Supporting Information

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Melting points, measured in capillary tubes on a Büchi B-540 apparatus, are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer.

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on Bruker spectrometers: Avance 300 MHz (QNP - ^{13}C, ^{31}P, ^{19}F - probe or Dual ^{13}C probe) and Avance 500 MHz (BB0 - ATM probe or BBI - ATM probe). Chemical shifts (δ) are reported in parts per million (ppm) with reference to $CDCl_3$ (^{1}H: 7.26; ^{13}C: 77.13) or CD_2Cl_2 (^{1}H: 5.32; ^{13}C: 53.80). The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, quint.: quintuplet, sept.: septuplet, m: multiplet, br: broad. Coupling constants (*J*) are reported in Hertz (Hz). The multiplicity of carbons was given using 2D spectra (HMQC and HMBC). Some quaternary carbons were determined using HMBC couplings.

UPLC-MS analyses were run using a Acquity Waters UPLC equipped with a Waters LCT Premier XE (ESI ionization) and a Waters Acquity PDA detector, using a column BEH C_{18} 1.7 µm, 2.1 mm × 50 mm. Gradients were run using water and acetonitrile (1:1) with 0.1% of acetic acid. Temperature: 40 °C. UV detection from 210 to 410 nm. ESI+ detection in the 80−1500 *m/z* range.

Thin-layer chromatography was performed on silica gel 60 F_{254} on aluminum plates (Merck) and visualized under a UVP Mineralight UVLS-28 lamp (254 nm). Flash chromatography was performed on silica gel 60 (230-400 mesh).

All reagents were obtained from commercial suppliers (Sigma-Aldrich and Acros Organics) and were used as received.

General procedure A for Passerini-Smiles reaction

Aldehydes

To 1.0 equiv. of phenol were added successively 1.0 equiv. of DABCO, 2.0 equiv. of aldehyde and 1.0 equiv. of isocyanide. The resulting mixture was stirred neat at 55 °C during 12h. The crude product was purified by flash chromatography on silica gel.

Ketones

To 1.0 equiv. of phenol were added successively 1.0 equiv. of ketone and 1.0 equiv. of isocyanide under inert atmosphere. The resulting mixture was stirred neat at 55 °C during 3 days. The crude product was purified by flash chromatography on silica gel.

General procedure B for Smiles cyclization

To a 0.2 M solution of Passerini-Smiles adduct in DMF were added 1.5 equiv. (aldehyde) or 2.0 equiv. (ketone) of potassium *tert*-butoxide. The resulting mixture was stirred for 1 hour at 100 °C. The resulting mixture was diluted with HCl 1M. The aqueous layer was extracted three times with CH_2Cl_2. Organic layers were combined, washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel.

General procedure C for Passerini-Smiles-Smiles reaction (one-pot)

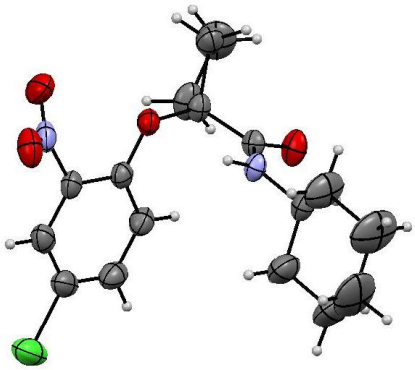
To 1.0 equiv. of phenol were added successively 1.0 equiv. of DABCO (only for aldehydes), 2.0 equiv. of aldehyde (1.0 equiv. of ketone) and 1.0 equiv. of isocyanide under inert atmosphere. The resulting mixture was stirred neat at 55 °C during 12 h for aldehyde (3 days for ketone). Then, DMF (c = 0.2 M) and 1.5 equiv. (aldehyde) or 2.0 equiv. (ketone) of potassium *tert*-butoxide were added. The resulting mixture was stirred for 1 hour at 100 °C. The resulting mixture was diluted CH_2Cl_2 then washed with H_2O and HCl 1M. The aqueous layer was extracted three times with CH_2Cl_2. Organic layers were combined, washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel.

***N*-cyclohexyl-3,3,3-trifluoro-2-methyl-2-(2-nitrophenoxy)propanamide (1a)**

Compound **1a** was prepared according to the general procedure A (add 2 equiv. of ketone instead of one). Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 80/20) as eluant gave the desired product (565 mg, **78%**) as an off-white solid. **MP:** 91-92 °C. **^{1}H NMR ($CDCl_3$, 300 MHz):** δ (ppm) 7.81 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.54 (ddd, *J* = 8.3, 7.6, 1.7 Hz, 1H), 7.28 (ddd, *J* = 7.6, 8.1, 1.1 Hz, 1H), 7.22 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.76 (br d, *J* = 7.7 Hz, 1H), 3.91-3.75 (m, 1H), 1.97-1.83 (m, 2H), 1.77-1.55 (m, 3H), 1.66 (s, 3H), 1.45-1.28 (m, 2H), 1.28-1.09 (m, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 164.0, 146.1, 144.0, 133.6, 125.5, 125.0, 123.3 (q, $J_{C\text{-}F}$ = 287.6 Hz), 122.9, 84.2 (q, $J_{C\text{-}F}$ = 28.8 Hz), 49.1, 32.6, 32.5, 25.5, 24.8, 15.4. **^{19}F NMR ($CDCl_3$, 282 MHz):** δ (ppm) -78.0. **IR (Neat):** (cm^{-1}) 3307, 2940, 2859, 1664, 1605, 1536, 1481, 1449, 1379, 1360, 1295, 1267, 1240, 1198, 1178, 1134, 1106. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{16}H_{19}F_3N_2O_4$ 361.1375, found 361.1365.

1-(4-chloro-2-nitrophenoxy)-N-cyclohexylcyclobutanecarboxamide (1b)

Compound **1b** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 100/0 to 90/10) as eluant gave the desired product (350 mg, **50%**) as a yellow solid. **MP:** 127-128 °C. **^{1}H NMR ($CDCl_3$, 300 MHz):** δ (ppm) 7.78 (d, *J* = 2.7 Hz, 1H), 7.37 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.67 (d, *J* = 9.0 Hz, 1H), 6.16 (br d, *J* = 8.4 Hz, 1H), 3.81-3.62 (m, 1H), 2.83-2.71 (m, 2H), 2.48-2.33 (m, 2H), 2.08-1.86 (m, 2H), 1.76-1.64 (m, 2H), 1.64-1.47 (m, 3H), 1.38-1.19 (m, 2H), 1.19-0.90 (m, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 170.2, 147.3, 140.8, 133.7, 126.6, 125.5, 117.8, 83.3, 48.2, 32.7, 32.0, 25.4, 24.6, 13.8. **IR (Neat):** (cm^{-1}) 3264, 2938, 2852, 1640, 1606, 1533, 1481, 1359, 1281, 1255, 1226, 1160, 1129, 1077. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{17}H_{21}ClN_2O_4$ 353.1246, found 353.1244.



***N*-(4-methoxybenzyl)-1-(2-nitrophenoxy)cyclobutanecarboxamide (1c)**

Compound **1c** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 80/20) as eluant gave the desired product (223 mg, **63%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.75 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.39 (td, *J* = 7.9, 1.7 Hz, 1H), 7.05 (td, *J* = 7.9, 1.3 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.75-6.68 (m, 3H), 6.64 (br t, *J* = 5.9 Hz, 1H), 4.33 (d, *J* = 5.9 Hz, 1H), 3.76 (s, 3H), 2.86-2.77 (m, 2H), 2.51-2.40 (m, 2H), 2.10-1.91 (m, 2H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 171.5, 158.9, 148.5, 140.6, 133.9, 130.0, 128.7, 125.6, 121.5, 116.7, 114.0, 82.9, 55.3, 42.8, 32.1, 13.8. **IR (Neat):** (cm^{-1})

3328, 2947, 2836, 1664, 1605, 1584, 1510, 1479, 1350, 1303, 1275, 1243, 1174, 1154, 1128, 1078, 1032. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{19}H_{20}N_2O_5$ 357.1450, found 357.1447.

1-(4-bromo-2-nitrophenoxy)-*N*-(3,4-dimethoxyphenethyl)cyclobutanecarboxamide (1d)

Compound **1d** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 70/30) as eluant gave the desired product (277 mg, **58%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.89 (d, *J* = 2.4 Hz, 1H), 7.44 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.66 (d, *J* = 8.9 Hz, 1H), 6.59 (d, *J* = 1.8 Hz, 1H), 6.50-6.42 (d, *J* = 8.9 Hz, 2H), 6.23 (br t, *J* = 5.6 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.50 (q, *J* = 6.5 Hz, 2H), 2.77-2.69 (m, 2H), 2.66 (t, *J* = 6.9 Hz, 2H), 2.41-2.32 (m, 2H), 2.05-1.88 (m, 2H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 171.3, 149.0, 147.7, 147.5, 140.7, 136.5, 130.4, 128.4, 120.4, 117.9, 113.1, 111.4, 111.1, 83.1, 55.9, 55.8, 40.3, 34.8, 31.9, 13.8. **IR (Neat):** (cm^{-1}) 3358, 2940, 1664, 1602, 1513, 1473, 1417, 1346, 1259, 1235, 1155, 1127, 1103, 1077, 1026. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{21}H_{23}BrN_2O_6$ 479.0818, found 479.0822.

***N*-cyclohexyl-3-methoxy-2-methyl-2-(2-nitrophenoxy)propanamide (1e)**

Compound **1e** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in heptane (from 90/10 to 70/30) as eluant gave the desired product (438 mg, **65%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.84 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.51 (ddd, *J* = 8.5, 7.4, 1.8 Hz, 1H), 7.31 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.32-7.24 (m, 1H), 7.18 (ddd, *J* = 8.1, 7.4, 1.3 Hz, 1H), 3.83-3.71 (m, 1H), 3,71 (d, *J* = 10.8 Hz, 1H), 3.50 (d, *J* = 10.8 Hz, 1H), 3.22 (s, 3H), 1.98-1.87 (m, 2H), 1.78-1.66 (m, 2H), 1.64-1.55 (m, 1H), 1.47 (s, 3H), 1.42-1.10 (m, 5H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 170.1, 148.0, 144.0, 133.6, 125.7, 123.6, 123.5, 86.8, 75.0, 59.2, 48.4, 32.7, 25.5, 24.8, 19.6. **IR (Neat):** (cm^{-1}) 3399, 2930, 2854, 1671, 1602, 1582, 1521, 1478, 1450, 1353, 1239, 1199, 1107. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{17}H_{24}N_2O_5$ 337.1763, found 337.1752.

2-(4-chloro-2-nitrophenoxy)-3-methoxy-2-methyl-*N*-phenethylpropanamide (1f)

Compound **1f** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 80/20) as eluant gave the desired product (466 mg, **59%**) as an orange oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.83 (d, *J* = 2.7 Hz, 1H), 7.43 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.33-7.20 (m, 7H), 3.69 (d, *J* = 10.8 Hz, 1H), 3.67-3.54 (m, 2H), 3.49 (d, *J* = 10.8 Hz), 3.24 (s, 3H), 2.91 (dt, *J* = 15.5, 7.2 Hz, 1H), 2.88 (dt, *J* = 15.5, 7.2 Hz, 1H), 1.45 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 171.0, 146.6, 144.2, 138.8, 133.6, 128.9, 128.6, 126.5, 125.6, 124.8, 87.2, 75.1, 59.3, 41.0, 35.6, 19.7. **IR (Neat):** (cm^{-1}) 3412, 2930, 1670, 1603, 1527, 1497, 1475, 1454, 1353, 1240, 1198, 1150, 1104. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{19}H_{21}ClN_2O_5$ 393.1217, found 393.1206.

***N*-cyclohexyl-2-(2-nitrophenoxy)butanamide (1g)**

Compound **1g** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 60/40) as eluant gave the desired product (269 mg, **88%**) as an off-white solid. **MP:** 107-108 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.91 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54 (ddd, *J* = 7.5, 8.4, 1.7 Hz, 1H), 7.15-7.02 (m, 3H), 4.84 (t,

J = 5.0 Hz, 1H), 3.77 (m, 1H), 2.11-1.99 (m, 2H), 1.98-1.87 (m, 1H), 1.79-1.50 (m, 4H), 1.44-1.04 (m, 5H), 0.98 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 168.8, 150.8, 139.9, 134.9, 126.5, 121.5, 115.1, 80.3, 48.1, 33.1, 32.8, 25.6, 25.4, 24.8, 8.7. **IR (Neat):** (cm^{-1}) 3259, 2934, 2854, 1652, 1608, 1583, 1557, 1520, 1484, 1445, 1349, 1276, 1245, 1233, 1165, 1153, 1089, 1047, 1026. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{16}H_{22}N_2O_4$ 307.1658, found 307.1652.

***N*-cyclohexyl-3,3-dimethyl-2-(2-nitrophenoxy)butanamide (1h)**

Compound **1h** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 80/20) as eluant gave the desired product (283 mg, **85%**) as a white solid. **MP:** 126-127 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.83 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.50 (ddd, *J* = 8.5, 7.5, 1.6 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.07 (ddd, *J* = 8.1, 7.5, 1.0 Hz, 1H), 6.64 (br d, *J* = 8.5 Hz, 1H), 4.46 (s, 1H), 3.73-3.67 (m, 1H), 1.93-1.86 (m, 1H), 1.72-1.63 (m, 1H), 1.54-1.45 (m, 3H), 1.39-1.07 (m, 4H), 1.11 (s, 9H), 0.94-0.84 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 167.4, 150.8 (C_3), 140.1, 134.5, 125.8, 121.4, 114.9, 87.0, 47.8, 34.7, 33.1, 32.5, 26.3, 25.4, 24.7, 24.6. **IR (Neat):** (cm^{-1}) 3259, 2926, 2853, 1646, 1607, 1584, 1568, 1522, 1479, 1449, 1365, 1344, 1309, 1279, 1248, 1197, 1167, 1151, 1099, 1060, 1019. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{18}H_{26}N_2O_4$ 335.1971, found 335.197.

***N*-cyclohexyl-2-(2-nitrophenoxy)-4-phenylbutanamide (1i)**

Compound **1i** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 90/10) as eluant gave the desired product (647 mg, **85%**) as a yellow solid. **MP:** 97-98 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.91 (dd, *J* = 8.1, 1.7 Hz, 1H, 7.50 (ddd, *J* = 8.6, 7.5, 1.7 Hz, 1H, 7.28-7.22 (m, 2H), 7.20-7.14 (m, 3H), 7.13-7.05 (m, 2H), 6.94 (d, *J* = 8.6 Hz, 1H), 4.84 (t, *J* = 5.4 Hz, 1H), 3.83-3.72 (m, 1H), 2.86-2.71 (m, 2H), 2.32 (dt, *J* = 5.4, 7.9 Hz, 2H), 1.97-1.90 (m, 1H), 1.78-1.68 (m, 2H), 1.67-1.58 (m, 2H), 1.43-1.05 (m, 5H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 168.7, 150.4, 140.5, 139.8, 134.7, 128.6, 128.5, 126.2, 121.5, 114.9, 78.6, 48.0, 33.9, 32.9, 32.7, 30.6, 25.4, 24.7, 24.6. **IR (Neat):** (cm^{-1}) 3263, 3028, 2930, 2853, 1651, 1607, 1582, 1518, 1496, 1482, 1449, 1345, 1307, 1271, 1246, 1165, 1152, 1084, 1047, 1028. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{22}H_{26}N_2O_4$ 383.1971, found 383.1972.

***N*-cyclohexyl-3-methyl-2-(2-nitrophenoxy)butanamide (1j)**

Compound **1j** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 80/20) as eluant gave the desired product (291 mg, **91%**) as a yellow solid. **MP:** 121-122 °C. **^{1}H NMR ($CDCl_3$, 300 MHz):** δ (ppm) 7.86 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.52 (ddd, *J* = 8.6, 7.5, 1.8 Hz, 1H), 7.11-7.04 (m, 2H), 6.93 (br d, *J* = 8.2 Hz, 1H), 4.68 (d, *J* = 3.8 Hz, 1H), 3.83-3.68 (m, 1H), 2.36 (sept. d, *J* = 6.9, 3.8 Hz, 1H), 1.98-1.87 (m, 1H), 1.76-1.50 (m, 5H), 1.43-0.90 (m, 4H), 1.06 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 168.4, 151.0, 140.0, 134.6, 126.0, 121.4, 115.0, 84.0, 47.9, 33.0, 32.6, 31.5, 25.4, 24.7, 24.6, 18.8, 17.0. **IR (Neat):** (cm^{-1}) 3261, 3080, 2937, 2856, 1649, 1607, 1584, 1557, 1521, 1484, 1449, 1388, 1351, 1309, 1276, 1259, 1248, 1233, 1165, 1154, 1091, 1048, 1036. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{17}H_{24}N_2O_4$ 321.1814, found 321.1812.

***N*-(tert-butyl)-2-(4-chloro-2-nitrophenoxy)butanamide (1k)**

Compound **1k** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 80/20) as eluant gave the desired product (500 mg, **79%**) as an off-white solid. **MP:** 107-108 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.92 (d, *J* = 2.5 Hz, 1H), 7.51 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.02 (d, *J* = 9.1 Hz, 1H), 6.88 (br s, 1H), 4.70 (t, *J* = 4.8 Hz, 1H), 2.12-1.93 (m, 2H), 1.36 (s, 9H), 0.97 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 168.4, 149.3, 139.8, 134.6, 126.4, 126.2, 116.3, 80.8, 51.5, 28.7, 25.1, 8.4. **IR (Neat):** (cm^{-1}) 3308, 2973, 1655, 1606, 1555, 1527, 1481, 1461, 1393, 1349, 1270, 1249, 1221, 1163, 1120, 1107, 1057. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{14}H_{19}ClN_2O_4$ 315.1112, found 315.1106.

2-(4-cyano-2-nitrophenoxy)-N-(4-methoxybenzyl)butanamide (1l)

Compound **1l** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 60/40) as eluant gave the desired product (226 mg, **61%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 300 MHz):** δ (ppm) 8.17 (d, *J* = 2.1 Hz, 1H), 7.80 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.19-7.00 (m, 3H), 6.81 (m, 2H), 4.92 (t, *J* = 5.2 Hz, 1H), 4.40 (d, *J* = 5.9 Hz, 2H), 3.78 (s, 3H), 2.18-2.00 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 168.6, 159.2, 153.6, 139.8, 138.1, 130.3, 129.6, 129.1, 116.4, 116.1, 114.2, 105.7, 81.4, 55.4, 42.9, 25.4, 8.8. **IR (Neat):** (cm^{-1}) 3262, 3073, 2973, 2938, 2234, 1647, 1615, 1533, 1514, 1496, 1460, 1441, 1357, 1283, 1250, 1175, 1136, 1103, 1087, 1061, 1028. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{19}H_{19}N_3O_5$ 370.1403, found 370.1404.

***N*-(4-chlorobenzyl)-4-methyl-2-(4-methyl-2-nitrophenoxy)pentanamide (1m)**

Compound **1m** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 99/1 to 95/5) as eluant gave the desired product (291 mg, **72%**) as a yellow solid. **MP:** 102-103 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.60 (d, *J* = 2.2 Hz, 1H), 7.45 (br t, *J* = 6.7 Hz, 1H), 7.31 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 1H), 4.87 (dd, *J* = 8.1, 4.0 Hz, 1H), 4.43 (dd, *J* = 14.9, 6.4 Hz, 1H), 4.34 (dd, *J* = 14.9, 6.4 Hz, 1H), 2.35 (s, 3H), 1.94-1.77 (m, 3H), 0.96 (d, *J* = 6.2 Hz, 3H), 0.93 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 171.0, 148.3, 139.7, 136.5, 135.2, 133.3, 131.9, 129.0, 128.8, 126.2, 114.7, 78.7, 42.5, 41.7, 24.7, 23.2, 22.1, 20.3. **IR (Neat):** (cm^{-1}) 3262, 3062, 2956, 2870, 1651, 1566, 1528, 1490, 1467, 1350, 1282, 1257, 1163, 1088, 1014. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{20}H_{23}ClN_2O_4$ 391.1425, found 391.1410.

***N*-(3,4-dimethoxyphenethyl)-4,8-dimethyl-2-(2-nitro-4-(trifluoromethyl)phenoxy)non-7-enamide (1n)**

Compound **1n** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 90/10) as eluant gave the desired product (908 mg, **82%**) as a 1:1 mixture of unseparable diastereomers (yellow oil). **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 8.12 (d, *J* = 2.0 Hz, 0.5H), 8.11 (d, *J* = 2.0 Hz, 0.5H), 7.75 (dd, *J* = 8.4, 2.0 Hz, 0.5H), 7.74 (dd, *J* = 8.4, 2.0 Hz, 0.5H), 7.11 (d, *J* = 8.4 Hz, 0.5H), 7.10 (d, *J* = 8.4 Hz, 0.5H), 6.78 (br t, *J* = 5.7 Hz, 0.5H), 6.78 (br t, *J* = 5.7 Hz, 0.5H), 6.67 (d, *J* = 8.0 Hz, 0.5H), 6.66 (d, *J* = 8.0 Hz,

0.5H), 6.64 (d, *J* = 1.9 Hz, 0.5H), 6.63 (d, *J* = 1.9 Hz, 0.5H), 6.56 (dd, *J* = 8.0, 2.0 Hz, 0.5H), 6.54 (dd, *J* = 8.0, 2.0 Hz, 0.5H), 5.05 (t, *J* = 7.1 Hz, 0.5H), 4.99 (t, *J* = 7.1 Hz, 0.5H), 4.88-4.82 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.62-3.45 (m, 2H), 2.73 (br t, *J* = 6.6 Hz, 2H), 2.05-1.57 (m, 5H), 1.66 (s, 1.5H), 1.61 (s, 1.5H), 1.58 (s, 1.5H), 1.54 (s, 1.5H), 1.39-1.11 (m, 2H), 0.94 (d, *J* = 6.5 Hz, 1.5H), 0.89 (d, *J* = 6.5 Hz, 1.5H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 170.0, 169.9, 152.9, 152.8, 149.1, 147.8, 139.5, 139.4, 131.8, 131.7, 131.4 (q, J_{C-F} = 3.3 Hz), 130.6, 130.5, 124.5, 124.4, 124.2, 124.1, 123.7 (q, J_{C-F} = 3.9 Hz), 122.9 (q, J_{C-F} = 272.2 Hz), 120.6, 115.2, 115.1, 111.8, 111.7, 111.3, 111.2, 79.3, 79.2, 55.9, 55.8, 40.3, 40.2, 40.0, 39.9, 37.4, 36.4, 35.0, 34.9, 29.0, 28.8, 25.7, 25.6, 25.3, 25.1, 19.9, 19.1, 17.7, 17.6. **^{19}F NMR ($CDCl_3$, 282 MHz):** δ (ppm) -62.2. **IR (Neat):** (cm^{-1}) 3393, 2932, 1671, 1627, 1590, 1539, 1515, 1453, 1419, 1357, 1324, 1261, 1236, 1157, 1128, 1093, 1027. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{28}H_{35}F_3N_2O_6$ 553.2525, found 553.2526.

N-(*tert*-butyl)-2-(4-chloro-2-nitrophenoxy)-3-methylbutanamide (1o)

Compound **1o** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 90/10) as eluant gave the desired product (224 mg, **68%**) as an off-white solid. **MP:** 111-112 °C. **^{1}H NMR ($CDCl_3$, 300 MHz):** δ (ppm) 7.87 (d, *J* = 2.7 Hz, 1H), 7.50 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 1H), 6.68 (br s, 1H), 4.51 (d, *J* = 4.1 Hz, 1H), 2.32 (sept. d, *J* = 6.9, 4.1 Hz, 1H), 1.31 (s, 9H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 168.2, 149.7, 140.0, 134.4, 126.5, 125.9, 116.2, 84.7, 51.5, 31.5, 28.6, 18.7, 17.2. **IR (Neat):** (cm^{-1}) 3275, 3082, 2972, 1649, 1605, 1531, 1483, 1470, 1391, 1361, 1277, 1250, 1223, 1162, 1119, 1031, 1010. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{15}H_{21}ClN_2O_4$ 329.1268, found 329.1271.

2-(4-chloro-2-nitrophenoxy)-*N*-(4-chlorobenzyl)-3,3-dimethylbutanamide (1p)

Compound **1p** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 90/10) as eluant gave the desired product (352 mg, **86%**) as a yellow solid. **MP:** 130-131 °C. **^{1}H NMR ($CDCl_3$, 300 MHz):** δ (ppm) 7.77 (d, *J* = 2.6 Hz, 1H), 7.44 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.18 (m, 2H), 7.03-6.97 (m, 4H), 4.48 (s, 1H), 4.40 (dd, *J* = 14.6, 6.6 Hz, 1H), 4.30 (dd, *J* = 14.6, 5.6 Hz, 1H), 1.09 (s, 9H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 168.3, 149.4, 140.0, 136.4, 134.4, 133.5, 129.1, 128.8, 126.9, 125.8, 116.2, 87.7, 42.6, 35.0, 26.3. **IR (Neat):** (cm^{-1}) 2959, 2873, 1669, 1610, 1517, 1494, 1480, 1434, 1399, 1348, 1313, 1271, 1248, 1163, 1118, 1090, 1077, 1052, 1001. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{19}H_{20}Cl_2N_2O_4$ 411.0878, found 411.0865.

2-(4-bromo-2-nitrophenoxy)-*N*-(3,4-dimethoxyphenethyl)-3-methylbutanamide (1q)

Compound **1q** was prepared according to the general procedure A. Purification on a column of silica gel with ethyl acetate in petroleum ether (70/30) as eluant gave the desired product (462 mg, **96%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.95 (d, *J* = 2.4 Hz, 1H), 7.57 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.79 (br t, *J* = 5.4 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.63 (d, *J* = 1.6 Hz, 1H), 6.56 (dd, *J* = 8.1, 1.6 Hz, 1H), 4.56 (d, *J* = 4.0 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.60-3.48 (m, 2H), 2.74 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.71 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.34-2.25 (m, 1H), 1.01 (d, *J* = 7.5 Hz, 3H), 0.99 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 169.1, 150.1, 149.1, 147.8, 140.2, 137.3, 130.7, 128.8, 120.6, 116.4, 113.2, 111.7, 111.3, 84.6, 56.0, 55.9, 40.1, 35.0, 31.6,

18.8, 17.0. **IR (Neat):** (cm^{-1}) 3387, 2966, 1666, 1602, 1514, 1465, 1418, 1345, 1261, 1235, 1156, 1140, 1100, 1026, 1000. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{21}H_{25}BrN_2O_6$ 481.0974, found 481.0969.

2-(4-bromo-2-nitrophenoxy)-3,3-dimethyl-*N*-phenethylbutanamide (1r)

Compound **1r** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 90/10) as eluant gave the desired product (338 mg, **78%**) as a yellow solid. **MP:** 62-63 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.89 (d, *J* = 2.5 Hz, 1H), 7.54 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.20-7.12 (m, 3H), 7.01-6.97 (m, 2H), 6.86 (d, *J* = 9.1 Hz, 1H), 6.58-6.50 (m, 1H), 4.35 (s, 1H), 3.62 (dq, *J* = 13.6, 6.7 Hz, 1H), 3.47 (dtd, *J* = 13.6, 6.9, 5.2 Hz, 1H), 2.73 (t, *J* = 6.9 Hz, 2H), 1.03 (s, 9H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 168.2, 149.9, 140.0, 138.0, 137.3, 128.8, 128.6, 128.4, 126.5, 116.1, 113.0, 87.3, 39.8, 35.2, 34.8, 26.2. **IR (Neat):** (cm^{-1}) 2959, 1663, 1603, 1522, 1477, 1396, 1338, 1262, 1246, 1163, 1095, 1048. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{20}H_{23}BrN_2O_4$ 435.0919, found 435.0904.

***N*-(4-methoxybenzyl)-3,3-dimethyl-2-(4-methyl-2-nitrophenoxy)hex-5-enamide (1s)**

Compound **1s** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 80/20) as eluant gave the desired product (344 mg, **83%**) as a yellow solid. **MP:** 64-65 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.56 (d, *J* = 2.3 Hz, 1H), 7.26 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.07 (br t, *J* = 5.8 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 2H), 5.87-5.76 (m, 1H), 5.04 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.96 (dd, *J* = 17.0, 1.4 Hz, 1H), 4.55 (s, 1H), 4.35 (dd, *J* = 14.5, 6.0 Hz, 1H), 4.28 (dd, *J* = 14.5, 6.0 Hz, 1H), 3.75 (s, 3H), 2.33 (s, 3H), 2.26 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.11 (dd, *J* = 13.7, 6.8 Hz, 1H), 1.08 (s, 3H), 1.06 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 168.7, 158.9, 148.5, 139.5, 135.1, 134.1, 131.6, 130.1, 128.9, 126.0, 118.7, 114.7, 114.0, 85.1, 55.3, 43.7, 42.6, 37.8, 23.5, 23.4, 20.3. **IR (Neat):** (cm^{-1}) 3381, 2967, 2932, 2837, 1666, 1613, 1575, 1527, 1512, 1465, 1440, 1390, 1349, 1320, 1301, 1277, 1245, 1174, 1158, 1111, 1086, 1034, 1001. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{23}H_{28}N_2O_5$ 413.2076, found 413.2081.

2-(4-methoxy-2-nitrophenoxy)-3,3-dimethyl-*N*-phenethylbutanamide (1t)

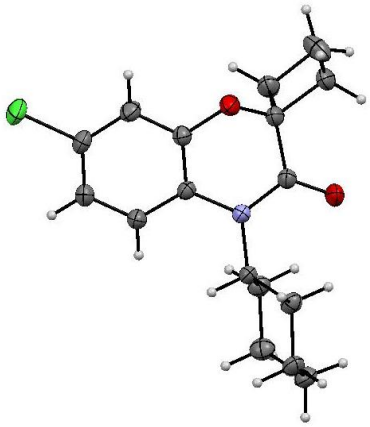
Compound **1t** was prepared according to the general procedure A. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 80/20) as eluant gave the desired product (301 mg, **78%**) as a yellow solid. **MP:** 88-89 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.32 (d, *J* = 3.1 Hz, 1H), 7.20-7.10 (m, 3H), 7.05-6.99 (m, 3H), 6.93 (d, *J* = 9.3 Hz, 1H), 6.75 (br t, *J* = 5.7 Hz, 1H), 4.34 (s, 1H), 3.82 (s, 3H), 3.57 (dq, *J* = 13.5, 6.6 Hz, 1H), 3.47 (ddt, *J* = 13.6, 5.4, 7.2 Hz, 1H), 2.73 (dt, *J* = 16.6, 7.1 Hz, 1H), 2.70 (dt, *J* = 16.6, 7.1 Hz, 1H), 1.04 (s, 9H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 168.9, 153.4, 145.0, 139.5, 138.3, 128.5, 126.5, 121.0, 115.6, 110.5, 87.2, 56.2, 40.0, 35.4, 34.9, 26.3. **IR (Neat):** (cm^{-1}) 3026, 2959, 1660, 1520, 1492, 1442, 1346, 1289, 1277, 1256, 1219, 1164, 1092, 1082, 1051, 1035, 1004. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{21}H_{26}N_2O_5$ 387.1920, found 387.1929.

4-cyclohexyl-2-methyl-2-(trifluoromethyl)-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2a)

Compound **2a** was prepared according to the general procedure B. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 99/1 to 98/2) as eluant gave the desired product (76 mg, **81%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.17-7.12 (m, 1H), 7.08-6.99 (m, 3H), 4.18 (tt, *J* = 12.3, 3.7 Hz, 1H), 2.49-2.32 (m, 2H), 1.94-1.87 (m, 2H), 1.84-1.76 (m, 2H), 1.75-1.68 (m, 1H), 1.70 (s, 3H), 1.44-1.32 (m, 2H), 1.32-1.03 (m, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 162.8, 143.1, 128.6, 124.4, 123.7 (q, J_{C-F} = 288.4 Hz), 123.2, 117.7, 115.6, 79.5 (q, J_{C-F} = 28.1 Hz), 57.9, 29.2, 28.9, 26.5, 26.4, 25.4, 18.3. **^{19}F NMR ($CDCl_3$, 282 MHz):** δ (ppm) -77.2. **IR (Neat):** (cm^{-1}) 2934, 2857, 1685, 1611, 1592, 1498, 1453, 1413, 1379, 1361, 1324, 1299, 1274, 1248, 1191, 1148, 1102, 1044. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{16}H_{18}F_3NO_2$ 314.1368, found 314.1360.

7-chloro-4-cyclohexylspiro[benzo[*b*][1,4]oxazine-2,1'-cyclobutan]-3(4*H*)-one (2b)

Compound **2b** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (98/2) as eluant gave the desired product (45 mg, **91%**) as a yellow solid. **MP:** 77-78 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.04 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.96 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.17 (tt, *J* = 12.5, 3.7 Hz, 1H), 2.60-2.46 (m, 2H), 2.38-2.15 (m, 4H), 2.02-1.82 (m, 4H), 1.80-1.65 (m, 3H), 1.42-1.12 (m, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 168.6, 145.4, 128.9, 128.3, 122.5, 118.7, 116.7, 80.4, 56.8, 30.9, 29.5, 26.5, 25.5, 13.2. **IR (Neat):** (cm^{-1}) 2932, 2855, 1678, 1581, 1491, 1452, 1424, 1405, 1360, 1336, 1270, 1245, 1147, 1118, 1081, 1045. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{17}H_{20}ClNO_2$ 306.1261, found 306.1259.



4-(4-methoxybenzyl)spiro[benzo[*b*][1,4]oxazine-2,1'-cyclobutan]-3(*4H*)-one (2c)

Compound **2c** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluant gave the desired product (79 mg, **86%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.18 (d, *J* = 8.6 Hz, 2H), 7.01 (dd, *J* = 7.7, 1.1 Hz, 1H), 6.95 (td, *J* = 7.9, 1.5 Hz, 1H), 6.92-6.86 (m, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.08 (s, 2H), 3.77 (s, 3H), 2.72-2.64 (m, 2H), 2.39-2.31 (m, 2H), 2.07-1.94 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 167.8, 159.0, 143.7, 129.5, 128.6, 128.0, 123.7, 122.7, 117.9, 115.3, 114.4, 79.7, 55.3, 44.8, 31.5, 13.3. **IR (Neat):** (cm^{-1}) 2954, 2835, 1675, 1609, 1587, 1512, 1498, 1464, 1387, 1331, 1303, 1243,

1175, 1148, 1105, 1032, 1011. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{19}H_{19}NO_3$ 310.1443, found 310.1436.

7-bromo-4-(3,4-dimethoxyphenethyl)spiro[benzo[*b*][1,4]oxazine-2,1'-cyclobutan]-3(*4H*)-one (2d)

Compound **2d** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (80/20) as eluant gave the desired product (111 mg, **86%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.18 (d, *J* = 2.0 Hz, 1H), 7.12 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.75 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.73 (d, *J* = 1.9 Hz, 1H), 4.08 (dd, *J* = 8.8, 6.8 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.87 (dd, *J* = 8.8, 6.8 Hz, 2H), 2.60-2.51 (m, 2H), 2.32-2.22 (m, 2H), 2.04-1.85 (m, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 166.9, 149.1, 148.0, 144.6, 130.6, 128.4, 125.7, 121.3, 120.8, 115.6, 115.5, 112.2, 111.5, 79.9, 56.05, 55.98, 43.4, 33.1, 31.4, 13.2. **IR (Neat):** (cm^{-1}) 2953, 2834, 1677, 1590, 1515, 1491, 1453, 1418, 1386, 1332, 1275, 1259, 1235, 1179, 1140, 1121, 1075, 1027. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{21}H_{22}BrNO_4$ 432.0810, found 432.0815.

4-cyclohexyl-2-(methoxymethyl)-2-methyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2e)

Compound **2e** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (98/2) as eluant gave the desired product (73 mg, **83%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.17-7.10 (m, 1H), 7.05-6.95 (m, 3H), 4.18 (tt, *J* = 12.4, 3.8 Hz, 1H), 3.83 (d, *J* = 10.4 Hz, 1H), 3.60 (d, *J* = 10.4 Hz, 1H), 3.43 (s, 3H), 2.50-2.27 (m, 2H), 1.96-1.66 (m, 5H), 1.49-1.18 (m, 3H), 1,34 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 168.6, 144.3, 129.6, 123.9, 122.3, 118.5, 115.6, 80.9, 75.7, 60.2, 57.2, 29.7, 29.2, 26.7, 26.6, 25.7, 18.9. **IR (Neat):** (cm^{-1}) 2930, 2854, 1674, 1607, 1497, 1452, 1411, 1357, 1327, 1299, 1277, 1248, 1204, 1109, 1045. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{17}H_{23}NO_3$ 290.1756, found 290.1754.

7-chloro-2-(methoxymethyl)-2-methyl-4-phenethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2f)

Compound **2f** was prepared according to the general procedure B. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 95/5 to 90/10) as eluant gave the desired product (77 mg, **74%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.33-7.28 (m, 2H), 7.25-7.21 (m, 3H), 7.00 (d, *J* = 2.3 Hz, 1H), 6.95 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 4.15 (dt, *J* = 13.9, 7.8 Hz, 1H), 4.06 (dt, *J* = 13.9, 7.8 Hz, 1H), 3.82 (d, *J* = 10.4 Hz, 1H), 3.58 (d, *J* = 10.4 Hz, 1H), 3.38 (s, 3H), 2.94 (t, *J* = 7.9 Hz, 2H), 1.40 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 166.3, 144.2, 138.0, 129.0, 128.7, 128.6, 127.1, 126.8, 122.2, 118.1, 114.8, 80.9, 76.0, 60.0, 43.3, 33.3, 19.5. **IR (Neat):** (cm^{-1}) 2932, 1674, 1603, 1587, 1496, 1454, 1425, 1393, 1368, 1326, 1286, 1189, 1154, 1109, 1087, 1030. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{19}H_{20}ClNO_3$ 346.1210, found 346.1206.

4-cyclohexyl-2-ethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2g)

Compound **2g** was prepared according to the general procedure B. Purification on a column of silica gel with petroleum ether/ethyl acetate (98/2) as eluant gave the desired product (62 mg, **80%**) as an orange oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.10-7.04 (m, 1H), 6.97-6.88 (m, 3H), 4.25 (dd, *J* = 8.6, 4.5 Hz, 1H), 4.11 (tt, *J* = 12.3, 3.7 Hz, 1H), 2.38-2.20 (m, 2H), 1.90-1.58 (m, 7H), 1.39-1.10 (m, 3H), 0.98 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 167.9, 145.3, 129.9, 123.7,

122.3, 117.7, 115.9, 79.0, 56.8, 29.5, 29.4, 26.4, 25.4, 23.3, 9.5. **IR (Neat):** (cm^{-1}) 2931, 2854, 1676, 1604, 1589, 1496, 1454, 1411, 1363, 1322, 1298, 1269, 1245, 1211, 1191, 1150, 1118, 1049. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{16}H_{21}NO_2$ 260.1651, found 260.1654.

2-(tert-butyl)-4-cyclohexyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2h)

Compound **2h** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (98/2) as eluant gave the desired product (61 mg, **71%**) as an orange oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.13-7.07 (m, 1H), 6.98-6.92 (m, 3H), 4.24 (tt, *J* = 12.6, 3.9 Hz, 1H), 4.20 (s, 1H), 2.45 (qd, *J* = 12.4, 3.7 Hz, 1H), 2.36 (qd, *J* = 12.4, 3.7 Hz, 1H), 1.94-1.85 (m, 2H), 1.85-1.74 (m, 2H), 1.74-1.67 (m, 1H), 1.46-1.32 (m, 2H), 1.32-1.22 (m, 1H), 0.99 (s, 9H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 166.0, 146.3, 129.6, 123.8, 121.9, 117.1, 115.7, 84.8, 56.8, 36.6, 29.8, 29.1, 26.8, 26.7, 26.5, 25.6. **IR (Neat):** (cm^{-1}) 2931, 2870, 1672, 1605, 1589, 1498, 1476, 1463, 1453, 1410, 1361, 1325, 1296, 1271, 1245, 1216, 1184, 1149, 1123, 1062, 1016. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{18}H_{25}NO_2$ 288.1964, found 288.1959.

4-cyclohexyl-2-phenethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2i)

Compound **2i** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluant gave the desired product (85 mg, **84%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 300 MHz):** δ (ppm) 7.31-7.10 (m, 6H), 7.07-6.95 (m, 3H), 4.35 (dd, *J* = 9.2, 4.3 Hz, 1H), 4.18 (tt, *J* = 12.3, 3.7 Hz, 1H), 2.97-2.73 (m, 2H), 2.44-2.26 (m, 2H), 2.26-1.99 (m, 2H), 1.94-1.82 (m, 2H), 1.82-1.63 (m, 3H), 1.46-1.21 (m, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 167.9, 145.4, 141.1, 130.0, 128.7, 128.5, 126.1, 123.9, 122.6, 117.8, 116.1, 76.9, 57.0, 31.6, 31.2, 29.6, 29.5, 26.5, 25.5. **IR (Neat):** (cm^{-1}) 3027, 2930, 2854, 1675, 1604, 1589, 1495, 1453, 1412, 1359, 1297, 1269, 1245, 1178, 1150, 1122, 1059. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{22}H_{25}NO_2$ 336.1964, found 336.1961.

4-cyclohexyl-2-isopropyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (2j)

Compound **2j** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (98/2) as eluant gave the desired product (73 mg, **89%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.17-7.10 (m, 1H), 7.02-6.94 (m, 3H), 4.20 (tt, *J* = 12.2, 3.8 Hz, 1H), 4.15 (d, *J* = 6.7 Hz, 1H), 2.45-2.32 (m, 2H), 2.21-2.10 (m, 1H), 1.93-1.66 (m, 5H), 1.44-1.22 (m, 3H), 1.04 (d, *J* = 6.8 Hz, 3H) , 0.99 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 167.1, 145.6, 129.7, 123.8, 122.2, 117.7, 115.9, 82.8, 56.8, 29.8, 29.3, 28.9, 26.6, 26.5, 25.5, 18.7, 17.8. **IR (Neat):** (cm^{-1}) 2931, 2854, 1675, 1605, 1496, 1464, 1411, 1361, 1320, 1298, 1262, 1245, 1125, 1042, 1015. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{17}H_{23}NO_2$ 274.1807, found 274.1797.

4-(tert-butyl)-7-chloro-2-ethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2k)

Compound **2k** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (98/2) as eluant gave the desired product (76 mg, **95%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.07 (d, *J* = 8.7 Hz, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.96 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.22 (dd, *J* = 8.2, 4.0 Hz, 1H), 1.91 (dqd, *J* = 14.4, 7.5, 4.2 Hz, 1H), 1.77 (dquint., *J* = 14.4, 7.5 Hz, 1H), 1.62 (s, 9H), 1.04 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR ($CDCl_3$,**

125 MHz): δ (ppm) 172.9, 149.2, 129.4, 128.9, 121.8, 121.7, 118.3, 82.3, 59.1, 29.9, 23.7, 9.5. **IR (Neat):** (cm^{-1}) 2972, 2936, 1683, 1579, 1489, 1418, 1398, 1355, 1337, 1276, 1245, 1202, 1190, 1122, 1096, 1079, 1055, 1017. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{14}H_{18}ClNO_2$ 268.1104, found 268.1098.

