An eco-friendly synthesis of novel 3,5-disubstituted-1,2-isoxazoles in PEG-400, employing the Et_3N-promoted hydroamination of symmetric and unsymmetric 1,3-diyne-indole derivatives

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Supplementary Information

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Synthetic Procedures

2-Methyl-1*H*-indole (1d)[1]

A mixture of phenyl hydrazine (2.16 g, 20 mmol), acetone (20 mL) and AcOH (6 drops) in EtOH (20 mL) was heated to reflux for 6 h. After cooling, the organic solvent was removed and the residue was partitioned between H_2O (50 mL) and EtOAc (2 × 50 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The resulting hydrazone was treated dropwise with polyphosphoric acid until the color changed from red to black (10 mL). When the reaction began to give off gas, it was neutralized with 1M NaOH until a clear solution. The reaction was diluted with brine (50 mL) and the product was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified chromatographically, affording **1m** (1.89 g, 72%), as a brown solid, m.p.: 51-53 °C (Lit.:[2] 52 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 6.18 (s, 1H), 7.23-7.01 (m, 3H), 7.52-7.48 (m, 1H) and 7.69 (bs, 1H).

5-(*p*-Tolyl)-1*H*-indole (1e)[3]

5-Bromoindole (**1c**, 2.0 g, 10.2 mmol), $Pd(PPh_3)_4$ (1.17 g, 10 mol%) and toluene (20 mL) were successively added to a round bottom flask and the stirred mixture was treated with a solution of *p*-tolueneboronic acid (2.08 g, 15.2 mmol) in EtOH (10 mL) and saturated $NaHCO_3$ (6 mL) under argon. The reaction was heated to reflux for 24 h, when the system was cooled to room temperature, treated with brine (10 mL) and extracted with EtOAc (2 × 30 mL). The organic phase was washed with water (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give **1e** (1.56 g, 74%), as a beige solid, m.p.: 76-77 °C (Lit.:[4] 78-79 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.38 (s, 3H), 6.57-7.55 (m, 1H), 7.14-7.11 (m, 1H), 7.24 (d, *J* = 8.0, 2H), 7.34 (d, *J* = 8.5, 1H), 7.43 (dd, *J* = 8.5 and 1.5, 1H), 7.54 (d, *J* = 8.0, 2H), 7.83 (s, 1H) and 7.97 (bs, 1H).

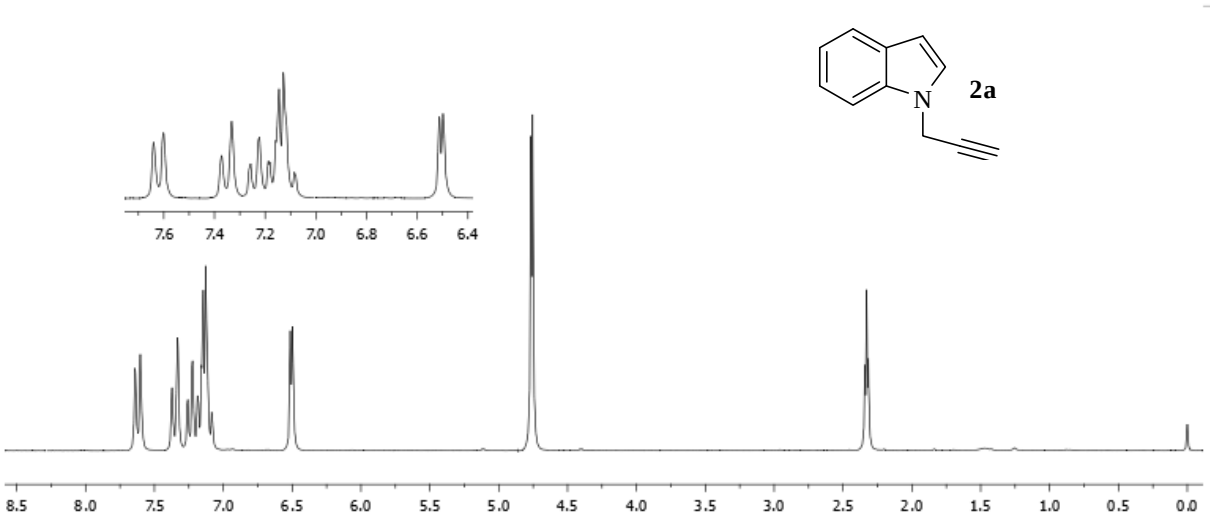


Figure S1. 200 MHz ^{1}H NMR spectrum of compound **2a** in $CDCl_3$.

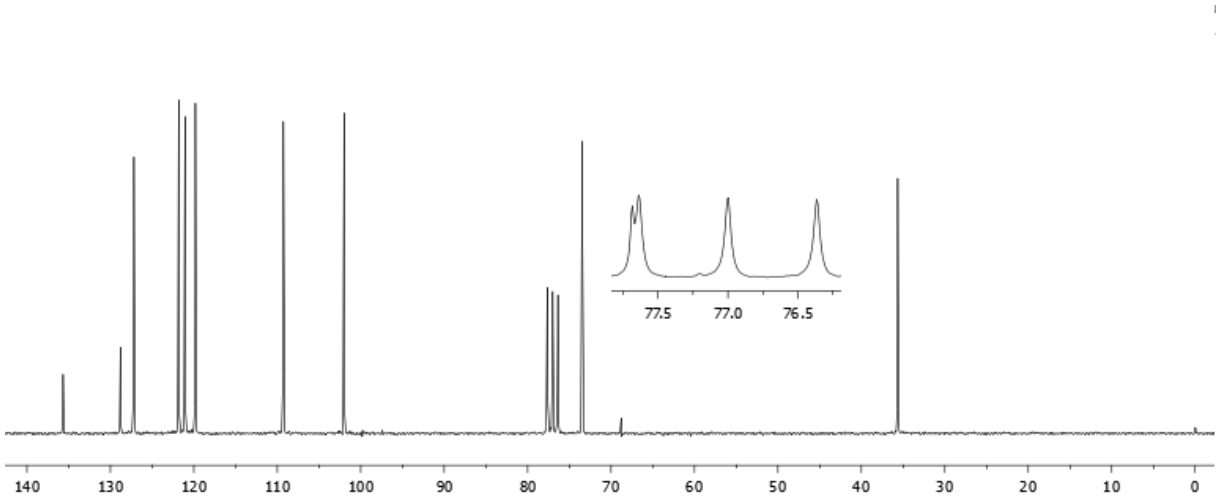


Figure S2. 50 MHz ^{13}C NMR spectrum of compound **2a** in $CDCl_3$.

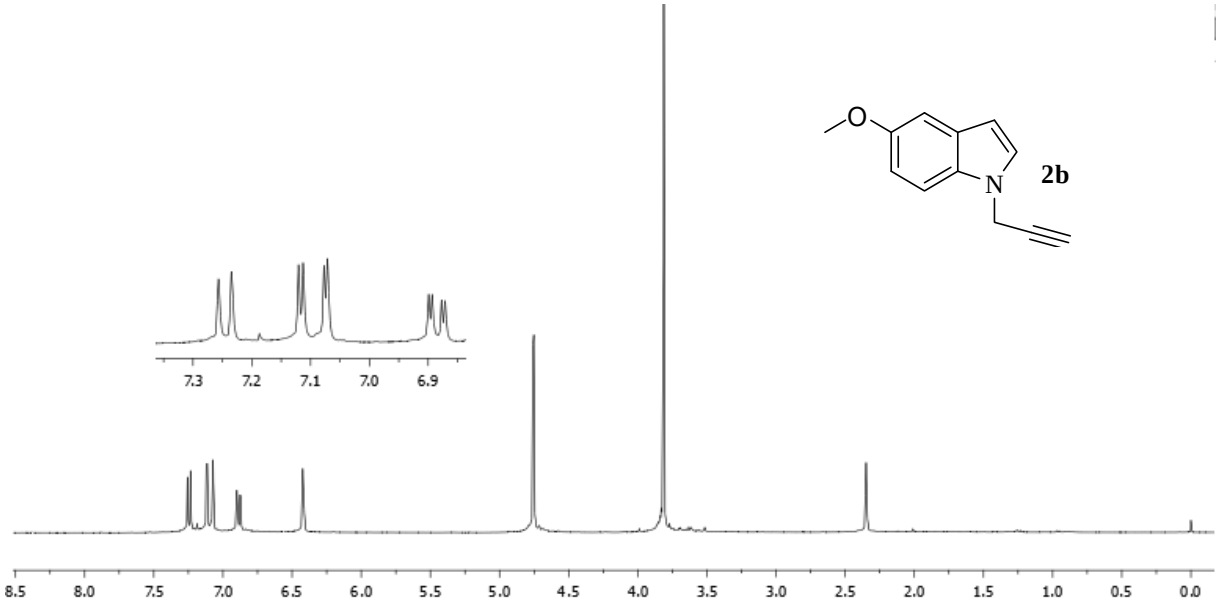


Figure S3. 400 MHz ^{1}H NMR spectrum of compound **2b** in $CDCl_3$.

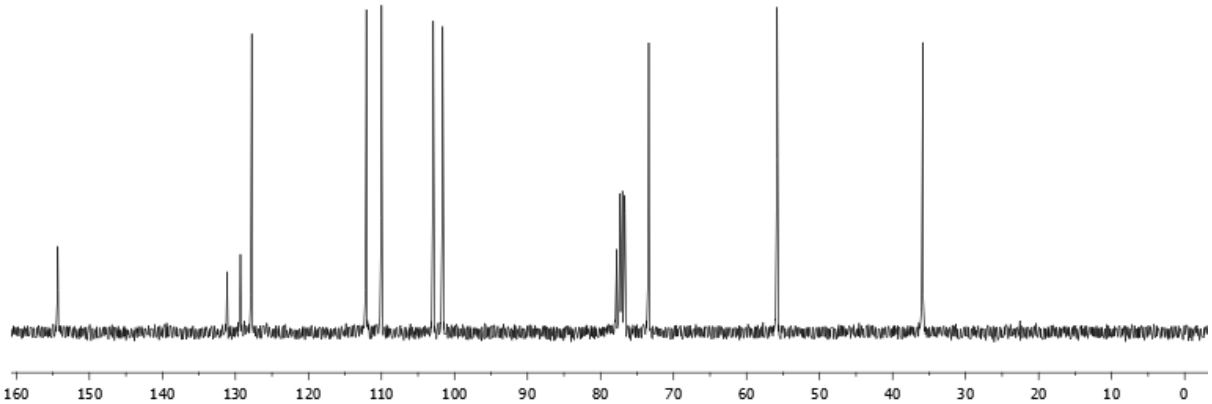


Figure S4. 100 MHz ^{13}C NMR spectrum of compound **2b** in $CDCl_3$.

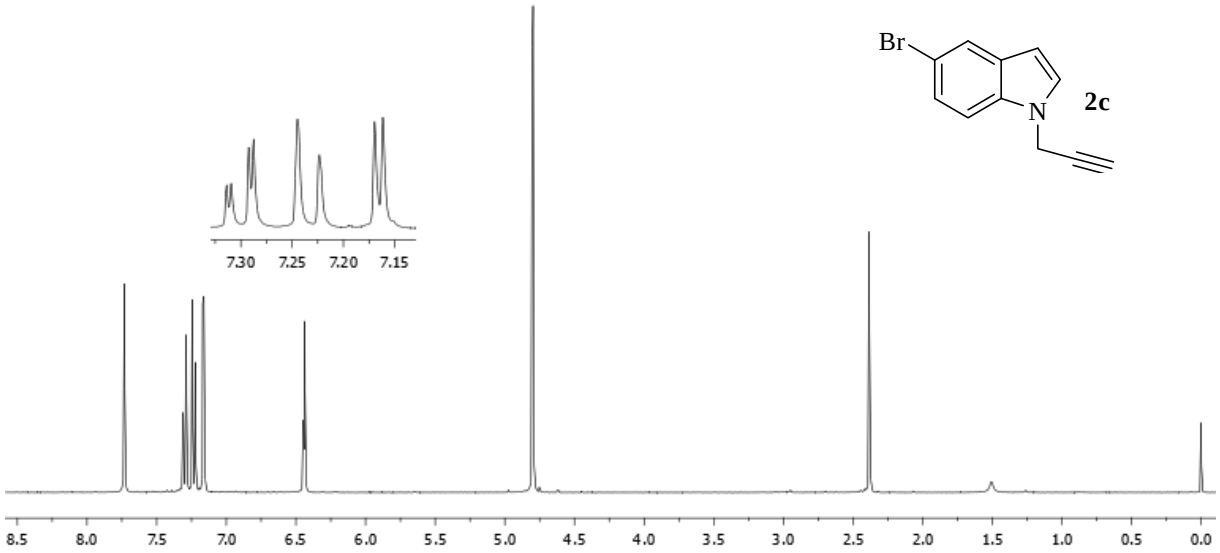


Figure S5. 400 MHz ^{1}H NMR spectrum of compound **2c** in $CDCl_3$.

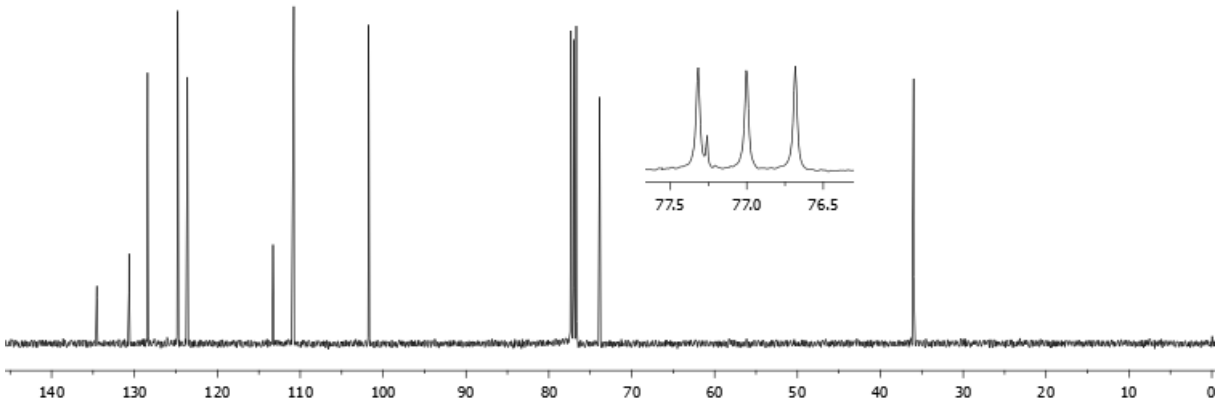


Figure S6. 100 MHz ^{13}C NMR spectrum of compound **2c** in $CDCl_3$.

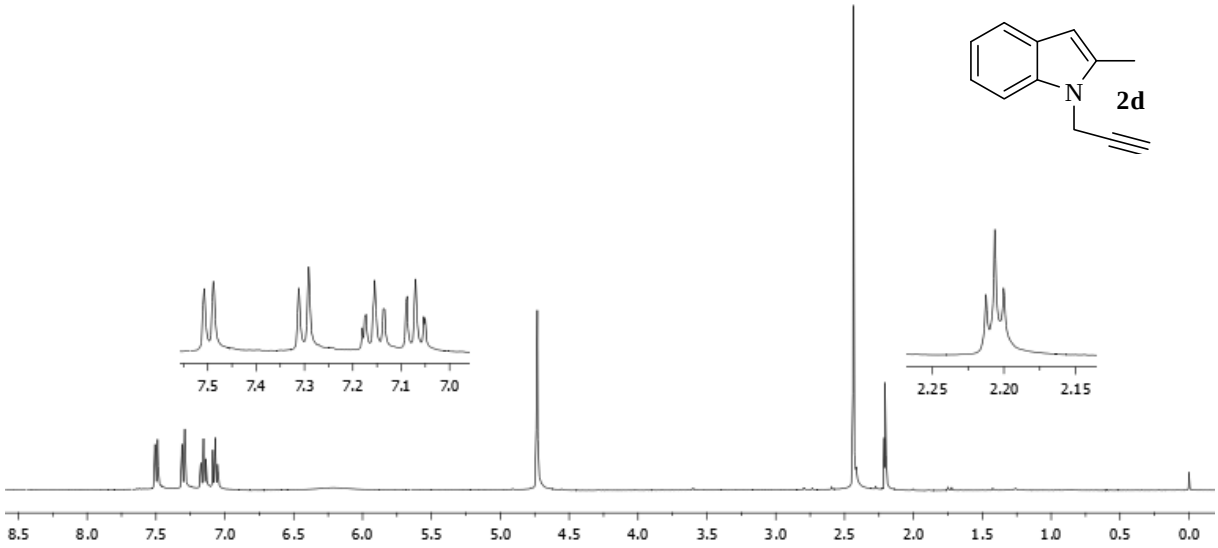


Figure S7. 400 MHz ^{1}H NMR spectrum of compound **2d** in $CDCl_3$.

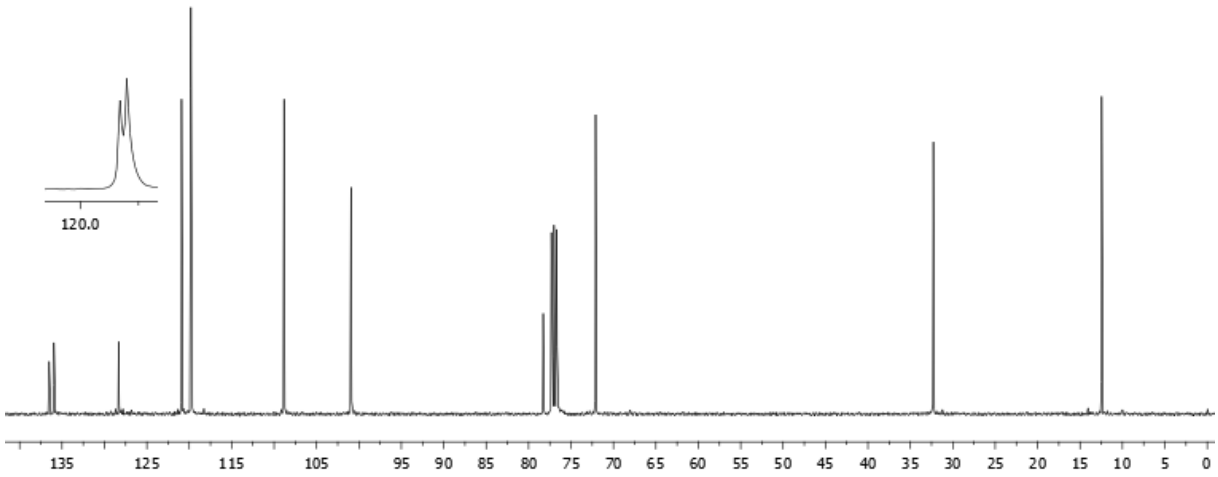


Figure S8. 100 MHz ^{13}C NMR spectrum of compound **2d** in $CDCl_3$.

