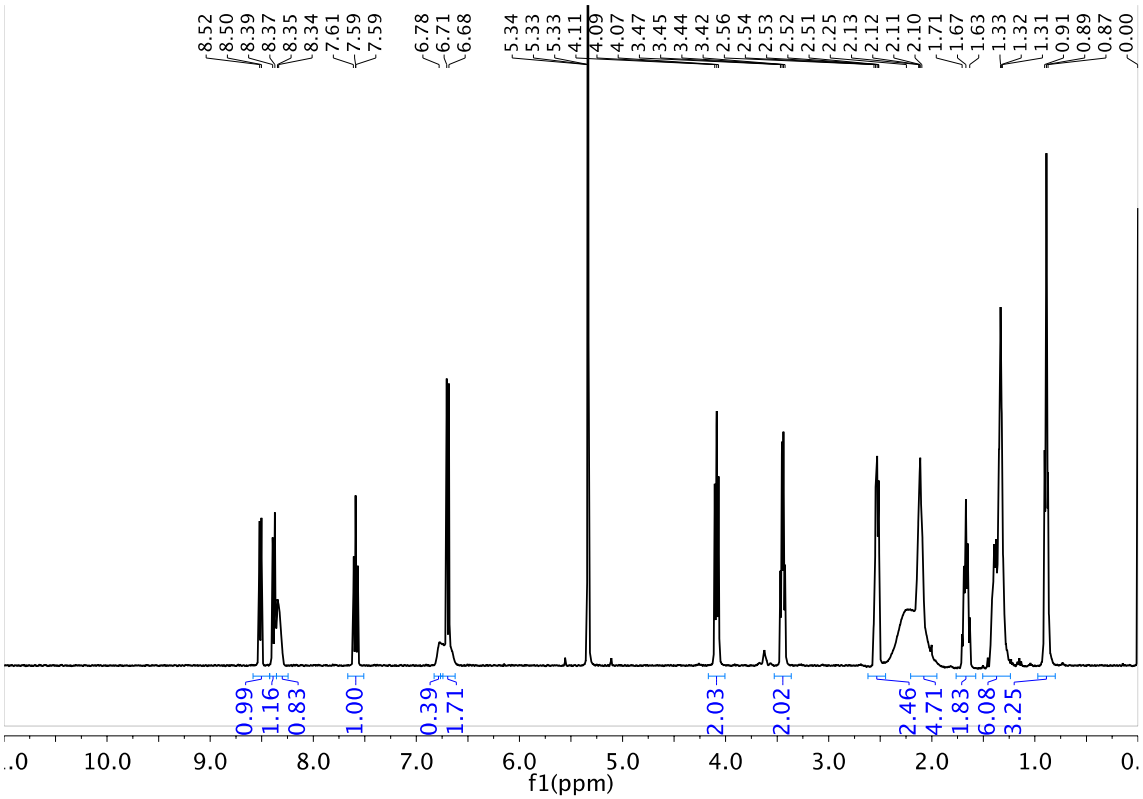

Figure S24. ^{1}H NMR spectrum of **5a** in CD_2Cl_2/DMSO-d_6 95:5.

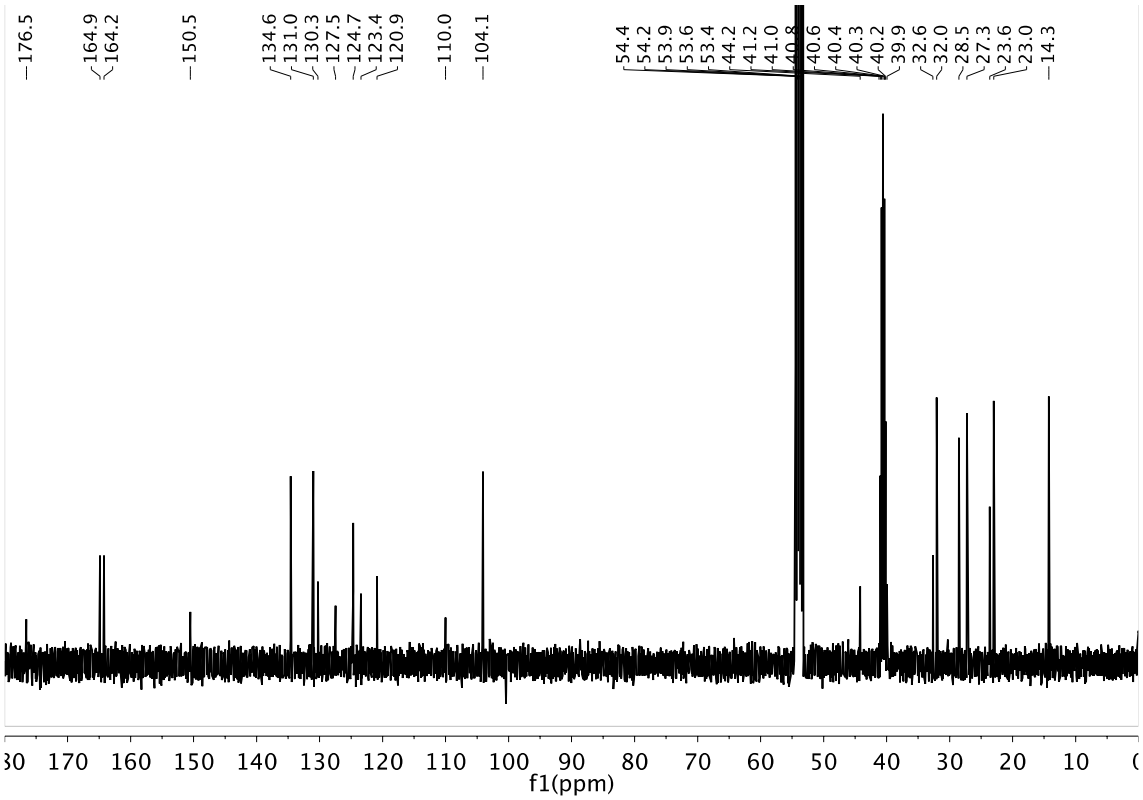

Figure S25. ^{13}C NMR spectrum of **5a** in CD_2Cl_2/DMSO-d_6 95:5.

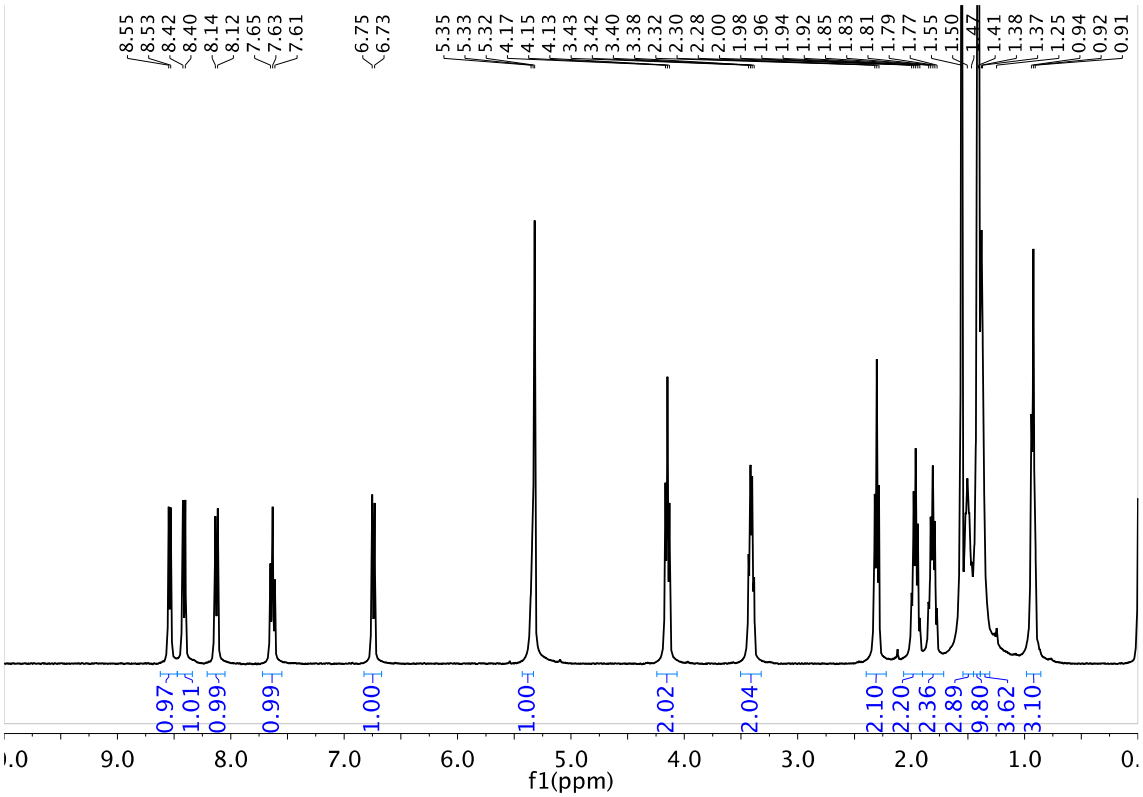

Figure S26. ^{1}H NMR spectrum of **31** in CD_2Cl_2.

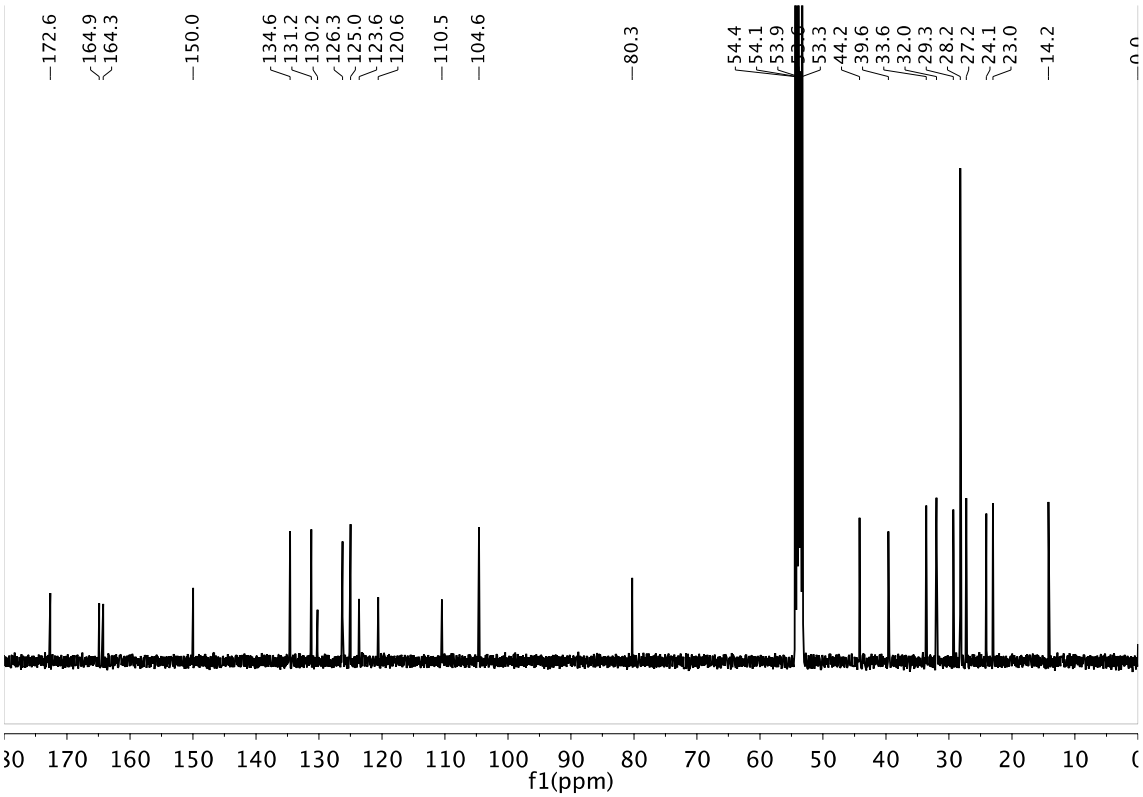

Figure S27. ^{13}C NMR spectrum of **31** in CD_2Cl_2.

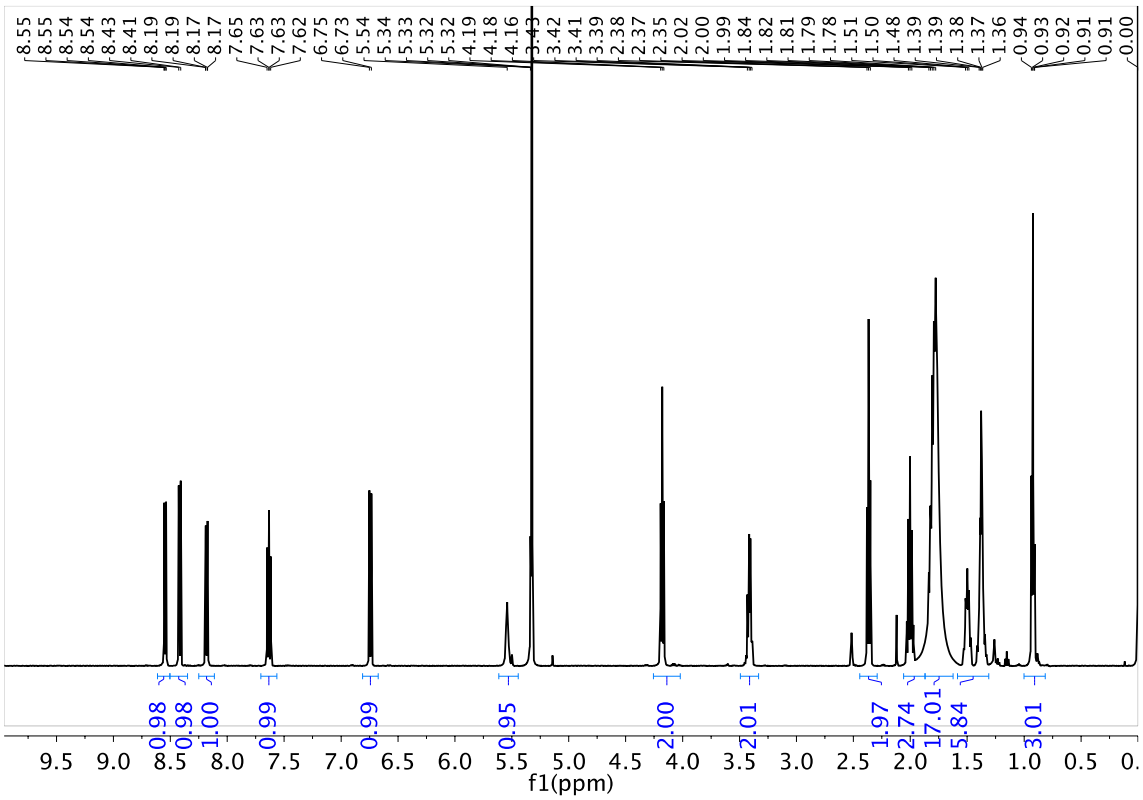

Figure S28. ^{1}H NMR spectrum of **5p** in CD_2Cl_2/DMSO-d_6 95:5.

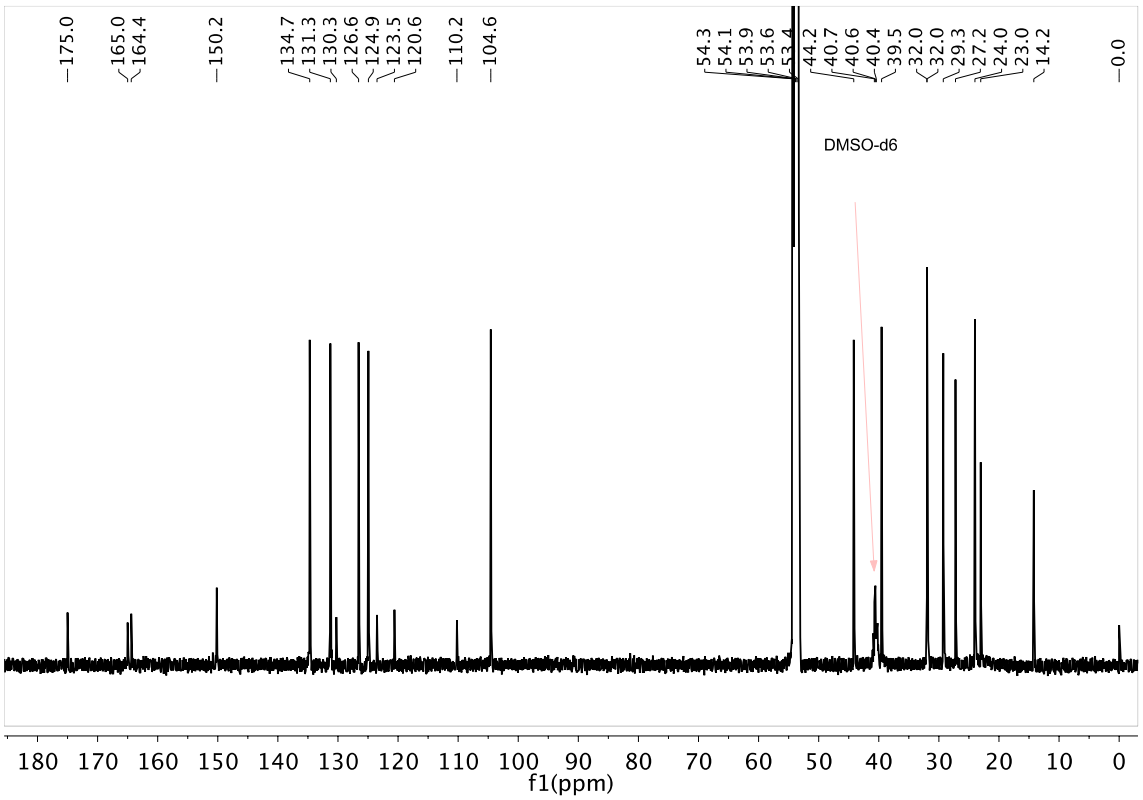

Figure S29. ^{13}C NMR spectrum of **5p** in CD_2Cl_2/DMSO-d_6 95:5.

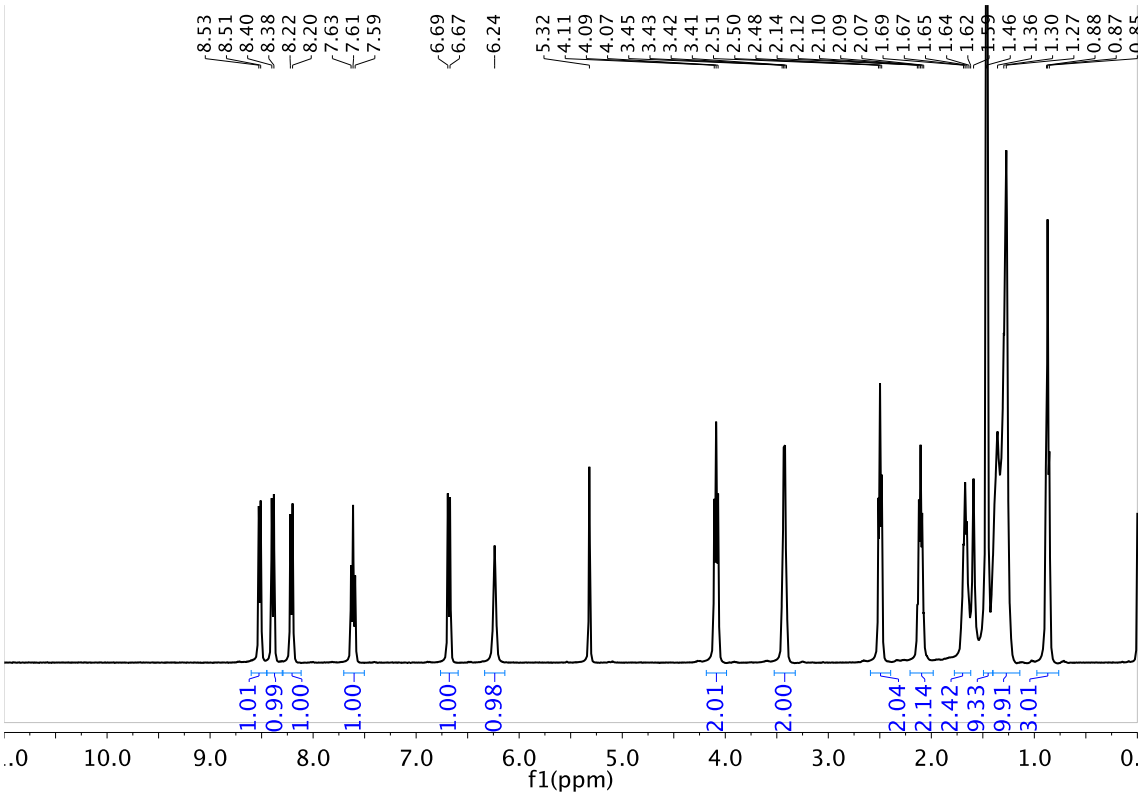

Figure S30. ^{1}H NMR spectrum of **34** in CD_2Cl_2.

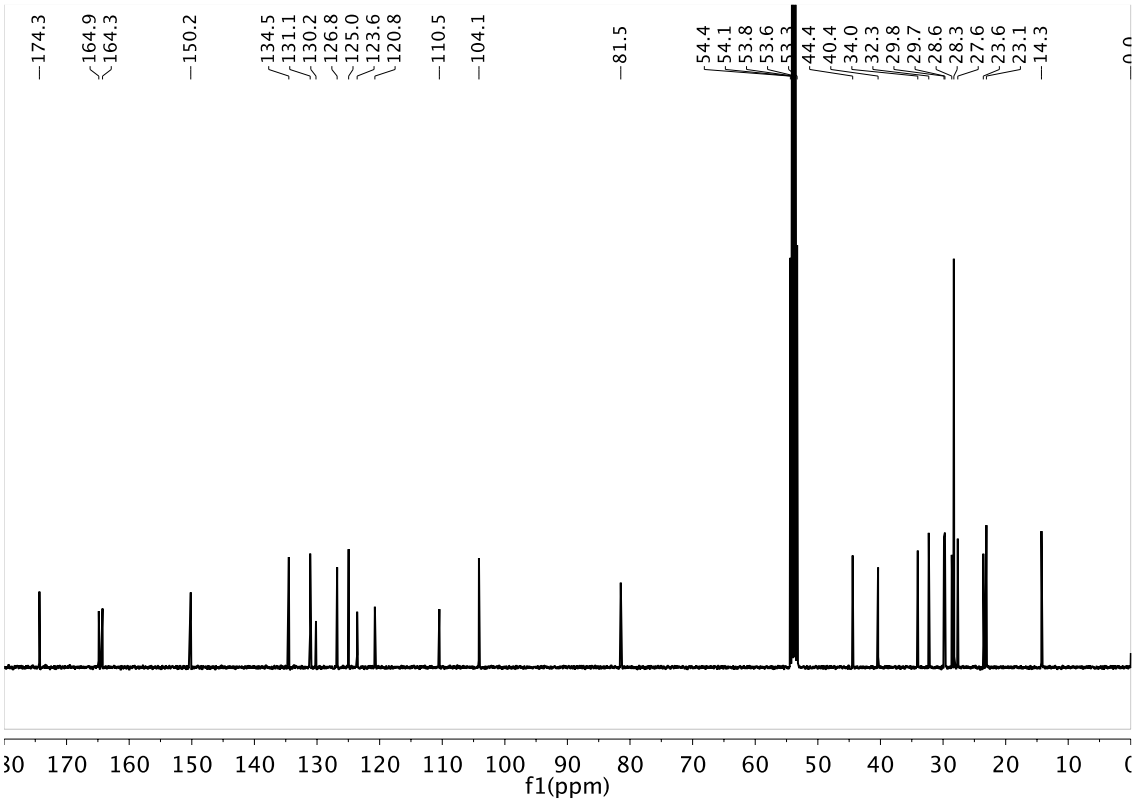

Figure S31. ^{13}C NMR spectrum of **34** in CD_2Cl_2.

