Electronic supplementary materials *Mendeleev Commun.*, 2026, **36**, 167–170

Synthesis and antioxidant activity of apiol-derived 3-arylpropanamines

Alexander N. Blinnikov, Martha M. Malibiche, Olga I. Adaeva, Sergey S. Krylov, Oksana G. Shevchenko, Dmitry V. Demchuk, Marina N. Semenova and Victor V. Semenov

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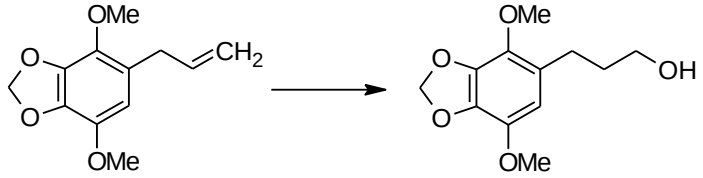
*Chemistry. Materials and methods***.** Melting points were measured on a Boetius melting point apparatus and were uncorrected. Reaction mixtures were stirred magnetically. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument [working frequencies of 300.13 MHz (^{1}H) and 75.47 MHz (^{13}C)] and Bruker DRX-500 instrument [working frequencies of 500.13 MHz (^{1}H) and 125.76 MHz (^{13}C)]. Chemical shifts in the ^{1}H NMR spectra are given relative to the residual proton signal of the solvent ($CHCl_3$ – δ_H 7.27 ppm, DMSO-d_5 – δ_H 2.50 ppm), in the ^{13}C NMR spectra – relative to the solvent signal ($CDCl_3$ – δ_C 77.0 ppm, DMSO-d_6 – δ_C 39.5 ppm).
Spin-spin coupling constants (*J*) were reported in hertz (Hz). NMR spectra (Supplementary Materials) were prepared using original software designed at N. D. Zelinsky Institute of Organic Chemistry RAS (Moscow, Russian Federation) (http://nmr.ioc.ac.ru:8080/SDF2PDF.kl1). High-resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI). Elemental analysis was performed on an automated PerkinElmer 2400 CHN microanalyzer. Solvents and amines of the highest commercial quality were purchased from Acros Organics (Belgium) and used as received.

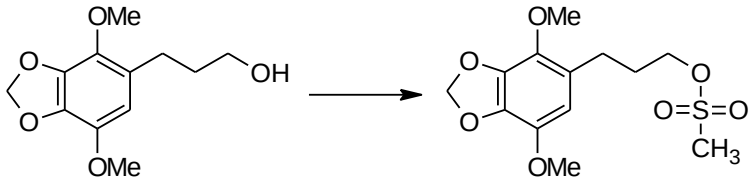
Apiol **6** was isolated using liquid CO_2 extraction of parsley variety Sakharnaya at the company Karavan Ltd. (Krasnodar, Russia).[S1] Pure **6** with 98−99% was obtained by high-efficiency distillation using a pilot plant device at N.D. Zelinsky Institute of Organic Chemistry RAS (Moscow, Russia).
A sample of hydrogenated apiol **13** for biological testing was obtained using the published method.[S2]

3-(4,7-Dimethoxy-1,3-benzodioxol-5-yl)propan-1-ol (11)