2-ethyl-4-(4-methoxybenzyl)-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazine-7-carbonitrile (2l)

Compound **2l** was prepared according to the general procedure B. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 90/10 to 80/20) as eluant gave the desired product (72 mg, **74%**) as a white solid. **MP:** 138-139 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.26-7.24 (m, 1H), 7.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.17 (d, *J* = 15.9 Hz, 1H), 5.02 (d, *J* = 15.9 Hz, 1H), 4.64 (dd, *J* = 8.5, 4.5 Hz, 1H), 3.78 (s, 3H), 2.08-1.97 (m, 1H), 1.92 (dquint., *J* = 14.9, 7.3 Hz, 1H), 1.12 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 166.2, 159.3, 144.3, 133.1, 128.0, 127.2, 127.0, 120.7, 118.3, 115.9, 114.6, 107.1, 78.5, 55.4, 44.8, 24.2, 9.5. **IR (Neat):** (cm^{-1}) 3063, 2964, 2934, 2836, 2226, 1687, 1610, 1587, 1509, 1463, 1446, 1395, 1333, 1292, 1280, 1246, 1190, 1177, 1142, 1118, 1097, 1073, 1047, 1028. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{19}H_{18}N_2O_3$ 323.1396, found 323.1380.

4-(4-chlorobenzyl)-2-isobutyl-7-methyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2m)

Compound **2m** was prepared according to the general procedure B. Purification on a column of silica gel with a gradient of ethyl acetate in petroleum ether (from 98/2 to 95/5) as eluant gave the desired product (69 mg, **67%**) as a yellow solid. **MP:** 77-78 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.28 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.81 (br s, 1H), 6.70 (br d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.16 (d, *J* = 16.2 Hz, 1H), 4.99 (d, *J* = 16.2 Hz, 1H), 4.70 (dd, *J* = 10.2, 3.9 Hz, 1H), 2.26 (s, 3H), 2.03-1.90 (m, 1H), 1.81 (ddd, *J* = 14.4, 10.2, 5.1 Hz, 1H), 1.70 (ddd, *J* = 14.2, 8.9, 3.9 Hz, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 167.0, 143.8, 135.0, 134.3, 133.3, 129.1, 128.1, 126.3, 123.1, 118.3, 115.0, 75.9, 44.6, 38.8, 24.6, 23.3, 21.7, 20.8. **IR (Neat):** (cm^{-1}) 2957, 2870, 1675, 1511, 1490, 1469, 1430, 1397, 1368, 1317, 1294, 1260, 1207, 1156, 1089, 1059, 1030, 1013. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{20}H_{22}ClNO_2$ 344.1417, found 344.1417.

4-(3,4-dimethoxyphenethyl)-2-(2,6-dimethylhept-5-en-1-yl)-7-(trifluoromethyl)-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2n)

Compound **2n** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (90/10) as eluant gave the desired product (108 mg, **71%**) as a 1:1 mixture of unseparable diastereomers (yellow oil). **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.31-7.27 (m, 1H), 7.23 (d, *J* = 2.1 Hz, 0.5H), 7.22 (d, *J* = 2.1 Hz, 0.5H), 7.02 (d, *J* = 8.5 Hz, 0.5H), 7.01 (d, *J* = 8.5 Hz, 0.5H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.75 (br d, *J* = 8.0 Hz, 1H), 6.73-6.70 (s, 1H), 5.09 (t, *J* = 7.0 Hz, 0.5H), 5.05 (t, *J* = 7.0 Hz, 0.5H), 4.67-4.61 (m, 1H), 4.21-4.05 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.88 (br t, *J* = 7.3 Hz, 2H), 2.09-1.87 (m, 2H), 1.84-1.73 (m, 2H), 1.71-1.51 (m, 1H), 1.68 (s, 1.5H), 1.66 (s, 1.5H), 1.60 (s, 1.5H), 1.55 (s, 1.5H), 1.51-1.13 (m, 2H), 0.99 (d, *J* = 6.5 Hz, 1.5H), 0.98 (d, *J* = 6.5 Hz, 1.5H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 166.4, 166.2, 149.1, 148.0, 144.2, 144.0, 131.7, 131.6, 130.3, 126.5 (q, J_{C-F} = 33.0 Hz), 124.5, 124.3, 123.8 (q, J_{C-F} = 268.9 Hz), 120.9, 119.8 (q, J_{C-F} = 3.8 Hz), 115.0 (q, J_{C-F} = 3.4 Hz), 114.6, 112.1, 111.4, 76.0, 75.4, 56.0, 43.2, 43.1, 37.5, 37.3,

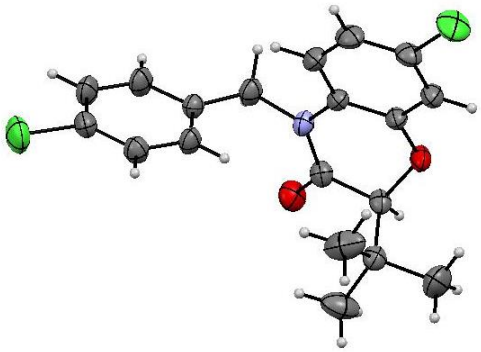
36.9, 36.1, 33.0, 29.2, 28.4, 25.8, 25.7, 25.4, 25.3, 20.0, 18.8, 17.8, 17.7. **^{19}F NMR ($CDCl_3$, 282 MHz):** δ (ppm) -62.1. **IR (Neat):** (cm^{-1}) 2926, 1689, 1622, 1591, 1516, 1443, 1395, 1325, 1305, 1261, 1237, 1142, 1119, 1074, 1028. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{28}H_{34}F_3NO_4$ 506.2518, found 506.2533.

4-(tert-butyl)-7-chloro-2-isopropyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2o)

Compound **2o** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluant gave the desired product (79 mg, **94%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.05 (d, *J* = 8.7 Hz, 1H), 7.03 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.03 (d, *J* = 4.5 Hz, 1H), 2.36-2.25 (m, 1H), 1.62 (s, 9H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 172.6, 149.7, 129.4, 128.9, 121.7, 118.1, 85.5, 59.2, 29.9, 29.7, 19.2, 16.9. **IR (Neat):** (cm^{-1}) 2969, 2936, 1683, 1579, 1489, 1466, 1419, 1398, 1367, 1347, 1324, 1292, 1269, 1247, 1191, 1136, 1079, 1020. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{15}H_{20}ClNO_2$ 282.1261, found 282.1263.

2-(tert-butyl)-7-chloro-4-(4-chlorobenzyl)-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2p)

Compound **2p** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluant gave the desired product (104 mg, **95%**) as an off-white solid. **MP:** 142-143 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.30 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 2.2 Hz, 1H), 6.83 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 5.18 (d, *J* = 16.1 Hz, 1H), 5.00 (d, *J* = 16.1 Hz, 1H), 4.43 (s, 1H), 1.07 (s, 9H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 164.3, 146.1, 134.8, 133.6, 129.2, 129.1, 128.4, 127.3, 122.0, 117.0, 115.7, 84.6, 44.9, 37.2, 26.7. **IR (Neat):** (cm^{-1}) 2966, 1671, 1582, 1494, 1463, 1421, 1391, 1369, 1329, 1277, 1186, 1142, 1085, 1054, 1015. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{19}H_{19}Cl_2NO_2$ 364.0871, found 364.0879.



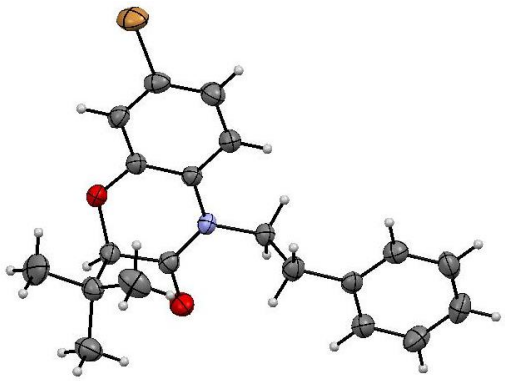
7-bromo-4-(3,4-dimethoxyphenethyl)-2-isopropyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2q)

Compound **2q** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (80/20) as eluant gave the desired product (91 mg, **70%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.15 (d, *J* = 2.1 Hz, 1H), 7.11 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 6.75 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 4.26 (d, *J* = 6.4 Hz, 1H), 4.18 (dt, *J* = 14.1, 7.8 Hz, 1H), 4.03 (dt, *J* = 14.1, 7.8 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.87 (t, *J* = 7.0 Hz, 2H), 2.20 (oct., *J* = 6.8 Hz, 1H), 1.04 (d,

J = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 164.9, 149.2, 148.0, 145.5, 130.5, 127.9, 125.3, 120.9, 120.6, 115.8, 115.7, 112.2, 111.6, 82.0, 56.1, 56.0, 43.0, 33.0, 29.6, 18.7, 17.5. **IR (Neat):** (cm^{-1}) 2963, 2934, 2835, 1678, 1590, 1515, 1493, 1463, 1420, 1388, 1323, 1260, 1235, 1182, 1156, 1140, 1075, 1027. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{21}H_{24}BrNO_4$ 434.0967, found 434.0975.

7-bromo-2-(tert-butyl)-4-phenethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2r)

Compound **2r** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluant gave the desired product (110 mg, **95%**) as an off-white solid. **MP:** 117-118 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.35-7.29 (m, 2H), 7.28-7.21 (m, 3H), 7.14 (d, *J* = 2.1 Hz, 1H), 7.09 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 4.29 (s, 1H), 4.20 (ddd, *J* = 14.0, 9.9, 6.0 Hz, 1H), 4.04 (ddd, *J* = 14.0, 9.9, 6.0 Hz, 1H), 2.97 (ddd, *J* = 13.3, 9.9, 6.0 Hz, 1H), 2.91 (ddd, *J* = 13.3, 9.9, 6.0 Hz, 1H), 1.02 (s, 9H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 163.7, 146.3, 138.0, 128.9, 128.8, 127.7, 126.9, 124.9, 119.9, 115.9, 115.4, 84.4, 43.1, 37.1, 33.5, 26.6. **IR (Neat):** (cm^{-1}) 2965, 1667, 1581, 1494, 1463, 1420, 1395, 1370, 1330, 1276, 1229, 1186, 1141, 1056, 1018. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{20}H_{22}BrNO_2$ 388.0912, found 388.0898.



4-(4-methoxybenzyl)-7-methyl-2-(2-methylpent-4-en-2-yl)-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2s)

Compound **2s** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluant gave the desired product (102 mg, **93%**) as a yellow oil. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.22 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 1.8 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.66 (dd, *J* = 8.4, 1.8 Hz, 1H), 5.93-5.81 (m, 1H), 5.14-5.07 (m, 3H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.45 (s, 1H), 3.77 (s, 3H), 2.32 (dd, *J* = 14.0, 7.7 Hz, 1H), 2.25 (s, 3H), 2.20 (dd, *J* = 14.0, 7.7 Hz, 1H), 1.06 (s, 3H), 1.00 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ (ppm) 164.7, 158.9, 145.3, 134.4, 134.0, 128.8, 128.4, 126.2, 122.5, 118.4, 117.0, 115.0, 114.2, 82.5, 55.4, 44.8, 43.9, 39.8, 24.1, 23.4, 20.8. **IR (Neat):** (cm^{-1}) 2963, 2932, 2836, 1670, 1639, 1613, 1586, 1511, 1440, 1396, 1325, 1289, 1245, 1175, 1143, 1112, 1035. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{23}H_{27}NO_3$ 366.2069, found 366.2069.

2-(tert-butyl)-7-methoxy-4-phenethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2t)

Compound **2t** was prepared according to the general procedure B. Purification on a column of silica gel with ethyl acetate in petroleum ether (95/5) as eluant gave the desired product (98 mg, **96%**) as a

yellow solid. **MP:** 82-83 °C. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ (ppm) 7.32 (t, *J* = 7.4 Hz, 2H), 7.29-7.26 (m, 2H), 7.25-7.21 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.53 (dd, *J* = 9.0, 2.8 Hz, 1H), 4.28 (s, 1H), 4.19 (ddd, *J* = 13.9, 10.0, 6.0 Hz, 1H), 4.04 (ddd, *J* = 13.9, 10.0, 6.0 Hz, 1H), 3.79 (s, 3H), 2.98 (ddd, *J* = 13.4, 10.0, 6.0 Hz, 1H), 2.92 (ddd, *J* = 13.4, 10.0, 6.0 Hz, 1H), 1.02 (s, 9H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ (ppm) 163.6, 156.4, 146.4, 138.4, 128.9, 128.7, 126.7, 122.0, 114.7, 107.1, 103.0, 84.4, 55.7, 43.1, 37.0, 33.6, 26.6. **IR (Neat):** (cm^{-1}) 3029, 2969, 1671, 1624, 1592, 1511, 1476, 1454, 1431, 1397, 1367, 1329, 1306, 1274, 1238, 1194, 1159, 1126, 1072, 1057, 1039, 1022. **HRMS (ESI+, m/z):** $[M+H]^+$ calcd. for $C_{21}H_{25}NO_3$ 340.1913, found 340.1915.

***N*-cyclohexyl-2-(1-(2-nitrophenoxy)propoxy)butanamide (3g)**

This product **3g** was isolated during the first step of the reaction as a mixture of two diastereomers, and one of them cannot be separated from the Passerini-Smiles adduct.

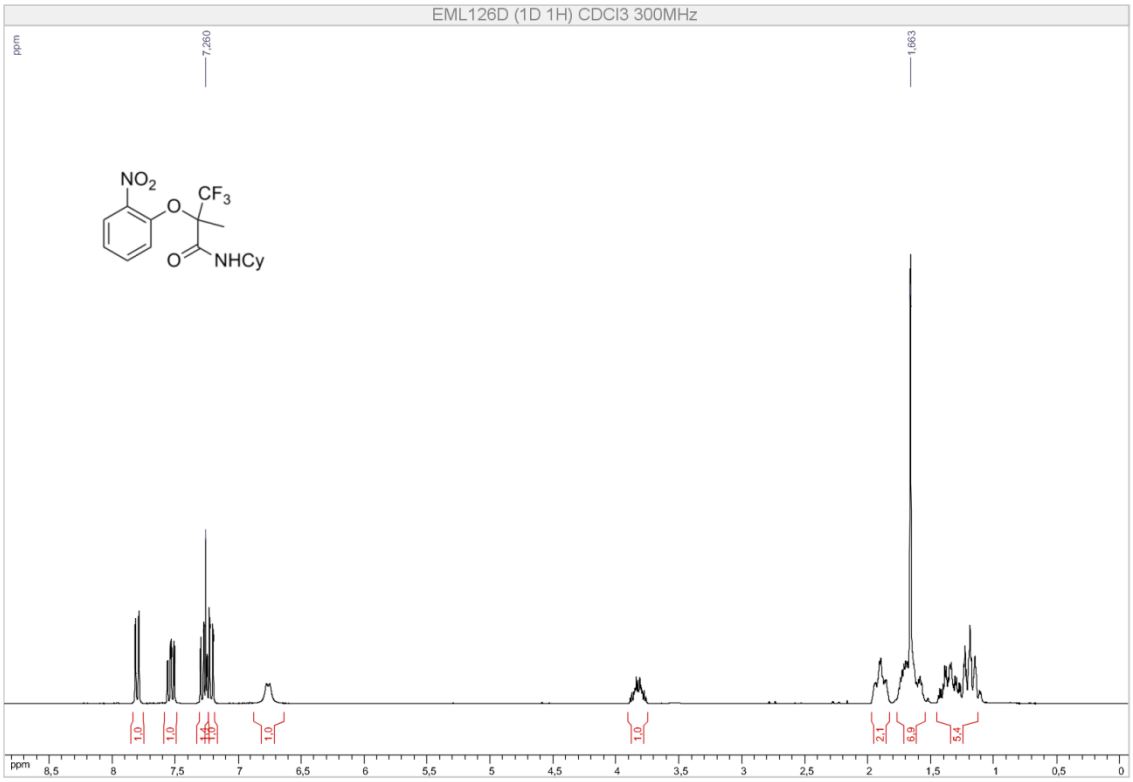
Diastereomer 1 (contaminated by Passerini-Smiles adduct)

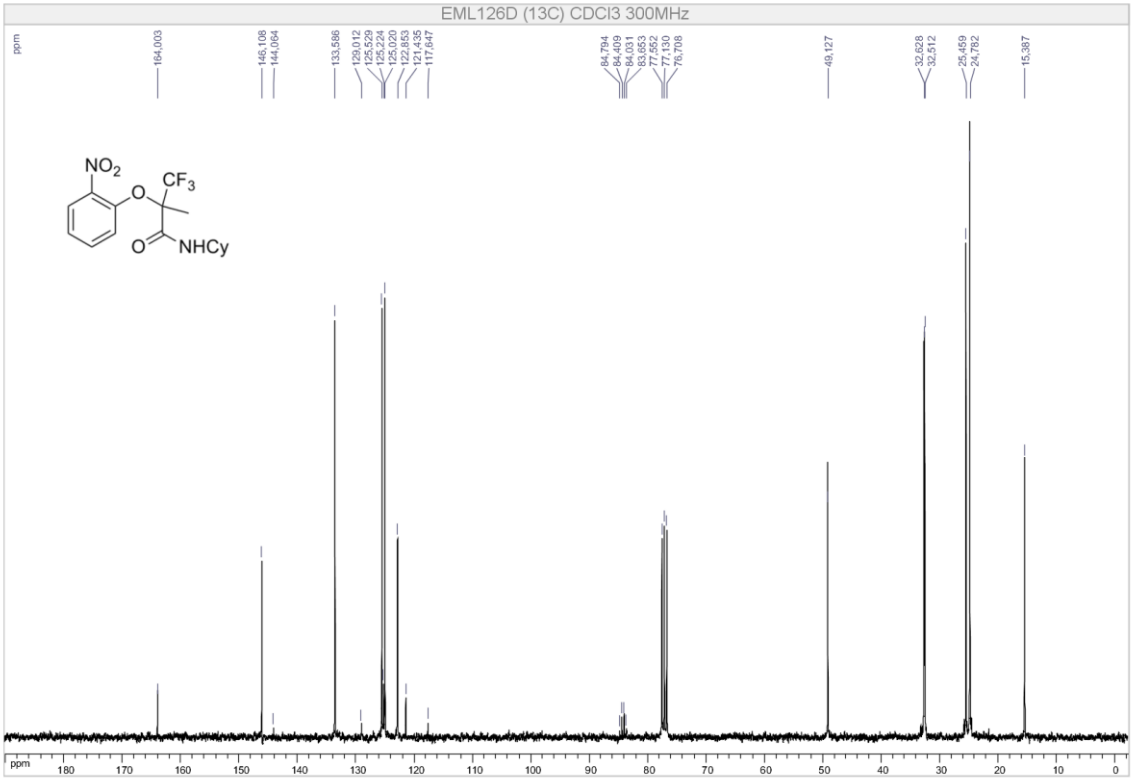
^{1}H NMR (CD_2Cl_2, 500 MHz): δ (ppm) 7.75 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.51 (td, *J* = 8.0, 2.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.12 (br d, *J* = 7.7 Hz, 1H), 5.30 (t, *J* = 5.3 Hz, 1H), 4.06 (t, *J* = 5.5 Hz, 1H), 3.72-3.61 (m, 1H), 1.97-1.62 (m, 8H), 1.61-1.54 (m, 1H), 1.38-1.24 (m, 2H), 1.21-1.01 (m, 3H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (CD_2Cl_2, 125 MHz):** δ (ppm) 170.5, 149.9, 141.9, 134.0, 125.7, 122.1, 117.9, 105.1, 79.1, 48.1, 33.4, 33.3, 27.6, 26.8, 25.9, 25.22, 25.17, 8.9, 8.8.

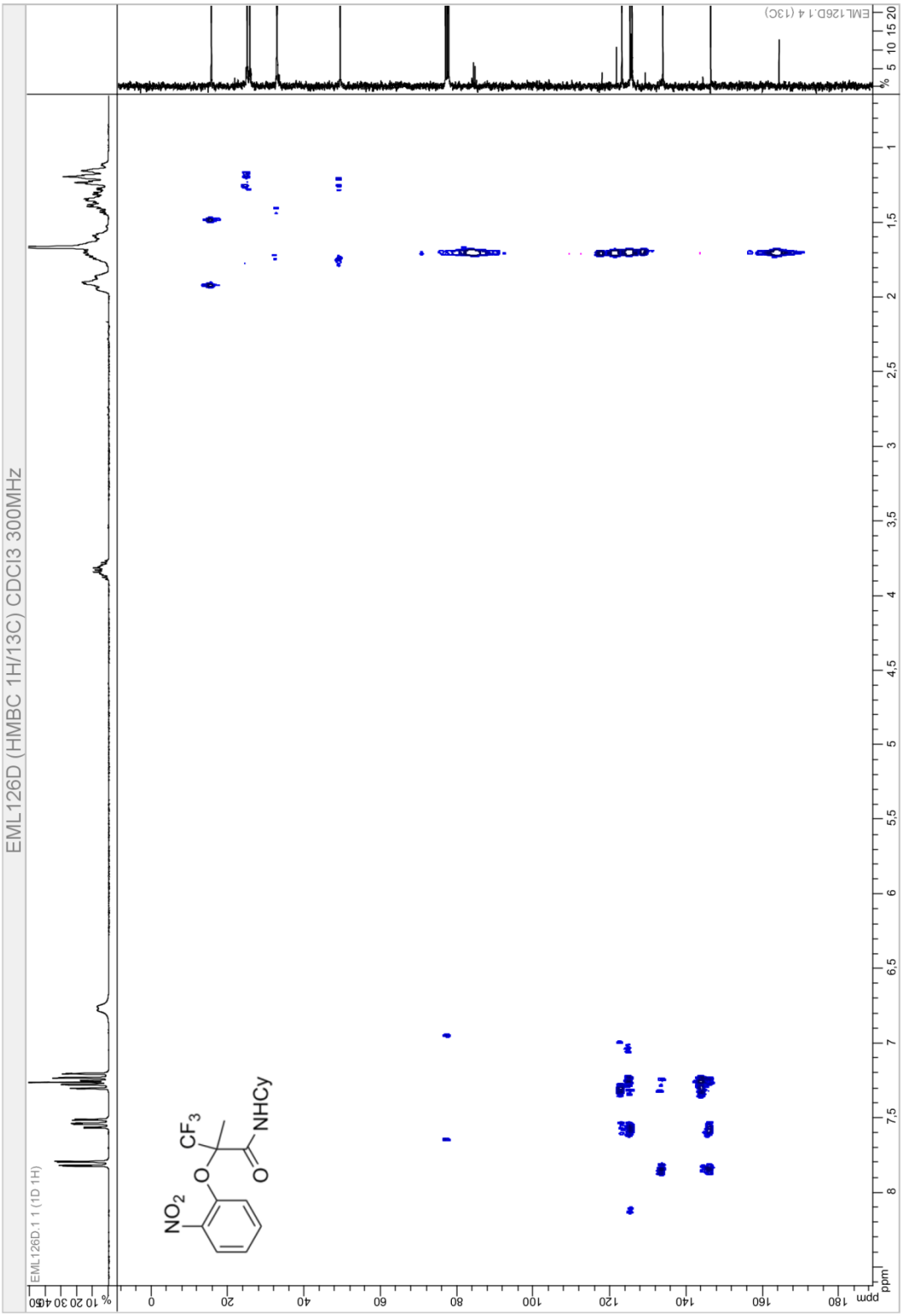
Diastereomer 2

^{1}H NMR (CD_2Cl_2, 500 MHz): δ (ppm) 7.76 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.52 (td, *J* = 8.0, 1.7 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.42 (br d, *J* = 7.1 Hz, 1H), 5.39 (t, *J* = 5.3 Hz, 1H), 4.07 (t, *J* = 5.1 Hz, 1H), 3.72-3.62 (m, 1H), 1.98-1.64 (m, 8H), 1.64-1.58 (m, 1H), 1.39-1.29 (m, 2H), 1.23-1.08 (m, 3H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H) . **^{13}C NMR (CD_2Cl_2, 125 MHz):** δ (ppm) 170.4, 149.9, 141.7, 134.1, 125.7, 122.2, 118.0, 105.5, 79.4, 48.2, 33.4, 33.0, 27.6, 26.1, 26.0, 25.3, 8.7, 8.5. **IR (Neat):** (cm^{-1}) 3301, 2931, 2855, 1654, 1605, 1583, 1524, 1484, 1451, 1350, 1313, 1276, 1249, 1150, 1110, 1087, 1024. **HRMS (ESI-, m/z):** $[M+H]^-$ calcd. for $C_{19}H_{28}N_2O_5$ 409.1975, found 409.1990.

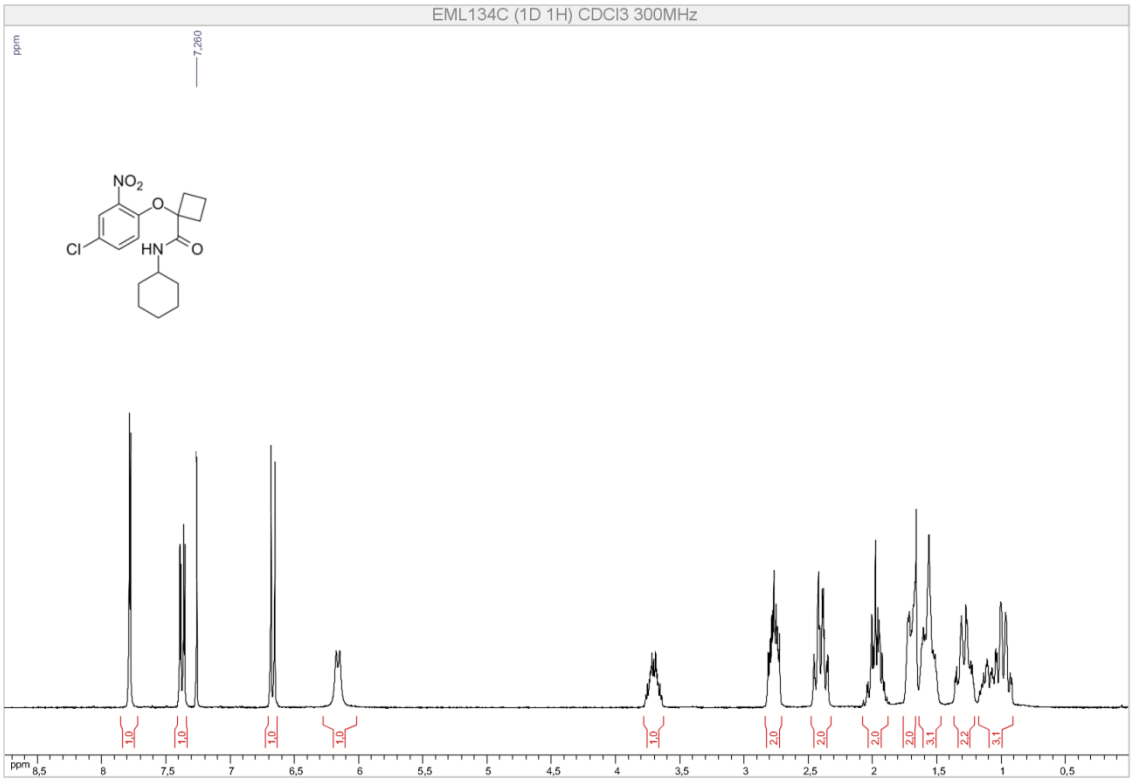
_N_-cyclohexyl-3,3,3-trifluoro-2-methyl-2-(2-nitrophenoxy)propanamide (1a)

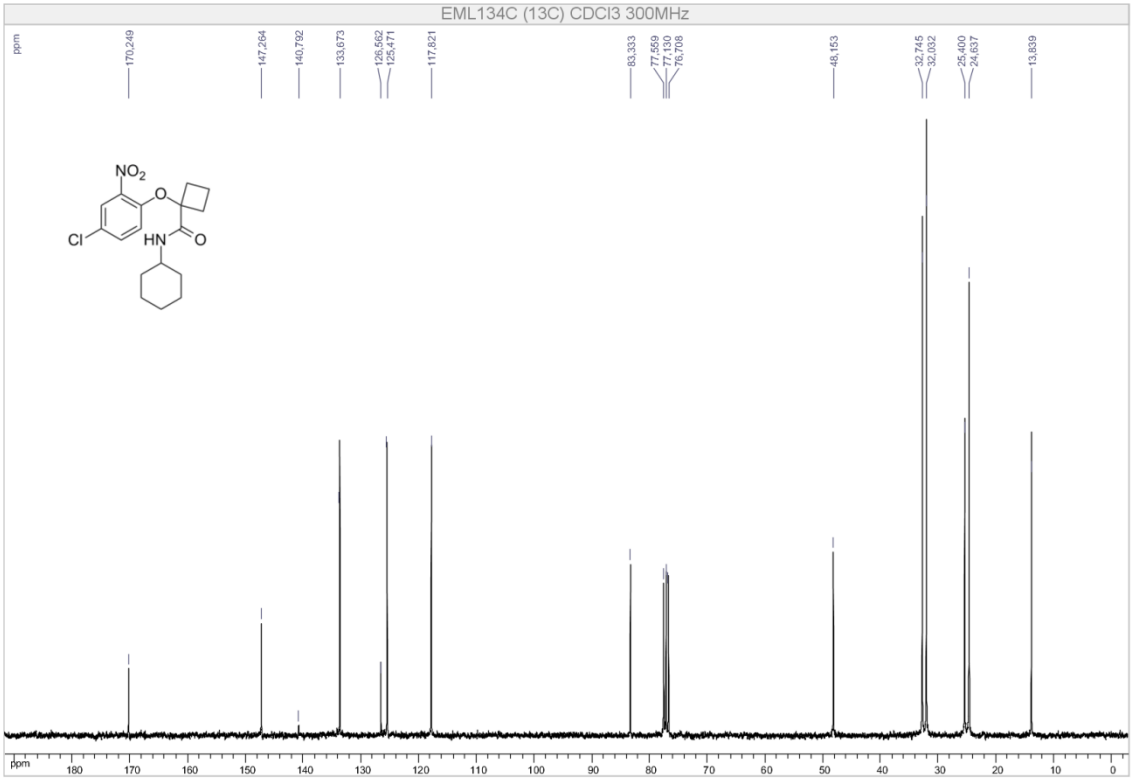




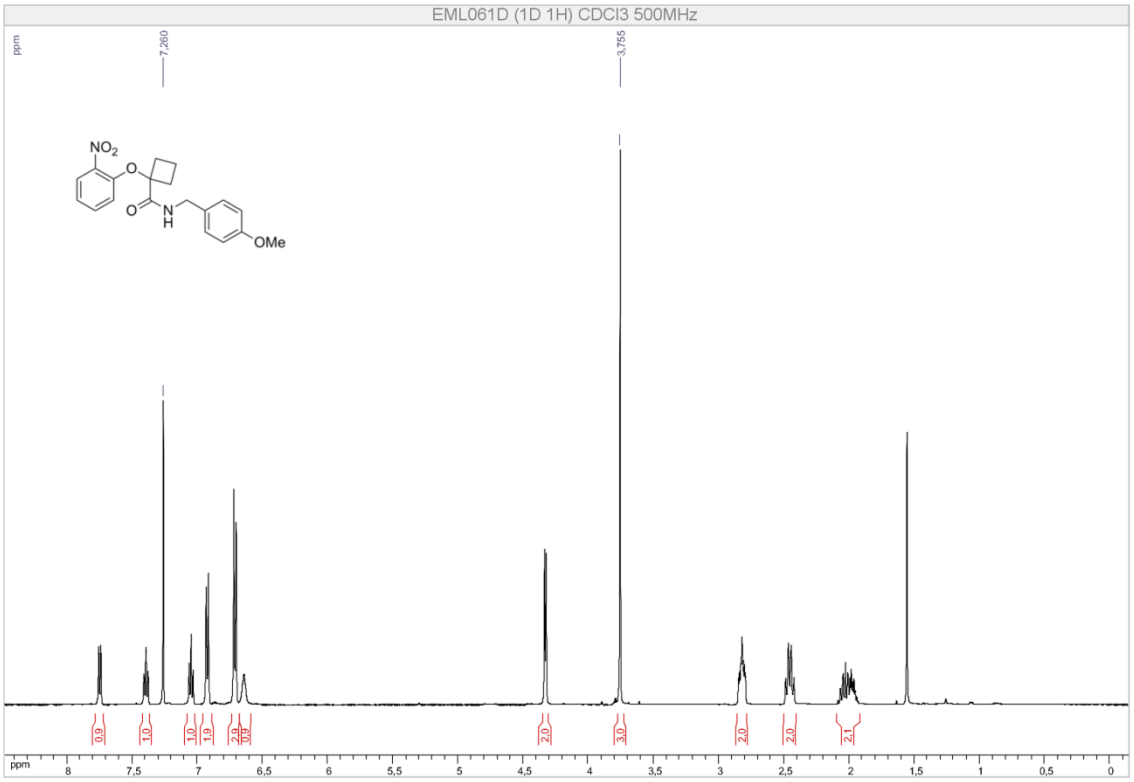

EML126D (HMBC 1H/13C) CDCl3 300MHz
EML126D.1 1 (1D 1H)
EML126D.1 4 (13C)
NHCy
CF3
O
O
NO2
ppm

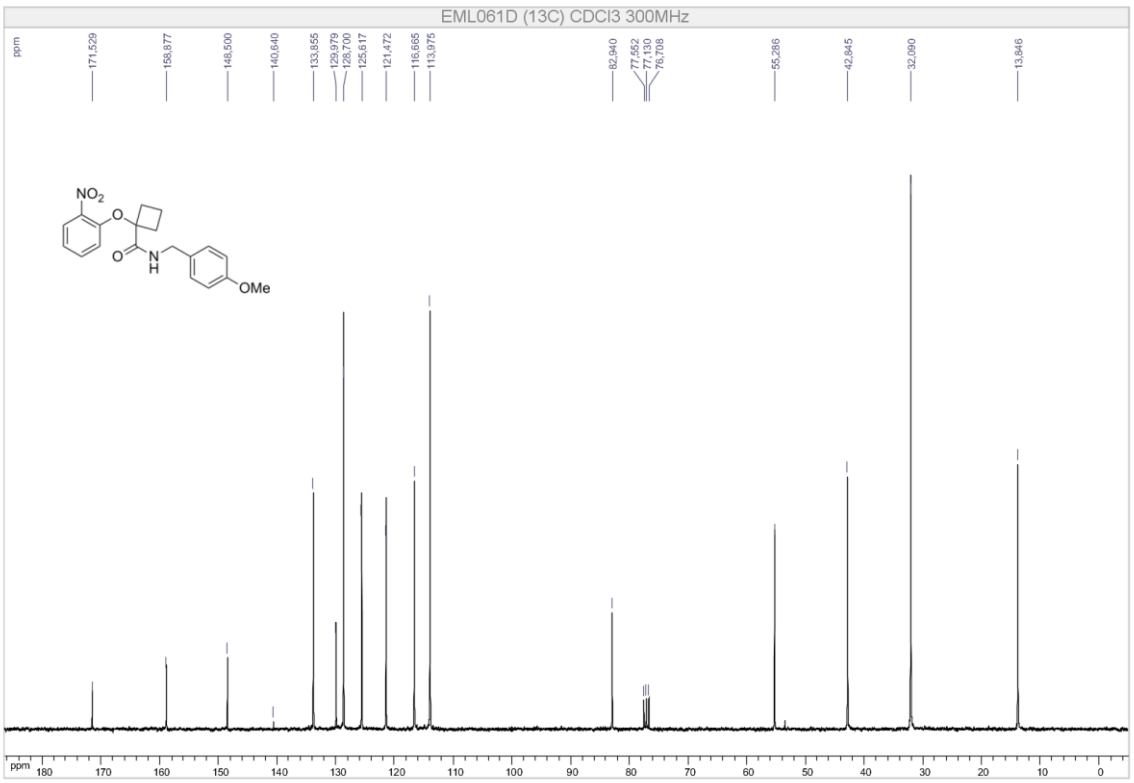
1-(4-chloro-2-nitrophenoxy)-N-cyclohexylcyclobutanecarboxamide (1b)

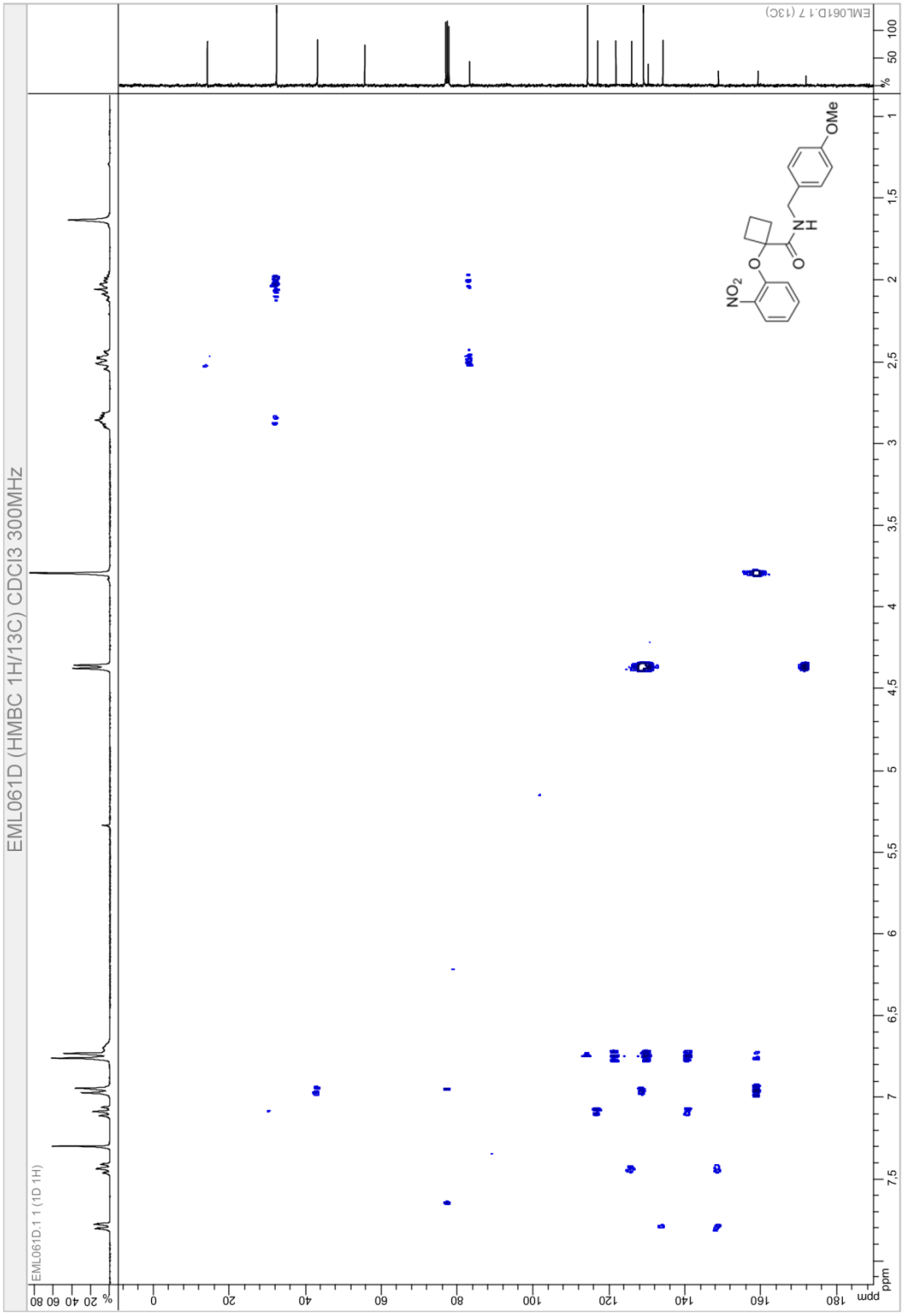




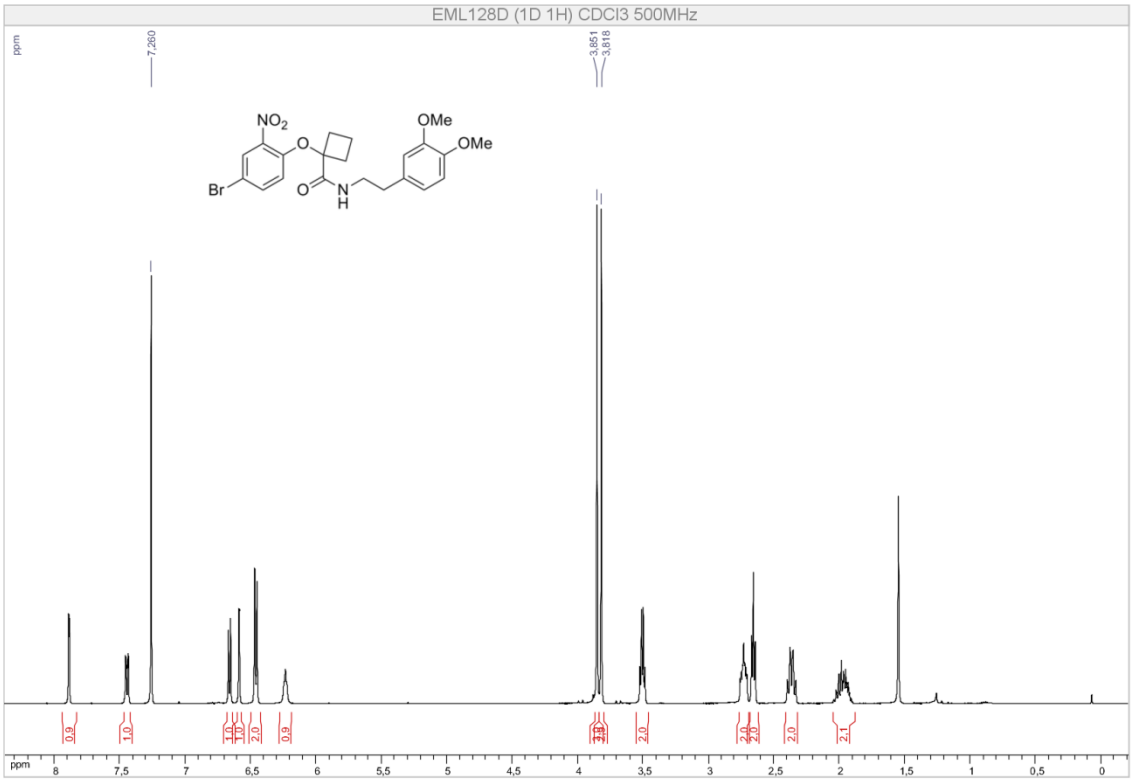
_N_-(4-methoxybenzyl)-1-(2-nitrophenoxy)cyclobutanecarboxamide (1c)