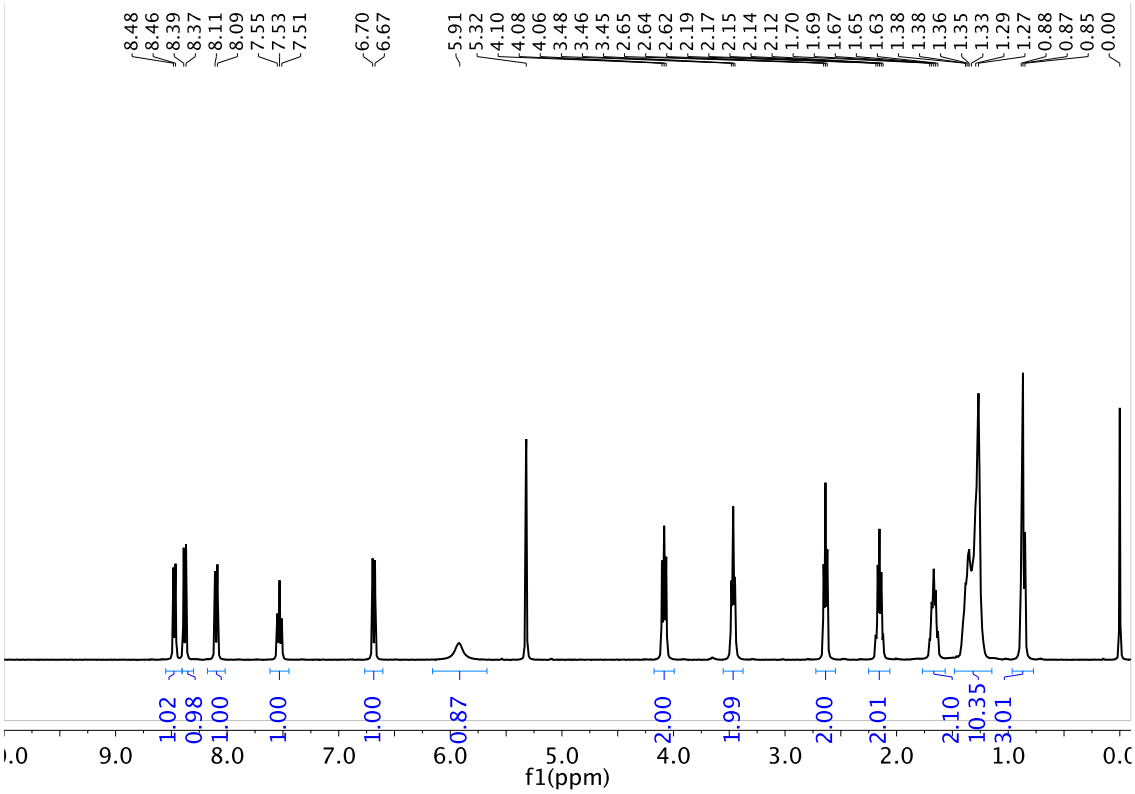

Figure S32. ^{1}H NMR spectrum of **6a** in CD_2Cl_2.

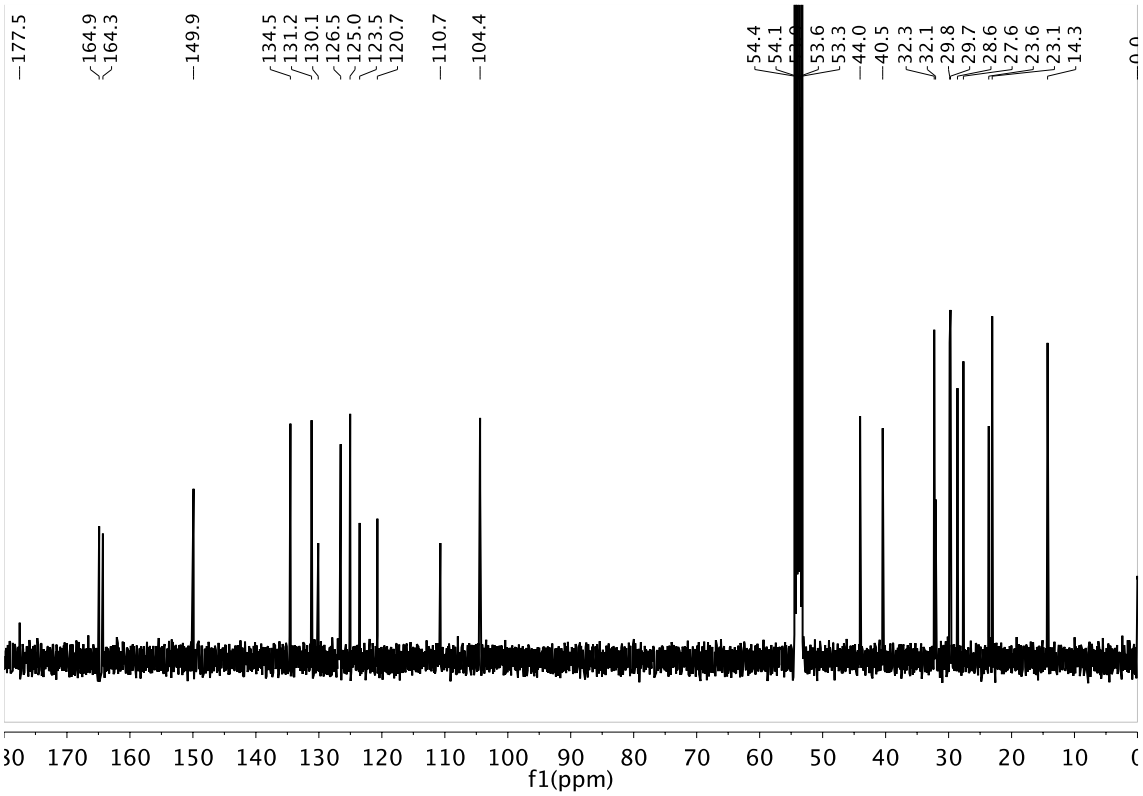

Figure S33. ^{13}C NMR spectrum of **6a** in CD_2Cl_2.

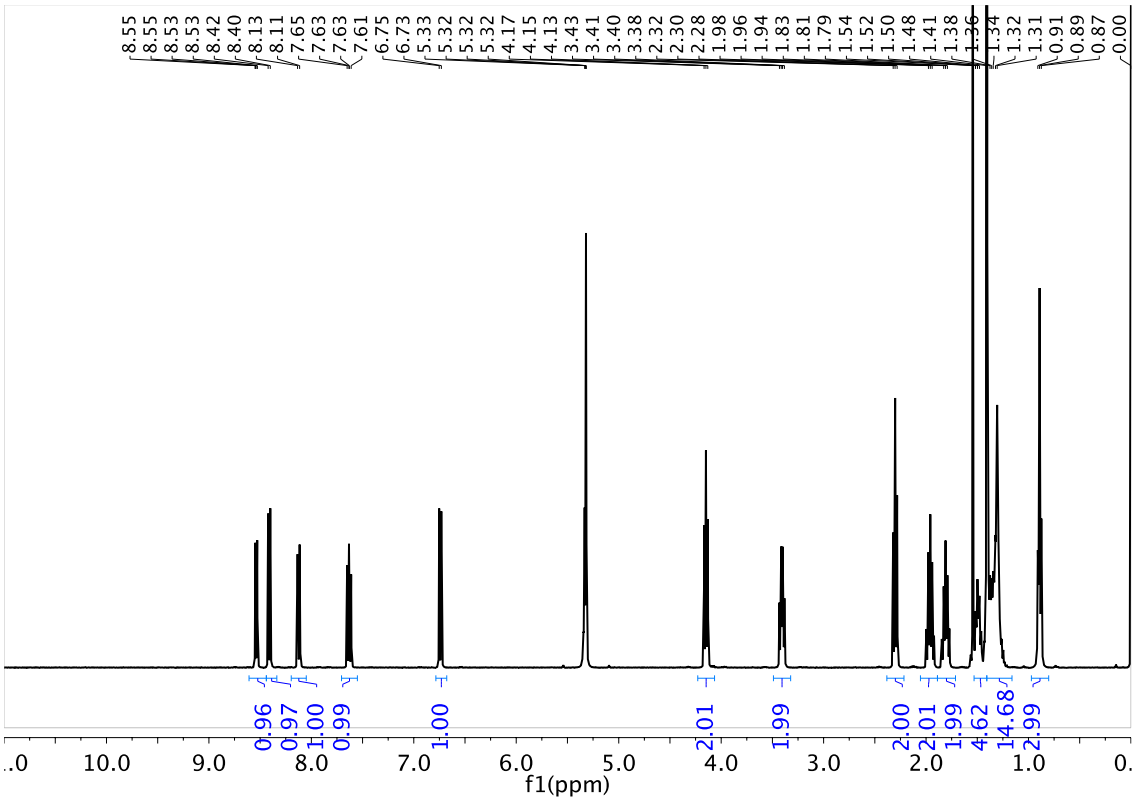

Figure S34. ^{1}H NMR spectrum of **35** in CD_2Cl_2.

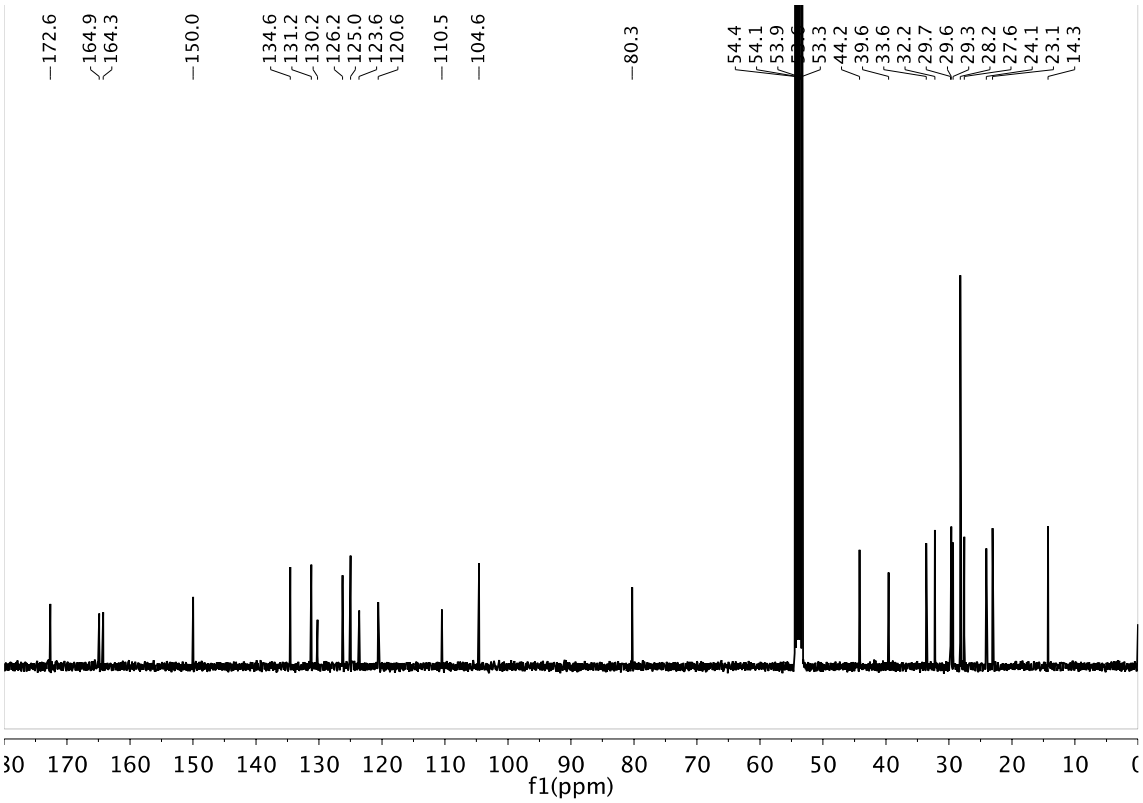

Figure S35. ^{13}C NMR spectrum of **35** in CD_2Cl_2.

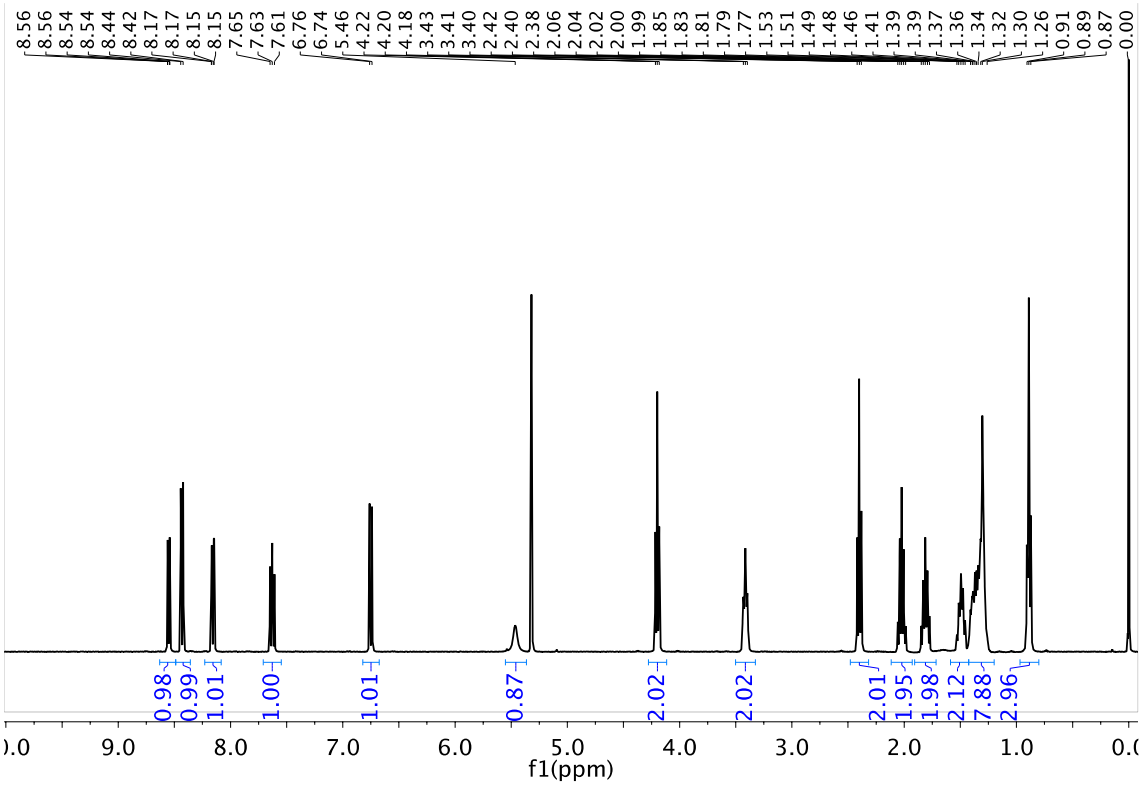

Figure S36. ^{1}H NMR spectrum of **6p** in CD_2Cl_2.

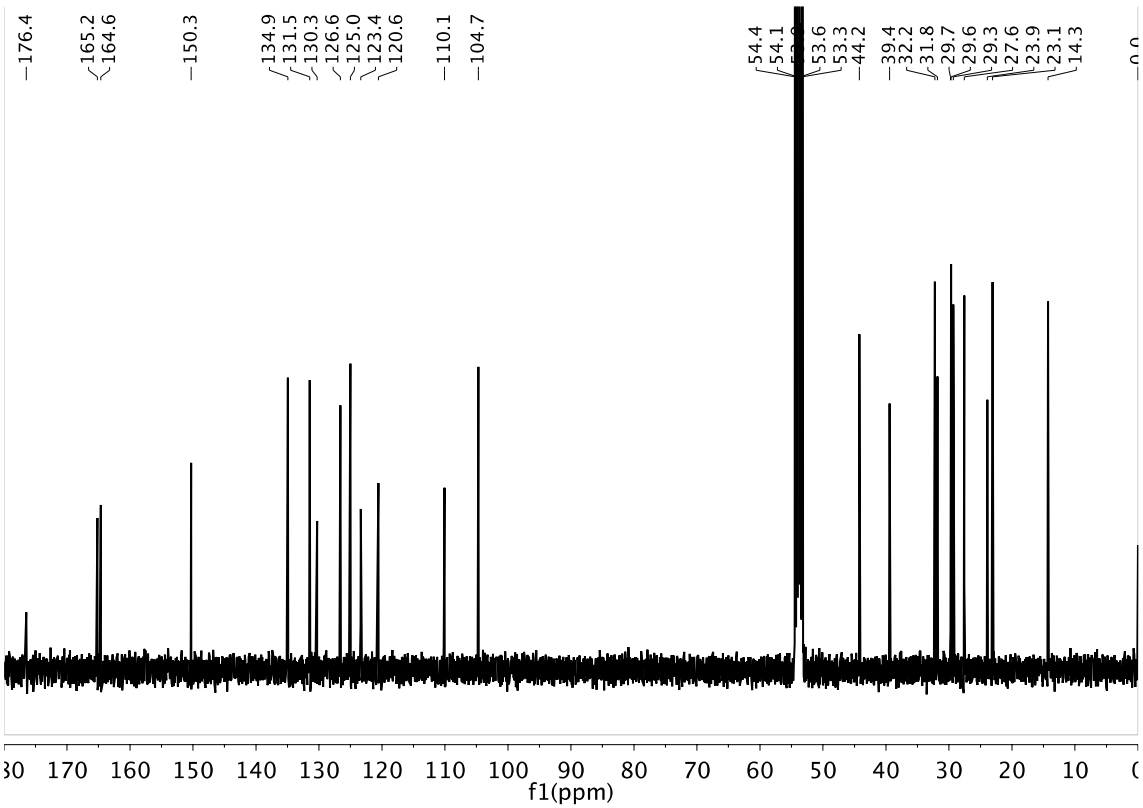

Figure S37. ^{13}C NMR spectrum of **6p** in CD_2Cl_2.

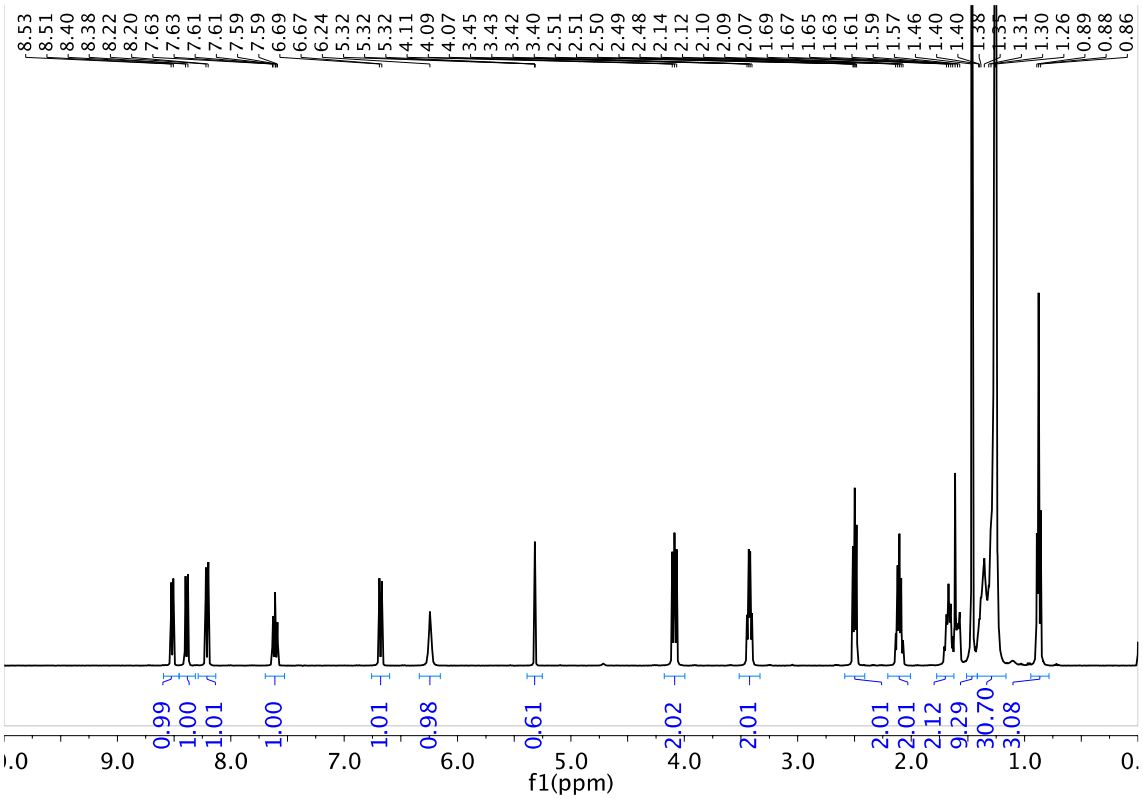

Figure S38. ^{1}H NMR spectrum of **38** in CD_2Cl_2.

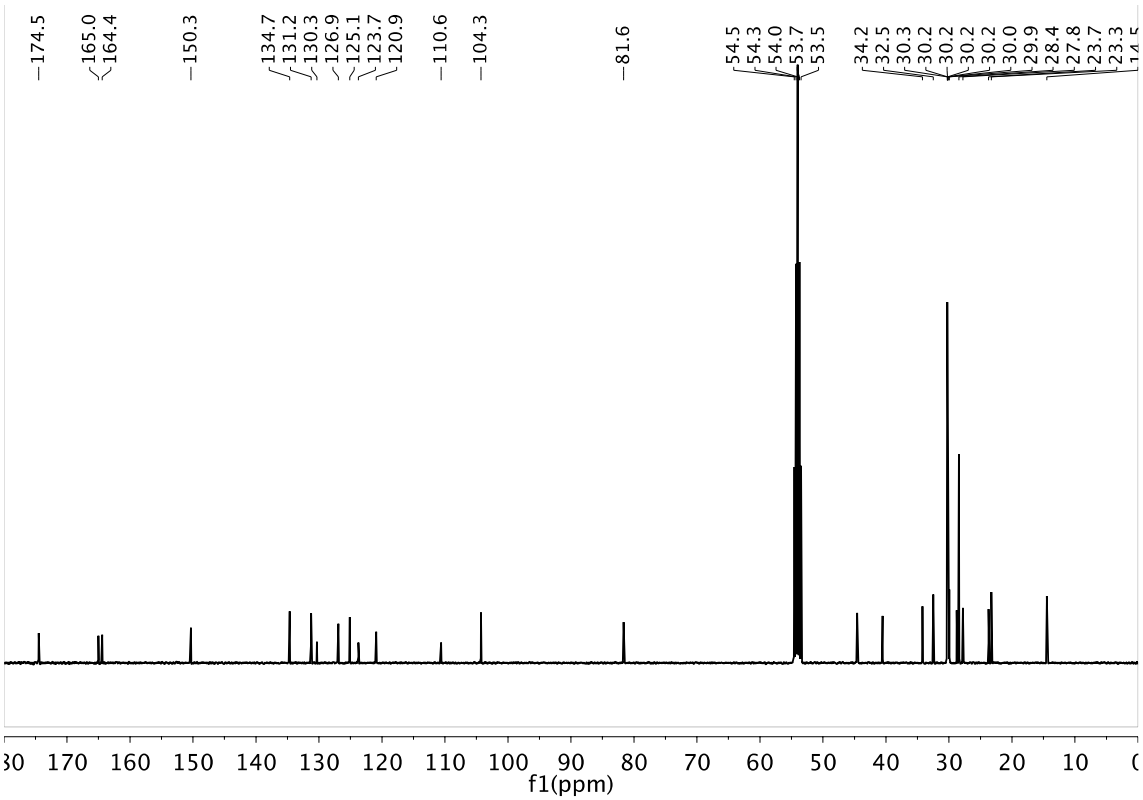

Figure S39. ^{13}C NMR spectrum of **38** in CD_2Cl_2.

