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Unveiling an underestimated potential of vanillin-derived alkynes: synthesis of highly functionalized 3(2*H*)-furanone with antiradical activity

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General remarks

All chemicals and solvents if not stated otherwise were purchased from commercial sources and used without further purification. Toluene was distilled over sodium before use. Alkyne **3** was prepared following the published procedures [S1]. Deionized water of Milli-Q grade was used for spectrophotometric study.

NMR spectra were recorded from solutions in $CDCl_3$ on Bruker DPX-400 and AV-400 spectrometers (400.1 MHz for ^1H and 100.6 MHz for ^{13}C). Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ_H 7.26 and δ_C 77.16, was used as a reference. Coupling constants (*J*) are reported in Hertz (Hz). The multiplicity abbreviations used are: s singlet, d doublet, dd doublet of doublet, t triplet, m multiplet, br s broad signal. High-resolution mass spectra were recorded from acetonitrile solution with 0.1% HFBA on HPLC Agilent 1200/Agilent 6210 TOF instrument equipped with electrospray ionization (ESI) source. Melting points were measured on a digital melting point apparatus Electrothermal IA 9200. Absorption spectra during $ABTS^{\bullet+}$-scavenging assay were recorded using an PE-5300V spectrophotometer (ECROSKHIM Co. Ltd, St. Petersburg, Russia).

Procedure for the synthesis of Boc-protected alkyne 4

A 50-mL round-bottom open-flask with a stir bar was sequentially charged with freshly purified alkyne **3** (0.40 g, 2.7 mmol, 1.0 equiv), di-*tert*-butyl dicarbonate (0.87 g, 4.0 mmol, 1.5 equiv) in dry DCM (20 mL), *N*,*N*-dimethylpyridin-4-amine (33 mg, 0.27 mmol, 0.1 equiv) and triethylamine (560 μL, 4.0 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature (20-24 °C) for 2.5 h, then washed with 5% aq HCl (10 mL) and water (10 mL), dried over Na_2SO_4. The residue after solvent evaporation was purified by column chromatography over silica gel using hexane/diethyl ether (9/1, v/v) as eluent to afford *tert*-butyl (4-ethynyl-2-methoxyphenyl) carbonate (**4**) as a white solid (0.63 g, 94% yield), R_f = 0.49 (hexane/diethyl ether, 3/1, v/v), mp 82-84 °C. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 7.10-7.05 (m, 3H), 3.84 (s, 3H), 3.05 (s, 1H), 1.54 (s, 9H). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ = 151.2, 151.1, 141.0, 125.1, 122.7, 120.7, 116.1, 83.8, 83.2, 77.2, 56.1, 27.7.

Procedure for the synthesis of alkynone 5

A 10-mL round-bottom flask with a stir bar was sequentially charged with cyclohexanecarbonyl chloride (0.53 g, 3.6 mmol, 1.5 equiv), Boc-protected alkyne **4** (0.60 g, 2.4 mmol, 1.0 equiv) in dry THF (6 mL), bis(triphenylphosphine)palladium(II) dichloride (17 mg, 0.024 mmol, 1 mol%) and copper(I) iodide (14 mg, 0.072 mmol, 3 mol%) under an argon atmosphere. After 1 min of stirring, triethylamine (420 μL, 3.0 mmol, 1.25 equiv) was added, the reaction flask was capped with a glass stopper, and the reaction mixture was stirred at room temperature (20-24 °C) for

14 h. The reaction mixture was diluted with diethyl ether (30 mL), washed with 5% aq HCl (10 mL) and water (10 mL), and dried over Na_2SO_4. The residue after solvent evaporation was purified by column chromatography over silica gel using hexane/diethyl ether (9/1, v/v) as eluent to afford *tert*-butyl (4-(3-cyclohexyl-3-oxoprop-1-yn-1-yl)-2-methoxyphenyl) carbonate (**5**) as a light yellow oil (0.72 g, 84% yield), R_f = 0.29 (hexane/diethyl ether, 3/1, v/v). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.15 (dd, J = 1.5 Hz, J = 8.2 Hz, 1H), 7.11 (d, J = 1.5 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 3.83 (s, 3H), 2.51-2.43 (m, 1H), 2.03-1.99 (m, 2H), 1.80-1.75 (m, 2H), 1.66-1.62 (m, 1H), 1.51 (s, 9H), 1.50-1.40 (m, 2H), 1.36-1.18 (m, 3H). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 191.2, 151.3, 150.8, 142.3, 126.1, 122.9, 118.5, 116.7, 90.6, 87.0, 83.9, 56.1, 52.2, 28.3, 27.6, 25.8, 25.4. HRMS (ESI-TOF) calcd for $[C_{21}H_{26}O_5+H]^+$ 359.1859, found 359.1857.

Procedure for the synthesis of Boc-protected 3(2*H*)-furanone 6

A 5-mL round-bottom flask with a stir bar was sequentially charged with alkynone **5** (358 mg, 1.0 mmol) and toluene (2 mL). Then sodium *tert*-butoxide (24 mg, 0.25 mmol) was added, the reaction flask was capped with a glass stopper, and the reaction mixture was stirred at room temperature (20-24 °C) for 24 hours. The reaction mixture was then quenched with water (10 mL), neutralized with 10% aq HCl (90 μL), and extracted with diethyl ether (3×10 mL). The combined organic extracts were washed with water (10 mL) and dried over Na_2SO_4. The residue after solvent evaporation was purified by column chromatography over silica gel using hexane/diethyl ether (from 6/1 to 1/1, v/v) as eluent to afford (*Z*)-4-((4-((4-((*tert*-butoxycarbonyl)oxy)-3-methoxyphenyl)(cyclohexylidene)methyl)-5-cyclohexyl-3-oxofuran-2(3*H*)-ylidene)methyl)-2-methoxyphenyl *tert*-butyl carbonate (**6**) as a light yellow oil (140 mg, 39% yield), R_f = 0.29 (hexane/diethyl ether, 1/1, v/v). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.50 (d, J = 1.5 Hz, 1H), 7.29 (dd, J = 1.5 Hz, J = 8.2 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 1.5 Hz, 1H), 6.71 (dd, J = 1.5 Hz, J = 8.2 Hz, 1H), 6.66 (s, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 2.65-2.58 (m, 1H), 2.25 (br s, 2H), 2.13 (br s, 2H), 1.78-1.45 (m, 13H), 1.54 (s, 9H), 1.53 (s, 9H), 1.30-1.19 (m, 3H). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 187.0, 182.8, 151.7, 151.4, 151.2, 150.9, 145.5, 145.1, 141.3, 140.4, 138.7, 131.3, 124.7, 122.9, 121.9, 121.3, 119.8, 118.5, 114.8, 113.5, 111.5, 83.8, 83.3, 56.1, 55.9, 38.1, 33.1, 31.8, 29.3, 28.5, 28.3, 27.7, 27.7, 26.6, 25.9, 25.8. HRMS (ESI-TOF) calcd for $[C_{42}H_{52}O_{10}+H]^+$ 717.3639, found 717.3636.

Procedure for the synthesis of 3(2*H*)-furanone 7

A 5-mL round-bottom flask equipped with a stir bar and a reflux condenser was sequentially charged with Boc-protected 3(2*H*)-furanone **6** (120 mg, 0.17 mmol), 1,4-dioxane (1 mL) and 10% aq HCl (1 mL). The obtained mixture was stirred at 100 °C (silicon oil bath) for 3 hours. After reaction

completion, the mixture was cooled to room temperature, diluted with diethyl ether (30 mL), washed with water (2×10 mL), and dried over Na_2SO_4. The residue after solvent evaporation was purified by column chromatography over silica gel using hexane/diethyl ether (1/1, v/v) as eluent to afford (*Z*)-5-cyclohexyl-4-(cyclohexylidene(4-hydroxy-3-methoxyphenyl)methyl)-2-(4-hydroxy-3-methoxybenzylidene)furan-3(2*H*)-one (**7**) as a yellow solid (31 mg, 36% yield), R_f = 0.62 (diethyl ether), mp 118-120 °C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 1.6 Hz, 1H), 7.27 (dd, *J* = 1.6 Hz, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 1.6 Hz, 1H), 6.68 (s, 1H), 6.65 (dd, *J* = 1.6 Hz, *J* = 8.2 Hz, 1H), 6.09 (s, 1H), 5.61 (s, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 2.67-2.59 (m, 1H), 2.28 (br s, 2H), 2.14 (br s, 2H), 1.79-1.52 (m, 13H), 1.33-1.22 (m, 3H). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ = 187.1, 182.0, 147.7, 146.8, 146.2, 144.7, 144.2, 144.1, 133.9, 126.5, 125.1, 122.1, 120.4, 119.0, 115.1, 113.8, 113.2, 112.8, 112.0, 56.1, 55.9, 38.1, 33.2, 31.8, 29.5, 28.6, 28.4, 26.8, 26.0, 25.9. HRMS (ESI-TOF) calcd for $[C_{32}H_{36}O_6+H]^+$ 517.2590, found 517.2591.

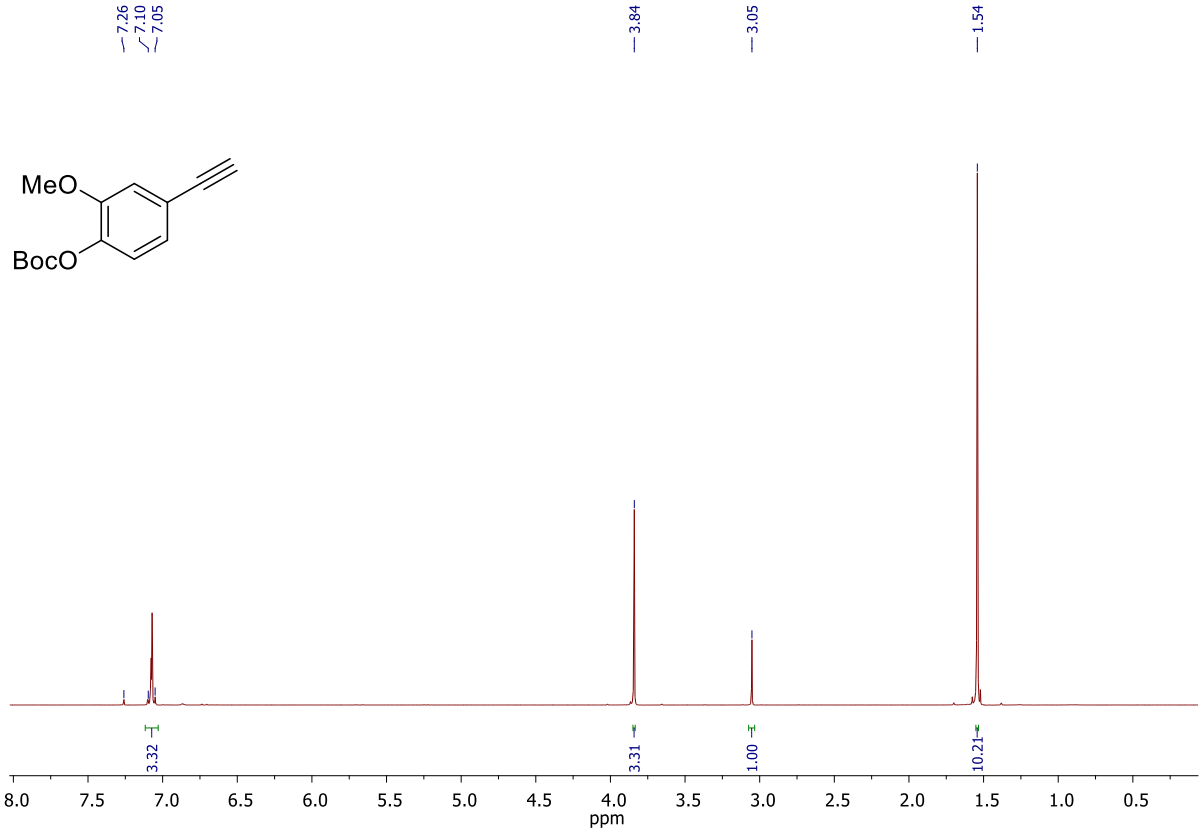
Preparation of the ABTS$^{\bullet+}$ working solution

A 7 mM stock solution of ABTS$^{\bullet+}$ radical-cation was prepared by dissolving ABTS in Milli-Q grade water. Ammonium persulfate (2.45 mM final concentration) was added to this stock solution, and the mixture was allowed to stand for 12-16 h in the dark at room temperature until a dark blue-green color appeared. Before each analysis session, aliquot of the ABTS$^{\bullet+}$ stock solution was diluted to an absorbance of <0.8 using ethanol.

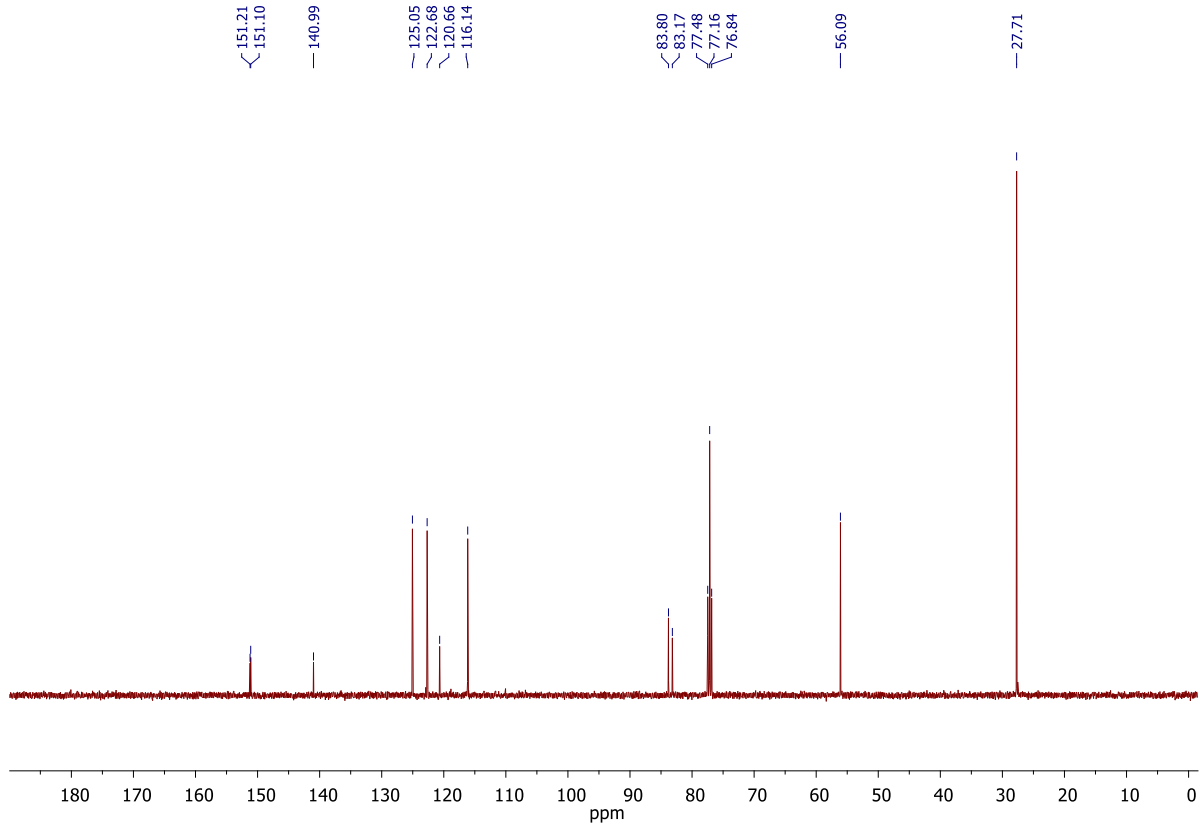
Procedure for the ABTS$^{\bullet+}$-scavenging assay

A 85 μM ethanol solution of compound **7** was prepared. Next, 20 μL of the resulting antioxidant solution were added every 4 minutes (10-11 times) to 2 mL of ABTS$^{\bullet+}$ working solution, and the absorbance at 734 nm was measured. Baseline absorbance was measured using ethanol. In a similar manner, the ABTS$^{\bullet+}$-scavenging assay for Trolox as a standard antioxidant was performed. According to the published procedure [S2], the TEAC value was calculated as the ratio between the slopes of the linear plots for scavenging of ABTS$^{\bullet+}$ radical-cation by compound **7** and Trolox.

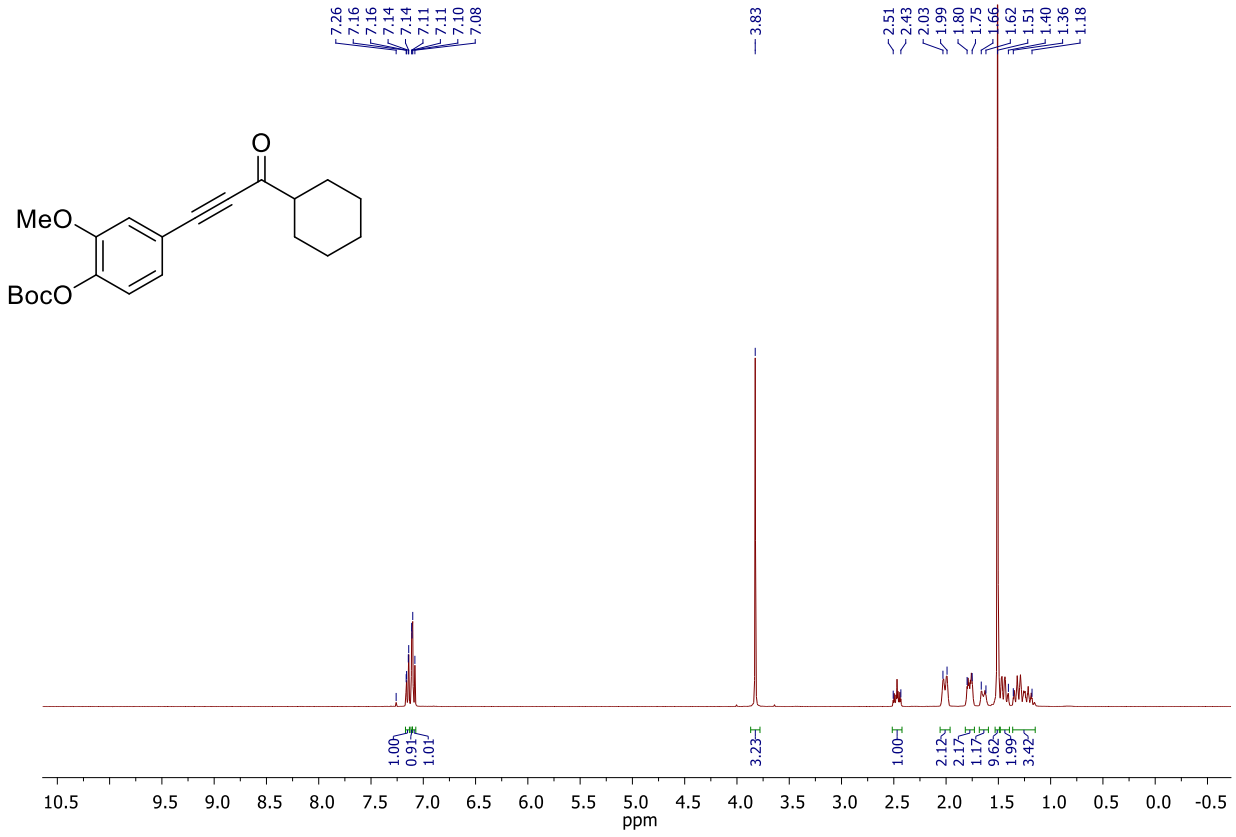
Copies of ^{1}H and ^{13}C NMR spectra



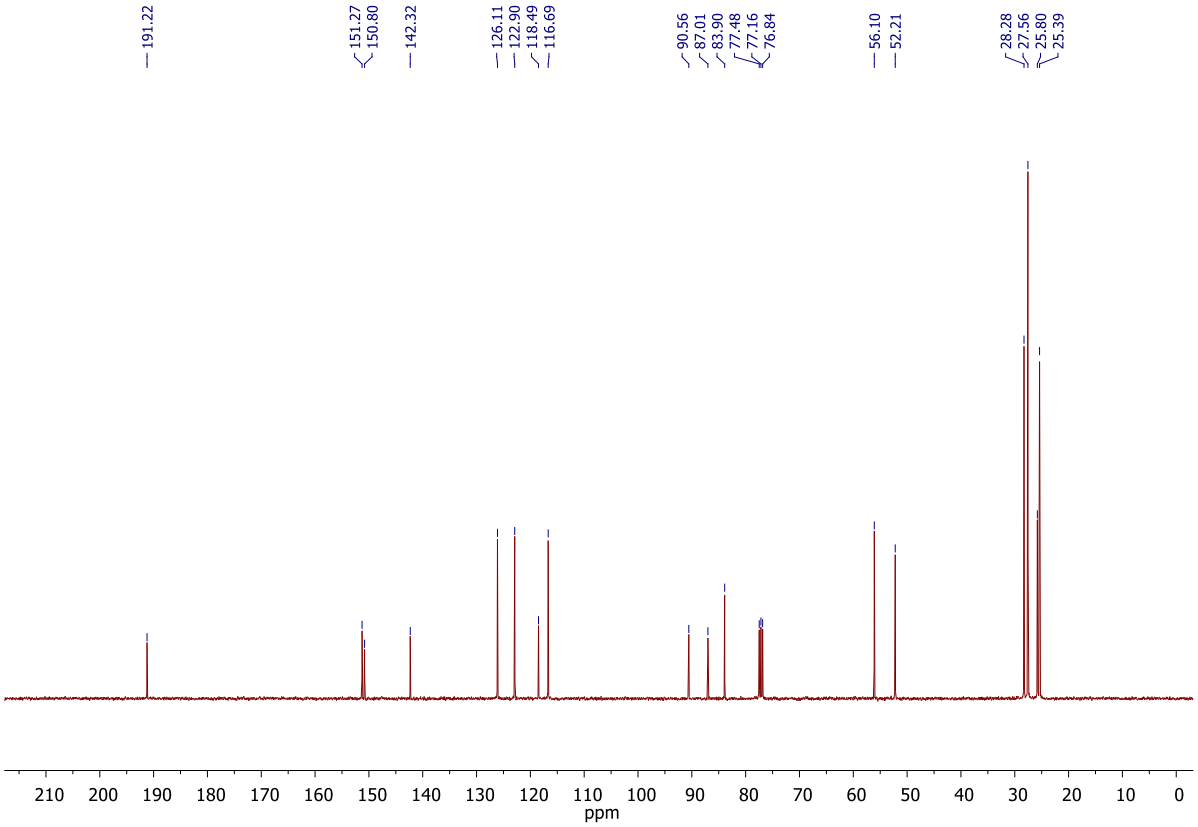
^{1}H NMR Spectrum of **4** (400.1 MHz, $CDCl_3$)



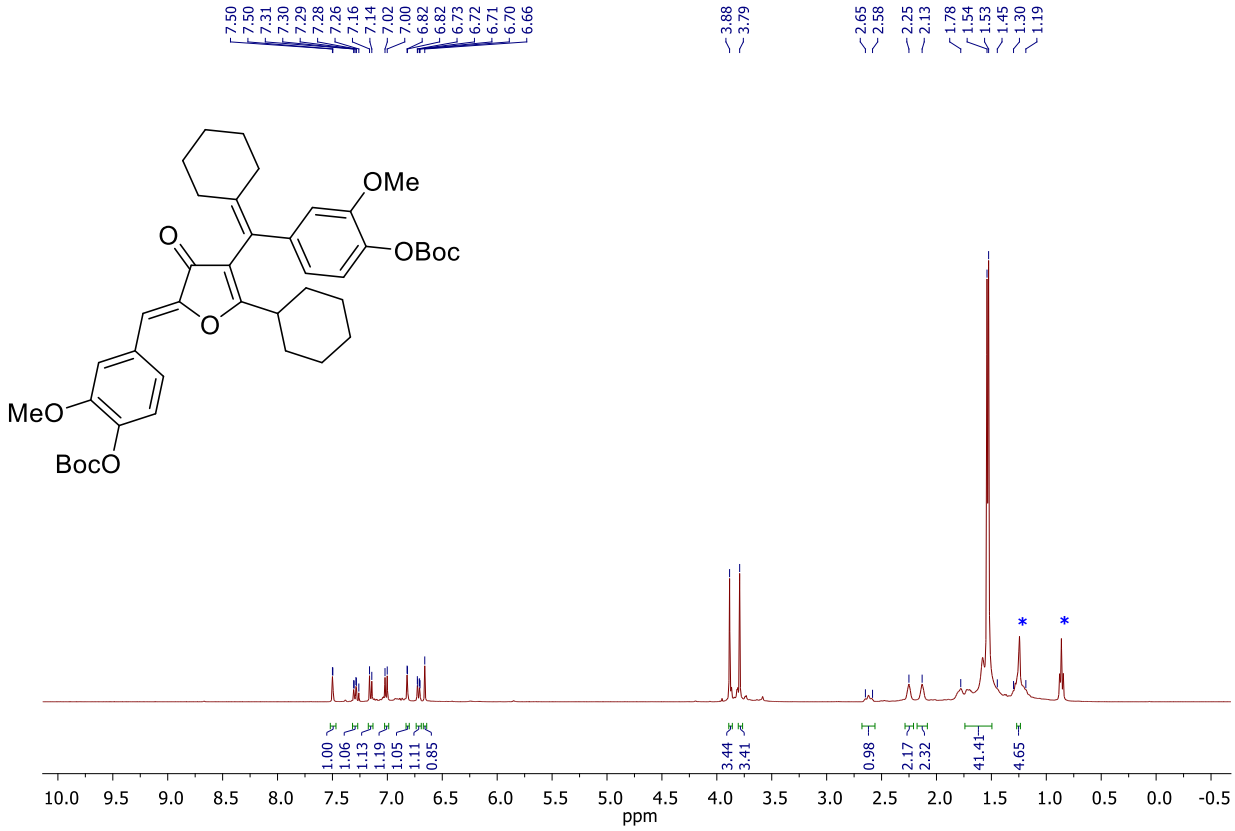
^{13}C NMR Spectrum of **4** (100.6 MHz, $CDCl_3$)



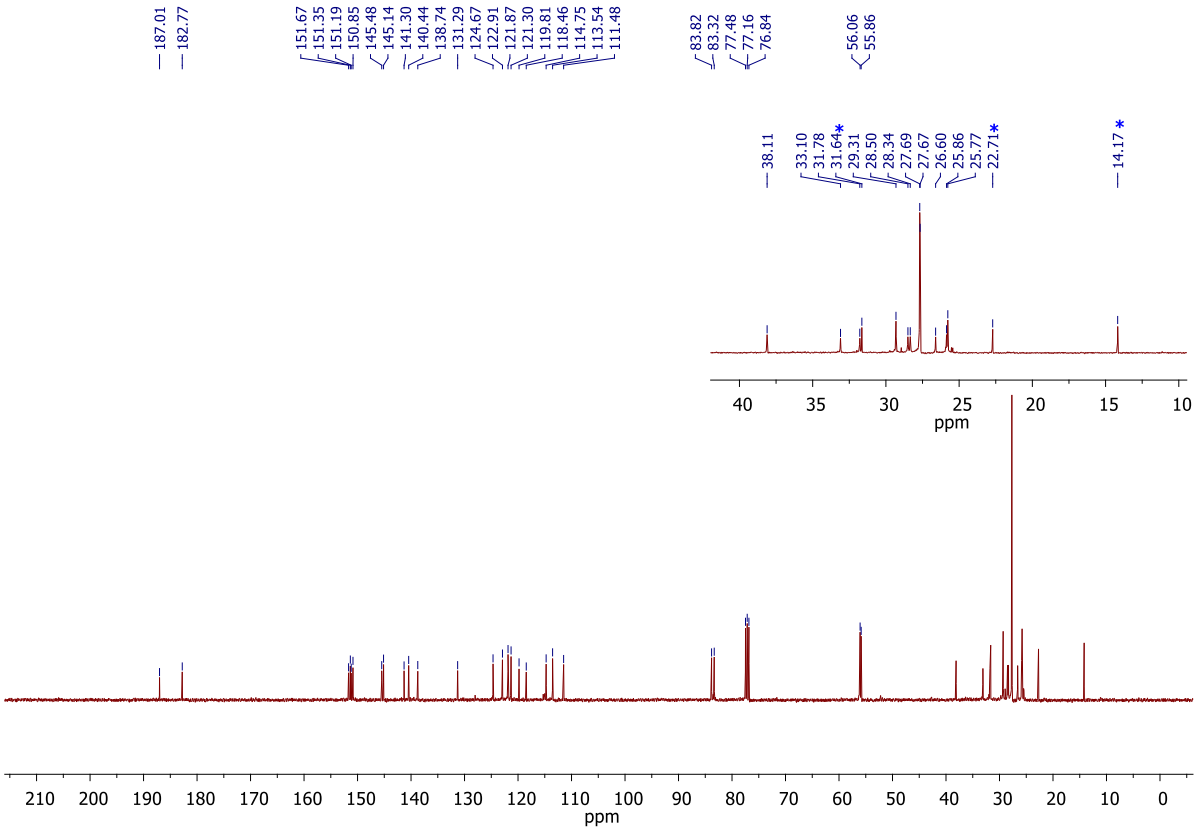
^{1}H NMR Spectrum of **5** (400.1 MHz, $CDCl_3$)



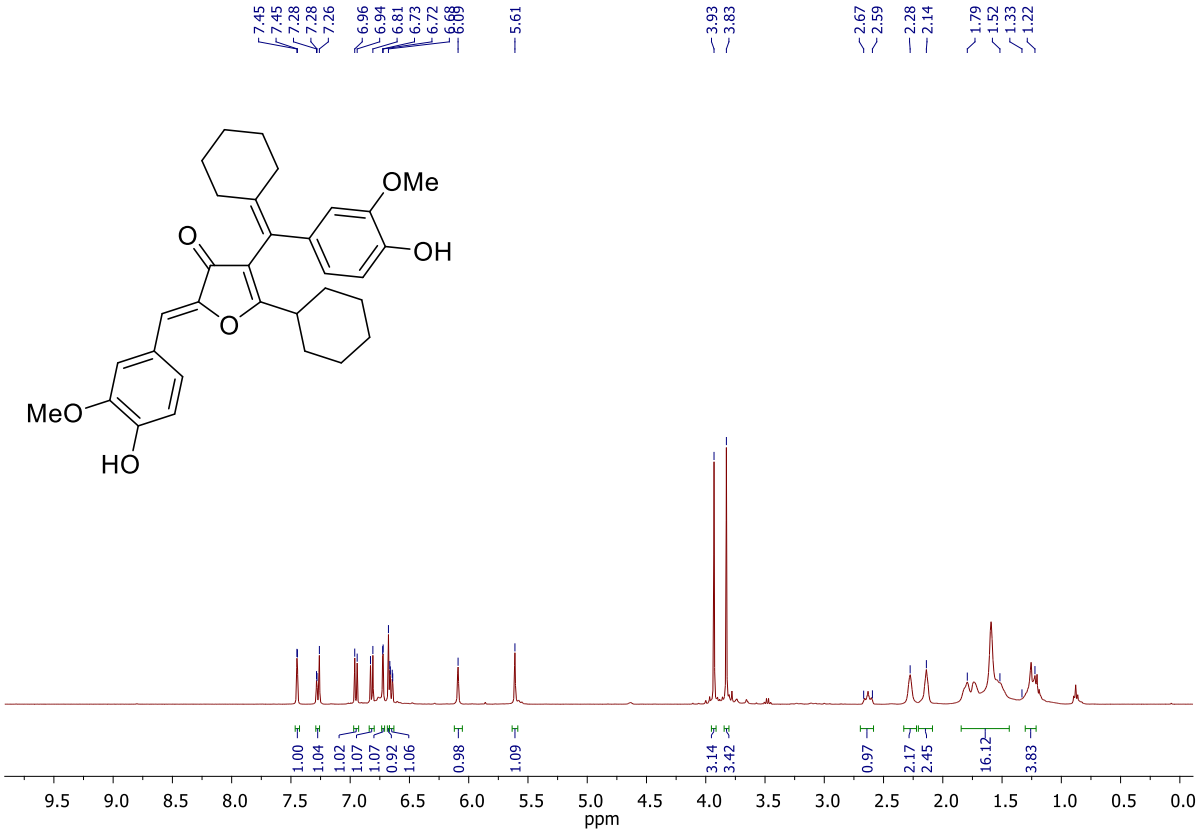
^{13}C NMR Spectrum of **5** (100.6 MHz, $CDCl_3$)



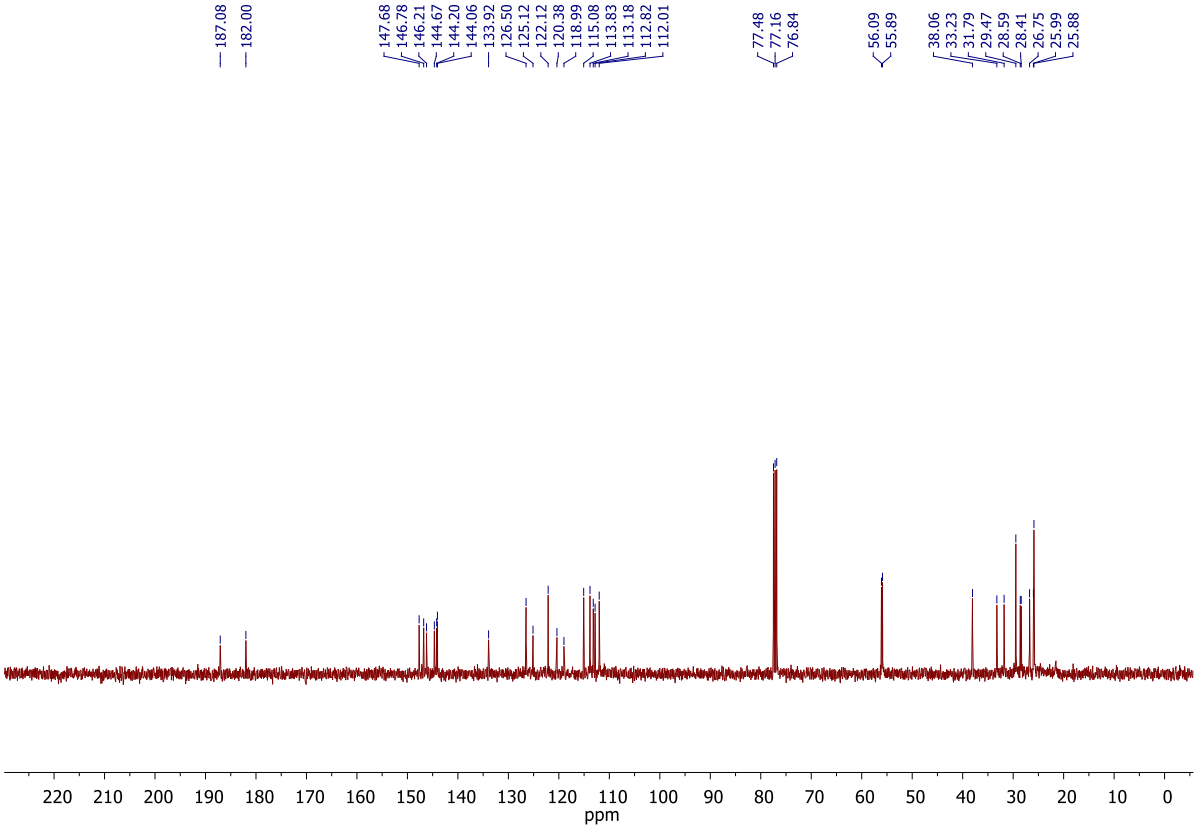
^{1}H NMR Spectrum of **6** (400.1 MHz, $CDCl_3$)



^{13}C NMR Spectrum of **6** (100.6 MHz, $CDCl_3$, *hexane)

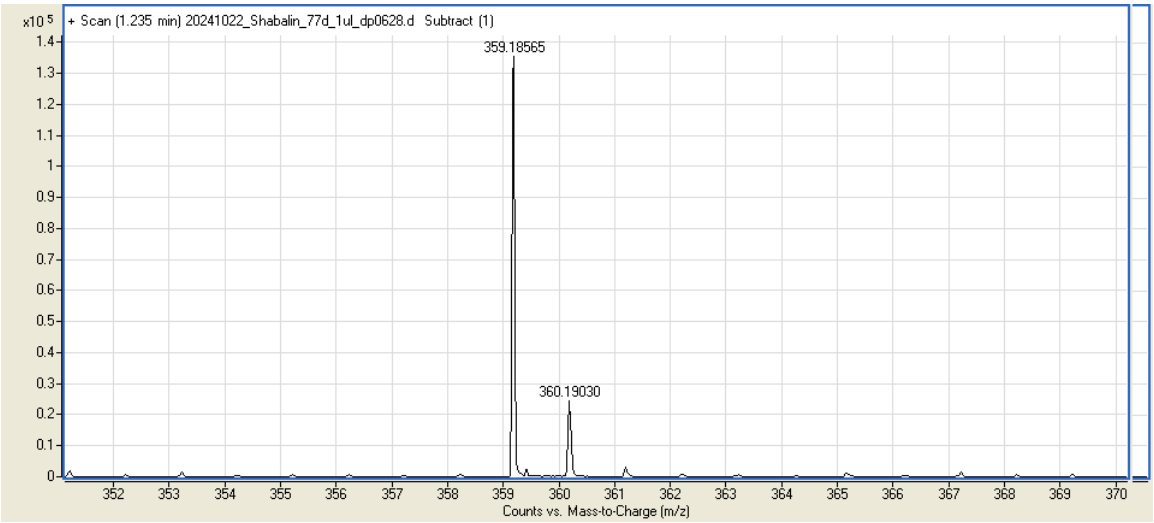


^{1}H NMR Spectrum of **7** (400.1 MHz, $CDCl_3$)

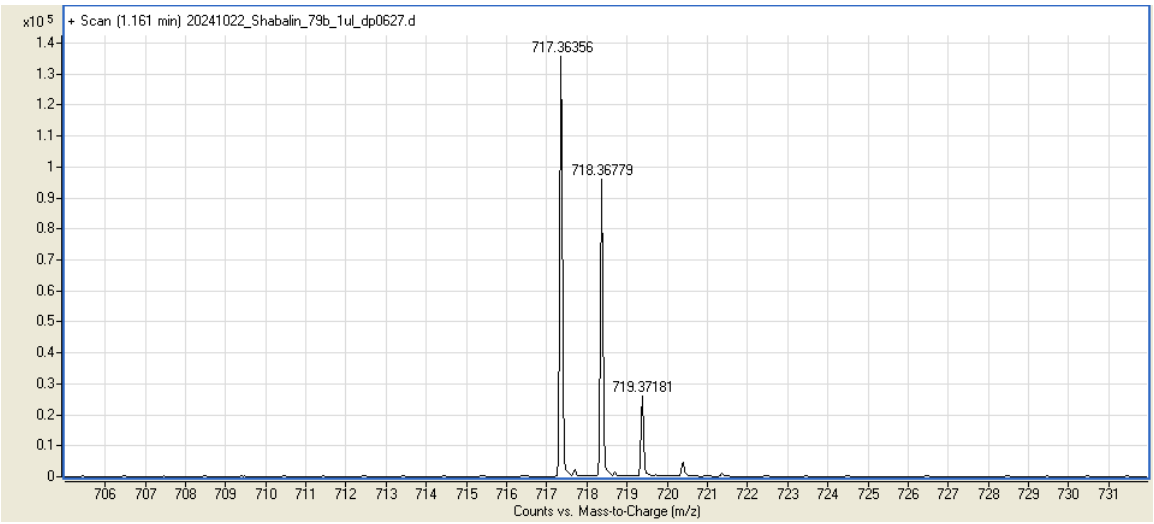


^{13}C NMR Spectrum of **7** (100.6 MHz, $CDCl_3$)

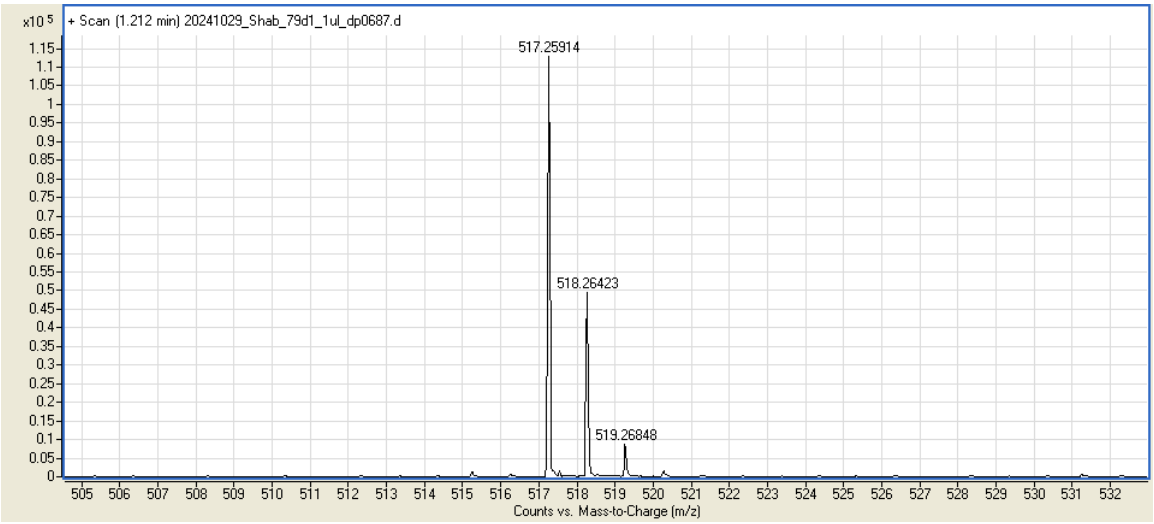
HRMS Data



HRMS spectrum of **5**



HRMS spectrum of **6**



HRMS spectrum of **7**

References

S1. J. Pecourneau, R. Losantos, A. Monari, S. Parant, A. Pasc and M. Mourer, *J. Org. Chem.*, 2021, **86**, 8112; https://doi.org/10.1021/acs.joc.1c00598.

S2. N. J. Miller, C. Rice-Evans, M. J. Davies, V. Gopinathan and A. Milner, *Clin. Sci.*, 1993, **84**, 407; https://doi.org/10.1042/cs0840407.