Supplementary Information

Emerging Platform from Renewable Resources: Selection Guidelines for Human Exposure of Furfural-related Compounds

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Procedures

General Remarks

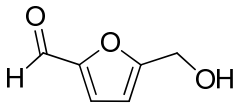
All solvents were freshly distilled from commercial grade sources. Commercially available reagents were used as received without further purification otherwise notice. Preparative thin-layer chromatography plate was prepared with silica gel 60 GF_{254} MercK (ref 1.07730.1000), whereas flash chromatography was carried out on silica gel 60M purchased from MN (Ref. 815381). Reaction mixtures were analyzed by TLC using ALUGRAM SIL G/UV254 from MN (Ref. 818133, silica gel 60), and visualization by UV and phosphomolybdic acid stain.

HPLC analysis was performed on Dionex P680 pump, Dionex UVD 340S diode array detector, detection at 275 and 225 nm, manual injector with 20 μL loop, column HICHROM C18, 250x4.6mm, or Kromasil 100, C18, 250x4.6mm. Mobile phase gradient from 1:99 to 50:50 for 40 min acetonitrile:water, and then 50:50 for the time indicated in the chromatogram, flow 1 mL/min, The HPLC purity was determined by comparing the integration area of the main signal with other observed minor peaks and are represented in the chromatograms by relative area. Retention times were determined by using the mobile phase gradient from 1:99 to 90:10 in 50 min.

GC–MS analyses were performed on Gas Chromatograph Mass Spectrometer-QP2010S, *Shimadzu* by using the column TRB-5MS-Teknokroma (30 m × 0.25 mm × 0.25 μm). GC program: column oven $T_{initial}$=: 50.0 °C, T_{final}=: 250.0 °C, slope = 5ºC/min ; injection temperature: 250 °C; pressure: 77.9 kPa, total flow: 17.7 mL/min; column flow: 1.34 mL/min; linear velocity: 42.0 cm/sec; purge flow: 3.0 mL/min split ratio: 10.0, high press. inj. pressure: 100.0 kPa, high press. inj. time: 1.00 min. MS program: start time: 3.00 min; end time: 50.00 min; event time: 0.50 s; scan speed: 666; start: m/z = 40.00; end: m/z = 350.00.

NMR spectra were recorded at room temperature in a Bruker AMX 300 or Bruker AMX 400 using $CDCl_3$, D_2O or DMSO-d_6 as solvents and $(CH_3)_4Si(^1H)$ as internal standard.

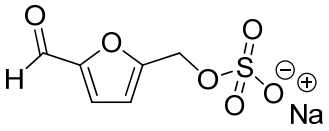
5-(Hydroxymethyl)furfural, HMF (1)[1]



To a round-bottom flask D-fructose (6 g, 33.3 mmol) and DMSO (200 mL) were added followed by the addition of Amberlyst-15-powder (0.4 g, 15% w/w). The reaction was allowed to stir for 120 minutes at 120 ºC under inert atmosphere. After reaction the DMSO was removed by distillation and the crude reaction mixture was purified by column chromatography with silica gel (hexane/ethyl acetate 1:1) to yield the product (2.9 g, 70% yield) as a pale yellow oil that crystalizes in the freezer (0ºC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 1H), 4.71 (s, 2H), 6.51 (d, J = 3.5 Hz, 1H), 7.21 (d, J = 3.5 Hz, 1H), 9.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.7, 110.1, 123.1, 152.4, 160.8, 177.9.

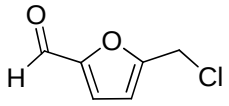
As alternative, HMF was synthetized using the recently reported protocol from our group, using tetraethylammonium bromide and Amberlyst-15.[2]

Sodium (5-formylfuran-2-yl)methyl sulfate (2)[3]



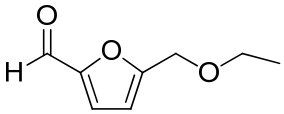
To a solution of *N,N'*-Dicyclohexylcarbodiimide (1.0 g, 5 mmol) in DMF (3 mL) at 0 ºC, HMF (128 mg, 1 mmol) dissolved in DMF (0.5 mL) was added with vigorous stirring. A cold solution of sulfuric acid (2 mmol) in DMF (1 mL) was added. The mixture was allowed to stir at 0 ºC for 1h. The mixture was then centrifuged and the solution neutralized with methanolic NaOH 1M. The resulting solution was once again centrifuged. The precipitate was washed with DMF and centrifuged. The collected organic phases were concentrated under vacuum and the crude dissolved in ethanol and centrifuged. To the solution 10 volumes of Et_2O was slowly added and the precipitate centrifuged. The precipitate was then washed with Et_2O to give the product as a pale orange solid (55 mg, 24% yield); mp 128 ºC.

5-(Chloromethyl)furan-2-carbaldehyde (3)[4]



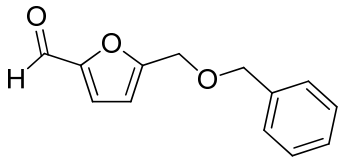
To a flame dried round bottom flask, HMF (1 g, 7.9 mmol) and $CHCl_3$ were added. Trimethylsilyl chloride (6 mL, 47.3 mmol, 6 equiv.) was added dropwise at 45 ºC and the resulting mixture stirred for 24 h at 45ºC under inert atmosphere. The mixture was then quenched with saturated aqueous solution of $NaHCO_3$ and extracted with DCM. The collected organic layers were dried over Na_2SO_4 and the solvent removed. The crude product was purified by dissolution in hot hexane and filtration through a pad of celite and activated carbon. The hexane was removed under vacuum to give the desired product (0.7 g, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.59 (s, 2H), 6.57 (d, J = 3.57 Hz, 1H), 7.19 (d, J = 3.57 Hz, 1H), 9.60 (s, 1H).

5-(Ethoxymethyl)furan-2-carbaldehyde (4)[5]



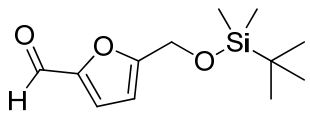
HMF (1.0 g, 8.0 mmol) was dissolved in absolute EtOH (15 mL) then 3 drops of concentrated H_2SO_4 were added and mixture was stirred for 5 h at reflux temperature. The reaction mixture was neutralized with aqueous saturated solution of $NaHCO_3$ and extracted with EtOAc. The organic phase was dried with $MgSO_4$ and evaporated. The product was purified by silica flash chromatography using EtOAc/Hexane to give 703 mg (57% yield) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3H), 3.55 (q, J = 7 Hz, 2H), 4.49 (s, 2H), 6.49 (d, J = 3.52 Hz, 1H), 7.18 (d, J = 3.52 Hz, 1H), 9.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 64.8, 66.7, 111.1, 152.6, 158.8, 177.9.

5-((Benzyloxy)methyl)furan-2-carbaldehyde (5)[6]



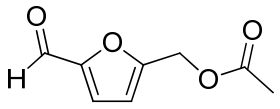
Benzyl bromide (3.8 g, 22.2 mmol) and silver oxide (2.6 g, 11.1 mmol) were successively added to a stirred solution of HMF (1.4 g, 11.1 mmol) dissolved in DMF (15 mL). The mixture was stirred for 50 h at RT. The solution was evaporated under reduced pressure and the residue was chromatographed (silica; hexane-EtOAc, 1:1) to give the desired product (1.2 g, 50 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 3H), 1.27-1.31 (m, 4H), 1.63 (quint, J = 7.4 Hz, 2H), 2.35 (t, J = 7.6, 2H), 5.12 (s, 2H), 6.58 (d, J = 3.55 Hz, 1H), 7.21 (d, J = 3.55 Hz, 1H), 9.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.2, 73.0, 111.4, 122.0, 128.0, 128.1, 128.6, 137.3, 152.7, 158.5, 177.8.

5-(((tert-Butyldimethylsilyl)oxy)methyl)furan-2-carbaldehyde (6)[7]



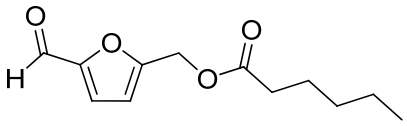
To a solution of HMF (1.6 g, 12.7 mmol) in DMF (3.2 mL) were added imidazole (2.2 g, 31.7 mmol, 2.5 equiv.) and *tert*-butyldimethylsilyl chloride (2.3 g, 15.2 mmol, 1.2 equiv.). The solution was stirred for 22 h. The silylated compound was extracted with hexane (5 x 20 mL). The collected organic layers were washed with brine, dried over Na_2SO_4, and the solvent removed to give the crude product that was distillated (100ºC/0.8 mbar) giving the product (1.9 g, 63 % yield) as a light yellow liquid that solidifies in the freezer (0ºC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.89 (s, 9H), 4.71 (s, 2H), 6.45 (d, J = 3.53 Hz, 1H), 7.19 (d, J = 3.53 Hz, 1H), 9.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 18.4, 25.8, 58.7, 109.5, 122.6, 152.3, 161.5, 175.6.

(5-Formylfuran-2-yl)methyl acetate (7)[6]



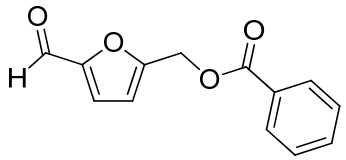
To a flame dried round-bottom flask, HMF (3.5 g, 27.8 mmol), MeCN (50 mL) and acetic anhydride (4.3 mL, 45.6 mmol) were added followed by catalytic amount of pyridine (0.5 mL, 6.2 mmol). The reaction mixture was allowed to stir at room temperature for 22h under argon atmosphere. The solvent was removed and the product purified by column chromatography with silica gel (hexane/ethyl acetate 8:2) to give the product (4.3 g, 93% yield) as a pale yellow oil that crystallized in the freezer (0ºC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11 (s, 3H), 5.12 (s, 2H), 6.58 (d, J = 3.55 Hz, 1H), 7.21 (d, J = 3.55 Hz, 1H), 9.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 57.9, 112.7, 121.8, 153.0, 155.6, 170.5, 178.0.

(5-Formylfuran-2-yl)methyl hexanoate (8)[8]



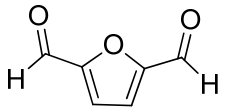
To a flame dried round-bottom flask, HMF (0.250 g, 1.98 mmol), MeCN (10 mL) and hexanoic anhydride (0.51 mL, 2.2 mmol, 1.1 equiv.) were added followed by catalytic amount of pyridine (32 µL, 0.4 mmol, 0.2 equiv.). The reaction mixture was allowed to stir at room temperature for 66 h under argon atmosphere. The mixture was quenched with cold water, acidified with HCl 1M and extracted with Et_2O. The combined organic layers were dried over MgSO4, filtered and the solvent removed to give the crude product that was purified by column chromatography with silica gel (hexane/ethyl acetate 8:2) to give the product (0.315 g, 71% yield) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.9 Hz, 3H), 1.27-1.31 (m, 4H), 1.63 (quint, J = 7.4 Hz, 2H), 2.35 (t, J = 7.6, 2H), 5.12 (s, 2H), 6.58 (d, J = 3.55 Hz, 1H), 7.21 (d, J = 3.55 Hz, 1H), 9.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.4, 24.6, 31.3, 34.06, 57.8, 112.6, 121.9, 152.9, 155.8, 173.3, 178.0.

(5-Formylfuran-2-yl)methyl benzoate (9)[9]



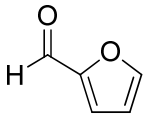
To a flame dried round-bottom flask, HMF (1.0 g, 7.9 mmol) and pyridine (4 mL) were added followed by benzoyl chloride (1 mL, 8.7 mmol, 1.1 equiv.). The reaction mixture was allowed to stir at reflux for 1.5 h under argon atmosphere. The mixture was quenched with cold water (50 mL), acidified with HCl 1M and extracted with Et_2O. The combined organic layers were dried over MgSO4, filtered and the solvent removed to give the crude product that was recrystallized from Et_2O/hexane as a pale orange solid (0.86 g, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (s, 2H), 6.68 (d, J = 3.55 Hz, 1H), 7.24 (d, J = 3.55 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.58 (tt, J = 7.45, 1.30 Hz, 1H), 8.06 (m, 2H), 9.65 (s, 1H).

Furan-2,5-dicarbaldehyde (10)[10]



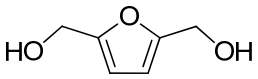
To a flame dried schlenk with CH_2Cl_2 (100 mL) at -78ºC under argon atmosphere oxalyl chloride (0.85 mL, 1.25 equiv.) was added followed by dropwise addition of DMSO (1.13 mL, 2 equiv.). After stirring for 15 minutes, a solution of HMF (1.0 g, 8.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the resulting mixture was stirred at -78ºC for an additional 30 minutes. Et_3N was then added dropwise and the mixture was allowed to warm up to RT. After 1 hour of stirring at RT, water (50 mL) was added and the resulting mixture was washed with HCl 1M, extracted with CH_2Cl_2 and finally dried over Na_2SO_4. The resulting crude mixture was purified by flash chromatography with Et_2O/Hexane. The collected solid was further recrystallized from hexane/EtOAc to give 305 mg (31% yield) of the product as white needles. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (s, 2H), 9.86 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.4, 154.4, 179.4.

Furan-2-carbaldehyde (11)



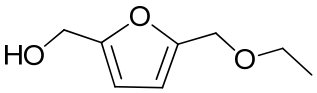
The commercial available compound was purified by distillation under vacuum to give a colorless oil.

Furan-2,5-diyldimethanol (12)[11]



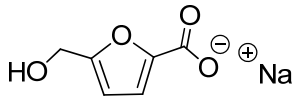
To a solution of HMF (2g, 16mmol) in dry THF (10 mL), $NaBH_4$ (2.4g, 64 mmol) was added portionwise. The reaction mixture was stirred at RT overnight. MeOH (7 mL) and acetic acid (9 mL) were added and stirred at RT for 15 min then 50 mL of MeOH was added and the solvent removed under vacuum. Then twice 50 ml MeOH were added and evaporated. The mixture was dissolved in DCM/MeOH 9:1 and passed through a pad of silica gel. The solvent was evaporated and the product was purified by silica flash chromatography using EtOAc/Hexane to give 1.6g (80% yield) of the product. ^{1}H NMR (300 MHz, D_2O) δ 4.51 (s, 4H), 6.31 (s, 2H); ^{13}C NMR (100 MHz, D_2O) δ 55.8, 109.0, 153.6.

(5-(Ethoxymethyl)furan-2-yl)methanol (13)[12]



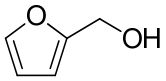
5-(ethoxymethyl)furan-2-carbaldehyde (154 mg, 1 mmol) were dissolved in MeOH (5 mL) then $NaBH_4$ (148mg, 4 mmol) was added on 3 portions at RT. The reaction mixture was stirred for 15 min and quenched with H_2O. The MeOH was evaporated and the water phase extracted with EtOAc. The organic phase was dried with $MgSO_4$ and evaporated. The product was purified by silica flash chromatography using EtOAc/Hexane to give 148mg (95% yield) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J = 7.0 Hz, 3H), 2.62-2.74 (b, 1H), 3.51 (q, J = 7 Hz, 2H), 4.39 (s, 2H), 6.53 (s, 2H), 6.20 (m, 1H), 6.23 (m, 1H).

Sodium 5-(hydroxymethyl)furan-2-carboxylate (14)[13]



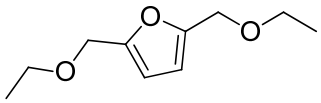
To a closed vessel containing a solution of HMF (3 g, 24 mmol) in water (30 mL), NaOH (0.87 g, 22 mmol) was added at 0ºC, and the resulting mixture stirred for 18h at 0 ºC. The water was removed under vacuum and ethyl acetate (2 x 50 mL) was added to the solid residue to separate the furan-2,5-diyldimethanol (0.85g, 30% yield). From the remaining solid, the title compound was isolated by recrystallization with ethanol (2 mL)/ethyl acetate (100 mL) to give the product as a hygroscopic solid (1.4 g, 41% yield). ^{1}H NMR (400MHz, D_2O): δ 6.90 (d, J = 3.3Hz, 1H), 6.43 (d, J = 3.3Hz, 1H), 4.54 (s, 2H); ^{13}C NMR (100 MHz, D_2O): δ 166.5, 155.6, 149.0, 115.7, 109.9, 55.9; ESI (-) MS: m/z 140.89.

Furan-2-ylmethanol (15)



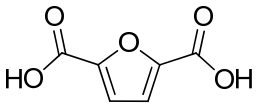
The commercial available compound was purified by distillation under vacuum to give a colorless oil.

2,5-Bis(ethoxymethyl)furan (16)[12]



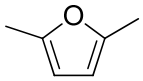
(5-(ethoxymethyl)furan-2-yl)methanol (390mg, 2.5mmol) was dissolved in acetonitrile (5 mL) then NaH (0.2g, 8.3mmol) was added followed by dropwise addition of bromoethane (0.6 mL, 8 mmol). The reaction mixture was stirred at RT overnight. The reaction was quenched with H_2O and the acetonitrile was evaporated and the water phase extracted with Et_2O. The organic phase was dried with $MgSO_4$ and evaporated. The product was purified by silica flash chromatography using EtOAc/Hexane to give 180 mg (39%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 6H), 3.52 (q, J = 7 Hz, 4H), 4.41 (s, 4H), 6.24 (s, 2H).

Furan-2,5-dicarboxylic acid, FDCA (17)[14]



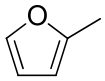
To a solution of sodium hydroxide (958 mg, 23 mmol) in water (10 mL), HMF (126 mg, 1 mmol) was added at 20 ºC, followed by the addition of potassium permanganate (363 mg, 2.3 mmol). After 10 minutes stirring at 20ºC the precipitate was filtered off and a concentrated HCl solution was added to the filtrate until pH 1. The resulted precipitate was separated by filtration, washed with water and dried under vacuum to give FDCA (106 mg, 68% yield) as a white powder. ^{1}H NMR (300 MHz, D_2O) δ 7.25 (s).

2,5-Dimethylfuran (18)



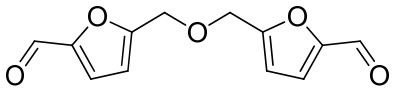
The commercial available source was used as received.

2-Methylfuran (19)



The commercial available source was used as received.

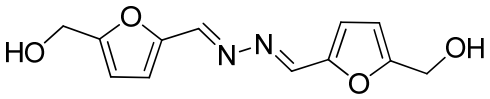
(5,5'-(Oxybis(methylene))bis(furan-5,2-diyl))dimethanol (20)[15]



The title compound was isolated by silica gel column chromatography EtOAc/Hexane as a 10% side product from the following reaction. To 9.1g of Et_4NBr (1% water content w/w) was mixed with 2g of fructose and 0.2g of smashed Amberlyst-15® (10% w/w). The mixture was placed at 80 ˚C and heated up to 100 ˚C for 10 min. Then the mixture was stirred at 100 ˚C for 30 min. The mixture was cooled down to RT and the resulting solid was washed with EtOAc (50 mL). The solvent was decanted and the solid was

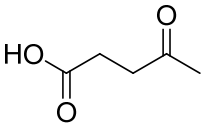
dissolved in hot EtOH (2 mL) then under vigorous stirring EtOAc (200 mL) was added. The resulting precipitated was filtered out and the combined solutions were filtered through a pad of silica gel (10g) and evaporated to give brown liquid of HMF (1.25g, 71%) in 88% purity by HPLC and 10% of the desire compound which was isolated by silica flash chromatography, EtOAc/Hexane. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 4H), 6.57 (d, J = 3.55 Hz, 2H), 7.21 (d, J = 3.55 Hz, 2H), 9.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.8, 112.0, 122.0, 152.9, 157.4, 177.9.

(5,5'-((1E,1'E)-hydrazine-1,2-diylidenebis(methanylylidene))bis(furan-5,2-diyl))dimethanol (21)[16]



HMF (1.0 g, 8.0 mmol) and hydrazine monohydrate (0.4 mL, 8.0 mmol) was dissolved in absolute EtOH (15 mL) then 3 drops of concentrated H_2SO_4. The mixture was stirred at RT for 1h. The resulting solid was filtered and washed with absolute EtOH to give the desired product 1.7 g (86% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.45 (s, 2H), 4.47 (s, 2H), 5.43 (t, 2H), 6.50 (s, 2H), 7.02 (s, 2H), 8.44 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.8, 109.6, 118.4, 148.4, 150.2, 159.4.

4-Oxopentanoic acid, levulinic acid (22)



The commercial available source was used as received.

HPLC

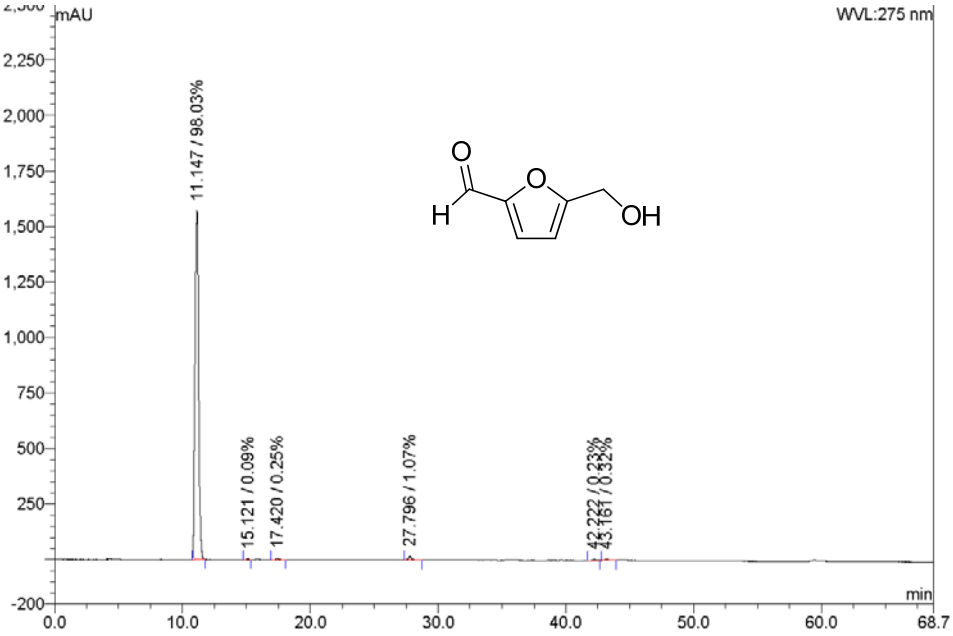


Figure 1. HPLC chromatogram of **1.**

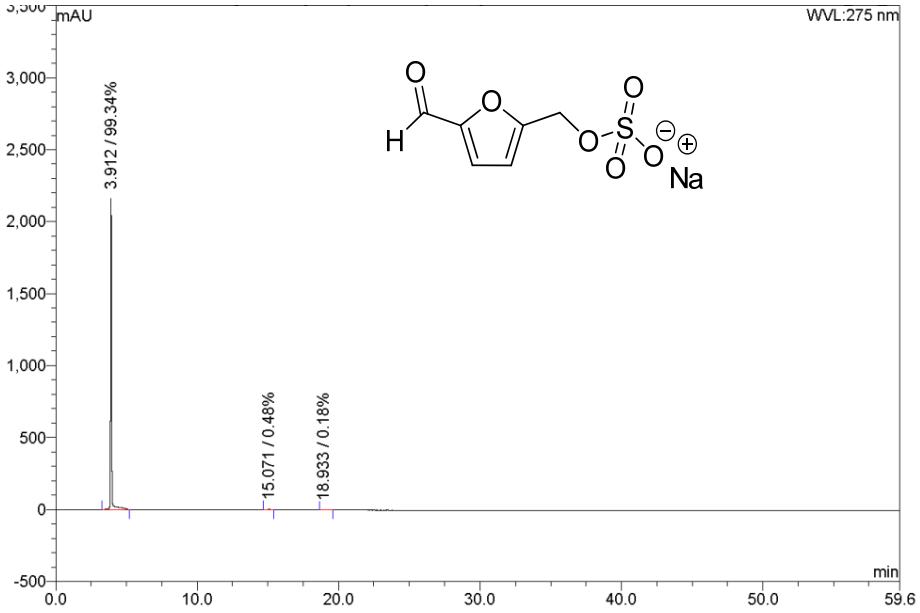


Figure 2. HPLC chromatogram of **2**.

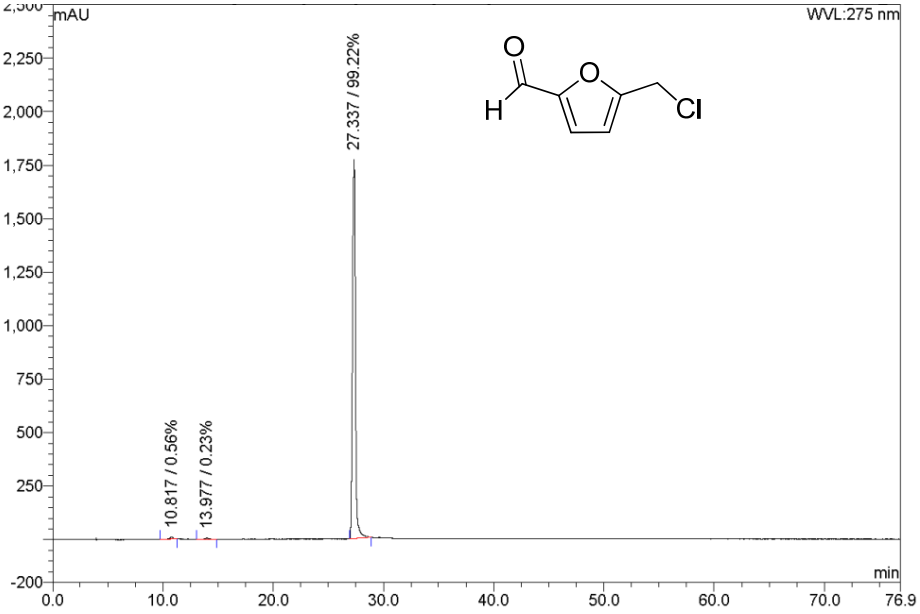


Figure 3. HPLC chromatogram of **3**.