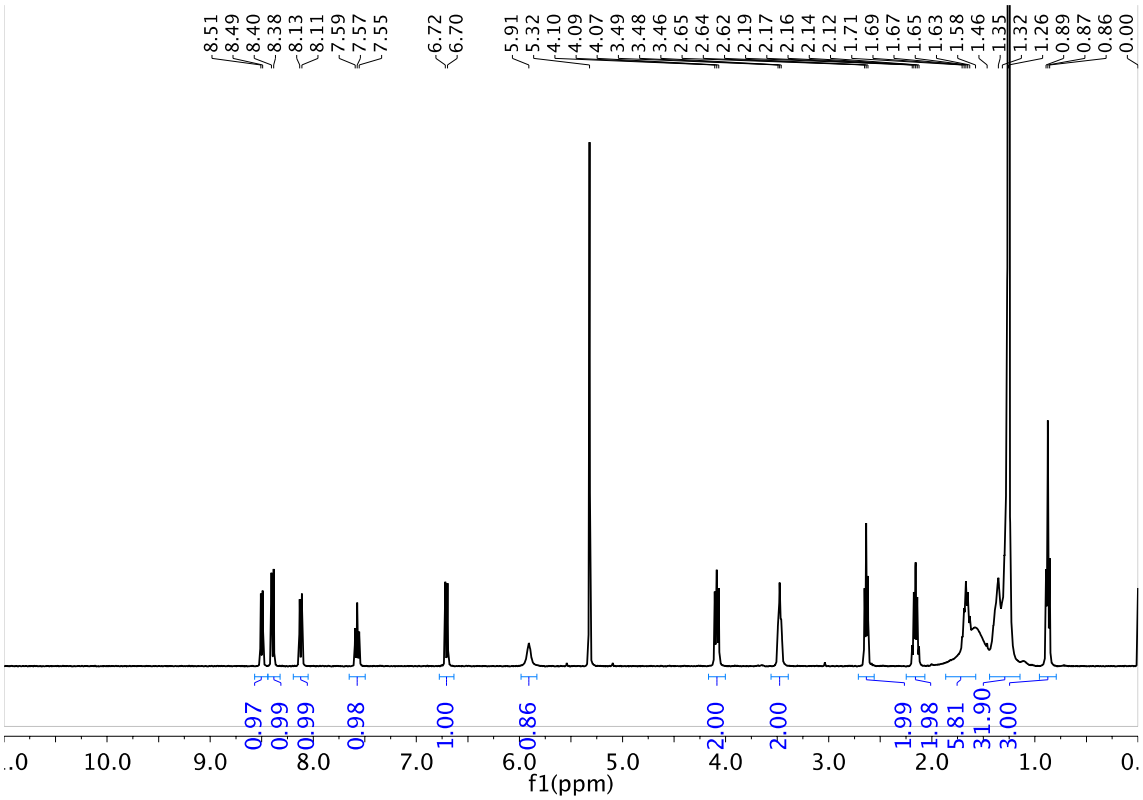

Figure S40. ^{1}H NMR spectrum of **8a** in CD_2Cl_2.

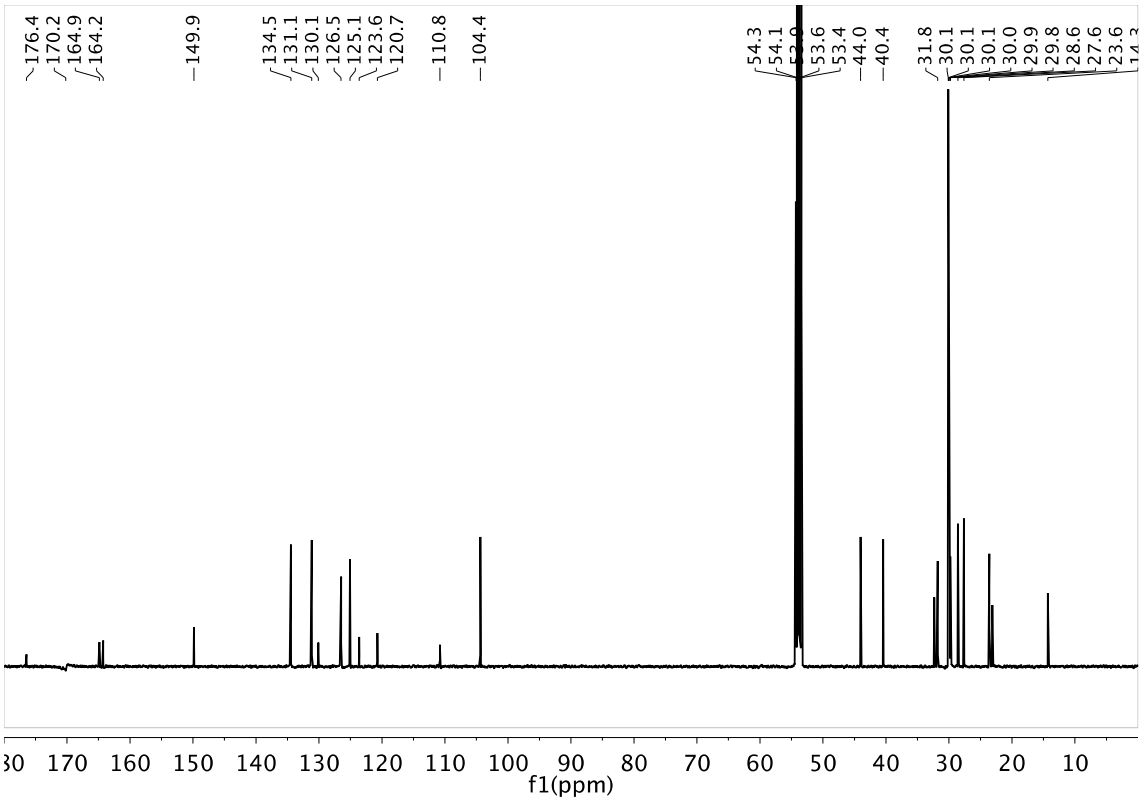

Figure S41. ^{13}C NMR spectrum of **8a** in CD_2Cl_2.

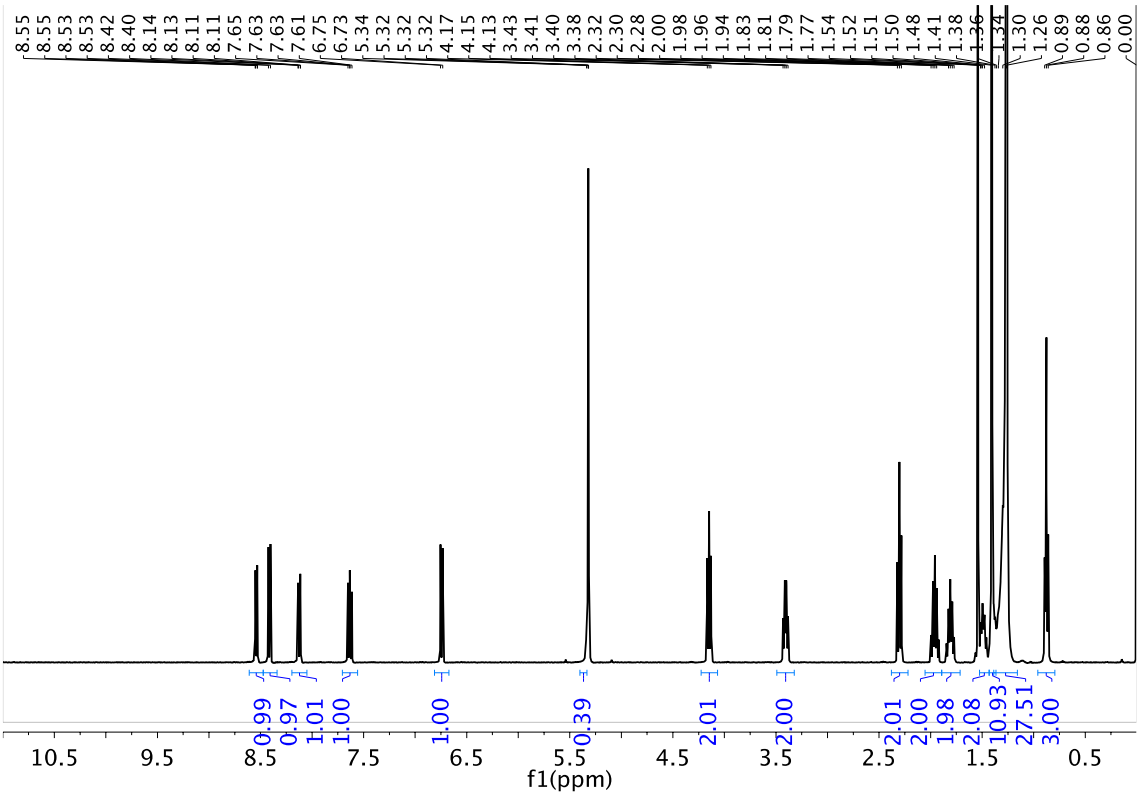

Figure S42. ^{1}H NMR spectrum of **39** in CD_2Cl_2.

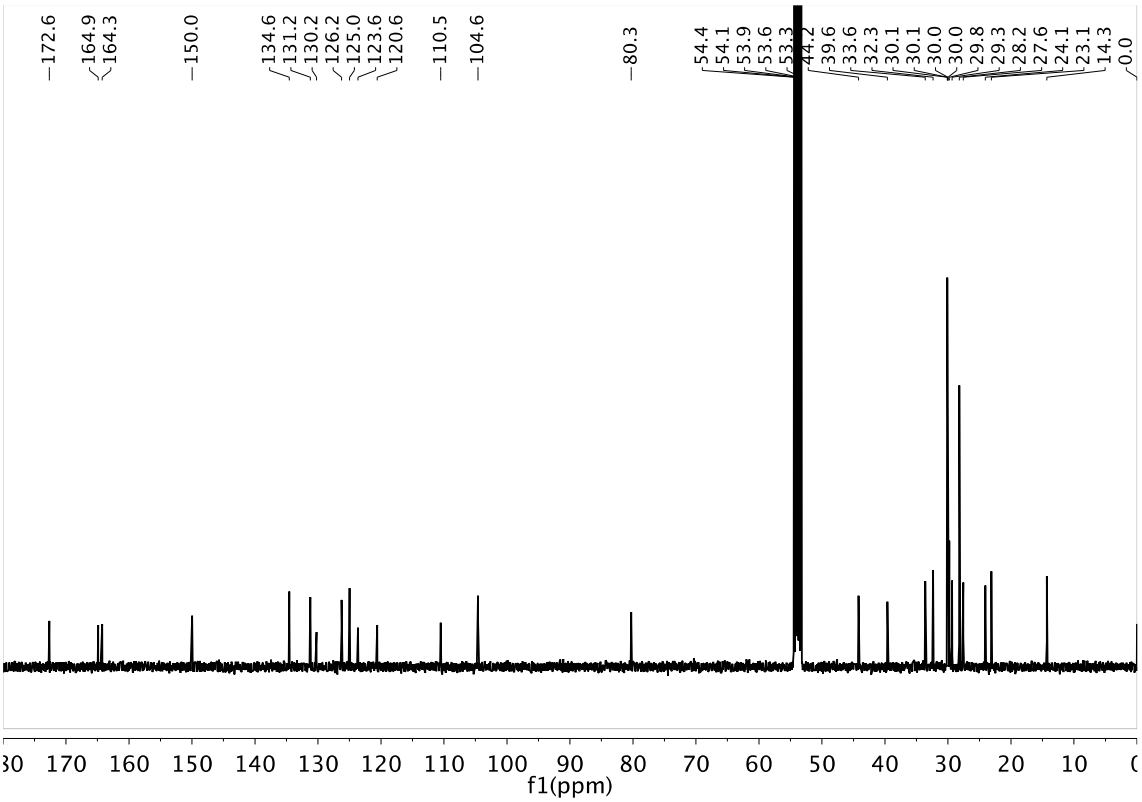

Figure S43. ^{13}C NMR spectrum of **39** in CD_2Cl_2.

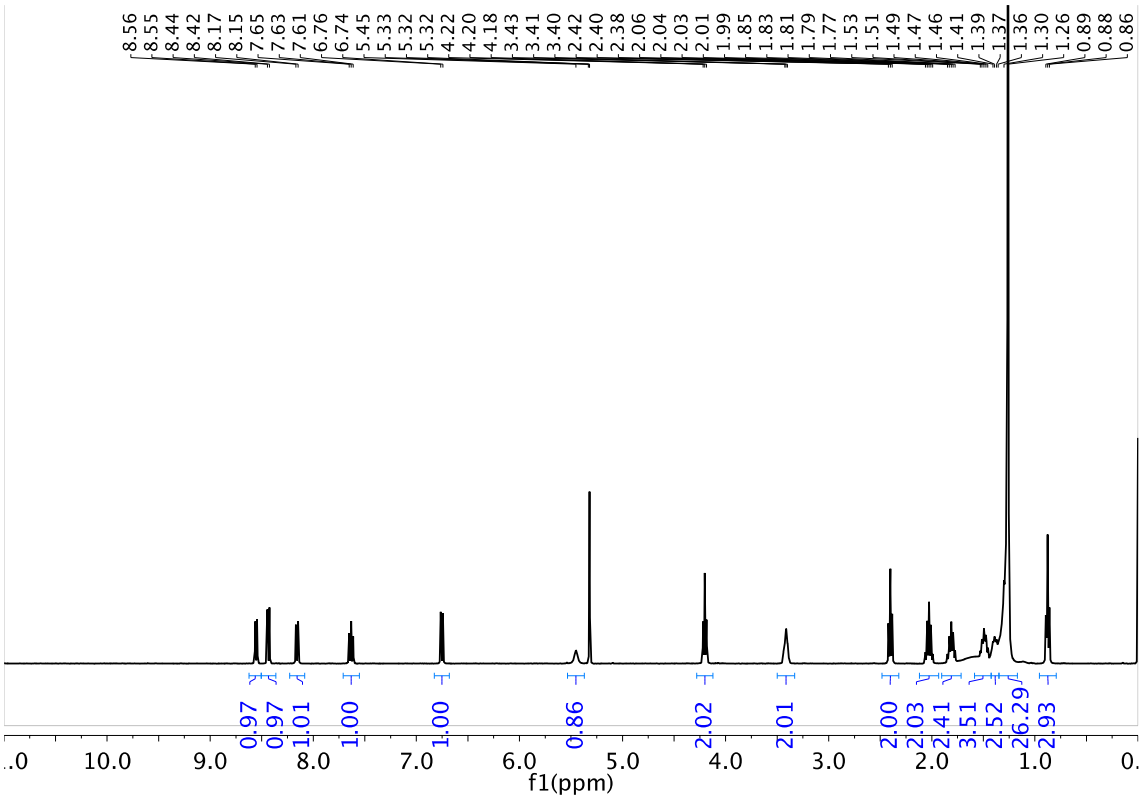

Figure S44. ^{1}H NMR spectrum of **8p** in CD_2Cl_2.

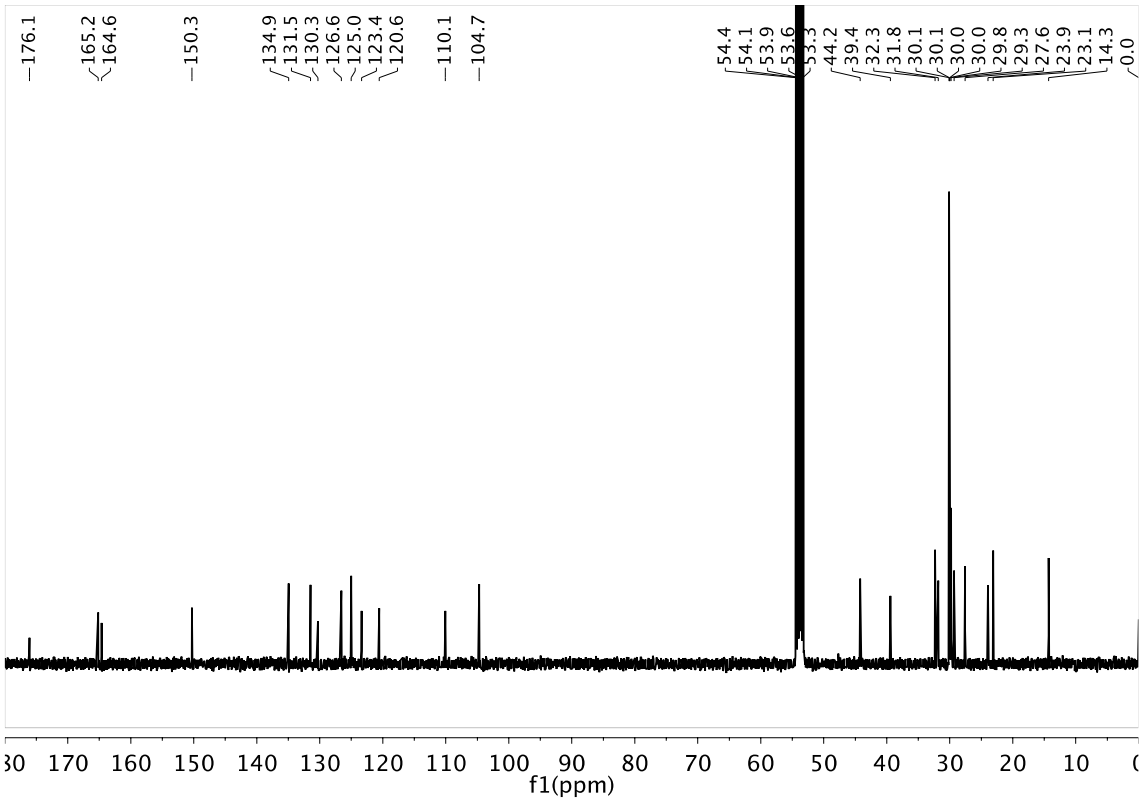

Figure S45. ^{13}C NMR spectrum of **8p** in CD_2Cl_2.

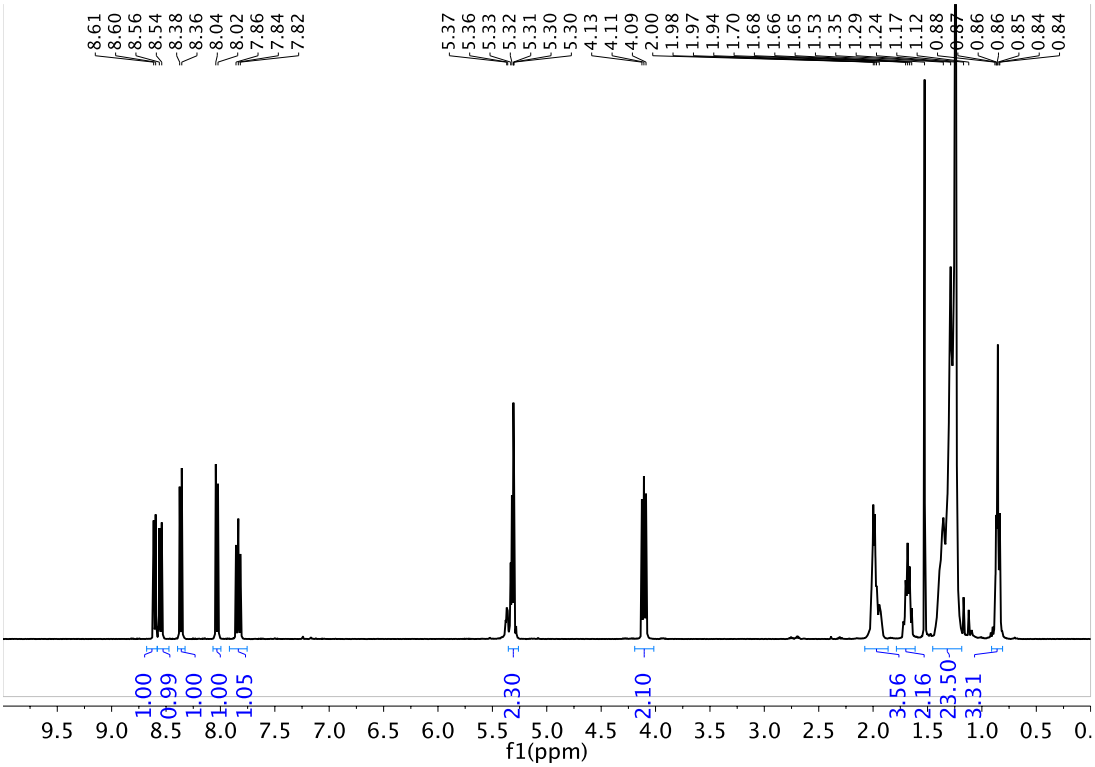

Figure S46. ^{1}H NMR spectrum of **41** in CD_2Cl_2.

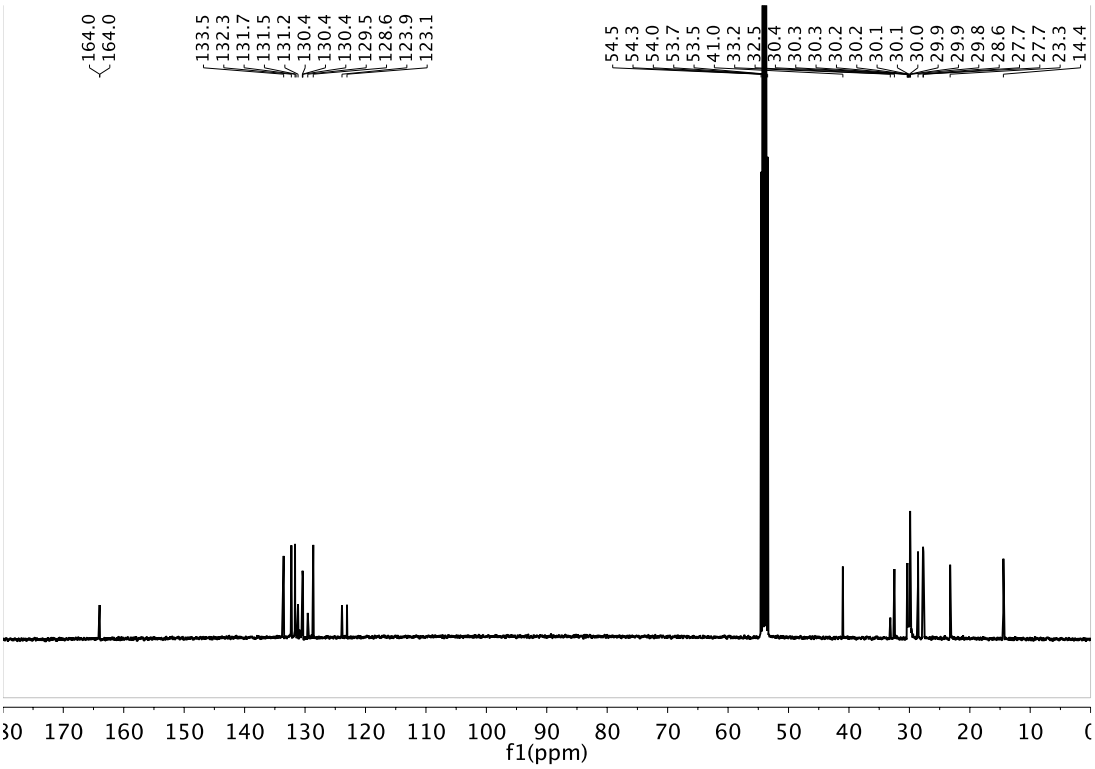

Figure S47. ^{13}C NMR spectrum of **41** in CD_2Cl_2.

