Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information

A bio-based click reaction leading to the dihydropyridazinone platform for nitrogen-containing scaffolds

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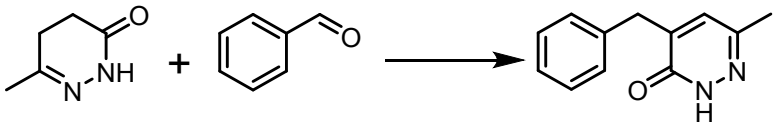
Chemicals. All reagents were used as received from commercial sources unless specified otherwise or prepared as described in the literature. Levulinic acid (LA) (99.0%), ethyl levulinic acid (99.0%), phenylhydrazine (98.0%), Raney®-Nickel (50 um), Raney®-Cobalt (50 um), ethanol (99.7%) were purchased from Macklin Biochemical Co., Ltd. (Shanghai, China). Hydrazine hydrate (80.0%) was purchased from Tianjinoubokai Chemical Co., Ltd (Tianjin, China). Dodecanoic (99.0%) was purchased from Alfa Aesar Co. Ltd. (Shanghai, China).

DHMP Crystallization. 1.0 mmol LA, 1.25 mmol hydrazine hydrate (NH_2-NH_2, 80%) and 3 mL ethanol were added into a 25 mL glass tube, and stirred 10 min at room temperature. Then, the solution was transferred in a petri dish and placed in fume cupboard for natural volatile. After the ethanol was completely evaporated, needle-like white DHMP crystals were obtained. Finally, the DHMP crystals were collected with tweezers and stored at a brown reagent bottle with seal.

GC analysis. DHMP, MPD, DMP and BMP were quantified by this GC (Agilent 8860 GC System) test procedure, and GC equipped with a HP-5 column. After the reaction, the internal standard was added into the reaction mixture, then the GC test was carried out after dilution with ethanol. The following programmed temperature was used in the analysis: 100 ^oC (3 min)-5 ^oC /min - 220 ^oC (10 min). The carrier gas was N_2 and the split ratio was 1:20.

Preparation of DMP. The preparation of pure BMP referred to the synthetic method from Giovannoni et al[1]. Typically, 1.39 mmol of DHMP and 1.39 mmol of benzaldehyde were dissolved in ethanol containing 5% KOH (w/v). Then, the mixture was refluxed under stirring at 90 ^oC for 3 h. After cooling to room temperature, the mixture was concentrated in vacuo, diluted with ice-cold water (10 mL), and acidified with 2 N HCl. The obtained solution was extracted with CH_2Cl_2

three times. Finally, column chromatography was used to purify the product (cyclohexane/ethyl acetate=3:1).



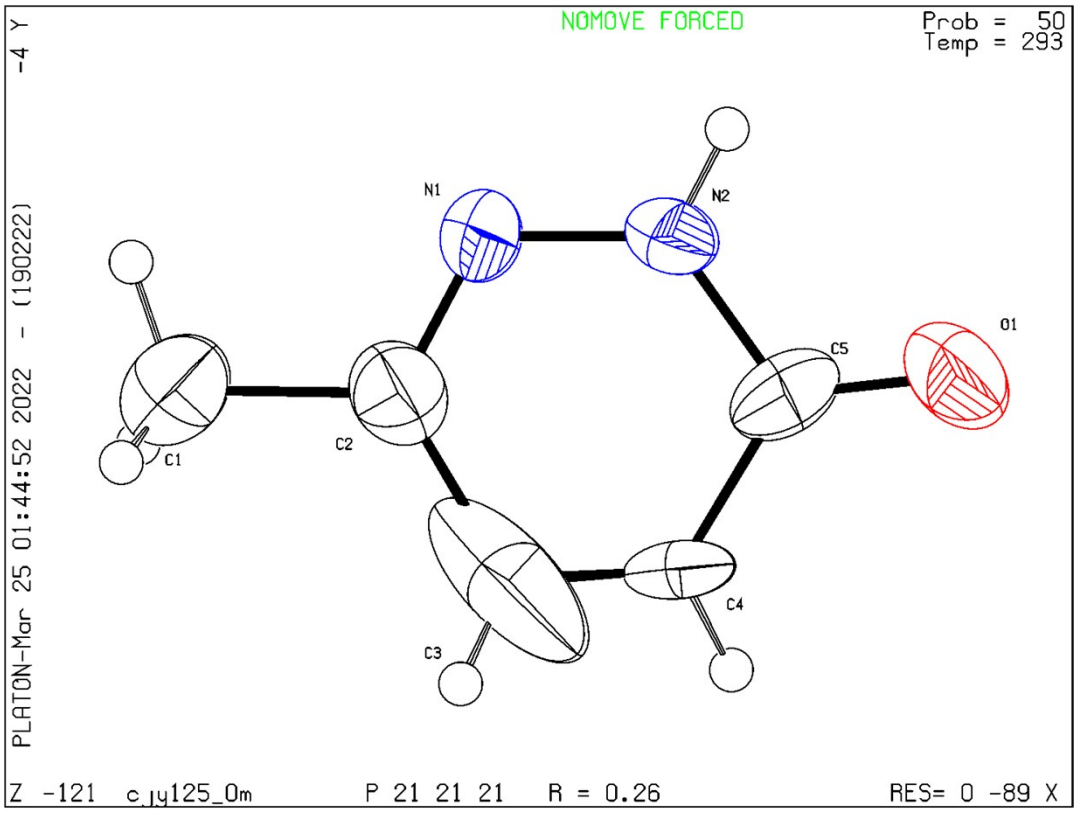


Fig. S1. X-ray structure of DHMP. The data were collected on a Bruker D8 venture PHOTON100 CMOS diffractometer with Mo sealed tube.

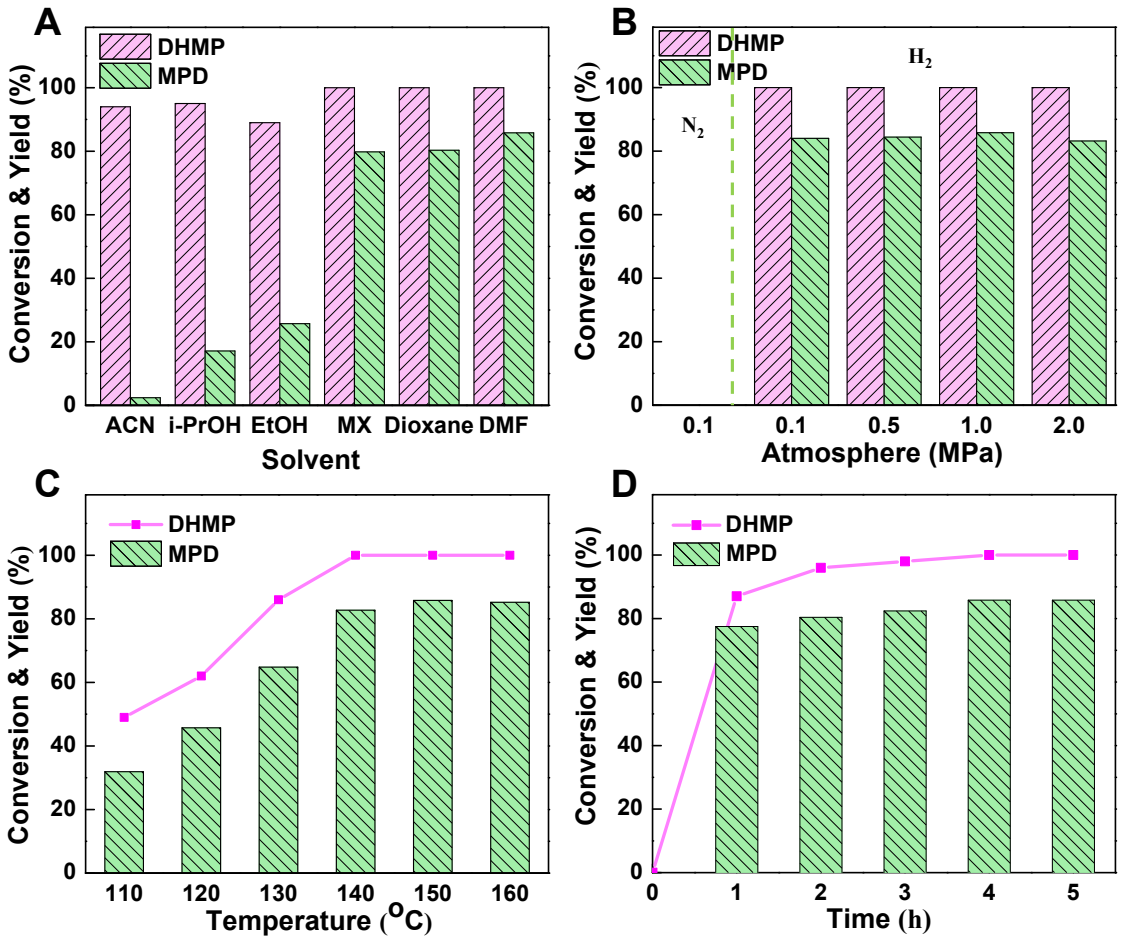


Fig. S2. Influences of (A) solvent (B) gas pressure, (C) temperature, and (D) time on the reductive denitrification of DHMP to MPD. Reaction conditions: (A) 0.5 mmol DHMP, 200 mg Raney Ni, 10 mL solvent, 1 MPa H_2, 150 °C, 4 h; (B) 0.5 mmol DHMP, 200 mg Raney Ni, 10 mL DMF, 0.1-2.0 MPa H_2 (or 1 bar N_2), 150 °C, 4 h; (C) 0.5 mmol DHMP, 200 mg Raney Ni, 10 mL DMF, 1 MPa H_2, 4 h, and temperature at 110-160 °C; (D) 0.5 mmol DHMP, 200 mg Raney Ni, 10 mL DMF, 1 MPa H_2, 150 °C, and time at 1-5 h.

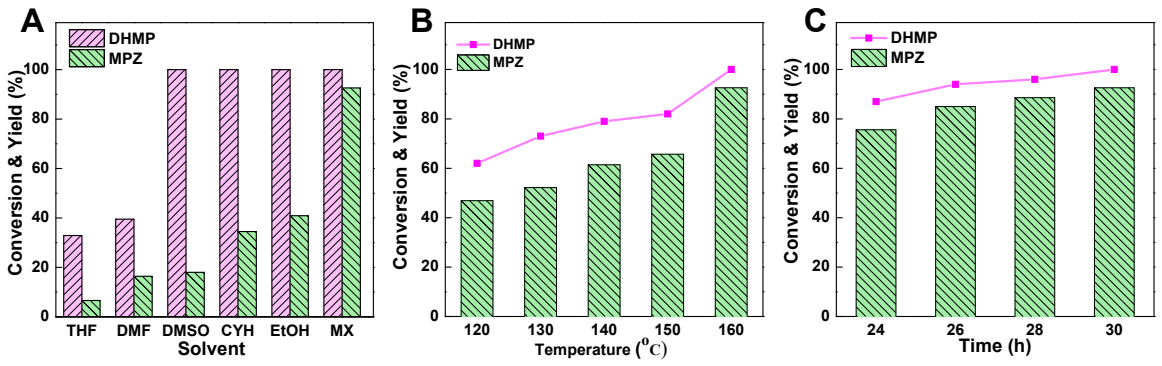


Fig. S3. Influences of (A) solvent, (B) temperature, and (C) time on the dehydrogenation of DHMP to MPZ. Reaction conditions: (A) 0.2 mmol DHMP, 30 mg Pd/C, 3 mL solvent, 1 bar air, 160 °C, 30 h; (B) 0.2 mmol DHMP, 30 mg Pd/C, 3 mL m-xylene, 1 bar air, 30 h, and temperature at 120-160 °C; (C) 0.2 mmol DHMP, 30 mg Pd/C, 3 mL m-xylene, 1 bar air, 160 °C and time at 24-30 h.

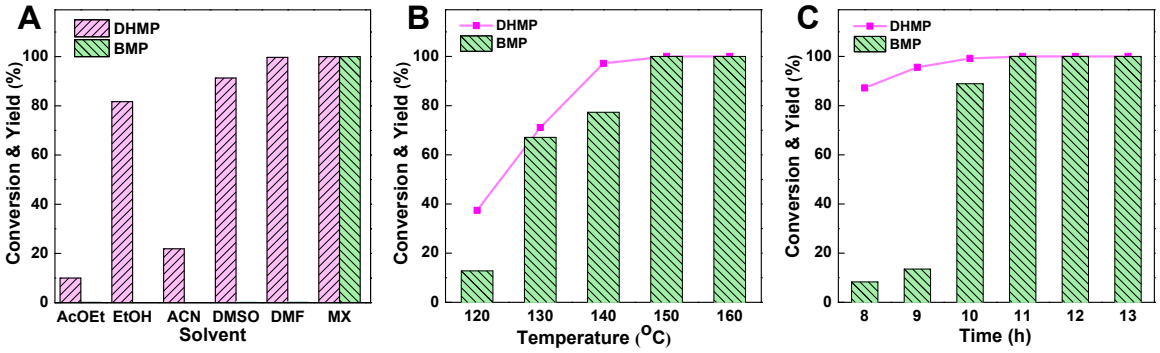


Fig. S4. Influences of (A) solvent, (B) temperature, and (C) time on the hydroxyalkylation of DHMP to BMP. Conditions: (A) 0.2 mmol DHMP, 0.2 mmol benzaldehyde, 100 mg CaO, 3 mL solvent, 1 bar N_2, 150 °C, 11 h; (B) 0.2 mmol DHMP, 0.2 mmol benzaldehyde, 100 mg CaO, 3 mL m-xylene, 1 bar N_2, 150 °C, and time at 8-13 h; (C) 0.2 mmol DHMP, 0.2 mmol benzaldehyde, 100 mg CaO, 3 mL m-xylene, 1 bar N_2, 11 h and temperature at 120-160 °C.

