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Supporting Information

# Generation of Complex Azabicycles and Carbobicycles from Two Simple Compounds in a Single Operation through a Metal-Free Six-Step Domino Reaction

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**Contents:**



## 1 General information

All chemicals used for synthesis were purchased from commercial sources and were used without further purification. All solvents were purified by distillation using rotary evaporation or were purchased in HPLC-grade-quality. All products were dried in high vacuum (up to $10^{-3}$ bar). Thin layer chromatography (TLC) was performed on pre-coated aluminum sheets ALUGRAM® SIL G/$UV_{254}$ (0.2 mm silica gel with fluorescent indicator, MachereyNagel & Co).$^{1}$H-NMR ($^{13}$C-NMR) spectra were recorded at room temperature on a Bruker Avance 300 or 400 or JEOL JNM GX 400 spectrometer operating at 300 MHz or 400 MHz. All chemical shifts are given in the ppm-scale and refer to the non-deuterized proportion of the solvent. ESI and APPI mass spectra were recorded on a Bruker Daltonik maXis 4G or a Bruker Daltonik micrOTOF II focus. IR spectra were recorded on a Varian IR-660 apparatus. The absorption is indicated in wave numbers [$cm^{-1}$]. Elemental Analysis (C, H, N), carried out with an Elementar vario MICRO cube machine, is within ±0.40% of the calculated values confirming a purity of >95%. X-Ray crystallography was performed on a SuperNova, Dual, Cu at zero, Atlas diffractometer.

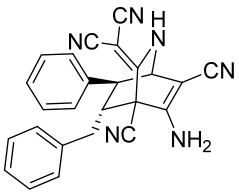
## 2 General synthetic procedure and characterizations of domino products

### 2.1 General procedure for the domino reaction

Aldehyde (0.24 mmol), malononitrile (24 mg, 0.36 mmol) and the appropriate catalyst (0.018 mmol) were dissolved in toluene ($c_{aldehyde}$ = 0.48 mol/L). The reaction mixture was stirred at room temperature until malononitrile was completely consumed. By evaporation of the solvent the reaction was stopped. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 3/1).

### 2.2 Characterization of domino products

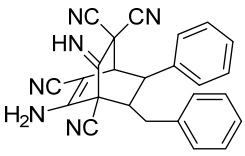
**(1*R*,4*R*,8*S*)-5-amino-8-benzyl-3-(dicyanomethylene)-7-phenyl-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile 3a** (*dr >99:1*, **3a'**:**3a''**)




Isoquinuclidine ***anti*-3a'**was obtained as white solid. Elem. anal.: Found: C, 74.64; H, 4.51; N, 20.91. Calcd for $C_{25}H_{18}N_6$: C, 74.61; H, 4.51; N, 20.88%. $^1$H-NMR (300 MHz, $CD_3OD$): $\delta$ = 2.40 (dd, $J_1$ = 12.0 Hz, $J_2$ = 12.8 Hz, 1H), 3.06 (dd, $J_1$ = 1.8 Hz, $J_2$ = 4.5 Hz, 1H), 3.15 (dt, $J_1$ = 4.1 Hz, $J_2$ = 11.7 Hz, 1H), 3.53 (dd, $J_1$ = 3.7 Hz, $J_2$ = 13.0 Hz, 1H), 4.18 (d, $J$ = 1.9 Hz, 1H), 6.75-6.78 (m, 2H), 6.97-7.14 ppm (m, 8H). $^{13}$C-NMR (100 MHz, $CD_3OD$): $\delta$ =39.9, 49.7, 50.0, 53.3, 53.9, 58.0, 77.1, 113.6, 116.5, 127.9, 128.2, 128.7, 129.5, 129.6, 130.6, 137.7, 141.1, 154.3, 163.9 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3457, 3321, 3267, 3220, 3063, 2937, 2201, 1659, 1604, 1563, 1497, 1296, 1215, 986, 730, 713, 702, 589, 540. MS (MALDI) *m/z* = 403 ([M+H]$^+$), 425 ([M+Na]$^+$), 441 ([M+K]$^+$). HRMS (ESI) calcd for ($C_{25}H_{18}N_6Na^+$): 425.1485; found: *m/z* = 425.1490 ([M+Na]$^+$).

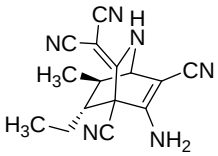
**(1*S*,4*S*)-6-amino-7-benzyl-2-imino-8-phenylbicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4a**

*(two diastereomers, dr 46:54)*



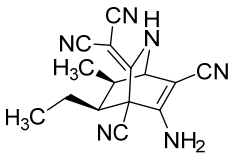

Compound **4a** (carbobicycle) was obtained as white solid. Elem. anal.: Found: C, 74.36; H, 4.62; N, 20.55. Calcd for $C_{25}H_{18}N_6$: C, 74.61; H, 4.51; N, 20.88%. $^1$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.41-2.58 (m, 2H), 3.36-3.49 (m, 6H), 3.79-3.85 (1×d, 1×s, 2×1H), 6.91-7.14 (m, 24H), 12.10-12.89 ppm (2×s, 2×1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 39.7, 43.2, 44.5, 46.5, 47.7, 48.6, 48.8, 49.0, 57.1, 58.8, 70.2, 70.8, 113.0, 113.3, 113.5, 113.9, 114.3, 116.8, 116.9, 127.8, 127.9, 128.2, 128.2, 128.6, 128.6, 129.3, 129.3, 129.3, 129.6, 130.2, 130.2, 137.2, 137.4, 141.3, 141.4, 155.3, 156.4, 160.7, 161.9 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3441, 3354, 3263, 3211, 3030, 2920, 2361, 2197, 1639, 1605, 1493, 1454, 1314, 1224, 967, 918, 843, 764, 734, 696, 557, 514. MS (MALDI) *m/z* = 425 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{25}H_{18}N_6Na^+$): 425.1485; found: *m/z* = 425.1479 ([M+Na]$^+$).

**(7*R*,8*R*)-5-amino-3-(dicyanomethylene)-8-ethyl-7-methyl-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile 3b'** (*dr38:62,* **3b'**: **3b''**)



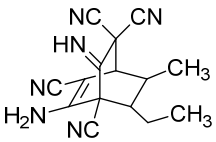
Isoquinuclidine ***anti*-3b'** was obtained as white solid. $^{1}$H-NMR (400 MHz, $CD_3OD$): $\delta$ = 1.04 (t, $J$ = 7.3 Hz, 3H), 1.06 (d, $J$ = 6.8 Hz, 3H), 1.13-1.21 (m, 1H), 1.72 (ddd, $J_1$ = 3.2 Hz, $J_2$ = 4.0 Hz, $J_3$ = 11.4 Hz), 1.84-1.91 (m, 1H), 1.98-2.08 (m, 1H), 4.18 ppm (d, $J$ = 2.0 Hz, 1H).$^{13}$C-NMR (100 MHz, $CD_3OD$): $\delta$ = 11.5, 20.4, 26.9, 42.5, 48.0, 51.5, 53.0, 57.5, 76.8, 113.9, 115.6, 115.6, 116.7, 154.2, 164.0 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3404, 3335, 3287, 3268, 3209, 3135, 2972, 2934, 2918, 2892, 2879, 2223, 2195, 1649, 1611, 1582, 1455, 1437, 1403, 1293, 1229, 1206, 1104, 1029, 976, 933, 872, 788, 721. MS (MALDI) *m/z* = 301 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{15}H_{14}N_6Na^+$): 301.1172; found: *m/z* = 301.1177 ([M+Na]$^+$).

**(7*R*,8*S*)-5-amino-3-(dicyanomethylene)-8-ethyl-7-methyl-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile 3b''**



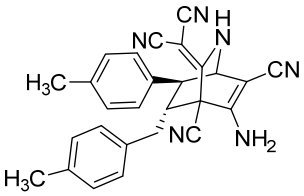
Isoquinuclidine ***syn*-3b''** was obtained as white solid. $^{1}$H-NMR (300 MHz, $CD_3OD$): $\delta$ = 1.06-1.13 (m, 6H), 1.46-1.61 (m, 1H), 1.82-1.95 (m, 1H), 2.31 (ddd, $J_1$ = 2.4 Hz, $J_2$ = 10.1 Hz, $J_3$ = 10.3 Hz), 2.38-2.49 (m, 1H), 4.20 ppm (d, $J$ = 1.8 Hz, 1H). $^{13}$C-NMR (100 MHz, $CD_3OD$): $\delta$ = 14.6, 15.1, 22.7, 38.7, 48.1, 50.3, 54.2, 58.4, 76.9, 114.8, 116.6, 156.5, 162.5 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3448, 3359, 3290, 3008, 2938, 2187, 1651, 1605, 1564, 1461, 1397, 1385, 1296, 1206, 1039, 972, 752, 588, 519, 433. HRMS (APPI) calcd for ($C_{15}H_{15}N_6^+$): 279.1353; found: *m/z* = 279.1350 ([M+H]$^+$).

**(1*S*,4*S*)-6-amino-7-ethyl-2-imino-8-methylbicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4b**



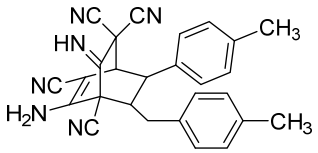
Compound **4b** (carbobicycle) was obtained as white solid. $^{1}$H-NMR (400 MHz, $(CD_3)_2CO$): $\delta$ = 1.06-1.09 (m, 1H), 1.11-1.17 (m, 7H), 1.23-1.25 (m, 7H), 1.48 (dd, $J_1$ = 1.6 Hz, $J_2$ = 7.2 Hz, 2H), 1.84-1.99 (m, 5H), 2.10-2.30 (m, 3H), 3.68-3.87 (2×d, 2×s, 4×1H), 11.59-12.60 ppm (4×s, 4×1H). MS (MALDI) *m/z* = 301 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{15}H_{14}N_6Na^+$): 301.1172; found: *m/z* = 301.1175 ([M+Na]$^+$).

**(1*R*,4*R*,8*S*)-5-amino-3-(dicyanomethylene)-8-(4-methylbenzyl)-7-(*p*-tolyl)-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile 3c** *(dr >99:1)*



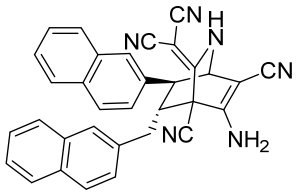
Isoquinuclidine **3c** was obtained as white solid. $^1$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.15 (s, 3H), 2.20 (s, 3H), 2.50 (t, $J$ = 12.3 Hz, 1H), 3.26(dd,$J_1$ = 1.7 Hz, $J_2$ = 4.2 Hz,1H), 3.35-3.42 (m, 1H), 3.50 (dd, $J_1$ = 3.2 Hz, $J_2$ = 13.0 Hz, 1H), 4.39 (d, $J$ = 1.5 Hz, 1H), 6.85-6.96 (m, 8H), 7.10 (d, $J$ = 7.8 Hz, 2H), 9.28 ppm (brs, 1H). $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$): $\delta$ = 20.6, 21.1, 39.9, 50.7, 53.1, 57.1, 57.3, 58.9, 78.3, 113.3, 113.6, 115.3, 116.0, 127.9, 129.2, 129.9, 130.5, 130.9, 134.6, 137.0, 137.3, 138.0, 153.2, 163.1 ppm. MS (MALDI) *m*/*z* = 453 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{27}H_{22}N_6Na$): 453.1798; found: *m/z* = 453.1799 ([M+Na]$^+$).

**6-amino-2-imino-7-(4-methylbenzyl)-8-(*p*-tolyl)bicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4c** *(two diastereomers, dr 47:53)*



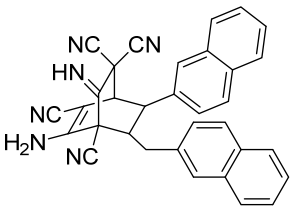
Compound **4c** (carbobicycle) was obtained as white solid. $^1$H-NMR (300 MHz, $(CD_3)_2CO$):$\delta$ = 2.17 (2×s, 6H), 2.22 (2×s, 6H), 2.38-2.53 (m, 2H), 3.29-3.42 (m, 6H), 3.74-3.81 (1×d, 1×s, 2×1H), 6.80-6.83 (m, 4H), 6.89-7.03 (m, 16H), 12.06-12.85 ppm (2×s, 2×1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 20.7, 21.9, 22.1, 23.8, 40.3, 44.1, 45.4, 47.1, 48.8, 49.7, 49.9, 50.1, 58.1, 59.8, 71.3, 71.9, 114.1, 114.3, 114.5, 114.9, 115.0, 115.3, 117.8, 117.9, 129.5, 129.5, 130.9, 130.9, 130.9, 130.9, 131.1, 131.1, 135.1, 135.4, 138.2, 138.4, 138.7, 138.8, 139.4, 139.5, 156.2, 157.3, 161.8, 162.9 ppm. MS (MALDI) *m*/*z* = 453 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{27}H_{22}N_6Na$):453.1798; found: *m/z* = 453.1794 ([M+Na]$^+$).

**(1*R*,4*R*,8*S*)-5-amino-3-(dicyanomethylene)-7-(naphthalen-2-yl)-8-(naphthalen-2-ylmethyl)-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile 3d** *(dr >99:1)*



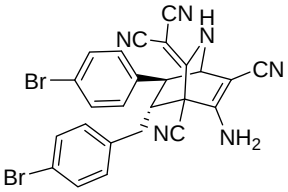
Isoquinuclidine **3d** was obtained as white solid. $^1$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.84 (dd, $J_1$ = 12.7 Hz, $J_2$ = 13.2 Hz, 1H), 3.60-3.61 (m, 1H,) 3.76-3.81 (m, 2H), 4.54 (d, $J$ = 1.8 Hz, 1H), 6.99 (s, 2H), 7.07-7.11 (m, 1H), 7.34-7.39 (m, 5H), 7.45-7.48 (m, 2H), 7.51-7.61 (m, 3H), 7.67-7.69 (m, 2H), 7.83 (s, 1H), 9.34 ppm (brs, 1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 40.9, 49.6, 51.9, 54.0, 54.4, 58.7, 79.4, 114.3, 115.7, 116.2, 116.9, 127.5, 127.8, 127.9, 127.9, 128.4, 129.2, 129.2, 129.4, 129.7, 129.8, 130.3, 134.3, 134.4, 135.2, 135.4, 136.2, 139.3, 154.3, 164.1 ppm. MS (MALDI) *m*/*z* = 525 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{33}H_{22}N_6Na$): 525.1798; found: *m/z* = 525.1806 ([M+Na]$^+$).

**(1*S*,4*S*)-6-amino-2-imino-8-(naphthalen-2-yl)-7-(naphthalen-2-lmethyl)bicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4d** *(two diastereomers, dr 45:55)*



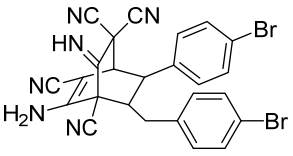
Compound **4d** (carbobicycle) was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$):$\delta$ = 2.69-2.80 (m, 2H), 3.57-3.69 (m, 6H), 3.92-3.99 (1×d, 1×s, 2×1H), 7.06-7.27 (m, 7H), 7.33-7.44 (m, 13H), 7.55-7.73 (m, 11H), 12.19-12.96 ppm (2×s, 2×1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 41.0, 41.0, 43.8, 44.2, 44.3, 45.6, 47.8, 47.8, 48.7, 49.5, 49.5, 49.6, 58.2, 59.9, 71.3, 71.9, 114.0, 114.4, 114.5, 114.9, 115.0, 115.4, 117.8, 117.9, 127.2, 127.3, 127.6, 127.7, 127.9, 128.0, 128.0, 128.0, 128.1, 128.9, 129.0, 129.3, 129.3, 129.3, 129.4, 129.6, 129.6, 129.9, 130.0, 130.0, 130.1, 130.1, 130.2, 130.9, 134.4, 134.4, 135.0, 135.3, 135.8, 136.1, 139.5, 139.6, 156.4, 157.5, 161.8, 162.9 ppm. MS (MALDI) *m/z* = 525 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{33}H_{22}N_6Na$): 525.1798; found: *m/z* = 525. 1793 ([M+Na]$^+$).

**(1*R*,4*R*,8*S*)-5-amino-8-(4-bromobenzyl)-7-(4-bromophenyl)-3-(dicyanomethylene)-2-azabicycle [2.2.2]oct-5-ene-4,6-dicarbonitrile 3e** *(dr >99:1)*



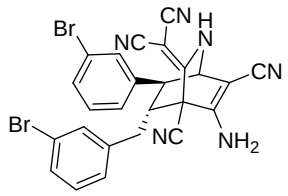
Isoquinuclidine **3e** was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.57 (t, *J* = 12.0 Hz,1H), 3.30 (dd, $J_1$ = 1.5 Hz, $J_2$ = 4.6 Hz, 1H), 3.46-3.56 (m, 2H), 4.43 (d, *J* = 1.8 Hz, 1H), 6.91-6.99 (m, 4H), 7.21-7.28 (m, 4H), 7.33(m, 2H), 9.30 ppm (brs, 1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 39.7, 49.3, 52.1, 53.6, 53.6, 58.3, 79.4, 114.0, 114.3, 116.7, 119.7, 122.2, 122.5, 131.8, 133.2, 133.2, 133.6, 138.0, 141.2, 153.8, 164.0 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3434, 3335, 3203, 2922, 2201, 1649, 1569, 1488, 1405, 1295, 1217, 1072, 1009, 819, 702, 662, 515. MS (MALDI) *m/z*= 583 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{25}H_{16}Br_2N_6Na$): 580.9695, found: *m/z* = 580.9708 ([M+Na]$^+$).

**(1*S*,4*S*)-6-amino-7-(4-bromobenzyl)-8-(4-bromophenyl)-2-iminobicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4e** *(two diastereomers, dr 47:53)*



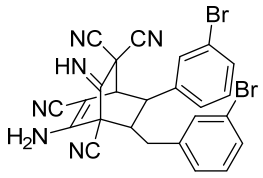
Compound **4e** (carbobicycle) was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.42-2.57 (m, 2H), 3.35-3.47 (m, 6H), 3.80-3.87 (1×d, 1×s, 2×1H), 6.84-6.94 (m, 6H), 6.97-7.07 (m, 10H), 7.16-7.22 (m, 4H), 12.12-12.90 ppm (2×s, 2×1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 39.8, 39.9, 43.1, 45.5, 47.1, 47.2, 48.4, 49.2, 49.6, 49.8, 58.0, 59.6, 70.5, 71.1, 113.8, 114.0, 114.3, 114.6, 114.7, 115.2, 117.7, 122.5, 122.5, 122.9, 122.9, 123.0, 131.7, 131.7, 132.5, 133.2, 133.3, 133.3, 133.4, 133.4, 133.5, 137.6, 137.8, 141.5, 141.6, 156.5, 157.6, 161.4, 162.5ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3437, 3335, 3206, 2922, 2202, 1649, 1569, 1488, 1405, 1294, 1216, 1072, 1009, 819, 702, 662, 544. MS (MALDI) *m/z* = 583 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{25}H_{16}Br_2N_6Na$): 580.9695; found: *m/z* = 580.9710 ([M+Na]$^+$).

**(1*R*,4*R*,8*S*)-5-amino-8-(3-bromobenzyl)-7-(3-bromophenyl)-3-(dicyanomethylene)-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile 3f** *(dr >99:1)*



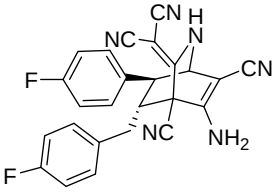
Isoquinuclidine **3f** was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.57 (t, $J$ = 13.3 Hz, 1H), 3.30 (dd, $J_1$ = 1.6 Hz, $J_2$ = 4.8 Hz, 1H), 3.52-3.61 (m, 2H),4.48 (d, $J$ = 1.8 Hz, 1H), 6.91 (s, 2H), 6.99-7.13 (m, 4H), 7.22-7.31 (m, 3H), 7.49 (s, 1H) 9.34 ppm (brs, 1H).$^{13}$C-NMR (75 MHz, $(CD_3)_2CO$): $\delta$ = 38.9, 52.2, 53.6, 54.3, 57.2, 59.0, 79.7, 113.8, 116.4, 116.8, 123.7, 123.7, 123.8, 131.2, 131.4, 131.5, 131.7, 132.0, 132.3, 132.4, 132.6, 134.4, 141.1, 144.3, 153.6, 163.9 ppm. MS (MALDI) *m/z* = 583 ([M+Na]$^+$). HRMS (APPI) calcd for ($C_{25}H_{17}Br_2N_6$): 558.9876; found: *m/z* = 558.9871 ([M+H]$^+$).

**(1*S*,4*S*)-6-amino-7-(3-bromobenzyl)-8-(3-bromophenyl)-2-iminobicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4f** *(two diastereomers, dr 46:54)*



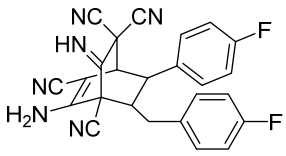
Compound **4f** (carbobicycle) was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.40-2.57 (m, 2H), 3.27-3.29 (m, 2H), 3.41-3.56 (m, 4H), 3.89-3.96 (1×d, 1×s, 2×1H), 7.05-7.37 (m, 22H), 12.16-12.93 ppm (2×s, 2×1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 39.8, 39.9, 44.4, 45.7, 47.4, 48.3, 49.1, 49.6, 49.7, 70.4, 71.0, 113.8, 114.0, 114.3, 114.5, 114.7, 115.1, 117.7, 117.8, 123.9, 123.9, 124.0, 124.1, 128.4, 130.3, 130.3, 132.0, 132.1, 132.2, 132.2, 132.2, 132.5, 132.5, 132.8, 132.9, 134.2, 134.3, 140.8, 141.1, 144.6, 144.7, 156.6, 157.7, 161.4, 162.5 ppm. MS (MALDI) *m/z* = 583 ([M+Na]$^+$). HRMS (APPI) calcd for ($C_{25}H_{17}Br_2N_6$): 558.9876; found: *m/z* = 558.9871 ([M+H]$^+$).

**(1*R*,4*R*,8*S*)-5-amino-3-(dicyanomethylene)-8-(4-fluorobenzyl)-7-(4-fluorophenyl)-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile3g** *(dr >99:1)*



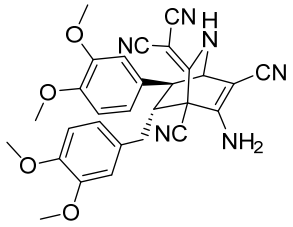
Isoquinuclidine **3g** was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.56 (t, $J$ = 12.0 Hz, 1H), 3.29 (dd, $J_1$ = 1.6 Hz, $J_2$ = 4.7 Hz, 1H), 3.40-3.47 (m, 1H), 3.55 (dd, $J_1$ = 3.6 Hz, $J_2$ = 12.8 Hz, 1H), 4.40 (d, $J$ = 1.8 Hz, 1H), 6.80-6.92 (m, 6H), 6.99-7.04 (m, 2H), 7.25-7.30 (m, 2H), 9.30 ppm (brs, 1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 39.5, 49.9, 52.0, 53.5, 53.7, 53.7, 58.5, 79.6, 79.6, 114.0, 114.4, 116.2, 116.2, 116.7 (d, $J_{C\text{-}F}$ = 4.9 Hz), 116.8, 116.9 (d, $J_{C\text{-}F}$ = 4.8 Hz), 131.6 (d, $J_{C\text{-}F}$ = 8.2 Hz), 133.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 134.7 (d, $J_{C\text{-}F}$ = 3.2 Hz), 138.0 (d, $J_{C\text{-}F}$ = 3.2 Hz), 153.9 (d, $J_{C\text{-}F}$ = 6.6 Hz), 162.5, 164.2, 164.9 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3440, 3342, 3225, 2923, 2202, 2026, 1987, 1649, 1570, 1511, 1440, 1296, 1224, 1160, 1101, 1013, 831, 762, 689, 533. MS (MALDI) *m/z* = 461 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{25}H_{16}F_2N_6Na$): 461.1297; found: *m/z* = 461.1297 ([M+Na]$^+$).

**(1*S*,4*S*)-6-amino-7-(4-fluorobenzyl)-8-(4-fluorophenyl)-2-iminobicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4g** *(two diastereomers, dr 47:53)*



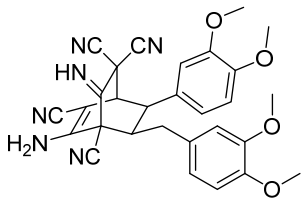

Compound **4g** (carbobicycle) was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.40-2.56 (m, 2H), 3.33-3.46 (m, 6H), 3.79-3.86 (1×d, 1×s, 2×1H), 6.83-7.10 (m, 16H), 7.15-7.21 (m, 4H), 12.12-12.90 ppm (2×s, 2×1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 39.6, 44.2, 45.5, 46.9, 48.6, 49.5, 50.1, 50.2, 59.6, 70.7, 71.3, 113.8, 114.0, 114.6, 114.7, 115.1, 116.8 (q, $J_{1C-F}$ = 2.4 Hz, $J_{2C-F}$ = 3.8 Hz), 117.0 (q, $J_{1C-F}$ = 2.4 Hz, $J_{2C-F}$ = 3.8 Hz), 117.7, 131.5 (q, $J_{1C-F}$ = 1.7 Hz, $J_{2C-F}$ = 8.3 Hz), 133.0 (q, $J_{1C-F}$ = 1.3 Hz, $J_{2C-F}$ = 8.1 Hz), 134.2 (d, $J_{C-F}$ = 3.2 Hz), 134.4 (d, $J_{C-F}$ = 3.2 Hz), 138.2 (d, $J_{C-F}$ = 3.1 Hz), 138.3 (d, $J_{C-F}$ = 3.1 Hz), 156.3 (d, $J_{C-F}$ = 6.7 Hz), 157.4, 161.4, 162.5, 165.0 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3425, 3334, 3204, 2958, 2835, 2201, 2050, 1649, 1608, 1570, 1512, 1459, 1393, 1246, 1178, 1114, 1029, 827, 775, 546. MS (MALDI) *m/z* = 461 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{25}H_{16}F_2N_6Na$): 461.1297; found: *m/z* = 461.1294 ([M+Na]$^+$).

**5-amino-3-(dicyanyomethylene)-8-(3,4-dimethoxybenzyl)-7-(3,4-dimethoxy)-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile 3h**



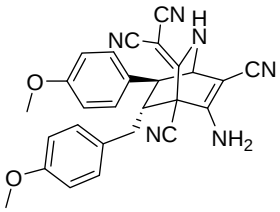

Isoquinuclidine **3h** was obtained as white solid. $^{1}$H-NMR (400 MHz, $(CD_3)_2SO$): $\delta$ = 2.20 (t, *J* = 12.5 Hz, 1H), 2.90 (d, *J* = 2.8 Hz, 1H), 3.27-3.28 (m, 2H), 3.40 (s, 3H), 3.61 (s, 3H), 3.64 (s, 3H), 3.67 (s, 3H), 4.08 (d, *J* = 1.1 Hz, 1H), 6.36-6.41 (m, 2H), 6.64-6.71 (m, 4H), 7.40 (s, 2H), 10.65 ppm (bs, 1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2SO$): $\delta$ = 37.9, 47.1, 51.2, 51.6, 55.0, 55.1, 55.4, 55.5, 56.6, 74.7, 111.3, 111.4, 111.4, 112.5, 112.9, 113.7, 115.3, 116.2, 119.4, 121.4, 128.8, 132.8, 147.3, 147.4, 148.1, 148.4, 152.6, 161.9 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3735, 3471, 3378, 3228, 2933, 2834, 2362, 2197, 1647, 1582, 1515, 1557, 1416, 1263, 1253, 1145, 1023, 797, 764, 661, 610, 552. MS (MALDI) *m/z* = 545 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{29}H_{26}N_6NaO_4^+$): 545.1908; found: *m/z* = 545.1918 ([M+Na]$^+$).

**(1*S*,4*S*,7*R*)-6-amino-7-(3,4-dimethoxybenzyl)-8-(3,4-dimethoxyphenyl)-2-iminobicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4h**



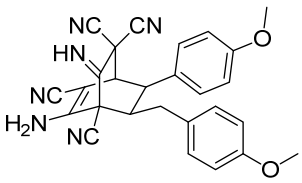

Compound **4h** (carbobicycle) was obtained as white solid. $^{1}$H-NMR (400 MHz, $(CD_3)_2CO$): $\delta$ = 2.12-2.15 (m, 1H), 2.31-2.45 (m, 2H), 3.26-3.34 (m, 3H), 3.47 (s, 3H), 3.47 (s, 3H), 3.69 (s, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 3.72 (s, 3H), 3.80-3.81 (m, 2H), 6.42-6.47 (m, 4H), 6.67-6.74 (m, 8H), 6.94-6.99 (m, 4H), 12.03-12.81 ppm (2×s, 2×1H).

**(1*R*,4*R*,8*S*)-5-amino-3-(dicyanomethylene)-8-(4-methoxybenzyl)-7-(4-methoxyphenyl)-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile 3i** *(dr >99:1)*



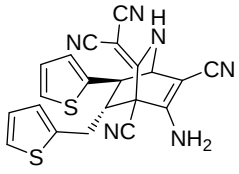
Isoquinuclidine **3i** was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.47 (t, $J$ = 12.3 Hz, 1H), 3.21-3.22 (m, 1H), 3.28-3.34 (m, 1H), 3.50 (dd, $J_1$ = 3.2 Hz, $J_2$ = 13.0 Hz, 1H), 4.36 (d, $J$ = 1.1 Hz, 1H), 6.62-6.70 (m, 4H), 6.85-6.90 (m, 4H), 7.13 (d, $J$ = 8.4 Hz, 2H), 9.31 ppm (brs, 1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 39.7, 50.2, 51.5, 53.4, 53.9, 56.4, 56.5, 58.9, 79.3, 114.2, 115.5, 115.6, 116.9, 119.7, 130.4, 130.7, 132.4, 133.9, 154.0, 154.1, 160.6, 160.7, 164.2 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3443, 3337, 3212, 2933, 2836, 2360, 2200, 1650, 1608, 1570, 1512, 1459, 1396, 1247, 1179, 1115, 1029, 830, 753, 547. MS (MALDI) $m/z$ = 485 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{27}H_{22}N_6O_2Na^+$): 485.1697; found: $m/z$ = 485.1689 ([M+Na]$^+$).

**(1*S*,4*S*)-6-amino-2-imino-7-(4-methoxybenzyl)-8-(4-methoxyphenyl)bicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4i** *(two diastereomers, dr 50:50)*



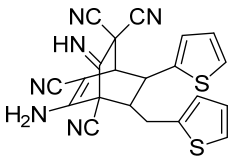
Compound **4i** (carbobicycle) was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.40-2.51 (m, 2H), 3.23-3.40 (m, 6H), 3.68 (s,6H), 3.72 (s, 6H), 3.79-3.80 (1×d, 1×s, 2×1H), 6.63-6.72 (m, 8H), 6.85-6.99 (m, 8H), 7.03-7.06 (m, 4H), 12.04-12.83 ppm (2×s, 2×1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 39.8, 39.8, 46.7, 48.4, 48.5, 48.9, 49.7, 50.2, 50.3, 50.4, 56.5, 56.5, 59.8, 59.8, 71.3, 71.9, 114.1, 114.3, 115.0, 115.3, 115.6, 115.7, 115.8, 130.0, 130.3, 130.7, 130.7, 131.7, 132.2, 132.2, 134.4, 134.5, 138.0, 157.5, 157.5, 160.8, 160.9, 160.9, 160.9 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3426, 3333, 3206, 2957, 2835, 2200, 2042, 1648, 1607, 1569, 1511, 1458, 1393, 1299, 1246, 1178, 1114, 1029, 826, 775, 544. MS (MALDI) $m/z$ = 485 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{27}H_{22}N_6O_2Na^+$): 485.1697; found: $m/z$ = 485.1689([M+Na]$^+$).

**(1*R*,4*R*,8*S*)-5-amino-3-(dicyanomethylene)-7-(thiophen-2-yl)-8-(thiophen-2-ylmethyl)-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile 3j** *(dr >99:1)*



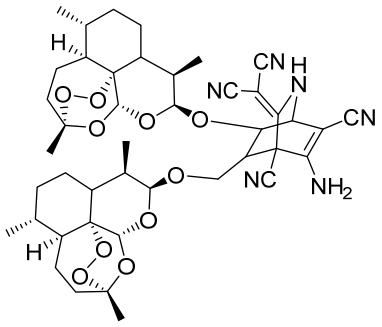
Isoquinuclidine **3j** was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.94 (dd, $J_1$ = 11.8 Hz, $J_2$ = 13.9 Hz, 1H), 3.19-3.25 (m, 1H), 3.65-3.72 (m, 2H), 4.58 (d, $J$ = 2.0 Hz, 1H), 6.64 (d, $J$ = 3.3 Hz, 1H), 6.80 (dd, $J_1$ = 3.6 Hz, $J_2$ = 5.1 Hz, 1H), 6.85 (dd, $J_1$ = 3.5 Hz, $J_2$ = 5.1 Hz, 1H), 6.89 (brs, 1H), 7.02 (d, $J$ = 3.3 Hz, 1H), 7.20-7.24 (m, 2H), 9.46 ppm (brs, 1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 34.6, 49.5, 52.1, 52.8, 53.4, 58.4, 78.9, 113.9, 113.9, 114.3, 116.7, 126.6, 127.1, 127.5, 128.6, 128.8, 129.5, 140.2, 145.2, 153.8, 163.7 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3442, 3347, 3201, 2200, 1649, 1567, 1409, 1300, 1220, 1010, 944, 829, 689, 497. MS (MALDI) $m/z$ = 437 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{21}H_{14}N_6S_2Na^+$): 437.0614; found: $m/z$ = 437.0608 ([M+Na]$^+$).

**(1*S*,4*S*)-6-amino-2-imino-8-(thiophen-2-yl)-7-(thiophen-2-ylmethyl)bicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4j** *(two diastereomers, dr 50:50)*



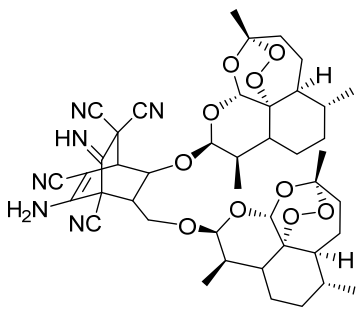
Compound **4j** (carbobicycle) was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 2.25-2.27 (m, 2H), 3.12-3.14 (m, 2H), 3.49-3.62 (s, 2H), 3.83-3.86 (m, 2H), 3.98-4.05 (1×d, 1×s, 2×1H), 6.52-6.54 (m, 2H), 6.78-681 (m, 2H), 6.88-6.90 (m, 2H), 6.95-6.96 (m, 2H), 6.98-7.01 (m, 2H), 7.06-7.07 (m, 2H), 7.24-7.30 (m, 2H), 12.11-12.92 ppm (2×s, 2×1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 31.2, 34.2, 49.1, 51.7, 52.3, 52.4, 53.0, 53.1, 58.0, 67.5, 71.3, 78.5, 78.5, 113.5, 113.8, 113.9, 115.8, 115.8, 116.3, 126.1, 126.2, 126.5, 126.5, 126.7, 127.1, 128.0, 128.2, 128.4, 129.1, 139.8, 139.8, 144.8, 153.3, 153.4, 163.3, 163.3 ppm. IR(ATR, solid) $\tilde{\nu}$/cm$^{-1}$: 3435, 3345, 3248, 3199, 2919, 2851, 2199, 1719, 1647, 1601, 1566, 1460, 1409, 1258, 1221, 1076, 1016, 799, 685, 616, 585, 486. MS (MALDI) *m*/*z* = 437 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{21}H_{14}N_6S_2Na^+$): 437.0614; found: *m*/*z* = 437.0608 ([M+Na]$^+$).

