

Supporting Information

Continuous Flow as an Enabling Technology: A Fast and Versatile Entry to Functionalized Glyoxal Derivatives

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Table of contents

Table of contents	II
1 General information	1
1.1 General experimental and analytical methods	1
2 Procedures and analytical data of synthesized compounds	2
2.1 Approach A: access to α,α' -bis-chloroketones	2
2.2 Approach B: access to ketoacetals.....	7
2.3 Approach B: extension of electrophile scope	14
3 References	19
4 NMR spectra	20
4.1 Approach A: access to α,α' -bis-chloroketones	20
4.2 Approach B: access to ketoacetals.....	37
4.3 Approach B: extension of electrophile scope	62

1 General information

1.1 General experimental and analytical methods

General methods: Reagents were purchased from different commercial sources and used without further purification. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator.

Solvents: All chemistry involving organolithium species was performed using dry solvent grades, the solvent was used as purchased. Solvents for flash column chromatography are standard commercial grade.

Chromatography: Flash column chromatography silica gel 60 from Merck, with a particle size between 40 and 63 μm , was used.

NMR spectroscopy: ^1H -NMR spectra were recorded on a Bruker Avance DRX-500 spectrometer at 500 MHz and are reported as follows: chemical shift δ in ppm (multiplicity, coupling constants J in Hz, number of protons, assignment). The multiplicity and shape of the ^1H signals are designated by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, or combinations thereof. These chemical shifts δ are reported to the nearest 0.01 ppm with the residual solvent peak as the internal reference (DMSO- $\text{d}^6 = 2.50$ ppm). ^{13}C -NMR spectra were recorded on the same spectrometer at 126 MHz with ^1H decoupling. All ^{13}C resonances are reported to the nearest 0.1 ppm with the central resonance of the solvent peak as the internal reference (DMSO- $\text{d}^6 = 40.0$ ppm). ^{19}F -NMR spectra were recorded on the same spectrometer at 470 MHz with ^1H decoupling.

High-resolution mass spectrometry (HRMS) was performed using a Waters Micromass LCT PremierTM spectrometer using time of flight (TOF) mass detection and positive ESI ionization method. Unless otherwise stated, reported mass correspond to the parent molecular ion associated with a proton $[\text{M}+\text{H}]^+$ or a sodium cation $[\text{M}+\text{Na}]^+$ (^{23}Na isotope). All m/z values are reported to four decimal places and within ± 5 ppm of the calculated value.

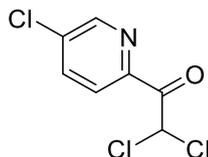
2 Procedures and analytical data of synthesized compounds

2.1 Approach A: access to α,α' -bis-chloroketones

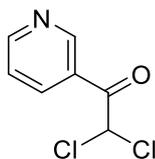
GP(I): Three Syrrdos2 pumps (connected to three pressure sensors) were used to pump the different feedstocks from closed bottles under argon. *Feedstock 1* consisted of dichloromethane dissolved in abs. THF (0.3 M). As *Feedstock 2* commercially available n-butyllithium (1.6 M in hexane) was used directly from the supplied bottle. *Feedstock 3* consisted of the appropriate ester electrophile (0.3 M in THF). All solutions were prepared and used under argon. All feedstocks were chilled to -30 °C over 25 seconds residence time using precooling loops (1/8" OD, PFA) prior to mixing (It was confirmed by in-line thermocouples that the precooling loops are appropriate to cool the different streams down to the same inner temperature). *Feedstock 1* (Flow rate = 18.46 mL/min, 1.3 equiv.) and *Feedstock 2* (Flow rate = 3.20 mL/min, 1.20 equiv.) were mixed using a Teflon "T-piece" with 0.5 mm ID before entering the first reactor (0.18 mL, 1/16" OD, PFA, 0.5 sec residence time, -30 °C). The outcome of the first reactor was then mixed with *Feedstock 3* (Flow rate = 14.2 mL/min, 1.0 equiv.) in a second Teflon "T-piece" with 0.5 mm ID before entering the second reactor (0.60 mL of 1/16" OD, PFA, 1.0 sec residence time, -30 °C). After the system reached steady state (~1.5 min), the outgoing reaction mixture were directly quenched in a semi-batch manner in 5 mL of 10% AcOH in water for 2.0 min (8.5 mmol of ester processed) at room temperature. After the collection, the phases were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The organic phases were combined and dried over MgSO₄. Solvents were removed *in vacuo* to yield a crude mixture, depending on its NMR purity it was analyzed as such or purified by flash column chromatography (mixture of EtOAc in heptane) to yield the pure compound.

2,2-dichloro-1-(pyridin-2-yl)ethan-1-one (3a)

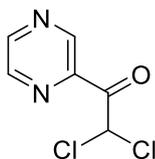
The reaction was carried out according to **GP(I)** at 8.5 mmol scale (2.0 min collection) without further purification afforded product **3a** (1.50 g, 8.0 mmol) as a yellowish oil in 94% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 8.84 – 8.71 (m, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.14 – 8.01 (m, 1H), 7.83 (s, 1H), 7.85 – 7.70 (m, 2H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 186.9, 150.0, 149.3, 138.7, 129.5, 124.5, 68.4. NMR spectra in accordance with those already reported for the same compound.¹

2,2-dichloro-1-(5-chloropyridin-2-yl)ethan-1-one (3b)

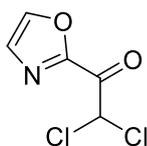
The reaction was carried out according to **GP(I)** at 8.5 mmol scale (2.0 min collection) without further purification afforded product **3b** (1.69 g, 7.5 mmol) as an orange oil in 88% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** 8.77 (d, *J* = 5.2 Hz, 1H), 8.21 – 8.14 (m, 1H), 7.95 – 7.84 (m, 1H), 7.76 (s, 1H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 185.7, 151.4, 150.8, 145.4, 129.2, 124.3, 68.5. **HRMS (LCMS-TOF) *m/z* for C₇H₄Cl₃NO [M+H]⁺** calculated 223.9431 found 223.9429.

2,2-dichloro-1-(pyridin-3-yl)ethan-1-one (3c)

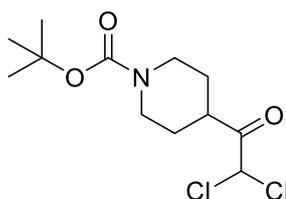
The reaction was carried out according to **GP(I)** at 8.5 mmol scale (2.0 min collection) without further purification afforded product **3c** (1.60 g, 8.4 mmol) as a yellowish oil in 99% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 9.22 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.86 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.42 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.91 (s, 1H), 7.65 (ddd, *J* = 8.1, 4.8, 0.9 Hz, 1H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 186.1, 154.9, 150.7, 137.5, 128.1, 124.6, 69.6. NMR spectra in accordance with those already reported for the same compound.²

2,2-dichloro-1-(pyridin-3-yl)ethan-1-one (3d)

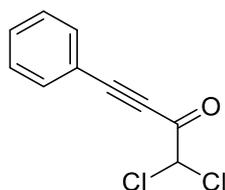
The reaction was carried out according to **GP(I)** at 8.5 mmol scale (2.0 min collection) without further purification afforded product **3d** (1.59 g, 8.3 mmol) as a brownish oil in 98% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 9.30 (d, *J* = 1.5 Hz, 1H), 8.99 (d, *J* = 2.5 Hz, 1H), 8.89 (dd, *J* = 2.4, 1.5 Hz, 1H), 7.73 (s, 1H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 186.1, 149.8, 145.2, 144.7, 144.5, 68.5. **HRMS (LCMS-TOF) *m/z* for C₆H₄Cl₂N₂O** [**M+H**]⁺ calculated 190.9773 found 190.9771.

2,2-dichloro-1-(oxazol-2-yl)ethan-1-one (3e)

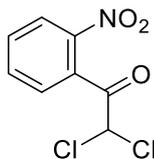
The reaction was carried out according to **GP(I)** at 8.5 mmol scale (2.0 min collection) without further purification afforded product **3e** (1.38 g, 7.7 mmol) as a yellow oil in 91% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 8.57 (d, J = 0.7 Hz, 1H), 7.70 (d, J = 0.8 Hz, 1H), 7.48 (s, 1H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 173.9, 154.5, 145.2, 130.5, 68.5. **HRMS (LCMS-TOF) m/z for C₅H₃Cl₂NO₂ [M+H]⁺** calculated 179.9614 found 179.9611.

tert-butyl 4-(2,2-dichloroacetyl)piperidine-1-carboxylate (3f)

The reaction was carried out according to **GP(I)** at 8.5 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (2% to 10% EtOAc in heptane) afforded product **3f** (1.28 g, 5.6 mmol) as a colorless oil in 51% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.07 (s, 1H), 3.94 (d, J = 13.3 Hz, 2H), 3.06 (tt, J = 11.4, 3.6 Hz, 1H), 2.81 (s, 2H), 1.92 – 1.80 (m, 2H), 1.39 (s, 9H), 1.35 (dd, J = 12.2, 4.2 Hz, 2H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 198.8, 154.2, 79.3, 70.1, 60.4, 44.0, 28.5. NMR spectra in accordance with those already reported for the same compound.³

1,1-dichloro-4-phenylbut-3-yn-2-one (3g)

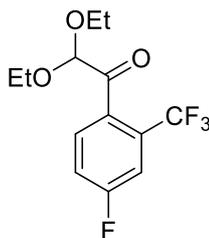
The reaction was carried out according to **GP(I)** at 8.5 mmol scale (2.0 min collection) without further purification afforded product **3g** (1.71 g, 8.1 mmol) as a reddish oil in 95% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.74 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.69 – 7.61 (m, 1H), 7.60 – 7.51 (m, 2H), 7.11 (s, 1H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 173.93, 133.36, 132.37, 129.30, 117.79, 96.95, 83.75, 70.81. NMR spectra in accordance with those already reported for the same compound.¹

2,2-dichloro-1-(2-nitrophenyl)ethan-1-one (3h)

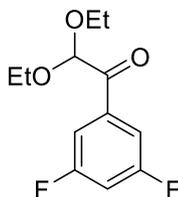
The reaction was carried out according to **GP(I)** at 8.5 mmol scale (2.0 min collection) without further purification afforded product **3h** (1.63 g, 7.0 mmol) as a yellowish amorphous solid in 82% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 8.34 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.99 (td, *J* = 7.5, 1.1 Hz, 1H), 7.89 (ddd, *J* = 8.7, 7.6, 1.5 Hz, 1H), 7.75 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.46 (s, 1H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 189.7, 145.9, 135.8, 133.3, 131.9, 130.5, 125.1, 70.6. NMR spectra in accordance with those already reported for the same compound.⁴

2.2 Approach B: access to ketoacetals

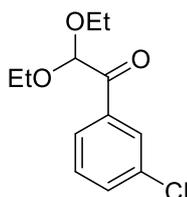
GP(II): Three Syrrdos2 pumps (connected to three pressure sensors) were used to pump the different feedstocks from closed bottles under argon. *Feedstock 1* consisted of the appropriate aryl bromide dissolved in abs. THF (0.3 M). As *Feedstock 2* commercially available n-butyllithium (1.6 M in hexane) was used directly from the supplied bottle. *Feedstock 3* consisted of ethyl diethoxyacetate (0.3 M in THF). All solutions were prepared and used under argon. All feedstocks were chilled to -30 °C over 25 seconds residence time using precooling loops (1/8" OD, PFA) prior to mixing (It was confirmed by in-line thermocouples that the precooling loops are appropriate to cool the different streams down to the same inner temperature). *Feedstock 1* (Flow rate = 17.00 mL/min, 1.00 equiv.) and *Feedstock 2* (Flow rate = 3.50 mL/min, 1.10 equiv.) were mixed using a Teflon "T-piece" with 0.5 mm ID before entering the first reactor (0.22 mL, 1/16" OD, PFA, 0.5 sec residence time, -30 °C). The outcome of the first reactor was then mixed with *Feedstock 3* (Flow rate = 20.4 mL/min, 1.2 equiv.) in a second Teflon "T-piece" with 0.5 mm ID before entering the second reactor (0.68 mL of 1/16", 1.0 sec residence time, -30 °C). After the system reached steady state (~2 min), the outgoing reaction mixture were directly quenched in a semi-batch manner in 25 mL of 10% AcOH in water for 2 min (10.2 mmol of aryl bromide processed) at room temperature. After the collection, the phases were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The organic phases were combined and dried over MgSO₄. Solvents were removed *in vacuo* and the crude mixture purified by flash column chromatography (mixture of EtOAc in heptane) to yield the pure compound.

2,2-diethoxy-1-(4-fluoro-2-(trifluoromethyl)phenyl)ethan-1-one (5a)

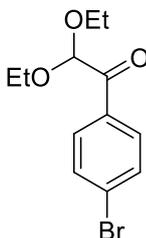
The reaction was carried out according to **GP(II)** at 10.2 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (2% to 10% EtOAc in heptane) afforded product **5a** (1.74 g, 9.0 mmol) as a colorless oil in 88% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.98 (dd, $J = 8.7, 5.5$ Hz, 1H), 7.79 (dt, $J = 9.4, 2.6$ Hz, 1H), 7.68 (td, $J = 8.5, 2.5$ Hz, 1H), 5.34 (s, 1H), 3.69 (dq, $J = 9.7, 7.0$ Hz, 2H), 3.59 (dq, $J = 9.7, 7.0$ Hz, 2H), 1.11 (t, $J = 7.1$ Hz, 6H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 197.0, 163.1 (d, $J = 251.4$ Hz), 133.0, 132.2 (d, $J = 9.0$ Hz), 130.4 – 129.2 (m), 124.1, 122.0, 119.6, 119.4, 115.4 (dd, $J = 25.7, 5.2$ Hz), 101.8, 63.5, 15.4. **¹⁹F-NMR (471 MHz, DMSO-*d*₆)** δ -57.26 (d, $J = 7.1$ Hz), -107.05 (d, $J = 7.1$ Hz). **HRMS (LCMS-TOF) *m/z* for C₁₃H₁₄F₄O₃ [M+Na]⁺** calculated 317.0771 found 317.0777.

1-(3,5-difluorophenyl)-2,2-diethoxyethan-1-one (5b)

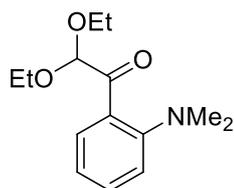
The reaction was carried out according to **GP(II)** at 10.2 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (1% to 3% EtOAc in heptane) afforded product **5b** (2.36 g, 9.7 mmol) as a colorless oil in 95% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.67 (ddd, $J = 7.2, 5.8, 3.2$ Hz, 2H), 7.64 – 7.49 (m, 1H), 5.47 – 5.39 (m, 1H), 3.71 (dq, $J = 9.7, 7.0$ Hz, 2H), 3.63 (dq, $J = 9.8, 7.0$ Hz, 2H), 1.14 (t, $J = 7.1$ Hz, 6H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 191.9, 162.7 (d, $J = 247.9$ Hz), 162.6 (d, $J = 248.0$ Hz), 137.1, 113.0 – 112.5 (m), 109.6 (t, $J = 25.8$ Hz), 101.7, 63.6, 15.6. **¹⁹F-NMR (471 MHz, DMSO-*d*₆)** δ -108.50 (dd, $J = 11.7, 5.8$ Hz). **HRMS (LCMS-TOF) *m/z* for C₁₂H₁₄F₂O₃ [M+Na]⁺** calculated 267.0803 found 267.0801.

1-(3-chlorophenyl)-2,2-diethoxyethan-1-one (5c)

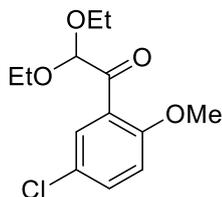
The reaction was carried out according to **GP(II)** at 10.2 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (1% to 4% EtOAc in heptane) afforded product **5c** (2.25 g, 9.3 mmol) as a colorless oil in 91% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 8.01 (s, 1H), 7.98 (d, $J = 7.8$ Hz, 1H), 7.73 (d, $J = 7.1$ Hz, 1H), 7.58 (t, $J = 7.9$ Hz, 1H), 5.43 (s, 1H), 3.77 – 3.66 (m, 2H), 3.67 – 3.57 (m, 2H), 1.15 (t, $J = 7.0$ Hz, 6H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 193.0, 135.8, 133.8, 133.7, 131.0, 129.3, 128.3, 102.0, 63.6, 15.5. **HRMS (LCMS-TOF) *m/z* for C₁₂H₁₅ClO₃ [M+Na]⁺** calculated 265.0602 found 267.0600.

1-(4-bromophenyl)-2,2-diethoxyethan-1-one (5d)

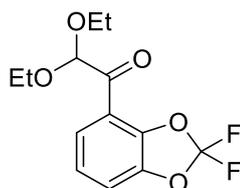
The reaction was carried out according to **GP(II)** at 10.2 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (1% to 3% EtOAc in heptane) afforded product **5d** (2.36 g, 8.2 mmol) as an amorphous white solid in 81% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.96 (d, $J = 8.6$ Hz, 2H), 7.75 (d, $J = 8.6$ Hz, 2H), 5.37 (s, 1H), 3.71 (dq, $J = 9.7, 7.1$ Hz, 2H), 3.61 (dq, $J = 9.7, 7.0$ Hz, 2H), 1.14 (t, $J = 7.1$ Hz, 6H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 193.4, 133.0, 132.2, 131.8, 128.3, 102.2, 63.6, 15.6. NMR spectra in accordance with those already reported for the same compound in CDCl₃.⁵

1-(2-(dimethylamino)phenyl)-2,2-diethoxyethan-1-one (5e)

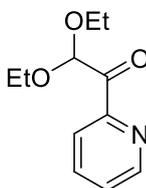
The reaction was carried out according to **GP(II)** at 10.2 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (2% to 8% EtOAc in heptane) afforded product **5e** (1.92 g, 7.6 mmol) as a yellow oil in 75% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.50 – 7.31 (m, 2H), 7.11 – 7.00 (m, 1H), 6.92 (td, *J* = 7.4, 1.0 Hz, 1H), 5.55 (s, 1H), 3.63 (dq, *J* = 9.7, 7.1 Hz, 2H), 3.55 (dq, *J* = 9.7, 7.0 Hz, 2H), 2.70 (s, 1H), 1.09 (t, *J* = 7.1 Hz, 6H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 198.6, 152.3, 132.6, 130.1, 129.3, 120.0, 117.6, 99.9, 62.8, 44.5, 15.6. **HRMS (LCMS-TOF) *m/z* for C₁₄H₂₁NO₃ [M+H]⁺** calculated 252.1594 found 252.1594.

1-(4-chloro-2-methoxyphenyl)-2,2-diethoxyethan-1-one (5f)

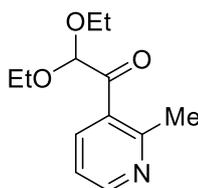
The reaction was carried out according to **GP(II)** at 10.2 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (1% to 5% EtOAc in heptane) afforded product **XX** (1.91 g, 7.0 mmol) as a colorless oil in 69% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.54 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 1.9 Hz, 1H), 7.15 – 7.01 (m, 1H), 5.41 (s, 1H), 3.89 (s, 3H), 3.66 – 3.51 (m, 4H), 1.10 (t, *J* = 7.1 Hz, 6H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 196.0, 159.3, 138.6, 131.7, 125.7, 121.0, 113.1, 101.5, 63.0, 56.8, 15.6. **HRMS (LCMS-TOF) *m/z* for C₁₃H₁₇ClO₄ [M+Na]⁺** calculated 295.0708 found 295.0716.

1-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-2,2-diethoxyethan-1-one (5g)

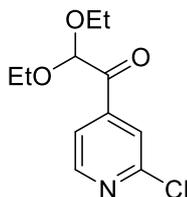
The reaction was carried out according to **GP(II)** at 10.2 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (1% to 3% EtOAc in heptane) afforded product **5g** (2.52 g, 8.8 mmol) as a colorless oil in 86% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.76 (dd, $J = 8.2, 1.2$ Hz, 1H), 7.70 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.35 (t, $J = 8.1$ Hz, 1H), 5.40 (s, 1H), 3.73 (dq, $J = 9.6, 7.0$ Hz, 2H), 3.64 (dq, $J = 9.5, 7.0$ Hz, 2H), 1.15 (t, $J = 7.1$ Hz, 6H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 190.6, 143.9, 142.5, 131.7 (t, $J = 253.6$ Hz), 125.0 (d, $J = 30.3$ Hz), 118.9, 115.3, 101.3, 63.5, 15.5. **¹⁹F-NMR (471 MHz, DMSO-*d*₆)** δ -48.89. **HRMS (LCMS-TOF) m/z for C₁₃H₁₄F₂O₅ [M+Na]⁺** calculated 311.0702 found 311.0706.

2,2-diethoxy-1-(pyridin-2-yl)ethan-1-one (5h)

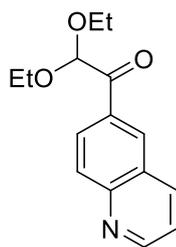
The reaction was carried out according to **GP(II)** at 10.2 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (3% to 10% EtOAc in heptane) afforded product **5h** (1.92 g, 9.2 mmol) as a colorless oil in 90% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 8.75 (ddd, $J = 4.7, 1.7, 0.9$ Hz, 1H), 8.02 (dd, $J = 7.5, 1.7$ Hz, 1H), 7.98 (dt, $J = 7.8, 1.3$ Hz, 1H), 7.68 (ddd, $J = 7.4, 4.7, 1.5$ Hz, 1H), 6.10 (s, 1H), 3.78 – 3.59 (m, 4H), 1.12 (t, $J = 7.1$ Hz, 6H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 193.7, 152.3, 149.8, 138.2, 128.4, 123.3, 97.2, 63.2, 15.7. Data in accordance with those already reported for the same compound.⁶

2,2-diethoxy-1-(2-methylpyridin-3-yl)ethan-1-one (5i)

The reaction was carried out according to **GP(II)** at 10.2 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (3% to 20% EtOAc in heptane) afforded product **5i** (2.13 g, 9.6 mmol) as a colorless oil in 94% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 8.58 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.25 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.36 (dd, *J* = 7.9, 4.8 Hz, 1H), 5.34 (s, 1H), 3.69 (dq, *J* = 9.7, 7.1 Hz, 2H), 3.60 (dq, *J* = 9.7, 7.0 Hz, 2H), 2.56 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 6H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 197.70, 157.82, 151.65, 137.74, 130.31, 121.14, 102.27, 63.47, 24.30, 15.58. **HRMS (LCMS-TOF) *m/z* for C₁₂H₁₇NO₃ [M+H]⁺** calculated 224.1281 found 224.1280.

1-(2-chloropyridin-4-yl)-2,2-diethoxyethan-1-one (5j)

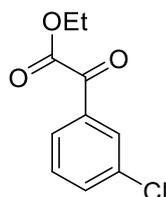
The reaction was carried out according to **GP(II)** at 10.2 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (2% to 8% EtOAc in heptane) afforded product **5j** (1.93 g, 7.9 mmol) as a colorless oil in 78% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** 8.65 (dd, *J* = 5.1, 0.8 Hz, 1H), 7.93 – 7.90 (m, 1H), 7.86 (dd, *J* = 5.1, 1.4 Hz, 1H), 5.50 (s, 1H), 3.79 – 3.58 (m, 4H), 1.15 (t, *J* = 7.1 Hz, 6H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 193.0, 151.7, 151.5, 143.9, 123.5, 122.1, 101.2, 63.6, 15.6. **HRMS (LCMS-TOF) *m/z* for C₁₁H₁₄ClNO₃ [M+H]⁺** calculated 224.0735 found 224.0732.

2,2-diethoxy-1-(quinolin-6-yl)ethan-1-one (5k)

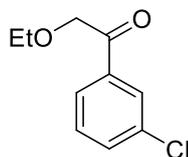
The reaction was carried out according to **GP(II)** at 10.2 mmol scale (2.0 min collection). Purification by column chromatography on silica gel (3% to 12% EtOAc in heptane) afforded product **5k** (1.21 g, 4.7 mmol) as a colorless oil in 46% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 9.04 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.79 (d, $J = 1.9$ Hz, 1H), 8.64 – 8.51 (m, 1H), 8.28 (dd, $J = 8.8, 2.0$ Hz, 1H), 8.11 (d, $J = 8.8$ Hz, 1H), 7.64 (dd, $J = 8.3, 4.2$ Hz, 1H), 5.58 (s, 1H), 3.76 (dq, $J = 9.7, 7.0$ Hz, 2H), 3.68 (dq, $J = 9.7, 7.0$ Hz, 2H), 1.17 (t, $J = 7.1$ Hz, 6H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 193.8, 153.6, 150.0, 138.4, 132.1, 131.8, 129.7, 128.7, 127.5, 122.9, 101.8, 63.4, 15.7. **HRMS (LCMS-TOF) *m/z*** for **C₁₅H₁₇NO₃** [**M+H**]⁺ calculated 260.1281 found 260.1282.

2.3 Approach B: extension of electrophile scope

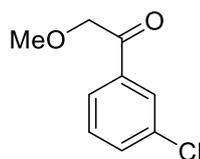
GP(III): Three Syrrdos2 pumps (connected to three pressure sensors) were used to pump the different feedstocks from closed bottles under argon. *Feedstock 1* consisted of 3-bromochlorobenzene dissolved in abs. THF (0.3 M). As *Feedstock 2* commercially available n-butyllithium (1.6 M in hexane) was used directly from the supplied bottle. *Feedstock 3* consisted of the appropriate ester electrophile (0.3 M in THF). All solutions were prepared and used under argon. All feedstocks were chilled to -30 °C over 25 seconds residence time using precooling loops (1/8" OD, PFA) prior to mixing (It was confirmed by in-line thermocouples that the precooling loops are appropriate to cool the different streams down to the same inner temperature). *Feedstock 1* (Flow rate = 17.00 mL/min, 1.00 equiv.) and *Feedstock 2* (Flow rate = 3.50 mL/min, 1.10 equiv.) were mixed using a Teflon "T-piece" with 0.5 mm ID before entering the first reactor (0.22 mL, 1/16" OD, PFA, 0.5 sec residence time, -30 °C). The outcome of the first reactor was then mixed with *Feedstock 3* (Flow rate = 20.4 mL/min, 1.2 equiv.) in a second Teflon "T-piece" with 0.5 mm ID before entering the second reactor (0.68 mL of 1/16" OD, 1.0 sec residence time, -30 °C). After the system reached steady state (~2 min), the outgoing reaction mixture were directly quenched in a semi-batch manner in 5 mL of 10% AcOH in water for 20 sec (1.7 mmol of 3-bromochlorobenzene processed) at room temperature. After the collection, the phases were separated and the aqueous phase was extracted with EtOAc (2 x 20 mL). The organic phases were combined and dried over MgSO₄. Solvents were removed *in vacuo* and the crude mixture purified by flash column chromatography (mixture of EtOAc in heptane) to yield the pure compound.

ethyl 2-(3-chlorophenyl)-2-oxoacetate (6a)

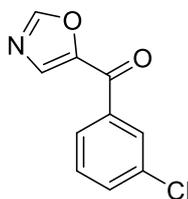
The reaction was carried out according to **GP(III)** at 1.7 mmol scale (20 sec collection). Purification by column chromatography on silica gel (1% to 4% EtOAc in heptane) afforded product **6a** (281 mg, 1.3 mmol) as a yellowish oil in 78% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.99 (dd, $J = 4.0, 2.1$ Hz, 1H), 7.95 – 7.91 (m, 1H), 7.87 – 7.81 (m, 1H), 7.68 – 7.60 (m, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 1.33 (t, $J = 7.1$ Hz, 3H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 185.3, 162.9, 135.3, 134.4, 134.3, 131.6, 129.6, 129.1, 63.0, 14.3. NMR spectra in accordance with those already reported for the same compound.⁷

1-(3-chlorophenyl)-2-ethoxyethan-1-one (6b)

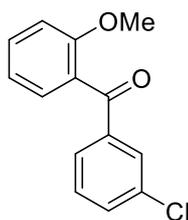
The reaction was carried out according to **GP(III)** at 1.7 mmol scale (20 sec collection). Purification by column chromatography on silica gel (1% to 4% EtOAc in heptane) afforded product **6b** (276 mg, 1.4 mmol) as a melted solid in 82% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.92 (s, 1H), 7.87 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.71 (dd, $J = 7.7, 2.6$ Hz, 1H), 7.56 (t, $J = 7.9$ Hz, 1H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 196.4, 137.1, 134.1, 133.6, 131.2, 127.9, 126.8, 73.4, 66.5, 15.5. **HRMS (LCMS-TOF) m/z for C₁₀H₁₁ClO₂ [M+Na]⁺** calculated 221.0340 found 221.0337.

1-(3-chlorophenyl)-2-methoxyethan-1-one (6c)

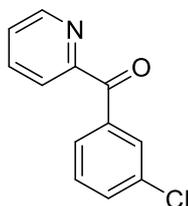
The reaction was carried out according to **GP(III)** at 1.7 mmol scale (20 sec collection). Purification by column chromatography on silica gel (1% to 8% EtOAc in heptane) afforded product **6c** (231 mg, 1.3 mmol) as an amorphous white solid in 74% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.91 (t, *J* = 1.9 Hz, 1H), 7.86 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.71 (ddd, *J* = 8.0, 2.2, 1.0 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 4.80 (s, 2H), 3.36 (s, 3H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 196.2, 137.0, 134.2, 133.6, 131.2, 127.8, 126.8, 75.1, 59.0. NMR spectra in accordance with those already reported for the same compound.⁸

(3-chlorophenyl)(oxazol-5-yl)methanone (6d)

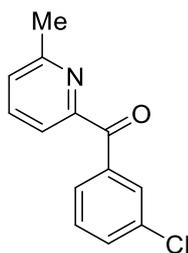
The reaction was carried out according to **GP(III)** at 1.7 mmol scale (20 sec collection). Purification by column chromatography on silica gel (5% to 20% EtOAc in heptane) afforded product **6d** (169 mg, 0.8 mmol) as a yellowish amorphous solid in 48% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 8.82 (s, 1H), 8.16 (s, 1H), 7.99 – 7.89 (m, 2H), 7.79 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 180.2, 156.4, 148.6, 138.5, 136.6, 134.2, 133.7, 131.4, 128.9, 128.1. **HRMS (LCMS-TOF) *m/z* for C₁₀H₆ClN [M+H]⁺ calculated 208.0165 found 208.0163.**

(3-chlorophenyl)(2-methoxyphenyl)methanone (6e)

The reaction was carried out according to **GP(III)** at 1.7 mmol scale (20 sec collection). Purification by column chromatography on silica gel (1% to 4% EtOAc in heptane) afforded product **6e** (247 mg, 1.0 mmol) as a colorless oil in 59% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.75 – 7.69 (m, 1H), 7.65 (t, $J = 1.9$ Hz, 1H), 7.63 – 7.52 (m, 3H), 7.37 (dd, $J = 7.5, 1.8$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 1H), 7.10 (td, $J = 7.4, 0.9$ Hz, 1H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 194.9, 157.2, 139.6, 134.0, 133.5, 133.1, 131.2, 129.6, 128.7, 128.5, 128.0, 121.2, 112.6, 56.1. **HRMS (LCMS-TOF) *m/z* for C₁₄H₁₁ClO₂ [M+H]⁺** calculated 247.0526 found 247.0541.

