SUPPORTING MATERIAL

Isocyanide Chemistry Enabled by Continuous Flow Technology

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General methods

Unless otherwise noted, chemicals were obtained from commercial suppliers and used without further purification. Melting points were determined using a electrothermal apparatus (Buchi 535, B-535, Büchi, Switzerland) and are uncorrected. NMR spectra were recorded on a Bruker AC 400 MHz spectrometer in the indicated solvent. Chemical shifts are reported in parts per million (ppm) and are relative to $CDCl_3$ (7.26 ppm and 77.0 ppm), CD_3OD (3.33 ppm and 49.3 ppm) or d^6-DMSO (2.49 ppm and 39.7 ppm). The abbreviations used are as follows: s, singlet; brs, broad singlet; d, doublet; dd, double doublet; ddd, doublet of doublet of doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; brm, broad multiplet. Coupling constants (J) are reported in Hertz (Hz). Thin-layer chromatography was performed on aluminum backed silica plates (silica gel 60 F-254, Merck, Darmstadt, Germany). Spots were visualized by UV detector (λ: 254 nm) and/or by staining and warming with ninydrine (5% wt in EtOH) or $KMnO_4$. Flash chromatographic purifications were performed using Biotage Isolera™ Prime (Biotage, Uppsala, Sweden). All flow experiments were performed using a commercially available modular Syrris Asia system composed by two-channels Asia syringe pumps (Asia blue syringes, 0.50 mL/1.0 mL and Asia red syringes 2.5 mL/5 mL), external HPLC pumps (Jasco PU-980, Jasco, Easton, MD – USA), thermocouple-controlled coil reactors (1/16” OD, 0.8 mm ID, 10 mL, PTFE), glass tubular mesoreactors (Omnifit Labware DIBA HIT™ column, ID × L 6.6 mm x 150 mm), T-shaped mixing elements (0.5 mm ID), back pressure regulators (BPR, 40 psi and 100 psi, PEEK, 1/16" OD, 1/4"-28), 4-way valves (PTFE, 1/4"-28, 0.5-4 mm OD, 1.5 mm ID, DIBA) and a fraction collector (Gilson FC 203B, Gilson Inc., Middleton, WI – USA). High resolution mass spectrometry (HRMS) measurements were recorded on Agilent 6500 Q-TOF series instrument (Agilent technologies, USA). The MS system was set with an electrospray ionization source (ESI) in the negative mode with optimized parameters. MassHunter software version B.05.01 (Agilent Technology) was used to control the LC–MS/MS system, for data prediction, acquisition, analysis, and processing. Samples were dissolved in MeOH.

Flow synthesis of isocyanides

A solution of formamide **2a-j** (1.8 mmol, 0.6 M) and Et_3N (9 mmol, 3 M) in $CHCl_3$ (3 mL) and a solution of $POCl_3$ (1.8 mmol, 0.6 M) in $CHCl_3$ (3 mL) were injected through the loops and pumped with a total flow rate of 0.5 mL min^{-1}. After loading and switching the 6-way valves injector, the components were mixed in a T-junction and flowed through a 10 mL coil reactor at 25 °C. The reactor outcome was filtered through an Omnifit Labware DIBA HIT™ column (ID × L: 6.6 mm x 150

mm) packed with silica gel (70-230 mesh, 1.5 g/ mmol^{-1}). A back pressure regulator (BPR, 100 psi) was used to pressurize the system. The reaction mixture was collected by an automated fraction collector into sealed vials (4 mL for each fraction, 5 min collecting time). The reaction yield was determined by calibrated quantitative ^{1}H-NMR analysis (400 MHz, $CDCl_3$) using dimethyl sulfone (TraceCERT®) as the internal standard. Based on the determined yield and title, the solution of the desired isocyanide **1** in $CHCl_3$ can be varied (diluted) to reach the concentration required for the next post-modification step. For substrate **2a**, the reaction was scaled up 18 mmol (2 g) using the same conditions described above. The reactor outcome was filtered through a Michel-Miller columns (ID × L: 15 mm x 250 mm) packed with silica (70-230 mesh, 1.5 g/ mmol^{-1}, 27 g) and the desired *t*-butylisocyanide (**1a**) in 84% yield.

***t*-Butylisocyanide (1a).** Yield: 89%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H, 3 x C*H*$_3$). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 30.7, 54.1, 152.2.

Benzylisocyanide (1b). Yield: 87%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.56 (s, 2H, C*H*$_2$), 7.24-7.31 (m, 5H, C$_6$*H*$_5$). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 45.7, 126.8, 128.6, 129.1, 132.5, 157.7.

Cyclohexylisocyanide (1c). Yield: 79%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.35-1.47 (m, 4H, 2 x C*H*$_2$), 1.66-1.78 (m, 4H, 2 x C*H*$_2$), 1.86-1.88 (m, 2H, C*H*$_2$), 3.59 (brs, 1H, C*H*). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 22.9, 25.1, 32.8, 51.8, 153.9.

Cyclopropylisocyanide (1d). Yield: 69%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.83-0.85 (m, 2H, C*H*$_2$), 0.93-0.95 (s, 2H, C*H*$_2$), 2.65-2.71 (m, 1H, C*H*), ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 7.5 (2x), 75.8, 153.5.

2,6-Dimethylphenylisocyanide (1g). Pale yellow solid. Reaction performed at 0.15 M concentration of **2g**. Isolated yield: 44%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 6H, 2 x C*H*$_3$), 7.09 (d, *J*= 4.10 Hz, 2H, 3,5-C*H*), 7.18 (t, *J*= 8.12 Hz, 1H, 4-C*H*). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 19.1, 127.9 (2x), 128.8, 135.0, 167.6.

4-Methoxyphenylisocyanide (1h). Yield: 77%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H, C*H*$_3$), 6.87 (d, *J*= 9.02 Hz, 2H, 3,5-C*H*), 6.31 (d, *J*= 9.10 Hz, 2H, 2,6-C*H*). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 55.5, 114.5, 127.7, 159.8, 161.5.

4-Chlorophenylsocyanide (1i). Reaction performed at 0.36 M concentration of **2i**. Yield: 79%. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.28 (d, *J*= 8.67 Hz, 2H), 7.33 (d, *J*= 8.51 Hz, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 124.8, 127.7, 129.6, 135.1, 165.2.

Ethylisocyanoacetate (1j). Colorless oil. Isolated yield: 80%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.27 (t, 3H, CH_2CH_3), 4.20-4.26 (m, 4H, CH_2CH_3 + CH_2NC). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 13.9, 43.5, 62.7, 160.8, 163.9.

Table S1. Flow synthesis of 2,6-dimethylphenyl isocyanide (**1g**) under diverse reaction conditions.

Entry	Base (equiv.)	Solvent	[SM]	Solubility	Yield[a]
1	Et_2NH	Et_2NH	0.1-0.6	Not soluble	-
2	Et_2NH (10)	10% DMSO in $CHCl_3$	0.6	Soluble	Traces
3	Et_3N (5)	10% 1,2-diCl-Ph in $CHCl_3$	0.1-0.6	Not soluble	-
4	Et_3N (5)	50% 1,2-diCl-Ph in $CHCl_3$	0.15-0.6	Soluble at 0.3 M	Traces
5	Et_3N (5)	20% (v/v) DMSO in $CHCl_3$	0.5-0.6	Soluble at 0.45 M	Traces
6	Et_3N (5)	10% (v/v) DMSO in $CHCl_3$	0.35-0.4	Soluble at 0.35 M	22%
7	Et_3N (5)	5% (v/v) DMSO in $CHCl_3$	0.15-0.6	Soluble at 0.15 M	44%

[a]Isolated yield.

Procedure for the yield determination of phenylisocyanide (1f)

A solution of phenyl formamide (**2f**, 1.8 mmol, 0.6 M) and Et_3N (9 mmol, 3 M) in $CHCl_3$ (3 mL) and a solution of $POCl_3$ (1.8 mmol, 0.6 M) in $CHCl_3$ (3 mL) were injected through the loops and pumped with a total flow rate of 0.5 mL min^{-1}. After loading and switching the 6-way valves injector, the components were mixed in a T-junction and flowed through a 10 mL coil reactor (t= 20 min) at 25 °C. The reactor outcome was filtered through an Omnifit Labware DIBA HIT™ column (ID × L: 6.6 mm x 150 mm) packed with silica gel (1.5 g/mmol^{-1}) under a 100 psi BPR regime. The isocyanide thus formed (0.45 M) was readily reacted with a solution of 4-bromoaniline (1 equiv., 1 M in MeOH) and a solution of 2-pyrindincarboxaldehyde (1 equiv., 1 M in MeOH) with a total flow rate of 0.1 mL min^{-1}. The resulting mixture was flowed through a four-ways mixer with a solution of fumaric acid monoethyl ester (1 equiv., 1 M in MeOH) and phenylisocyanide (1 equiv., 0.18 mmol, 0.3 M in $CHCl_3$). The mixture was pumped through a 10 mL reactor coil (10 mL, t= 66 min) heated

at 55 °C. The system was maintained at constant pressure through a BPR element (40 psi). The reactor outcome was collected, concentrated under reduced pressure and purified by automated silica gel flash chromatography (Eluent: Petroleum ether/EtOAc from 100:0 to 0:100, v/v). Yield (over two steps): 36%. When the same reaction was performed using the commercially available phenylisocyanide (**1f,** CAS: 931-54-4, 97% purity, Merck) under the same flow conditions, the corresponding β-lactam derivative was isolated in 42% yield. Therefore, the yield of phenylisocyanide (**1f**) was 87%.

Continuous flow synthesis of oxazoles

A solution of formamide **2a** (1.8 mmol, 0.6 M) and Et_3N (9 mmol, 3 M) in $CHCl_3$ (3 mL) and a solution of $POCl_3$ (1.8 mmol, 0.6 M) in $CHCl_3$ (3 mL) were pumped with a total flow rate of 0.5 mL min^{-1} through a 10 mL coil reactor at 25 °C. The reactor outcome was filtered through an Omnifit Labware DIBA HIT™ column (ID × L: 6.6 mm x 150 mm) packed with silica gel (70-230 mesh, 1.5 g/ $mmol^{-1}$) under 100 psi BPR regime. The $CHCl_3$ solution of *t*-butylisocyanide (**1a**) (2 equiv., 0.3 M) collected into a Erlenmeyer flask with screw cap was then mixed in a four-ways mixer with a solution of benzoic acid (**3**) (1 equiv., 1 M in $CHCl_3$) and of phenylglyoxal (**4**) (1 equiv., 1 M in $CHCl_3$) with a residence time of 33 minutes within a 10 mL coil reactor at 25 °C. The system was maintained at constant pressure through a BPR element (40 psi). The reactor outcome was collected, dried under *vacuo* and crystallized from Et_2O. The product was dissolved in AcOH (0.5 M) and treated with ammonium formate in AcOH at reflux for 1 h. The mixture was allowed to cool to 25 °C and the solid was collected by filtration.

***N*-(*tert*-Butyl)-2,4-diphenyloxazole-5-carboxamide (7).** White solid (m.p.: 214-216 °C). Yield: 75%. ^{1}H-NMR (400 MHz, *d*^{6}-DMSO): δ 1.37 (s, 9H, 3 x C*H*$_3$), 7.40-8.08 (m, 10H, Ar). ^{13}C-NMR (100.6 MHz, *d*^{6}-DMSO): δ 29.1, 50.3, 126.1, 128.2, 128.5, 129.2, 129.3, 129.9 (2x), 130.1, 132.2, 134.4, 144.8, 162.4. HRMS–ESI: m/z $[M + H]^+$ calcd for $C_{13}H_{17}ClN_3^+$: 320.1525; found: 320.1529.

***N*-(Cyclohexyl)-2,4-diphenyloxazole-5-carboxamide (8).**[1] White solid (m.p.: 168-170 °C). Yield: 52%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.18-2.08 (m, 10H, 5 x C*H*$_2$ cyclohexane), 3.96-4.01 (m, 1H, CH cyclohexane), 6.28 (d, *J*= 8.1 Hz, 1H, N*H*), 7.40-8.29 (m, 10H, Ar). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 24.9, 25.4, 33.1, 48.4, 126.4, 127.0, 128.1, 128.8, 129.3 (2x), 130.4, 131.3, 138.8, 144.3, 157.0, 160.0.

Continuous flow synthesis of 4-substituted 5-aminoimidazole

A solution of formamide **2a** (1.8 mmol, 0.6 M) and Et_3N (9 mmol, 3 M) in $CHCl_3$ (3 mL) and a solution of $POCl_3$ (1.8 mmol, 0.6 M) in $CHCl_3$ (3 mL) were pumped with a total flow rate of 0.5 mL min^{-1} through a 10 mL coil reactor at 25 °C. The reactor outcome was filtered through an Omnifit Labware DIBA HIT™ column (ID × L: 6.6 mm x 150 mm) packed with silica gel (70-230 mesh, 1.5 g/ $mmol^{-1}$) under 100 psi BPR regime. The $CHCl_3$ solution of *t*-butylisocyanide (**1a**) (2 equiv., 0.2 M) collected into a Erlenmeyer flask with screw cap was then pumped and mixed with $CHCl_3$ solutions of the desired *p*-substituted phenyl 2-amino-acetonitrile (1 equiv., 0.1 M) and $Yb(OTf)_3$ (0.6 equiv., 0.06 M) with a total flow rate of 1.0 mL min^{-1}. The reaction mixture was flowed through a 10 mL coil reactor heated at 130 °C using a 140 psi BPR. The out flow was washed with an aqueous saturated solution of $NaHCO_3$, H_2O, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by automated silica gel flash chromatography (Eluent: CH_2Cl_2/MeOH from 100:0 to 95:5, v/v). The product was dissolved in dry 1,4-dioxane (2 mL) and treated with 4 M solution of HCl in 1,4-dioxane (1 mL) at 0 °C. The solvent was removed under *vacuo* and the product was precipitated and triturated from *n*-hexane/Et_2O to give the chlorohydrate form.

1-*tert*-Butyl-4-(4'-chlorophenyl)-5-aminoimidazole chlorohydrate (10a).[2] Orange amorphous solid. Yield: 51%. ^{1}H-NMR (400 MHz, CD_3OD): δ 1.80 (s, 9H, 3 x C*H*$_3$), 7.52-7.54 (m, 2H, 3'-C*H* + 5'-C*H*), 7.61-7.63 (m, 2H, 2'-C*H* + 6'-C*H*), 8.67 (s, 1H, 2-C*H*). ^{13}C-NMR (100.6 MHz, CD_3OD): δ 27.4, 60.2, 116.8, 126.1, 128.1, 129.0, 134.1, 134.9. HRMS–ESI: m/z $[M + H]^+$ calcd for $C_{13}H_{17}ClN_3^+$: 250.1106; found: 250.1106.

1-*tert*-Butyl-4-phenyl-5-aminoimidazole chlorohydrate (10b).[2] Grey solid (m.p.: 59-61 °C). Yield: 40%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.69 (s, 9H, 3 x C*H*$_3$), 3.31 (brs, 2H), 7.21 (t, *J*= 8.06 Hz, 1H, 4'-C*H*), 7.38-7.41 (m, 3H, 3'-C*H* + 5'-C*H* + 2-C*H*), 7.68 (d, *J*= 8.05 Hz, 2H, 2'-C*H* + 6'-C*H*). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 29.6, 55.9, 125.8, 126.1, 128.4, 128.6, 129.8, 131.4, 135.2. HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{18}N_3^+$: 216.1495; found: 216.1496.