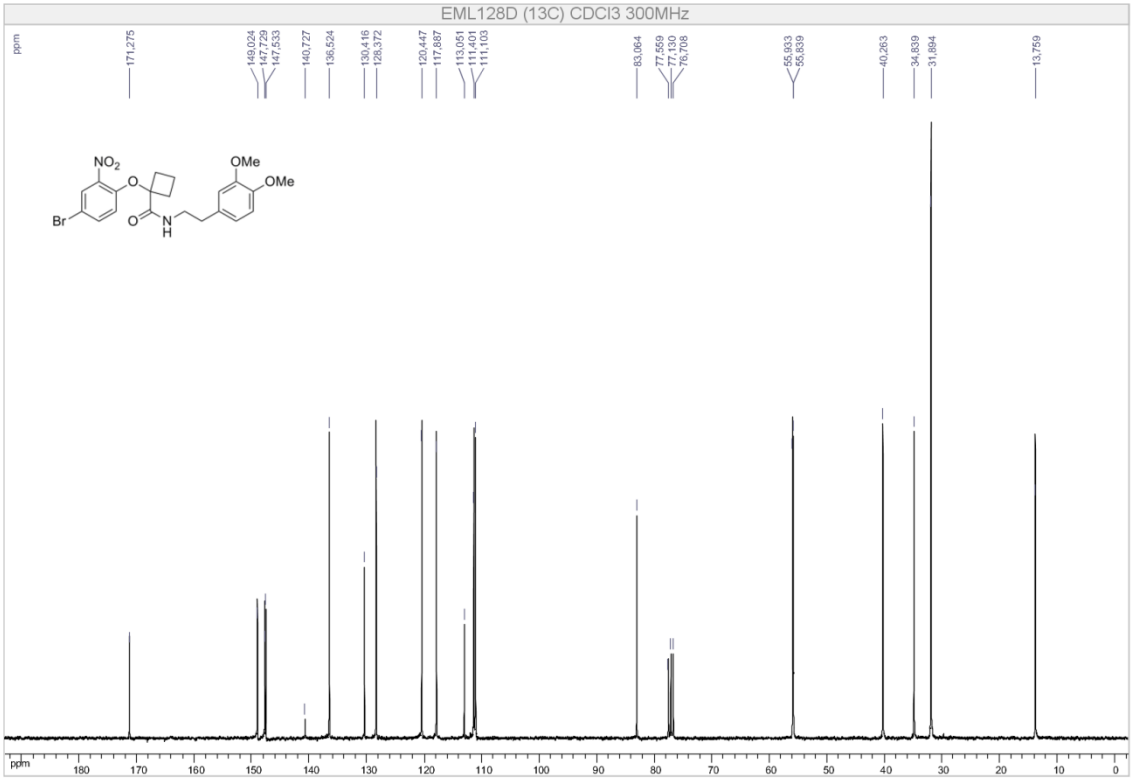




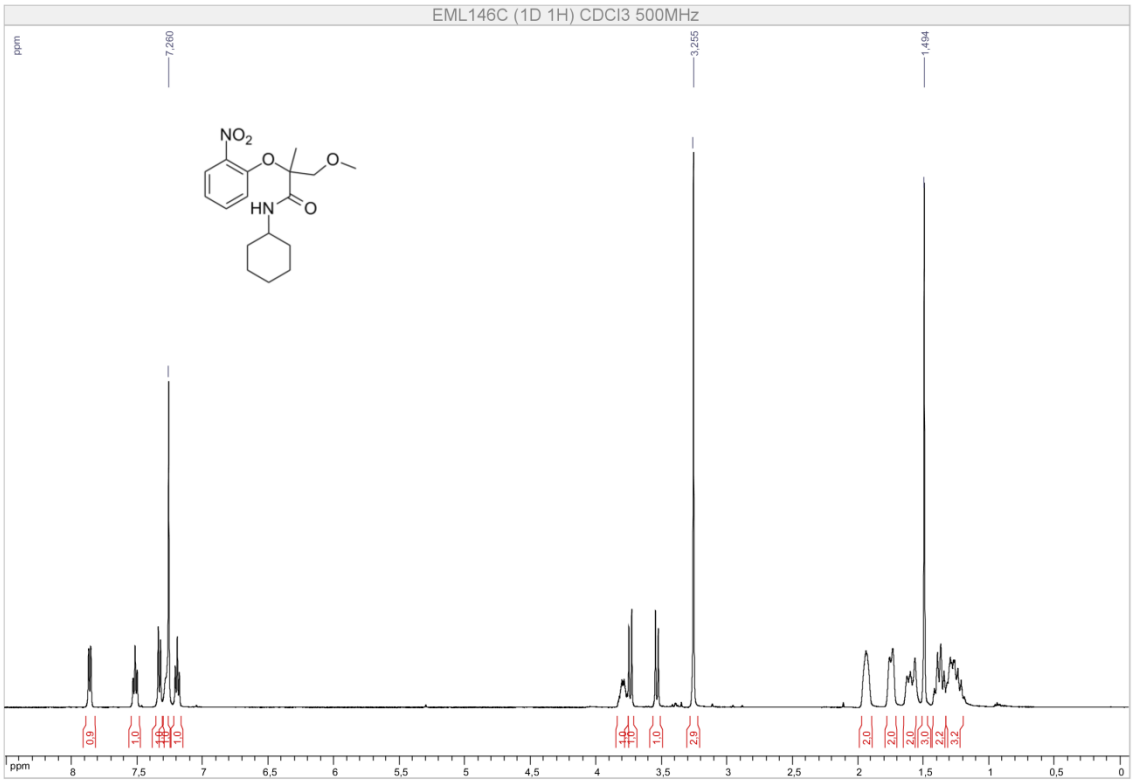

EML061D (HMBC 1H/13C) CDCl3 300MHz
EML061D.1.1 (1D 1H)
EML061D.1.7 (13C)
OMe
NH
O
O
NO2
ppm

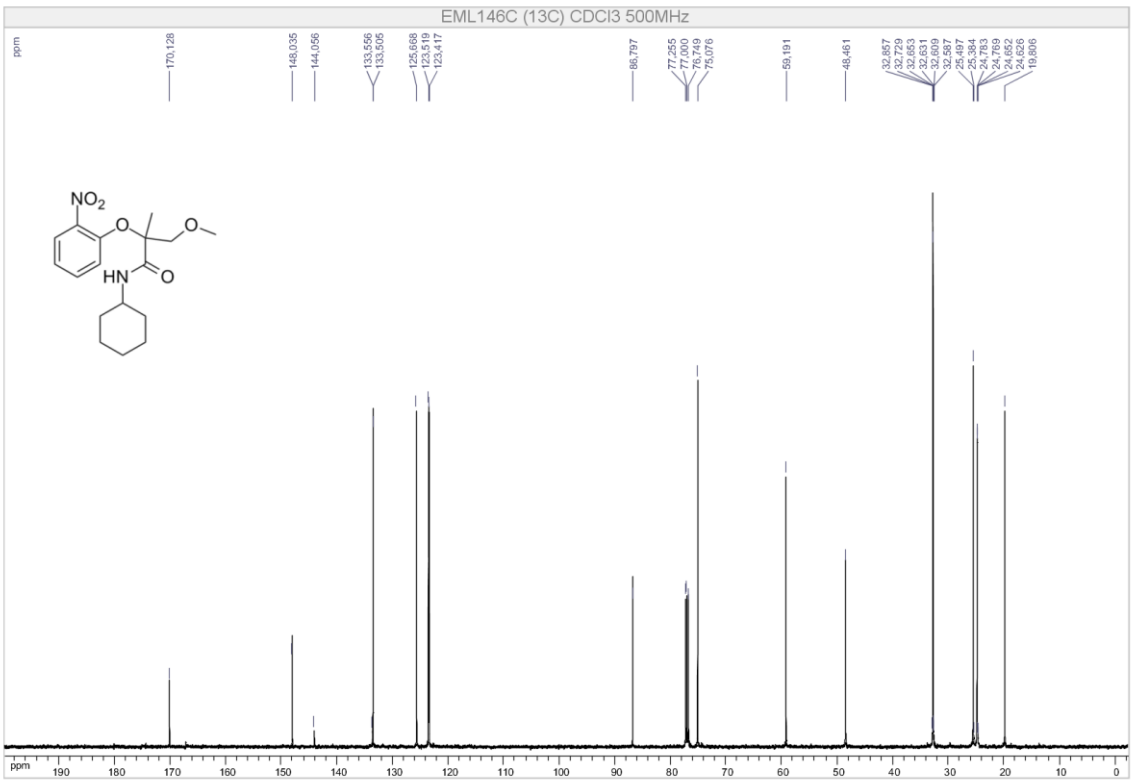
1-(4-bromo-2-nitrophenoxy)-*N*-(3,4-dimethoxyphenethyl)cyclobutanecarboxamide (1d)



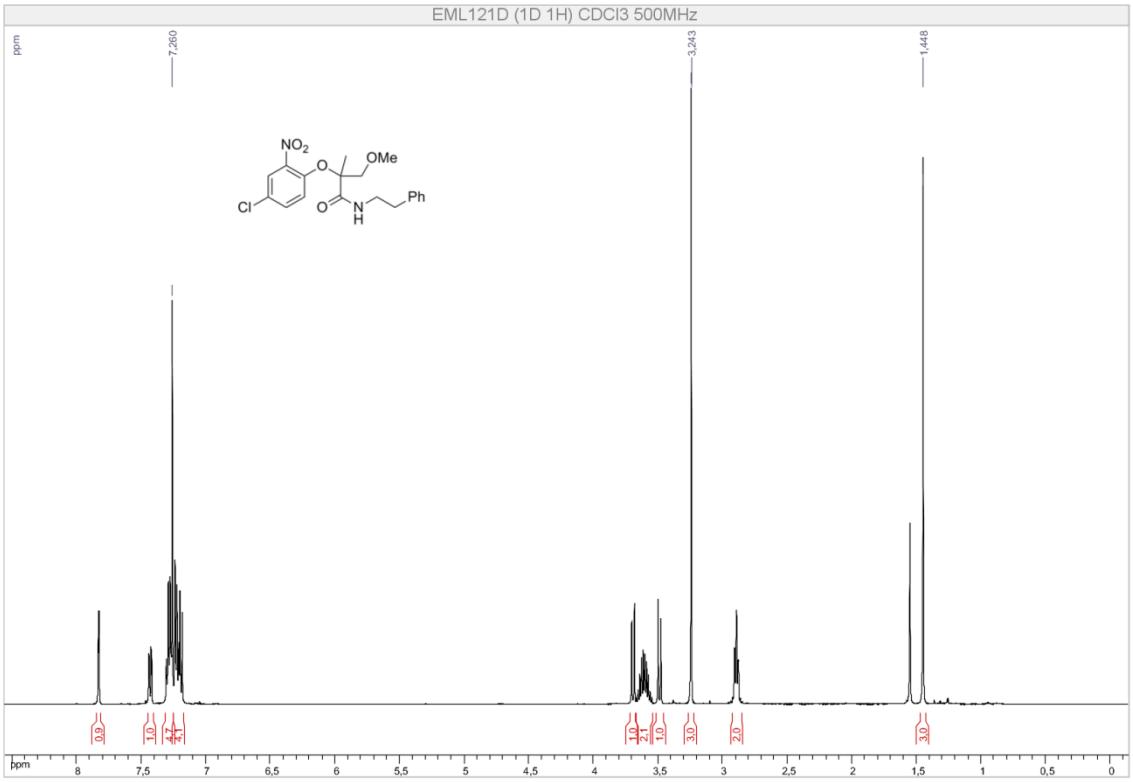


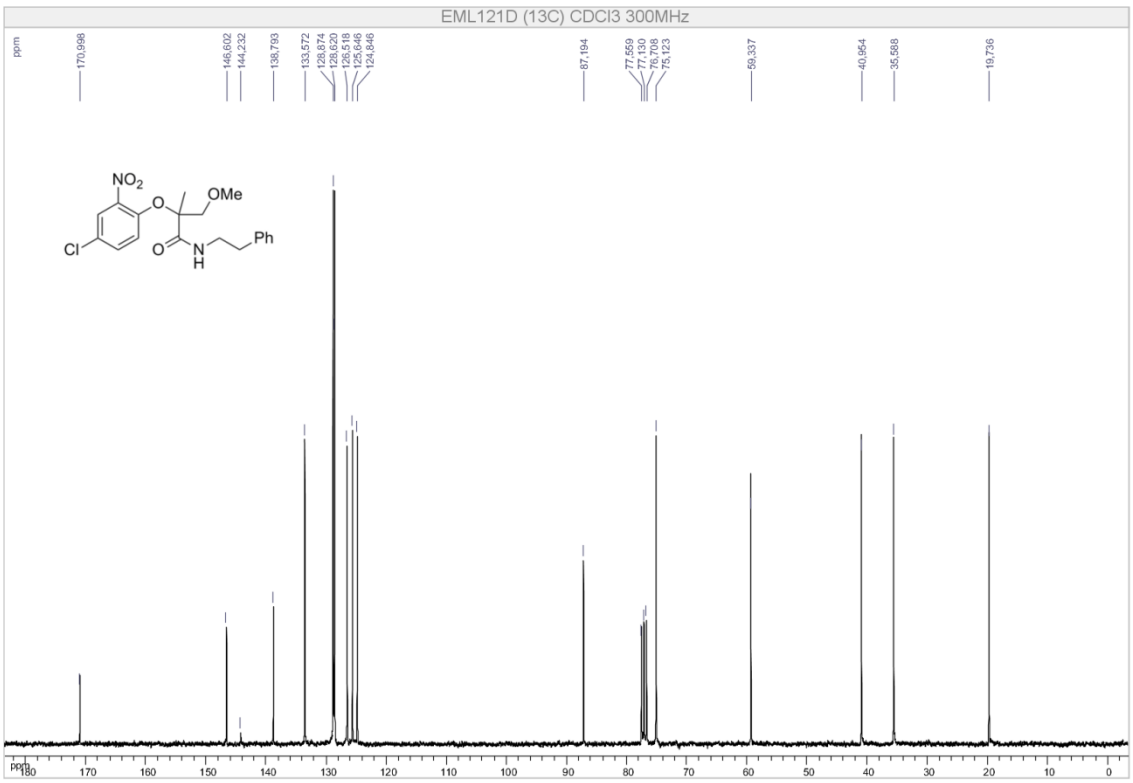
_N_-cyclohexyl-3-methoxy-2-methyl-2-(2-nitrophenoxy)propanamide (1e)



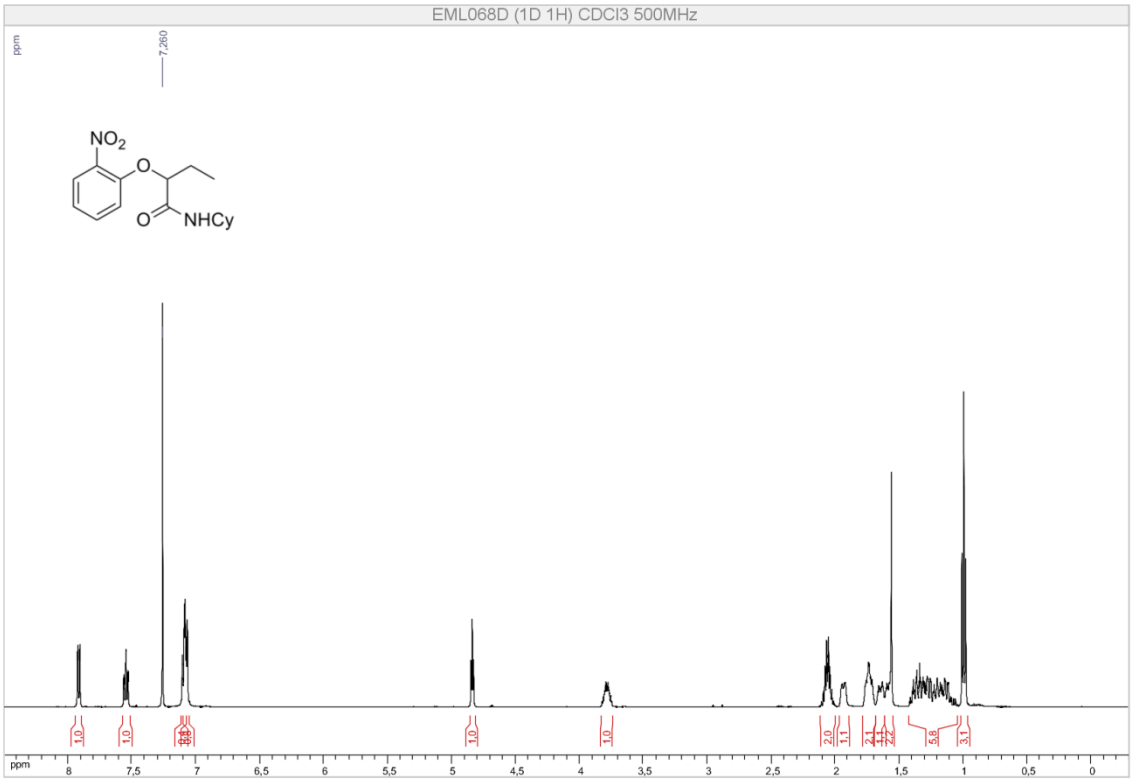


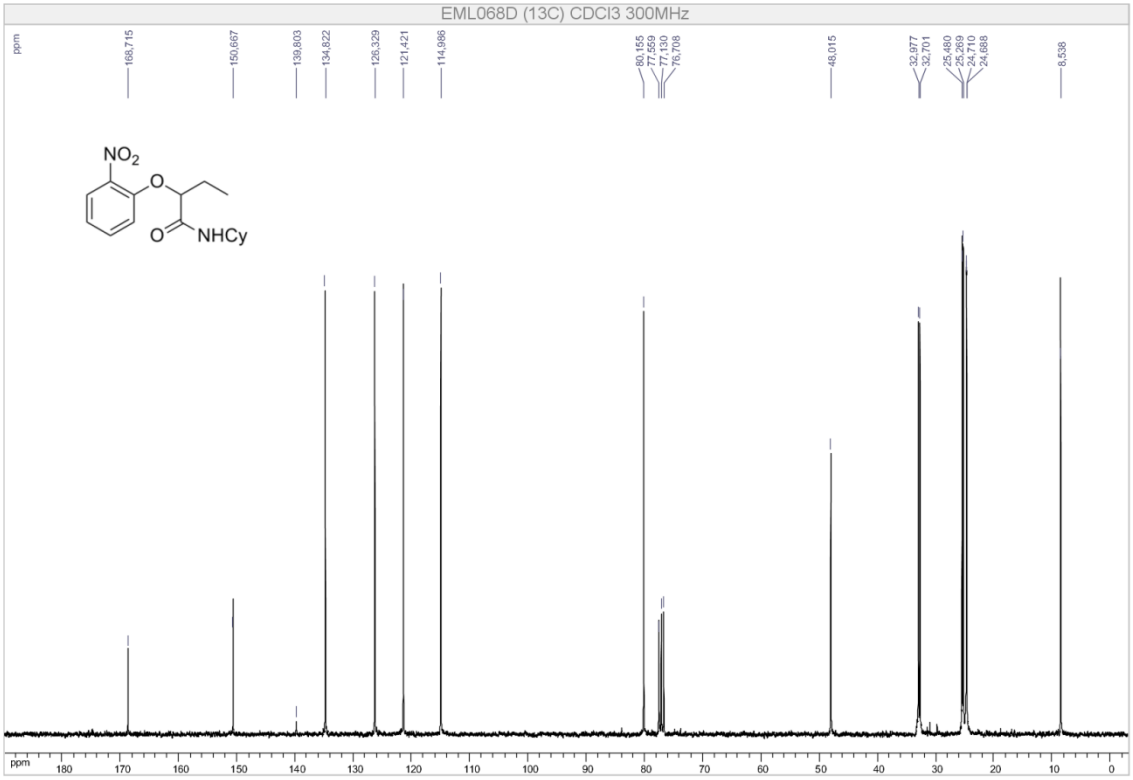
2-(4-chloro-2-nitrophenoxy)-3-methoxy-2-methyl-*N*-phenethylpropanamide (1f)

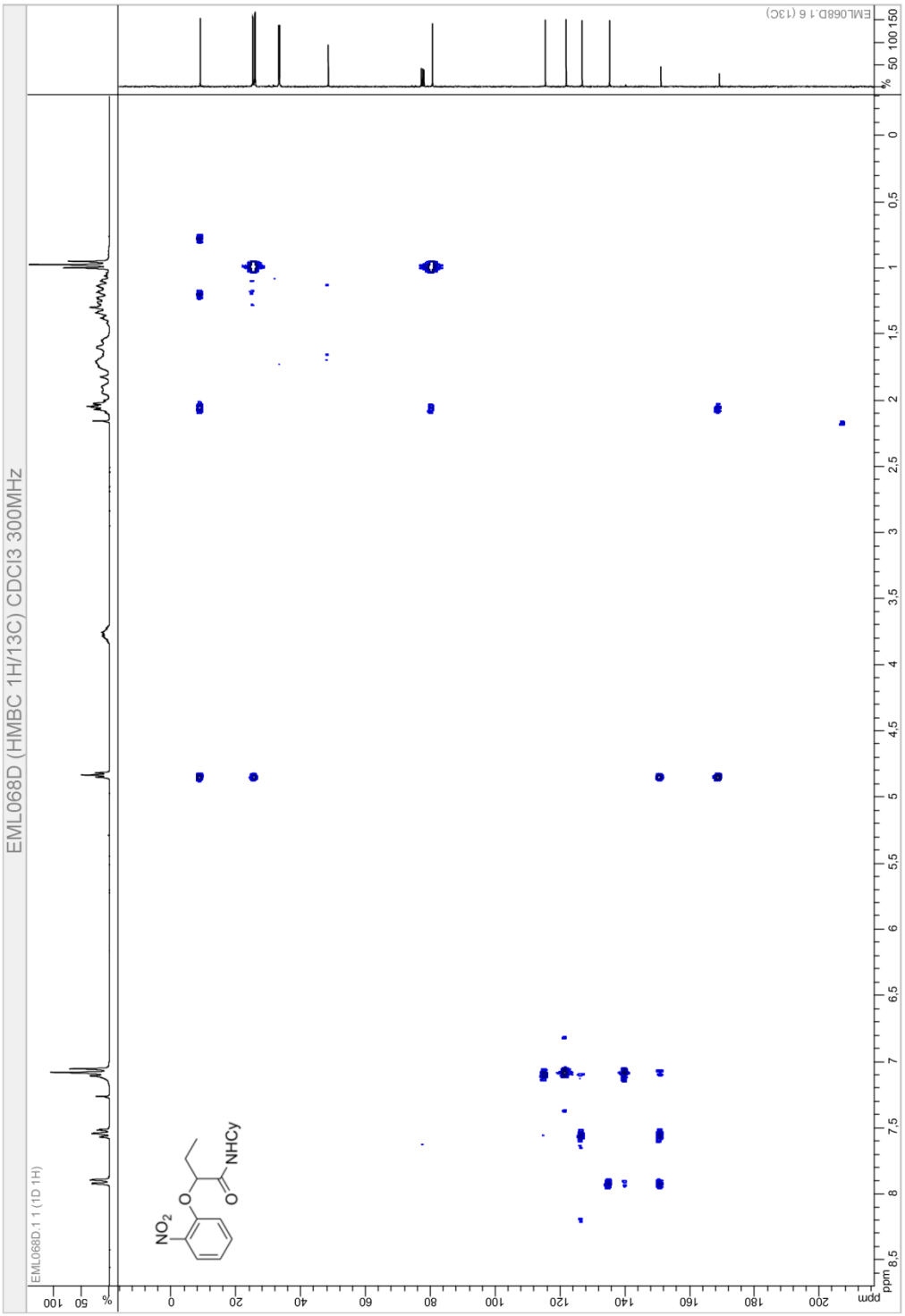




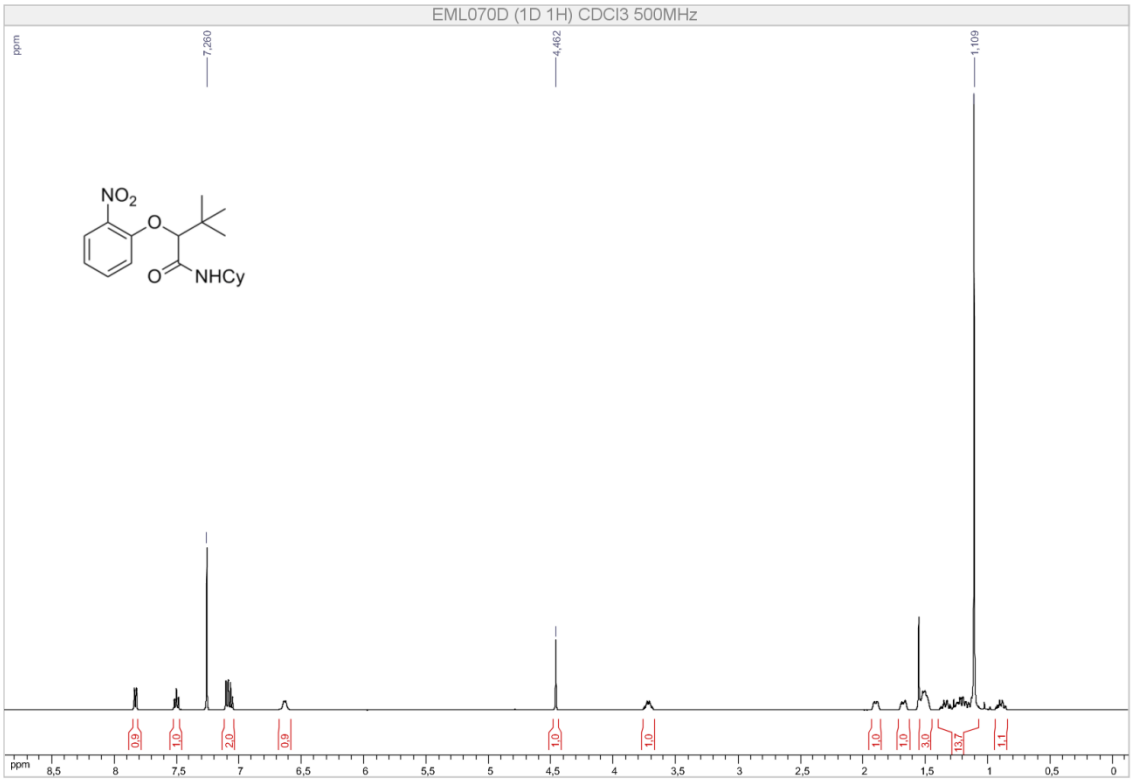
_N_-cyclohexyl-2-(2-nitrophenoxy)butanamide (1g)

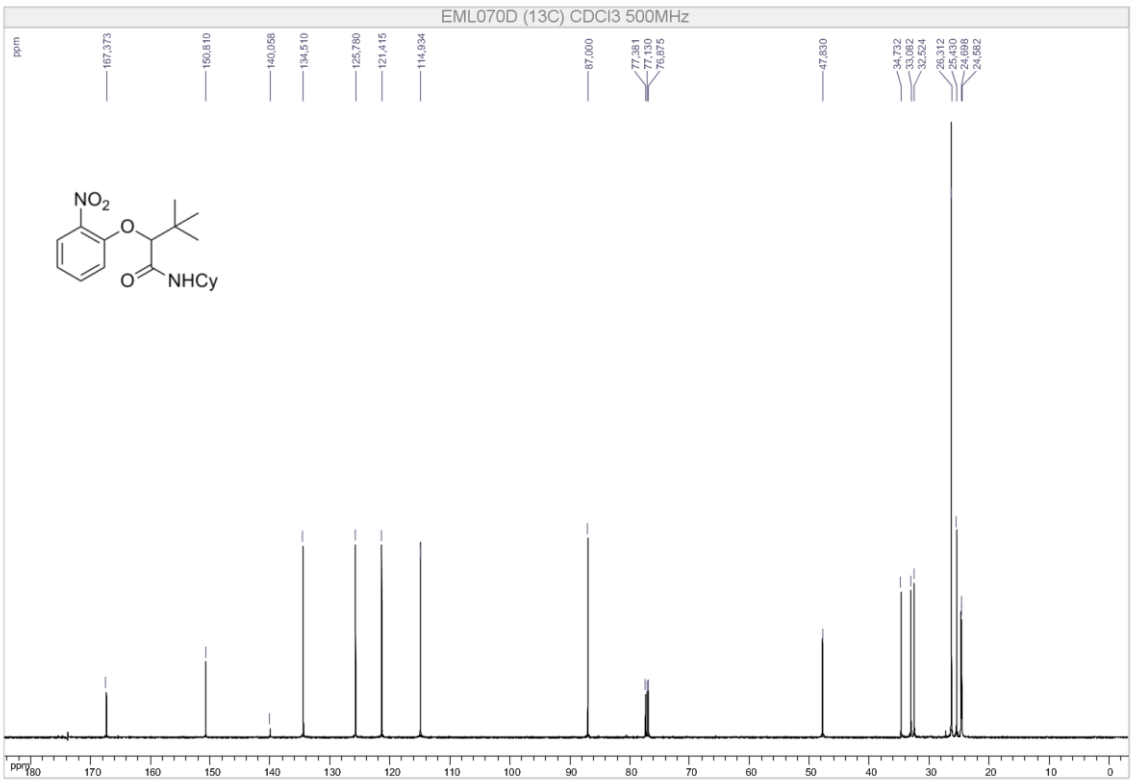


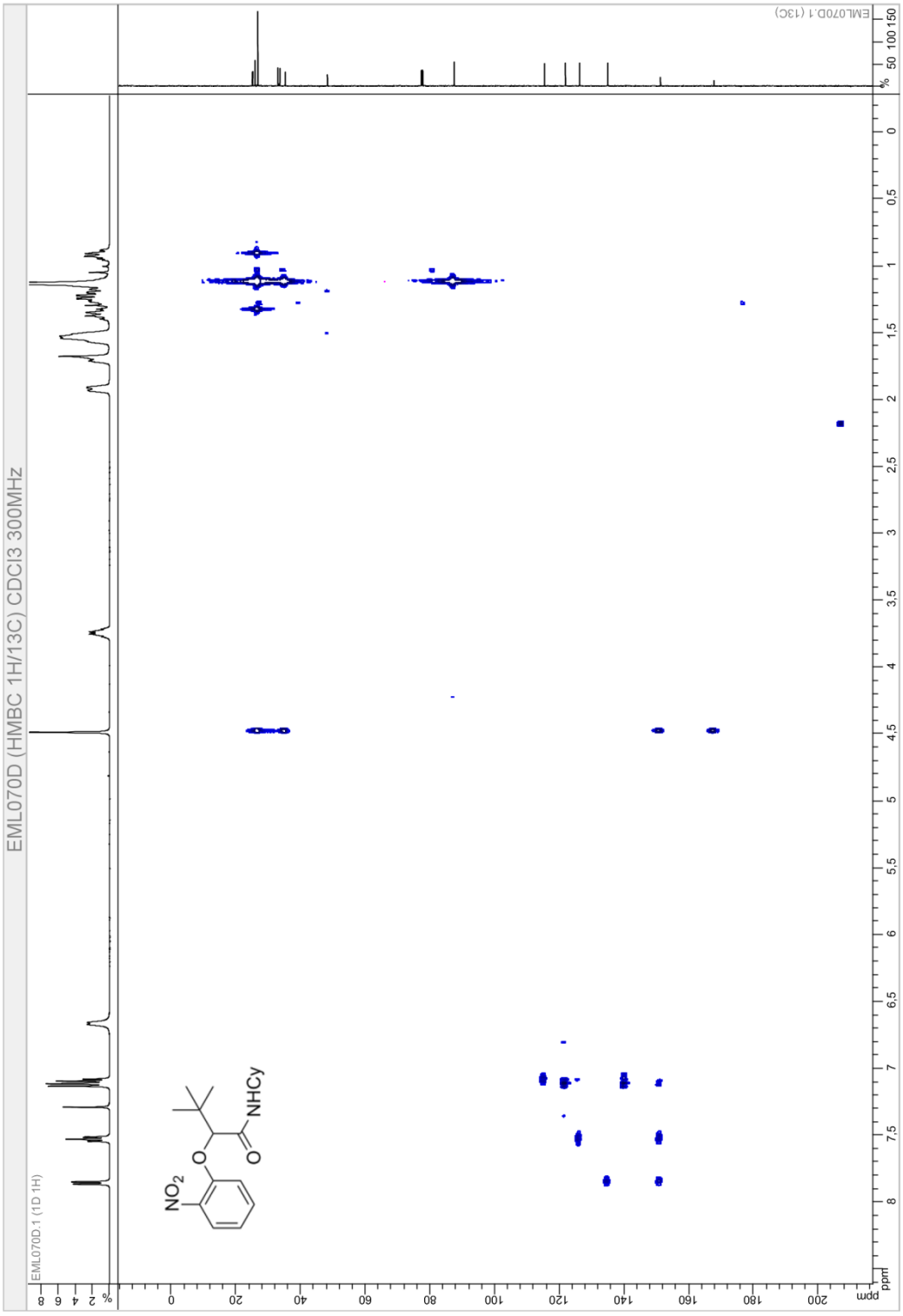



EML068D (HMBC 1H/13C) CDCl3 300MHz
EML068D.1 1 (1D 1H)
EML068D.1 6 (13C)
NHCy
O
O
NO2
ppm
%

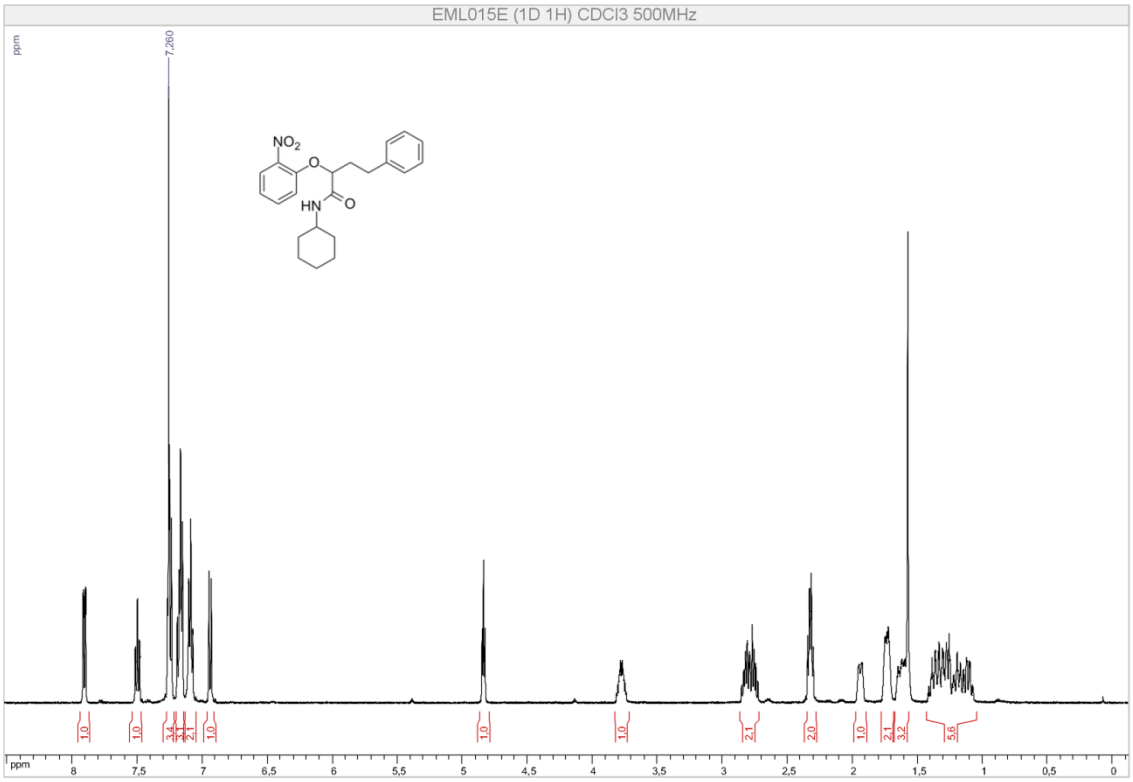
_N_-cyclohexyl-3,3-dimethyl-2-(2-nitrophenoxy)butanamide (1h)

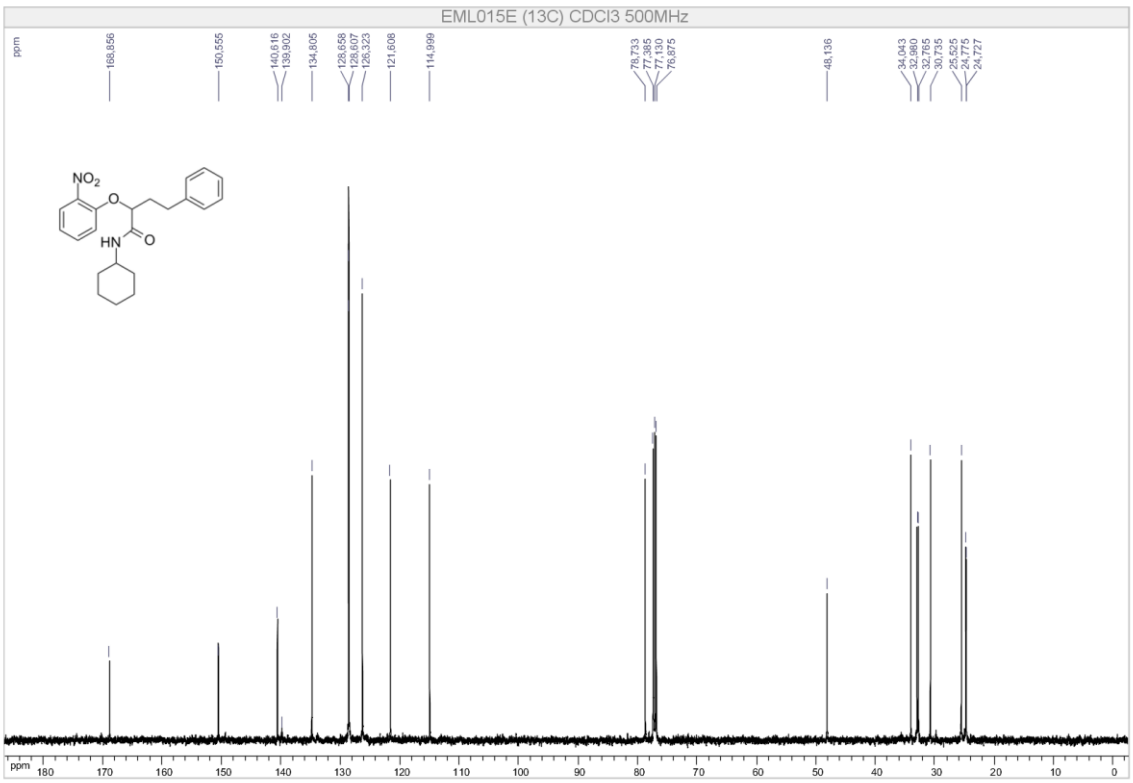


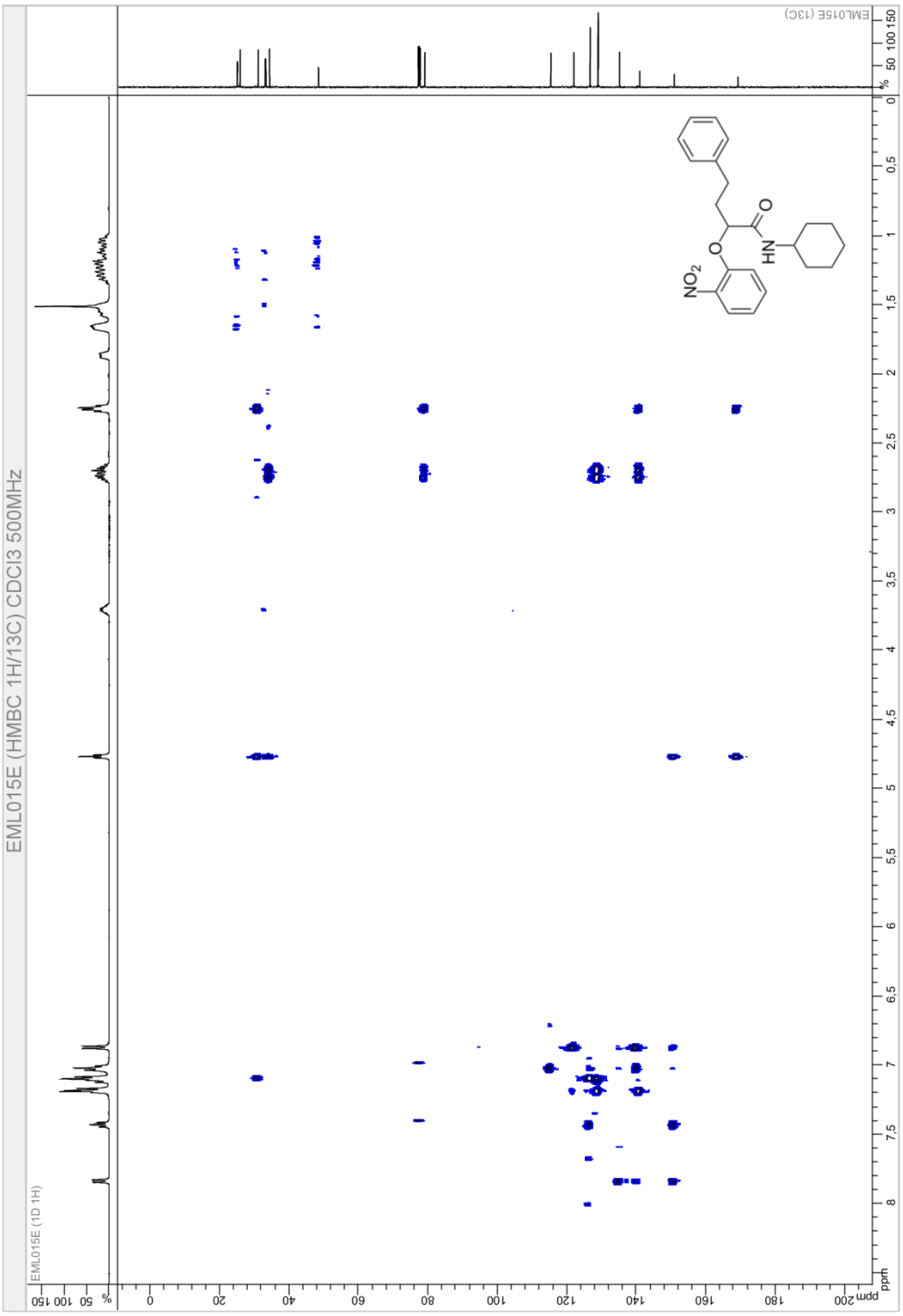



EML070D (HMBC 1H/13C) CDCl3 300MHz
EML070D.1 (1D 1H)
EML070D.1 (13C)
NHCy
O
O
NO_2
ppm

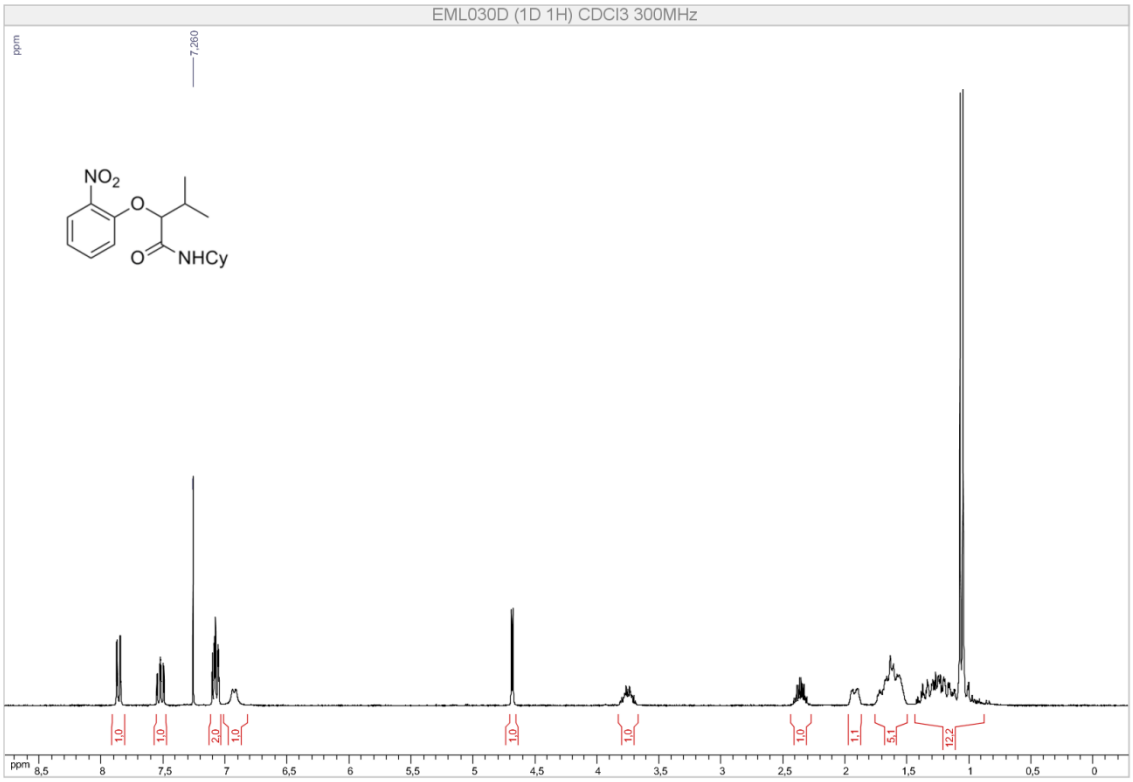
_N_-cyclohexyl-2-(2-nitrophenoxy)-4-phenylbutanamide (1i)

