Supporting Information

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General Comments

Commercially available chemicals were used as received. Dry solvents were dried using activated 3 Å molecular sieves or from commercial sources. PBS buffer was purchased from Carl Roth (Roti-CELL 10x PBS CELLPURE, pH 7.3–7.5).

Tritylium tetrafluoroborate[1], tropylium tetrafluoroborate[1] and tropone[2] were prepared following literature procedures.

Solid-Phase Peptide Synthesis was performed on a Liberty Blue Peptide Synthesizer (CEM). The following protected amino acids were dissolved in DMF: Fmoc-Ala-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Asp(O^{t}Bu)-OH, Fmoc-Glu(O^{t}Bu)-OH, Fmoc-Gly-OH, Fmoc-His(Boc)-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Phe-OH, Fmoc-Pro-OH, Fmoc-Ser(O^{t}Bu)-OH, Fmoc-Thr(O^{t}Bu)-OH, Fmoc-Tyr(O^{t}Bu)-OH, Fmoc-Val-OH, Fmoc-Lys(Alloc)-OH and Boc-Ala-OH.

Flash column chromatography was performed using silica gel (pore size 60 Å, 400 mesh, 40-63 µm particle size) on a Biotage Isolera One using eluent gradients or by manual flash column chromatography.

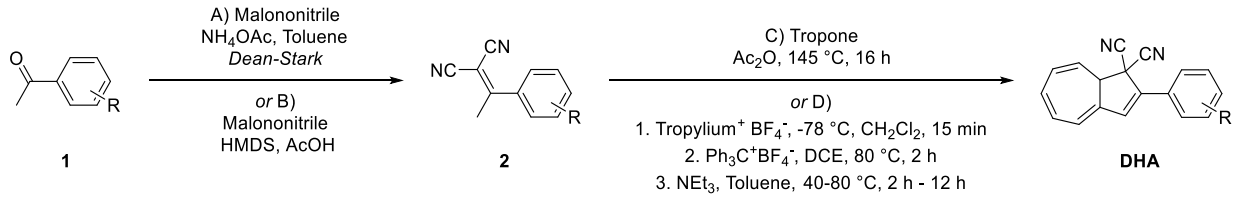
^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance Neo 400, Avance III HD 400, Avance III 400 or Avance III HD 300 at 25 °C. Chemical shifts (δ) are given in parts per million (ppm) relative to the residual solvent signal (for ^{1}H detection, δ = 7.26 ppm ($CDCl_3$), 1.94 (CD_3CN), 3.31 (CD_3OD), 2.50 (DMSO-d6); for ^{13}C detection, δ = 77.16 ppm ($CDCl_3$), 1.32 ppm (CD_3CN), 49.00 (CD_3OD), 39.25 (DMSO-d6). The splitting pattern of peaks is designated as followed: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), or combinations of these signals. ^{13}C APT NMR is indicated with a (+) for positive or upwards pointing signals with an odd number of attached protons and is indicated (-) for negative or downwards pointing signals. Coupling constants (*J*) are given in Hz. NMR irradiation experiments were performed with NMR samples in CD_3CN or CD_3OD at 2 µM. The samples were irradiated with a 365 nm LED (1.2 A) shielded from ambient light and immediately analysed.

LC-MS was performed on an Agilent 1260 Infinity II combined with an InfinityLab LC/MSD iQ mass detector (ESI) using an InfinityLab Poroshell 120 EC-C18 column at 40 °C eluted with MeCN/H_2O + 0.1% formic acid.

Absorption spectroscopy was done on a Specord S600 or Jasco V-670 in quartz cuvettes (path 1.00 cm) at a controlled temperature of 20 °C. Irradiation was performed with a home-built LED setup at a fixed distance, orthogonal to the detector light path. Molar attenuation coefficients (ε) were determined by fitting the slope of absorbance vs. concentration taken from at least three separate dilutions.

Computational details can be found in the experimental section of the body text.

Synthetic Details



Scheme S1. Synthesis routes towards the dihydroazulene switches.

Synthesis of malononitrile-condensed products (2)

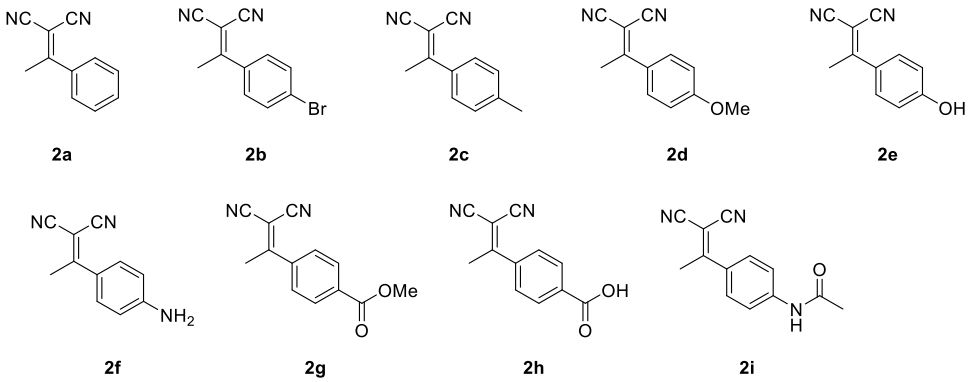


Figure S1. Used malononitrile-condensed products.

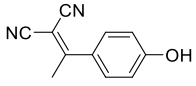
Method A

In an adapted literature procedure,[3] the appropriate acetophenone (**1**, 1.0 equiv.) and malononitrile (2.8 equiv.) were dissolved in toluene (M) and a solution of ammonium acetate (3.4 equiv.) in acetic acid (6.5 equiv.) was added. The mixture was heated at reflux using a Dean-Stark apparatus to remove the formed water. After completion of the reaction (TLC), the mixture was allowed to cool to room temperature, diluted with Et_2O and washed subsequently with water, saturated Na_2CO_3 and brine. Volatiles were removed under reduced pressure. The obtained malononitrile-condensed products (**2**) could be used directly in the next transformation.

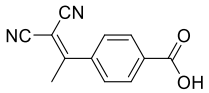
Method B

Hexamethyldisilazane (1.2 equiv.) was slowly added to stirring acetic acid (2 M) at room temperature using a water bath. The mixture was stirred for 15 minutes and transferred to a solution of the appropriate acetophenone (**1**, 1.0 equiv.) and malononitrile (2.0 equiv.) in acetic acid (3 M). The reaction mixture was stirred at 70 °C for 16 h. The mixture was poured onto water and extracted with CH_2Cl_2. The organic phase was washed with $NaHCO_3$ and brine and the obtained malononitrile-condensed products could be used directly in the subsequent transformation.

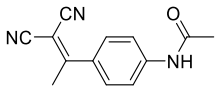
Compounds **2a**,[4] **2c**,[5] and **2d**[4] were obtained via Method A and NMR analysis was in agreement with literature. Compounds **2b**,[4] **2g**[6] and **2f**[5] were obtained via Method B and NMR analysis was in agreement with literature.



2-(1-(4-hydroxyphenyl)ethylidene)malononitrile (**2e**).
Compound **2e** was obtained via method A starting from 4-hydroxy acetophenone (5.48 g, 40.3 mmol) and obtained as a yellow solid in 77% yield (5.70 g, 31.0 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.52 (m, 2H), 6.97 – 6.87 (m, 2H), 5.94 (br s, 1H), 2.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 160.0, 130.2, 128.1, 116.2, 113.8, 113.4, 81.9, 24.0. HRMS (ESI Neg): for $[C_{11}H_8N_2O - H]^-$ calcd. m/z = 183.0564, found m/z = 183.0566.



4-(1,1-dicyanoprop-1-en-2-yl)benzoic acid (**2h**).
Compound 2h was obtained via method B starting from 4-acetylbenzoic acid (4.0 g, 24.3 mmol) and obtained as a pale-yellow solid in 93% yield (4.81 g, 22.7 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.22 (m, 2H), 7.67 – 7.60 (m, 2H), 2.68 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 170.4, 140.9, 132.4, 131.1, 127.6, 112.3, 86.8, 24.5. HRMS (ESI Neg): for $[C_{12}H_8N_2O_2 - H]^-$ calcd. m/z = 211.0513, found m/z = 211.0516.



***N*-(4-(1,1-dicyano-1,8a-dihydroazulen-2-yl)phenyl)acetamide** (**2i**).
2-(1-(4-Aminophenyl)ethylidene)malononitrile (**2f**, 1.0 g, 5.5 mmol, 1.0 equiv.) was suspended in a 1:1 mixture of 1,4-dioxane/water (20 mL, 0.3 M) and acetic anhydride (0.87 mL, 8.5 mmol, 1.5 equiv.) was added. The mixture was heated to 70 °C for 30 min. The mixture was allowed to cool to room temperature and volatiles were removed under reduced pressure. The product was obtained as a pale-yellow powder (75%, 920 mg, 4.1 mmol) and could be used directly in further transformations. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.33 (1H, m), 7.70 (m, 4H), 2.60 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d6, APT) δ 175.8 (+), 169.0 (+), 143.1 (+), 129.9 (+), 129.2 (-), 118.4 (-), 113.71 (+), 81.1 (+), 24.2 (-), 23.8 (-).[5]

Synthesis of dihydroazulenes

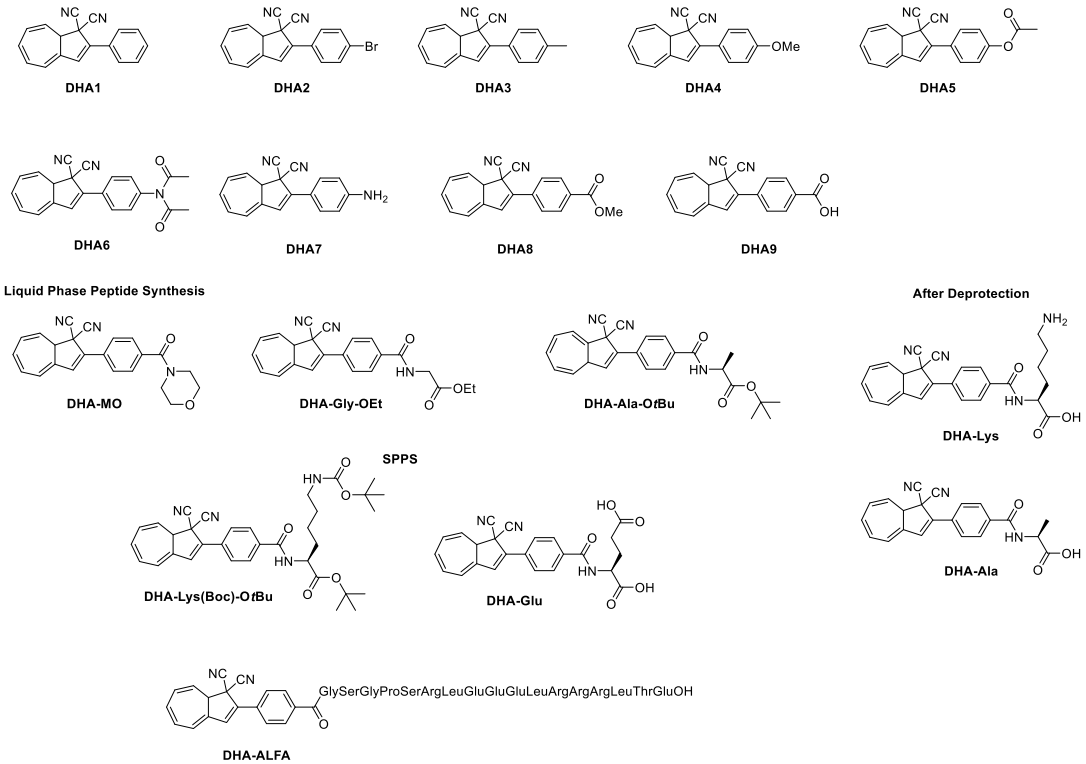


Figure S2. Overview of numbered dihydroazulene targets.

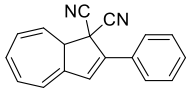
Method C

In an adapted literature procedure,[2] the appropriate malononitrile condensed product (**2**, 1.1 equiv.) and tropone (1.0 equiv.) were added to acetic anhydride (0.2 M). The mixture was heated to 145 °C for 16 h. After the mixture was allowed to cool down, acetic anhydride was removed under reduced pressure with the aid of toluene. The products were purified by flash column chromatography (silica gel, EtOAc/*n*-pentane gradients) followed by trituration and repeated washing with methanol.

Method D

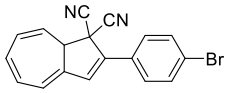
In an adapted literature procedure,[7] the appropriate malononitrile condensed product (**2**) was dissolved in CH_2Cl_2 (0.1 M) and cooled to -78 °C. Tropylium tetrafluoroborate (1.2 equiv.) was added and the mixture was stirred at -78 °C for 15 min. The reaction was quenched by adding 1 M HCl (aq) at -78 °C after which the mixture was allowed to warm up to room temperature. The organic and aqueous phase were separated, the aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were washed with water and brine.

The crude cycloheptatrienyl intermediate (1.0 equiv.) and trityl tetrafluoroborate (1.1 equiv.) were dissolved in 1,2-dichloroethane (0.2 M) and heated to 80 °C for 2 h. The reaction mixture is cooled to 0 °C and first toluene (0.4 M) was added followed by the slow addition of NEt_3 (1.0 equiv.). The reaction mixture is heated to 40 °C for 12 h *or* 80 °C for 2 h to ensure completion of the thermal ring closing reaction. The product is purified by flash column chromatography (silica gel, EtOAc/*n*-pentane gradient) followed by trituration and repeated washing with MeOH.



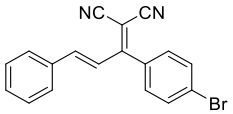
2-Phenylazulene-1,1(8aH)-dicarbonitrile (**DHA1**).

DHA1 was synthesised via method C starting from 2-(1-phenylethylidene)malononitrile (**2a**, 344 mg, 2.0 mmol) and obtained as a yellow powder in 15% yield (79 mg, 0.3 mmol). R_f = 0.53 (EtOAc/*n*-pentane, 1:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.46 (m, 3H), 6.89 (s, 1H), 6.57 (dd, *J* = 11.3, 6.3 Hz, 1H), 6.48 (dd, *J* = 11.3, 6.0 Hz, 1H), 6.38 – 6.26 (m, 2H), 5.83 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.79 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, APT) δ 140.3 (-), 138.8 (-), 132.5 (+), 131.0 (+), 131.0 (-), 130.6 (+),130.2 (+), 129.4 (+),127.8 (+), 126.4 (+), 121.1 (+), 119.6 (+), 115.3 (-), 112.9 (-), 51.3 (+), 45.3 (-). HRMS (ESI Pos): for [$C_{18}H_{12}N_2$ + H] calcd. m/z = 230.0964, found m/z = 230.0969; for [$C_{18}H_{12}N_2$ + Na]$^+$ calcd. m/z = 279.0893, found m/z = 279.0900.

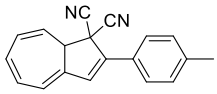


2-(4-Bromophenyl)azulene-1,1(8aH)-dicarbonitrile (**DHA2**).

DHA2 was synthesised via method C from 2-[1-(4-bromophenyl) ethylidene] malononitrile (**2b**, 1.9 g, 7.7 mmol) and obtained as a yellow powder in 17% yield (409 mg, 1.2 mmol). R_f = 0.39 (EtOAc/*n*-pentane, 1:7). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 4H), 6.88 (s, 1H), 6.54 (m, 2H), 6.33 (m, 2H), 5.81 (1H, dd, J = 10.3, 3.8 Hz), 3.79 (1H, dt, J = 4.1, 2.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, APT) δ 139.1 (-), 138.5 (-), 133.1 (+), 132.6 (+), 131.3 (+), 131.0 (+), 129.5 (-), 127.9 (+), 127.8 (+), 124.5 (-), 121.6 (+), 119.6 (+), 115.1 (-), 112.7 (-), 51.2 (+), 45.3 (-). HRMS (ESI Pos): for [$C_{18}H_{11}BrN_2$ + Na]$^+$ calcd. m/z = 356.9998, found m/z = 356.9992.

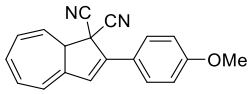


During the synthesis of **DHA2** a side product (*E*)-2-(1-(4-bromophenyl)-3-phenylallylidene)malononitrile (**3**) was observed, which could be crystallized and analyzed by X-ray crystallography (see page 62 of this Supporting Information). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 15.4 Hz, 1H), 7.55 – 7.52 (m, 2H), 7.46 – 7.42 (m, 3H), 7.29 – 7.26 (m, 2H), 6.87 (d, *J* = 15.4 Hz, 1H).



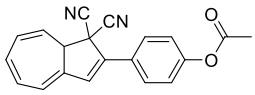
2-(*p*-Tolyl)azulene-1,1(8aH)-dicarbonitrile (**DHA3**).

DHA3 was synthesised via method C from 2-[1-(4-methylphenyl) ethylidene] malononitrile (**2c**, 1.6 g, 8.7 mmol) and obtained as a yellow powder in 11% yield (221 mg, 0.82 mmol). R_f = 0.61 (*n*-pentane:ethyl acetate, 7:1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 2H), 7.28 (dd, *J* = 8.5, 1.9 Hz, 2H), 6.84 (d, *J* = 1.6 Hz, 1H), 6.57 (dd, *J* = 11.3, 6.3 Hz, 1H), 6.46 (dd, *J* = 11.4, 6.0 Hz, 1H), 6.30 (m, 2H), 5.82 (m, 1H), 3.78 (m, 1H), 2.41 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$, APT) δ 140.6 (-), 140.4 (-), 139.0 (-), 131.5 (+), 131.1 (+), 130.7 (+), 130.1 (+), 127.8 (-), 127.7 (+), 126.3 (+), 120.6 (+), 119.6 (+), 115.4 (-), 113.0 (-), 51.3 (+), 45.3 (-), 21.5 (+). HRMS (ESI Pos): for $[C_{19}H_{14}N_2 + Na]^+$ calcd. m/z = 293.1049, found m/z = 293.1037.



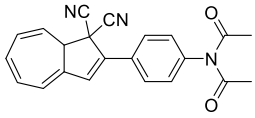
2-(4-Methoxyphenyl)azulene-1,1(8aH)-dicarbonitrile (**DHA4**).

DHA4 was synthesised via method C from 2-[1-(4-methoxyphenyl) ethylidene] malononitrile (**2d**, 350 mg, 1.77 mmol) and obtained as a yellow powder in 22% yield (100 mg, 0.35 mmol) Rf = 0.39 (*n*-pentane:ethyl acetate, 7:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 2H), 6.99 (m, 2H), 6.76 (d, J = 1.4 Hz, 1H), 6.55 (dd, *J* = 11.3, 6.4 Hz, 1H), 6.30 (m, 2H), 5.81 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.86 (s, 3H), 3.78 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, APT) δ 161.1 (-), 140.1 (-), 139.2 (-), 131.1 (+), 130.4 (+), 130.3 (+), 128.0 (+), 127.8 (+), 123.2 (-), 120.1 (+), 119.4 (+), 115.4 (-), 114.8 (+), 113.0 (-), 55.6 (+), 51.28 (+), 45.4 (-). HRMS (ESI Pos): for $[C_{19}H_{14}N_2O_1 + Na]^+$ calcd. m/z = 309.0998, found m/z = 309.0993.



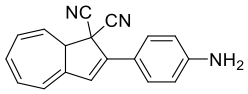
4-(1,1-Dicyano-1,8a-dihydroazulen-2-yl)phenyl acetate (**DHA5**).

DHA5 was synthesised via method C from 2-[1-(4-hydroxyphenyl) ethylidene] malononitrile (**2e**, 1.7 g, 9.4 mmol), whereupon acetylation of the phenol moiety occurred. The product was obtained as a yellow powder in 6% yield (137 mg, 0.44 mmol). R_f = 0.19 (*n*-pentane:ethyl acetate, 7:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.24 (m, 2H), 6.85 (s, 1H), 6.57 (dd, *J* = 11.3, 6.3 Hz, 1H), 6.48 (dd, *J* = 11.2, 6.0 Hz, 1H), 6.32 (m, 2H), 5.81 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.79 (m, 1H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, APT) δ 169.2 (-), 152.0 (-), 139.3 (-), 138.7 (-), 132.7 (+), 131.1 (+), 131.0 (+), 128.3 (-), 127.8 (+),127.6 (+), 122.7 (+), 121.3 (+), 119.6 (+), 115.2 (-), 112.8 (-), 51.3 (+), 45.4 (-), 21.3 (+). HRMS (ESI Pos): for $[C_{20}H_{14}N_2O_2 + Na]^+$ calcd. m/z = 337.0947, found m/z = 337.0948.



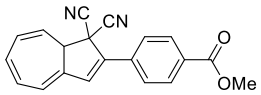
***N*-acetyl-N-(4-(1,1-dicyano-1,8a-dihydroazulen-2-yl)phenyl)acetamide** (**DHA6**).

DHA6 was synthesised from *N*-(4-(1,1-dicyano-1,8a-dihydroazulen-2-yl)phenyl)acetamide (**2i**, 2.34 g, 10.4 mmol) via method C, whereupon an additional acetylation reaction occurred on the monoacetylated aniline functional group. The product was obtained as a yellow powder in 9% yield (323 g, 0.85 mmol). R_f = 0.79 (*n*-pentane:ethyl acetate, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.27 (m, 2H), 6.94 (s, 1H), 6.56 (m, 2H), 6.35 (m, 3H), 5.83 (d, *J* = 10.1 Hz, 1H), 3.81 (dd, *J* = 3.9, 2.0 Hz, 1H), 2.33 (s, *J* = 1.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, APT) δ 172.8 (-), 140.8 (-), 138.7 (-), 138.3 (-), 133.9 (+), 131.6 (+), 131.3 (-), 131.0 (+), 129.9 (+), 127.9 (+), 127.7 (+), 122.0 (+), 119.6 (+), 115.0 (-), 112.6 (-), 51.3 (+), 45.3 (-), 27.1 (+). HRMS (ESI Pos): for $[C_{22}H_{17}N_3O_2 + Na]$ calcd. m/z = 378.1213, found m/z = 378.1207.



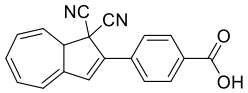
2-(4-Aminophenyl)azulene-1,1(8aH)-dicarbonitrile (**DHA7**).

N-acetyl-N-(4-(1,1-dicyano-1,8a-dihydroazulen-2-yl)phenyl)acetamide (**DHA6**, 0.2 g, 0.6 mmol, 1.2 equiv.) was taken up in a mixture of 12 mL HCl (aq, 6 M) and EtOH (12 mL) and the reaction mixture was heated at reflux for 20 min. Afterwards, the mixture was allowed to cool down to room temperature and was neutralized by slow addition of saturated $NaHCO_3$ (aq). The aqueous phase was thrice extracted with Et_2O and the combined organic phases were washed with water and brine, dried over Na_2SO_4 and volatiles were removed under reduced pressure. The product was purified by trituration from methanol and obtained as a brown powder in 88% yield (0.1 g, 0.5 mmol). R_f = 0.83 (EtOAc/*n*-pentane, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 2H), 6.73 – 6.70 (m, 2H), 6.68 (s, 1H), 6.54 (dd, *J* = 11.2, 6.4 Hz, 1H), 6.41 (dd, *J* = 11.2, 6.1 Hz, 1H), 6.35 – 6.19 (m, 2H), 5.80 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.81 – 3.67 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, APT) δ 148.4 (-), 140.7 (-), 139.6 (-), 131.2 (+), 129.9 (+), 128.5 (+), 127.9 (+), 127.7 (+), 120.6 (+), 119.3 (+), 119.2 (+),115.6 (+),115.2 (+), 113.2 (+), 51.3 (+), 45.2 (+). HRMS (ESI Pos): for $[C_{18}H_{13}N_3 + H]^+$ calcd. m/z = 272.1182, found m/z = 272.1187.



Methyl 4-(1,1-dicyano-1,8a-dihydroazulen-2-yl)benzoate (**DHA8**).

DHA8 was synthesized via method D starting from methyl 4-(1,1-dicyanoprop-1-en-2-yl)benzoate (**2g**, 2.1 g, 9.4 mmol) and obtained as a yellow powder in 32% yield (950 mg, 3.0 mmol). ^{1}H NMR (400 MHz, CH_3CN) δ 8.11 (d, *J* = 8.6 Hz, 2H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.26 (s, 1H), 6.66 – 6.58 (m, 1H), 6.57 – 6.46 (m, 2H), 6.40 – 6.31 (m, 1H), 5.80 (dd, *J* = 10.4, 3.9 Hz, 1H), 3.94 – 3.87 (m, 3H). ^{13}C NMR (101 MHz, CH_3CN) δ 166.9, 139.4, 139.2, 136.7, 135.8, 132.3, 132.0, 131.8, 131.1, 128.6, 127.3, 123.7, 120.9, 116.0, 113.9, 52.9, 51.9, 46.2. HRMS (ESI Neg): for $[C_{20}H_{13}N_2O_2]^-$ calcd. m/z = 313.0983, found m/z = 313.0984.



4-(1,1-Dicyano-1,8a-dihydroazulen-2-yl)benzoic acid (**DHA9**).

DHA9 was synthesised via method C starting from 4-(1,1-dicyanoprop-1-en-2-yl)benzoic acid (**2h**, 1.05 g, 5.0 mmol) and obtained as a yellow powder in 20% yield (290 mg, 0.97 mmol). ^{1}H NMR (400 MHz, DMSO-d6) δ 13.19 (br s, 1H), 8.09 (d, *J* = 8.3 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.62 (s, 1H), 6.65 – 6.58 (m, 1H), 6.56 – 6.48 (m, 2H), 6.37 (ddd, *J* = 10.4, 6.1, 2.3 Hz, 1H), 5.74 (dd, *J* = 10.3, 3.5 Hz, 1H), 4.02 – 3.95 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d6) δ 166.6, 138.2, 137.5, 136.2, 134.1, 131.4, 131.4, 130.8, 130.2, 127.6, 126.1, 122.9, 119.9, 114.9, 112.9, 50.5, 45.0. HRMS (ESI Neg): for $[C_{19}H_{11}N_2O_2]^-$ calcd. m/z = 299.0826, found m/z = 299.0833.

<u>Synthesis of amino acid- and peptide functionalised dihydroazulenes</u>

Method E - Solid-Phase Peptide Synthesis of DHA-amino acid conjugates

Initial Fmoc-deprotection of the resin-bound AA was performed with a 20% solution of piperidine in NMP. The resin-filled syringe was filled with 2 mL of deprotecting solution and left shaking for 10 minutes. The solvent was eliminated, and the procedure was repeated once. The resin was then washed with NMP/DCM/NMP (3x).

The synthesis of the **DHA-AA** conjugates (on a 0.04 mmol scale) was carried out on a preloaded Fmoc-**AA**-Wang resin (0.30 mmol/g loading). **DHA-9** (2.5 equiv.), DEPBT (2.5 equiv.) and DIPEA (5.0 equiv.) were dissolved in NMP (800 µL) and added to the resin-filled BD-syringe. The reaction mixture was left shaking for 2 h at rt, then washed with NMP/DCM/NMP (3x).

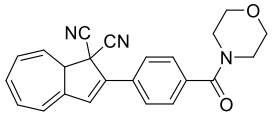
The cleavage of the **DHA-AA** conjugates from the resin was performed in a BD syringe with a PE frit. The resin was shaken at room temperature for 2 h in a TFA/TIS/H_2O solution (95:2.5:2.5, *v/v/v*). After cleavage the

solution was concentrated under a nitrogen stream and the crude compound was precipitated with diethyl ether. The crude compound was isolated by centrifugation (9000 rpm, -10 °C, 10 min), washed two times with ether and dried under reduced pressure.

The **DHA-AA** conjugates were purified by reverse-phase column chromatography (Biotage Isolera One, with Biotage Sfär C18 Duo 100 Å, 30 µm, MeCN/H_2O gradients with 0.1% formic acid).

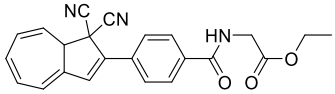
Method F (Liquid phase)

Liquid phase synthesis of the **DHA-AA** conjugates was performed by dissolving the **NH_2-AA-OtBu** (1 equiv.), **DHA-9** (1 equiv.), and DEBPT (1.1 equiv.) in THF. The reaction was cooled down to 0 °C to prevent possible racemization of the amino acid, and NEt_3 was added. After 30 min at 0 °C, the reaction was left stirring at rt overnight. Volatiles were evaporated and the DHA-AA products were purified by reverse-phase column chromatography (Biotage Isolera One, with Biotage Sfär C18 Duo 100 Å, 30 µm, MeCN/H_2O gradients with 0.1% formic acid).



4-(4-(1,1-Dicyano-1,8a-dihydroazulen-2-yl)benzoyl)morpholin-4-ium (**DHA-MO**).

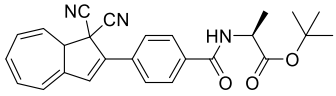
DHA-MO was synthesised via method F starting from **DHA-9** (20 mg, 0.067 mmol) and obtained as a yellow powder in 5% yield (2.34 mg, 0.006 mmol). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.98 – 7.91 (AA'BB', 2H), 7.63 – 7.56 (AA'BB', 2H), 7.32 (s, 1H), 6.65 (dd, *J* = 11.3, 6.3 Hz, 1H), 6.59 – 6.49 (m, 2H), 6.37 (ddd, *J* = 10.3, 6.1, 2.3 Hz, 1H), 5.82 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.84 – 3.43 (m, 8H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 170.1, 138.7, 138.6, 136.1, 134.3, 132.3, 130.9, 130.6, 127.4, 126.2, 122.0, 119.4, 115.0, 112.7, 66.4, 51.1, 45.2. HRMS (ESI Pos): for $[C_{23}H_{20}N_3O_2]^+$ calcd. m/z = 370.1550, found m/z = 370.1539.



Ethyl (4-(1,1-dicyano-1,8a-dihydroazulen-2-yl)benzoyl)glycinate (**DHA-Gly-OEt**).

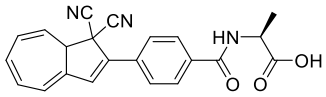
DHA-Gly-OEt was synthesised via method F starting from **DHA-9** (20 mg, 0.067 mmol) and obtained as a yellow powder in 10% yield (2.55 mg, 0.0066 mmol).

^{1}H NMR (400 MHz, MeOD) δ 8.01 – 7.97 (m, 2H), 7.96 – 7.90 (m, 2H), 7.34 (s, 1H), 6.63 (dd, *J* = 11.3, 6.3 Hz, 1H), 6.59 – 6.48 (m, 2H), 6.40 – 6.30 (m, 1H), 5.81 (dd, *J* = 10.3, 3.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 3H), 4.13 (s, 2H), 3.85 (dt, *J* = 3.9, 2.0 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.4, 169.5, 140.1, 136.2, 135.8, 135.2, 132.4, 132.0, 129.3, 128.8, 127.5, 123.6, 120.8, 116.4, 114.1, 62.4, 52.5, 46.6, 42.6, 14.5. MS (LCMS, ESI Neg): for $[C_{23}H_{18}N_3O_3]^-$ calcd. m/z = 384.1, found m/z = 384.1, HRMS (ESI Pos): for $[C_{23}H_{19}N_3O_3 + Na]^+$ calcd. m/z = 408.1319, found m/z = 408.1306.



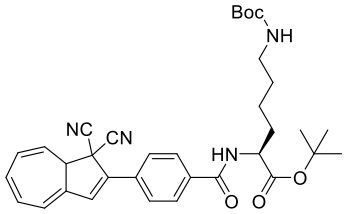
***Tert*-butyl (4-(1,1-dicyano-1,8a-dihydroazulen-2-yl)benzoyl)-L-alaninate** (**DHA-Ala-O*t*Bu**).

DHA-Ala-O*t*Bu was synthesised via method F starting from **DHA-9** (20 mg, 0.067 mmol) and obtained as a yellow powder in 20% yield (5.38 mg, 0.001 mmol). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.02 – 7.97 (AA'BB', 2H), 7.95 – 7.89 (AA'BB', 2H), 7.34 (s, 1H), 6.65 (dd, *J* = 11.3, 6.3 Hz, 1H), 6.59 – 6.49 (m, 2H), 6.36 (ddd, *J* = 10.3, 6.1, 2.2 Hz, 1H), 5.83 (dd, *J* = 10.3, 3.7 Hz, 1H), 4.51 (q, *J* = 7.3 Hz, 1H), 3.86 (dt, *J* = 3.9, 2.0 Hz, 1H), 1.50 (Me and ^{t}Bu, 12H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 172.2, 167.7, 138.7, 138.6, 134.7, 134.6, 133.7, 130.9, 130.6, 127.9, 127.4, 126.0, 122.1, 119.4, 115.0, 112.7, 81.3, 51.1, 49.6, 45.2, 26.8, 15.8. HRMS (ESI Pos): for $[C_{26}H_{25}N_3NaO_3]^+$ calcd. m/z = 450.1788, found m/z = 450.1782.



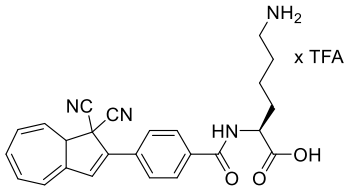
(4-(1,1-Dicyano-1,8a-dihydroazulen-2-yl)benzoyl)-L-alanine (**DHA-Ala**).

DHA-Ala was synthesised from **DHA**-**Ala-tBu** (5.38 mg, 0.013 mmol). The starting material was dissolved in DCM (300 µL) and treated with TFA (50 µL) and stirred at ambient temperature overnight. After evaporation of the solvents, the product was obtained as a yellow powder in *quant*. yield (2.1 mg, 0.013 mmol). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.05 – 7.98 (AA'BB', 2H), 7.97 – 7.91 (AA'BB', 2H), 7.35 (s, 1H), 6.65 (dd, *J* = 11.3, 6.3 Hz, 1H), 6.59 – 6.50 (m, 2H), 6.37 (ddd, *J* = 10.3, 6.1, 2.2 Hz, 1H), 5.83 (dd, *J* = 10.3, 3.7 Hz, 1H), 4.64 (q, *J* = 7.3 Hz, 1H), 3.87 (dt, *J* = 4.0, 2.0 Hz, 1H), 2.05 (s, 1H), 1.56 (d, *J* = 7.3 Hz, 3H). Due to the small amount of sample, a Carbon NMR could not be obtained. HRMS (ESI Pos): for $[C_{22}H_{17}N_3NaO_3]^+$ calcd. m/z = 394.1162, found m/z = 394.1164.



tert-butyl N6-(tert-butoxycarbonyl)-N2-(4-(1,1-dicyano-1,8a-dihydroazulen-2-yl)benzoyl)-L-lysinate (**DHA-Lys(Boc)-O*t*Bu**).