A cold solution (0–5 °C) of I_2 (25 mmol, 6.4 g) in tetrahydrofuran (THF, 75 mL) was added dropwise to a suspension of $NaBH_4$ (95 mmol, 3.6 g) in dry THF at 0–5 °C under Ar, monitoring iodine decoloration. Then the solution was stirred for 10 min, and a cold solution (0–5 °C) of apiol **6** (90 mmol) in THF (50 mL) was added. The resulting mixture was stirred for 1 h at room temperature, cooled to 7–10 °C, and diluted gradually with water (25 mL) to obtain a clear solution. Then a cooled solution (7–10 °C) of 3 M NaOH (25 mL) was added followed by careful addition of 30% hydrogen peroxide (9 mL), maintaining the temperature below 30 °C, taking into account the strong exothermic effect. The resulting mixture was stirred for 1 h at room temperature, the organic layer was separated, and the aqueous layer was washed with THF. The remaining water solution was diluted with water (15 mL), saturated with NaCl (5 mL), extracted with EtOAc (100 mL), and dried with $MgSO_4$. All organic layers (THF and EtOAc) were combined and evaporated. The resulting oil was collected to afford target 3-arylpropan-1-ol **11** that could contain 1-2% of isomeric 3-(4,7-dimethoxy-1,3-benzodioxol-5-yl)propan-2-ol and 3–5% of starting apiol **6** according to NMR spectra. Pure sample was obtained from the CH_2Cl_2 solution of **11** by re-precipitation with hexane. White solid (20.5 g, 92%); mp 50–51 °C (lit.[S3] 49–51 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (s, 1H, H_{Ar}), 5.95 (s, 2H, OCH_2O), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.60 (t, J = 6.1 Hz, 2H, CH_2OH), 2.65 (t, J = 7.3 Hz, 2H, $C_{Ar}CH_2$), 1.80 (p, J = 6.7 Hz, 2H, $C_{Ar}CH_2C\underline{H}_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 138.5, 136.3, 134.9, 127.1, 108.3, 101.4, 61.6, 60.1, 56.8, 33.7, 25.9; Calc. for $C_{12}H_{16}O_5$, C 60.0; H 6.71; Found C 60.02; H 6.68.

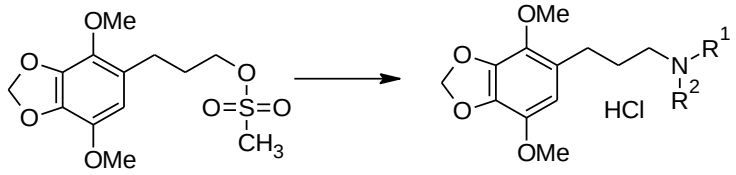
***3-(4,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl methanesulfonate* (12).**



Mesyl chloride (1.97 mL, 25.55 mmol) was added dropwise to a cooled to 0 °C solution of primary alcohol **11** (5.00 g, 20.83 mmol) and triethylamine (3.7 mL, 26.74 mmol) in dichloromethane (50 mL). The solution was stirred at room temperature for 2 h, washed with water and 10% aqueous HCl, and dried with magnesium sulfate. The drying agent was filtered off, the solvent was evaporated to obtain mesylate **12**. White solid (5.90 g, 89%); mp 52–53 °C (MeOH) (lit.[S4] 53–55 °C (MeOH)).

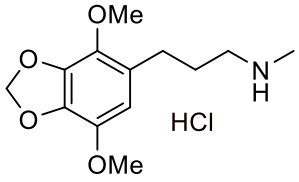
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (s, 1H, H_{Ar}); 5.95 (s, 2 H, OCH_2O); 4.22 (t, 2 H, $CH_2SO_3CH_3$, J = 6.3 Hz); 3.90 (s, 3 H, OCH_3); 3.85 (s, 3H, OCH_3); 3.01 (s, 3 H, SO_3CH_3); 2.66 (t, 2 H, $C_{Ar}CH_2$, J = 7.4 Hz); 2.00 (q, 2 H, $C_{Ar}CH_2C\underline{H}_2$, J = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$), δ: 138.9; 138.5; 136.4; 135.3; 125.7; 108.5; 101.5; 69.5; 60.0; 56.9; 37.3; 30.0; 26.3; Calc. for $C_{13}H_{18}O_7S$, C, 49.05; H, 5.70; S,10.07; Found C, 49.06; H, 5.71; S, 10.06.

General procedure for the synthesis of amines 10a–e



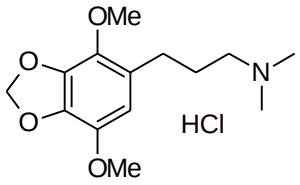
Amine (10 mmol) was added to a solution of mesylate **12** (0.30 g, 0.94 mmol) in propan-2-ol (5 mL), and the mixture was kept at room temperature for 3 days. The solvent was evaporated, then CCl_4 (10 mL), water (7 mL) and K_2CO_3 (0.14 g, 1 mmol) were added to the residue. The mixture was stirred on a magnetic stirrer, the organic layer was separated, and the aqueous layer was extracted with CCl_4 (2 × 5 mL). The organic phases were washed with water (7 mL), the organic layer was separated, and the aqueous layer was extracted with CCl_4 (3 mL). The combined organic solutions were dried with Na_2SO_4 while stirring on a magnetic stirrer and evaporated. Hydrochloric acid (~5%) was added to adjust to pH 1. The resulting solution was evaporated to dryness, the residue was rinsed with CCl_4 (2 × 5 mL) and dried *in vacuo*.