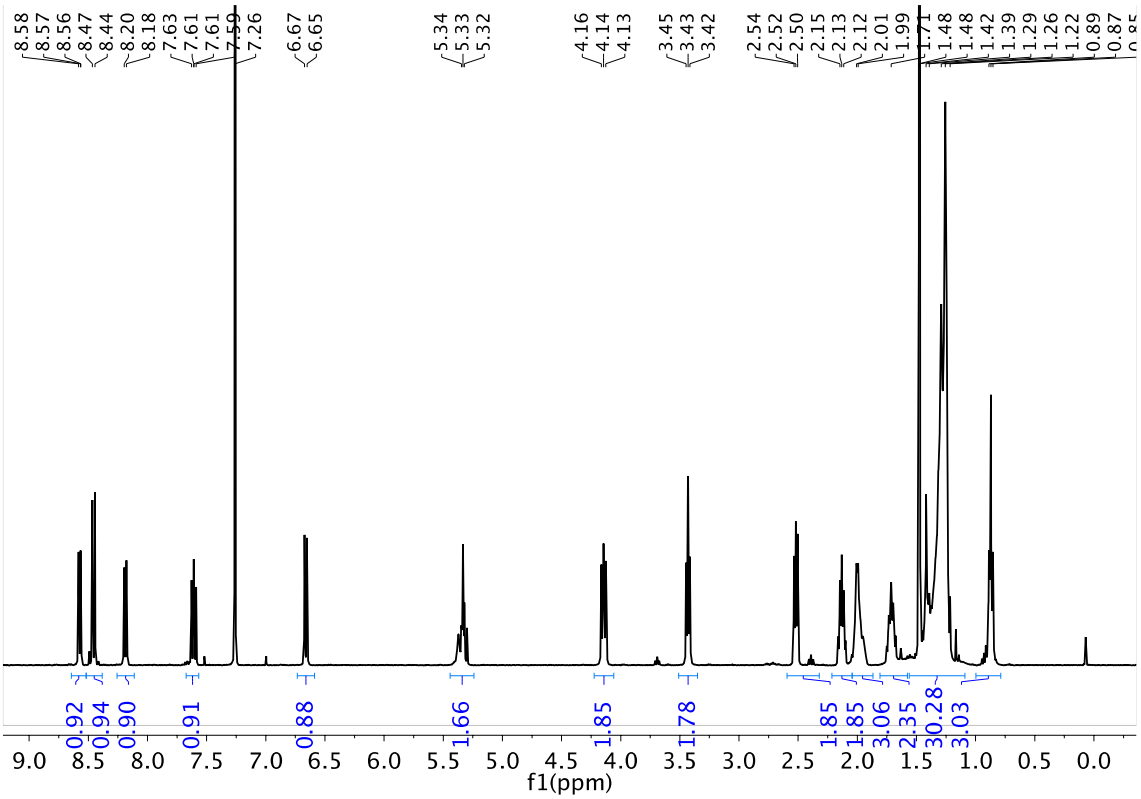

Figure S48. ^{1}H NMR spectrum of **42** in CD_2Cl_2.

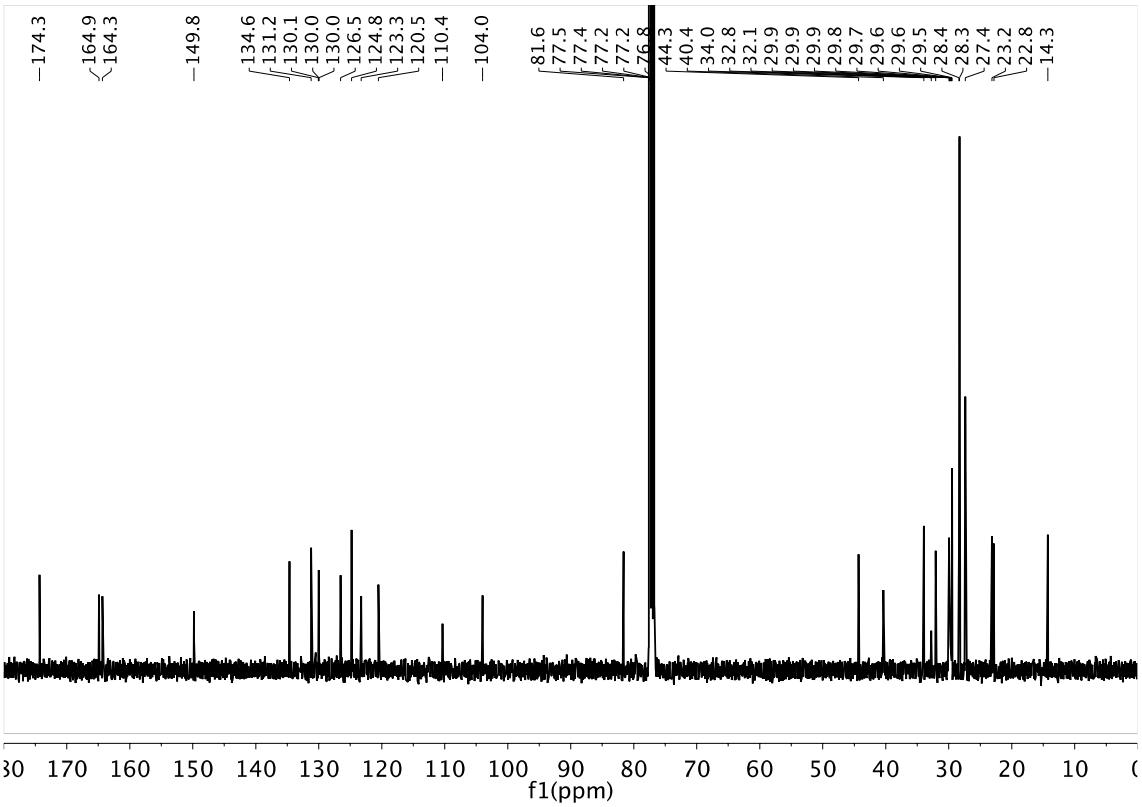

Figure S49. ^{13}C NMR spectrum of **42** in CD_2Cl_2.

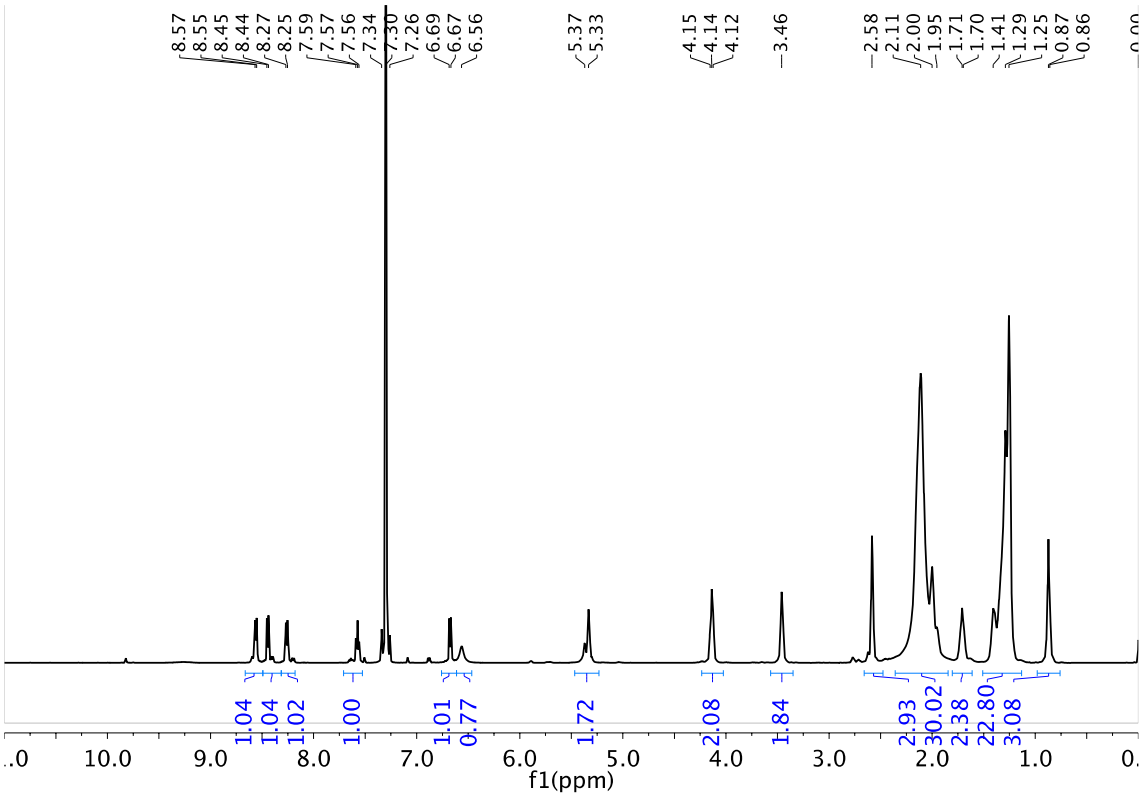

Figure S50. ^{1}H NMR spectrum of **9a** in $CDCl_3$.

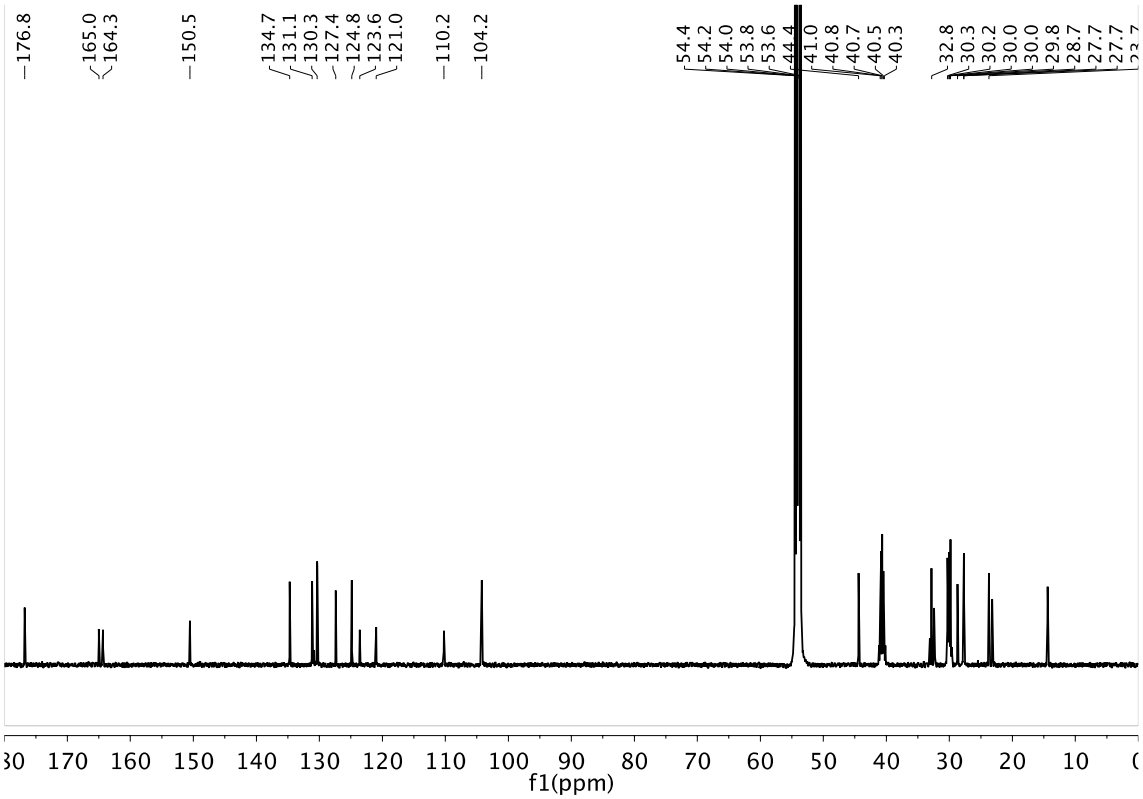

Figure S51. ^{13}C NMR spectrum of **9a** in CD_2Cl_2.

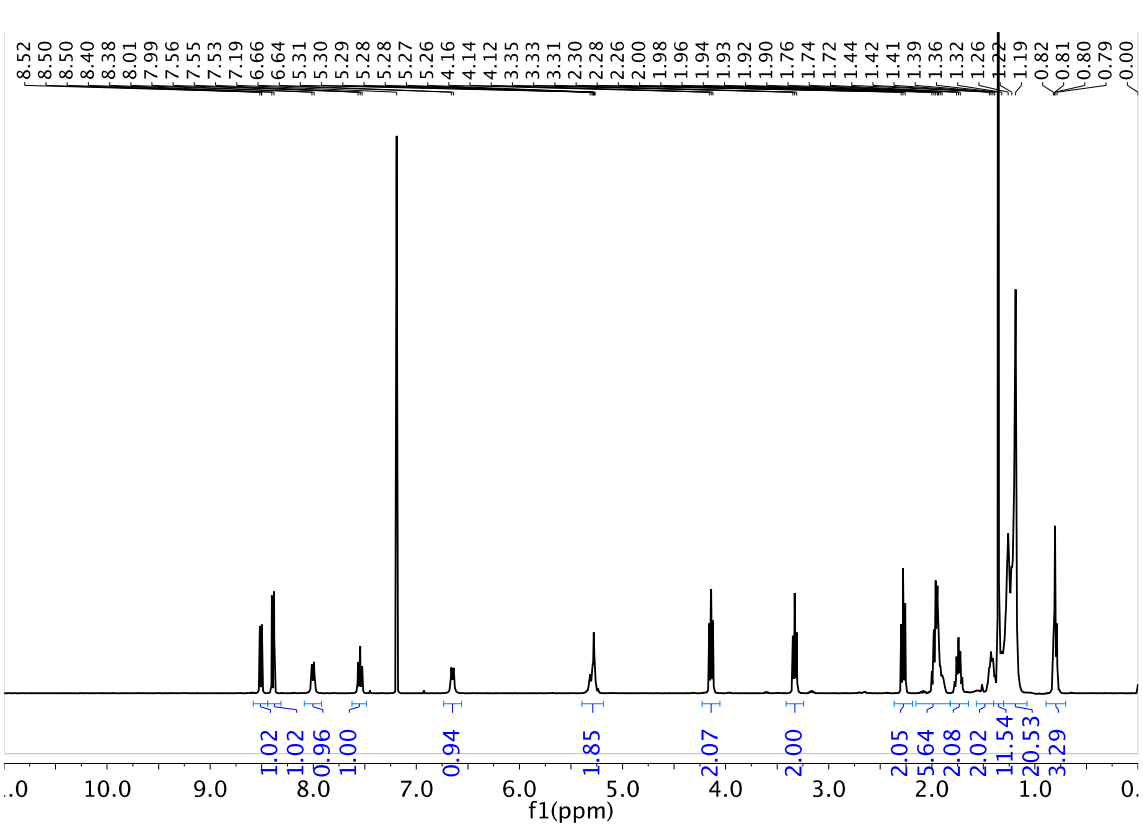

Figure S52. ^{1}H NMR spectrum of **43** in $CDCl_3$.

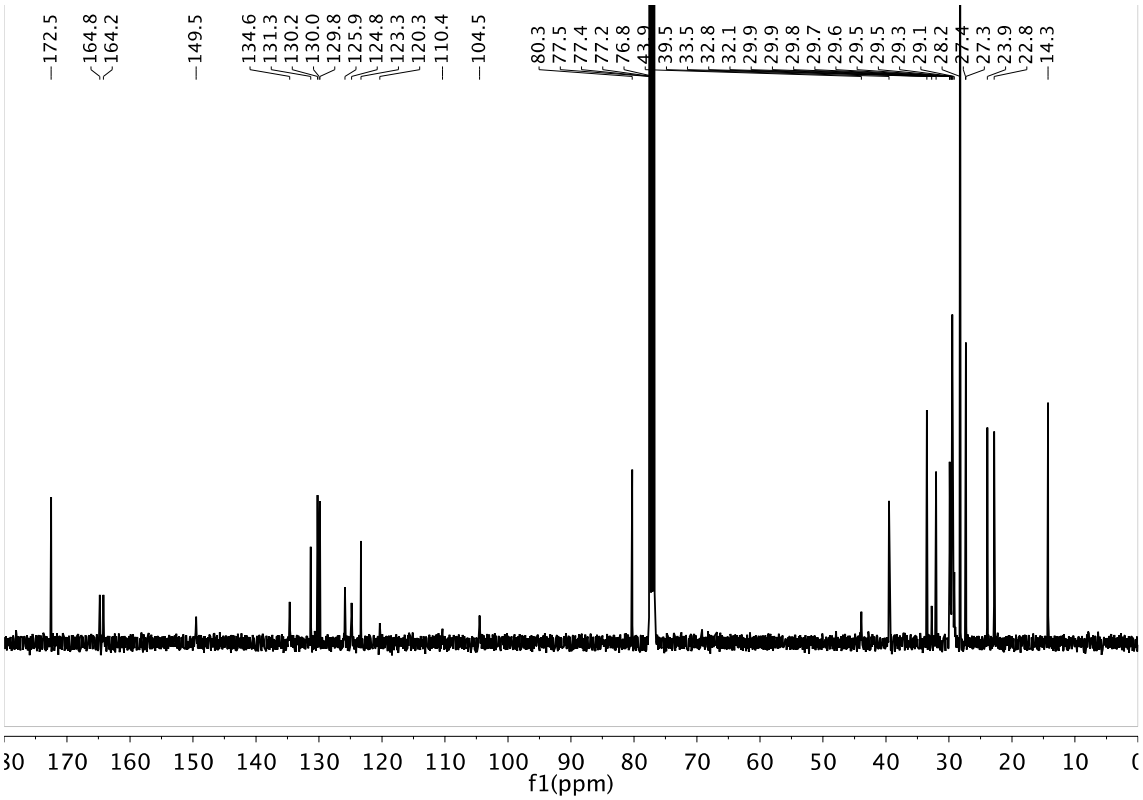

Figure S53. ^{13}C NMR spectrum of **43** in $CDCl_3$.

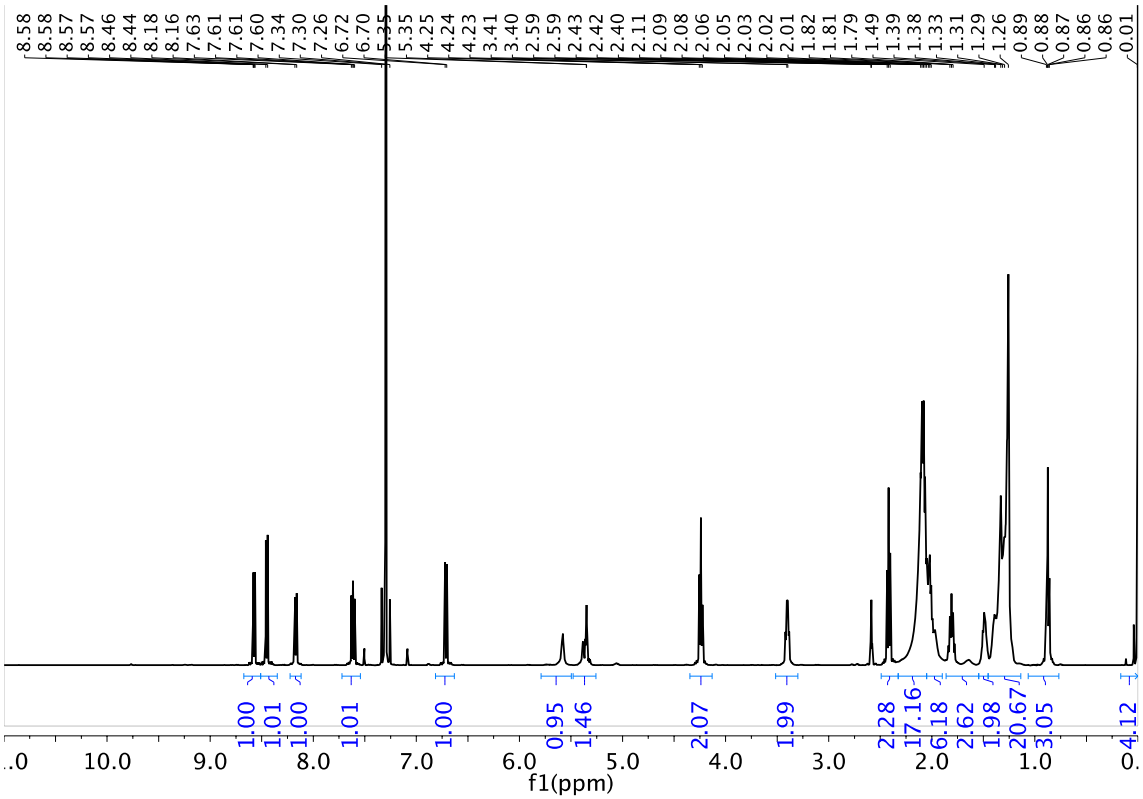

Figure S54. ^{1}H NMR spectrum of **9p** in $CDCl_3$.

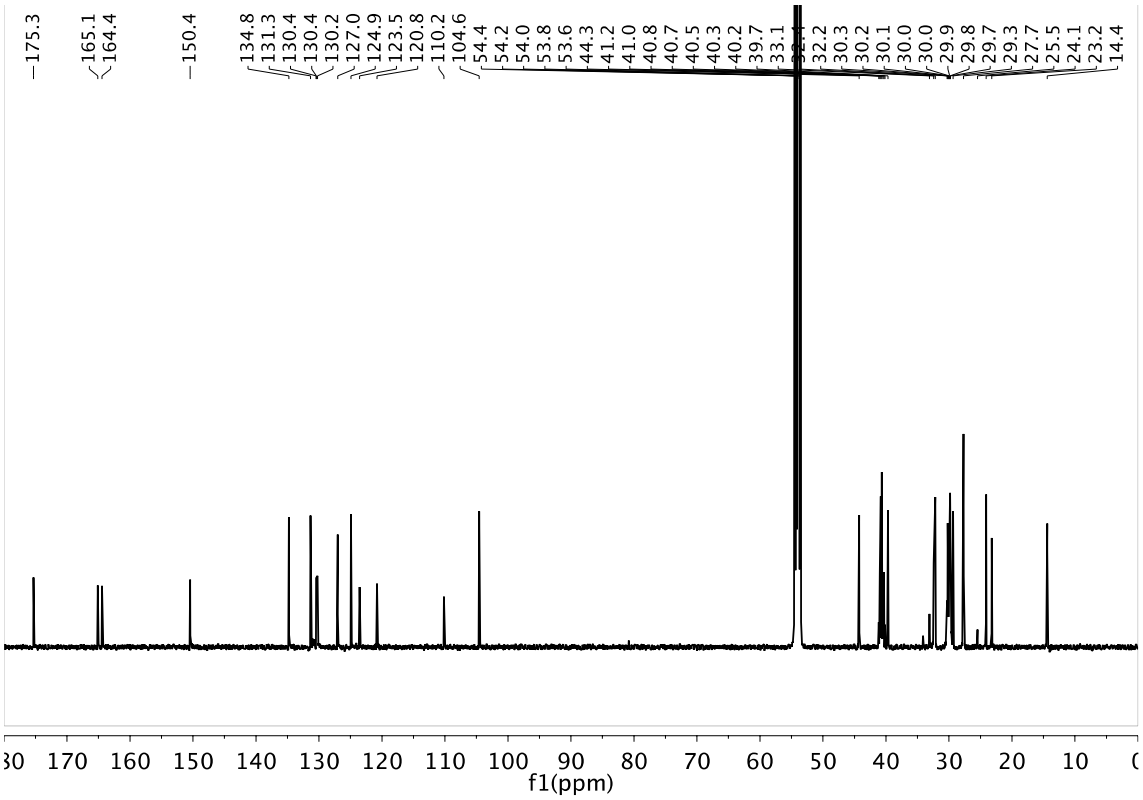

Figure S55. ^{13}C NMR spectrum of **9p** in CD_2Cl_2.

