Electronic supplementary information

Triflic-acid promoted post-Ugi condensation for the assembly of 2,6-diarylmorpholin-3-ones

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General Remarks

Materials and solvents. Unless otherwise specified, all reagents and solvents were purchased from commercial sources and used without further purification. 2-Oxoaldehydes **1** were used in a hydrate form and were synthesized following literature procedure.[1]

NMR spectroscopy. NMR spectroscopic data were recorded with JEOL JNM-ECA 500 MHz spectrometer (500.16 MHz for ^{1}H and 125.78 MHz for $^{13}C\{^{1}H\}$) and Bruker Avance III 300 MHz spectrometer (282.40 MHz for $^{19}F\{^{1}H\}$), in $CDCl_3$ and were referenced to solvent residual proton signal (7.26 ppm) or to TMS signal (0 ppm), solvent carbon signal (77.16 ppm) and hexafluorobenzene fluorine signal (-164.9 ppm). Hexafluorobenzene was used as external reference.

Mass spectrometry. Mass spectra were recorded on Agilent 6530 ESI-QTOF mass spectrometer equipped with UHPLC inlet and UV detector.

Melting points. Melting points were determined in open capillary tubes on Stuart Scientific SMP3 melting point apparatus.

Optical rotations. Optical rotations were obtained with a Perkin-Elmer 343 polarimeter.

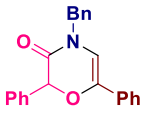
Chiral HPLC. The enantiomeric purity was determined by HPLC using Waters 501 pump, Waters 486 detector and CHIRALPAK® IB column for the samples dissolved in hexane (~1mg/ml concentration).

[1] A. A. Peshkov, D. Gapanenok, A. Puzyk, N. Amire, A. S. Novikov, S. D. Martynova, S. Kalinin, D. Dar'in, V. A. Peshkov and M. Krasavin, *The Journal of Organic Chemistry*, 2023, **88**, 10508–10524.

Synthesis and characterization

General procedure for the post-Ugi synthesis of 2,6-diarylmorpholin-3-ones 28

2-Hydroxycarboxylic acid **26** (0.4 mmol) was placed in a screw-cap vial and dissolved in methanol (2.5 mL) followed by addition of 2-oxoaldehyde hydrate **1·H₂O** (0.4 mmol), amine **3** (0.4 mmol) and *tert*-butyl isocyanide (**9**, 33 mg, 45 µL, 0.4 mmol). The vial was sealed and the mixture was stirred for 24 hours at room temperature. Upon completion of this time, the mixture was concentrated and dried under reduced pressure until the formation of powder-like product. The obtained crude Ugi adduct **27** was dissolved in DCM (4-8 mL) followed by addition of triflic acid (102 mg, 60 µL, 0.68 mmol). The reaction was stirred for 10-15 minutes at room temperature. Upon completion of reaction as indicated by TLC analysis, the resulting mixture was concentrated with silica on vacuo and submitted to column chromatography with DCM/*i*PrOH (0→1%) or hexane/EtOAc (10→30%) mixture as an eluent do deliver pure 2,6-diarylmorpholin-3-one **28**. Some products, especially those derived from 2-oxoaldehydes bearing electron donating substituents in the aromatic ring, showed traces of degradation upon long-term storage at 5 °C.



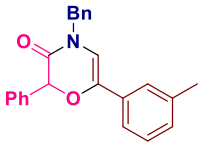
4-Benzyl-2,6-diphenyl-2*H*-1,4-oxazin-3(4*H*)-one (28a):

Rac-28a: yellowish oil; yield: 70-79 mg, 51-58% (condensation on 0.4 mmol scale in 4 or 8 mL of DCM).

(*R*)-28a: white solid; mp: 126-128 °C; yield: 66-85 mg, 48-62% (condensation on 0.4 mmol scale in 4 or 8 mL of DCM); $[\alpha]^{27}_{D}$ = -10.6° (c = 0.33, EtOAc).

The reaction was also conducted on a larger 1.2 mmol scale (0.6 mmol × 2, combined for purification) with the yields falling in the range observed for 0.4 mmol scale reactions. The best obtained result is 239 mg, 58%.

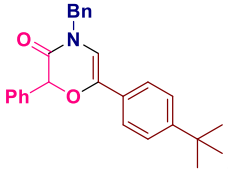
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 4H), 7.39 – 7.29 (m, 10H), 7.28 – 7.24 (m, 1H), 6.18 (s, 1H), 5.80 (s, 1H), 4.88 (d, *J* = 14.9 Hz, 1H), 4.84 (d, *J* = 14.9 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 163.1, 139.0, 136.1, 135.5, 132.3, 129.0, 128.8, 128.7, 128.6, 128.2, 128.04, 128.00, 126.8, 123.8, 106.0, 78.7, 49.1; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{23}H_{20}NO_2]^+$ 342.1489, found 342.1491.



4-Benzyl-2-phenyl-6-(m-tolyl)-2*H*-1,4-oxazin-3(4*H*)-one (28b):

Rac-28b: yellowish oil; yield: 58 mg, 41% (condensation on 0.4 mmol scale in 8 mL of DCM).

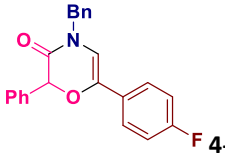
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.40 – 7.27 (m, 10H), 7.24 – 7.19 (m, 1H), 7.11 – 7.06 (m, 1H), 6.17 (s, 1H), 5.79 (s, 1H), 4.88 (d, J = 14.9 Hz, 1H), 4.83 (d, J = 14.9 Hz, 1H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 163.1, 139.2, 138.3, 136.1, 135.6, 132.2, 129.0, 128.9, 128.8, 128.7, 128.5, 128.0, 127.9, 126.8, 124.3, 120.9, 105.9, 78.7, 49.1, 21.6; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{24}H_{22}NO_2]^+$ 356.1646, found 356.1650.



4-Benzyl-6-(4-(*tert*-butyl)phenyl)-2-phenyl-2*H*-1,4-oxazin-3(4*H*)-one (28c):

Rac-28c: yellowish oil; yield: 83 mg, 52% (condensation on 0.4 mmol scale in 4 mL of DCM).

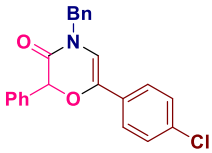
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.39 – 7.28 (m, 10H), 6.13 (s, 1H), 5.80 (s, 1H), 4.87 (d, J = 15.0 Hz, 1H), 4.84 (d, J = 15.1 Hz, 1H), 1.31 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 163.0, 151.4, 139.1, 136.2, 135.6, 129.5, 128.9, 128.75, 128.66, 128.0, 126.8, 125.5, 123.6, 105.4, 78.6, 49.1, 34.7, 31.3; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{27}H_{28}NO_2]^+$ 398.2115, found 398.2113.



4-Benzyl-6-(4-fluorophenyl)-2-phenyl-2*H*-1,4-oxazin-3(4*H*)-one (28d):

Rac-28d: transparent oil; yield: 59 mg, 41% (condensation on 0.4 mmol scale in 4 mL of DCM).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 4H), 7.39 – 7.27 (m, 8H), 7.05 – 6.95 (m, 2H), 6.09 (s, 1H), 5.77 (s, 1H), 4.88 (d, J = 14.9 Hz, 1H), 4.82 (d, J = 14.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.0, 162.7 (d, J = 248.2 Hz), 138.4, 136.1, 135.4, 129.0, 128.9, 128.7, 128.5 (d, J = 3.2 Hz), 128.1, 128.0, 126.8, 125.7 (d, J = 8.2 Hz); 115.6 (d, J = 21.9 Hz), 105.7 (d, J = 1.6 Hz), 78.7, 49.1; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ -115.5; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{23}H_{19}FNO_2]^+$ 360.1394, found 360.1396.

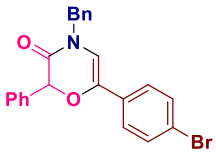


4-Benzyl-6-(4-chlorophenyl)-2-phenyl-2*H*-1,4-oxazin-3(4*H*)-one (28e):

Rac-28e: beige solid; mp: 84-87 °C; yield: 98 mg, 65% (condensation on 0.4 mmol scale in 8 mL of DCM).

(*R*)-28e: white solid; mp: 111-114 °C; yield: 108 mg, 72% (condensation on 0.4 mmol scale in 8 mL of DCM); $[\alpha]^{27}_D$ = -36.7° (c = 0.26, EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.40 – 7.26 (m, 12H), 6.15 (s, 1H), 5.77 (s, 1H), 4.87 (d, J = 14.9 Hz, 1H), 4.82 (d, J = 14.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.0, 138.1, 136.0, 135.3, 133.8, 130.8, 129.0, 128.9, 128.8, 128.7, 128.1, 128.0, 126.7, 124.9, 106.4, 78.7, 49.1; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{23}H_{19}ClNO_2]^+$ 376.1099, found 376.1097.

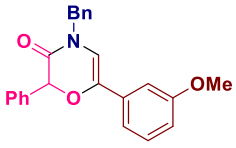


4-Benzyl-2,6-diphenyl-2*H*-1,4-oxazin-3(4*H*)-one (28f):

Rac-28f: beige solid; mp: 104-107 °C; yield: 113 mg, 67% (condensation on 0.4 mmol scale in 4 mL of DCM).

(*R*)-28f: white solid; mp: 113-116 °C; yield: 156 mg, 62% (condensation on 0.6 mmol scale in 6 mL of DCM); $[\alpha]^{27}_D$ = -42.9° (c = 0.24, EtOAc).

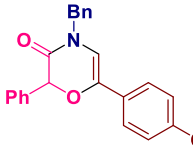
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 4H), 7.38 – 7.27 (m, 10H), 6.17 (s, 1H), 5.77 (s, 1H), 4.87 (d, J = 14.9 Hz, 1H), 4.82 (d, J = 14.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.0, 138.1, 136.0, 135.3, 131.7, 131.3, 129.0, 128.9, 128.7, 128.1, 128.0, 126.7, 125.2, 122.0, 106.5, 78.7, 49.1; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{23}H_{19}BrNO_2]^+$ 420.0594, found 420.0594.



4-Benzyl-6-(3-methoxyphenyl)-2-phenyl-2*H*-1,4-oxazin-3(4*H*)-one (28g):

Rac-28g: yellow oil; yield: 64 mg, 43% (condensation on 0.4 mmol scale in 8 mL of DCM).

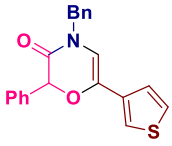
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.46 (m, 2H), 7.39 – 7.27 (m, 8H), 7.25 – 7.20 (m, 1H), 7.07 – 7.01 (m, 2H), 6.84 – 6.77 (m, 1H), 6.17 (s, 1H), 5.79 (s, 1H), 4.87 (d, J = 14.9 Hz, 1H), 4.82 (d, J = 14.9 Hz, 1H), 3.79 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.1, 159.8, 138.8, 136.1, 135.5, 133.8, 129.6, 129.0, 128.8, 128.7, 128.03, 127.97, 126.7, 116.2, 113.5, 109.6, 106.4, 78.6, 55.4, 49.1; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{24}H_{22}NO_3]^+$ 372.1594, found 372.1595.



4-Benzyl-6-(4-methoxyphenyl)-2-phenyl-2*H*-1,4-oxazin-3(4*H*)-one (28h):

Rac-28h: yellow oil; yield: 85 mg, 38% (condensation on 0.6 mmol scale in 6 mL of DCM).

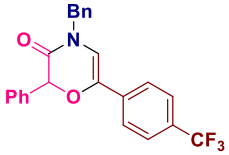
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H), 7.43 – 7.27 (m, 10H), 6.85 (d, J = 8.4 Hz, 2H), 6.04 (s, 1H), 5.77 (s, 1H), 4.87 (d, J = 14.9 Hz, 1H), 4.82 (d, J = 14.9 Hz, 1H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.9, 159.7, 139.2, 136.2, 135.6, 128.9, 128.8, 128.7, 127.99, 127.97, 126.8, 125.4, 125.0, 114.0, 104.5, 78.7, 55.4, 49.0; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{24}H_{22}NO_3]^+$ 372.1594, found 372.1601.



4-Benzyl-2-phenyl-6-(thiophen-3-yl)-2*H*-1,4-oxazin-3(4*H*)-one (28i):

Rac-28i: yellow oil; yield: 65 mg, 47% (condensation on 0.4 mmol scale in 8 mL of DCM).

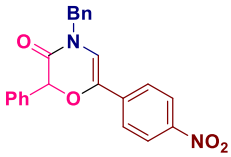
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H), 7.43 – 7.40 (m, 1H), 7.38 – 7.23 (m, 9H), 7.00 (dd, J = 5.1, 1.2 Hz, 1H), 6.02 (s, 1H), 5.78 (s, 1H), 4.84 (d, J = 15.0 Hz, 1H), 4.80 (d, J = 15.0 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.9, 136.6, 136.1, 135.5, 134.3, 129.0, 128.8, 128.7, 128.0, 127.9, 126.6, 126.5, 123.4, 120.7, 105.9, 78.6, 49.0; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{21}H_{18}NO_2S]^+$ 348.1053, found 348.1055.



4-Benzyl-2-phenyl-6-(4-(trifluoromethyl)phenyl)-2*H*-1,4-oxazin-3(4*H*)-one (28j):

Rac-28j: yellowish oil; yield: 115 mg, 70% (condensation on 0.4 mmol scale in 4 mL of DCM).

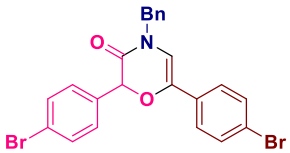
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 9.4 Hz, 2H), 7.56 (d, J = 9.4 Hz, 2H), 7.49 – 7.45 (m, 2H), 7.42 – 7.27 (m, 8H), 6.32 (s, 1H), 5.83 (s, 1H), 4.91 (d, J = 14.9 Hz, 1H), 4.86 (d, J = 14.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.1, 137.6, 135.9, 135.8 (q, J = 1.1 Hz), 135.2, 129.8 (q, J = 32.7 Hz), 129.1, 129.0, 128.8, 128.2, 128.0, 126.7, 125.6 (q, J = 3.9 Hz), 124.1 (q, J = 271.9 Hz), 123.7, 107.9, 78.7, 49.2; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ -65.7; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{24}H_{19}F_3NO_2]^+$ 410.1362, found 410.1364.



4-Benzyl-6-(4-nitrophenyl)-2-phenyl-2*H*-1,4-oxazin-3(4*H*)-one (28k):

Rac-28k: orange solid; mp: 143-145 °C; yield: 116 mg, 75% (condensation on 0.4 mmol scale in 4 mL of DCM).

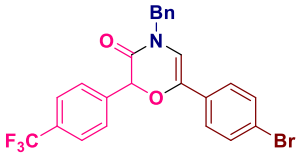
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.6 Hz, 2H), 7.45 – 7.40 (m, 2H), 7.40 – 7.27 (m, 8H), 6.41 (s, 1H), 5.81 (s, 1H), 4.91 (d, J = 14.9 Hz, 1H), 4.86 (d, J = 14.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.0, 146.9, 138.6, 136.8, 135.7, 134.9, 129.14, 129.12, 128.8, 128.3, 128.0, 126.7, 124.1, 123.8, 109.8, 78.7, 49.3; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{23}H_{19}N_2O_4]^+$ 387.1339, found 387.1340.



4-Benzyl-2,6-bis(4-bromophenyl)-2*H*-1,4-oxazin-3(4*H*)-one (28l):

Rac-28l: beige solid; mp: 118-121 °C; yield: 130 mg, 65% (condensation on 0.4 mmol scale in 4 mL of DCM).

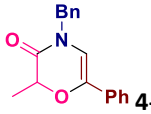
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.38 – 7.26 (m, 9H), 6.18 (s, 1H), 5.69 (s, 1H), 4.86 (d, J = 14.9 Hz, 1H), 4.78 (d, J = 14.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.5, 138.1, 135.8, 134.3, 131.9, 131.8, 131.1, 129.1, 128.5, 128.2, 128.0, 125.1, 123.1, 122.2, 106.6, 78.1, 49.2; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{23}H_{18}Br_2NO_2]^+$ 499.9678, found 499.9681.



4-Benzyl-6-(4-bromophenyl)-2-(4-(trifluoromethyl)phenyl)-2*H*-1,4-oxazin-3(4*H*)-one (28m):

Rac-28m: white solid; mp: 134-137 °C; yield: 183 mg, 62% (condensation on 0.6 mmol scale in 6 mL of DCM).

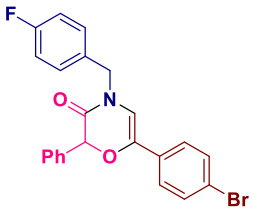
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.39 – 7.30 (m, 5H), 7.30 – 7.26 (m, 2H), 6.22 (s, 1H), 5.80 (s, 1H), 4.87 (d, J = 14.9 Hz, 1H), 4.81 (d, J = 14.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.3, 139.2 (q, J = 1.3 Hz), 138.1, 135.7, 131.9, 131.0 (q, J = 32.6 Hz), 130.9, 129.1, 128.3, 128.0, 127.0, 125.7 (q, J = 3.8 Hz), 125.1, 124.0 (q, J = 272.5 Hz), 122.2, 106.6, 78.1, 49.3; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ -65.5; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{24}H_{18}BrF_3NO_2]^+$ 488.0468, found 488.0464.



4-Benzyl-2-methyl-6-phenyl-2*H*-1,4-oxazin-3(4*H*)-one (28n):

Rac-28n: transparent oil; yield: 61 mg, 36% (condensation on 0.6 mmol scale in 6 mL of DCM).

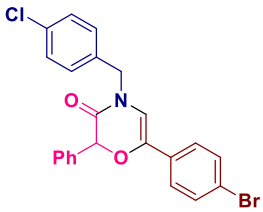
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.39 – 7.28 (m, 7H), 7.28 – 7.23 (m, 1H), 6.15 (s, 1H), 4.80 (d, J = 15.5 Hz, 1H), 4.77 (d, J = 15.6 Hz, 1H), 4.68 (q, J = 6.8 Hz, 1H), 1.62 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.3, 139.4, 136.3, 132.5, 129.0, 128.6, 128.2, 128.0, 127.9. 123.8, 106.5, 73.8, 48.8, 15.8; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{18}H_{18}NO_2]^+$ 280.1332, found 280.1332.



6-(4-Bromophenyl)-4-(4-fluorobenzyl)-2-phenyl-2*H*-1,4-oxazin-3(4*H*)-one (28o):

Rac-28o: beige solid; mp: 113-116 °C; yield: 96 mg, 55% (condensation on 0.4 mmol scale in 4 mL of DCM).

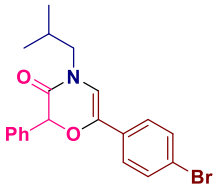
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 4H), 7.38 – 7.31 (m, 5H), 7.30 – 7.24 (m, 2H), 7.08 – 6.99 (m, 2H), 6.17 (s, 1H), 5.76 (s, 1H), 4.82 (d, J = 14.9 Hz, 1H), 4.78 (d, J = 14.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.9, 162.5 (d, J = 246.7 Hz), 138.2, 135.2, 131.8 (d, J = 3.2 Hz), 131.7, 131.2, 129.7 (d, J = 8.2 Hz), 128.9, 128.7, 126.6, 125.2, 122.1, 115.9 (d, J = 21.6 Hz), 106.3, 78.6, 48.5; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{23}H_{18}BrFNO_2]^+$ 438.0500, found 438.0499.



6-(4-Bromophenyl)-4-(4-chlorobenzyl)-2-phenyl-2*H*-1,4-oxazin-3(4*H*)-one (28p):

Rac-28p: white solid; mp: 142-145 °C; yield: 127 mg, 70% (condensation on 0.4 mmol scale in 4 mL of DCM); 205 mg, 75% (condensation on 0.6 mmol scale in 6 mL of DCM).

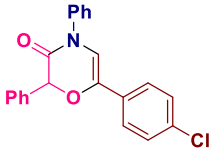
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 4H), 7.38 – 7.29 (m, 7H), 7.21 (d, J = 8.4 Hz, 2H); 6.14 (s, 1H), 5.76 (s, 1H), 4.81 (d, J = 15.0 Hz, 1H), 4.77 (d, J = 15.0 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.0, 138.4, 135.1, 134.5, 134.0, 131.8, 131.2, 129.3, 129.2, 129.0, 128.8, 126.6, 125.2, 122.2, 106.3, 78.7, 48.6; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{23}H_{18}BrClNO_2]^+$ 454.0204, found 454.0207.



6-(4-Bromophenyl)-4-isobutyl-2-phenyl-2*H*-1,4-oxazin-3(4*H*)-one (28q):

Rac-28q: yellow oil; yield: 129 mg, 56% (condensation on 0.6 mmol scale in 6 mL of DCM).

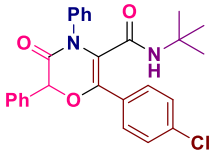
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 8.7 Hz, 2H), 7.44 – 7.41 (m, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.36 – 7.29 (m, 3H), 6.19 (s, 1H), 5.71 (s, 1H), 3.49 (dd, J = 13.4, 7.6 Hz, 1H), 3.40 (dd, J = 13.4, 7.4 Hz, 1H), 2.12 – 1.99 (m, 1H), 0.96 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.9, 137.4, 135.4, 131.8, 131.5, 128.8, 128.7, 126.6, 125.1, 121.8, 107.6, 78.7, 53.6, 28.0, 20.1; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{20}H_{21}BrNO_2]^+$ 386.0750, found 386.0758.



6-(4-Chlorophenyl)-2,4-diphenyl-2*H*-1,4-oxazin-3(4*H*)-one (28r):

Rac-28r: brownish solid; mp: 182-185 °C; yield: 27-30 mg, 19-21% (condensation on 0.4 mmol scale in 4 or 8 mL of DCM, upper spot on TLC).

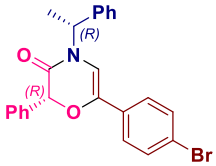
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 2H), 7.50 – 7.44 (m, 4H), 7.44 – 7.39 (m, 8H), 6.47 (s, 1H), 5.86 (s, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.4, 139.2, 138.2, 135.0, 134.1, 130.9, 129.5, 129.0, 128.94, 128.86, 127.8, 126.7, 125.8, 125.1, 108.4, 79.2; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{22}H_{17}ClNO_2]^+$ 362.0942, found 362.0947.



***N*-(*tert*-Butyl)-6-(4-chlorophenyl)-3-oxo-2,4-diphenyl-3,4-dihydro-2*H*-1,4-oxazine-5-carboxamide (29):**

Rac-29: beige solid; mp: 108-110 °C; yield: 63-68 mg, 34-37% (condensation on 0.4 mmol scale in 4 or 8 mL of DCM, lower spot on TLC).

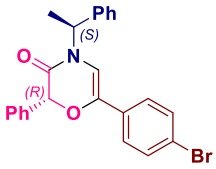
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 2H), 7.47 – 7.34 (m, 10H), 7.30 (d, J = 8.6 Hz, 2H), 5.76 (s, 1H), 5.14 (bs, 1H), 0.90 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.4, 160.4, 139.1, 136.6, 135.3, 134.4, 130.9, 129.4, 129.2, 129.0, 128.9, 128.6, 128.5, 128.2, 127.3, 120.7, 79.3, 51.8, 27.8; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{27}H_{26}ClN_2O_3]^+$ 461.1627, found 461.1638.



(*R*)-6-(4-Bromophenyl)-2-phenyl-4-((*R*)-1-phenylethyl)-2*H*-1,4-oxazin-3(4*H*)-one ((*R*,*R*)-28s):

(*R*,*R*)-28s: beige solid; mp: 97-100 °C; yield: 122 mg, 70% (condensation on 0.4 mmol scale in 4 mL of DCM); $[\alpha]^{27}_D$ = -75.8° (c = 0.33, EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.45 (m, 2H), 7.43 – 7.31 (m, 10H), 7.25 (d, J = 8.7 Hz, 2H), 6.13 – 6.06 (m, 2H), 5.71 (s, 1H), 1.66 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.7, 139.7, 138.5, 135.4, 131.6, 131.5, 128.92, 128.91, 128.7, 128.0, 127.2, 126.9, 125.2, 121.8, 103.1, 78.8, 50.8, 17.6; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{24}H_{21}BrNO_2]^+$ 434.0750, found 434.0755.



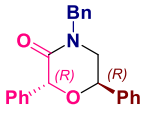
(*R*)-6-(4-Bromophenyl)-2-phenyl-4-((*S*)-1-phenylethyl)-2*H*-1,4-oxazin-3(4*H*)-one ((*R*,*S*)-28s):

(*R*,*S*)-28s: transparent oil; yield: 144 mg, 83% (condensation on 0.4 mmol scale in 4 mL of DCM); $[\alpha]^{27}_{D}$ = +10.0° (c = 0.30, EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 4H), 7.38 – 7.25 (m, 10H), 6.11 (q, J = 7.1 Hz, 1H), 6.00 (s, 1H), 5.80 (s, 1H), 1.70 (d, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.5, 139.3, 138.4, 135.4, 131.65, 131.58, 128.92, 128.87, 128.7, 128.1, 127.3, 126.6, 125.2, 121.9, 102.7, 78.6, 50.6, 17.7; HRMS (ESI^{+}): m/z $[M+H]^{+}$ calcd for $[C_{24}H_{21}BrNO_2]^{+}$ 434.0750, found 434.0756.

Procedure for the hydrogenation of 2,6-diphenylmorpholin-3-one 28a

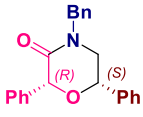
Compound **28a** (239 mg, 0.7 mmol) was placed in 50 ml round bottom flask and dissolved in methanol (12 mL). The solution was purged with argon followed by addition of Pd/C (149 mg, 0.07 mmol, 5 wt. % Pd loading). The resulting suspension was consecutively flashed with argon and hydrogen and left stirred under the atmosphere of hydrogen gas (1 atm) for 24 hours at room temperature. The reaction mixture was diluted with DCM and filtered through a glass filter with an extra fine porosity to remove Pd catalyst. The filter was washed with DCM and filtrate was concentrated with silica gel under reduced pressure and submitted to column chromatography with hexane/EtOAc (10→50%) mixture as an eluent to deliver two diastereomers of 2,6-diphenylmorpholin-3-one **30**.



(2*R*,6*R*)-4-Benzyl-2,6-diphenylmorpholin-3-one ((*R*,*R*)-30):

(*R*,*R*)-30: yield: 26-34 mg, 11-14% (upper spot on TLC).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 2H), 7.42 – 7.27 (m, 13H), 5.61 (s, 1H), 4.95 (d, J = 14.6 Hz, 1H), 4.86 (dd, J = 10.5, 3.6 Hz, 1H), 4.56 (d, J = 14.6 Hz, 1H), 3.52 (dd, J = 12.1, 10.6 Hz, 1H), 3.36 (dd, J = 12.2, 3.6 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.0, 137.9, 137.0, 136.3, 129.0, 128.74, 128.70, 128.6, 128.5, 128.3, 128.0, 127.6, 126.2, 77.8, 69.7, 52.1, 50.0; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{23}H_{22}NO_2]^+$ 344.1645, found 344.1658.



