

Supplementary Information

Brønsted Acid-Catalyzed Dipeptides Functionalization through Azlactones

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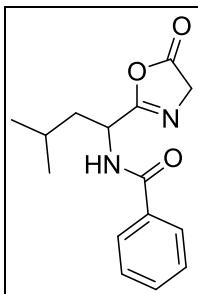
Experimental

General remarks

All reagents were commercially obtained and used with no further purification. Unless otherwise noted, all reactions were carried out in flame-dried glassware under a positive pressure of dry nitrogen. Thin layer chromatography (TLC) was performed on Merck precoated glass-backed TLC plates (silica gel 60 F254) and visualized by UV lamp (254 nm). Yields refer to chromatographically and spectroscopically pure compounds. ^1H and ^{13}C spectra were recorded on a Bruker Avance III 500 MHz spectrometer. Chemical shifts are reported in parts *per* million (ppm). ^1H NMR spectra were referenced to CDCl_3 (7.28 ppm) and ^{13}C NMR spectra were referenced to CDCl_3 (77.23 ppm). All ^{13}C spectra were measured with complete proton decoupling. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; q, quartet; qu, quintet; sext, sextet and J , coupling constant in hertz (Hz). High-resolution mass spectra were acquired in the positive ion mode using a mass spectrometer Waters Xevo G2-XS QToF.

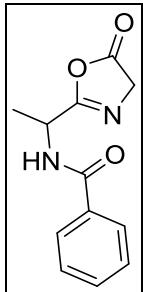
*e-mail: giovanni.amarante@ufjf.edu.br

Characterization data



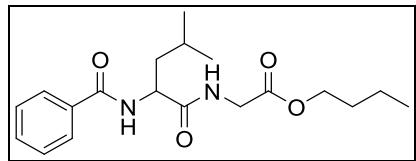
N-(3-Methyl-1-(5-oxo-4,5-dihydrooxazol-2-yl)butyl)benzamide

The product **2a** (42 mg, 85%) was obtained as a yellow oil after the reaction mixture was diluted in 10 mL of CH₂Cl₂ and washed 5 times with 5 mL of distilled water. The organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure, affording the desired azlactones without the need of chromatography column. IR (KBr) ν / cm⁻¹ 3295, 3067, 2963, 2924, 2860, 1827, 1646, 1529, 1281, 1027; ¹H NMR (500 MHz, CDCl₃) δ 7.81-7.79 (m, 2H), 7.50 (tt, 1H, *J* 1.4, 7.8 Hz), 7.41 (t, 2H, *J* 7.6 Hz), 6.81 (d, 1H, *J* 8.0 Hz), 5.16-5.11 (m, 1H), 4.17 (d, 2H, *J* 1.6 Hz), 1.81-1.72 (m, 3H), 0.99-0.97 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 175.5, 167.4, 167.3, 133.6, 132.1, 128.8, 127.2, 54.2, 47.1, 41.4, 25.0, 22.9, 22.0.



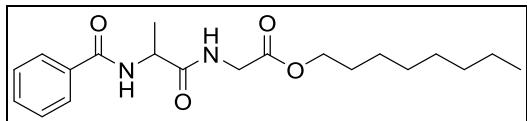
N-(1-(5-Oxo-4,5-dihydrooxazol-2-yl)ethyl)benzamide

The product **2b** (56 mg, 75%) was obtained as a yellow oil after the reaction mixture was diluted in 10 mL of CH₂Cl₂ and washed 5 times with 5 mL of distilled water. The organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure, affording the desired azlactones without the need of chromatography column. ¹H NMR (500 MHz, CDCl₃) δ 7.81-7.79 (m, 2H), 7.50 (tt, 1H, *J* 1.5, 7.8 Hz), 7.43-7.39 (m, 2H), 6.98 (d, 1H, *J* 7.2 Hz), 5.08 (qut, 1H, *J* 1.9, 7.2 Hz), 4.18 (d, 2H, *J* 2.0 Hz), 1.57 (d, 3H, *J* 7.1 Hz), ¹³C NMR (125 MHz, CDCl₃) δ 175.4, 167.6, 167.1, 133.6, 132.0, 128.7, 127.2, 54.2, 44.6, 18.3.



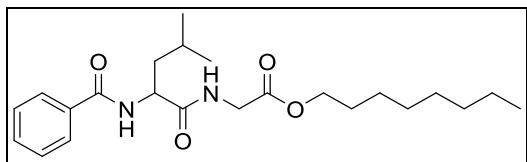
Butyl N-benzoylleucylglycinate

The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product **3a** (37 mg, 69%) as a yellow solid; m.p. 83 °C; IR (ZnSe) ν / cm⁻¹ 3289, 3080, 2958, 2925, 2867, 1746, 1660, 1629, 1536, 1199; ¹H NMR (500 MHz, CDCl₃) δ 7.80-7.79 (m, 2H), 7.51 (tt, 1H, *J* 1.5, 7.4 Hz), 7.44-7.41 (m, 2H), 6.89 (t, 1H, *J* 5.1 Hz), 6.77 (d, 1H, *J* 8.2 Hz), 4.79-4.74 (m, 1H), 4.13 (t, 2H, *J* 6.7 Hz), 4.07 (dd, 1H, *J* 5.6, 18.2 Hz), 3.98 (dd, 1H, *J* 5.2, 18.2 Hz), 1.81-1.67 (m, 3H), 1.60 (qu, 2H, *J* 7.1 Hz), 1.35 (sext, 2H, *J* 7.5 Hz), 0.98-0.96 (m, 6H), 0.91 (t, 3H, *J* 7.4 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 172.6, 169.8, 167.6, 133.8, 132.0, 128.7, 127.3, 65.5, 52.0, 41.5, 41.3, 30.6, 25.0, 23.0, 22.3, 19.1, 13.8; HRMS: calcd. for [C₁₉H₂₈N₂NaO₄]⁺ [M + Na]⁺: *m/z* 371.1947, found 371.1939.



Octyl N-benzoylalanylglycinate

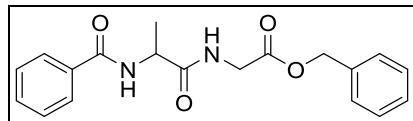
The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product **3b** (50 mg, 71%) as a yellow oil; IR (ZnSe) ν / cm⁻¹ 3309, 3270, 2957, 2928, 2865, 1722, 1658, 1632, 1531, 1223; ¹H NMR (500 MHz, CDCl₃) δ 7.82-7.80 (m, 2H), 7.49 (tt, 1H, *J* 1.6, 7.8 Hz), 7.43-7.40 (m, 2H), 7.13 (t, 1H, *J* 5.1 Hz), 7.10 (d, 1H, *J* 7.5 Hz), 4.81 (qu, 1H, *J* 7.1 Hz), 4.06-4.03 (m, 4H), 1.50 (d, 3H, *J* 7.0 Hz), 1.34-1.25 (m, 10H), 0.87-0.84 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 172.9, 169.9, 167.4, 133.8, 132.0, 128.7, 127.3, 68.1, 49.2, 41.5, 38.8, 30.4, 29.0, 23.7, 23.0, 18.5, 14.1, 11.0; HRMS: calcd. for [C₂₀H₃₁N₂O₄]⁺ [M + H]⁺: *m/z* 363.2284, found 363.2287.



Octyl N-benzoylleucylglycinate

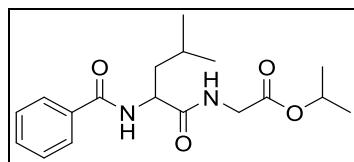
The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product **3c** (44 mg, 87%) as a white solid; m.p. 62 °C; IR (ZnSe) ν / cm⁻¹ 3263, 3087, 2956, 2924, 2860, 1746, 1670, 1632, 1567, 1529, 1190; ¹H NMR (500 MHz, CDCl₃) δ 7.81-7.79 (m, 2H), 7.50 (tt, 1H, *J* 1.5, 7.4 Hz), 7.43-7.40 (m, 2H), 6.92 (t, 1H, *J* 4.9 Hz), 6.81 (d, 1H,

J 8.2 Hz), 4.79-4.75 (m, 1H), 4.11-3.96 (m, 4H), 1.80-1.67 (m, 4H), 1.59-1.54 (m, 1H), 1.35-1.26 (m, 8H), 0.97-0.85 (m, 11H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.5, 169.9, 167.6, 133.8, 132.0, 128.7, 127.3, 68.1, 52.0, 41.5, 41.4, 38.8, 30.4, 29.0, 25.0, 23.8, 23.1, 22.3, 14.2, 11.0; HRMS: calcd. for $[\text{C}_{23}\text{H}_{37}\text{N}_2\text{O}_4]^+$ $[\text{M} + \text{H}]^+$: *m/z* 405.2753, found 405.2758.



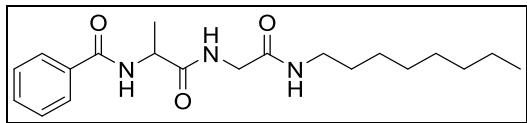
Benzyl *N*-benzoylalanylglycinate

The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product **3d** (50 mg, 69%) as a white solid; m.p. 144 °C; IR (ZnSe) ν / cm^{-1} 3292, 3069, 1738, 1650, 1627, 1540, 1199; ^1H NMR (500 MHz, CDCl_3) δ 7.80-7.78 (m, 2H), 7.51 (tt, 1H, *J* 1.5, 7.8 Hz), 7.44-7.41 (m, 2H), 7.37-7.31 (m, 5H), 7.02 (t, 1H, *J* 5.2 Hz), 6.94 (d, 1H, *J* 7.6 Hz), 5.16 (s, 2H), 4.79 (qu, 1H, *J* 7.1 Hz), 4.09 (d, 2H, *J* 5.5 Hz), 1.49 (d, 3H, *J* 7.0 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 172.8, 169.6, 167.4, 135.2, 133.8, 132.0, 128.8, 128.7, 128.6, 128.5, 127.2, 67.4, 49.2, 41.6, 18.4; HRMS: calcd. for $[\text{C}_{19}\text{H}_{20}\text{N}_2\text{NaO}_4]^+$ $[\text{M} + \text{Na}]^+$: *m/z* 363.1321, found 363.1321.



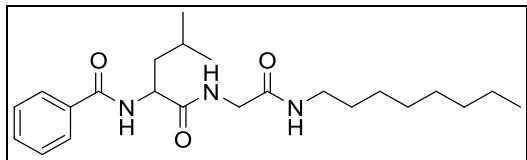
Isopropyl *N*-benzoylleucylglycinate

The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product **3e** (36 mg, 62%) as a yellow solid; m.p. 136 °C; IR (ZnSe) ν / cm^{-1} 3286, 3080, 2958, 2927, 2862, 1744, 1667, 1634, 1566, 1532, 1200, 1105; ^1H NMR (500 MHz, CDCl_3) δ 7.81-7.79 (m, 2H), 7.50 (tt, 1H, *J* 1.6, 7.7 Hz), 7.44-7.41 (m, 2H), 6.89 (t, 1H, *J* 5.0 Hz), 6.81 (d, 1H, *J* 8.3 Hz), 5.05 (hept, 1H, *J* 6.3 Hz), 4.77 (dt, 1H, *J* 5.8, 8.6 Hz), 4.03 (dd, 1H, *J* 5.6, 18.2 Hz), 3.95 (dd, 1H, *J* 5.2, 18.2 Hz), 1.82-1.66 (m, 3H), 1.24 (d, 6H, *J* 6.3 Hz), 0.97 (d, 3H, *J* 4.2 Hz), 0.96 (d, 3H, *J* 4.1 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 172.5, 169.2, 167.6, 133.8, 132.0, 128.8, 127.3, 69.5, 52.0, 41.8, 41.4, 29.8, 25.0, 23.0, 22.4, 21.9, HRMS: calcd. for $[\text{C}_{18}\text{H}_{26}\text{N}_2\text{NaO}_4]^+$ $[\text{M} + \text{Na}]^+$: *m/z* 357.1790, found 357.1791.



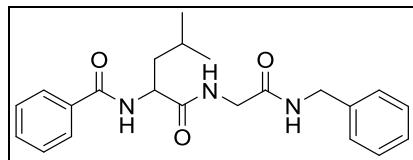
N-(1-((2-Octylamino)-2-oxoethyl)amino)-1-oxopropan-2-ylbenzamide

The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product **3f** (48 mg, 63%) as a white solid; m.p. 132 °C; IR (ZnSe) ν / cm⁻¹ 3332, 3288, 3085, 2924, 2855, 1692, 1637, 1527; ¹H NMR (500 MHz, CDCl₃) δ 7.82-7.81 (m, 2H), 7.52-7.47 (m, 2H), 7.40 (t, 2H, *J* 7.6 Hz), 7.34 (d, 1H, *J* 6.7 Hz), 6.79 (t, 1H, *J* 5.2 Hz), 4.64 (qu, 1H, *J* 6.9 Hz), 3.98 (dd, 1H, *J* 6.0, 16.3 Hz), 3.85 (dd, 1H, *J* 5.4, 16.5 Hz), 3.20-3.16 (m, 2H), 1.48 (d, 3H, *J* 7.1 Hz), 1.26-1.21 (m, 12H), 0.85 (t, 3H, *J* 7.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 173.4, 169.0, 167.9, 133.5, 132.1, 128.7, 127.4, 50.2, 43.4, 39.9, 31.9, 29.5, 29.4, 29.3, 27.0, 22.7, 18.1, 14.2; HRMS: calcd. for [C₂₀H₃₁N₃NaO₃]⁺ [M + Na]⁺: *m/z* 384.2263, found 384.2263.



N-(4-Methyl-1-((2-octylamino)-2-oxoethyl)amino)-1-oxopentan-2-ylbenzamide

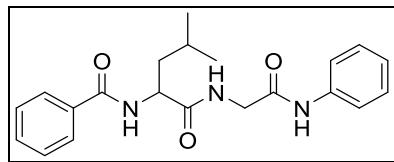
The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product **3g** (68 mg, 91%) as a yellow oil; IR (ZnSe) ν / cm⁻¹ 3295, 2955, 2926, 2854, 1638, 1536; ¹H NMR (500 MHz, CDCl₃) δ 7.81-7.79 (m, 2H), 7.72 (t, 1H, *J* 5.8 Hz), 7.57 (d, 1H, *J* 7.2 Hz), 7.47-7.44 (m, 1H), 7.37-7.33 (m, 2H), 6.98 (t, 1H, *J* 5.5 Hz), 4.59 (q, 1H, *J* 7.2 Hz), 3.95 (dd, 1H, *J* 6.3, 16.6 Hz), 3.81 (dd, 1H, *J* 5.5, 16.6 Hz), 3.14 (q, 2H, *J* 6.8 Hz), 1.68-1.65 (m, 3H), 1.43 (qu, 2H, *J* 7.1 Hz), 1.24-1.20 (m, 10H), 0.90 (d, 3H, *J* 6.0 Hz), 0.87 (d, 3H, *J* 6.1 Hz), 0.84 (t, 3H, *J* 7.0 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 173.3, 169.0, 168.1, 133.4, 131.9, 128.5, 127.4, 53.1, 43.3, 40.7, 39.7, 31.8, 29.4, 29.3, 29.2, 26.9, 24.9, 22.9, 22.0, 22.6, 14.1; HRMS: calcd. for [C₂₃H₃₇N₃NaO₃]⁺ [M + Na]⁺: *m/z* 426.2733, found 426.2735.