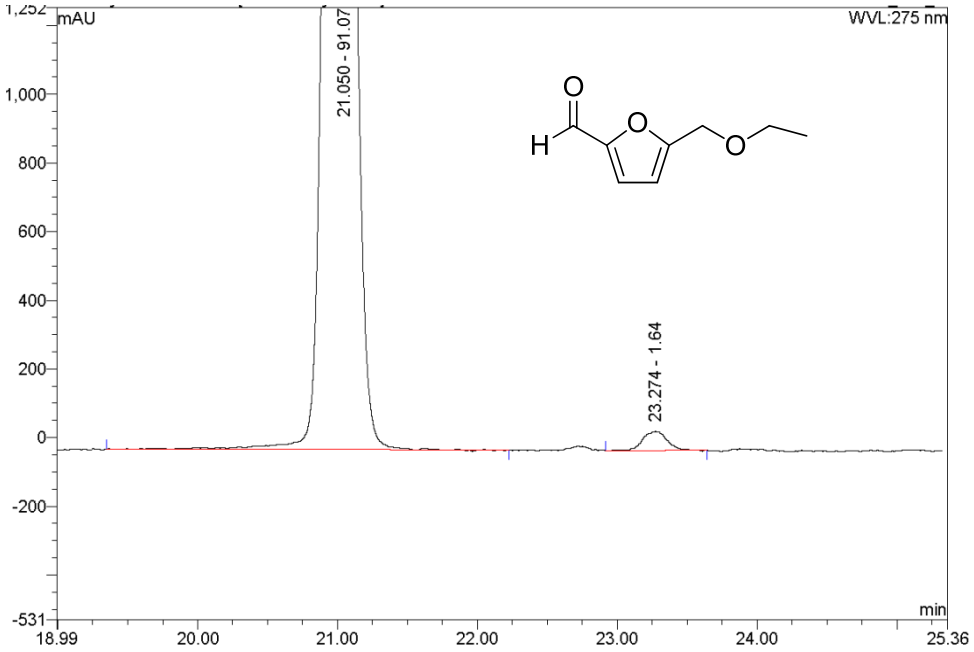


Figure 4. HPLC chromatogram of **4**.

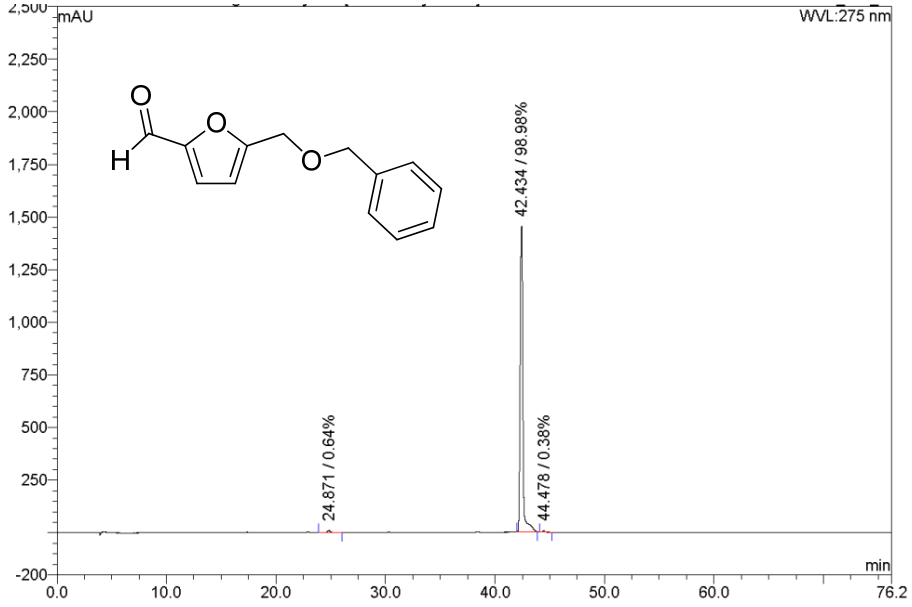


Figure 5. HPLC chromatogram of **5**.

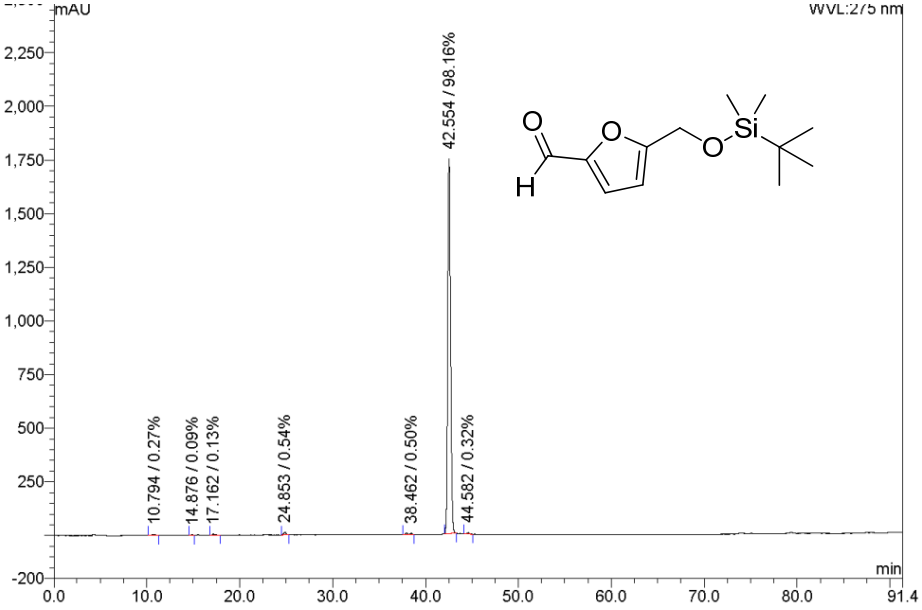


Figure 6. HPLC chromatogram of **6**.

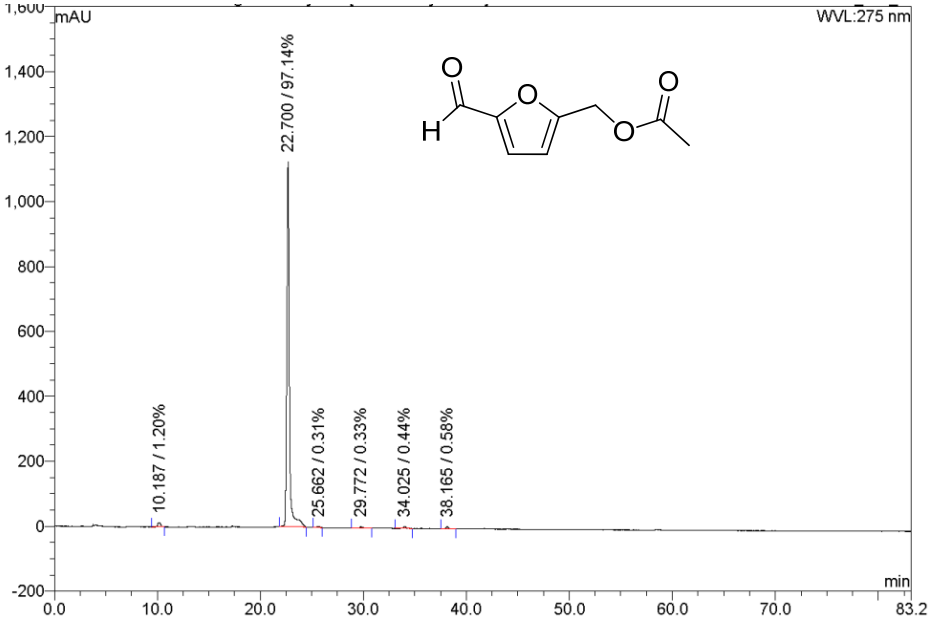


Figure 7. HPLC chromatogram of **7**.

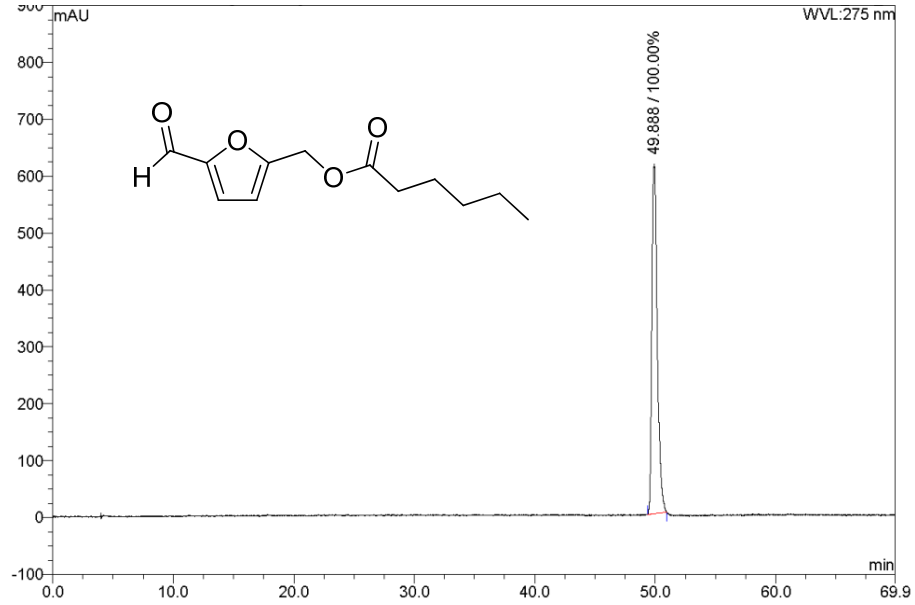


Figure 8. HPLC chromatogram of **8**.

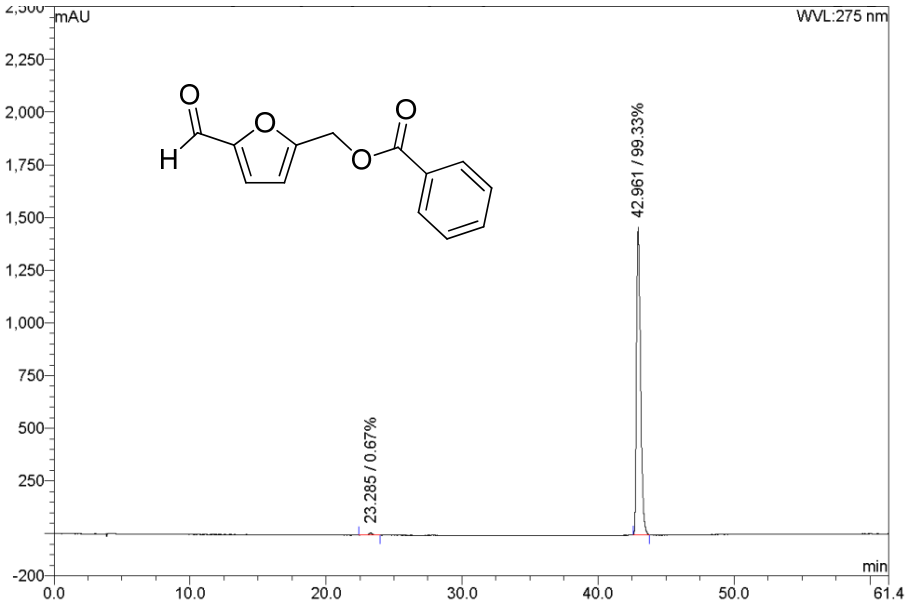


Figure 9. HPLC chromatogram of **9**.

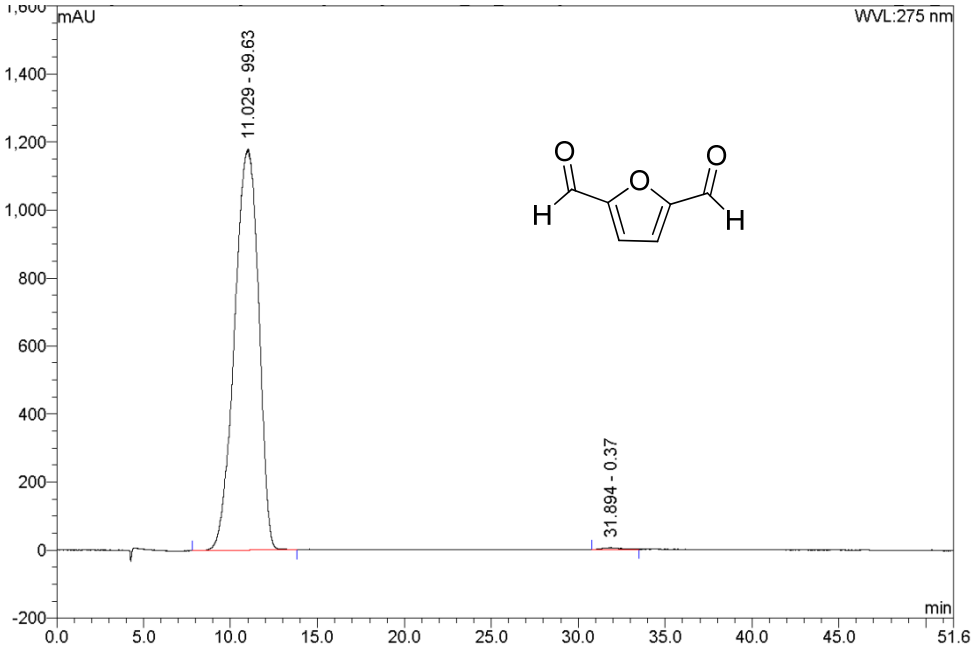


Figure 10. HPLC chromatogram of **10**.

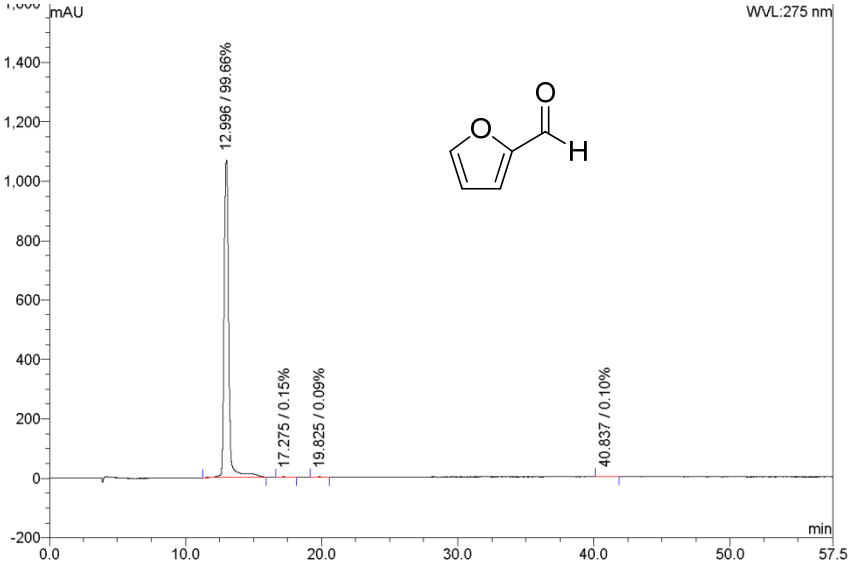


Figure 11. HPLC chromatogram of **11**.

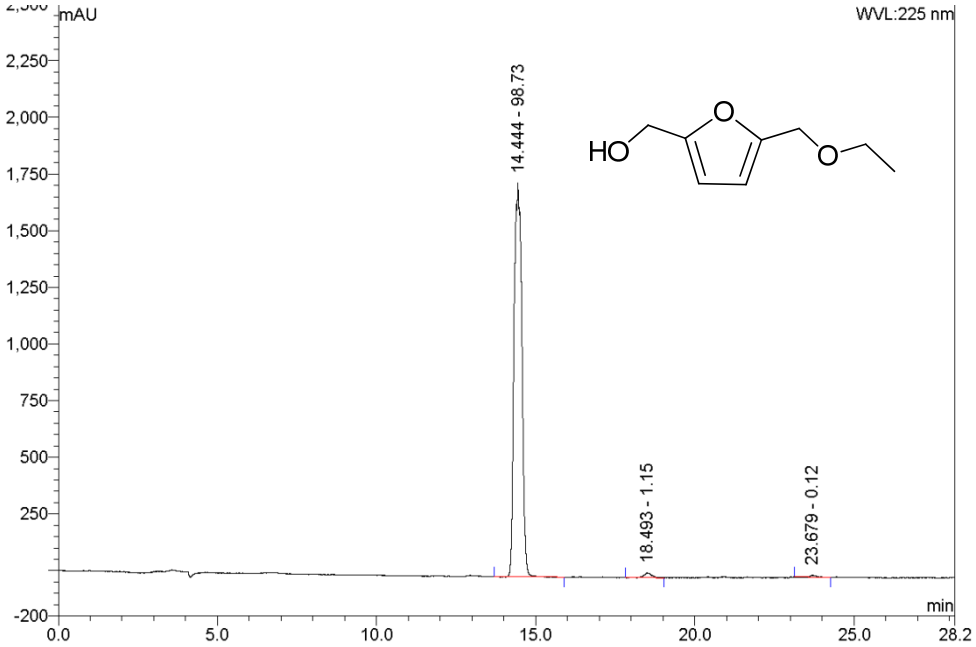


Figure 12. HPLC chromatogram of **13**.

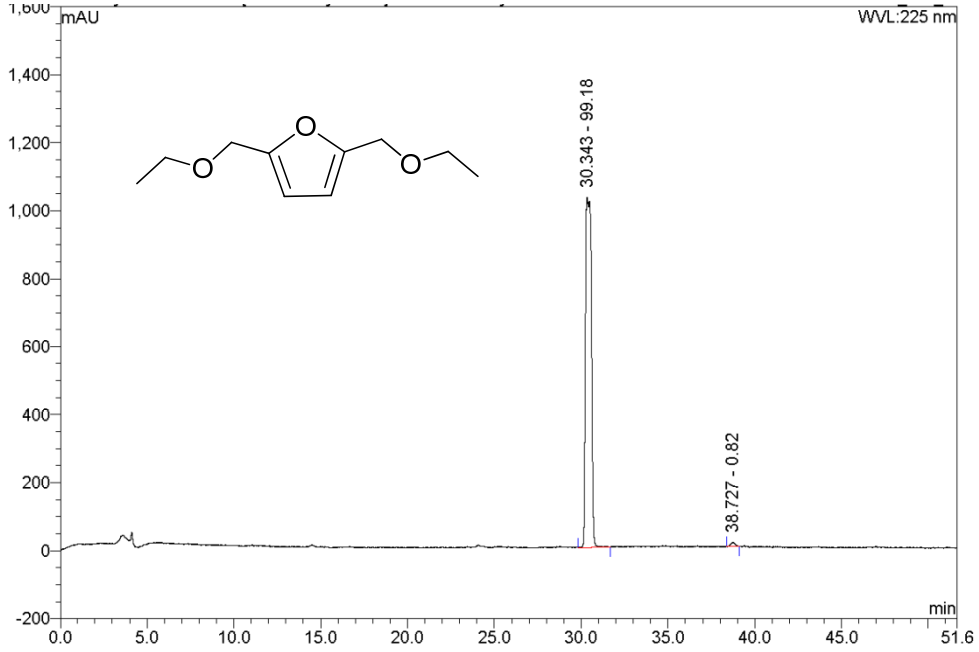


Figure 13. HPLC chromatogram of **16**.

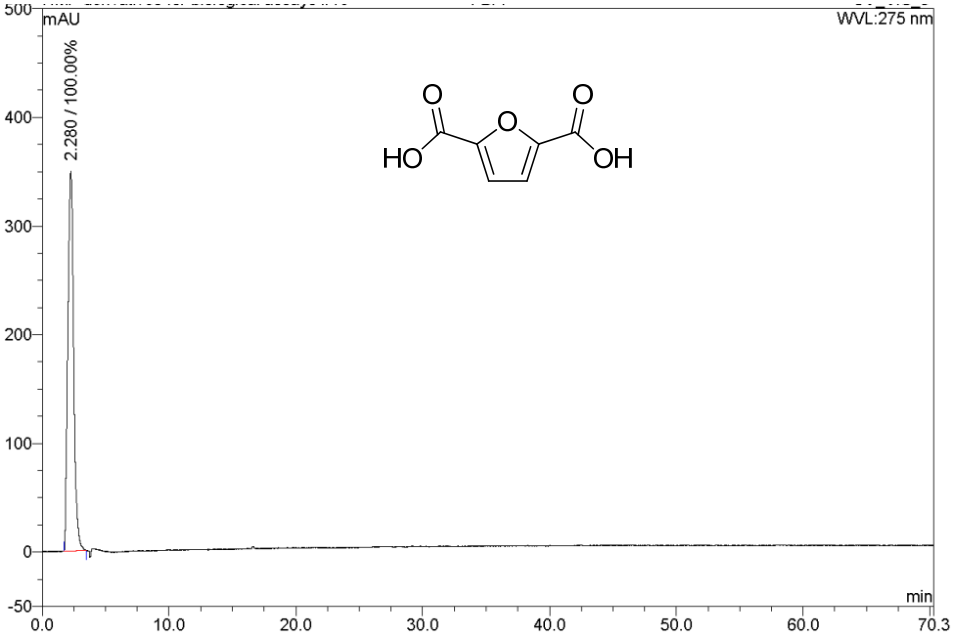


Figure 14. HPLC chromatogram of **17**.

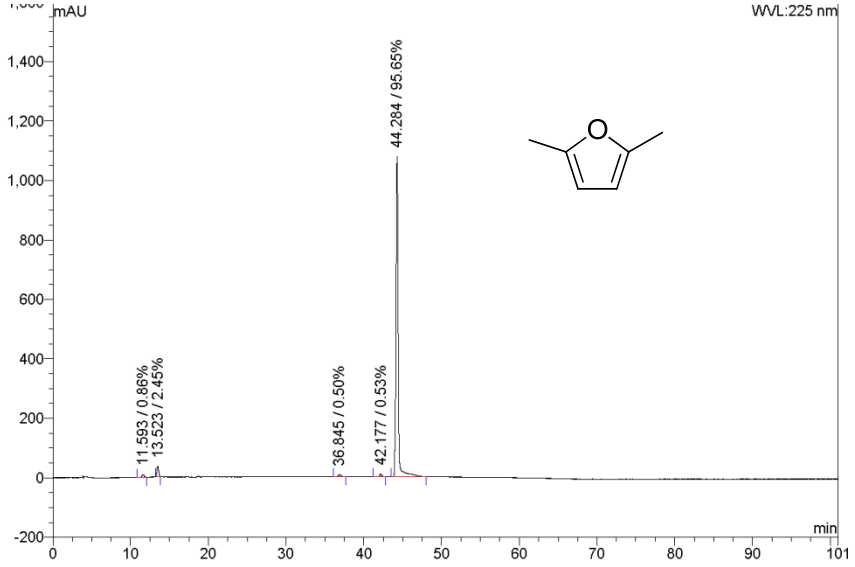


Figure 15. HPLC chromatogram of **18**.

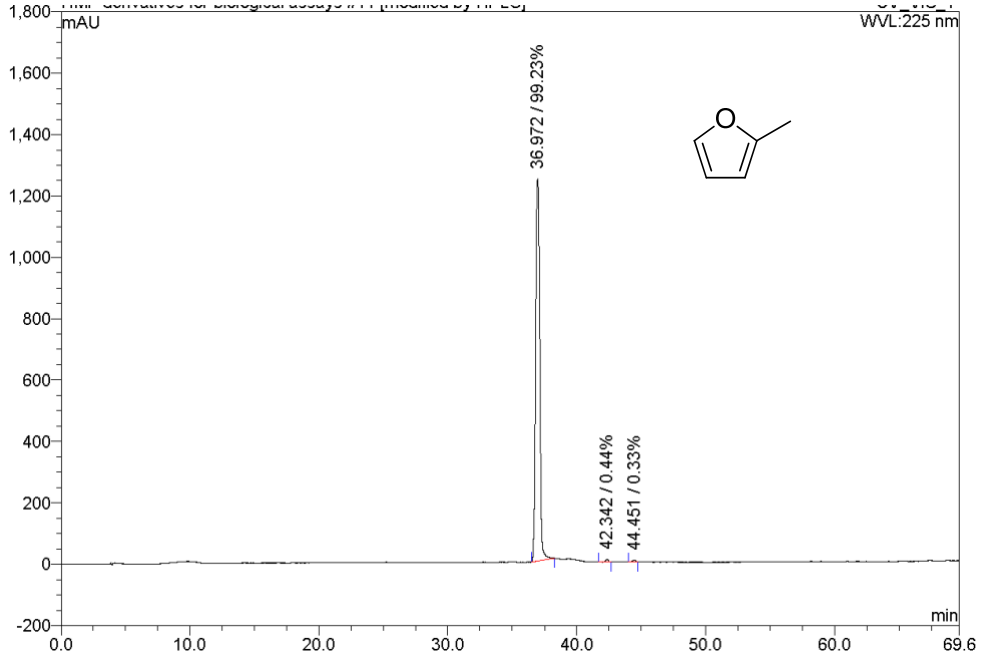


Figure 16. HPLC chromatogram of **19**.

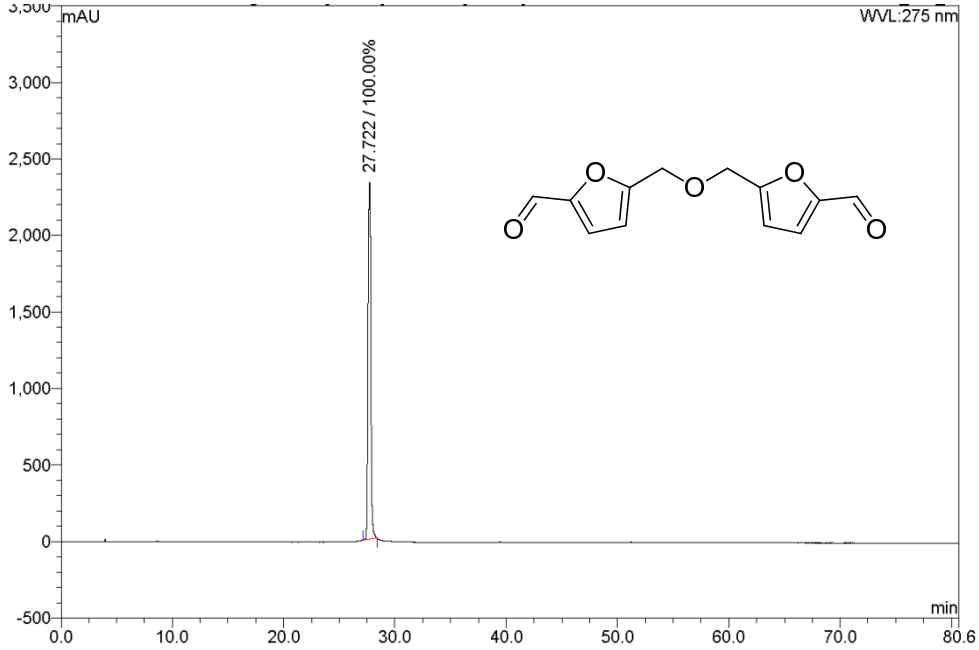


Figure 17. HPLC chromatogram of **20**.