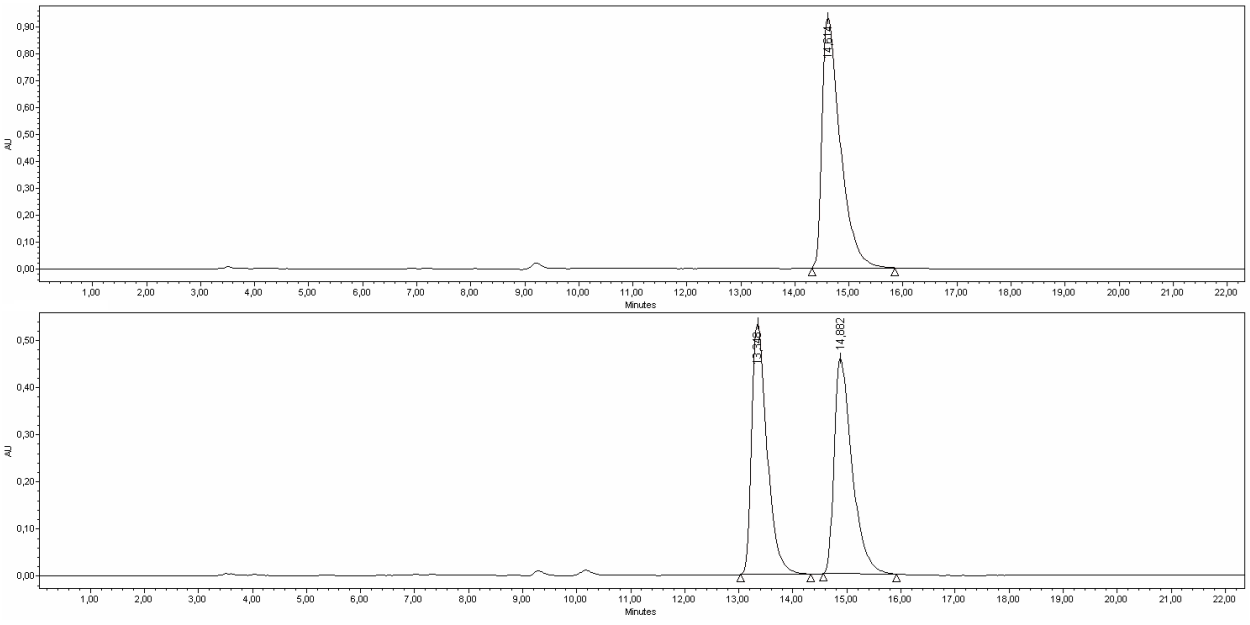
(2R,6S)-4-Benzyl-2,6-diphenylmorpholin-3-one ((*R*,*S*)-30):

(*R*,*S*)-30: white solid; mp: 177-180 °C; yield: 140-185 mg, 58-77% (lower spot on TLC); $[\alpha]^{27}_D$ = -65.6° (c = 0.45, EtOAc).

Rac-cis-30: white solid; mp: 155-158 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.57 (m, 2H), 7.48 – 7.28 (m, 13H), 5.44 (s, 1H), 5.02 (dd, J = 10.6, 3.2 Hz, 1H), 4.73 (d, J = 14.6 Hz, 1H), 4.64 (d, J = 14.6 Hz, 1H), 3.66 (dd, J = 12.4, 10.8 Hz, 1H), 3.40 (dd, J = 12.4, 3.2 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.8, 137.9, 137.7, 136.3, 128.9, 128.63, 128.56, 128.5, 128.44, 128.41, 128.0, 127.9, 126.1, 80.7, 75.2, 52.8, 50.4; HRMS (ESI$^+$): m/z $[M+H]^+$ calcd for $[C_{23}H_{22}NO_2]^+$ 344.1645, found 344.1654.

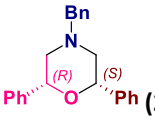
Chiral HPLC chromatograms of enantiopure **(*R*,*S*)-30** and racemic **cis-30** samples of 4-benzyl-2,6-diphenylmorpholin-3-one obtained with hexane/isopropanol (9:1) mixture as an eluent and 1.0 mL/min flow rate:



Procedure for the reduction of 2,6-diphenylmorpholin-3-one (*R*,*S*)-30

Compound **(*R*,*S*)-30** (155 mg, 0.45 mmol) was placed in a screw cap vial and dissolved in anhydrous diethyl ether (2 mL) followed by addition of lithium aluminum hydride (68 mg, 1.8 mmol) in one portion at 0 °C. The reaction vial was purged with argon, sealed, and removed from an ice bath. After stirring for 24 hours at room temperature the reaction mixture was subjected to Fieser workup to deliver pure 2,6-diphenylmorpholine **(*R*,*S*)-31**.

Fieser workup procedure. The reaction mixture was diluted with diethyl ether (4 mL) and cooled down to 0 °C. Then water (68 µL) was carefully added followed by slow addition of 15 % aqueous sodium hydroxide solution (68 µL). Then the second portion of water (204 µL) was added and the mixture was allowed to warm up to room temperature under stirring for approximately 15 minutes. The resulting mixture was dried from water with anhydrous sodium sulfate. Solids were filtered off and washed with diethyl ether. The filtrate was concentrated under reduced pressure.



(2R,6S)-4-Benzyl-2,6-diphenylmorpholine ((*R*,*S*)-31):

(*R*,*S*)-31: white solid; mp: 95-98 °C; yield: 147 mg, 99%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 4H), 7.37 – 7.30 (m, 8H), 7.30 – 7.24 (m, 3H), 4.82 (dd, J = 10.6, 2.4 Hz, 2H), 3.58 (s, 2H), 3.03 – 2.97 (m, 2H), 2.16 (t, J = 11.1 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.6, 137.5, 129.4, 128.5, 128.4, 127.8, 127.4, 126.4, 78.4, 63.2, 60.1; HRMS (ESI^{+}): m/z $[M+H]^{+}$ calcd for $[C_{23}H_{24}NO]^{+}$ 330.1852, found 330.1856.

X-Ray diffraction analysis

Single crystals of **(*R*)-28a** and **(*R,S*)-30** were obtained by slow evaporation from EtOAc.

Single crystals of **(*R,S*)-31** were obtained by diluting the NMR sample in $CDCl_3$ with EtOAc and subsequent slow evaporation from the resulting solution.

The single crystals of **(*R*)-28a, (*R,S*)-30, (*R,S*)-31** were immersed in a film of NVH or perfluoropolyether oil, mounted on a polyimide microloop (MiTeGen), and transferred to a stream of cold nitrogen (Cryostream 700 cooling system by Oxford Cryosystems), and measured at a temperature of 100 K. The X-ray diffraction data were collected on a Rigaku XtaLAB Synergy R or SuperNova Dualflex diffractometers with a HyPix-Arc 100 detector using mirror-monochromated Cu Kα (λ = 1.54184 Å) radiation (INCOATEC microfocus sealed tube). The frames were integrated with the CrysAlisPro software package using a narrow-frame algorithm. The CrysAlisPro program package was used for cell refinements and data reductions. The structure was solved using the intrinsic phasing method,[2,3] refined and visualized with the OLEX2-1.5 program.[4] A semiempirical absorption correction (SADABS) was applied to all data. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in structure factors calculations. All Hydrogen atoms were assigned to idealized geometric positions. The crystallographic details are summarized in Table S1. CCDC 2372877–2372879 contains supplementary crystallographic data for this paper.

[2] G. M. Sheldrick, *Acta Cryst. A*, 2015, **71**, 3–8.

[3] G. M. Sheldrick, *Acta Cryst. C*, 2015, **71**, 3–8.

[4] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339–341.

Table S1. Crystal data and structure refinement for **(*R*)-28a, (*R,S*)-30, (*R,S*)-31**.

Identification code	**(*R*)-28a**	**(*R,S*)-30**	**(*R,S*)-31**
CCDC number	2372879	2372877	2372878
Empirical formula	$C_{23}H_{19}NO_2$	$C_{23}H_{21}NO_2$	$C_{23}H_{23}NO$
Formula weight	341.39	343.41	329.42
Temperature [K]	120.0		
Crystal system	monoclinic	monoclinic	monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$
a [Å] b [Å] c [Å] α [°] β [°] γ [°]	5.39260(10) 9.5816(2) 16.9103(4) 90 90.234(2) 90	8.55890(10) 9.73360(10) 10.97970(10) 90 102.6880(10) 90	8.43300(10) 9.10750(10) 11.9147(2) 90 101.368(2) 90
Volume [$Å^3$]	873.74(3)	892.370(16)	898.17(2)
Z	2	2	2
ρ_{calc} [g/cm^3]	1.298	1.278	1.218
M [mm^{-1}]	0.655	0.642	0.570
F(000)	360.0	364.0	352.0
Crystal size [mm^3]	0.1 × 0.07 × 0.06	0.098 × 0.04 × 0.033	0.11 × 0.05 × 0.04
Radiation	Cu Kα (λ = 1.54184)		
2Θ range for data collection [°]	5.226 to 158.51	8.254 to 157.658	7.566 to 152.528
ϕ	-6 ≤ h ≤ 6, -11 ≤ k ≤ 12, -21 ≤ l ≤ 21	-10 ≤ h ≤ 10, -9 ≤ k ≤ 12, -13 ≤ l ≤ 13	-10 ≤ h ≤ 10, -11 ≤ k ≤ 11, -14 ≤ l ≤ 14
Reflections collected	13716	14859	18692
Independent reflections	3373 [R_{int} = 0.0486, R_{sigma} = 0.0330]	3273 [R_{int} = 0.0211, R_{sigma} = 0.0179]	3675 [R_{int} = 0.0357, R_{sigma} = 0.0215]
Data/restraints/parameters	3373/1/235	3273/1/235	3675/1/227
Goodness-of-fit on F^2 [(a)]	1.067	1.025	1.084
Final R indexes [I>=2σ (I)] [(b)]	R_1 = 0.0329, wR_2 = 0.0881	R_1 = 0.0257, wR_2 = 0.0663	R_1 = 0.0277, wR_2 = 0.0673
Final R indexes [all data] [(b)]	R_1 = 0.0345, wR_2 = 0.0894	R_1 = 0.0260, wR_2 = 0.0665	R_1 = 0.0283, wR_2 = 0.0677
Largest diff. peak/hole [$e/Å^3$]	0.18/-0.18	0.17/-0.16	0.18/-0.16
Flack parameter	-0.04(11)	0.02(6)	-0.05(8)

[(a)] GooF = S = $[[\sum w(F_o^2-F_c^2)^2]/(m-n)]^{1/2}$, where m = number of reflexes and n = number of parameters. [(b)] $R_1 = \sum||F_o|-|F_c||/\sum|F_o|$; $wR_2 = [\sum[w(F_o^2-F_c^2)^2/\sum[(wF_o^2)^2]]^{1/2}$; $w = 1/[\sigma^2(F_o^2)+(aP)^2+bP]$, where $P = (F_o^2+2F_c^2)/3$.

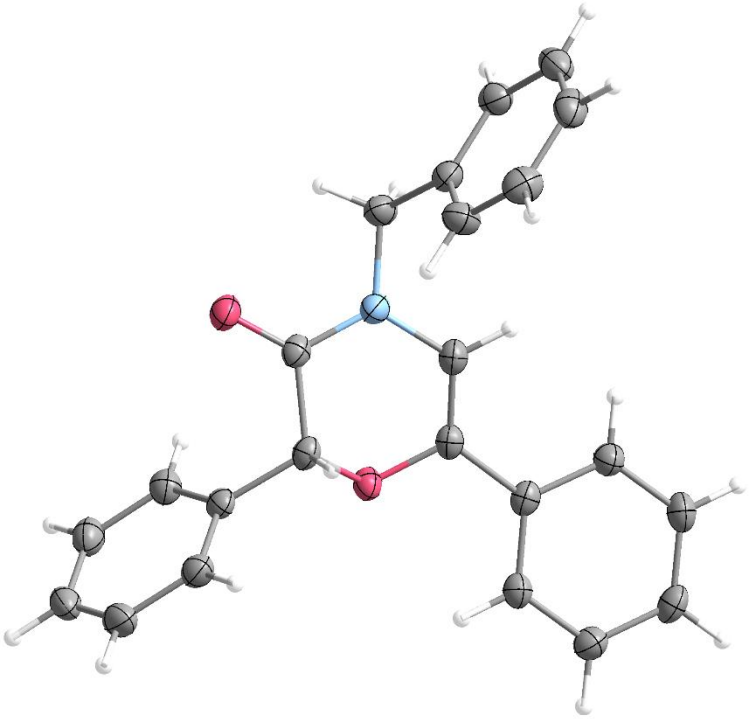


Figure S1. Molecular view of **(*R*)-28a** (thermal ellipsoids are shown at the 50% probability level, color code: grey – carbon, blue – nitrogen, pink – oxygen, white – hydrogen).

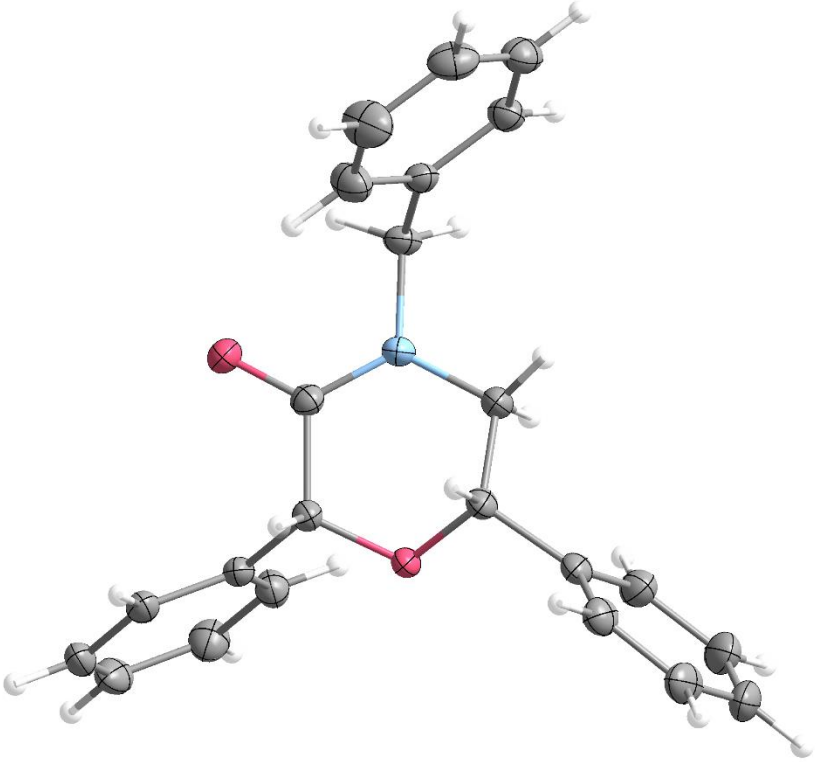


Figure S2. Molecular view of **(*R,S*)-30** (thermal ellipsoids are shown at the 50% probability level, color code: grey – carbon, blue – nitrogen, pink – oxygen, white – hydrogen).

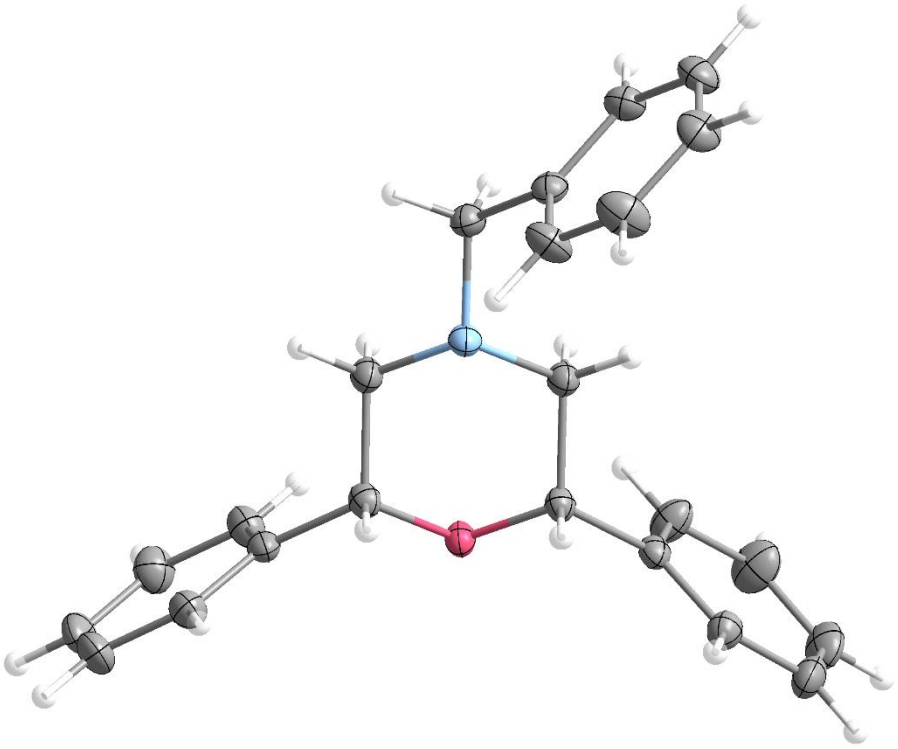
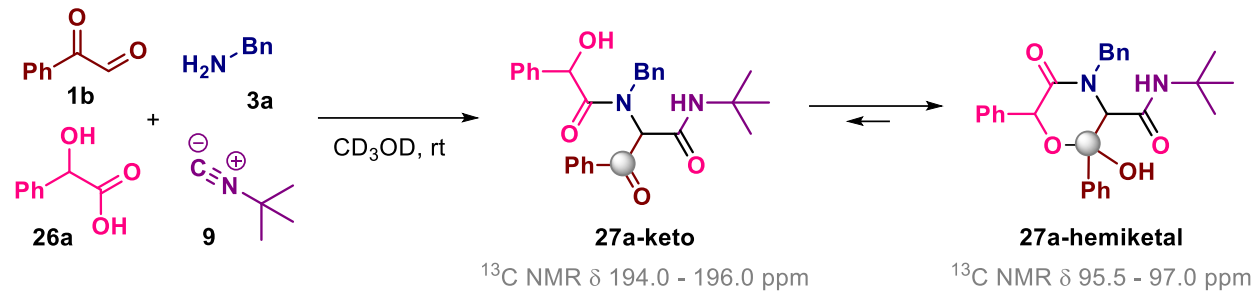
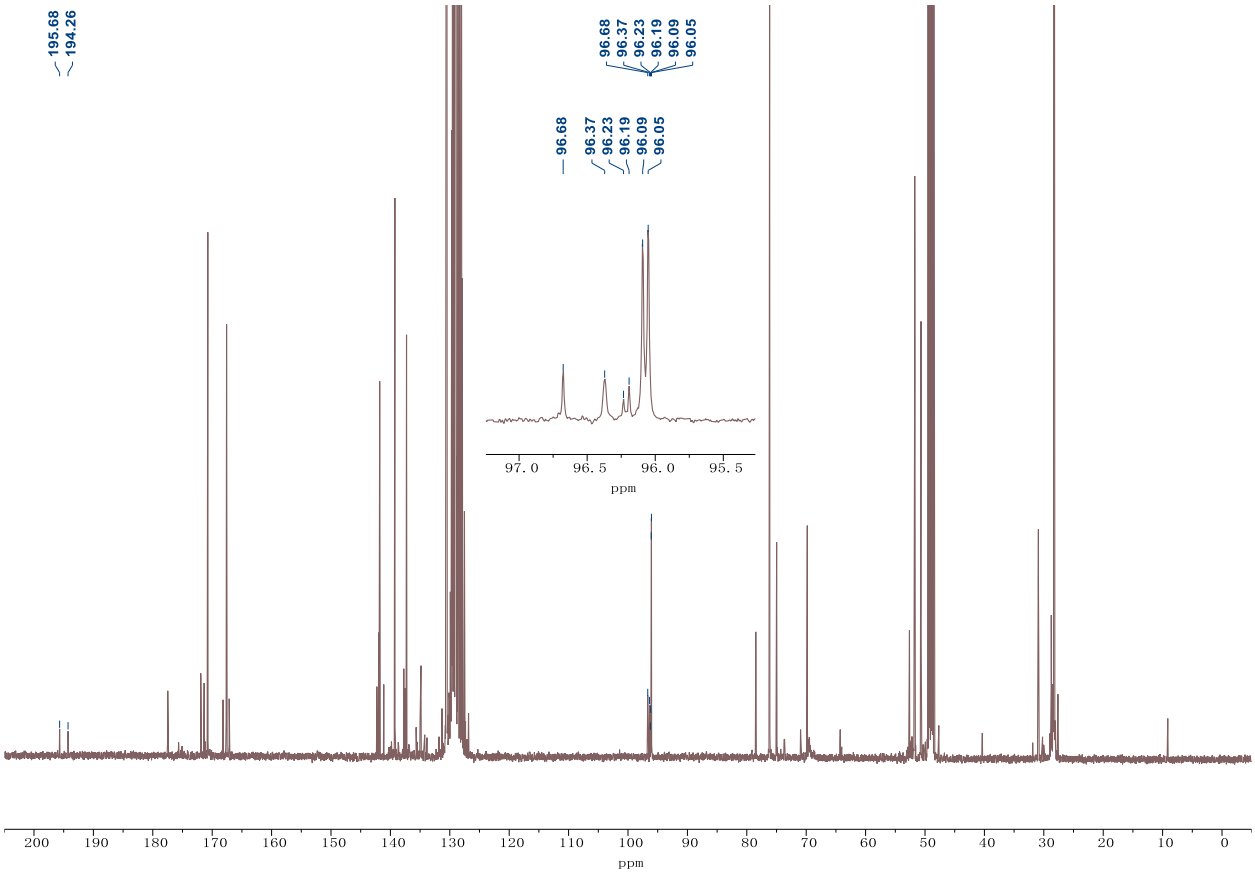


Figure S3. Molecular view of **(*R,S*)-31** (thermal ellipsoids are shown at the 50% probability level, color code: grey – carbon, blue – nitrogen, pink – oxygen, white – hydrogen).

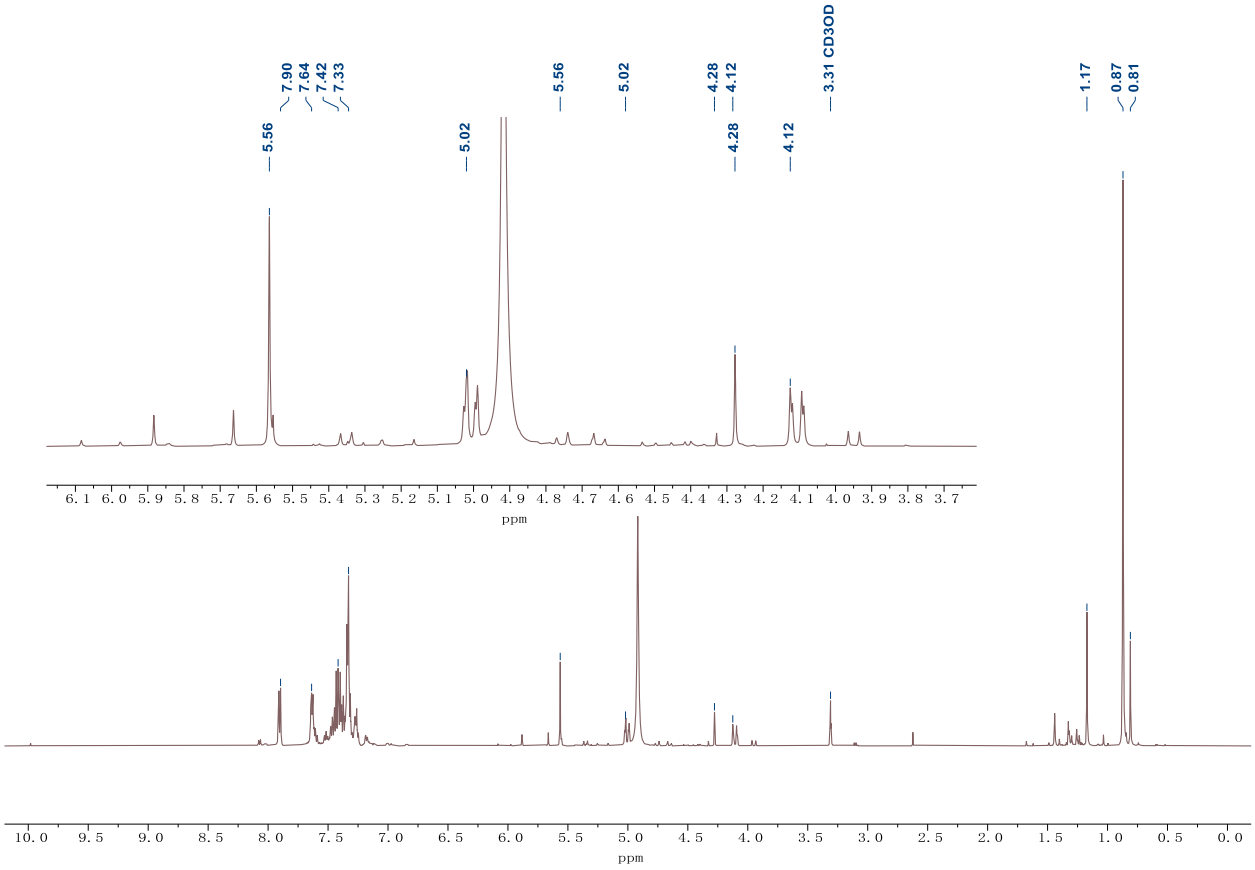
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra

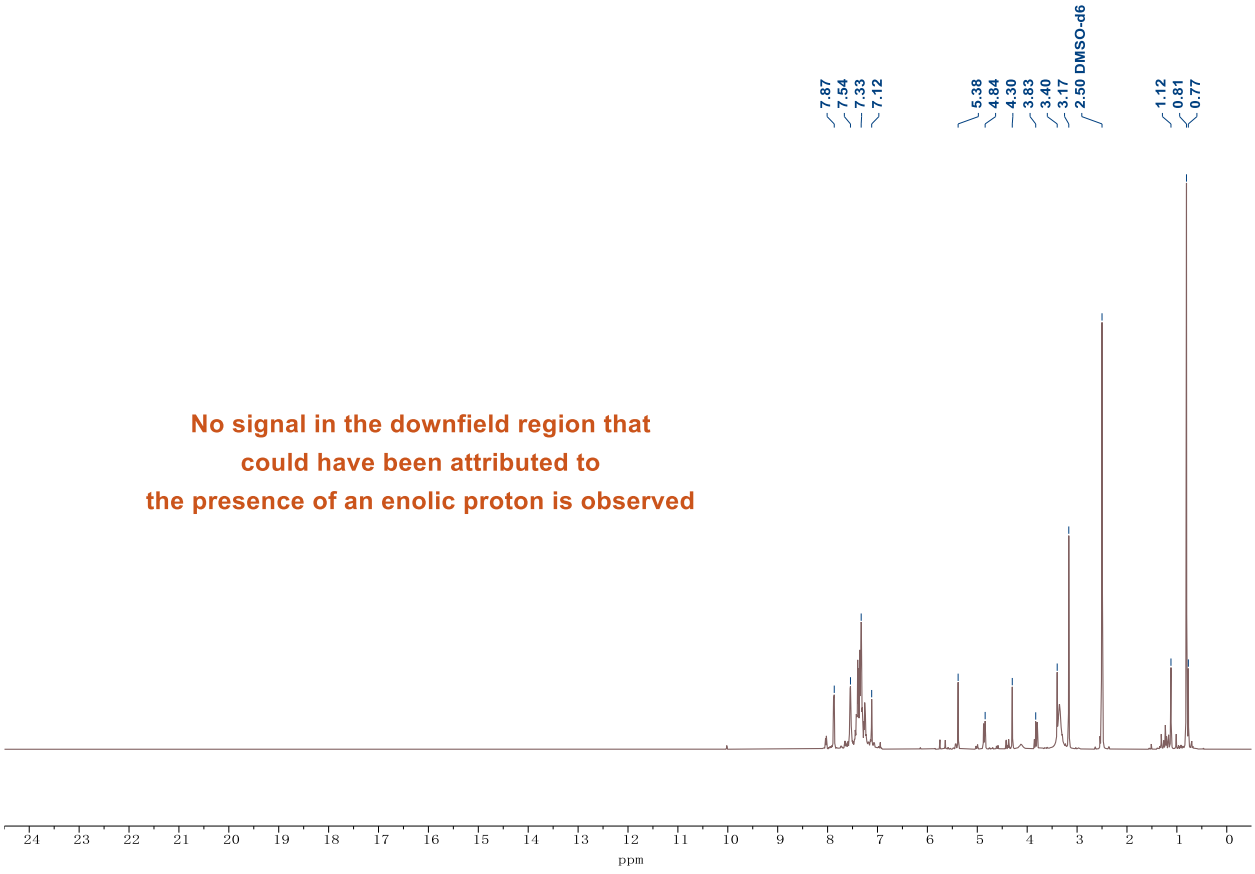
Copy of $^{13}C\{^{1}H\}$ spectrum of crude reaction mixture of Ugi adduct **27a** in CD_3OD