N-(1-((2-(Benzylamino)-2-oxoethyl)amino)-4-methyl-1-oxopentan-2-ylbenzamide

The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product **3h** (40 mg, 77%) as a yellow oil; IR (ZnSe) ν / cm⁻¹ 3274, 3064, 2961, 2930, 2869, 1633, 1537; ¹H NMR (500 MHz, CDCl₃) δ 7.66-7.64 (m, 2H), 7.51-7.47 (m, 1H),

7.37 (t, 2H, *J* 7.7 Hz), 7.25-7.21 (m, 5H), 7.16 (t, 1H, *J* 5.0 Hz), 7.09 (t, 1H, *J* 4.8 Hz), 6.87 (d, 1H, *J* 6.9 Hz), 4.54 (q, 1H, *J* 7.1 Hz), 4.45-4.37 (m, 2H), 4.06 (dd, 1H, *J* 6.5, 16.7 Hz), 3.86 (dd, 1H, *J* 5.3, 16.7 Hz), 1.75-1.66 (m, 3H), 0.95 (d, 3H, *J* 6.2 Hz), 0.93 (d, 3H, *J* 6.2 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 173.4, 169.1, 168.2, 138.1, 133.4, 132.0, 128.7, 128.6, 127.7, 127.4, 127.3, 53.1, 43.5, 43.4, 40.8, 25.0, 22.9, 22.2; HRMS: calcd. for [C₂₂H₂₈N₃O₃]⁺ [M + H]⁺: *m/z* 382.2131, found 382.2131.



N-(4-Methyl-1-oxo-1-((2-oxo-2-(phenylamino)ethyl)amino)pentan-2-yl)benzamide

The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product **3i** (75 mg, 61%) as a yellow solid; m.p. 178 °C; IR (ZnSe) ν / cm⁻¹ 3290, 2956, 2925, 2861, 1701, 1645, 1625, 1519, 1497, 1444; ¹H NMR (500 MHz, CDCl₃) δ 8.90 (s, 1H), 7.78-7.76 (m, 3H), 7.58 (d, 2H, *J* 7.7 Hz), 7.44-7.41 (m, 2H), 7.32 (t, 2H, *J* 7.8 Hz), 7.22 (t, 2H, *J* 7.9 Hz), 7.05 (t, 1H, *J* 7.4 Hz), 4.61 (q, 1H, *J* 7.1 Hz), 4.13 (dd, 1H, *J* 6.4, 16.8 Hz), 3.95 (dd, 1H, *J* 5.4, 16.7 Hz), 1.69-1.68 (m, 2H), 1.29-1.25 (m, 1H), 0.89 (d, 3H, *J* 5.4 Hz), 0.86 (d, 3H, *J* 5.1 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 173.5, 168.5, 167.5, 137.9, 133.3, 132.2, 129.0, 128.7, 127.4, 124.5, 120.3, 53.4, 44.2, 40.6, 25.1, 22.9, 22.2; HRMS: calcd. for [C₂₁H₂₅N₃NaO₃]⁺ [M + Na]⁺: *m/z* 390.1794, found 390.1792.

Elemental analysis data

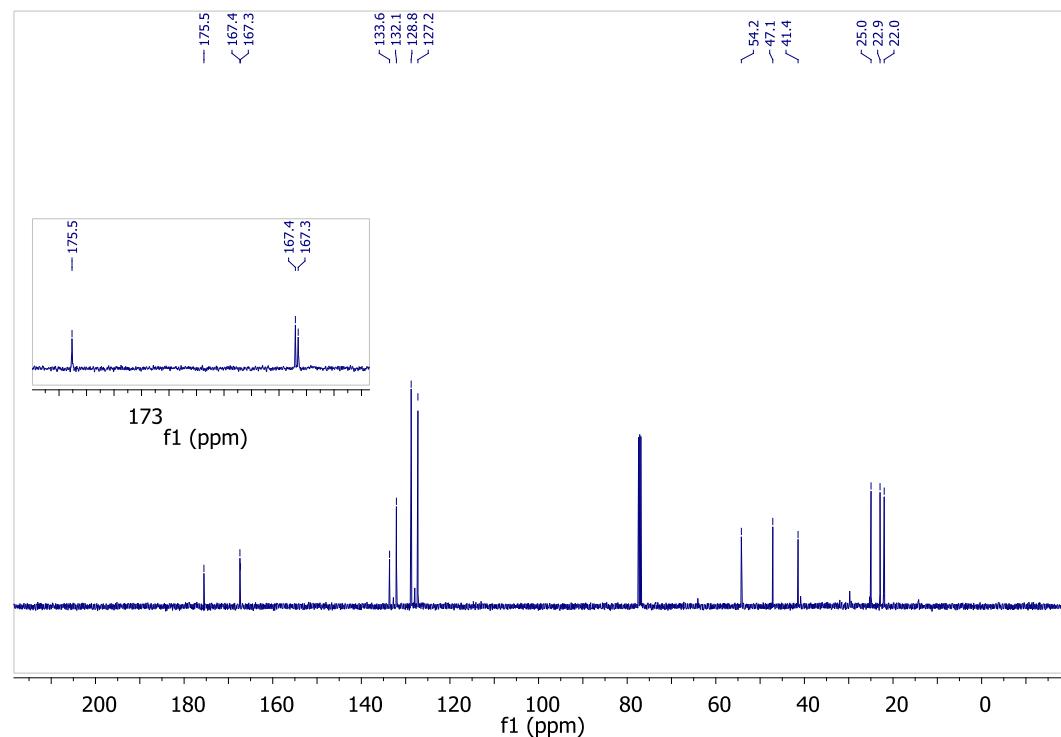
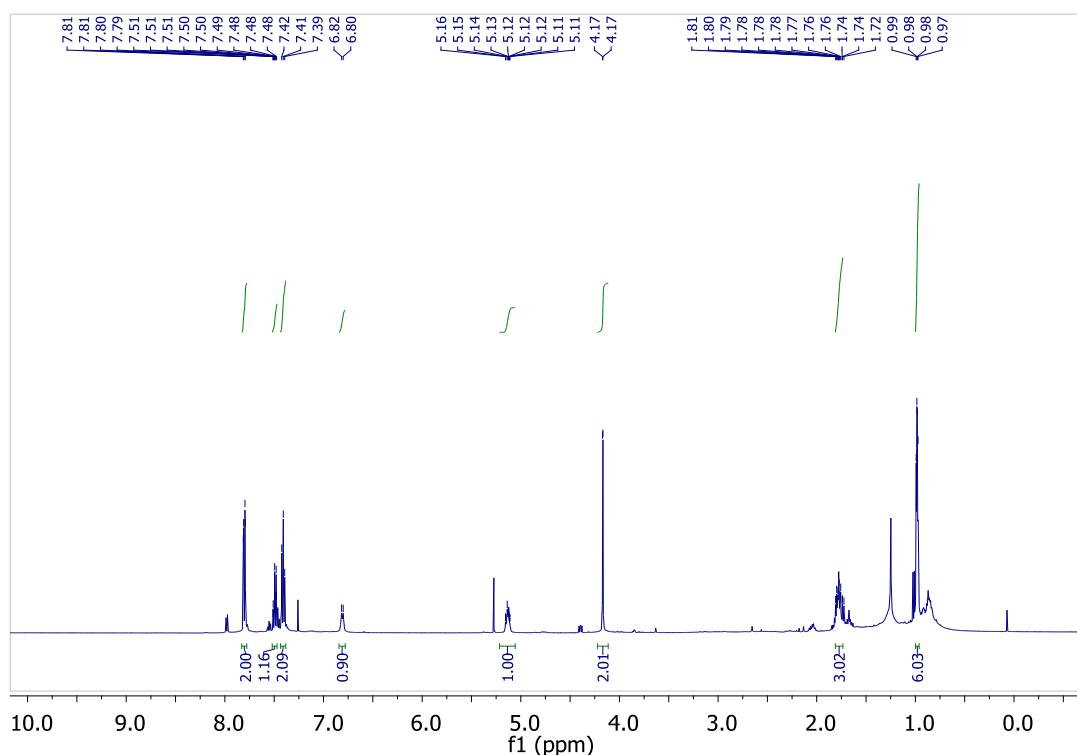


Figure S1. ^1H NMR (500 MHz, CDCl_3) of compound 2a.

Figure S2. ^{13}C NMR (125 MHz, CDCl_3) of compound 2a.

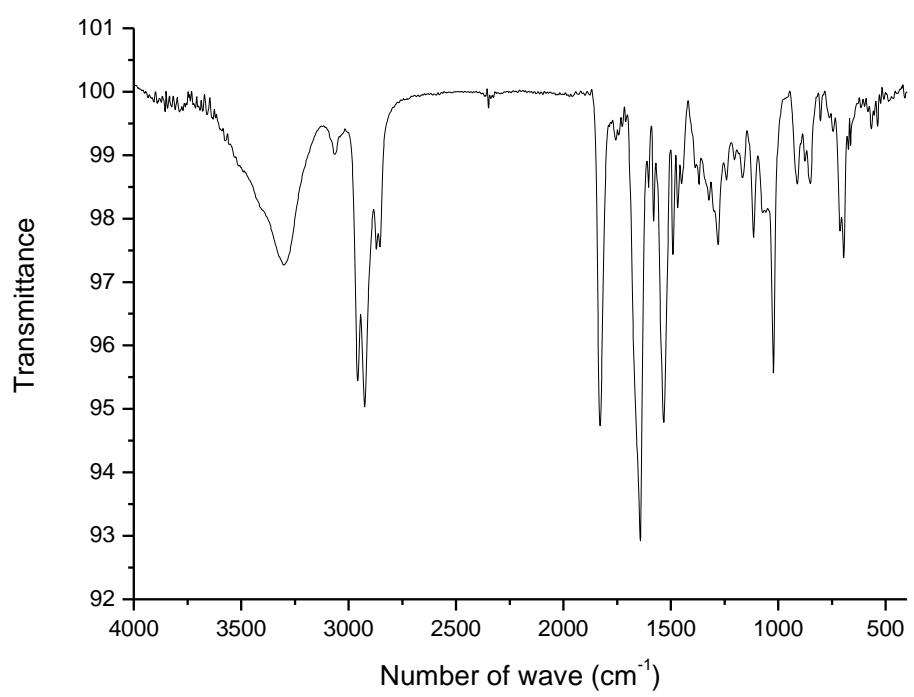


Figure S3. IR (KBr) spectra of compound **1a**.

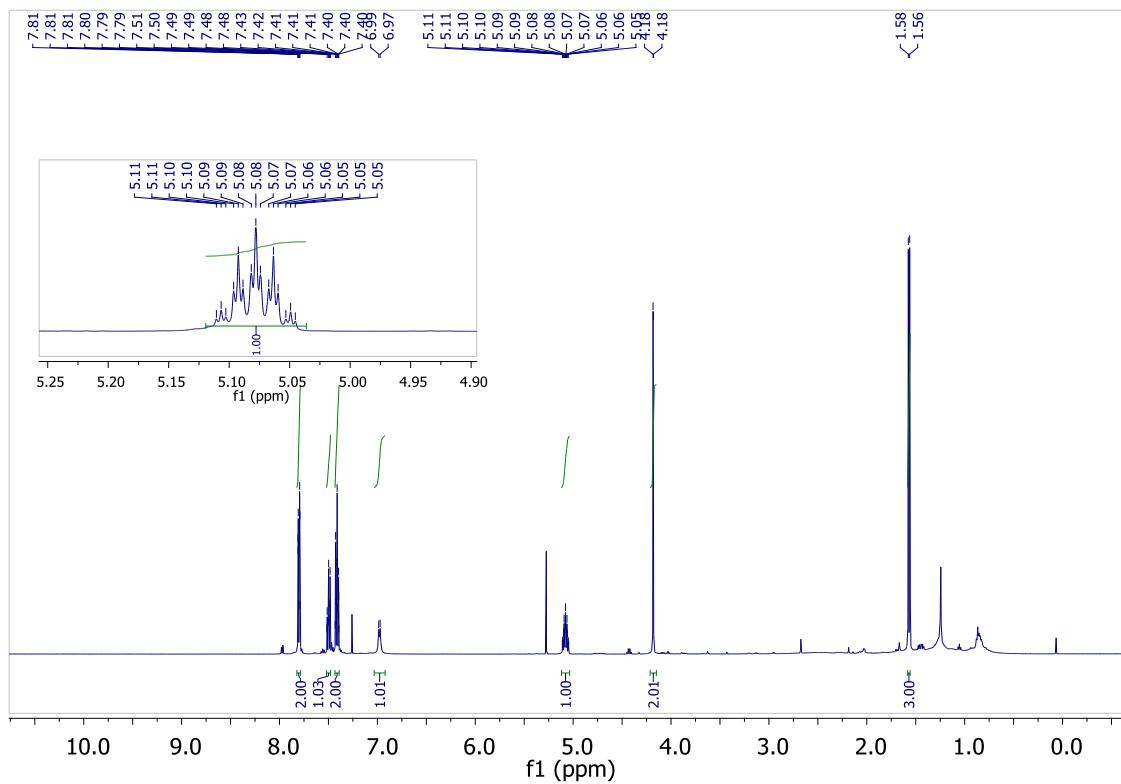


Figure S4. ¹H NMR (500 MHz, CDCl₃) of compound **2b**.

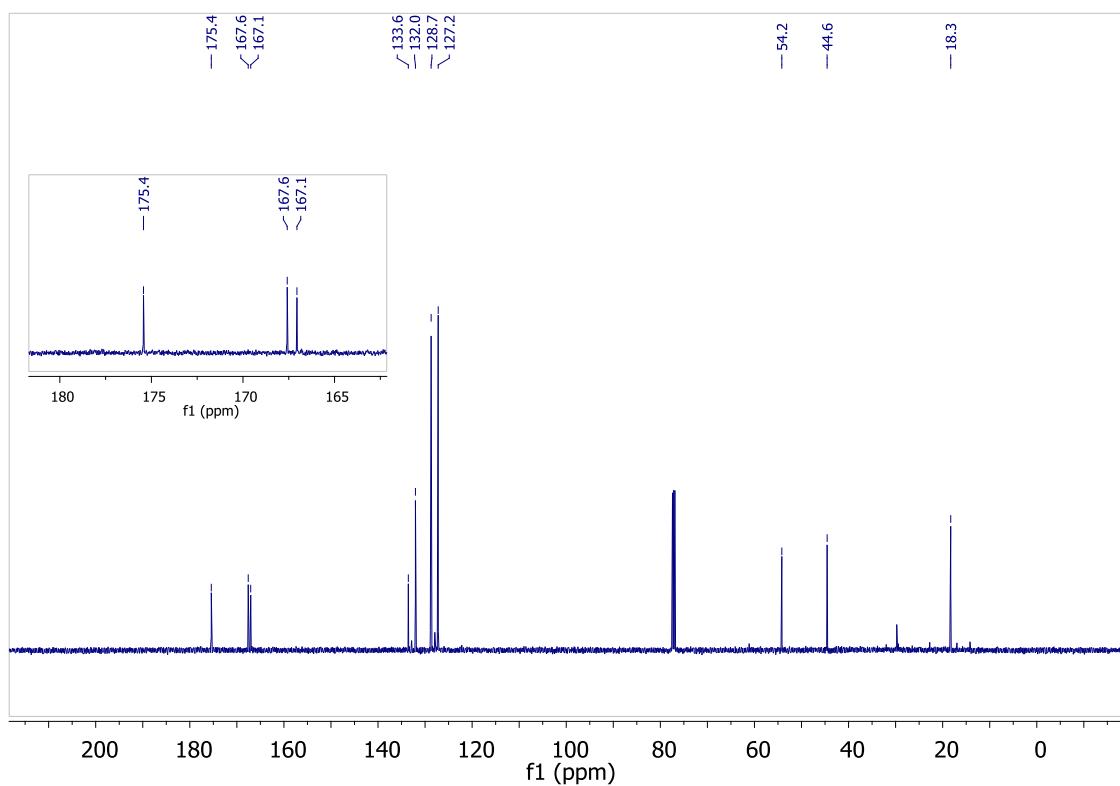


Figure S5. ^{13}C NMR (125 MHz, CDCl_3) of compound **2b**.

