Design and Biological Evaluation of Antifouling Dihydrostilbene Oxime Hybrids

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Supporting Information Contents

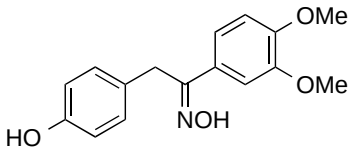
General Experimental Procedures

^{1}H and ^{13}C-NMR spectra were acquired on a Varian 7000e 400 MHz spectrometer. ^{1}H Chemical shifts are reported in δ values relative to tetramethylsilane and referenced to the residual solvent peak (CD_3OD: δ_H = 3.310, δ_C = 49.00 ppm; $CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). Coupling constants are reported in Hz. High-resolution mass spectroscopy was recorded on an LTQ Orbitrap XL Hybrid Fourier transform mass spectrometer from Thermo Scientific. Infrared spectra were recorded on an Avatar 320 FT-IR spectrometer from Nicolet. Solvents and reagents were purchased from commercial suppliers and used without further purification. Air-sensitive reactions were carried out under an argon atmosphere. Thin-layer chromatography was carried out on aluminum-backed plates coated with silica gel and visualized under UV light at 254 nm and ethanolic vanillin dip. Chromatography was carried out on silica gel using petroleum ether and ethyl acetate as eluents. All the compounds were tested at the purity shown in the SI. Names for novel compounds are depicted in italics. Spectral data for reported compounds is included if previously reported experimental data is incomplete. 3,4,*N*-Trimethoxy-*N*-methyl-benzamide (Yamazaki et al., 2012) and *N*,3,5-trimethoxy-*N*-methyl benzamide (Romines et al., 2006) were prepared accordingly to a reported protocol.

Synthesis of compounds 7-15

Compounds synthesised using Method A (see main text)

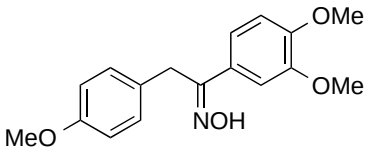
1-(3,4-dimethoxyphenyl)-1-hydroxyimino-2-(4'-hydroxyphenyl)-ethane (**8**)



8

Acylation (Medarde et al., 1994): 67% yield (0.7 mmol scale). Oxime formation: 93% yield (0.1 mmol scale). IR (neat) ν_{max} 3427, 1601, 1511, 1252, 1225, 1021, 964 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.26 (1H, d, *J* = 2.1 Hz), 7.15 (1H, dd, *J* = 8.4, 2.1 Hz), 7.06 (2H, d, *J* = 8.4 Hz), 6.87 (1H, d, *J* = 8.4 Hz), 6.65 (2H, d, *J* = 8.5 Hz), 4.06 (2H, s), 3.81 (3H, s), 3.78 (3H, s); ^{13}C NMR (CD_3OD, 101 MHz) δ 158.0, 156.7, 151.2, 150.1, 130.7, 130.4, 129.5, 121.0, 116.2, 112.2, 110.9, 56.3, 56.3, 31.6; HRMS *m/z* 310.1055 (calcd for $C_{16}H_{17}NNaO_4$: 310.1050).

1-(3,4-dimethoxyphenyl)-1-hydroxyimino-2-(4'-methoxyphenyl)-ethane (**9**)

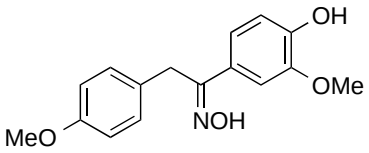


9

Acylation (Napolitano et al., 1983): 63% yield (0.6 mmol scale): IR (neat) ν_{max} 1672, 1513, 1417, 1242, 1149, 816 cm^{-1} ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (1H, dd, *J* = 8.4, 2.0 Hz), 7.55 (1H, d, *J* = 2.0 Hz), 7.23 – 7.16 (2H, m), 6.89 – 6.79 (3H, m), 4.18 (2H, s), 3.93

(3H, s), 3.91 (3H, s), 3.78 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 196.8, 158.6, 153.4, 149.2, 130.4, 129.9, 127.1, 123.5, 114.2, 110.8, 110.1, 56.2, 56.1, 55.4, 44.4; HRMS *m/z* 309.1101 (calcd for $C_{17}H_{18}NaO_4$: 309.1097). Oxime formation: 69% yield (0.1 mmol scale). IR (neat) ν_{max} 3443, 2549, 1693, 1510, 1243, 1178, 1023, 817, 764 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.27 (1H, d, *J* = 1.9 Hz), 7.15 (2H, d, *J* = 8.7 Hz), 7.13 (1H, dd, *J* = 8.4, 2.1 Hz), 6.87 – 6.82 (1H, m), 6.76 (2H, d, *J* = 8.7 Hz), 4.08 (2H, s), 3.78 (3H, s), 3.76 (3H, s), 3.70 (3H, s); ^{13}C NMR (CD_3OD, 101 MHz) δ 159.5, 157.8, 151.2, 150.1, 131.3, 130.7, 130.4, 120.9, 114.8, 112.2, 110.9, 56.3, 56.3, 55.6, 31.5; HRMS *m/z* 324.1211 (calcd for $C_{17}H_{19}NNaO_4$: 324.1206).

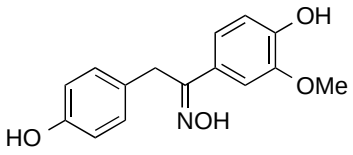
1-(3-methoxy-4-hydroxyphenyl)-1-hydroxyimino-2-(4'-methoxyphenyl)-ethane (**11**)



11

Acylation: 46% yield (0.6 mmol scale): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.21 – 7.16 (m, 2H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.89 – 6.83 (m, 2H), 4.17 (s, 2H), 3.91 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (CD_3OD, 101 MHz) δ 196.8, 158.6, 150.5, 146.8, 130.4, 129.6, 127.1, 124.2, 114.2, 114.0, 110.5, 56.1, 55.4, 44.3. Oxime formation: 83% yield (0.1 mmol scale). IR (neat) ν_{max} 3384, 1509, 1244, 1224, 1028 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.23 (1H, d, *J* = 2.0 Hz), 7.15 (2H, d, *J* = 8.6 Hz), 7.05 (1H, dd, *J* = 8.3, 2.0 Hz), 6.77 (2H, d, *J* = 8.7 Hz), 6.72 (1H, d, *J* = 8.3 Hz), 4.07 (2H, s), 3.79 (3H, s), 3.71 (3H, s); ^{13}C NMR (CD_3OD, 101 MHz) δ 159.5, 158.2, 148.7, 148.7, 131.3, 130.7, 129.2, 121.1, 115.8, 114.8, 110.8, 56.3, 55.6, 31.6; HRMS *m/z* 310.1054 (calcd for $C_{16}H_{17}NNaO_4$: 310.1050).

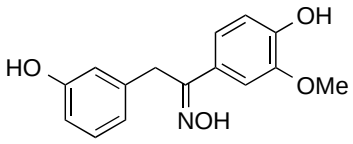
1-(3-methoxy-4-hydroxyphenyl)-1-hydroxyimino-2-(4'-hydroxyphenyl)-ethane (**12**)



12

Acylation (Ley et al., 2012): 48% yield (0.7 mmol scale). Oxime formation: 74% yield (0.1 mmol scale). IR (neat) ν_{max} 3327, 1596, 1512, 1261, 1220, 1173, 1028 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.22 (1H, d, *J* = 1.9 Hz), 7.06 (2H, d, *J* = 8.6 Hz), 7.05 (1H, dd, *J* = 8.3, 2.1 Hz), 6.72 (1H, d, *J* = 8.3 Hz), 6.65 (2H, d, *J* = 8.6 Hz), 4.04 (2H, s), 3.80 (3H, s); ^{13}C NMR (CD_3OD, 101 MHz) δ 158.4, 156.6, 148.7, 148.6, 130.7, 129.6, 129.3, 121.1, 116.2, 115.8, 110.9, 56.3, 31.7; HRMS *m/z* 296.0898 (calcd for $C_{15}H_{15}NNaO_4$: 296.0893).