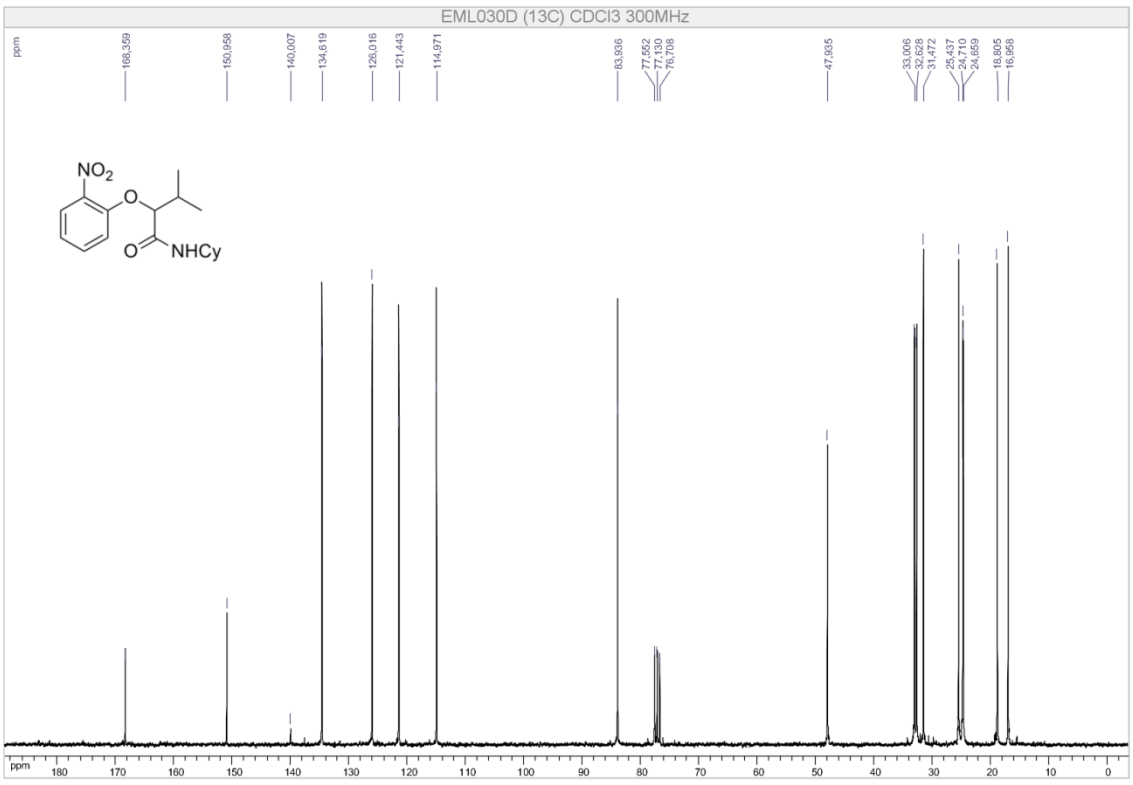




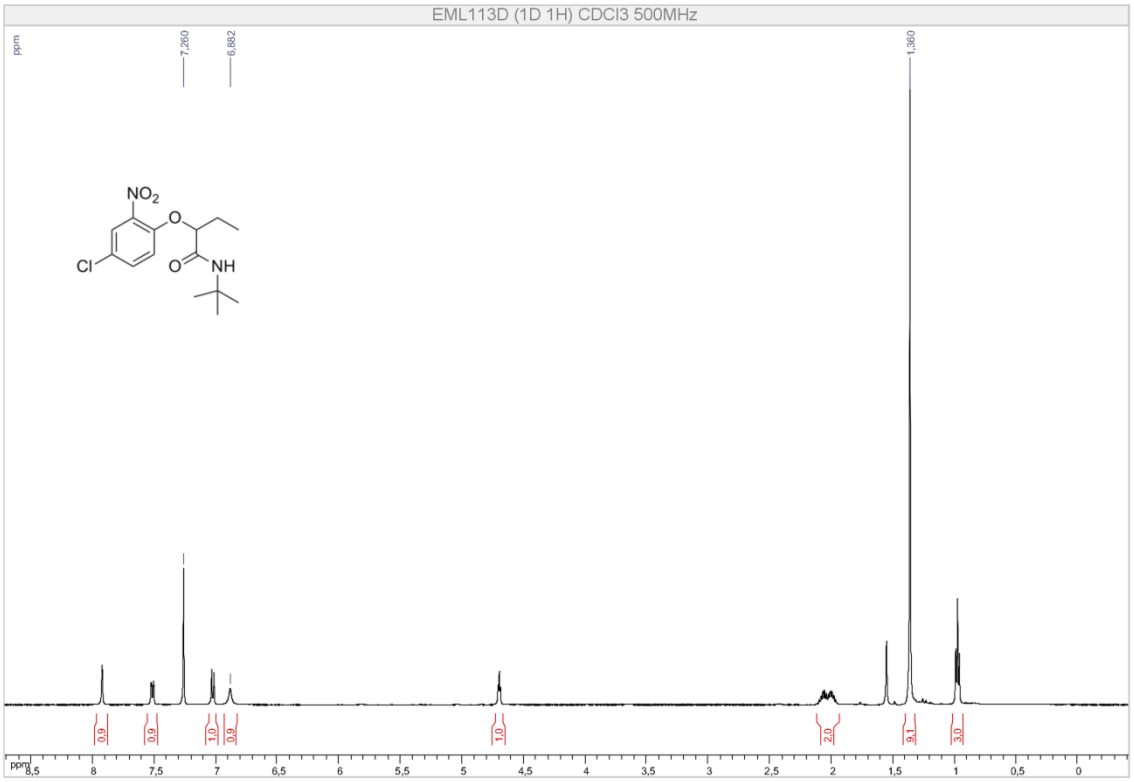

EML015E (HMBC 1H/13C) CDCl3 500MHz
EML015E (1D 1H)
EML015E (13C)
ppm
NO2
O
HN
O

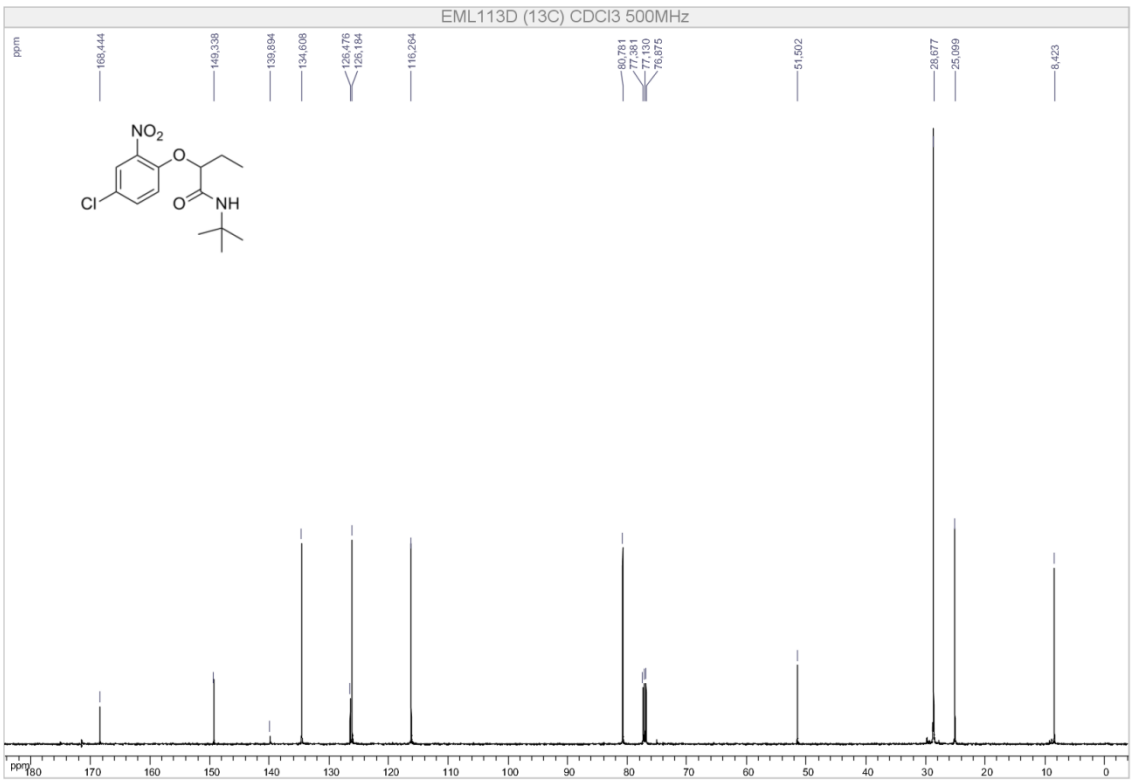
_N_-cyclohexyl-3-methyl-2-(2-nitrophenoxy)butanamide (1j)

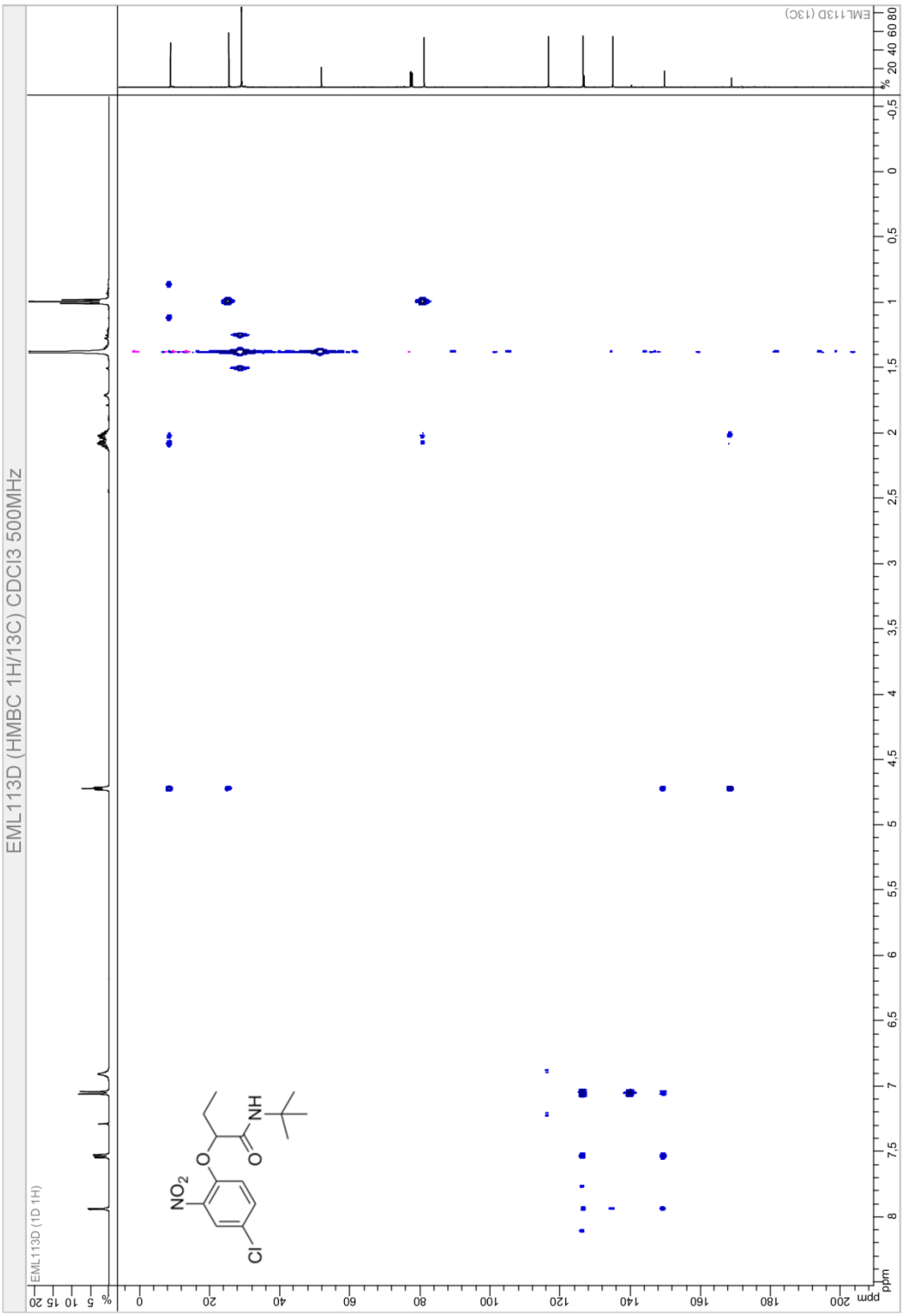




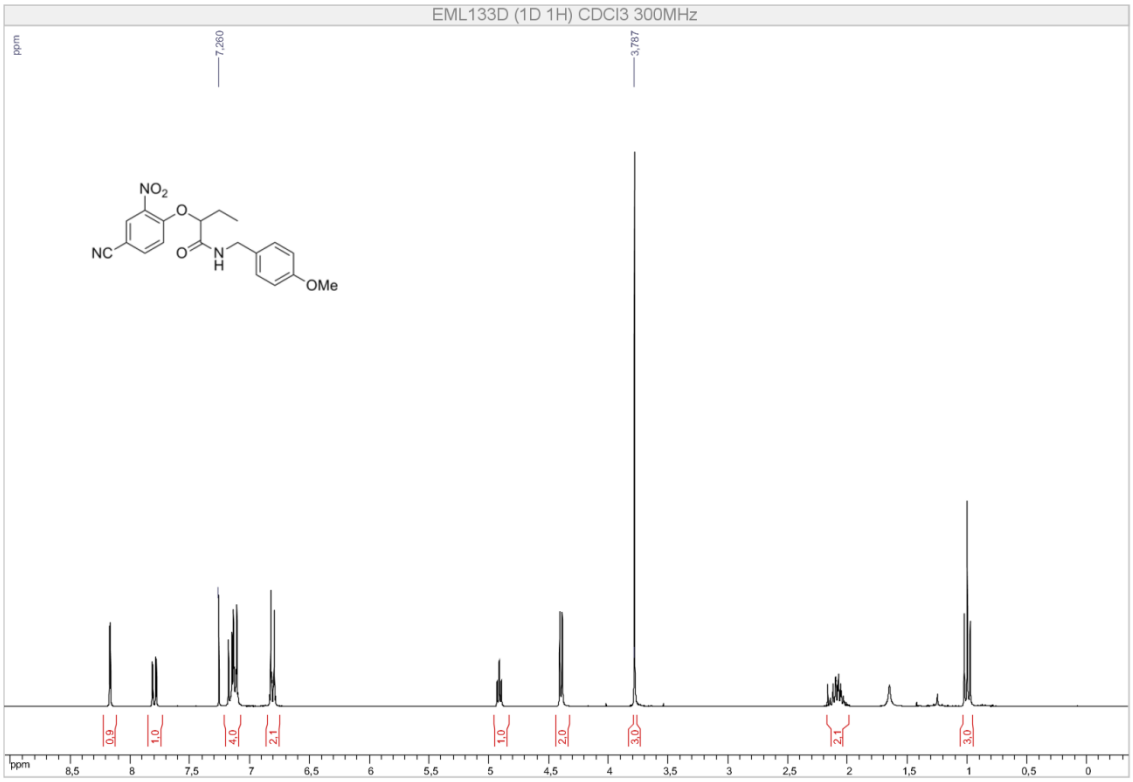
_N_-(tert-butyl)-2-(4-chloro-2-nitrophenoxy)butanamide (1k)

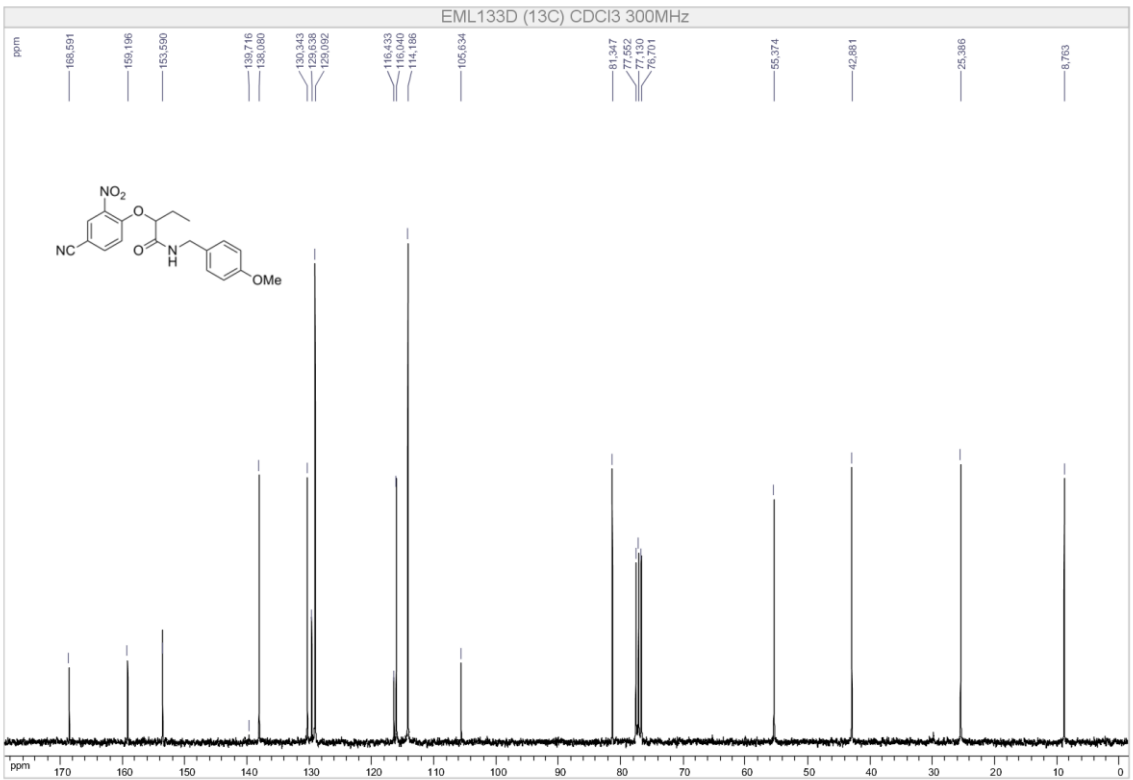


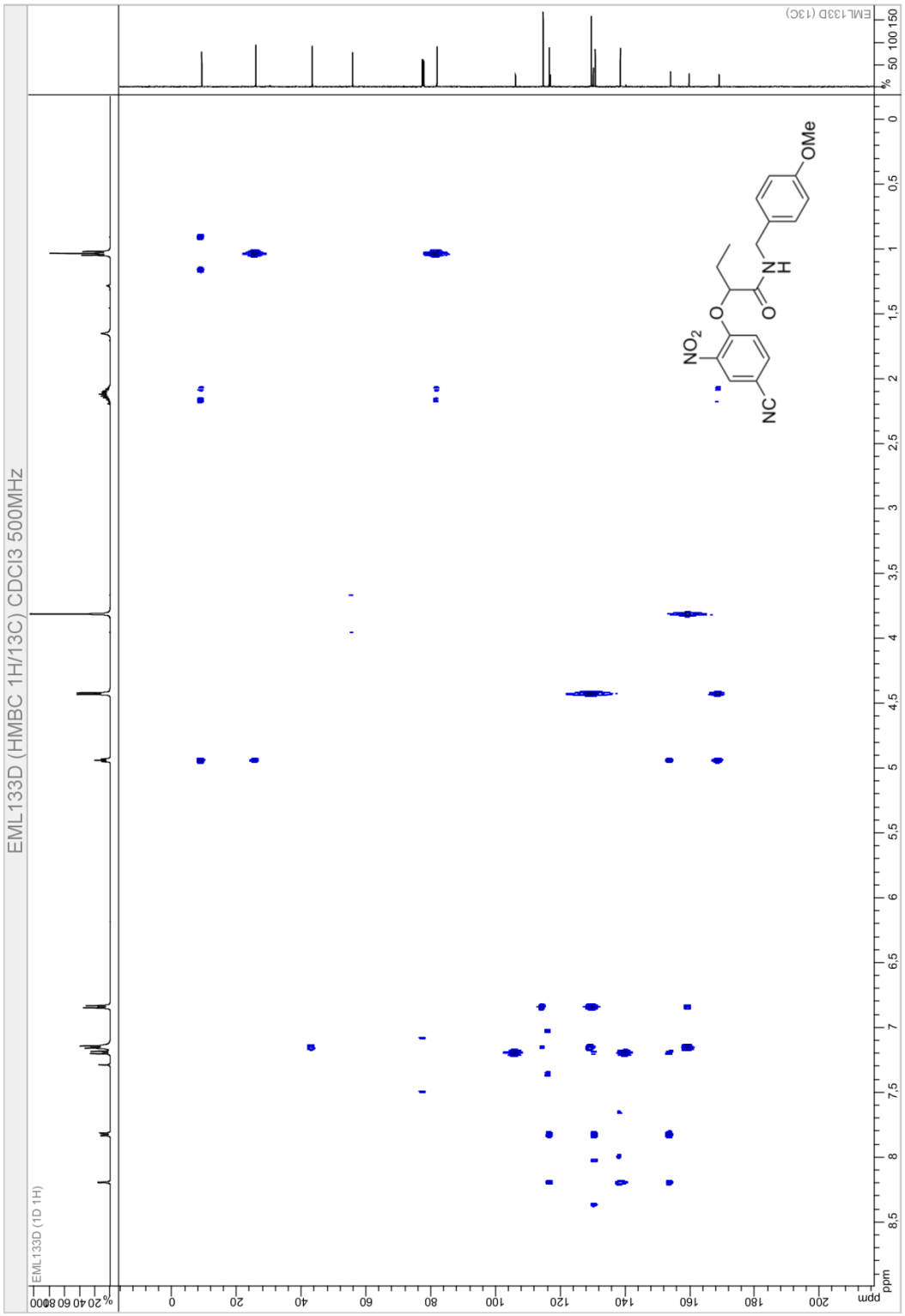



EML113D (HMBC 1H/13C) CDCl3 500MHz
EML113D (1D 1H)
EML113D (13C)
ppm
NO2
Cl
O
NH

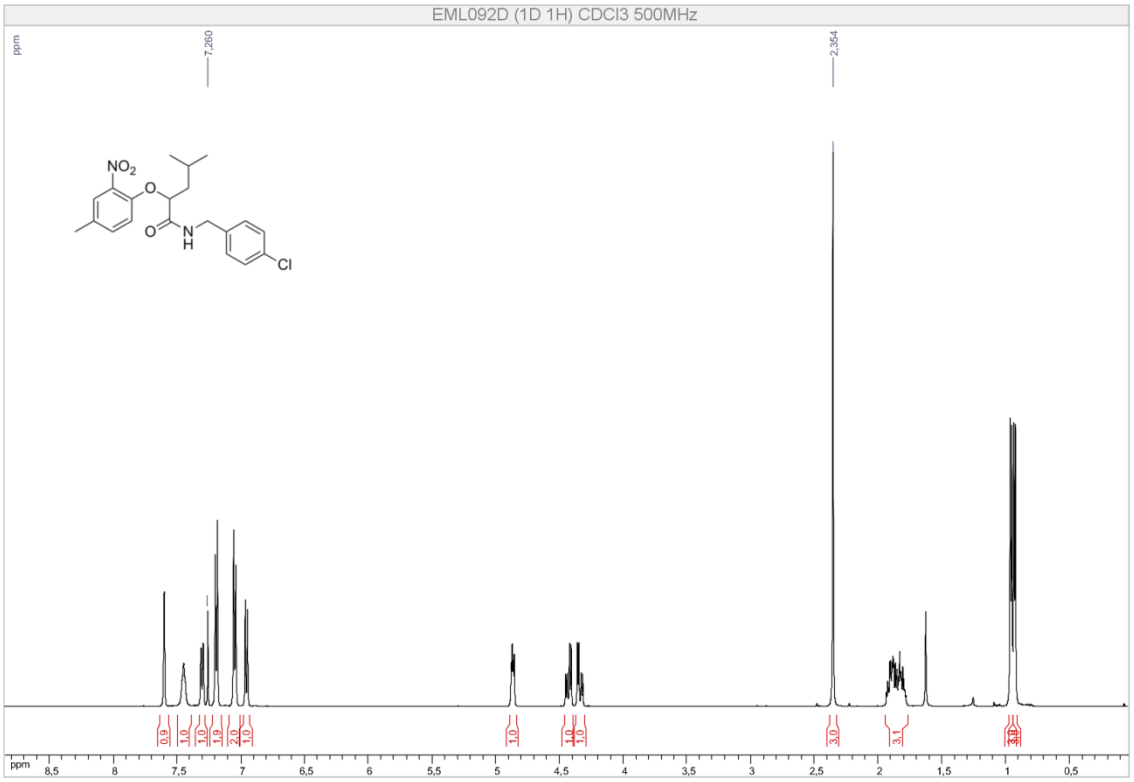
2-(4-cyano-2-nitrophenoxy)-N-(4-methoxybenzyl)butanamide (1l)

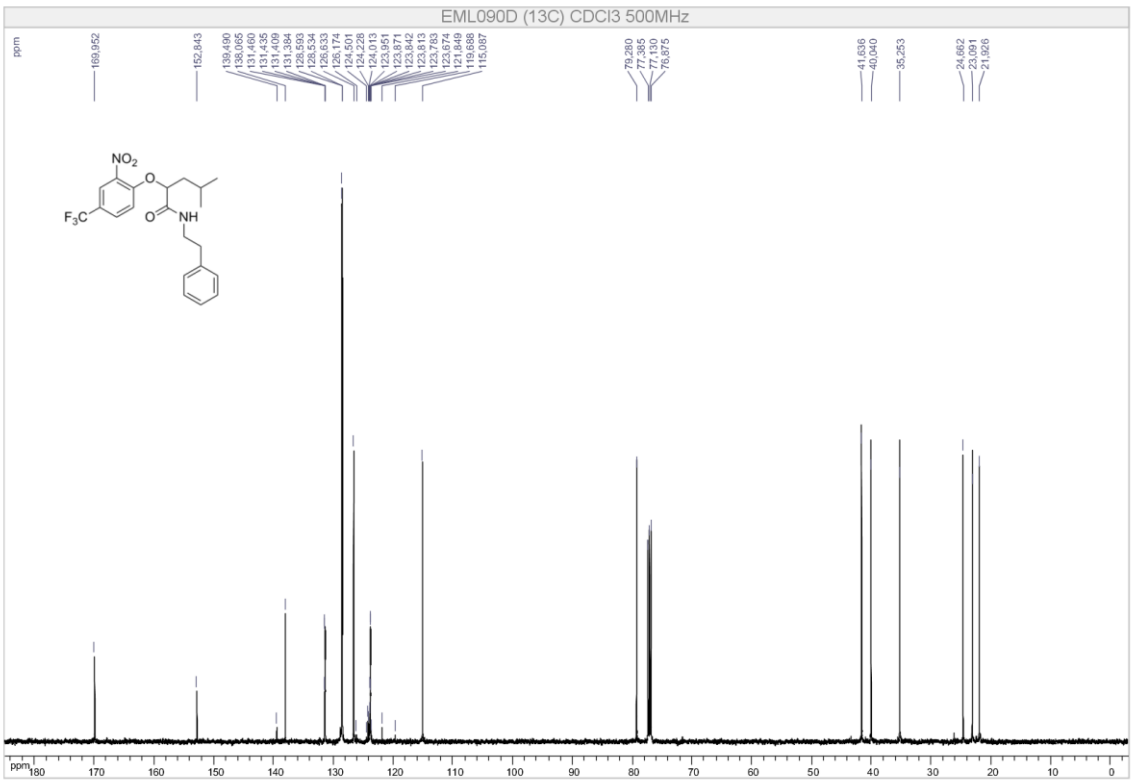




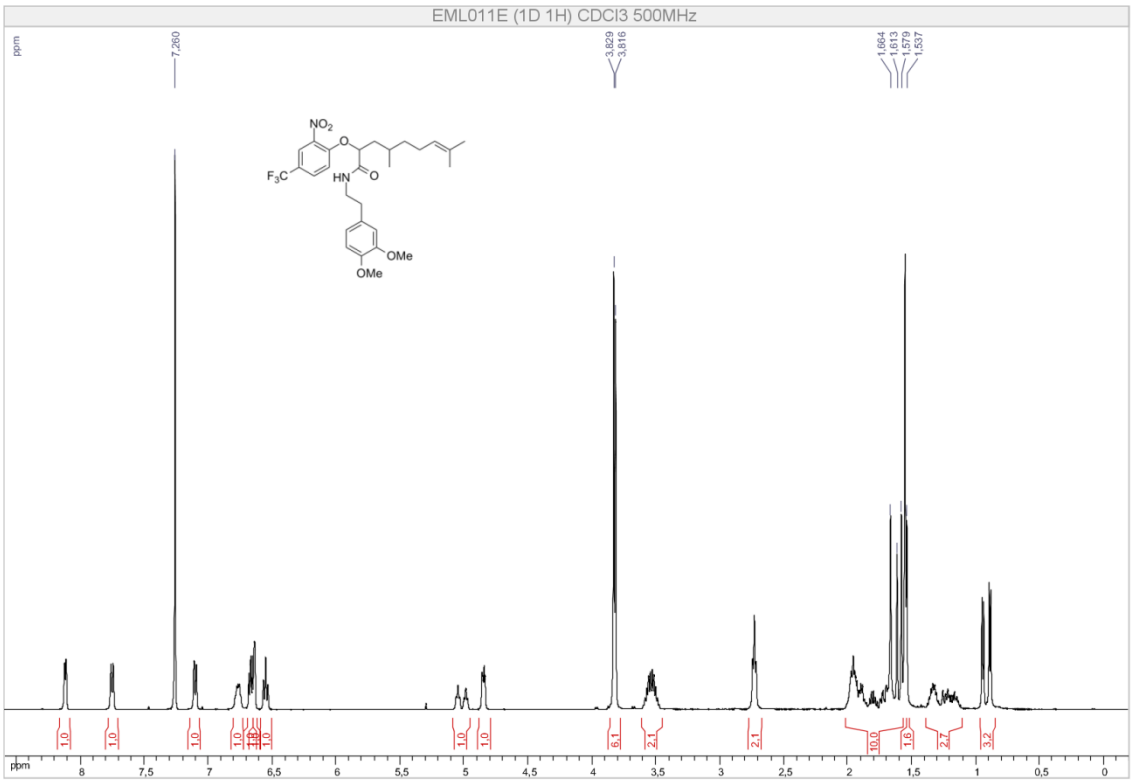

EML133D (HMBC 1H/13C) CDCl3 500MHz
EML133D (1D 1H)
EML133D (13C)
OMe
NH
O
O
NO2
NC
ppm
%

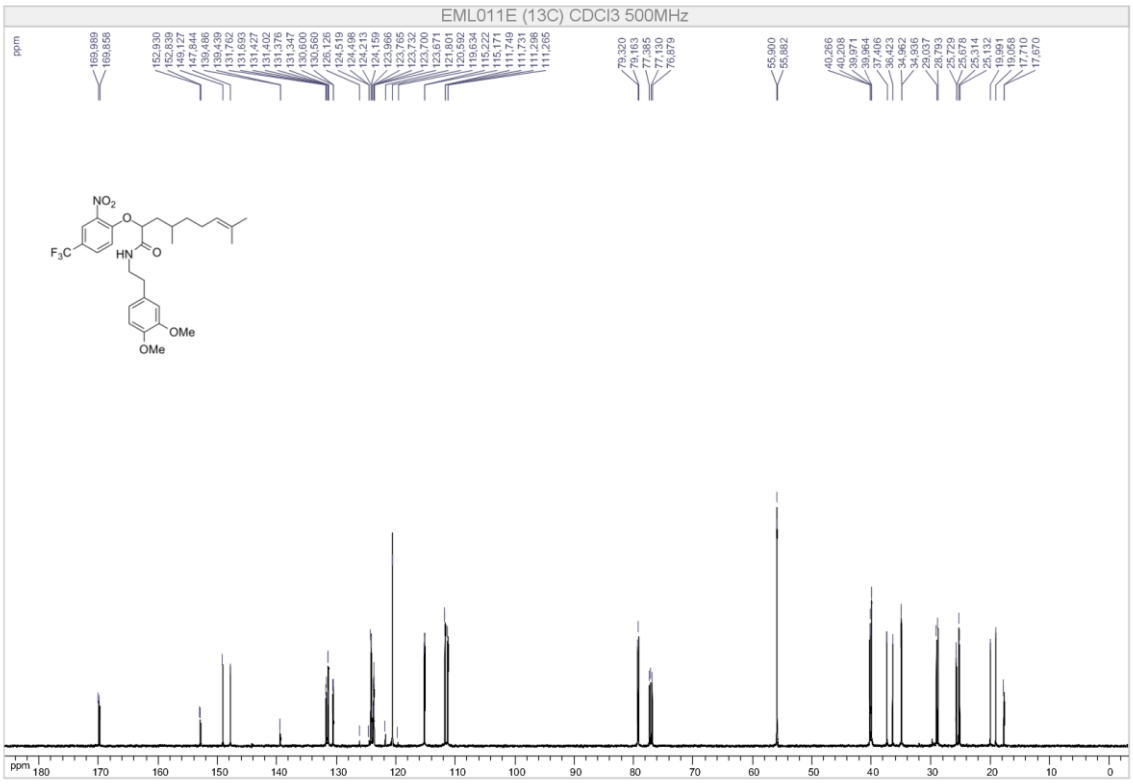
_N_-(4-chlorobenzyl)-4-methyl-2-(4-methyl-2-nitrophenoxy)pentanamide (1m)



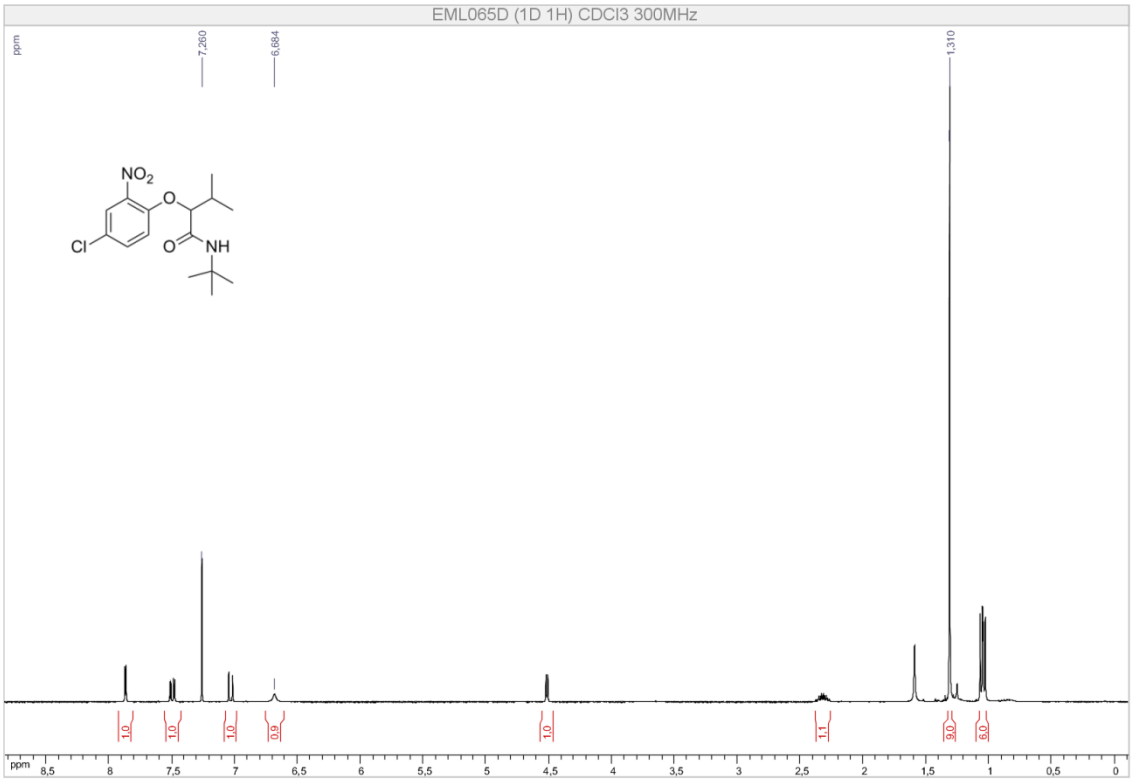


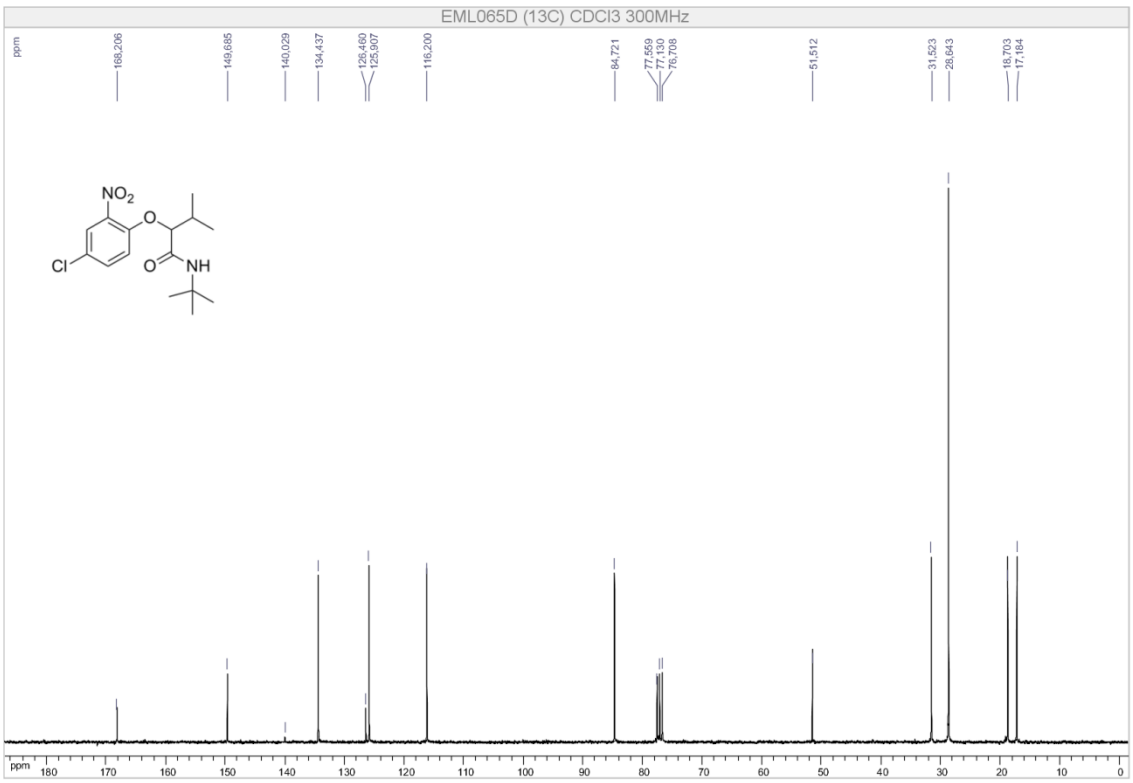
_N_-(3,4-dimethoxyphenethyl)-4,8-dimethyl-2-(2-nitro-4-(trifluoromethyl)phenoxy)non-7-enamide (1n)