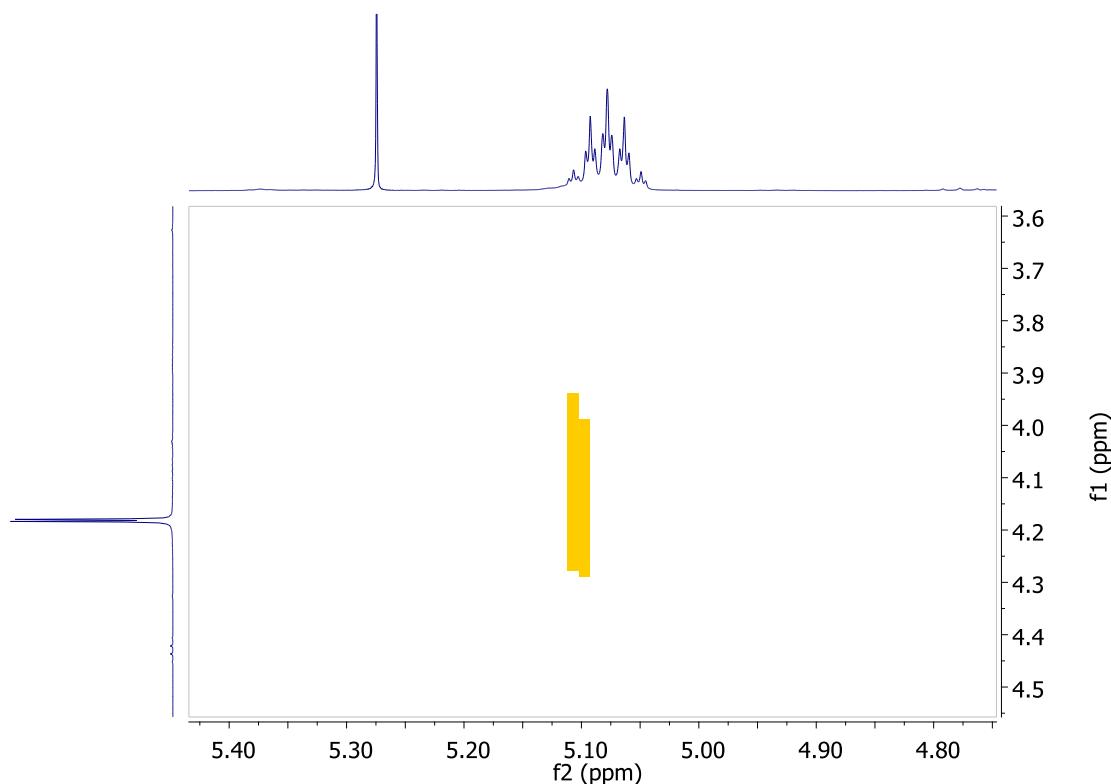


Figure S6. COSY spectra (expansion) of compound **2b**.

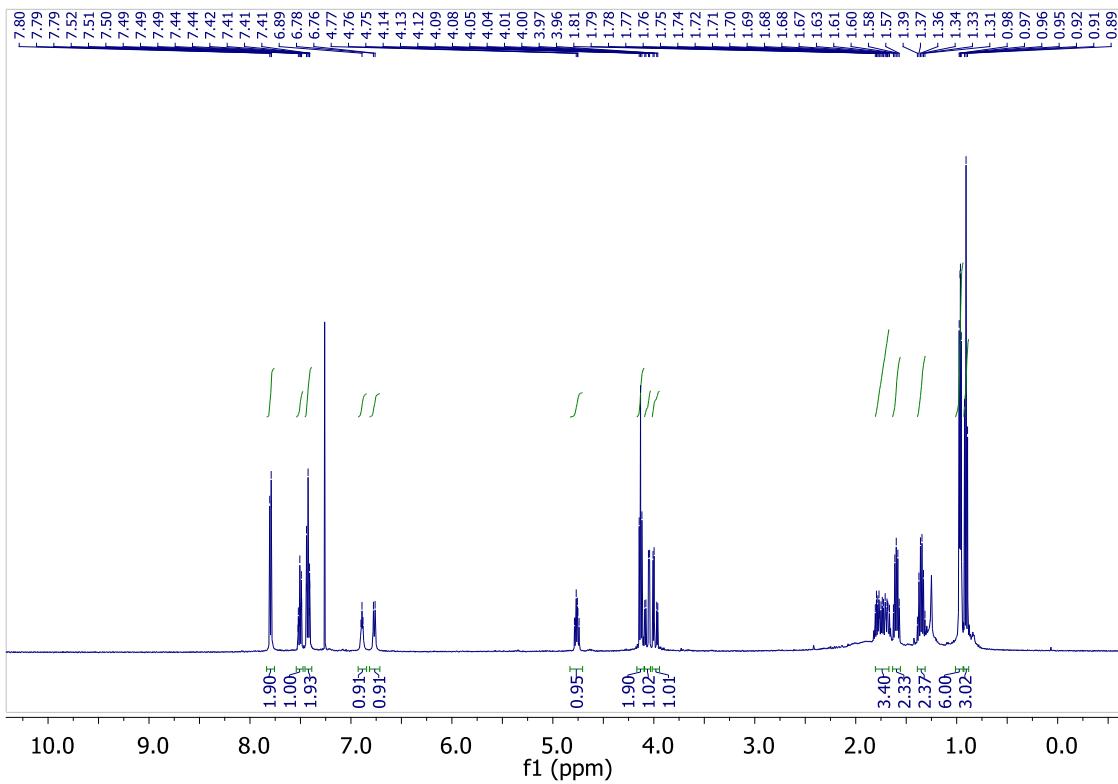


Figure S7. ^1H NMR (500 MHz, CDCl_3) of compound **3a**.

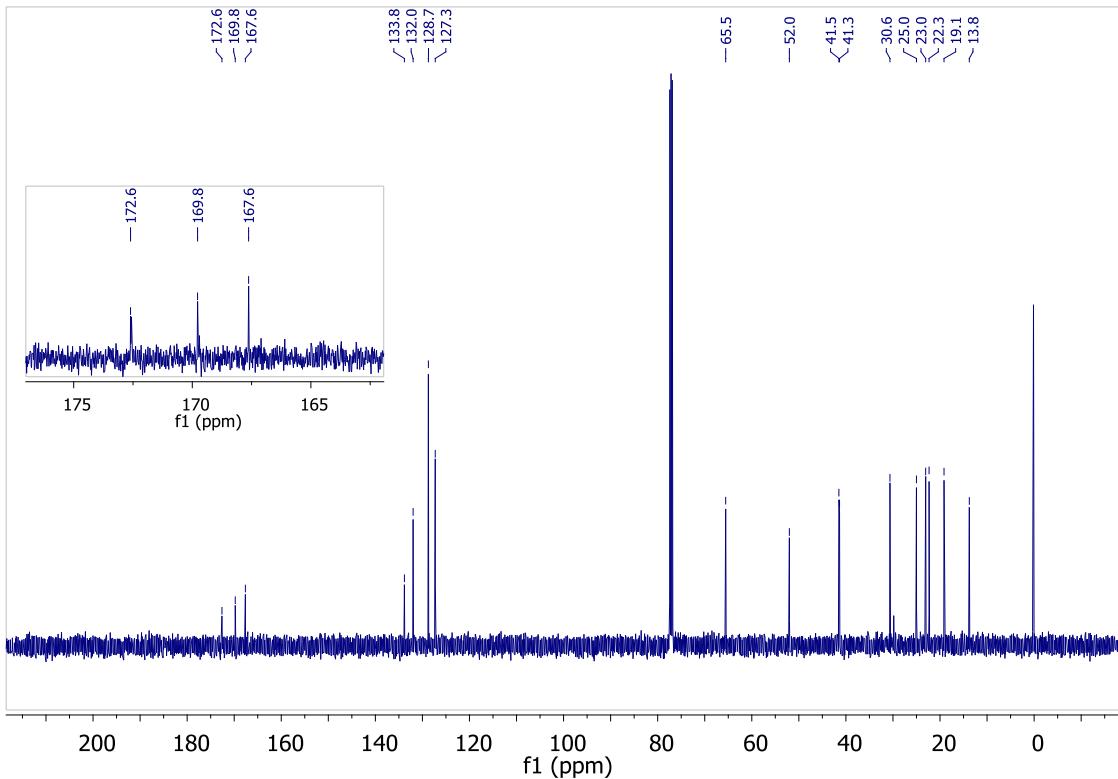


Figure S8. ^{13}C NMR (125 MHz, CDCl_3) of compound **3a**.

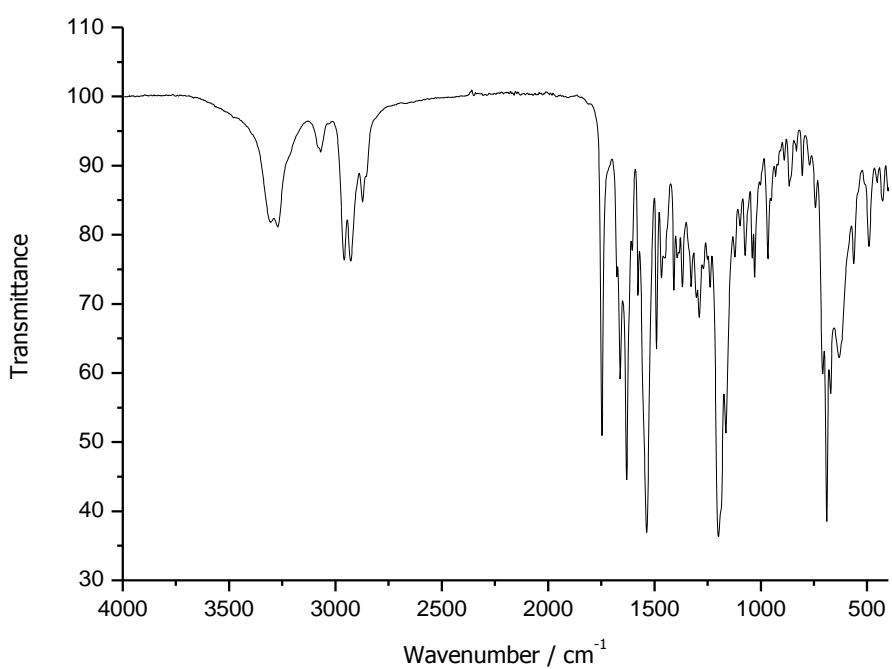


Figure S9. IR (ZnSe) spectra of compound **3a**.

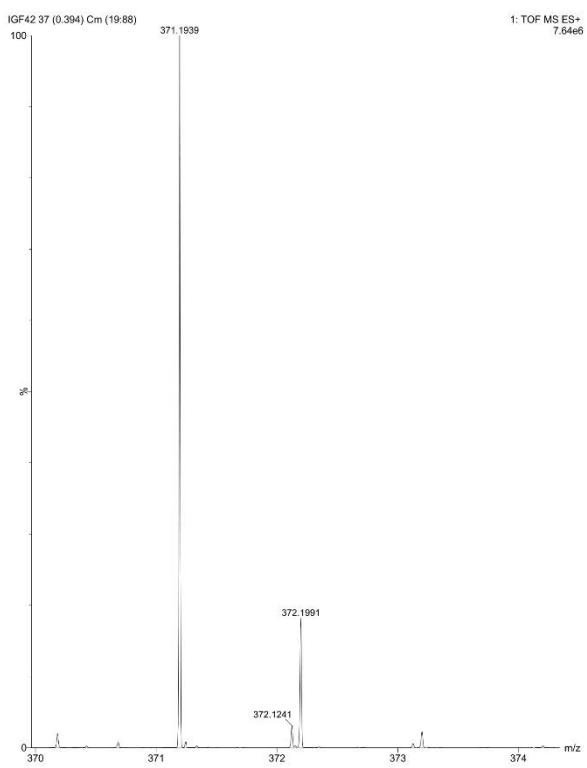


Figure S10. HRMS of compound **3a**.

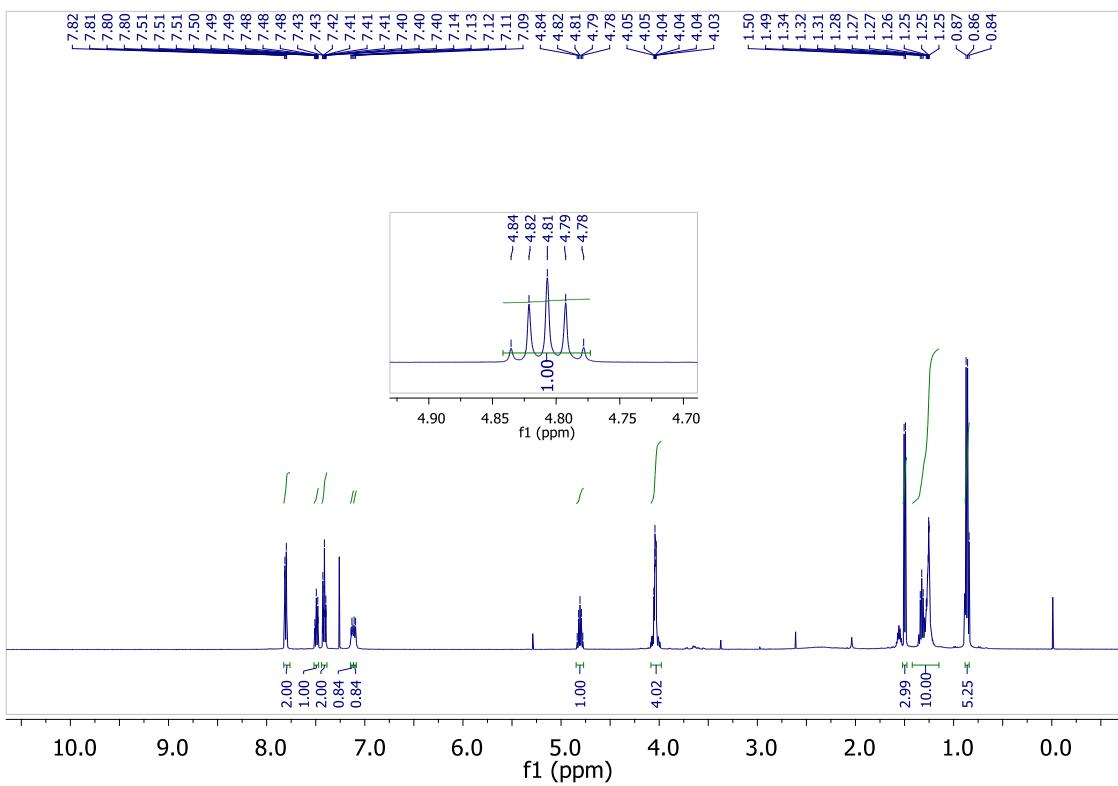


Figure S11. ^1H NMR (500 MHz, CDCl_3) of compound **3b**.