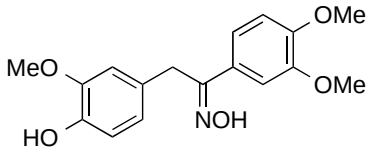
1-(3-methoxy-4-hydroxyphenyl)-1-hydroxyimino-2-(3'-hydroxyphenyl)-ethane (**13**)



13

Acylation: 66% yield (0.7 mmol scale): IR (neat) ν_{max} 3392, 3200, 1577, 1454, 1274, 1223, 1126, 692 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.63 (1H, dd, *J* = 8.3, 2.0 Hz), 7.55 (1H, d, *J* = 1.9 Hz), 7.10 (1H, t, *J* = 7.8 Hz), 6.85 (1H, d, *J* = 8.3 Hz), 6.77 – 6.68 (2H, m), 6.64 (1H, dd, *J* = 8.2, 2.1 Hz), 4.17 (2H, s), 3.87 (3H, s); ^{13}C NMR (CD_3OD, 101 MHz) δ 199.0, 158.6, 153.4, 149.0, 138.2, 130.6, 129.9, 125.4, 121.6, 117.2, 115.8, 114.6, 112.5, 56.4, 45.9; HRMS *m/z* 281.0788 (calcd for $C_{15}H_{14}NaO_4$: 281.0784). Oxime formation: 74% yield (0.1 mmol scale). IR (neat) ν_{max} 3350, 1587, 1516, 1259, 1220, 1028, 965, 741 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.24 (1H, d, *J* = 2.0 Hz), 7.05 (1H, dd, *J* = 8.3, 2.1 Hz), 7.04 (1H, t, *J* = 7.9 Hz), 6.75 – 6.67 (3H, m), 6.57 (1H, dd, *J* = 7.9, 2.0 Hz), 4.08 (2H, s), 3.81 (3H, s); ^{13}C NMR (CD_3OD, 101 MHz) δ 158.5, 157.8, 148.7, 148.7, 140.4, 130.3, 129.3, 121.1*, 116.6, 115.8, 114.0, 110.8, 56.3, 32.5 *Corresponds to two carbon signals; HRMS *m/z* 274.1078 (calcd for $C_{15}H_{16}NO_4$: 274.1074).

1-(3,4-dimethoxyphenyl)-1-hydroxyimino-2-(3'-methoxy-4'-hydroxyphenyl)-ethane (**14**)

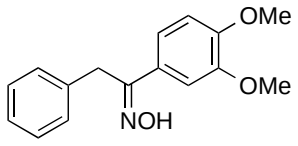


14

Acylation (Barclay et al., 1994): 79% yield (0.5 mmol scale). Oxime formation: 84% yield (0.1 mmol scale). IR (neat) ν_{max} 3293, 1602, 1513, 1271, 1250, 1224, 1146, 1020 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.27 (d, *J* = 2.0 Hz, 1H), 7.16 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.87 – 6.82 (m, 2H), 6.68 – 6.63 (m, 2H), 4.07 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (CD_3OD, 101 MHz) δ 158.0, 151.2, 150.1, 149.1, 146.3, 130.5, 129.8, 122.3, 121.0, 116.3, 113.4, 112.2, 111.0, 56.3*, 56.3, 32.0 *Corresponds to two carbon signals; HRMS *m/z* 340.1158 (calcd for $C_{17}H_{19}NNaO_5$: 340.1155).

Compounds synthesised using Method B (see main text)

1-(3,4-dimethoxyphenyl)-1-hydroxyimino-2-phenylethane (**7**)



7

Grignard (Kaito et al., 2006) 74% yield (0.3 mmol scale). Oxime formation:(Chen et al., 2016) 70% yield (0.2 mmol scale). IR (neat) ν_{max} 3446, 3221, 1601, 1514, 1252, 1227, 1023, 717 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.28 (1H, d, *J* = 2.1 Hz), 7.25 – 7.17 (4H, m), 7.15 – 7.10 (2H, m), 6.82 (1H, d, *J* = 8.4 Hz), 4.16 (2H, s,), 3.77 (3H, s), 3.75 (3H, s); ^{13}C

NMR (CD_3OD, 101 MHz) δ 157.4, 151.2, 150.1, 138.8, 130.3, 129.7, 129.4, 127.1, 120.9, 112.2, 110.8, 56.3, 56.3, 32.3; HRMS m/z 294.1102 (calcd for $C_{16}H_{17}NNaO_3$: 294.1101).

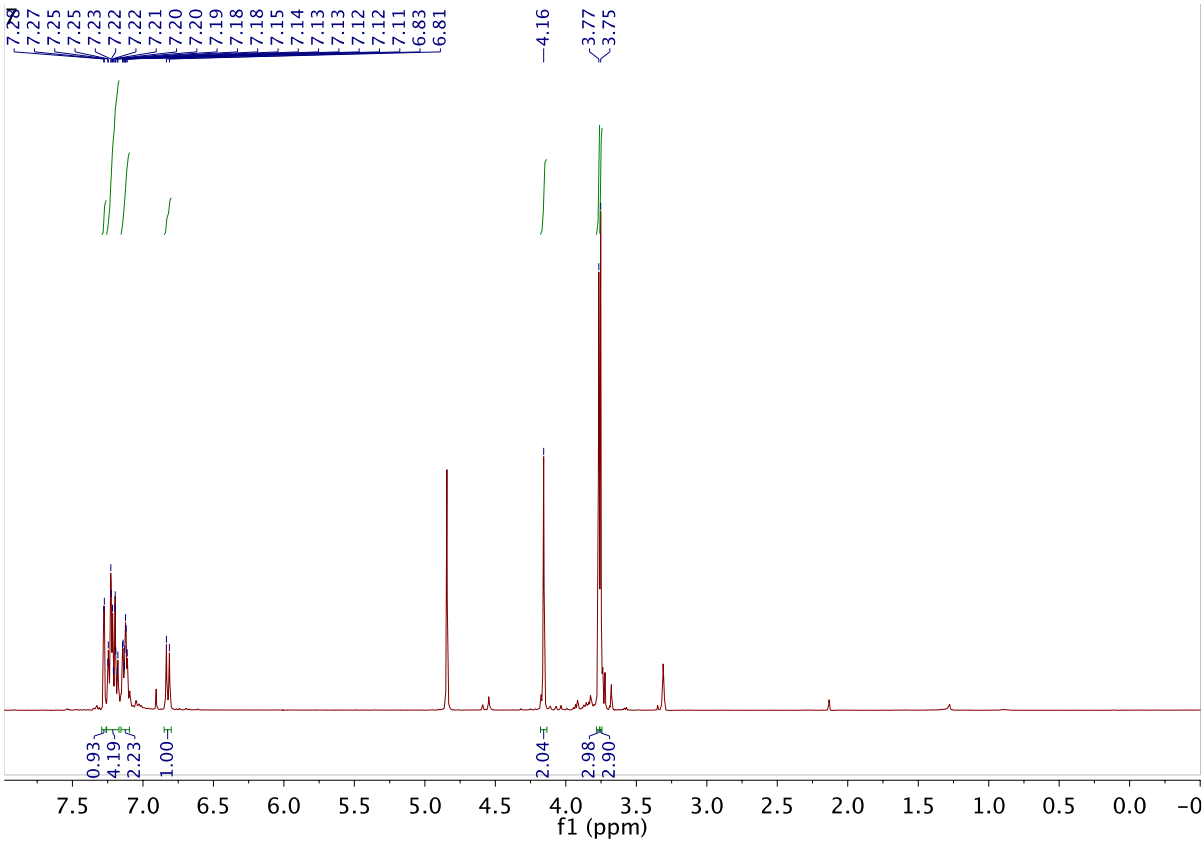


Figure S1. ^{1}H-NMR of **7** in CD_3OD.

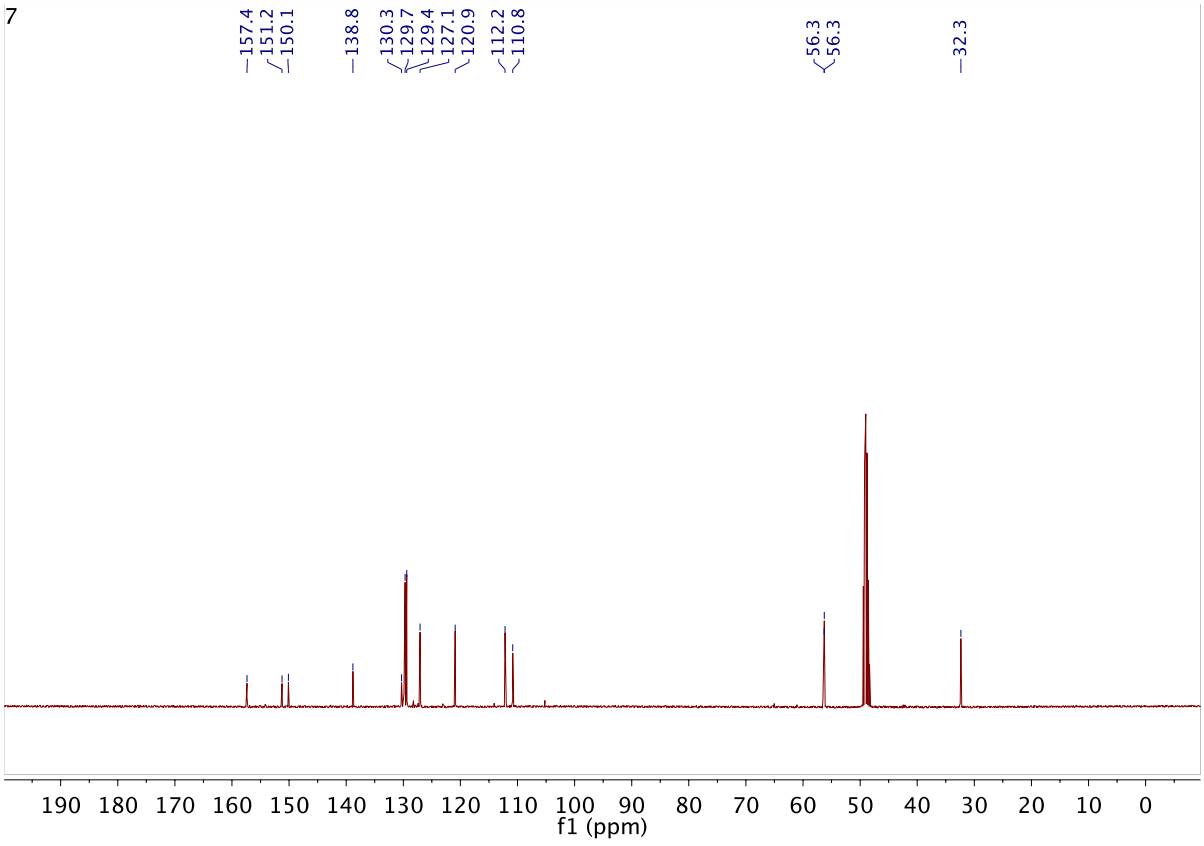


Figure S2. ^{13}C-NMR of **7** in CD_3OD.