3-(4,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)-N-methylpropan-1-amine hydrochloride (10a)



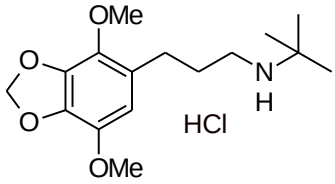
White solid (0.18 g, 66.0%); mp 140–141 °C. ^{1}H NMR (300 MHz, DMSO-d_6)□δ□8.97 (br s, 2H, NH·HCl), 6.48 (s, 1H, H_{Ar}), 5.96 (s, 2H, OCH_2O), 3.80 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.80 (t, 2 H, NH·HCl-CH_2, J = 7.7 Hz), 2.54 (t, 2H, $C_{Ar}CH_2$, J = 7.4 Hz), 2.49 (s, 3H, NCH_3), 1.82 (p, 2H, $C_{Ar}CH_2C\underline{H}_2$, J = 7.4 Hz); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 138.6, 138.4, 135.8, 134.8, 125.9, 108.5, 101.4, 59.8, 56.6, 47.6, 32.2, 26.5, 26.4; HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calc for $C_{16}H_{26}NO_4$ 254.1387; Found 254.1381.

3-(4,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)-N,N-dimethylpropan-1-amine hydrochloride (10b)



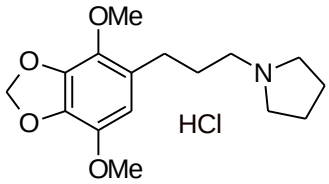
White solid (0.19 g, 66.5%); mp 143–144 °C. ^{1}H NMR (300 MHz, DMSO-d_6)□δ 10.83 (br s, 1H, N·HCl), 6.49 (s, 1H, H_{Ar}), 5.97 (s, 2H, OCH_2O), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.01–2.94 (m, 2H, NH·HCl-CH_2), 2.69 (d, 6H, HN^+Me_2, J = 4.8 Hz), 2.53 (t, 2H, $C_{Ar}CH_2$, J = 7.5 Hz), 1.88 (p, 2H, $C_{Ar}CH_2C\underline{H}_2$, J = 7.7 Hz); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ: 138.6, 138.3, 135.8, 134.8, 125.7, 108.5, 101.3, 59.8, 56.6, 55.8, 41.7 (2C), 26.4, 24.7; HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calc for $C_{14}H_{22}NO_4$ 268.1543; Found 268.1541.

N-(tert-Butyl)-3-(4,7-dimethoxybenzo[d][1,3]dioxol-5-yl)propan-1-amine hydrochloride (10c)



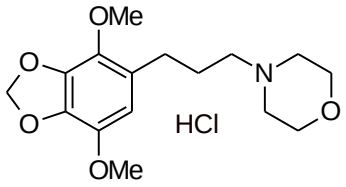
White solid (0.20 g, 62.4%); mp 169–170.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6)□δ8.94 (br s, 2H, NH·HCl), 6.51 (s, 1H, H_{Ar}), 5.97 (s, 2H, OCH_2O), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.81 (m, 2H, NH·HCl-CH_2), 2.57 (t, 2H, $C_{Ar}CH_2$, J = 7.5 Hz), 1.89 (p, 2H, $C_{Ar}CH_2C\underline{H}_2$, J = 7.5 Hz), 1.28 (s, 9H, $NC(CH_3)_3$); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 138.59, 138.36, 135.80, 134.72, 126.13, 108.37, 101.34, 59.81, 56.57, 55.81, 40.19, 27.16, 26.74, 25.02(3C); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calc for $C_{16}H_{26}NO_4$ 296.1856; Found 296.1849.