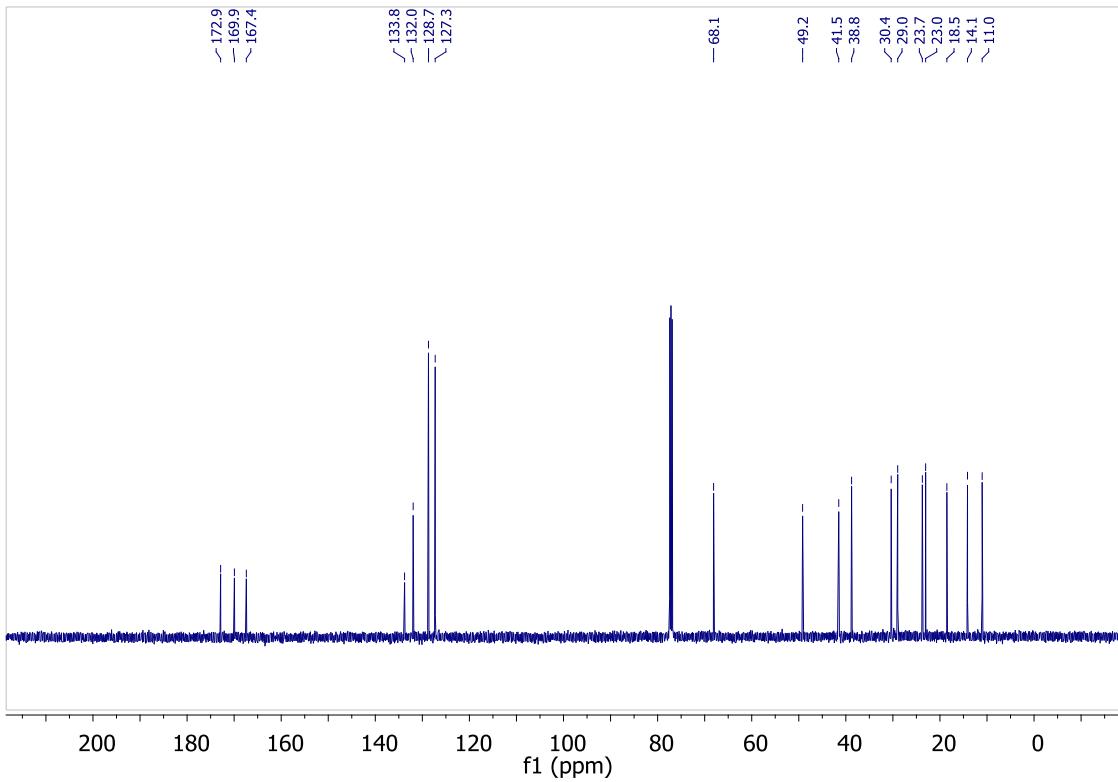


Figure S12. ^{13}C NMR (125 MHz, CDCl_3) of compound **3b**.

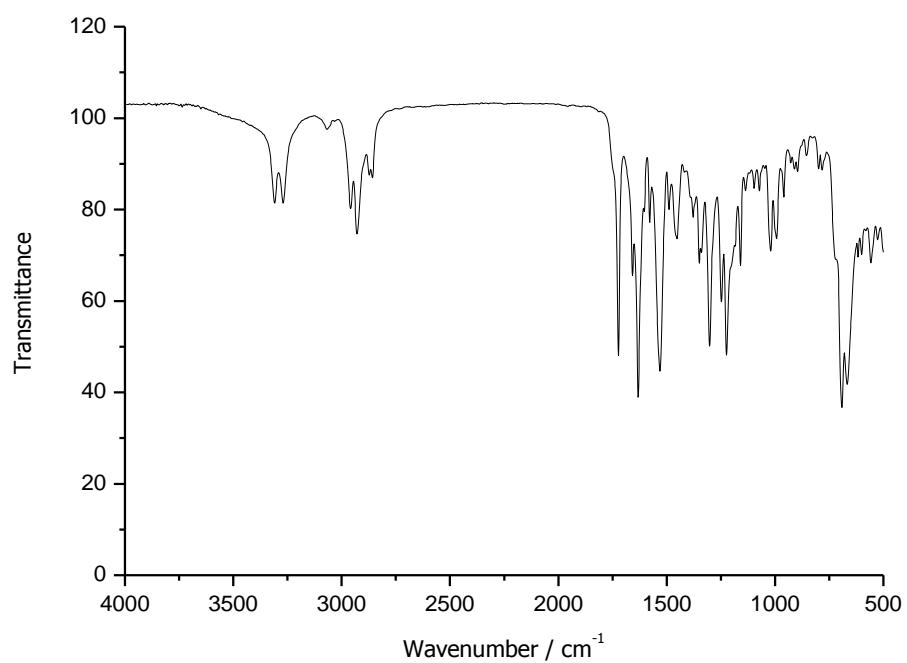


Figure S13. IR (ZnSe) spectra of compound **3b**.

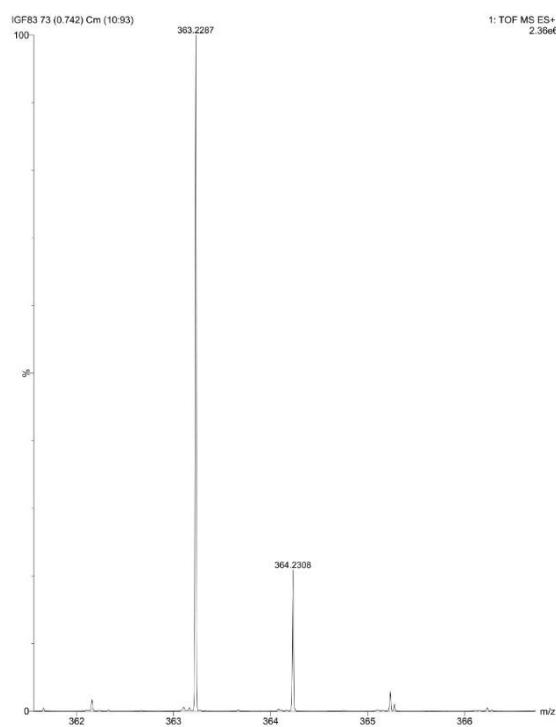


Figure S14. HRMS of compound **3b**.

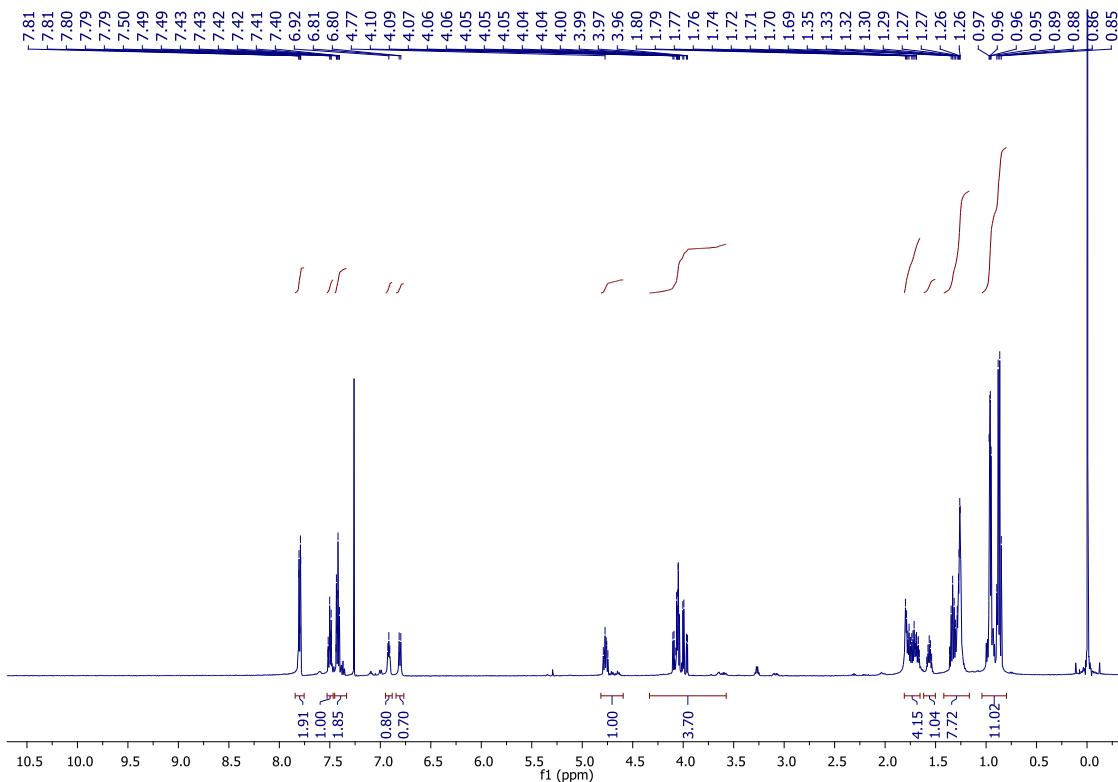


Figure S15. ^1H NMR (500 MHz, CDCl_3) of compound **3c**.

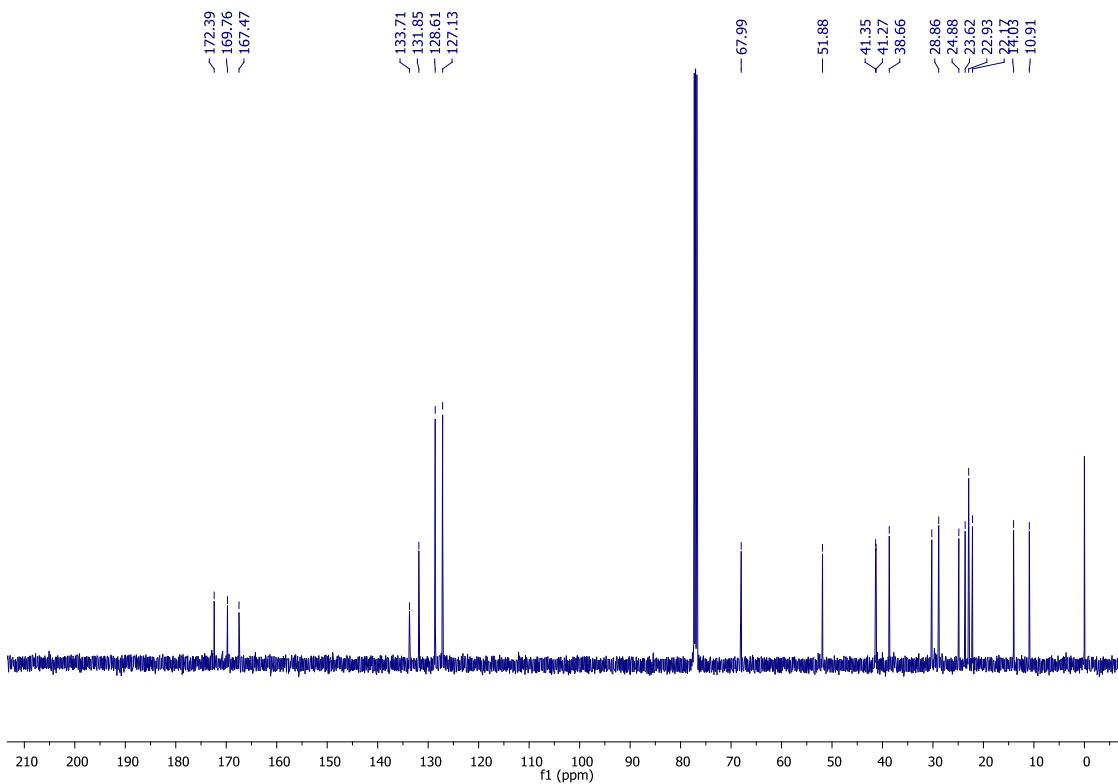


Figure S16. ^{13}C NMR (125 MHz, CDCl_3) of compound **3c**.

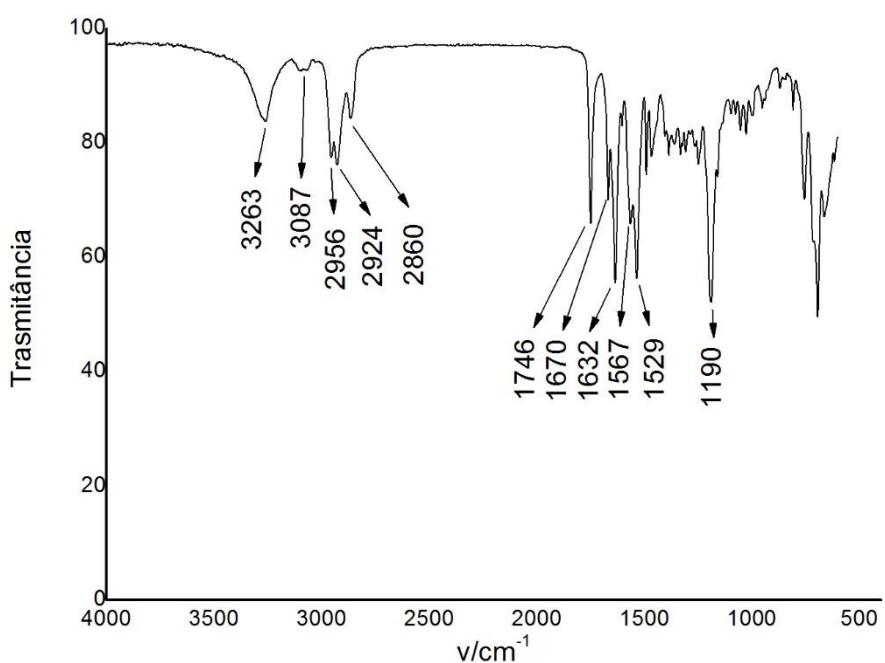


Figure S17. IR (ZnSe) spectra of compound **3c**.

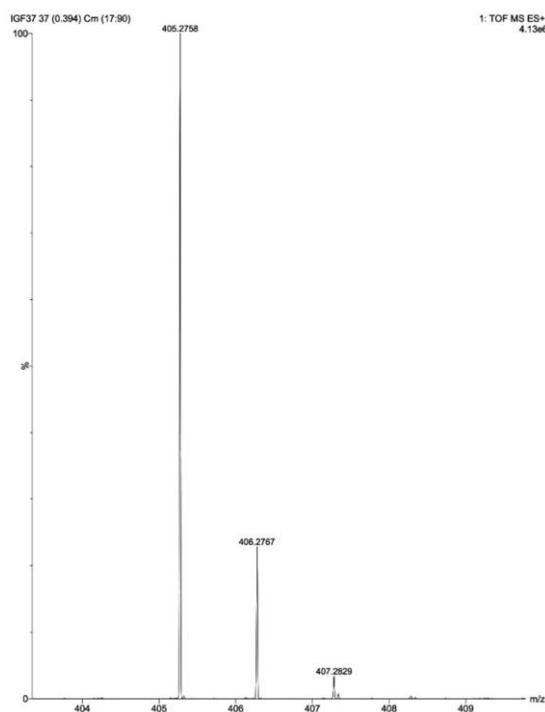


Figure S18. HRMS of compound **3c**.