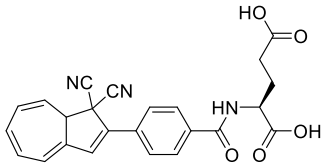
DHA-Lys(Boc)-O*t*Bu was synthesised via method F starting from **DHA**-**9** (20 mg, 0.067 mmol) and obtained as a yellow powder in 5% yield (1.82 mg, 0.003 mmol). ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.07 – 7.81 (2 x AA'BB', 4H), 7.35 (s, 1H), 6.68 – 6.50 (m, 3H), 6.44 – 6.28 (m, 1H), 5.83 (dd, *J* = 10.2, 3.7 Hz, 1H), 4.60 (s, 2H), 4.48 (dd, *J* = 8.8, 5.5 Hz, 1H), 3.87 (dd, *J* = 3.7, 1.9 Hz, 1H), 3.16 – 2.94 (m, 2H), 2.03 – 1.77 (m, 2H), 1.51 (s, 9H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, Methanol-d_4) δ 171.7, 168.1, 138.7, 138.6, 134.8, 134.6, 133.7, 130.9, 130.6, 128.0, 127.4 , 126.0, 122.1, 119.4, 115.0, 112.7, 81.5, 78.5, 53.9, 51.1, 45.2, 39.6, 30.6, 29.2, 27.4, 26.9, 23.0, one quaternary carbon atom could not be resolved. HRMS (ESI Pos): for $[C_{34}H_{40}N_4NaO_5]^+$ calcd. m/z = 607.2891, found m/z = 607.2884.



(4-(1,1-Dicyano-1,8a-dihydroazulen-2-yl)benzoyl)-L-lysine x TFA (**DHA-Lys**).

DHA-Lys was synthesised from **DHA**-**Lys(Boc)-tBu** (1.82 mg, 0.003 mmol). The starting material was dissolved in DCM (300 µL) and treated with TFA (50 µL) and stirred at ambient temperature overnight. After evaporation of the solvents, the product was obtained as a yellow powder in 90% yield (1.53 mg, 0.003 mmol). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.05 – 7.97 (AA'BB', 2H), 7.97 – 7.92 (AA'BB', 2H), 7.36 (s, 1H), 6.66 (dd, *J* = 11.3, 6.2 Hz, 1H), 6.54 (td, *J* = 7.1, 5.9, 3.3 Hz, 2H), 6.37 (ddd, *J* = 10.3, 6.1, 2.3 Hz, 1H), 5.83 (dd, *J* = 10.2, 3.7 Hz, 1H), 4.68 (dd, *J* = 9.6, 4.9 Hz, 1H), 3.87 (dt, *J* = 3.9, 2.0 Hz, 1H), 2.97 (td, *J* = 8.3, 7.8, 2.5 Hz, 2H), 2.15 – 1.86 (m, 2H), 1.84 – 1.69 (m, 2H), 1.59 (dtd, *J* = 8.9, 5.8, 2.4 Hz, 2H). ^{1}H-NMR analysis showed a small amount of protected material left. Due to the small amount of sample, a Carbon NMR could not be obtained.

HRMS (ESI Pos): for $[C_{25}H_{25}N_4O_3]^+$ calcd. m/z = 429.1921, found m/z = 429.1923.



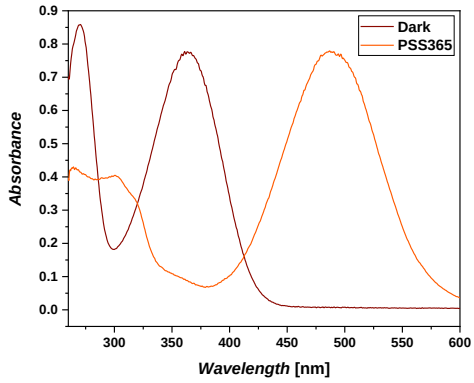
(4-(1,1-dicyano-1,8a-dihydroazulen-2-yl)benzoyl)-L-glutamic acid (**DHA-Glu**).

DHA-Glu was synthesised via method E starting from **DHA**-**9** (20 mg, 0.067 mmol) and obtained as a yellow powder in 10% yield (2.84 mg, 0.007 mmol). ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.05 – 7.99 (AA'BB', 2H), 7.97 – 7.92 (AA'BB', 2H), 7.35 (s, 1H), 6.66 (dd, *J* = 11.4, 6.3 Hz, 1H), 6.55 (dd, *J* = 11.8, 6.0 Hz, 2H), 6.43 – 6.27 (m, 1H), 5.83 (dd, *J* = 10.2, 3.7 Hz, 1H), 4.68 (dd, *J* = 9.4, 4.9 Hz, 1H), 3.92 – 3.74 (m, 1H), 2.53 (t, *J* = 7.4 Hz, 2H), 2.45 – 2.02 (m, 2H). Due to the small amount of sample, a Carbon NMR could not be obtained. HRMS (ESI Neg): for $[C_{24}H_{18}N_3O_5]^-$ calcd. m/z = 428.1252, found m/z = 428.1248.

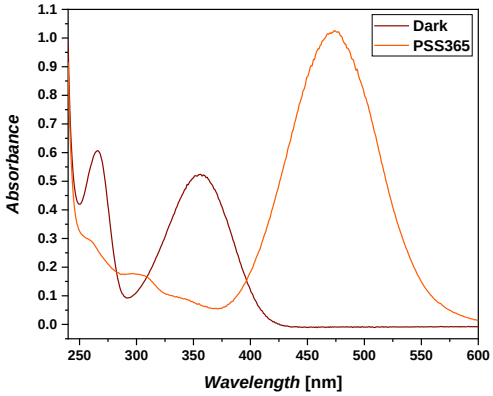
UV-Vis spectra

Absorbance spectra of the dihydroazulenes in the indicated solvents at 33 µM before (Dark) and after irradiation with 365 nm LED until no change to the spectrum was observed (PSS365).

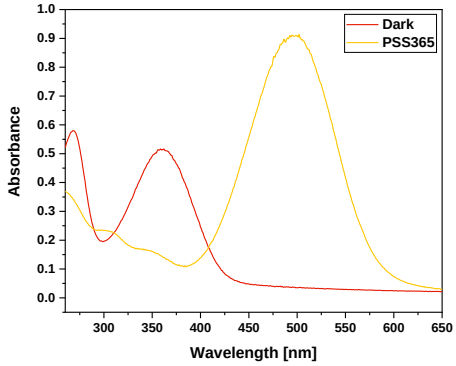
DHA1



DMSO

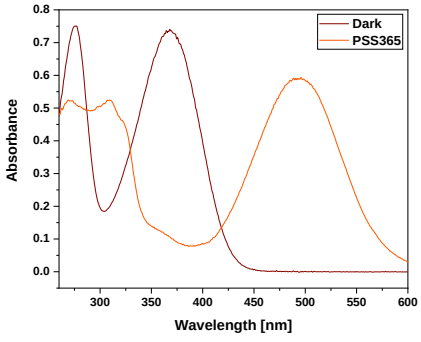


MeCN



PBS Buffer

DHA2



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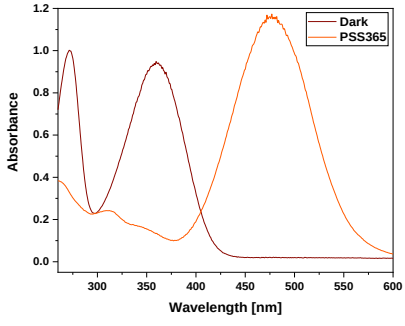

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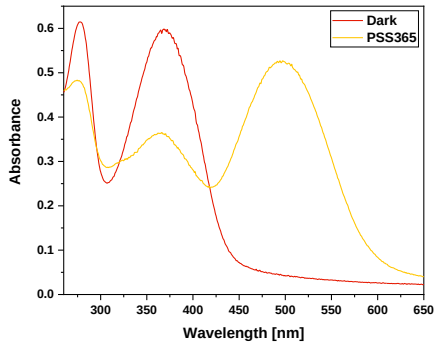
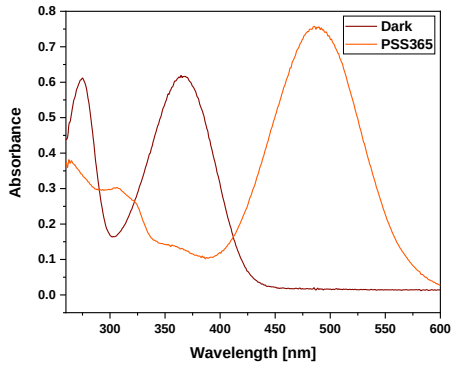


PBS Buffer

DHA3



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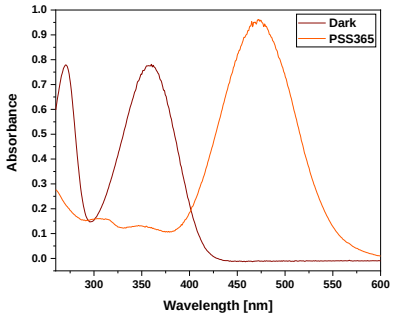

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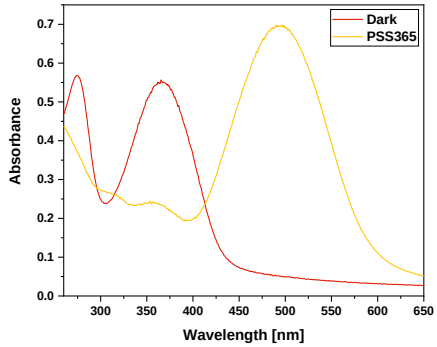
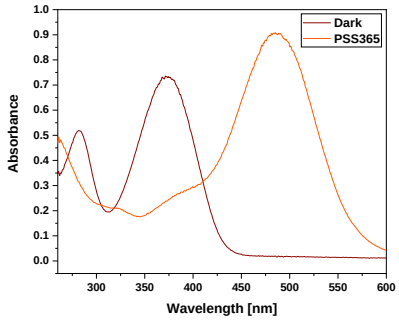


PBS Buffer

DHA4



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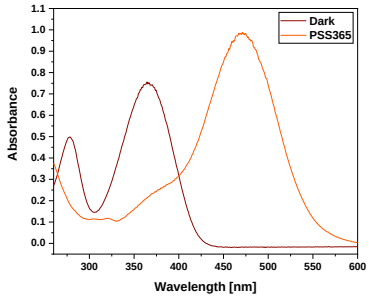
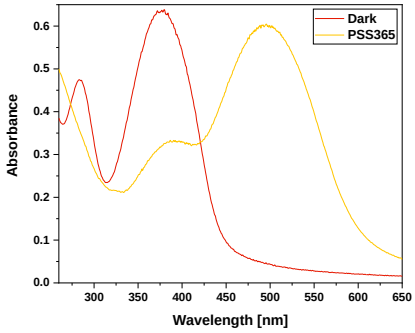
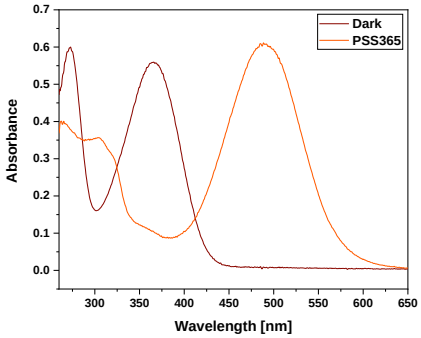


MeCN



PBS Buffer

DHA5



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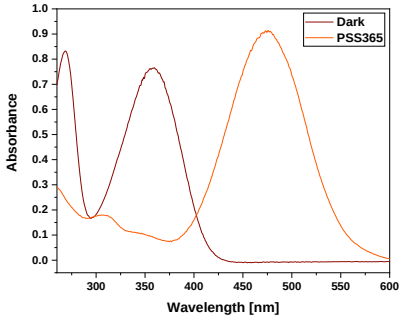
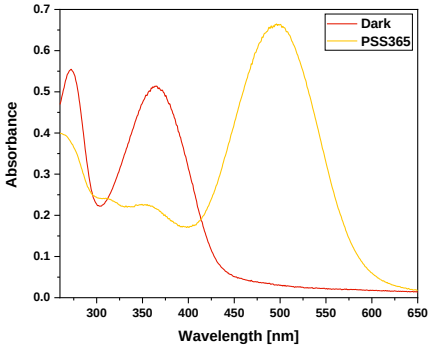
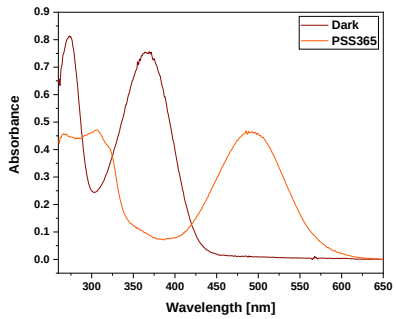


MeCN

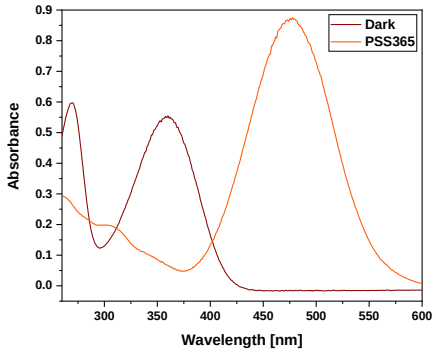


PBS Buffer

DHA6



DMSO



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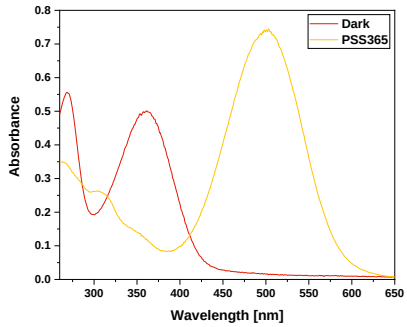
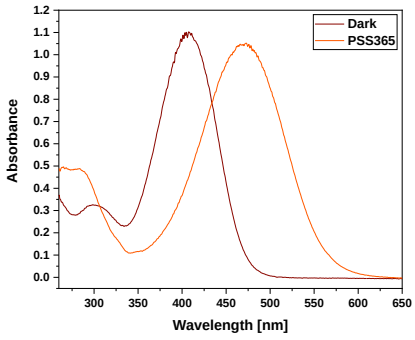
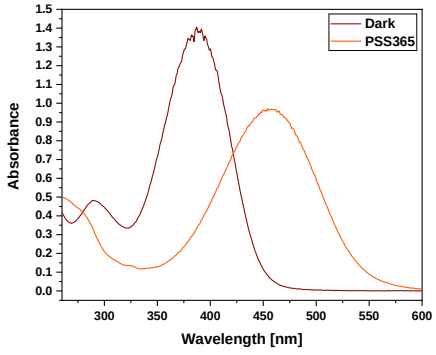


PBS Buffer

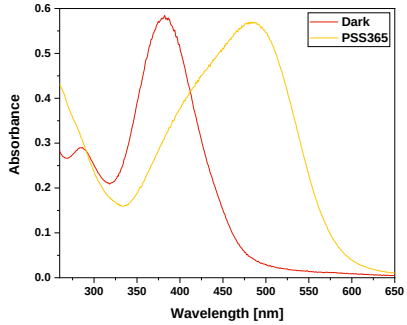
DHA7



DMSO

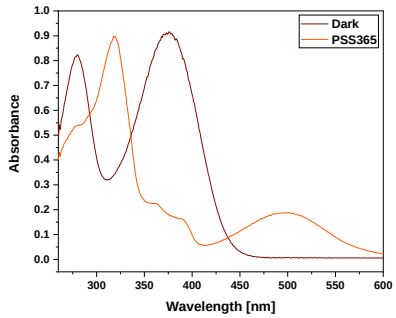


MeCN



PBS Buffer

DHA8



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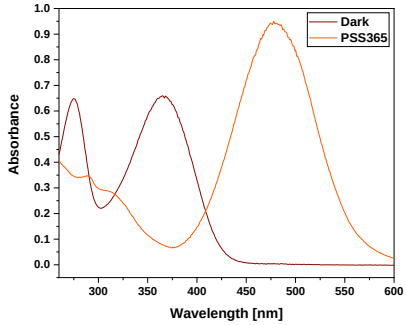

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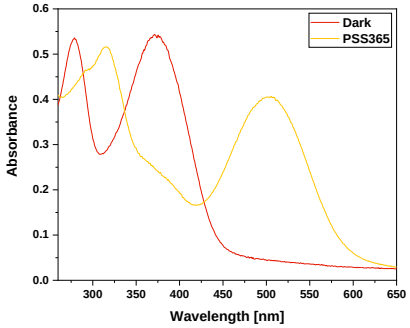
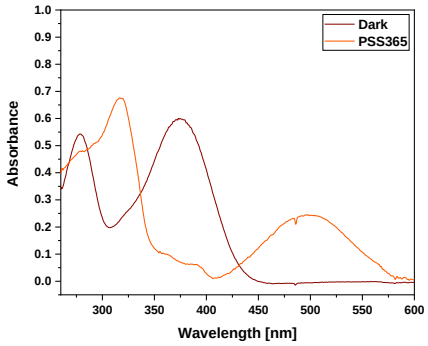


PBS Buffer

DHA9



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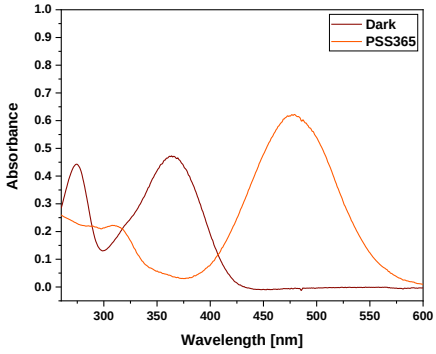

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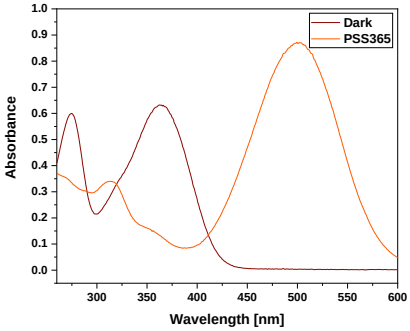
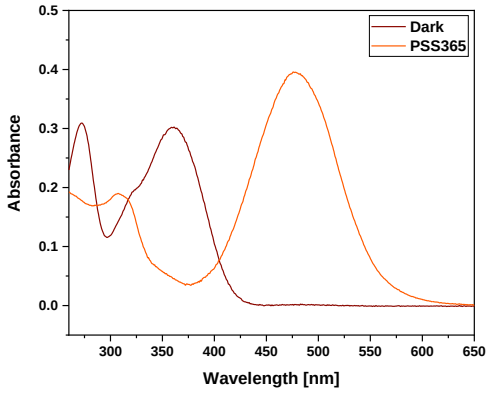


PBS Buffer

DHA-MO



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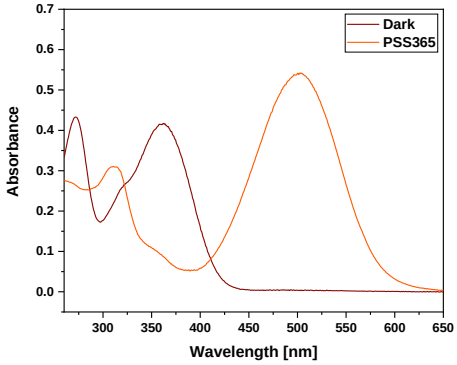
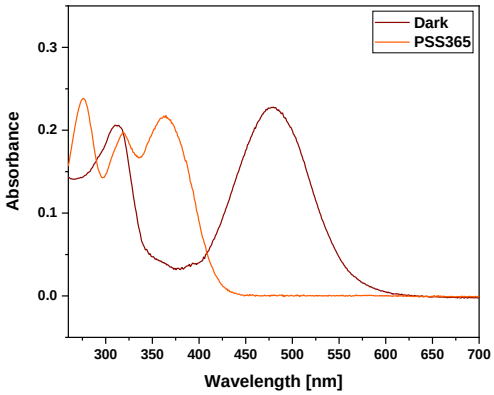


PBS Buffer

DHA-Gly-OEt



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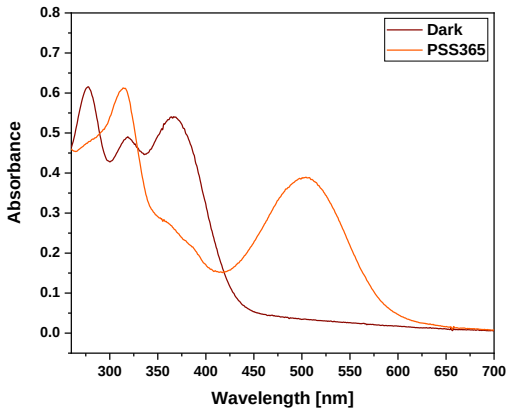
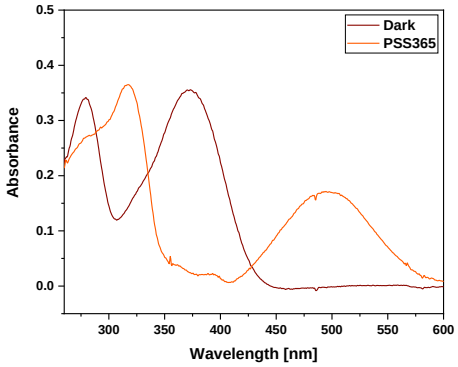


PBS Buffer

DHA-Ala-OtBu



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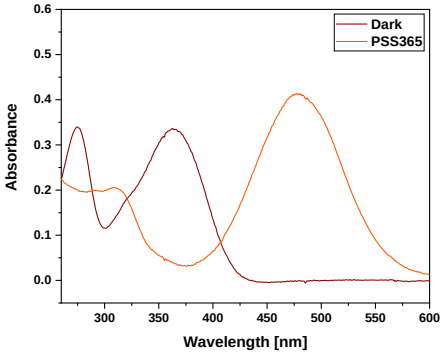

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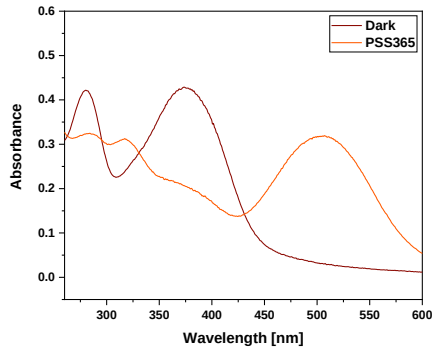
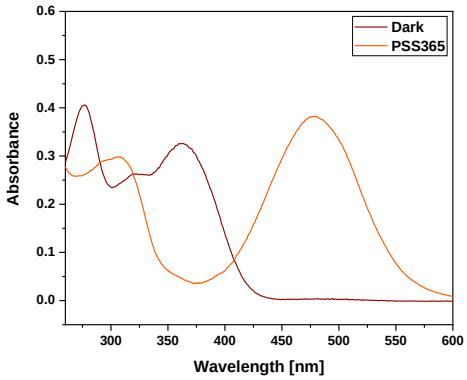


PBS Buffer

DHA-Lys(Boc)-OtBu



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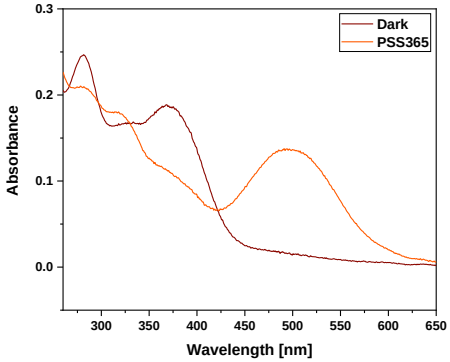
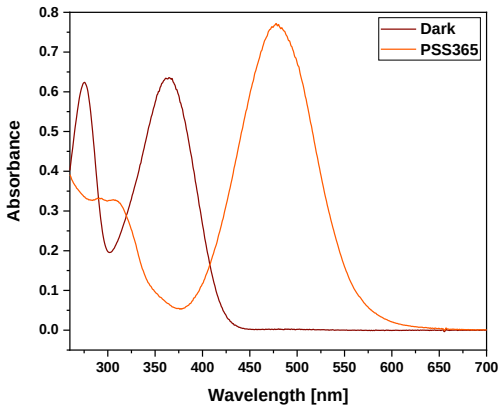
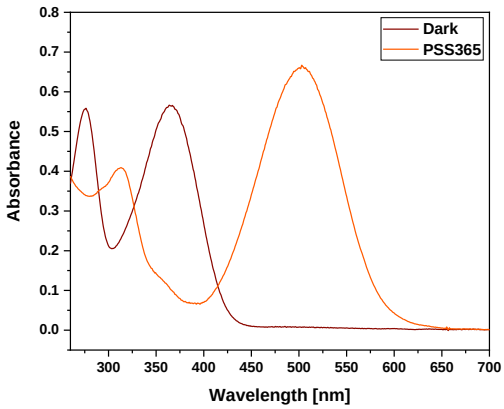


PBS Buffer

DHA-Glu

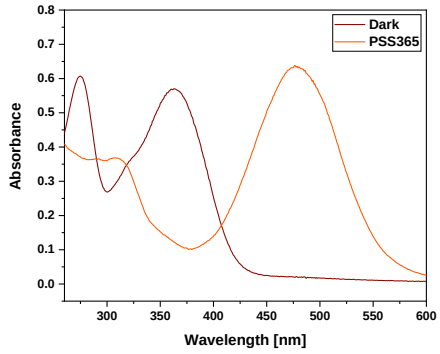


MeOH

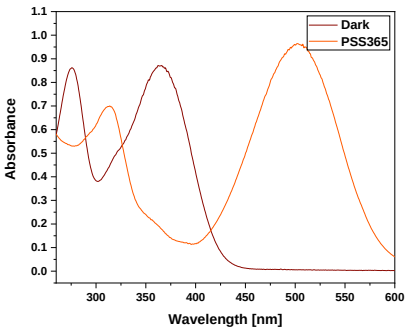


PBS Buffer

BPC-Ala-OH

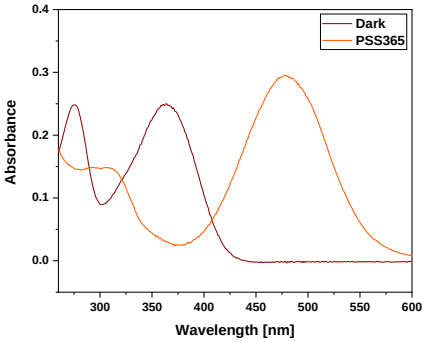


MeOH

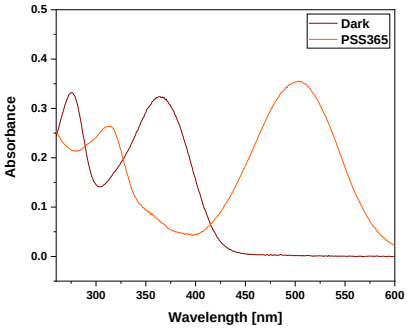


PBS Buffer

DHA-Lys(TFA)



MeOH



PBS Buffer

Fits for quantum yield determination and thermal ring closing

Chemical actinometry

A modification of a standard protocol was applied for the determination of the photon flux.[8] An aqueous H_2SO_4 solution (0.05 M) containing freshly recrystallized $K_3[Fe(C_2O_4)_3]$ (41 mM, 2 mL) was irradiated at 20 °C for a given period of time in the dark with a 365 nm and 405 nm LED at a controlled, fixed, low intensity. The solution was then diluted with 1.0 mL of an aqueous H_2SO_4 solution (0.5 M) containing phenanthroline (1 g/L) and NaOAc (122.5 g/L) and left to react for 10 min. The absorption at 510 nm was measured and compared to an identically prepared non-irradiated sample. The concentration of $[Fe(phenanthroline)_3]^{2+}$ complex was calculated using its molar absorptivity (ε = 11100 M^{-1} cm^{-1}) and considering the dilution. The quantity of Fe^{2+} ions expressed in mol was plotted against time and the slope, obtained by linear fitting the data points to the equation y = ax +b, equals the rate of formation of the Fe^{2+} ion at the given wavelengths. The rate can be converted into the photon flux (I) by dividing it by the quantum yield of $[Fe(phenanthroline)_3]^{2+}$ complex (Φ_{365nm} = 1.29, Φ_{405nm} = 1.13). The obtained photon fluxes were I_{365nm} = 1.10996 x 10^{-5} mE s^{-1} and I_{405nm} = 1.35523 x 10^{-5} mE s^{-1}.

Quantum yield

The quantum yield of the photochemical ring opening is determined using an initial slope method. The sample is irradiated with an LED and the natural logarithm of the absorbance data is plotted against time. From equation 1,[8] we can determine the quantum yield of the photochemical ring opening.

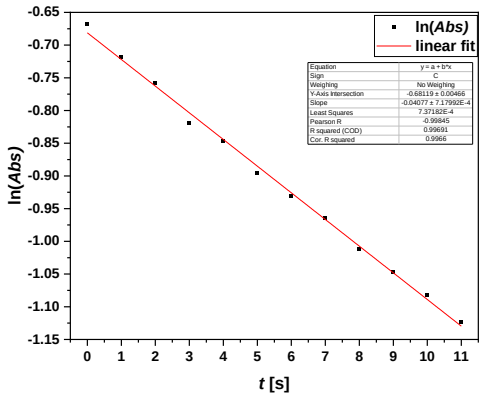
Eq. 1 $$\phi = \frac{-k\,[X]_0\;V}{I\;\;(1-10^{-Abs(0)})}$$

Where ϕ is the quantum yield; $-k$ is the reaction rate; [X] is the concentration of the closed form in M^{-1}; V is the volume in mL and I is the photon flux in mE s^{-1}. Applying first order kinetics, the rate $-k$ can be taken from the slope of the natural logarithm of absorbance vs. time.

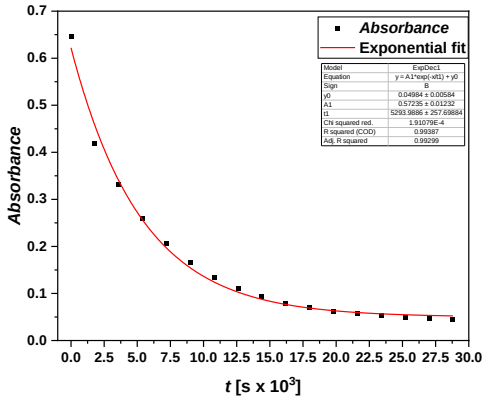
Thermal ring closing

The thermal ring closing reaction is spectroscopically analysed by the decay of the absorbance at 500 nm at 20 °C. The traces are fitted to a mono-exponential decay.

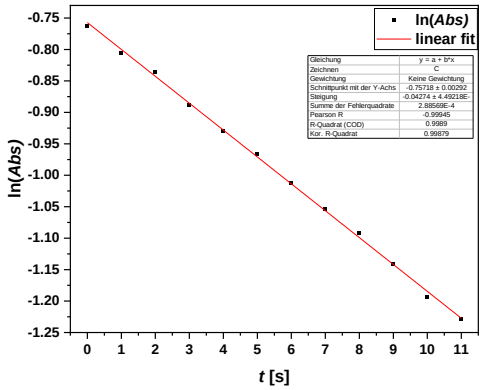
DHA1



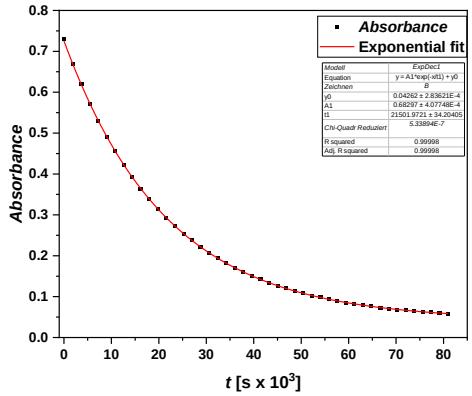
Quantum Yield fit in DMSO



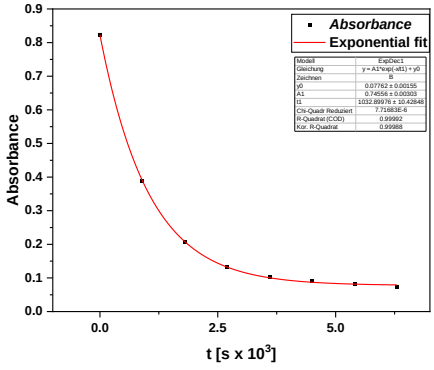
Thermal ring closing fit in DMSO



Quantum Yield fit in MeCN

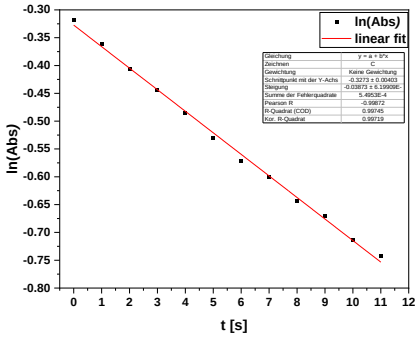


Thermal ring closing fit in MeCN

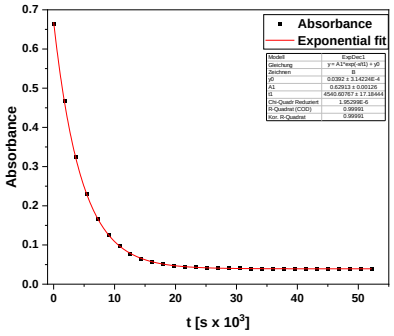


Thermal ring closing fit in PBS buffer

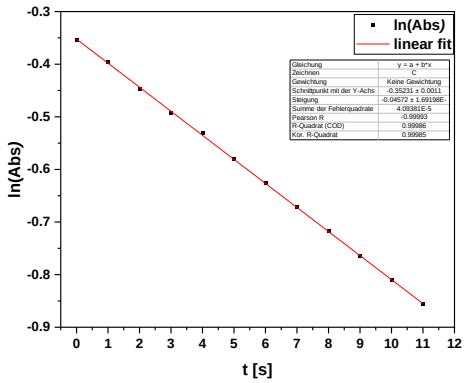
DHA2



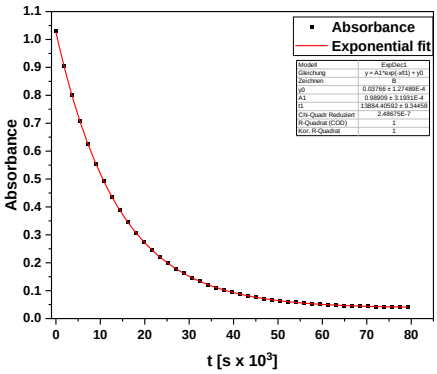
Quantum Yield fit in DMSO



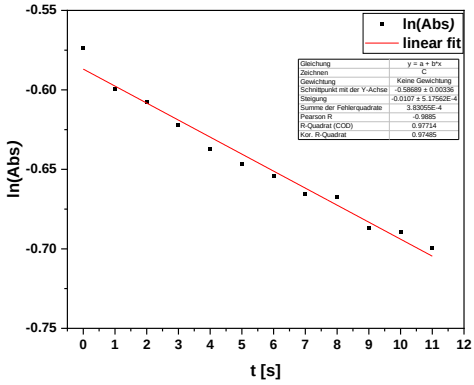
Thermal ring closing fit in DMSO



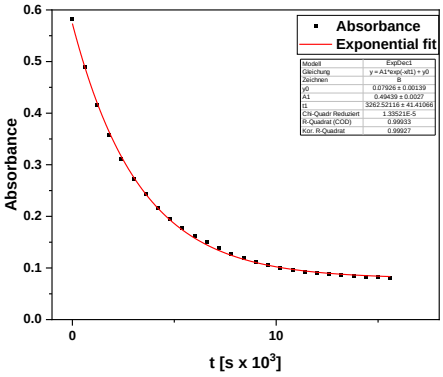
Quantum Yield fit in MeCN



Thermal ring closing fit in MeCN

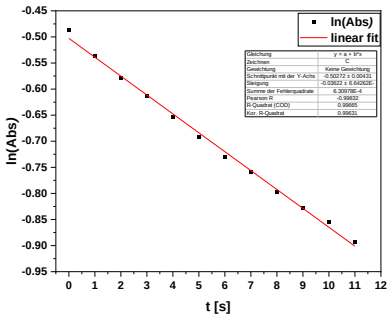


Quantum Yield fit in PBS buffer

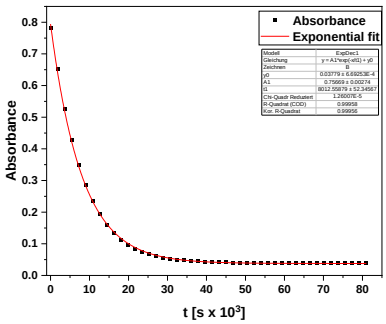


Thermal ring closing fit in PBS buffer

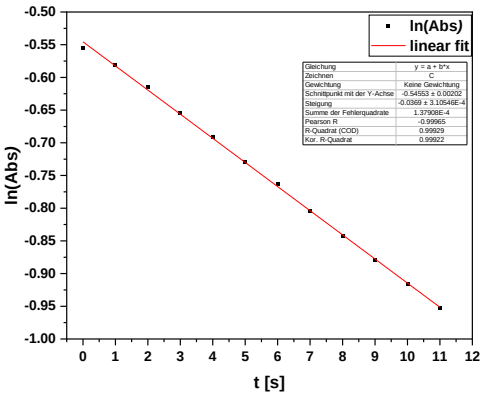
DHA3



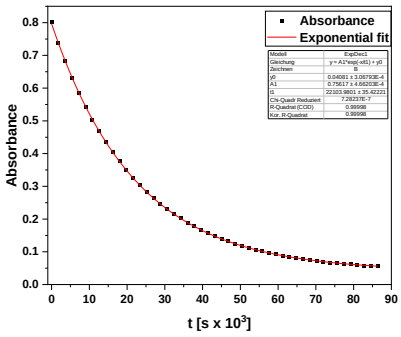
Quantum Yield fit in DMSO



Thermal ring closing fit in DMSO



Quantum Yield fit in MeCN



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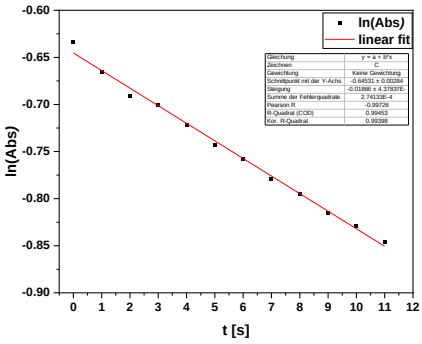
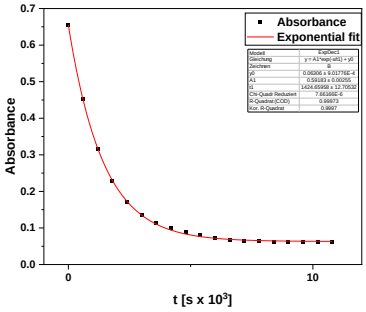
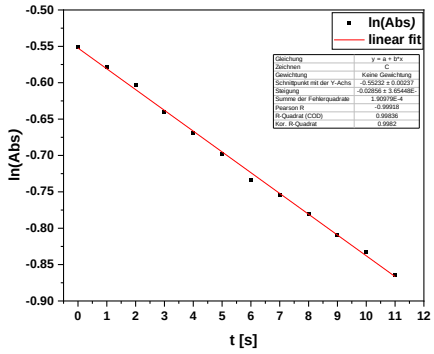