1-[3-(4,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl]pyrrolidine hydrochloride (10d)

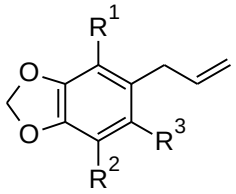


White solid (0.21 g, 67.7%); mp 153–154.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6)□δ□10.93 (br s, H, N·HCl), 6.49 (s, 1H, H_{Ar}), 5.97 (s, 2H, OCH_2O), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.47 (m, 2H, HCl·N-CH_2), 3.04 (m, 2H, N·HCl-CH_2), 2.92 (m, 2H, HCl·N-$(CH)_2$), 2.54 (t, 2H, $C_{Ar}CH_2$, J = 7.6 Hz), 1.90 (m, 6H, $C_{Ar}CH_2C\underline{H}_2$, C-$CH_2CH_2$-C); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 138.62, 138.35, 135.80, 134.79, 125.80, 108.45, 101.36, 59.81, 56.58, 53.27, 52.62 (2C), 26.60, 26.15, 22.67(2C); HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calc for $C_{16}H_{24}NO_4$ 294.1700; Found 294.1695.

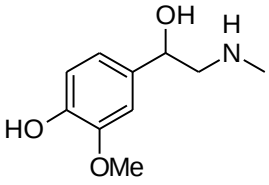
4-[3-(4,7-Dimethoxy-2H-1,3-benzodioxol-5-yl)propyl]morpholine hydrochloride (10e)



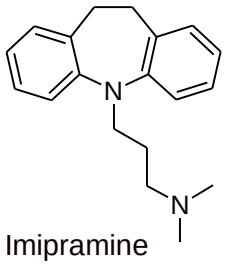
White solid (0.21 g, 64.6%); mp 176.5–178 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.45 (br s, H, N·HCl), 6.48 (s, 1H, H_{Ar}), 5.97 (s, 2H, OCH_2O), 4.01–3.83 (m, 4H, $(CH)_2O$), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.35 (m 2H, N-CH_2), 3.02 (m, 4H HCl·N-CH_2), 2.53 (t, 2H, $C_{Ar}CH_2$, J = 7.6 Hz), 1.95 (m, 2H, $C_{Ar}CH_2C\underline{H}_2$); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ 138.6, 138.3, 135.8, 134.8, 125.7, 108.4, 101.3, 63.0 (2C), 59.8, 56.6, 55.4, 50.8 (2C), 26.5, 23.7; HRMS (ESI/QTOF) m/z: $[M+H]^+$ Calc for $C_{16}H_{24}NO_5$ 310.1649; Found 310.1640.



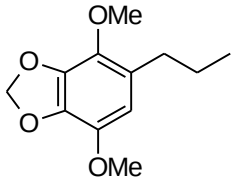
Myristicin: R^1=R^3=H, R^2=OMe
Apiol: R^1=R^2=OMe, R^3=H
Dillapiol: R^1=H, R^2=R^3=OMe
Hydroxyapiol: R^1=R^2=OMe, R^3=OH
Nothoapiol: R^1=R^2=R^3=OMe



Metanephrine



Imipramine



Hydrogenated apiol

Figure S1 Structure of allylpolyalkoxybenzenes, inhibitors of catecholamine uptake metanephrine and imipramine, and hydrogenated apiol.

Biology. Antioxidant activity assays.

In vitro procedures were used exclusively, no experiments on animals were carried out. Phosphate buffered saline (PBS, pH 7.4), 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH) (Sigma-Aldrich, Germany), 2-thiobarbituric acid (TBA) (Alfa Aesar, USA), trichloroacetic acid (Alfa Aesar, USA), ascorbic acid (ICN Biomedical Inc., USA), $FeSO_4$ (reagent grade), (OOO Reakhim, Russia), 2,2′-azinobis(3-ethylbenzthiazoline-6-sulfonic acid) diammonium salt (ABTS) (Alfa Aesar, USA), 2,2-diphenyl-1-picrylhydrazyl (DPPH) (Alfa Aesar, USA), and H_2O_2 (pure grade) solution were used for the assay. Trolox (6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid, Sigma-Aldrich, Germany) served as a reference compound.