(3-chlorophenyl)(pyridin-2-yl)methanone (6f)

The reaction was carried out according to **GP(III)** at 1.7 mmol scale (20 sec collection). Purification by column chromatography on silica gel (2% to 10% EtOAc in heptane) afforded product **6f** (332 mg, 1.5 mmol) as a white amorphous solid in 90% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 8.77 – 8.72 (m, 1H), 8.14 – 8.03 (m, 2H), 7.98 (t, $J = 1.9$ Hz, 1H), 7.95 – 7.89 (m, 1H), 7.73 (ddd, $J = 8.0, 2.2, 1.0$ Hz, 1H), 7.69 (ddd, $J = 7.2, 4.7, 1.5$ Hz, 1H), 7.57 (t, $J = 7.9$ Hz, 1H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 192.3, 154.1, 149.1, 138.4, 138.3, 133.4, 133.0, 130.7, 130.6, 129.7, 127.7, 124.9. NMR spectra in accordance with those already reported for the same compound.⁹

(3-chlorophenyl)(6-methylpyridin-2-yl)methanone (6g)

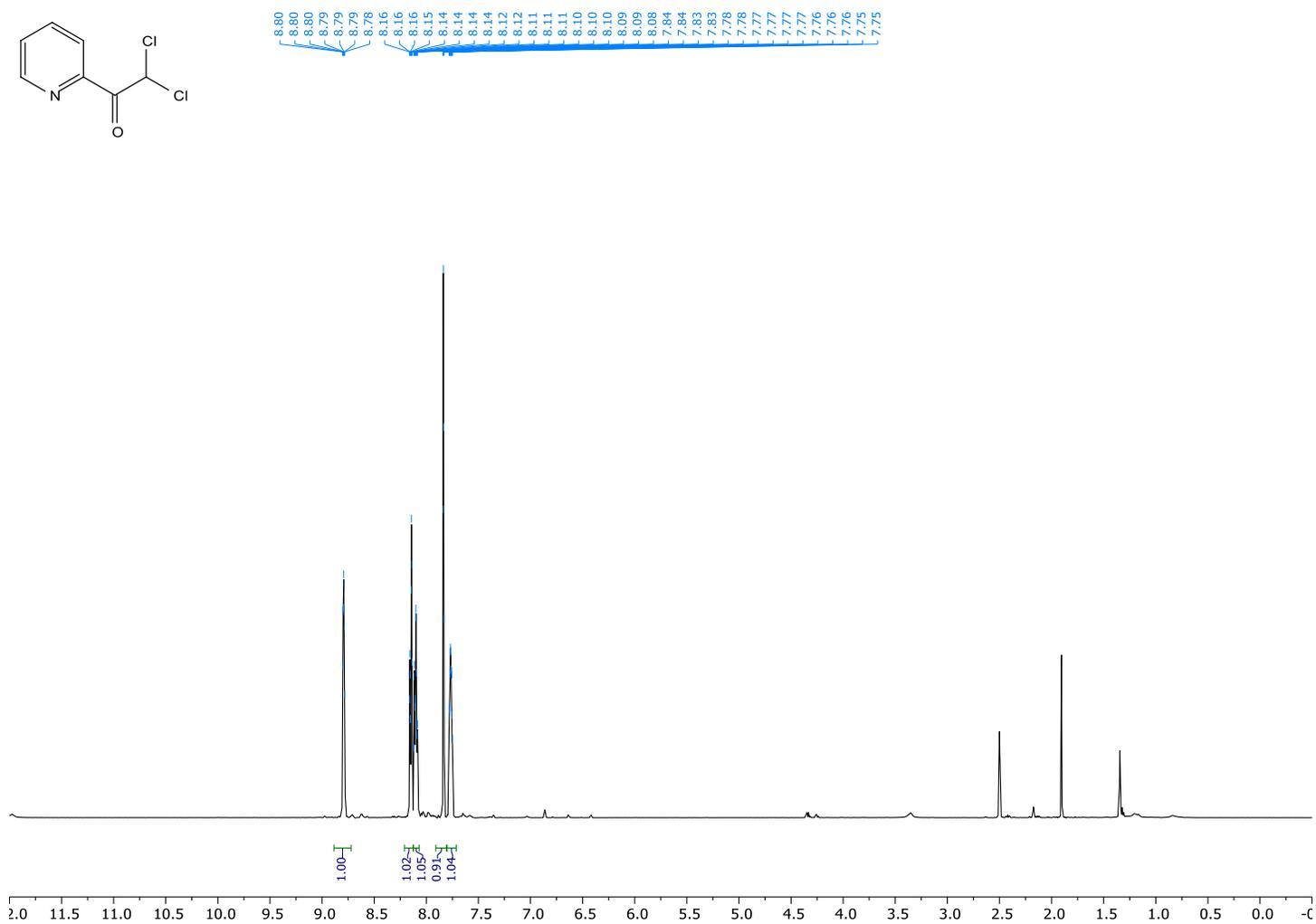
The reaction was carried out according to **GP(III)** at 1.7 mmol scale (20 sec collection). Purification by column chromatography on silica gel (2% to 10% EtOAc in heptane) afforded product **6g** (372 mg, 1.6 mmol) as a colorless oil in 95% yield. **¹H-NMR (500 MHz, DMSO-*d*₆)** δ 7.96 (t, J = 1.8 Hz, 1H), 7.94 – 7.88 (m, 2H), 7.78 (d, J = 7.7 Hz, 1H), 7.69 (dt, J = 8.0, 1.1 Hz, 1H), 7.56 – 7.49 (m, 2H). **¹³C-NMR (126 MHz, DMSO-*d*₆)** δ 192.3, 157.8, 153.7, 138.5, 138.3, 133.4, 133.0, 130.6, 130.6, 129.8, 127.1, 122.0, 24.5. **HRMS (LCMS-TOF) m/z for C₁₃H₁₀ClNO [M+H]⁺** calculated 232.0529 found 232.0525.

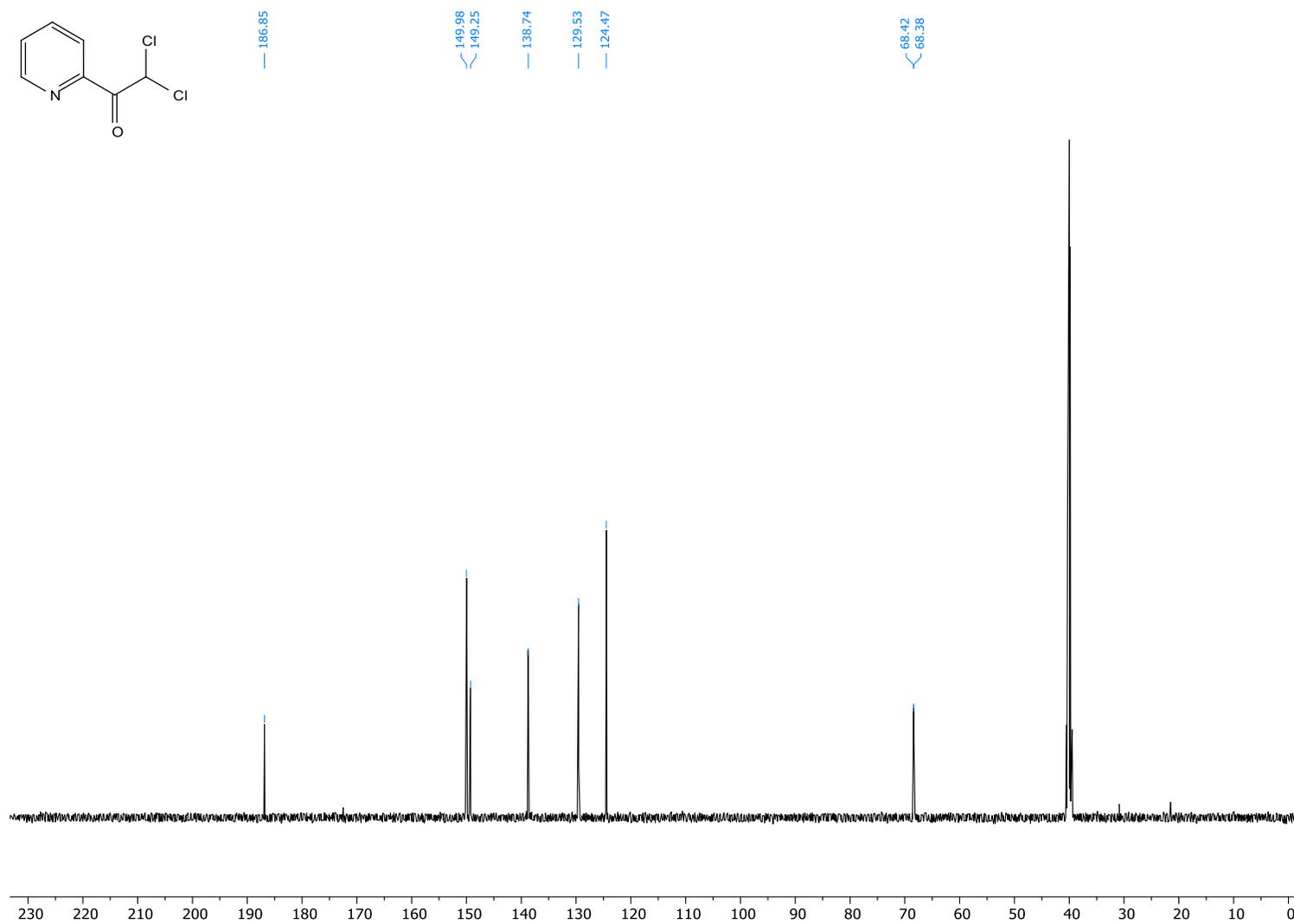
3 References

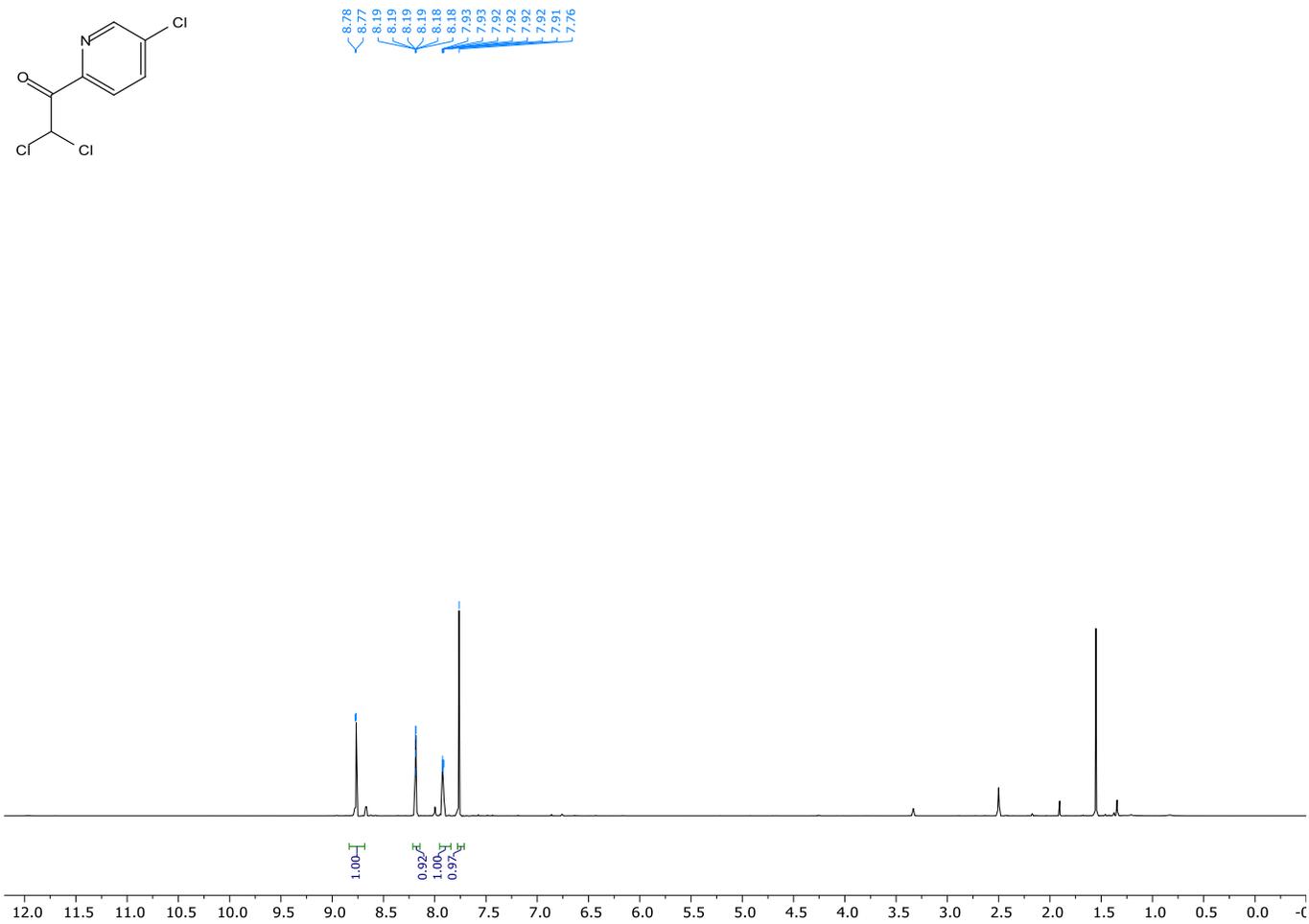
- (1) Ganiek, M. A.; Ivanova, M. V.; Martin, B.; Knochel, P. *Angew. Chemie Int. Ed.* **2018**, *52*, 17249–17253.
- (2) Zhang, S. L.; Yang, Z.; Hu, X.; Tam, K. Y. *Bioorganic Med. Chem. Lett.* **2018**, *28* (21), 3441–3445.
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- (5) Kharkongor, I.; Myrboh, B. *Tetrahedron Lett.* **2015**, *56*, 4359–4362.
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- (9) Maerten, E.; Sauthier, M.; Castanet, Y. *Tetrahedron* **2007**, *63*, 682–689.

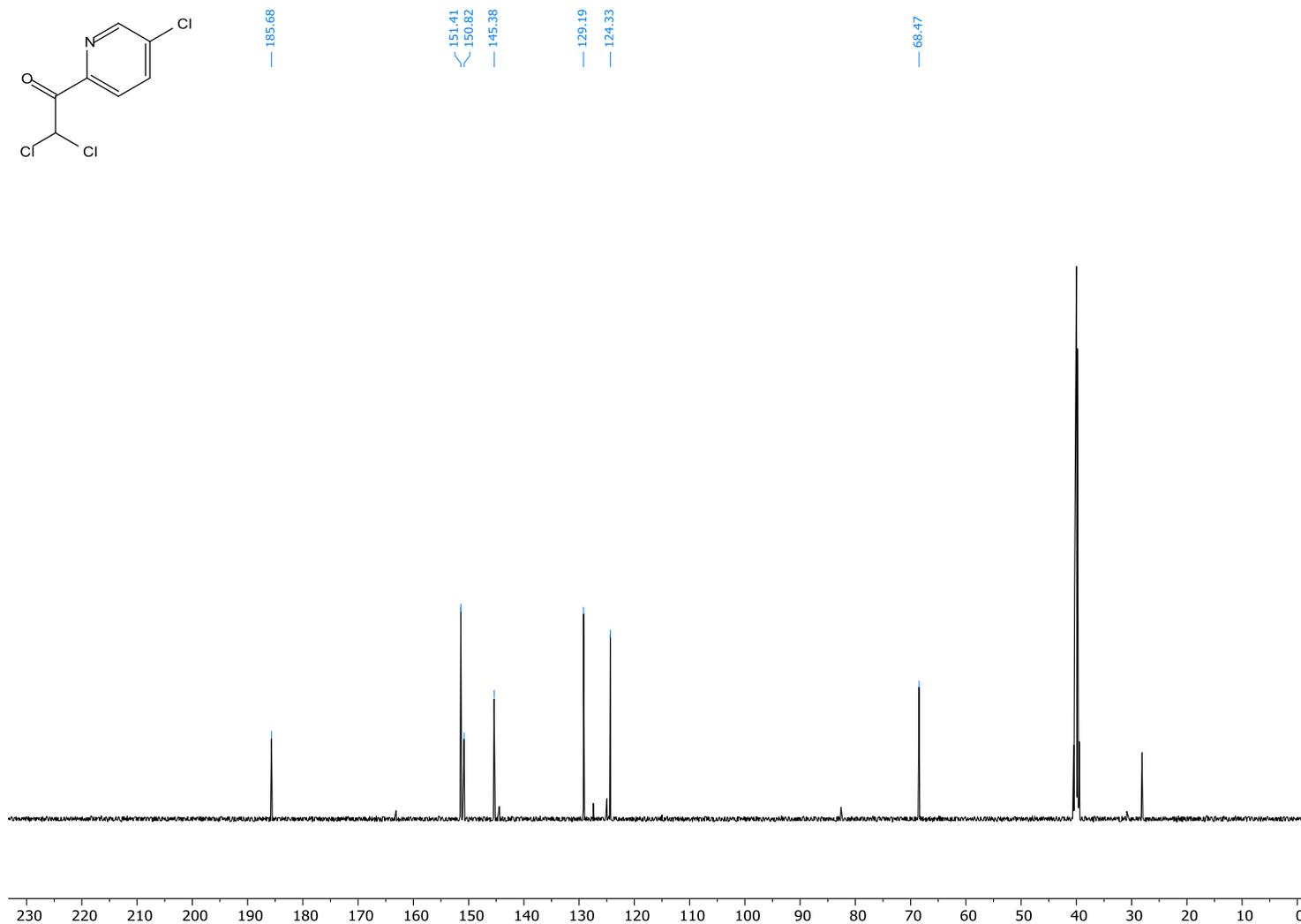
4 NMR spectra

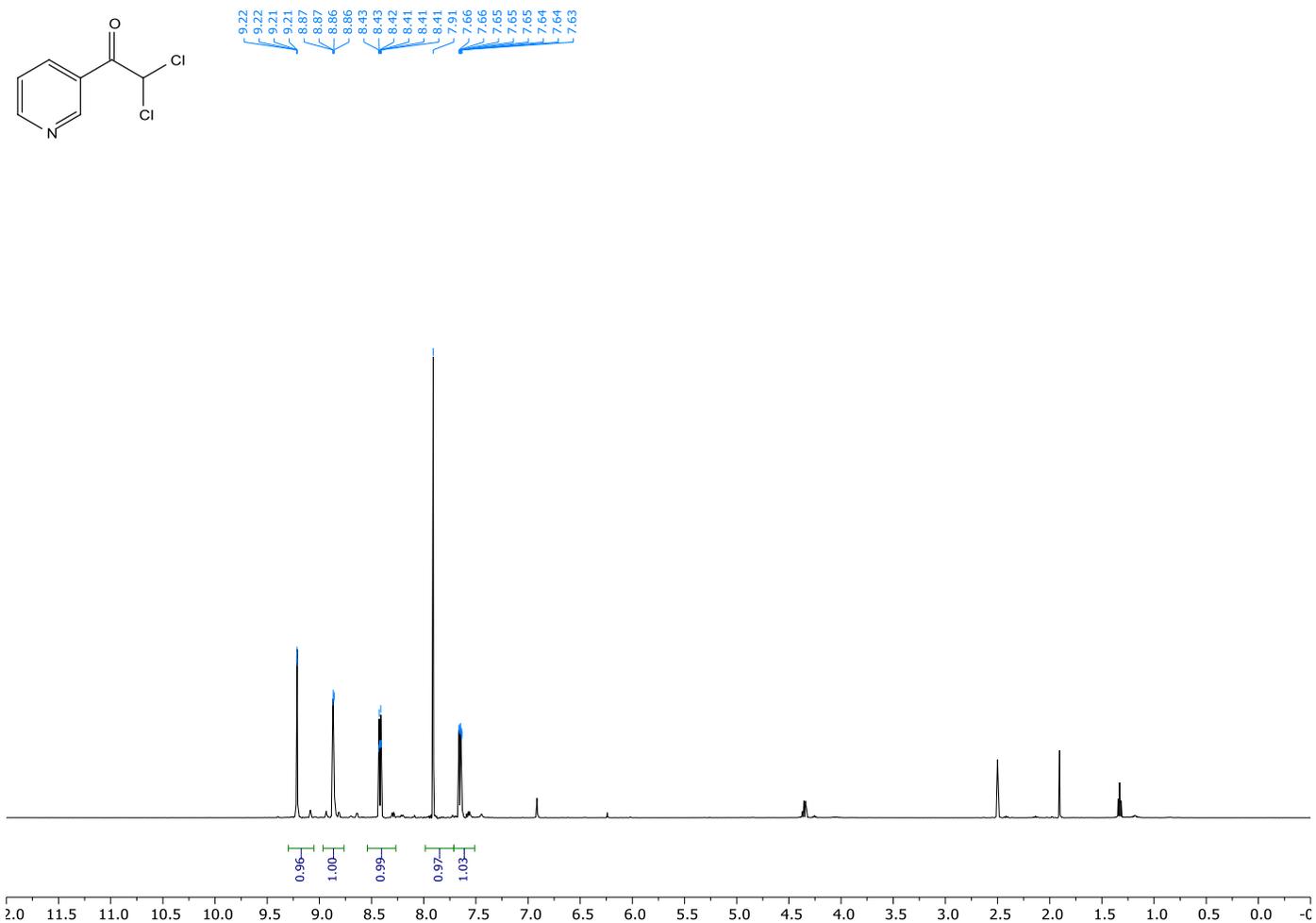
4.1 Approach A: access to α,α' -bis-chloroketones

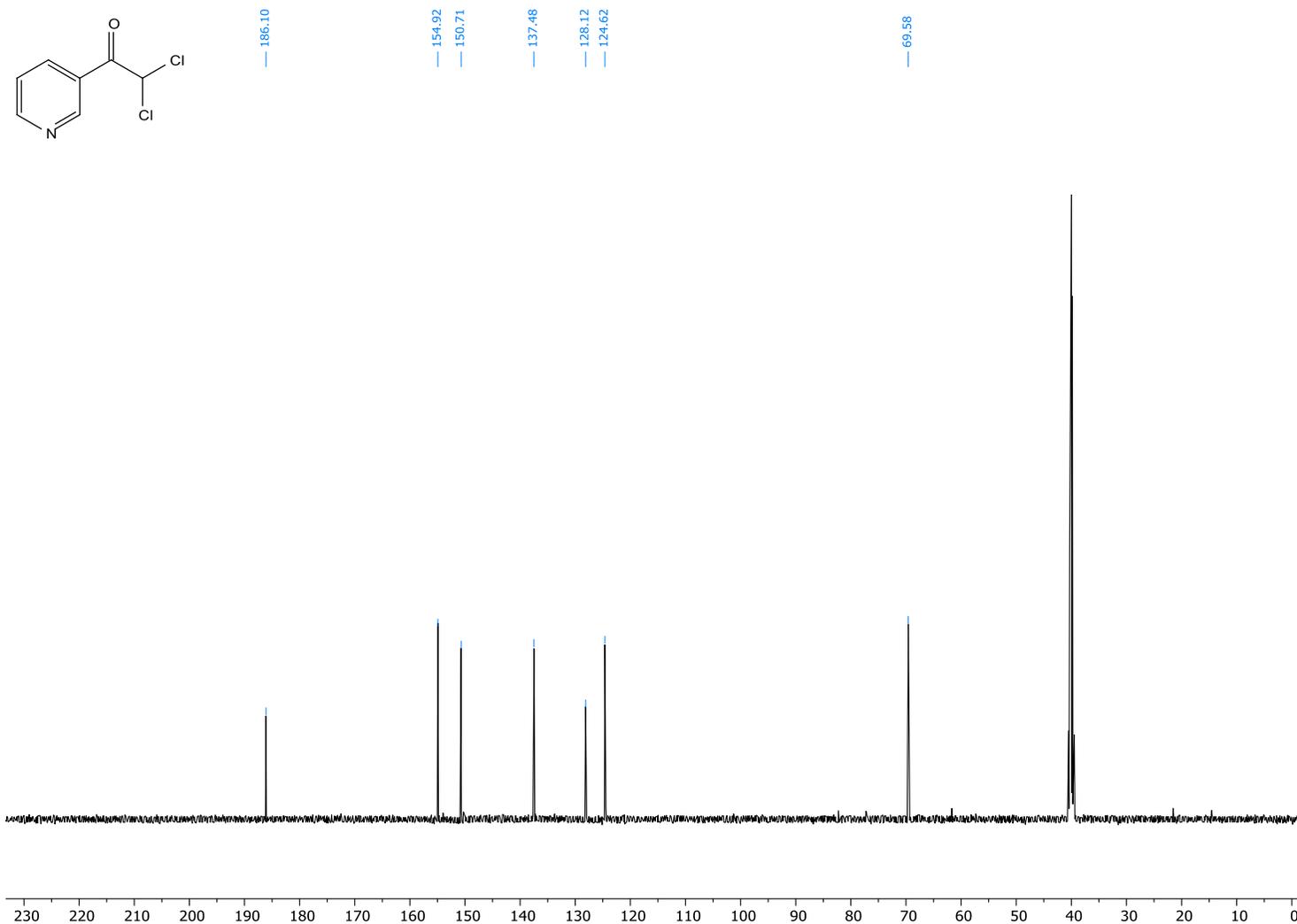
2,2-dichloro-1-(pyridin-2-yl)ethan-1-one (3a) **$^1\text{H-NMR}$ (500 MHz, DMSO-d_6)**

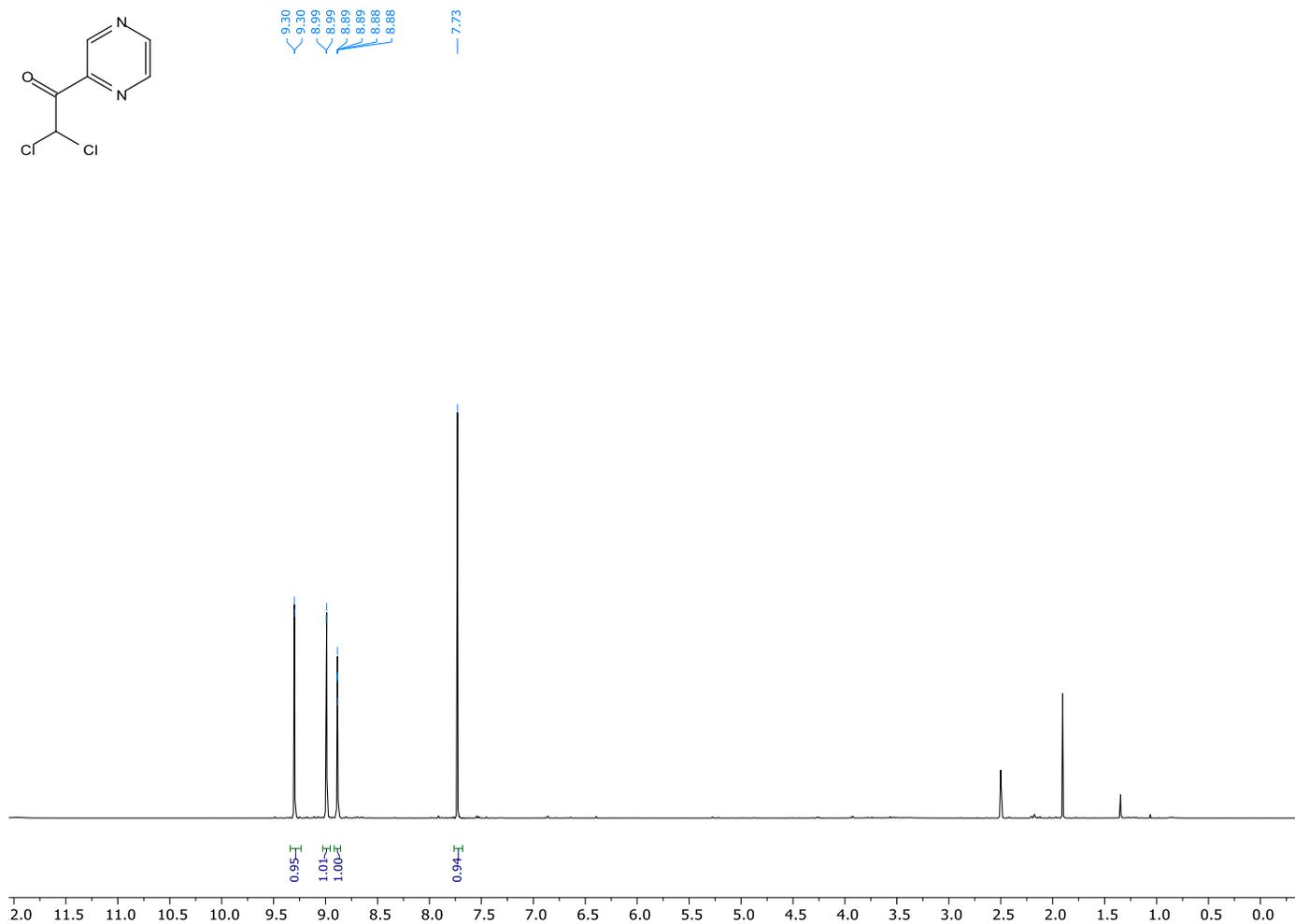
^{13}C -NMR (126 MHz, DMSO- d_6)