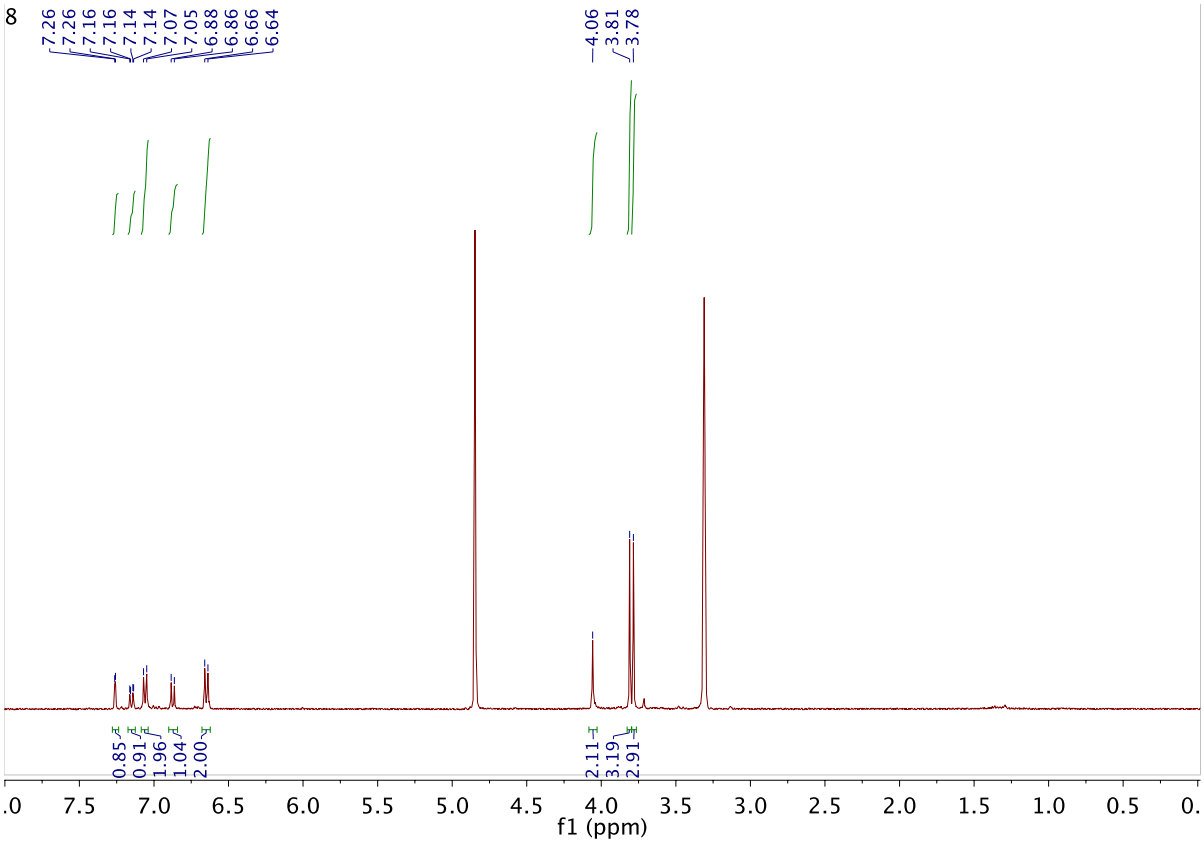


Figure S3. ^{1}H-NMR of **8** in CD_3OD.

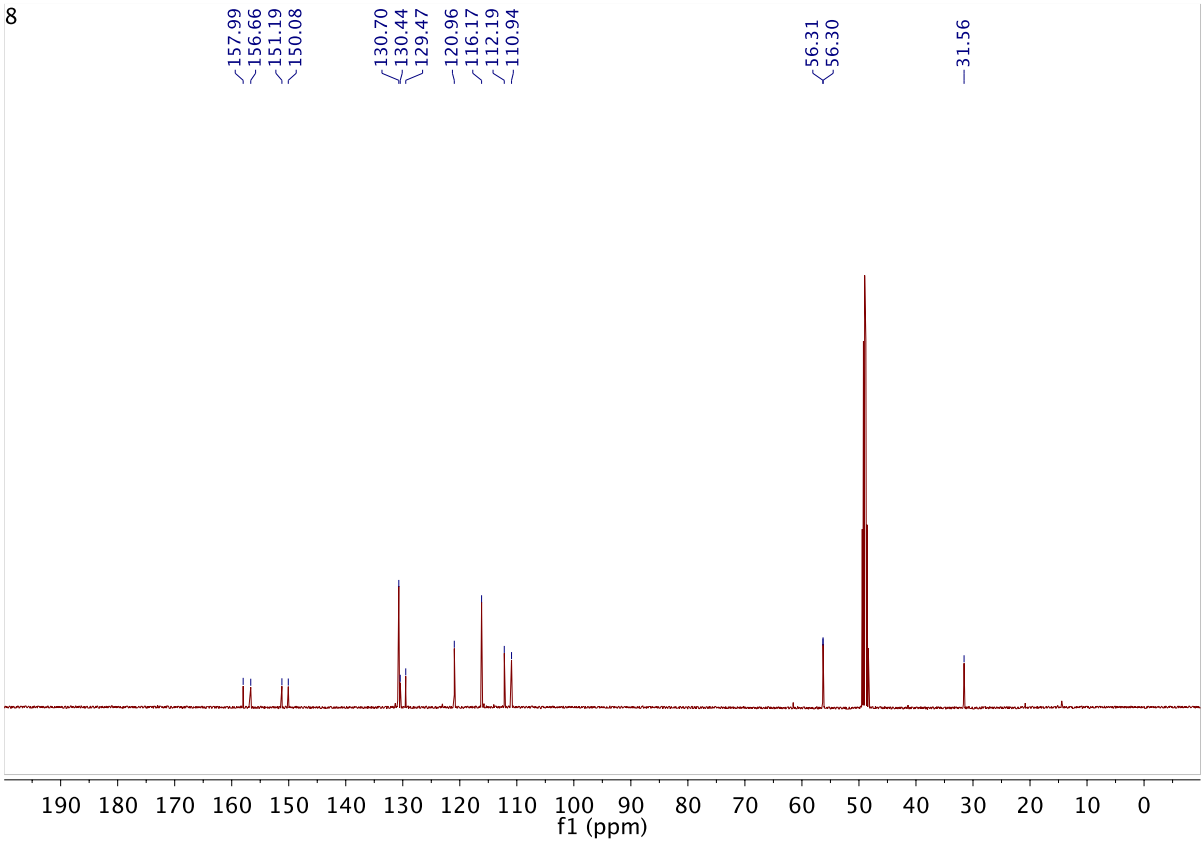


Figure S4. ^{13}C-NMR of **8** in CD_3OD.

