Electronic Supporting Information

Diastereoselective Preparation of Azetidines and Pyrrolidines

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Experimental Section

Commercially available solvents and reagents were used without further purification. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AVIII300 NMR spectrometer, at 400 MHz on a AV400 NMR spectrometer and at 500 MHz on a DRX500 spectrometer, ^{13}C NMR spectra at 100 MHz on a Bruker AVIII400 NMR spectrometer are proton decoupled and were recorded at room temperature unless otherwise stated, data was processed with Mestrec version 5.2.5-4731 and Topspin 2.0 (Version of: Nov 9th 2006). Chemical shifts (δ) are reported in ppm relative to TMS (δ 0.00) for the ^{1}H NMR and to chloroform (δ 77.0) for the ^{13}C NMR measurements, coupling constant *J* are expressed in Hertz, pendant technique was used for ^{13}C NMR assignment. Mass spectra were recorded with electrospray MS Waters LCT Time of Flight Mass Spectrometer and with EI (GC/MS) Waters GCT Premier Time of Flight Mass Spectrometer.

General Procedures

General Procedure A:

Five equivalent of $NaHCO_3$ and 3 equivalent of I_2 were added to homoallylamine in CH_3CN, the mixture was stirred at room temperature for 16 hours and was monitored by TLC. When the reaction was complet solvent was removed *in vacuo*. To the residue thus obtained a solution of $Na_2S_SO_3$ was added, the compound was extracted with EtOAc, washed with water, dried over $MgSO_4$ and dried *in vacuo* to deliver "post-work-up" material.

General Procedure B:

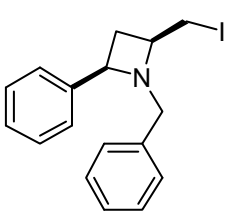
Azetidines were refluxed for 4 hours in CH_3CN. At which point the reactions were judged to be complete (by TLC), the solvent was removed *in vacuo* to deliver isomerised product.

General Procedure C:

Azetidines were stirred at room temperature for 24 hours in neat benzylamine, after which time unreacted benzylamine was removed *in vacuo*, the residue was purified by flash chromatography.

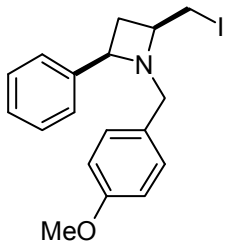
Experimental Procedures

(2a) *cis*-1-Benzyl-2-(Iodomethyl)-4-phenylazetidine.



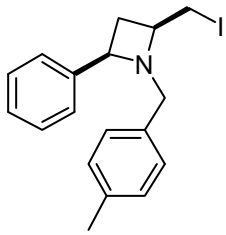
General Procedure A was used, homoallylamine (500 mg, 2.1 mmol), iodine (1.60 g, 6.3 mmol), sodium bicarbonate (885 mg, 11 mmol) and acetonitrile (50 mL). Yield (post work-up) 732 mg, 96%; after flash chromatography 343 mg, 45%. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.74 (1H, *dt*, *J* = 12.0 & 9.0, PhCHCH*H*), 2.65 (1H, *dt*, *J* = 9.0 & 6.0, PhCHC*H*H), 2.91 (1H, *dd*, *J* = 10.5 & 3.0, CH*H*I), 2.98 (1H, *t*, *J* = 9.0, C*H*HI), 3.28 (1H, *m*, NC*H*CH_2I), 3.61 (1H, *d*, *J* = 15.0, NC*H*HPh), 3.99 (1H, *d*, *J* = 12.0, NCH*H*Ph), 4.01 (1H, *t*, *J* = 9.0, NC*H*Ph), 7.36 (7H, *m*, ArH), 7.55 (2H, *m*, ArH). ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$) δ 12.77 (CH_2), δ 35.65 (CH_2), 60.75 (CH_2), 62.96 (CH), 63.00 (CH), 126.94 (CH), 127.37 (CH), 128.29 (CH), 128.34 (CH), 129.37 (CH), 138.16(C), 143.02 (C). High-resolution MS calcd for $C_{17}H_{18}NI$: 363.0484; found: 363.0485.

(2b) *cis*-2-(Iodomethyl)-1-(4-methoxybenzyl)-4-phenylazetidine.



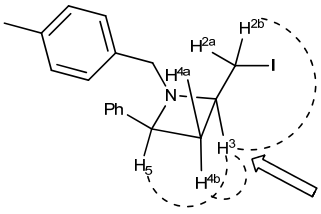
General Procedure A was used, homoallylamine (644 mg, 2.54 mmol), iodine (1.94 g, 7.63 mmol), sodium bicarbonate (1.07 g, 12.7 mmol) and acetonitrile (50 mL). Yield (post-work up) 849 mg, 85%; after flash chromatography 409 mg, 41%. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.68 (1H, *dt*, *J* = 12.0 & 9.0, PhCHCH*H*), 2.60 (1H, *dt*, *J* = 9.0 & 6.0, PhCHC*H*H), 2.86 (1H, *dd*, *J* = 9.0 & 6.0, CH*H*I), 2.93 (1H, *t*, *J* = 9.0, C*H*HI), 3.21 (1H, *m,* NC*H*CH_2I), 3.50 (1H, *d*, *J* = 12.0, NC*H*HAr), 3.82 (3H, *s*, O*Me*), 3.90 (1H, *d*, *J* = 12.0, NCH*H*Ar), 3.95 (1H, *t*, *J* = 9.0, NC*H*Ph), 6.86 (2H, *d*, *J* = 9.0, ArH), 7.29 (3H, *m*, ArH), 7.38 (2H, *t*, *J* = 6.0, ArH), 7.50 (2H, *d*, *J* = 9.0, ArH). ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$) δ 12.89 (CH_2), 35.56 (CH_2), 55.28 (CH_3), 59.95 (CH_2), 62.68 (CH), 62.76 (CH), 113.65 (CH), 126.89 (CH), 127.29 (CH), 128.31 (CH), 130.20 (C), 130.44(CH), 143.08 (C), 158.91 (C). High-resolution MS calcd for formula $C_{18}H_{21}NOI$: 394.0668; found: 394.0674.

(2c) *cis*-2-(Iodomethyl)-1-(4-methylbenzyl)-4-phenylazetidine.



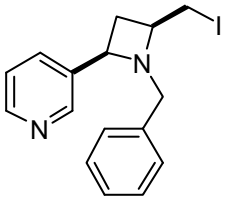
General Procedure A was used, homoallylamine (1.0 g, 3.98 mmol), iodine (3.02 g, 11.9 mmol), sodium bicarbonate (1.67 g, 19.9 mmol) and acetonitrile (50 mL). Yield (post -work up) 1.40 g , 93%; after flash chromatography 615 mg , 45%. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.72 (1H, *dt*, *J* = 12.0 & 9.0, PhCHCH*H*), 2.40 (3H, *s*, tolyl-*Me*), 2.64(1H, *dt*, *J* = 9.0 & 6.0, PhCHC*H*H), 2.90 (1H, *dd*, *J* = 9.0 & 6.0, CH*H*I), 2.96 (1H, *t*, *J* = 9.0, CH*H*I), 3.26 (1H, *m*, NC*H*CH_2I), 3.54 (1H, *d*, *J* = 12.0, NC*H*HAr), 3.96 (1H, *d*, *J* = 12.0, NCH*H*Ar),

3.99 (1H, *t*, *J* = 9.0, NC*H*Ph), 7.17 (2H, *d*, *J* = 9.0, ArH), 7.32 (3H, *m*, ArH), 7.42 (2H, *t*, *J* = 6.0, ArH), 7.55 (2H, *d*, *J* = 9.0, ArH). $^{13}C\{^{1}H\}$ NMR (δ; 100 MHz, $CDCl_3$) δ 12.94 (CH_2), δ 21.25 (CH_3), 35.63 (CH_2), 60.29 (CH_2), 62.79 (CH), 126.91 (CH), 127.31 (CH), 128.33 (CH), 128.98 (CH), 129.30(CH), 135.04 (C), 136.90 (C), 143.09 (C). High-resolution MS calcd for formula $C_{18}H_{21}NI$: 378.0719; found: 378.0725



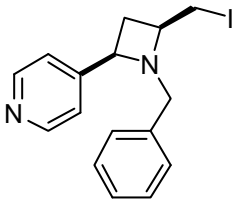
2c Exciting H_3
NOE has been seen with H^5, H^{2a}, H^{2b} ,H^{4b}

(2d) 3-*cis*-1-Benzyl-4-(iodomethyl)azetidin-2-yl)pyridine.



General Procedure A was used, homoallylamine (1.50 g, 6.29 mmol), iodine (4.80 g, 19 mmol), sodium bicarbonate (2.64 g, 31.5 mmol), and acetonitrile (50 mL). Yield (post work-up), 2.08g, 91%; after flash chromatography 961 mg, 42%. ^{1}H NMR (δ; 300 MHz, $CDCl_3$) ; 1.68 (1H, *dt*, *J* = 12.0 & 9.0, PyCHCH*H*), 2.60 (1H, *dt*, *J* = 9.0 & 6.0, PyCHC*H*H), 2.93 (2H, *d*, *J* = 9.0, CH_2I), 3.24 (1H, *m*, *J* = 6.0, NC*H*CH_2I), 3.64 (1H, *d*, *J* = 12.0, NC*H*HPh), 3.82 (1H, *d*, *J* = 12.0, NCH*H*Ph), 3.98 (1H, *t*, *J* = 9.0, NC*H*Py), 7.26 (6H, *m*, ArH), 7.82 (1H, *dt*, *J* = 6.0 & 3.0, PyH), 8.47 (1H, *d*, *J* = 3.0, PyH), 8.59 (1H, *s*, PyH). $^{13}C\{^{1}H\}$ NMR (δ; 100 MHz, $CDCl_3$) δ 12.32 (CH_2), δ 35.22 (CH_2), 60.72 (CH_2), 60.76 (CH), 62.84 (CH), 123.30 (CH), 127.45 (CH), 128.24 (CH), 129.27 (CH), 134.68 (CH), 137.31 (C), 138.14 (C), 148.71 (CH). High-resolution MS calcd for formula $C_{16}H_{17}N_2Na$: 387.0334; found: 387.0349.

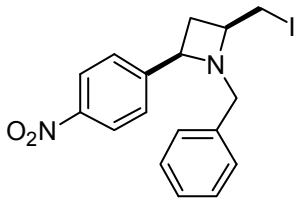
(2e) 4-(*cis*-1-Benzyl-4-(iodomethyl)azetidin-2-yl)pyridine.



General Procedure A was used, homoallylamine (1.00g, 4.2 mmol), iodine (3.30 g, 13 mmol), sodium bicarbonate (1.76g, 21 mmol) and acetonitrile (50 mL). Yield (post work-up), 1.45 g, 95%; after flash chromatography 642 mg, 51%. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.60 (1H, *dt*, *J* = 12.0 & 9.0, PyCHCH*H*), 2.59 (1H, *dt*, *J* = 9.0 & 6.0, PyCHC*H*H), 2.89 (2H, *d*, *J* = 9.0, CH_2I), 3.23 (1H, *m*, NC*H*CH_2I), 3.63 (1H, *d*, *J* = 12.0, NC*H*HPh), 3.80 (1H, *d*, *J* = 12.0, NCH*H*Ph), 3.93 (1H, *t*, *J* = 9.0, NC*H*Py), 7.25 (7H, *m*, ArH), 8.50 (2H, *d*, *J* = 3.0, PyH). $^{13}C\{^{1}H\}$ NMR (δ; 100 MHz, $CDCl_3$) δ 12.29 (CH_2), δ 34.76 (CH_2), 60.89 (CH_2), 61.70 (CH), 62.75 (CH), 121.62 (CH), 127.53 (CH), 128.29 (CH), 129.29 (CH), 137.36(C), 149.74

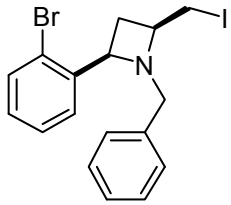
(CH), 151.53 (C). High-resolution MS calcd for formula $C_{16}H_{17}N_2NaI$: 387.0334; found: 387.0341.

(2f) *cis*-1-Benzyl-2-(iodomethyl)-4-(4-nitrophenyl)azetidine.



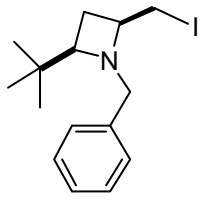
General Procedure A was used, homoallylamine (350 mg, 1.24 mmol), iodine (944mg, 3.72 mmol), sodium bicarbonate (520 mg, 6.2 mmol) and acetonitrile (50 mL). Yield (post-work up) 459 mg, 90%; after flash chromatography 233 mg, 46%. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.65 (1H, *dt*, *J* = 12.0 & 9.0, ArCHCH*H*), 2.66 (1H, *m*, ArCHC*H*H), 2.96 (2H, *m*, C*H*$_2$I), 3.28(1H, *m*, NC*H*CH$_2$I), 3.70 (1H, *d*, *J* = 12.0, NC*H*HPh), 3.83 (1H, *d*, *J* = 12.0, NCH*H*Ph), 4.07 (1H, *t*, *J* = 9, NC*H*HAr), 7.28 (5H, *m*, ArH), 7.58 (2H, *d*, *J* = 6.0, ArH), 8.16 (2H, *d*, *J* = 9.0, ArH) ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$) δ 11.96 (CH_2), δ 35.29 (CH_2), 60.90 (CH_2), 62.37 (CH), 62.63 (CH), 123.50 (CH), 127.39 (CH), 127.55 (CH), 128.27 (CH), 129.28(CH), 137.18 (C), 147.12 (C), 150.56 (C). High-resolution MS calcd for formula $C_{17}H_{17}N_2O_2I$: 408.0334; found: 408.0318.

(2g) *cis*-1-Benzyl-2-(2-bromophenyl)-4-(iodomethyl)azetidine.



General Procedure A was used, homoallylamine (750 mg, 2.4 mmol), iodine (1.81 g, 7.14 mmol), sodium bicarbonate (1.00g, 12 mmol), and acetonitrile (50 mL). Yield (post work-up), 881 mg, 83%; after flash chromatography 445 mg; 42%. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 1.51 (1H, *dt*, *J* = 12.0 & 9.0, ArCHCH*H*), 2.85 (3H, *m*, ArCHC*H*H and C*H*$_2$I), 3.30 (1H, *m*, NC*H*CH$_2$I), 3.60 (1H, *d*, *J* = 12.0, NC*H*HPh), 3.95 (1H, *d*, *J* = 12.0, NCH*H*Ph), 4.29 (1H, *t*, *J* = 9.0, NC*H*Ar), 7.12 (1H, *td*, *J* = 9.0 & 6.0, ArH), 7.35 (6H, m, ArH), 7.50 (*dd*, 1H, *J* = 9.0 & 6.0, ArH), 7.87 (1H, *dd*, *J* = 6.0 & 3.0, ArH). ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$) δ 12.88 (CH_2), δ 34.37 (CH_2), 60.92 (CH_2), 62.04 (CH), 62.87 (CH), 121.85 (C), 127.43 (CH), 127.45 (CH), 128.23 (CH), 128.33(CH), 129.28 (CH), 132.22 (CH), 137.97 (C), 142.04 (C). High-resolution MS calcd for formula $C_{17}H_{18}NBrI$: 441.9667; found: 441.9660.

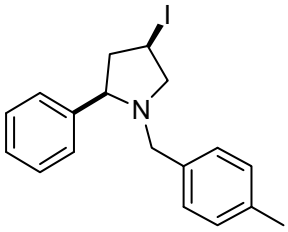
(2h) *cis*-1-Benzyl-2-(tert-butyl)-4-(iodomethyl)azetidine.



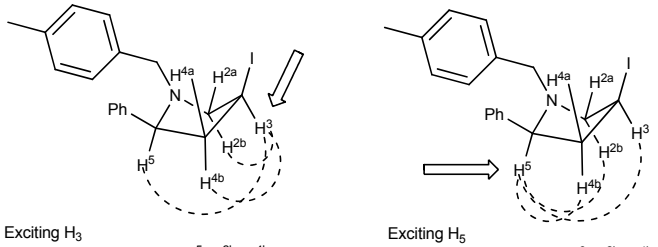
General Procedure A was used, homoallylamine (900 mg 4 mmol), iodine (3.00 g, 12 mmol), sodium bicarbonate (1.74g, 21 mmol) and acetonitrile (50 mL). Yield (post- work up) 1.20 g, 87%; after flash chromatography 563 mg, 41%. ^{1}H NMR (δ; 300 MHz, $CDCl_3$) ; 0.91 (9H, *s*, Me *tert*-Bu), 1.45 (1H, *dt*, *J* = 12.0 & 9.0, *tert*-BuCHCH*H*), 2.17 (1H, *dt*, *J* = 9.0 & 6.0, *tert*-BuCHC*H*H),

2.60 (1H, *dd*, *J* = 9.0 & 3.0, CH*H*I), 2.75 (2H, *m*, C*H*HI and *tert*-BuC*H*), 3.04 (1H, *m*, NC*H*CH_2I), 3.46 (1H, *d*, *J* = 12.0, NC*H*HPh), 4.01 (1H, *d*, *J* = 12.0, NC*H*HPh), 7.32 (5H, *m*, ArH). $^{13}C\{^1H\}$ NMR (δ; 100 MHz, $CDCl_3$) δ 12.75 (CH_2), 25.92 (CH_3), 26.52 (CH_2), 26.52 (CH_2), 33.44 (C), 63.28 (CH_2), 69.40 (CH), 127.15 (CH), 128.21 (CH), 128.94 (CH), 139.41 (C). High-resolution MS calcd for formula $C_{15}H_{23}NI$: 344.0875; found: 344.0874.

(3c) *cis*-4-Iodo-1-(4-methylbenzyl)-2-phenylpyrrolidine.

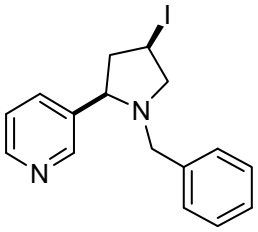


General Procedure B was used, **2c** (20 mg, 0.053 mmol) and acetonitrile (20 mL). Yield= 19 mg, 97%. ^1H NMR (δ; 500 MHz, $CDCl_3$); δ 2.35 (*s*, 3H, Me), δ 2.41(*m*, 1H, PhCHC*H*H), 2.76 (1H, *dd*, *J* = 10.0 & 5.0, NCH*H*CHI), 2.94 (1H, *dt*, *J* = 15.0 & 10.0, PhCHCH*H*), 3.17 (1H, *d*, *J* = 15.0, NC*H*HAr), 3.43 (1H, *dd*, *J* = 10.0 & 5.0, NC*H*HCHI), 3.57 (1H, *t*, *J* = 10.0, PhC*H*CH_2), 3.87 (1H, *d*, *J* = 15.0, NCH*H*Ar), 4.40 (1H, *m*, NCH_2C*H*I), 7.14 (2H, *d*, *J* = 10.0, ArH), 7.23 (2H, *d*, *J* = 10.0, ArH), 7.30 (1H, *t*, *J* = 5.0, ArH), 7.39 (2H, *t*, *J* = 10.0, ArH), 7.57 (2H, *d*, *J* = 5.0, ArH). $^{13}C\{^1H\}$ NMR (δ; 100 MHz, $CDCl_3$) δ 17.97 (CH), 21.07 (CH_3), 48.85 (CH_2), 56.32 (CH_2), 64.29 (CH_2), 69.28 (CH), 127.44 (CH), 127.78 (CH), 128.26 (CH), 128.33 (CH), 128.54(CH), 128.59(CH), 128.89 (CH), 128.94 (CH), 128.96 (CH), 129.22 (CH), 135.73 (C), 136.41(C), 141.92 (C). High-resolution MS calcd for formula $C_{18}H_{21}NNaI$: 400.0538; found: 400.0542.



3c

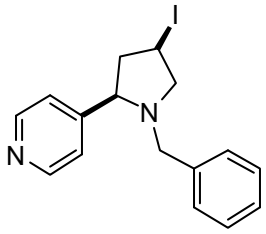
(3d) 3-(*cis*-1-Benzyl-4-iodopyrrolidin-2-yl)pyridine.



General Procedure B was used, **2d** (50 mg, 0.14 mmol) and acetonitrile (20 mL). Yield= 47 mg 95%. ^1H NMR (δ; 300 MHz, $CDCl_3$); 2.36(1H, *m*, PyCHC*H*H), 2.77 (1H, *dd*, *J* = 12.0 & 6.0, NCH*H*CHI), 2.99 (1H, *dt*, *J* = 15.0 &12.0, PyCHCH*H*), 3.26 (1H, *d*, *J* = 12.0, NC*H*HPh), 3.42 (1H, *dd*, *J* = 9.0 & 3.0, NC*H*HCHI), 3.64 (1H, *t*, *J* = 9.0, PyC*H*CH_2), 3.85 (1H, *d*, *J* = 12.0, NCH*H*Ph), 4.40 (1H, *m*, NCH_2C*H*I), 7.14 (2H, *d*, *J* = 10.0, ArH), 7.28 (6H, *m*, ArH), 8.02 (1H, *d*, *J* = 9.0, PyH), 8.55 (1H, *d*, *J* = 6.0, PyH), 8.68 (1H, *s*, PyH).