GC-MS

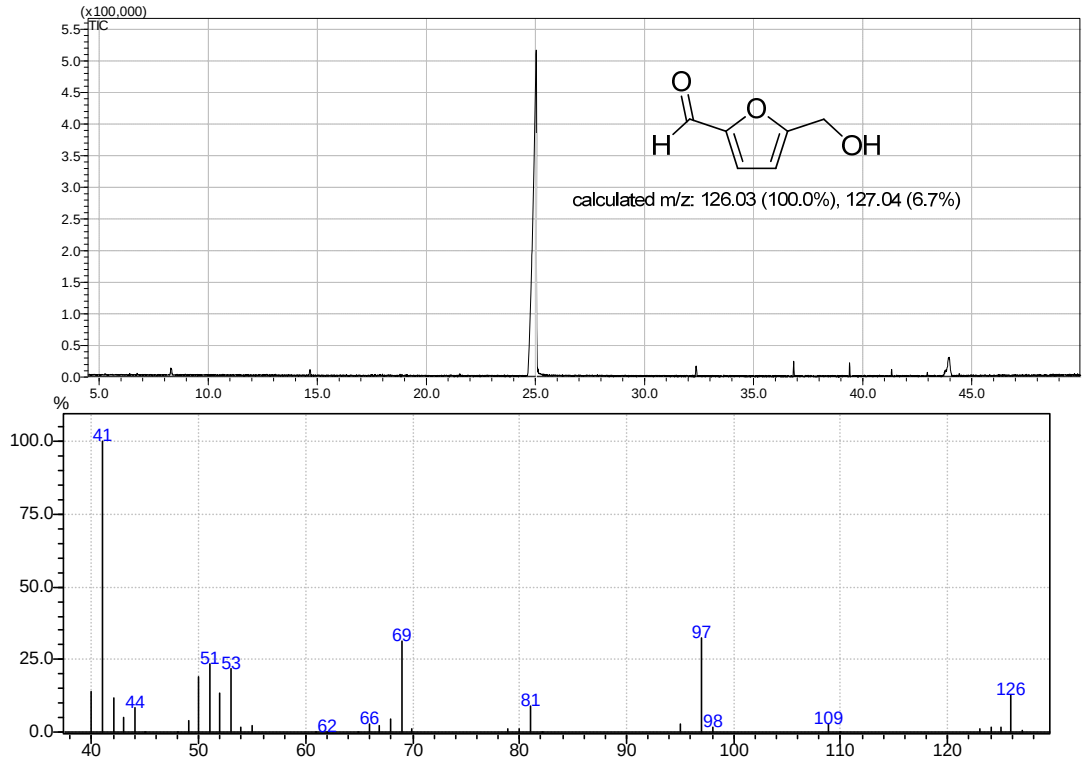


Figure 18. GC-MS chromatogram and MS of major signal of **1**.

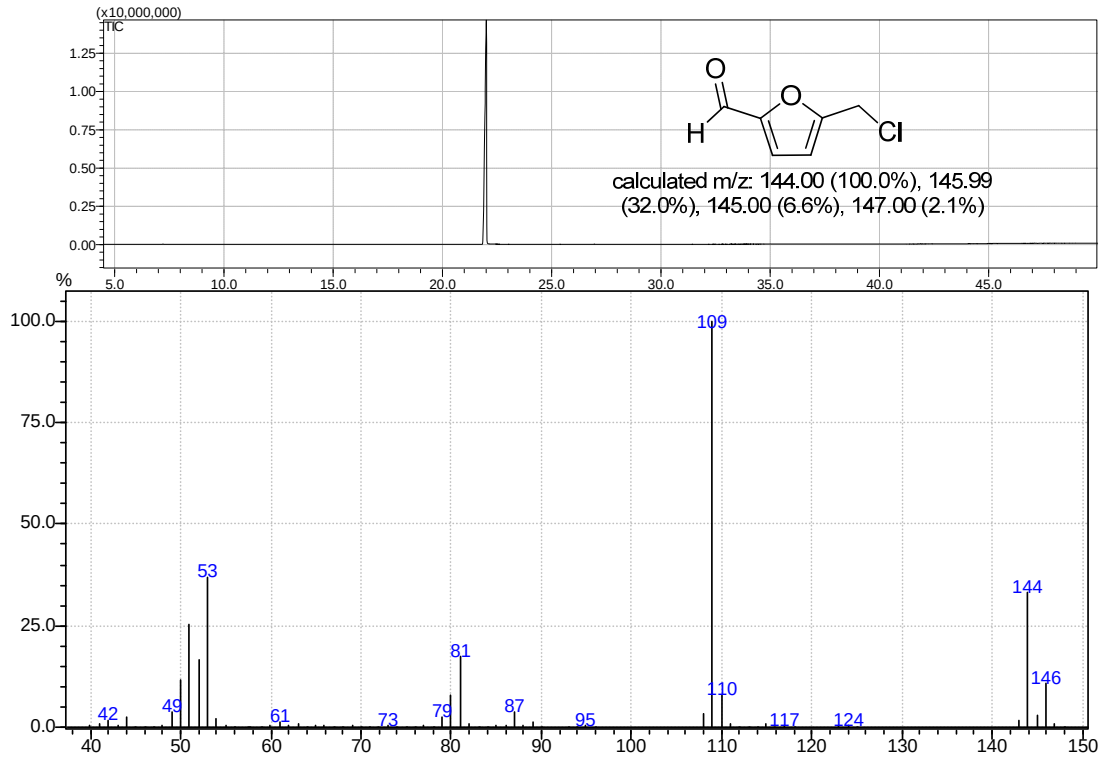


Figure 19. GC-MS chromatogram and MS of major signal of **3**.

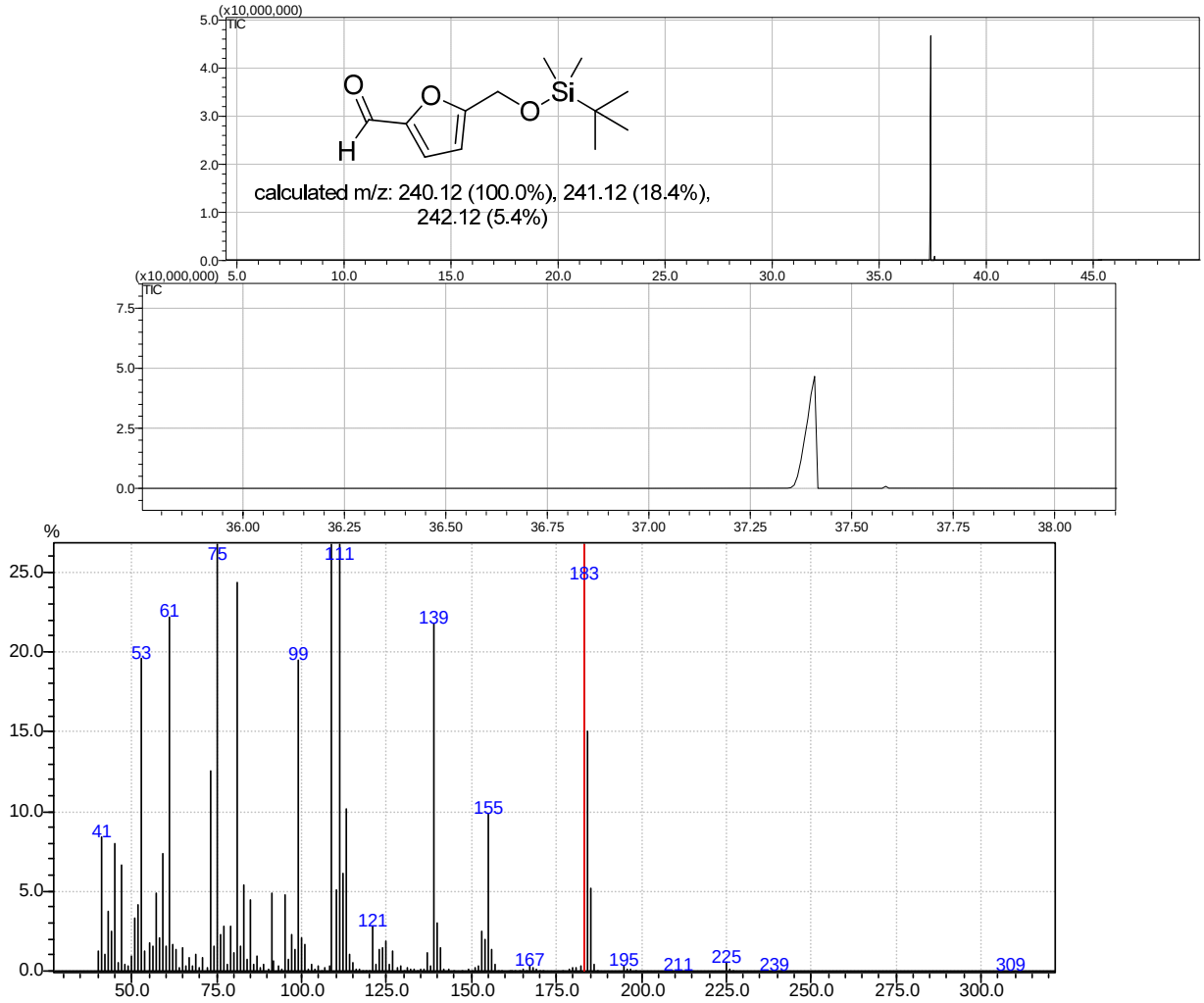


Figure 20. GC-MS chromatogram and MS of major signal of **6**.

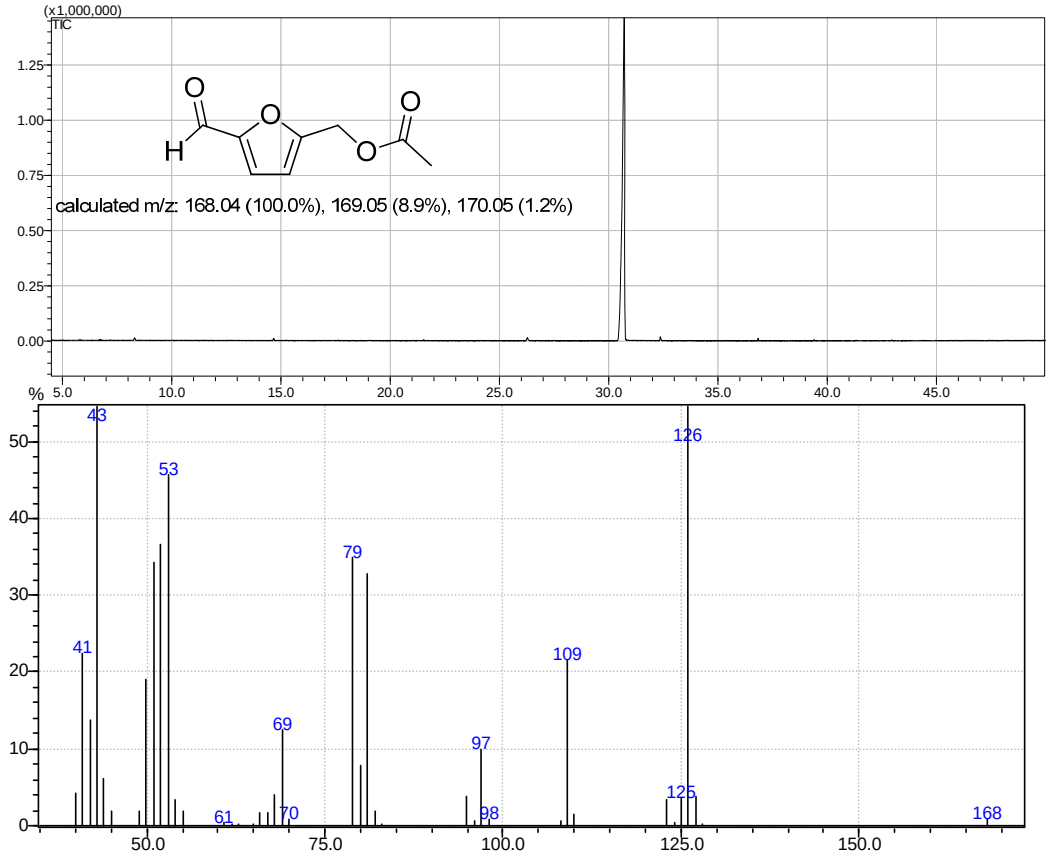


Figure 21. GC-MS chromatogram and MS of major signal of 7.

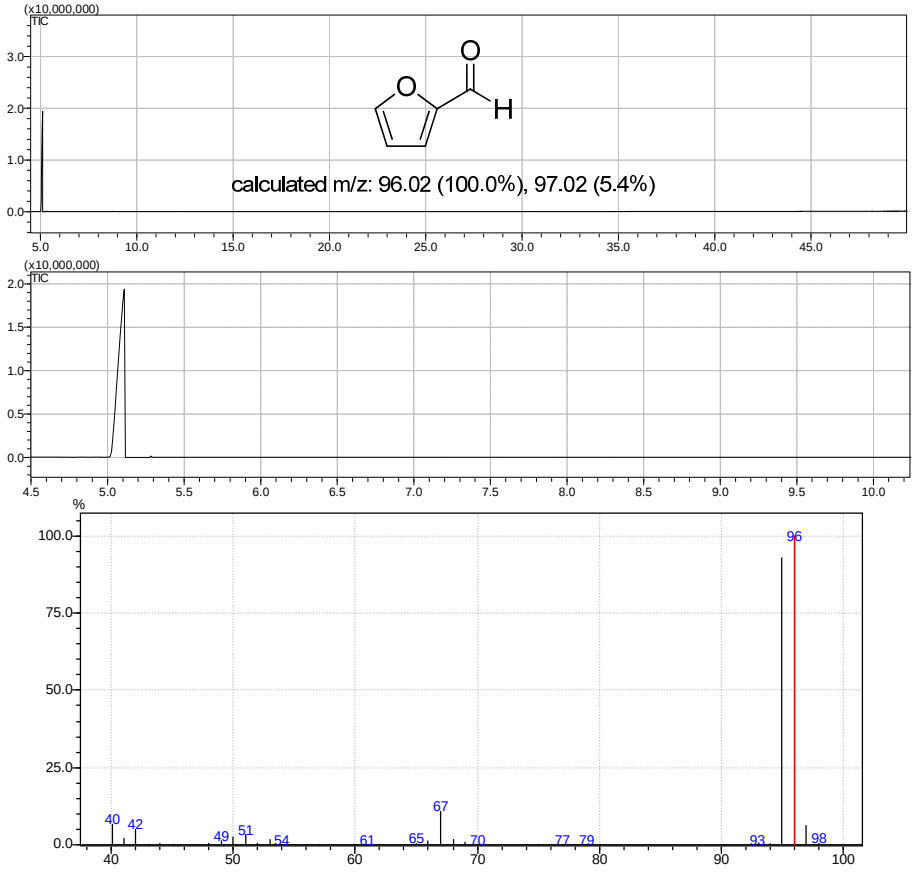


Figure 22. GC-MS chromatogram and MS of major signal of **11**.

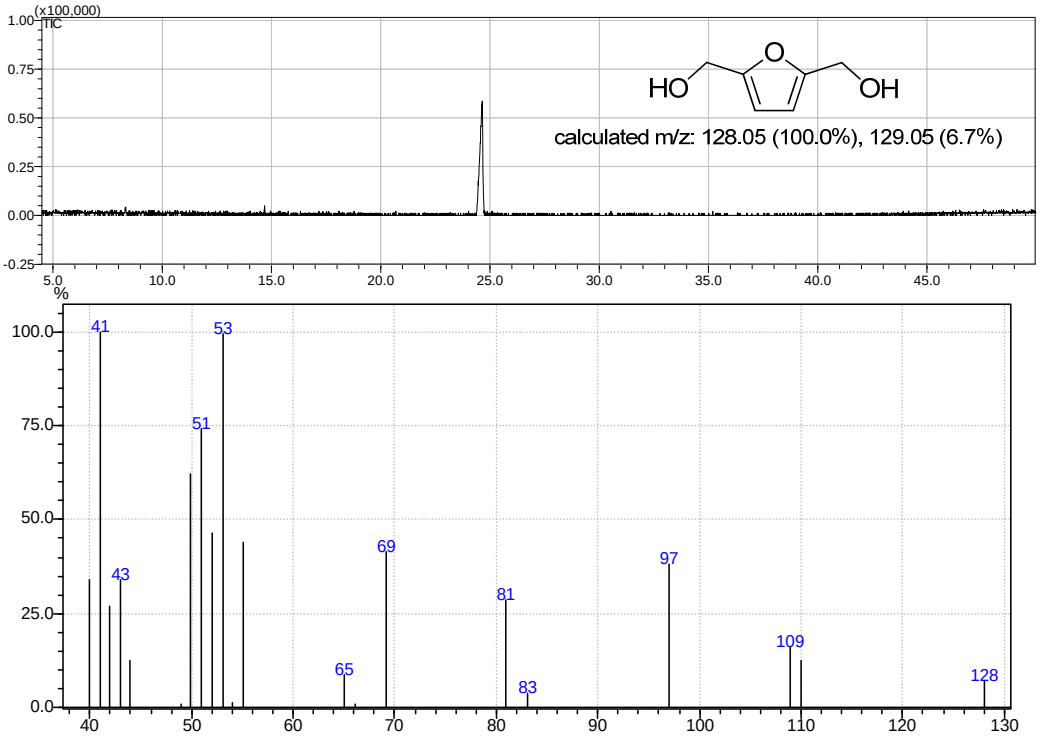


Figure 23. GC-MS chromatogram and MS of major signal of **12**.

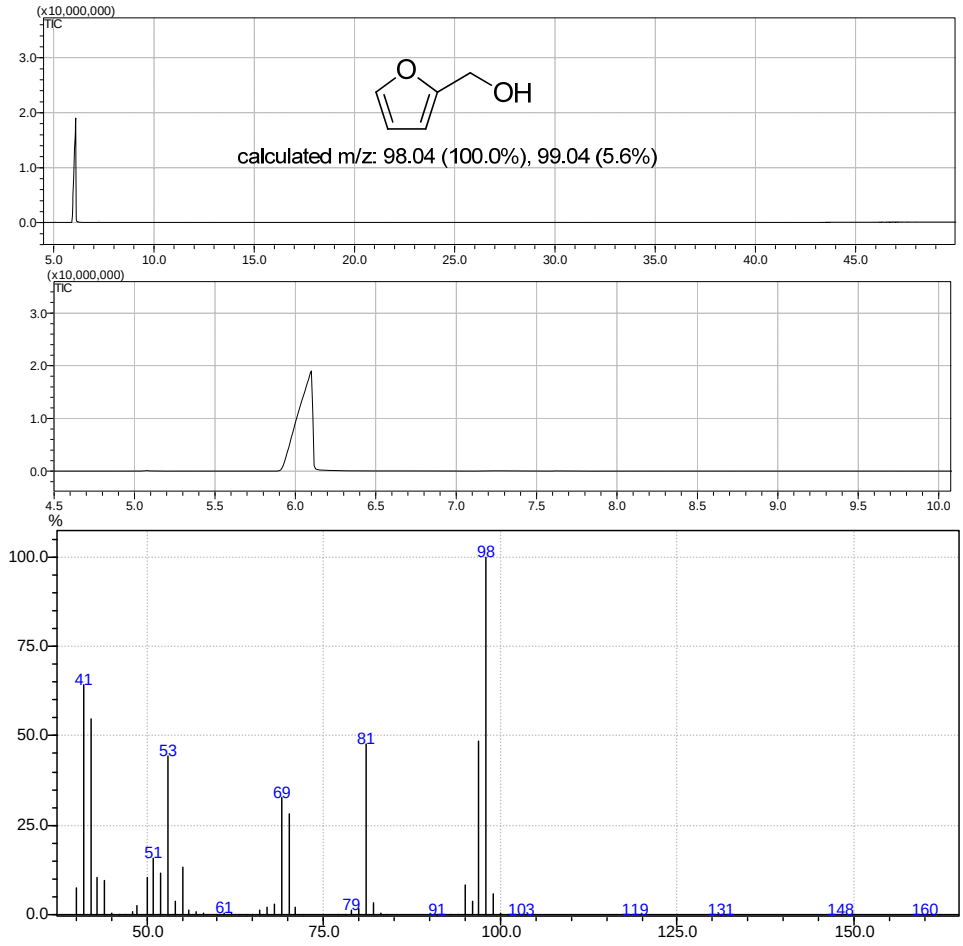


Figure 24. GC-MS chromatogram and MS of major signal of **15**.

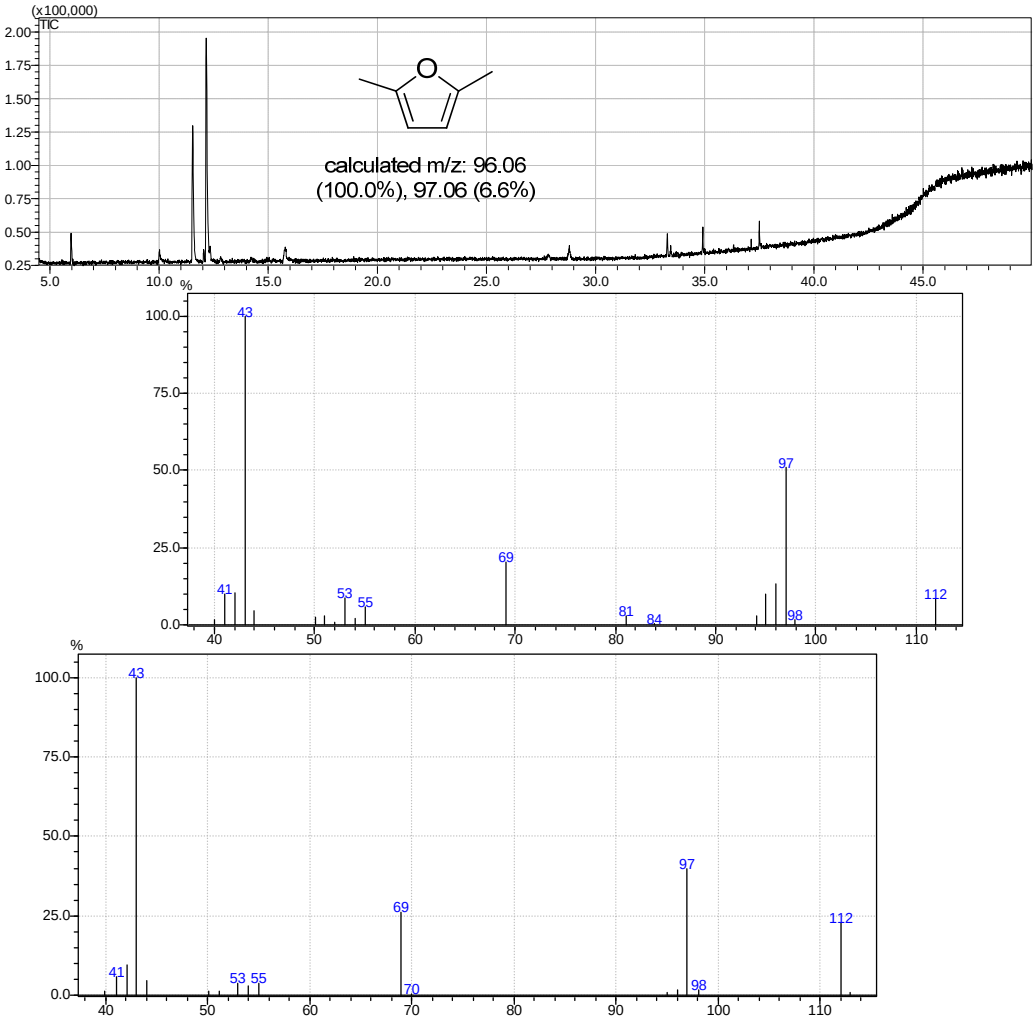


Figure 25. GC-MS chromatogram and MS of the major signals of **18**.

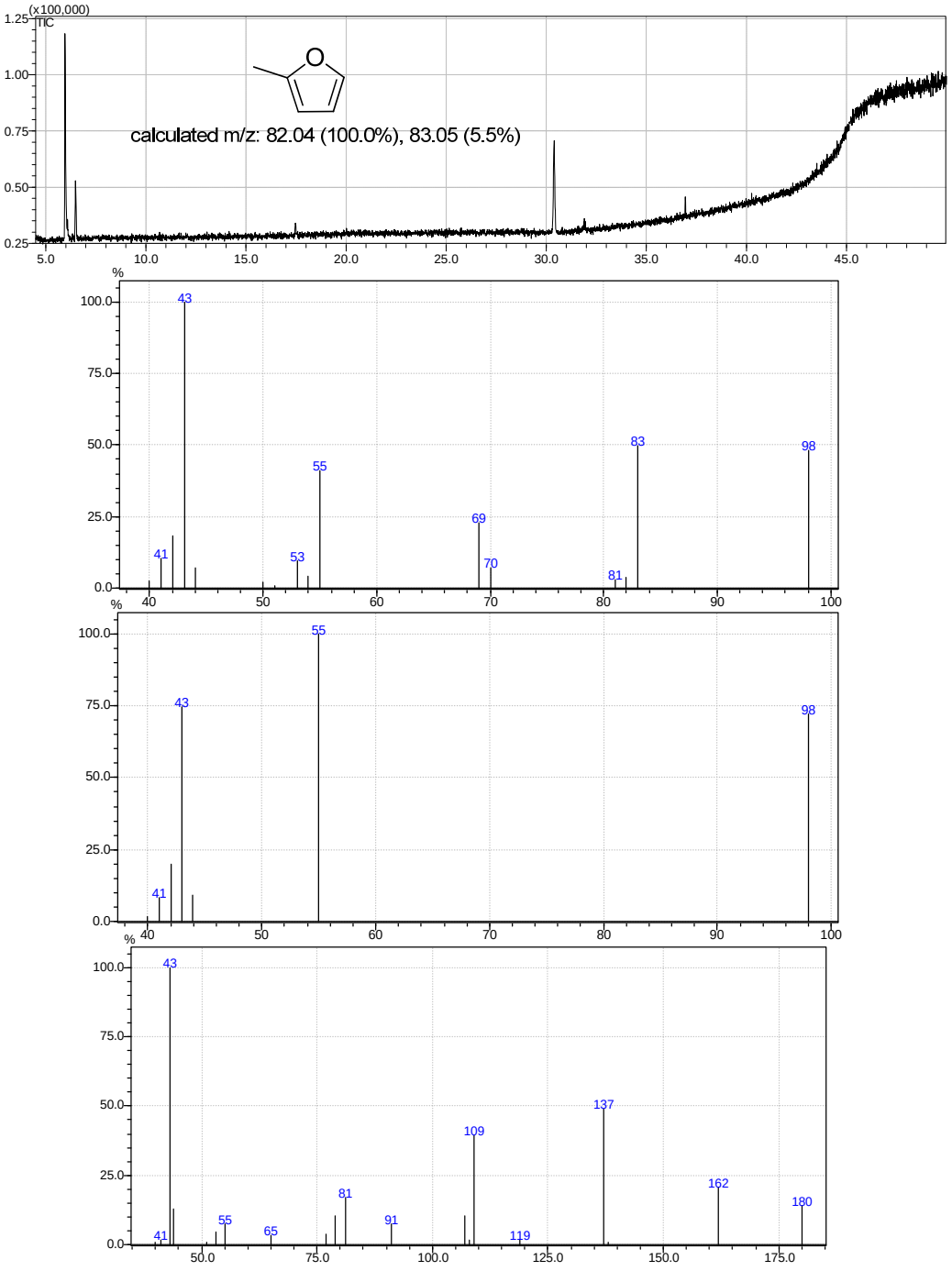


Figure 26. GC-MS chromatogram and MS of the major signals of **19**.