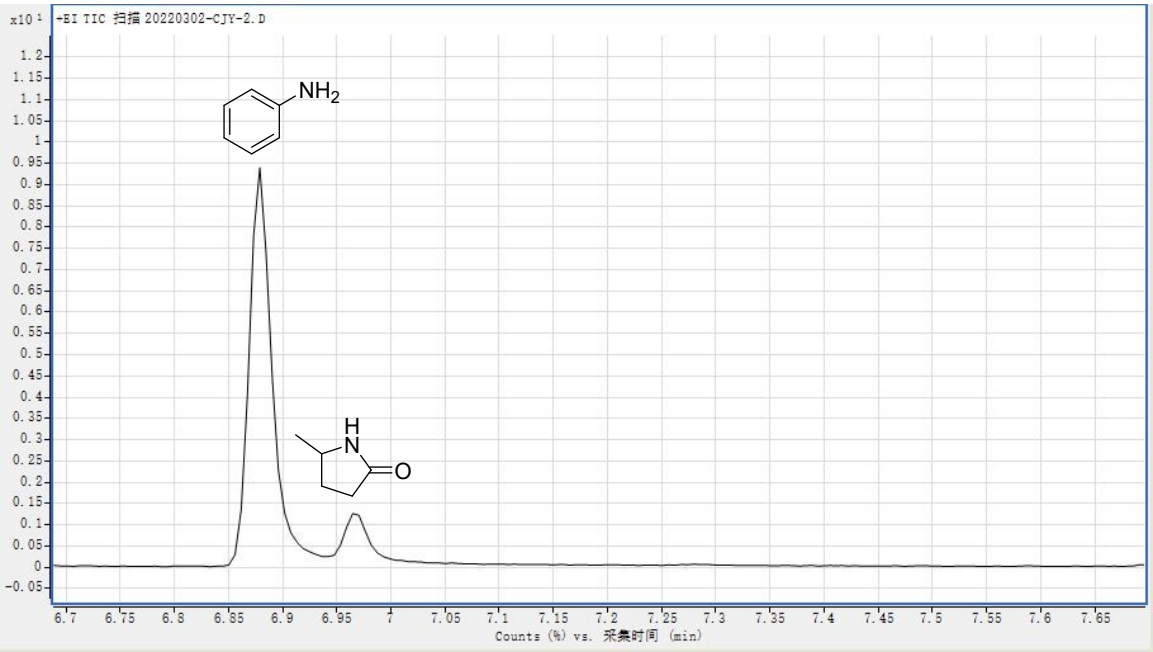


Fig. S5. Product distribution of 6-methyl-2-phenyl-4,5-dihydropyridazin-3 (2H)-one hydrogenation reaction detected by GC-MS. Reaction conditions: 0.3 mmol 6-methyl-2-phenyl-4,5-dihydropyridazin-3 (2H)–one, 200 mg Raney Ni, 10 mL DMF, 3 MPa H_2, 160 ^oC, 8 h.

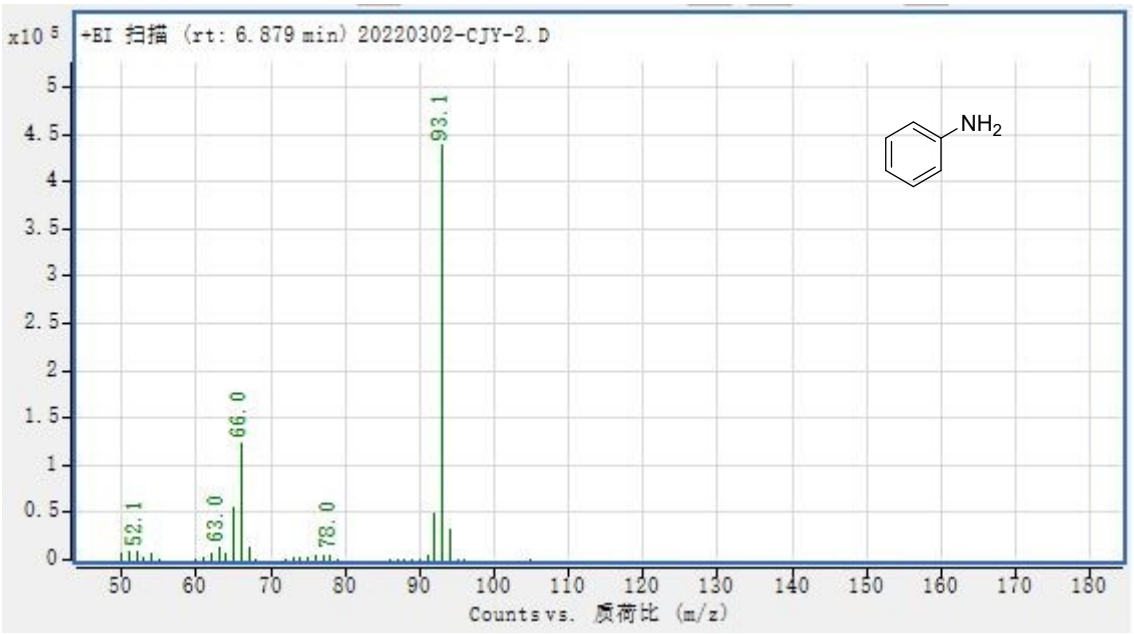


Fig. S6. Mass spectrogram of aniline from the results in Fig. S5.

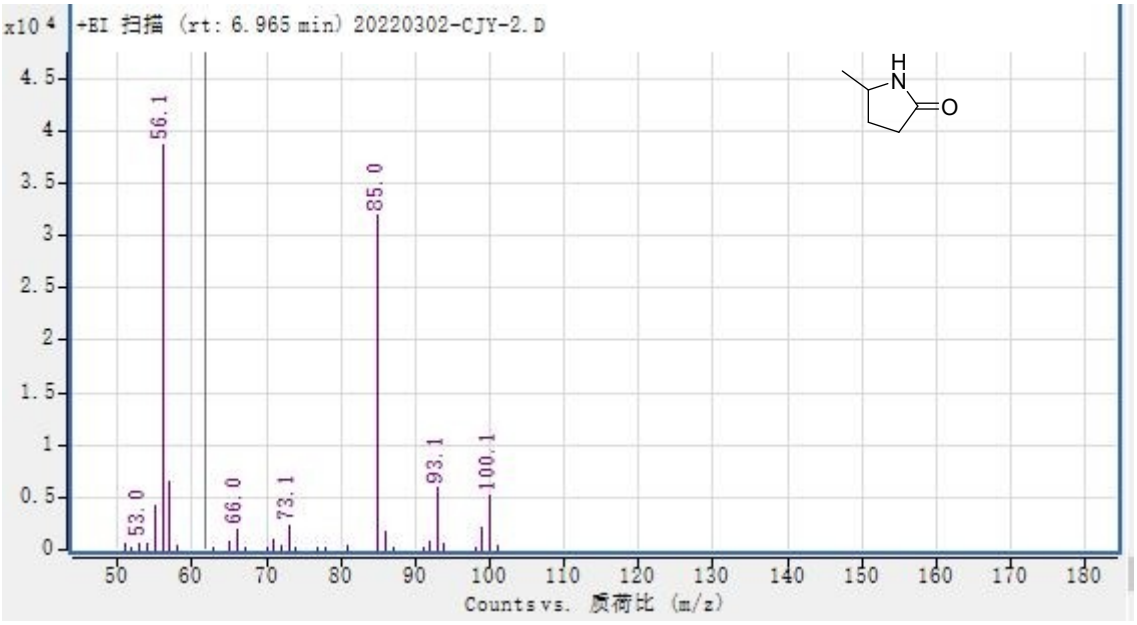


Fig. S7. Mass spectrogram of MPD from the results in Fig. S5.

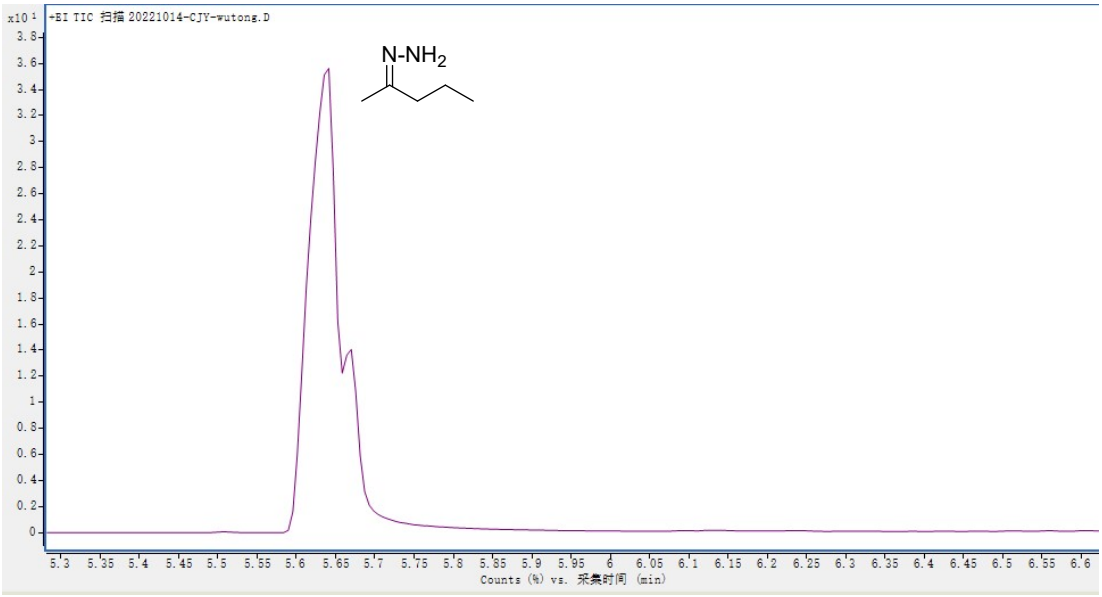


Fig. S8. Product distribution of condensation of 2-pentanone with hydrazine hydrate. Reaction conditions: (A) 1 mmol substrate, 1.5 mmol hydrazine hydrate, 10 mL ethanol, room temperature, 100 min.

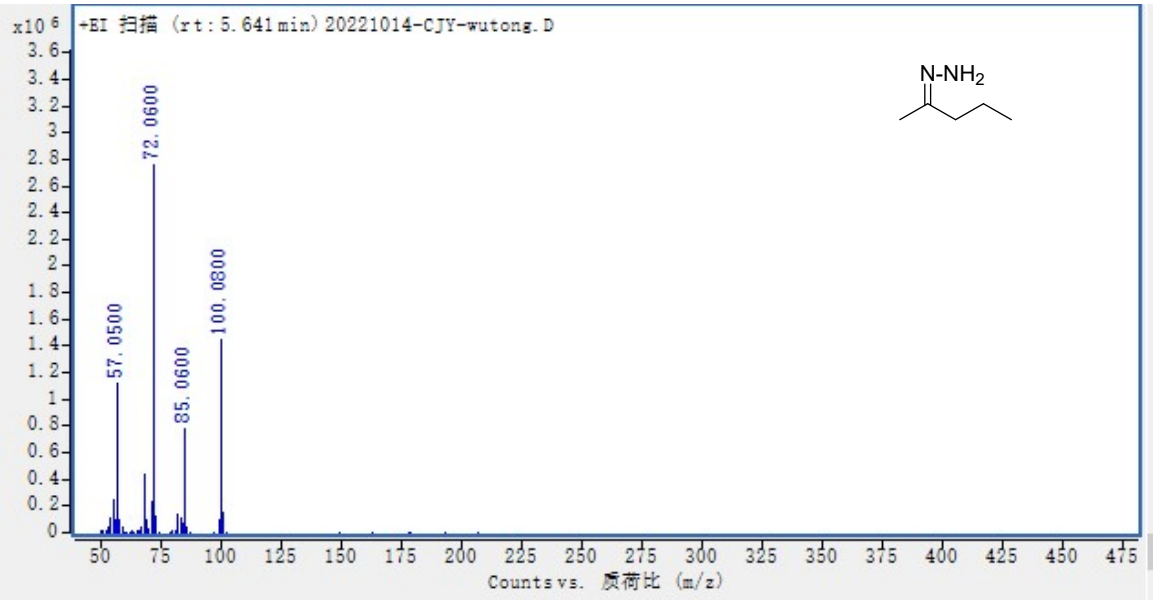


Fig. S9. Mass spectrogram of (Z)-pentan-2-ylidenehydrazine from the results in Fig. S8.

Table S1. Summary of click reactions

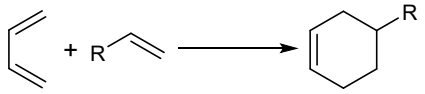
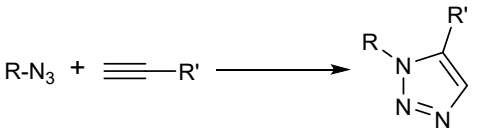
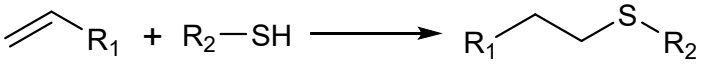
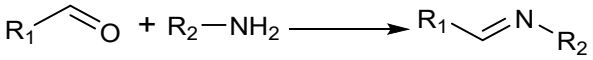
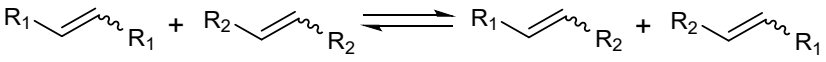
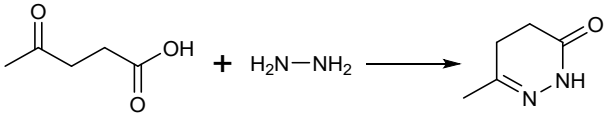
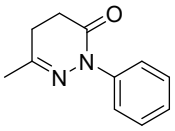
Entry	Click reaction	Ref
	Diels–Alder reaction	
1		**2**
	Cu-catalyzed azide–alkyne cycloaddition	
2		**3**
	Thiol-Michael addition reaction	
3		**4**
	Oxime click chemistry	
4		**5**
	Olefin cross-metathesis	
5		**6**
6		**This work**

Table S2. 6-Methyl-2-phenyl-4, 5-dihydropyridazin-3(2H)-one hydrogenation

Entry	Substrate	Condition	Conversion (%)	Aniline Yield (%)	MPD Yield (%)
1		160 °C，8 h，3 MPa H_2	56.9%	47.2%	20.9%

Reaction condition: 0.3 mmol substrate, 200 mg Raney Ni.

Table S3. X-ray analysis data of DHMP

Bond precision:	C-C = 0.0215 A		Wavelength= 0.71076
Cell:	a= 6.4175(15)	b= 6.8982(18)	c= 15.622(4)
	alpha=90	beta=90	gamma=90
Temperature: 293 K			

	Calculated	Reported
Volume	691.6(3)	691.6(3)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C5 H6 N2 O	4(C5 H6 N2 O)
Sum formula	C5 H6 N2 O	C5 H8 N2 O
Mr	110.12	112.13
Dx, g cm-3	1.058	0.269
Z	4	1
Mu (mm-1)	0.077	0.019
F000	232.0	60.0
F000’	232.09	
h, k, l max	8, 8, 20	8, 8, 20
Nref	1588[952]	1587
Tmin, Tmax	0.994, 0.996	0.672, 0.746
Tmin’	0.991	

Correction method= # Reported T Limits: Tmin=0.672 Tmax=0.746 AbsCorr = MULTI-SCAN

Data completeness= 1.67/1.00 Theta(max)= 27.539

R(reflections)= 0.2599(1224) wR2(reflections)= 0.6314(1587)

S = 3.124 Npar= 74

References

[1] M. P. Giovannoni, I. A. Schepetkin, A. Cilibrizzi, L. Crocetti, A. I. Khlebnikov, C. Dahlgren, A. Graziano, V. Dal Piaz, L. N. Kirpotina, S. Zerbinati, C. Vergelli and M. T. Quinn, *Eur. J. Med. Chem.*, 2013, **64**, 512-528.

[2] O. Diels and K. Alder, *Justus Liebig's Annalen der Chemie*, 1928, **460**, 98-122.