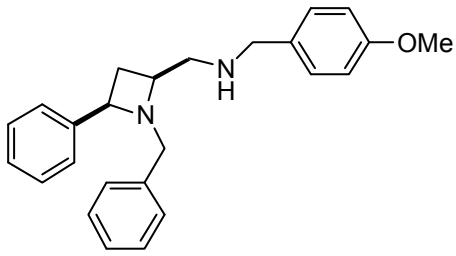
$^{13}C\{^{1}H\}$ NMR (δ; 100 MHz, $CDCl_3$) δ 17.41 (CH), 48.44 (CH_2), 56.73 (CH_2), 64.38 (CH_2), 66.60 (CH), 123.88 (CH), 126.96 (CH), 128.03 (CH), 128.24(CH), 128.32 (CH), 135.40 (CH), 138.32 (C), 147.60(C), 149.14 (CH), 149.74 (CH). High-resolution MS calcd for formula $C_{16}H_{17}N_2I$: 364.0437; found: 364.0440.

(3e) 4-(*cis*-1-Benzyl-4-iodopyrrolidin-2-yl)pyridine.



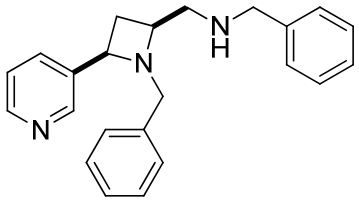
General Procedure B was used, **2e** (50 mg, 0.14 mmol) and acetonitrile (20 mL). Yield = 49 mg, 98%. ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.36(1H, *m*, PyCHC*H*H), 2.80 (1H, *dd*, *J* = 12.0 & 6.0, NCH*H*CHI), 2.99 (1H, *dt*, *J* = 15.0 & 9.0, PyCHCH*H*), 3.30 (1H, *d*, *J* = 15.0, NC*H*HPh), 3.43 (1H, *dd*, *J* = 12.0 & 3.0, NC*H*HCHI), 3.65 (1H, *t*, *J* = 9.0, PyC*H*CH_2), 3.88 (1H, *d*, *J* = 12.0, NCH*H*Ph), 4.40 (1H, *m*, NCH_2CHI), 7.30 (5H *m*, ArH), δ 7.52 (2H, *d*, *J* = 6.0, PyH), 8.61 (2H, *d*, *J* = 6.0, PyH). $^{13}C\{^{1}H\}$ NMR (δ; 100 MHz, $CDCl_3$) δ 17.23 (CH), 48.17 (CH_2), 56.98 (CH_2), 64.31 (CH_2), 67.94 (CH), 122.78 (CH), 127.17 (CH), 128.25 (CH), 128.37(CH), 138.21 (C), 150.15 (CH), 151.47 (C). High-resolution MS calcd for formula $C_{18}H_{21}NI$: 364.0437; found 364.0440.

(4) *N*-Benzyl-1-(*cis*-1-benzyl-4-(pyridin-3-yl)azetidin-2-yl)methanamine.



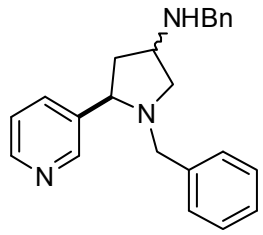
Method: Post-work up **2a** azetidine (300 mg, was stirred at room temperature for 24 hours in neat paramethoxybenzylamine (5 mL), after which time unreacted benzylamine was removed *in vacuo*, the residue was purified by flash chromatography. Yield (2 steps) = 256 mg 78%. ^{1}H NMR (δ; 400 MHz, $CDCl_3$); 1.61 (1H, *br*, N*H*), 1.88 (1H, *m*, PhCHCH*H*), 2.27 (2H, *m*, PhCHC*H*H and NHCH*H*CH), 2.40 (1H, *dd*, *J* = 12.0 & 6.0, NHC*H*HCH), 3.19 (1H, *m*, C*H*CH_2NH), 3.38 (1H, *d*, *J* = 9.0, NC*H*HPh), 3.40 (1H, *d*, *J* = 3.0, NHC*H*HAr), 3.68 (1H, *d*, *J* = 3.0, NHCH*H*Ar), 3.68 (1H, *d*, *J* = 9.0, NCH*H*Ph) 3.69 (3H, *s*, OMe), 3.89 (1H, *t*, *J* = 12.0, PhC*H*CH_2), 6.70 (2H, *d*, *J* = 6.0, ArH), 7.00 (2H, *d*, *J* = 9.0, ArH), 7.12 (8H, *m*, ArH), 7.34 (2H, *d*, *J* = 9.0, ArH); $^{13}C\{^{1}H\}$ NMR (δ; 100 MHz, $CDCl_3$) δ 30.78 (CH_2), 53.15 (CH_2), 53.96 (CH_2), 61.48 (CH_2), 62.52 (CH), 62.96 (CH), 123.29 (CH), 126.96 (CH), 127.30 (CH), 128.10 (CH), 128.24 (CH), 129.16 (CH), 134.66 (CH), 138.10 (C), 138.58 (C), 139.80 (C), 148.52 (CH), 148.74 (CH). High-resolution MS calcd for formula $C_{25}H_{29}N_2O$: 373.2280; found: 373.2277

(5) *N*-Benzyl-1-(*cis*-1-benzyl-4-(pyridin-3-yl)azetidin-2-yl)methanamine.



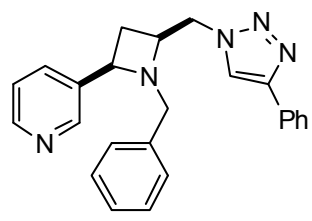
General Procedure C was used, post-work up **2d** azetidine (500mg, 1.37mmol) and benzylamine (5 mL). Yield (2 steps) = 340 mg 72%. IR 3302, 3027, 2819, 1643, 1578, 1494, 1479, 1453, 1427, 1356, 1314, 1207, 1156; ^{1}H NMR (δ; 400 MHz, $CDCl_3$) ; 1.31(1H, *br*, NH), 2.16 (1H, *q*, *J* = 8.0, PyCHCH*H*), 2.52 (2H, *m*, PyCHC*H*H and NCHCH*H*NH), 2.83 (1H, *dd*, *J* = 12.0 & 4.0, NCHC*H*HNH), 3.56 (1H, *m*, NC*H*CH_2NH), 3.59 (1H, *d*, *J* = 12.0, NCH*H*Ph), 3.77 (1H, *d*, *J* = 12.0, NC*H*HPh), 3.80 (1H, *d*, *J* = 12.0, NHCH*H*Ph), 4.04 (1H, *d*, *J* = 12.0, NHC*H*HPh), 4.08 (1H, *t*, *J* = 8.0, PyC*H*CH_2), 7.16 (1H, *t*, *J* = 8.0, ArH), 7.21 (1H, *t*, *J* = 8.0, ArH), 7.23 (2H, *t*, *J* = 8.0, ArH), 7.28 (1H, *d*, *J* = 8.0, ArH), 7.29 (2H, *d*, *J* = 8.0, ArH), 7.34 (2H, *m*, ArH), 7.38 (2H, *d*, *J* = 12.0, ArH), 7.69 (1H, *dt*, *J* = 8.0 & 4.0, ArH), 8.42 (*dd*, 1H, *J* = 6.0 & 4.0, PyH), 8.91 (1H, *s*, PyH). ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$) δ 30.78 (CH_2), 53.15 (CH_2), 53.96 (CH_2), 61.48 (CH_2), 62.52 (CH), 62.96 (CH), 123.29 (CH), 126.96 (CH), 127.30 (CH), 128.10 (CH), 128.24(CH), 129.16 (CH), 134.66 (CH), 138.10 (C), 138.58 (C), 139.80 (C), 148.52 (CH), 148.74 (CH). High-resolution MS calcd for formula $C_{23}H_{25}N_3Na$: 366.1949; found: 366.1949.

(6) *N*,1-Dibenzyl-5-(pyridin-3-yl)pyrrolidin-3-amine.



Method: Post-work up **2d** azetidine (500 mg, 1.37 mmol) was stirred at refluxing in acetonitrile (20 mL), after 4 hours acetonitrile was removed and benzylamine (5 mL) was added and the mixture was left stirring for 24 h, solvent was removed *in vacuo* and flash chromatography (silica) to deliver pyrrolidine **6**, yield (2 steps) = 420 mg, 75%.

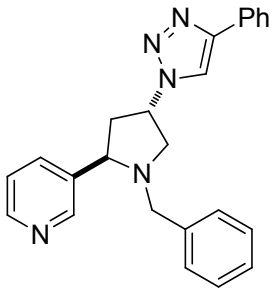
(7) 3-(*cis*-1-Benzyl-4-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)azetidin-2-yl)pyridine.



Method: Post-work up **2d** azetidine (500 mg, 1.37 mmol) and sodium azide (178 mg, 2.74 mmol) were dissolved in DMF (20 mL) and were stirred at room temperature for 16 hours. Ethynylbenzene (140 mg, 1.37 mmol), copper(I) iodide (521 mg, 2.74 mmol) were added and the reaction mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo*, ethyl acetate was added and the resulting suspension was filtered through Celite to remove the inorganic salts. The filtrate was concentrated under reduced pressure and the product was purified by flash chromatography.

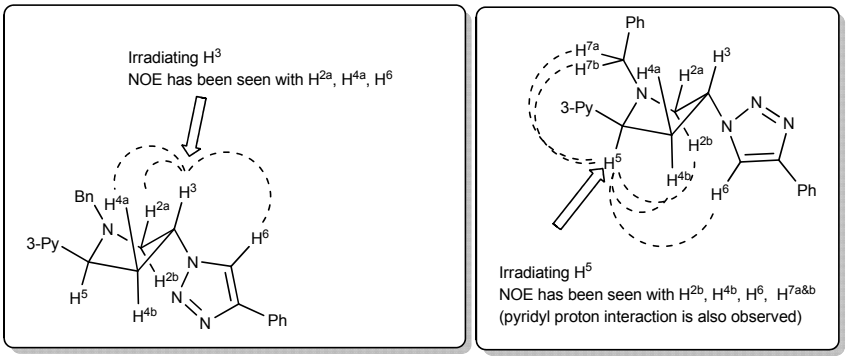
Yield (2 steps) = 303 mg 46%. IR 3029, 2915, 2850, 1578, 1454, 1427, 1383, 1311, 1222, 1178; ^{1}H NMR (δ; 500 MHz, $CDCl_3$); 1.82 (1H, *q*, *J* = 10.0, PyCHCH*H*), 2.56 (1H, *q*, *J* = 10.0, PyCHC*H*H), 3.60 (1H, *d*, *J* = 10.0, NCH*H*Ph), 3.74 (1H, *m*, NC*H*CH_2N), 3.77 (1H, *d*, *J* = 10.0, NC*H*HPh), 4.08 (1H, *dd*, *J* = 12.5 & 5.0, NCHCH*H*N), 4.15 (1H, *m*, PyC*H*CH_2), 4.36 (1H, *d*, *J* = 15.0, NCHC*H*HN), 7.10 (1H, *m*, PyH), 7.27 (1H, *t*, *J* = 10.0, ArH), 7.29 (2H, *d*, *J* = 5.0,ArH), 7.31 (2H, *t*, *J* = 10.0, ArH), 7.37 (1H, *t*, *J* = 10.0, ArH), 7.47 (2H, *t*, *J* = 10.0, ArH), 7.59 (1H, *d*, *J* = 5.0, ArH), 7.62 (1H, *s*, C*H*N_3), 7.81 (2H, *d*, *J* = 10.0), 8.35 (2H, *br*, PyH). ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$) δ 28.97 (CH_2), 52.54 (CH_2), 60.75 (CH), 60.75 (CH_2), 61.75 (CH), 121.84 (CH), 123.64 (CH), 125.20 (CH), 125.22 (CH), 127.77 (CH), 128.03 (CH), 128.58 (CH), 128.83 (CH), 129.39 (CH), 130.06 (C), 137.00 (C), 137.20 (C), 146.70 (C), 147.80 (CH), 148.40 (CH). High-resolution MS calcd for formula $C_{24}H_{23}N_5Na$: 404.1851; found 404.1839.

(8) 3-(*trans*-1-Benzyl-4-(4-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidin-2-yl)pyridine.



Method: Post-work up **2d** azetidine (110 mg, 0.3 mmol) was heated at 70 °C in DMF (20 mL) for 4h, sodium azide (30 mg, 0.45 mmol) was added and the mixture was stirred at room temperature for 16 hours. Ethynylbenzene (32 mg, 0.3 mmol), copper(I) iodide (115 mg, 0.6mmol) were added and the reaction mixture was heated at 80 °C for 4 hours. The solvent was removed *in vacuo* , ethyl acetate was added and the resulting suspension was filtered through Celite to remove the inorganic salts. The filtrate was concentrated under reduced pressure and the product was purified by flash chromatography. Yield (2 steps)= 86 mg, 57%. IR 3127, 3026, 2920, 2822, 1579, 1495, 1481, 1455, 1428, 1375, 1322, 1289, 1229, 1178, 1160; ^{1}H NMR (δ; 300 MHz, $CDCl_3$); 2.43(1H, *dt*, *J* = 15.0 & 9.0, PyCHCH*H*), 2.78 (1H, *m*, PyCHC*H*H), 2.86 (1H, *dd*, *J* = 9.0 & 6.0, CH*H*N_3), 3.29 (1H, *d*, *J* = 15.0, NCH*H*Ph), 3.71 (1H, *t*, *J* = 9.0, C*H*HN_3), 3.86 (1H, *d*, *J* = 12.0, NC*H*HPh), 4.07 (1H, *t*, *J* = 9.0, PyC*H*CH_2), 5.21 (1H, *m*, NC*H*CH_2N_3), 7.33 (9H, *m*, ArH), 7.75 (1H, *s*, C*H*N_3), 7.81 (2H, *d*, *J* = 9.0, ArH), 7.87 (1H, *d*, *J* = 6.0, ArH), 8.61 (1H, *br*, PyH), 8.78 (1H, *br*, PyH), ^{13}C{^{1}H} NMR (δ; 100 MHz, $CDCl_3$), δ42.30 (CH_2), 56.20 (CH_2), 57.82 (CH), 59.42 (CH_2), 65.45 (CH), 118.87 (CH), 125.71(CH), 127.36 (CH), 128.25 (CH), 128.45 (CH), 128.65 (CH), 128.87 (CH), 130.47 (C), 135.15 (CH), 137.93(C), 147.87(C), 149.29(CH), 149.57(CH) (quat C=$\underline{C}_{triazole}$ not observed). High-resolution MS calcd for formula $C_{24}H_{23}N_5Na$:404.1851; found: 404.1867.

To confirm stereochemistry nOe experiments were performed, revealing a *trans* substitution arrangement about the pyrrolidine ring, suggesting compound **2d**, formed *in situ* is cleanly converted via an S_N2 mechanism to the corresponding azide which is subsequently converted to the corresponding traizole:

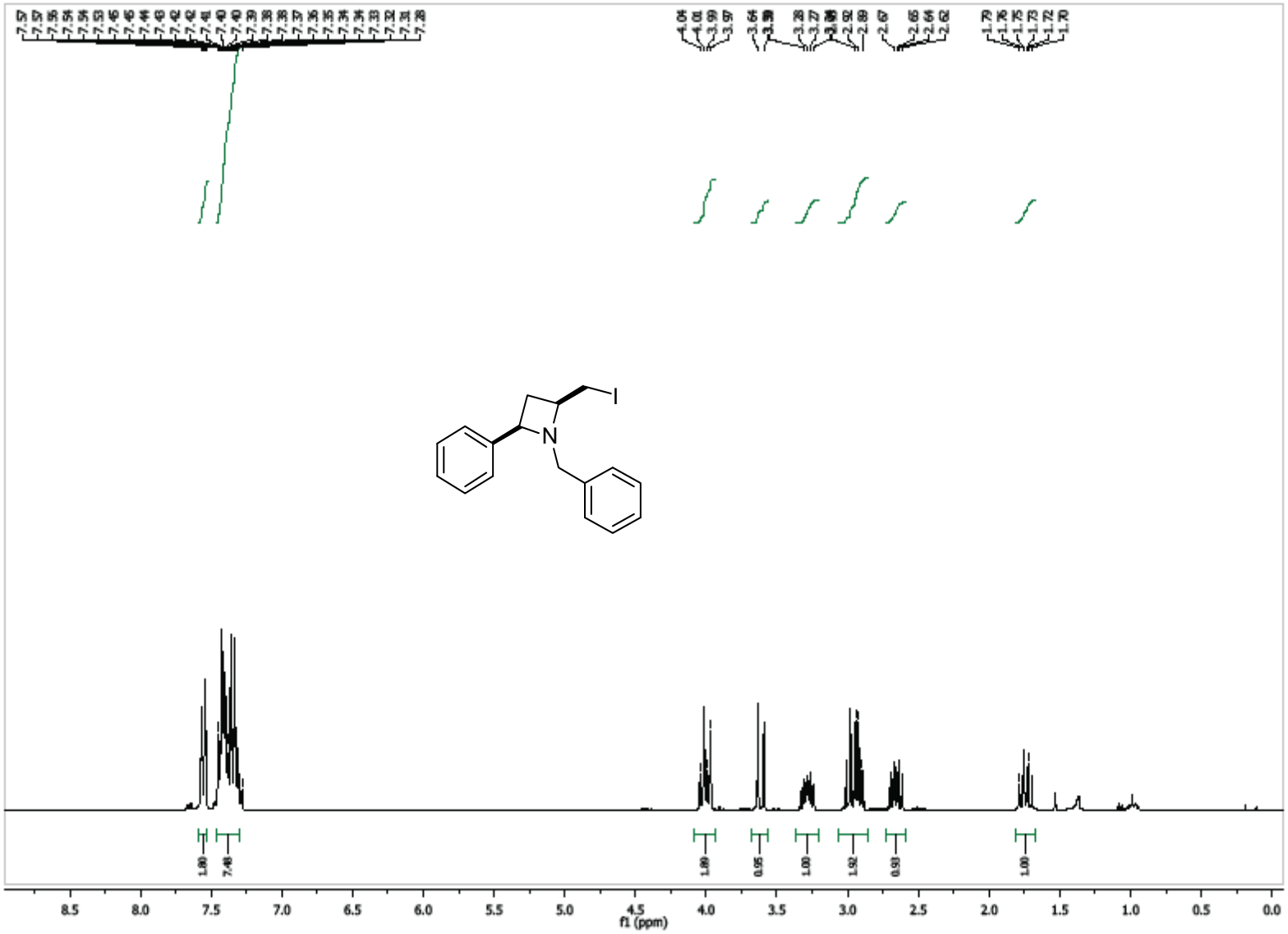


That H^3 and H^5 display nOe between different protons on the same methylene carbons (corresponding to $H^{2a\&b}$ and $H^{4a\&b}$) is convincing evidence of *trans* geometry. Also, no nOe between H^3 and H^5 was observed.