NMR Spectra

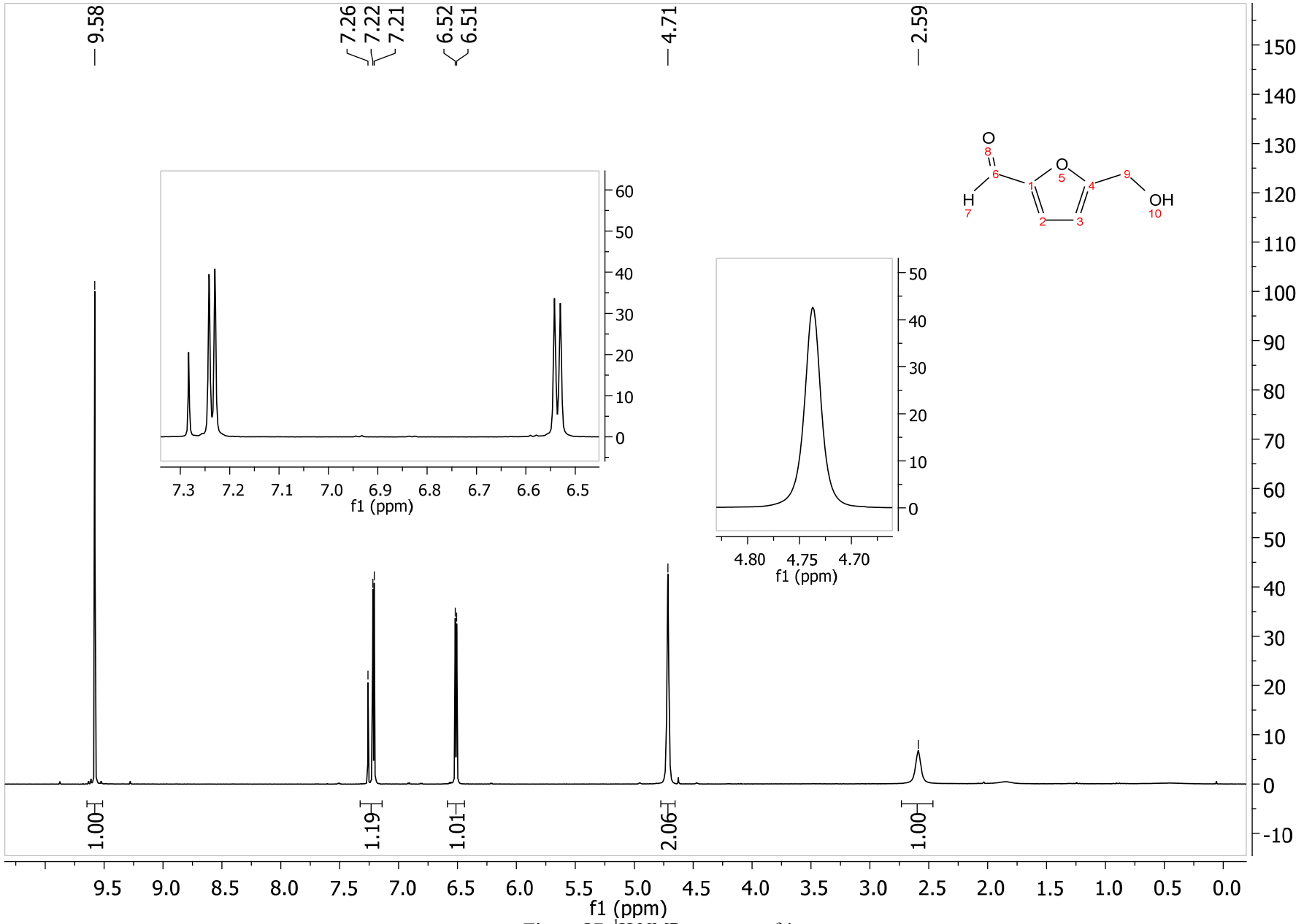


Figure 27. ^{1}H NMR spectrum of 1.

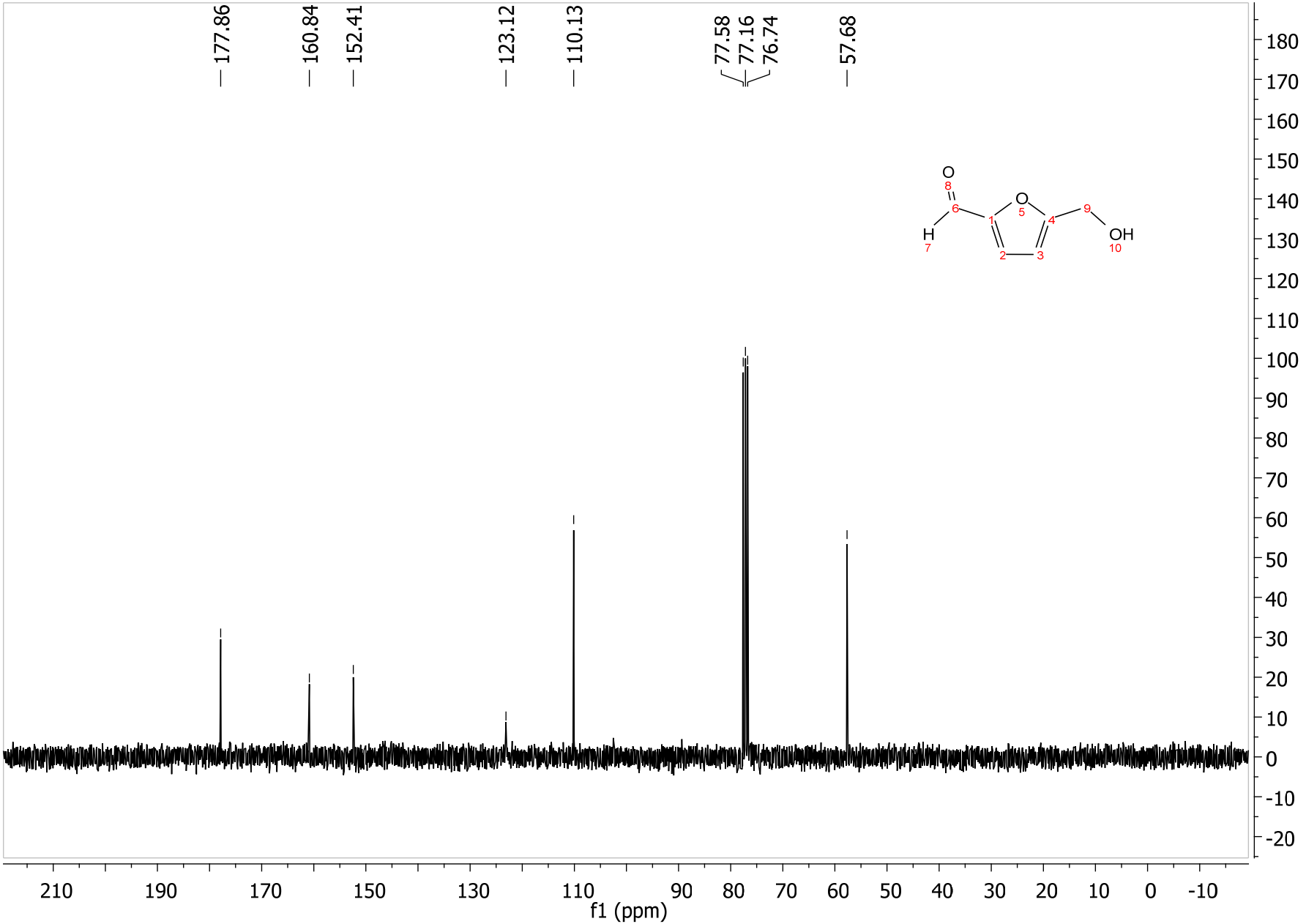


Figure 28. ^{13}C NMR spectrum of 1.

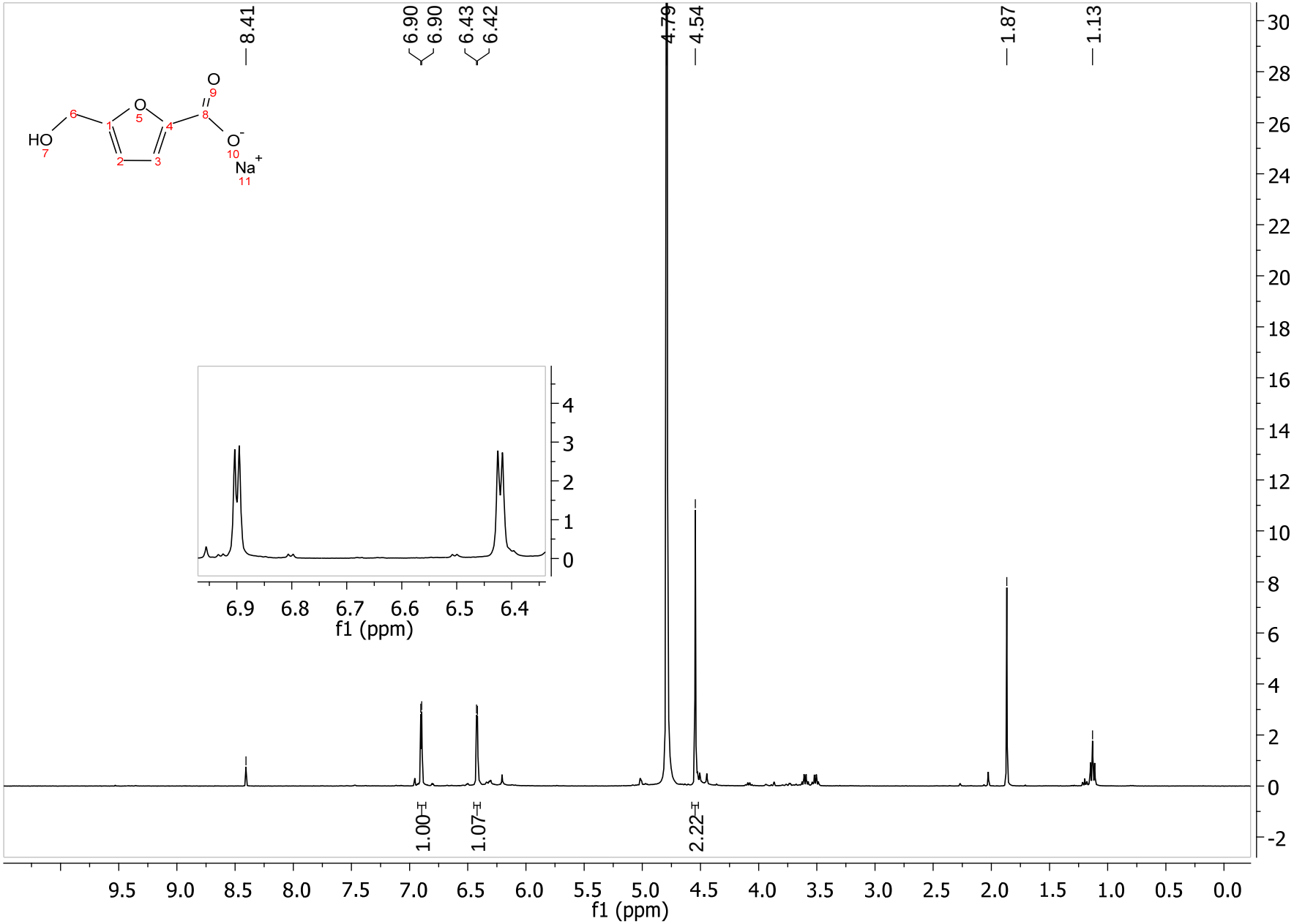


Figure 29. ^{1}H NMR spectrum of 2.

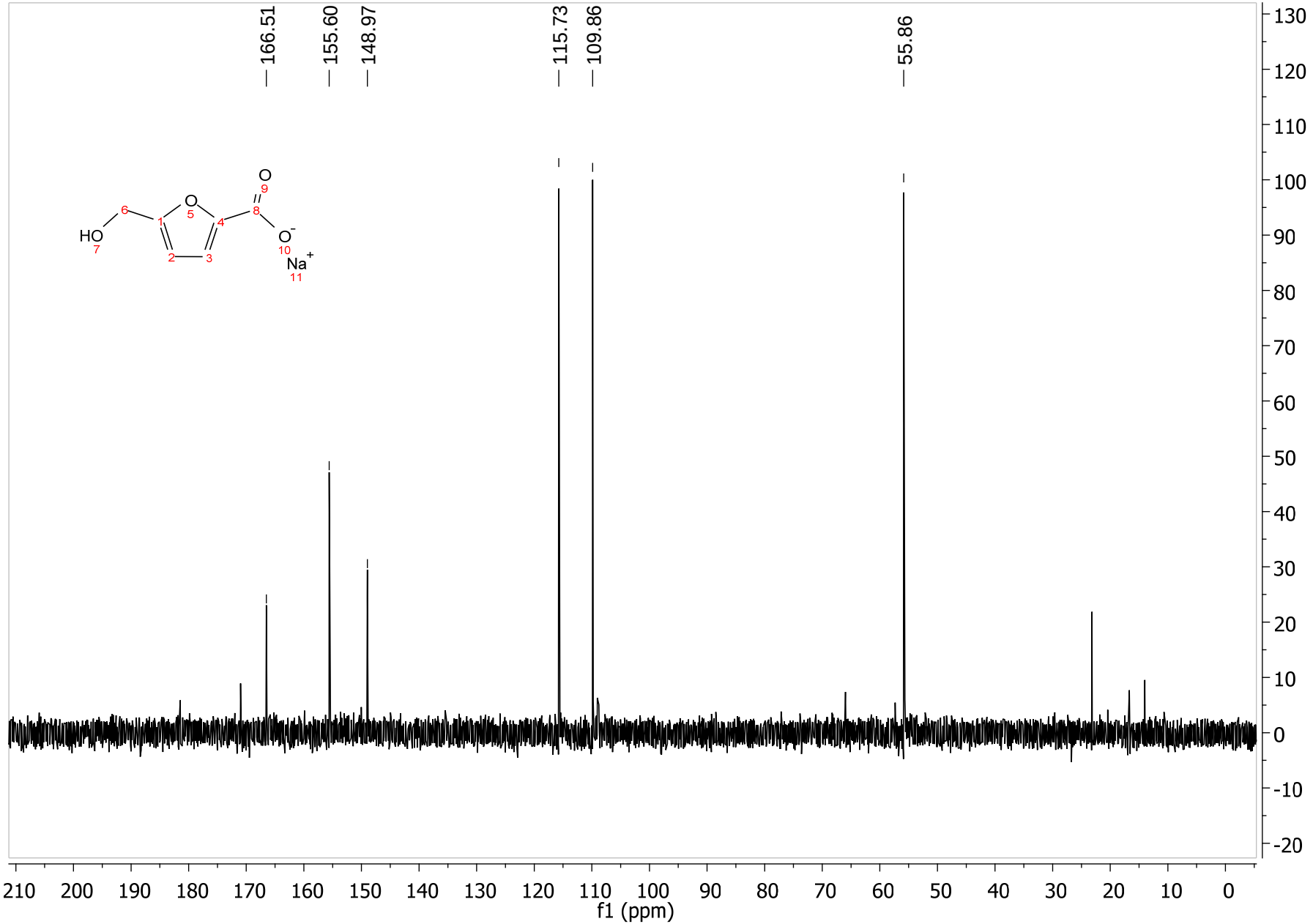


Figure 30. ^{13}C NMR spectrum of 2.

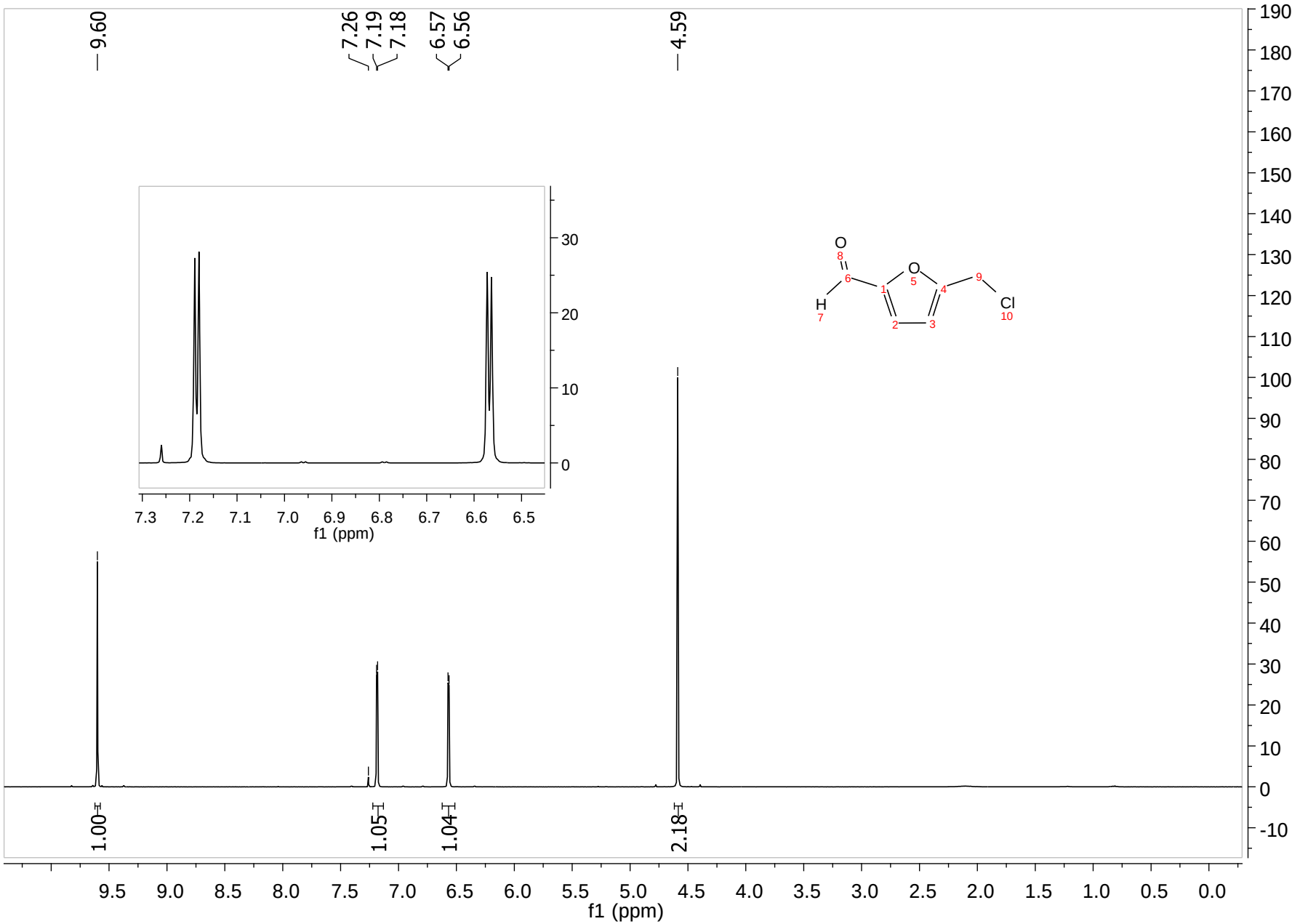


Figure 31. ^{1}H NMR spectrum of 3.

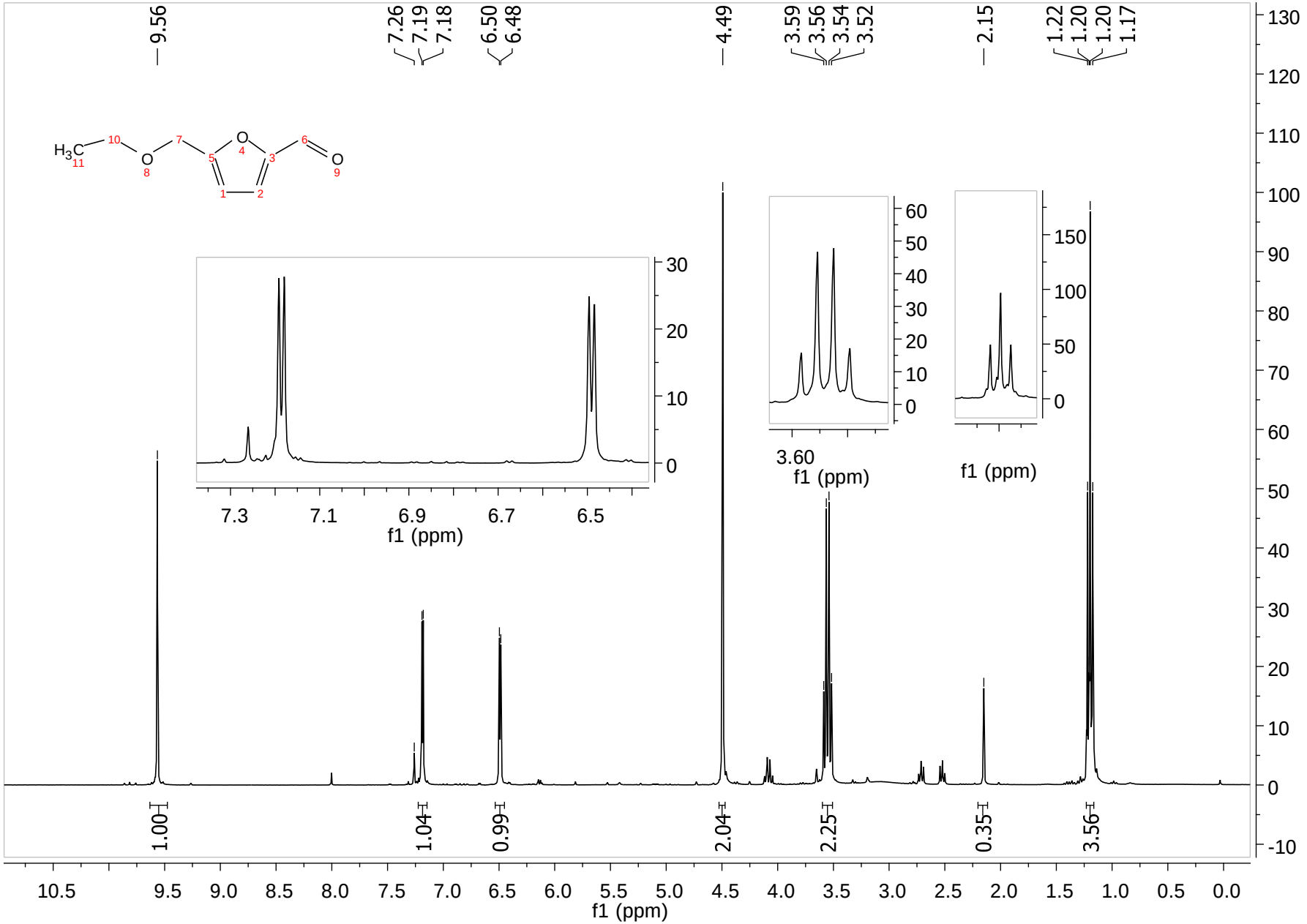


Figure 32. ^{1}H NMR spectrum of 4.

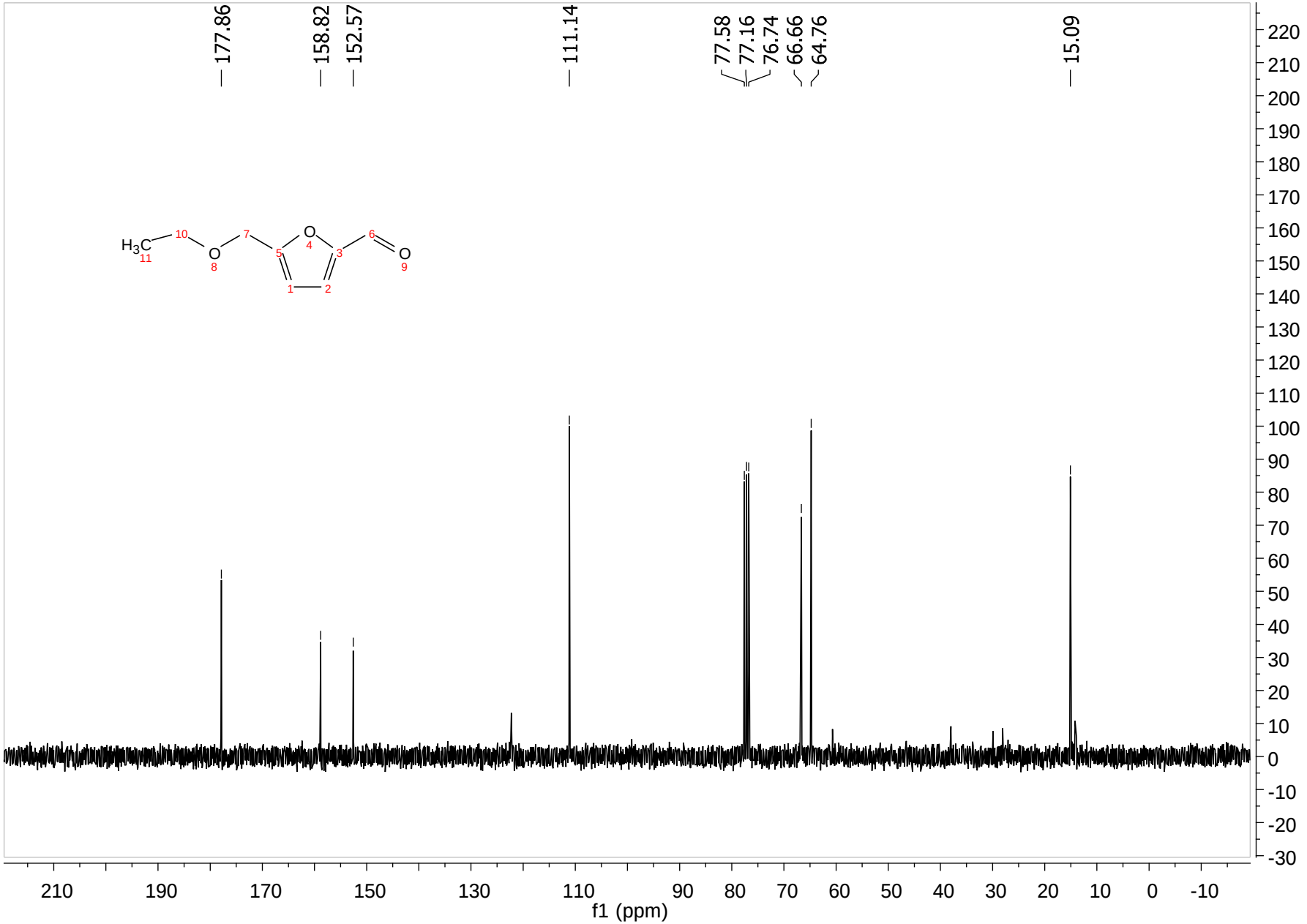


Figure 33. ^{13}C NMR spectrum of 4.

