Electronic Supplementary Information

(Thio)urea-Mediated Benzoxazinone Opening: Mild Approach Towards Synthesis of *o*-(substituted amido)benzamides

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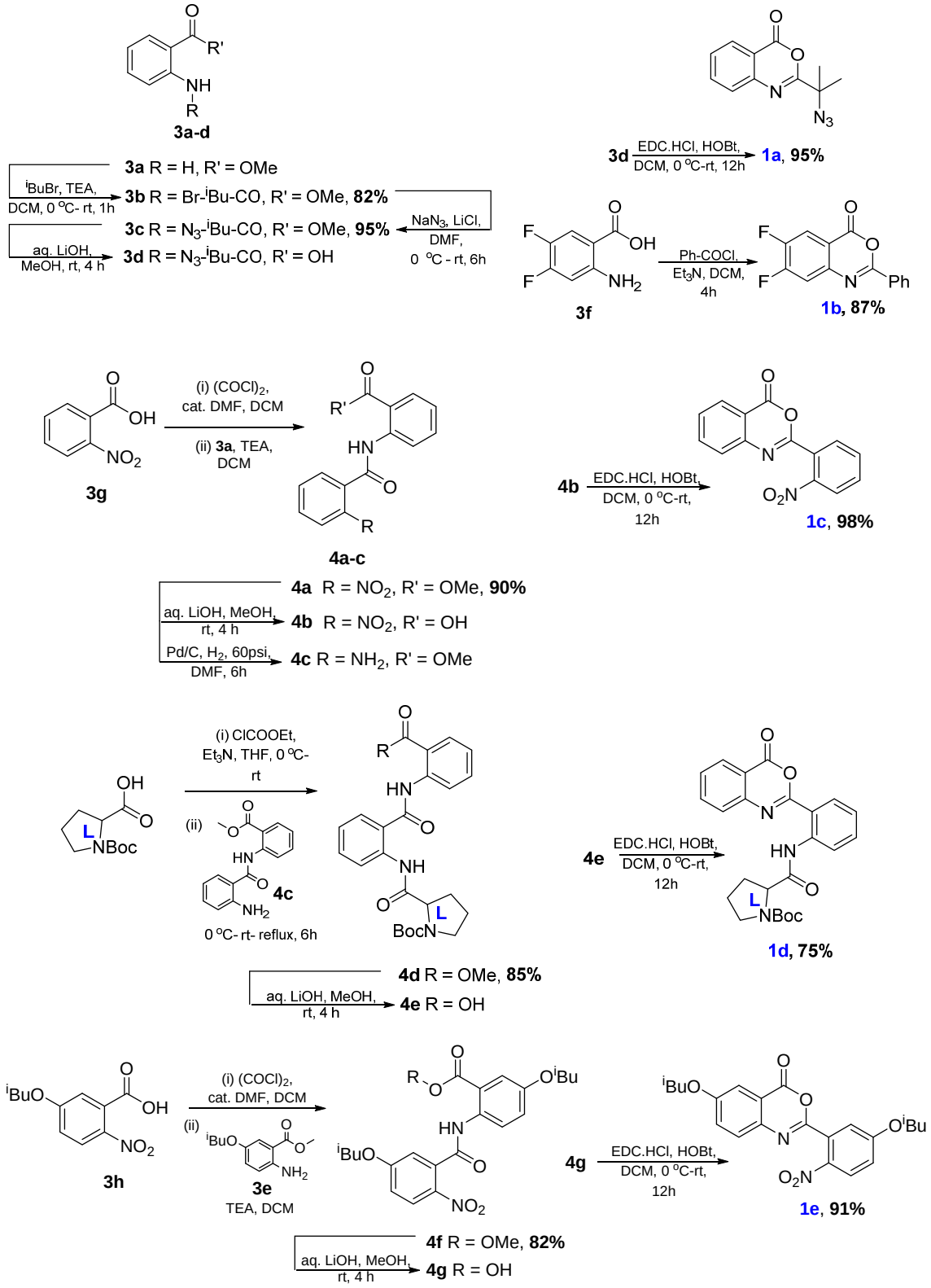
General Methods.

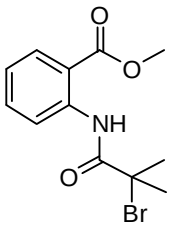
Unless otherwise stated, all the chemicals and reagents were obtained commercially. Dry solvents were prepared by the standard procedures. Analytical Thin Layer Chromatography was done on precoated silica gel plates (Kieselgel $60F_{254}$, Merck). Unless otherwise stated Column Chromatographic purifications were done with 100-200 Mesh Silica gel. NMR spectra were recorded in $CDCl_3$ on AV 200 MHz, AV 400 MHz or AV 500 MHz spectrometers. All chemical shifts are reported in δ ppm downfield to TMS and peak multiplicities as singlet (s), doublet (d), quartet (q), broad singlet (bs), and multiplet (m). The titration studies were done in $CDCl_3$. Elemental analyses were performed on an Elmentar-Vario-EL (Heraeus Company Ltd., Germany). IR spectra were recorded in $CHCl_3$ using Shimadzu FTIR-8400 spectrophotometer. Melting points were determined on a Buchi Melting Point B-540. MALDI-TOF mass spectra were obtained from ABSCIEX TOF/TOF^{TM} 5800 mass spectrometer.

SCHEME: Synthesis of oxazinones **1a-e**



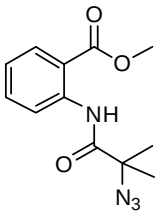
Experimental Procedures:

methyl 2-(2-bromo-2-methylpropanamido)benzoate 3b:



To an ice cold solution of anthranilic methyl ester (10 g, 72.99 mmol, 1 equiv) and triethylamine, TEA (12.95 mL, 99.89 mmol, 1.1 equiv) in dry DCM (100 mL) bromo isobutyryl bromide (9.92 mL, 80.29 mmol, 1.2 equiv) was slowly added. The reaction mixture was stirred for 1 hr at room temperature. After completion, the reaction mixture was diluted with DCM (100 mL) and washed sequentially with saturated $NaHCO_3$, dil. HCl and brine solution. The organic layer was dried over Na_2SO_4, filtered and solvent was stripped off under reduced pressure. Column chromatographic purification (eluent: 10% AcOEt/pet. Ether, Rf: 0.3) of the residue afforded **3b** as a white solid (16.2g, 82%). mp: 44-45 °C; IR ($CHCl_3$) ν (cm^{-1}): 3264, 3020, 2927, 2400, 1685, 1590, 1528, 1451, 1381, 1272, 1088, 1048, 967; ^{1}H NMR (200 MHz, $CDCl_3$): 11.85 (s, 1H), 8.71-8.66 (dd, J = 1.01 Hz, J = 8.59 Hz, 1H), 8.06-8.01 (dd, J = 1.77 Hz, J = 8.08 Hz, 1H), 7.59-7.5 (m, 1H), 7.14-7.06 (m, 1H), 3.93 (s, 3H), 2.06 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 170.6, 168.3, 140.9, 134.4, 130.8, 122.9, 120.1, 115.4, 60.1, 52.4, 31.7; Anal. Calcd. For $C_{12}H_{14}BrNO_3$: C, 48.02; H, 4.70; Br, 26.62; N, 4.67; Found: C, 48.10; H, 4.89; Br, 26.66; N, 4.29.

methyl 2-(2-azido-2-methylpropanamido)benzoate 3c:

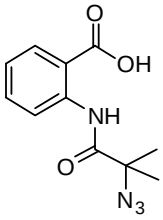


To a solution of **3b** (10 g, 34.85 mmol, 1 equiv) in dry DMSO (60 mL) was added sodium azide (3.40 g, 52.28 mmol, 1.5 equiv) and catalytic amount of LiCl (0.15g, 3.48 mmol, 0.1 equiv), the reaction mixture was allowed to proceed at rt for 6h. After completion, the reaction mixture was added to water and the aqueous layer was extracted with DCM. The combined organic layer was washed repeatedly with water and brine solution. The organic layer was dried over Na_2SO_4, filtered and solvent was stripped off under reduced pressure. . Column chromatographic purification (eluent: 10% AcOEt/pet. Ether, Rf: 0.3) of the residue afforded **3c** as a white solid (8 g, 88%). mp: 40-42 °C; IR ($CHCl_3$) ν (cm^{-1}): 3261, 3020, 2980, 2956, 2401, 1694, 1605, 1589, 1525. 1450, 1386, 1275, 1217, 1166, 1089, 967, 920; ^{1}H NMR (200 MHz, $CDCl_3$): 11.78 (s, 1H), 8.71-8.66 (d, J = 8.65 Hz, 1H), 8.04-8.0 (dd, J = 1.64 Hz, J = 7.96 Hz, 1H), 7.56-7.47 (m, 1H), 7.13-7.05 (m, 1H),

3.93 (bs, 3H), 1.6 (bs, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): 171.5, 168.1, 140.5, 134.3, 130.8, 122.9, 120.2, 115.7, 64.7, 52.3, 24.5; Anal. Calcd. For $C_{12}H_{14}N_4O_3$: C, 54.96; H, 5.38; N, 21.36; Found: C, 54.81; H, 5.23; N, 21.38.

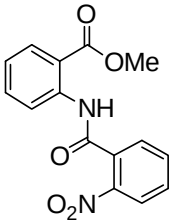
***General Procedures for 3d, 4b, 4e and 4g*:**

2-(2-azido-2-methylpropanamido)benzoic acid 3d:

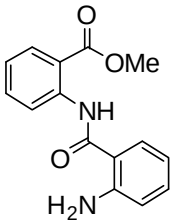


To a solution of **3c** (6.97 g, 27.88 mmol, 1 equiv.) in methanol (25 mL) and water (10 mL), $LiOH{\cdot}H_2O.2H_2O$ (5.02 g, 8.64 mmol, 3 equiv.) was added and the reaction mixture was stirred for 18 hrs. The solvent was stripped off under reduced pressure. To the residue water (50 mL) was added and acidified with dilute HCl. The water layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water and brine solution, dried over Na_2SO_4 and used for next reaction without further purification. Yield = 6.4 g (97.3%).

methyl 2-(2-nitrobenzamido)benzoate 4b:



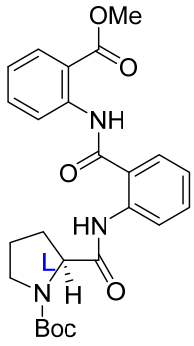
4b



4c

Compound **4b** and **4c** were synthesized as per the reported procedure.[1]

***tert*-butyl (*S*)-2-((2-((2-(methoxycarbonyl)phenyl)carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylater 4d:**

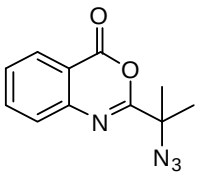


To a solution of Boc-^{L}Pro-OH (6g, 27.9 mmol, 1.02 equiv.) and Et_3N (3.807 mL, 1.02 equiv.) in THF (60mL) at 0 °C, ethyl chloroformate (3.028 mL, 1.02 equiv.) was added drop wise and the reaction mixture was stirred for 1 h at 0 °C. A solution of the amine **4c** (7.38 g, 27.3 mmol, 1 equiv.) in THF (40 mL) was added slowly to the mixed anhydride solution, prepared above. The reaction mixture was stirred at 0 °C for an hour, then at room temperature for 2 h, followed by reflux at 70 °C for 6 h. After completion of reaction, THF was removed under reduced pressure

and then the compound was taken into DCM. The combined organic layers were washed sequentially with solutions of $KHSO_4$, $NaHCO_3$ and brine. Organic layer was then dried over Na_2SO_4 and was evaporated *in vacuo*. The crude product was purified by column chromatography (eluent: 30% AcOEt/pet. Ether, R_f: 0.3) to furnish **9a** (10.3 g, 90%) as a fluffy white solid. mp: 71-73 °C; $[\alpha]^{24.87}_D$: -119.448° (*c* 1, $CHCl_3$); IR ($CHCl_3$) *v* (cm^{-1}): 3448, 2976, 1693, 1655, 1607, 1584, 1524, 1435, 1388, 1318, 1271, 1164, 1097; ^1H NMR (200 MHz, $CDCl_3$) δ: $12.09_{rotamer}$ (s, 0.6H, amide), $12.05_{rotamer}$ (s, 0.4H, amide), $11.82_{rotamer}$ (s, 0.4H, amide), $11.76_{rotamer}$ (s, 0.6H, amide), 8.9-8.71(m, 2H), 8.11-8.07 (dd, *J* = 1.52 Hz, *J* = 7.96Hz, 1H), 7.92-7.85 (m, 1H), 7.88-7.49 (m, 2H), 7.29-7.12 (m, 2H), 4.5-4.27 (m, 1H), 3.96 (s, 3H), 3.85-3.74 (m, 2H), 2.37-2.11 (m, 2H), 2.04- 1.87 (m, 2H), $1.45_{rotamer}$ (s, 3H), $1.33_{rotamer}$ (s, 6H); ^{13}C NMR (50 MHz, CDCl3) δ: 172.2, 171.7, 168.9, 168.8, 167.4, 167.3, 154.8, 154.0, 141.2, 141.0, 139.8, 134.9, 134.3, 132.9, 130.8, 127.0, 123.2, 122.9, 121.1, 120.5, 115.4, 115.2, 80.0, 79.8, 62.5, 61.9, 52.47, 49.9, 47.7, 36.5, 31.4, 30.4, 29.5, 28.3, 28.2, 28.1, 24.5, 24.1, 23.8, 23.6, 23.3; MALDI-TOF/TOF: 490.310 $(M+Na)^+$, 506.3015 $(M+K)^+$; Elemental analysis calculated for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99. Found: C, 64.21; H, 6.33; N, 9.02.

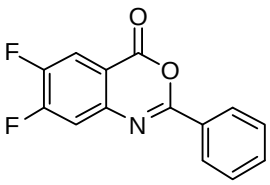
General Procedures for 1a, 1d and 1e:

2-(2-azidopropan-2-yl)-4H-benzo[d][1,3]oxazin-4-one 1a:



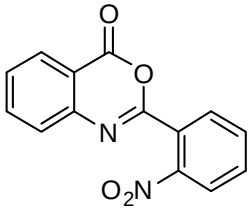
To a solution of **3d** (3 g, 12.096 mmol, 1 equiv) in DCM, EDC.HCl (2.54 g, 13.306 mmol, 1.2 equiv) was added. The solution was allowed to stir for 2h. After the completion, reaction mixture was diluted with DCM (30 mL), the organic layer was combined and was washed with water, followed by $NaHCO_3$ solution and brine solution. The organic layer was then dried over Na_2SO_4 and was removed *in vacuo*. Colorless liquid was isolated with 94% yield. Characterization was difficult due to unstable nature of the oxazinone. IR ($CHCl_3$) *v* (cm^{-1}): 3020, 2979, 2401, 2117, 1678, 1606, 1587, 1524, 1450, 1409, 1299, 1165, 1046, 1607, 1584, 1524, 1435, 1388, 1318, 1271, 1164, 1097, 927; ^1H NMR (200 MHz, $CDCl_3$): 8.22-8.18 (d, *J* = 1.01 Hz, *J* = 7.83 Hz, 1H), 7.88-7.79 (m, 1H), 7.68-7.64 (d, *J* = 7.58 Hz, 1H), 7.59-7.51 (m, 1H), 1.69 (s, 6H); ^{13}C NMR (50 MHz, CDCl3) δ 161.9, 158.8, 145.6, 136.6, 128.9, 128.5, 127.4, 116.8, 62.4, 24.8.

6,7-difluoro-2-phenyl-4H-benzo[d][1,3]oxazin-4-one 1b:



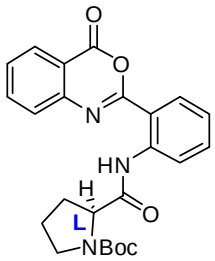
Compound **1b** was synthesized as per the reported procedure.[2]

2-(2-nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one 1c:



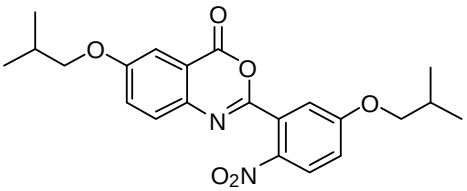
Compound **3c** was synthesized as per the reported procedure.[1]

(*S*)-*tert*-butyl 2-((2-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)phenyl)carbamoyl) pyrrolidine-1-carboxylate 1d:



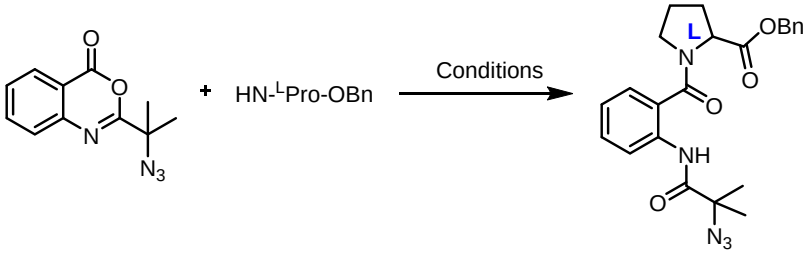
The crude product was purified by column chromatography (eluent: 30% AcOEt/pet. Ether, R_f: 0.3) to furnish **1d** (4.5 g, 98%) as a fluffy white solid. mp: 95-97°C; $[\alpha]^{25.58}$: -18.316° (*c* 1, $CHCl_3$); IR ($CHCl_3$) *v* (cm^{-1}): 3448, 2977, 1770, 1694, 1606, 1584, 1520, 1477, 1446, 1388, 1293, 1251, 1163, 1119, 1036, 1009; ^1H NMR (200 MHz, $CDCl_3$) δ: $12.05_{rotamer}$ (0.8H, amide), $11.79\text{-}11.72_{rotamer}$ (0.2H, amide), 8.9-8.68 (m, 1H), 8.23-8.19 (m, 1H), 8.06-8.02 (m, 1H), 7.94-7.85 (m, 1H), 7.58-7.50 (m, 2H), 7.22-7.12 (m, 1H), 4.44-4.23 (m, 1H), 3.76-3.39 (m, 2H), 2.43-2.28 (m, 1H), 2.24-2.05 (m, 1H), 1.96-1.86 (m, 2H), $1.43\text{-}1.36_{rotamer}$ (m, 3H), $1.31_{rotamer}$ (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.2, 167.2, 158.1, 156.9, 154.9, 145.3, 141.0, 139.8, 137.0, 133.7, 132.8, 130.7, 129.5, 128.7, 128.4, 127.1, 126.8, 123.0, 120.9, 120.6, 120.5, 116.4, 115.7, 95.9, 80.5, 79.9, 62.8, 62.4, 61.5, 52.4, 47.4, 46.6, 31.7, 28.0, 27.2, 24.0; MALDI-TOF: 458.1276 ($M+Na^+$); 474.0995 ($M+K^+$);. Anal. calcd for $C_{15}H_{12}N_2O_5$: C, 66.19; H, 5.79; N, 9.65. Found: C, 66.39; H, 5.89; N, 9.55.

6-isobutoxy-2-(5-isobutoxy-2-nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one 1e:



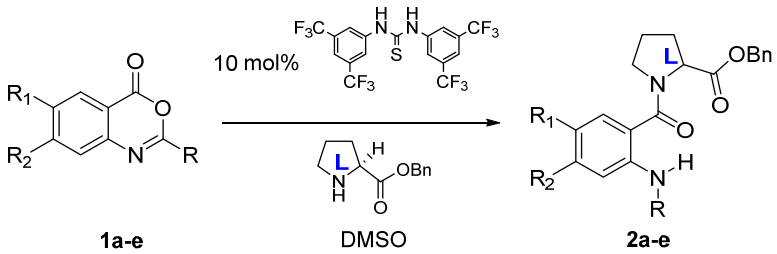
The crude product was purified by column chromatography (eluent: 15% AcOEt/pet. Ether, R_f: 0.3) to furnish **1e** (98%) as a waxy solid. IR ($CHCl_3$) ν (cm^{-1}): 3438, 2980, 1772, 1686, 1580, 1483, 1447, 1369, 1299, 1158; ^1H NMR (200 MHz, $CDCl_3$) δ: 7.81-7.76 (d, J = 8.97 Hz, 1H), 7.32-7.31 (m, 1H), 7.14-7.08 (dd, J = 2.78 Hz, J = 9.09 Hz, 1H), 7.00-6.97 (dd, J = 2.78 Hz, J = 8.84 Hz, 1H), 3.58-3.53 (dd, J = 3.03 Hz, J = 6.57 Hz, 4H), 1.91-1.77 (m, 2H), 0.76-0.73 (dd, J = 3.16 Hz, J = 6.69 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.9, 159.6, 159.0, 153.7, 140.7, 140.1, 129.1, 128.7, 127.1, 126.1, 117.8, 116.5, 116.4, 105.6, 75.4, 75.1, 29.6, 28.1, 19.1, 19.0; LC-MS: 435.06 ($M+Na^+$); 467.08 ($M+K^+$);. Anal. calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79; Found: C, 64.21; H, 5.89; N, 6.80.

Table 1: Optimisation of coupling of 2-(2-azidopropan-2-yl)-2H-benzo[d][1,3]oxazin-4-one **1a** with H-^{L}Pro-OBn.

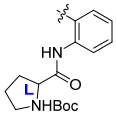
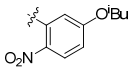


S. No.	Condition	Inference
1	$Ti(O^iPr)_4$, DCM, heat	No coupling, oxazinone decomposed
2	$Sc(OTf)_3$, DCM, 80 °C	Coupling trace
3	Dry Toluene, heat	Coupling trace
4	Acetonitrile, MW, 280W, 20 min	No coupling observed
5	DBU, 4Å MS, DMF	Coupling trace
6	Dry Toluene, MW, MW, 280W, 20 min	Coupling trace
7	10% Schreiner's (thio)urea, toluene, 24h	65% product formation

Table 2: Comparison of coupling of oxazinones **1a-e** with H-^{L}Pro-OBn in DMSO



1a-e **2a-e**

	-R_1	-R_2	-R	Time (h)	Conversion (%)	Yield (%)[a]
2a		H	H	24	100	81
2b		F	F	36	92	70[b]
2c		H	H	9	100	97
2d		H	H	24	100	75
2e		OiBu	H	48	52	91[c]

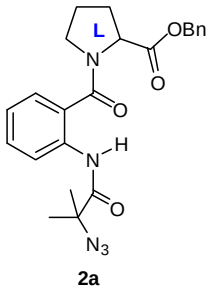
[a]Unless specified, reaction was carried out at 25 °C with oxazinone (1 equiv.) and H-^{L}Pro-OBn (1.5 equiv.). [b]Yield calculated after 8% oxazinone recovery. [c]Yield calculated after 48% oxazinone recovery.

***General Procedures for 2a-e*:**

To a solution of oxazinone (1 equiv.) and amine (1.5 equiv.) taken in DMSO (1 mL), 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea (10 mol%) was added. Completion of the reaction was constantly monitored by TLC. After the complete/maximum conversion of the oxazinone moiety, water (2 mL) was added to the reaction mixture. Compound was then extracted into DCM (3 x 5 mL) from the aqueous layer. Organic layer was pooled together and was washed with $KHSO_4$ solution followed by brine solution. The organic layer was then dried over Na_2SO_4 and was evaporated *in vacuo* to afford coupled product. Compounds were purified by silica gel column chromatography.

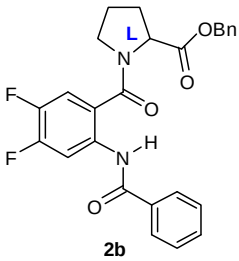
benzyl 1-(2-(2-azido-2-methylpropanamido)benzoyl)pyrrolidine-2-carboxylate 2a:

The crude product was purified by column chromatography (eluent: 25% AcOEt/pet. Ether, R_f: 0.4) to furnish **2a** (81%) as a pale yellow glassy solid. $[\alpha]^{24.7}_D$: -67.56° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3307, 2923, 2852, 2115, 1744, 1692, 1629, 1597, 1520, 1454, 1412, 1305, 1269, 1166; ^{1}H NMR (200 MHz, $CDCl_3$) δ: $10.12_{rotamer}$ (0.8H, amide), $9.59_{rotamer}$ (0.2H, amide), 8.39-8.35 (d, J = 8.34 Hz, 0.8H), 8.39-8.35 (d, J = 8.08 Hz, 0.2H), 7.50-7.38 (m, 6H), 7.19-6.56 (m, 2H), 5.26 (s, 2H), 5.04-4.72 (m, 1H), 3.94-3.78 (m, 0.4H), 3.73-3.54 (m,1.6H), 2.24-2.05 (m, 1H), 2.38-2.27 (m, 1H), 2.14-1.85 (m, 3H), 1.63 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.5, 171.2, 169.3, 168.5, 136.3, 135.6, 135.0, 131.1, 130.6, 128.5, 128.2, 128, 127.4, 126.4, 124.7, 123.3, 122.6, 121.9, 66.8, 64.5, 61.6, 59.2, 50.2, 46.6, 31.3, 29.1, 25.1, 24.5, 24.4; MALDI-TOF/TOF: 458.1152 ($M+Na^+$); 474.0970 ($M+K^+$); Anal. calcd for $C_{23}H_{25}N_5O_4$: C, 63.44; H, 5.79; N, 16.08. Found: C, 63.66; H, 5.98; N, 16.10.



2a

benzyl 1-(2-benzamido-4,5-difluorobenzoyl)pyrrolidine-2-carboxylate 2b:

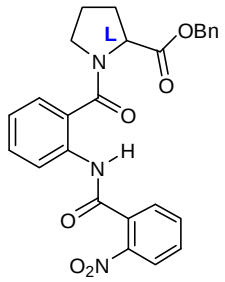


2b

The crude product was purified by column chromatography (eluent: 15% AcOEt/pet. Ether, R_f: 0.4) to furnish **2b** (70% after 8% recovery of starting material) as a pale yellow solid. mp: 78-80 °C;$[\alpha]^{25.84}_D$: -39.14° (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm-1): 3347, 2924, 1744, 1681, 1615, 1533, 1440, 1409, 1279, 1167; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 10.4 (1H, amide), 8.65-8.54 (dd, *J*= 7.58 Hz, *J*= 12.88 Hz, 1H), 8.11-7.92 (m, 2H), 7.61-7.31 (m, 9H), 5.27- 5.12 (m, 2H), 4.78-4.72 (m, 1H), 3.70-3.61 (m, 2H), 2.41-2.27 (m, 1H), 2.09-1.91 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 171.4, 167.4, 165.4, 135.3, 134.8, 133.8, 133.4, 132.1, 130.0, 128.6, 128.4, 128.0, 127.4, 119.5, 116.3, 115.9, 111.7, 111.3, 67.0, 598.5, 50.5, 29.6, 29.0, 25.2; MALDI-TOF/TOF: 487.2480 ($M+Na^+$); 503.1575 ($M+K^+$); Anal. calcd for $C_{26}H_{22}F_2N_2O_4$: C, 67.23; H, 4.77; F, 8.18; N, 6.03. Found: C, 67.45; H, 4.84; F, 8.40; N, 6.0.

