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Room temperature MgI_2-catalyzed Friedel–Crafts reaction between electron-rich (het)arenes and ethyl glyoxylate

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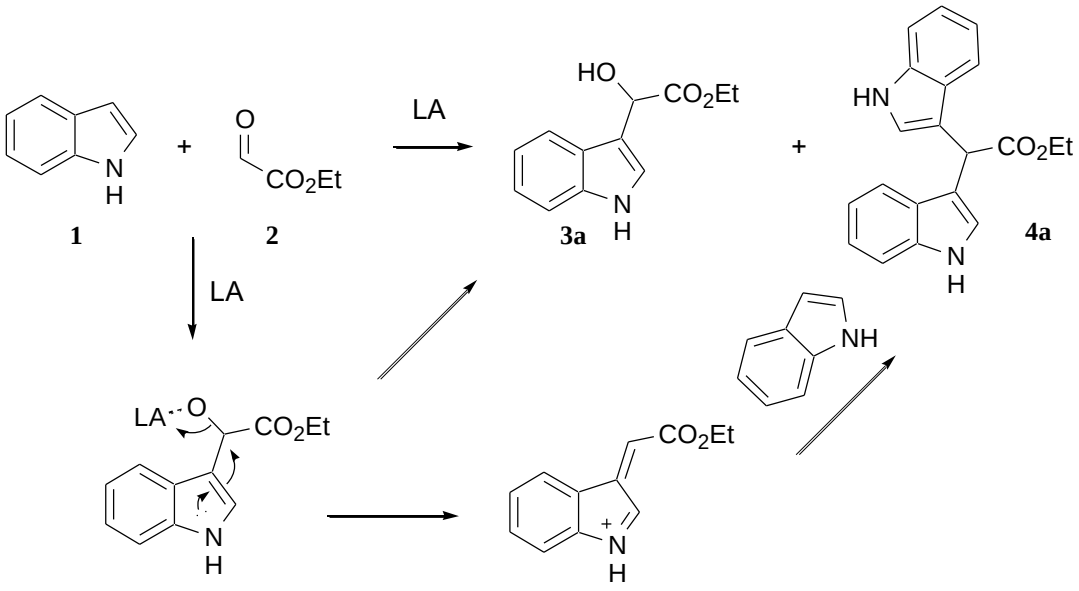

Scheme S1. Mechanism for the formation of mono- **(3a)** and bis-adducts **(4a)** in the course of reaction between indole **1a** and ethyl glyoxylate **2**.

Experimental

All commercially available reagents were used without further purification. Solvents were purified using known procedures. All reactions were performed under an air atmosphere. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 with Bruker Avance-400 and Agilent 400-MR spectrometers at room temperature. ^{13}C spectra were ^{1}H decoupled. Chemical shifts are reported in δ-scale in parts per million (ppm) relative to the residual solvent peak ($CHCl_3$: δ = 7.26 ppm for ^{1}H) or to solvent ($CDCl_3$: δ = 77.00 ppm for ^{13}C) as internal standards or to an external standard (CF_3COOH: δ = –78.5 for ^{19}F). Accurate-mass measurements (HRMS) were performed by MALDI-TOF with poly(ethylene glycols) as internal standards with Bruker Autoflex II spectrometer. Analytical TLC was carried out using Macherey-Nagel silica gel 60 F254 plates, the spots were visualized by UF. Preparative column chromatography was performed using Macherey-Nagel silica gel 60 (0.040– 0.063 mm, 230–400 mesh). Melting points were measured with an Electrothermal IA 9200 apparatus and are uncorrected.

The Friedel – Crafts hydroxyalkylation (general procedure

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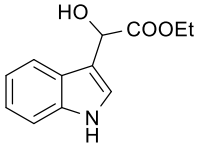
Magnesium iodide (0.025 mmol, 10 mol%, 6.9 mg) and ethyl glyoxylate (**2**) (50 mg, 50% solution in toluene, 0.25 mmol) were dissolved in CH_2Cl_2 (0.5 ml), and the mixture was stirred at room temperature for 30 min in a glass vial. The appropriate aromatic compound (0.5 mmol) was then added. After the completion of the process the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography to afford the desired product.

Ethyl 2-hydroxy-2-(1*H*-indol-3-yl)acetate (3a) [S1]

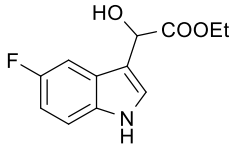


Compound **3a** was synthesized according to the general procedure from indole **1a** (58.5 mg, 0.5 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (PE/EtOAc = 2:1) the product was obtained as an oil.

Yield 43 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s; 1H), 7.72 (d, J=8.2 Hz; 1H), 7.34 (d, J=8.2 Hz; 1H), 7.12-7.23 (m; 3H), 5.47 (d, J=2.7 Hz; 1H), 4.26-4.34 (m; 1H), 4.13-4.21 (m; 1H), 1.22 (t, J=7.2 Hz; 3H).

Ethyl 2-(5-fluoro-1*H*-indol-3-yl)-2-hydroxyacetate (3b) [S1]



Compound **3b** was synthesized according to the general procedure from indole **1b** (68 mg, 0.5 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (PE/EtOAc = 2:1) the product was obtained as an oil.

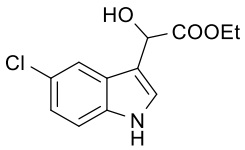
Yield 54 mg (92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s; 1H), 7.33 (dd, J=9.7, 2.2 Hz; 1H), 7.17 (dd, J=8.8, 4.4 Hz; 1H), 7.11 (d, J=2.7; 1H), 6.91 (dt, J=9.1, 2.5 Hz; 1H), 5.39 (d, J=2.9 Hz; 1H), 4.12-4.31 (m; 2H), 3.64 (s; 1H), 1.20 (t, J=7.1 Hz; 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 157,8 (d, J=234.2 Hz) 132.9, 125.5 (d, J=10.1 Hz), 125.1, 113.4 (d, J=5.1 Hz), 112.1 (d, J=10.1 Hz), 110.8 (d, J=26.1 Hz), 104.3 (d, J=23.6 Hz), 67.1, 62.2, 14.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -119.42 (td, J=9.2, 4.2 Hz; 1F).

Ethyl 2-(5-chloro-1*H*-indol-3-yl)-2-hydroxyacetate (3c) [S1]



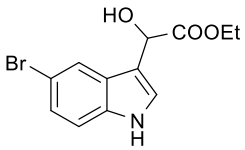
Compound **3c** was synthesized according to the general procedure from indole **1c** (76 mg, 0.5 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (PE/EtOAc = 3:1) the product was obtained as an oil.

Yield: 57 mg (90%).

^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6) δ 10.18 (s; 1H), 7.52 (d, J=1.6 Hz; 1H), 7.09 (d, J=8.7 Hz; 1H), 7.05 (d, J=2.5 Hz; 1H), 6.87 (dd, J=8.7, 2.0 Hz; 1H), 5.22 (d, J=4.9 Hz; 1H), 4.70 (d, J=4.9 Hz; 1H), 3.90-4.08 (m; 2H), 1.01 (t, J=7.07 Hz; 3H).

^{13}C NMR (101 MHz, $CDCl_3$+ DMSO-d_6) δ 173.0, 134.5, 126.1, 124.6, 124.3, 121.4, 118.4, 112.6, 112.2, 66.7, 60.8, 13.6.

Ethyl 2-(5-bromo-1*H*-indol-3-yl)-2-hydroxyacetate (3d) [S1]



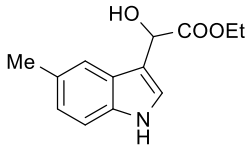
Compound **3d** was synthesized according to the general procedure from indole **1d** (98 mg, 0.5 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (PE/EtOAc = 3:1) the product was obtained as an oil.

Yield: 60 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$+ DMSO-d_6) δ 10.34 (s; 1H), 7.50 (s; 1H), 6.89 (d, J=6.0 Hz; 1H), 6.88 (s; 1H), 6.80 (dd, J=8.7, 1.7 Hz; 1H), 5.02 (d, J=5.2 Hz; 1H), 4.94 (d, J=5.2 Hz; 1H), 3.70-3.88 (m; 2H), 0.84 (t, J=7.1 Hz; 3H).

^{13}C NMR (101 MHz, $CDCl_3$+ DMSO-d_6) δ 172.3, 134.3, 126.4, 124.0, 123.2, 121.1, 112.3, 111.2, 66.2, 60.0, 13.2 (one quaternary carbon was not normally assigned).

Ethyl 2-hydroxy-2-(5-methyl-1*H*-indol-3-yl)acetate (3e) [S1]



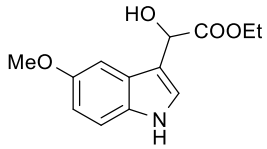
Compound **3e** was synthesized according to the general procedure from indole **1e** (66 mg, 0.5 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (PE/EtOAc = 2:1) the product was obtained as an oil.

Yield 51 mg (87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s; 1H), 7.50 (s; 1H), 7.20 (d, J=8.2 Hz; 1H), 7.09 (s; 1H), 7.03 (dd, J=8.3, 1.1 Hz; 1H), 5.44 (s; 1H), 4.13-4.34 (m; 2H), 3.38 (s; 1H), 2.45 (s; 3H), 1.23 (t, J=7.1 Hz; 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 134.7, 129.3, 125.5, 124.0, 123.5, 118.9, 113.0, 111.0, 67.3, 62.0, 21.4, 14.0.

Ethyl 2-hydroxy-2-(5-methoxy-1*H*-indol-3-yl)acetate (3f) [S1]



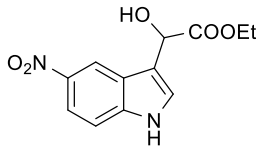
Compound **3f** was synthesized according to the general procedure from indole **1f** (73 mg, 0.5 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (PE/EtOAc = 2:1) the product was obtained as an oil.

Yield 55 mg (89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s; 1H), 7.18 (dd, J=8.8, 1.8 Hz; 1H), 7.15 (d, J=2.4 Hz; 1H), 7.08 (m; 1H), 6.84 (dd, J=8.8, 2.5 Hz; 1H), 5.42 (d, J=5.3 Hz; 1H), 4.13-4.32 (m; 2H), 3.82 (s; 3H), 3.46 (brs; 1H), 1.21 (t, J=7.1 Hz; 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 154.2, 131.4, 125.7, 124.0, 113.1, 112.8, 112.2, 100.8, 67.2, 62.0, 55.7, 14.0.

Ethyl 2-hydroxy-2-(5-nitro-1*H*-indol-3-yl)acetate (3g) [S1]



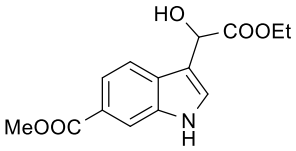
Compound **3g** was synthesized according to the general procedure from indole **1g** (81 mg, 0.5 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (PE/EtOAc = 2:1) the product was obtained as an oil.

Yield 52 mg (79%).

^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 10.89 (s; 1H), 8.50 (d, J=1.8 Hz; 1H), 7.76 (dd, J=9.1, 2.1 Hz; 1H), 7.16-7.19 (m; 2H), 5.27 (d, J=5.2 Hz; 1H), 5.11 (d, J=5.2 Hz; 1H), 3.87-4.04 (m; 2H), 0.97 (t, J=7.7 Hz; 3H)

^{13}C NMR (101 MHz, $CDCl_3$+DMSO-d_6) δ 172.5, 140.6, 139.3, 127.1, 126.2, 124.2, 116.5, 115.4, 111.1, 66.5, 60.7, 13.4.

Methyl 3-(2-ethoxy-1-hydroxy-2-oxoethyl)-1*H*-indole-6-carboxylate (3h)



Compound **3h** was synthesized according to the general procedure from indole **1h** (88 mg, 0.5 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (PE/EtOAc = 2:1) the product was obtained as an oil.

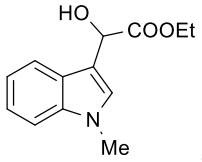
Yield 66 mg (95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (s; 1H), 8.03 (s; 1H), 7.75 (dd, J=8.5, 1.4 Hz; 1H), 7.68 (d, J=8.6 Hz; 1H), 7.29 (d, J=2.9 Hz; 1H), 5.45 (d, J=2.9 Hz; 1H), 4.10-4.28 (m; 2H), 3.89 (s; 3H), 3.84 (d, J=2.9 Hz; 1H), 1.16 (t, J=7.1 Hz; 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 168.3, 135.7, 128.9, 126.8, 123.7, 120.8, 118.9, 113.9, 113.7, 67.0, 62.1, 52.0, 13.9.

HRMS (MALDI, dithranol, PEG-300) m/z calcd. for $C_{14}H_{14}NO_4$ $(M\text{-}OH)^{\cdot+}$ 260.0917; found 260.0991.

Ethyl 2-hydroxy-2-(1-methyl-1*H*-indol-3-yl)acetate (3i) [S2]



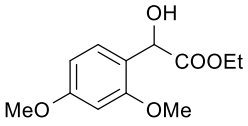
Compound **3i** was synthesized according to the general procedure from indole **1i** (66 mg, 0.5 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (PE/EtOAc = 3:1) the product was obtained as an oil.

Yield 34 mg (58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.73 (m;1H), 7.33 (m;1H) 7.26 (dt, J=7.6, 1.0 Hz; 1H), 7.15 (ddd, J=8.3, 8.1, 1.3 Hz; 1H), 7.12 (s; 1H), 4.27-4.35 (m; 1H), 4.14-4.22 (m; 1H), 3.76 (s; 3H) 3.32 (d, J=4.6 Hz; 1H), 1.24 (t, J=7.1 Hz; 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 137.2, 127.7, 125.8, 122.0, 119.6, 119.4, 112.2, 109.4, 67.1, 61.9, 32.7, 14.1.