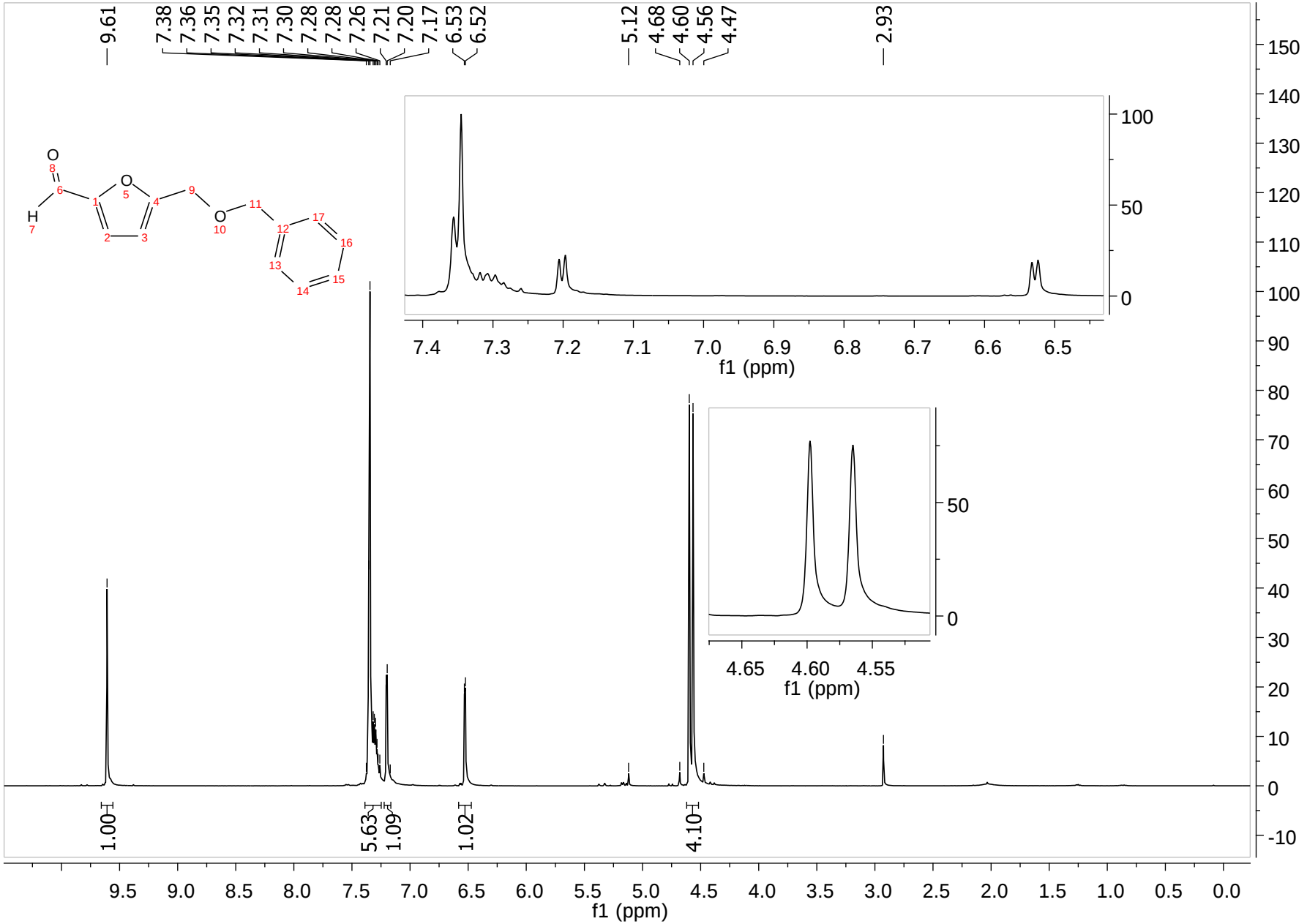


Figure 34. ^{1}H NMR spectrum of 5.

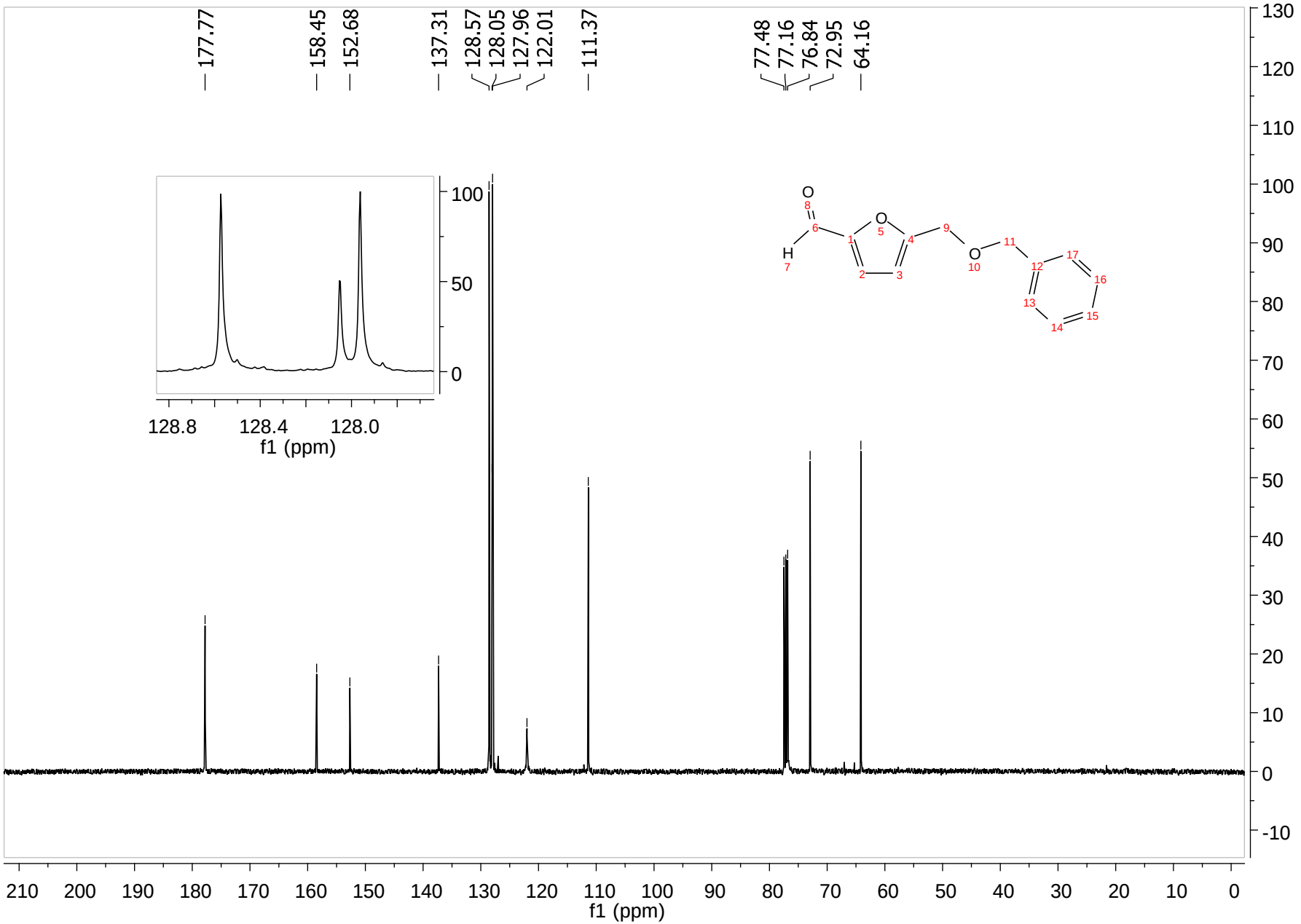


Figure 35. ^{13}C NMR spectrum of 5.

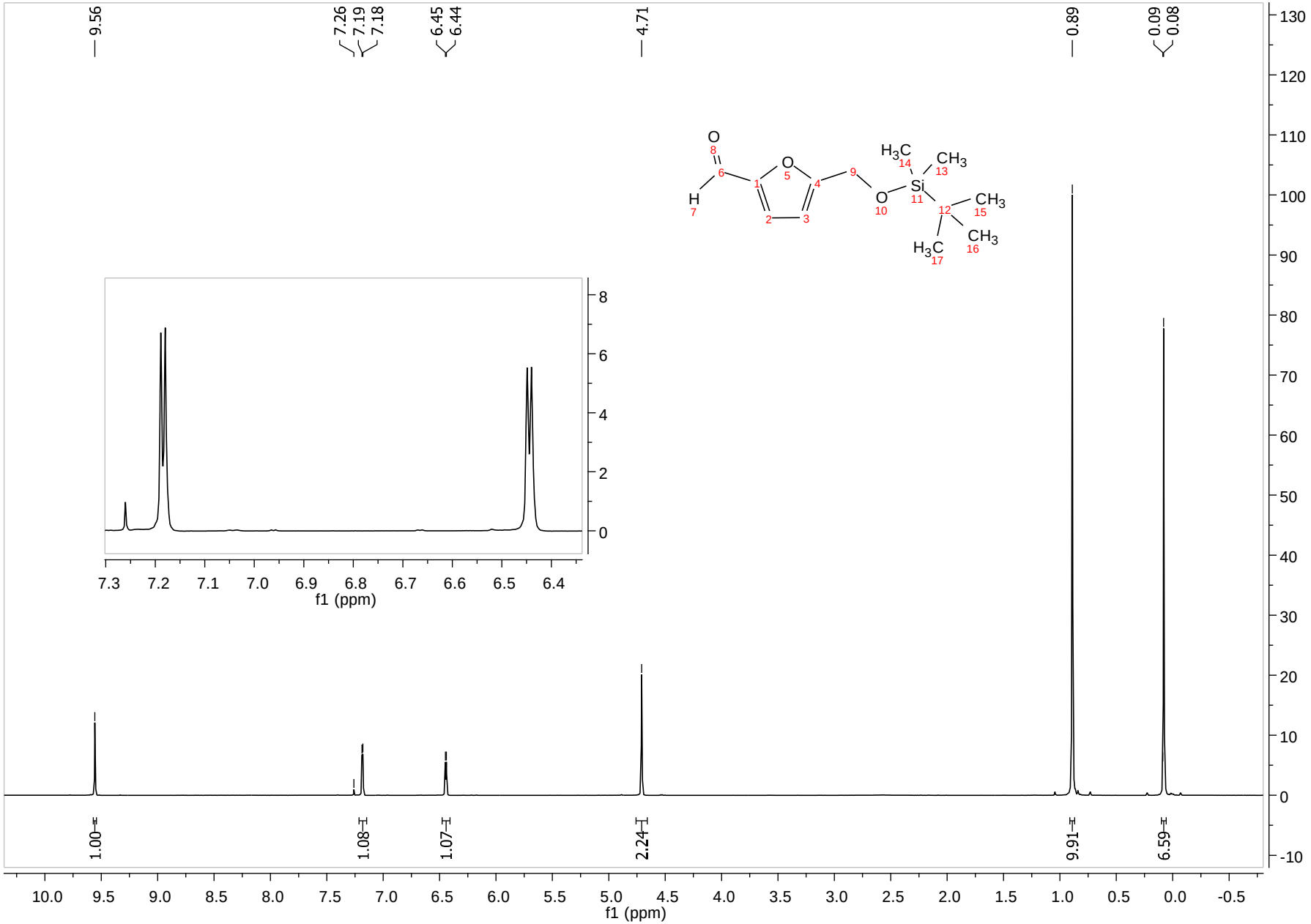


Figure 36. ^{1}H NMR spectrum of 6.

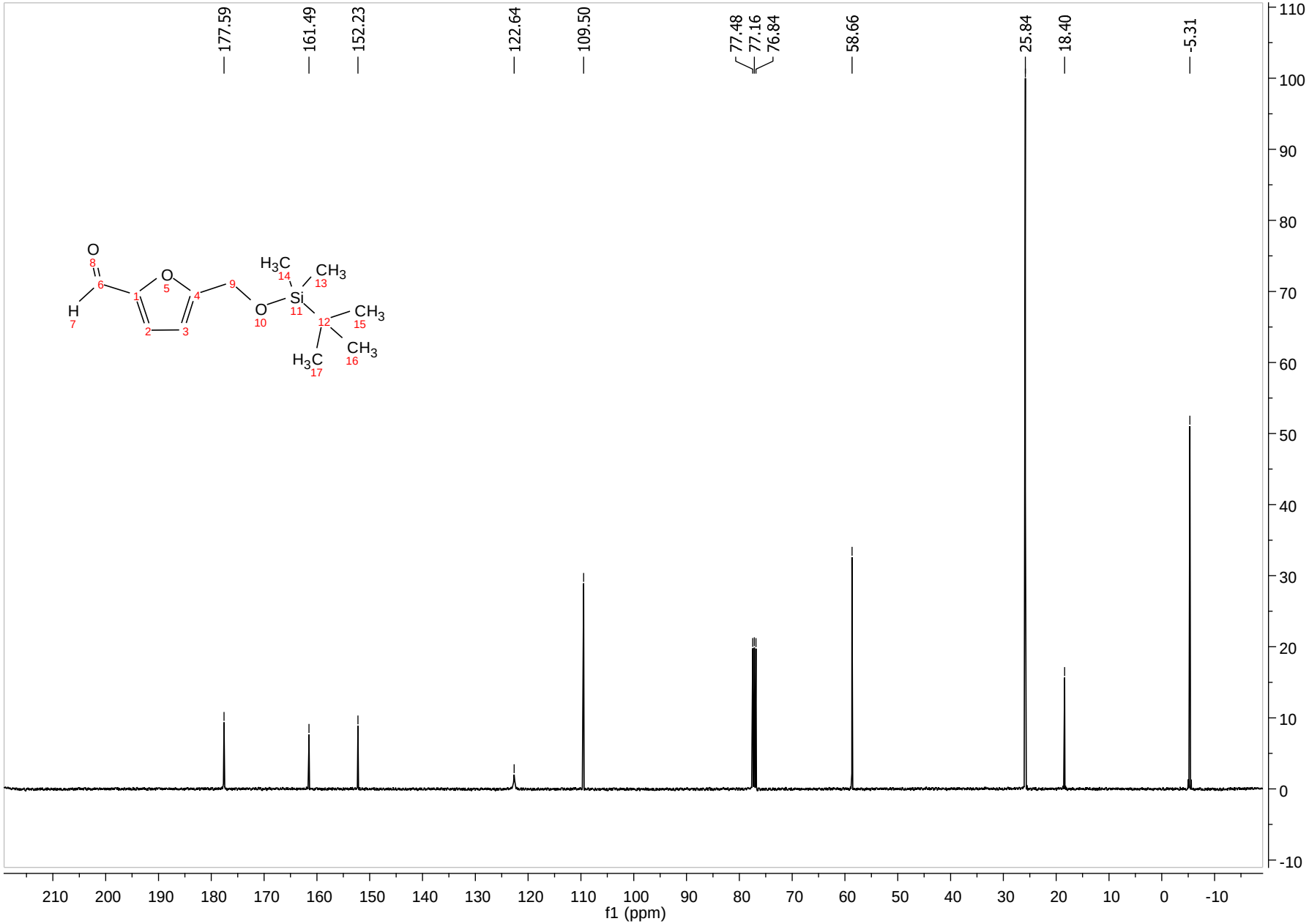


Figure 37. ^{13}C NMR spectrum of 6.

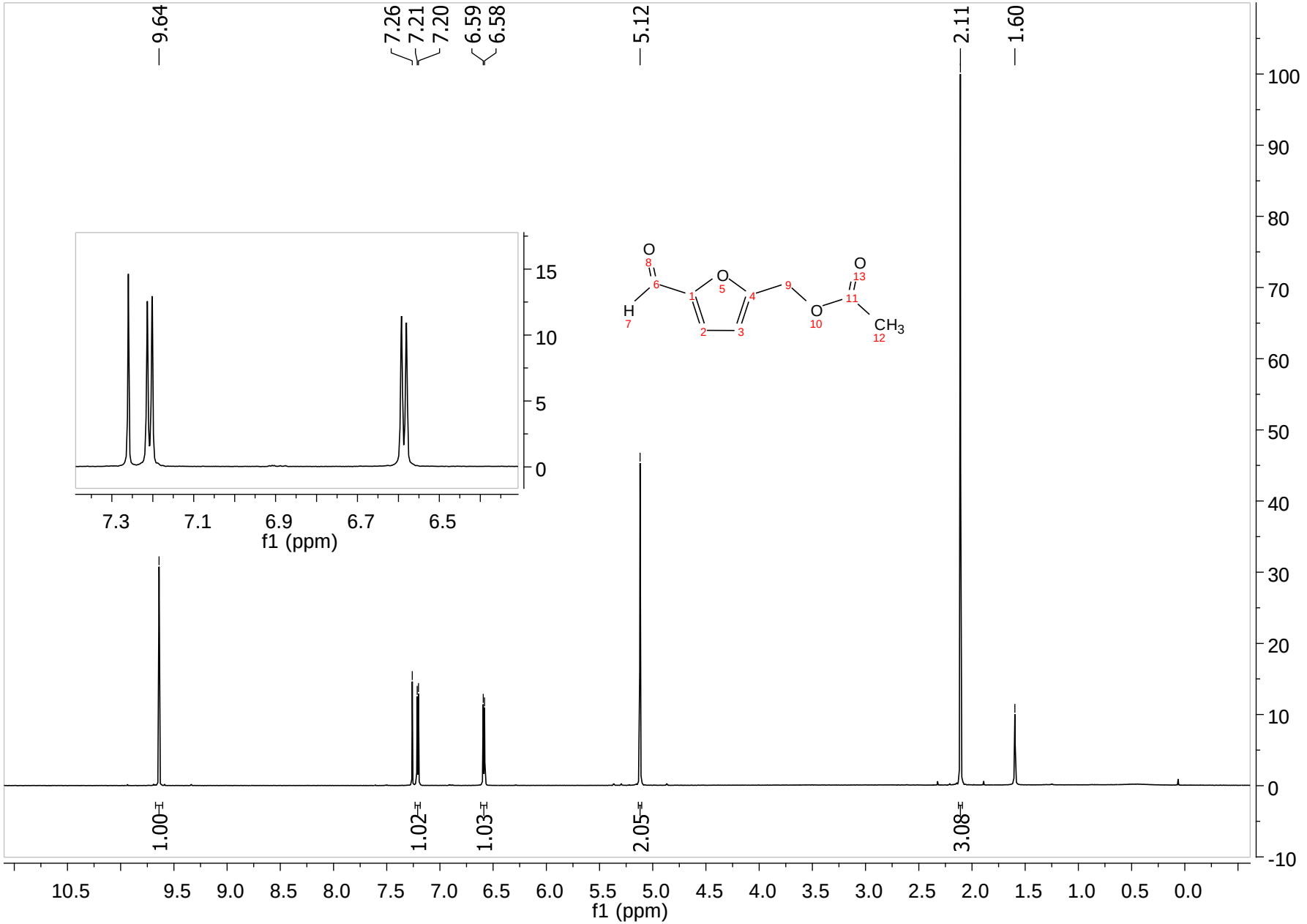


Figure 38. ^{1}H NMR spectrum of 7.

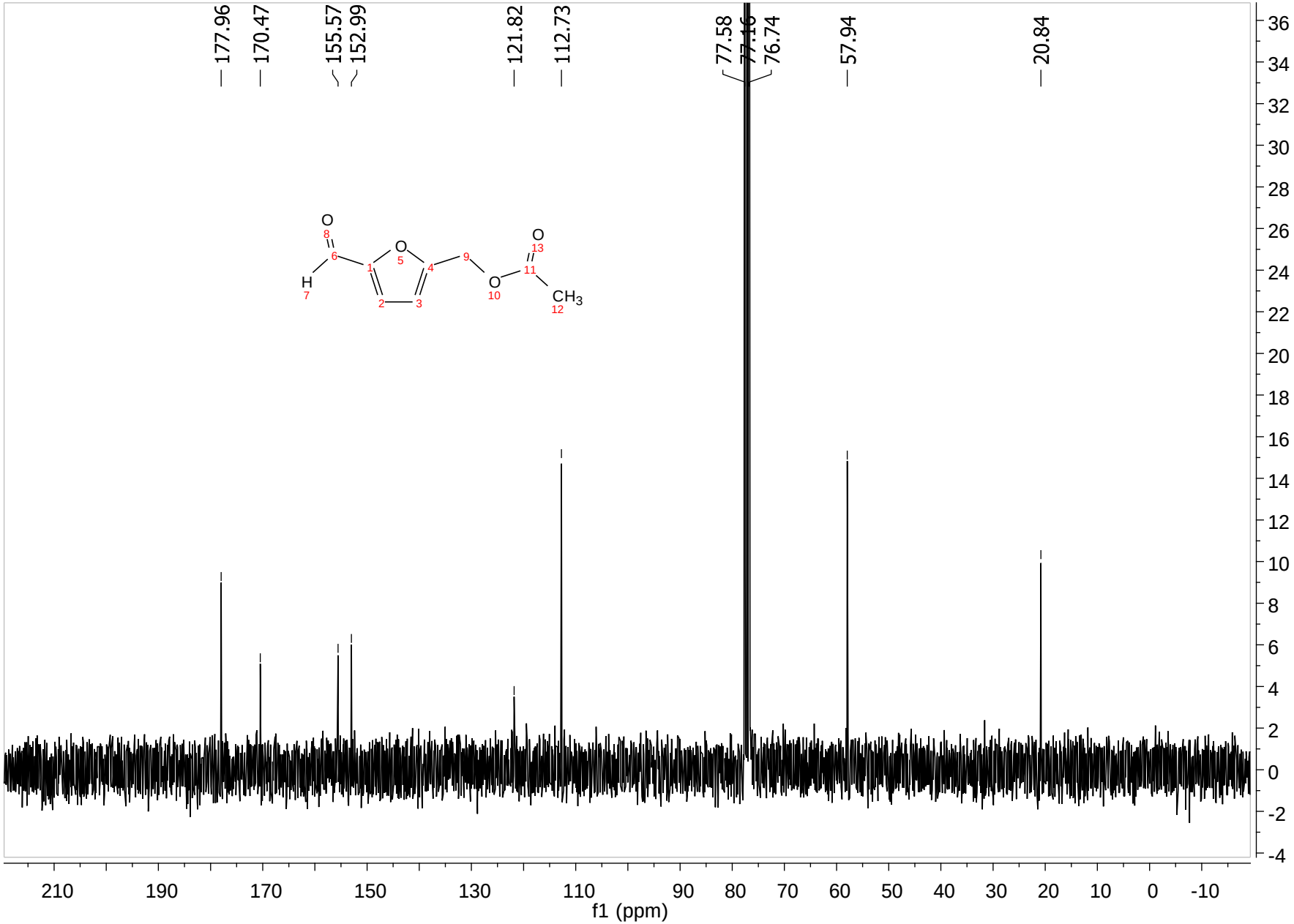


Figure 39. ^{13}C NMR spectrum of 7.

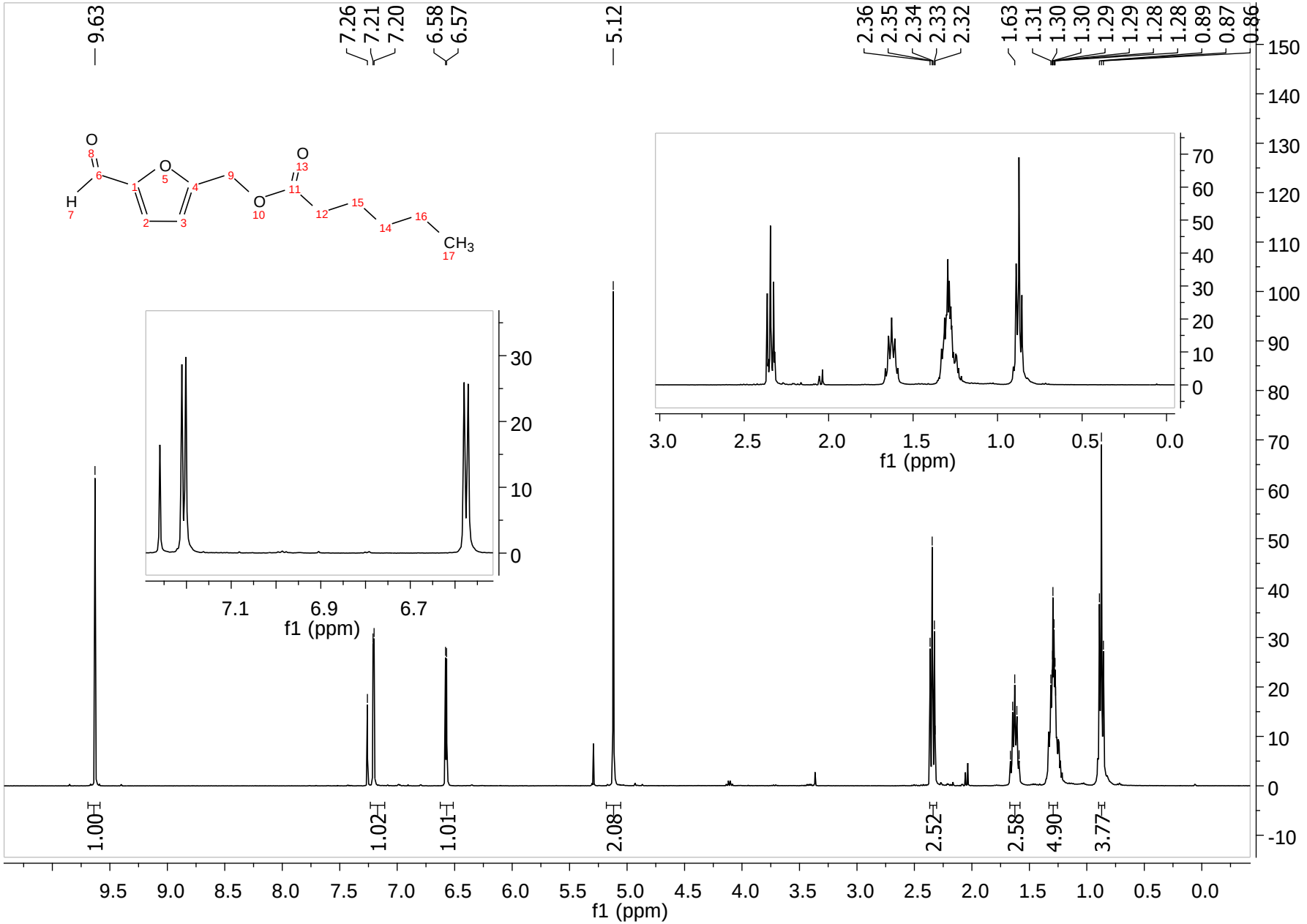


Figure 40. ^{1}H NMR spectrum of 8.

