

**Synthesis of substituted benzofuran-3-ylacetic acids
based on three-component condensation of polyalkoxyphenols,
arylglyoxals and Meldrum's acid**

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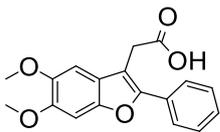
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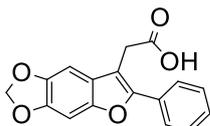
1. General. Unless otherwise noted, all the reagents were purchased from commercial suppliers and used without further purification. Arylglyoxals were prepared according to the procedure [H.A. Riley, A.R. Gray, Phenylglyoxal, *Org. Synth.* **15** (1935) 67–69]. ¹H and ¹³C NMR spectra were recorded on a Bruker AM 300 MHz and Bruker AV 600 MHz spectrometers in DMSO-d₆; the chemical shifts (δ) for ¹H and ¹³C NMR spectra are reported in parts per million (ppm) with the solvent resonance as the internal standard. High-resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI). The melting points were determined on a Kofler hot stage.

2. Synthesis of benzofuran-3-ylacetic acids **8a-o (general procedure).** A solution of the corresponding phenol **4a-c** (3 mmol), arylglyoxal hydrate **7a-g** (5 mmol), Meldrum's acid (0.90 g, 6.25 mmol) and triethylamine (0.76 g, 7.5 mmol) in acetonitrile (7 ml) was kept at room temperature for 3 days. Then AcOH (2 ml) was added, and the mixture was evaporated *in vacuo*. Acetic acid (5 ml) and conc. HCl (3 ml) were added to the residue, and the obtained solution was refluxed for 15 min. Then water (2 ml) was added, and the resulting mixture was stirred at room temperature for 2 h and left overnight. The precipitate formed was collected by filtration and washed with 50% aqueous acetic acid (3 x 7 ml). To remove traces of AcOH and HCl, the precipitate was kept for 24 h in water (50 ml) at room temperature, filtered off and washed with water (3 x 10 ml).

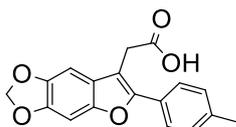
3. Characterization of products.



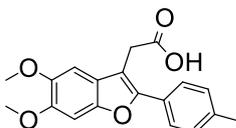
2-(5,6-Dimethoxy-2-phenylbenzofuran-3-yl)acetic acid (8a), 650 mg, yield 69%, white powder, mp. 178–180 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 3.76 – 3.95 (m, 8H), 7.21 (s, 1H, H_{Ar}), 7.31 (s, 1H, H_{Ar}), 7.36 – 7.47 (m, 1H, H_{Ar}), 7.48 – 7.59 (m, 2H, H_{Ar}), 7.75 (d, $J = 7.7$ Hz, 2H, H_{Ar}), 12.60 (s, 1H, COOH); $^{13}\text{C NMR}$ (151 MHz, DMSO- d_6) δ 31.31, 57.17, 57.25, 96.76, 103.06, 111.35, 122.97, 127.11, 129.27, 130.12, 131.56, 147.61, 149.09, 149.53, 151.57, 173.12; HRMS Calcd for ($\text{C}_{18}\text{H}_{16}\text{O}_5$) [$\text{M}+\text{H}$] $^+$: 313.1071; Found: 313.1079.



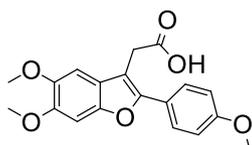
[6-Phenylfuro[2,3-*f*][1,3]benzodioxol-7-yl]acetic acid (8b), 490 mg, yield 55%, grey powder, mp. 195–197 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 3.81 (s, 2H, CH_2), 6.06 (s, 2H, OCH_2O), 7.14 (s, 1H, H_{Ar}), 7.27 (s, 1H, H_{Ar}), 7.34 – 7.46 (m, 1H, H_{Ar}), 7.46 – 7.63 (m, 2H, H_{Ar}), 7.72 (d, $J = 7.6$ Hz, 2H, H_{Ar}), 12.61 (s, 1H, COOH); $^{13}\text{C NMR}$ (151 MHz, DMSO- d_6) δ 31.27, 94.50, 99.74, 102.52, 111.64, 124.50, 127.18, 129.42, 130.13, 131.30, 145.44, 147.40, 149.54, 152.20, 173.03; HRMS Calcd for ($\text{C}_{17}\text{H}_{12}\text{O}_5$) [$\text{M}+\text{H}$] $^+$: 297.0757; Found: 297.0752.



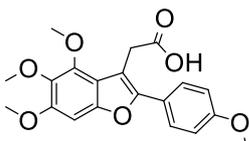
[6-(4-Methylphenyl)furo[2,3-*f*][1,3]benzodioxol-7-yl]acetic acid (8c), 490 mg, isolated yield 53%, grey powder, mp. 214–216 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 2.35 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 6.05 (s, 2H, OCH_2O), 7.12 (s, 1H, H_{Ar}), 7.26 (s, 1H, H_{Ar}), 7.32 (d, $J = 7.9$ Hz, 2H, H_{Ar}), 7.60 (d, $J = 7.9$ Hz, 2H, H_{Ar}), 12.56 (s, 1H, COOH); $^{13}\text{C NMR}$ (151 MHz, DMSO- d_6) δ 22.03, 31.25, 94.47, 99.66, 102.47, 110.95, 124.55, 127.15, 128.57, 130.68, 139.01, 145.36, 147.20, 149.39, 152.45, 173.07; HRMS Calcd for ($\text{C}_{18}\text{H}_{14}\text{O}_5$) [$\text{M}+\text{H}$] $^+$: 311.0914; Found: 311.0912.



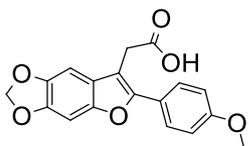
2-(5,6-Dimethoxy-2-(4-methylphenyl)benzofuran-3-yl)acetic acid (8d), 625 mg, yield 64%, white powder, mp. 170–172 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 2.35 (s, 3H, CH_3), 3.78 – 3.85 (m, 8H), 7.17 (s, 1H, H_{Ar}), 7.27 (s, 1H, H_{Ar}), 7.32 (d, $J = 7.9$ Hz, 2H, H_{Ar}), 7.62 (d, $J = 7.9$ Hz, 2H, H_{Ar}), 12.55 (s, 1H, COOH); $^{13}\text{C NMR}$ (75 MHz, DMSO- d_6) δ 20.85, 30.13, 56.00, 56.09, 95.61, 101.88, 109.46, 121.88, 125.93, 127.65, 129.50, 137.66, 146.38, 147.78, 148.18, 150.67, 171.98; HRMS Calcd for ($\text{C}_{19}\text{H}_{18}\text{O}_5$) [$\text{M}+\text{H}$] $^+$: 327.1227; Found: 327.1221.



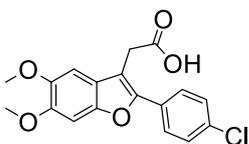
2-(5,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)acetic acid (8e), 625 mg, yield 61%, grey powder, mp. 134–136 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 3.74 – 3.87 (m, 11H), 7.09 (d, $J = 8.4$ Hz, 2H, H_{Ar}), 7.16 (s, 1H, H_{Ar}), 7.27 (s, 1H, H_{Ar}), 7.67 (d, $J = 8.4$ Hz, 2H, H_{Ar}), 12.57 (s, 1H, COOH); $^{13}\text{C NMR}$ (75 MHz, DMSO- d_6) δ 30.13, 55.25, 56.02, 56.11, 95.65, 101.85, 108.53, 114.45, 121.95, 122.96, 127.55, 146.34, 147.67, 147.97, 150.73, 159.19, 172.08; HRMS Calcd for (C₁₉H₁₈O₆) [M+H]⁺: 343.1176; Found: 343.1172.



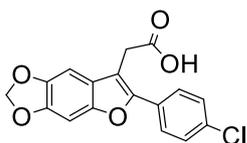
2-(4,5,6-Trimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)acetic acid (8f), 500 mg, yield 45%, white powder, mp. 157–159 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 3.74 (s, 3H, OCH₃), 3.77 – 3.83 (m, 5H), 3.84 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃), 7.01 – 7.13 (m, 3H, H_{Ar}), 7.57 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 12.57 (s, 1H, COOH); $^{13}\text{C NMR}$ (75 MHz, DMSO- d_6) δ 30.60, 55.25, 56.32, 60.69, 60.96, 91.55, 108.09, 114.47, 122.45, 127.64, 127.95, 137.93, 146.16, 149.70, 150.66, 152.12, 159.35, 172.24; HRMS Calcd for (C₂₀H₂₀O₇) [M+H]⁺: 373.1282; Found: 373.1280.



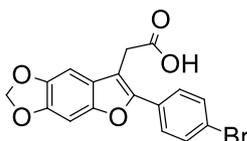
[6-(4-Methoxyphenyl)furo[2,3-*f*][1,3]benzodioxol-7-yl]acetic acid (8g), 685 mg, yield 70%, grey powder, mp. 198–200 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 3.75 (s, 2H, OCH₂O), 3.81 (s, 3H, OCH₃), 6.05 (s, 2H, CH₂), 7.04 – 7.15 (m, 3H, H_{Ar}), 7.26 (s, 1H, H_{Ar}), 7.65 (d, $J = 8.5$ Hz, 2H, H_{Ar}), 12.60 (s, 1H, COOH); $^{13}\text{C NMR}$ (75 MHz, DMSO- d_6) δ 30.08, 55.25, 93.28, 98.41, 101.25, 108.85, 114.45, 122.69, 123.43, 127.61, 144.12, 145.80, 148.08, 151.33, 159.27, 171.98; HRMS Calcd for (C₁₈H₁₄O₆) [M+H]⁺: 327.0863; Found: 327.0857.



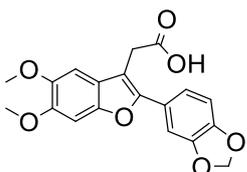
2-(2-(4-Chlorophenyl)-5,6-dimethoxybenzofuran-3-yl)acetic acid (8h), 590 mg, yield 57%, white powder, mp. 176–178 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 3.82 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 3.87 (s, 2H, CH₂), 7.20 (s, 1H, H_{Ar}), 7.29 (s, 1H, H_{Ar}), 7.59 (d, $J = 8.6$ Hz, 2H, H_{Ar}), 7.75 (d, $J = 8.6$ Hz, 2H, H_{Ar}), 12.63 (s, 1H, COOH); $^{13}\text{C NMR}$ (151 MHz, DMSO- d_6) δ 31.22, 57.14, 57.19, 96.65, 102.90, 112.06, 122.83, 128.65, 130.20, 130.39, 133.77, 147.66, 149.12, 149.70, 150.36, 173.00; HRMS Calcd for (C₁₈H₁₅ClO₅) [M+H]⁺: 347.0681; Found: 347.0682.



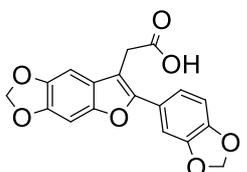
[6-(4-Chlorophenyl)furo[2,3-f][1,3]benzodioxol-7-yl]acetic acid (8i), 600 mg, yield 60%, white powder, mp. 217–219 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 3.81 (s, 2H, CH₂), 6.06 (s, 2H, OCH₂O), 7.14 (s, 1H, H_{Ar}), 7.27 (s, 1H, H_{Ar}), 7.57 (d, J = 8.3 Hz, 2H, H_{Ar}), 7.73 (d, J = 8.3 Hz, 2H, H_{Ar}), 12.65 (s, 1H, COOH); $^{13}\text{C NMR}$ (151 MHz, DMSO- d_6) δ 30.05, 93.41, 98.60, 101.47, 111.18, 123.26, 127.65, 129.00, 129.15, 132.81, 144.41, 146.50, 148.47, 149.86, 171.79; HRMS Calcd for (C₁₇H₁₁ClO₅) [M+Na]⁺: 353.0187; Found: 353.0179.



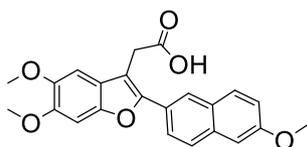
[6-(4-Bromophenyl)furo[2,3-f][1,3]benzodioxol-7-yl]acetic acid (8j), 700 mg, yield 62%, white powder, mp. 221–223 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 3.81 (s, 2H, CH₂), 6.06 (s, 2H, -O-CH₂-O-), 7.14 (s, 1H, H_{Ar}), 7.27 (s, 1H, H_{Ar}), 7.53 – 7.86 (m, 4H, H_{Ar}), 12.61 (s, 1H, COOH); $^{13}\text{C NMR}$ (126 MHz, DMSO- d_6) δ 30.07, 93.36, 98.59, 101.48, 111.26, 121.45, 123.27, 127.83, 129.35, 131.96, 144.43, 146.52, 148.49, 149.91, 171.72; HRMS Calcd for (C₁₇H₁₁BrO₅) [M+Na]⁺: 398.9662; Found: 398.9655.



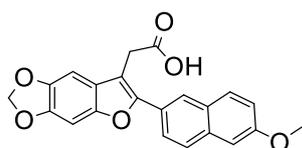
[2-(1,3-Benzodioxol-5-yl)-5,6-dimethoxy-1-benzofuran-3-yl]acetic acid (8k), 570 mg, yield 53%, grey powder, mp. 144–146 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 3.78 (s, 2H, CH₂), 3.80 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 6.10 (s, 2H, OCH₂O), 7.07 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.15 (s, 1H, H_{Ar}), 7.20 – 7.27 (m, 3H, H_{Ar}), 12.56 (s, 1H, COOH); $^{13}\text{C NMR}$ (126 MHz, DMSO- d_6) δ 30.18, 56.03, 56.11, 95.62, 101.45, 101.84, 106.35, 108.89, 109.03, 120.37, 121.86, 124.37, 146.41, 147.34, 147.65, 147.82, 148.15, 150.53, 172.11; HRMS Calcd for (C₁₉H₁₆O₇) [M+H]⁺: 357.0969; Found: 357.0959.



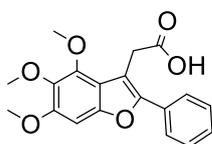
[6-(1,3-Benzodioxol-5-yl)furo[2,3-f][1,3]benzodioxol-7-yl]acetic acid (8l), 700 mg, yield 69%, grey powder, mp. 236–238 °C. $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ 3.76 (s, 2H, CH₂), 6.07 (s, 2H, OCH₂O), 6.11 (s, 2H, OCH₂O), 7.05 – 7.15 (m, 2H, H_{Ar}), 7.20 – 7.28 (m, 3H, H_{Ar}), 12.60 (s, 1H, COOH); $^{13}\text{C NMR}$ (75 MHz, DMSO- d_6) δ 30.06, 93.29, 98.43, 101.29, 101.44, 106.36, 108.86, 109.28, 120.45, 123.31, 124.06, 144.19, 145.97, 147.41, 147.79, 148.05, 151.11, 171.89; HRMS Calcd for (C₁₈H₁₂O₇) [M+H]⁺: 341.0656; Found: 341.0648.



2-(5,6-Dimethoxy-2-(6-methoxynaphthalen-2-yl)benzofuran-3-yl)acetic acid (8m), 650 mg, yield 55%, yellowish powder, mp. 170–172 °C. $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.93 (s, 2H, CH_2), 7.17 – 7.27 (m, 2H, H_{Ar}), 7.31 (s, 1H, H_{Ar}), 7.37 (s, 1H, H_{Ar}), 7.80 – 7.98 (m, 3H, H_{Ar}), 8.19 (s, 1H, H_{Ar}), 12.60 (s, 1H, COOH); $^{13}\text{C NMR}$ (151 MHz, $\text{DMSO-}d_6$) δ 31.39, 56.46, 57.17, 57.21, 96.71, 102.93, 107.08, 111.08, 120.57, 123.16, 125.34, 126.00, 126.82, 128.52, 129.49, 130.98, 134.89, 147.56, 149.07, 149.39, 151.84, 159.00, 173.28; HRMS Calcd for $(\text{C}_{23}\text{H}_{20}\text{O}_6)$ $[\text{M}+\text{Na}]^+$: 415.1152; Found: 415.1148.

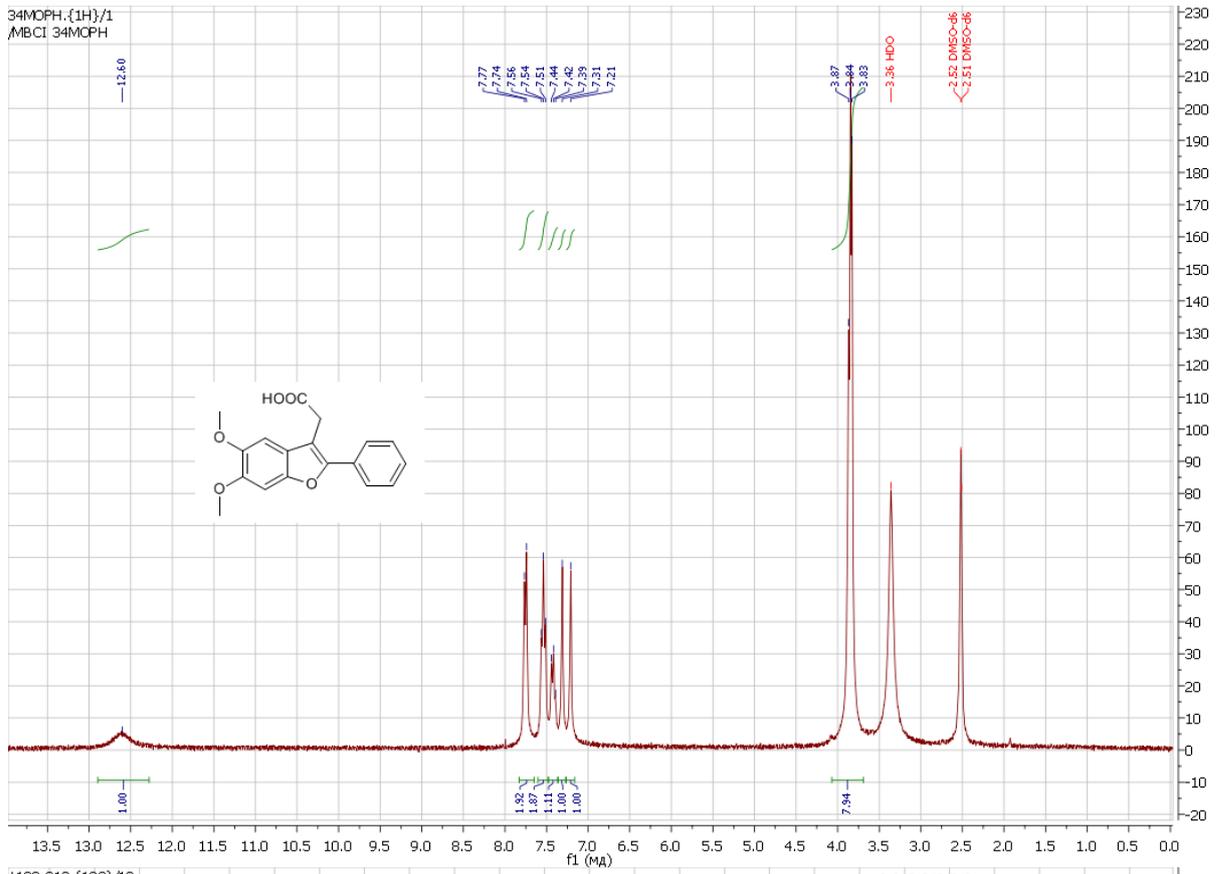


[6-(6-Methoxy-2-naphthyl)furo[2,3-f][1,3]benzodioxol-7-yl]acetic acid (8n), 700 mg, yield 62%, grey powder, mp. 205–207 °C. $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 3.83 – 4.02 (m, 5H), 6.09 (s, 2H, OCH_2O), 7.11 – 7.44 (m, 4H, H_{Ar}), 7.77 – 8.03 (m, 3H, H_{Ar}), 8.21 (s, 1H, H_{Ar}), 12.66 (s, 1H, COOH); $^{13}\text{C NMR}$ (126 MHz, $\text{DMSO-}d_6$) δ 30.23, 55.33, 93.35, 98.55, 101.39, 105.98, 110.22, 119.43, 123.56, 124.20, 124.99, 125.42, 127.40, 128.35, 129.87, 133.85, 144.30, 146.17, 148.41, 151.37, 157.94, 172.02; HRMS Calcd for $(\text{C}_{22}\text{H}_{16}\text{O}_6)$ $[\text{M}+\text{H}]^+$: 377.1220; Found: 377.1017.

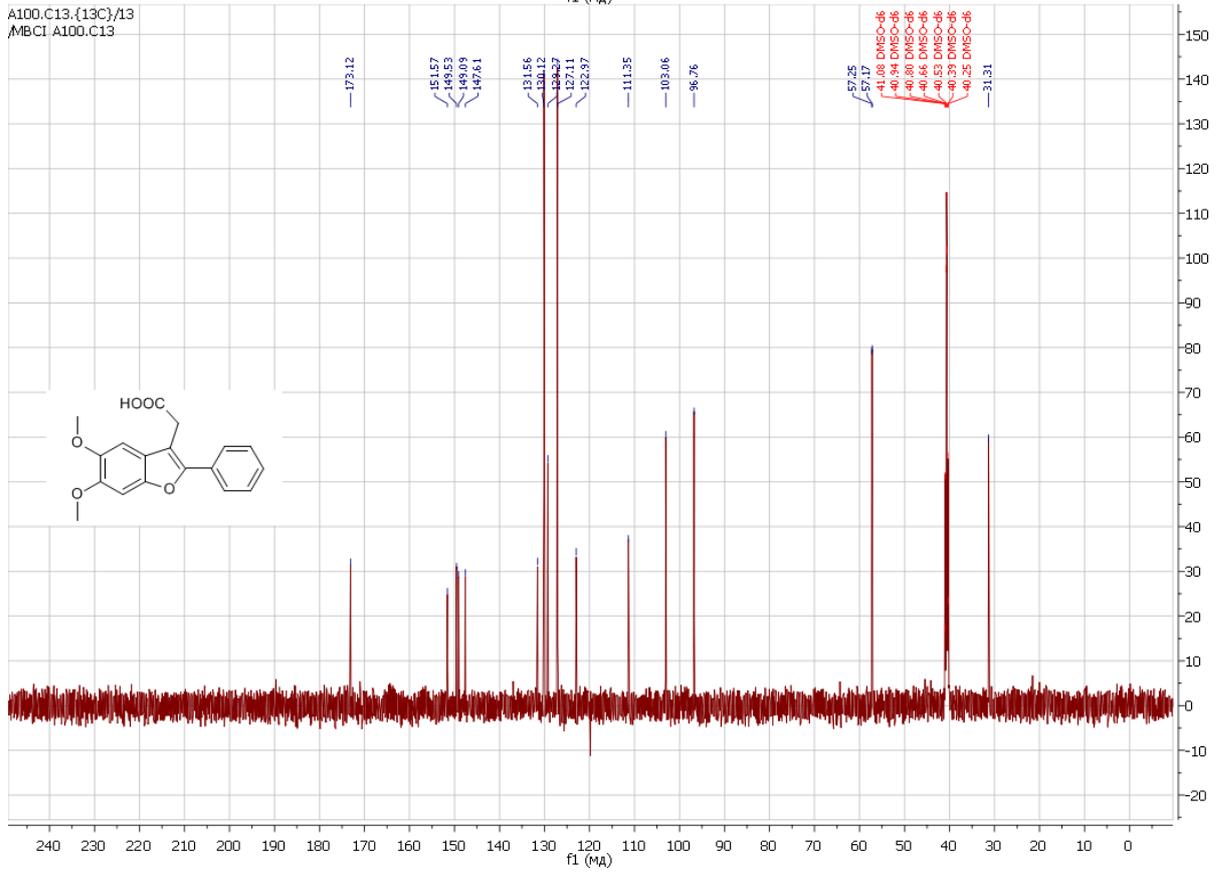


2-(4,5,6-Trimethoxy-2-phenylbenzofuran-3-yl)acetic acid (8o), 480 mg, yield 47%, grey powder, mp. 181–183 °C. $^1\text{H NMR}$ (300 MHz, $\text{DMSO-}d_6$) δ 3.75 (s, 3H, OCH_3), 3.82 – 3.88 (m, 5H), 3.90 (s, 3H, OCH_3), 7.10 (s, 1H, H_{Ar}), 7.37 – 7.46 (m, 1H, H_{Ar}), 7.48 – 7.57 (m, 2H, H_{Ar}), 7.62 – 7.69 (m, 2H, H_{Ar}), 12.47 (s, 1H, COOH); $^{13}\text{C NMR}$ (75 MHz, $\text{DMSO-}d_6$) δ 30.61, 56.33, 60.70, 60.97, 91.52, 109.62, 115.62, 126.39, 128.37, 128.97, 129.95, 137.97, 146.34, 149.93, 150.39, 152.53, 172.07; HRMS Calcd for $(\text{C}_{19}\text{H}_{18}\text{O}_6)$ $[\text{M}+\text{H}]^+$: 343.1176; Found: 343.1165.

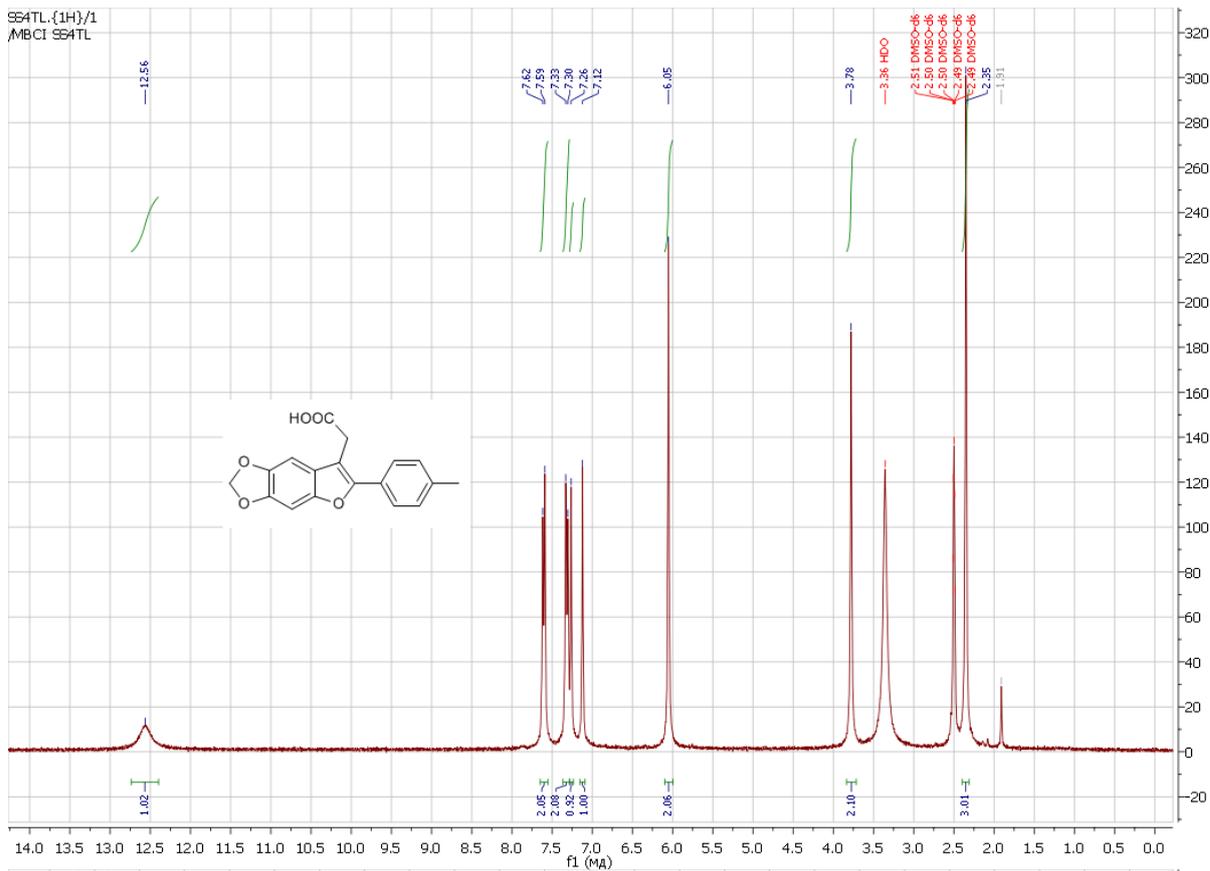
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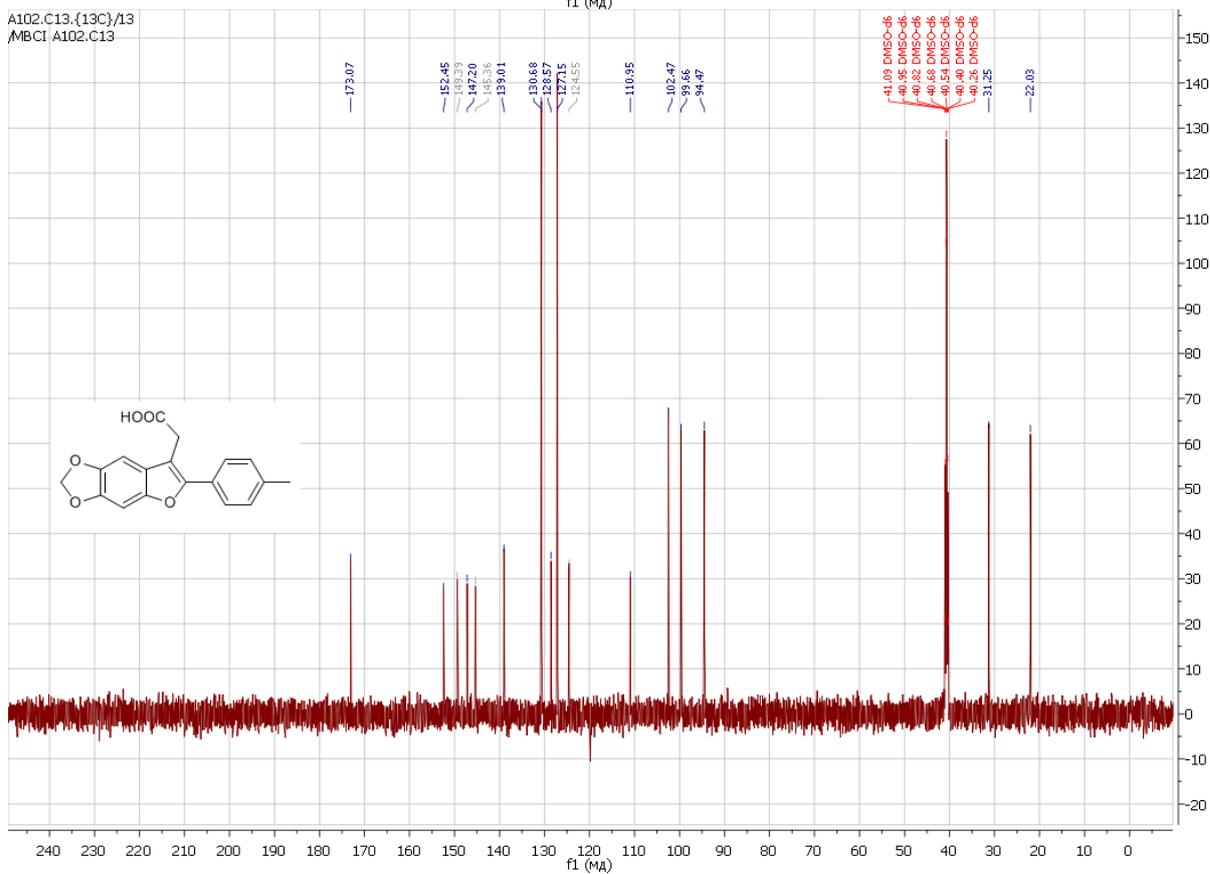
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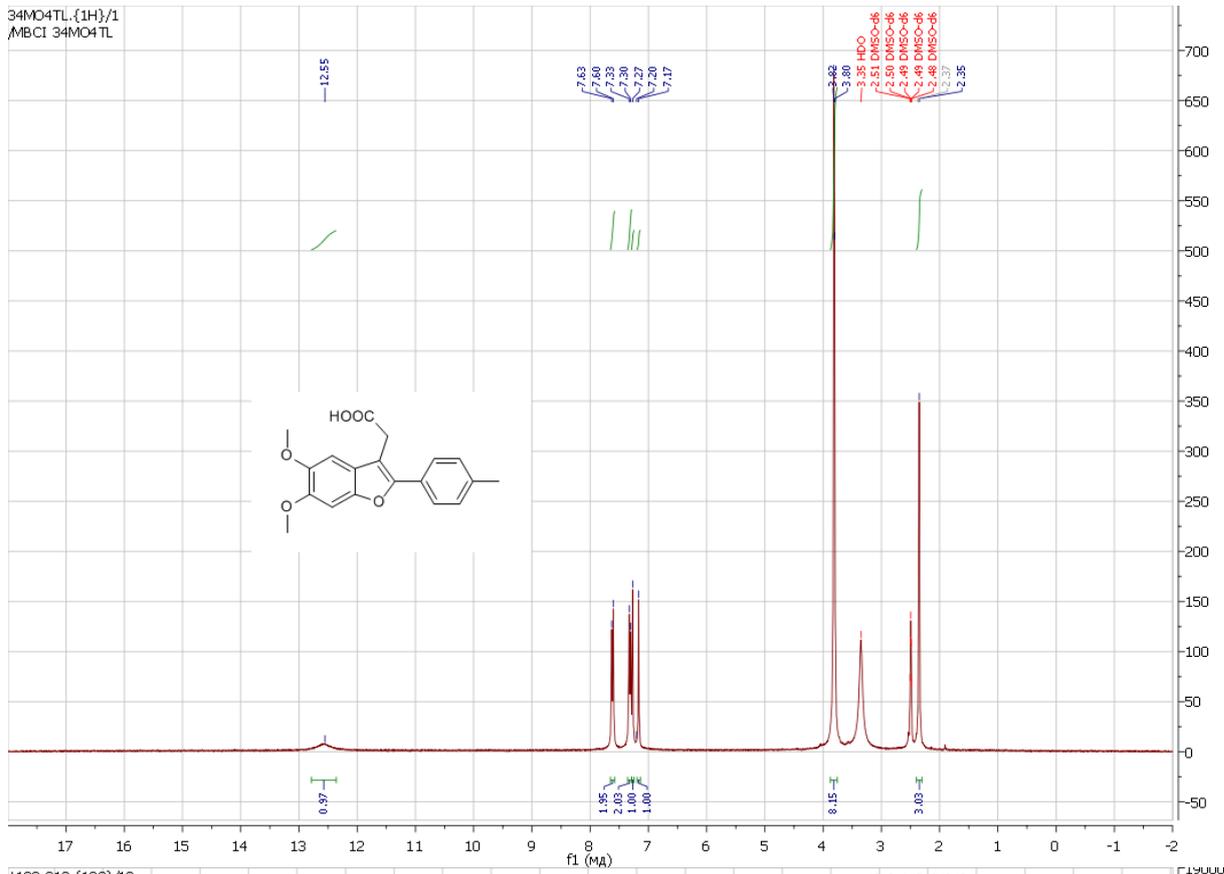
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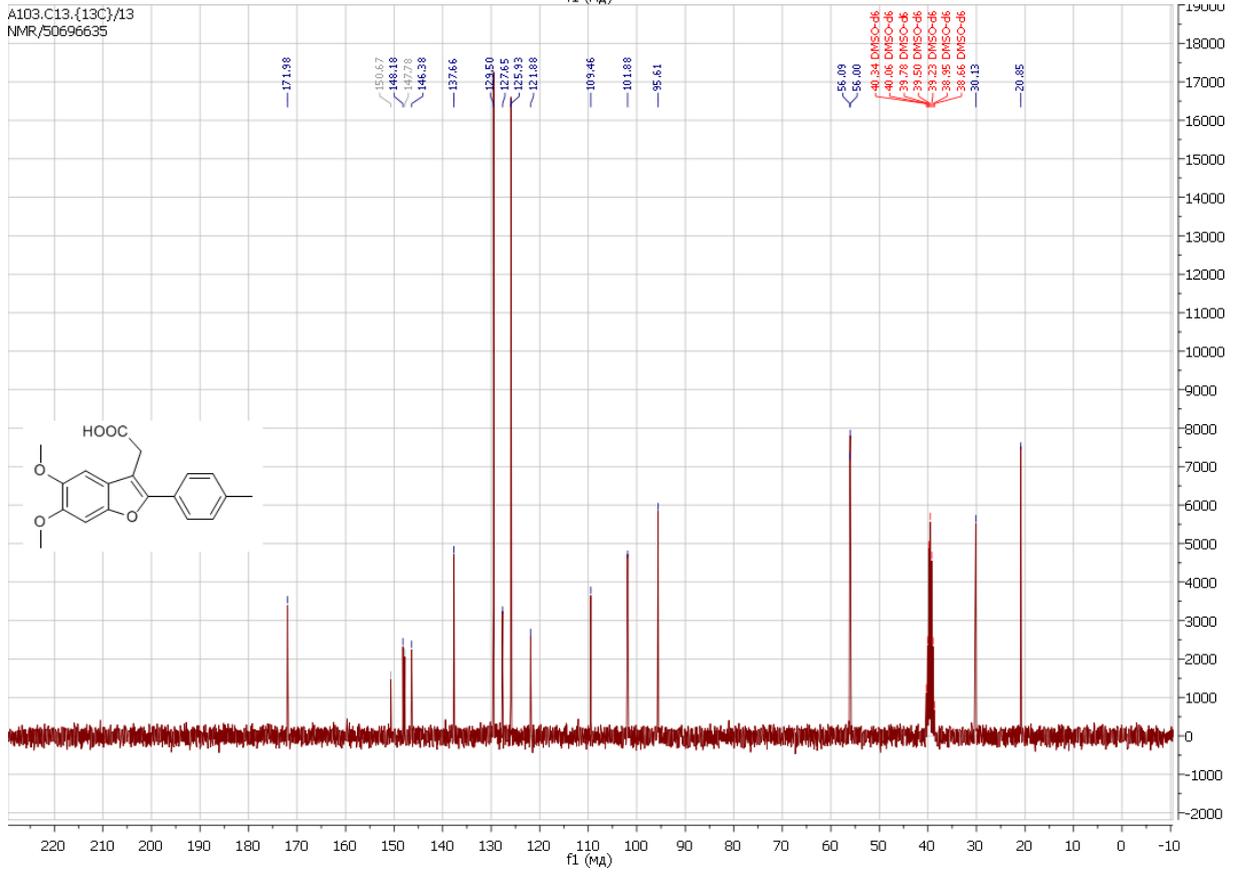
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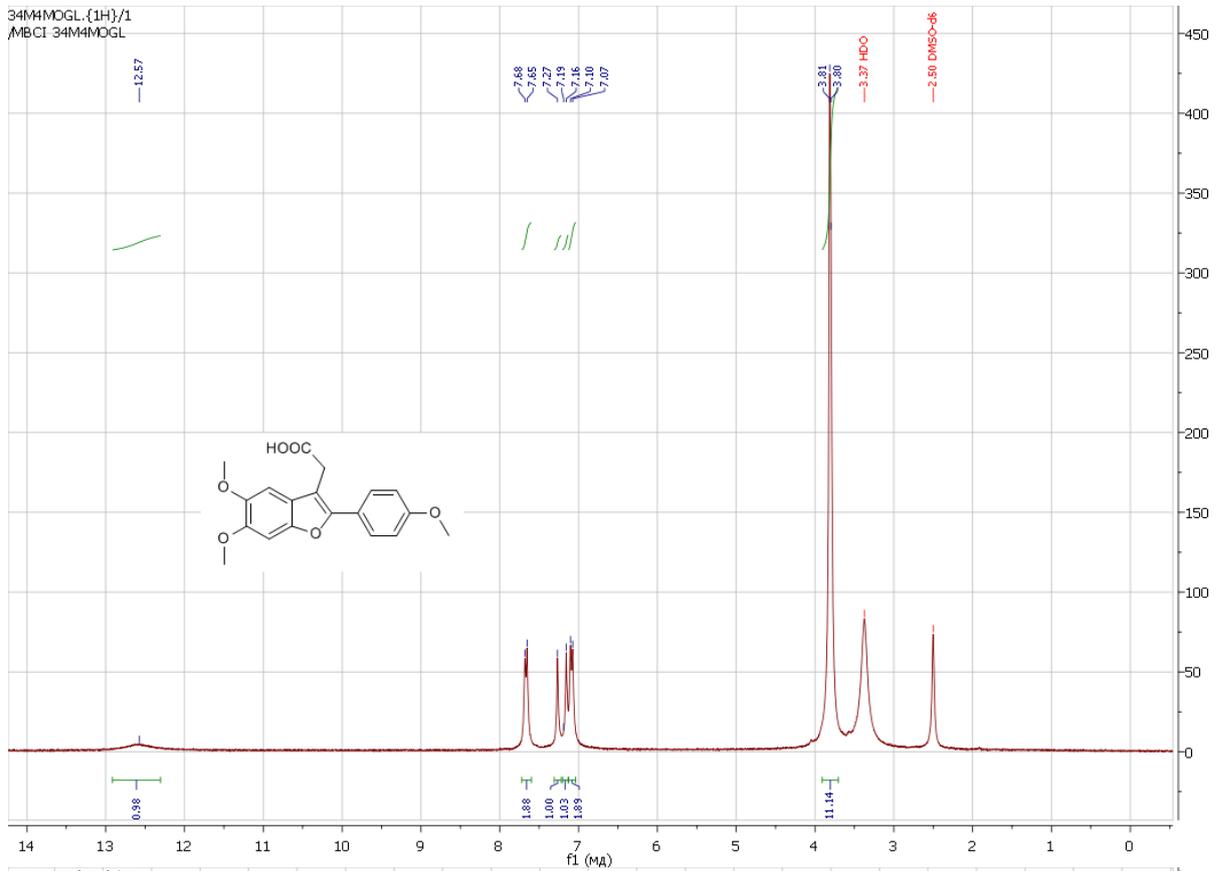
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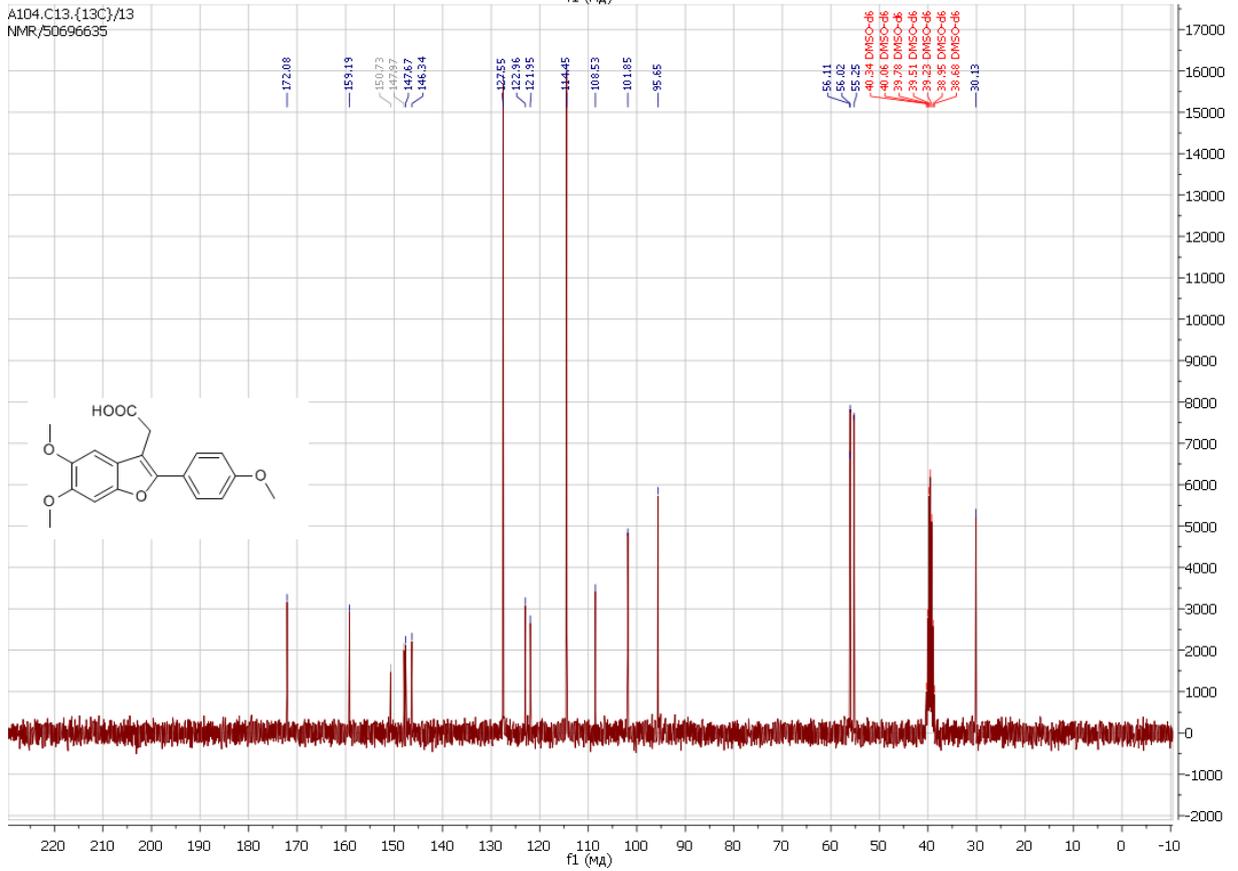
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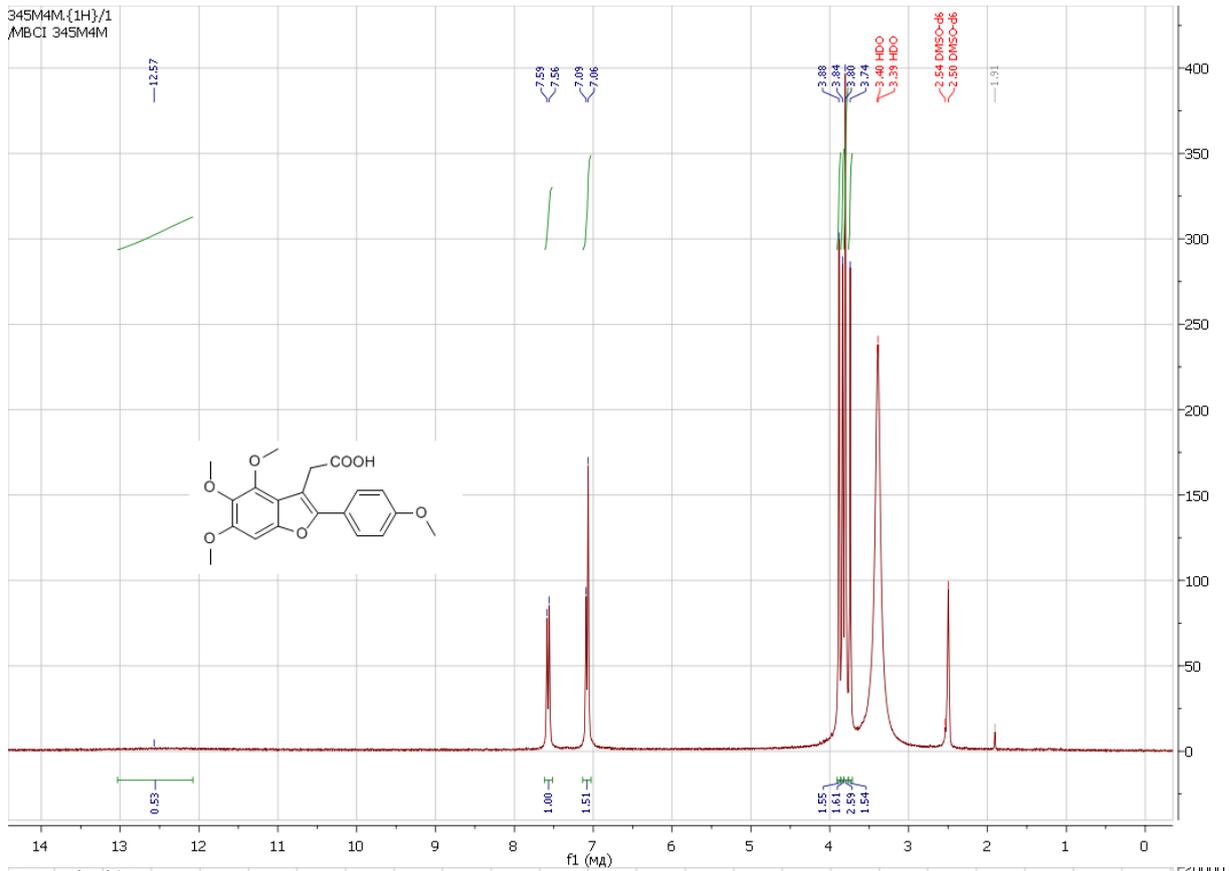
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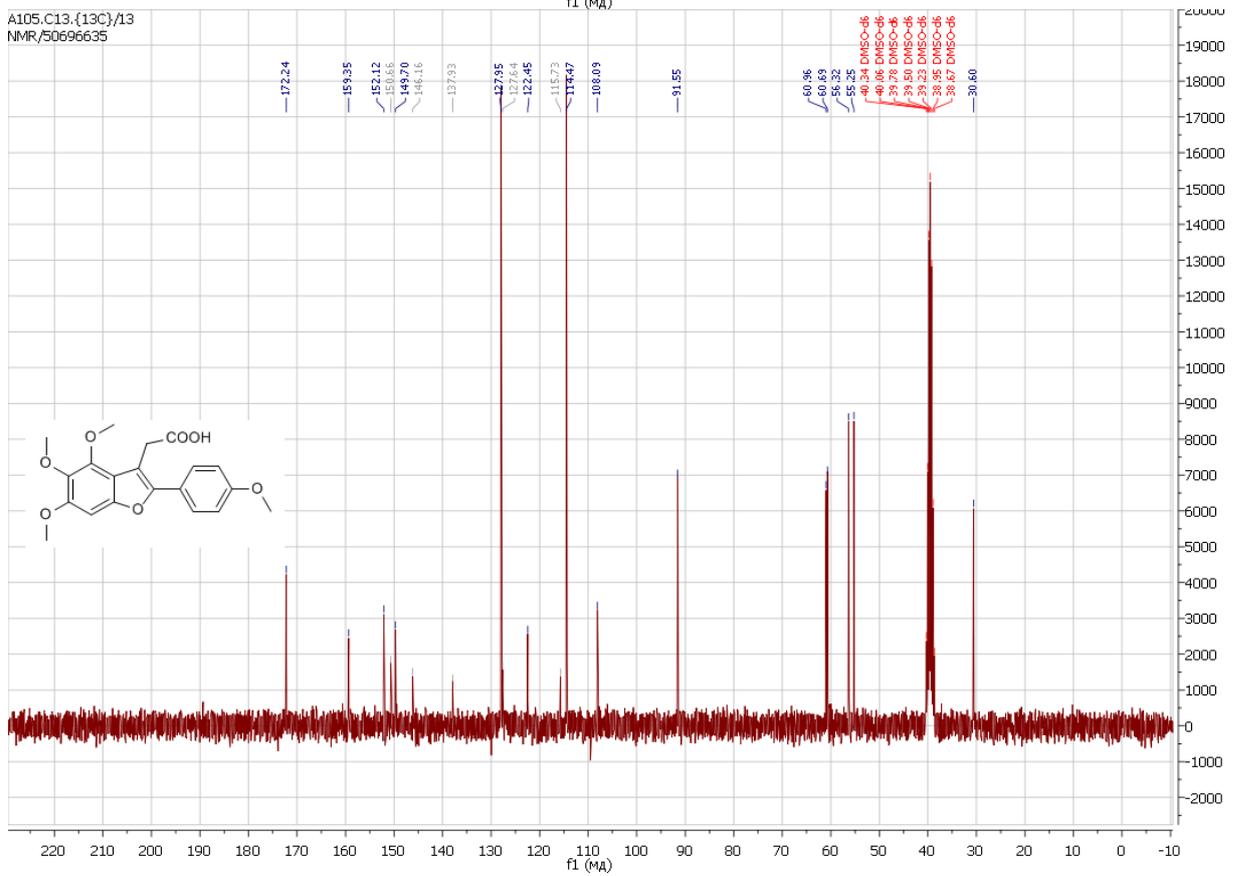
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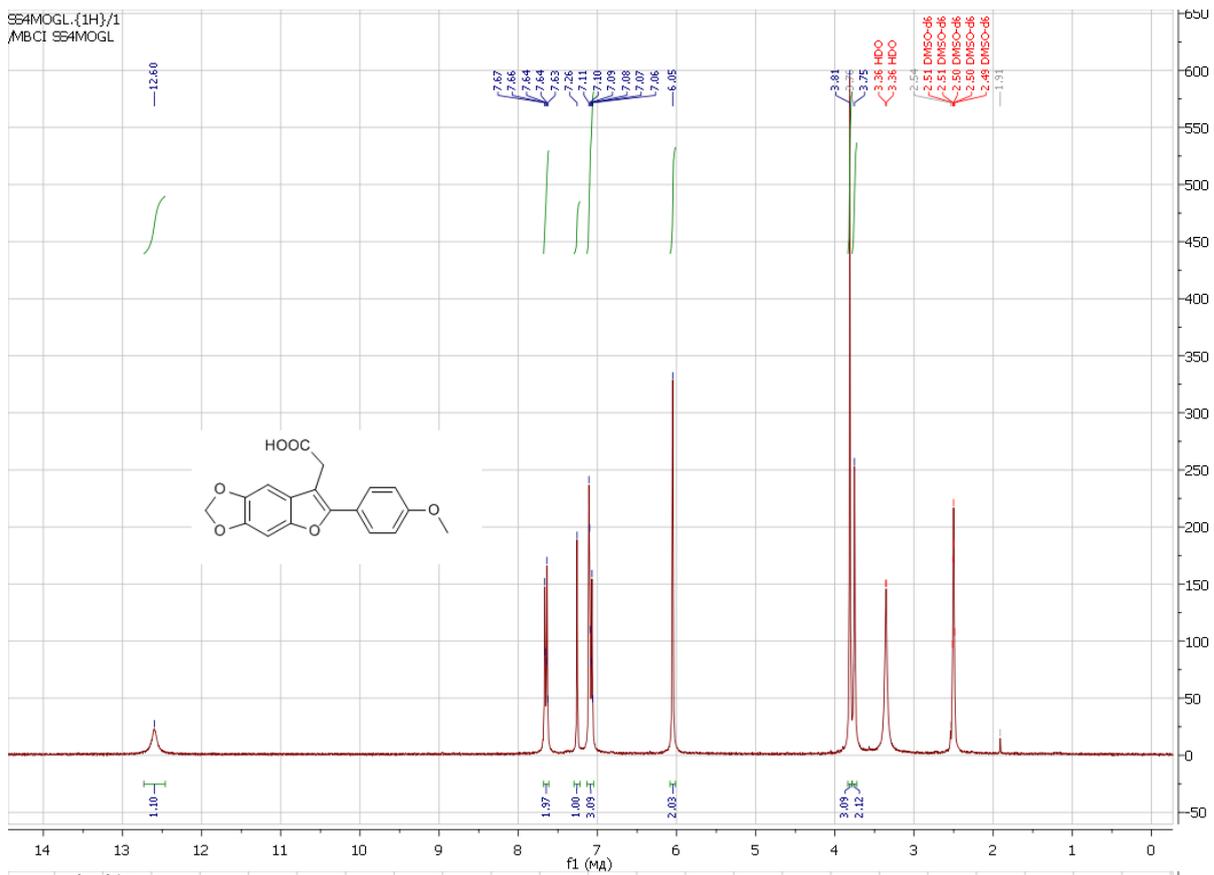
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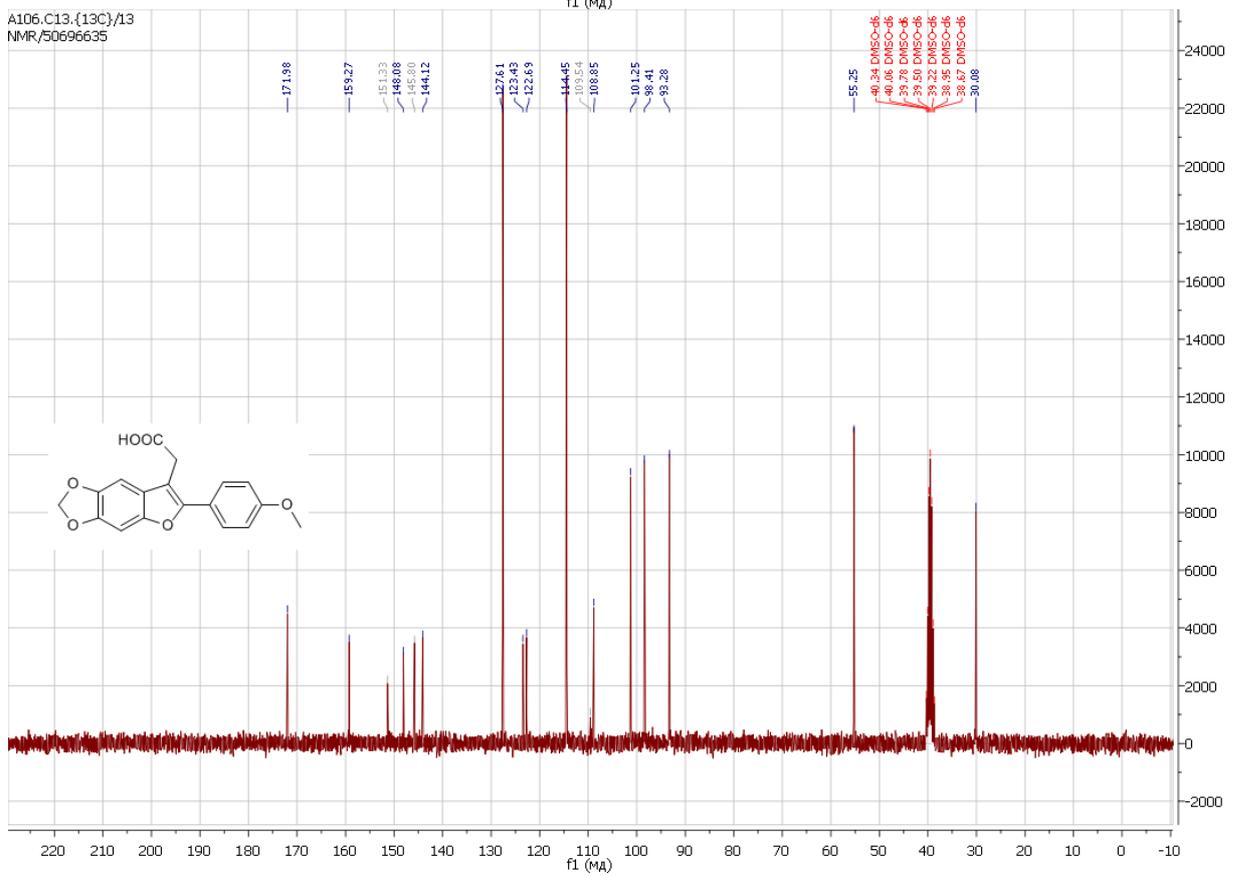
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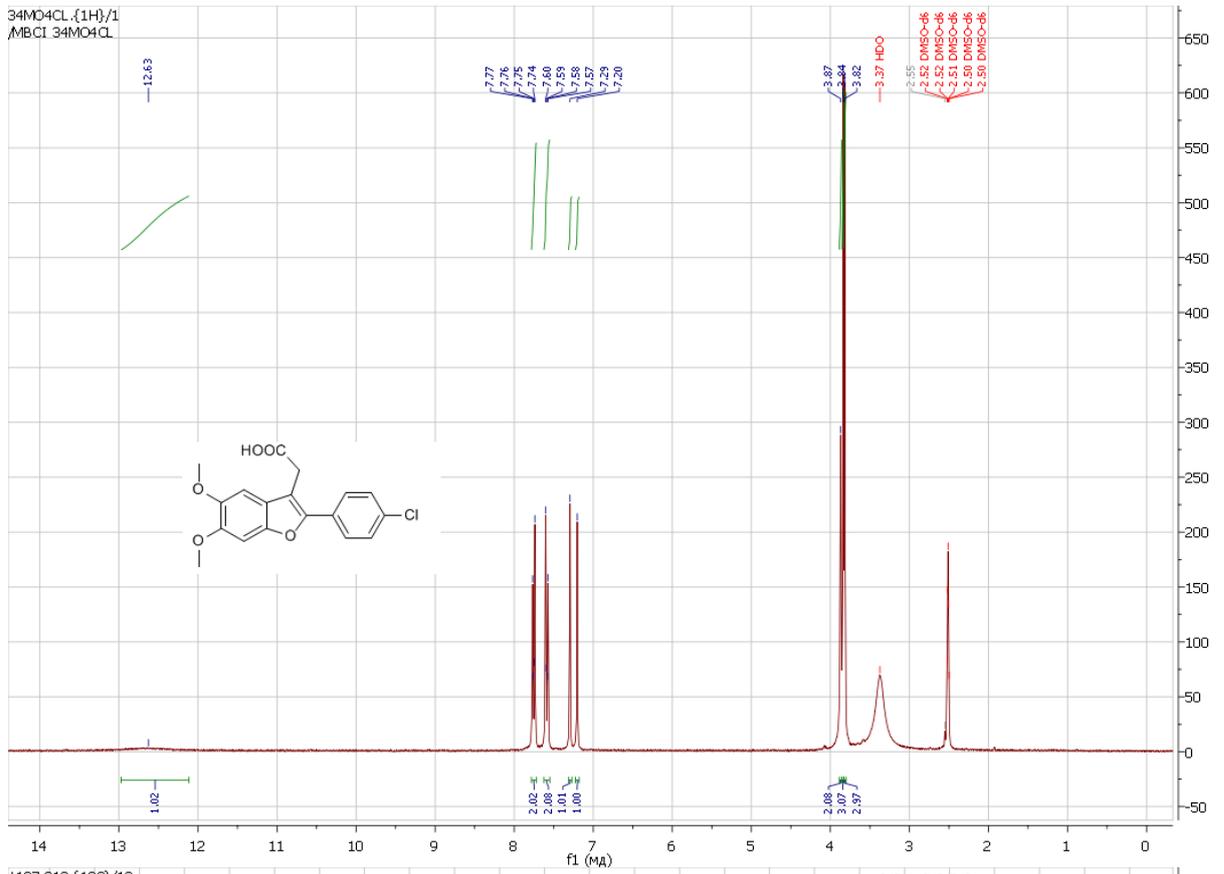
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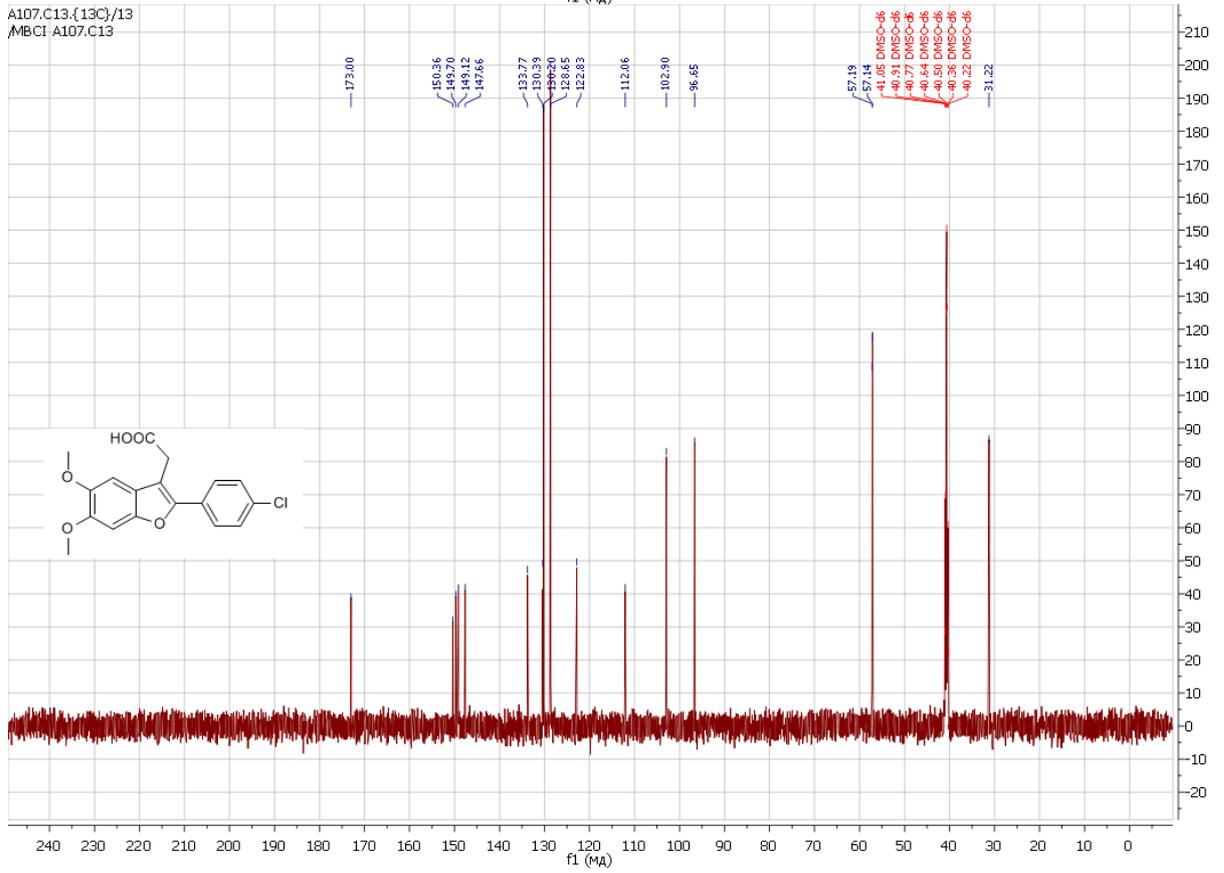
A106.C13.{13C}/13
 NMR/50696635



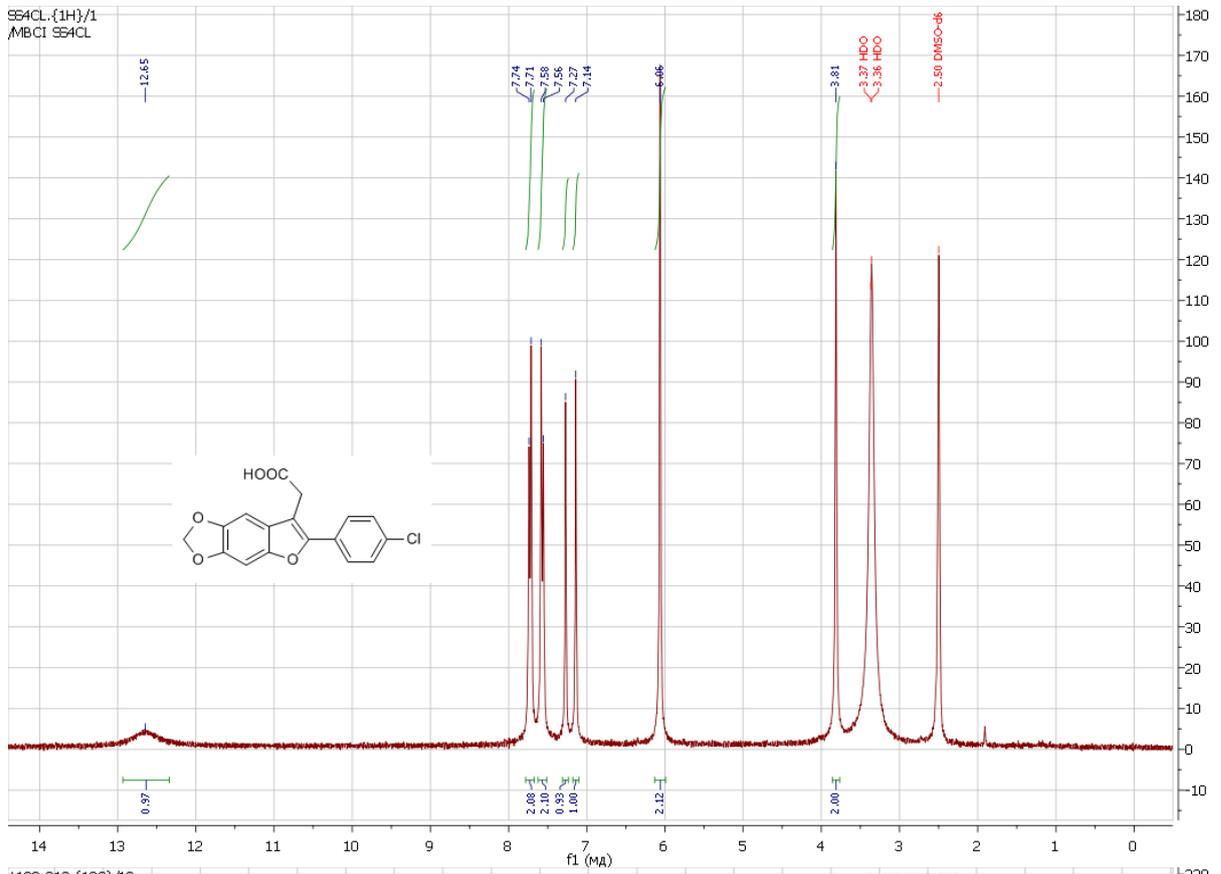
34M04CL.{1H}/1
MBCI 34M04CL



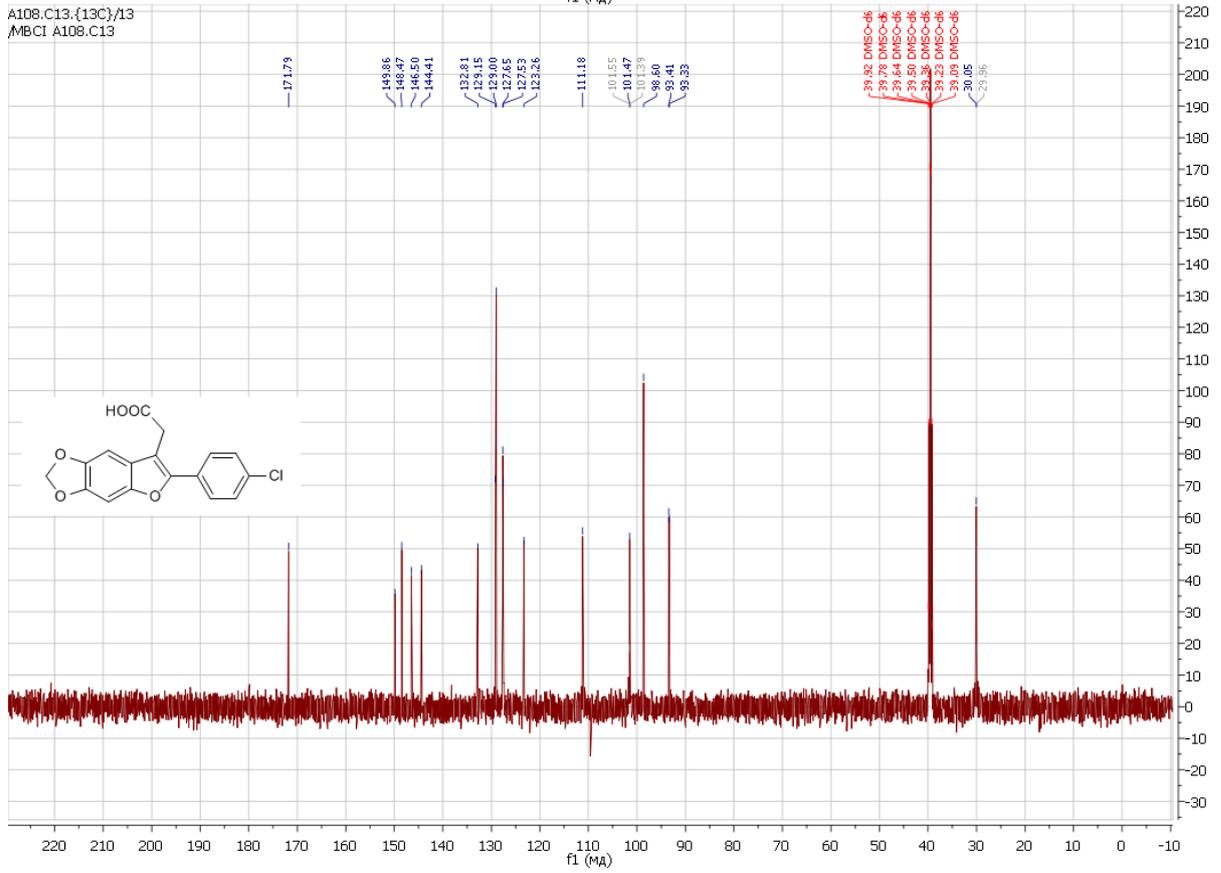
A107.C13.{13C}/13
MBCI A107.C13



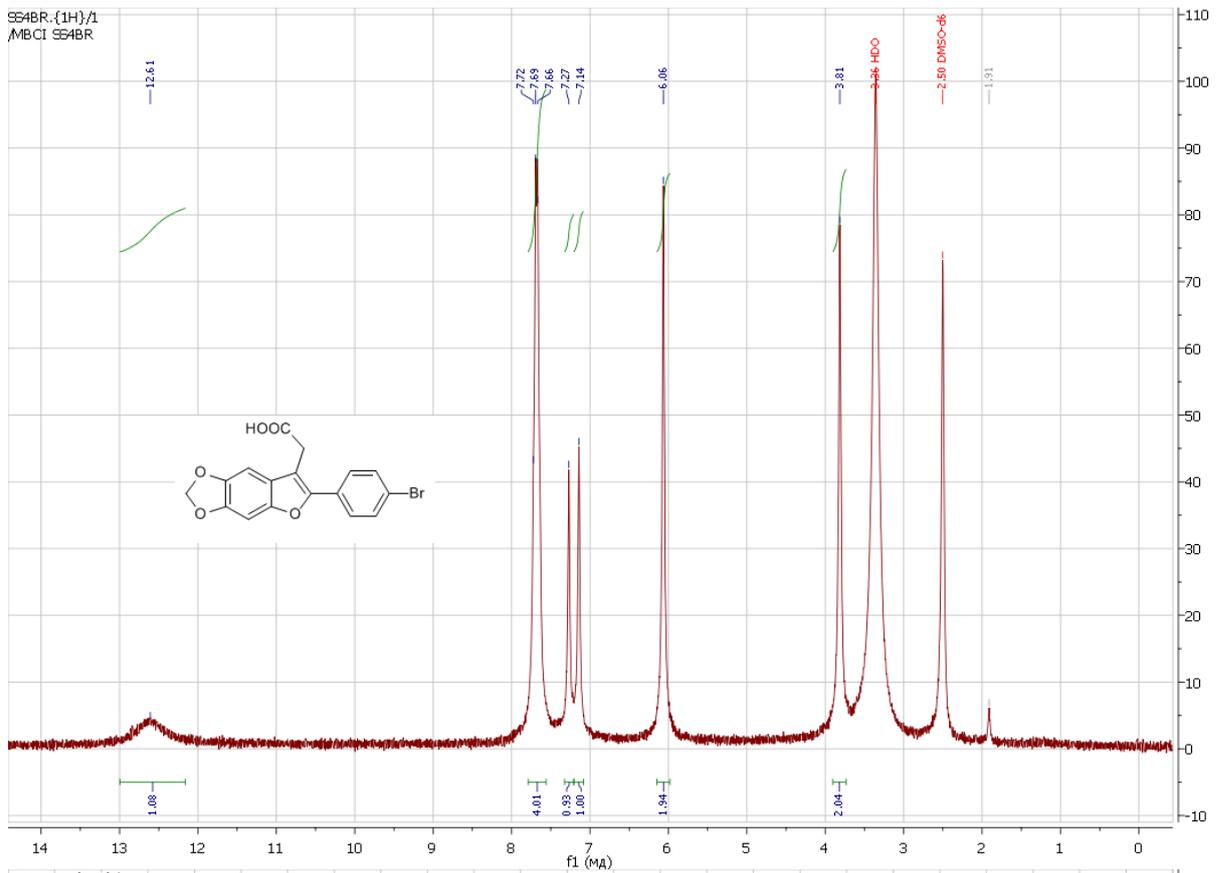
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MBCI 954CL



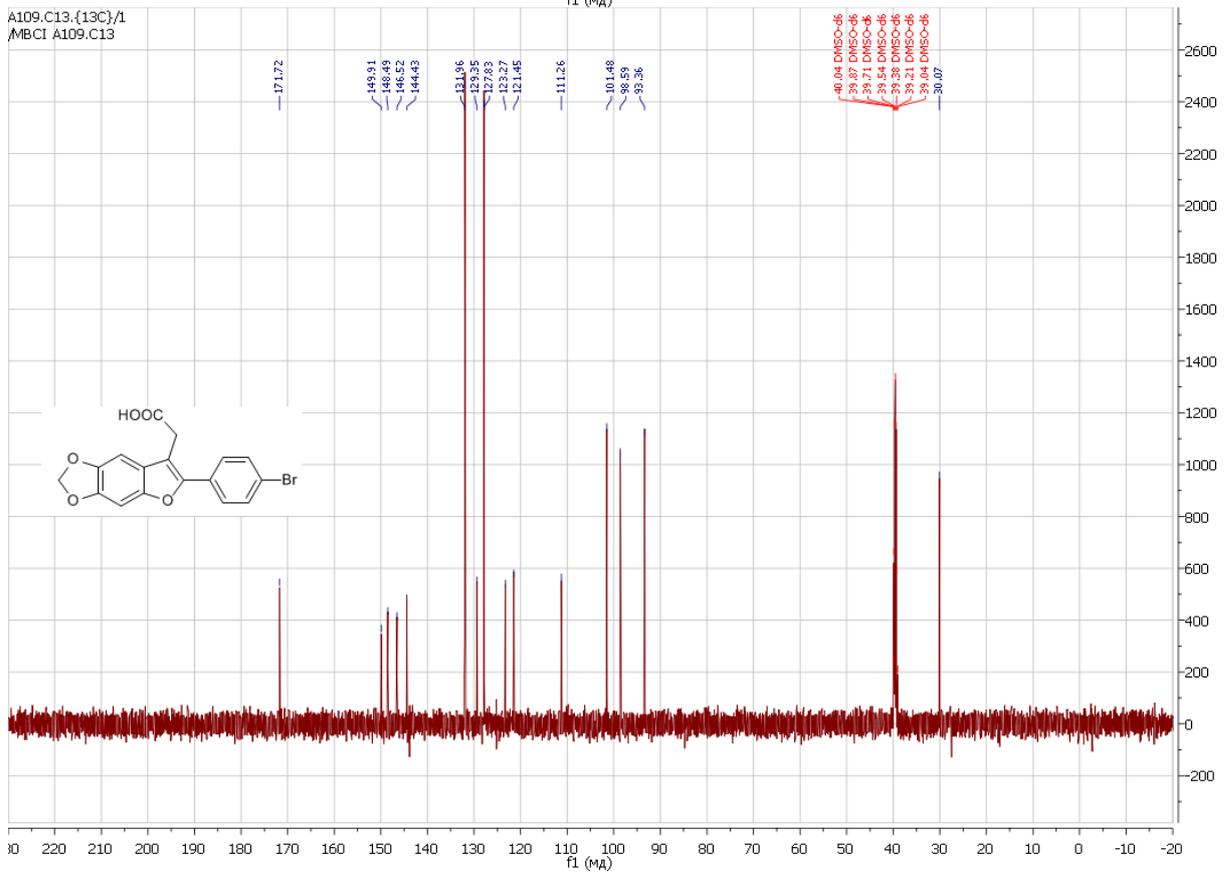
A108.C13-{13C}/13
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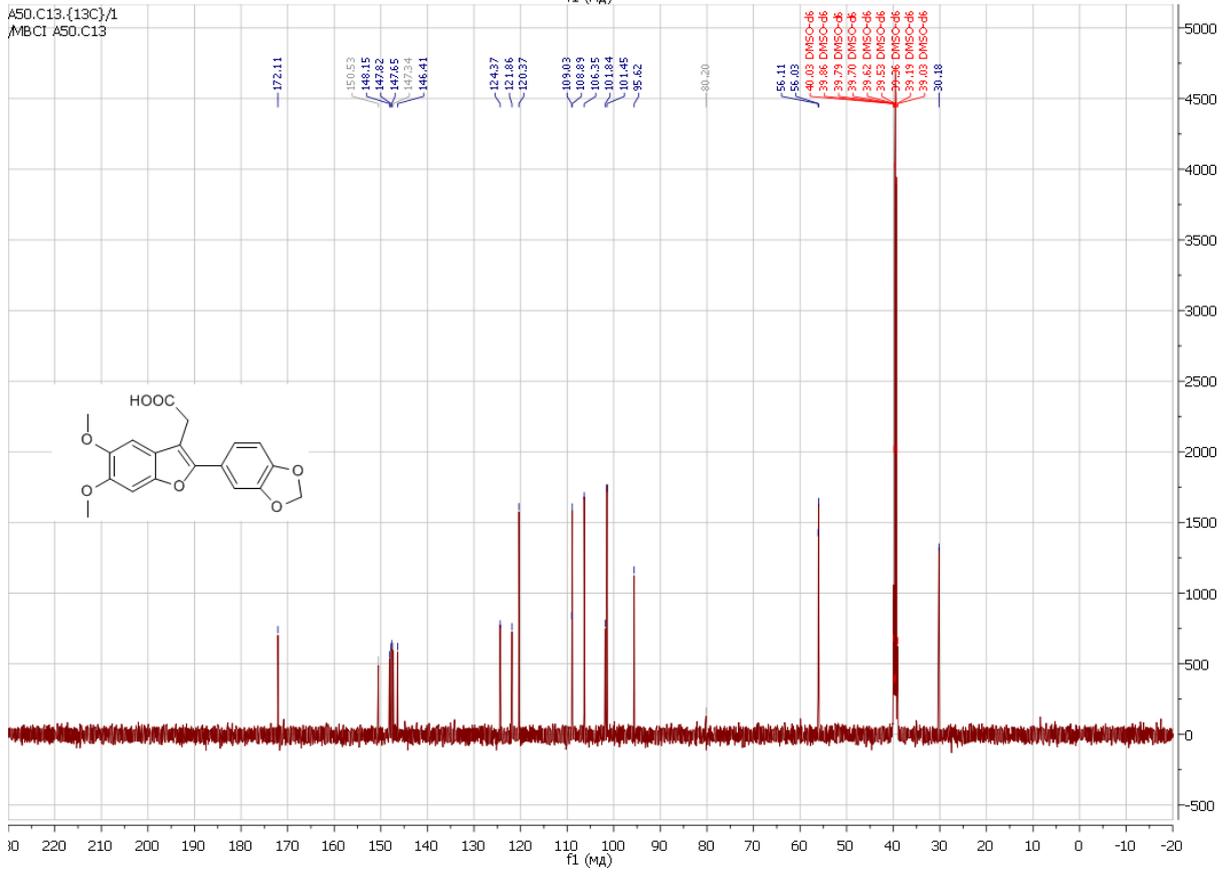
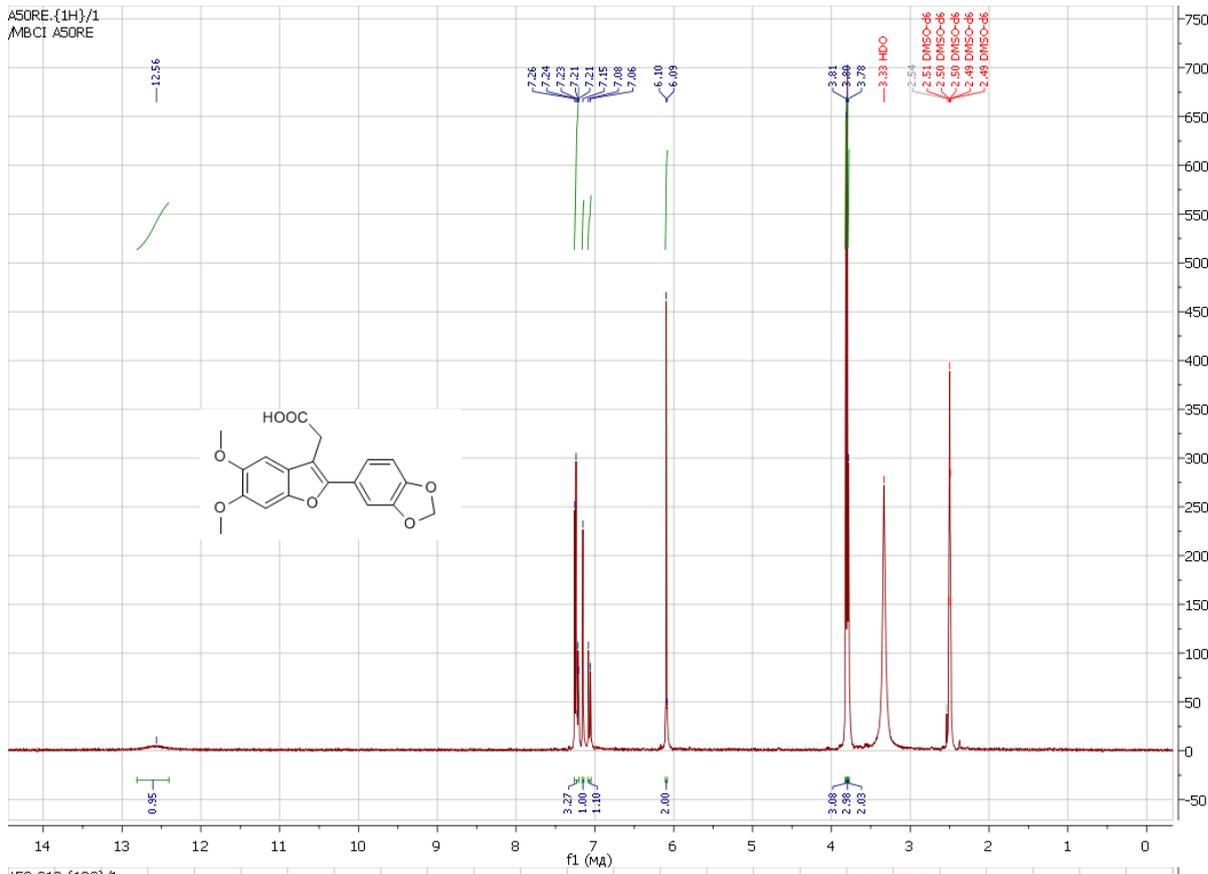


954BR-{1H}/1
MBCI 954BR

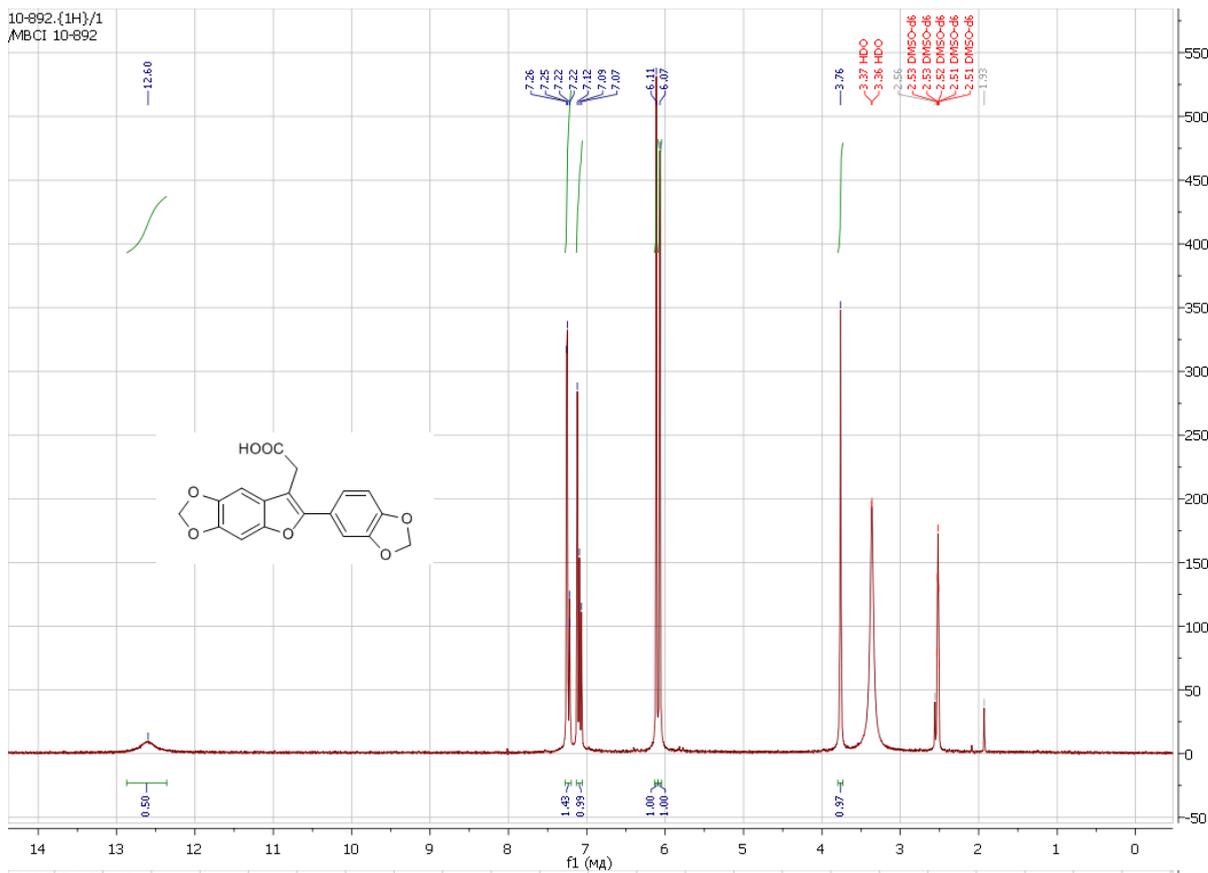


A109.C13-{13C}/1
MBCI A109.C13

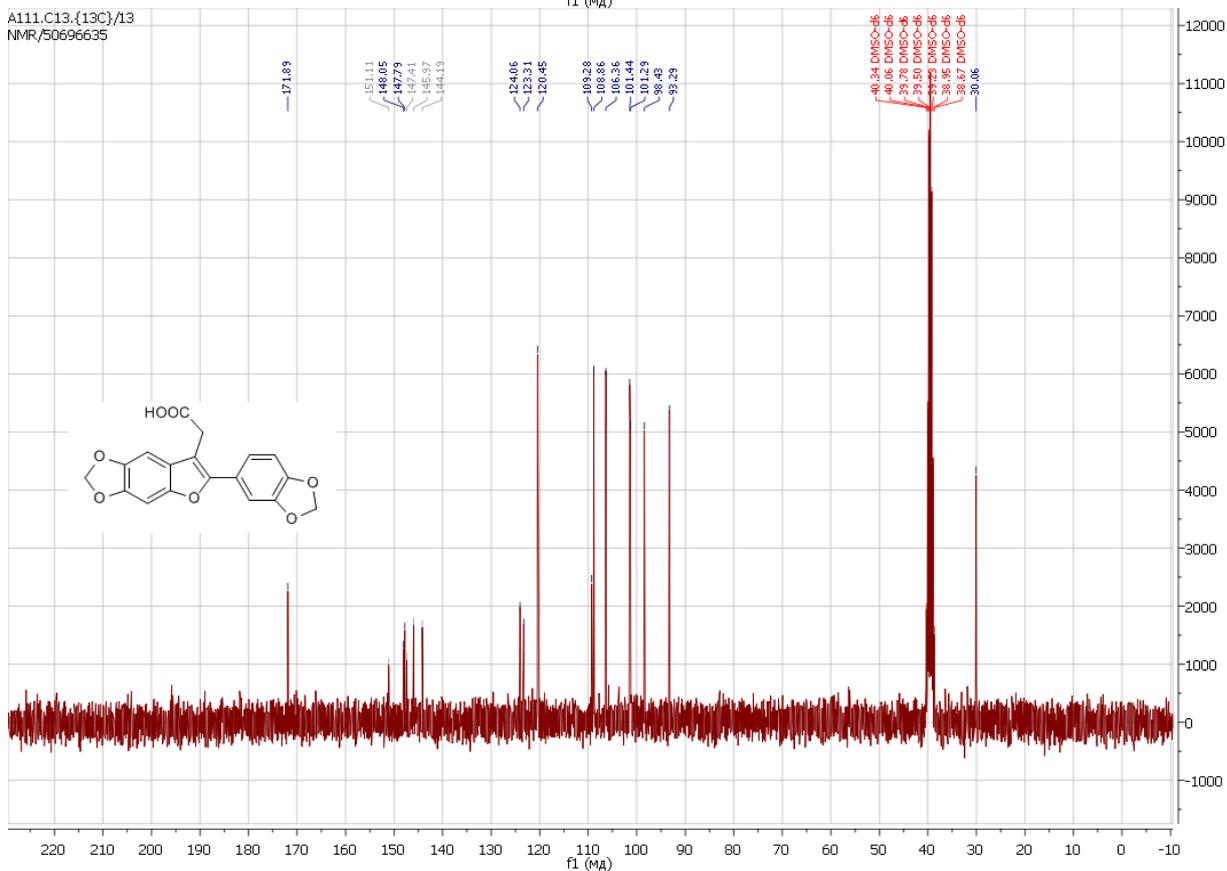




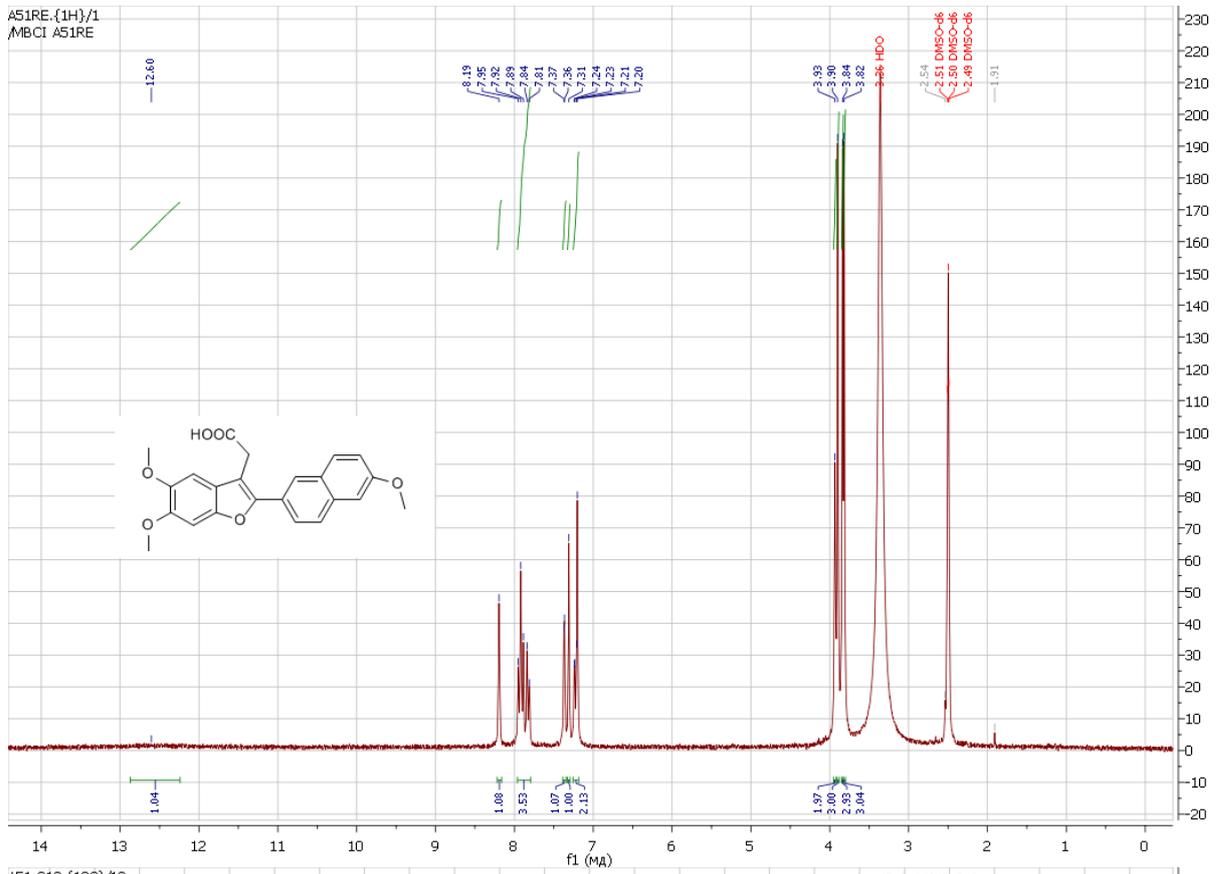
10-892.{1H}/1
MBCI 10-892



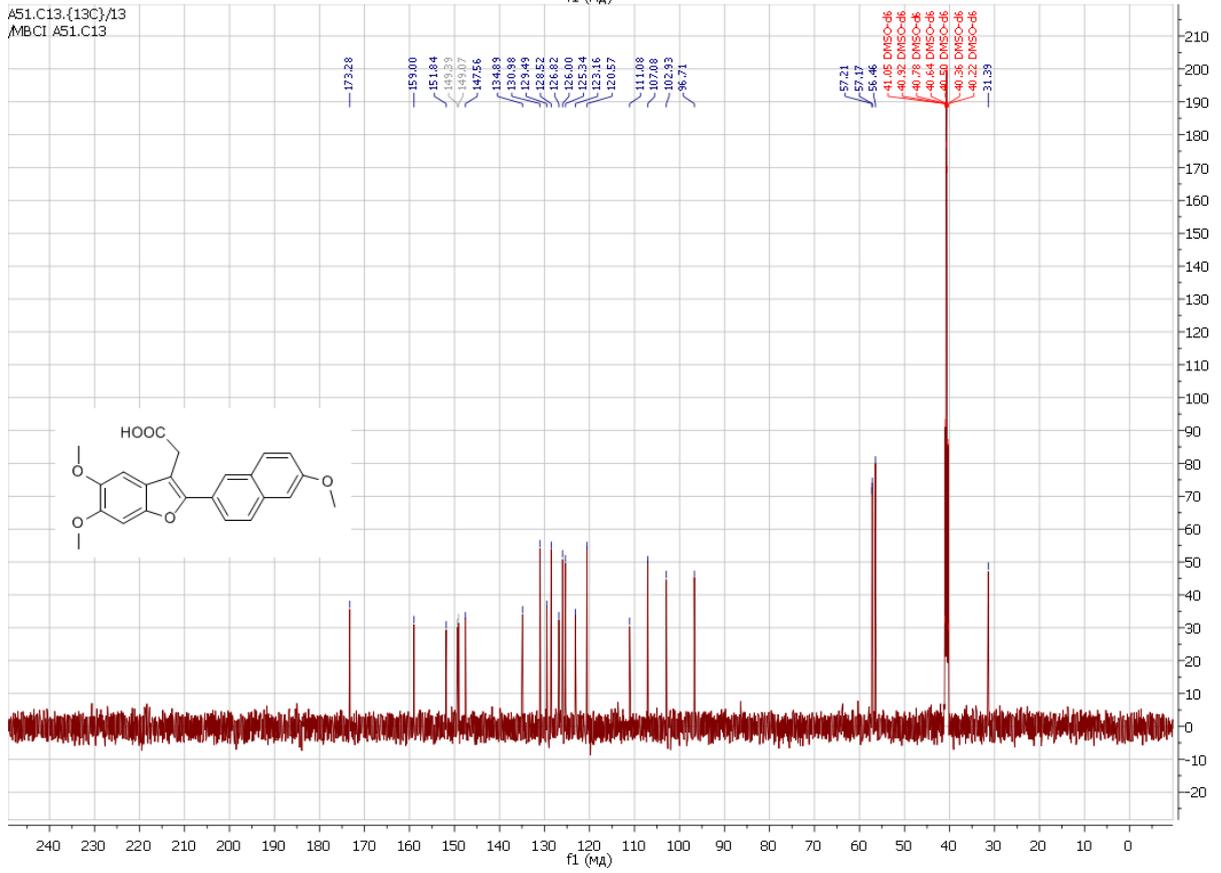
A111.C13.{13C}/13
NMR/50696635



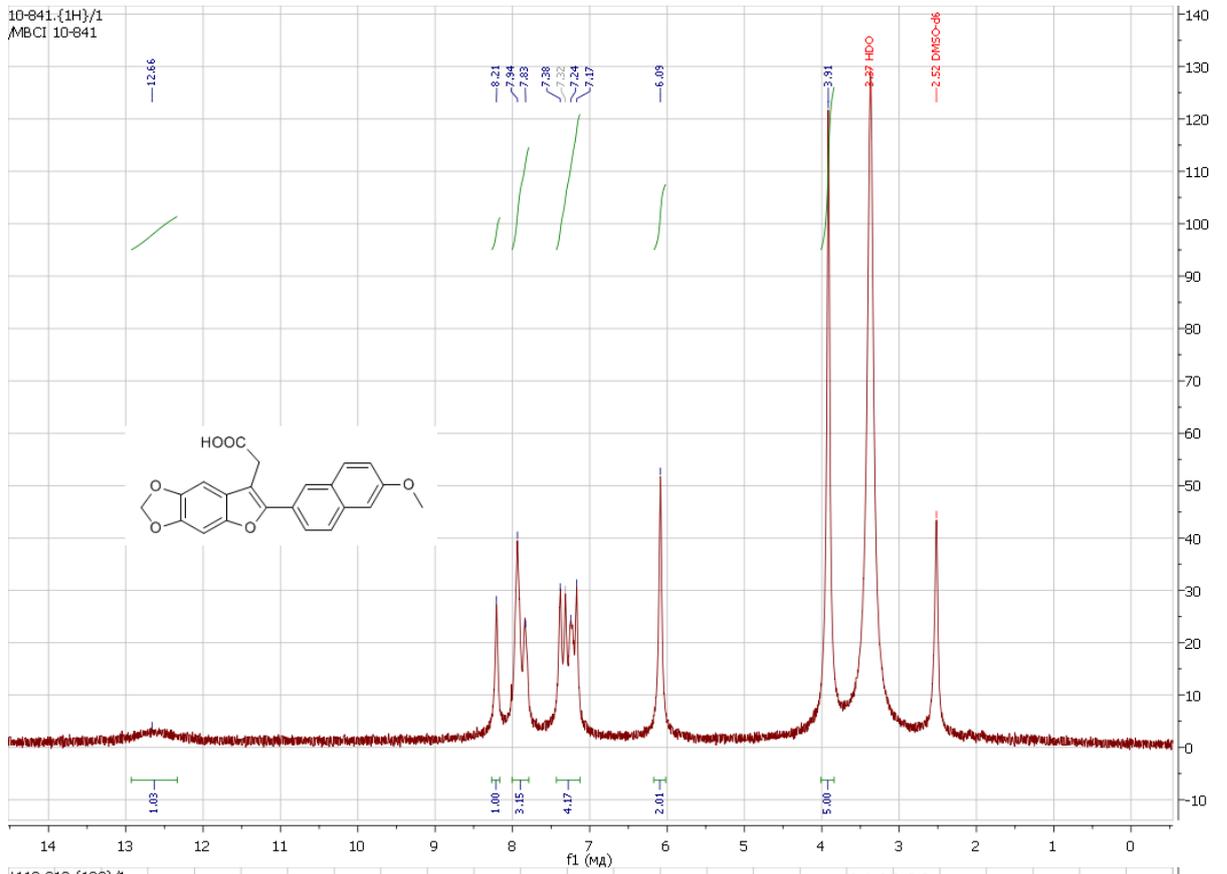
A51RE.(1H)/1
MBCI A51RE



A51.C13.(13C)/13
MBCI A51.C13



10-841-{1H}/1
MBCI 10-841



A113.C13-{13C}/1
MBCI A113.C13

