SUPPLEMENTARY MATERIAL

The polyphenol EGCG directly targets intracellular amyloid-β aggregates and promotes their lysosomal degradation

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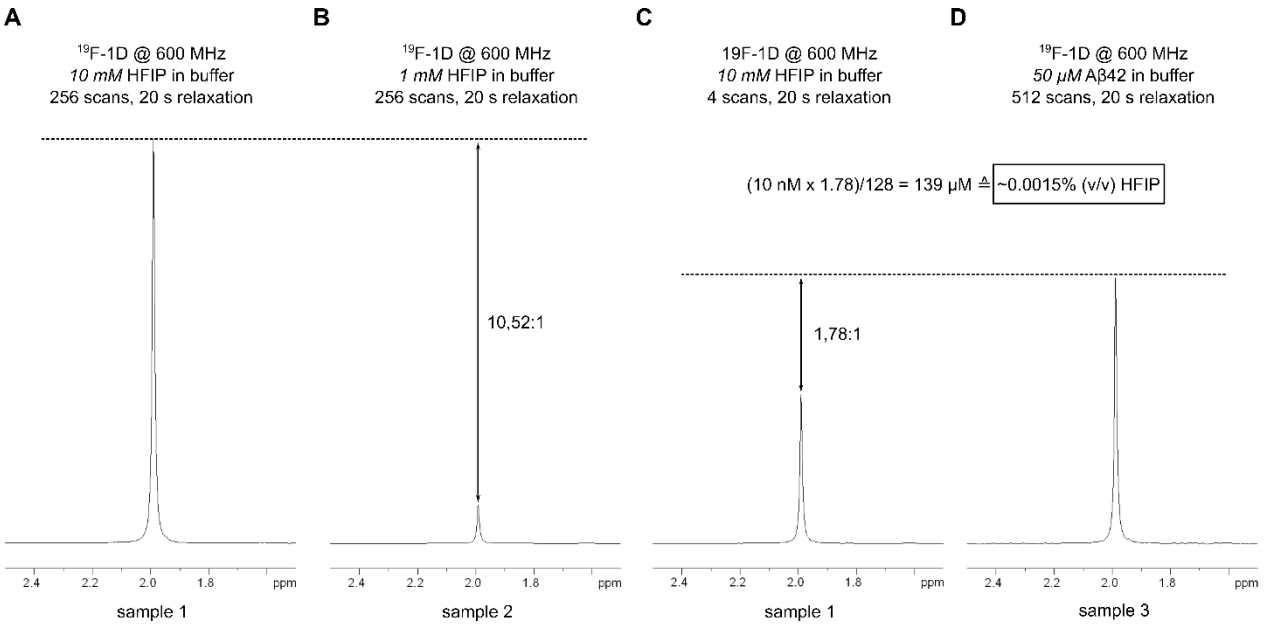
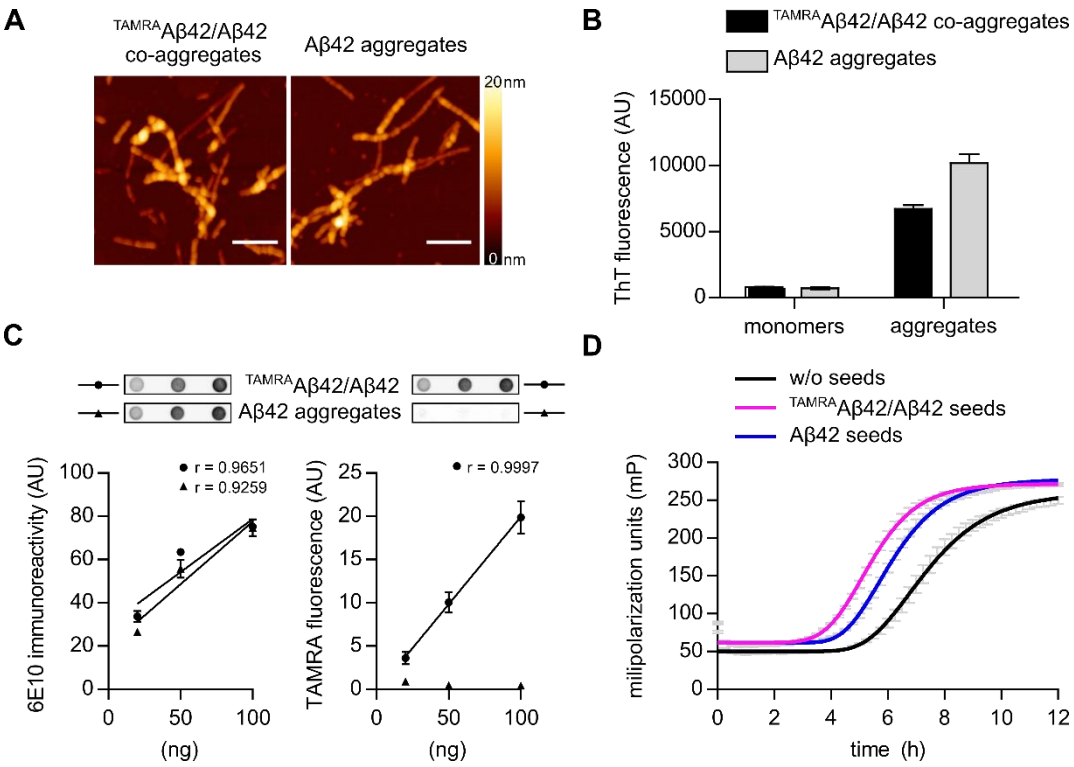
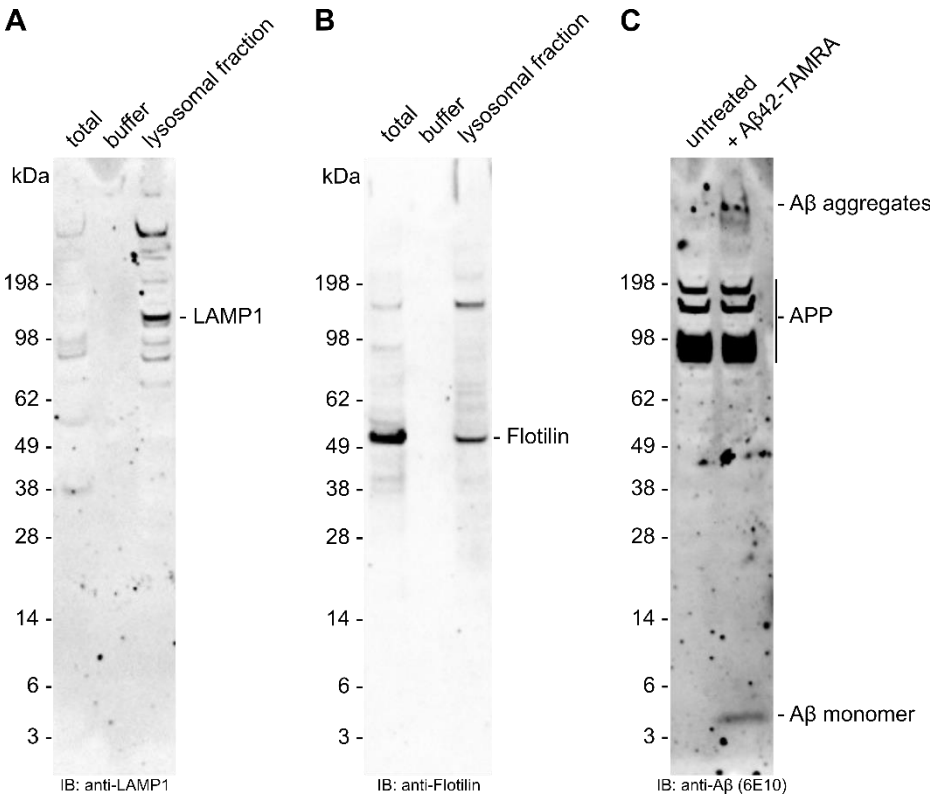


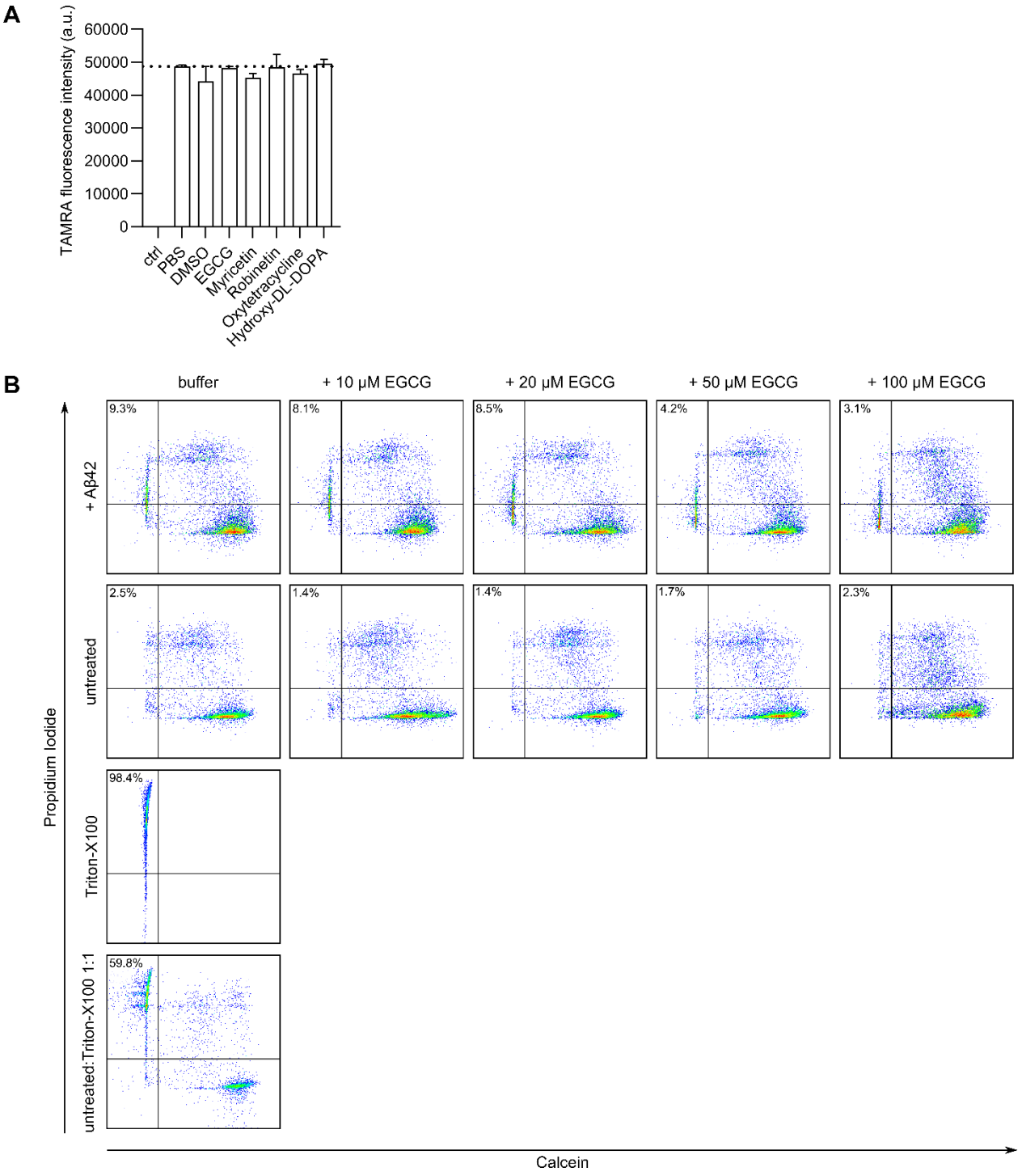
Supplementary Figure 1 (related to Figure 1). (**A,B**) 19F-NMR spectra of 10 mM (sample 1, **A**) and 1 mM (sample 2, **B**) HFIP dissolved in 600 µl low salt buffer (2 mM KH_2PO_4, 8 mM K_2HPO_4, 10 mM NaCl) containing 90% H2O and 10% D2O. Since the lineshapes of the peaks were identical, the ratios of the peak maxima were used to determine the ratios of the concentrations. For the test whether concentrations could be reliably determined, 256 scans were recorded for samples 1 and 2. The experiments in A and B yielded a ratio of 10.52 :1, which is in good agreement with the theoretical value of 10:1 (10 mM:1 mM). (**C,D**) Relative quantification of HFIP content in Aβ solution by comparing the spectra of 10 mM HFIP (sample 1, **C**) to a 50 µM Aβ42 solution with low salt buffer (2 mM KH_2PO_4, 8 mM K_2HPO_4, 10 mM NaCl) containing 90% H2O and 10% D2O (sample 3, **D**). To determine the concentration of HFIP in the Aβ42 sample, 4 scans were recorded with sample 1 and 512 scans with sample 3. The experiments (**C,D**) yielded a ratio of 1:1.78 which had to be corrected using the ratio of the number of scans (512 / 4 = 128) and thus resulted in a residual HFIP concentration in the Aβ 42 solution of ~0.0015% (**D**).