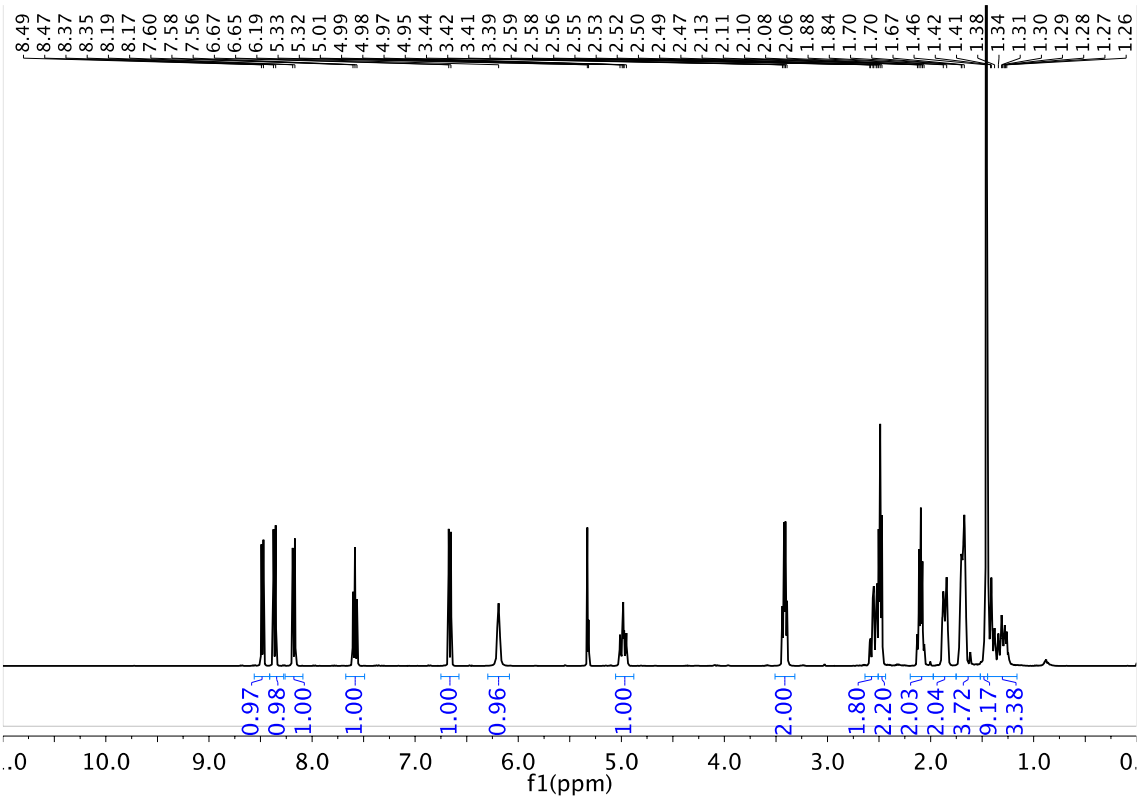

Figure S56. ^{1}H NMR spectrum of **46** in CD_2Cl_2.

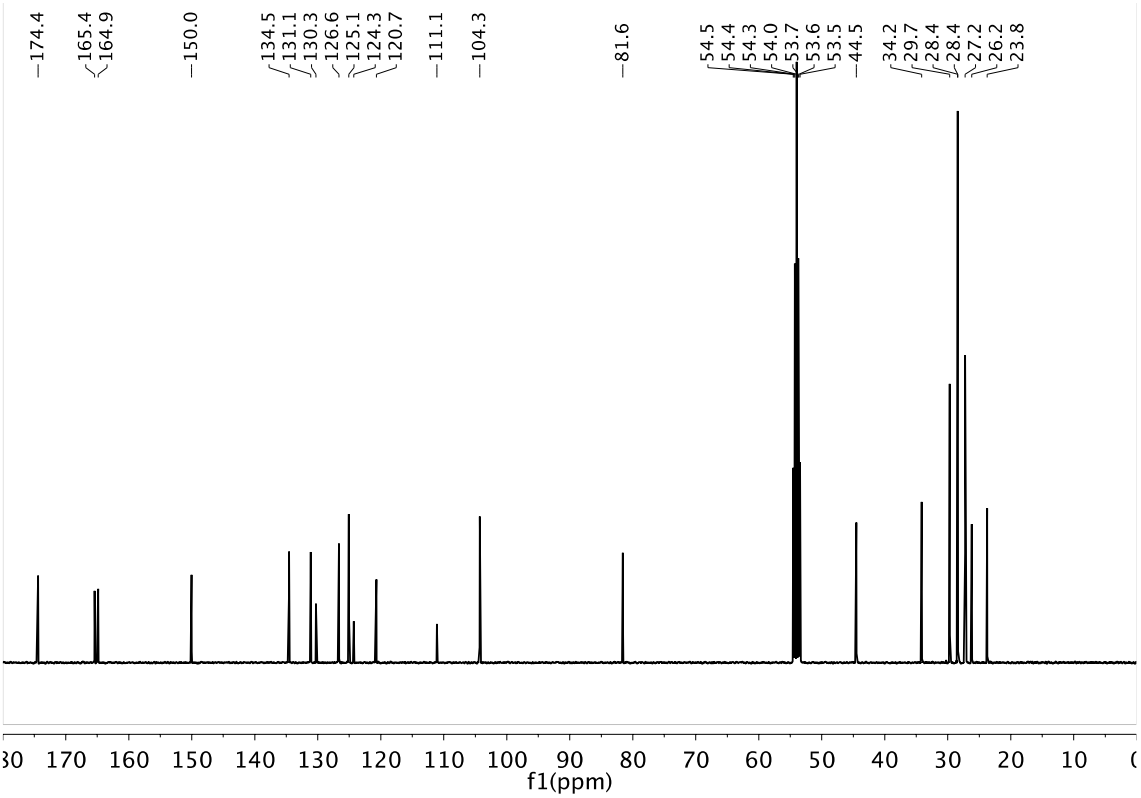

Figure S57. ^{13}C NMR spectrum of **46** in CD_2Cl_2.

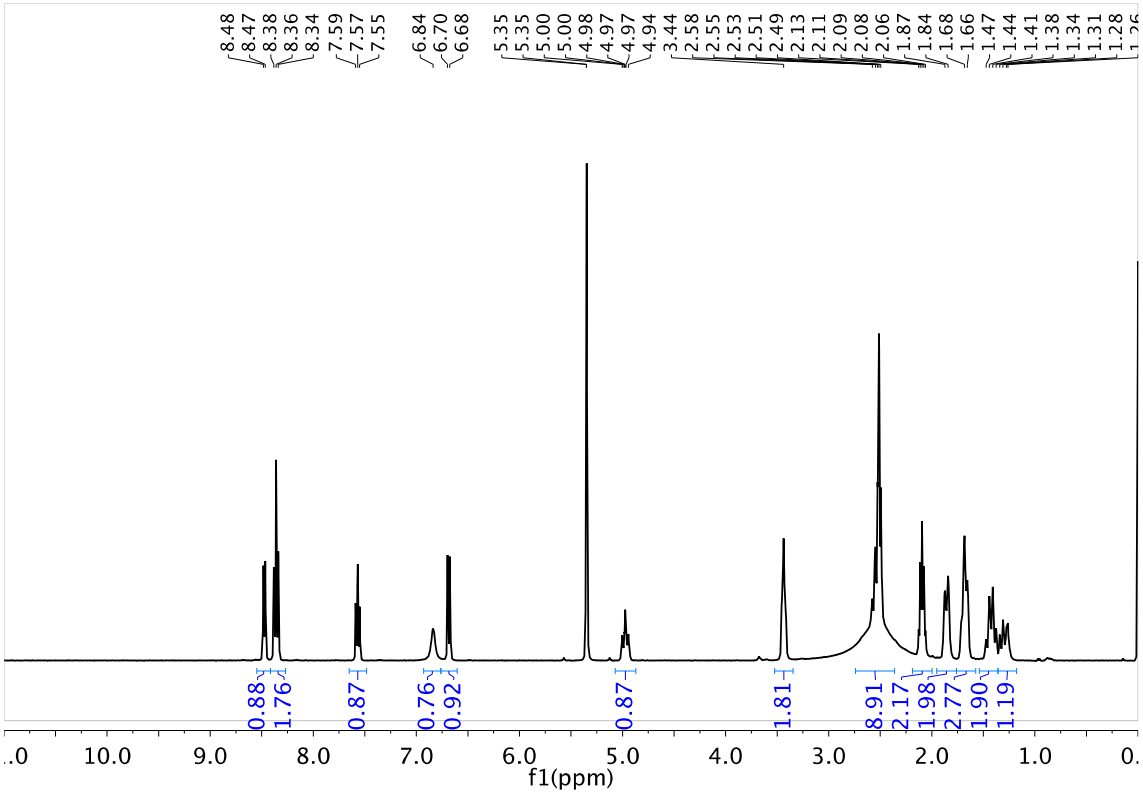

Figure S58. ^{1}H NMR spectrum of **10a** in CD_2Cl_2/DMSO-d_6 95:5.

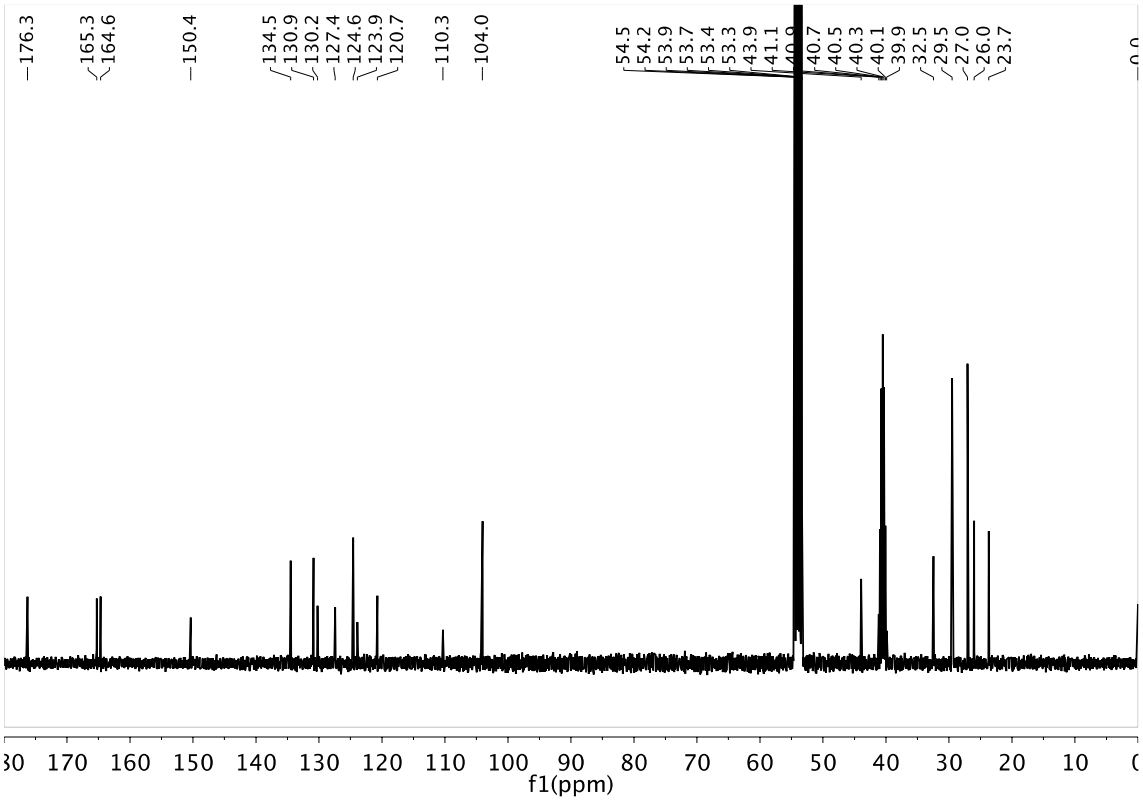

Figure S59. ^{13}C NMR spectrum of **10a** in CD_2Cl_2/DMSO-d_6 95:5.

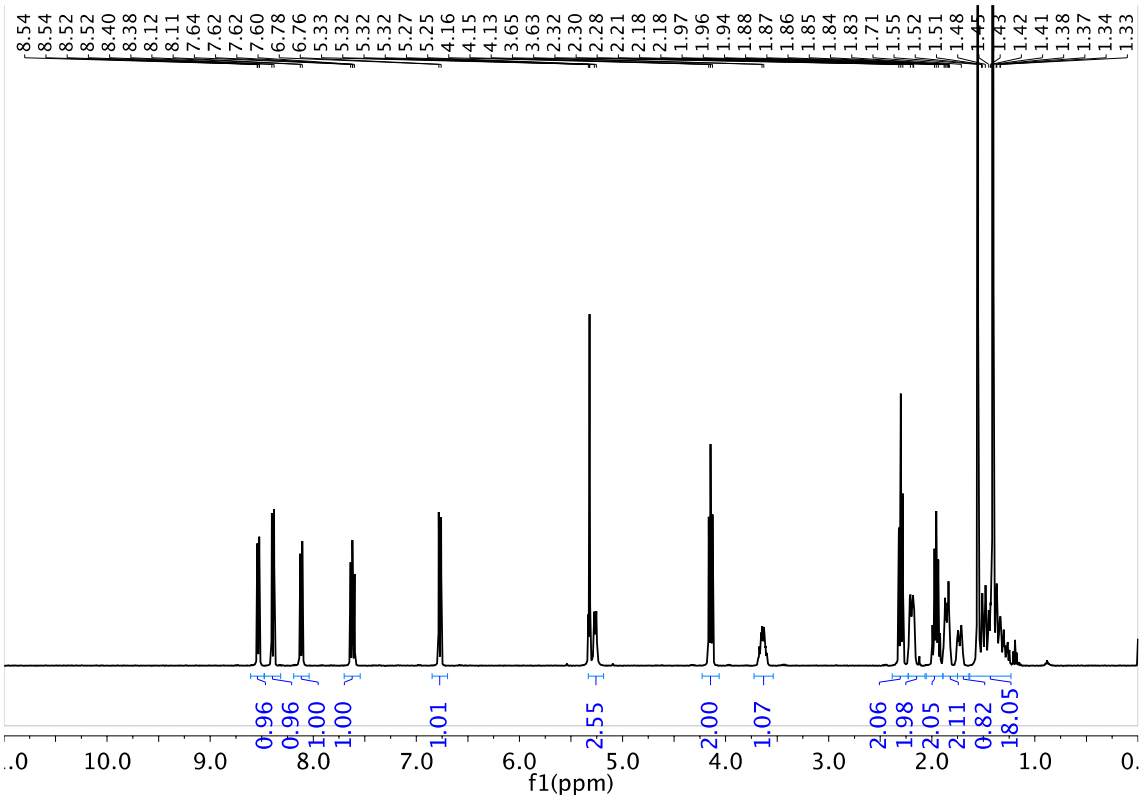

Figure S60. ^{1}H NMR spectrum of **47** in CD_2Cl_2.

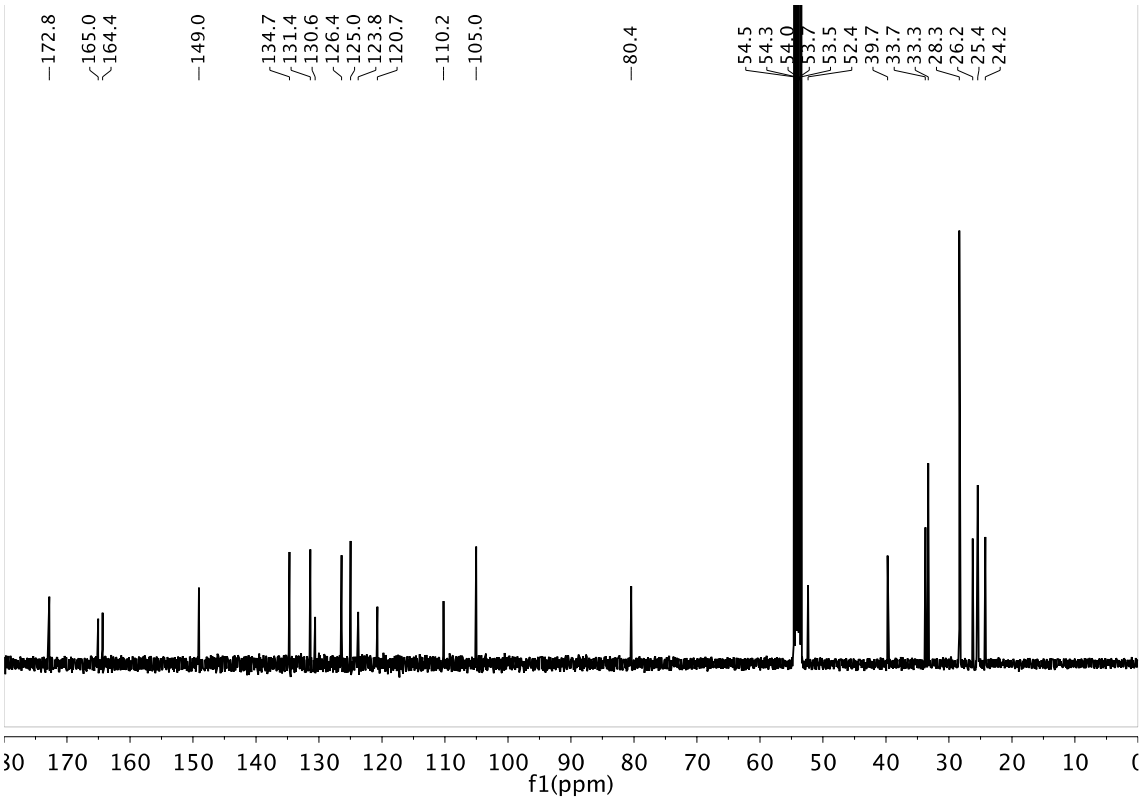

Figure S61. ^{13}C NMR spectrum of **47** in CD_2Cl_2.

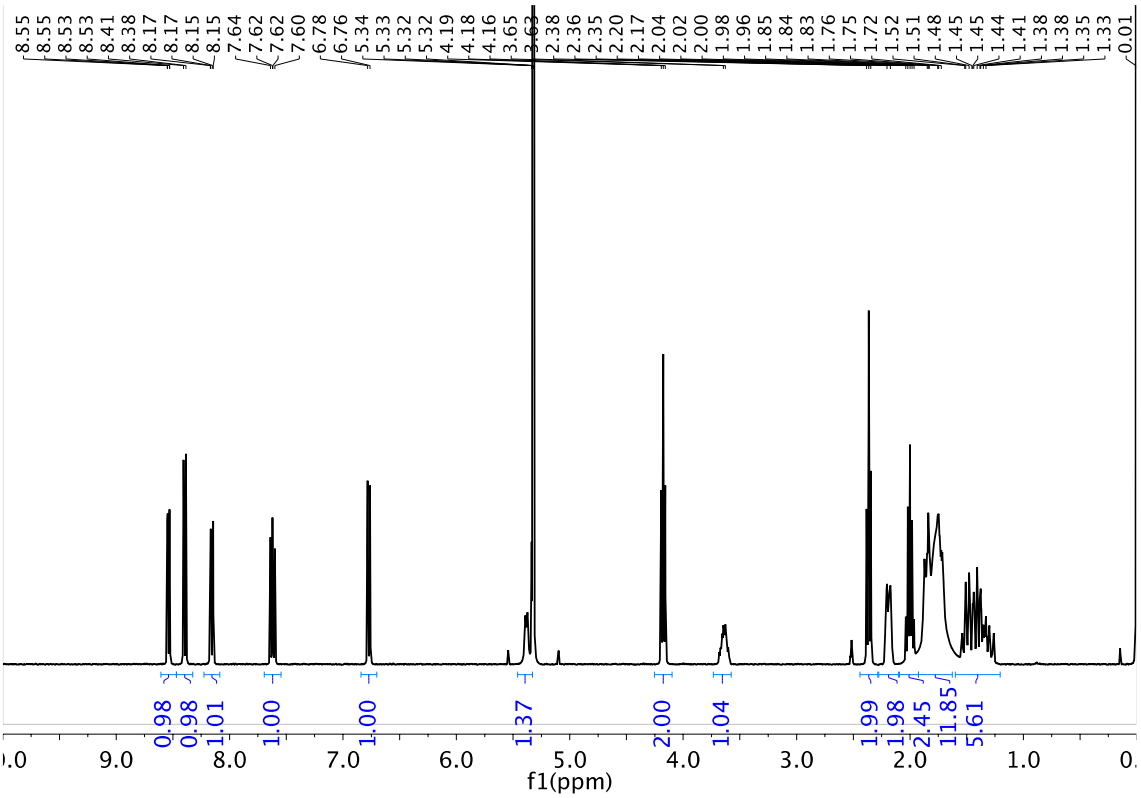

Figure S62. ^{1}H NMR spectrum of **10p** in CD_2Cl_2/DMSO-d_6 95:5.

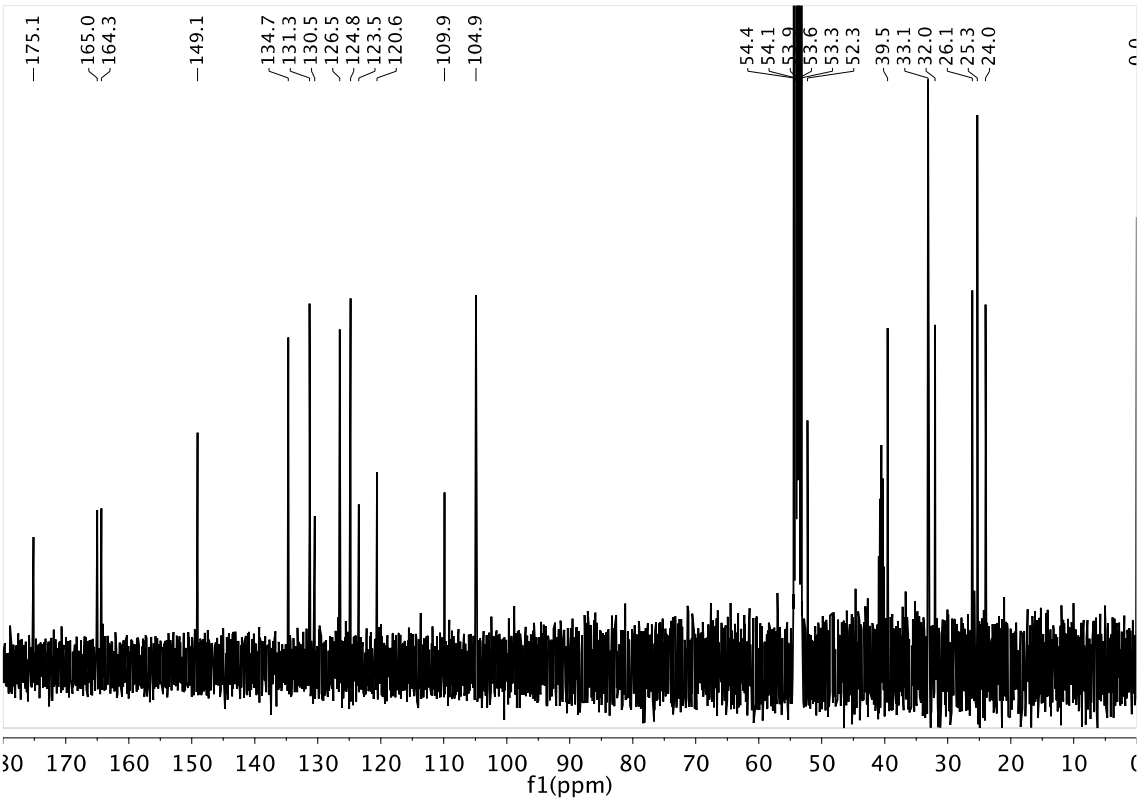

Figure S63. ^{13}C NMR spectrum of **10p** in CD_2Cl_2/DMSO-d_6 95:5.

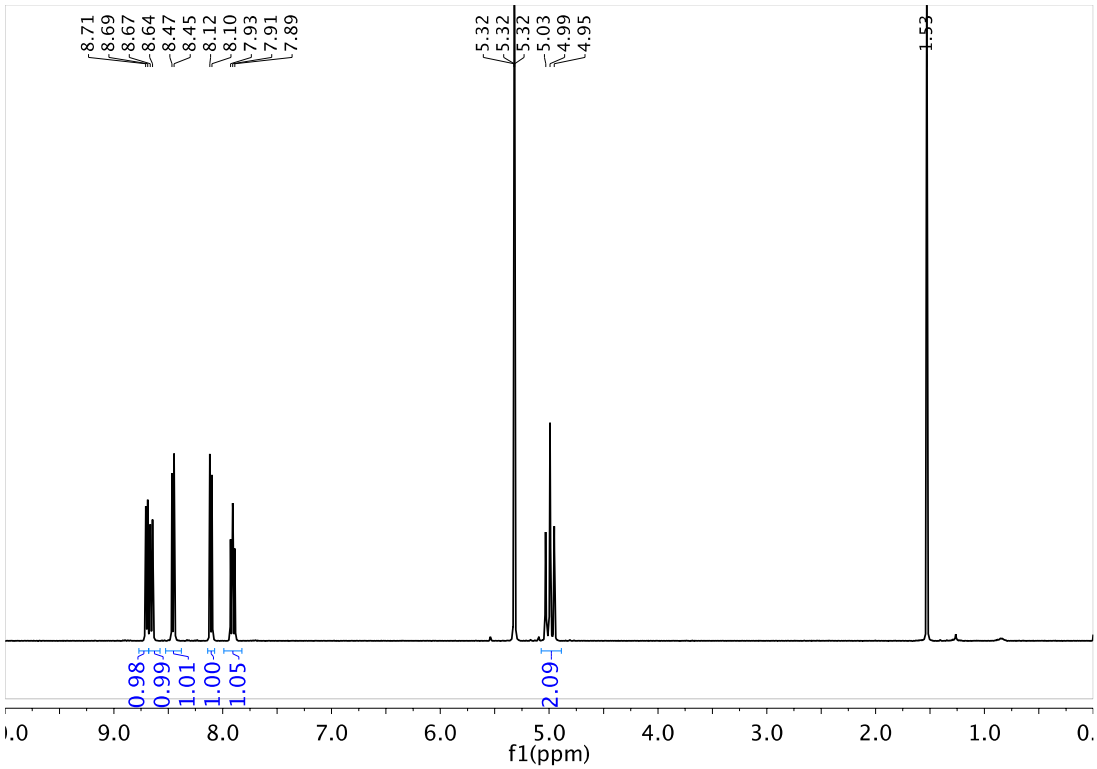

Figure S64. ^{1}H NMR spectrum of **49** in CD_2Cl_2.

