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In-situ mechanochemical synthesis of nitrones followed by 1,3-dipolar cycloaddition: a catalyst-free, "green" route to *cis*-fused chromano[4,3-*c*]isoxazoles

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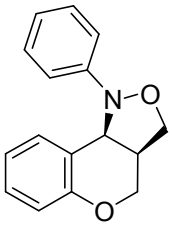
General procedure for the *O*-allylation of salicylaldehyde derivatives[1]: synthesis of 2-(allyloxy)-5-methoxybenzaldehyde (1e).

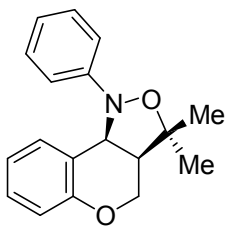
In a round bottom flask equipped with a magnetic stirring bar was charged with 2-hydroxy-5-methoxybenzaldehyde (1.52 g, 10 mmol) and K_2CO_3 (2.76 g, 20 mmol) in DMF (20 mL). To this stirring solution allyl bromide (1.04 mL, 12 mmol) was added dropwise. After stirring the solution for 2 days excess water was added and the crude product was extracted with EtOAc (3 x 10 mL). The combined organic phases was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (5% EtOAc in petroleum ether) to afford **1e** (178 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) δ (ppm) 3.81 (s, 3H), 4.61-4.63 (m, 2H), 5.33 (dd, J_1 = 1.5 Hz, J_2 = 10.8 Hz, 1H), 5.43 (dt, J_1 = 1.5 Hz, J_2 = 17.6 Hz, 1H), 6.02-6.10 (m, 1H), 6.94 (d, J = 9.2 Hz, 1H), 7.12 (dd, J_1 = 3.2 Hz, J_2 = 9.2 Hz, 1H), 7.33 (d, J = 3.2 Hz, 1H), 10.50 (s, 1H).

Spectral data of chromano[4,3-*c*]isoxazoles

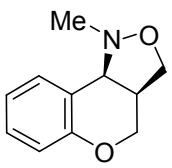
3,3a,4,9b-Tetrahydro-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4a): White solid, m.p.: 85-87 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.99-3.09 (m, 1H), 4.03-4.14 (m, 2H), 4.23-4.35 (m, 2H), 4.87 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 7.04-7.14 (m, 2H), 7.25-7.29 (m, 3H), 7.38-7.43 (m, 2H), 7.51 (d, J = 10.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 40.8, 63.4, 65.3, 68.1, 115.5, 117.1, 121.9, 122.3, 122.8, 128.9, 129.2, 130.3, 151.0, 155.9; IR (KBr): 3031, 2873, 1587, 1487, 1303, 1125, 1088 cm^{-1}; ESI-MS (m/z): 254 [M + H]; Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.80; H, 5.91; N, 5.44.



3,3a,4,9b-Tetrahydro-3,3-dimethyl-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4b): Light brown solid, m.p.: 72-75 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.38 (s, 3H), 1.42 (s, 3H), 2.71-2.74 (m, 1H), 4.17 (t, J = 10.5 Hz, 1H), 4.36 (dd, J_1 = 4.8 Hz, J_2 = 10.8 Hz, 1H), 4.64 (d, J = 6.9 Hz, 1H), 6.86-7.01 (m, 3H), 7.10 (t, J = 7.2 Hz, 1H), 7.19-7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 22.1, 29.5, 48.5, 62.5, 64.6, 82.2, 116.8, 117.7, 121.07, 121.14, 123.3, 128.7, 129.0, 130.7, 151.4, 155.0; IR (KBr): 3036, 2975, 1590, 1488, 1224, 1121 cm^{-1}; ESI-MS (*m/z*): 282 [M + H]$^+$; Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.71; H, 6.86; N, 4.84.

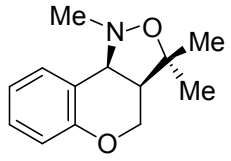


3,3a,4,9b-Tetrahydro-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole (4c): Light yellow viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.89 (s, 3H), 2.99-3.06 (m, 1H), 3.54 (d, J = 5.6 Hz, 1H), 3.72-3.75 (m, 1H), 4.08-4.20 (m, 2H), 4.29 (t, J = 8.2 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H), 7.00 (td, J = 1.2, 7.8 Hz, 1H), 7.23 (dd, J_1 = 1.6

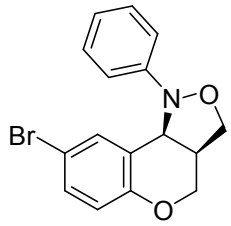


Hz, J_2 = 7.6 Hz, 1H), 7.25 (dd, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 40.2, 43.6, 64.7, 66.1, 67.4, 117.4, 119.6, 121.2, 129.5, 130.9, 155.7; IR (neat): 2966, 2869, 1584, 1490, 1247, 1219,1053 cm^{-1}; ESI-MS (*m/z*): 192 $[M + H]^+$; Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.90; H, 6.96; N, 7.38.

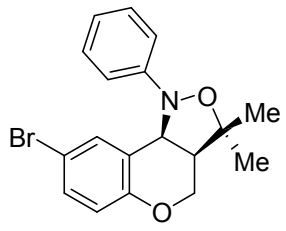
3,3a,4,9b-Tetrahydro-1,3,3-trimethyl-1*H*-chromeno[4,3-*c*]isoxazole (4d): Yellow solid, m.p.: 48-49 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.27 (s, 3H), 1.40 (s, 3H), 2.40-2.48 (m, 1H), 2.87 (s, 3H), 3.59 (d, J = 7.6 Hz, 1H), 4.19-4.22 (m, 2H), 6.90-6.95 (m, 2H), 7.19-7.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 22.7, 29.7, 43.8, 48.0, 61.6, 64.3, 79.1, 117.0, 118.9, 120.7, 129.4, 130.8, 155.2; IR (KBr): 2975, 2850, 1583, 1493, 1278, 1226, 1116 cm^{-1}; ESI-MS (*m/z*): 220 $[M + H]^+$; Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.30; H, 7.92; N, 6.38.



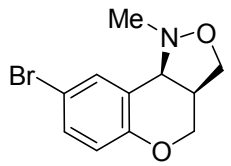
8-Bromo-3,3a,4,9b-tetrahydro-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4e): Pale yellow solid, m.p.: 110-113 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.02-3.08 (m, 1H), 4.05 (dd, J_1 = 5.4 Hz, J_2 = 8.0 Hz, 1H), 4.11 (dd, J_1 = 5.4 Hz, J_2 = 12.3 Hz, 1H), 4.22-4.34 (m, 2H), 4.83 (d, J = 7.5 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.6 Hz, 2H), 7.29-7.39 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 40.5, 63.0, 65.3, 68.0, 114.0, 115.2, 119.0, 123.0, 129.2, 130.9, 131.9, 132.7, 150.5, 155.0; IR (KBr): 2970, 2884, 1590,1479, 1331, 1287,1070 cm^{-1}; ESI-MS (*m/z*): 332 $[M + H]^+$ (for ^{79}Br), 334 $[M + H]^+$ (for ^{81}Br); Anal. Calcd for $C_{16}H_{14}BrNO_2$: C, 57.85; H, 4.25; N, 4.22. Found: C, 57.70; H, 4.36; N, 4.31.



8-Bromo-3,3a,4,9b-tetrahydro-3,3-dimethyl-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4f): Yellow viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.36 (s, 3H), 1.40 (s, 3H), 2.70-2.74 (m, 1H), 4.12 (dd, J_1 = 9.2 Hz, J_2 = 11.2 Hz, 1H), 4.34 (dd, J_1 = 4.8 Hz, J_2 = 11.2 Hz, 1H), 4.65 (d, J = 6.9 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 7.15 (d, J = 1.5 Hz, 1H), 7.24-7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 22.2, 29.5, 48.2, 61.9, 64.6, 82.7, 113.2, 117.0, 118.7, 123.3, 123.6, 128.9, 131.9, 133.0, 151.2, 154.2; IR (neat): 3059, 2976, 1597, 1481, 1223, 1125, 1027 cm^{-1}; ESI-MS (*m/z*): 360 $[M + H]^+$ (for ^{79}Br), 362 $[M + H]^+$ (for ^{81}Br); Anal. Calcd for $C_{18}H_{18}BrNO_2$: C, 60.01; H, 5.04; N, 3.89. Found: C, 60.20; H, 5.15; N, 3.88.

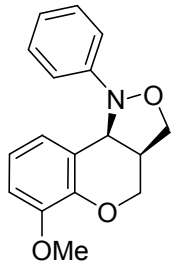


8-Bromo-3,3a,4,9b-tetrahydro-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole (4g): White solid, m.p.: 52-55 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.88 (s, 3H), 3.00-3.07 (m, 1H), 3.56 (d, J = 5.6 Hz, 1H), 3.74 (dd, J_1 = 4.4 Hz, J_2 = 8.0 Hz,

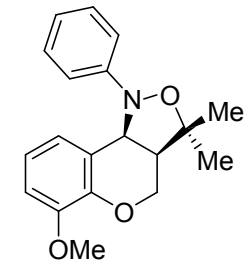


1H), 4.08 (dd, J_1 = 8.0 Hz, J_2 = 11.2 Hz, 1H), 4.17 (dd, J_1 = 4.8 Hz, J_2 = 11.2 Hz, 1H), 4.29 (t, J = 8.0 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 7.33 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 40.0, 43.8, 64.3, 66.1, 67.3, 113.3, 119.2, 122.1, 132.4, 133.3, 154.8; IR (KBr): 2966, 2892, 1572, 1482, 1246, 1223, 1100 cm^{-1}; ESI-MS (*m/z*): 270 $[M + 1]^+$ (for ^{79}Br), 272 $[M + H]^+$ (for ^{81}Br); Anal. Calcd for $C_{11}H_{12}BrNO_2$: C, 48.91; H, 4.48; N, 5.19. Found: C, 49.03; H, 4.55; N, 5.12.

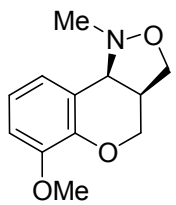
3,3a,4,9b-Tetrahydro-6-methoxy-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4j): Yellow viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.04-3.08 (m, 1H), 3.89 (s, 3H), 4.07 (dd, J_1 = 5.2 Hz, J_2 = 8.0 Hz, 1H), 4.17 (dd, J_1 = 5.2 Hz, J_2 = 11.6 Hz, 1H), 4.29-4.33 (m, 2H), 4.87 (d, J = 7.6 Hz, 1H), 6.82 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 7.02-7.09 (m, 2H), 7.19-7.26 (m, 2H), 7.32-7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 40.8, 56.1, 63.4, 65.8, 68.1, 110.6, 115.5, 121.5, 121.8, 122.9, 123.1, 129.3, 145.6, 148.4, 151.0; IR (neat): 3060, 2940, 1590, 1485, 1263, 1218, 1087 cm^{-1}; ESI-MS (*m/z*): 284 $[M + H]^+$; Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.01; H, 6.09; N, 5.02.



3,3a,4,9b-Tetrahydro-6-methoxy-3,3-dimethyl-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4k): White Solid, m.p.: 148-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.32 (s, 3H), 1.43 (s, 3H), 2.70-2.76 (m, 1H), 3.90 (s, 3H), 4.21 (t, J = 10.2 Hz, 1H), 4.46 (dd, J_1 = 4.8 Hz, J_2 = 11.2 Hz, 1H), 4.68 (d, J = 6.8 Hz, 1H), 6.64 (dd, J_1 = 2.2 Hz, J_2 = 6.8 Hz, 1H), 6.81-6.86 (m, 2H), 7.08 (dt, J_1 = 1.0 Hz, J_2 = 6.8 Hz, 1H), 7.24-7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.2, 29.5, 48.5, 56.1, 62.3, 65.1, 82.6, 110.6, 117.5, 120.7, 122.2, 122.3, 123.2, 128.9, 144.7, 148.4, 151.6; IR (KBr): 3059, 2976, 1590, 1485,1260, 1219, 1099 cm^{-1}; ESI-MS (*m/z*): 334 $[M + 23]^+$; Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.40; H, 6.85; N, 4.63.