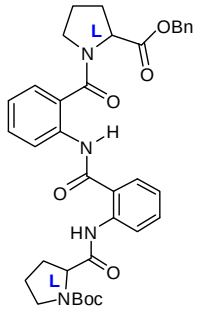
benzyl 1-(2-(2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxylate 2c:

The crude product was purified by column chromatography (eluent: 40% AcOEt/pet. Ether, R_f: 0.3) to furnish **2c** (90%) as a waxy solid. $[\alpha]^{25.86}_D$: -19.0687° (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 2924, 2853, 1739, 1688, 1625, 1531, 1456, 1415, 1348, 1310, 1186; ^1H NMR (500 MHz, $CDCl_3$) δ: $9.43_{rotamer}$ (s, 0.9H, amide), $9.10_{rotamer}$ (s, 0.1H, amide), $8.50\text{-}8.49_{rotamer}$ (d, J = 8.24 Hz, 0.9H), $8.24\text{-}8.22_{rotamer}$ (m, 0.1H), 8.08-8.06 (d, J = 8.24 Hz, 0.9H), 8.01-7.99 (m, 0.1H), 7.73-7.65 (m, 2H), 7.58-7.55 (m, 1H), 7.51-7.48 (m, 1H), 7.41-7.14 (m, 7H), 5.07-4.98 (m, 2H), $4.71\text{-}4.69_{rotamer}$ (m, 0.9H), $4.51\text{-}4.49_{rotamer}$ (m, 0.1H), 3.64-3..6 (m, 1H), 3.51-3.47 (m, 1H), 2.37-2.27 (m, 1H), 2.01-1.86 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.1, 168.5, 164.9, 146.4, 135.5, 135.3, 133.7, 133.0, 130.9, 130.4, 129.1, 128.6, 128.4, 128.0, 126.6, 125.9, 124.3, 124.1, 122.3, 67.0, 58.9, 49.7, 29.2, 25.0; MALDI-TOF/TOF: 496.4159 ($M+Na^+$); 512.3204 ($M+K^+$); Anal. calcd for $C_{26}H_{23}N_3O_6$: C, 65.95; H, 4.90; N, 8.87;. Found: C, 65.74; H, 4.69; N, 8.95.



2c

tert-butyl 2-((2-((2-(2-((benzyloxy)carbonyl)pyrrolidine-1-carbonyl)phenyl) carbamoyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate 2d:

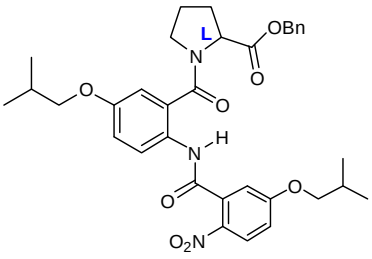


2d

The crude product was purified by column chromatography (eluent: 50% AcOEt/pet. Ether, R_f: 0.3) to furnish **2d** (75%) as a waxy solid. $[\alpha]^{25.6}_D$: -48.768° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3276, 2925, 2853, 1742, 1694, 1626, 1585, 1520, 1449, 1411, 1298, 1216, 1165, 1121, 1089, 917; ^1H NMR (200 MHz, $CDCl_3$) δ: $11.68_{rotamer}$ (0.6H, amide), $11.63_{rotamer}$ (0.4H, amide), $10.37_{rotamer}$ (0.6H, amide), $10.21_{rotamer}$ (0.4H, amide), $8.65\text{-}8.61$ (d, J = 8.34 Hz, 1H), $8.50\text{-}8.46_{rotamer}$ (d, J = 7.83 Hz, 0.9H), $8.37\text{-}8.33_{rotamer}$ (d, J = 8.08 Hz, 0.1H), 7.70-7.66 (m, 1H), 7.43-7.39 (m, 3H), 7.13-6.98 (m, 2H), 5.12 (s, 2H), 4.41-4.35 (m, 1H), $4.69\text{-}4.65_{rotamer}$ (m, 0.4H), $4.25\text{-}4.18_{rotamer}$ (m, 0.6H), 3.77-3.36 (m, 2H), 2.33-2.06 (m, 4H), 1.95-1.78 (m, 4H), $1.39_{rotamer}$ (s, 3H), $1.27_{rotamer}$ (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.1, 171.6, 171.5, 169, 166.9, 154.8, 154.0, 139.7, 136.8, 135.3, 132.8, 131.5, 131.0, 128.4, 128.2, 127.8, 127.4, 127.3, 124.3, 123.1, 122.9, 121.9, 120.8, 120.2, 80.0, 79.8, 77.2, 66.8, 62.4, 61.8, 52.3, 50.4, 46.9, 46.6, 38.4, 36.5, 31.7, 31.3, 30.4, 29.5, 29.0, 28.1, 25.1, 24.5, 24.1, 23.6; MALDI-TOF/TOF:

663.4386 ($M+Na^+$); 679.4749 ($M+K^+$); Anal. calcd for $C_{36}H_{40}N_4O_7$: C, 67.48; H, 6.29; N, 8.74;. Found: C, 67.68; H, 6.16; N, 8.89.

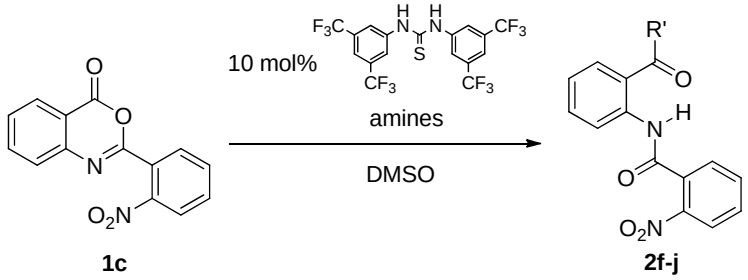
benzyl 1-(5-isobutoxy-2-(5-isobutoxy-2-nitrobenzamido)benzoyl)pyrrolidine-2-carboxylate 2e:

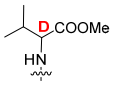


2e

The crude product was purified by column chromatography (eluent: 35% AcOEt/pet. Ether, R_f: 0.3) to furnish **2e** (91% after 48% recovery of starting material) as a waxy solidWaxy solid. $[\alpha]^{25.6}_D$: -48.768° (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3327, 3020, 2964, 2930, 2401, 1735, 1680, 1630, 1590, 1471, 1446, 1397, 1341, 1030; ^1H NMR (200 MHz, $CDCl_3$) δ: $8.94_{rotamer}$ (0.9H, amide), $8.53_{rotamer}$ (0.1H, amide), $8.34\text{-}8.30_{rotamer}$ (d, J = 9 Hz, 0.9H), 8.12-8.07 (d, J = 9.22 Hz, 1H), $8.02\text{-}7.97_{rotamer}$ (d, J = 9 Hz, 0.1H), 7.37-7.23 (m, 5H), 7.07-6.87 (m, 4H), 5.11-4.93 (2H), $4.71\text{-}4.64_{rotamer}$ (m, 0.9H), $4.54\text{-}4.51_{rotamer}$ (m, 0.1H), 3.83-3.80 (d, J = 6.57 Hz, 2H), 3.73-3.70 (d, J = 6.57 Hz, 2H), 3.65-3.42 (m, 2 H), 2.38-1.91 (m, 7H), 1.04-0.98 (dd, J = 2.65 Hz, J = 6.69 Hz, 4H); ^{13}C NMR (200 MHz, $CDCl_3$) δ: 172.1, 168.1, 165.0, 163.6, 155.7, 138.4, 135.7, 135.3, 128.5, 128.3, 128.0, 127.94, 127.9, 126.9, 124.1, 116.4, 115.4, 114.3, 112.4, 75.3, 74.8, 67.0, 58.8, 49.6, 29.6, 29.2, 28.2, 28.0, 24.9, 19.2, 19.0; MALDI-TOF/TOF: 640.8233 ($M+Na^+$); 656.9022 ($M+Na^+$); Anal. calcd for $C_{34}H_{39}N_3O_8$: C, 66.11; H, 6.36; N, 6.80;. Found: C, 66.34; H, 6.50; N, 6.85.

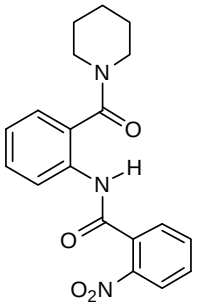
Table 3. Comparison of coupling of different amines with oxazinone **1c**



	-R'	Time (h)	Conversion (%)	Yield (%)[a]
2f		0.5	100	94
2g		0.12	100	94
2h		48	60	82[b]
2i		36	100	89
2j		0.05	100	97

[a]Unless specified, reaction was carried out at 25 °C with oxazinone (1 equiv.) and amine (1.5 equiv.). [b]Yield calculated after 40% oxazinone recovery.

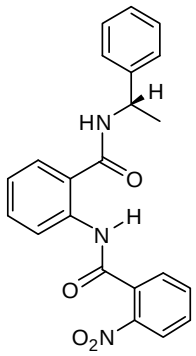
2-nitro-N-(2-(piperidine-1-carbonyl)phenyl)benzamide 2f:


2f

The crude product was purified by column chromatography (eluent: 50% AcOEt/pet. Ether, R_f: 0.4) to furnish **2f** (94%) as a white solid. mp: 136-138°C; IR ($CHCl_3$) ν (cm^{-1}): 3230, 3004, 2938, 2857, 1678, 1615, 1600, 1531, 1436, 1348, 1310, 1287, 1257, 1125, 1003, 856; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 9.3 (1H, amide), 8.27-8.23 (d, *J*= 8.21 Hz, 1H), 8.11-8.07 (d, *J*= 8.21 Hz, 1H), 7.76-7.57 (m, 3H), 7.52-7.43 (dt, *J*= 1.77 Hz, *J*= 8.46 Hz, 1H), 7.28-7.14 (m, 2H), 3.58 (bs, 4H), 1.67 (bs, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.7, 164.5, 146.4, 135.9, 133.9, 132.8, 130.7, 130.6, 128.7, 127.2, 125.9, 124.7, 124.2, 124.0, 64.7, 43.6, 43.3, 29.7, 26.4, 25.6, 24.4;

MALDI-TOF/TOF: 376.1107 ($M+Na^+$); 392.0699 ($M+K^+$); Anal. calcd for C19H19N3O4: C, 64.58; H, 5.42; N, 11.89;. Found: C, 64.69; H, 5.23; N, 11.87.

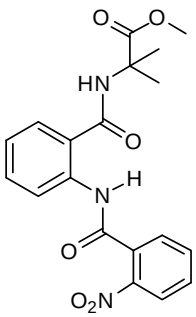
(*S*)-2-nitro-N-(2-((1-phenylethyl)carbamoyl)phenyl)benzamide 2g:



2g

The crude product was purified by column chromatography (eluent: 40% AcOEt/pet. Ether, R_f: 0.3) to furnish **2g** (94%) as a white solid. $[\alpha]^{25.72}_D$: -0.612° (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm-1): 3251, 2924, 2853, 1681, 1600, 1531, 1437, 1348, 1287, 856; ^1H NMR (200 MHz, $CDCl_3$) δ: 11.61 (1H, amide), 8.65-8.61 (d, *J*= 8.21 Hz, 1H), 8.06-8.02 (m, 1H), 7.73-7.60 (m, 3H), 7.59-7.46 (m, 2H), 7.38-7.28 (m, 5H), 7.18-7.10 (dt, *J* = 0.88 Hz, *J*= 7.58 Hz, 1H), 6.68 (bs, 1H), 5.29-5.15 (pentet, *J* = 7.07 Hz, 1H), 1.61-1.57 (d, *J* = 6.95 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.0, 164.4, 146.9, 142.5, 139.0, 133.7, 132.8, 132.7, 130.8, 128.8, 128.4, 127.6, 126.5, 126.0, 124.7, 123.7, 122.0, 120.8, 49.4, 29.7, 21.6; MALDI-TOF/TOF: 412.1174 ($M+Na^+$); 428.0916 ($M+K^+$); Anal. calcd for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.92; N, 10.79. Found: C, 67.78; H, 4.69; N, 10.89.

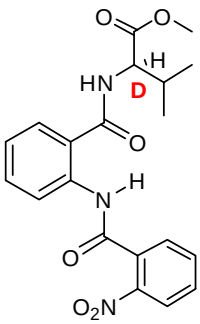
methyl 2-methyl-2-(2-(2-nitrobenzamido)benzamido)propanoate 2h:



2h

The crude product was purified by column chromatography (eluent: 40% AcOEt/pet. Ether, R_f: 0.4) to furnish **2h** (82% after 40% recovery of the starting material) as a white solid. mp: 125-126°C; IR ($CHCl_3$) ν (cm^{-1}): 3325, 2925, 2854, 1740, 1680, 1645, 1601, 1532, 1447, 1348, 1306, 1193, 1153, 904; ^1H NMR (200 MHz, $CDCl_3$) δ: 11.39 (1H, amide), 8.64-8.60 (d, *J*= 8.08 Hz, 1H), 8.07-8.03 (d, *J*= 8.08 Hz, 1H), 7.75-7.49 (m, 5H), 7.18-7.10 (t, *J*= 7.71 Hz, 1H), 6.99 (t, 1H), 3.71 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 174.7, 168.4, 164.4, 146.8, 138.9, 133.7, 132.9, 132.7, 130.8, 128.4, 16.8, 124.6, 123.6, 122.0, 120.9, 57.0, 52.7, 24.6; MALDI-TOF/TOF: 408.4238 ($M+Na^+$); 424.3958 ($M+K^+$); Anal. calcd for $C_{19}H_{19}N_3O_6$: C, 59.22; H, 4.97; N, 10.90. Found: C, 59.38; H, 4.69; N, 10.81.

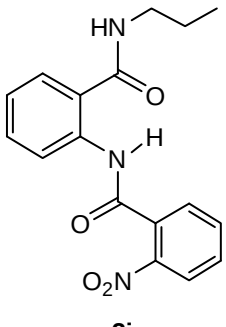
(*R*)-methyl 3-methyl-2-(2-(2-nitrobenzamido)benzamido)butanoate 2i:



2i

The crude product was purified by column chromatography (eluent: 40% AcOEt/pet. Ether, R_f: 0.4) to furnish **2i** (89%) as a pale yellow solid. mp: 145-146°C; $[\alpha]^{26.18}_D$: -7.336° (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 3332, 2925, 2853, 1740, 1687, 1646, 1588, 1532, 1447, 1349, 1311, 1210; ^1H NMR (200 MHz, $CDCl_3$) δ: 11.46 (1H, amide), 8.72-8.68 (d, *J*= 8.21 Hz, 1H), 8.07-8.03 (d, *J*= 7.83 Hz, 1H), 7.76-7.53 (m, 5H), 7.23-7.15 (t, *J*= 7.71 Hz, 1H), 6.87-6.82 (d, *J*= 8.34 Hz, 1H), 4.68-4.62 (dd, *J*= 5.05 Hz, *J*= 8.46 Hz, 1H), 3.77 (s, 3H), 2.34-2.18 (m, 1H), 1.01-0.97 (dd, *J*= 1.14 Hz, *J*= 6.82 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 172.0, 168.6, 164.3, 146.9, 139.1, 133.7, 133.1, 132.9, 130.7, 128.4, 126.7, 124.6, 123.7, 121.9, 120.2, 57.4, 52.4, 31.4, 18.9, 18.0; MALDI-TOF/TOF: 400.3518 ($M+H^+$); 422.3262 ($M+Na^+$); 438.2873 ($M+K^+$); Anal. calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 60.01; H, 5.39; N, 10.85.

2-nitro-N-(2-(propylcarbamoyl)phenyl)benzamide 2j:



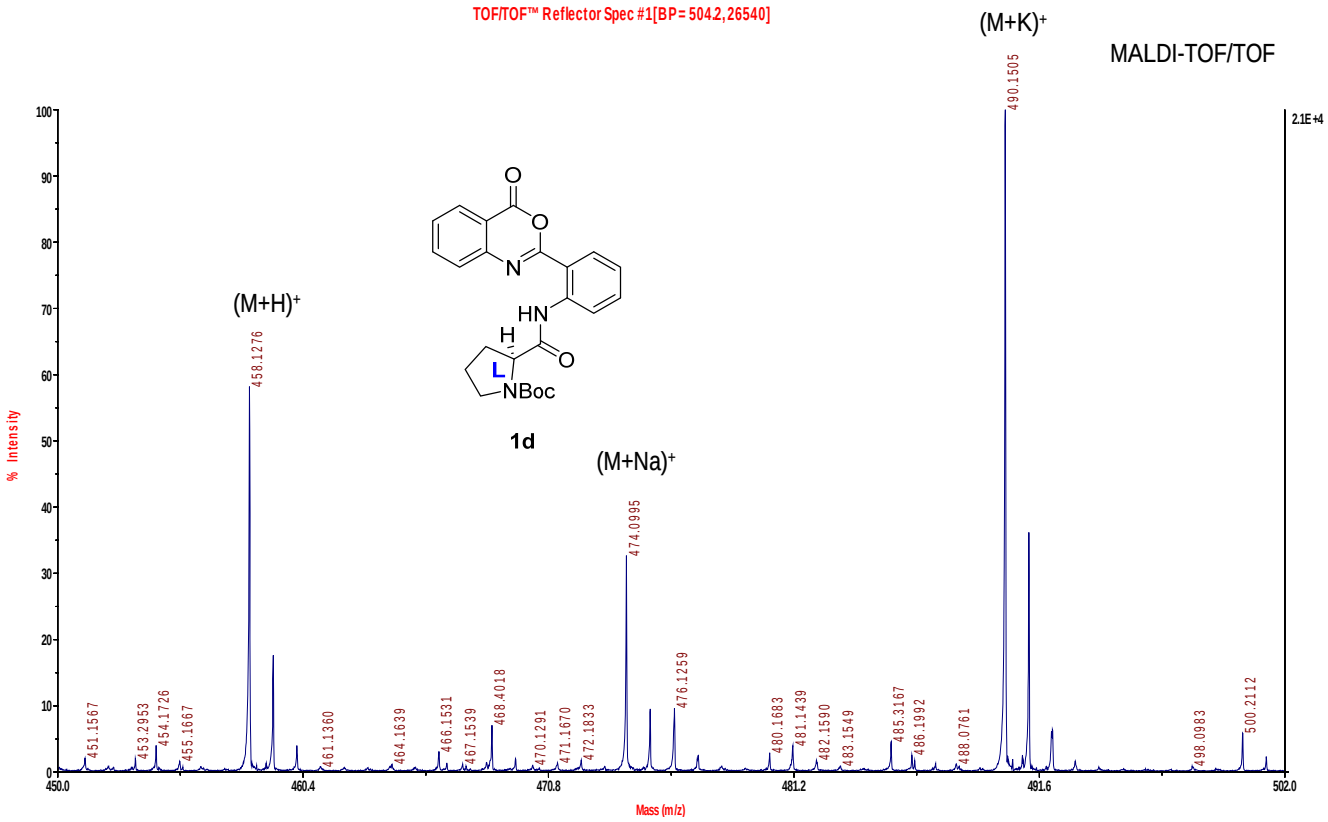
2j

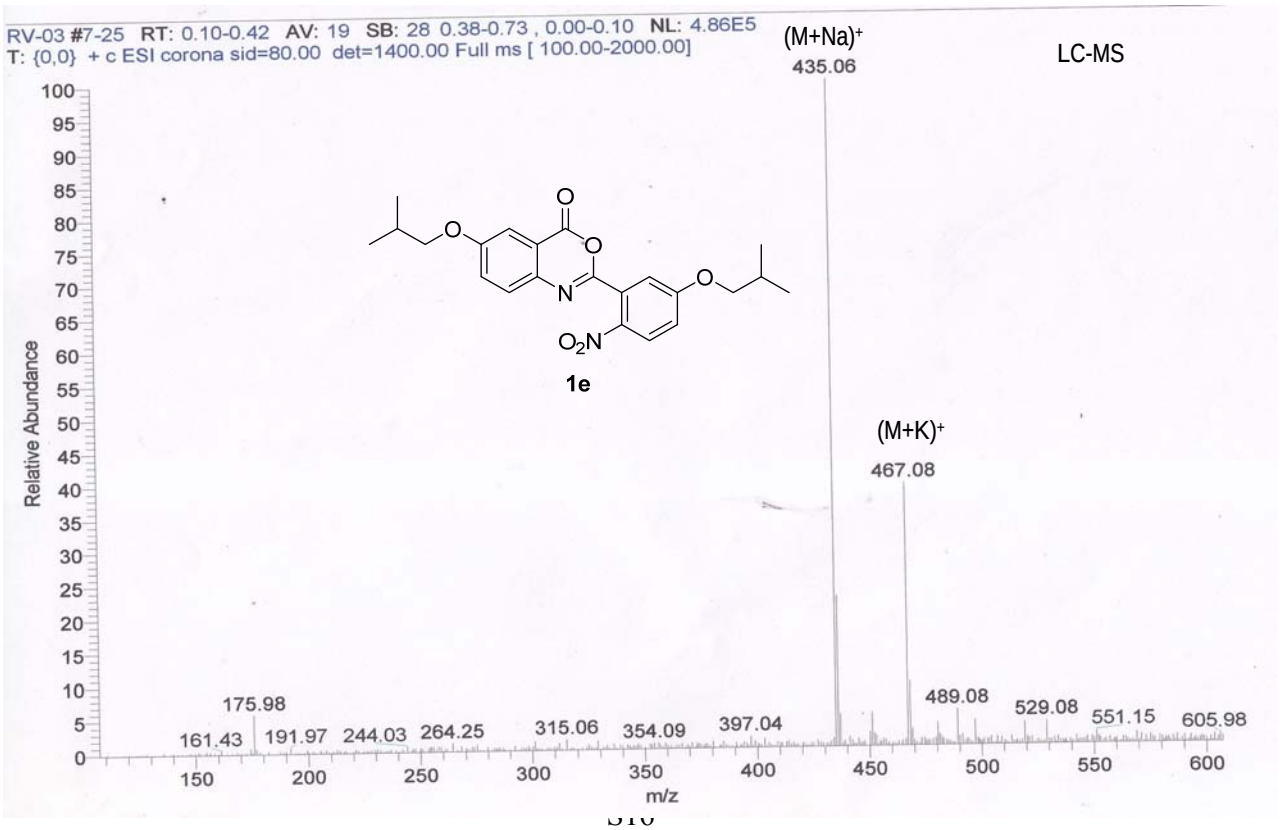
The crude product was purified by column chromatography (eluent: 35% AcOEt/pet. Ether, R_f: 0.3) to furnish **2j** (97%) as a white solid. mp: 167-169°C; IR ($CHCl_3$) ν (cm^{-1}): 3449, 2925, 1641, 1599, 1525, 1448, 1347; ^1H NMR (200 MHz, $CDCl_3$) δ: 11.72 (1H, amide), 8.70-8.65 (d, *J*= 8.21 Hz, 1H), 8.07-8.03 (d, *J*= 7.96 Hz, 1H), 7.73-7.49 (m, 5H), 7.18-7.10 (t, *J*= 7.83 Hz, 1H), 6.47 (s, 1H), 3.4-3.29 (m, 7.33 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.8, 164.3, 139.1, 133.7, 133.0, 132.7, 130.7, 128.4, 126.4, 124.7, 123.6, 121.9, 120.8, 63.6, 63.1, 41.7, 29.7, 22.6, 11.4; MALDI-TOF: 350.2100 ($M+Na^+$); 366.2022 ($M+K^+$); Anal. calcd for C17H17N3O4: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.60; H, 5.21; N, 12.88.

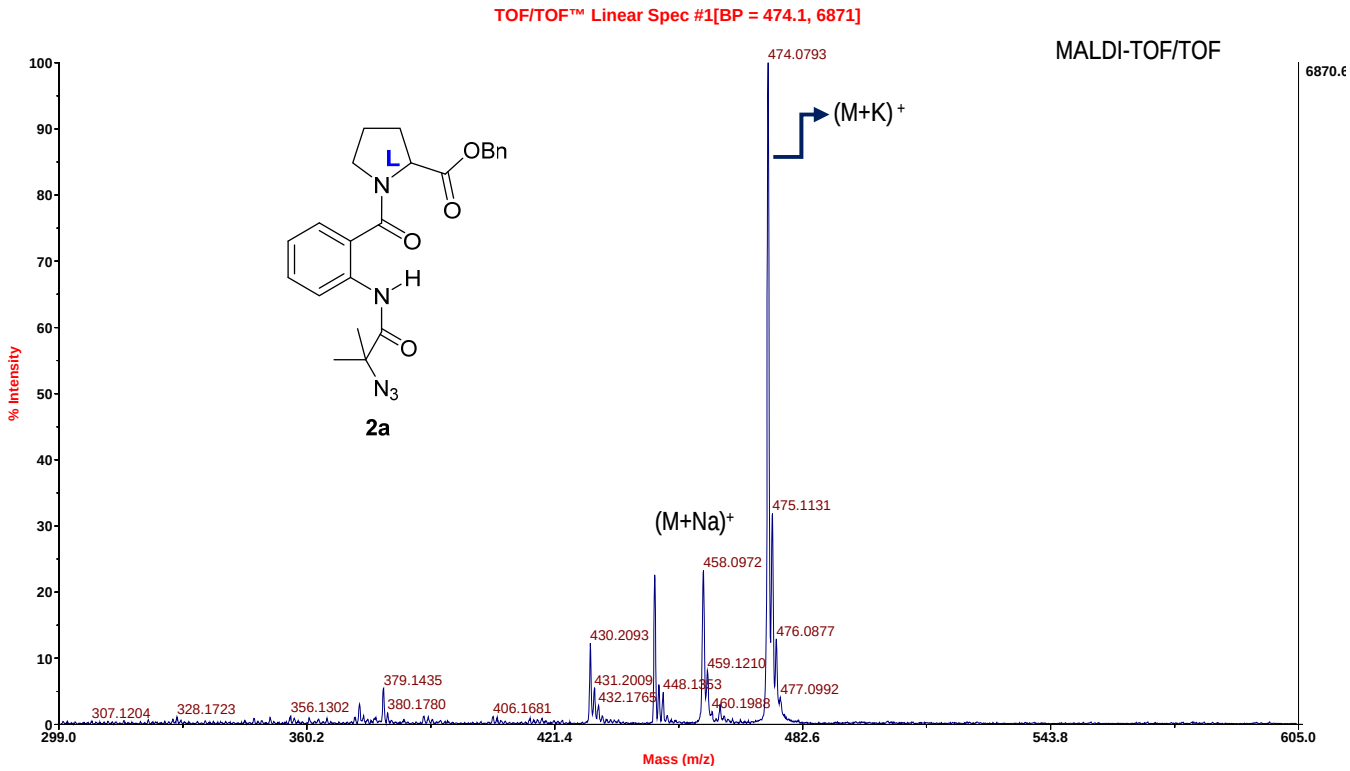
References:

1] Y. Hamuro, S. J. Geib and A. D. Hamilton, *J. Am. Chem. Soc.*, 1997, ***119***, 10587-10593.