Quantum Yield fit in PBS buffer

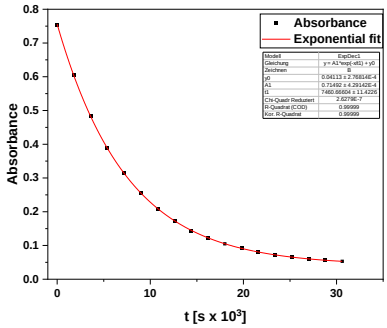


Thermal ring closing fit in PBS buffer

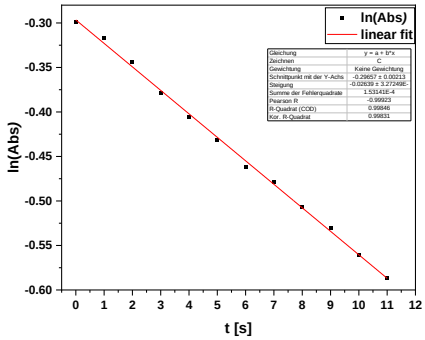
DHA4



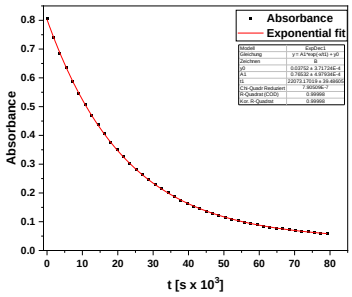
Quantum Yield fit in DMSO



Thermal ring closing fit in DMSO



Quantum Yield fit in MeCN



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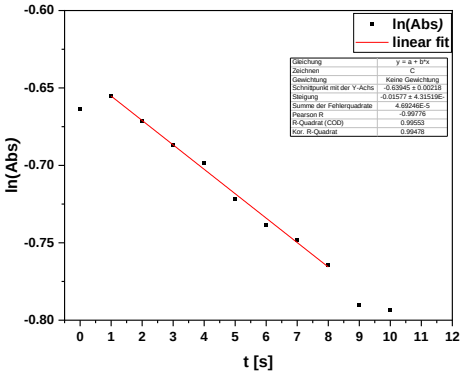
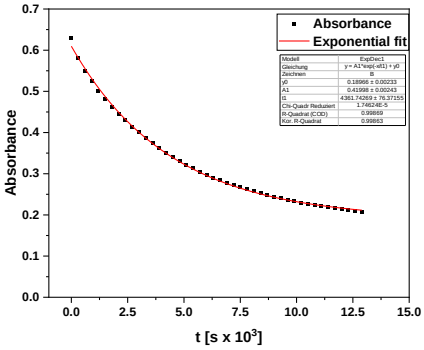
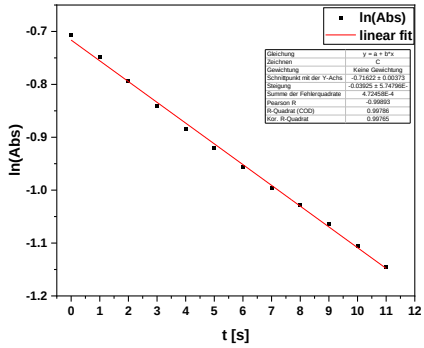


Quantum Yield fit in PBS buffer
405 nm irradiation

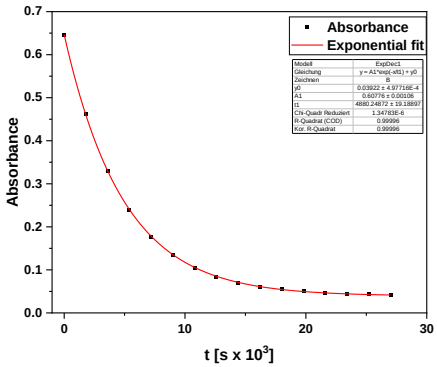


Thermal ring closing fit in PBS buffer

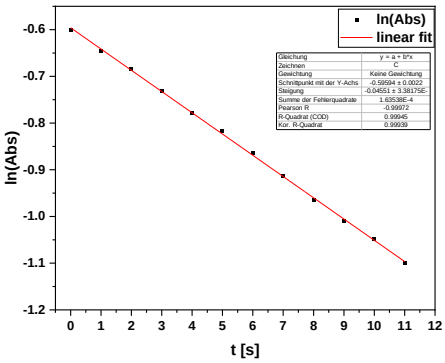
DHA5



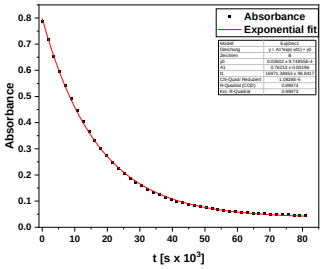
Quantum Yield fit in DMSO



Thermal ring closing fit in DMSO



Quantum Yield fit in MeCN



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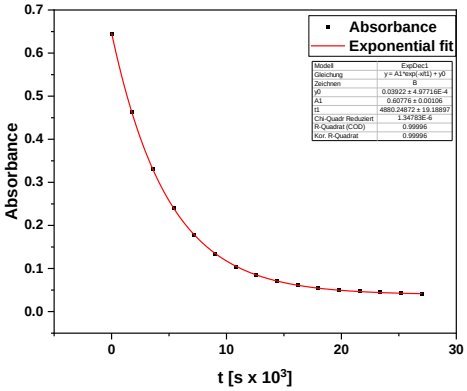
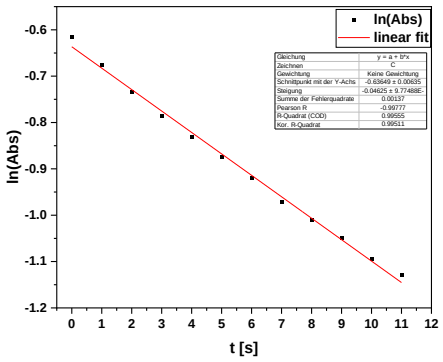
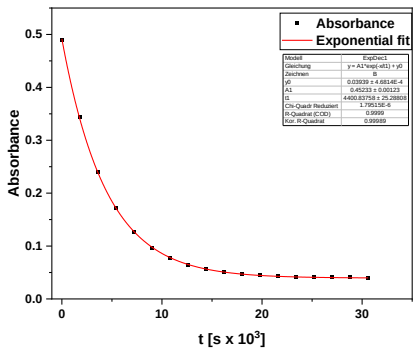


Thermal ring closing fit in PBS buffer

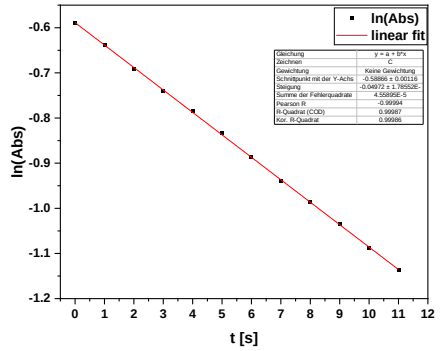
DHA6



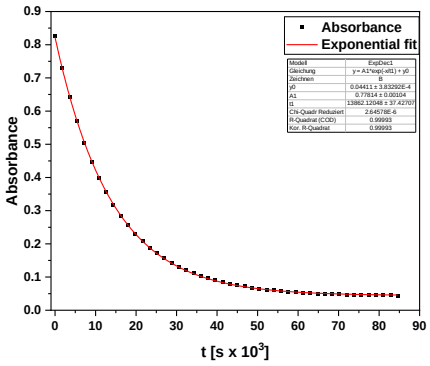
Quantum Yield fit in DMSO



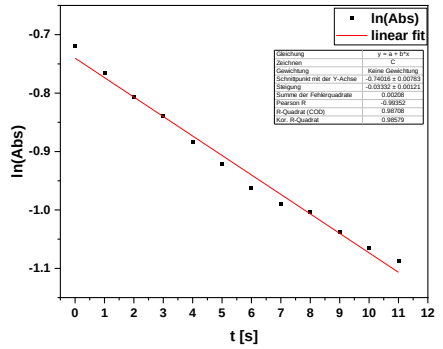
Thermal ring closing fit in DMSO



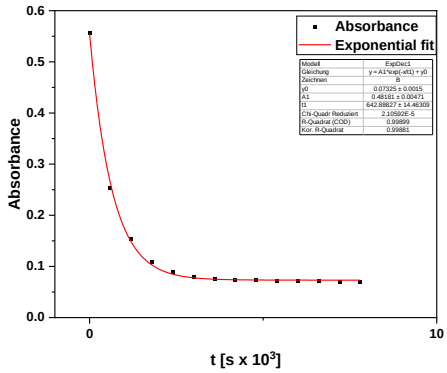
Quantum Yield fit in MeCN



Thermal ring closing fit in MeCN

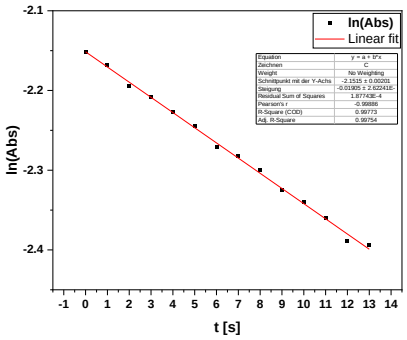


Quantum Yield fit in PBS buffer

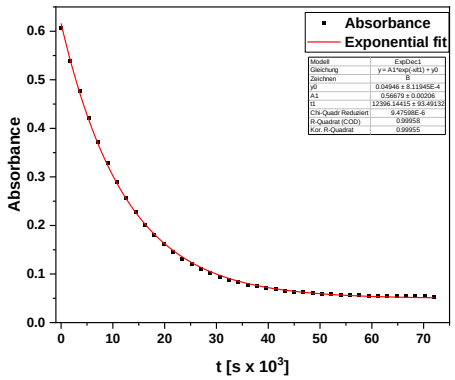


Thermal ring closing fit in PBS buffer

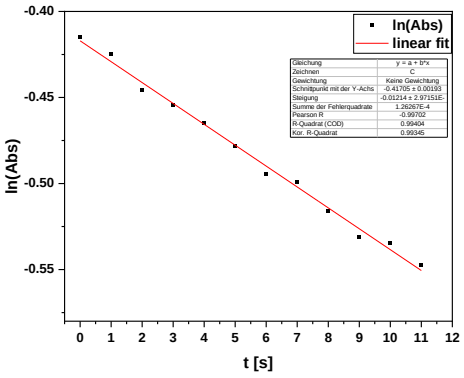
DHA7



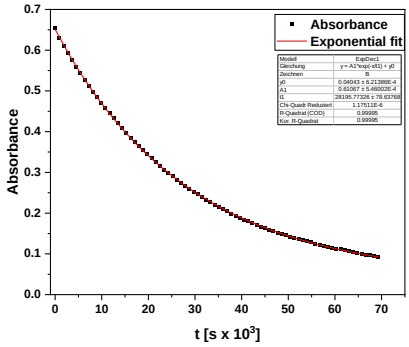
Quantum Yield fit in DMSO
(405 nm)



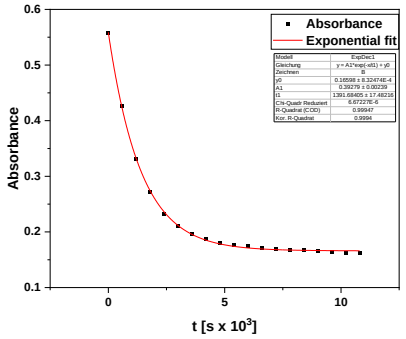
Thermal ring closing fit in DMSO



Quantum Yield fit in MeCN
(405 nm)

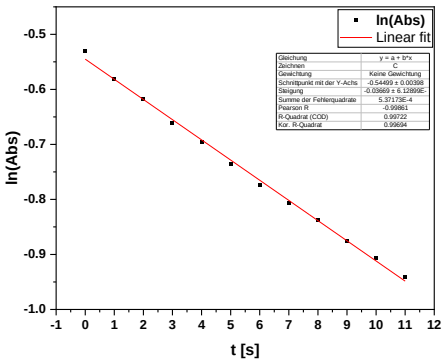


Thermal ring closing fit in MeCN

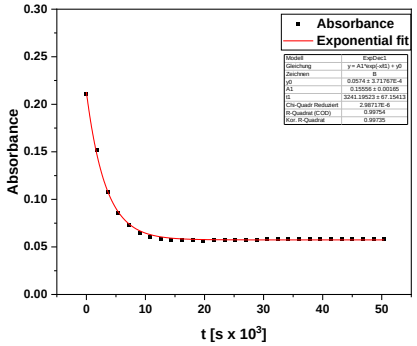


Thermal ring closing fit in PBS buffer

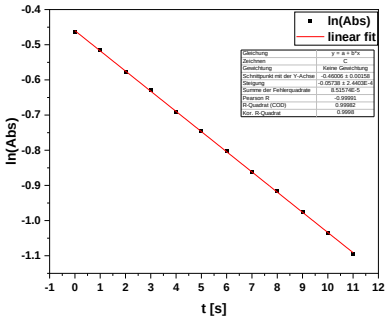
DHA8



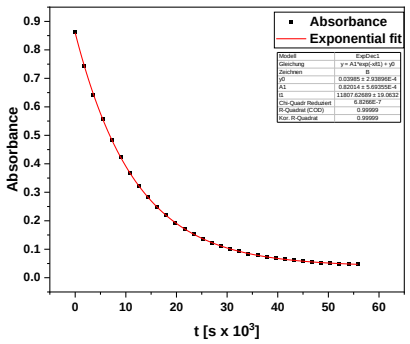
Quantum Yield fit in DMSO



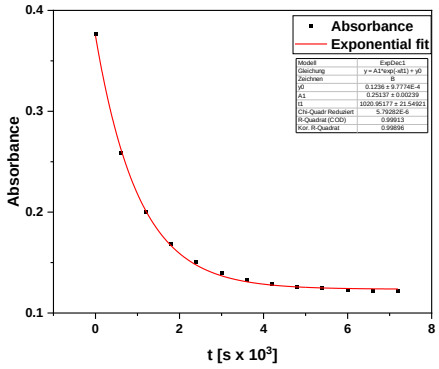
Thermal ring closing fit in DMSO



Quantum Yield fit in MeCN

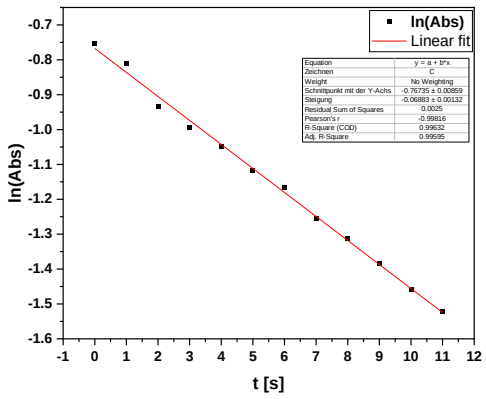


Thermal ring closing fit in MeCN

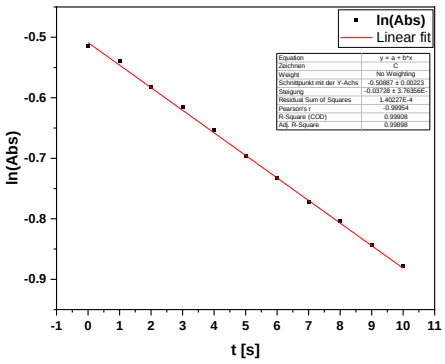


Thermal ring closing fit in PBS buffer

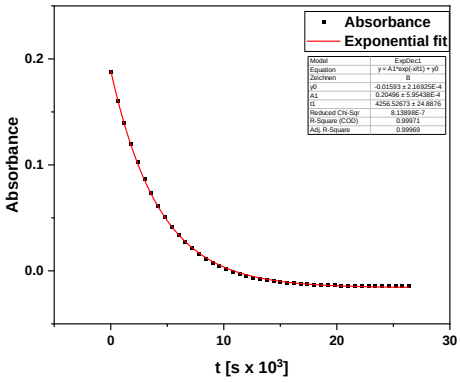
DHA9



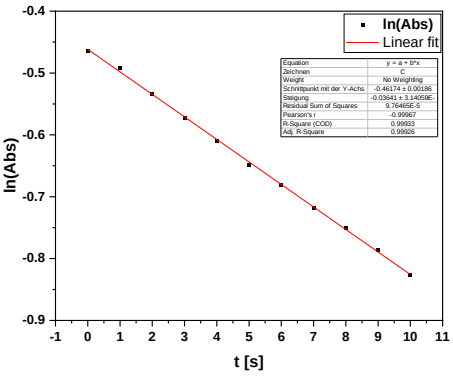
Quantum Yield fit in MeOH



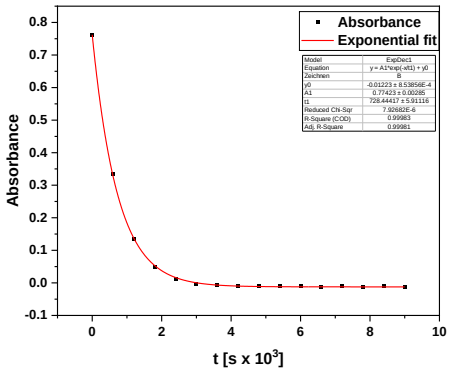
Quantum Yield fit in DMSO



Thermal ring closing fit in DMSO

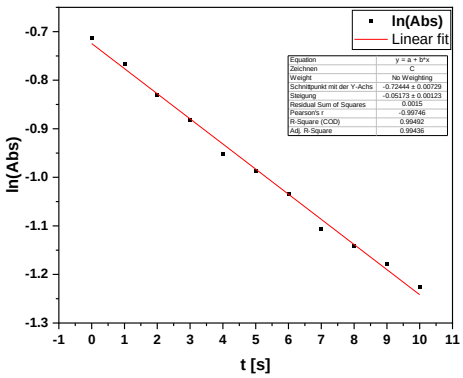


Quantum Yield fit in PBS buffer

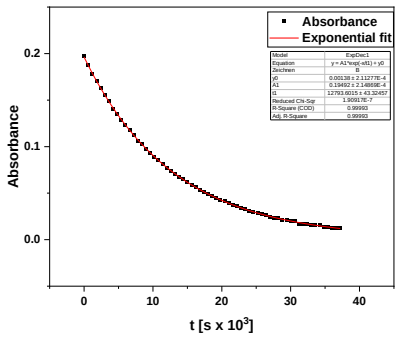


Thermal ring closing fit in PBS buffer

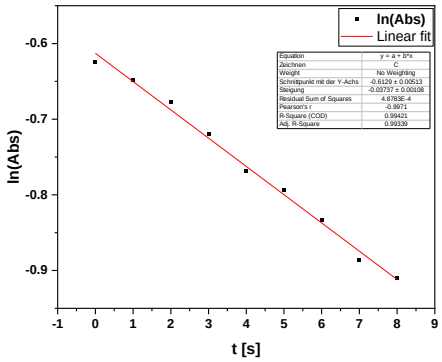
DHA-Gly-OEt



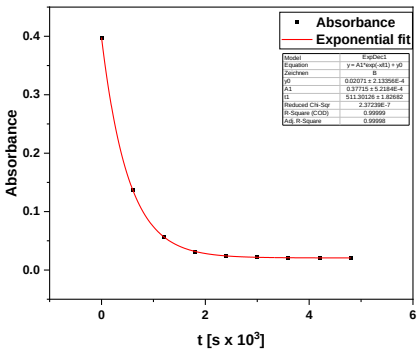
Quantum Yield fit in MeOH



Thermal ring closing fit in MeOH

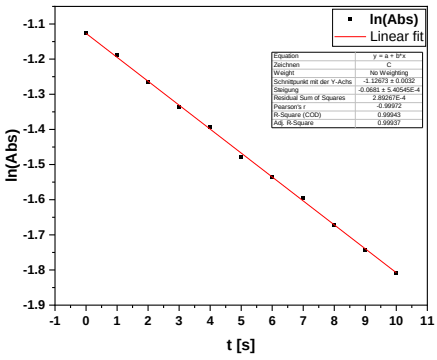


Quantum Yield fit in PBS buffer

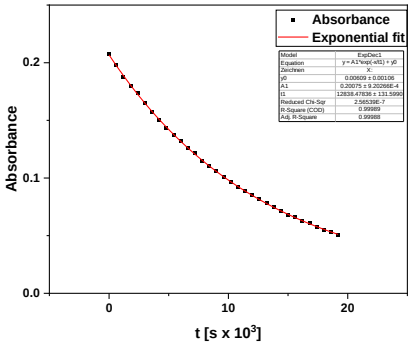


Thermal ring closing fit in PBS buffer

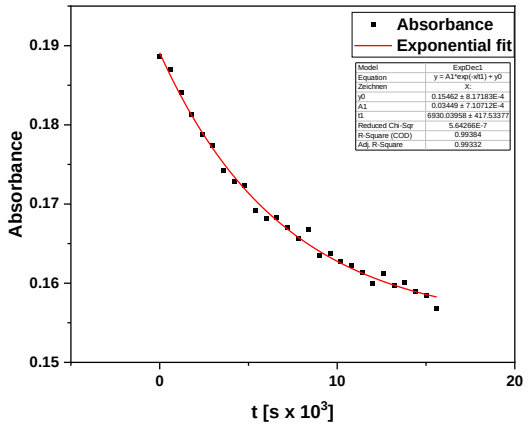
DHA-Lys(Boc)-OtBu



Quantum Yield fit in MeOH

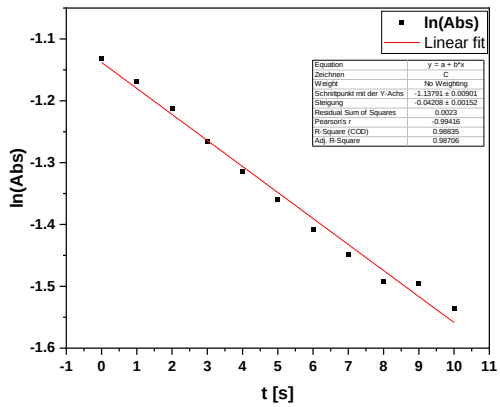


Thermal ring closing fit in MeOH

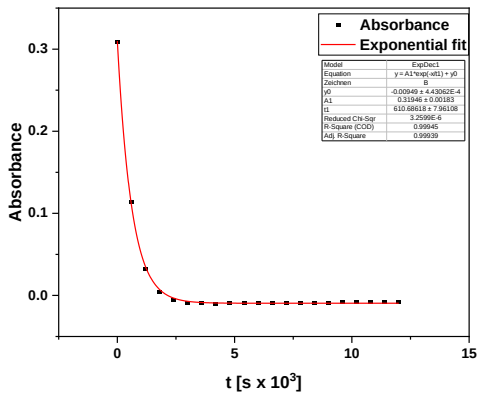


Thermal ring closing fit in PBS

DHA-Lys(TFA)

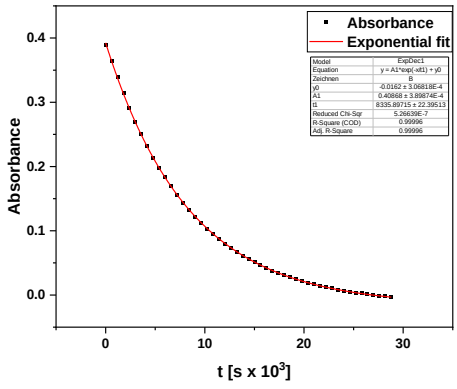


Quantum Yield fit in PBS Buffer

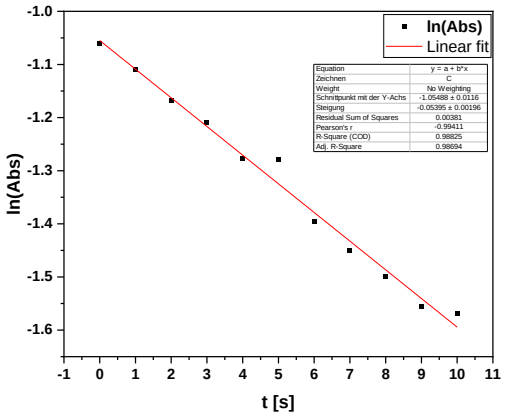


Thermal ring closing fit in PBS Buffer

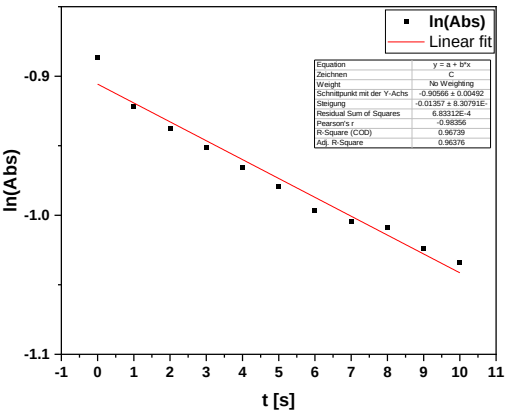
DHA-Ala-OtBu



Thermal ring closing fit in MeOH

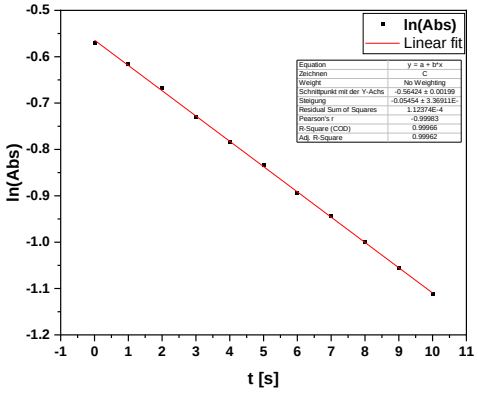


Quantum Yield fit in DMSO

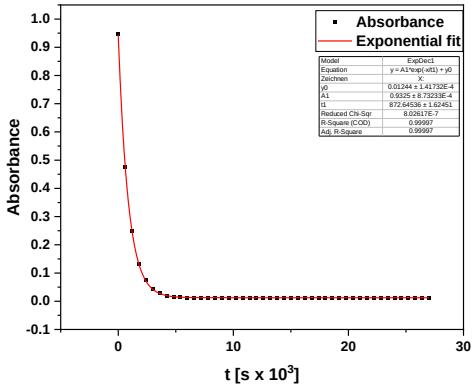


Quantum Yield fit in PBS Buffer

DHA-Ala

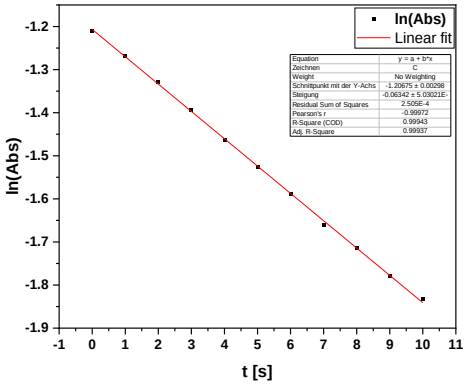


Quantum Yield fit in MeOH

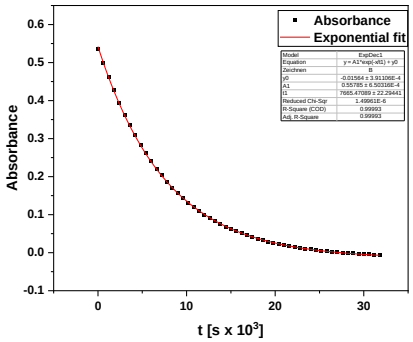


Thermal ring closing fit in PBS

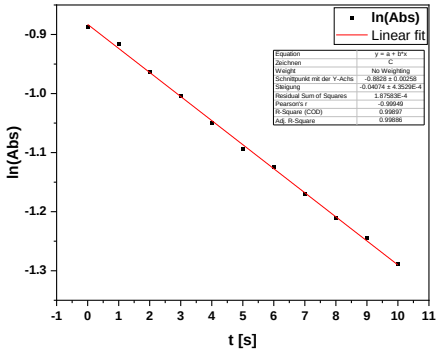
DHA-MO



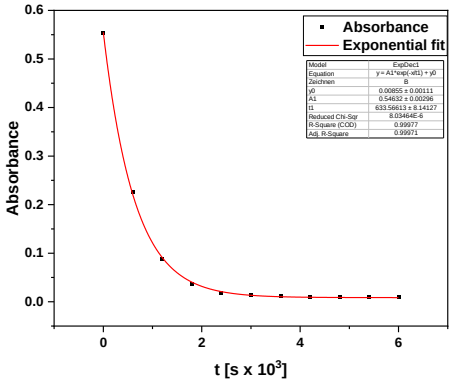
Quantum Yield fit in MeOH



Thermal ring closing fit in MeOH

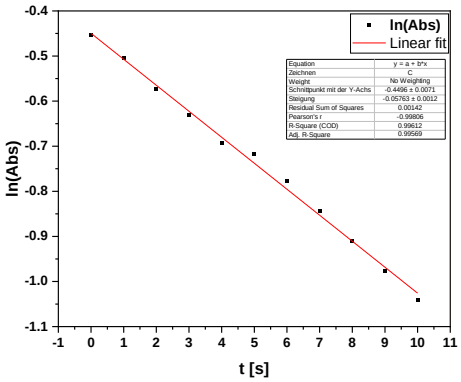


Quantum Yield fit in PBS Buffer

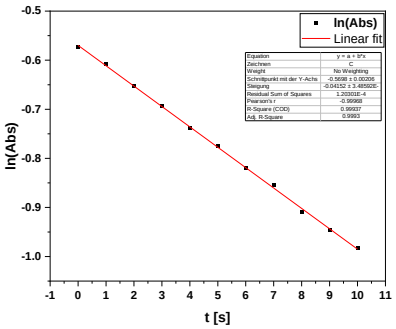


Thermal ring closing fit in PBS

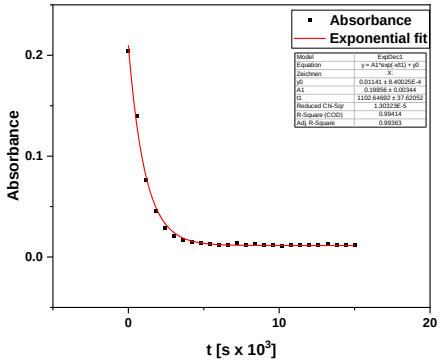
DHA-Glu



Quantum Yield fit in MeOH



Quantum Yield fit in PBS Buffer



Thermal ring closing fit in PBS

DHA-ALFA

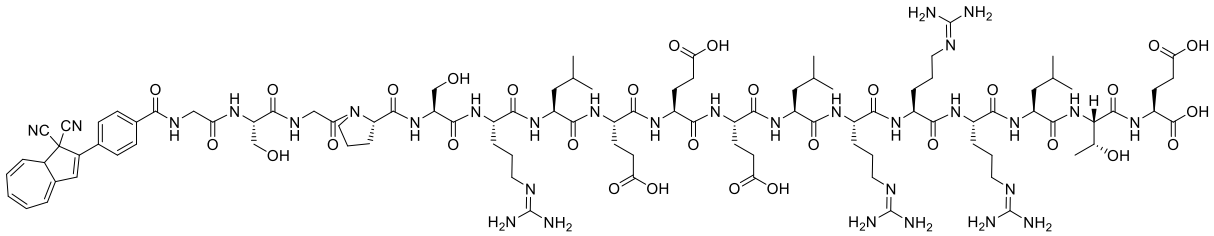


Figure S3. Structure of **DHA-ALFA**.

ALFA peptide (GSGPSRLEEELRRRLTE)

The **ALFA peptide** was synthesized via microwave-assisted solid phase peptide synthesis. The synthesis (on a 0.025 mmol scale) was carried out on a preloaded Fmoc-Lys-Wang resin (0.30 mmol/g loading). DIC (0.25 M in DMF) and Oxyma (0.25 M in DMF) were employed as activators, while deprotection was carried out with a 20% solution of piperidine in DMF (*v*/*v*).

The non-preloaded resin (1.0 equiv.) was placed in the reaction vessel of the peptide synthesizer and was swollen for 30 min in DMF. First, the *N*-terminal Fmoc protecting group was removed by addition of piperidine (20 % in DMF, *v/v*) under microwave irradiation (1: 75 °C, 90 W, 15 s; 2: 90 °C, 20 W, 50 s). To achieve a complete cleavage of the Fmoc-group, the deprotection step was repeated twice. After washing of the resin with DMF (5 x 4 mL) the amino acid, DIC, and Oxyma were added to the reaction vessel. The coupling reaction was performed under microwave irradiation (1: 75 °C, 170 W, 15 s; 2: 90 °C, 30 W, 110 s). For the coupling of Fmoc-Arg(Pbf)-OH (75 °C, 30 W, 300 s) coupling cycles were used to suppress the γ-lactam formation for arginine.