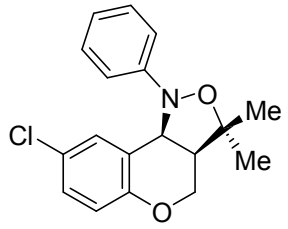


3,3a,4,9b-Tetrahydro-6-methoxy-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole (4l): Light yellow solid, m.p.: 52-53 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.84 (s, 3H), 2.94-3.00 (m, 1H), 3.51 (d, J = 3.6 Hz, 1H), 3.70 (dd, J_1 = 3.3 Hz, J_2 = 6.0 Hz, 1H), 3.84 (s, 3H), 4.12 (t, J = 7.5 Hz, 1H), 4.21-4.26 (m, 2H), 6.80-6.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 40.0, 43.7, 56.0, 64.4, 66.3, 67.2, 111.0, 120.3,120.7, 122.4, 145.1, 148.6; IR (neat): 3006, 2836, 1583,



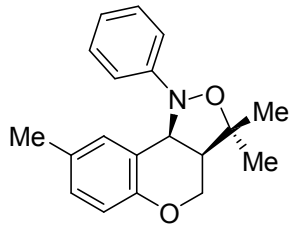
1485, 1262, 1211, 1084 cm^{-1}; ESI-MS (*m/z*): 244 $[M + 23]^+$; Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.40; H, 6.89; N, 6.47.

8-Chloro-3,3a,4,9b-tetrahydro-3,3-dimethyl-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4n):

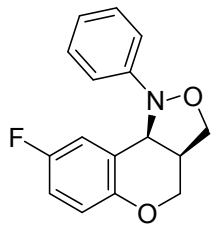


Light brown solid, m.p.: 57-58 °C; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.36 (s, 3H), 1.41 (s, 3H), 2.70-2.75 (m, 1H), 4.13 (dd, J_1 = 9.2 Hz, J_2 = 11.2 Hz, 1H), 4.35 (dd, J_1 = 4.8 Hz, J_2 = 11.2 Hz, 1H), 4.66 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 7.11 (t, J = 7.0 Hz, 1H), 7.17 (dd, J_1 = 2.8 Hz, J_2 = 8.4 Hz, 1H), 7.24-7.26 (m, 2H), 7.28-7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.3, 29.7, 48.4, 62.1, 64.9, 82.9, 117.0, 118.4, 123.3, 123.4, 126.1, 129.1, 129.2, 130.2, 151.4, 153.8; IR (KBr): 3059, 2972, 1596, 1483, 1259, 1146, 1011 cm^{-1}; ESI-MS (*m/z*): 338 $[M + 23]^+$ (major peak, for ^{35}Cl), 340 $[M + 23]^+$ (minor peak, for ^{37}Cl); Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.75; N, 4.44. Found: C, 68.34; H, 5.85; N, 4.54.

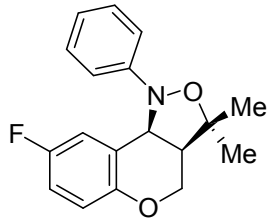
3,3a,4,9b-tetrahydro-3,3,8-trimethyl-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4p): Yellow solid, m.p.: 54-56 °C; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.36 (s, 3H), 1.42 (s, 3H), 2.23 (s, 3H), 2.71-2.76 (m, 1H), 4.12 (dd, J_1 = 9.2 Hz, J_2 = 11.2 Hz, 1H), 4.34 (dd, J_1 = 4.8 Hz, J_2 = 11.2 Hz, 1H), 4.69 (d, J = 7.2 Hz, 1H), 6.83-6.88 (m, 2H), 7.02 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.08-7.10 (m, 1H), 7.26-7.28 (m, 2H), 7.34-7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.8, 22.3, 29.7, 48.9, 62.4, 64.8, 82.9, 116.7, 117.0, 121.4, 123.0, 128.9, 129.8, 130.7, 130.8, 152.0, 153.0; ESI-MS (*m/z*): 296 $[M + H]^+$; Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.17; H, 7.27; N, 4.68.



8-Fluoro-3,3a,4,9b-tetrahydro-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4q): Light gray solid, m.p.: 84-87 °C; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.06-3.10 (m, 1H), 4.04-4.11 (m, 2H), 4.25 (dd, J_1 = 4.4 Hz, J_2 = 11.6 Hz, 1H), 4.34 (t, J = 8.2 Hz, 1H), 4.84 (d, J = 8.0 Hz, 1H), 6.87-7.00 (m, 2H), 7.09 (t, J = 7.4 Hz, 1H), 7.12-7.22 (m, 3H), 7.36-7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 40.8, 63.5, 65.7, 68.2, 115.3, 116.0 (d, J = 10 Hz), 116.2 (d, J = 10 Hz), 118.4 (d, J = 8 Hz), 123.1, 123.8 (d, J = 8 Hz), 129.4, 150.8, 152.1, 157.7 (d, J = 239 Hz); IR (KBr): 3063, 2878, 1597, 1489, 1247,1208, 1087 cm^{-1}; ESI-MS (*m/z*): 272 $[M + H]^+$; Anal. Calcd for $C_{16}H_{14}FNO_2$: C, 70.84; H, 5.20; N, 5.16. Found: C, 70.68; H, 5.25; N, 5.04.

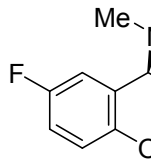


8-Fluoro-3,3a,4,9b-tetrahydro-3,3-dimethyl-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole (4r):



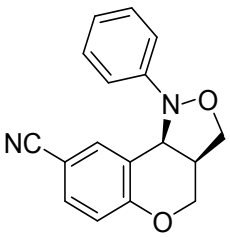
White solid, m.p.: 118-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.36 (s, 3H), 1.42 (s, 3H), 2.71-2.77 (m, 1H), 4.10 (dd, J_1 = 9.6 Hz, J_2 = 11.2 Hz, 1H), 4.34 (dd, J_1 = 4.8 Hz, J_2 = 11.2 Hz, 1H), 4.67 (d, J = 7.2 Hz, 1H), 6.77 (dd, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 1H), 6.87-6.95 (m, 2H), 7.08-7.12 (m, 1H), 7.24-7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.2, 29.6, 48.7, 62.3, 65.0, 82.9, 116.1 (d, J = 23 Hz), 116.4 (d, J = 23 Hz), 117.1, 118.1 (d, J = 8 Hz), 123.0 (d, J = 7 Hz), 123.4, 129.1, 151.3, 151.5, 157.3 (d, J = 237 Hz); IR (KBr): 3059, 2974, 1599, 1490, 1256, 1193, 1017 cm^{-1}; ESI-MS (*m/z*): 300 $[M + H]^+$; Anal. Calcd for $C_{18}H_{18}FNO_2$: C, 72.22; H, 6.06; N, 4.68. Found: C, 72.17; H, 6.13; N, 4.62.

8-Fluoro-3,3a,4,9b-tetrahydro-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole (4s): Yellow viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.85 (s, 3H), 3.01-3.03 (m, 1H), 3.54-3.56 (m, 1H), 3.74 (dd, J_1 = 4.4 Hz, J_2 = 8.4 Hz, 1H), 4.03- 4.15 (m, 2H), 4.27 (t, J = 8.0 Hz, 1H), 6.85 (dd, J_1 = 4.8 Hz, J_2 = 8.8 Hz, 1H), 6.91 (dd, J_1 = 2.8 Hz, J_2 = 8.4 Hz, 1H), 6.95-6.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 40.1, 43.7, 64.5, 66.1, 67.2, 116.2 (d, J = 13 Hz), 116.4 (d, J = 13 Hz), 118.3, 121.1 (d, J = 7 Hz), 151.7, 157.0 (d, J = 238 Hz); IR (neat): 2961, 2871, 1495, 1436, 1243, 1205, 1048 cm^{-1}; ESI-MS (*m/z*): 210 $[M + H]^+$; Anal. Calcd for $C_{11}H_{12}FNO_2$: C, 63.15; H, 5.78; N, 6.69. Found: C, 63.03; H, 5.86; N, 6.58.



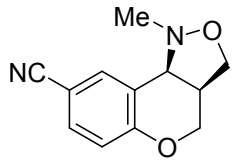
8-Nitro-1-phenyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole (4t): Yellow solid, m.p. 147-149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.09-3.14 (1H, m), 4.05 (dd, J_1 = 5.8 Hz, J_2 = 8.0, Hz, 1H), 4.29 (dd, J_1 = 4.8 Hz, J_2 = 11.6, Hz, 1H), 4.36 (dd, J_1 = 3.6 Hz, J_2 = 11.6, Hz, 1H), 4.39 (d, J = 8.4 Hz, 1H), 4.92 (d, J = 7.8 Hz, 1H), 7.00 (d, J = *9*.0 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.22 (d, J = 7.8 Hz, 2H), 7.38 (dd, J = 7.8 Hz, 2H), 8.12 (dd, J = 2.4, 9.0 Hz, 1H), 8.42 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 39.6, 62.8, 65.5, 67.8, 115.4, 117.9, 122.7, 123.4, 124.8, 126.7, 129.4, 142.2, 149.9, 160.9. ESI-MS (*m/z*): 299 $[M + H]^+$; Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.54; H, 4.59; N, 9.48.

3,3a,4,9b-Tetrahydro-1-phenyl-1*H*-chromeno[4,3-*c*]isoxazole-8-carbonitrile (4u): White solid, m.p.: 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.09-3.12 (m, 1H), 4.04 (dd, J_1 = 5.6 Hz, J_2 = 8.0 Hz, 1H), 4.23 (dd, J_1 = 4.8 Hz, J_2

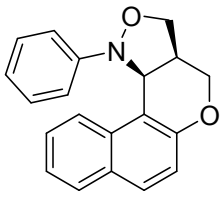


= 11.6 Hz, 1H), 4.32-4.39 (m, 2H), 4.85 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.09-7.13 (m, 1H), 7.18-7.21 (m, 2H), 7.36-7.40 (m, 2H), 7.49 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz,1H), 7.81 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 40.1, 62.8, 65.6, 68.1, 105.4, 115.6, 118.5, 119.0, 123.56, 123.60, 129.5, 132.9, 135.2, 150.2, 159.4; IR (KBr): 3090, 2888, 2221, 1609, 1493, 1247, 1017 cm^{-1}; ESI-MS (*m/z*): 279 $[M + H]^+$; Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.20; H, 5.18; N, 10.01.

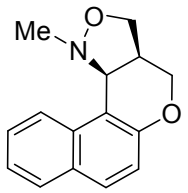
3,3a,4,9b-Tetrahydro-1-methyl-1*H*-chromeno[4,3-*c*]isoxazole-8-carbonitrile (4w): White solid, m.p.: 114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.86 (s, 3H), 3.00-3.07 (m, 1H), 3.62 (d, *J* = 5.2 Hz, 1H), 3.73 (dd, J_1 = 4.4 Hz, J_2 = 8.0 Hz, 1H), 4.11-4.16 (m, 1H), 4.21 (dd, J_1 = 4.8 Hz, J_2 = 11.2 Hz, 1H), 4.28 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 7.62 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 39.8, 43.7, 64.2, 66.1, 67.2, 117.4, 120.0, 126.3, 128.5, 132.2, 158.7, 169.0; ESI-MS (*m/z*): 217 $[M + H]^+$; Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.73; H, 5.68; N, 12.87.



3,3a,4,9b-Tetrahydro-1-phenyl-1H-benzo[f]chromeno[4,3-*c*]isoxazole (4x): Brown solid, m.p.: 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.02-3.08 (m, 1H), 4.16-4.30 (m, 3H), 4.38 (dd, J_1 = 7.6 Hz, J_2 = 10.0 Hz, 1H), 5.60 (d, *J* = 7.6 Hz, 1H), 7.10-7.15 (m, 2H), 7.36-7.44 (m, 5H), 7.53 (dd, J_1 = 1.2 Hz, J_2 = 6.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 40.7, 60.1, 65.1, 68.1, 113.2, 115.1, 118.9, 122.8, 123.4, 123.9, 127.0, 128.8, 129.5, 130.1, 130.2, 133.0, 150.2, 155.3; IR (KBr): 3059, 2885, 1597, 1485, 1342, 1225, 1102 cm^{-1}; ESI-MS (*m/z*): 304 $[M + H]^+$; Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.24; H, 5.68; N, 4.59.