2] A. A. Laeva, E. V. Nosova, G. N. Lipunova, A. V. Golovchenko, N. Yu. Adonin, V. N. Parmon, and V. N. Charushin. *Russ. J. Org. Chem.,* 2009, ***45***, 913–920.



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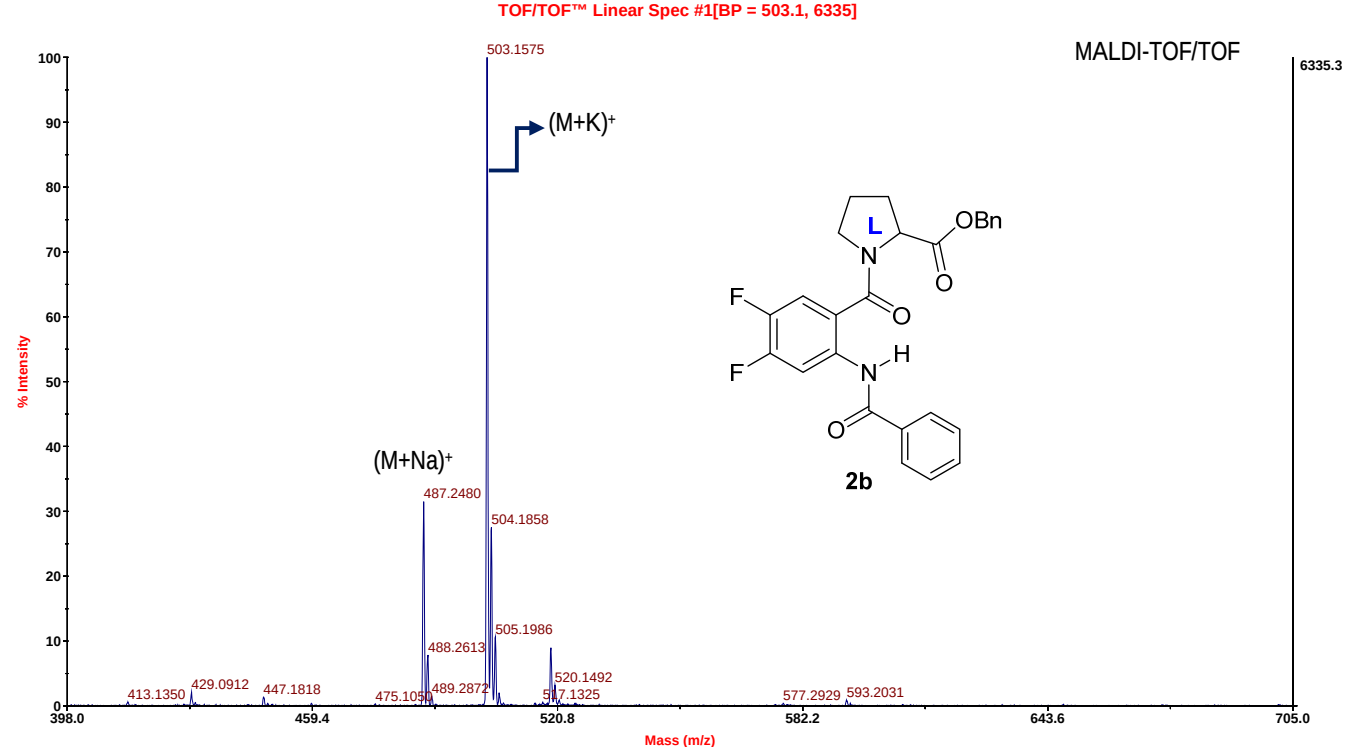
% Intensity
Mass (m/z)
2a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Mass (m/z)
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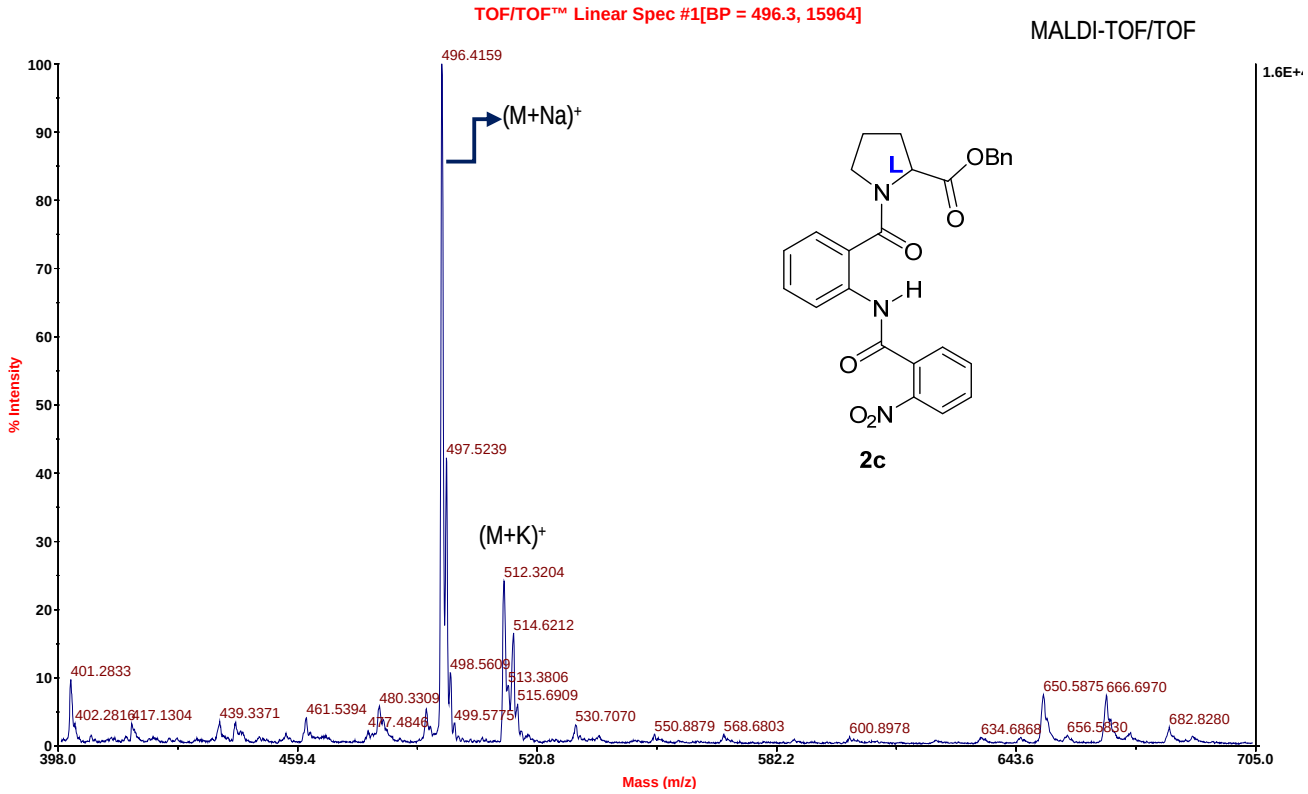
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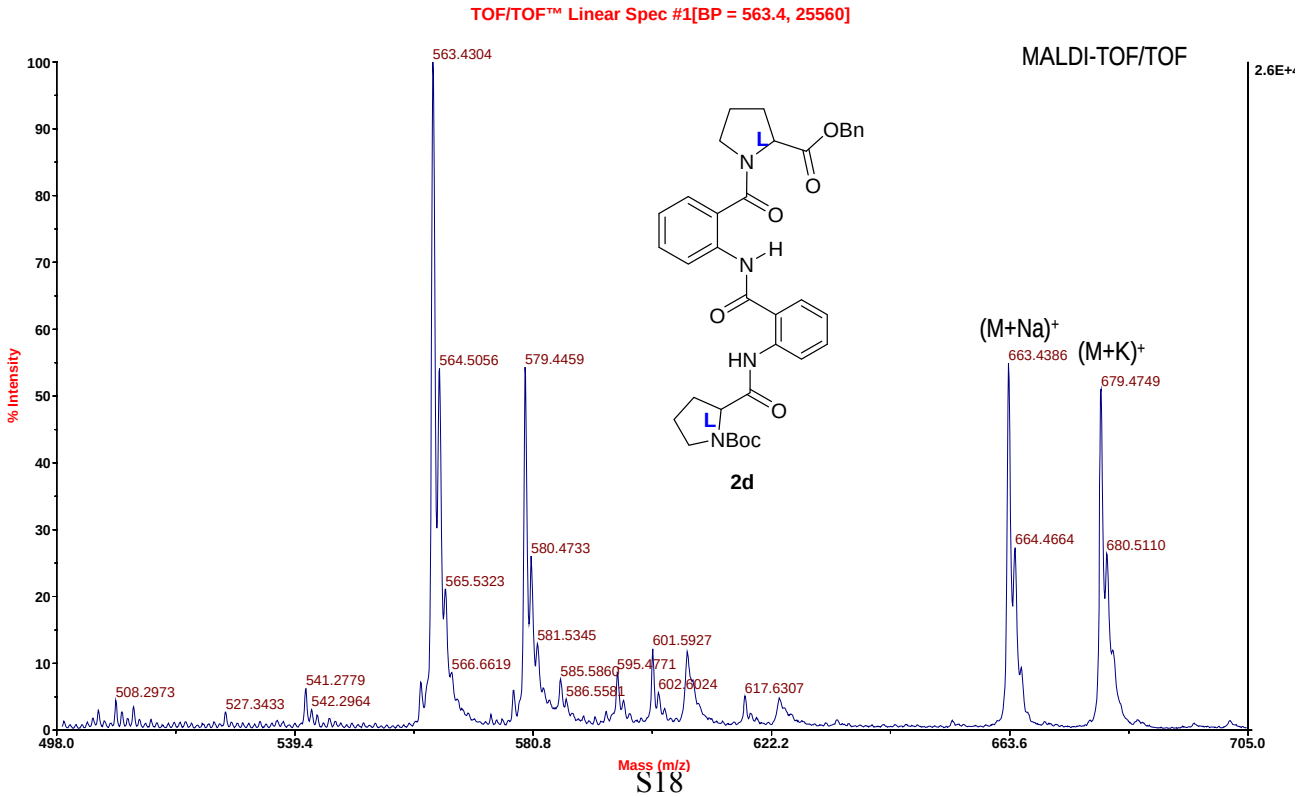
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580.4733
565.5323
581.5345
566.6619
585.5860
586.5581
595.4771
601.5927
602.6024
617.6307
508.2973
527.3433
541.2779
542.2964
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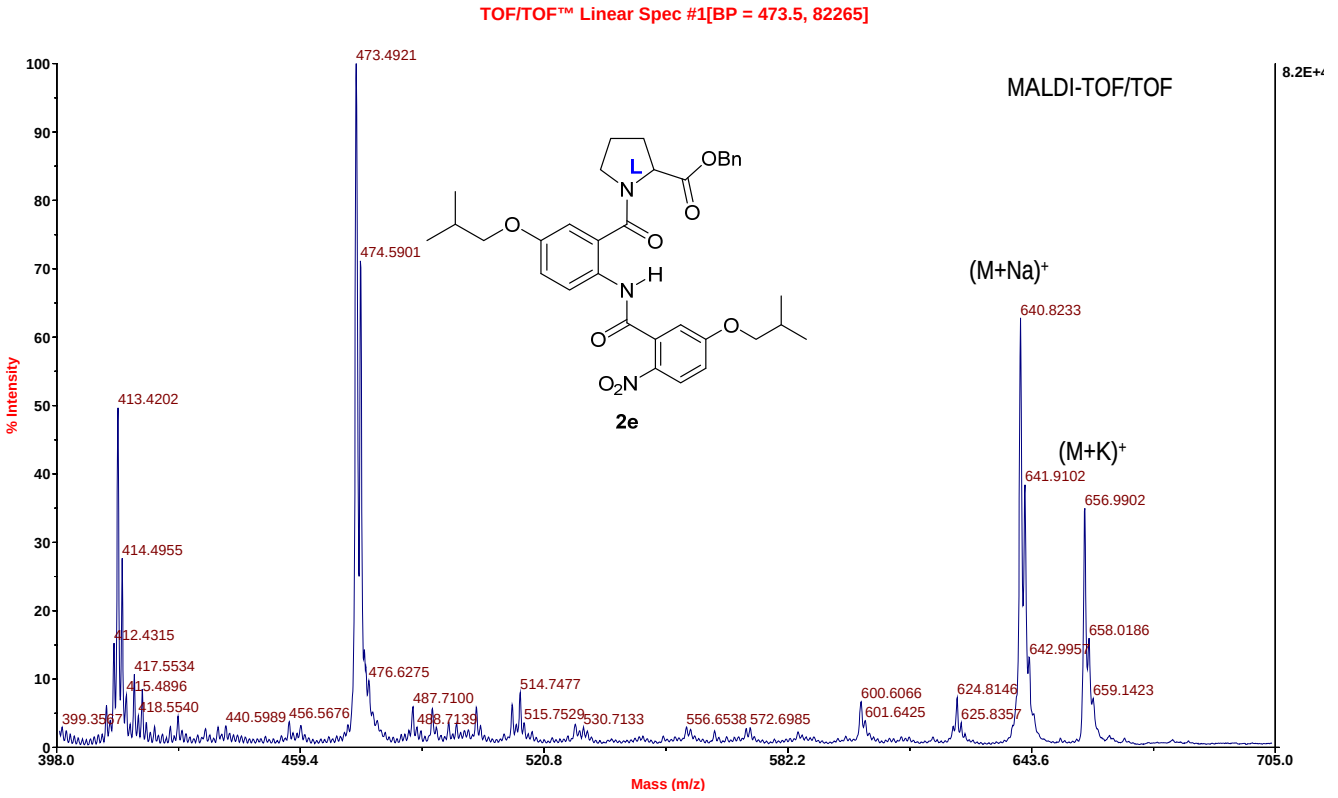
663.4386
(M+K)+
679.4749
664.4664
680.5110
OBn
HN
NBoc
2d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MALDI-TOF/TOF
% Intensity
Mass (m/z)
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474.5901
413.4202
414.4955
412.4315
417.5534
415.4896
418.5540
399.3567
440.5989
456.5676
476.6275
487.7100
488.7139
514.7477
515.7529
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624.8146
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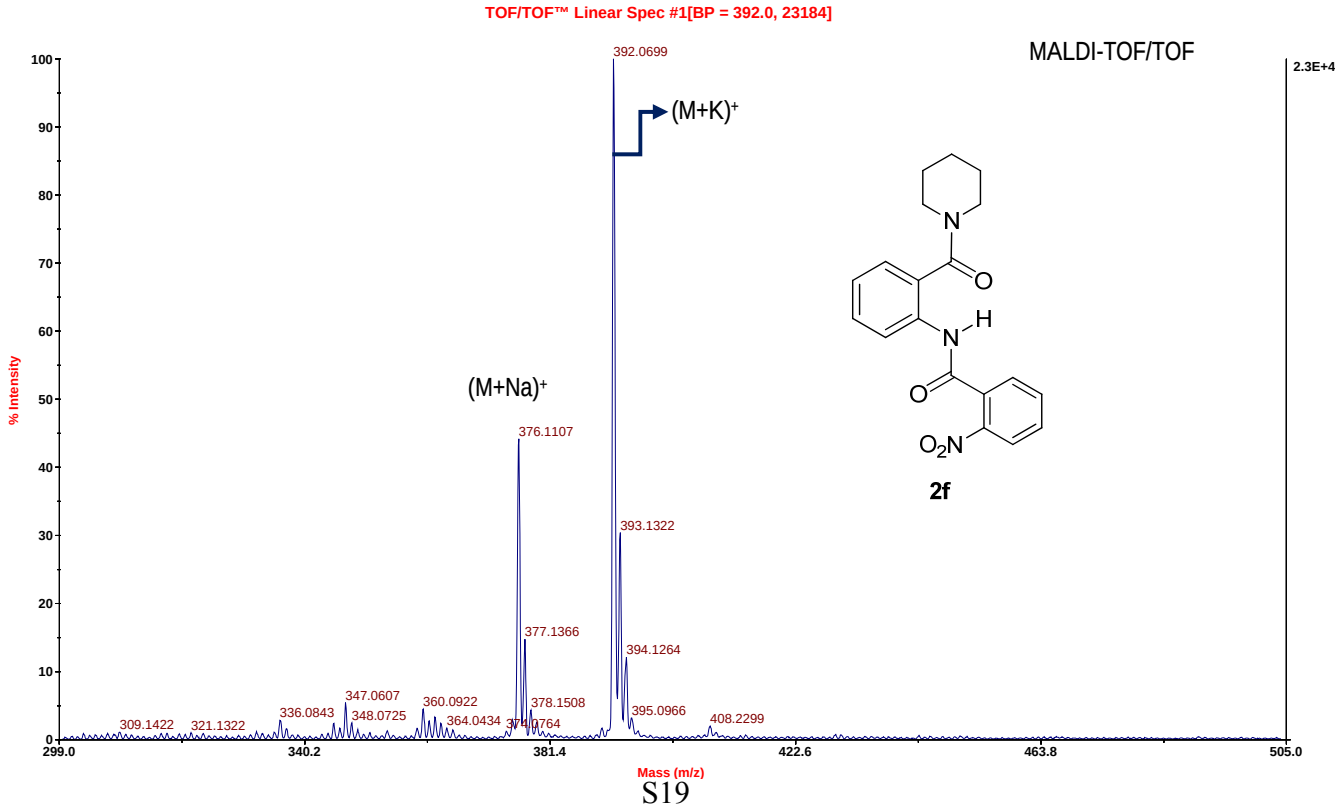
(M+Na)+
(M+K)+
OBn
2e