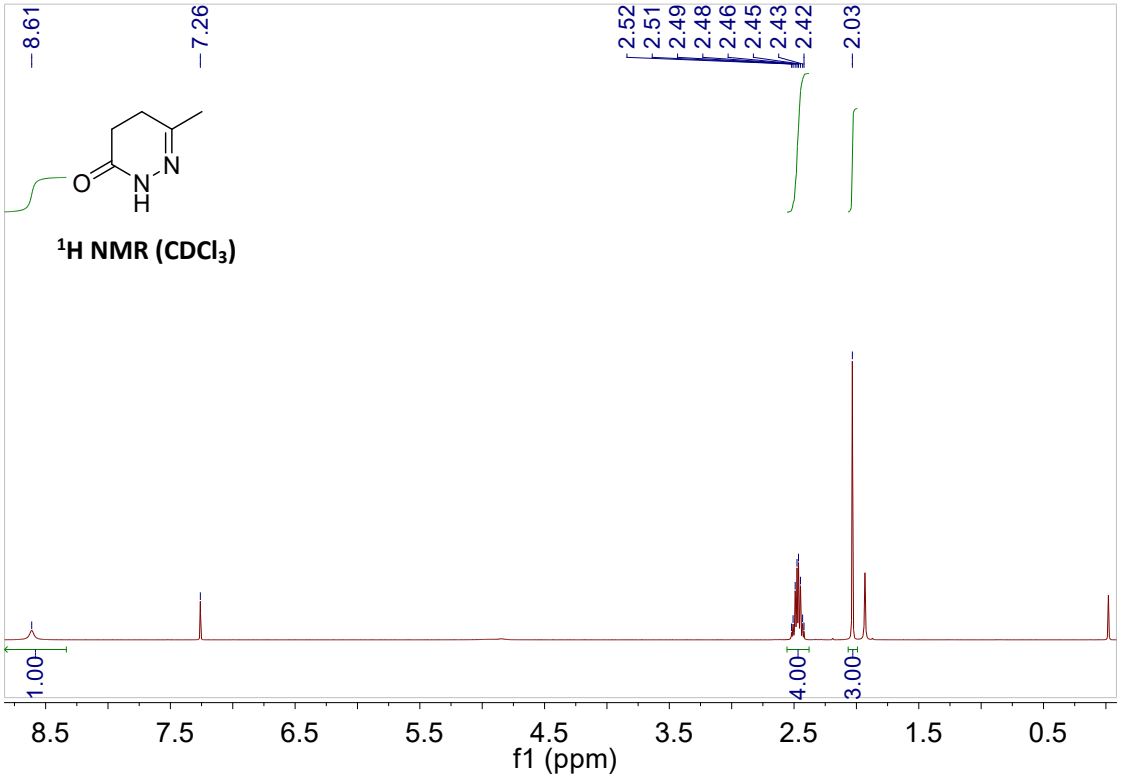
[3] E. Lallana, R. Riguera and E. Fernandez-Megia, *Angew. Chem. Int. Ed. Engl*., 2011, **50**, 8794-804.

[4] A. Michael, *Am. Chem. J.*, 1887, **9**, 115.

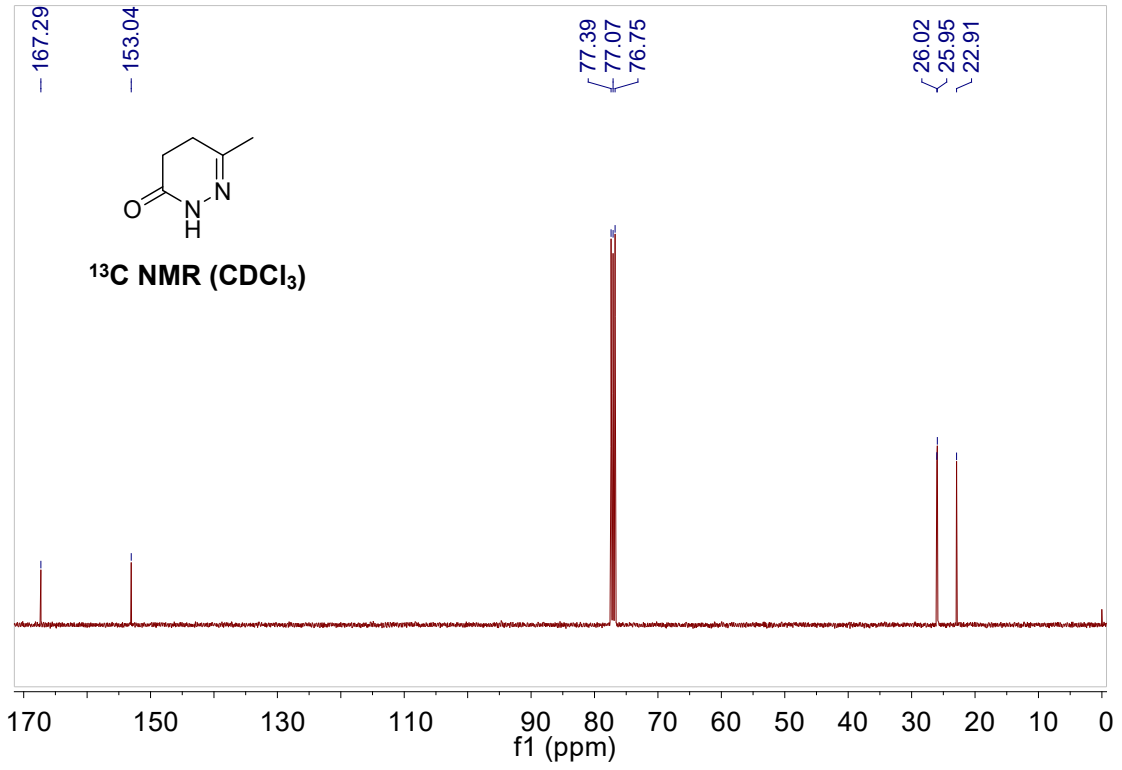
[5] R. Novoa-Carballal and A. H. Muller, *Chem. Commun. (Camb)*, 2012, **48**, 3781-3.

[6] K. Malzahn, F. Marsico, K. Koynov, K. Landfester, C. K. Weiss and F. R. Wurm, *ACS Macro. Lett.,* 2014, **3**, 40-43.

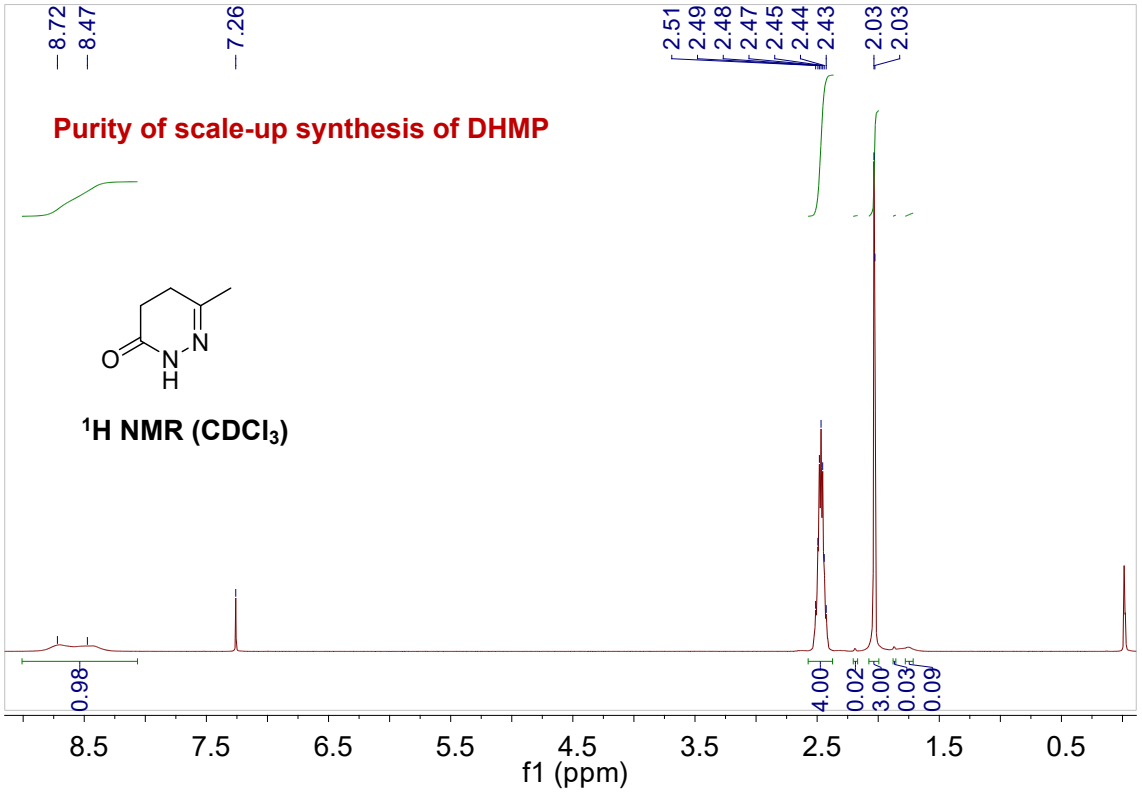
NMR spectra

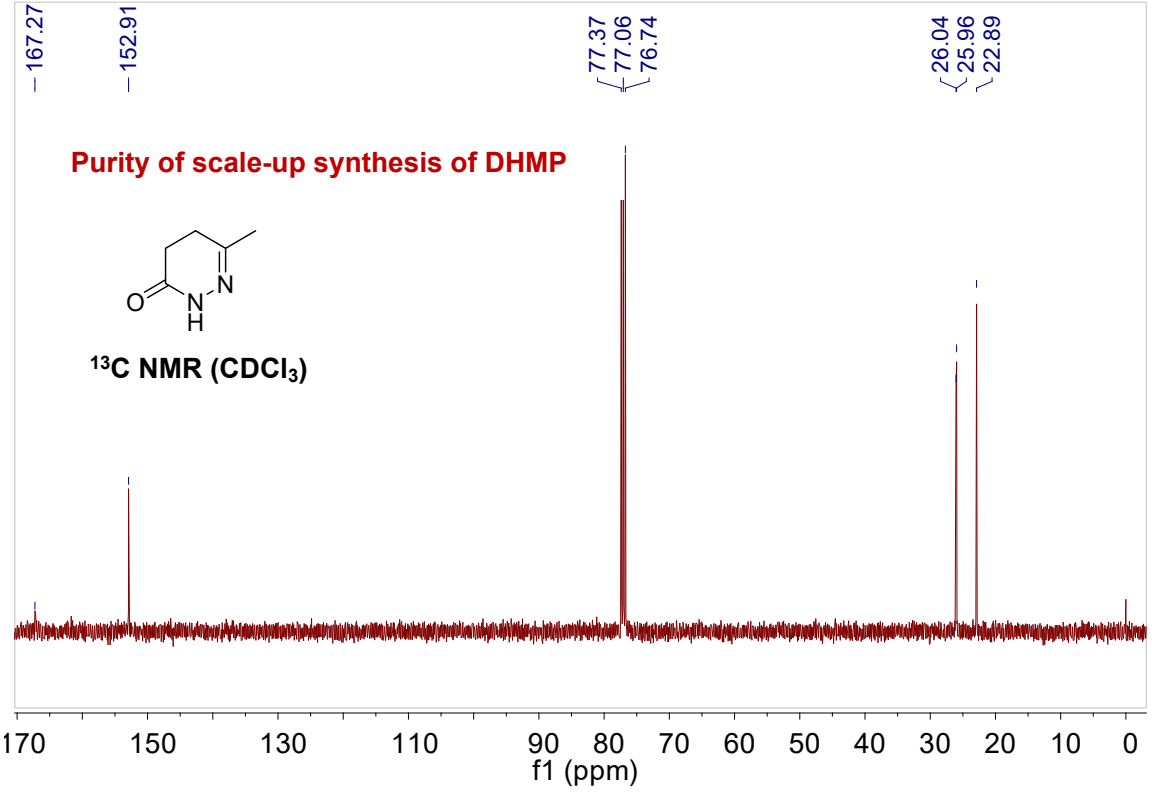


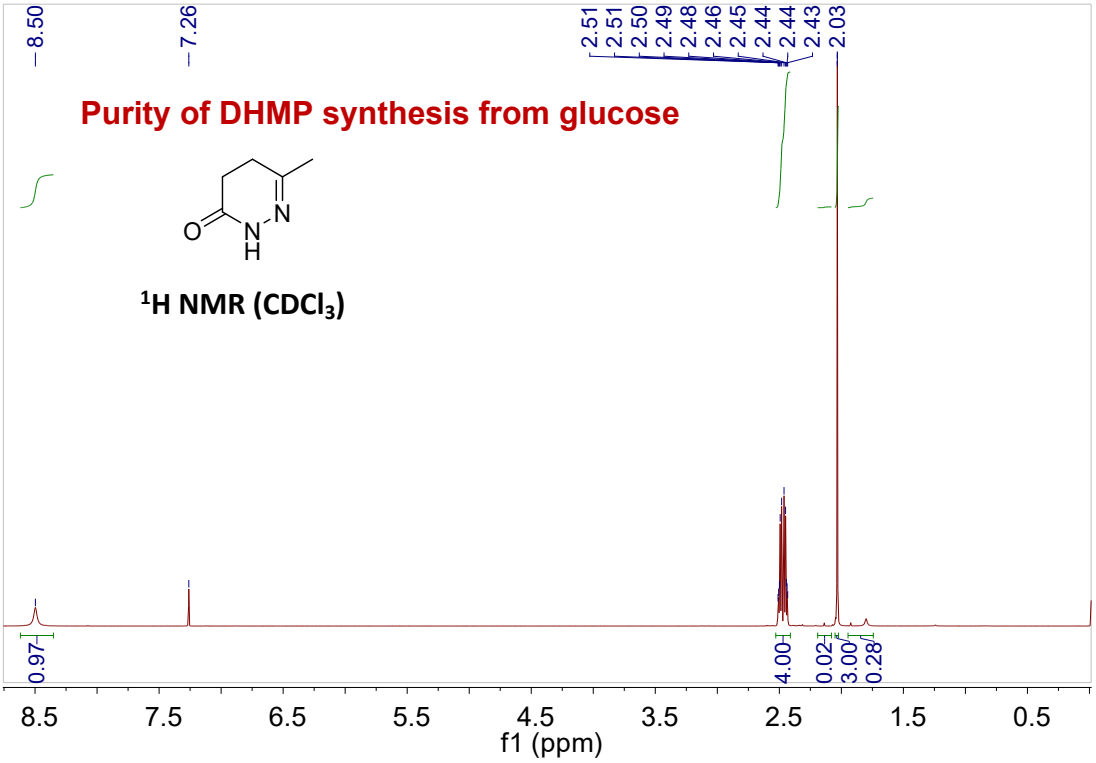
^{1}H NMR ($CDCl_3$)