Stock solutions of tested molecules **10a–e** and **13** were prepared in acetone at 1 and 10 mM concentration. Mouse RBCs and brain homogenate were incubated at 37 °C in thermostated Biosan ES-20 shaker (Latvia). Absorption was measured using a Thermo Spectronic Genesys 20 spectrophotometer (USA). Each experiment was repeated 4–20 times. Statistical analysis was conducted using Microsoft Office Excel 2010 and Statistica 6.0 software packages. Experimental data is presented as mean values with standard errors (SE). The statistical significance of the differences (*p* value) was assessed using Mann–Whitney U-test.

Radical scavenging activity of compounds was measured according to previously reported procedures by their ability to interact with DPPH[S5] and ABTS.[S6,S7] Antioxidant activity of the compounds was assessed by their ability to inhibit lipid peroxidation in substrates obtained from the brain of laboratory mice.[S8,S9] Antioxidant and membrane-protective effect of apiol-derived propylamines **10a–e** and apiol propyl derivative **13** were evaluated using mammalian RBCs as a cell test system.[S10] The activity of tested molecules was estimated as their ability to increase RBC survival at 10 μM concentration under oxidative hemolysis initiated by H_2O_2 (1.8 mM) or AAPH (3 mM) as described previously.[S11-S14]

Study of compounds effect on sea urchin embryos.[S15]

Experiments were carried out in a biological laboratory in Cyprus. Adult sea urchins *Paracentrotus lividus* were collected from the coastal area and kept in an aerated seawater aquarium. Spawning was stimulated by intracoelomic injection of 0.5 M solution of KCl (1–2 mL). The resulting eggs were washed with seawater filtered through a nylon filter and fertilized by adding a few drops of diluted sperm.

Stock solutions of compounds were prepared in DMSO at a concentration of 10 mM, followed by a 10-fold dilution with 96% EtOH. This procedure enhanced the solubility of test compounds in the salt-containing medium (seawater). Solubility of tested molecules was examined using MBS-10 stereomicroscope (Lytkarino, Moscow Region, Russia). The maximal tolerated concentrations of DMSO and EtOH in the *in vivo* assay were determined to be 0.05% and 1%, respectively. Higher concentrations of either DMSO (≥0.1%) or EtOH (>1%) caused non-specific alteration and retardation of the sea urchin embryo development independent of the exposed stage.

For treatment with test compounds, 5 mL aliquots of fertilized egg suspension were transferred to six-well plates and incubated in filtered seawater at room temperature (18–23 °C) as a monolayer at a concentration up to 2000 eggs(embryos)/mL. The effect was assessed by exposing fertilized eggs (8–20 min after fertilization, 43–55 min before the first mitotic cycle completion) to 2-fold decreasing concentrations of the compound and estimated quantitatively as an effective threshold concentration (EC), resulting in developmental abnormalities. Embryo development was monitored using a microscope MBS-10 until the beginning of active feeding (four-arm middle pluteus stage, 34–36 h postfertilization).

Experiments with sea urchin embryos fulfill the requirements of biological ethics. The artificial spawning procedure did not affect the viability of the animals, embryos developed outside the female organism, and both post-spawned adult sea urchins and the excess intact embryos were returned to the sea, their natural habitat.

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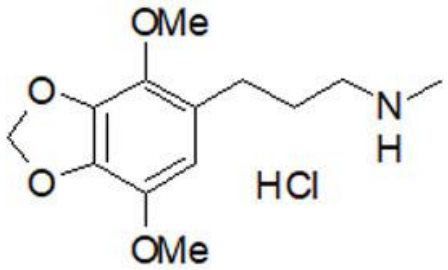
10a



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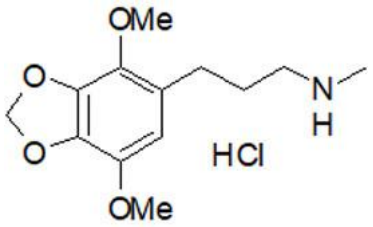
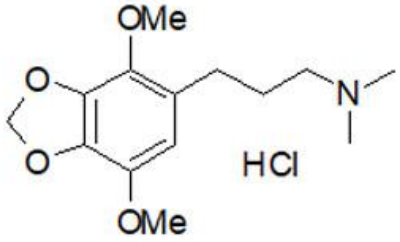