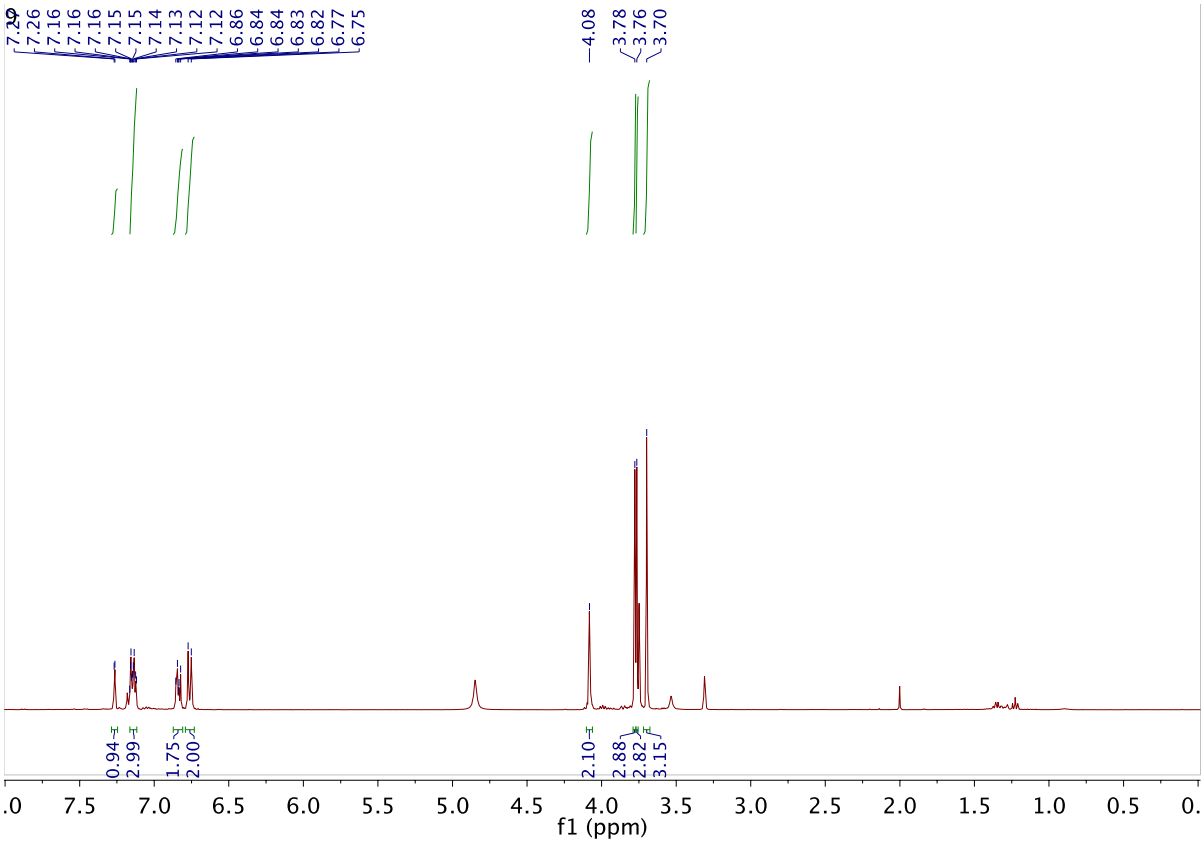


Figure S5. ^{1}H-NMR of **9** in CD_3OD.

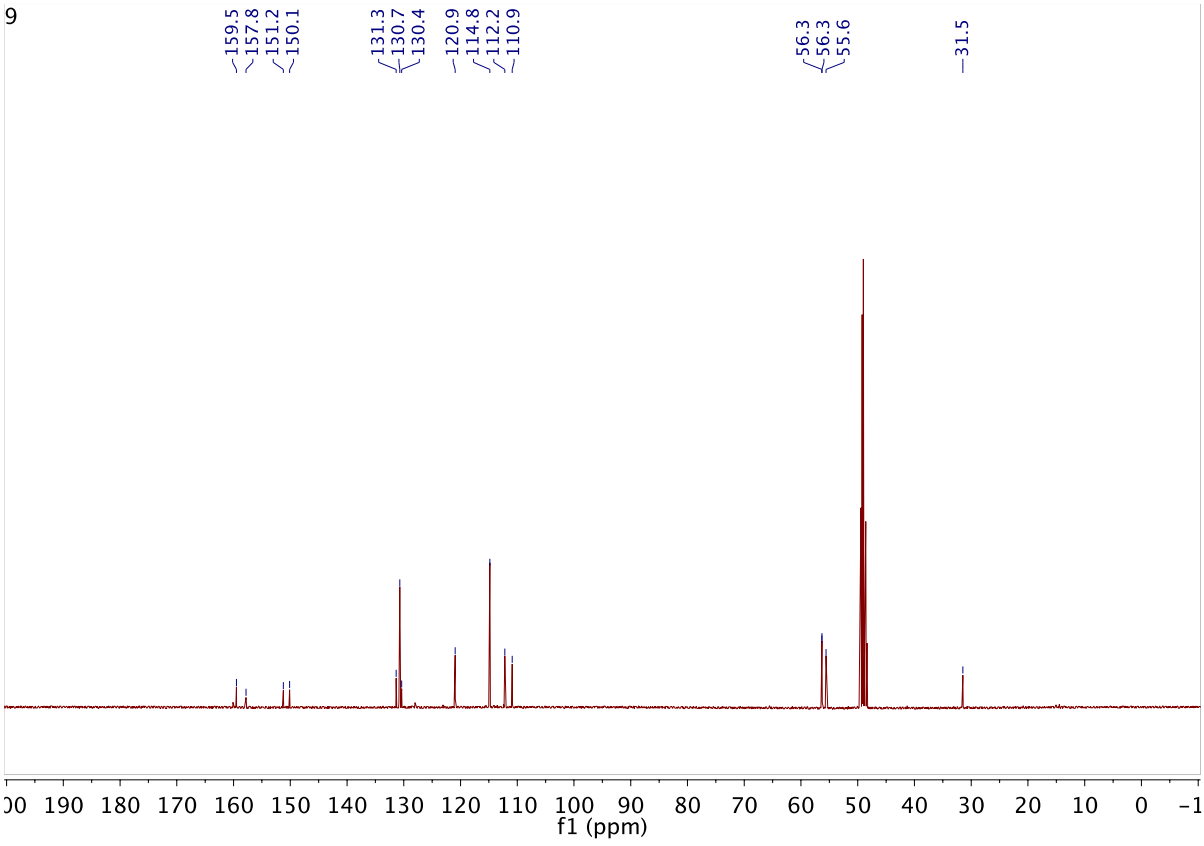


Figure S6. ^{13}C-NMR of **9** in CD_3OD.

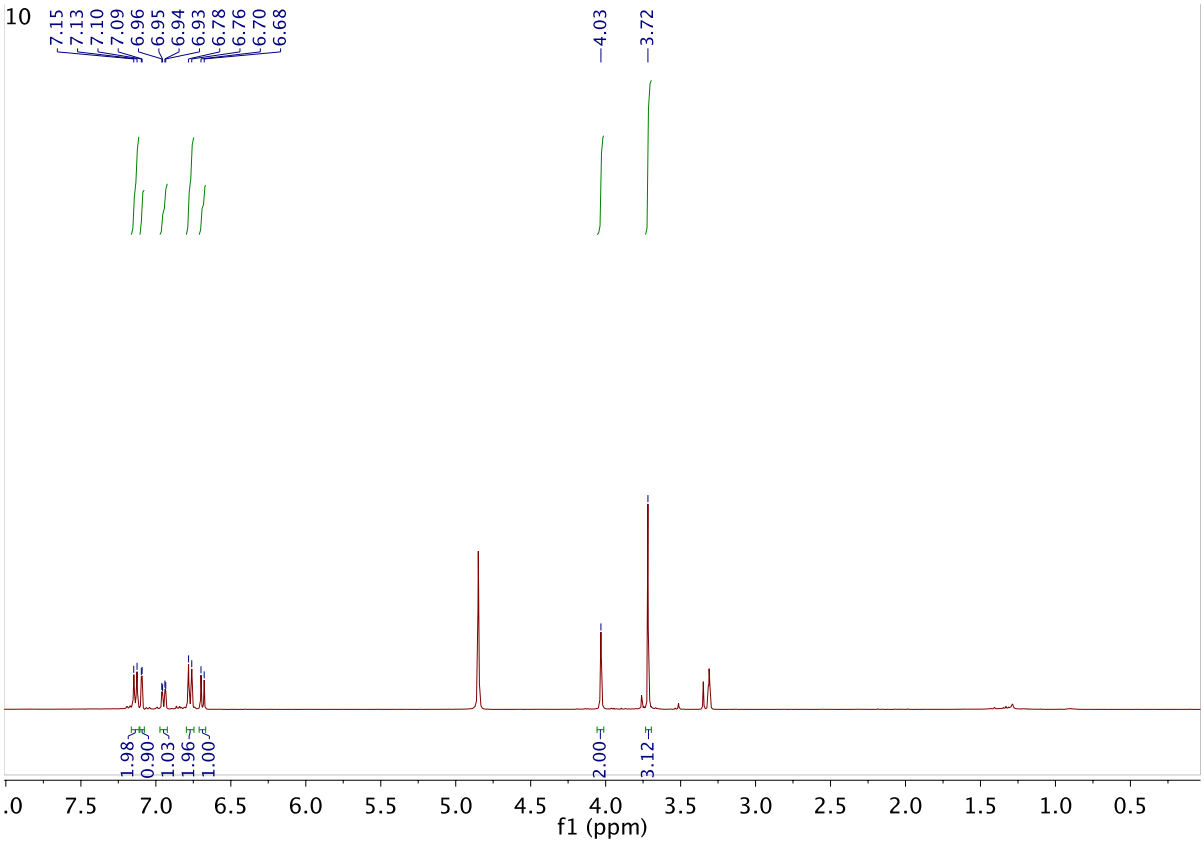


Figure S7. ^{1}H-NMR of **10** in CD_3OD.