Ethyl 2-(2,4-dimethoxyphenyl)-2-hydroxyacetate (6a) [S3]



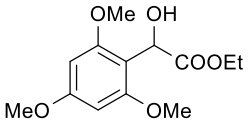
Compound **6a** was synthesized according to the general procedure from 1,3-dimethoxybenzene **5a** (69 mg, 0.25 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (CH_2Cl_2/PE = 3:1) the product was obtained as an oil.

Yield: 16 mg (32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J=8.5 Hz; 1H), 6.48 (d, J=2.3 Hz; 1H), 6.46 (s; 1H), 5.19 (d, J=6.8 Hz; 1H), 4.16-4.27 (m; 2H), 3.80 (s; 6H), 3.47 (d, J=6.8 Hz; 1H), 1.21 (t, J=7.2 Hz; 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 161.2, 158.2, 130.2, 119.8, 104.3, 99.0, 69.9, 61.7, 55.4, 55.3, 14.1.

Ethyl 2-hydroxy-2-(2,4,6-trimethoxyphenyl)acetate (6b).



Compound **6b** was synthesized according to the general procedure from 1,3.5-trimethoxybenzene **5b** (84 mg, 0.5 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (CH_2Cl_2) the product was obtained as white solid.

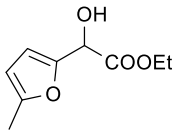
Yield: 49 mg (75%), m.p. 77-79 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (s; 2H), 5.54 (d, J=7.3 Hz; 1H), 4.13-4.26 (m; 2H), 3.79 (s; 3H), 3.78 (s; 6H), 3.46 (d, J=7.3 Hz; 1H), 1.20 (t, J=7.1 Hz; 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 161.5, 158.9 (2C), 108.4, 90.67 (2C) 64.1, 61.3, 55.7 (2C), 55.3, 14.1.

HRMS (MALDI, dithranol, PEG-300) m/z calcd. for $C_{13}H_{18}NaO_6$ $(M^{\cdot}+Na)^+$ 293.1001; found 293.0992.

Ethyl 2-hydroxy-2-(5-methylfuran-2-yl)acetate (6c) [S4]



Compound **6c** was synthesized according to the general procedure from 2-methylfuran **5c** (42 mg, 0.5 mmol) and **2** (50 mg, 50% solution in toluene, 0.25 mmol) at room temperature. After purification by column chromatography (CH_2Cl_2/PE = 3:1) the product was obtained as an oil.

Yield 32 mg (70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (d, J=3.2 Hz; 1H), 5.92-5.93 (m; 1H), 5.10 (s; 1H), 4.21-4.34 (m; 1H), 3.31 (s; 1H), 2.26 (s; 3H), 1.26 (t, J=7.2 Hz; 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 152.9, 149.0, 109.7, 106.4, 66.9, 62.4, 14.0, 13.5.

References

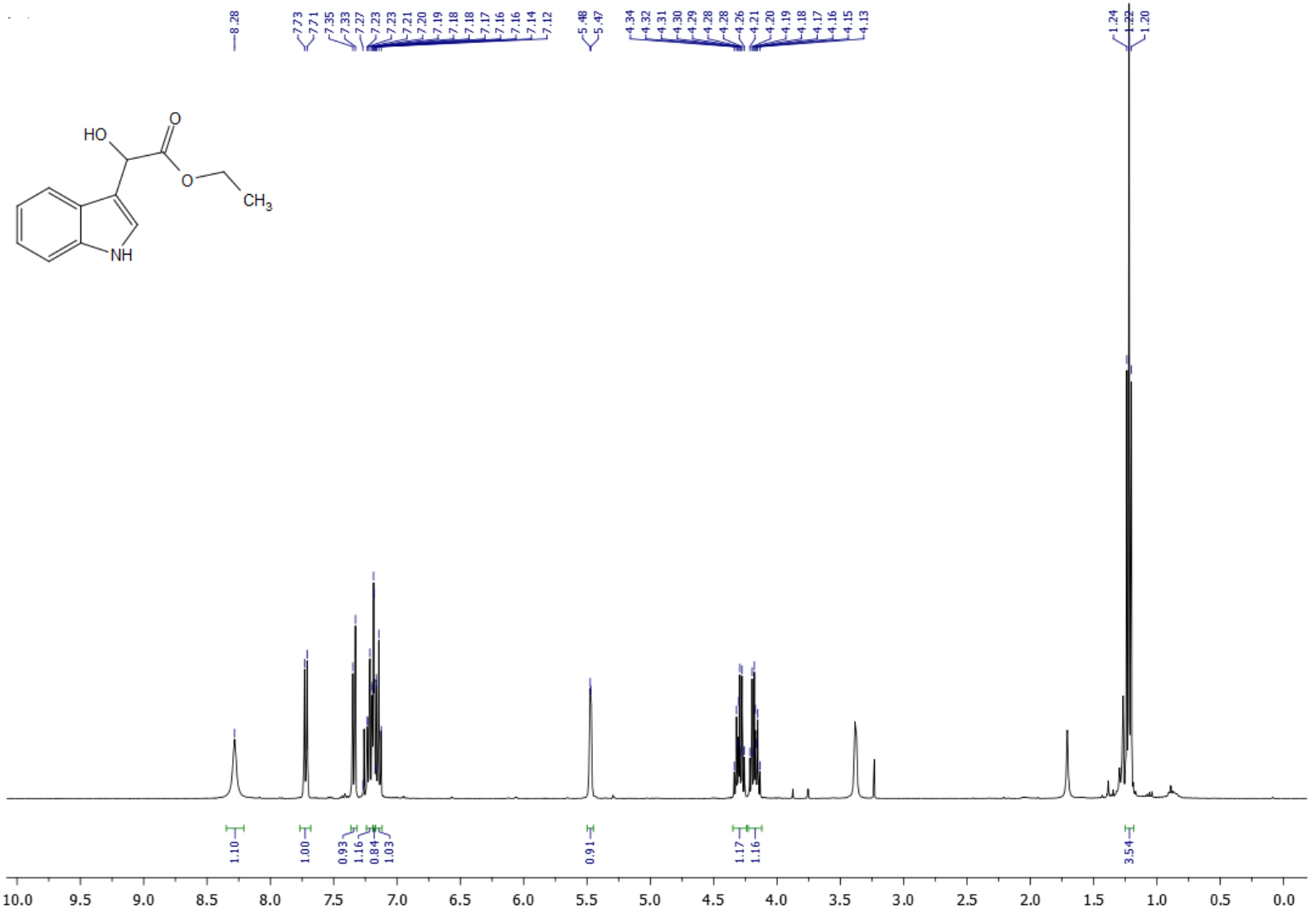
[S1] Y. Hui, Q. Zhang, J. Jiang, L. Lin, X. Liu and X. Feng, *J. Org. Chem.*, 2009, **74**, 6878

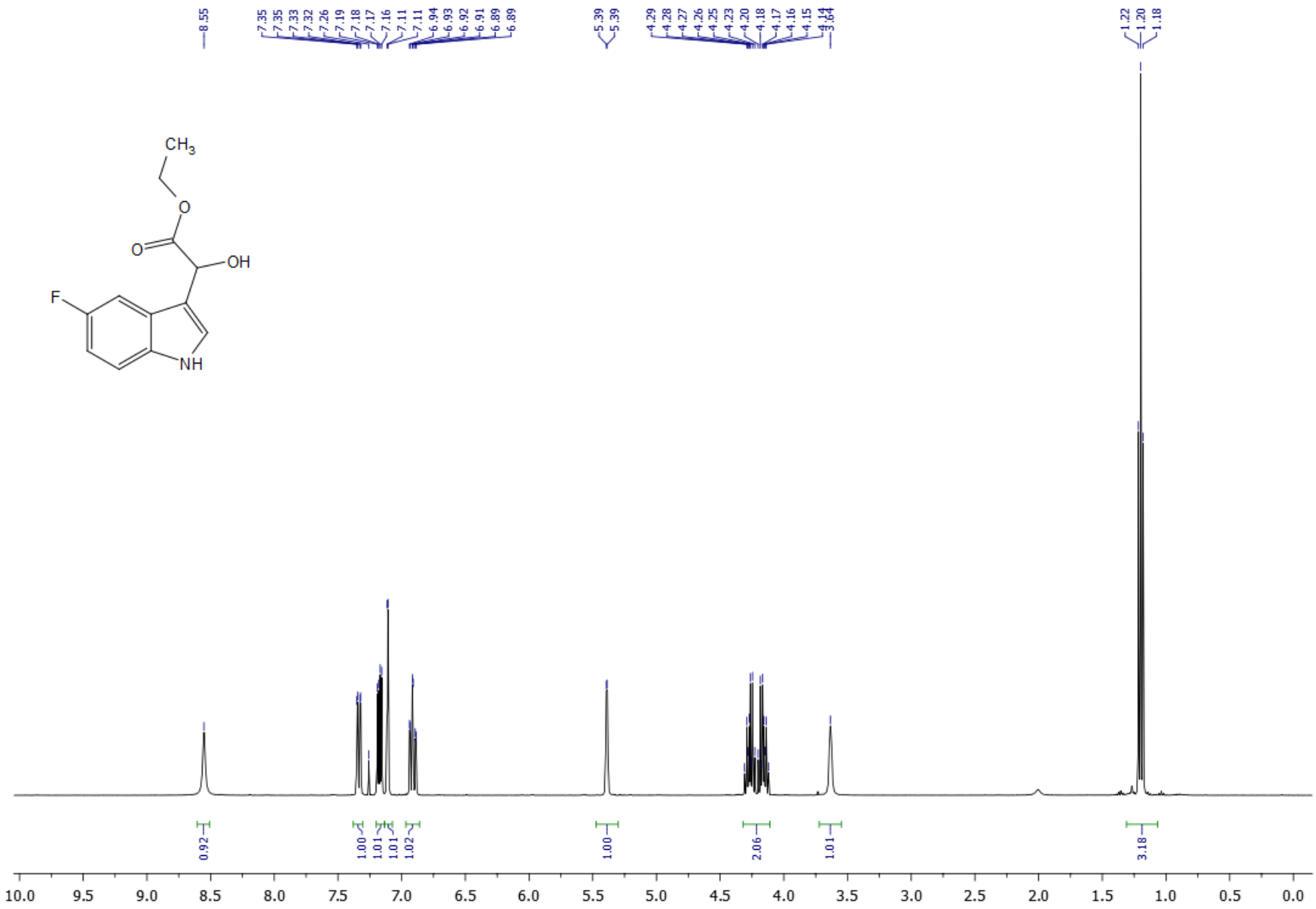
[S2] J. Hao, S. Taktak, K. Aikawa, Y. Yusa, M. Hatano and K. Mikami, *Synlett*, 2001, 1443.

[S3] S. P. Roche, S. S. Samanta and M. M. J. Gosselin, *Chem. Commun.*, 2014, **50**, 2632.

[S4] K. Aikawa, Y. Asai, Y. Hioki and K. Mikami, *Tetrahedron: Asymmetry*, 2014, **25**, 1104.

^{1}H, ^{13}C,^{19}F NMR spectra of Friedel-Crafts products.