After the peptide synthesis was completed, the resin was transferred into a BD Syringe with PE-frit and was washed with DMF (6 x 4 mL) and DCM (6 x 4 mL). Following, the resin was dried under reduced pressure.

Initial Fmoc-deprotection of the resin-bound peptide strand was performed with a 20% solution of piperidine in NMP. The resin-filled syringe was filled with 2 mL of deprotecting solution and left shaking for 10 minutes. The solvent was eliminated, and the procedure was repeated once. The resin was then washed with NMP/DCM/NMP (3x) prior to coupling with the switch.

Coupling with **DHA-9** (on a 0.0125 mmol scale) was performed by dissolving **DHA-9** (5 equiv.), DEPBT (5.0 equiv.) and DIPEA (10.0 equiv.) in NMP (800 µL) and adding the solution to a resin-filled BD-syringe equipped with a PE frit. The reaction mixture was left shaking for 2 h at rt, then washed with NMP/CH_2Cl_2/NMP (3x).

The cleavage of **DHA-ALFA** from the resin was performed in a BD syringe with a PE frit. The resin was shaken at room temperature for 2 h in a TFA/Thioanisole/EDT/anisole solution (90:5:3:2 v/v/v/v). After cleavage the solution was concentrated under a nitrogen stream and the crude peptide was precipitated with diethyl ether. The precipitate was isolated by centrifugation (9000 rpm, -10 °C, 10 min), washed twice with ether and dried under vacuum.

DHA-ALFA was isolated by reverse-phase HPLC. The compound was identified by high-resolution mass spectrometry (ESI-Pos: for $[C_{100}H_{151}N_{31}O_{30} + 3\ H]^{3+}$ calcd. m/z = 756.3820, found m/z = 756.3800, the $[M+H]^+$ ion was observed as well at m/z = 2266.1).

The obtained fraction was diluted in PBS buffer and analysed by UV-Vis spectroscopy (Figure S3). We observed a λ_{max} for **DHA-ALFA** of 364 nm and for **VHF-ALFA** of 506 nm. Irradiation showed fast ring-opening of the photoswitch.

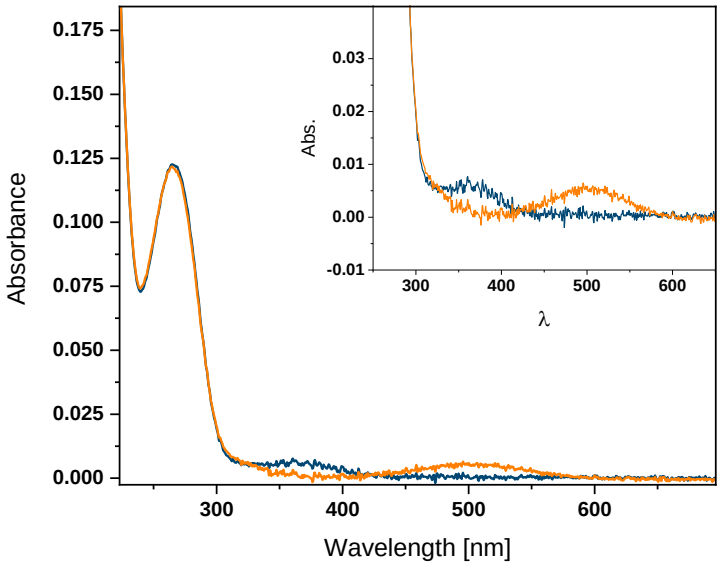
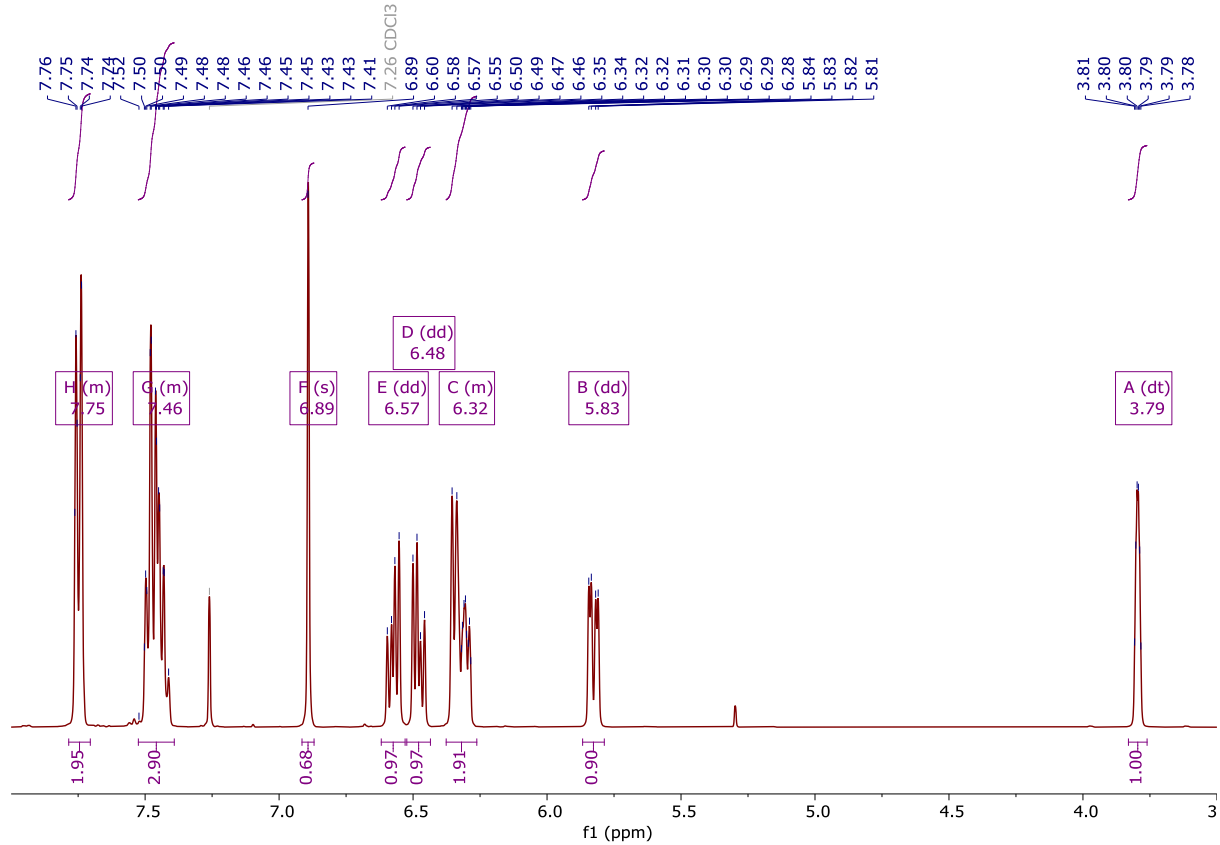
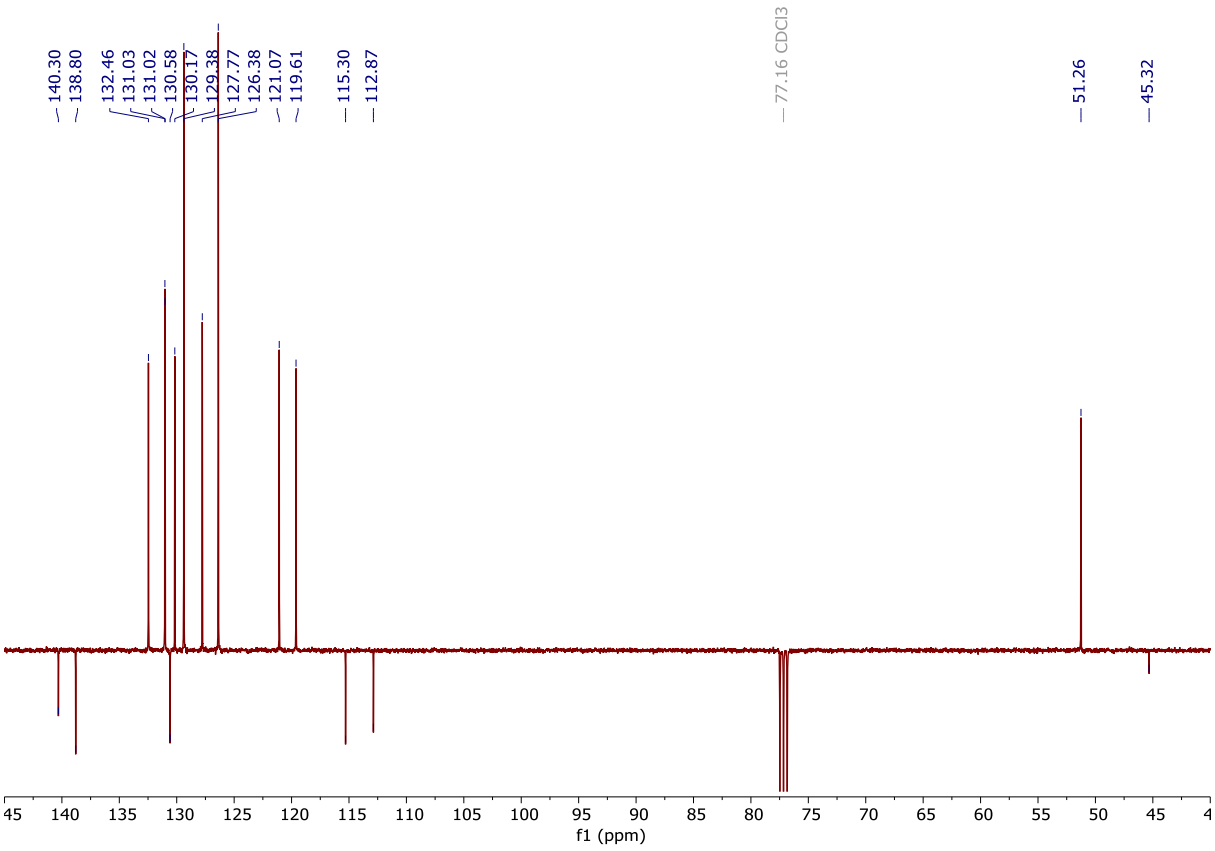


Figure S3. Absorbance spectrum of **DHA-ALFA** in PBS buffer before (blue) and after (orange) irradiation with 365 nm LED.

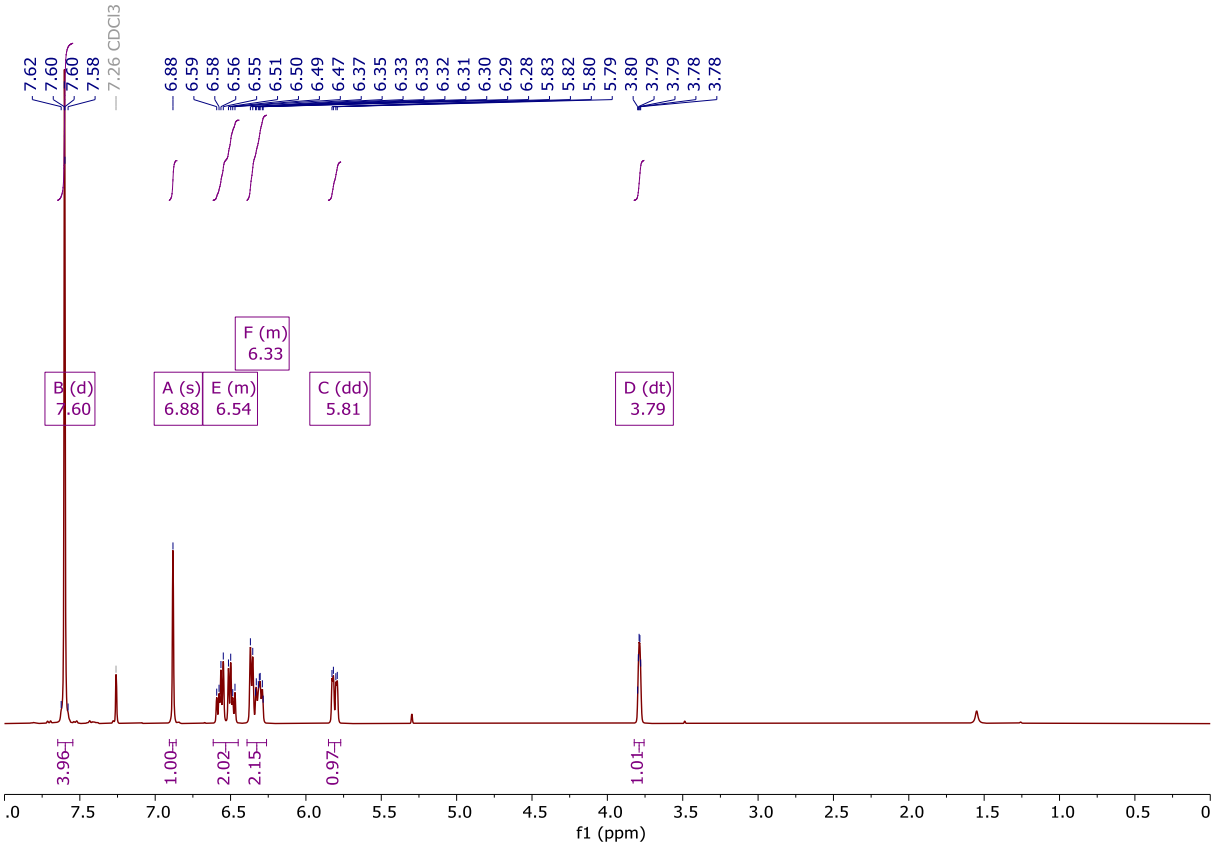
NMR spectra

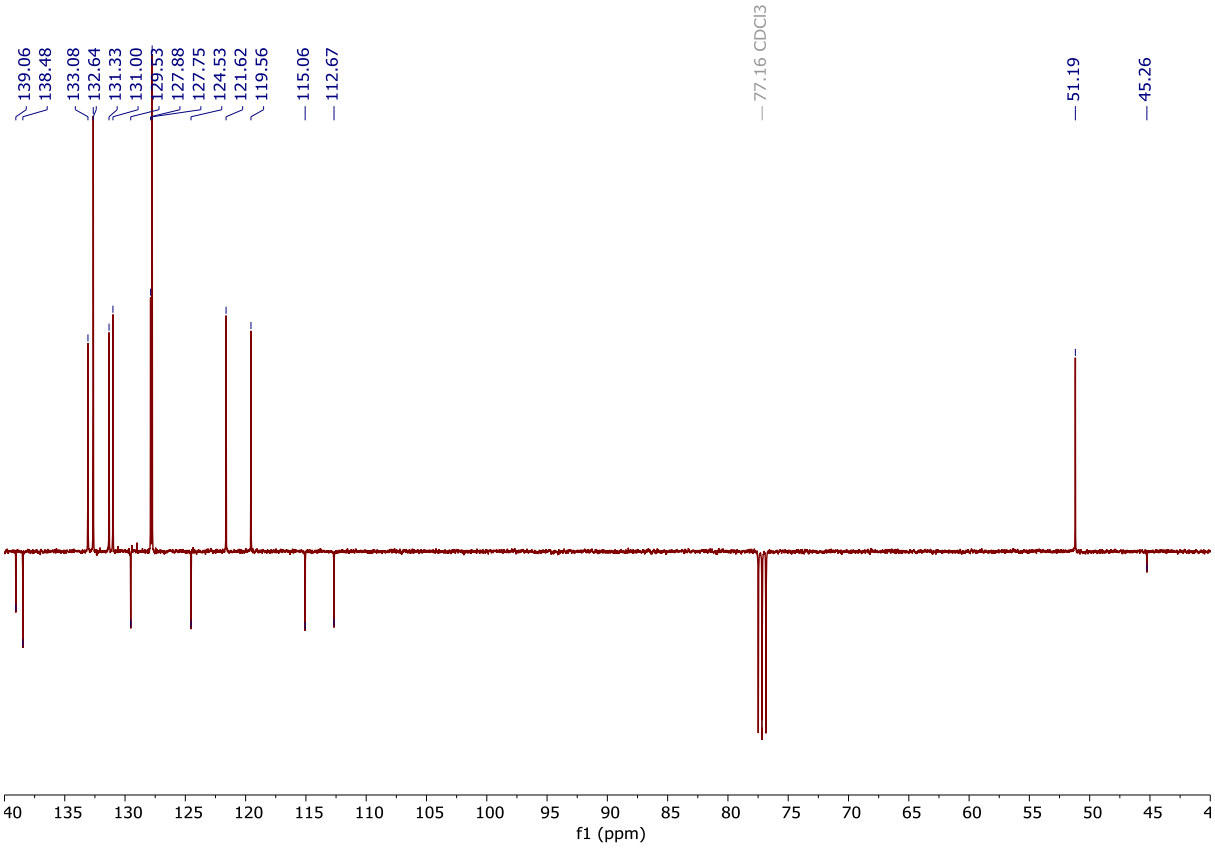
DHA1



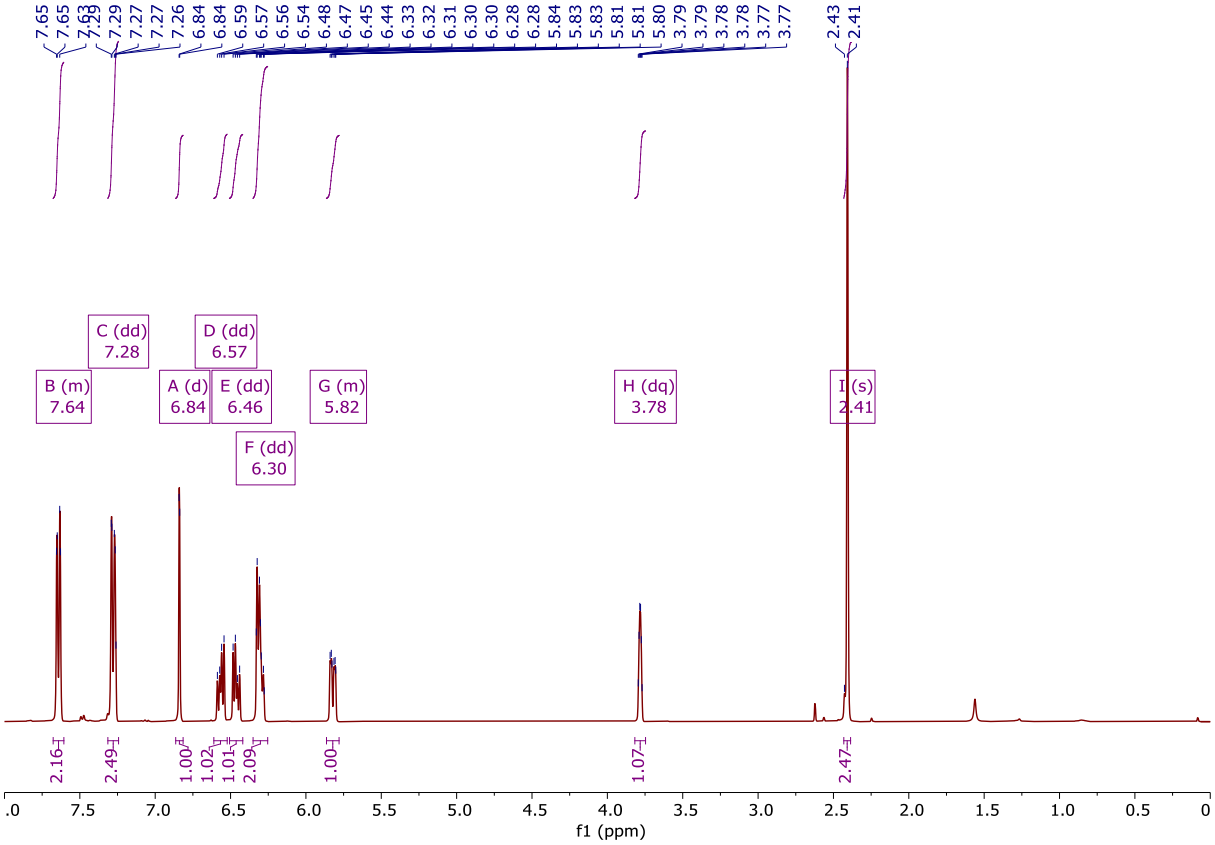


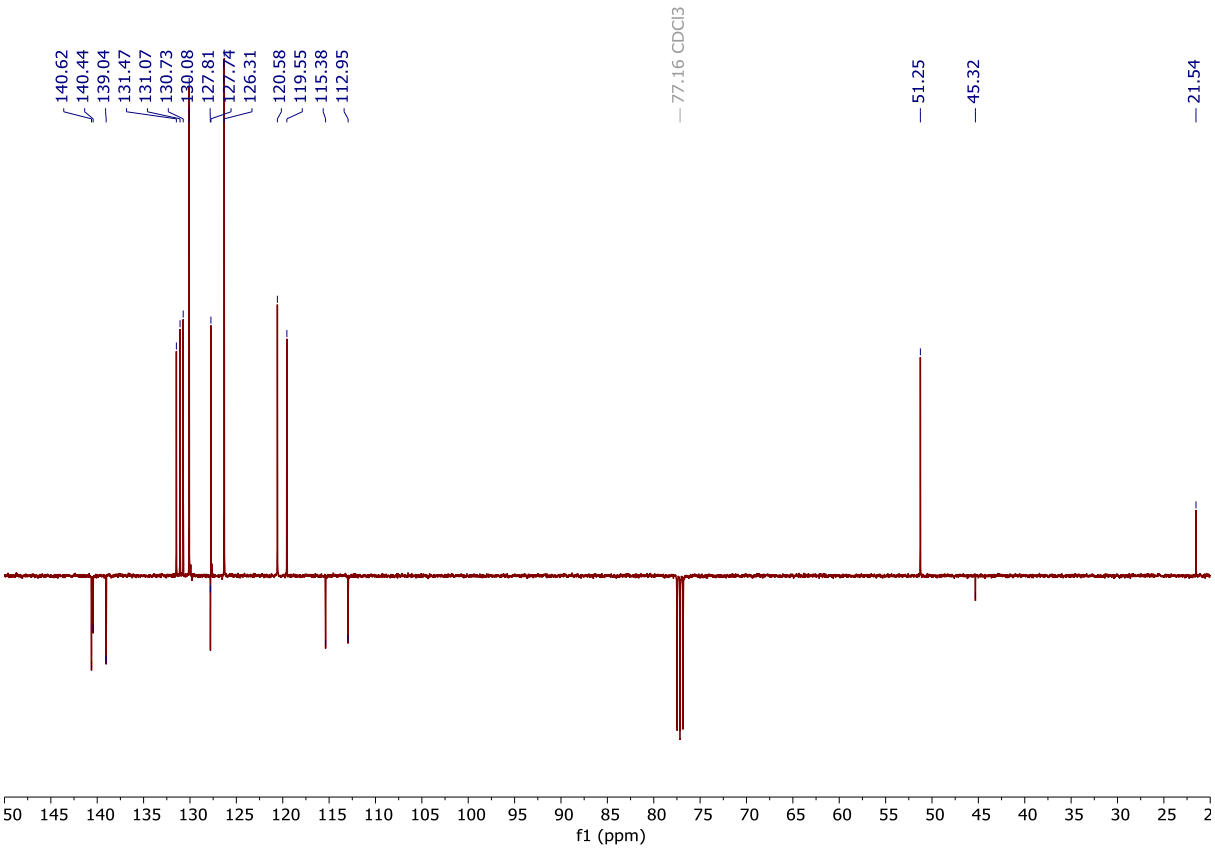
DHA2


7.62
7.60
7.60
7.58
7.26 CDCl3
6.88
6.59
6.58
6.56
6.55
6.51
6.50
6.49
6.47
6.37
6.35
6.33
6.33
6.32
6.31
6.30
6.29
6.28
5.83
5.82
5.80
5.79
3.80
3.79
3.79
3.78
3.78
F (m)
6.33
B (d)
7.60
A (s)
6.88
E (m)
6.54
C (dd)
5.81
D (dt)
3.79
3.96
1.00
2.02
2.15
0.97
1.01
f1 (ppm)

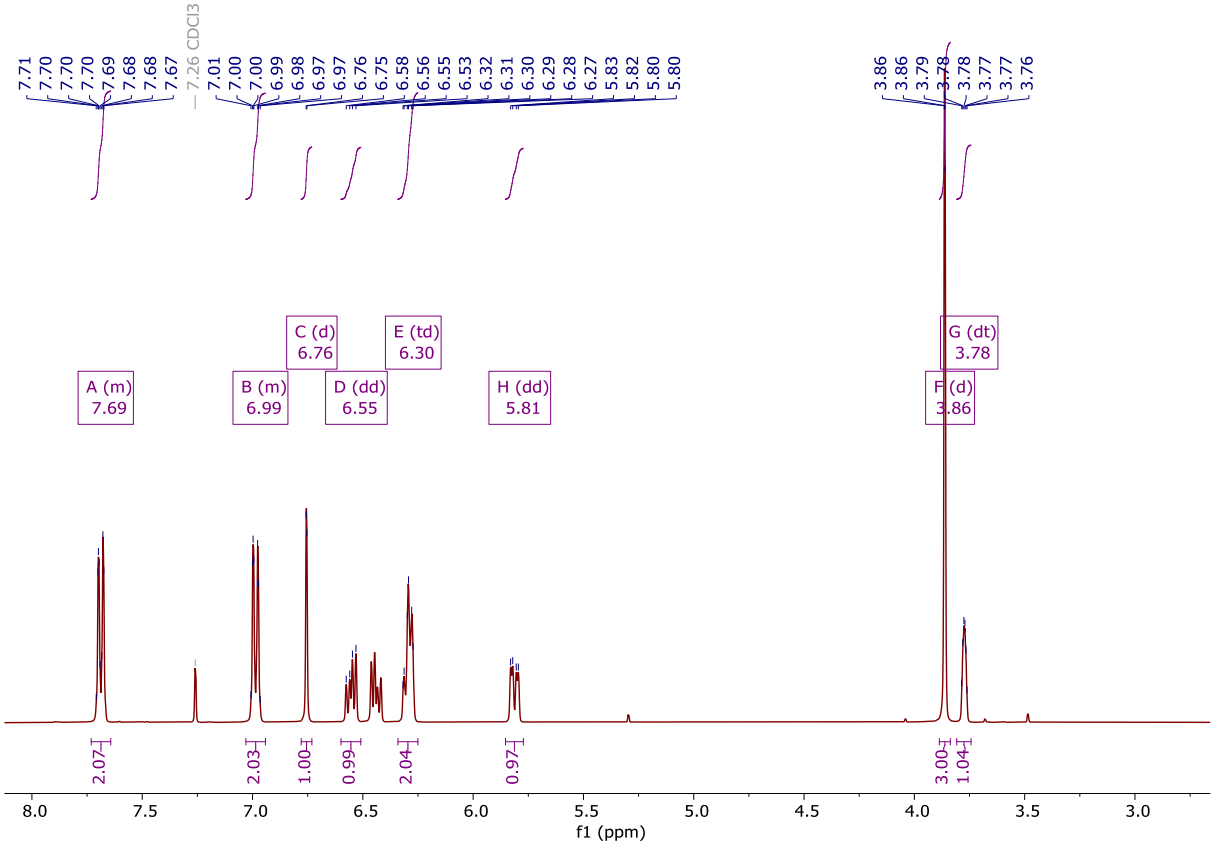

139.06
138.48
133.08
132.64
131.33
131.00
129.53
127.88
127.75
124.53
121.62
119.56
115.06
112.67
77.16 CDCl3
51.19
45.26
f1 (ppm)

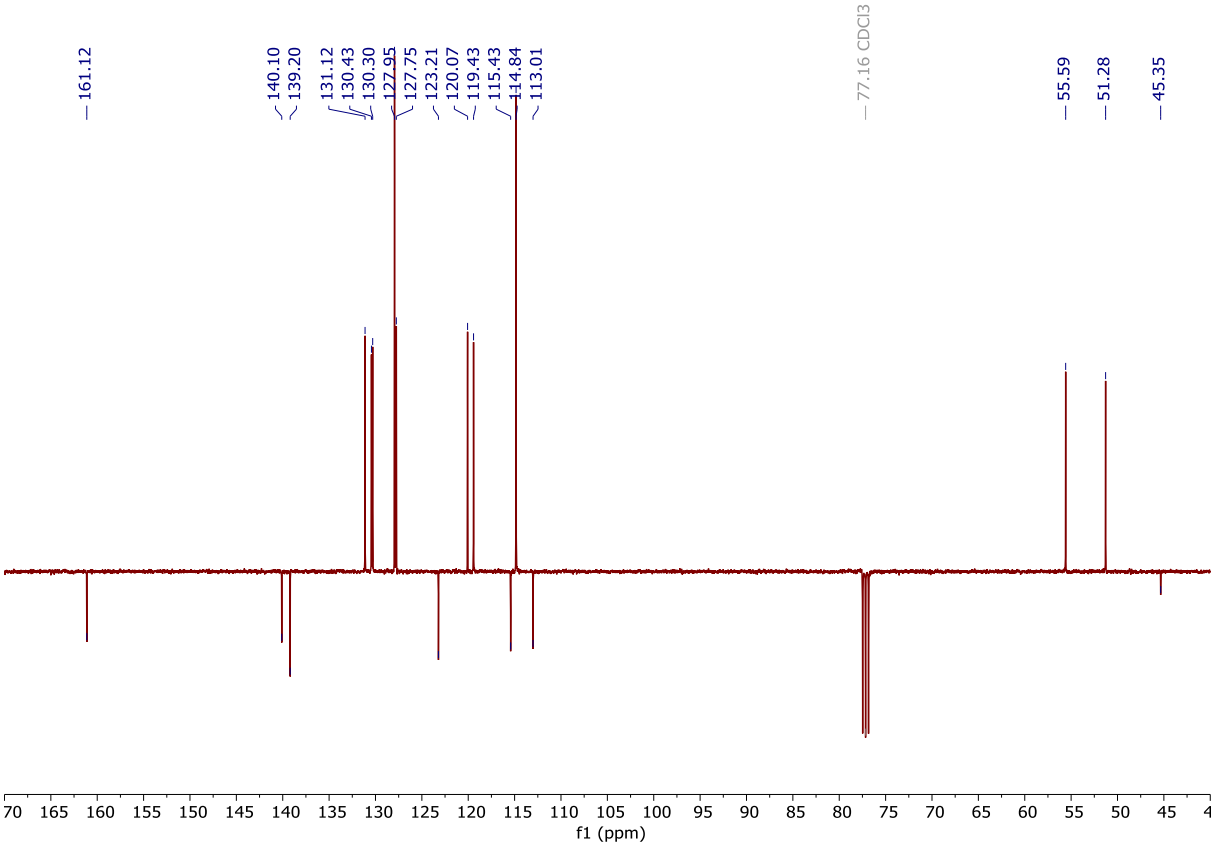
DHA3


7.65
7.65
7.63
7.29
7.27
7.27
7.26
6.84
6.84
6.59
6.57
6.56
6.54
6.48
6.47
6.45
6.44
6.33
6.32
6.31
6.30
6.30
6.28
6.28
5.84
5.83
5.83
5.81
5.81
5.80
3.79
3.79
3.78
3.78
3.77
3.77
2.43
2.41
C (dd) 7.28
D (dd) 6.57
B (m) 7.64
A (d) 6.84
E (dd) 6.46
G (m) 5.82
H (dq) 3.78
I (s) 2.41
F (dd) 6.30
2.16
2.49
1.00
1.02
1.01
2.09
1.00
1.07
2.47
f1 (ppm)

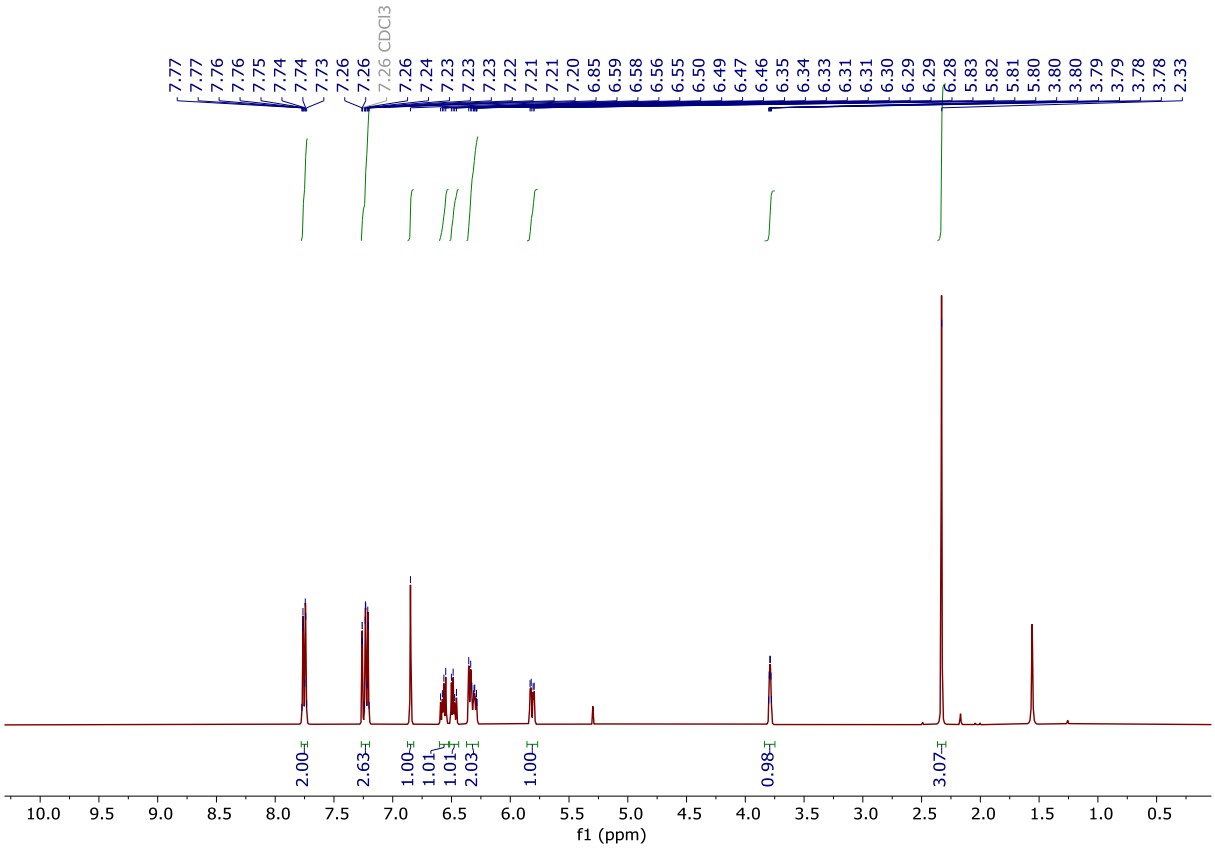

140.62
140.44
139.04
131.47
131.07
130.73
130.08
127.81
127.74
126.31
120.58
119.55
115.38
112.95
77.16 CDCl3
51.25
45.32
21.54
f1 (ppm)