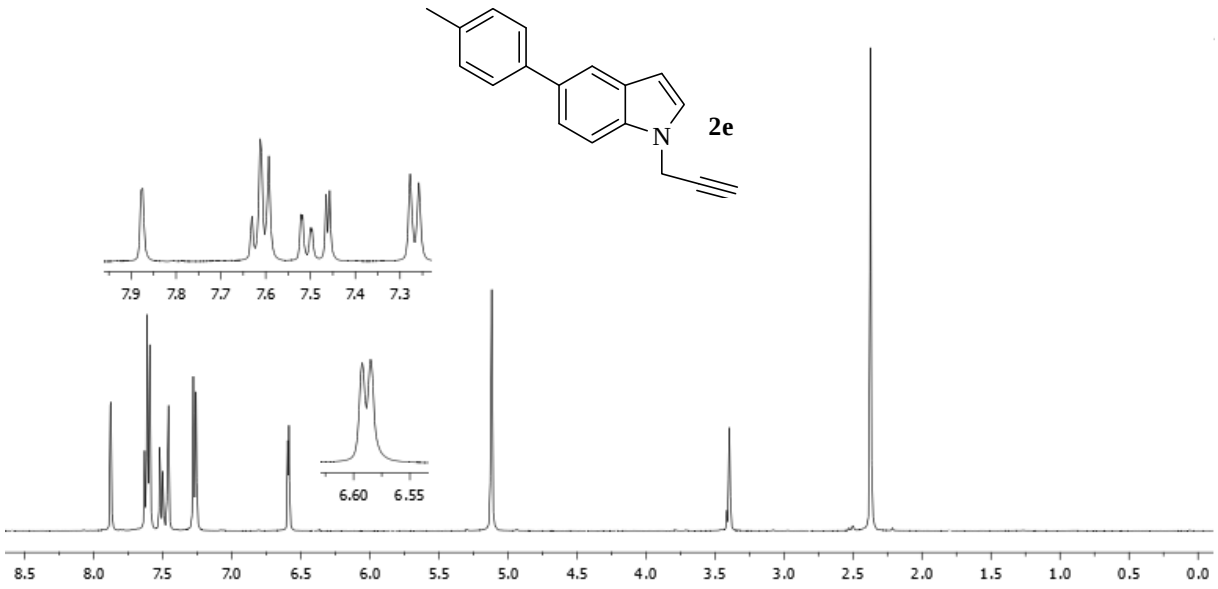


Figure S9. 400 MHz ^{1}H NMR spectrum of compound **2e** in DMSO-d_6.

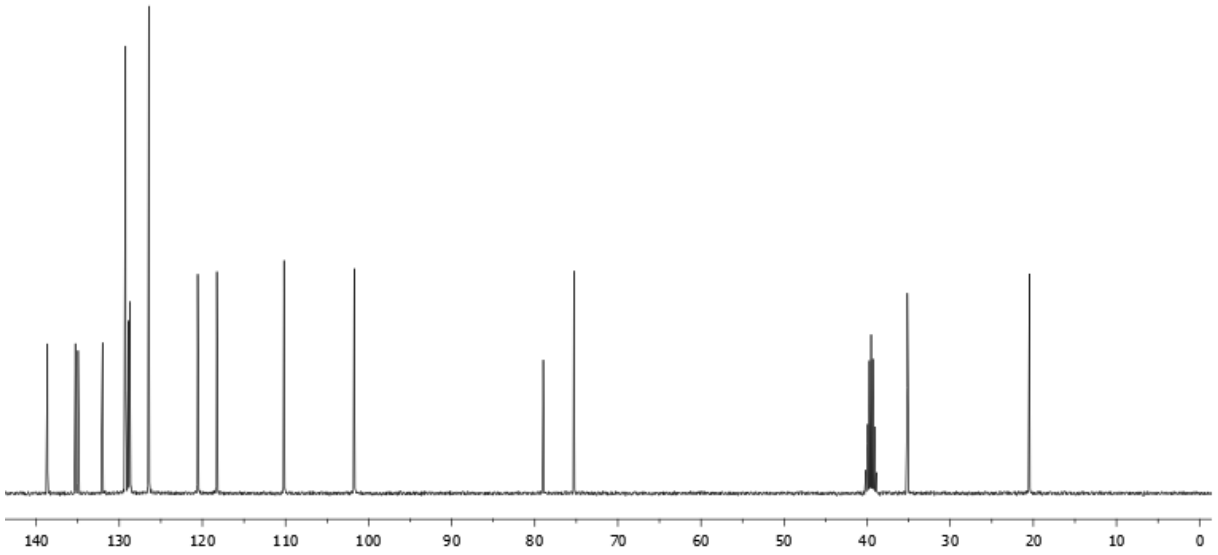


Figure S10. 100 MHz ^{13}C NMR spectrum of compound **2e** in DMSO-d_6.

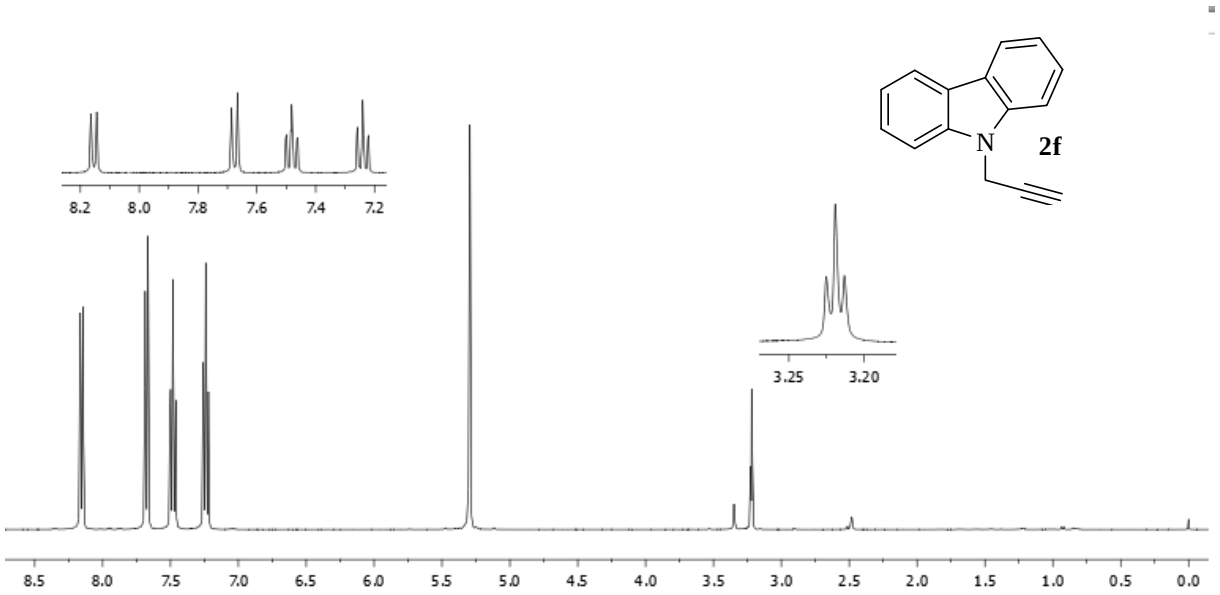


Figure S11. 400 MHz ^{1}H NMR spectrum of compound **2f** in DMSO-d_6.

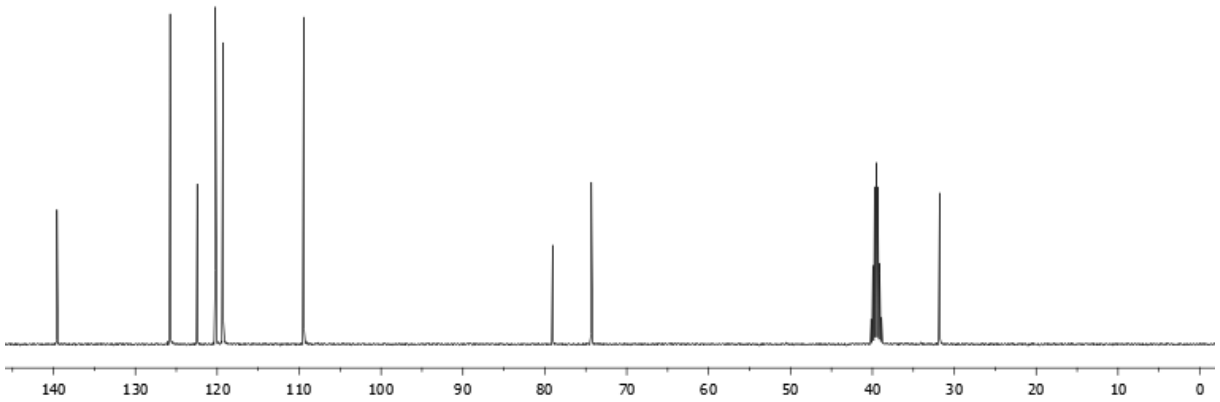


Figure S12. 100 MHz ^{13}C NMR spectrum of compound **2f** in DMSO-d_6.

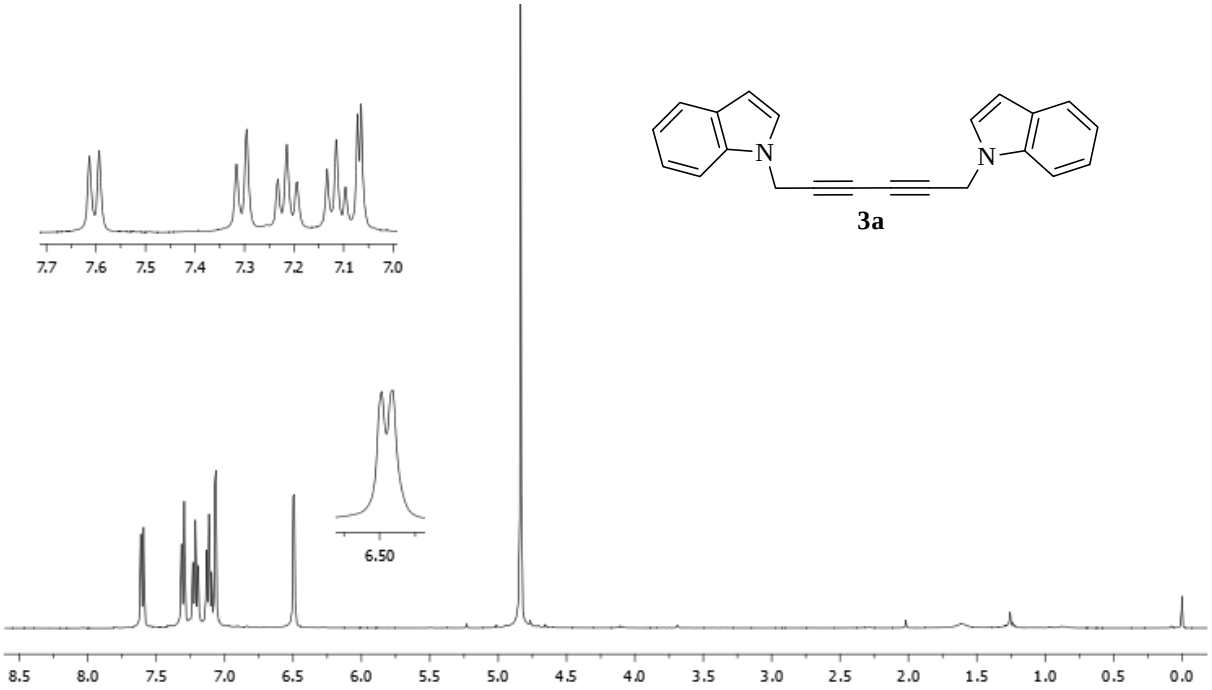


Figure S13. 400 MHz ^{1}H NMR spectrum of compound **3a** in $CDCl_3$.

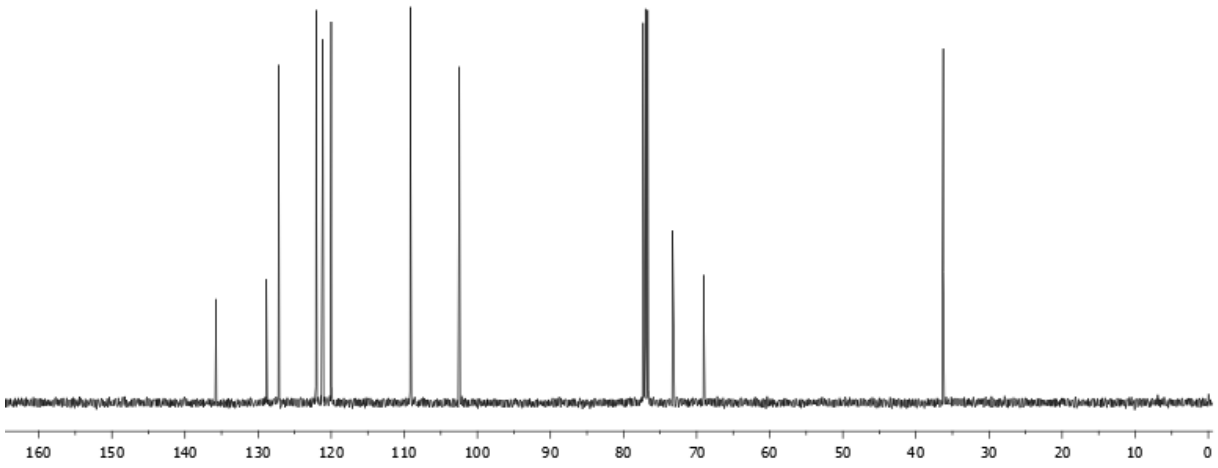


Figure S14. 100 MHz ^{13}C NMR spectrum of compound **3a** in $CDCl_3$.

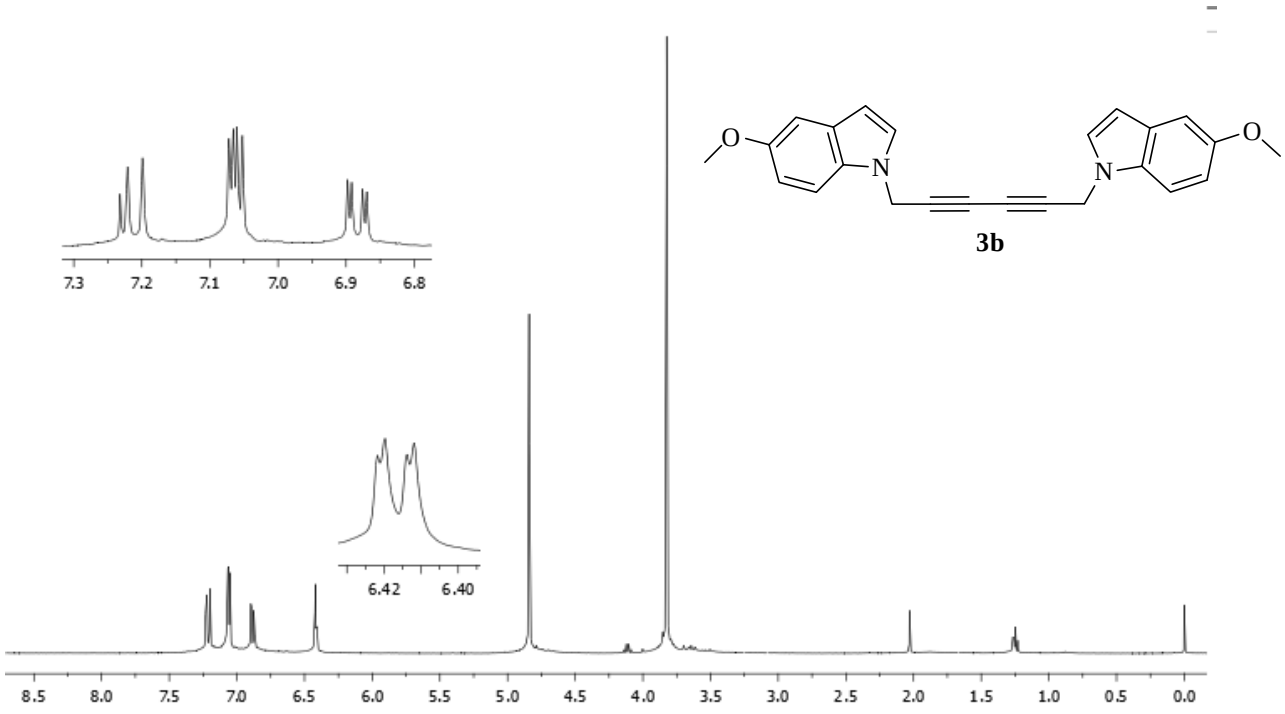


Figure S15. 400 MHz ^{1}H NMR spectrum of compound **3b** in $CDCl_3$.

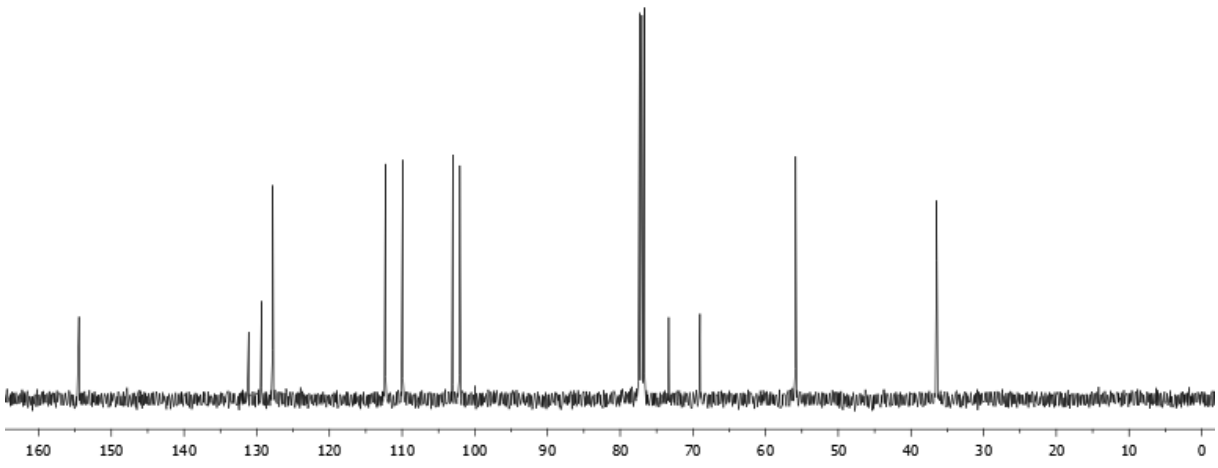


Figure S16. 100 MHz ^{13}C NMR spectrum of compound **3b** in $CDCl_3$.

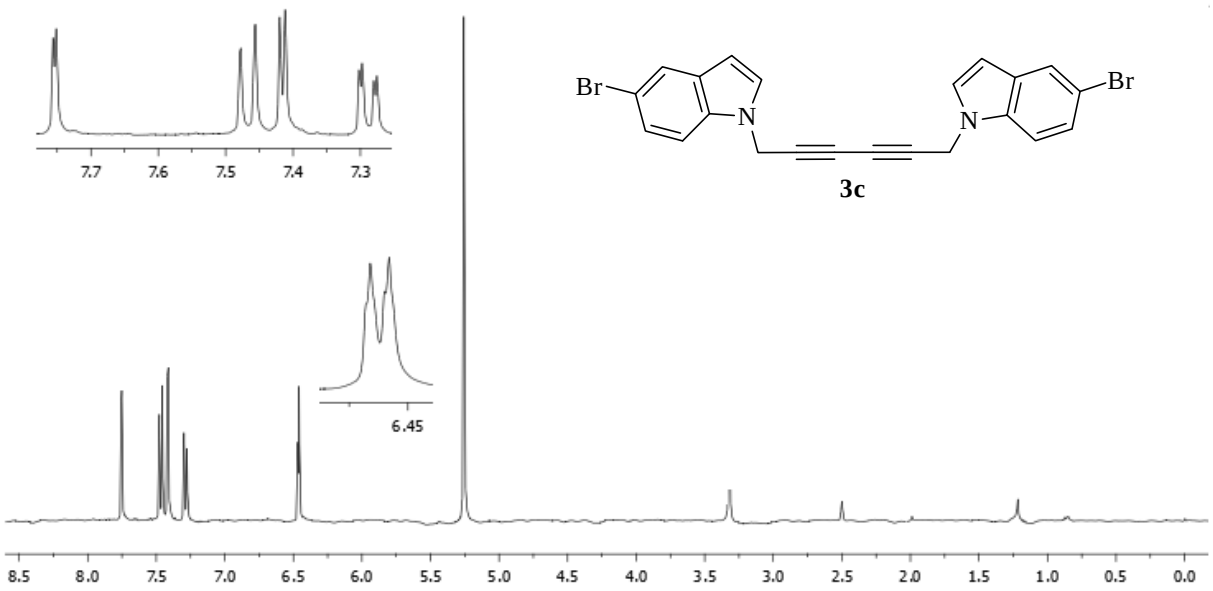


Figure S17. 400 MHz ^{1}H NMR spectrum of compound **3c** in DMSO-d_6.