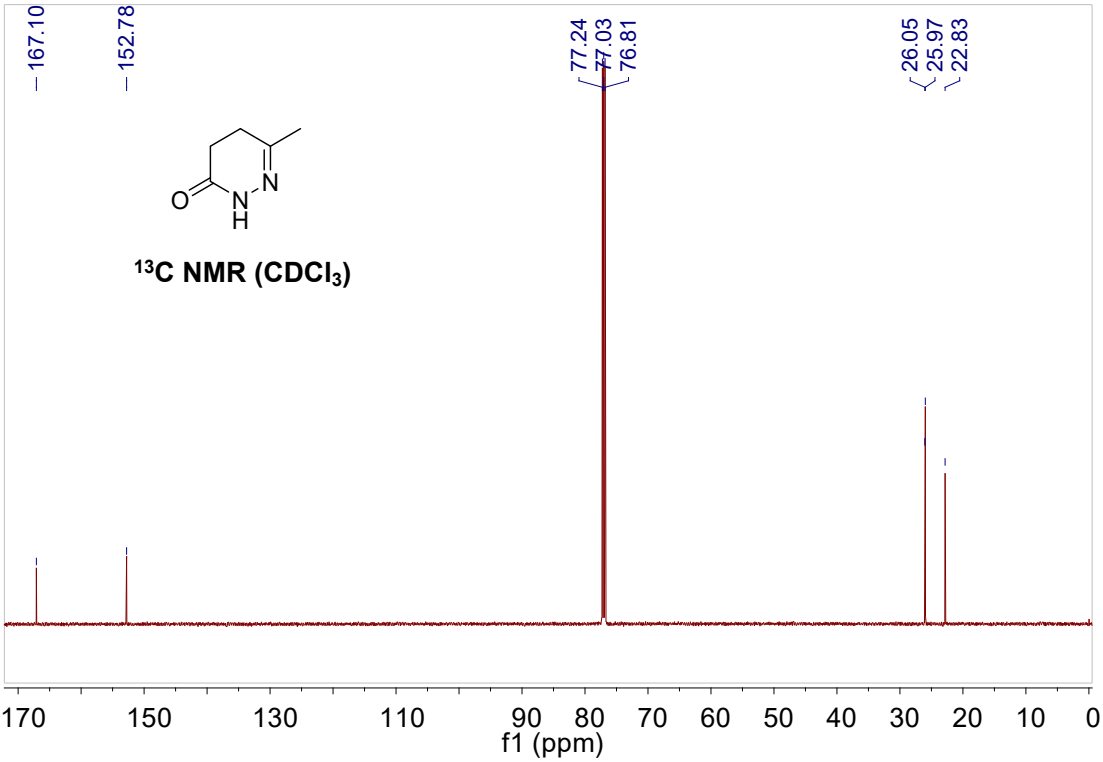


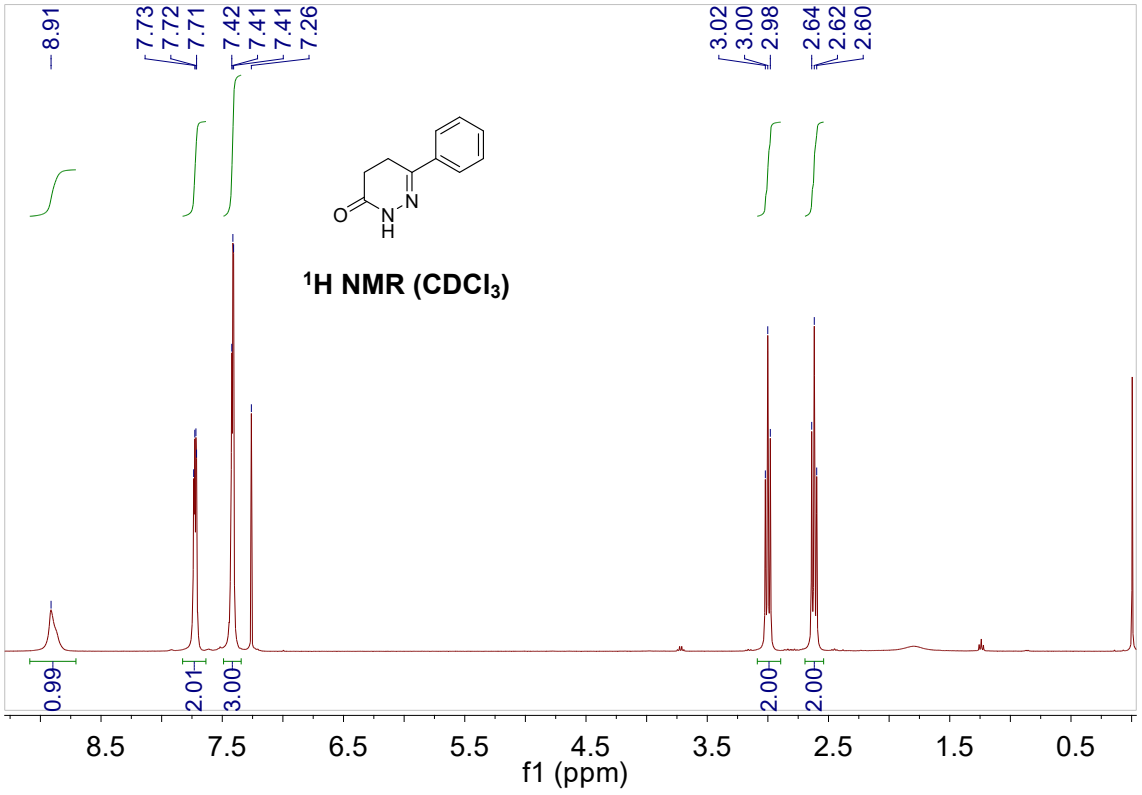
^{13}C NMR ($CDCl_3$)


8.72
8.47
7.26
2.51
2.49
2.48
2.47
2.45
2.44
2.43
2.03
2.03
Purity of scale-up synthesis of DHMP
O
N
N
H
1H NMR (CDCl3)
0.98
4.00
0.02
3.00
0.03
0.09
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

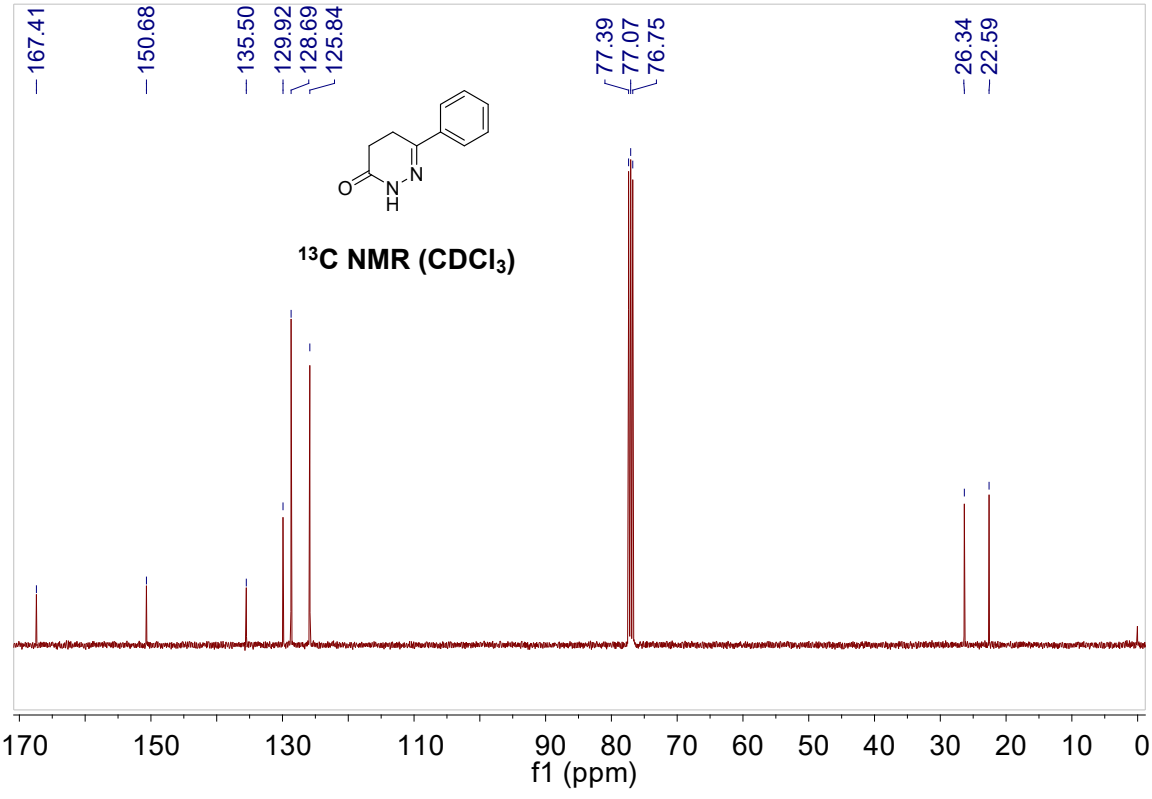

167.27
152.91
77.37
77.06
76.74
26.04
25.96
22.89
Purity of scale-up synthesis of DHMP
O
N
N
H
13C NMR (CDCl3)
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Purity of DHMP synthesis from glucose
^{1}H NMR ($CDCl_3$)
8.50
7.26
2.51
2.51
2.50
2.49
2.48
2.46
2.45
2.44
2.44
2.43
2.03
0.97
4.00
0.02
3.00
0.28
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

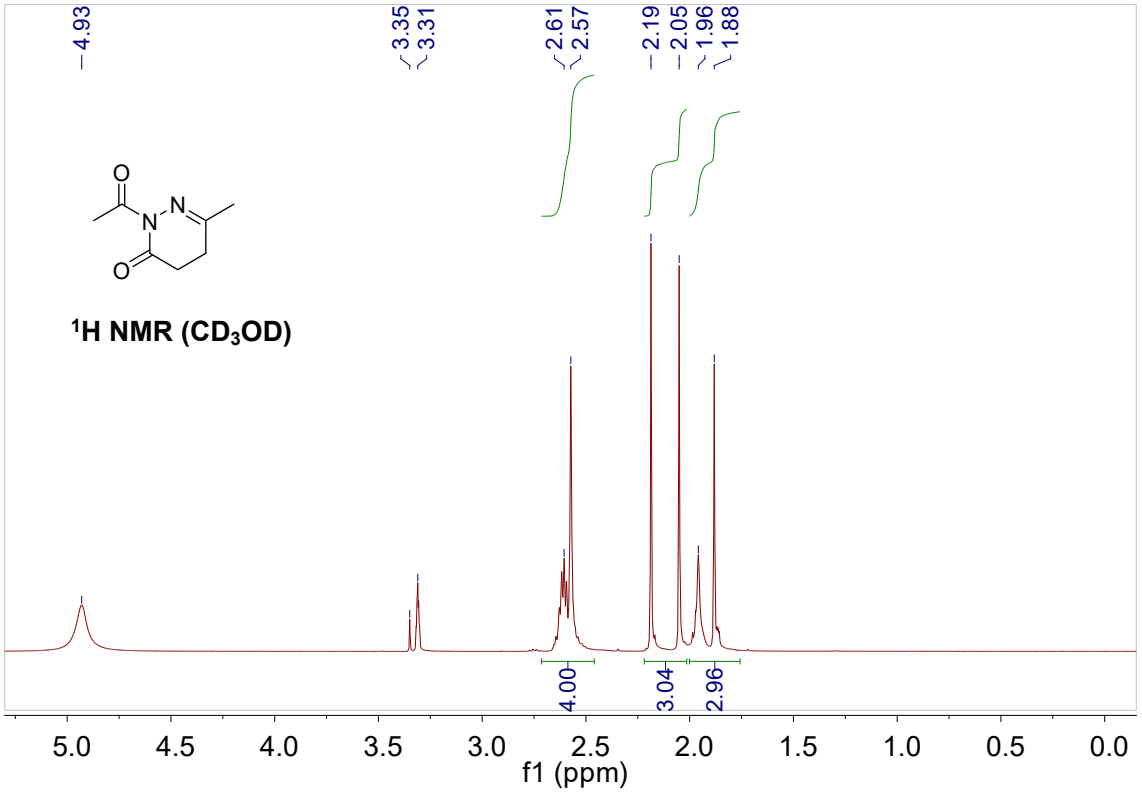

^{13}C NMR ($CDCl_3$)
167.10
152.78
77.24
77.03
76.81
26.05
25.97
22.83
170
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



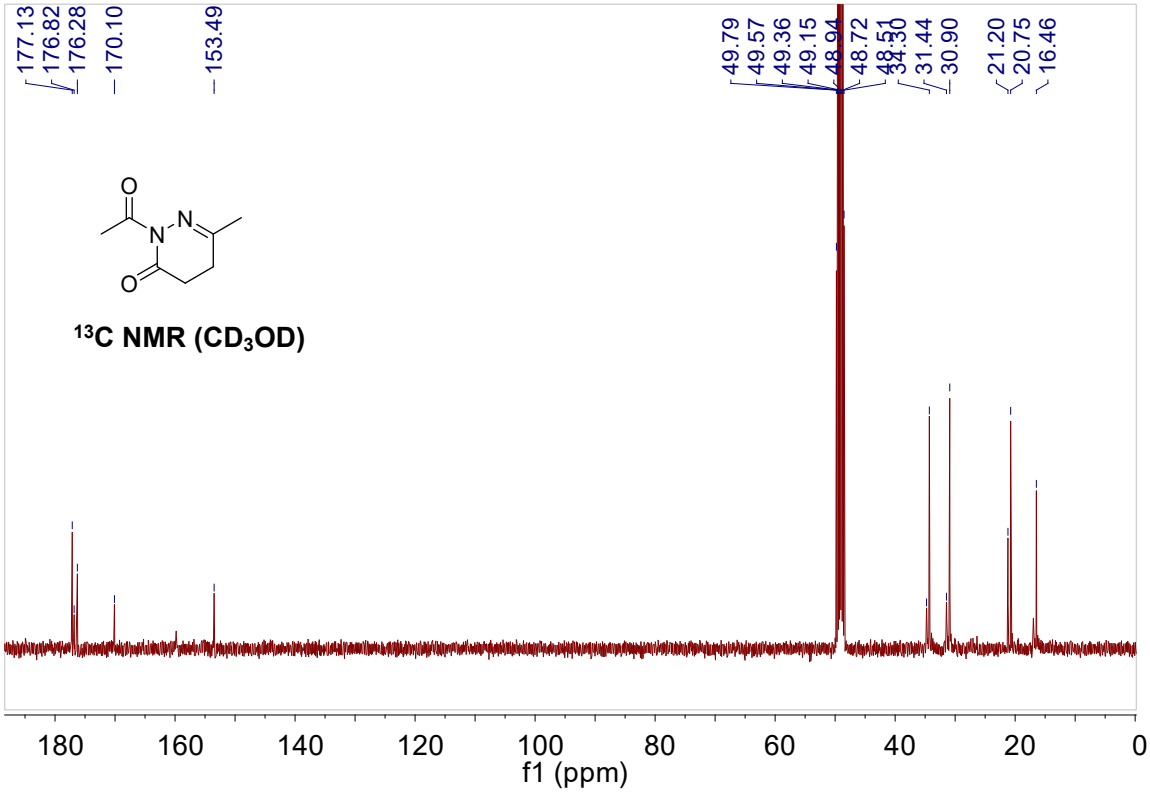
^{1}H NMR ($CDCl_3$)