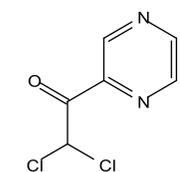
2,2-dichloro-1-(5-chloropyridin-2-yl)ethan-1-one (3b)**¹H-NMR (500 MHz, DMSO-d₆)**

^{13}C -NMR (126 MHz, DMSO- d_6)

2,2-dichloro-1-(pyridin-3-yl)ethan-1-one (3c)**¹H-NMR (500 MHz, DMSO-d₆)**

^{13}C -NMR (126 MHz, DMSO- d_6)

2,2-dichloro-1-(pyridin-3-yl)ethan-1-one (3d)**¹H-NMR (500 MHz, DMSO-d₆)**

^{13}C -NMR (126 MHz, DMSO- d_6)

186.09

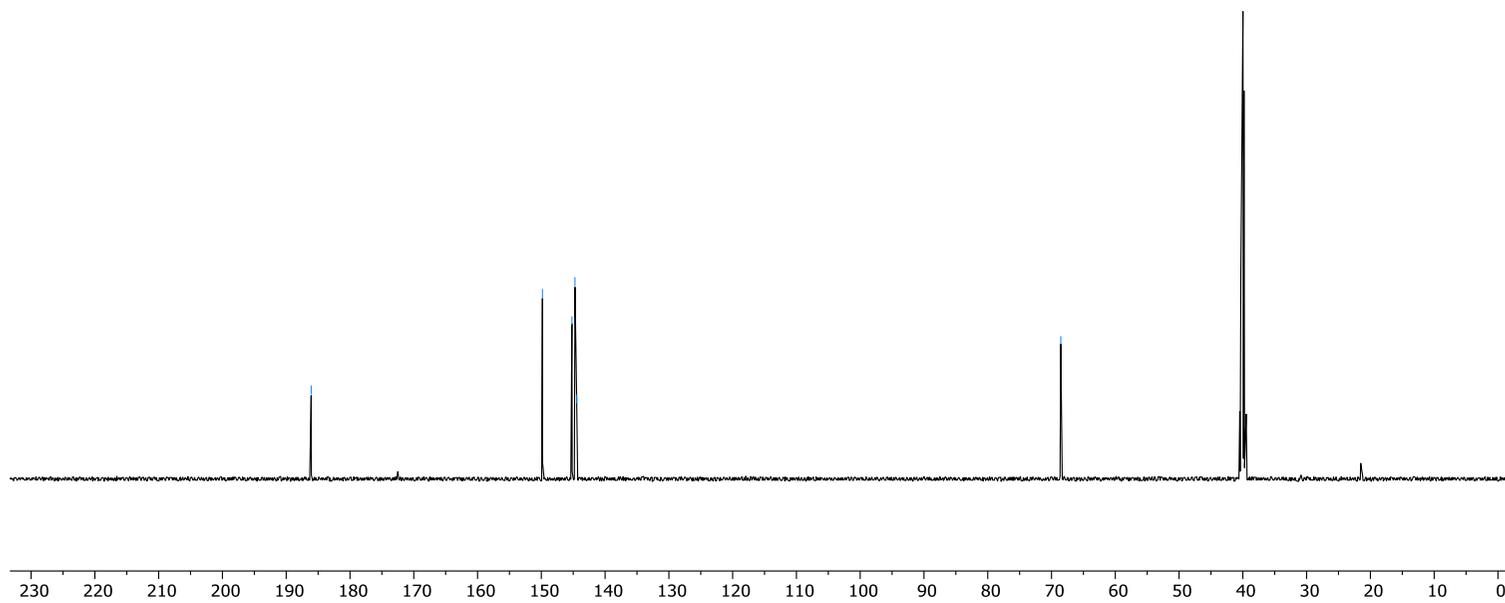
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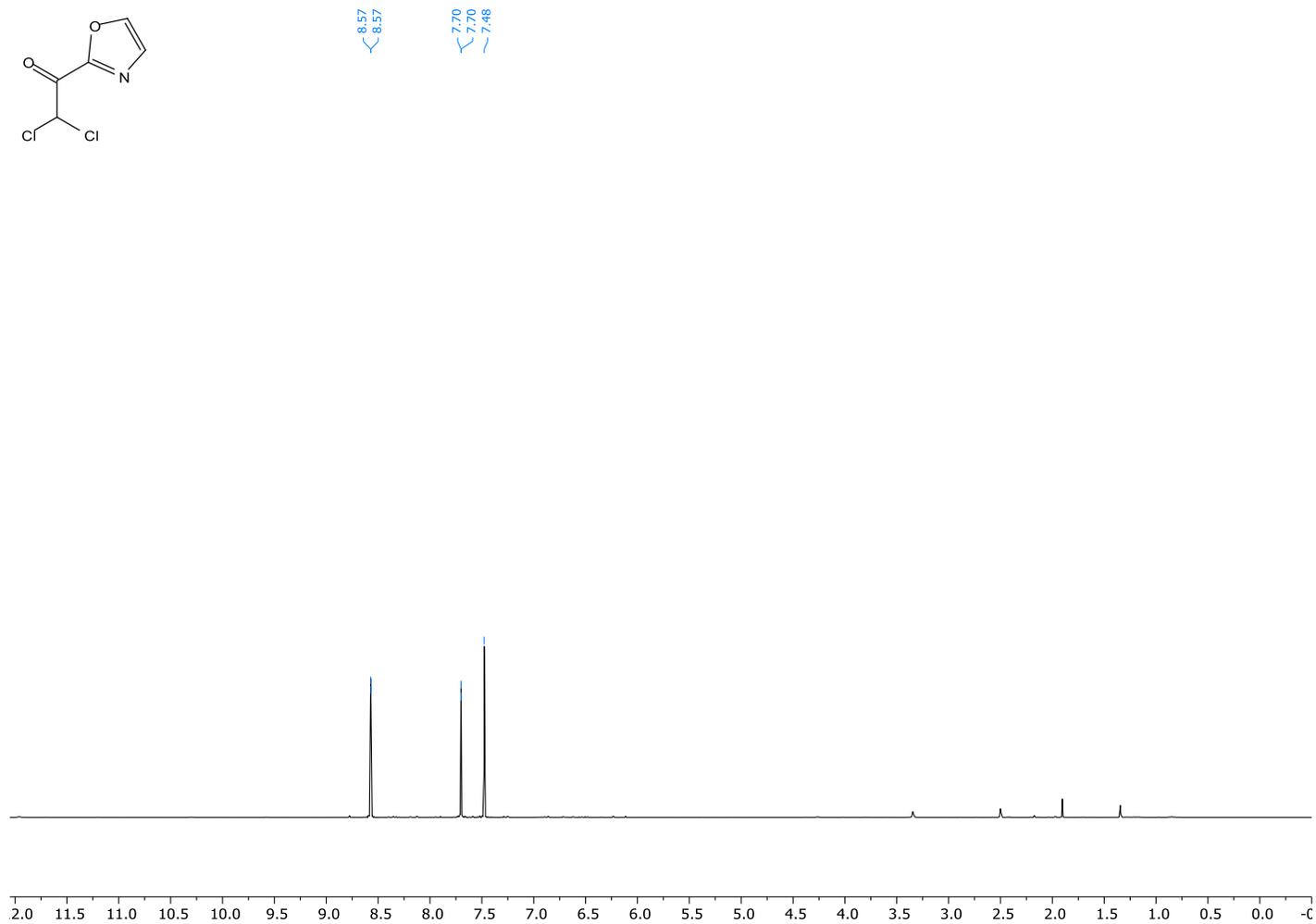
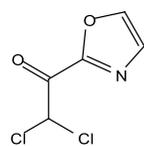
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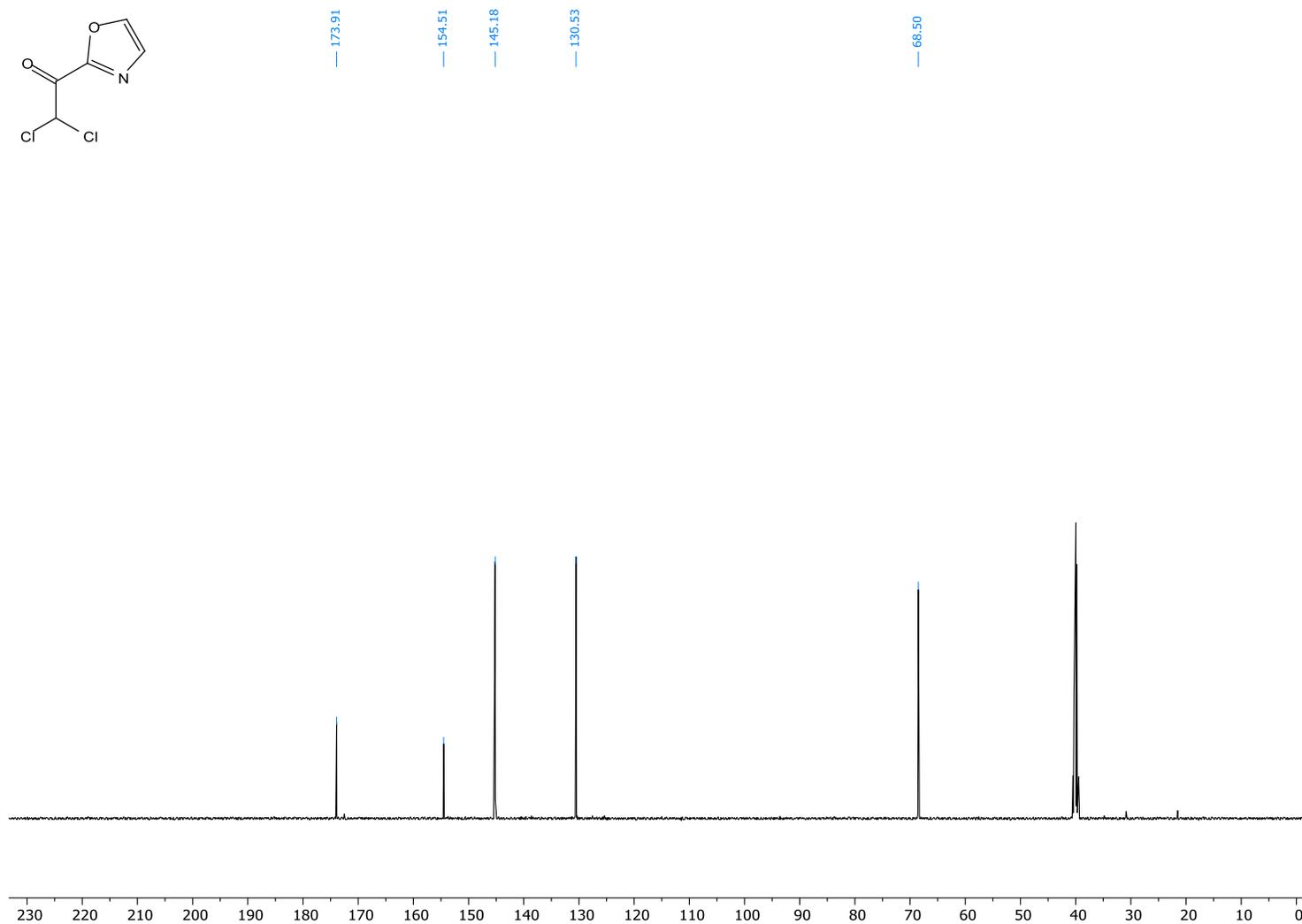
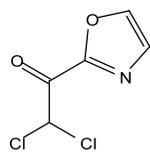
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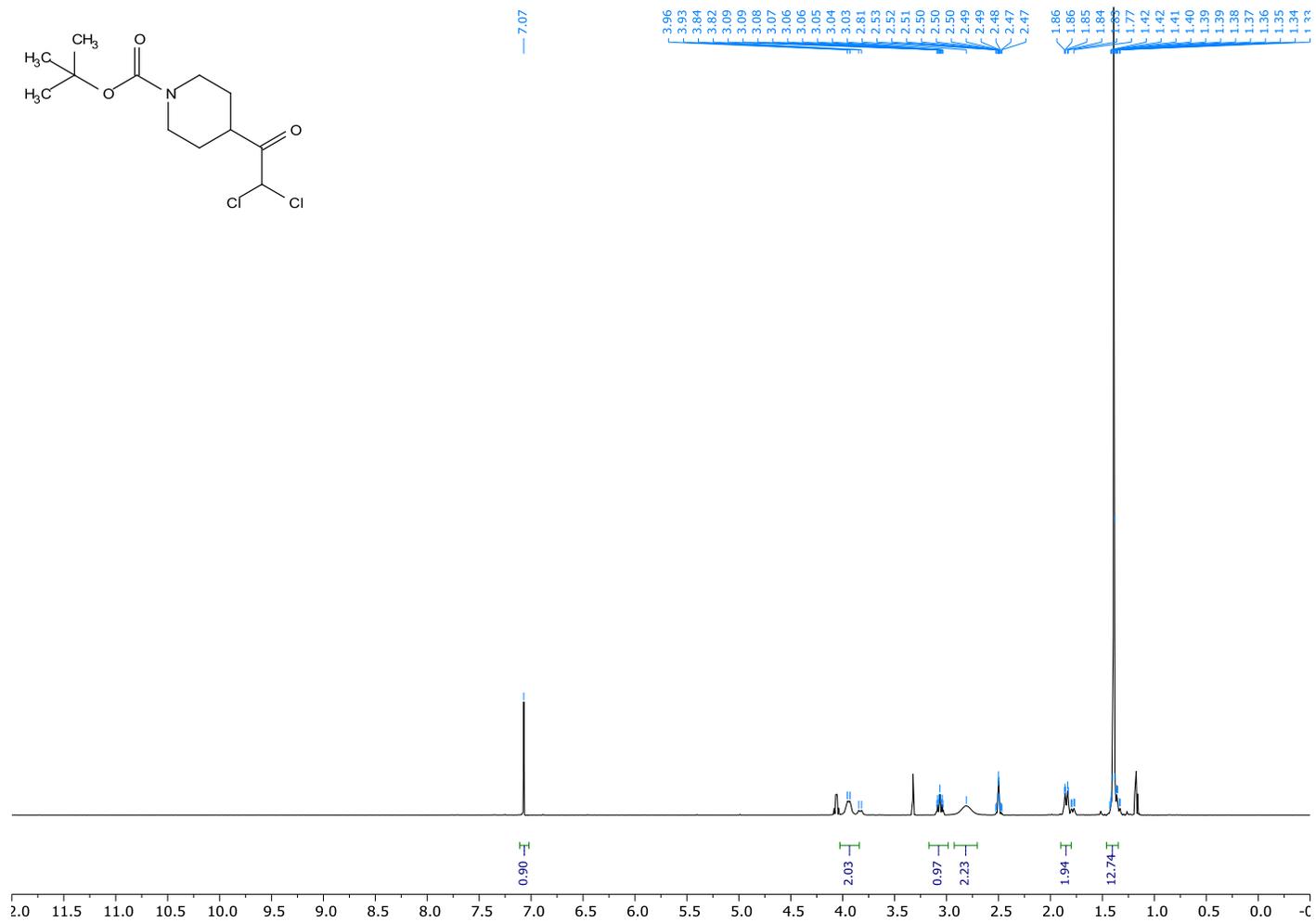
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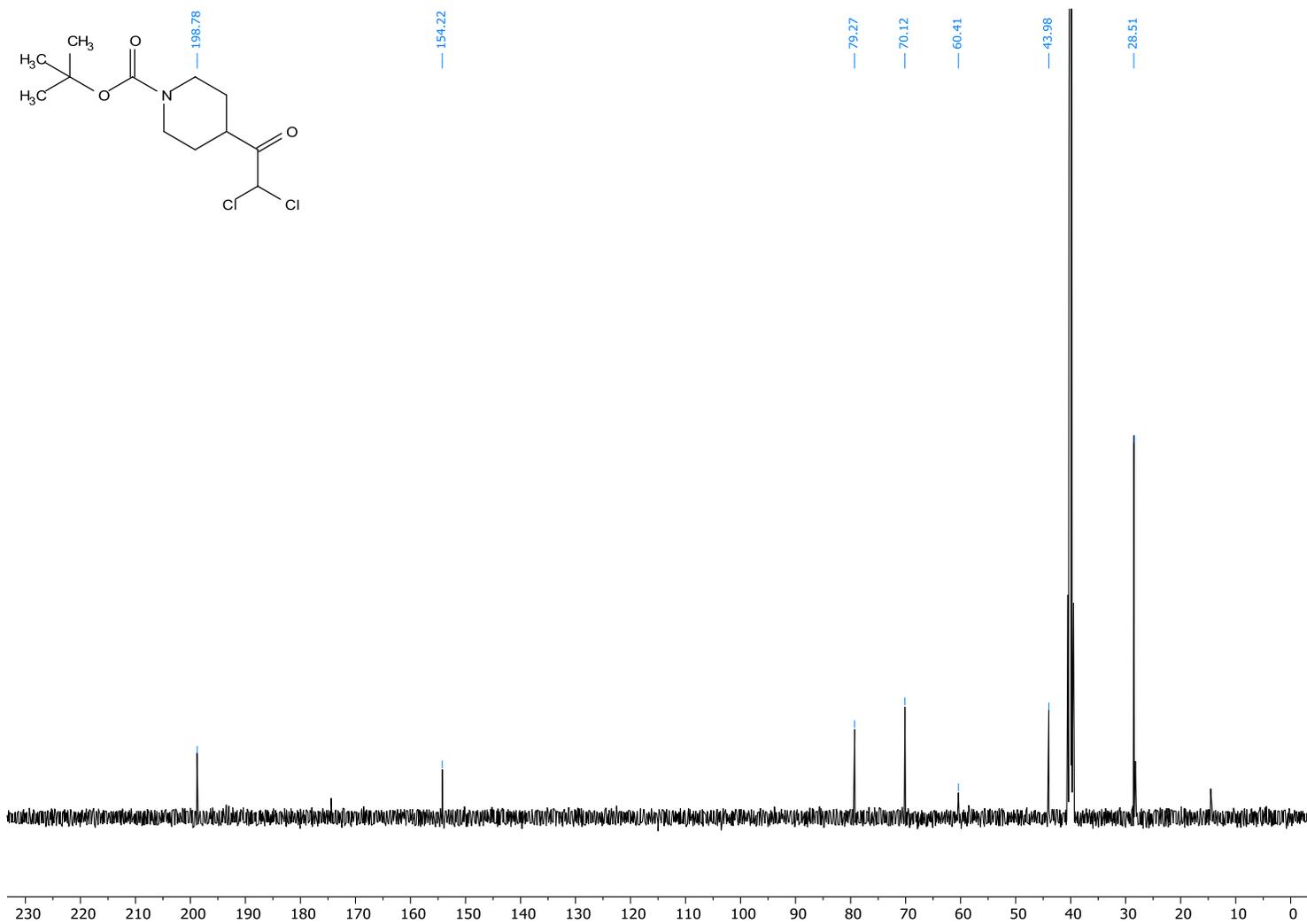
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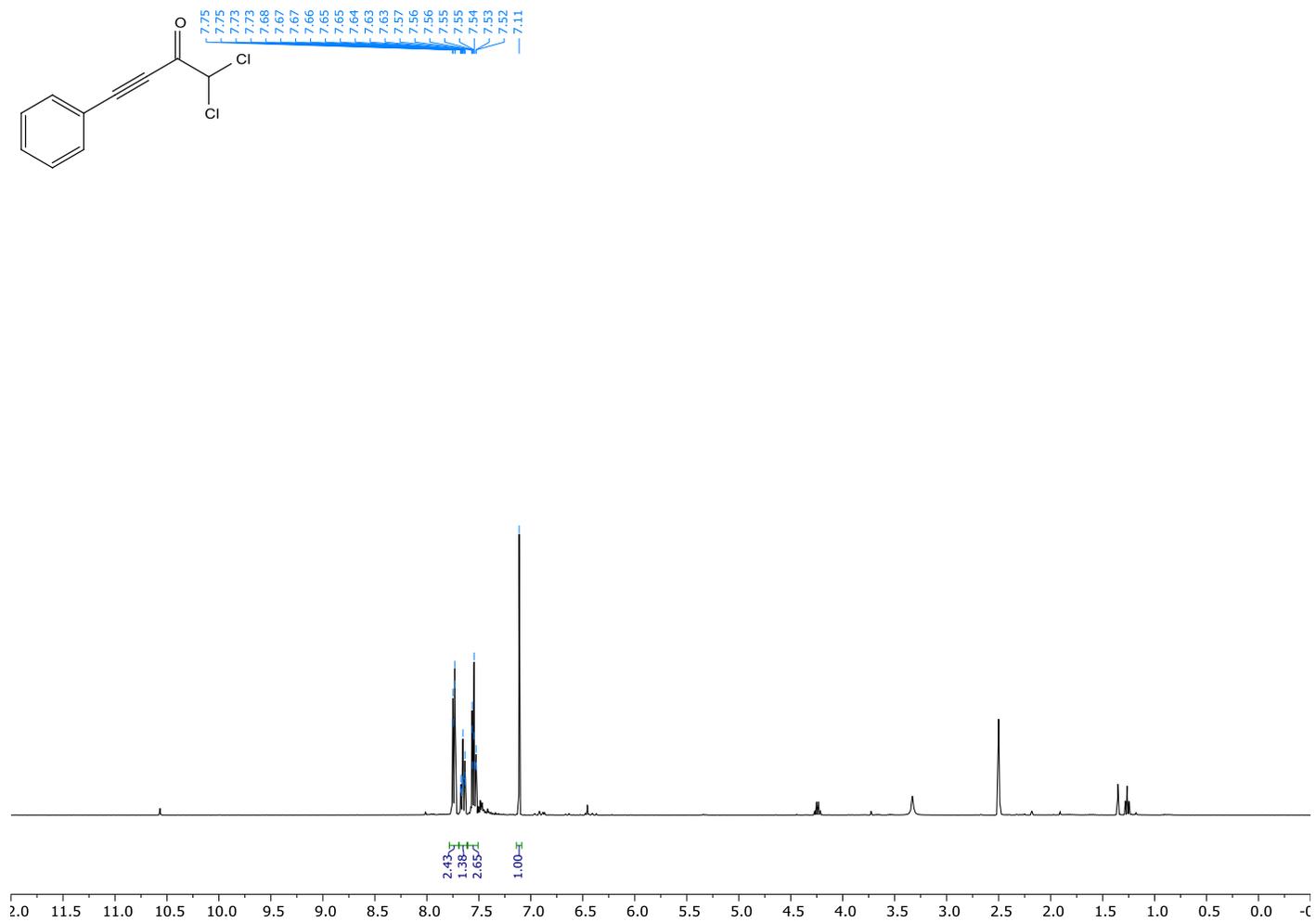


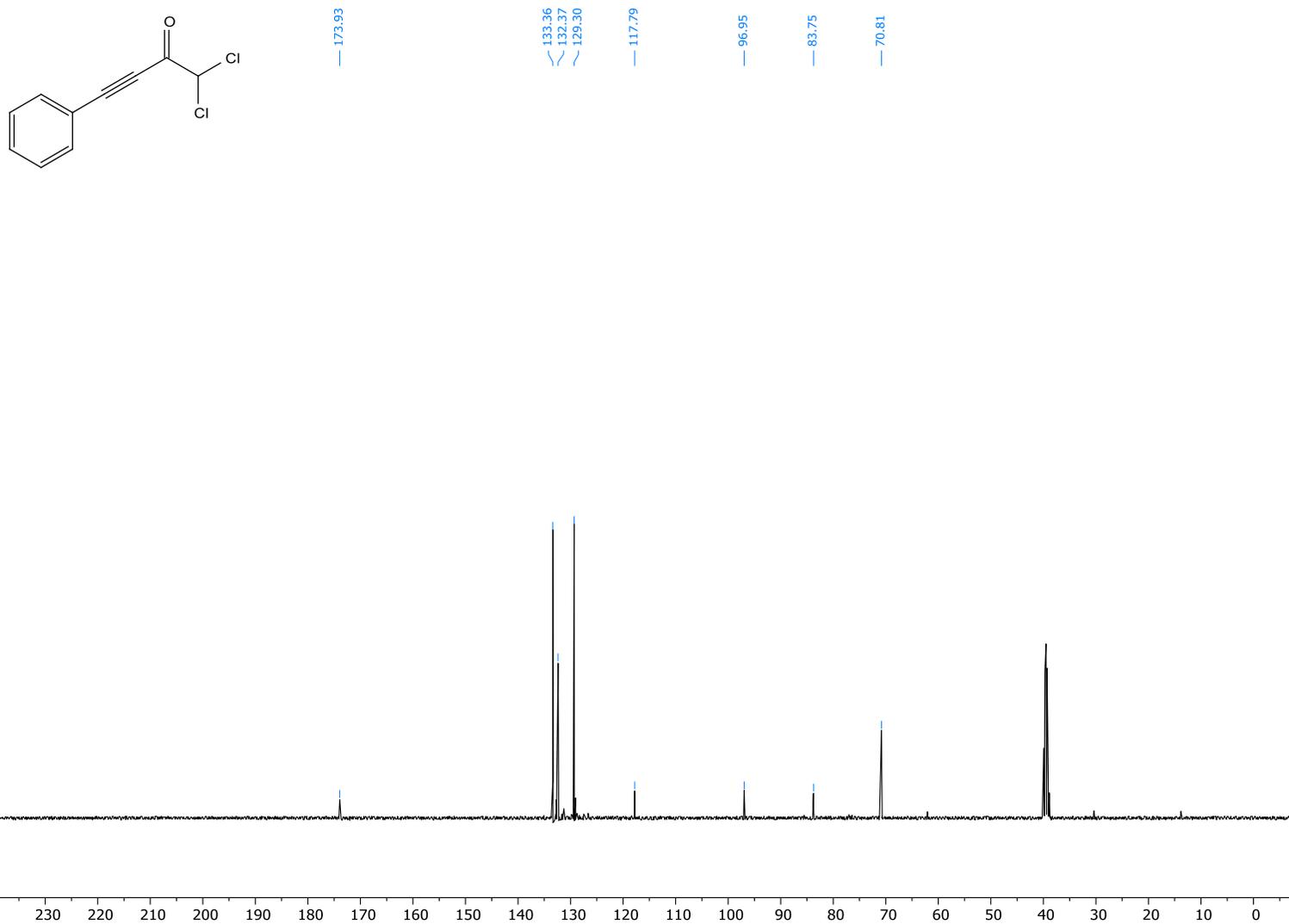
2,2-dichloro-1-(oxazol-2-yl)ethan-1-one (3e)**¹H-NMR (500 MHz, DMSO-d₆)**

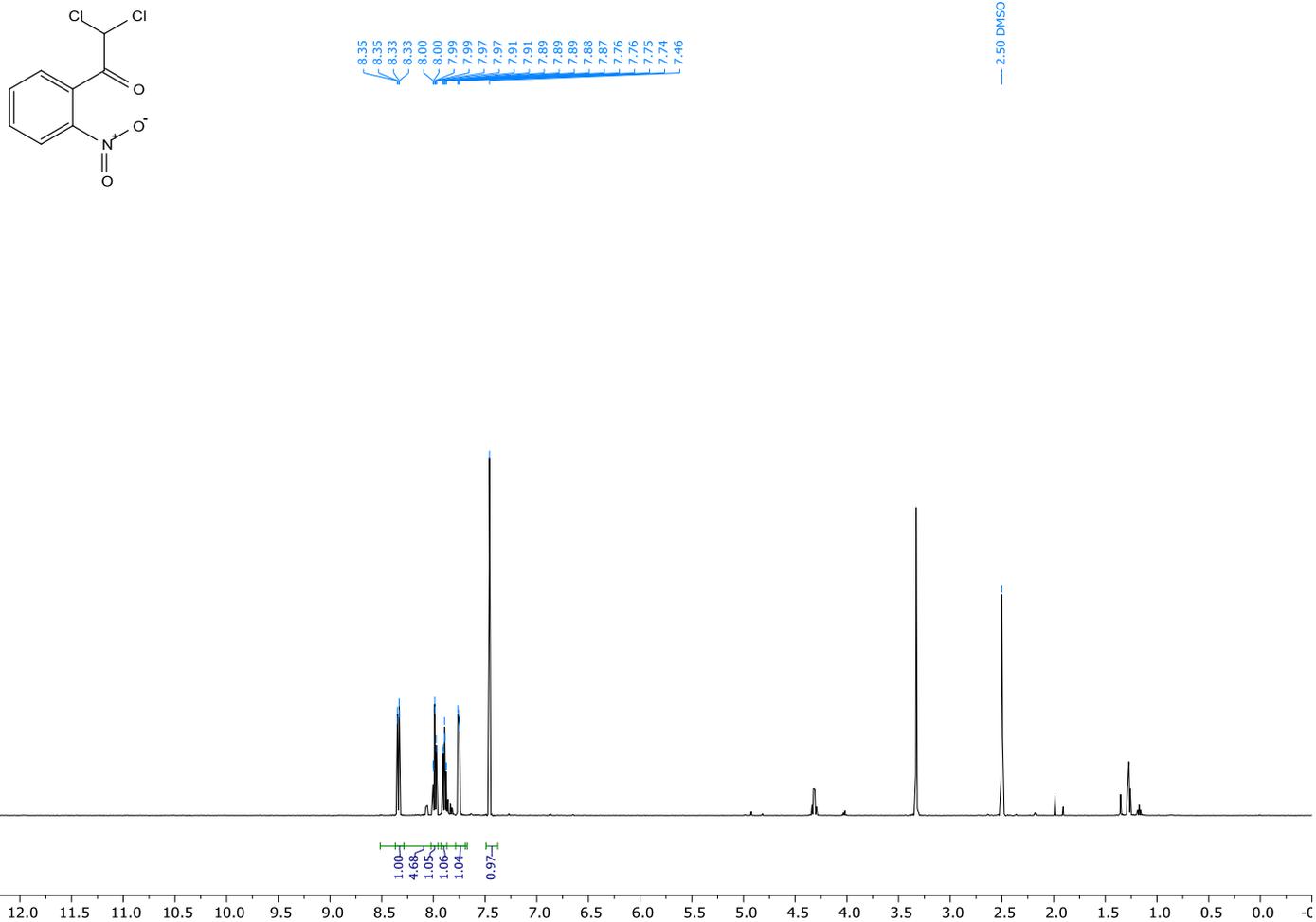
^{13}C -NMR (126 MHz, DMSO- d_6)