138.613
138.357
135.817
134.799
125.908
108.505
101.361
59.811
56.589
47.654
40.334
40.059
39.780
39.502
39.224
38.947
38.667
32.215
26.509
26.457

145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 ppm

10b



138.609
138.312
135.785
134.790
125.726
125.410
108.462
101.336
63.006
59.779
56.573
55.862
55.394
50.768
41.747
40.328
40.049
39.770
39.492
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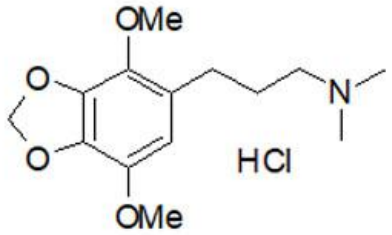
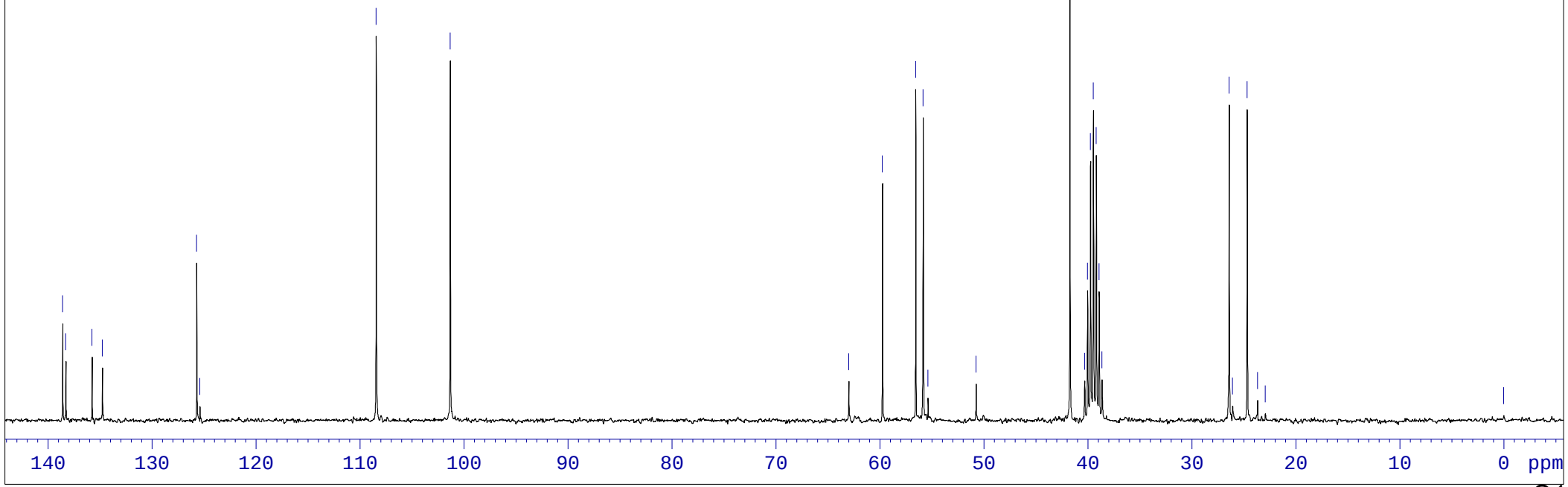
38.936
38.661
26.429
26.107
24.699
23.695
22.955
0.026

10b





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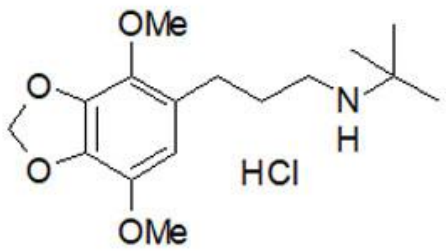