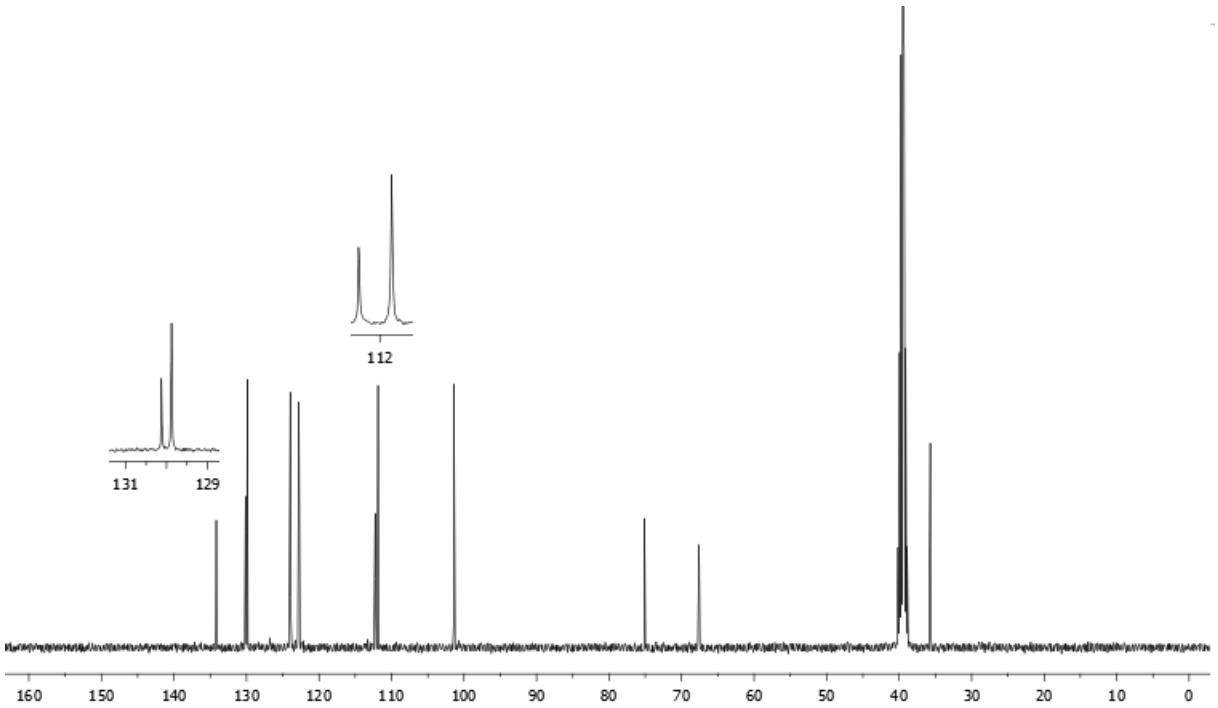


Figure S18. 100 MHz ^{13}C NMR spectrum of compound **3c** in DMSO-d_6.

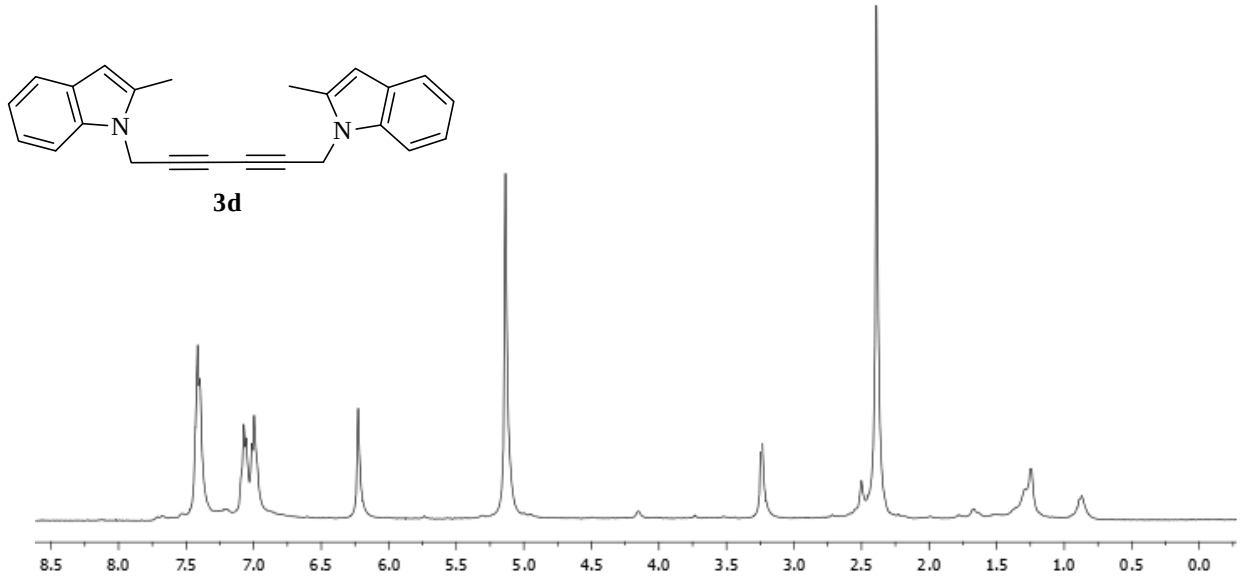


Figure S19. 400 MHz ^{1}H NMR spectrum of compound **3d** in DMSO-d_6

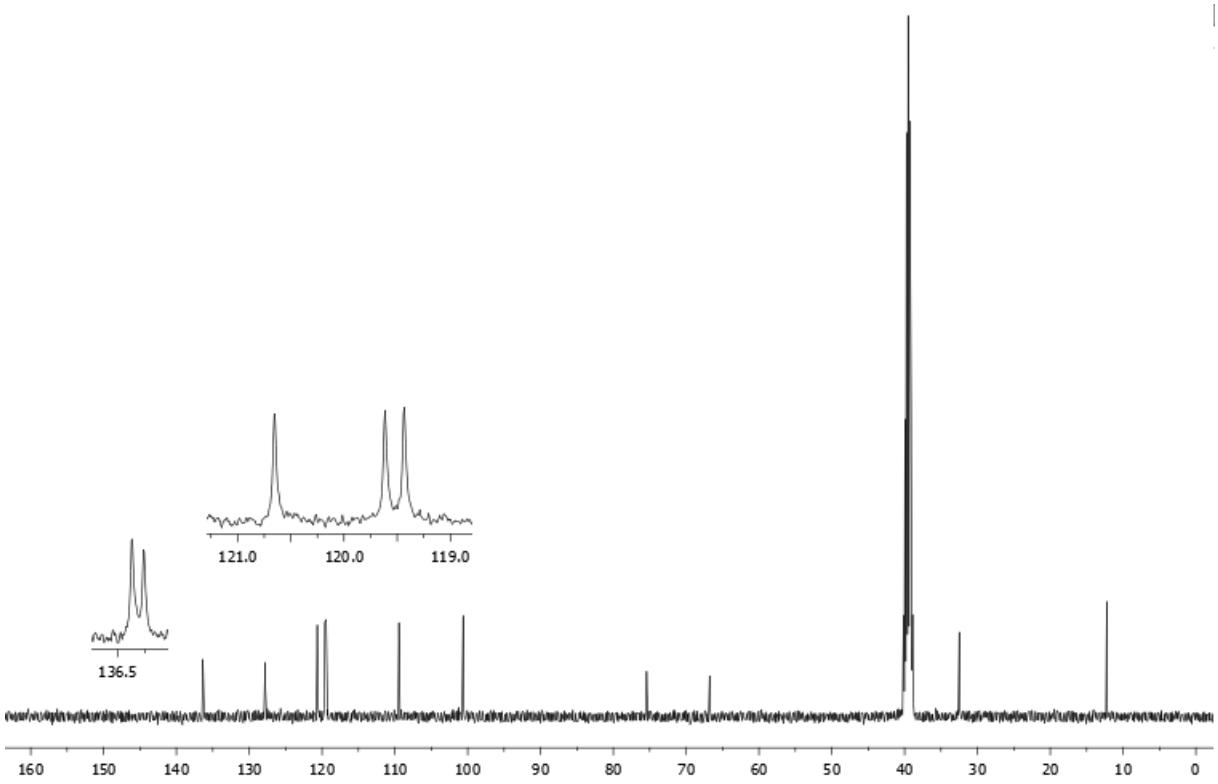
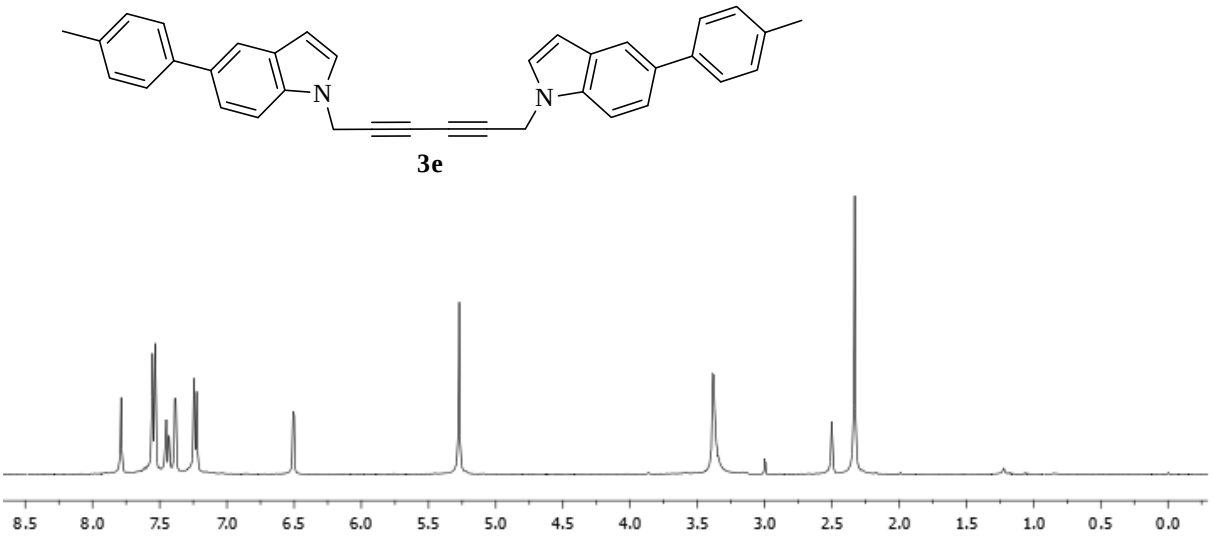


Figure S20. 100 MHz ^{13}C NMR spectrum of compound **3d** in DMSO-d_6.



3e

Figure S21. 400 MHz ^{1}H NMR spectrum of compound **3e** DMSO-d_6.

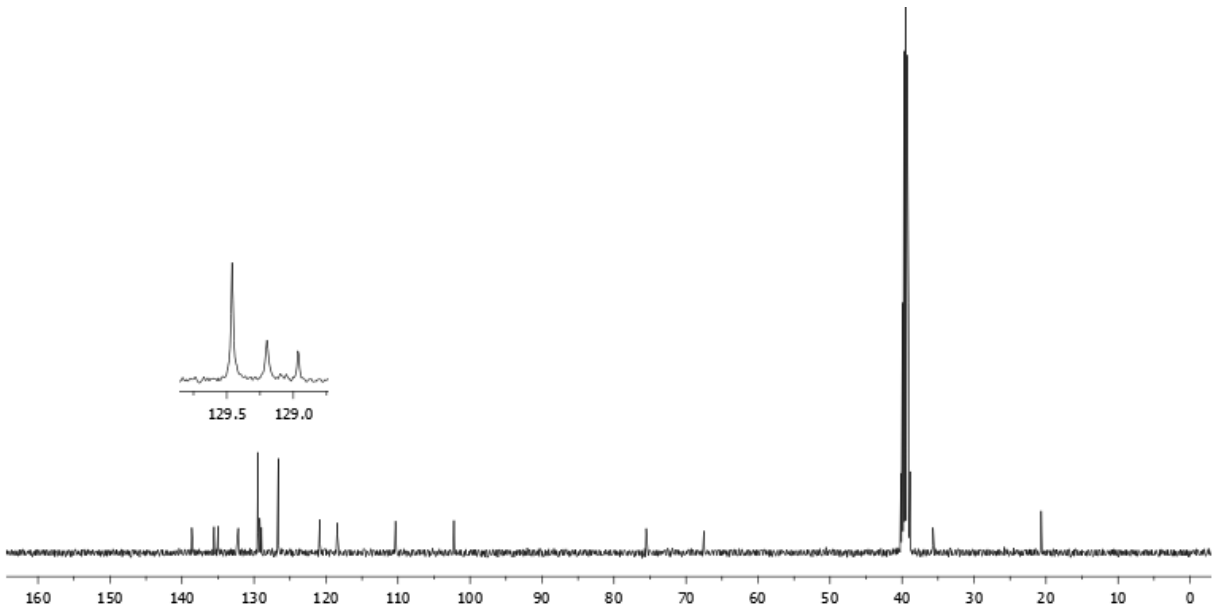
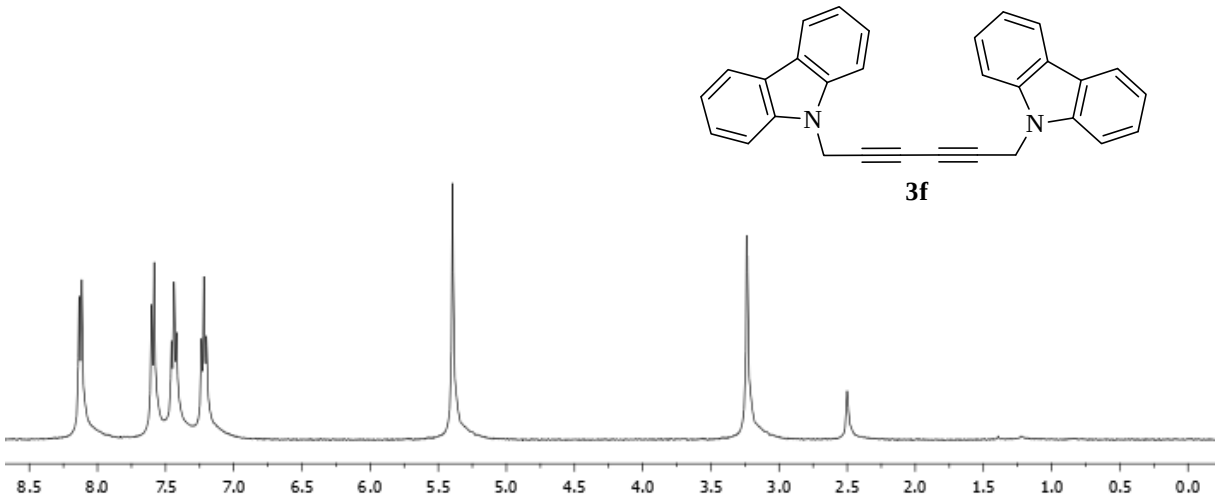


Figure S22. 100 MHz ^{13}C NMR spectrum of compound **3e** in DMSO-d_6.



3f

Figure S23. 400 MHz ^{1}H NMR spectrum of compound **3f** in DMSO-d_6.

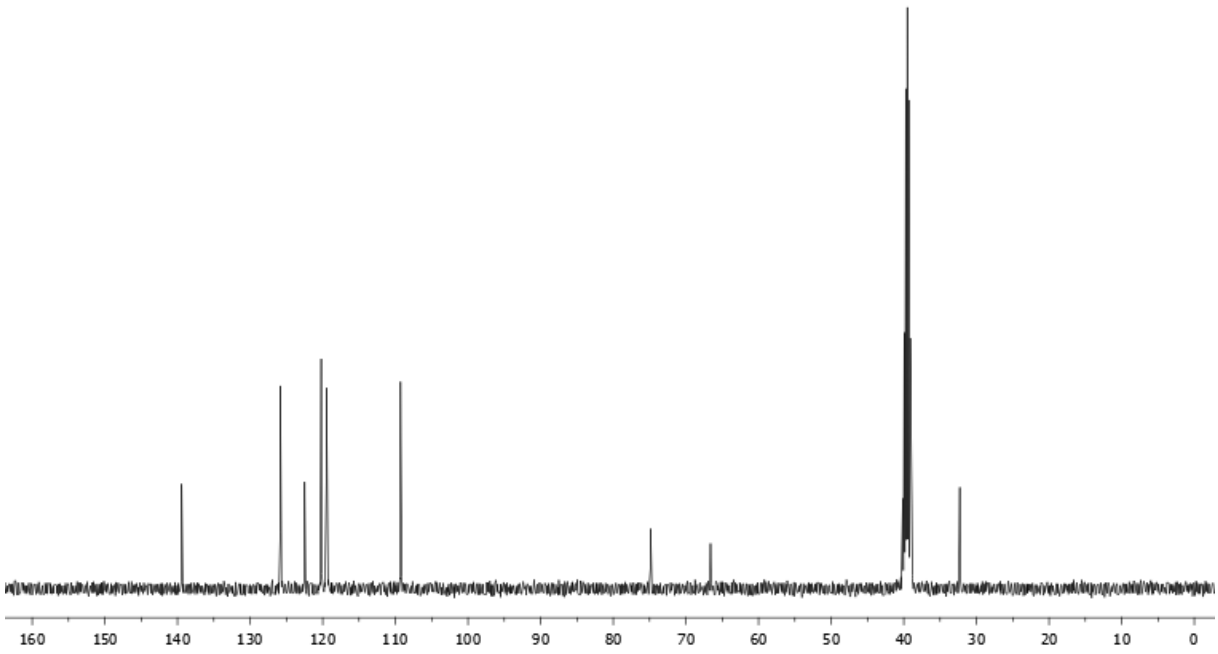


Figure S24. 100 MHz ^{13}C NMR spectrum of compound **3f** in DMSO-d_6.

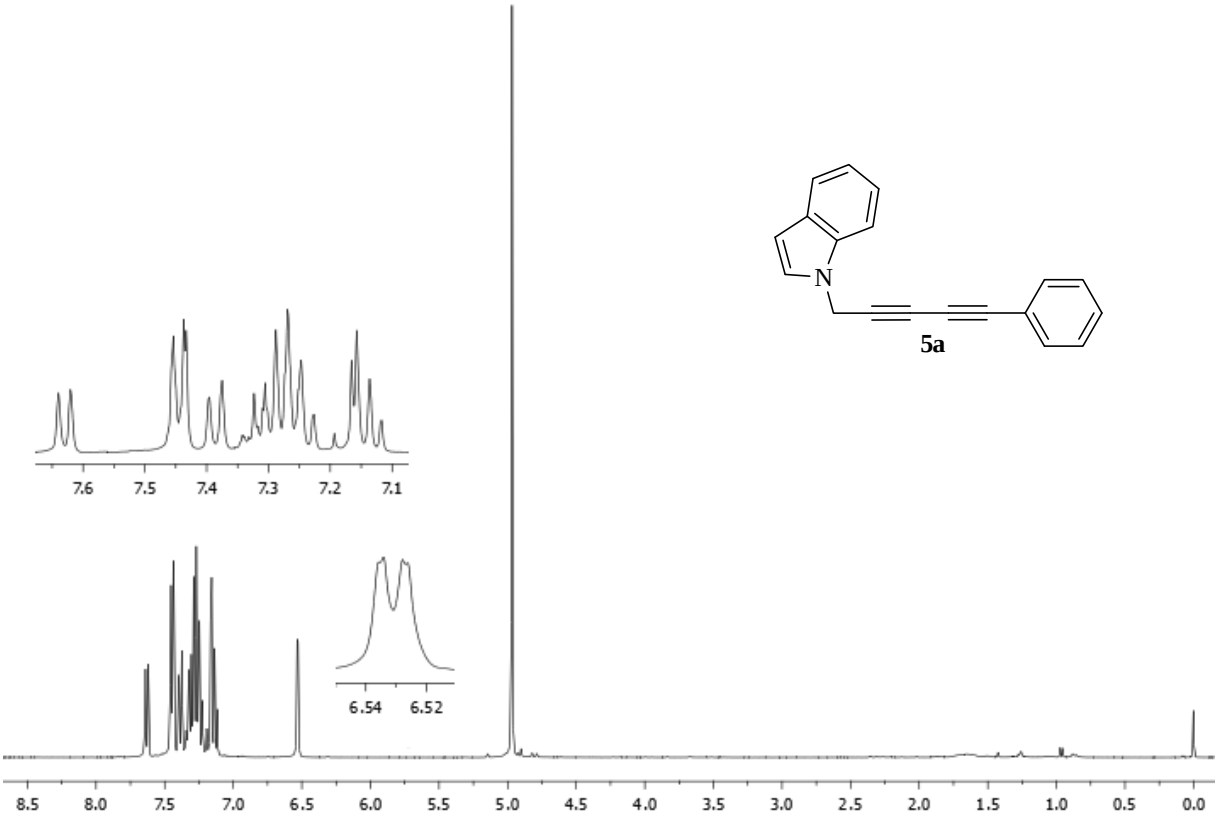


Figure S25. 400 MHz ^{1}H NMR spectrum of compound **5a** in $CDCl_3$.