**(1*S*,4*R*,7*R*)-5-amino-3-(dicyanomethylene)-7-(((3*R*,5a*S*,6*R*,9*R*,10*R*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)-8-((((3*R*,5a*S*,6*R*,9*R*,10*R*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)methyl)-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile 3k** *(dr >75:25)*



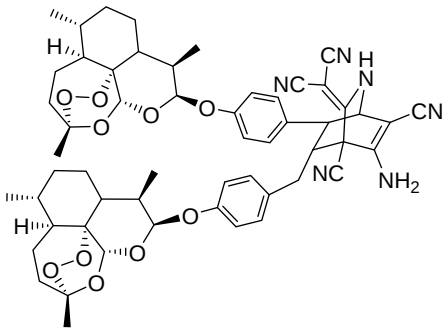
Isoquinuclidine **3k** was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 0.89-0.96 (m, 18H), 1.0-1.03 (m, 6H), 1.10-1.33 (m, 15H), 1.42-1.48 (m, 8H), 1.61-1.85 (m, 12H), 2.24-2.33 (m, 3H), 2.60-2.62 (m, 3H), 3.48-3.66 (m, 2H), 3.71-3.98 (m, 3H), 4.28-4.44 (m, 4H), 4.78-4.91 (m, 3H), 5.49-5.58 (m, 3H), 6.44-6.86 ppm (m, 4H). $^{13}$C-NMR (100 MHz, $CDCl_3$): $\delta$ =12.5, 12.8, 13.0, 20.2, 20.3, 24.4, 24.7, 24.9, 25.0, 25.9, 26.0, 30.3, 30.5, 30.5, 30.7, 31.4, 34.3, 34.5, 36.0, 36.2, 36.2, 37.1, 37.5, 37.5, 37.6, 39.0, 42.7, 43.6, 44.0, 52.4, 52.4, 65.6, 66.2, 74.5, 80.5, 80.6, 87.7, 88.0, 101.8, 103.4, 104.4, 104.4, 111.7, 113.0, 114.4, 115.9, 148.3 ppm. MS (MALDI) *m*/*z* = 837 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{43}H_{54}N_6O_{10}Na$): 837.3794; found: *m*/*z* = 837.3784 ([M+Na]$^+$).

**(1*S*,4*S*)-6-amino-2-imino-8-(((3*R*,5a*S*,6*R*,9*R*,10*R*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)-7-((((3*R*,5a*S*,6*R*,9*R*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)methyl)bicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4k** *(two diastereomers, dr 51:49)*



Compound **4k** (carbobicycle) was obtained as white solid. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$):$\delta$ = 0.94-0.98 (m, 25H), 1.01-1.06 (m, 8H), 1.20-1.27 (m, 5H), 1.31-1.32 (m, 16H), 1.43-1.47 (m, 15H), 6.60-6.69 (m, 6H), 1.74-1.87 (m, 14H), 2.23-2.29 (m, 5H), 2.61-2.63 (m, 5H), 3.43-3.53 (m, 2H), 3.63-3.72 (m, 2H), 3.71-3.94 (m, 4H), 4.19-4.35 (m, 4H), 4.41-4.55 (m, 2H), 4.87-4.90 (m, 4H), 5.37-5.49 (m, 4H), 6.42-6.71 ppm (2×s, 2×2H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 14.1, 14.2, 14.2, 21.6, 21.6, 21.7, 26.5, 26.5, 27.1, 32.6, 32.6, 32.7, 32.9, 36.3, 36.4, 36.4, 37.3, 38.1, 38.6, 38.7, 38.8, 38.9, 39.0, 39.0, 39.0, 41.0, 43.2, 44.1, 46.0, 46.1, 46.1, 46.2, 46.2, 54.4, 54.5, 68.0, 68.1, 69.8, 70.0, 74.0, 74.0, 74.1, 82.4, 82.5, 89.7, 89.8, 89.9, 90.0, 104.5, 105.0, 105.2, 105.6, 105.6, 105.7, 114.8, 114.8, 114.8, 115.2, 115.2, 115.9, 117.8, 118.8, 152.1 ppm. MS (MALDI) *m/z* = 837 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{43}H_{54}N_6O_{10}Na^+$): 837.3794; found: *m/z* = 837.3803 ([M+Na]$^+$).

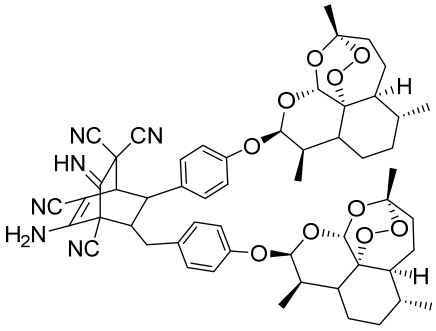
**(1*R*,4*R*,7*S*,8*R*)-5-amino-3-(dicyanomethylene)-8-(4-(((3*R*,5a*S*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)benzyl)-7-(4-(((3*R*,5a*S*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)phenyl)-2-azabicyclo[2.2.2]oct-5-ene-4,6-dicarbonitrile 3l** *(dr >90:10)*



Isoquinuclidine **3l** was obtained as white solid. Elem. anal.: Found: C, 67.48; H, 6.65; N, 8.17. Calcd for $C_{55}H_{64}N_6O_{11}$: C, 67.06; H, 6.55; N, 8.53%. $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 0.94-0.98 (m, 6H), 1.0-1.03 (m, 6H), 1.21-1.24 (m, 2H), 1.31-1.33 (m, 6H), 1.40-1.55 (m, 7H), 1.65-1.71 (m, 2H), 1.85-1.91 (m, 6H), 2.23-2.34 (m, 2H), 2.46-2.56 (m, 1H), 2.62-2.72 (m, 2H), 3.25-3.28 (m, 1H), 3.30-3.39 (m, 1H), 3.52 (dd, $J_1$ = 3.2 Hz, $J_2$ = 13.0 Hz, 1H), 4.41 (s, 1H), 5.28-5.43 (m, 4H), 6.83-6.90 (m, 8H), 7.16-7.20 (m, 3H), 9.37 ppm (brs, 1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 14.2, 14.2, 14.3, 14.5, 15.3, 21.6, 21.7, 26.1, 26.1, 26.2, 26.2, 26.4, 26.5, 27.1, 27.2, 32.7, 32.7, 32.8, 33.6, 36.4, 38.1, 38.1, 39.0, 39.1, 39.8, 46.2, 46.3, 56.4, 50.5, 51.5, 53.1, 53.4, 53.6, 53.9, 54.5, 58.7, 58.8, 79.5, 82.4, 82.4, 89.9, 89.9, 89.9, 101.9, 101.9, 102.1, 103.1, 105.6, 105.7, 105.7, 105.8, 118.5, 118.6, 119.0, 119.4, 131.9, 132.3, 132.5, 132.5, 135.4, 135.5, 154.0, 154.1, 154.1, 158.4, 158.5, 158.5, 158.9, 164.2 ppm. MS (MALDI) *m/z* = 990 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{55}H_{62}N_6O_{10}Na$): 989.4420; found: *m/z* = 989.4421 ([M+Na]$^+$).

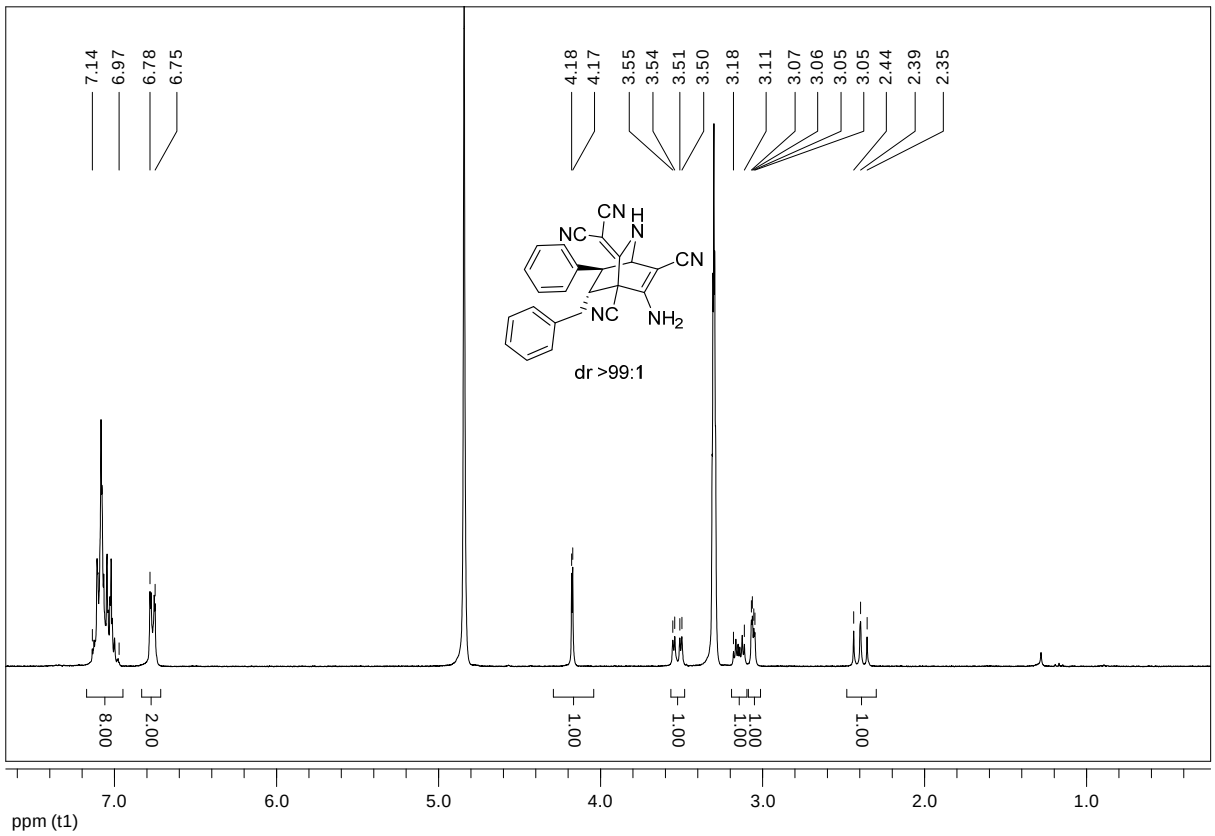
**(1*S*,4*S*)-6-amino-2-imino-7-(4-(((3*R*,5a*S*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)benzyl)-8-(4-(((3*R*,5a*S*,6*R*,9*R*,10*S*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxy[1,2]dioxepino[4,3-i]isochromen-10-yl)oxy)phenyl)bicyclo[2.2.2]oct-5-ene-1,3,3,5-tetracarbonitrile 4l**

*(two diastereomers, dr 46:54)*

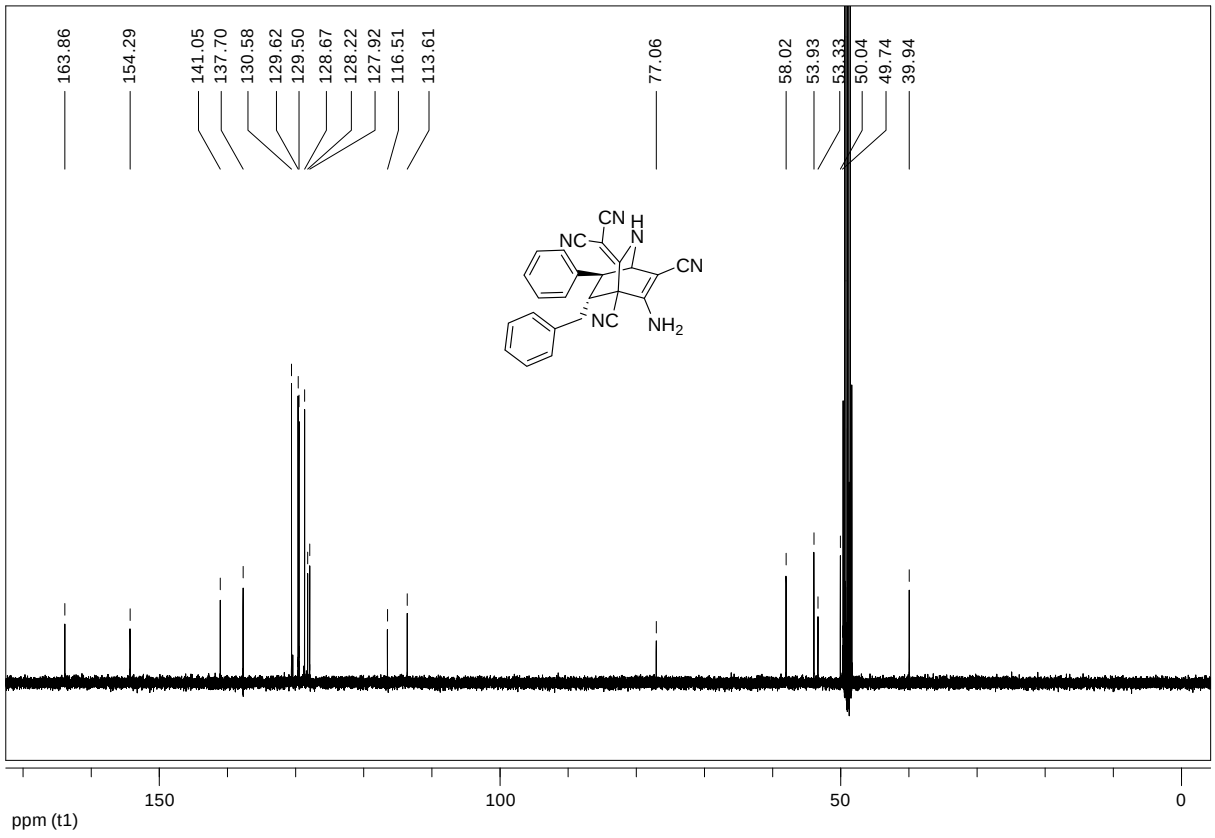



Compound **4l** (carbobicycle) was obtained as white solid. Elem. anal.: Found: C, 67.47; H, 6.72; N, 8.04. Calcd for $C_{55}H_{64}N_6O_{11}$: C, 67.06; H, 6.55; N, 8.53%. $^1$H-NMR (300 MHz, $(CD_3)_2CO$): $\delta$ = 0.95-0.97 (m, 12H), 1.0-1.03 (m, 12H), 1.29-1.32 (m, 22H), 1.42-1.57 (m, 15H), 1.67-1.72 (m, 5H), 1.84-1.92 (m, 11H), 2.24-2.29 (m, 4H), 2.34-2.54 (m, 2H), 2.67-2.71 (m, 6H), 3.15-3.42 (m, 6H), 3.75-3.87 (m, 2H), 5.31-5.50 (m, 8H), 6.83-7.33 (m, 20H), 12.06-12.85 ppm (2×s, 2×1H). $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$): $\delta$ = 14.2, 14.2, 14.3, 14.3, 15.5, 21.6, 21.7, 23.9, 26.1, 26.2, 26.4, 26.5, 26.6, 27.1, 27.1, 27.2, 32.7, 32.7, 32.8, 36.4, 38.0, 38.1, 38.1, 38.9, 39.0, 39.0, 39.2, 46.6, 46.7, 46.9, 46.9, 48.5, 49.4, 50.8, 50.9, 54.5, 54.5, 56.0, 71.3, 82.4, 82.4, 89.8, 89.9, 101.6, 101.6, 102.2, 102.7, 102.7, 103.3, 103.3, 105.7, 105.8, 105.8, 114.1, 114.3, 114.5, 114.9, 114.9, 115.3, 118.2, 118.5, 118.5, 119.3, 119.4, 119.8, 119.8, 130.7, 130.7, 131.5, 131.7, 132.1, 132.2, 132.2, 132.3, 132.3, 132.3, 135.8, 135.9, 136.1, 136.2, 158.6, 158.6, 158.7, 158.9, 159.1, 159.1, 161.8 ppm. MS (MALDI) *m/z* = 990 ([M+Na]$^+$). HRMS (ESI) calcd for ($C_{55}H_{62}N_6O_{10}Na^+$): 989.4420; found: *m/z* = 989.4436 ([M+Na]$^+$).

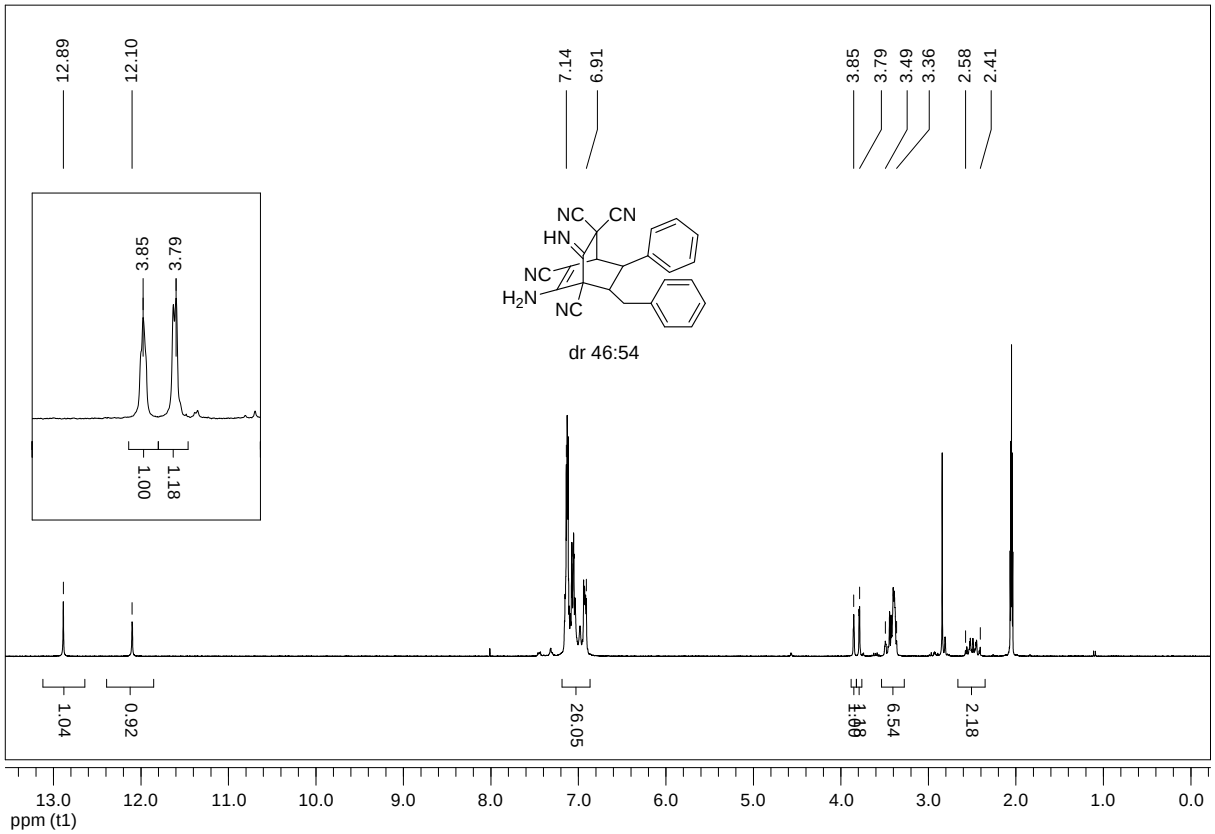
**Compound 3a: $^{1}$H-NMR (400 MHz, $CD_3OD$)**



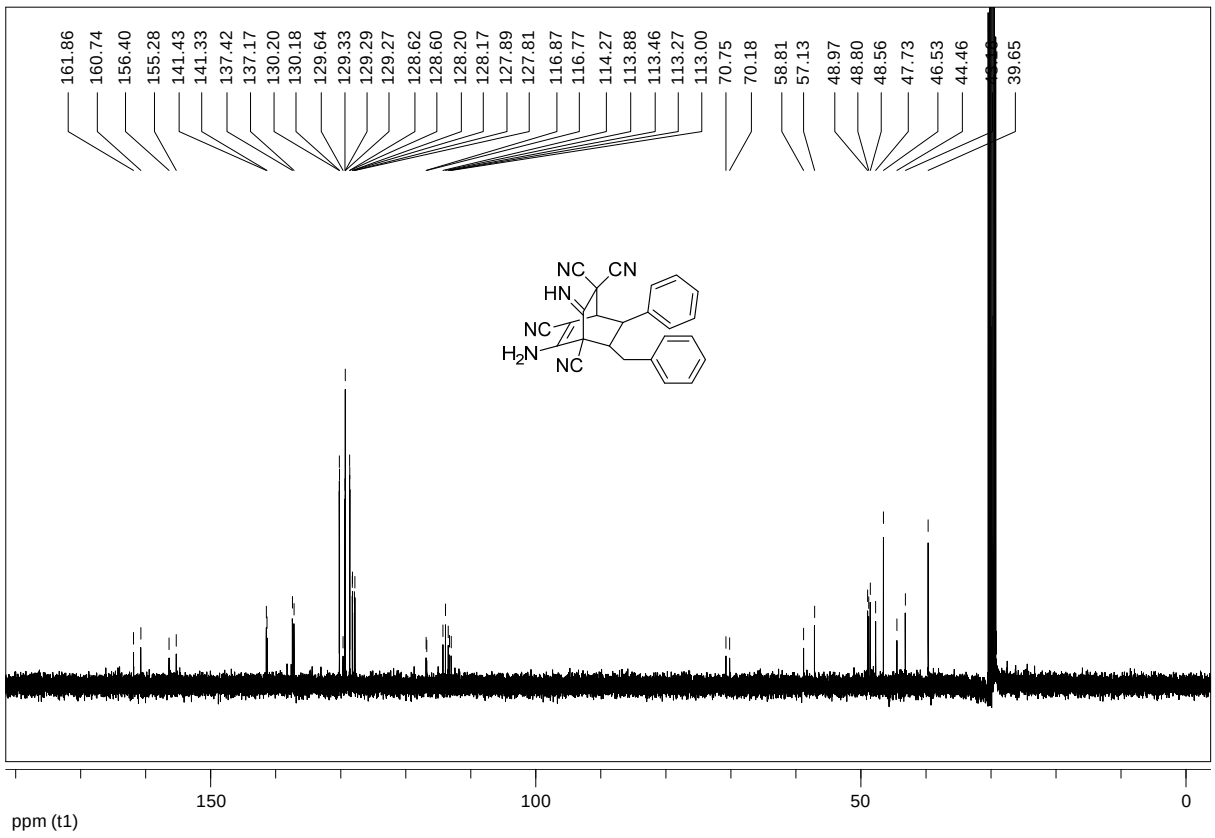

**Compound 3a: $^{13}$C-NMR (100 MHz, $CD_3OD$)**



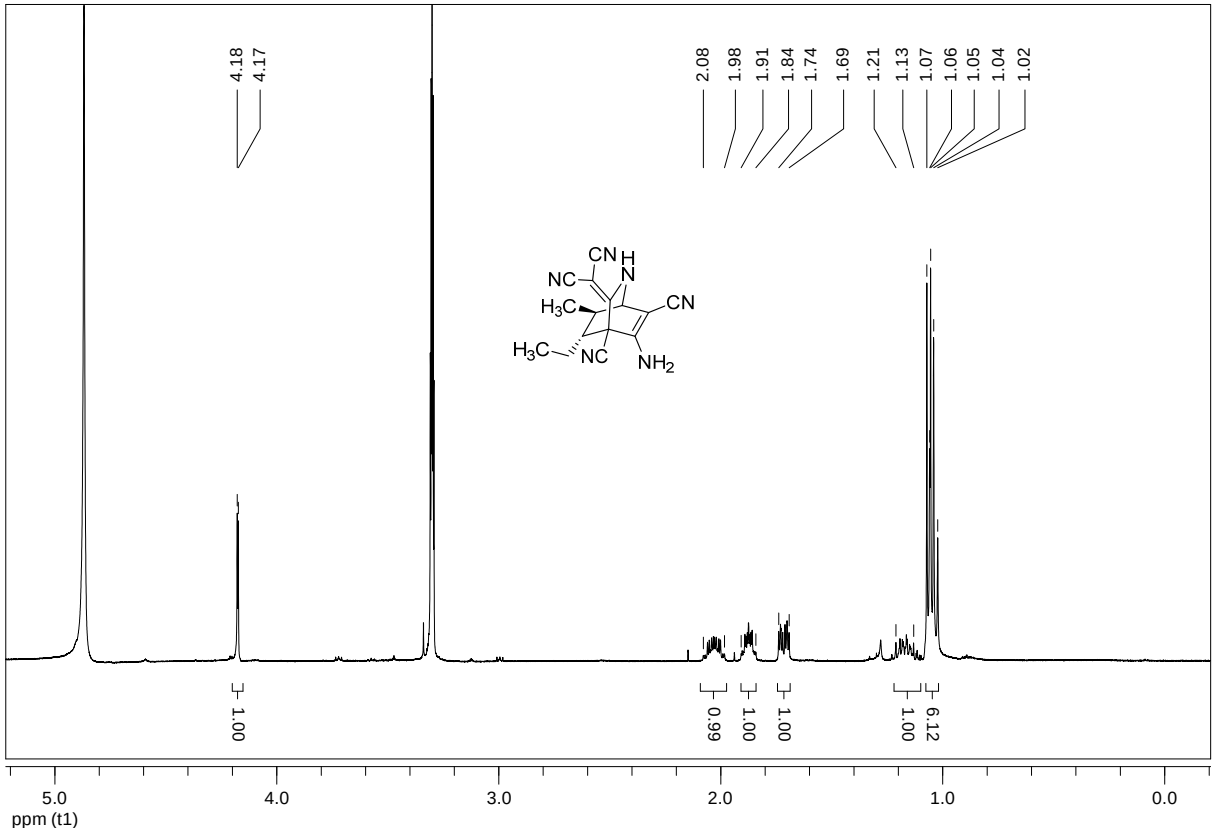
**Compound 4a: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



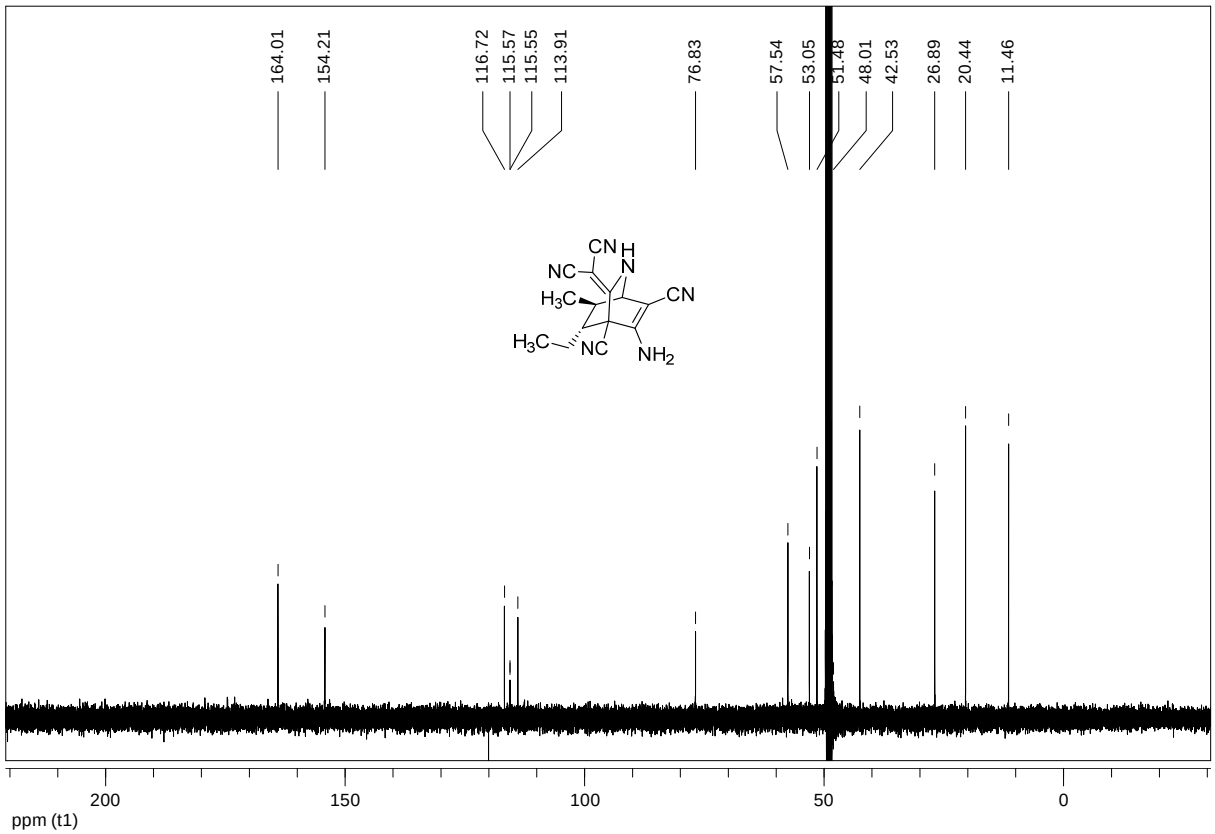

**Compound 4a: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



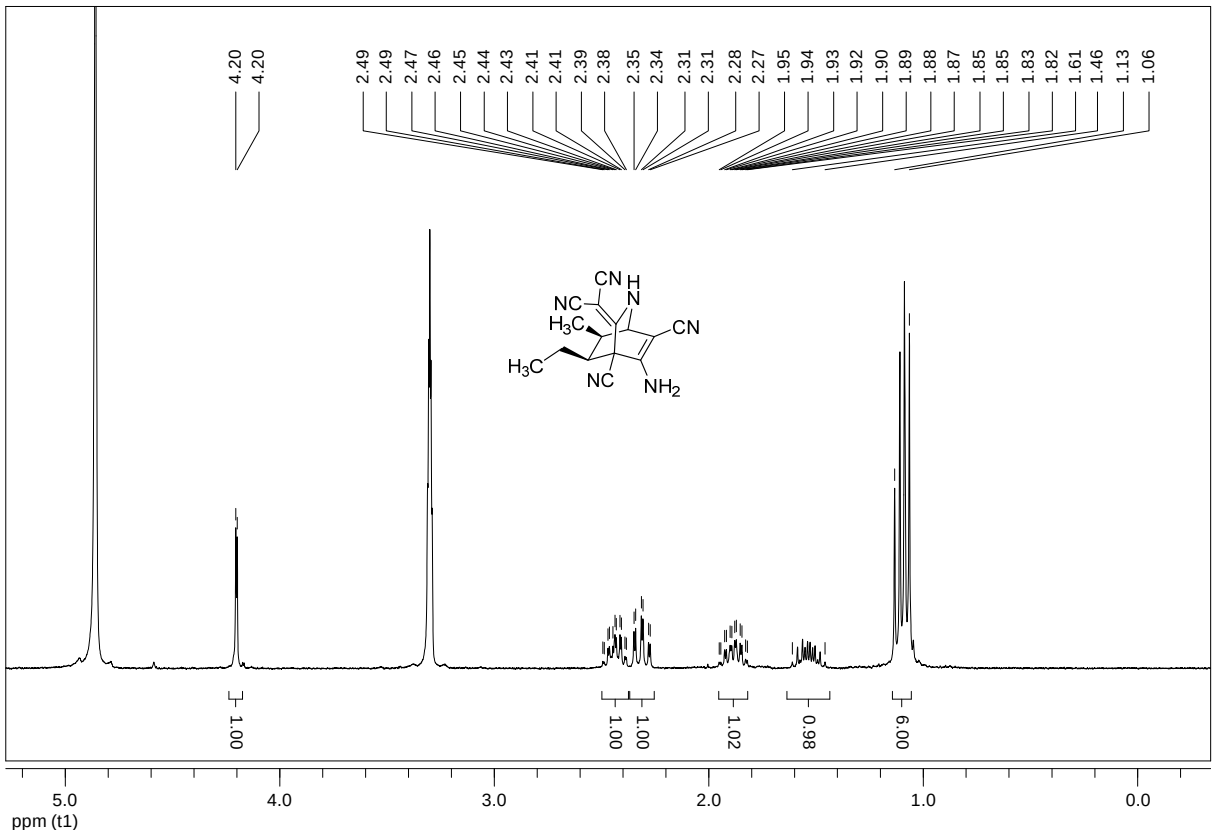
**Compound *anti*-3': $^{1}$H-NMR (400 MHz, $CD_3OD$)**



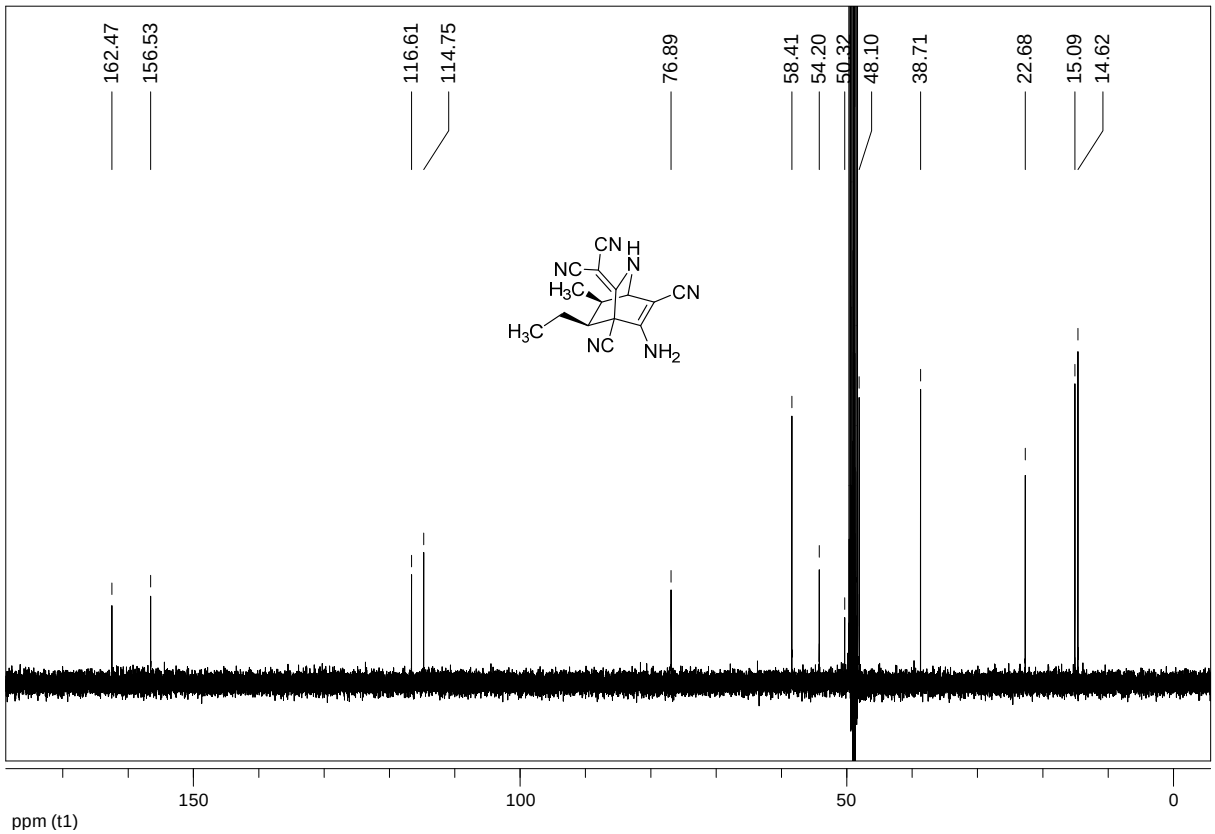

**Compound *anti*-3': $^{13}$C-NMR (100 MHz, $CD_3OD$)**



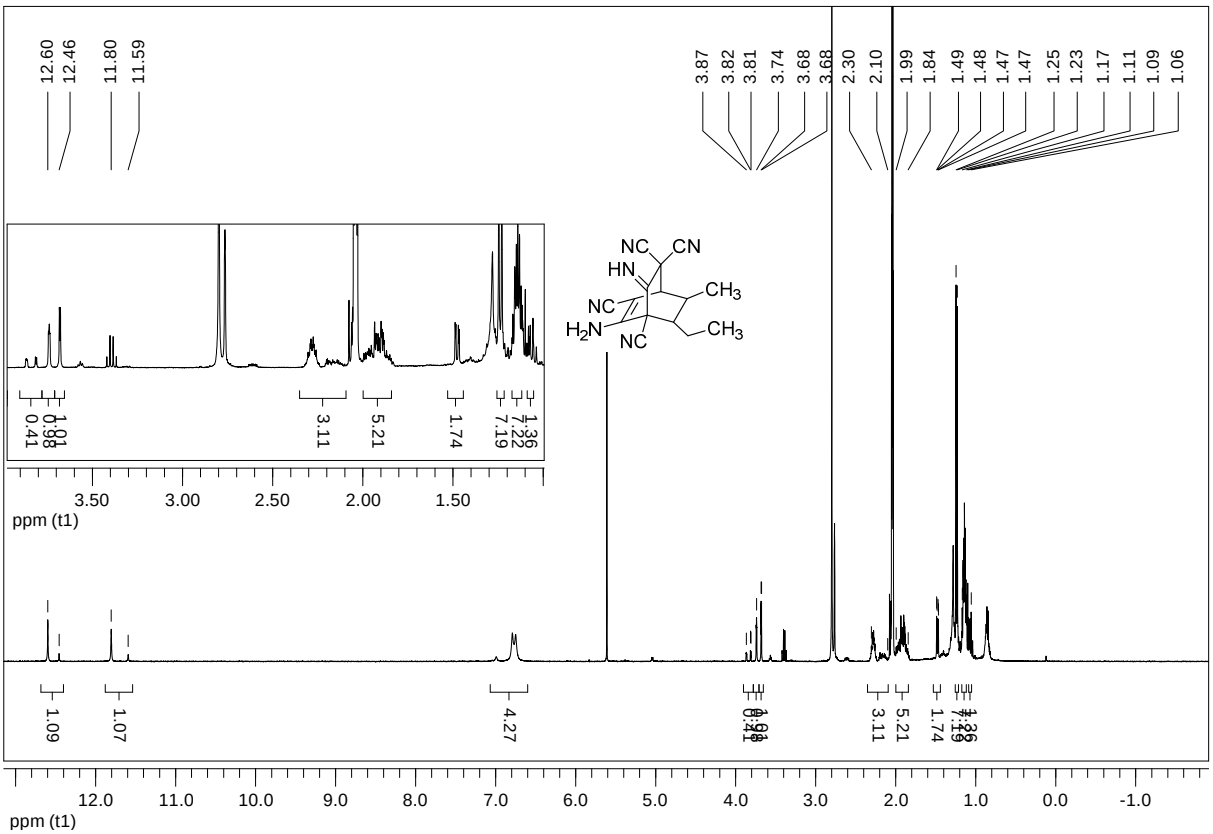
**Compound *syn*-3b'': $^{1}$H-NMR (300 MHz, $CD_3OD$)**