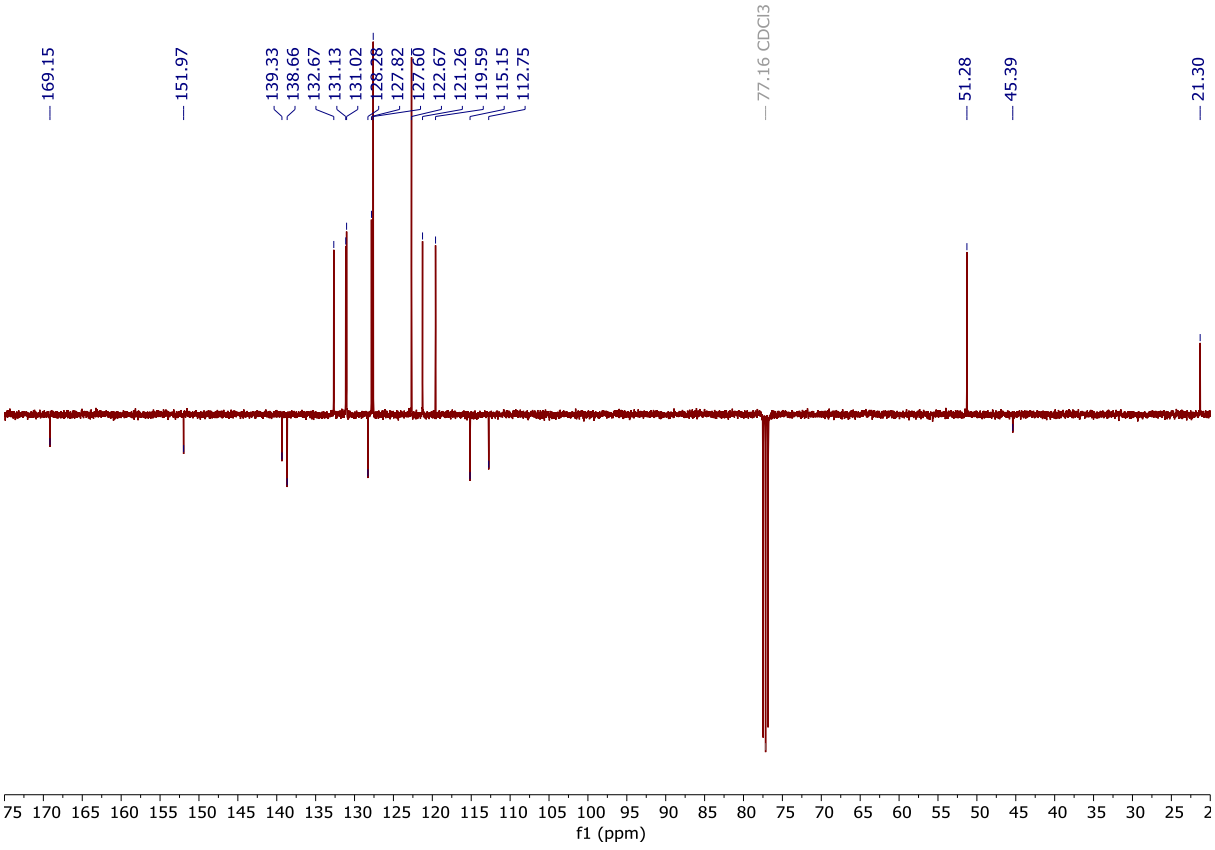
DHA4


7.71
7.70
7.70
7.70
7.69
7.68
7.68
7.67
7.26 CDCl3
7.01
7.00
7.00
6.99
6.98
6.97
6.97
6.76
6.75
6.58
6.56
6.55
6.53
6.32
6.31
6.30
6.29
6.28
6.27
5.83
5.82
5.80
5.80
3.86
3.86
3.79
3.78
3.78
3.77
3.77
3.76
A (m) 7.69
B (m) 6.99
C (d) 6.76
D (dd) 6.55
E (td) 6.30
H (dd) 5.81
G (dt) 3.78
F (d) 3.86
2.07
2.03
1.00
0.99
2.04
0.97
3.00
1.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
f1 (ppm)

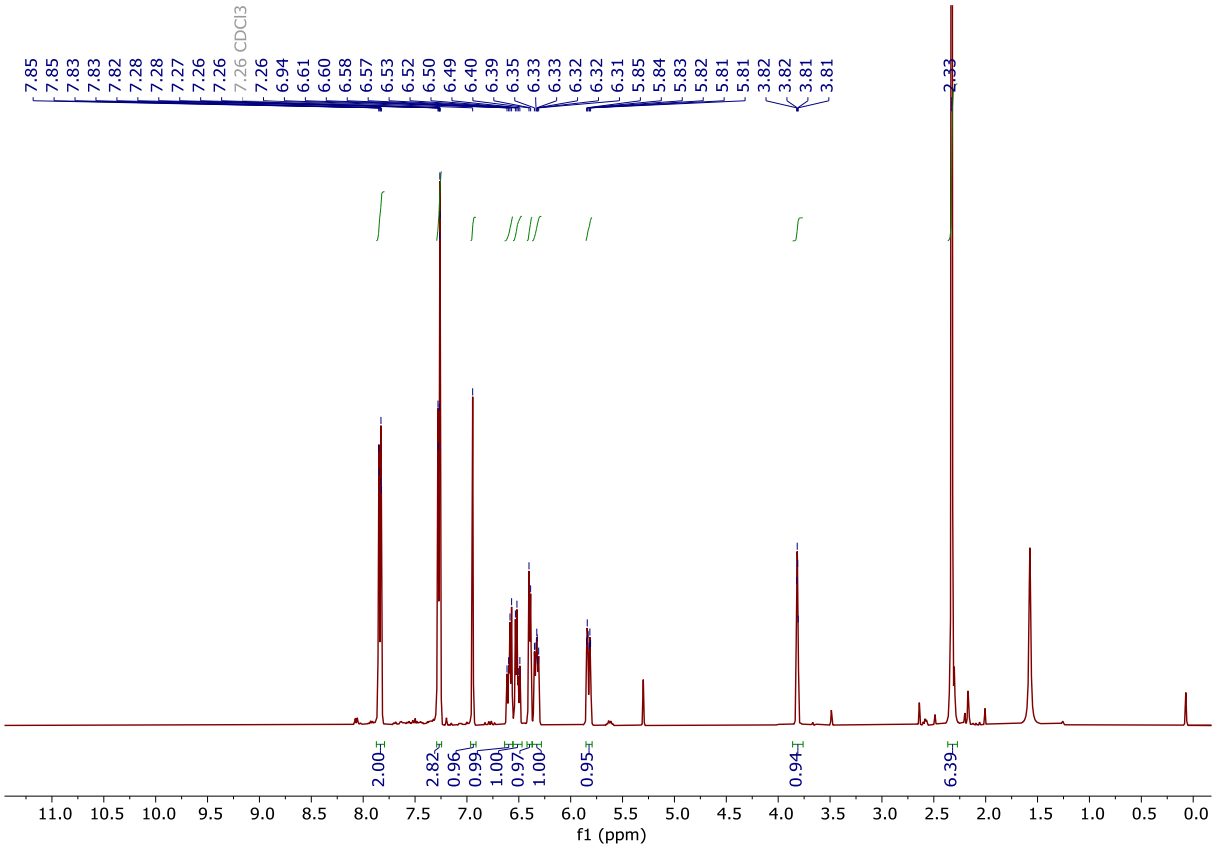

161.12
140.10
139.20
131.12
130.43
130.30
127.95
127.75
123.21
120.07
119.43
115.43
114.84
113.01
77.16 CDCl3
55.59
51.28
45.35
70
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
4
f1 (ppm)

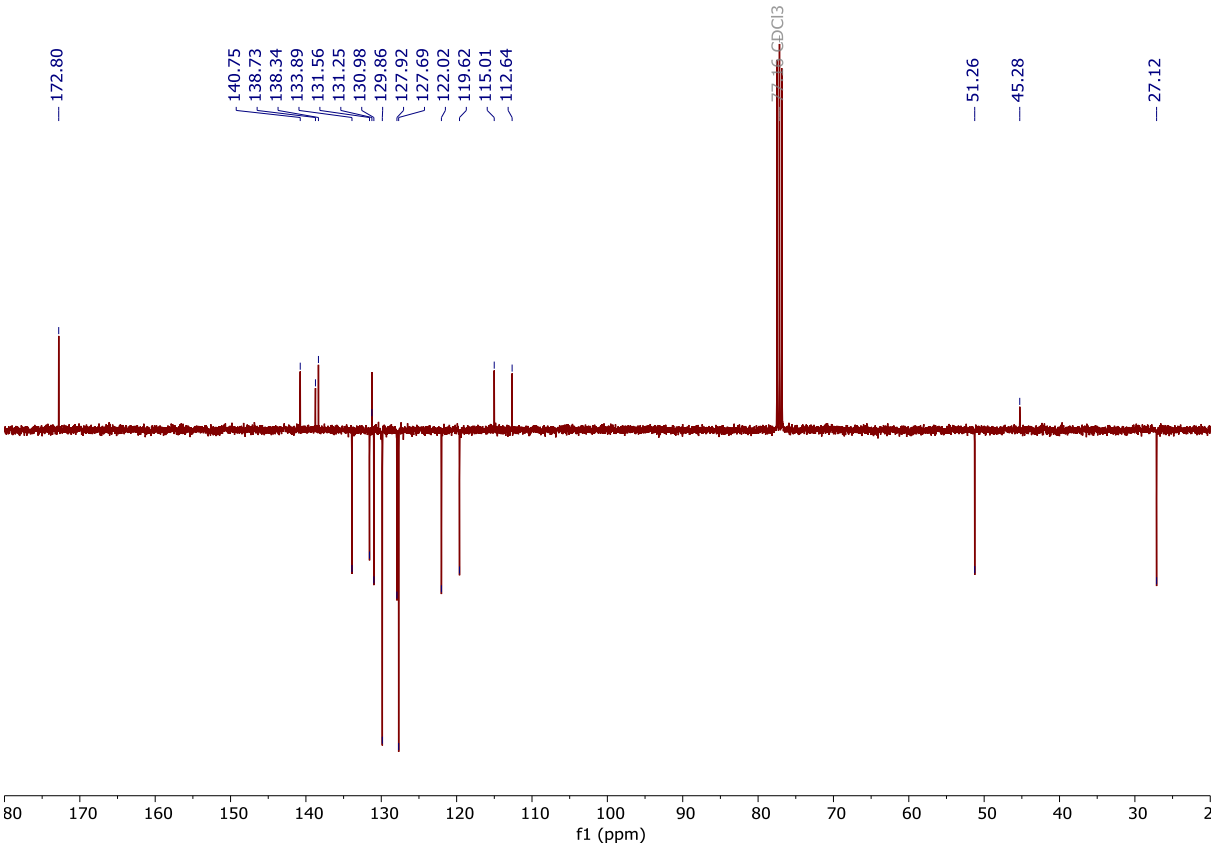
DHA5


7.77 7.77 7.76 7.76 7.75 7.74 7.74 7.73 7.26 7.26 7.26 CDCl3 7.24 7.23 7.23 7.23 7.22 7.21 7.21 7.20 6.85 6.59 6.58 6.56 6.55 6.50 6.49 6.47 6.46 6.35 6.34 6.33 6.31 6.31 6.30 6.29 6.29 6.28 5.83 5.82 5.81 5.80 3.80 3.80 3.79 3.79 3.78 3.78 2.33
2.00 2.63 1.00 1.01 1.01 2.03 1.00 0.98 3.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

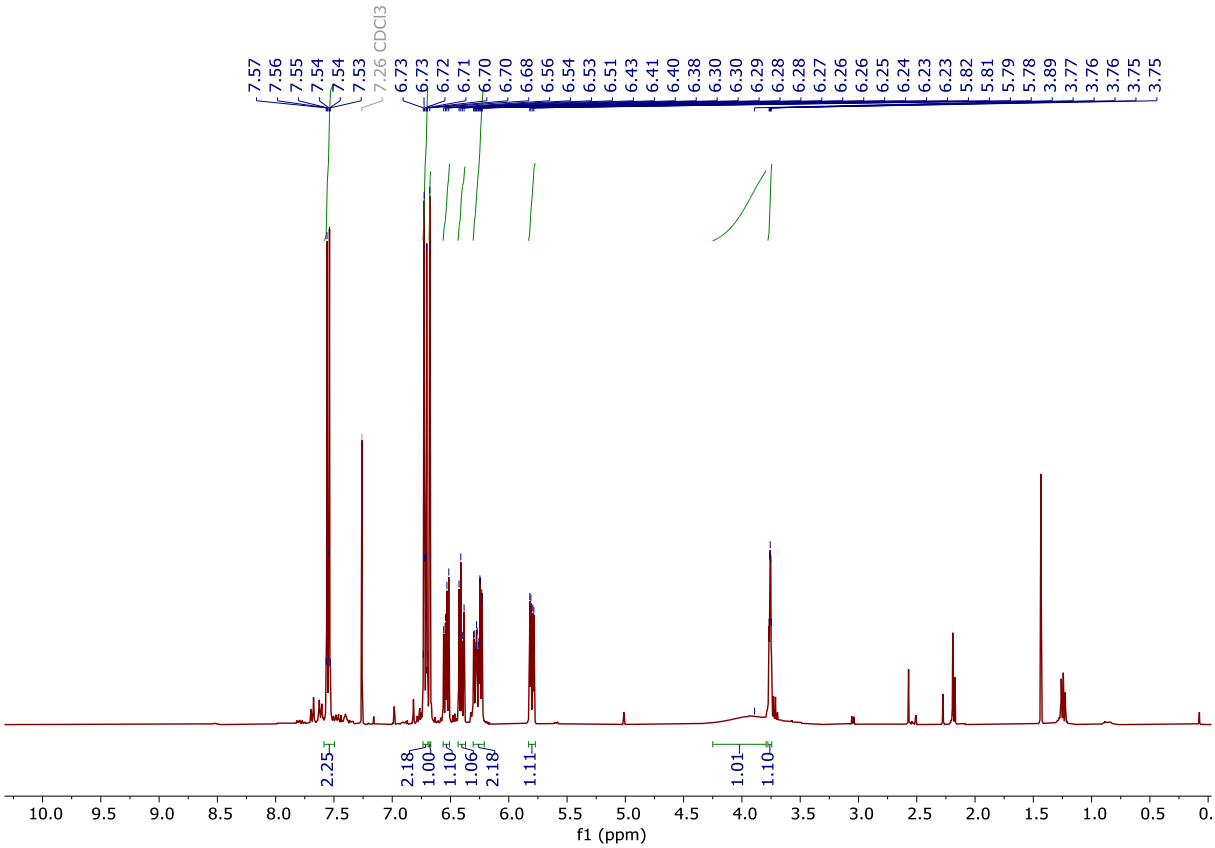

169.15 151.97 139.33 138.66 132.67 131.13 131.02 128.28 127.82 127.60 122.67 121.26 119.59 115.15 112.75 77.16 CDCl3 51.28 45.39 21.30
75 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 2
f1 (ppm)

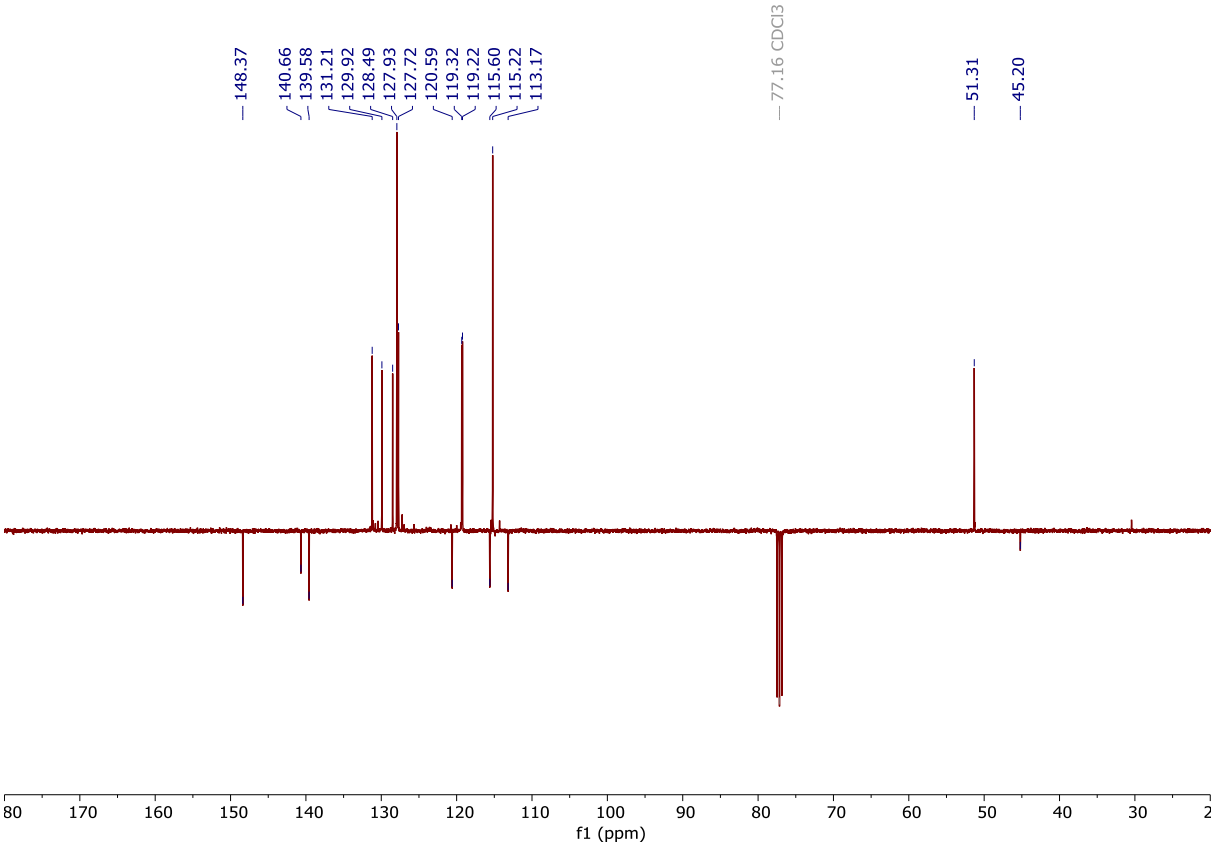
DHA6


7.85
7.85
7.83
7.83
7.82
7.28
7.28
7.27
7.26
7.26
7.26 CDCl3
7.26
6.94
6.61
6.60
6.58
6.57
6.53
6.52
6.50
6.49
6.40
6.39
6.35
6.33
6.33
6.32
6.31
5.85
5.84
5.83
5.82
5.81
5.81
3.82
3.82
3.81
3.81
2.33
2.00
2.82
0.96
0.99
1.00
0.97
1.00
0.95
0.94
6.39
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

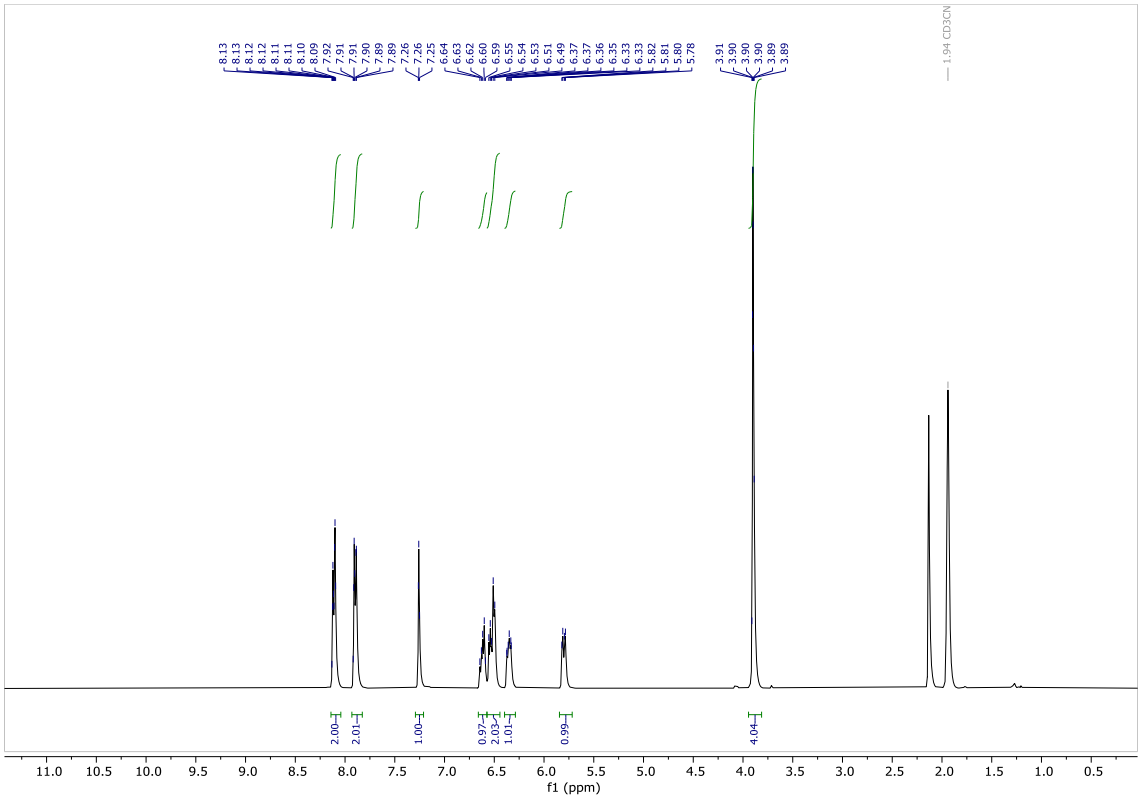

172.80
140.75
138.73
138.34
133.89
131.56
131.25
130.98
129.86
127.92
127.69
122.02
119.62
115.01
112.64
77.16 CDCl3
51.26
45.28
27.12
80 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 2
f1 (ppm)

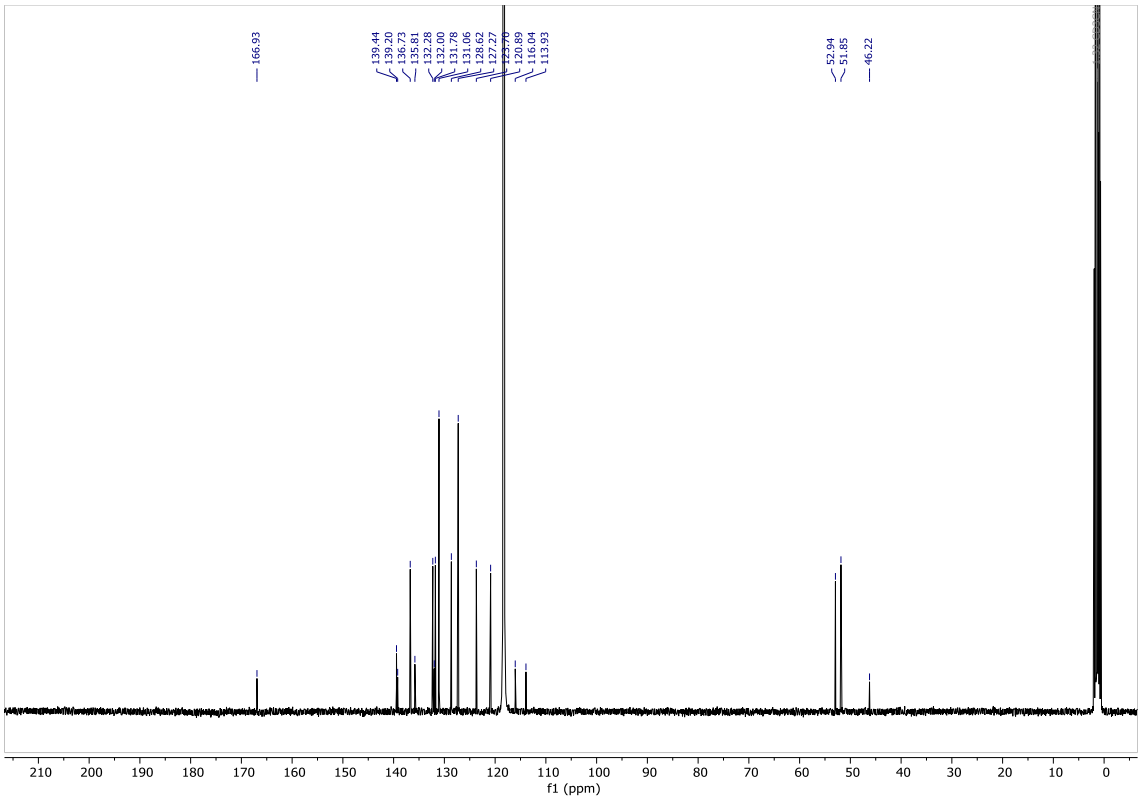
DHA7


7.57
7.56
7.55
7.54
7.54
7.53
7.26 CDCl3
6.73
6.73
6.72
6.71
6.70
6.70
6.68
6.56
6.54
6.53
6.51
6.43
6.41
6.40
6.38
6.30
6.30
6.29
6.28
6.28
6.27
6.26
6.26
6.25
6.24
6.23
6.23
5.82
5.81
5.79
5.78
3.89
3.77
3.76
3.76
3.75
3.75
2.25
2.18
1.00
1.10
1.06
2.18
1.11
1.01
1.10
f1 (ppm)

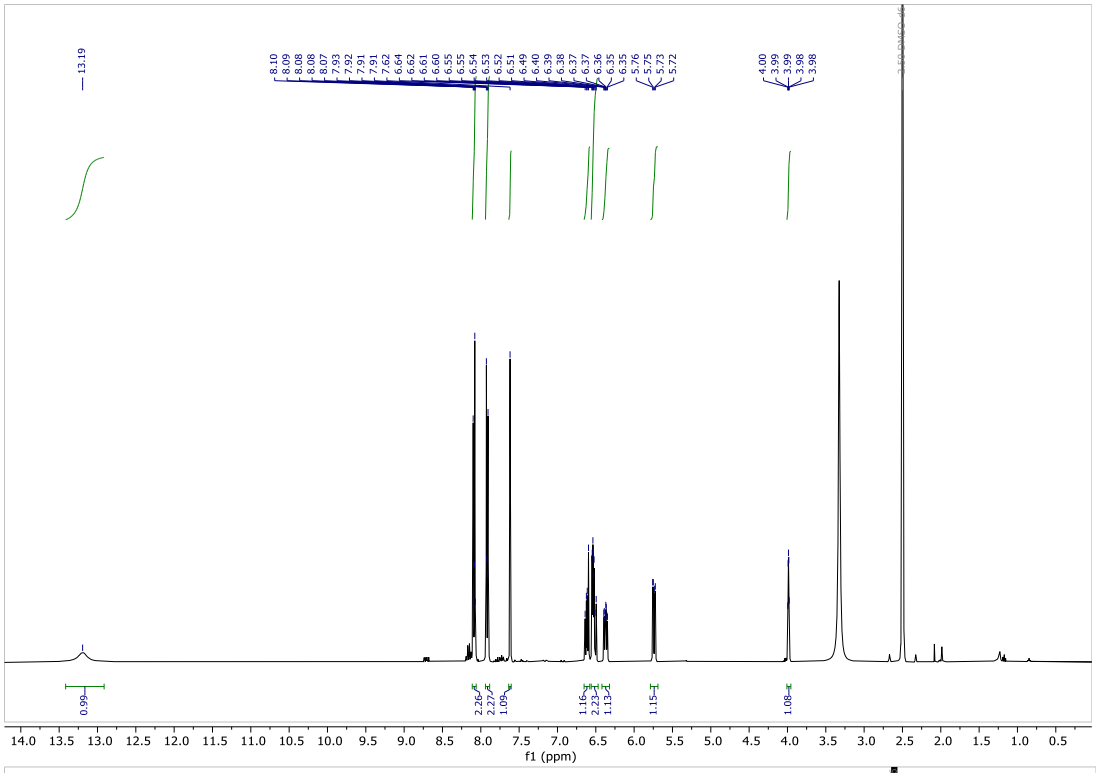

148.37
140.66
139.58
131.21
129.92
128.49
127.93
127.72
120.59
119.32
119.22
115.60
115.22
113.17
77.16 CDCl3
51.31
45.20
f1 (ppm)

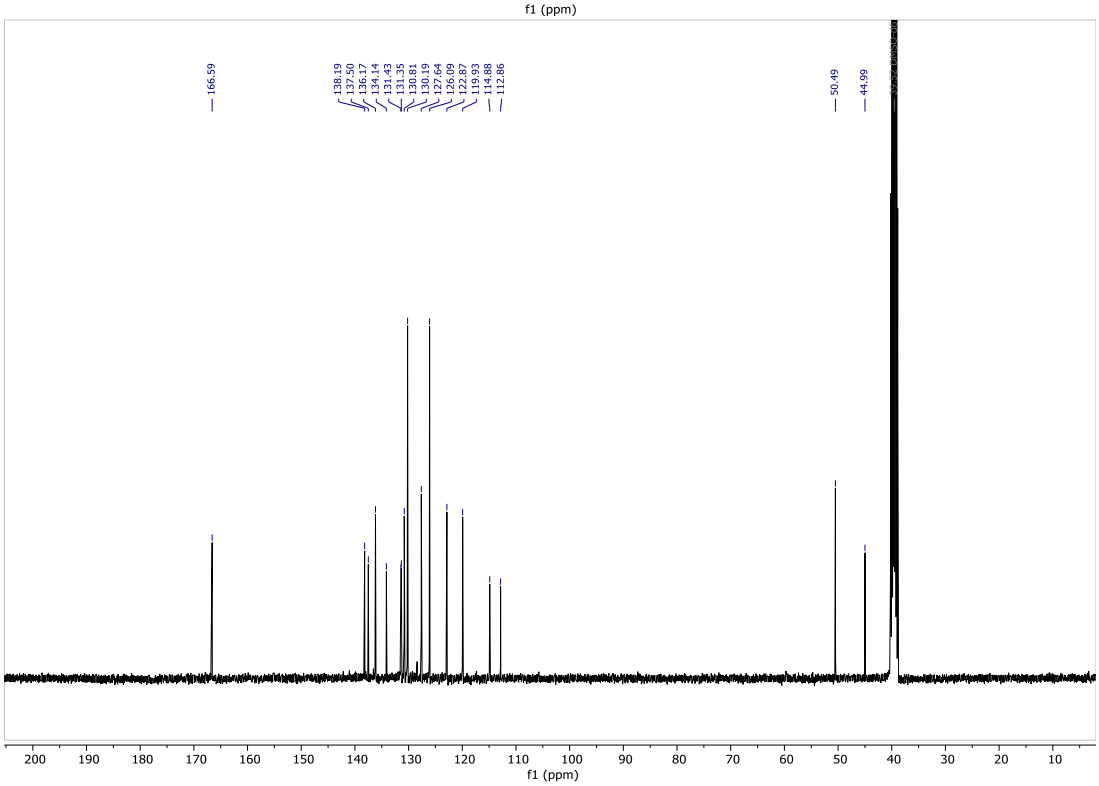
DHA8


8.13
8.13
8.12
8.12
8.11
8.11
8.10
8.09
7.92
7.91
7.91
7.90
7.89
7.89
7.26
7.26
7.25
6.64
6.63
6.62
6.60
6.59
6.55
6.54
6.53
6.51
6.49
6.37
6.37
6.36
6.35
6.33
6.33
5.82
5.81
5.80
5.78
3.91
3.90
3.90
3.90
3.89
3.89
1.94 CD3CN
2.00
2.01
1.00
0.97
2.03
1.01
0.99
4.04
f1 (ppm)

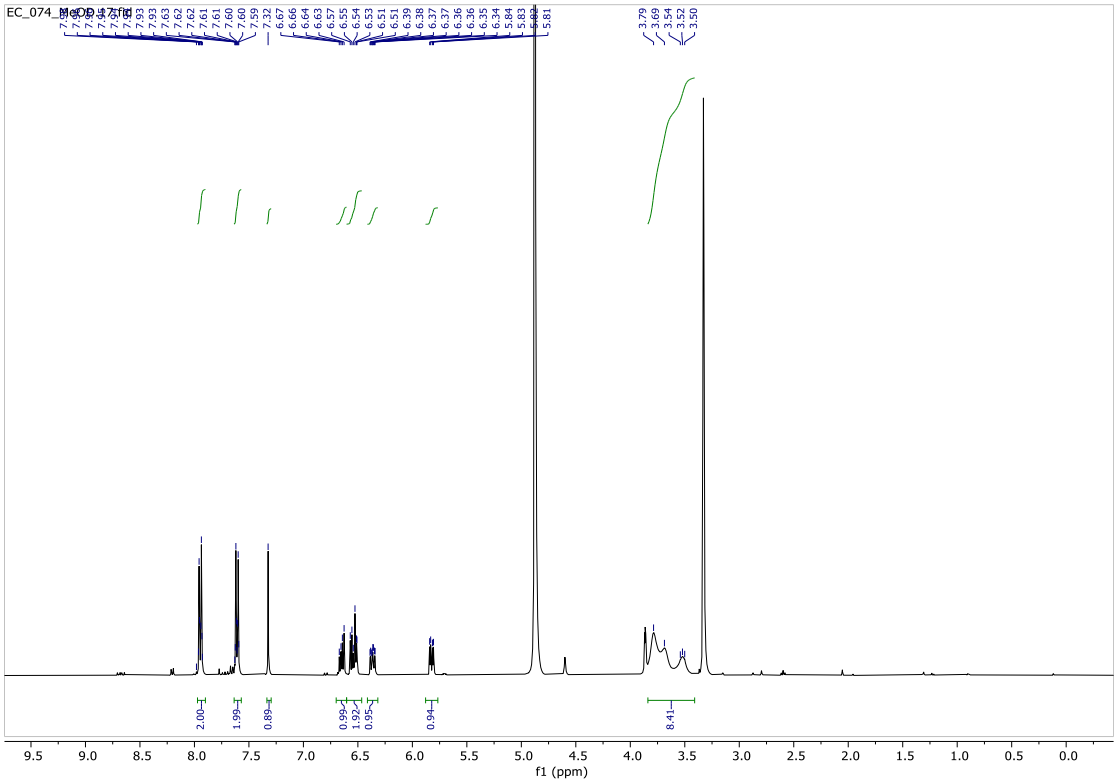

166.93
139.44
139.20
136.73
135.81
132.28
132.00
131.78
131.06
128.62
127.27
120.89
116.04
113.93
52.94
51.85
46.22
f1 (ppm)

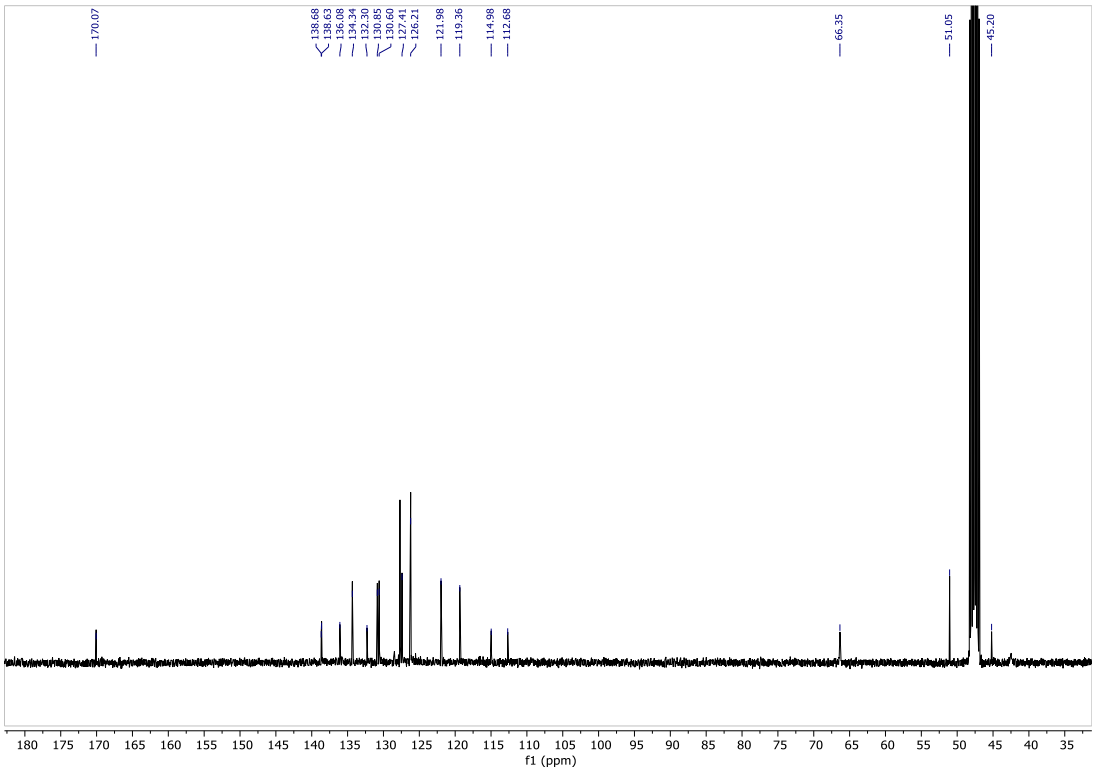
DHA9


13.19
8.10
8.09
8.08
8.08
8.07
7.93
7.92
7.91
7.91
7.62
6.64
6.62
6.61
6.60
6.55
6.54
6.53
6.52
6.51
6.49
6.40
6.39
6.38
6.37
6.37
6.36
6.35
5.76
5.75
5.73
5.72
4.00
3.99
3.99
3.98
3.98
0.99
2.26
2.27
1.09
1.16
2.23
1.13
1.15
1.08
f1 (ppm)