TOF/TOF™ Linear Spec #1[BP = 392.0, 23184]
MALDI-TOF/TOF
% Intensity
Mass (m/z)
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(M+K)+
(M+Na)+
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393.1322
377.1366
394.1264
347.0607
360.0922
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378.1508
395.0966
309.1422
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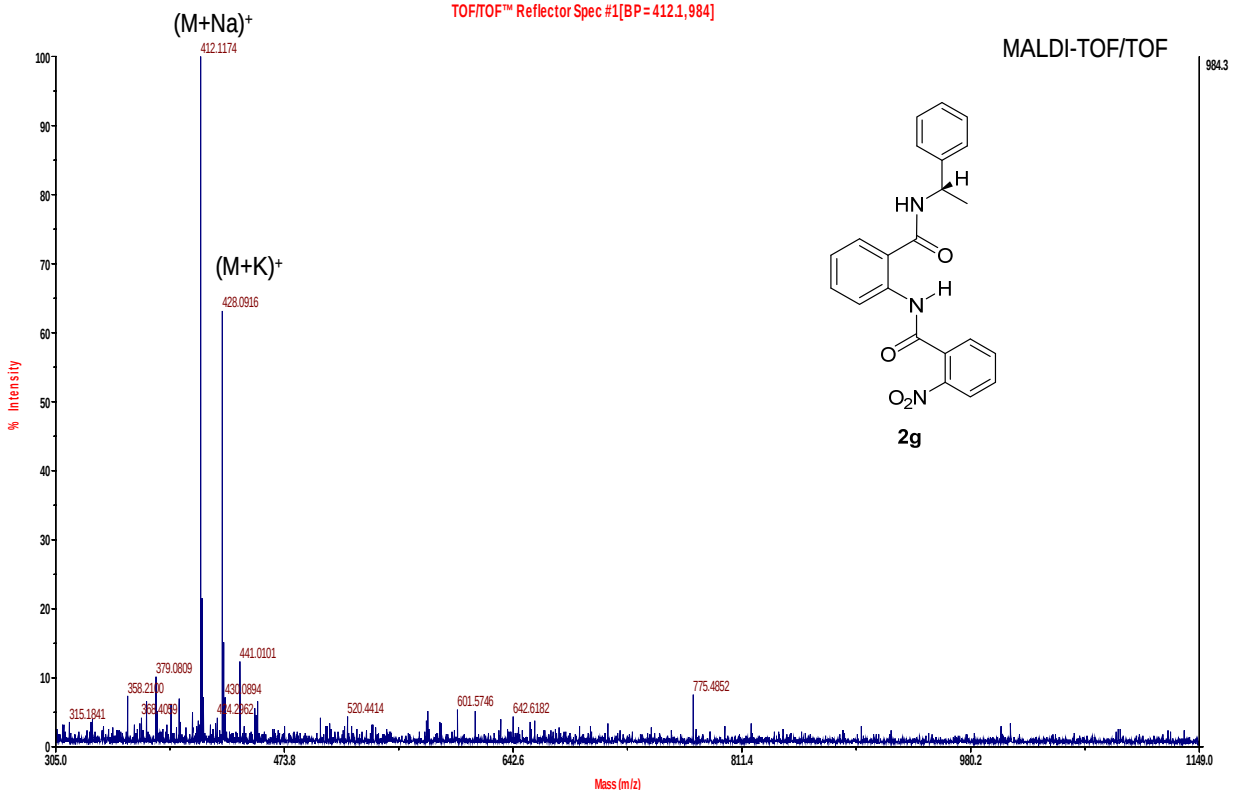
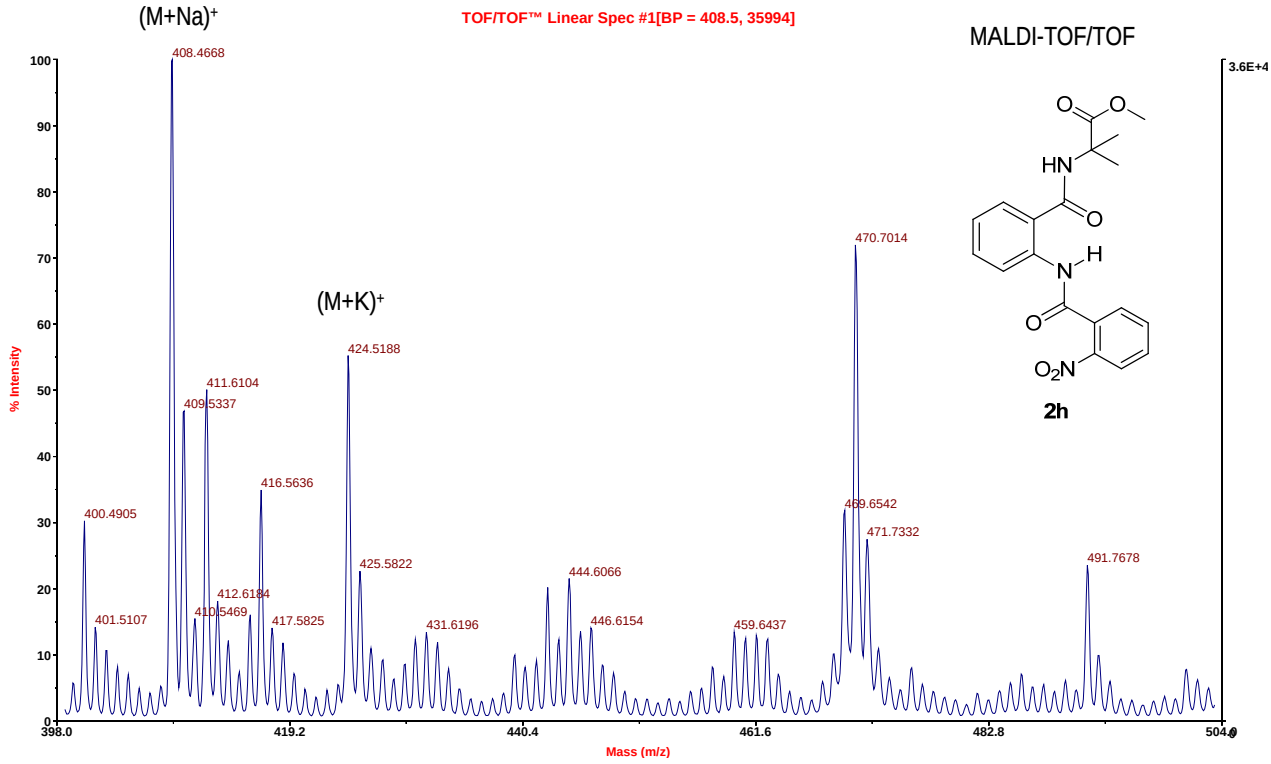
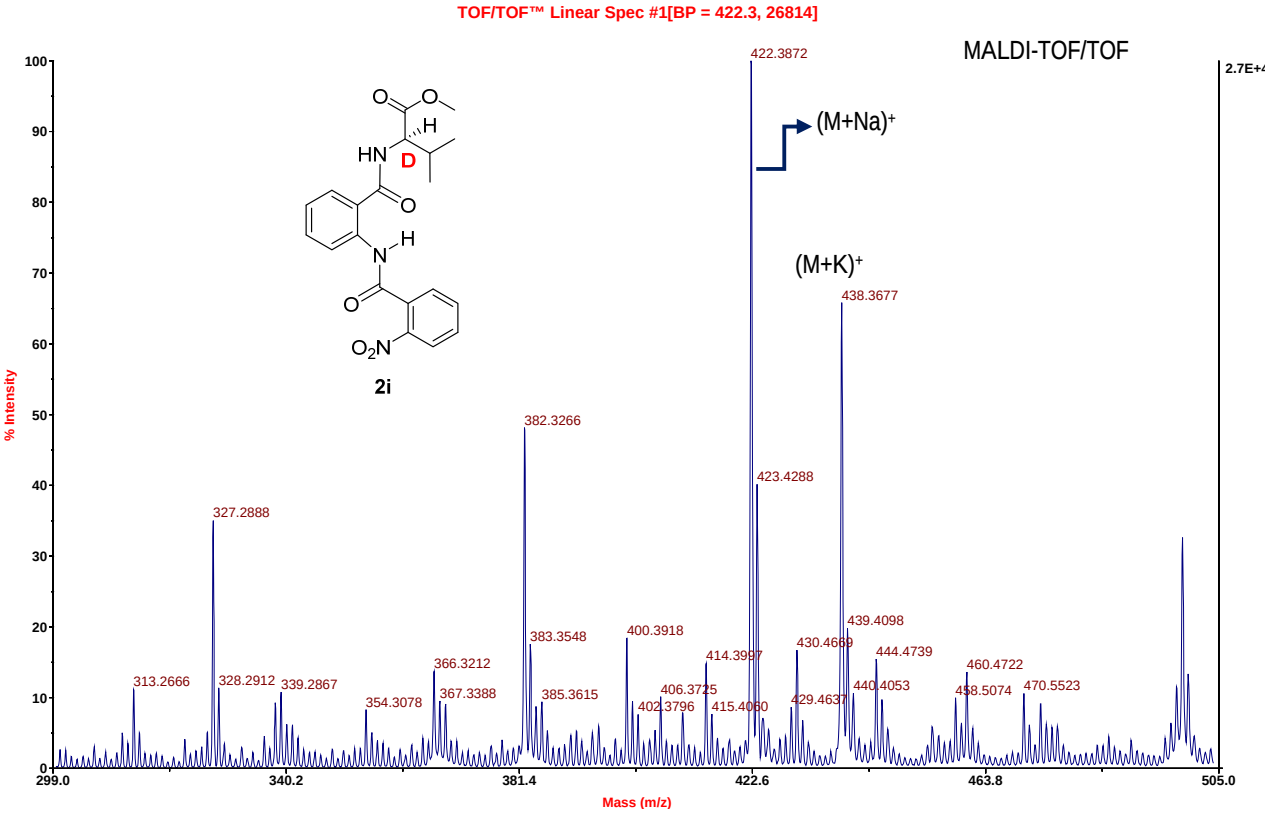
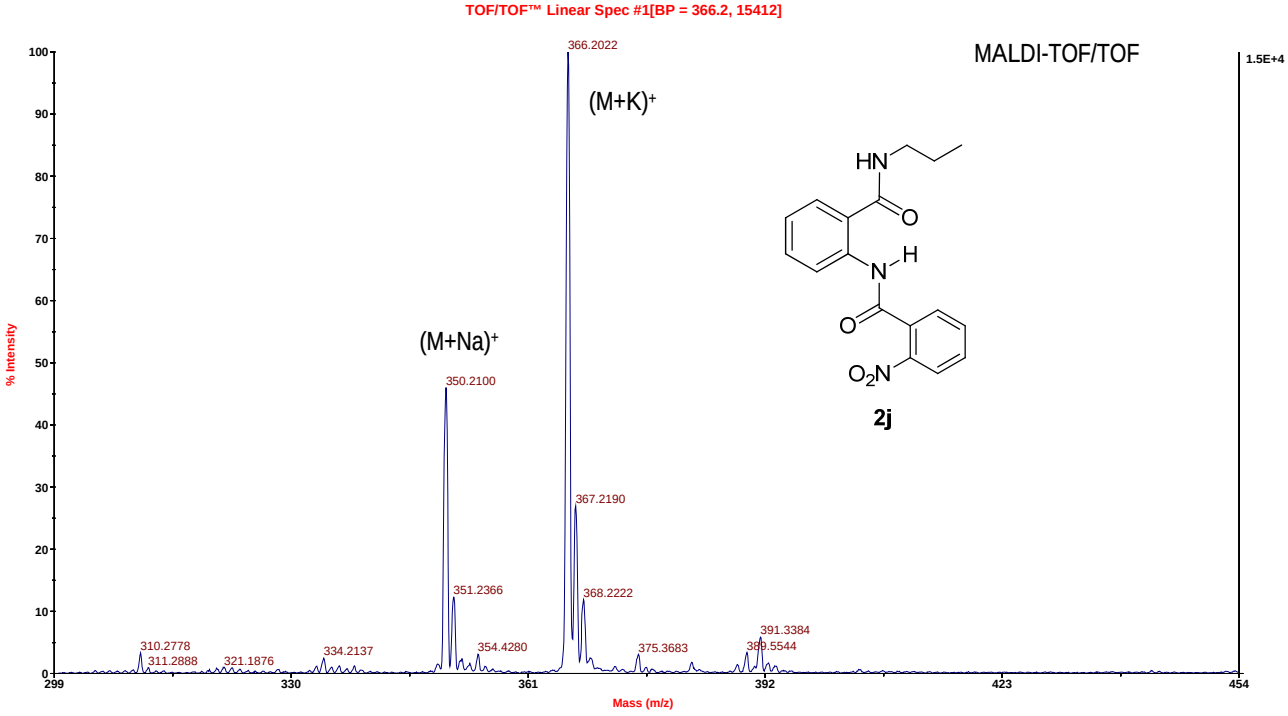
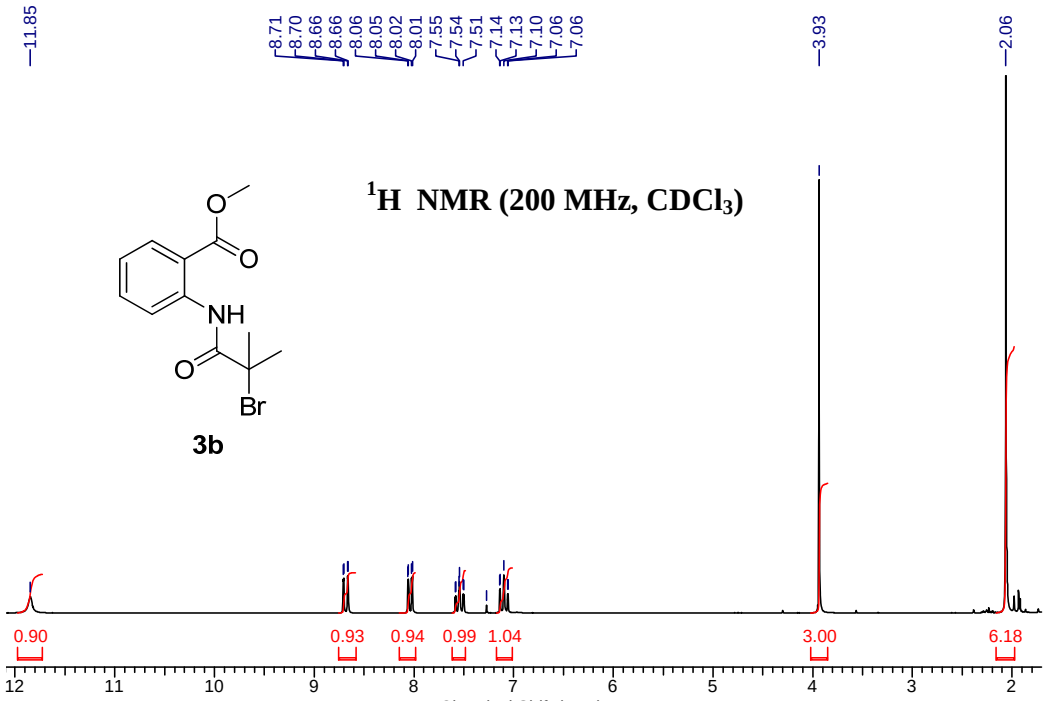
408.2299
2f





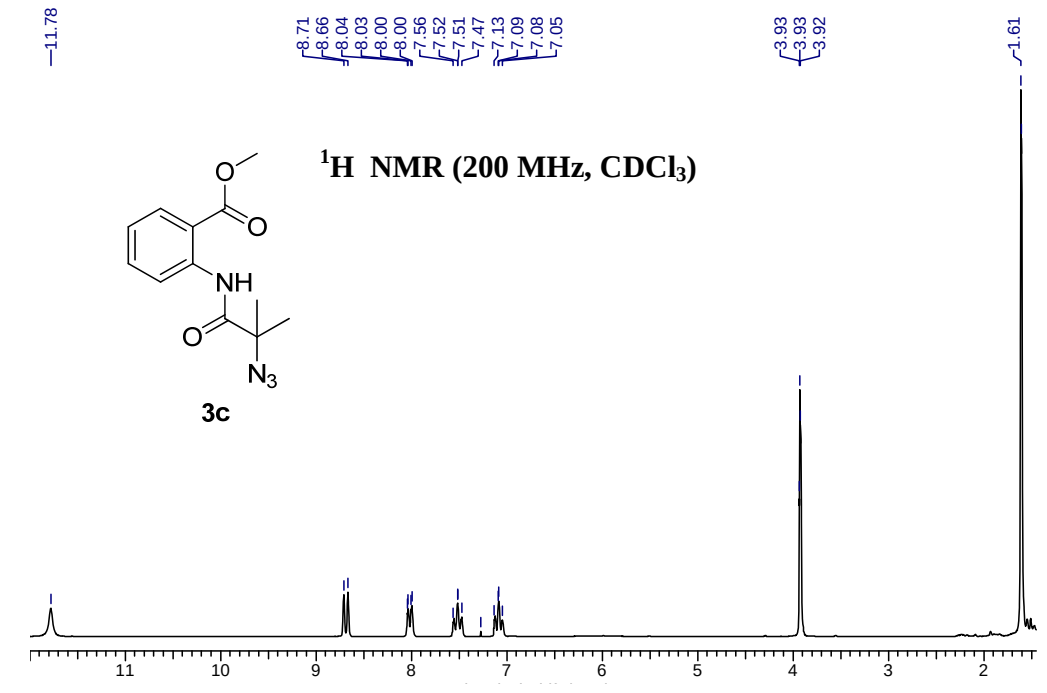






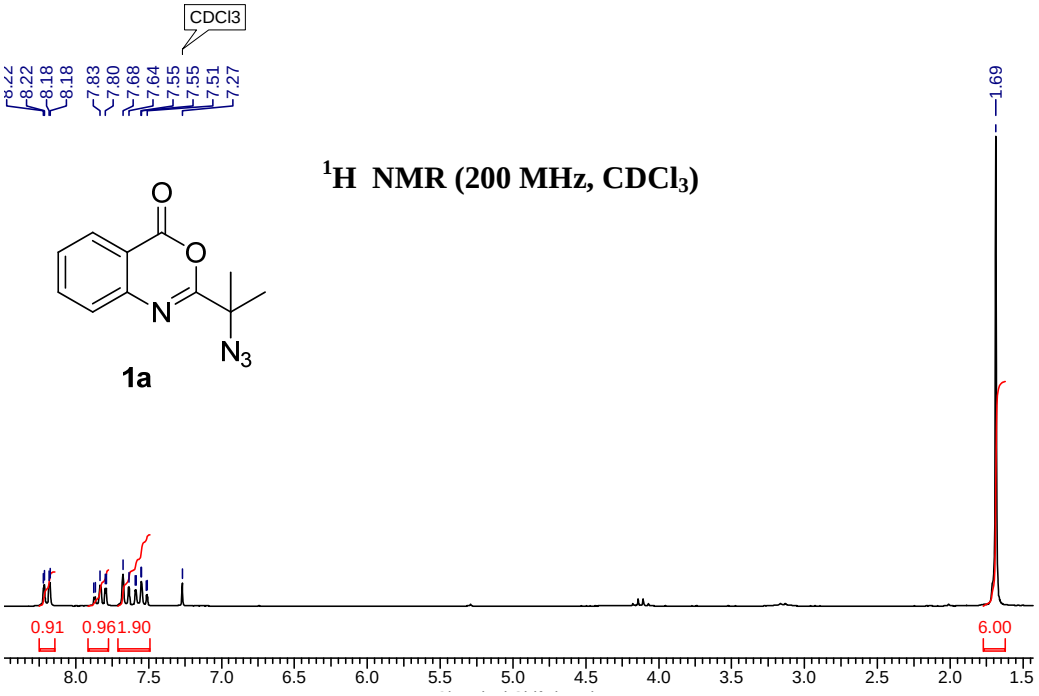
^{1}H NMR (200 MHz, $CDCl_3$)

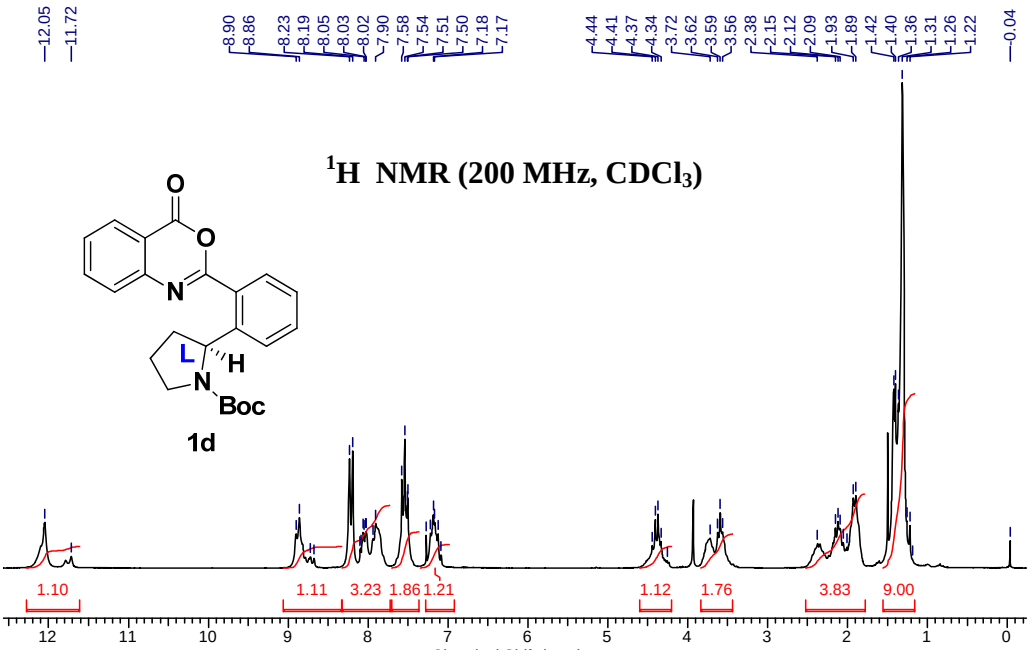
3b

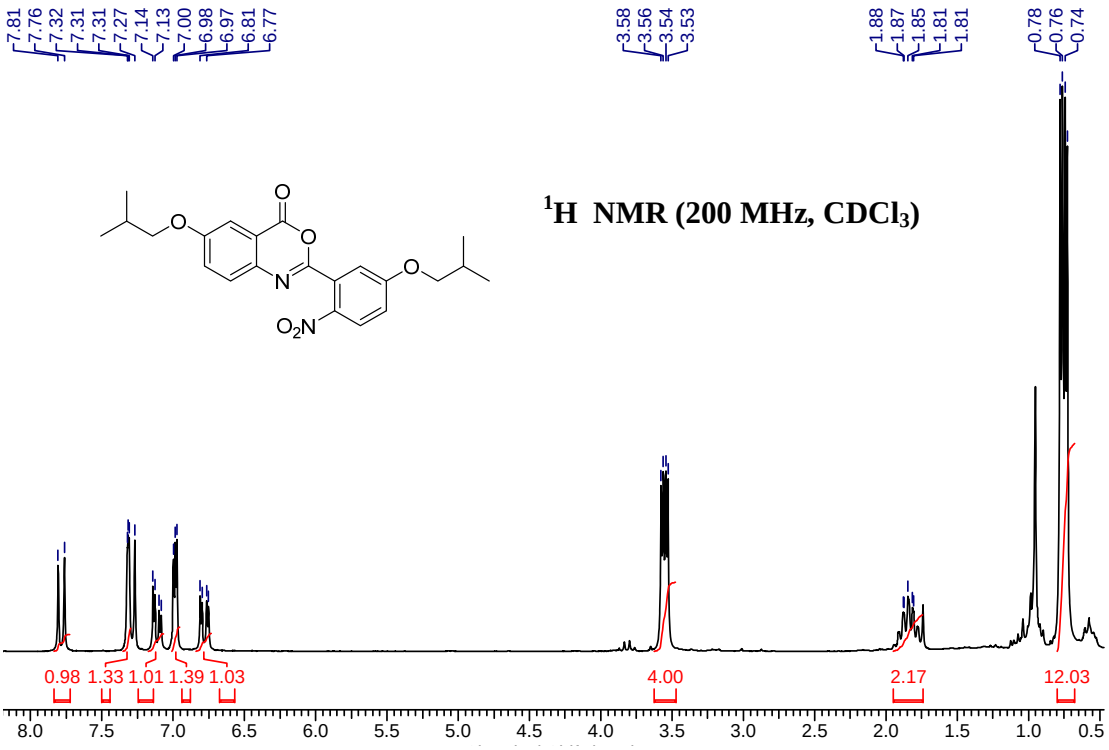


^{1}H NMR (200 MHz, $CDCl_3$)

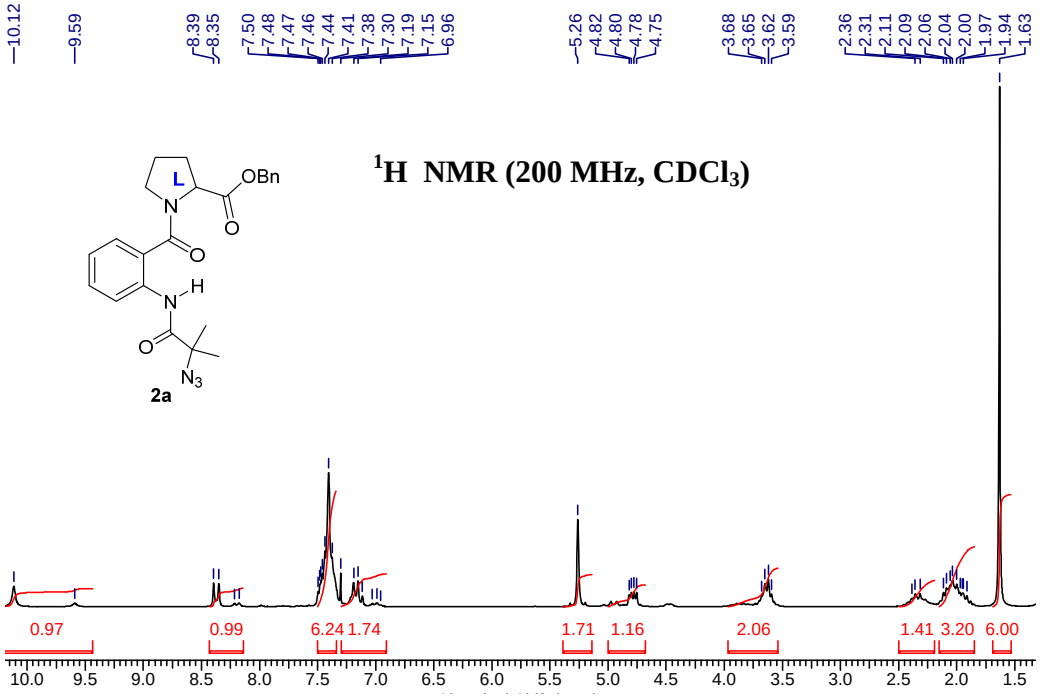
3c





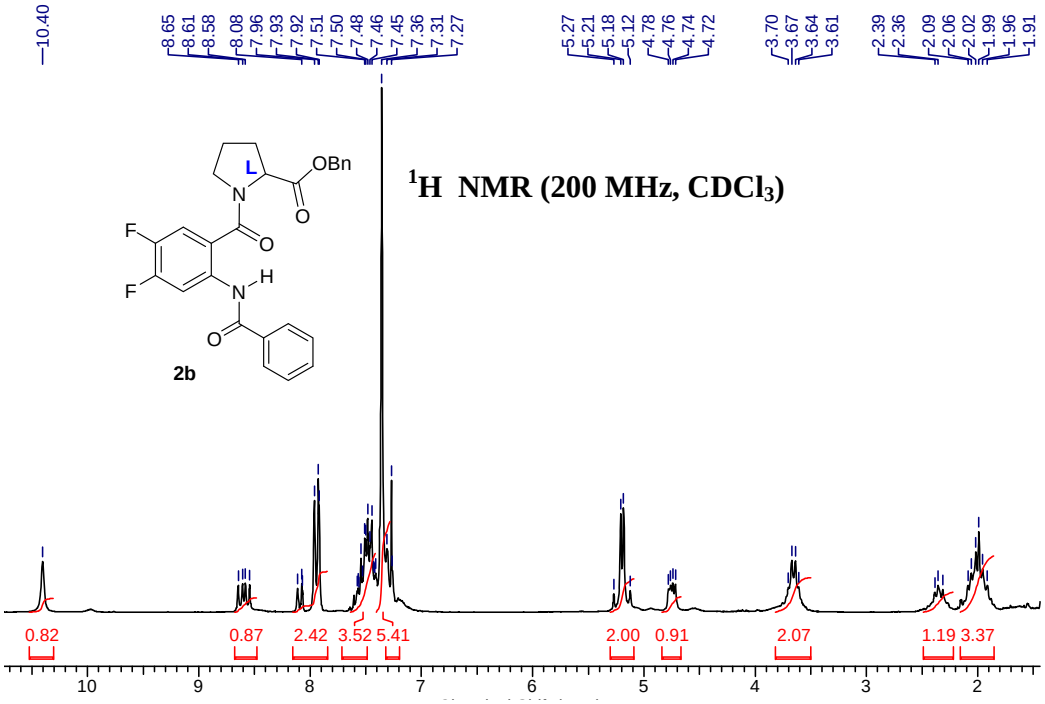


^{1}H NMR (200 MHz, $CDCl_3$)

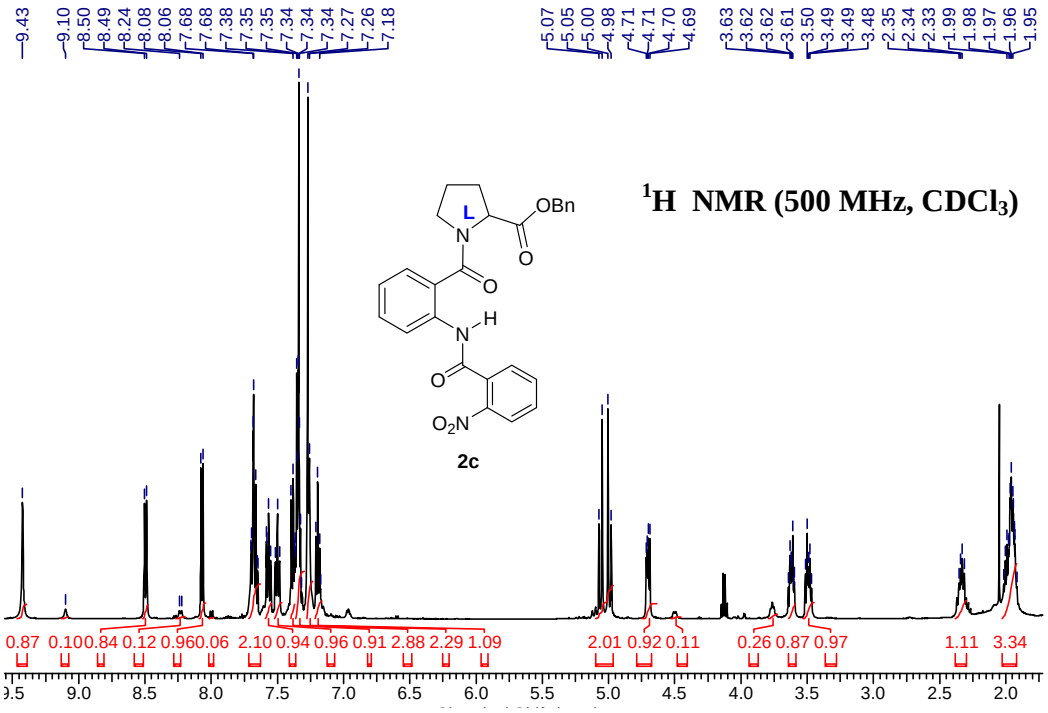


^{1}H NMR (200 MHz, $CDCl_3$)