3,3a,4,9b-Tetrahydro-1-methyl-1*H*-benzo[*f*]-chromeno[4,3-*c*]isoxazole (4z): Yellow solid, m.p.: 94-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.87 (s, 3H), 3.18-3.44 (m, 1H), 4.06-4.28 (m, 3H), 4.43 (t, *J* = 8.6 Hz, 1H), 4.65 (d, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.52-7.55 (m, 1H), 7.71 (d, J = 9.2 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.94-7.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 40.8, 48.2, 64.4, 65.6, 68.0, 111.3, 118.9, 122.3, 123.2, 123.9, 126.9, 128.7, 130.0, 133.4, 151.3; IR (KBr): 3072, 2882, 1598, 1509,



1434, 1226, 1184, 1104 cm^{-1}; ESI-MS (*m/z*): 242 $[M + H]^+$; Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.46; H, 6.22; N, 5.74.

Studies to establish necessity of "Grinding":

As a part of the study to establish the necessity of grinding for smooth formation of intermediate nitrone (**3**) reactions between 2-(allyloxy)benzaldehyde (**1a**) and phenylhydroxylamine (**2a**) were carried out in solution phase and under "neat-mixing" for 24 h and results are tabulated below (Table S2). In all the cases the reactions formed a mixture of nitrone (**3a**), product (**4a**) and unreacted starting materials in various proportions. Noticeably, neat-mixing gave better result in terms of product formation after 24 h (Table S2, entry 5). However, further progress of reaction was slowed down with time (Table S2, entry 6).

Table S1. Nitrone formation by conventional methods

Sl. No.	Solvent[a]	Time (h)	% nitrone (3a)[b]	% product (4a)[c]	% starting material recovered (1a)[c]
1	$CHCl_3$	24	44	16	40
2	EtOH	24	54	12	34
3	EtOH-H_2O (1:1)	24	30	06	64
4	H_2O	24	trace amount[d]	nil	--
5	Neat	24	52	26	22
6	Neat	48	42	43	15

[a]Equimolar mixture of **1a** and **2a** (in 0.05 mmol scale) were stirred either in solution or under neat condition. [b]The percentage of nitrone remaining in reaction mixture was approximated by subtracting % of product formed and % of starting material left. As nitrone (**3a**) to chromano isoxazole (**4a**) formation was continuous process, no attempt was made to isolate **3a** in pure form. [c]Yields refer to the isolated product (and starting material). They were isolated by preparative TLC. [d]Not isolated.

Infrared Spectroscopic studies:

Infrared spectroscopic studies were conducted to capture the progress of the reaction. The reaction between 2-(allyloxy)benzaldehyde and phenylhydroxylamine was monitored by taking IR spectra of the crude reaction mixture at different time interval. The study was conducted by grinding in an Agate mortar and by taking small portion of the reaction mixture for IR spectra at a given time. As shown in Fig. S1, the characteristic stretching bands of starting materials like

carbonyl of aromatic aldehyde at 1682 cm^{-1} and phenylhydroxylamine O-H and N-H bands at 3240 cm^{-1} and 3118 cm^{-1} . This characteristic peak almost disappeared after grinding the reaction mixture for 5 min. In contrast, a new peak at 1545 cm^{-1} was appeared in the IR spectrum which is supposed to be the C=N stretching band of intermediate nitrone. As the reaction progressed further (see IR spectra after 10 min) this peak significantly developed indicating the formation of intermediate nitrone. The IR spectrum of the crude reaction mixture after heating revealed the formation of chromenoisoxazole by intramolecular 1,3-dipolar cycloaddition.

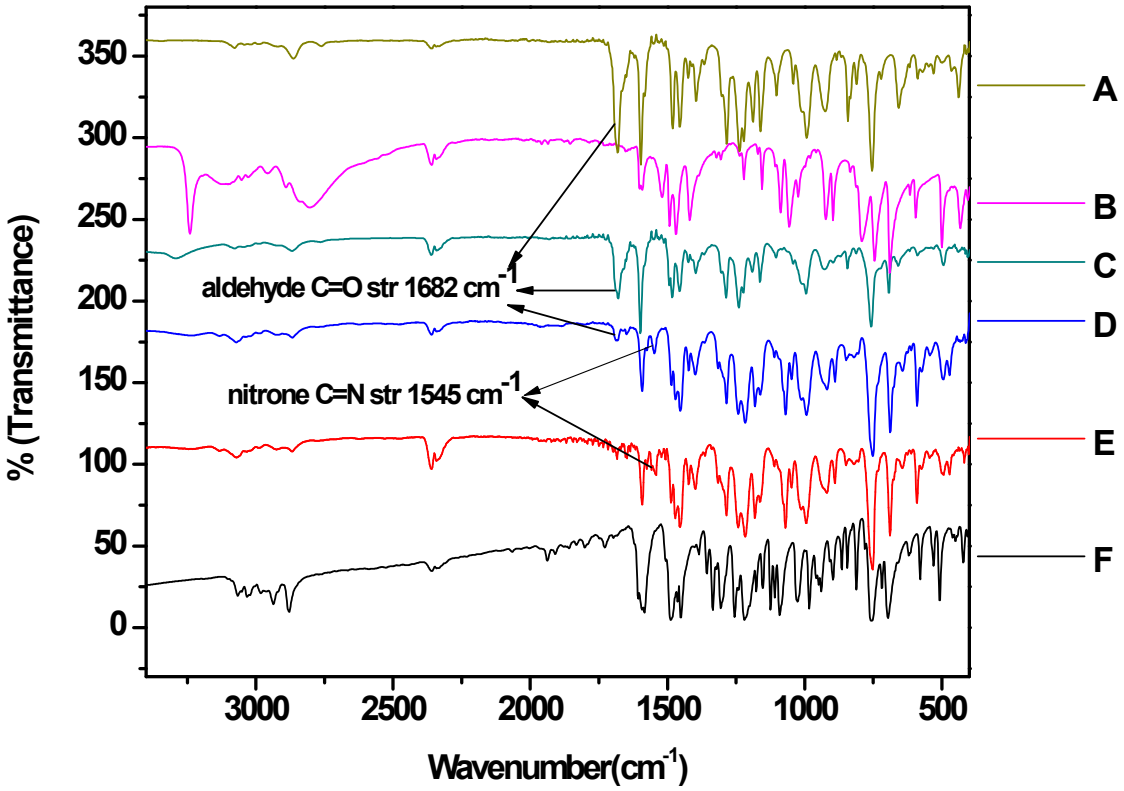


Fig. S1. IR studies to monitor the progress of the reaction between 2-(allyloxy)benzaldehyde and phenylhydroxylamine: "A" represents the IR spectra of pure 2-(allyloxy)benzaldehyde, "B" represents the IR spectra of pure phenylhydroxylamine, "C" represents the reaction mixture just after few seconds of mixing, "D" represents the reaction mixture after 5 min of grinding, "E" represent the reaction mixture after 10 min of grinding, "F" represents the reaction mixture after heating at 60 °C for 90 min; str is abbreviation of stretching.

Table S2. Coupling constant values ($J_{H3a\text{-}H9b}$) of ring junction protons of **4**

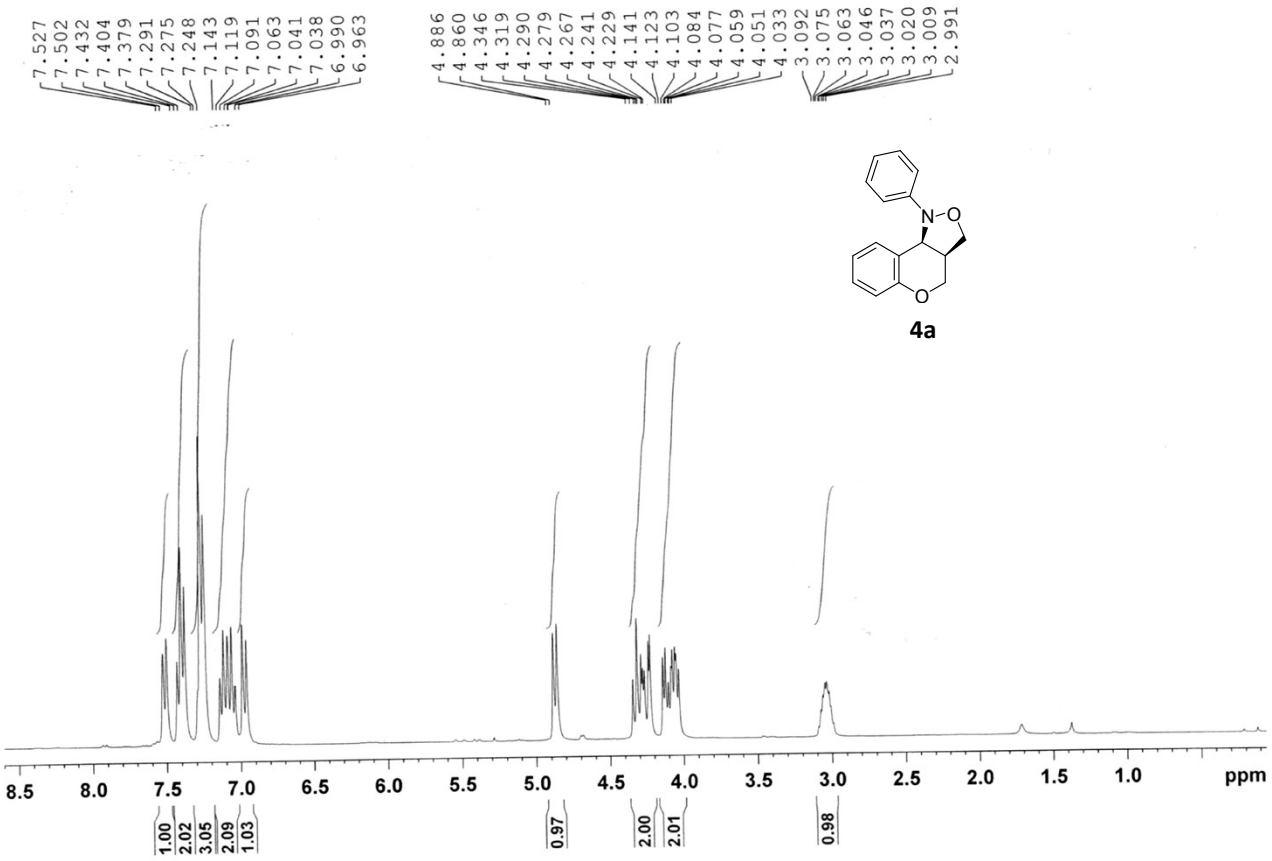
Entry	Product (**4**)	$J_{H3a\text{-}H9b}$
1	**4a**	J = 7.8 Hz
2	**4b**	J = 6.9 Hz
3	**4c**	J = 5.6 Hz
4	**4d**	J = 7.6 Hz
5	**4e**	J = 7.5 Hz
6	**4f**	J = 6.9 Hz
7	**4g**	J = 5.6 Hz
8	**4h**	J = 7.8 Hz
9	**4i**	J = 6.8 Hz
10	**4j**	J = 7.6 Hz
11	**4k**	J = 6.8 Hz
12	**4l**	J = 4.8 Hz
13	**4m**	J = 7.6 Hz
14	**4n**	J = 7.2 Hz
15	**4o**	J = 8.0 Hz
16	**4p**	J = 7.2 Hz
17	**4q**	J = 8.0 Hz
18	**4r**	J = 7.2 Hz
19	**4s**	J = 5.2 Hz
20	**4t**	J = 7.8 Hz
21	**4u**	J = 7.6 Hz
22	**4v**	J = 6.8 Hz
23	**4w**	J = 5.2 Hz
24	**4x**	J = 7.6 Hz
25	**4y**	J = 6.0 Hz
26	**4z**	J = 7.6 Hz