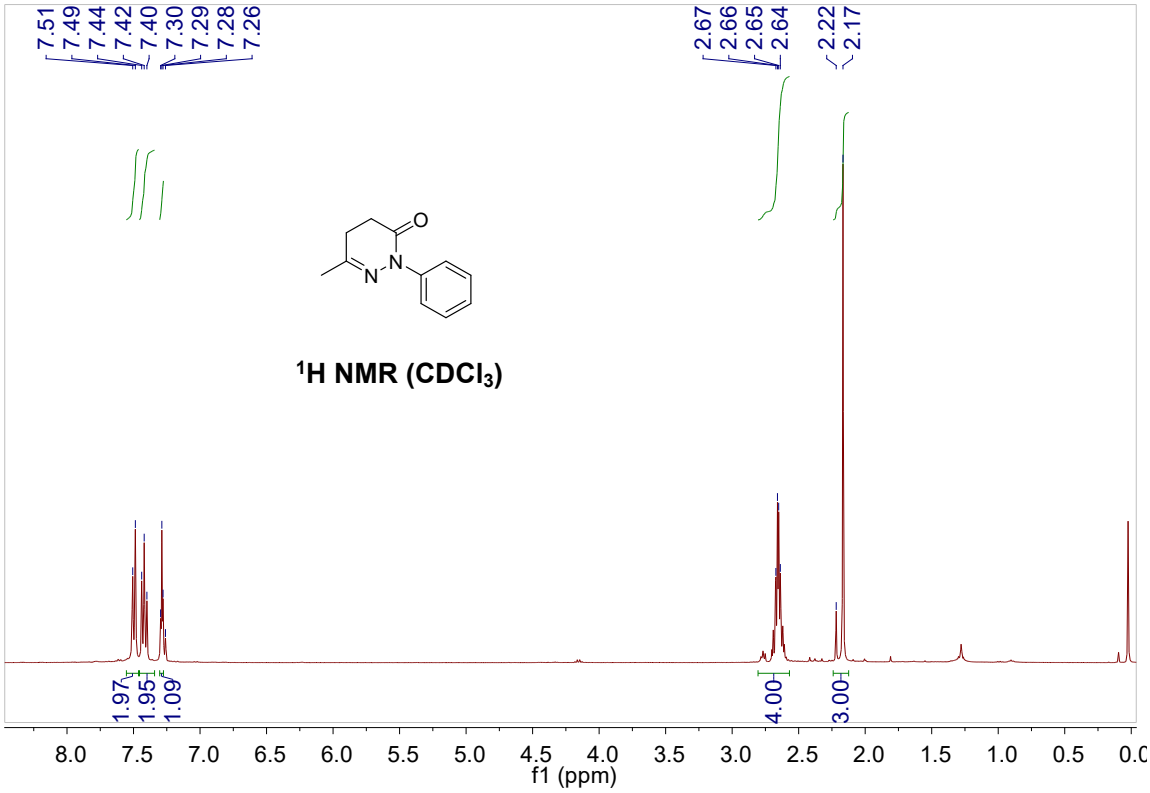
^{13}C NMR ($CDCl_3$)



^{1}H NMR (CD_3OD)



^{13}C NMR (CD_3OD)



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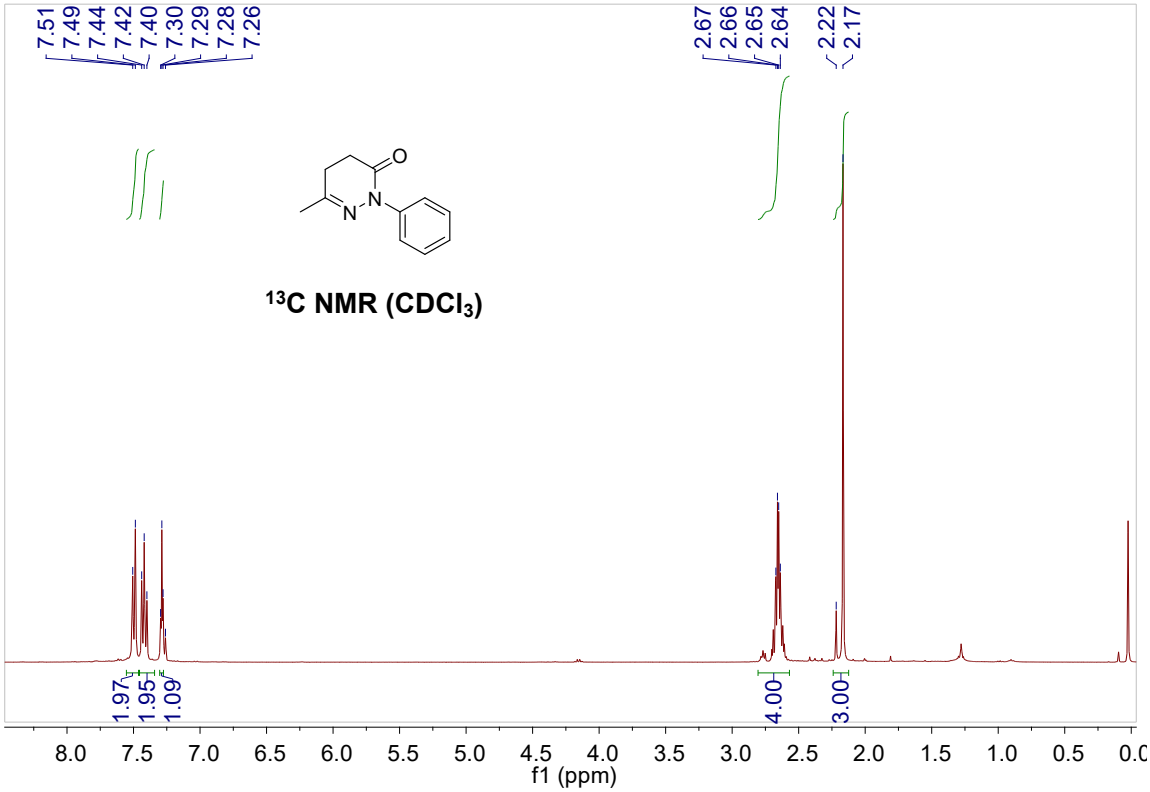
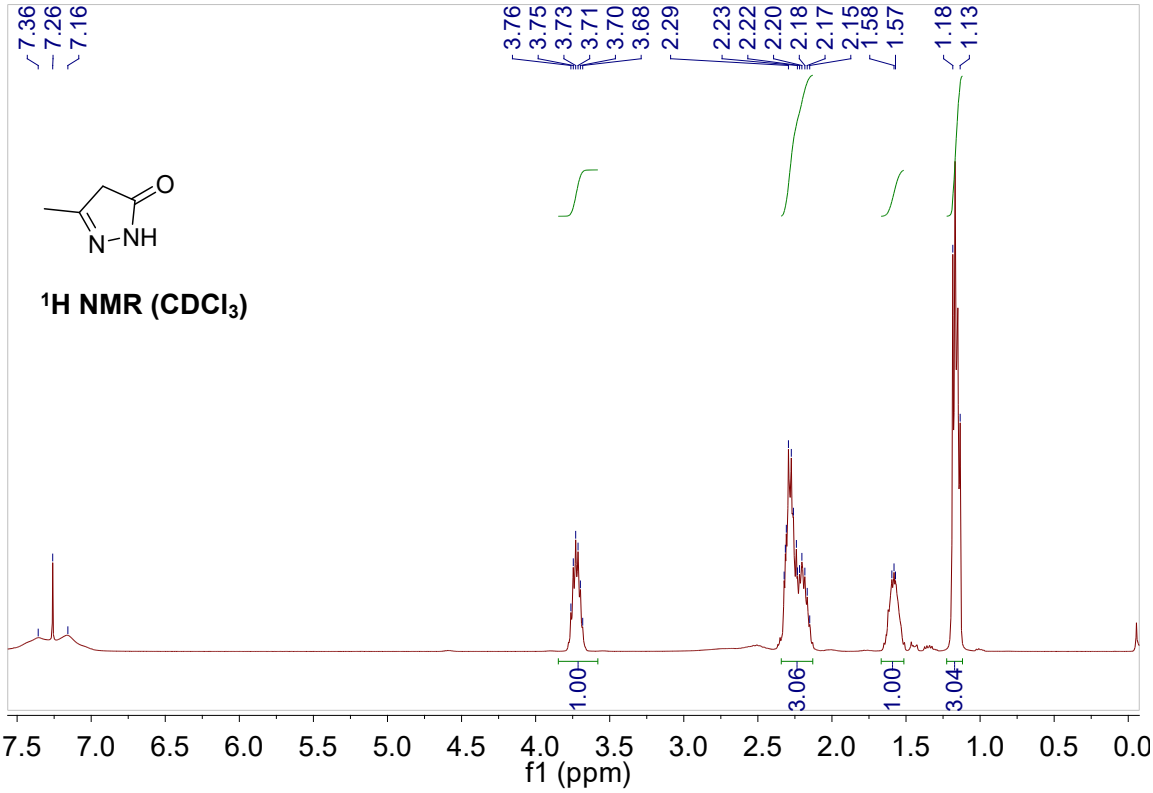
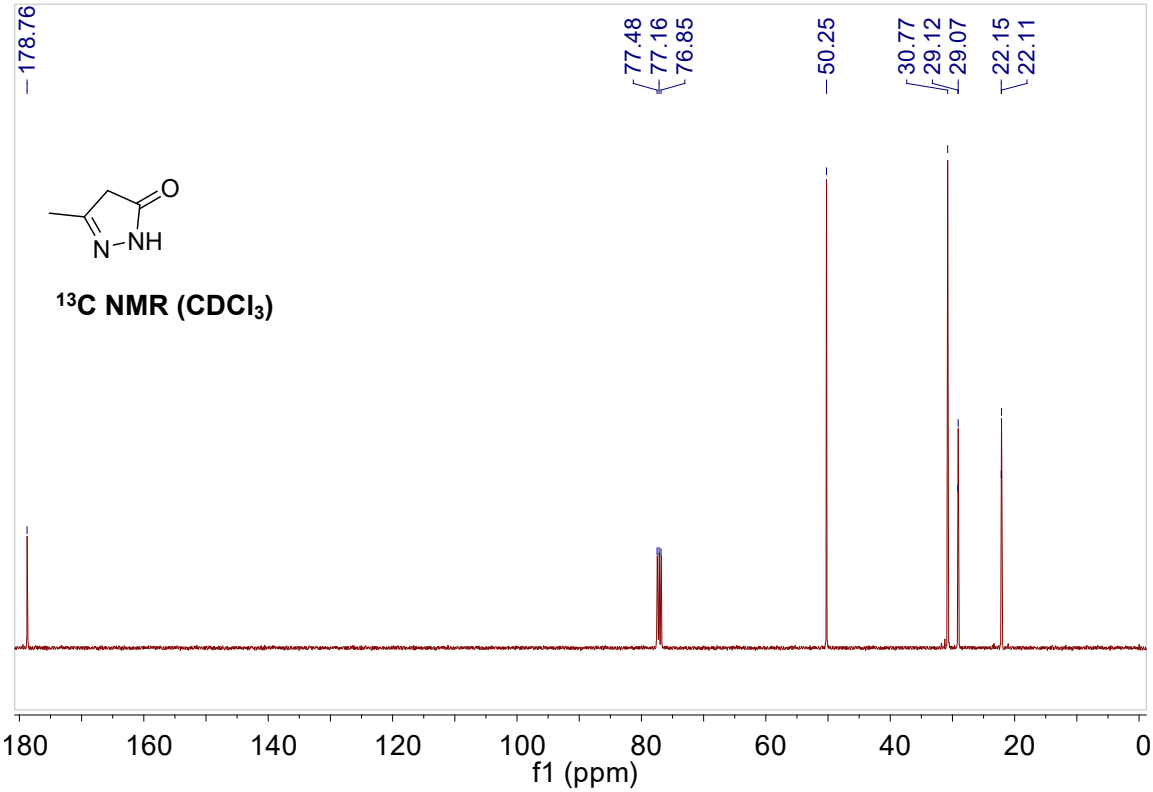
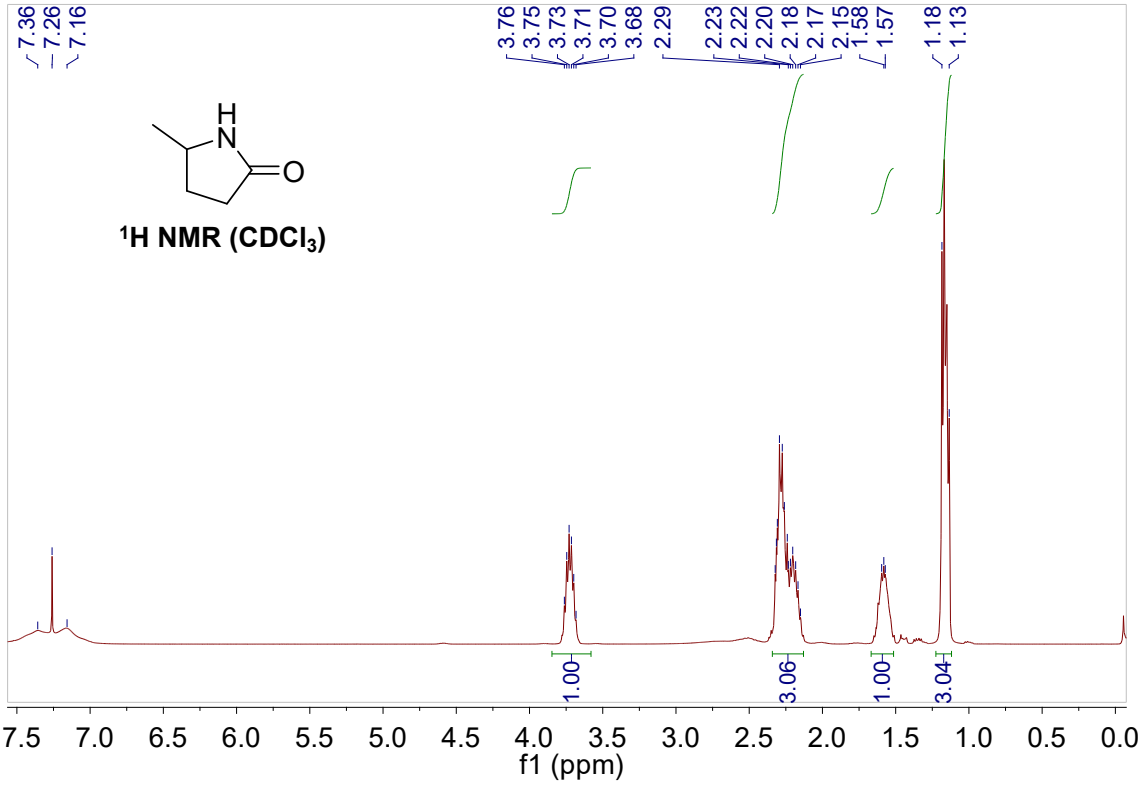
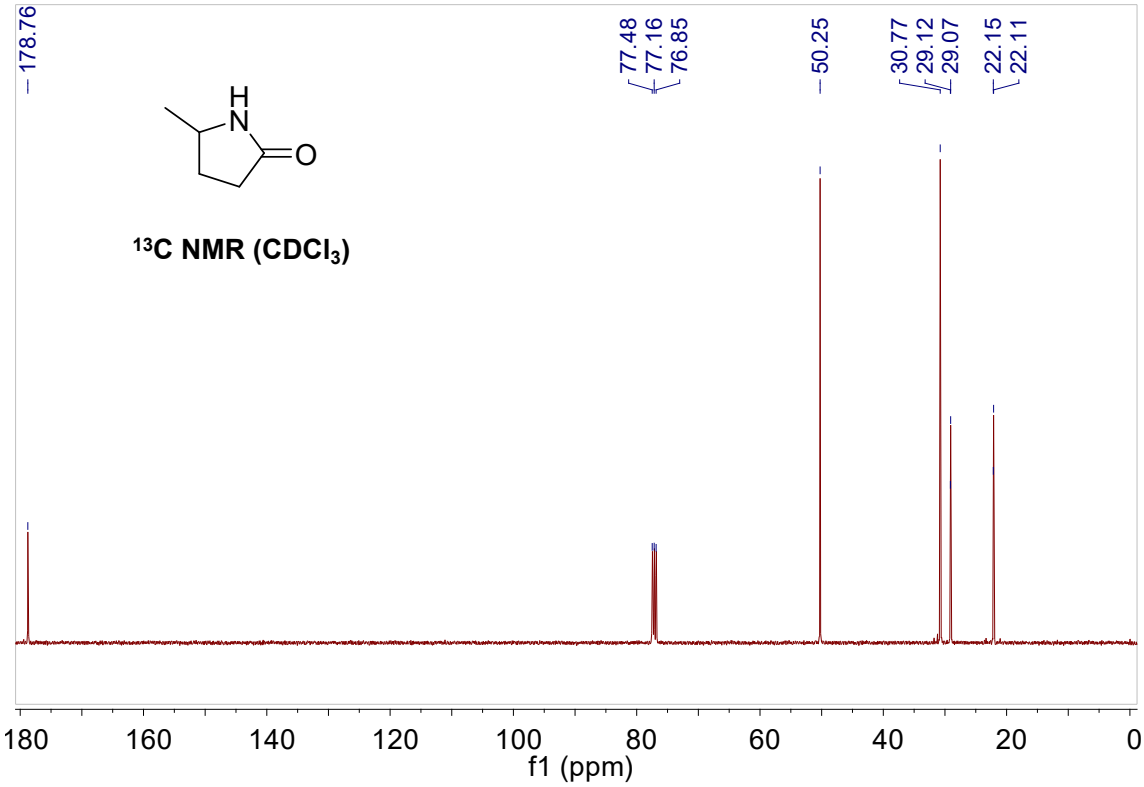