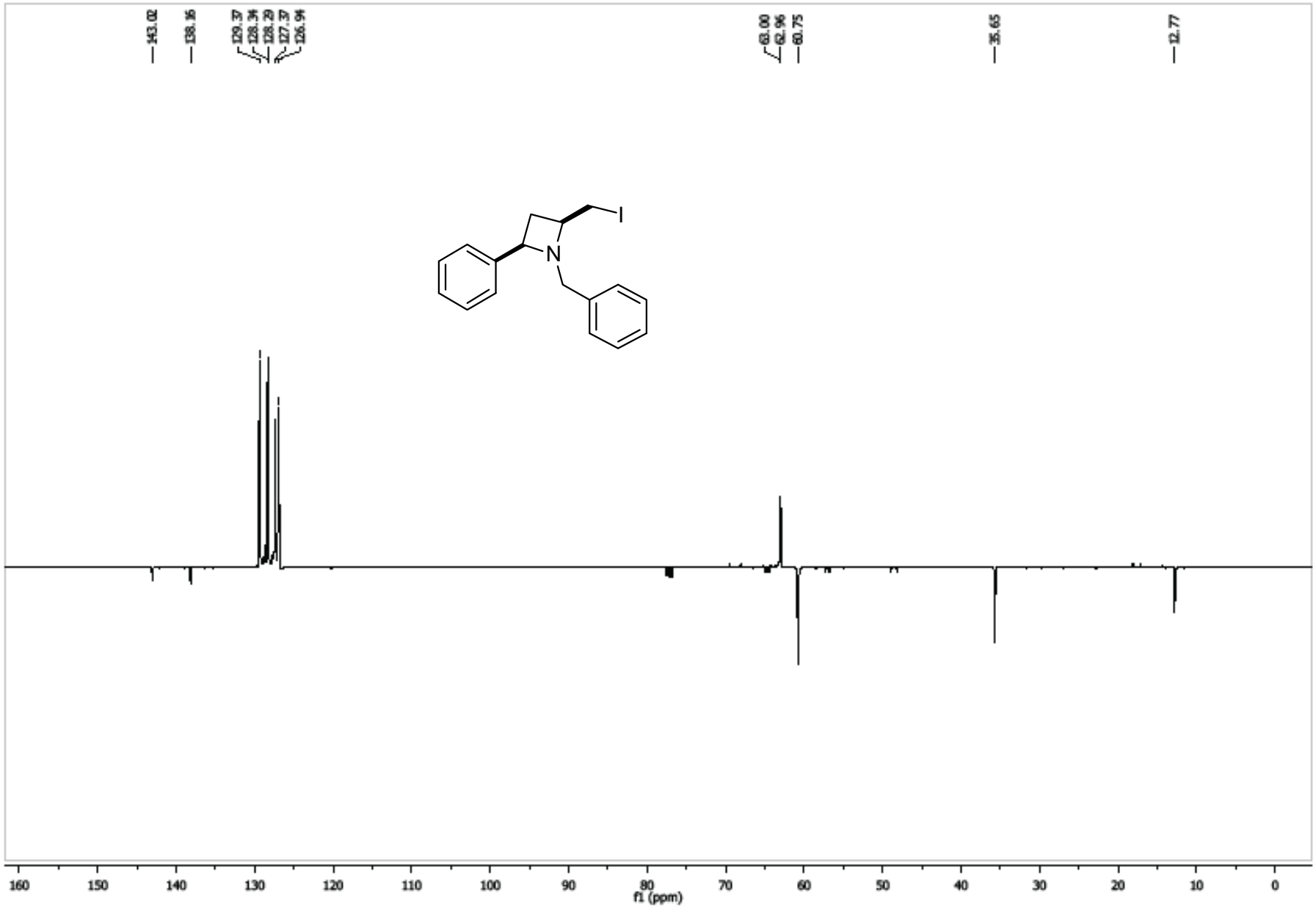
trans-**8**

NMR Spectra

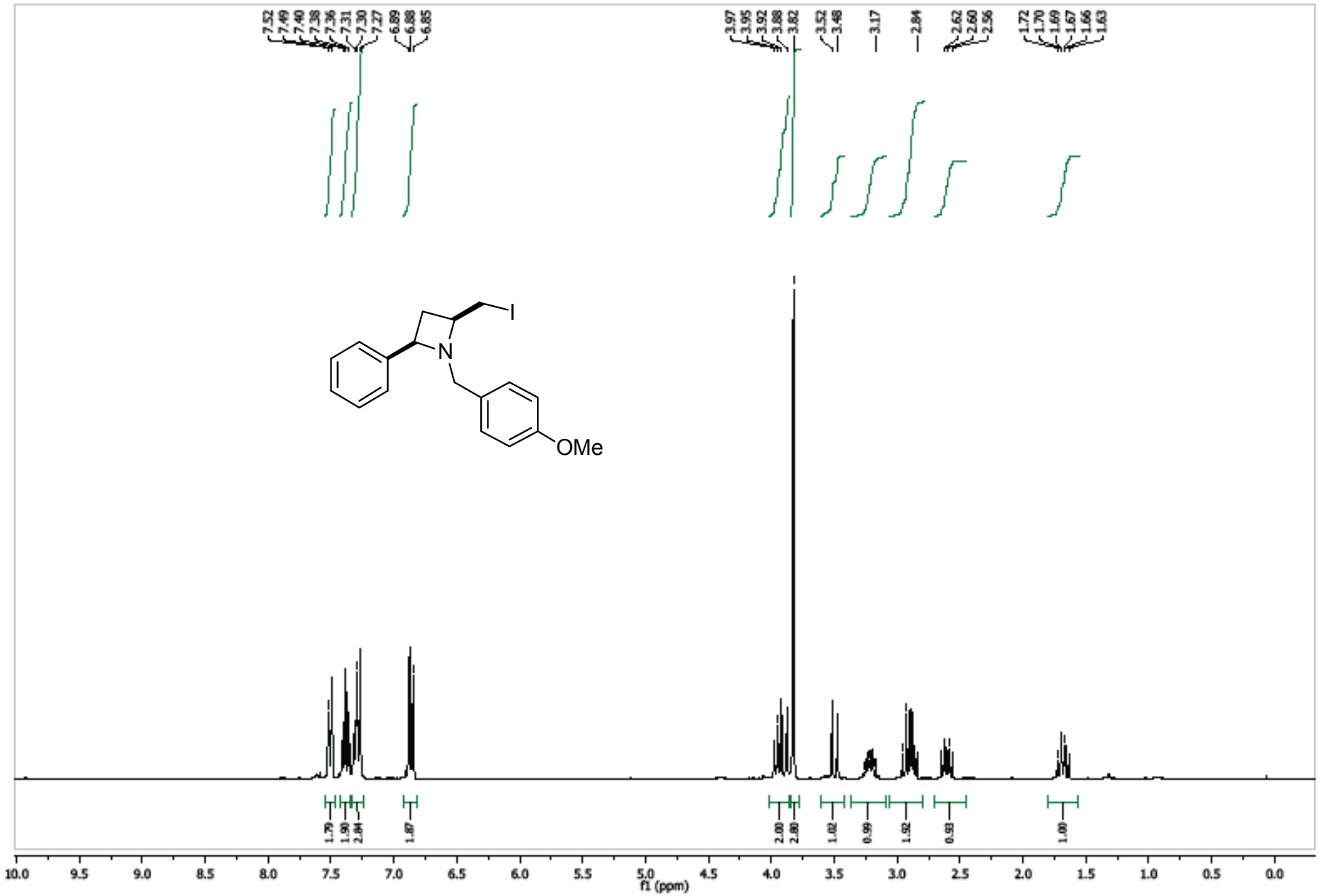
^{1}H NMR Spectrum of 2a



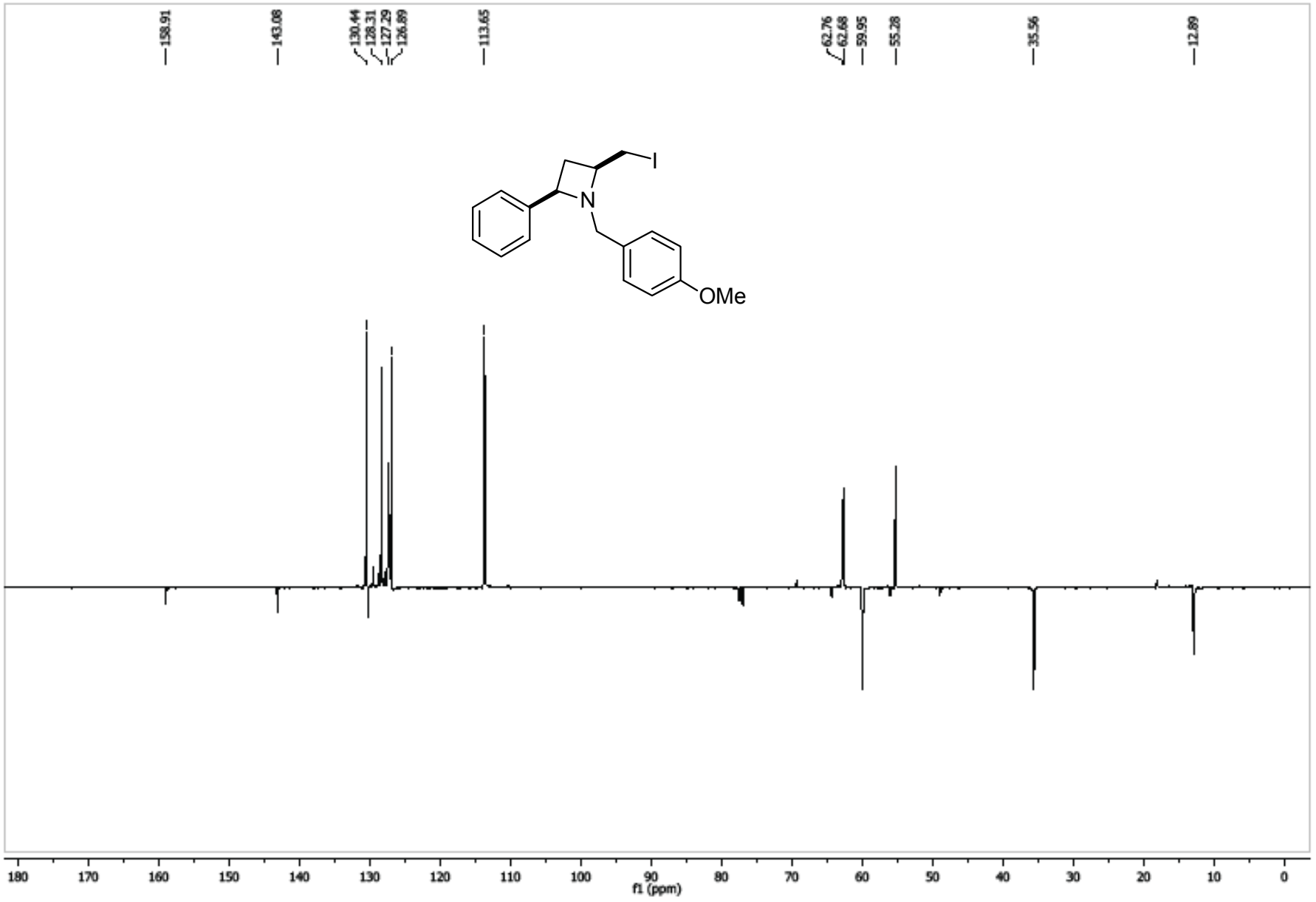
$^{13}C\{^{1}H\}$ NMR Spectrum (Pendant) of 2a



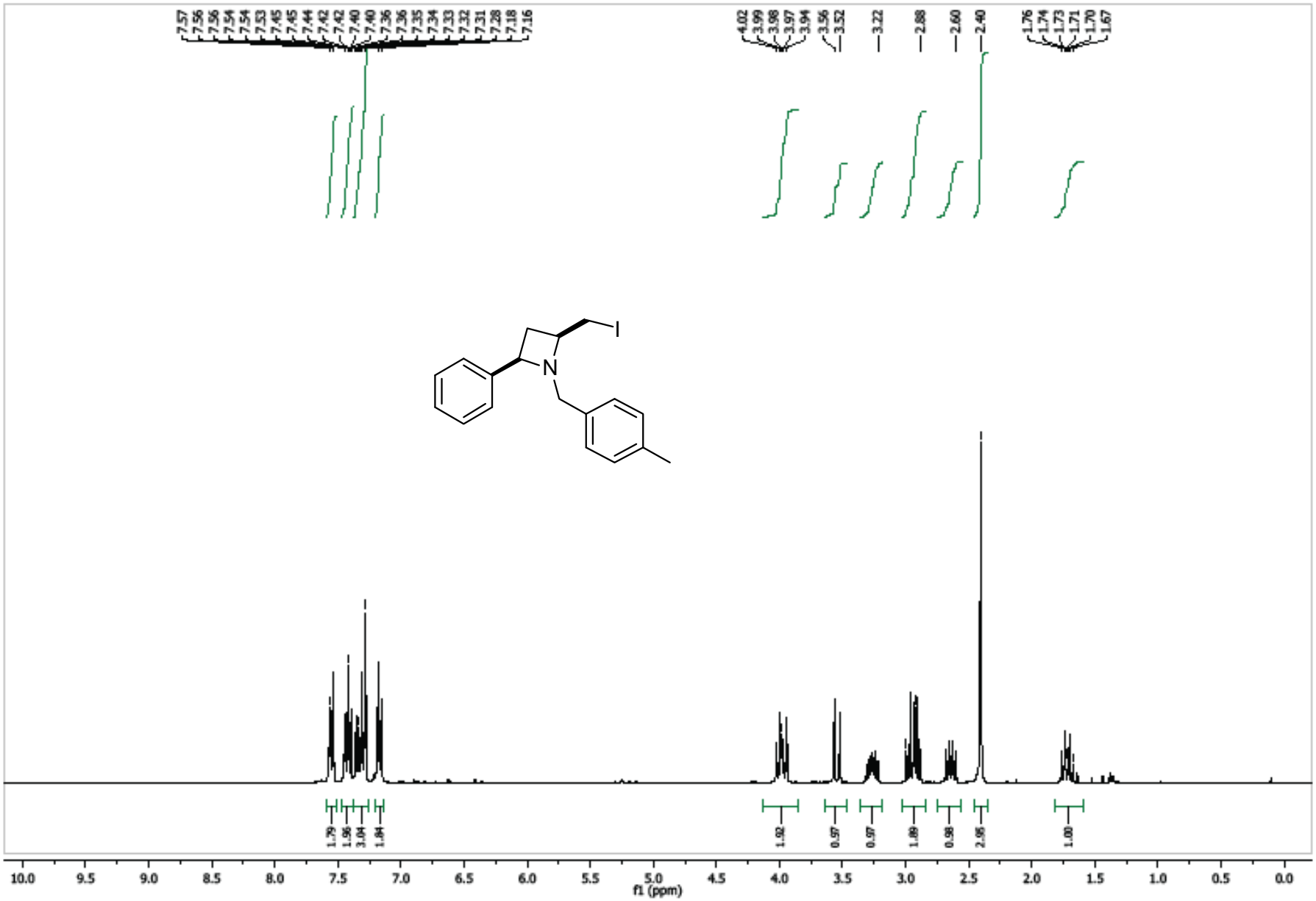
^{1}H NMR Spectrum of 2b



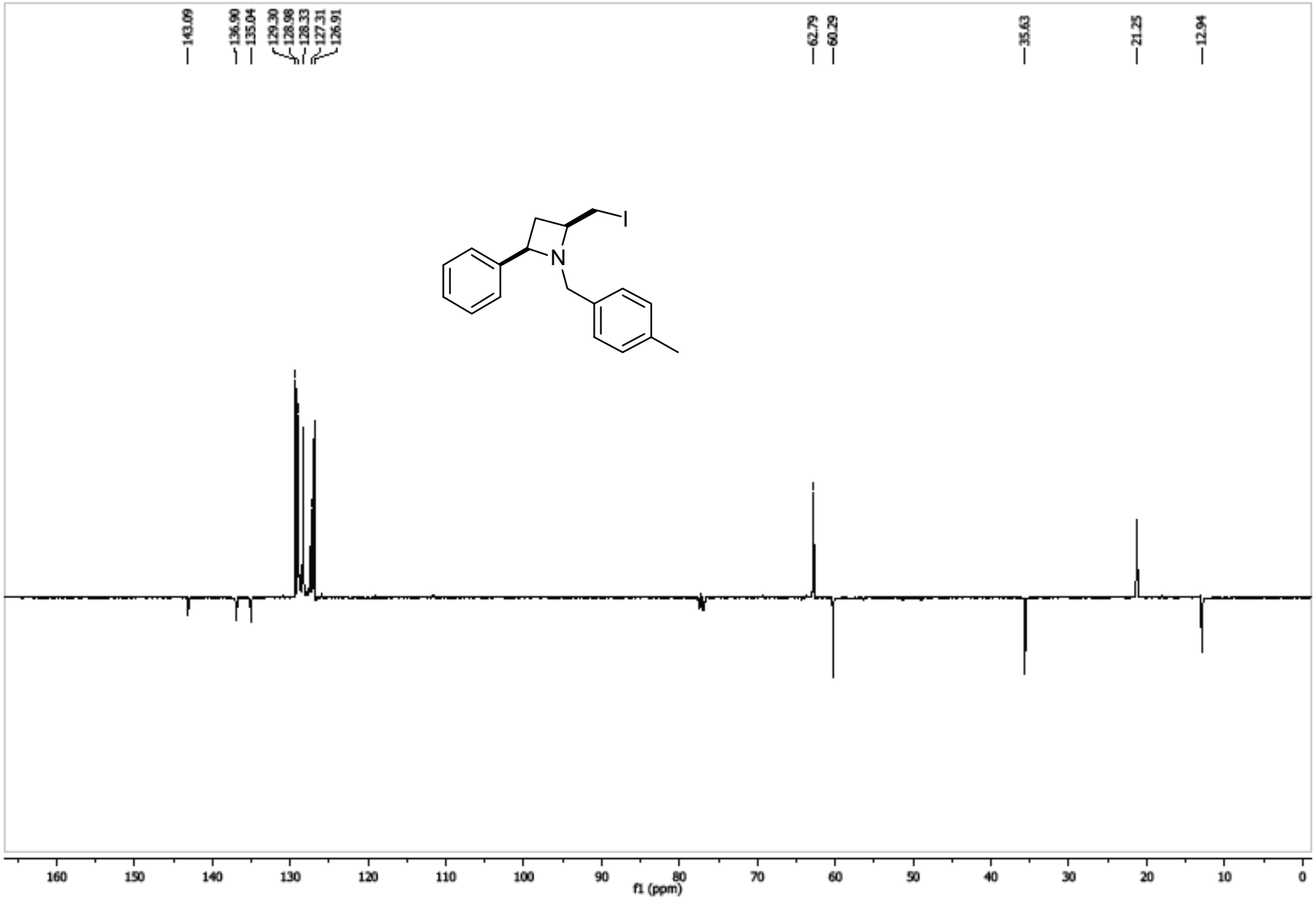
$^{13}C\{^{1}H\}$ NMR Spectrum (Pendant) 2b