Supplementary Figure 2 (related to Figure 1). Comparison of ^{TAMRA}Aβ42/Aβ42 co-aggregates and unlabeled Aβ42 aggregates. (**A**) Atomic force microscopy of ^{TAMRA}Aβ42/Aβ42 co-aggregates. Aβ42 peptides (20 µM) were aggregated with or without 5% ^{TAMRA}Aβ42 peptides for aggregate labeling. Scale bars: 500 nm. (**B**) Thioflavin T staining of ^{TAMRA}Aβ42/Aβ42 co-aggregates and unlabeled Aβ42 aggregates (Aβ42:ThT 1:1, 20 µM). Data points represent means ± SD from three independent stainings (*n* = 3). (**C**) Quantification of ^{TAMRA}Aβ42/Aβ42 co-aggregates (20 µM) with SDS filter retardation assays. Aβ42 aggregates (20, 50 or 100 ng) or ^{TAMRA}Aβ42/Aβ42 co-aggregates were filtered and retained Aβ species were detected with an Aβ-specific antibody (6E10) and a peroxidase-labeled secondary antibody (left panel) or by measuring TAMRA fluorescence (right panel). Data points represent means ± SD from three independent filter assays (*n* = 3). Regression analysis and determination of Pearson's r were performed to assess the linear increase of signal intensity with filtered aggregate load. (**D**) Assessment of seeding activity