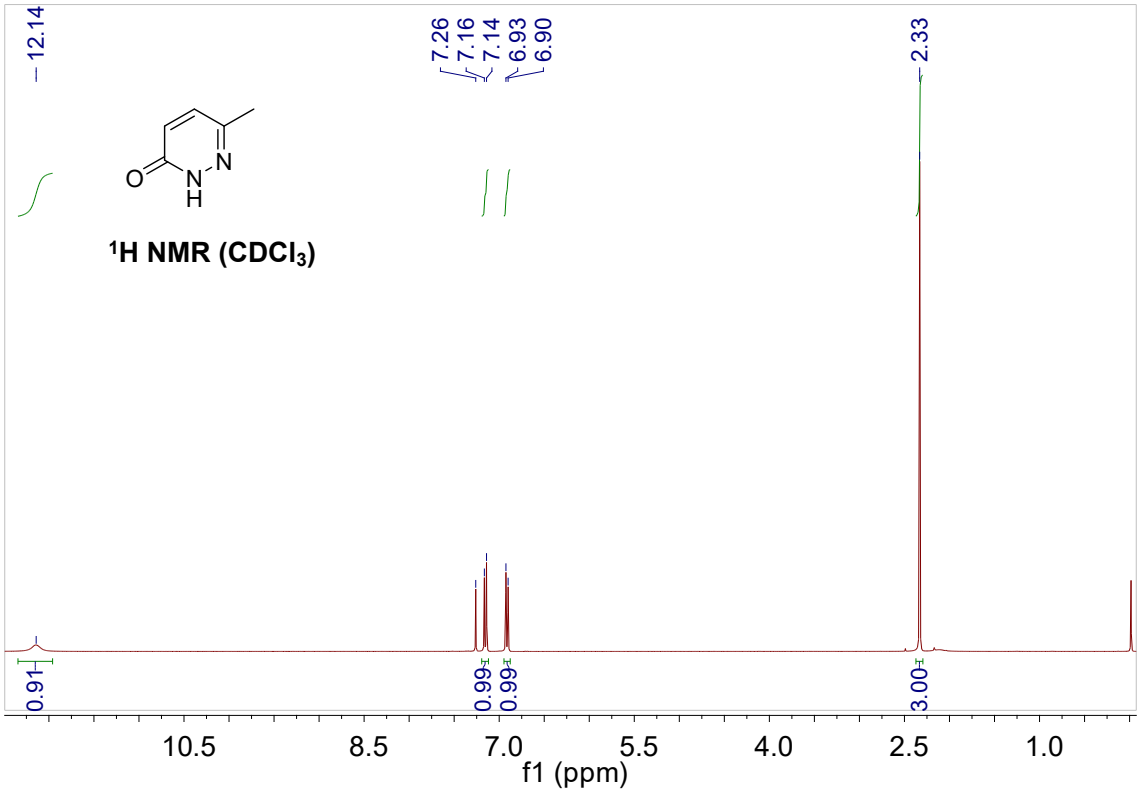
^{13}C NMR ($CDCl_3$)


7.36
7.26
7.16
3.76
3.75
3.73
3.71
3.70
3.68
2.29
2.23
2.22
2.20
2.18
2.17
2.15
1.58
1.57
1.18
1.13
O
N
NH
1H NMR (CDCl3)
1.00
3.06
1.00
3.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

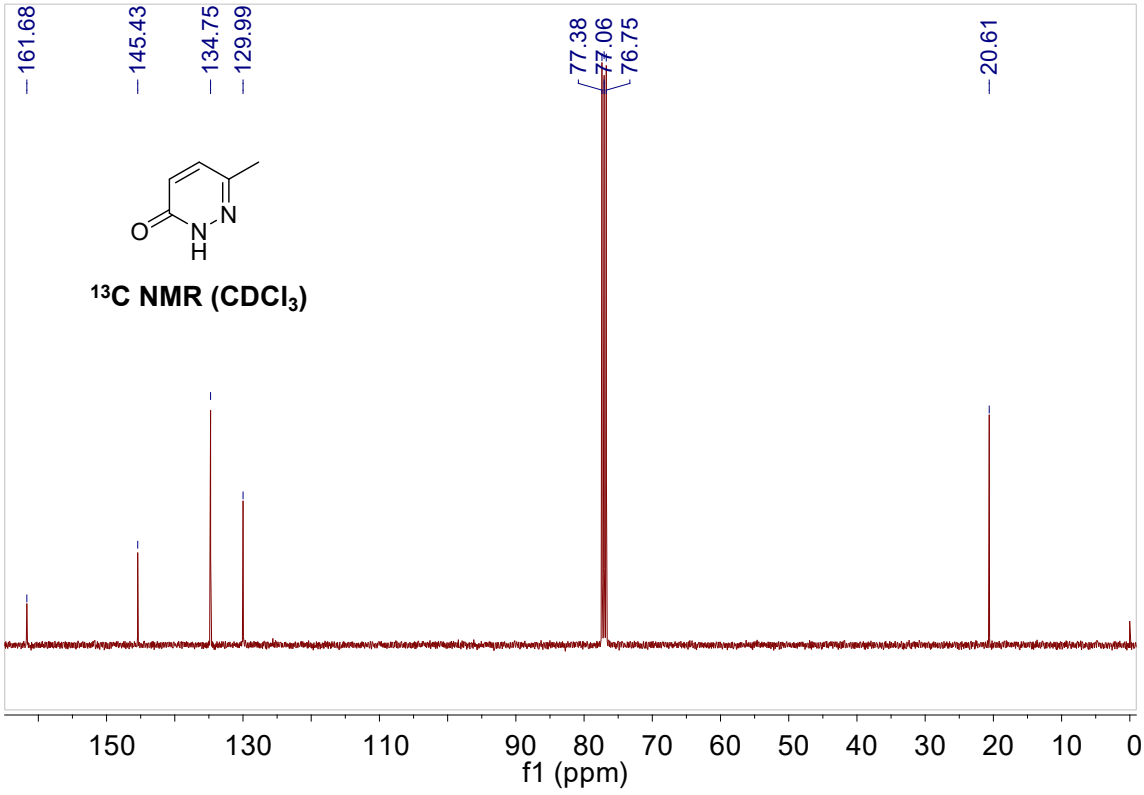

178.76
77.48
77.16
76.85
50.25
30.77
29.12
29.07
22.15
22.11
O
N
NH
13C NMR (CDCl3)
180 160 140 120 100 80 60 40 20 0
f1 (ppm)


7.36
7.26
7.16
3.76
3.75
3.73
3.71
3.70
3.68
2.29
2.23
2.22
2.20
2.18
2.17
2.15
1.58
1.57
1.18
1.13
H
N
O
1H NMR (CDCl3)
1.00
3.06
1.00
3.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

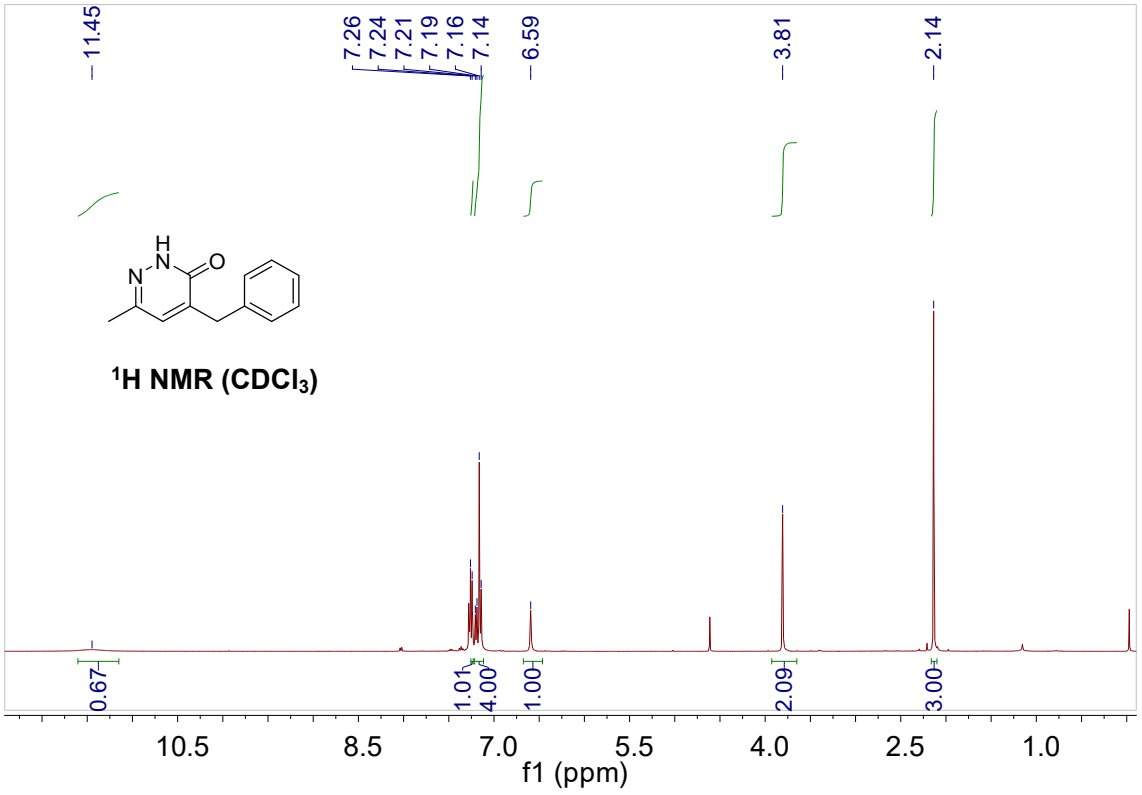

178.76
77.48
77.16
76.85
50.25
30.77
29.12
29.07
22.15
22.11
H
N
O
13C NMR (CDCl3)
180 160 140 120 100 80 60 40 20 0
f1 (ppm)