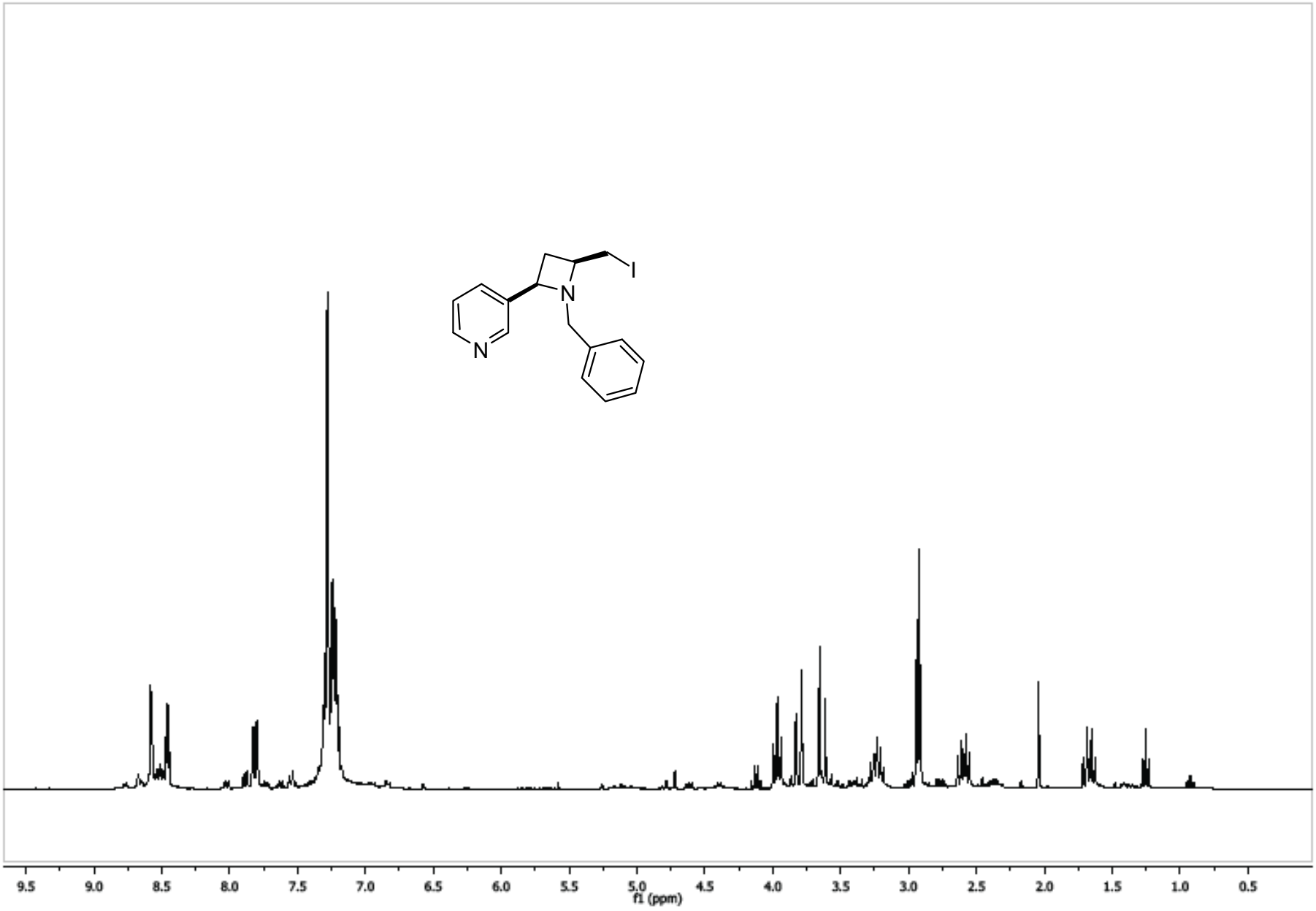
^{1}H NMR Spectrum of 2c



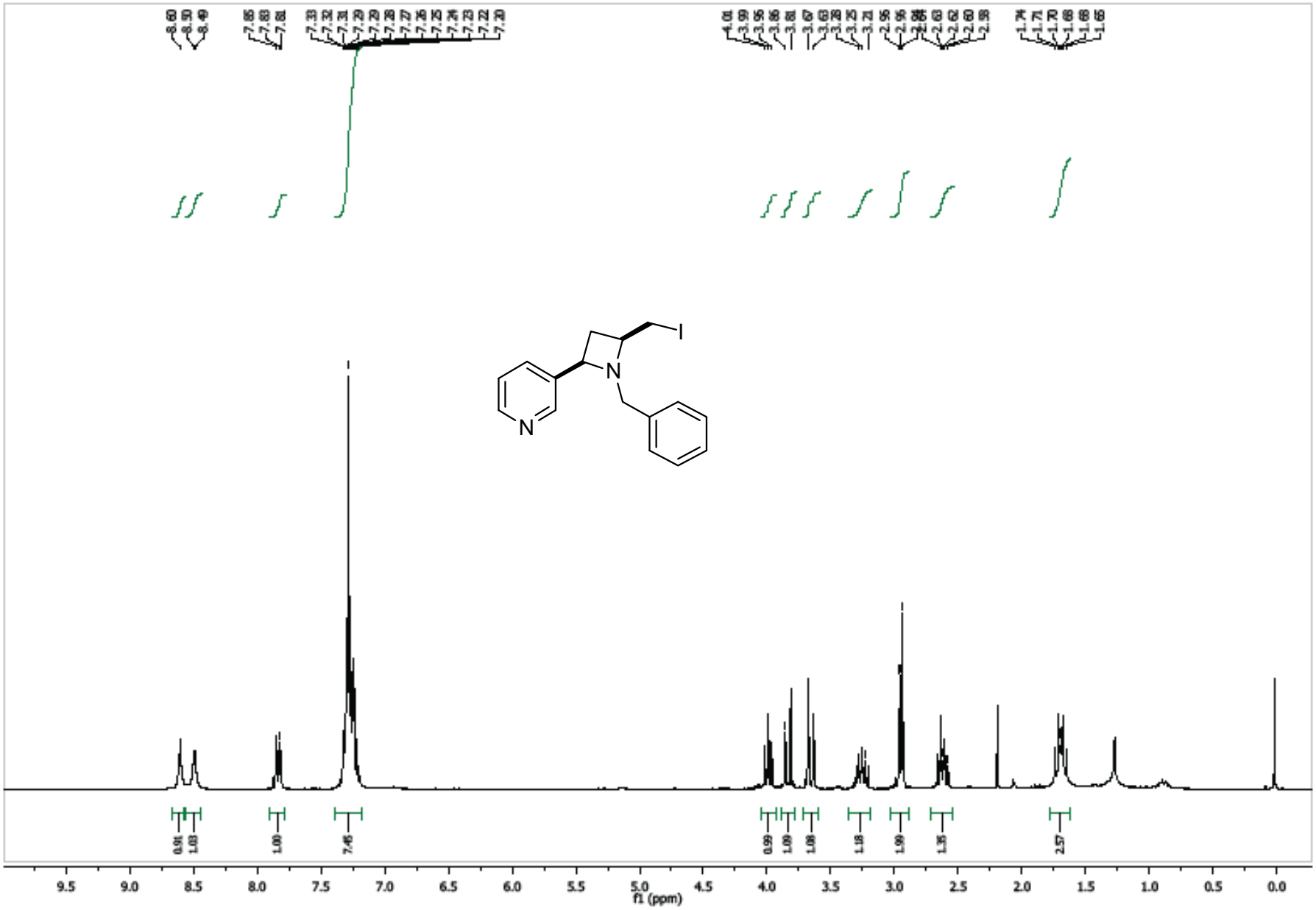
$^{13}C\{^{1}H\}$ NMR Spectrum (Pendant) of 2c



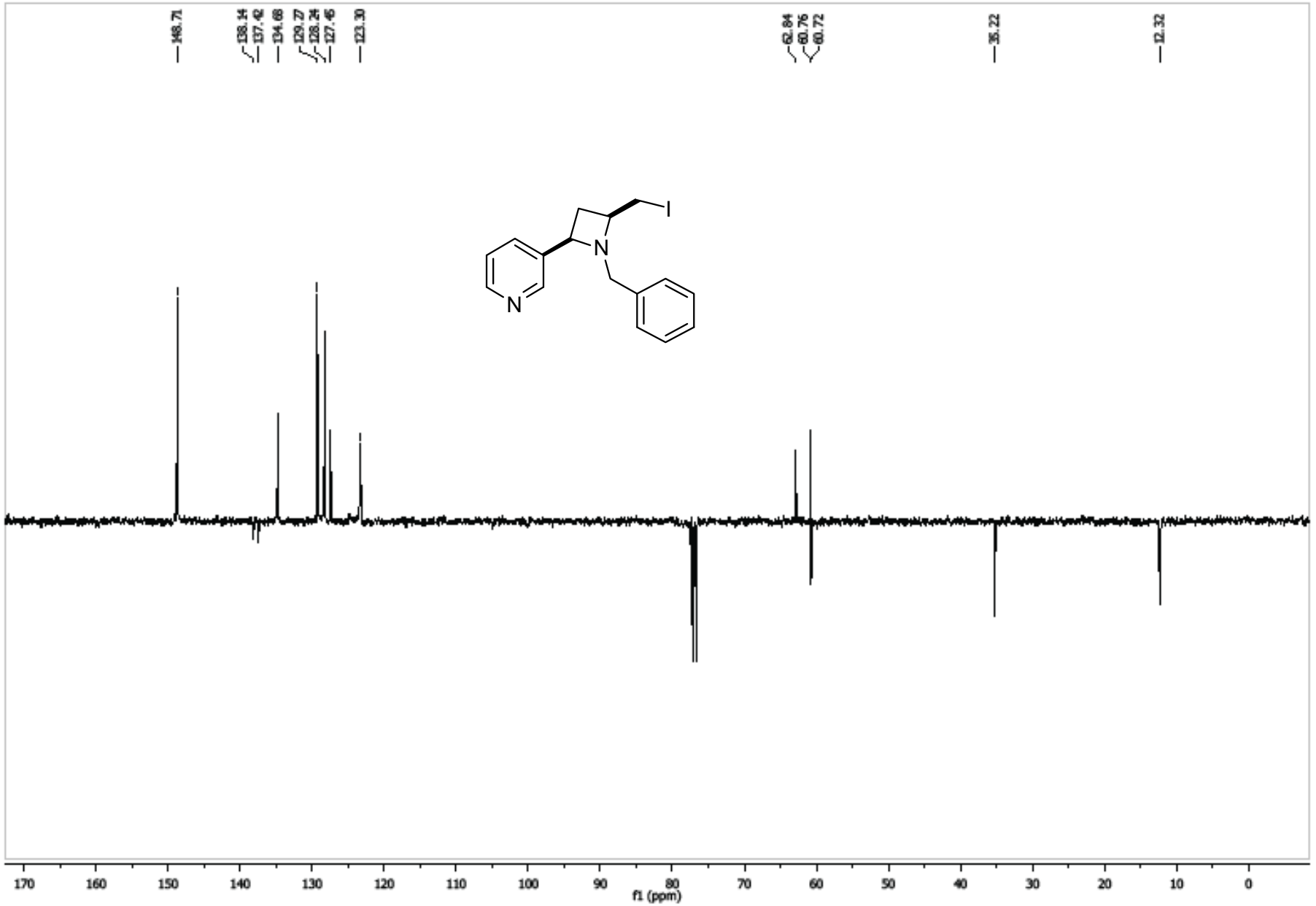
^{1}H NMR Spectrum of 2d (Post-Work Up)



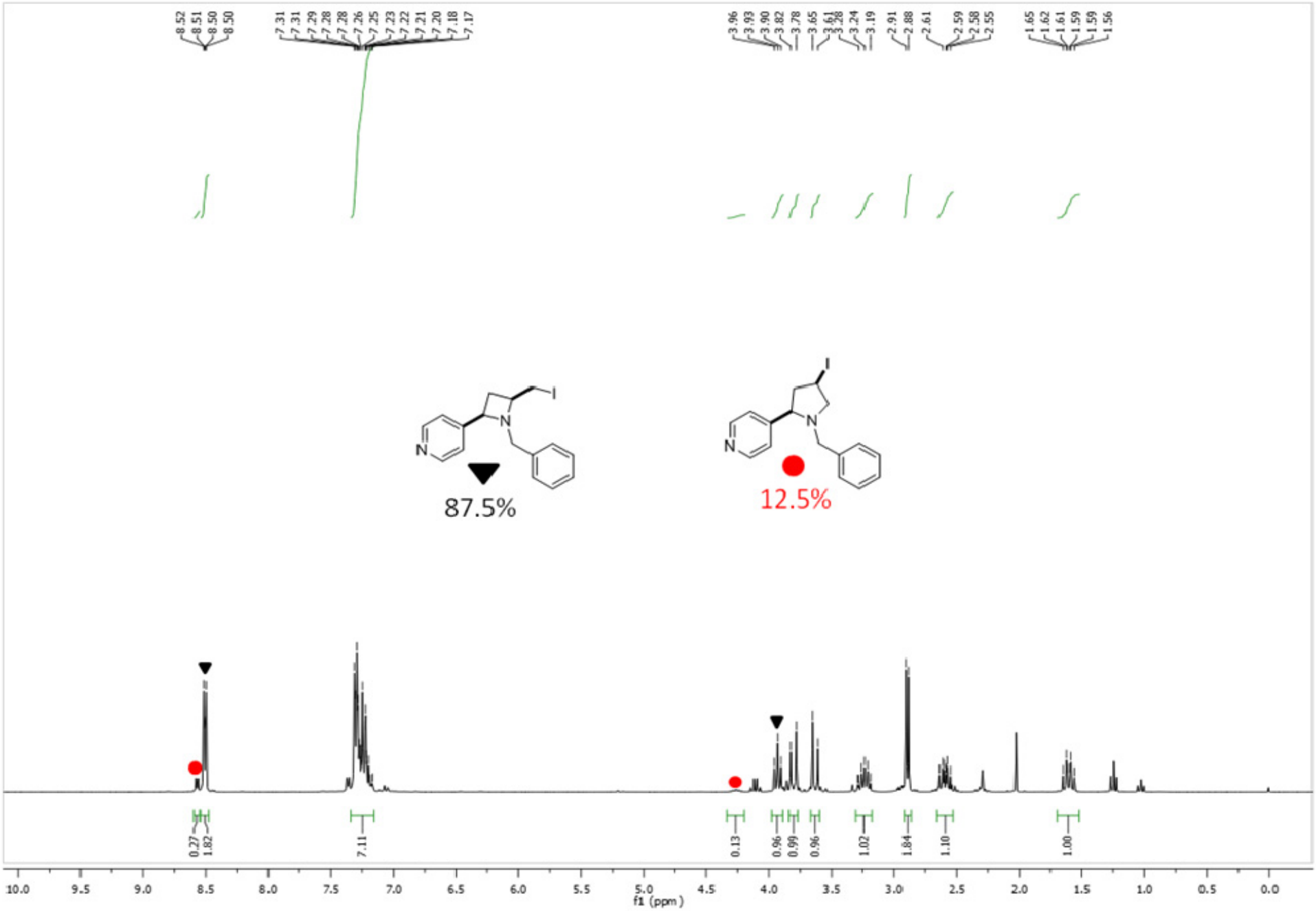
^{1}H NMR Spectrum of 2d (After Flash Chromatography)



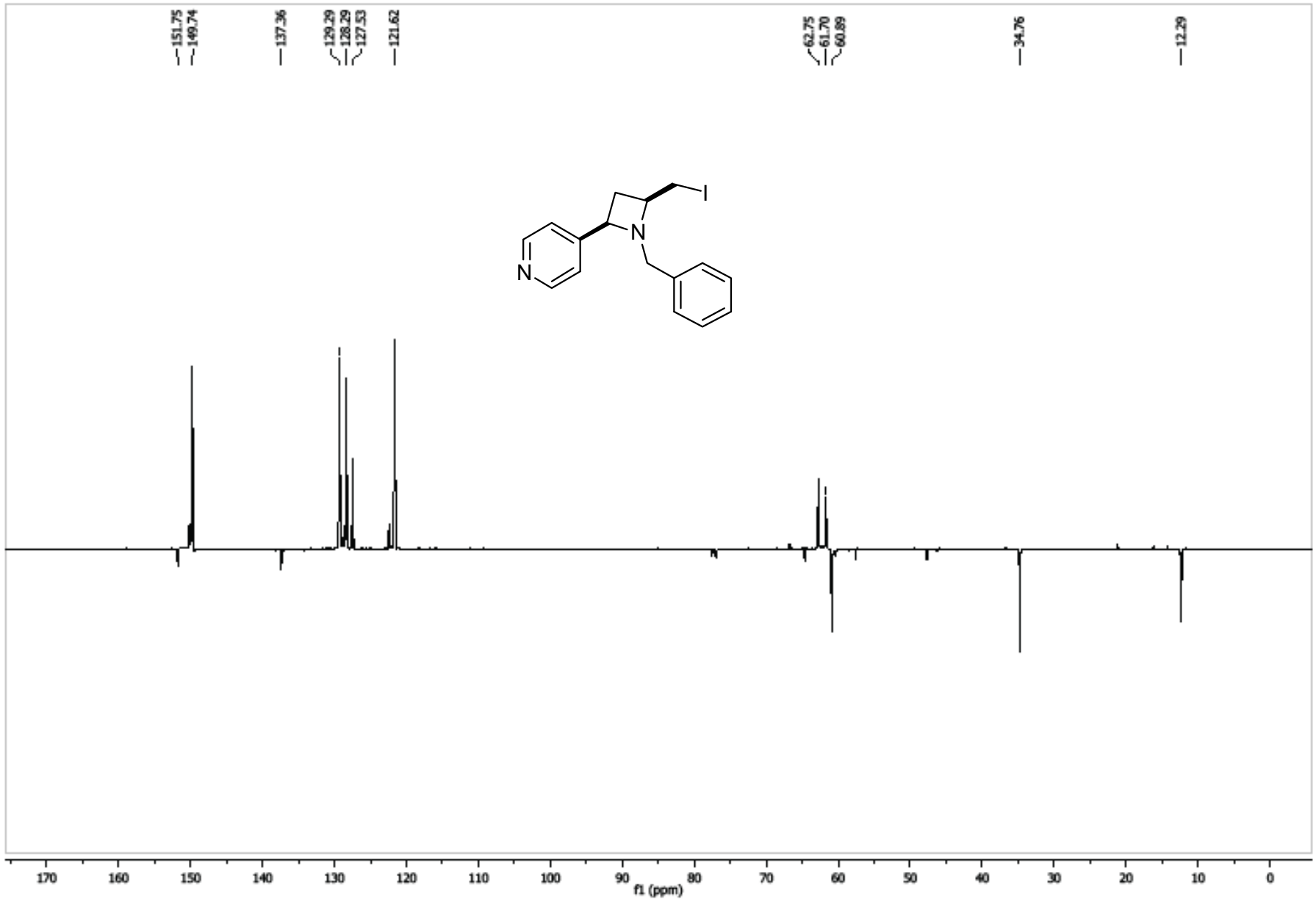
$^{13}C\{^{1}H\}$ NMR Spectrum (Pendant) of 2d