References

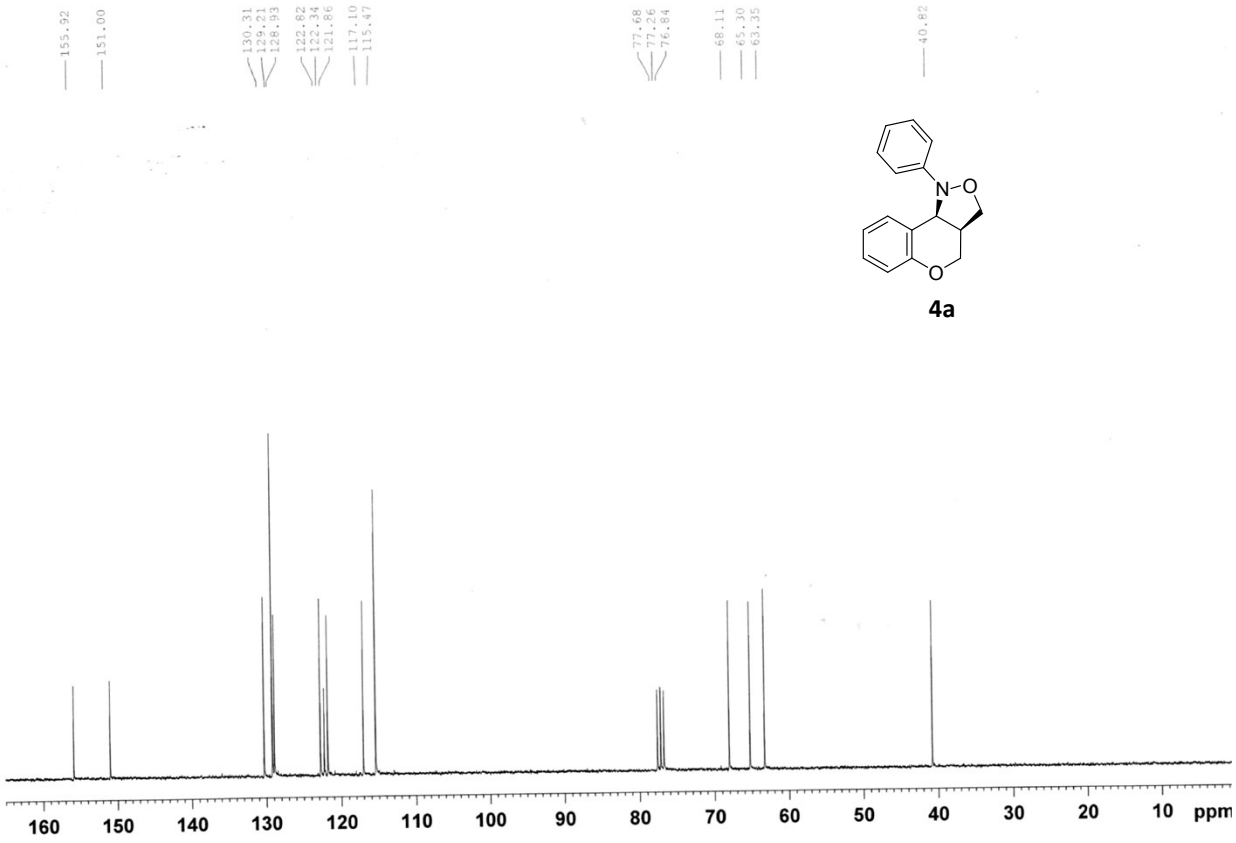
1. R. Rohlmann, C.-G. Daniliuc and O. Garćia Mancheño, *Chem. Commun.,* **2013**, 49, 11665-11667.

Selected NMR Spectra

^{1}H-NMR of 4a



^{13}C-NMR of 4a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40.82
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O
4a
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130
120
110
100
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80
70
60
50
40
30
20
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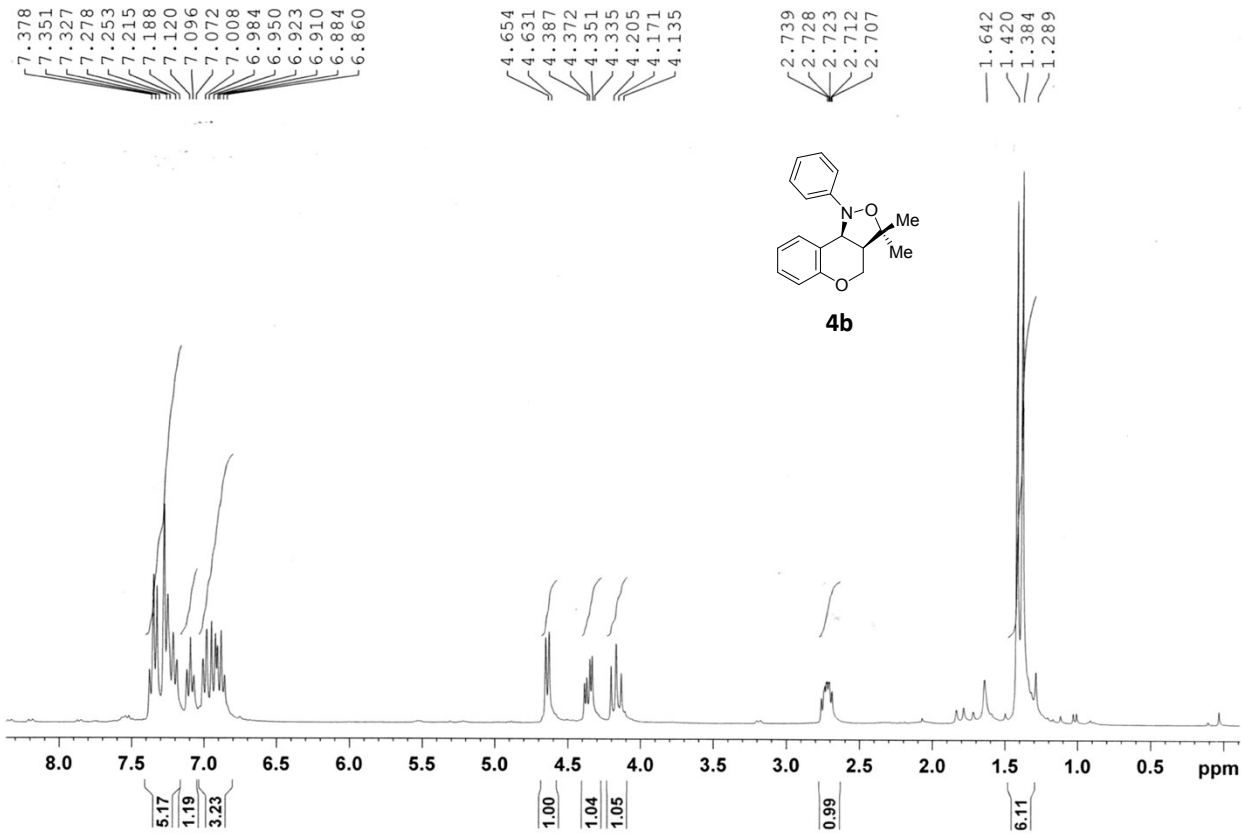
ppm