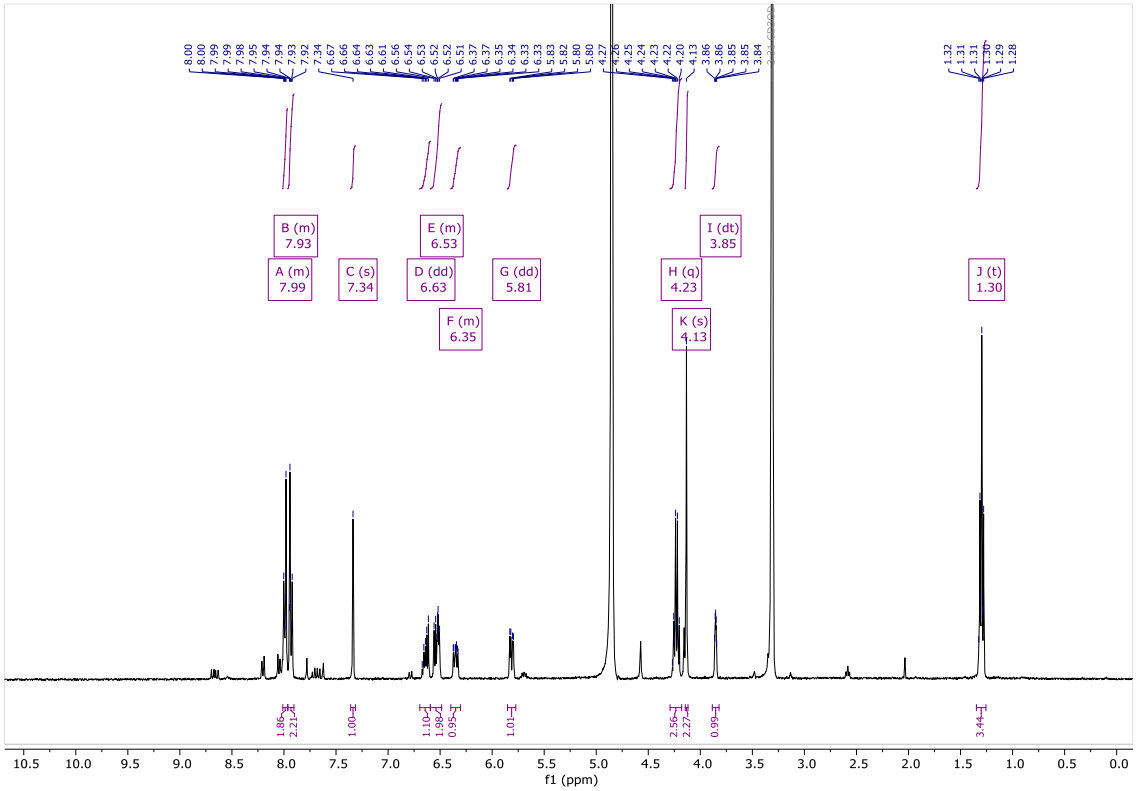

166.59
138.19
137.50
136.17
134.14
131.43
131.35
130.81
130.19
127.64
126.09
122.87
119.93
114.88
112.86
50.49
44.99
f1 (ppm)

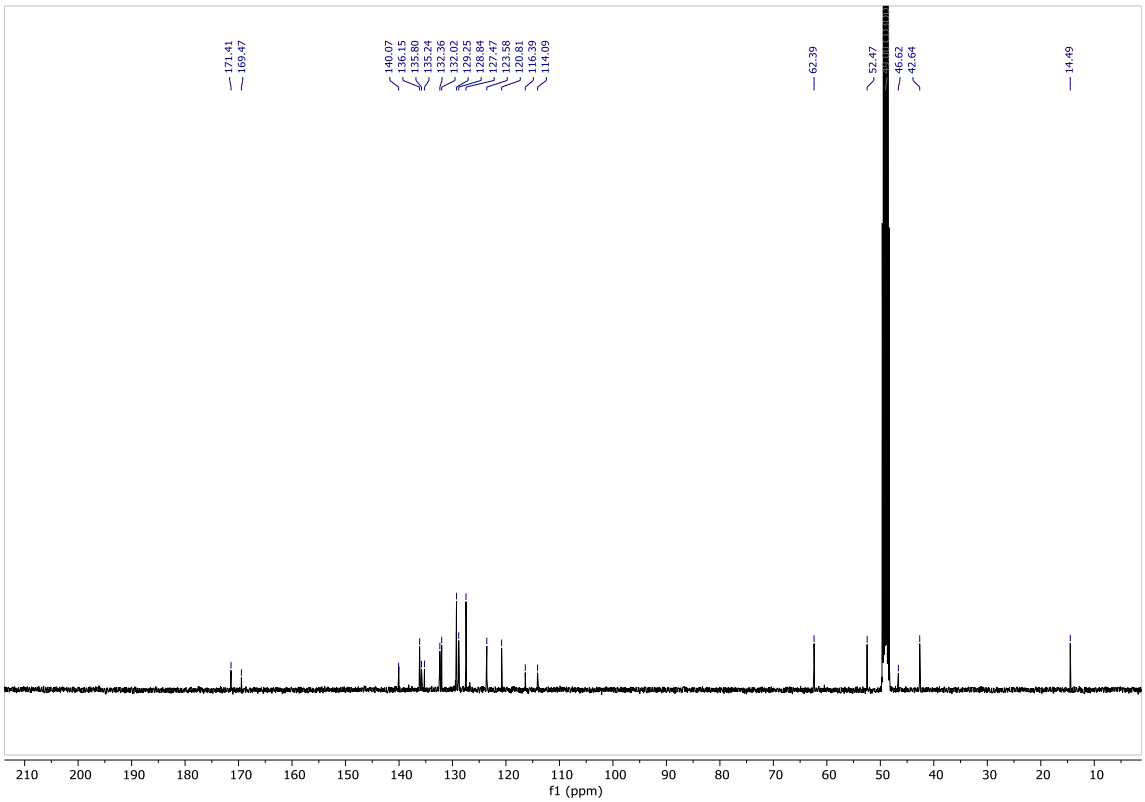
DHA-MO



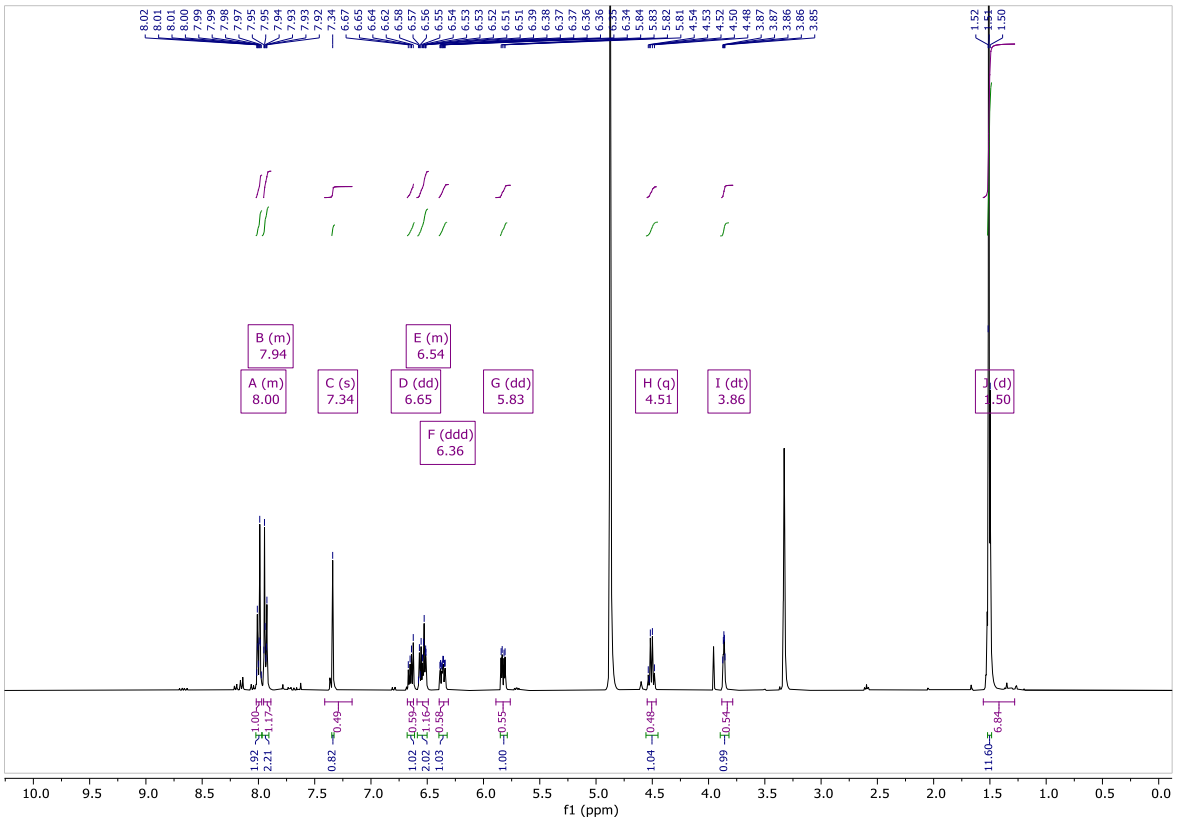


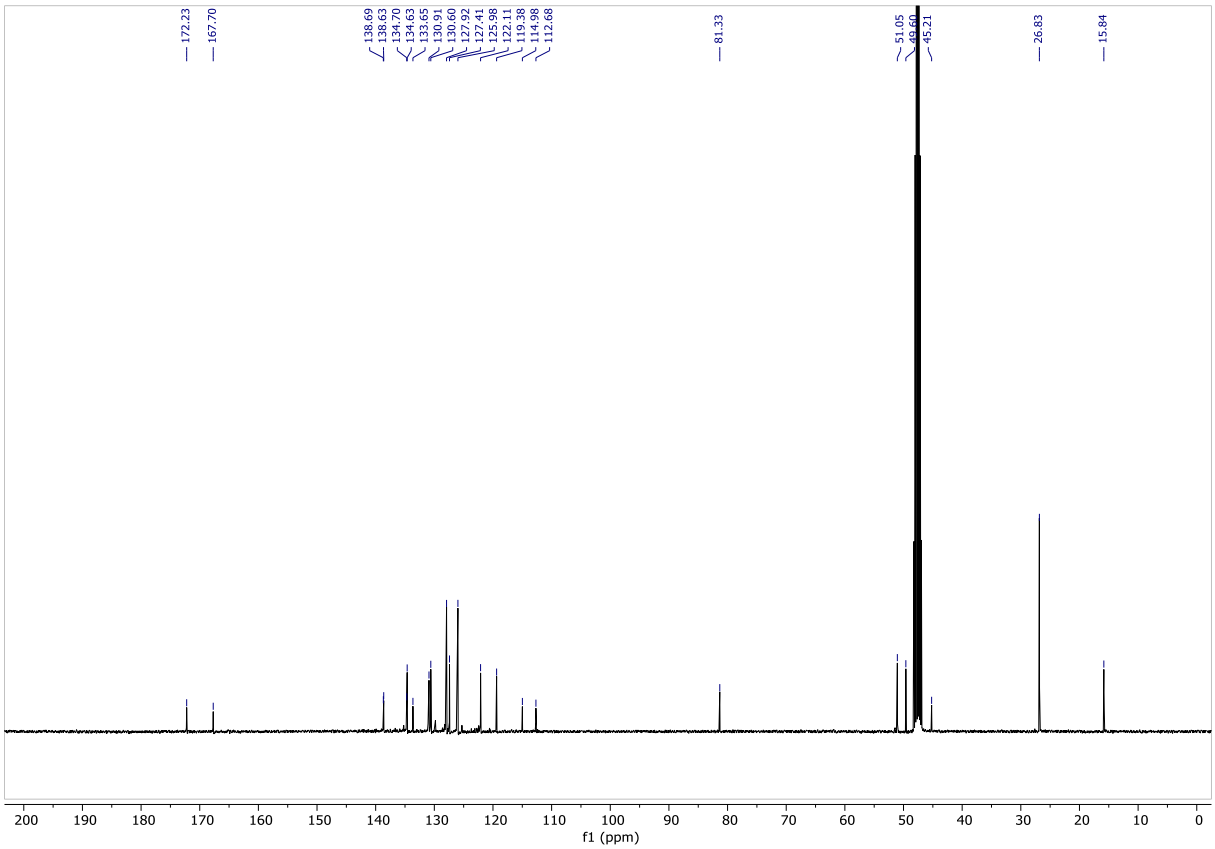
DHA-Gly-OEt


B (m)
7.93
A (m)
7.99
C (s)
7.34
E (m)
6.53
D (dd)
6.63
F (m)
6.35
G (dd)
5.81
I (dt)
3.85
H (q)
4.23
K (s)
4.13
J (t)
1.30
f1 (ppm)

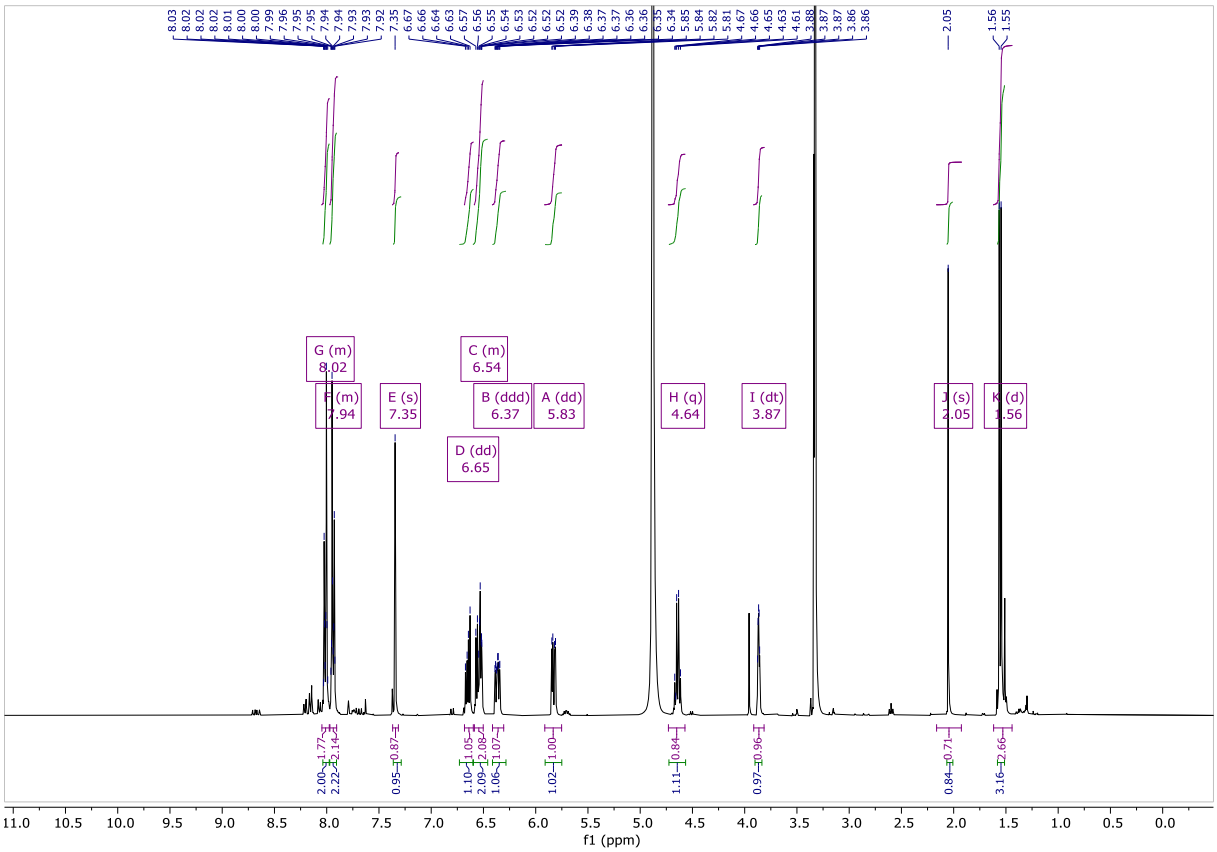

171.41
169.47
140.07
136.15
135.80
135.24
132.36
132.02
129.25
128.84
127.47
125.58
120.81
116.39
114.09
62.39
52.47
46.62
42.64
14.49
f1 (ppm)

DHA-Ala-O*t*Bu

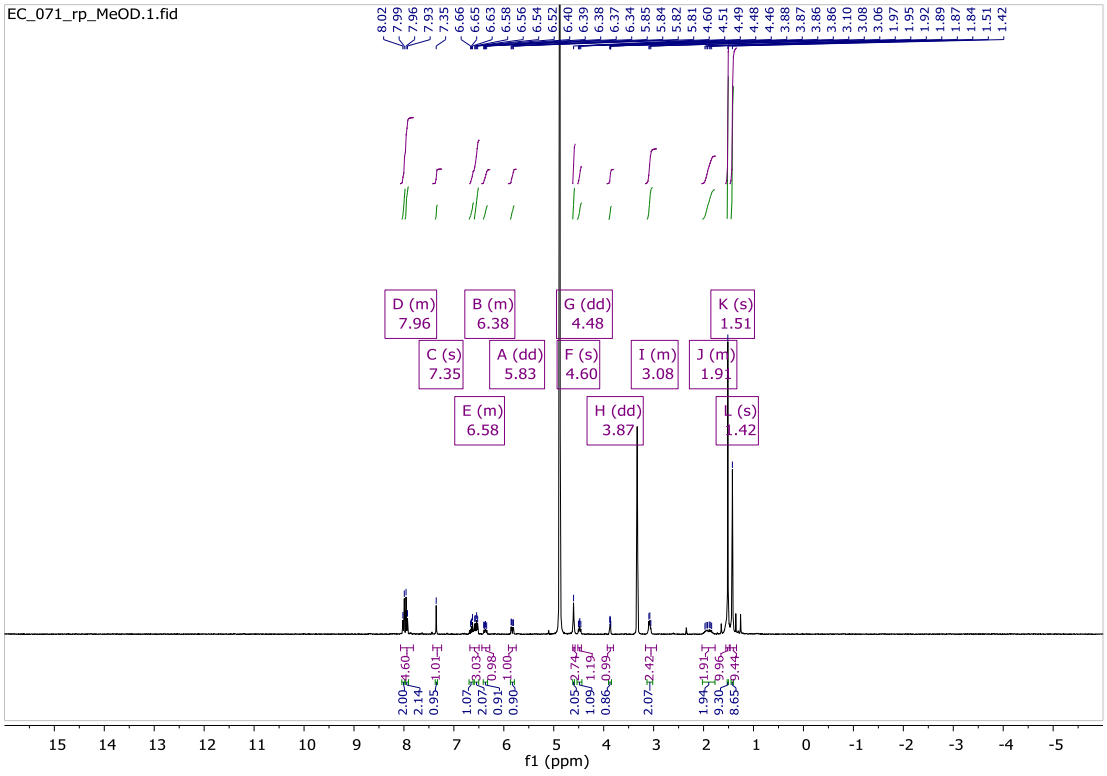

B (m)
7.94
E (m)
6.54
A (m)
8.00
C (s)
7.34
D (dd)
6.65
G (dd)
5.83
H (q)
4.51
I (dt)
3.86
J (d)
1.50
F (ddd)
6.36
f1 (ppm)

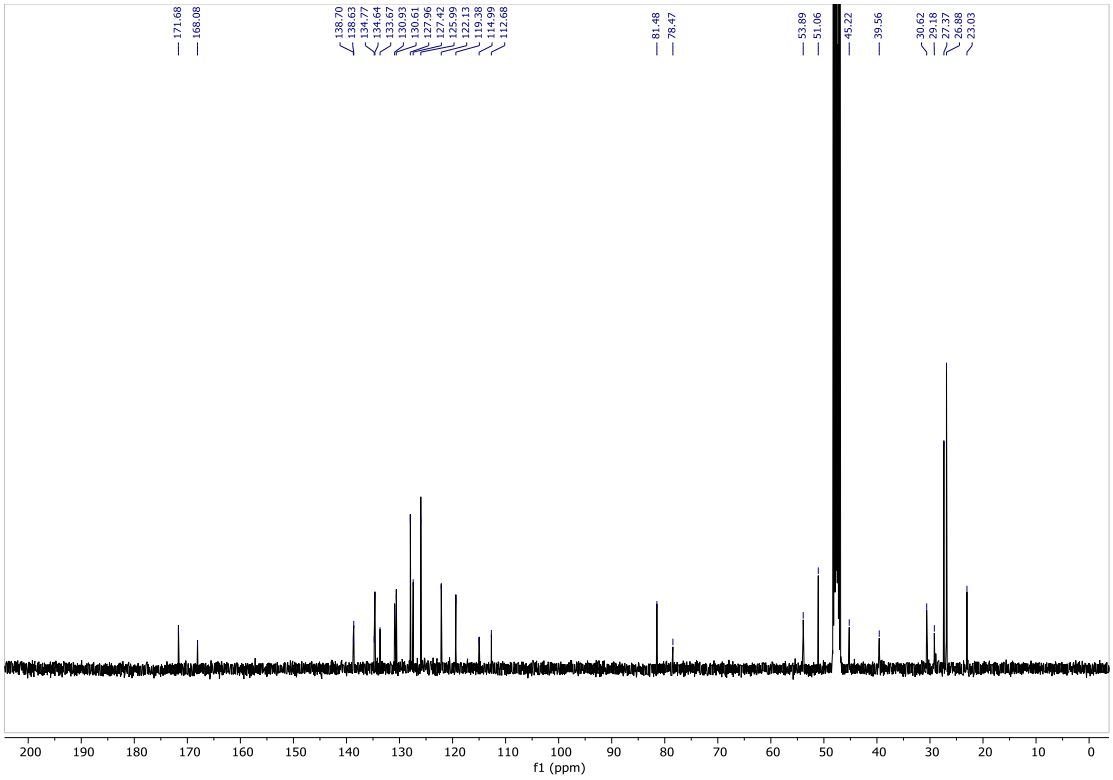

f1 (ppm)

DHA-Ala

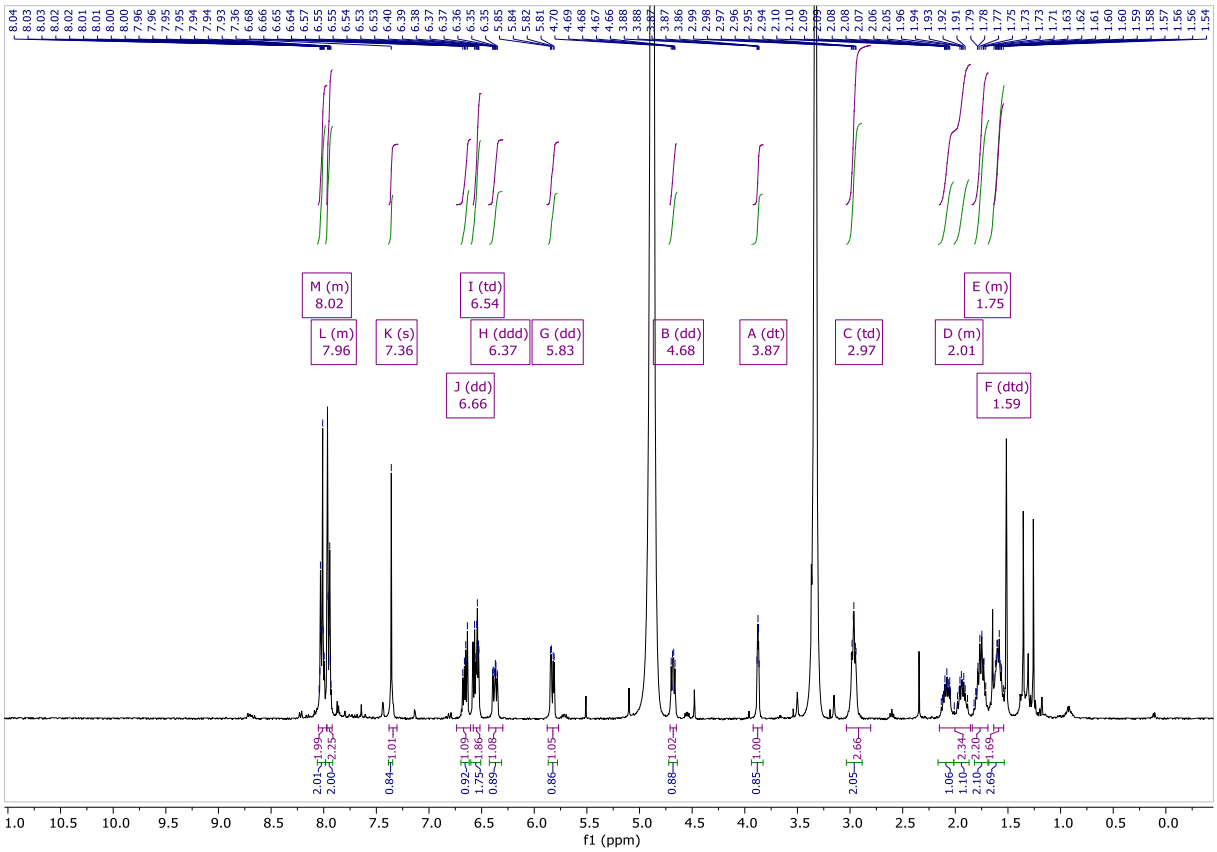

G (m) 8.02
F (m) 7.94
E (s) 7.35
C (m) 6.54
B (ddd) 6.37
A (dd) 5.83
D (dd) 6.65
H (q) 4.64
I (dt) 3.87
J (s) 2.05
K (d) 1.56
f1 (ppm)

DHA-Lys(Boc)-O*t*Bu

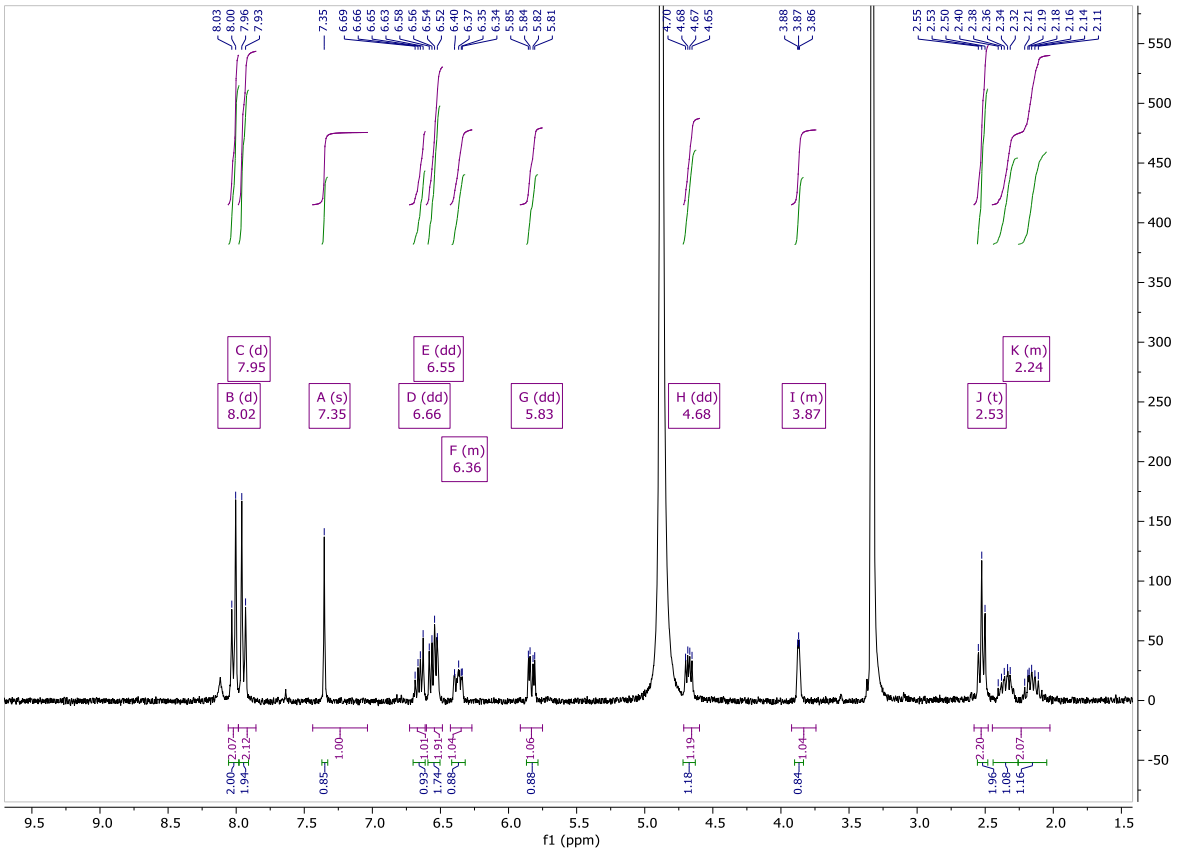




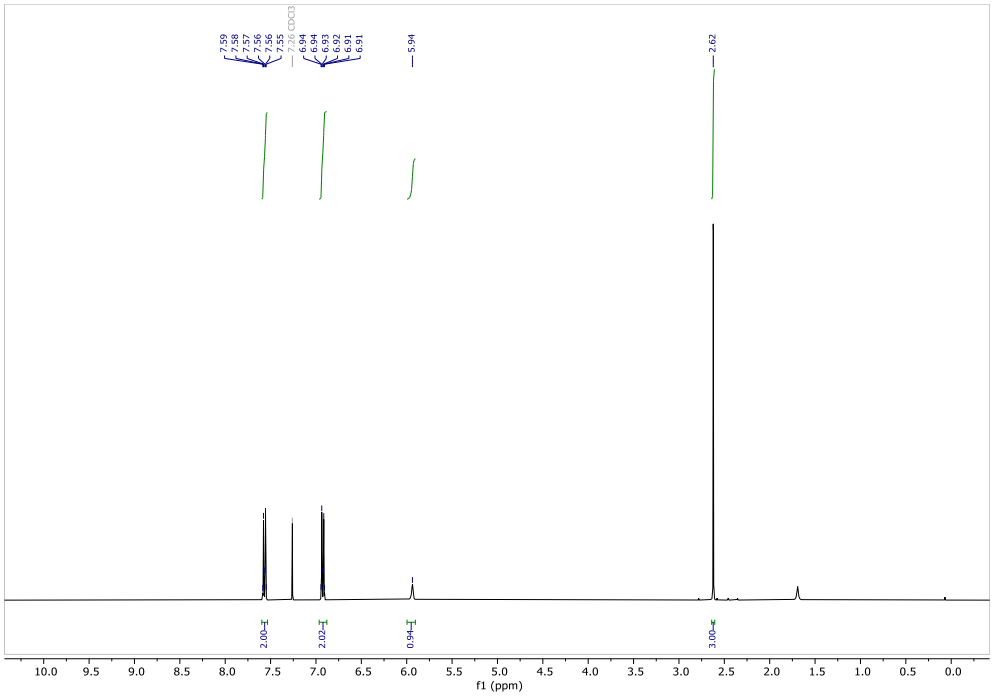
DHA-Lys

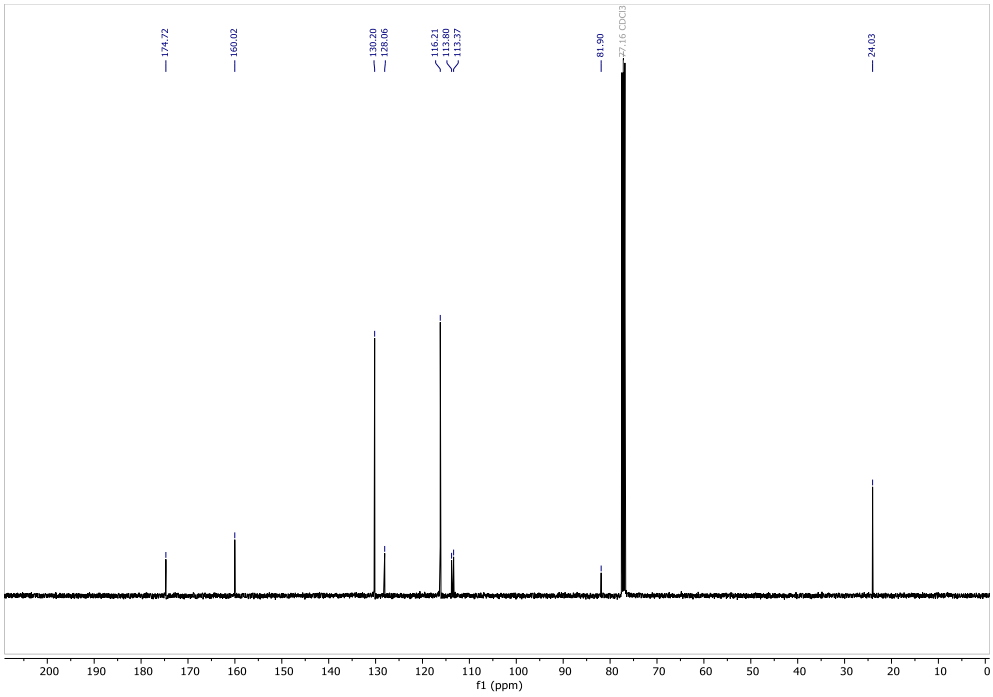

M (m)
8.02
L (m)
7.96
K (s)
7.36
I (td)
6.54
J (dd)
6.66
H (ddd)
6.37
G (dd)
5.83
B (dd)
4.68
A (dt)
3.87
C (td)
2.97
E (m)
1.75
D (m)
2.01
F (dtd)
1.59
f1 (ppm)