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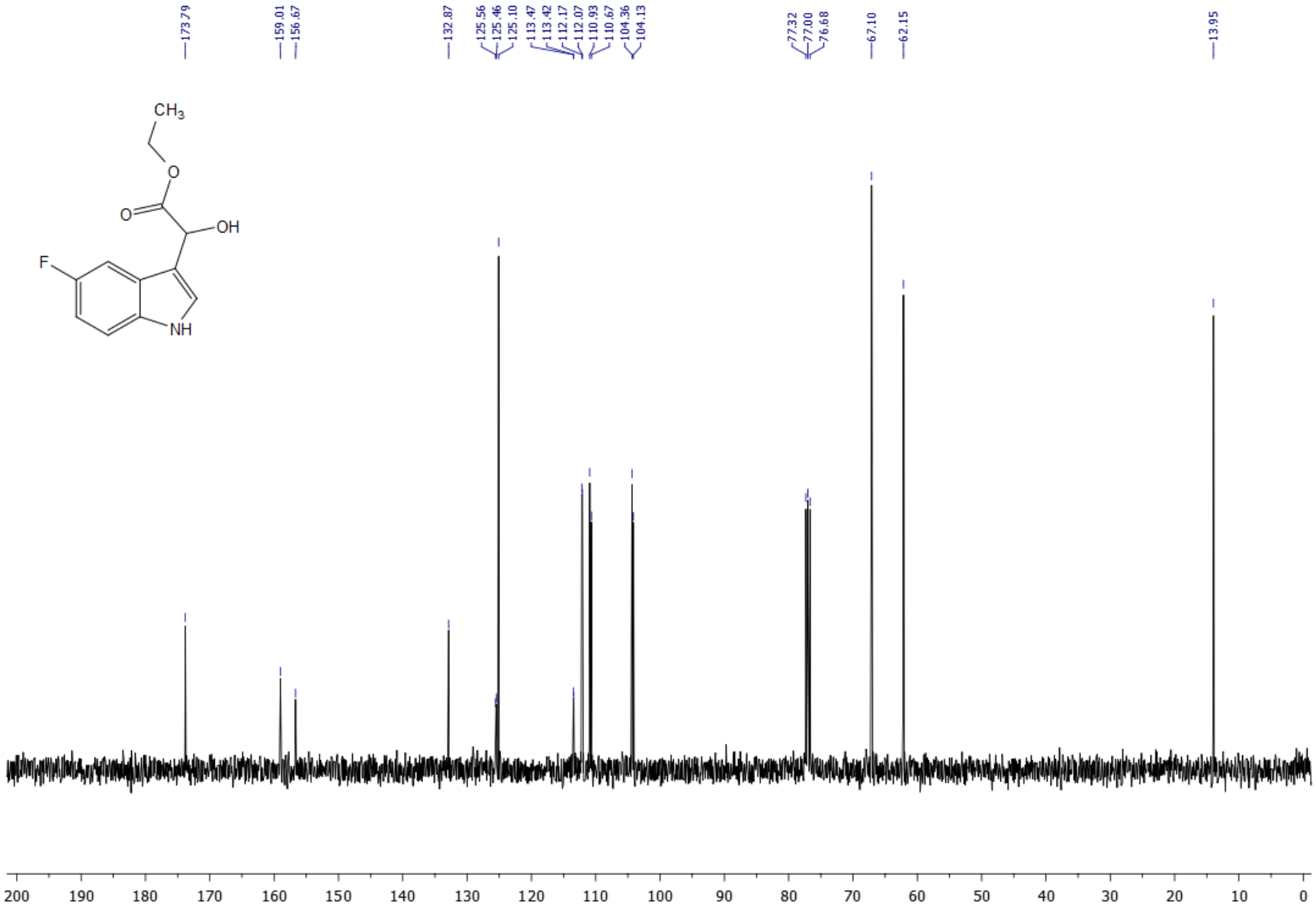
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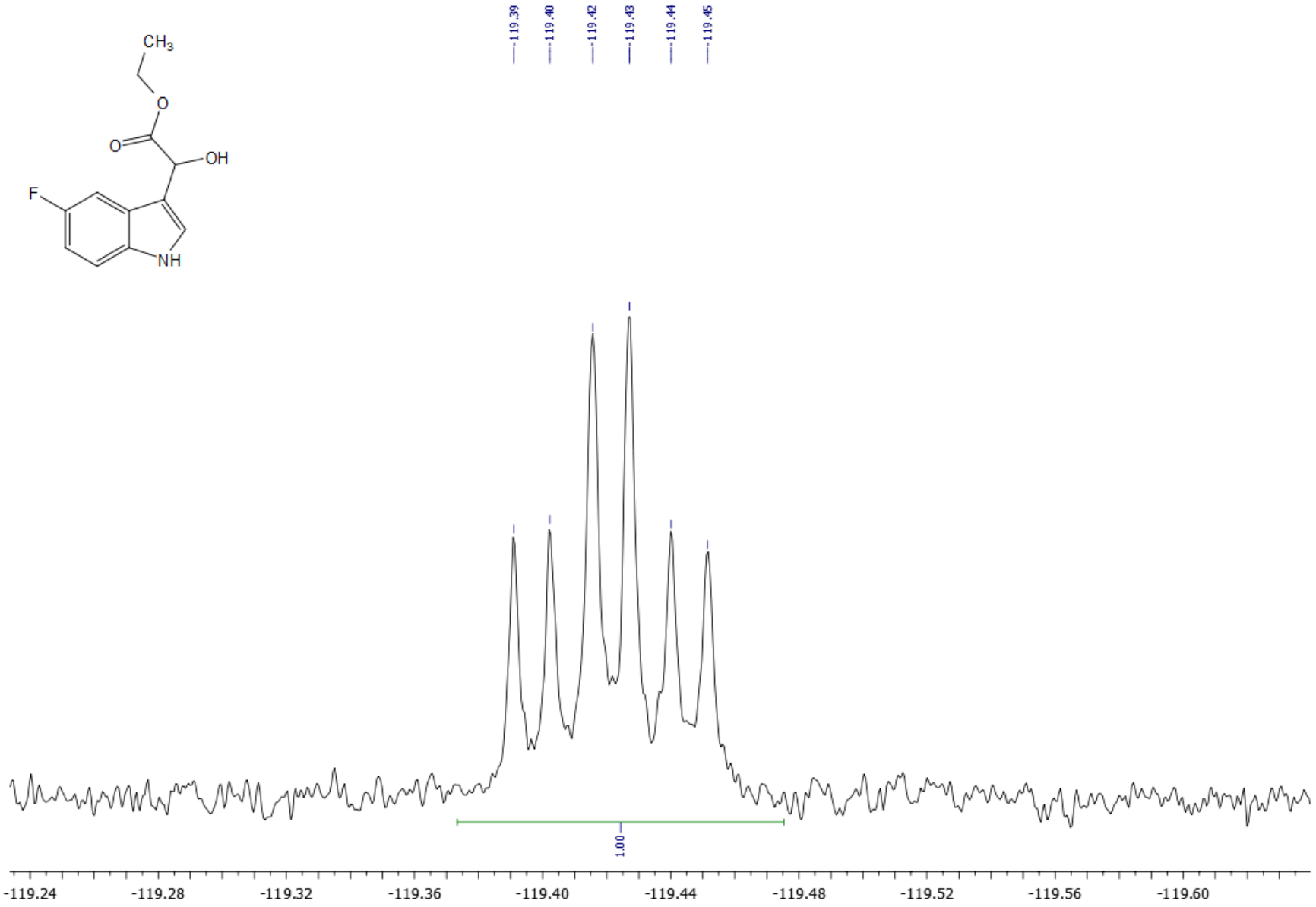
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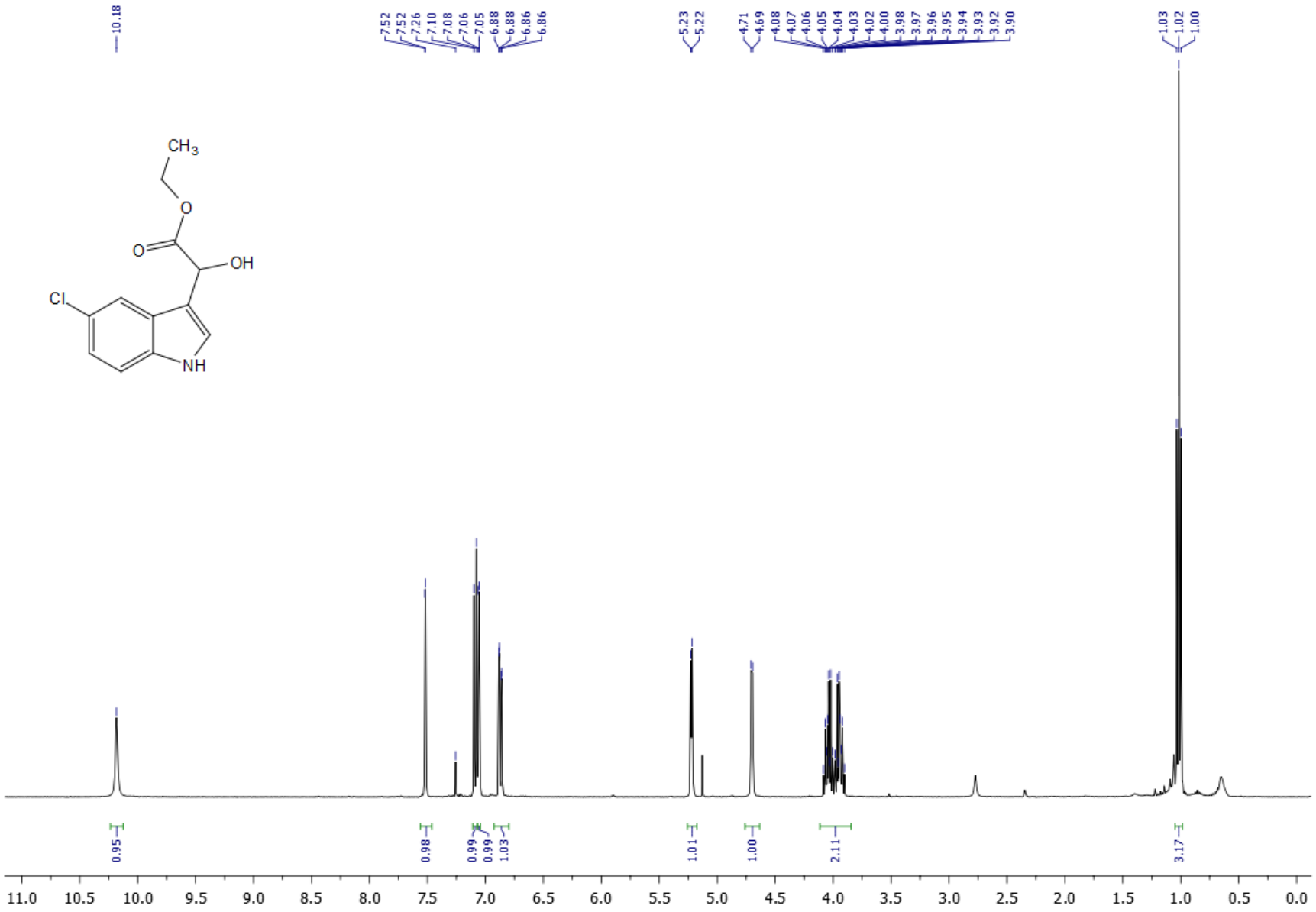
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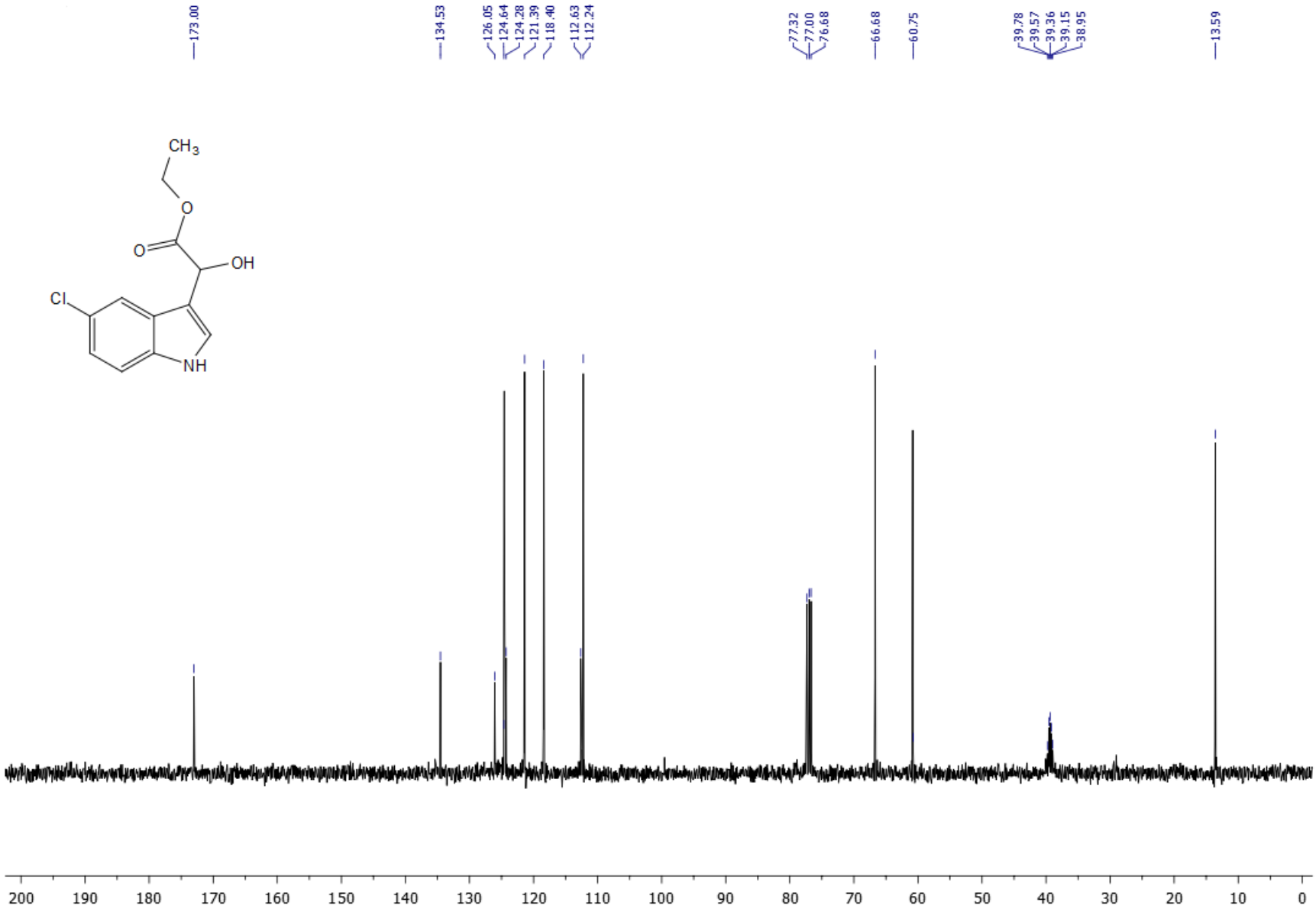
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OH
Cl
NH