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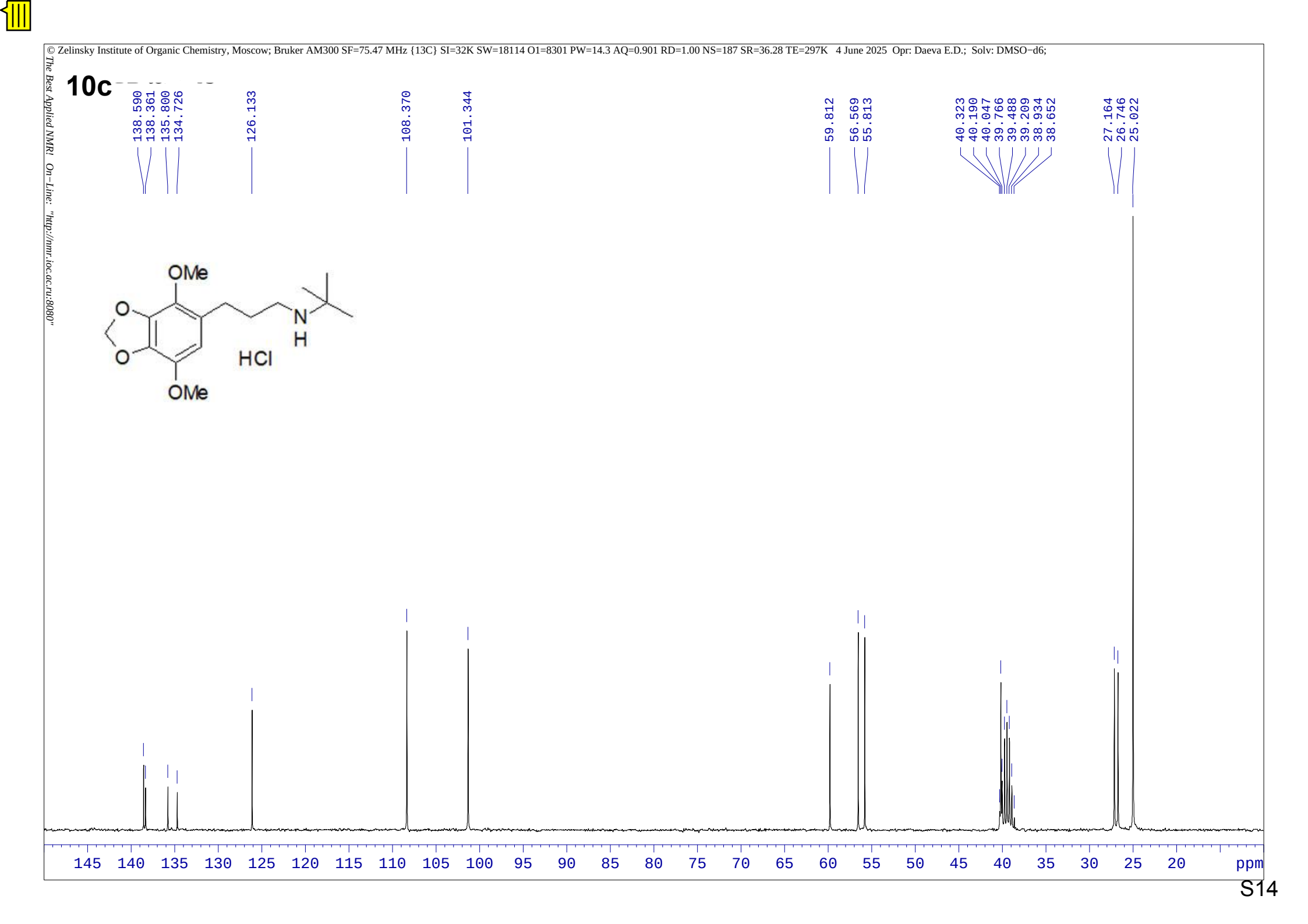

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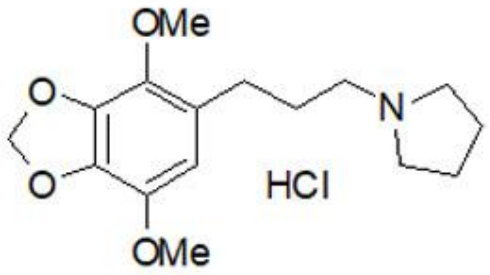