1-*tert*-Butyl-4-[((4'-morpholyn)-4-yl)phenyl]-5-aminoimidazole chlorohydrate (10c).[2] Brown solid (m.p.: 59-62 °C). Yield: 34%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.60 (s, 9H, 3 x C*H*$_3$), 3.16-3.28 [m, 8H, -O(C*H*$_2$C*H*$_2$)$_2$N-], 7.35 (d, *J*= 8.08 Hz, 2H, 3'-C*H* + 5'-C*H*), 7.71 (d, *J*= 8.06 Hz, 2H, 2'-C*H* + 6'-C*H*), 8.46 (s, 1H, 2-C*H*). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 27.2, 48.9, 61.2, 66.6, 114.3, 115.7, 117.7, 128.3,

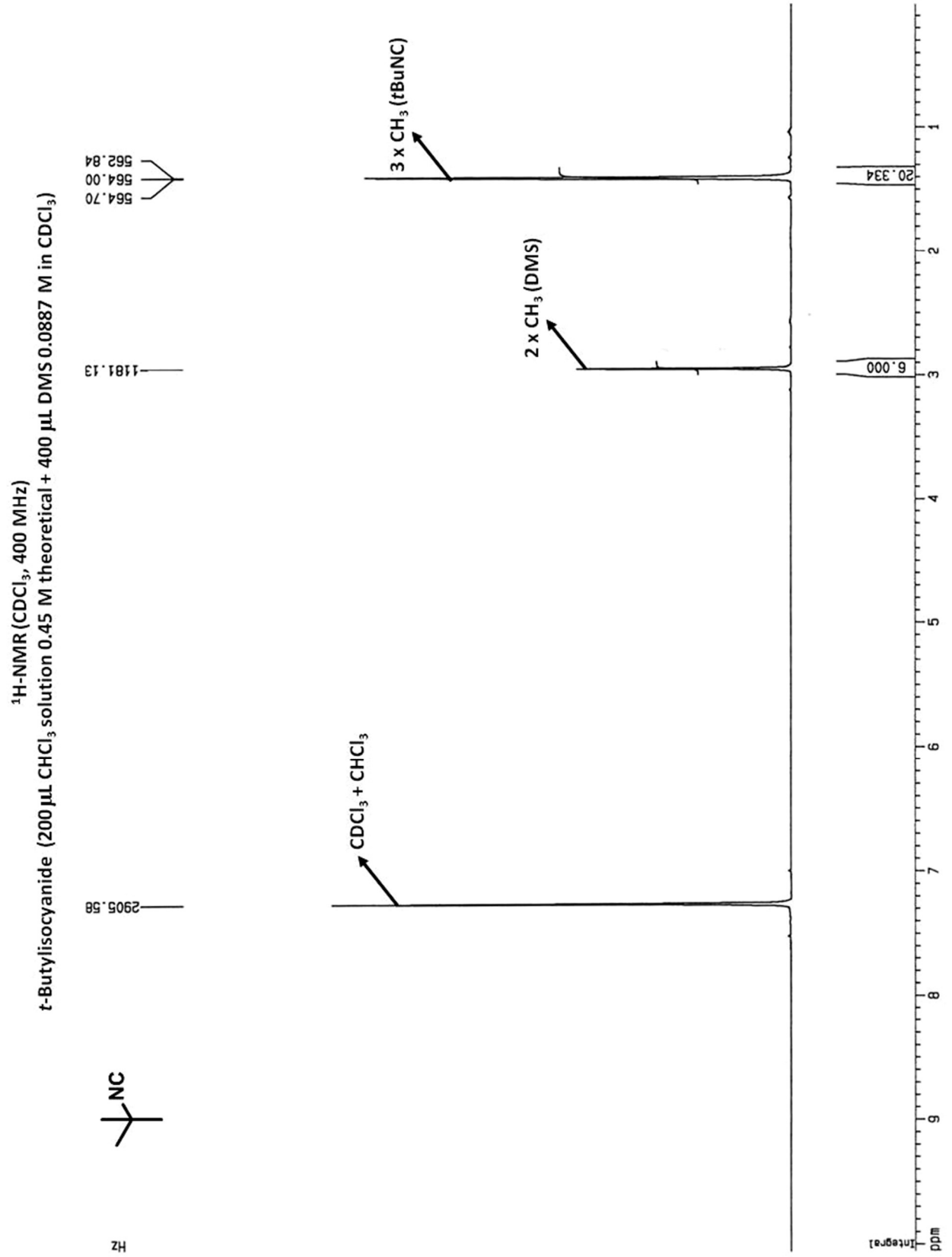
130.3, 151.6, 153.5. HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{18}N_3^+$: 336.1717; found: 336.1719.

Continuous flow synthesis of lidocaine (12)[3]

A solution of formamide **2g** (0.15 M) and Et_3N (0.75 M) in $CHCl_3$/DMSO (95:5, v/v) and a $CHCl_3$ solution of $POCl_3$ (0.15 M) were pumped with a total flow rate of 0.5 mL min^{-1} through a 10 mL coil reactor at 25 °C. The reactor outcome was collected into a sealed flask, concentrated under reduced pressure (T: ≤30 °C) and purified by automated flash chromatography on silica gel (Biotage Isolara One, Eluent: *n*-hexane/Et_2O from 100:0 to 60:40, v/v). The resulting 2,6-dimethylphenyl isocyanide (**1g**, 44% isolated yield) was dissolved in $CHCl_3$ (0.1 M) and mixed *via* a four ways connector with a MeOH solution of diethylamine (0.1 M) and a solution containing formaldehyde (0.1 M in MeOH) and 2-hydroxymethylbenzoic (**11**) (0.1 M in MeOH), and reacted in a 10 mL coil reactor (τ= 66 min) heated at 80° C. The crude reaction mixture was loaded into a automated flash chromatography to afford 2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide (lidocaine, **12**) in 69% yield.

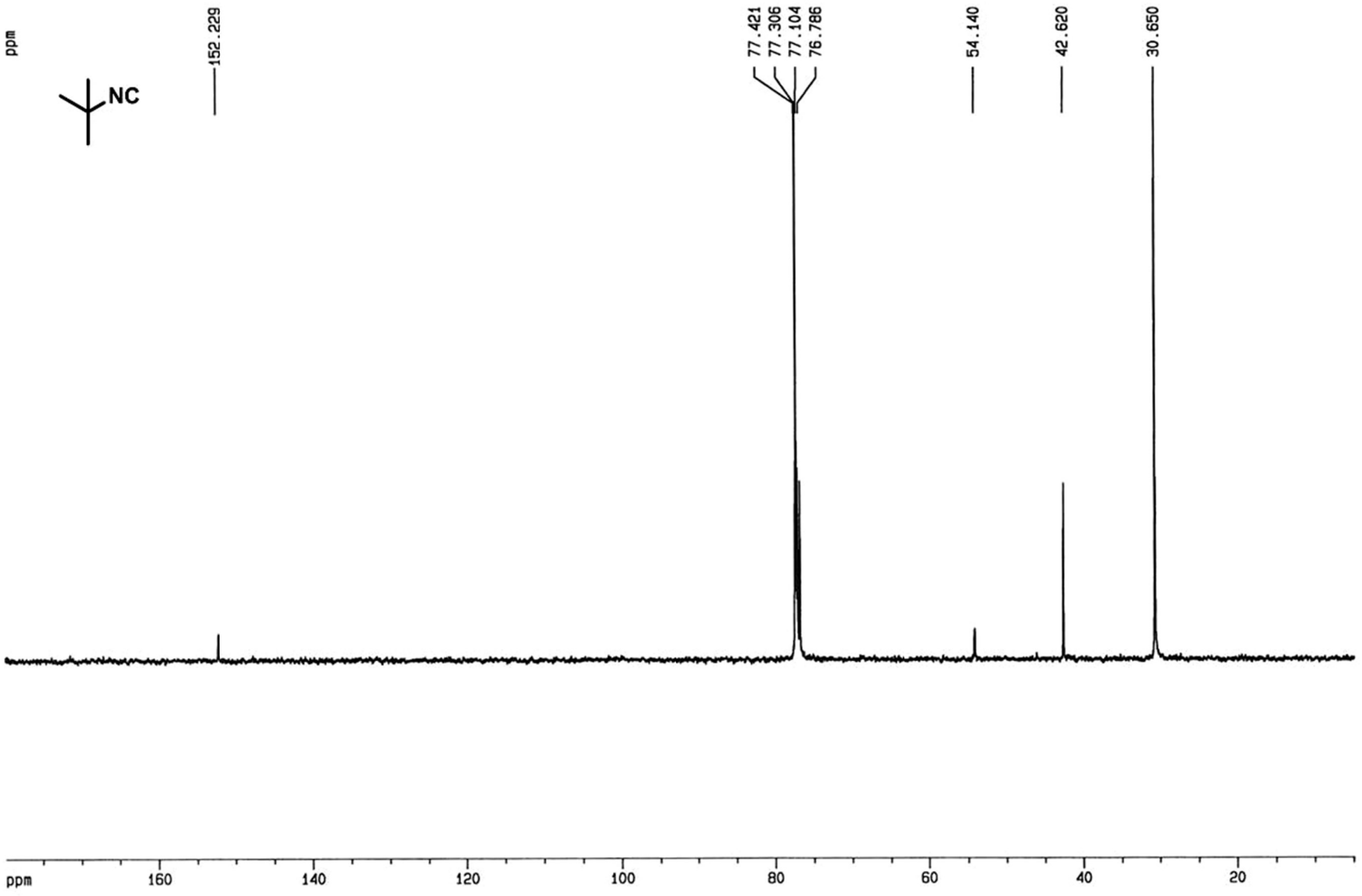
White solid (m.p.: 76-78 °C). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.14 (t, *J*= 7.6, 6H, 2 x CH_2CH_3), 2.23 (s, 6H, 2 x Ph-CH_3), 2.69 (q, J= 7.6 Hz, 4H, 2 x CH_2CH_3), 3.22 (s, 2H, CH_2NEt_2), 7.09-7.12 (m, 3H, -*CH*). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 12.6, 18.5, 48.9, 57.4, 127.0, 128.1, 133.9, 135.0, 170.2.

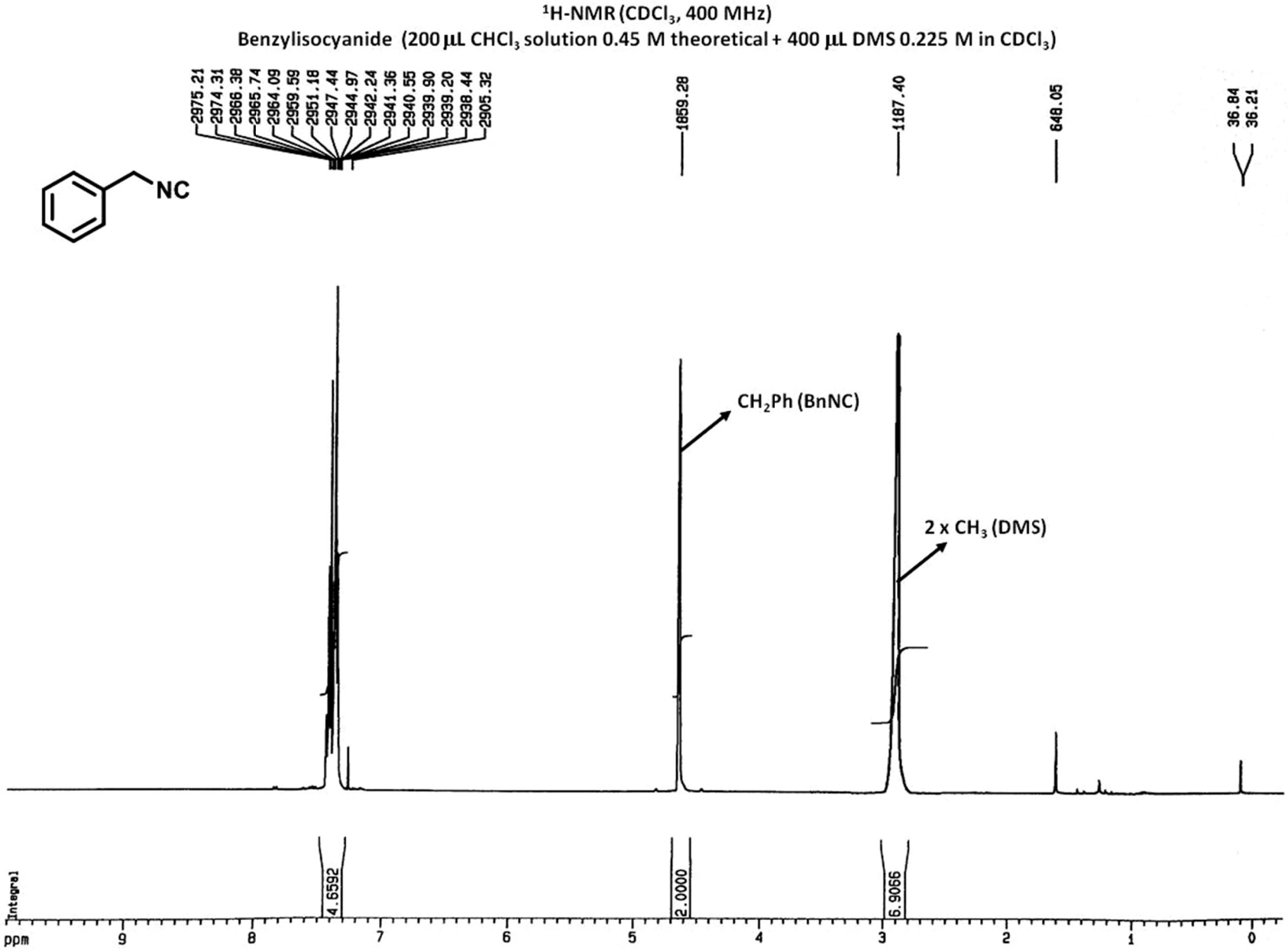
Copies of NMR Spectra



^{13}C-NMR ($CDCl_3$, 100.6 MHz)