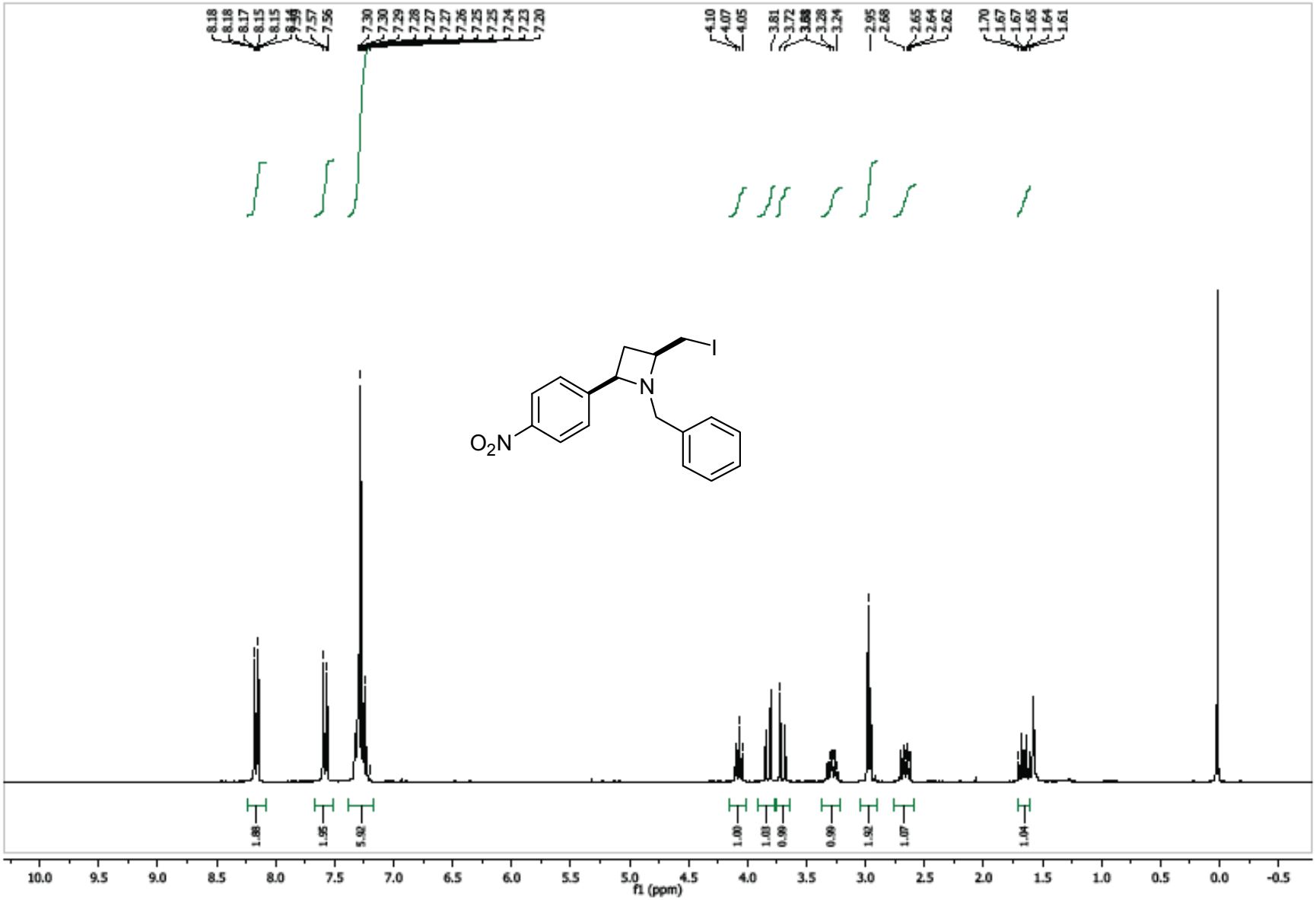
^{1}H NMR Spectrum of 2e



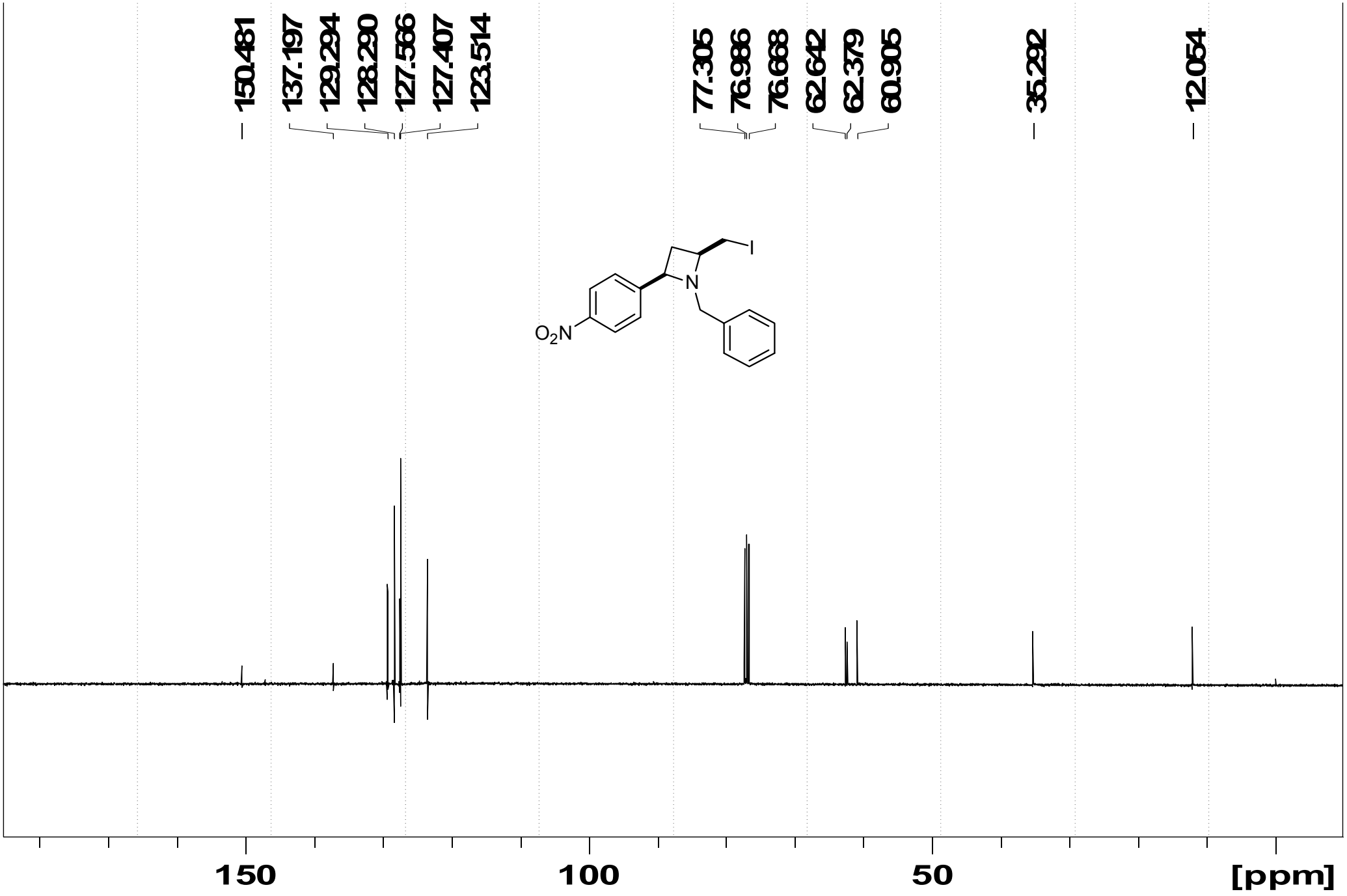
13C{1H} NMR Spectrum (Pendant) of 2e



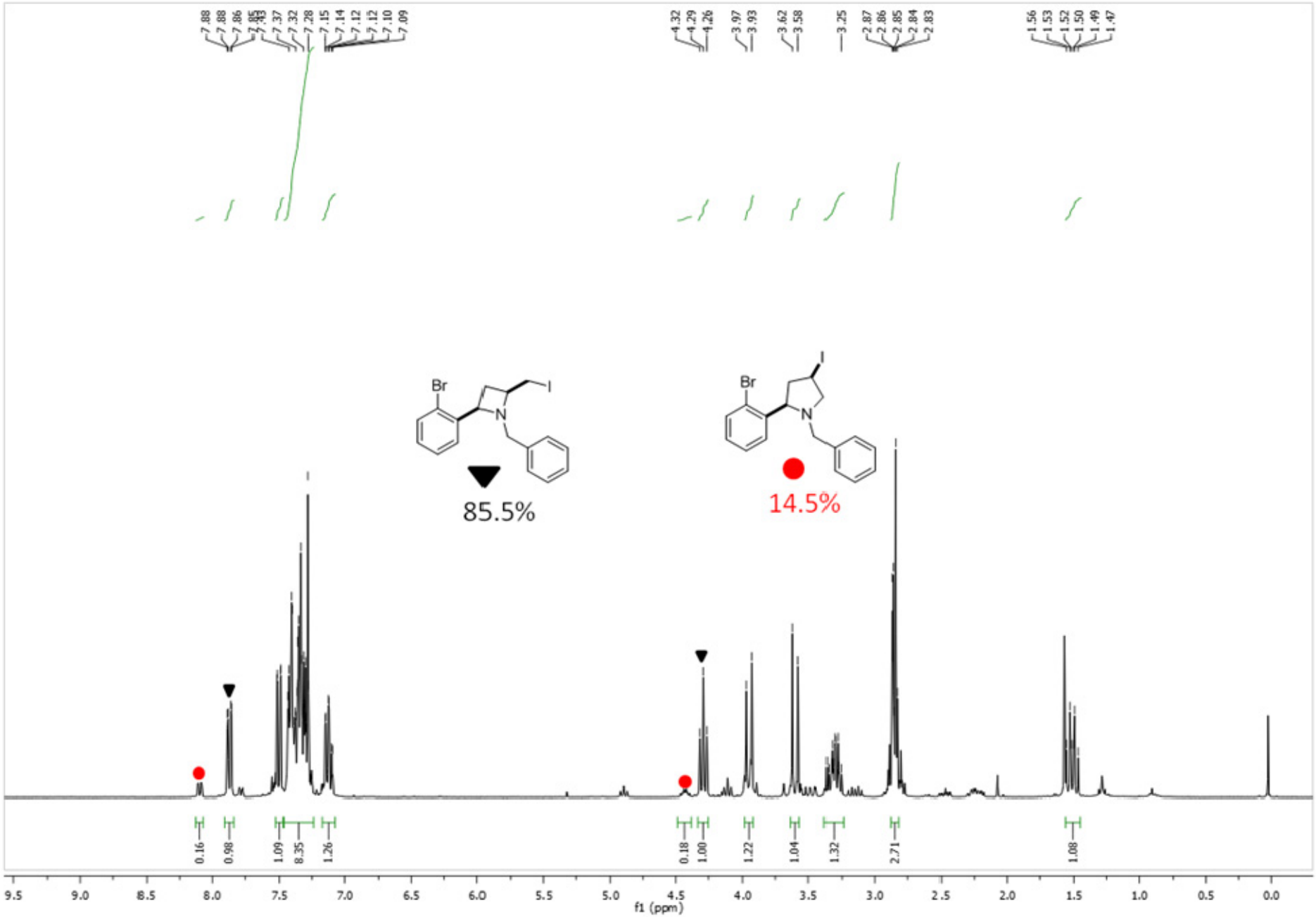
^{1}H NMR Spectrum of 2f



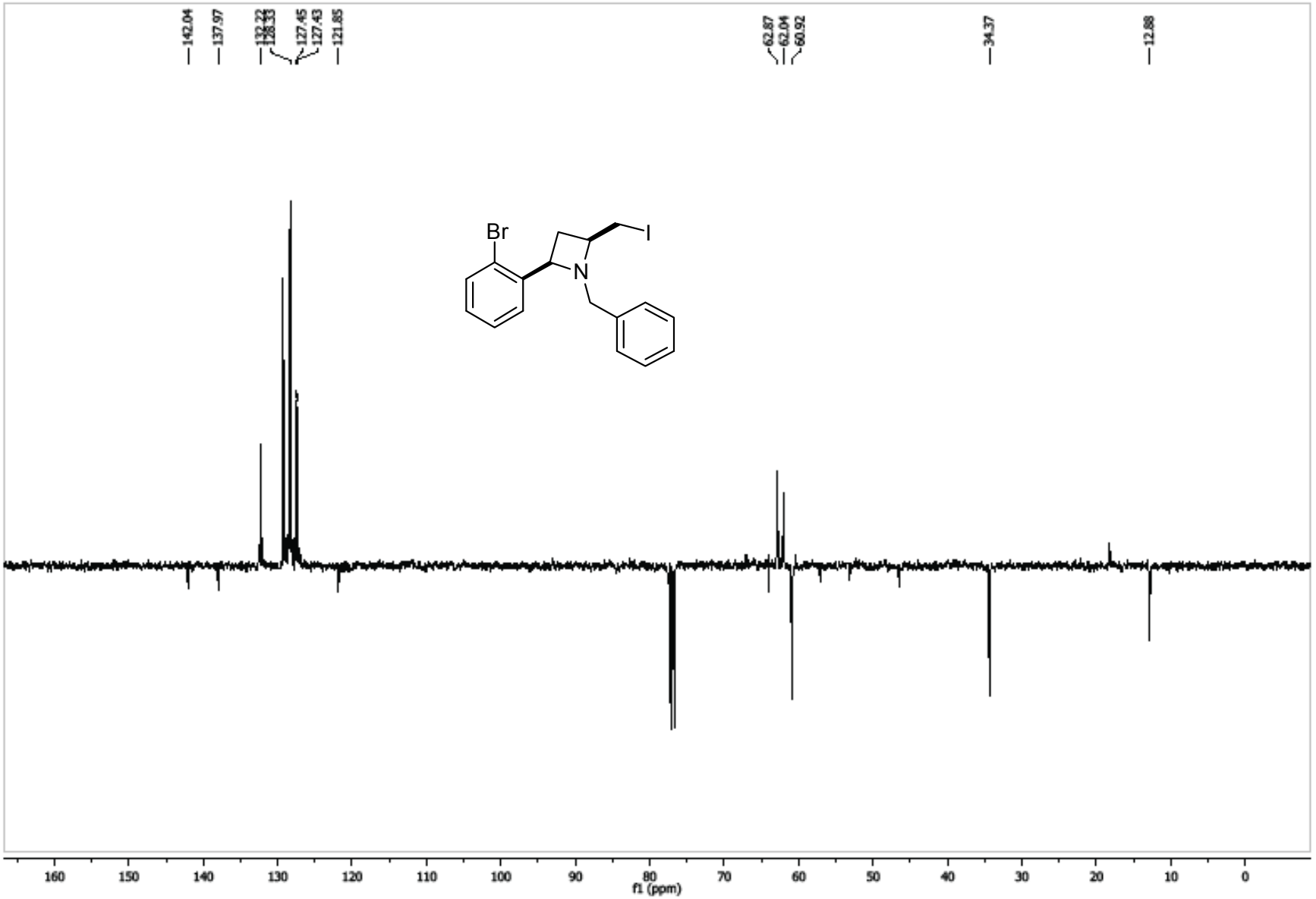
$^{13}C\{^{1}H\}$ NMR Spectrum of 2f



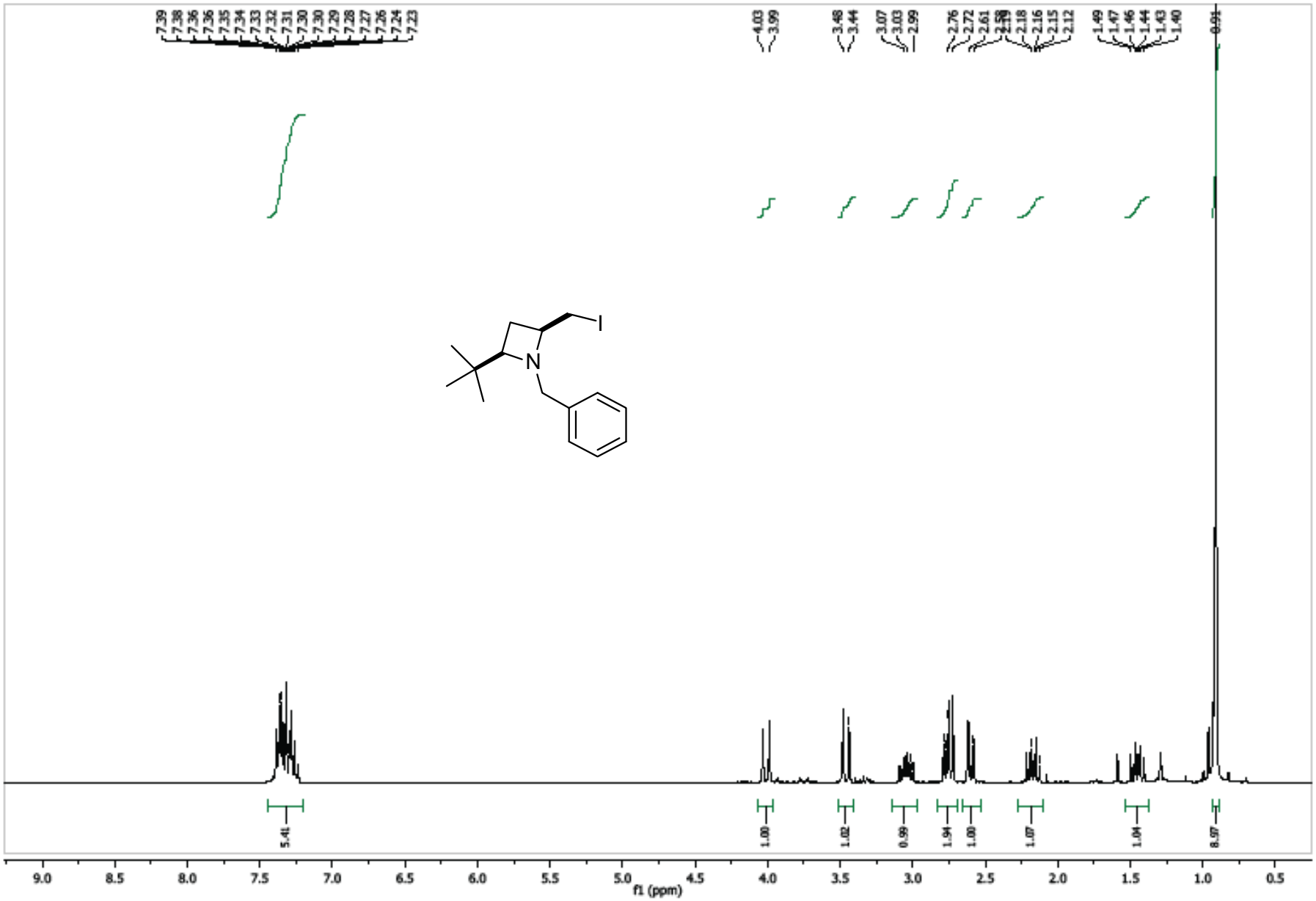
^{1}H NMR Spectrum of 2g



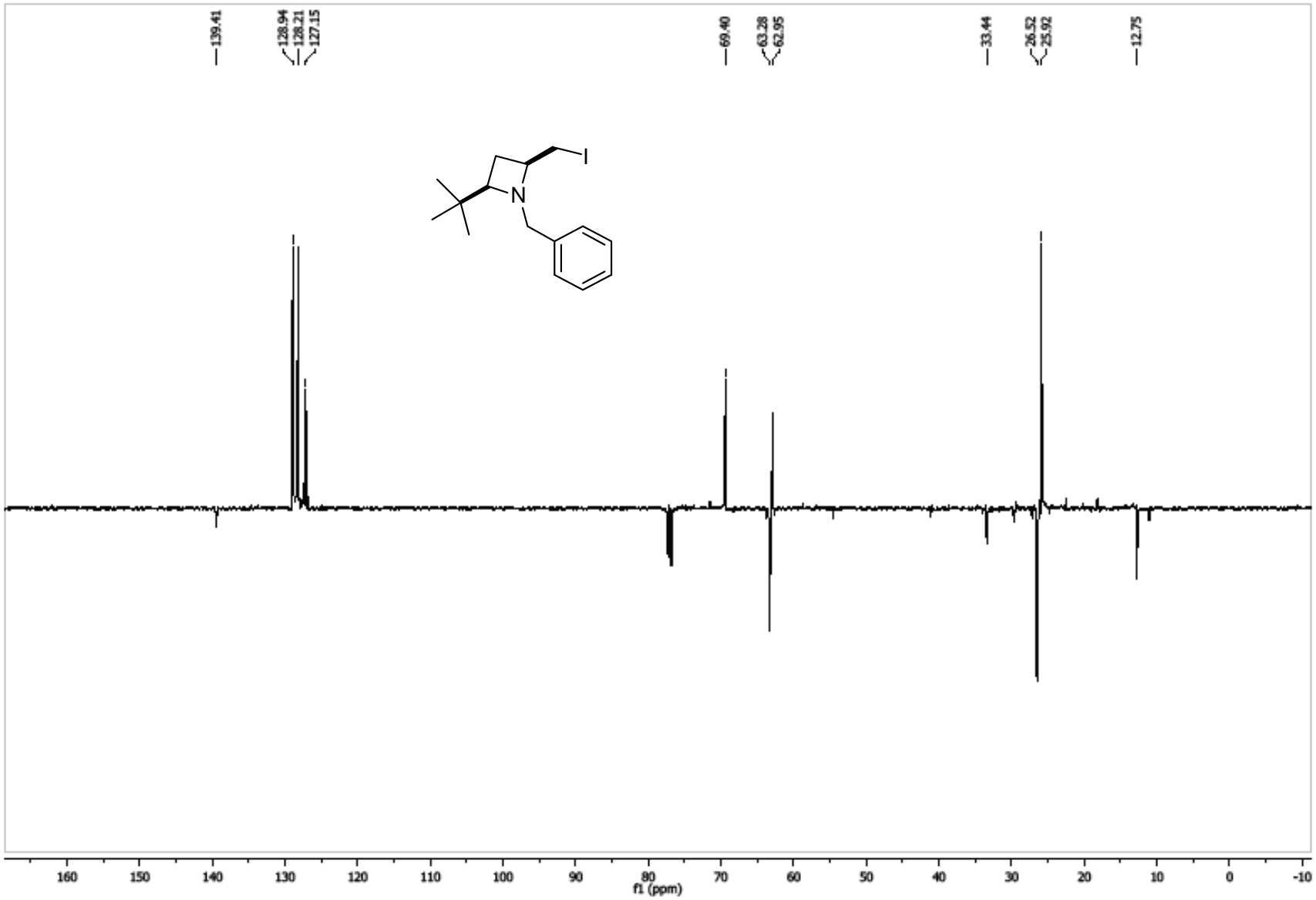
$^{13}C\{^{1}H\}$ NMR Spectrum (Pendant) of 2g