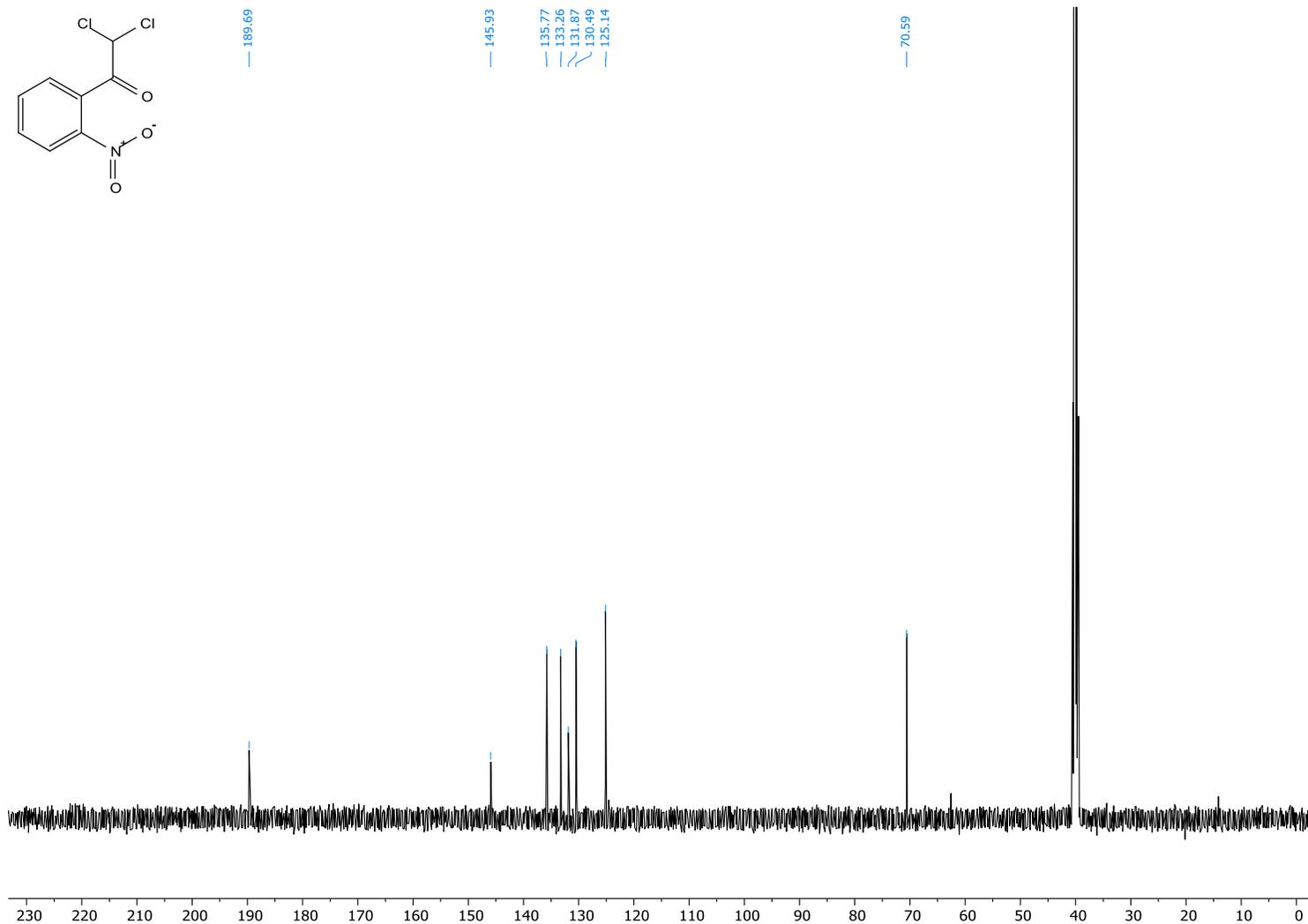
tert-butyl 4-(2,2-dichloroacetyl)piperidine-1-carboxylate (3f)**¹H-NMR (500 MHz, DMSO-d₆)**

^{13}C -NMR (126 MHz, DMSO- d_6)

1,1-dichloro-4-phenylbut-3-yn-2-one (3g)**¹H-NMR (500 MHz, DMSO-d₆)**

^{13}C -NMR (126 MHz, DMSO- d_6)

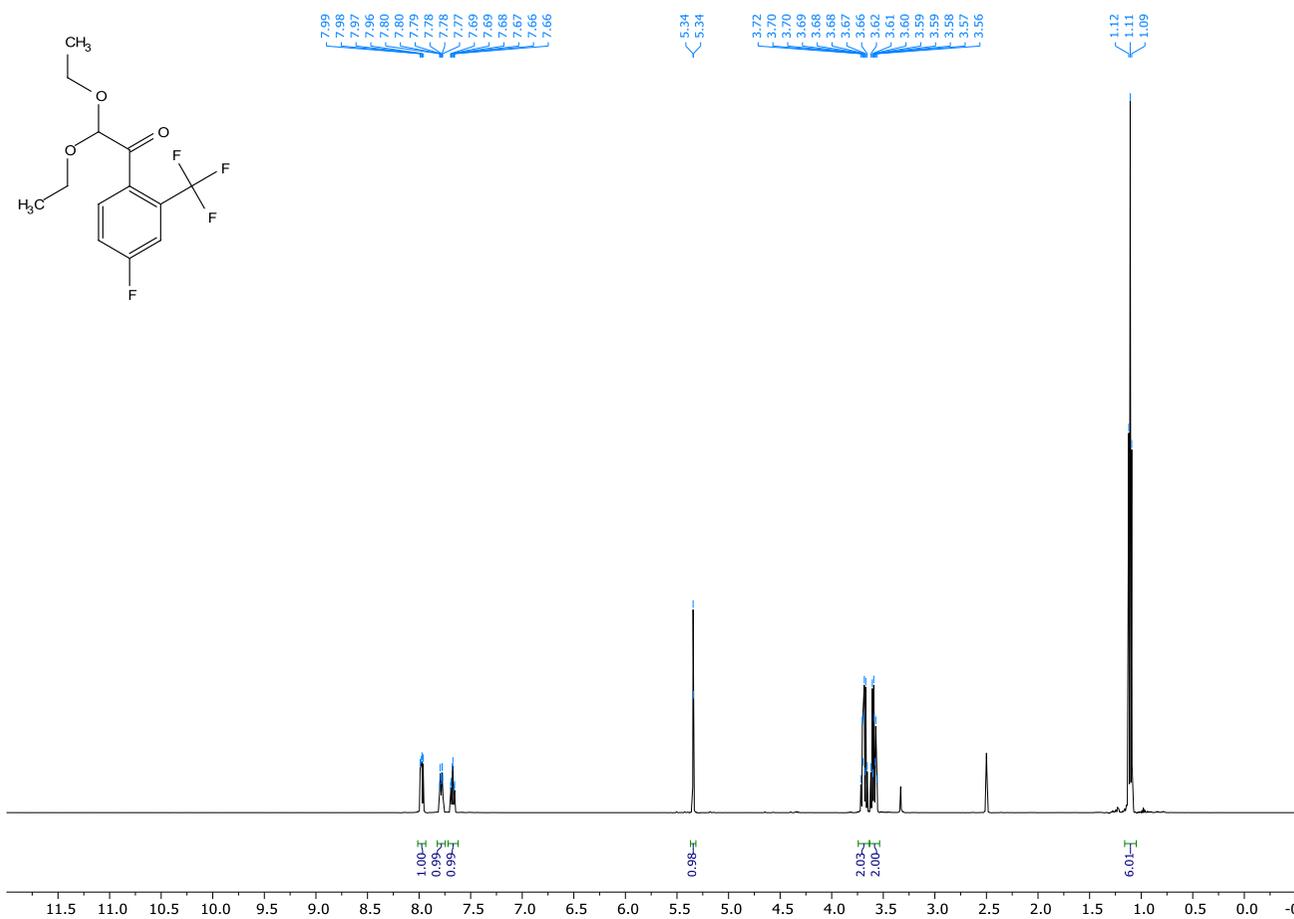
2,2-dichloro-1-(2-nitrophenyl)ethan-1-one (3h)**¹H-NMR (500 MHz, DMSO-d₆)**

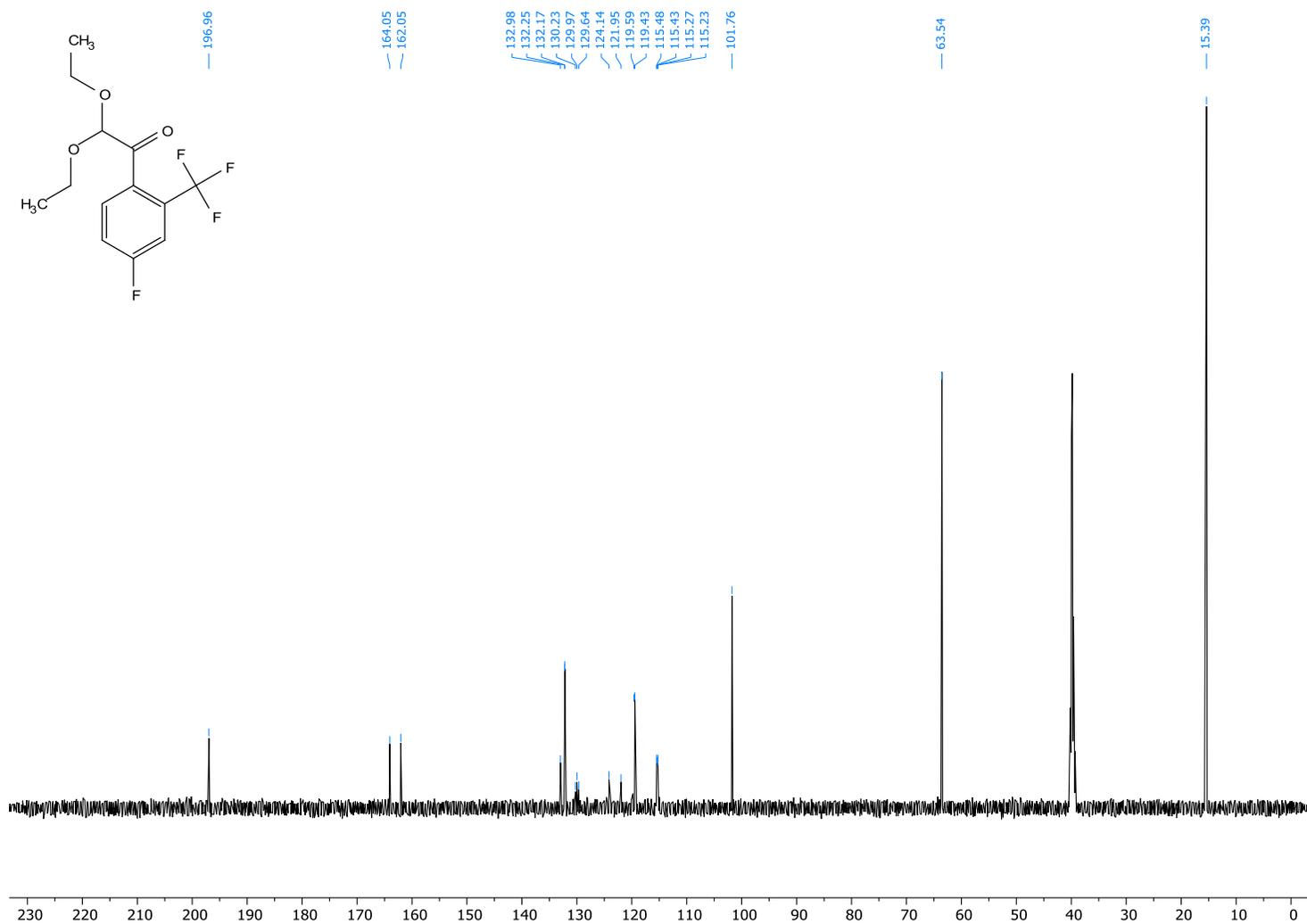
^{13}C -NMR (126 MHz, DMSO- d_6)

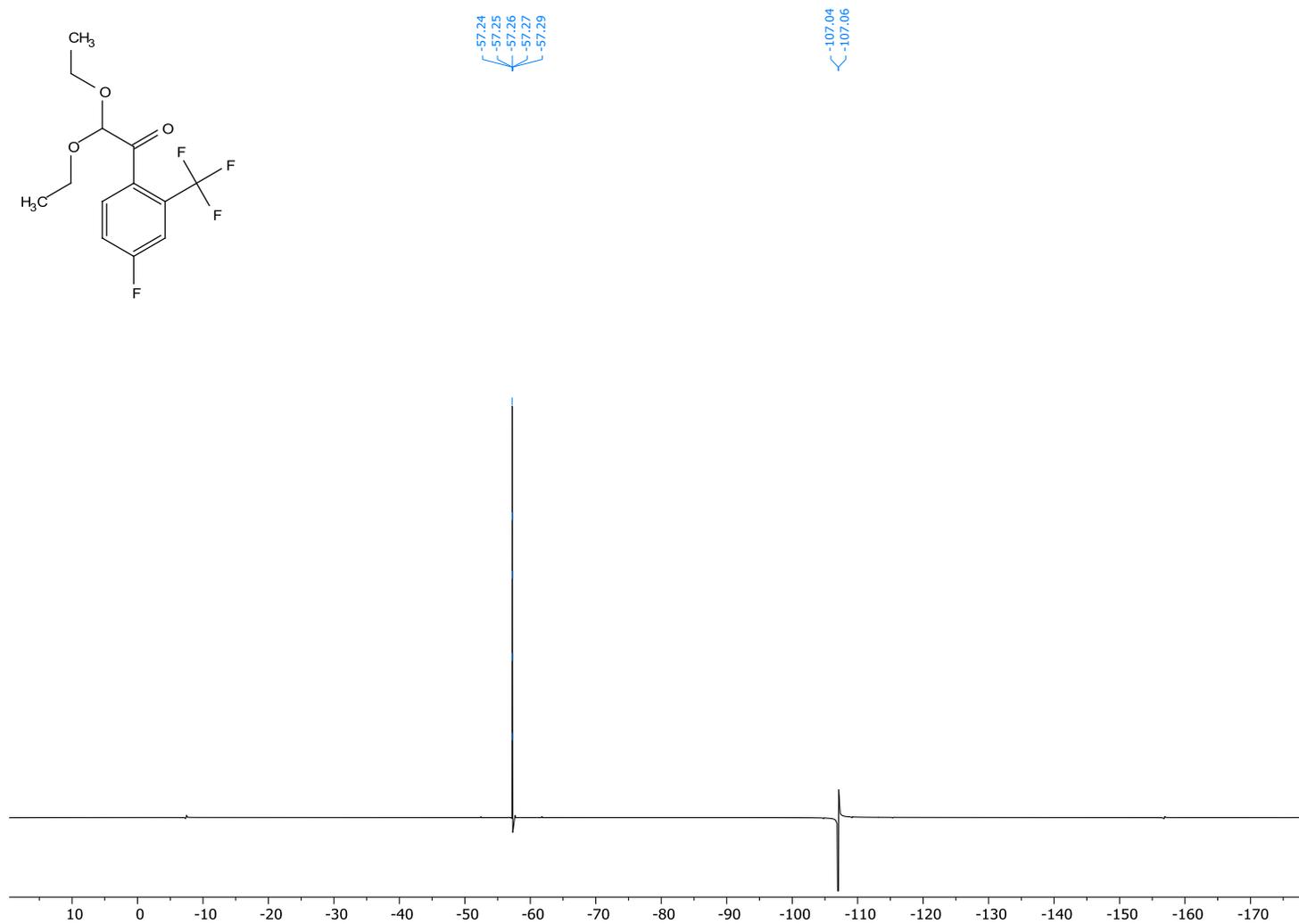
4.2 Approach B: access to ketoacetals

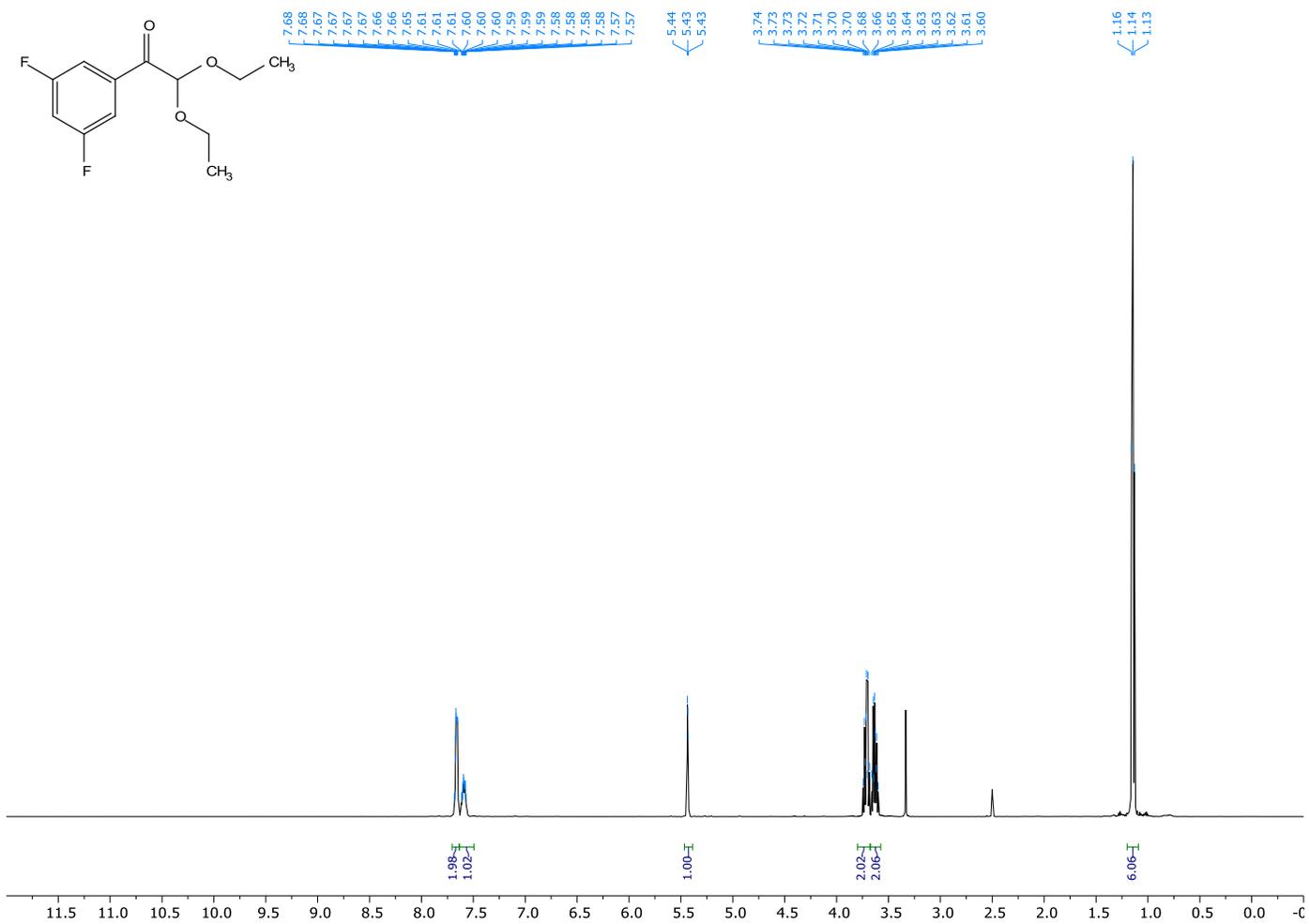
2,2-diethoxy-1-(4-fluoro-2-(trifluoromethyl)phenyl)ethan-1-one (5a)

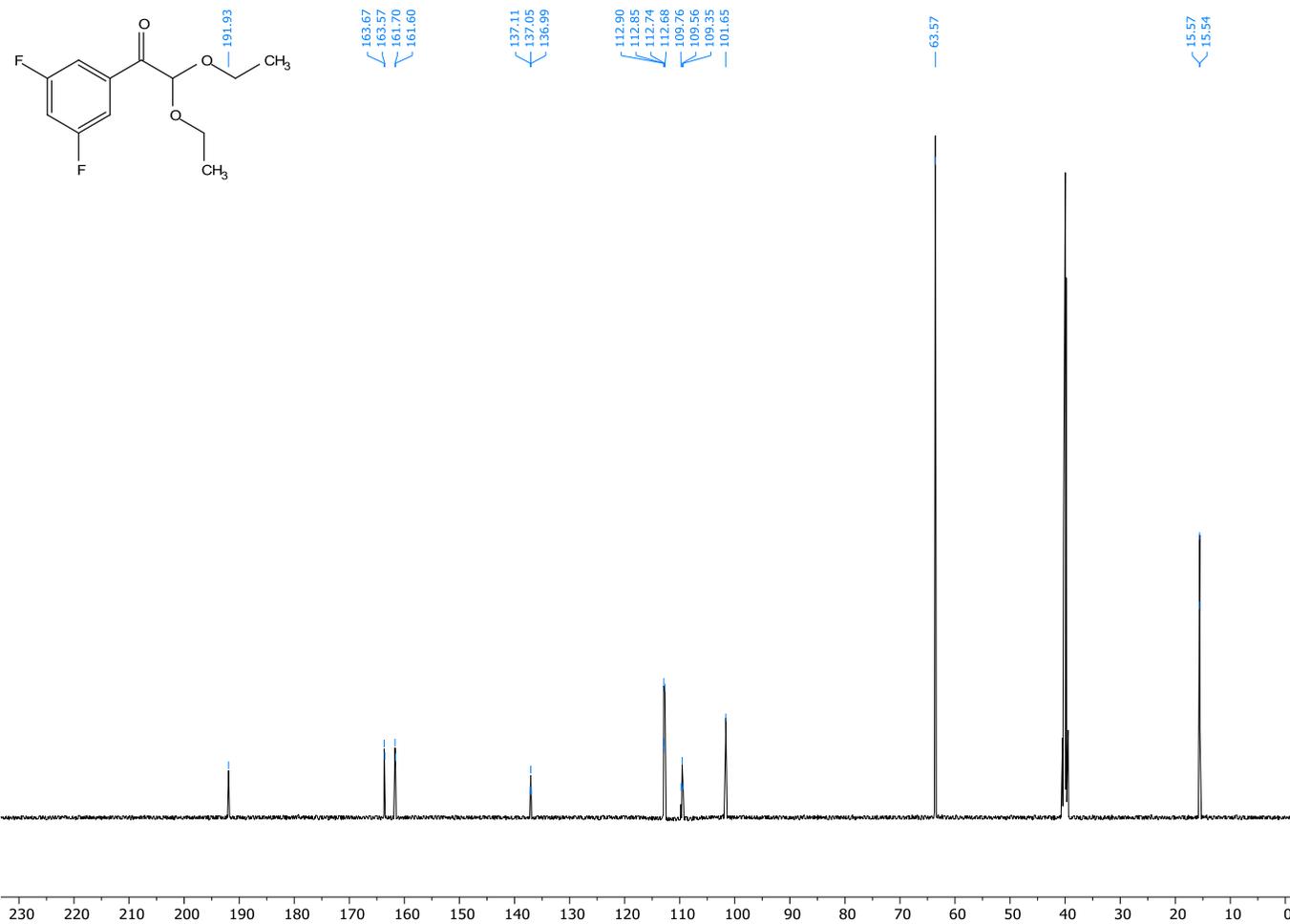
$^1\text{H-NMR}$ (500 MHz, DMSO-d_6)

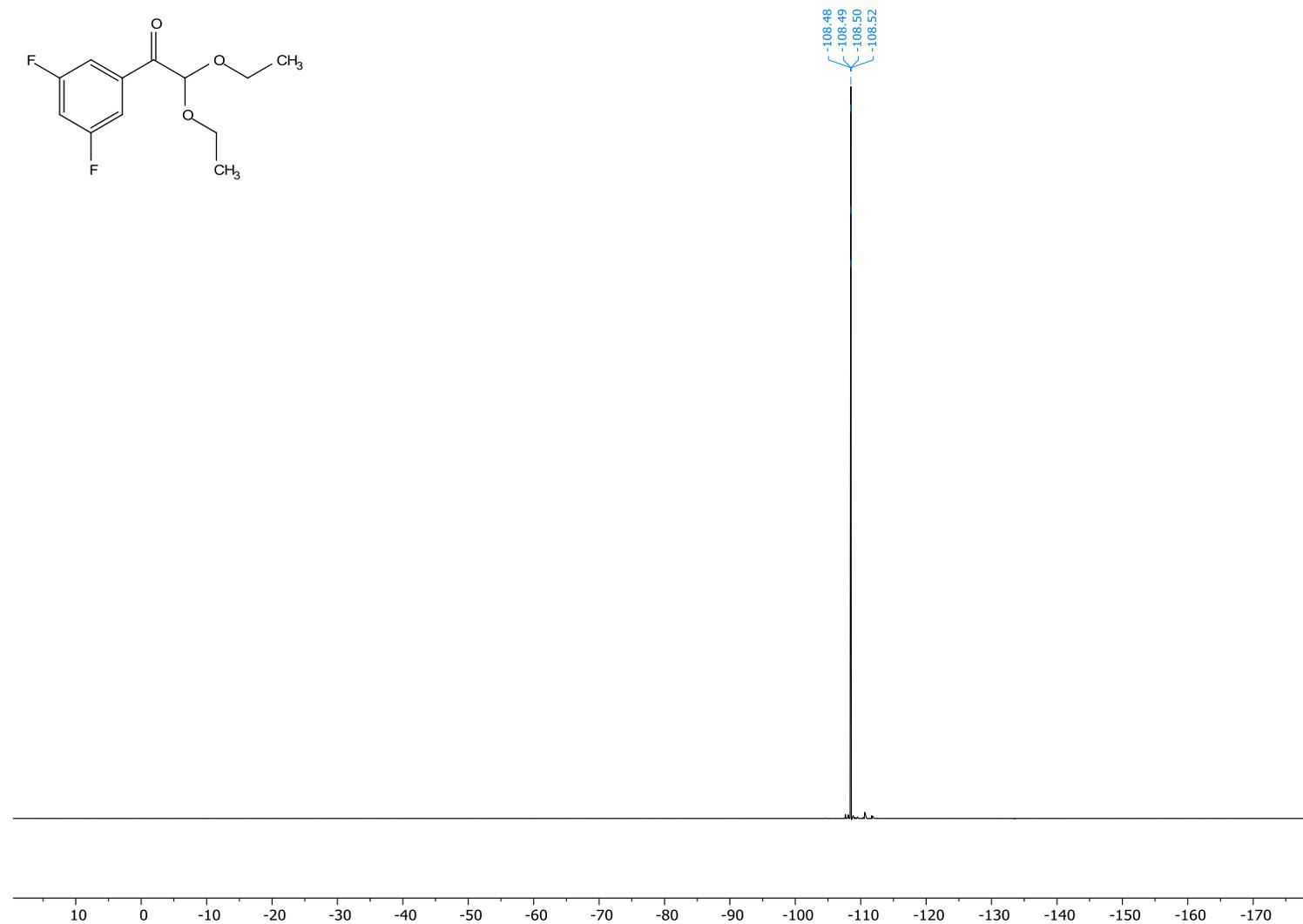
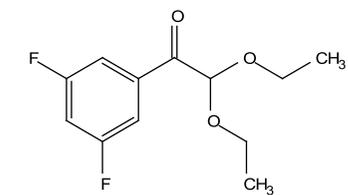


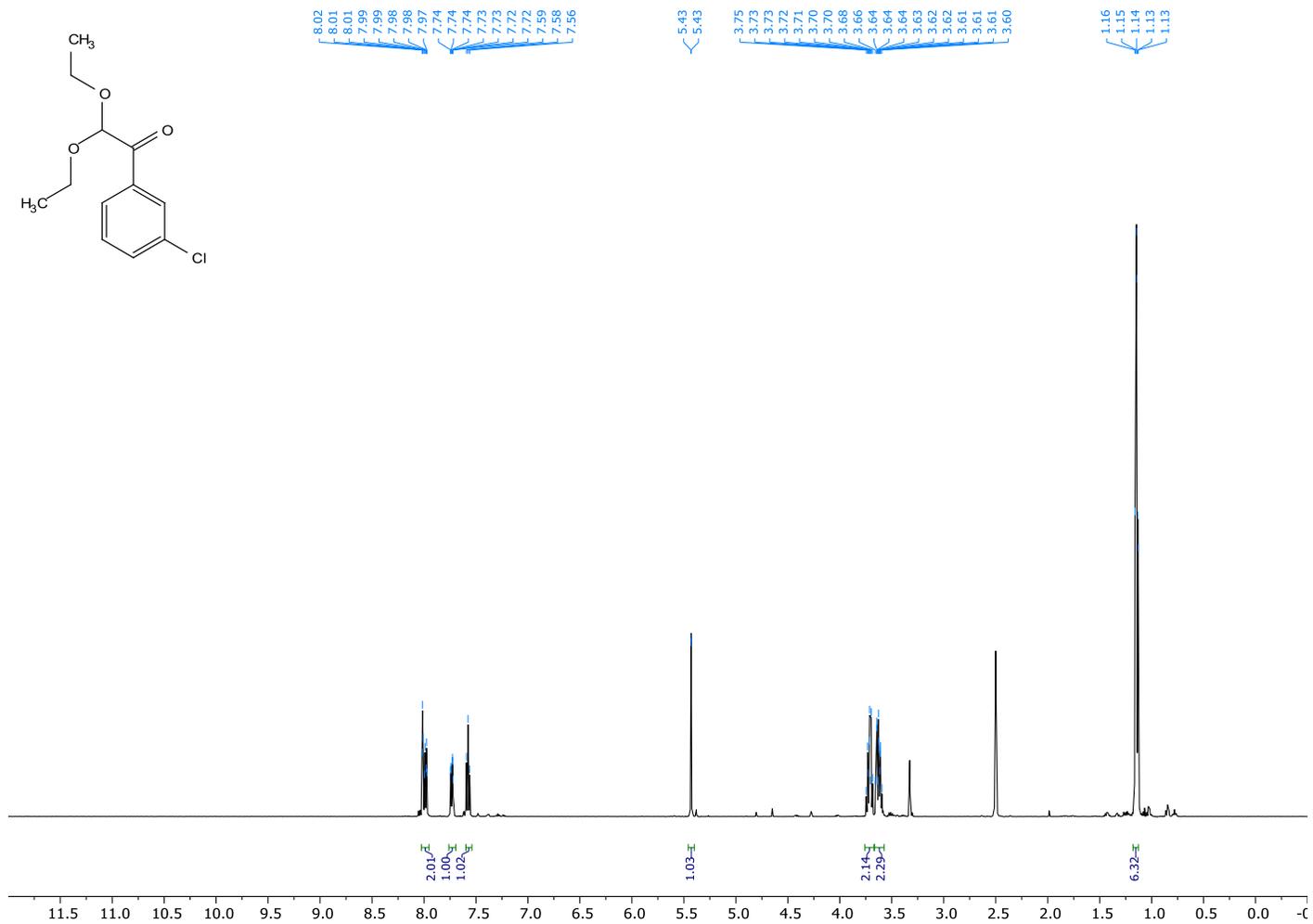
^{13}C -NMR (126 MHz, DMSO- d_6)