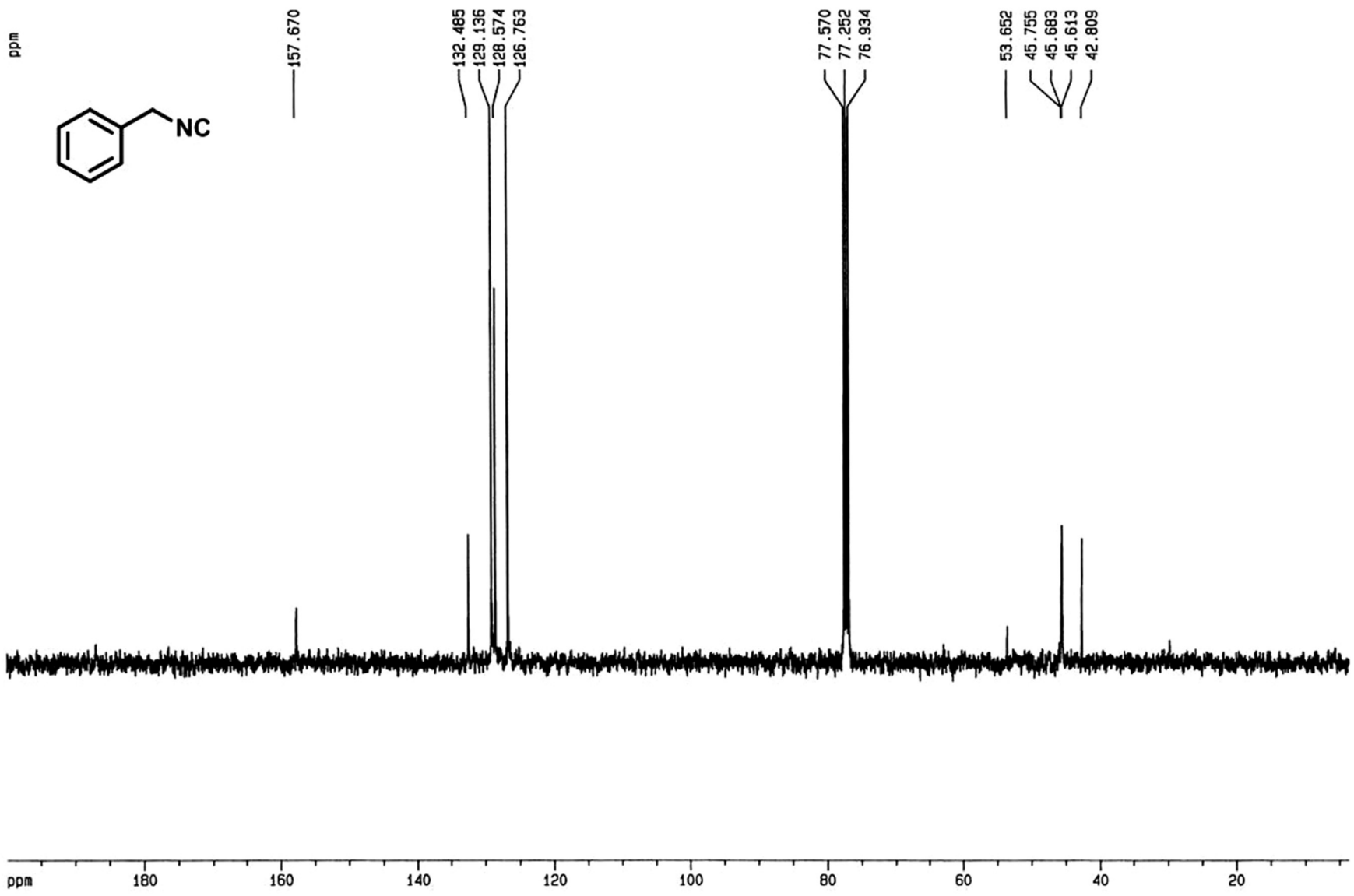
t-Butylisocyanide (200 µL $CHCl_3$ solution 0.45 M theoretical + 400 µL DMS 0.0887 M in $CDCl_3$)

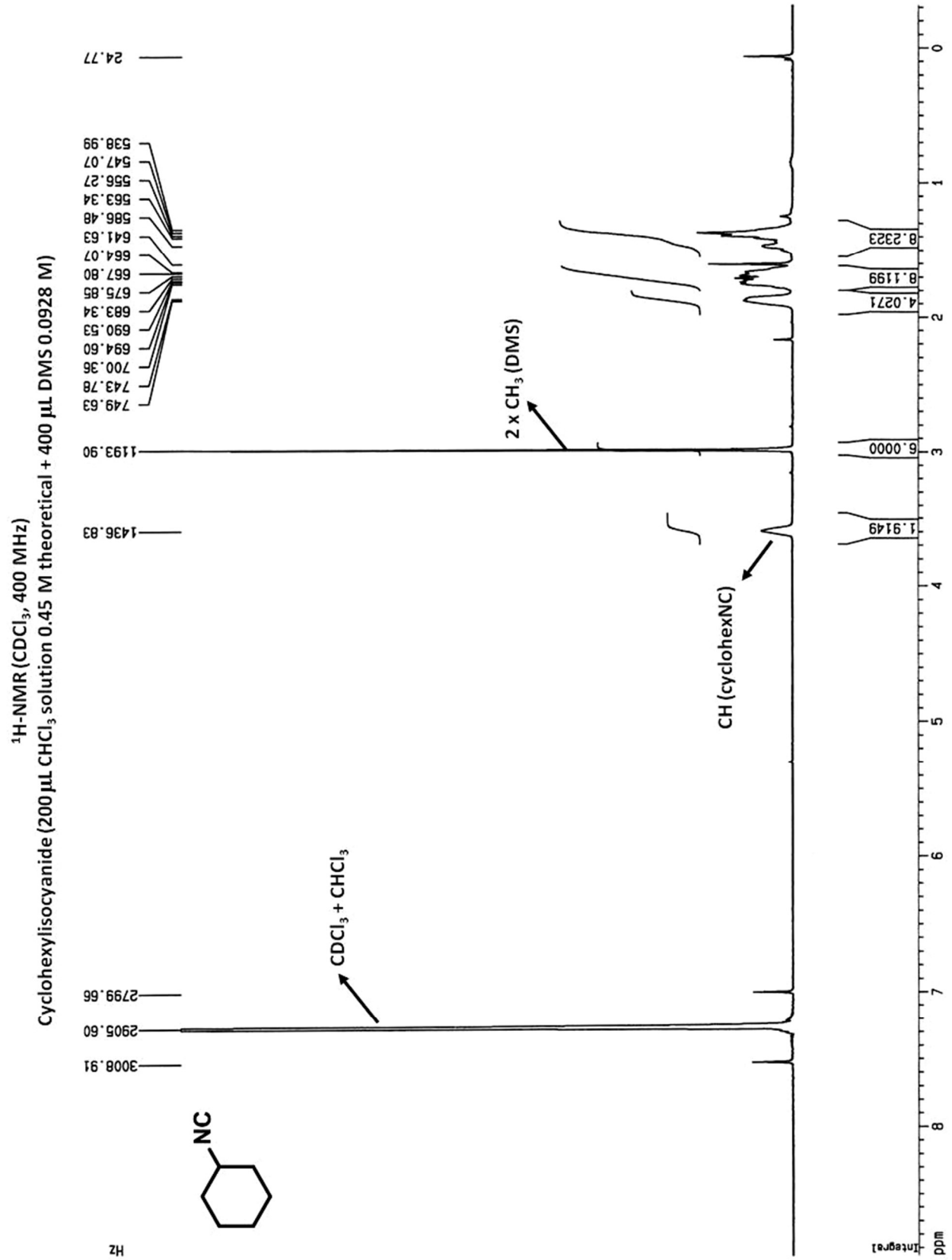



¹H-NMR (CDCl3, 400 MHz)
Benzylisocyanide (200 µL CHCl3 solution 0.45 M theoretical + 400 µL DMS 0.225 M in CDCl3)
2975.21
2974.31
2966.38
2965.74
2964.09
2959.59
2951.18
2947.44
2944.97
2942.24
2941.36
2940.55
2939.90
2939.20
2938.44
2905.32
1859.28
1187.40
648.05
36.84
36.21
NC
CH2Ph (BnNC)
2 x CH3 (DMS)
Integral
4.6592
2.0000
6.9066
ppm
9
8
7
6
5
4
3
2
1
0

^{13}C-NMR ($CDCl_3$, 100.6 MHz)

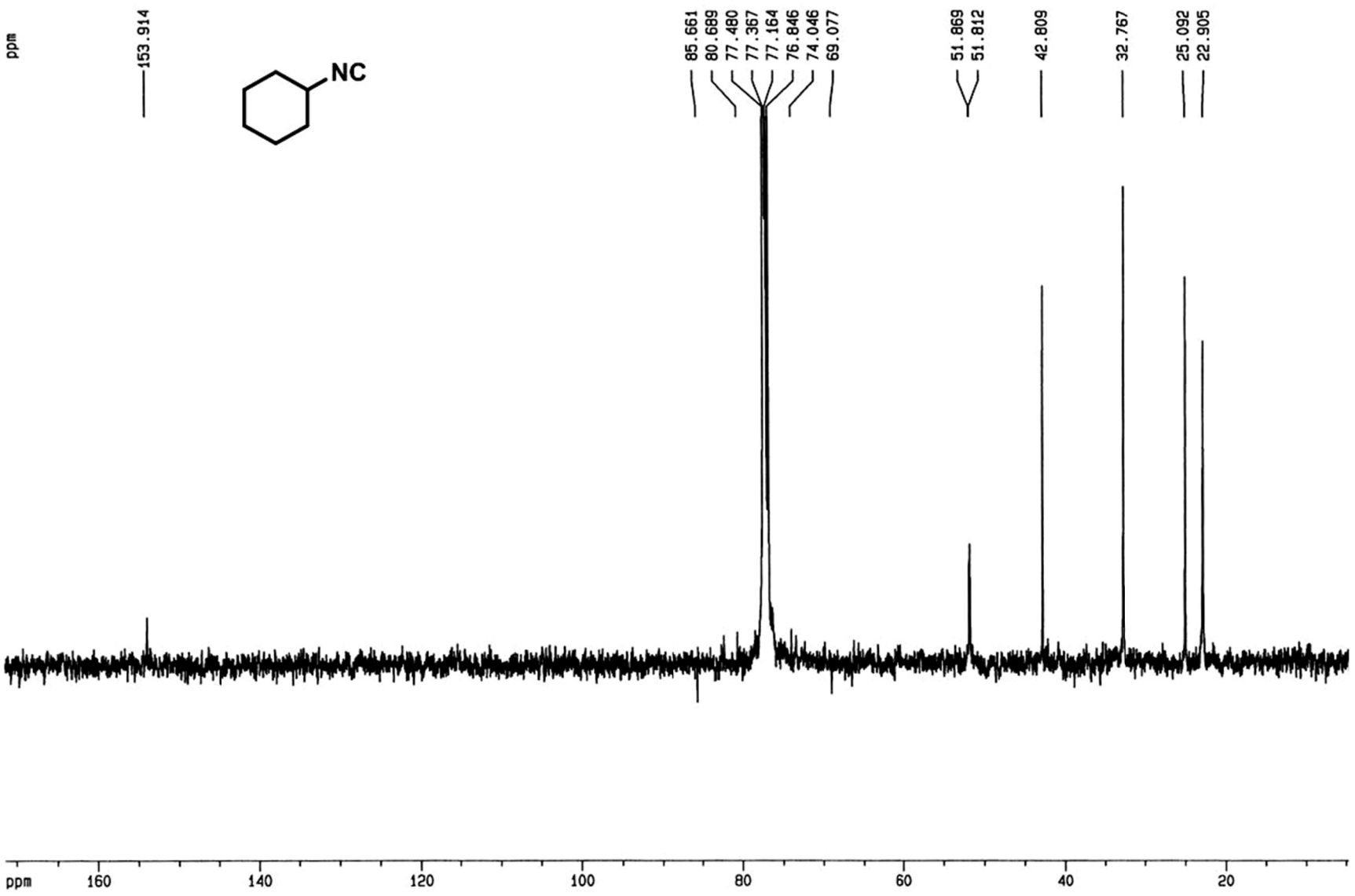
Benzylisocyanide (200 µL $CHCl_3$ solution 0.45 M theoretical + 400 µL DMS 0.225 M in $CDCl_3$)

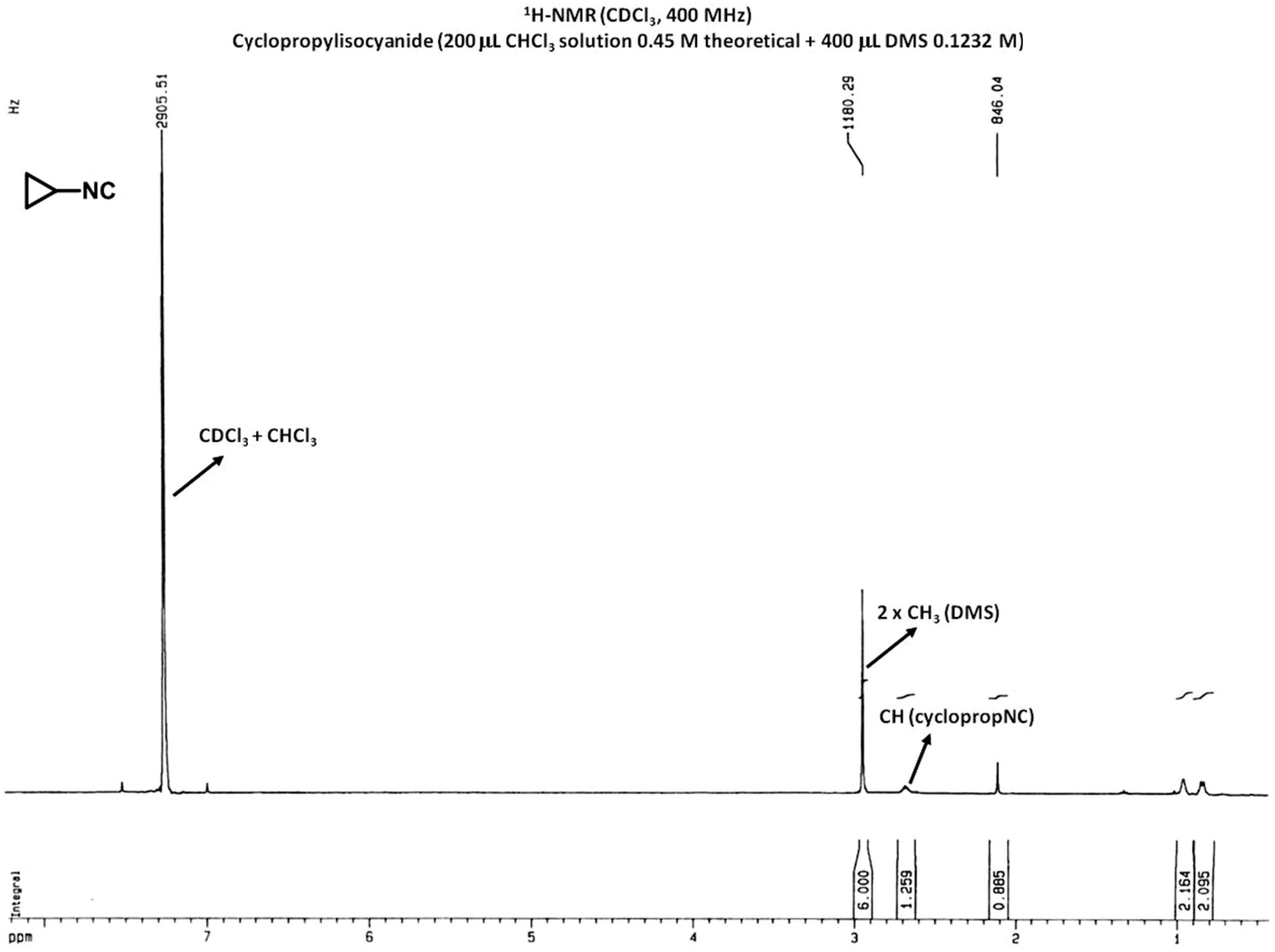



^{1}H-NMR ($CDCl_3$, 400 MHz)
Cyclohexylisocyanide (200 µL $CHCl_3$ solution 0.45 M theoretical + 400 µL DMS 0.0928 M)
Hz
3008.91
2905.60
2799.66
1436.83
1193.90
749.63
743.78
700.36
694.60
690.53
683.34
675.85
667.80
664.07
641.63
586.48
563.34
556.27
547.07
538.99
24.77
$CDCl_3 + CHCl_3$
2 x CH_3 (DMS)
CH (cyclohexNC)
NC
Integral
1.9149
6.0000
4.0271
8.1199
8.2323
ppm