[1]H-NMR of 4b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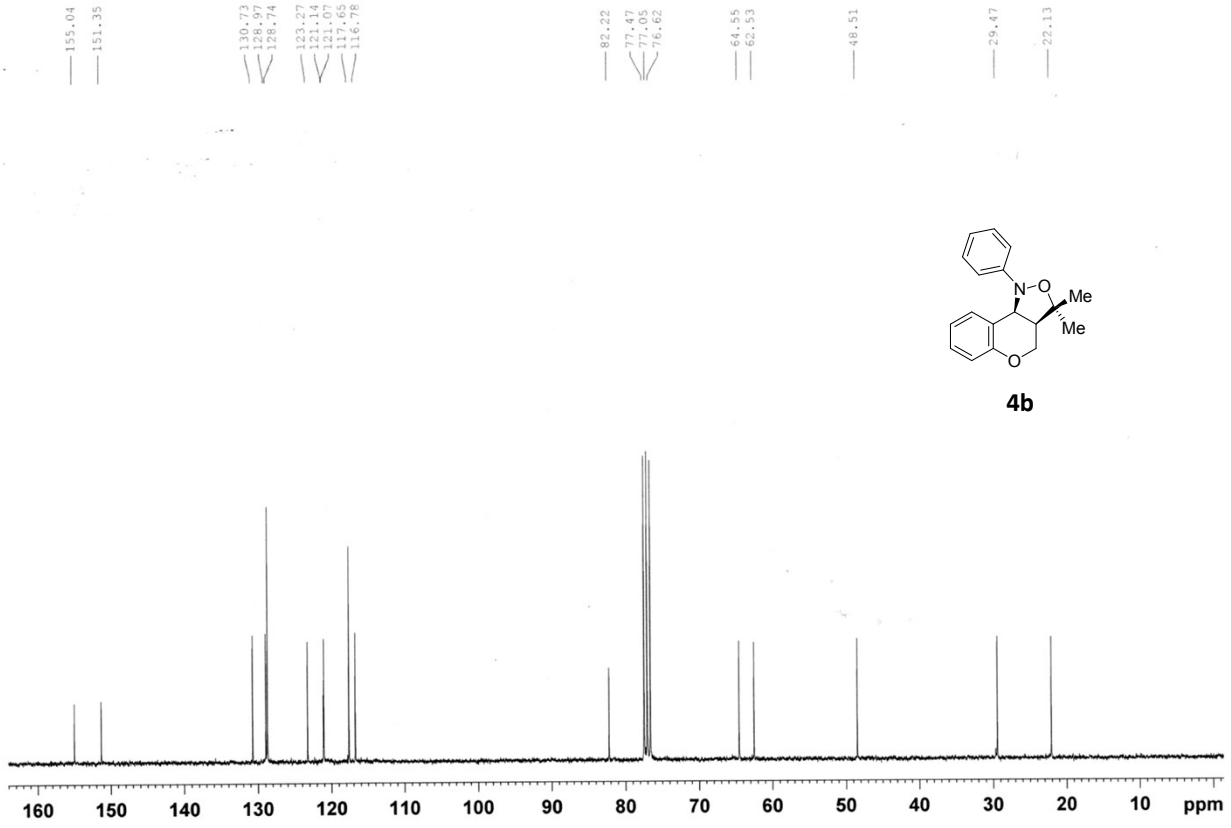
^{13}C-NMR of 4b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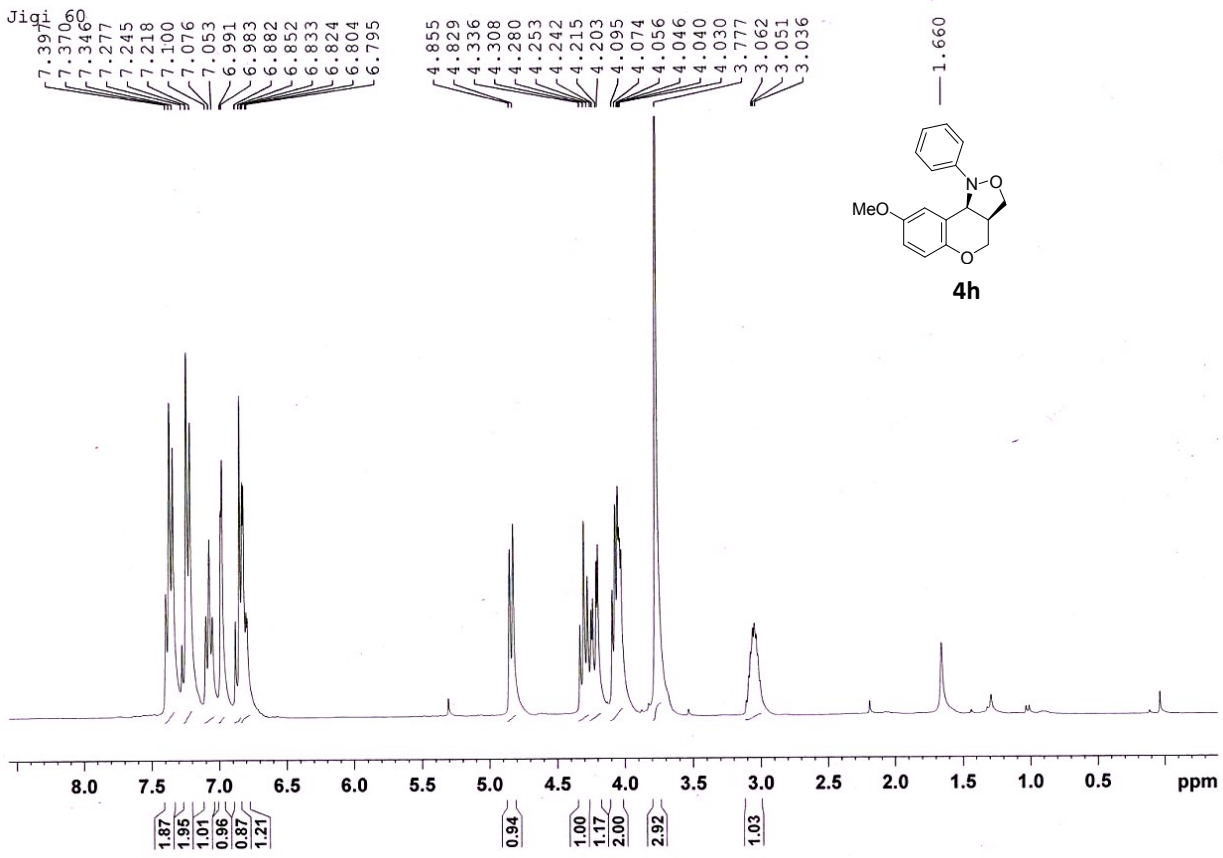
1H-NMR of 4h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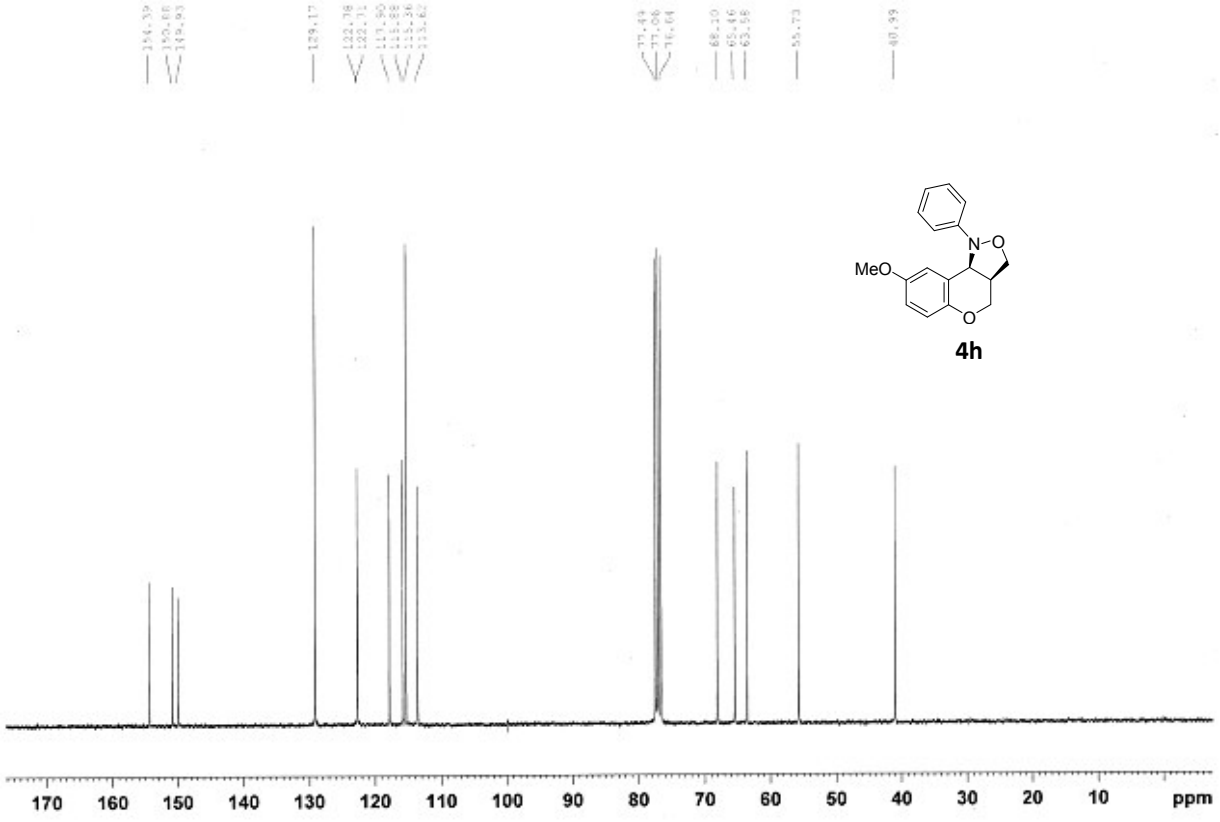
^{13}C-NMR of 4h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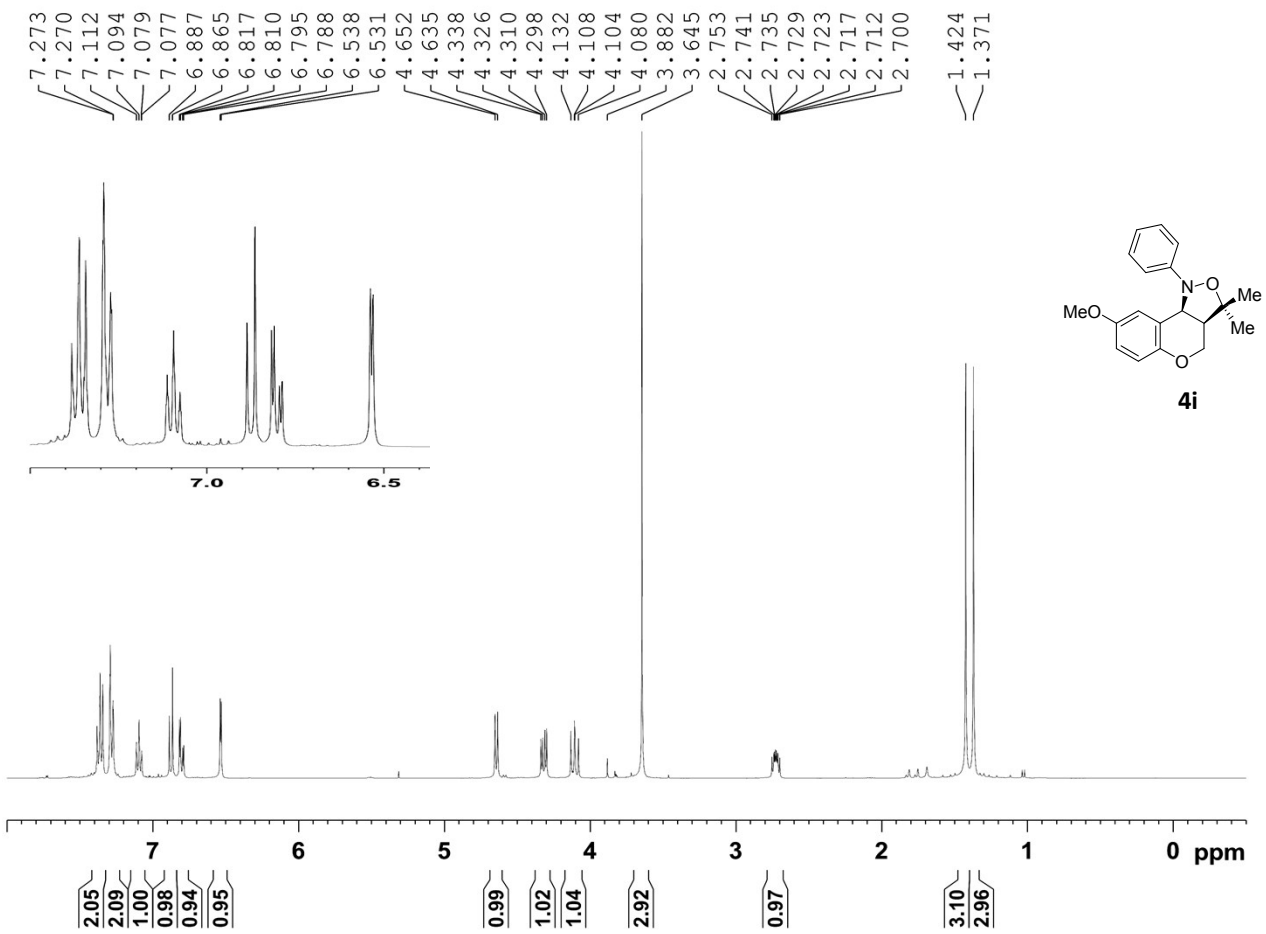
[1]H-NMR of 4i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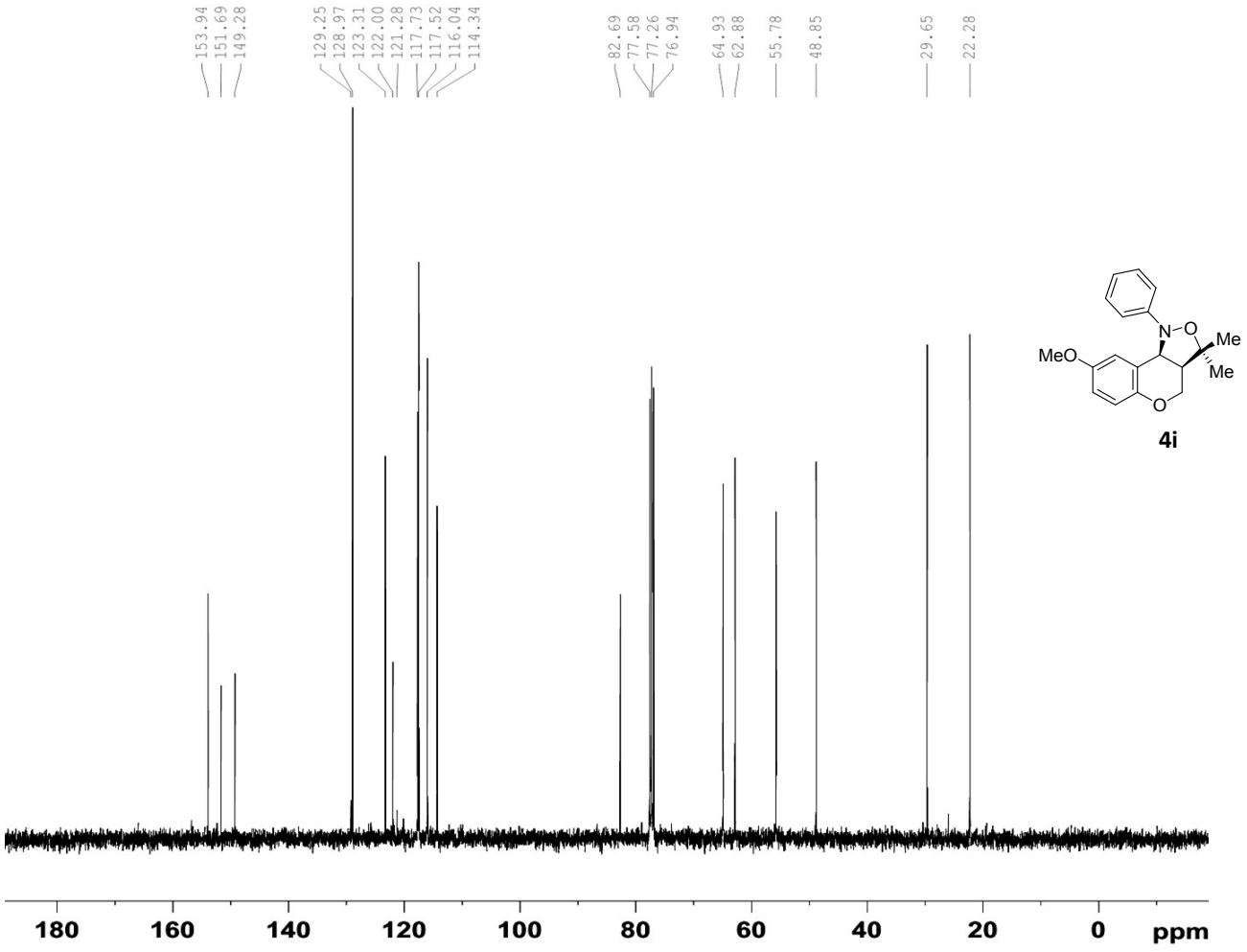
^{13}C-NMR of 4i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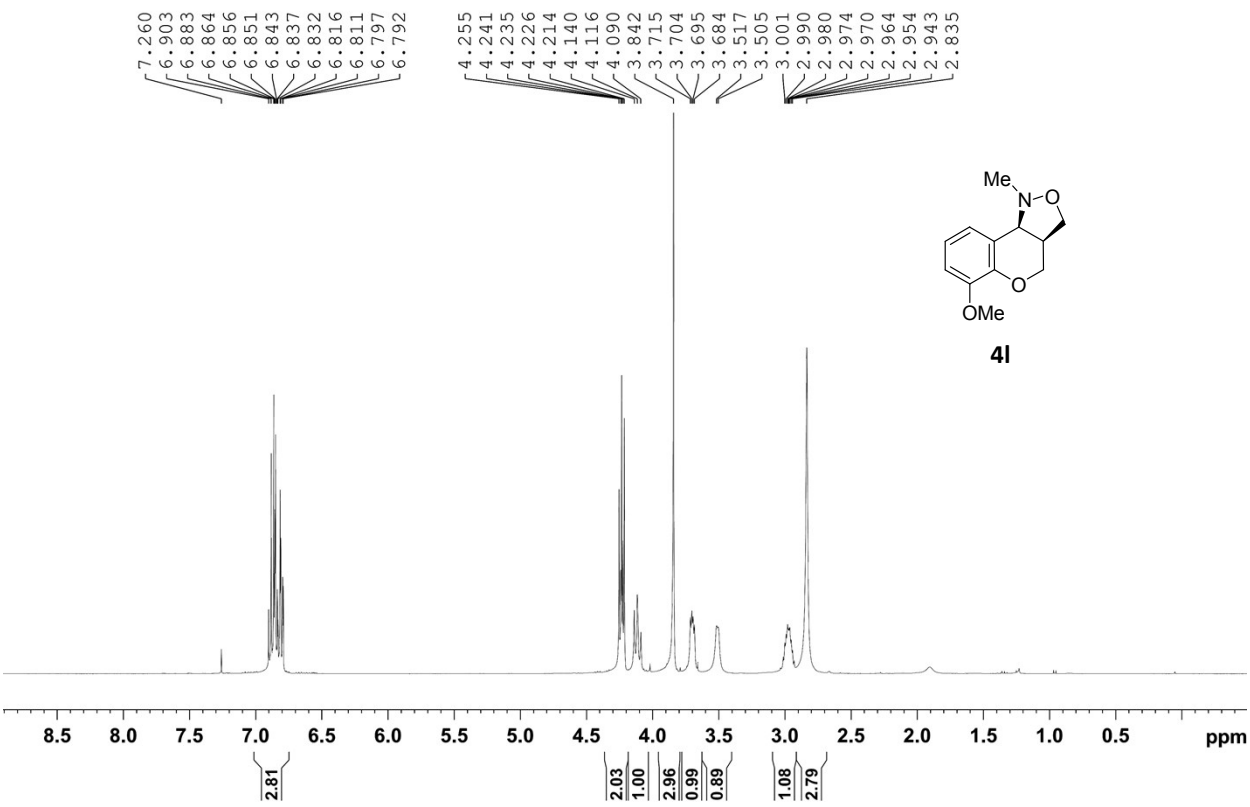
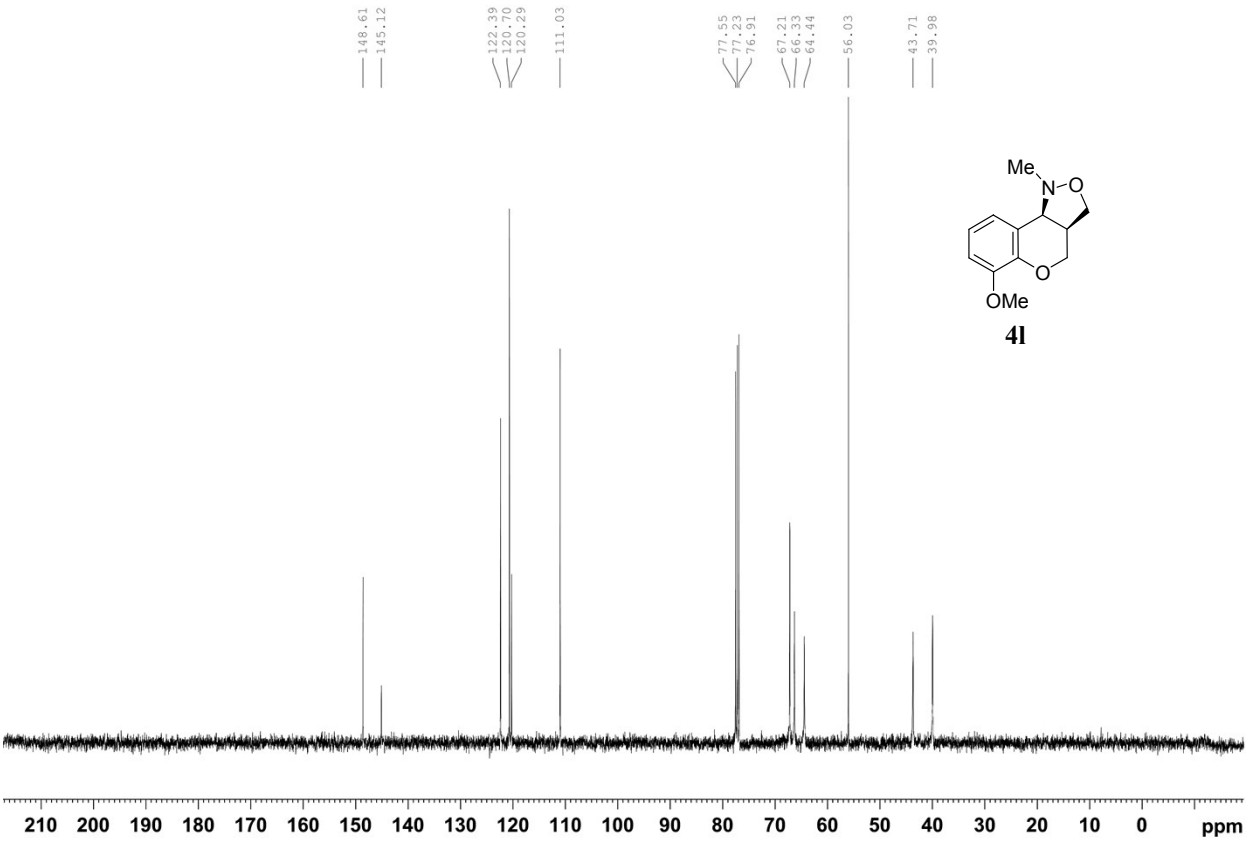
ppm