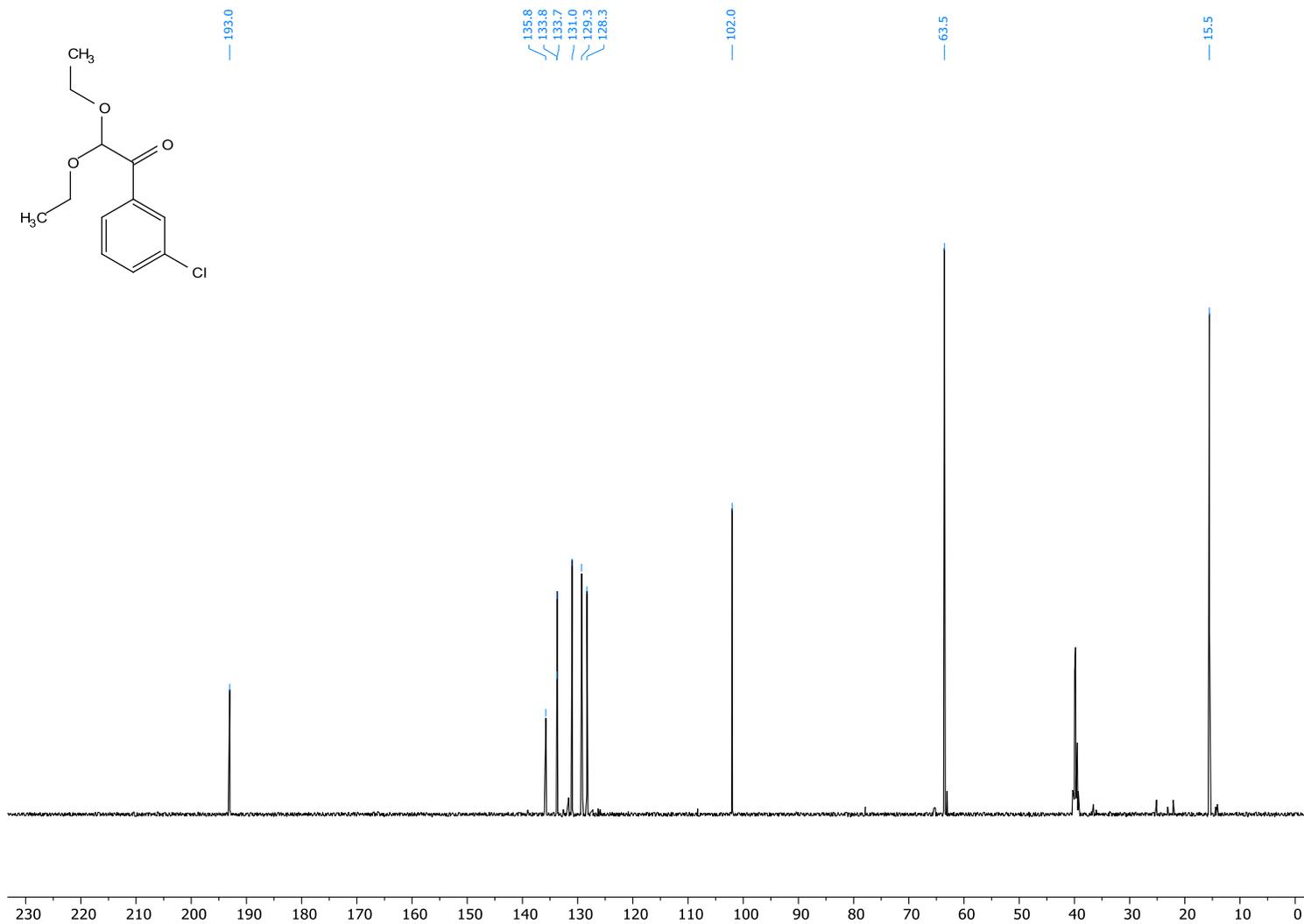
^{19}F -NMR (470 MHz, DMSO- d_6)

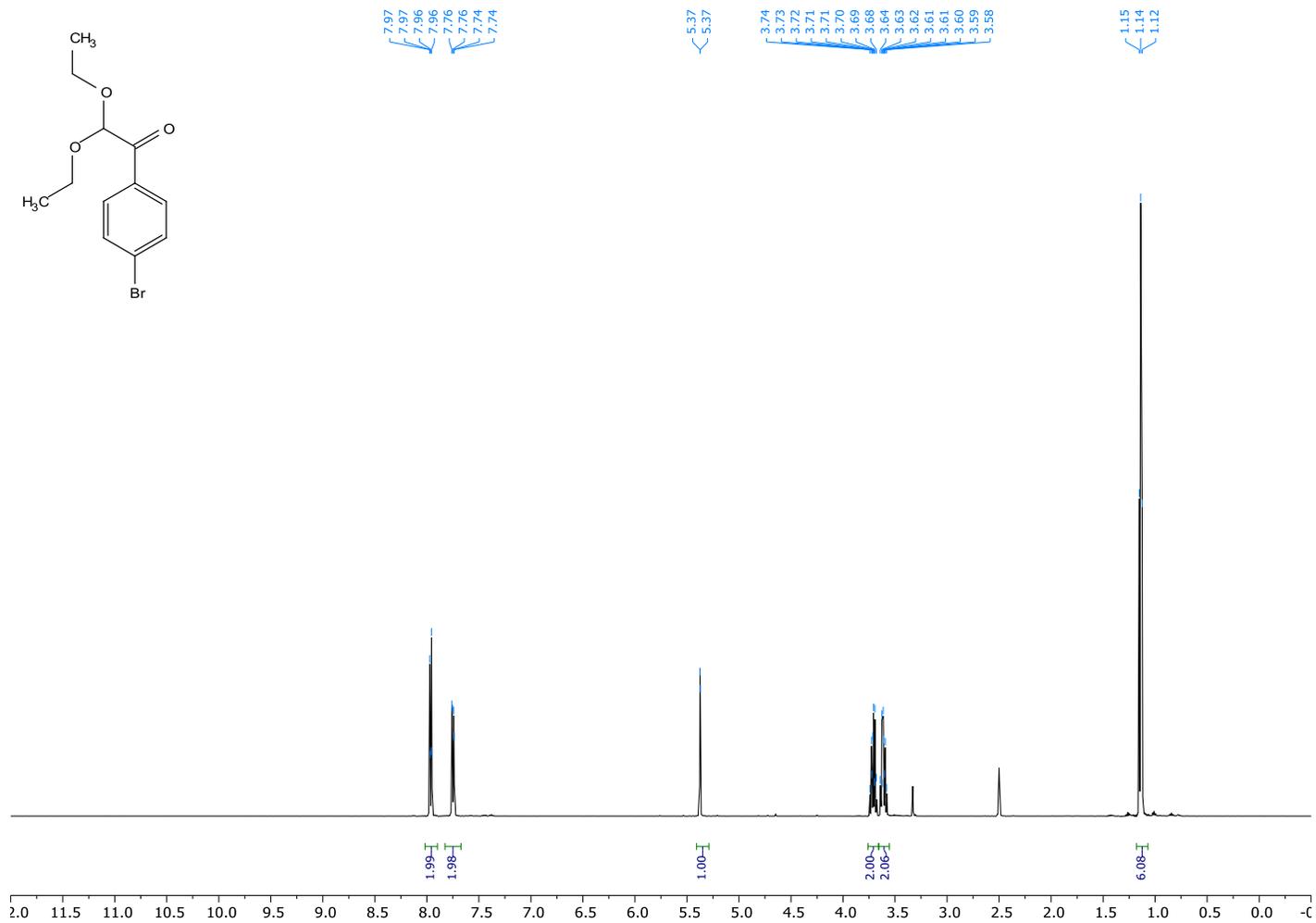
1-(3,5-difluorophenyl)-2,2-diethoxyethan-1-one (5b)**¹H-NMR (500 MHz, DMSO-d₆)**

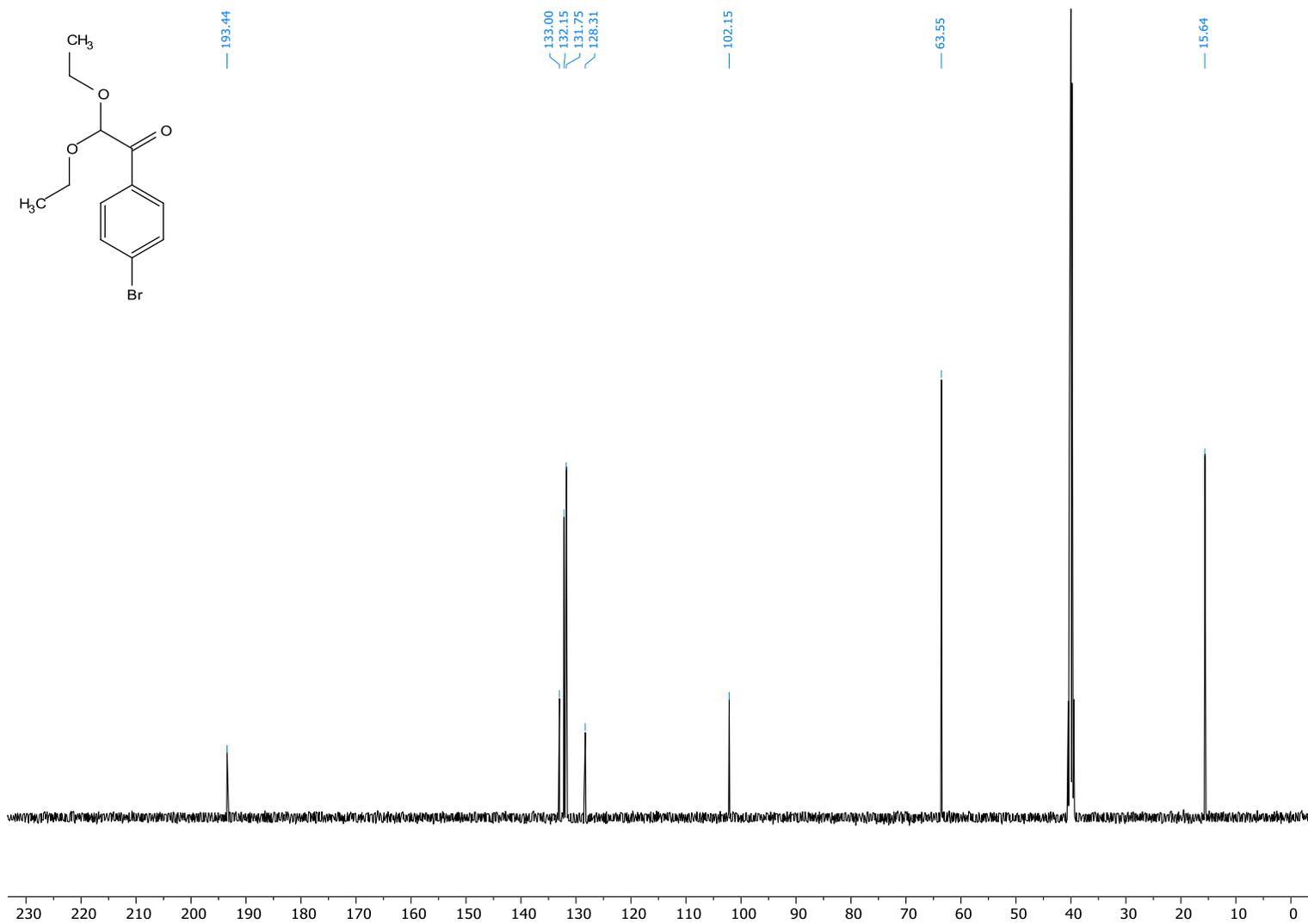
^{13}C -NMR (126 MHz, DMSO- d_6)

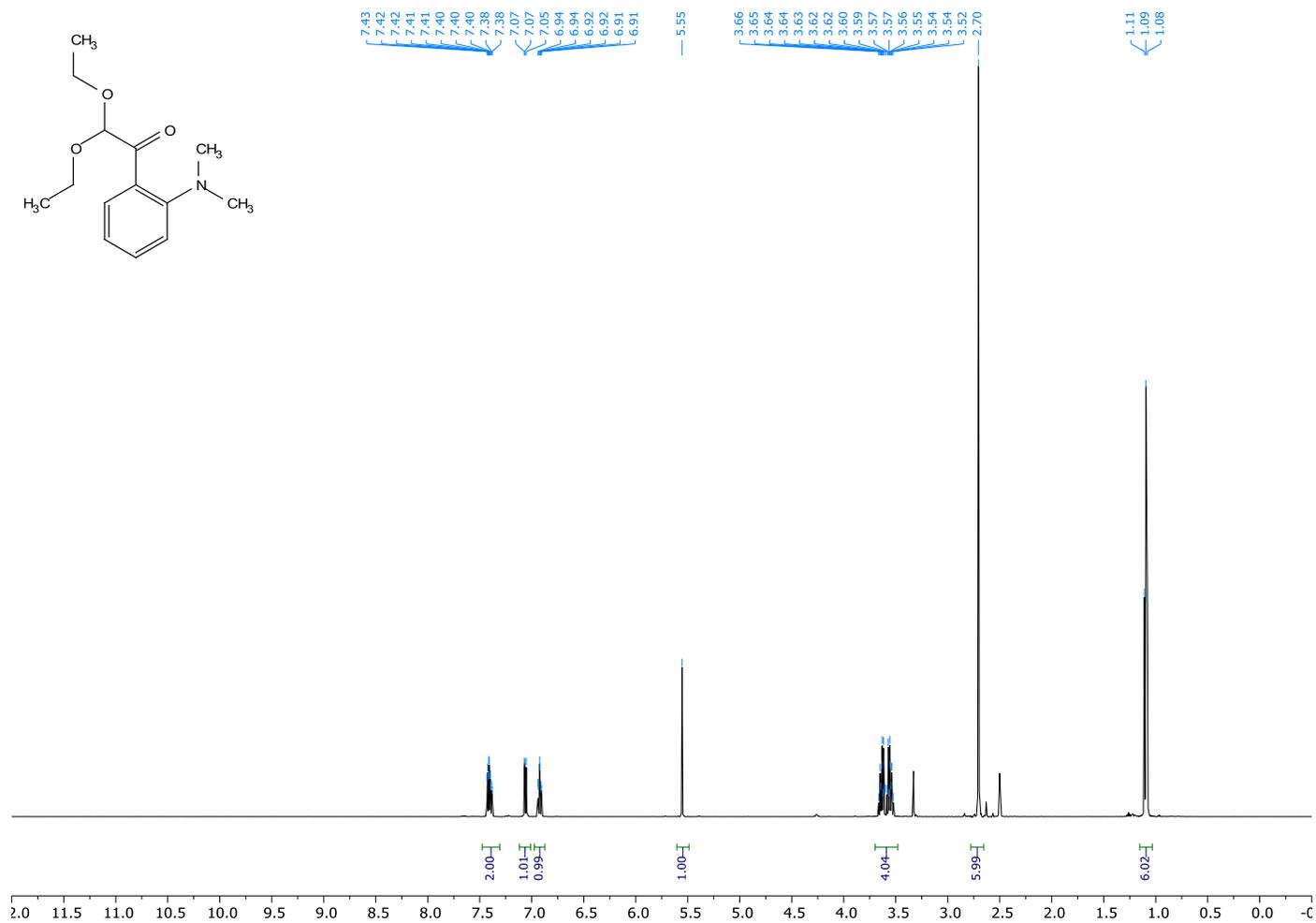
^{19}F -NMR (470 MHz, DMSO- d_6)

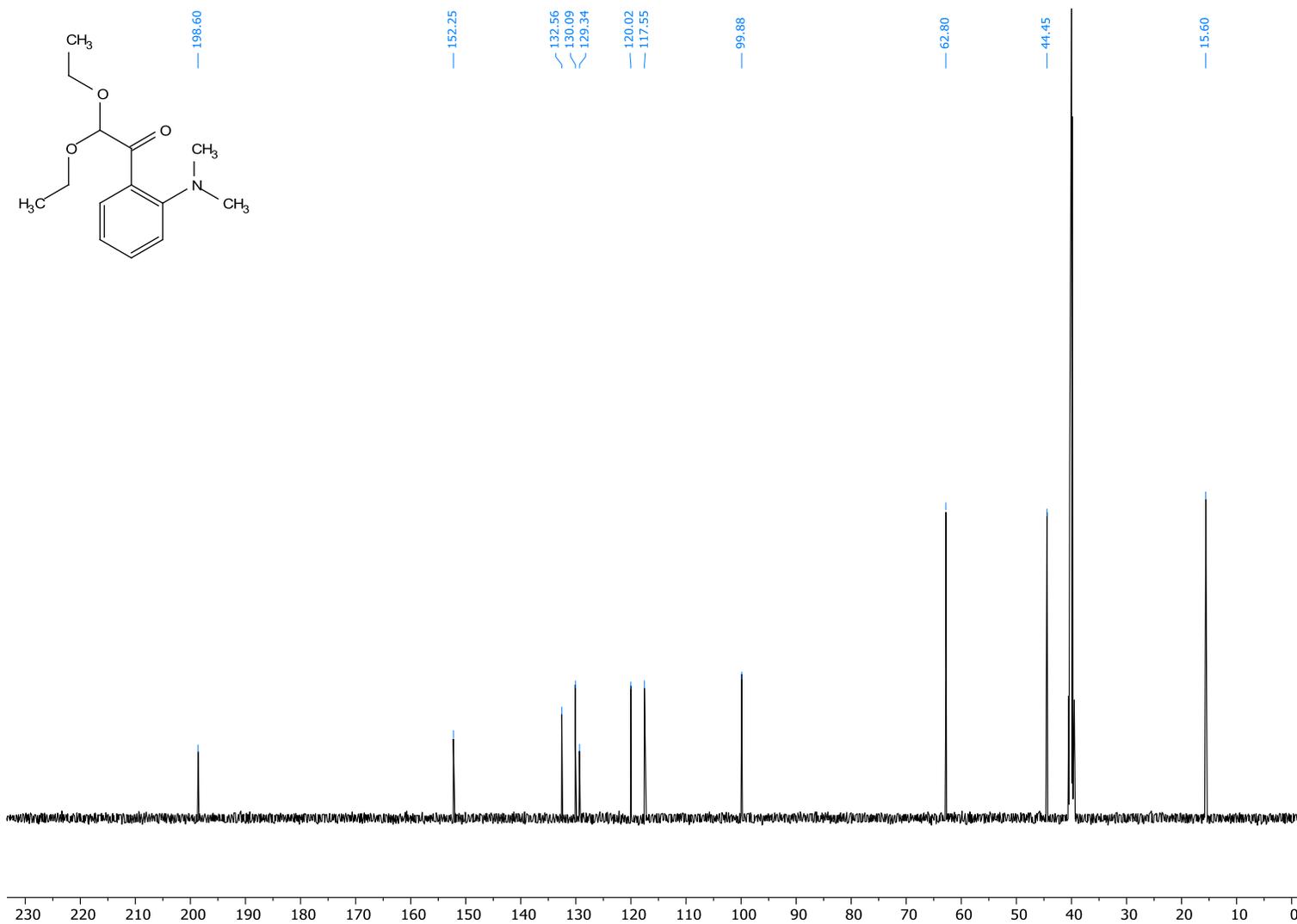
1-(3-chlorophenyl)-2,2-diethoxyethan-1-one (5c)**¹H-NMR (500 MHz, DMSO-d₆)**

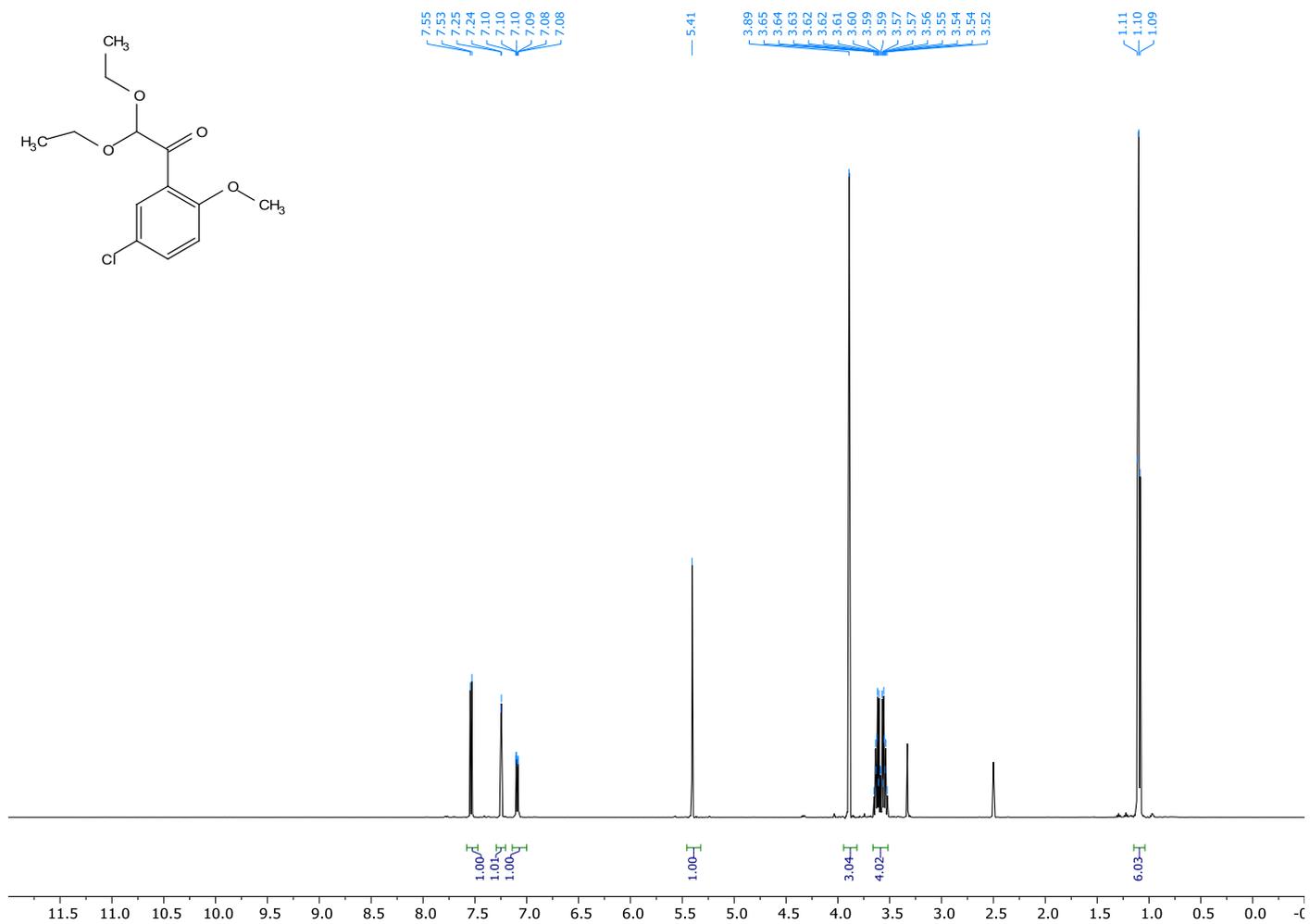
^{13}C -NMR (126 MHz, DMSO- d_6)

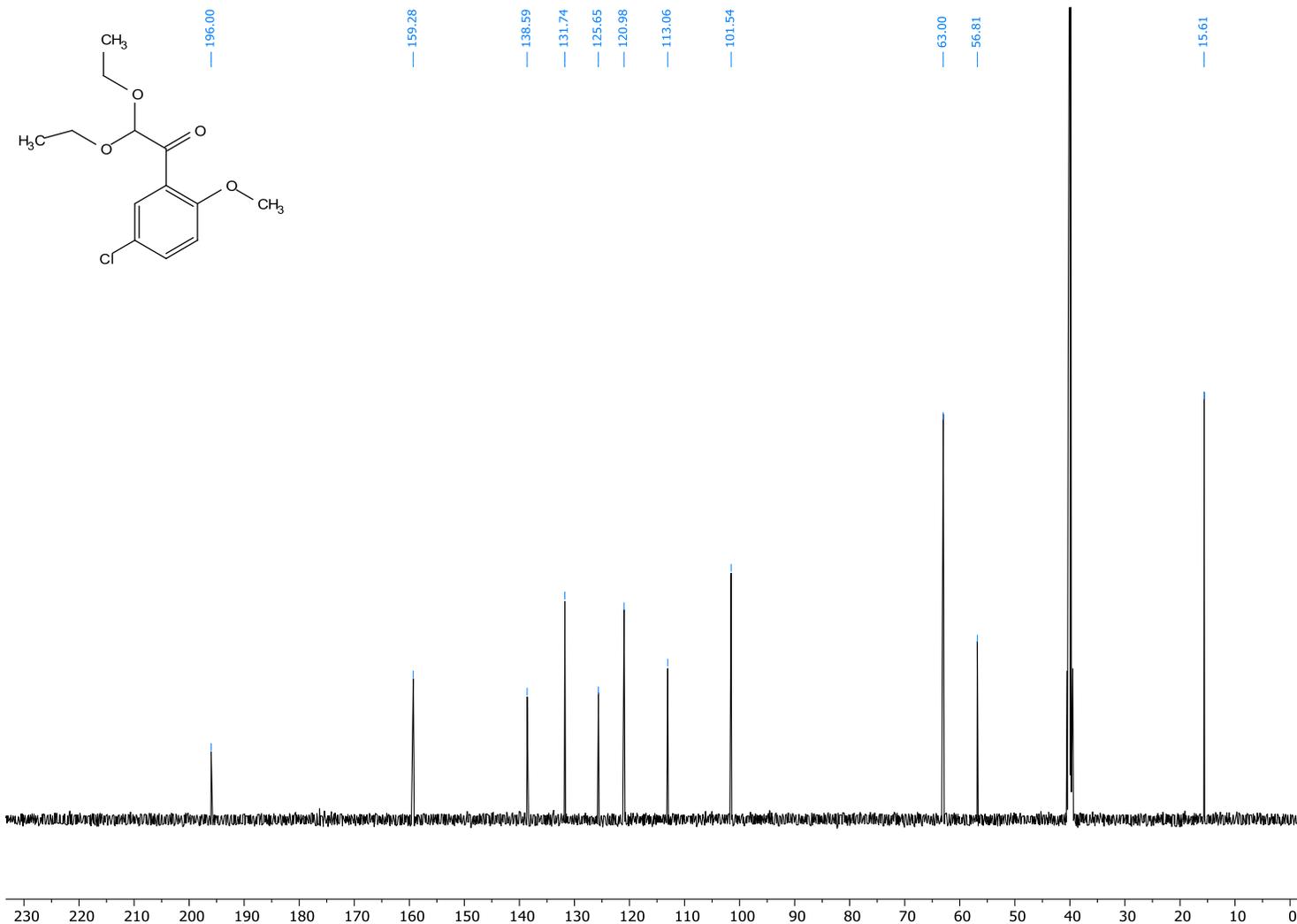
1-(4-bromophenyl)-2,2-diethoxyethan-1-one (5d)**¹H-NMR (500 MHz, DMSO-d₆)**

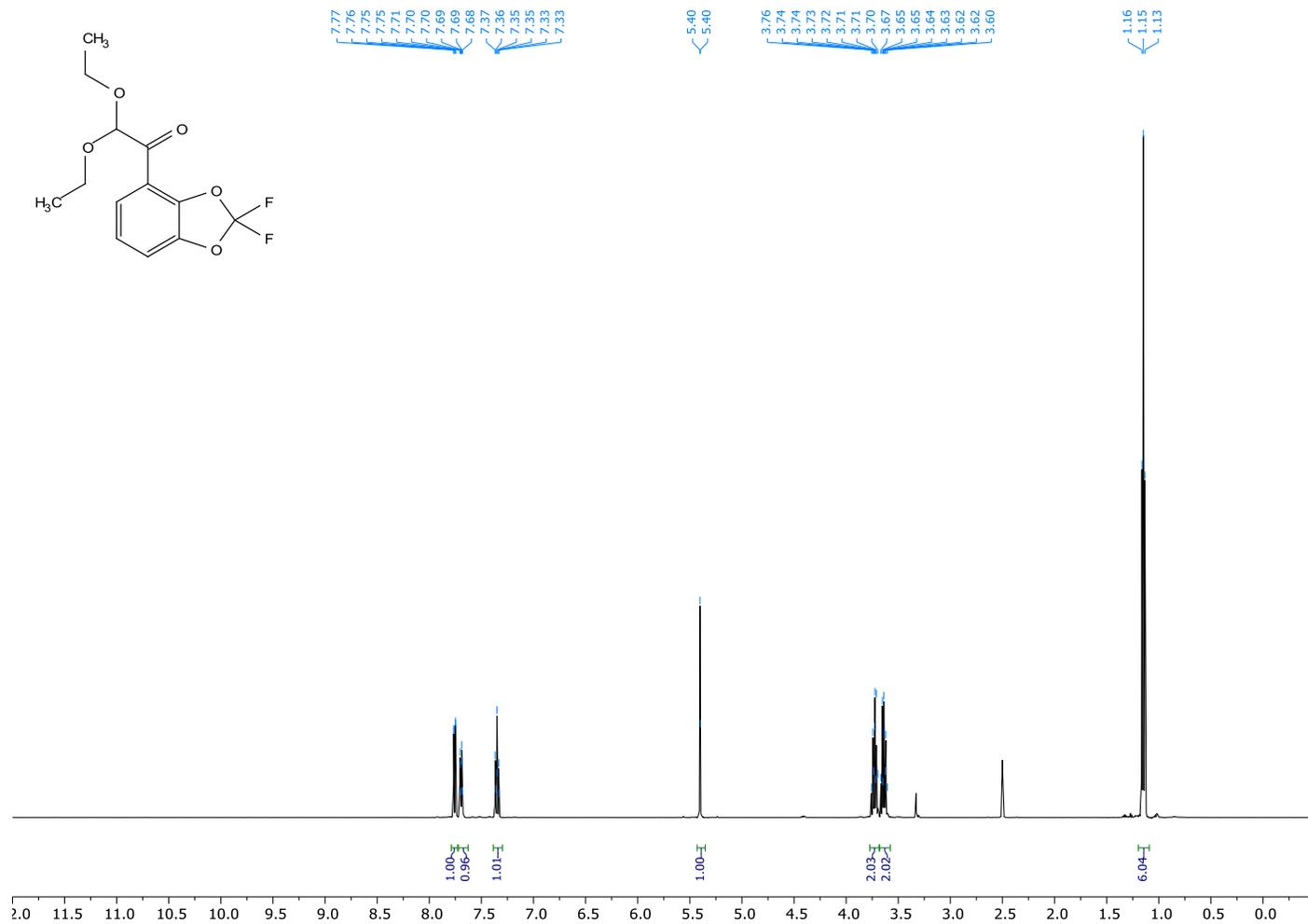
^{13}C -NMR (126 MHz, DMSO- d_6)