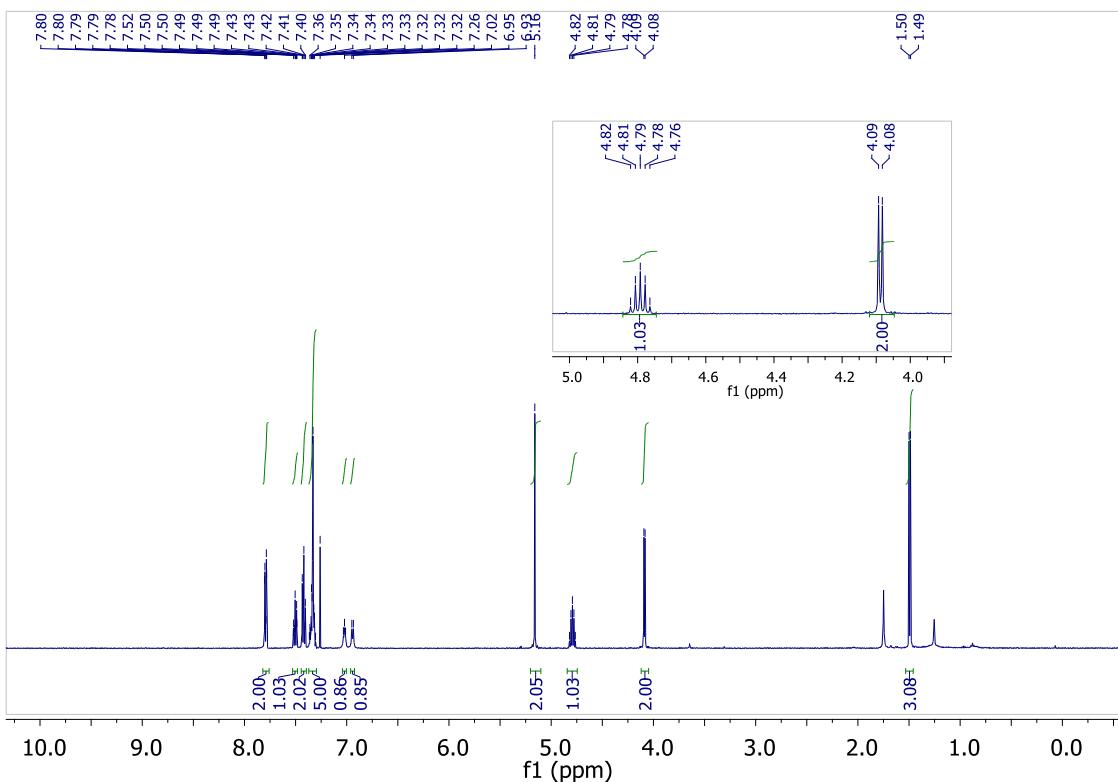


Figure S19. ^1H NMR (500 MHz, CDCl_3) of compound **3d**.

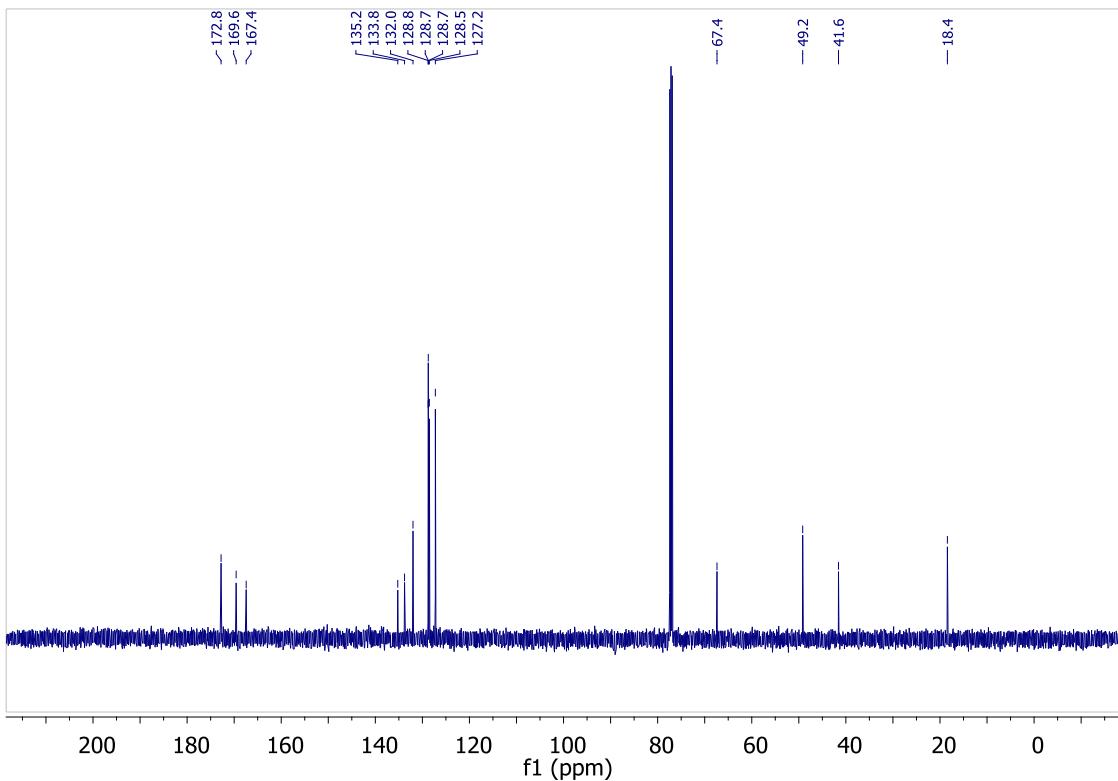


Figure S20. ^{13}C NMR (125 MHz, CDCl_3) of compound **3d**.

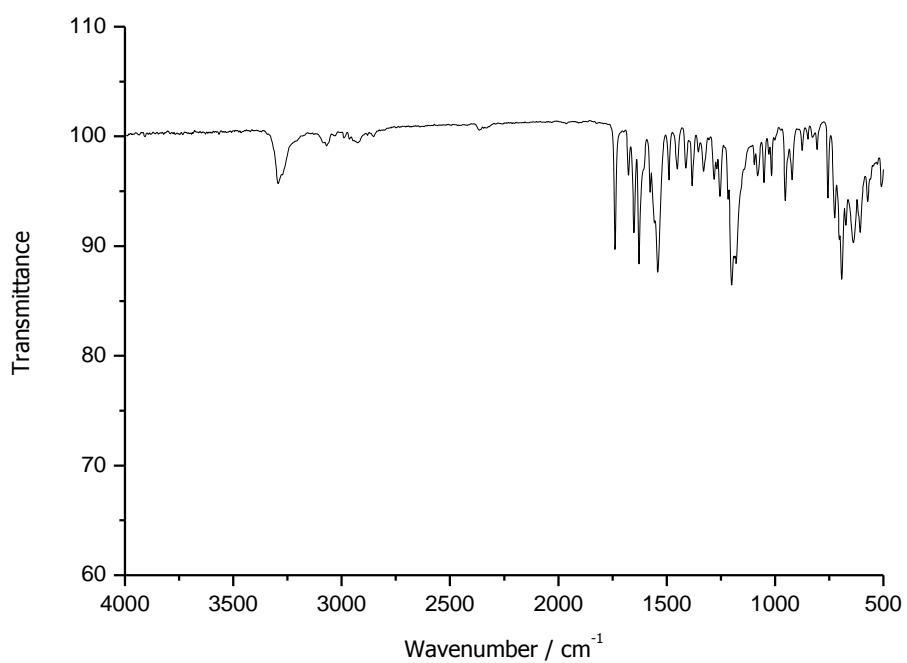


Figure S21. IR (ZnSe) spectra of compound **3d**.

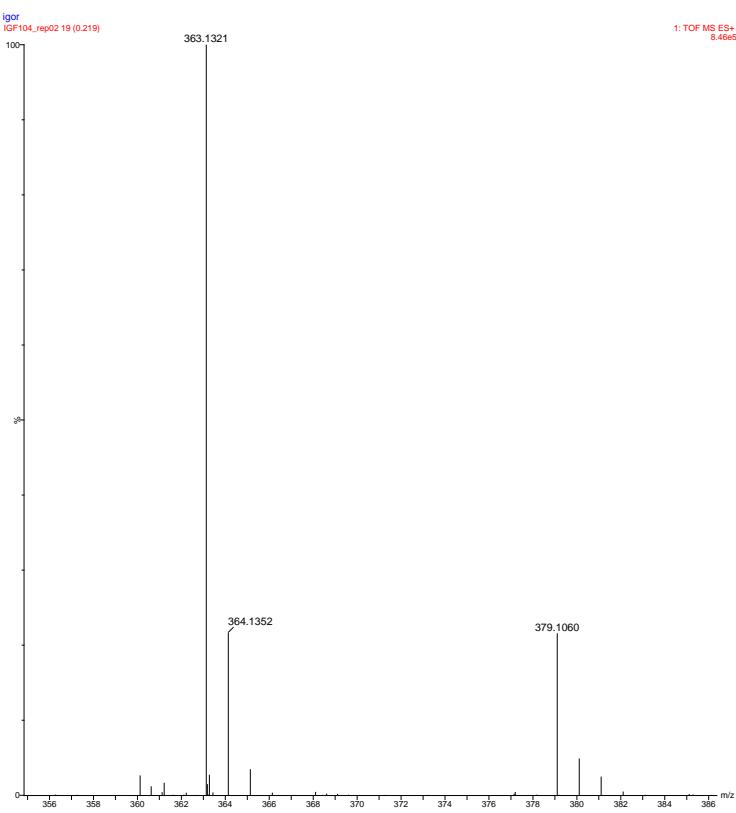


Figure S22. HRMS of compound **3d**.

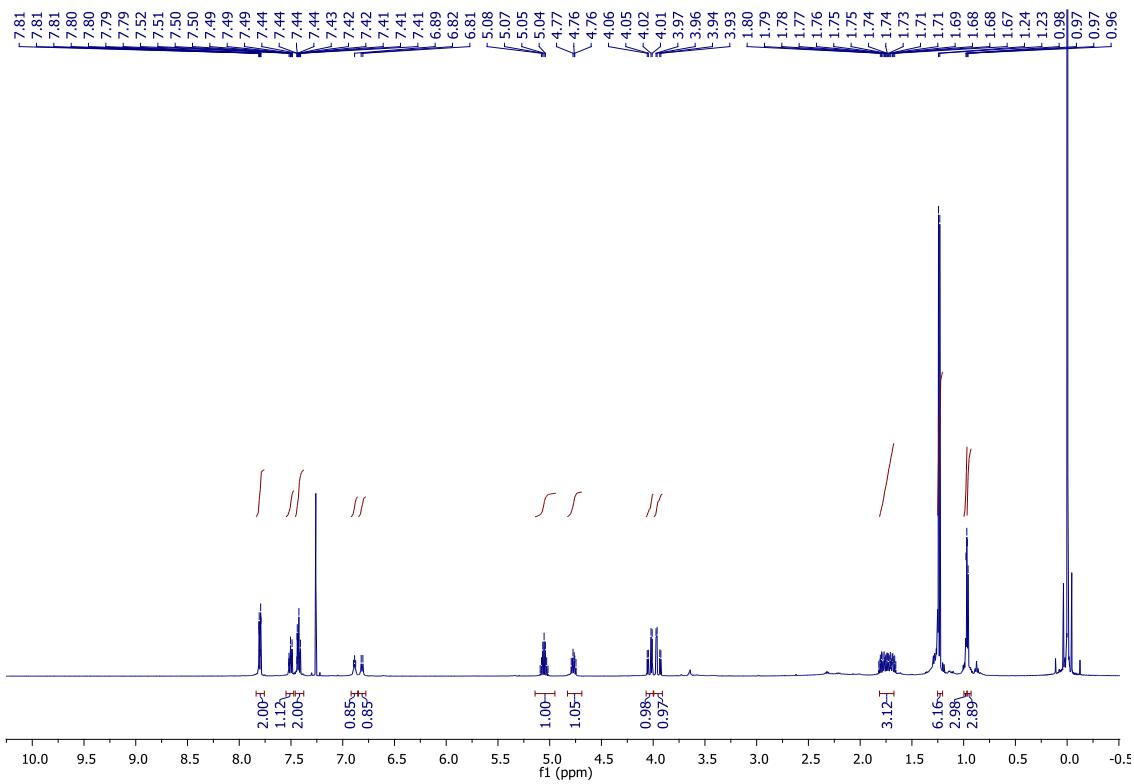


Figure S23. ^1H NMR (500 MHz, CDCl_3) of compound **3e**.

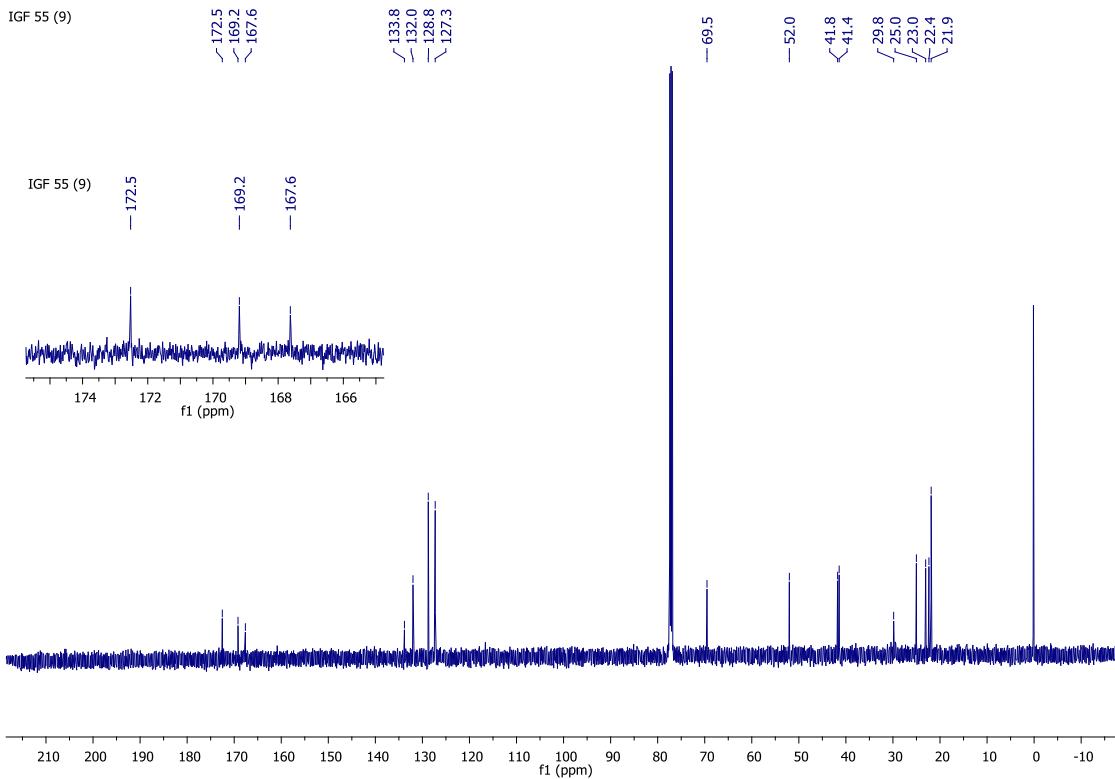


Figure S24. ^{13}C NMR (125 MHz, CDCl_3) of compound **3e**.