[1]H-NMR of 4l

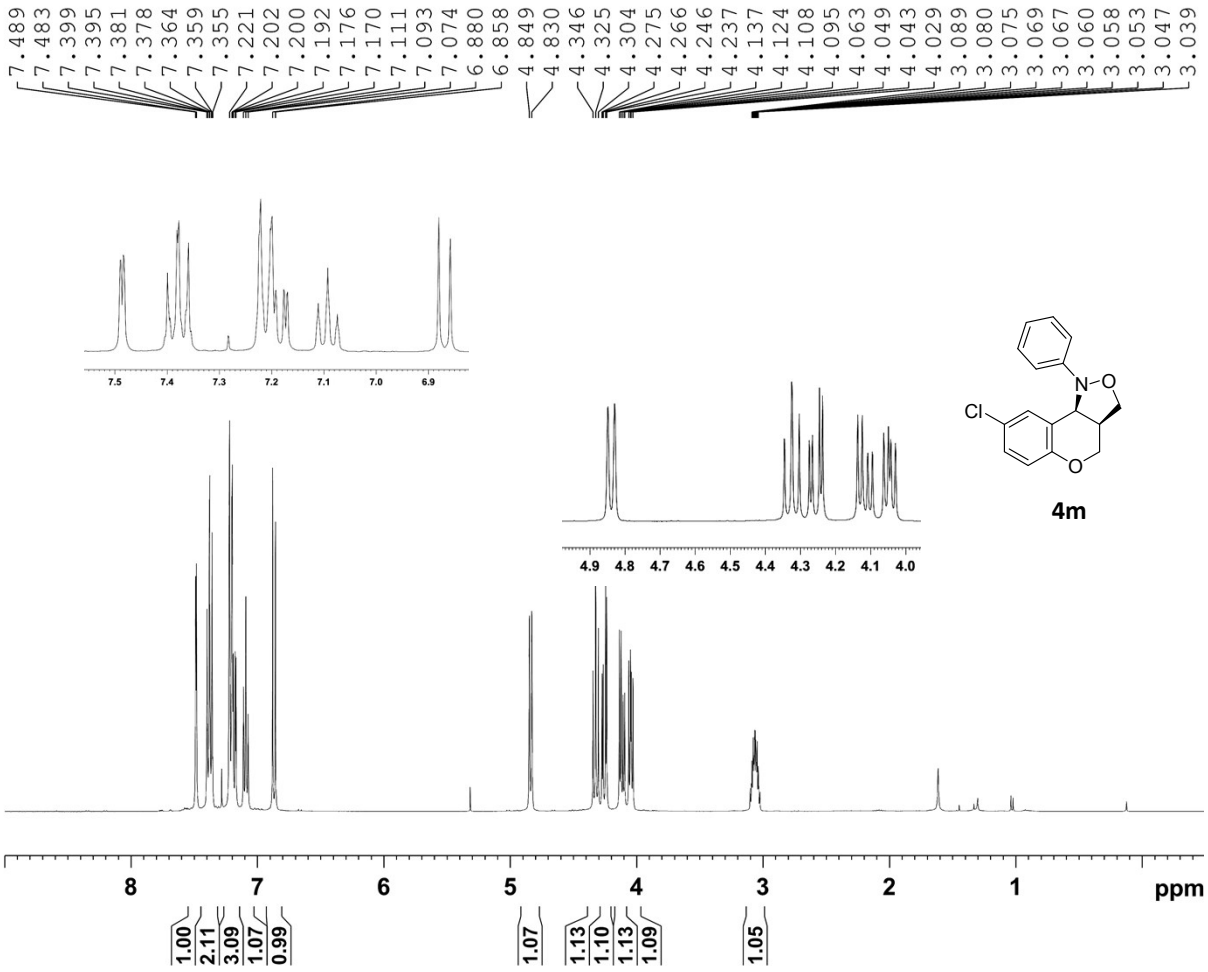

7.260
6.903
6.883
6.864
6.856
6.851
6.843
6.837
6.832
6.816
6.811
6.797
6.792
4.255
4.241
4.235
4.226
4.214
4.140
4.116
4.090
3.842
3.715
3.704
3.695
3.684
3.517
3.505
3.001
2.990
2.980
2.974
2.970
2.964
2.954
2.943
2.835
Me
N
O
O
OMe
4l
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.81
2.03
1.00
2.96
0.99
0.89
1.08
2.79