DHA-Glu

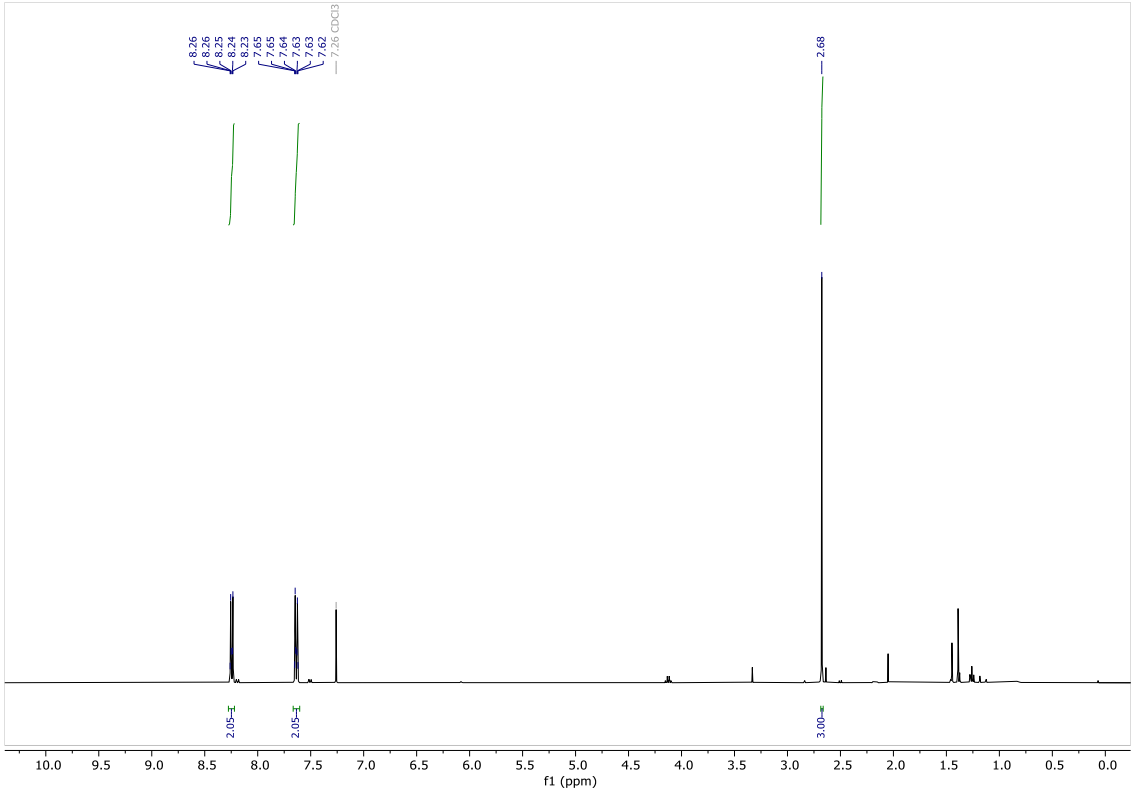

C (d)
7.95
B (d)
8.02
A (s)
7.35
E (dd)
6.55
D (dd)
6.66
F (m)
6.36
G (dd)
5.83
H (dd)
4.68
I (m)
3.87
K (m)
2.24
J (t)
2.53
f1 (ppm)

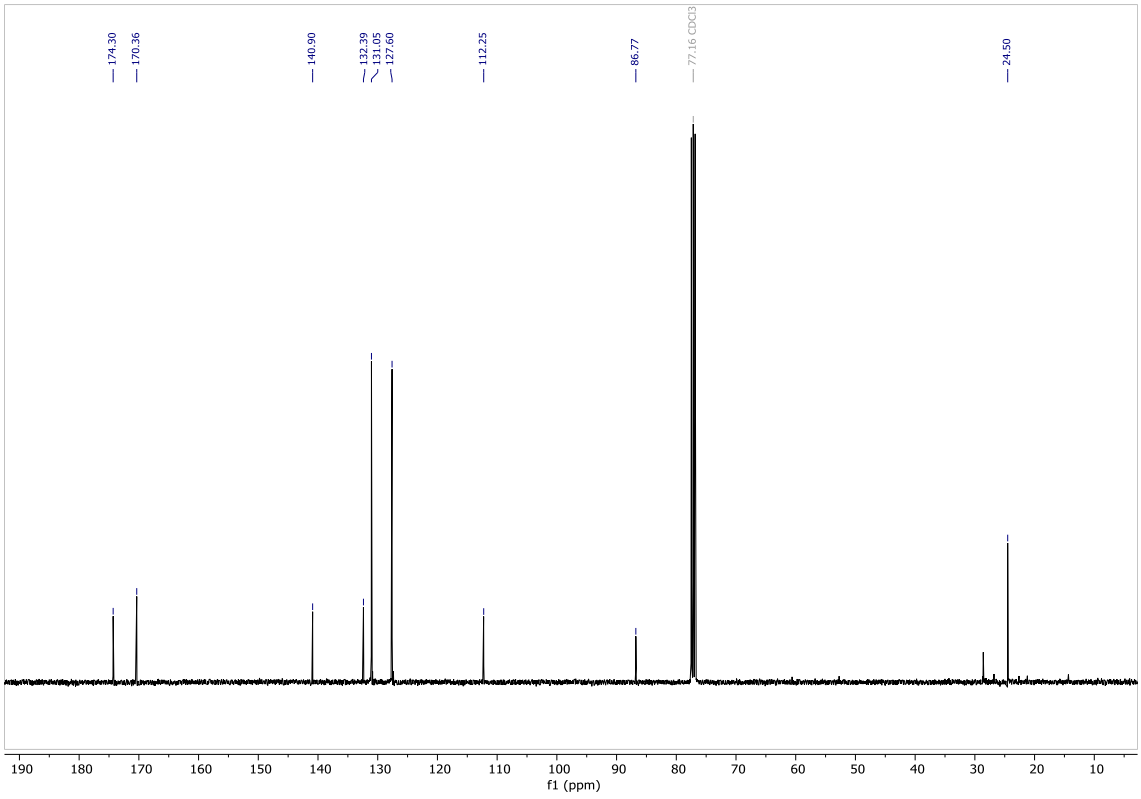
2e


7.59
7.58
7.57
7.56
7.56
7.55
7.26 CDCl3
6.94
6.94
6.93
6.92
6.91
6.91
5.94
2.62
2.00
2.02
0.94
3.00
f1 (ppm)

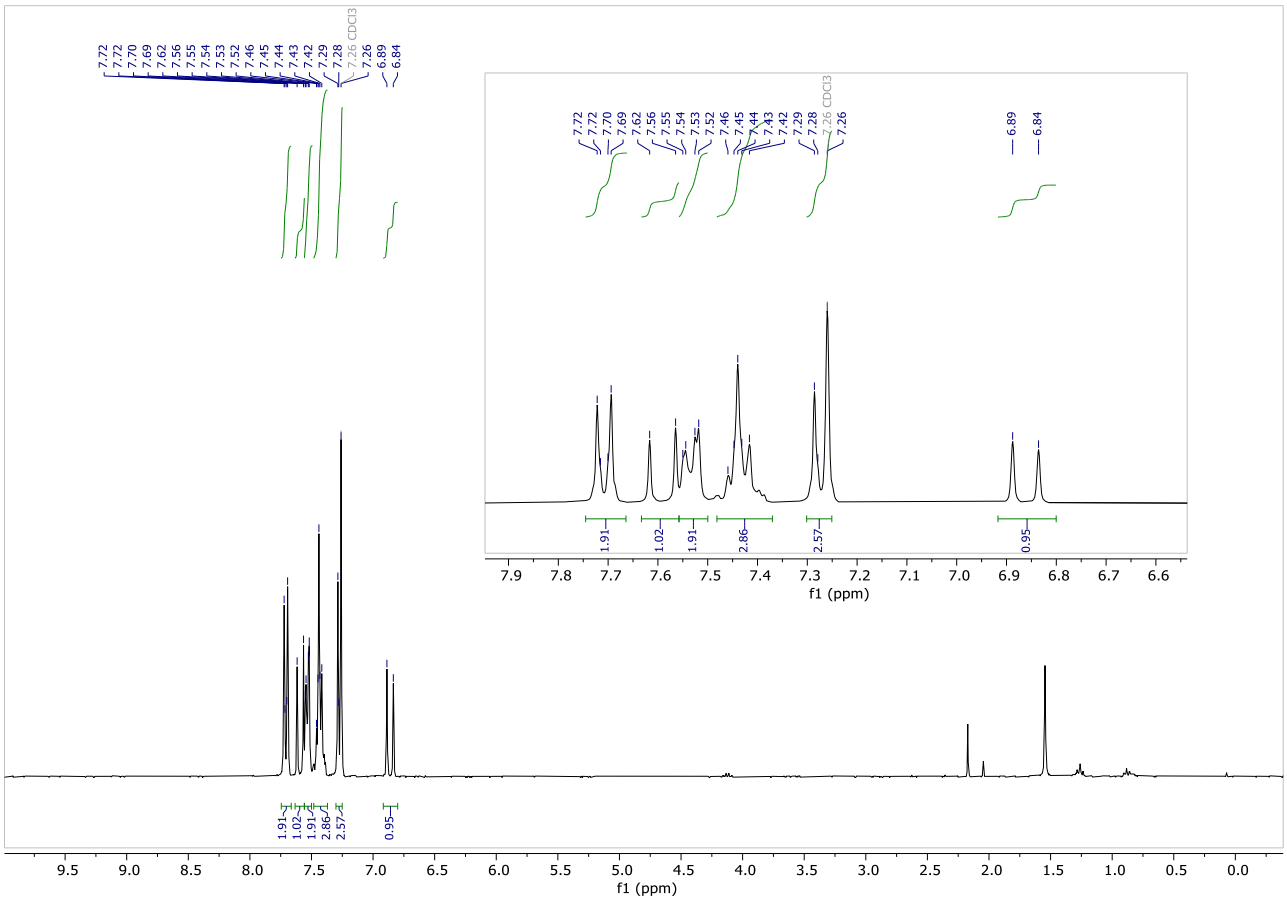

174.72
160.02
130.20
128.06
116.21
113.80
113.37
81.90
77.16 CDCl3
24.03
f1 (ppm)

2h

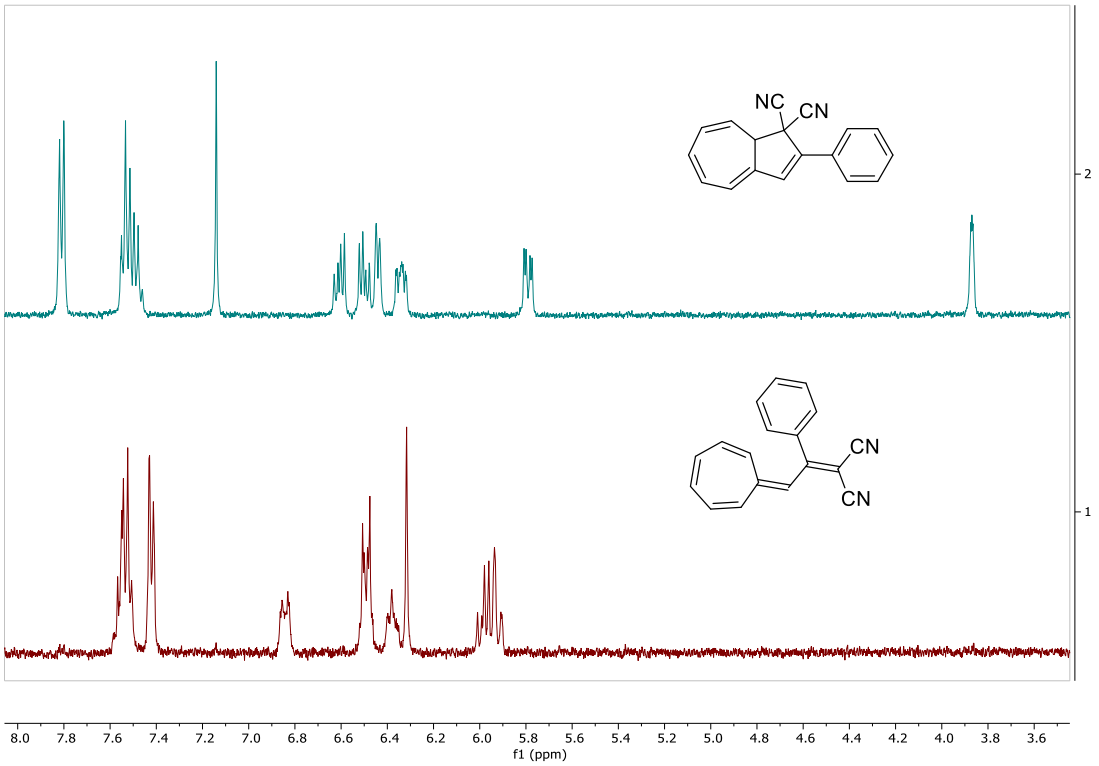

8.26
8.26
8.25
8.24
8.23
7.65
7.65
7.64
7.63
7.63
7.62
7.26 CDCl3
2.68
2.05
2.05
3.00
f1 (ppm)


174.30
170.36
140.90
132.39
131.05
127.60
112.25
86.77
77.16 CDCl3
24.50
f1 (ppm)

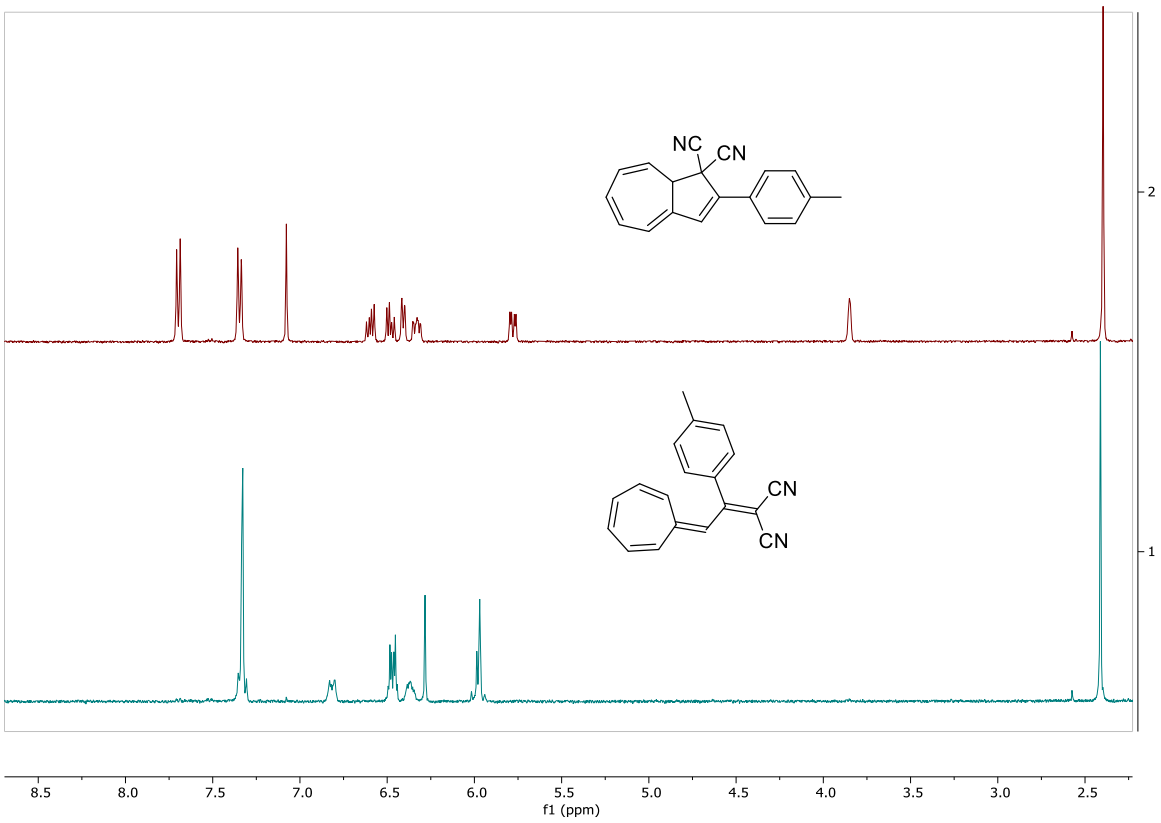
3 (side product from synthesis of **DHA2**)



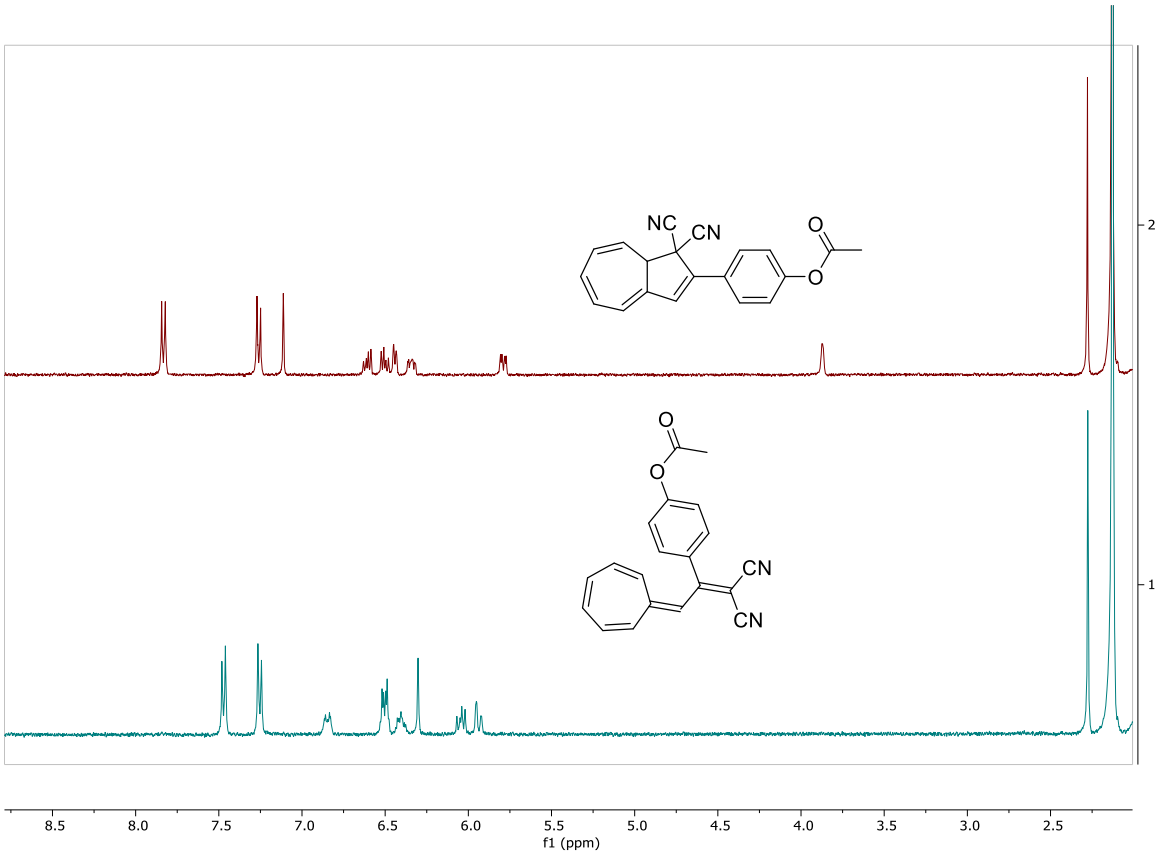
NMR Irradiation Experiments



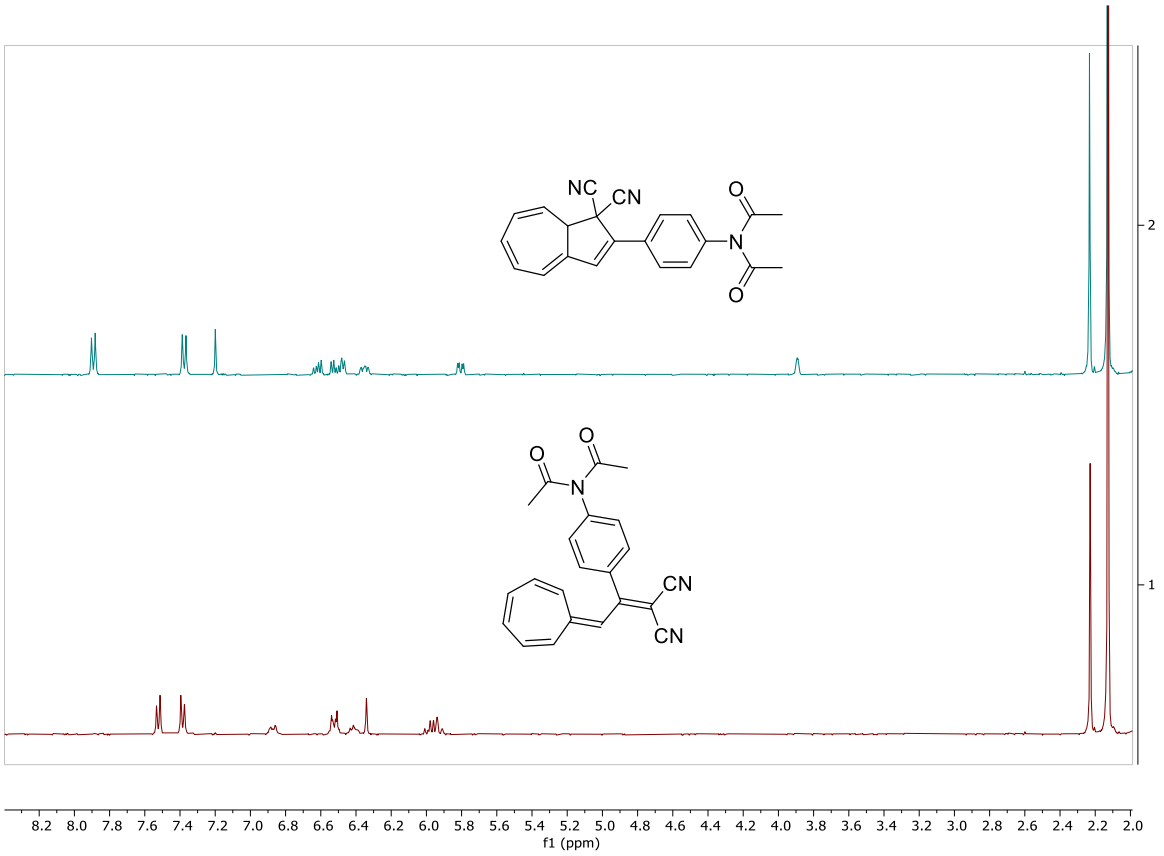
DHA1, CD_3CN, 400 MHz, dark (top), PSS 365 nm (bottom)



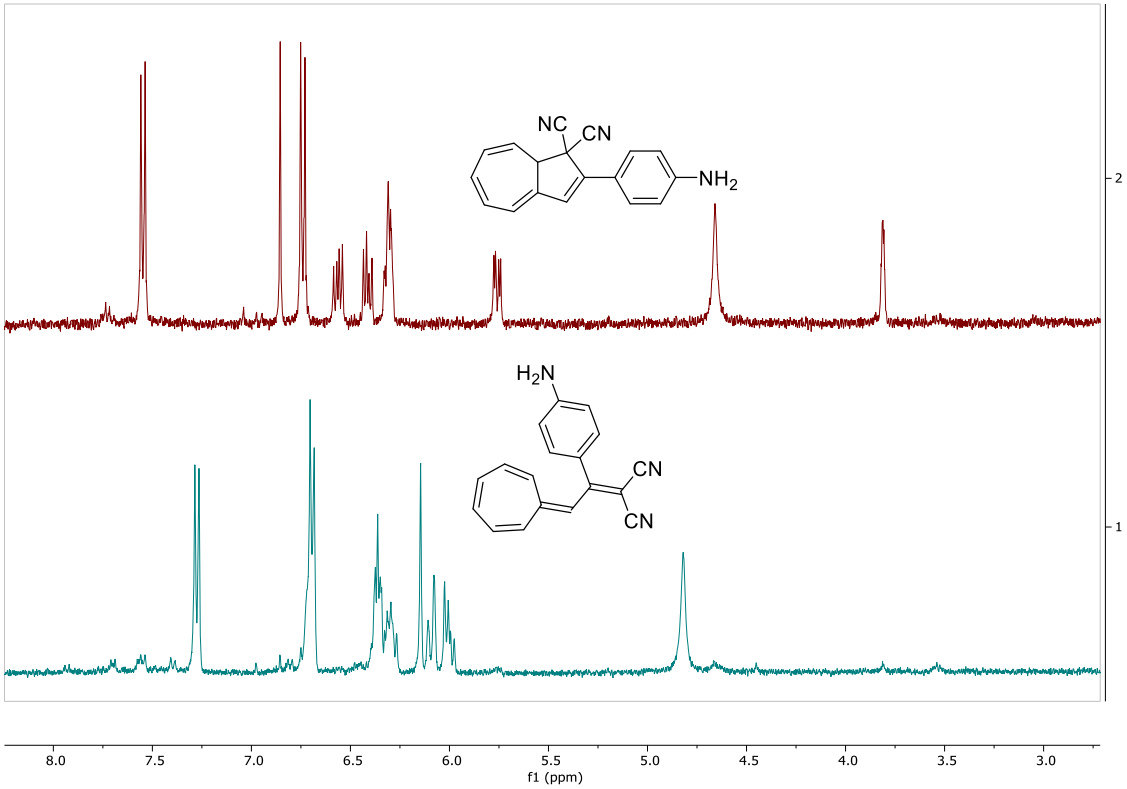
DHA3, CD_3CN, 400 MHz, dark (top), PSS 365 nm (bottom)



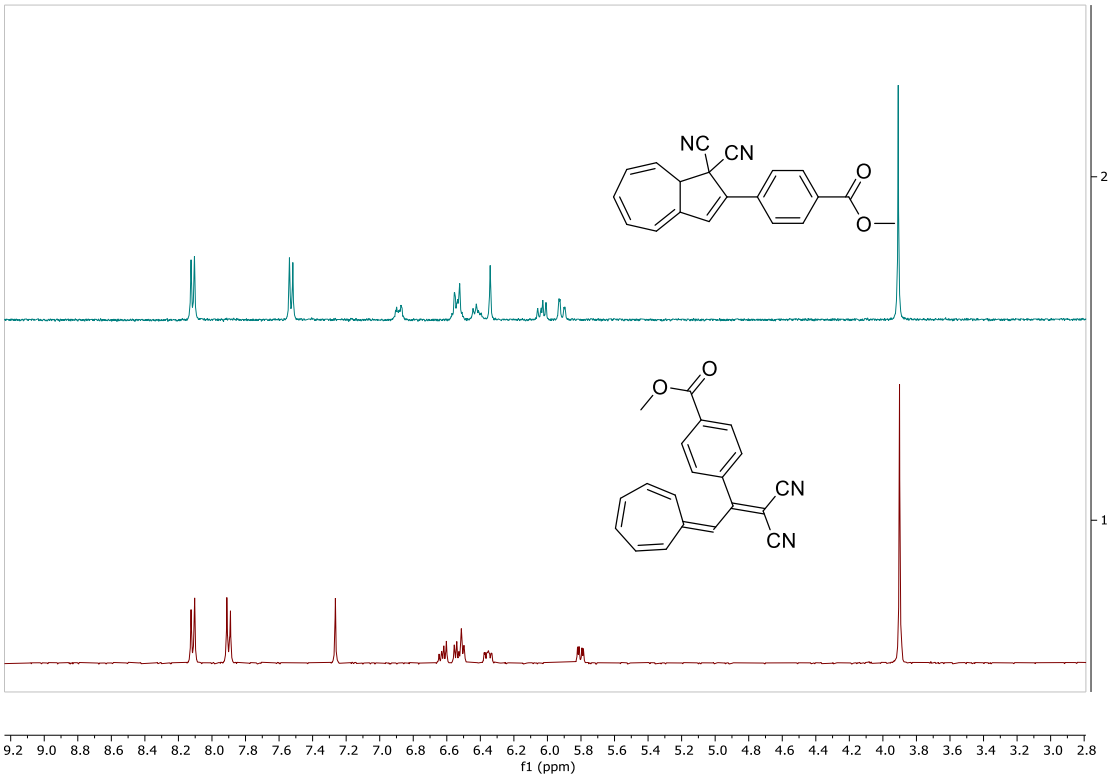
DHA5, CD_3CN, 400 MHz, dark (top), PSS 365 nm (bottom)



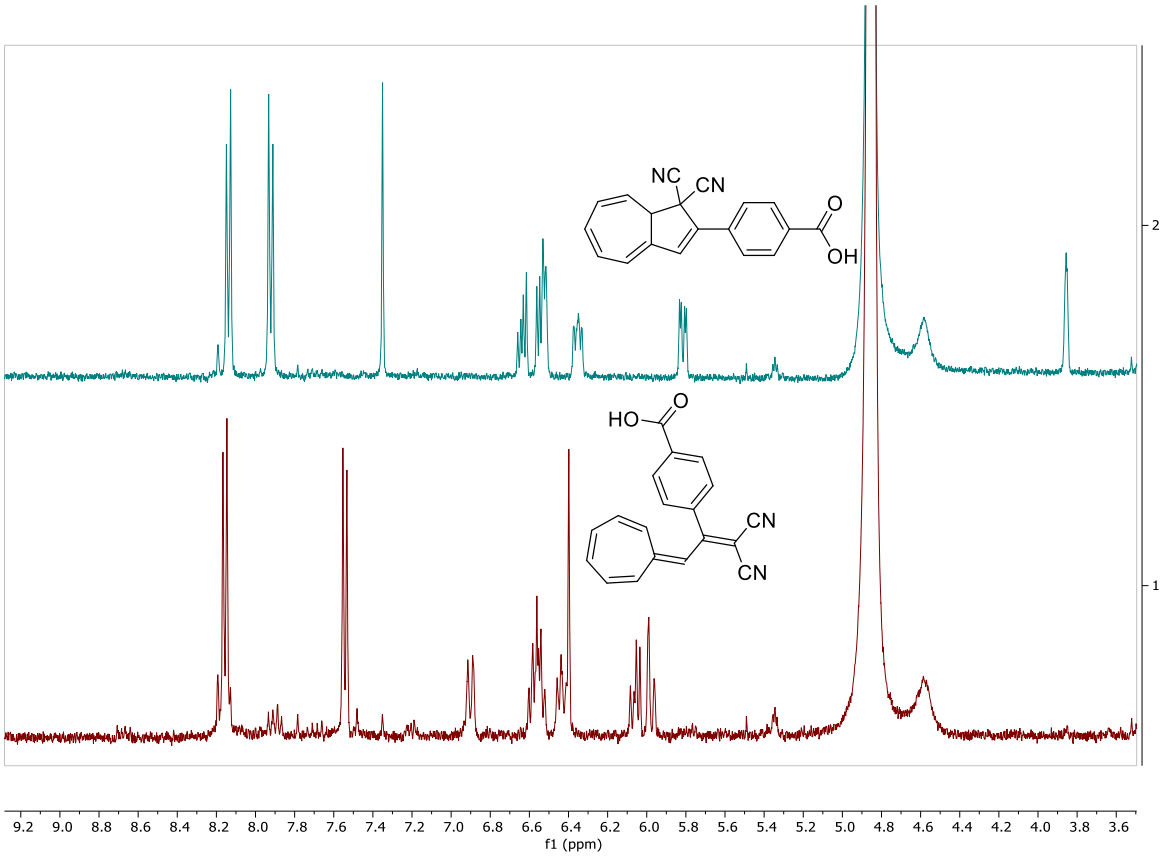
DHA6, CD_3CN, 400 MHz, dark (top), PSS 365 nm (bottom)



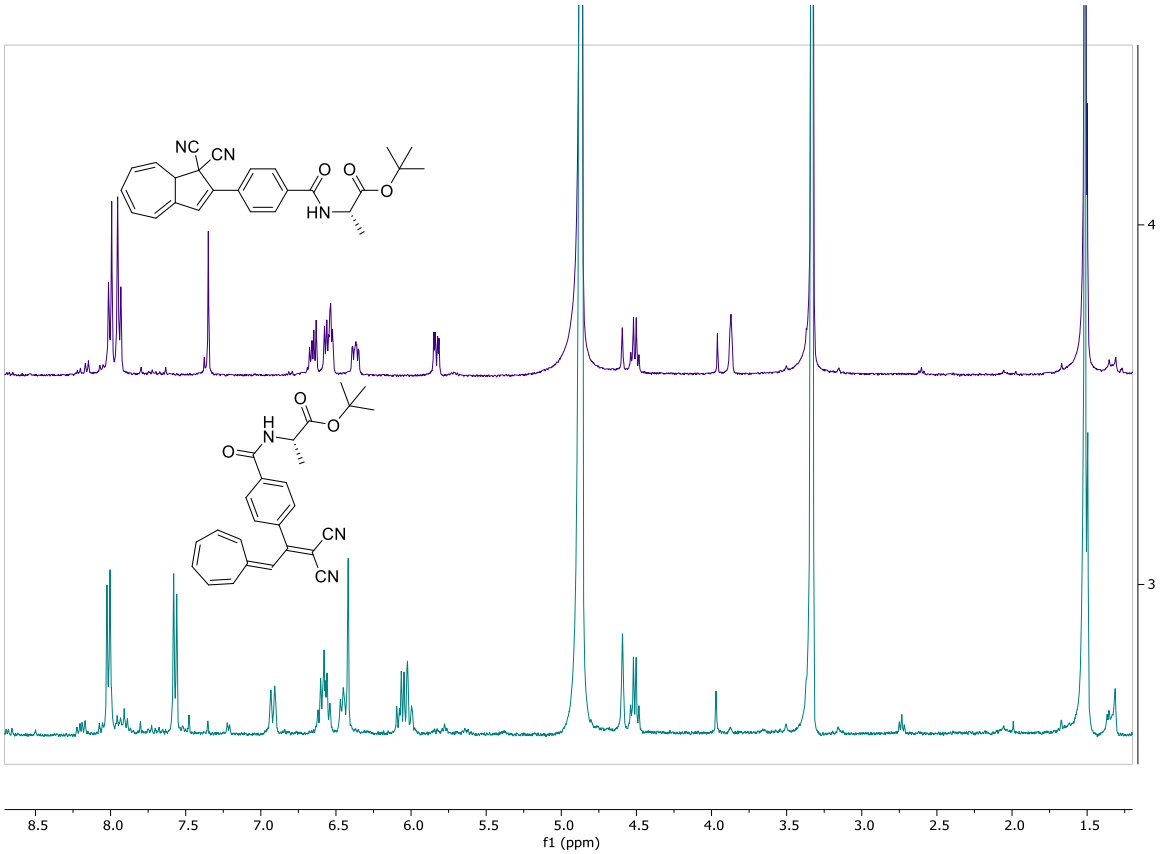
DHA7, CD_3CN, 400 MHz, dark (top), PSS 365 nm (bottom)