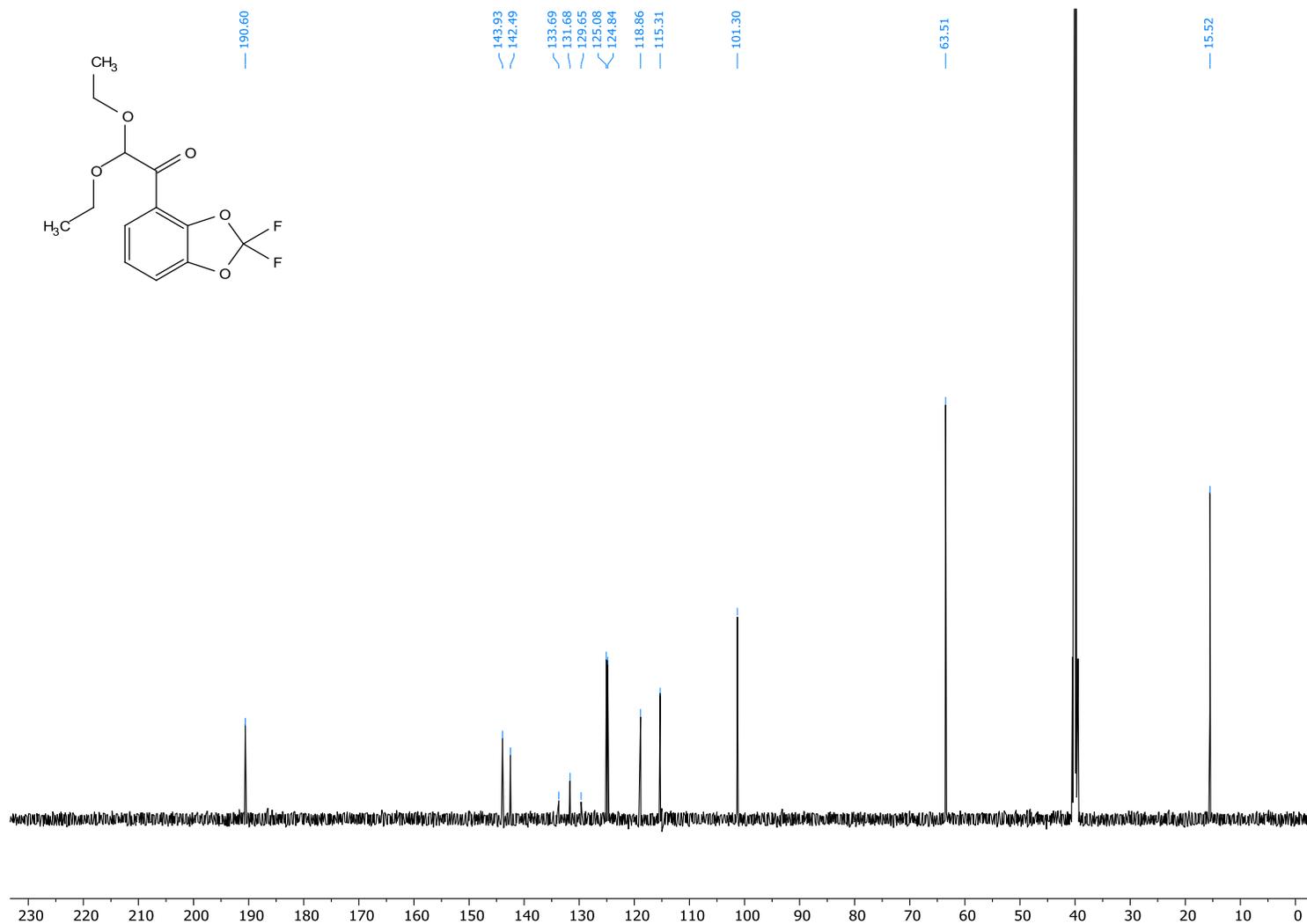
1-(2-(dimethylamino)phenyl)-2,2-diethoxyethan-1-one (5e)**¹H-NMR (500 MHz, DMSO-d₆)**

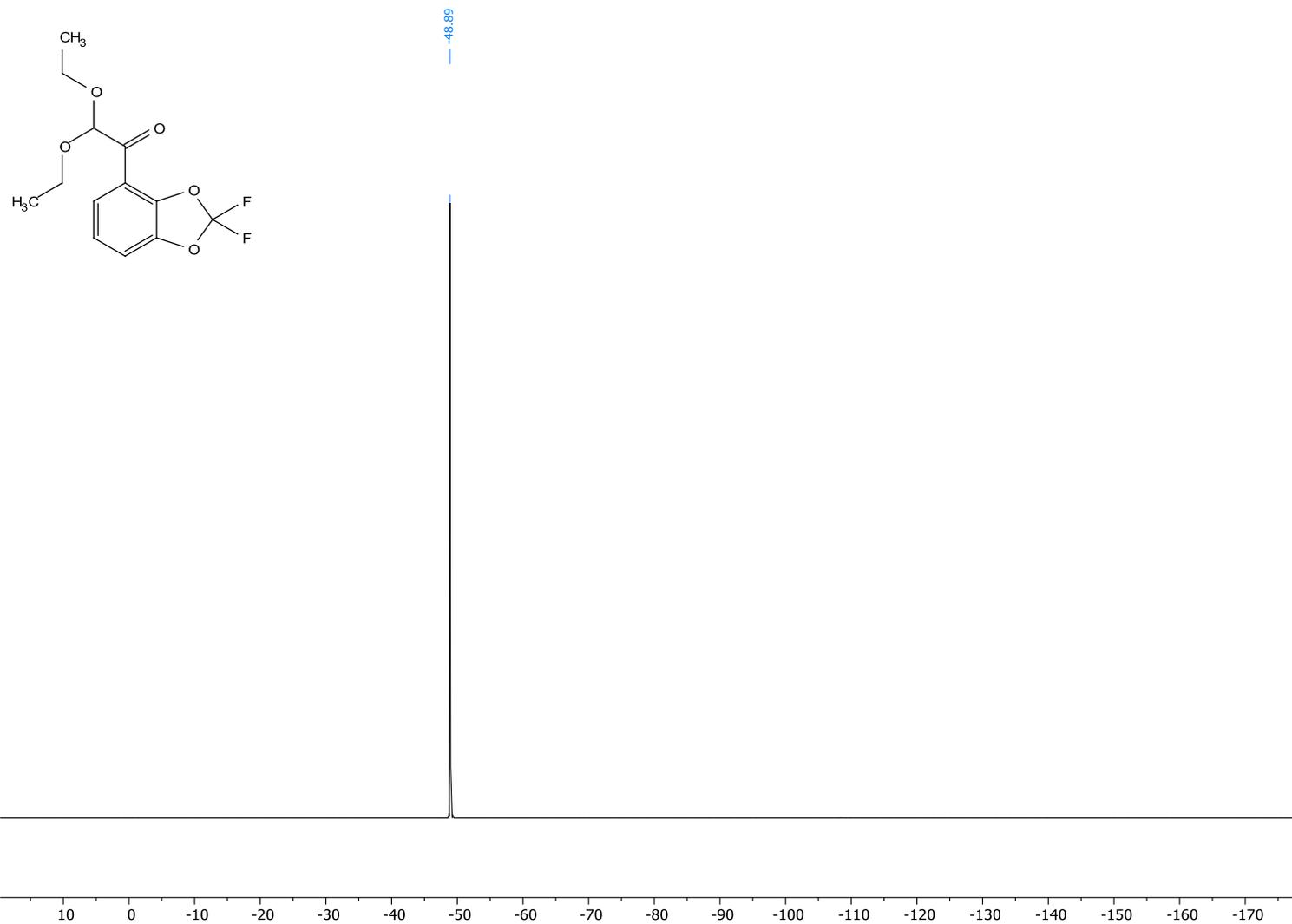
^{13}C -NMR (126 MHz, DMSO- d_6)

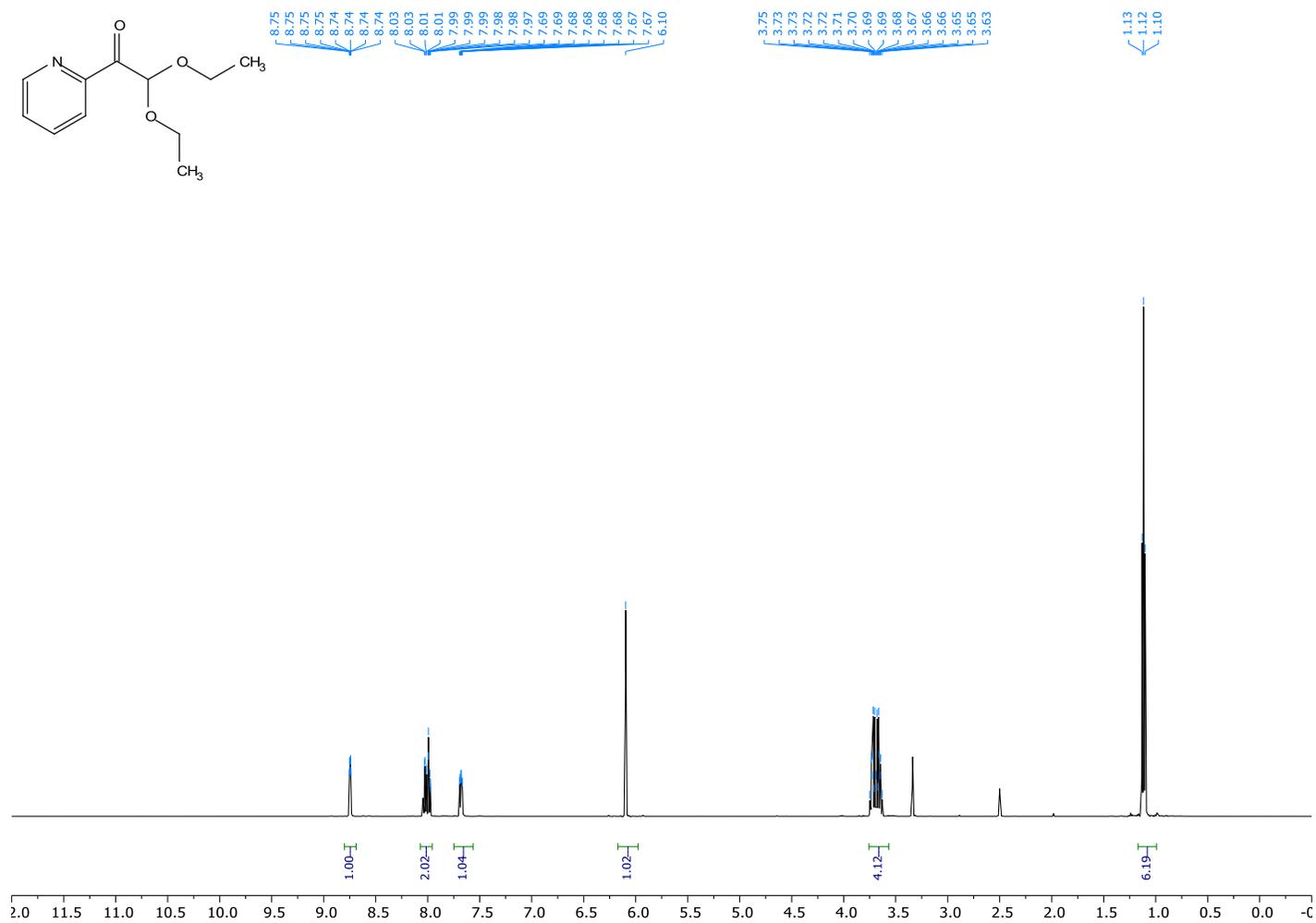
1-(4-chloro-2-methoxyphenyl)-2,2-diethoxyethan-1-one (5f)**¹H-NMR (500 MHz, DMSO-d₆)**

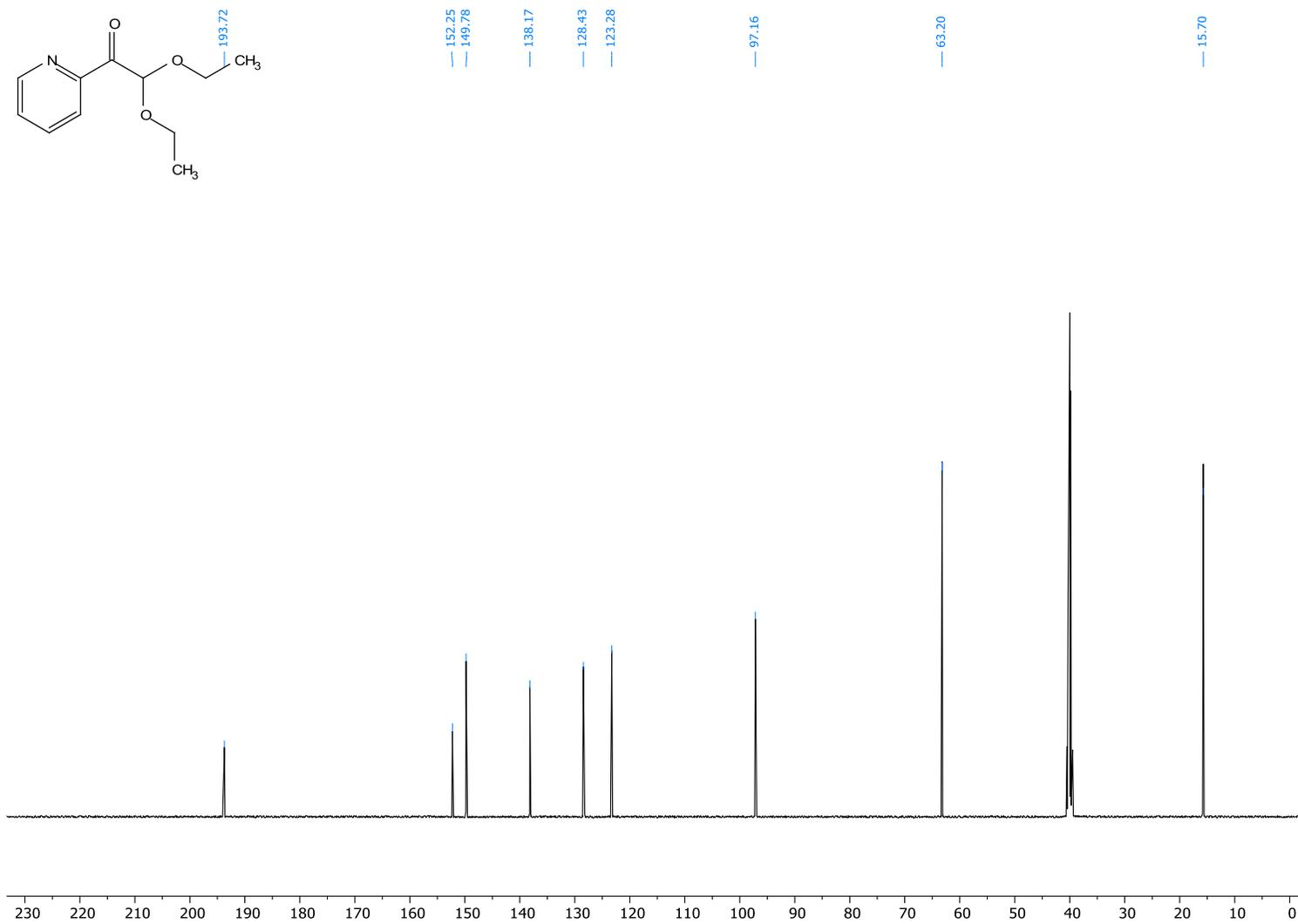
^{13}C -NMR (126 MHz, DMSO- d_6)

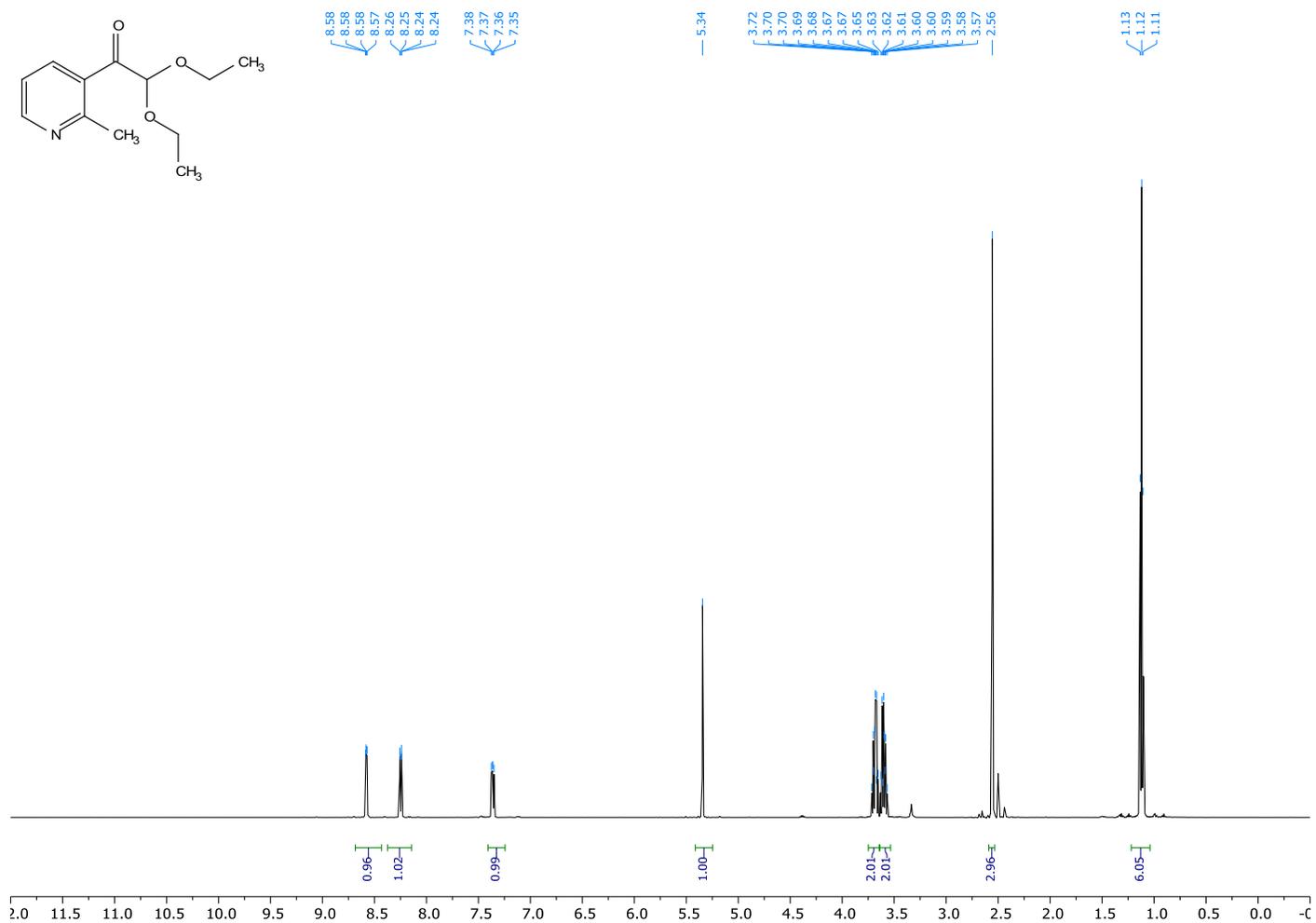
1-(2,2-difluorobenzo[d][1,3]dioxol-4-yl)-2,2-diethoxyethan-1-one (5g)**¹H-NMR (500 MHz, DMSO-d₆)**

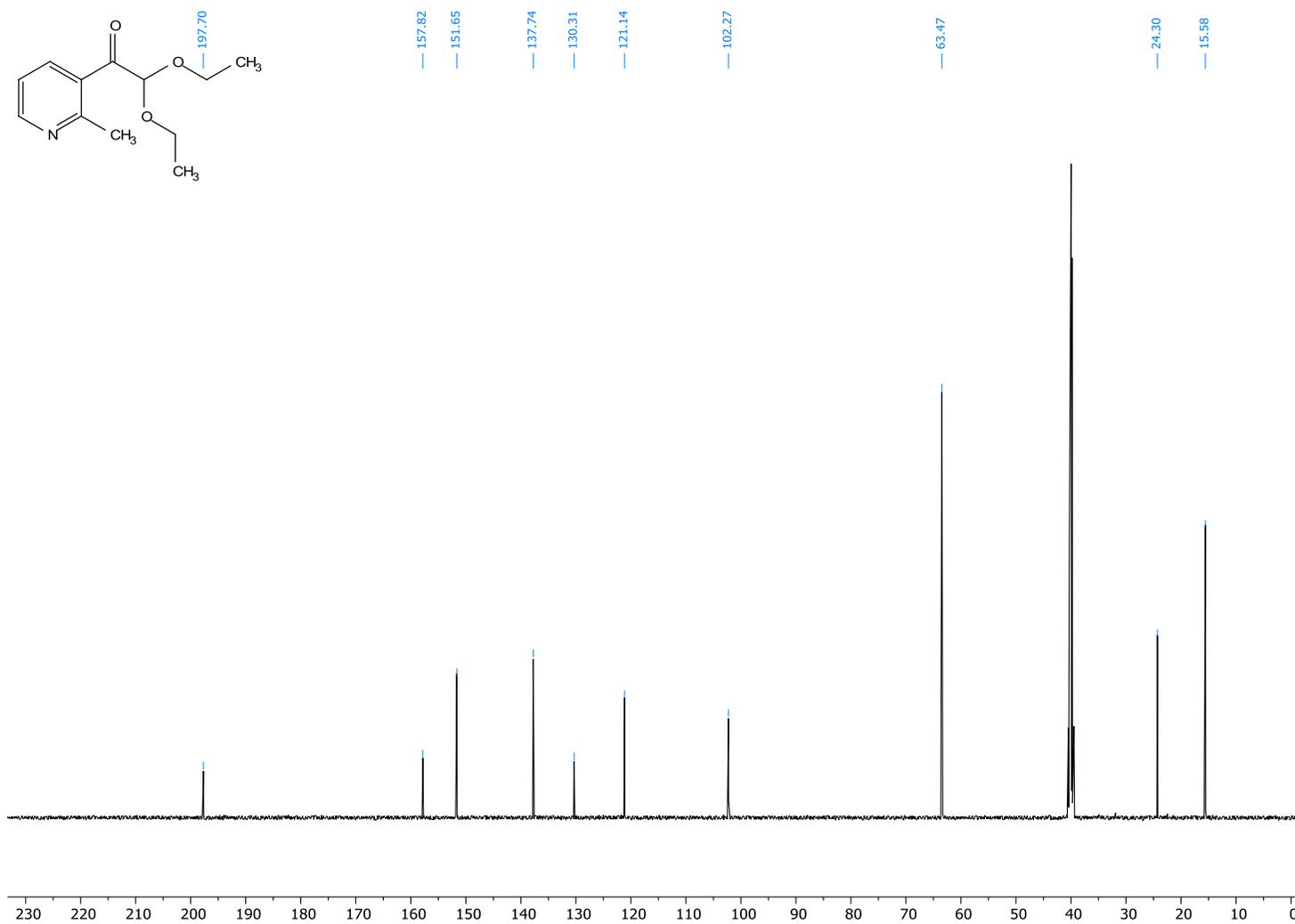
^{13}C -NMR (126 MHz, DMSO- d_6)

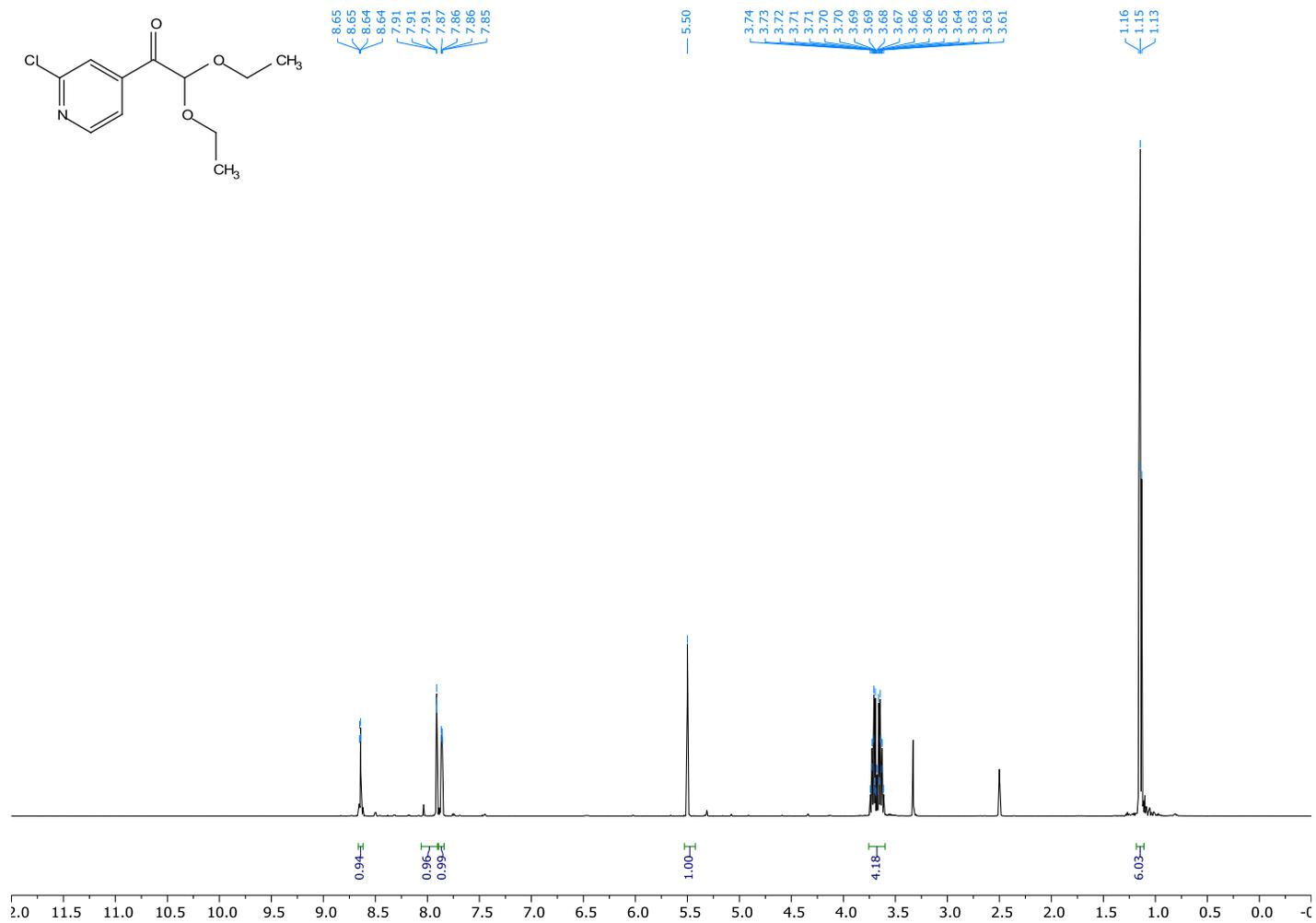
^{19}F -NMR (470 MHz, DMSO- d_6)