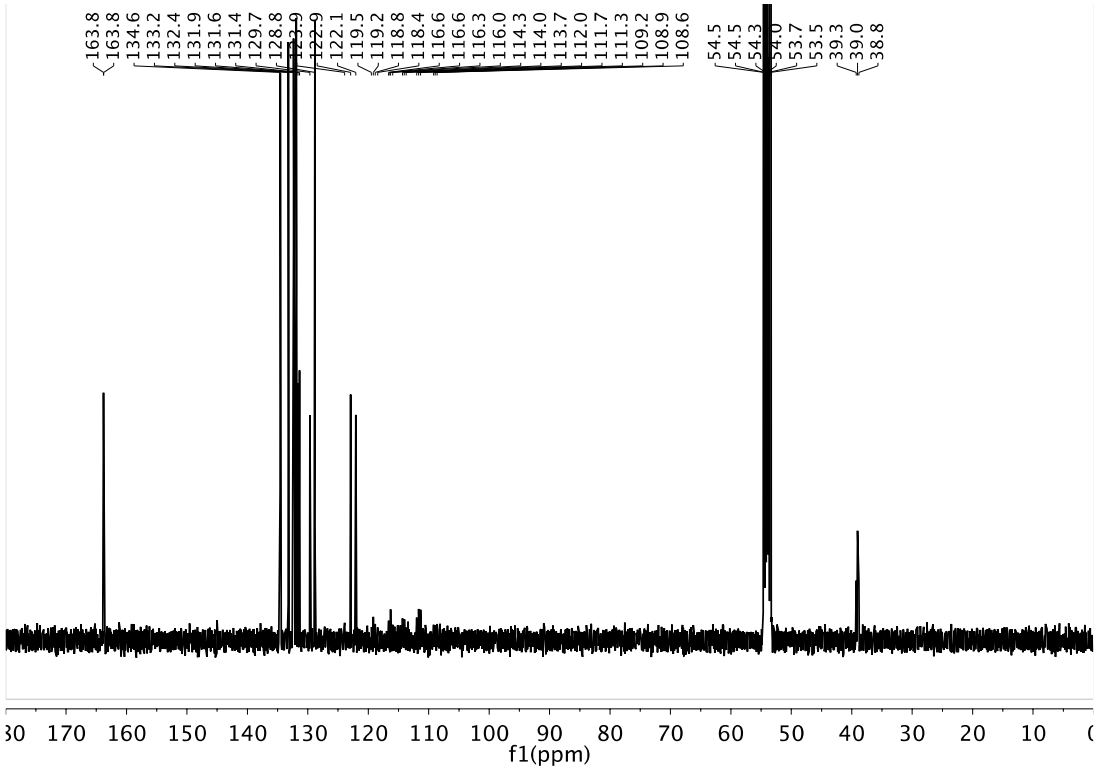

Figure S65. ^{13}C NMR spectrum of **49** in CD_2Cl_2.

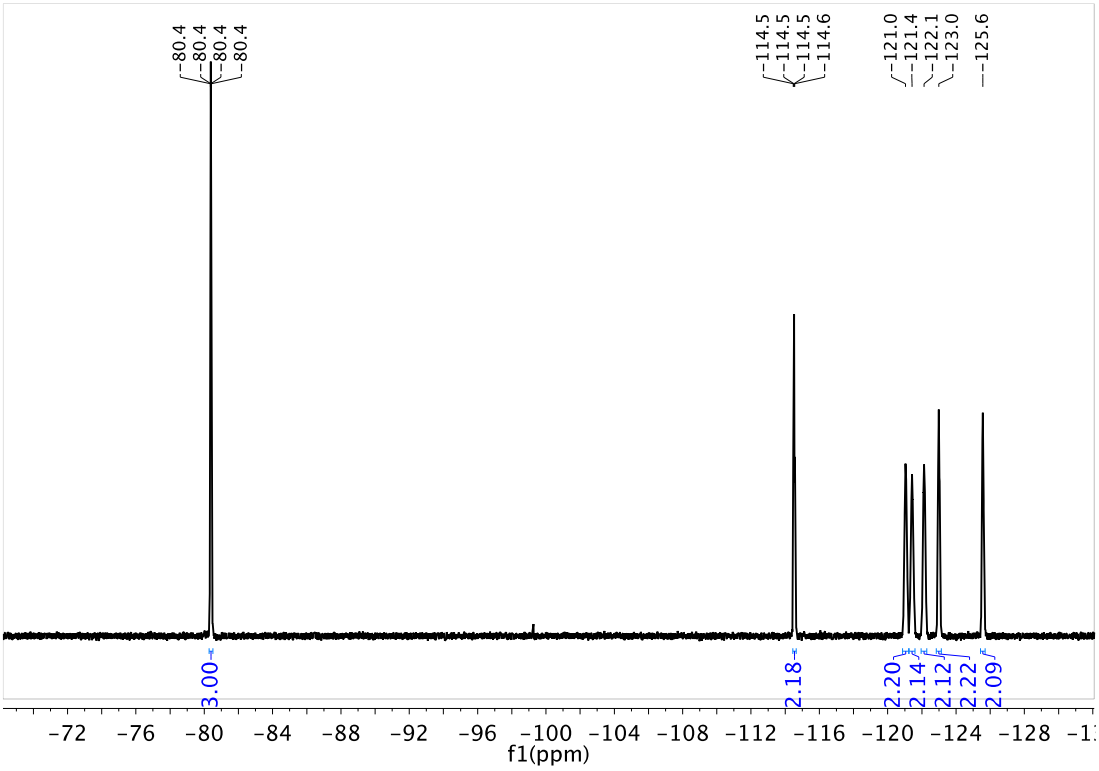

Figure S66. ^{19}F NMR spectrum of **49** in CD_2Cl_2.

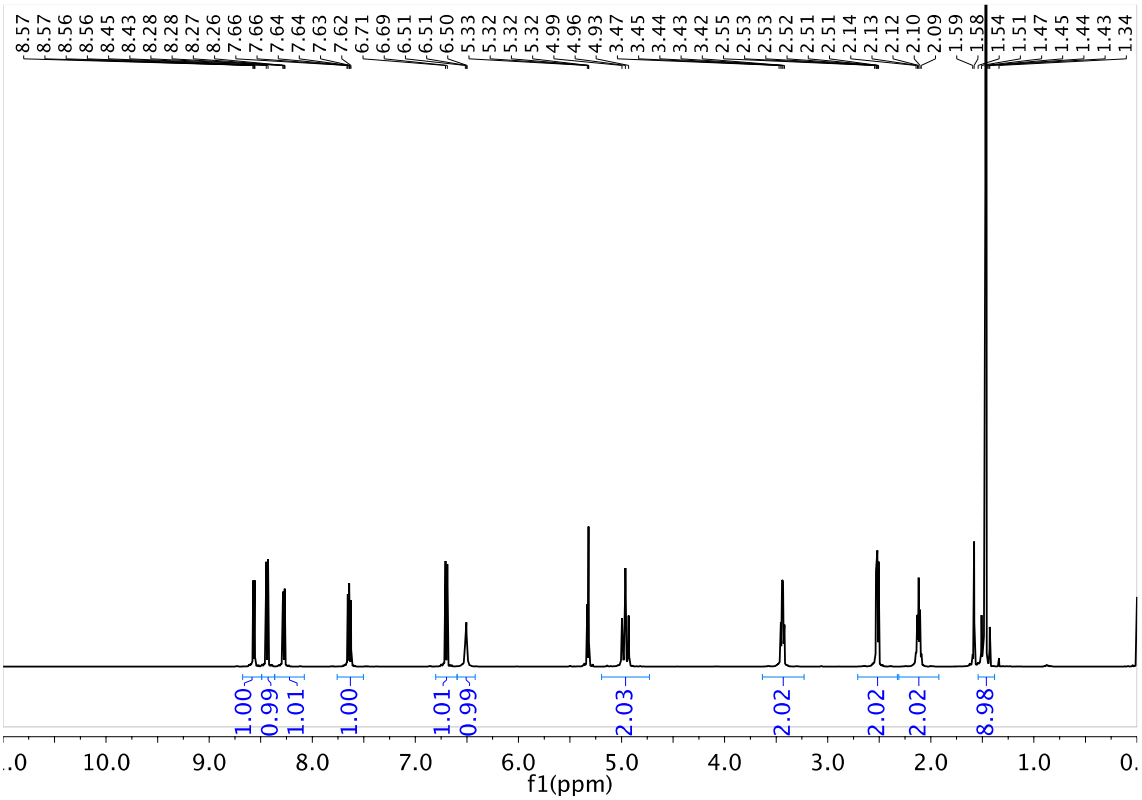

Figure S67. ^{1}H NMR spectrum of **50** in CD_2Cl_2.

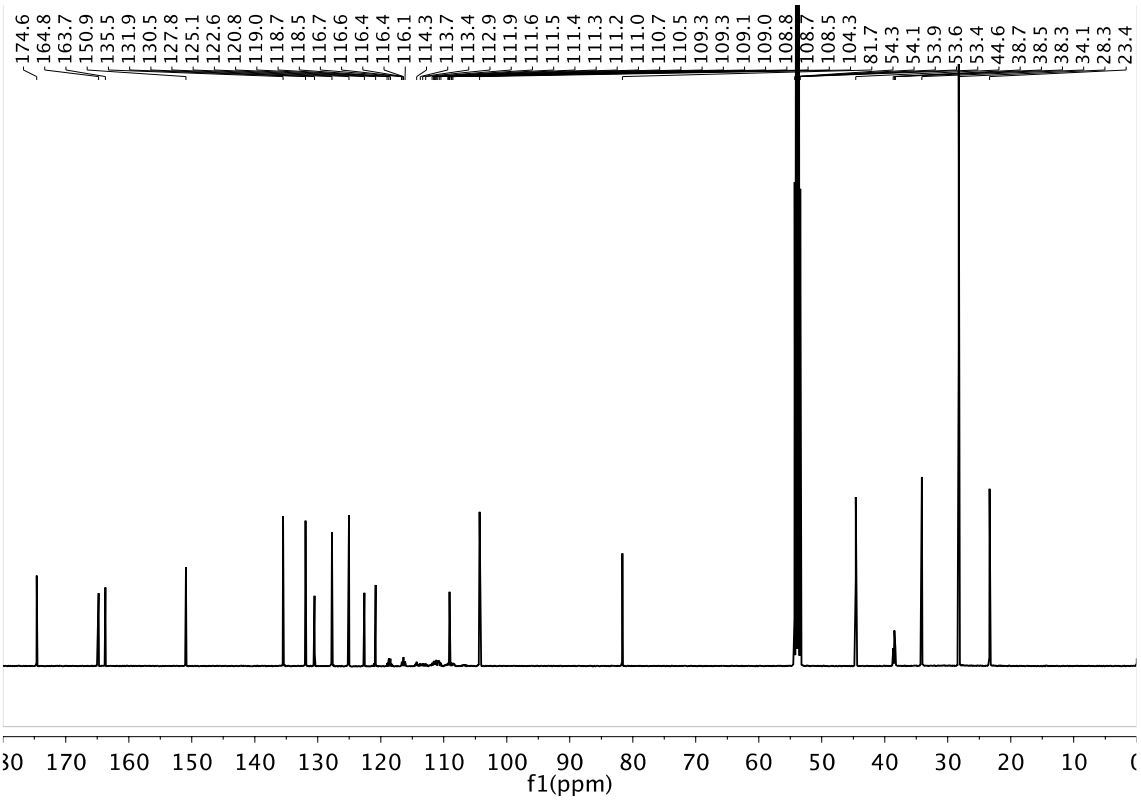

Figure S68. ^{13}C NMR spectrum of **50** in CD_2Cl_2.

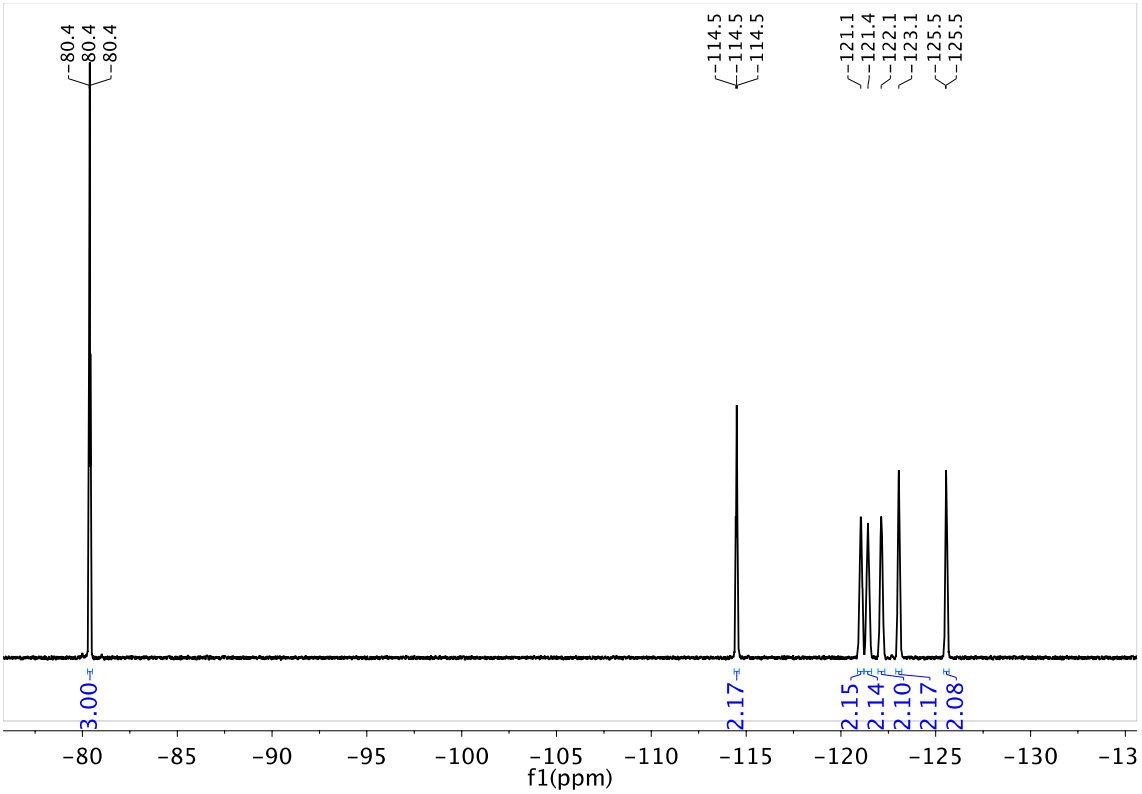

Figure S69. ^{19}F NMR spectrum of **50** in CD_2Cl_2.

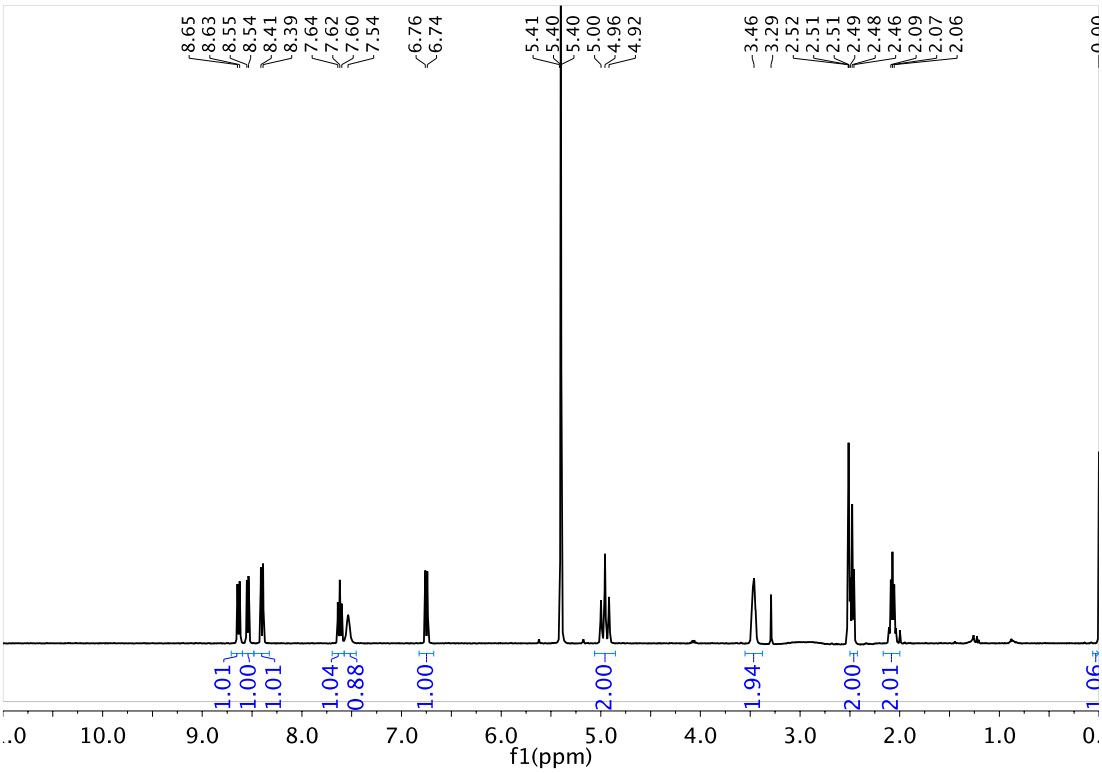

Figure S70. ^{1}H NMR spectrum of **11a** in CD_2Cl_2/DMSO-d_6 95:5

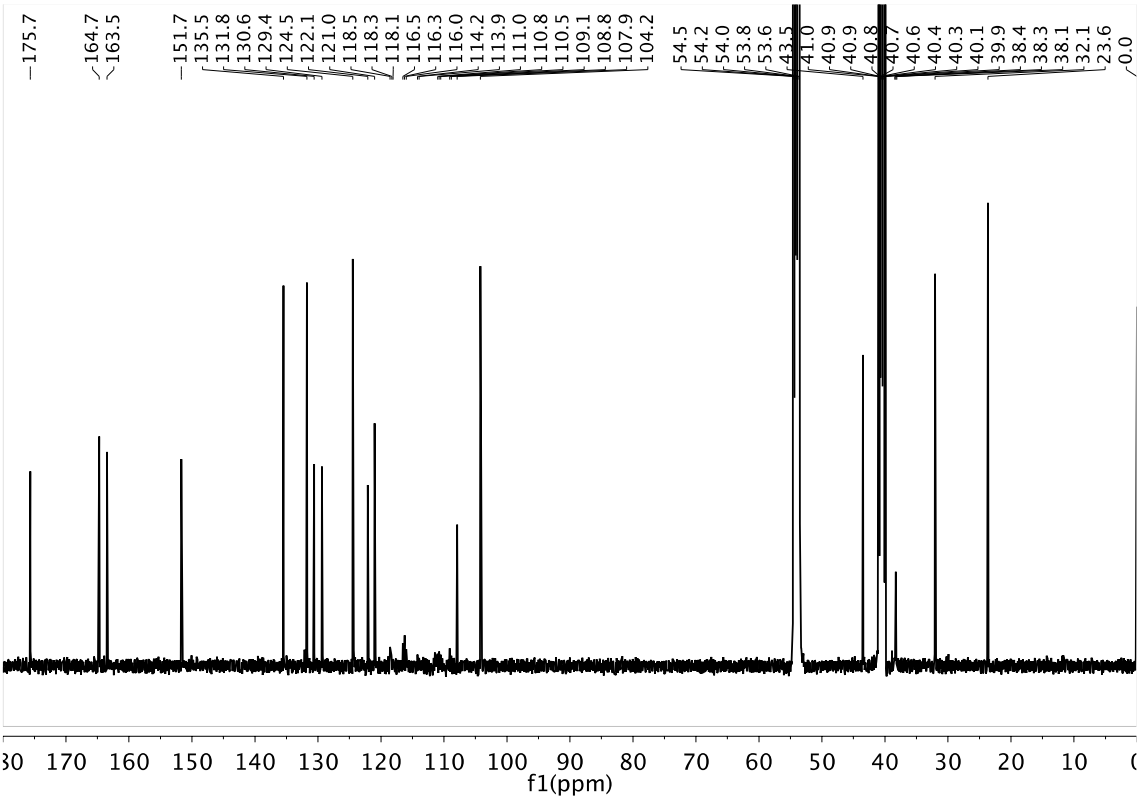

Figure S71. ^{13}C NMR spectrum of **11a** in CD_2Cl_2/DMSO-d_6 95:5

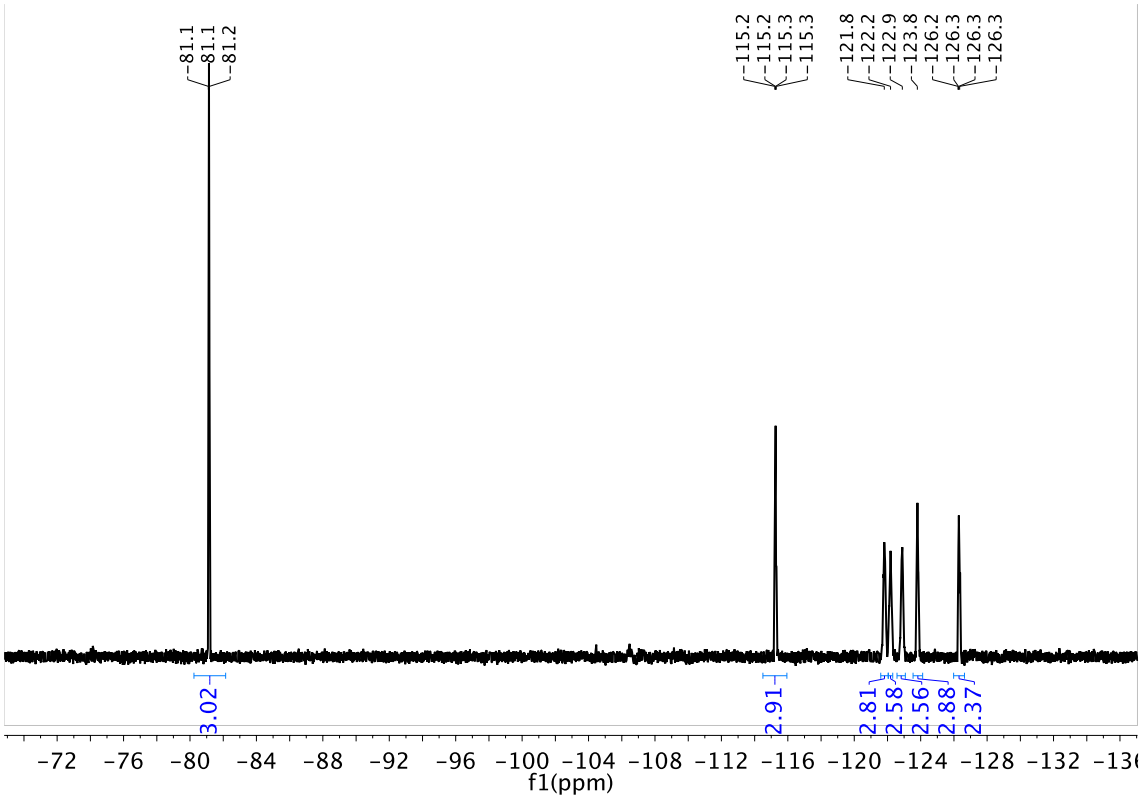

Figure S72. ^{19}F NMR spectrum of **11a** in CD_2Cl_2/DMSO-d_6 95:5

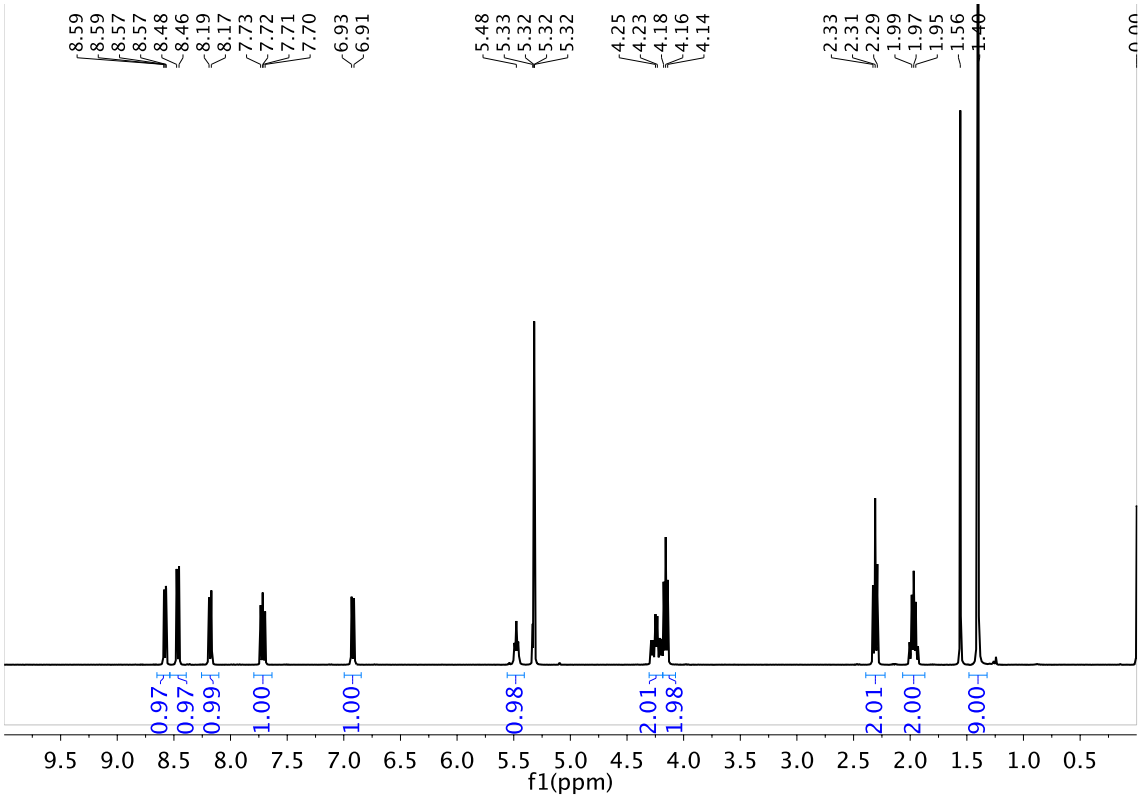

Figure S73. ^{1}H NMR spectrum of **51** in CD_2Cl_2.