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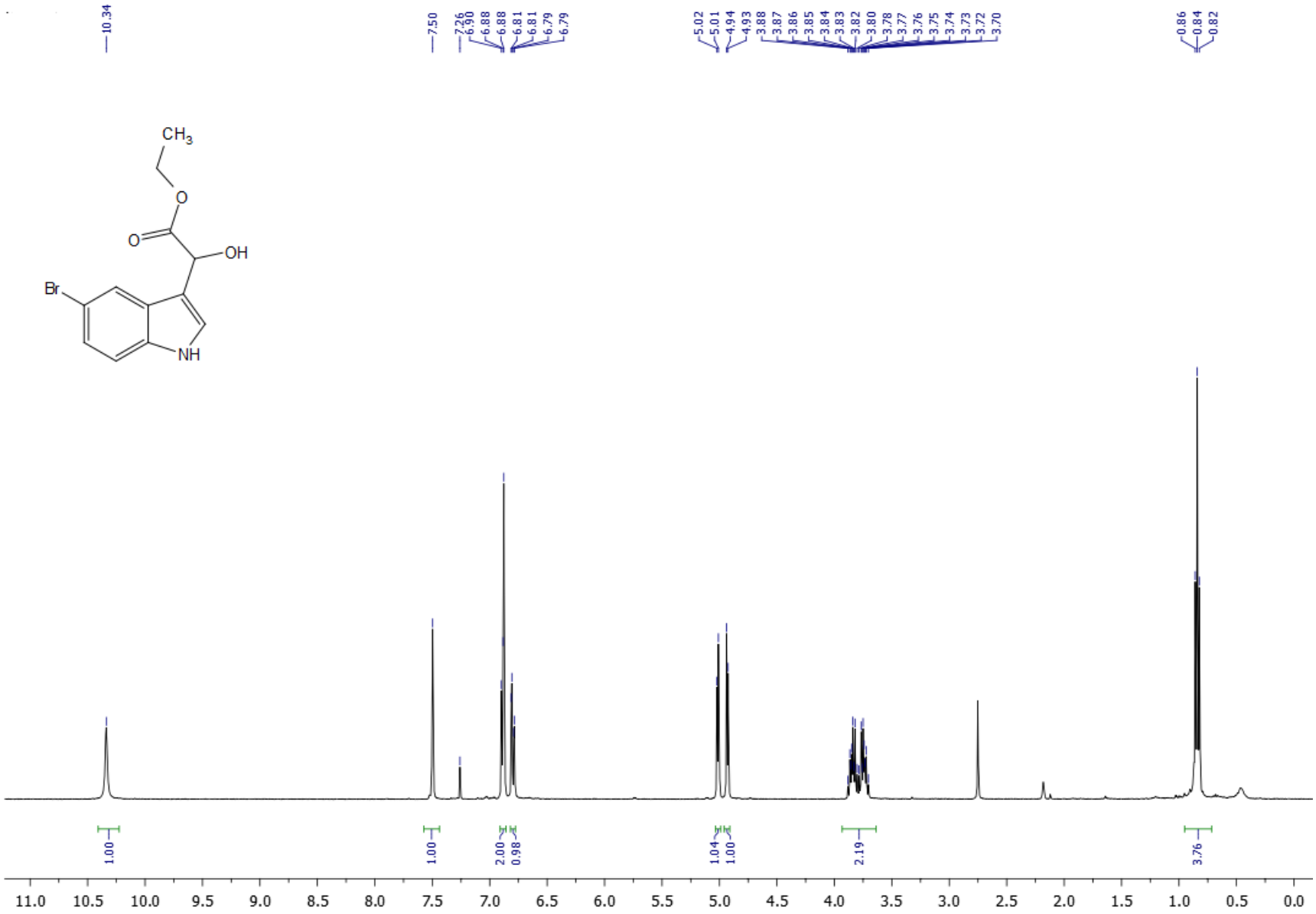
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OH
Br
NH
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1.00
2.00
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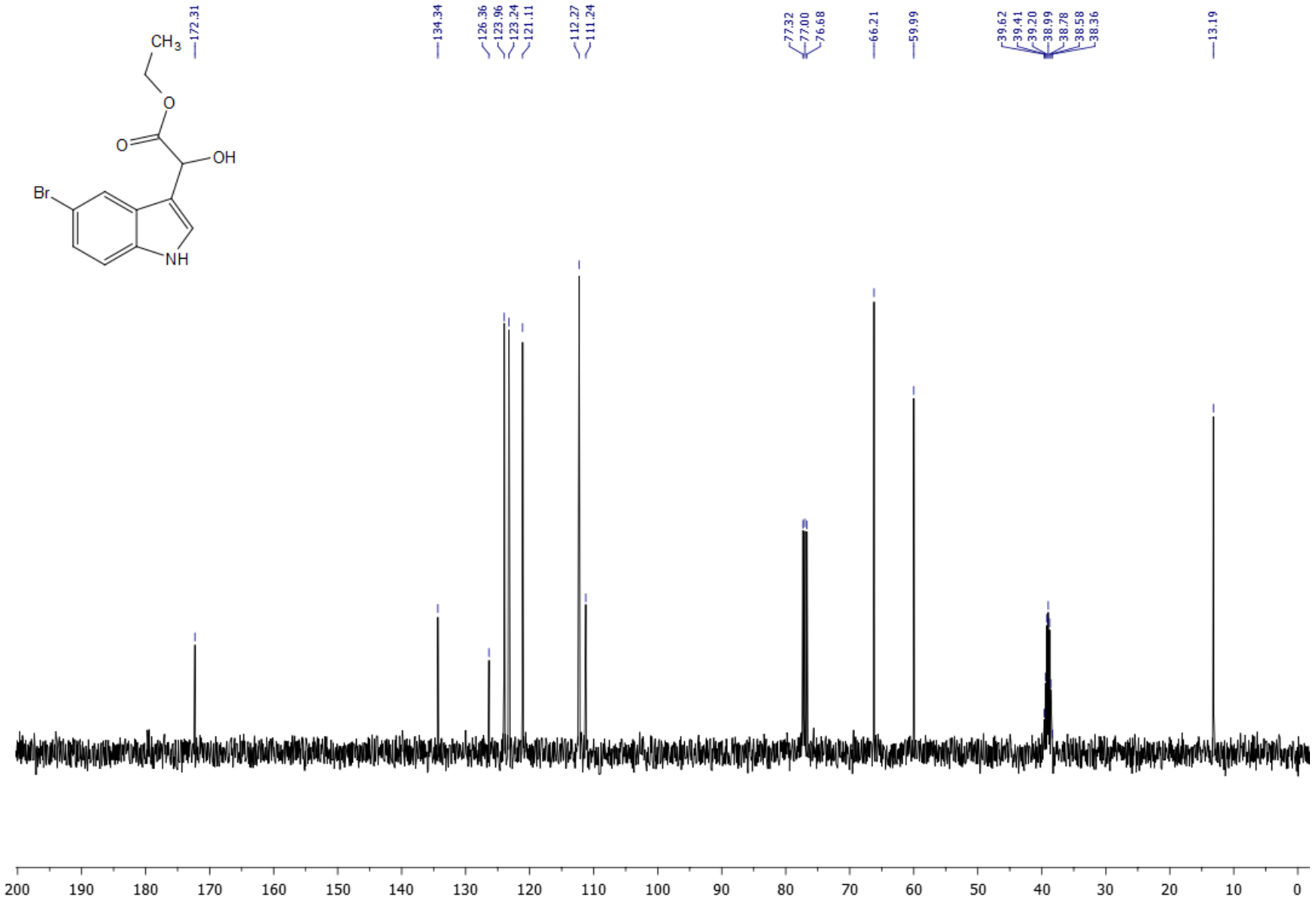
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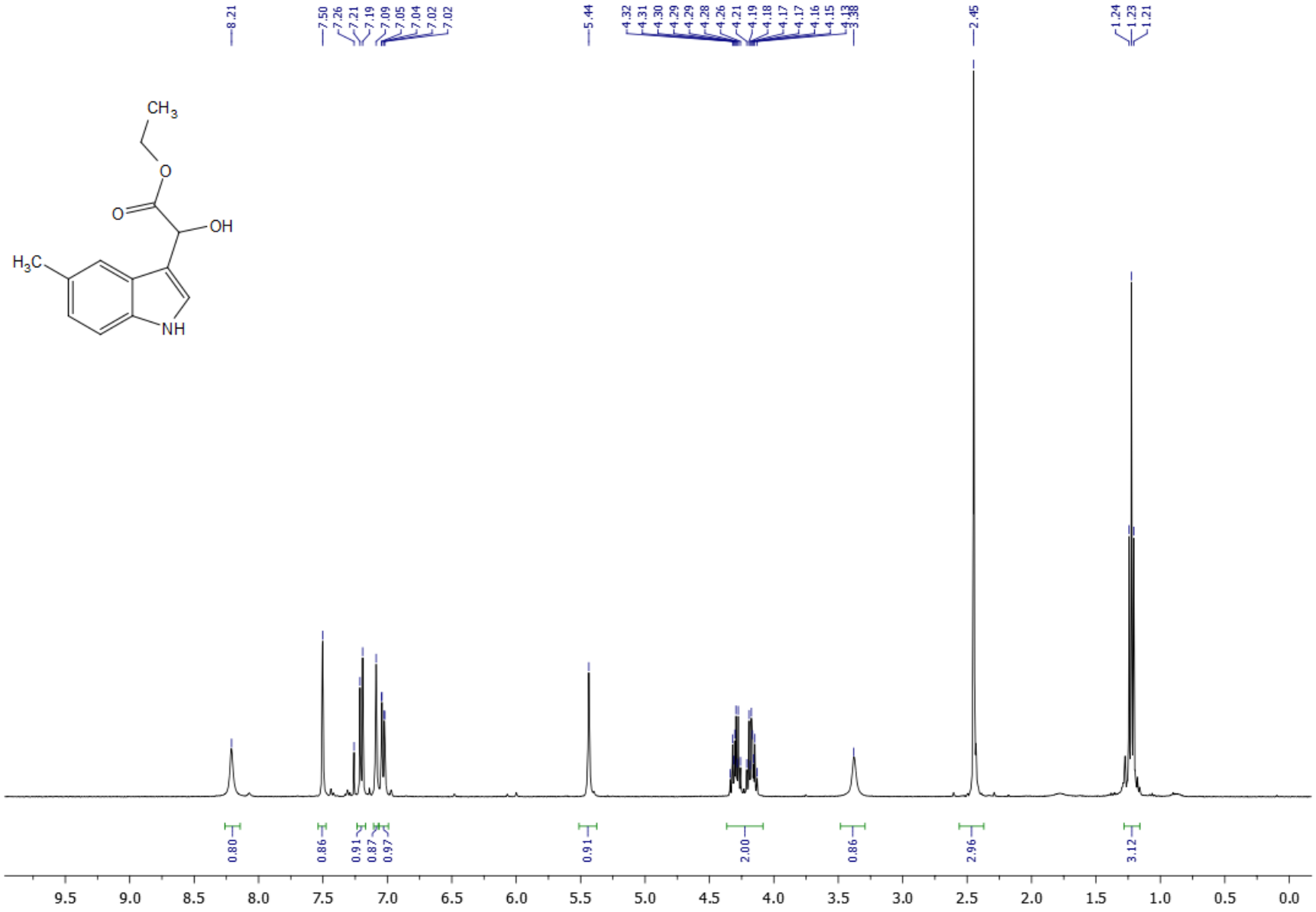
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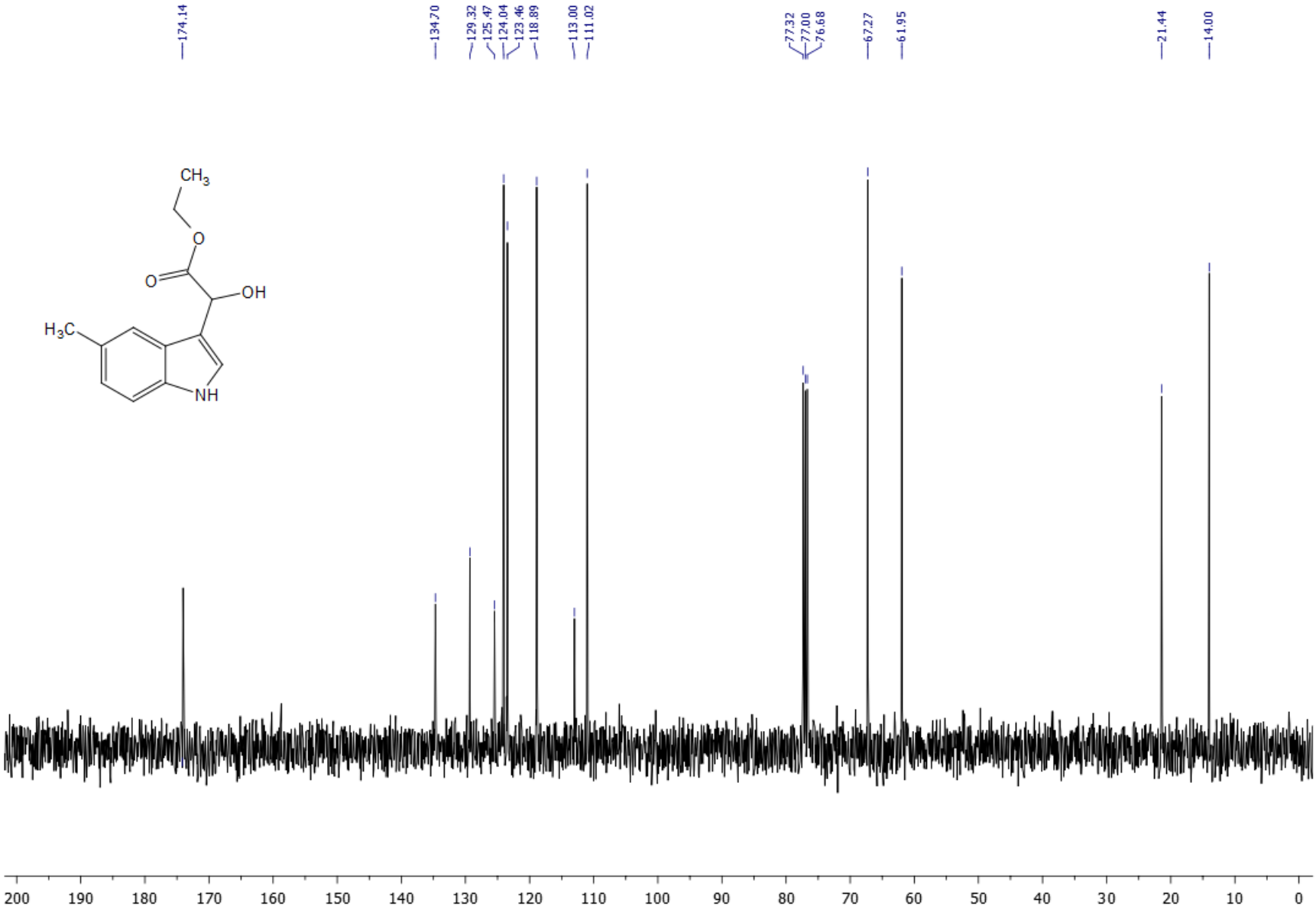