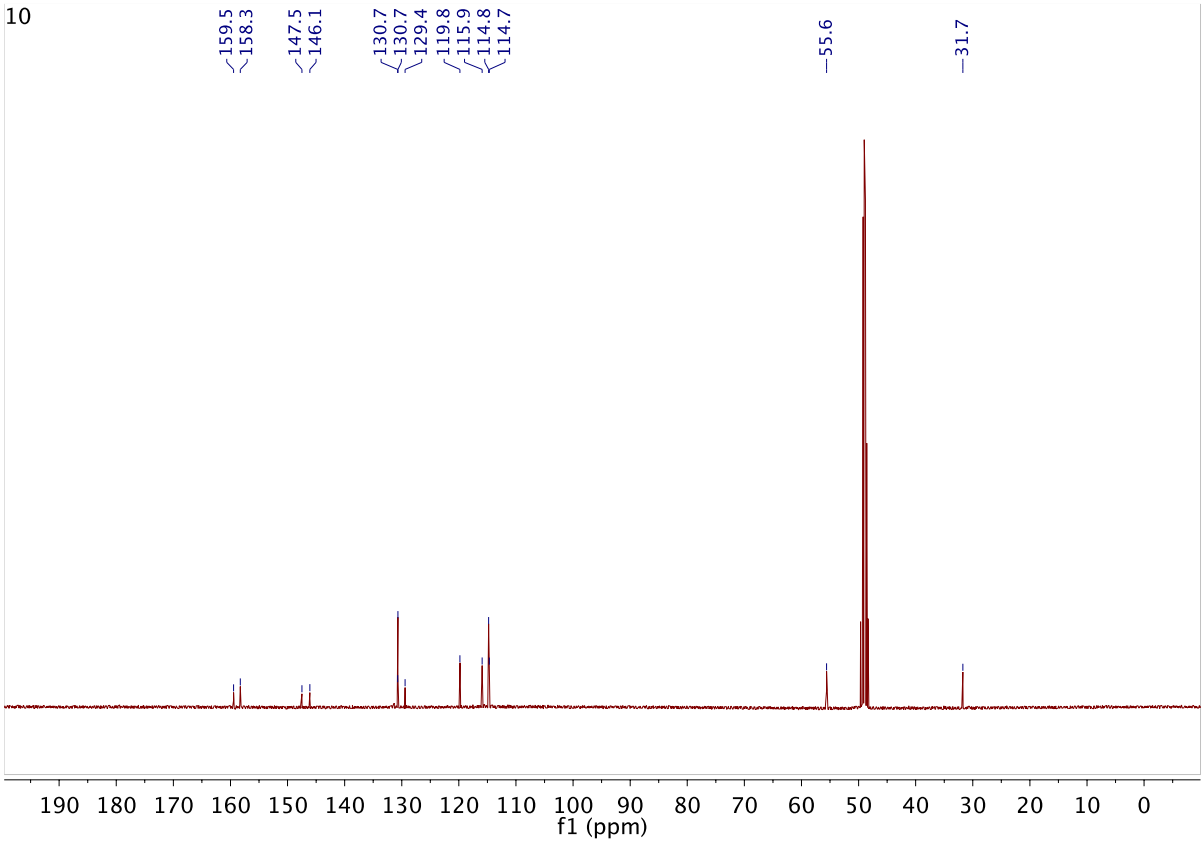


Figure S8. ^{13}C-NMR of **10** in CD_3OD.

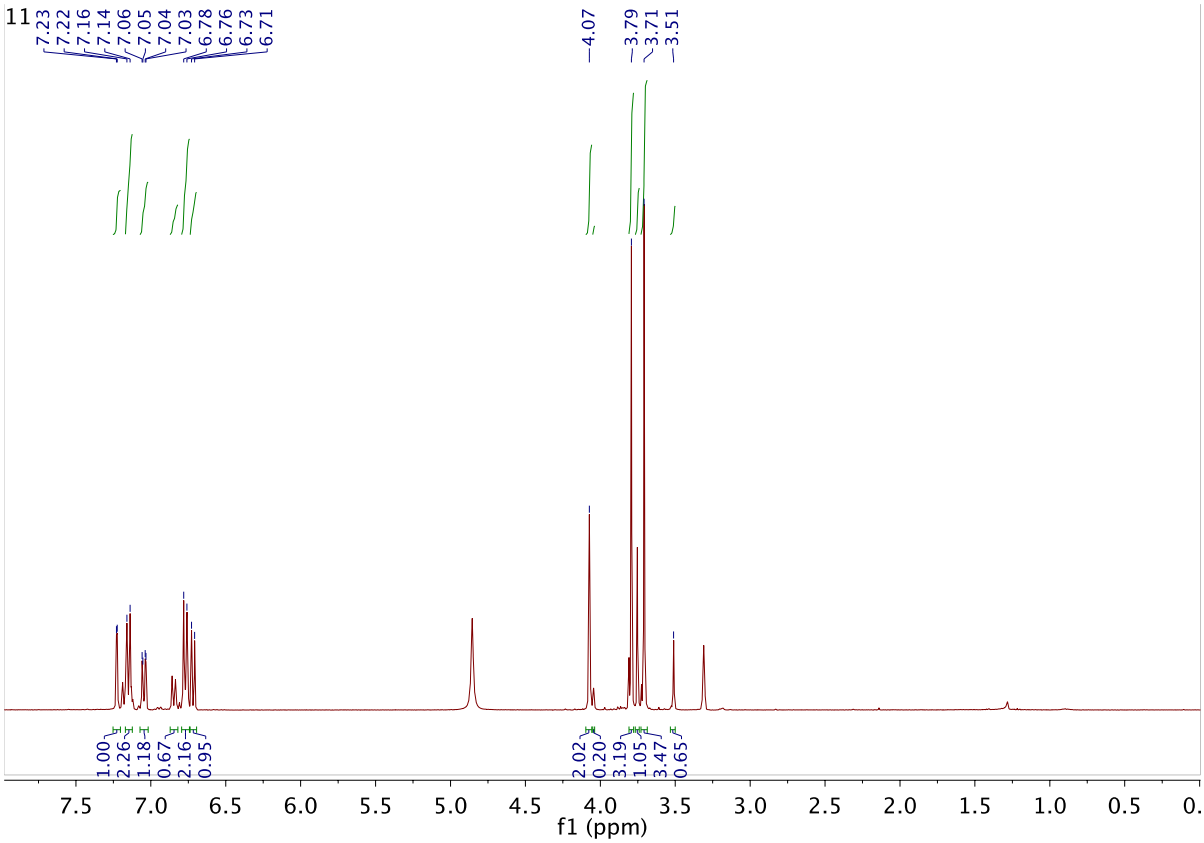


Figure S9. ^{1}H-NMR of **11** in CD_3OD.

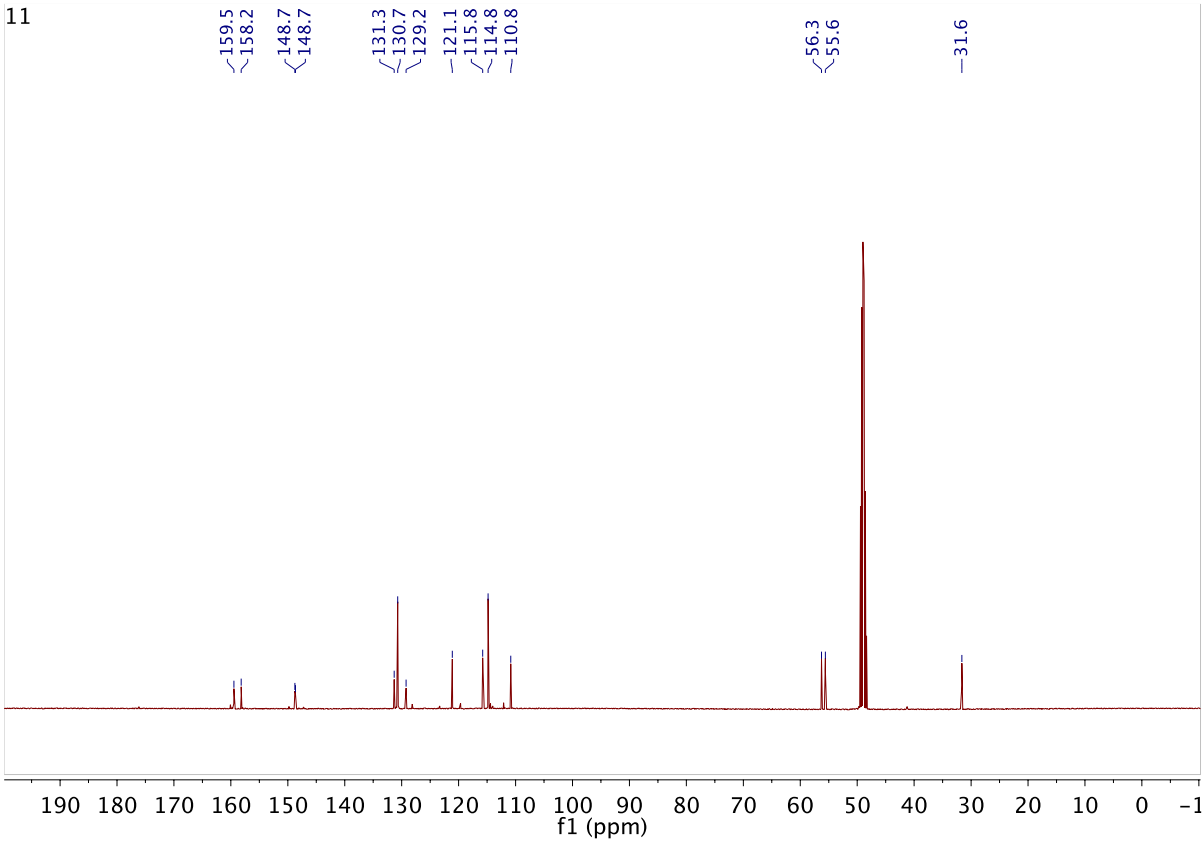


Figure S10. ^{13}C-NMR of **11** in CD_3OD.