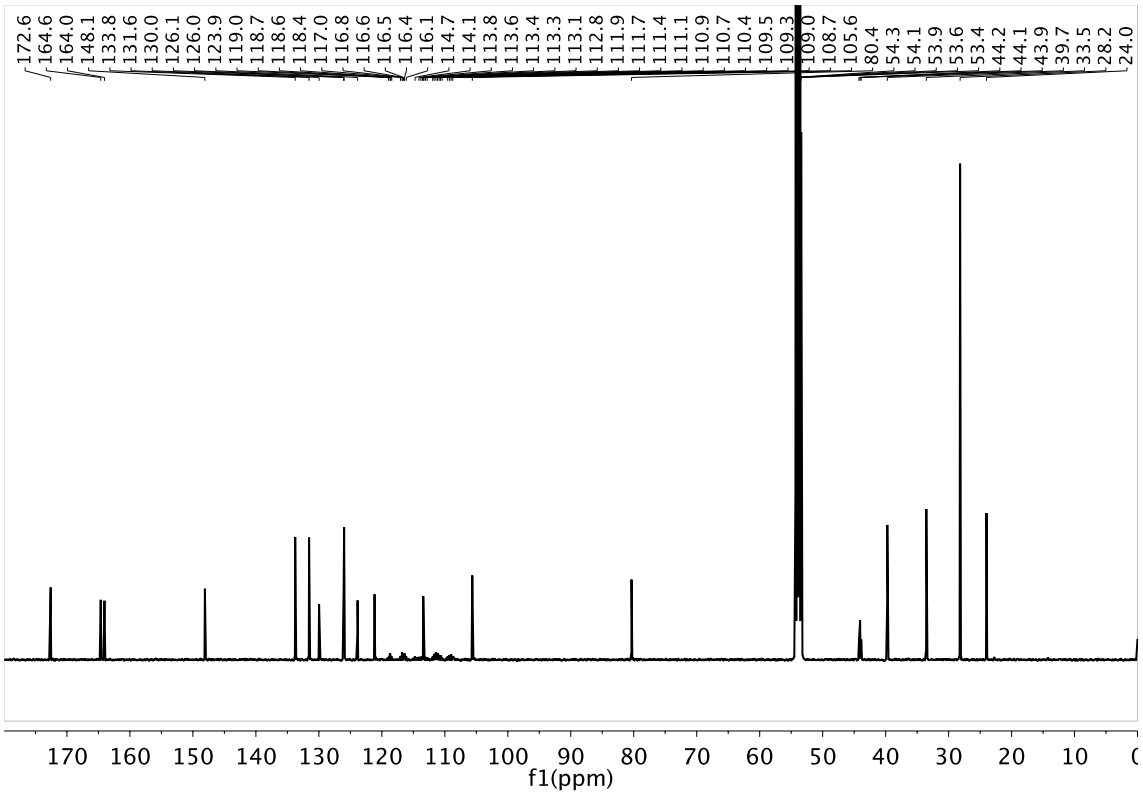

Figure S74. ^{13}C NMR spectrum of **51** in CD_2Cl_2.

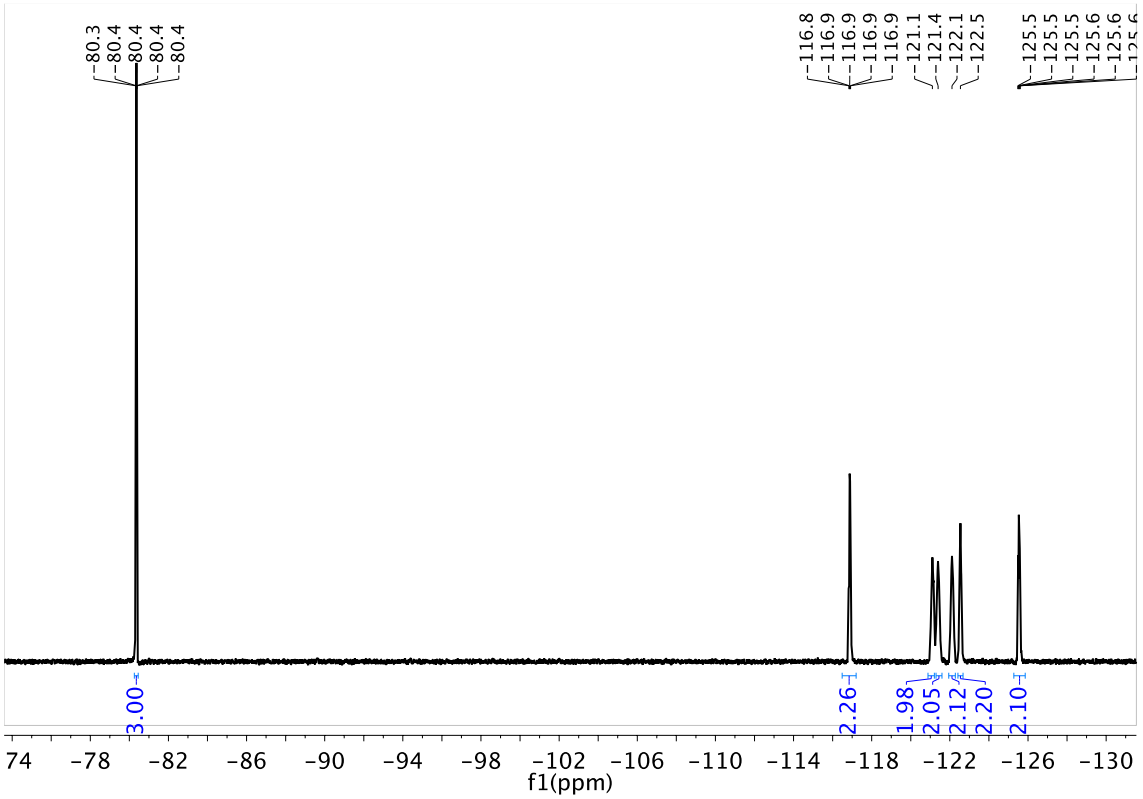

Figure S75. ^{19}F NMR spectrum of **51** in CD_2Cl_2.

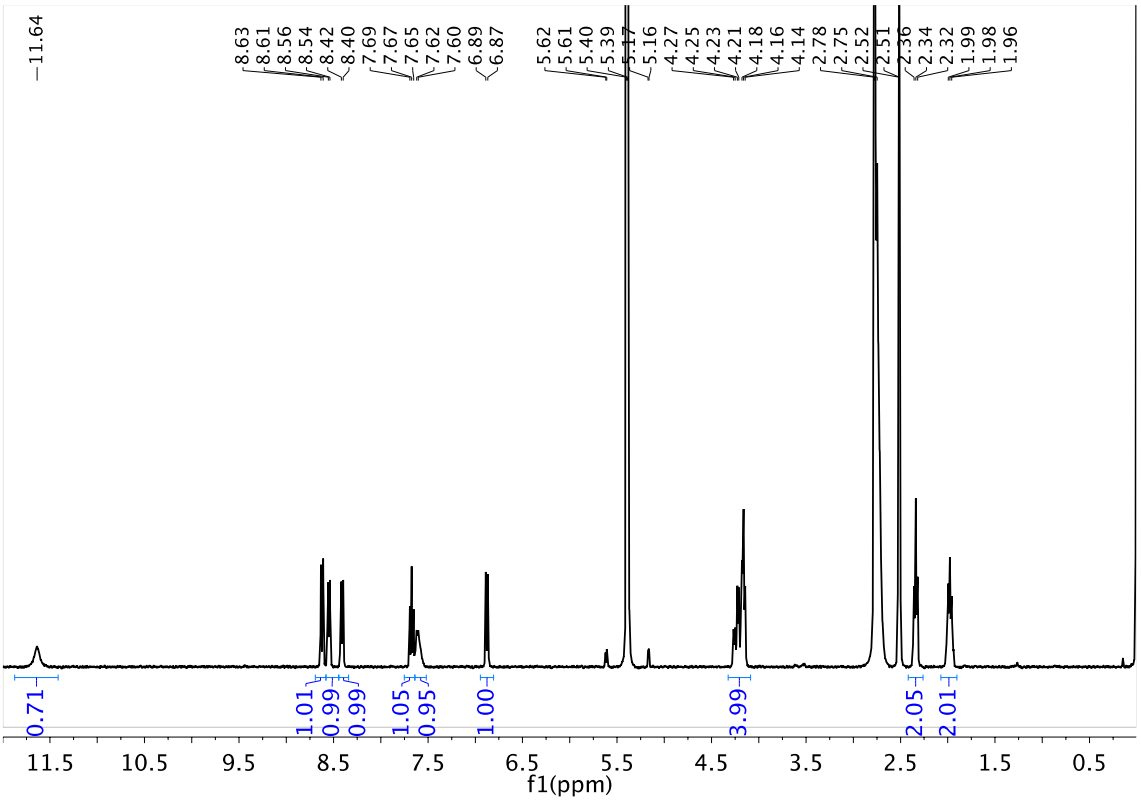

Figure S76 ^{1}H NMR spectrum of **11p** in CD_2Cl_2/DMSO-d_6 90:10.

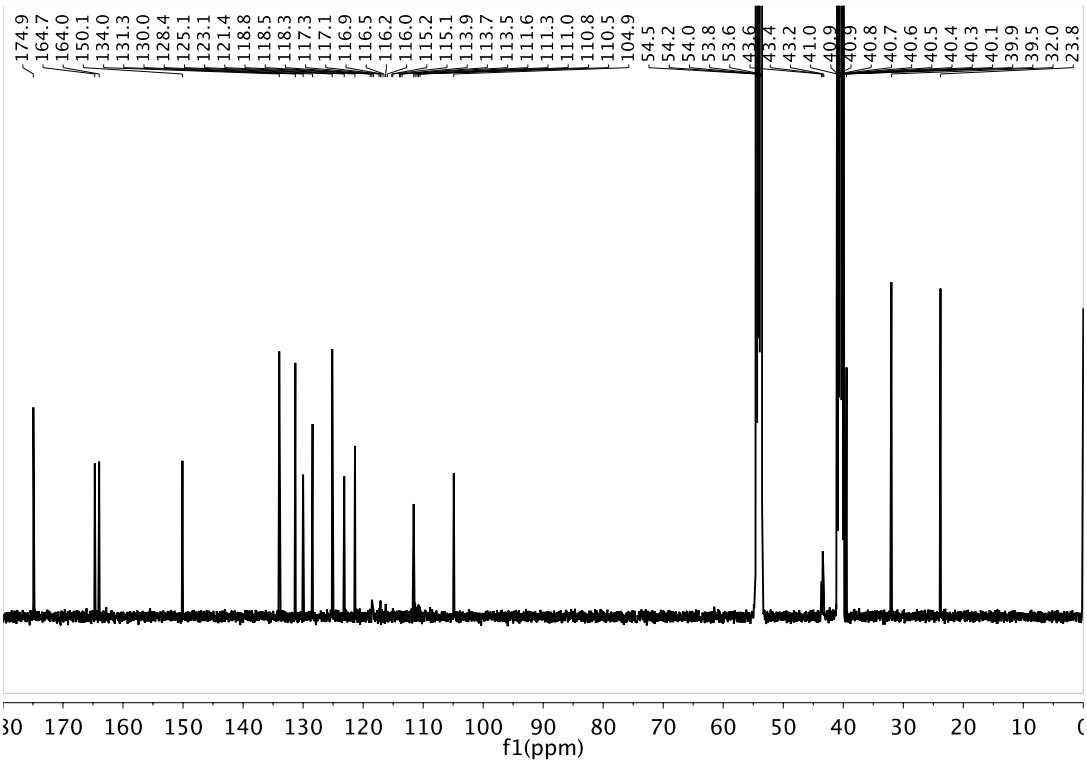

Figure S77. ^{13}C NMR spectrum of **11p** in CD_2Cl_2 /DMSO-d_6 90:10.

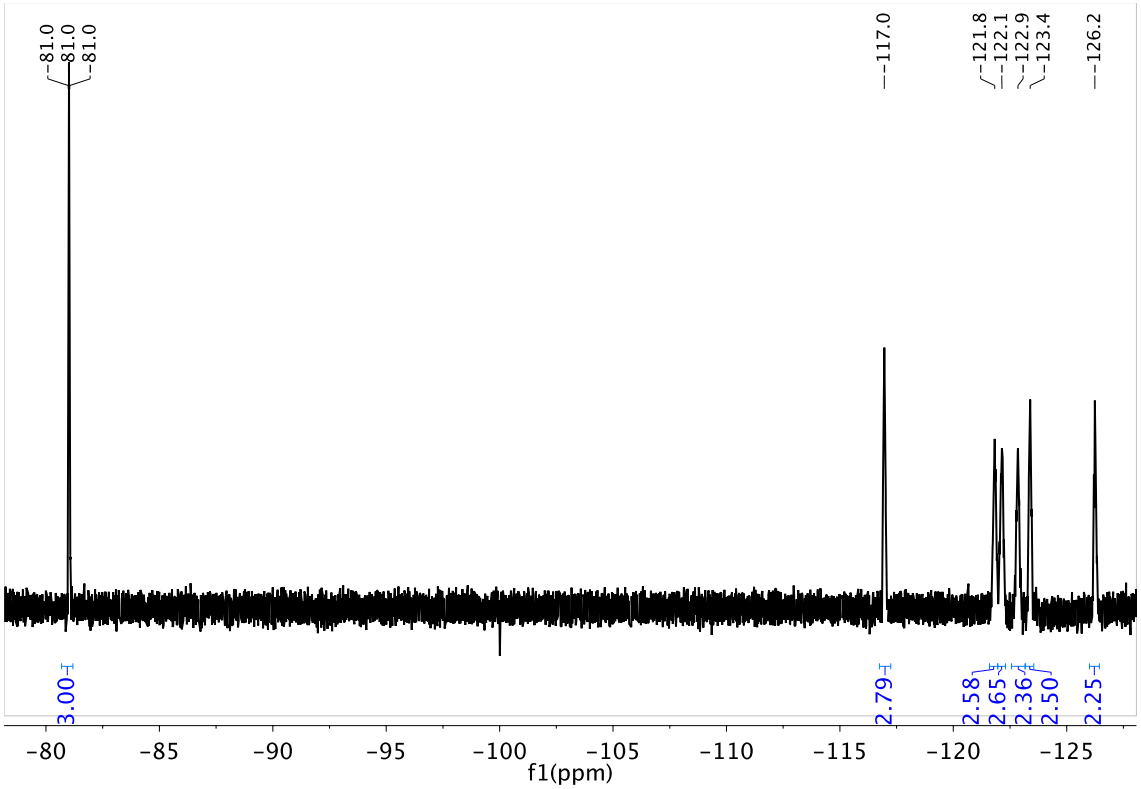

Figure S78. ^{19}F NMR spectrum of **11p** in CD_2Cl_2 /DMSO-d_6 90:10.

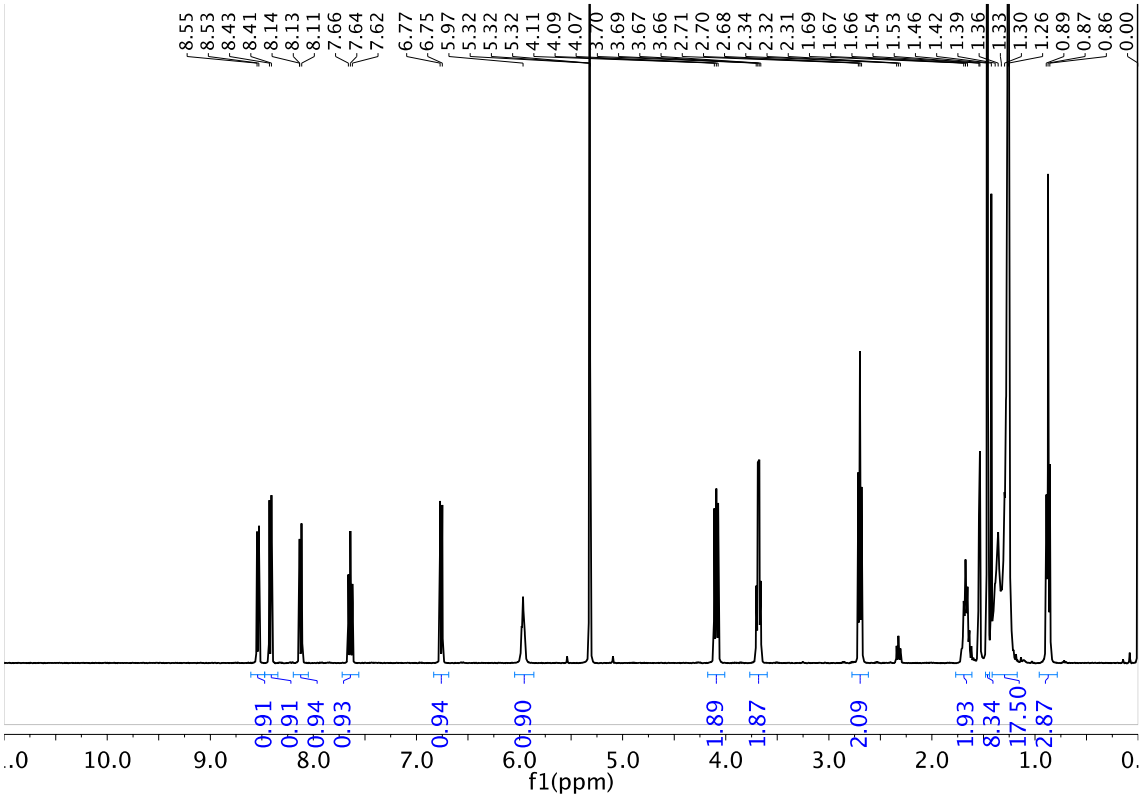

Figure S79. ^{1}H NMR spectrum of **53** in CD_2Cl_2.

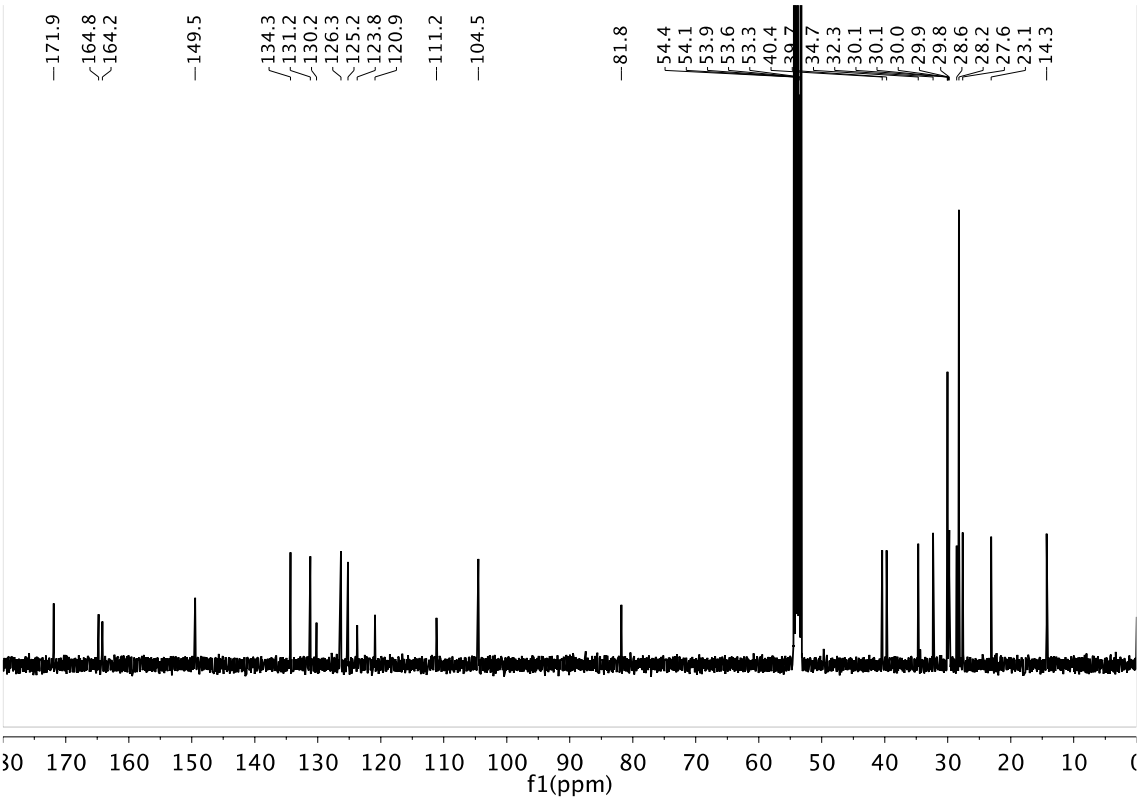

Figure S80. ^{13}C NMR spectrum of **53** in CD_2Cl_2.