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O
OH
H3C
NH
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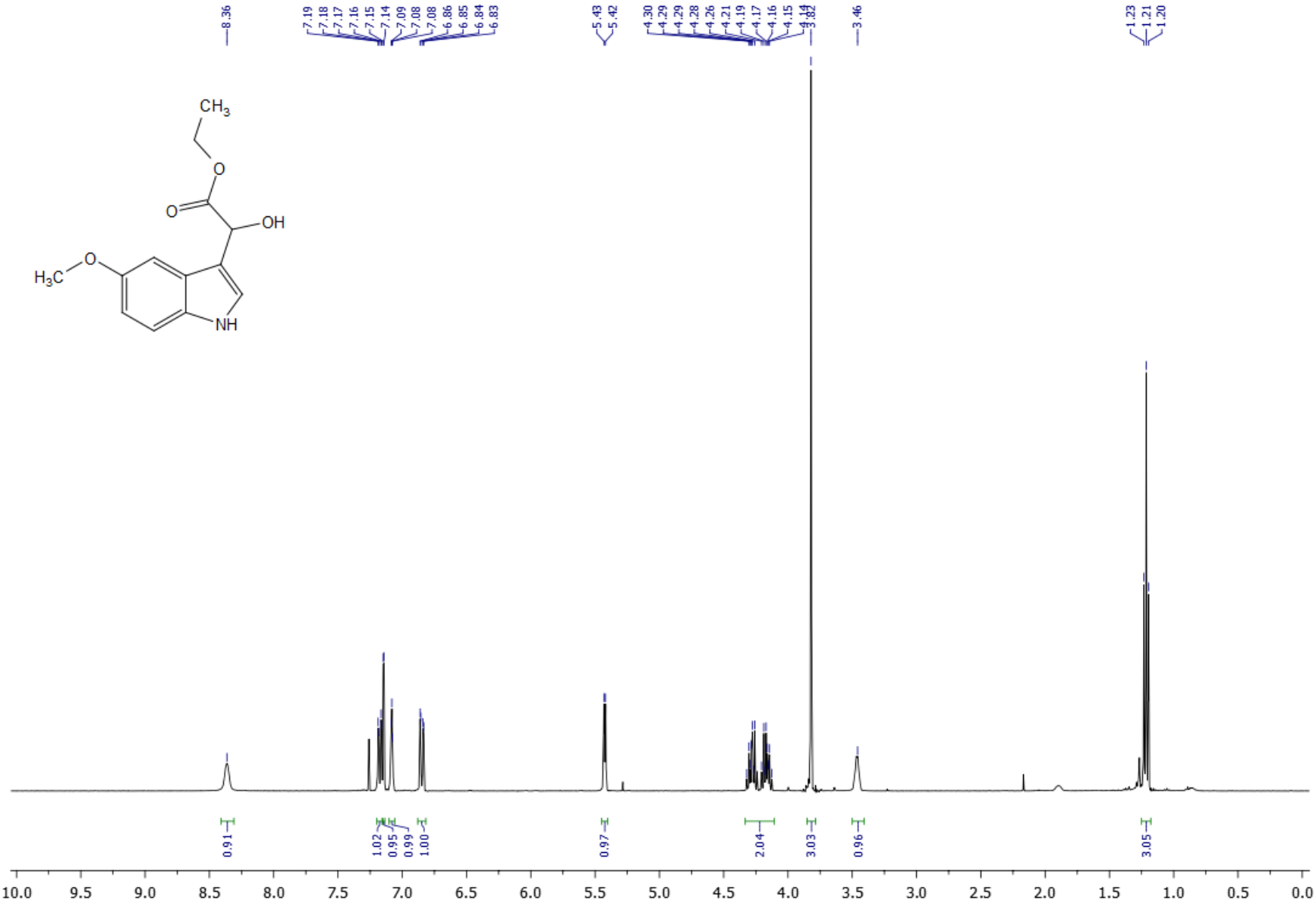
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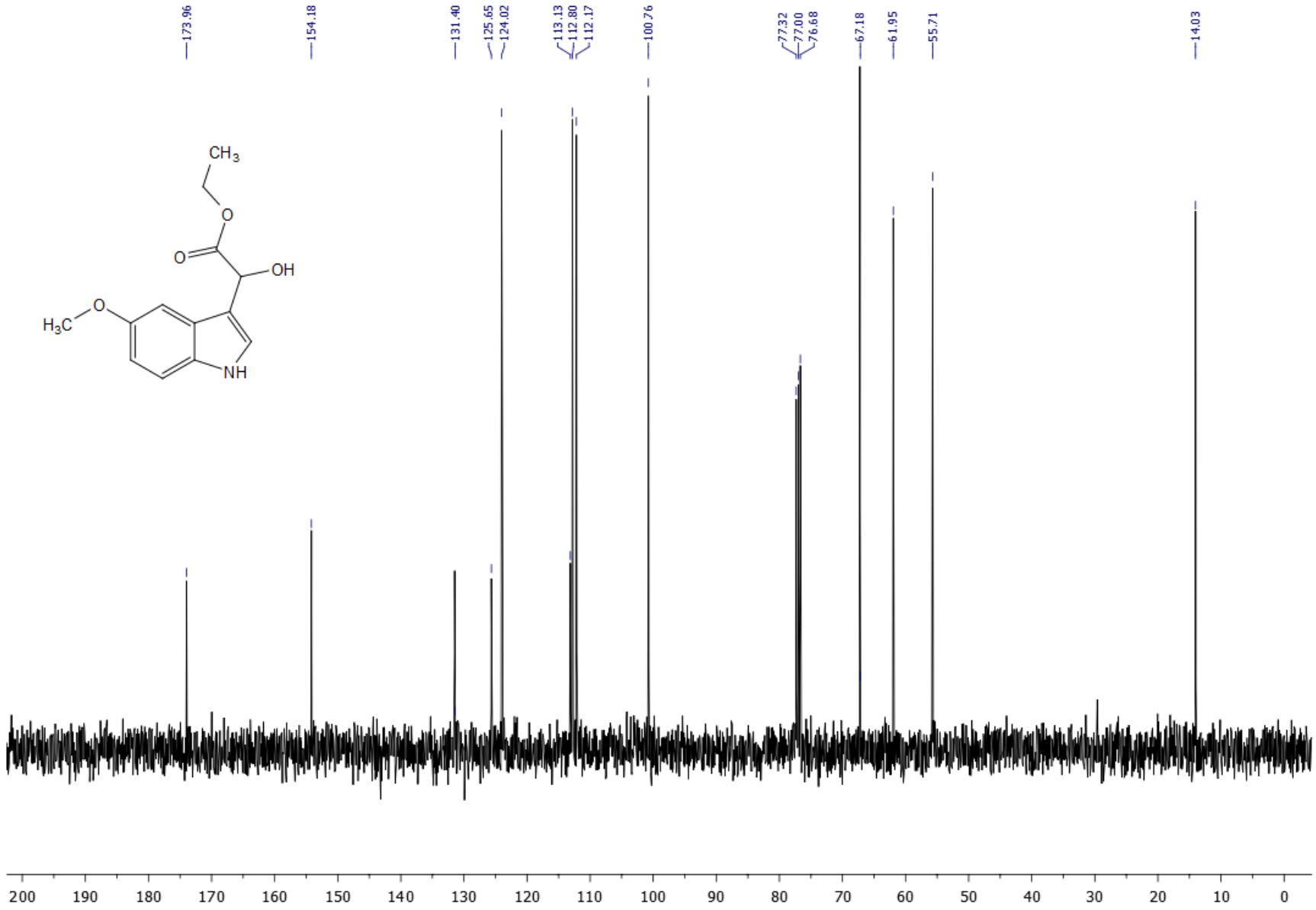
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NH
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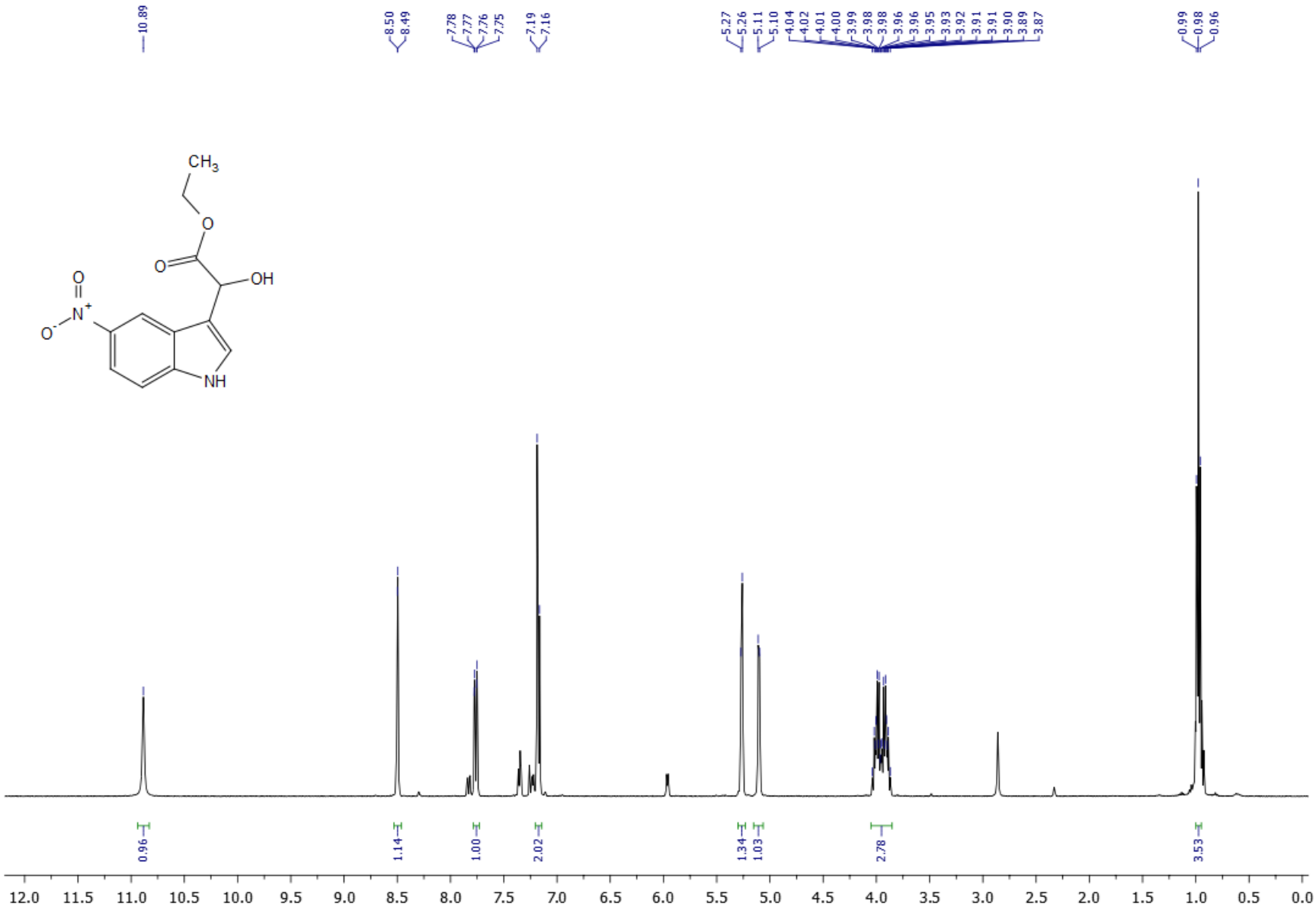
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O-