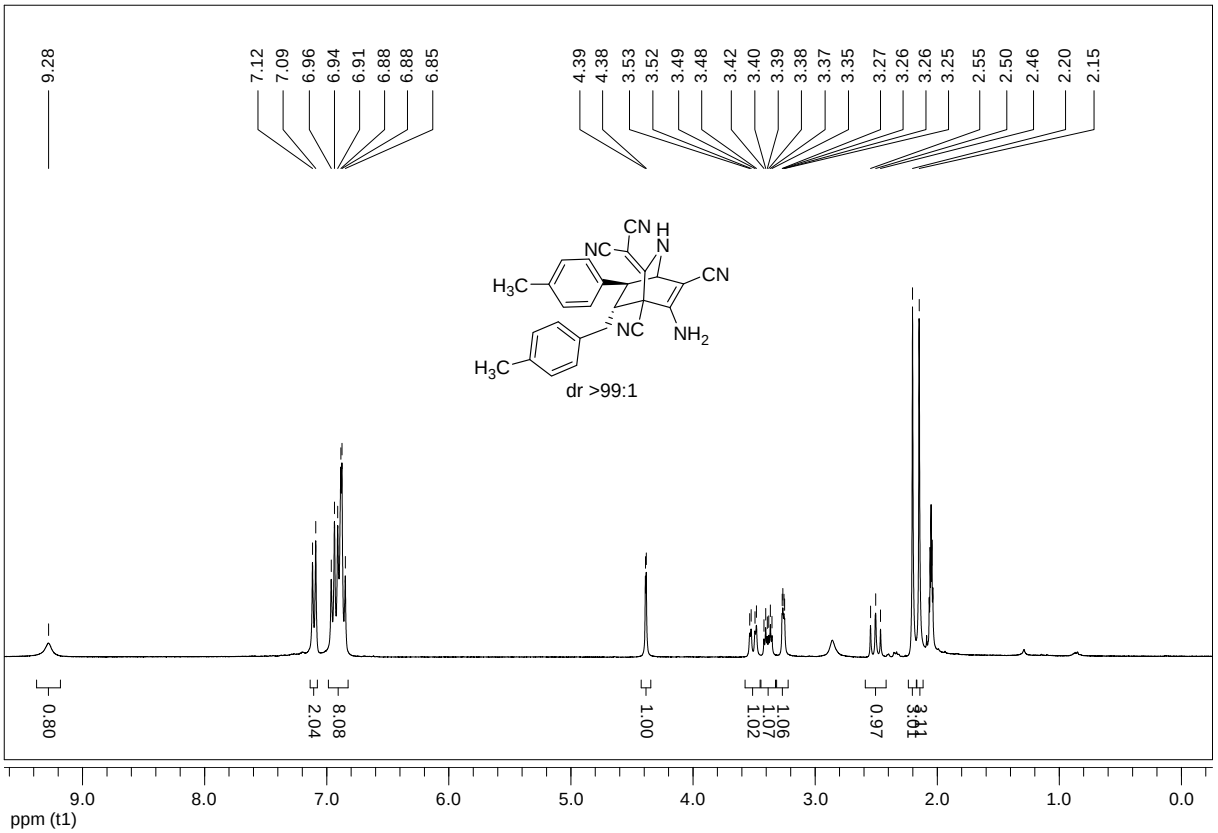

**Compound *syn*-3b'': $^{13}$C-NMR (100 MHz, $CD_3OD$)**



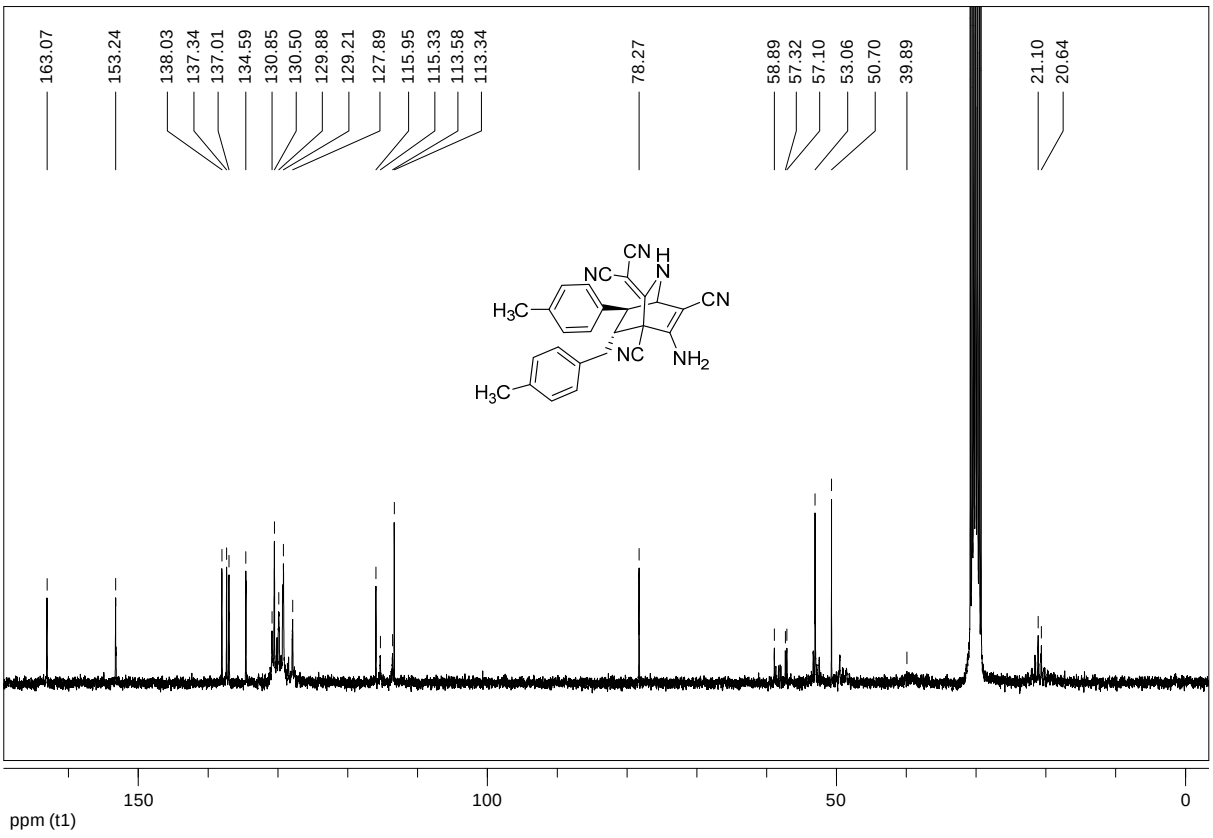
**Compound 4b: $^{1}$H-NMR (400 MHz, $(CD_3)_2CO$)**



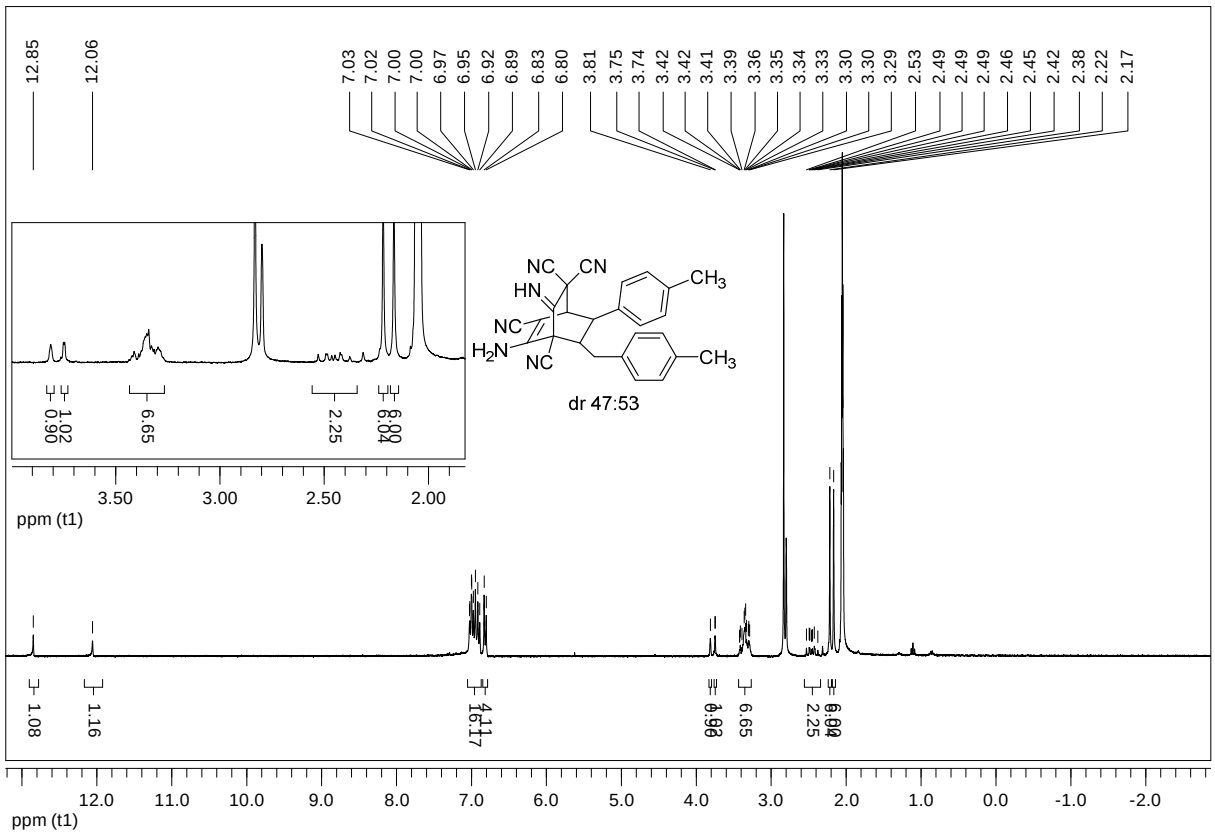
**Compound 3c: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



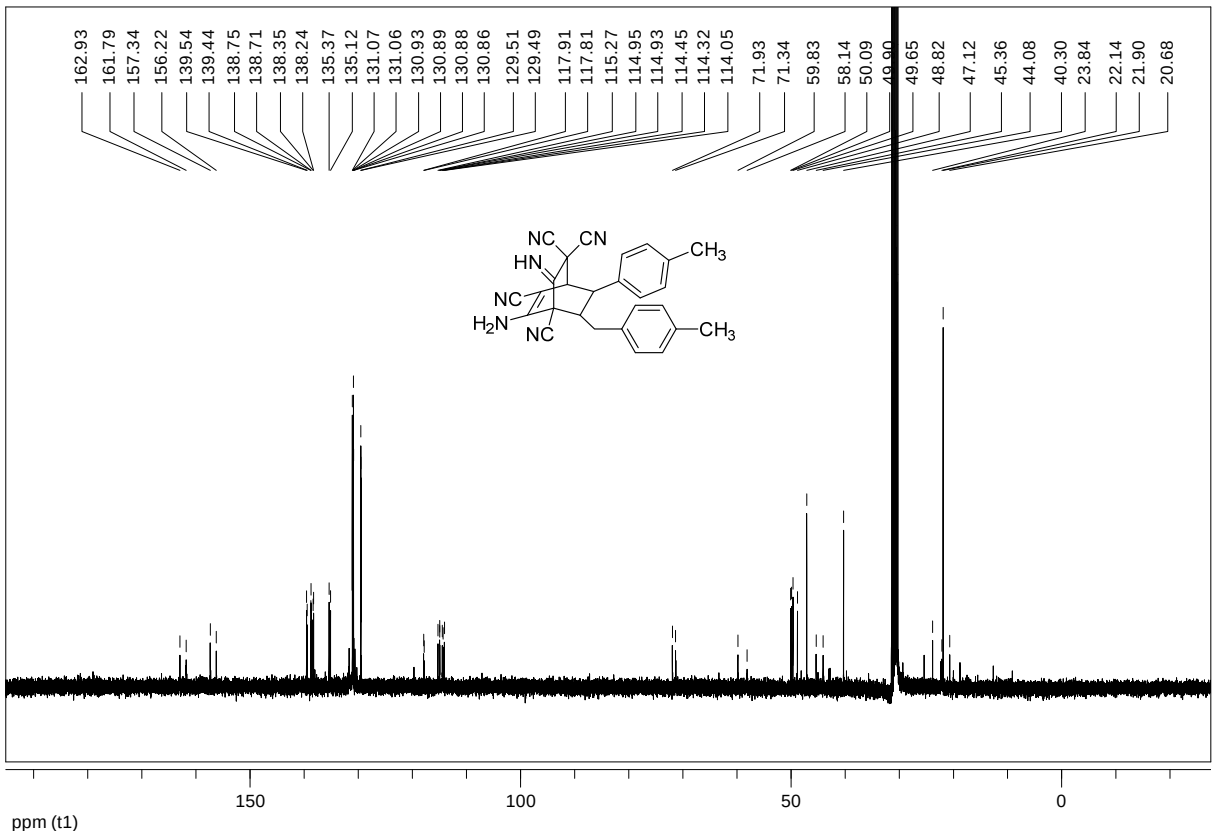

**Compound 3c: $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$)**



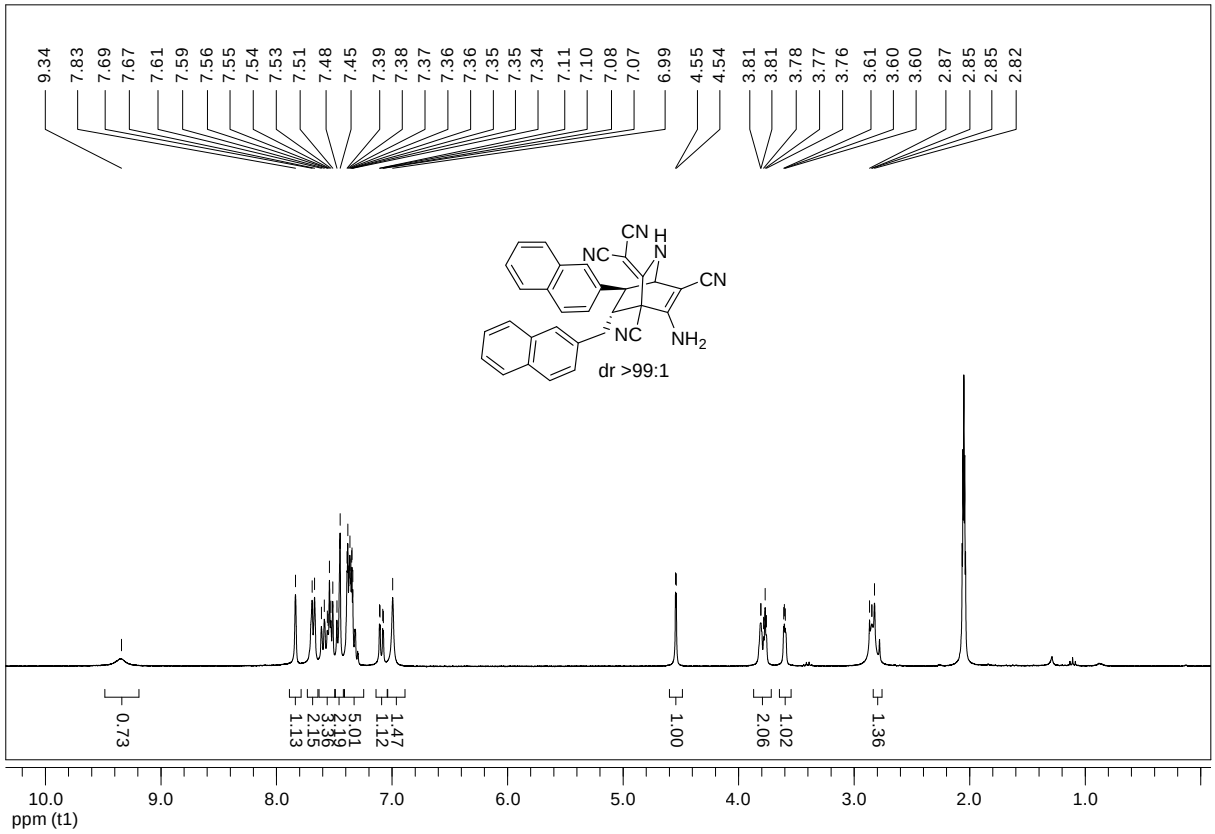
**Compound 4c: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



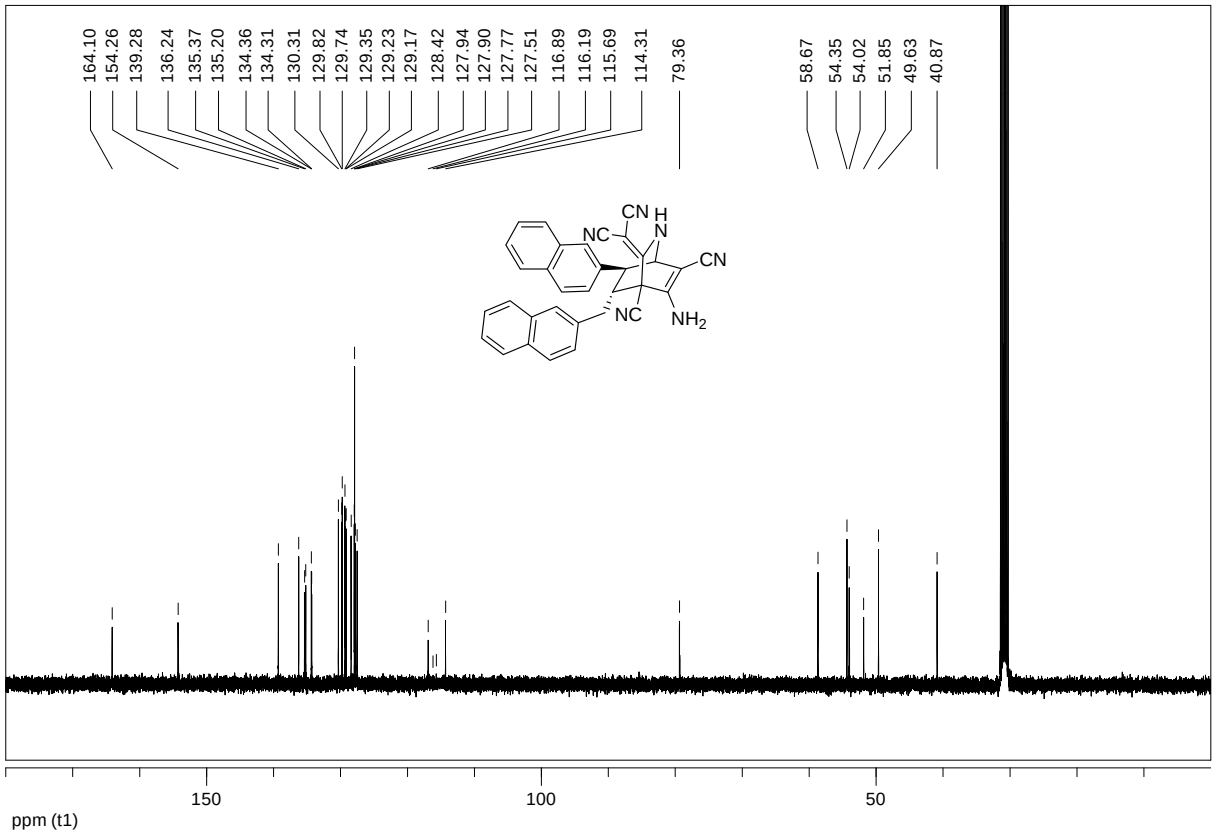

**Compound 4c: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



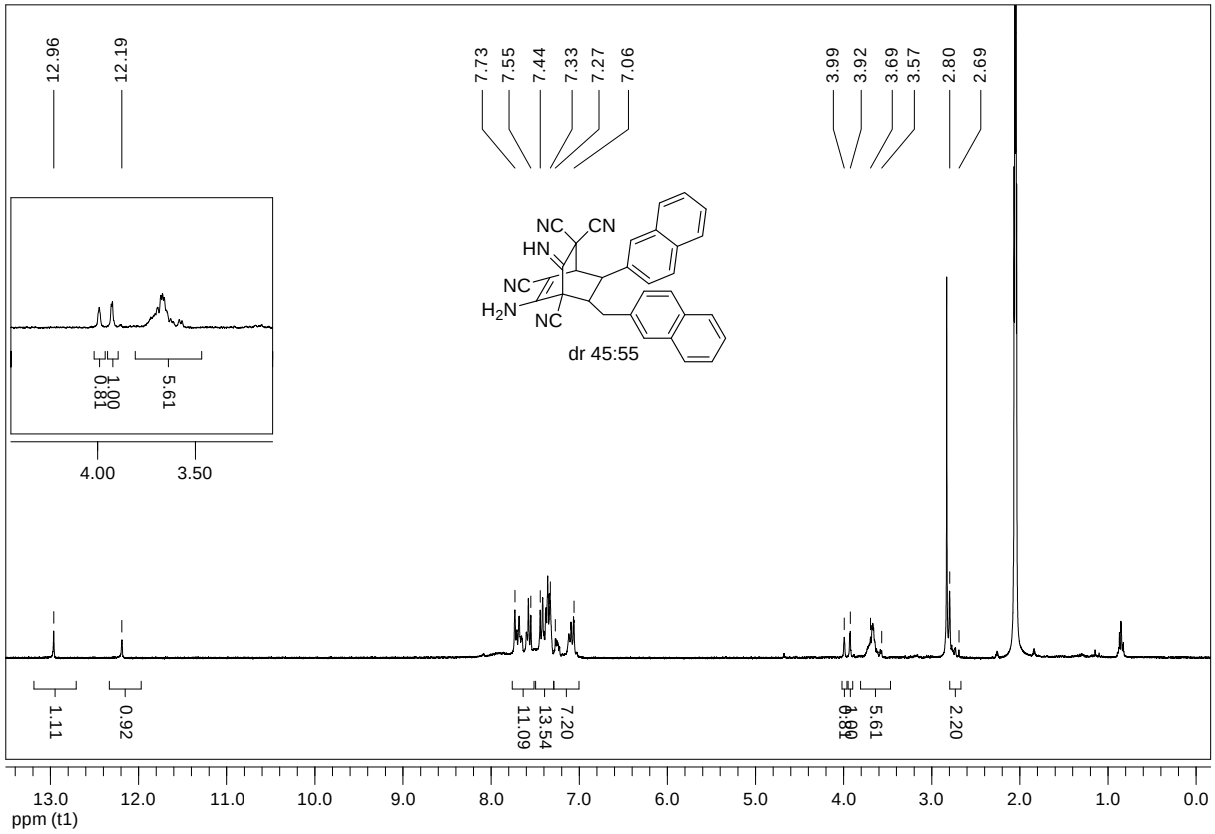
**Compound 3d: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



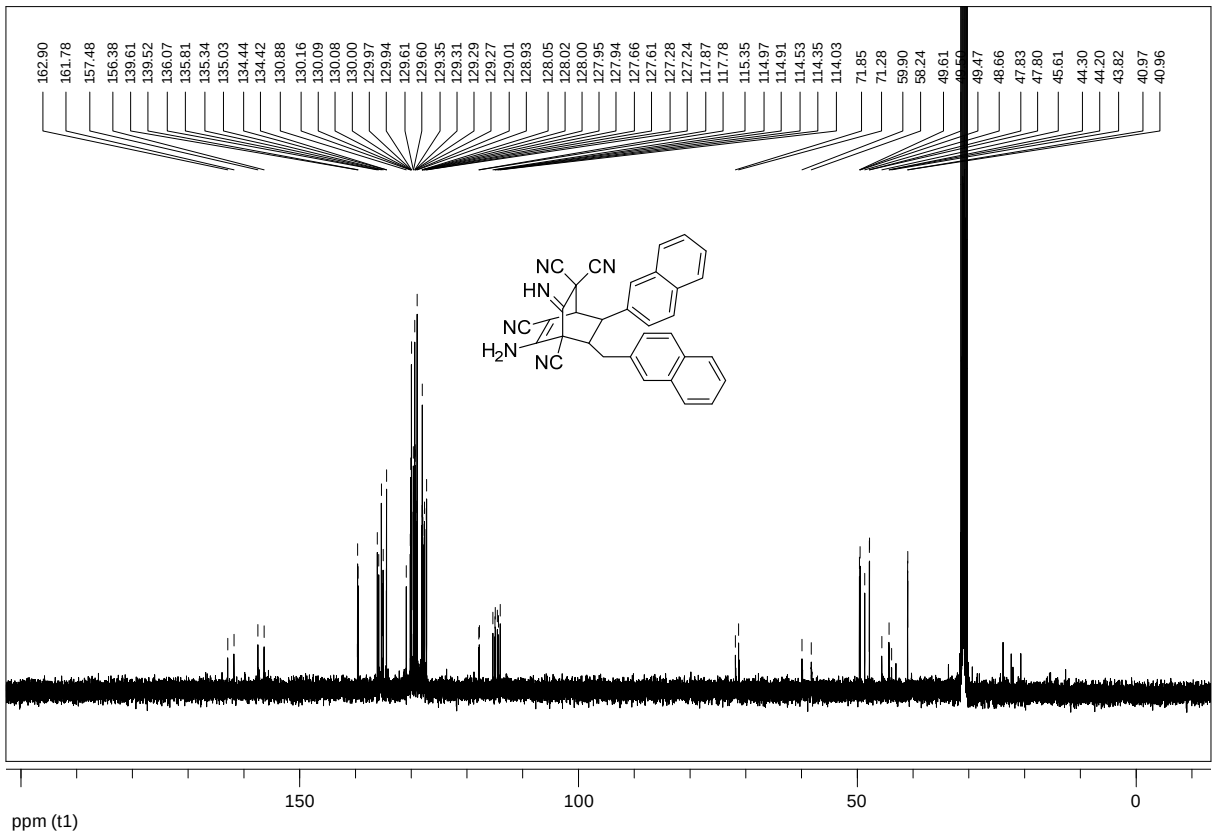

**Compound 3d: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



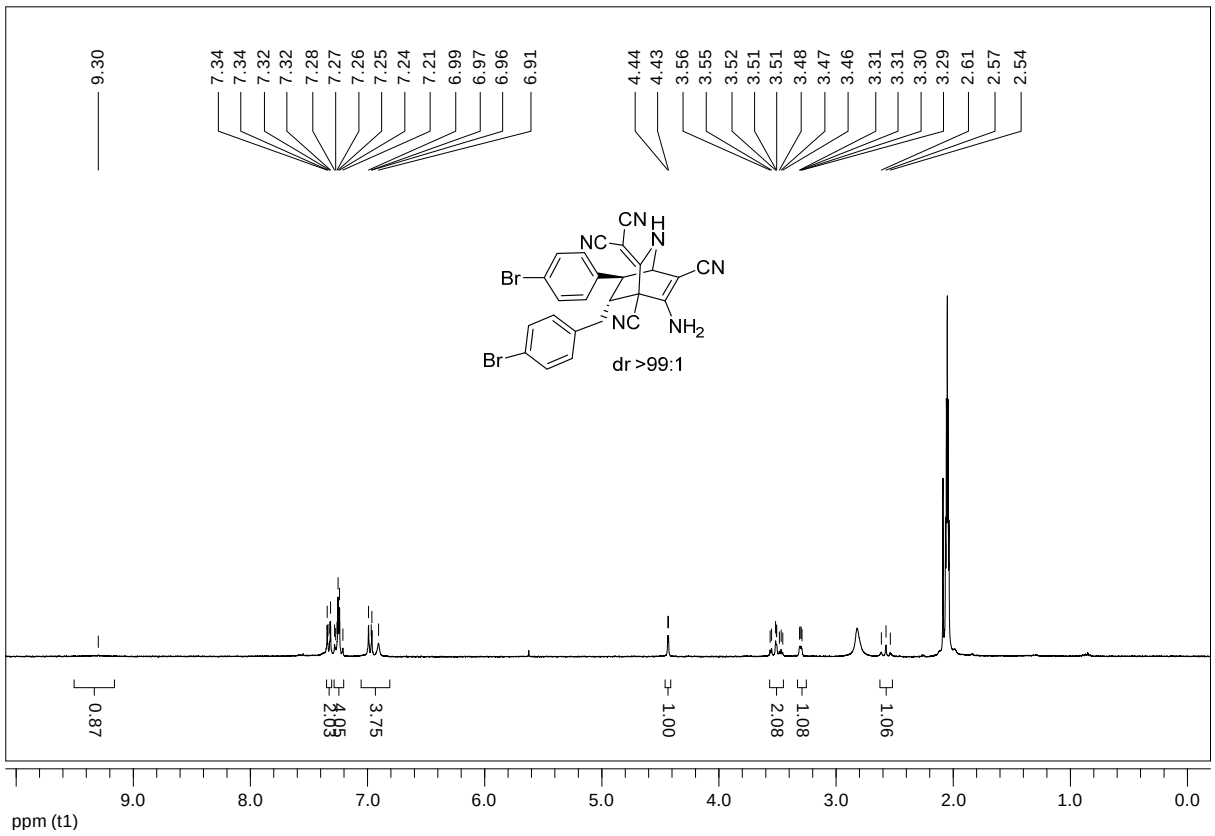
**Compound 4d: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



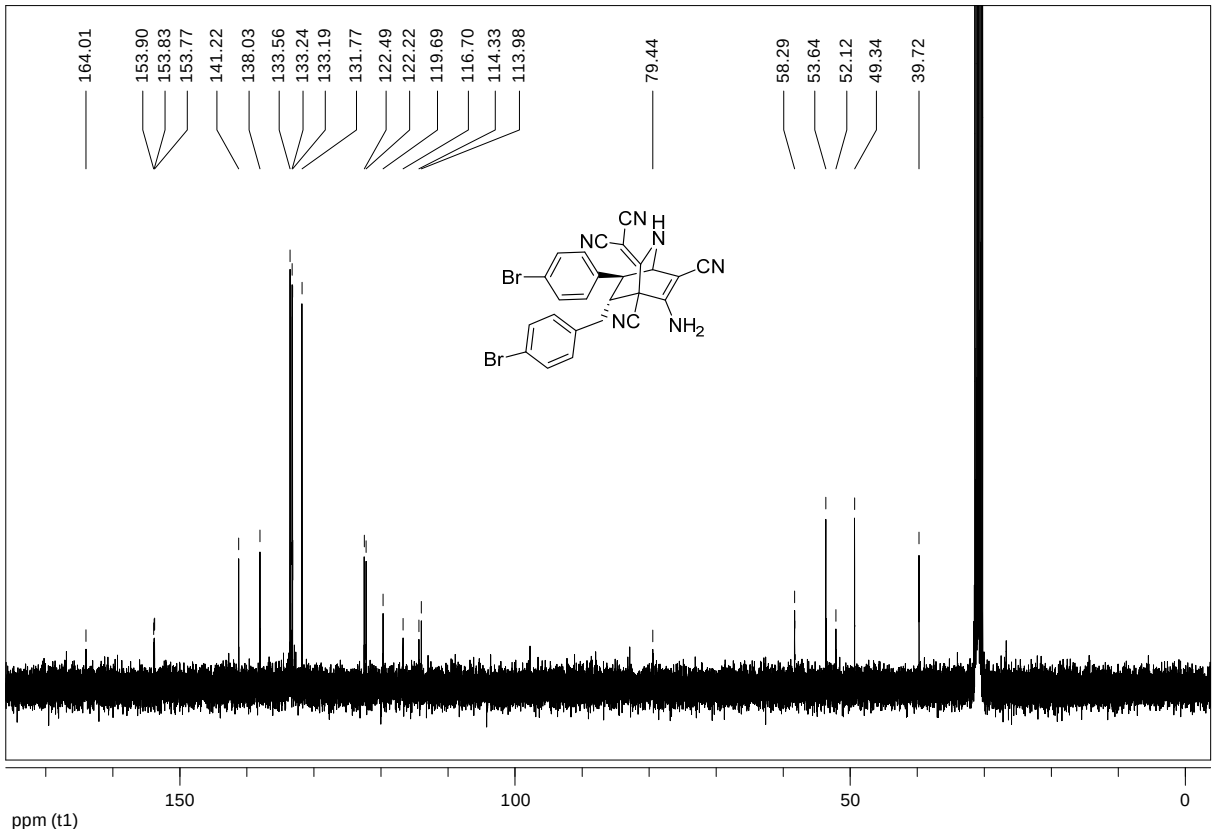

**Compound 4d: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



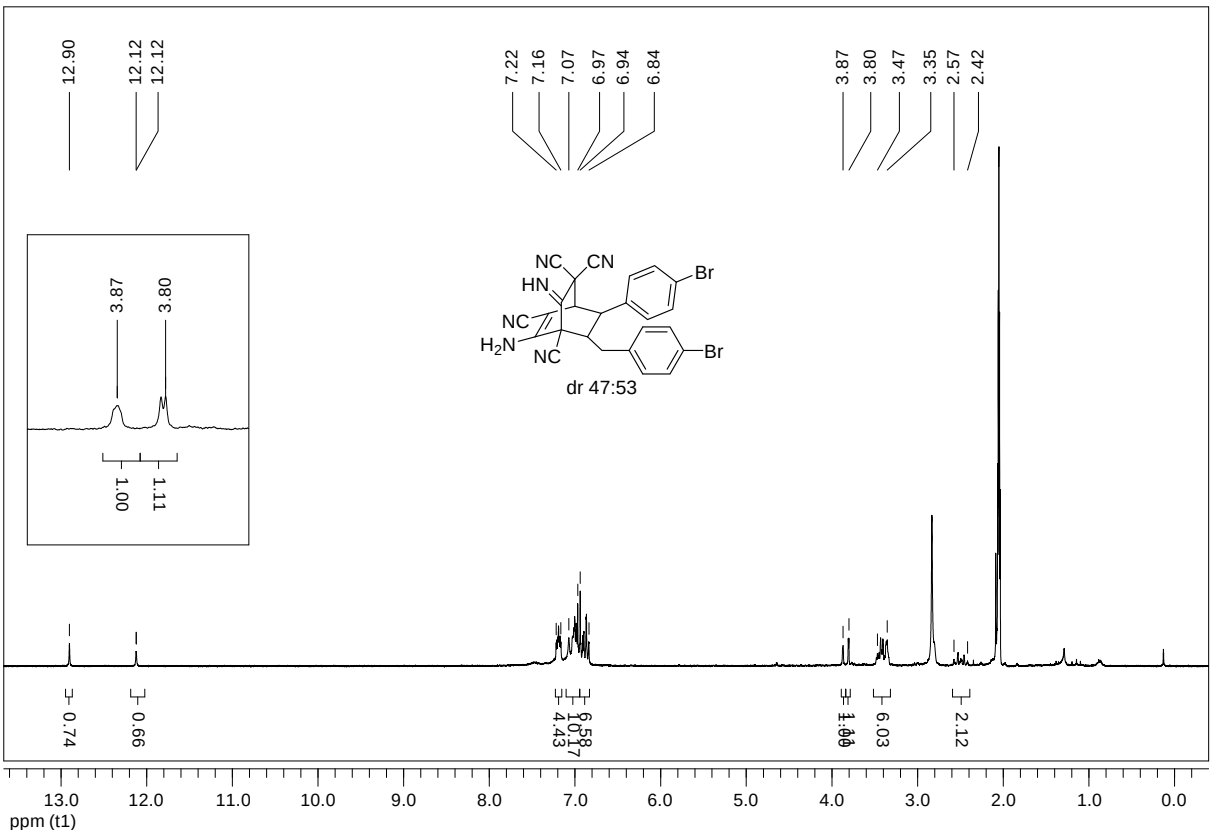
**Compound 3e: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