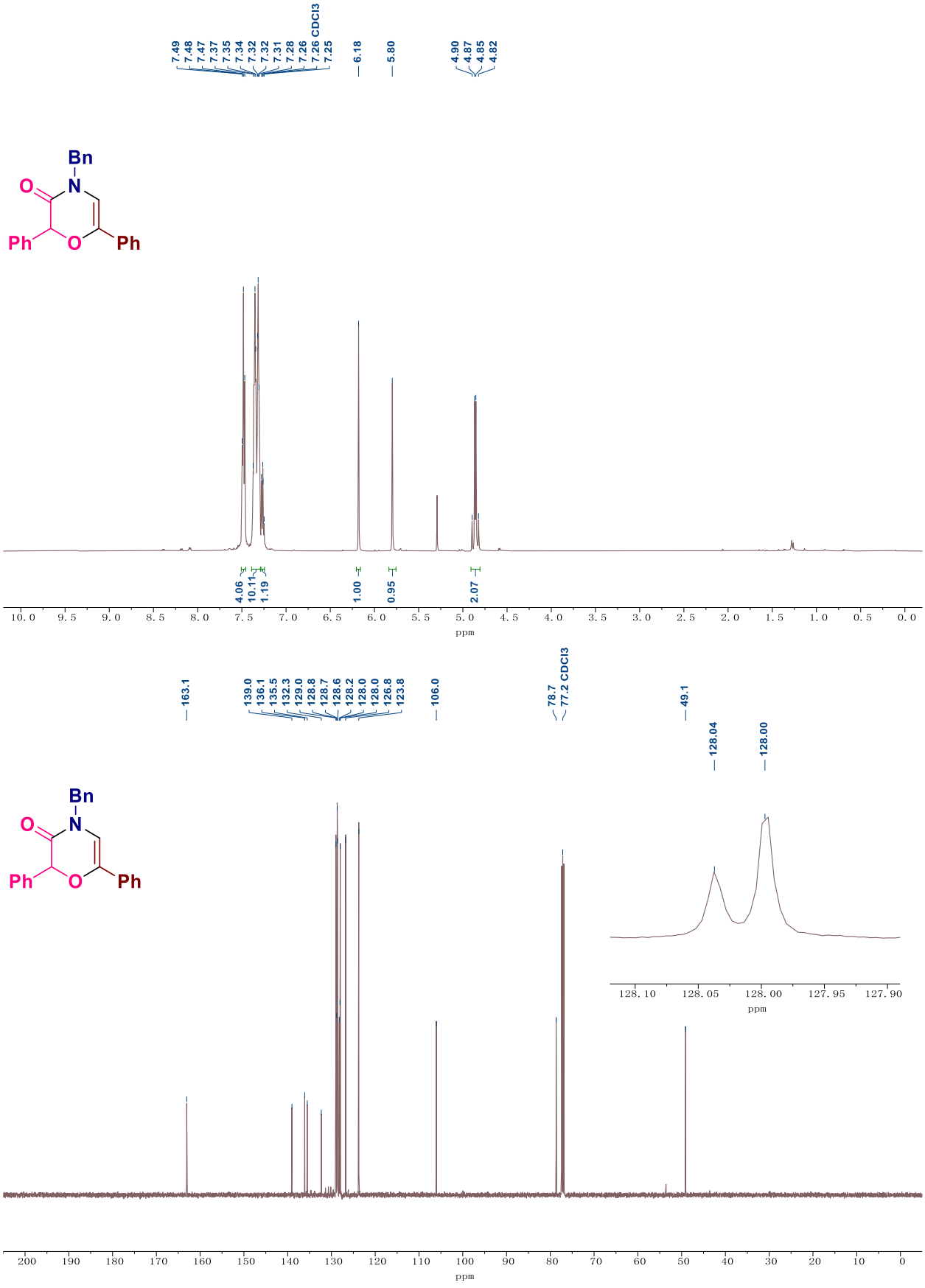
Copies of ^{1}H spectra of crude reaction mixture of Ugi adduct **27a** in CD_3OD and in DMSO-D6, respectively



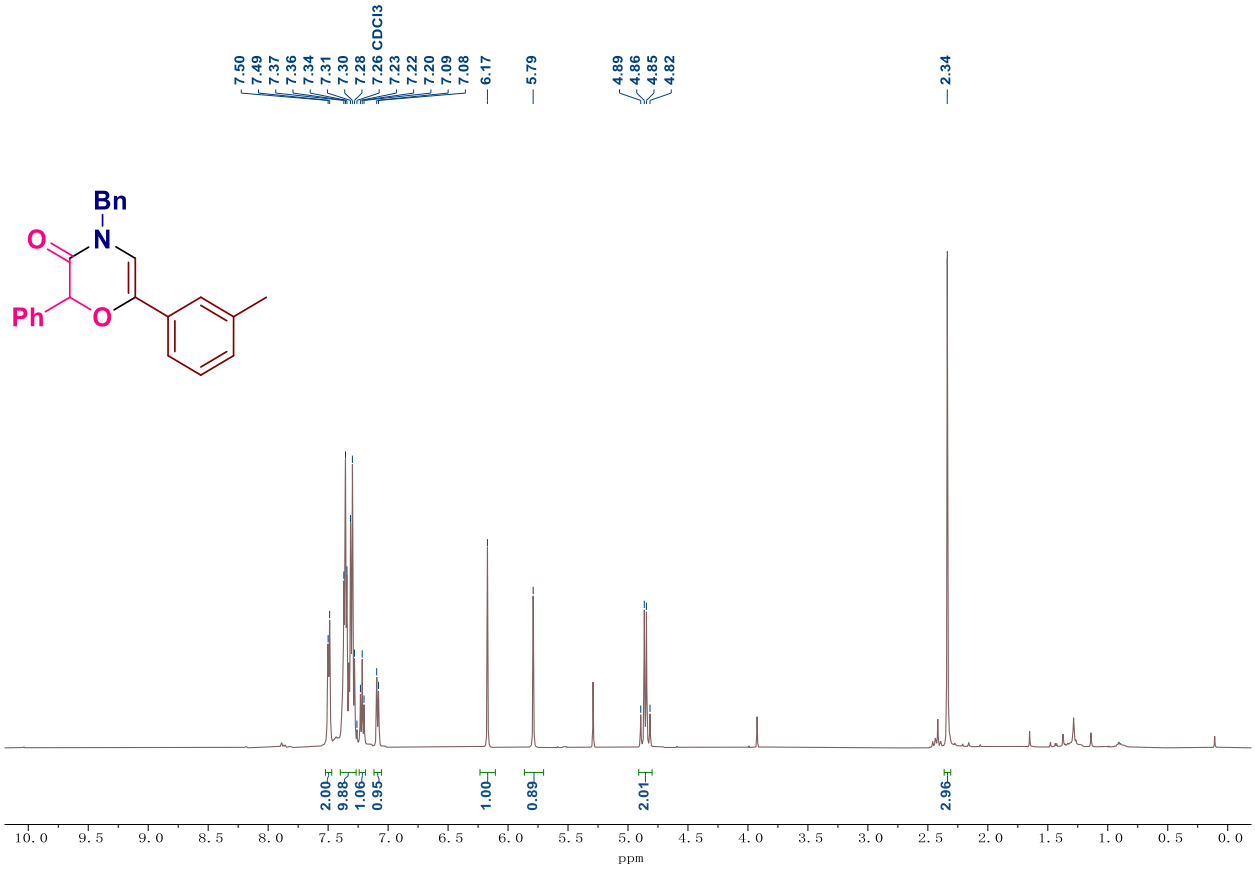


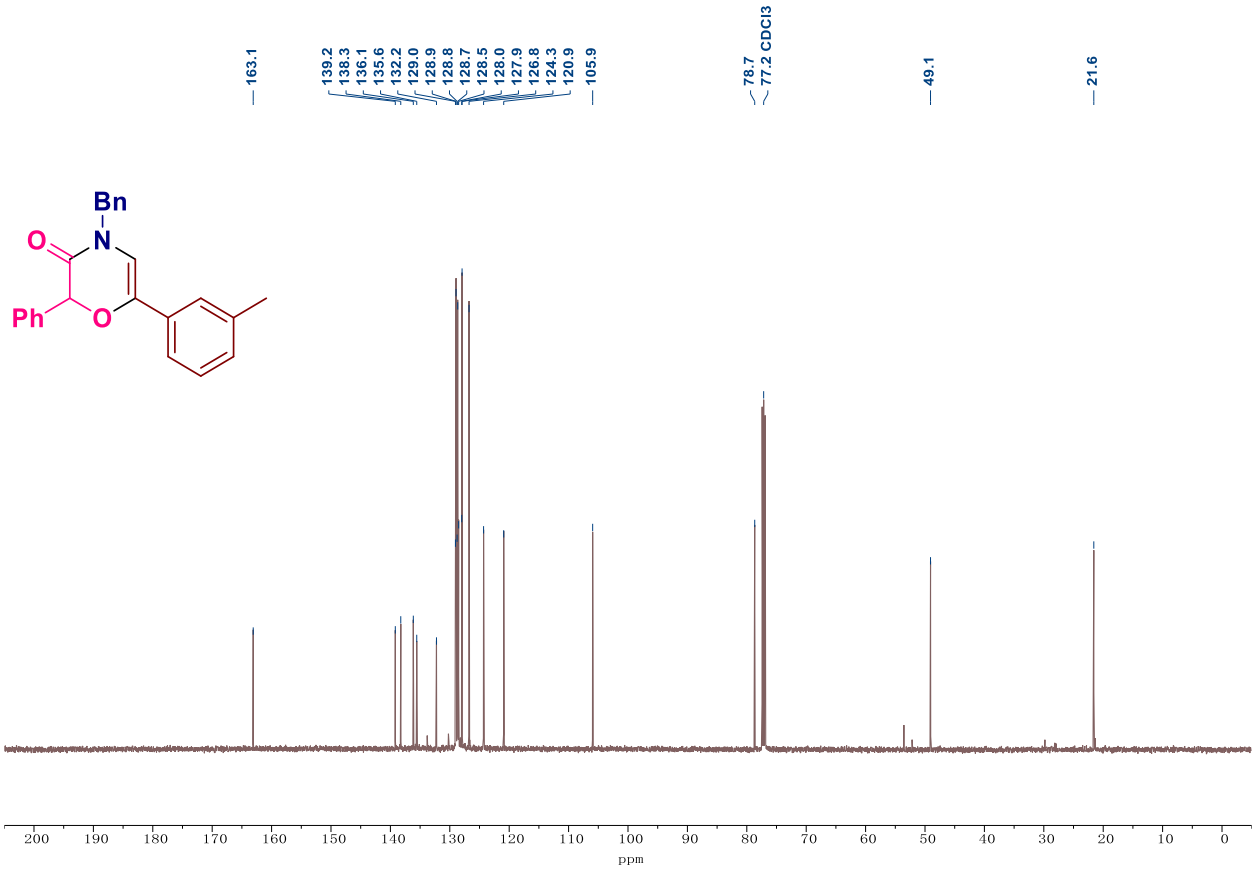
No signal in the downfield region that could have been attributed to the presence of an enolic proton is observed

Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28a**

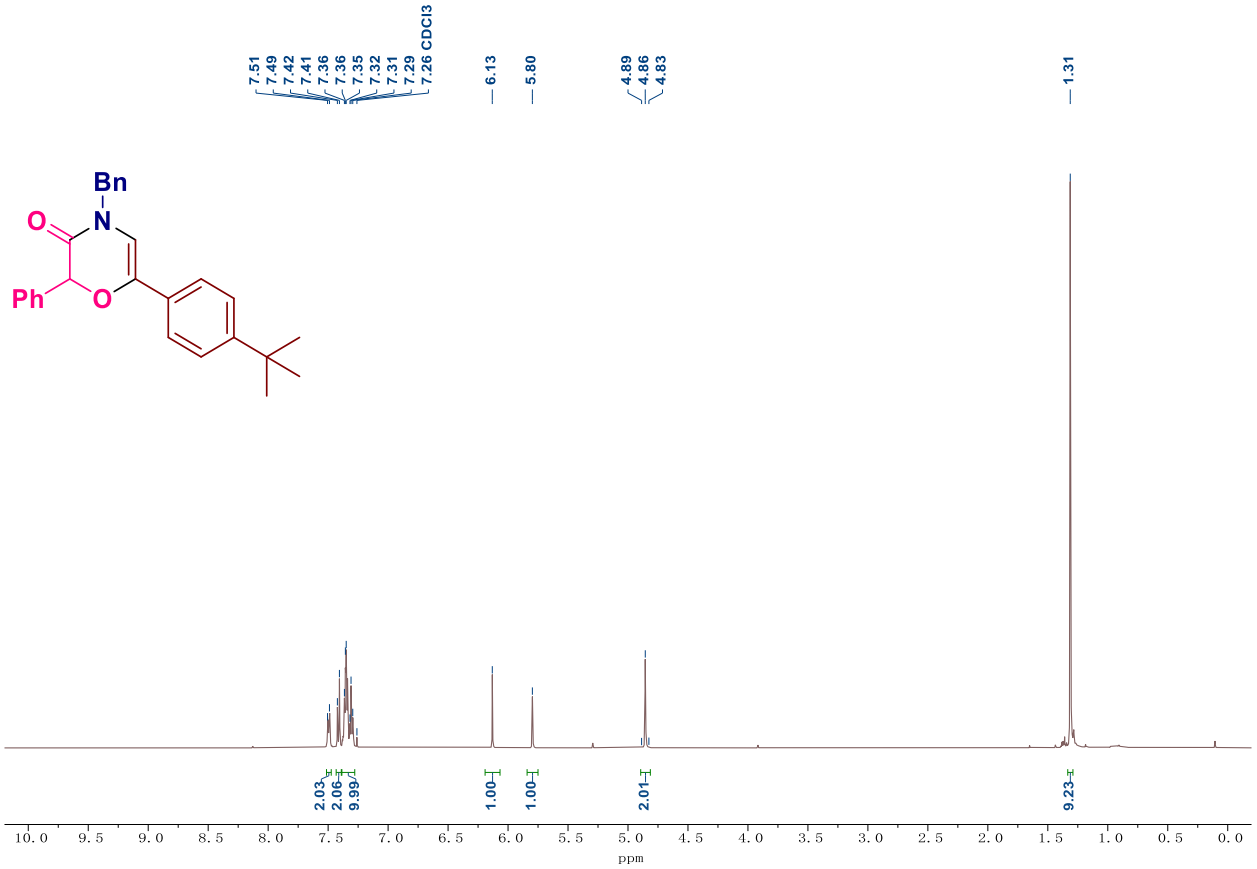


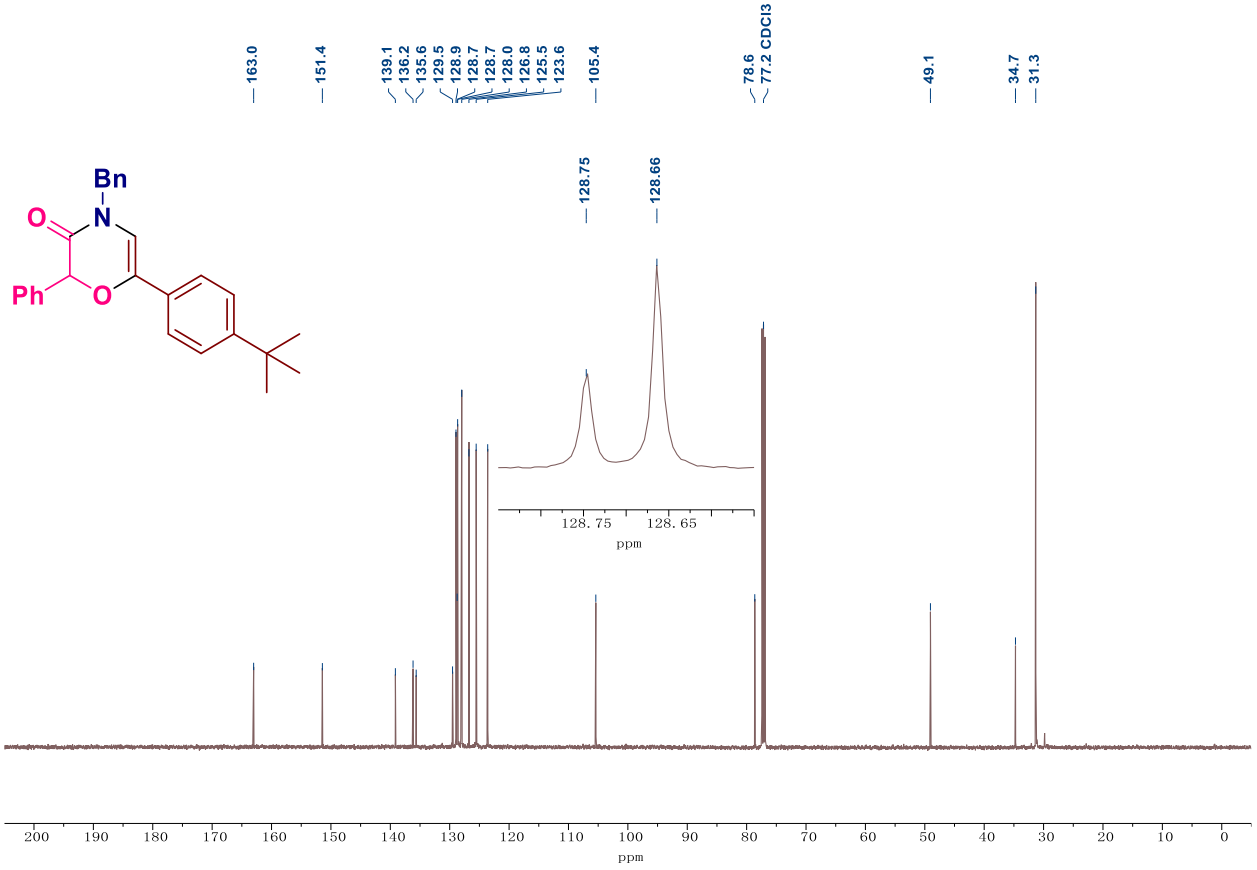
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28b**



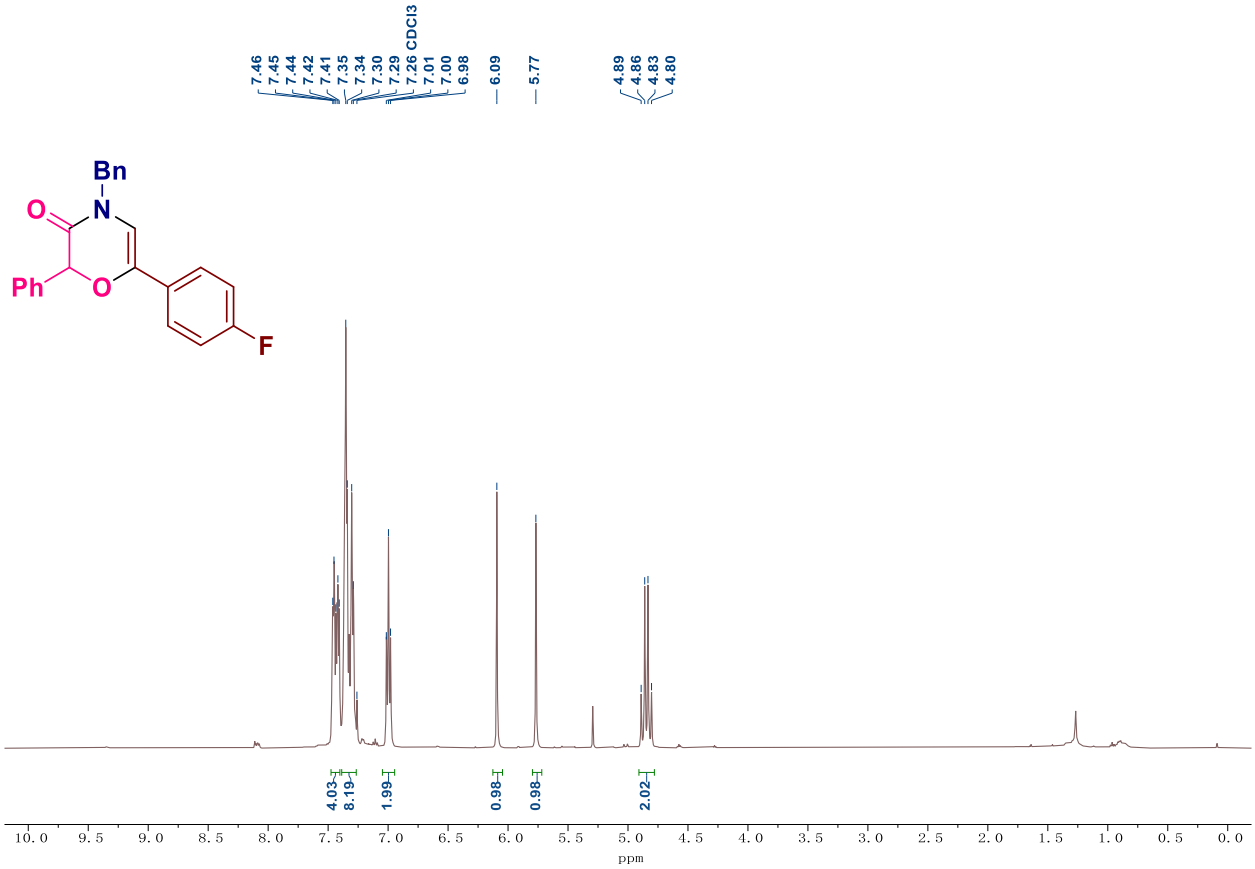


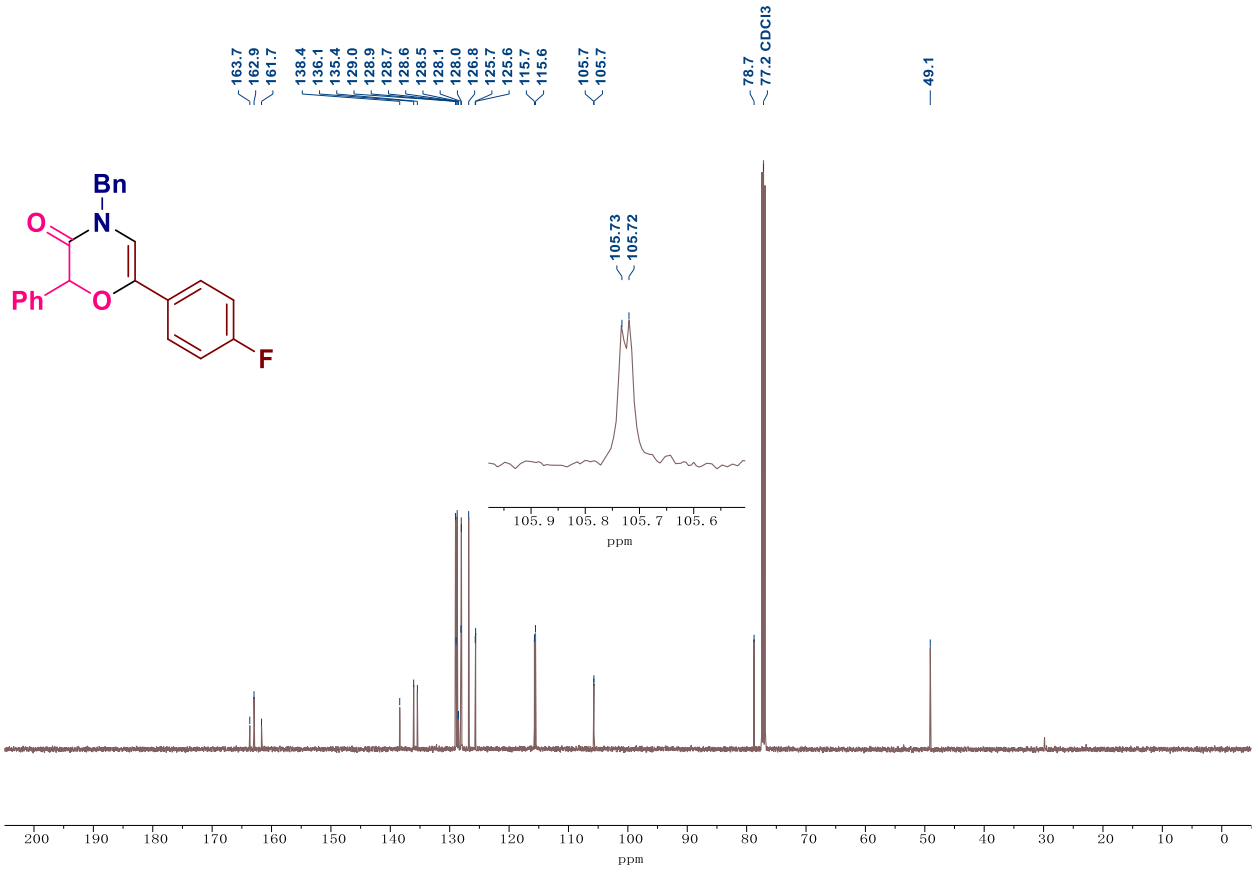
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28c**