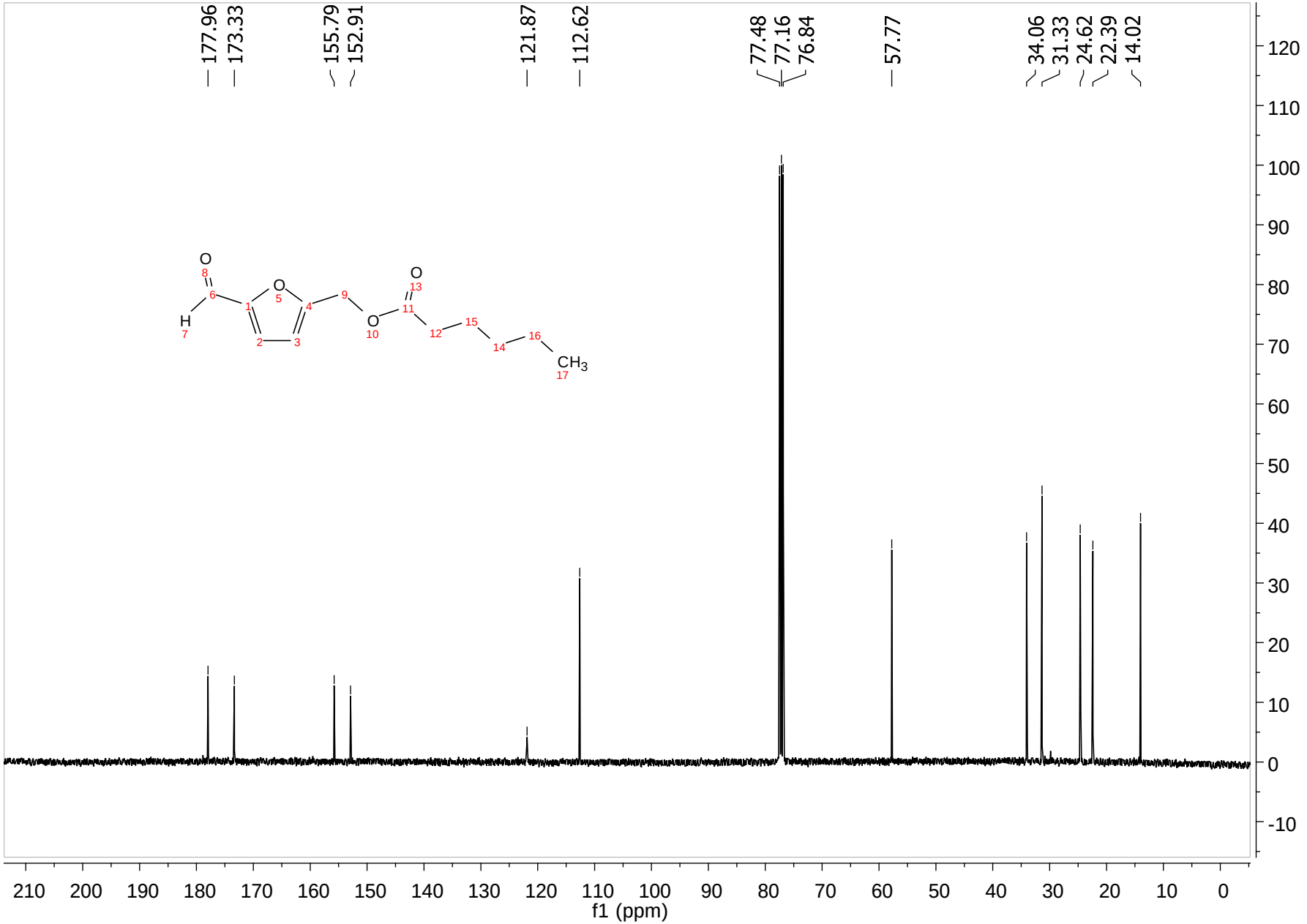


Figure 41. ^{13}C NMR spectrum of 8.

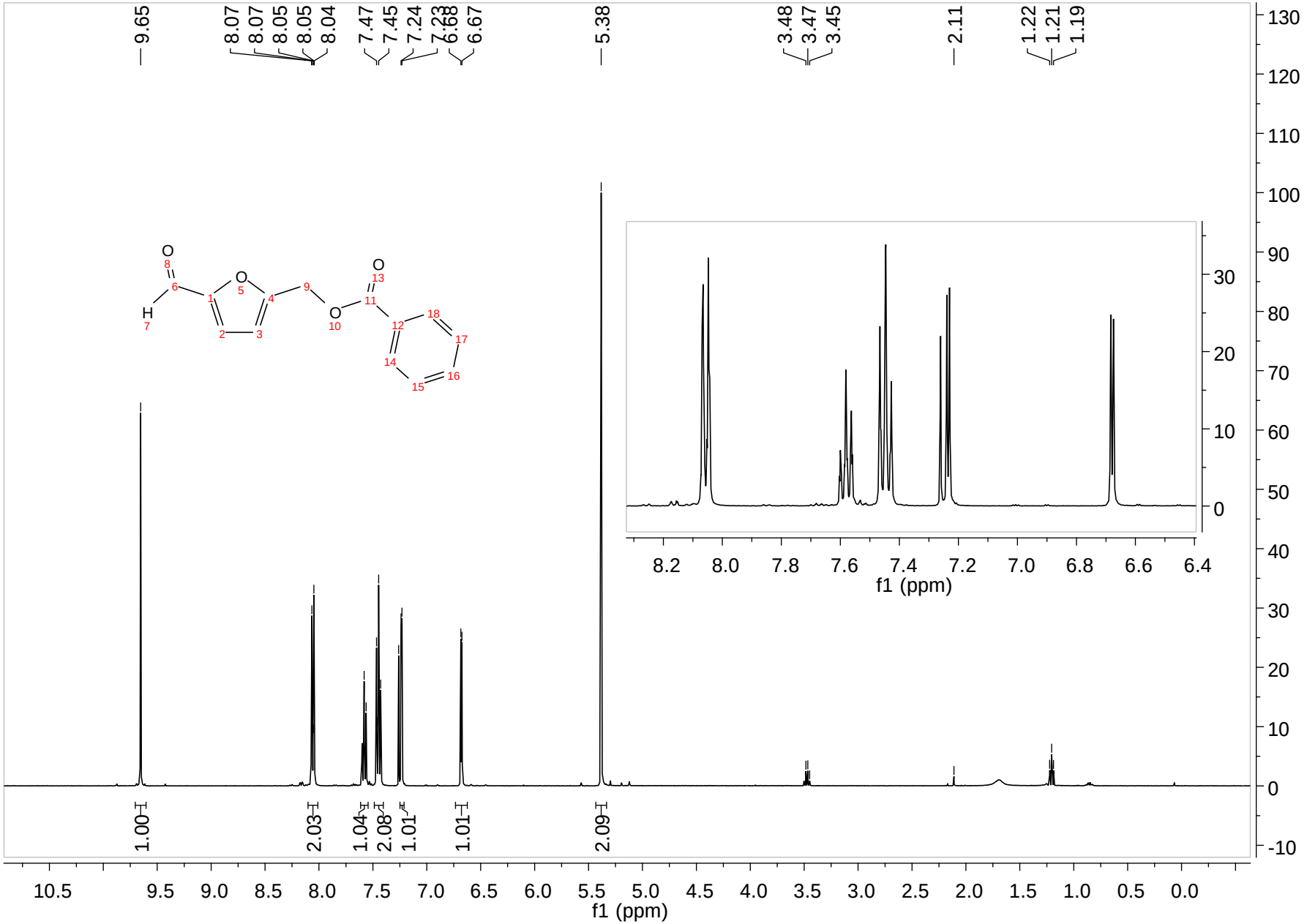


Figure 42. ^{1}H NMR spectrum of 9.

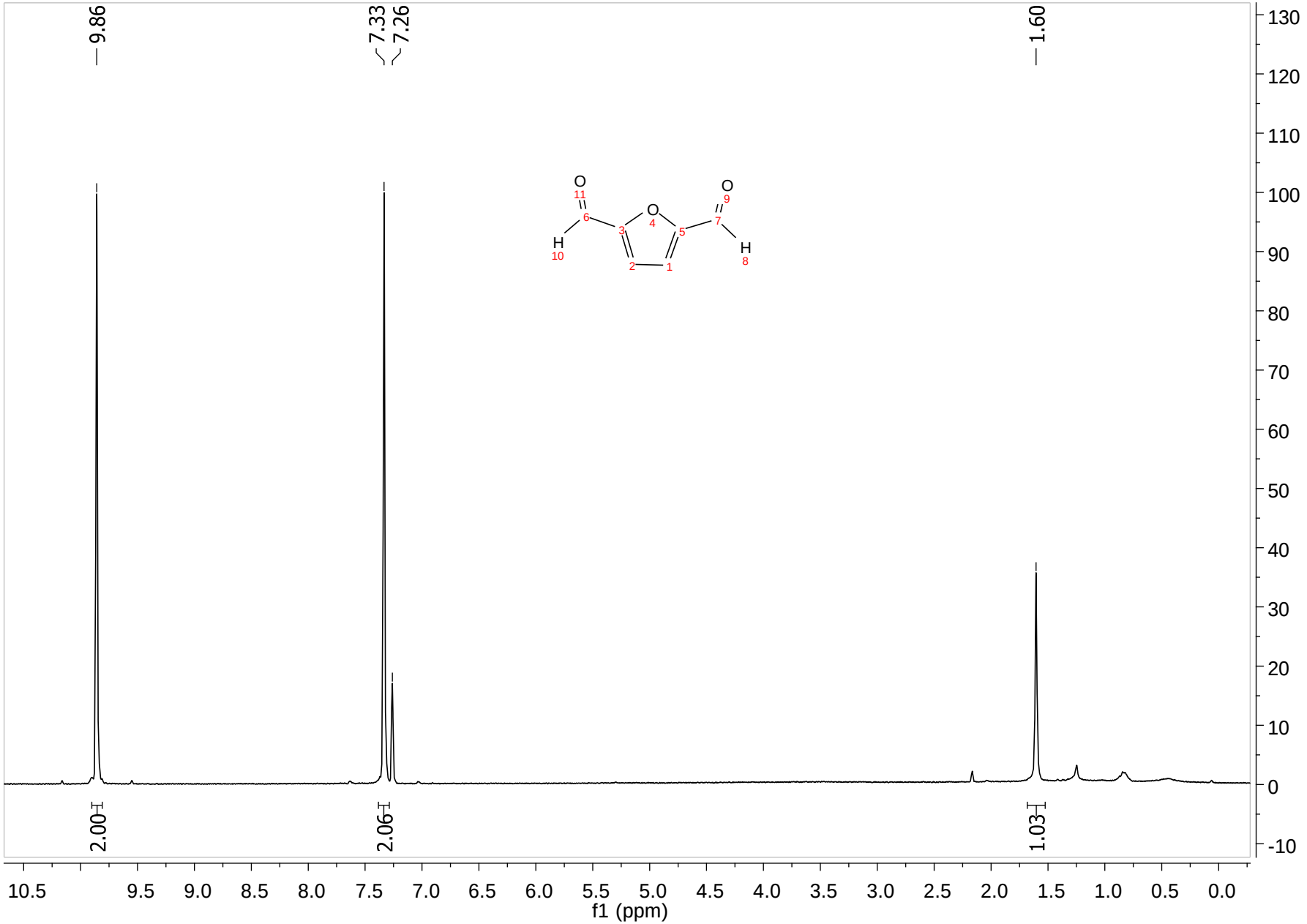


Figure 43. ^{1}H NMR spectrum of 10.

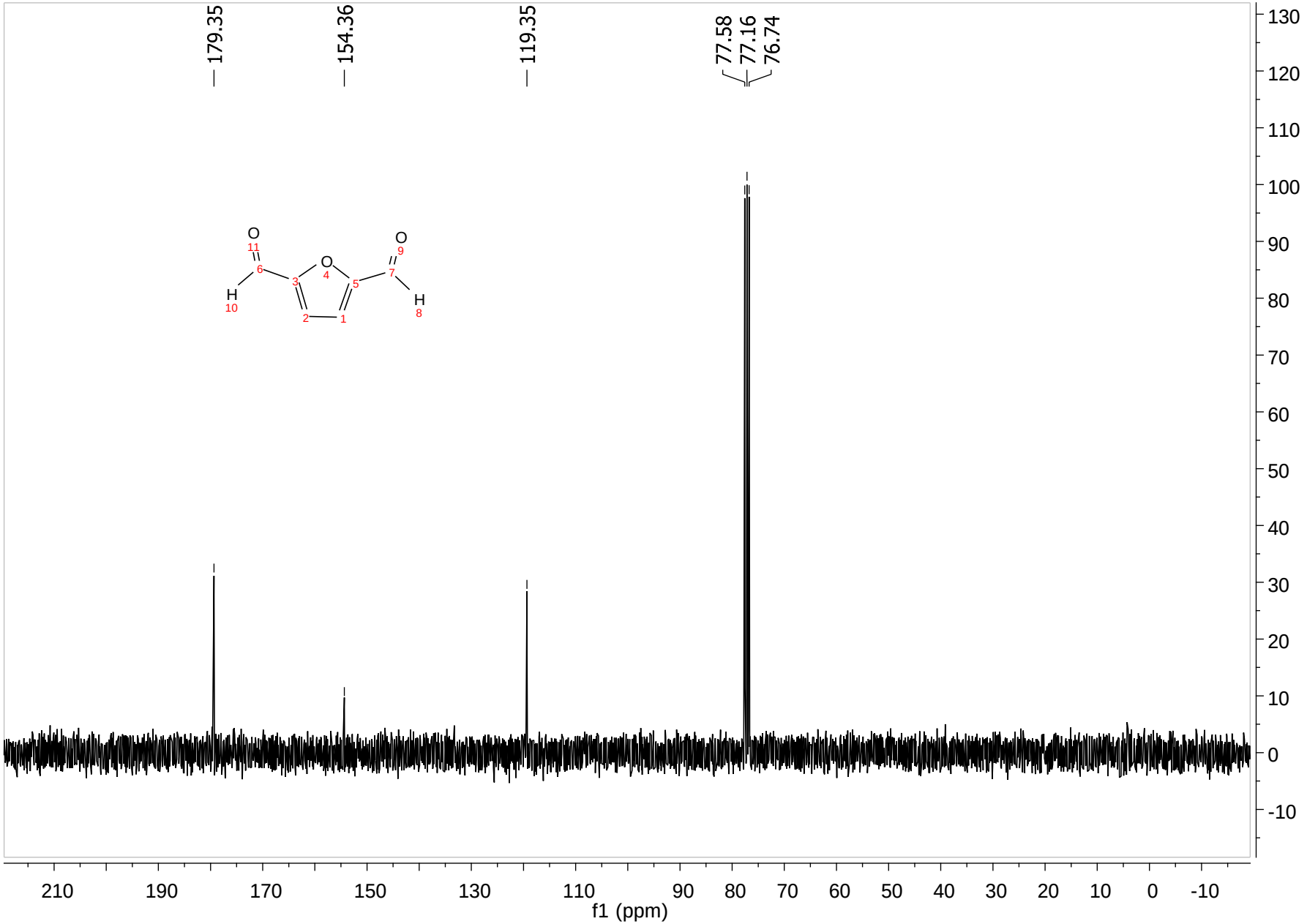


Figure 44. ^{13}C NMR spectrum of 10.

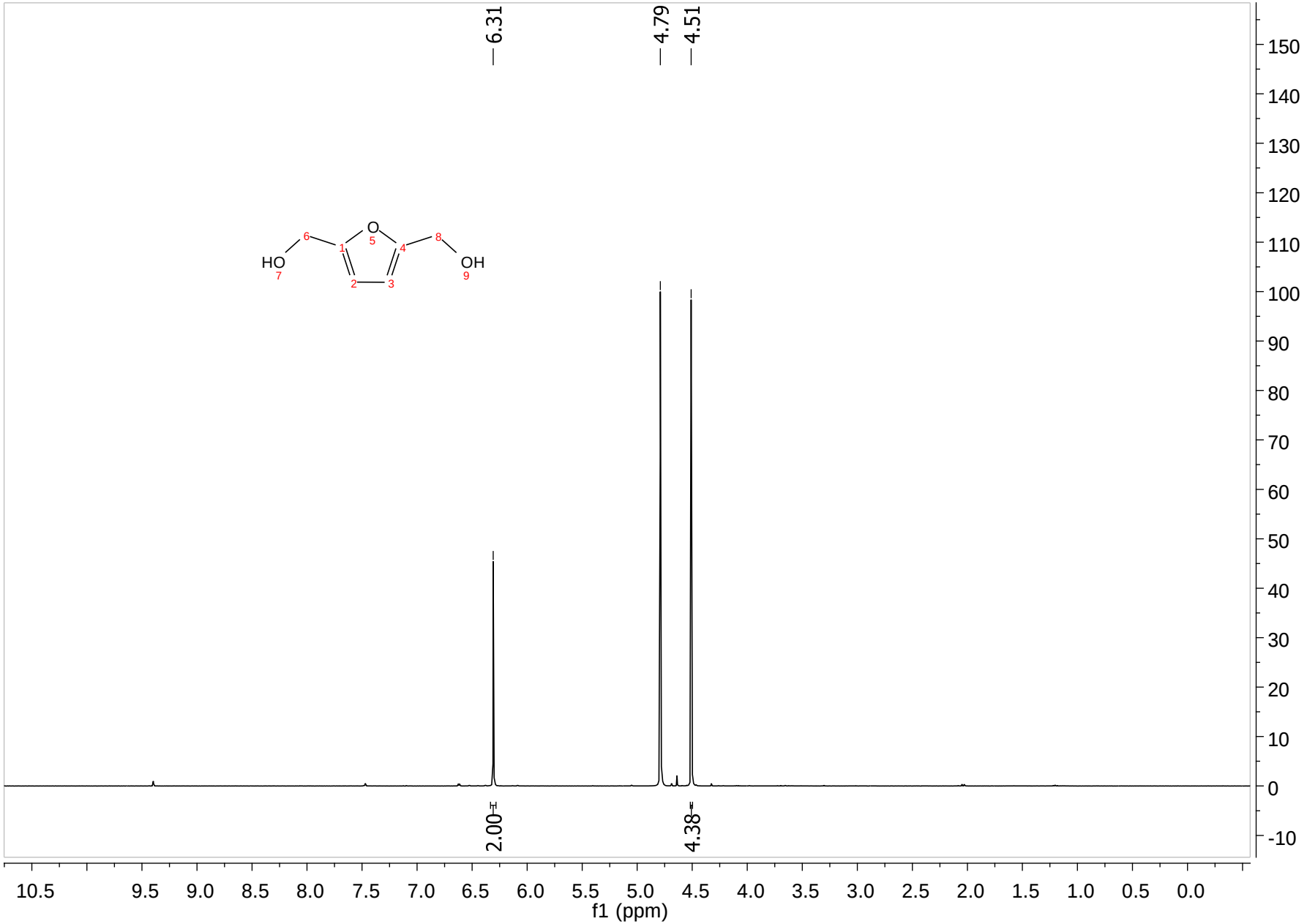


Figure 45. ^{1}H NMR spectrum of 12.

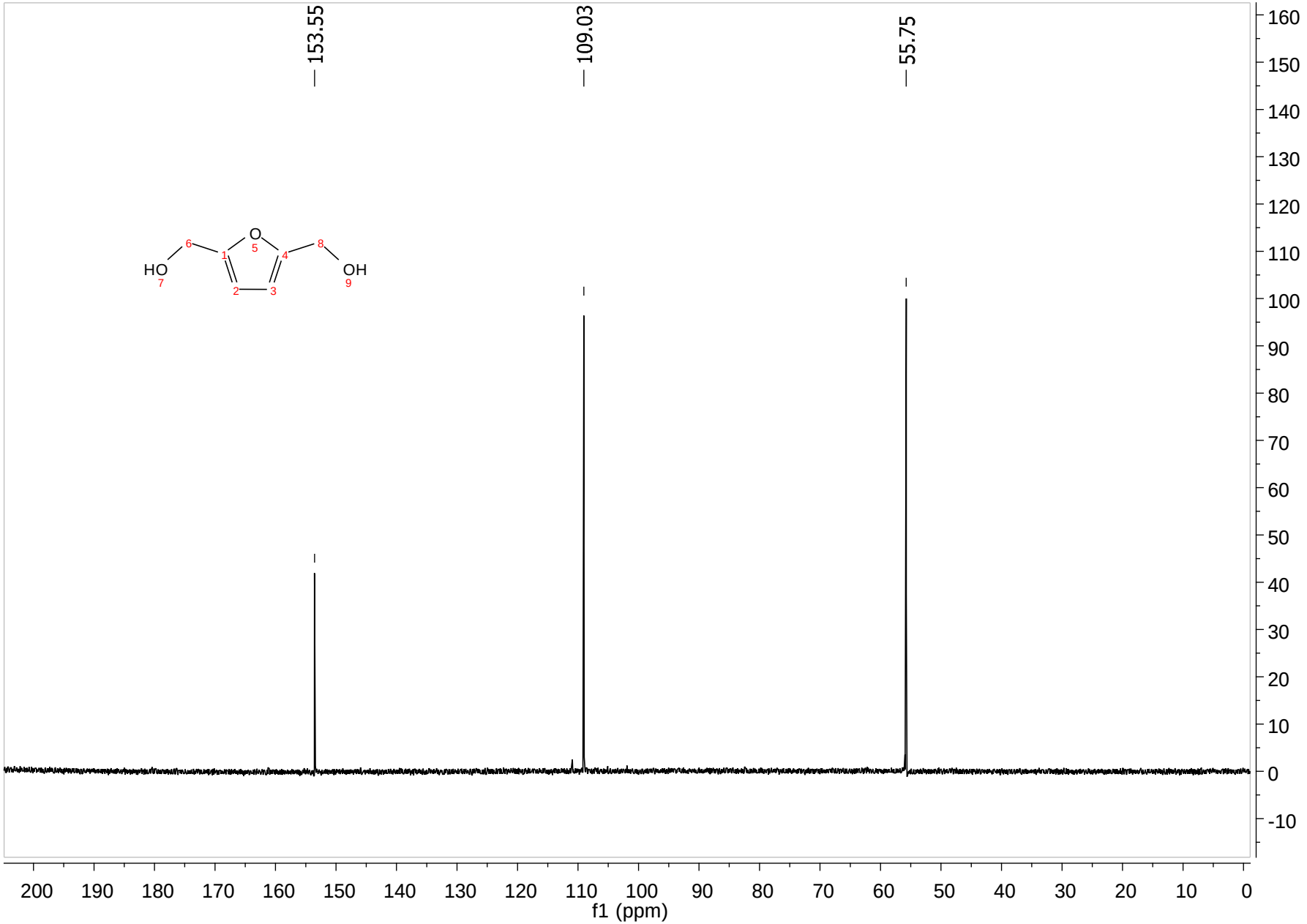


Figure 46. ^{13}C NMR spectrum of 12.

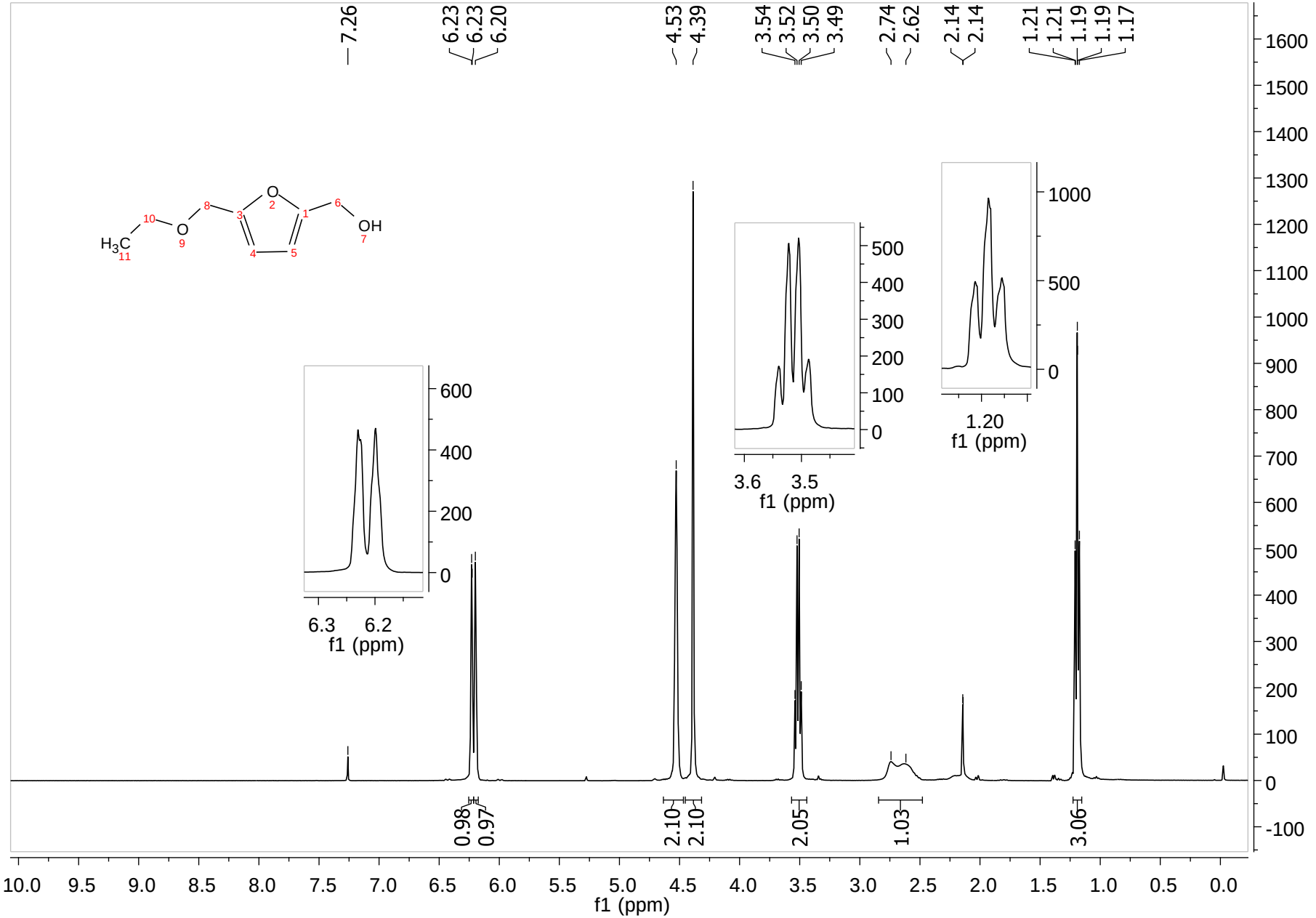


Figure 47. ^{1}H NMR spectrum of 13.