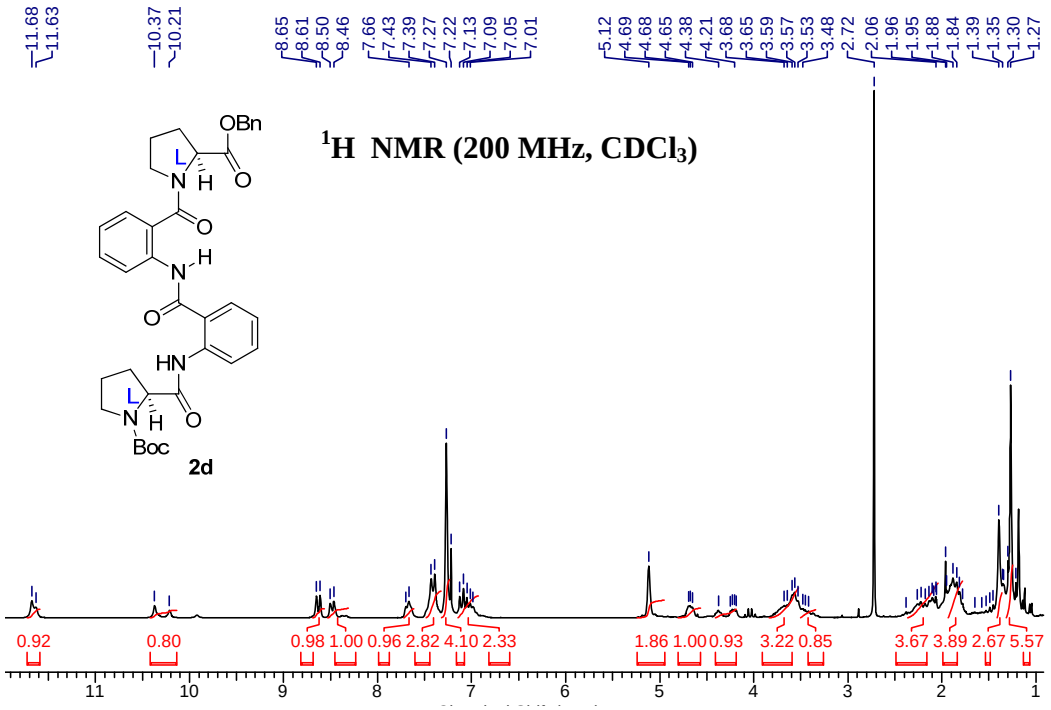
2a



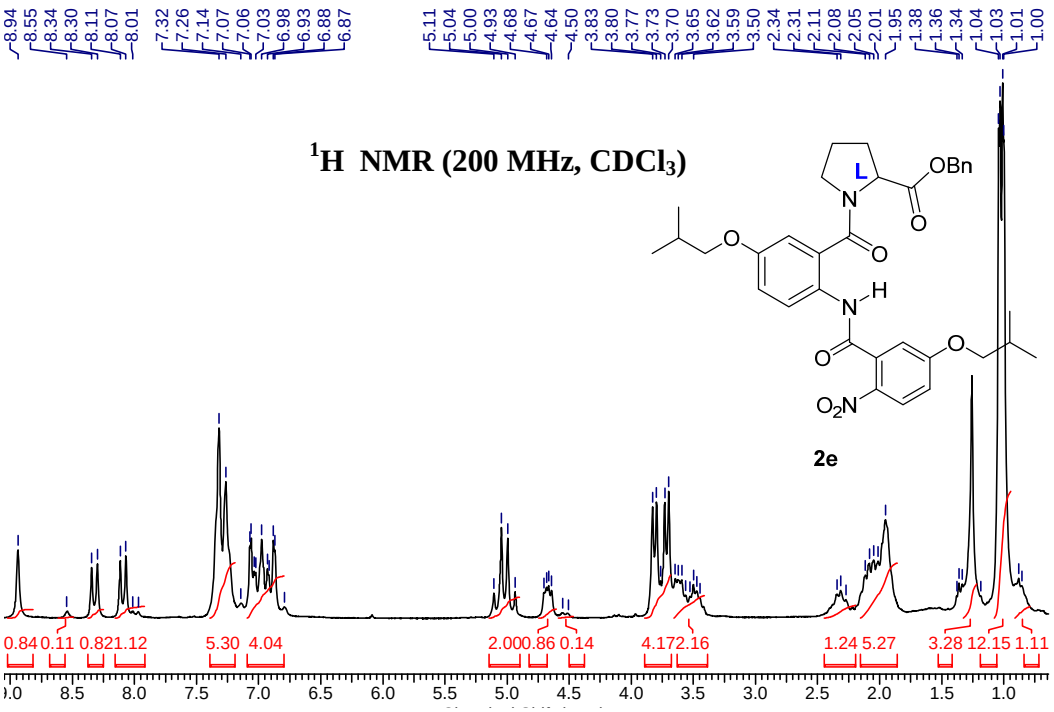
^{1}H NMR (200 MHz, $CDCl_3$)



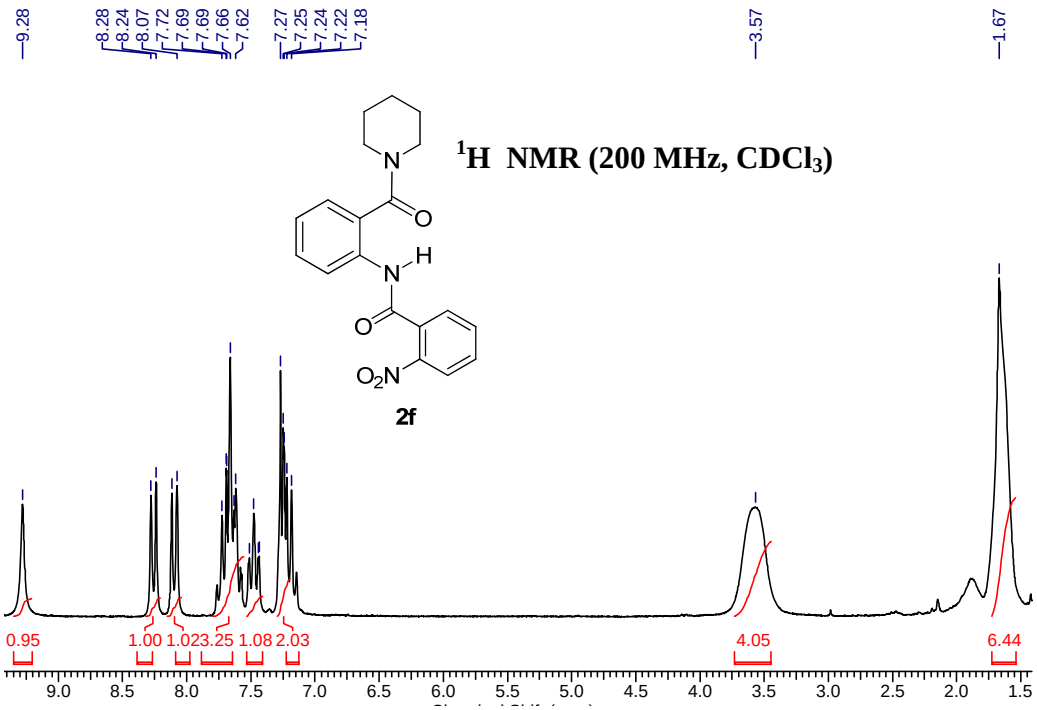
^{1}H NMR (500 MHz, $CDCl_3$)

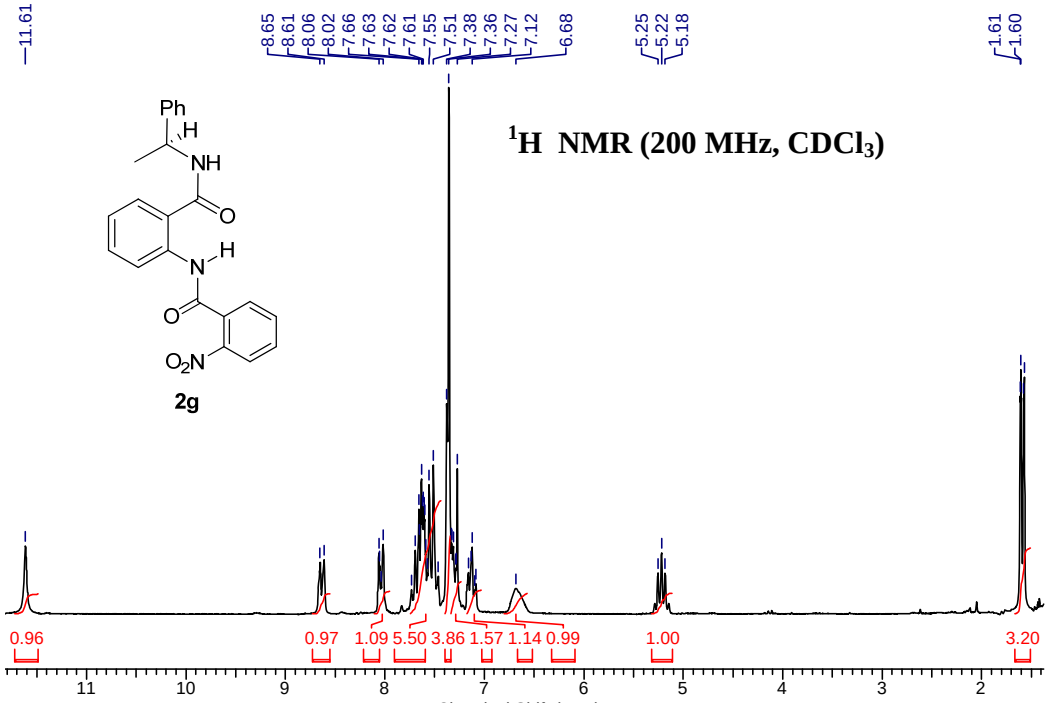


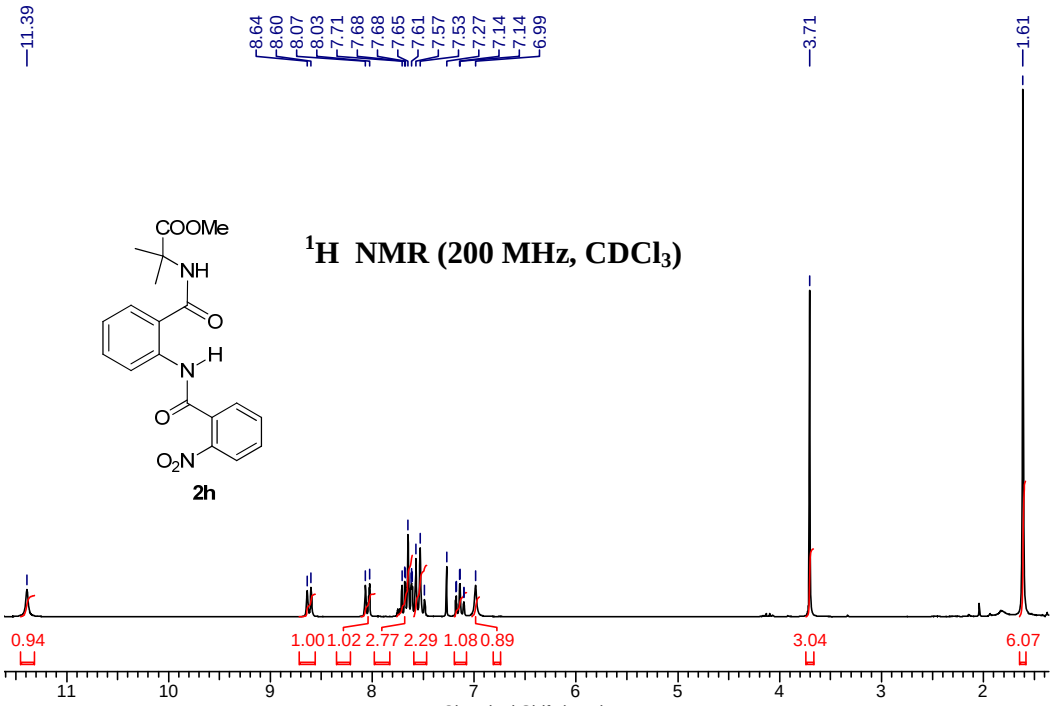
^{1}H NMR (200 MHz, $CDCl_3$)

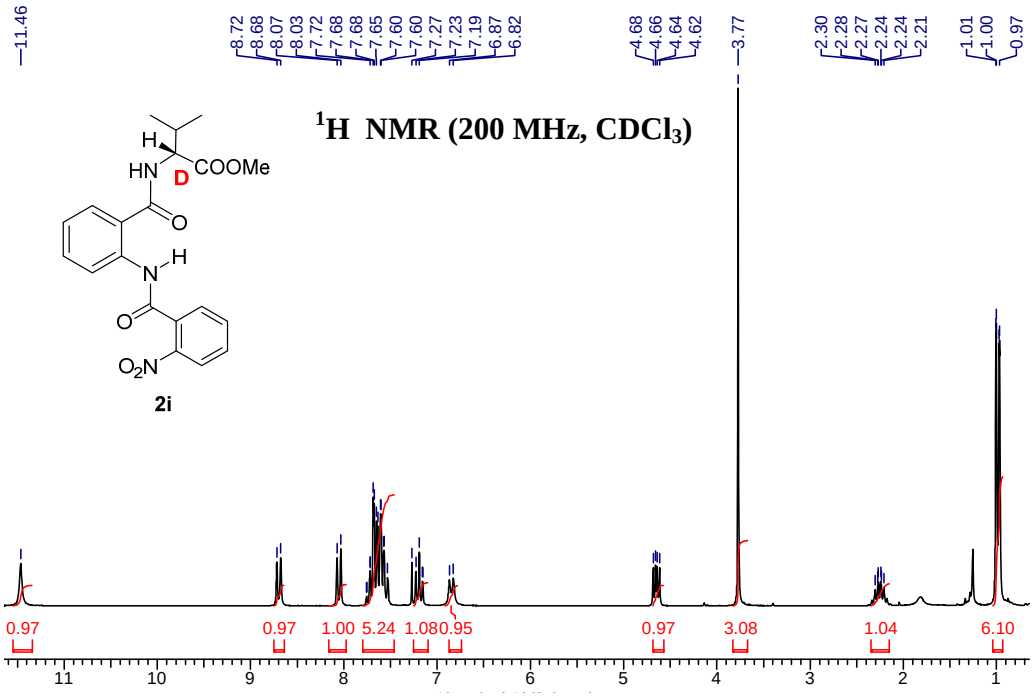


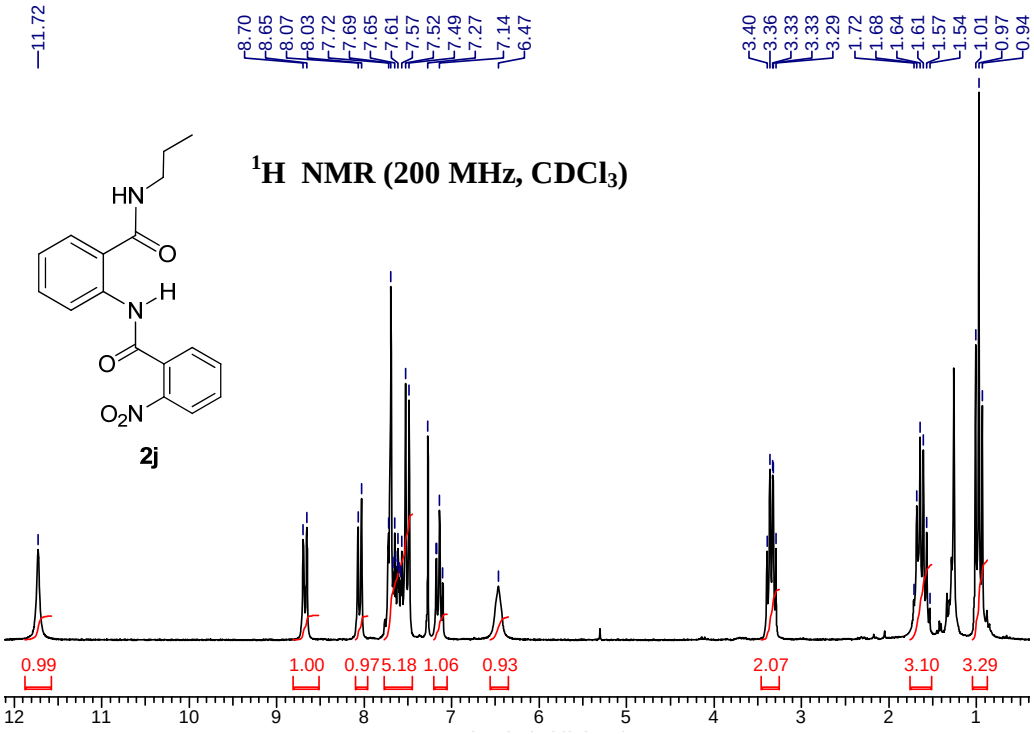
^{1}H NMR (200 MHz, $CDCl_3$)

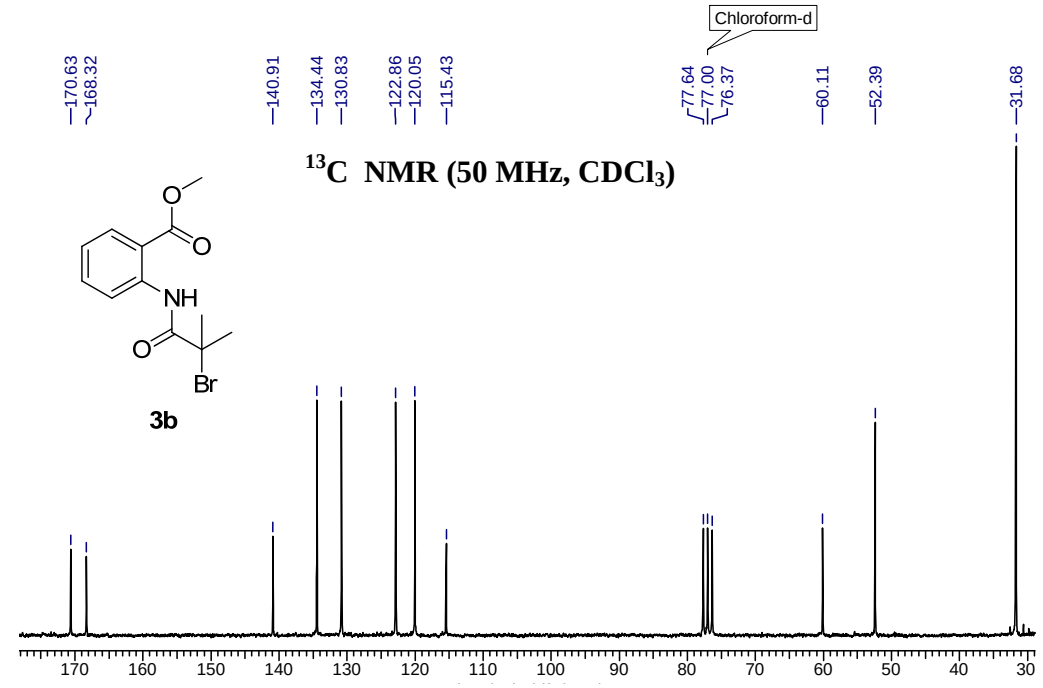


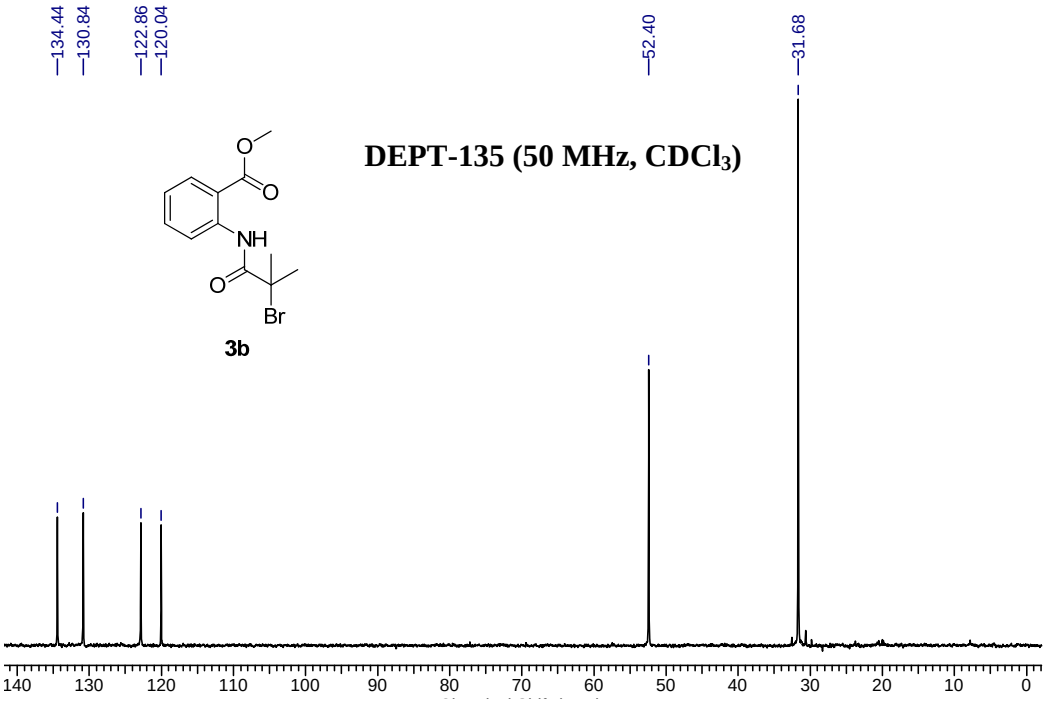


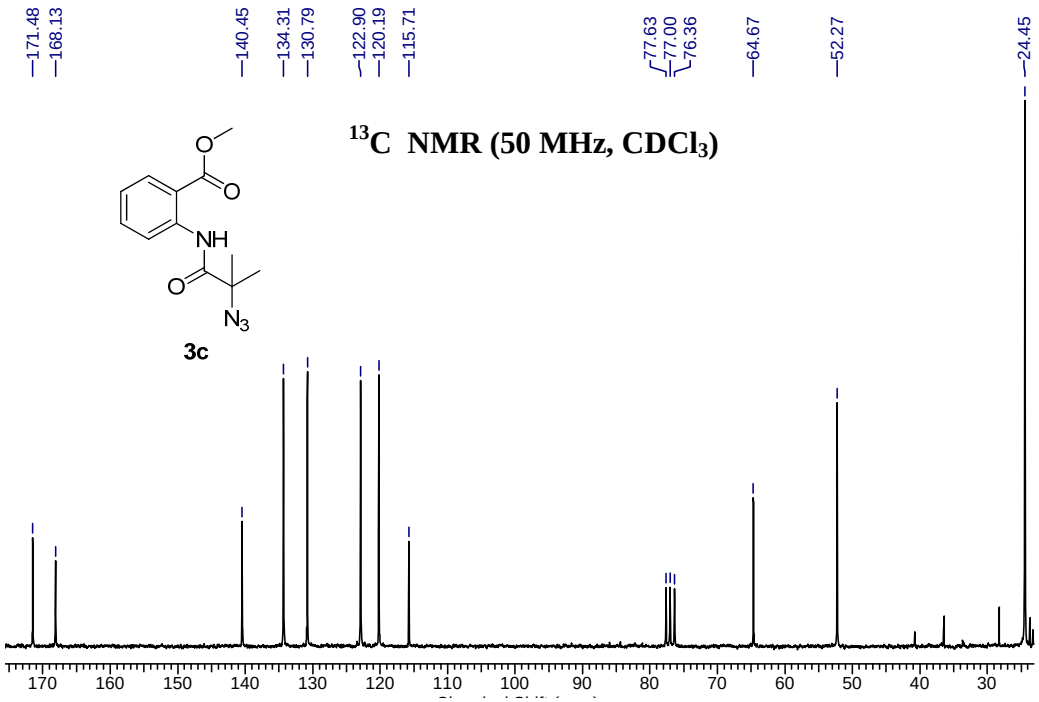

11.39
8.64
8.60
8.07
8.03
7.71
7.68
7.68
7.65
7.61
7.57
7.53
7.27
7.14
7.14
6.99
3.71
1.61
COOMe
NH
O
N
H
O
O2N
2h
1H NMR (200 MHz, CDCl3)
0.94
1.00
1.02
2.77
2.29
1.08
0.89
3.04
6.07
11
10
9
8
7
6
5
4
3
2


11.46
8.72
8.68
8.07
8.03
7.72
7.68
7.68
7.65
7.60
7.60
7.27
7.23
7.19
6.87
6.82
4.68
4.66
4.64
4.62
3.77
2.30
2.28
2.27
2.24
2.24
2.21
1.01
1.00
0.97
H
HN
D
COOMe
O
N
H
O
O2N
2i
1H NMR (200 MHz, CDCl3)
0.97
0.97
1.00
5.24
1.08
0.95
0.97
3.08
1.04
6.10
11
10
9
8
7
6
5
4
3
2
1



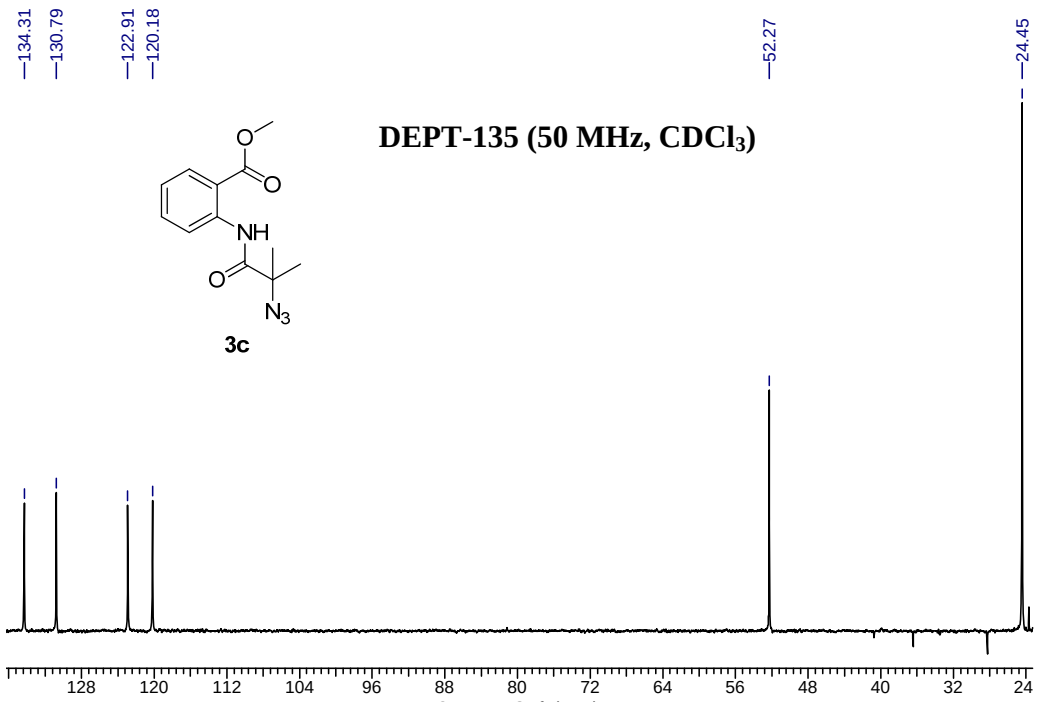






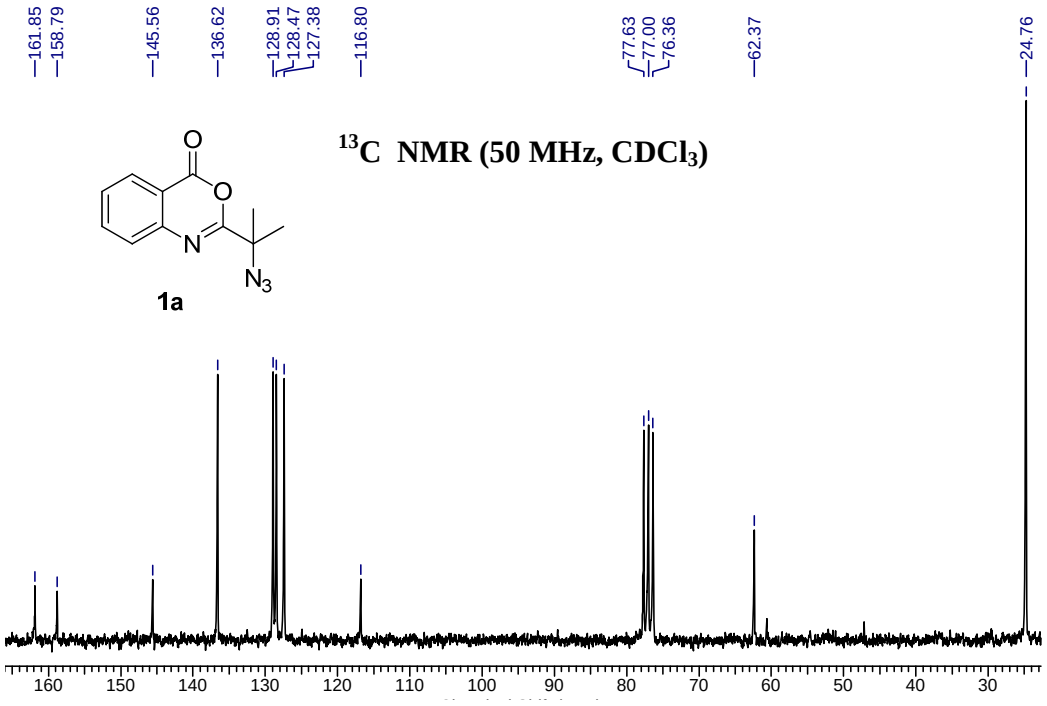
^{13}C NMR (50 MHz, $CDCl_3$)