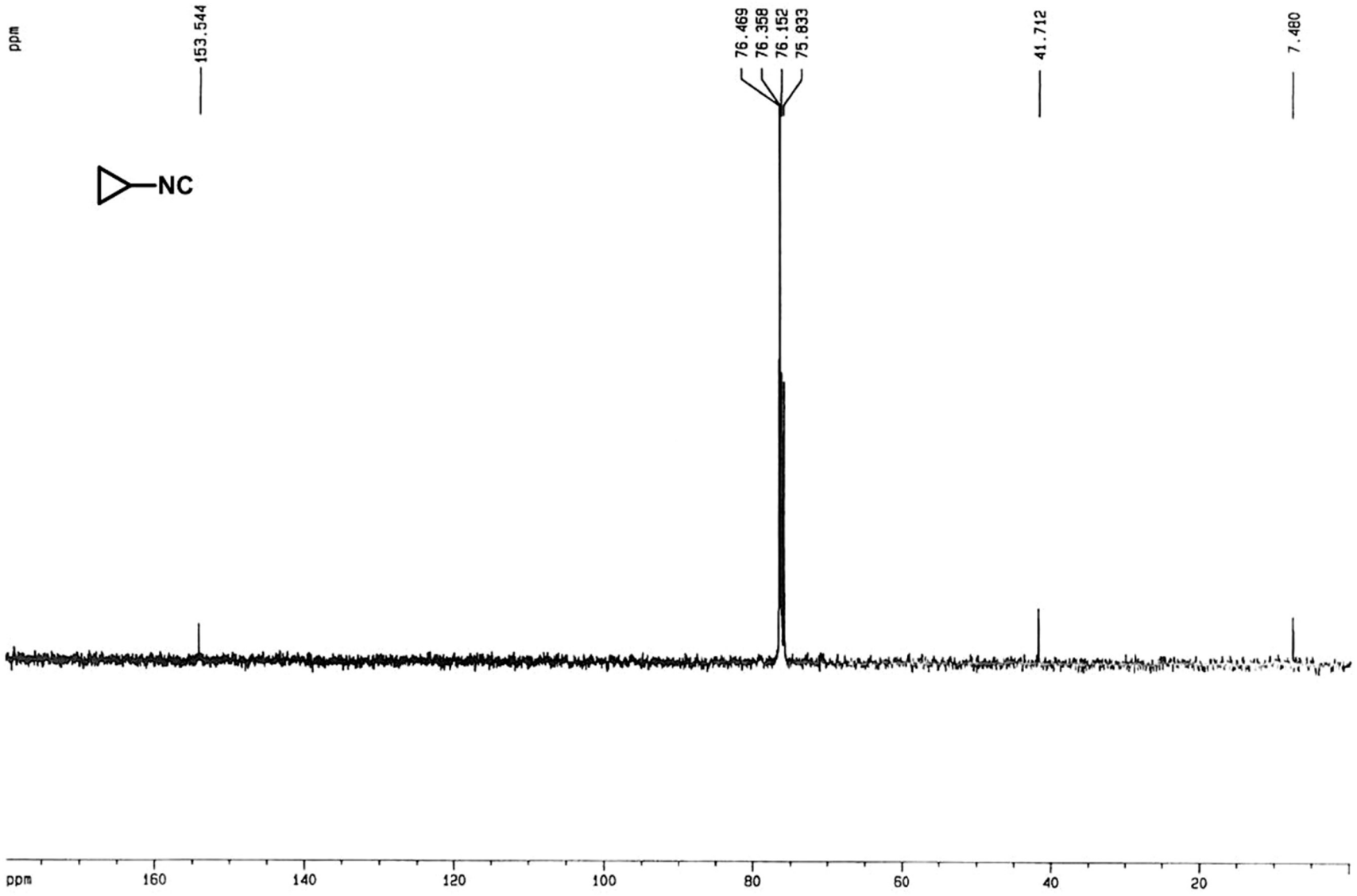
^{13}C-NMR ($CDCl_3$, 100.6 MHz)

Cyclohexylisocyanide (200 µL $CHCl_3$ solution 0.45 M theoretical + 400 µL DMS 0.0928 M)

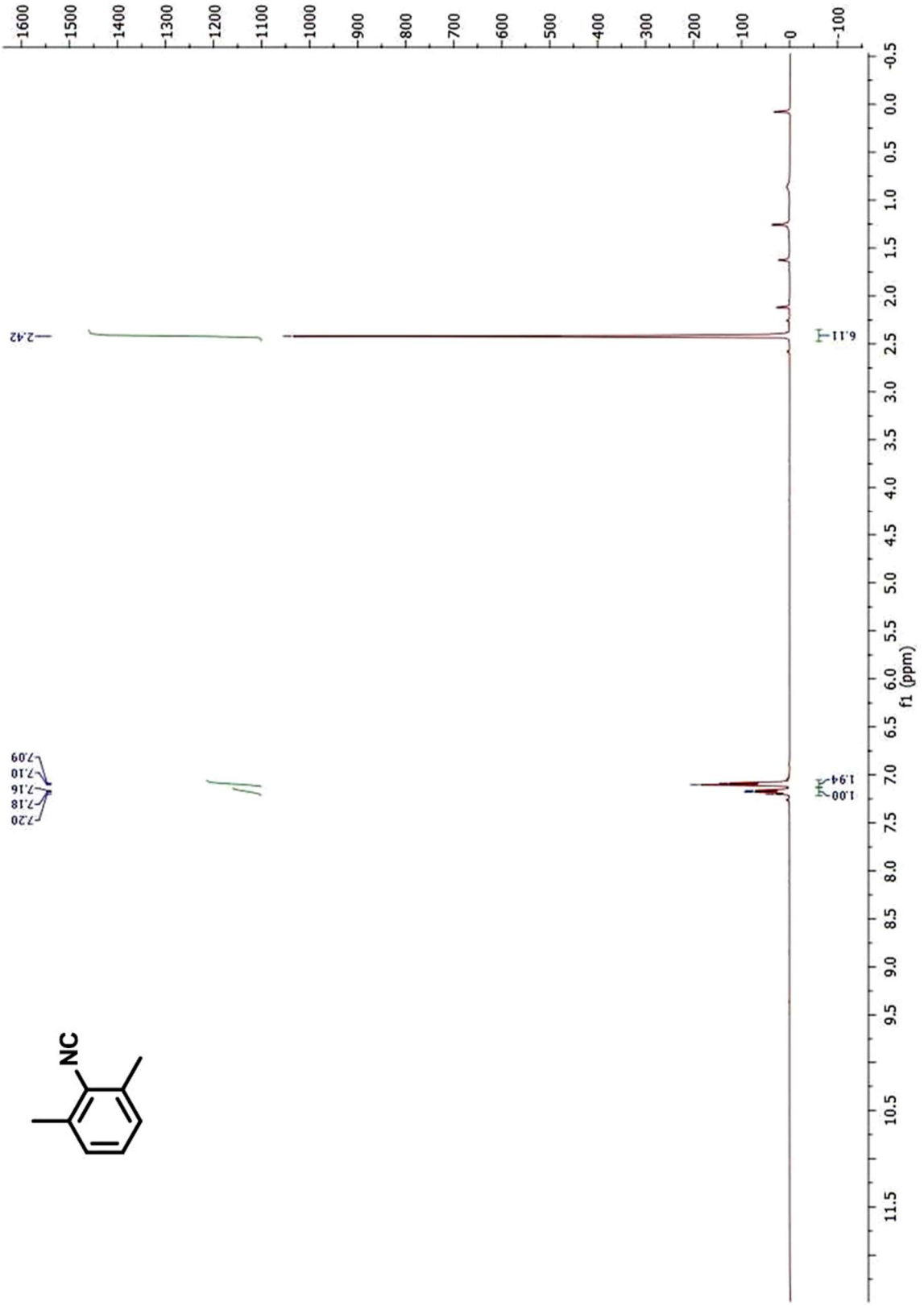


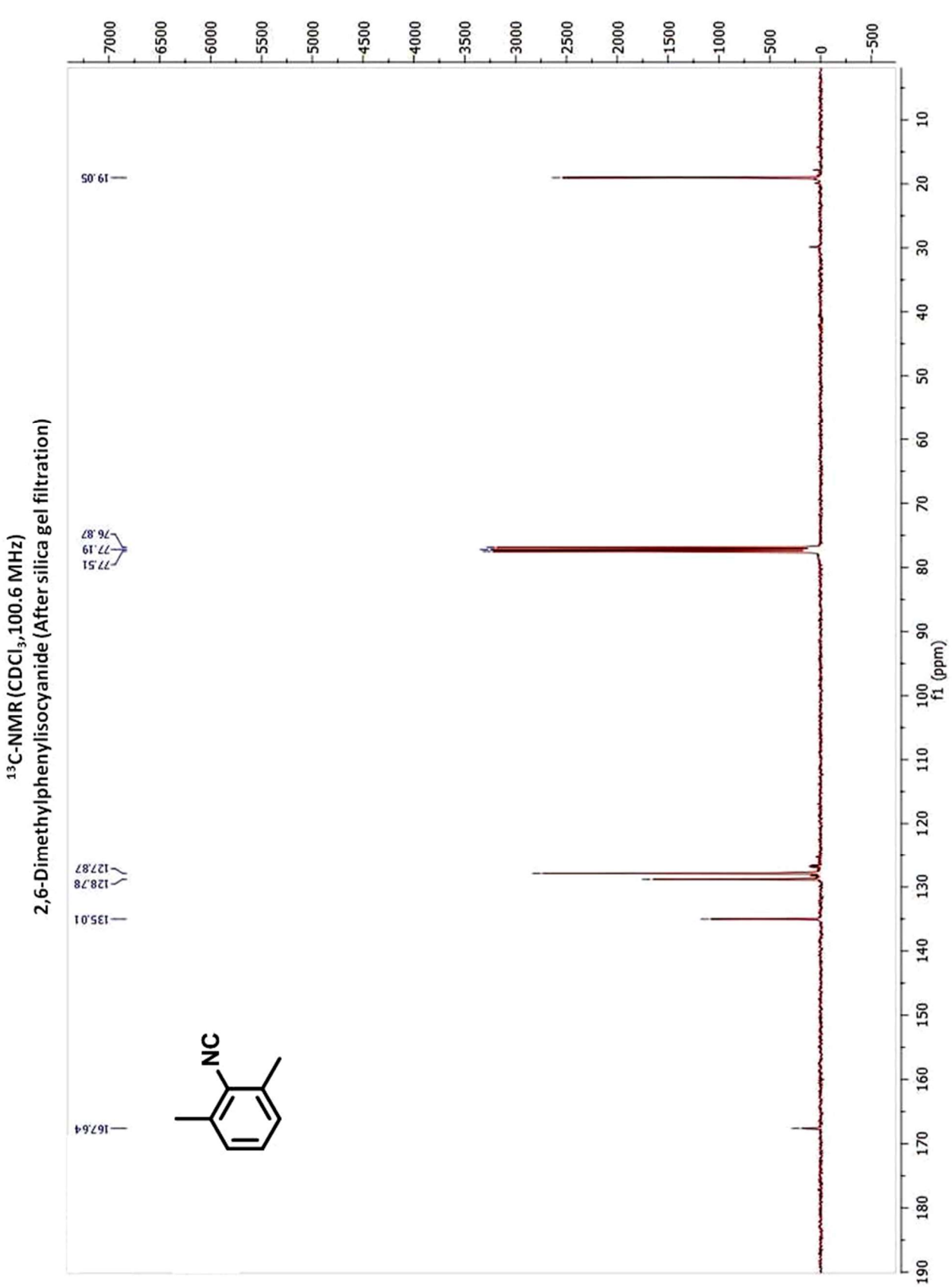

¹H-NMR (CDCl₃, 400 MHz)
Cyclopropylisocyanide (200 µL CHCl₃ solution 0.45 M theoretical + 400 µL DMS 0.1232 M)
Hz
2905.51
1180.29
846.04
NC
CDCl₃ + CHCl₃
2 x CH₃ (DMS)
CH (cyclopropNC)
Integral
6.000
1.259
0.885
2.164
2.095
ppm
7
6
5
4
3
2
1

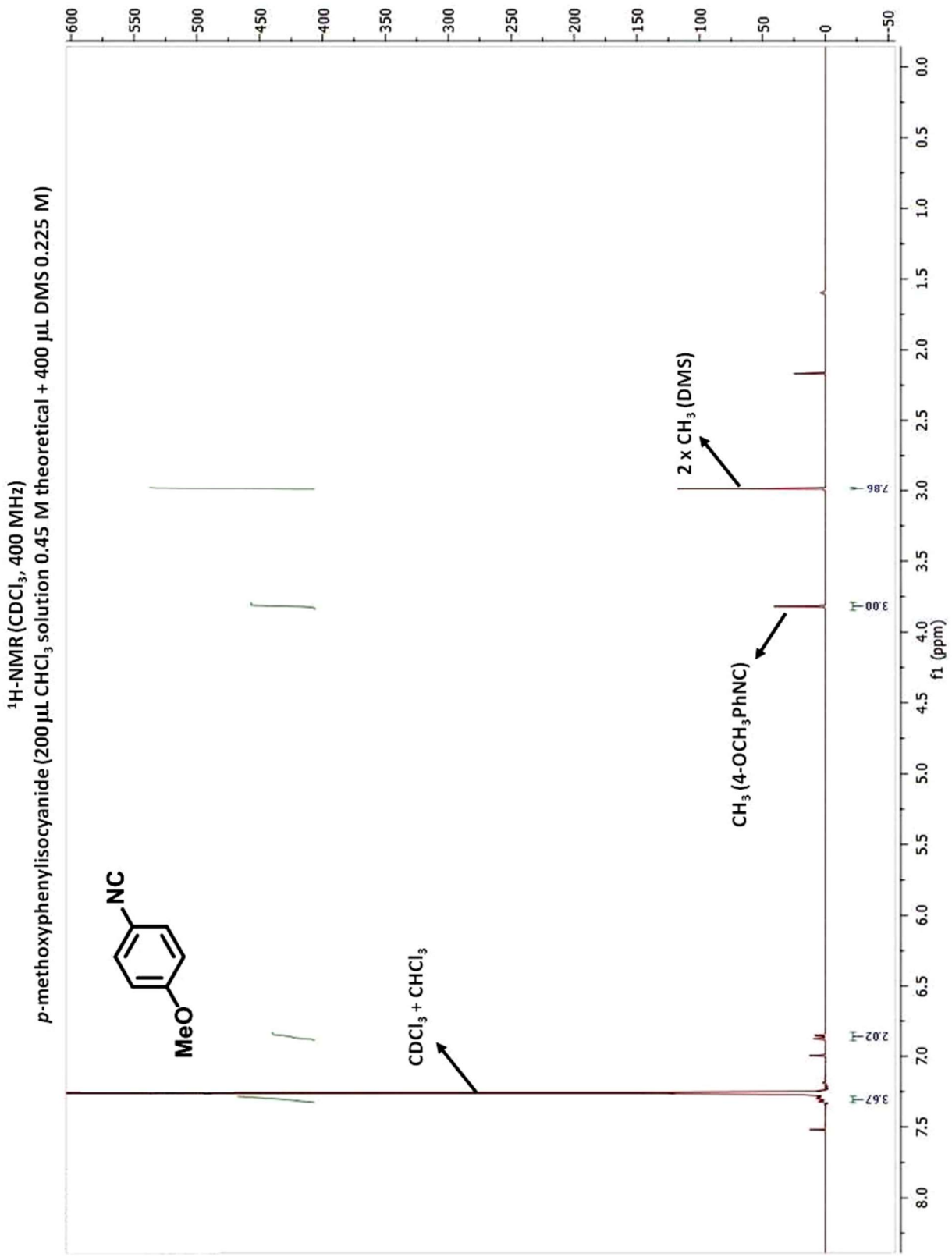
^{13}C-NMR ($CDCl_3$, 100.6 MHz)
Cyclopropylisocyanide (200 µL $CHCl_3$ solution 0.45 M theoretical + 400 µL DMS 0.1232 M)