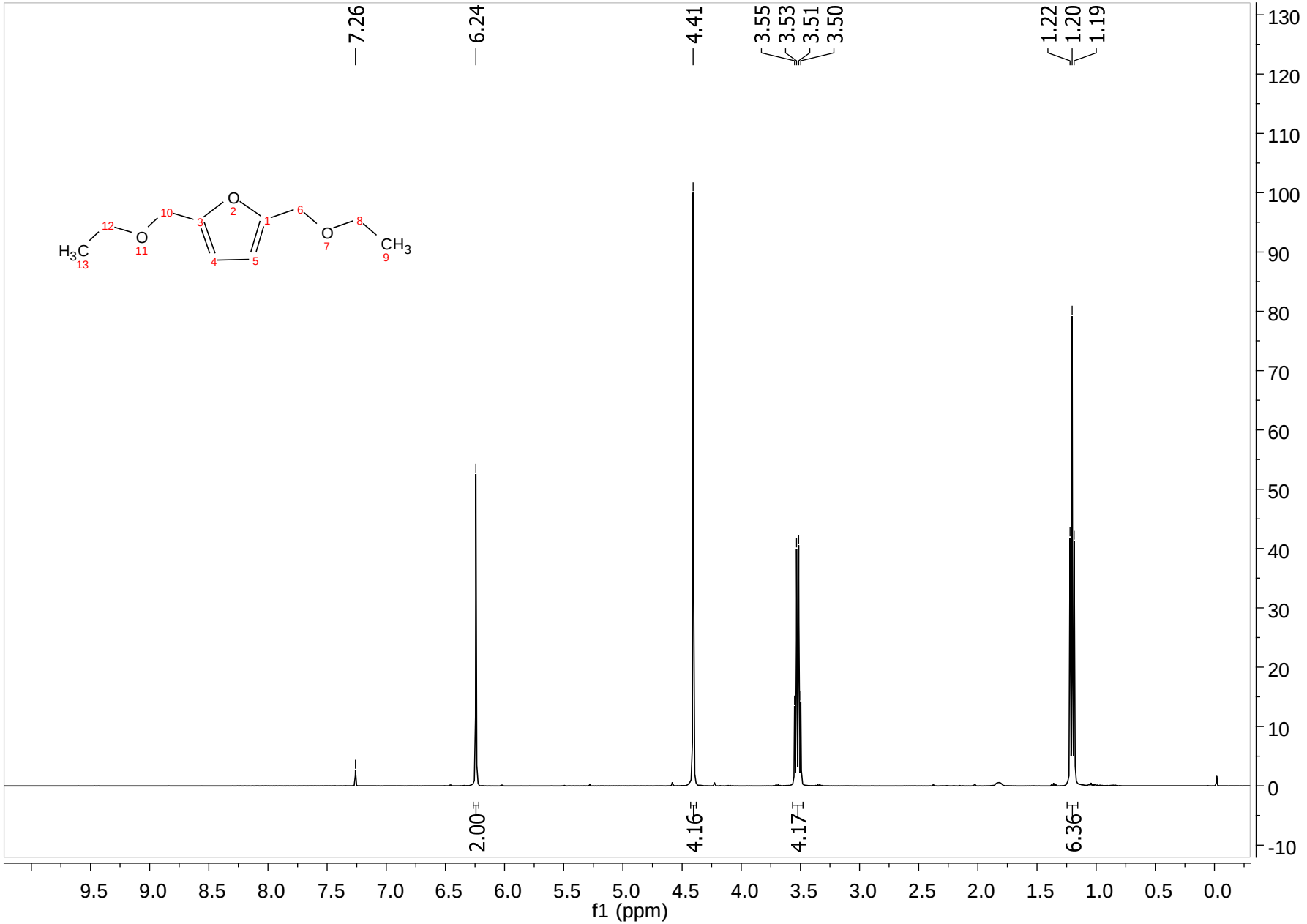


Figure 48. ^{1}H NMR spectrum of 16.

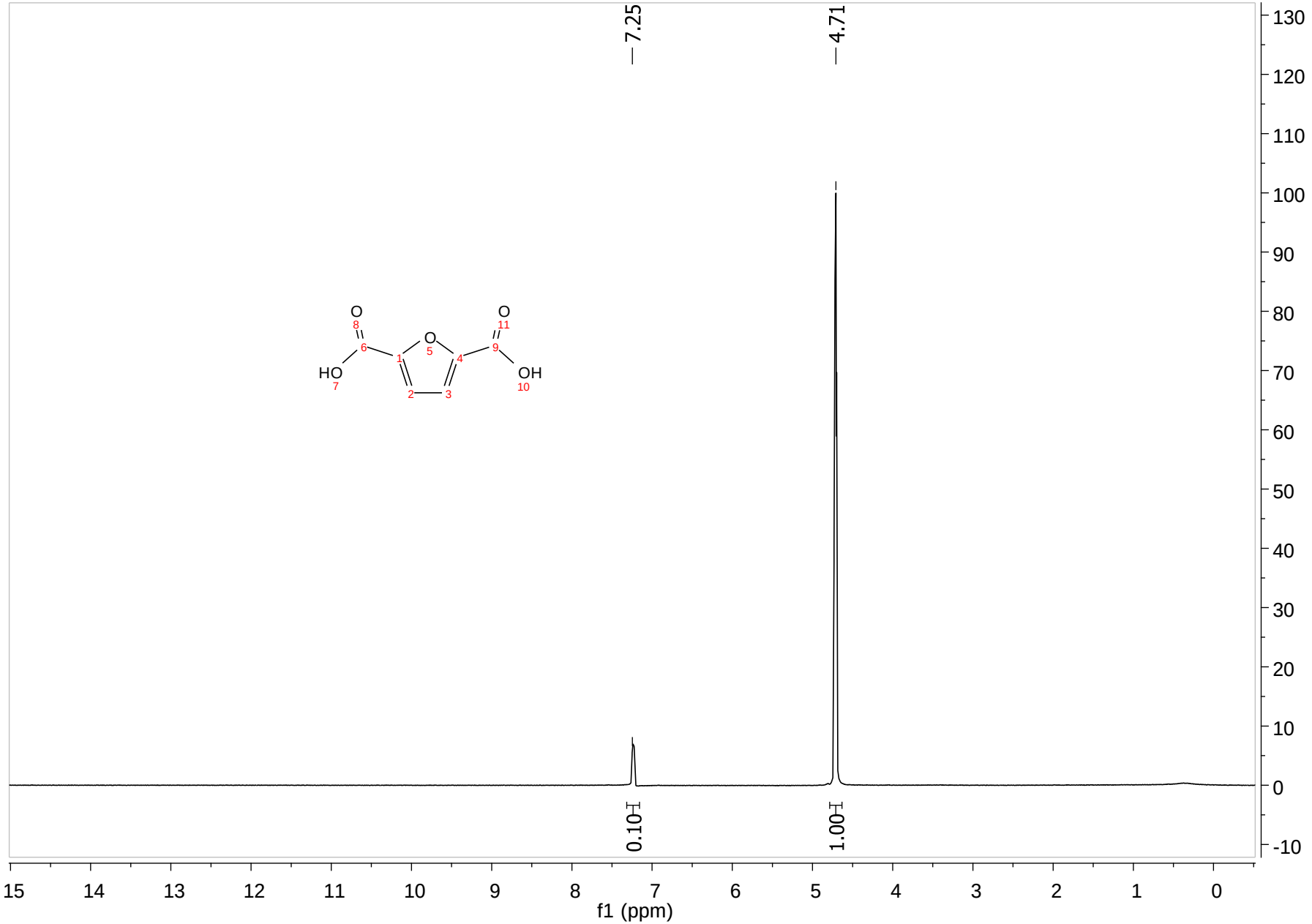


Figure 49. ^{1}H NMR spectrum of 17.

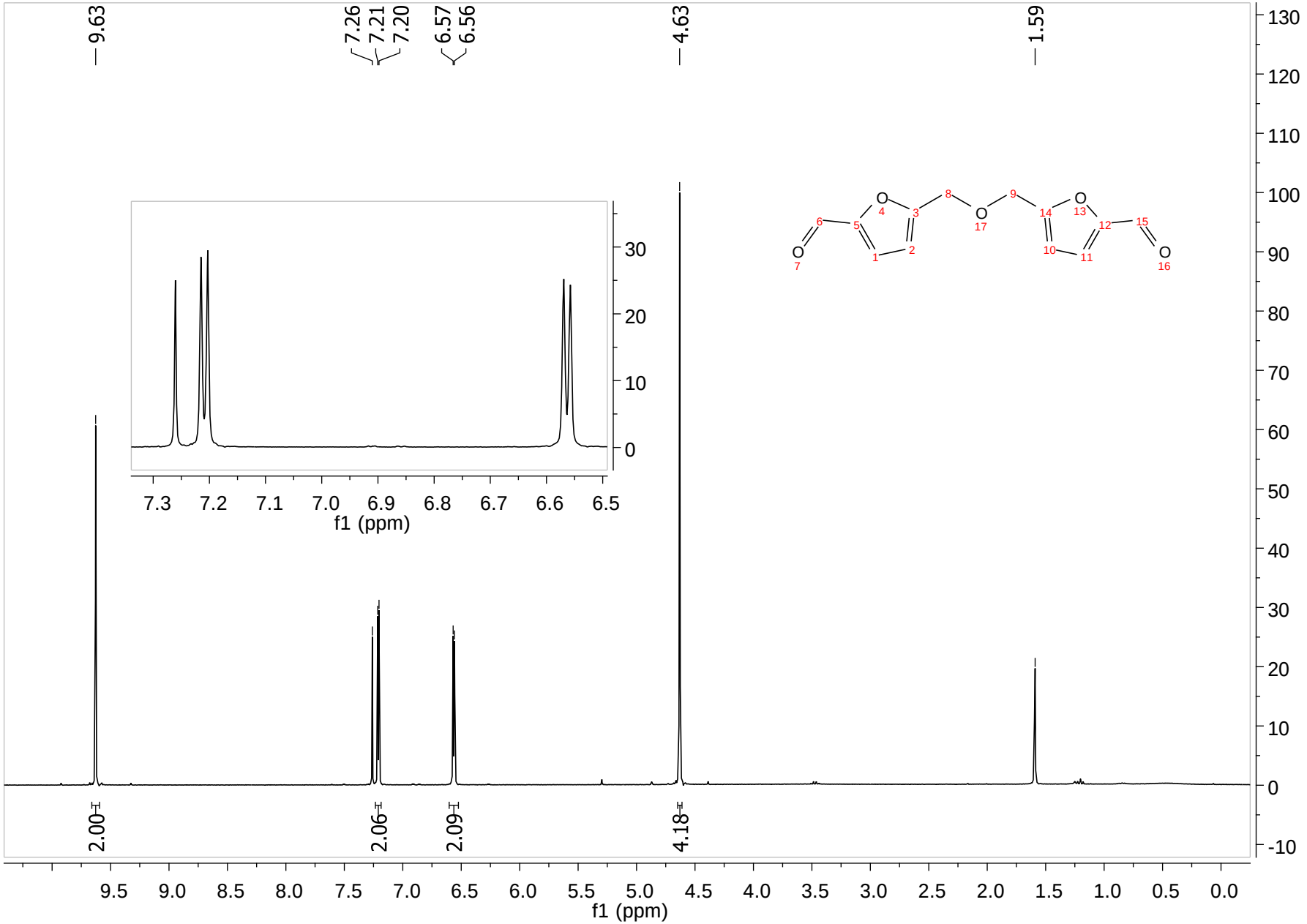


Figure 50. ^{1}H NMR spectrum of 20.

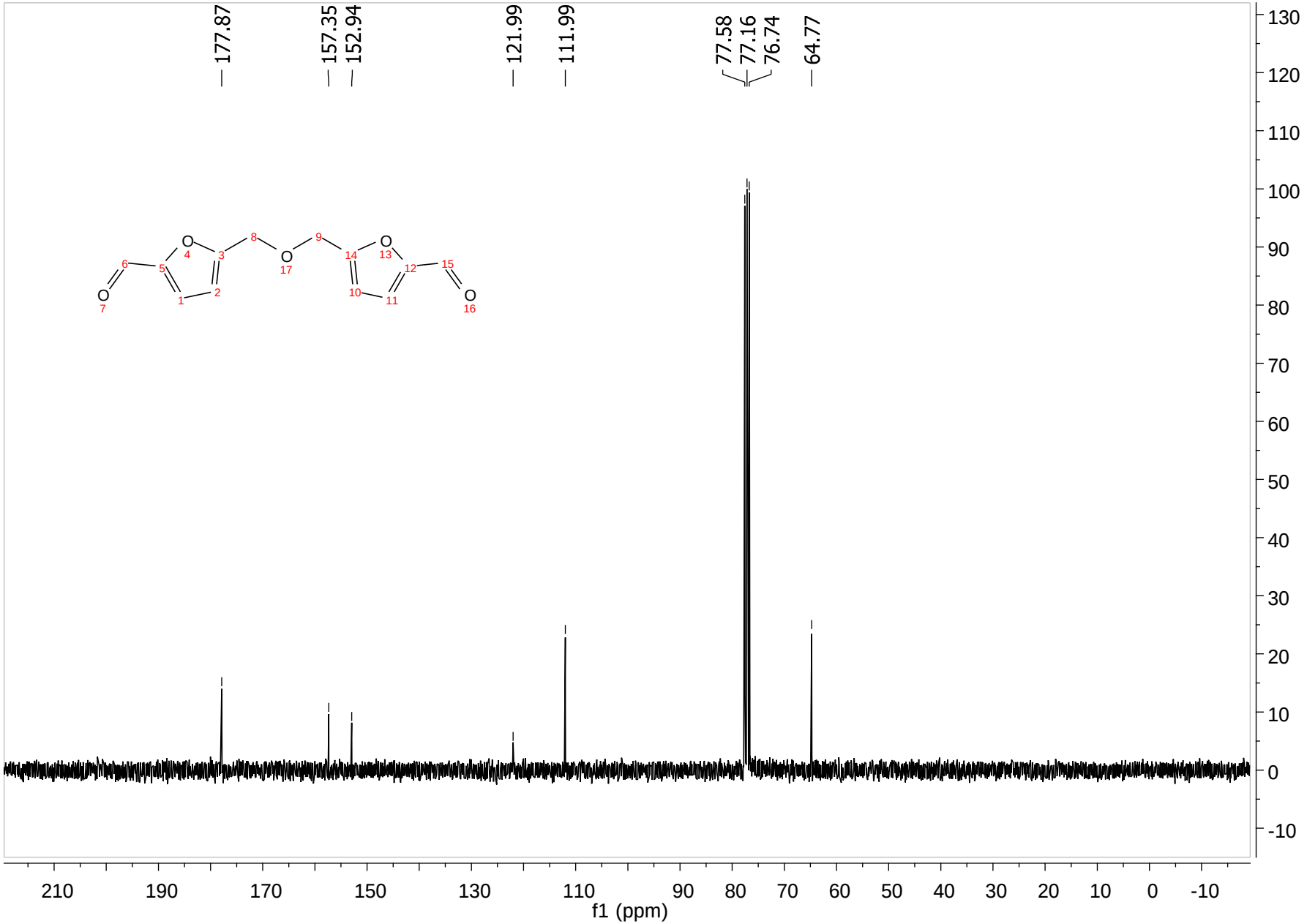


Figure 51. ^{13}C NMR spectrum of 20.

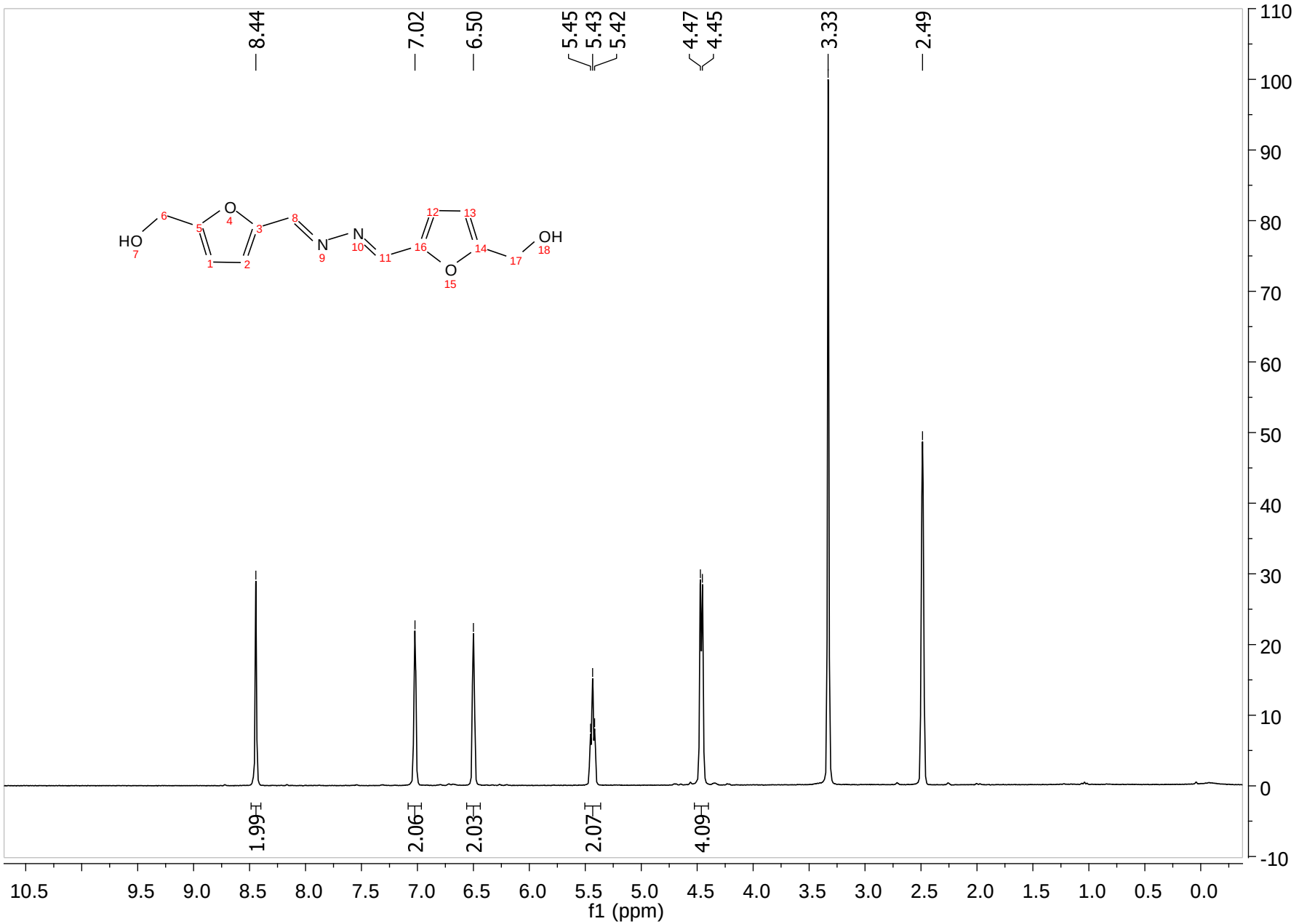


Figure 52. ^{1}H NMR spectrum of 21.

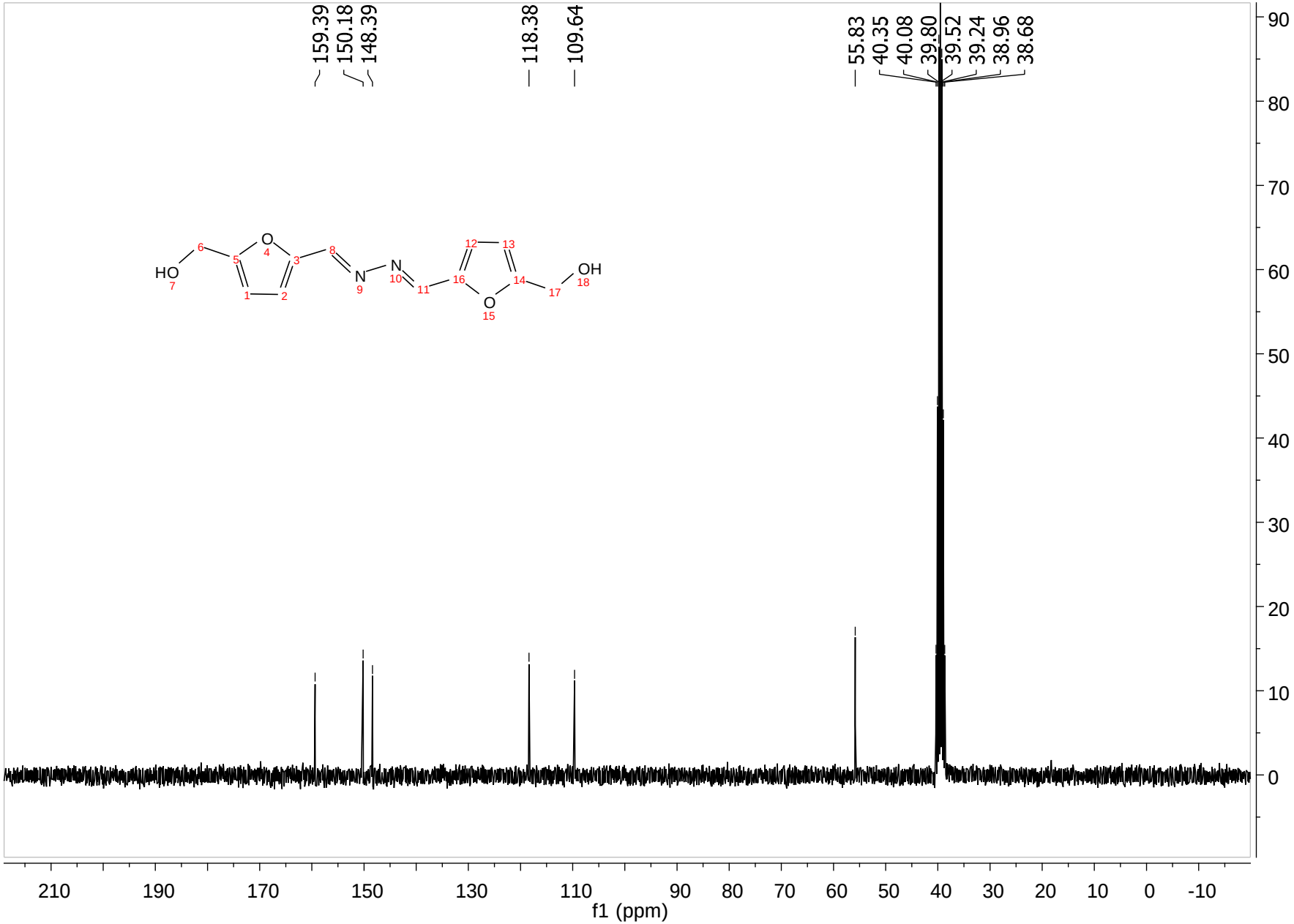
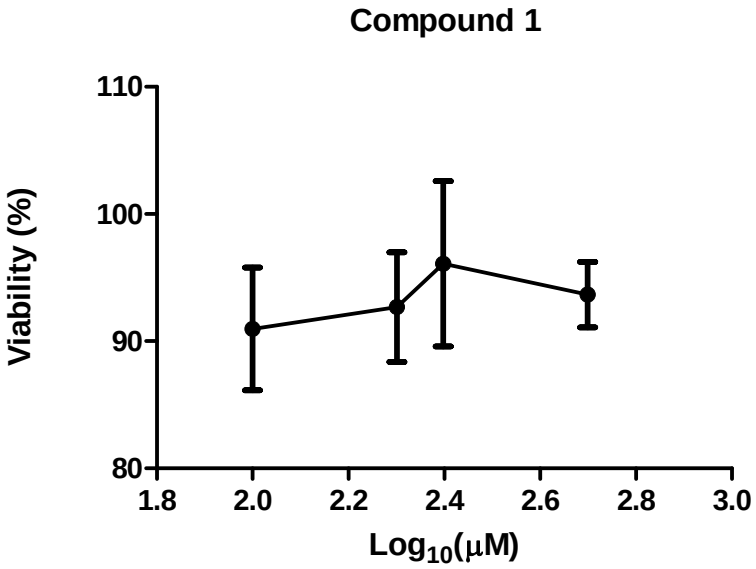
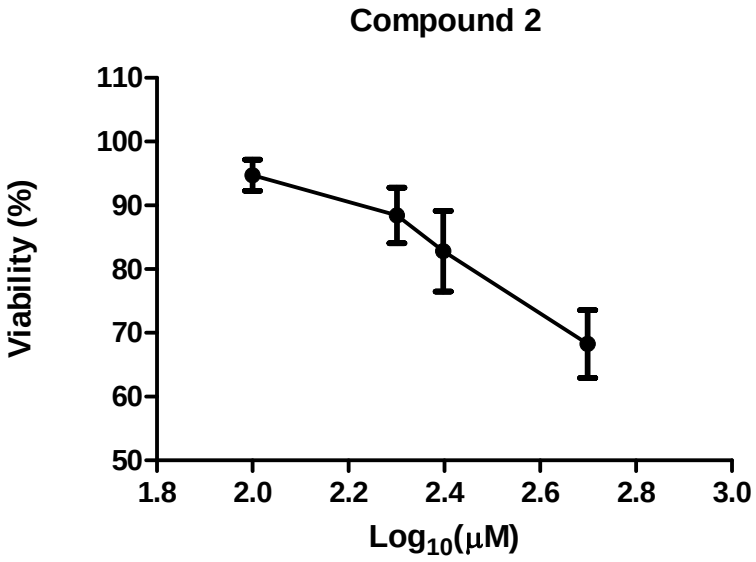
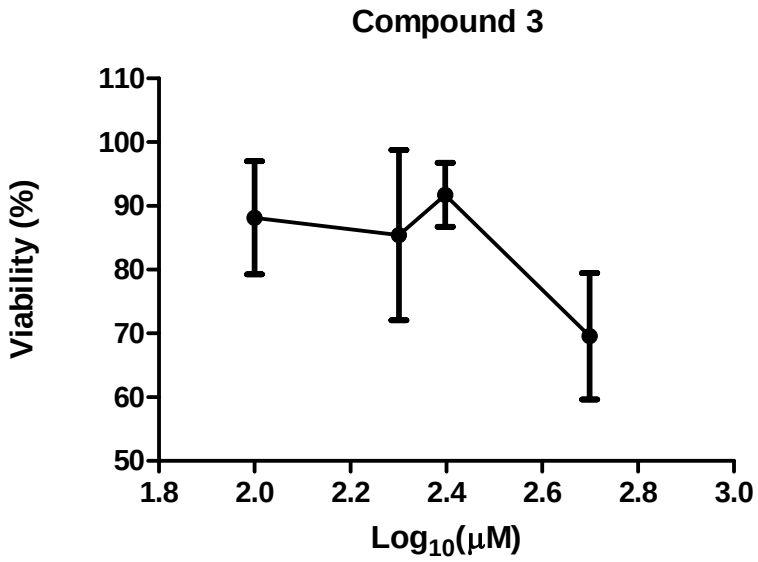


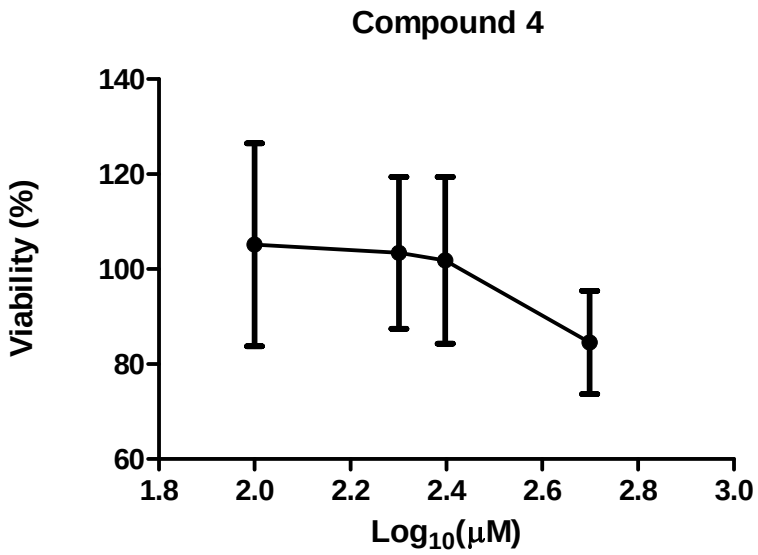
Figure 53. ^{13}C NMR spectrum of 21.