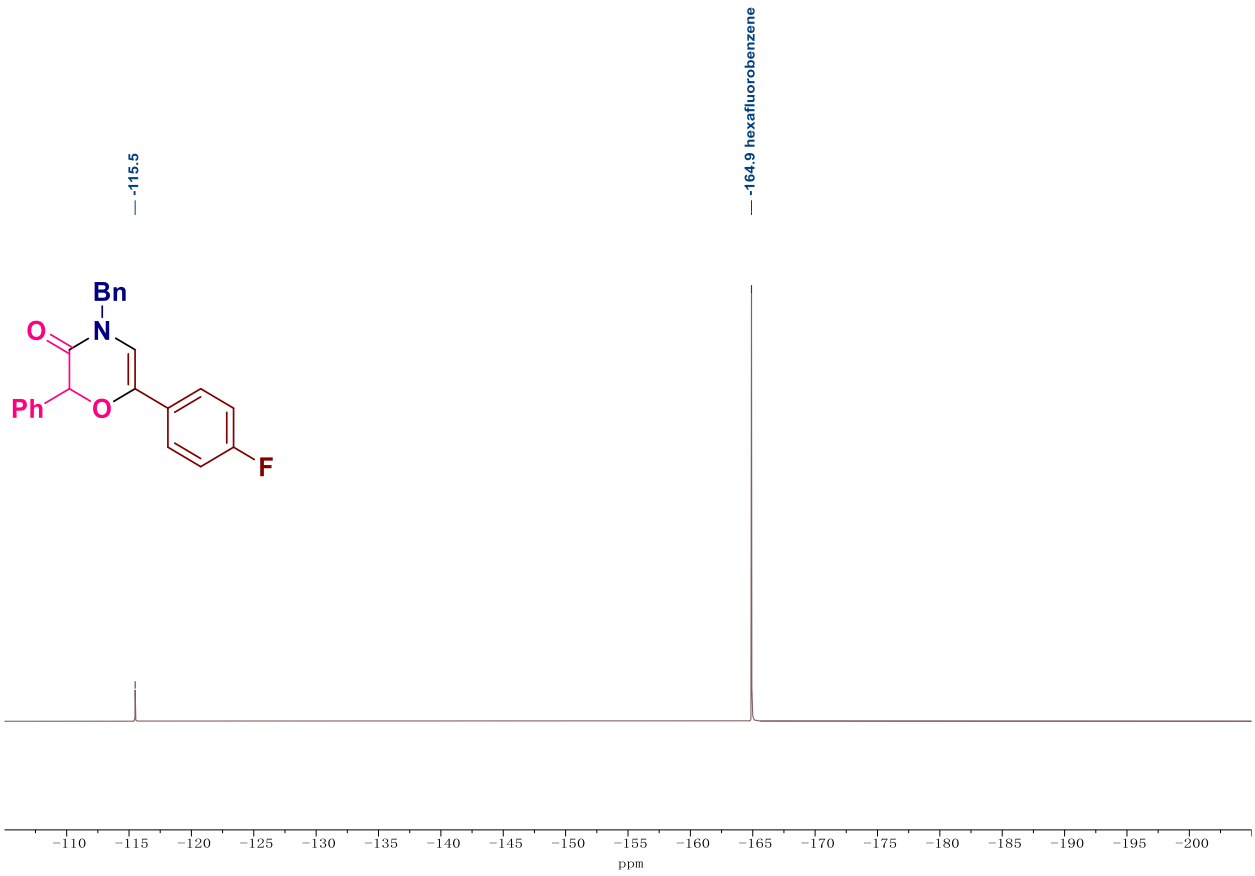




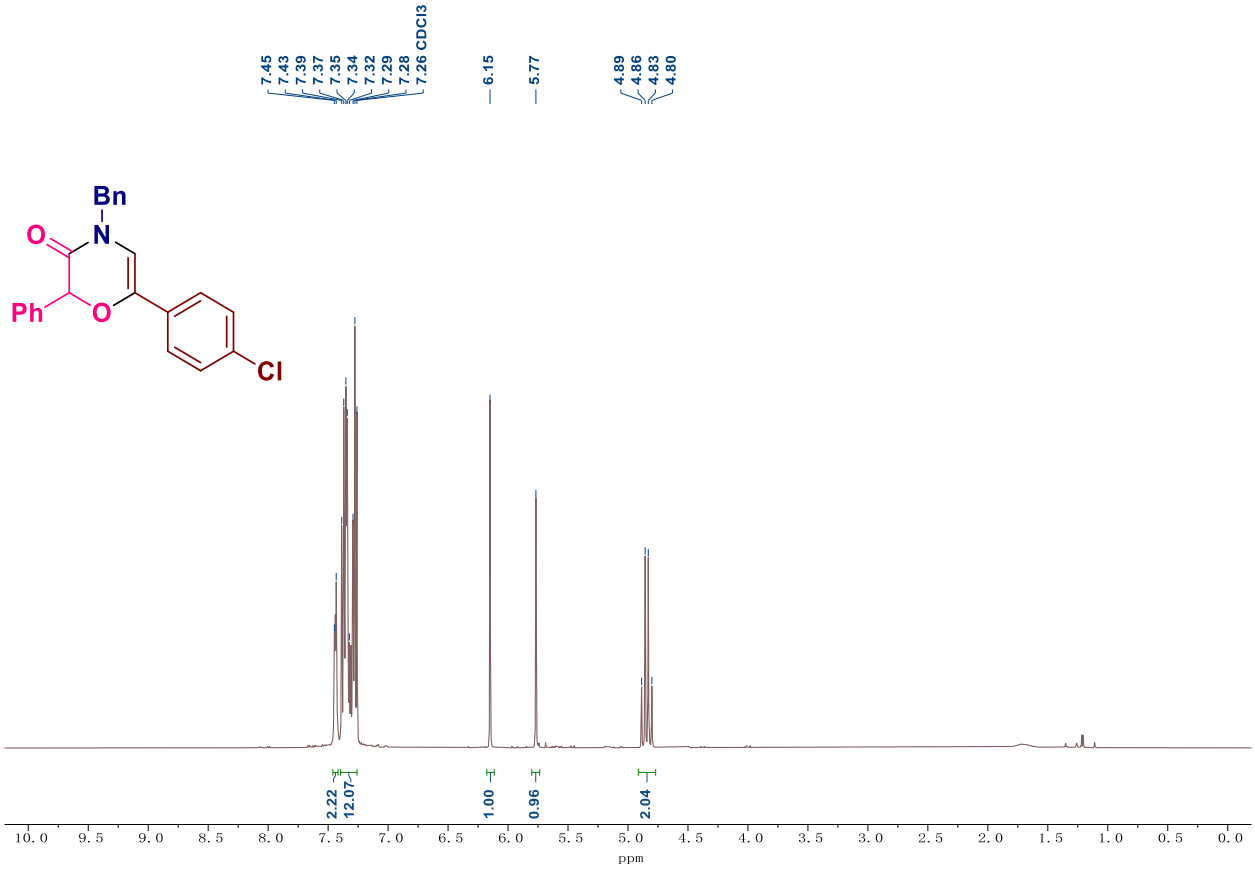
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28d**

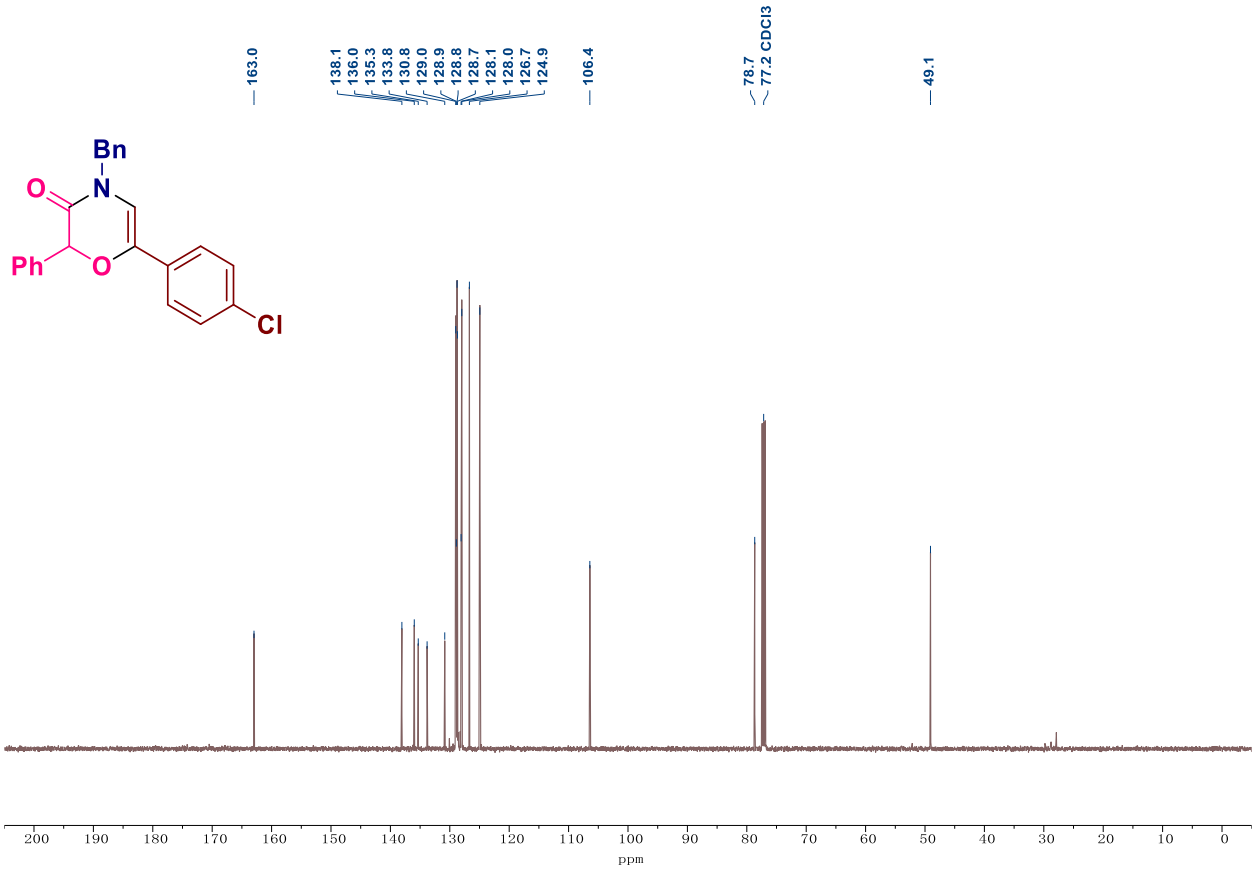




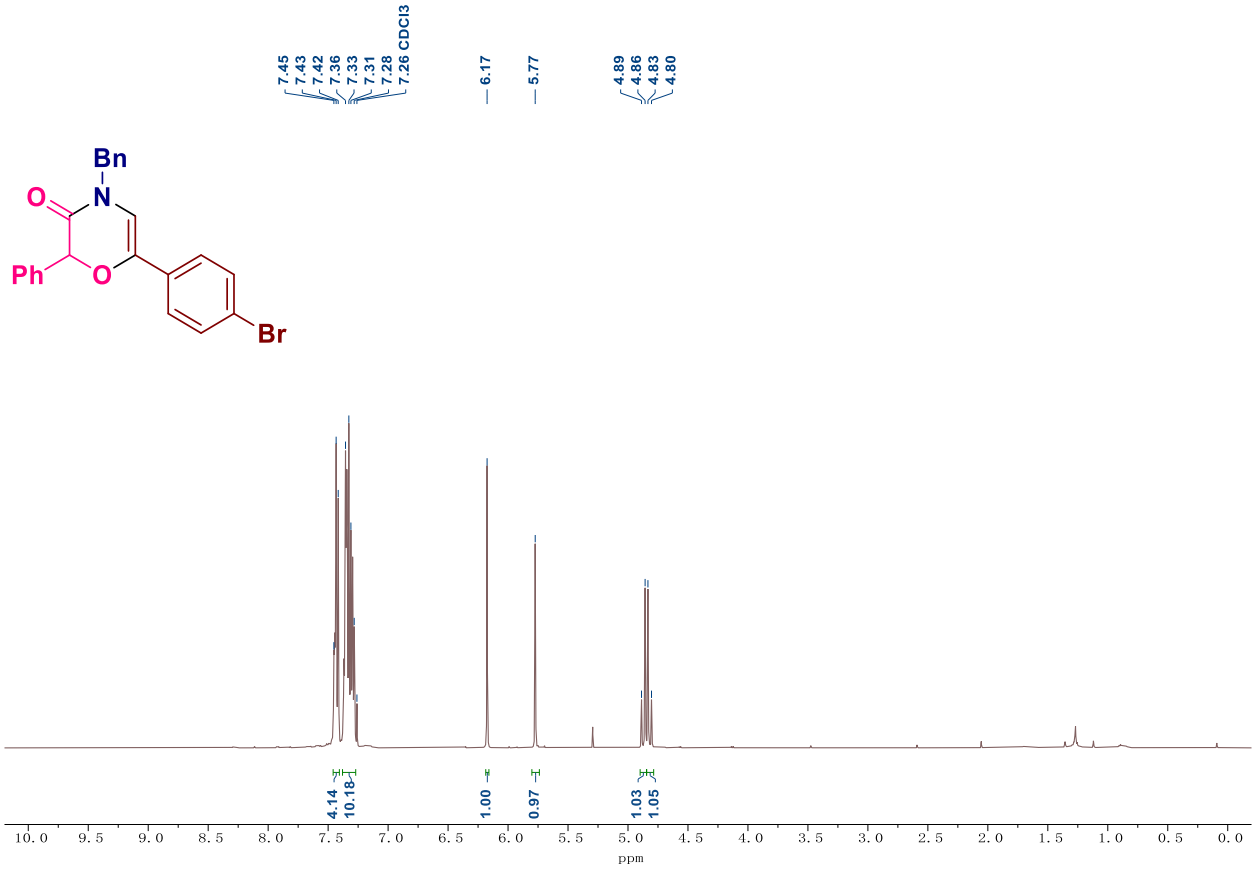

-115.5
-164.9 hexafluorobenzene
Bn
N
O
Ph
O
F
−110
−115
−120
−125
−130
−135
−140
−145
−150
−155
−160
−165
−170
−175
−180
−185
−190
−195
−200
ppm

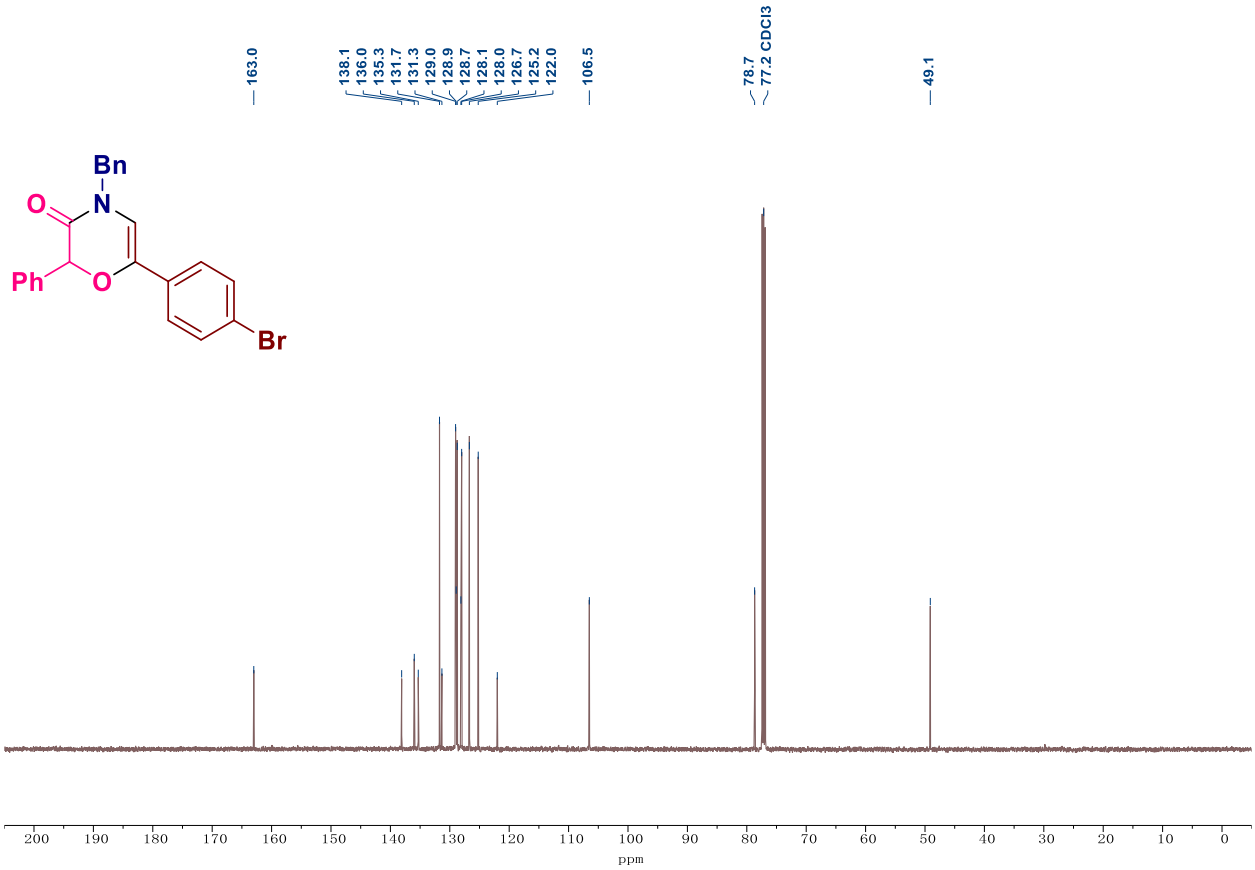
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28e**



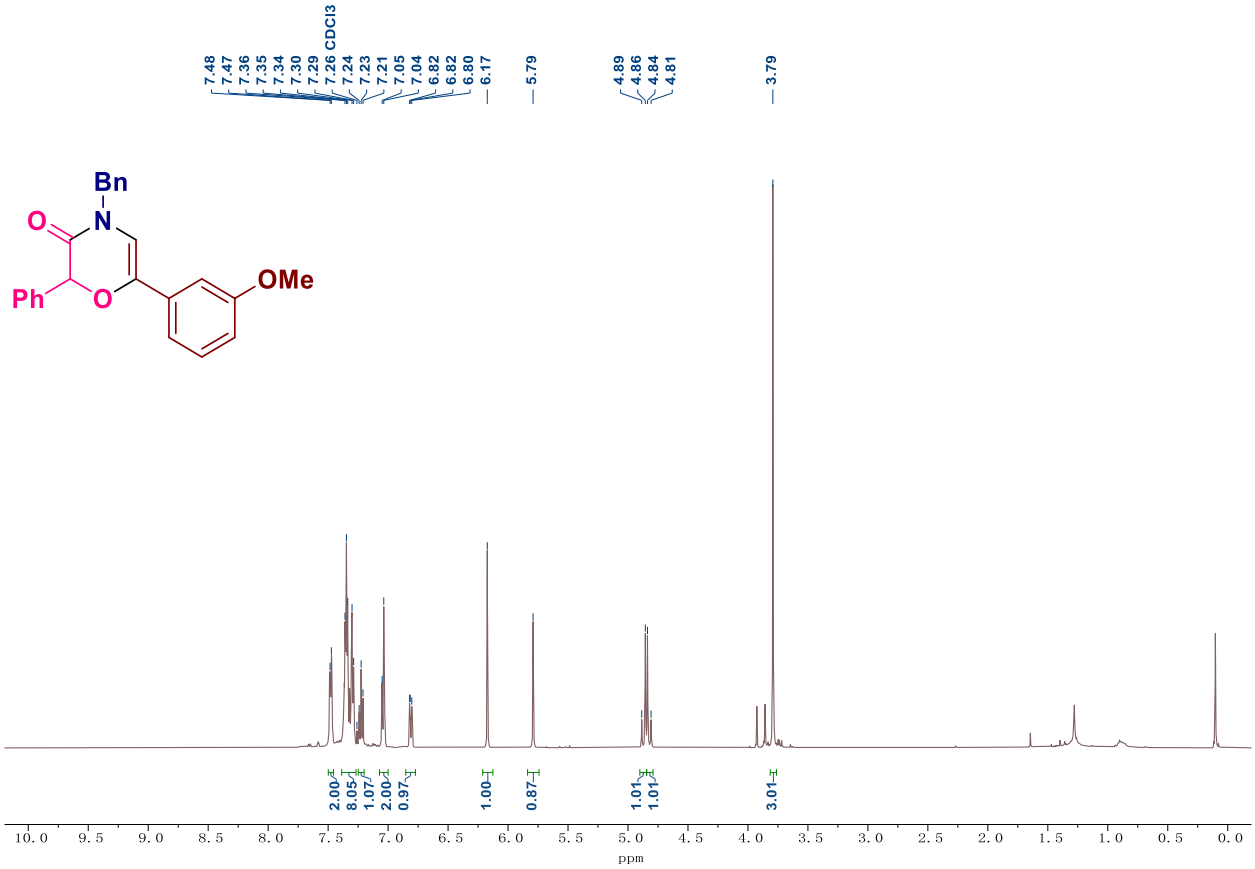


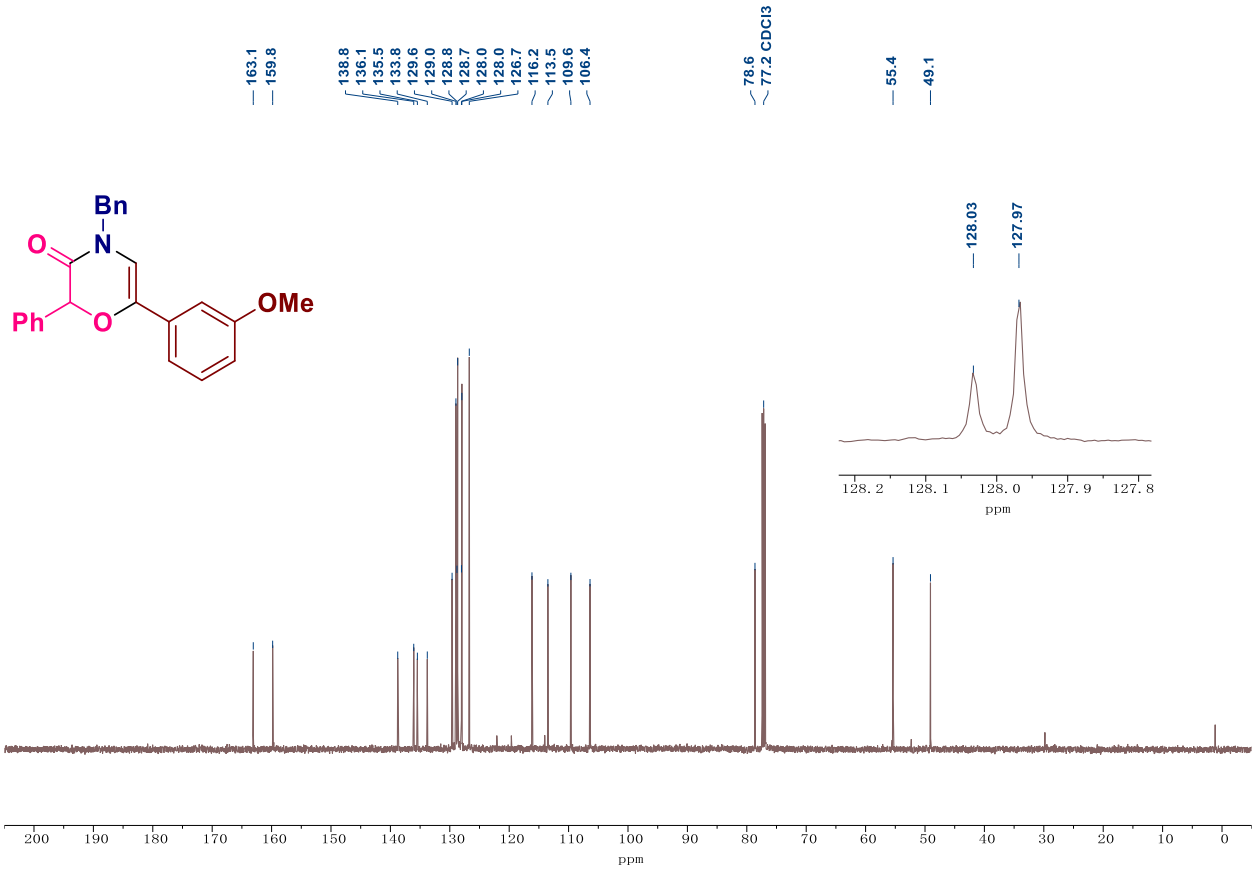
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28f**