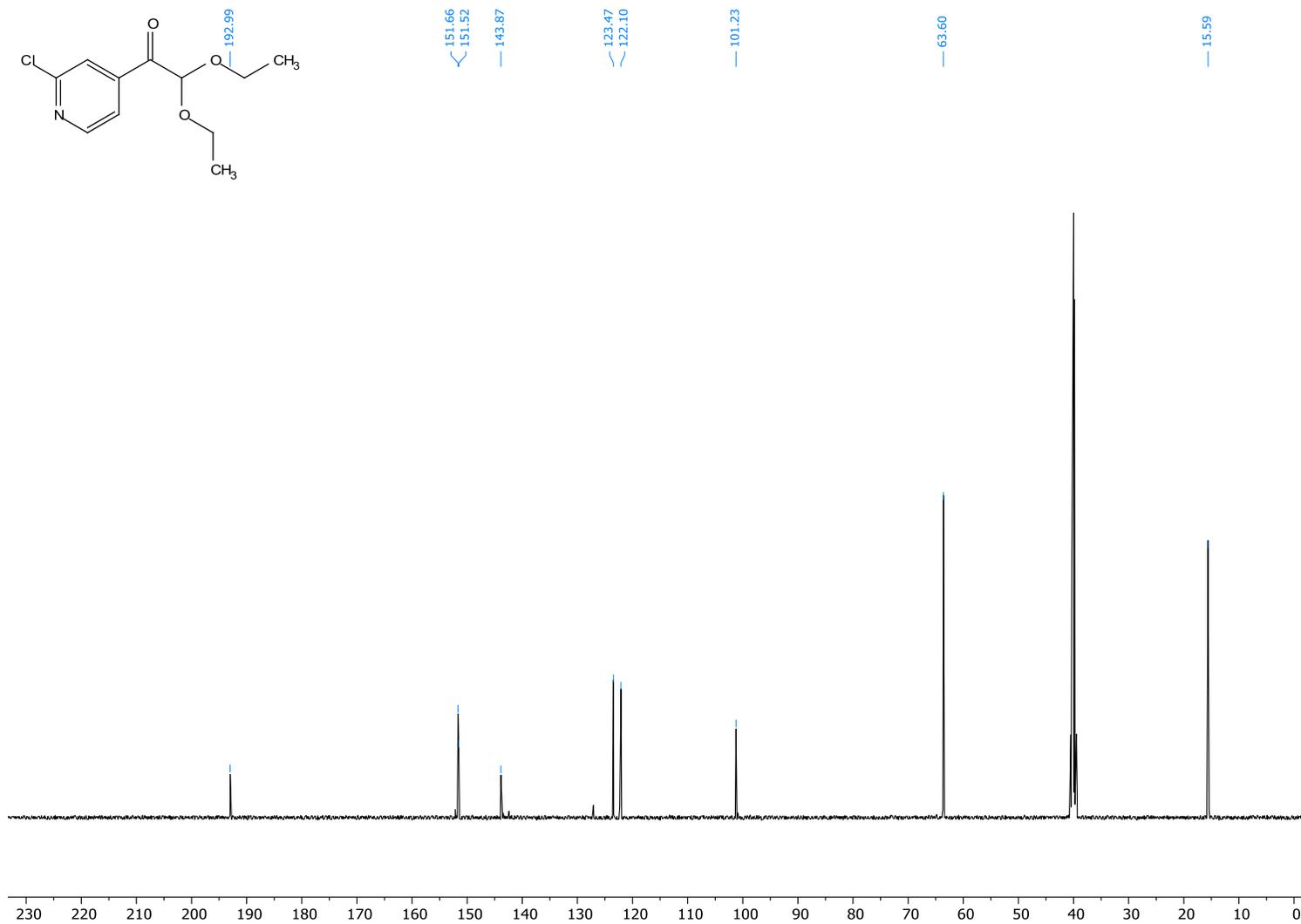
2,2-diethoxy-1-(pyridin-2-yl)ethan-1-one (5h)**¹H-NMR (500 MHz, DMSO-d₆)**

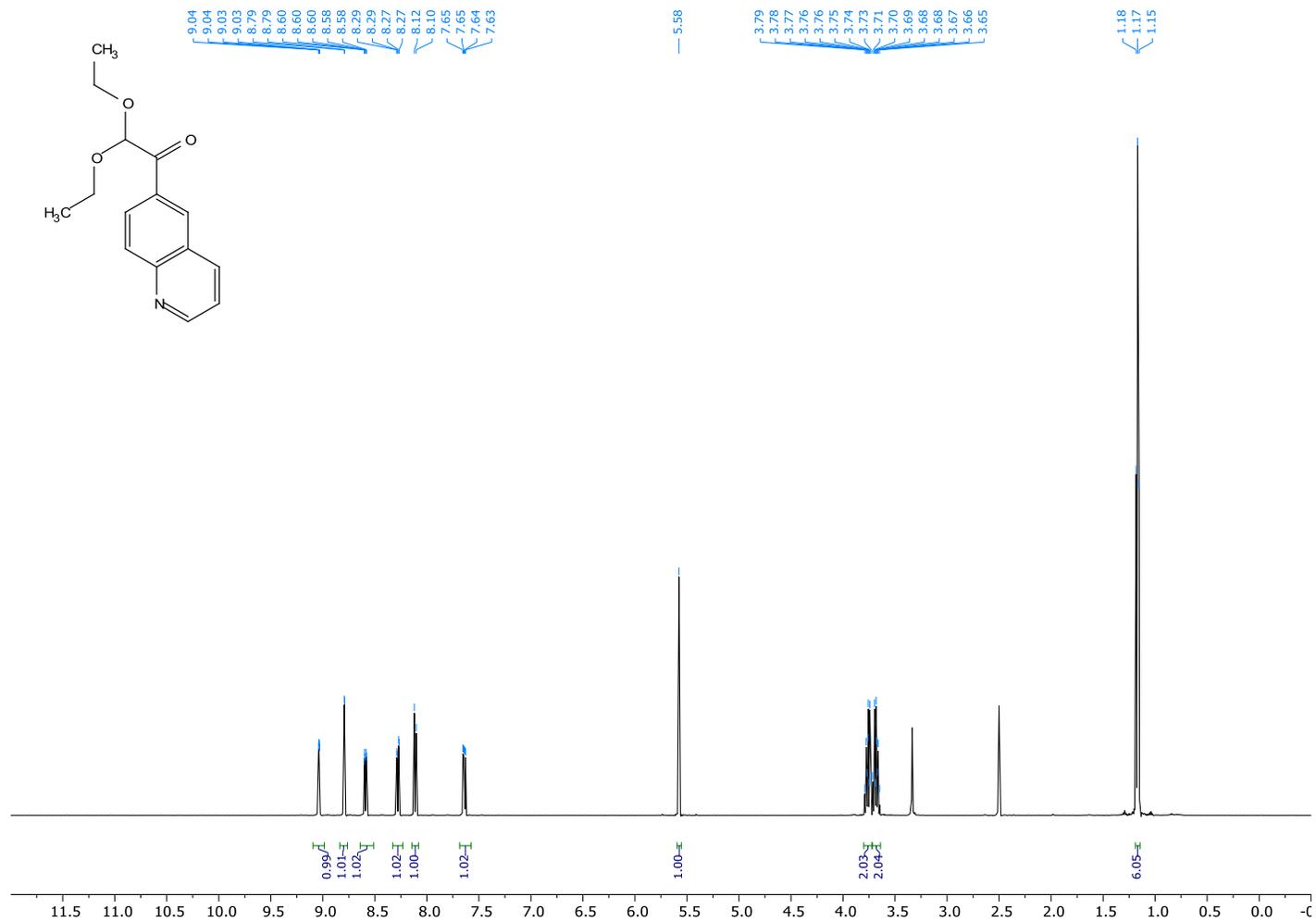
^{13}C -NMR (126 MHz, DMSO- d_6)

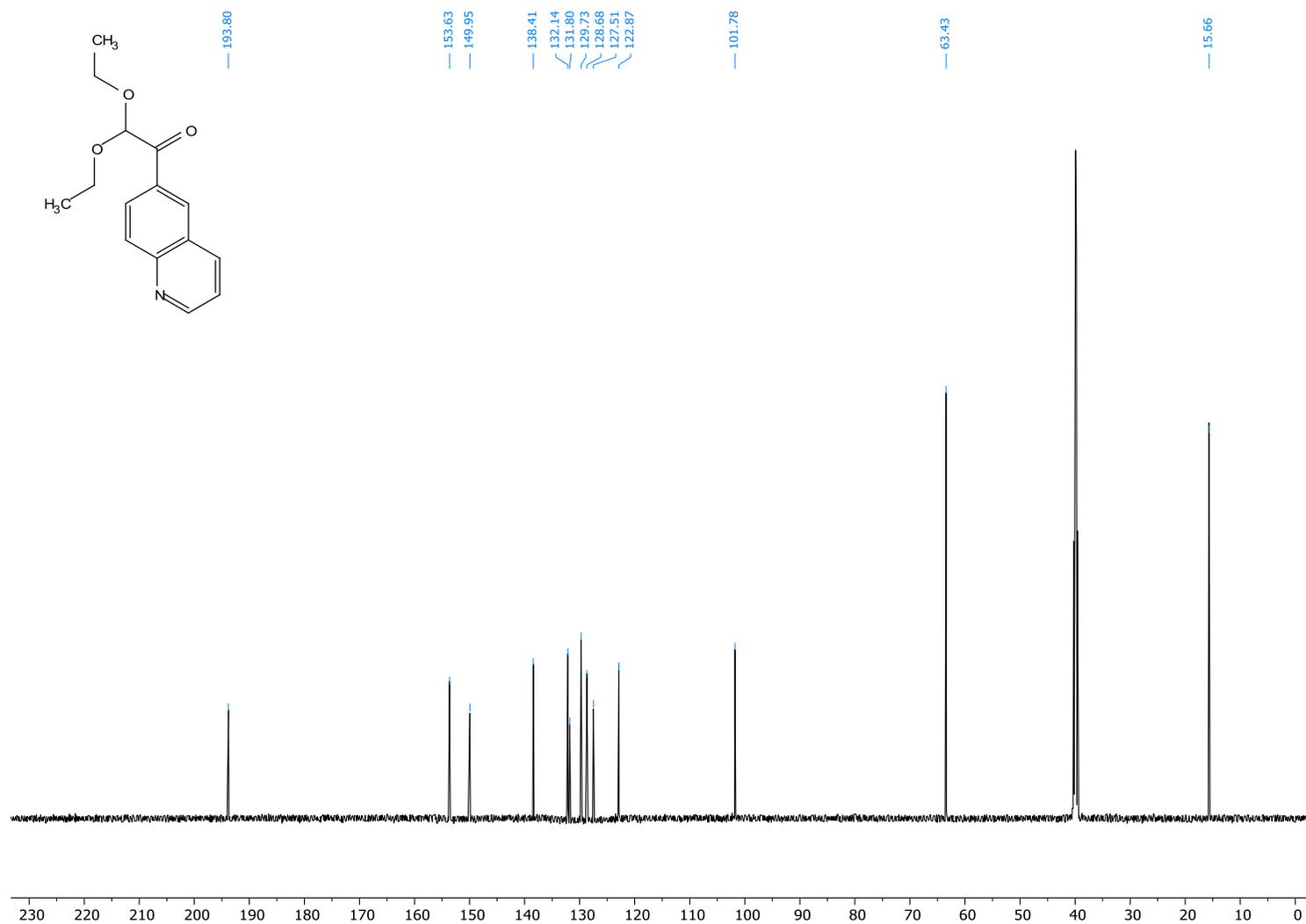
2,2-diethoxy-1-(2-methylpyridin-3-yl)ethan-1-one (5i)**¹H-NMR (500 MHz, DMSO-d₆)**

^{13}C -NMR (126 MHz, DMSO- d_6)

1-(2-chloropyridin-4-yl)-2,2-diethoxyethan-1-one (5j)**¹H-NMR (500 MHz, DMSO-d₆)**

^{13}C -NMR (126 MHz, DMSO- d_6)

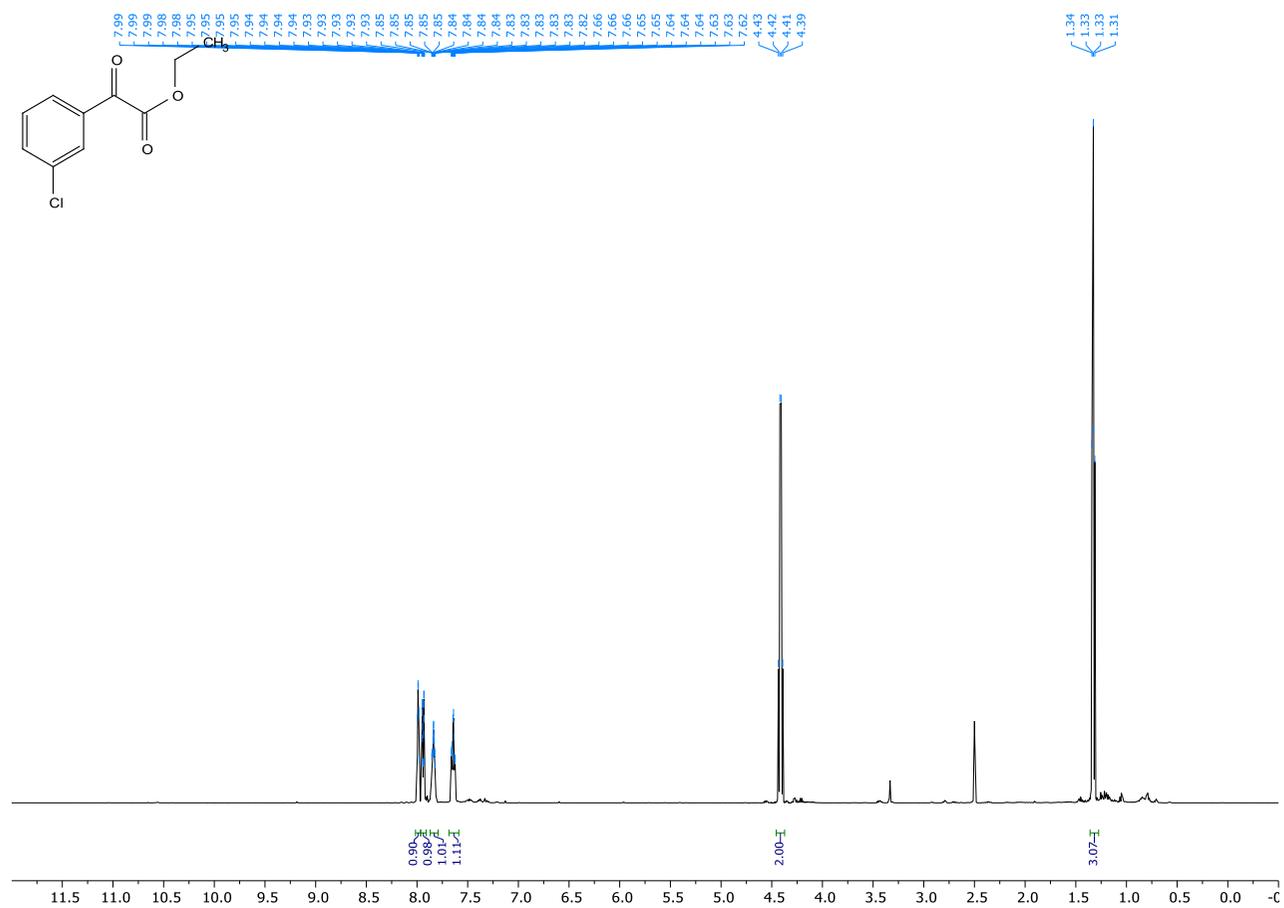
2,2-diethoxy-1-(quinolin-6-yl)ethan-1-one (5k)**¹H-NMR (500 MHz, DMSO-d₆)**

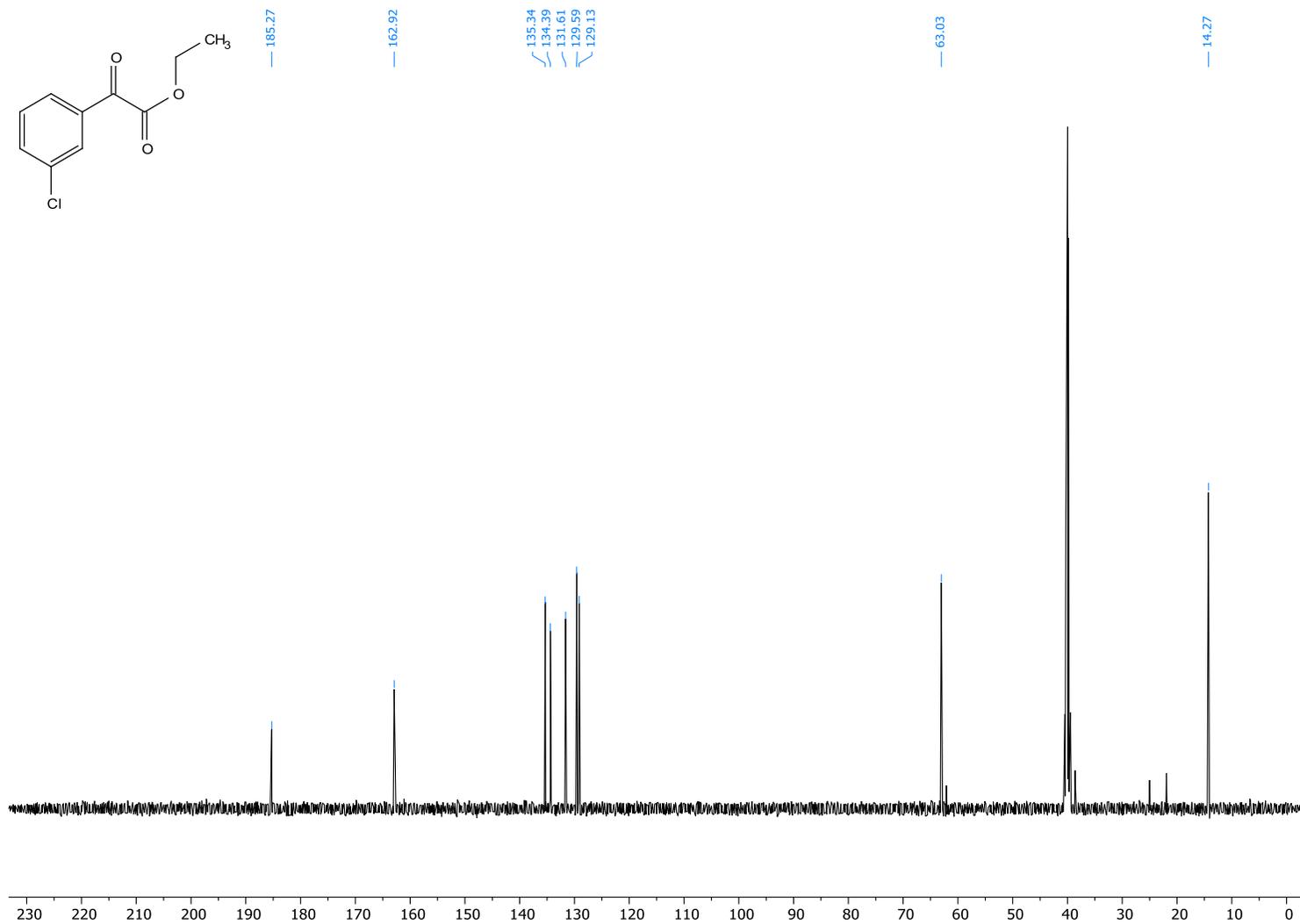
^{13}C -NMR (126 MHz, DMSO- d_6)

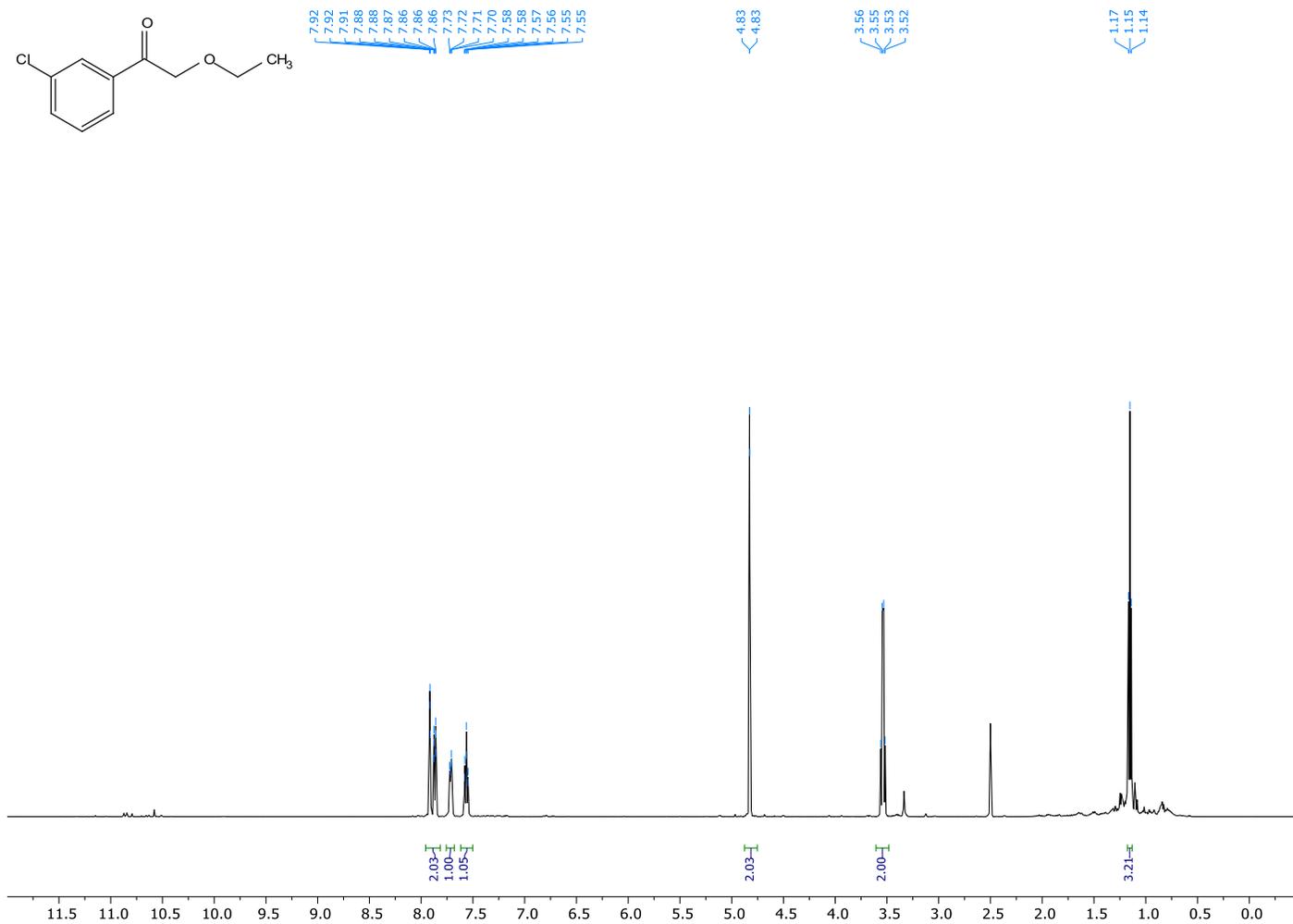
4.3 Approach B: extension of electrophile scope

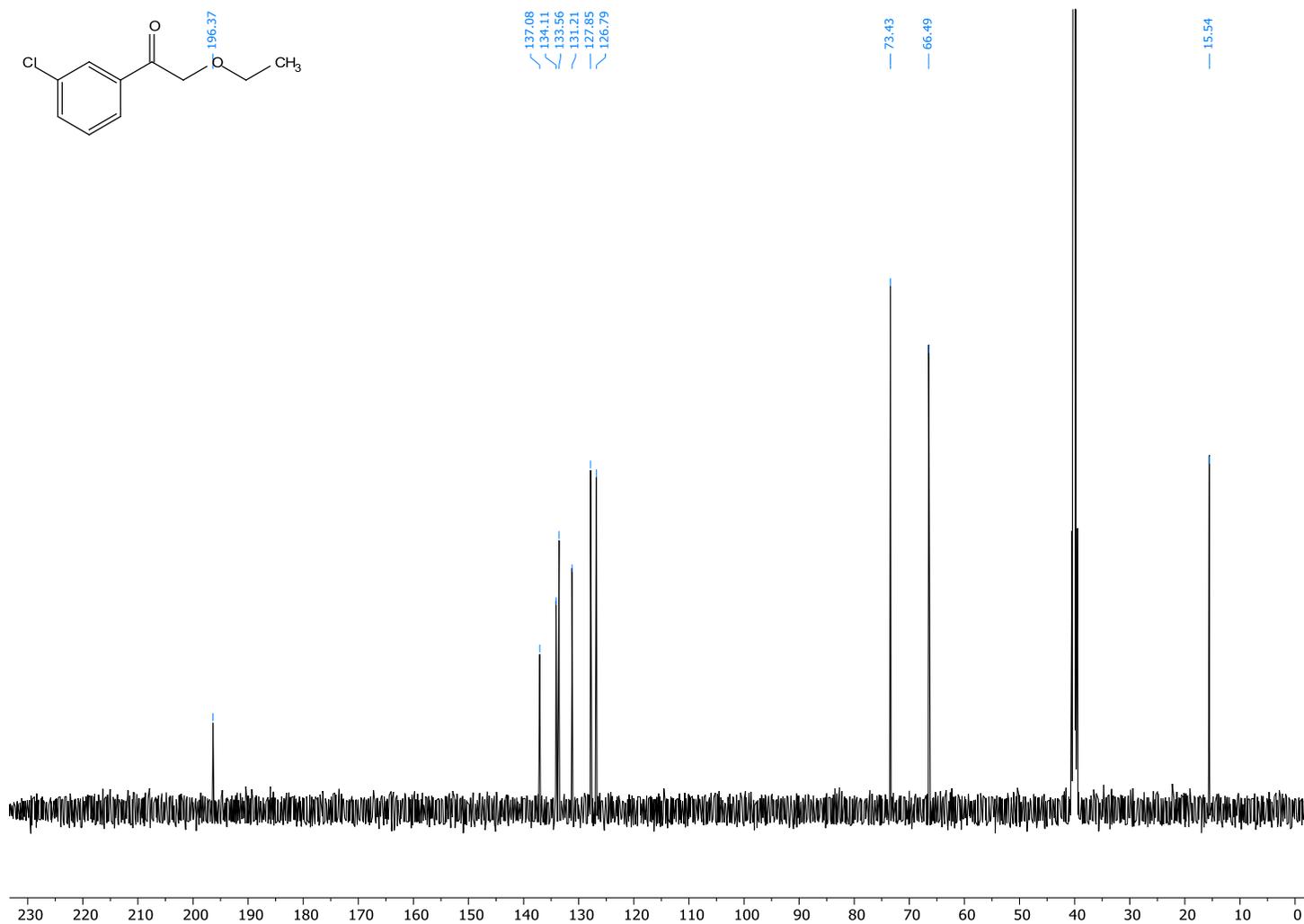
ethyl 2-(3-chlorophenyl)-2-oxoacetate (6a)

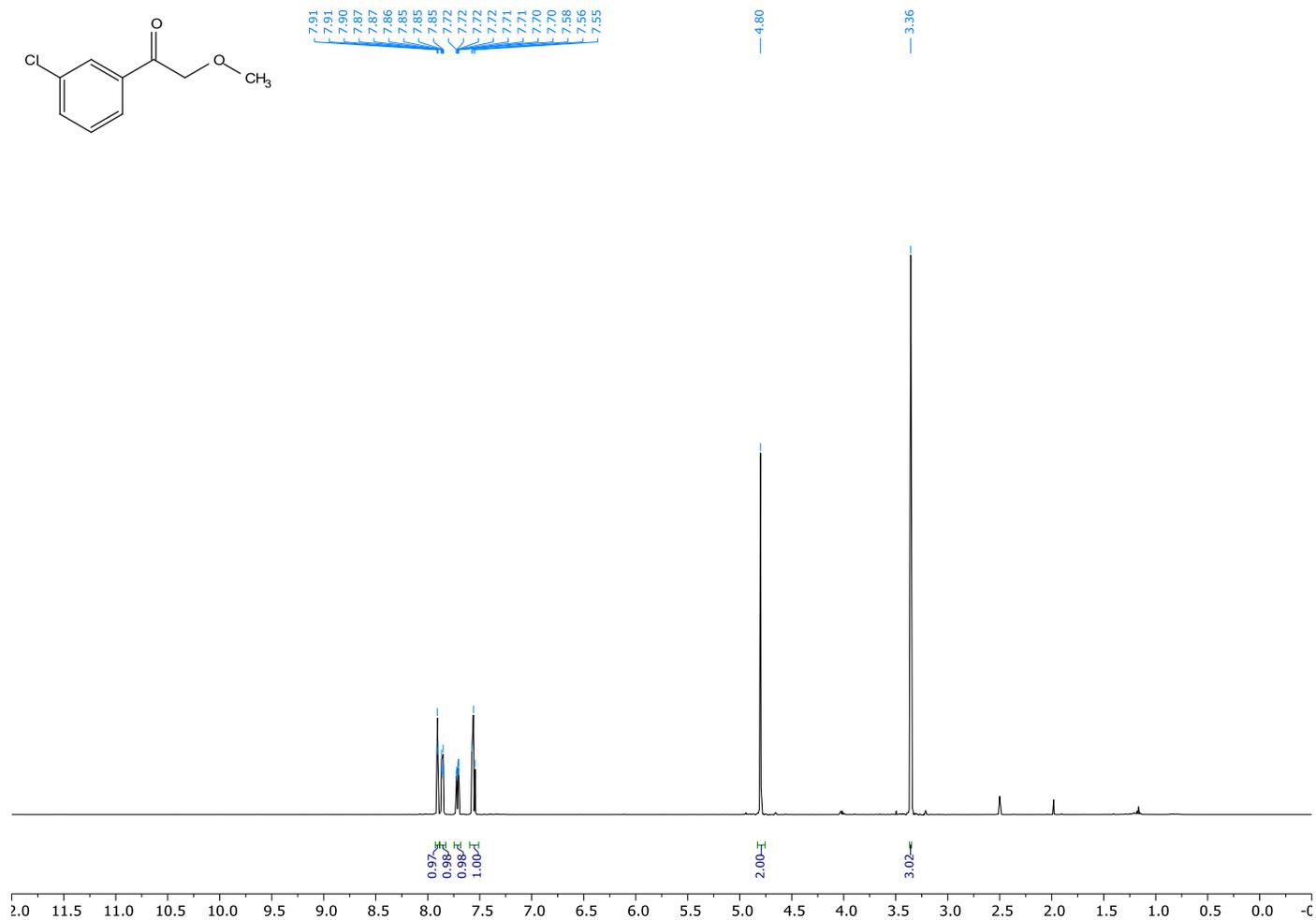
¹H-NMR (500 MHz, DMSO-d₆)