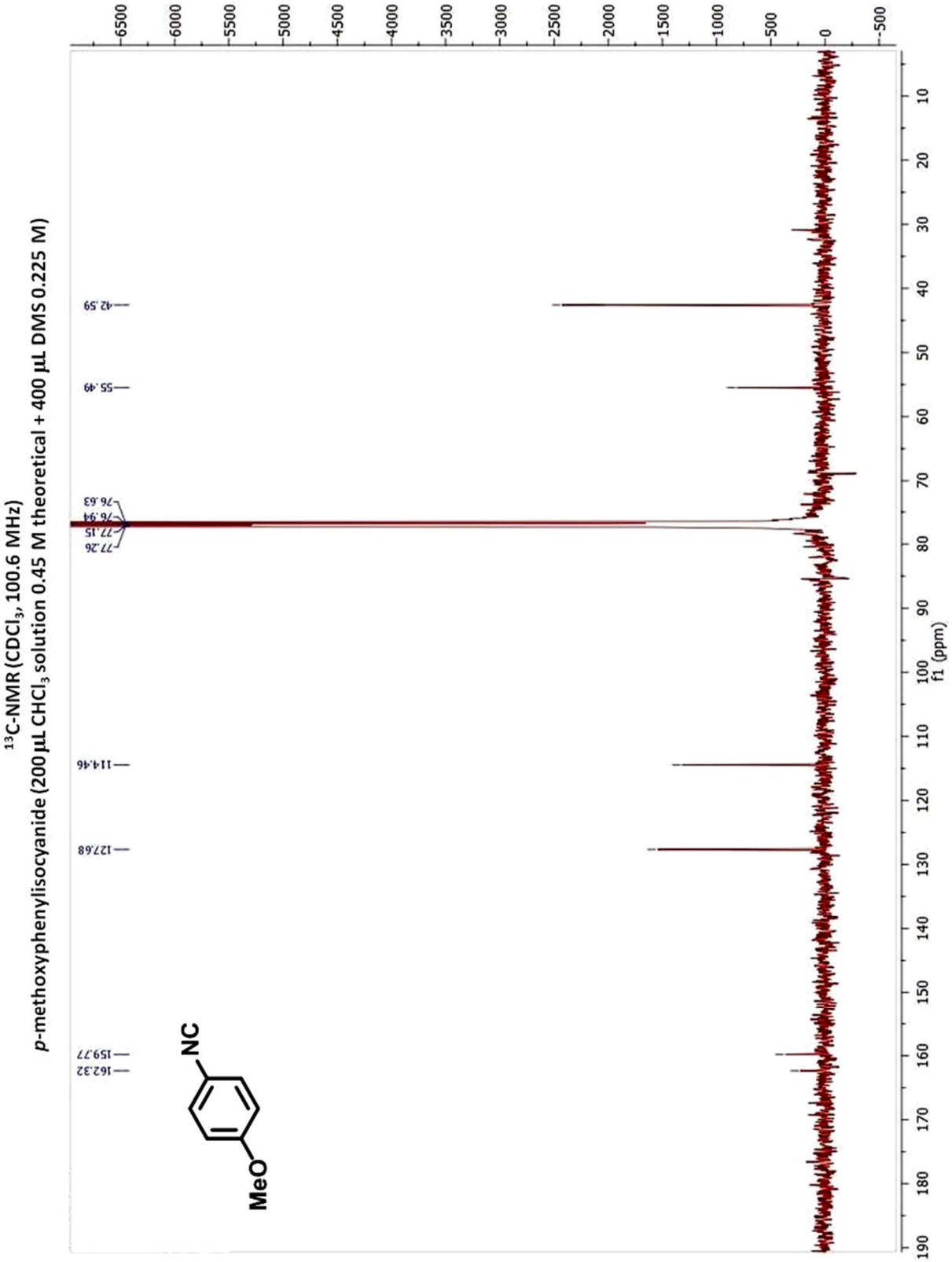


^{1}H-NMR ($CDCl_3$, 400 MHz)
2,6-Dimethylphenylisocyanide (After silica gel filtration)



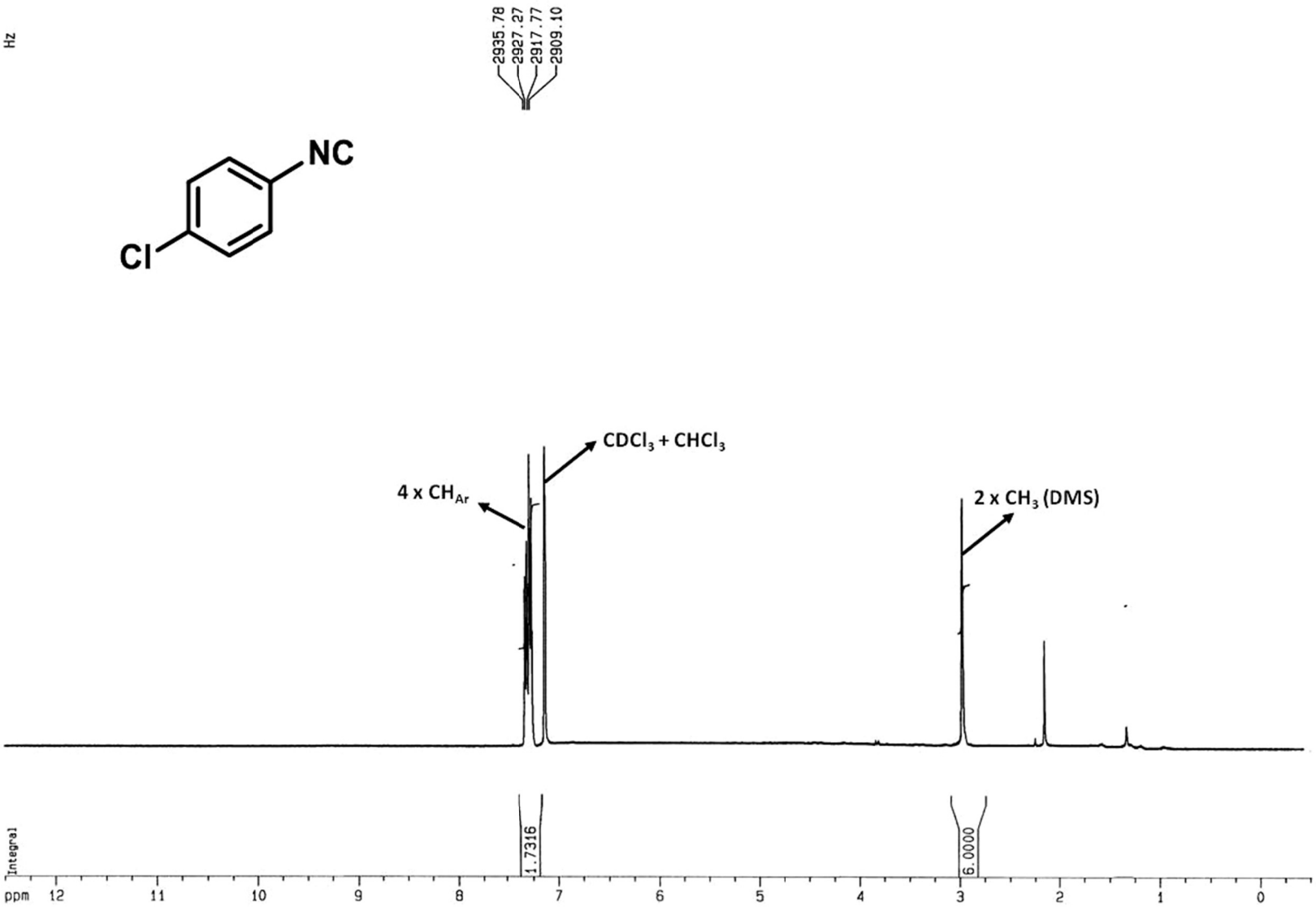

13C-NMR (CDCl3,100.6 MHz)
2,6-Dimethylphenylisocyanide (After silica gel filtration)
19.05
76.87
77.19
77.51
127.87
128.78
135.01
167.64
NC
f1 (ppm)


^{1}H-NMR ($CDCl_3$, 400 MHz)
p-methoxyphenylisocyanide (200 µL $CHCl_3$ solution 0.45 M theoretical + 400 µL DMS 0.225 M)
NC
MeO
$CDCl_3 + CHCl_3$
CH_3 (4-OCH_3PhNC)
2 x CH_3 (DMS)
3.67
2.02
3.00
7.86
f1 (ppm)


^{13}C-NMR ($CDCl_3$, 100.6 MHz)
p-methoxyphenylisocyanide (200 µL $CHCl_3$ solution 0.45 M theoretical + 400 µL DMS 0.225 M)
NC
MeO
162.32
159.77
127.68
114.46
77.26
77.15
76.94
76.63
55.49
42.59
f1 (ppm)

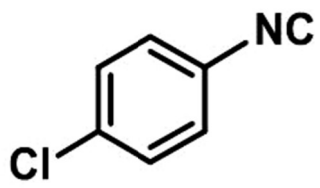
^{1}H-NMR ($CDCl_3$, 400 MHz)

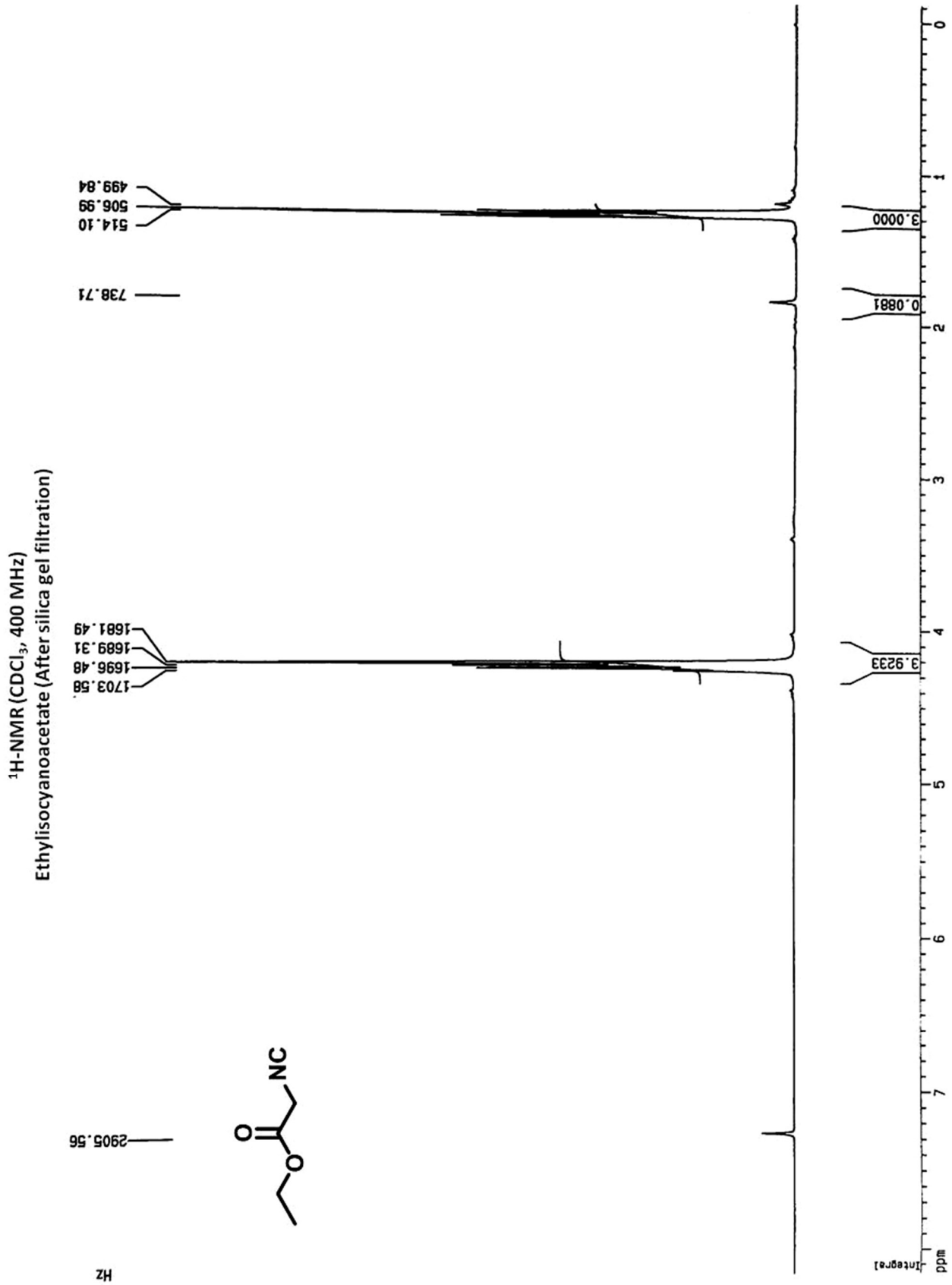
4-Chlorophenylsocyanide (200 µL $CHCl_3$ solution 0.45 M theoretical + 400 µL DMS 0.410 M in $CDCl_3$)



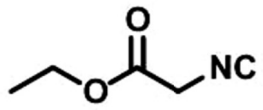
^{13}C-NMR ($CDCl_3$, 400 MHz)

4-Chlorophenylsocyanide (200 µL $CHCl_3$ solution 0.45 M theoretical + 400 µL DMS 0.410 M in $CDCl_3$)