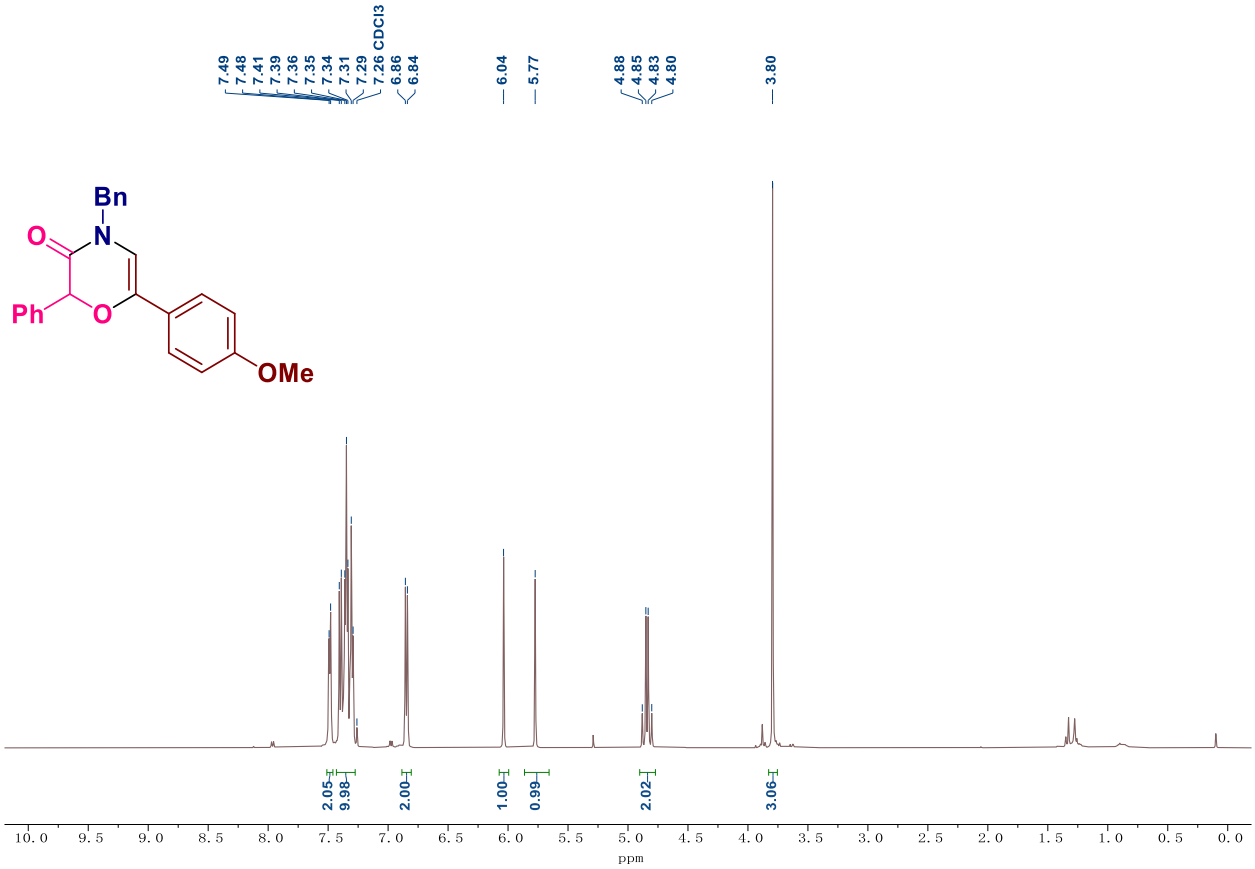


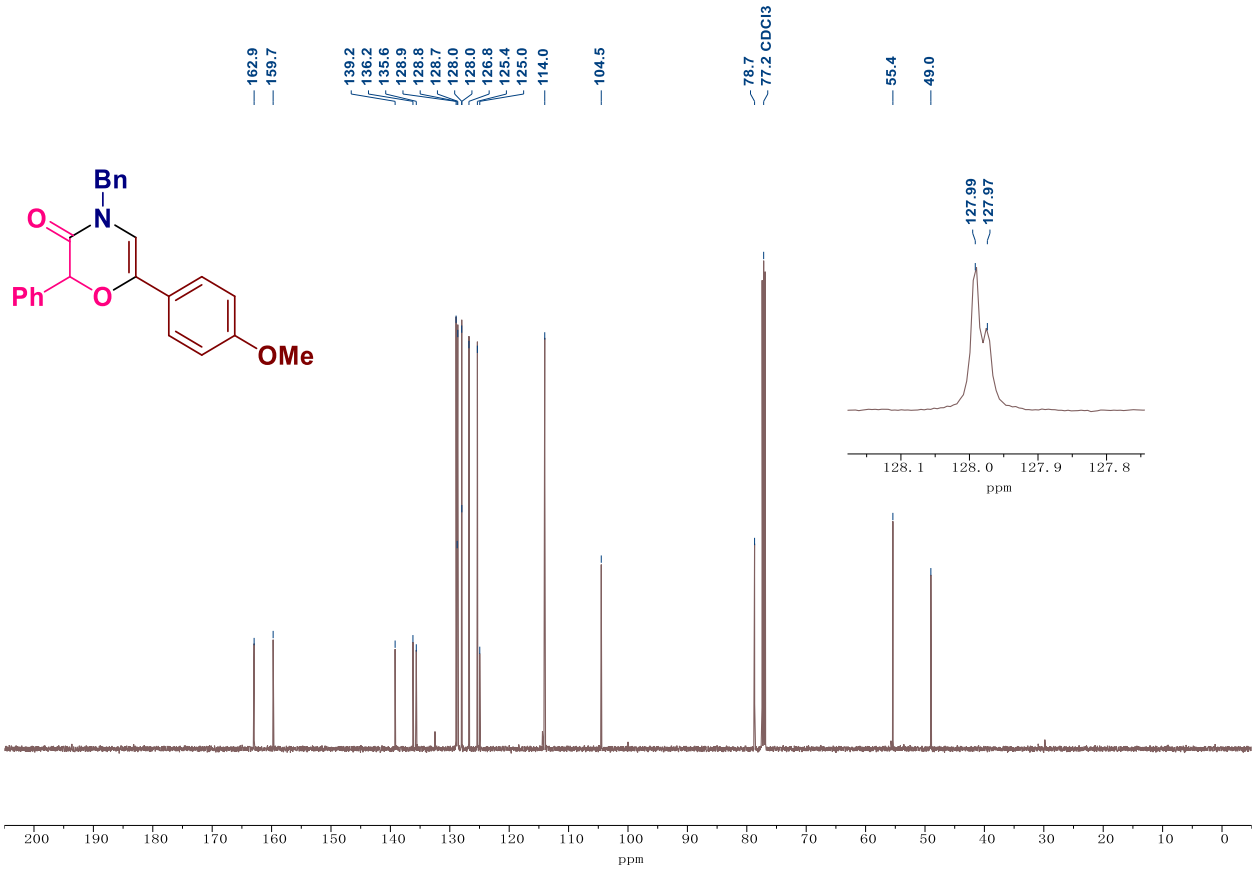
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28g**



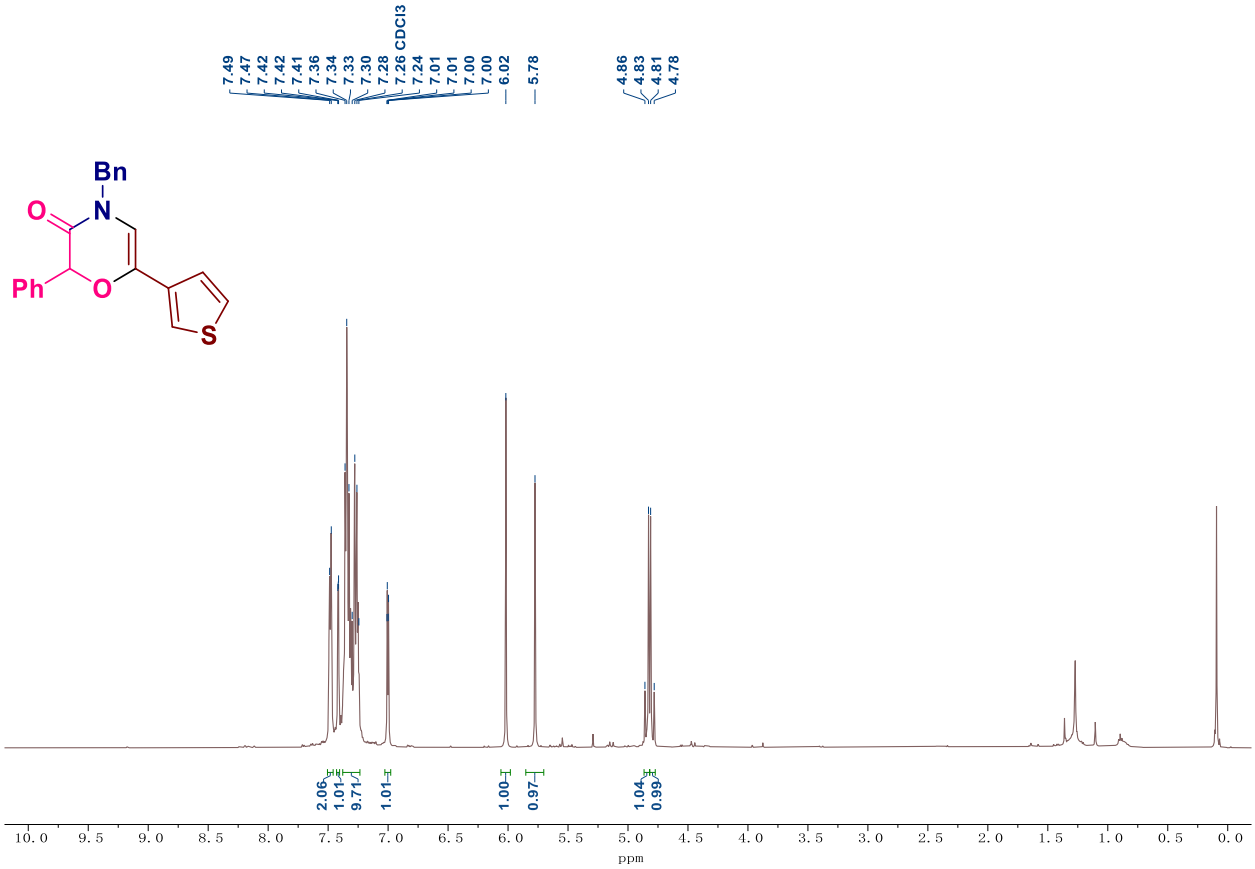


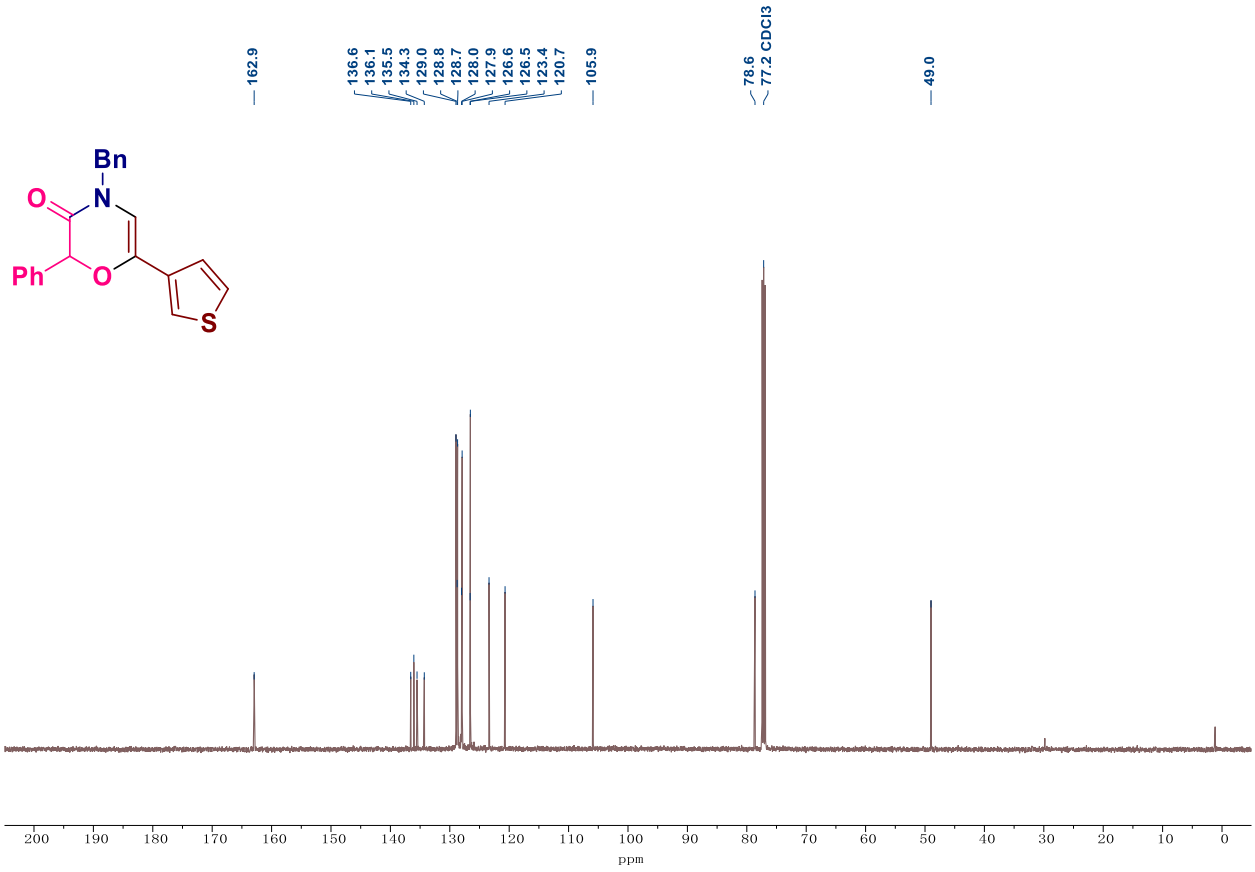
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28h**



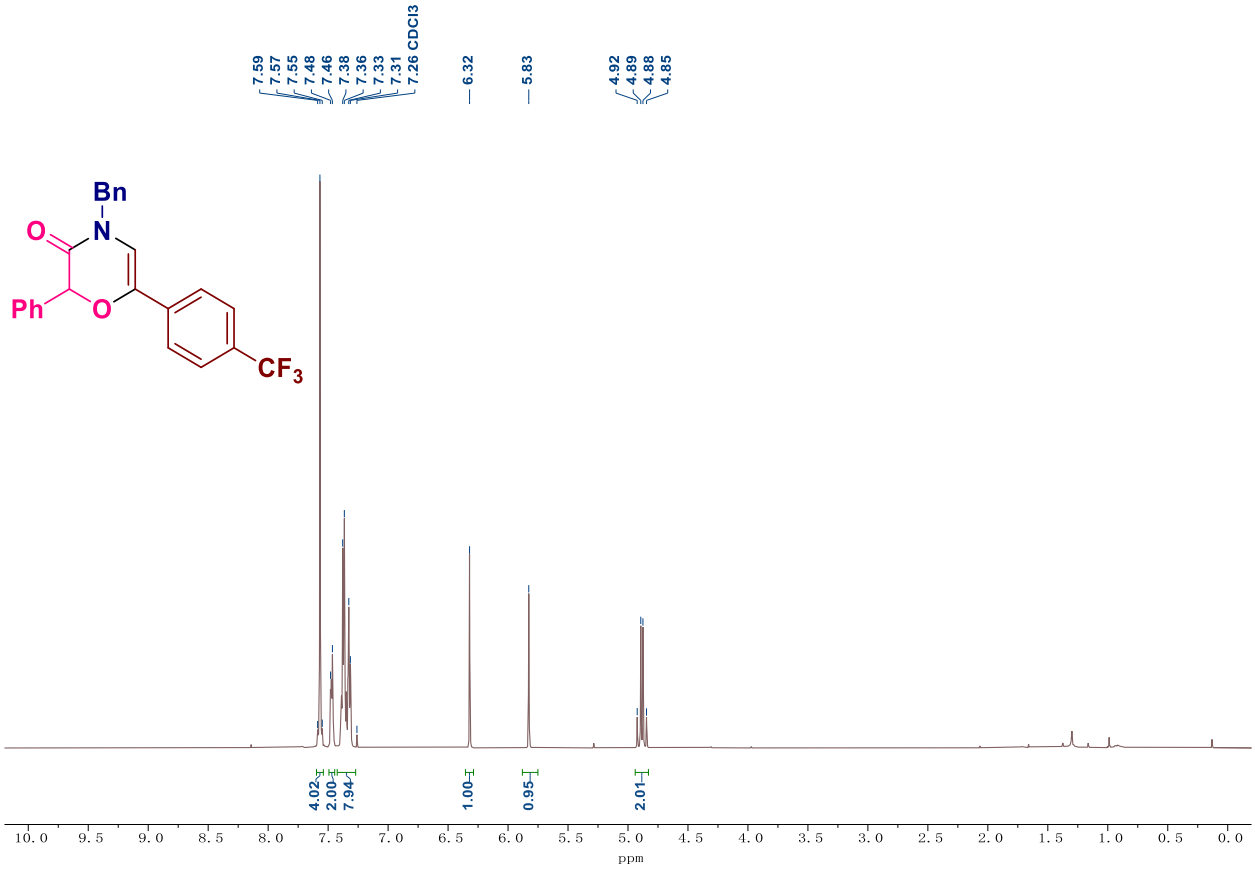


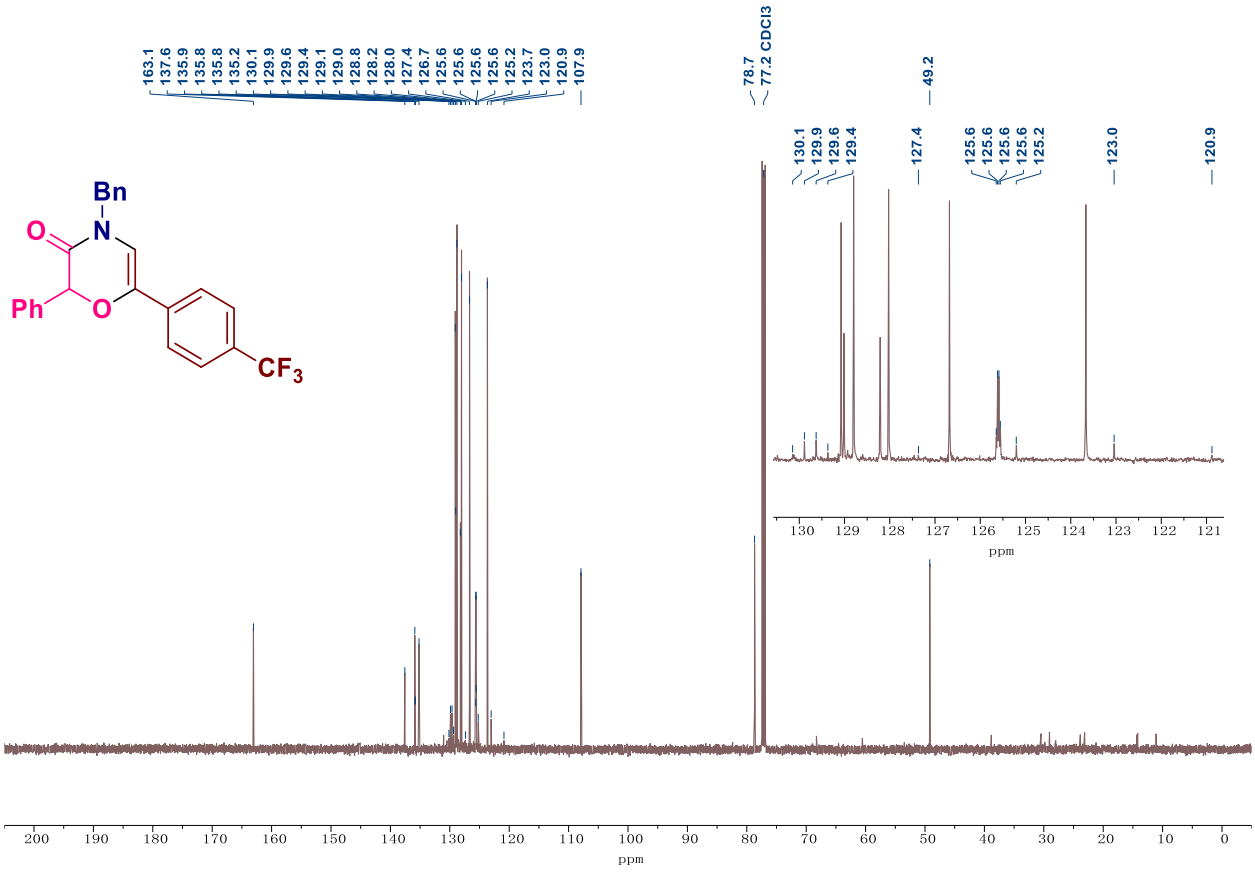
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28i**

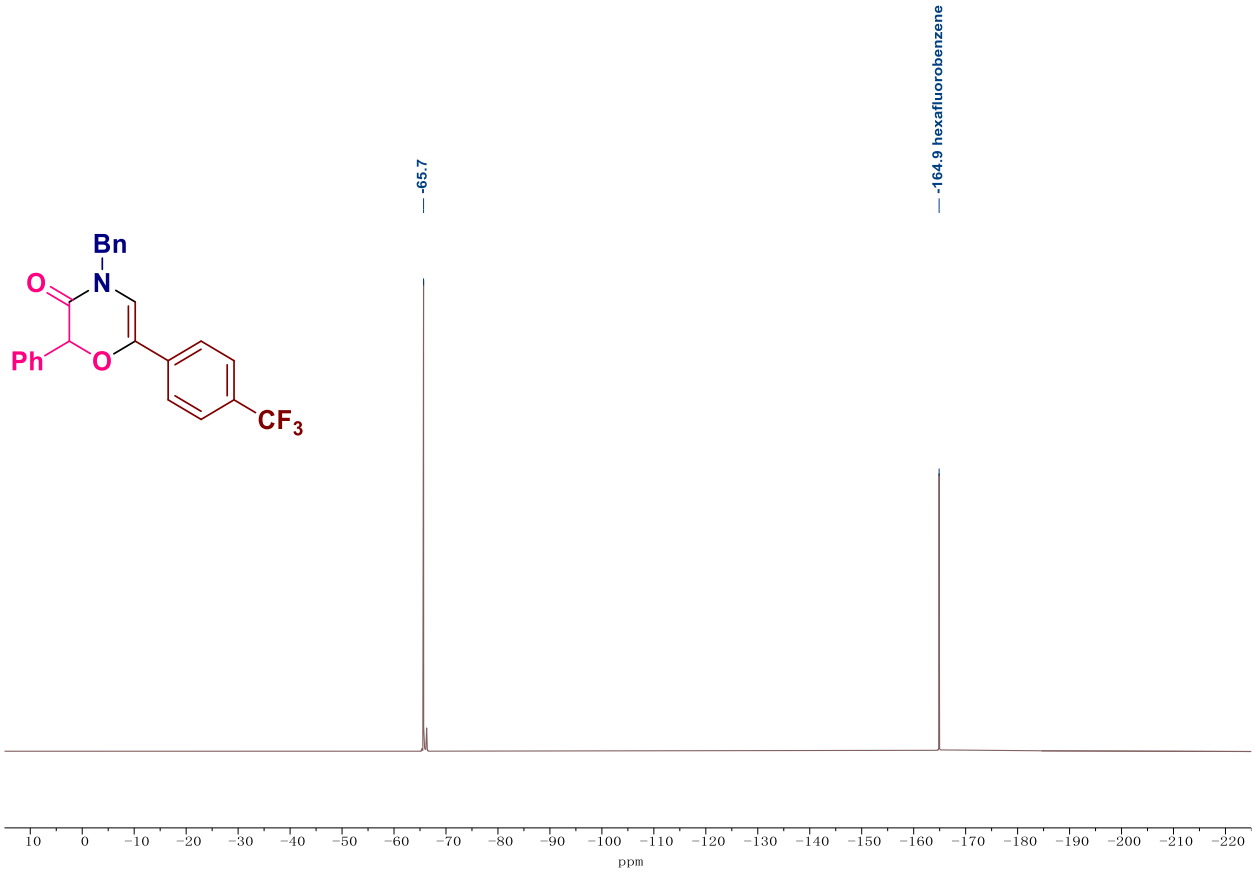




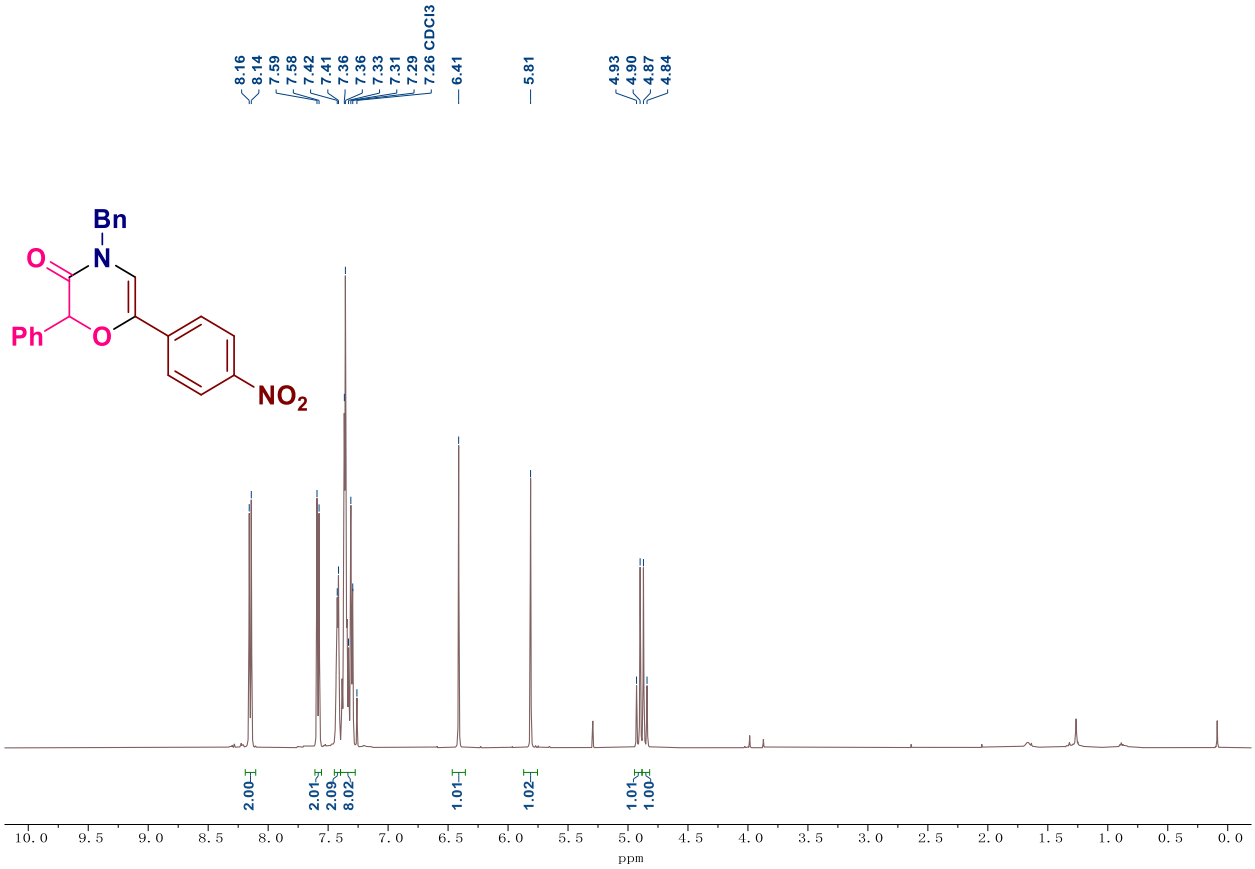
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28j**