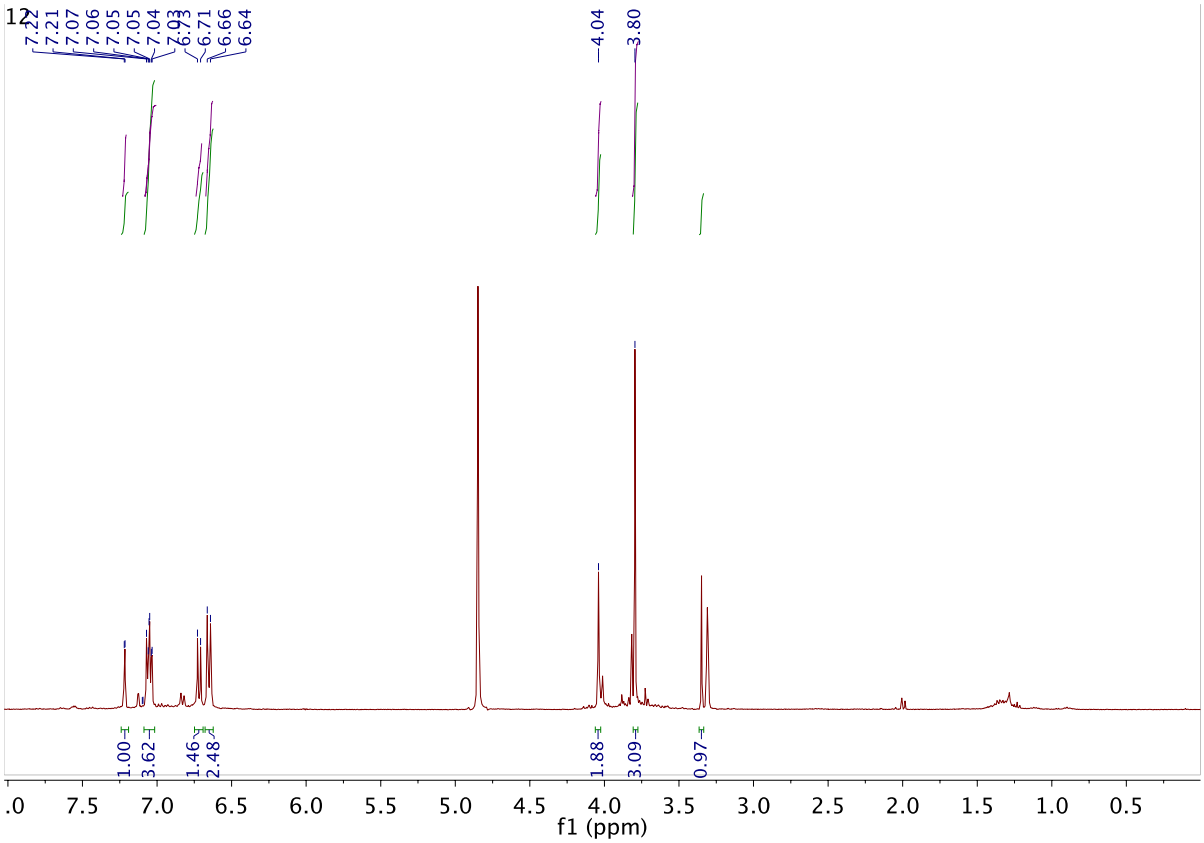


Figure S11. ^{1}H-NMR of **12** in CD_3OD.

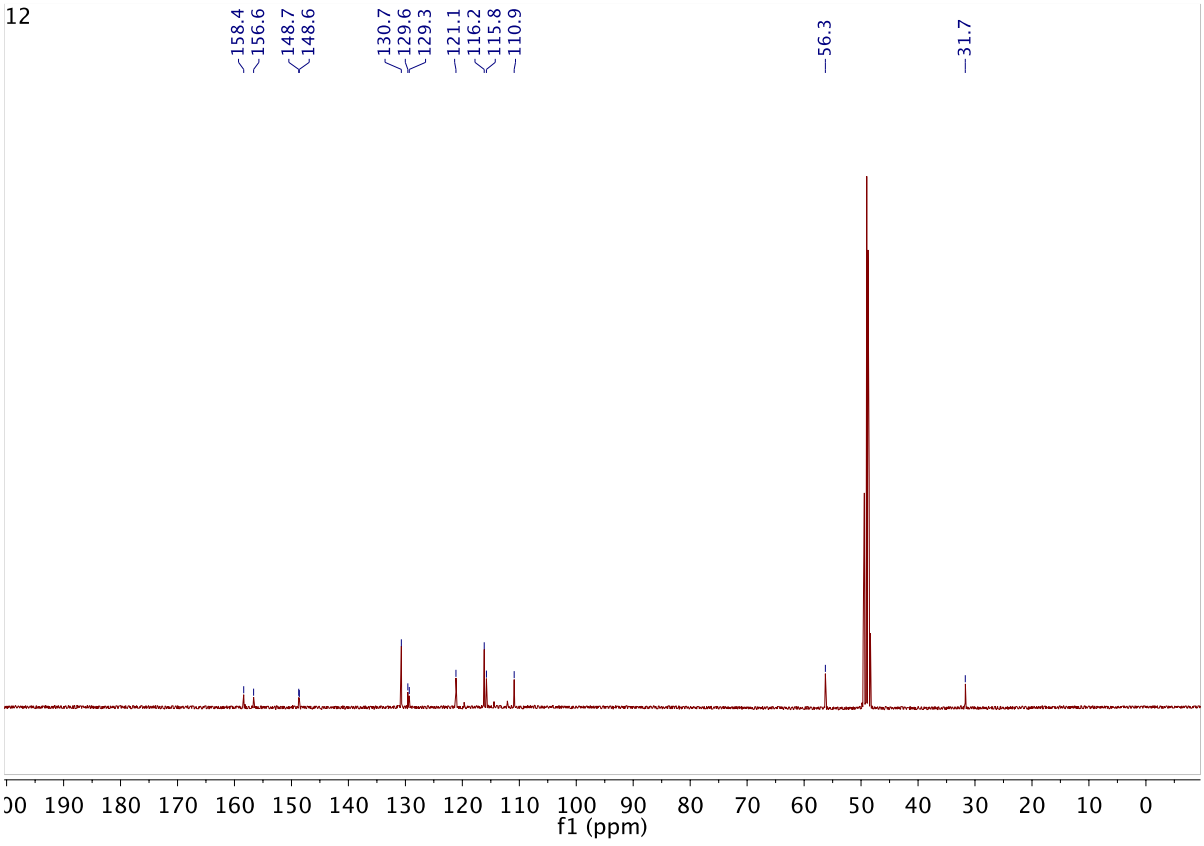


Figure S12. ^{13}C-NMR of **12** in CD_3OD.