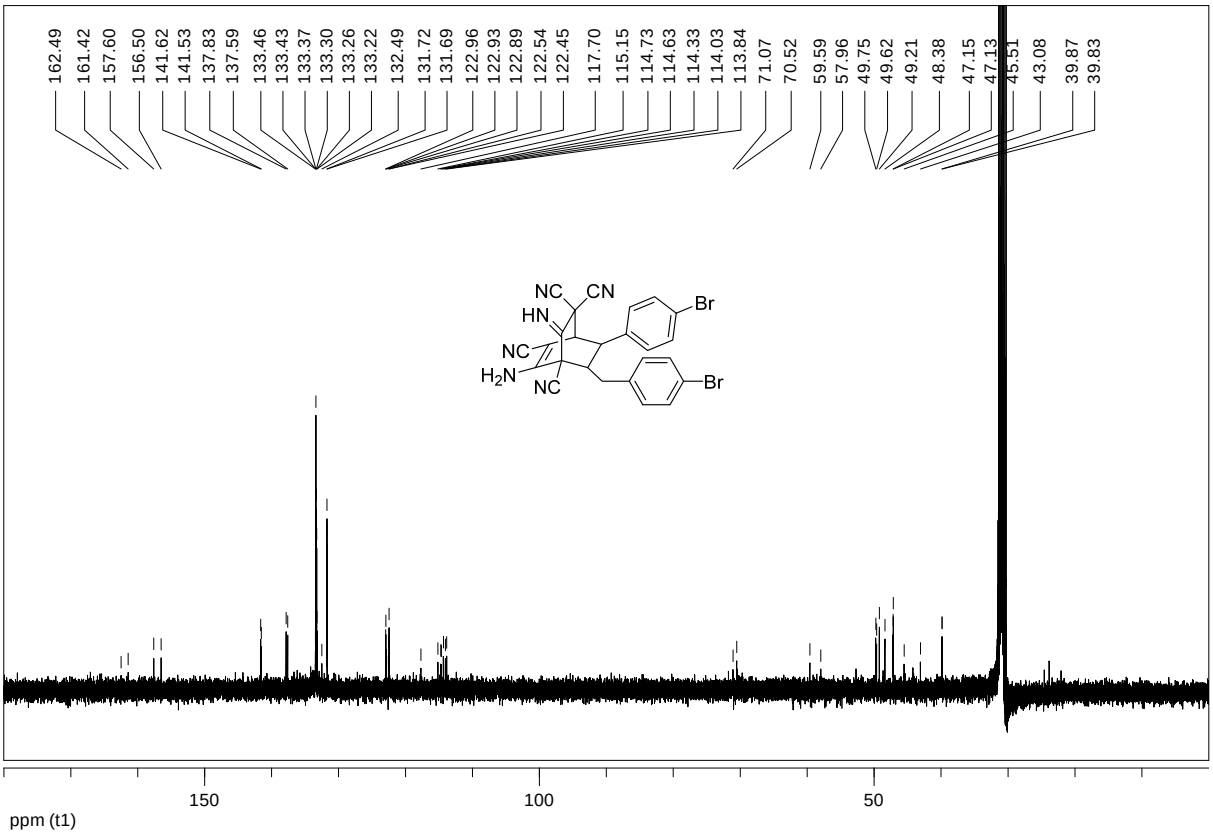

**Compound 3e: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



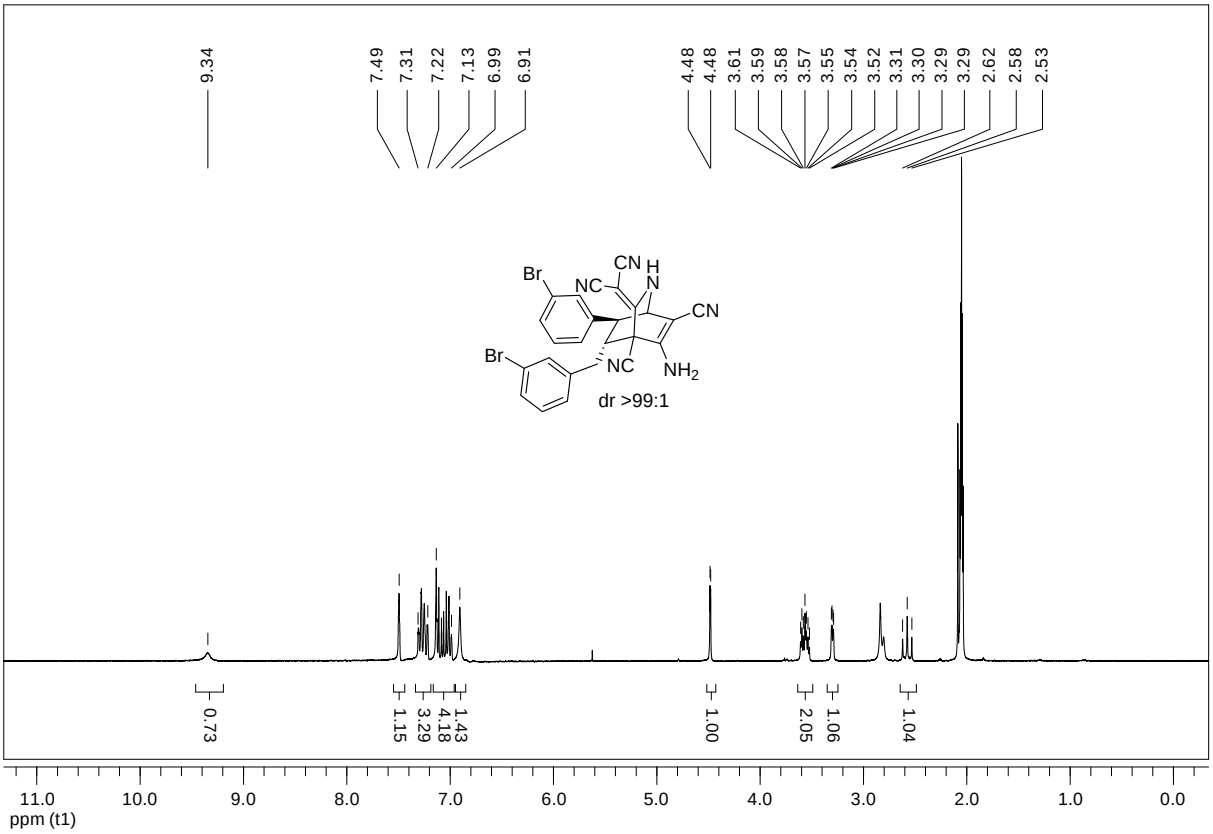
**Compound 4e: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



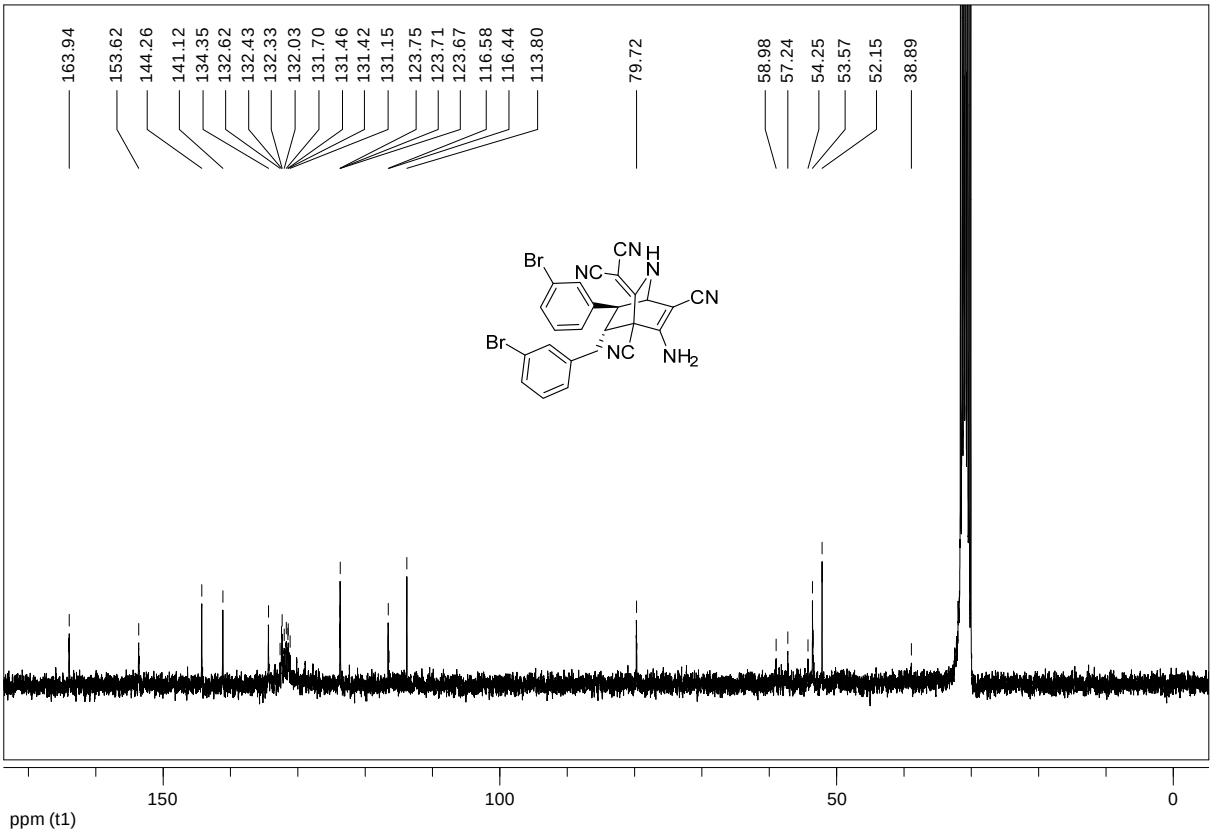

**Compound 4e: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



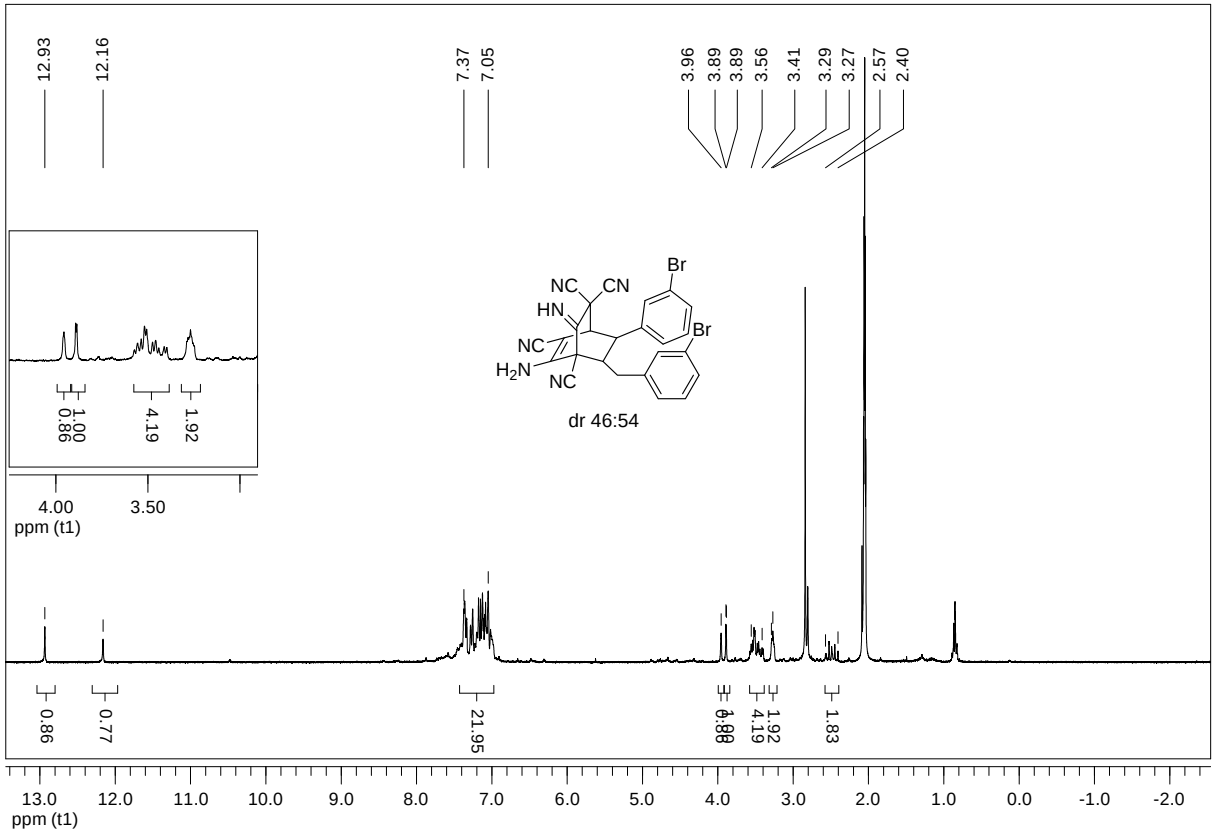
**Compound 3f: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



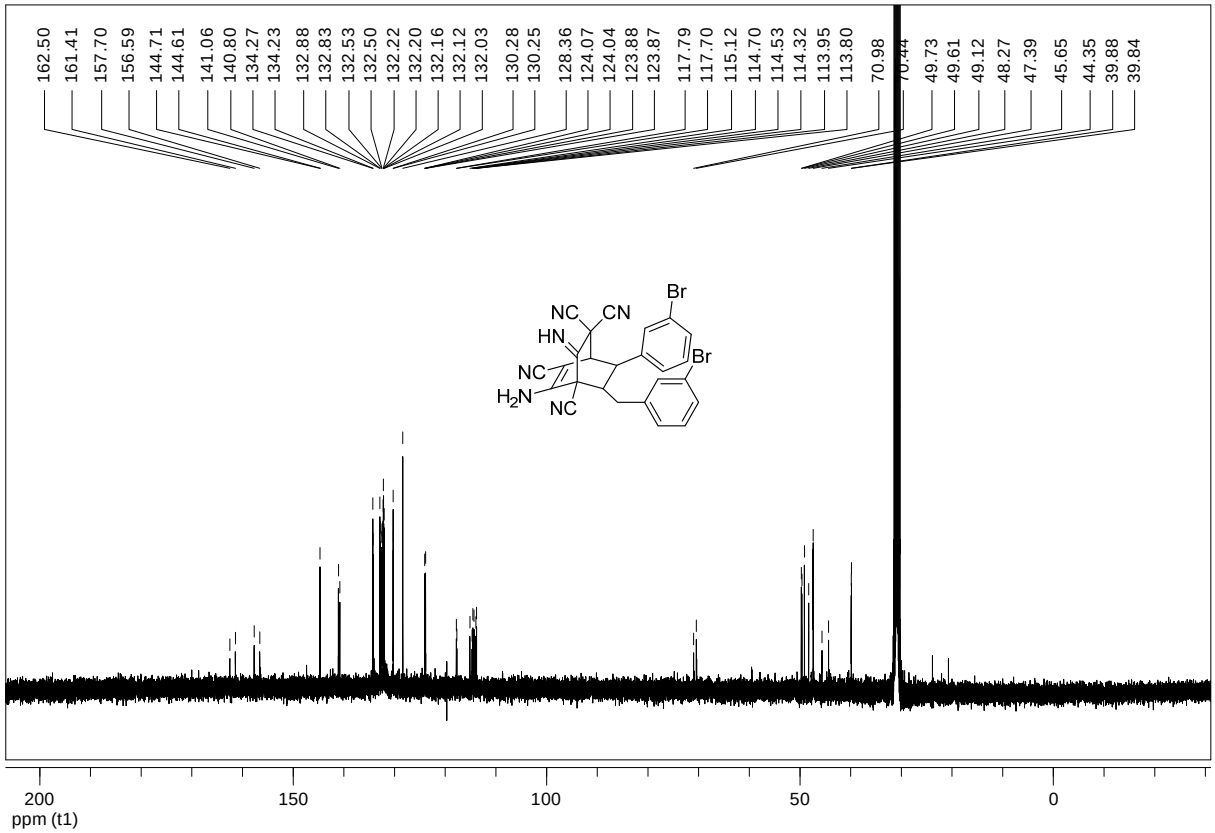

**Compound 3f: $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$)**



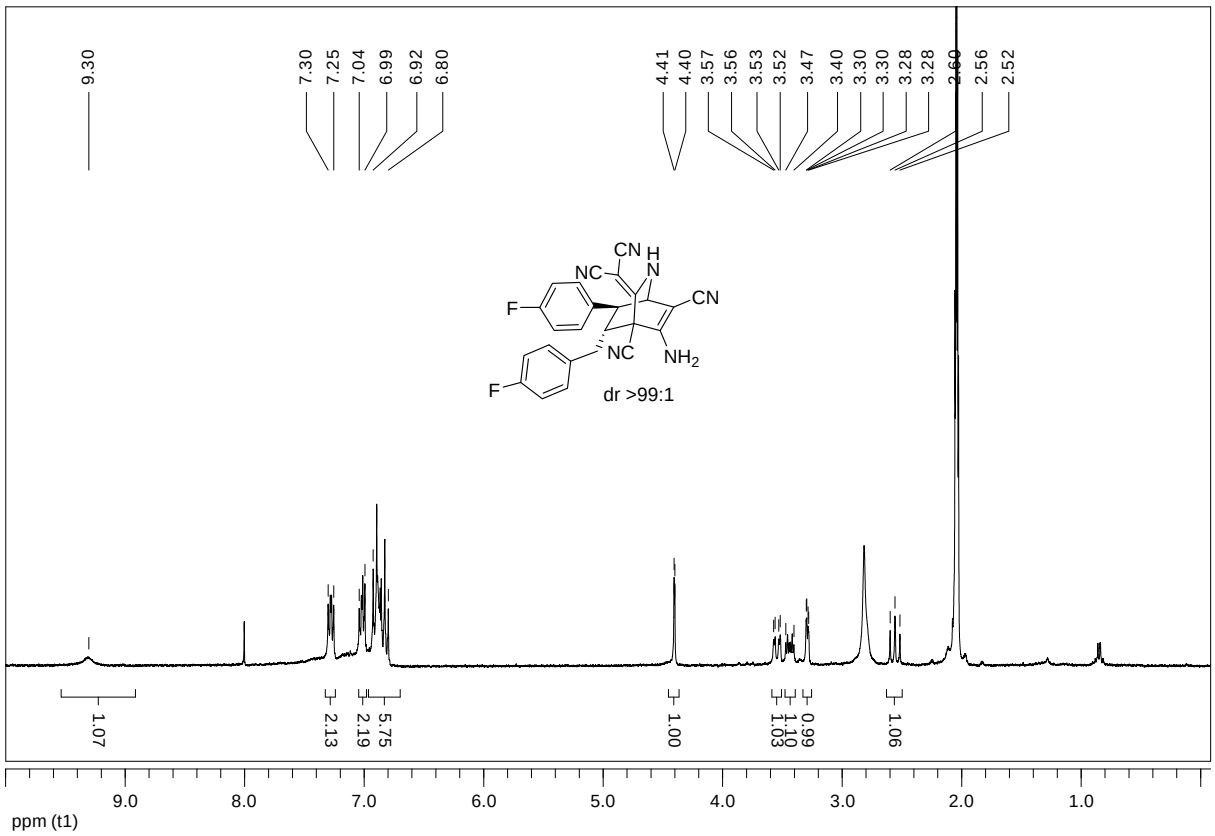
**Compound 4f: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



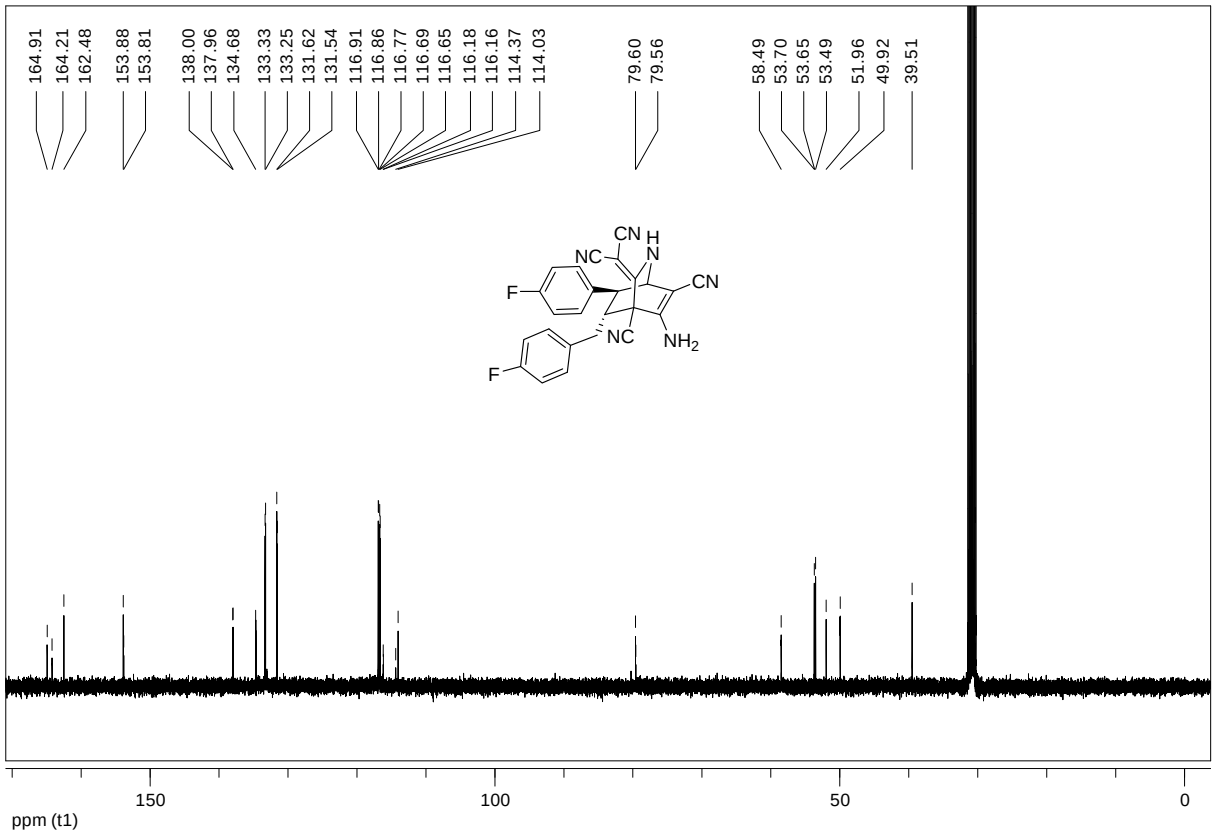

**Compound 3f: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



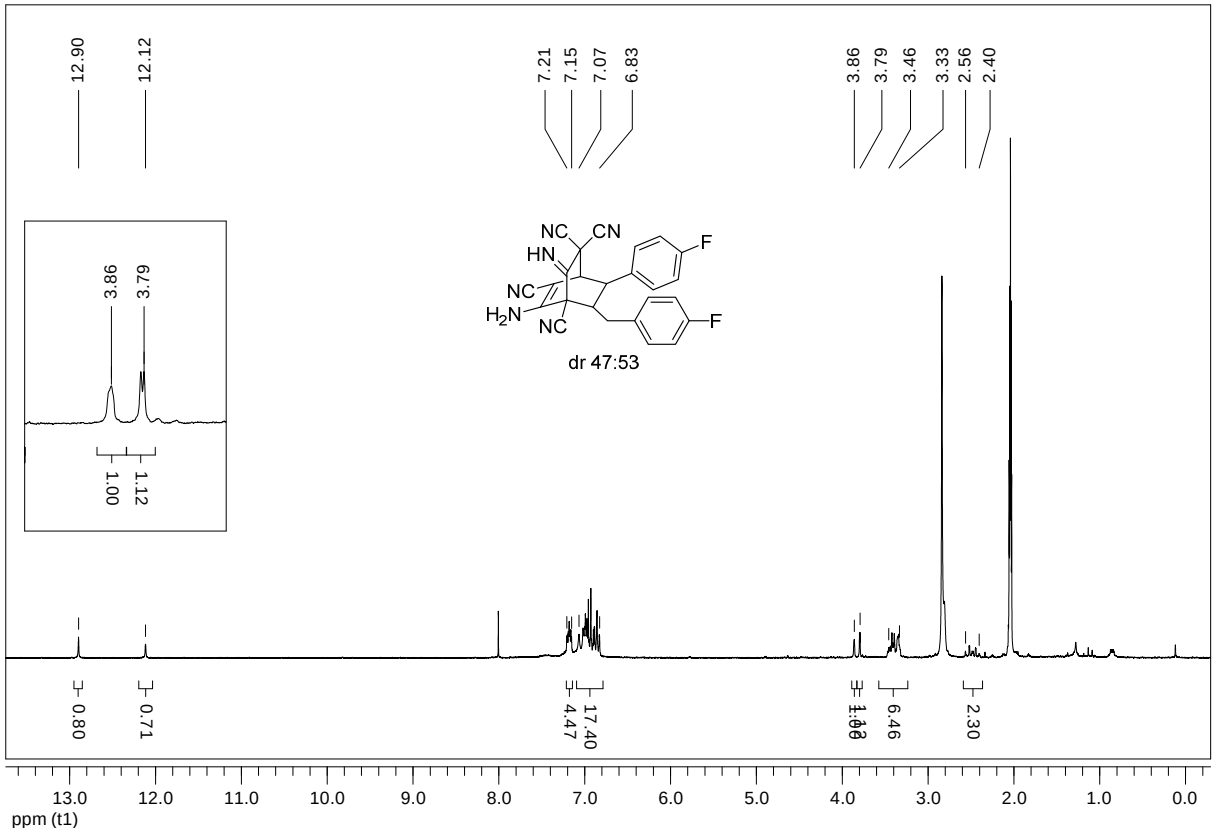
**Compound 3g: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



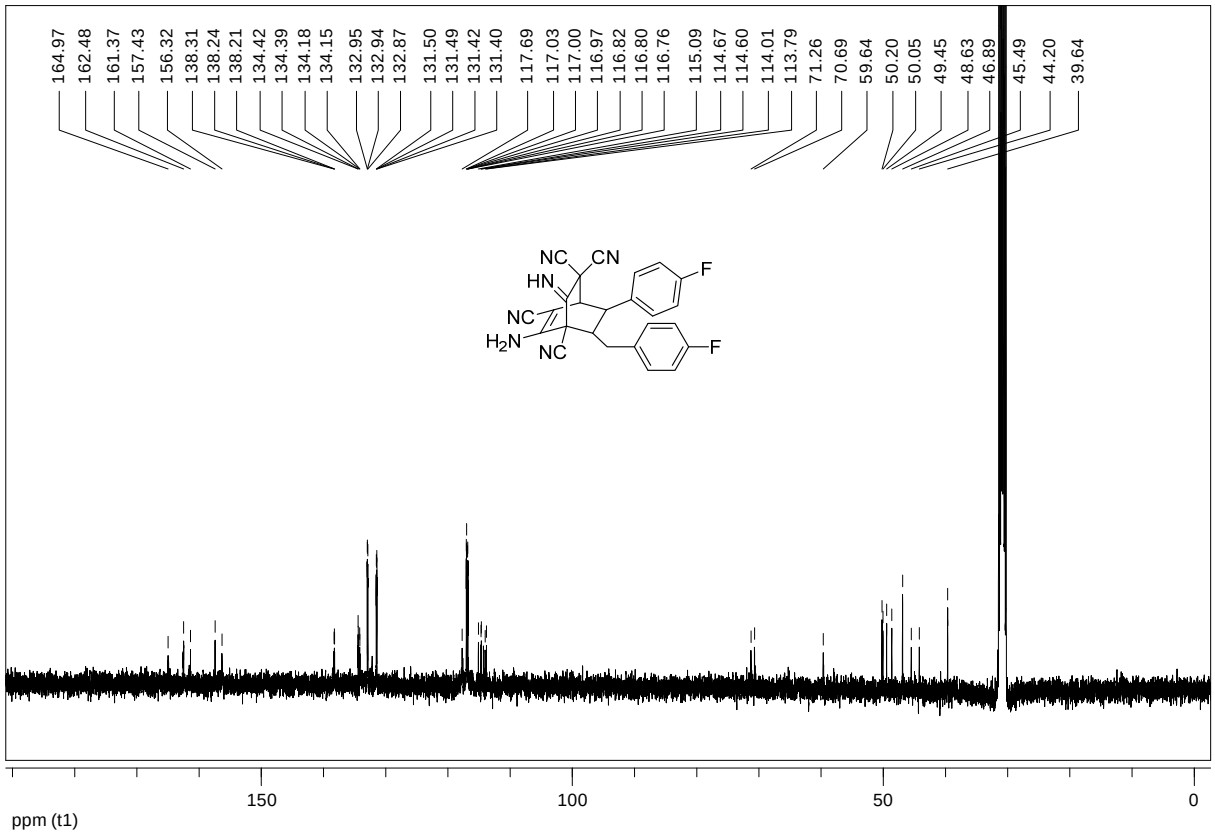

**Compound 3g: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



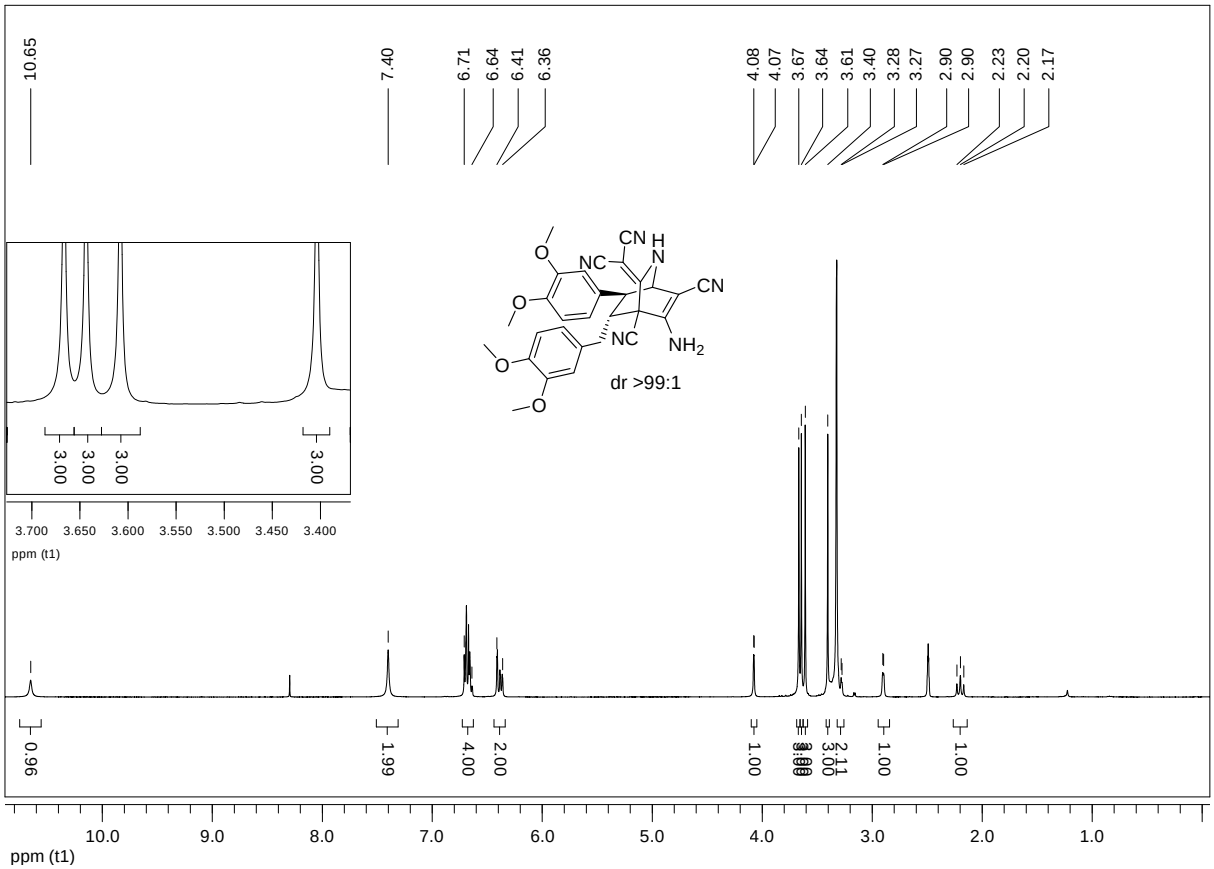
**Compound 4g: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