^{13}C-NMR of 4l

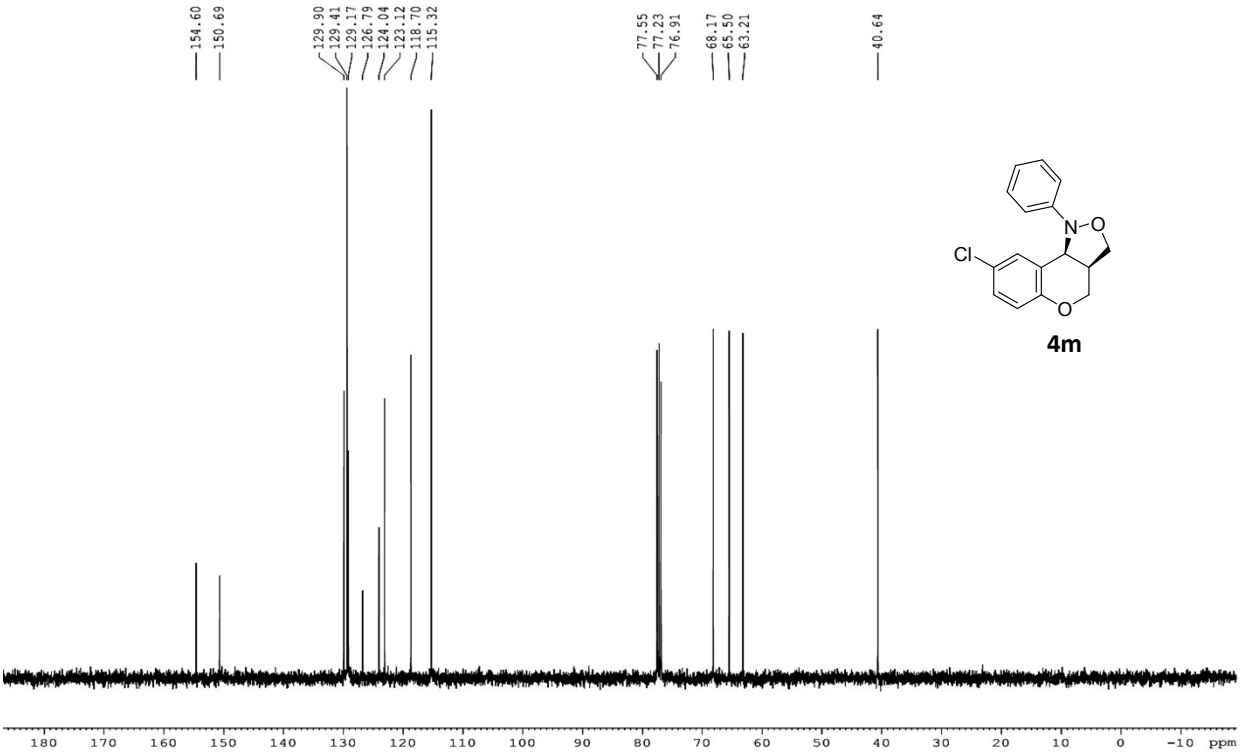


4l

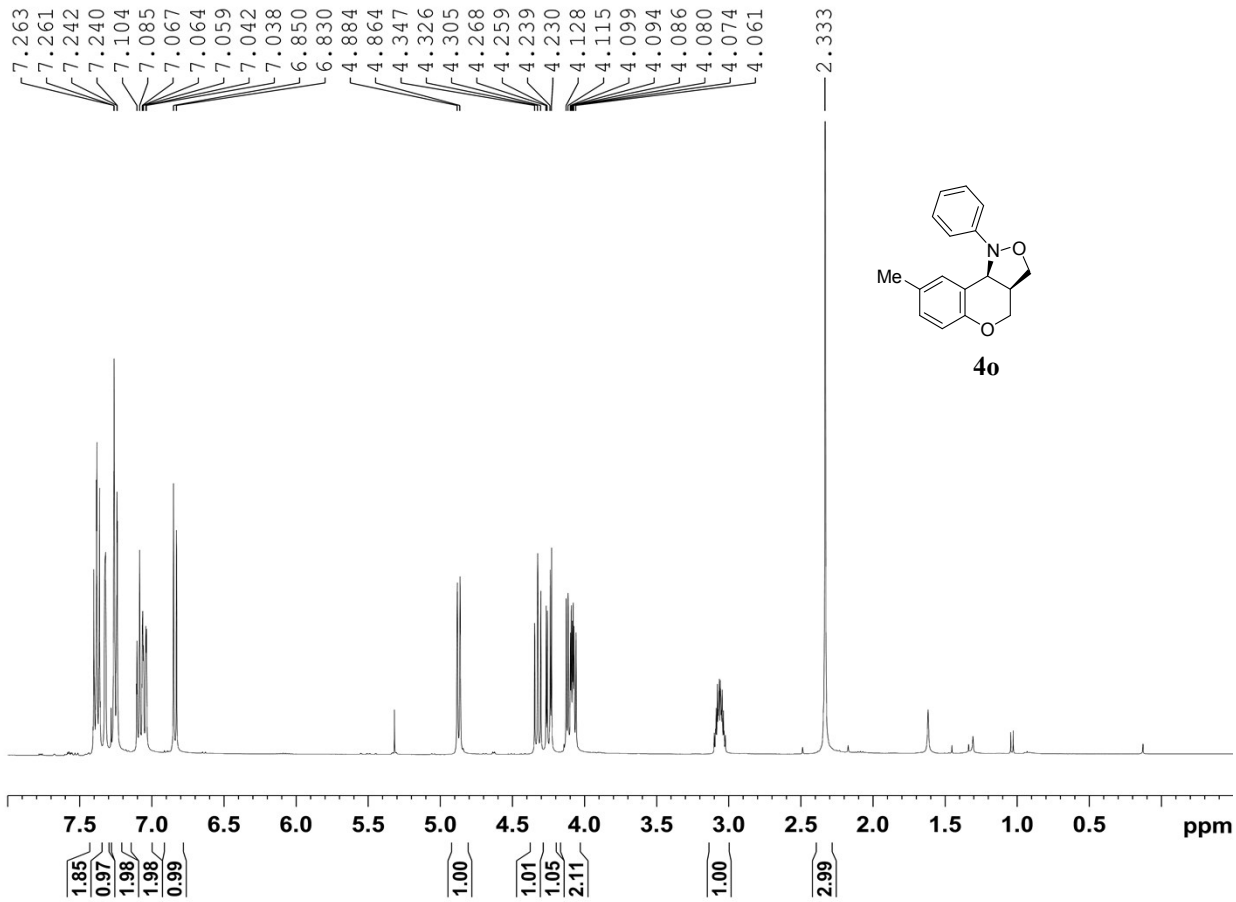
[1]H-NMR of 4m


7.489
7.483
7.399
7.395
7.381
7.378
7.364
7.359
7.355
7.221
7.202
7.200
7.192
7.176
7.170
7.111
7.093
7.074
6.880
6.858
4.849
4.830
4.346
4.325
4.304
4.275
4.266
4.246
4.237
4.137
4.124
4.108
4.095
4.063
4.049
4.043
4.029
3.089
3.080
3.075
3.069
3.067
3.060
3.058
3.053
3.047
3.039
Cl
N
O
O
4m
ppm
1.00
2.11
3.09
1.07
0.99
1.07
1.13
1.10
1.13
1.09
1.05

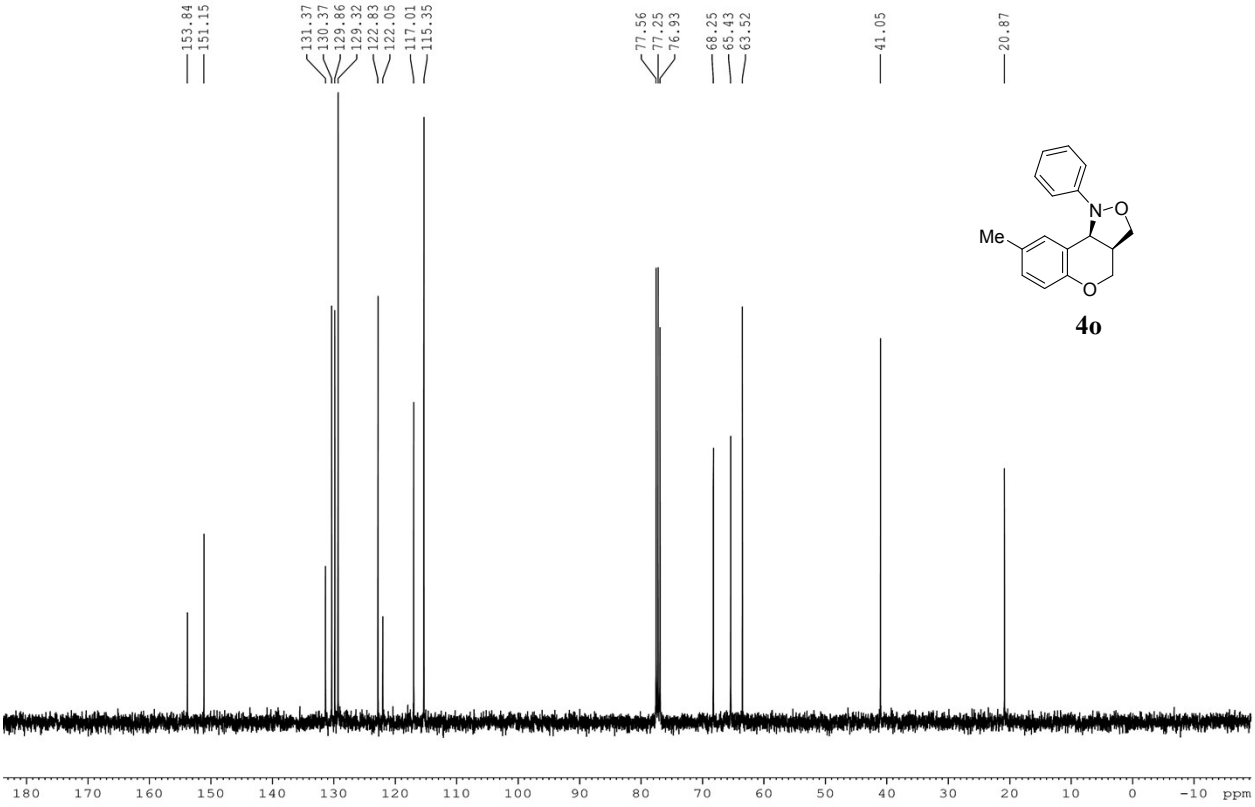
^{13}C-NMR of 4m


154.60
150.69
129.90
129.41
129.17
126.79
124.04
123.12
118.70
115.32
77.55
77.23
76.91
68.17
65.50
63.21
40.64
N
O
Cl
O
4m
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

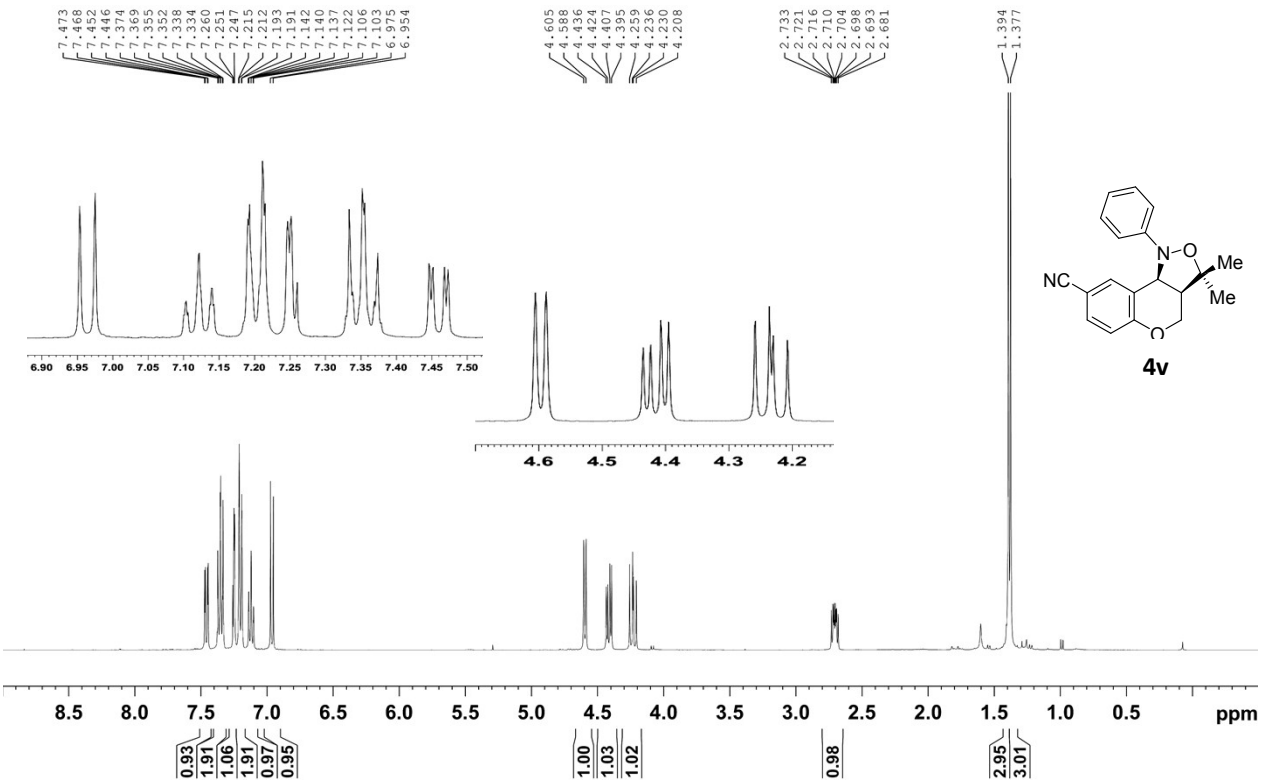
[1]H-NMR of 4o


7.263
7.261
7.242
7.240
7.104
7.085
7.067
7.064
7.059
7.042
7.038
6.850
6.830
4.884
4.864
4.347
4.326
4.305
4.268
4.259
4.239
4.230
4.128
4.115
4.099
4.094
4.086
4.080
4.074
4.061
2.333
N
O
Me
O
4o
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.85
0.97
1.98
1.98
0.99
1.00
1.01
1.05
2.11
1.00
2.99