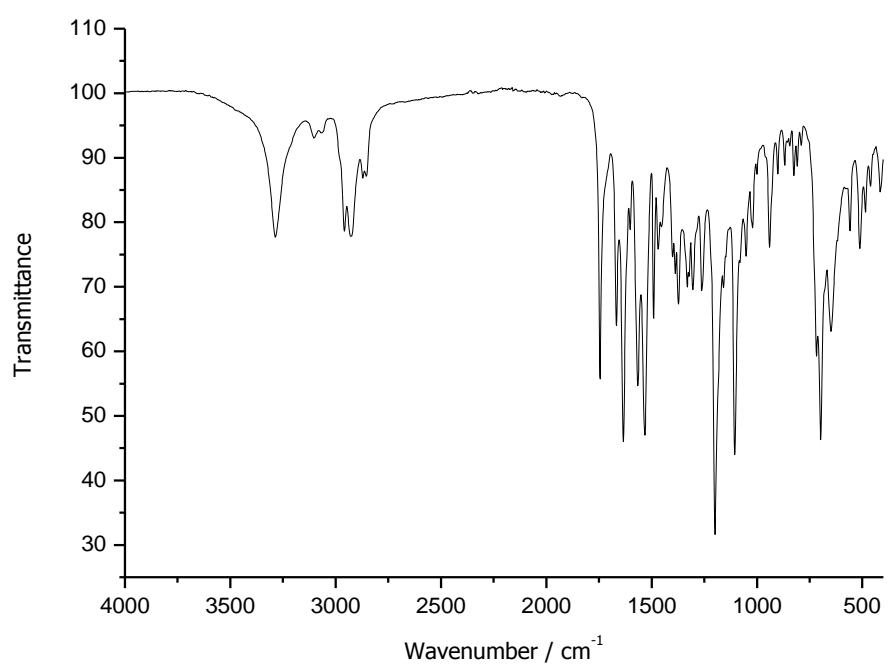


Figure S25. IR (ZnSe) spectra of compound **3e**.

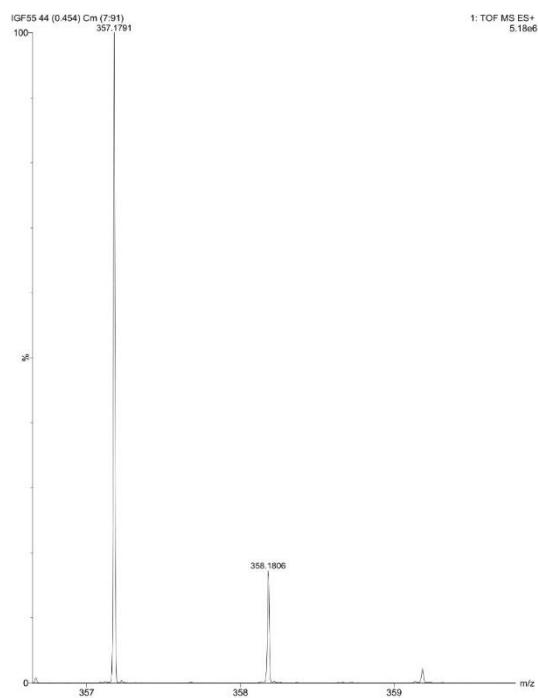


Figure S26. HRMS of compound **3e**.

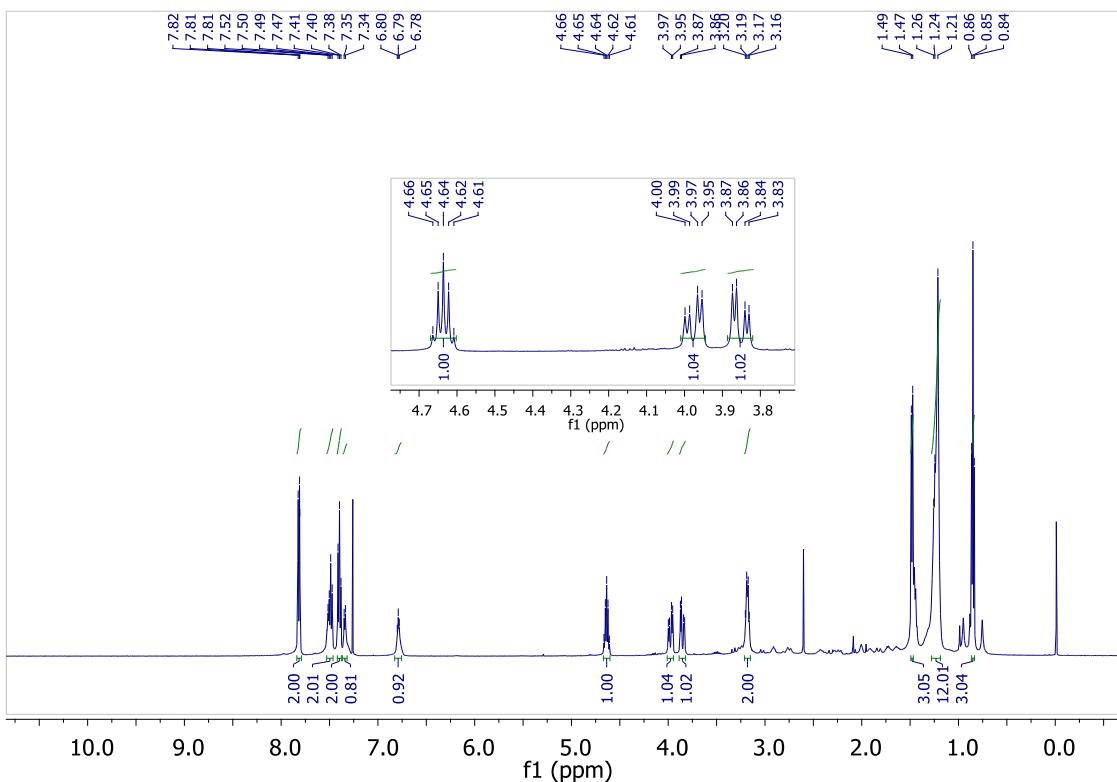


Figure S27. ¹H NMR (500 MHz, CDCl₃) of compound 3f.

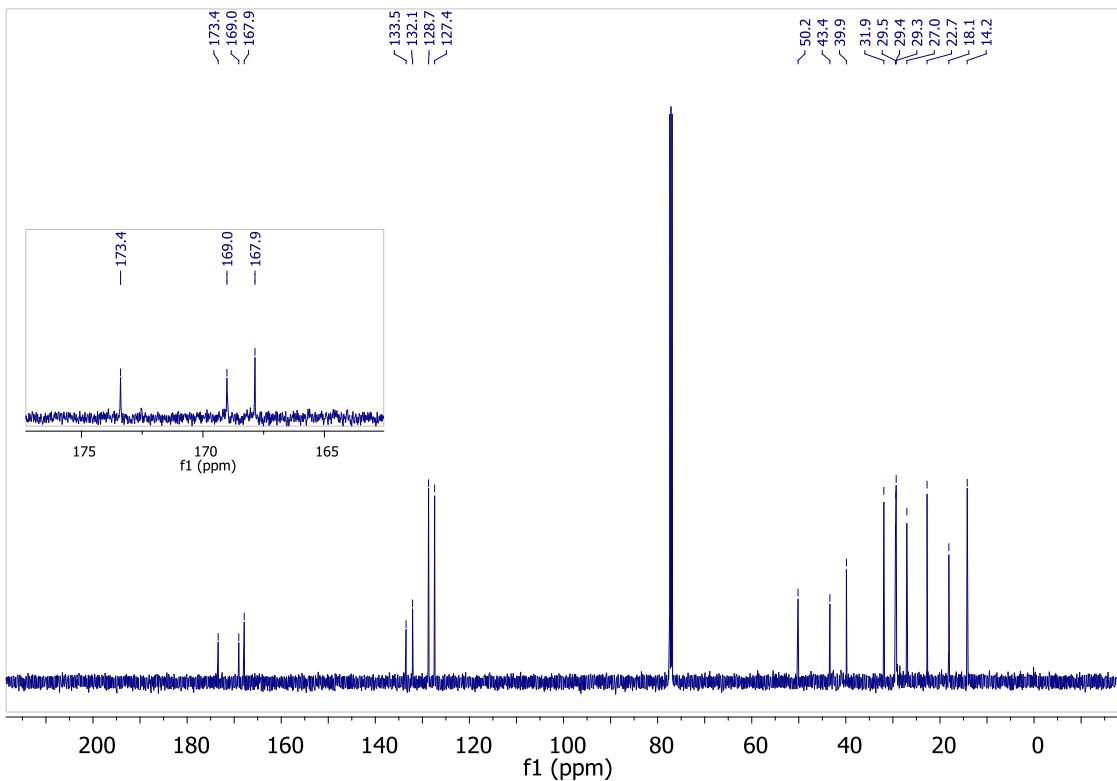


Figure S28. ¹³C NMR (125 MHz, CDCl₃) of compound 3f.

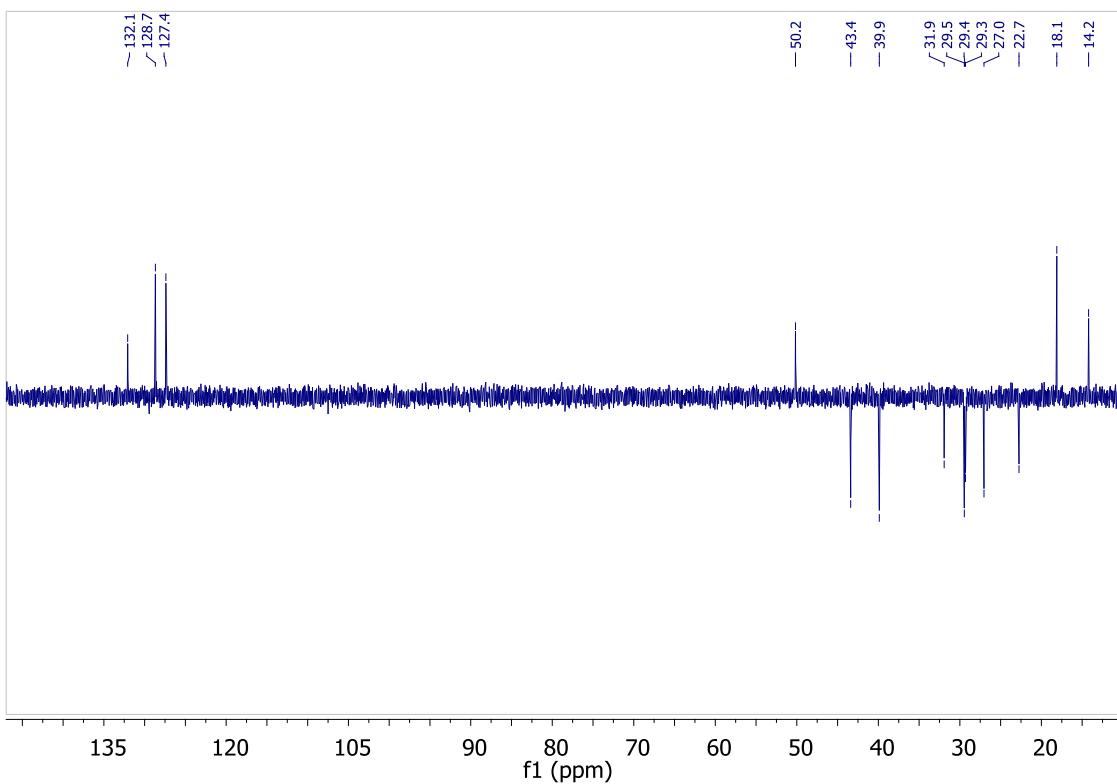


Figure S29. DEPT135 NMR (125 MHz, CDCl_3) of compound **3f**.

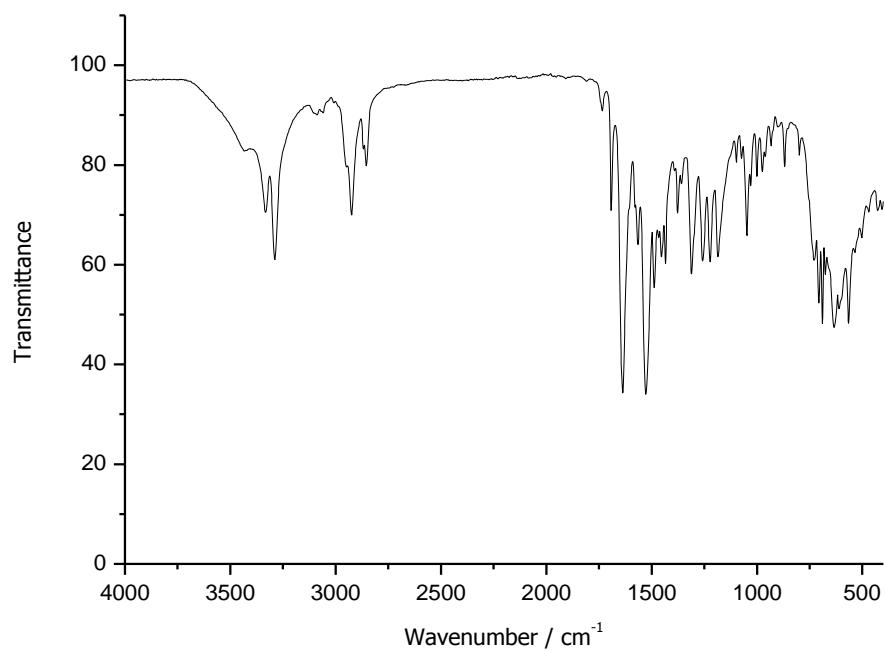


Figure S30. IR (ZnSe) spectra of compound **3f**.

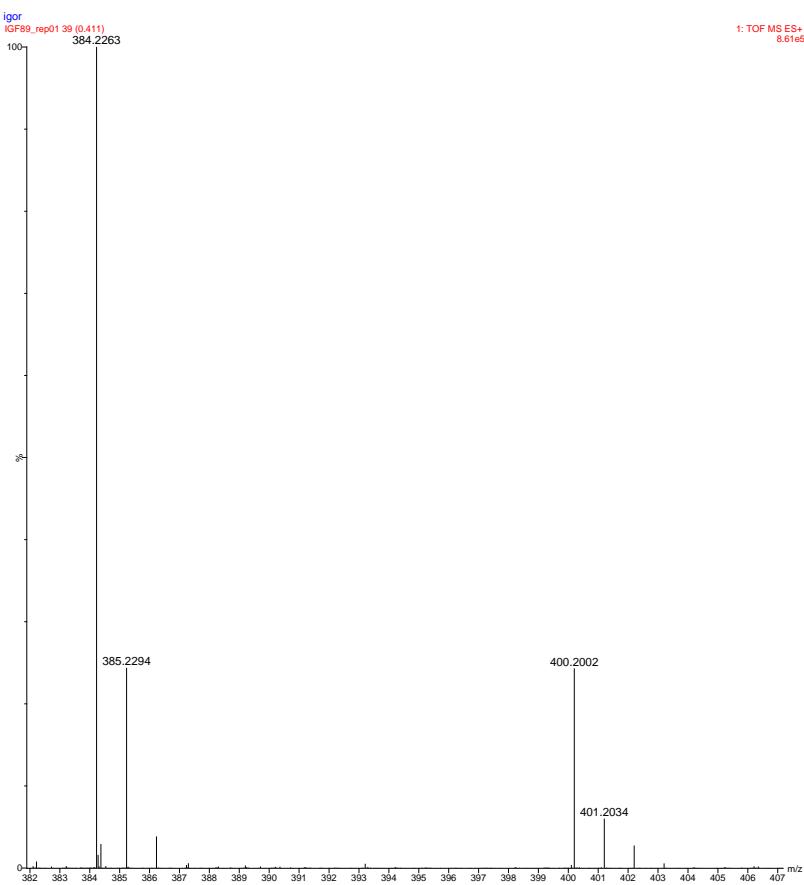


Figure S31. HRMS of compound 3f.