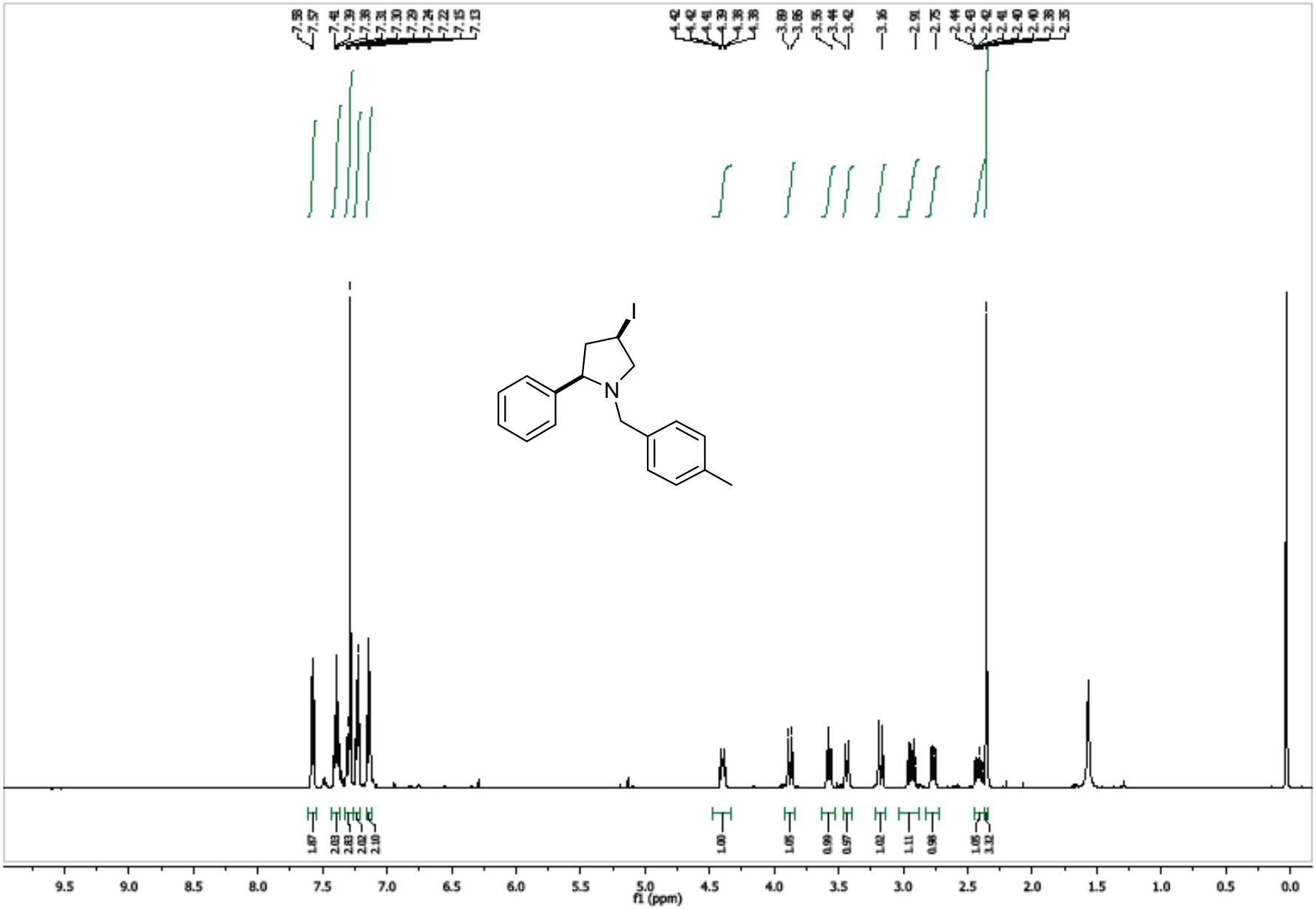
^{1}H NMR Spectrum of 2h



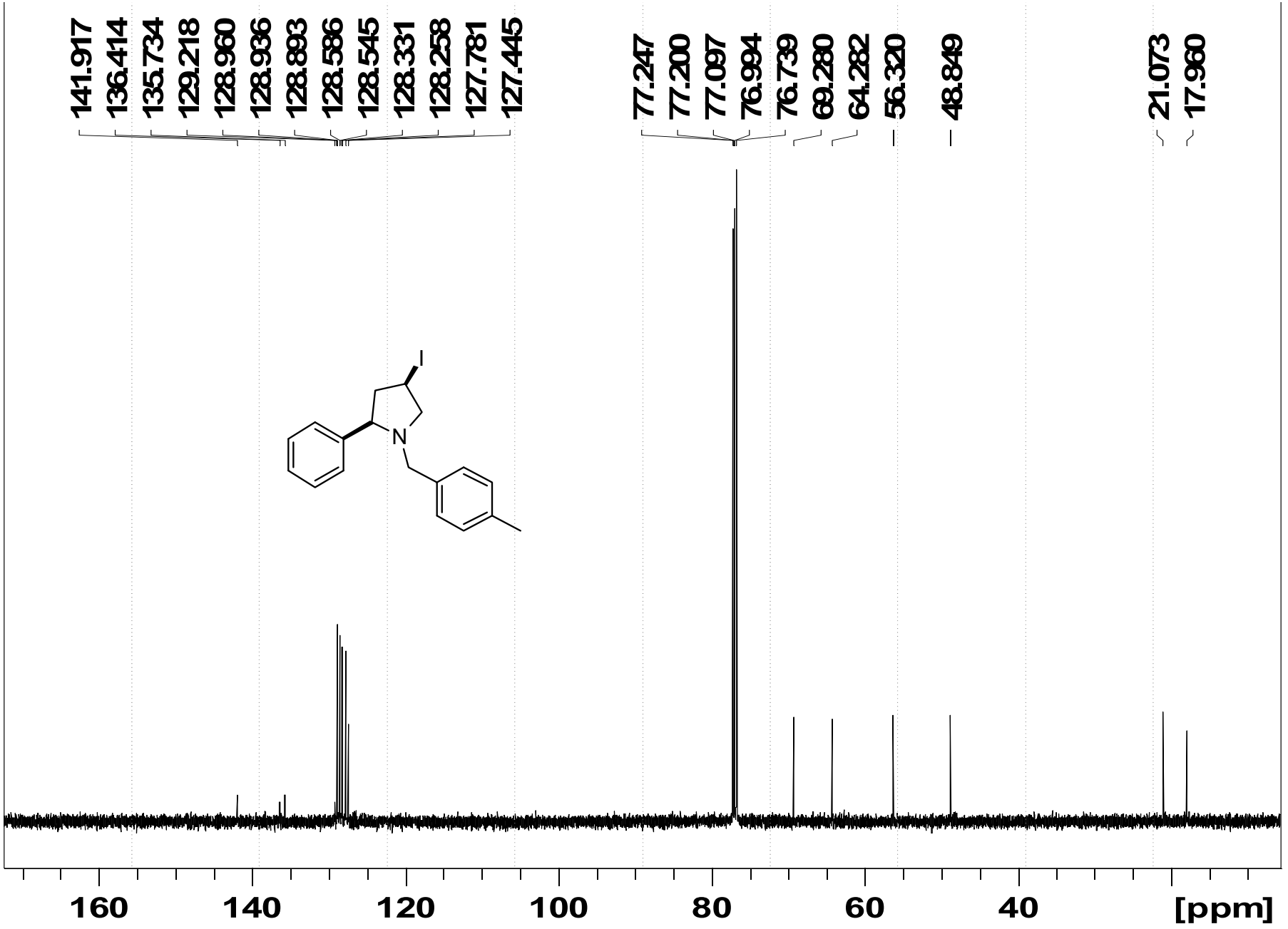
$^{13}C\{^{1}H\}$ NMR Spectrum (Pendant) of 2h



^{1}H NMR Spectrum of 3c

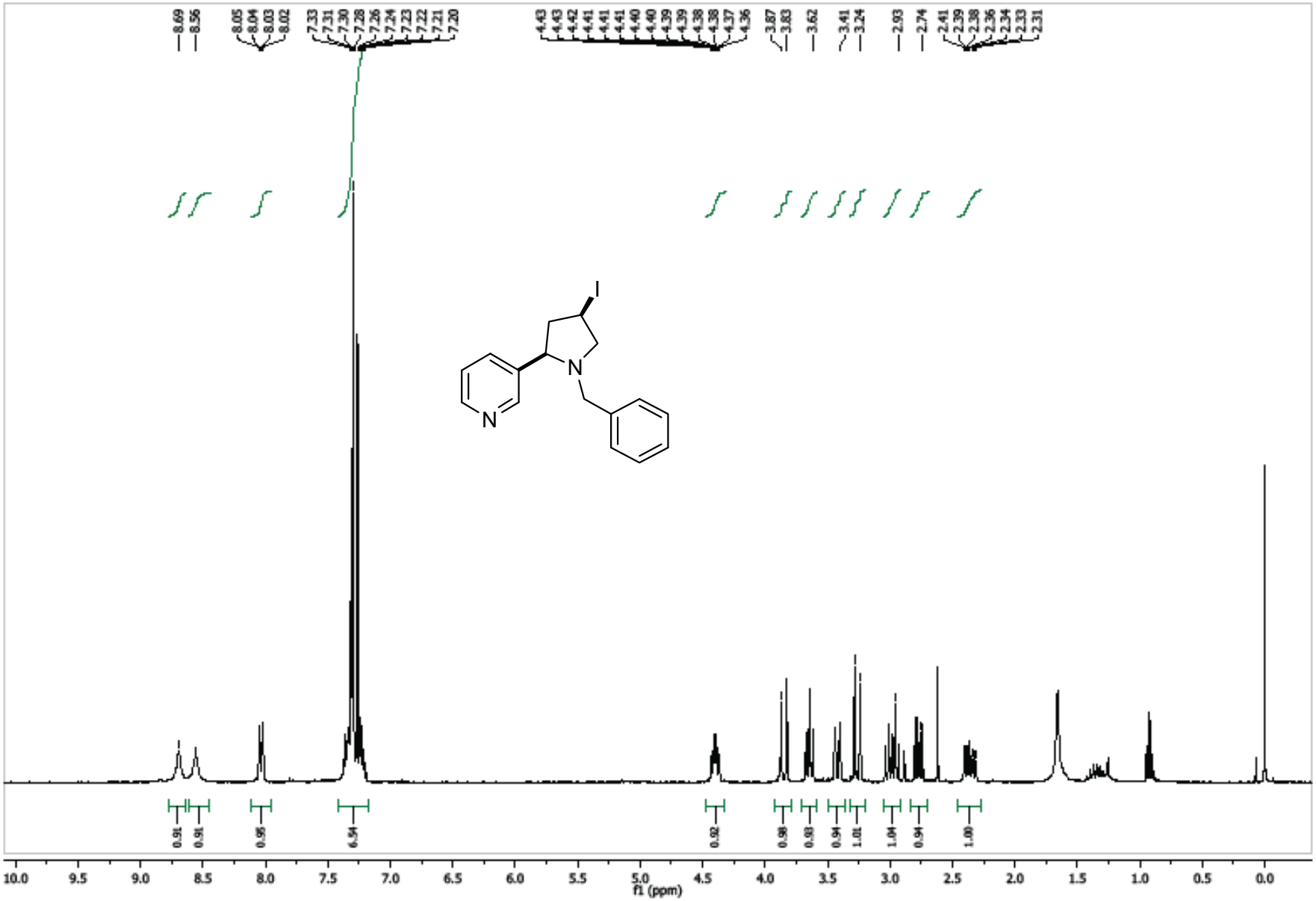


$^{13}C\{^{1}H\}$ NMR Spectrum of 3c

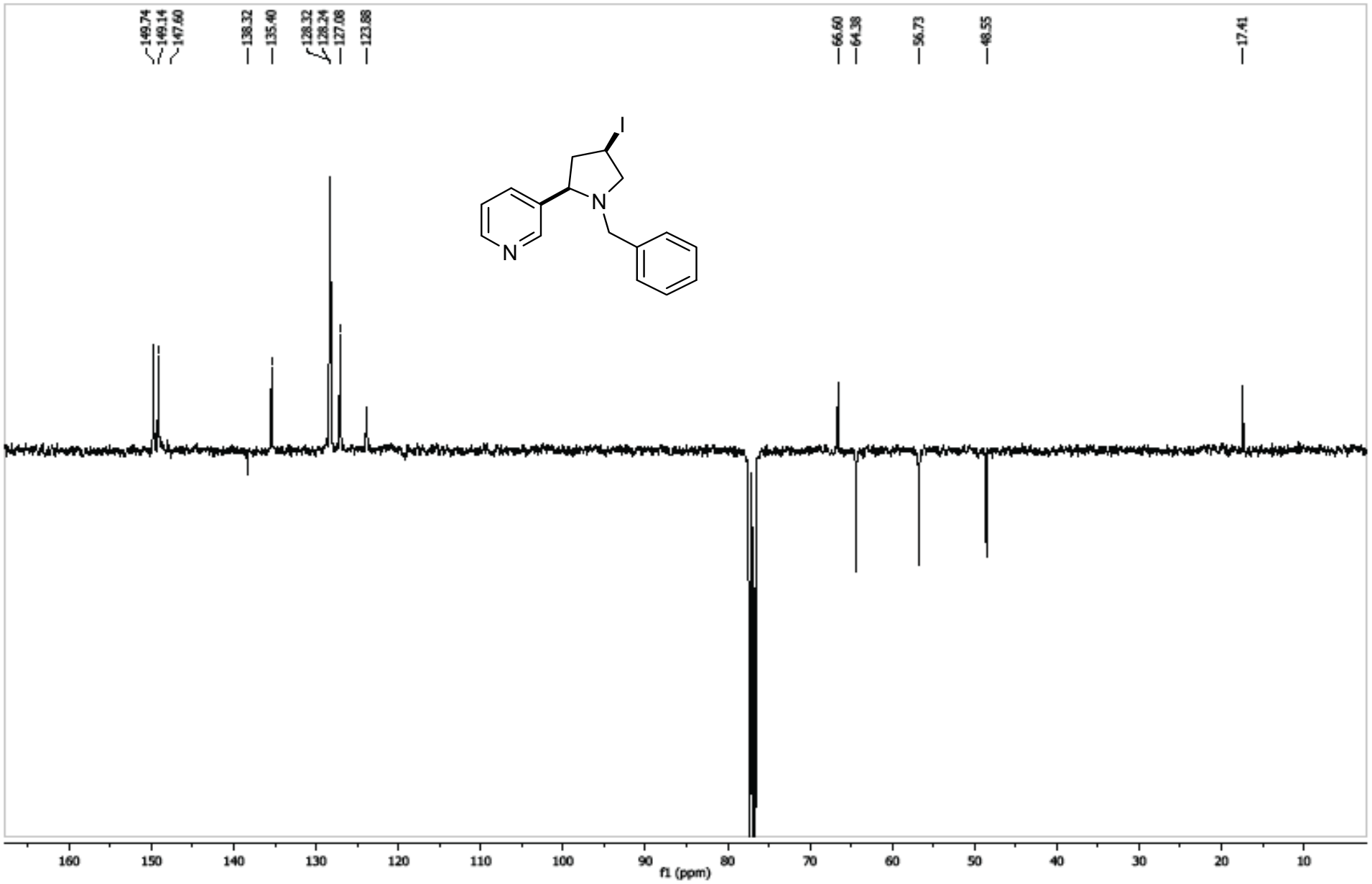


^{1}H NMR Spectrum of 3d

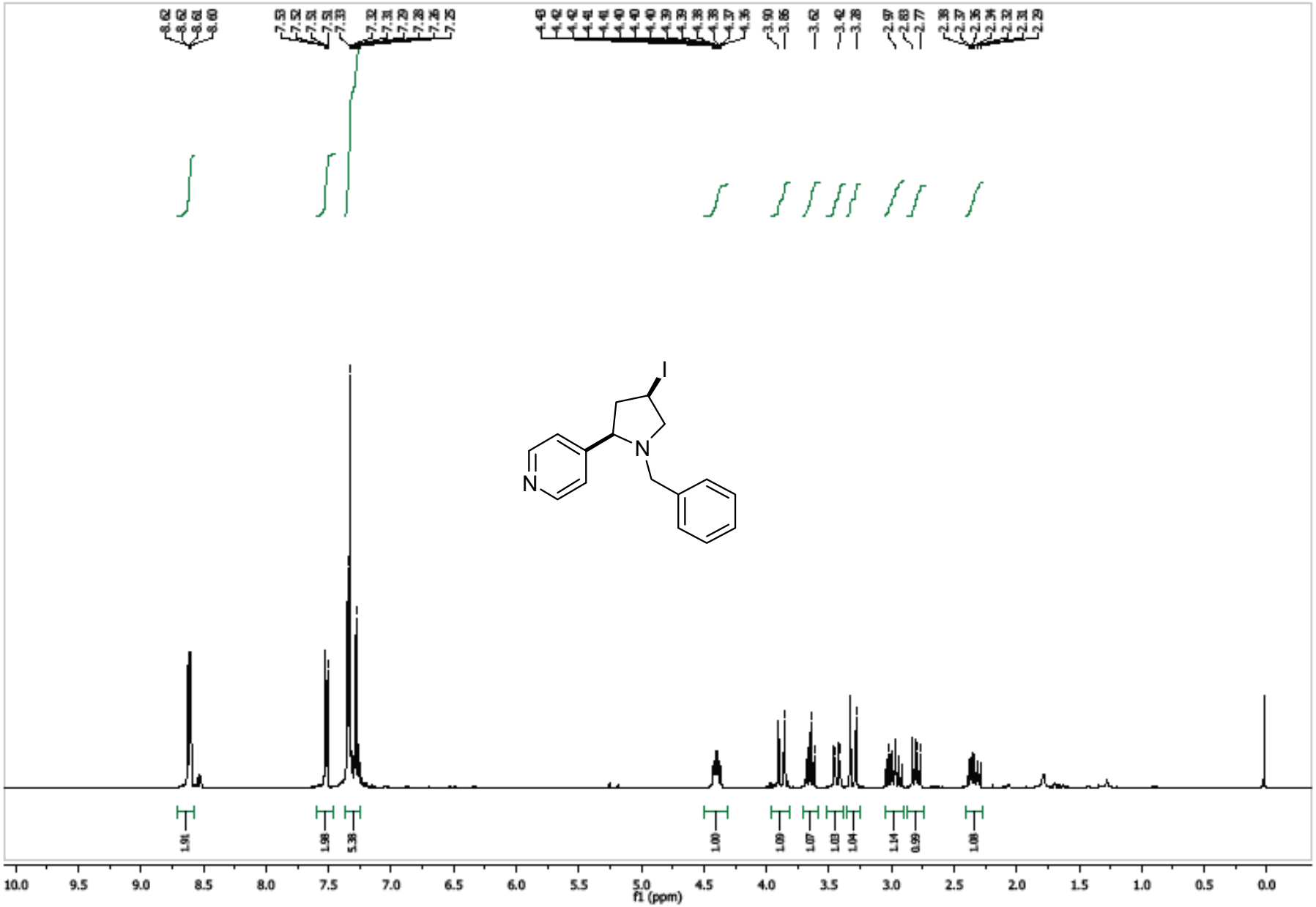
The existence of rotamers broadening some peaks cannot be denied at this stage, no dynamics arrested down to -60 °C



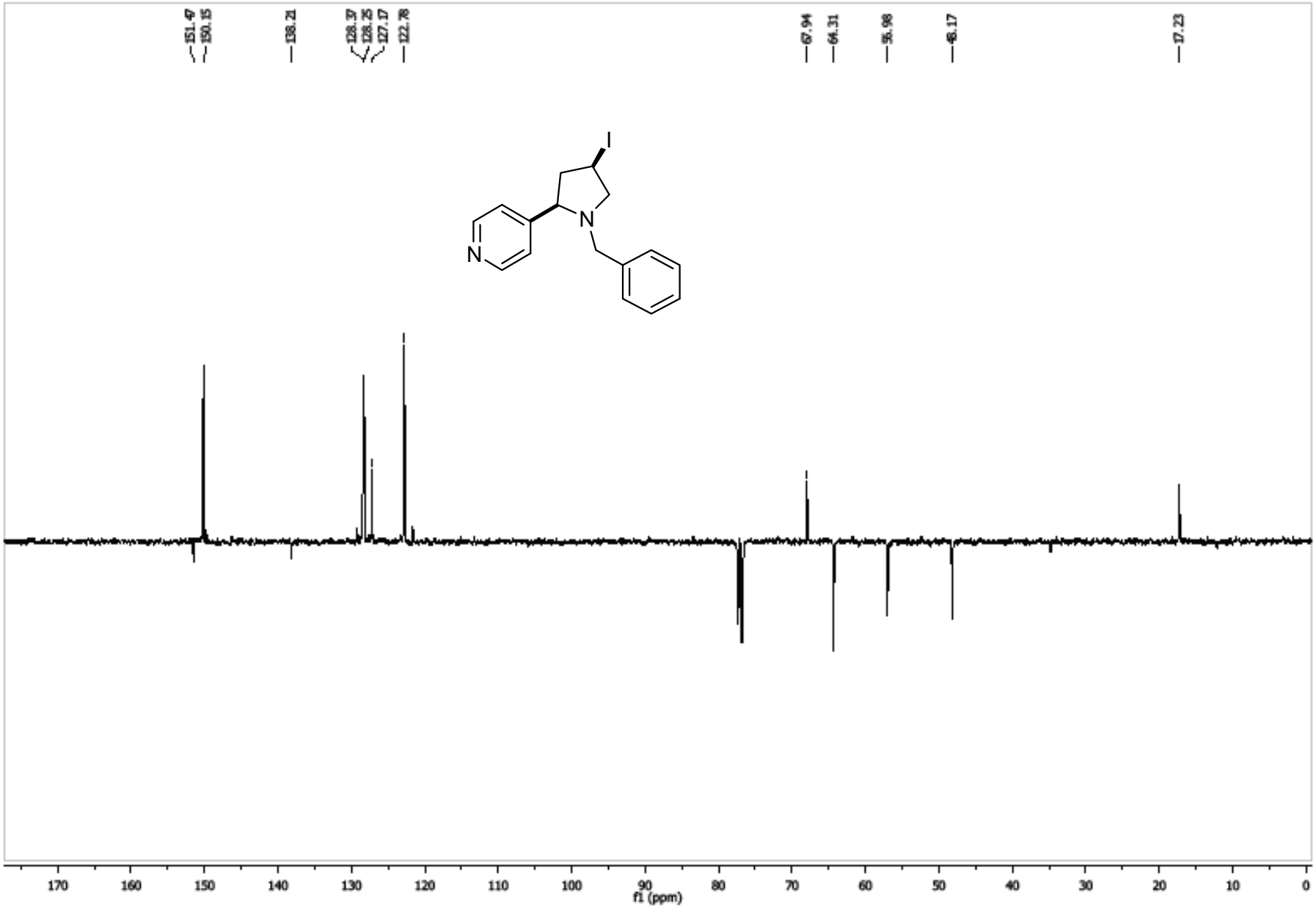
$^{13}C\{^{1}H\}$ NMR Spectrum (Pendant) of 3d