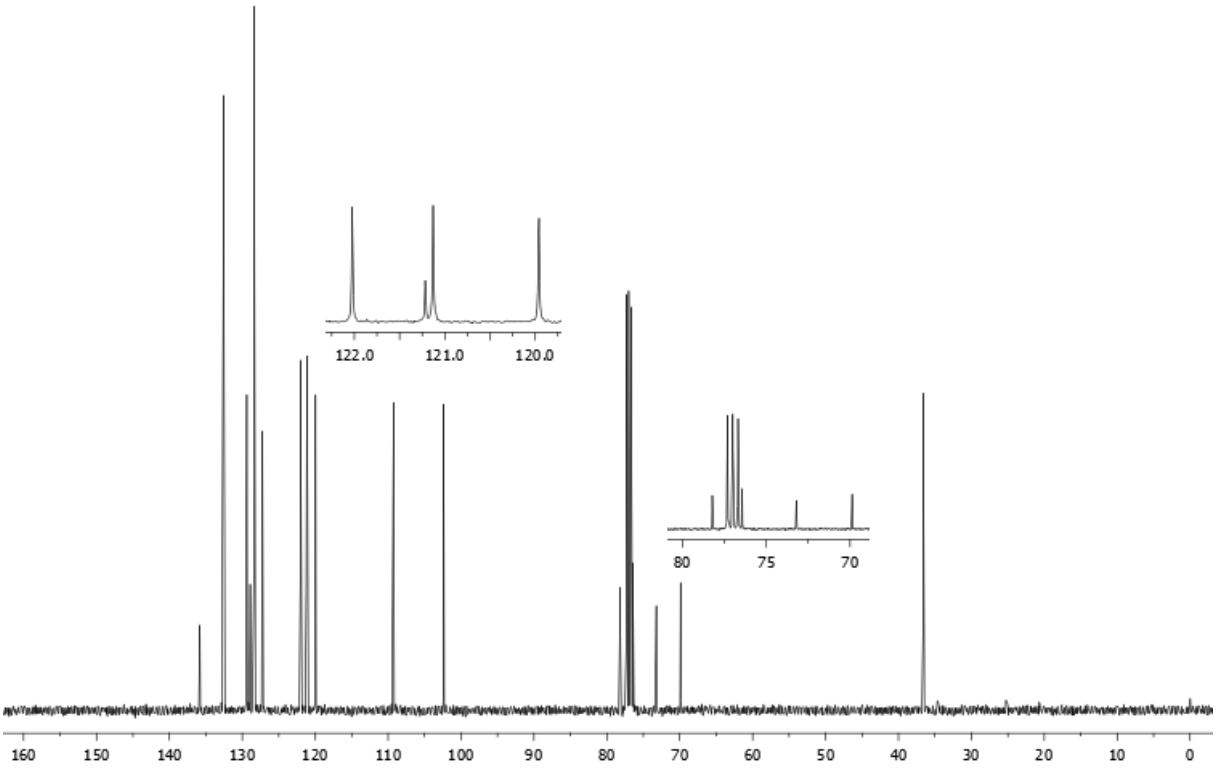


Figure S26. 100 MHz ^{13}C NMR spectrum of compound **5a** in $CDCl_3$.

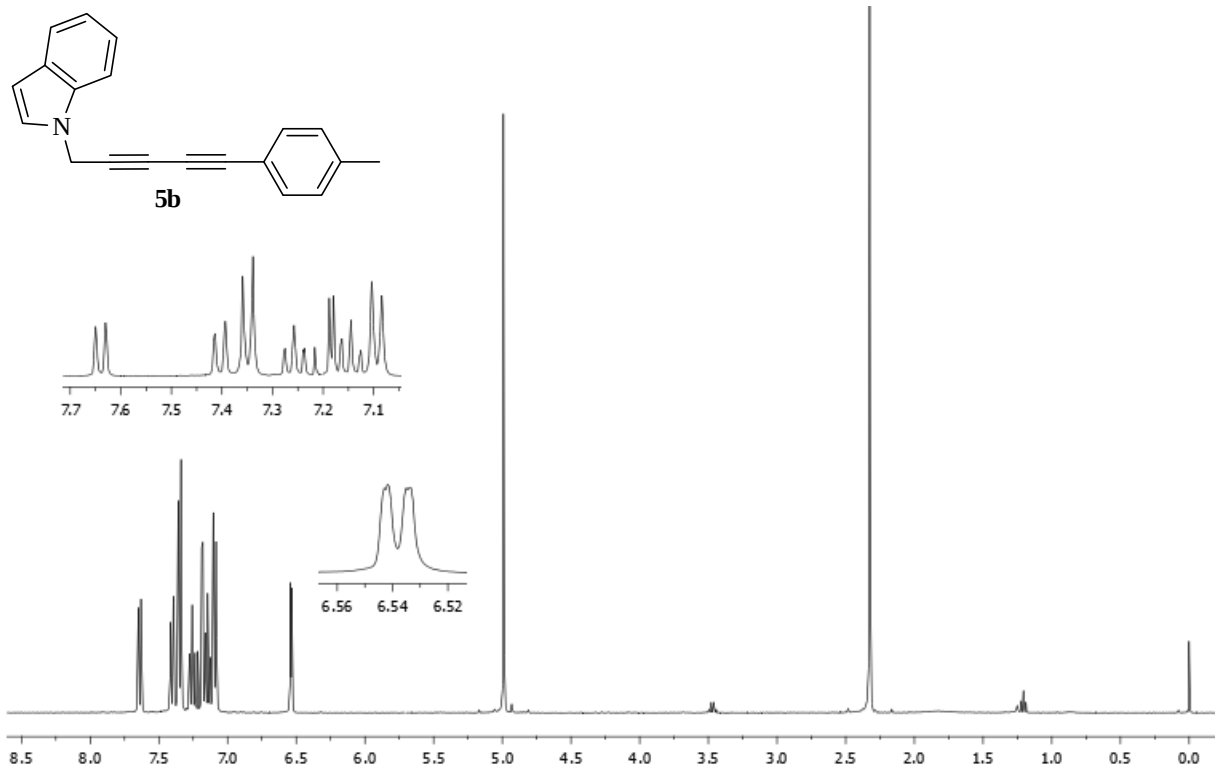


Figure S27. 400 MHz ^{1}H NMR spectrum of compound **5b** in $CDCl_3$.

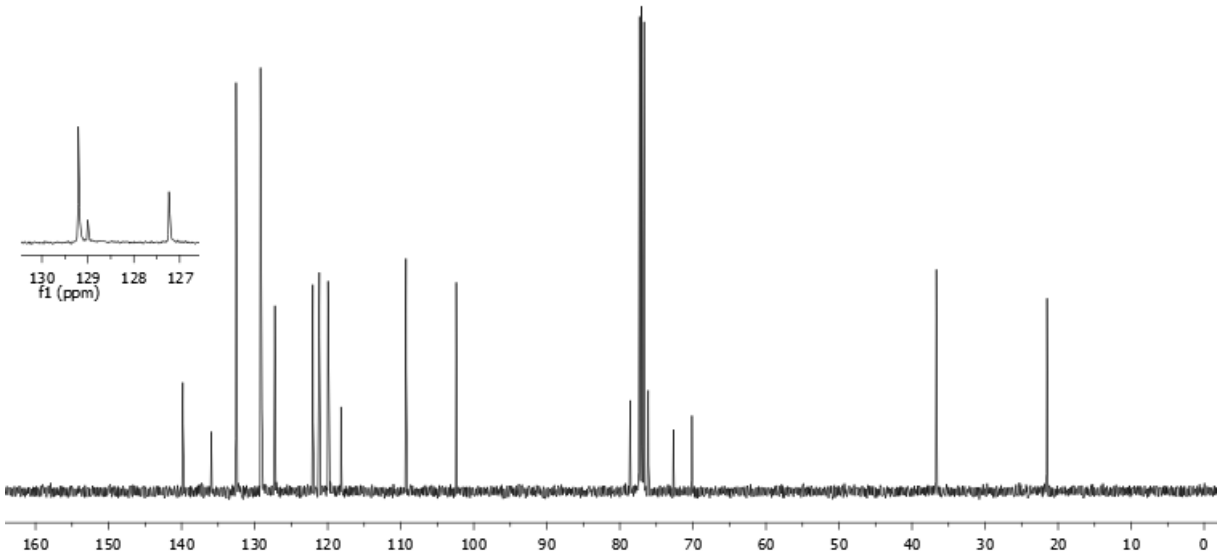


Figure S28. 100 MHz ^{13}C NMR spectrum of compound **5b** in $CDCl_3$.

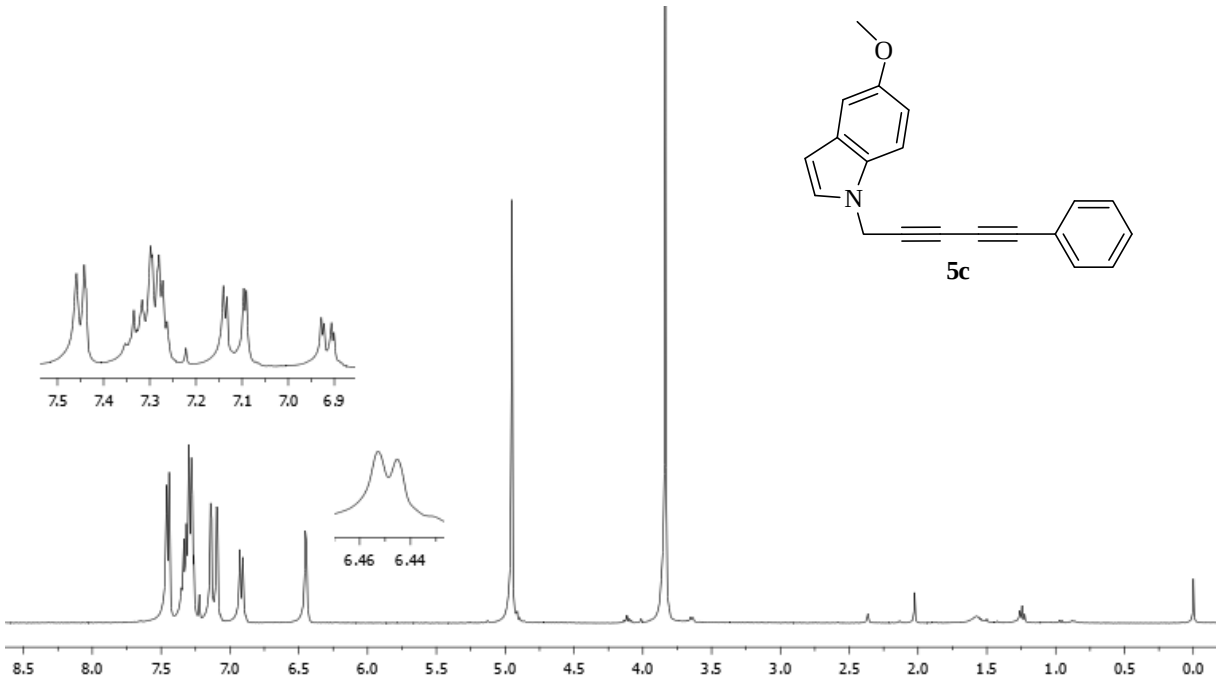


Figure S29. 400 MHz ^{1}H NMR spectrum of compound **5c** in $CDCl_3$.

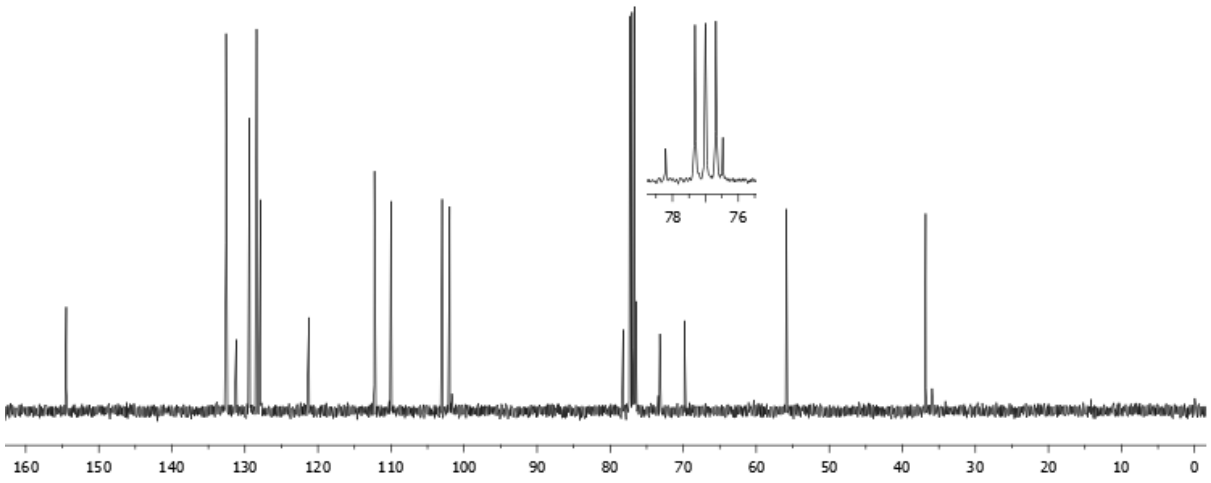


Figure S30. 100 MHz ^{13}C NMR spectrum of compound **5c** in $CDCl_3$.

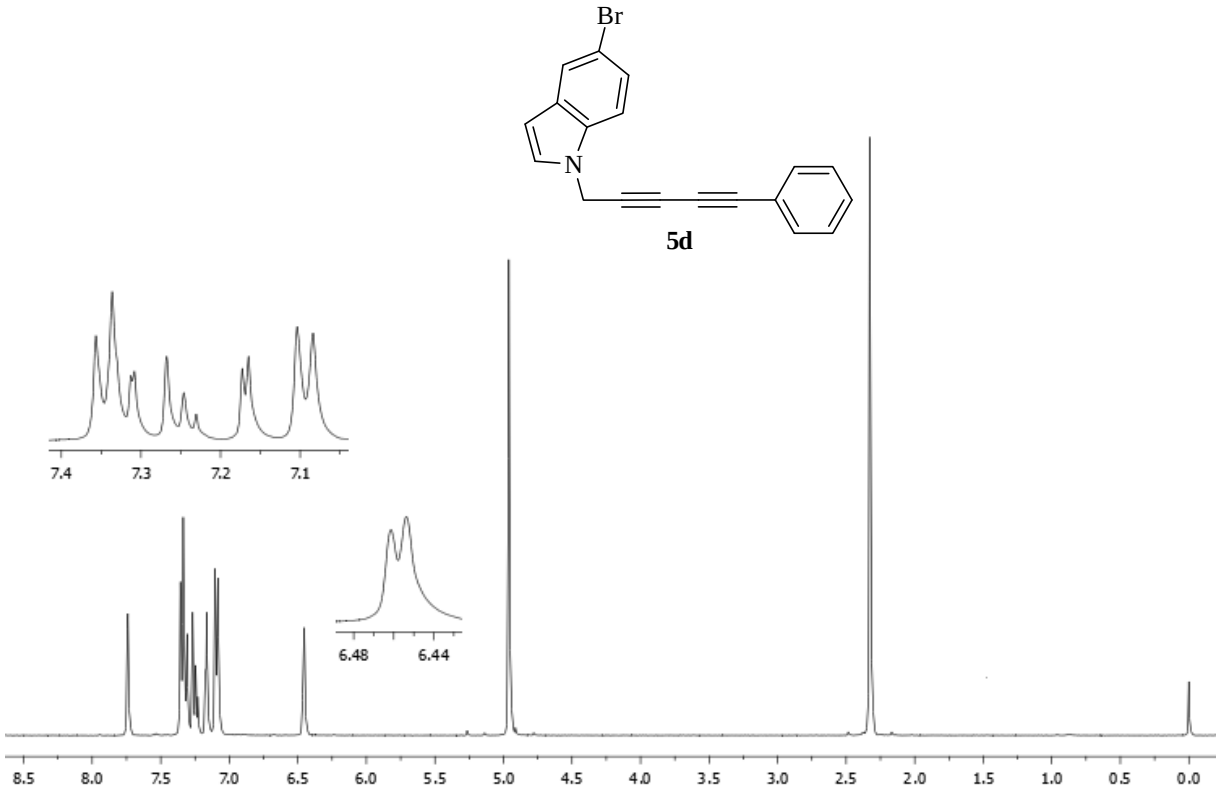


Figure S31. 400 MHz ^{1}H NMR spectrum of compound **5d** in $CDCl_3$.

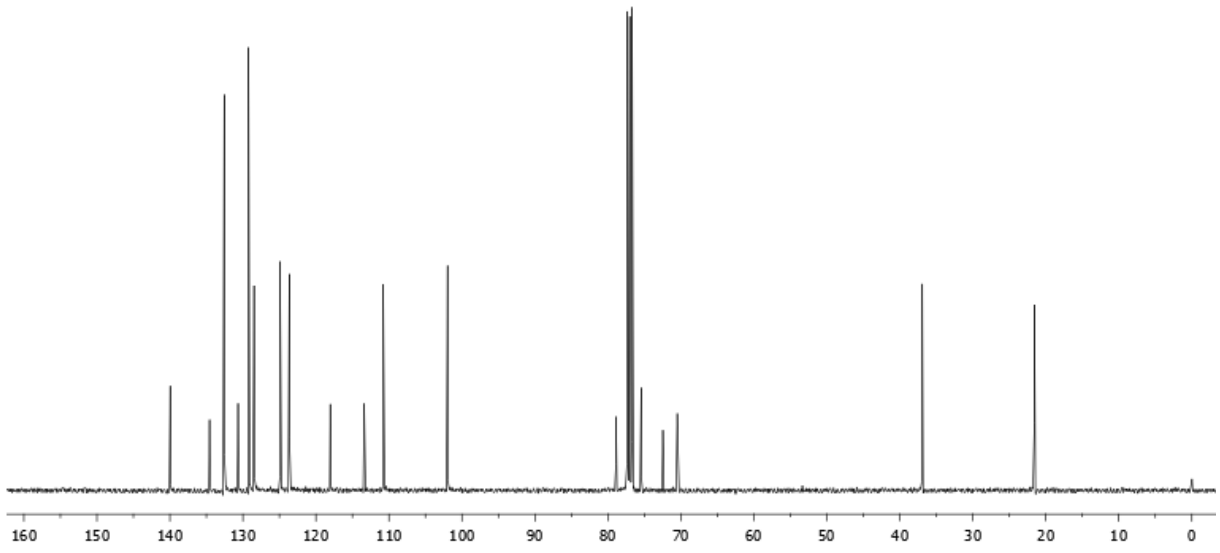


Figure S32. 100 MHz ^{13}C NMR spectrum of compound **5d** in $CDCl_3$.