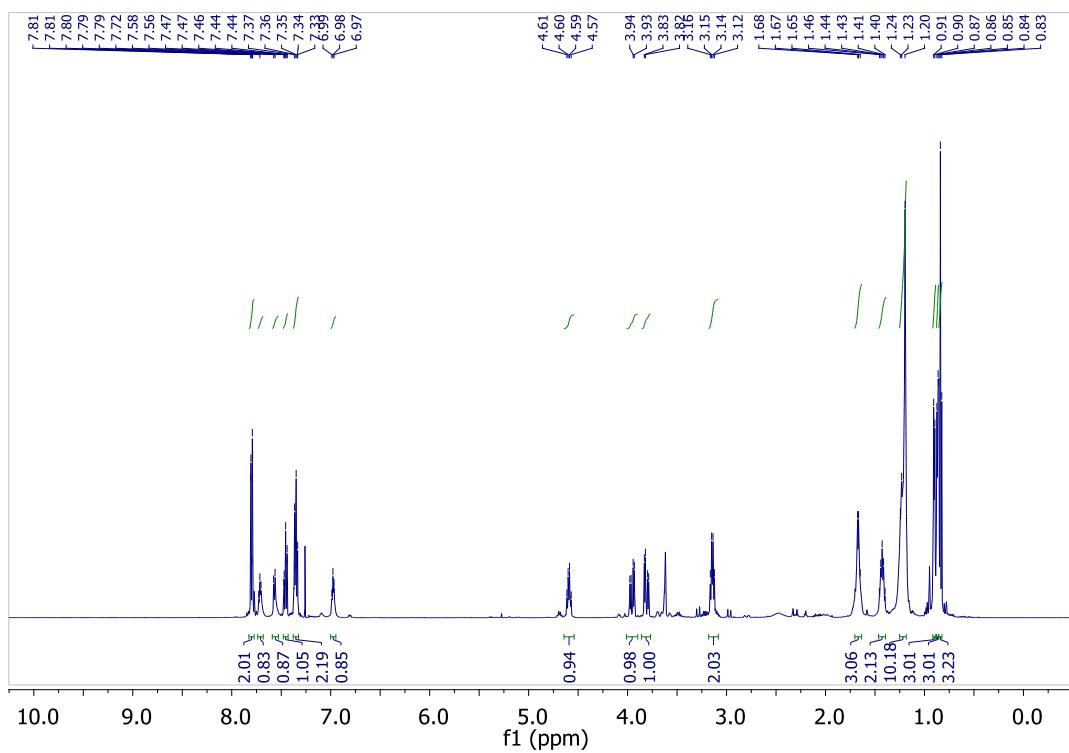


Figure S32. ¹H NMR (500 MHz, CDCl₃) of compound 3g.

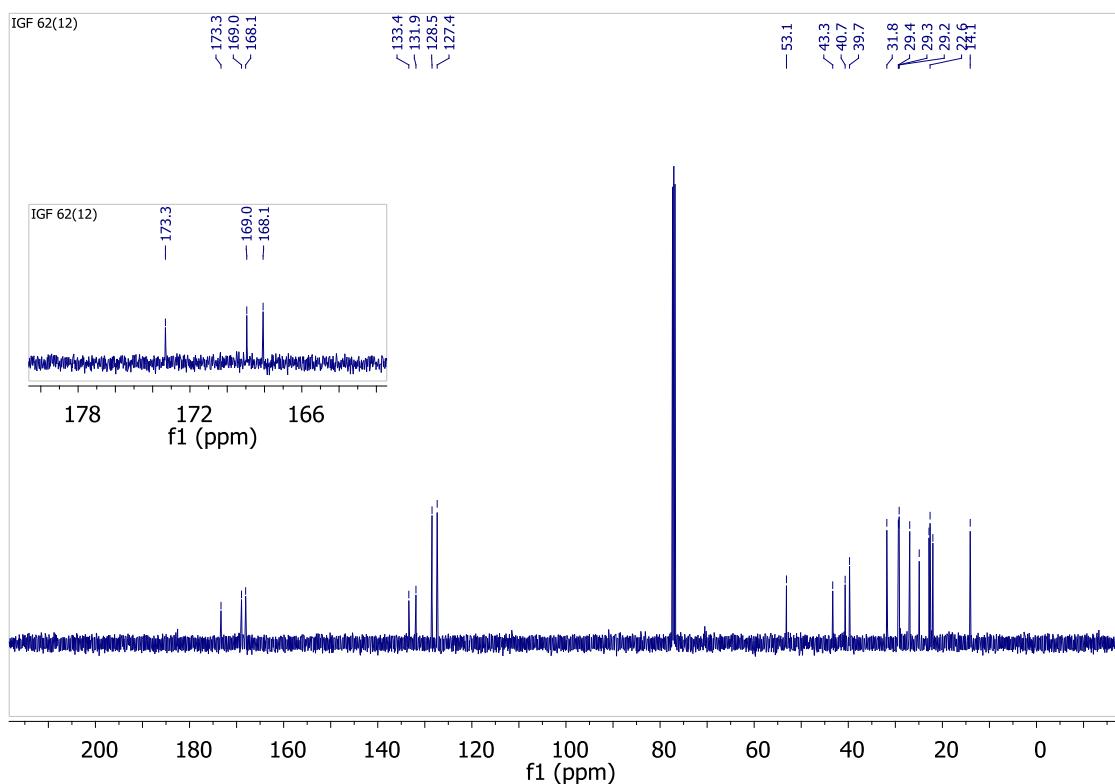


Figure S33. ^{13}C NMR (125 MHz, CDCl_3) of compound **3g**.

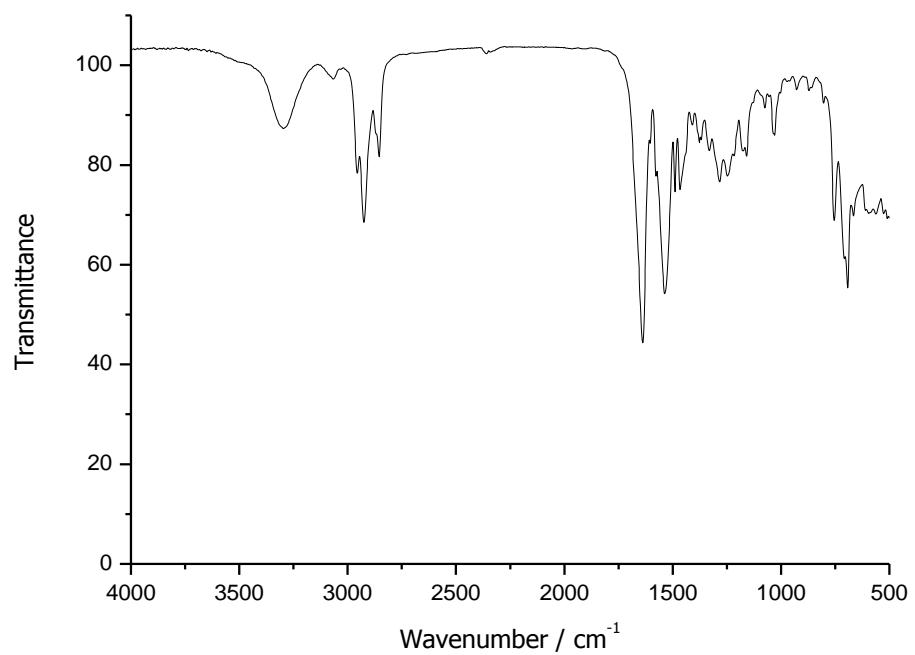


Figure S34. IR (ZnSe) spectra of compound **3g**.

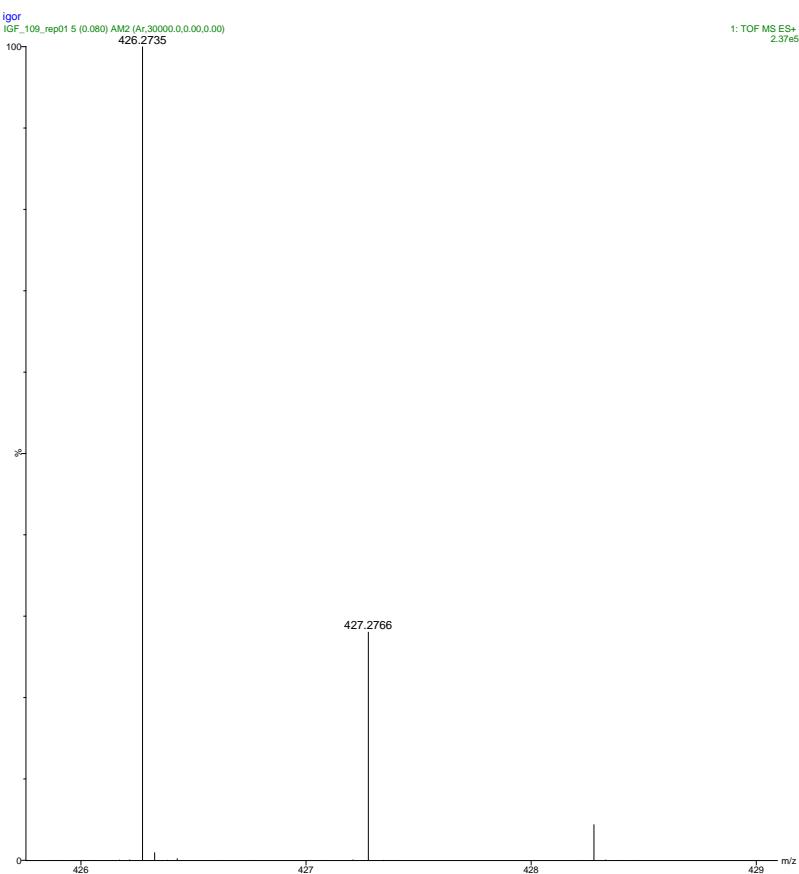


Figure S35. HRMS of compound **3g**.

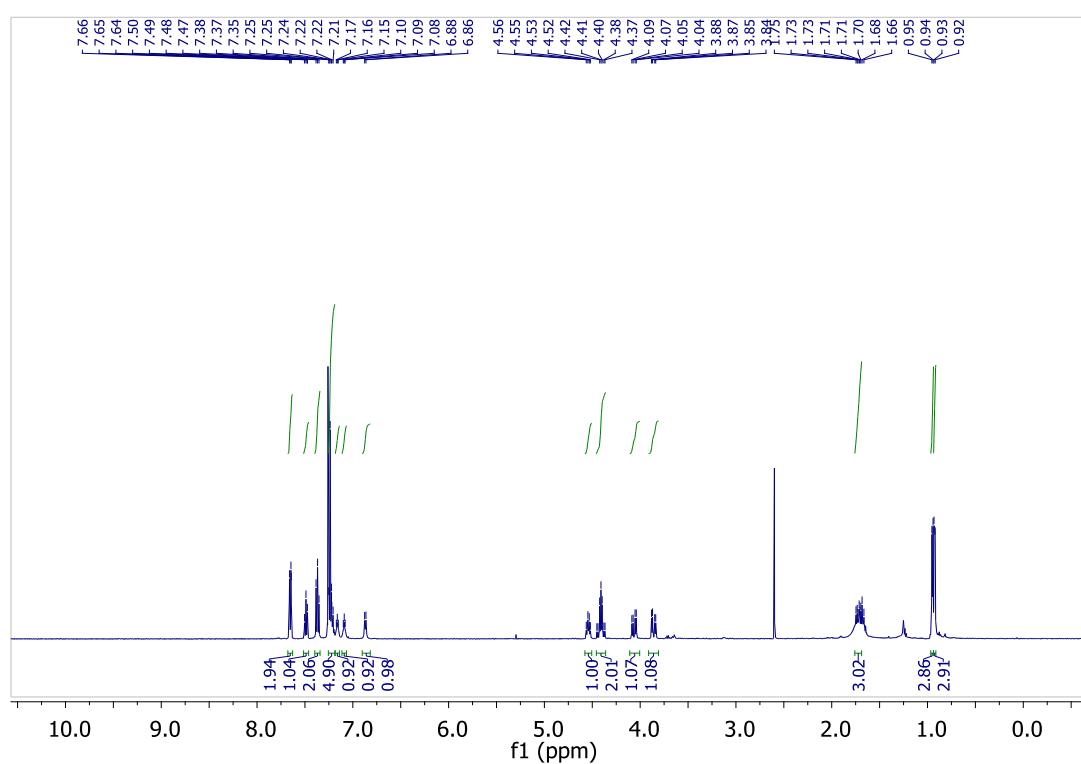


Figure S36. ¹H NMR (500 MHz, CDCl₃) of compound **3h**.

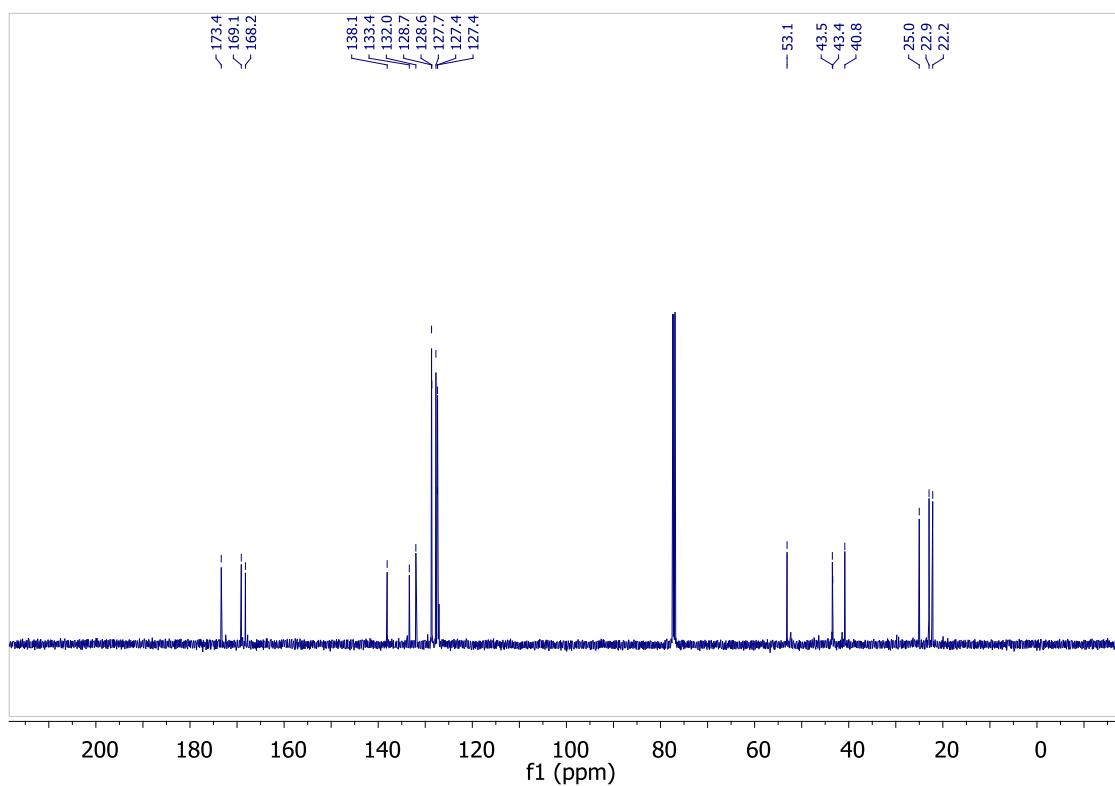


Figure S37. ¹³C NMR (125 MHz, CDCl₃) of compound **3h**.