3c

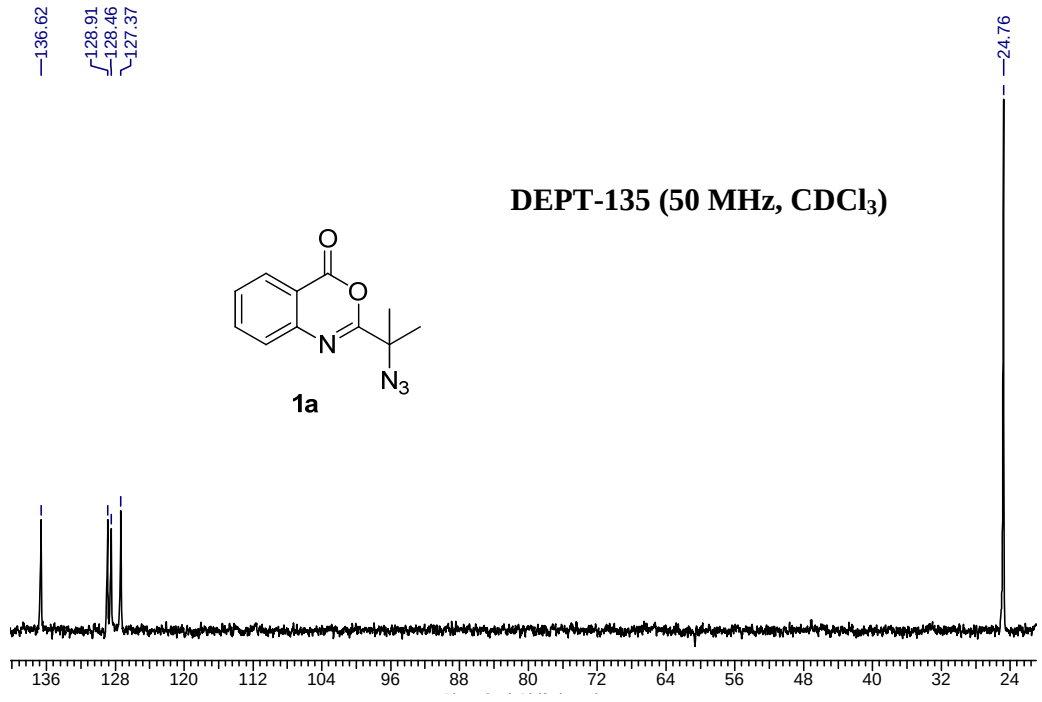


DEPT-135 (50 MHz, $CDCl_3$)

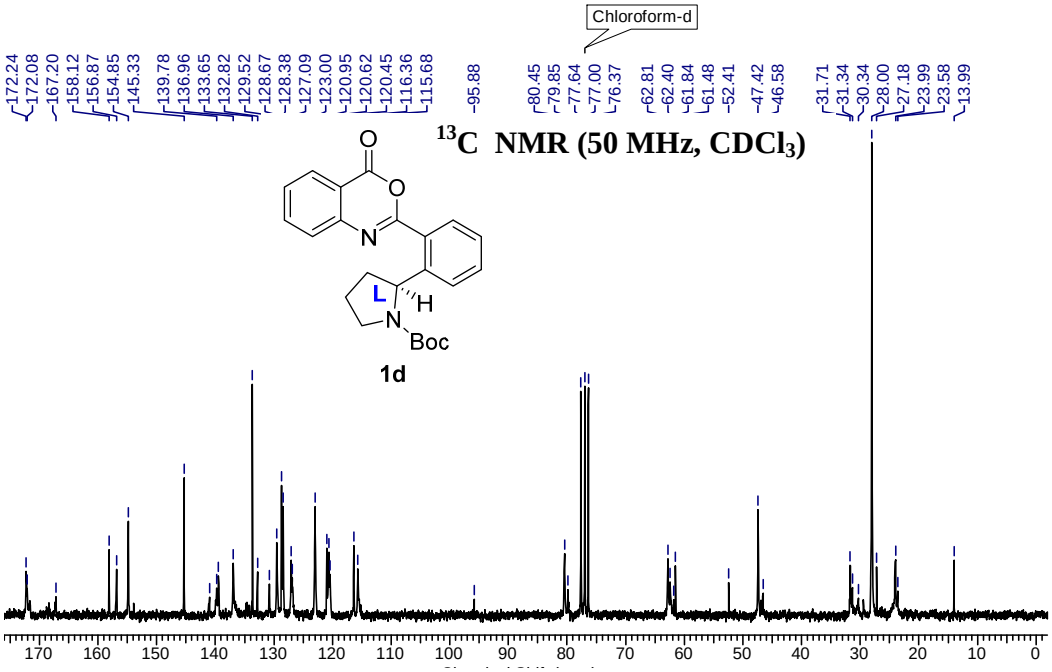
3c

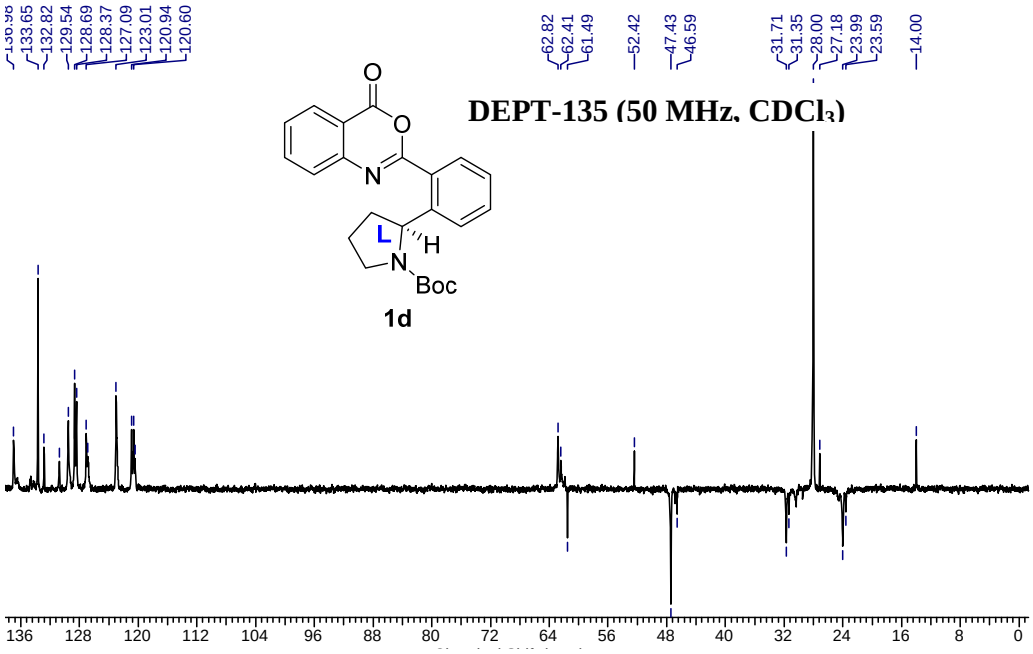


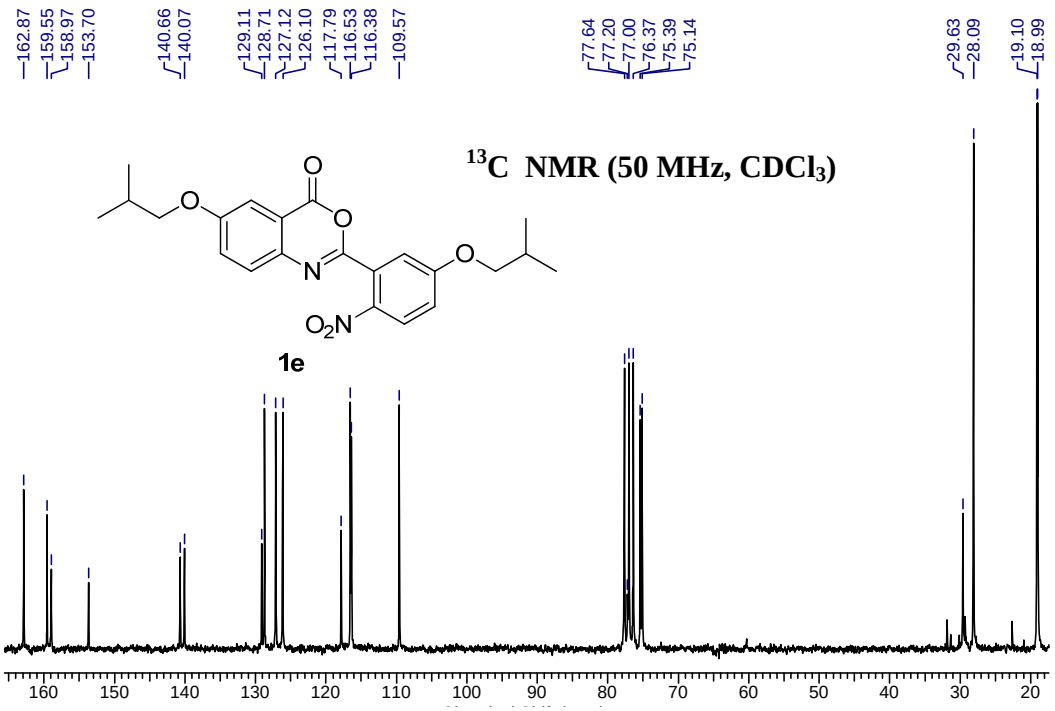
^{13}C NMR (50 MHz, $CDCl_3$)



DEPT-135 (50 MHz, $CDCl_3$)

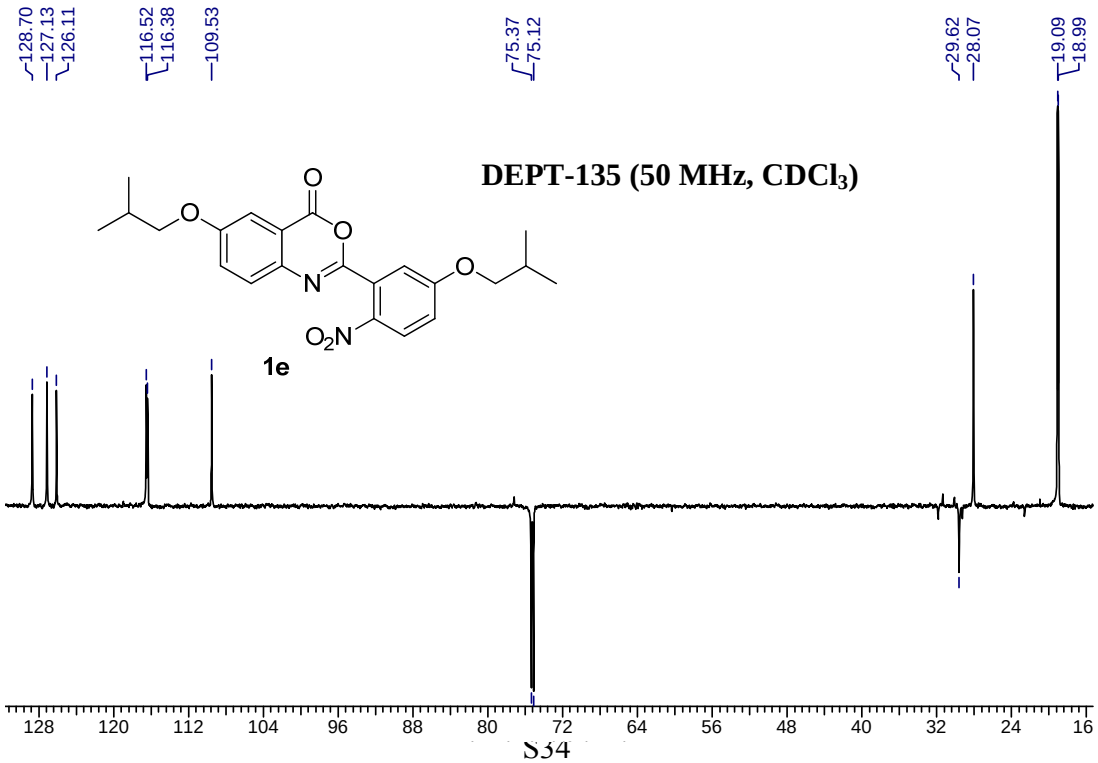






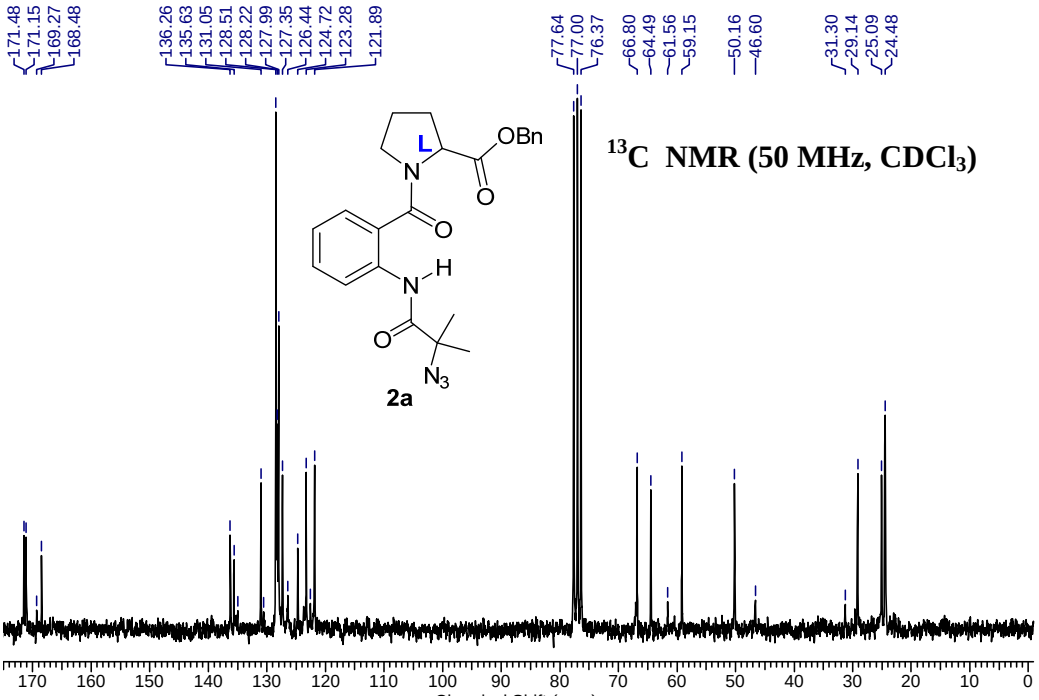
^{13}C NMR (50 MHz, $CDCl_3$)

1e

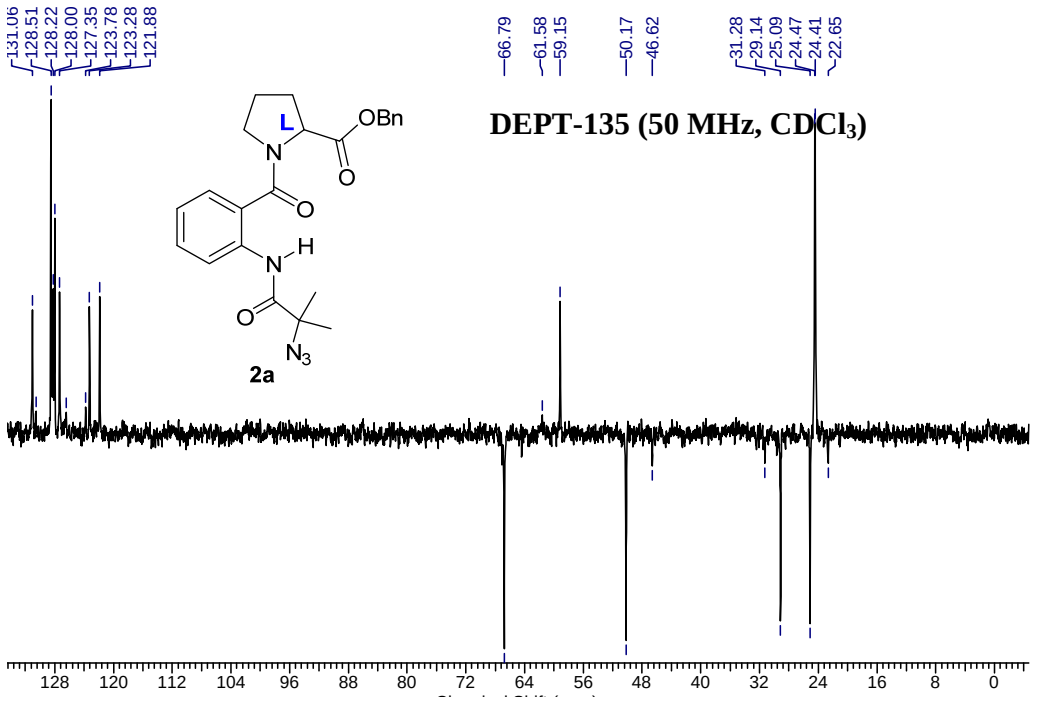


DEPT-135 (50 MHz, $CDCl_3$)

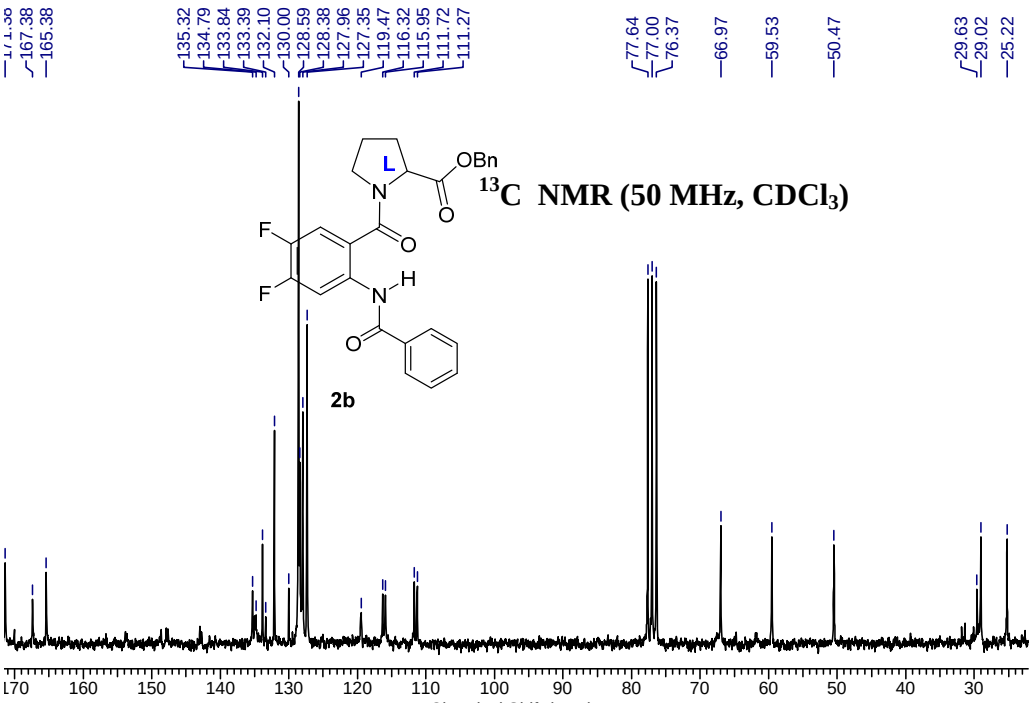
1e



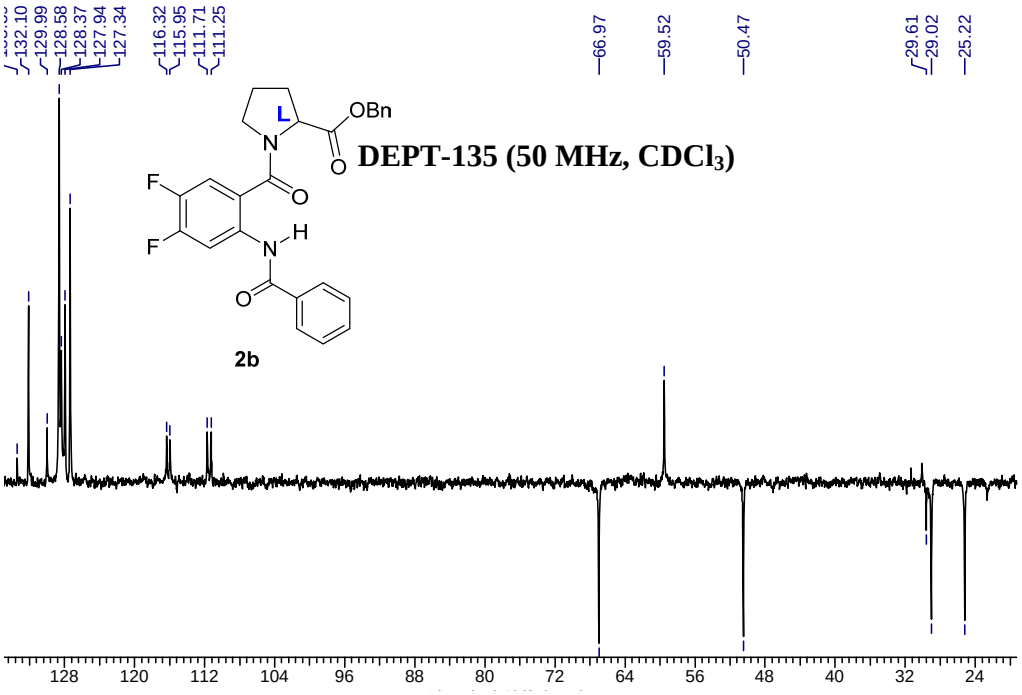
^{13}C NMR (50 MHz, $CDCl_3$)



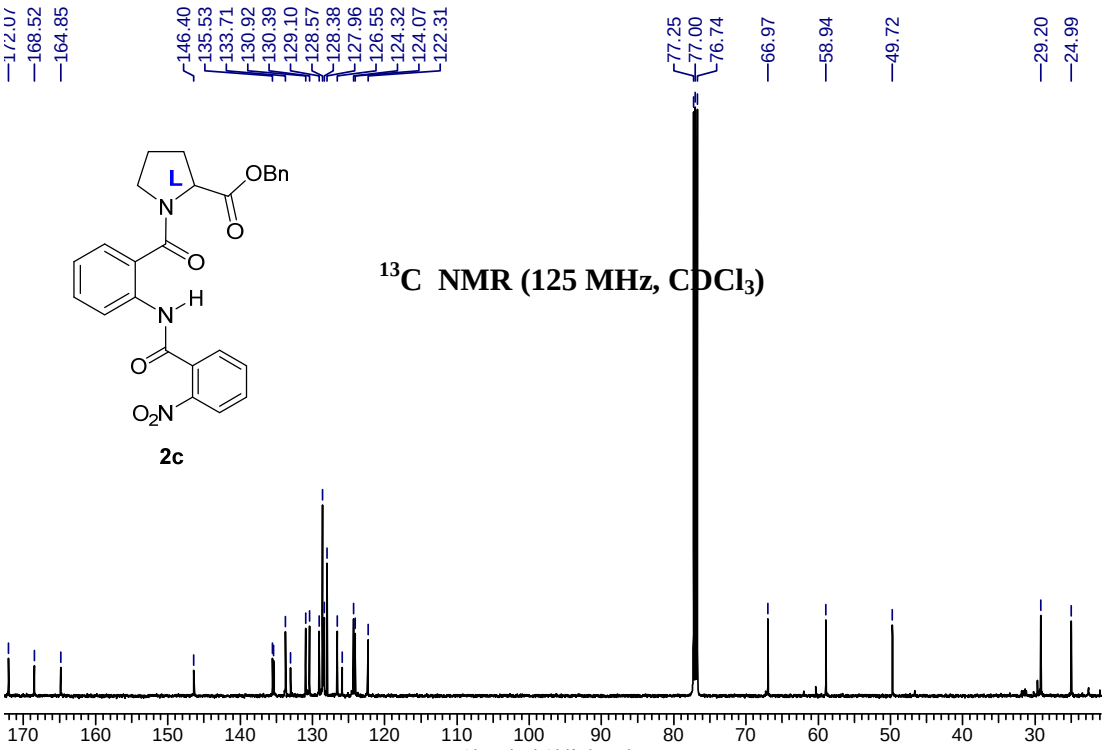
DEPT-135 (50 MHz, $CDCl_3$)