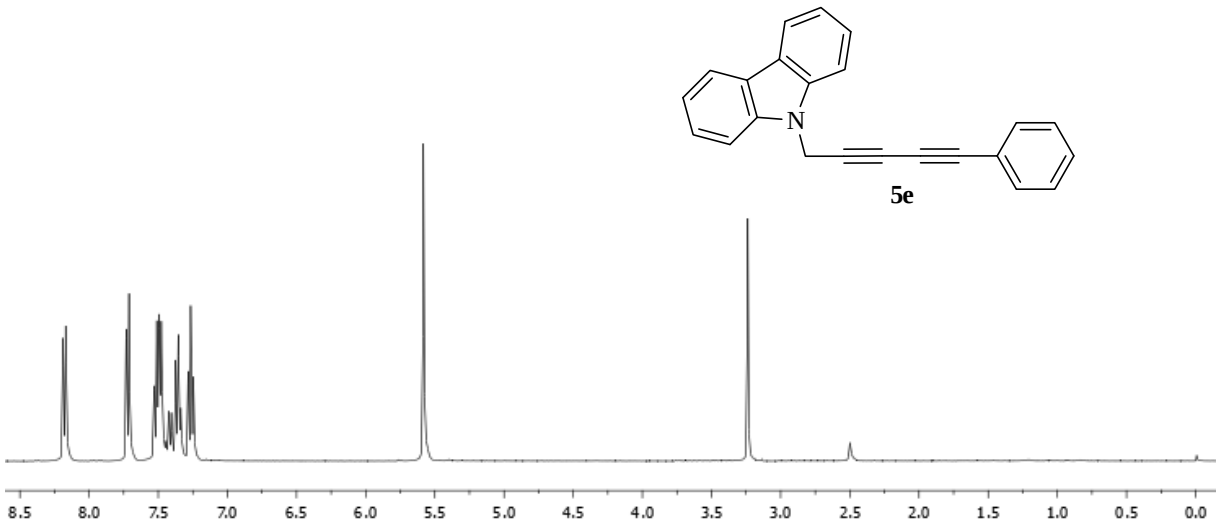


Figure S33. 400 MHz ^{1}H NMR spectrum of compound **5e** in DMSO-d_6.

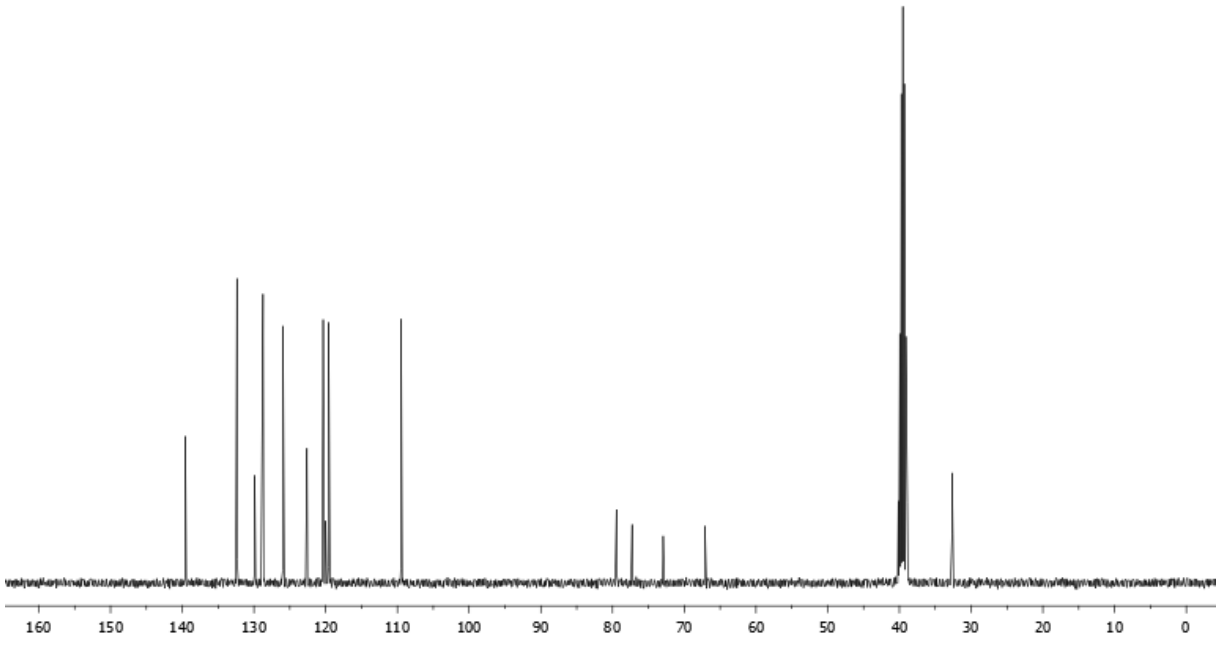


Figure S34. 100 MHz ^{13}C NMR spectrum of compound **5e** in DMSO-d_6.

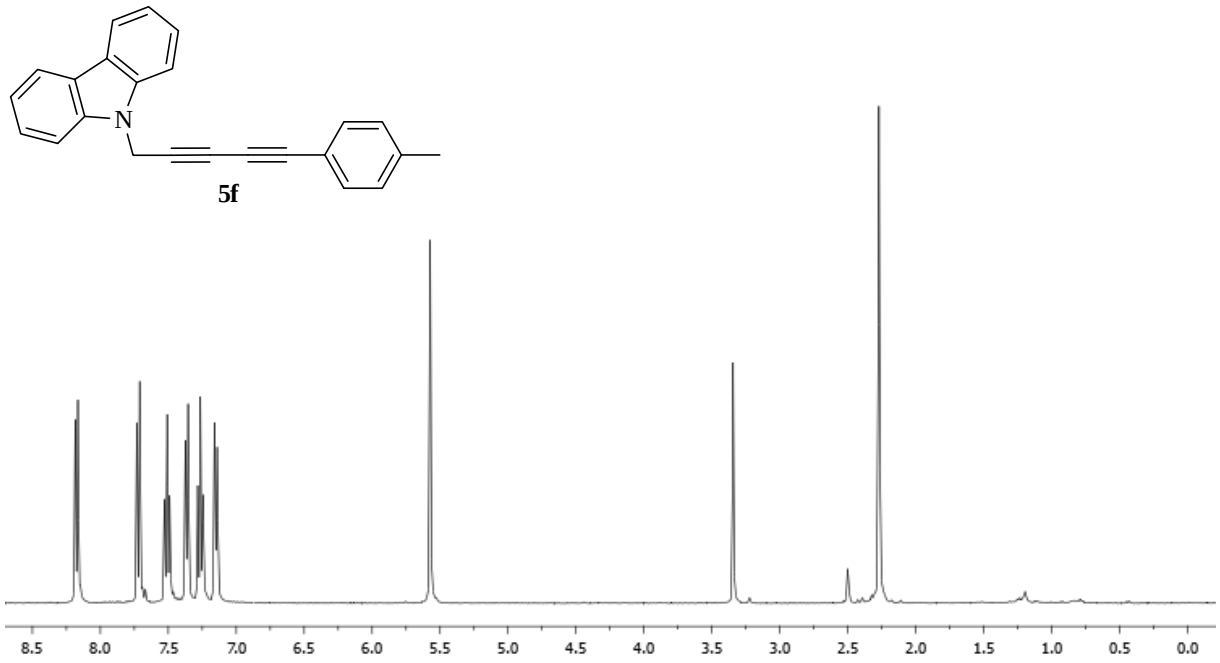


Figure S35. 400 MHz ^{1}H NMR spectrum of compound **5f** in DMSO-d_6.

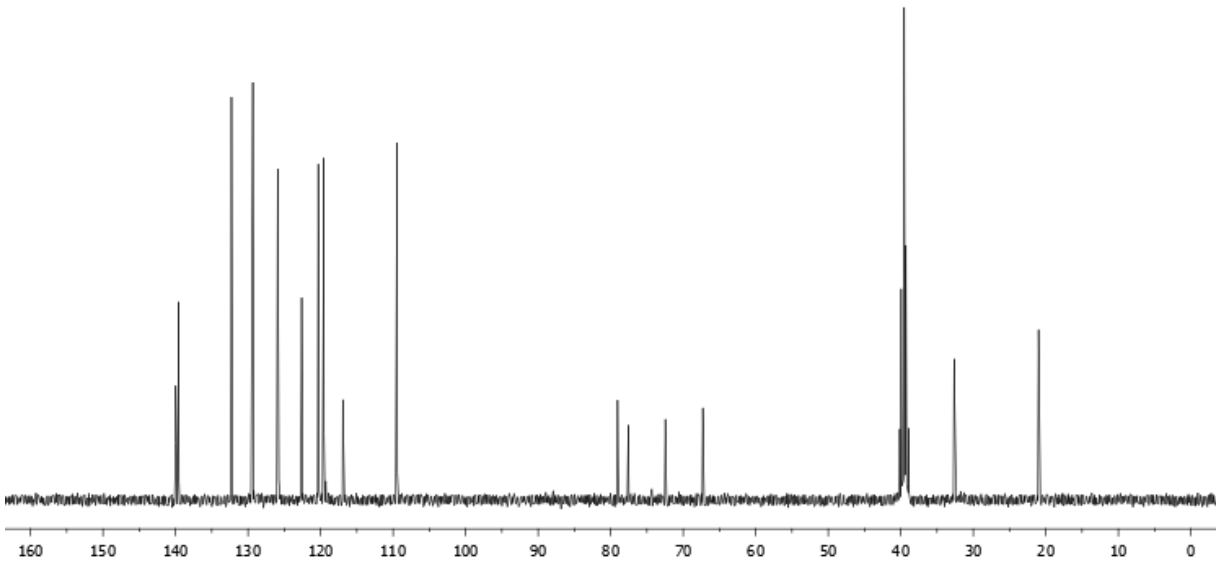


Figure S36. 100 MHz ^{13}C NMR spectrum of compound **5f** in DMSO-d_6.

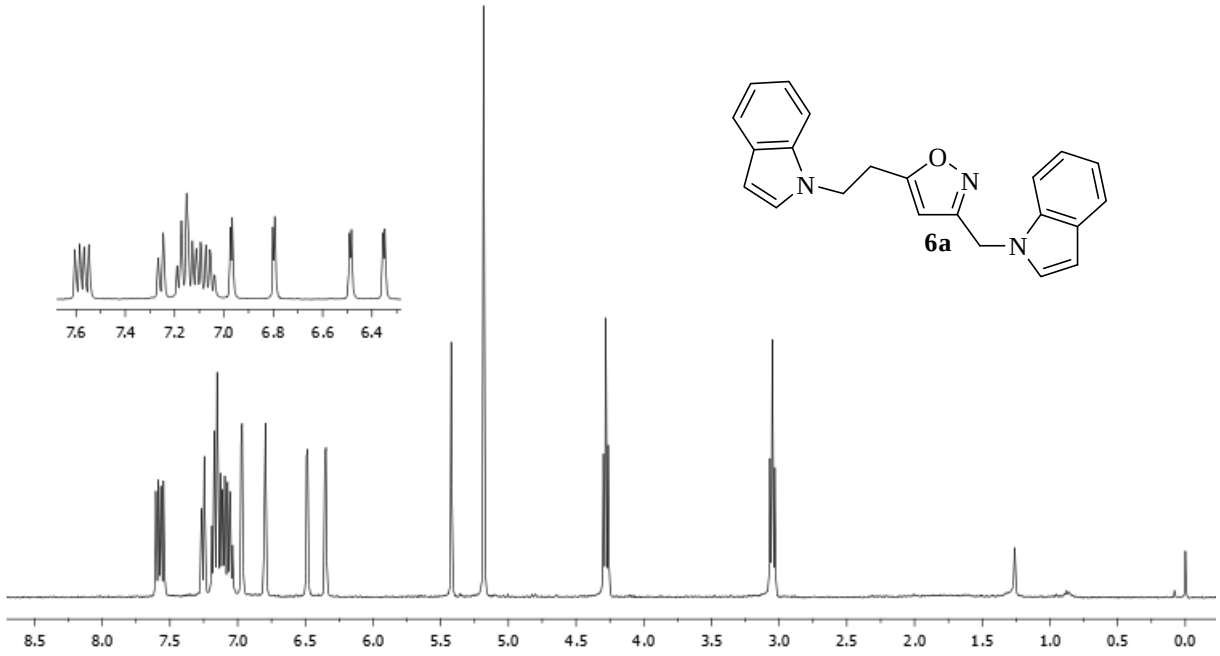


Figure S37. 400 MHz ^{1}H NMR spectrum of compound **6a** in CCl_3.

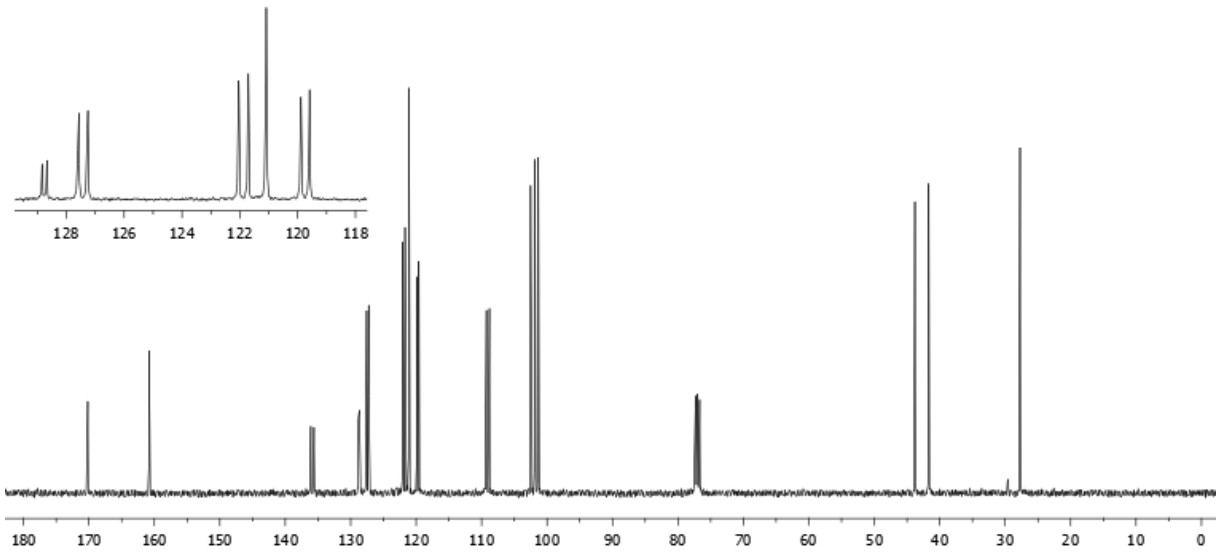


Figure S38. 100 MHz ^{13}C NMR spectrum of compound **6a** in CCl_3.

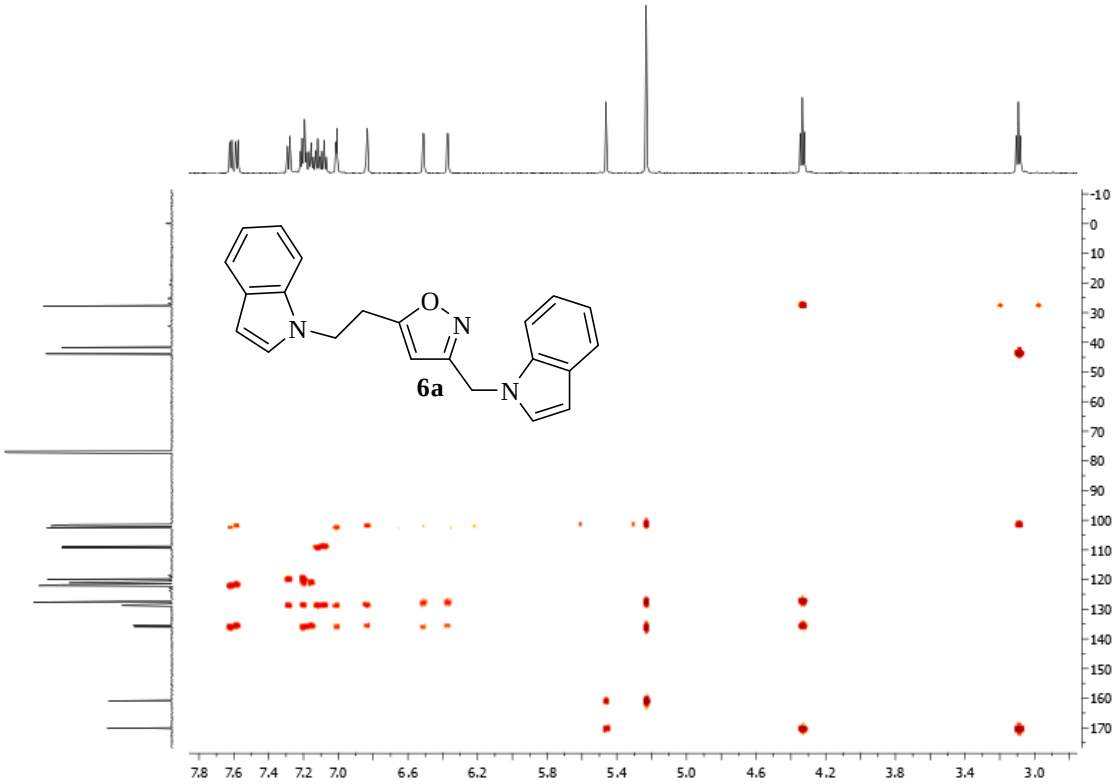


Figure S39. 600 MHz HMBC NMR spectrum of compound **6a** in CCl_3.

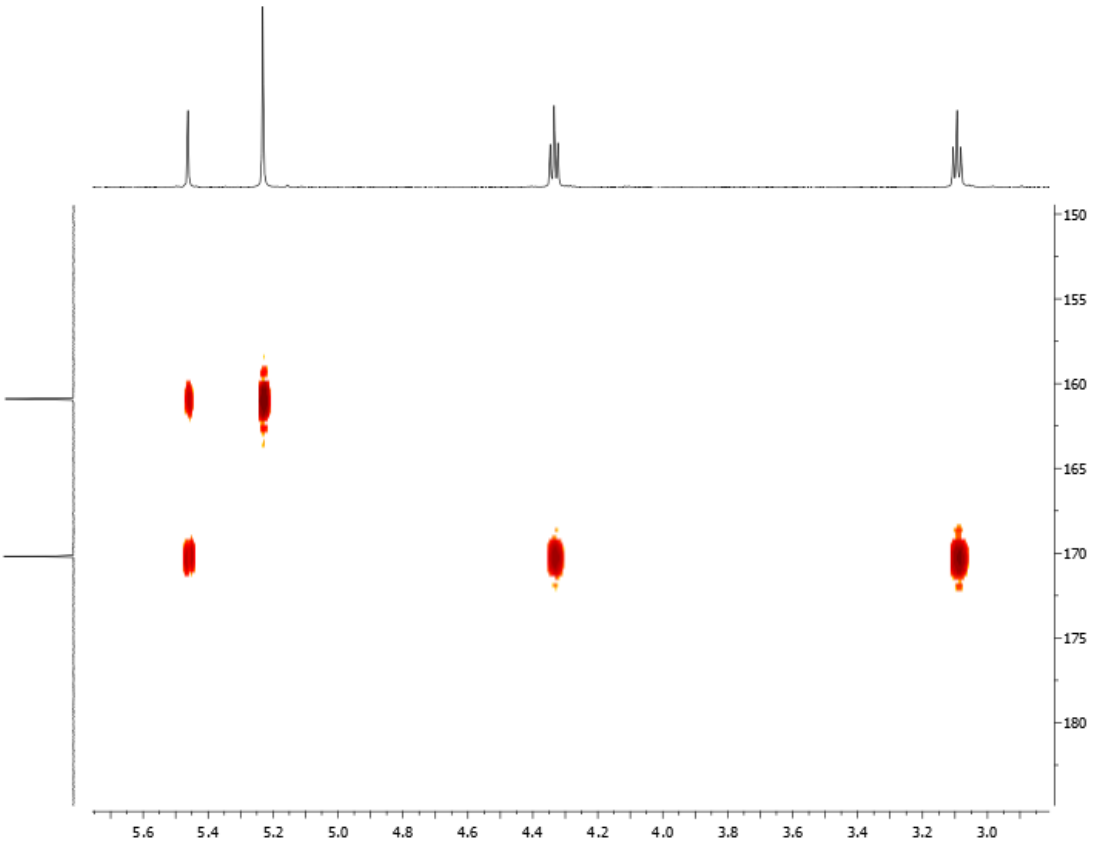


Figure S40. Expansion of the 600 MHz HMBC NMR spectrum of **6a**.