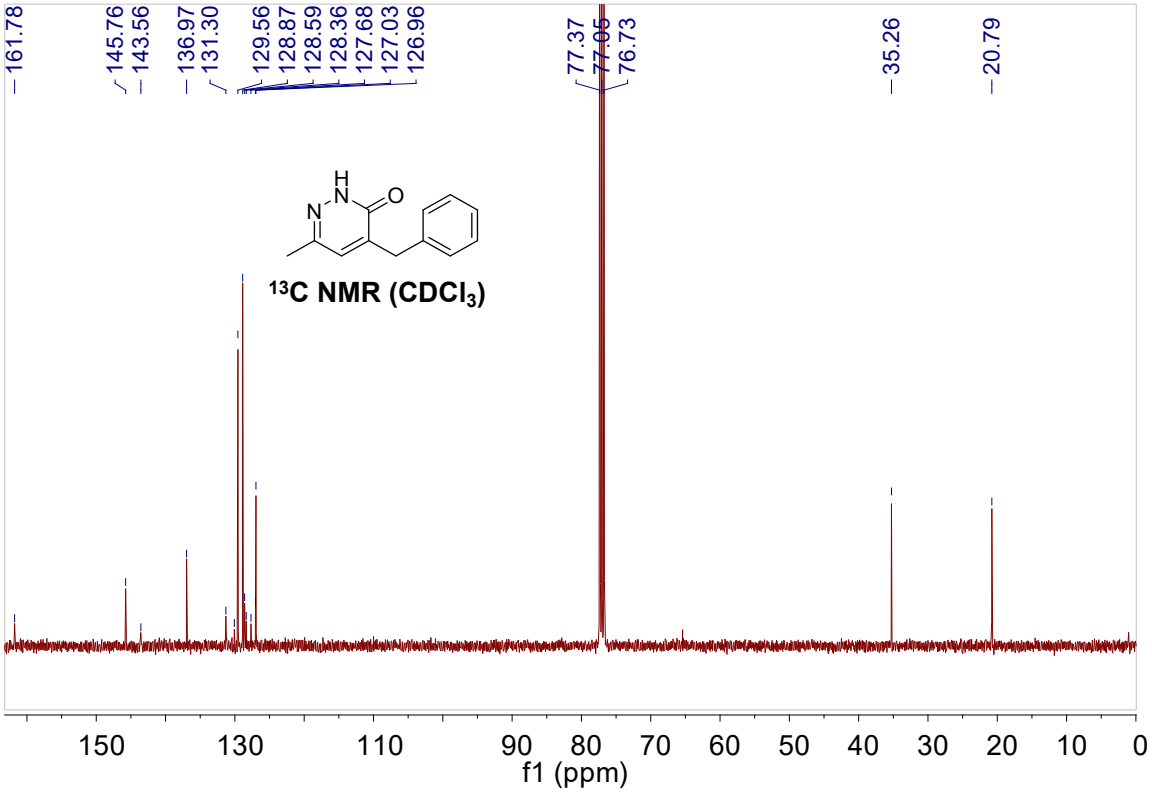


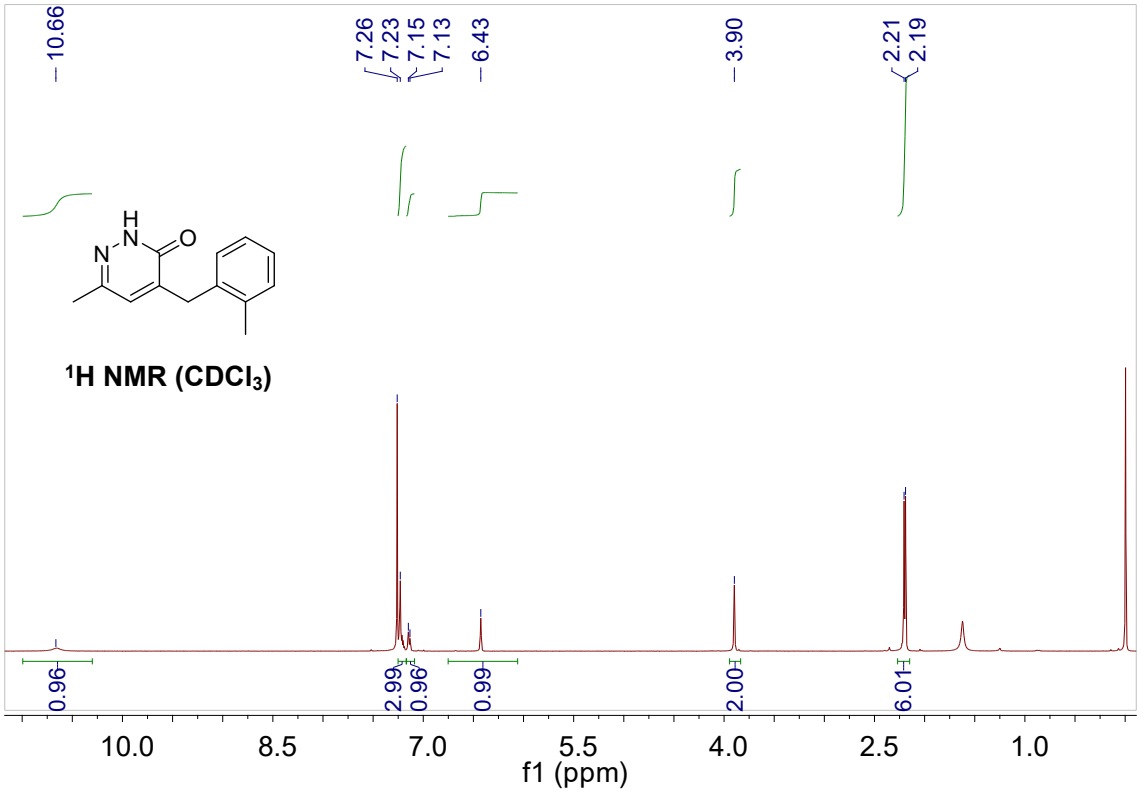
^{1}H NMR ($CDCl_3$)



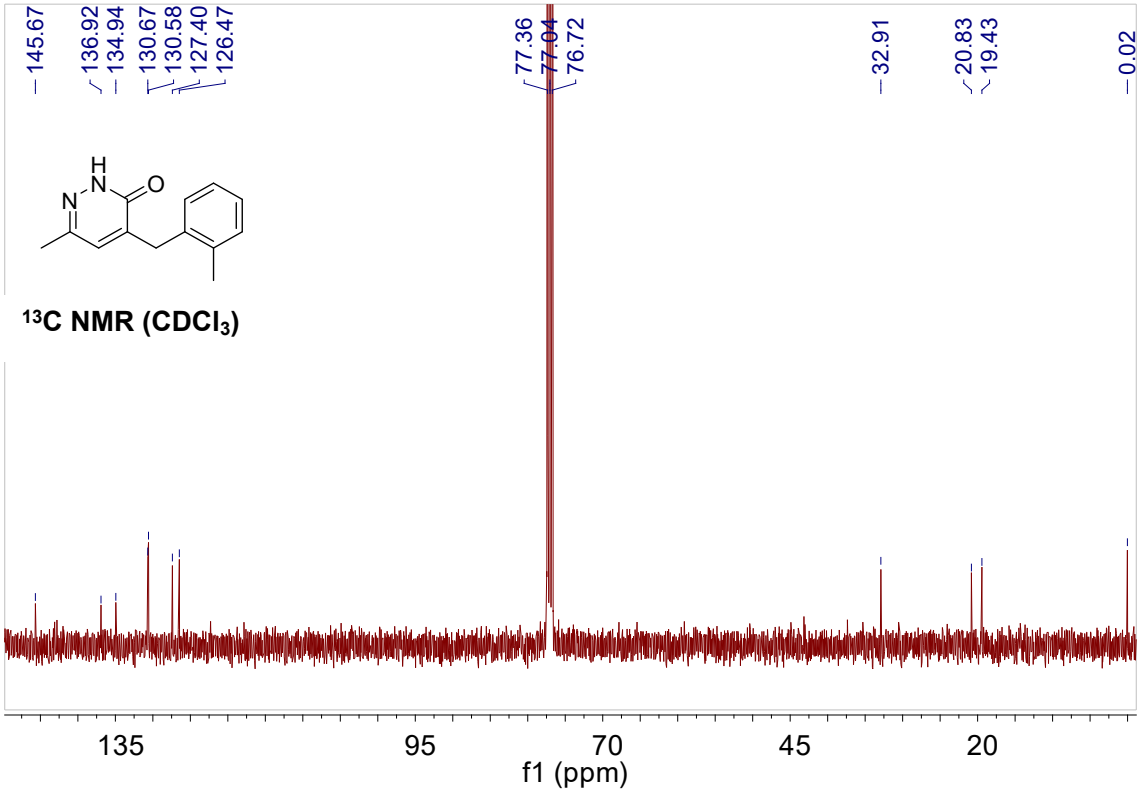
^{13}C NMR ($CDCl_3$)


11.45
7.26
7.24
7.21
7.19
7.16
7.14
6.59
3.81
2.14
0.67
1.01
4.00
1.00
2.09
3.00
10.5
8.5
7.0
5.5
4.0
2.5
1.0
f1 (ppm)
^{1}H NMR (CDCl$_3$)

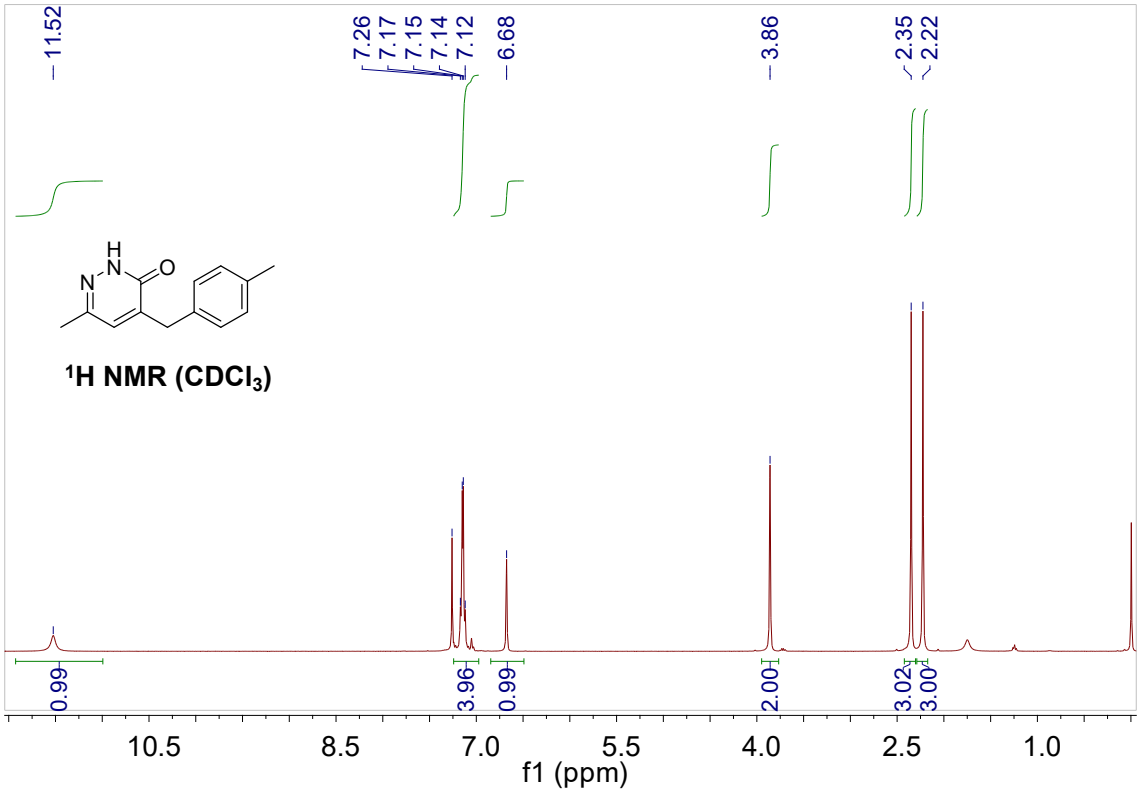

161.78
145.76
143.56
136.97
131.30
129.56
128.87
128.59
128.36
127.68
127.03
126.96
77.37
77.05
76.73
35.26
20.79
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
^{13}C NMR (CDCl$_3$)



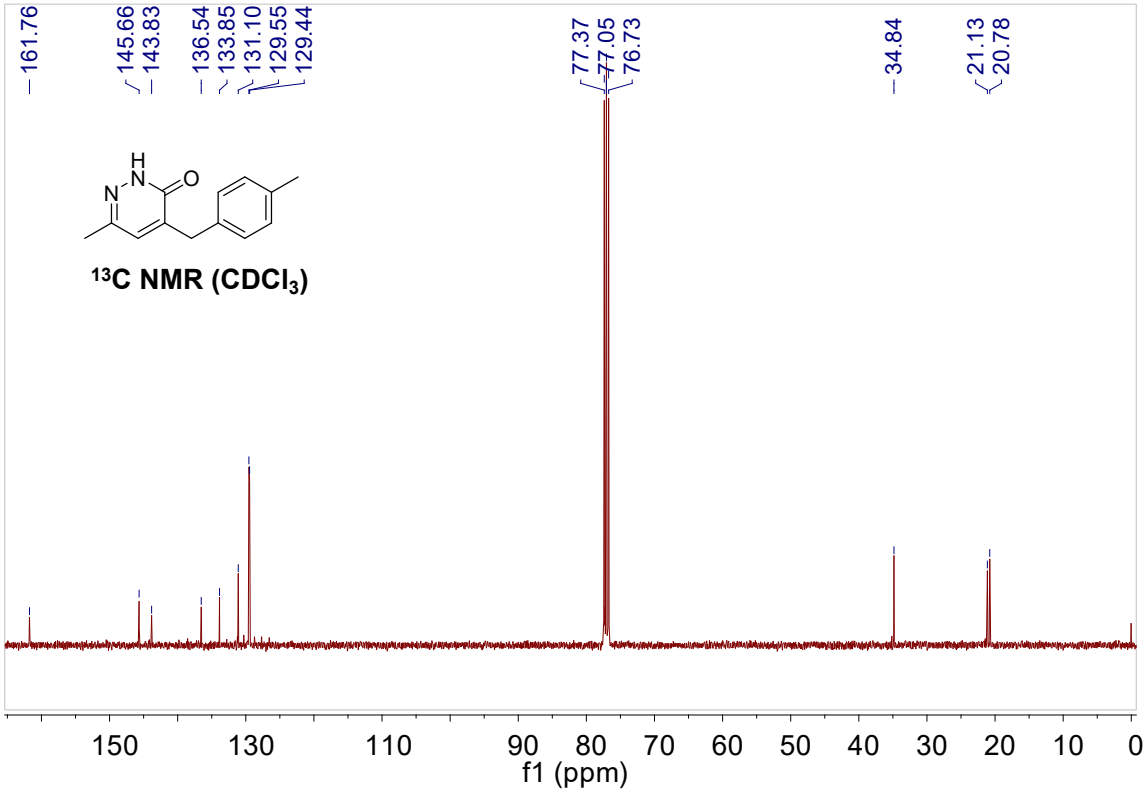
^{1}H NMR ($CDCl_3$)



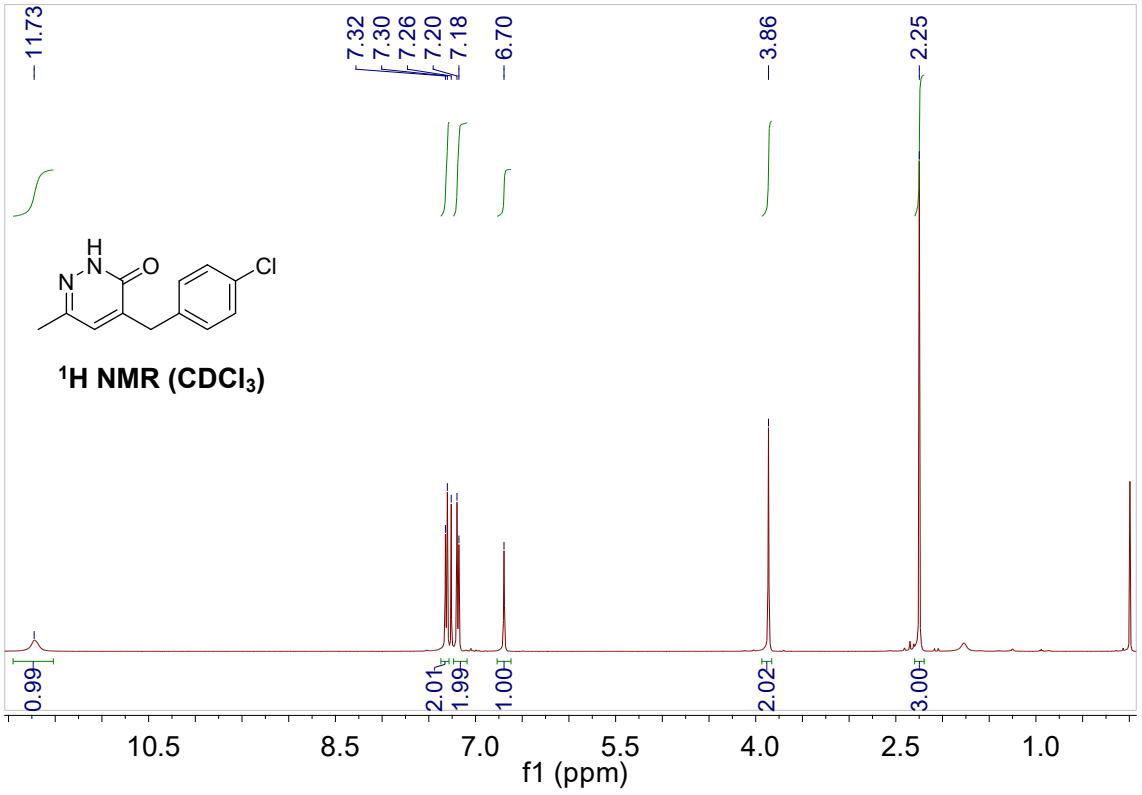
^{13}C NMR ($CDCl_3$)