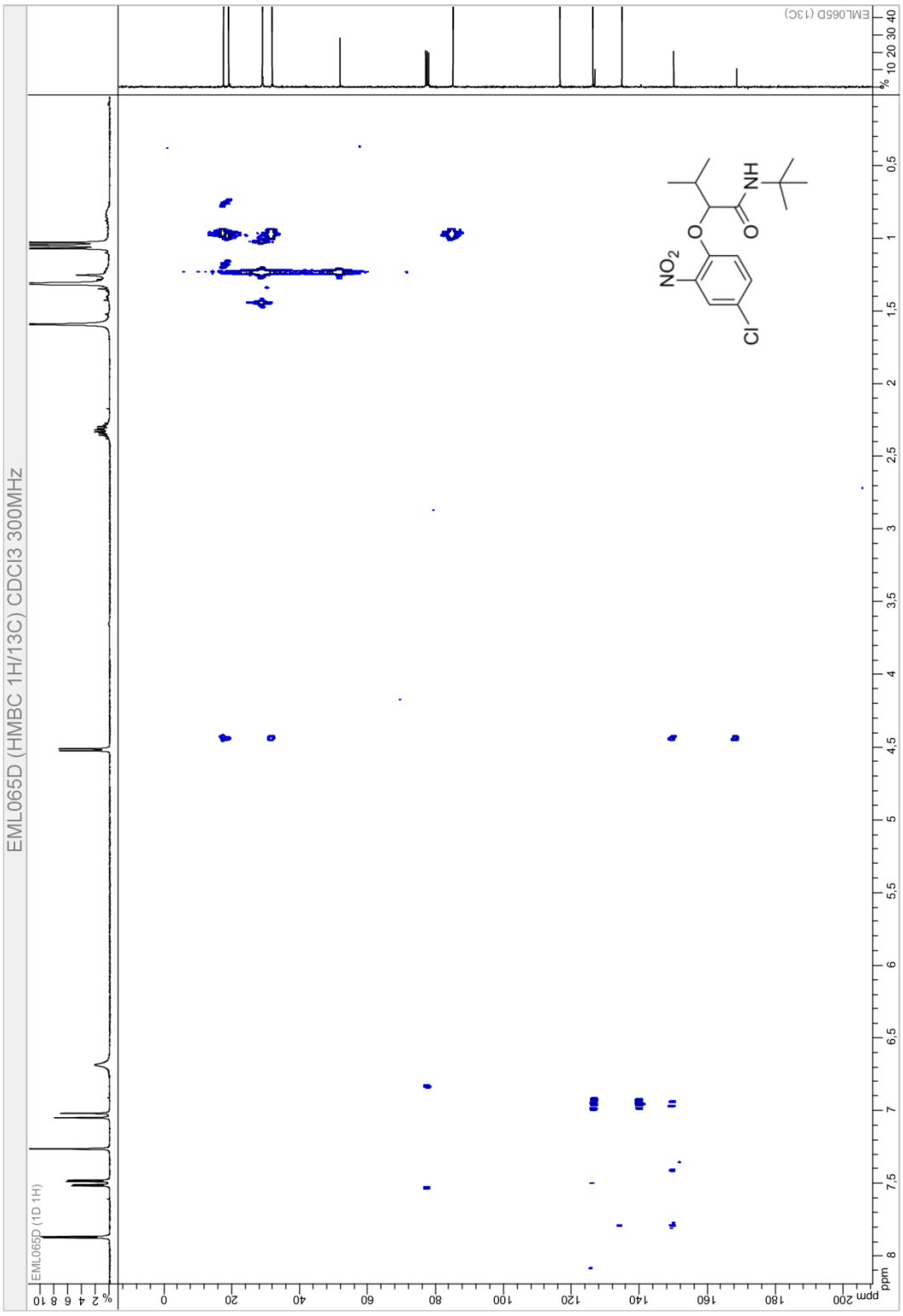




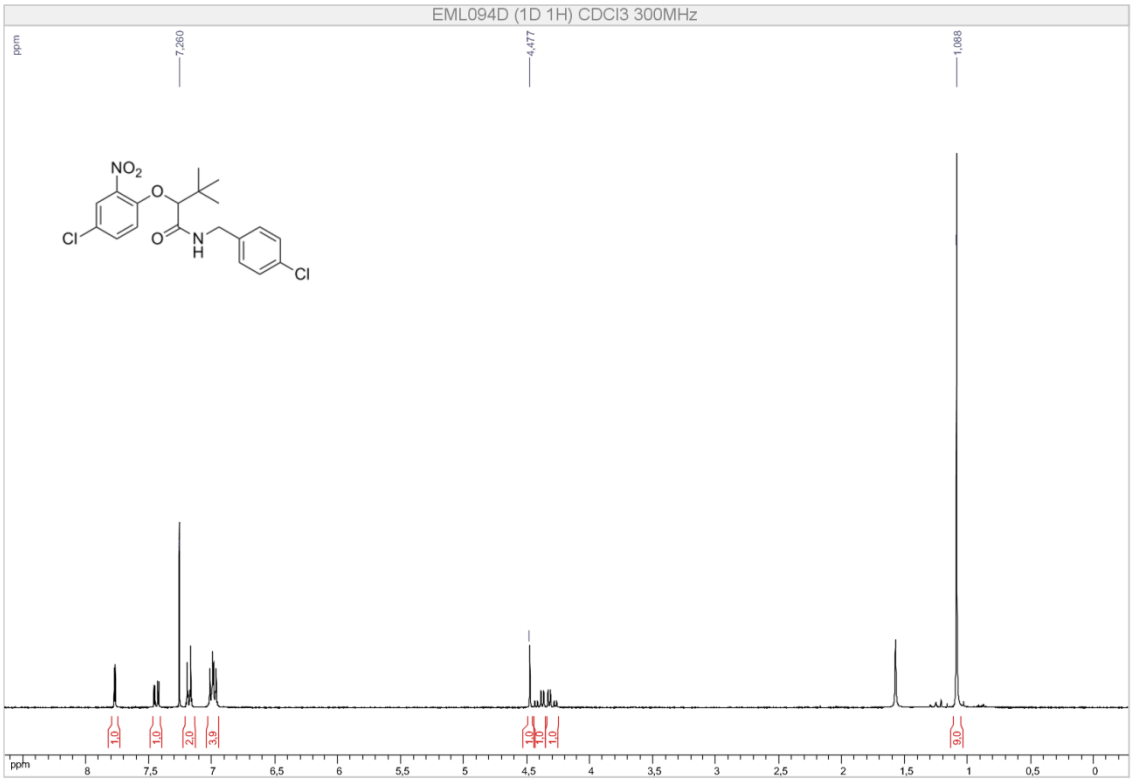
_N_-(_tert_-butyl)-2-(4-chloro-2-nitrophenoxy)-3-methylbutanamide (1o)

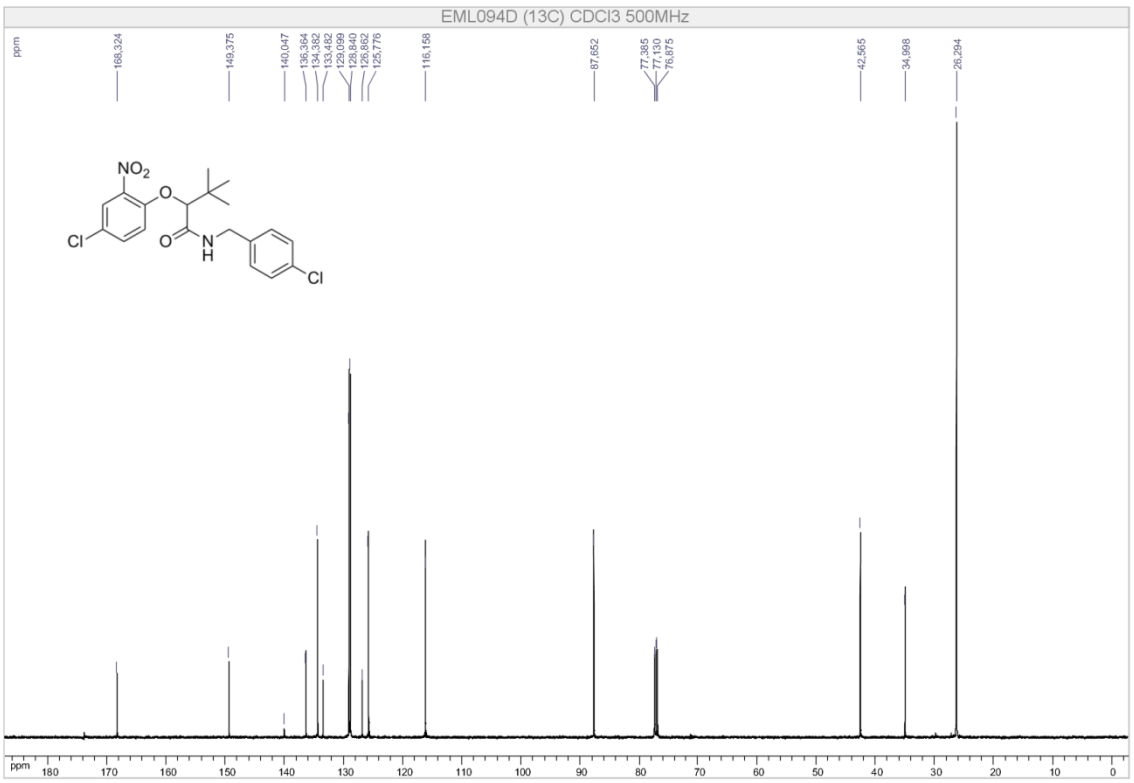




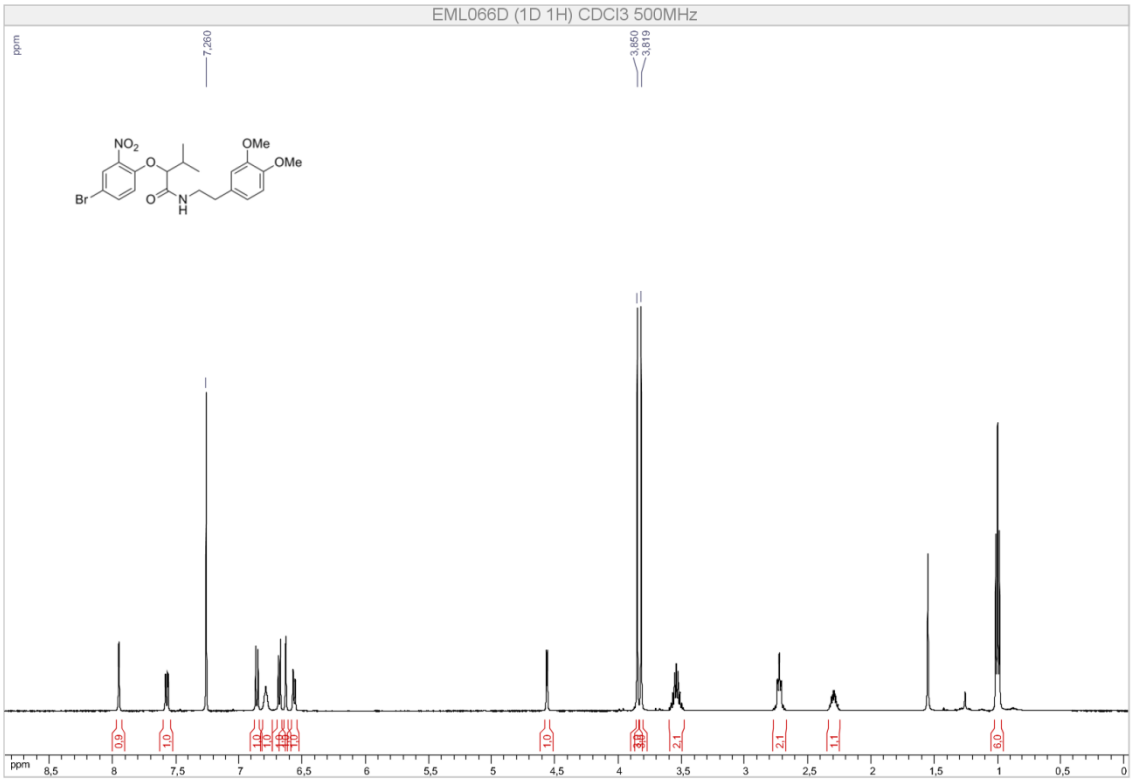

EML065D (HMBC 1H/13C) CDCl3 300MHz
EML065D (1D 1H)
EML065D (13C)
NO2
O
NH
O
Cl
ppm

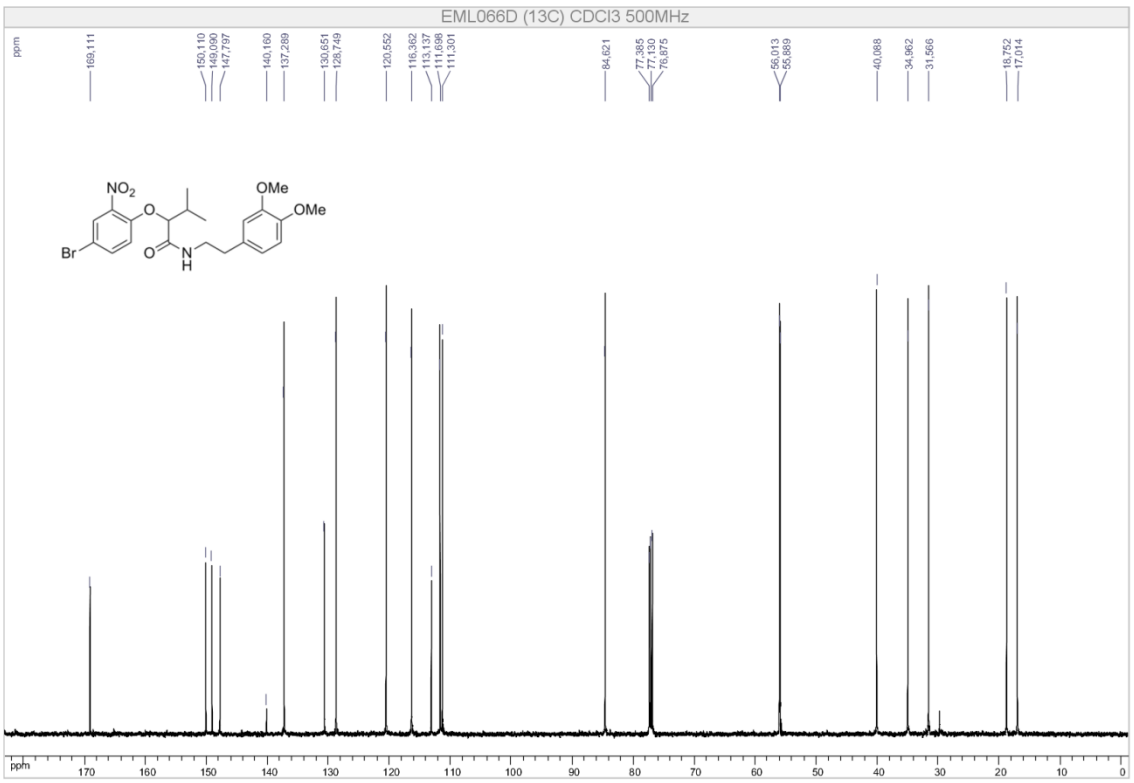
2-(4-chloro-2-nitrophenoxy)-*N*-(4-chlorobenzyl)-3,3-dimethylbutanamide (1p)

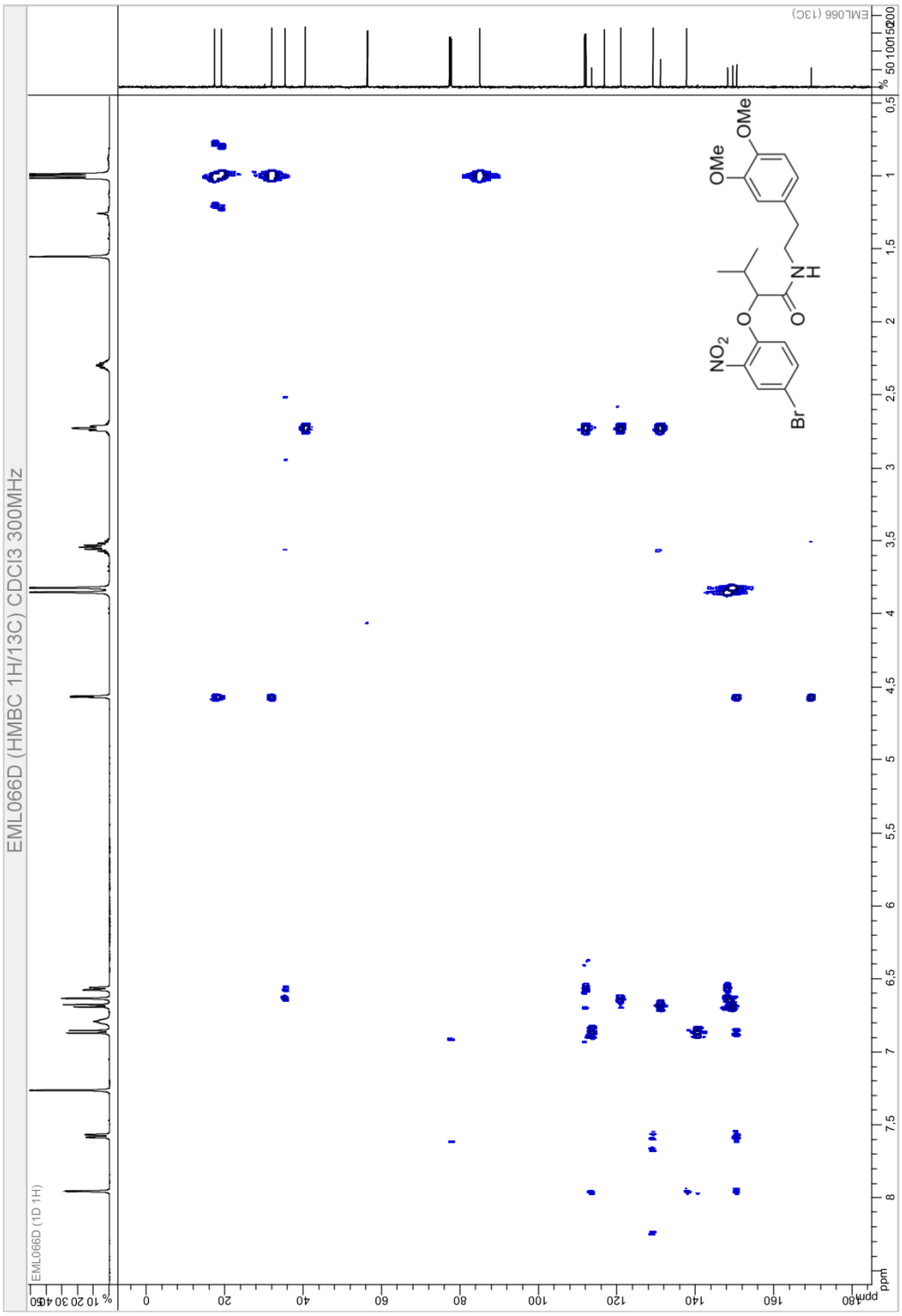




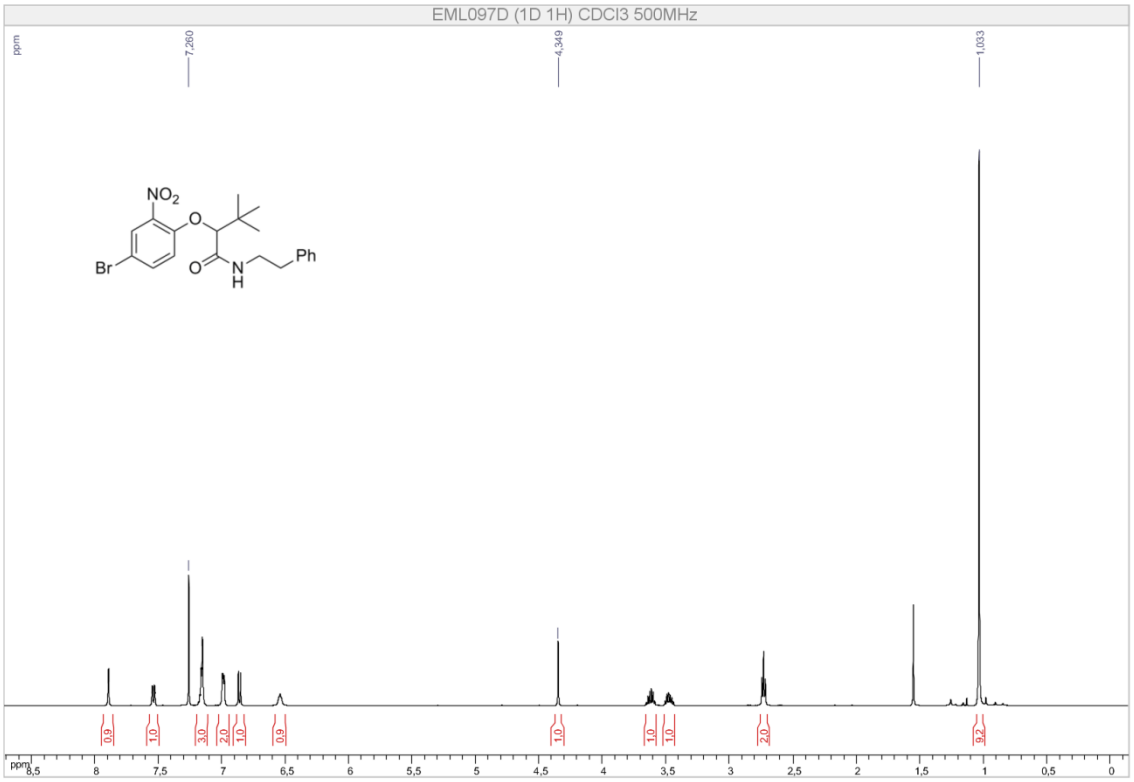
2-(4-bromo-2-nitrophenoxy)-*N*-(3,4-dimethoxyphenethyl)-3-methylbutanamide (1q)

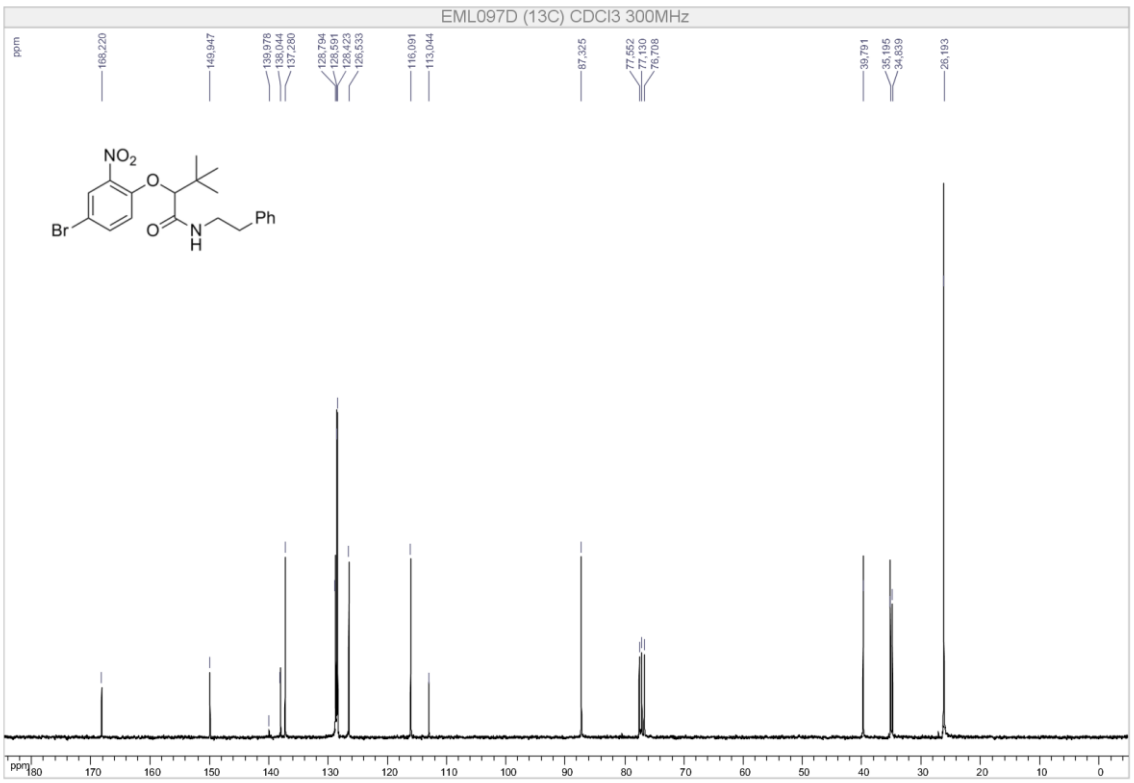


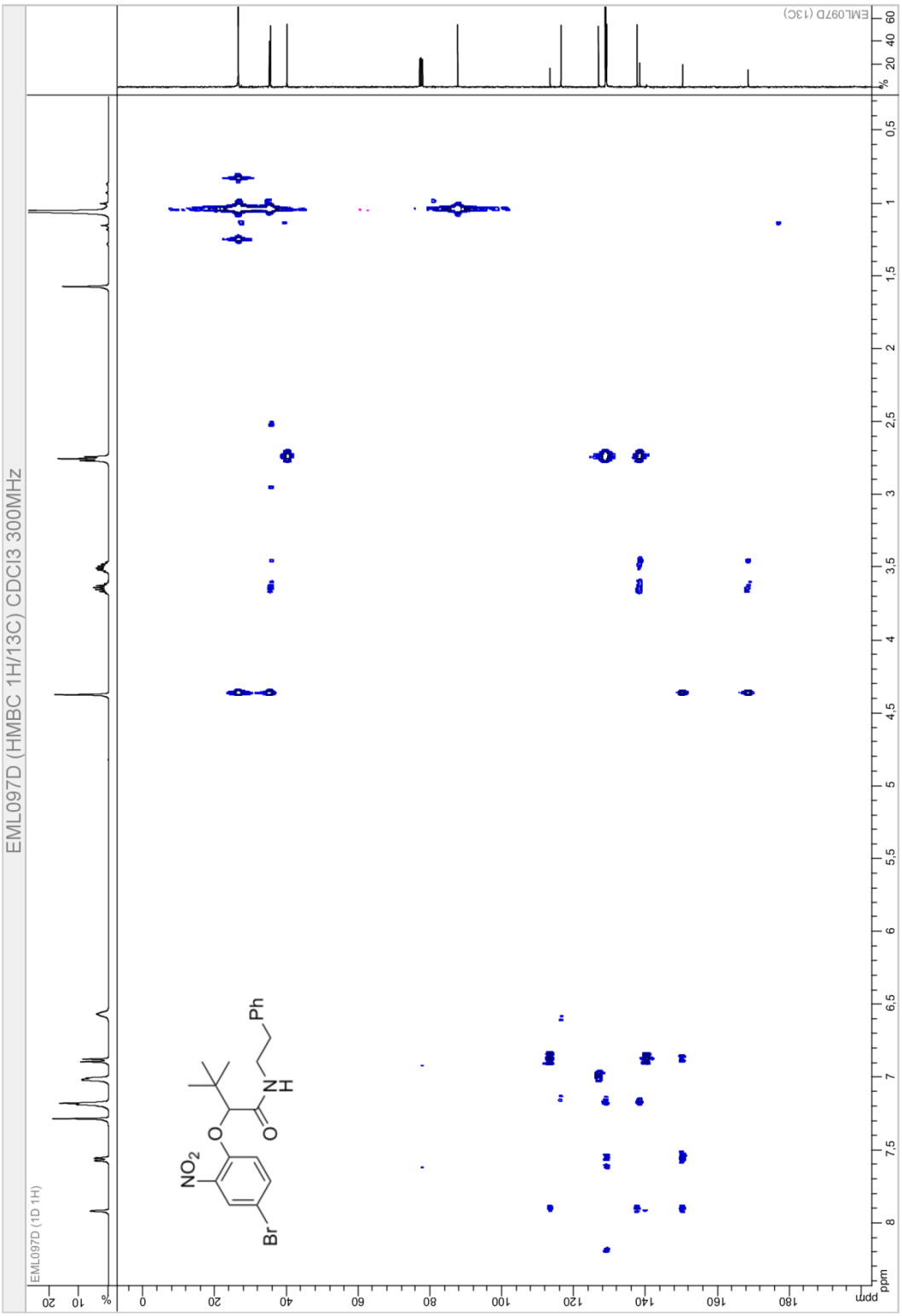



EML066D (HMBC 1H/13C) CDCl3 300MHz
EML066D (1D 1H)
EML066 (13C)
OMe
OMe
NO2
Br
O
O
N
H
ppm

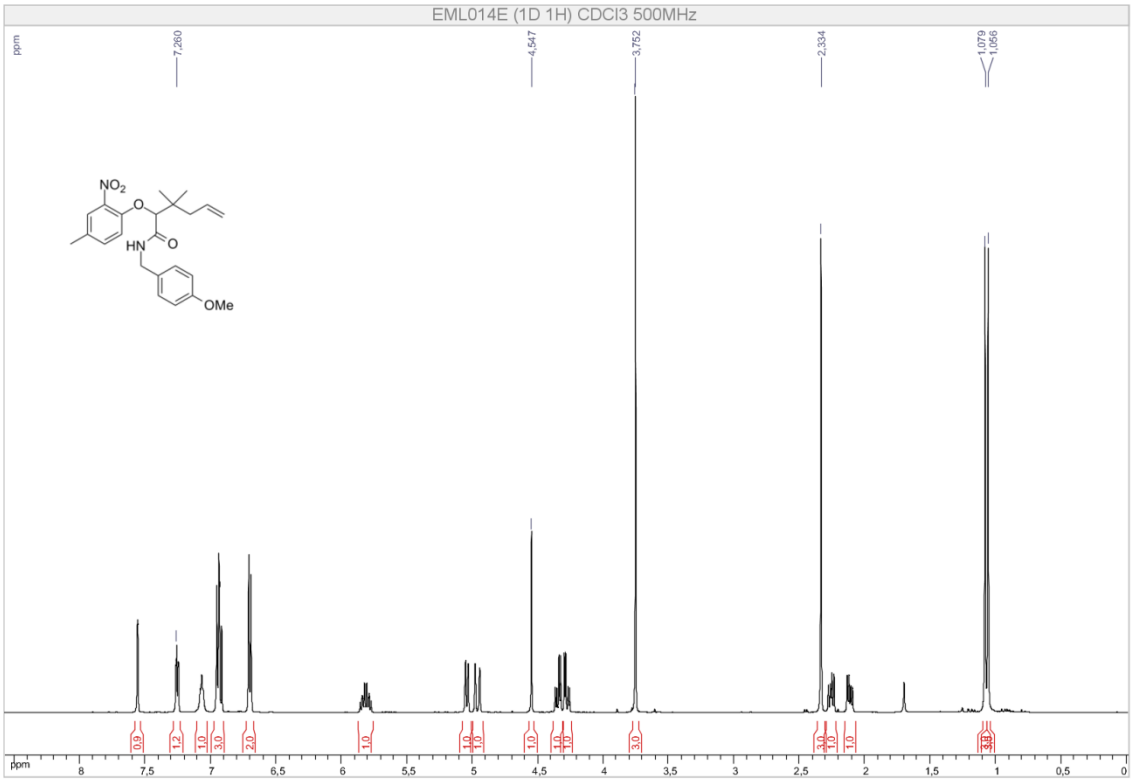
2-(4-bromo-2-nitrophenoxy)-3,3-dimethyl-*N*-phenethylbutanamide (1r)

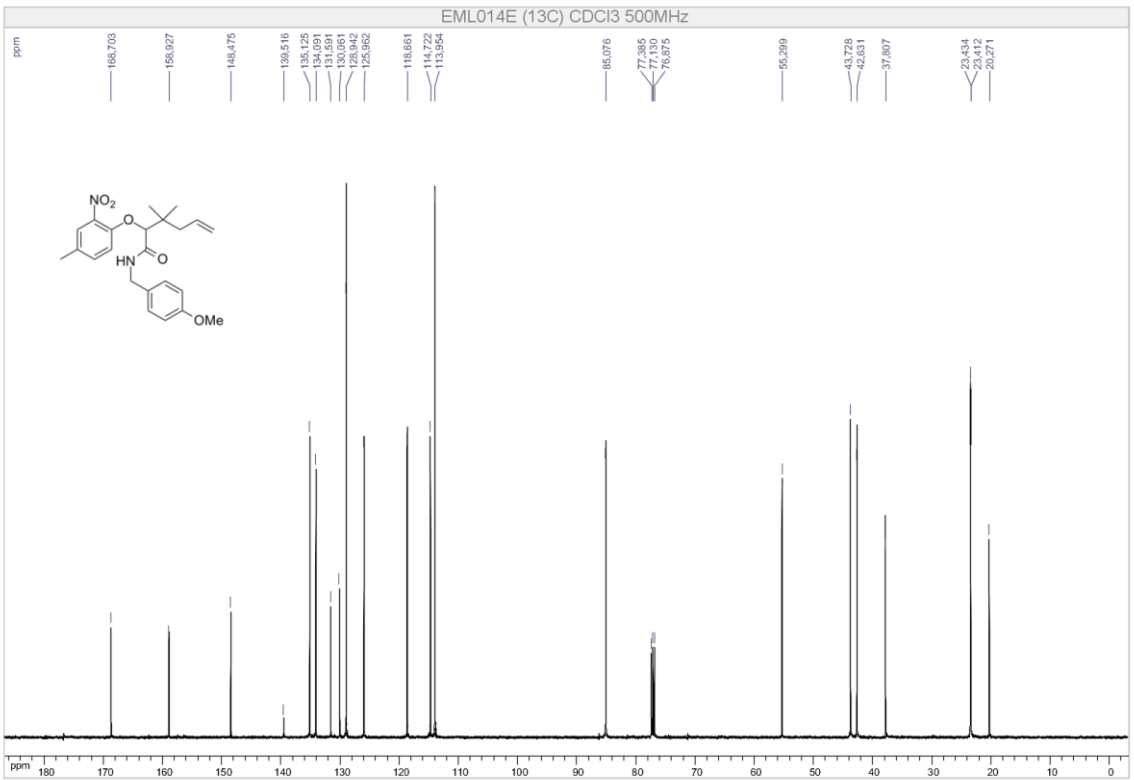




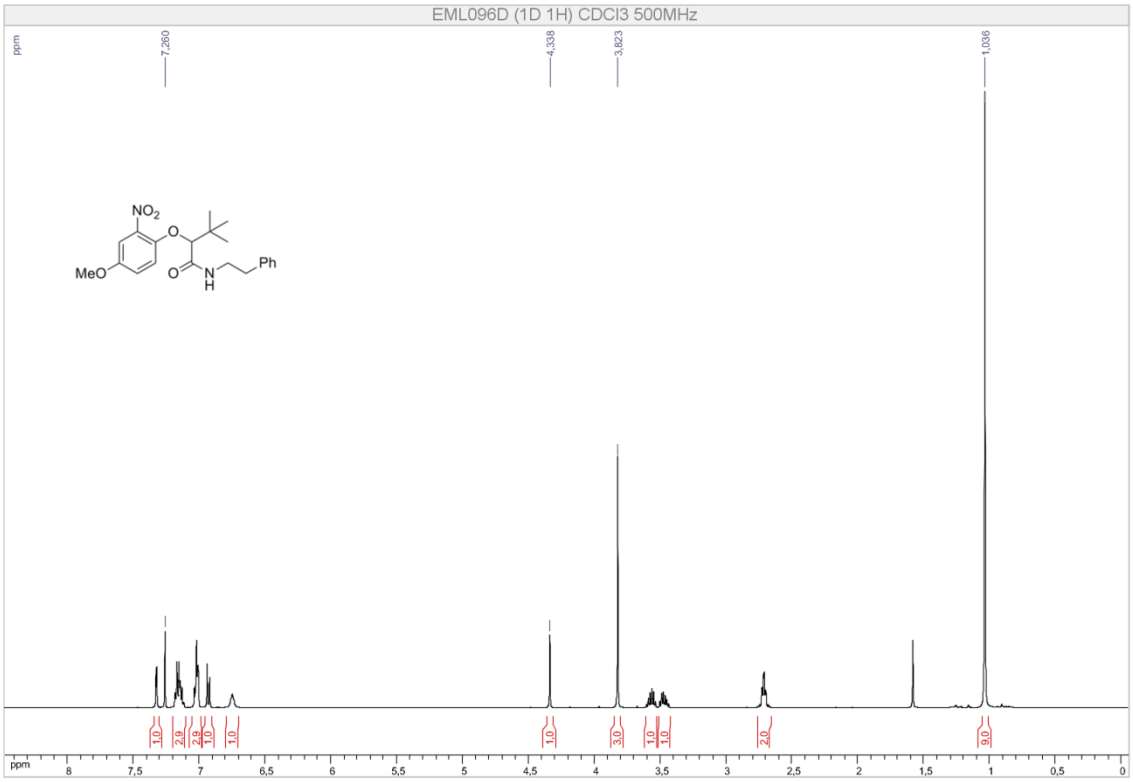

EML097D (HMBC 1H/13C) CDCl3 300MHz
EML097D (1D 1H)
EML097D (13C)
ppm
Ph
N
H
O
O
NO2
Br

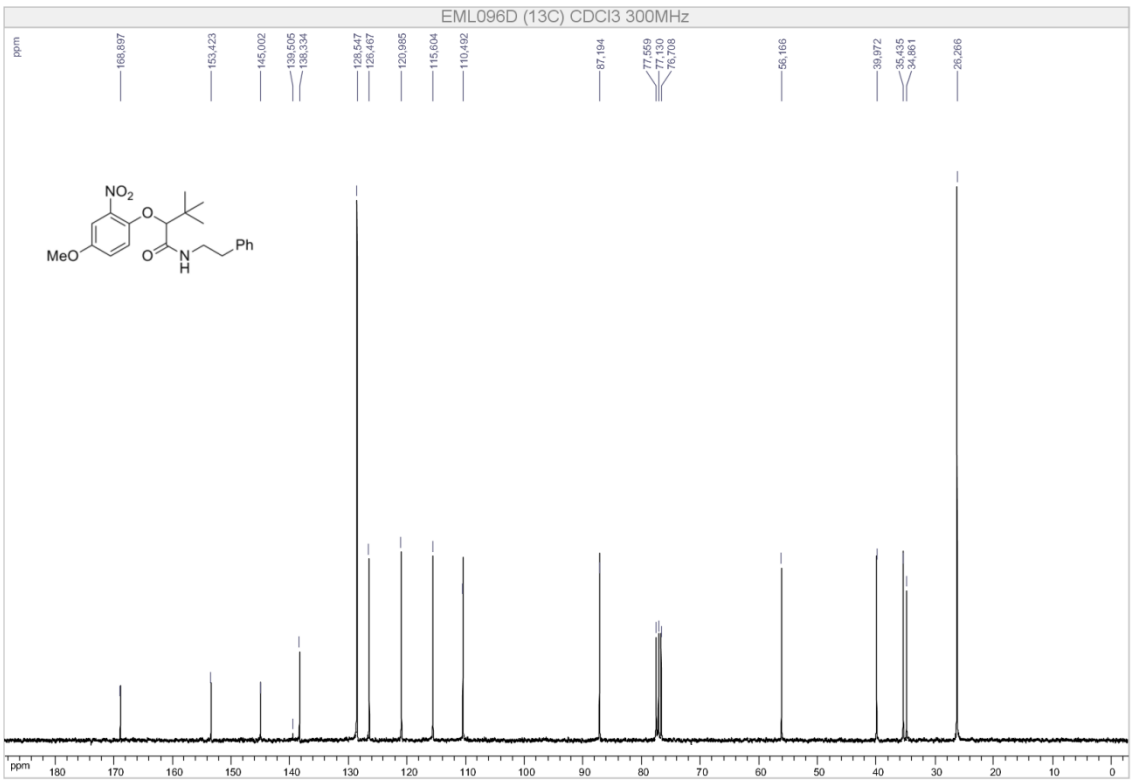
_N_-(4-methoxybenzyl)-3,3-dimethyl-2-(4-methyl-2-nitrophenoxy)hex-5-enamide (1s)

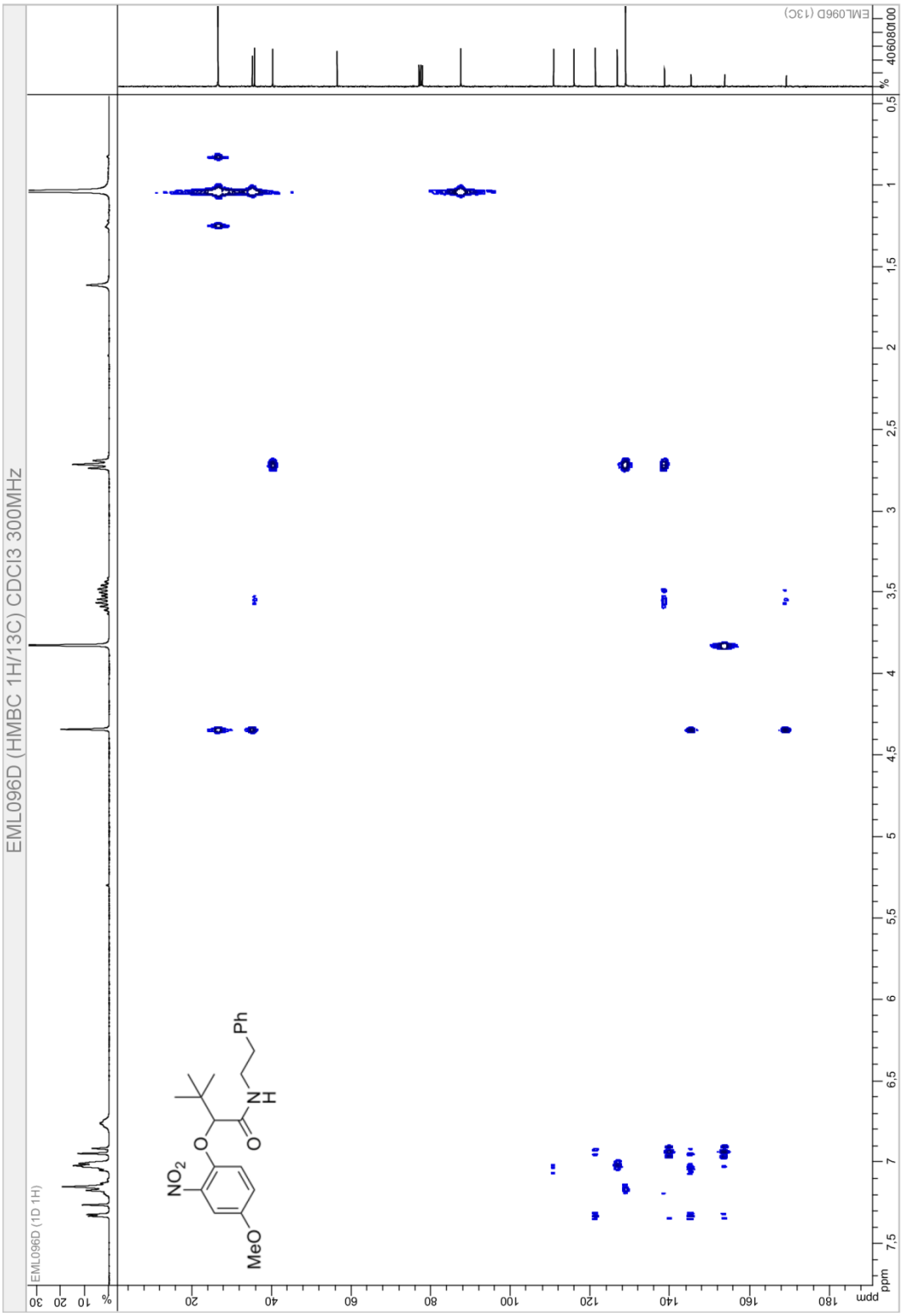




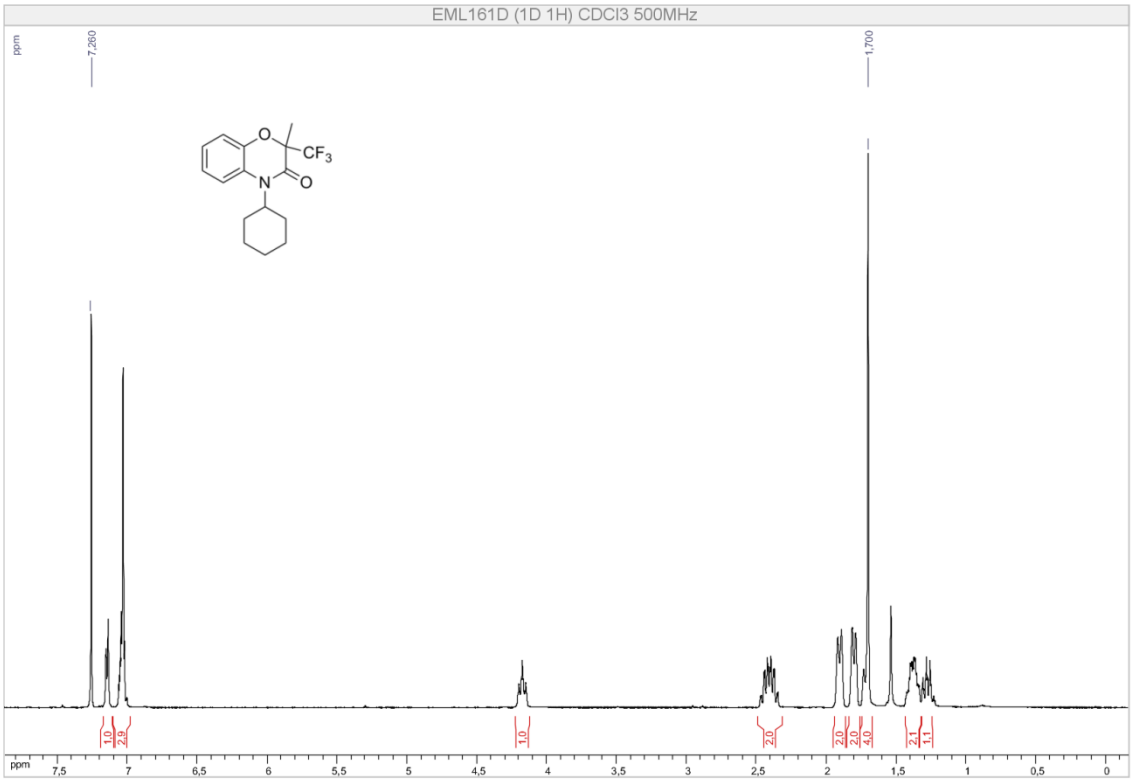
2-(4-methoxy-2-nitrophenoxy)-3,3-dimethyl-*N*-phenethylbutanamide (1t)