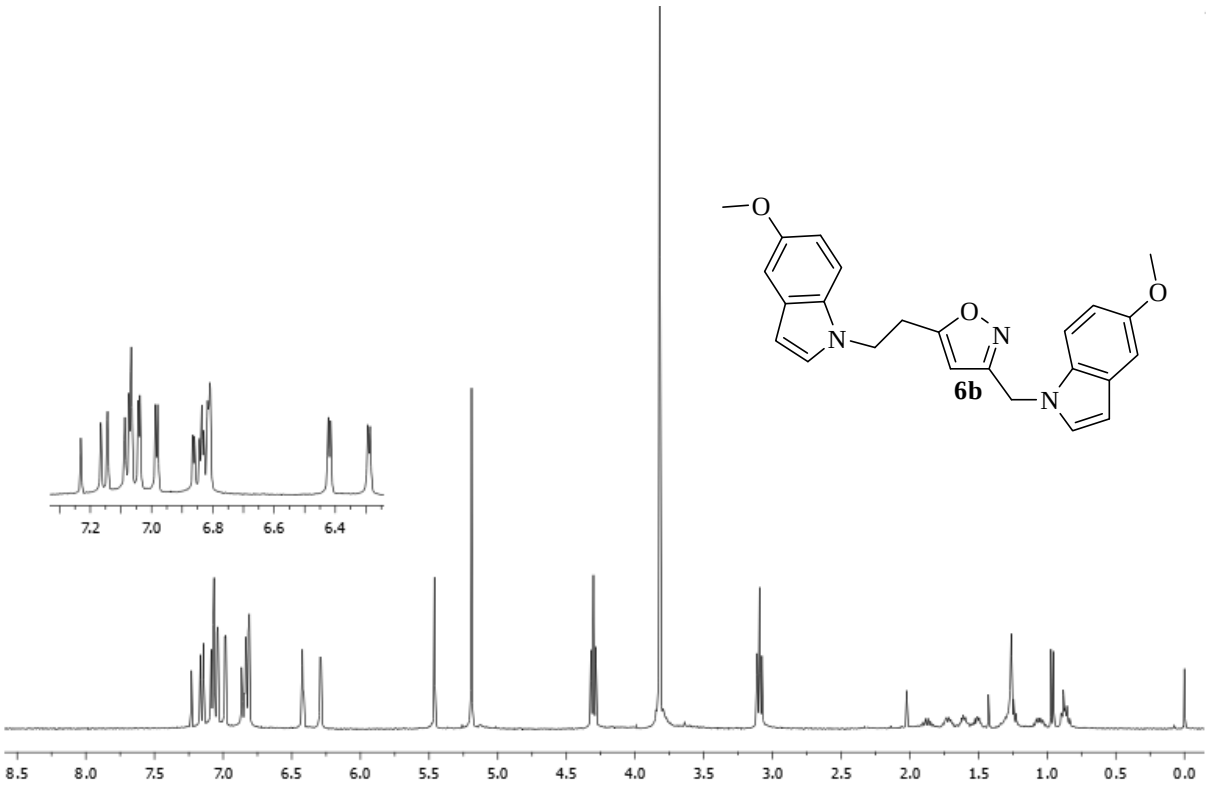


Figure S41. 400 MHz ^{1}H NMR spectrum of compound **6b** in $CDCl_3$.

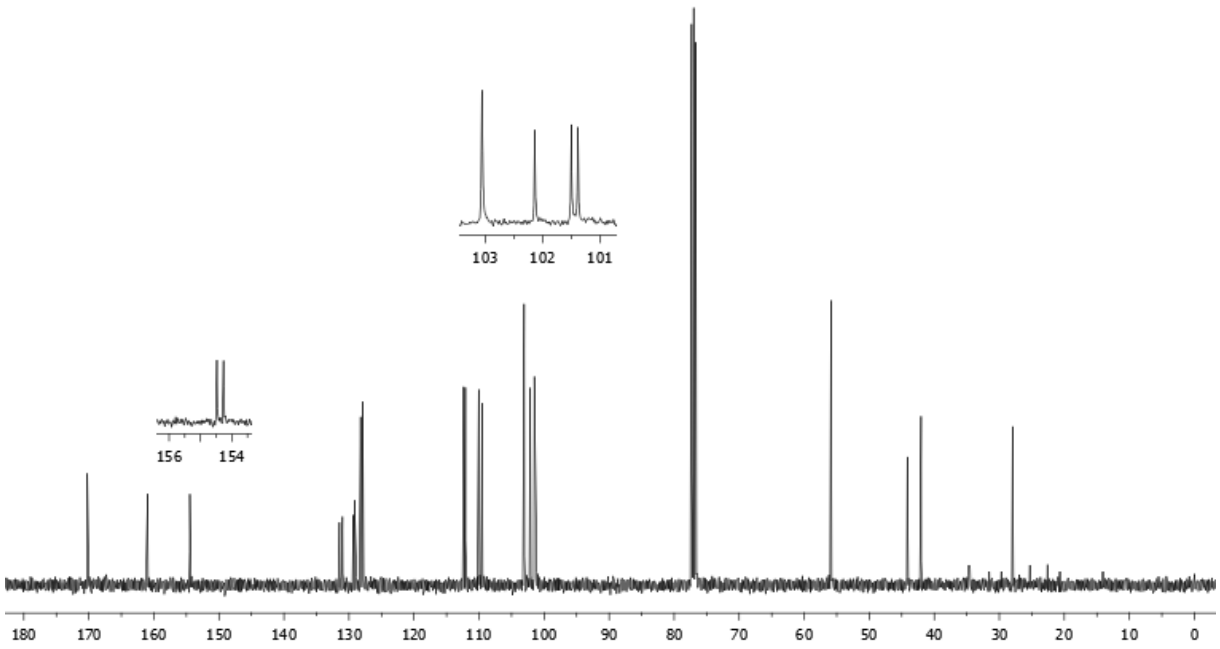


Figure S42. 100 MHz ^{13}C NMR spectrum of compound **6b** in $CDCl_3$.

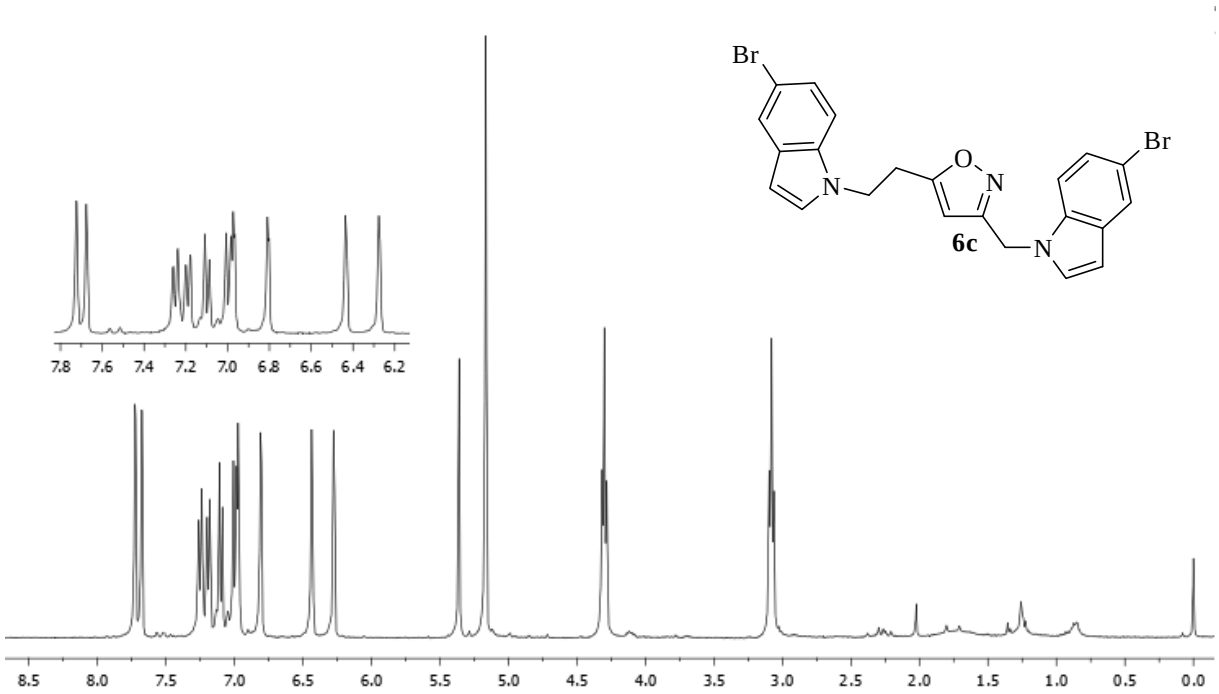


Figure S43. 400 MHz ^{1}H NMR spectrum of compound **6c** in $CDCl_3$.

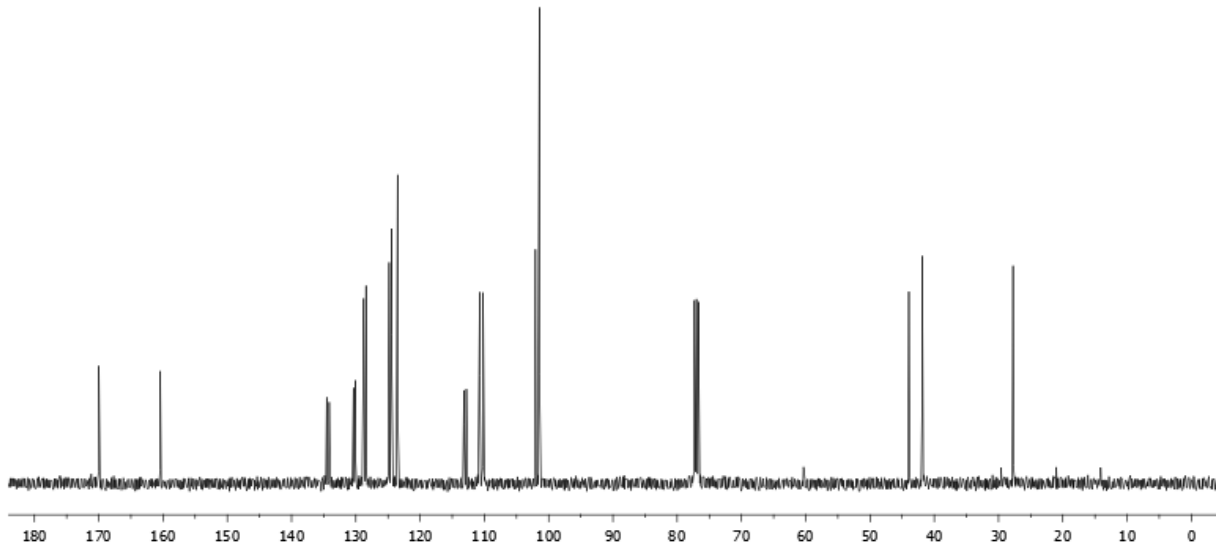


Figure S44. 100 MHz ^{13}C NMR spectrum of compound **6c** in $CDCl_3$.

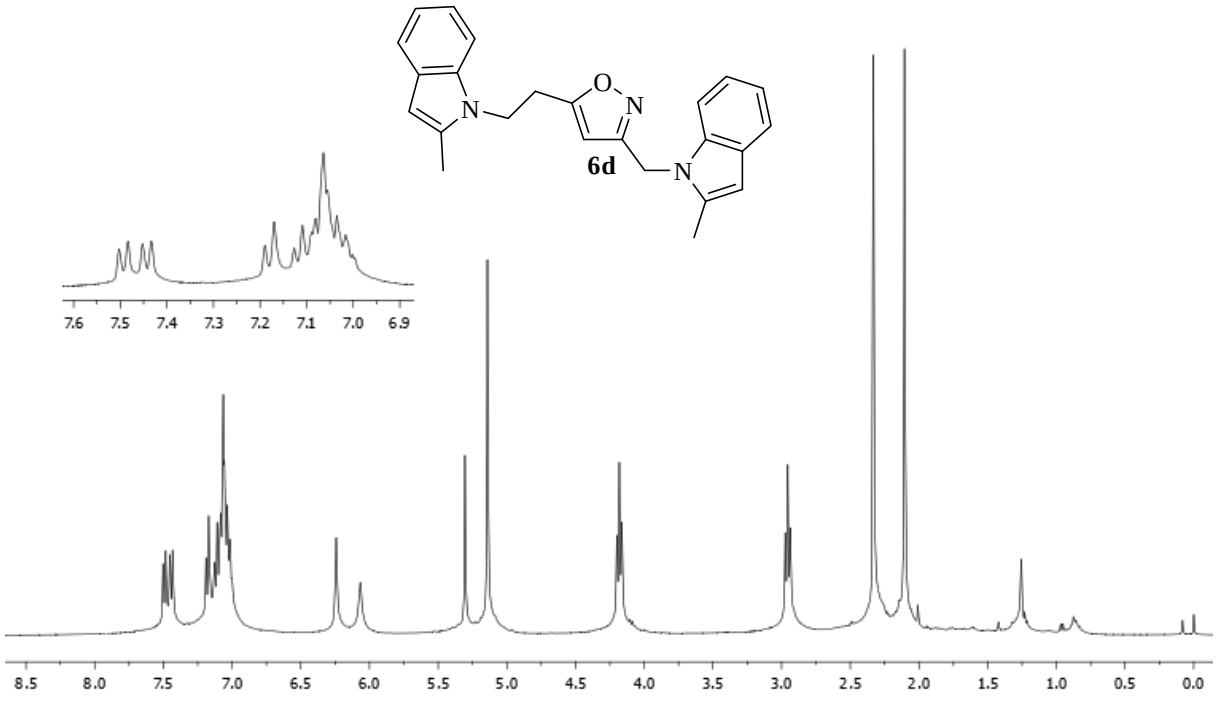


Figure S45. 400 MHz ^{1}H NMR spectrum of compound **6d** in $CDCl_3$.

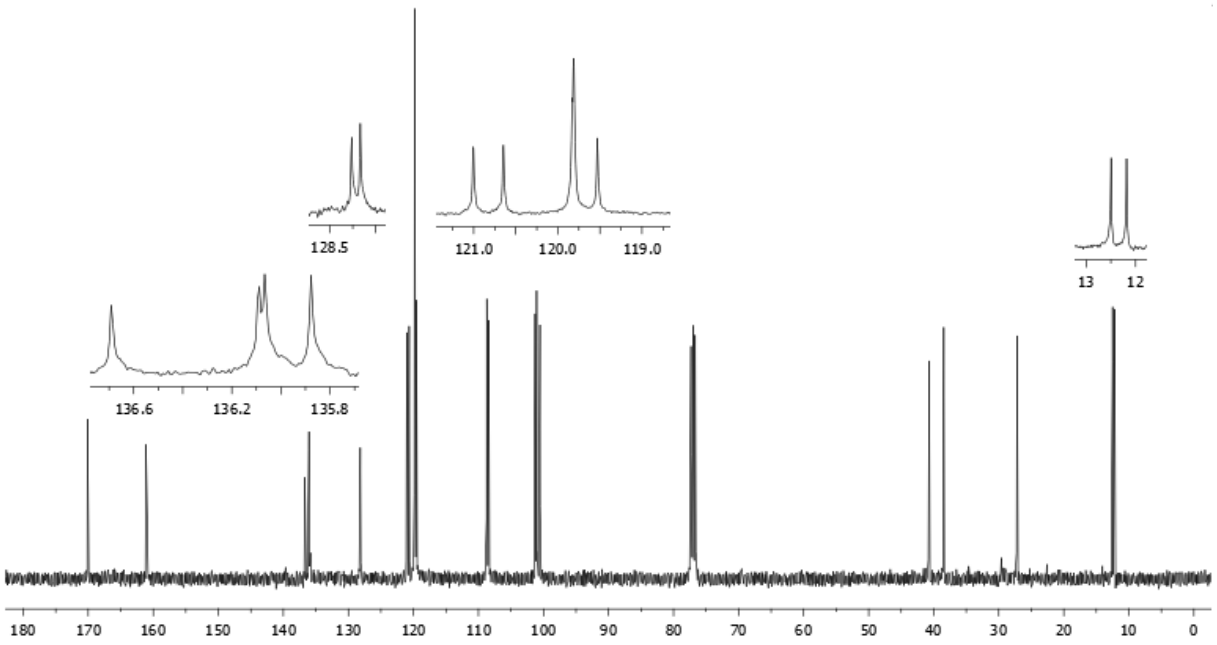


Figure S46. 100 MHz ^{13}C NMR spectrum of compound **6d** in $CDCl_3$.

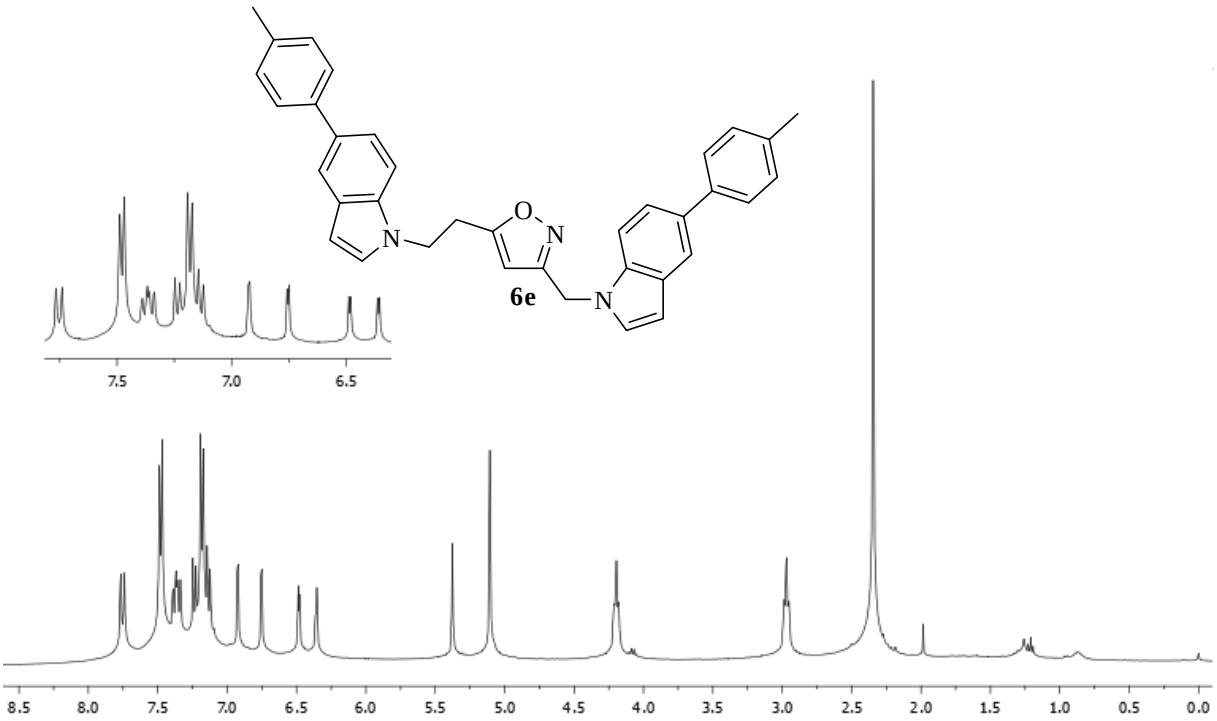


Figure S47. 400 MHz ^{1}H NMR spectrum of compound **6e** in $CDCl_3$.