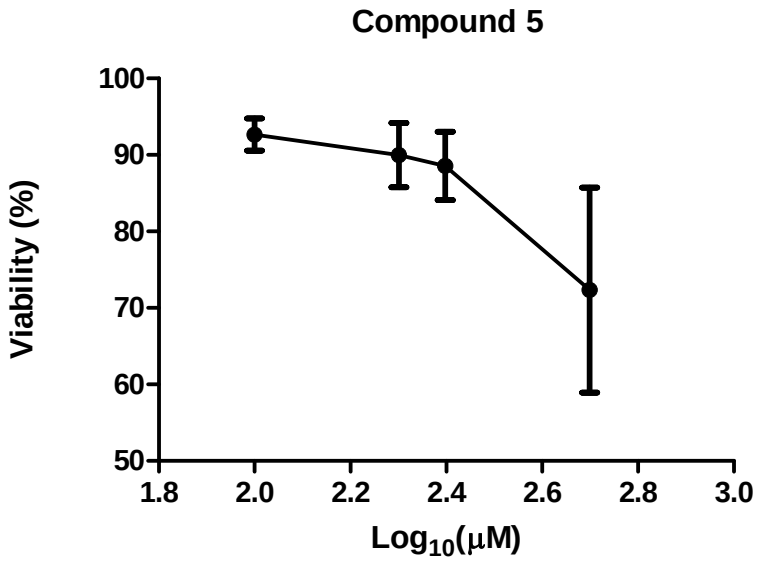
Toxicity curves

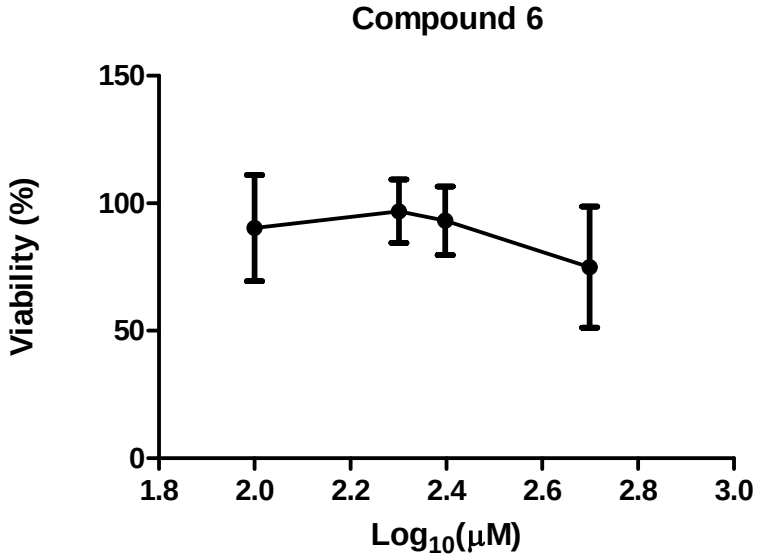


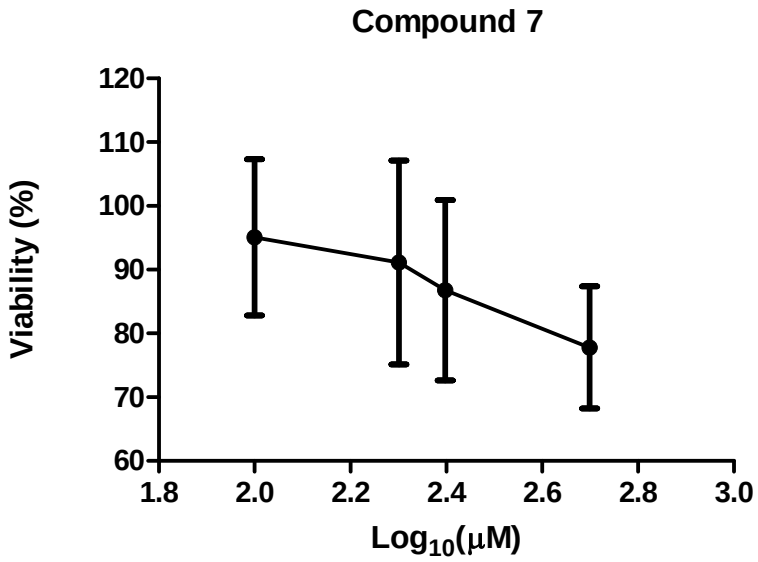


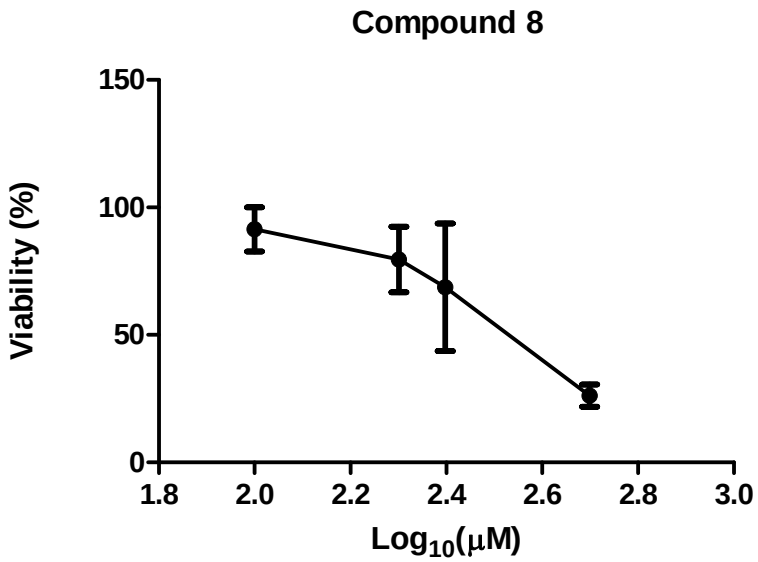

Compound 3
Viability (%)
110
100
90
80
70
60
50
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

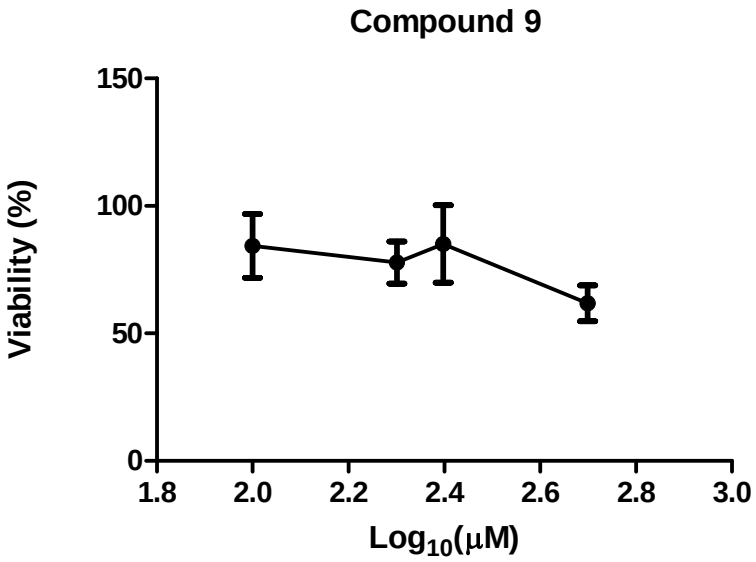

Compound 4
Viability (%)
140
120
100
80
60
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

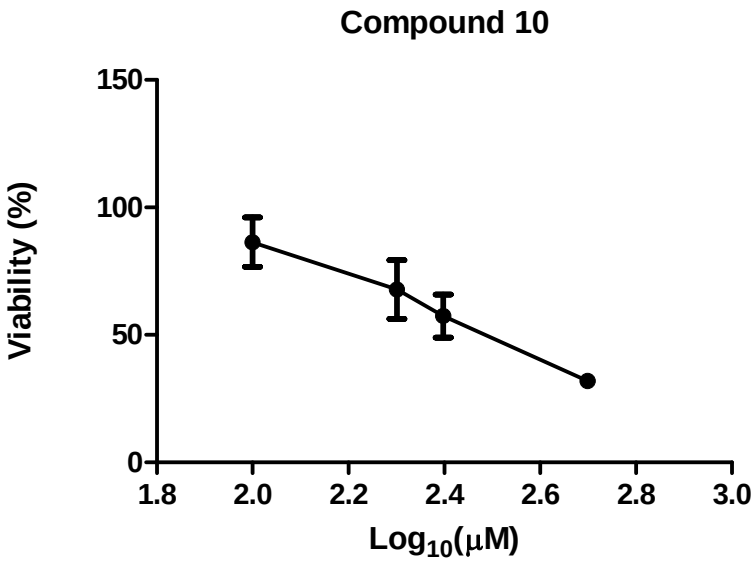

Compound 5
Viability (%)
100
90
80
70
60
50
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

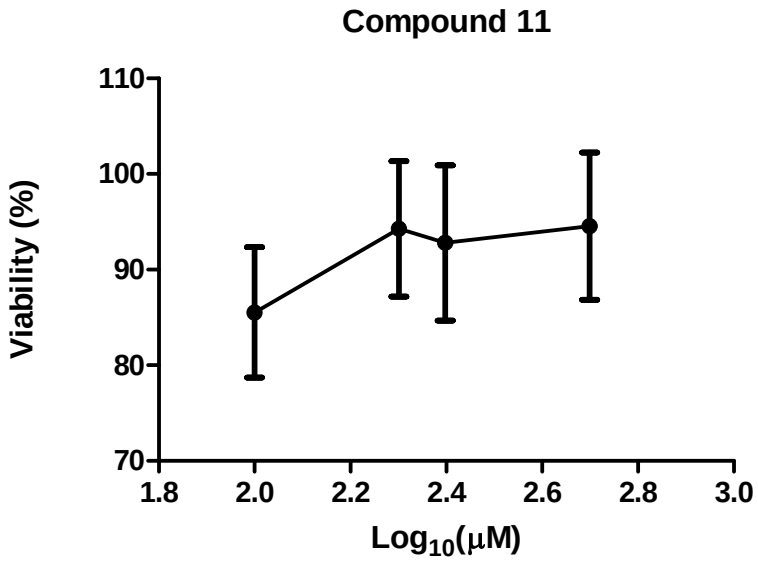

Compound 6
Viability (%)
150
100
50
0
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

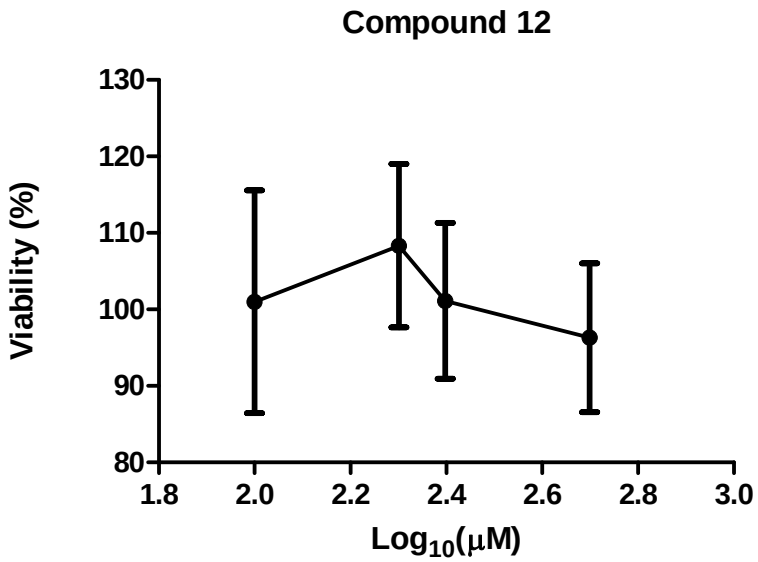

Compound 7
Viability (%)
120
110
100
90
80
70
60
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

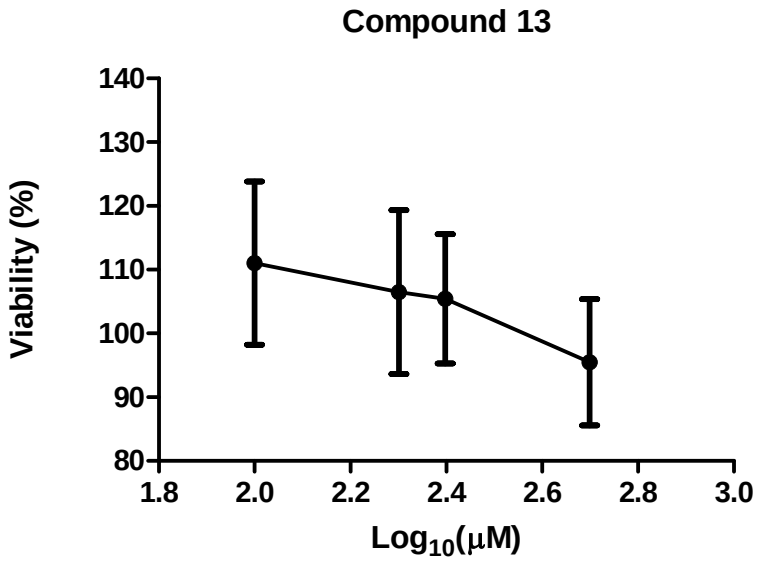

Compound 8
Viability (%)
150
100
50
0
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

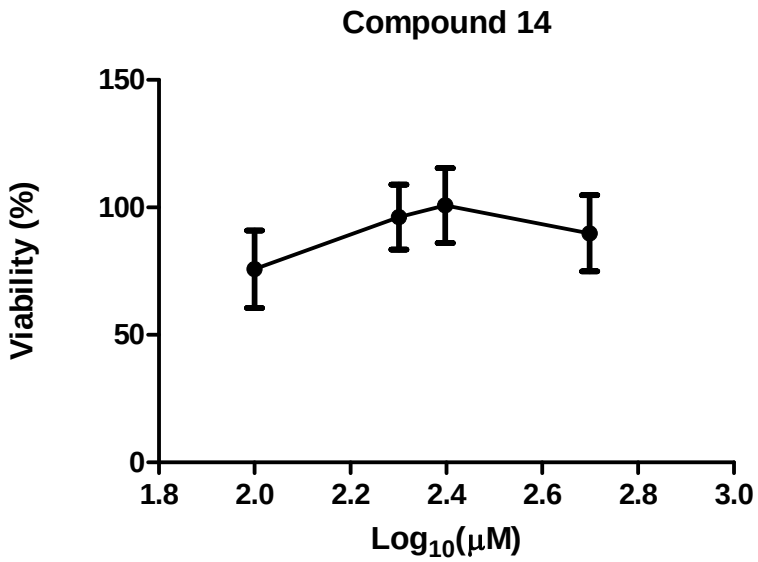

Compound 9
Viability (%)
150
100
50
0
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

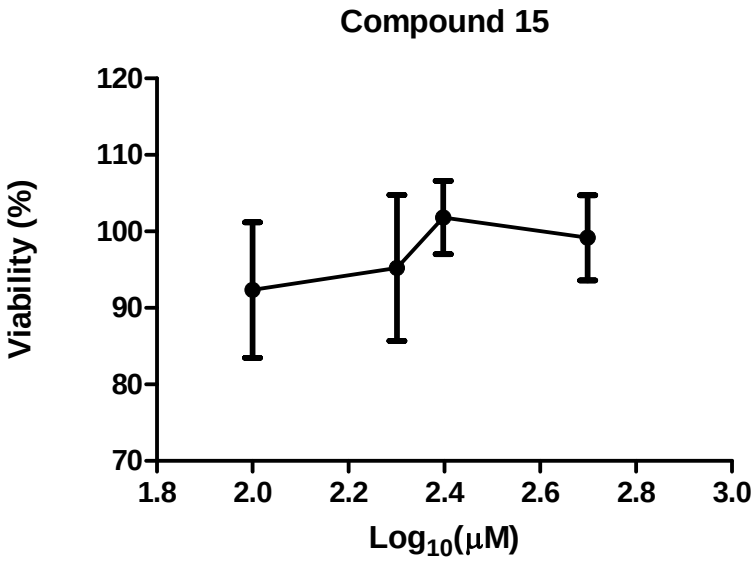

Compound 10
Viability (%)
150
100
50
0
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

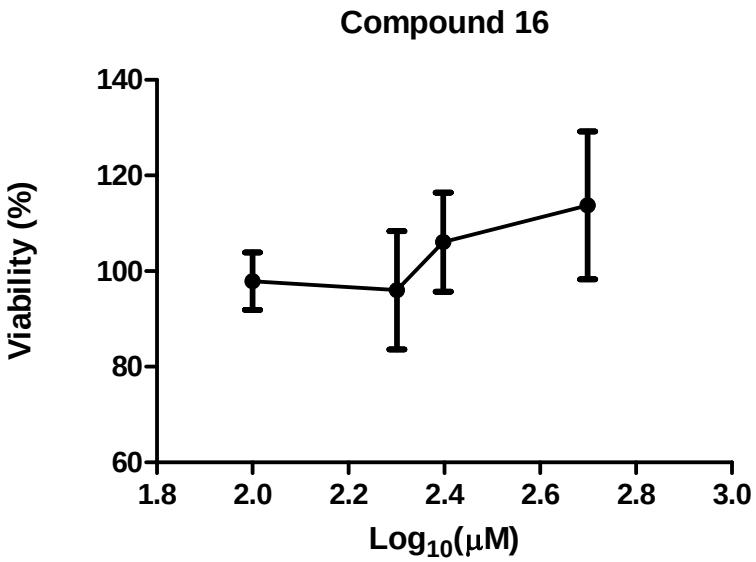

Compound 11
Viability (%)
110
100
90
80
70
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

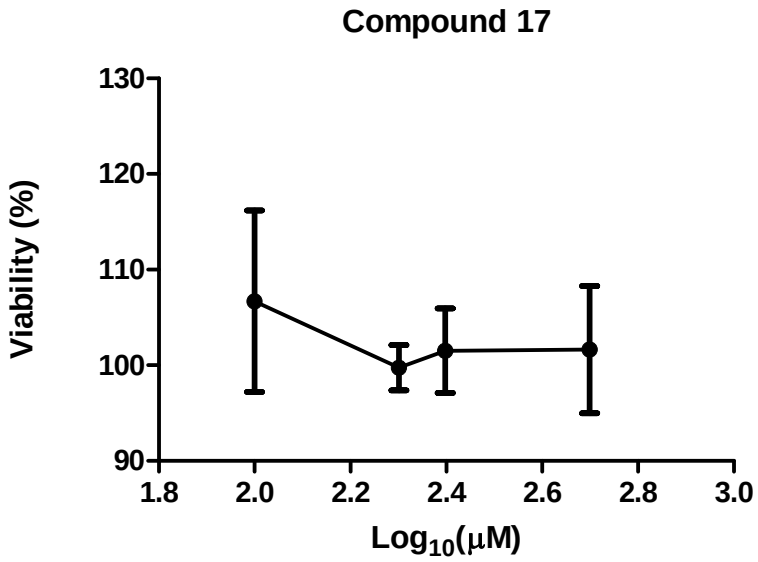

Compound 12
Viability (%)
130
120
110
100
90
80
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

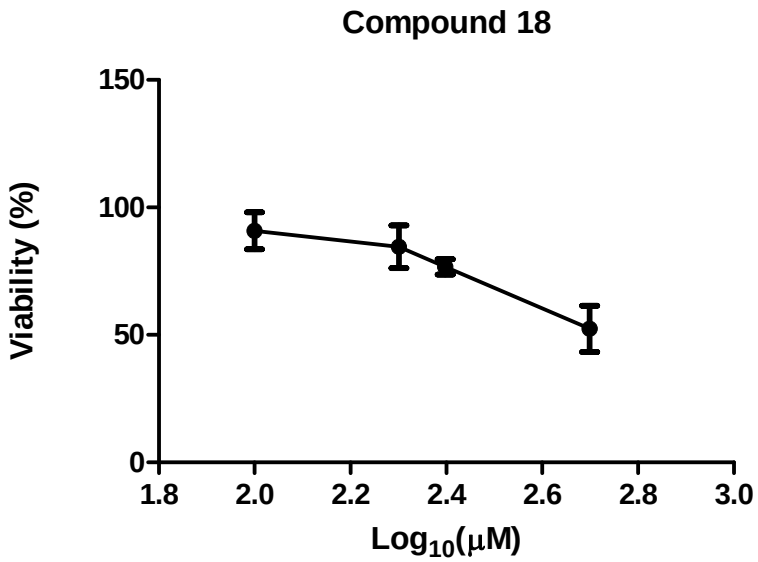

Compound 13
Viability (%)
140
130
120
110
100
90
80
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

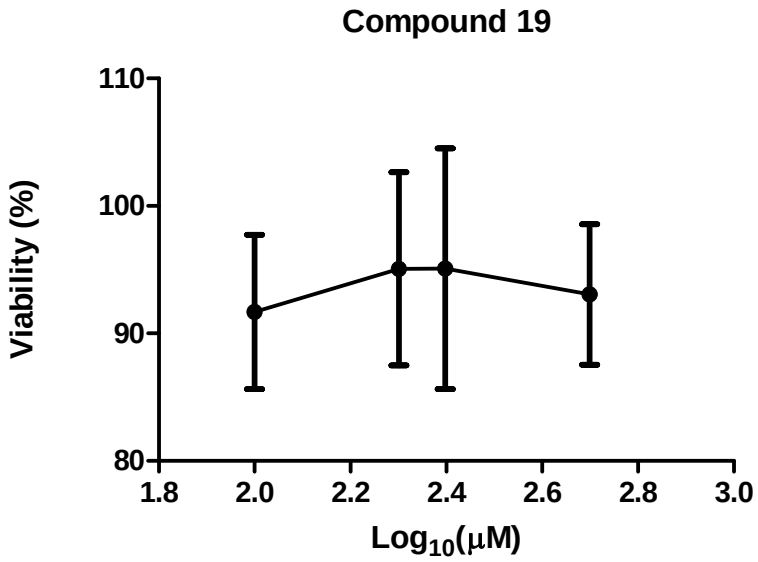

Compound 14
Viability (%)
150
100
50
0
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

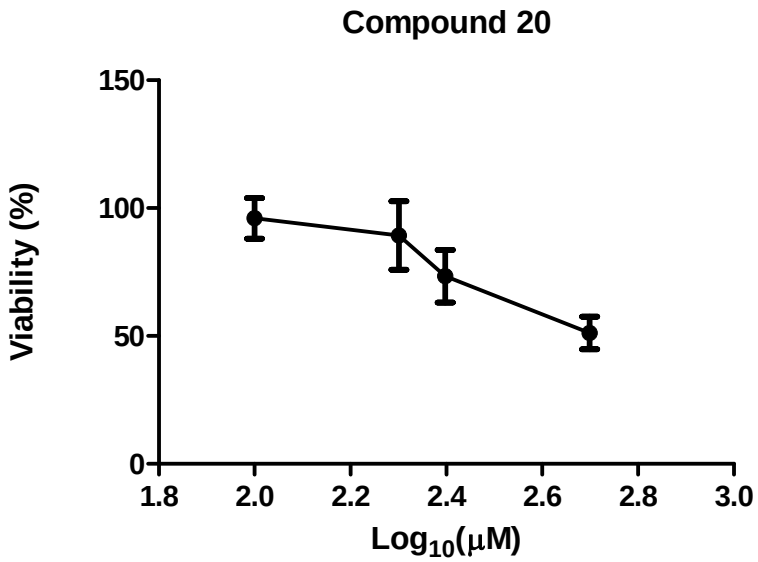

Compound 15
Viability (%)
120
110
100
90
80
70
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

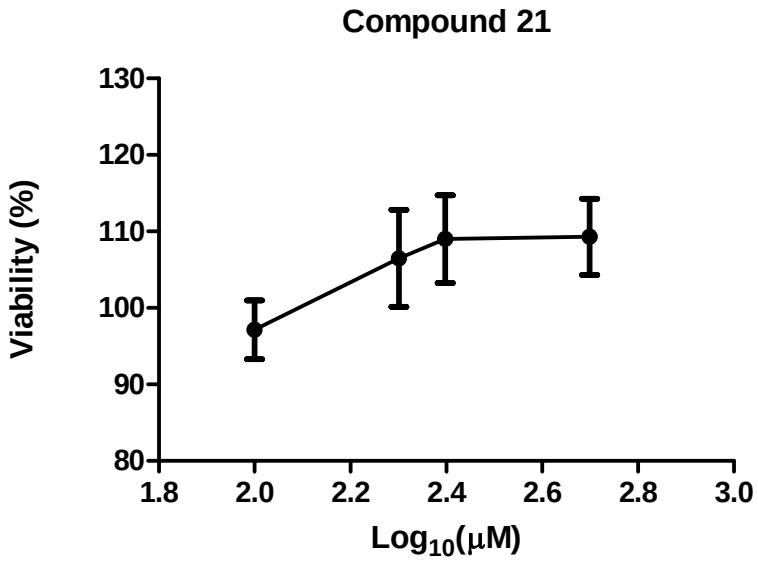

Compound 16
Viability (%)
140
120
100
80
60
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

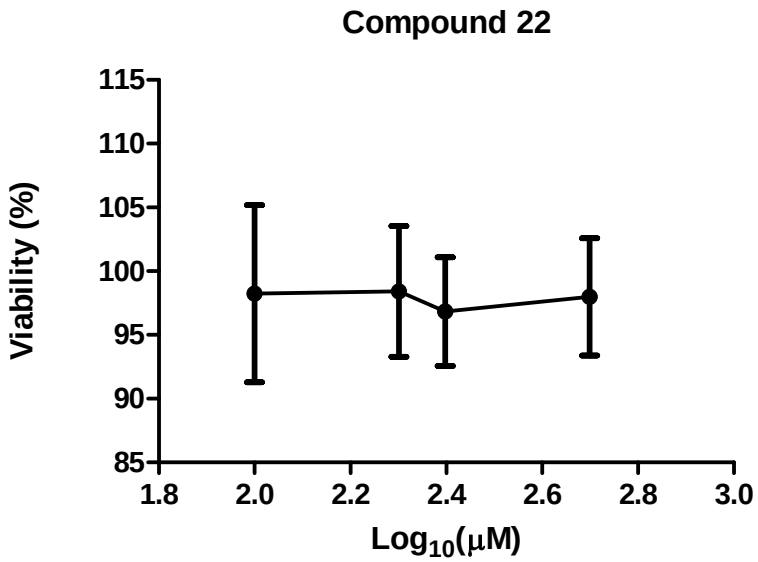

Compound 17
Viability (%)
130
120
110
100
90
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)


Compound 18
Viability (%)
150
100
50
0
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)


Compound 19
Viability (%)
110
100
90
80
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)


Compound 20
Viability (%)
150
100
50
0
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)


Compound 21
Viability (%)
130
120
110
100
90
80
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)


Compound 22
Viability (%)
115
110
105
100
95
90
85
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Log10(μM)

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