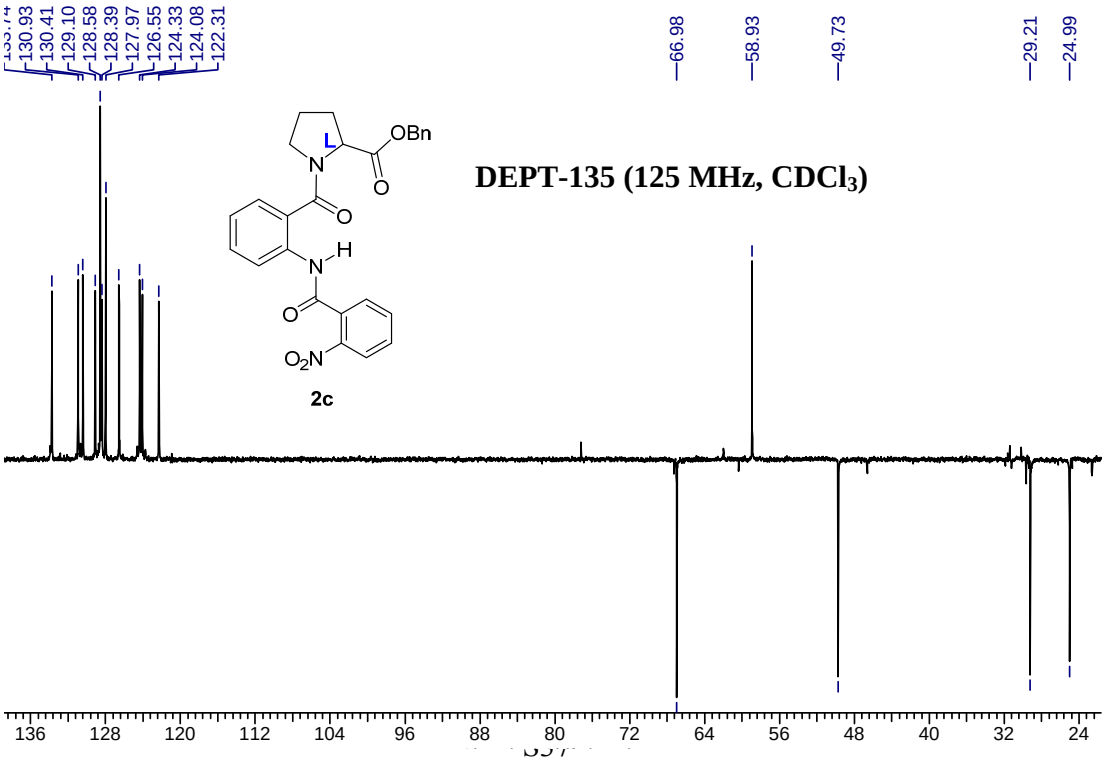
^{13}C NMR (50 MHz, $CDCl_3$)



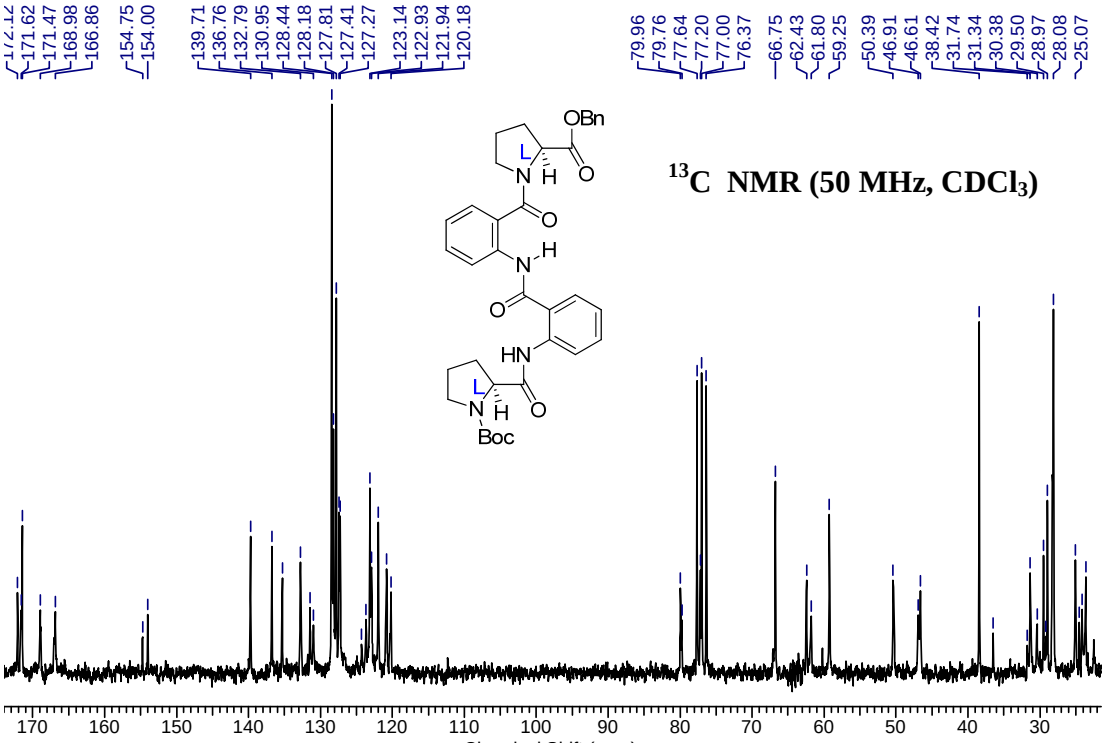
DEPT-135 (50 MHz, $CDCl_3$)



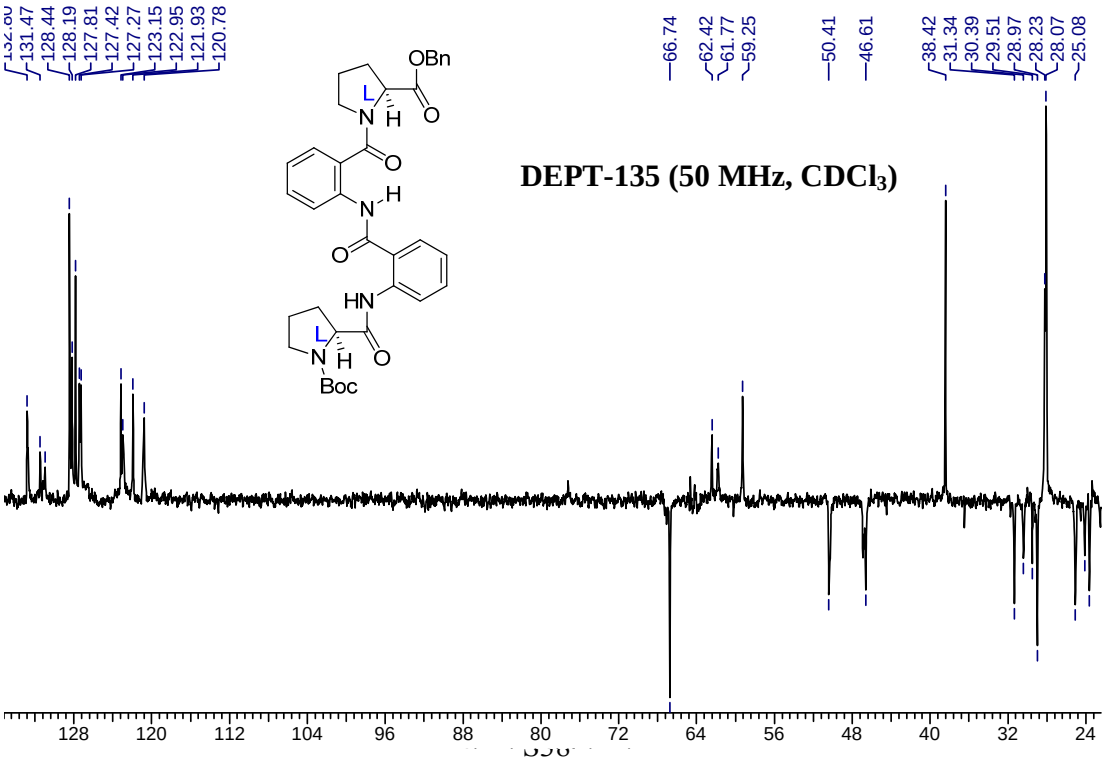
^{13}C NMR (125 MHz, $CDCl_3$)



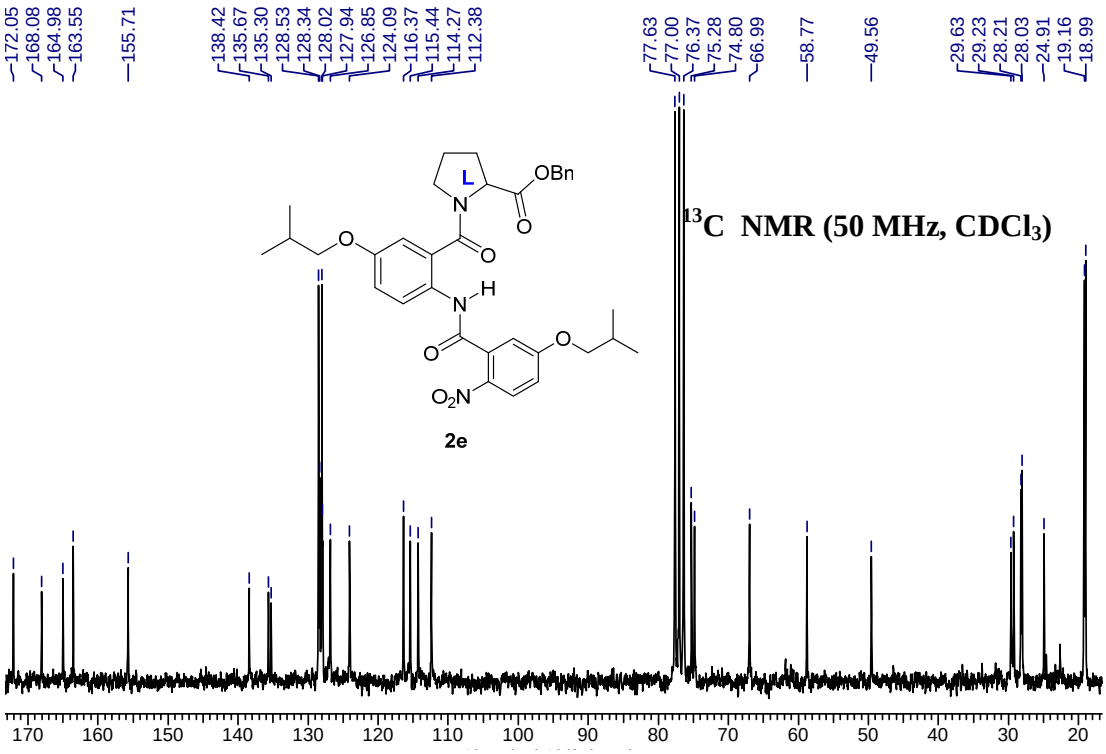
DEPT-135 (125 MHz, $CDCl_3$)



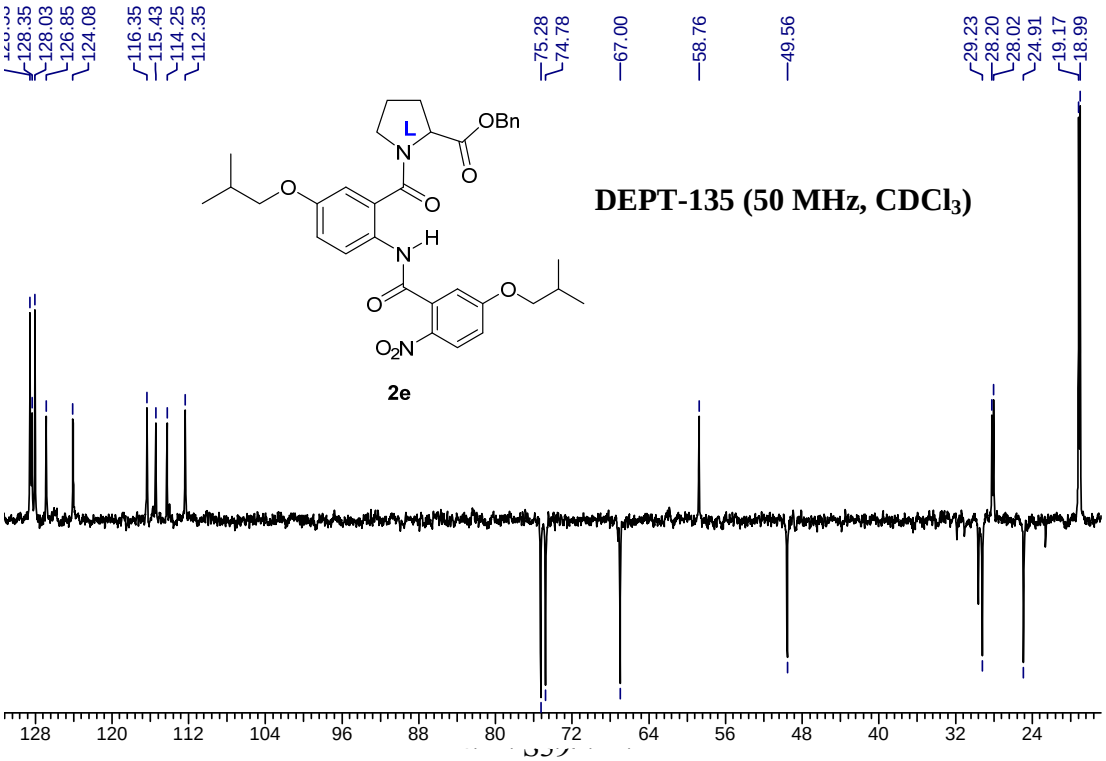
^{13}C NMR (50 MHz, $CDCl_3$)



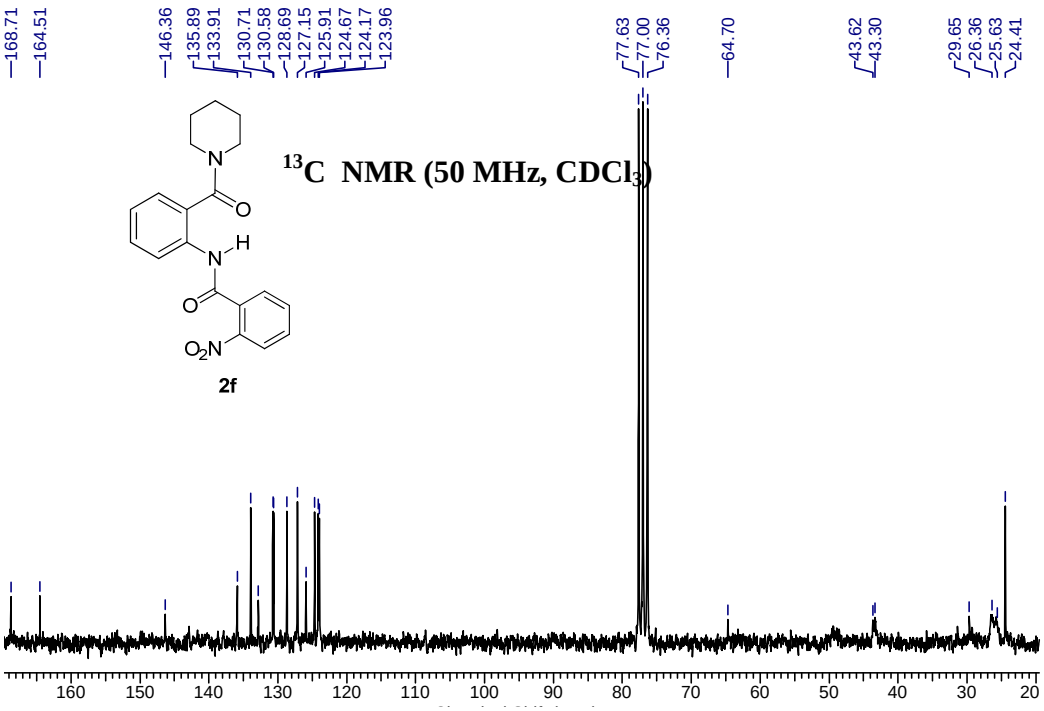
DEPT-135 (50 MHz, $CDCl_3$)



^{13}C NMR (50 MHz, $CDCl_3$)

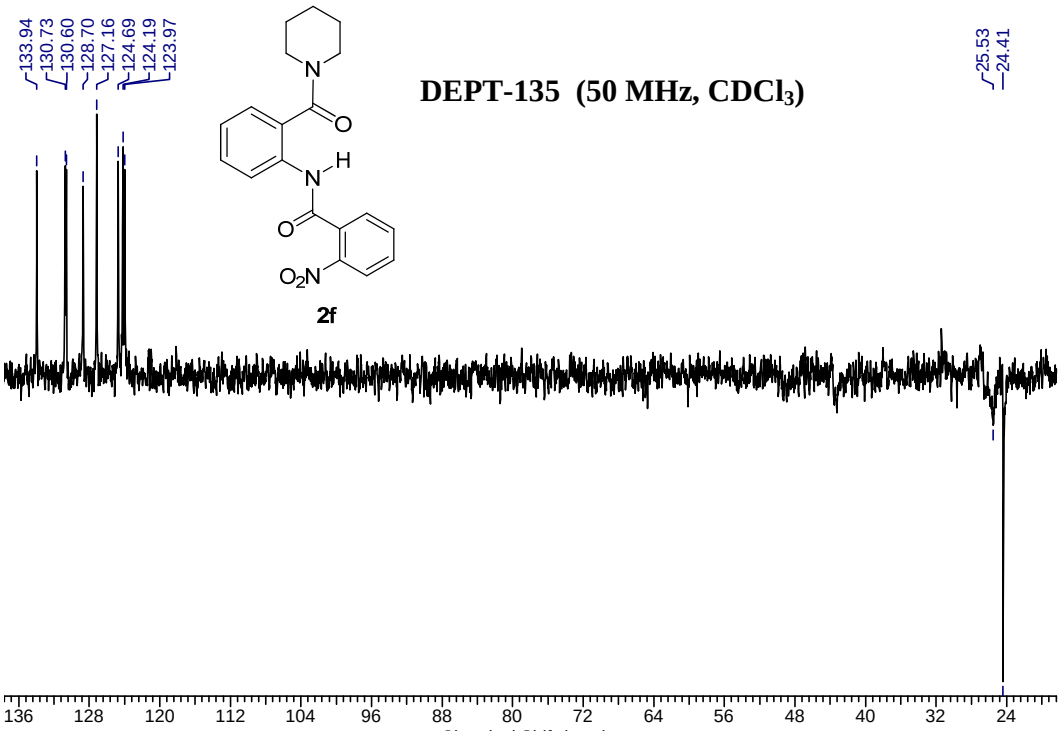


DEPT-135 (50 MHz, $CDCl_3$)



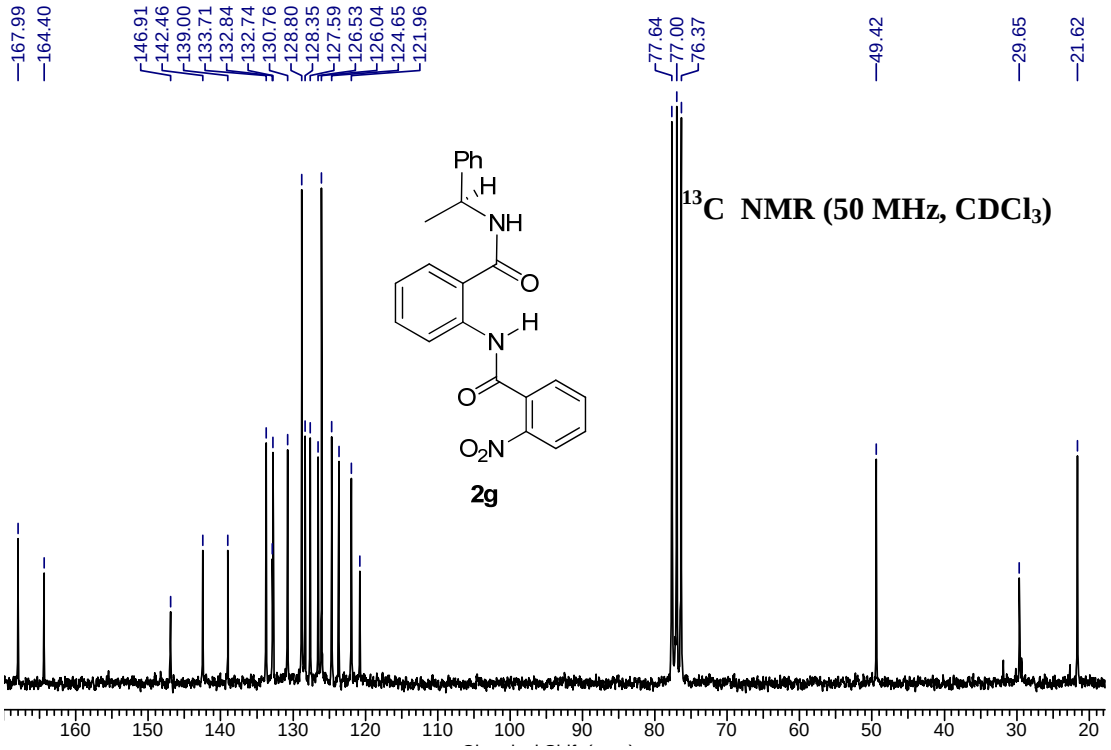
^{13}C NMR (50 MHz, $CDCl_3$)

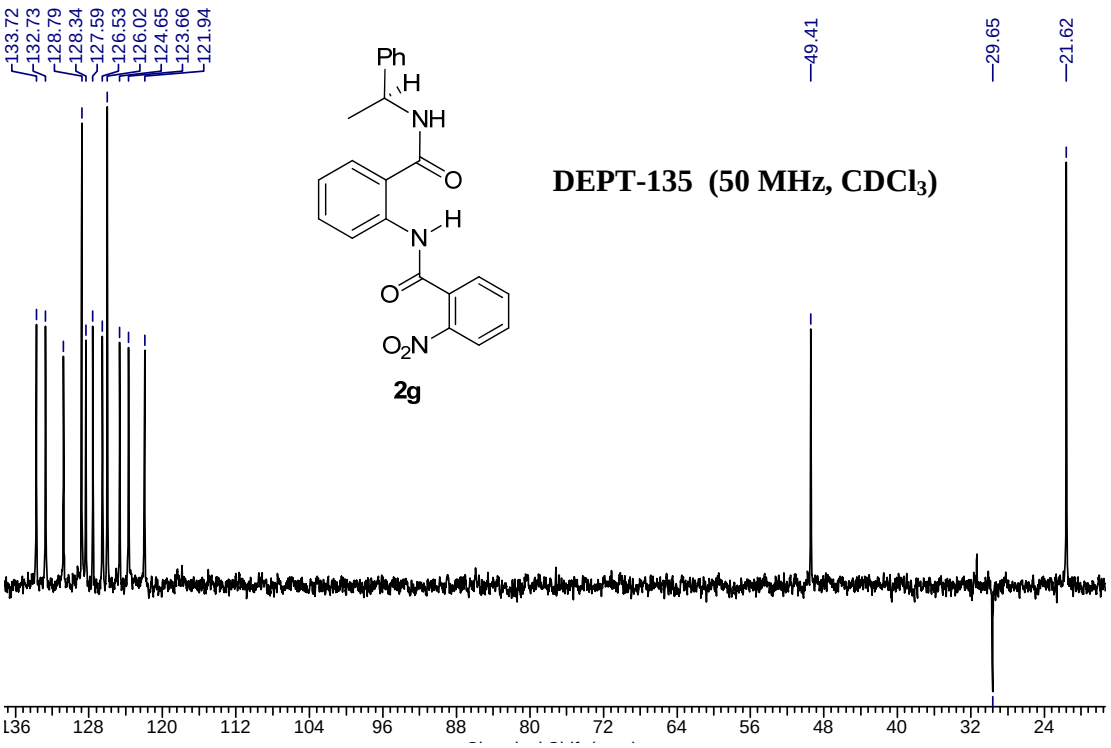
2f

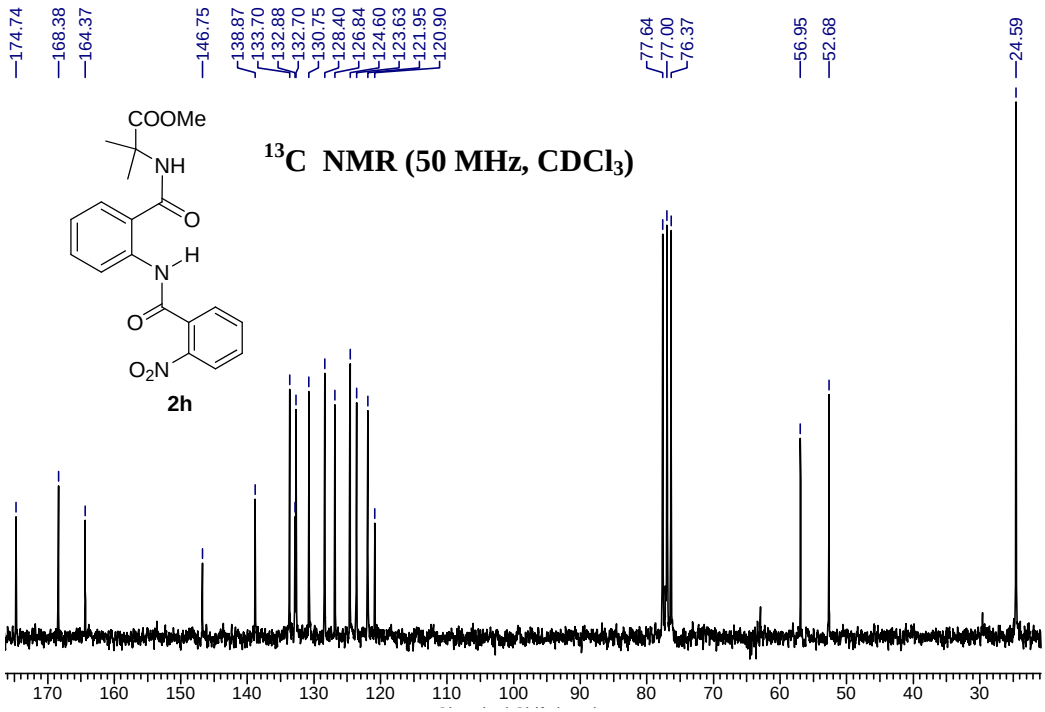


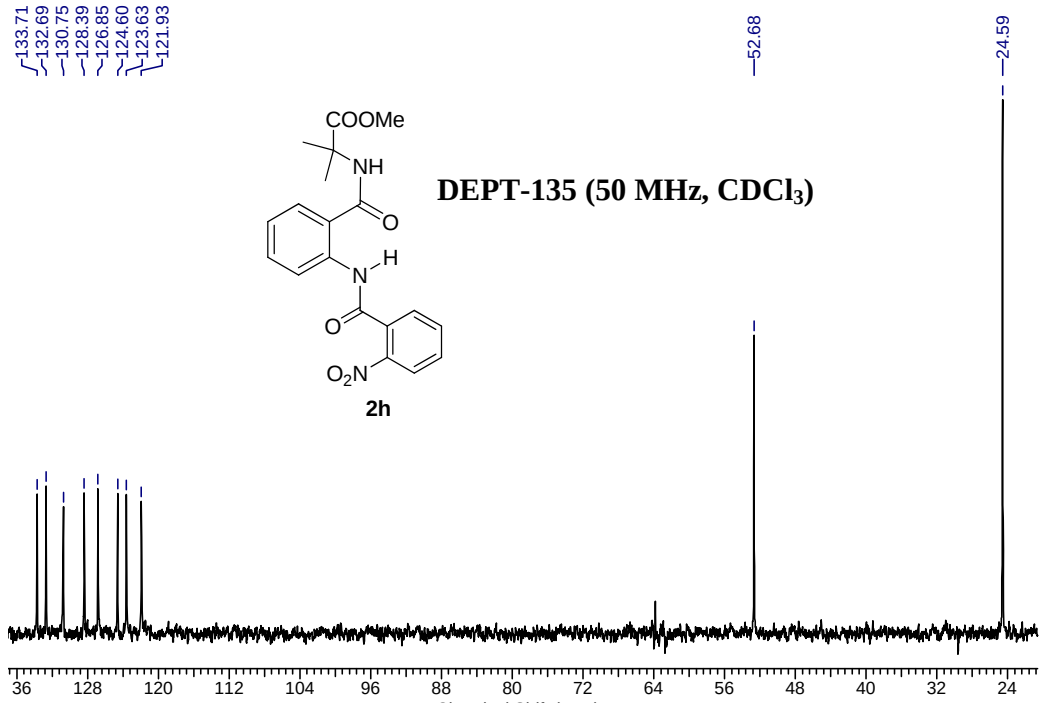
DEPT-135 (50 MHz, $CDCl_3$)