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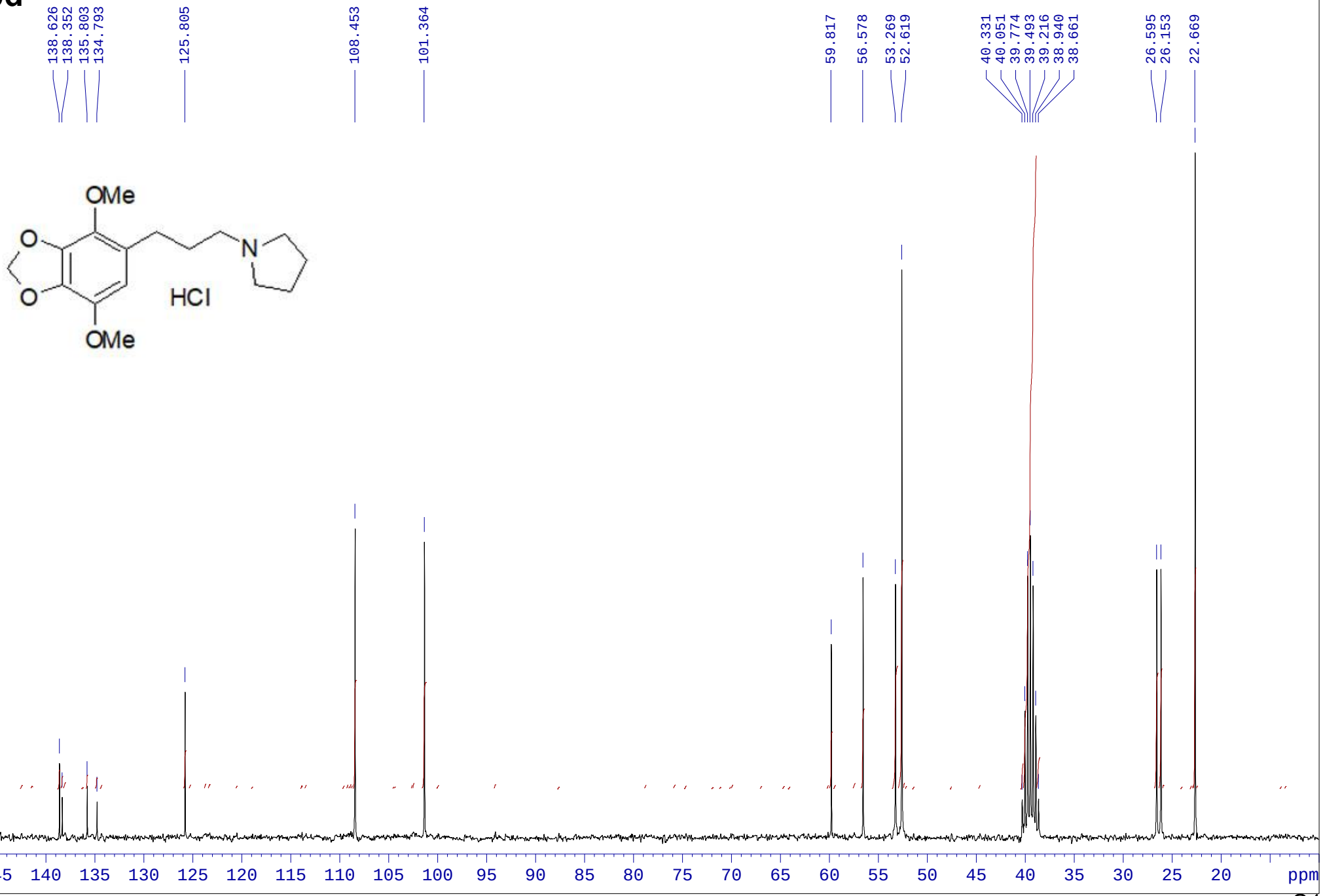

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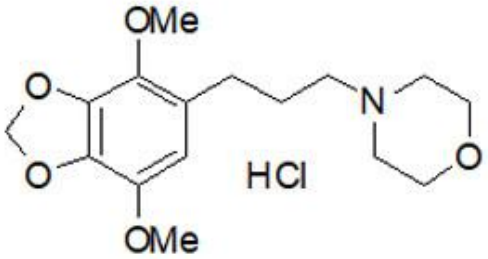

10e