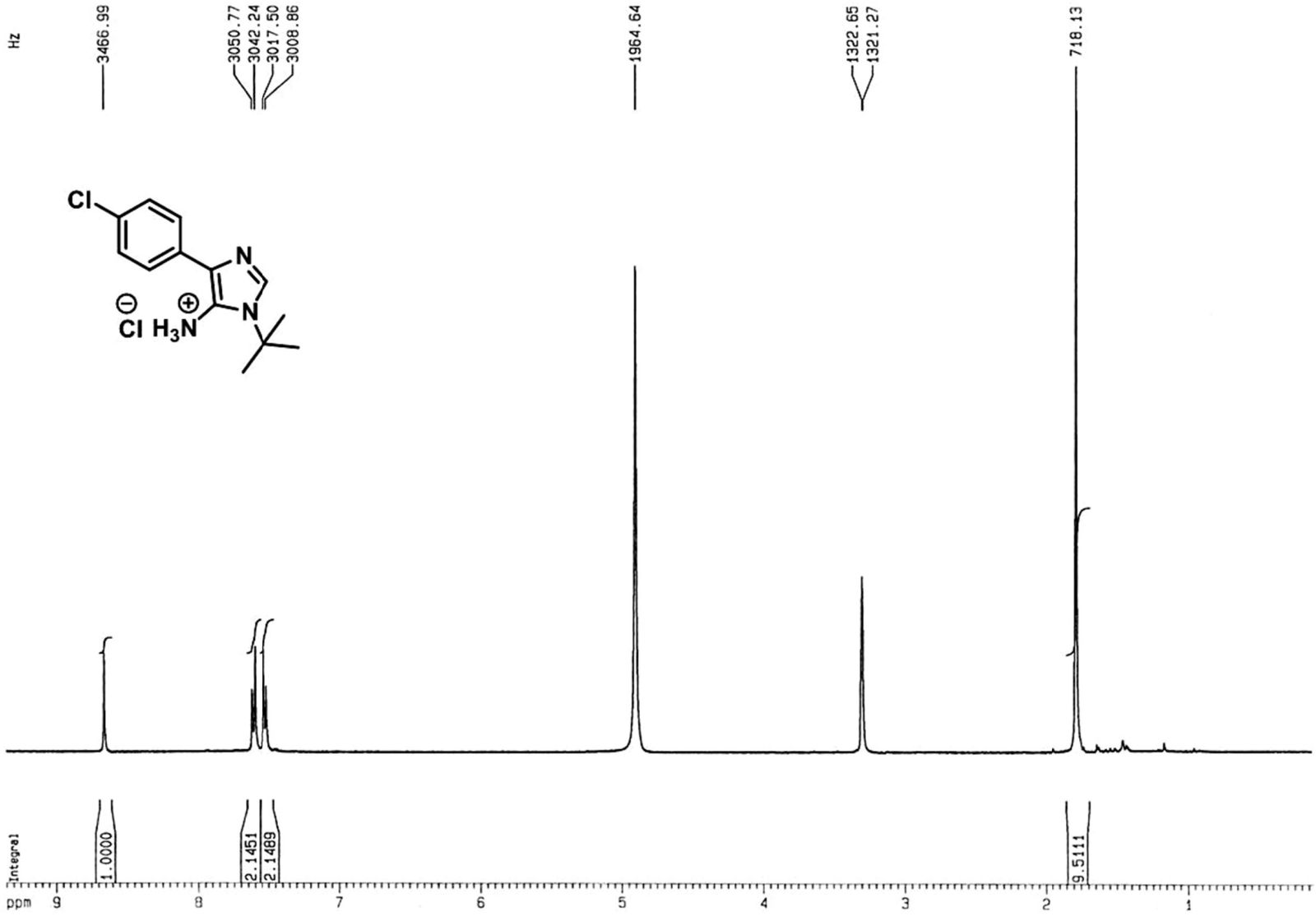



^{1}H-NMR ($CDCl_3$, 400 MHz)
Ethylisocyanoacetate (After silica gel filtration)
1703.58
1696.48
1689.31
1681.49
738.71
514.10
506.99
499.84
2905.56
Hz
NC
O
O
3.9233
0.0881
3.0000
Integral
ppm
0
1
2
3
4
5
6
7

^{13}C-NMR ($CDCl_3$, 100.6 MHz)
Ethylisocyanoacetate (After silica gel filtration)

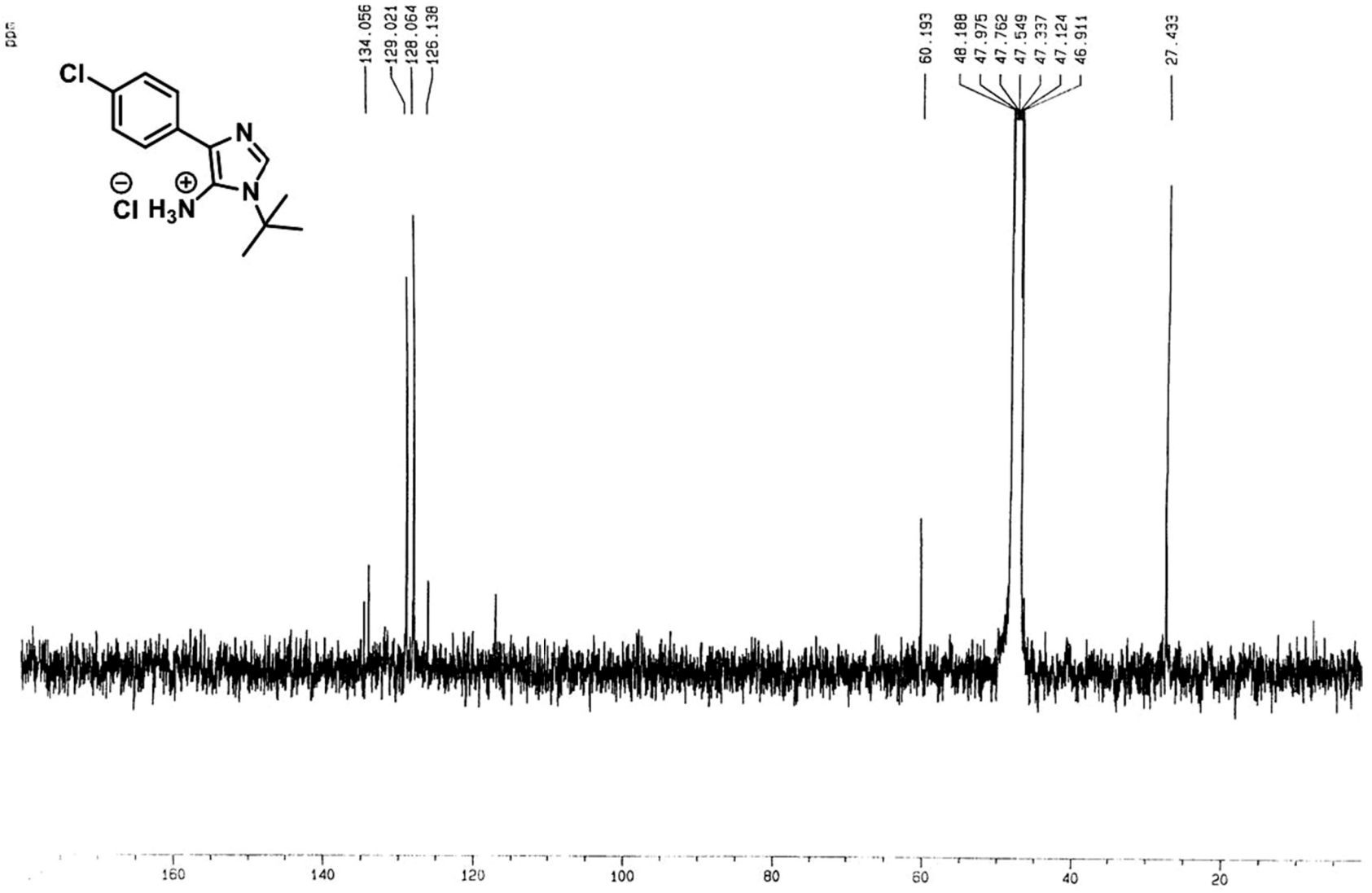


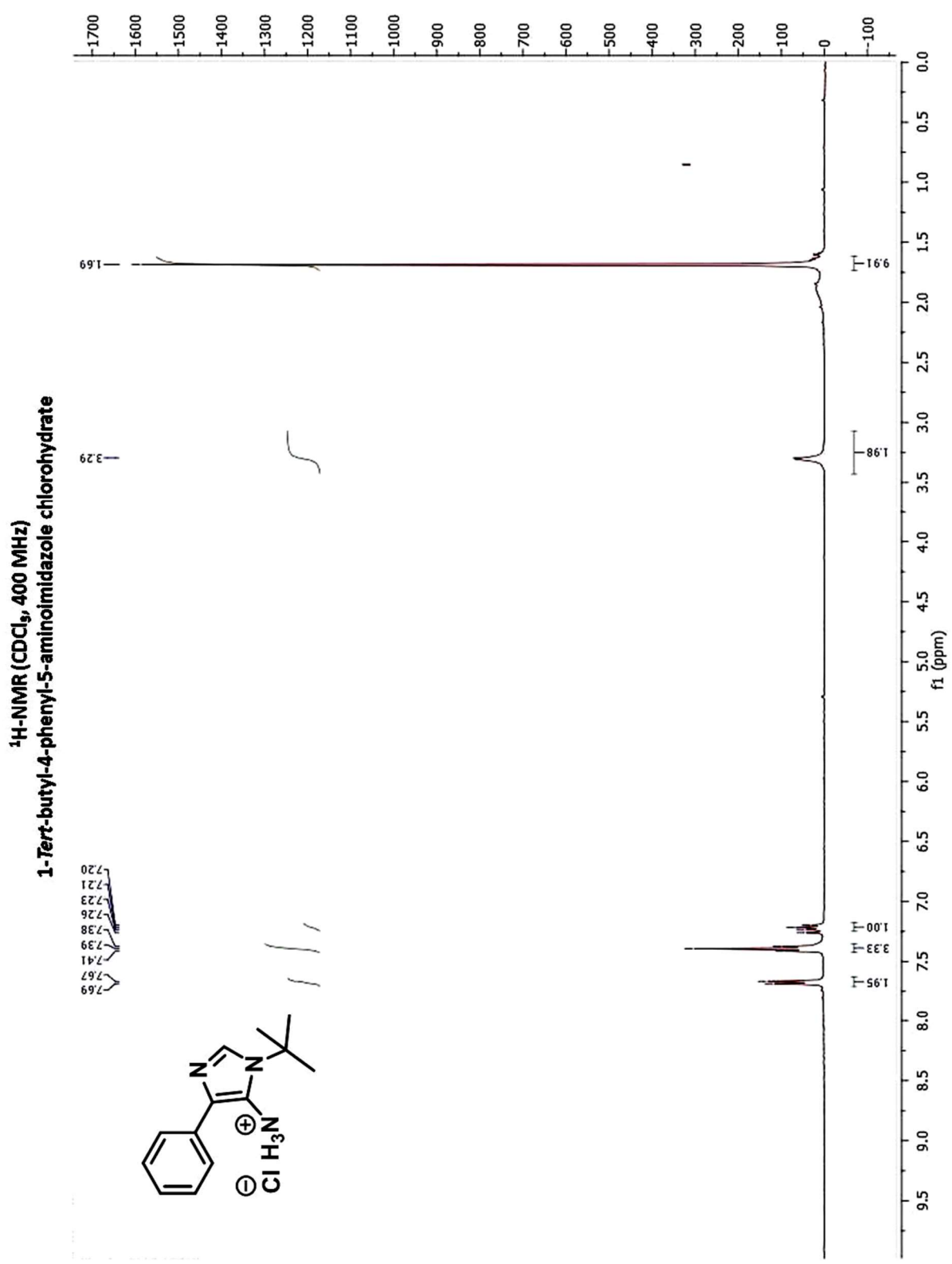
^{1}H-NMR (CD_3OD, 400 MHz)
1-*Tert*-butyl-4-(4'-chlorophenyl)-5-aminoimidazole chlorohydrate