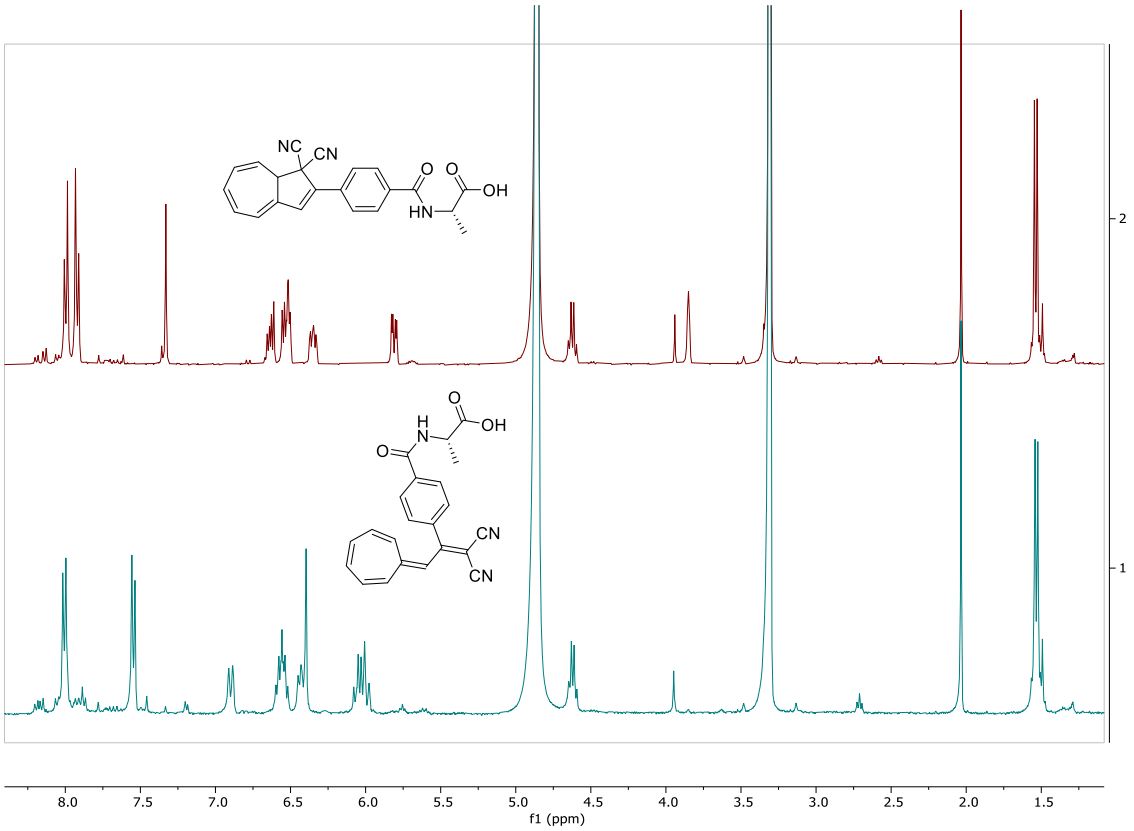
DHA8, CD_3CN, 400 MHz, dark (top), PSS 365 nm (bottom)



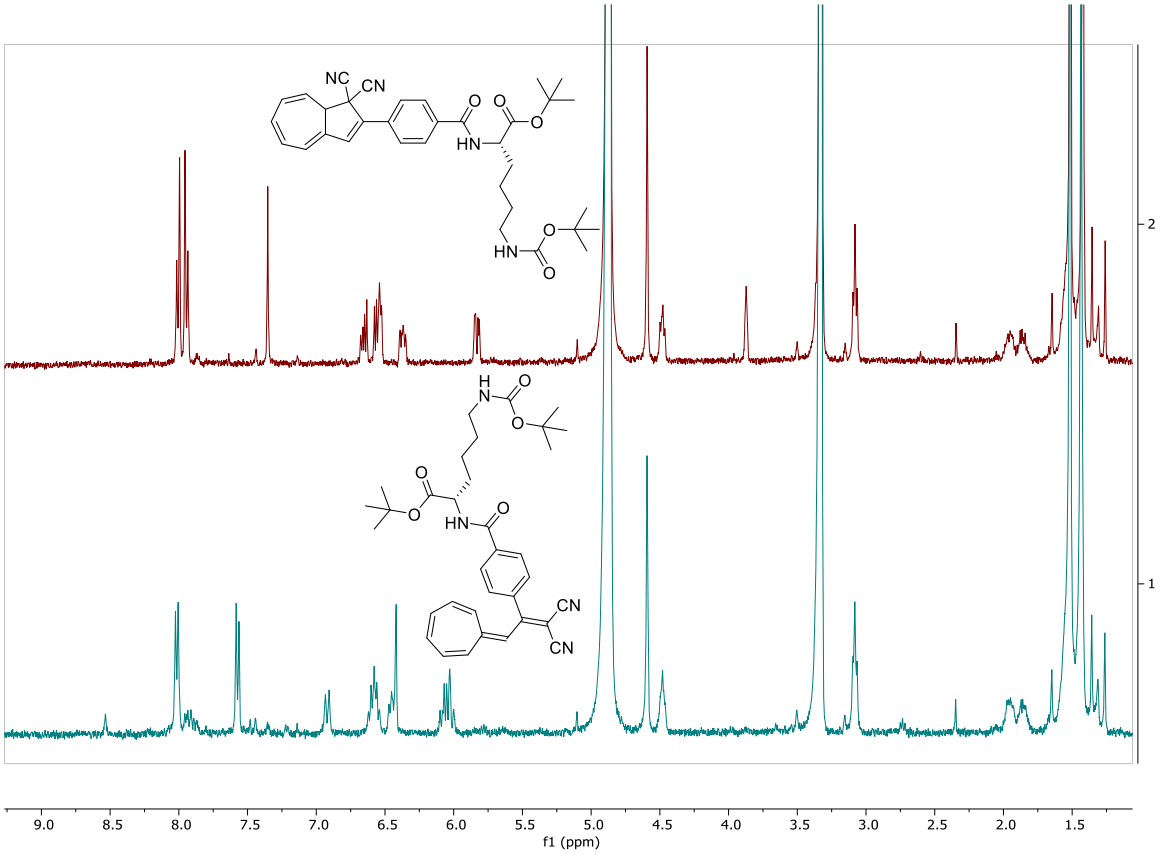
DHA9, CD_3OD, 400 MHz, dark (top), PSS 365 nm (bottom)



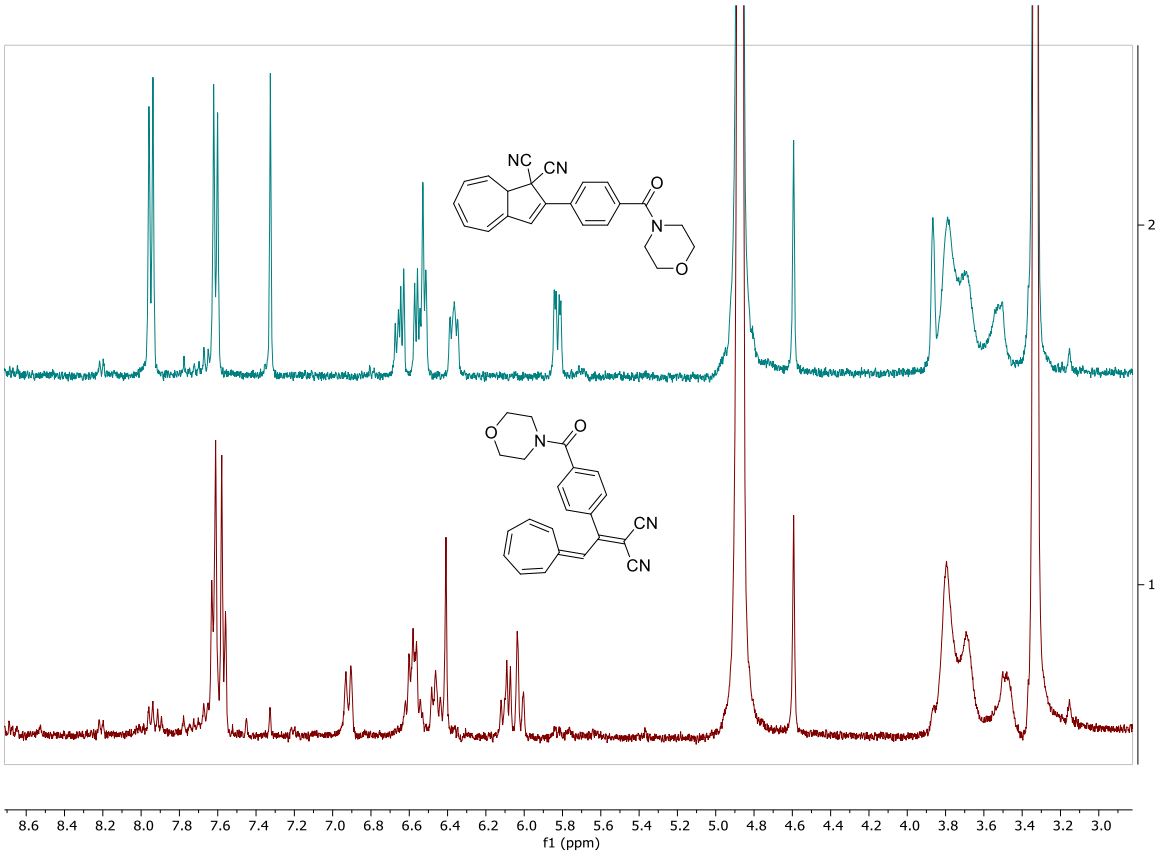
DHA-Ala-OtBu, ^1H NMR, CD_3OD, 400 MHz, dark (top), PSS 365 nm (bottom).



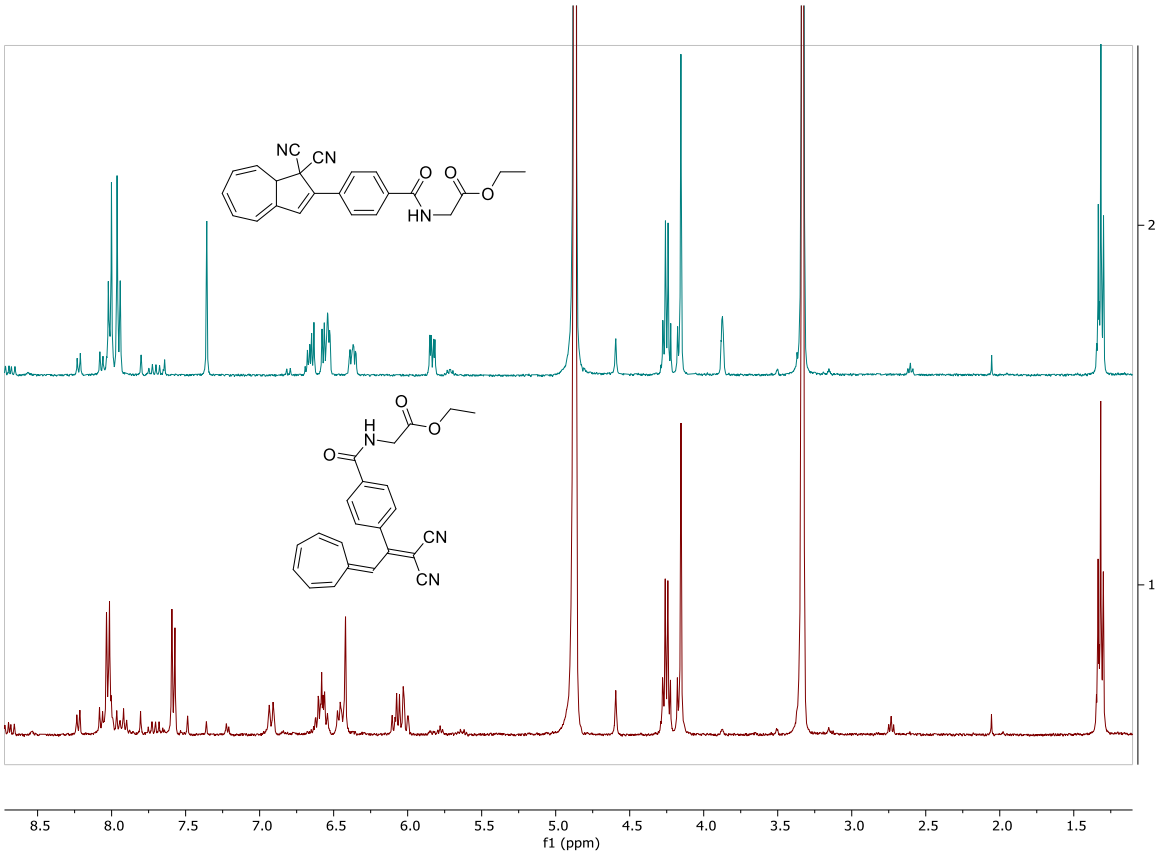
DHA-Ala, ^{1}H NMR, CD_3OD, 400 MHz, dark (top), PSS 365 nm (bottom).



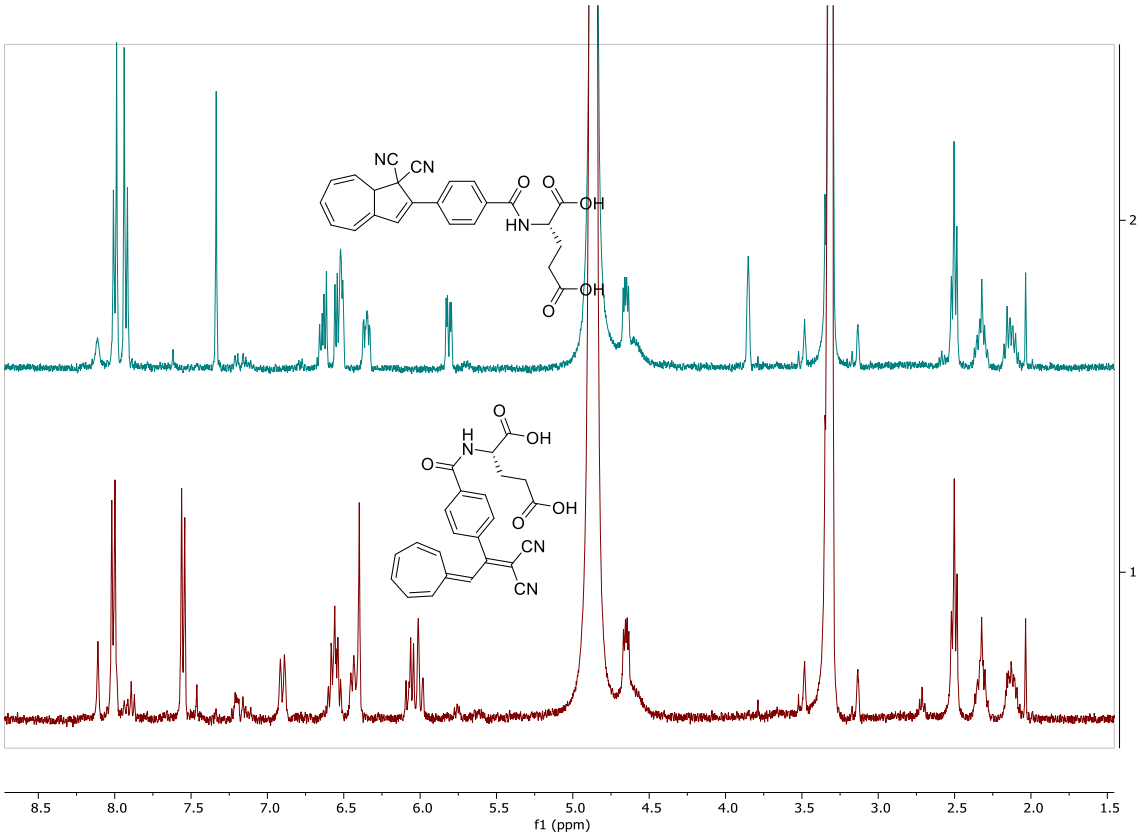
DHA-Lys(Boc)-OtBu, ^{1}H NMR, CD_3OD, 400 MHz, dark (top), PSS 365 nm (bottom).



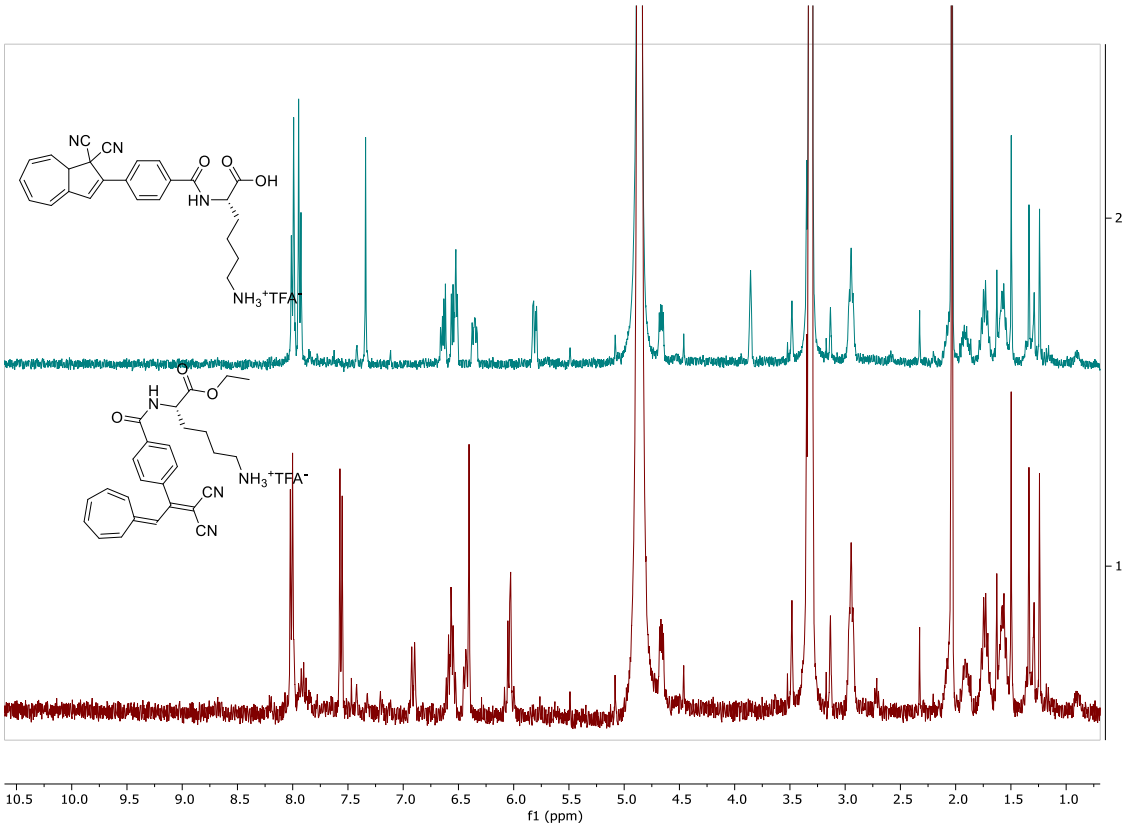
DHA-MO, ^{1}H NMR, CD_3OD, 400 MHz, dark (top), PSS 365 nm (bottom).



DHA-Gly-OEt, ^{1}H NMR, CD_3OD, 400 MHz, dark (top), PSS 365 nm (bottom).



DHA-Glu, ^{1}H NMR, CD_3OD, 400 MHz, dark (top), PSS 365 nm (bottom).



DHA-Lys, ^{1}H NMR, CD_3OD, 400 MHz, dark (top), PSS 365 nm (bottom).

X-ray Crystallography

Data collection was done on two dual source equipped Bruker D8 Venture four-circle-diffractometer from Bruker AXS GmbH; used X-ray sources: microfocus IμS 2.0 Cu/Mo and microfocus IμS 3.0 Ag/Mo from Incoatec GmbH with mirror optics HELIOS and single-hole collimator from Bruker AXS GmbH; used detector: Photon III CE14 (Cu/Mo) and Photon III HE (Ag/Mo) from Bruker AXS GmbH. Used programs: APEX3 Suite (v2019.11-0) for data collection and therein integrated programs SAINT V8.40A (Integration) und SADABS 2016/2 (Absorption correction) from Bruker AXS GmbH; structure solution was done with SHELXT, refinement with SHELXL-2018/3;[9] OLEX2 and FinalCIF V85 were used for data finalization[10,11]

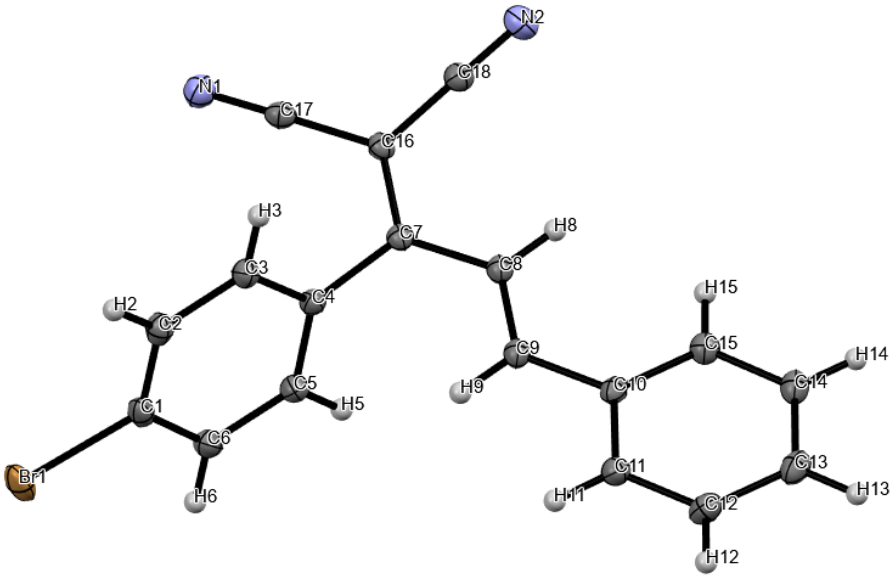


Figure S4. Para-bromo side product **3**, obtained during the synthesis of **DHA-2** (ellipsoids of 50% probability and explicit protons included).

Compound **3** was crystallised from MeOH

Table S1. Crystal data and structure refinement for **3**.

CCDC number	2215266
Empirical formula	$C_{18}H_{11}BrN_2$
Formula weight	335.20
Temperature [K]	100.00
Crystal system	monoclinic
Space group (number)	$P2_1/c$ (14)
a [Å]	10.1708(4)
b [Å]	17.6728(8)
c [Å]	8.7807(3)
α [°]	90
β [°]	113.3790(10)
γ [°]	90
Volume [Å^3]	1448.72(10)
Z	4
ρ_{calc} [gcm^{-3}]	1.537
μ [mm^{-1}]	2.831
F(000)	672
Crystal size [mm^3]	0.303×0.271×0.046
Crystal colour	yellow
Crystal shape	plate
Radiation	MoK_α (λ=0.71073 Å)
2Θ range [°]	4.36 to 61.03 (0.70 Å)
Index ranges	-14 ≤ h ≤ 14 -25 ≤ k ≤ 25 -12 ≤ l ≤ 12
Reflections collected	34775

Independent reflections	4421 R_{int} = 0.0260 R_{sigma} = 0.0145
Completeness to Θ = 25.242°	99.9 %
Data / Restraints / Parameters	4421/0/190
Goodness-of-fit on F^2	1.047
Final R indexes [I≥2σ(I)]	R_1 = 0.0225 wR_2 = 0.0563
Final R indexes [all data]	R_1 = 0.0247 wR_2 = 0.0575
Largest peak/hole [eÅ^{-3}]	0.45/-0.58

Table S2. Atomic coordinates and U_{eq} [Å^2] for **3**

Atom	***x***	***y***	***z***	U_{eq}
Br1	-0.02936(2)	0.20303(2)	0.53726(2)	0.02373(5)
N1	0.61769(12)	0.25358(6)	0.80058(14)	0.0213(2)
N2	0.83338(12)	0.42203(6)	0.60940(14)	0.0222(2)
C1	0.11631(12)	0.25882(7)	0.50495(14)	0.0169(2)
C2	0.20826(13)	0.22100(7)	0.44937(15)	0.0174(2)
H2	0.194899	0.168740	0.422235	0.021
C3	0.32043(12)	0.26077(6)	0.43395(15)	0.0161(2)
H3	0.384749	0.235458	0.396922	0.019
C4	0.33880(11)	0.33767(6)	0.47265(13)	0.01364(19)
C5	0.24153(12)	0.37531(6)	0.52242(14)	0.0163(2)
H5	0.251734	0.428100	0.544421	0.020
C6	0.12989(12)	0.33592(7)	0.53990(15)	0.0177(2)
H6	0.064262	0.361144	0.574996	0.021
C7	0.46610(11)	0.37775(6)	0.46862(13)	0.01330(19)
C8	0.44978(12)	0.43309(6)	0.34143(14)	0.01475(19)
H8	0.530874	0.461676	0.347704	0.018
C9	0.32271(12)	0.44547(6)	0.21376(14)	0.01497(19)
H9	0.242944	0.417774	0.214596	0.018
C10	0.29545(12)	0.49707(6)	0.07459(14)	0.01430(19)
C11	0.16124(12)	0.49413(7)	-0.05922(15)	0.0176(2)
H11	0.090925	0.459401	-0.056469	0.021
C12	0.13006(13)	0.54146(7)	-0.19567(16)	0.0207(2)
H12	0.039780	0.538116	-0.286621	0.025
C13	0.23129(14)	0.59372(7)	-0.19877(15)	0.0196(2)
H13	0.209400	0.626954	-0.290626	0.024
C14	0.36473(13)	0.59721(7)	-0.06699(15)	0.0183(2)
H14	0.433932	0.632733	-0.069524	0.022
C15	0.39731(13)	0.54915(6)	0.06798(14)	0.0166(2)
H15	0.489158	0.551481	0.156536	0.020
C16	0.59733(12)	0.35844(6)	0.58703(14)	0.01403(19)
C17	0.60981(12)	0.30042(6)	0.70676(14)	0.0157(2)
C18	0.72868(12)	0.39317(6)	0.59831(14)	0.0160(2)

U_{eq} is defined as 1/3 of the trace of the orthogonalized U_{ij} tensor.

Table S3. Bond lengths and angles for **3**.

Atom–Atom	**Length [Å]**
Br1–C1	1.8924(11)
N1–C17	1.1480(16)
N2–C18	1.1494(16)
C1–C2	1.3862(17)
C1–C6	1.3914(17)
C2–H2	0.9500
C2–C3	1.3916(16)
C3–H3	0.9500
C3–C4	1.3954(16)
C4–C5	1.3984(15)
C4–C7	1.4885(15)
C5–H5	0.9500
C5–C6	1.3914(16)
C6–H6	0.9500
C7–C8	1.4437(15)
C7–C16	1.3702(15)
C8–H8	0.9500
C8–C9	1.3509(15)
C9–H9	0.9500
C9–C10	1.4604(15)
C10–C11	1.4049(16)
C10–C15	1.4041(15)
C11–H11	0.9500
C11–C12	1.3907(17)
C12–H12	0.9500
C12–C13	1.3914(18)
C13–H13	0.9500
C13–C14	1.3923(17)
C14–H14	0.9500
C14–C15	1.3871(16)
C15–H15	0.9500
C16–C17	1.4377(16)
C16–C18	1.4374(15)
Atom–Atom–Atom	**Angle [°]**

C2–C1–Br1	118.64(9)
C2–C1–C6	121.87(10)
C6–C1–Br1	119.48(9)
C1–C2–H2	120.5
C1–C2–C3	118.97(11)
C3–C2–H2	120.5
C2–C3–H3	119.9
C2–C3–C4	120.26(11)
C4–C3–H3	119.9
C3–C4–C5	119.77(10)
C3–C4–C7	119.43(10)
C5–C4–C7	120.73(10)
C4–C5–H5	119.8
C6–C5–C4	120.39(11)
C6–C5–H5	119.8
C1–C6–H6	120.7
C5–C6–C1	118.66(11)
C5–C6–H6	120.7
C8–C7–C4	120.44(10)
C16–C7–C4	117.26(10)
C16–C7–C8	122.28(10)
C7–C8–H8	119.0
C9–C8–C7	122.01(10)
C9–C8–H8	119.0
C8–C9–H9	116.7

C8–C9–C10	126.65(10)
C10–C9–H9	116.7
C11–C10–C9	118.40(10)
C15–C10–C9	123.07(10)
C15–C10–C11	118.53(10)
C10–C11–H11	119.6
C12–C11–C10	120.80(11)
C12–C11–H11	119.6
C11–C12–H12	120.0
C11–C12–C13	119.91(11)
C13–C12–H12	120.0
C12–C13–H13	120.1
C12–C13–C14	119.86(11)
C14–C13–H13	120.1
C13–C14–H14	119.8
C15–C14–C13	120.44(11)
C15–C14–H14	119.8
C10–C15–H15	119.8
C14–C15–C10	120.44(11)
C14–C15–H15	119.8
C7–C16–C17	120.61(10)
C7–C16–C18	123.01(10)
C18–C16–C17	116.37(10)
N1–C17–C16	178.87(13)
N2–C18–C16	178.62(13)

Table S4. Torsion angles for **3**.

Atom–Atom–Atom–Atom	**Torsion Angle [°]**
Br1–C1–C2–C3	−176.53(9)
Br1–C1–C6–C5	177.19(9)
C1–C2–C3–C4	−0.54(17)
C2–C1–C6–C5	−1.72(17)
C2–C3–C4–C5	−1.88(17)
C2–C3–C4–C7	175.04(10)
C3–C4–C5–C6	2.56(17)
C3–C4–C7–C8	110.20(12)
C3–C4–C7–C16	−68.26(14)
C4–C5–C6–C1	−0.78(17)
C4–C7–C8–C9	−6.36(16)
C4–C7–C16–C17	1.46(15)
C4–C7–C16–C18	−179.40(10)
C5–C4–C7–C8	−72.91(14)
C5–C4–C7–C16	108.64(12)
C6–C1–C2–C3	2.38(18)
C7–C4–C5–C6	−174.33(10)
C7–C8–C9–C10	−176.81(10)
C8–C7–C16–C17	−176.97(10)
C8–C7–C16–C18	2.17(17)
C8–C9–C10–C11	170.58(11)
C8–C9–C10–C15	−9.08(18)
C9–C10–C11–C12	−179.36(11)
C9–C10–C15–C14	−179.44(11)
C10–C11–C12–C13	−1.53(18)
C11–C10–C15–C14	0.90(17)
C11–C12–C13–C14	1.53(18)
C12–C13–C14–C15	−0.32(18)
C13–C14–C15–C10	−0.90(18)
C15–C10–C11–C12	0.32(17)
C16–C7–C8–C9	172.02(11)

TD-DFT analysis

Table S5. Substituent effects on the first electronic transition in the DHAs switches. Computations were carried out at the TD-DSD-BLYP-D3BJ/def2-TZVPP//r^{2}SCAN-3c level.

Compound	Substituent	S0→S1 computed	Measured λmax (DMSO)
DHA-7	NH_2	415.8	408
DHA-4	OMe	395.5	375
DHA-6	NAc_2	380.8	369
DHA-1	H	377.8	365

Figure S5. Comparison of the experimental and computed λ_{max} reported in Table S5.

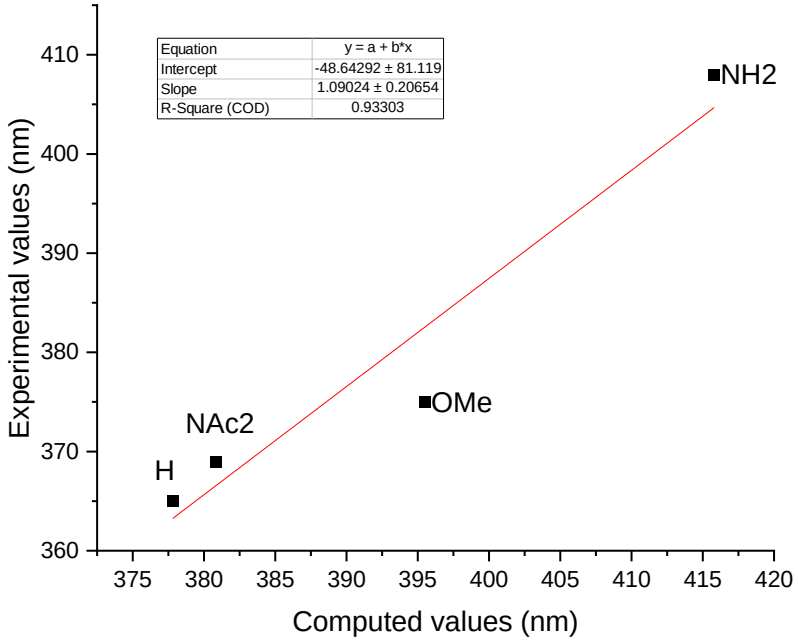
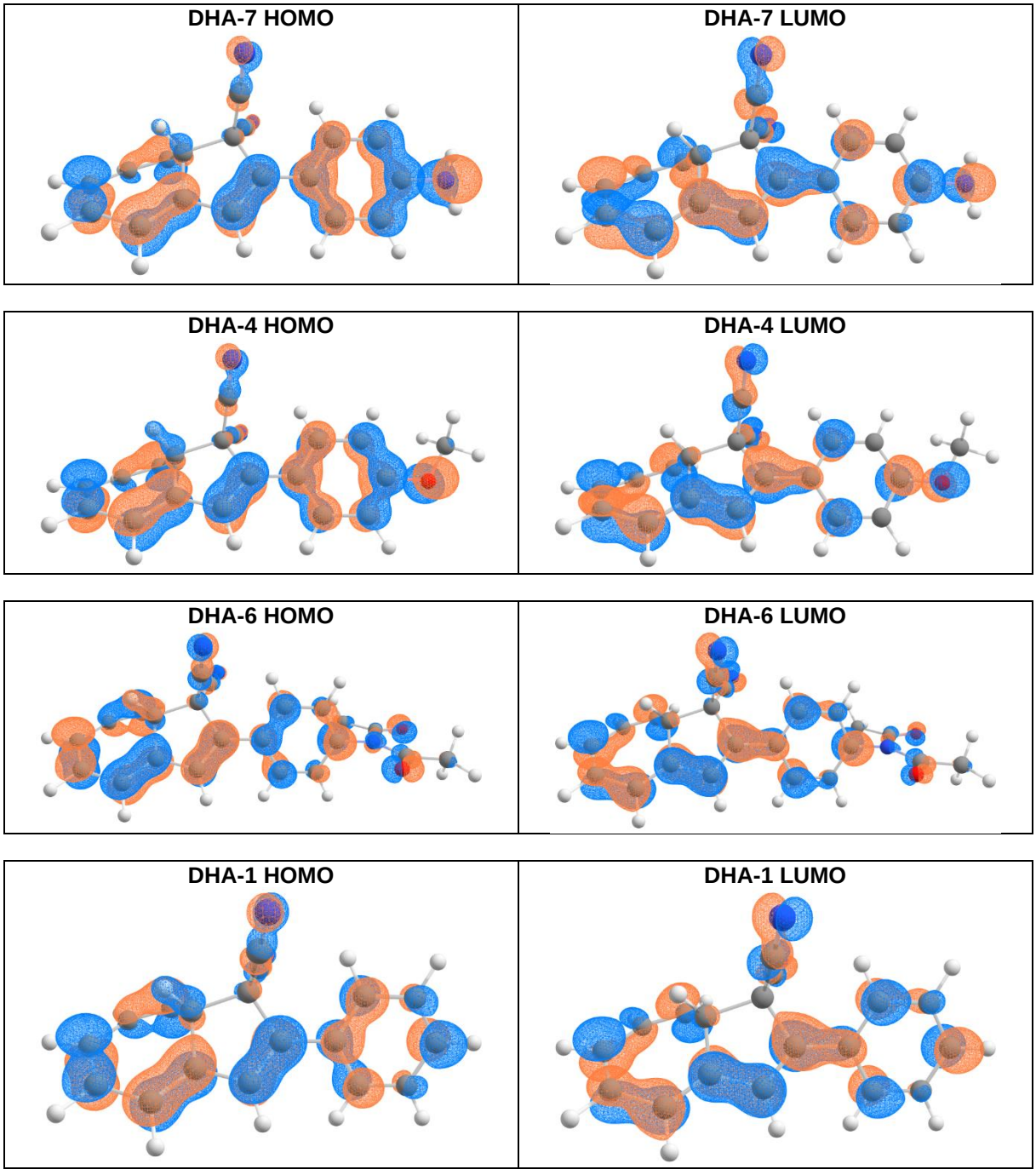


Figure S6. Comparison of the HOMO and LUMO of different DHAs computed at the TD-DSD-BLYP-D3BJ/def2-TZVPP//r^{2}SCAN-3c level.



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