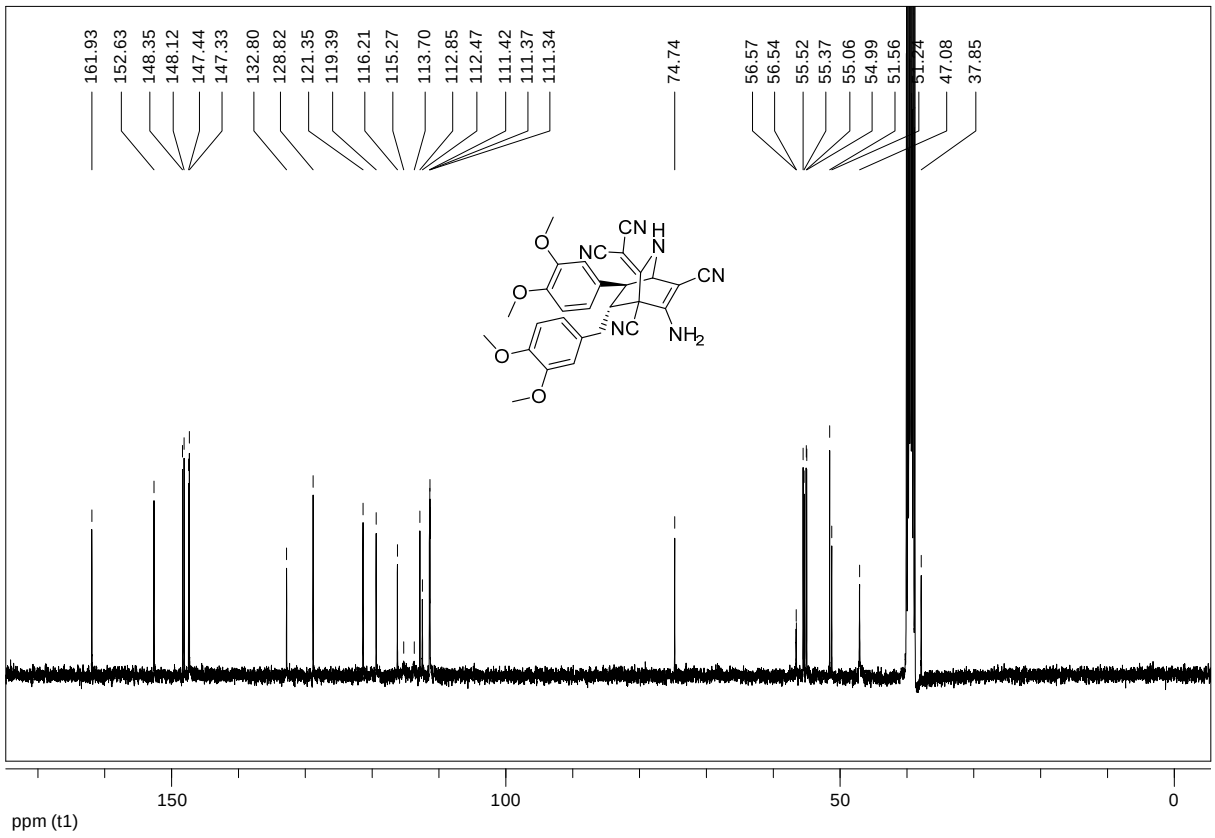

**Compound 4g: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



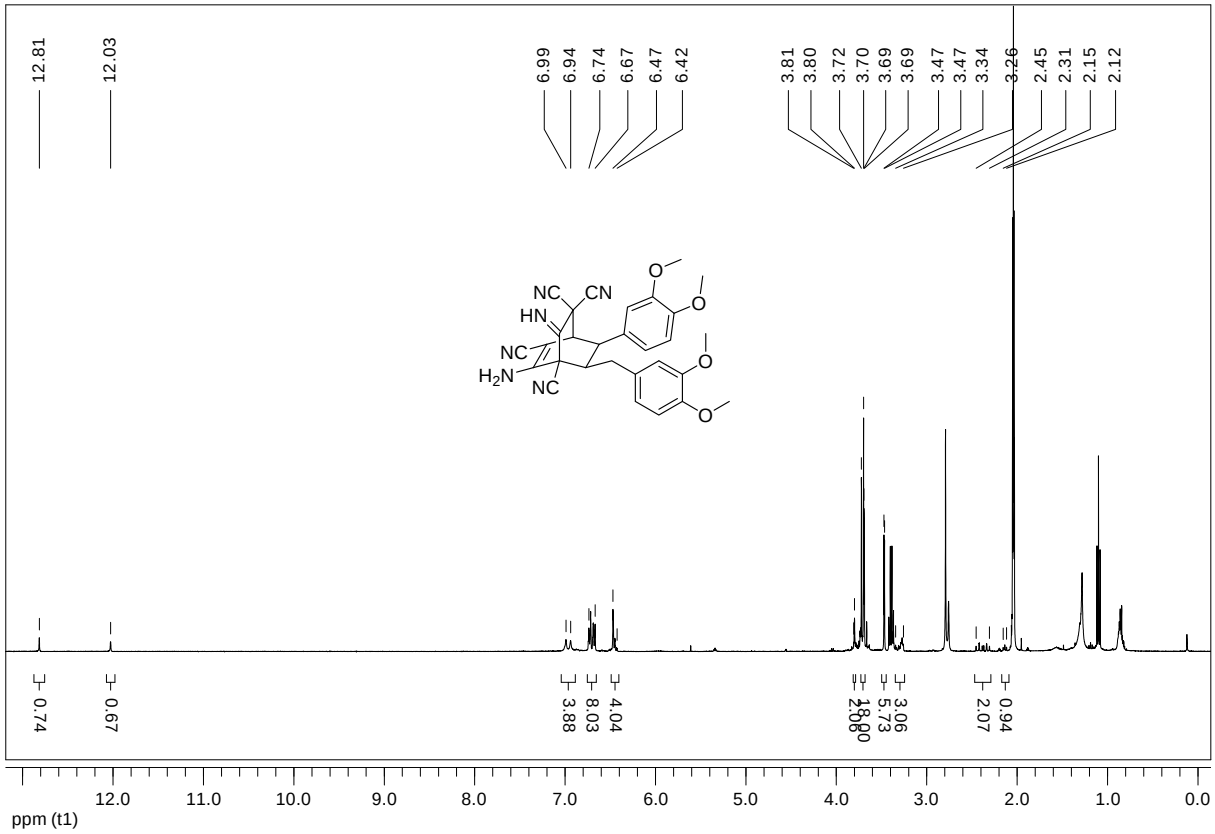
**Compound 3h: $^{1}$H-NMR (400 MHz, $(CD_3)_2SO$)**



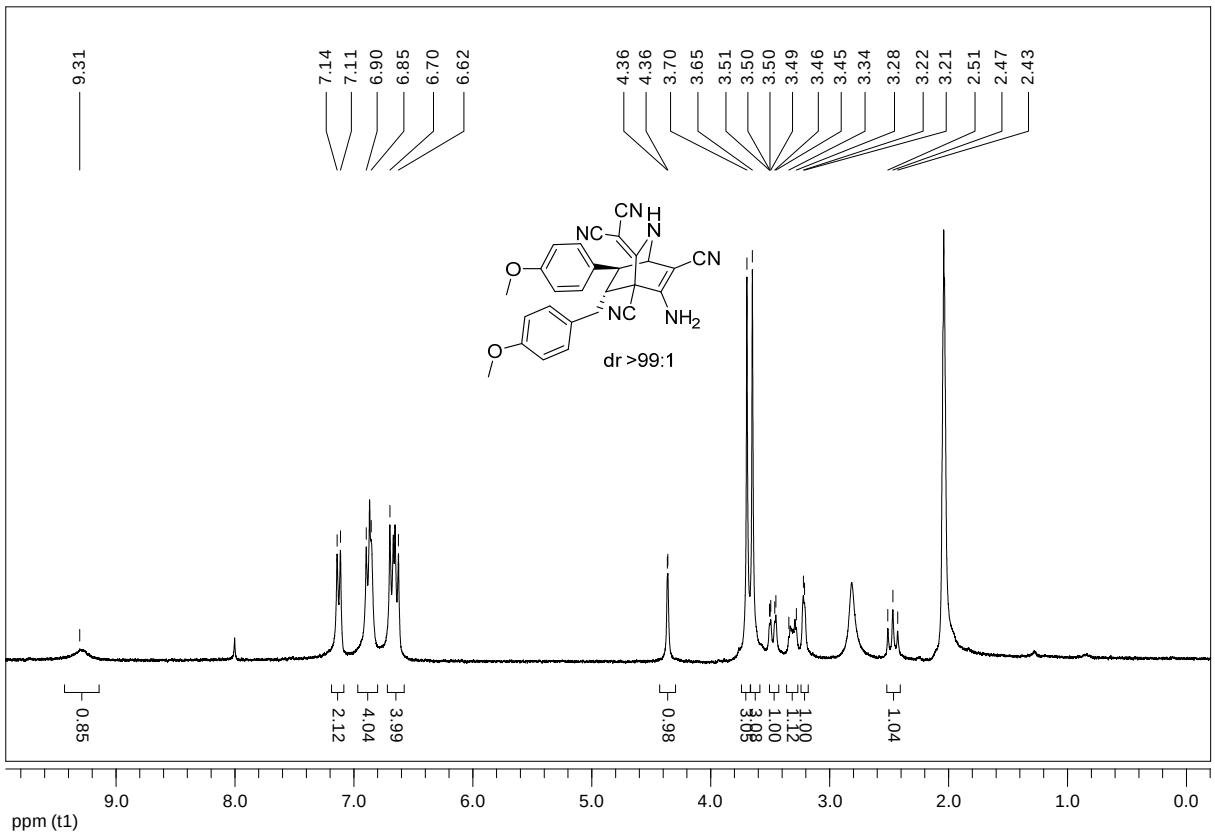

**Compound 3h: $^{13}$C-NMR (100 MHz, $(CD_3)_2SO$)**



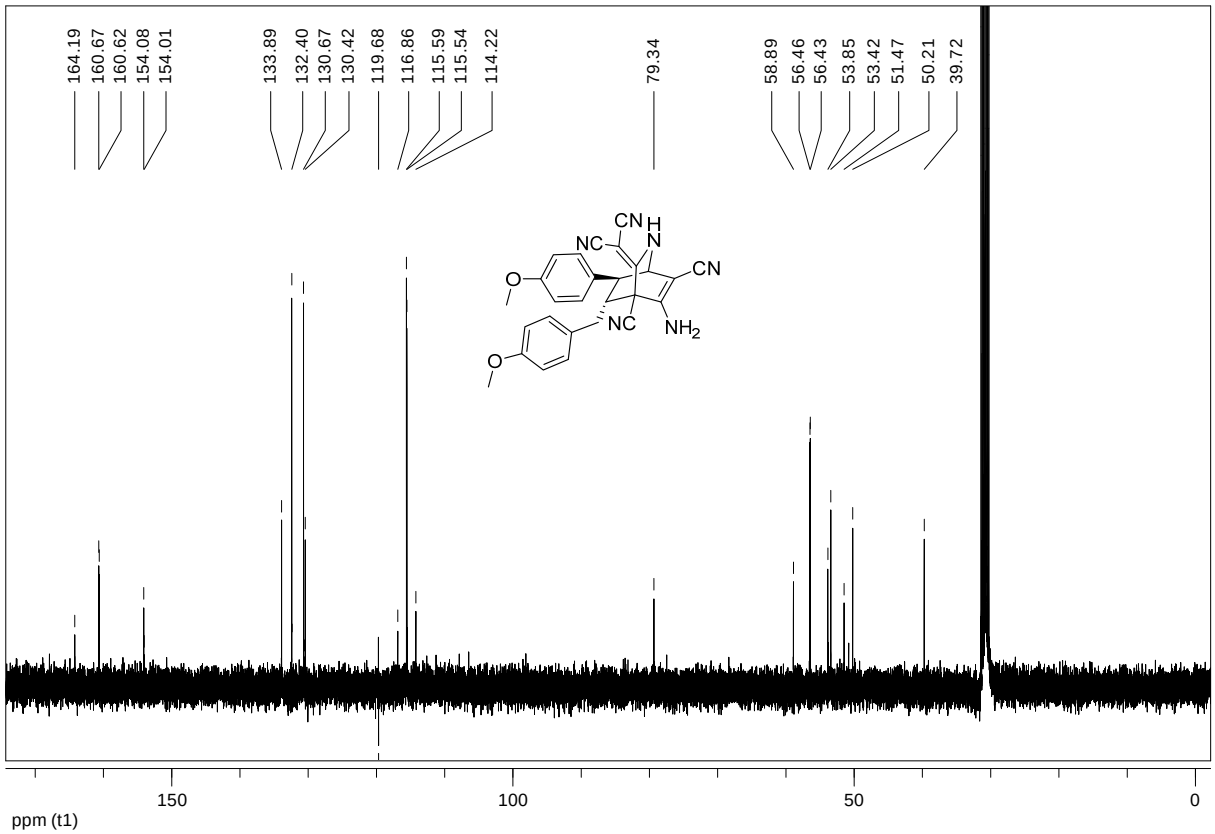
**Compound 4h: $^{1}$H-NMR (400 MHz, $(CD_3)_2CO$)**



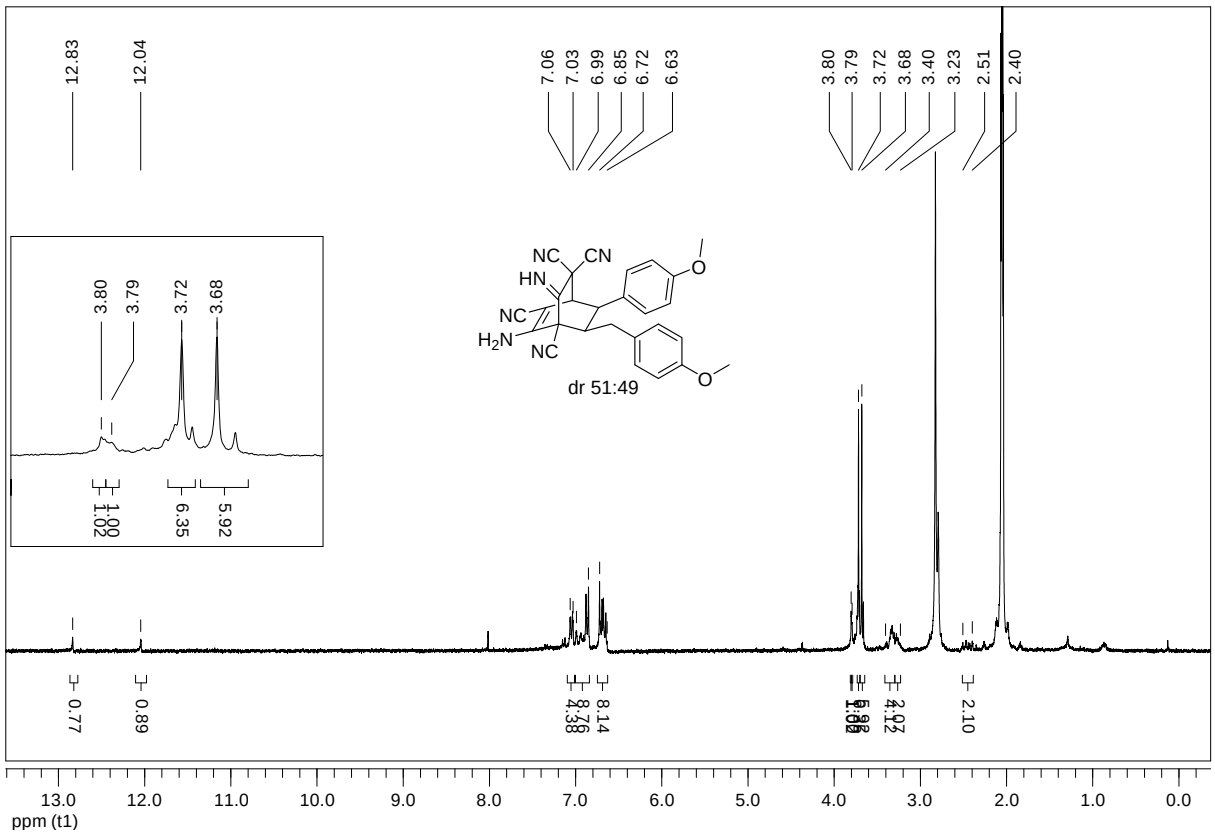
**Compound 3i: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



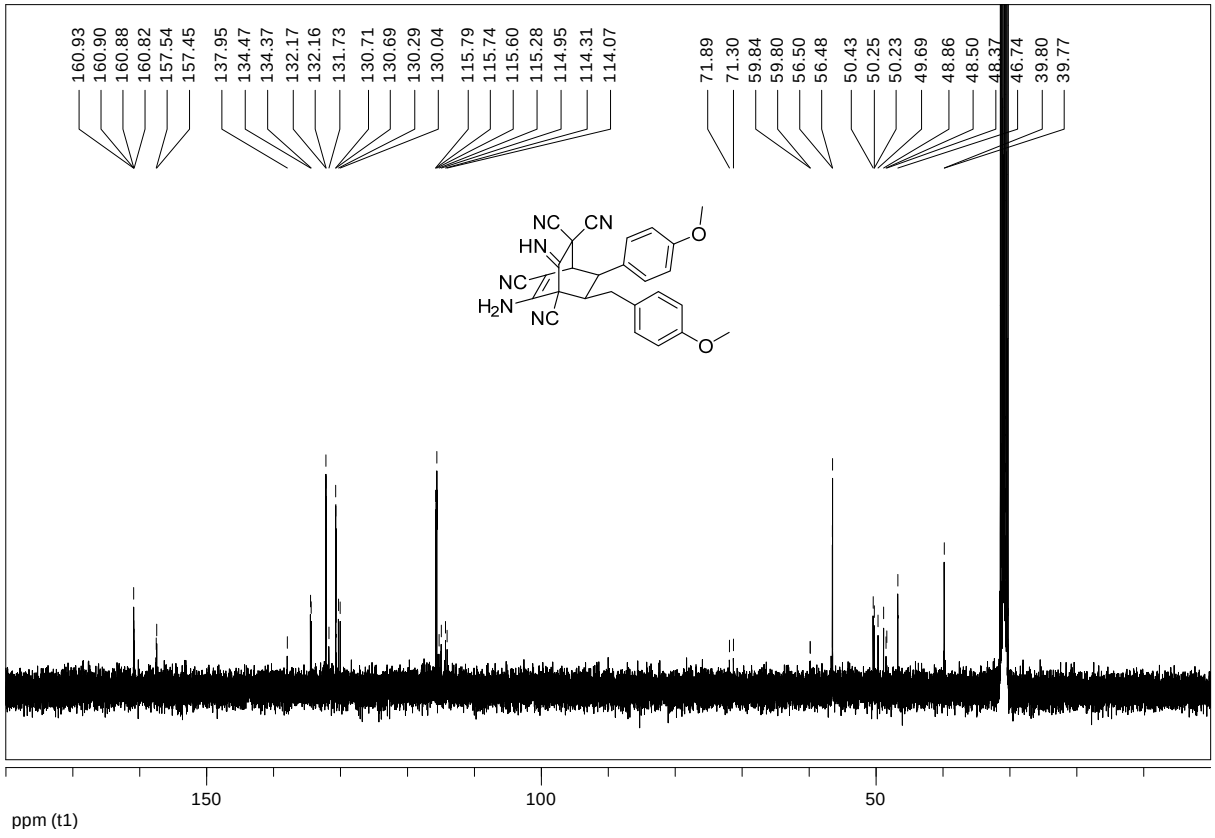

**Compound 3i: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



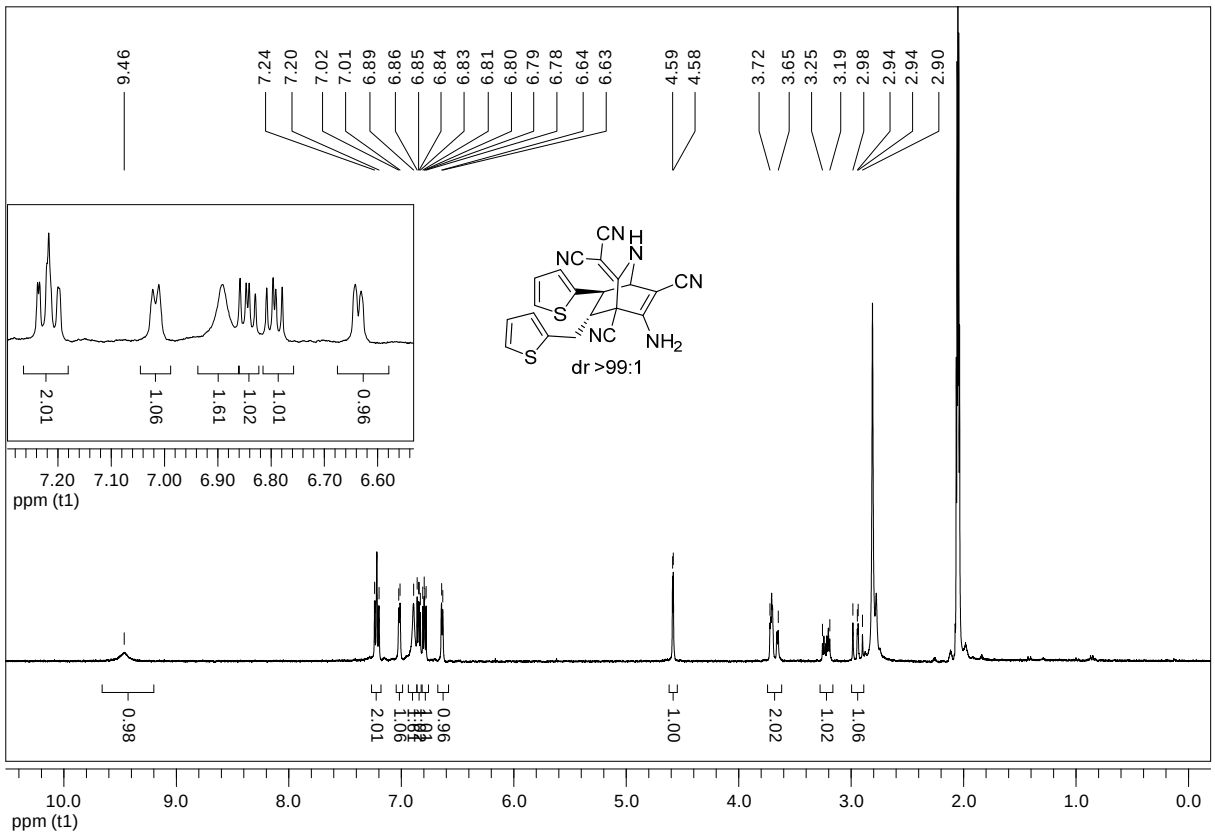
**Compound 4i: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



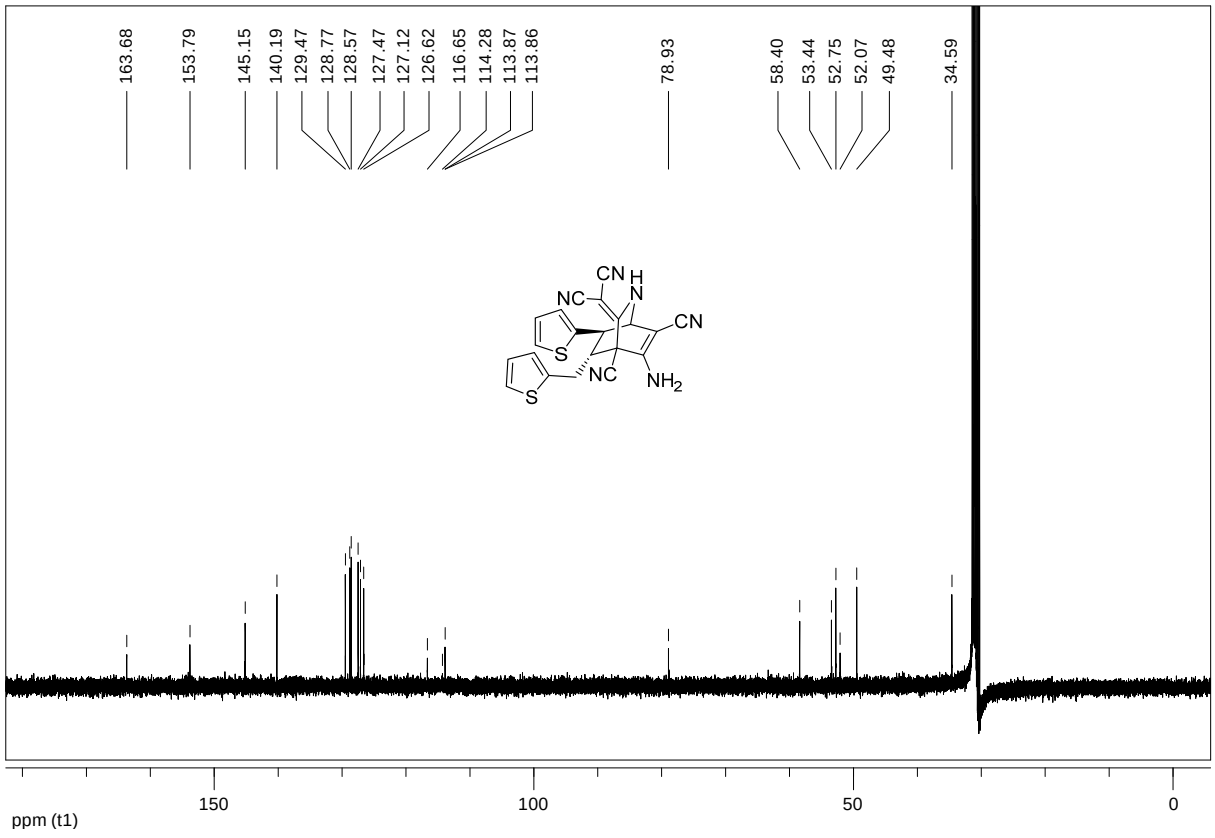

**Compound 4i: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



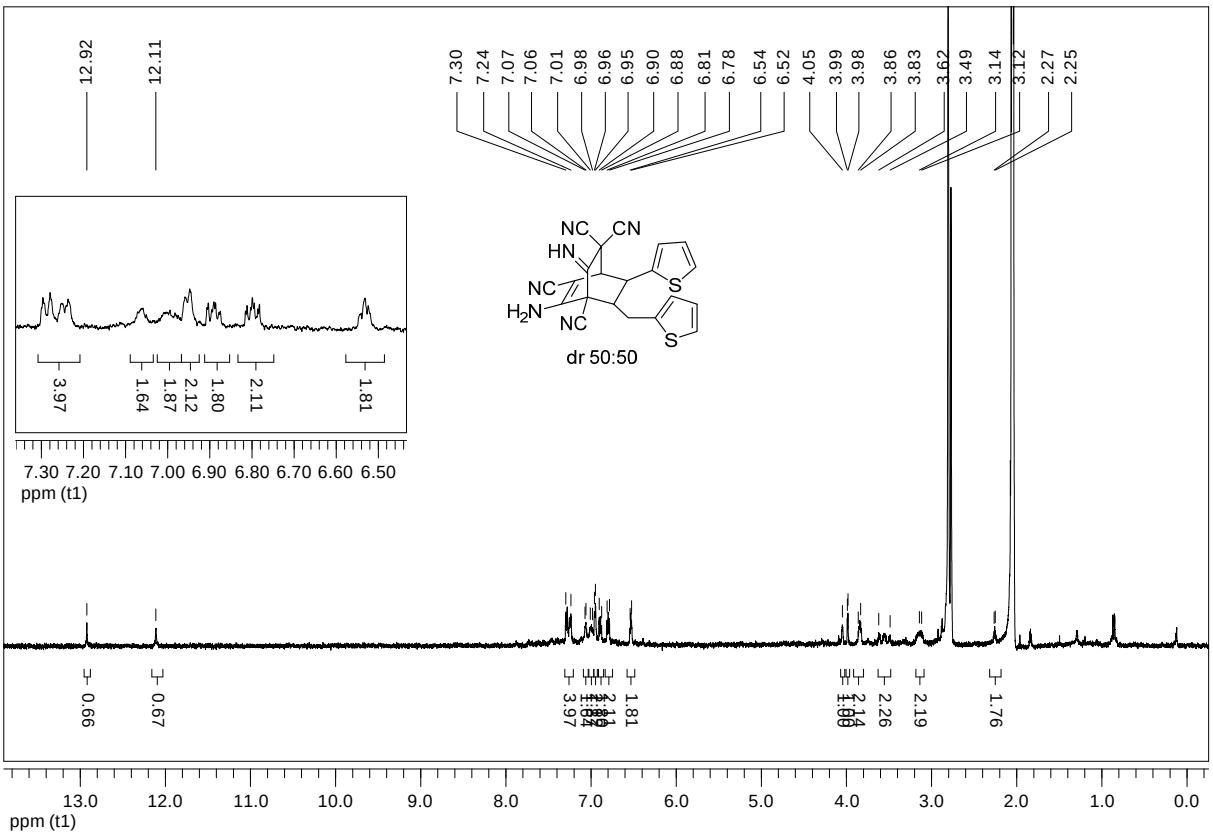
**Compound 3j: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



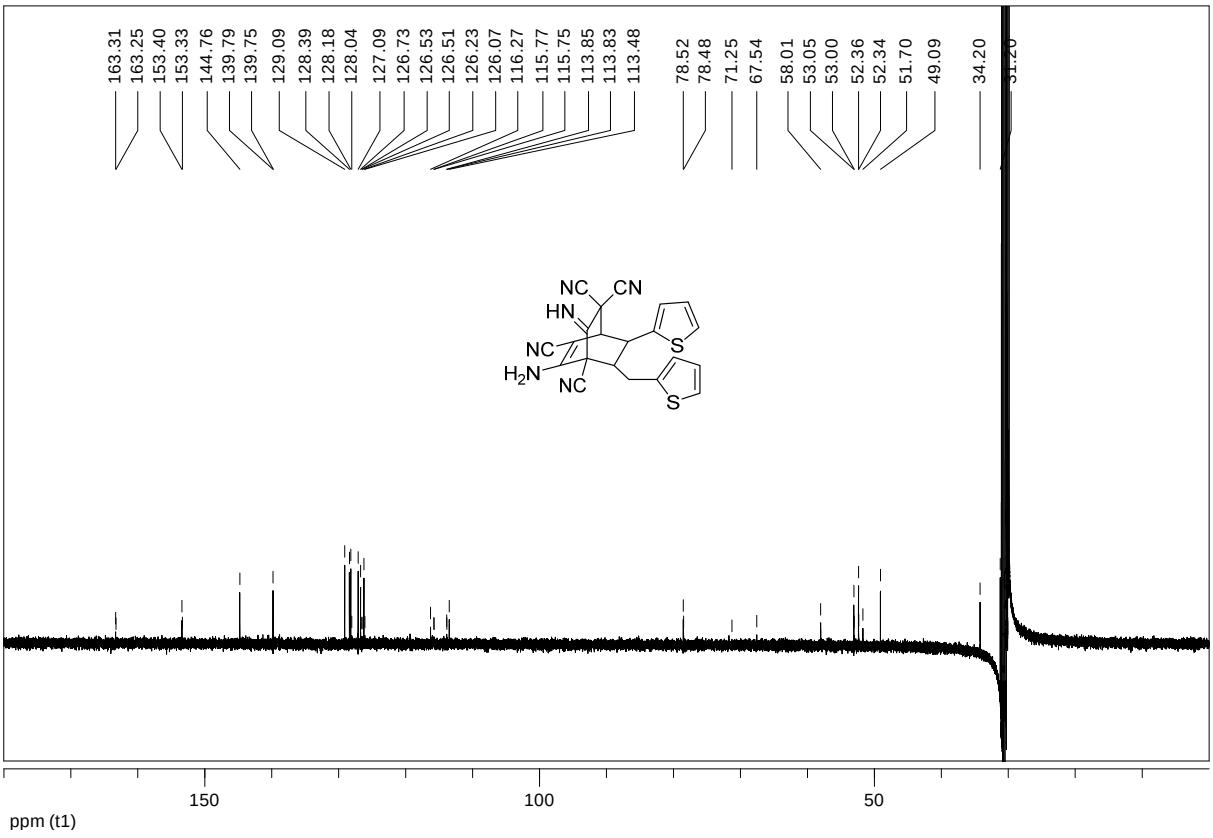

**Compound 3j: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



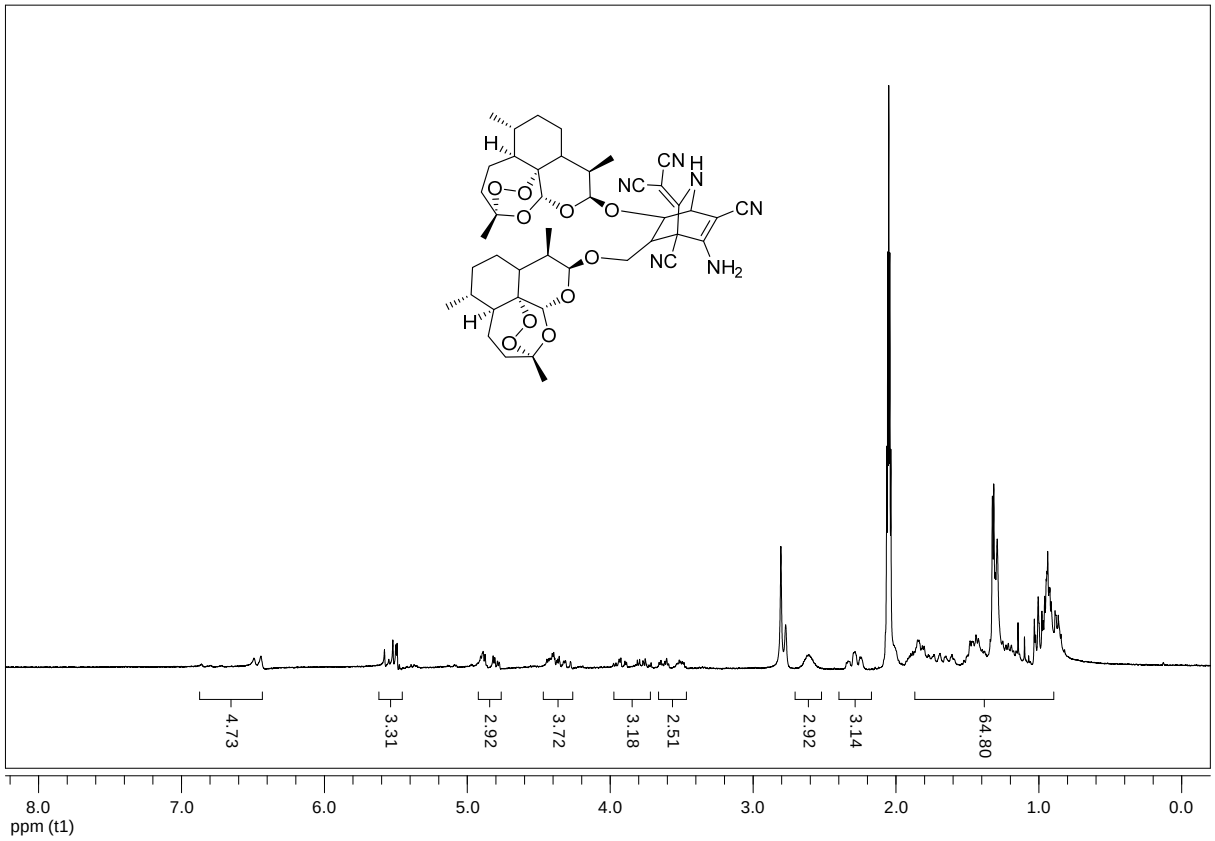
**Compound 4j: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