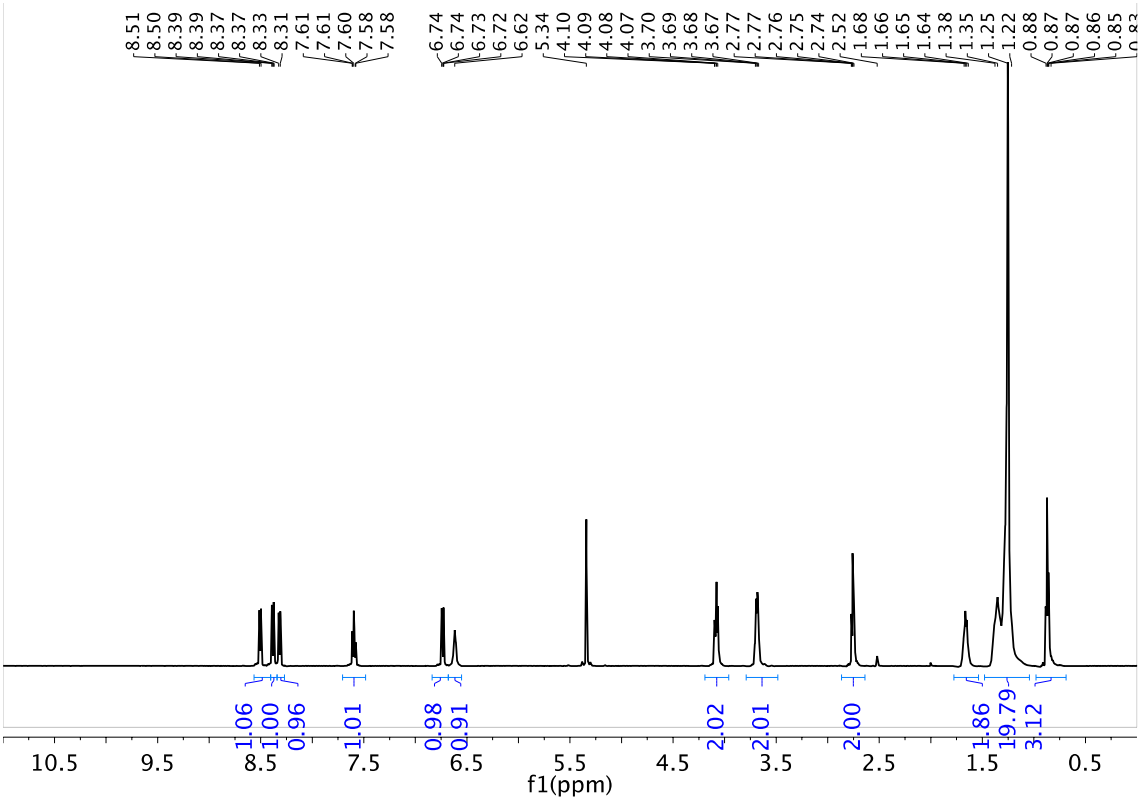

Figure S81. ^{1}H NMR spectrum of **12a** in CD_2Cl_2/DMSO-d_6 95:5.

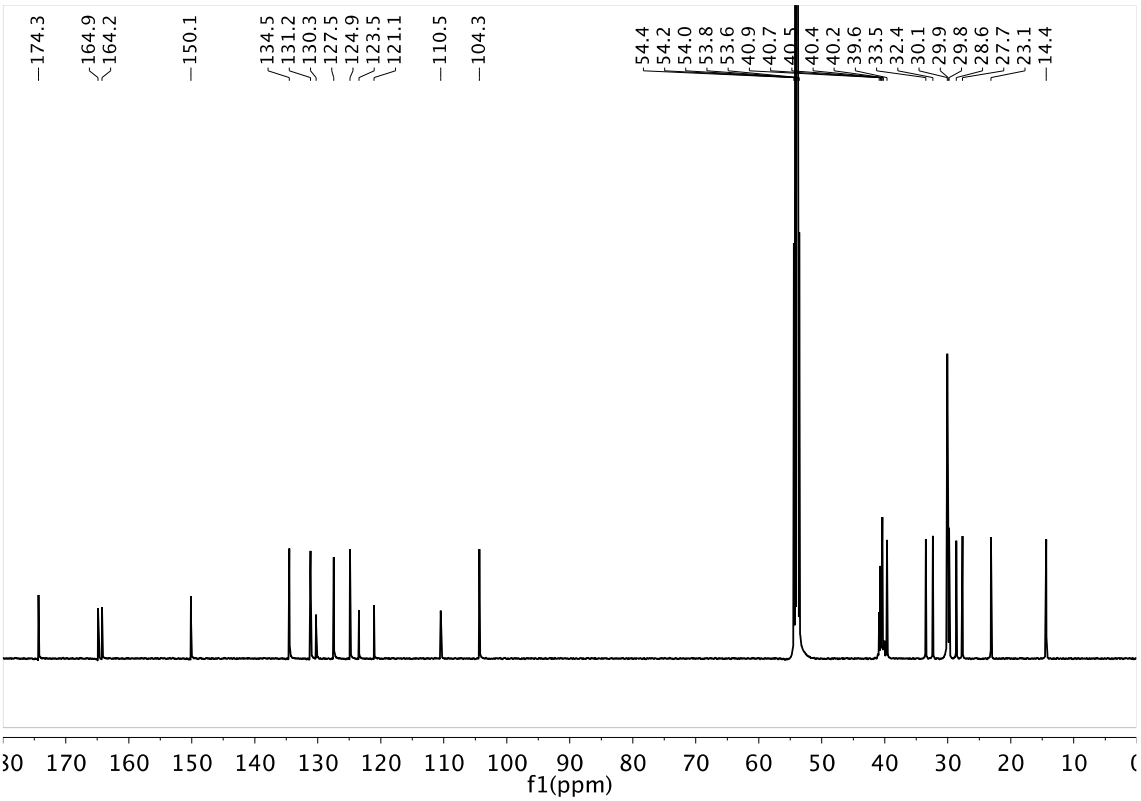

Figure S82. ^{13}C NMR spectrum of **12a** in CD_2Cl_2/DMSO-d_6 95:5.

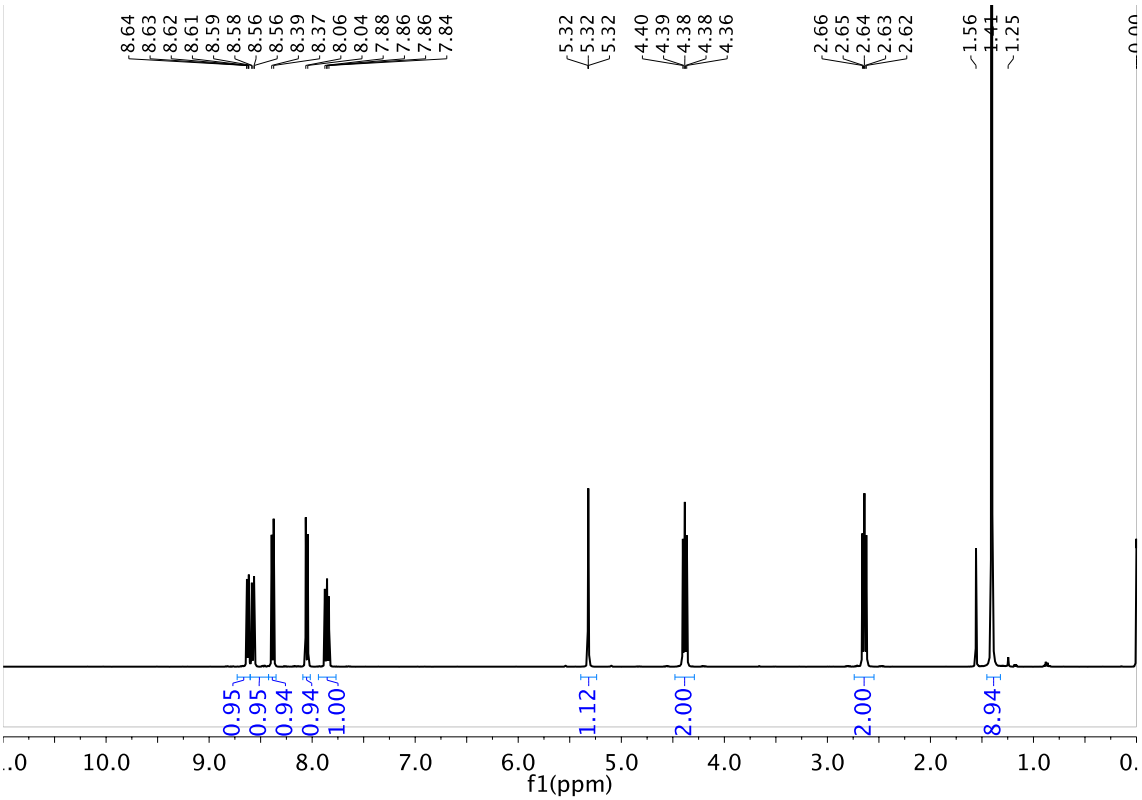

Figure S83. ^{1}H NMR spectrum of **54** in CD_2Cl_2.

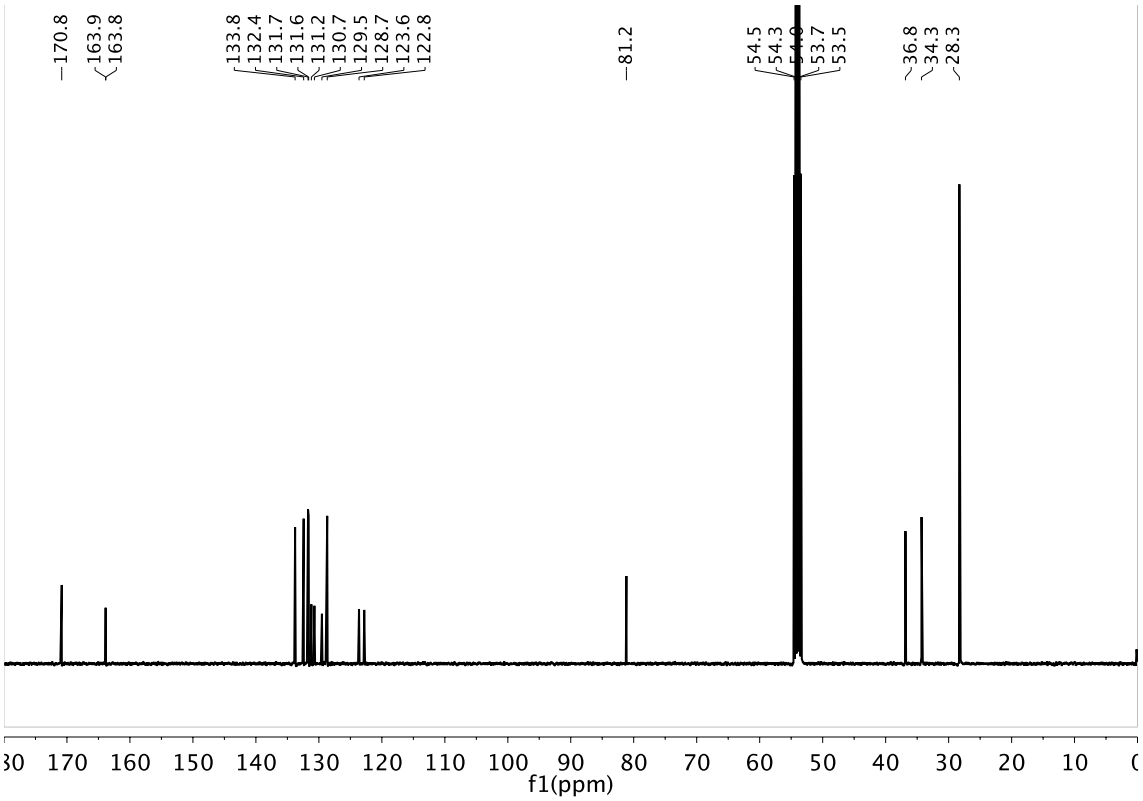

Figure S84. ^{13}C NMR spectrum of **54** in CD_2Cl_2.

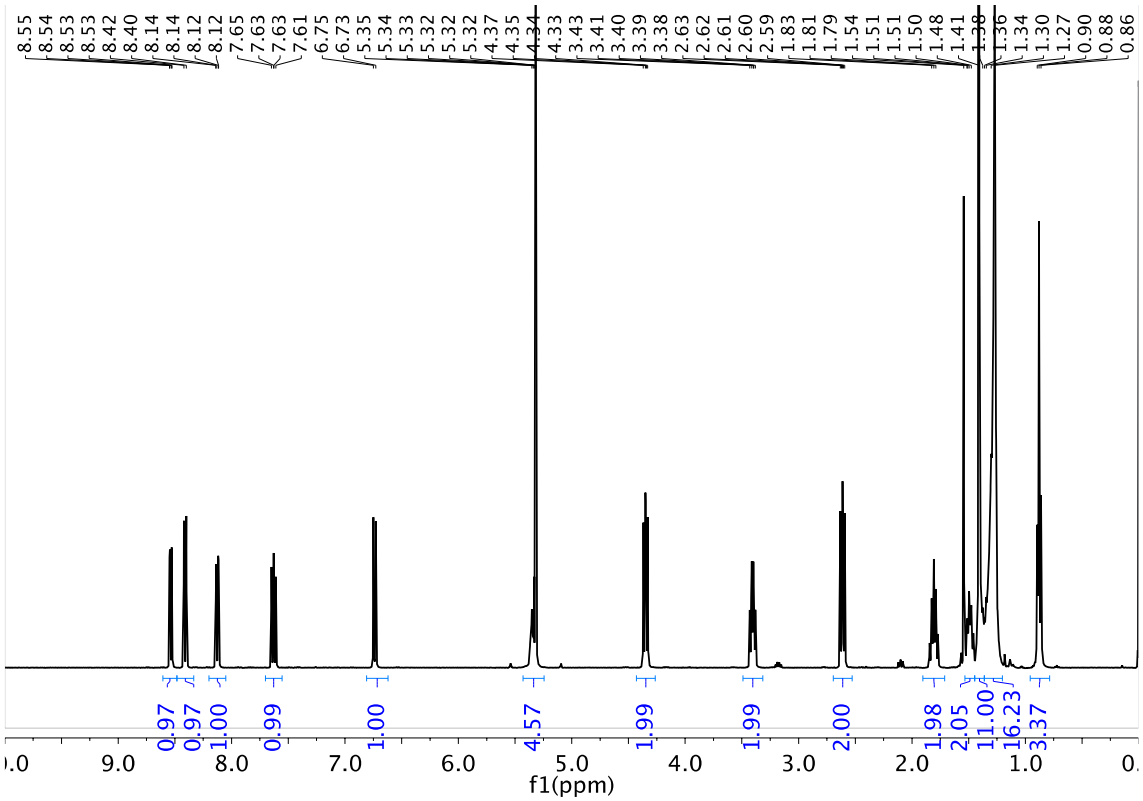

Figure S85. ^{1}H NMR spectrum of **55** in CD_2Cl_2.

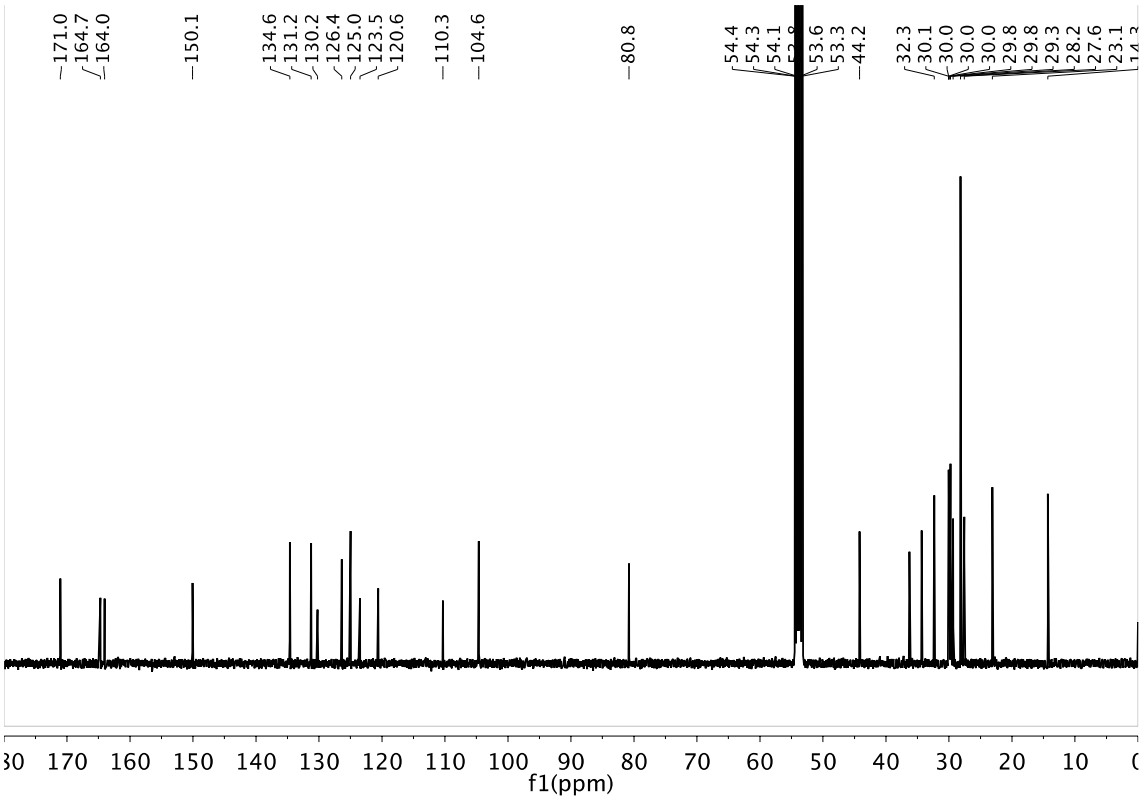

Figure S86. ^{13}C NMR spectrum of **55** in CD_2Cl_2.

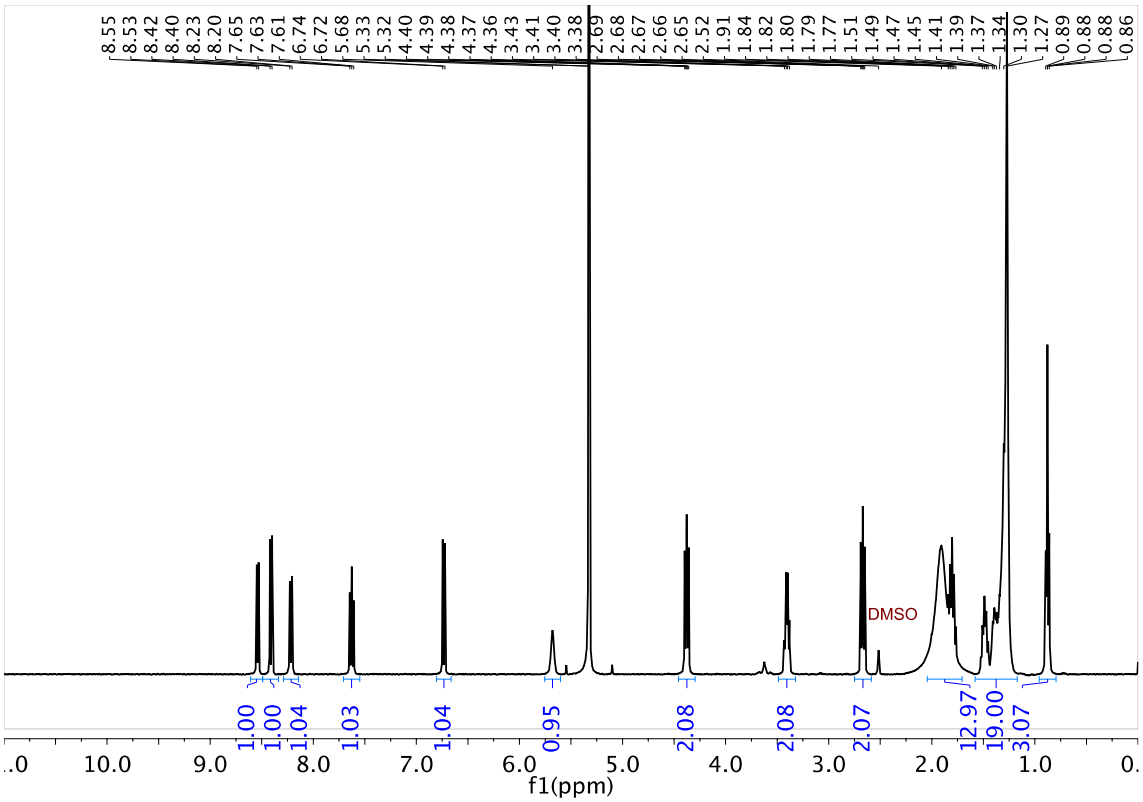

Figure S87. ^{1}H NMR spectrum of **12p** CD_2Cl_2/DMSO-d_6 95:5.

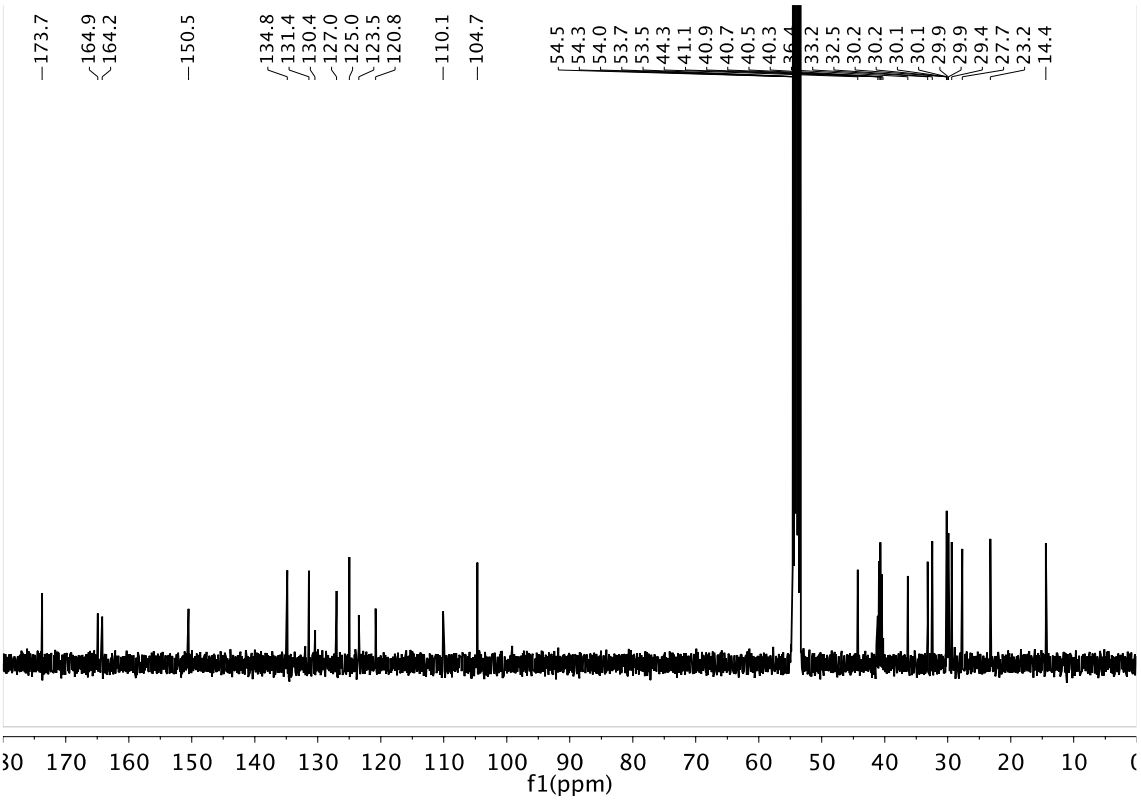

Figure S88. ^{13}C NMR spectrum of **12p** in CD_2Cl_2/DMSO-d_6 95:5.