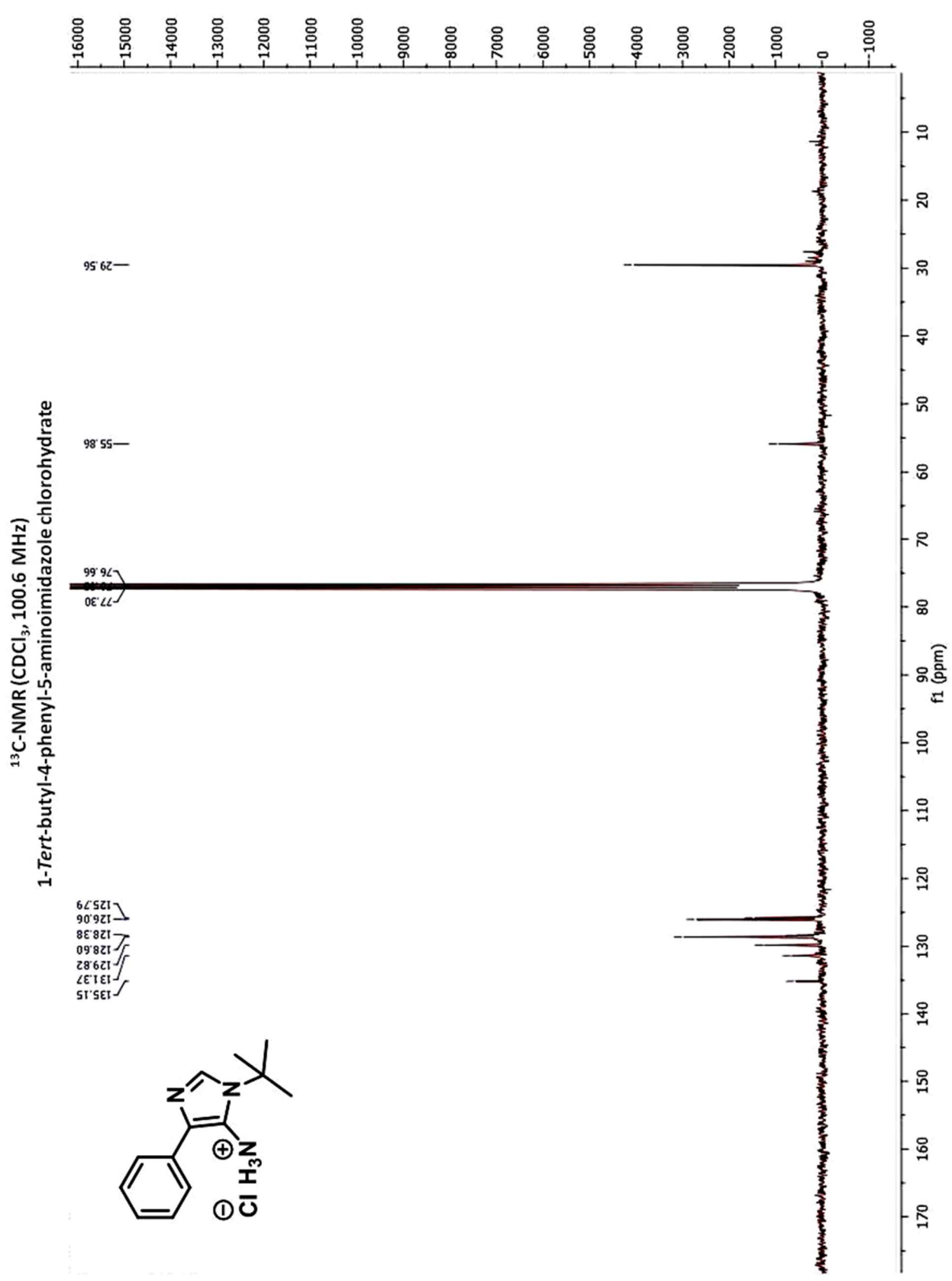


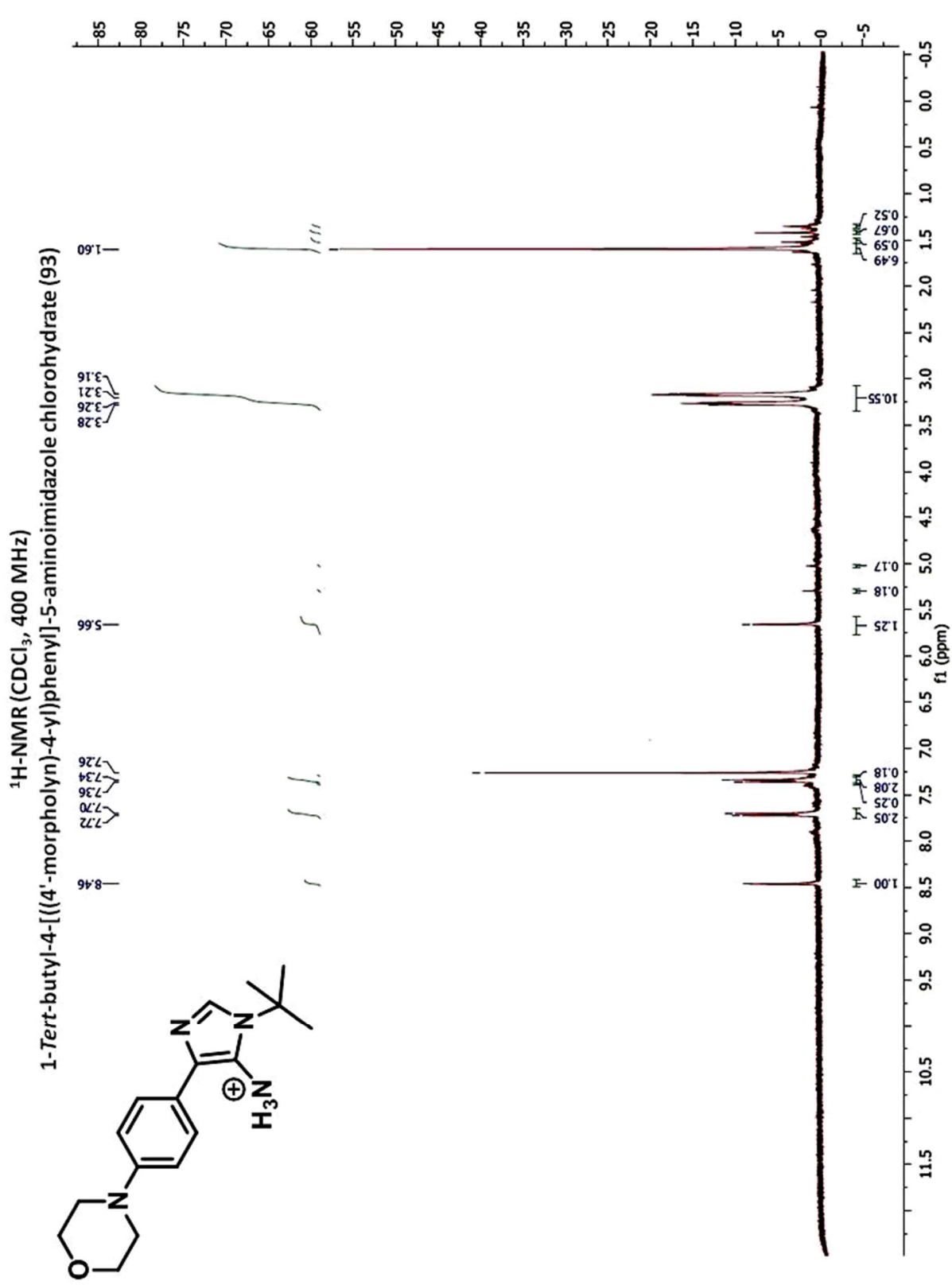
^{13}C-NMR (CD_3OD, 100.6 MHz)

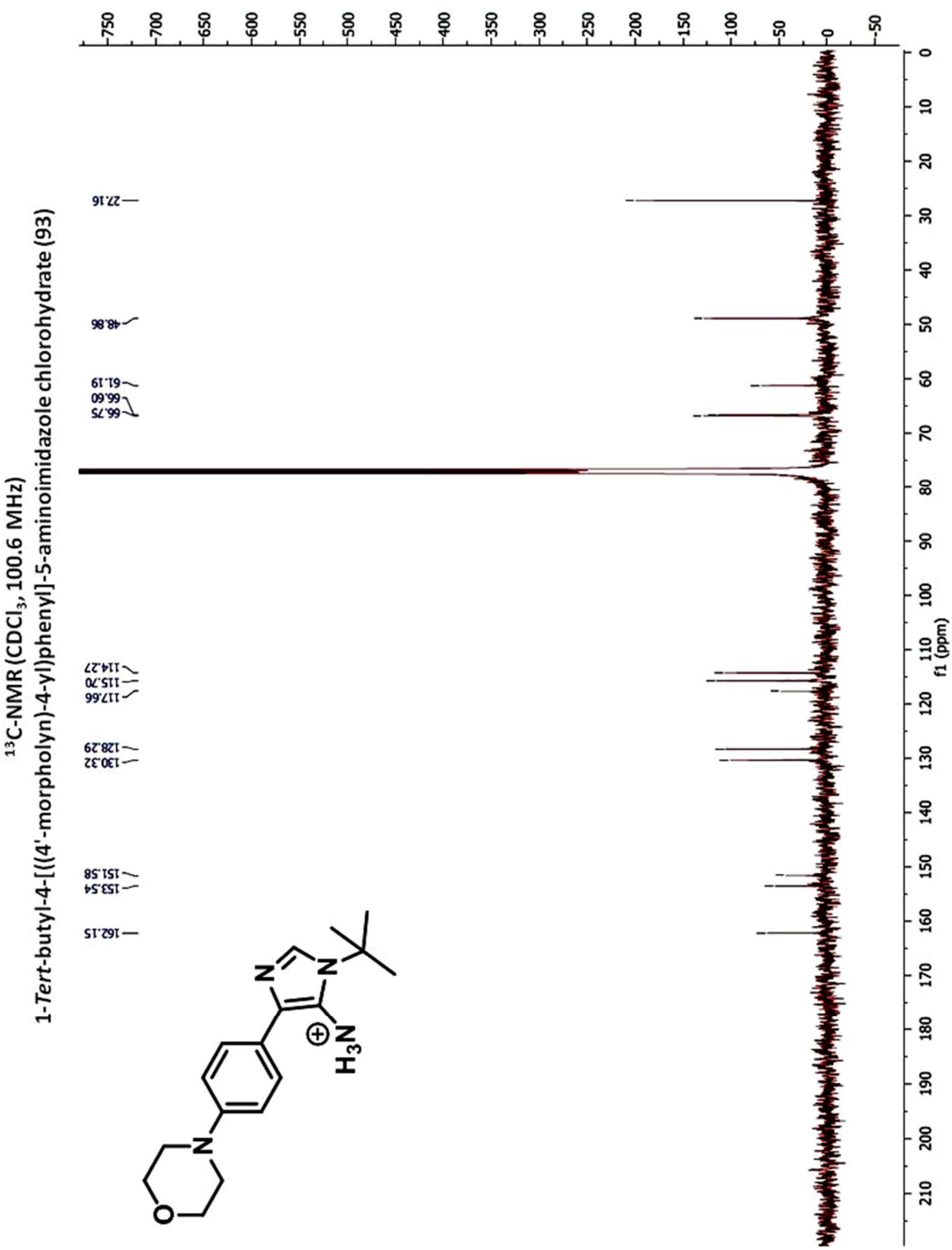
1-*Tert*-butyl-4-(4'-chlorophenyl)-5-aminoimidazole chlorohydrate

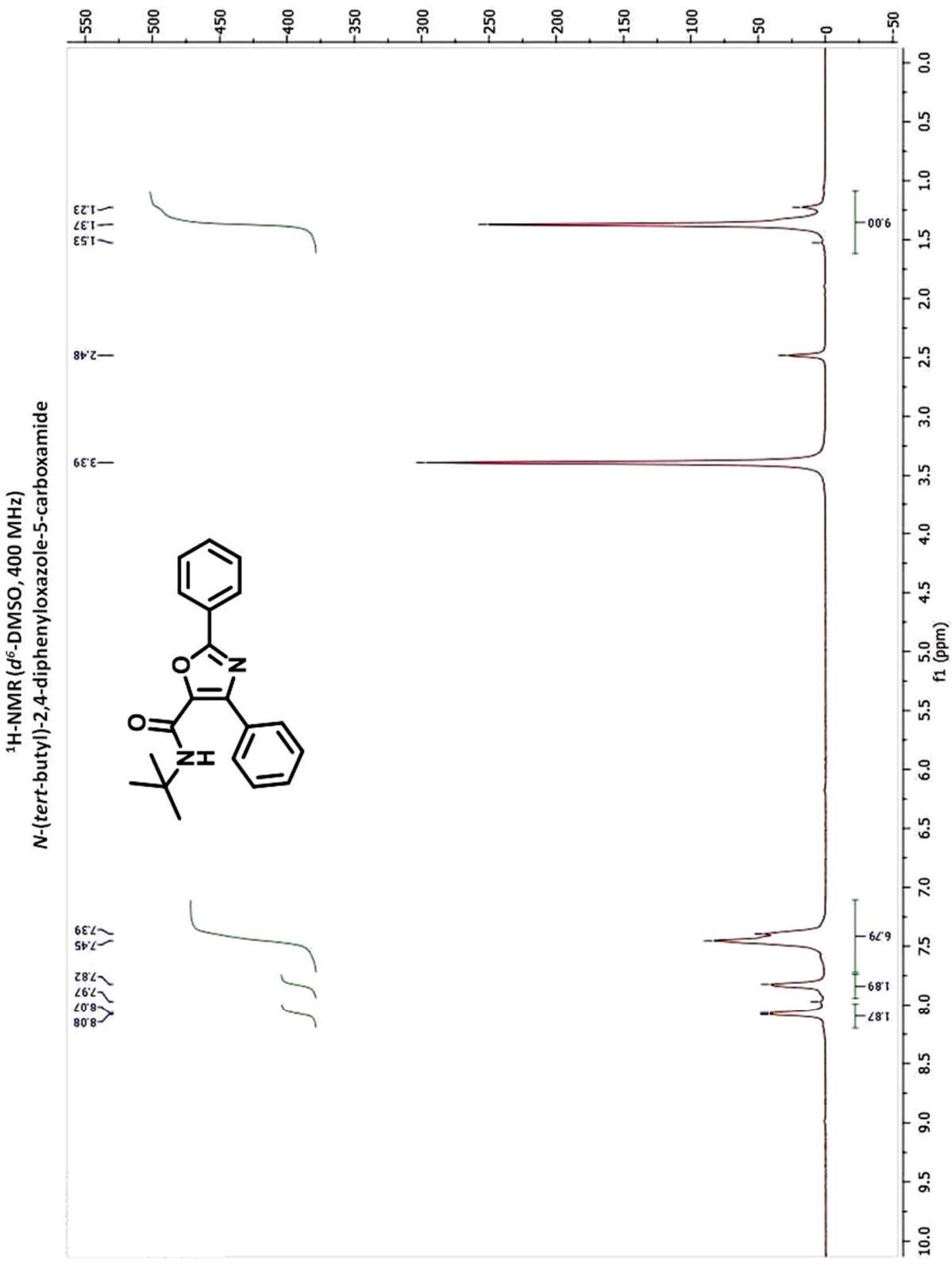


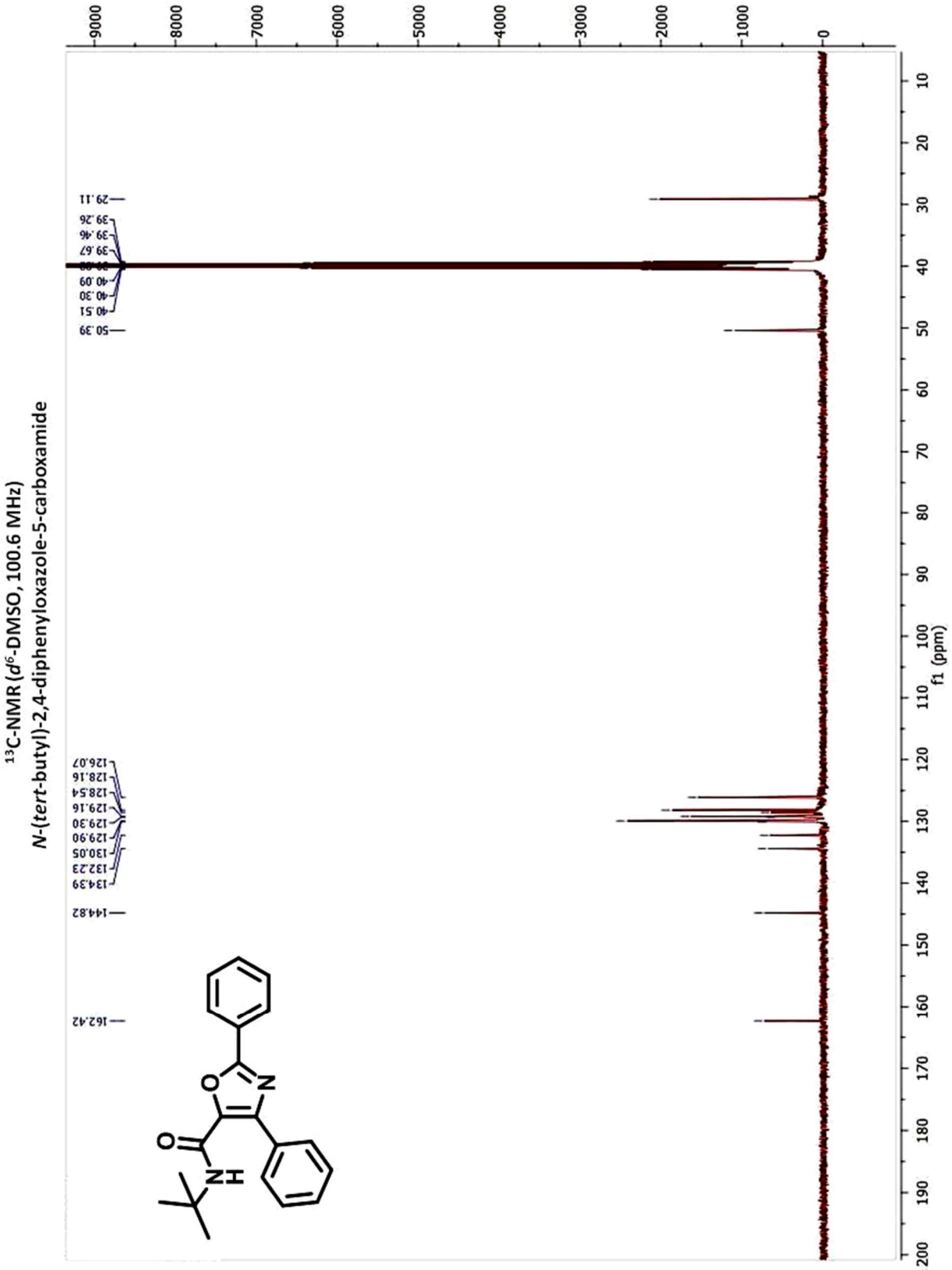

1H-NMR (CDCl3, 400 MHz)
1-Tert-butyl-4-phenyl-5-aminoimidazole chlorohydrate
1.69
3.29
7.20
7.21
7.23
7.26
7.38
7.39
7.41
7.67
7.69
9.91
1.98
1.00
3.33
1.95
f1 (ppm)
Cl H3N