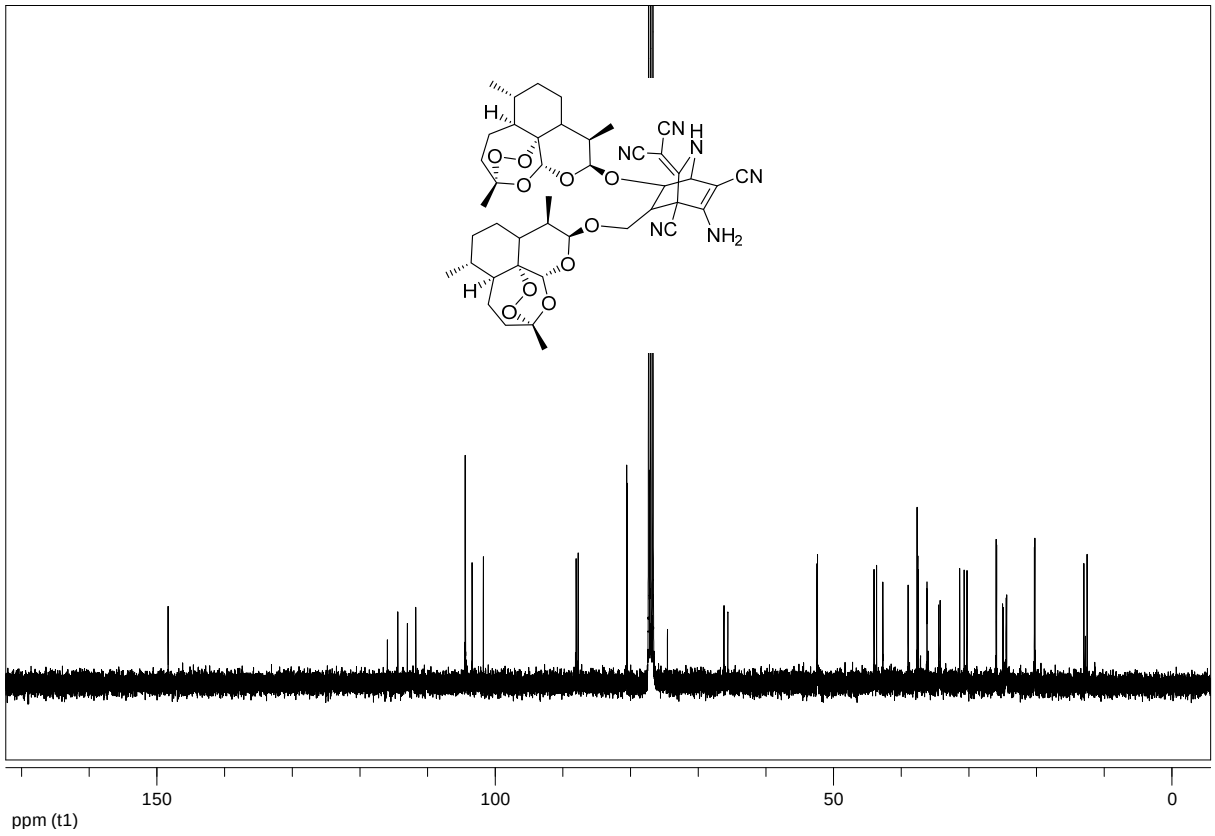

**Compound 4j: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



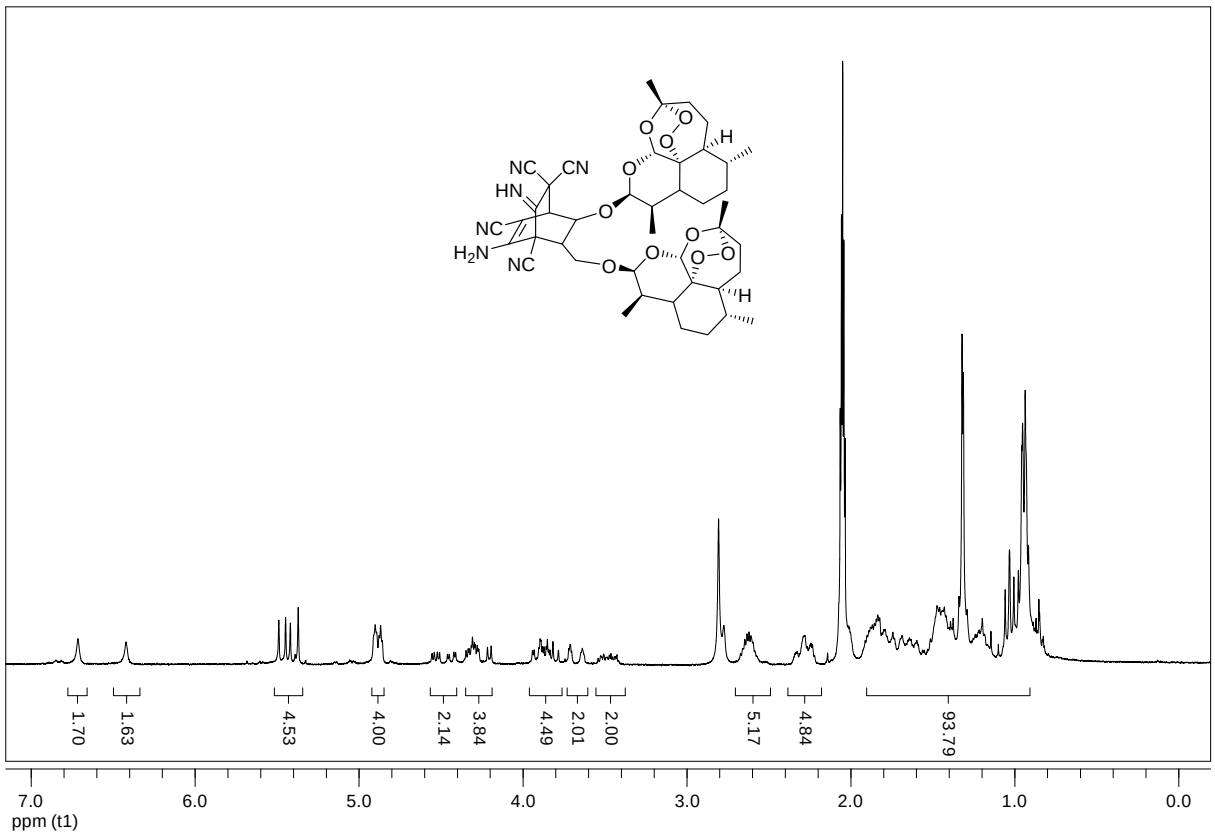
**Compound 3k: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



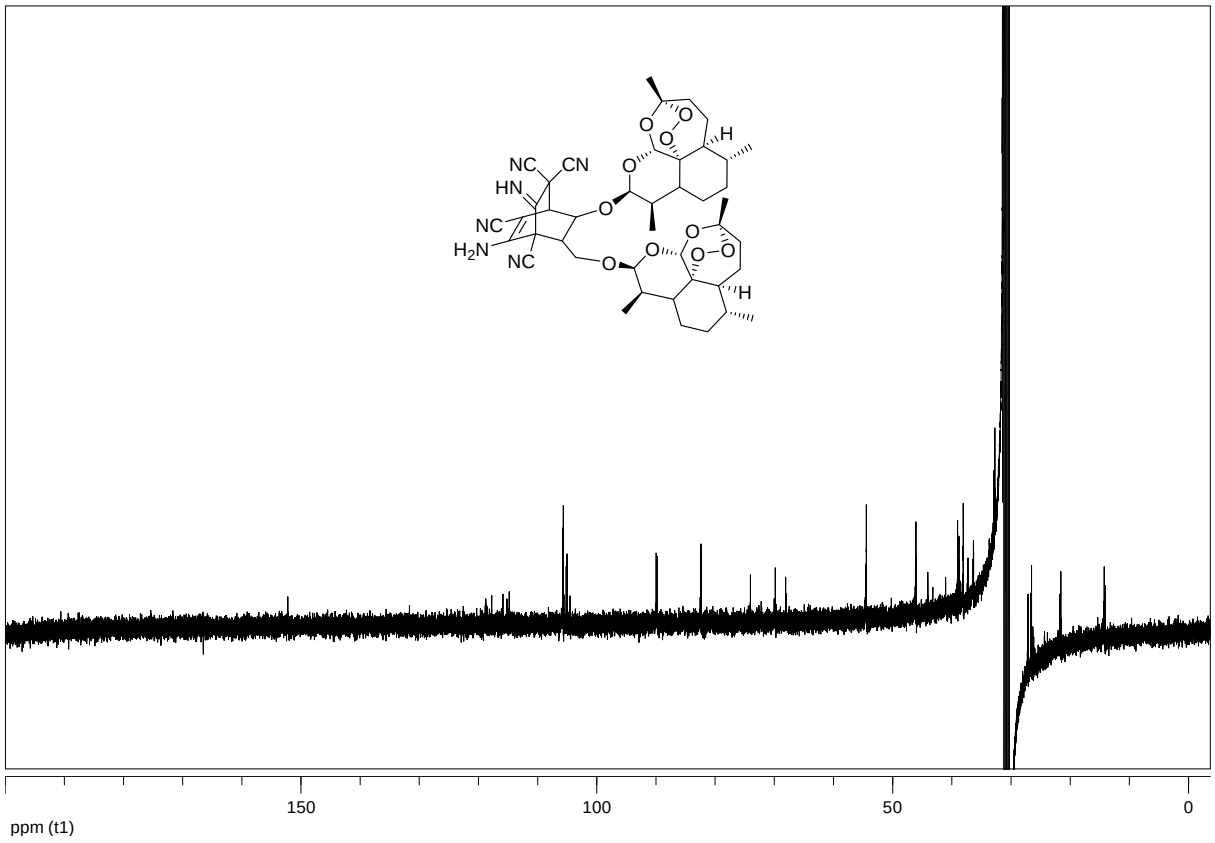

**Compound 3k: $^{13}$C-NMR (100 MHz, $CDCl_3$)**



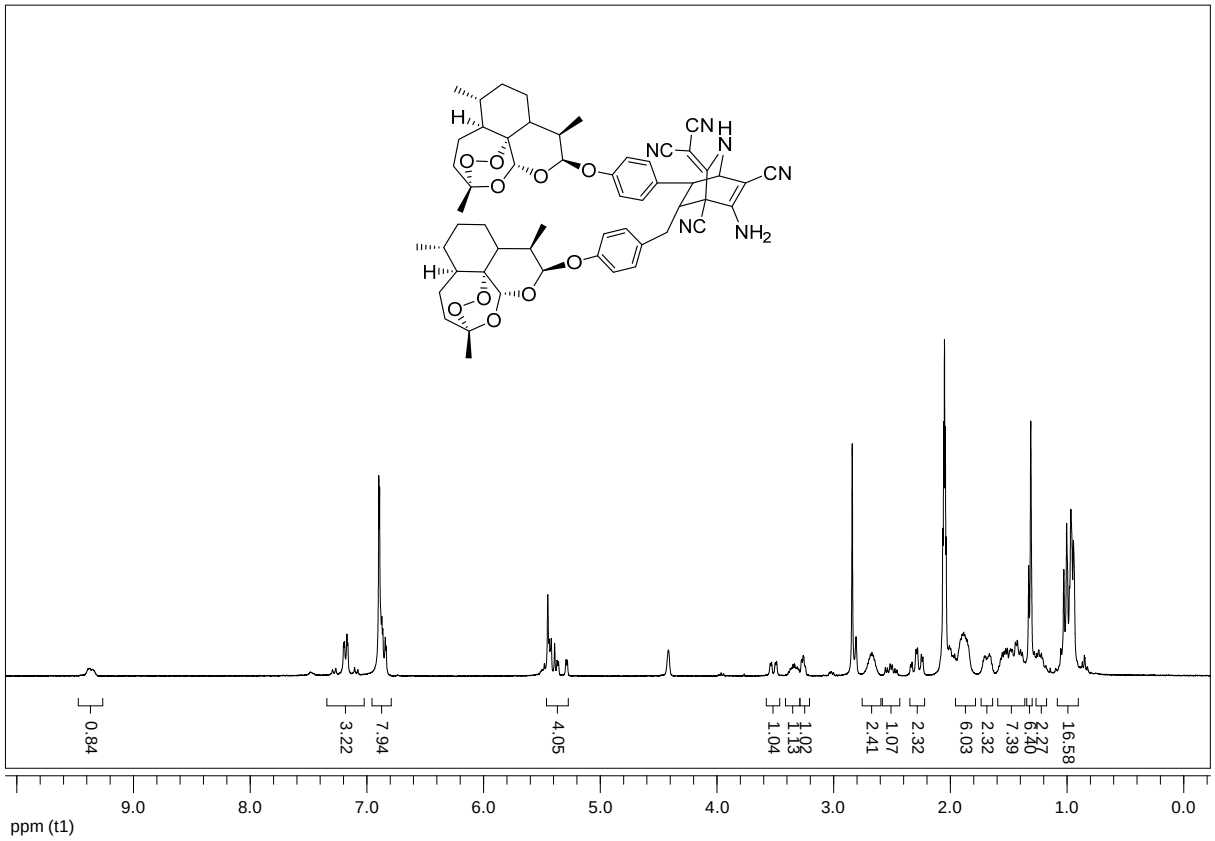
**Compound 4k: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



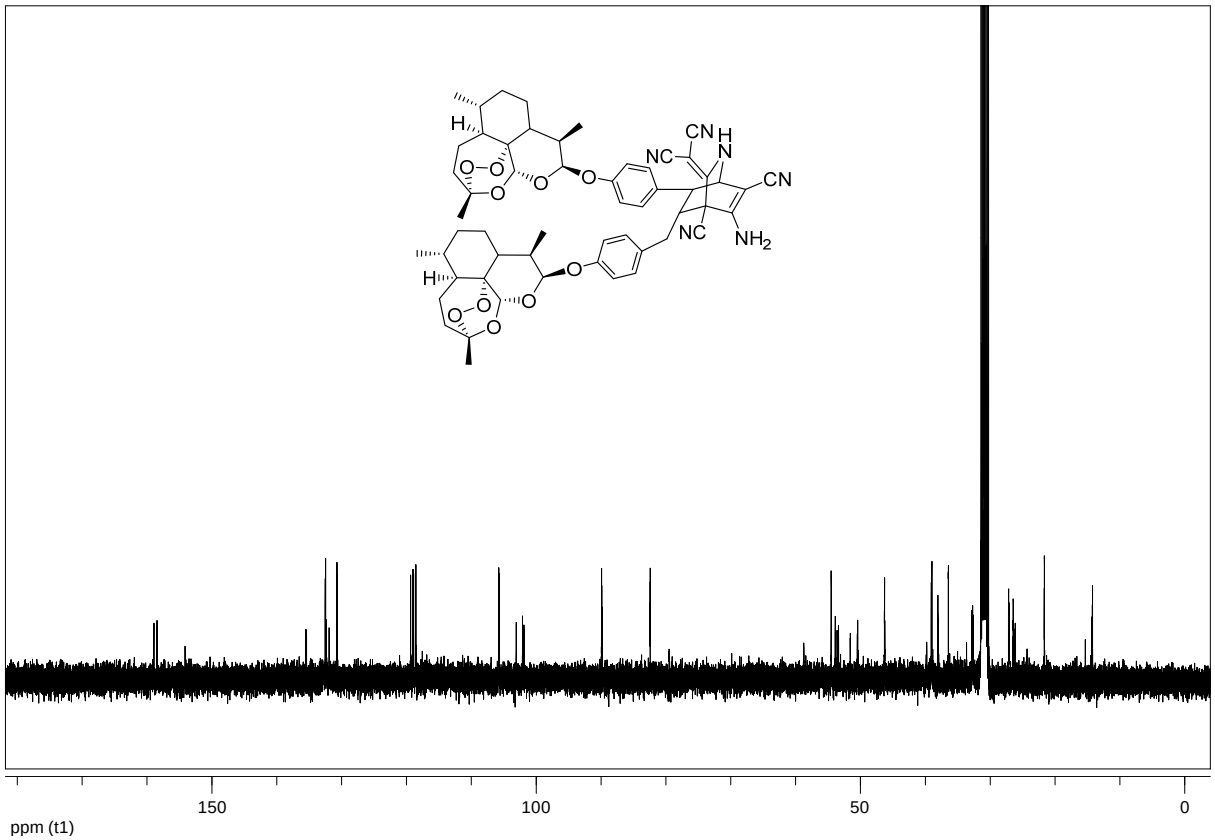

**Compound 4k: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



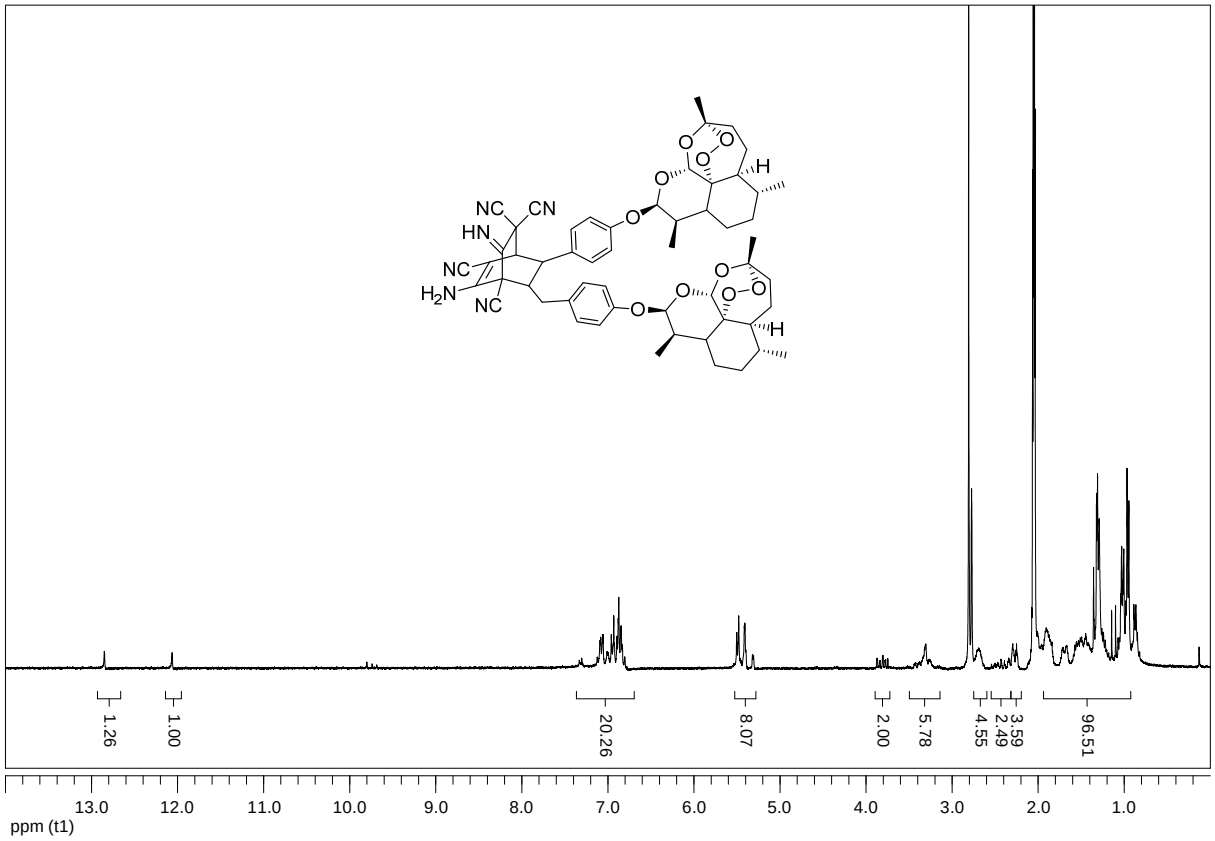
**Compound 3l: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**



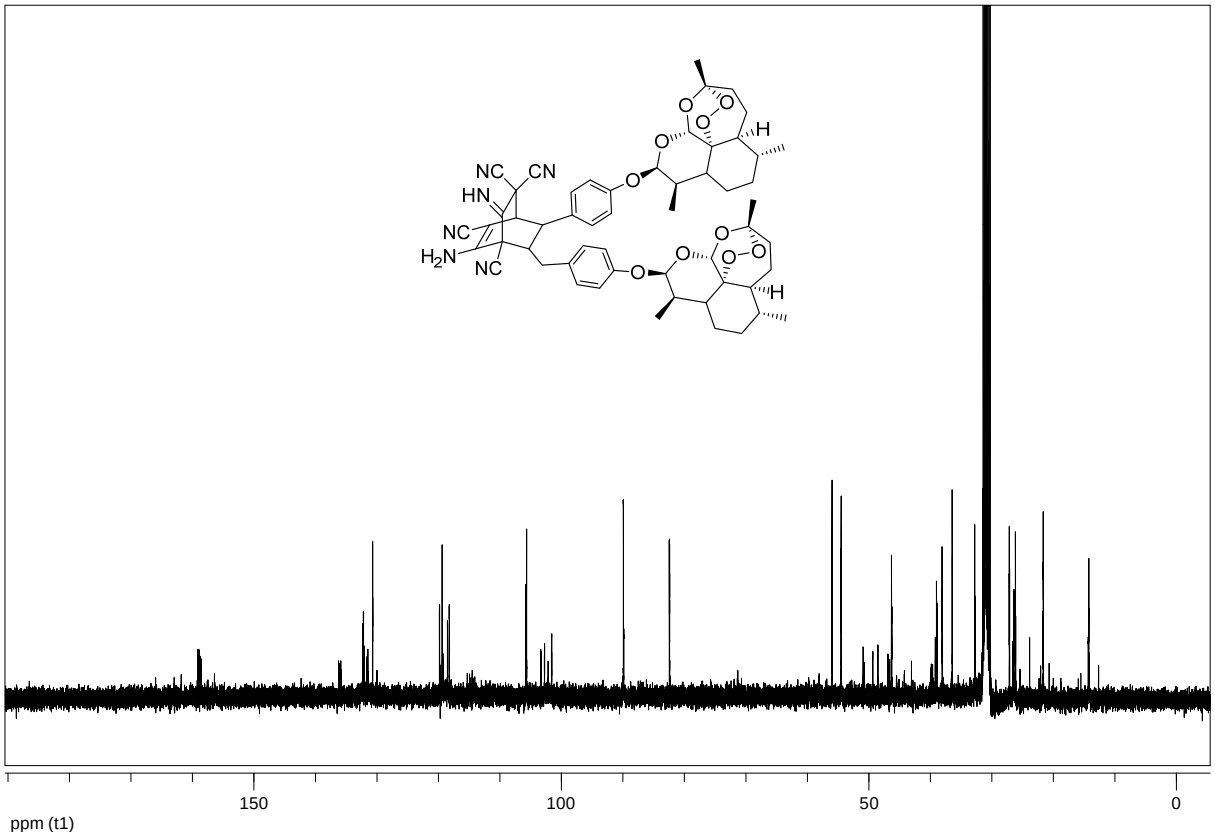

**Compound 3l: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**



**Compound 4l: $^{1}$H-NMR (300 MHz, $(CD_3)_2CO$)**

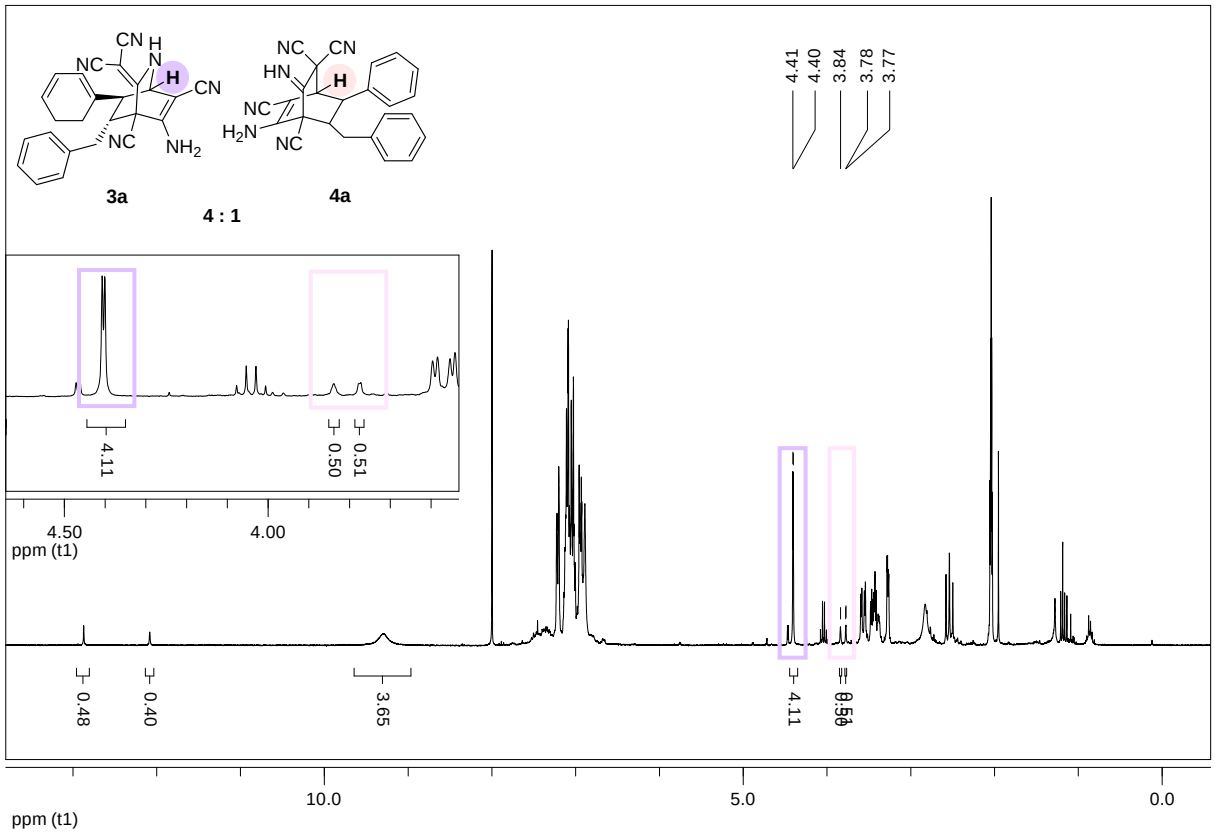



**Compound 4l: $^{13}$C-NMR (100 MHz, $(CD_3)_2CO$)**

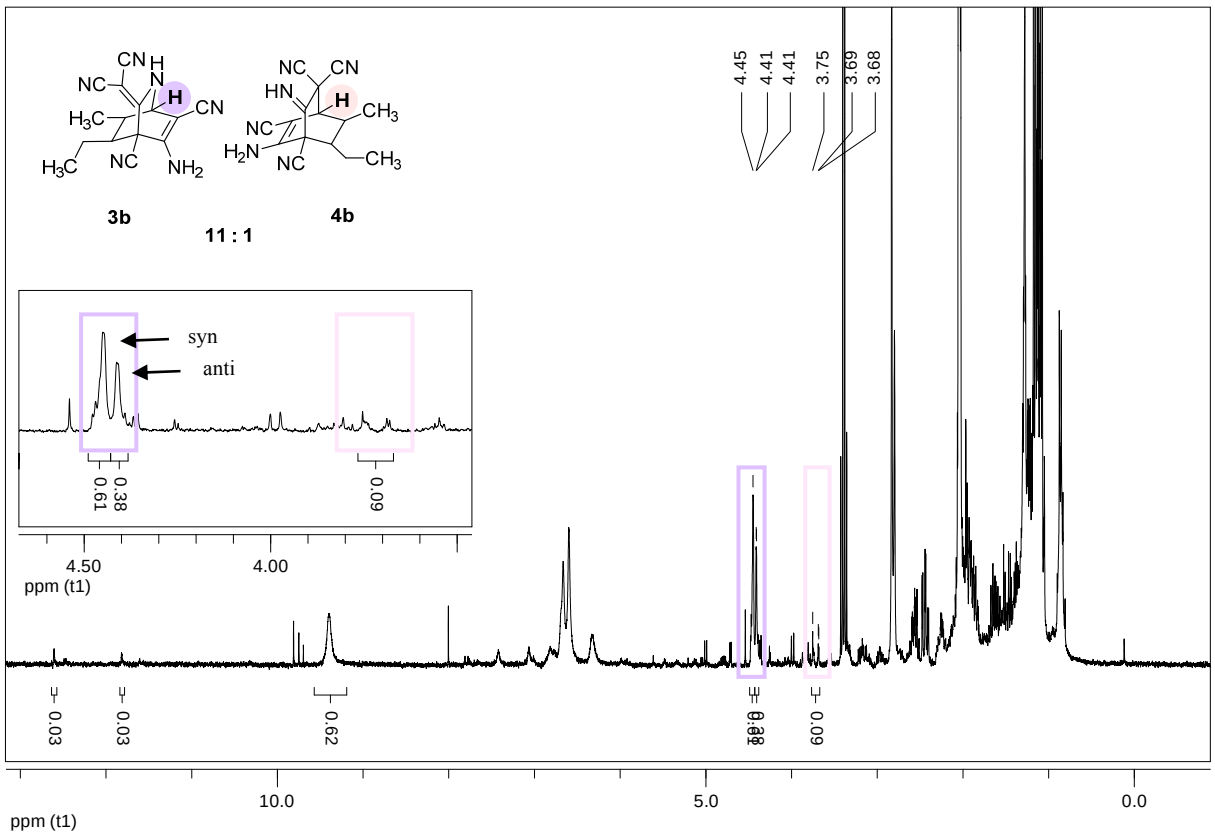


## 3 Determination ofisomers ratio 3 to 4

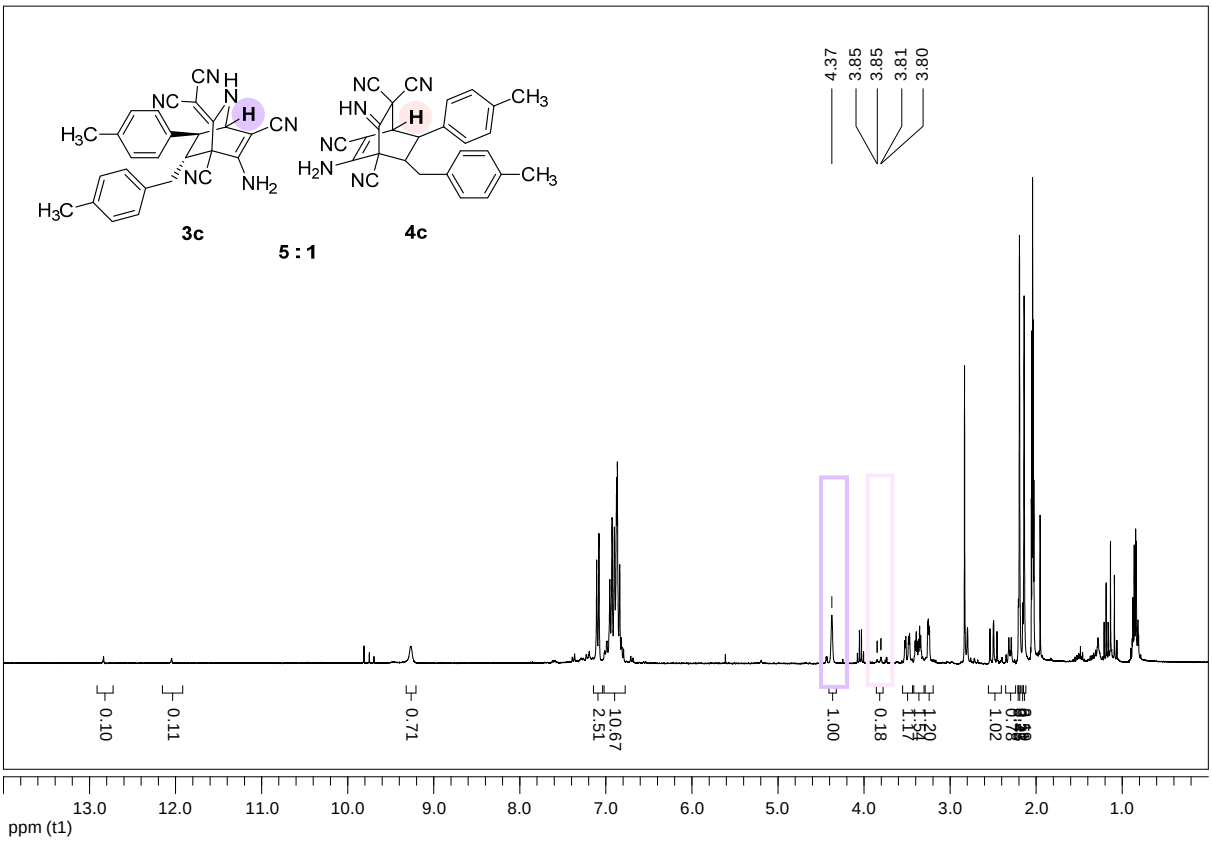
### 3.1 $^{1}$H-NMR spectrum of compound mixture 3a and 4a