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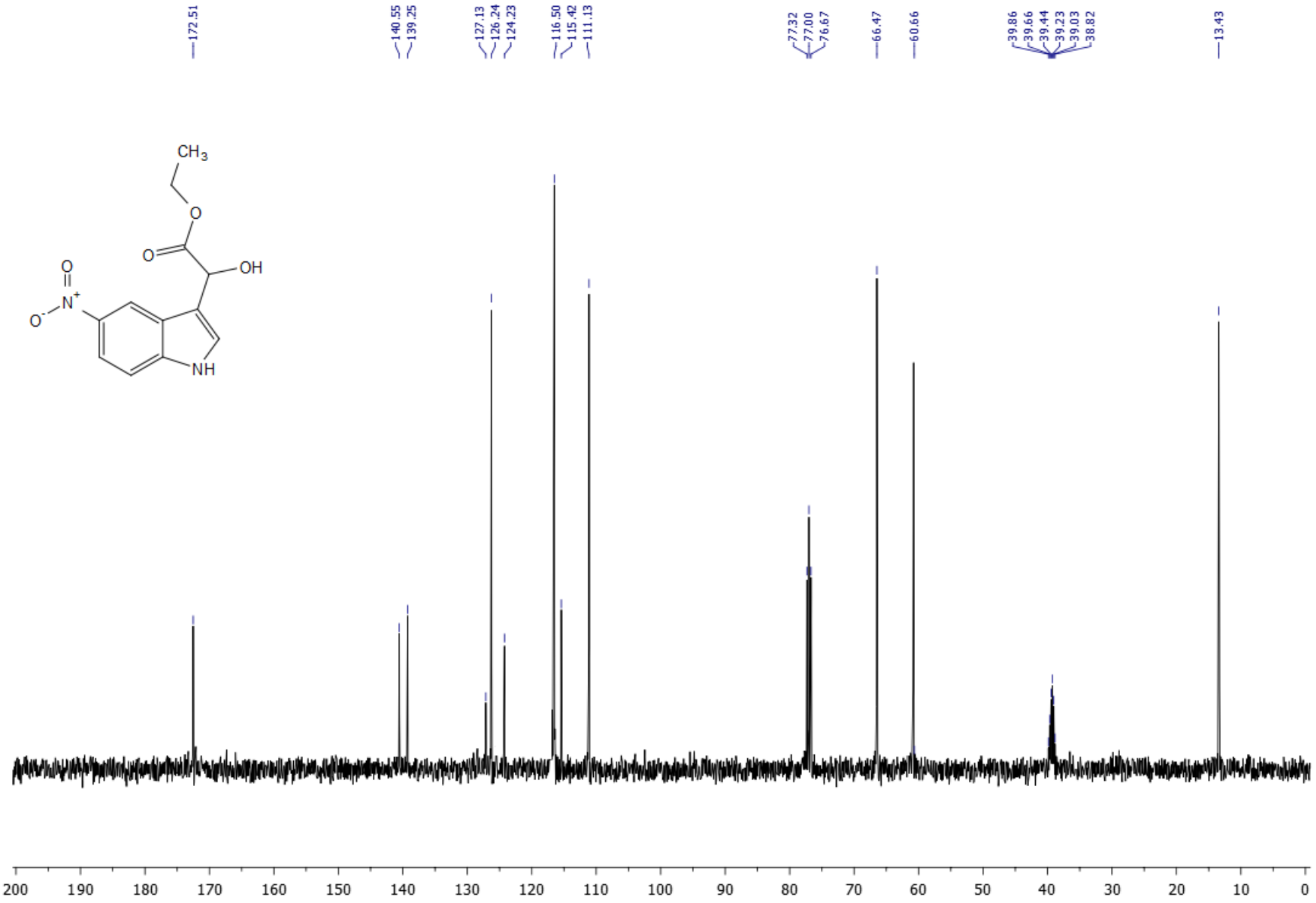
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N+
O-
NH
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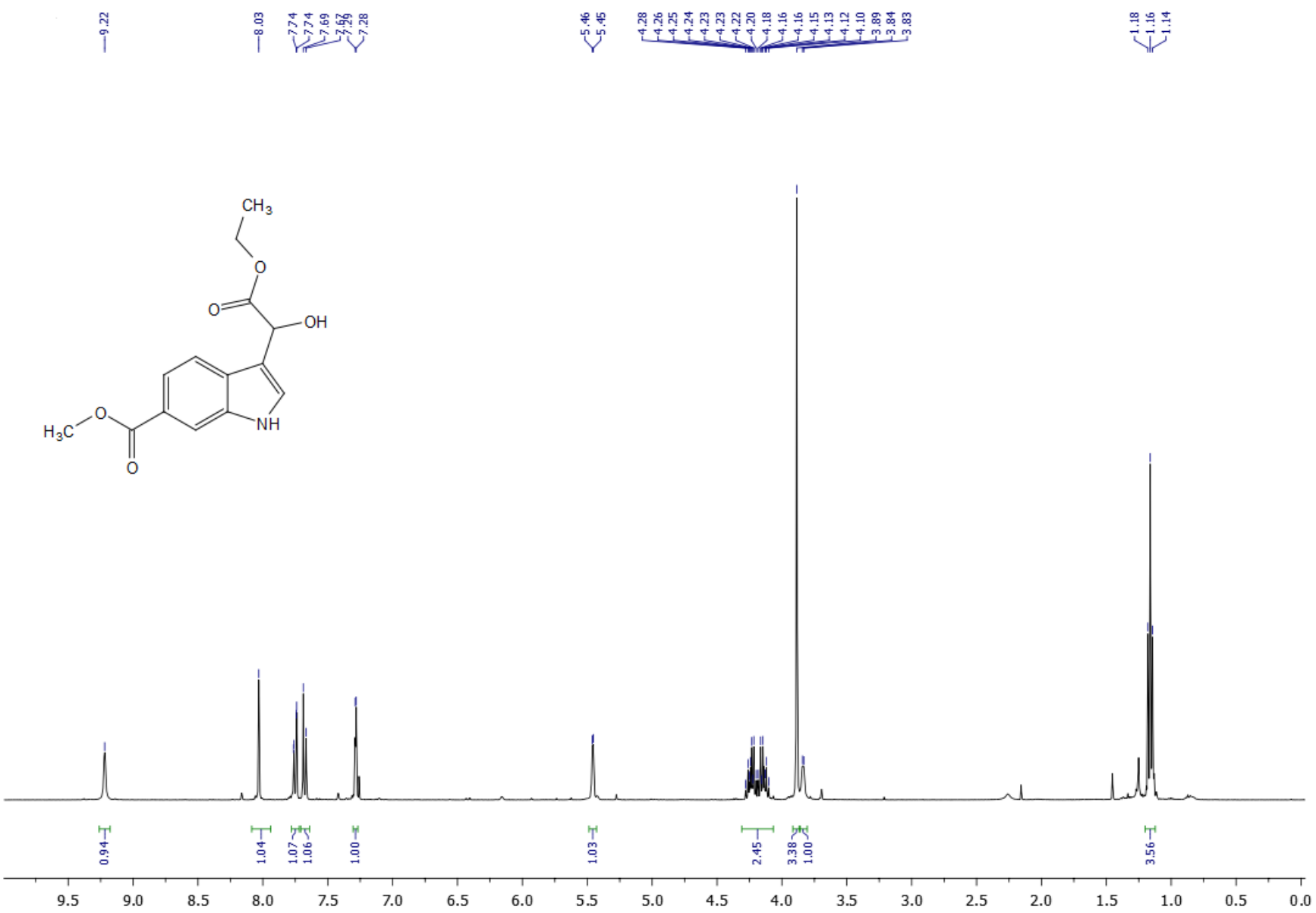
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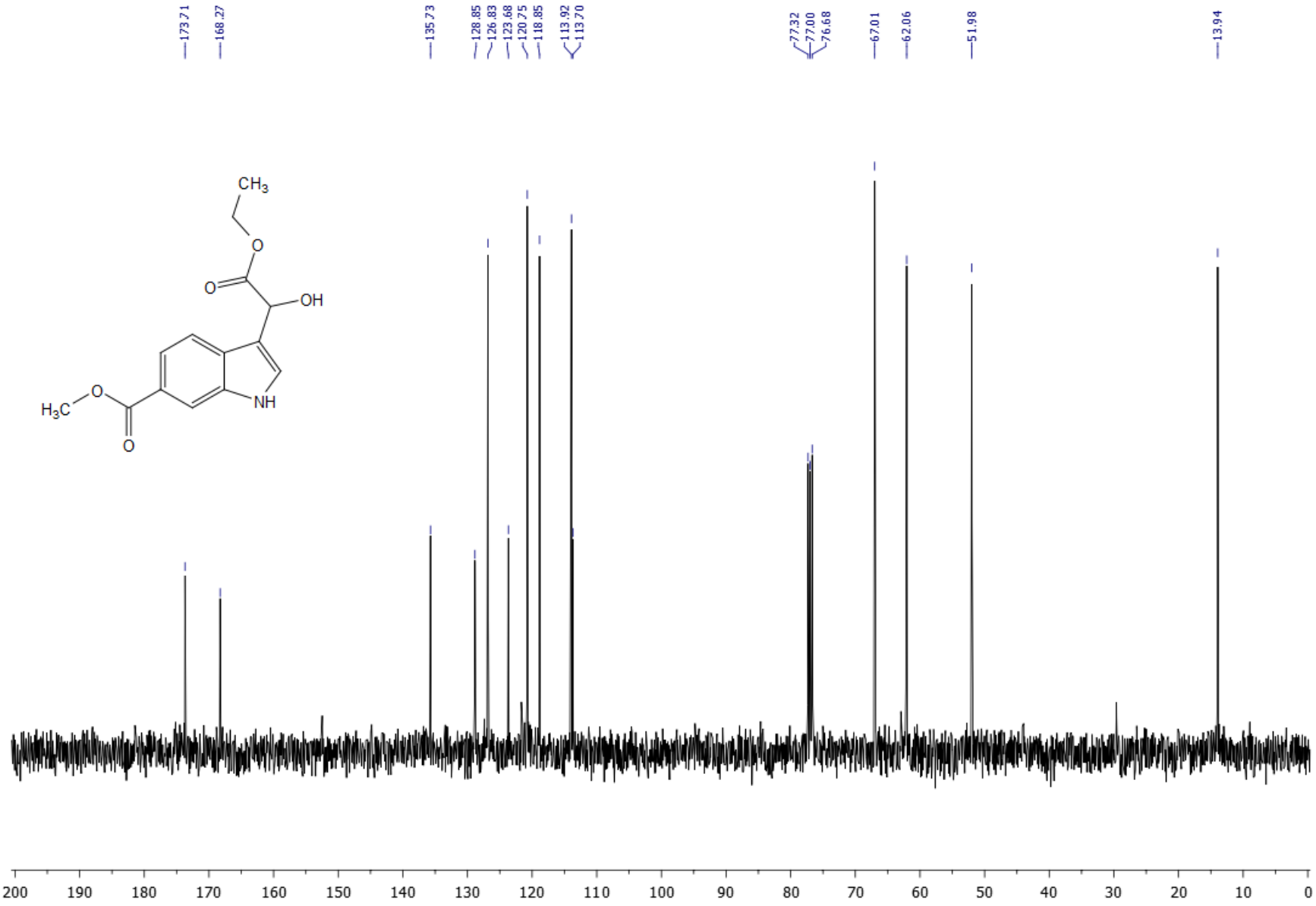
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OH
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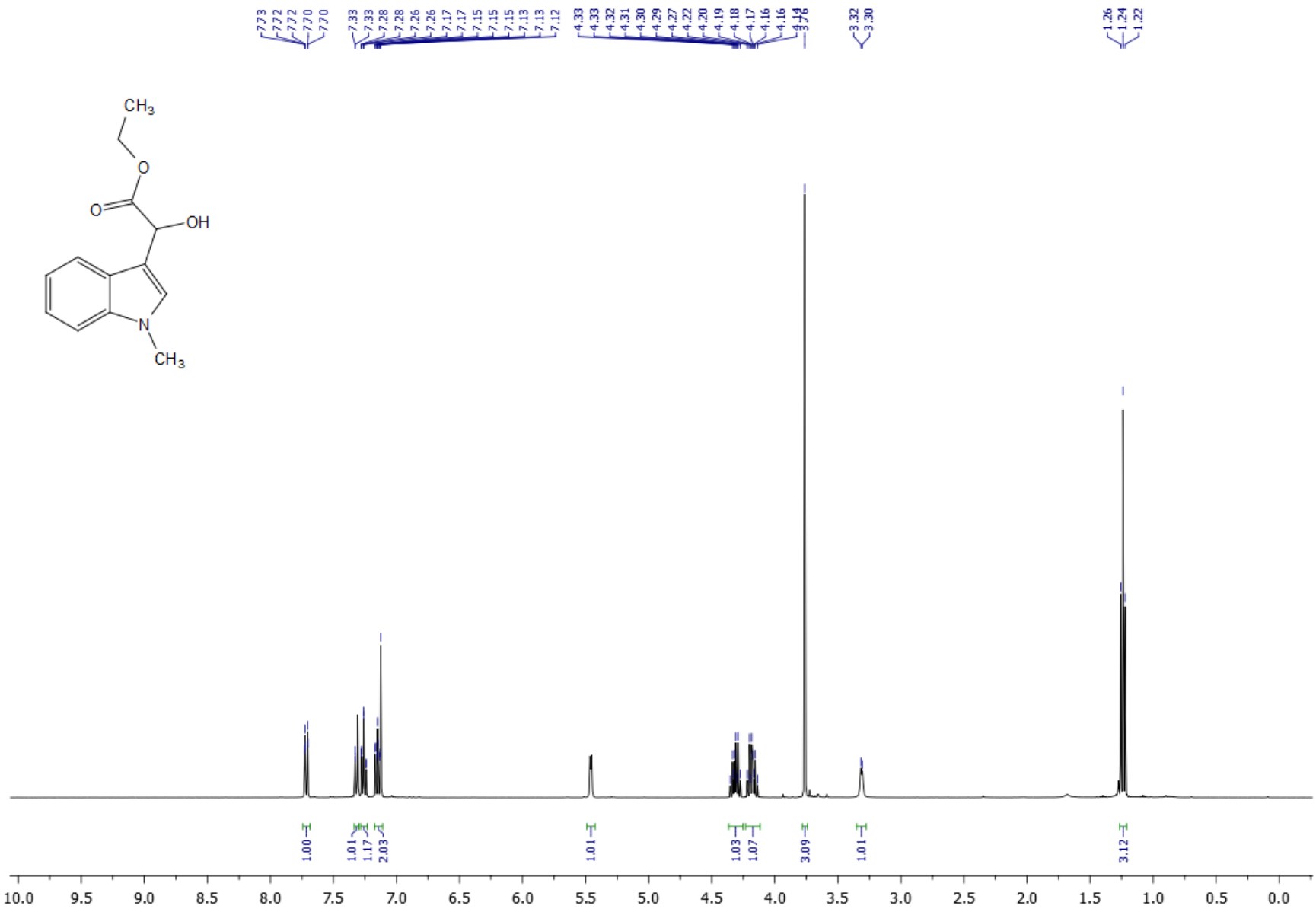