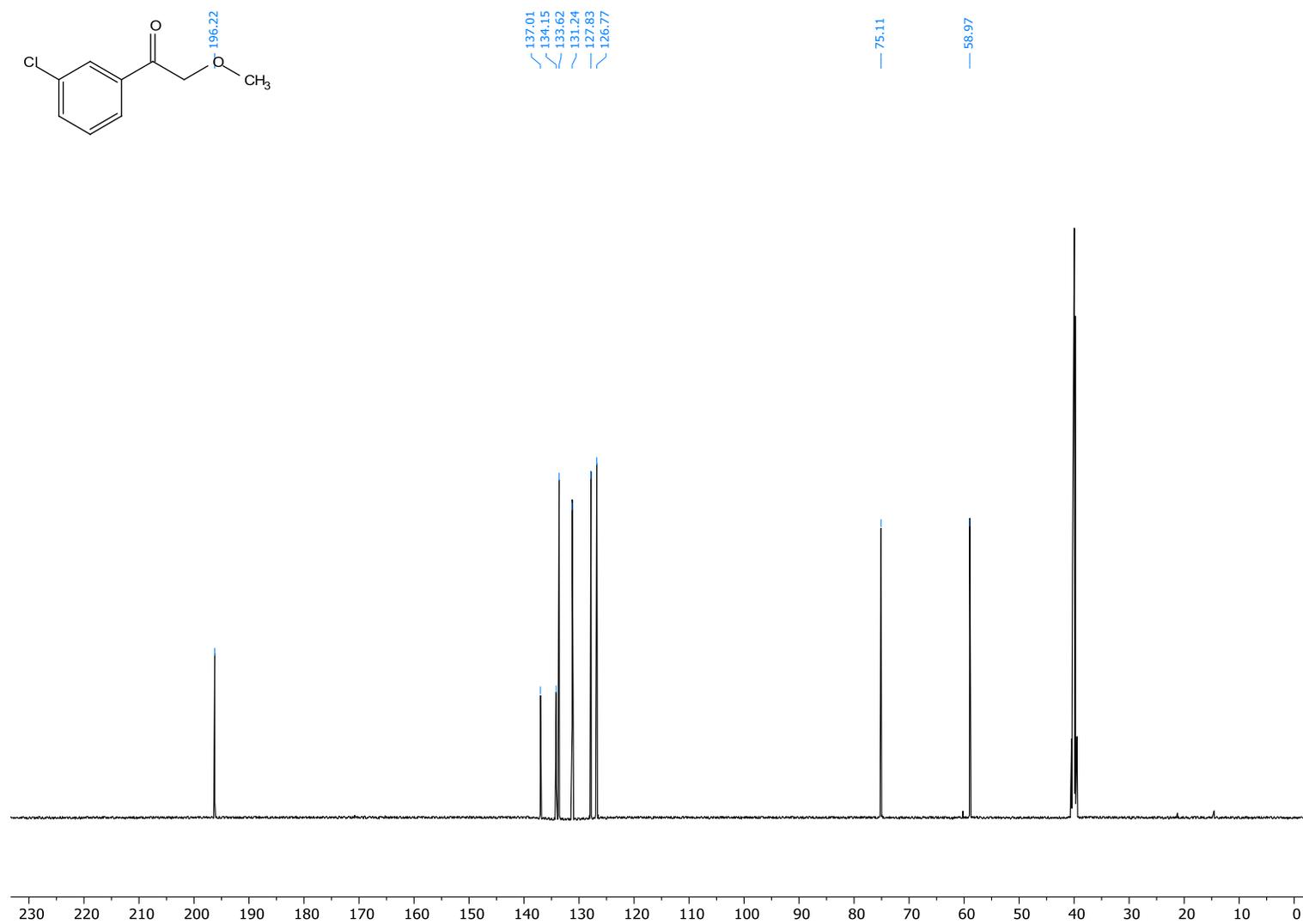
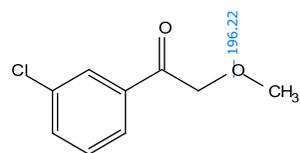


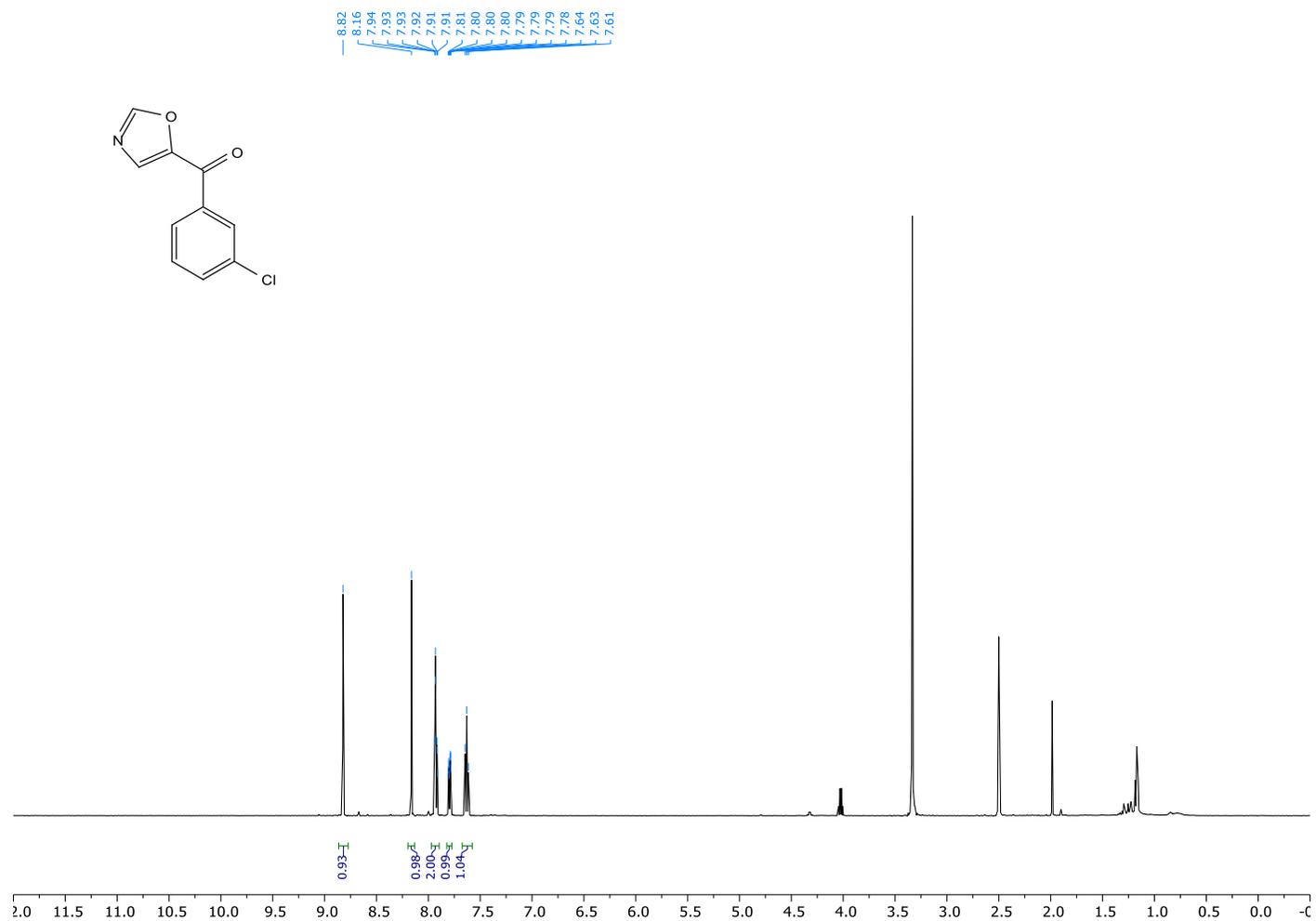
^{13}C -NMR (126 MHz, DMSO- d_6)

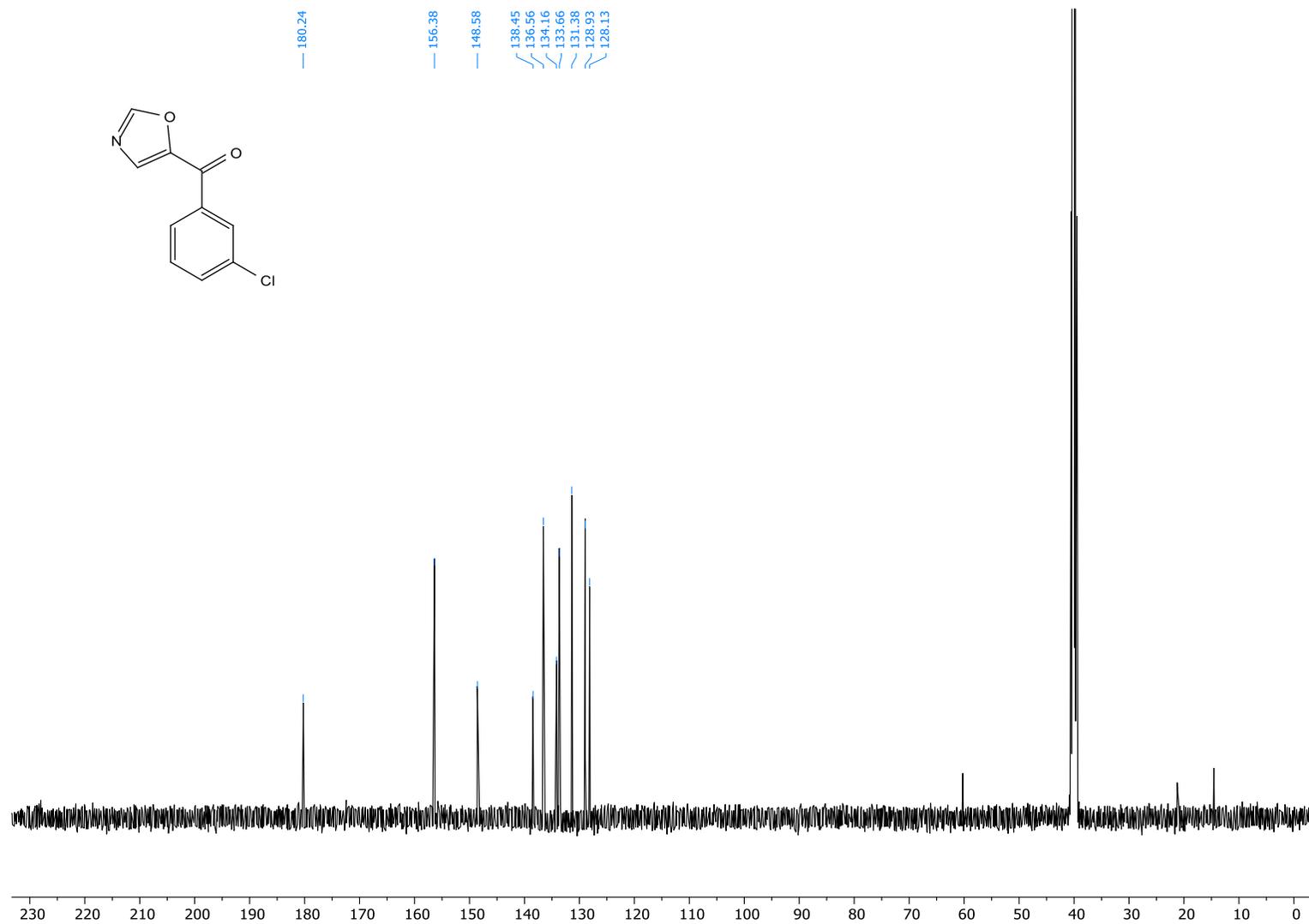
1-(3-chlorophenyl)-2-ethoxyethan-1-one (6b)**¹H-NMR (500 MHz, DMSO-d₆)**

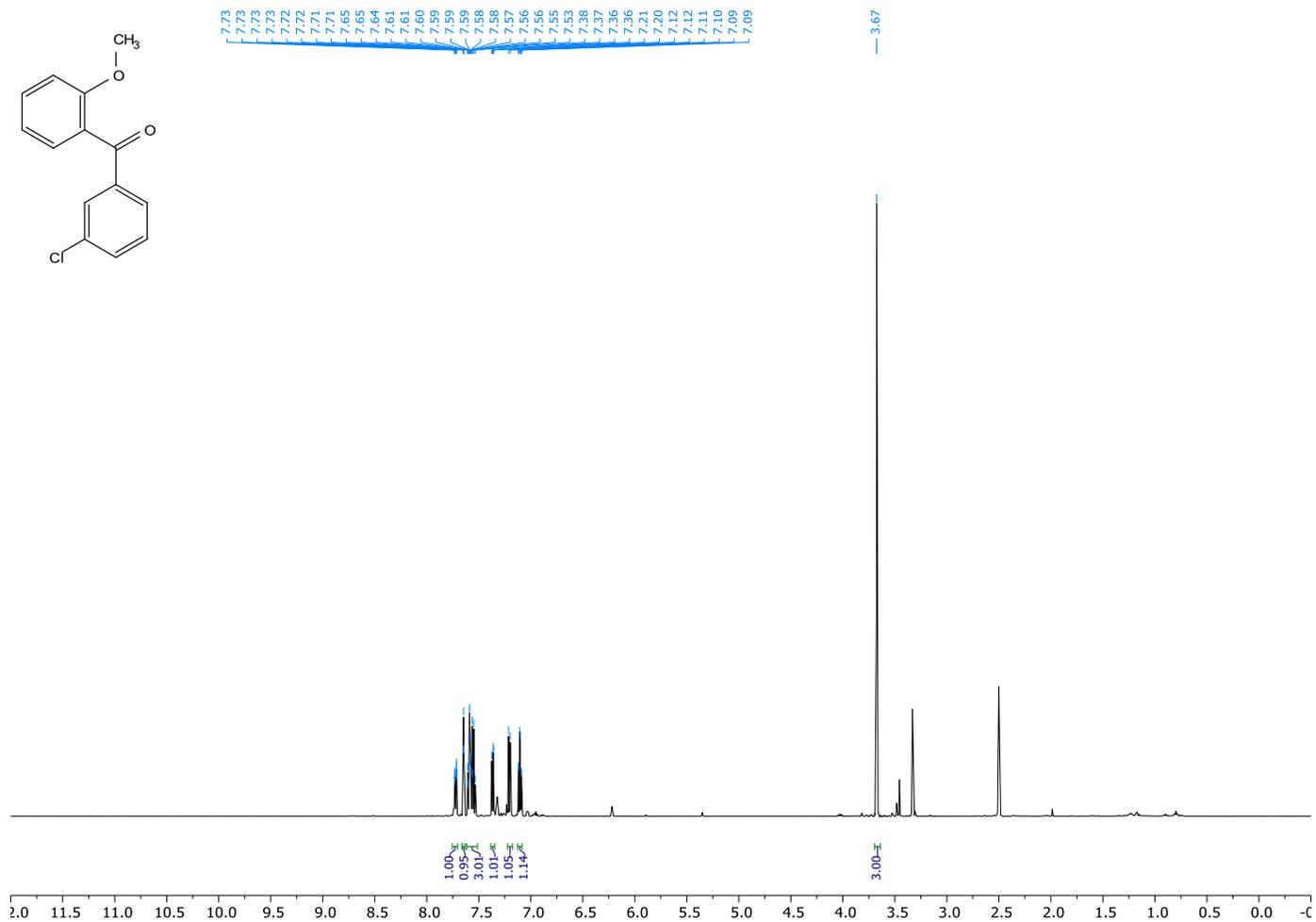
^{13}C -NMR (126 MHz, DMSO- d_6)

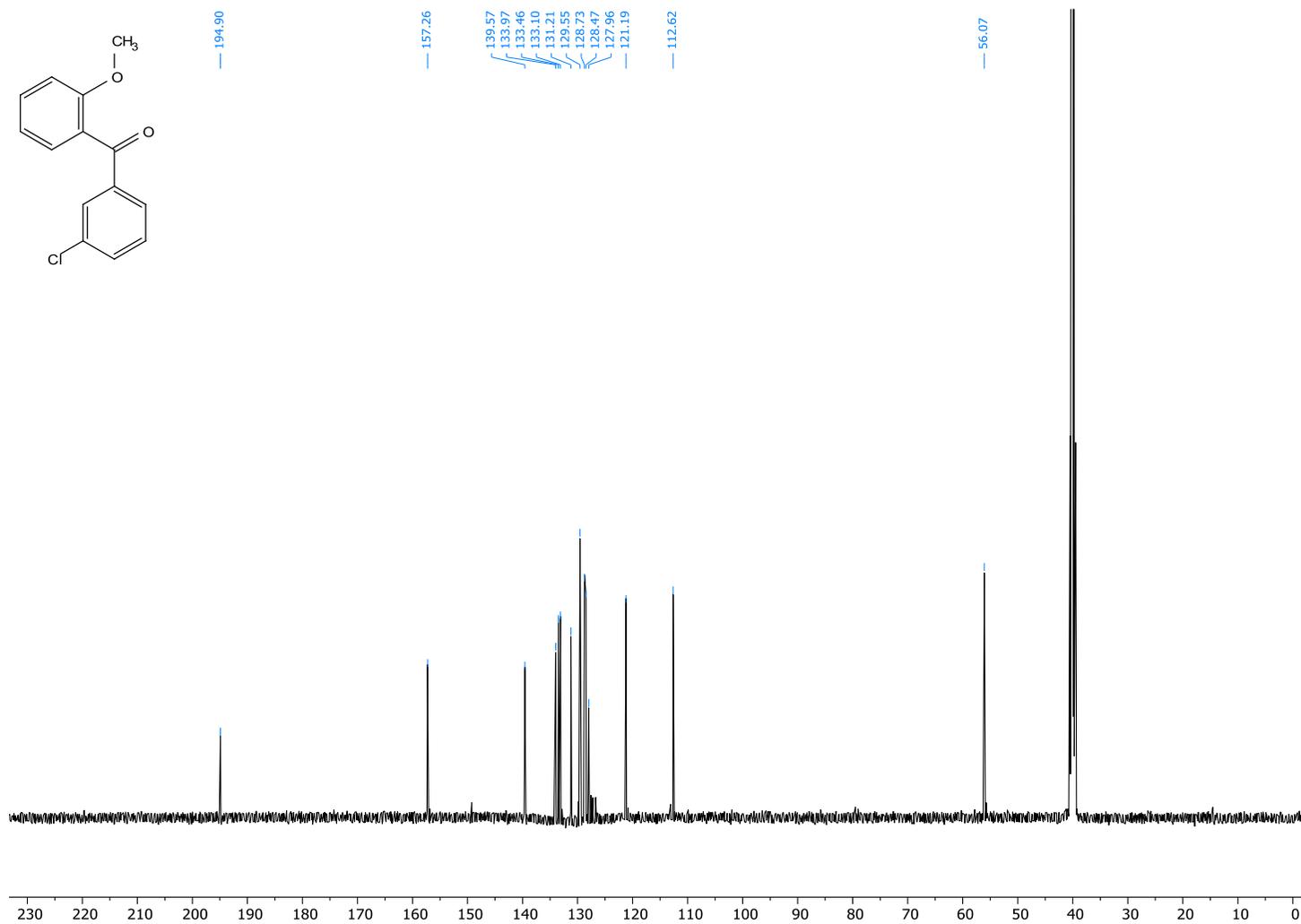
1-(3-chlorophenyl)-2-methoxyethan-1-one (6c)**¹H-NMR (500 MHz, DMSO-d₆)**

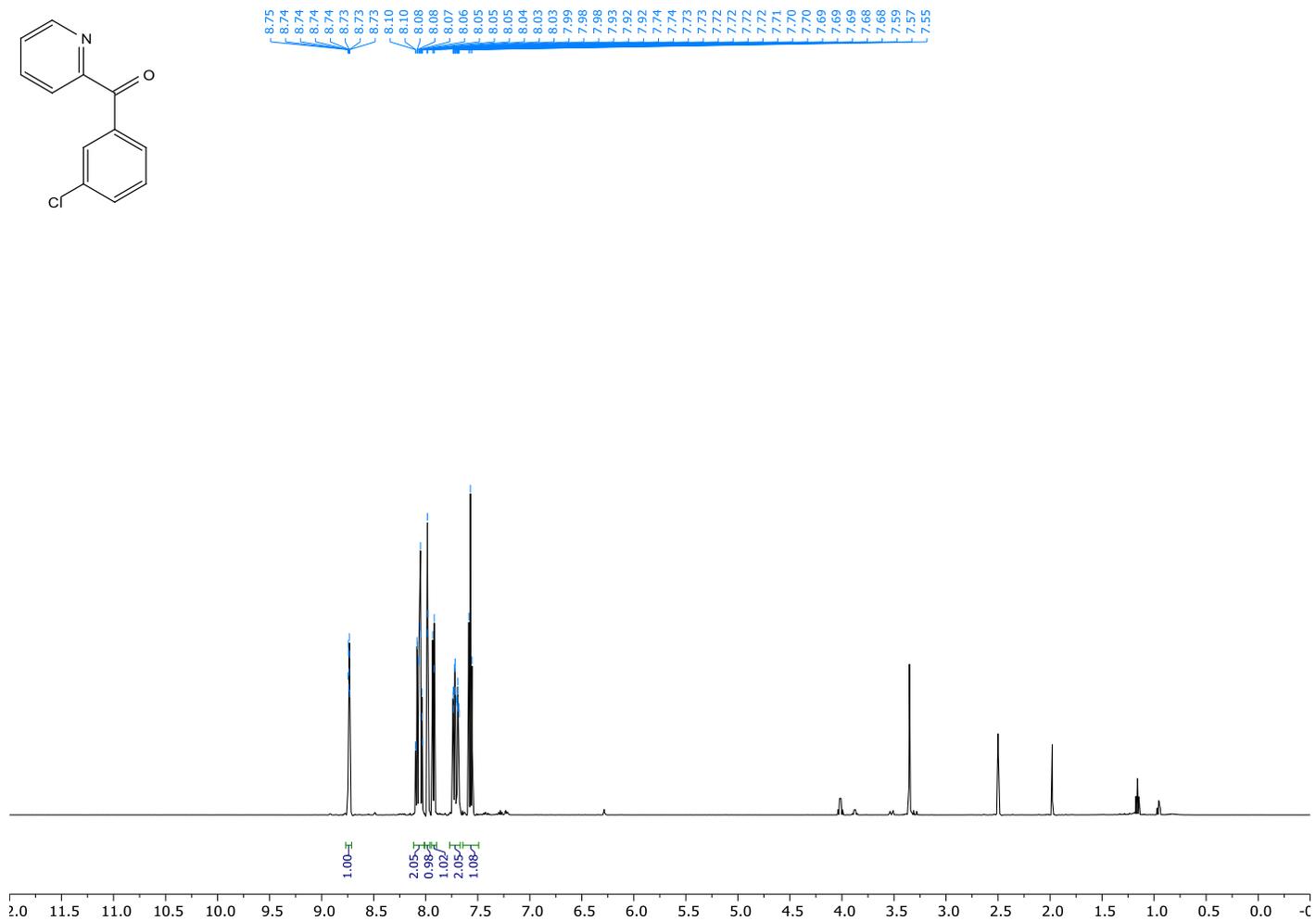
^{13}C -NMR (126 MHz, DMSO- d_6)

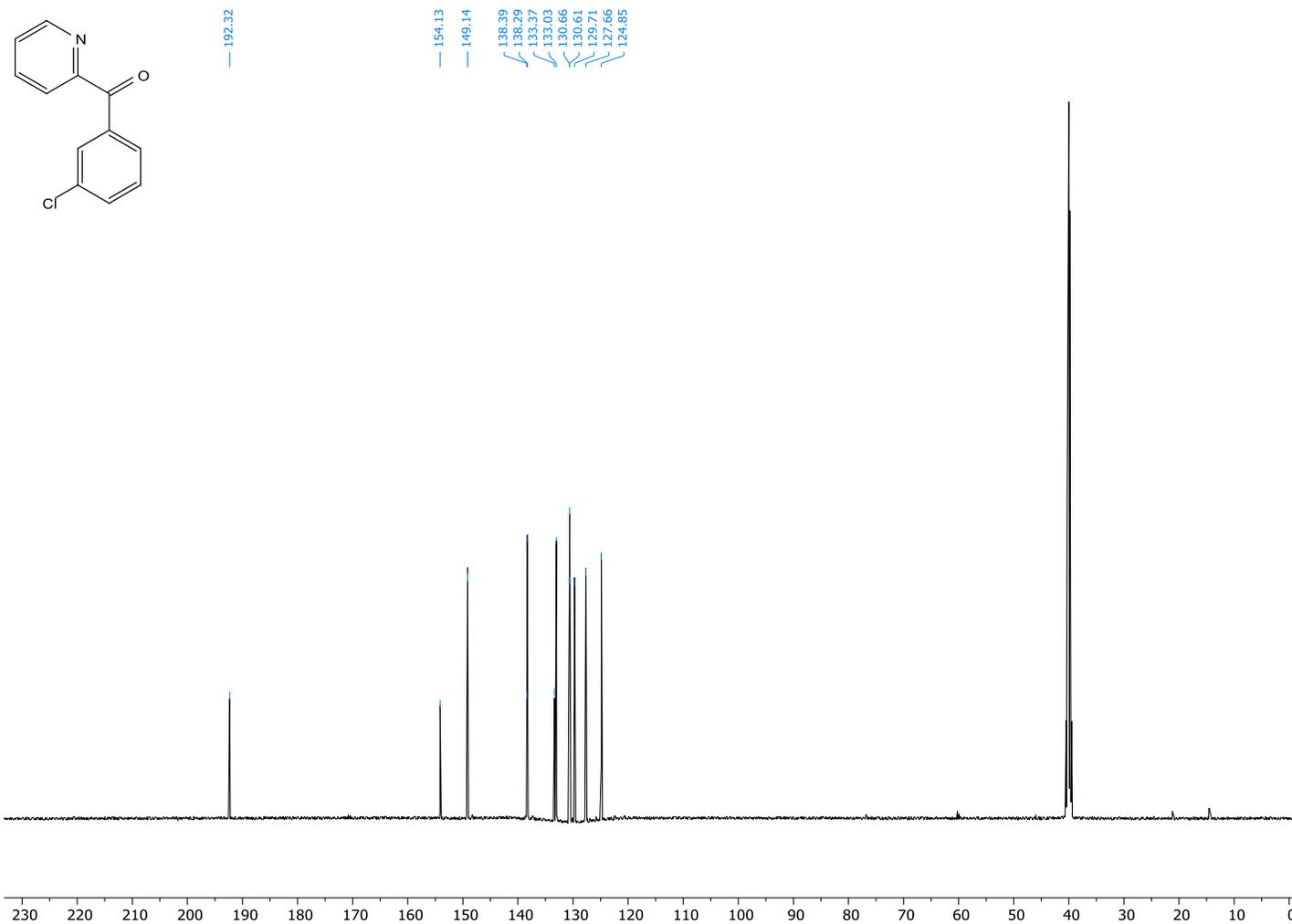
(3-chlorophenyl)(oxazol-5-yl)methanone (6d) **$^1\text{H-NMR}$ (500 MHz, DMSO-d_6)**

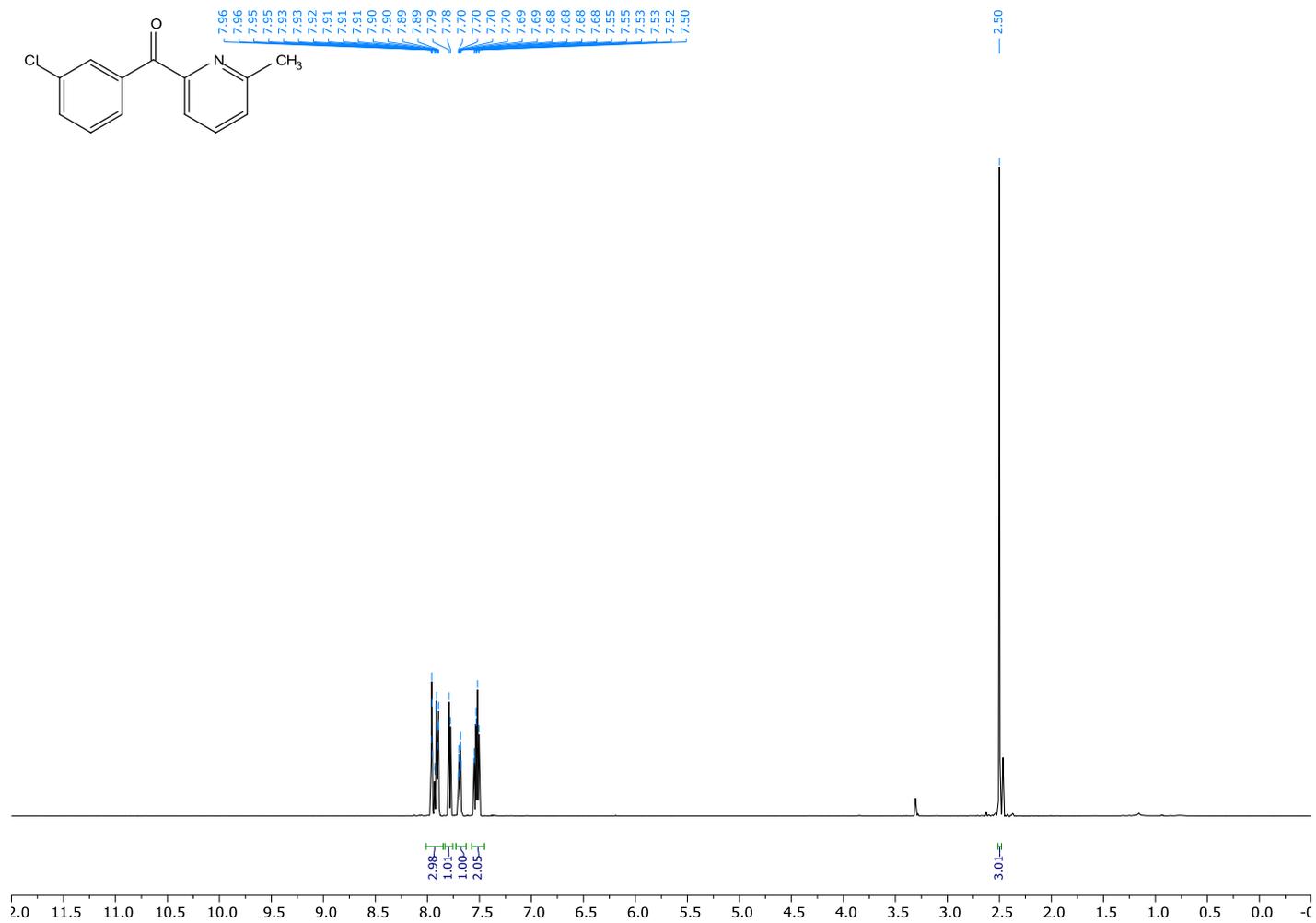
^{13}C -NMR (126 MHz, DMSO- d_6)

(3-chlorophenyl)(2-methoxyphenyl)methanone (6e)**¹H-NMR (500 MHz, DMSO-d₆)**

^{13}C -NMR (126 MHz, DMSO- d_6)

(3-chlorophenyl)(pyridin-2-yl)methanone (6f)**¹H-NMR (500 MHz, DMSO-d₆)**

^{13}C -NMR (126 MHz, DMSO- d_6)

(3-chlorophenyl)(6-methylpyridin-2-yl)methanone (6g)**¹H-NMR (500 MHz, DMSO-d₆)**

^{13}C -NMR (126 MHz, DMSO- d_6)