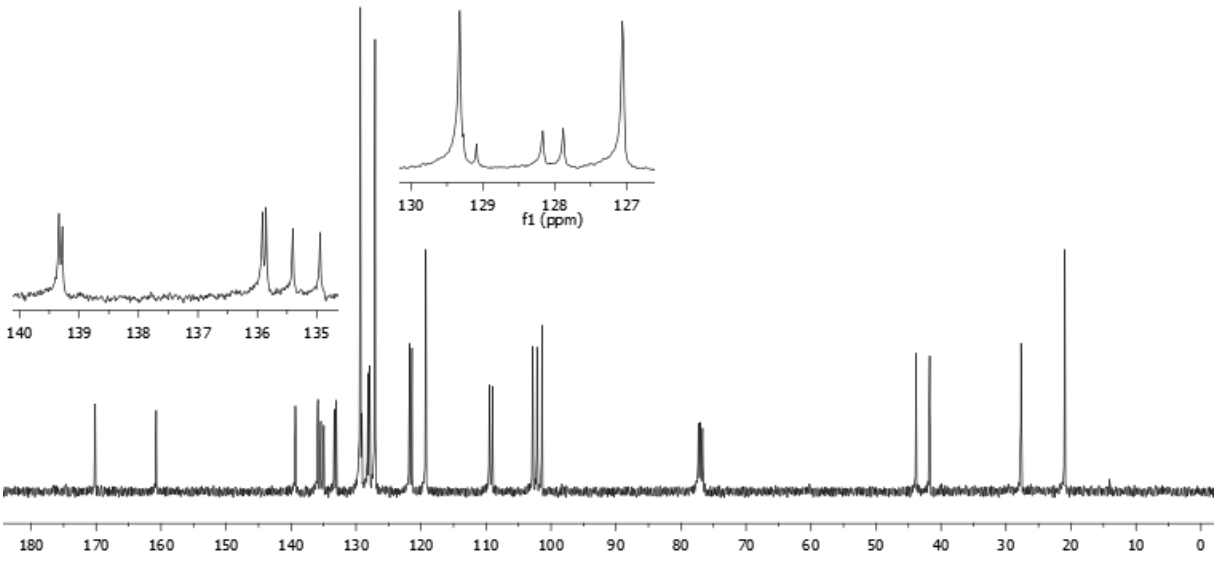


Figure S48. 100 MHz ^{13}C NMR spectrum of compound **6e** in $CDCl_3$.

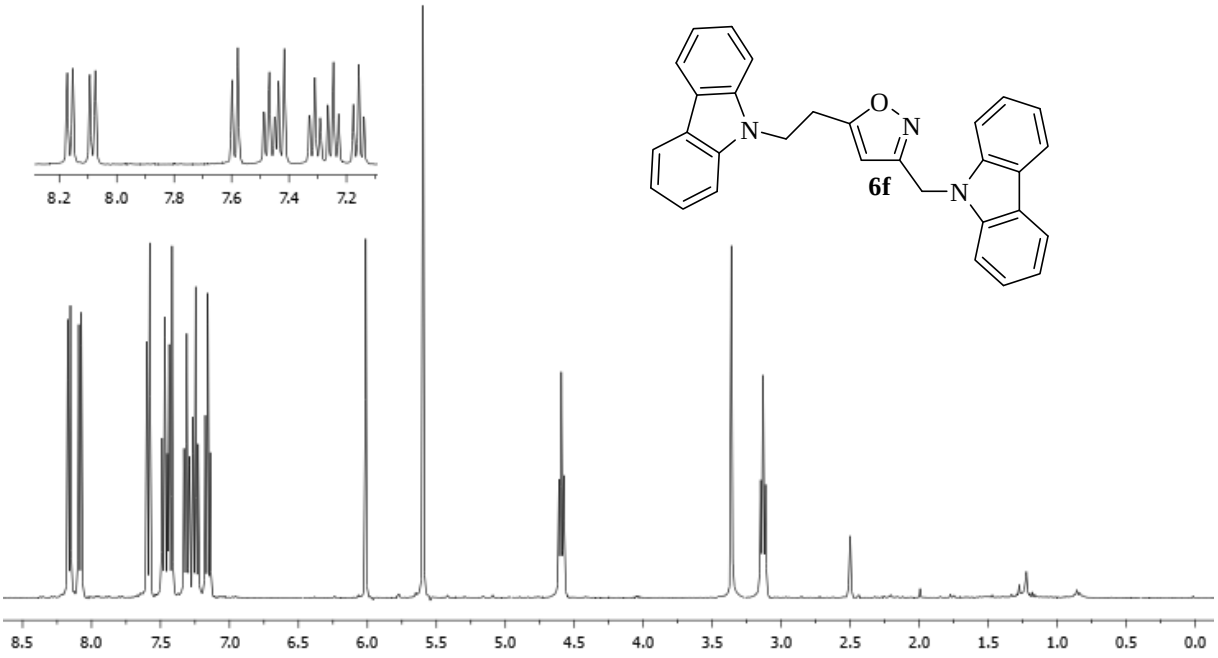


Figure S49. 400 MHz ^{1}H NMR spectrum of compound **6f** in DMSO-d_6.

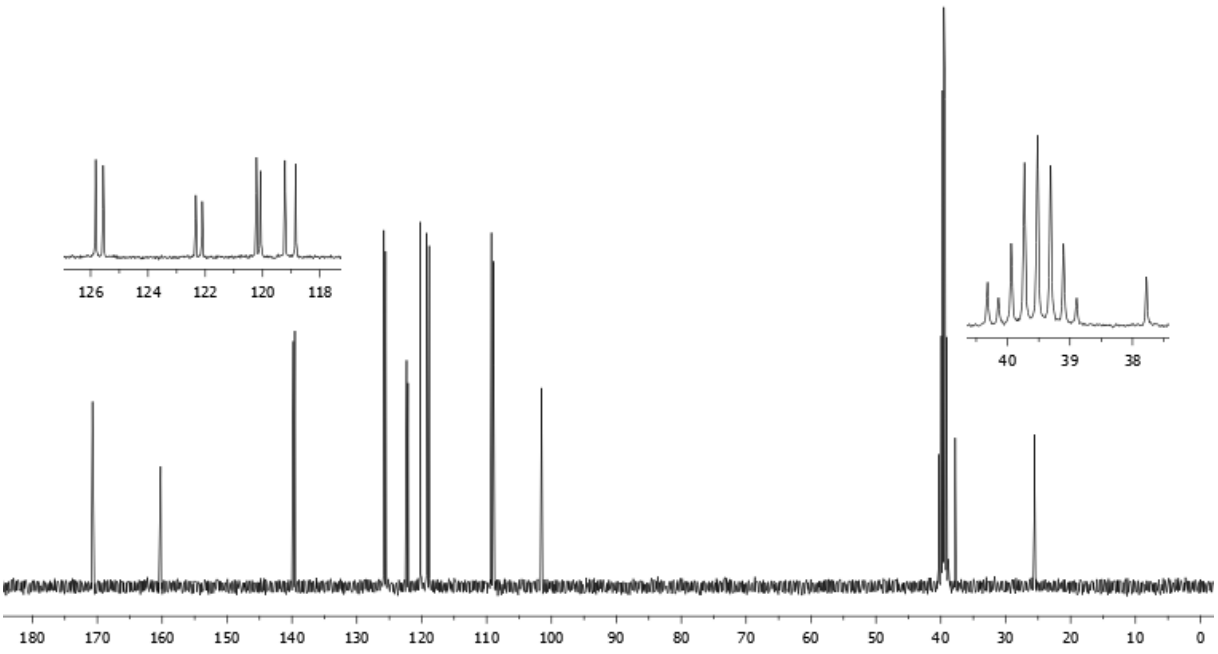


Figure S50. 100 MHz ^{13}C NMR spectrum of compound **6f** in DMSO-d_6.

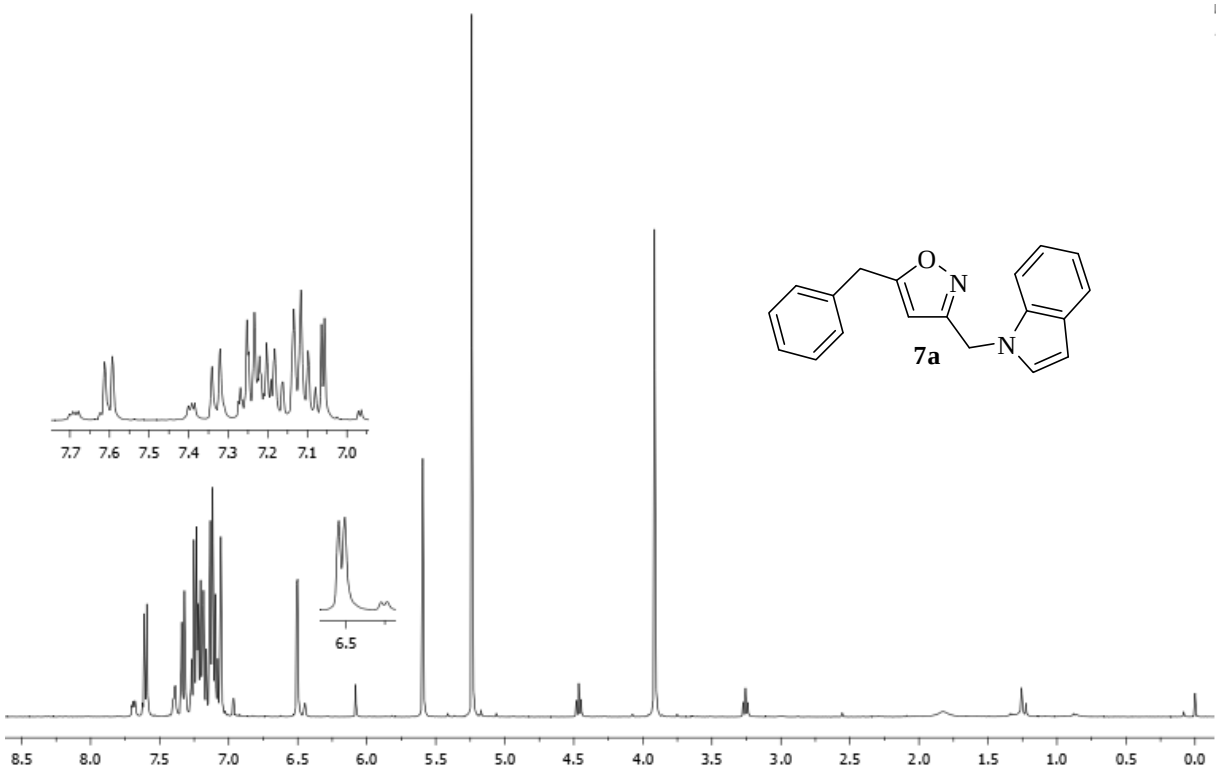


Figure S51. 400 MHz ^{1}H NMR spectrum of compound **7a** in $CDCl_3$.

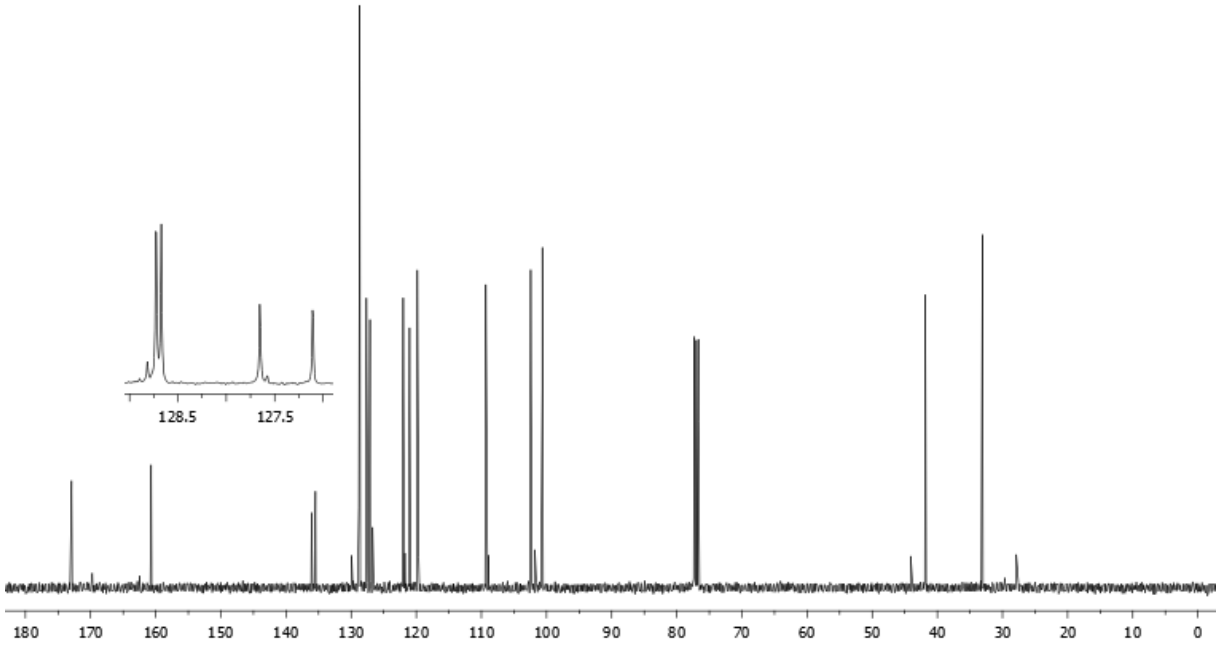


Figure S52. 100 MHz ^{13}C NMR spectrum of compound **7a** in $CDCl_3$.

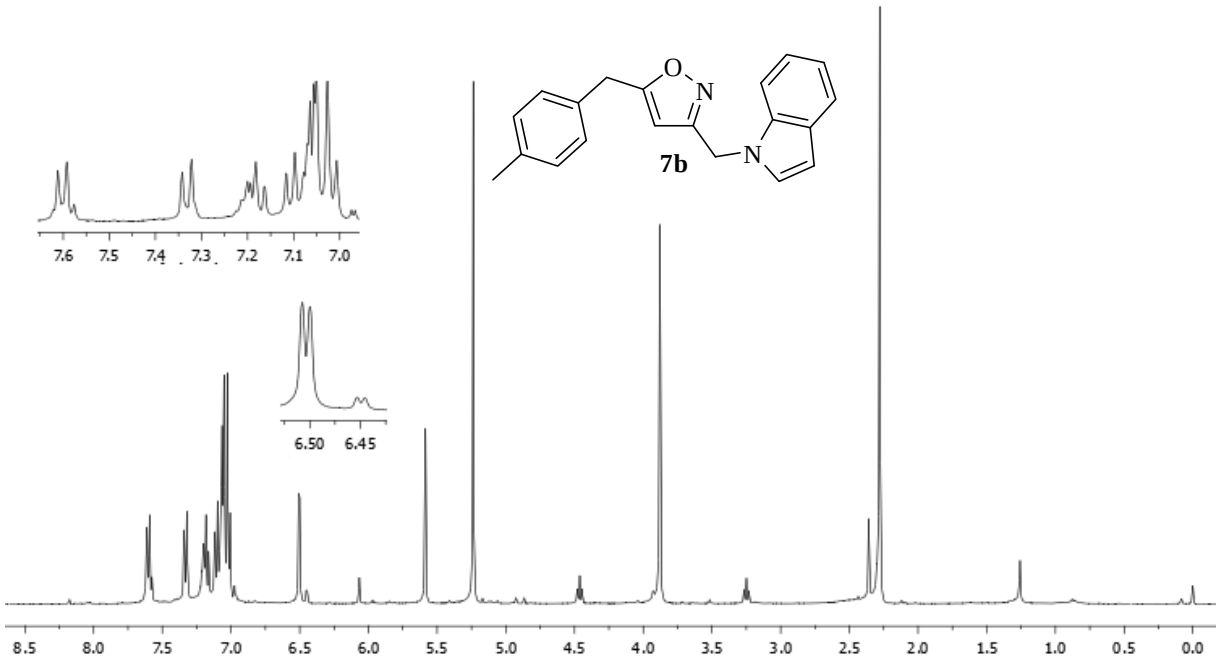


Figure S53. 400 MHz ^{1}H NMR spectrum of compound **7b** in $CDCl_3$.

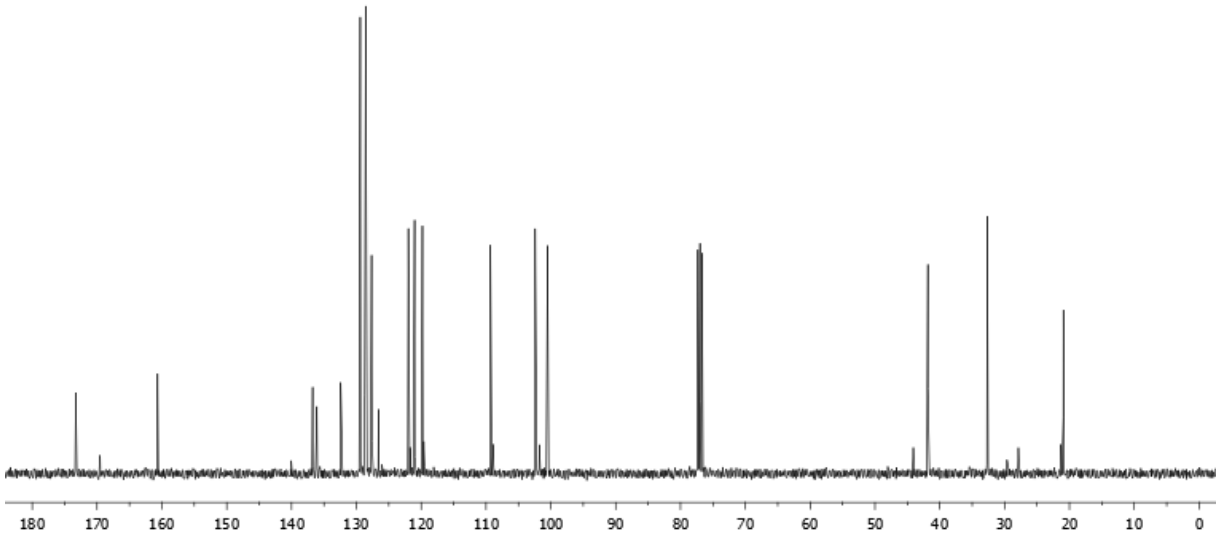


Figure S54. 100 MHz ^{13}C NMR spectrum of compound **7b** in $CDCl_3$.