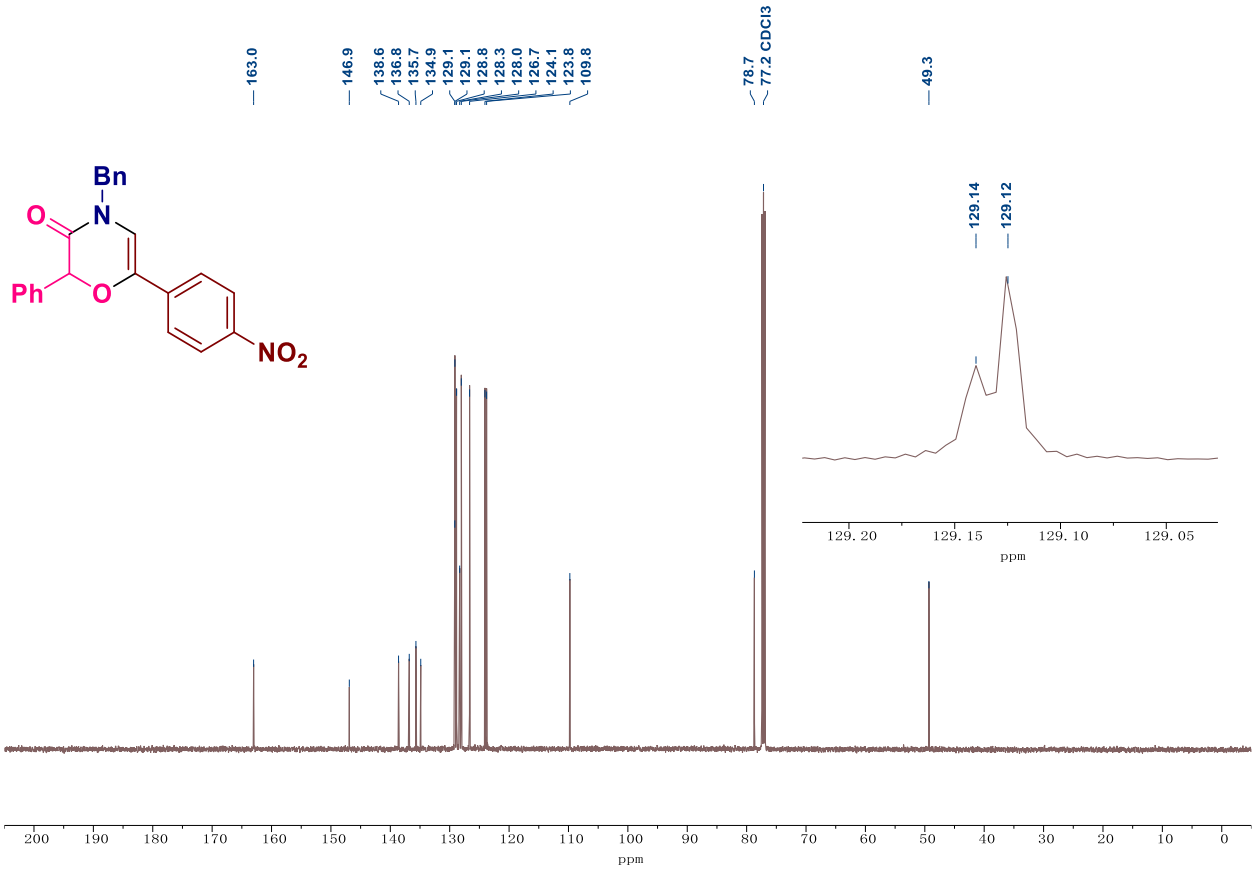




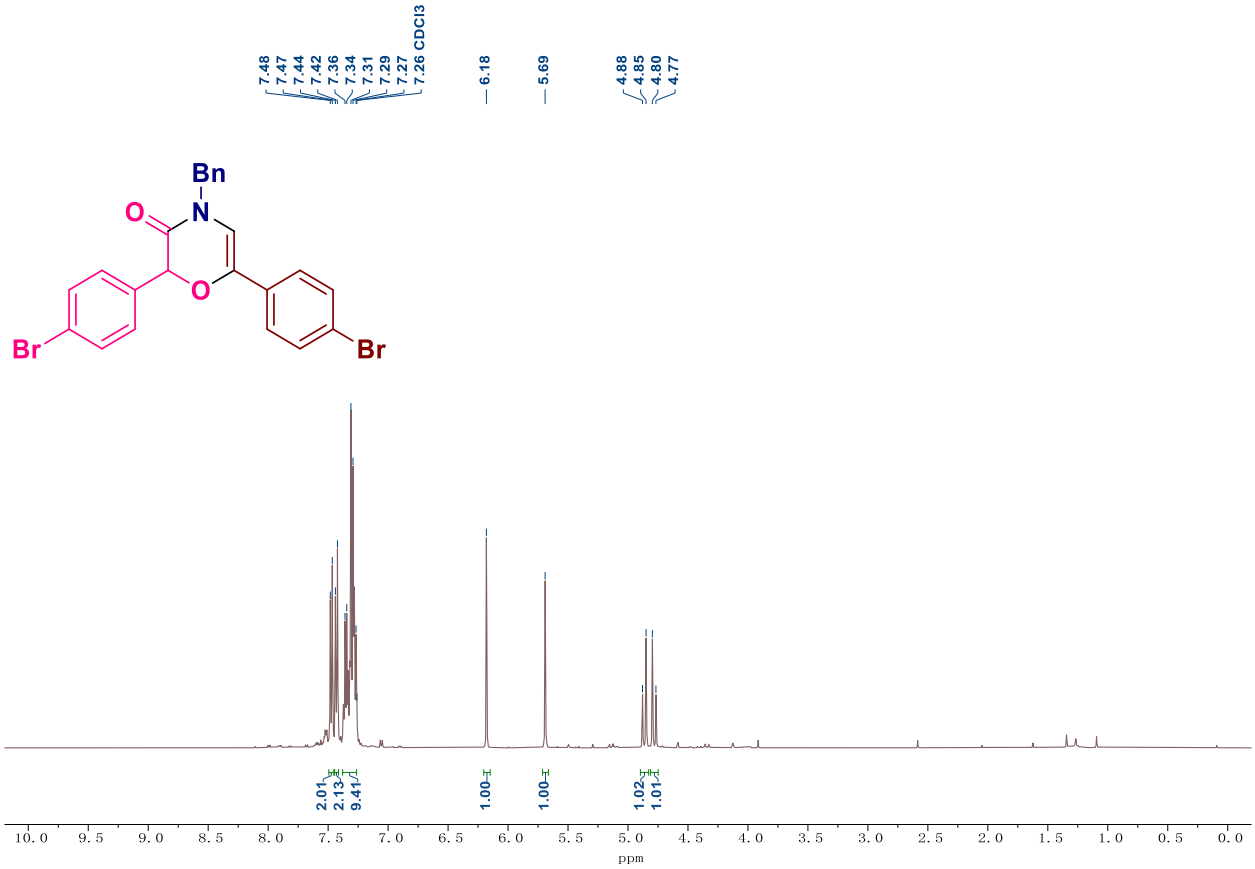

Bn
O
N
Ph
O
CF3
-65.7
-164.9 hexafluorobenzene
10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190 −200 −210 −220
ppm

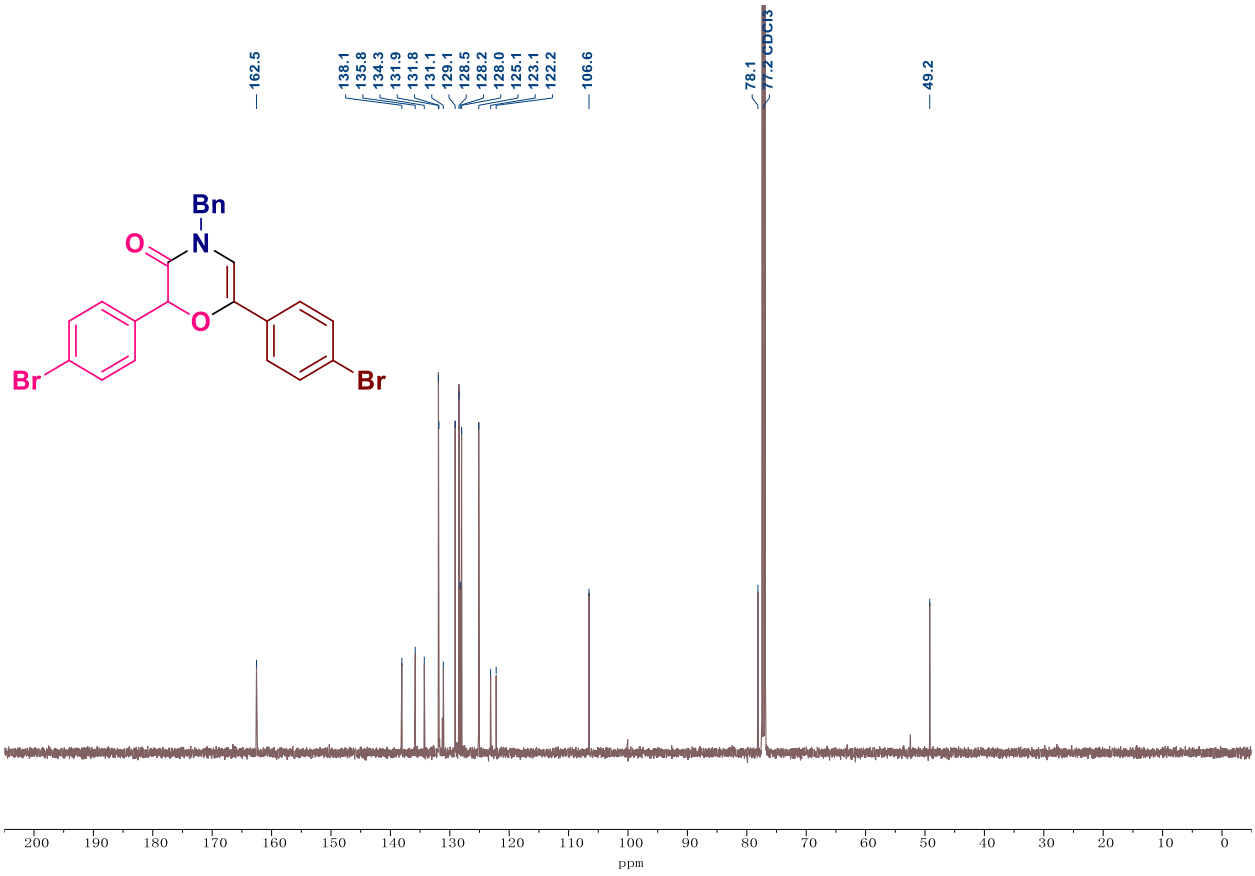
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28k**



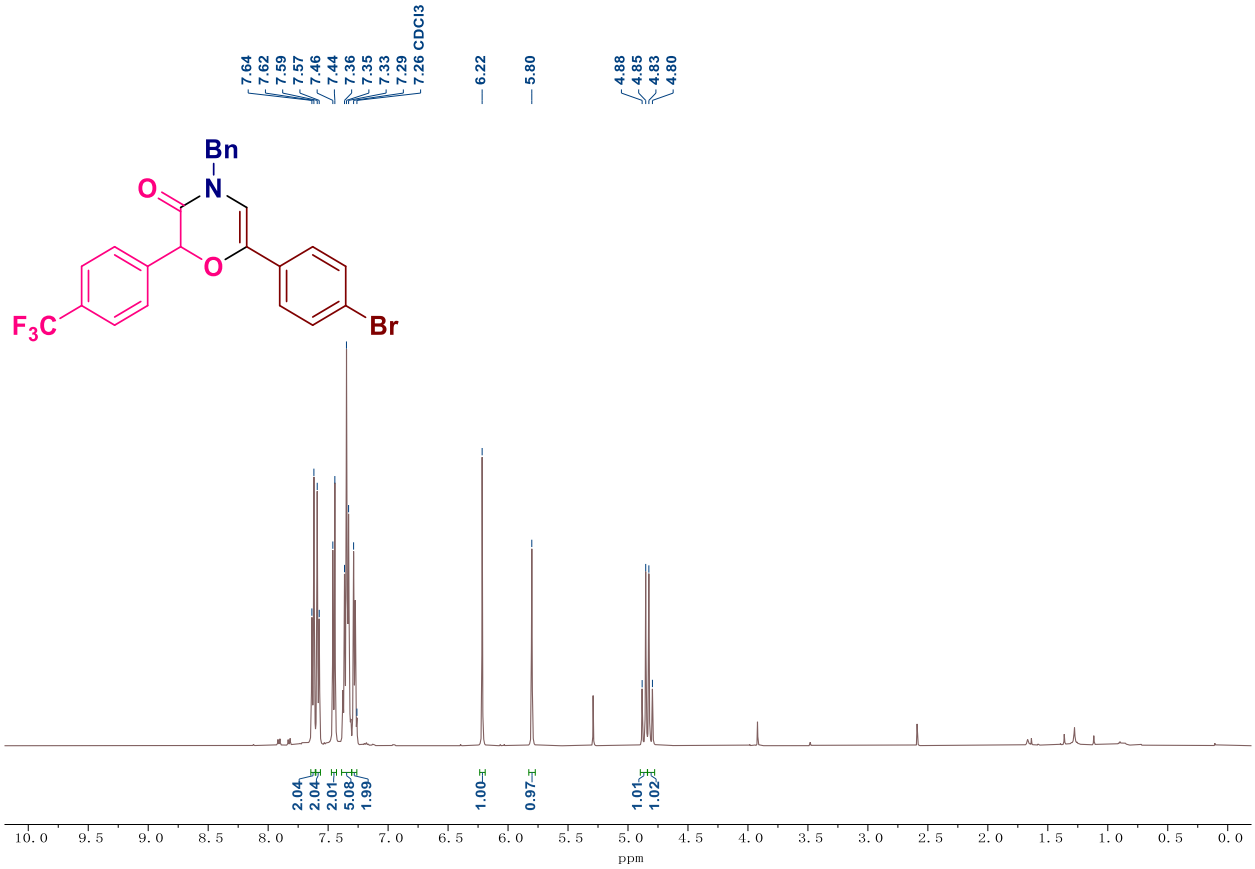


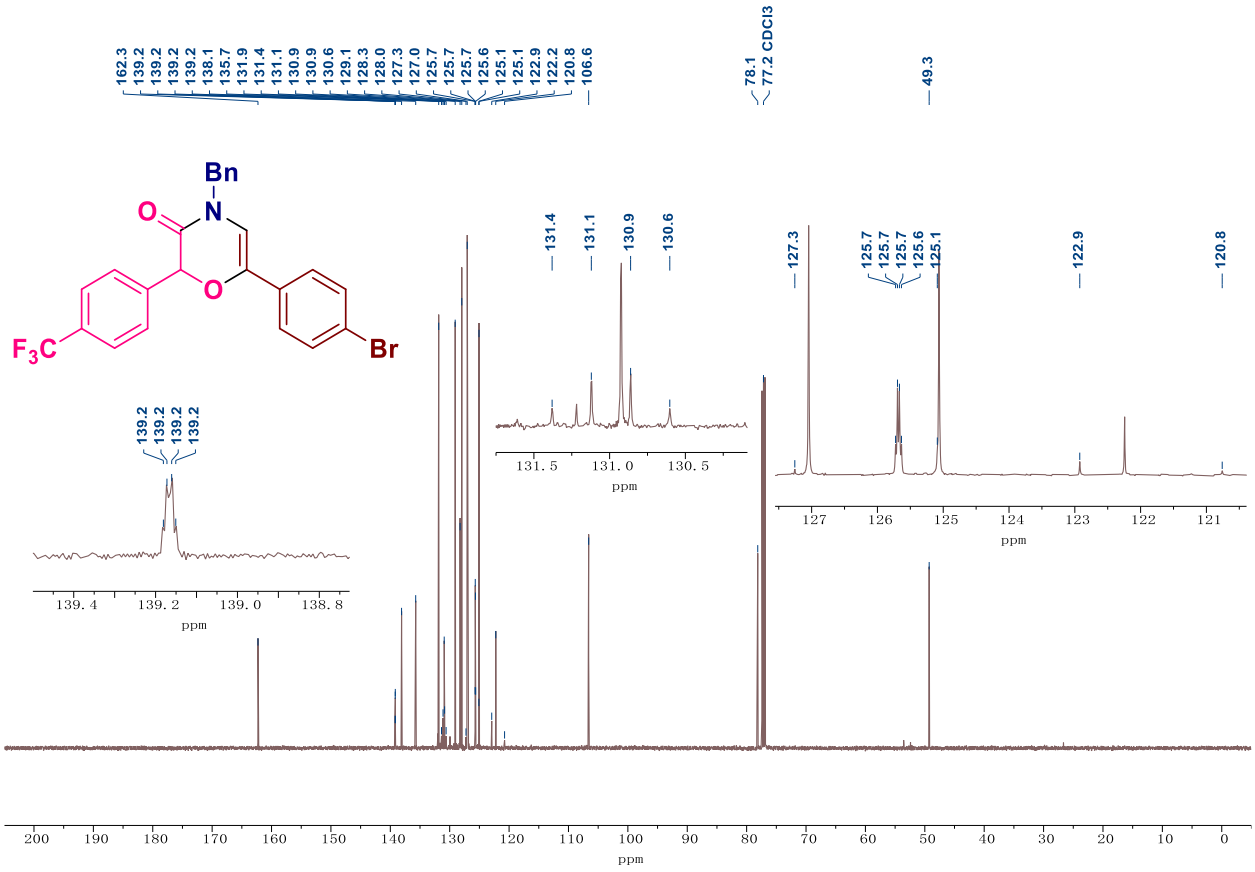
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28l**

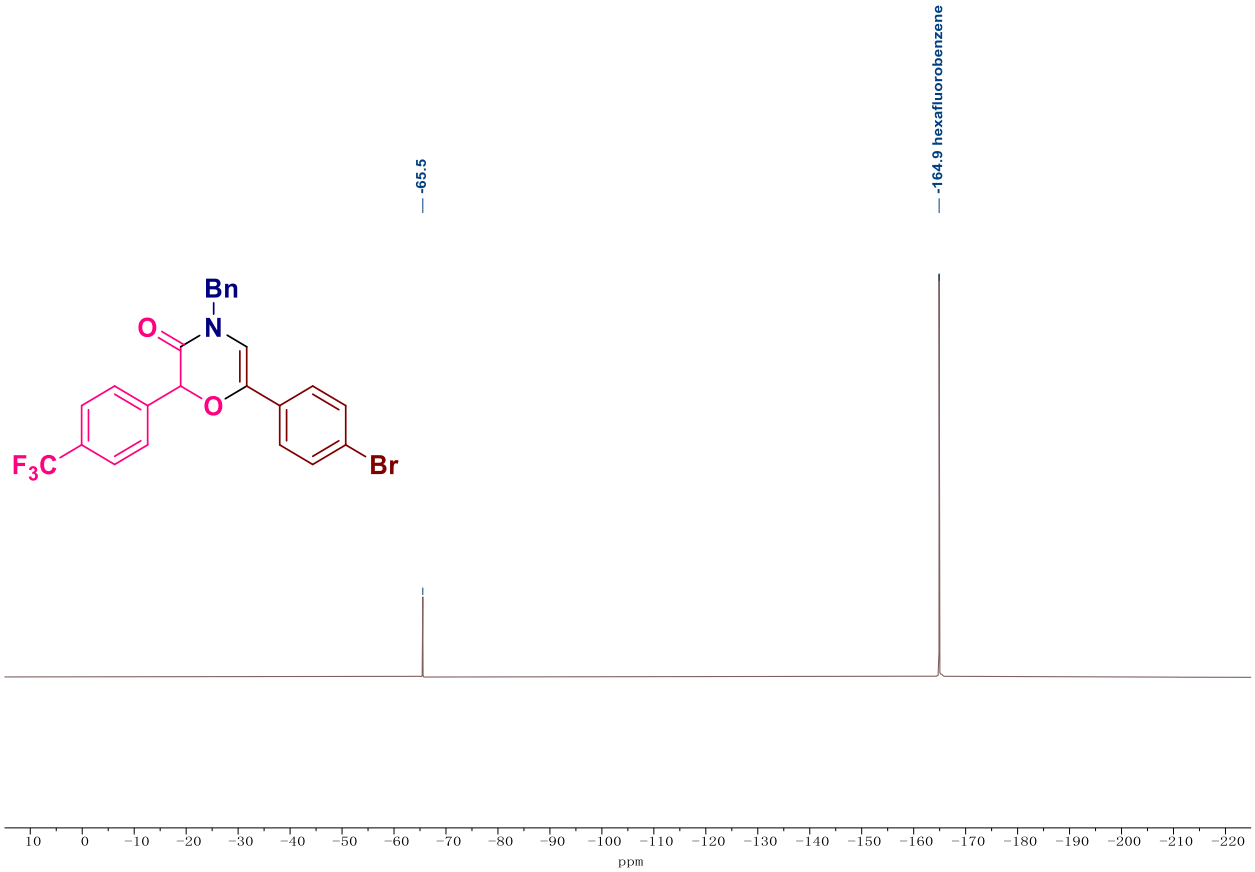




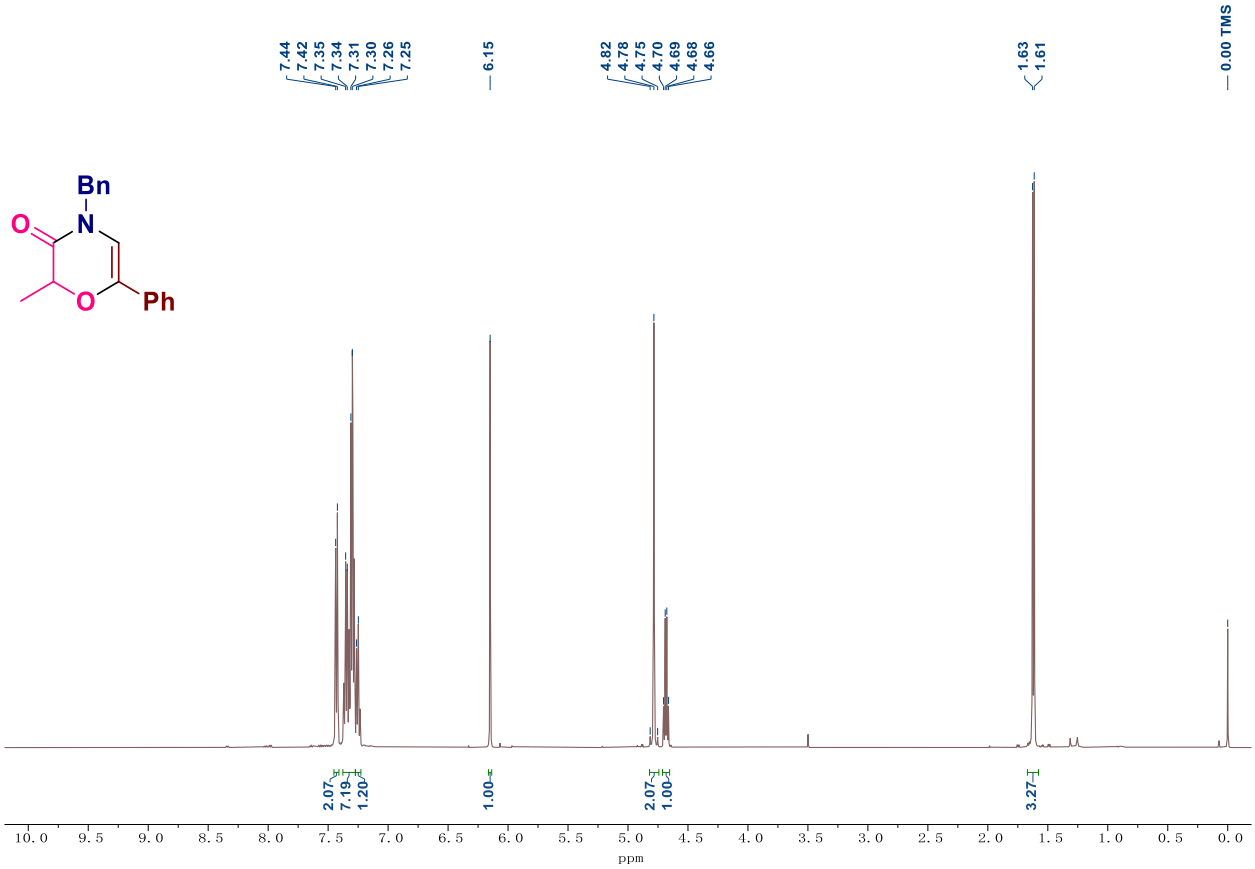
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28m**

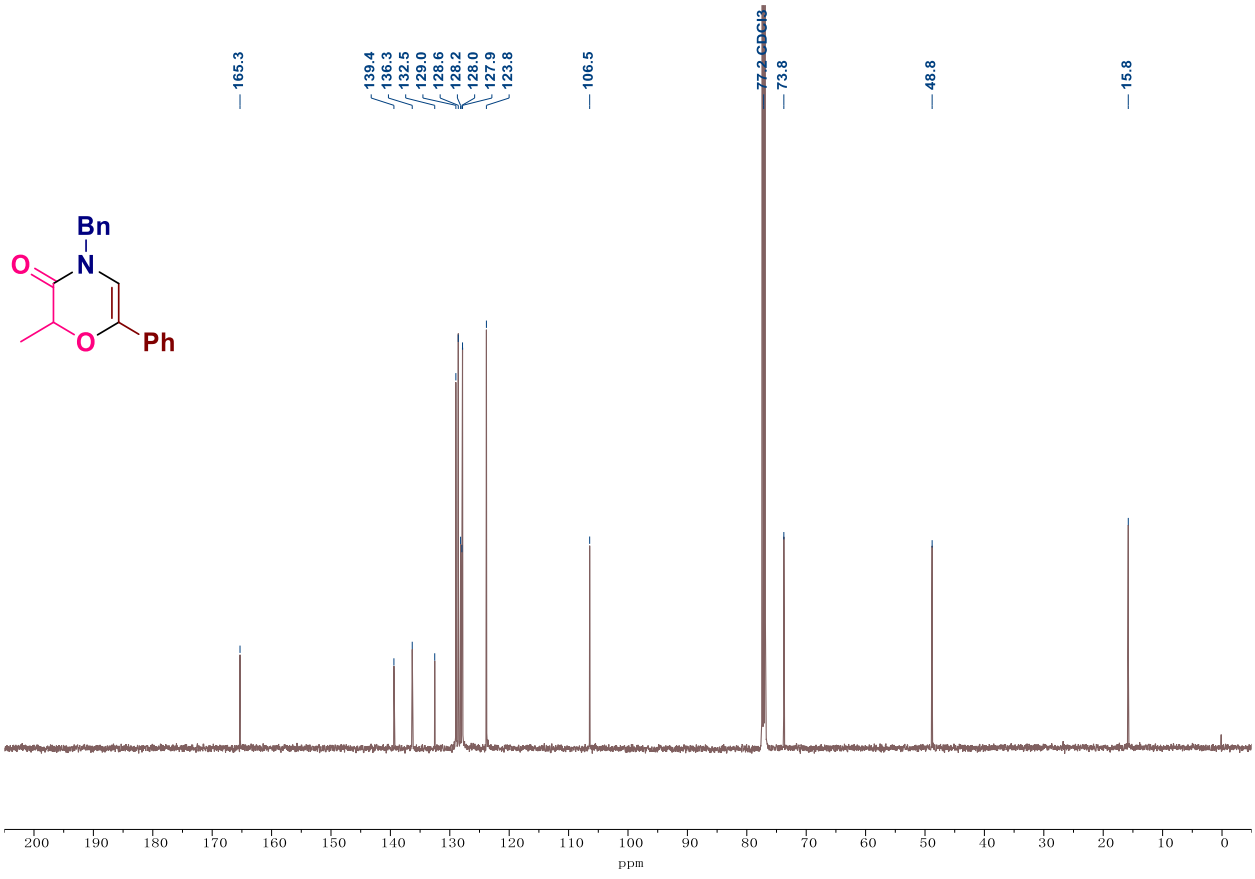




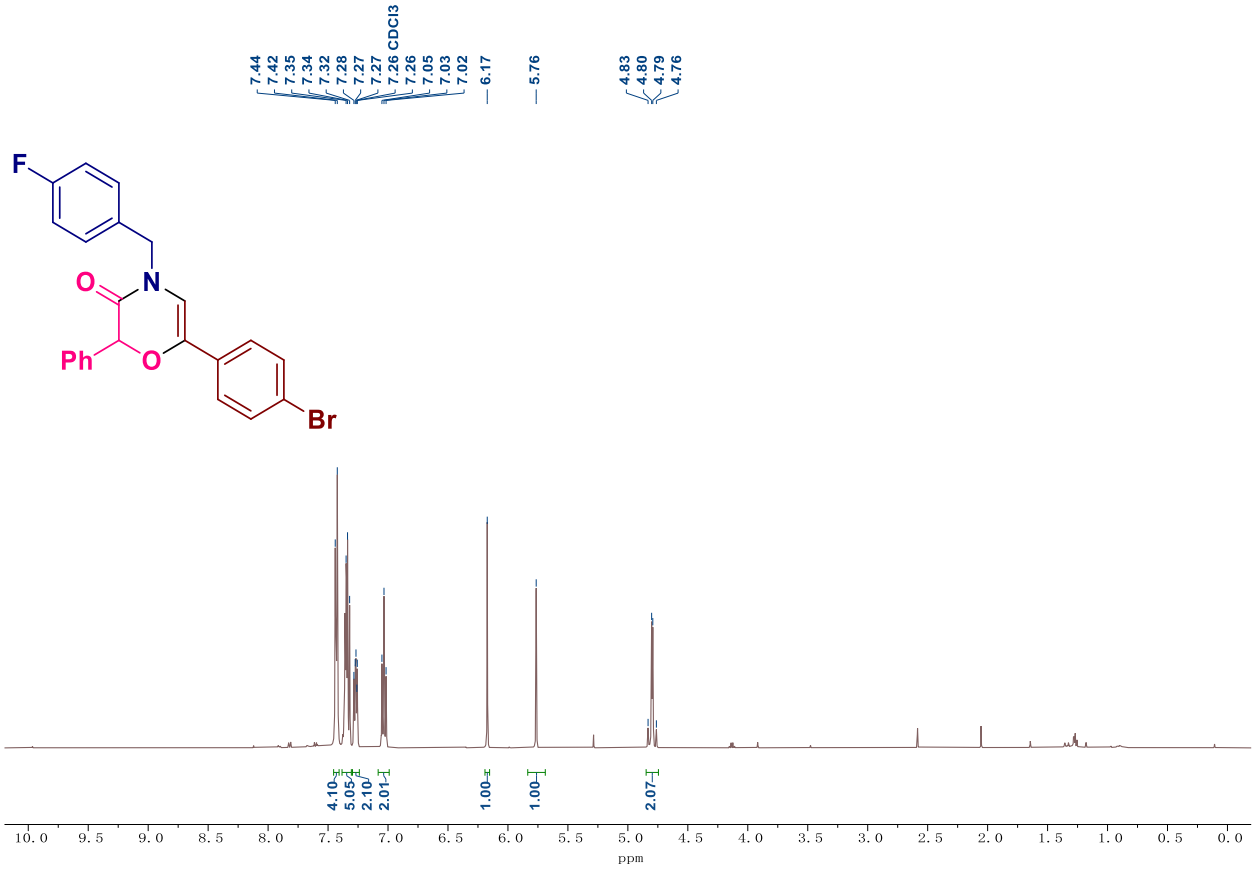

-65.5
-164.9 hexafluorobenzene
Bn
N
O
O
F3C
Br
10 0 −10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190 −200 −210 −220
ppm