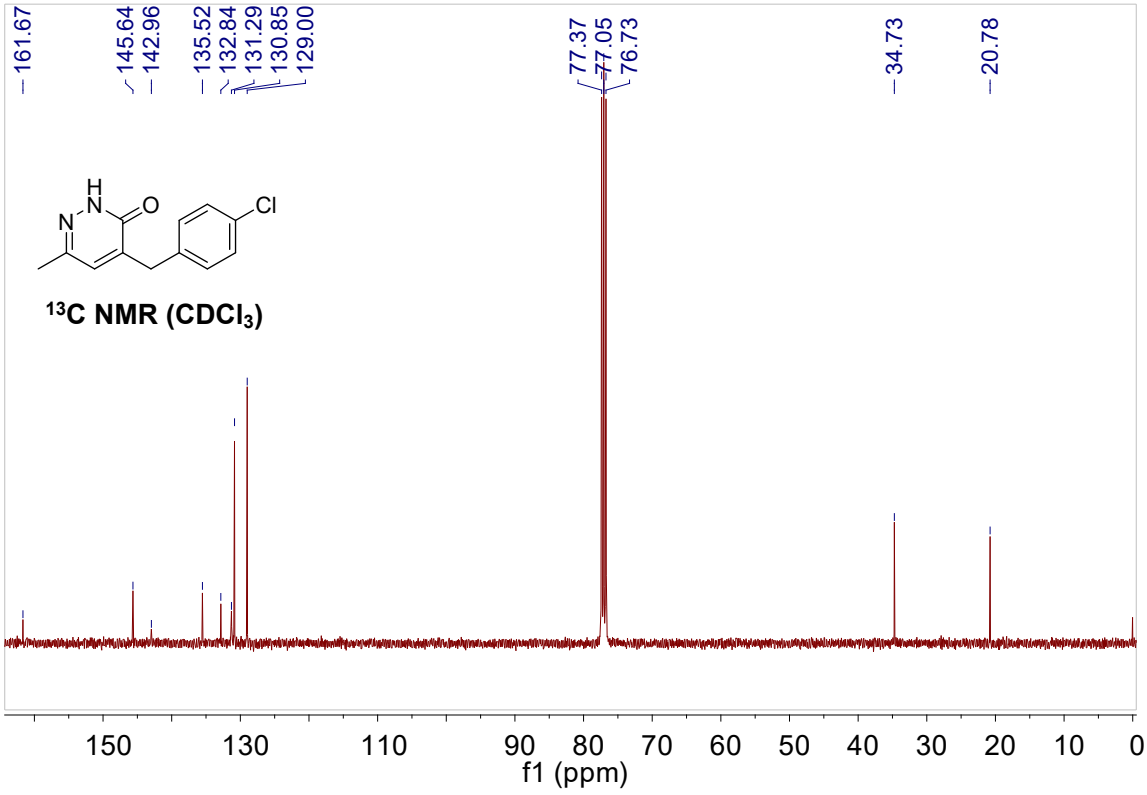


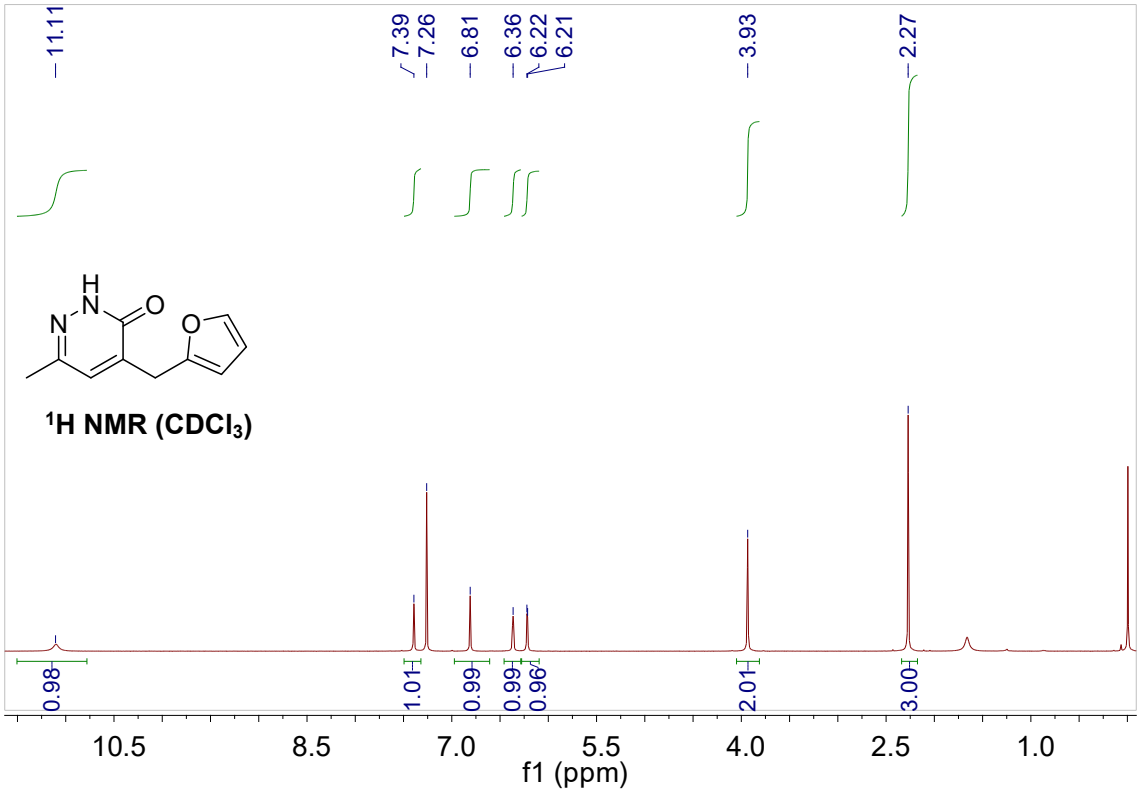
^{1}H NMR ($CDCl_3$)



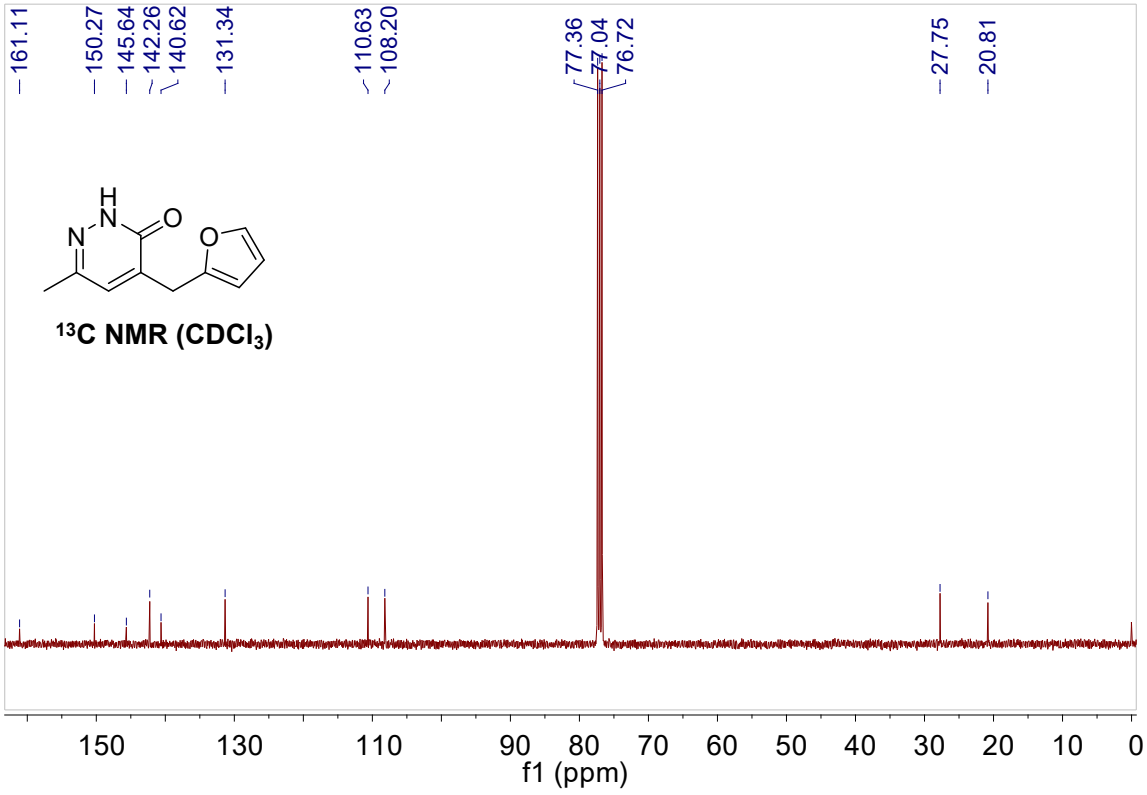
^{13}C NMR ($CDCl_3$)


11.73
7.32
7.30
7.26
7.20
7.18
6.70
3.86
2.25
0.99
2.01
1.99
1.00
2.02
3.00
10.5
8.5
7.0
5.5
4.0
2.5
1.0
f1 (ppm)
H
N
N
O
Cl
^{1}H NMR (CDCl$_3$)

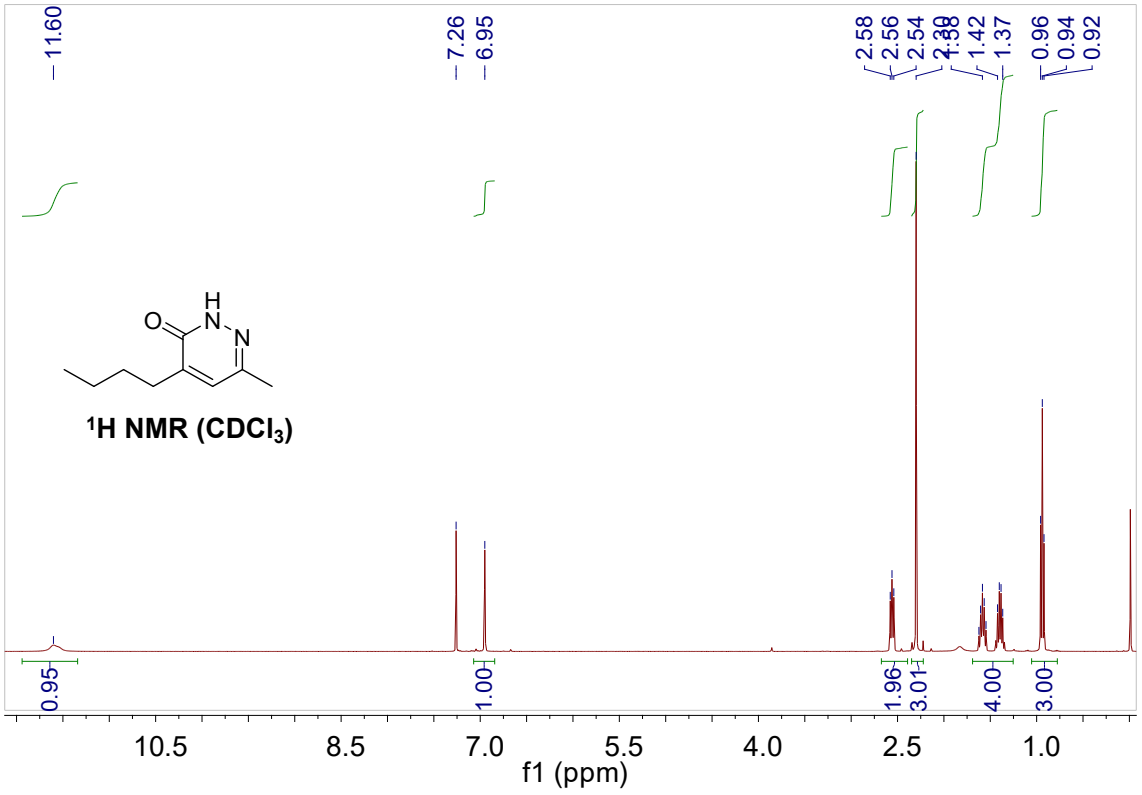

161.67
145.64
142.96
135.52
132.84
131.29
130.85
129.00
77.37
77.05
76.73
34.73
20.78
150
130
110
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
H
N
N
O
Cl
^{13}C NMR (CDCl$_3$)



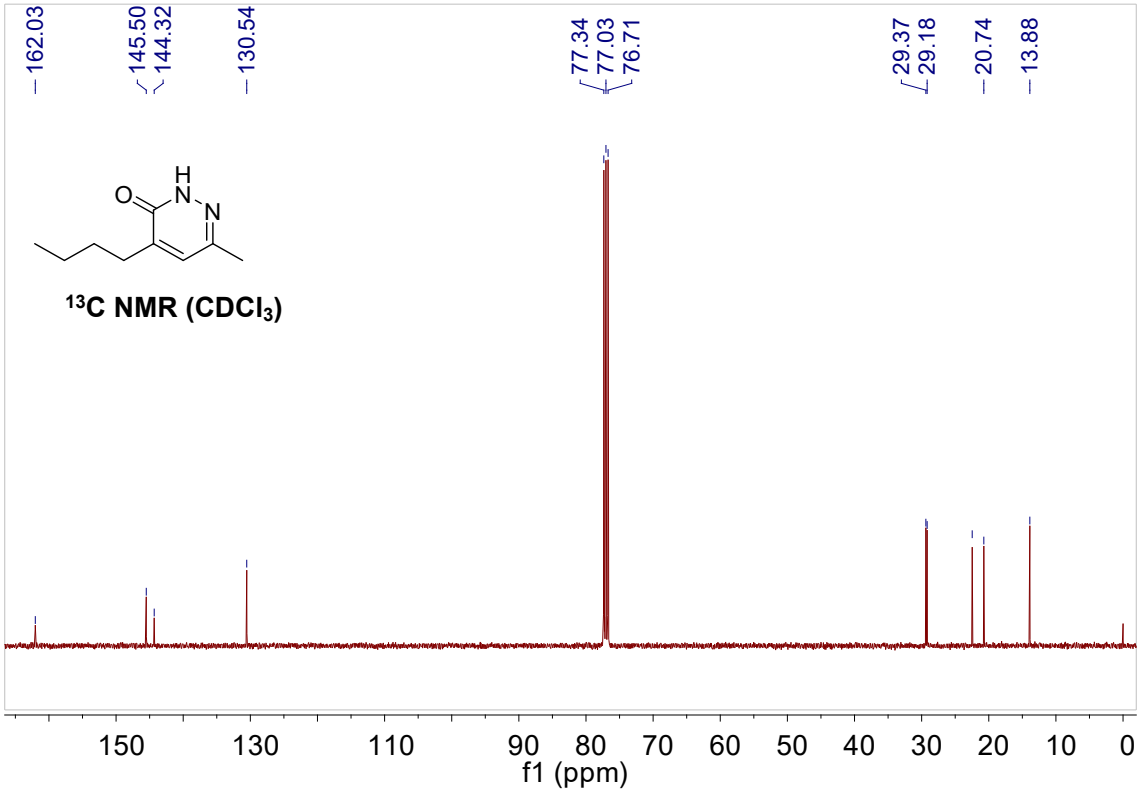
^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)



^{1}H NMR ($CDCl_3$)



^{13}C NMR ($CDCl_3$)