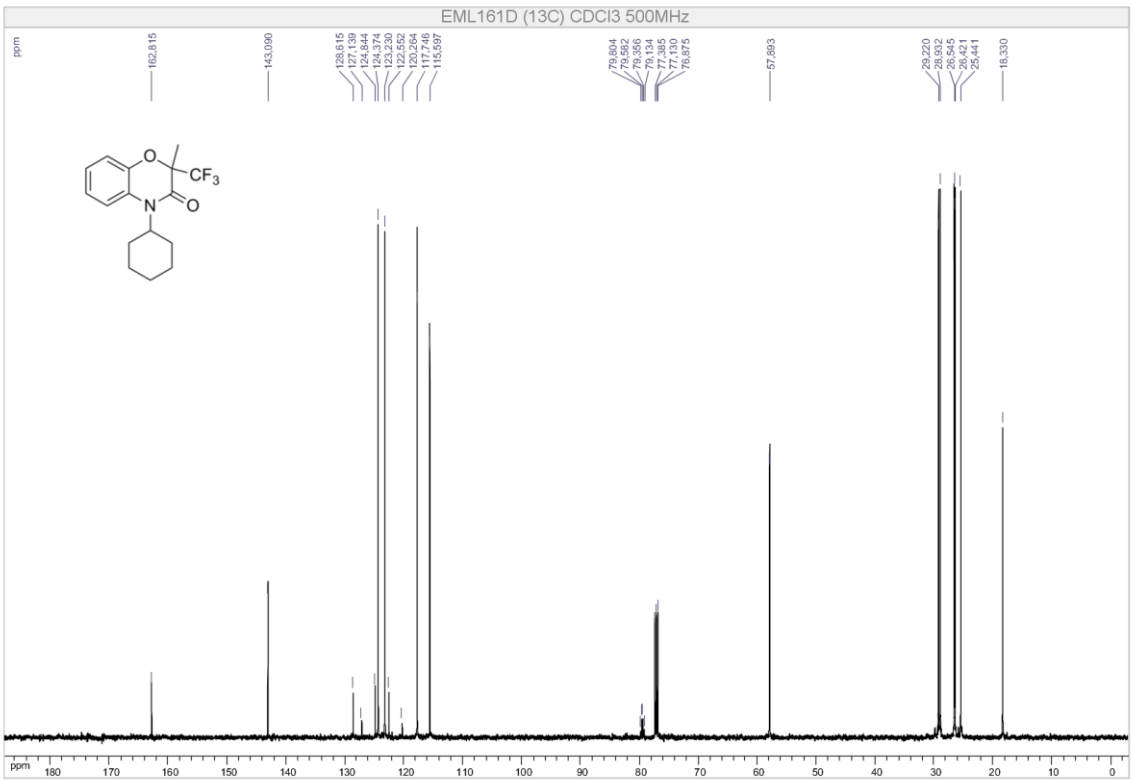




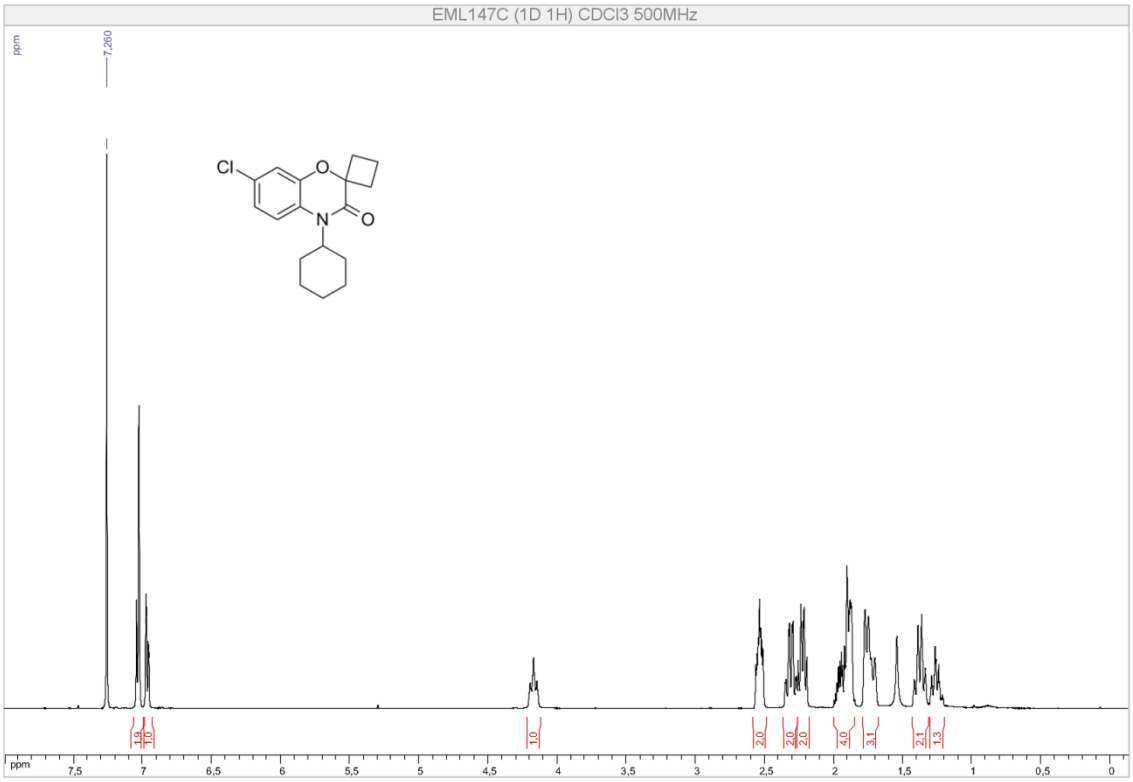

EML096D (HMBC 1H/13C) CDCl3 300MHz
EML096D (1D 1H)
EML096D (13C)
ppm
Ph
NH
O
O
NO2
MeO

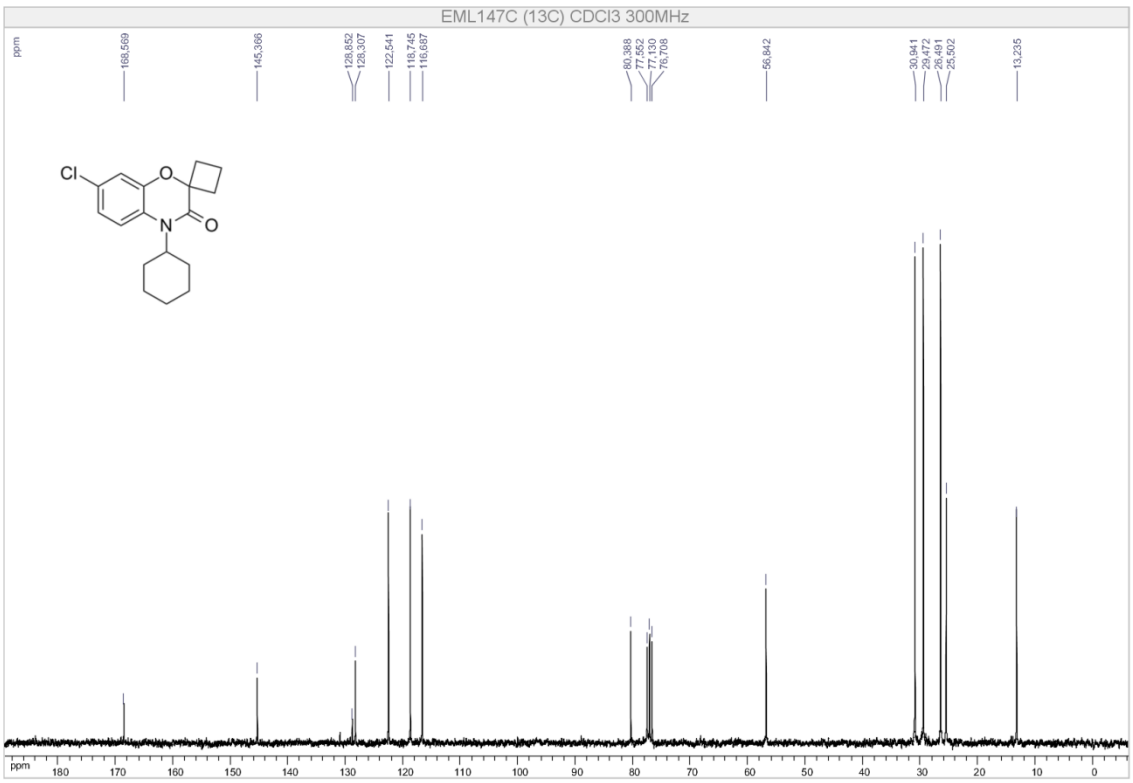
4-cyclohexyl-2-methyl-2-(trifluoromethyl)-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2a)



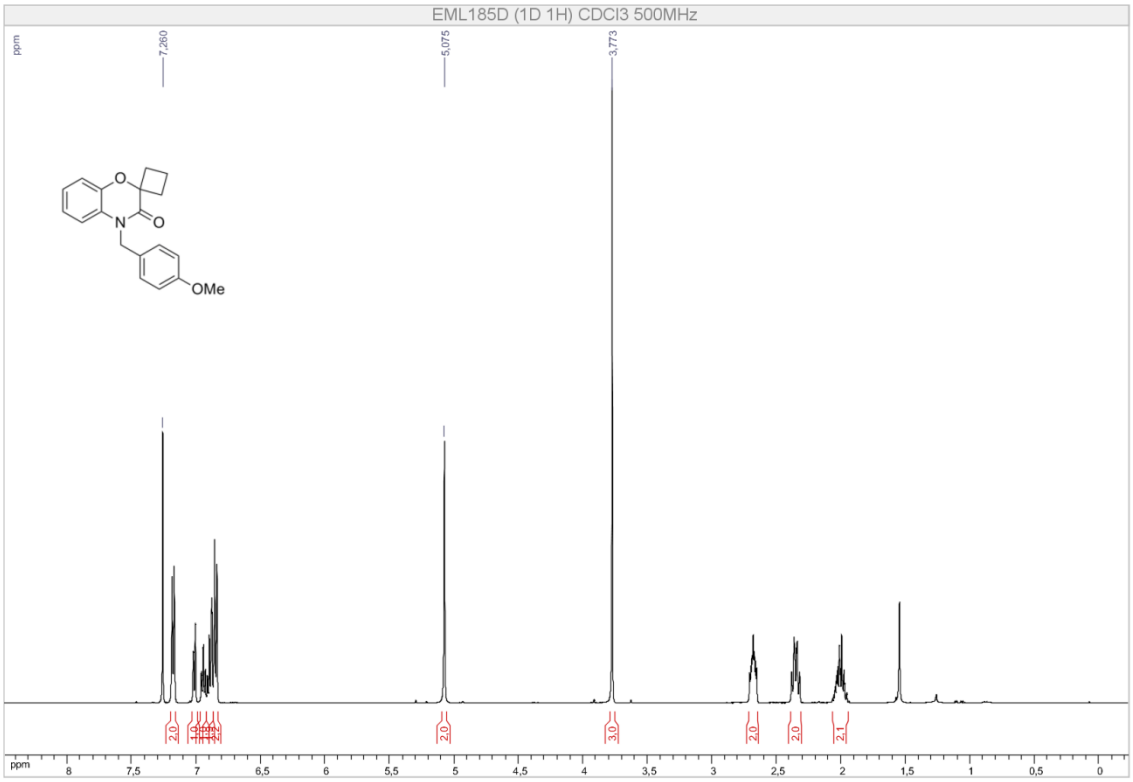


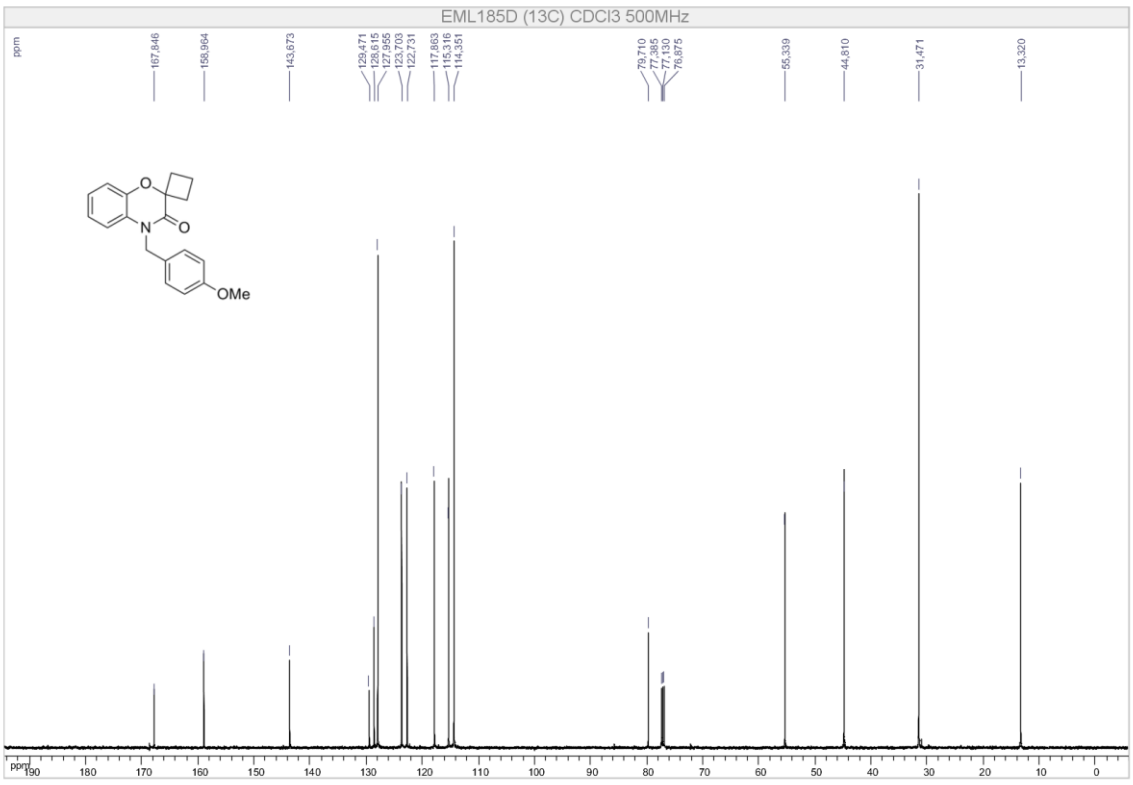
7-chloro-4-cyclohexylspiro[benzo[*b*][1,4]oxazine-2,1'-cyclobutan]-3(4*H*)-one (2b)



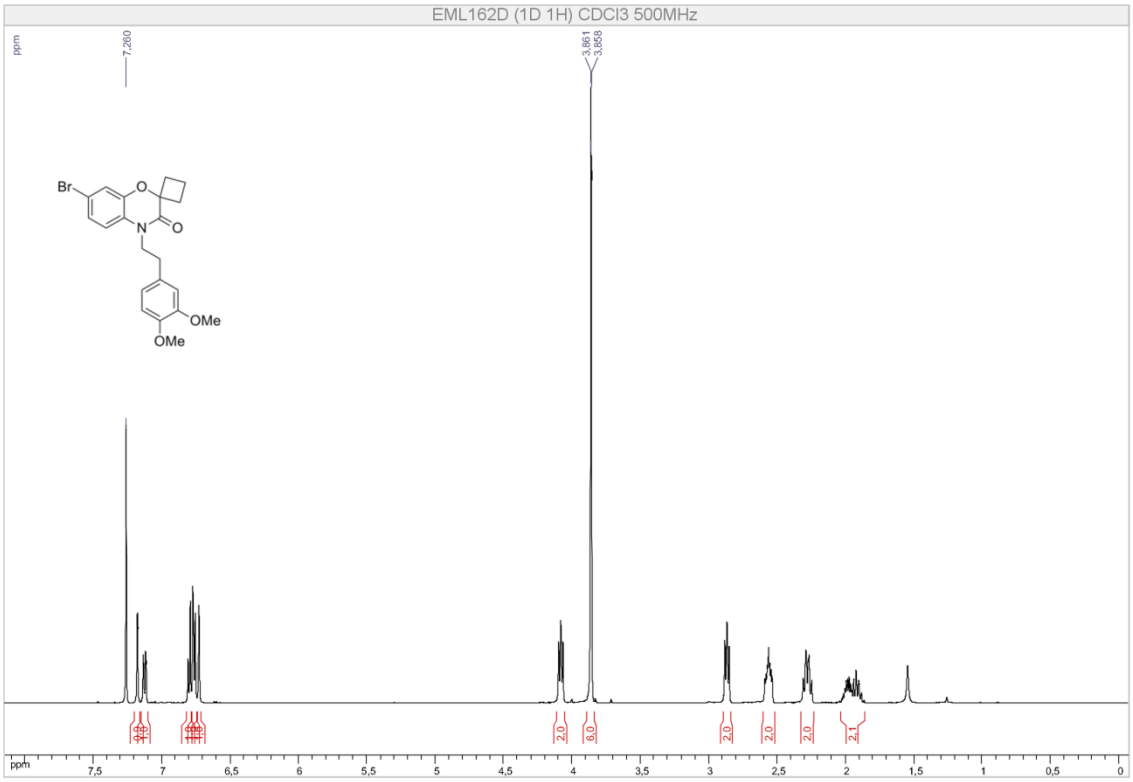


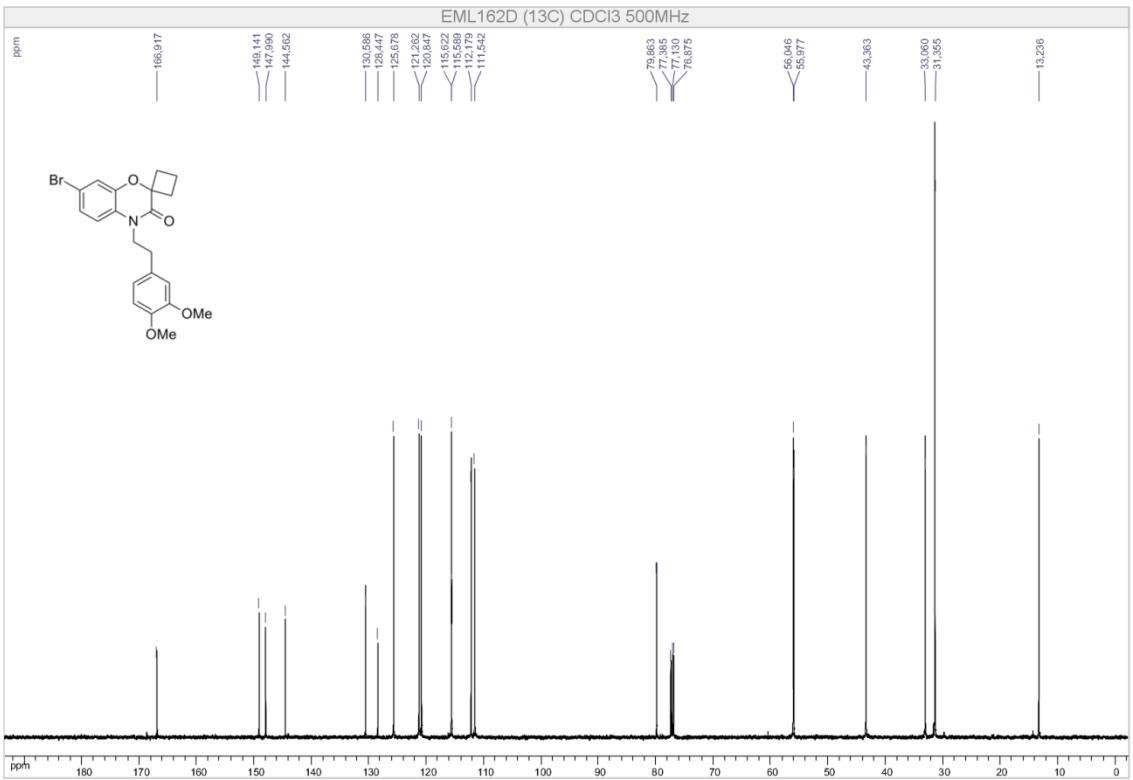
4-(4-methoxybenzyl)spiro[benzo[*b*][1,4]oxazine-2,1'-cyclobutan]-3(*4H*)-one (2c)



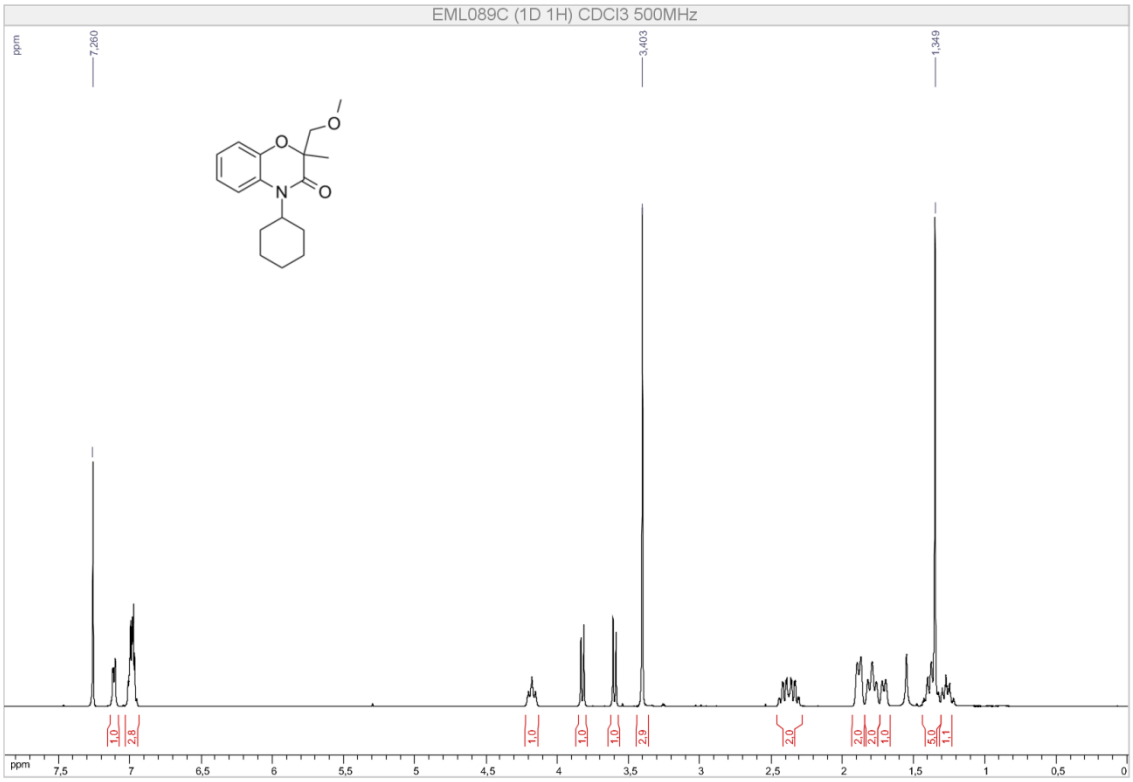


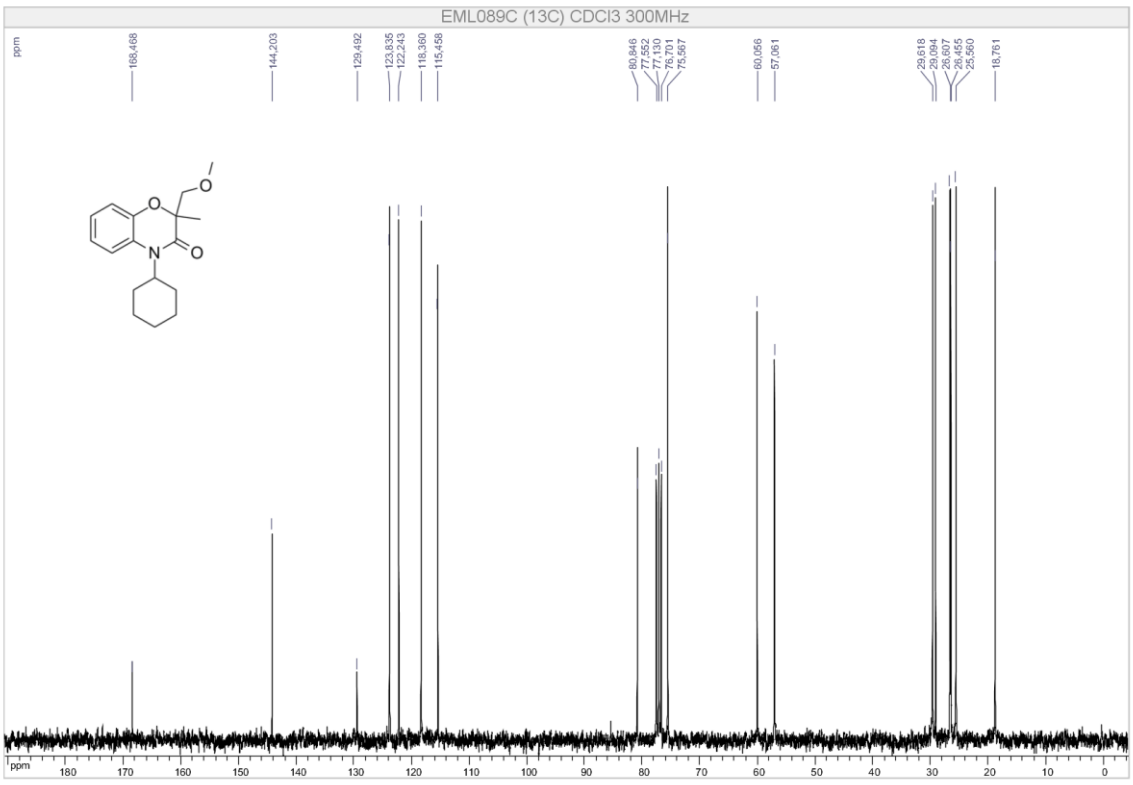
7-bromo-4-(3,4-dimethoxyphenethyl)spiro[benzo[*b*][1,4]oxazine-2,1'-cyclobutan]-3(*4H*)-one (2d)



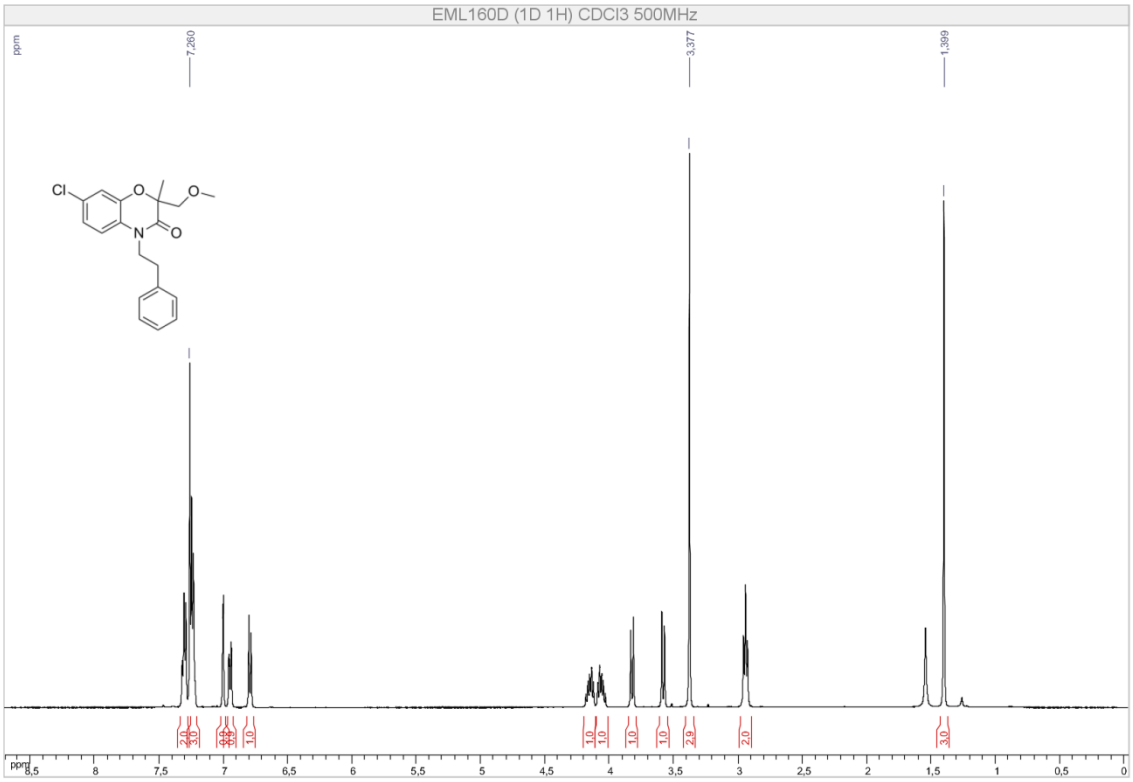


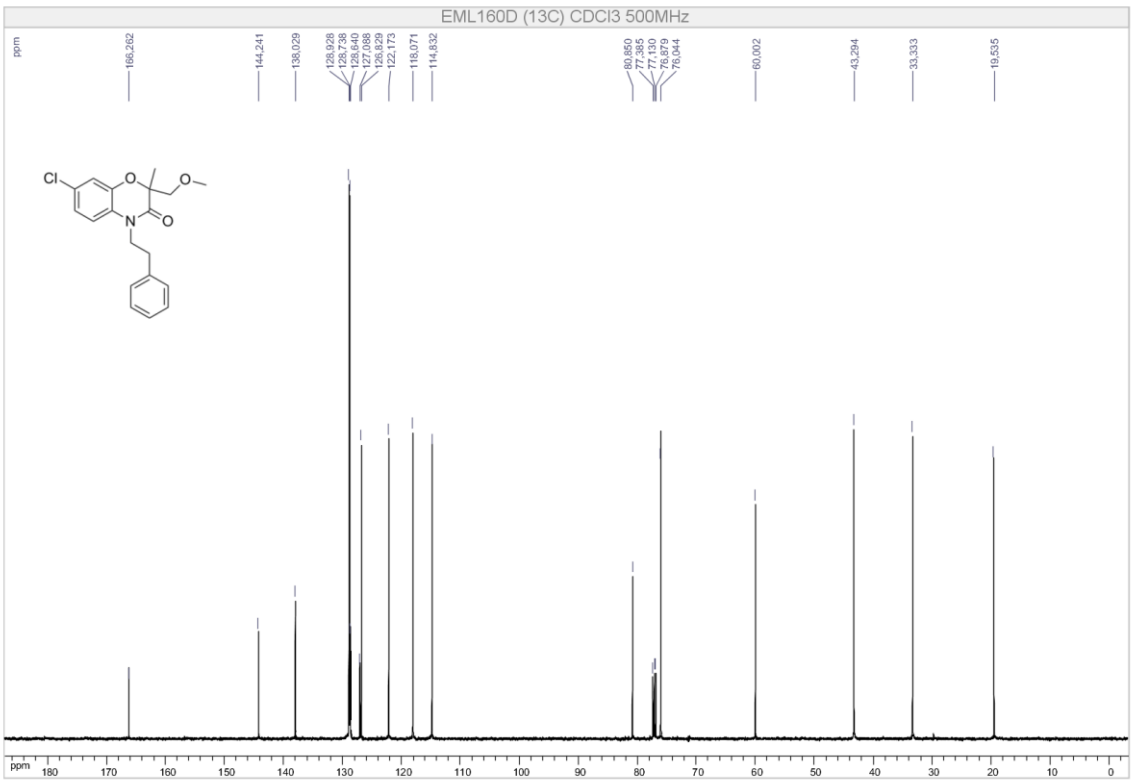
4-cyclohexyl-2-(methoxymethyl)-2-methyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2e)



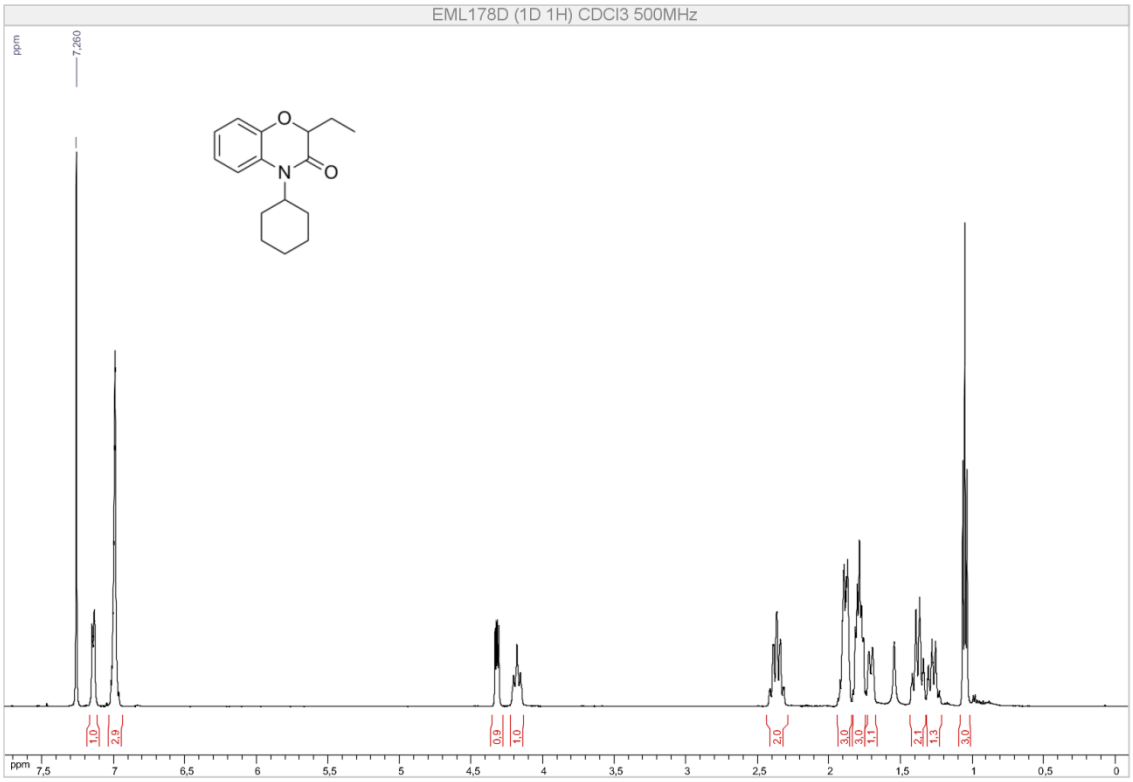


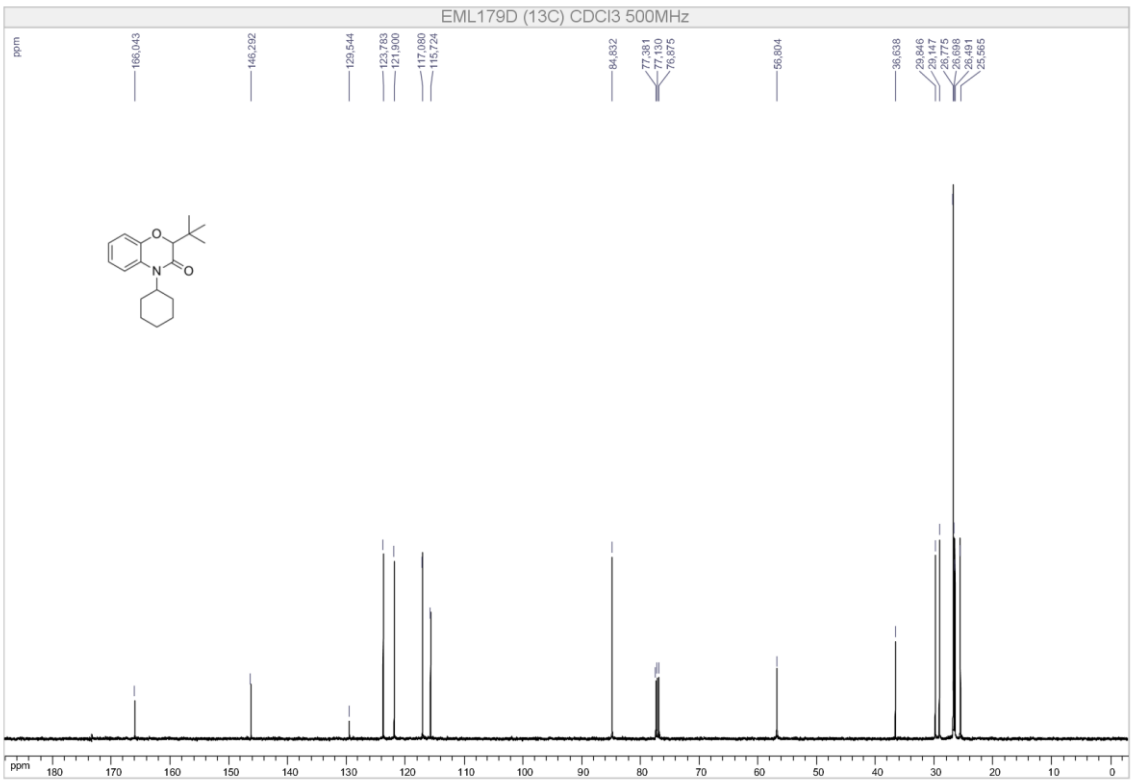
7-chloro-2-(methoxymethyl)-2-methyl-4-phenethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2f)



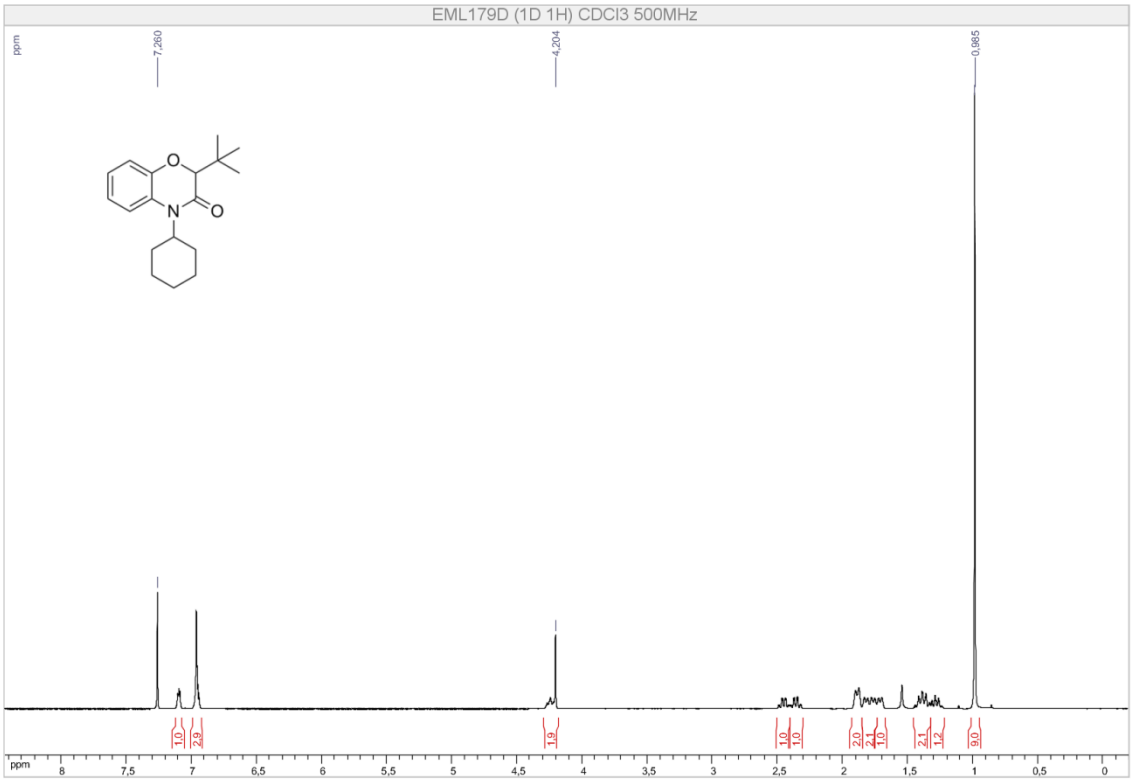


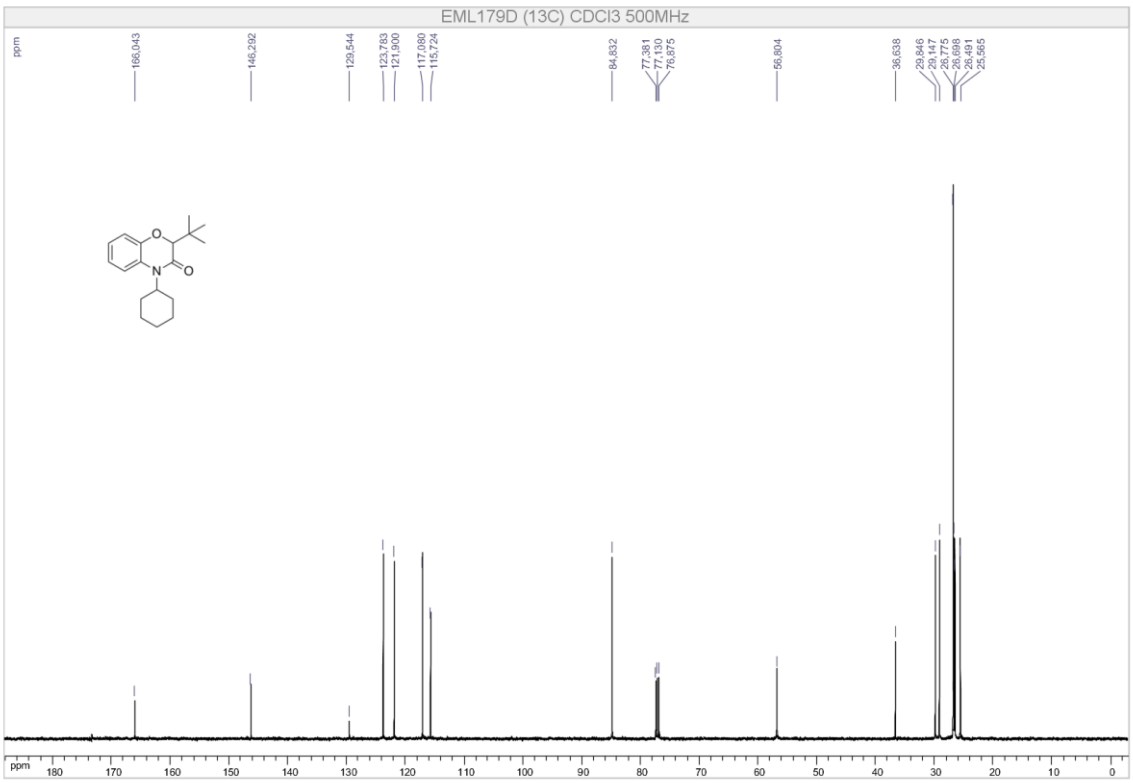
4-cyclohexyl-2-ethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2g)