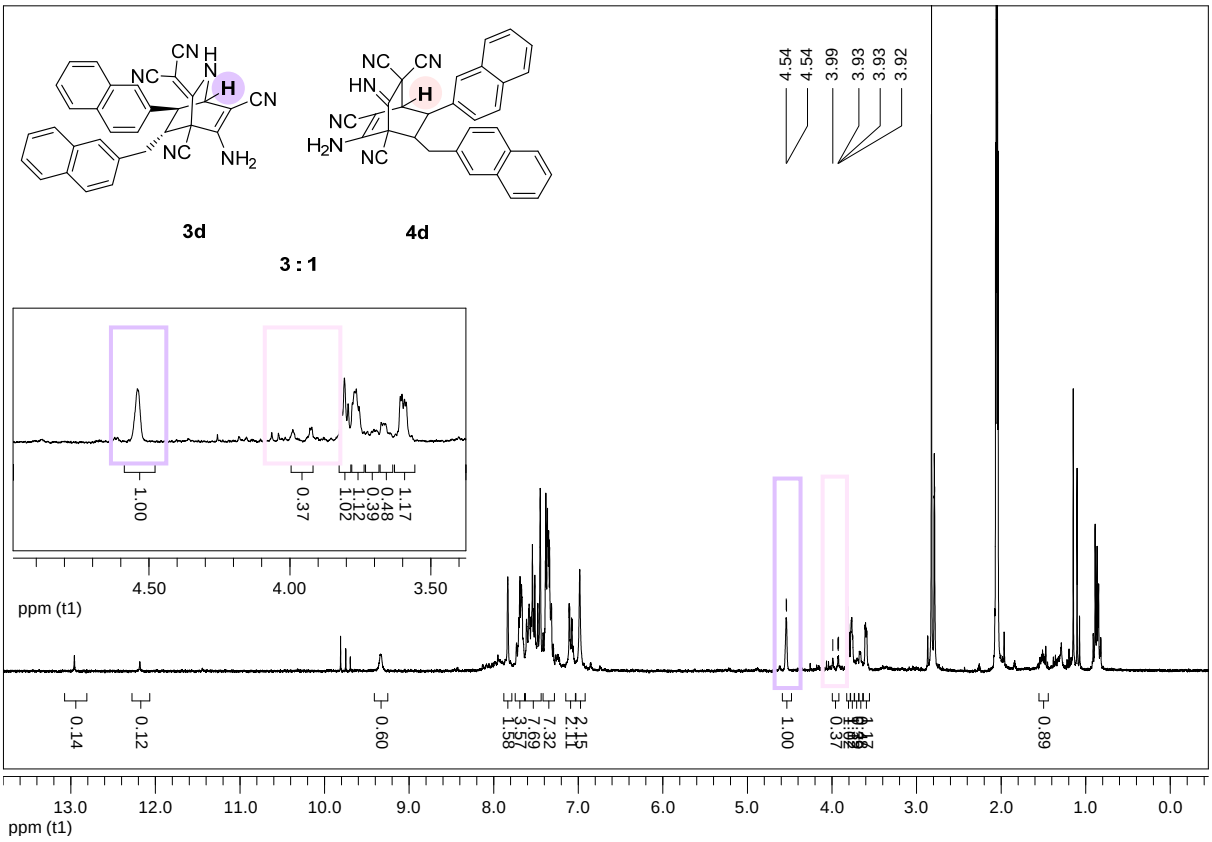

### 3.2 $^{1}$H-NMR spectrum of compound mixture 3b and 4b



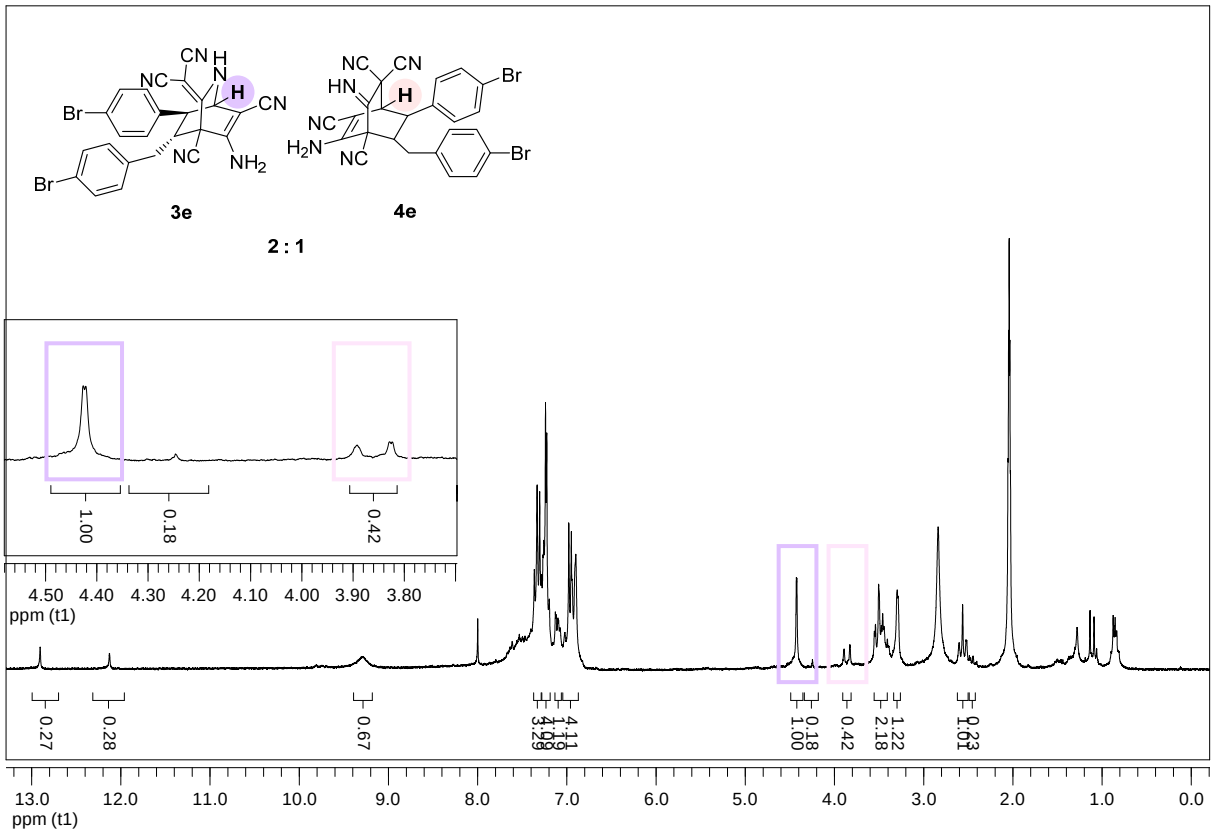
### 3.3 $^{1}$H-NMR spectrum of compound mixture 3c and 4c



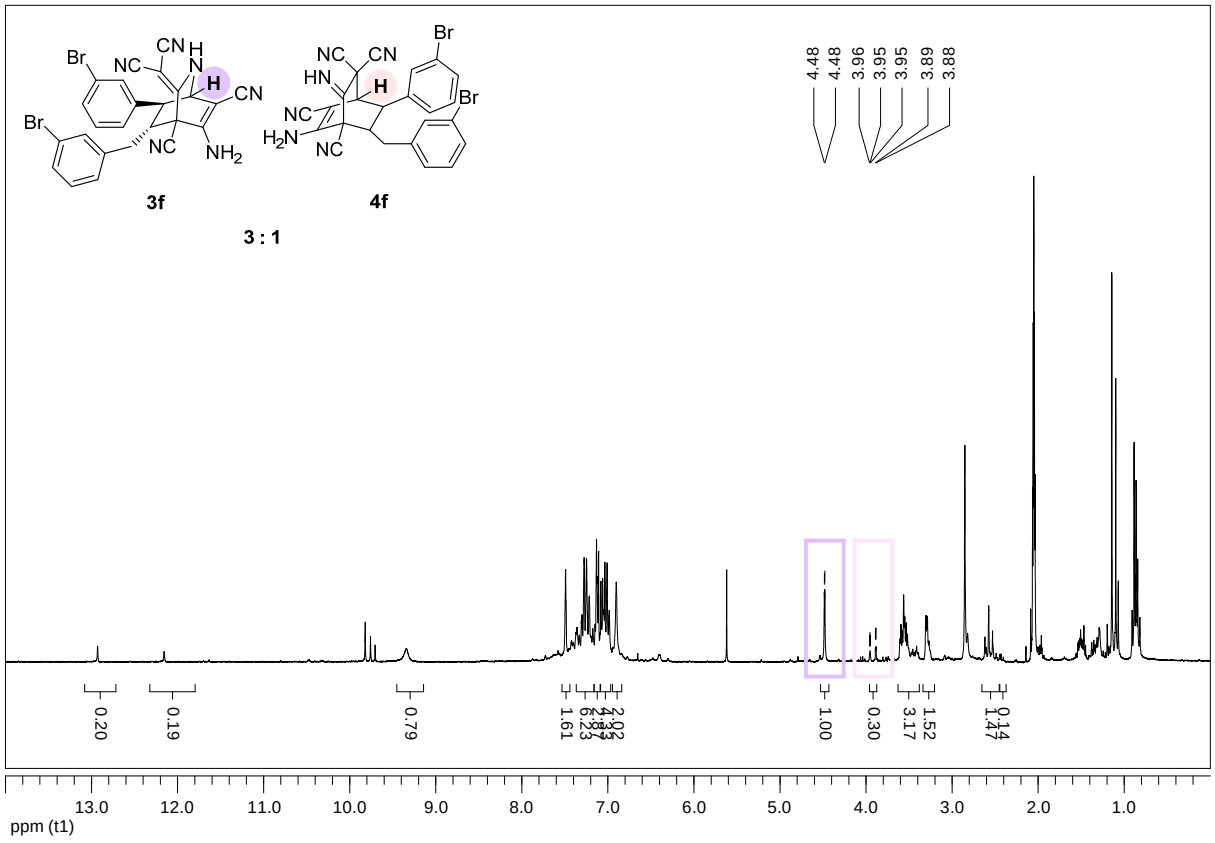

### 3.4 $^{1}$H-NMR spectrum of compound mixture 3d and 4d



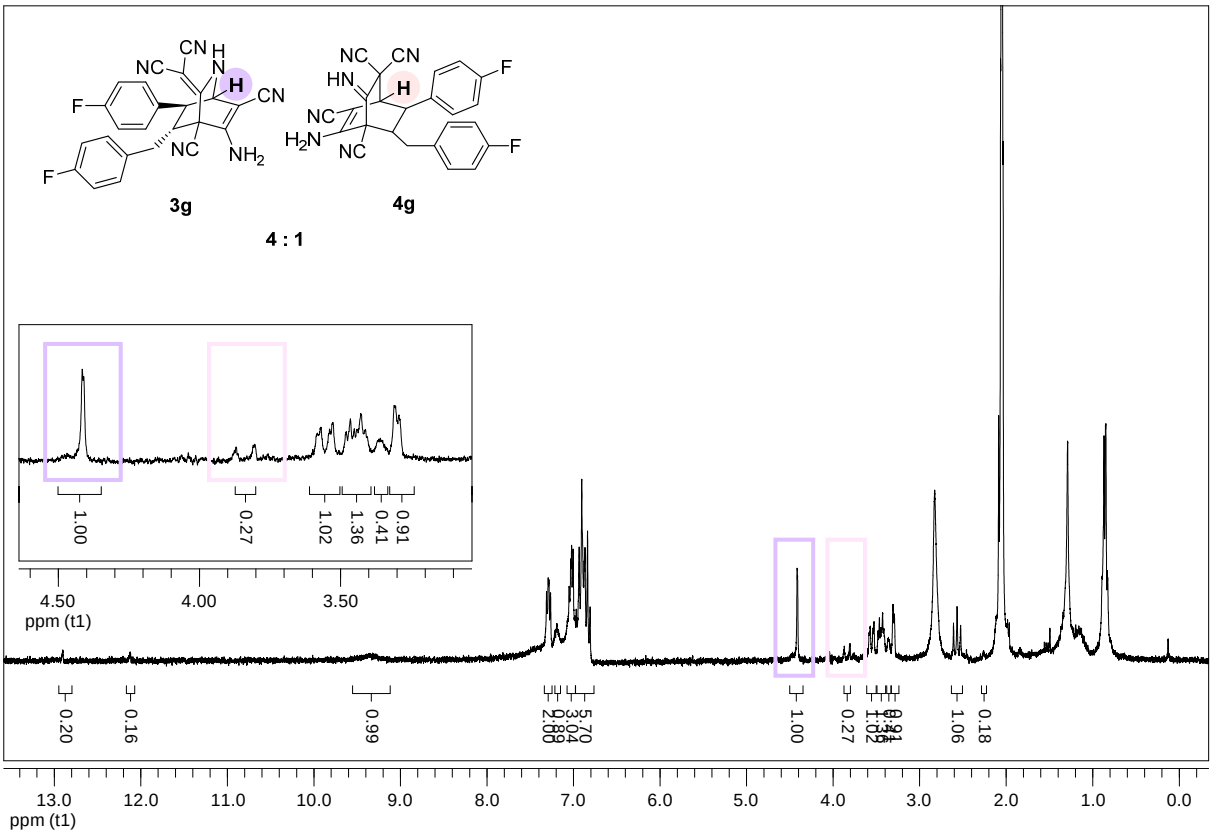
### 3.5 $^{1}$H-NMR spectrum of compound mixture 3e and 4e



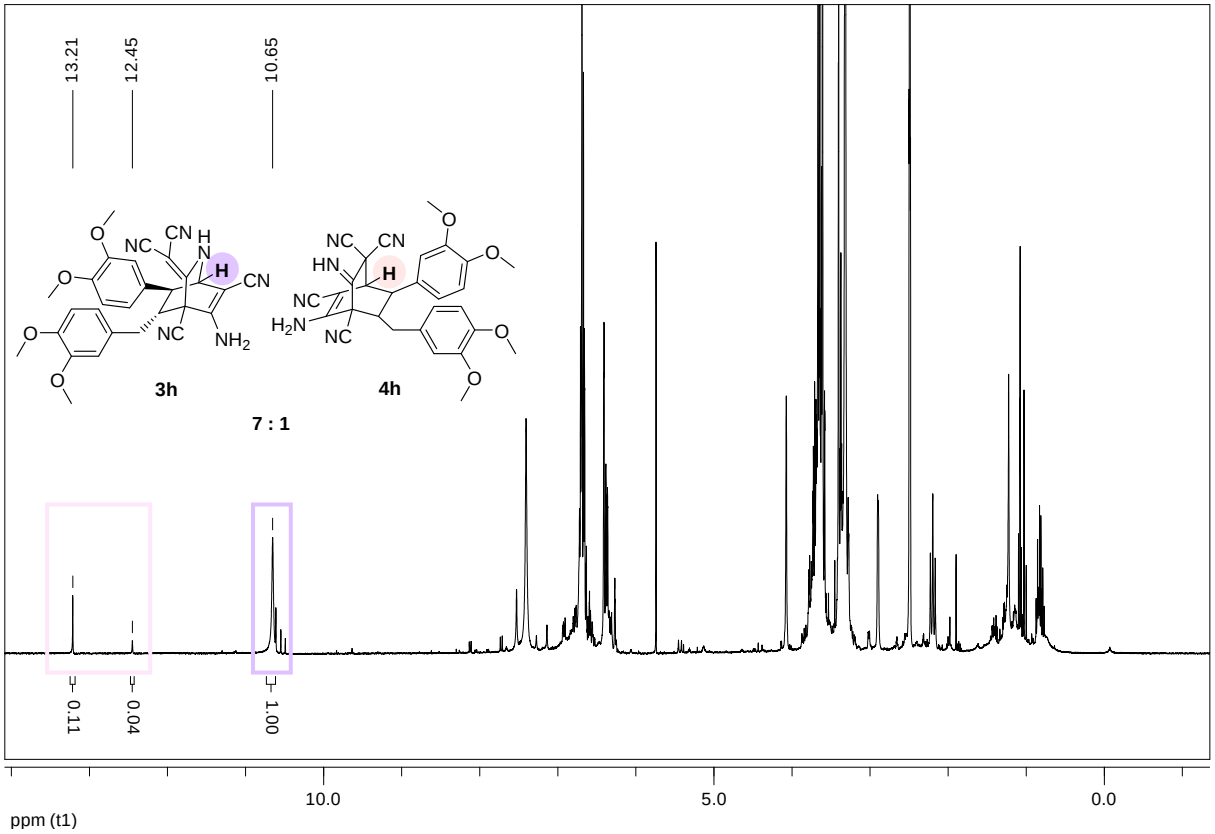

### 3.6 $^{1}$H-NMR spectrum of compound mixture 3f and 4f



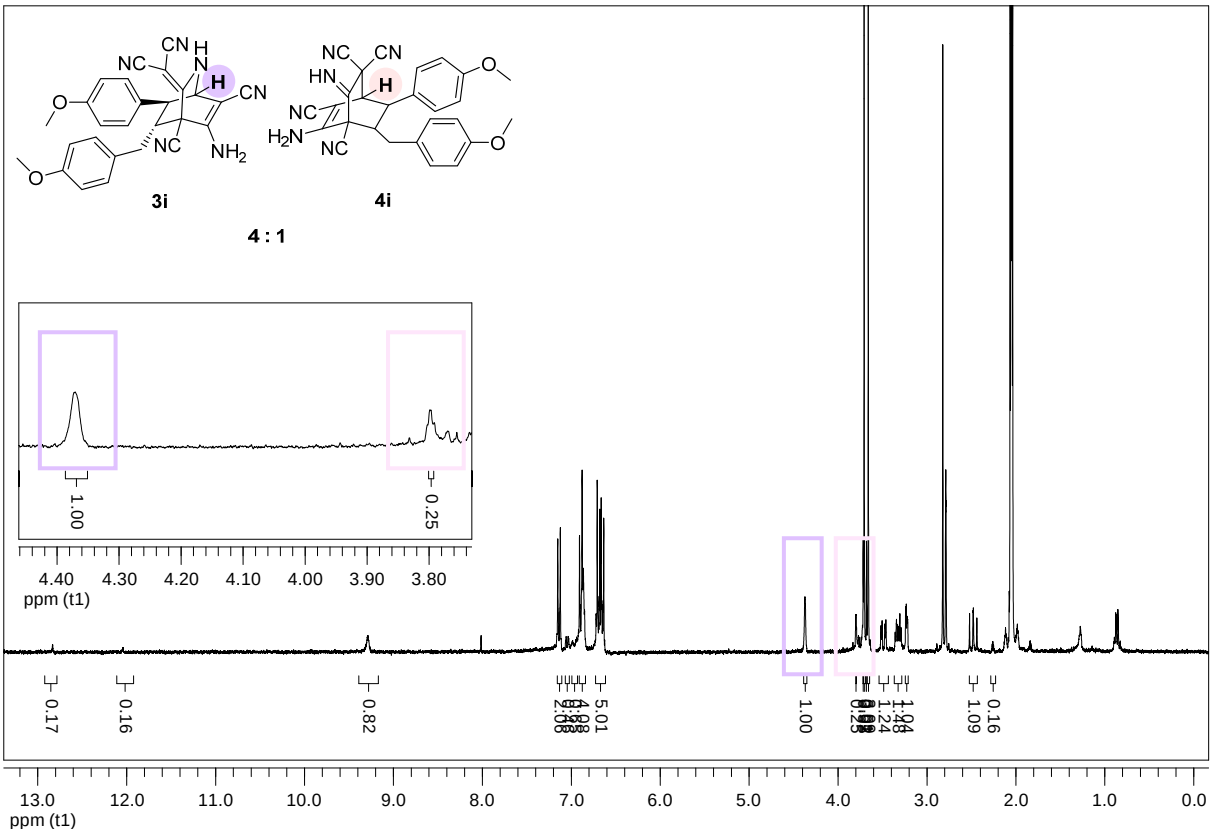
### 3.7 $^{1}$H-NMR spectrum of compound mixture 3g and 4g



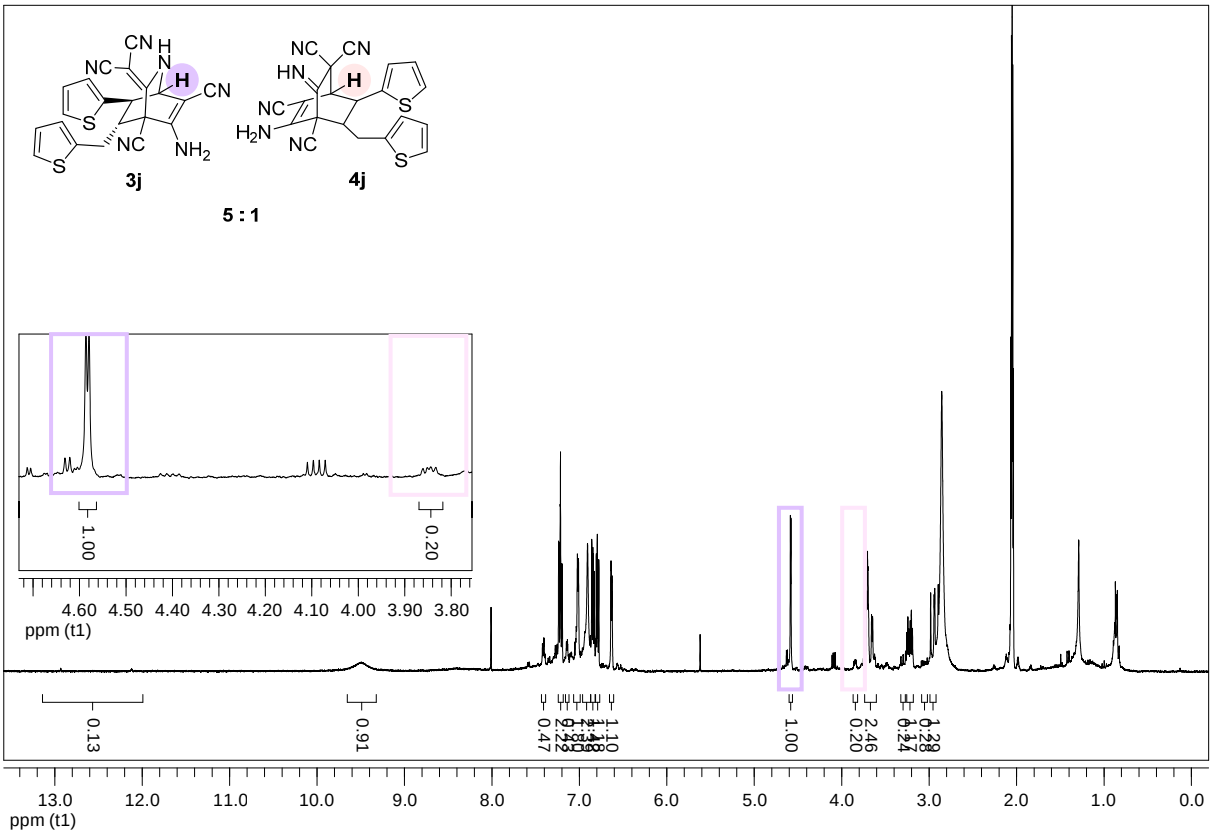

### 3.8 $^{1}$H-NMR spectrum of compound mixture 3h and 4h



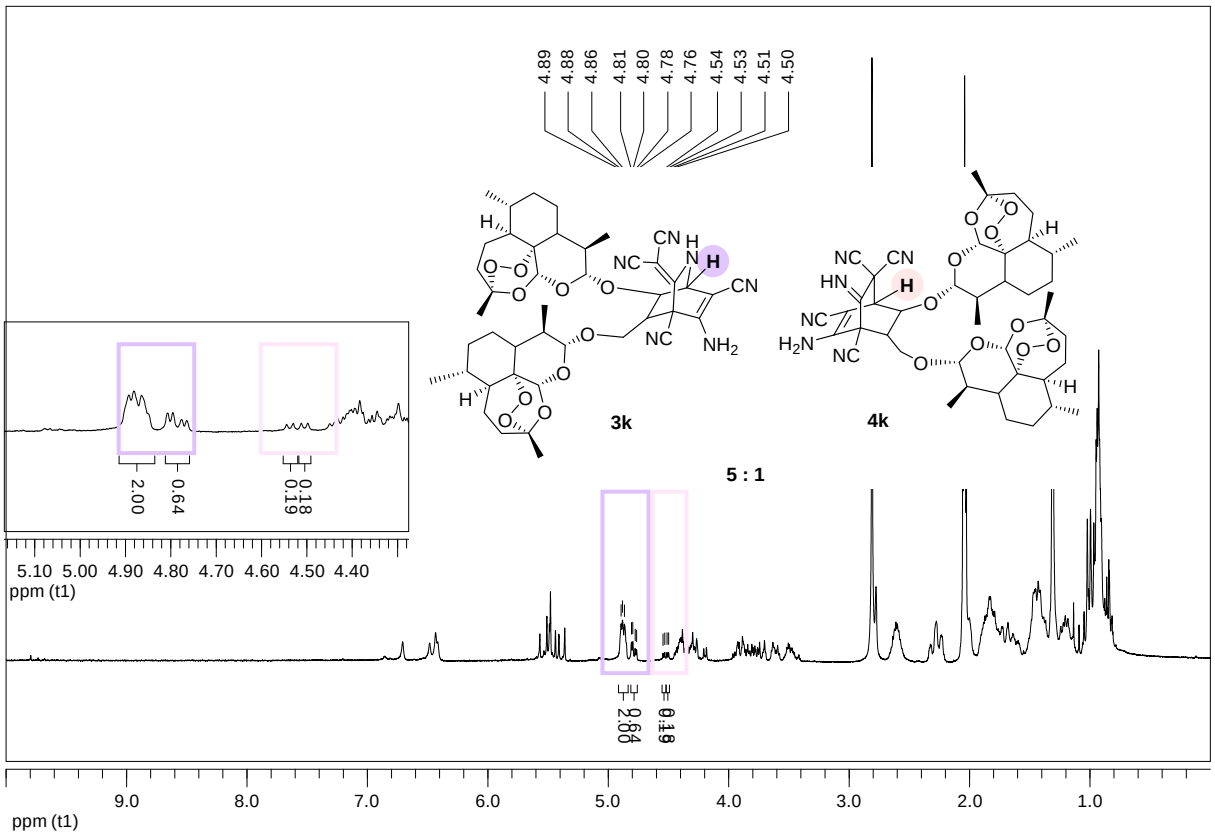
### 3.9 $^{1}$H-NMR spectrum of compound mixture 3i and 4i



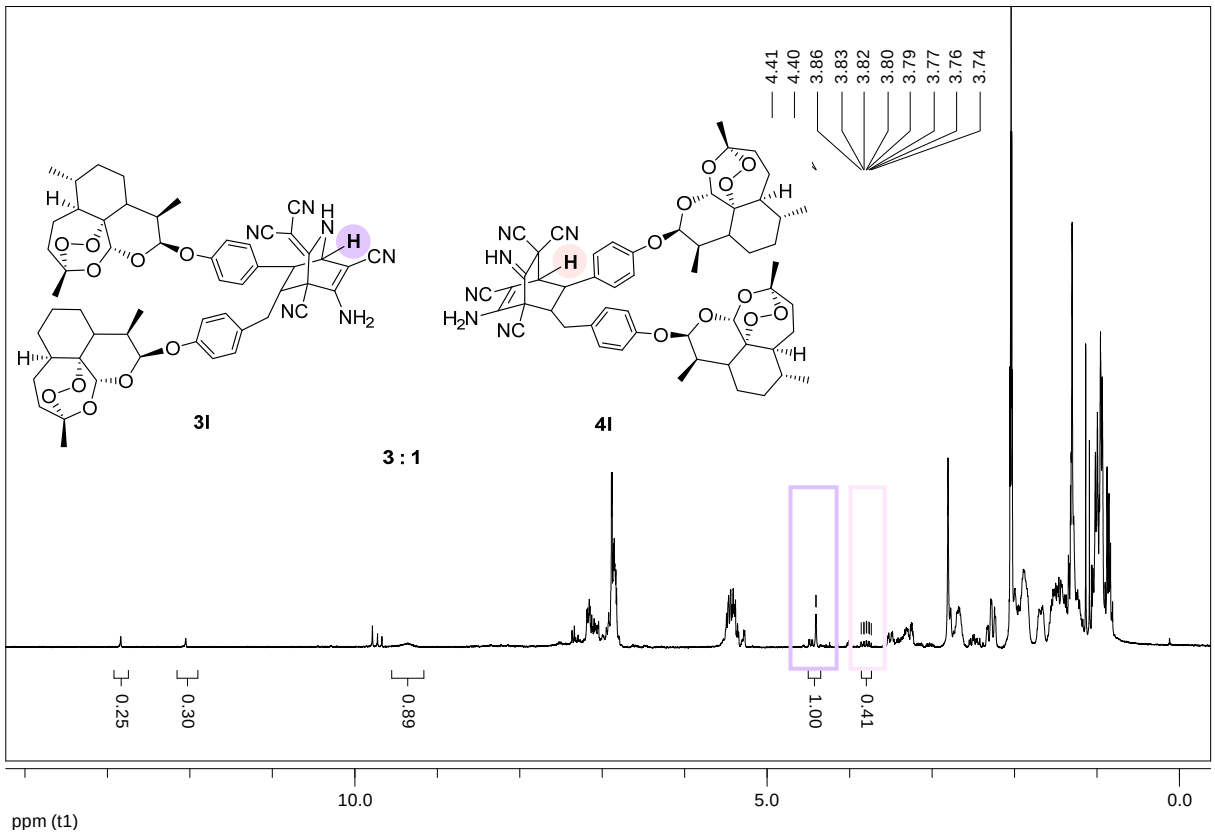

### 3.10 $^{1}$H-NMR spectrum of compound mixture 3j and 4j



### 3.11 [1]H-NMR spectrum of compound mixture 3k and 4k



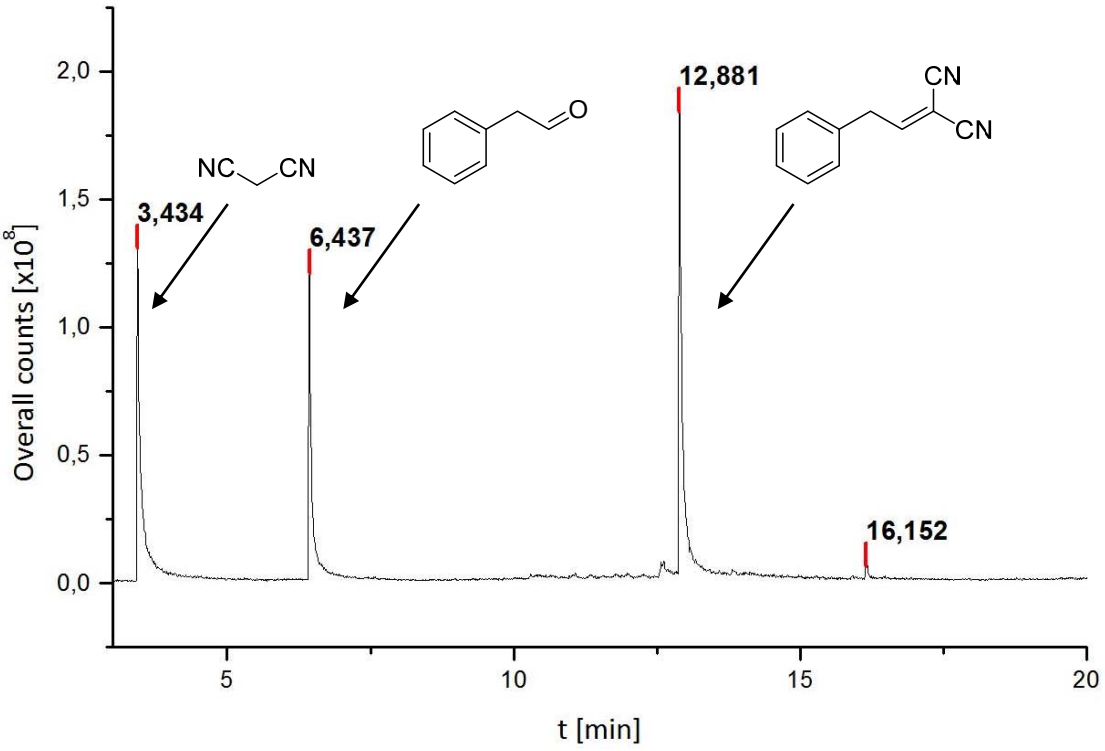

### 3.12 [1]H-NMR spectrum of compound mixture 3land 4l



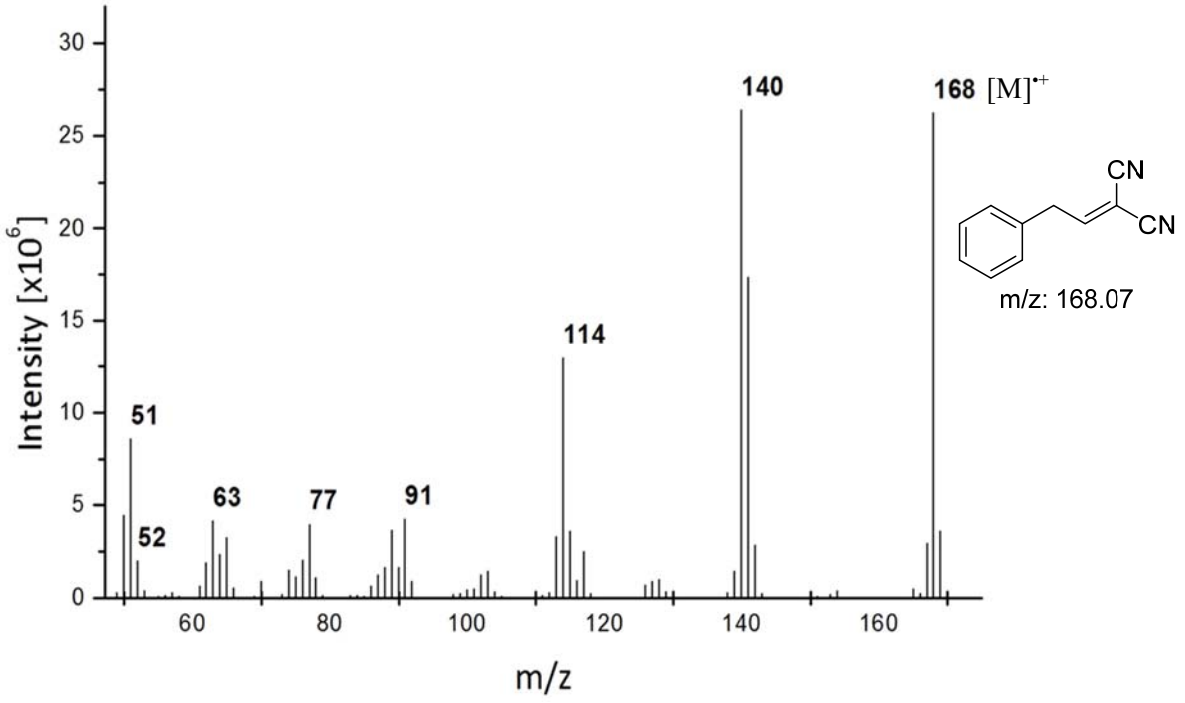
## 4 Mechanistic investigations using mass spectrometry

### 4.1 Domino reaction between phenylacetaldehyde and malononitrile catalyzed by imidazole (16h20min reaction time)

GC-MS spectrum measured on a Perkin Elmer GC-Clarus 680 and MS-Clarus SQ8C apparatus:

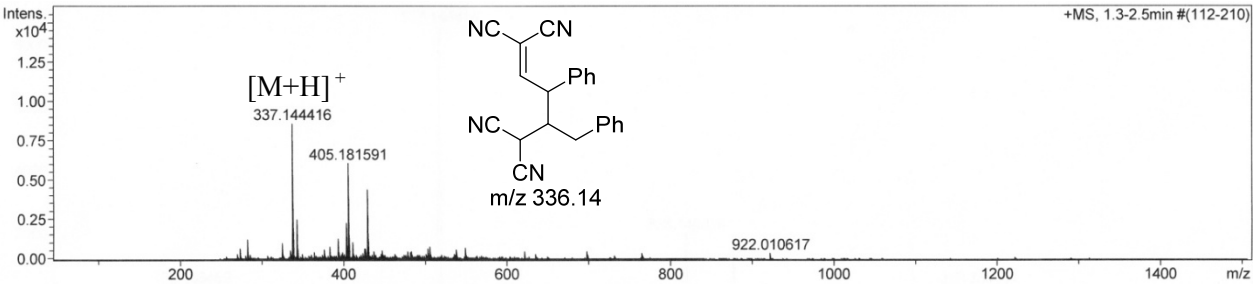



EI-MS spectrum at 12.88 min:

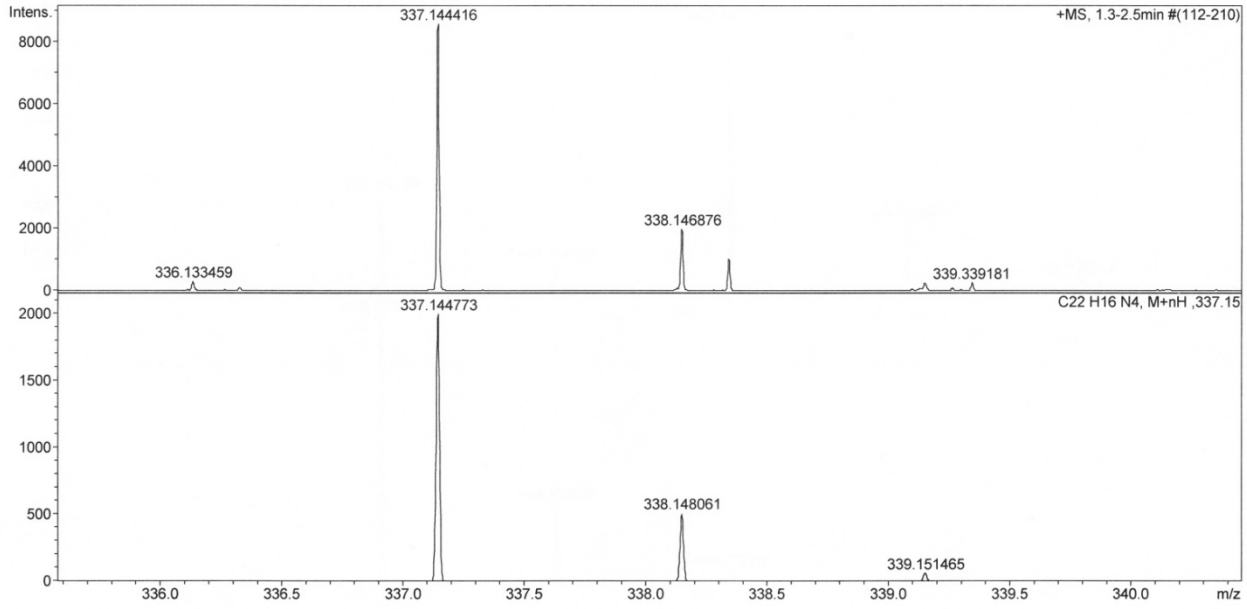


## 4.2 Domino reaction between phenylacetaldehyde and malononitrile catalyzed by imidazole

APPI-MS spectrum was measured on a BRUKER Daltonik maXis 4G apparatus

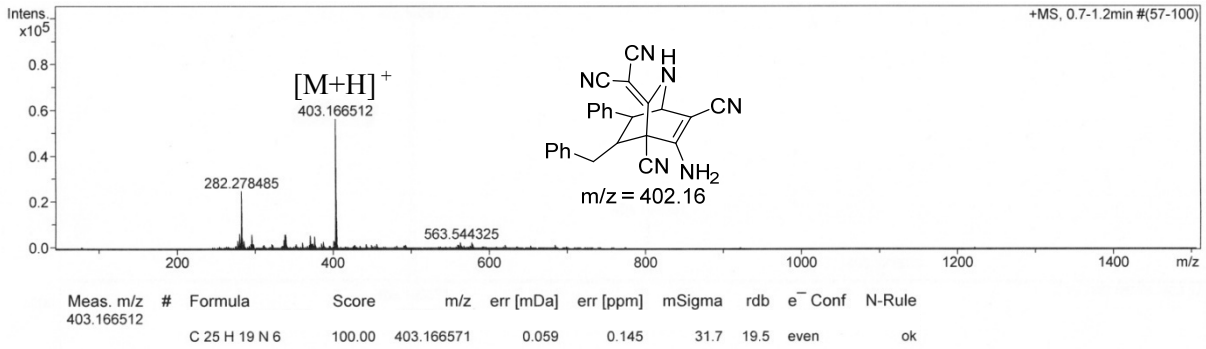



| Meas. m/z | # | Formula | Score | m/z | err [mDa] | err [ppm] | mSigma | rdb | e⁻ Conf | N-Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| 337.144416 | 1 | C 22 H 17 N 4 | 100.00 | 337.144773 | 0.357 | 1.060 | 21.6 | 16.5 | even | ok |

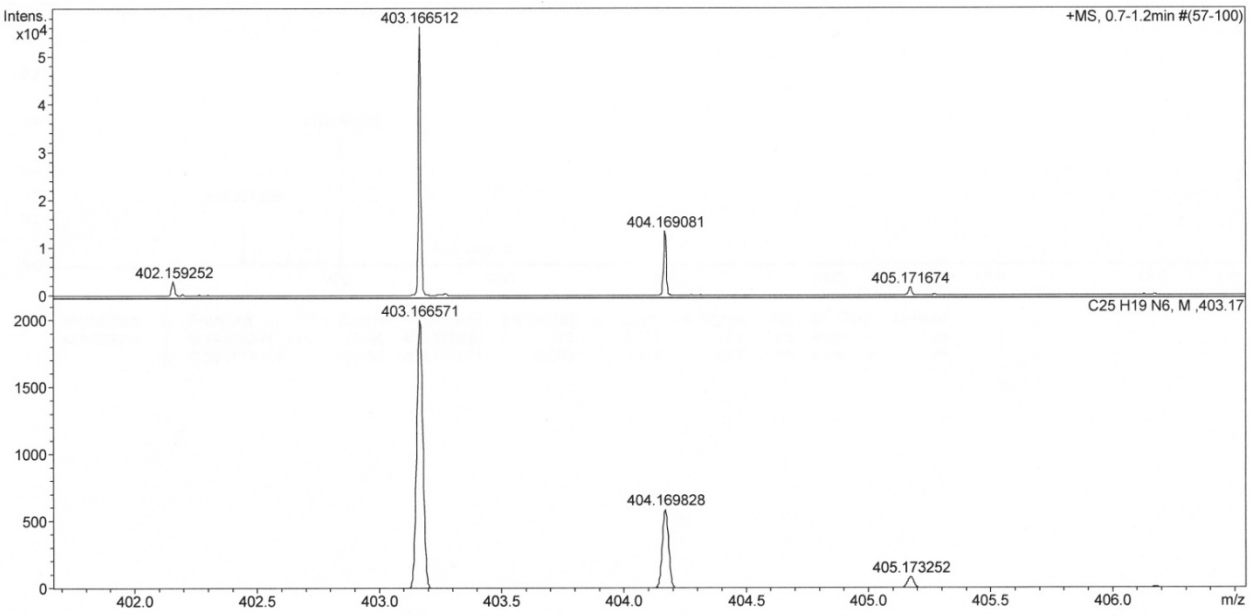


## 4.3 Domino reaction between phenylacetaldehyde and malononitrile catalyzed by imidazole

APPI-MS spectrum was measured on a BRUKER Daltonik maXis 4G apparatus

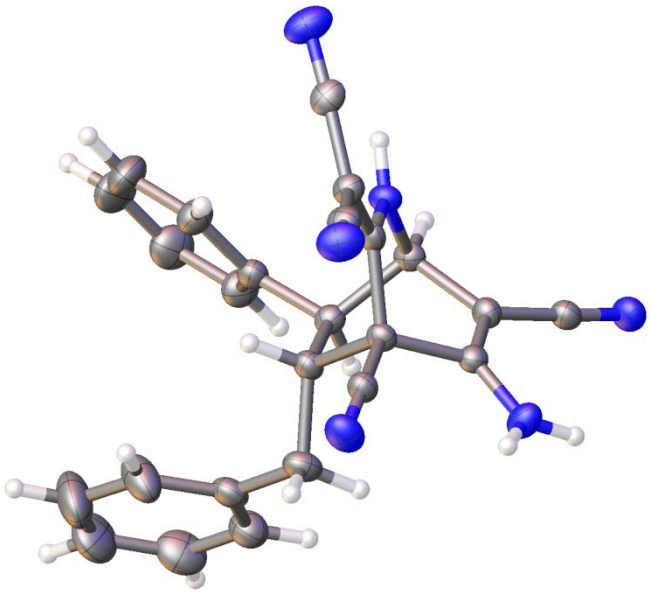



| Meas. m/z | # | Formula | Score | m/z | err [mDa] | err [ppm] | mSigma | rdb | e⁻ Conf | N-Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| 403.166512 | | C 25 H 19 N 6 | 100.00 | 403.166571 | 0.059 | 0.145 | 31.7 | 19.5 | even | ok |



## 5 X-ray crystallography

### 5.1 X-ray crystallography of compound 3a'



## Experimental

Single crystals of $C_{25}H_{18}N_6$were crystallized from MeOD. A suitable crystal was selected and mounted on a loop on a SuperNova, Dual, Cu at zero, Atlas diffractometer. The crystal was kept at 173.15 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimization.

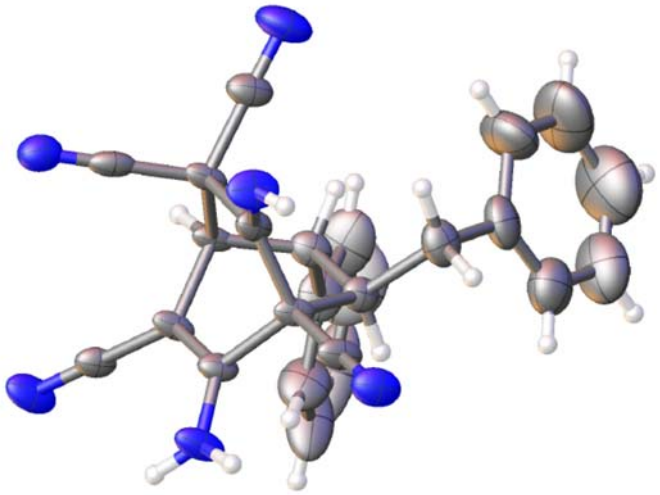

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. J. Appl. Cryst. (2009). 42, 339-341.
2. SHELXS, G.M. Sheldrick, Acta Cryst. (2008). A64, 112-122
3. SHELXL, G.M. Sheldrick, Acta Cryst. (2008). A64, 112-122


**Crystal Data.** $C_{25}H_{18}N_6$, $M$ =402.45, monoclinic, $a$ = 17.810(4) Å, $b$ = 9.2309(3) Å, $c$ = 23.679(5) Å, $\beta$ = 147.50(5)°, $V$ = 2091.4(6) Å$^3$, $T$ = 173.15, space group $P2_1/n$ (no. 14), $Z$ = 4, μ(Mo Kα) = 0.080, 6416 reflections measured, 3689 unique ($R_{int}$ = 0.0399) which were used in all calculations. The final $wR_2$ was 0.1283 (all data) and $R_1$ was 0.0478 (>2sigma(I)).

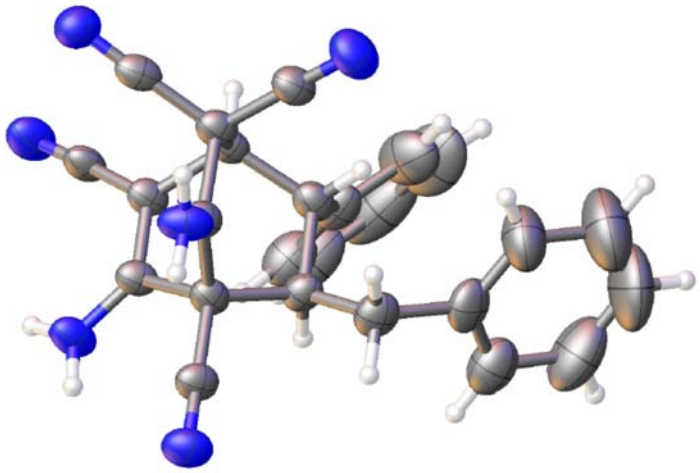
CCDC 991547 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

## 5.2 Structure solutions of compound 4a

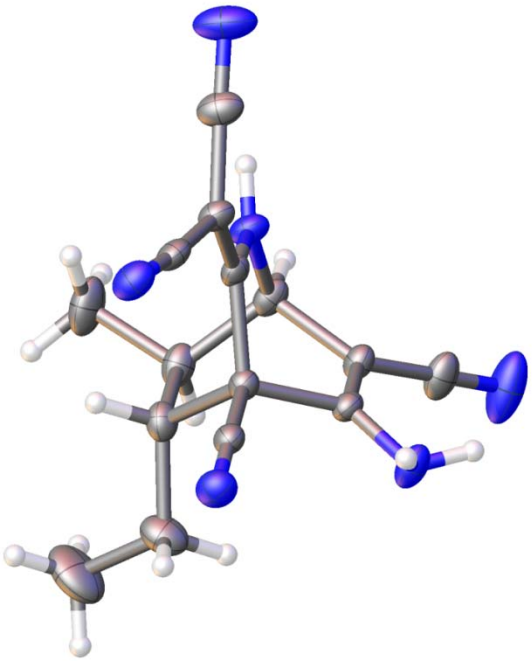
CHRH01 (C. Heckel) in P2(1)/c // Structure Solution only; no single crystal



CHRH03 (C. Heckel) in I2/a : Structure Solution only (Twin?)



### 5.3 X-ray crystallography of compound 3b'



## Experimental

Single crystals of $C_{15}H_{14}N_6$were crystallized from THF and cyclohexane. A suitable crystal was selected and mounted on a loop on a SuperNova, Dual, Cu at zero, Atlas diffractometer. The crystal was kept at 173.16 K during data collection. Using Olex2 [1], the structure was solved with the ShelXS [2] structure solution program using Direct Methods and refined with the ShelXL [3] refinement package using Least Squares minimization.

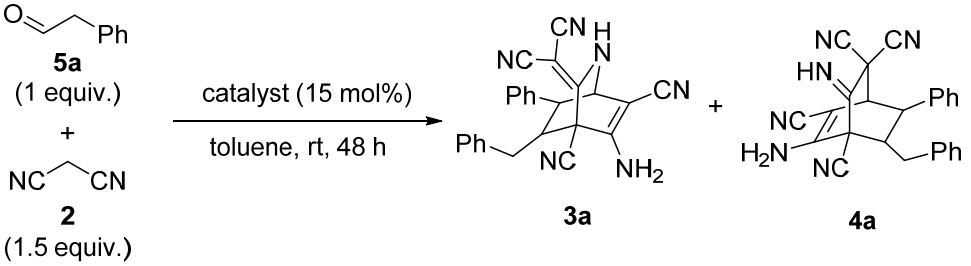

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. J. Appl. Cryst. (2009). 42, 339-341.
2. SHELXS, G.M. Sheldrick, Acta Cryst. (2008). A64, 112-122
3. SHELXL, G.M. Sheldrick, Acta Cryst. (2008). A64, 112-122

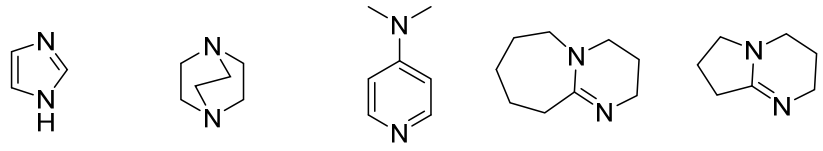

**Crystal Data.**$C_{15}H_{14}N_6$, M =278.32, monoclinic, a = 8.20751(17) Å, b = 14.2238(3) Å, c = 12.7530(3) Å, β = 95.703(2)°, V = 1481.44(5) Å3, T =173.1(6), space group P21/n (no. 14), Z= 4, μ(Cu Kα) = 0.647, 6640 reflections measured, 2276 unique ($R_{int}$ = 0.0366) which wereusedinall calculations. The final wR2 was 0.1324 (all data) and R1 was 0.0453 (I >2\s(I)).

CCDC 1435950 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

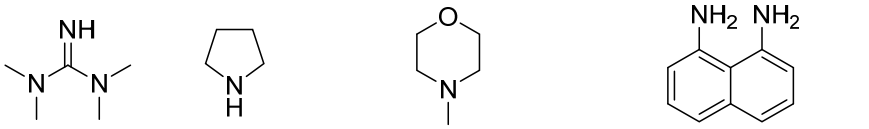
## 6 Catalyst Screening

Results of the organocatalyst screening for the reaction of phenylethanal **5a** with malononitrile **2**:



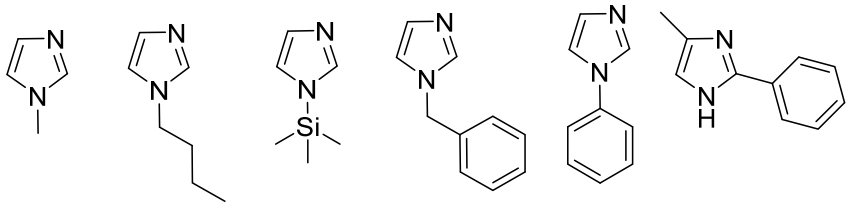



| | imidazole (**I**) | DABCO | DMAP | DBU | DBN |
|---|---|---|---|---|---|
| isolated yield: | 52% | 52% | 62% | 58% | 25% |
| **3a** : **4a** ratio | 4 : 1 | 2 : 1 | 2 : 1 | 2 : 1 | 1 : 2 |



| | TMG | pyrrolidine | N-methylmorpholine | 1,8-diaminonaphtalene |
|---|---|---|---|---|
| isolated yield: | 57% | 59% | 58% | *no conversion* |
| **3a** : **4a** ratio | 1 : 1 | 1 : 1 | 1 : 1 | |

Investigated imidazole derivatives for the reaction of phenylethanal **5a** with malononitrile **2**:



| | **II** | **V** | **VI** | **VII** | **VIII** | **IX** |
|---|---|---|---|---|---|---|
| isolated yield: | 50% | 61% | 53% | 54% | 44% | 61% |
| **3a** : **4a** ratio | 2 : 1 | 3 : 1 | 4 : 1 | 4 : 1 | 5 : 1 | 1 : 1 |

## 7 Mechanistic investigations using DFT methods in conjunction with semiempirical van der Waals interactions

### Computational details

The DFT study was performed with the TURBOMOLE program package [1]. The PBE density functional [2] was used throughout. In case of the thermodynamic study (data presented in Figure 4 of the main paper) of the reaction the def2-TZVP basis set [3] was applied, in case of the kinetic study (data presented in Figure 5 of the main paper) the geometries were first optimized applying the def2-TZVP basis set and afterwards re-optimized using the more diffuse aug-cc-pVTZ basis set [4] to account for the anionic nature of some of the species involved in the reactions. The resolution of identity approximation [5] in conjunction with the multipole approximation[6], which greatly speeds up the calculations without sacrifying accuracy, was used for all calculations. Since the species involved in the reaction contain many aryl-groups and double bonds we expected dispersion interactions to play an important role for the thermodynamic and kinetics of the studied reaction and therefore we included dispersion interactions in form of the semi-empiric dispersion interaction correction established by the group of S. Grimme [7] in all calculations. All energies refer to the Gibbs free energies ΔG obtained within harmonic approximation of the vibrational states and approximated as ideal gas.


[1] Turbomole 6.5 and 6.6, a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989-2007, Turbomole GmbH, since 2007; available from www.turbomole.com

[2] J. P. Perdew, K. Burke,M. Ernzerhof, *Phys. Rev. Lett.***1996**, *77*, 3865–3868.

[3] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.***2005**, *7*, 3297–3305.

[4] a) T.H. Dunning, *Jr. J. Chem. Phys.***1989,** *90*, 1007-1023. b) D. Feller, *J. Comp. Chem.***1996,***17,* 1571-1586. c) K.L. Schuchardt, B.T Didier,T. Elsethagen, L. Sun, V. Gurumoorthi, J. Chase, J. Li, and T.L. Windus, *J. Chem. Inf. Model.,* **2007**, *47*, 1045-1052.

[5] a) K. Eichkorn, O. Treutler, H. Öhm, M. Häser, R. Ahlrichs, *Chem. Phys. Letters***1995**, *240*, 283-290 and Chemical Physics Letters **1995**, *242*, 652-660. b) K. Eichkorn, F. Weigend, O. Treutler, R. Ahlrichs, *Theo. Chem. Acc.***1997**, *97*, 119-124.

[6] M. Sierka, A. Hogekamp, R. Ahlrichs, *J. Chem. Phys.***2003**, *118*, 9136-9148

[7] S. Grimme, J. Anthony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*,154104-1-154104-19.

**Thermodynamic study**

Molecule **6** contains two chiral centers (see Fig. 7, main text) which remain unchanged during the reaction. From the crystal structure of **3a'**(Fig. 5 main text)and a structure solution of **4a** (see page 48 of this SI) it has been deduced that the absolute configuration is RR (the enantiomeric SS configuration is of course also in the reaction mixture but all products possible from this configuration are enantiomeric to the one obtained from the RR reactant and have therefore the same energies). Unlike molecule **8**, structure **7** possesses an additional chiral center (labeled 3 in Fig S1). Since both the R and S diastereomer (**7-R** and **7-S**) can yield product **3a** as the intramolecular addition (see Fig. 7, main text) occurs via a planar allyl system both enantiomers have been taken into account.

All species contain various single bonds which allow a large number of conformers. To obtain the most stable conformer, the following procedure has been used: First all nine possible staggered conformers of **6** obtained by rotating around bond 1 and 2 (s. Figure S1 and 2 for all bond labels) were calculated. For the six energetically lowest conformations found in this way(entry 2-4,6,7,10 in Table S1), the corresponding molecules **8**, **7-R** and **7-S** were optimized with an individual starting configurations of the other labeled bonds in Figs. S1 and S2. The next step was to systematically rotate around the other labeled bonds for the two most stable conformers found this way. After the best conformation of one bond was found, the rotation around the next bond was checked while keeping the already optimized bond configurations. In case of **8** the bonds m1 and m2 were optimized simultaneously (4 configurations were studied: both H-Atoms of the $CH(CN)_2$-group pointing inwards, both pointing outwards and one pointing outwards and one inwards (2 structures)). In addition, various other promising conformations have been calculated. However, it cannot be ruled out that more stable conformations exist.

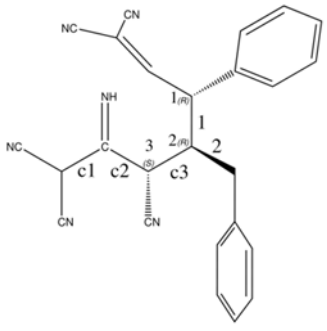



*Fig. S1: figure of **7-S** (entry 1) with bonds and chiral centers labeled*

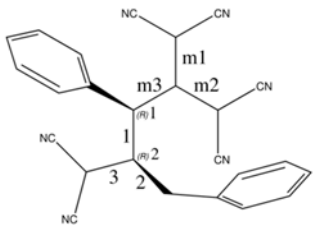



*Fig. S2: figure of **8** (entry 1) with bonds and chiral centers labeled*

[1] **8** with the conformation of bond 1 and 2 as in entry 4 of Table S1 converged towards the conformer of **8** obtained from entry 7 of Table S1.

Table S1: Free energies of the conformers of **6** relative to conformer #1 of **6**

| Entry | ΔG [kcal/mol] |
|---|---|
| 1 | 0.00 |
| 2 | 1.12 |
| 3 | 1.94 |
| 4 | 1.94 |
| 5 | 2.57 |
| 6 | 2.82 |
| 7 | 2.86 |
| 8 | 3.31 |
| 9 | 3.45 |
| 10 | 3.47 |
| 11 | 3.47 |
| 12 | 3.63 |
| 13 | 3.92 |
| 14 | 4.08 |
| 15 | 4.54 |
| 16 | 4.55 |
| 17 | 5.63 |
| 18 | 5.83 |
| 19 | 6.94 |
| 20 | 9.51 |

Table S2: Free energies of the conformers of **8** relative to conformer #1 of **6**

| Entry | ΔG [kcal/mol] |
|---|---|
| 1 | 8.65 |
| 2 | 9.18 |
| 3 | 10.17 |
| 4 | 10.53 |
| 5 | 10.68 |
| 6 | 12.47 |
| 7 | 12.67 |
| 8 | 13.06 |
| 9 | 13.44 |
| 10 | 13.46 |
| 11 | 13.88 |
| 12 | 14.29 |
| 13 | 14.55 |
| 14 | 14.80 |
| 15 | 15.24 |
| 16 | 15.66 |
| 17 | 15.68 |
| 18 | 16.13 |
| 19 | 16.30 |
| 20 | 16.46 |
| 21 | 16.68 |
| 22 | 17.80 |
| 23 | 17.87 |
| 24 | 18.91 |
| 25 | 20.23 |
| 26 | 20.67 |
| 27 | 21.11 |
| 28 | 24.11 |
| 29 | 26.00 |

Table S3: Free energies of the conformers of **7-S** relative to conformer #1 of **6**

| Entry | ΔG [kcal/mol] |
|---|---|
| 1 | 4.01 |
| 2 | 4.22 |
| 3 | 6.14 |
| 4 | 6.69 |
| 5 | 6.75 |
| 6 | 6.85 |
| 7 | 6.93 |
| 8 | 7.15 |
| 9 | 7.30 |
| 10 | 7.36 |
| 11 | 7.43 |
| 12 | 7.74 |
| 13 | 7.88 |
| 14 | 7.94 |
| 15 | 8.21 |
| 16 | 8.28 |
| 17 | 8.56 |
| 18 | 8.61 |
| 19 | 8.72 |
| 20 | 9.27 |
| 21 | 9.56 |
| 22 | 9.73 |
| 23 | 9.88 |
| 24 | 10.15 |
| 25 | 10.18 |
| 26 | 10.31 |
| 27 | 11.61 |
| 28 | 11.84 |
| 29 | 12.76 |
| 30 | 13.47 |
| 31 | 14.89 |
| 32 | 15.39 |

Table S4: Free energies of the conformers of **7-R** relative to conformer #1 of **6**

| Entry | ΔG [kcal/mol] |
|---|---|
| 1 | 6.23 |
| 2 | 6.42 |
| 3 | 6.69 |
| 4 | 6.71 |
| 5 | 6.80 |
| 6 | 7.05 |
| 7 | 7.11 |
| 8 | 7.56 |
| 9 | 7.93 |
| 10 | 8.40 |
| 11 | 8.50 |
| 12 | 8.89 |
| 13 | 9.21 |
| 14 | 10.29 |
| 15 | 10.57 |
| 16 | 11.20 |
| 17 | 11.60 |
| 18 | 11.67 |
| 19 | 12.32 |
| 20 | 12.36 |
| 21 | 12.60 |
| 22 | 13.15 |

**Kinetic study**

In order to study the kinetics of the branching point ("chemoselective step") a transition state search for the Michael(**6**→**8**) and the nucleophilic addition(**6**→**7**)pathway with imidazole as catalyst was conducted. Starting from promising guesses obtained from previous TS searches or from screening the reaction coordinate with the bond length of the forming bond fixed at various distances, a TS was obtained by the TS search implemented in TURBOMOLE. The TSs found by this procedure were checked by visualizing the normal mode corresponding to the imaginary frequency, and by following this reaction coordinate in both directions (which lead after a geometry optimization to the reactant complex and intermediate/product complex associated with the studied reaction). The reactant complexes contain deprotonated malononitrile, the imidazolium cation and molecule **6**. In case of the Michael reaction, deprotonated **8** is formed as intermediate at first. The product complex was finally obtained by protonating the intermediate and positioning imidazole close to this proton and optimizing the geometry.

Usually, the energetically lowest TSs are not connected with the most stable conformers. For the nucleophilic addition reaction(**6**→**7**) the lowest lying TS contains **6** in form of the conformer #5 and leads to **7-S** in form of the conformer #11. In case of the Michael reaction the lowest lying TS contains **6** in form of the conformer #4 and leads to **8** in form of the conformer #2. The TSs presented here are only exemplary because many conformations of the reactant/product could lead to the lowest lying TSs, and for each of these TSs several possible orientations of the imidazolium cation exist. The free energies relative to the reactants of the nucleophilic addition(**6**→**7**)and Michael addition(**6**→**8**)reactions, respectively, are tabulated in Tables S5 and S6.

Table S5: Free energies of the imidazole catalysed nucleophilic addition reaction(**6**→**7**) relative to the sum of conformer #1 of **6**, imidazole and malononitrile

| Species | ΔG [kcal/mol] |
|---|---|
| reactants | 0.00 |
| reactant complex | 13.55 |
| TS | 17.34 |
| product complex | 6.44 |
| product | 6.86 |

Table S6: Free energies of the imidazole catalysed Michael reaction(**6**→**8**) relative to the sum of conformer #1 of **6**, imidazole and malononitrile

| Species | ΔG [kcal/mol] |
|---|---|
| reactants | 0.00 |
| reactant complex | 12.81 |
| TS | 15.71 |
| intermediate | 10.26 |
| product complex | 8.35 |
| product | 8.63 |

The structure of the optimized reactant complex and product complex of the nucleophilic addition reaction is shown in Figure S3 and S4. The structure of the optimized reactant complex, the intermediate and the product complex of the Michael reaction is shown in Figure S5, S6 and S7

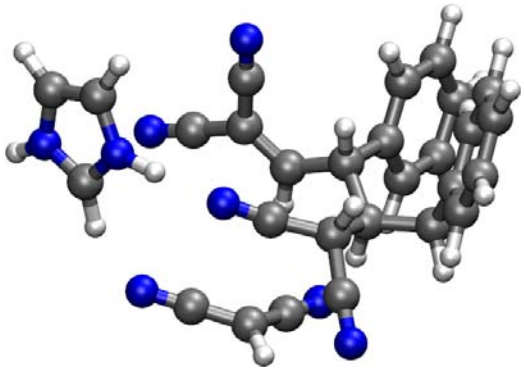


*Fig. S3: the optimized structure of the reactant complex of the nucleophilic addition reaction*

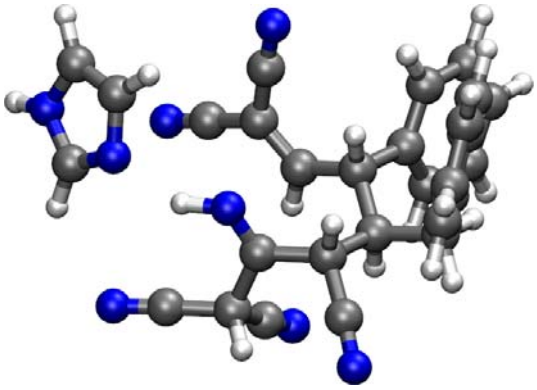


*Fig. S4: the optimized structure of the product complex of the nucleophilic additionreaction*

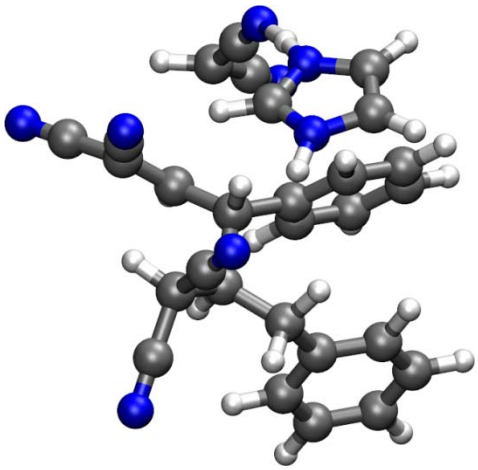


*Fig. S5: the optimized structure of the reactant complex of the Michael reaction*

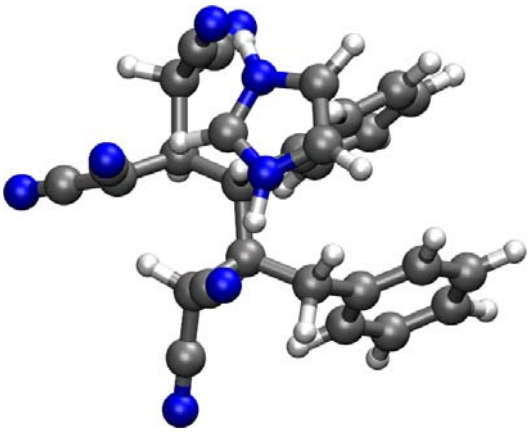


*Fig. S6: the optimized structure of the intermediate of the Michael reaction*

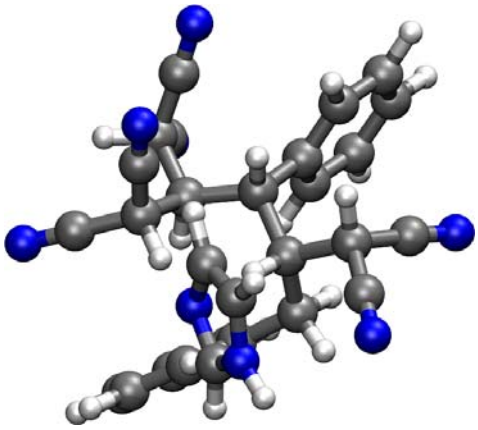


*Fig. S7: the optimized structure of the product complex of the Michael reaction*

**Influence of dispersion interactions**

The influence of dispersion interactions on the thermodynamics (Figure 4 of the main paper) has been studied by re-optimizing the six most stable conformers of each species (**6**, **7-S**, **7-R** and **8**) without applying the dispersion interaction corrections. The free energies relative to the conformer 1 of **6** are summarized in Table S7-S10. The conformers have the same numbering as in Table S1-4 but are sorted energetically. Figure S8 is Figure 8 of the main paper using energies without dispersion corrections.

Table S7:
Free energies of the conformers of **6** relative to conformer #1 of **6** without dispersion interaction

| Entry | ΔG [kcal/mol] |
|---|---|
| 1 | 0.00 |
| 2 | 1.77 |
| 3 | 2.05 |
| 4 | 2.89 |
| 6 | 3.14 |
| 5 | 3.47 |

Table S8:
Free energies of the conformers of **8** relative to conformer #1 of **6** without dispersion interaction

| Entry | ΔG [kcal/mol] |
|---|---|
| 1 | 17.22 |
| 2 | 17.65 |
| 3 | 18.15 |
| 4 | 18.63 |
| 5 | 19.67 |
| 6 | 20.56 |

Table S9:
Free energies of the conformers of **7-S**relative to conformer #1 of **6** without dispersion interaction

| Entry | ΔG [kcal/mol] |
|---|---|
| 1 | 8.51 |
| 2 | 9.42 |
| 3 | 11.06 |
| 5 | 11.73 |
| 6 | 12.12 |
| 4 | 12.51 |

Table S10:
Free energies of the conformers of **7-R**relative to conformer #1 of **6** without dispersion interaction

| Entry | ΔG [kcal/mol] |
|---|---|
| 5 | 11.29 |
| 1 | 11.34 |
| 2 | 11.35 |
| 6 | 11.71 |
| 4 | 12.29 |
| 3 | 12.42 |

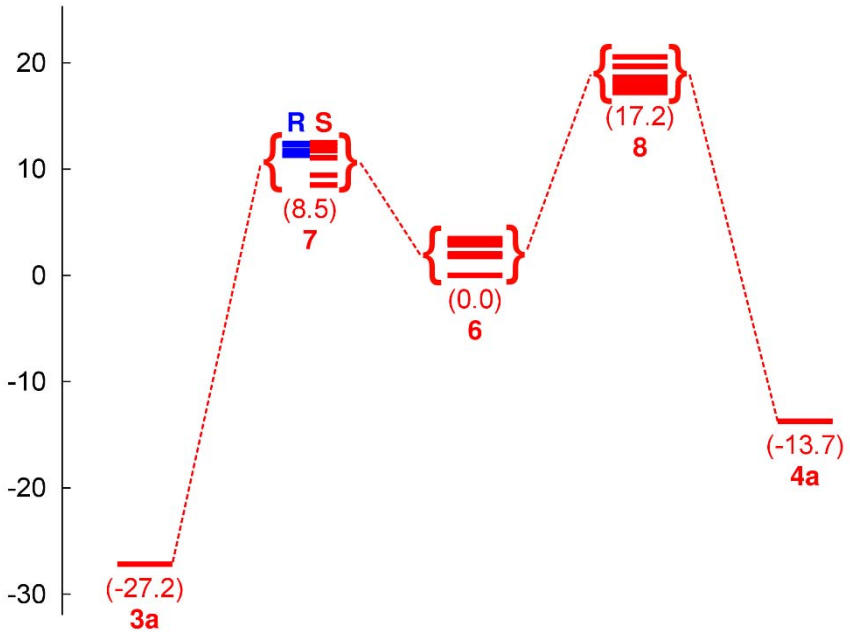



*Fig. S8: without dispersion interaction correction;*
*Energies (in kcal/mol) (see also for comparison Figure 8 of the main paper)*

The influence of dispersion interactions on the kinetics was estimated by subtracting the dispersion correction given in the TURBOMOLE output from the SCF-energies. No reoptimization was done in this case since these recalculations would be much more expensive in case of TS searches. The free energies obtained this way are presented in Table S11 and S12.

Table S11:
Free energies of the imidazole catalysed nucleophilic addition reaction relative to the sum of conformer #1 of **6**, imidazole and malononitrile without dispersion interactions

| Species | ΔG [kcal/mol] |
|---|---|
| reactants | 0.00 |
| reactant complex | 25.09 |
| TS | 28.85 |
| product complex | 17.73 |
| product | 13.21 |

Table S12:
Free energies of the imidazole catalysed Michael reaction relative to the sum of conformer #1 of **6**, imidazoleand malononitrile without dispersion interactions

| Species | ΔG [kcal/mol] |
|---|---|
| reactants | 0.00 |
| reactant complex | 26.32 |
| TS | 29.74 |
| intermediate | 23.96 |
| product complex | 23.19 |
| product | 17.84 |