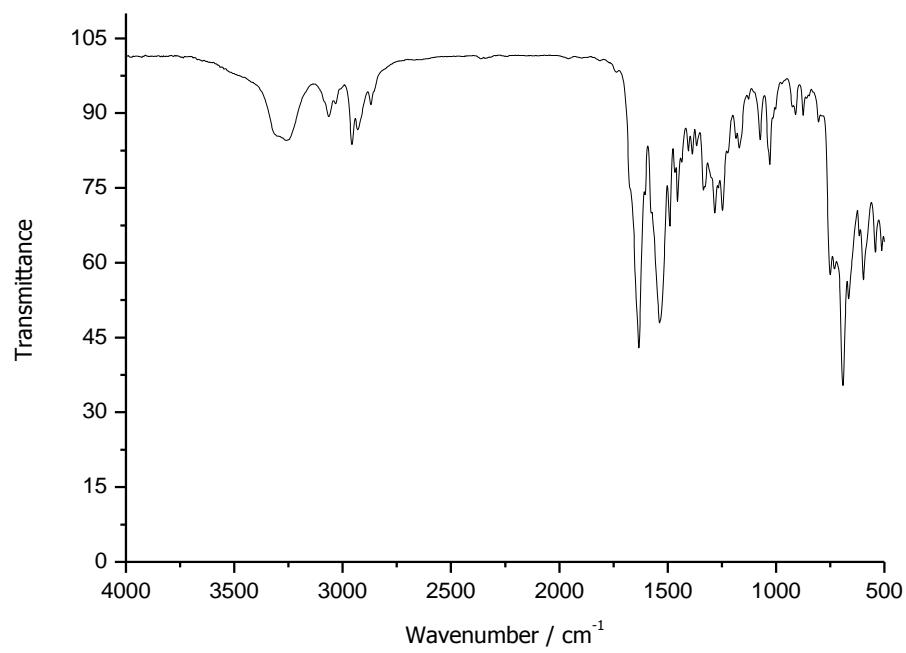


Figure S38. IR (ZnSe) spectra of compound **3h**.

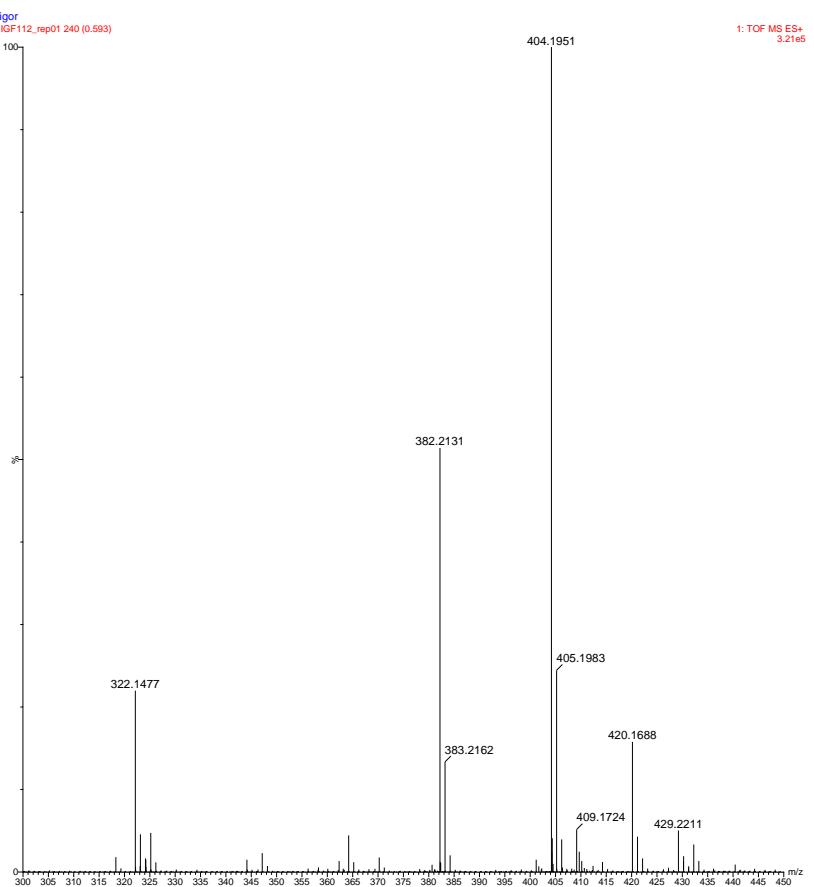


Figure S39. HRMS of compound **3h**.

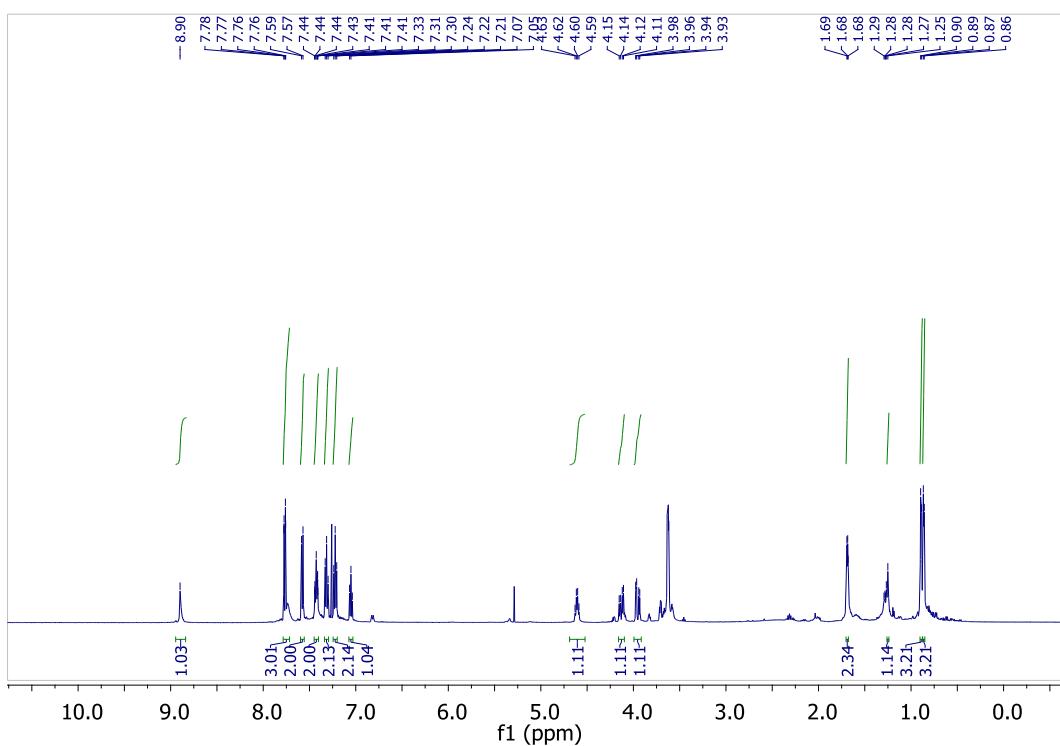


Figure S40. ¹H NMR (500 MHz, CDCl₃) of compound **3i**.

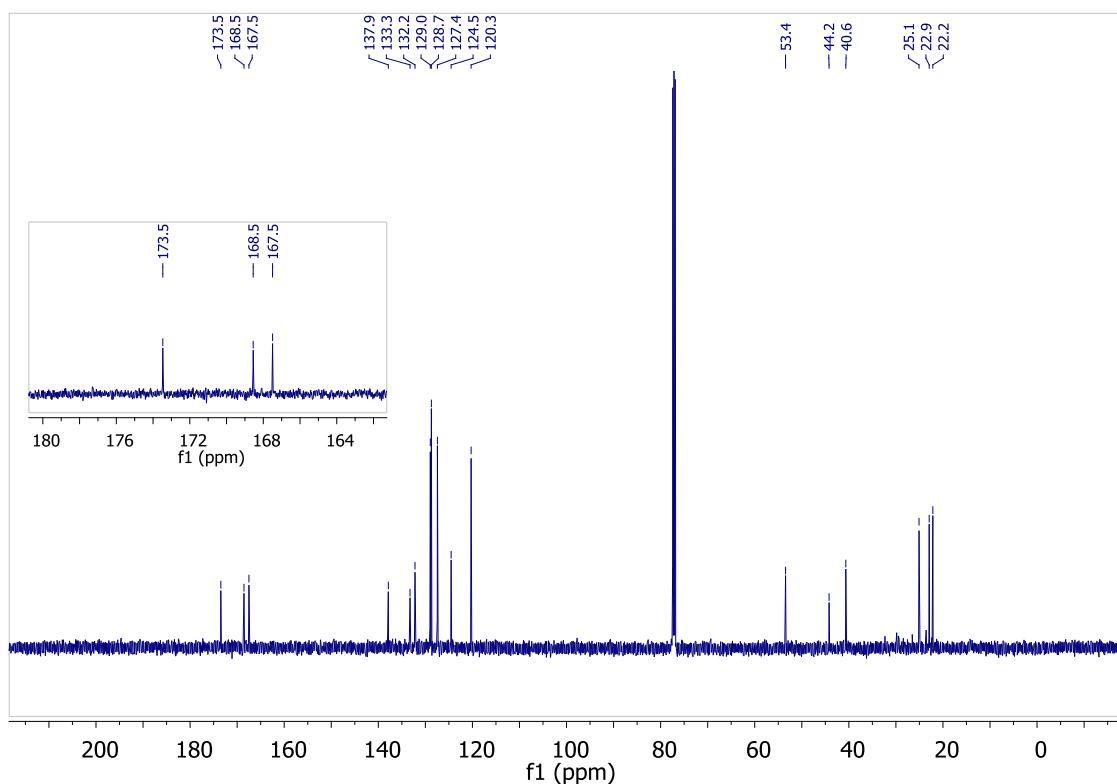


Figure S41. ^{13}C NMR (125 MHz, CDCl_3) of compound **3i**.

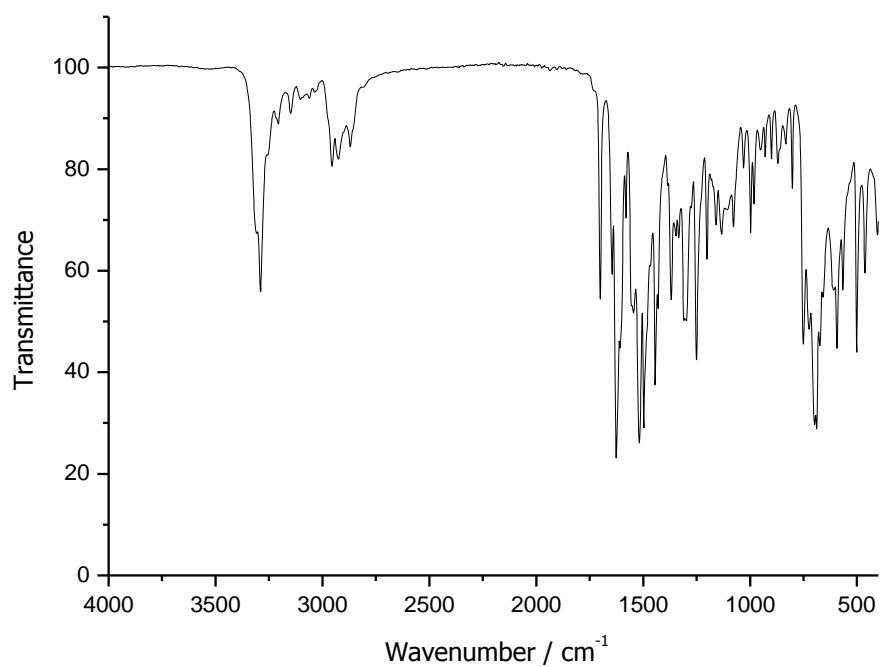


Figure S42. IR (ZnSe) spectra of compound **3i**.

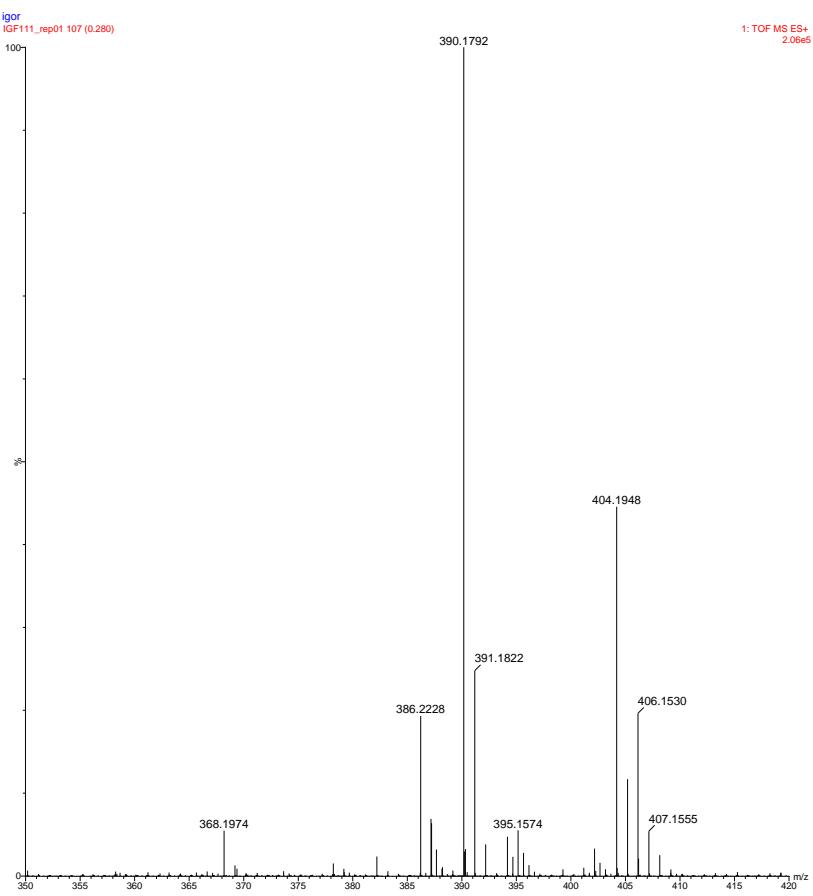


Figure S43. HRMS of compound **3i**.