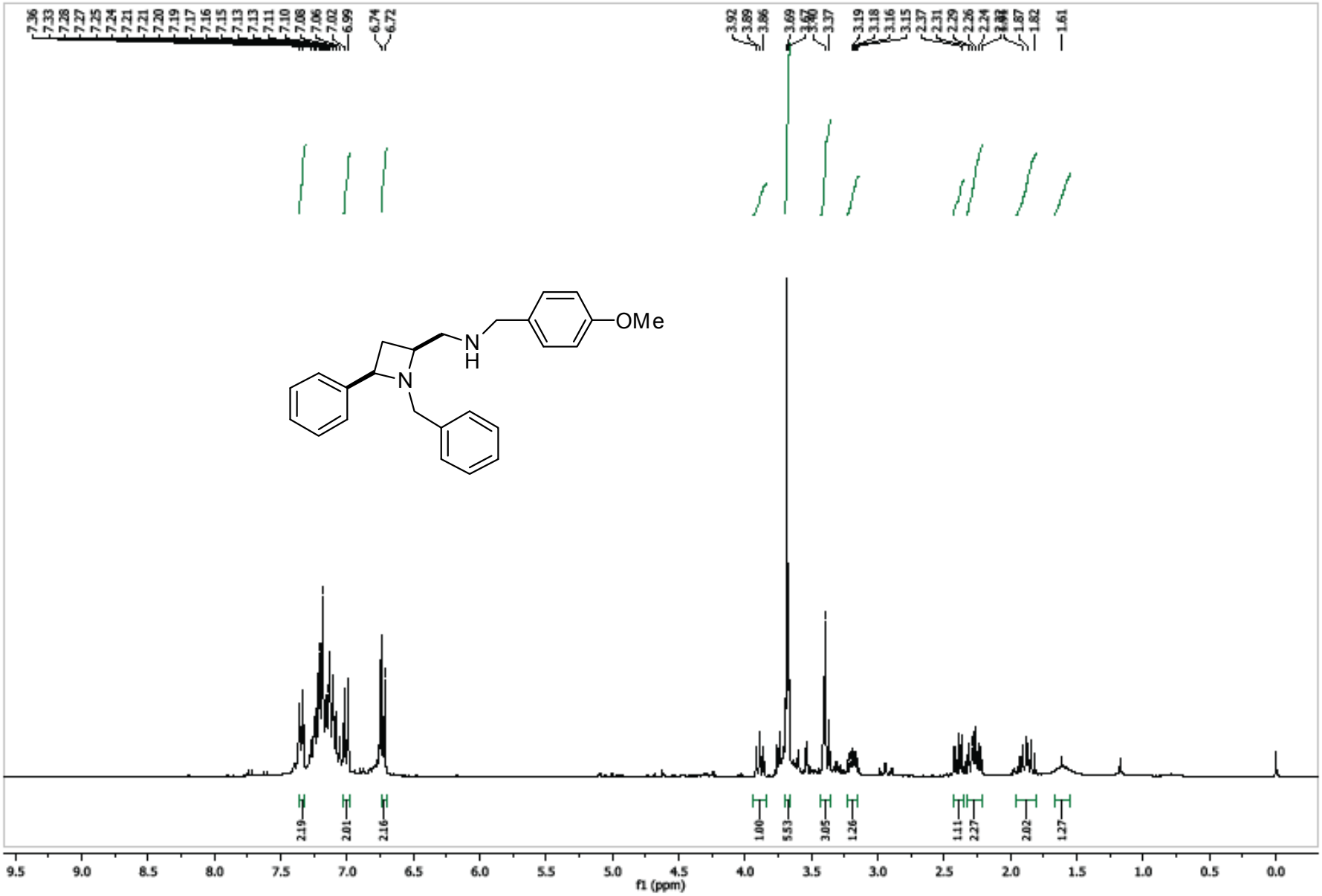
^{1}H NMR Spectrum of 3e



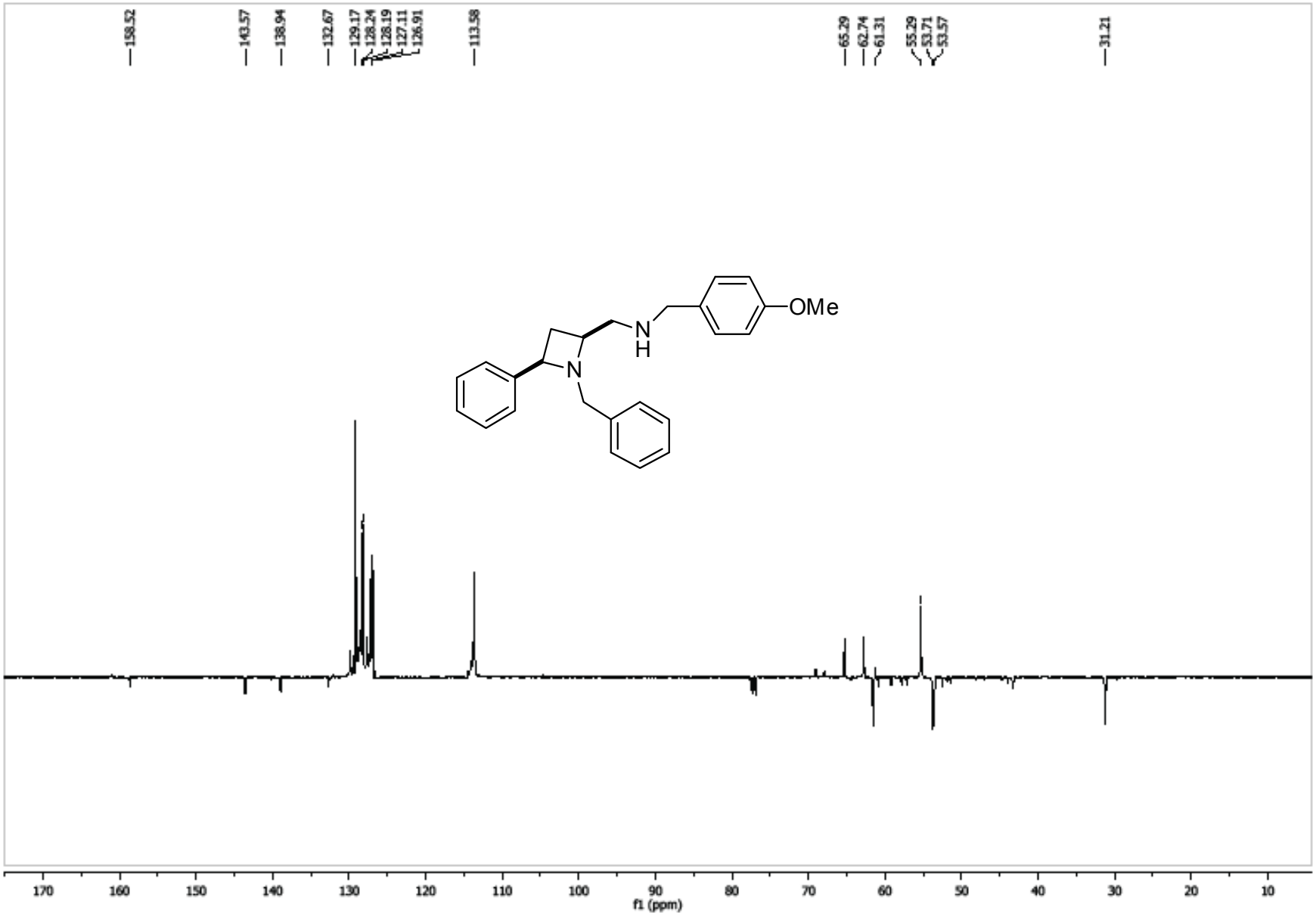
$^{13}C\{^{1}H\}$ NMR Spectrum (Pendant) of 3e



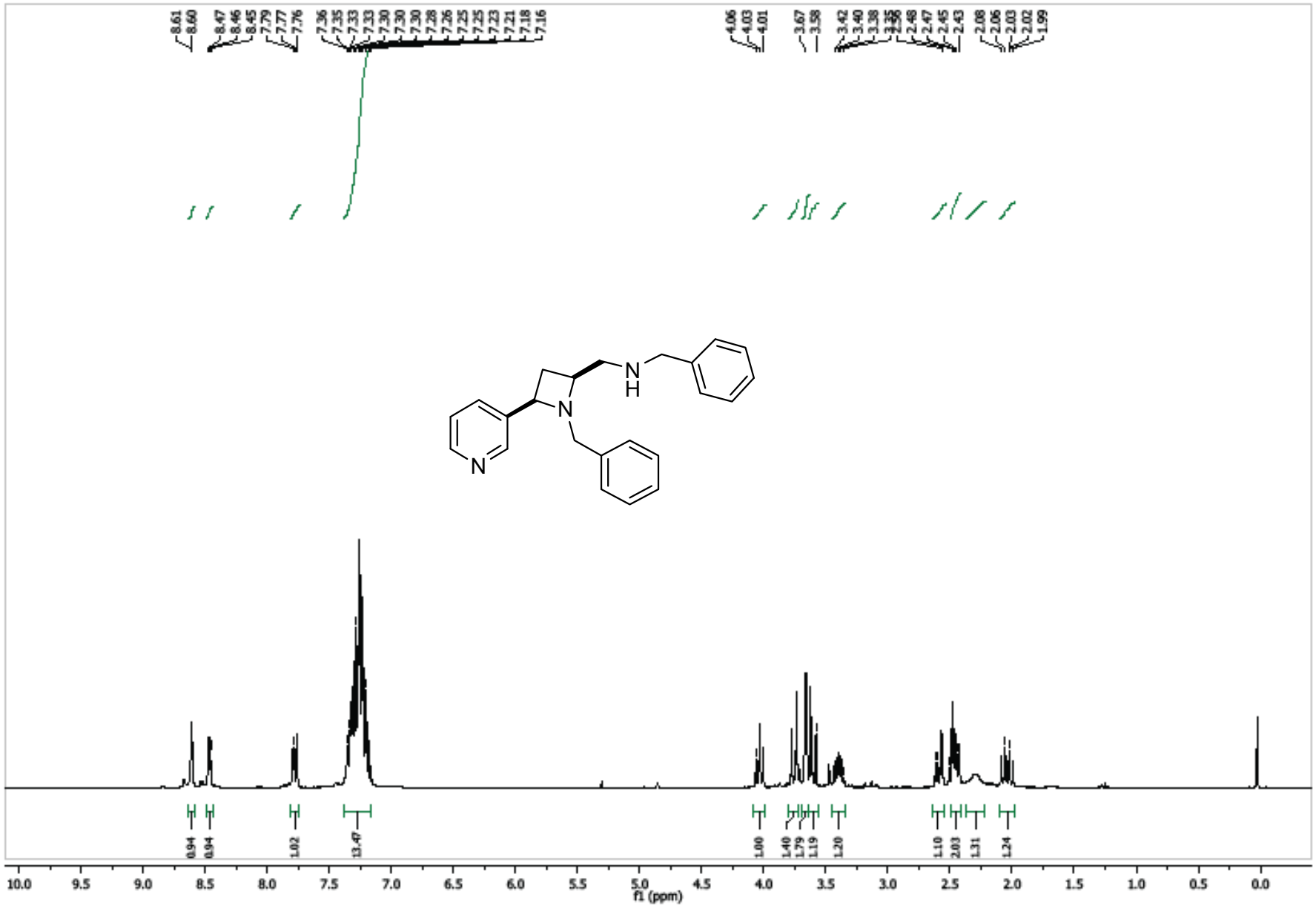
^{1}H NMR Spectrum of 4



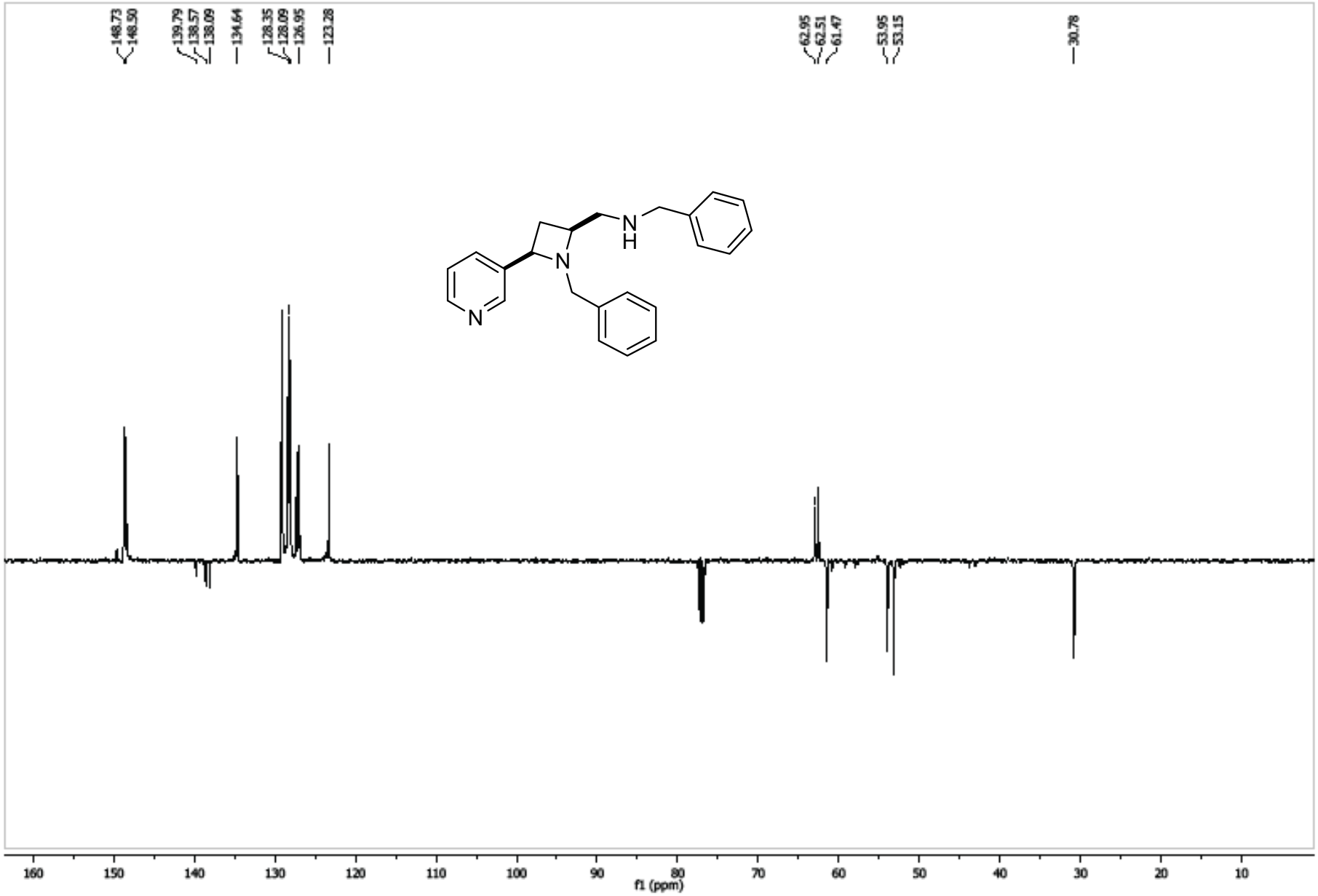
$^{13}C\{^{1}H\}$ NMR Spectrum (Pendant) of 4