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CH3
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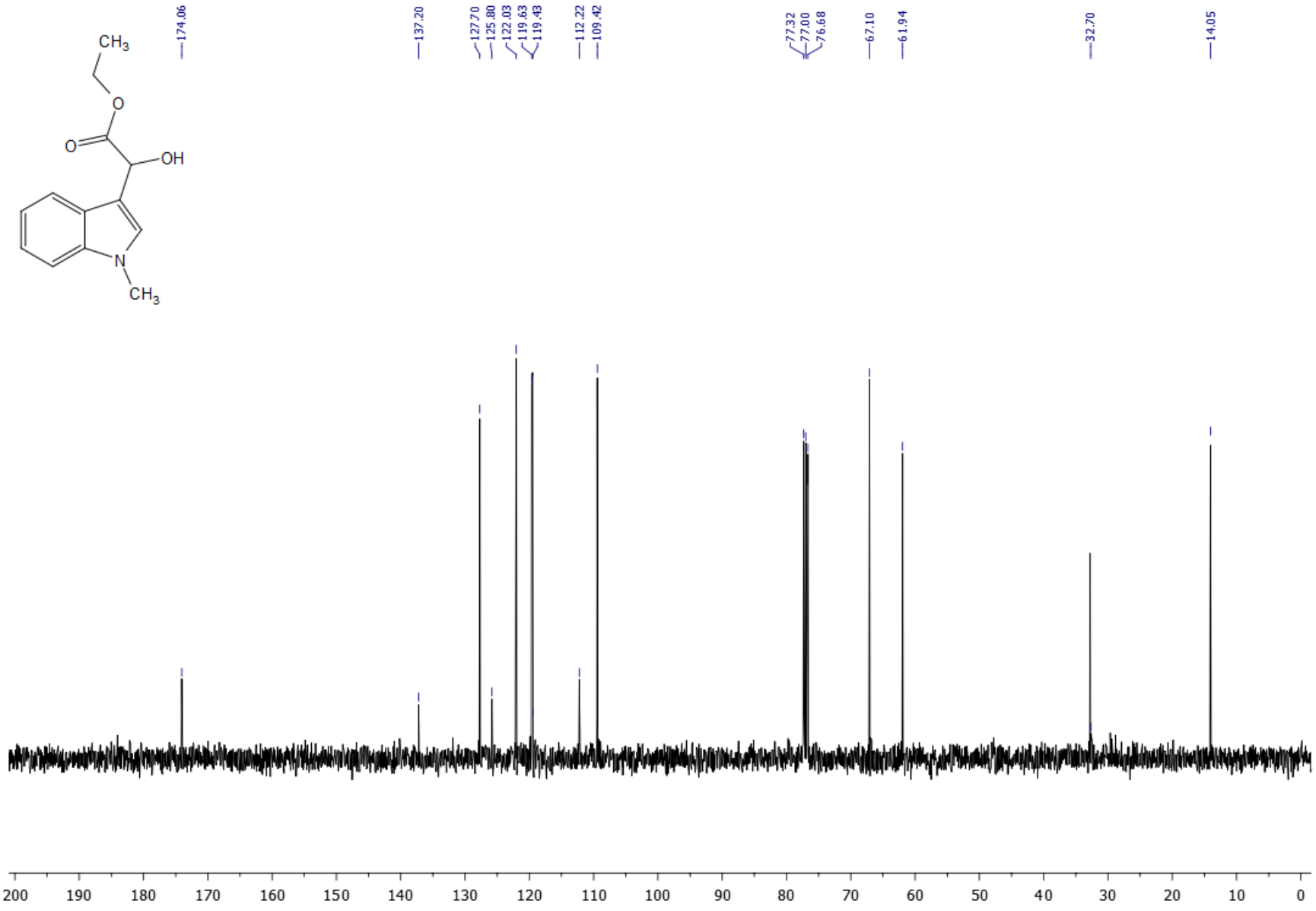
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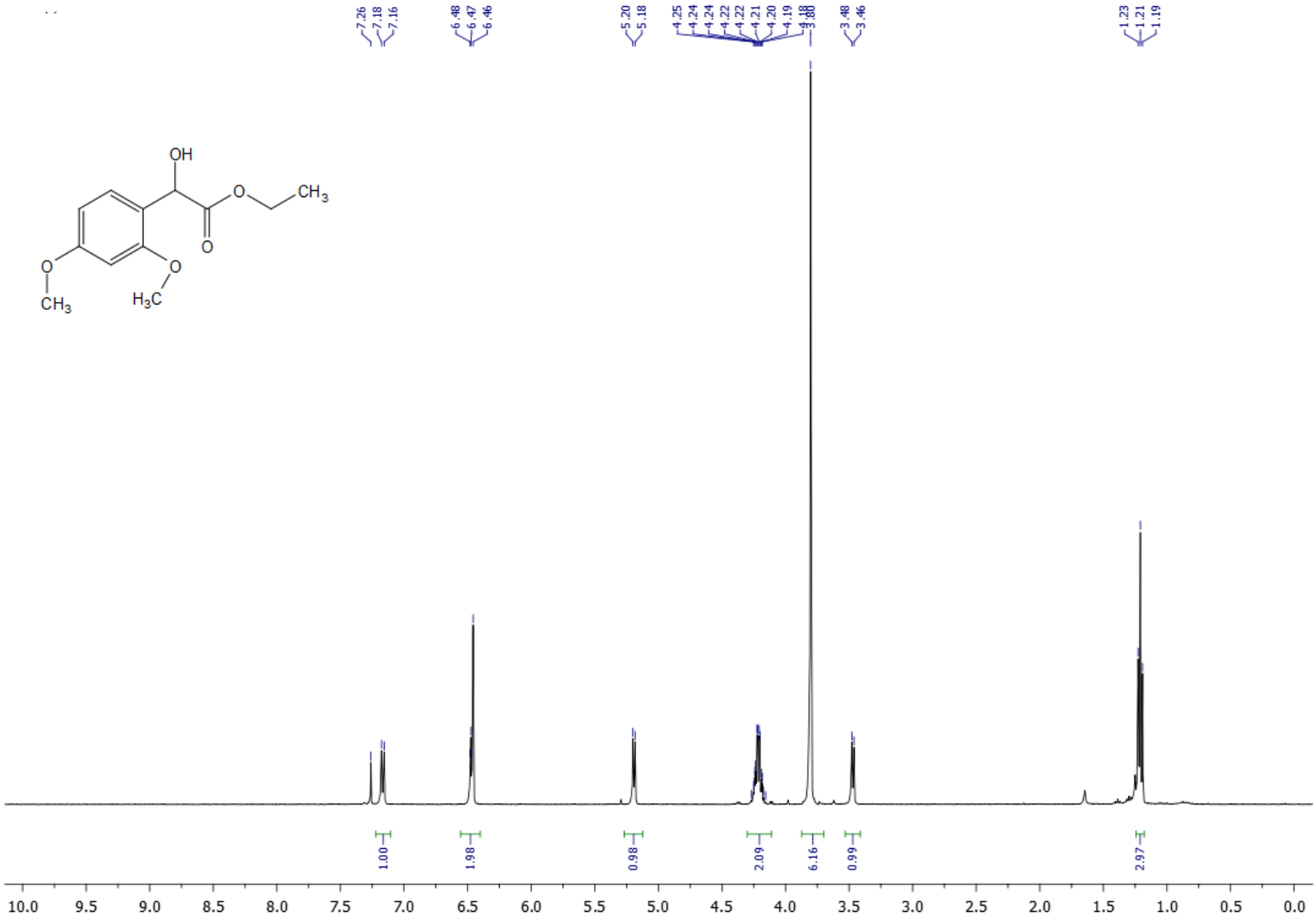
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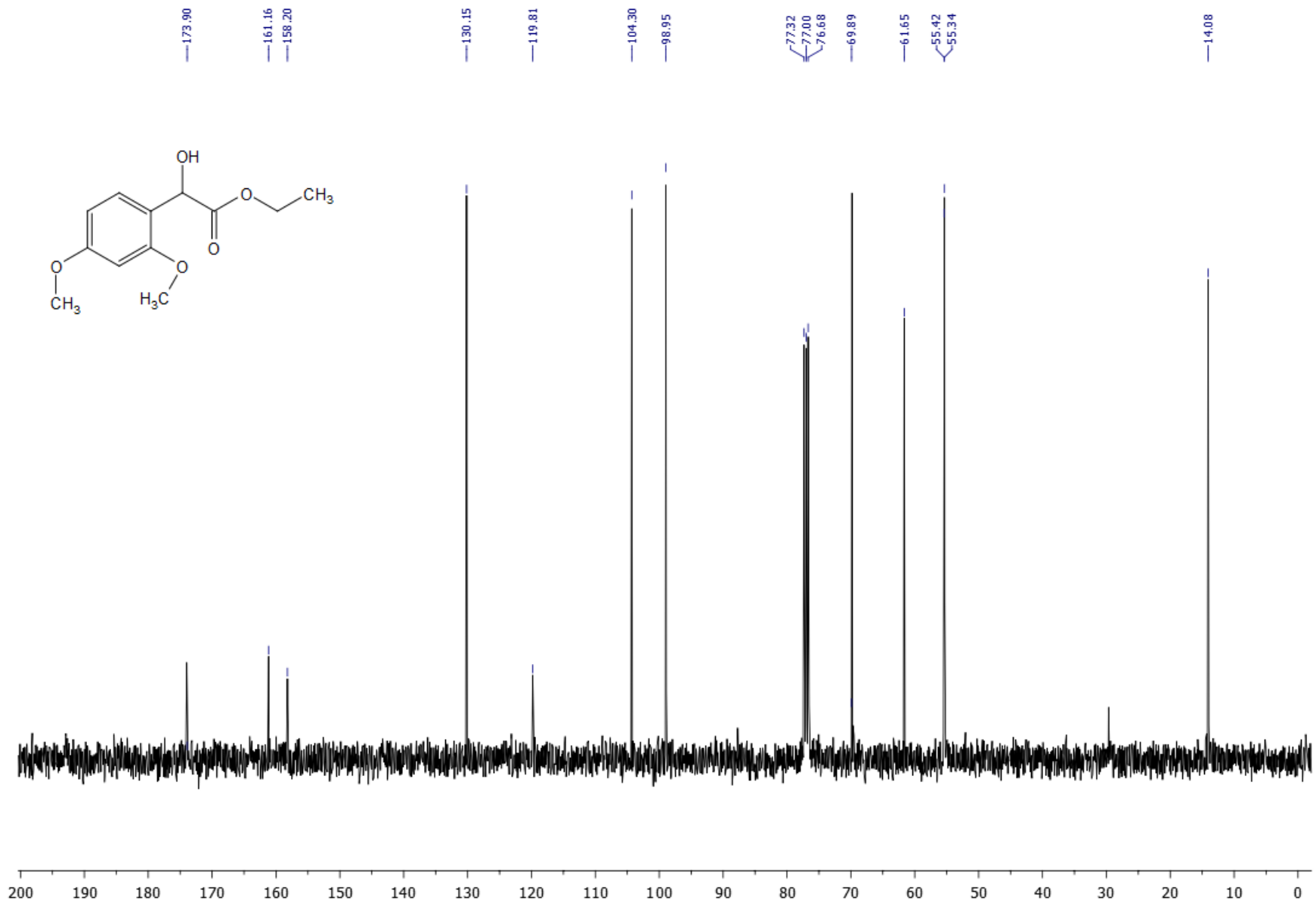
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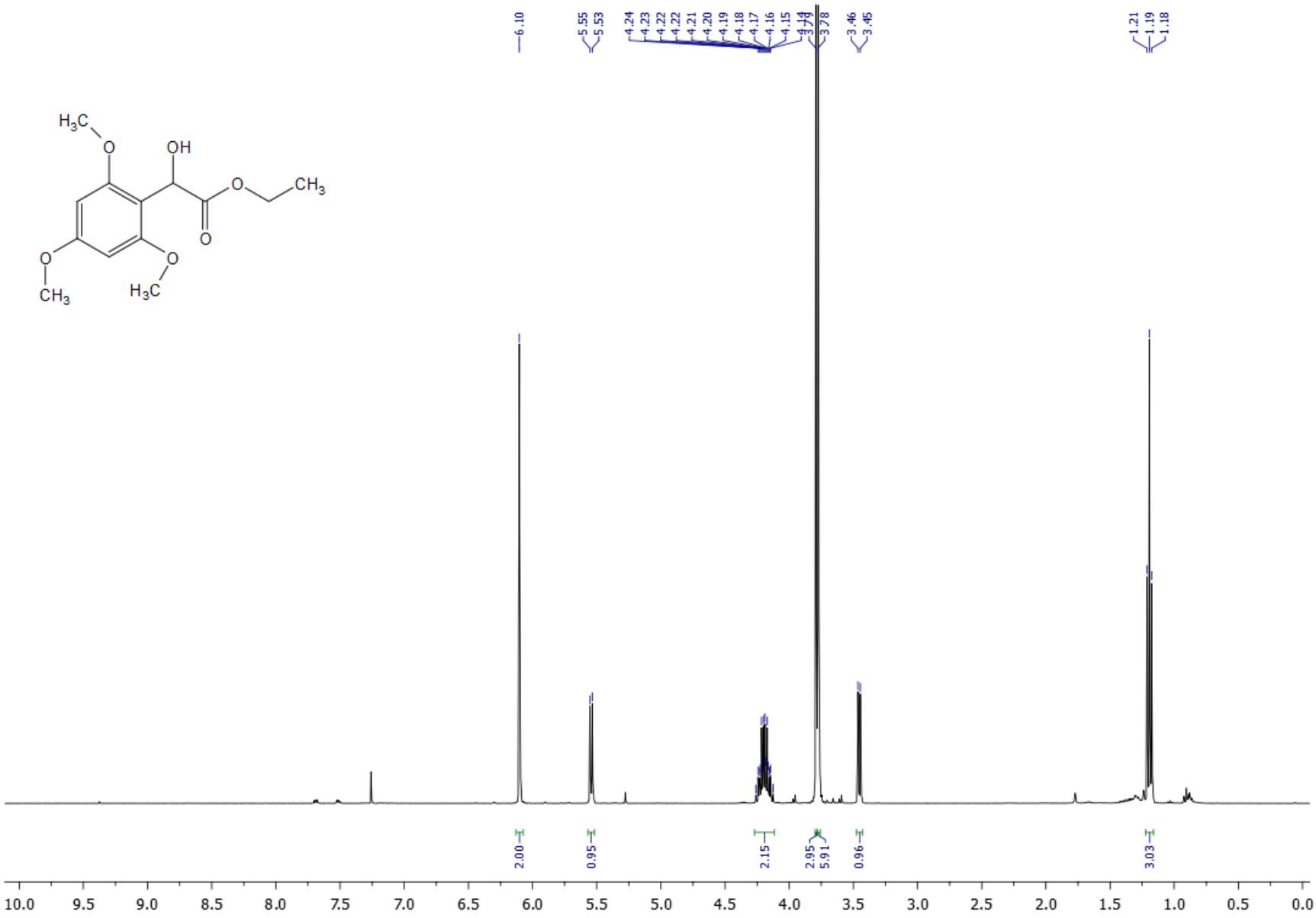