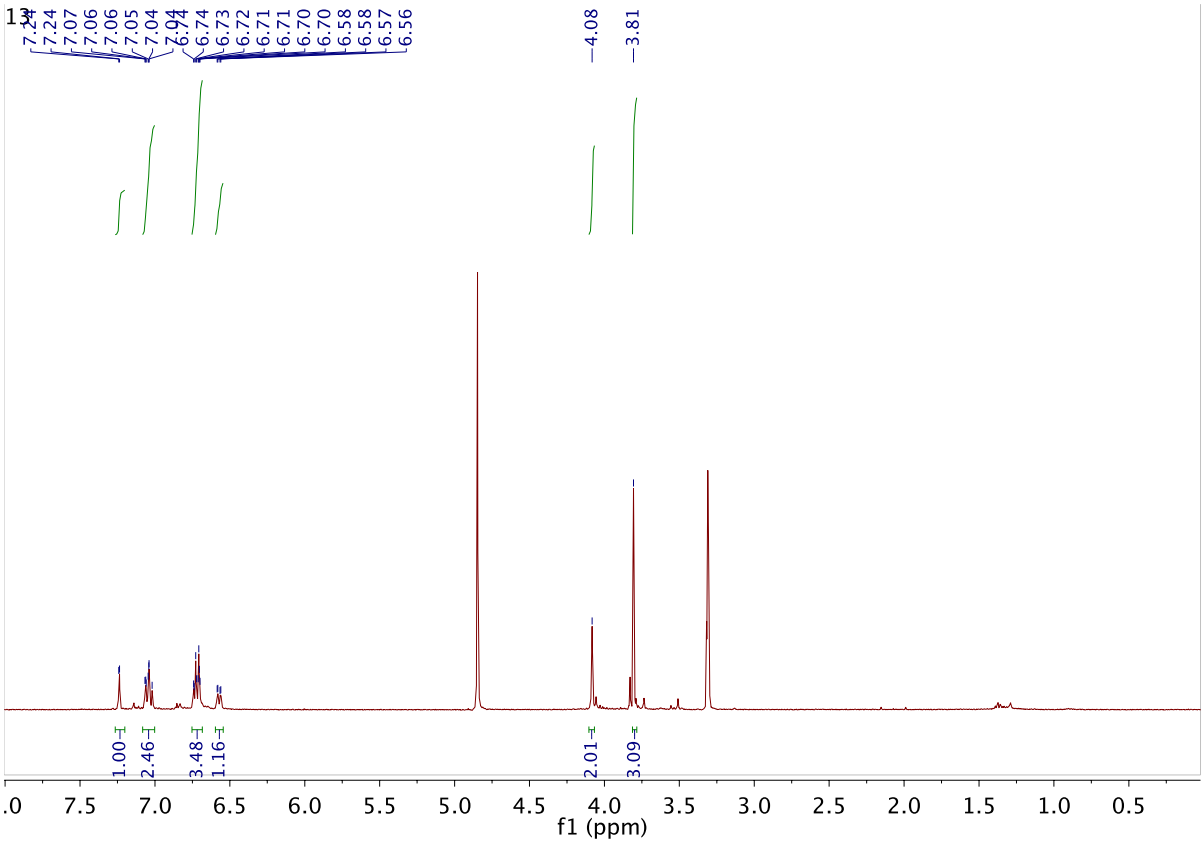


Figure S13. ^{1}H-NMR of **13** in CD_3OD.

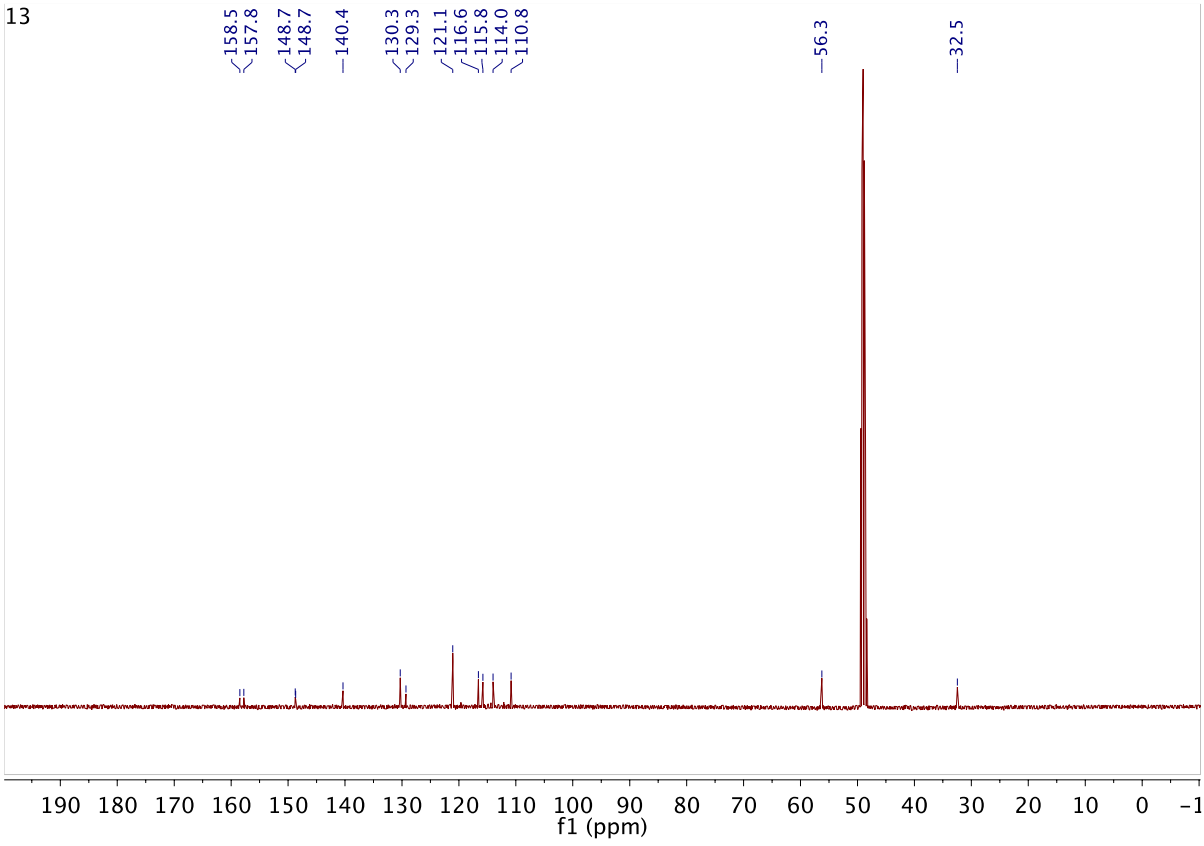


Figure S14. ^{13}C-NMR of **13** in CD_3OD.

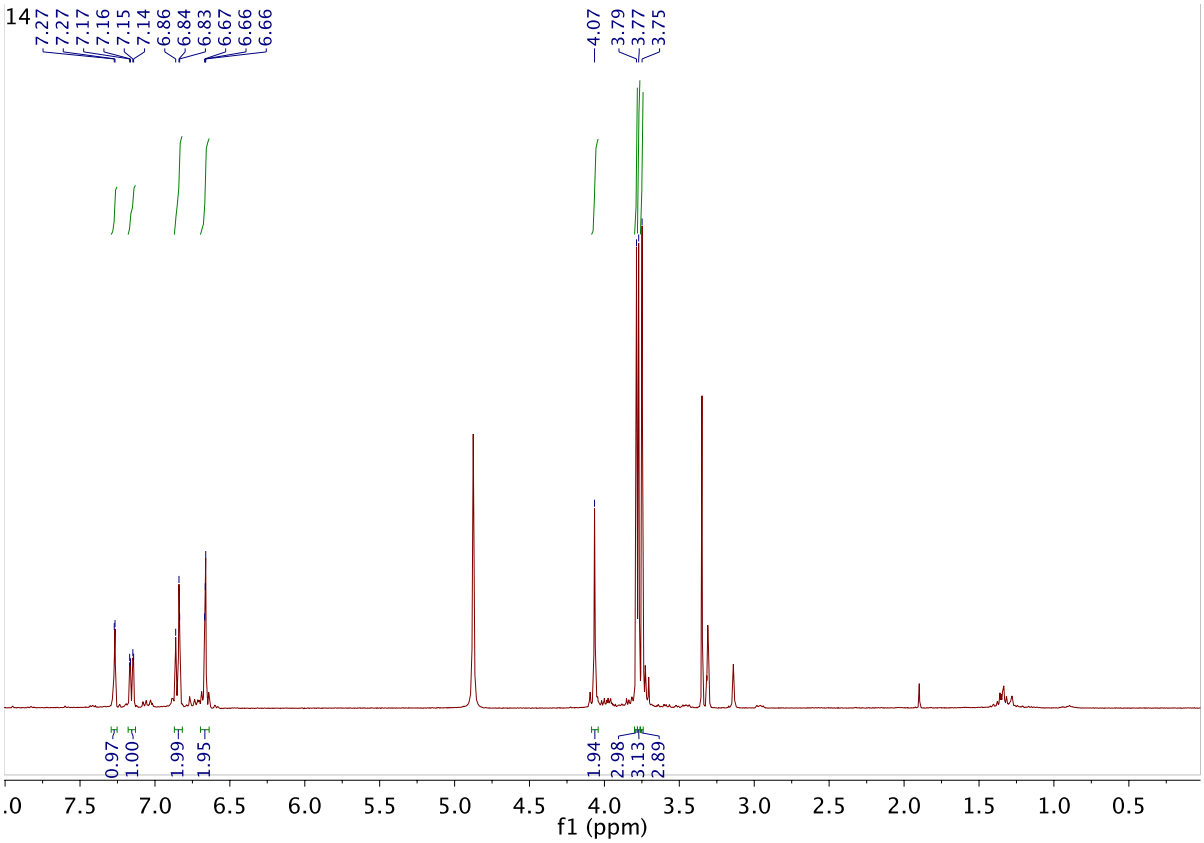


Figure S15. ^{1}H-NMR of **14** in CD_3OD.