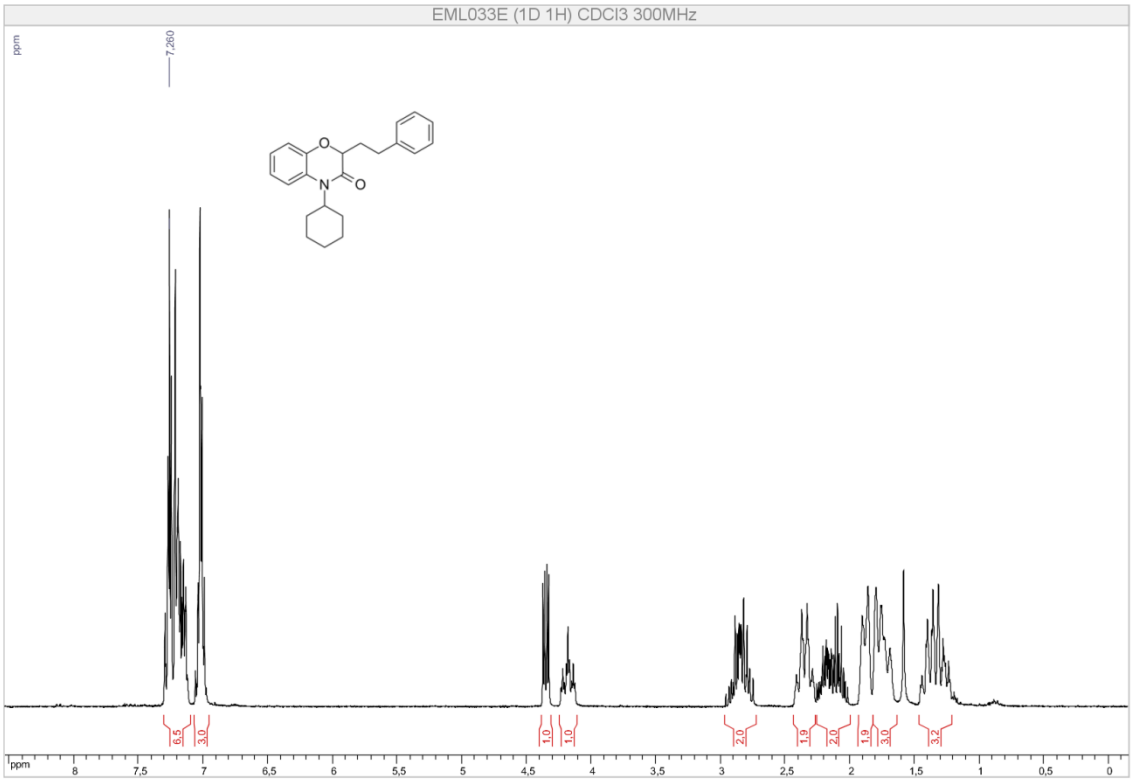


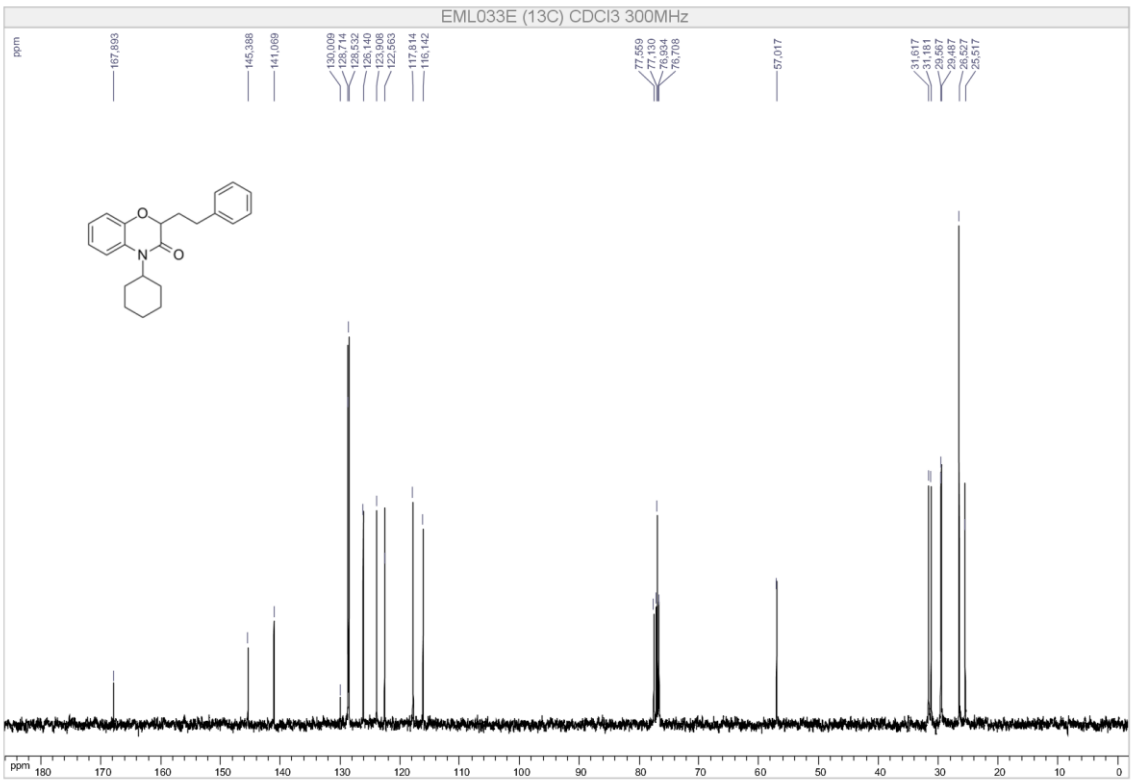
2-(tert-butyl)-4-cyclohexyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2h)



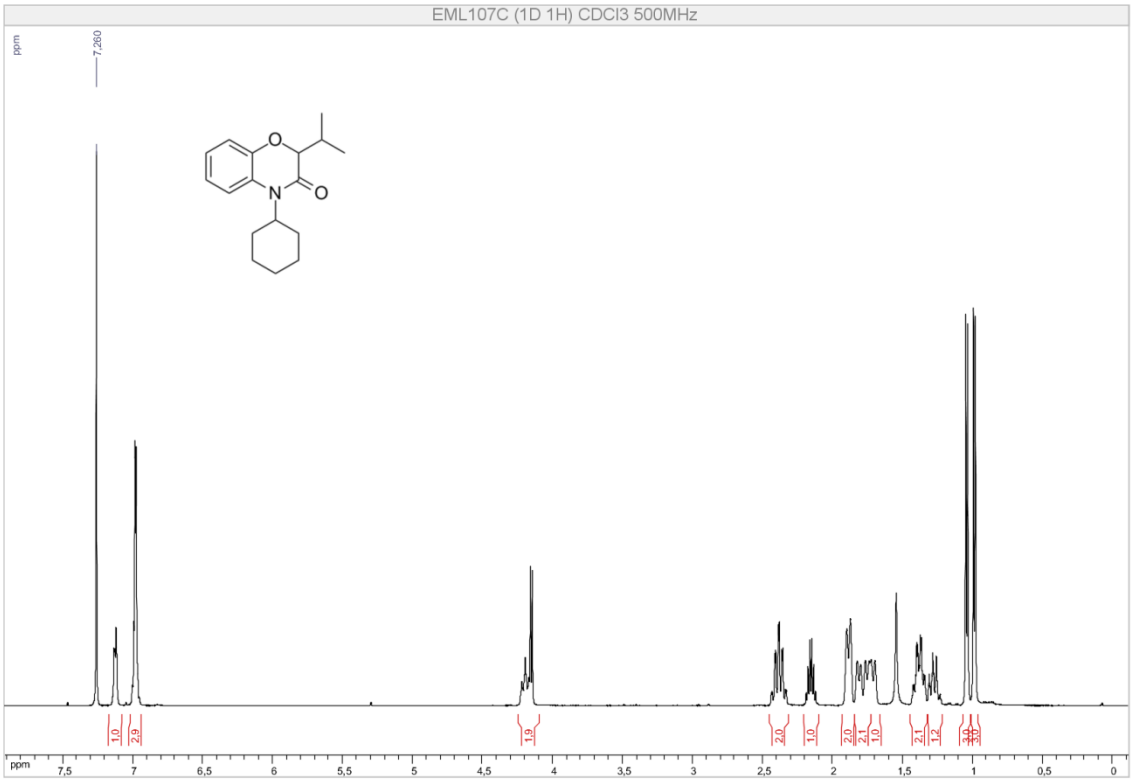


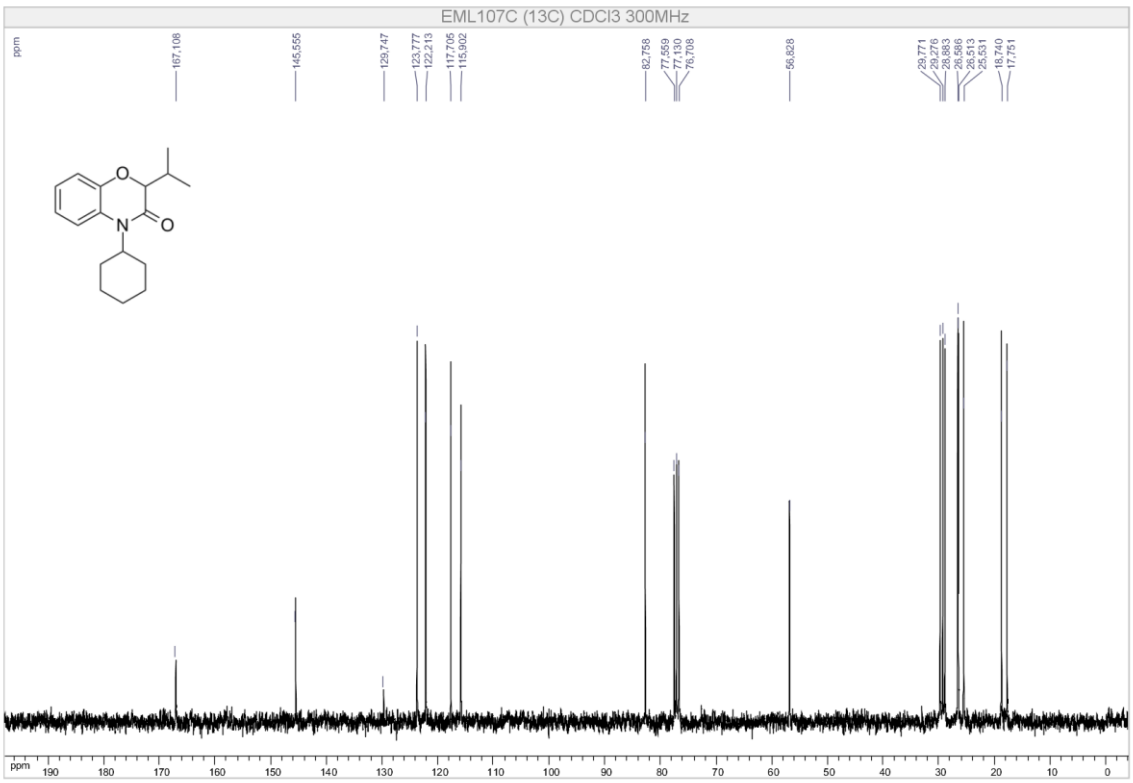
4-cyclohexyl-2-phenethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2i)



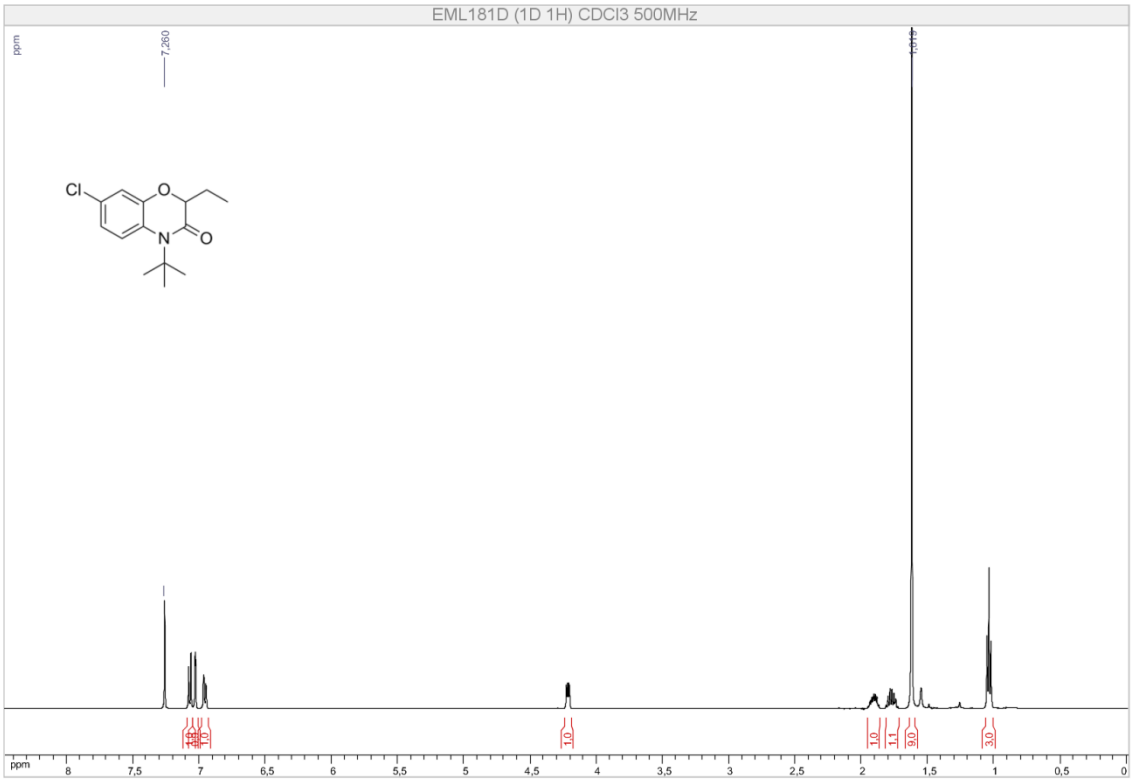


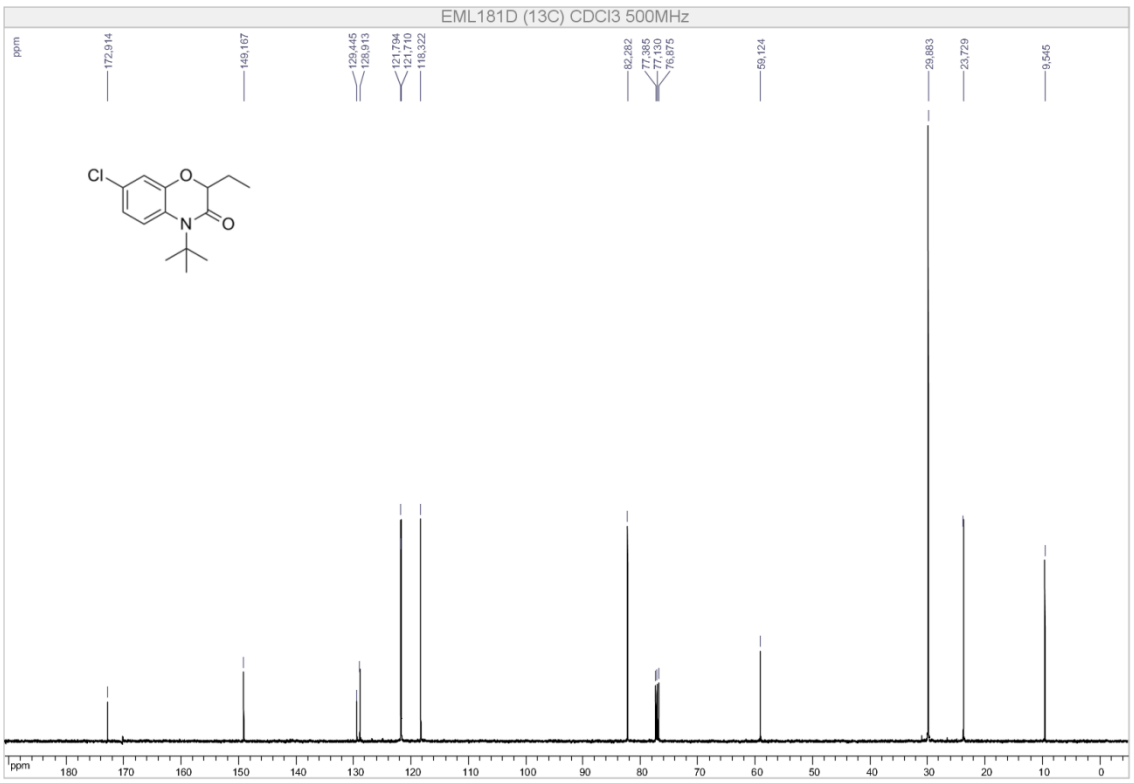
4-cyclohexyl-2-isopropyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (2j)



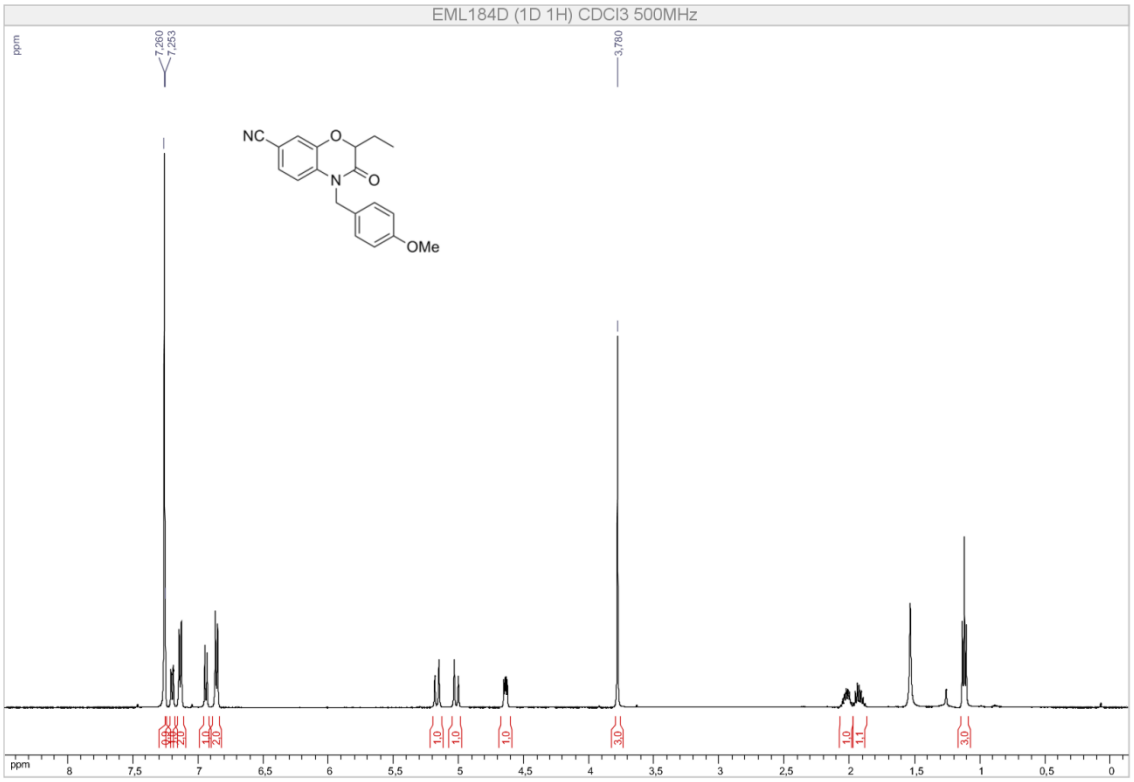


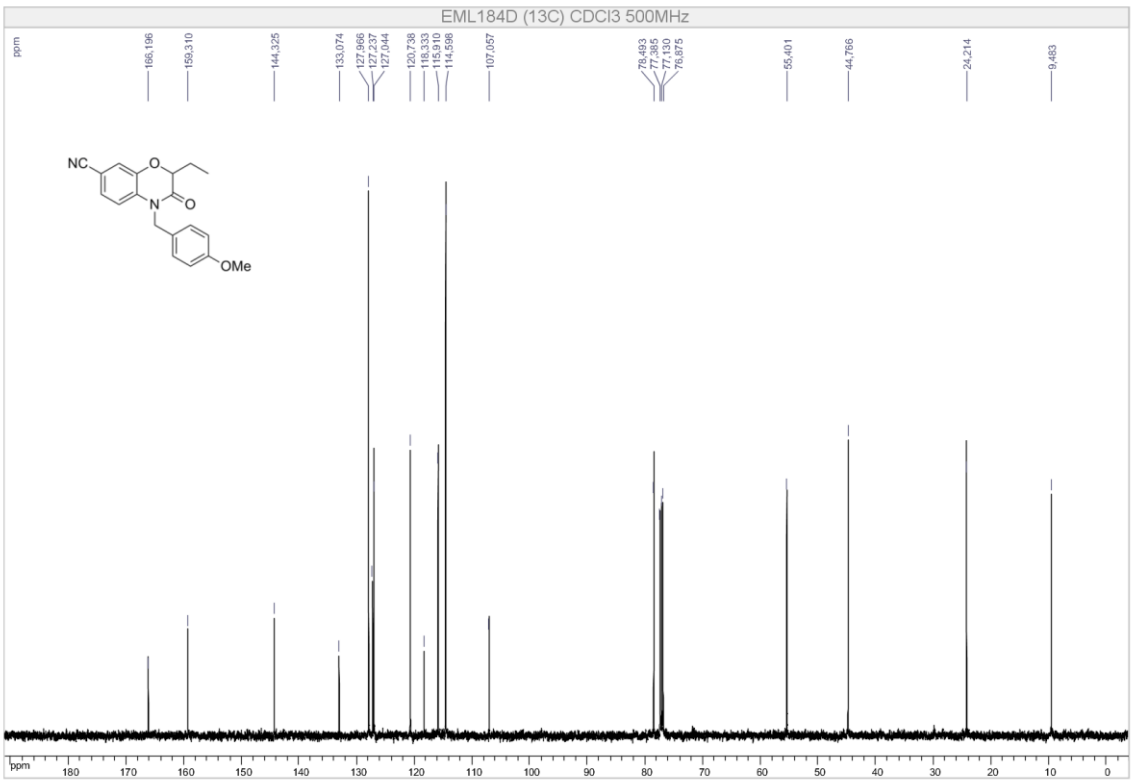
4-(tert-butyl)-7-chloro-2-ethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2k)



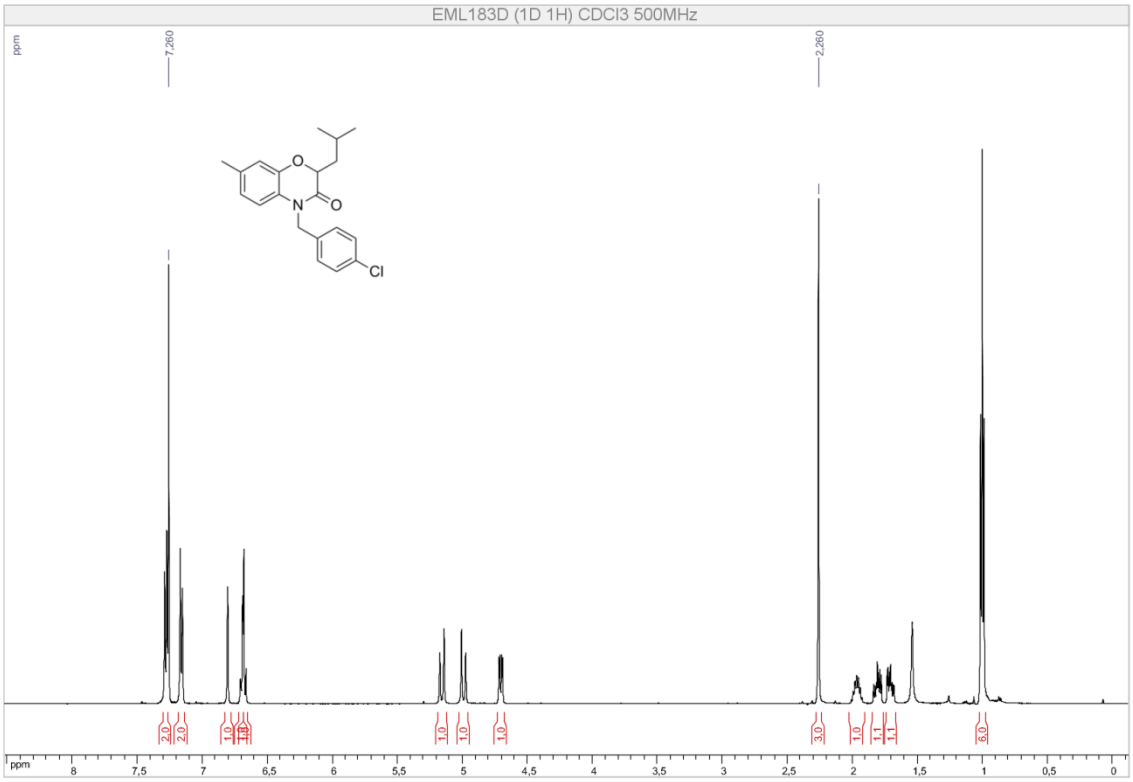


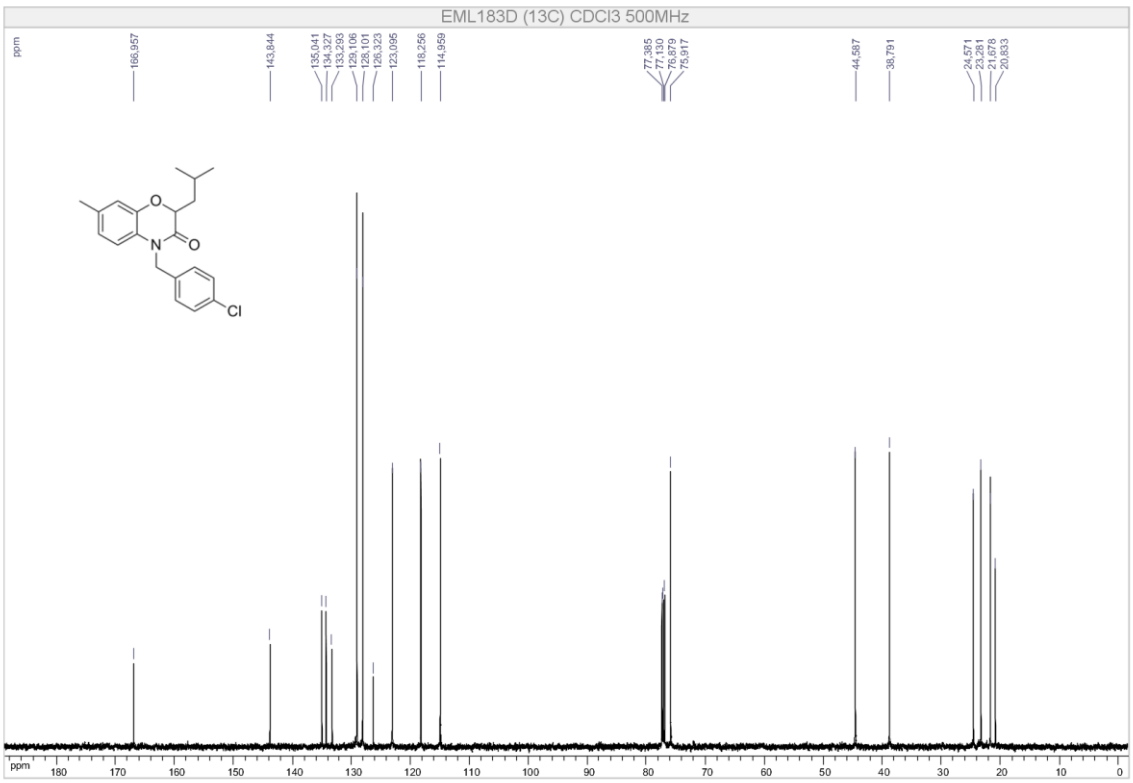
2-ethyl-4-(4-methoxybenzyl)-3-oxo-3,4-dihydro-*2H*-benzo[*b*][1,4]oxazine-7-carbonitrile (2l)



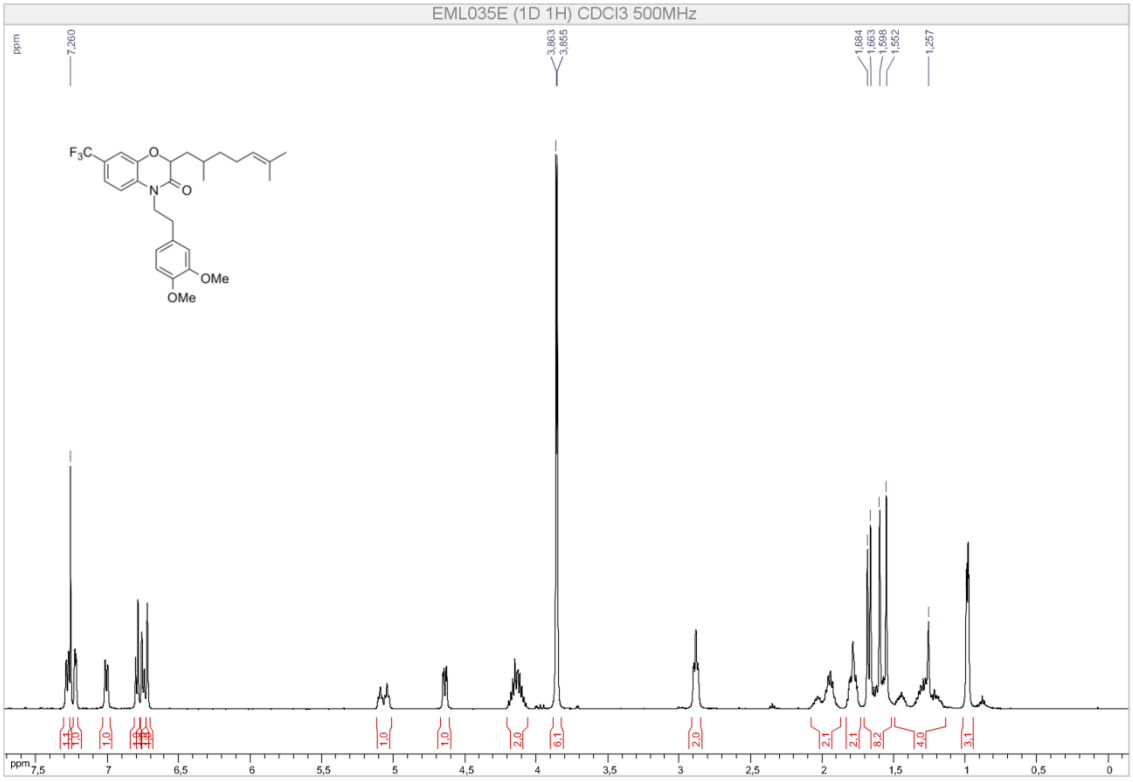


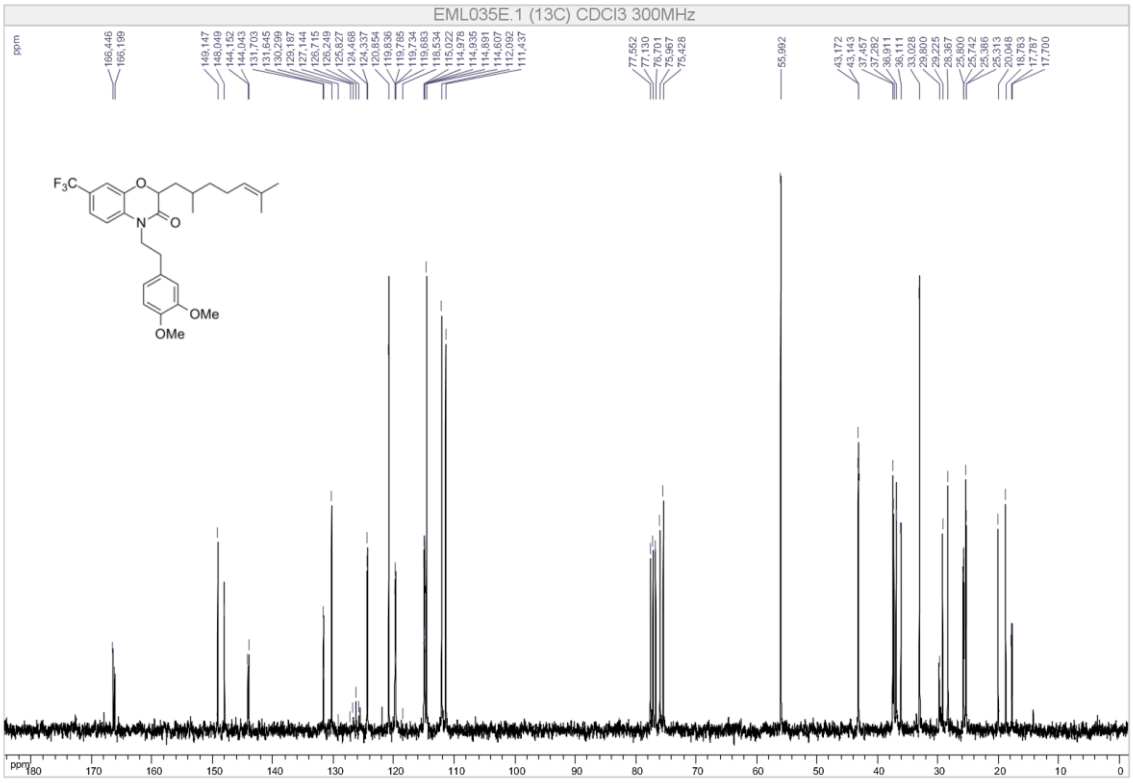
4-(4-chlorobenzyl)-2-isobutyl-7-methyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2m)



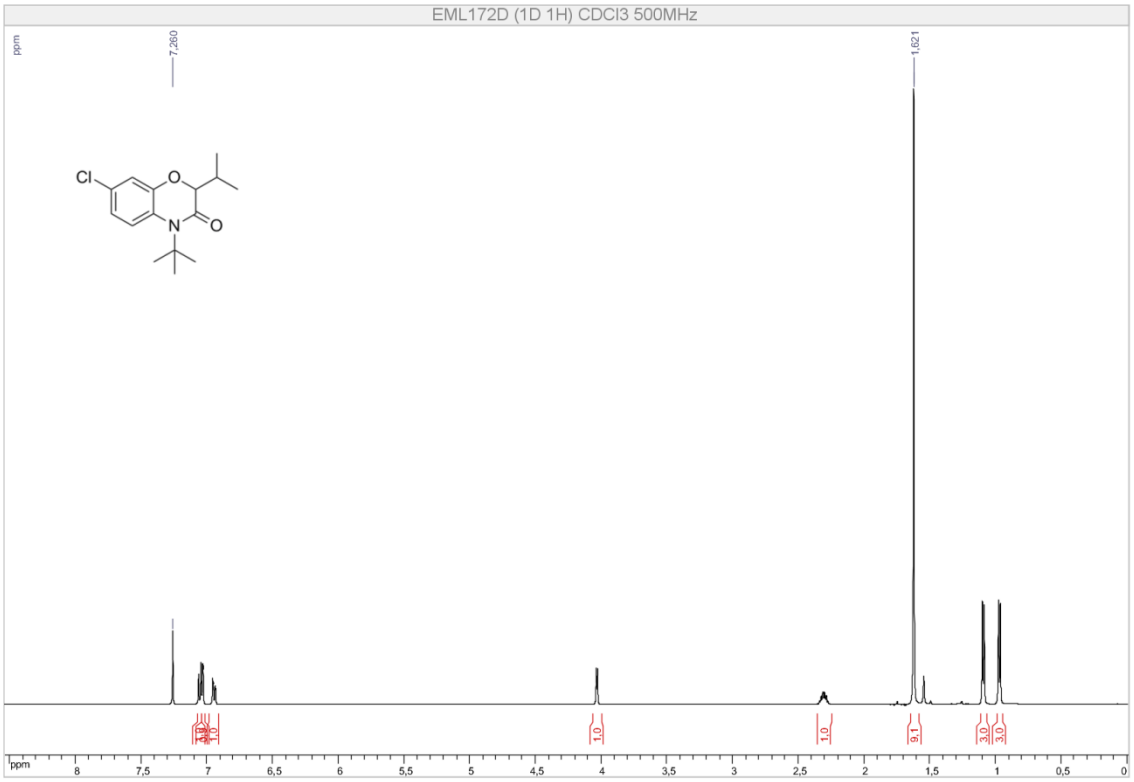


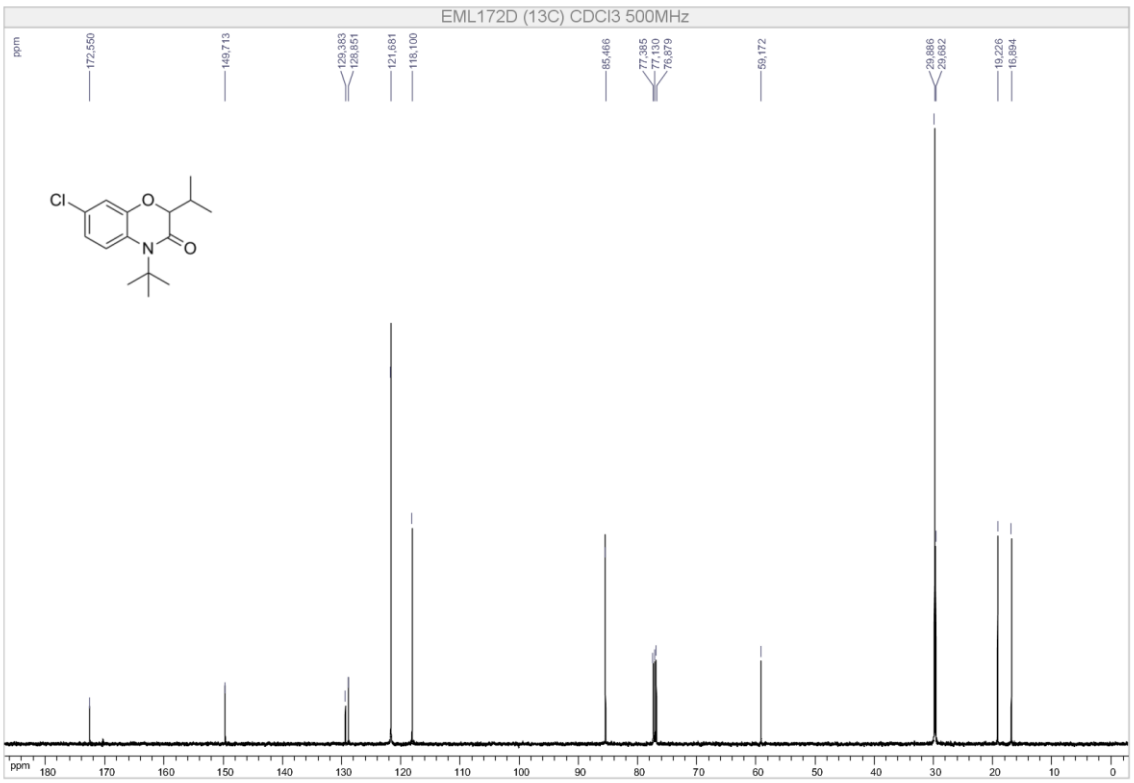
4-(3,4-dimethoxyphenethyl)-2-(2,6-dimethylhept-5-en-1-yl)-7-(trifluoromethyl)-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2n)



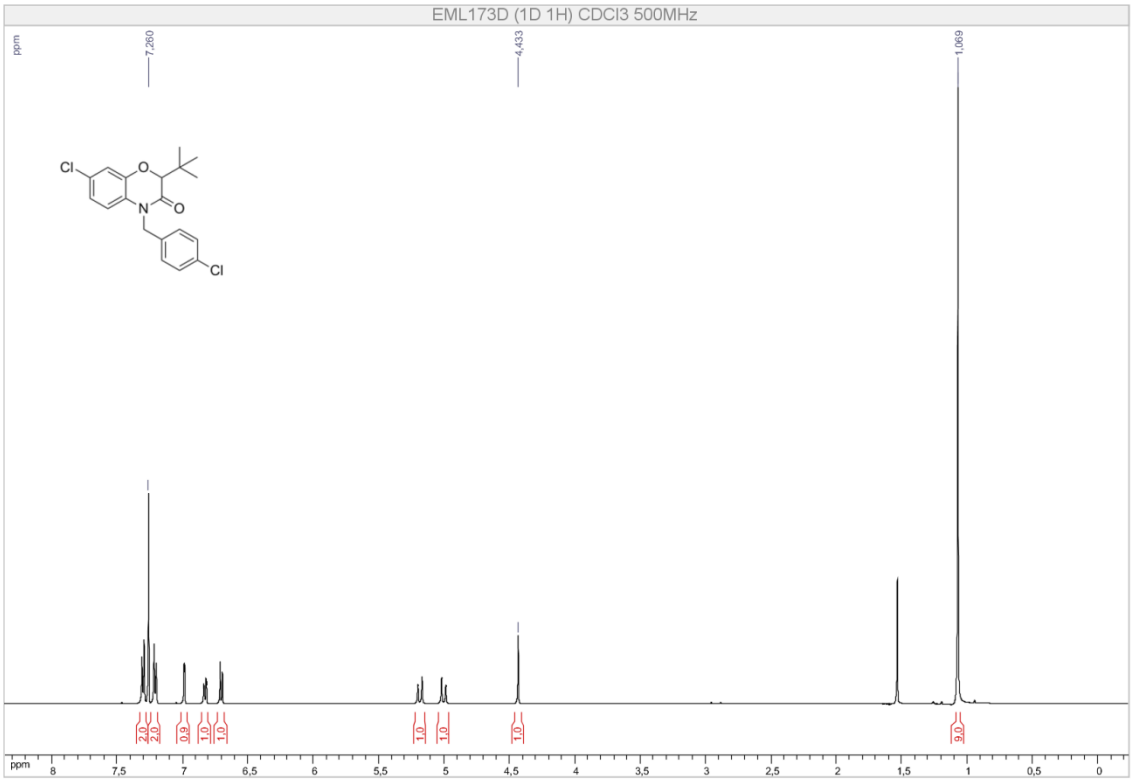


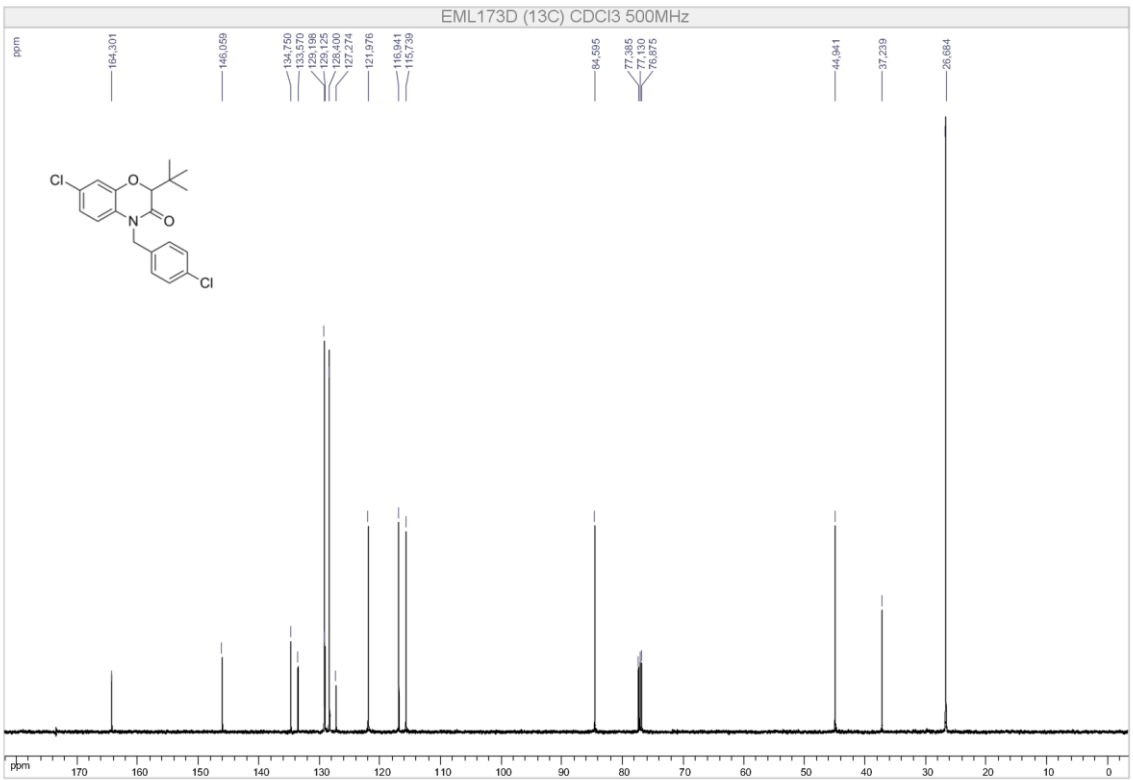
4-(tert-butyl)-7-chloro-2-isopropyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2o)