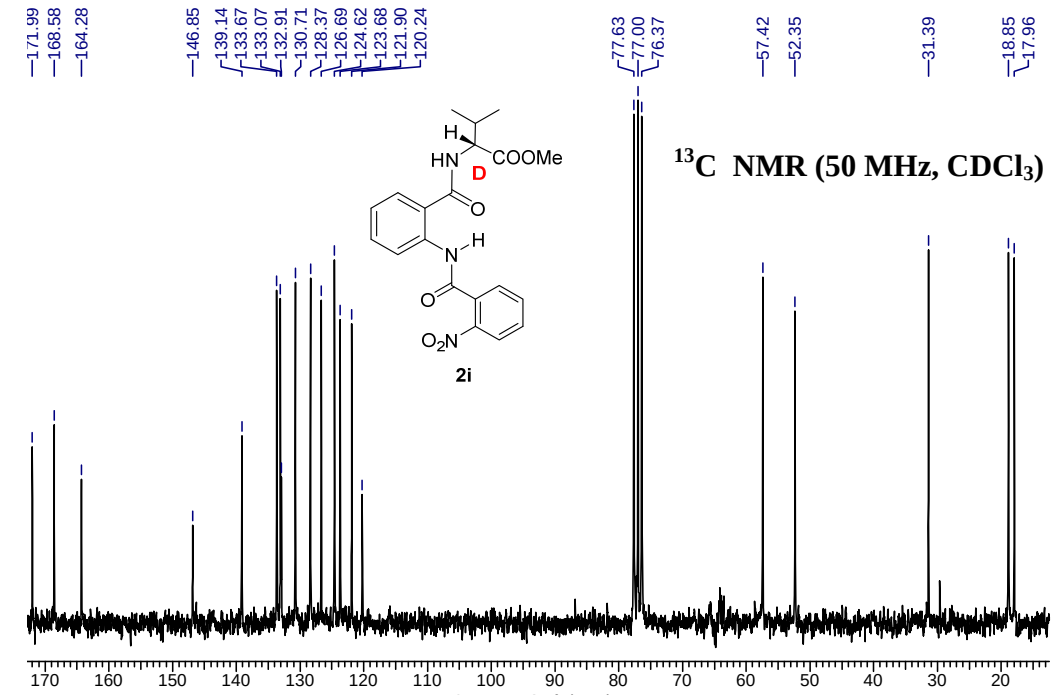
2f

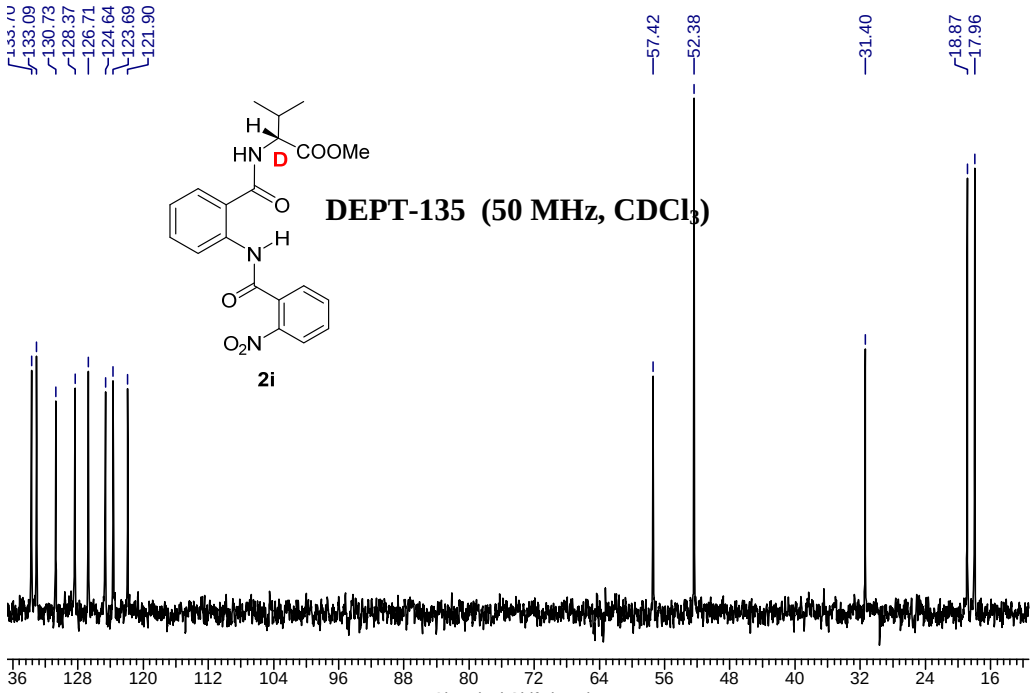

167.99
164.40
146.91
142.46
139.00
133.71
132.84
132.74
130.76
128.80
128.35
127.59
126.53
126.04
124.65
121.96
77.64
77.00
76.37
49.42
29.65
21.62
Ph
H
NH
O
N
H
O
O2N
2g
13C NMR (50 MHz, CDCl3)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

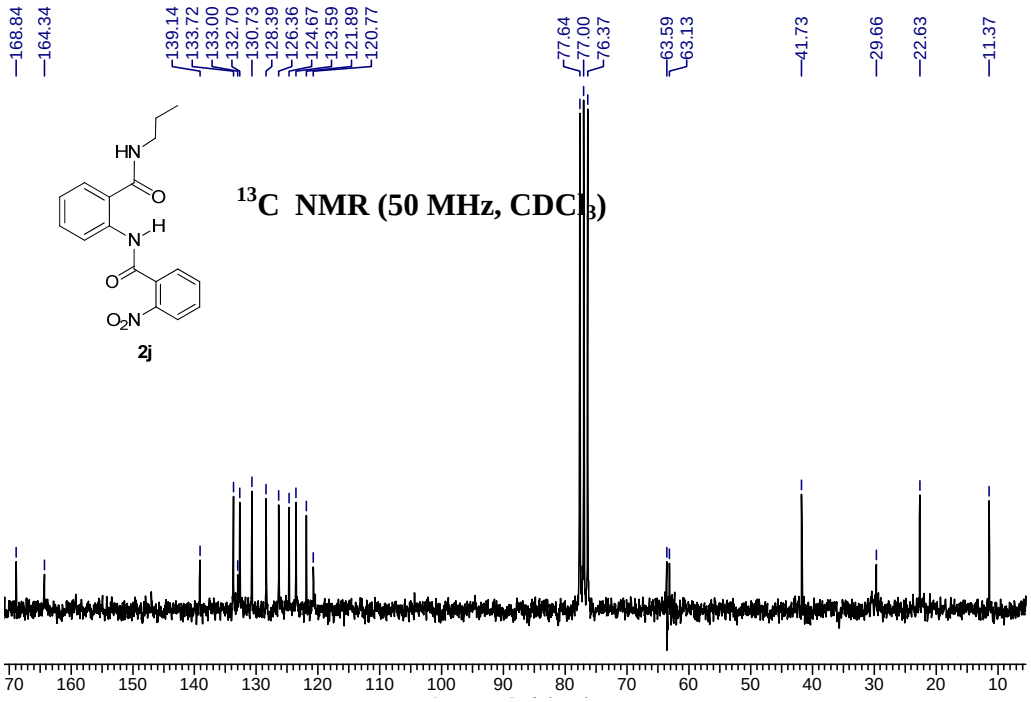

133.72
132.73
128.79
128.34
127.59
126.53
126.02
124.65
123.66
121.94
49.41
29.65
21.62
Ph
H
NH
O
N
H
O
O2N
2g
DEPT-135 (50 MHz, CDCl3)
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24

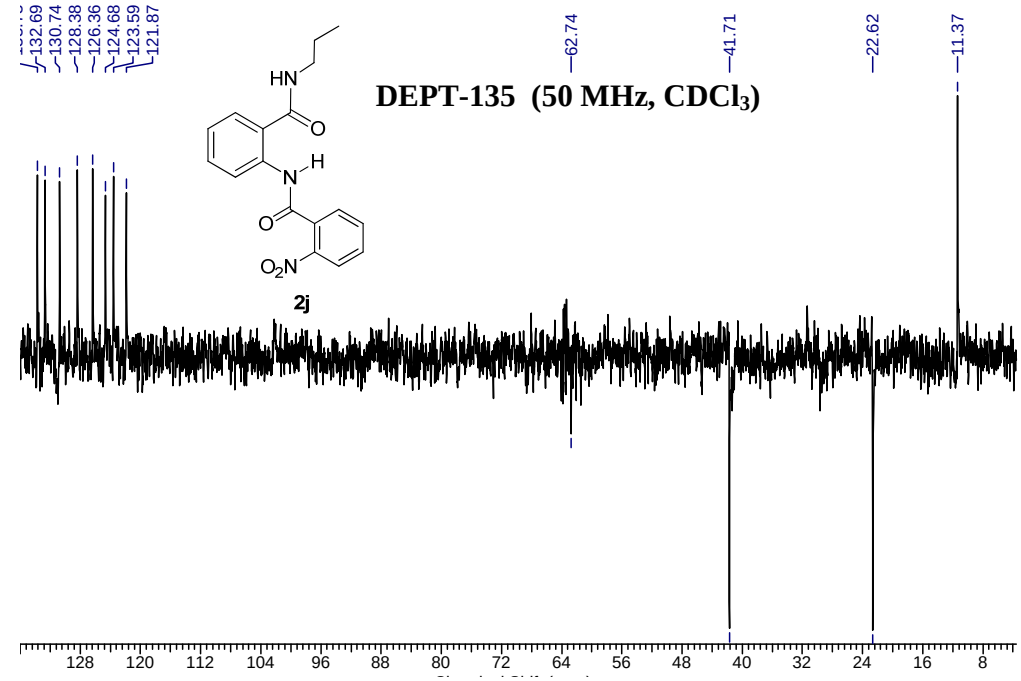


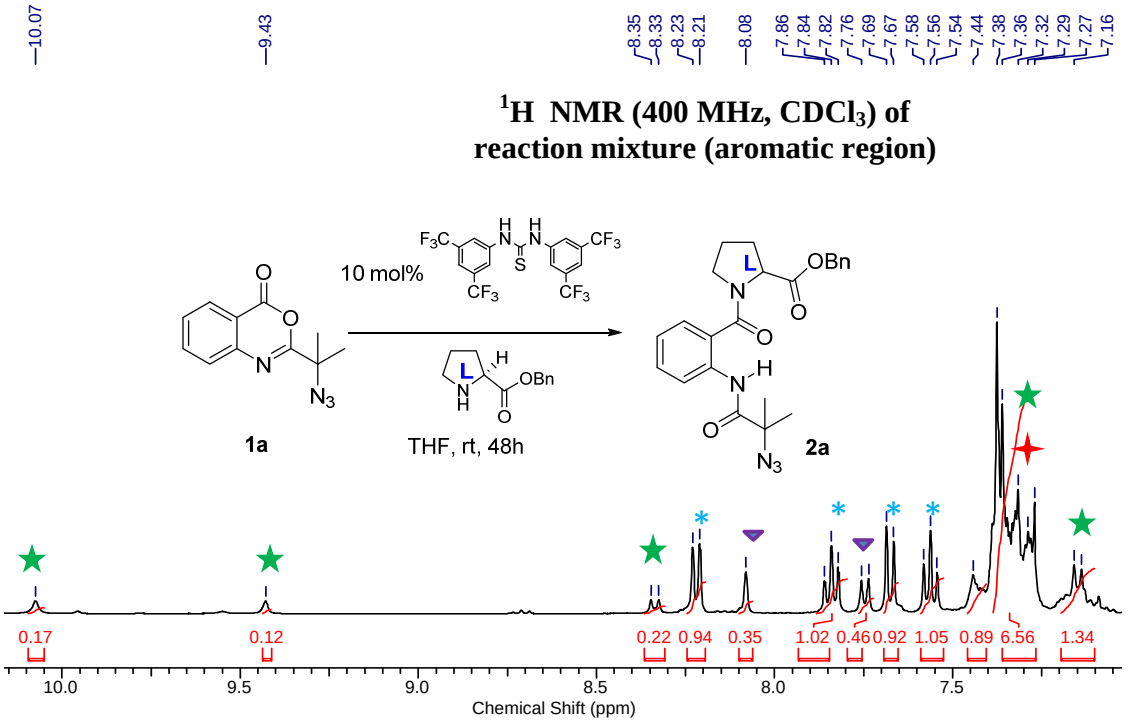




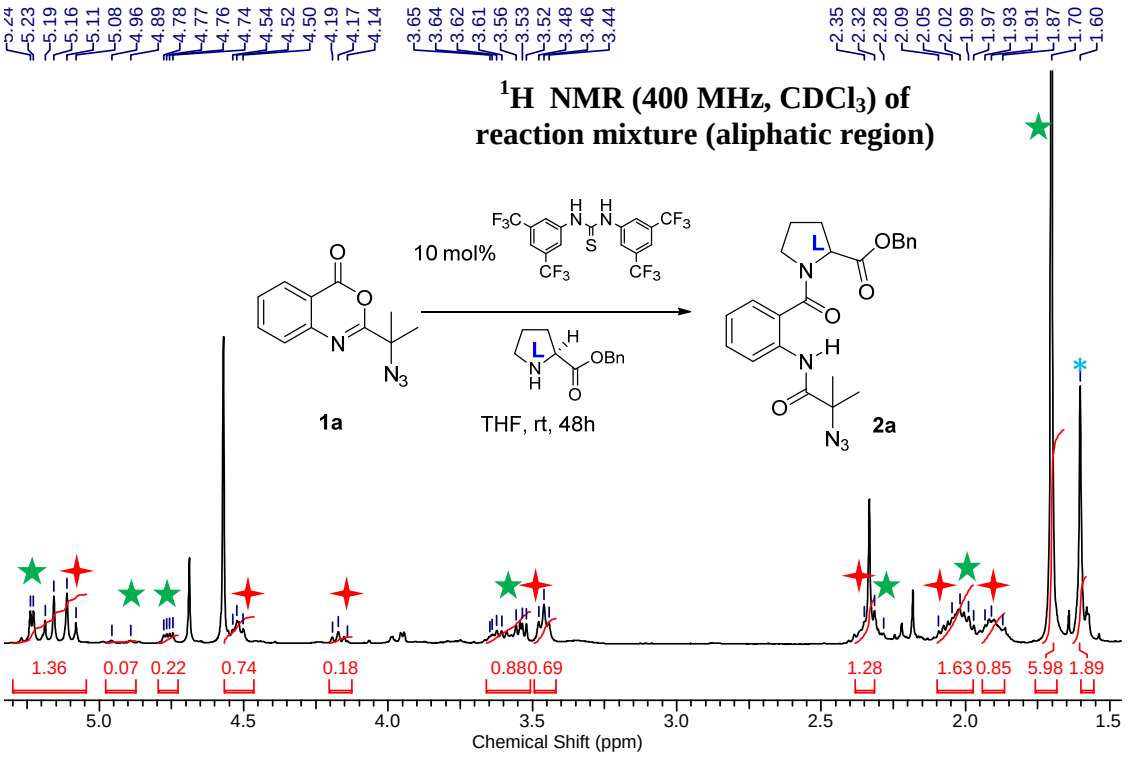


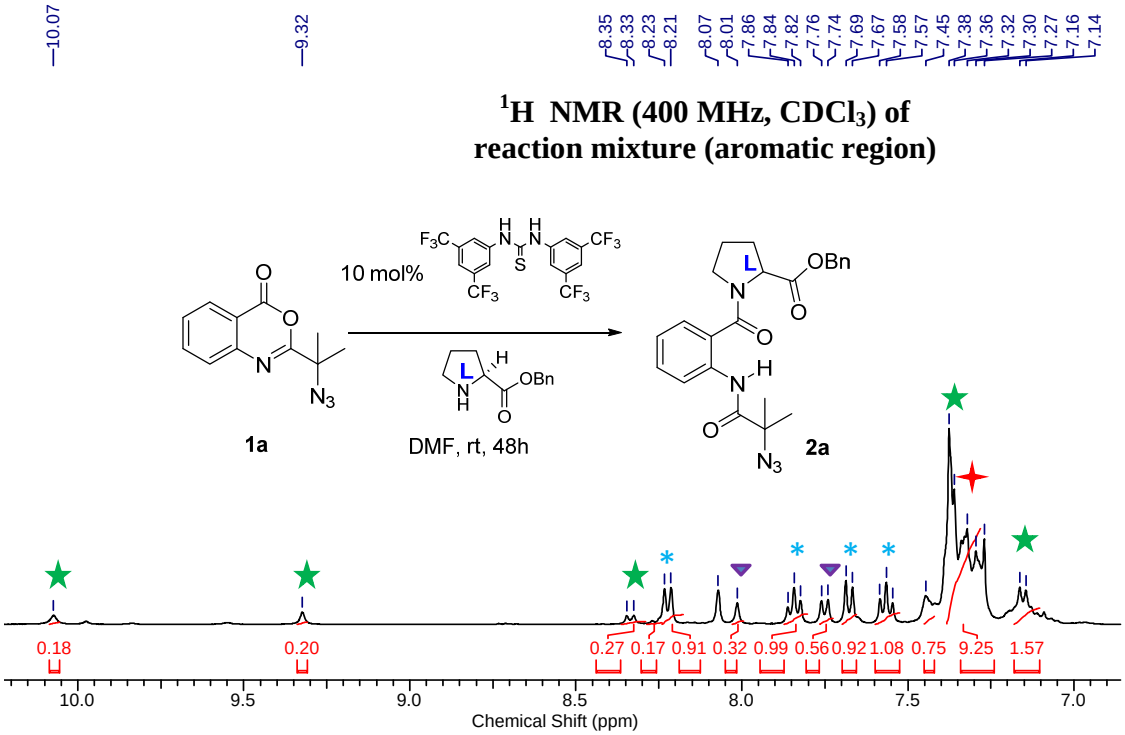

168.84
164.34
139.14
133.72
133.00
132.70
130.73
128.39
126.36
124.67
123.59
121.89
120.77
77.64
77.00
76.37
63.59
63.13
41.73
29.66
22.63
11.37
HN
O
N
H
O
O2N
2j
13C NMR (50 MHz, CDCl3)
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


132.69
130.74
128.38
126.36
124.68
123.59
121.87
62.74
41.71
22.62
11.37
HN
O
N
H
O
O2N
2j
DEPT-135 (50 MHz, CDCl3)
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8

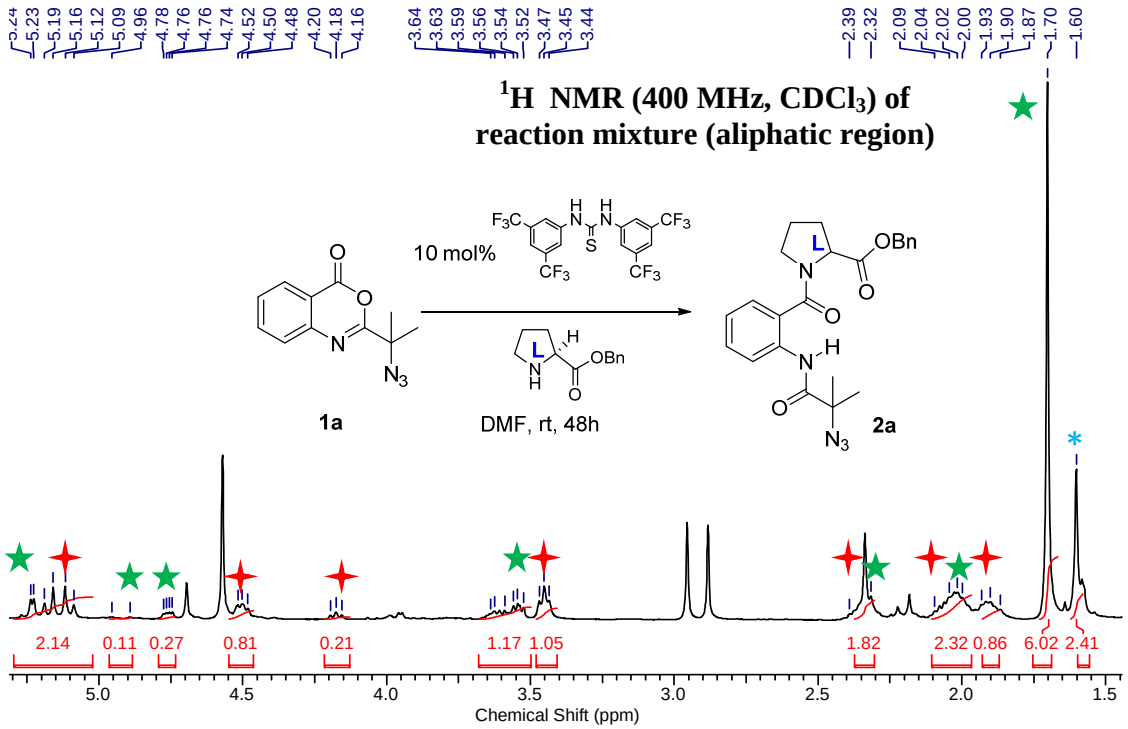


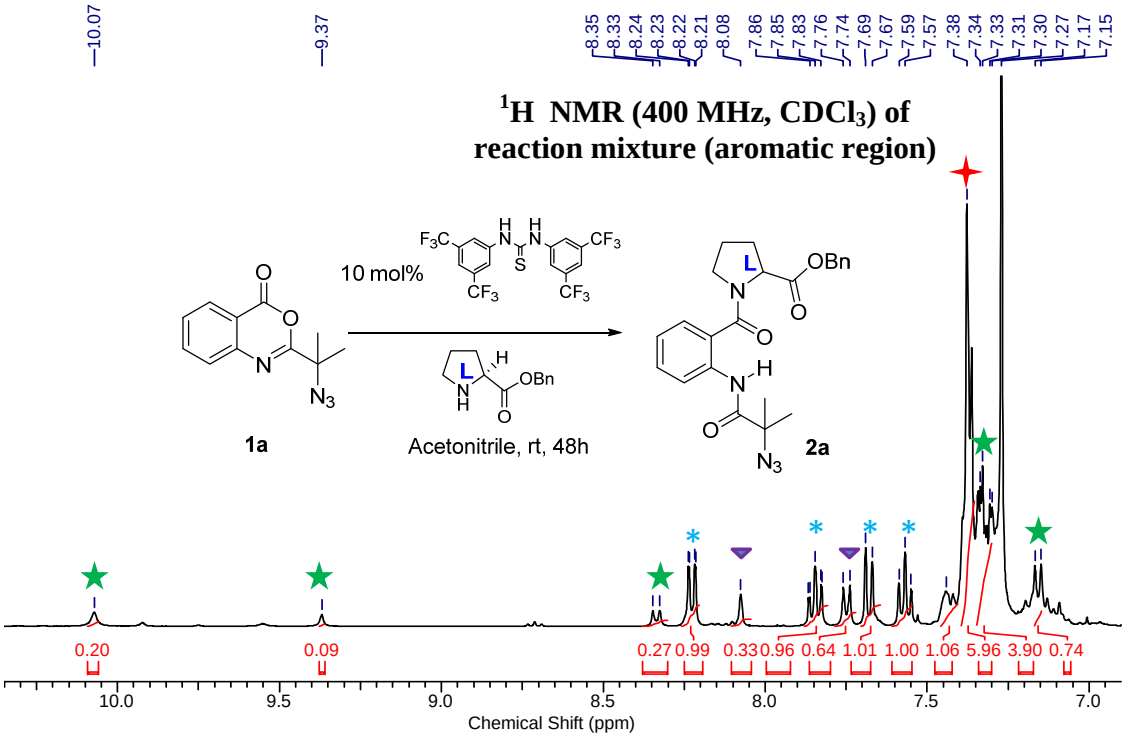
Note: The compounds are labeled using different symbols, *i.e.* Product **2a** (★), Oxazinone **1a** (*), thiourea (▼) and H-^{L}Pro-OBn (✦).





Note: The compounds are labeled using different symbols, *i.e.* Product **2a** (★), Oxazinone **1a** (*), thiourea (▼) and H-^{L}Pro-OBn (✦).





Note: The compounds are labeled using different symbols, *i.e.* Product **2a** (★), Oxazinone **1a** (*), thiourea (▼) and H-^{L}Pro-OBn (✦).