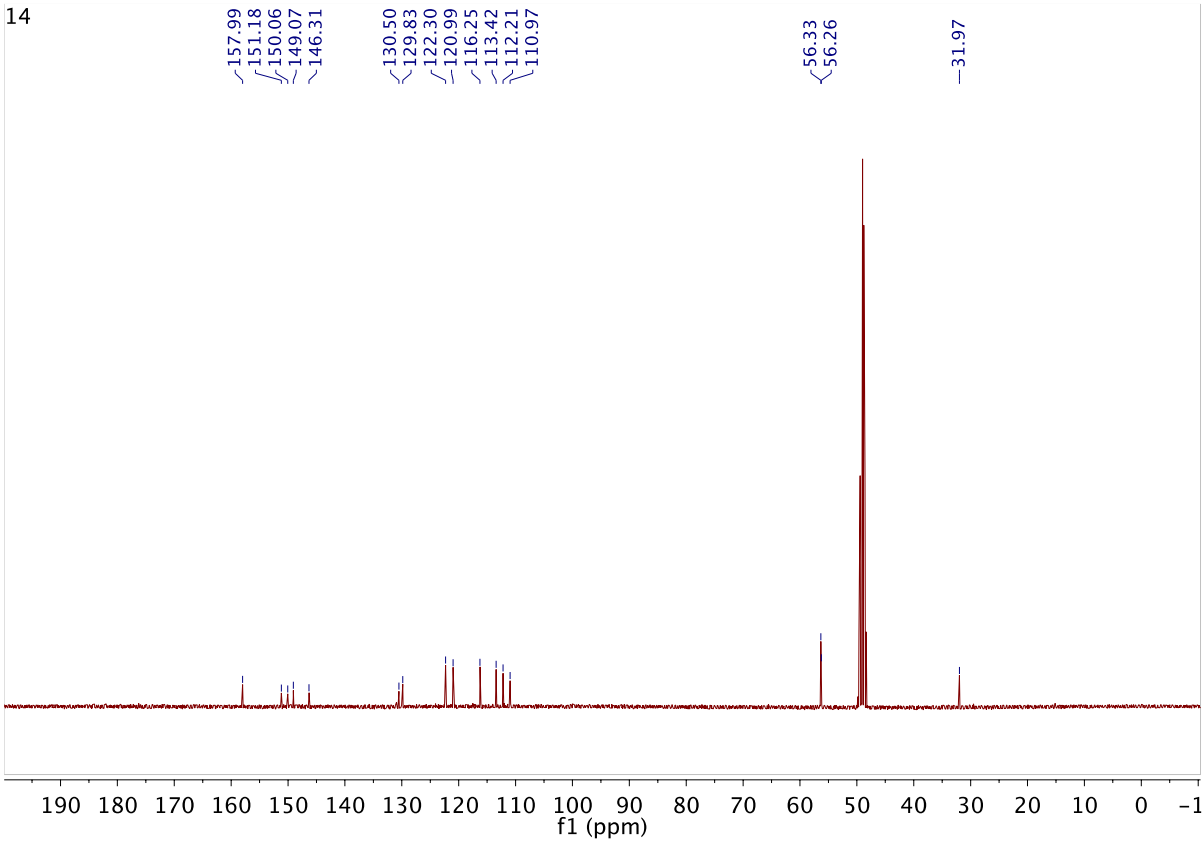


Figure S16. ^{13}C-NMR of **14** in CD_3OD.

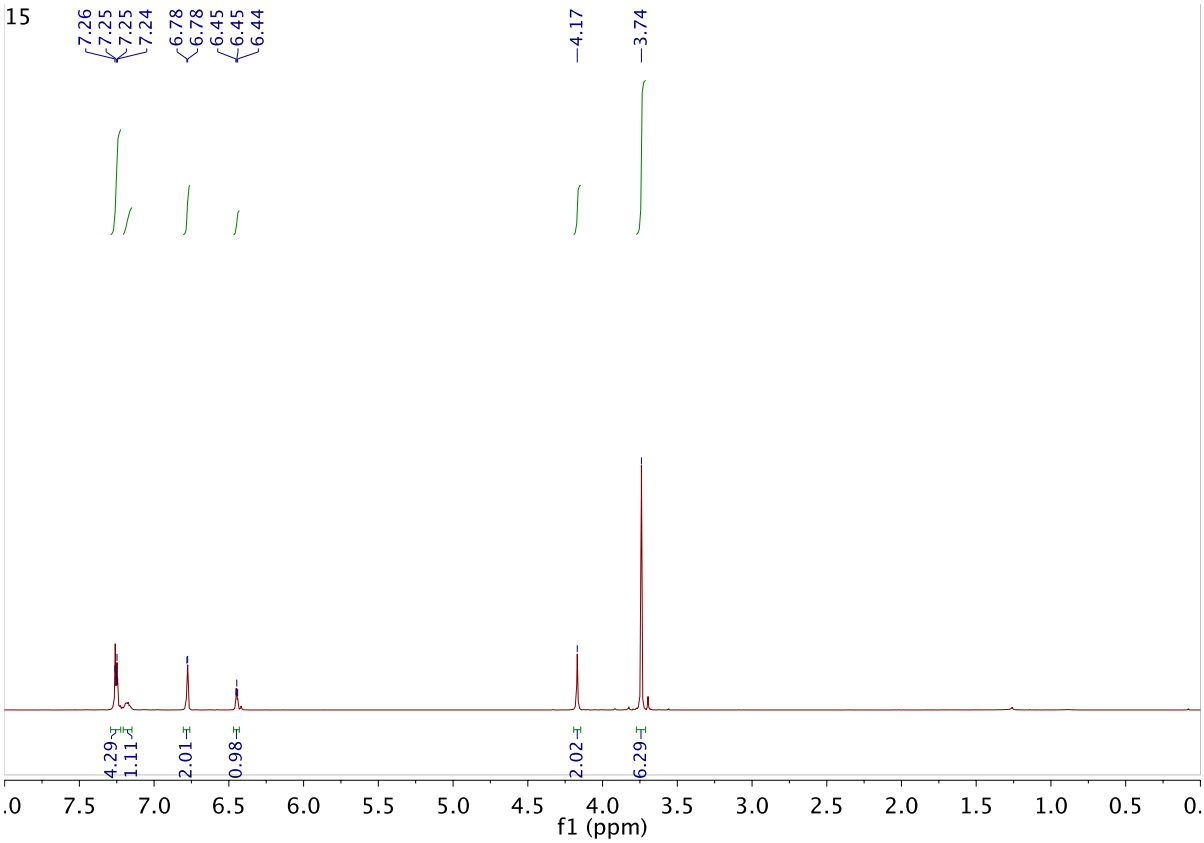


Figure S17. ^{1}H-NMR of **15** in $CDCl_3$.

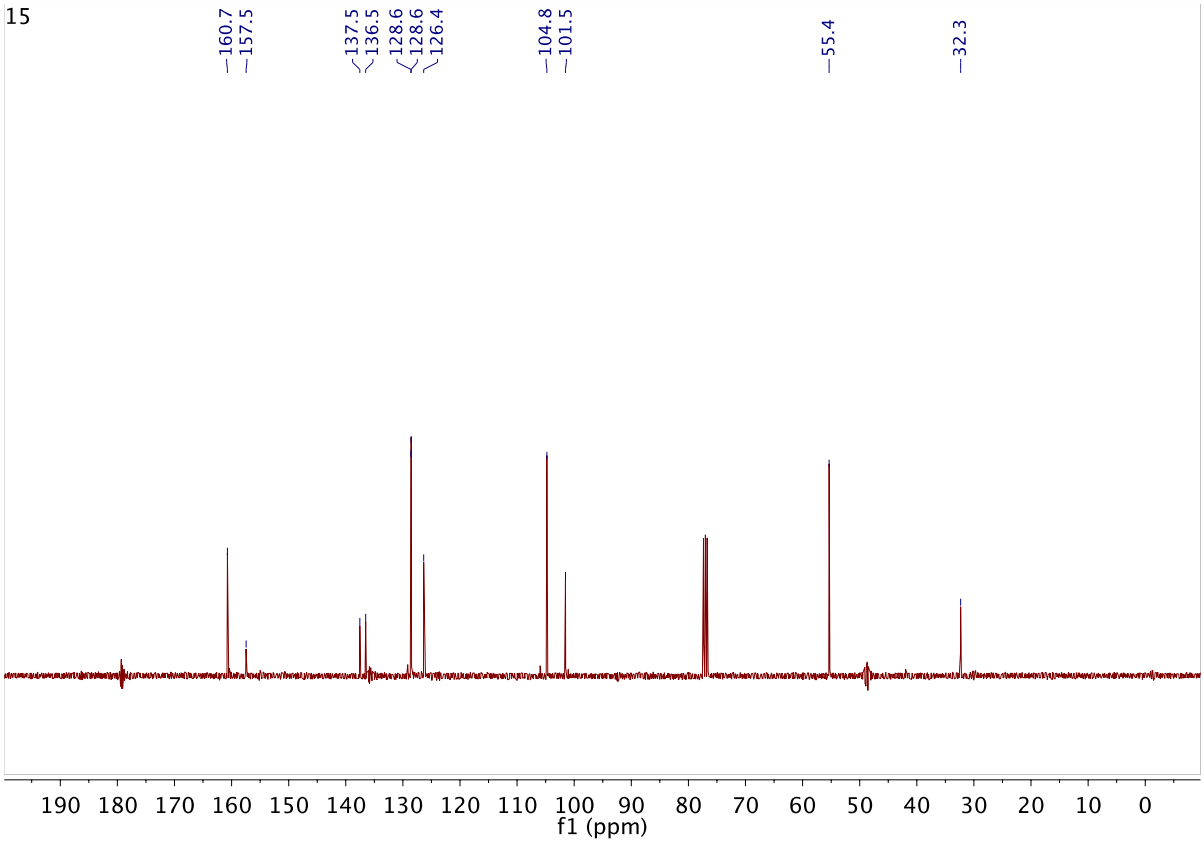


Figure S18. ^{13}C-NMR of **15** in $CDCl_3$.

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