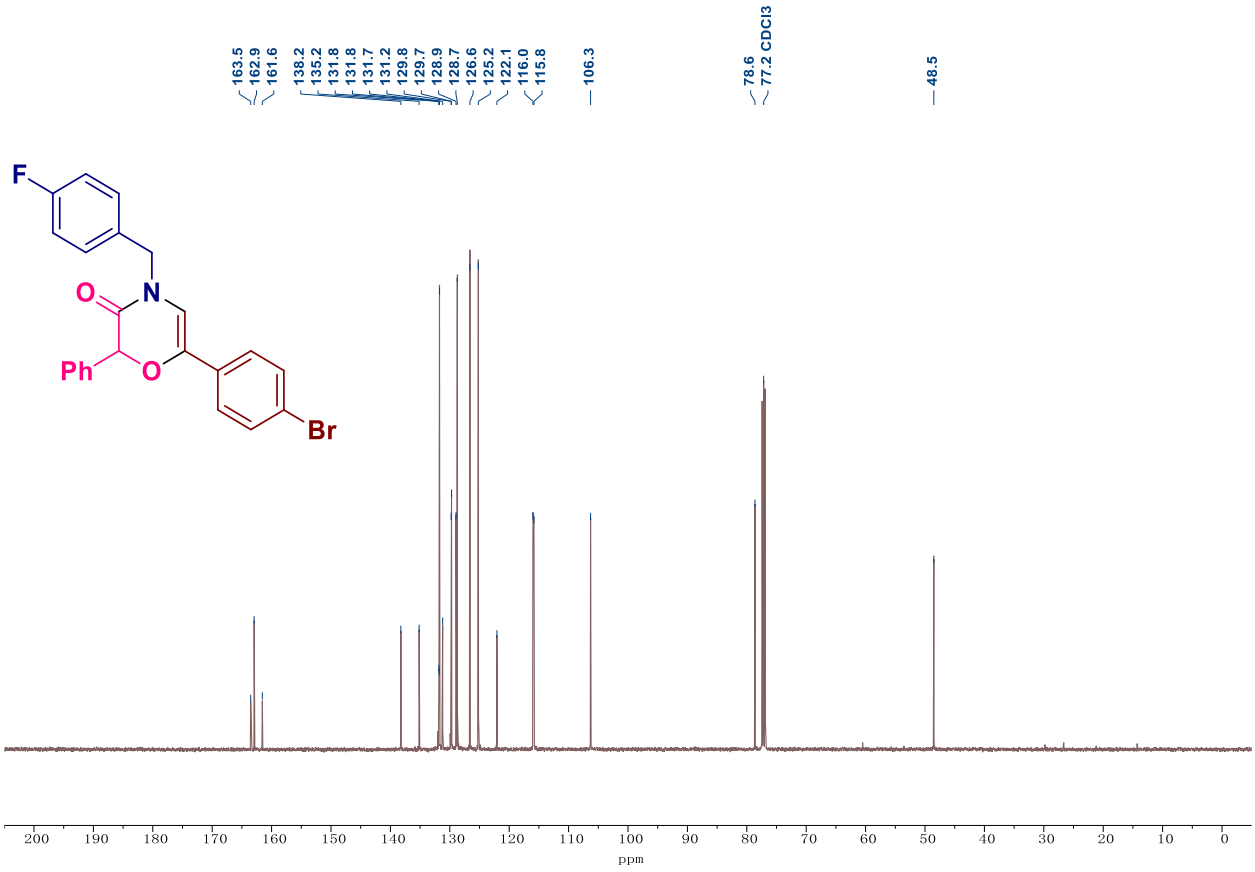
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28n**



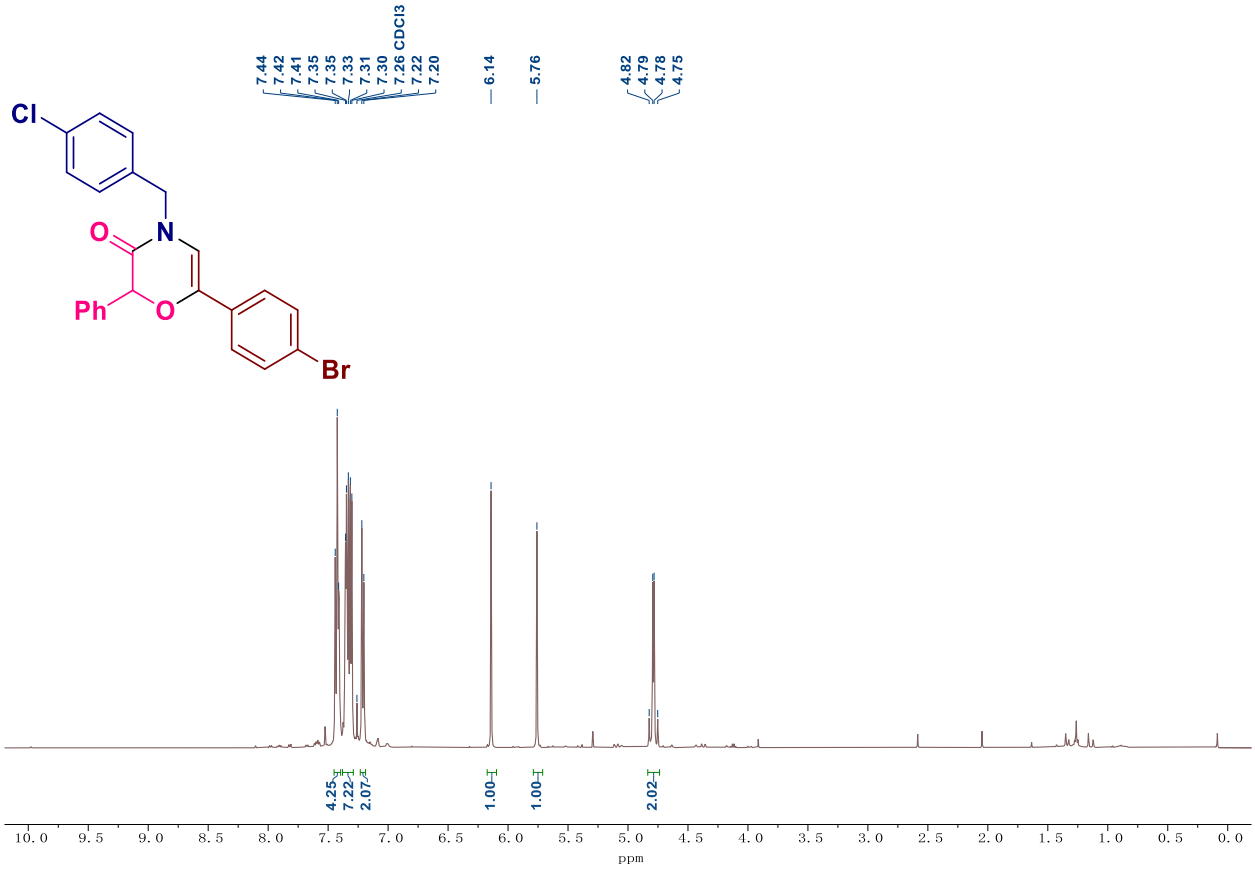


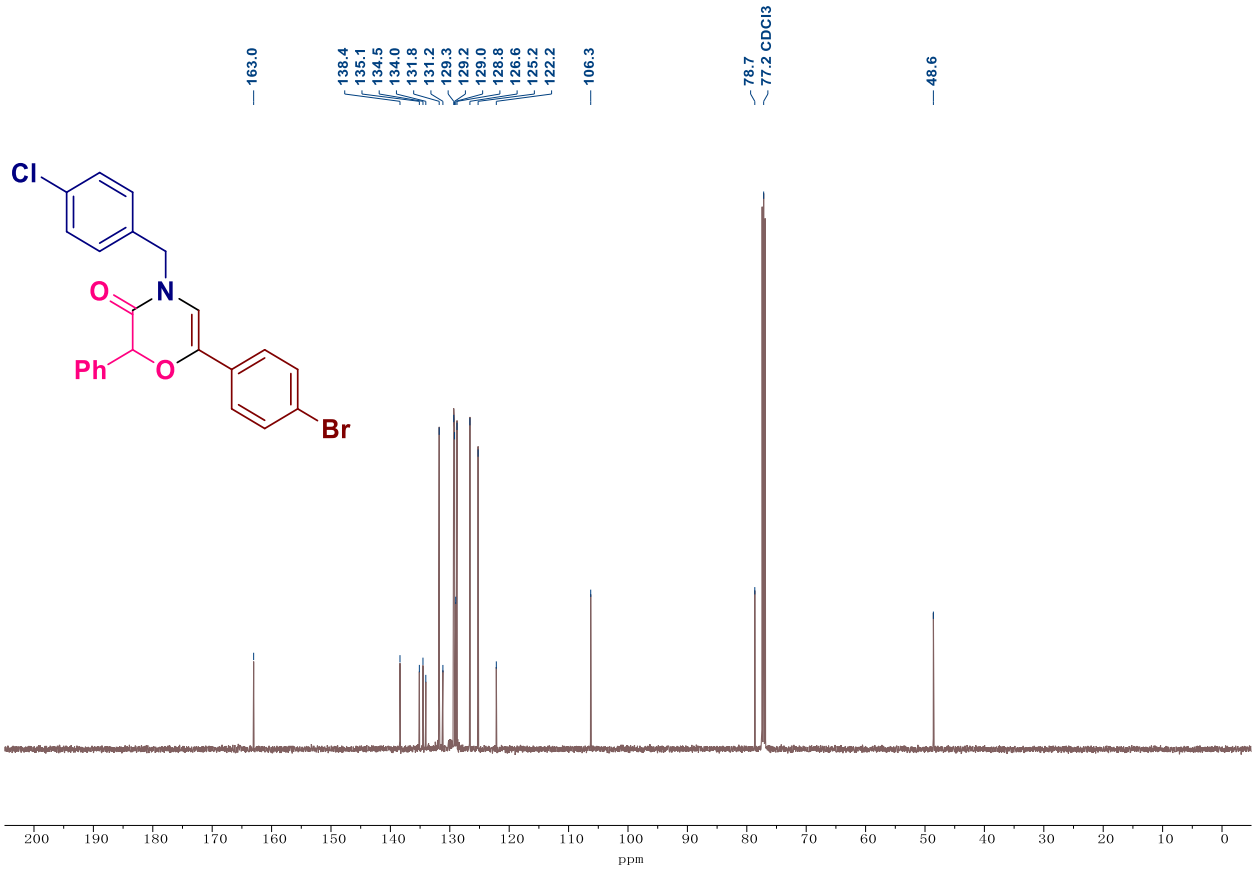
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28o**



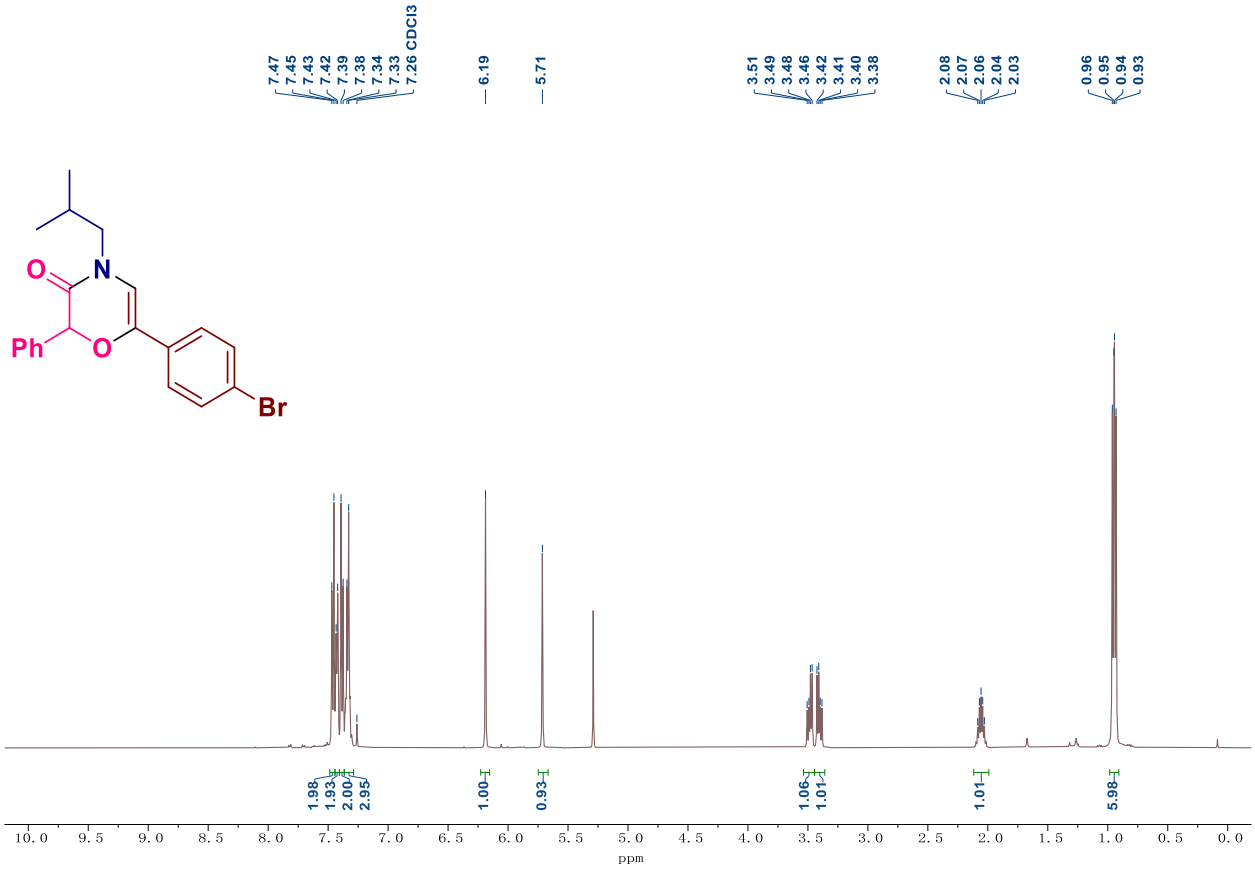


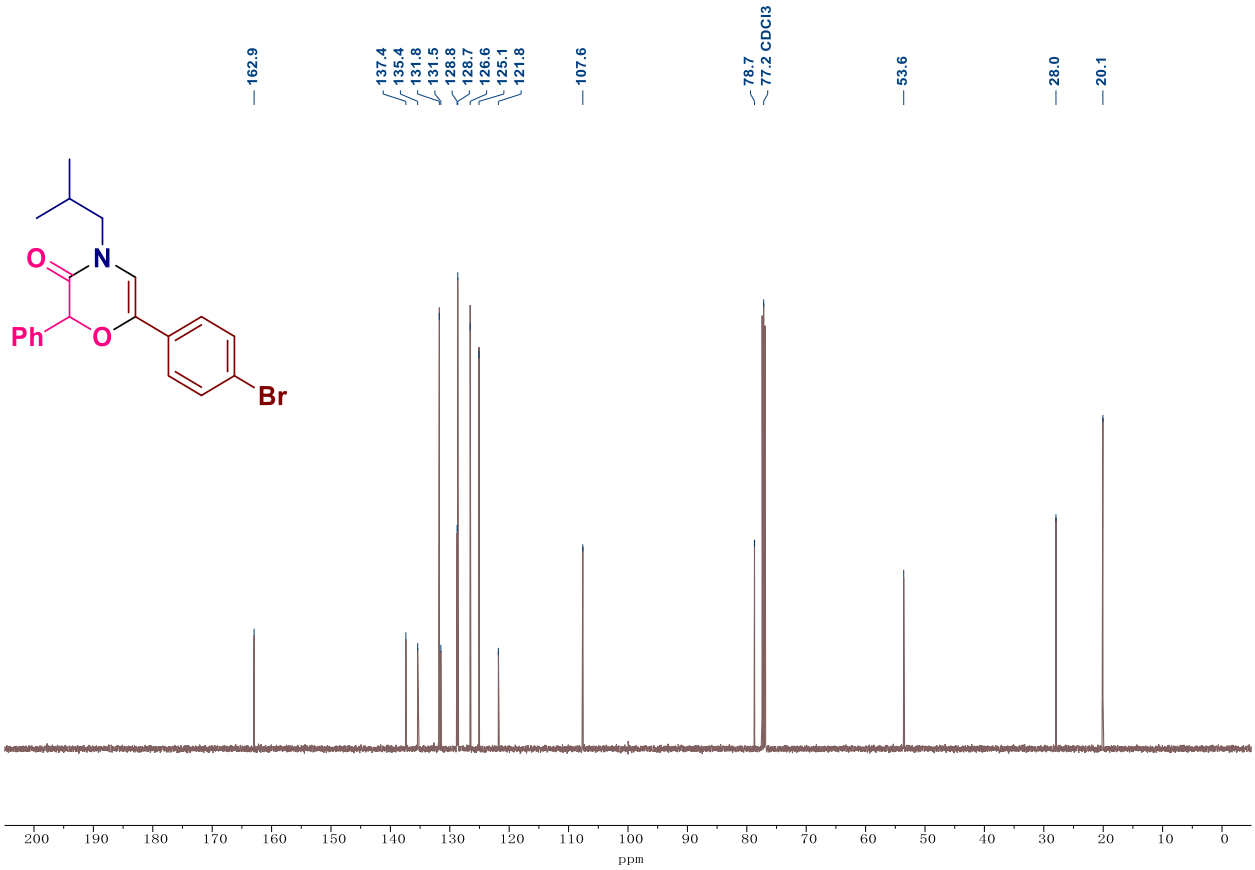
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28p**



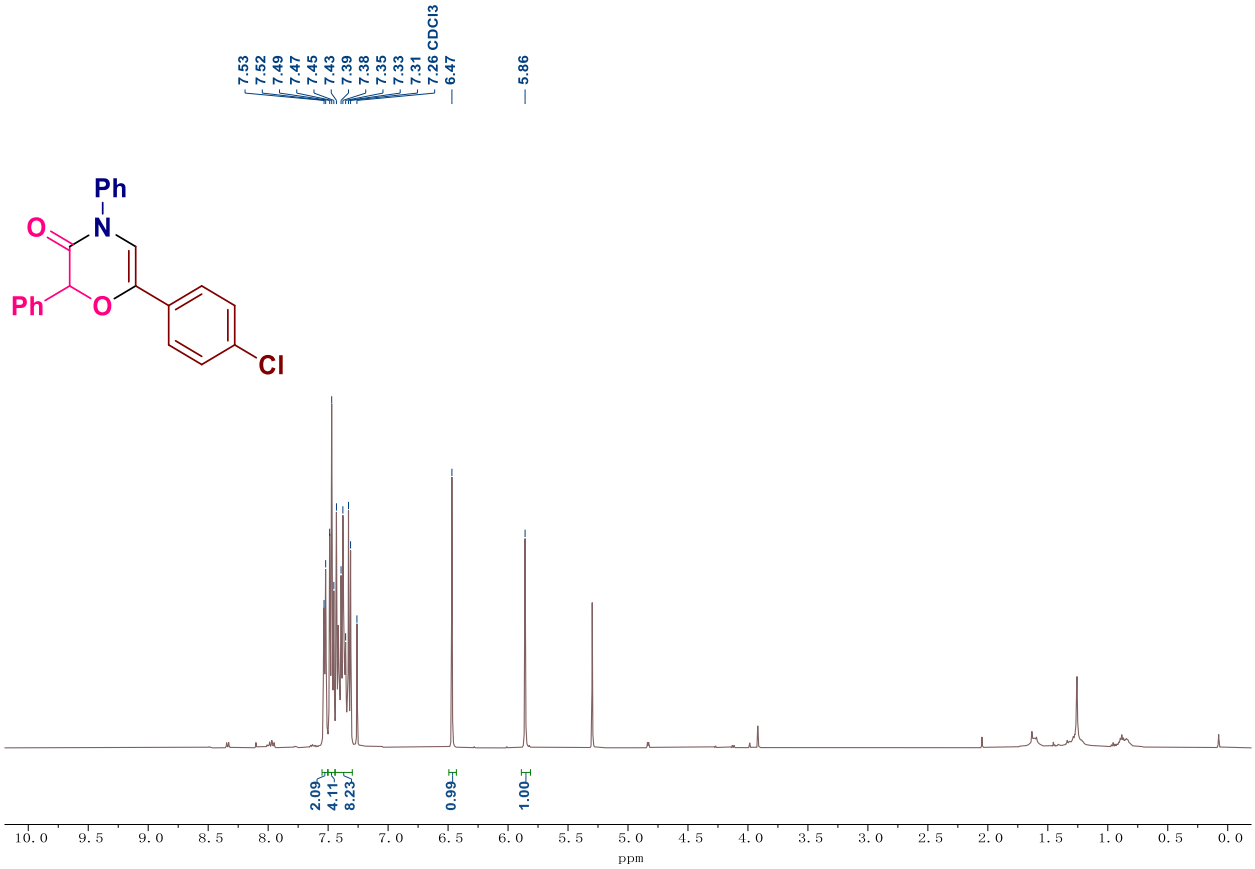


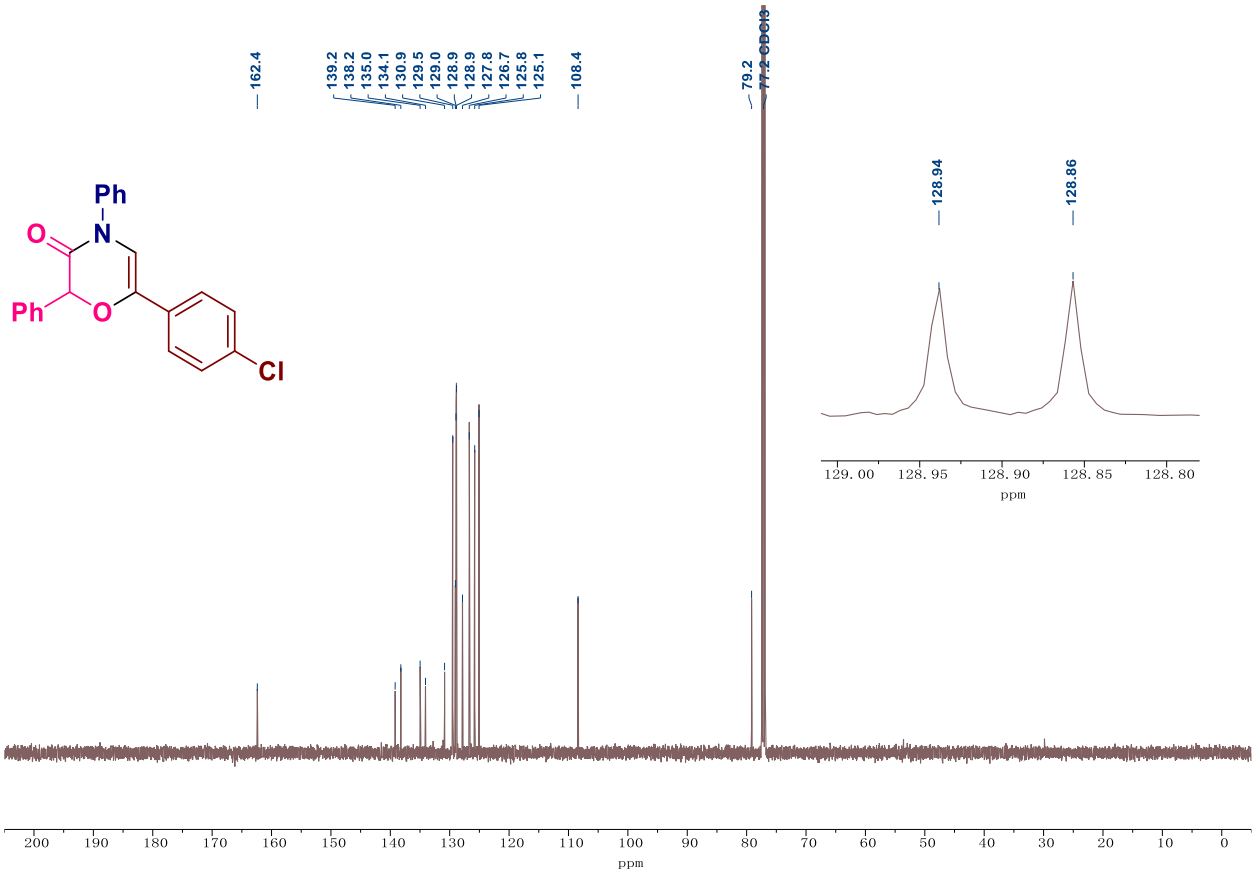
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28q**