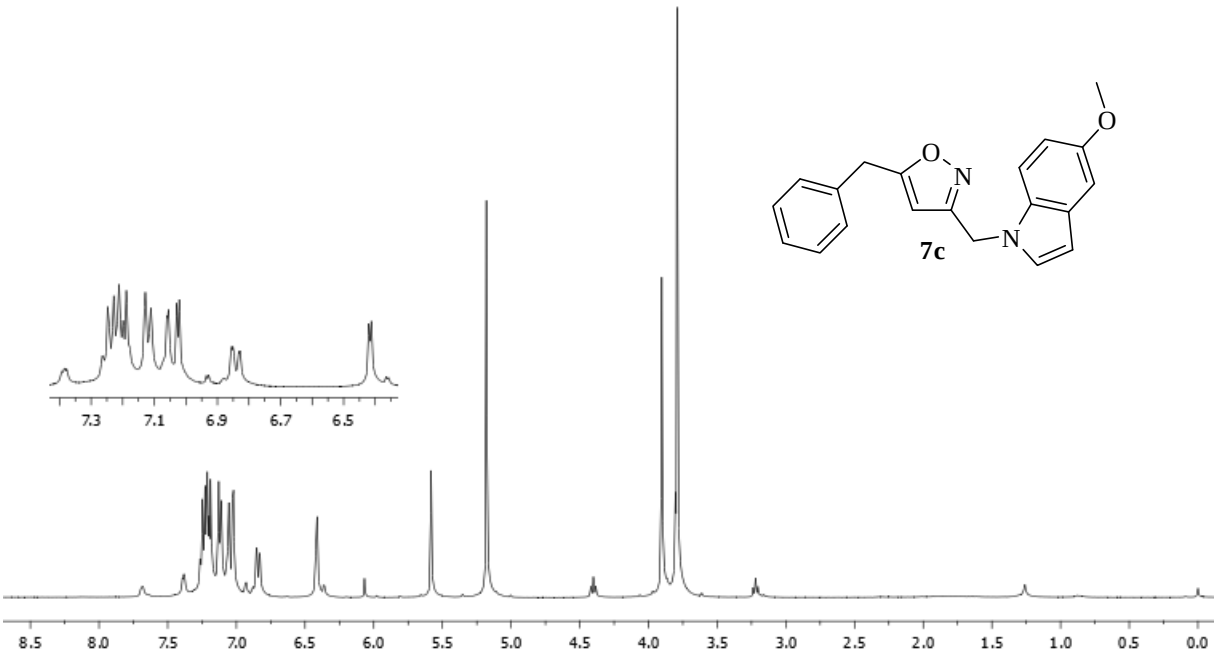


Figure S55. 400 MHz ^{1}H NMR spectrum of compound **7c** in $CDCl_3$.

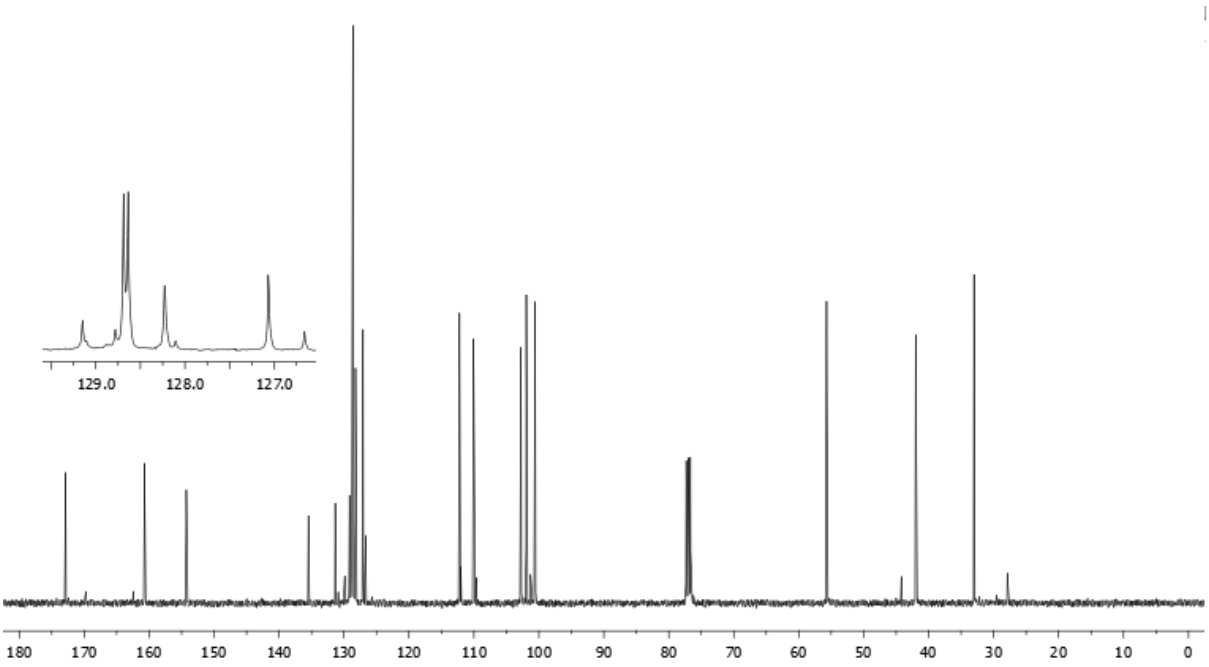


Figure S56. 100 MHz ^{13}C NMR spectrum of compound **7c** in $CDCl_3$.

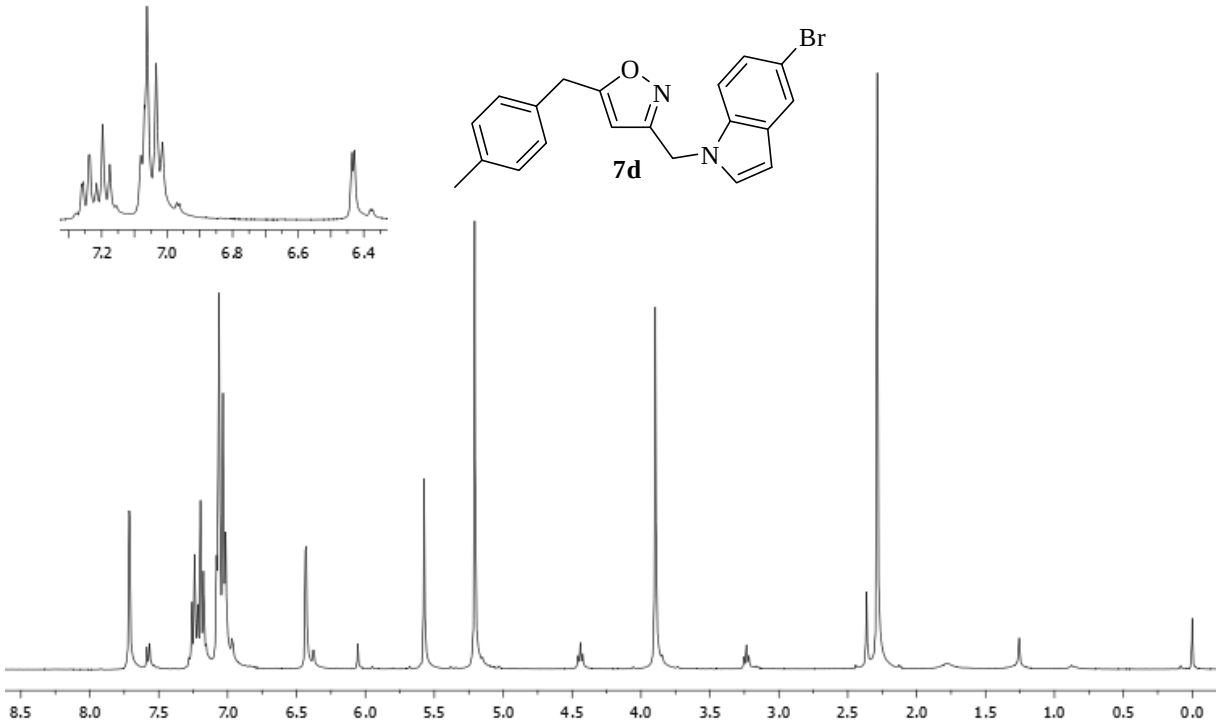


Figure S57. 400 MHz ^{1}H NMR spectrum of compound **7d** in $CDCl_3$.

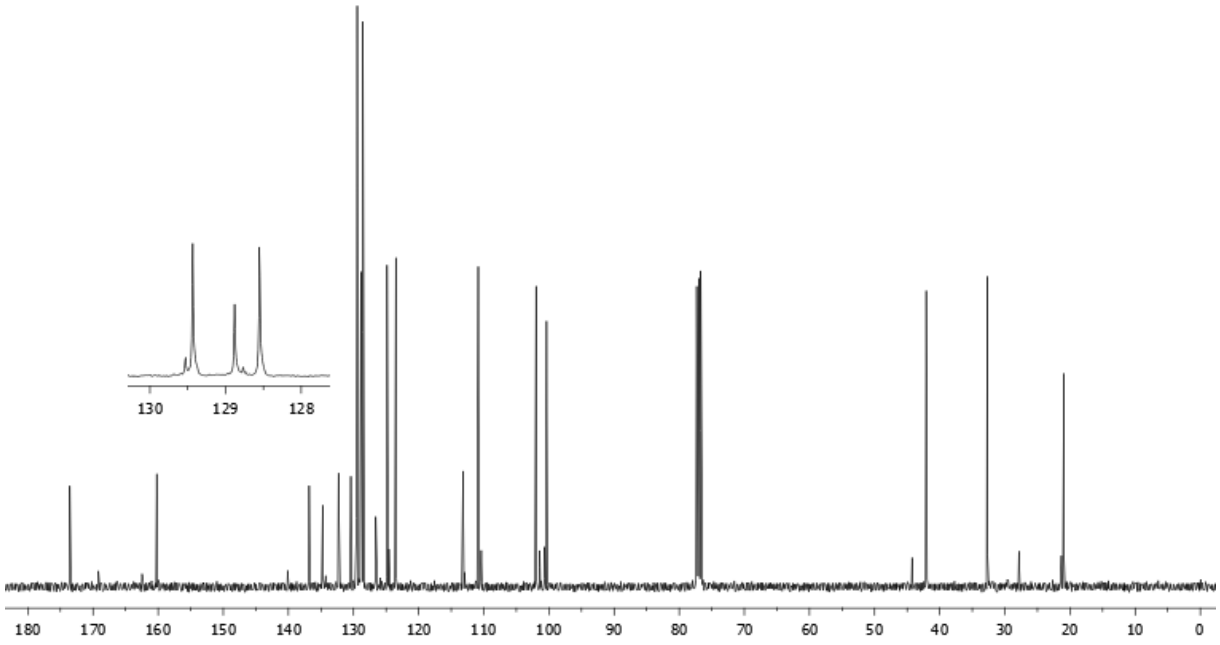


Figure S58. 100 MHz ^{13}C NMR spectrum of compound **7d** in $CDCl_3$.

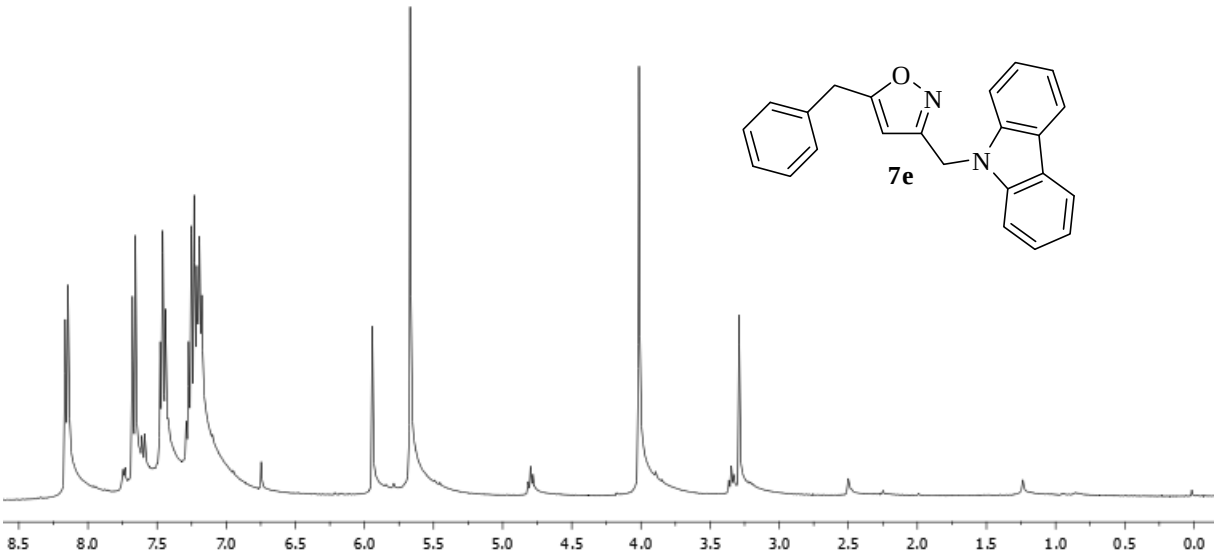


Figure S59. 400 MHz ^{1}H NMR spectrum of compound **7e** in DMSO-d_6.

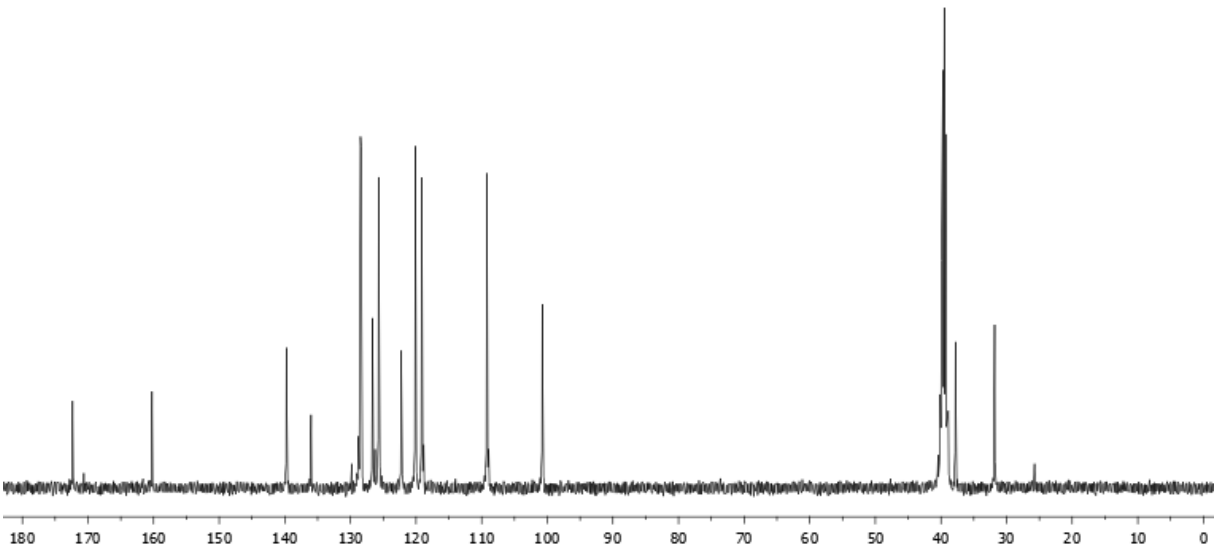


Figure S60. 100 MHz ^{13}C NMR spectrum of compound **7e** in DMSO-d_6.

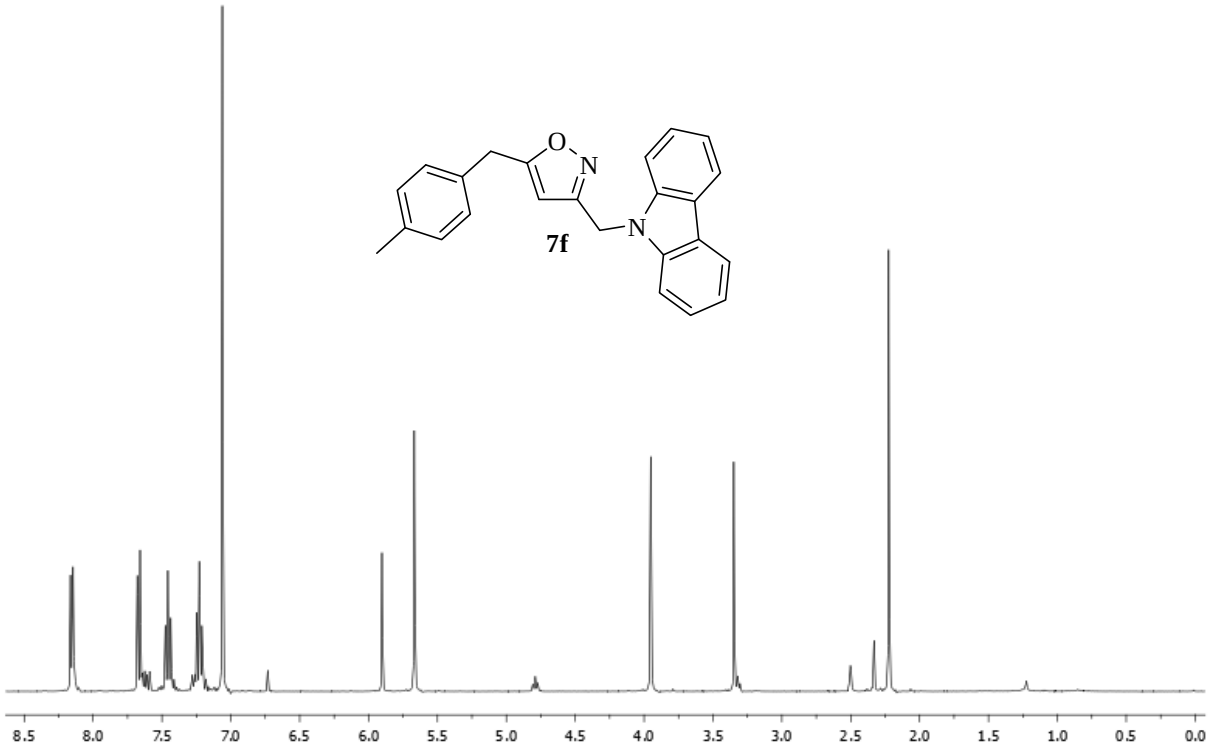


Figure S61. 400 MHz ^{1}H NMR spectrum of compound **7f** in DMSO-d_6.

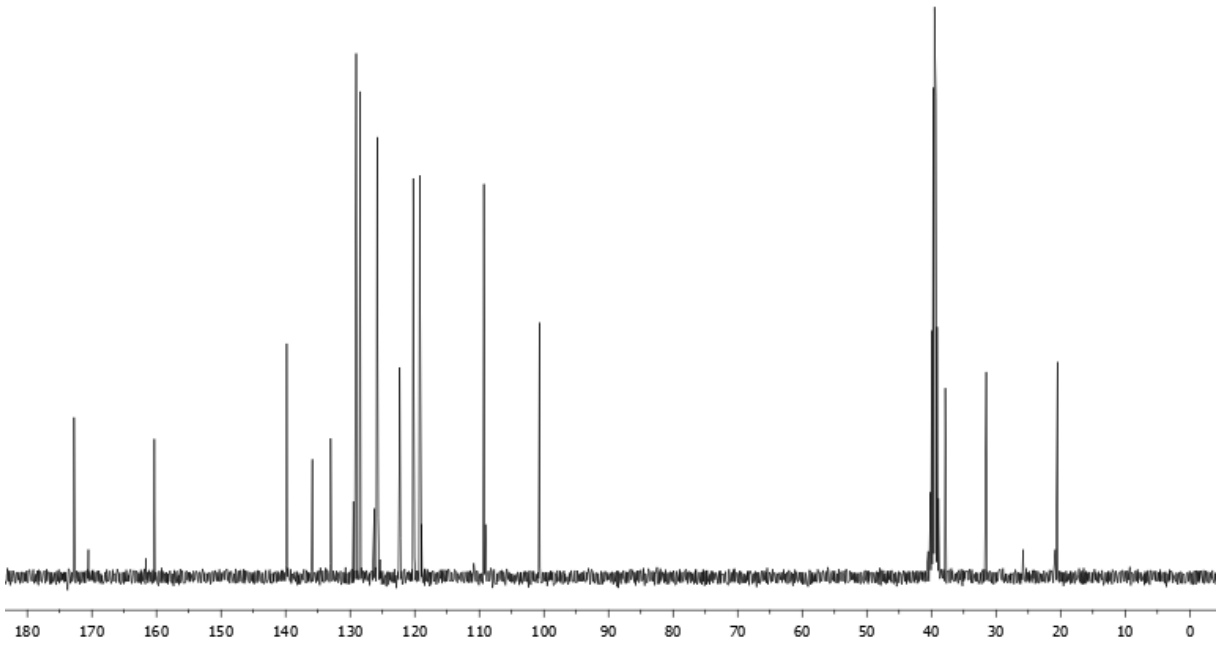


Figure S62. 100 MHz ^{13}C NMR spectrum of compound **7f** in DMSO-d_6.

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