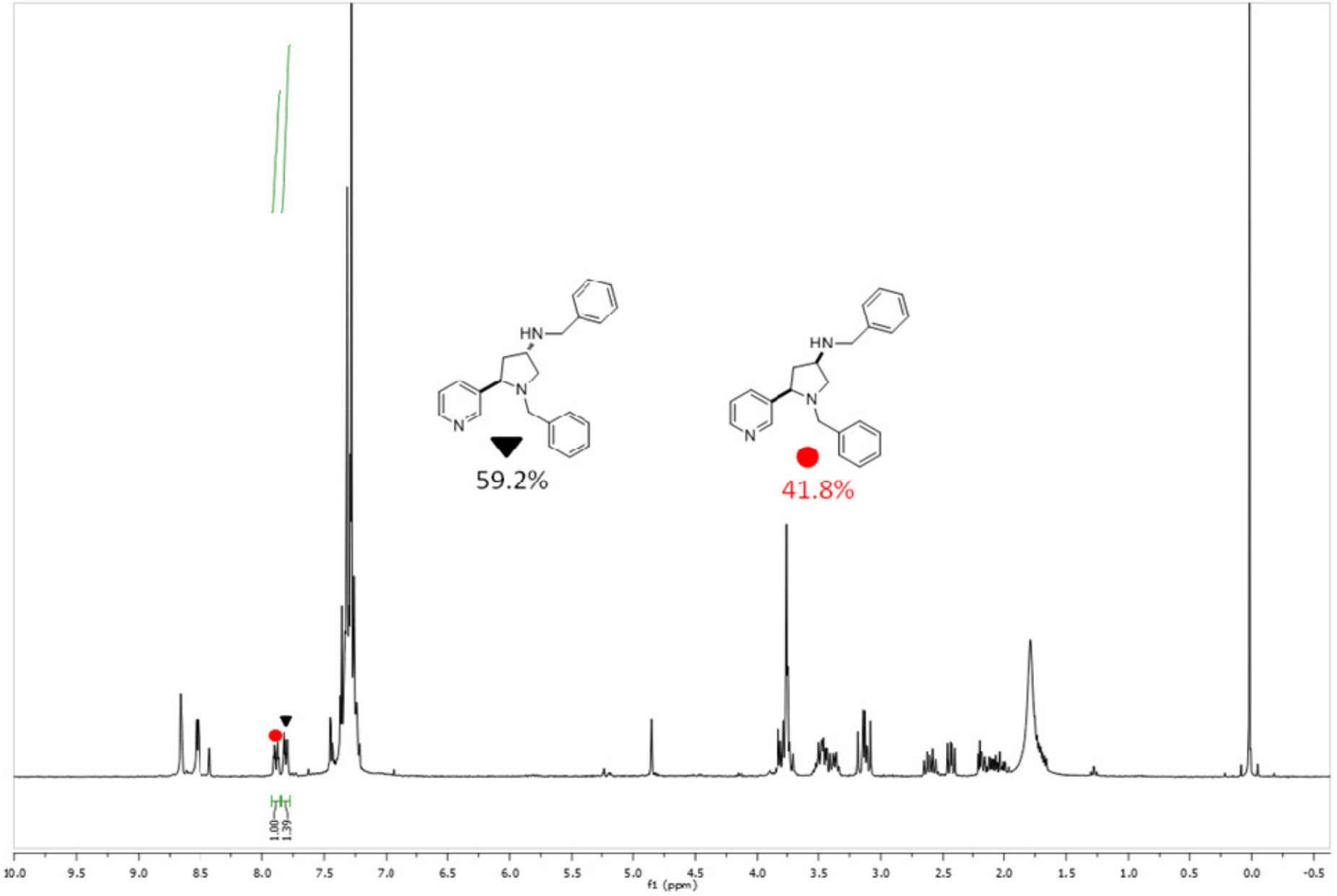
^{1}H NMR Spectrum of 5



$^{13}C\{^{1}H\}$ NMR Spectrum (Pendant) of 5

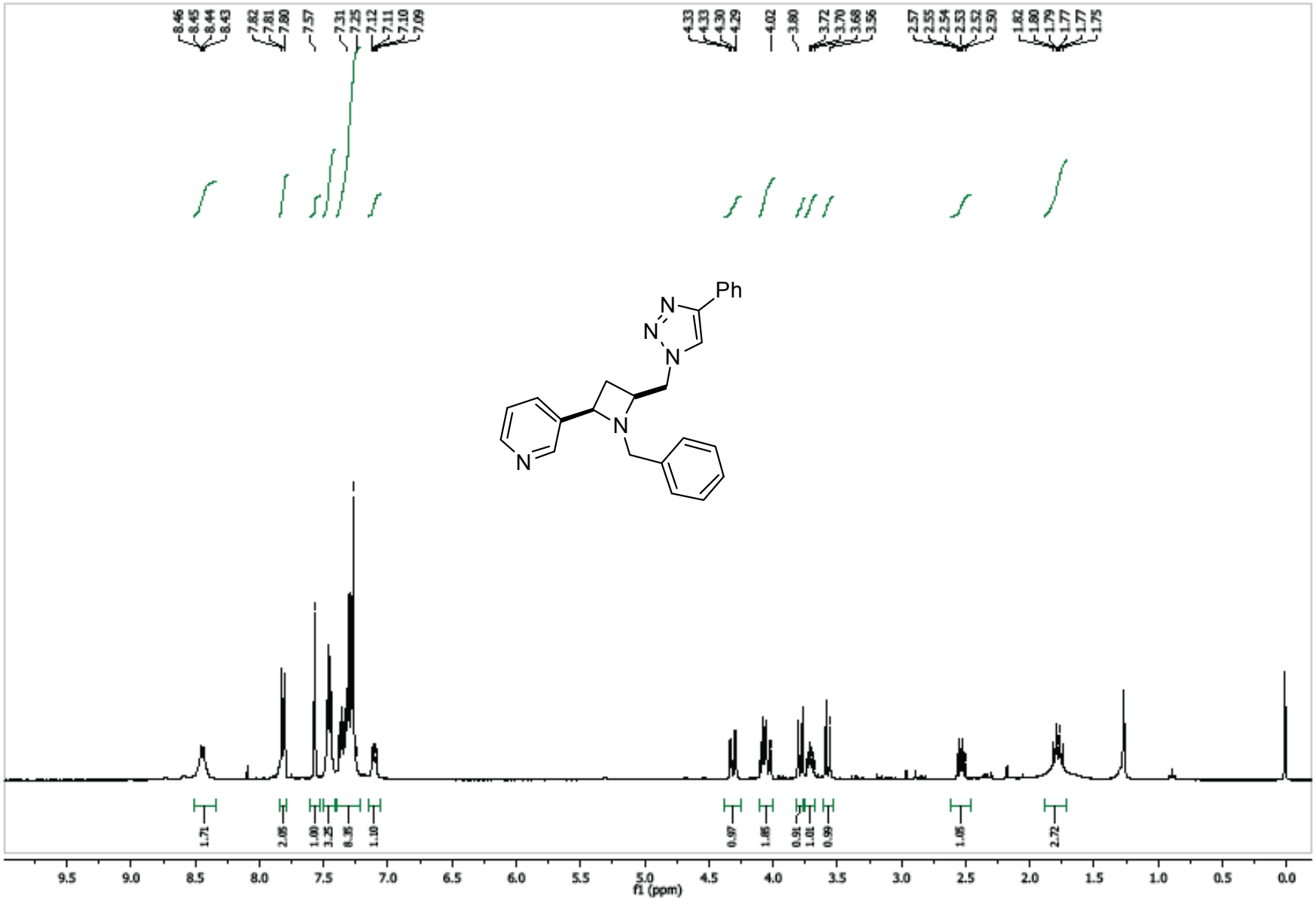


^{1}H NMR Spectrum of 6

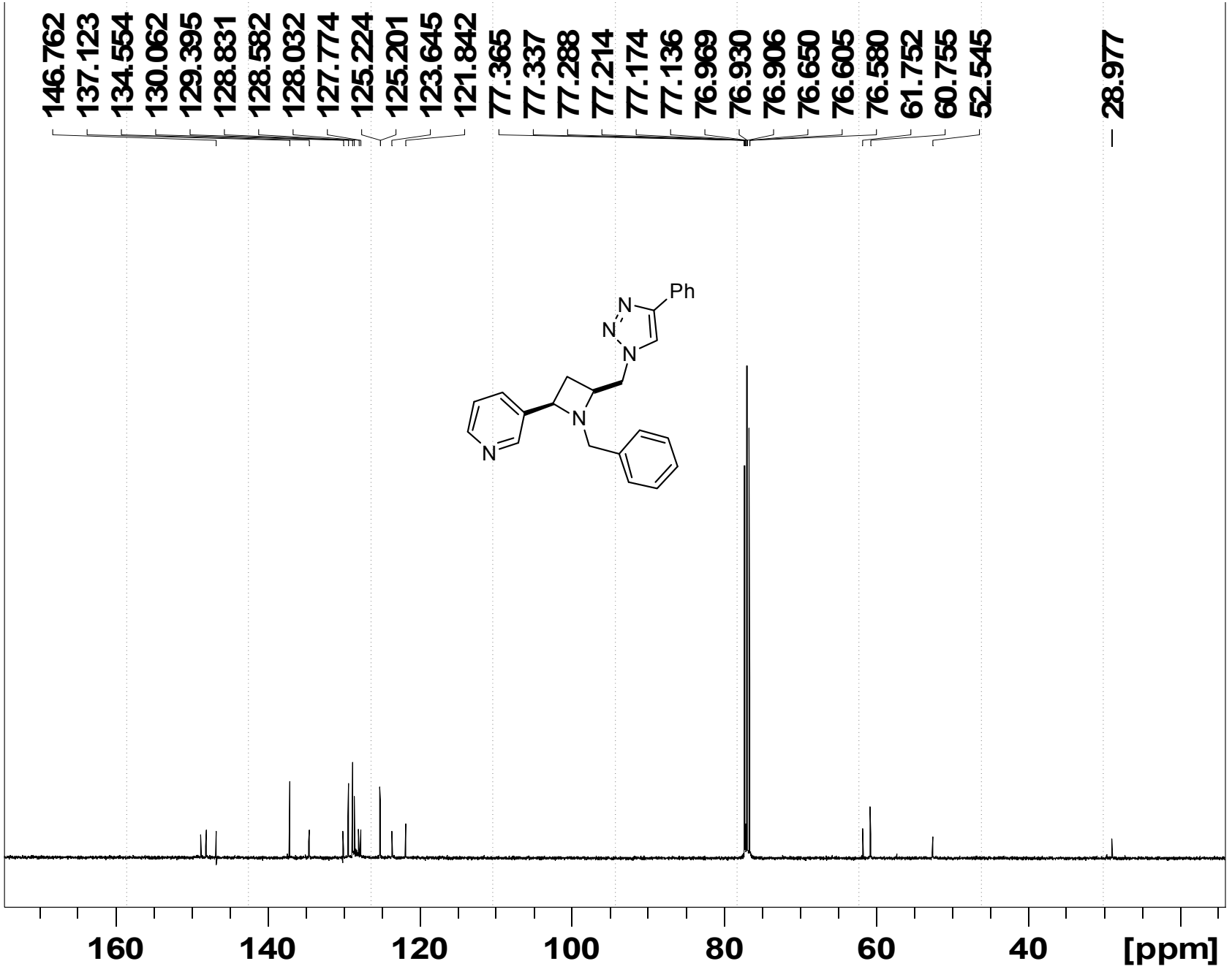


^{1}H NMR Spectrum of 7

The existence of rotamers broadening some peaks cannot be denied at this stage, no dynamics arrested down to -60 °C

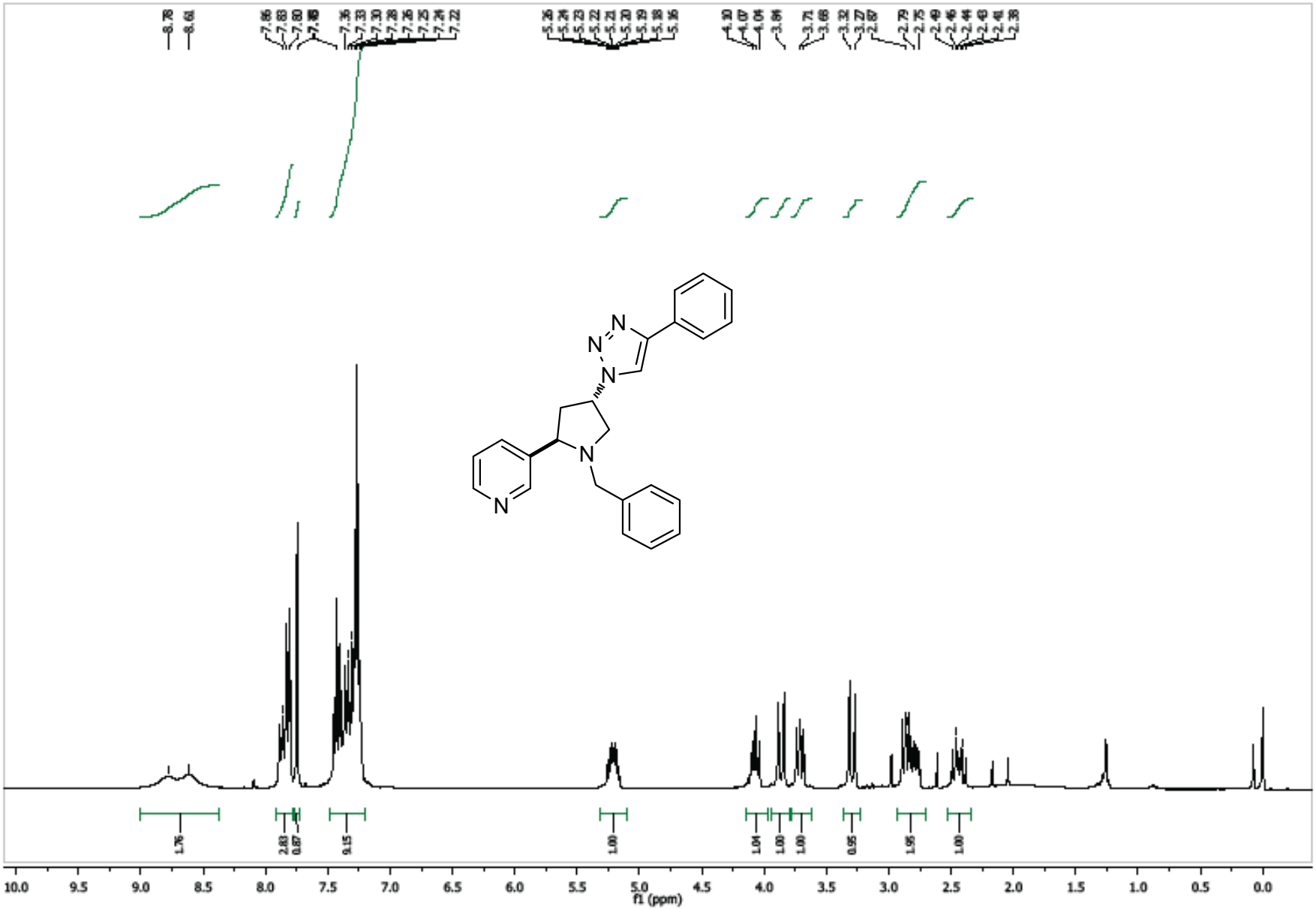


$^{13}C\{^{1}H\}$ NMR Spectrum of 7

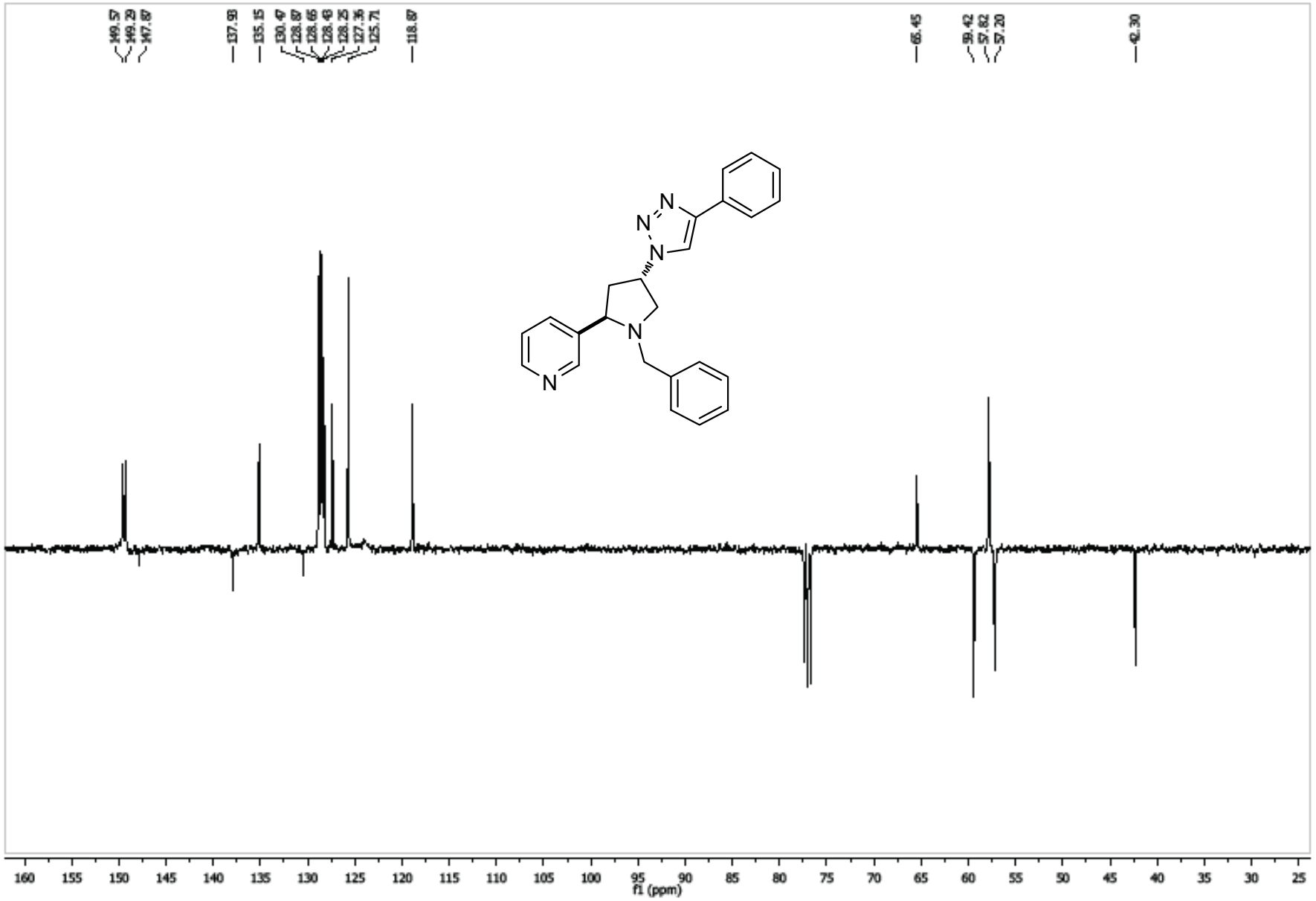


^{1}H NMR Spectrum of 8

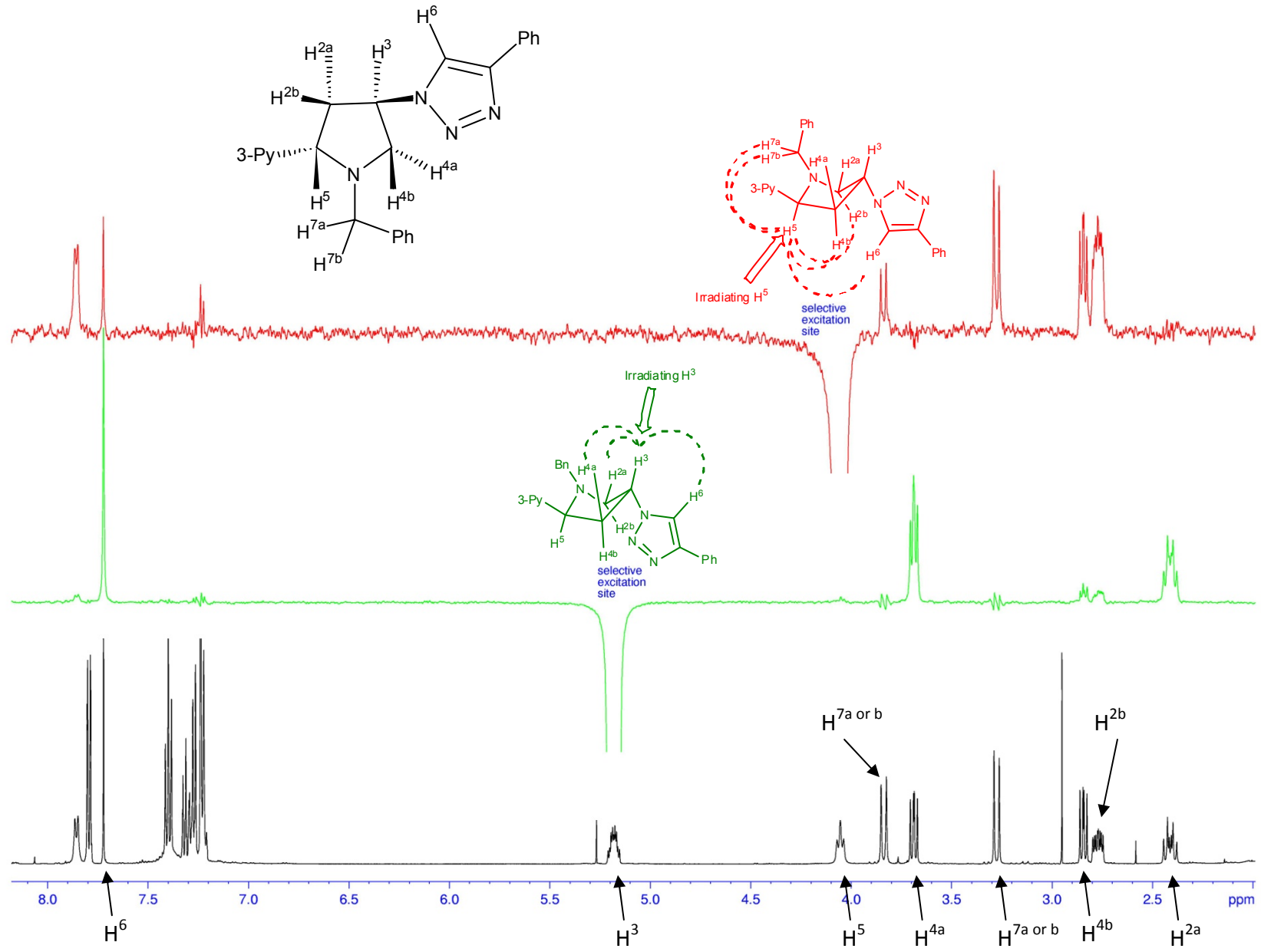
The existence of rotamers broadening some peaks cannot be denied at this stage, no dynamics arrested down to -60 °C



$^{13}C\{^{1}H\}$ NMR Spectrum (Pendant) of 8



nOe experiment confirming *trans* geometry of compound 8



X-Ray Crystallographic Information

Single Crystal Diffraction Data for cis-2c

$C_{18}H_{20}INO$, M_r = 393.25, light brown crystal, crystal dimensions: 0.70 x 0.45 x 0.12 mm, triclinic, space group: $P\ \bar{1}$, a = 10.6159 (3), b = 12.3314 (3), c = 13.4921 (3) Å, α = 81.7569 (15) °, β = 74.4479 (14)°, γ = 81.2906 (14)°, V = 1672.13 (7) Å^3, Z = 4, Z' = 2, ρ_{calcd} = 1.562 Mg/m^3, μ = 1.914 mm^{-1}, $\lambda_{Mo\text{-}K\alpha}$ = 0.71073 Å, T = 120 (2) K, $2\vartheta_{max}$ = 27.50°, 35064 reflections measured, 6641 observed reflections, R_1 = 0.0366 (observed reflections), *wR* = 0.1022 (all data), GOF = 1.149, largest diff. peak and hole: 1.500 and -1.591 e.Å^{-3}.

Single Crystal Diffraction Data for cis-3c

$C_{18}H_{20}IN$, M_r = 377.25, colourless crystal, crystal dimensions: 0.32 x 0.16 x 0.03 mm, monoclinic, space group: $P2_1/n$, a = 6.9828 (2), b = 9.0924 (5), c = 25.8129 (12) Å, β = 93.829 (3)°, V = 1635.21 (13) Å^3, Z = 4, Z' = 1, ρ_{calcd} = 1.532 Mg/m^3, μ = 1.949 mm^{-1}, $\lambda_{Mo\text{-}K\alpha}$ = 0.71073 Å, T = 120 (2) K, $2\vartheta_{max}$ = 27.48°, 18336 reflections measured, 2380 observed reflections, R_1 = 0.0503 (observed reflections), *wR* = 0.1240 (all data), GOF = 1.057, largest diff. peak and hole: 1.462 and -1.456 e.Å^{-3}.

General Remarks

The datasets were measured on a Bruker CCD diffractometer at the window of a Bruker FR591 rotating anode. The data collections were driven by COLLECT[1] and processed by DENZO.[2] Absorption corrections were applied using SADABS.[3] The structure was solved using ShelXS-97[4] and refined by a full-matrix least-squares procedure on F^2 in ShelXL-97.[4] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom. The CIFs for the crystal structure of **2c** and ***cis*-3c** are included as ESI to this report

References of Crystallography Section

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2 Z. Otwinowski, W. Minor in *Methods in Enzymology, Vol. 276* (Eds.: C. W. Carter, R. M. Sweet), Academic Press, New York, **1997**, pp. 307-326.

3 G. M. Sheldrick, SADABS. Bruker AXS Inc., Madison, Wisconsin (USA) **2007**.

4 G. M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112-122.