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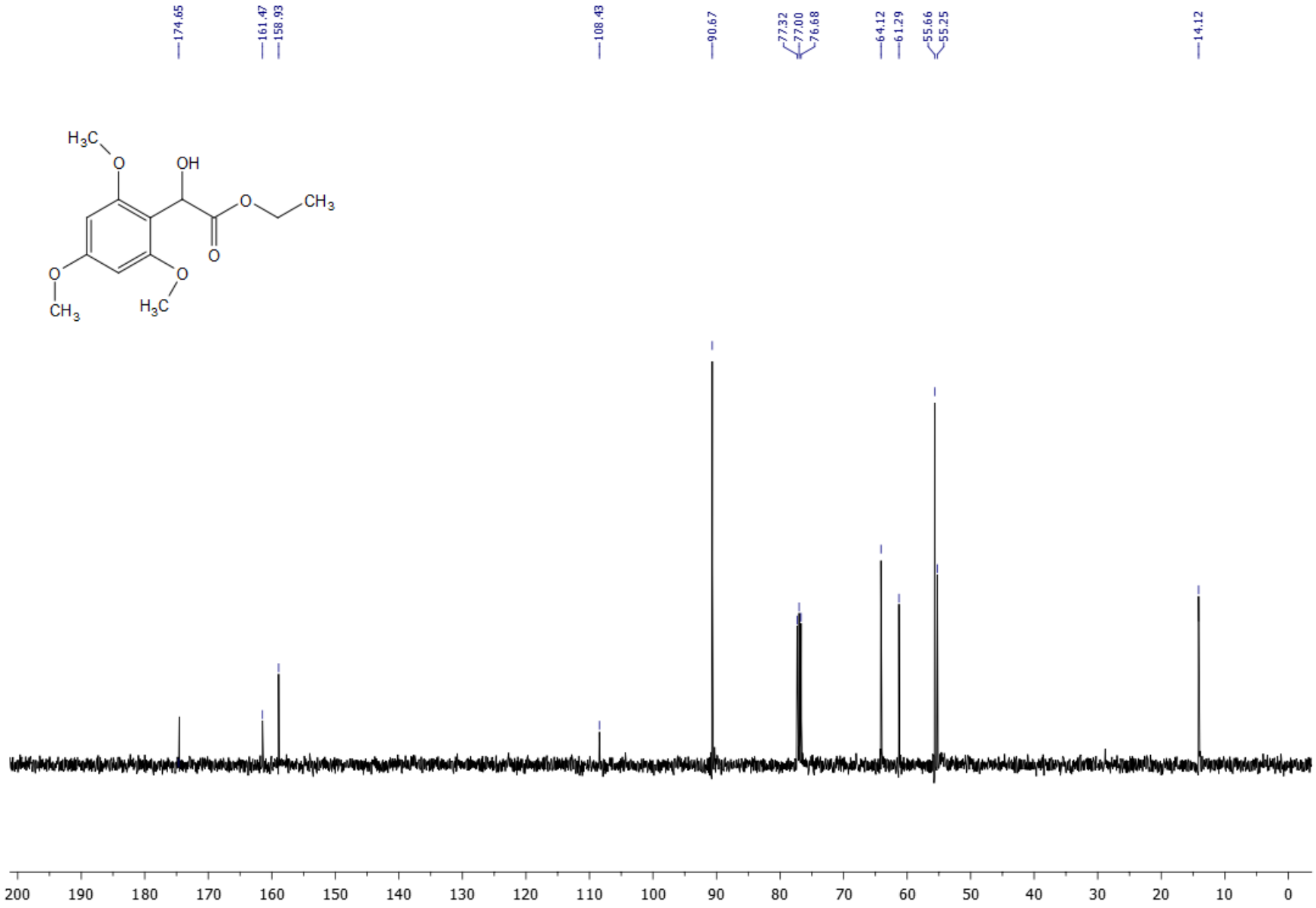
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OH
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O
CH3
H3C
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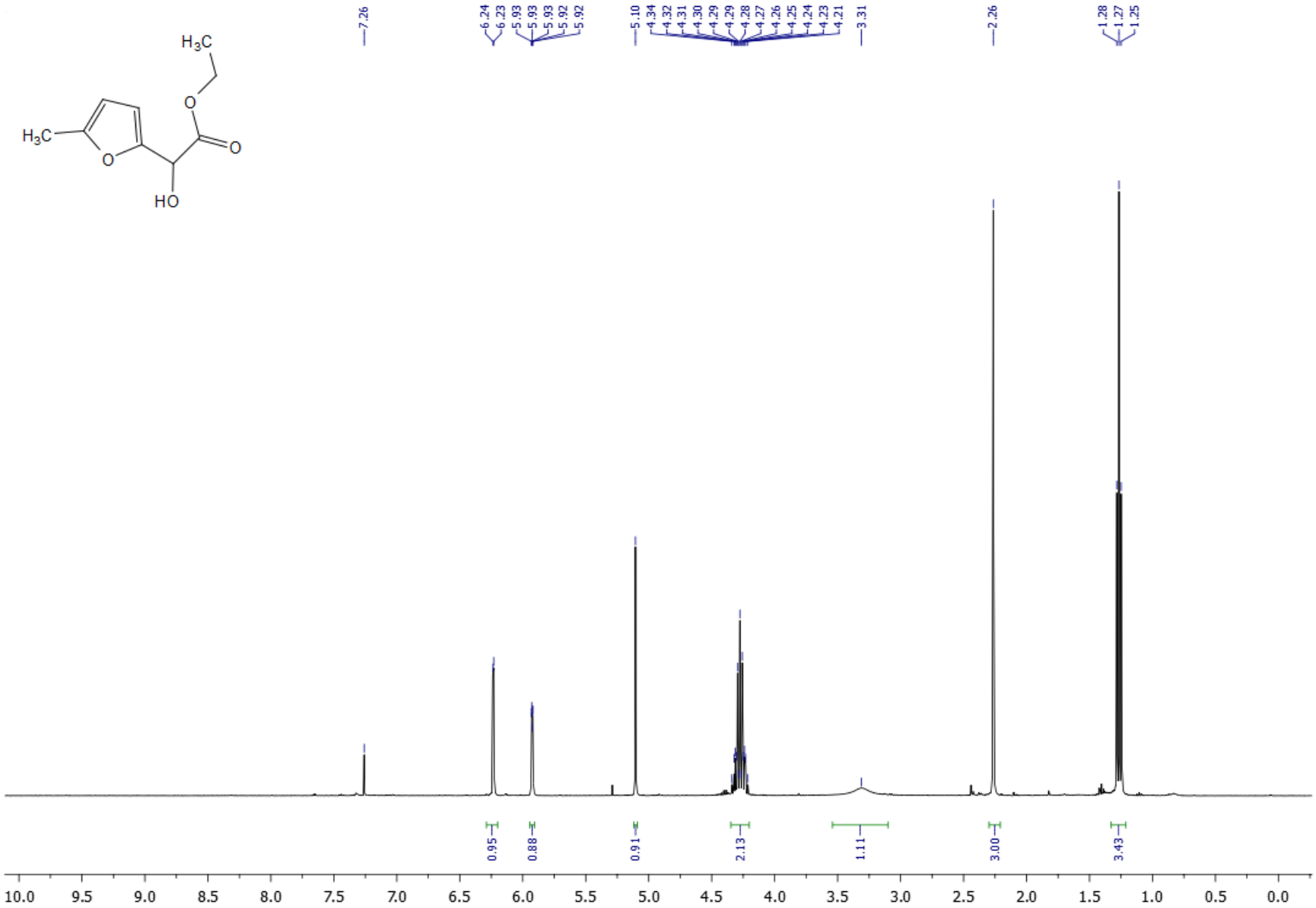
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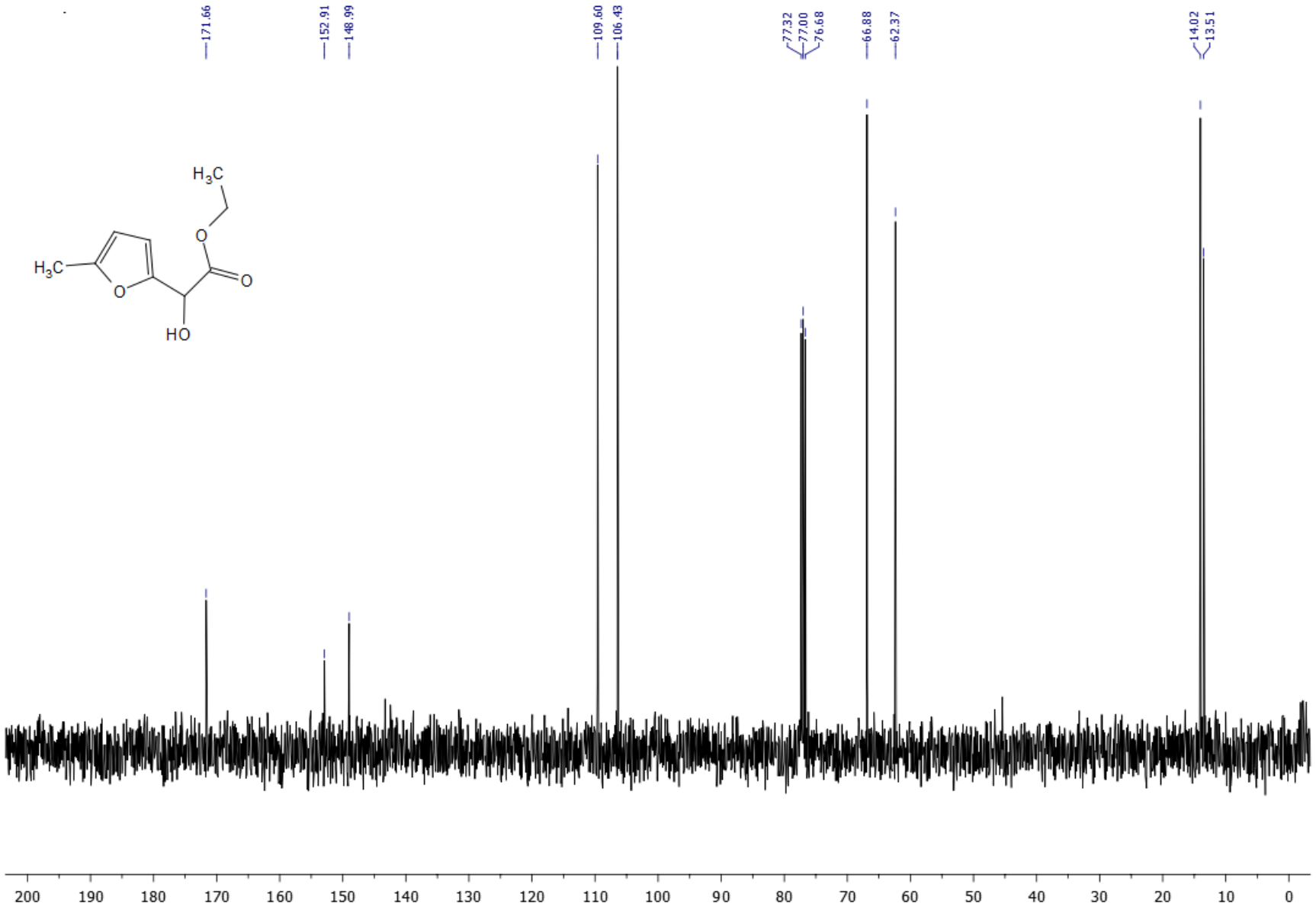
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H3C
O
O
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