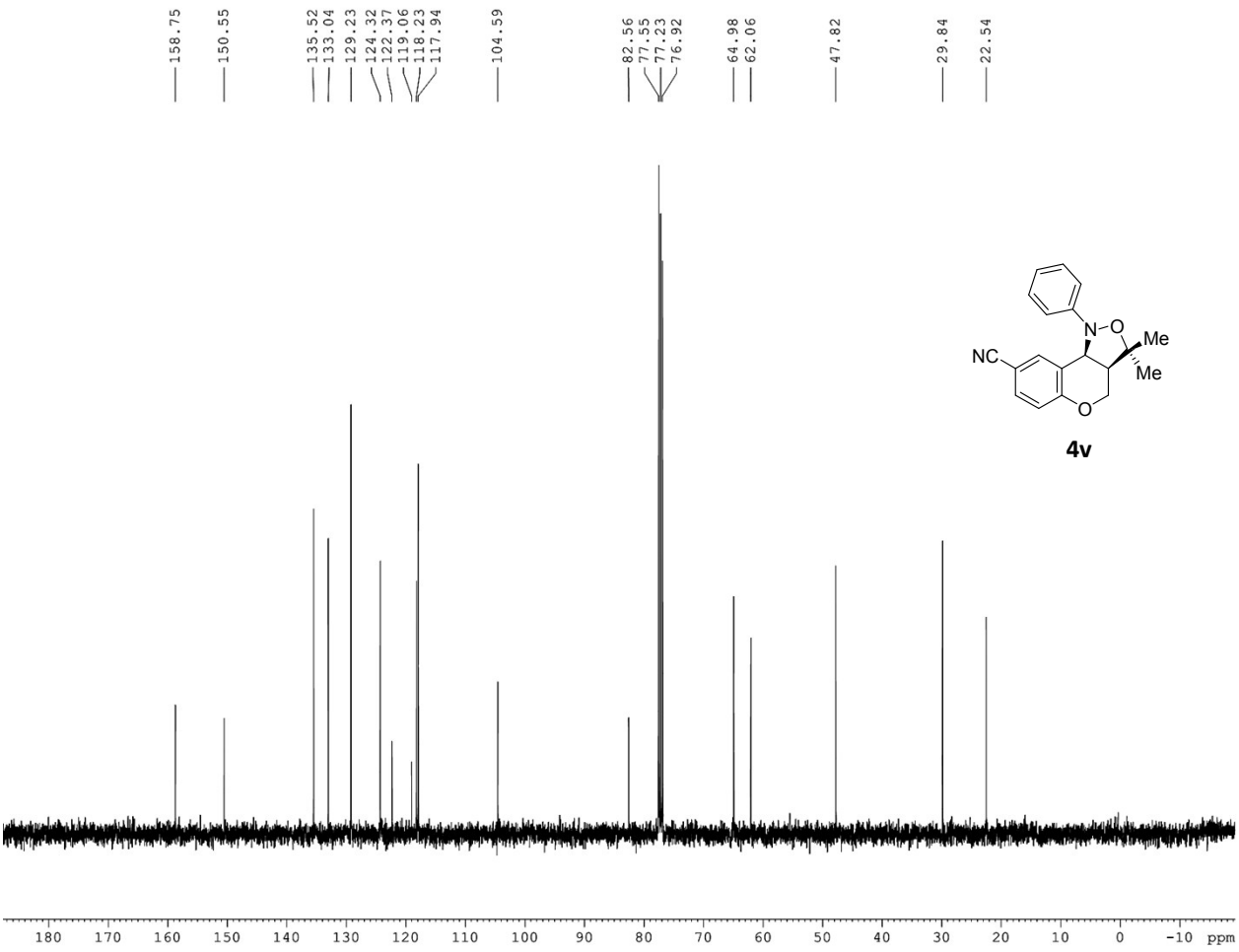
^{13}C-NMR of 4o


153.84
151.15
131.37
130.37
129.86
129.32
122.83
122.05
117.01
115.35
77.56
77.25
76.93
68.25
65.43
63.52
41.05
20.87
Me
O
N
O
4o
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
ppm

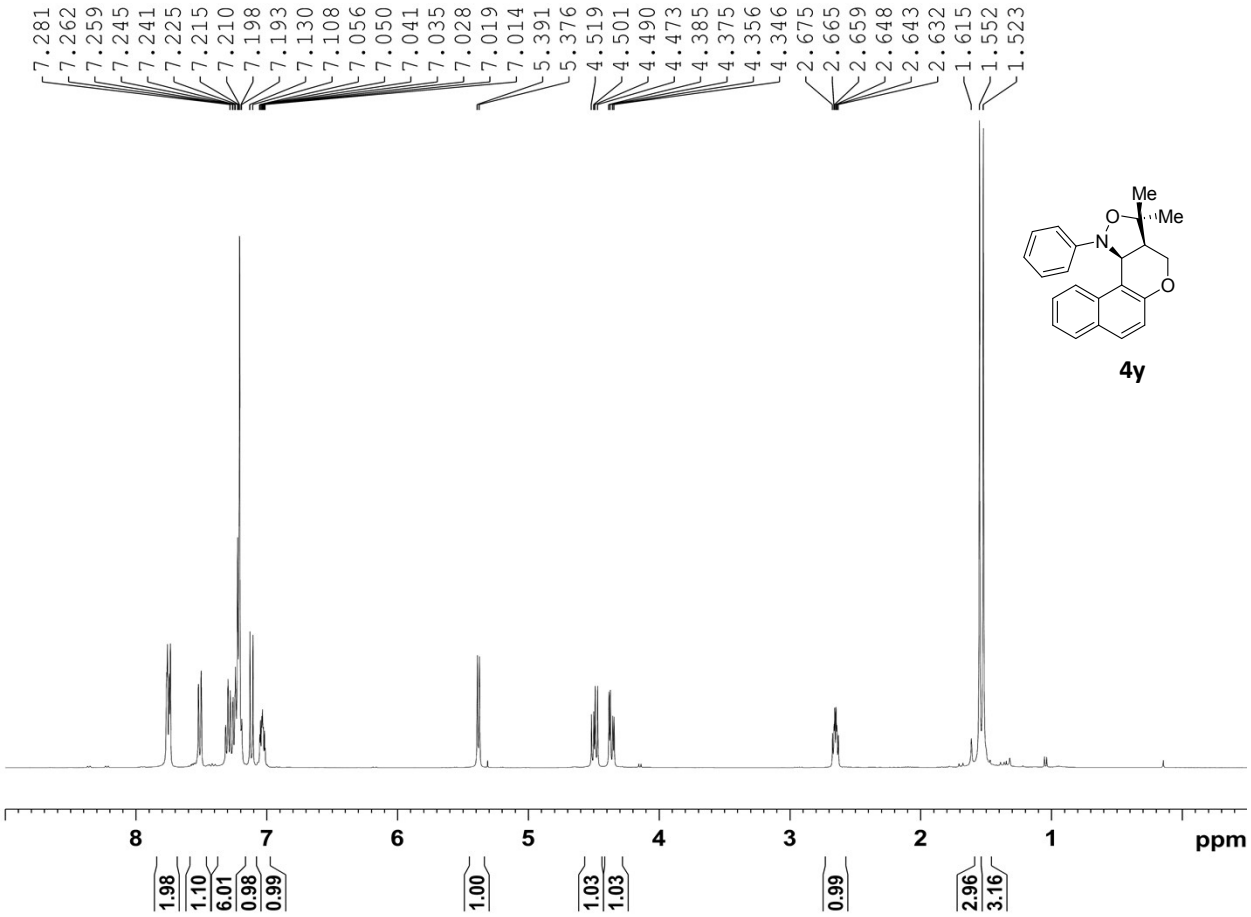
[1]H-NMR of 4v


7.473
7.468
7.452
7.446
7.374
7.369
7.355
7.352
7.338
7.334
7.260
7.251
7.247
7.215
7.212
7.193
7.191
7.142
7.140
7.137
7.122
7.106
7.103
6.975
6.954
4.605
4.588
4.436
4.424
4.407
4.395
4.259
4.236
4.230
4.208
2.733
2.721
2.716
2.710
2.704
2.698
2.693
2.681
1.394
1.377
NC
N
O
Me
Me
O
4v
ppm
0.93
1.91
1.06
1.91
0.97
0.95
1.00
1.03
1.02
0.98
2.95
3.01

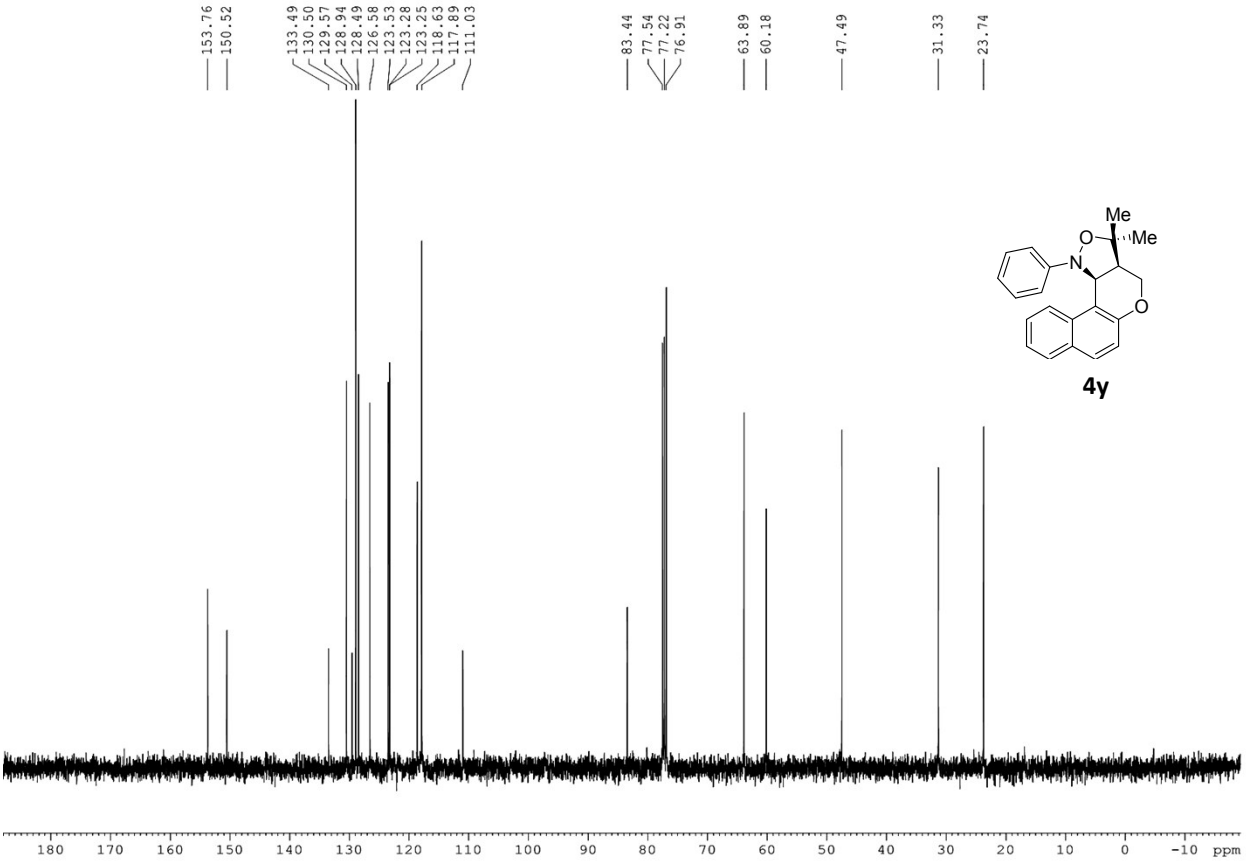
^{13}C-NMR of 4v


158.75
150.55
135.52
133.04
129.23
124.32
122.37
119.06
118.23
117.94
104.59
82.56
77.55
77.23
76.92
64.98
62.06
47.82
29.84
22.54
NC
N
O
Me
Me
O
4v
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

^{1}H-NMR of 4y


7.281
7.262
7.259
7.245
7.241
7.225
7.215
7.210
7.198
7.193
7.130
7.108
7.056
7.050
7.041
7.035
7.028
7.019
7.014
5.391
5.376
4.519
4.501
4.490
4.473
4.385
4.375
4.356
4.346
2.675
2.665
2.659
2.648
2.643
2.632
1.615
1.552
1.523
Me
Me
O
N
O
4y
8
7
6
5
4
3
2
1
ppm
1.98
1.10
6.01
0.98
0.99
1.00
1.03
1.03
0.99
2.96
3.16

^{13}C-NMR of 4y


153.76
150.52
133.49
130.50
129.57
128.94
128.49
126.58
123.53
123.28
123.25
118.63
117.89
111.03
83.44
77.54
77.22
76.91
63.89
60.18
47.49
31.33
23.74
Me
Me
O
N
O
4y
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm