Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Piperic acid derivative as a molecular modulator to accelerate IAPP aggregation process and alter its antimicrobial activity

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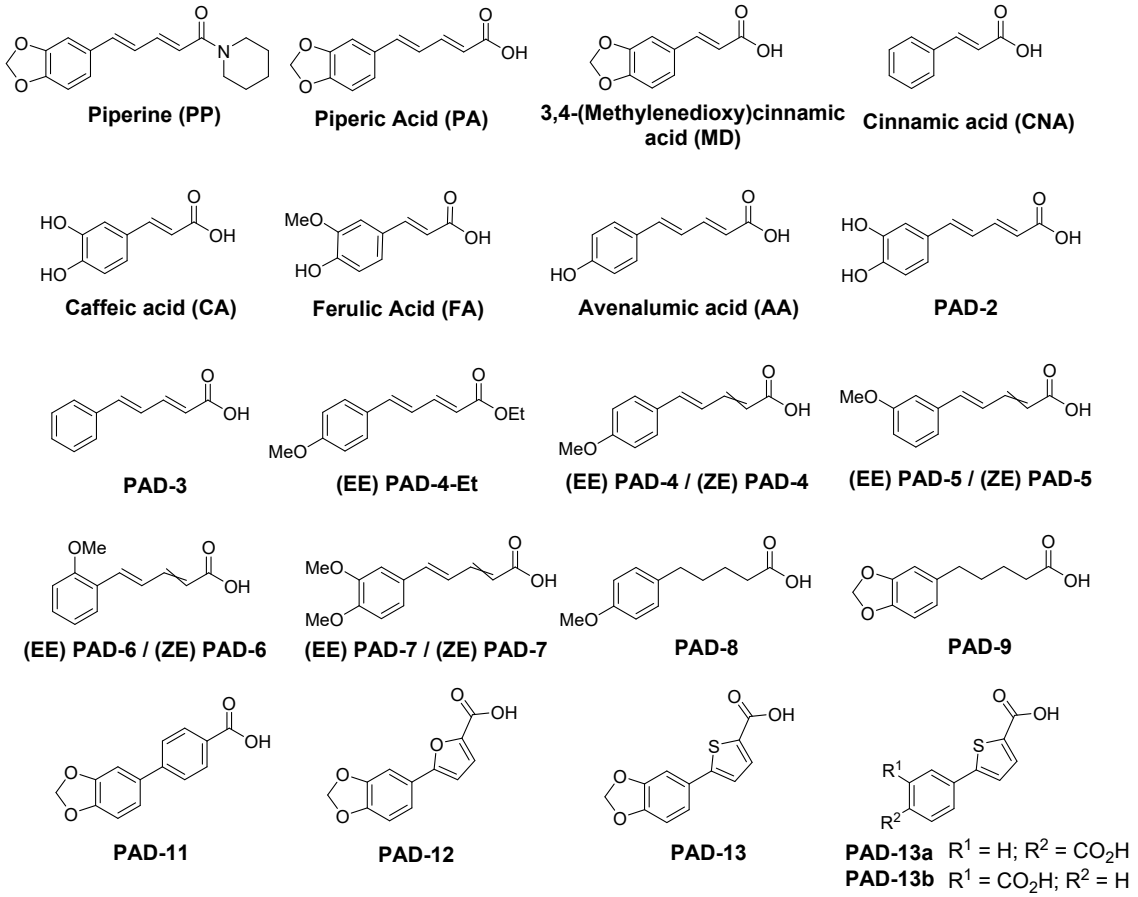


Figure S1. The structures of piperine and **PA** derivatives.

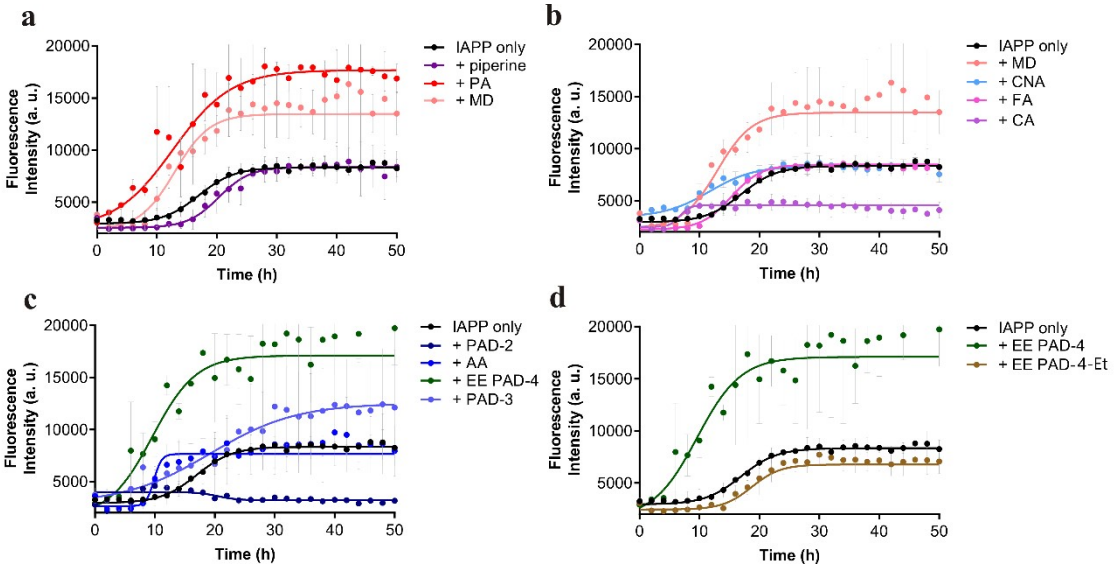


Figure S2. ThT monitored IAPP aggregation kinetics with **PA** derivatives including **MD**, **CNA**, **FA**, **AA**, **PAD-2**, **PAD-3**, **EE PAD-4**, and **EE PAD-4-Et**. The concentration of IAPP and all small molecules was fixed at 25 μM and 500 μM, respectively.

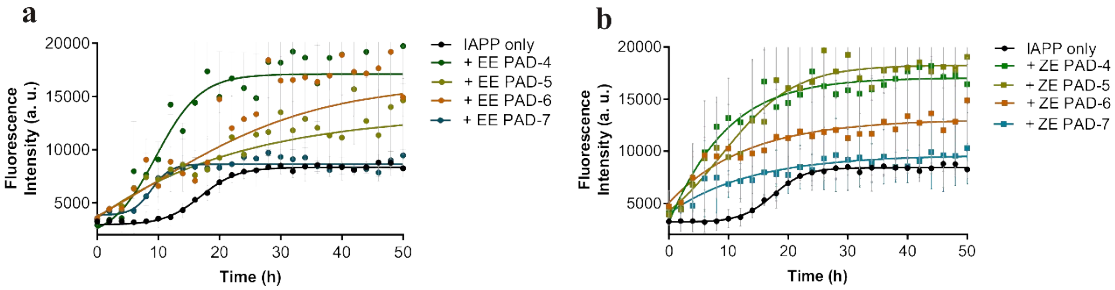


Figure S3. ThT monitored IAPP aggregation kinetics with **PA** derivatives including **EE PAD-4~PAD-7** and **ZE PAD-4~PAD-7**. The concentration of IAPP and all small molecules was fixed at 25 μM and 500 μM, respectively.

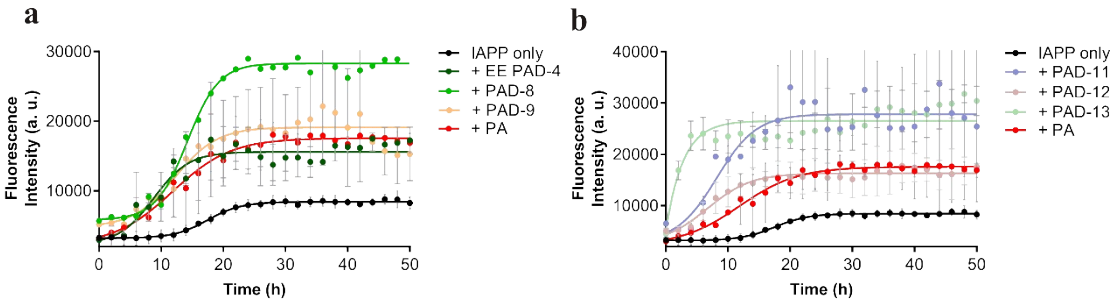


Figure S4. ThT monitored IAPP aggregation kinetics with **PA** derivatives including **PA**, **EE PAD-4**, **PAD-8**, **PAD-9**, and **PAD 11~13**. The concentration of IAPP and all small molecules was fixed at 25 μM and 500 μM, respectively.

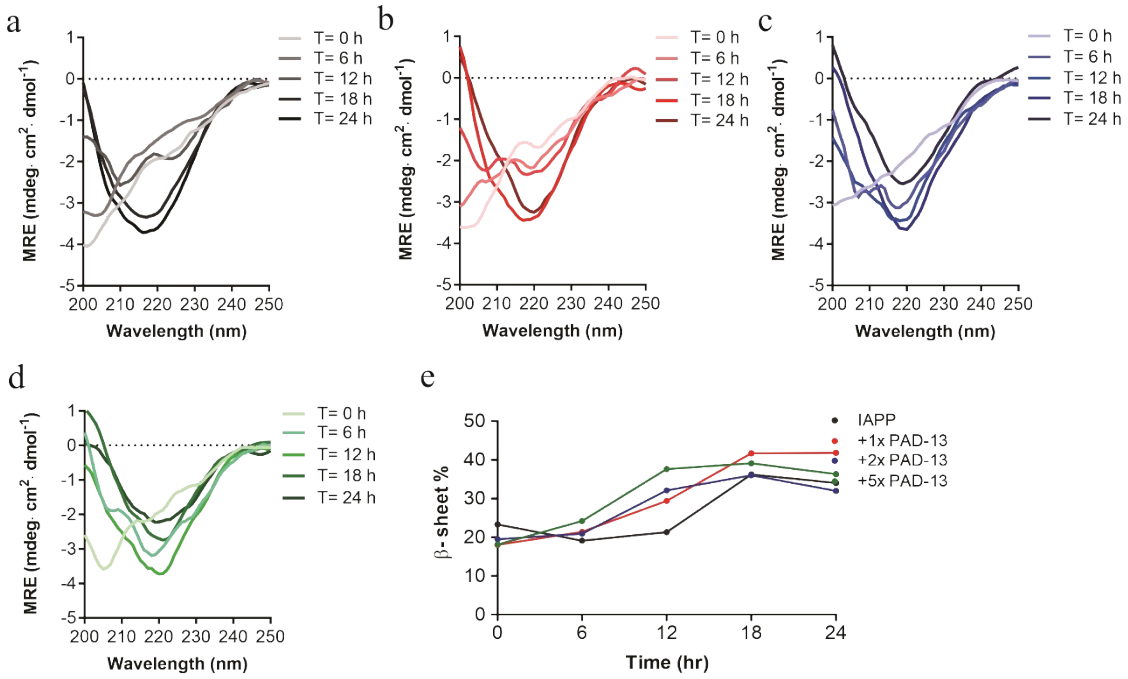


Figure S5. The conformational change of IAPP during aggregation. The CD spectra of (a) IAPP alone, (b) IAPP with 1-fold **PAD-13**, (c) IAPP with 2-fold excess **PAD-13**, and (d) IAPP with 5-fold excess **PAD-13** recorded after 0, 6, 12, 18, 24 h incubation. (e) The β-sheet component was estimated from each spectrum by the online software BeStSel.

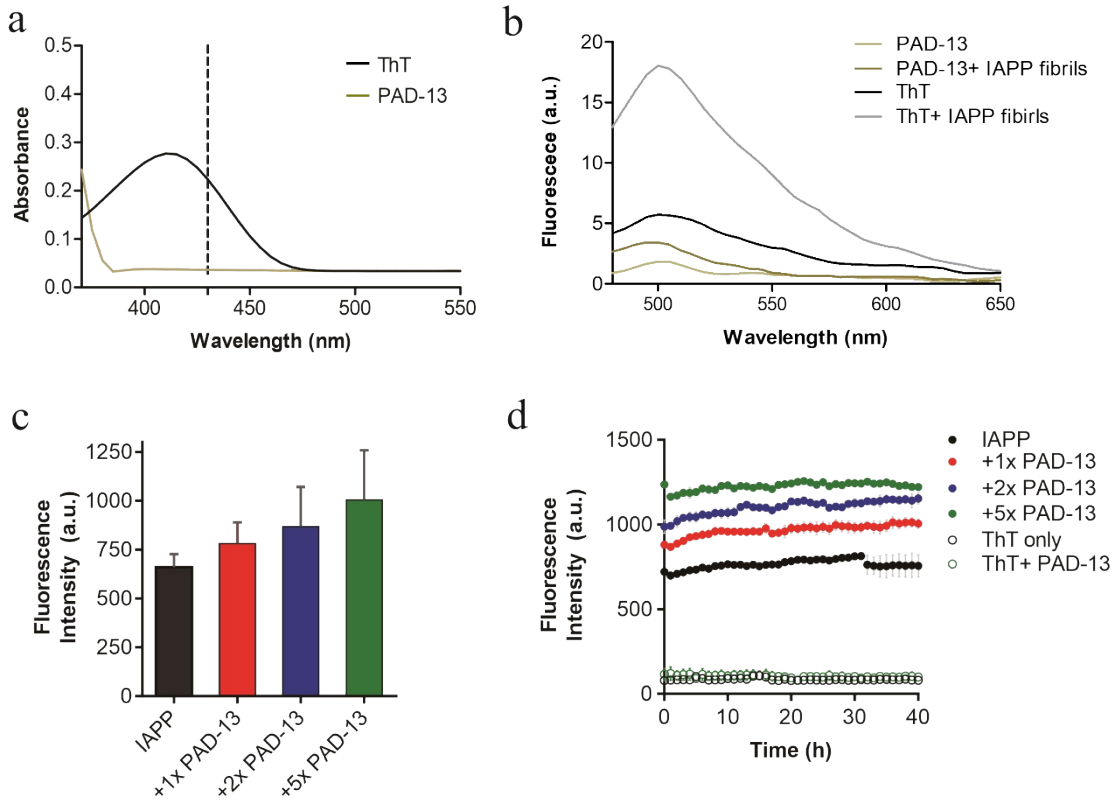


Figure S6. (a) The absorbance spectra of ThT and **PAD-13**. (b) The emission spectra of ThT and PAD-13 w/wo IAPP fibrils. (c) The ThT fluorescence intensity of IAPP fibrils was measured immediately right after the addition of **PAD-13**. (d) The time course of ThT monitoring for IAPP fibrils with the presence of **PAD-13**. IAPP fibrils were prepared in advance by incubating IAPP solution in microtubes for 2 days with continuous shaking at 500 rpm.

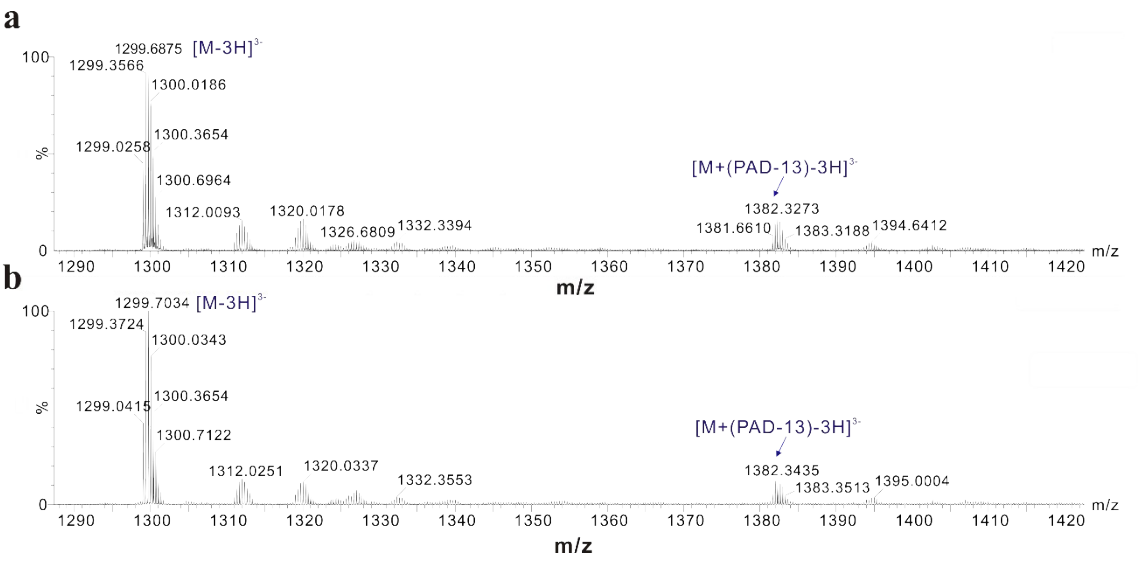


Figure S7. The mass spectra of IAPP with **PAD-13**. (a) Samples were incubated for 2 h before they were subjected to ESI-MS. (b) Samples were incubated for 4 h before they were subjected to ESI-MS.

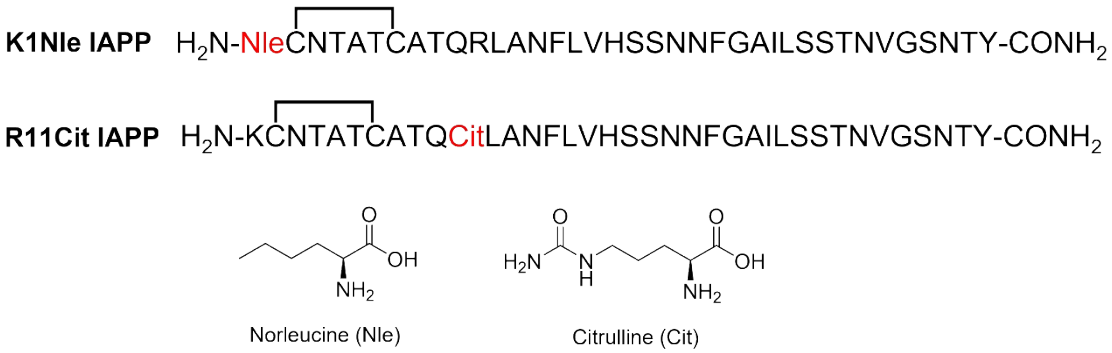


Figure S8. The primary sequence of K1Nle-IAPP and R11Cit-IAPP. The chemical structure of norleucine and citrulline.

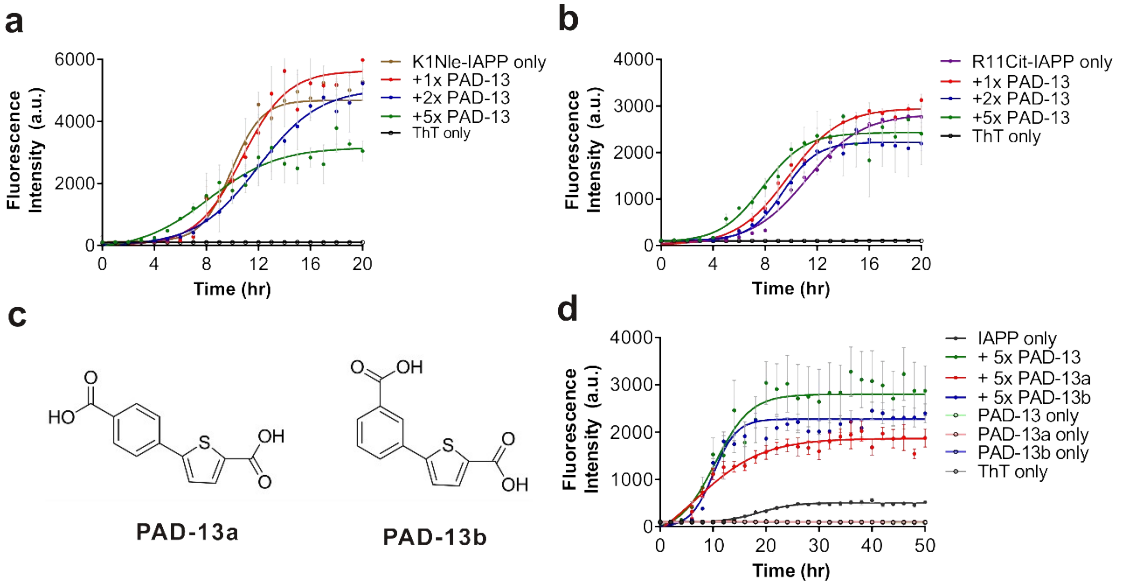


Figure S9. (a) The ThT kinetic studies for K1Nle-IAPP (brown) with 1-fold **PAD-13** (red), with 2-fold excess **PAD-13** (blue), and with 5-fold excess **PAD-13** (green). (b) The ThT kinetic studies for R11Cit-IAPP (purple) with 1-fold **PAD-13** (red), with 2-fold excess **PAD-13** (blue), and with 5-fold excess **PAD-13** (green). (c) The chemical structure of **PAD-13a** and **PAD-13b**. (d) The ThT kinetic studies for IAPP (black), with 5-fold excess **PAD-13** (green), **PAD-13a** (red), and **PAD-13b** (blue). IAPP and IAPP mutants were prepared at 30 μM in 10 mM, pH 7.4, Tris buffer.

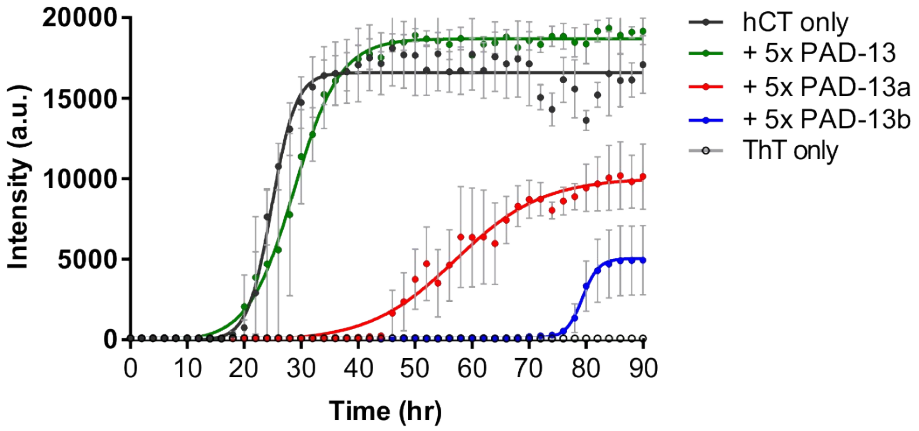


Figure S10. Time course of ThT fluorescence assay upon incubation of 64 μM hCT in the absence (black curve) and presence of 5-fold excess **PAD-13** (green curve), **PAD-13a** (red curve), and **PAD-13b** (blue curve).

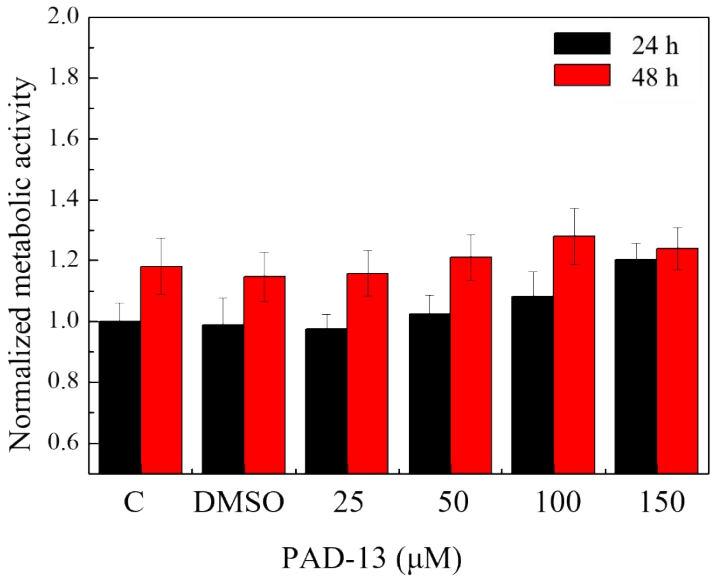


Figure S11. Cytocompatibility tests of **PAD-13** prepared at 25, 50, 100, and 150 μM toward mouse embryonic fibroblasts (MEFs). All MEF cultures contain 1% DMSO. C represents a controlled study without **PAD-13** and DMSO. The metabolic activity of MEFs was determined using the alamarBlue assay after 24 h and 48 h incubation.

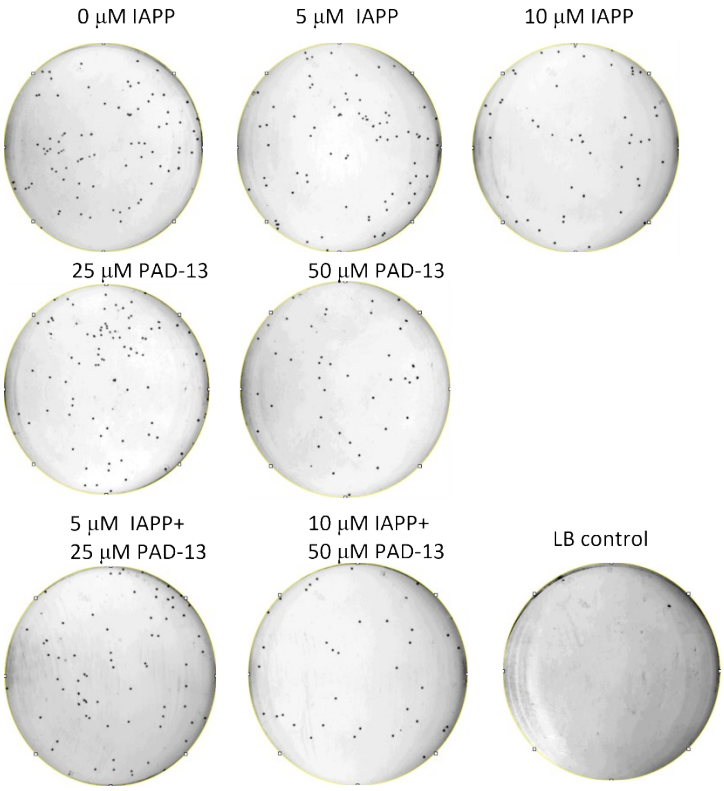


Figure S12. Representative images of colony formation assay.

Experimental methods

Peptide synthesis and purification. The synthesis of IAPP and its analogs was carried out using 9-fluorenylmethoxycarbonyl (Fmoc) chemistry at a scale of 0.05 mmole with the assistance of the Liberty Lite microwave peptide synthesizer (CEM Corporation, USA). A low loading Rink Amide ProTide Resin (CEM Corporation, 0.18 mmole/g) was utilized to provide an amidated C-terminus after peptide cleavage. In each synthesis cycle, the carboxylic group of the Fmoc-protected amino acid was activated using diisopropylcarbodiimide. The Fmoc group was removed using a solution of 10% piperazine (w/v) in a mixture of ethanol and N-methyl pyrrolidone (10:90). To facilitate the synthesis, Fmoc-protected pseudoproline dipeptide derivatives were incorporated at positions 8-9 and 27-28. Double coupling was employed for β-branched residues, the following residue, Arg, and all pseudoproline dipeptide derivatives to enhance the yield of synthesis. Histidine coupling was carried out at 50°C by default to minimize racemization. For the synthesis of K1Nle-IAPP, the Lys residue was replaced by the unnatural amino acid, Fmoc-L-Nle-OH (CAS. 77284-32-3). Another unnatural amino acid, Fmoc-Cit-OH (CAS.133174-15-9), was substituted for Arg to generate R11Cit-IAPP. Upon completion of the synthesis, the peptides were cleaved from the resin using standard trifluoroacetic acid (TFA) methods. Scavengers, including water, triisopropylsilane (TIS), and 3,6-dioxa-1,8-octanedithiol (DODT), were employed during the cleavage step (TFA/H_2O/TIS/DODT= 92.5: 2.5: 2.5: 2.5). To increase peptide solubility, crude peptides were partially treated with 20% acetic acid (v/v) and subjected to freeze-drying in multiple cycles. Subsequently, the crude peptides were dissolved in a 50% acetic acid solution (1 mg/mL) and mixed with I_2 in methanol to form the disulfide bond between Cys-2 and Cys-7. To remove residual scavengers, the crude peptides were initially treated with hexafluoro-2-propanol (HFIP) and lyophilized. Purification was then performed using reverse-phase high-performance liquid chromatography with a Proto 300 C18 semi-preparative column and a two-solution gradient. Solution A consisted of 100% H_2O and 0.045% HCl (v/v), while solution B comprised 80% acetonitrile, 20% H2O, and 0.045% HCl. The collected fractions were pooled and subsequently lyophilized.

The confirmation of peptide molecular weights was conducted using matrix-assisted laser

desorption ionization-time of flight mass spectrometry with an ultrafleXtreme™ device (Bruker, USA). The expected and actual $[M+H]^+$ values for IAPP were 3904.3 and 3904.0, respectively. For K1Nle-IAPP, the respective $[M+H]^+$ values were 3889.3 and 3889.2. For R11Cit-IAPP, the respective $[M+H]^+$ values were 3905.3 and 3905.3.

Thioflavin-T (ThT) assays. To prepare the protein solution, approximately 100 μg of protein powder was treated with 100 μL of hexafluoro-2-propanol (HFIP) for 5-6 hours at room temperature and then lyophilized. The resulting peptide powder was dissolved in 300 μL of 10 mM Tris buffer pH 7.4 and subjected to centrifugation at 15,000 rpm for 10 minutes to remove any preformed aggregates. The supernatant was carefully transferred to another microtube, and a 10 μL aliquot was taken to determine the peptide concentration using a BCA protein assay kit (Thermo Fisher Scientific, USA) with bovine serum albumin as the standard. The remaining supernatant was adjusted to a concentration of 30 μM and 15 μM of ThT was added. PAD-13 prepared in DMSO was added according to experimental need. The concentration of DMSO was fixed at 1%. For seeding experiments, preformed IAPP amyloid fibrils were generated by incubating the IAPP solution in microtubes for three days with shaking at 500 rpm. ThT assays were conducted at 25°C using a sealed 384-well nonbinding surface microplate (Corning 3575, USA) without any additional agitation. The measurements were performed using a SpectraMax M2 multimode microplate reader (Molecular Devices, USA) or a Hidex Sense multimode microplate reader (Hidex, Finland) with excitation at 430 nm and emission at 485 nm. Data points were collected every hour, and the average fluorescence with standard error of the mean was plotted against time using triplicate wells.

Transmission electron microscope (TEM). TEM images were recorded at the instrumentation center of the National Taiwan University utilizing a Hitachi model H-7100 transmission electron microscope (Japan) operating at an accelerating voltage of 120 kV. Five microliters of the peptide solution recovered following the ThT assay, were deposited onto a carbon-coated Formvar 300 mesh copper grid and allowed to sit for 1 minute. Subsequently, the sample was negatively stained by incubating it with 2% uranyl acetate for an additional 1 minute.

Fourier transform infrared spectroscopy (FTIR). Infrared spectra were obtained using FTIR with attenuated total reflectance (ATR, Bruker Tensor 27) technique at a

resolution of 1 cm^{-1}. Germanium was used as the internal reflection element (IRE). To prepare the samples, each solution, prepared at a concentration of 30 μM in 10 mM Tris buffer pH 7.4 with and without **PAD-13**, was incubated in microtubes with continuous shaking to allow the formation of amyloid fibrils. The fibril solutions were then subjected to centrifugation at 15,000 rpm for 30 minutes to remove the buffer. The resulting fibril pellets were washed twice with distilled deionized water and dissolved in 20 μL DDI water. For FTIR-ATR analysis, 5 μL of the washed fibril sample was spotted onto the IRE crystal and allowed to evaporate under a gentle flow of nitrogen gas (N_2) to remove excess water. Spectra were recorded by accumulating 64 scans, and a background spectrum was subtracted to account for any instrumental noise or interference.

Congo Red (CR) binding study. A stock solution (1 mM) of CR in ethanol was prepared. The working CR solution of 1% was applied with the protein solution. UV absorbance was measured in the spectral range of 450–650 nm using a SpectraMax M2 multimode microplate reader.

Gel electrophoresis. To analyze the remaining soluble peptide components obtained from the ThT assay, gel electrophoresis was performed, and the peptides were visualized using silver staining. The samples were first filtered through a 0.22-μm syringe filter to remove any large aggregates. Subsequently, the filtered samples were mixed with 4X SDS sample dye. The peptide samples were then loaded onto a 13.5% Tris-tricine SDS-polyacrylamide gel electrophoresis (SDS-PAGE) gel.

Circular dichroism (CD). CD experiments were performed using a J-715 circular dichroism spectrometer (JASCO, USA). The protein preparation for CD experiments followed the same protocol as the ThT assays, but PAD-13 was prepared in acetonitrile to avoid interference. Aliquots of 600 μL of peptide solutions were incubated in microtubes within a ThermoMixer, with 60 seconds of agitation at 500 rpm every 45 minutes at 25 °C. At defined time points, samples were individually transferred to a 1 mm path-length quartz cell for spectral measurements. CD spectra were recorded in the wavelength range of 200-250 nm with 1 nm intervals at 25°C. The data were obtained by averaging ten scans and corrected based on the background spectrum. To estimate the β-sheet component of the peptides, the online software BeStSel was employed.

Electrospray ionization-mass spectrometry (ESI-MS). The experiments were

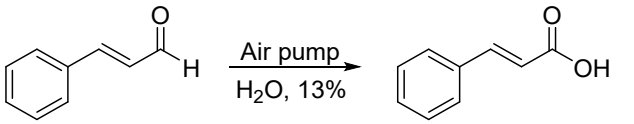
conducted on a Waters Synapt G2 HDMS instrument with a LockSpray ESI source. IAPP (30 μM) and **PAD-13** (150 μM) were prepared in 10 mM Tris buffer at pH 7.4 and first incubated for 2 and 4 h before they were infused into the ESI source at a flow rate of 6 μL/min by a syringe pump (KDS-100, KD Scientific). Data were collected and analyzed by using MassLynx 4.1.

Cytocompatibility study. Mouse embryonic fibroblasts (MEFs), harvested from C57BL/6N mice embryos, were used for the cytocompatibility study of **PAD-13**. MEFs were cultured in the DMEM supplemented with 10% bovine serum (FBS), 1% penicillin/streptomycin, and 1% HEPES under a humidified atmosphere of 5% CO_2 and 37°C. MEFs (104 cells/well) were placed in the 96-well culture plate and cultured with DMSO or **PAD-13** at 37 °C under 5% CO_2. The metabolic activity of the MEFs was determined with alamarBlue assay according to the protocol. Briefly, alamarBlue solutions (10% in serum-contained DMEM) were added to the cell-seeding wells and reacted for 4 h at 37 °C. The alamarBlue solutions were transferred to another 96-well culture plate, and the emission intensity of the solutions at 590 nm was determined with an excitation of 530 nm using a microplate reader (Synergy H1) with subtracted background emission from as-prepared alamarBlue solutions.

Antimicrobial test. Fifty microliters of *Staphylococcus aureus* from an overnight culture were added to 950 μL of Lysogeny broth (LB) and cultured for an additional 2.5 h. The bacterial concentration was calculated using the formula derived from the standard curve (y = 3×10^9 x - 2×10^8), and a bacterial solution with a concentration of 1×10^3 CFU/mL was prepared through serial dilution. Next, 360 μL of the diluted bacterial solution was mixed with 40 μL of test samples. The mixture was then incubated at 37 °C for 30 minutes. Subsequently, 100 μL of the bacterial culture was spread onto a 10 cm LB Agar plate. After incubating for 19 h at 37°C, the colonies were recorded using the LAS-4000 imaging system and analyzed with ImageJ software. Each condition was repeated at least three times and normalized to the DMSO control group. The statistics was analyzed by one way-analysis of variance with Tukey's post test. * $P<0.05$

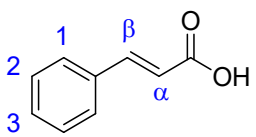
The preparation of piperine derivatives. Piperine (**PP**), caffeic acid (**CA**), ferulic acid (**FA**), 3,4-(Methylenedioxy)cinnamic acid (**MD**), (2E,4E)-5-(3,4-dihydroxyphenyl) penta-2,4-dienoic acid (**PAD-2**), and all other reagents and chemicals for synthesis were

used as purchased without further purification. All nuclear magnetic resonance spectra were recorded on a Bruker AV-300 spectrometer and Bruker Avance III HD-600 MHz operating at 300 MHz and 600 MHz for ^{1}H analysis and at 75 MHz and 150 MHz for ^{13}C analysis, respectively. The chemical shifts are expressed in ppm and referenced to solvent peaks ($CDCl_3$: ^{1}H 7.26 ppm, ^{13}C 77.16 ppm; CD_3OD: ^{1}H 3.31 ppm, ^{13}C 49.00 ppm; d_6-DMSO: ^{1}H 2.50 ppm, ^{13}C 39.52 ppm; D_2O: ^{1}H 4.79 ppm). Coupling constants (*J*) are reported in Hz. Splitting patterns are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). IR spectra were recorded on a Perkin–Elmer Spectrum 100 FTIR spectrometer and data are reported in cm^{-1}. High-resolution mass spectrometry (HRMS) was performed with a Thermo Finnigan LCQ Advantage (ESI-MS). Low-resolution mass spectrometry (LRMS) was performed with a Thermo Finnigan LCQ Advantage (ESI-MS) and a JEOL JMS- 700 spectrometer (EI-MS). Melting points were recorded with Melting Point Apparatus MP-2D and those are uncorrected. UV/Vis absorptions and fluorescent emissions were carried out on a SpectraMax M2 microplate readers.All reactions were monitored by thin-layer chromatography analysis using Merck105554TLC Silica gel 60 F_{254} 25 aluminum sheets 20 x 20 cm. Column chromatography was performed in a Chromatorex MB 70-40/75 (Fuji Silysia Chemicals Ltd.). Any reactions that required anhydrous conditions were conducted under argon. Anhydrous dichloromethane (DCM) was distilled from calcium hydride under nitrogen. Tetrahydrofuran (THF) and *N*, *N*-dimethylformamide (DMF) were dried with 3Å molecular sieves and stood overnight before use.



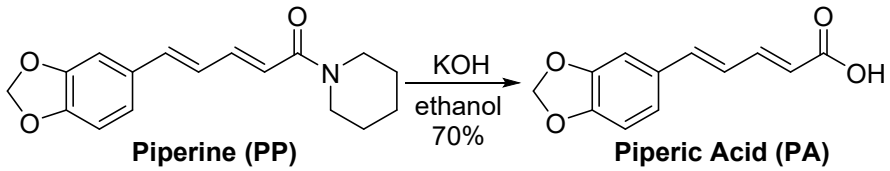
Cinnamic acid (CNA)

Scheme S1. Synthesis of cinnamic acid.

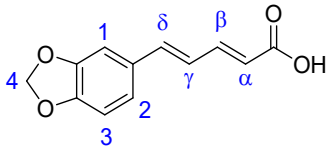


Cinnamic acid (CNA)

A solution of cinnamaldehyde (1.1 g, 8.3 mmol) in water was pumped with air at room temperature overnight. A pale solid precipitate was formed during the reaction. After completion of the reaction, 2M $NaOH_{(aq)}$ was added to the reaction mixture until the pH of the solution was basic, and the reaction mixture was subsequently washed with DCM. The water layer was separated and the pH value was adjusted to 1 with 1M $HCl_{(aq)}$. Thereafter, the acidified aqueous layer was extracted with DCM twice. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give compound **CNA** as a pale-yellow solid. (160.0 mg, 13%). Mp: 130˚C; ^{1}H NMR (300 MHz, $CDCl_3$, 295 K): δ = 6.47 (d, 1H, J = 15.9 Hz, H_α), 7.40-7.43 (m, 3H, H_2, H_3), 7.55-7.58 (m, 2H, H_1), 7.81 (d, 1H, J = 16.0 Hz, H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 117.4, 128.5 (2C), 129.1 (2C), 130.9, 134.2, 147.3, 172.7 ppm; LRMS (EI) m/z calcd. for $C_9H_8O_2$ $[M]^+$: 148.1; Found 148.1. The ^{1}H and ^{13}C NMR spectra were agreed with the reported literature[1].



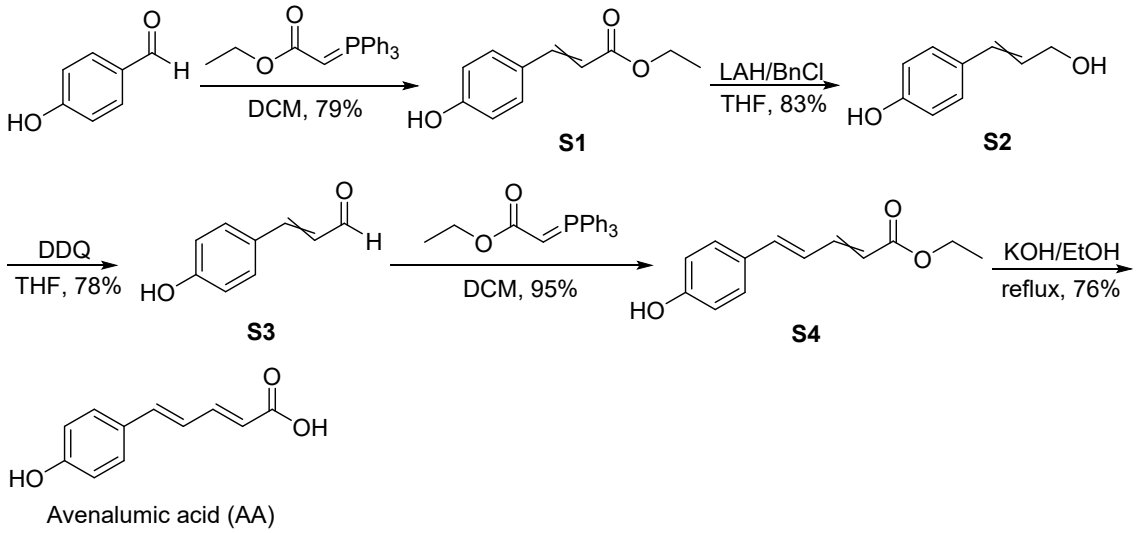
Scheme S2. Synthesis of piperic acid (PA).



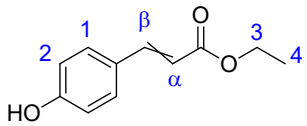
Piperic Acid (PA)

Piperine (900.0 mg, 3.2 mmol) was dissolved in 8.0 mL EtOH containing 10 w.t.% of KOH and the reaction mixture was refluxed overnight. After completion of the reaction, the remaining residue was filtered and that was washed with EtOH to yield compound **PA** as a brown solid (500.0 mg, 70%). Mp: > 400˚C; ^{1}H NMR (300 MHz, D_2O, 295 K): δ = 5.94 (s, 2H, H_4), 5.96 (d, 1H, J_1 = 15.2 Hz, H_α), 6.78-6.85 (m, 3H, H_γ, H_δ, H_3), 6.95-6.98 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.6 Hz, H_2), 7.05-7.13 (m, 2H, H_1, H_β) ppm; ^{13}C NMR (75 MHz, d_6-DMSO with 10% D_2O, 297 K): δ = 102.2, 106.6, 109.7, 123.2,

127.4, 131.2, 132.2, 136.8, 139.8, 148.4, 148.9, 173.7 ppm; HRMS (ESI) m/z calcd. for $C_{12}H_{11}O_4$ $[M+H]^+$: 219.0652; Found 219.0658. The ^1H and ^{13}C NMR spectra were agreed with the reported literature[2, 3].



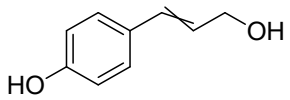
Scheme S3. Synthesis of avenalumic acid (AA).



(*E*)-ethyl 3-(4-hydroxyphenyl)acrylate (S1)

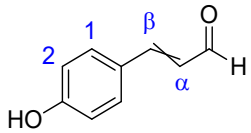
To a solution of 4-hydroxybenzaldehyde (5.0 g, 40.9 mmol) in dry DCM (40.0 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (21.4 g, 61.4 mmol). The reaction mixture was stirred at room temperature for overnight. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure and the crude residue was dissolved in hexane containing 10 w.t.% of ether. The white precipitate was removed by filtration. The filtrate was concentrated under reduced pressure and purified by column chromatography to yield ester **S1** (6.20g, 79%, *E*/*Z* ratio = 6:1) as a white solid. R_f = 0.55 (n-Hexane: EtOAc = 2:1v/v). ^1H NMR (300 MHz, $CDCl_3$, 297 K): δ = 1.34 (t, 3H, *J* = 14.2 Hz, H_4), 4.24-4.31 (q, 2H, J_1 = 21.4 Hz, H_3), 5.82 (d, 1H, *J* = 12.7 Hz, $H_{\alpha'}$), 6.29 (d, 1H, *J* = 16.0 Hz, H_α), 6.84-6.90 (m, 2H, H_2), 7.38-7.41 (d, 2H, *J* = 8.6 Hz, H_1), 7.64 (d, 1H, *J* = 15.9 Hz, H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ =14.4, 61.0, 115.2, 116.1 (2C), 126.7, 130.2 (2C), 145.4, 158.7, 168.7 ppm. The ^1H and ^{13}C

NMR spectra were agreed with reported literature[4].



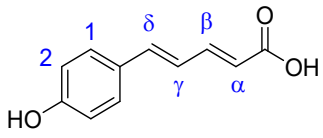
(*E*)-4-(3-hydroxyprop-1-en-1-yl)phenol (S2)

To a solution of lithium aluminum hydride (148.0 mg, 3.9 mmol) in dry THF (5.0 mL) was slowly added a dry THF (5.0 mL) solution containing BnCl (493.7 mg, 3.9 mmol) at 0°C. The resulting mixture was stirred for 15 min, and then a solution of compound **S1** (500.0 mg, 2.6 mmol) in dry THF (2.5 mL) was added dropwise to the reaction at 0°C. The reaction mixture was stirred at room temperature for 1.5 h. After completion of the reaction, it was carefully quenched by the addition of water and the solution mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to obtain crude product as a yellow oil (385 mg, 83%). R_f = 0.29 (n-Hexane: EtOAc = 1:1 v/v). The crude product was directly used in the next step without further purification.



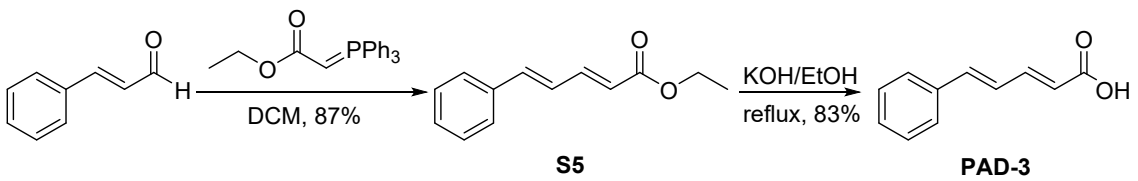
(*E*)-3-(4-hydroxyphenyl)acrylaldehyde (S3)

To a solution of crude **S2** (200.0 mg, 1.3 mmol) in dry THF (13.0 mL) was added DDQ (360.9 mg, 1.6 mmol) under an ice bath and then the reaction mixture was stirred at room temperature for overnight. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure and directly purified by column chromatography to yield aldehyde **S3** (153 mg, 78%, *E*/*Z* ratio = 10:1) as a light orange solid. R_f = 0.41 (n-Hexane: EtOAc = 1:1v/v). ^{1}H NMR (300 MHz, CD_3OD, 297 K): δ = 5.91-6.99 (dd, 1H, J_1 = 16.1 Hz, J_2 = 5.5 Hz, $H_{\alpha'}$), 6.57-6.65 (dd, 1H, J_1 = 15.8 Hz, J_2 = 7.8 Hz, H_α), 6.73-6.76 (m, 2H, $H_{2'}$), 6.82-6.87 (m, 2H, H_2), 7.25-7.28 (m, 2H, $H_{1'}$), 7.52-7.61 (m, 3H, H_1, H_β), 9.55 (d, 1H, J = 7.9 Hz, CHO) ppm; ^{13}C NMR (75 MHz, CD_3OD, 297 K): δ = 117.0 (2C), 126.4, 127.1, 132.0 (2C), 155.9, 162.3, 192.2 ppm. The ^{1}H and ^{13}C NMR spectra were agreed with reported literature[5].

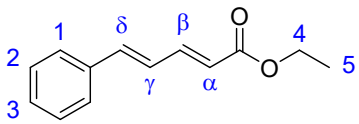


Avenalumic acid (AA)

To a solution of compound **S3** (100.0 mg, 0.7 mmol) in dry DCM (7.0 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (352.7 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature for overnight. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the crude residue was dissolved in hexane containing 10 w.t.% of ether. The white precipitate was removed by filtration. The filtrate was concentrated and then purified by column chromatography to yield ester **S4** (140.0 mg, 95%) as a light-yellow solid. R_f = 0.54 (n-Hexane: EtOAc = 1:1v/v). Then, compound **S4** (140.0 mg, 0.6 mmol) was dissolved in EtOH (30.0 mL) containing 10 w.t.% of KOH and the reaction mixture was refluxed for 14 hr. After cooling to room temperature, EtOH was removed under reduced pressure. Then, water was added to the crude residue and washed with DCM. The aqueous layer was separated and the pH value was adjusted to 1 by adding 1M $HCl_{(aq)}$. After the addition of 1 M $HCl_{(aq)}$, the remaining solution mixture was extracted with EtOAc twice. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield **AA** (93.0 mg, 76%) as a white solid. Mp: 223˚C; ^{1}H NMR (300 MHz, CD_3OD, 297 K): δ = 5.92 (d, 1H, *J* = 15.1 Hz, H_α), 6.75-6.92 (m, 4H, H_γ, H_δ, H_2), 7.37-7.46 (m, 3H, H_1, H_β) ppm; ^{13}C NMR (75 MHz, CD_3OD, 297 K): δ = 116.7 (2C), 120.4, 124.4, 129.2, 130.0 (2C), 142.2, 147.5, 159.9, 170.9 ppm; LRMS (EI) m/z calcd. for $C_{11}H_{10}O_3$ $[M]^+$: 190.1; Found 190.1. The ^{1}H and ^{13}C NMR spectra were agreed with the reported literature[6].

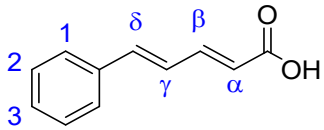


Scheme S4. Synthesis of PAD-3.



(2*E*,4*E*)-ethyl 5-phenylpenta-2,4-dienoate (S5)

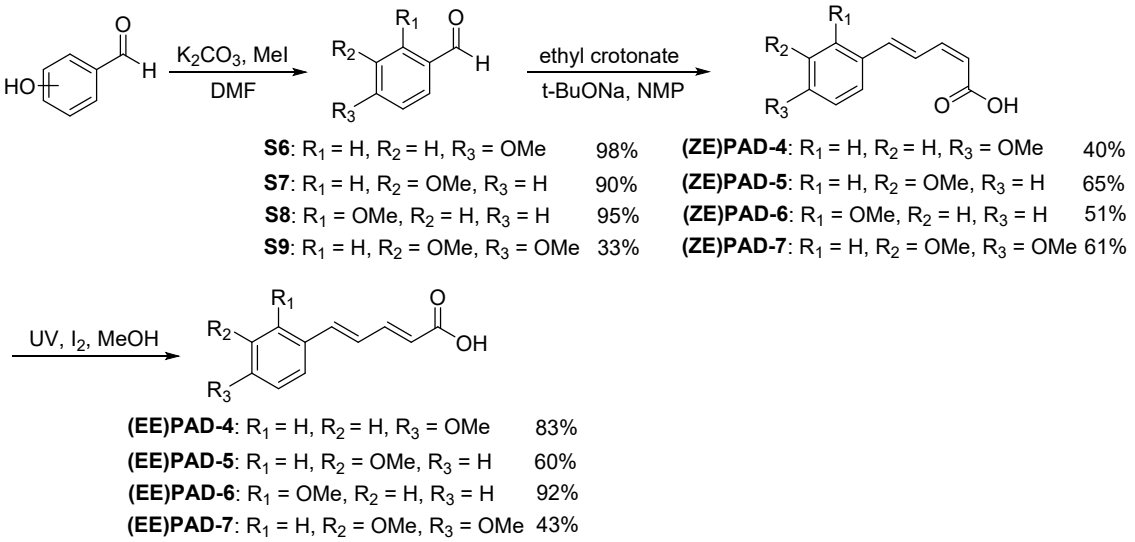
To a solution of (*E*)-cinnamaldehyde (1.0 g, 7.5 mmol) in DCM (20.0 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (2.8 g, 7.9 mmol) and then the reaction mixture was stirred at room temperature for overnight. After the completion of the reaction, the solvent was removed under reduced pressure and the crude residue was dissolved in hexane containing 10 w.t.% of ether. The white precipitate was removed and the filtrate was concentrated under reduced pressure and purified by column chromatography to yield ester **S1** (1.3 g, 87%) as a colorless oil. R_f = 0.42 (n-Hexane: EtOAc = 9:1 v/v). ^{1}H NMR (300 MHz, $CDCl_3$, 296 K): δ = 1.31 (t, 3H, J = 14.3 Hz, H_5), 4.24 (q, 2H, J_1 = 21.4 Hz, H_4), 6.00 (d, 1H, J = 15.3 Hz, H_α), 6.87-6.90 (m, 2H, H_γ, H_δ), 7.30-7.49 (m, 6H, H_β, H_1, H_2, H_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 14.5, 60.5, 121.5, 126.4, 127.3 (2C), 128.9 (2C), 129.2, 136.2, 140.5, 144.7, 167.2 ppm. The ^{1}H and ^{13}C NMR spectra were agreed with reported literature[7].



(2*E*,4*E*)-5-phenylpenta-2,4-dienoic acid (PAD-3)

Compound **S5** (640.0 mg, 3.5 mmol) was dissolved in 30.0 mL EtOH containing 10 w.t.% of KOH and the reaction mixture was refluxed for 14 hr. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The concentrated residue was diluted with water and washed with DCM. The aqueous layer was separated and the pH value was adjusted to 1 by adding 1M $HCl_{(aq)}$. After the addition of 1 M $HCl_{(aq)}$, a white precipitate was formed and then it was isolated by filtration. The filter cake was air-dried to yield **PAD-3** (502.0 mg, 83%) as a white solid. Mp: 170˚C; ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 6.01 (d, 1H, J = 15.2 Hz, H_α), 6.86-6.99 (m, 2H, H_γ, H_δ), 7.30-7.40 (m, 3H, H_2, H_3), 7.47-7.60 (m, 3H, H_1, H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 120.4, 126.1, 127.5 (2C), 129.0 (2C), 129.5, 135.9, 141.8, 147.1, 172.5 ppm; LRMS (EI) m/z calcd. for $C_{11}H_{10}O_2$ $[M]^+$: 174.1; Found 174.1. The ^{1}H and

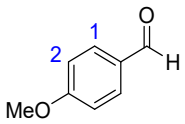
^{13}C NMR spectra were agreed with the reported literature[8].



Scheme S6. Synthesis of (ZE)PAD-4-7 and (EE)PAD-4-7.

General procedure A for the synthesis of S6 to S9

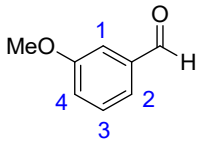
To a solution of hydroxybenzaldehyde (1.0 eq) and potassium carbonate (3.0 eq) in dry DMF (15–20 mL) was added methyl iodide (2.0 eq; 3.0 eq for compound **S9**) under an ice bath. The reaction mixture was stirred at room temperature for overnight. After completion of the reaction, it was diluted with EtOAc and the reaction mixture was extracted with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residues were purified by column chromatography to yield the desired products.



4-methoxybenzaldehyde (S6)

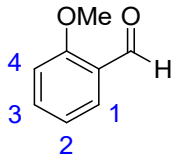
Compound **S6** (1.1 g, 98%) as a colorless oil was prepared from 4-hydroxybenzaldehyde (1.0 g, 8.2 mmol) according to the general procedure **A** described above. R_f = 0.47 (n-Hexane: EtOAc = 2:1v/v). ^{1}H NMR (300 MHz, $CDCl_3$, 296 K): δ = 3.89 (s, 3H, OCH_3), 6.98-7.02 (m, 2H, H_2), 7.81-7.86 (m, 2H, H_1), 9.88 (s, 1H, CHO)

ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 55.7, 114.4 (2C), 130.1, 132.1 (2C), 164.7, 190.9 ppm. The ^{1}H and ^{13}C NMR spectra were agreed with reported literature[9].



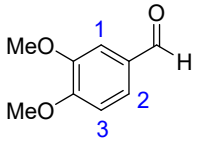
3-methoxybenzaldehyde (S7)

Compound **S7** (2.0 g, 90%) as a colorless oil was prepared from 3-hydroxybenzaldehyde (2.0 g, 16.4 mmol) according to the general procedure **A** described above. R_f = 0.55 (n-Hexane: EtOAc = 2:1 v/v). ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 3.86 (s, 3H, OCH_3), 7.16-7.20 (m, 1H, H_4),7.38-7.46 (m, 3H, H_1, H_2, H_3), 9.97 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ =55.6, 112.2, 121.7, 123.7, 130.2, 137.9, 160.3, 192.3 ppm. The ^{1}H and ^{13}C NMR spectra were agreed with reported literature[10].



2-methoxybenzaldehyde (S8)

Compound **S8** (2.1 g, 95%) as a colorless oil was prepared from 2-hydroxybenzaldehyde (2.0 g, 16.4 mmol) according to the general procedure **A** described above. R_f = 0.50 (n-Hexane: EtOAc = 2:1 v/v). ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 3.93 (s, 3H, OCH_3), 6.97-7.05 (m, 2H, H_2, H_4), 7.52-7.58 (m, 1H, H_3), 7.81-7.84 (dd,1H, J_1 = 7.6 Hz, J_2 = 1.7 Hz, H_1), 10.47 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 55.7, 111.7, 120.8, 124.9, 128.7, 136.1, 161.9, 189.9 ppm. The ^{1}H and ^{13}C NMR spectra were agreed with reported literature[11].

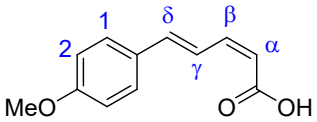


3,4-dimethoxybenzaldehyde (S9)

Compound **S9** (800.0 mg, 33%) as a white solid was prepared from 3,4-dihydroxybenzaldehyde (2.0 g, 14.5 mmol) according to the general procedure **A** described above. R_f = 0.27 (n-Hexane: EtOAc = 2:1 v/v). ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.97 (d, 2H, *J* = 8.2 Hz, H_3), 7.40-7.47 (m, 2H, H_1, H_2), 9.85 (s, 1H, CHO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 56.1, 56.3, 109.1, 110.5, 127.0, 130.3, 149.8, 154.6, 191.0 ppm. The ^{1}H and ^{13}C NMR spectra were agreed with reported literature[12].

General procedure B for the synthesis of (ZE)PAD-4 to (ZE)PAD-7

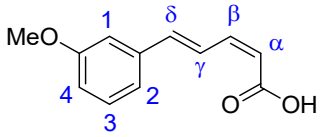
To a solution of methoxybenzaldehyde (1 eq, compound **S6** to **S9**) and ethyl crotonate (1.3 eq) in NMP (5–10 mL) was added sodium *tert*-butoxide (1.2 eq) under an ice bath. The reaction mixture was stirred at room temperature for overnight. After completion of the reaction, the reaction mixture was diluted with saturated $NaHCO_{3\ (aq)}$ and was extracted with DCM. The aqueous layer was separated and the pH value was adjusted to 1 with 1M $HCl_{\ (aq)}$. Thereafter, the solution mixture was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography to yield desired products.



(2Z,4E)-5-(4-methoxyphenyl)penta-2,4-dienoic acid ((ZE)PAD-4)

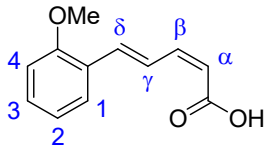
To a solution of 4-methoxybenzaldehyde (400.0 mg, 2.9 mmol) and *tert*-butoxide (396.0 mg, 3.5 mmol) in NMP (8 mL) was added ethyl crotonate (0.5 mL, 3.9 mmol), and the reaction mixture was stirred at room temperature for 18 h. The mixture was subsequently extracted with 1M $HCl_{\ (aq.)}$ and Et_2O, and the Et_2O layer was then washed with saturated $NaHCO_{3\ (aq.)}$. The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to afford **(ZE)PAD-4** (241.0 mg, 40%) as a pale-yellow solid. Mp:

126˚C; R_f = 0.30 (n-Hexane: EtOAc = 2:1v/v). ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 3.84 (s, 3H, OCH_3), 5.70 (d, 1H, J = 11.07 Hz, H_α), 6.82 (d, 1H, J = 10.86 Hz, H_γ), 6.87 (d, 1H, J = 5.67 Hz, H_β), 6.90 (d, 2H, J = 8.79 Hz, H_2), 7.50 (d, 2H, J = 8.76 Hz, H_1), 7.99 (ddd, 1H, J = 0.66 Hz, 11.37 Hz, 15.36 Hz, H_δ) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 55.5, 114.4, 115.2, 123.0, 129.1, 129.3, 142.4, 147.7, 160.7 ppm; IR (KBr, cm^{-1}): 2922, 2848, 1691, 1614, 1587, 1509, 1447, 1249, 1230, 1173; HRMS (ESI) m/z calcd. for $C_{12}H_{13}O_3$ ($[M+H]^+$): 205.0865; Found 205.0865.



(2*Z*,4*E*)-5-(3-methoxyphenyl)penta-2,4-dienoic acid ((ZE)PAD-5)

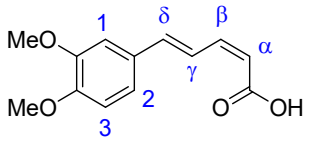
Compound **(ZE)PAD-5** (490.0 mg, 65%) as a yellow solid was prepared from compound **S12** (500.0 mg, 3.7 mmol) and ethyl crotonate (0.6 mL, 4.8 mmol) according to the general procedure **B** described above. Mp: 97˚C; R_f = 0.20 (n-Hexane: EtOAc = 2:1v/v). ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 3.84 (s, 3H, OCH_3), 5.77 (d, 1H, *J* = 11.3 Hz, H_α), 6.82-6.90 (m, 3H, H_β, H_δ, H_3), 7.04-7.06 (m, 1H, H_4), 7.13-7.16 (m, 1 H, H_2), 7.26-7.32 (m, 1H, H_1), 8.04-8.13 (ddd, 1H, *J* = 1.0 Hz, *J* = 11.6 Hz, *J* = 15.6 Hz, H_γ) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, 302 K): δ = 55.3, 112.8, 115.0, 116.7, 120.3, 125.1, 129.7, 137.5, 142.3, 146.9, 159.9, 171.7 ppm; IR (KBr, cm^{-1}): 2968, 2940, 2837, 2746, 2571, 1692, 1618, 1605, 1588, 1493, 1453, 1437, 1319, 1265, 1242, 1152, 1043, 1003, 962, 915, 824, 779, 770, 705, 678; LRMS (EI) m/z calcd. for $C_{12}H_{12}O_3$ $[M]^+$: 204.1; Found 204.1.



(2*Z*,4*E*)-5-(2-methoxyphenyl)penta-2,4-dienoic acid ((ZE)PAD-6)

Compound **(ZE)PAD-6** (260.0 mg, 51%) as a white solid was prepared from compound **S13** (340.0 mg, 2.5 mmol) and ethyl crotonate (0.4 mL, 3.3 mmol) according

to the general procedure **B** described above. Mp: 143˚C; R_f = 0.23 (n-Hexane: EtOAc = 2:1 v/v). ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 3.88 (s, 3H, OCH_3), 5.72 (d, 1H, J = 11.3 Hz, H_α), 6.85-7.00 (m, 3H, H_γ, H_δ, H_4), 7.25-7.33 (m, 2H, H_2, H_3), 7.63-7.66 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz, H_1), 8.07-8.16 (ddd, 1H, J_1 = 15.8 Hz, J_2 = 11.4 Hz, J_3 = 1.0 Hz, H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 55.7, 111.1, 115.9, 120.9 (2C), 125.3 (2C), 127.7, 130.6, 137.3, 148.1, 157.6 ppm; IR (KBr, cm^{-1}): 2946, 2741, 2588, 1693, 1666, 1604, 1590, 1570, 1484, 1470, 1446, 1434, 1325, 1294, 1244, 1225, 1175, 1160, 1114, 1025, 1003, 957, 906, 824, 778, 757, 695; LRMS (EI) m/z calcd. for $C_{12}H_{12}O_3$ $[M]^+$: 204.1; Found 204.1.

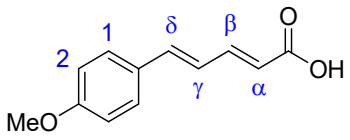


(2*Z*,4*E*)-5-(3,4-dimethoxyphenyl)penta-2,4-dienoic acid ((ZE)PAD-7)

Compound **(ZE)PAD-7** (257.0 mg, 61%) as a yellow solid was prepared from compound **S14** (300.0 mg, 1.8 mmol) and ethyl crotonate (0.3 mL, 2.3 mmol) according to the general procedure **B** described above. Mp: 151˚C; R_f = 0.08 (n-Hexane: EtOAc = 2:1 v/v).^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ =3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.70 (d, 1H, J = 11.2 Hz, H_α), 6.80-6.87 (m, 3H, H_γ, H_δ, H_3), 7.05-7.11 (m, 3H, H_1, H_2), 7.91-8.00 (ddd, 1H, J_1 = J_2 =15.9 Hz, J_3 = 1.1 Hz, H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 55.1 (2C), 109.8, 111.2, 115.4, 121.8, 123.2, 129.4, 142.8, 147.7, 149.3, 150.5, 172.2 ppm; IR (KBr, cm^{-1}) 2962, 2926, 2837, 2745, 2562, 1782, 1688, 1668, 1613, 1586, 1516, 1437, 1348, 1262, 1236, 1217, 998, 821, 798, 764, 739; LRMS (EI) m/z calcd. for $C_{13}H_{14}O_4$ $[M]^+$: 234.1; Found 234.1.

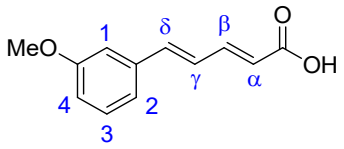
General procedure C for the synthesis of (EE)PAD-4 to (EE)PAD-7

To a solution of **(EZ)PAD-4** to **(EZ)PAD-7** in MeOH (10.0 mL) was added iodine (0.01 eq). The reaction mixture was placed in a UV photosynthesizer with a 254 nm light source and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography or recrystallized with hexane.



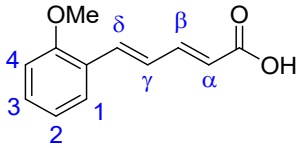
(2*E*,4*E*)-5-(4-methoxyphenyl)penta-2,4-dienoic acid ((EE)PAD-4)

Compound **(EE)PAD-4** (100.0 mg, 83%) as a white solid was prepared from compound **(ZE)PAD-4** (120.0 mg, 0.6 mmol) and iodine (1.5 mg) according to the general procedure **C** described above. R_f = 0.13 (n-Hexane: EtOAc = 2:1 v/v). Mp: 189˚C; ^{1}H NMR (300 MHz, d_6-DMSO, 297 K): δ = 3.77 (s, 3H, OCH_3), 5.94 (d, 1H, J = 15.1 Hz, H_α), 6.90-7.02 (m, 4H, H_γ, H_δ, H_2), 7.27-7.36 (ddd, 1H, J_1 = 15.2 Hz, J_2 = 8.3 Hz, J_3 = 1.9 Hz, H_β), 7.49-7.52 (d, 2H, J = 8.8 Hz, H_1) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 55.3, 114.4 (2C), 120.9, 124.4, 128.7, 128.8 (2C), 139.8, 144.8, 160.0, 167.8 ppm; LRMS (EI) m/z calcd. for $C_{12}H_{12}O_3$ $[M]^+$: 204.1; Found 204.1. The ^{1}H and ^{13}C NMR spectra were agreed with reported literature[13].



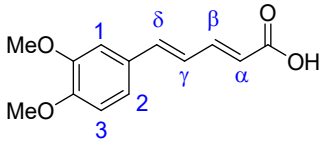
(2*E*,4*E*)-5-(3-methoxyphenyl)penta-2,4-dienoic acid ((EE)PAD-5)

Compound **(EE)PAD-5** (30.0 mg, 60%) as a white solid was prepared from compound **(ZE)PAD-5** (50.0 mg, 0.3 mmol) and iodine (0.6 mg) according to the general procedure **C** described above. R_f = 0.13 (n-Hexane: EtOAc = 2:1 v/v). Mp: 133˚C; ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 3.84 (s, 3H, OCH_3), 6.01 (d, 1H, J = 15.2 Hz, H_α), 6.83-6.96 (m, 3H, H_γ, H_δ, H_4), 6.99-7.00 (m, 1H, H_3), 7.06-7.09 (m, 1 H, H_2), 7.28-7.31 (d, 1H, J = 2.2 Hz, H_1), 7.50-7.58 (ddd, 1H, J_1 = 15.3 Hz, J_2 = 8.3 Hz, J_3 = 2.2 Hz, H_β) ppm; ^{13}C NMR (150 MHz, $CDCl_3$, 302 K): δ = 55.3, 112.4, 115.1, 120.1, 120.4, 126.3, 129.8, 137.2, 141.5, 146.8, 159.9, 172.2 ppm; LRMS (EI) m/z calcd. for $C_{12}H_{12}O_3$ $[M]^+$: 204.1; Found 204.1. The ^{1}H and ^{13}C NMR spectra were agreed with reported literature[13].



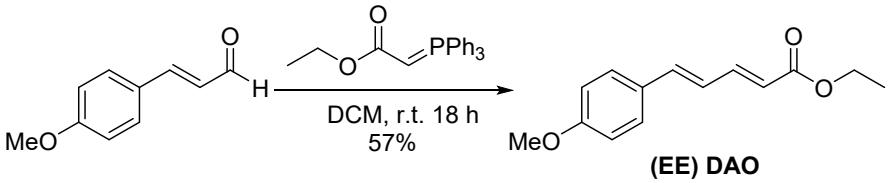
(2*E*,4*E*)-5-(2-methoxyphenyl)penta-2,4-dienoic acid ((EE)PAD-6)

Compound **(EE)PAD-6** (120.0 mg, 92%) as a white solid was prepared from compound **(ZE)PAD-6** (130.0 mg, 0.6 mmol) and iodine (1.6 mg) according to the general procedure **C** described above. Mp: 181˚C; R_f = 0.18 (n-Hexane: EtOAc = 2:1 v/v). ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 3.89 (s, 3H, OCH_3), 5.97 (d, 1H, *J* = 15.3 Hz, H_α), 6.89-7.01 (m, 3H, H_γ, H_δ, H_4), 7.27-7.31 (m, 2H, H_2, H_3), 7.49-7.61 (m, 2H, H_β, H_1) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 55.7, 111.2, 119.6, 120.9, 125.0, 126.7, 127.7, 130.6, 137.0, 148.2, 157.8, 172.2 ppm; IR (KBr, cm^{-1}): 3000, 2960, 2835, 2540, 1671, 1612, 1593, 1514, 1487, 1417, 1310, 1277, 1243, 1149, 1027, 1003, 748; LRMS (EI) m/z calcd. for $C_{12}H_{12}O_3$ $[M]^+$: 204.1; Found 204.1.

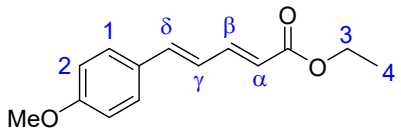


(2*E*,4*E*)-5-(3,4-dimethoxyphenyl)penta-2,4-dienoic acid ((EE)PAD-7)

Compound **(EE)PAD-7** (60.0 mg, 43%) as a yellow solid was prepared from compound **(ZE)PAD-7** (140.0 mg, 0.6 mmol) and iodine (1.7 mg) according to the general procedure **C** described above. Mp: 201˚C; R_f = 0.05 (n-Hexane: EtOAc = 2:1 v/v).^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.95 (d, 1H, *J* = 15.2 Hz, H_α), 6.74-6.92 (m, 3H, H_γ, H_δ, H_3), 7.01-7.06 (m, 2H, H_1, H_2), 7.49-7.57 (dd, J_1 = 15.2 Hz, J_2 = 10.6 Hz, H_β) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 56.1, 56.1, 109.3, 111.3, 119.1, 121.7, 124.2, 129.1, 141.7, 147.4, 149.4, 150.5, 171.9 ppm; IR (KBr, cm^{-1}): 2997, 2957, 2932, 2834, 2531, 1674, 1607, 1589, 1513, 1463, 1423, 1321, 1258, 1198, 1138, 1023, 1010, 872, 806, 760, 704; HRMS (EI) m/z calcd. for $C_{13}H_{14}O_4$ $[M]^+$: 234.1; Found 234.1.

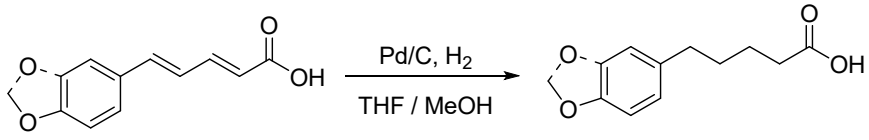


Scheme S6. Synthesis of (EE) DAO.



(2E,4E)-ethyl 5-(4-methoxyphenyl)penta-2,4-dienoate ((EE) DAO)

To a solution of (*E*)-3-(4-methoxyphenyl)acrylaldehyde (200 mg, 1.2 mmol) in dry DCM (12.5 mL) was added carbethoxymethylene)triphenyphosphorane (644 mg, 1.9 mmol). The reaction mixture was stirred at room temperature for 18 hr. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by column chromatography to give **(EE) DAO** (164 mg, 57%) as white solid. R_f = 0.37 (n-Hexane:EtOAc = 8:1 v/v). Mp: 65˚C; ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 1.31 (t, 3H, *J* = 7.08 Hz, H_4), 3.82 (s, 3H, OCH_3), 4.22 (q, 2H, *J* = 7.98 Hz, H_3), 5.93 (d, 1H, *J* = 15.21 Hz, H_α), 6.69-6.90 (m, 4H, H_γ, H_δ, H_2), 7.39-7.47 (m, 3H, H_β, H_1) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 14.5, 55.5, 60.4, 114.4, 120.2, 124.3, 128.8, 129.0, 140.2, 145.1, 160.5, 167.4 ppm; IR (KBr, cm^{-1}): 2923, 2848, 2334, 1704, 1623, 1600, 1311, 1260, 1232, 1135, 1026, 998; HRMS (ESI) m/z calcd. for $C_{14}H_{17}O_3$ ($[M+H]^+$): 233.1178; Found 233.1178.

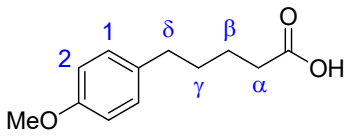


Scheme S7. Synthesis of PAD-8 and PAD-9

General procedure D for hydrogenation

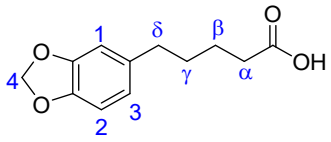
To a solution of diene compound (1 eq) in THF/MeOH (10 mL, v/v 1:1) was added 10 w.t.% Pd/C. The reaction mixture was stirred under an atmosphere of hydrogen for

overnight. Pd/C was removed by vacuum filtration and the filtrate was concentrated under reduced pressure. The crude residues were purified by column chromatography.



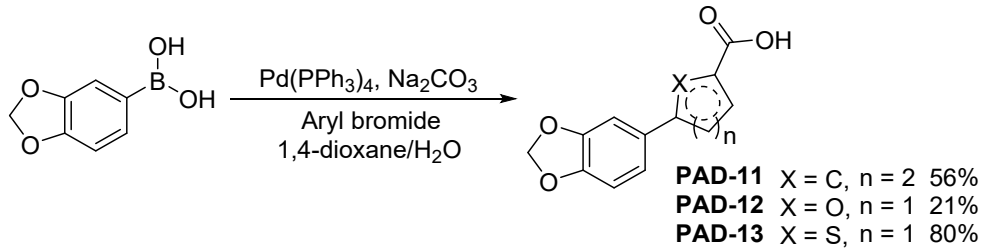
5-(4-methoxyphenyl)pentanoic acid (PAD-8)

Compound **PAD-8** (47.0 mg, 46%) as a white solid was prepared from compound **(EE)PAD-4** (100.0 mg, 0.5 mmol) according to the general procedure **D** described above. Mp: 113˚C; R_f = 0.14 (n-Hexane: EtOAc = 2:1 v/v). ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 1.64-1.67 (m, 4H, H_β, H_γ), 2.37 (t, 2H, *J* = 14.0 Hz, H_δ), 2.58 (t, 2H, *J* = 13.8 Hz, H_α), 3.79 (s, 3H, OCH_3), 6.81-6.84 (m, 2H, H_2), 7.07-7.10 (m, 2H, H_1) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 24.4, 31.1, 33.9, 34.7, 55.4, 113.9, 129.4, 134.2, 157.9, 179.5 ppm; LRMS (EI) m/z calcd. for $C_{12}H_{16}O_3$ $[M]^+$: 208.1; Found 208.1. The ^{1}H and ^{13}C NMR spectra were agreed with reported literature[14].



5-(benzo[*d*][1,3]dioxol-5-yl)pentanoic acid (PAD-9)

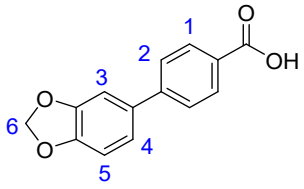
Compound **PAD-9** (130.0 mg, 81%) as a white solid was prepared from compound **PA** (157.0 mg, 0.7 mmol) according to the general procedure **D** described above. R_f = 0.26 (n-Hexane: EtOAc = 2:1 v/v). ^{1}H NMR (300 MHz, CD_3OD, 297 K): δ =1.59-1.62 (m, 4H, H_β, H_γ), 2.17 (t, 2H, *J* = 14.4 Hz, H_δ), 2.54 (t, 2H, *J* = 14.2 Hz, H_α), 5.86 (s, 2H, H_4), 6.61-6.69 (m, 3H, H_1, H_2, H_3) ppm; ^{13}C NMR (75 MHz, CD_3OD, 298 K): δ = 27.3, 33.1, 36.5, 39.1, 101.9, 108.8, 109.8, 122.2, 137.9, 146.9, 148.9, 182.9 ppm; LRMS (EI) m/z: $[M]^+$calcd. for $C_{12}H_{14}O_4$ 222.1; Found 222.1. The ^{1}H and ^{13}C NMR spectra were agreed with reported literature[15].



Scheme S8. Synthesis of PAD-11 to PAD-13

General procedure E for the synthesis of PAD-11 to PAD-13

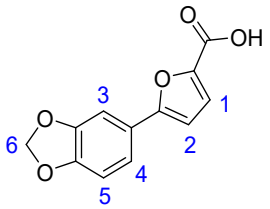
A solution mixture of 1,4-dioxane and water (1:1) was degassed by using argon. Boronic acid (1 eq, 1.2 mmol), aryl bromide (1 eq, 1.2 mmol), $Pd(PPh_3)_4$ (2 mol%) and sodium carbonate (7 eq) were dissolved in degassed solvent (12.0 mL) and then the reaction mixture was refluxed for overnight. After the completion of the reaction, it was cooled to room temperature, diluted with brine and washed with DCM. The aqueous layer was separated and the pH value was adjusted to 1 with 1M $HCl_{(aq)}$. The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure to yield the crude product, or the acidified aqueous layer was extracted with additional EtOAc (the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure). The crude product was purified by column chromatography or recrystallized with a water/EtOH solution mixture.



4-(benzo[d][1,3]dioxol-5-yl)benzoic acid (PAD-11)

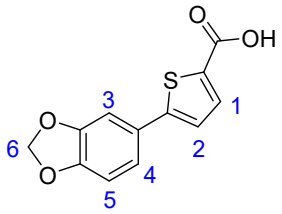
Compound **PAD-11** was obtained as a white solid (162.0 mg, 56%). Mp = 278°C; R_f = 0.20 (n-Hexane: EtOAc = 1:9 v/v). ^{1}H NMR (300 MHz, d_6-DMSO, 295 K): δ = 6.08 (s, 2H, H_6), 7.03 (d, 1H, J = 8.1 Hz, H_5), 7.22-7.25 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.8 Hz, H_4), 7.32 (d, 1H, J = 1.8 Hz, H_3), 7.72 (d, 2H, J = 8.4 Hz, H_2), 7.96 (d, 2H, J = 8.6 Hz, H_1) ppm; ^{13}C NMR (75 MHz, d_6-DMSO, 295 K): δ = 101.5, 107.4, 109.0, 121.1, 126.7, 129.4,

130.1, 133.4, 144.2, 147.7, 148.3, 167.5 ppm; LRMS (EI) m/z: $[M]^+$calcd. for $C_{14}H_{10}O_4$ 242.1; Found 242.1. The ^1H and ^{13}C NMR spectra were with reported literature[16].



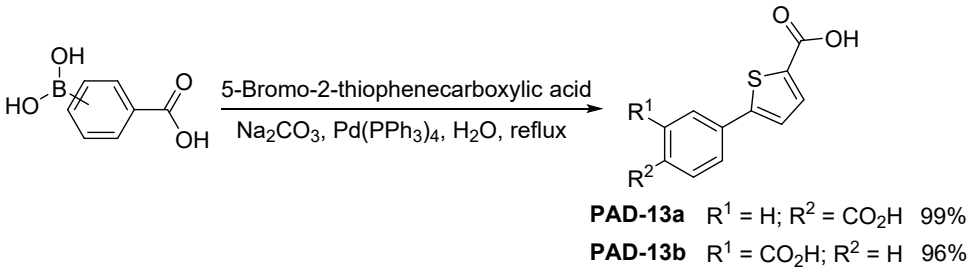
5-(benzo[d][1,3]dioxol-5-yl)furan-2-carboxylic acid (PAD-12)

Compound **PAD-12** was obtained as a beige solid (58.0 mg, 21%). Mp: 198–202°C; R_f = 0.20 (n-Hexane: EtOAc 1:9 v/v). ^1H NMR (300 MHz, d_6-DMSO, 295 K): δ = 6.09 (s, 2H, H_6), 7.01-7.04 (m, 2H, H_5, H_2), 7.27 (d, 1H, J = 3.6 Hz, H_1), 7.31-7.34 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.7 Hz, H_4), 7.36 (d, 1H, J = 1.7 Hz, H_3) ppm; ^{13}C NMR (75 MHz, d_6-DMSO, 298 K): δ = 101.5, 104.8, 106.9, 108.9, 118.7, 119.9, 123.5, 143.6, 148.0 (2C), 156.2, 159.3 ppm; IR (KBr, cm^{-1}): 3109, 3002, 2912, 2682, 1681, 1585, 1497, 1473, 1333, 1317, 1232, 1164, 1037, 1023, 934, 862, 810, 792, 756; LRMS (EI) m/z: $[M]^+$calcd. for $C_{12}H_8O_5$ 232.0; Found 232.0.



5-(benzo[d][1,3]dioxol-5-yl)thiophene-2-carboxylic acid (PAD-13)

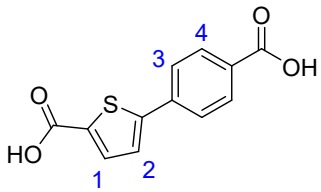
Compound **PAD-13** was obtained as a light brown solid (238 mg, 80%). Mp = 243°C; R_f = 0.20 (n-Hexane: EtOAc 1:9 v/v). ^1H NMR (300 MHz, d_6-DMSO, 295 K): δ = 6.08 (s, 2H, H_6), 6.99 (d, 1H, J = 8.1 Hz, H_5), 7.21-7.24 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.9 Hz, H_4), 7.35 (d, 1H, J = 1.8 Hz, H_3), 7.46 (d, 1H, J = 4.0 Hz, H_2), 7.66 (d, 1H, J = 3.9 Hz, H_1) ppm; ^{13}C NMR (75 MHz, d_6-DMSO, 296 K): δ = 101.6, 106.3, 108.9, 120.1, 123.9, 127.1, 132.3, 134.3, 147.9, 148.2, 149.8, 162.8 ppm; LRMS (EI) m/z: $[M]^+$calcd. for $C_{12}H_8O_4S$ 248.0; Found 248.0. The ^1H and ^{13}C NMR spectra were agreed with reported literature[16].



Scheme S9. Synthesis of PAD-13a and PAD-13b

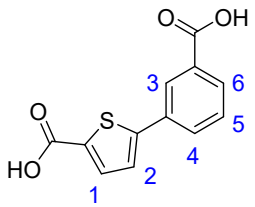
General procedure F for synthesis of PAD-13a and PAD-13b

5-Bromothiophene-2-carboxylic acid (1.0 equiv.), carboxyphenylboronic acid (1.1 equiv.), Na_2CO_3 (4.5 equiv.) and $Pd(PPh_3)_4$ (3 mol%) were mixed in degassed H_2O. The final concentration of the reaction is 0.08 M. The reaction mixture was heated to reflux for 6 h. After that, the mixture was cooled down to room temperature. The reaction mixture was washed with DCM until the color of aqueous layer became colorless. Thereafter, the pH value of aqueous layer was adjusted with concentrated HCl to 1 under an ice bath to form precipitate. The precipitate was filtered under reduced pressure to give desired PAD-13 derivatives.



5-(4-carboxyphenyl)thiophene-2-carboxylic acid (PAD-13a)

Compound **PAD-13a** was obtained as a white solid (238 mg, 99 %). Mp > 300 ^{o}C. ^{1}H NMR (300 MHz, d_6-DMSO, 308 K): δ = 7.66 (d, 1H, J = 3.90 Hz, H_1), 7.73 (d, 1H, J = 3.93 Hz, H_2), 7.84 (d, 2H, J = 8.46 Hz, H_3), 7.98 (d, 2H, J = 6.27 Hz, H_4) ppm; ^{13}C NMR (75 MHz, d_6-DMSO, 308 K): δ = 126.3, 126.5, 127.6, 130.5, 130.7, 131.0, 134.9, 135.0, 137.1, 148.7, 163.2, 167.3 ppm; IR (KBr, cm^{-1}): 3000 (br), 1683, 1600, 1510, 1289, 1113, 928; HRMS (ESI) m/z calcd. for $C_{12}H_8O_4S$ ($[M+H]^+$): 249.0222; Found: 249.0221. The ^{1}H and ^{13}C NMR spectra were agreed with reported literature[17].



5-(3-carboxyphenyl)thiophene-2-carboxylic acid (PAD-13b)

Compound **PAD-13b** was further purified by washing with methanol and was afforded as a white solid (229 mg, 96 %). Mp = 296 ^{o}C. ^{1}H NMR (300 MHz, d_6-DMSO, 312 K): δ = 7.59 (t, 1H, J = 7.80 Hz, H_5), 7.64 (d, 1H, J = 3.93 Hz, H_1), 7.73 (d, 1H, J = 3.93 Hz, H_2), 7.93 (d, 1H, J = 7.83 Hz, H_4), 7.98 (d, 1H, J = 7.83 Hz, H_6), 8.18 (s, 1H, H_3) ppm; ^{13}C NMR (75 MHz, d_6-DMSO, 313 K): δ = 125.6, 126.4, 129.7, 130.0, 130.3, 132.0, 133.3, 134.0, 134.7, 148.7, 162.9, 167.0 ppm; IR (KBr, cm^{-1}): 3000 (br), 1687, 1428, 1304, 1122, 931; HRMS (ESI) m/z calcd. for $C_{12}H_8O_4S$ ([M-H]$^-$): 247.0065; Found: 247.0066.

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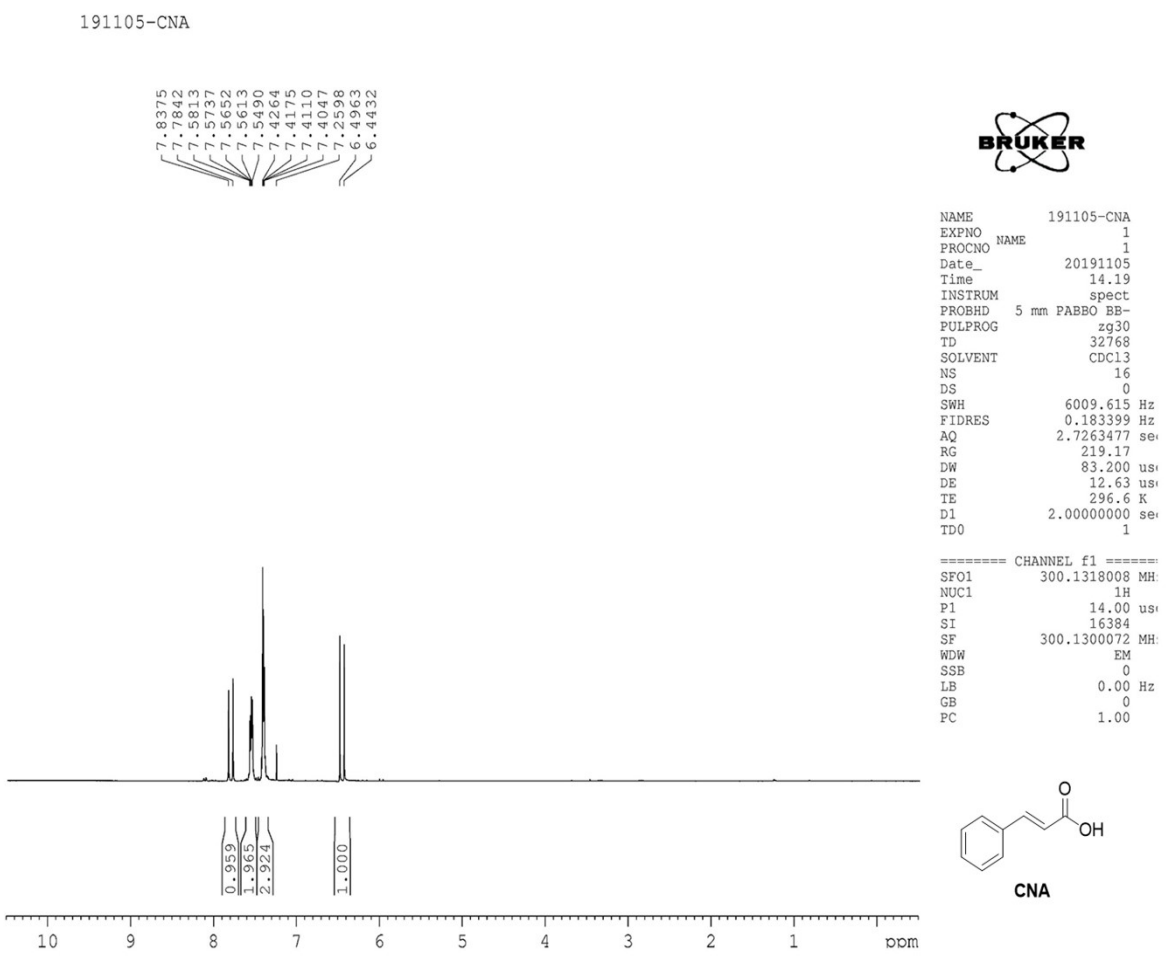
^{1}H and ^{13}C NMR Spectra

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TD                32768
SOLVENT           CDCl3
NS                   16
DS                    0
SWH            6009.615 Hz
FIDRES         0.183399 Hz
AQ             2.7263477 se
RG                219.17
DW                83.200 us
DE                12.63 us
TE                296.6 K
D1             2.00000000 se
TD0                   1

======== CHANNEL f1 =======
SFO1         300.1318008 MH
NUC1               1H
P1                14.00 us
SI                16384
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WDW                EM
SSB                 0
LB                0.00 Hz
GB                  0
PC                1.00
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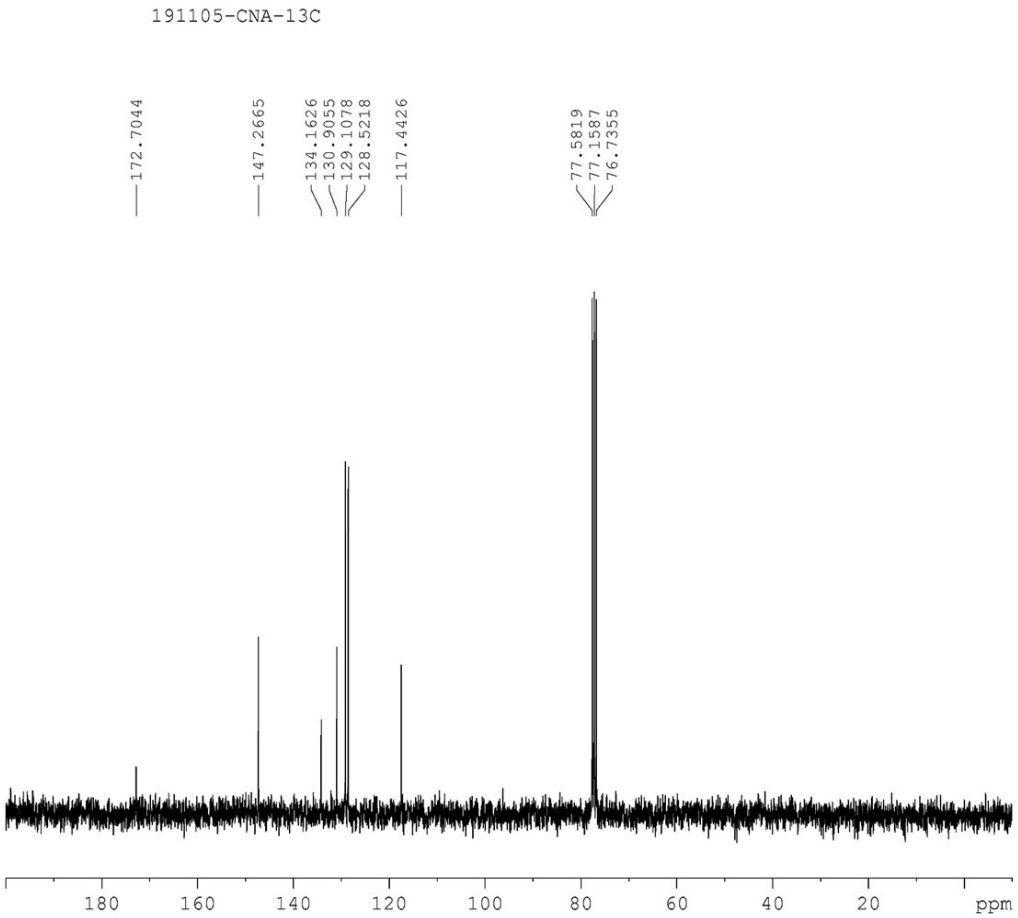
CNA

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PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                   33
DS                    0
SWH           18028.846 Hz
FIDRES         0.550197 Hz
AQ             0.9088159 sec
RG                219.17
DW               27.733 usec
DE                6.50 usec
TE               296.6 K
D1             2.00000000 sec
TD0                   1

======== CHANNEL f1 =======
SFO1          75.4756726 MHz
NUC1               13C
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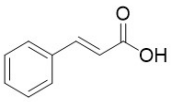
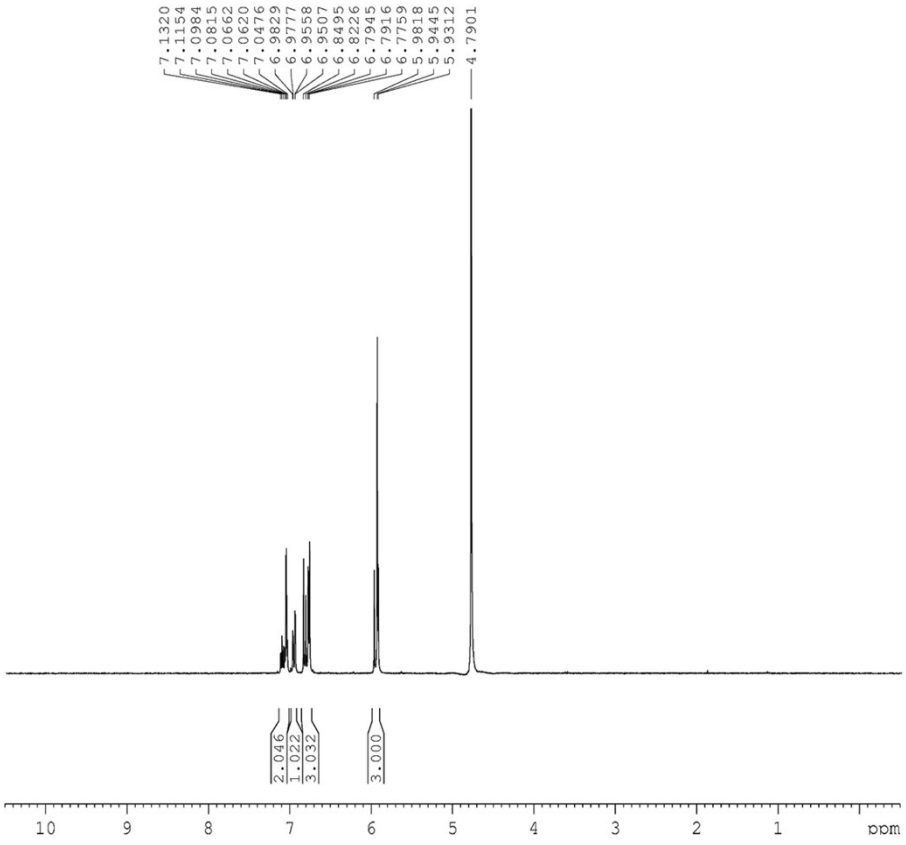


CNA

190104_314107-brown

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PROCNO            1
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Time             12.51
INSTRUM          spect
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PULPROG           zg30
TD               32768
SOLVENT            D2O
NS                  16
DS                   0
SWH           6009.615 Hz
FIDRES        0.183399 Hz
AQ            2.7263477 se
RG              219.17
DW              83.200 us
DE              12.53 us
TE              294.9 K
D1           2.00000000 se
TD0                  1

======== CHANNEL f1 ======
SFO1        300.1318008 MH
NUC1              1H
P1              14.50 us
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WDW               EM
SSB                  0
LB             0.00 Hz
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PC                1.00
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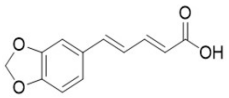

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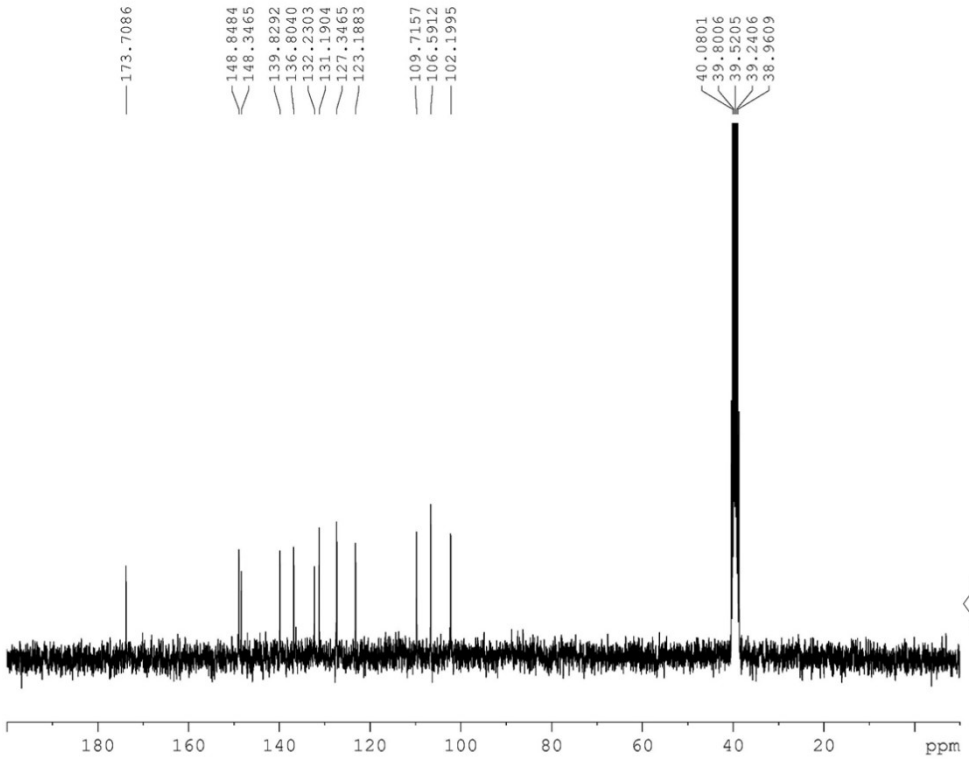


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PROCNO         1
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Time          17.42
INSTRUM       spect
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PULPROG     zgpg30
TD          32768
SOLVENT      DMSO
NS             384
DS               0
SWH      18028.846 Hz
FIDRES    0.550197 Hz
AQ        0.9088159 sec
RG           219.17
DW          27.733 usec
DE           6.50 usec
TE           297.6 K
D1        2.00000000 sec
D11       0.03000000 sec
TD0              1

======== CHANNEL f1 ======
SFO1      75.4756726 MHz
NUC1            13C
P1          10.00 usec
SI            32768
SF        75.4676937 MHz
WDW             EM
SSB              0
LB            2.00 Hz
GB               0
PC            1.00
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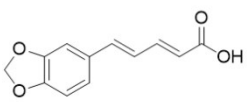
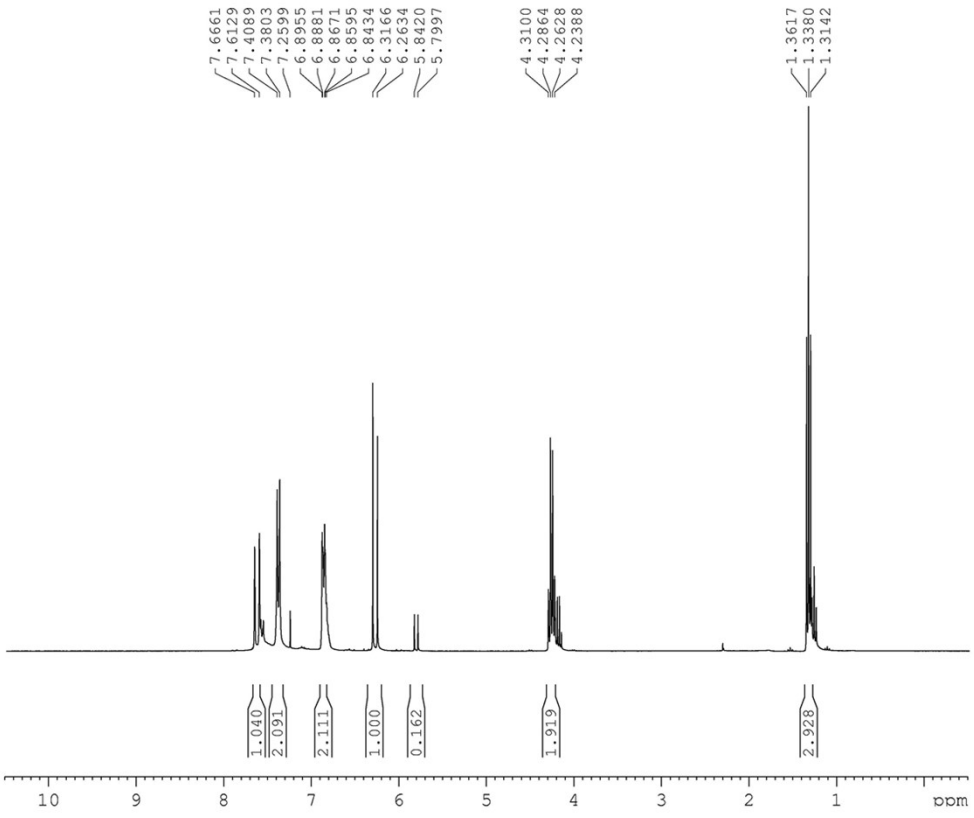
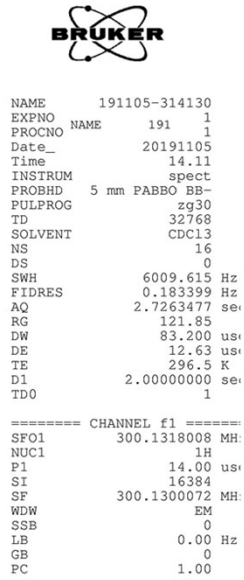
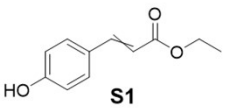


PA

191105-314130







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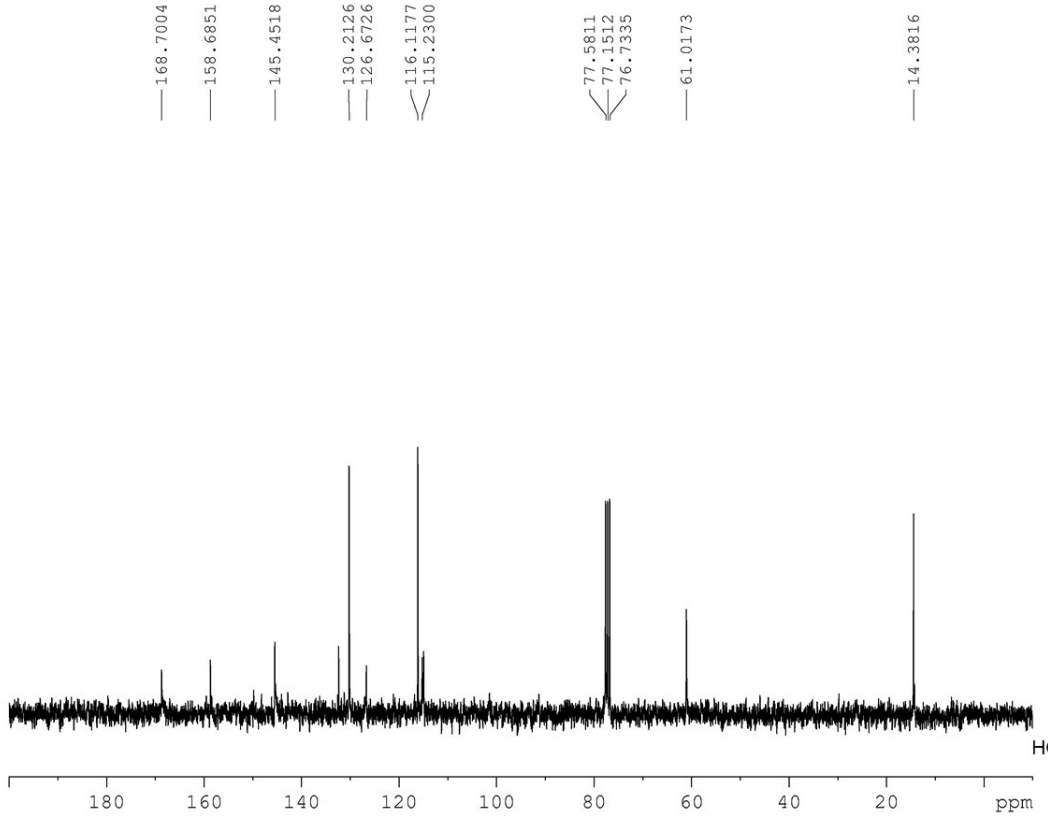

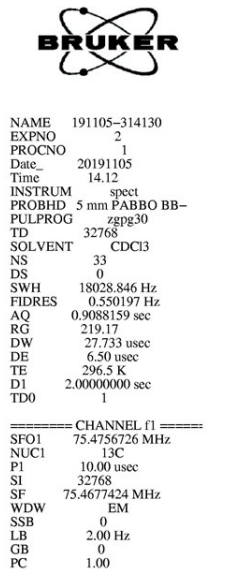

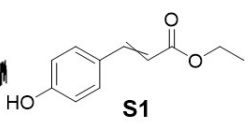

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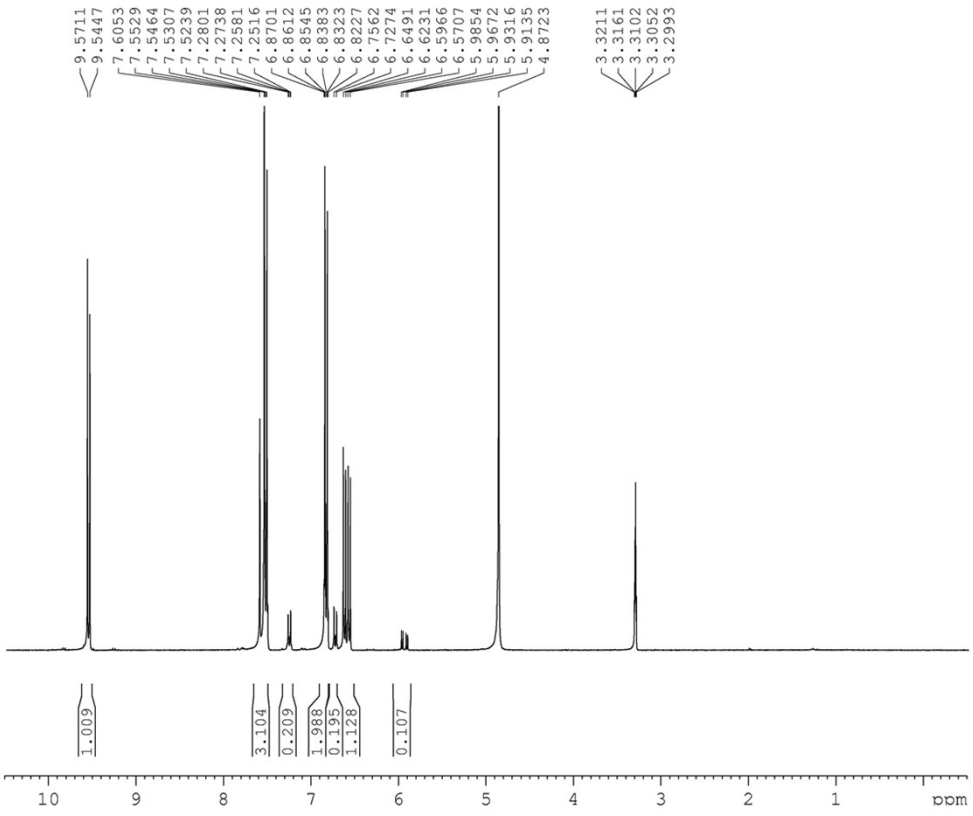

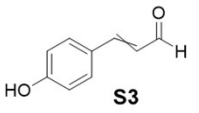

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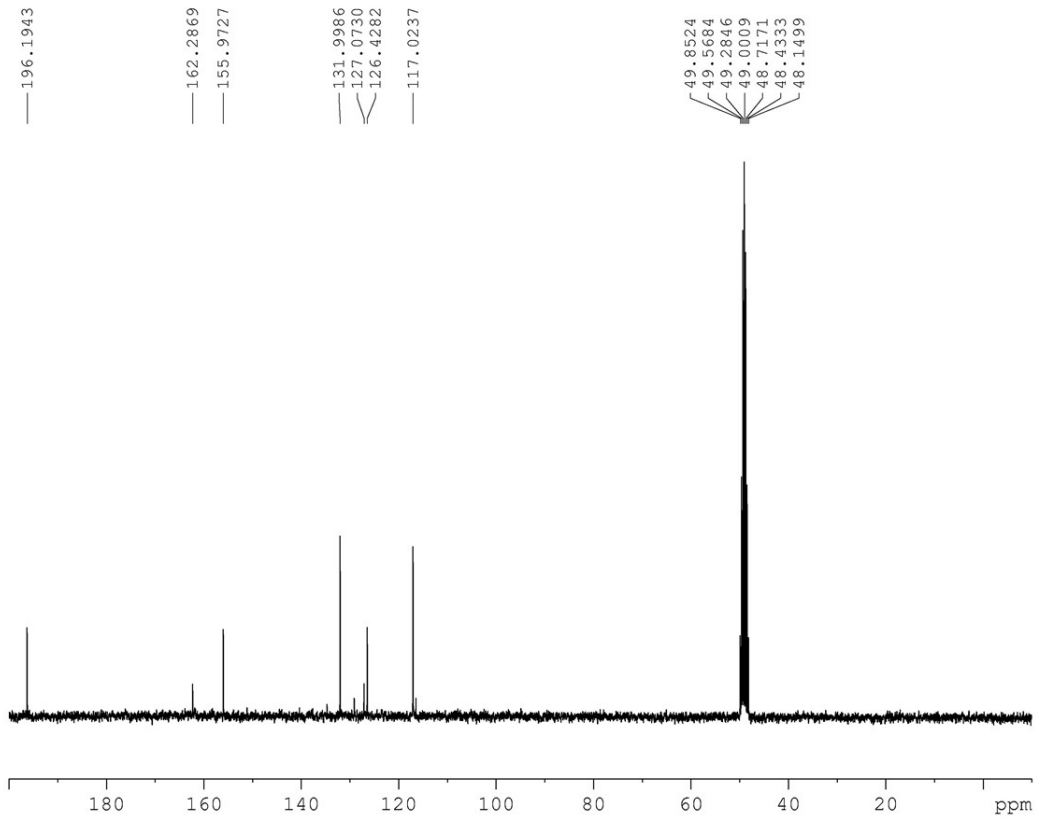
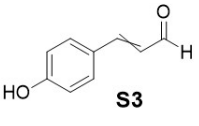
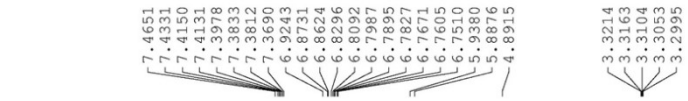
191105-314134-13C

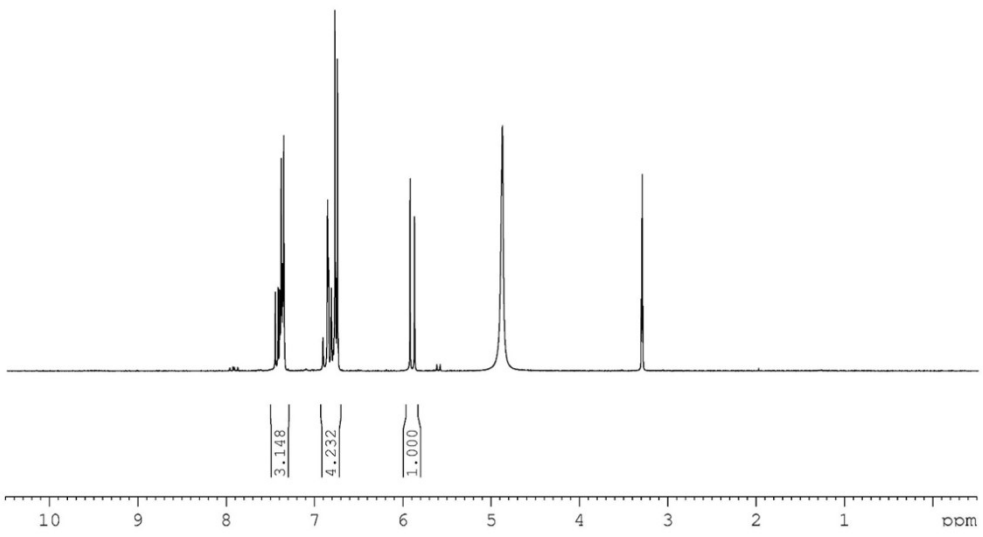




S3

191105-AA





BRUKER

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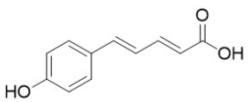
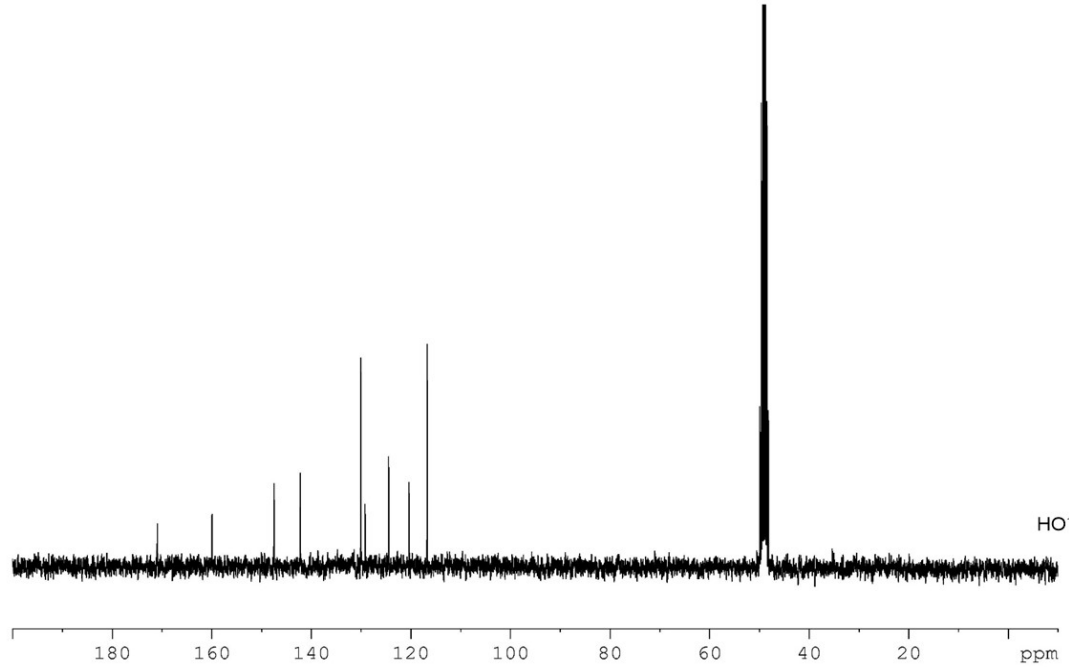
PULPROG	zg30
TD	32768
SOLVENT	MeOD
NS	16
DS	0
SWH	6009.615 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 se
RG	219.17
DW	83.200 us
DE	12.63 us
TE	296.9 K
D1	2.00000000 se
TD0	1
======== CHANNEL f1 =======	
SFO1	300.1318008 MH
NUC1	1H
P1	14.00 us
SI	16384
SF	300.1300053 MH
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00



AA

191105-AA-13C



BRUKER

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PULPROG	zgpg30
TD	32768
SOLVENT	MeOD
NS	129
DS	0
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	219.17
DW	27.733 usec
DE	6.50 usec
TE	296.8 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ======	
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NUC1	13C
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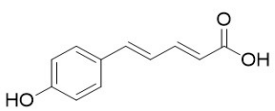
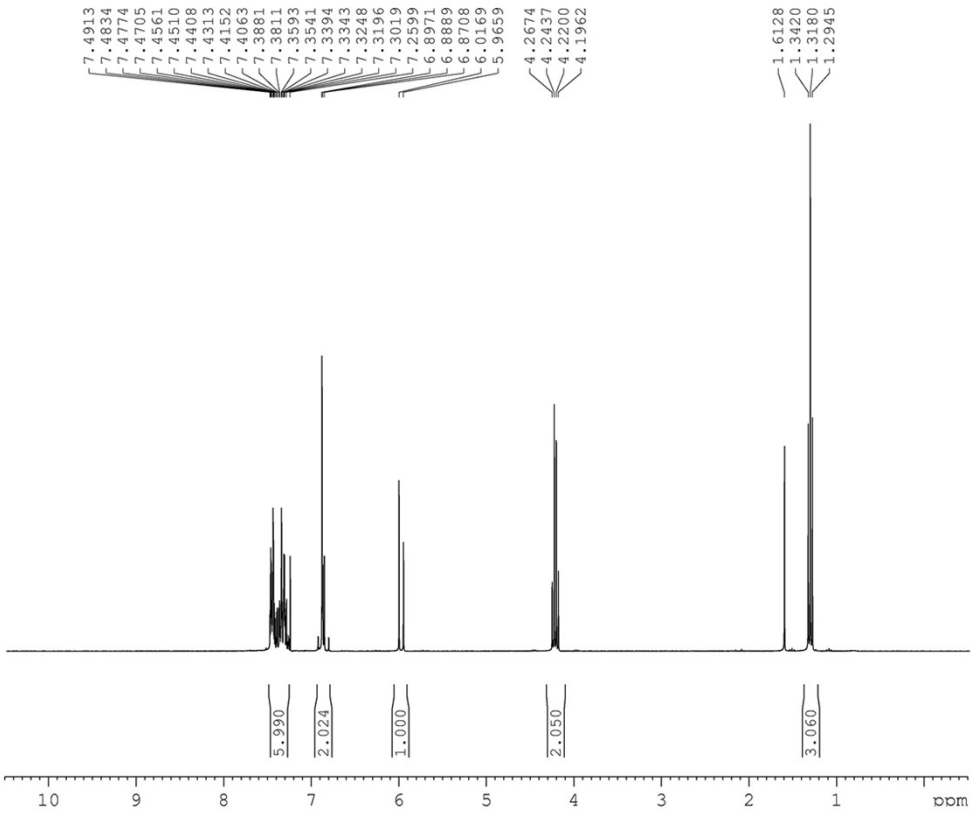
PC	1.00



AA

191109-318324

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TD                    32768
SOLVENT               CDCl3
NS                       16
DS                        0
SWH                6009.615 Hz
FIDRES             0.183399 Hz
AQ                2.7263477 se
RG                   219.17
DW                   83.200 us
DE                    12.63 us
TE                    296.4 K
D1                2.00000000 se
TD0                       1

======== CHANNEL f1 ======
SFO1             300.1318008 MH
NUC1                      1H
P1                     14.00 us
SI                     16384
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SSB                        0
LB                      0.00 Hz
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PC                      1.00
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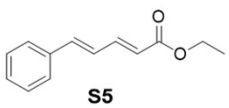
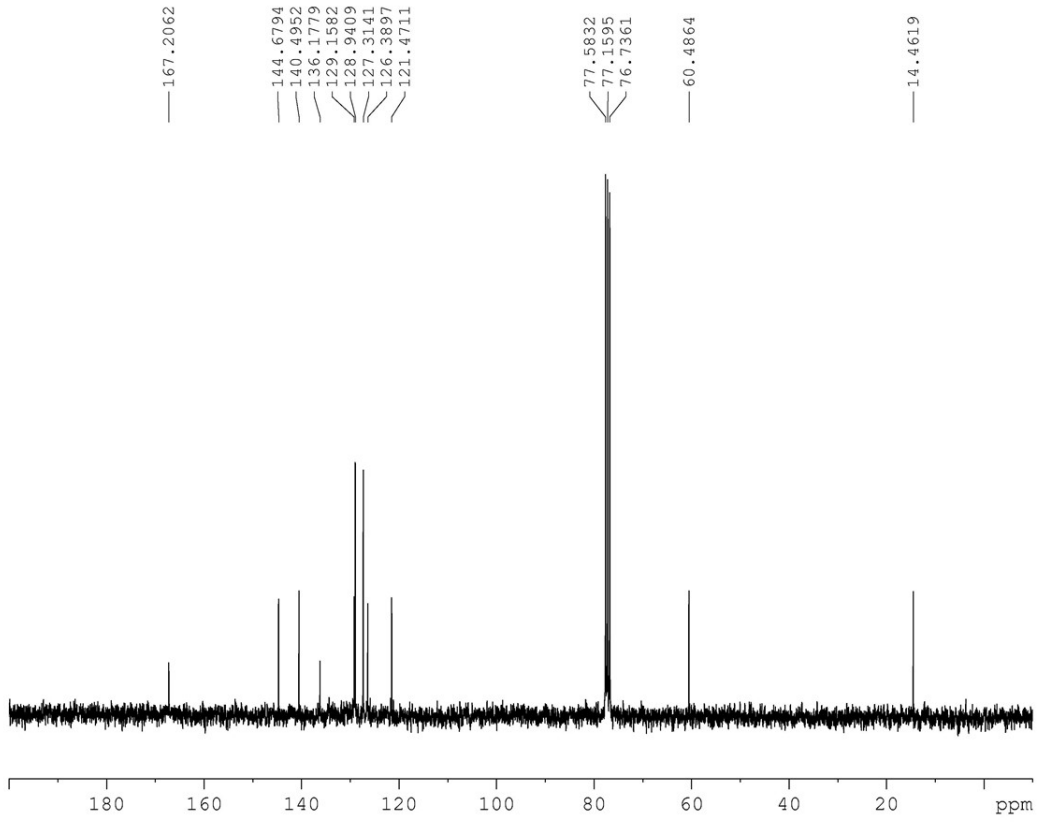


S5

191109-318324-13C

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TD                32768
SOLVENT           CDCl3
NS                  128
DS                    0
SWH           18028.846 Hz
FIDRES         0.550197 Hz
AQ             0.9088159 sec
RG                219.17
DW                27.733 usec
DE                 6.50 usec
TE                296.8 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                   1

======== CHANNEL f1 ======
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NUC1                  13C
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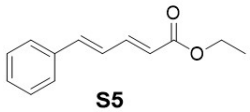
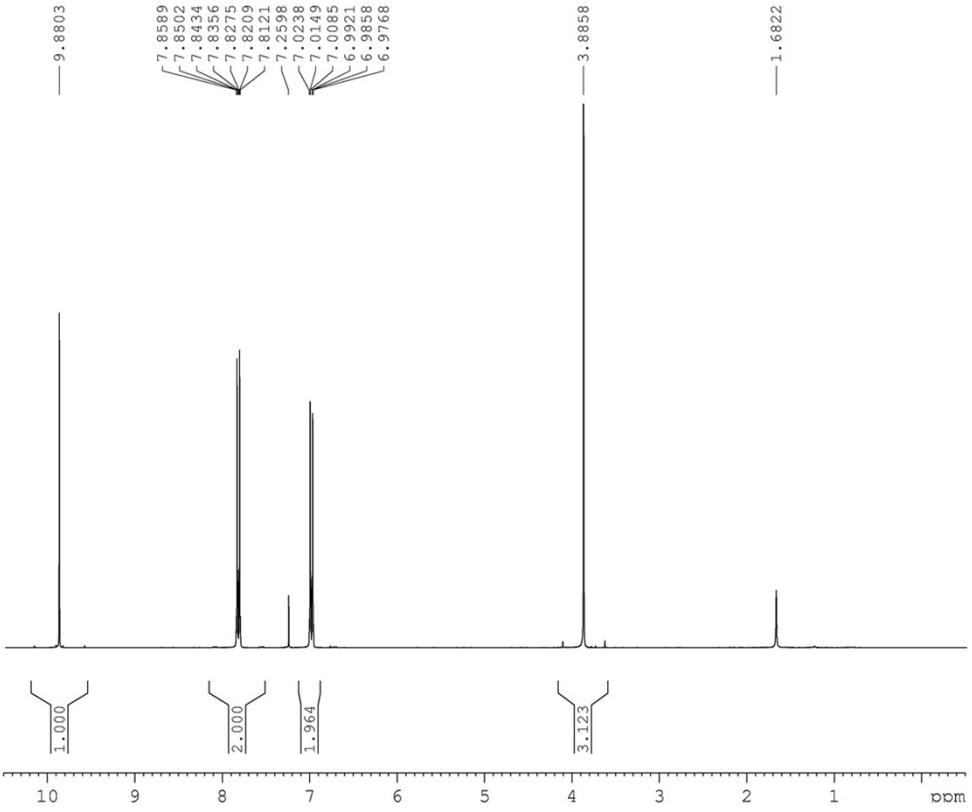


S5

191104-CNA-3-13C

191113-314191



BRUKER

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PROCNO	1
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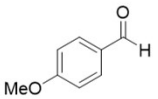
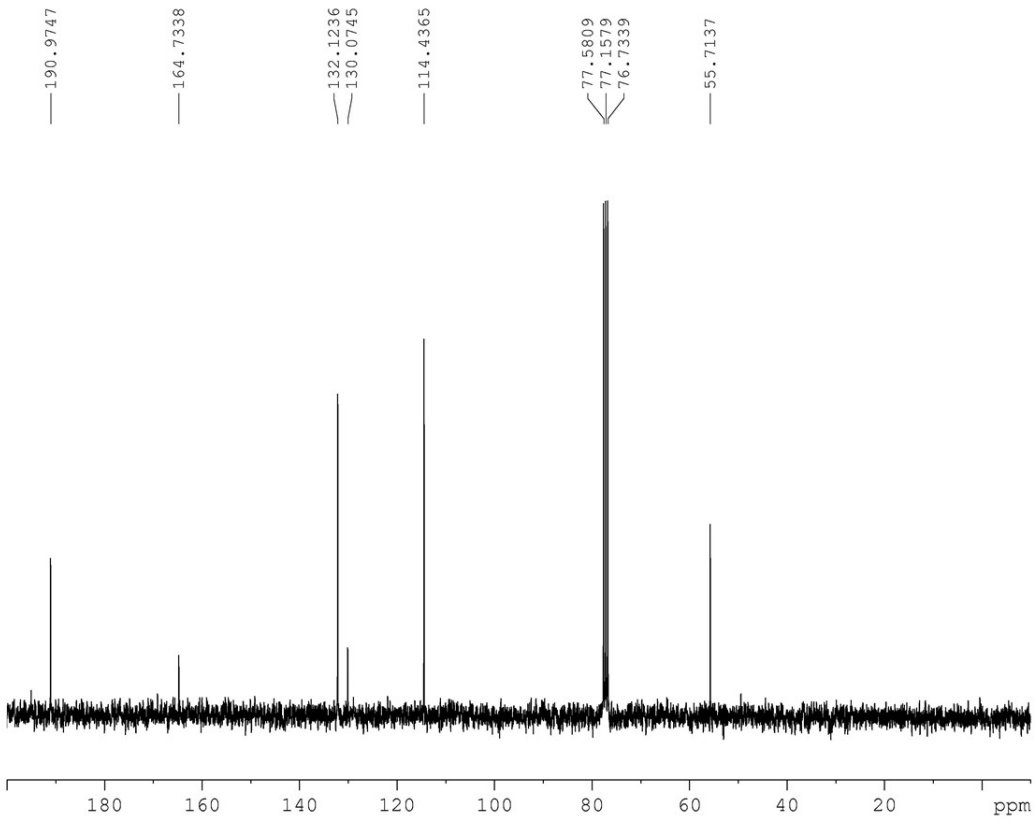
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	6009.615 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 se
RG	219.17
DW	83.200 us
DE	12.63 us
TE	295.8 K
D1	2.00000000 se
TD0	1
======== CHANNEL f1 ======	
SFO1	300.1318008 MH
NUC1	1H
P1	14.00 us
SI	16384
SF	300.1300072 MH
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00



S6

191113-314191-13C



BRUKER

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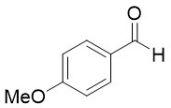
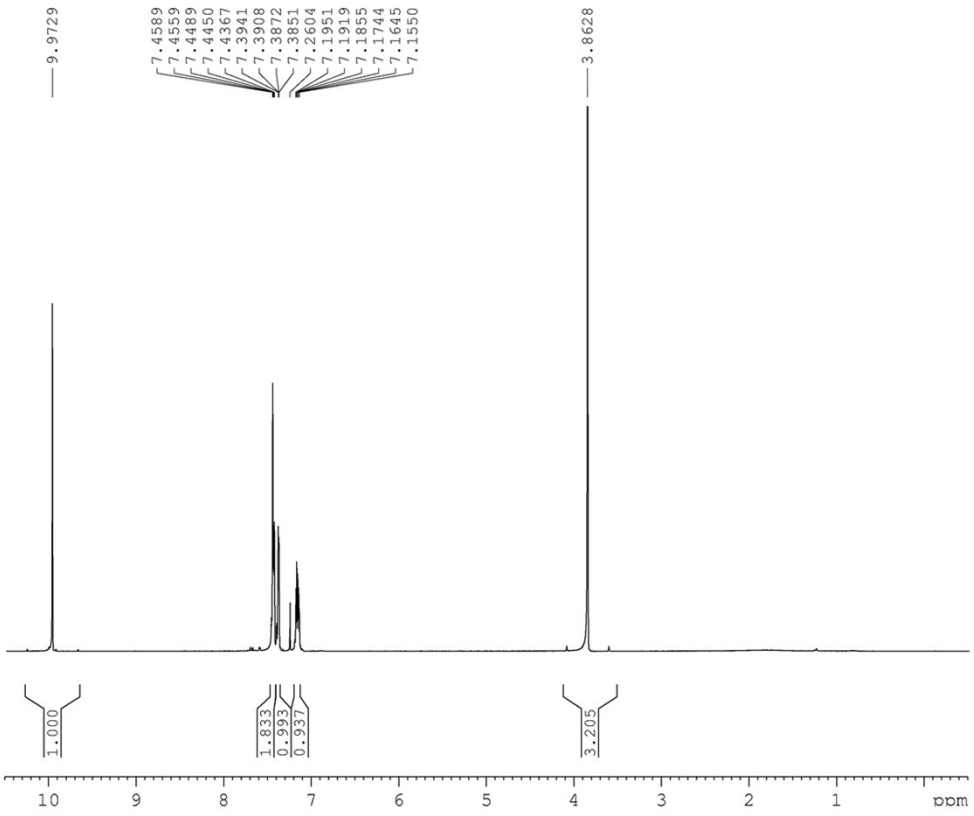
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	64
DS	0
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	219.17
DW	27.733 usec
DE	6.50 usec
TE	296.1 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ======	
SFO1	75.4756726 MHz
NUC1	13C
P1	10.00 usec
SI	32768
SF	75.4677403 MHz
WDW	EM
SSB	0
LB	2.00 Hz
GB	0
PC	1.00



S6

191107-314194

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PROCNO                1
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Time                15.34
INSTRUM             spect
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PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                     16
DS                      0
SWH              6009.615 Hz
FIDRES           0.183399 Hz
AQ               2.7263477 se
RG                 219.17
DW                 83.200 us
DE                  12.63 us
TE                  296.7 K
D1              2.00000000 se
TD0                     1

======== CHANNEL f1 ======
SFO1          300.1318008 MH
NUC1                   1H
P1                  14.00 us
SI                  16384
SF            300.1300067 MH
WDW                    EM
SSB                     0
LB                   0.00 Hz
GB                      0
PC                   1.00
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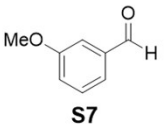
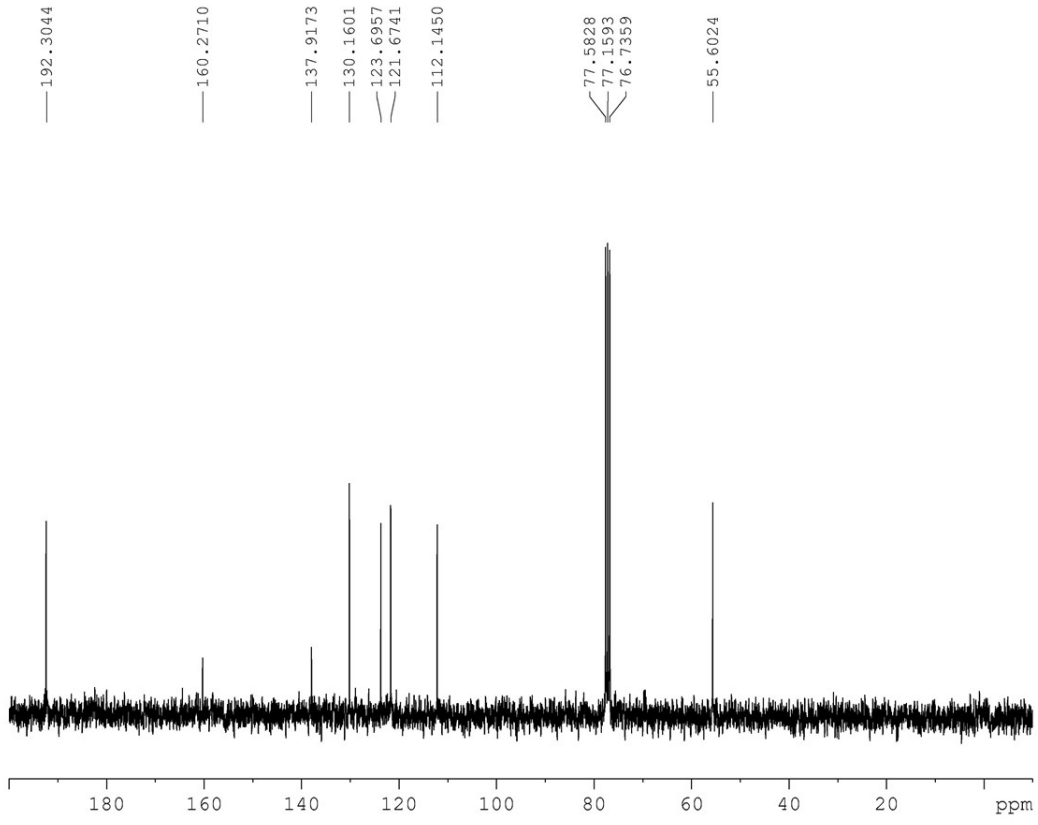
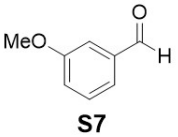


S7

191107-314194-13C

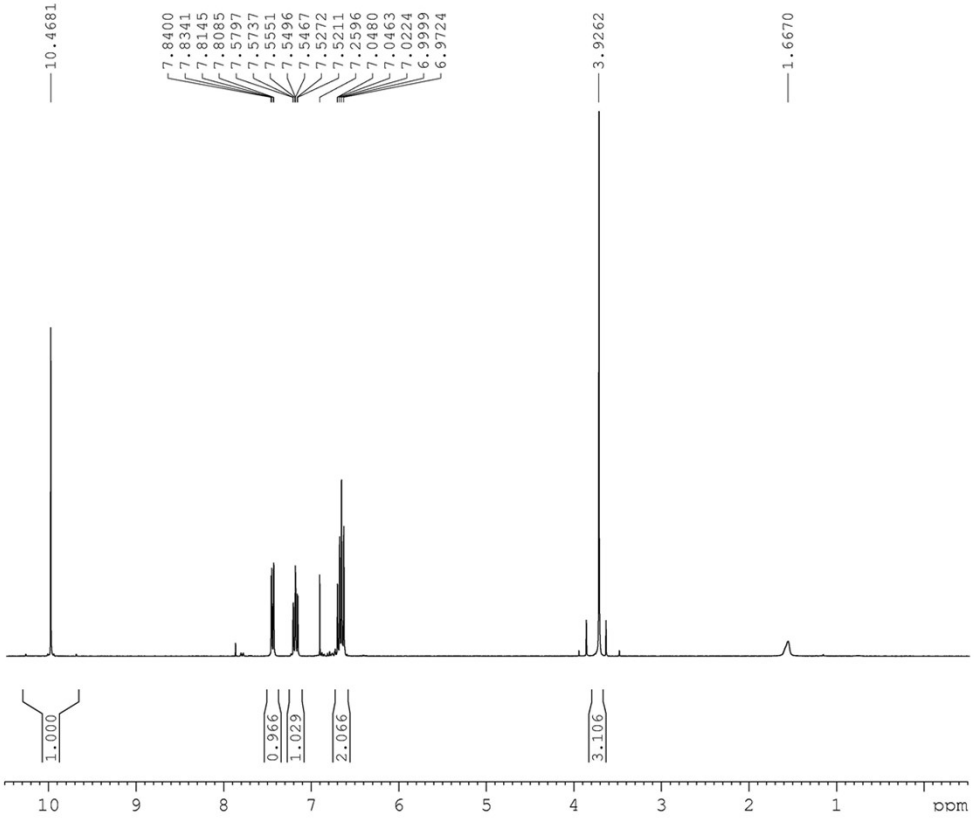



```
NAME      191107-314194
EXPNO                2
PROCNO               1
Date_         20191107
Time             15.36
INSTRUM          spect
PROBHD  5 mm PABBO BB-
PULPROG        zgpg30
TD              32768
SOLVENT         CDCl3
NS                 33
DS                  0
SWH         18028.846 Hz
FIDRES       0.550197 Hz
AQ          0.9088159 sec
RG              219.17
DW           27.733 usec
DE            6.50 usec
TE            296.7 K
D1         2.00000000 sec
TD0                 1

======== CHANNEL f1 ======
SFO1       75.4756726 MHz
NUC1               13C
P1           10.00 usec
SI              32768
SF         75.4677403 MHz
WDW                EM
SSB                 0
LB               2.00 Hz
GB                  0
PC               1.00
```

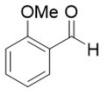


S7

191107-314195

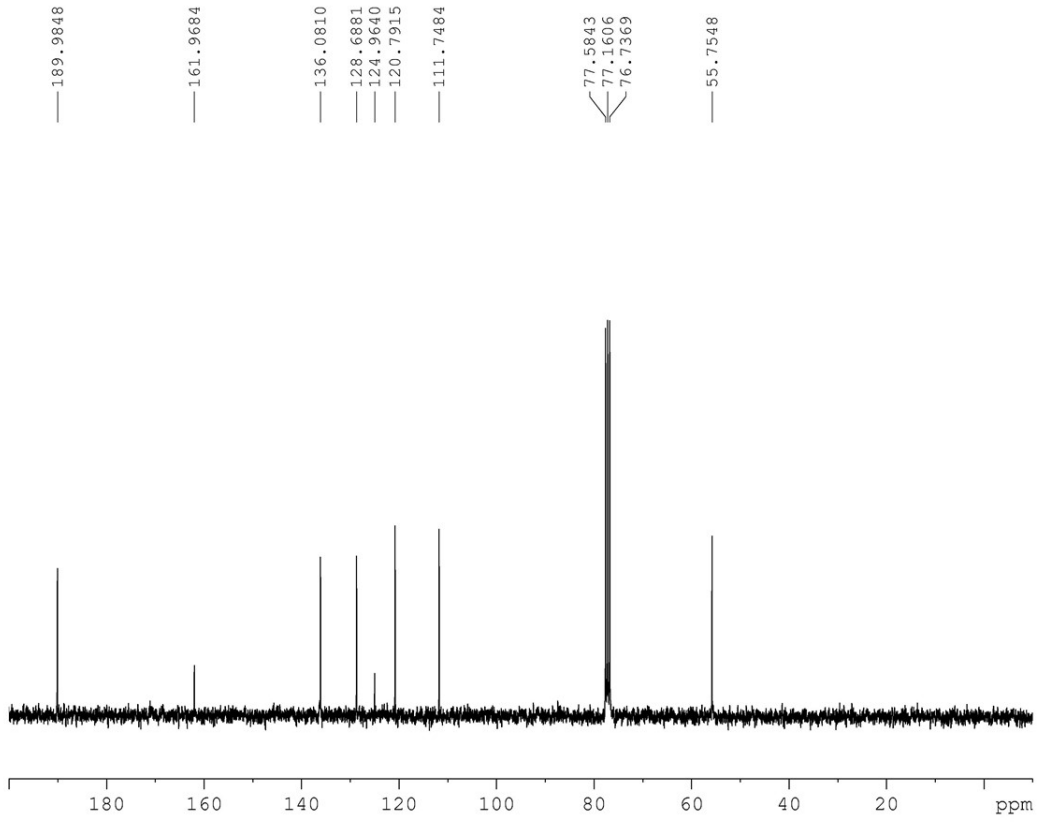



```
NAME        191107-314195
EXPNO  NAME      191    1
PROCNO                   1
Date_               20191107
Time                   15.42
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                       16
DS                        0
SWH                6009.615 Hz
FIDRES             0.183399 Hz
AQ                2.7263477 se
RG                   219.17
DW                   83.200 us
DE                    12.63 us
TE                    296.7 K
D1                2.00000000 se
TD0                       1

======== CHANNEL f1 ======
SFO1            300.1318008 MH
NUC1                     1H
P1                    14.00 us
SI                    16384
SF              300.1300072 MH
WDW                      EM
SSB                       0
LB                     0.00 Hz
GB                        0
PC                     1.00
```

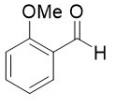


S8

191107-314195-13C

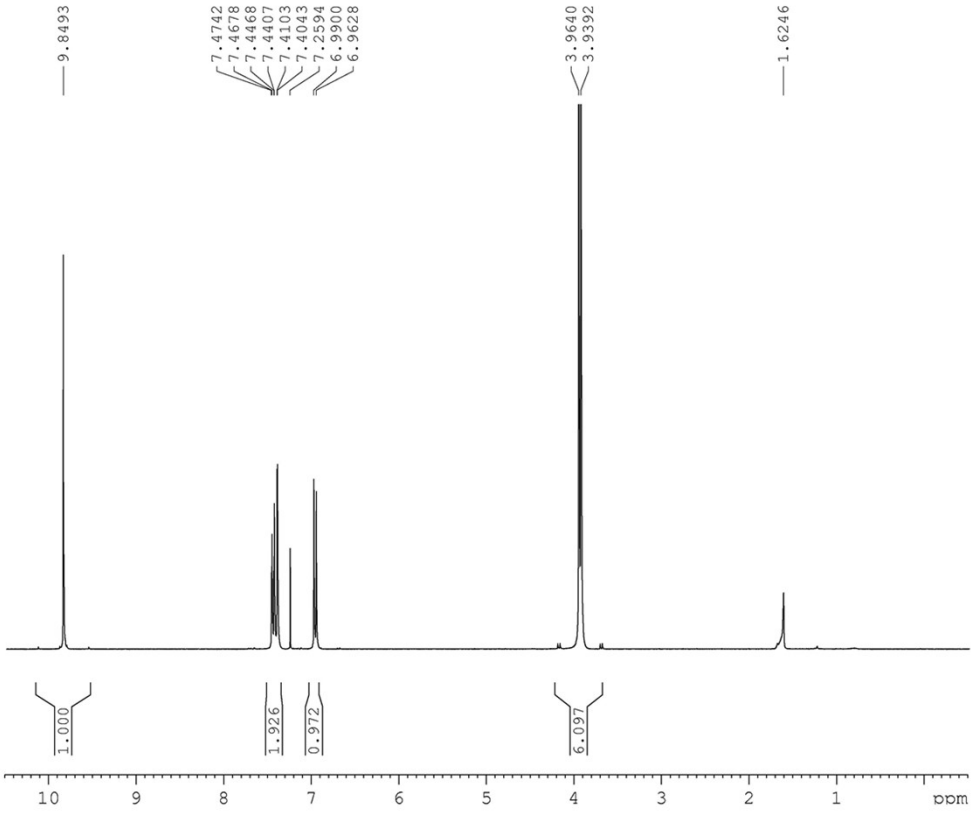



```
NAME      191107-314195
EXPNO                 3
PROCNO                1
Date_          20191107
Time              20.30
INSTRUM           spect
PROBHD  5 mm PABBO BB-
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  128
DS                    0
SWH           18028.846 Hz
FIDRES         0.550197 Hz
AQ             0.9088159 sec
RG                219.17
DW                27.733 usec
DE                 6.50 usec
TE                296.7 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                   1

======== CHANNEL f1 ======
SFO1          75.4756726 MHz
NUC1                  13C
P1                10.00 usec
SI                32768
SF            75.4677400 MHz
WDW                   EM
SSB                    0
LB                  2.00 Hz
GB                     0
PC                  1.00
```

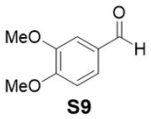


S8

191104-314192

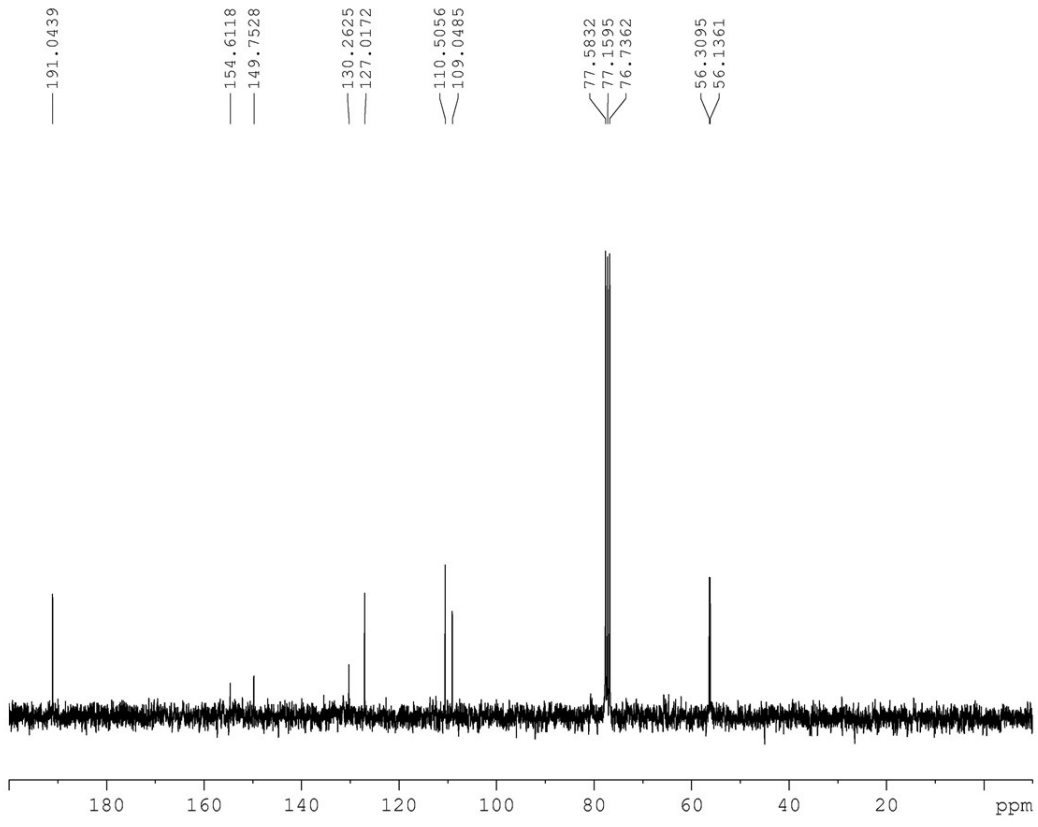


```
NAME        191104-314192
EXPNO  NAME      191     1
PROCNO               1
Date_         20191104
Time             16.09
INSTRUM          spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               32768
SOLVENT          CDCl3
NS                  16
DS                   0
SWH           6009.615 Hz
FIDRES        0.183399 Hz
AQ            2.7263477 se
RG              219.17
DW              83.200 us
DE              12.63 us
TE              296.8 K
D1           2.00000000 se
TD0                  1

======== CHANNEL f1 ======
SFO1       300.1318008 MH
NUC1              1H
P1              14.00 us
SI              16384
SF         300.1300072 MH
WDW               EM
SSB                  0
LB            0.00 Hz
GB                   0
PC            1.00
```

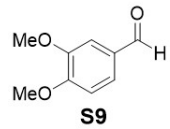


S9

191104-314192-13C

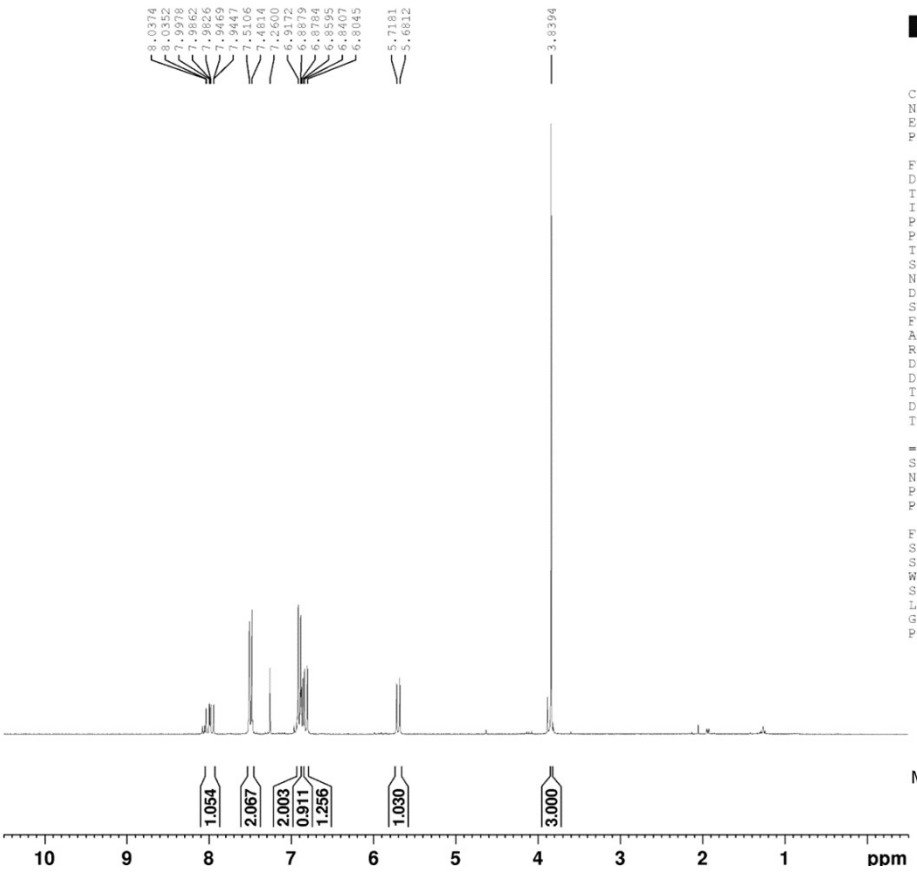


```
NAME      191104-314192
EXPNO             2
PROCNO            1
Date_      20191104
Time          16.10
INSTRUM       spect
PROBHD  5 mm PABBO BB-
PULPROG       zgpg30
TD             32768
SOLVENT        CDCl3
NS                65
DS                 0
SWH        18028.846 Hz
FIDRES      0.550197 Hz
AQ          0.9088159 sec
RG             219.17
DW            27.733 usec
DE             6.50 usec
TE             296.8 K
D1         2.00000000 sec
TD0                1

======== CHANNEL f1 ======
SFO1       75.4756726 MHz
NUC1             13C
P1            10.00 usec
SI             32768
SF         75.4677399 MHz
WDW               EM
SSB                0
LB            2.00 Hz
GB                 0
PC            1.00
```

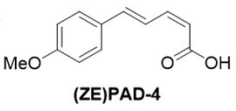


S9

220303-06494

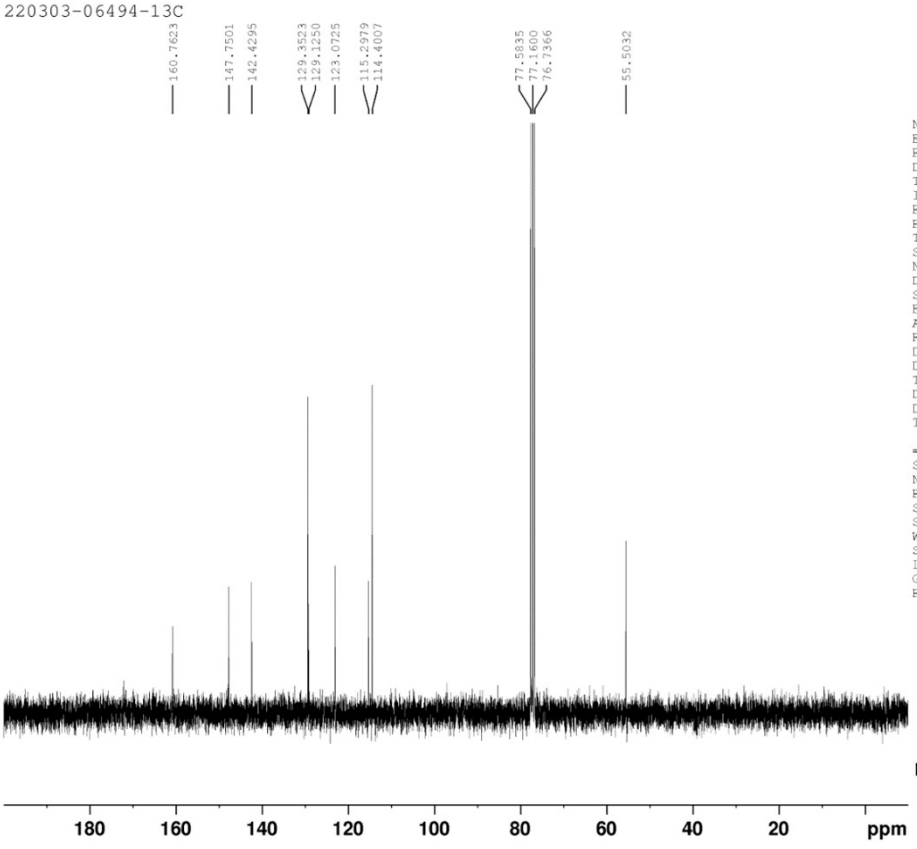



```
Current Data Parameters
NAME          220303-06494
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20220303
Time                 13.32
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  32768
SOLVENT              CDCl3
NS                      16
DS                       0
SWH             6009.615 Hz
FIDRES          0.183399 Hz
AQ              2.7262976 sec
RG                  219.17
DW                 83.200 usec
DE                 12.63 usec
TE                 296.6 K
D1              2.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1          300.1318008 MHz
NUC1                    1H
P1                  14.00 usec
PLW1           7.69999981 W

F2 - Processing parameters
SI                   16384
SF            300.1300071 MHz
WDW                     EM
SSB                      0
LB                    0 Hz
GB                       0
PC                    1.00
```

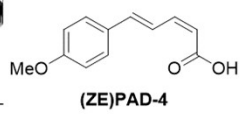


(ZE)PAD-4

220303-06494-13C

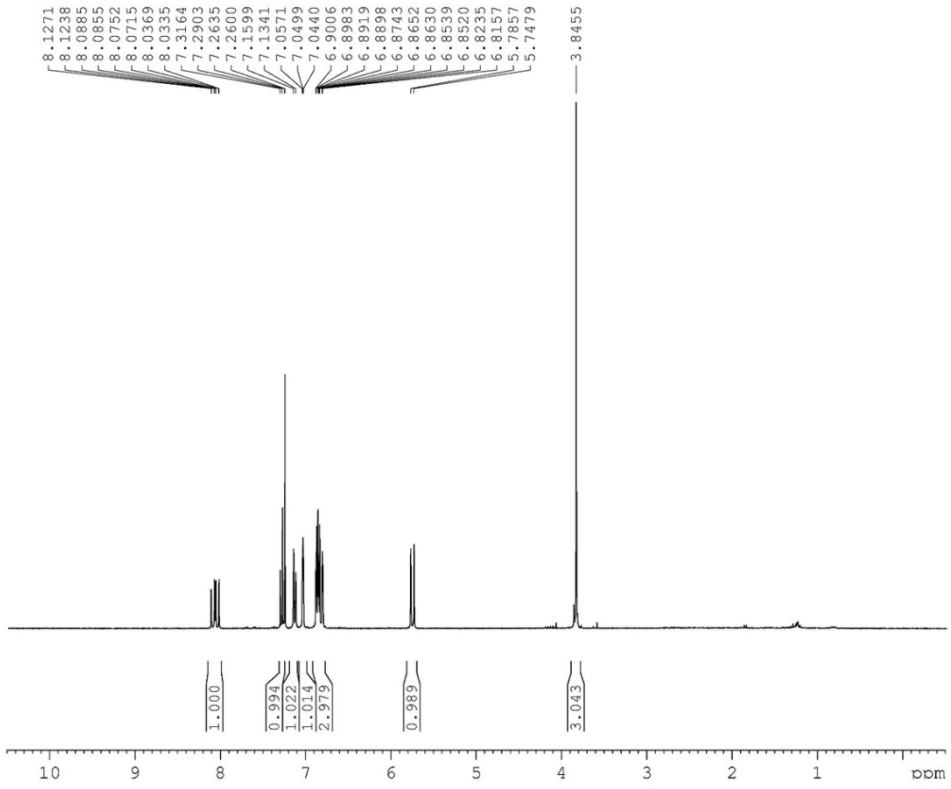



```
NAME          220303-06494
EXPNO                    2
PROCNO                   1
Date_              20220303
Time                 13.37
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                  32768
SOLVENT              CDCl3
NS                     128
DS                       0
SWH            18028.846 Hz
FIDRES          0.550197 Hz
AQ              0.9087659 sec
RG                  219.17
DW                 27.733 usec
DE                  6.50 usec
TE                 297.0 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1          75.4756726 MHz
NUC1                    13C
P1                  10.00 usec
SI                   32768
SF            75.4677388 MHz
WDW                     EM
SSB                      0
LB                    0.50 Hz
GB                       0
PC                    1.00
```

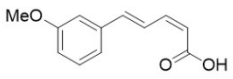


(ZE)PAD-4

191008-EZ-CNA5

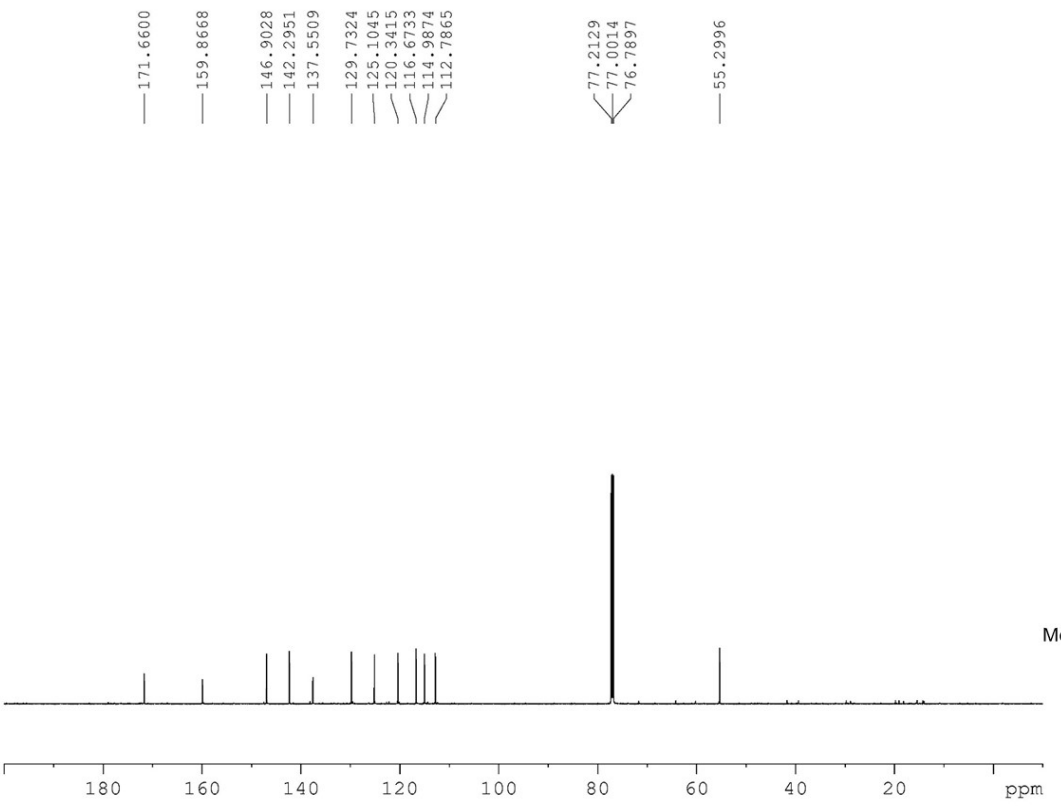



```
NAME        191008-EZ-CNA5
EXPNO  NAME      1910      1
PROCNO                      1
Date_                20191008
Time                    17.23
INSTRUM                 spect
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     32768
SOLVENT                CDCl3
NS                        16
DS                         0
SWH                 6009.615 Hz
FIDRES              0.183399 Hz
AQ                2.7263477 se
RG                    219.17
DW                   83.200 us
DE                   12.63 us
TE                   296.9 K
D1                2.00000000 se
TD0                        1

======== CHANNEL f1 =======
SFO1             300.1318008 MH
NUC1                       1H
P1                      14.00 us
SI                      16384
SF               300.1300072 MH
WDW                       EM
SSB                        0
LB                      0.00 Hz
GB                         0
PC                      1.00
```

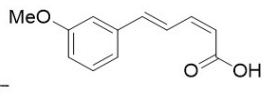


(ZE)PAD-5

13C of EZPAD5

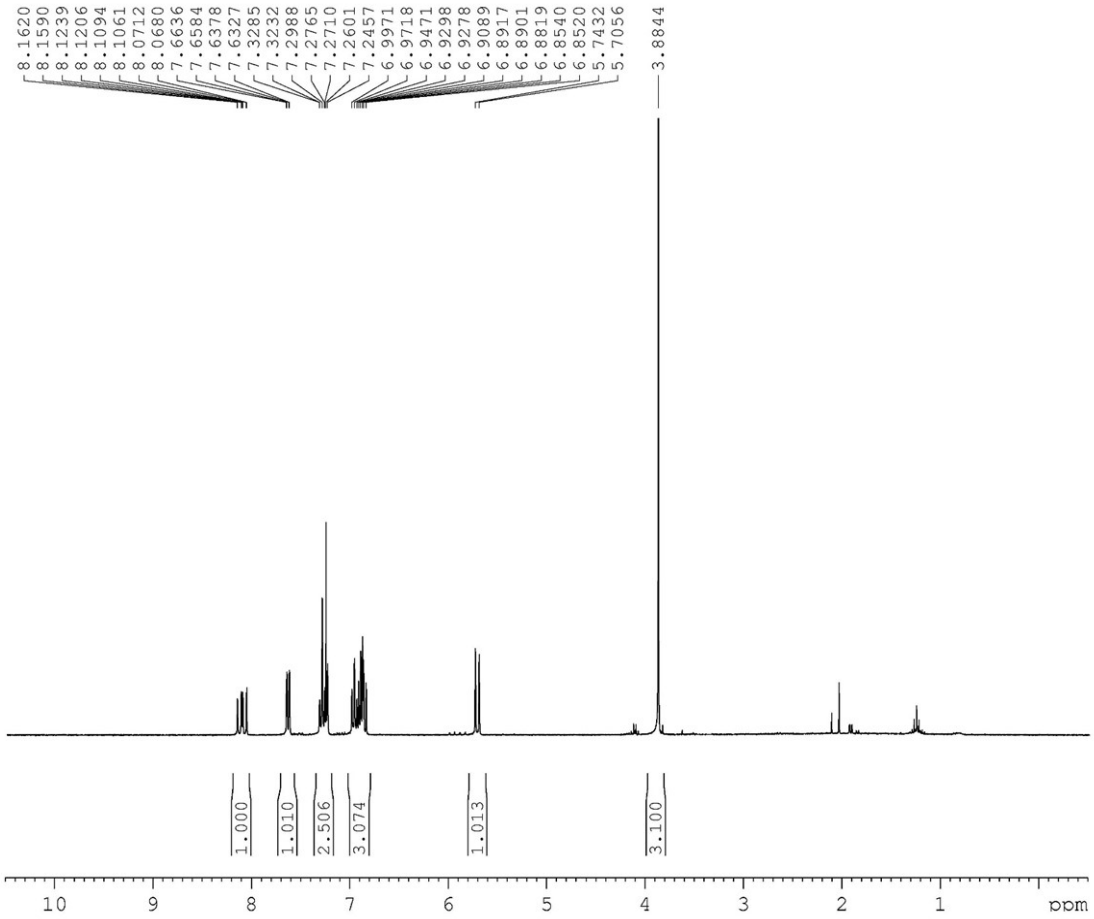



```
NAME          200706
EXPNO             16
PROCNO             1
Date_      20200709
Time           6.06
INSTRUM       spect
PROBHD  5 mm PATBO BB-
PULPROG      zgpg30
TD            65536
SOLVENT       CDCl3
NS             3000
DS                0
SWH       36057.691 Hz
FIDRES     0.550197 Hz
AQ        0.9088159 sec
RG              2050
DW          13.867 usec
DE              6.50 usec
TE             301.6 K
D1        2.00000000 sec
D11       0.03000000 sec
TD0               1

======== CHANNEL f1 ======
SFO1     150.9287115 MHz
NUC1             13C
P1           12.00 usec
SI            32768
SF     150.9128706 MHz
WDW              EM
SSB               0
LB             2.00 Hz
GB                0
PC             1.00
```

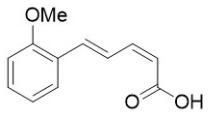


(ZE)PAD-5

190814-314183

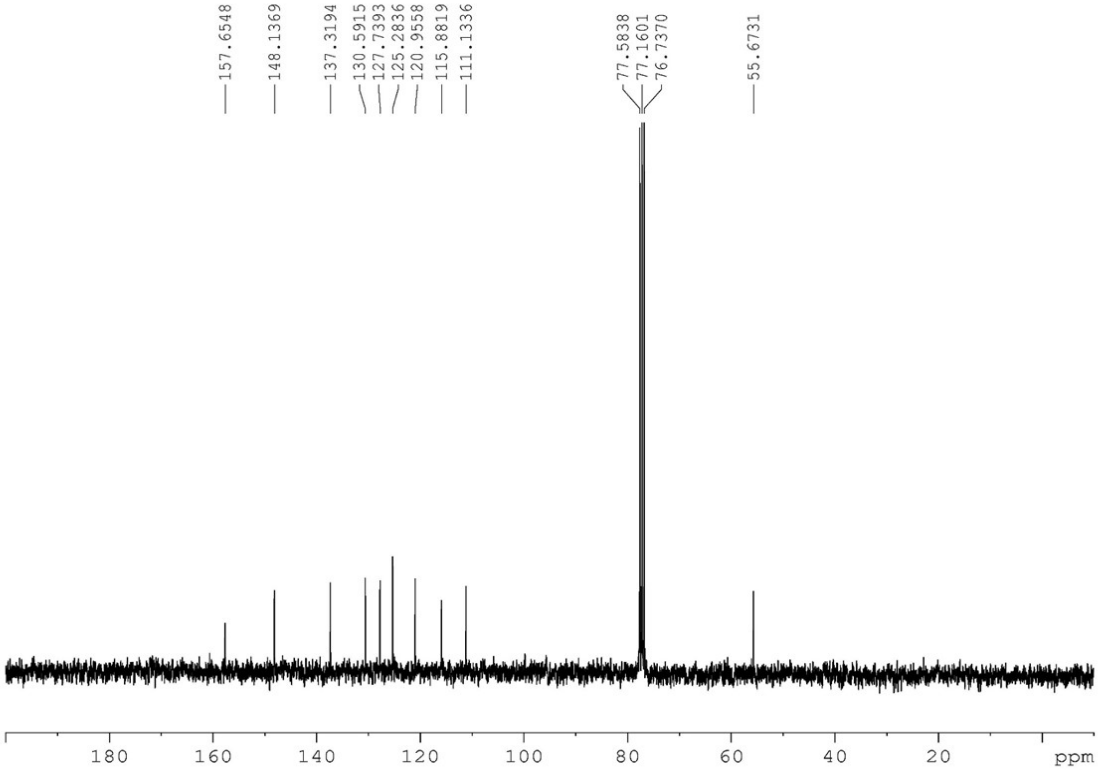


NAME	190814-314183
EXPNO	1
PROCNO NAME	190 1
Date_	20190814
Time	20.05
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	6009.615 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 se
RG	219.17
DW	83.200 us
DE	12.63 us
TE	296.9 K
D1	2.00000000 se
TD0	1
======== CHANNEL f1 =======	
SFO1	300.1318008 MH
NUC1	1H
P1	14.00 us
SI	16384
SF	300.1300071 MH
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

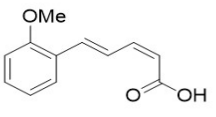


(ZE)PAD-6

191104-ZECNA-6-13C

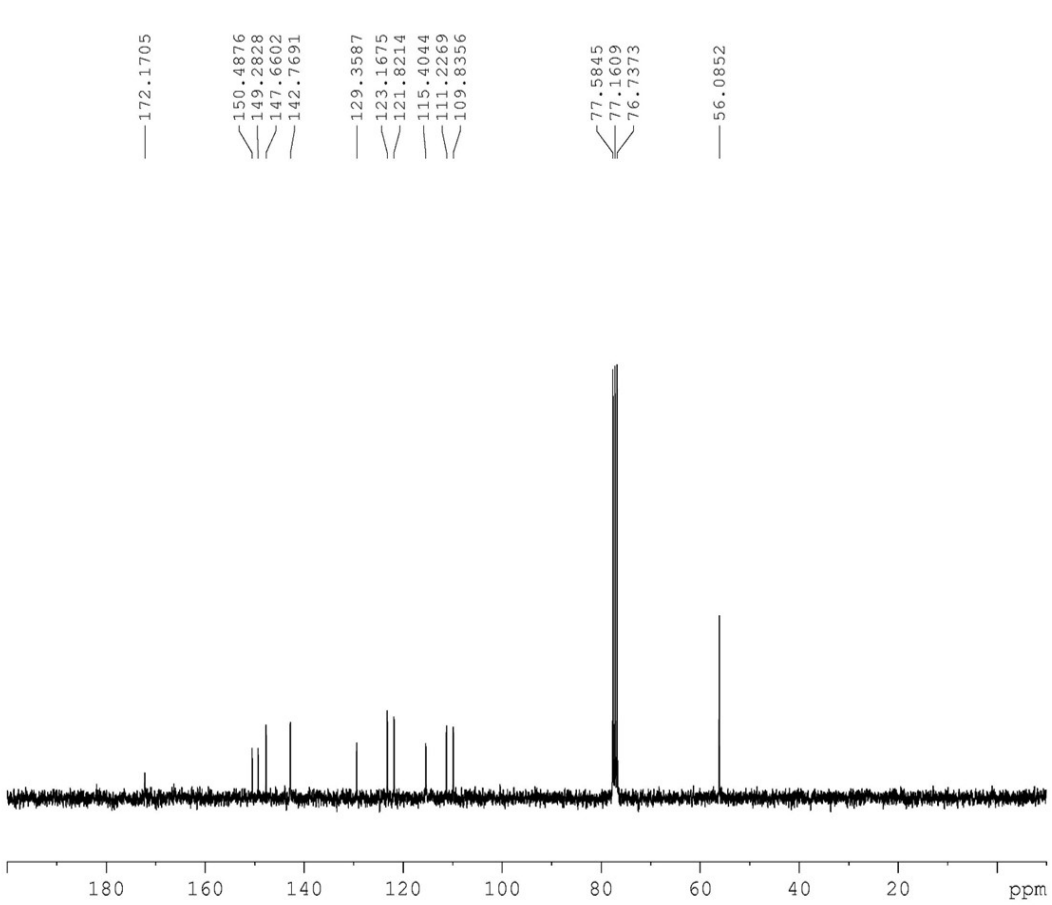


NAME	191104-ZECNA-6
EXPNO	2
PROCNO	1
Date_	20191104
Time	15.51
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	129
DS	0
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	219.17
DW	27.733 usec
DE	6.50 usec
TE	297.1 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ======	
SFO1	75.4756726 MHz
NUC1	13C
P1	10.00 usec
SI	32768
SF	75.4677389 MHz
WDW	EM
SSB	0
LB	2.00 Hz
GB	0
PC	1.00



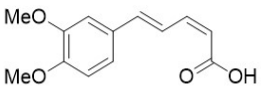
(ZE)PAD-6

190905-314184-fullspec-13C



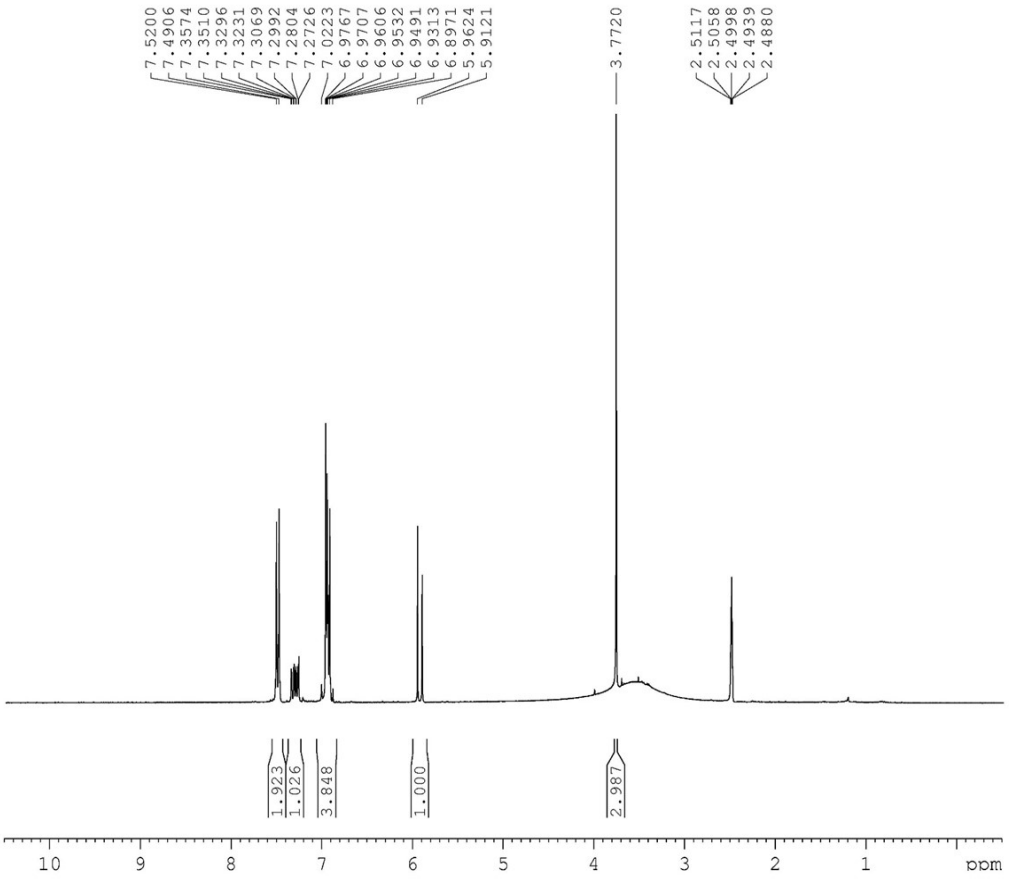
NAME 190905-314184-fullspe
EXPNO 2
PROCNO 1
Date_ 20190905
Time 22.07
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 161
DS 0
SWH 18028.846 Hz
FIDRES 0.550197 Hz
AQ 0.9088159 sec
RG 219.17
DW 27.733 usec
DE 6.50 usec
TE 296.8 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ======
SFO1 75.4756726 MHz
NUC1 13C
P1 10.00 usec
SI 32768
SF 75.4677398 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00



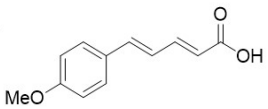
(ZE)PAD-7

191125-EECNA4-DMSO



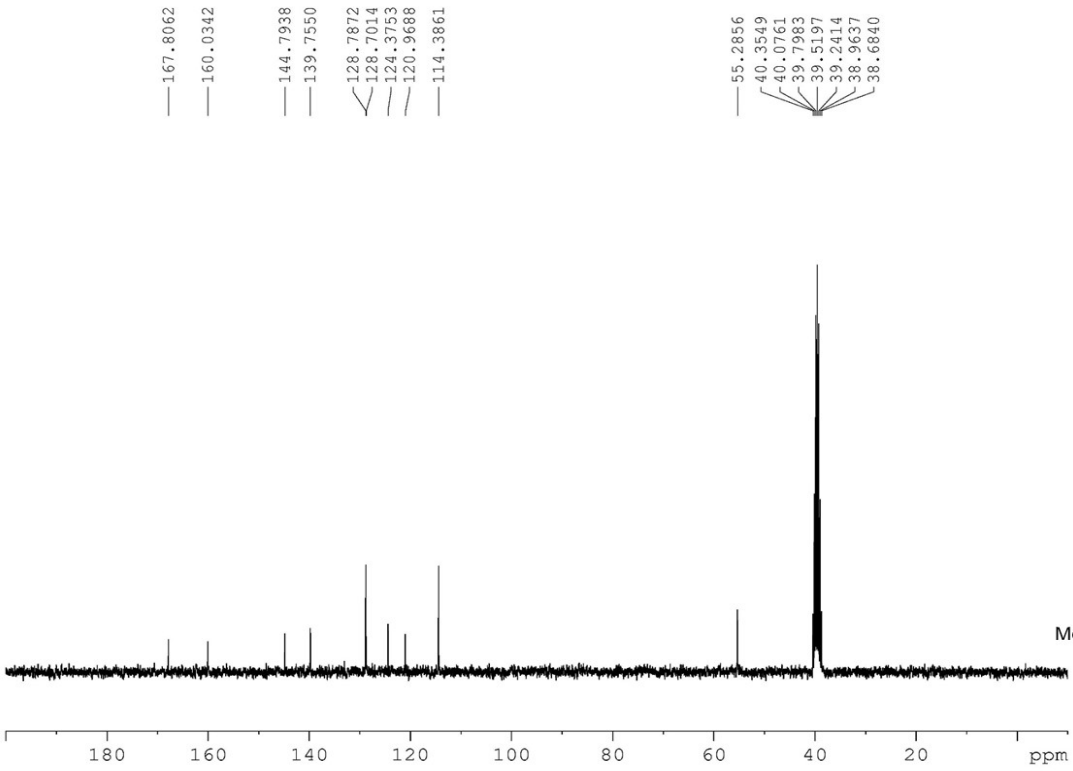
BRUKER

```
NAME      191125-EECNA4-DMS
EXPNO     NAME     1911     1
PROCNO                      1
Date_                20191125
Time                   19.27
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                 zg30
TD                     32768
SOLVENT                 DMSO
NS                        16
DS                         0
SWH                 6009.615 Hz
FIDRES              0.183399 Hz
AQ                 2.7263477 se
RG                    171.09
DW                    83.200 us
DE                     12.63 us
TE                     296.9 K
D1                2.00000000 se
TD0                        1

======== CHANNEL f1 =======
SFO1           300.1318008 MH
NUC1                    1H
P1                    14.00 us
SI                    16384
SF             300.1300024 MH
WDW                     EM
SSB                      0
LB                    0.00 Hz
GB                       0
PC                    1.00
```



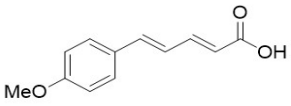
(EE)PAD-4

191125-EECNA4-DMSO-13C



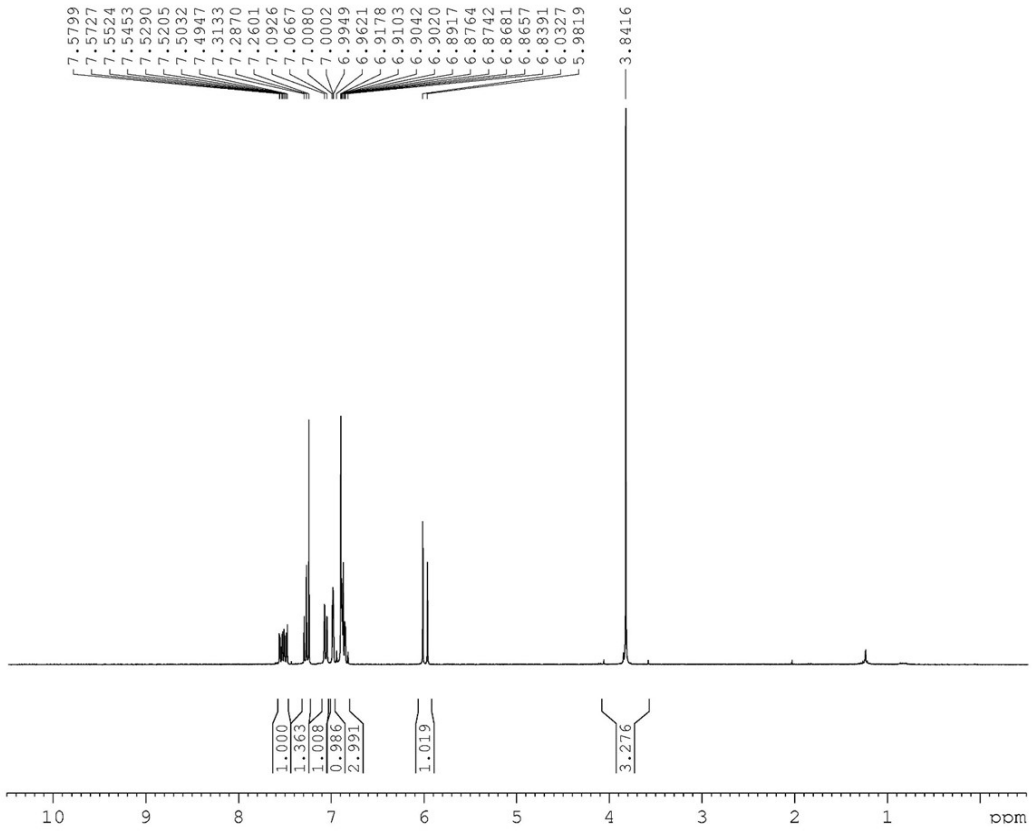
BRUKER

```
NAME    191125-EECNA4-DMS
EXPNO                    2
PROCNO                   1
Date_             20191125
Time                19.29
INSTRUM             spect
PROBHD  5 mm PABBO BB-
PULPROG             zgpg30
TD                   32768
SOLVENT              DMSO
NS                      64
DS                       0
SWH             18028.846 Hz
FIDRES           0.550197 Hz
AQ              0.9088159 sec
RG                  219.17
DW                27.733 usec
DE                 6.50 usec
TE                 296.9 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                      1

======== CHANNEL f1 ======
SFO1          75.4756726 MHz
NUC1                   13C
P1                10.00 usec
SI                 32768
SF            75.4677797 MHz
WDW                    EM
SSB                     0
LB                 2.00 Hz
GB                      0
PC                   1.00
```

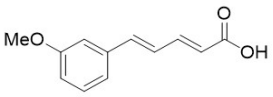


(EE)PAD-4

191008-EE-CNA5

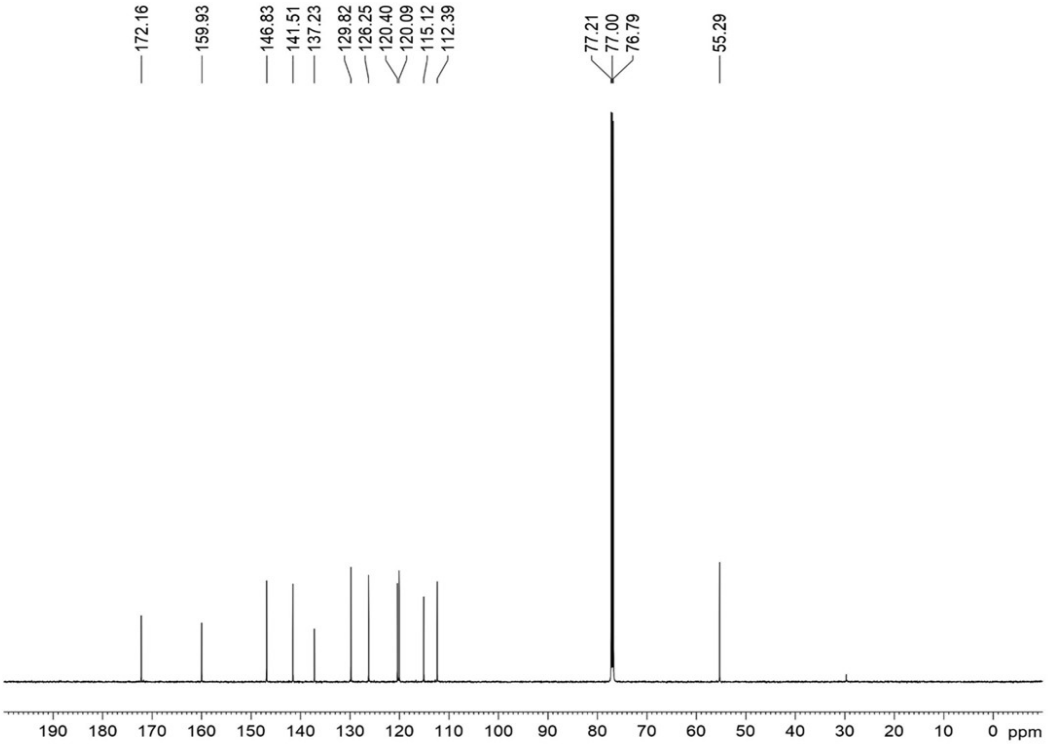



```
NAME       191008-EE-CNA5
EXPNO  NAME      1910      1
PROCNO                     1
Date_                20191008
Time                    16.58
INSTRUM                 spect
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     32768
SOLVENT                CDCl3
NS                        16
DS                         0
SWH                 6009.615 Hz
FIDRES              0.183399 Hz
AQ                  2.7263477 se
RG                     219.17
DW                     83.200 us
DE                     12.63 us
TE                     296.7 K
D1                2.00000000 se
TD0                        1

========= CHANNEL f1 =======
SFO1           300.1318008 MH
NUC1                     1H
P1                    14.00 us
SI                     16384
SF             300.1300071 MH
WDW                      EM
SSB                       0
LB                     0.00 Hz
GB                        0
PC                     1.00
```

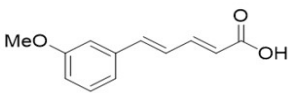


(EE)PAD-5

13C of EEPAD5

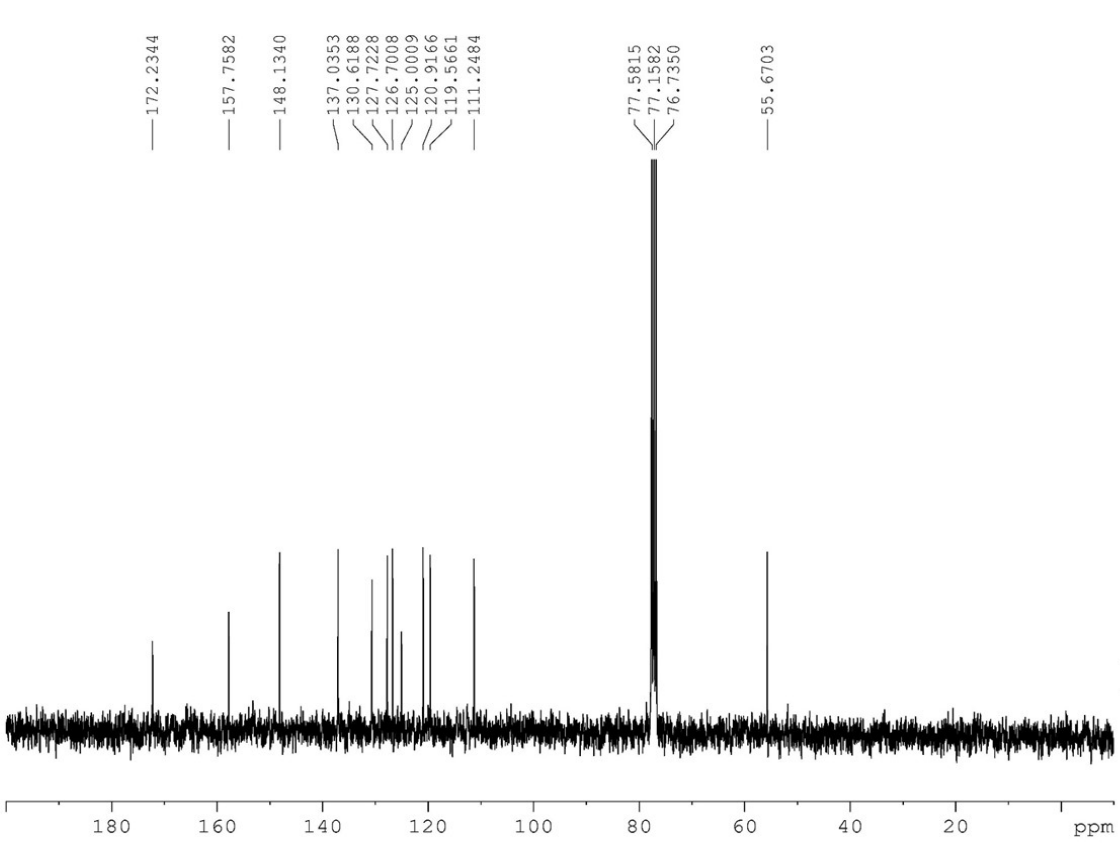



```
Current Data Parameters
NAME          20200060056
EXPNO                 116
PROCNO                  1

F2 - Acquisition Parameters
Date_          20200710
Time               6.03
INSTRUM           spect
PROBHD  5 mm PATBO BB-
PULPROG         zgpg30
TD              65536
SOLVENT         CDCl3
NS               2400
DS                  0
SWH         36057.691 Hz
FIDRES       0.550197 Hz
AQ           0.90857659 sec
RG                2050
DW              13.867 usec
DE                6.50 usec
TE              302.2 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1

========= CHANNEL f1 =======
SFO1        150.9287115 MHz
NUC1                   13C
P1                 12.00 usec
PLW1        40.20000076 W

========= CHANNEL f2 =======
SFO2        600.1724007 MHz
NUC2                   1H
CPDPRG[2          waltz64
PCPD2             70.00 usec
PLW2         23.50000000 W
PLW12         1.08000004 W
PLW13         0.52875000 W

F2 - Processing parameters
SI                  32768
SF          150.9128693 MHz
WDW                    EM
SSB  0
LB                 2.00 Hz
GB   0
PC                 1.00
```



(EE)PAD-5

200818-EEPAD6-13C

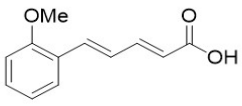


BRUKER

NAME	200818-EEPAD6
EXPNO	2
PROCNO	1
Date_	20200818
Time	15.31
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	641
DS	0
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	219.17
DW	27.733 usec
DE	6.50 usec
TE	297.8 K
D1	2.00000000 sec
TD0	1

======== CHANNEL f1 ======

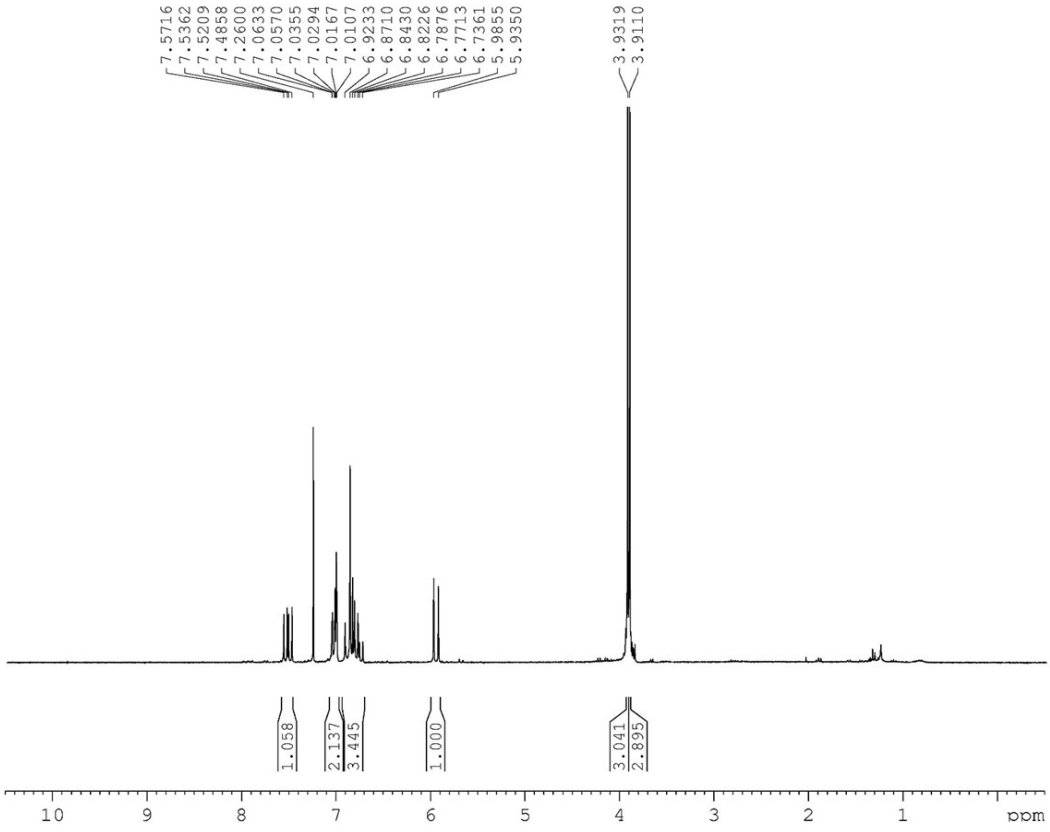
SFO1	75.4756726 MHz
NUC1	13C
P1	10.00 usec
SI	32768
SF	75.4677382 MHz
WDW	EM
SSB	0
LB	2.00 Hz
GB	0
PC	1.00



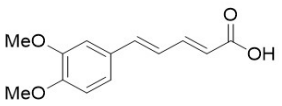
(EE)PAD-6

191008-EE-CNA6

191104-EECNA-7

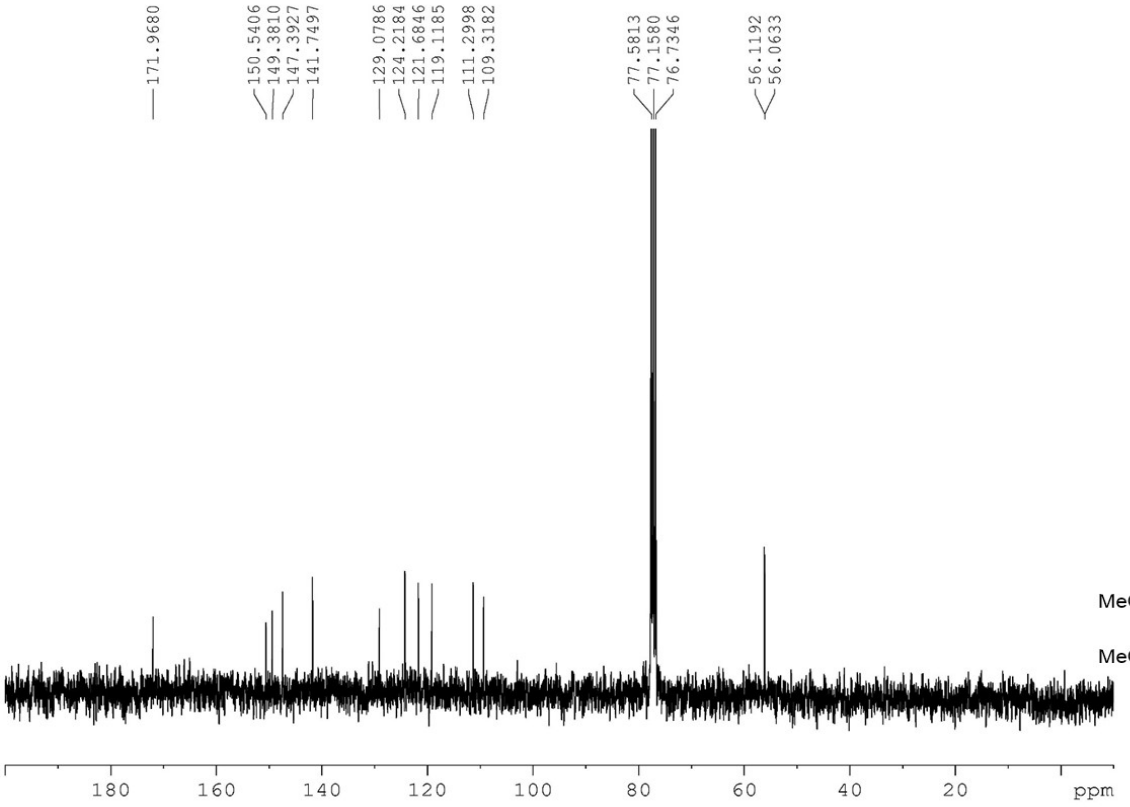



```
NAME      191104-EECNA-7
EXPNO NAME      1911     1
PROCNO                   1
Date_             20191104
Time                 16.28
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG               zg30
TD                   32768
SOLVENT              CDCl3
NS                      16
DS                       0
SWH                6009.615 Hz
FIDRES            0.183399 Hz
AQ                2.7263477 se
RG                   219.17
DW                   83.200 us
DE                   12.63 us
TE                   296.8 K
D1                2.00000000 se
TD0                      1

======== CHANNEL f1 ======
SFO1           300.1318008 MH
NUC1                    1H
P1                   14.00 us
SI                   16384
SF             300.1300072 MH
WDW                     EM
SSB                      0
LB                    0.00 Hz
GB                       0
PC                    1.00
```

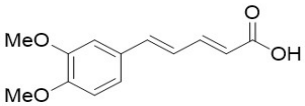


(EE)PAD-7

200818-EEPAD7-13C

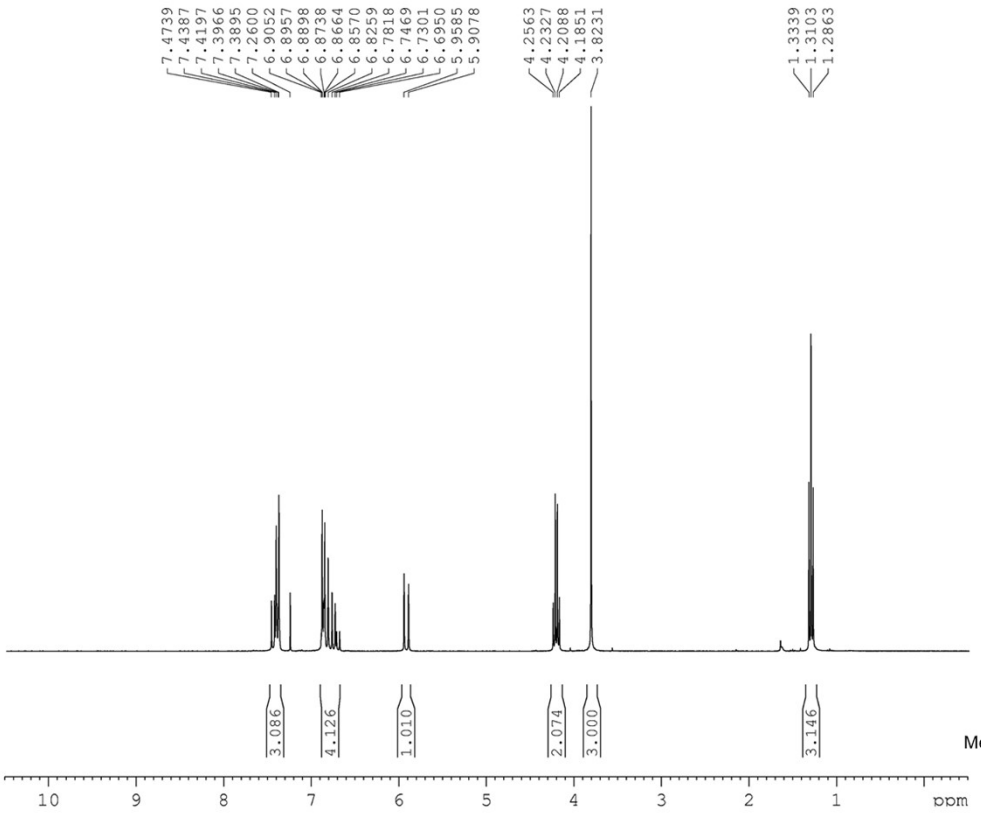



```
NAME     200818-EEPAD7
EXPNO               2
PROCNO              1
Date_        20200818
Time            15.43
INSTRUM         spect
PROBHD  5 mm PABBO BB-
PULPROG       zgpg30
TD             32768
SOLVENT        CDCl3
NS               513
DS                 0
SWH        18028.846 Hz
FIDRES      0.550197 Hz
AQ          0.9088159 sec
RG             219.17
DW           27.733 usec
DE            6.50 usec
TE            297.3 K
D1         2.00000000 sec
TD0                1

======== CHANNEL f1 ======
SFO1       75.4756726 MHz
NUC1               13C
P1          10.00 usec
SI              32768
SF         75.4677382 MHz
WDW                EM
SSB                 0
LB            2.00 Hz
GB                  0
PC               1.00
```

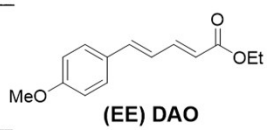


(EE)PAD-7

180104-306829 tube 23

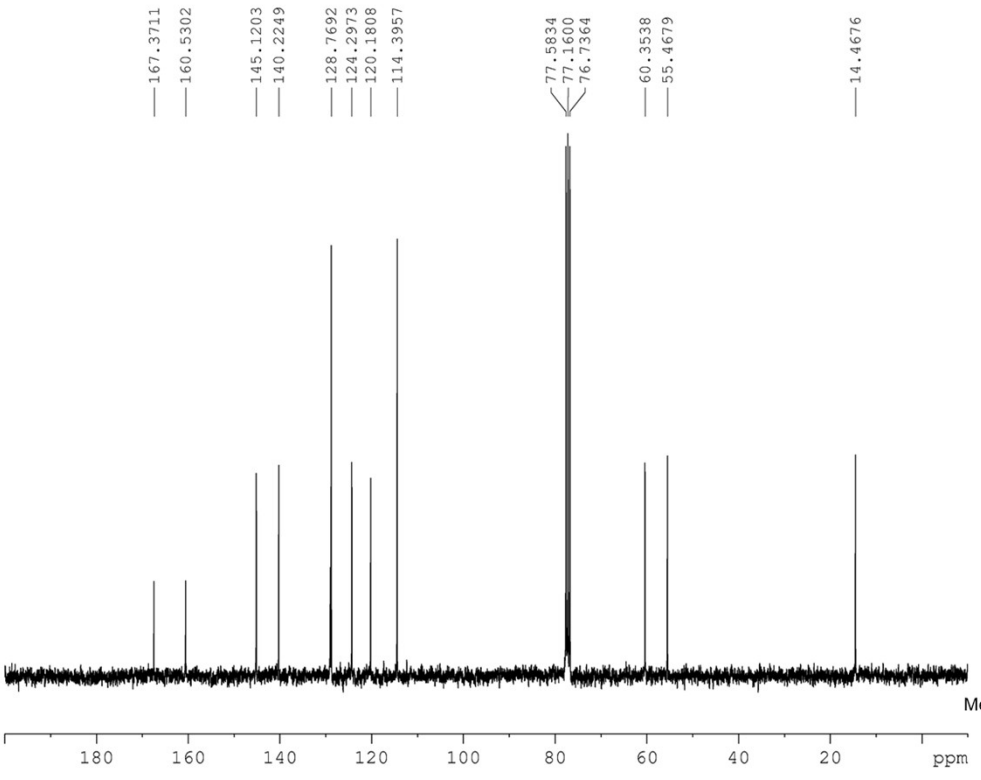


NAME	180104-306829
EXPNO	3
PROCNO	1
Date_	20180104
Time	14.56
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	8
DS	0
SWH	6009.615 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 se
RG	219.17
DW	83.200 us
DE	12.53 us
TE	297.4 K
D1	2.00000000 se
TD0	1
======== CHANNEL f1 ======	
SFO1	300.1318008 MH
NUC1	1H
P1	14.50 us
SI	16384
SF	300.1300072 MH
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

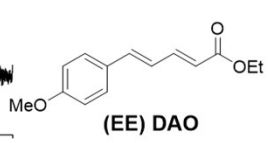


(EE) DAO

180104-306829 tube 23 13C

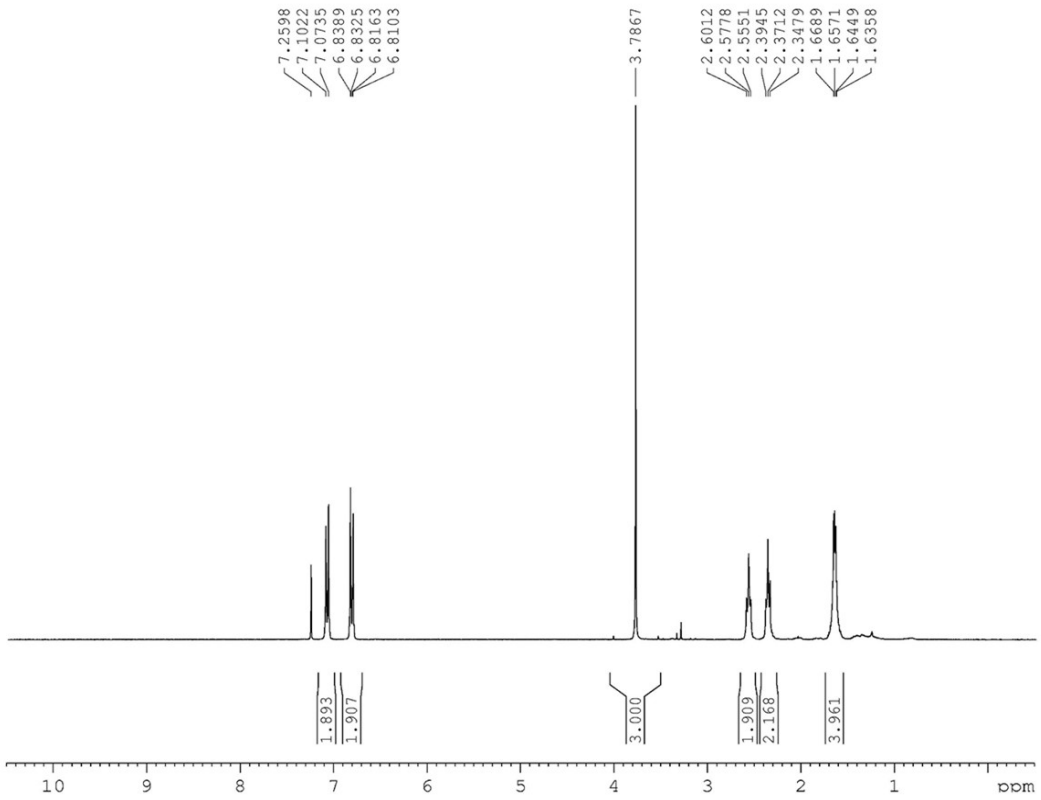


NAME	180104-306829
EXPNO	4
PROCNO	1
Date_	20180104
Time	14.57
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	256
DS	0
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	219.17
DW	27.733 usec
DE	6.50 usec
TE	297.4 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	75.4756726 MHz
NUC1	13C
P1	10.50 usec
SI	32768
SF	75.4677400 MHz
WDW	EM
SSB	0
LB	2.00 Hz
GB	0
PC	1.00



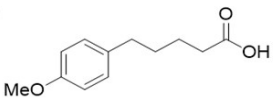
(EE) DAO

200730-PAD-8



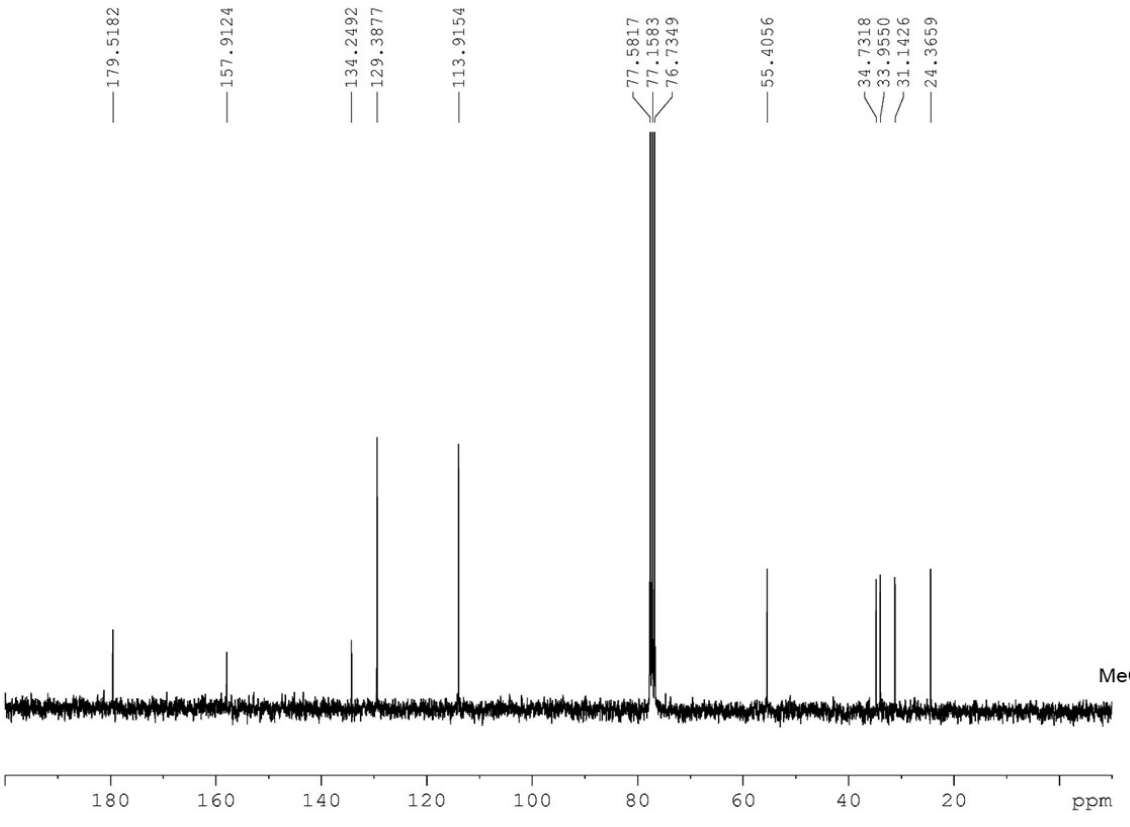
BRUKER

NAME	200730-PAD-8
EXPNO	2
PROCNO	1
Date_	20200730
Time	15.34
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	6009.615 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 se
RG	219.17
DW	83.200 us
DE	12.63 us
TE	298.5 K
D1	2.00000000 se
TD0	1
======== CHANNEL f1 =======	
SFO1	300.1318008 MH
NUC1	1H
P1	14.00 us
SI	16384
SF	300.1300072 MH
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00



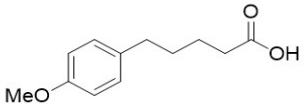
PAD-8

200730-PAD-8-13C



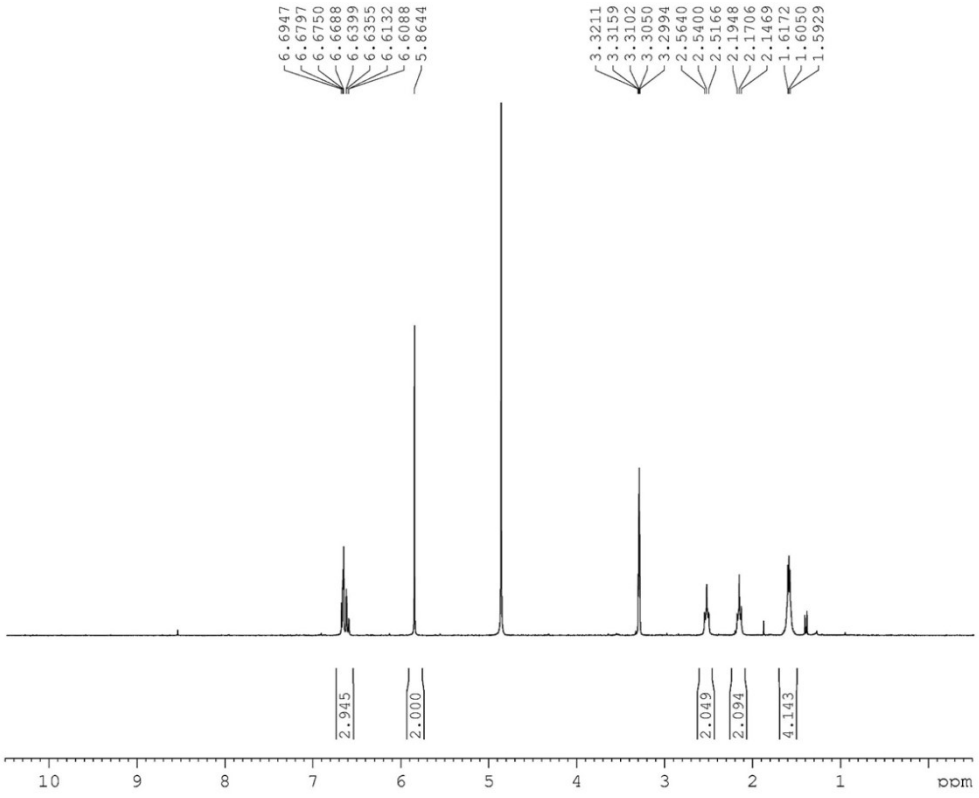
BRUKER

NAME	200730-PAD-8
EXPNO	3
PROCNO	1
Date_	20200730
Time	15.48
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	384
DS	0
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	219.17
DW	27.733 usec
DE	6.50 usec
TE	298.6 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ======	
SFO1	75.4756726 MHz
NUC1	13C
P1	10.00 usec
SI	32768
SF	75.4677382 MHz
WDW	EM
SSB	0
LB	2.00 Hz
GB	0
PC	1.00



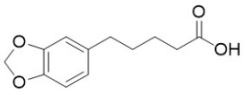
PAD-8

191119-318327



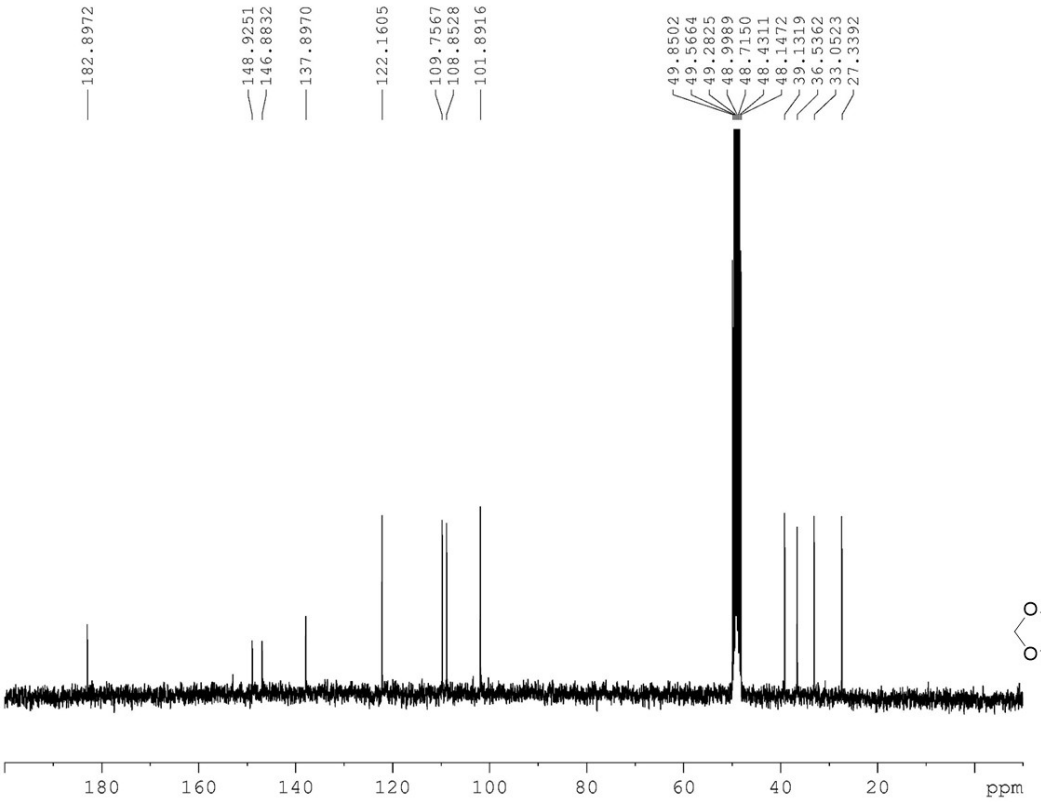
BRUKER

NAME	191119-318327
EXPNO	1
PROCNO	1
Date_	20191119
Time	14.16
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	MeOD
NS	16
DS	0
SWH	6009.615 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 se
RG	219.17
DW	83.200 us
DE	12.63 us
TE	296.7 K
D1	2.00000000 se
TD0	1
======== CHANNEL f1 =======	
SFO1	300.1318008 MH
NUC1	1H
P1	14.00 us
SI	16384
SF	300.1300057 MH
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00



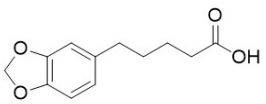
PAD-9

200730-PAD-9-13C



BRUKER

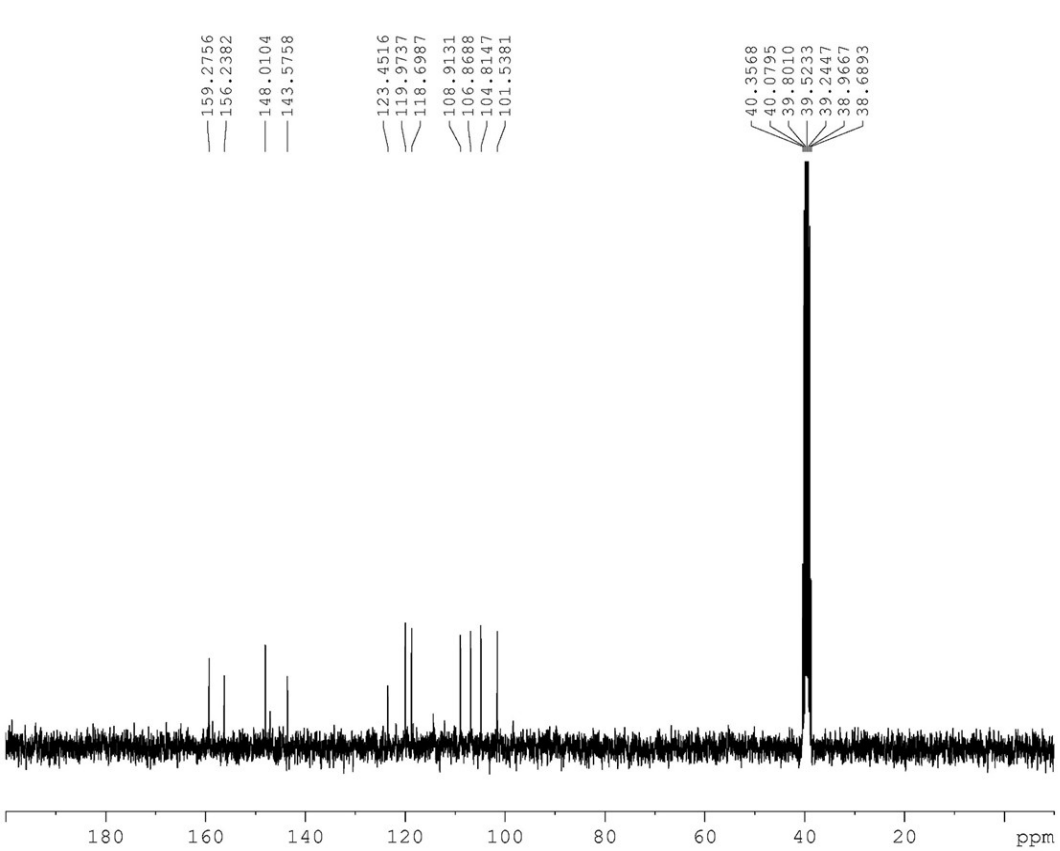
NAME	200730-PAD-9
EXPNO	2
PROCNO	1
Date_	20200730
Time	16.35
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	MeOD
NS	897
DS	0
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	219.17
DW	27.733 usec
DE	6.50 usec
TE	298.2 K
D1	2.00000000 sec
TD0	1
======== CHANNEL f1 ======	
SFO1	75.4756726 MHz
NUC1	13C
P1	10.00 usec
SI	32768
SF	75.4676427 MHz
WDW	EM
SSB	0
LB	2.00 Hz
GB	0
PC	1.00



PAD-9

200818-PAD11-13C

200818-PAD12-13C

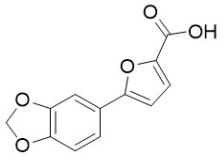


BRUKER

NAME	200818-PAD12
EXPNO	3
PROCNO	1
Date_	20200818
Time	18.18
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	DMSO
NS	65
DS	0
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	219.17
DW	27.733 usec
DE	6.50 usec
TE	297.5 K
D1	2.00000000 sec
TD0	1

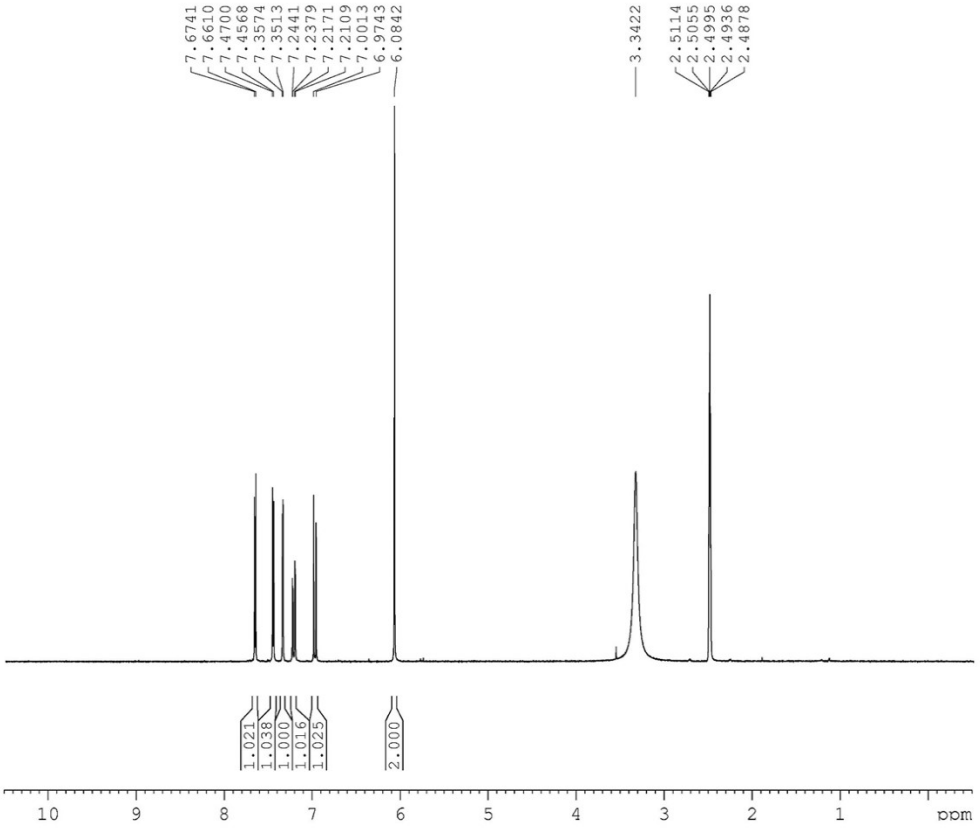
======== CHANNEL f1 ======

SFO1	75.4756726 MHz
NUC1	13C
P1	10.00 usec
SI	32768
SF	75.4677820 MHz
WDW	EM
SSB	0
LB	2.00 Hz
GB	0
PC	1.00



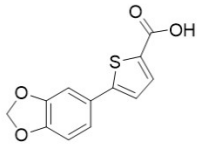
PAD-12

200514-PAD13-filtrated



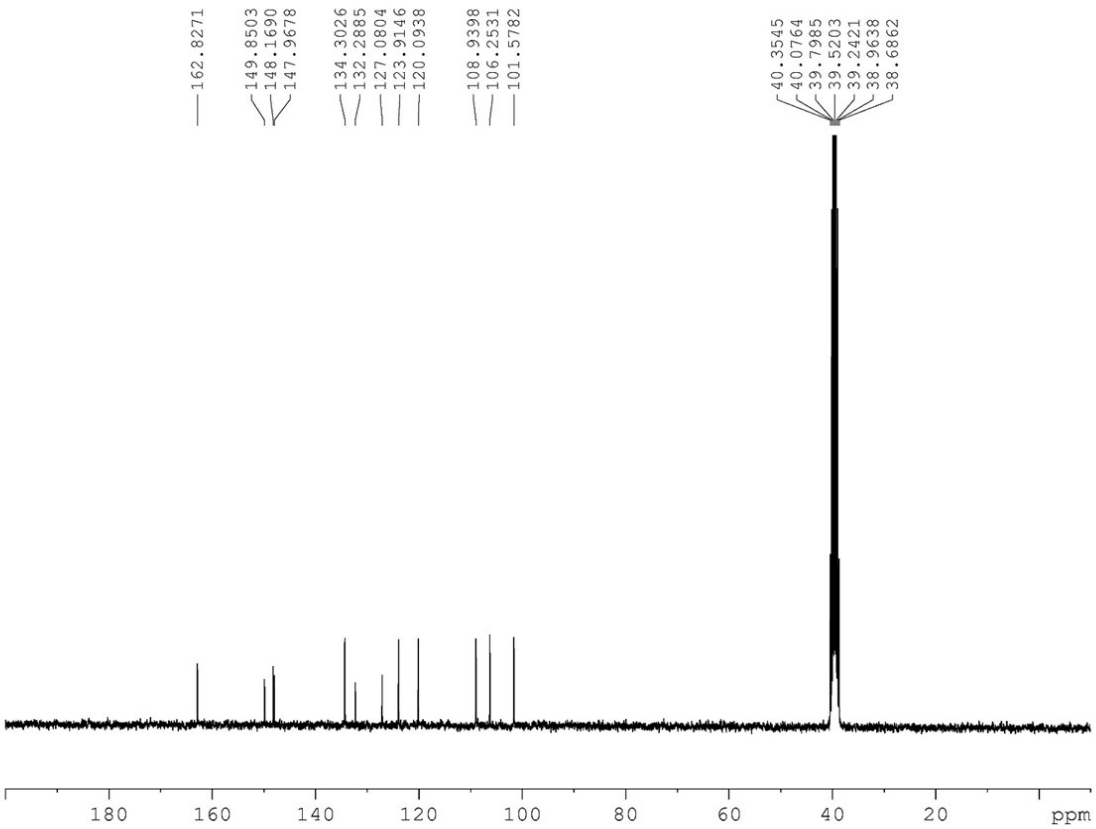
BRUKER

NAME	200514-PAD13-filt
EXPNO	1
PROCNO NAME	2005 1
Date_	20200514
Time	21.11
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	DMSO
NS	16
DS	0
SWH	6009.615 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 se
RG	219.17
DW	83.200 us
DE	12.63 us
TE	295.3 K
D1	2.00000000 se
TD0	1
======== CHANNEL f1 ======	
SFO1	300.1318008 MH
NUC1	1H
P1	14.00 us
SI	16384
SF	300.1300024 MH
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
PC	1.00



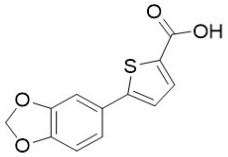
PAD-13

200515-PAD13-filtered-13C



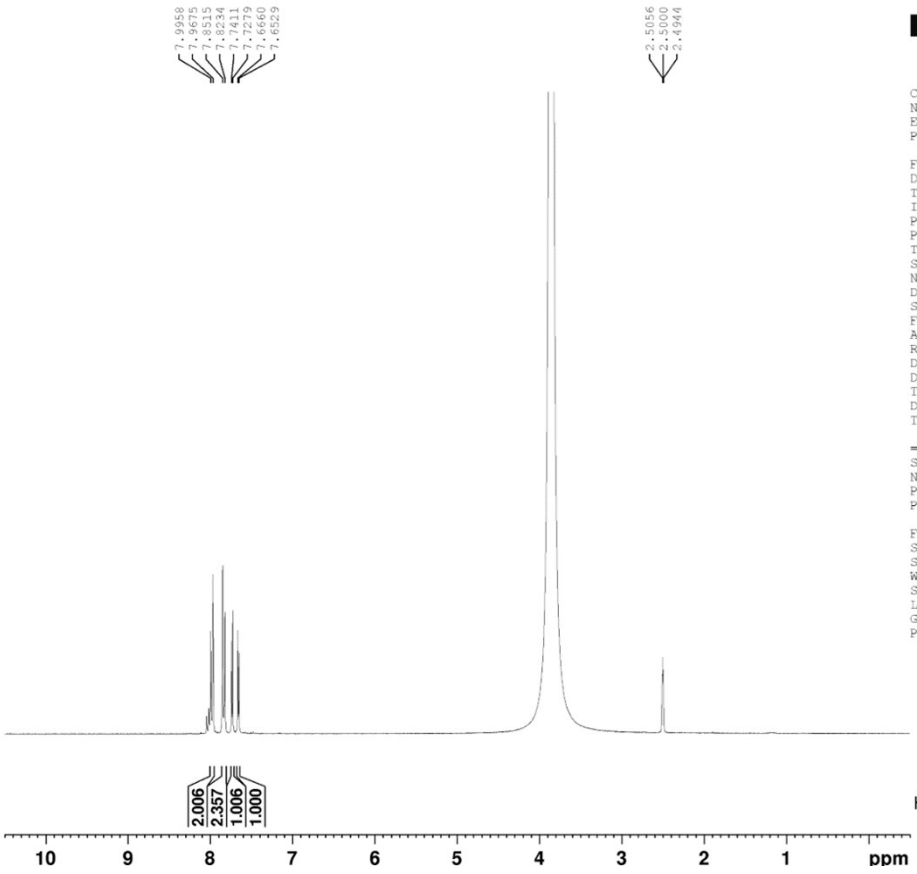
BRUKER

NAME	200515-PAD13-filtered
EXPNO	2
PROCNO	1
Date_	20200515
Time	16.55
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	32768
SOLVENT	DMSO
NS	640
DS	0
SWH	18028.846 Hz
FIDRES	0.550197 Hz
AQ	0.9088159 sec
RG	219.17
DW	27.733 usec
DE	6.50 usec
TE	295.8 K
D1	2.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ======	
SFO1	75.4756726 MHz
NUC1	13C
P1	10.00 usec
SI	32768
SF	75.4677818 MHz
WDW	EM
SSB	0
LB	2.00 Hz
GB	0
PC	1.00



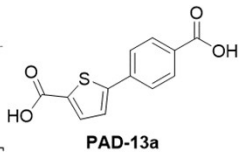
PAD-13

210615-05881



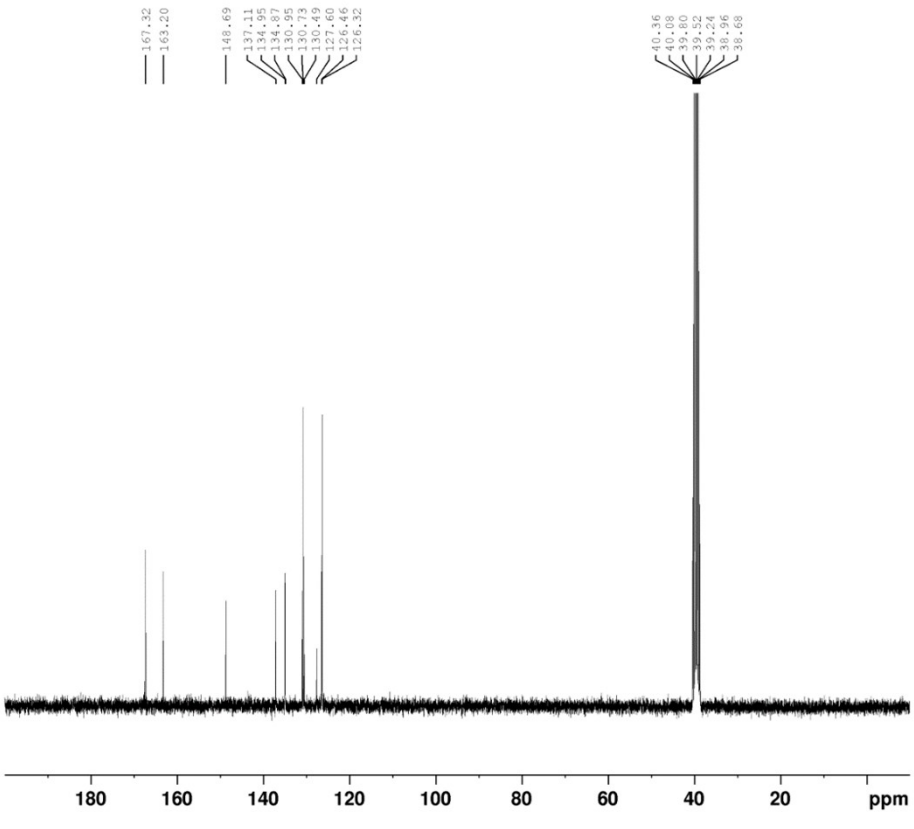
BRUKER

```
Current Data Parameters
NAME          210615-05881
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20210615
Time                   7.18
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    32768
SOLVENT                DMSO
NS                       16
DS                        0
SWH                6009.615 Hz
FIDRES            0.183399 Hz
AQ                2.7262976 sec
RG                     33.17
DW                   83.200 usec
DE                   12.63 usec
TE                   308.1 K
D1                2.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1             300.1318008 MHz
NUC1                     1H
P1                    14.00 usec
PLW1              7.69999981 W

F2 - Processing parameters
SI                       16384
SF               300.1300025 MHz
WDW                      EM
SSB                       0
LB                        0 Hz
GB                        0
PC                     1.00
```



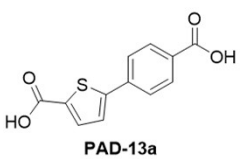
PAD-13a

210615-05881-13C



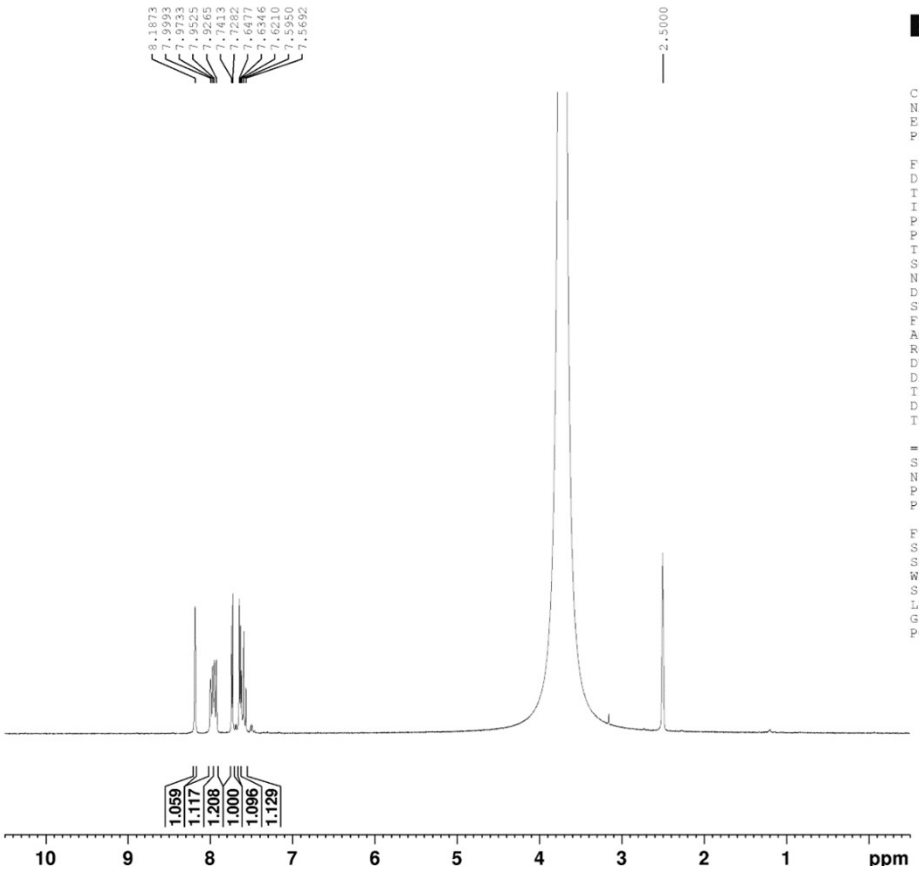
BRUKER

```
NAME          210615-05881
EXPNO                    2
PROCNO                   1
Date_              20210615
Time                   8.20
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    32768
SOLVENT                DMSO
NS                     1024
DS                        0
SWH               18028.846 Hz
FIDRES            0.550197 Hz
AQ                0.9087659 sec
RG                     219.17
DW                   27.733 usec
DE                    6.50 usec
TE                   308.3 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1             75.4756726 MHz
NUC1                     13C
P1                    10.00 usec
SI                    32768
SF               75.4677515 MHz
WDW                      EM
SSB                       0
LB                     0.50 Hz
GB                        0
PC                     1.00
```



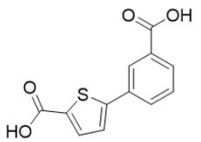
PAD-13a

210722-06412



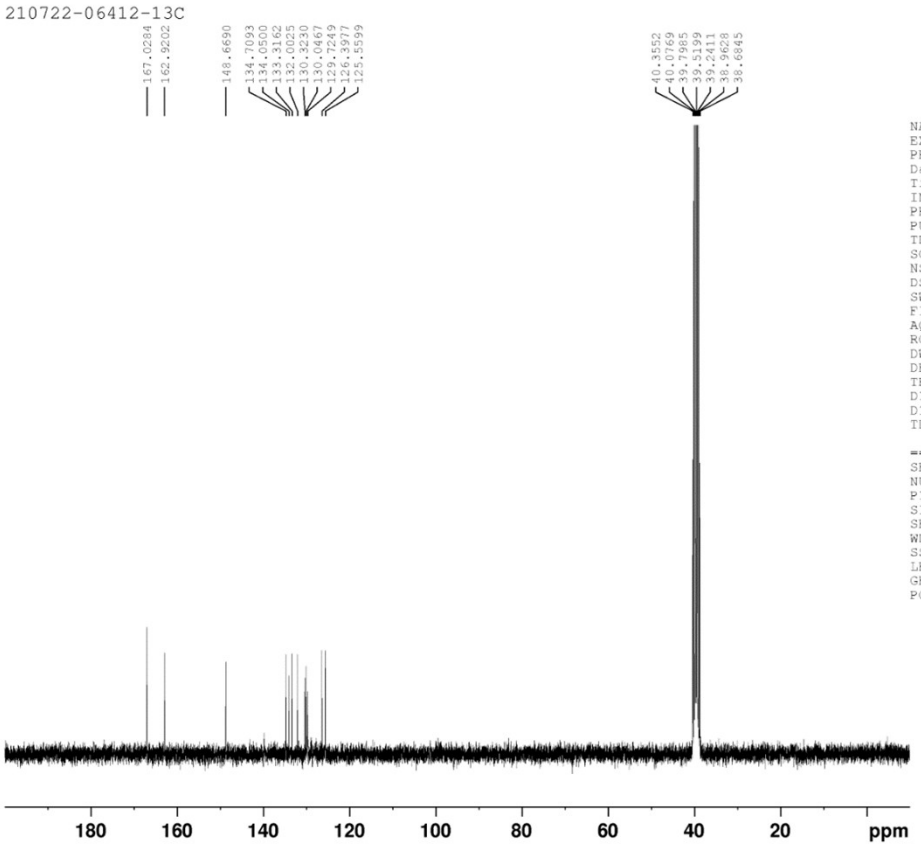
BRUKER

```
Current Data Parameters
NAME          210722-06412
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20210722
Time                   6.38
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    32768
SOLVENT                DMSO
NS                       16
DS                        0
SWH                6009.615 Hz
FIDRES            0.183399 Hz
AQ                2.7262976 sec
RG                     96.06
DW                    83.200 usec
DE                    12.63 usec
TE                    312.3 K
D1                2.00000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1             300.1318008 MHz
NUC1                       1H
P1                      14.00 usec
PLW1              7.69999981 W

F2 - Processing parameters
SI                       16384
SF               300.1300024 MHz
WDW                         EM
SSB                          0
LB                        0 Hz
GB                           0
PC                        1.00
```



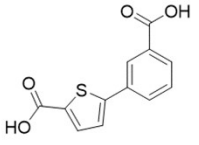
PAD-13b

210722-06412-13C

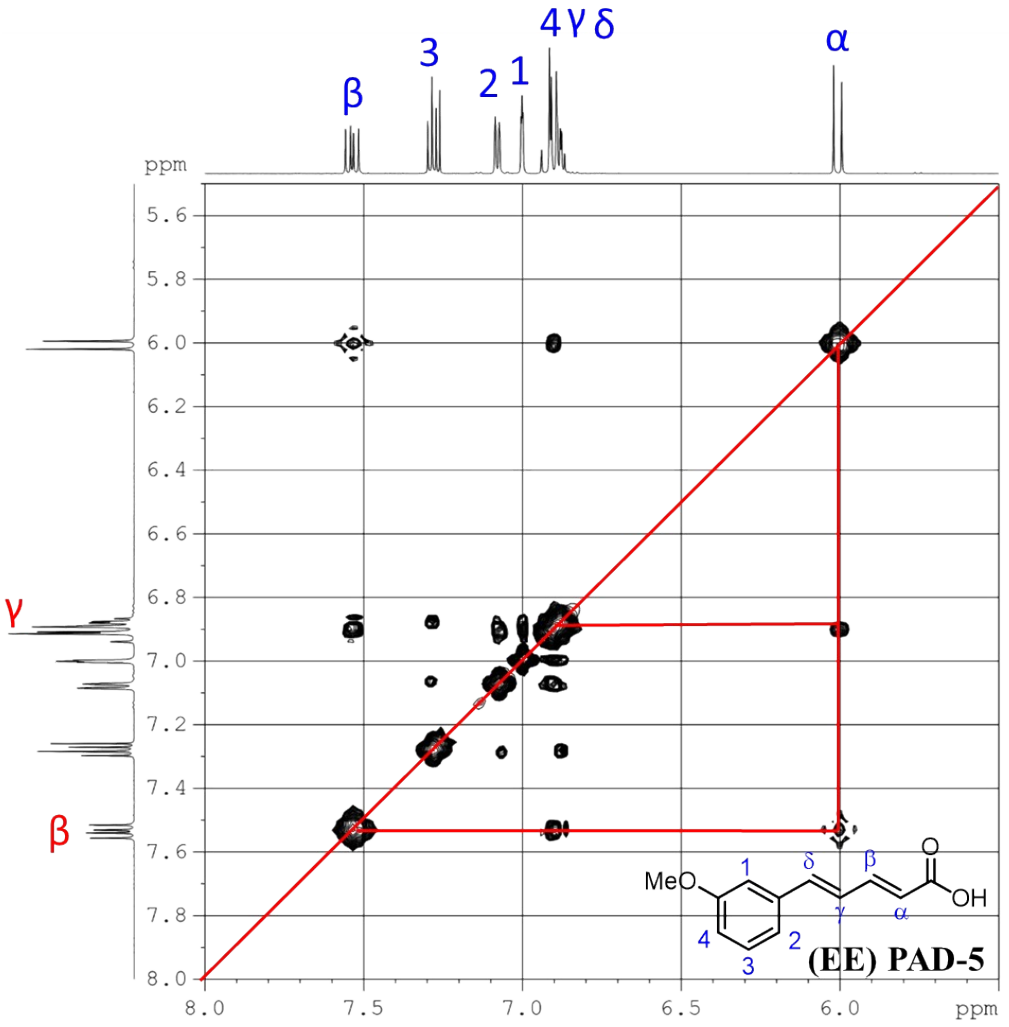


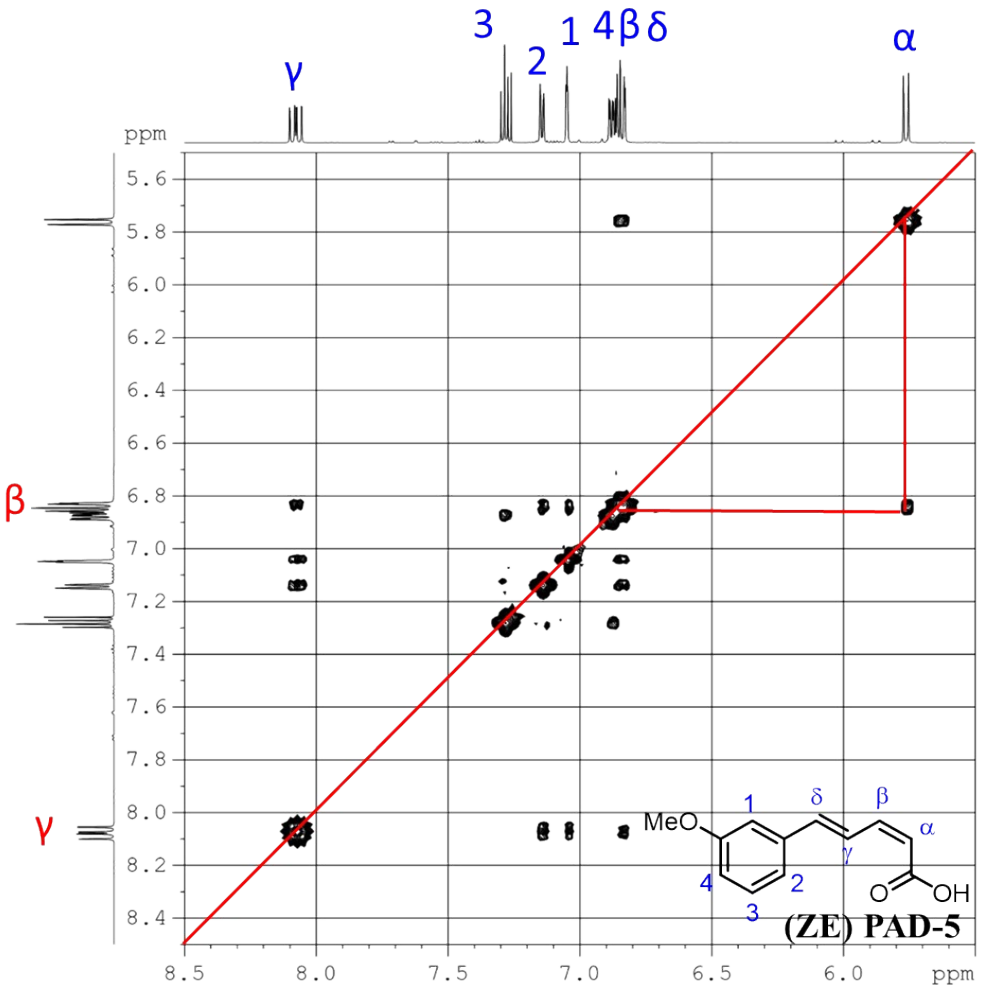
BRUKER

```
NAME          210722-06412
EXPNO                    2
PROCNO                   1
Date_              20210722
Time                   7.33
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                    32768
SOLVENT                DMSO
NS                     1089
DS                        0
SWH               18028.846 Hz
FIDRES            0.550197 Hz
AQ                0.9087659 sec
RG                    219.17
DW                    27.733 usec
DE                     6.50 usec
TE                    312.9 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
SFO1             75.4756726 MHz
NUC1                      13C
P1                      10.00 usec
SI                       32768
SF               75.4677680 MHz
WDW                         EM
SSB                          0
LB                     0.50 Hz
GB                           0
PC                        1.00
```



PAD-13b


β
3
2 1
4γδ
α
ppm
γ
β
MeO
OH
(EE) PAD-5


γ
3
2
1
4βδ
α
ppm
β
γ
MeO
OH
(ZE) PAD-5