^{13}C-NMR ($CDCl_3$, 100.6 MHz)
1-*Tert*-butyl-4-phenyl-5-aminoimidazole chlorohydrate
29.56
55.86
76.66
77.30
135.15
131.37
129.82
128.60
128.38
126.06
125.79
Cl H_3N
f1 (ppm)


^{1}H-NMR ($CDCl_3$, 400 MHz)
1-*Tert*-butyl-4-[((4'-morpholyn)-4-yl)phenyl]-5-aminoimidazole chlorohydrate (93)
f1 (ppm)

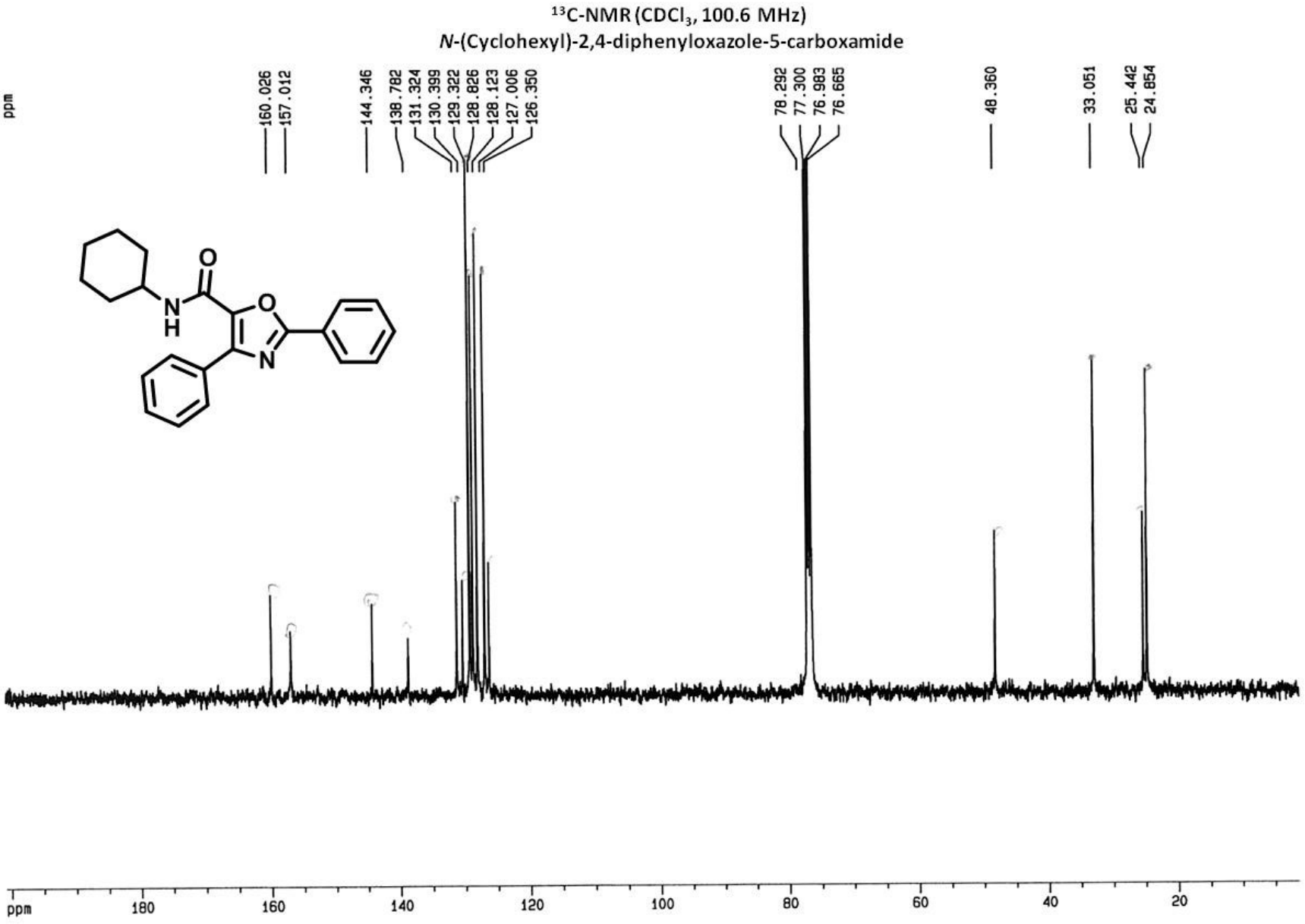

^{13}C-NMR ($CDCl_3$, 100.6 MHz)
1-*Tert*-butyl-4-[((4'-morpholyn)-4-yl)phenyl]-5-aminoimidazole chlorohydrate (93)
22.16
48.86
61.19
66.60
66.75
114.27
115.70
117.66
128.29
130.32
151.58
153.54
162.15
f1 (ppm)

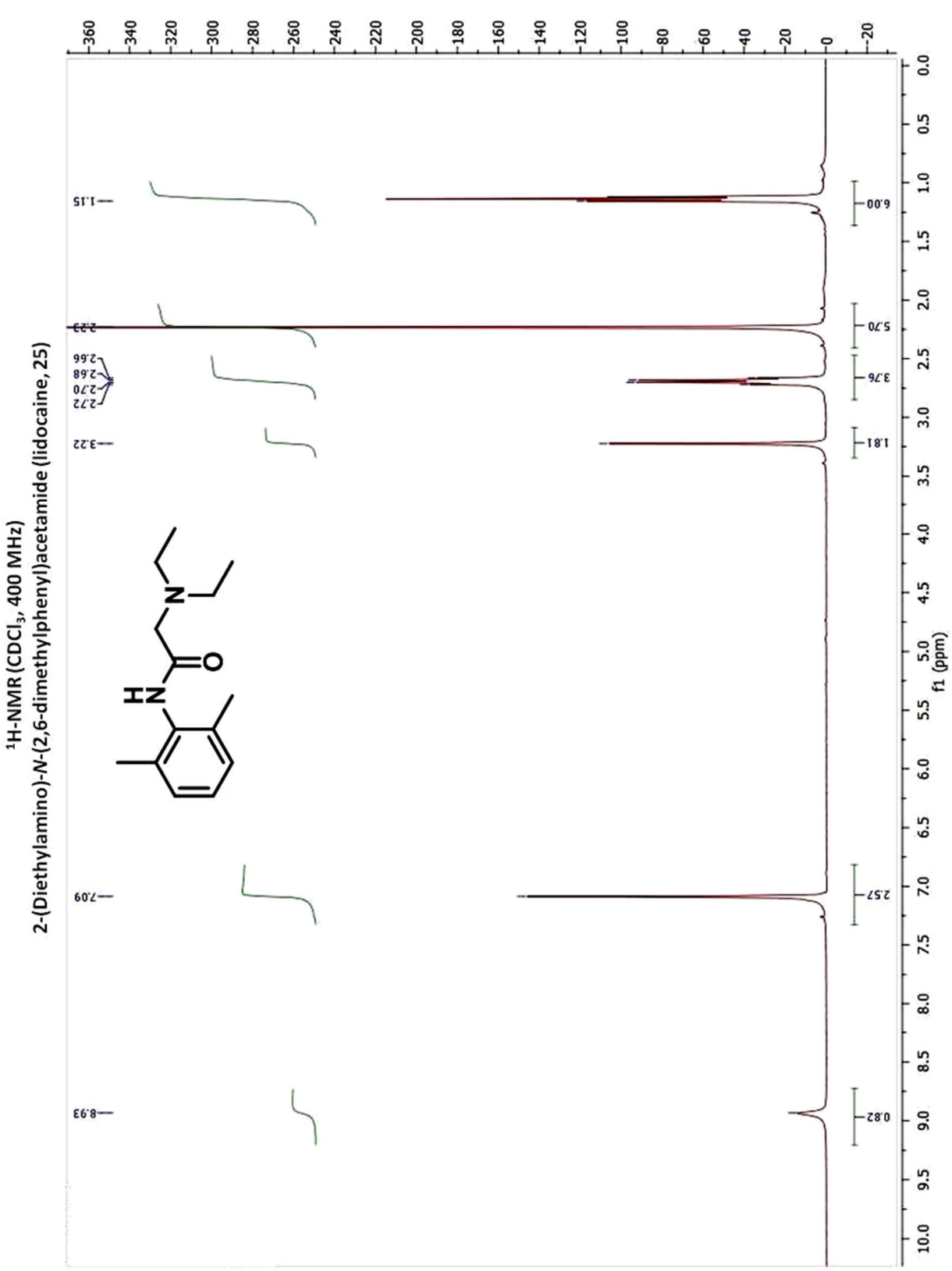

^{1}H-NMR (d^6-DMSO, 400 MHz)
N-(*tert*-butyl)-2,4-diphenyloxazole-5-carboxamide
f1 (ppm)


^{13}C-NMR (d^6-DMSO, 100.6 MHz)
N-(*tert*-butyl)-2,4-diphenyloxazole-5-carboxamide
162.42
144.82
134.39
132.23
130.05
129.90
129.30
129.16
128.54
128.16
126.07
50.39
40.51
40.30
40.09
39.88
39.67
39.46
39.26
29.11
f1 (ppm)

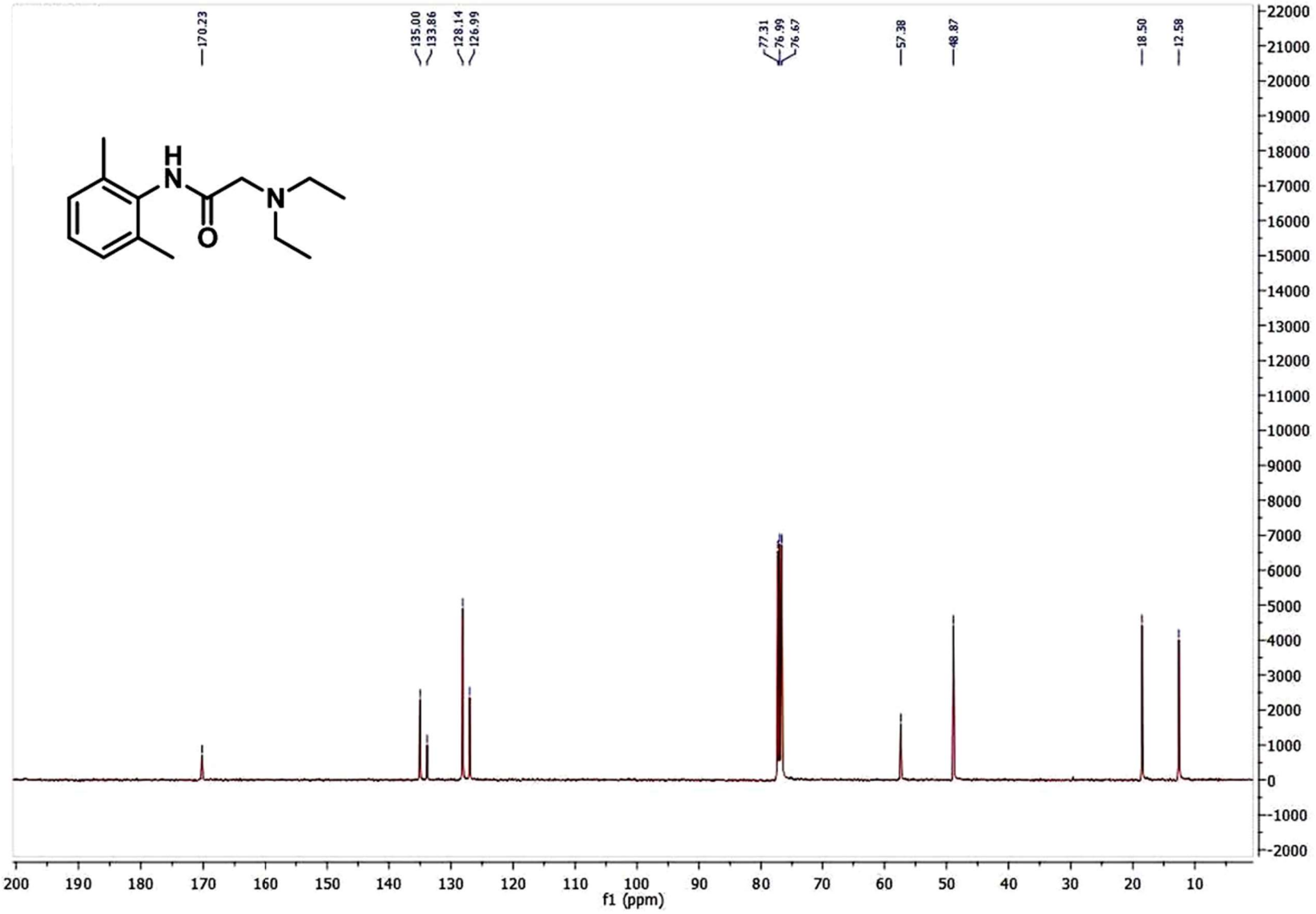
^{1}H-NMR ($CDCl_3$, 400 MHz)

N-(Cyclohexyl)-2,4-diphenyloxazole-5-carboxamide


^{13}C-NMR ($CDCl_3$, 100.6 MHz)
N-(Cyclohexyl)-2,4-diphenyloxazole-5-carboxamide
ppm
160.026
157.012
144.346
138.782
131.324
130.399
129.322
128.826
128.123
127.006
126.350
78.292
77.300
76.983
76.665
48.360
33.051
25.442
24.854
O
N
H
O
N
ppm
180
160
140
120
100
80
60
40
20


^{1}H-NMR ($CDCl_3$, 400 MHz)
2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide (lidocaine, 25)
f1 (ppm)

^{13}C-NMR ($CDCl_3$, 100.6 MHz)
2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide (lidocaine, 25)



Referenzes and notes

1. R. Bossio, S. Marcaccini and R. Pepino. *Liebigs Ann. Chem.* 1991*,* **10**, 1107-1108.
2. R. Cannalire, C. Russo, B. Cerra, A. Gioiello, F. Brunelli, G. C. Tron and M. Giustiniano, *Mol. Divesity*, 2022.
3. a) I. Ugi and C. Steinbruckner, *Patent,* 1966, US3247200; b) D. E. Fitzpatrick, T. Maujean, A. C. Evans and S. V. Ley, *Angew. Chem. Int. Ed.* 2018*,* **57**, 15128-15132. c) M. Lee, N. J. Vosburg, E. A. Shimizu, M. A. Rentería-Gómez, R. Gámez-Montaño and D. A. Vosburg, *J. Chem. Educ.*, 2022, **99**, 2399−2402.