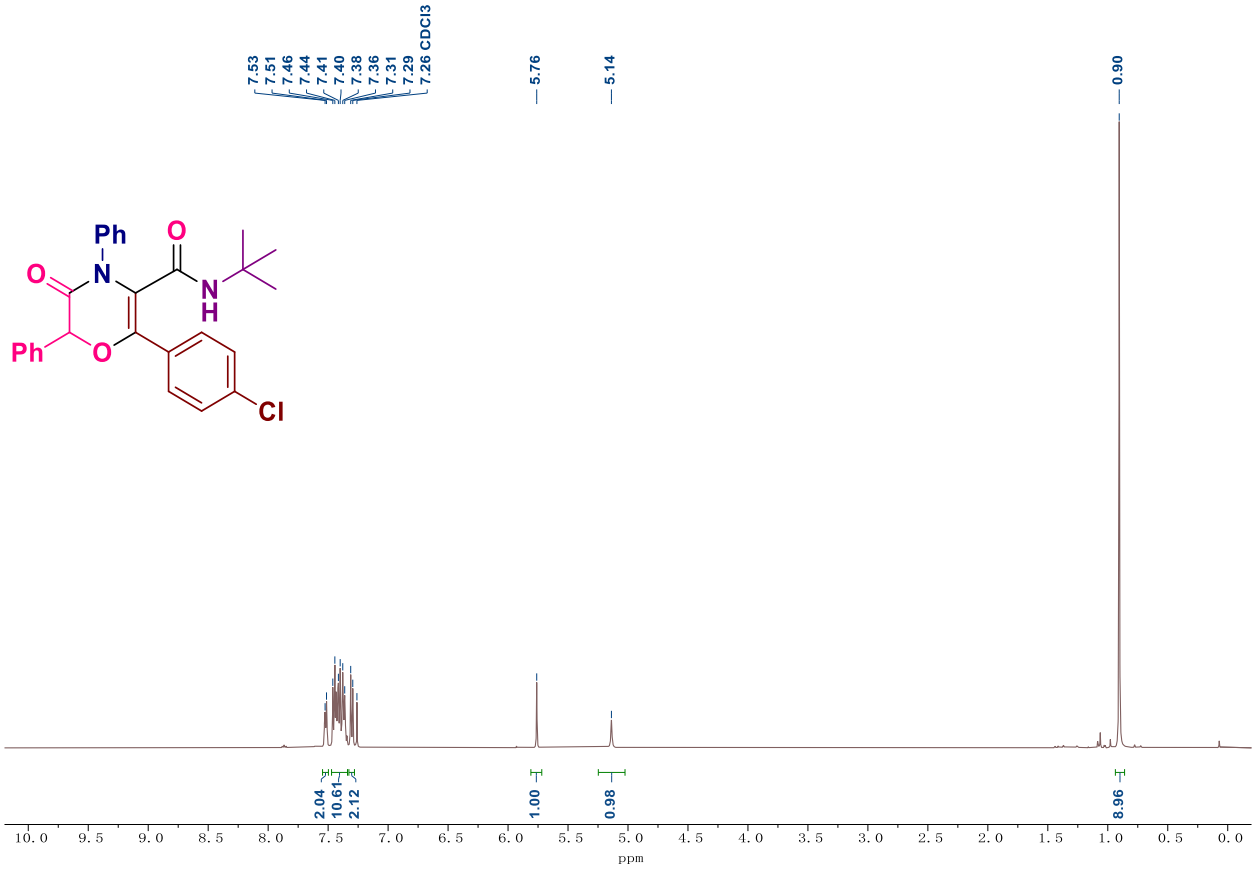


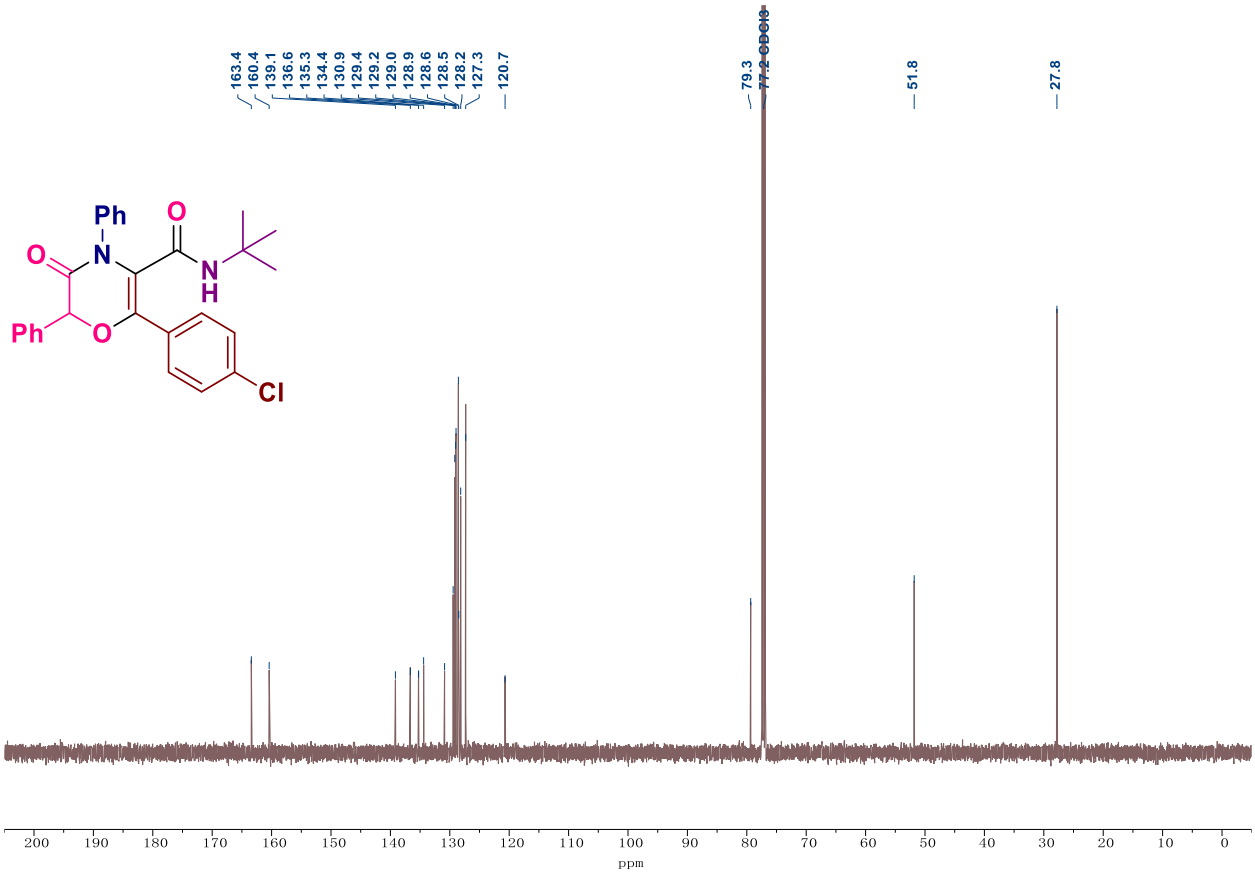
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **28r**



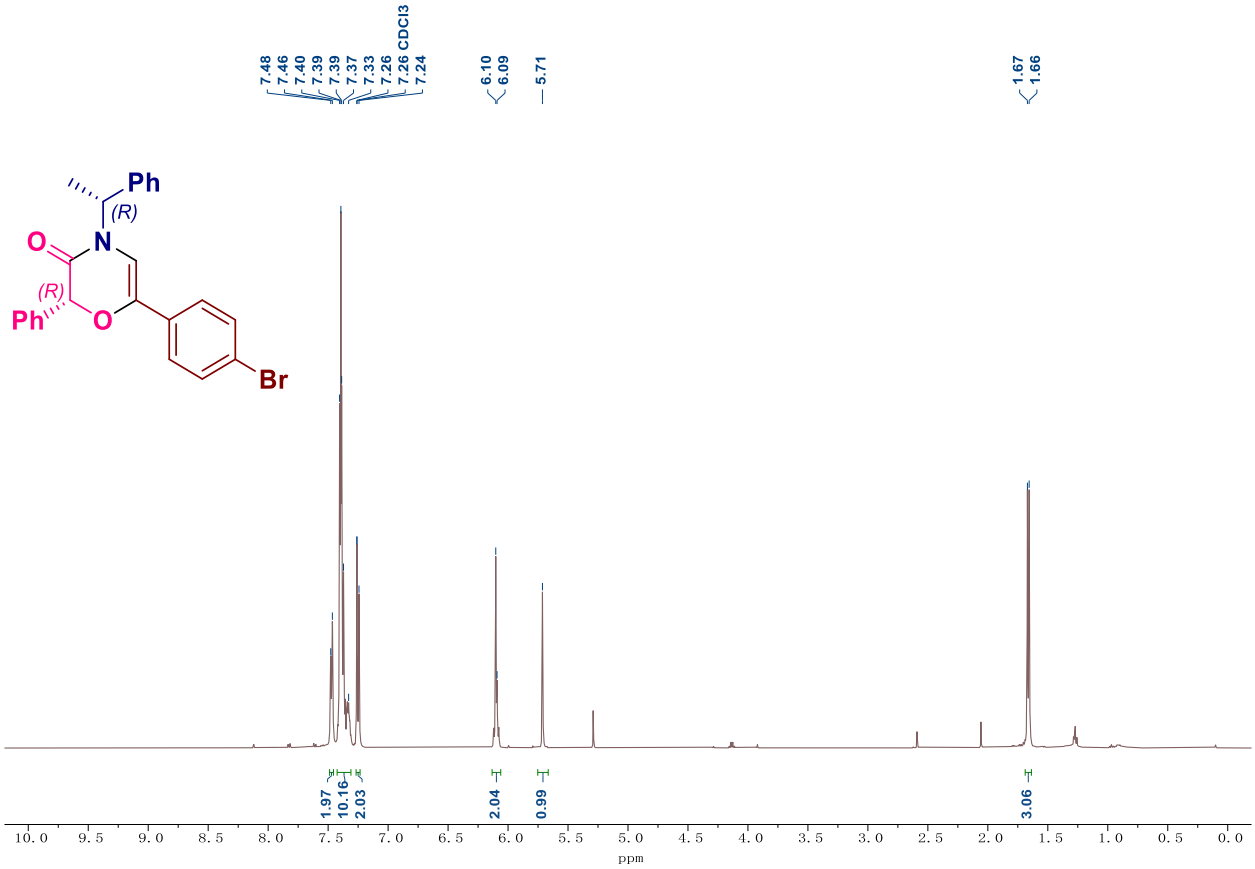


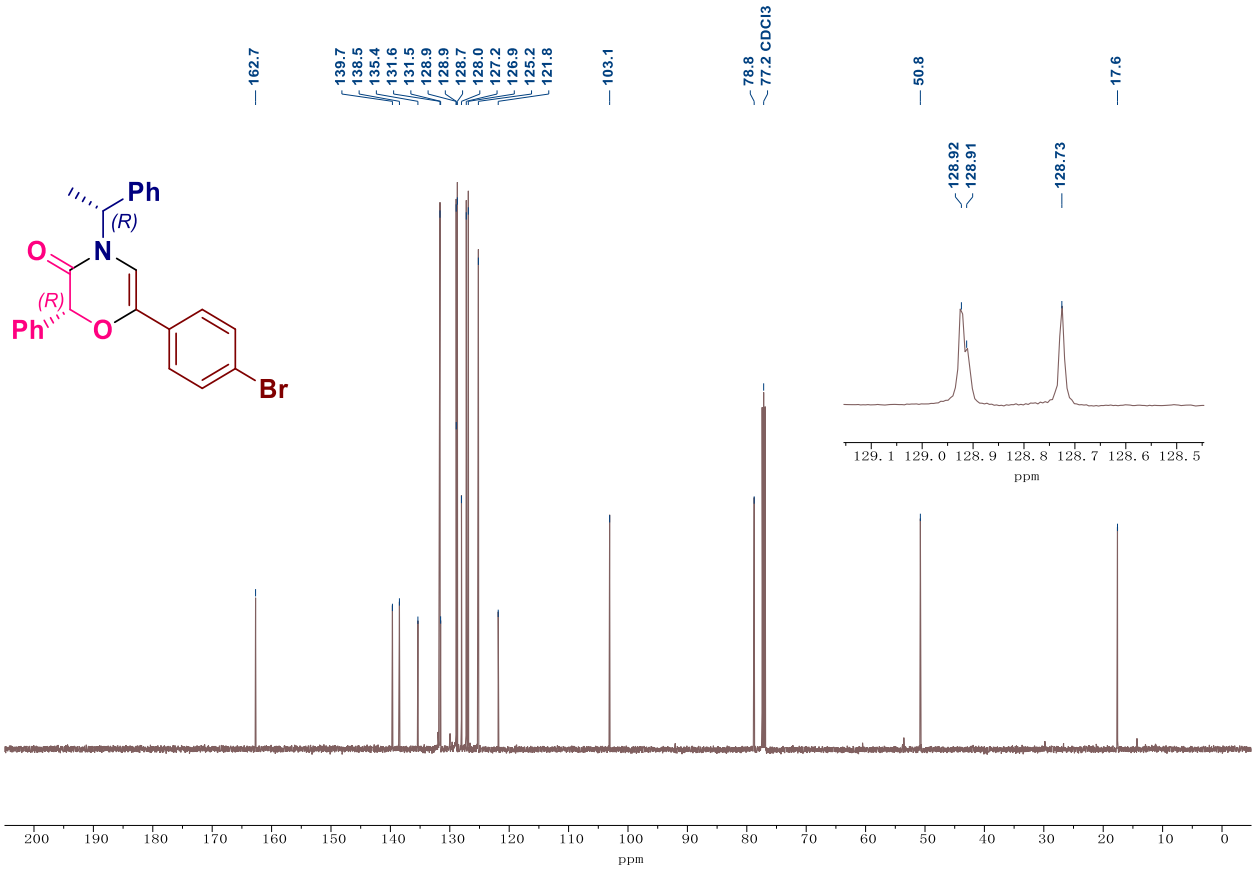
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **29**



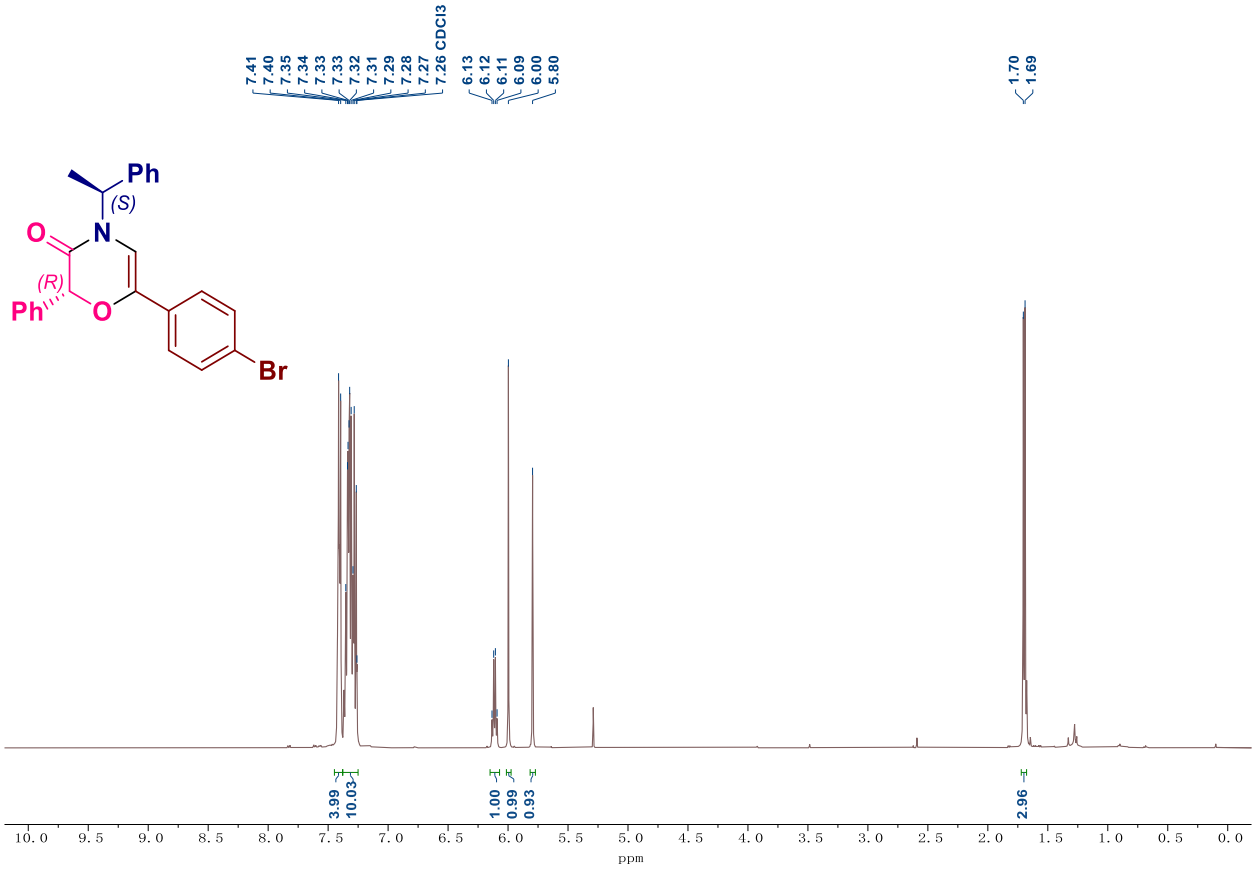


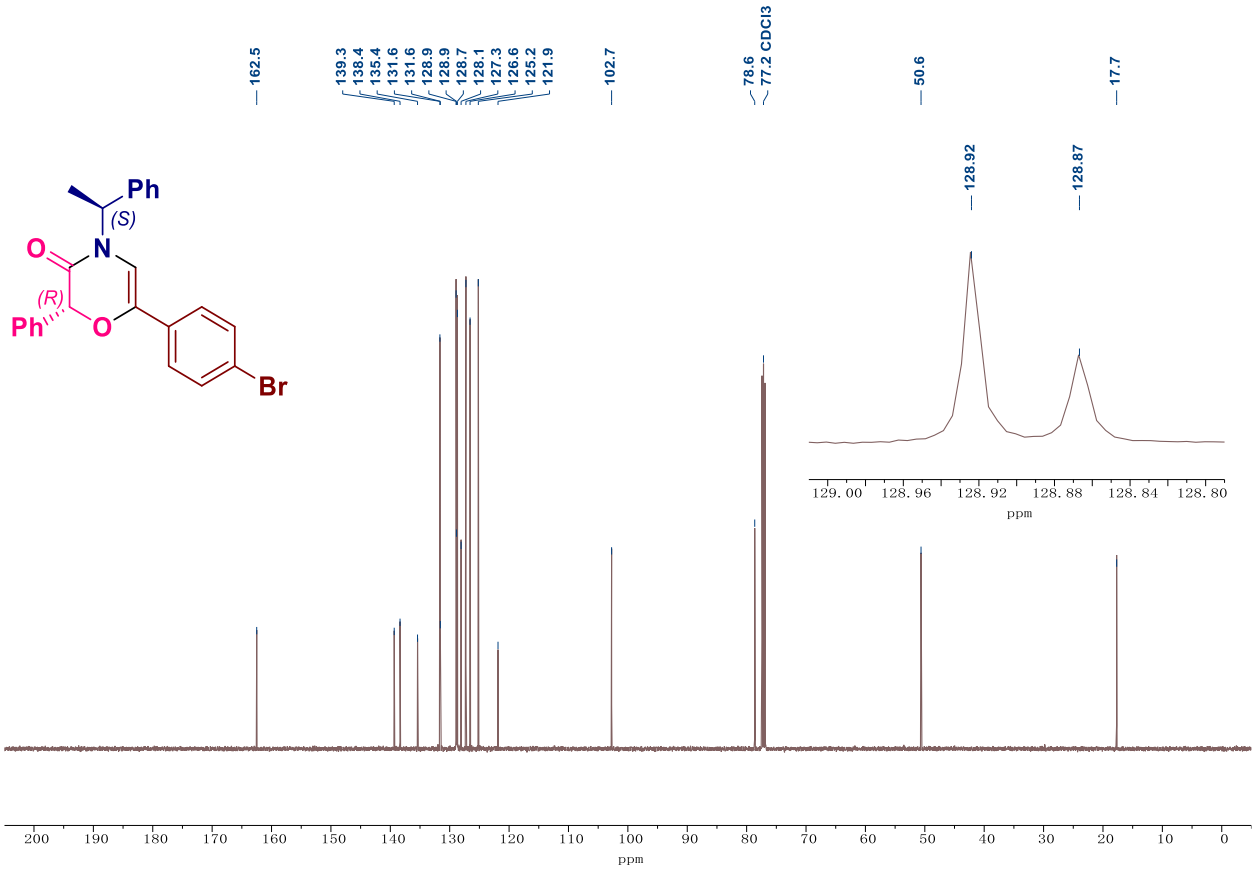
Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **(*R*,*R*)-28s**



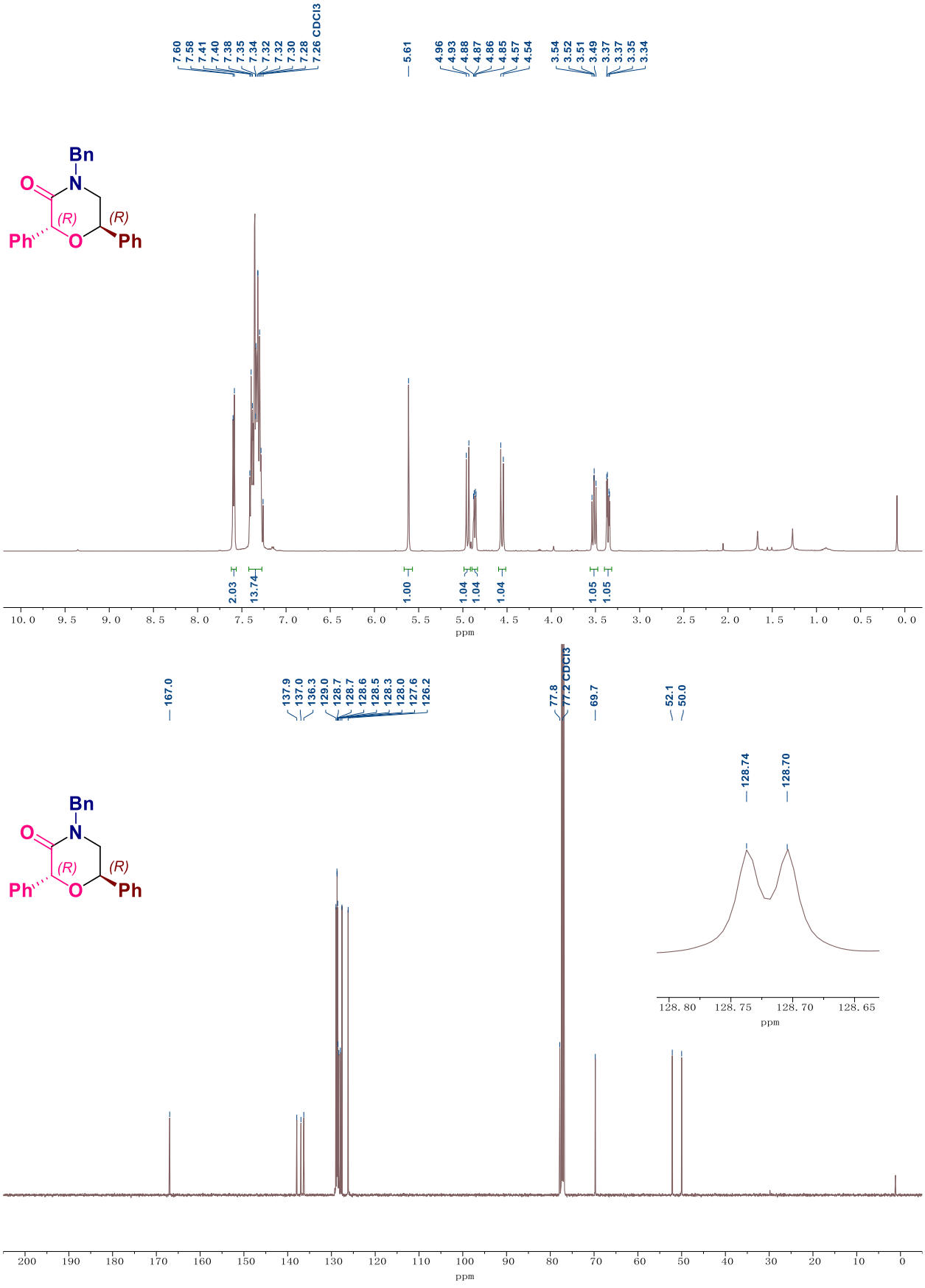


Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **(*R*,*S*)-28s**

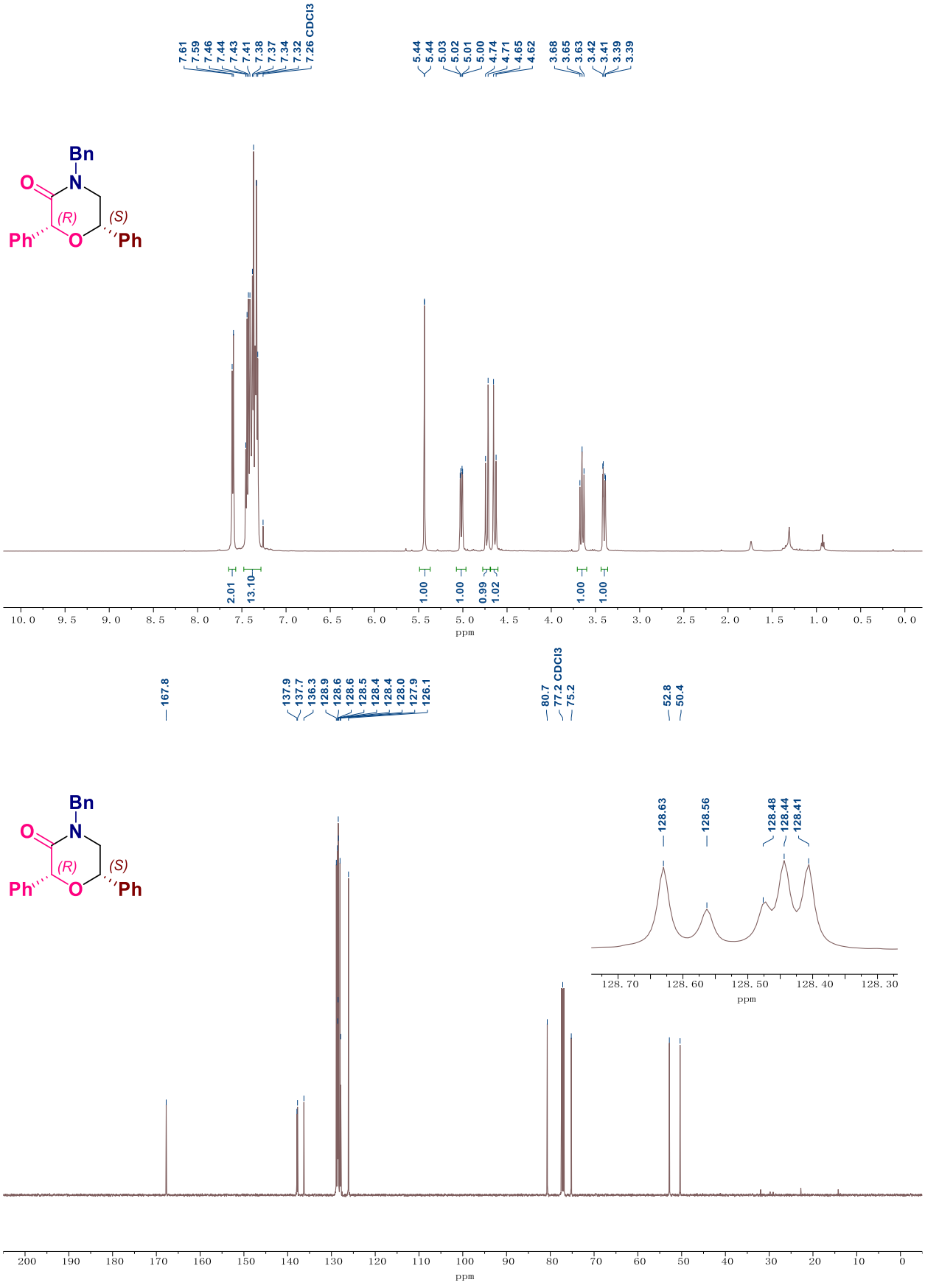




Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **(*R*,*R*)-30**



Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **(*R*,*S*)-30**



Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of compound **(*R*,*S*)-31**