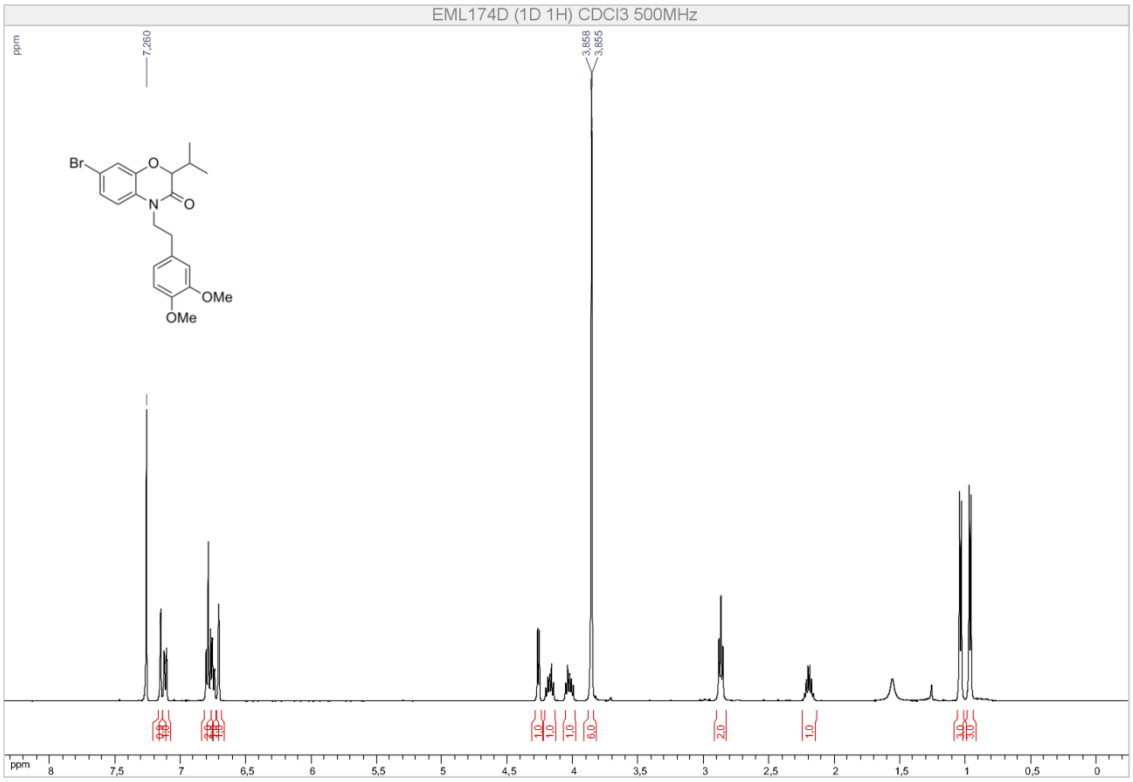


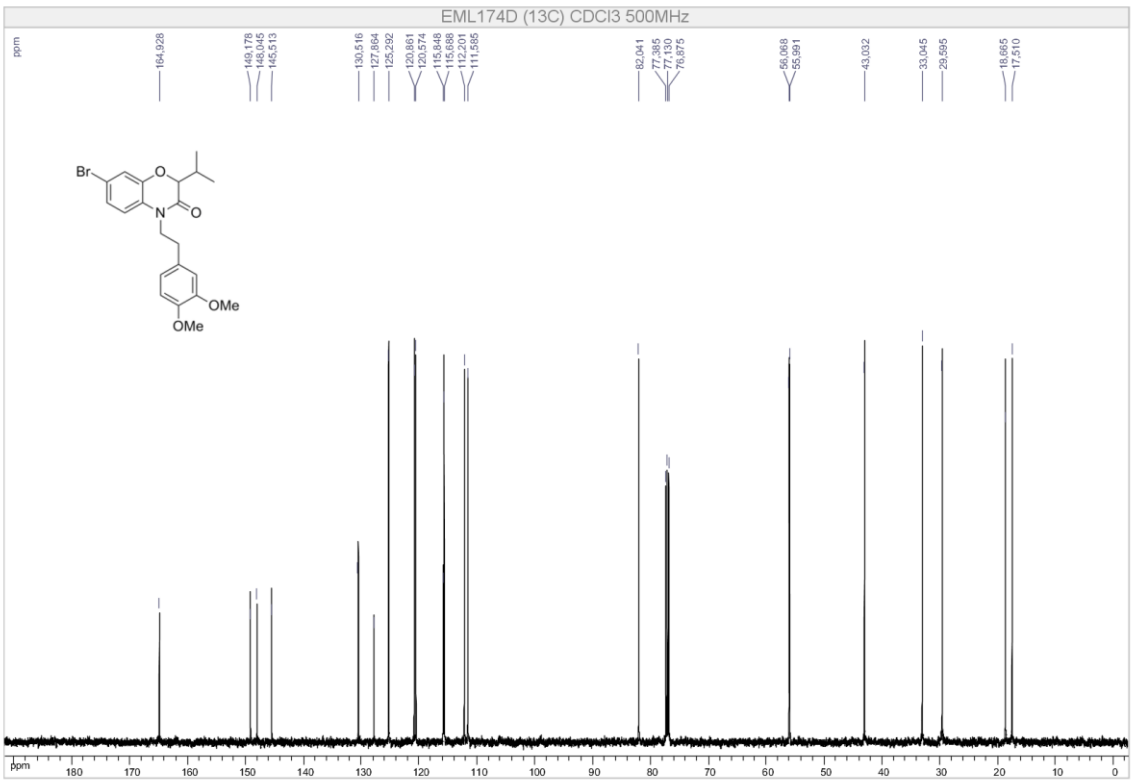
2-(tert-butyl)-7-chloro-4-(4-chlorobenzyl)-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2p)



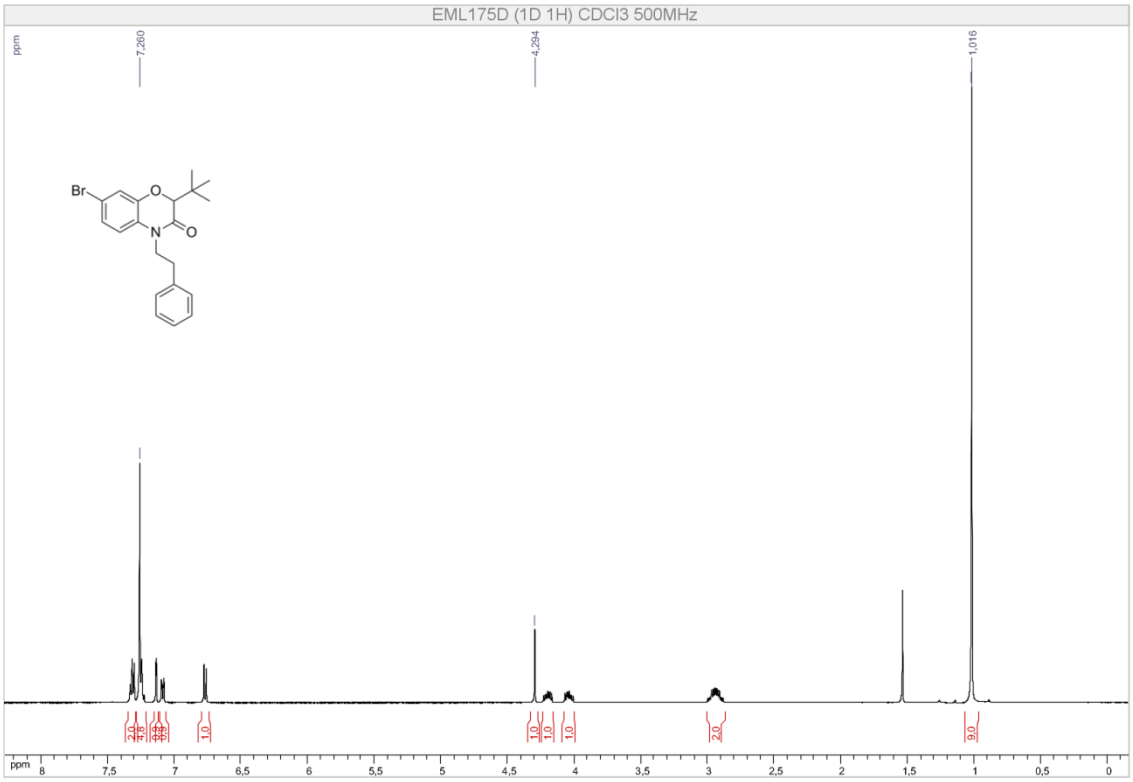


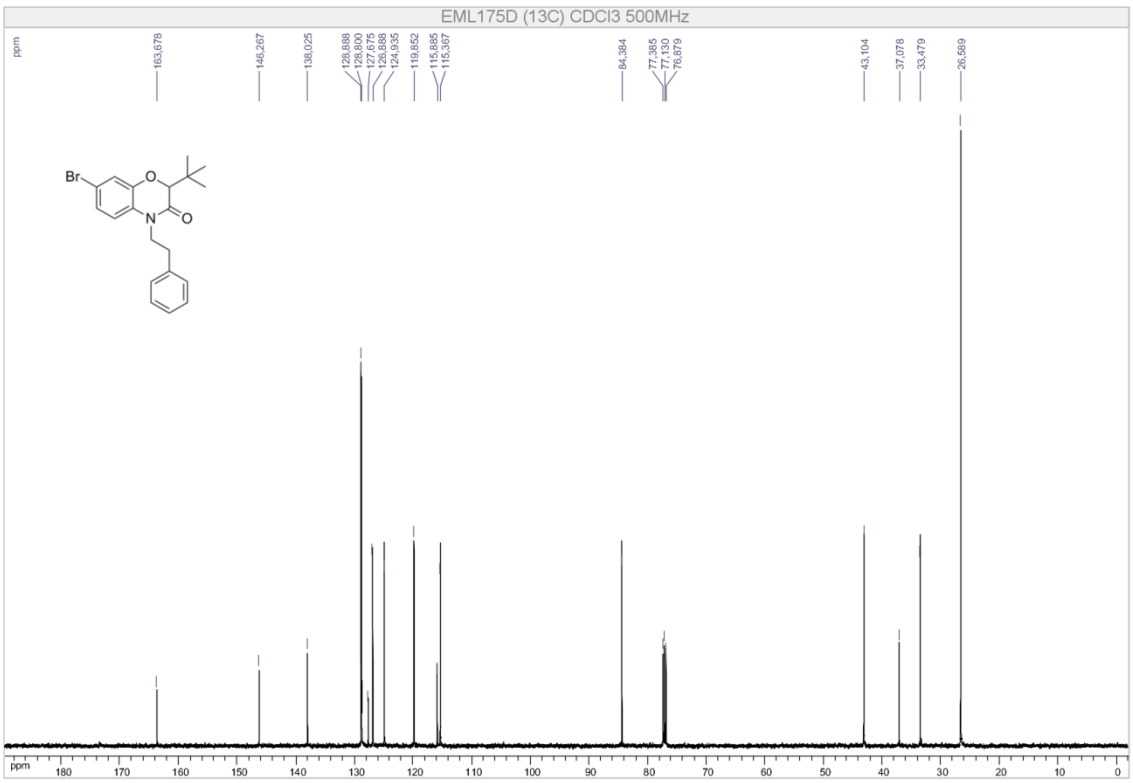
7-bromo-4-(3,4-dimethoxyphenethyl)-2-isopropyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2q)



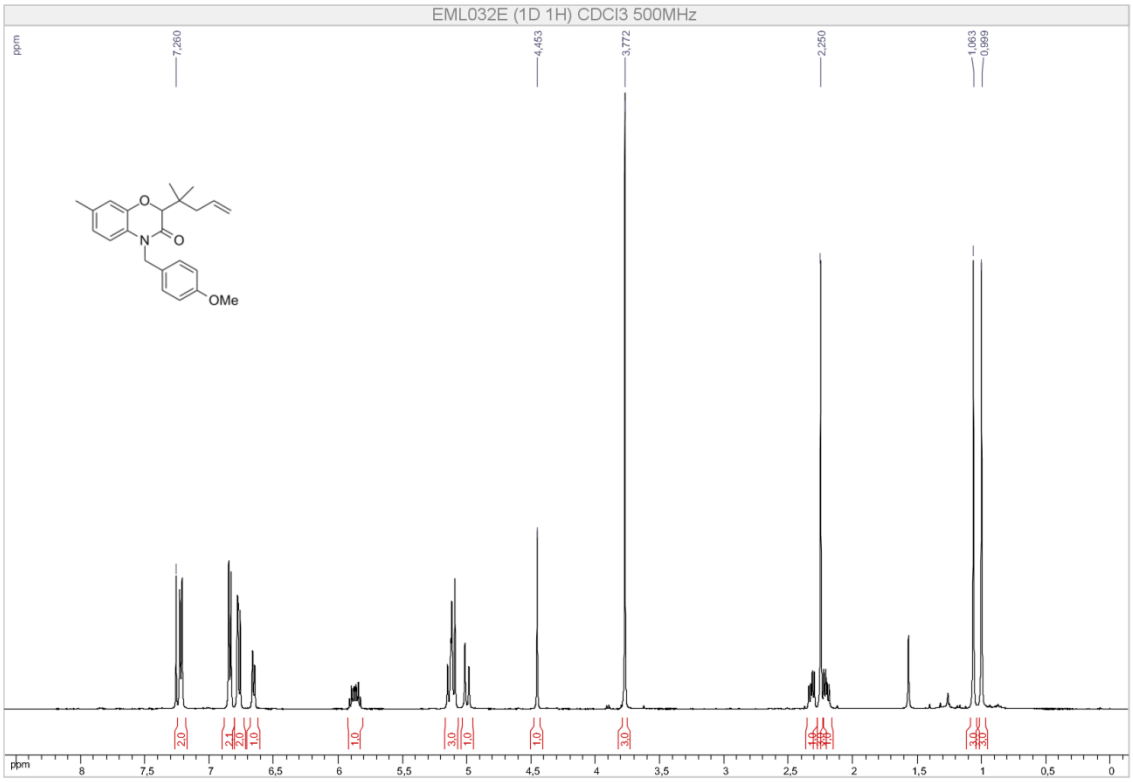


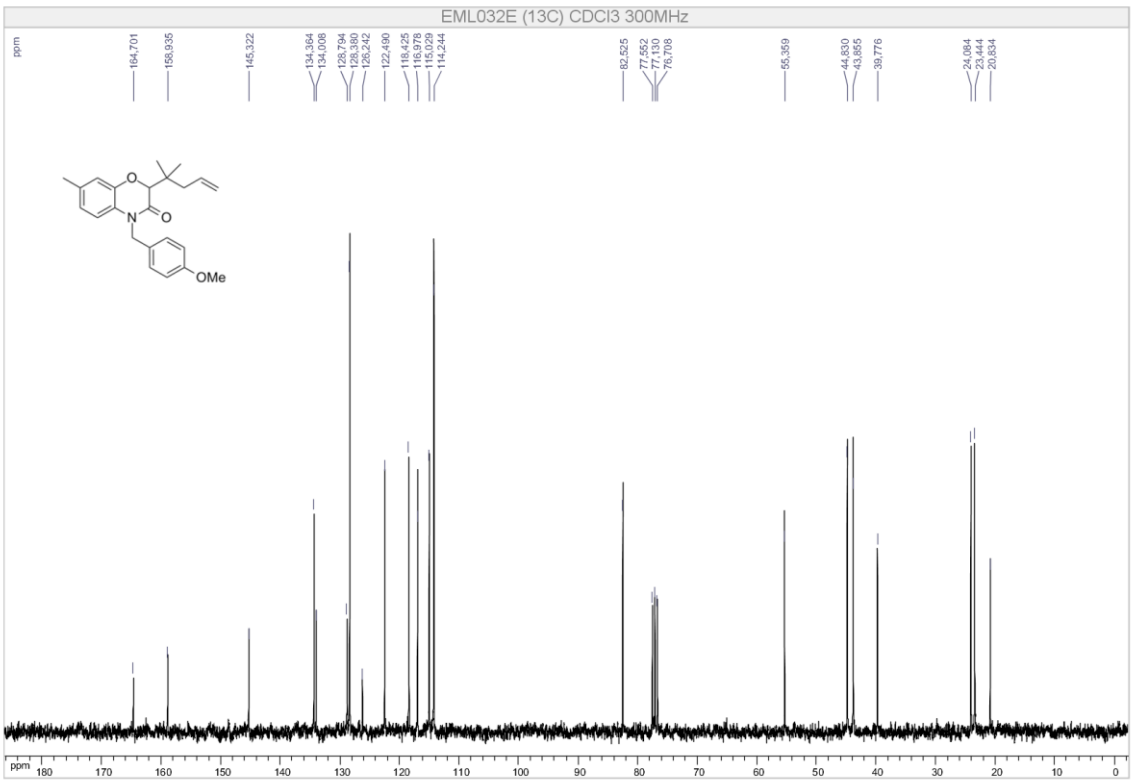
7-bromo-2-(tert-butyl)-4-phenethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2r)



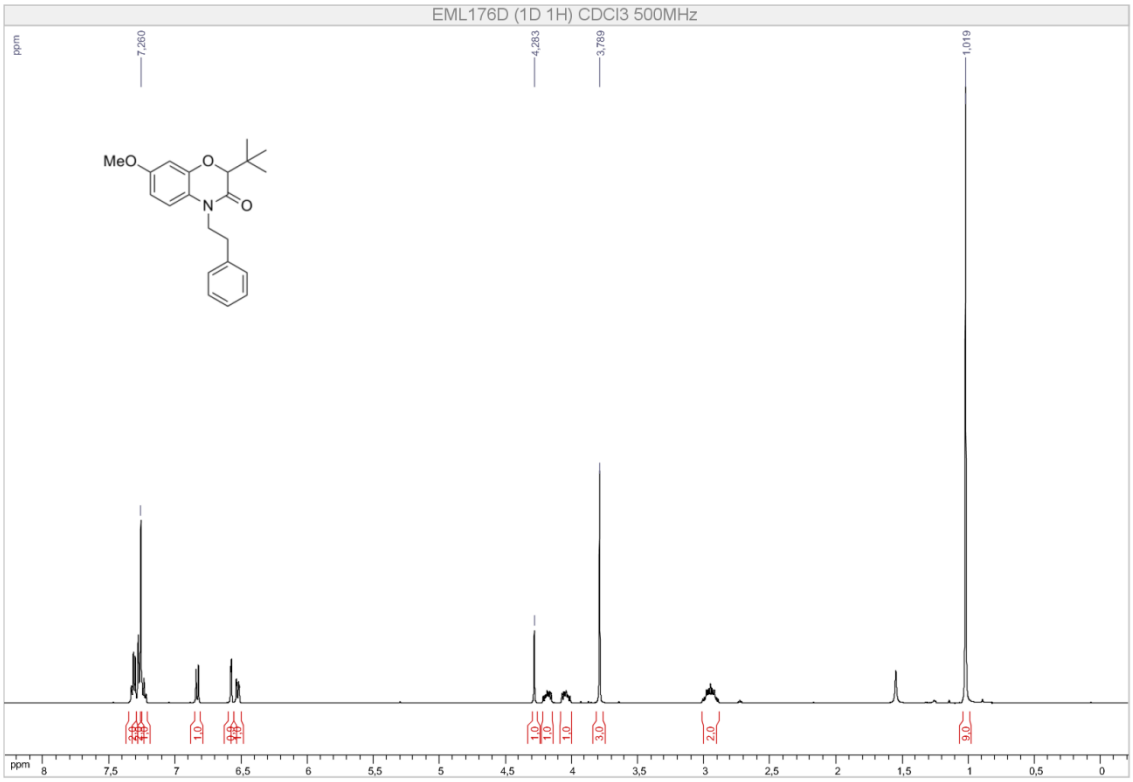


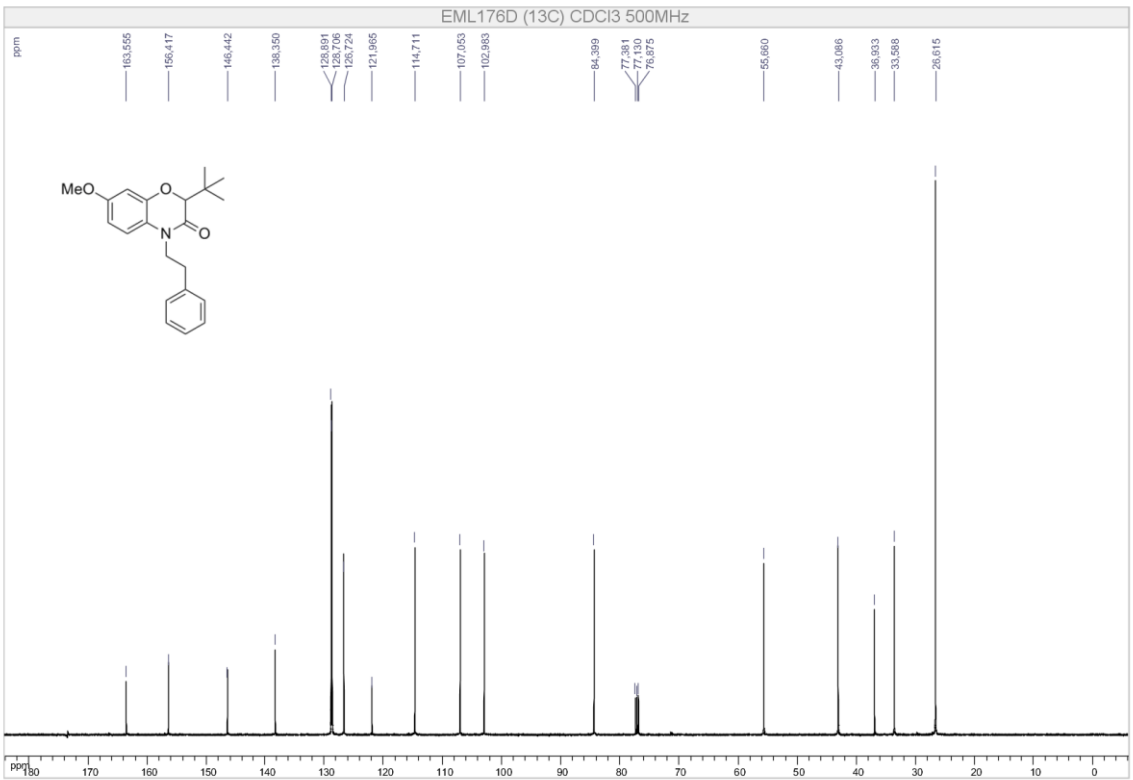
4-(4-methoxybenzyl)-7-methyl-2-(2-methylpent-4-en-2-yl)-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2s)





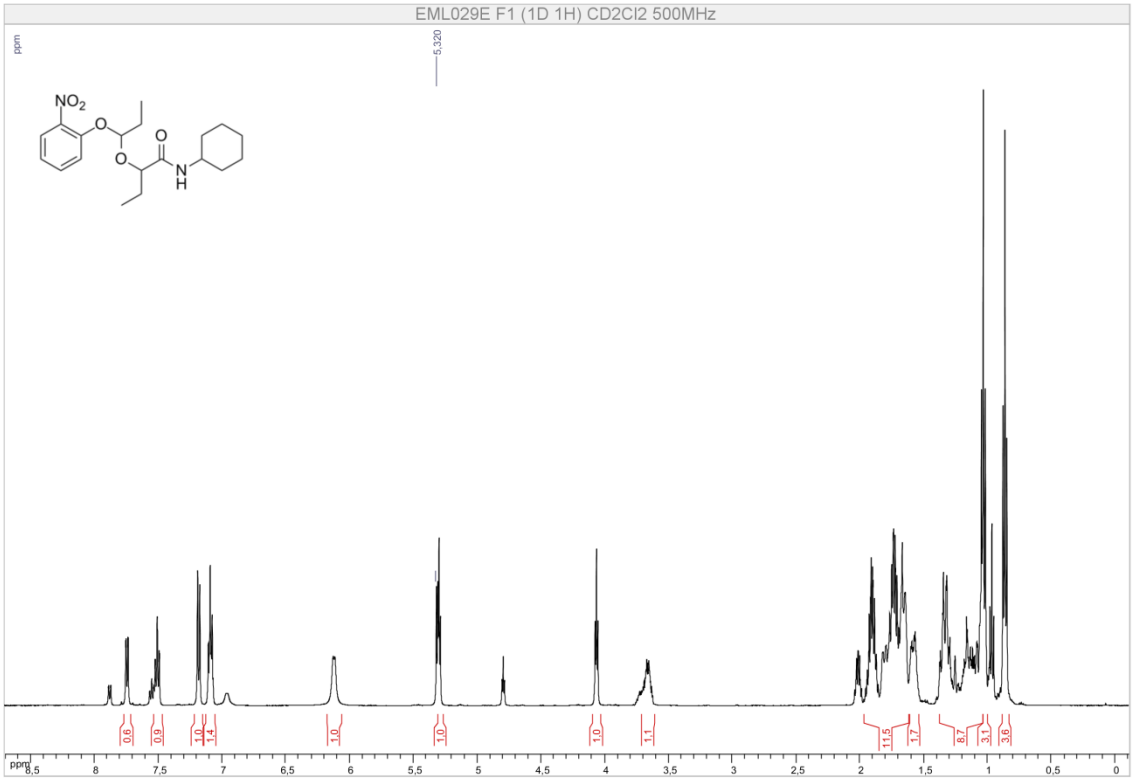
2-(tert-butyl)-7-methoxy-4-phenethyl-*2H*-benzo[*b*][1,4]oxazin-3(*4H*)-one (2t)

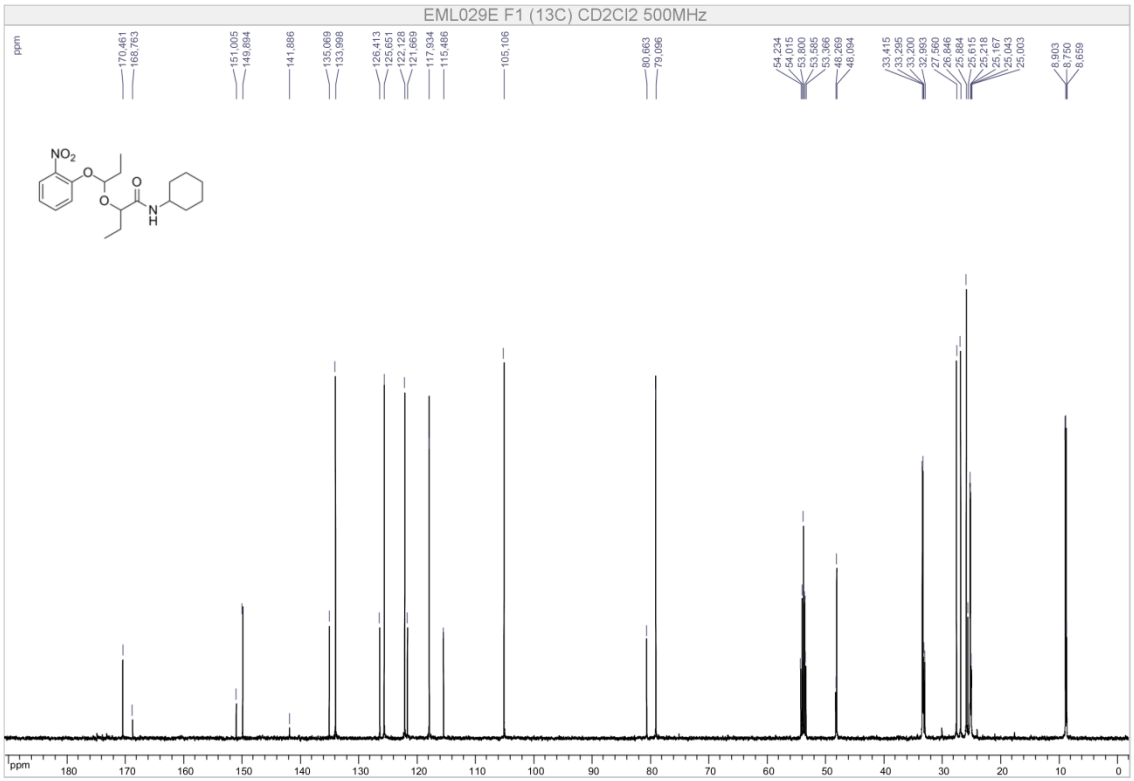




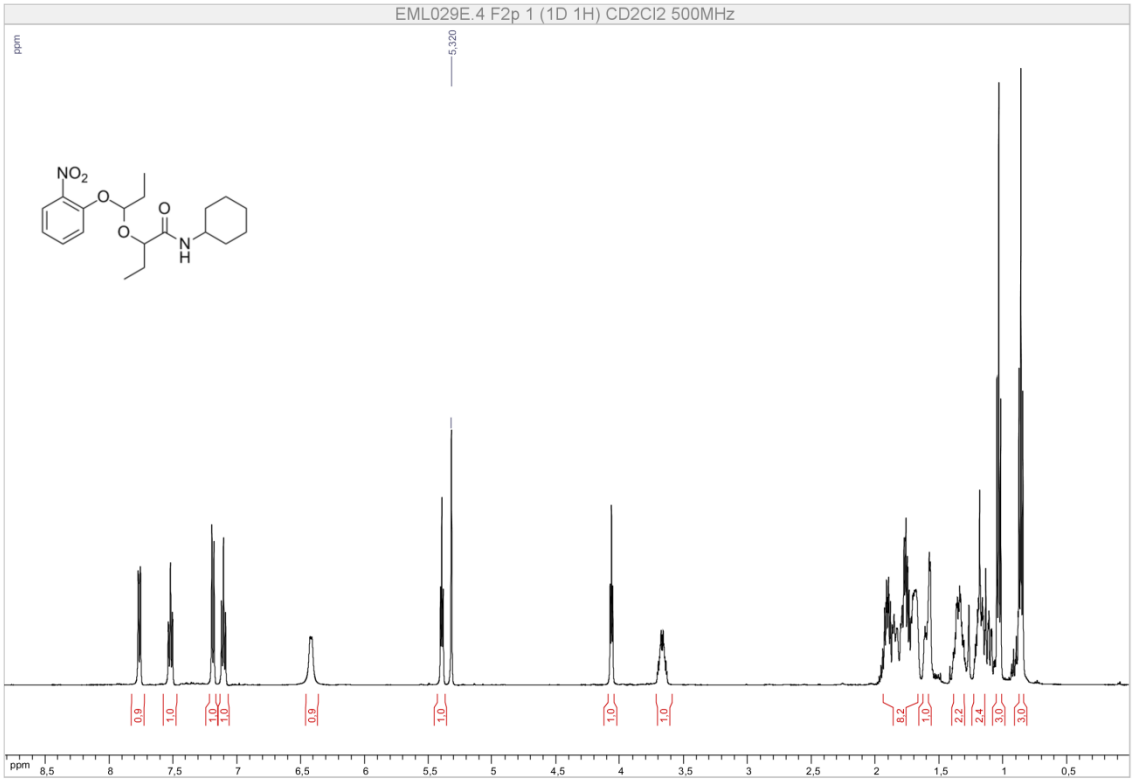
_N_-cyclohexyl-2-(1-(2-nitrophenoxy)propoxy)butanamide (3g)

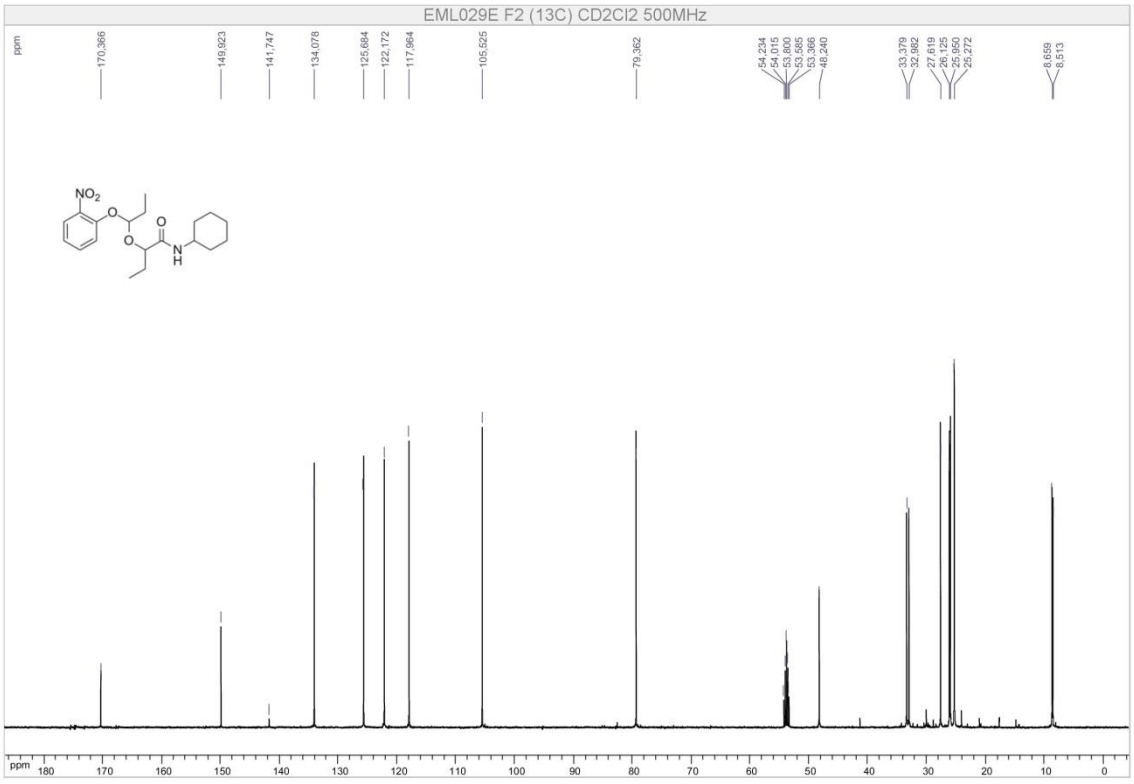
Diastereomer 1 (contaminated by Passerini-Smiles adduct)





Diastereomer 2





X-ray crystallographic studies

The single crystals of **1b**, **2b**, **2p**, and **2r** suitable for X-ray analysis were grown either after slow evaporation in isopropyl oxide (**2b**) or after concentration in dichloromethane for the three others. All the data collections were carried out by means of an Enraf–Nonius Kappa-CCD diffractometer using graphite-monochromated Mo-$K\alpha$ (λ= 0.71073 Å) radiation at ambient temperature. The determination of crystal class and unit cell parameters was carried out by the COLLECT program package[S1] running the Denzo-HKL2000 program.[S2] The raw frame data were integrated using Denzo and scaled and reduced merged after semi-empirical absorption correction using Scalepack[S2] to yield the reflection data file. The structures were solved by Direct Methods with the SHELX-S97 structure solution program [S3] and refined with the SHELX-L2012 refinement package on F^2 anisotropically for all the non-hydrogen atoms by the full-matrix least-squares method. The C9 atom of the cyclobutane in **1b** with elongated displacement was split over two positions with refined occupancy ratio of 0.82(2) – 0.18(2). Soft restraints on bond distances (SADI sd 0.002) and on anisotropic displacement parameters (DELU sd 0.01 and SIMU sd 0.04)) were applied to the atoms of the resulting puckered cyclobutane whose dihedral angles are 17.4 (3)° for the major conformer and 11.4(2)°**.** The hydrogen atoms located on Fourier difference maps were nevertheless placed at the calculated positions and were included in the structure calculation without further refinement of the parameters, except for the N-bound H atom in **1b** freely refined with U_{iso}(H)=1.2 U_{eq}(N). Thermal ellipsoid plots of the molecular structures were made using MERCURY.[S4] The ellipsoids enclose 50 % of the electronic density.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC- 965234 (**1b**), CCDC-965235 (**2b**), CCDC-965236 (**2b**), and CCDC-965237 (**2r**). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Identification code		***compound_1b***	***compound_2b***	***compound_2p***	***compound_2r***
Empirical formula		$C_{17}H_{21}ClN_2O_4$	$C_{17}H_{20}ClNO_2$	$C_{19}H_{19}Cl_2NO_2$	$C_{20}H_{22}BrNO_2$
Formula weight		352.81	305.79	364.25	388.30
Temperature (K)		293(2) K			
Wavelength (Å)		0.71073			
Crystal system		Monoclinic	Triclinic,	Monoclinic	Monoclinic
Space group		P $2_1/c$	P -1	P $2_1/c$	P $2_1/c$
Unit cell dimensions	*a (Å)*	11.6880(10)	5.8800(10)	5.9540(10)	7.2170(10)
	b	17.404(3)	9.120(2)	8.628(2)	11.276(2)
	c	9.965(2)	14.895(2)	34.703(5)	22.803(3)
	α (°)	90	77.537(2)	90	90
	β	113.76(5)	85.432(3)	93.476(2)	92.725(3)
	γ	90	77.725(3)	90	90

Volume (Å³)	1855.2(8)	761.6(2)	1779.5(6)	1853.6(5)
Z,	4	2	4	4
Calcd density (Mg/m³)	1.263	1.333	1.360	1.391
Absorpt° coeff (mm⁻¹)	0.228	0.255	0.376	2.229
F(000)	744	324	760	800
Crystal size (mm)	0.53 x 0.36 x 0.14	0.56 x 0.36 x 0.10	0.30 x 0.30 x 0.30	0.51 x 0.28 x 0.24
θ range for data collection (°)	3.27 to 25.36	3.55 to 26.34	3.33 to 26.23	3.35 to 25.51
Limiting indices	-14 ≤ h ≤ 14, -20 ≤ k ≤ 19, -11 ≤ l ≤ 12	-7 ≤ h ≤ 6, -11 ≤ k ≤ 11, -18 ≤ l ≤ 18	-7 ≤ h ≤ 7, -10 ≤ k ≤ 9, -42 ≤ l ≤ 42	-8 ≤ h ≤ 8, -12 ≤ k ≤ 13, -27 ≤ l ≤ 27
Reflections collected / unique	22970 / 3381	6531 / 3038	9987 / 3429	11449 / 3395
R(int)	0.0219	0.0237	0.0279	0.0350
Completeness to θ max	0.995	0.979	0.959	0.987
Absorption correction	Semi-empirical from equivalents			
Max. and min. transmission	0.96 and 0.88	0.98 and 0.92	0.89 and 0.78	0.58 and 0.44
Refinement method	Full-matrix least-squares on F^2			
Data / restraints / parameters	3381 / 21 / 231	3035 / 0 / 190	3420 / 0 / 221	3391 / 0 / 221
Goodness-of-fit on F²	1.037	1.017	1.032	1.027
Final R indices [I>2σ(I)]	R1 = 0.0449, wR2 = 0.1335	R1 = 0.0512, wR2 = 0.1098	R1 = 0.0473, wR2 = 0.1199	R1 = 0.0497, wR2 = 0.1178
R indices (all data)	R1 = 0.0762, wR2 = 0.1527	R1 = 0.0615, wR2 = 0.1217	R1 = 0.0773, wR2 = 0.1357	R1 = 0.0770, wR2 = 0.1362
Extinction coefficient	0.036(5)	n/a	0.024(4)	0.014(2)
Largest diff. peak and hole (e.A⁻³)	0.197 and -0.228	0.196 and -0.320	0.226 and -0.219	0.448 and -0.452

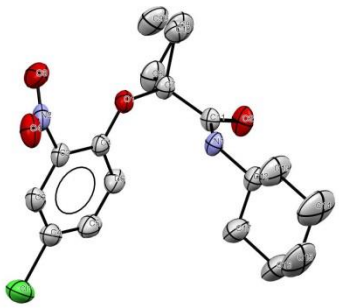
S1 Nonius (1999). COLLECT. Nonius BV, Delft, The Netherlands.

S2 Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology, Volume 276, Macromolecular Crystallography, part A, edited by C.W. Carter, Jr. & R.M. Sweet, 307-326, New York: Academic Press.*

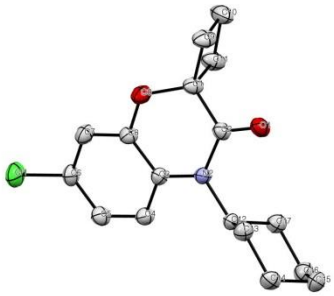
S3 Sheldrick, G.M. (2008). *Acta Cryst.* A**64**, 112-122; Welter, R. (2006). *Acta Cryst*. **A**62, s252.

S4 Macrae, C. F., Edgington, P. R., McCabe, P., Pidcock, E., Shields, G. P., Taylor, R., Towler, M. & van de Streek, J. (2006). *J.Appl. Cryst.* **39**, 453-457.

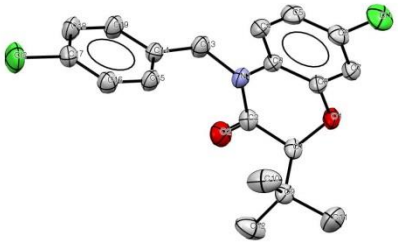
1b gradient of concentration in dichloromethane



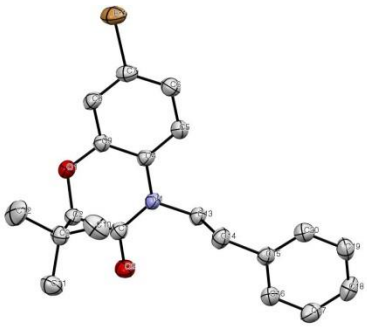
2b slow evaporation in diisopropyl oxide solution



2p in dichloromethane



2r in dichloromethane



Kinetic studies