of preformed ^{TAMRA}Aβ42/Aβ42 co-aggregates and unlabeled Aβ42 aggregate seeds (80 nM monomer equivalent) compared to buffer control using a fluorescence polarization-based Aβ42 aggregation assay. Data points show means ± SD from three independent aggregation reactions (*n* = 3).

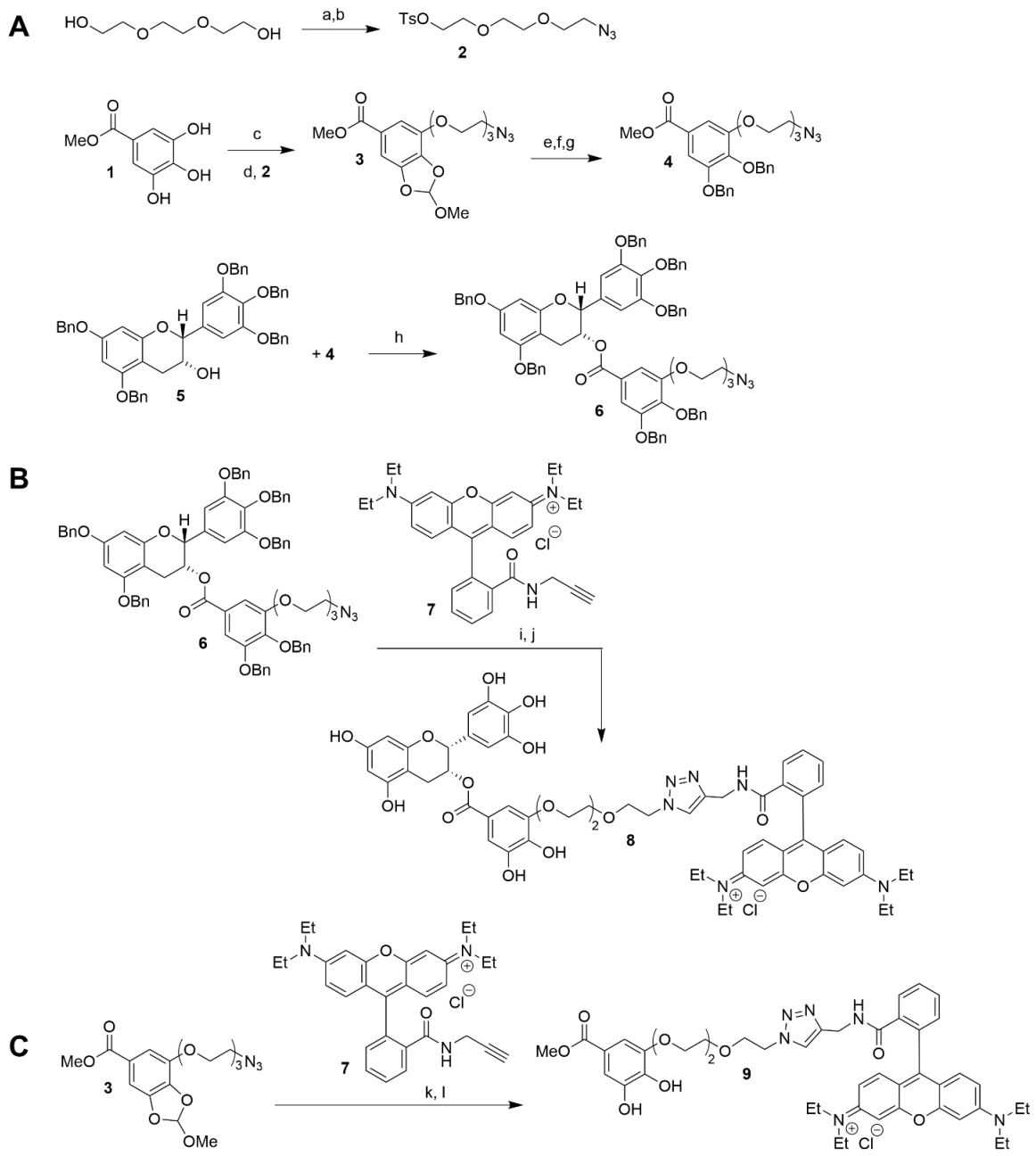


Supplementary Figure 3 (related to Figure 2). Enrichment of lysosomes from crude protein extracts of SH-EP cells and detection of ^{TAMRA}Aβ42/Aβ42 co-aggregates in lysosomal fraction. (**A**) Enrichment of the lysosome-associated membrane protein 1 (LAMP1) in lysosomal fractions of SH-EP cells compared to total fraction. (**B**) Decrease of the protein flotilin-1, which is a protein of the plasma membrane and not expected to be enriched in lysosomes. (**C**) SDS-stable aggregates (Aβ aggregates) and monomeric peptide species (Aβ monomer) are both detected in the lysosomal fraction of ^{TAMRA}Aβ42/Aβ42 co-aggregates treated SH-EP cells. No signals are detected in untreated cells.

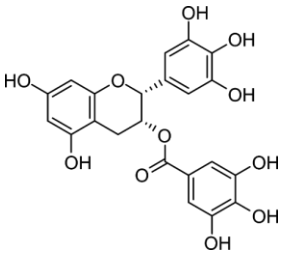
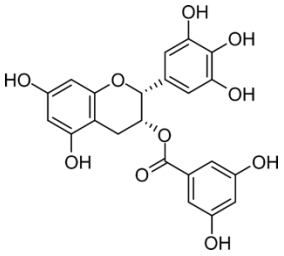
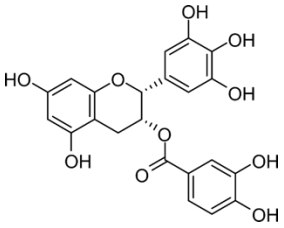
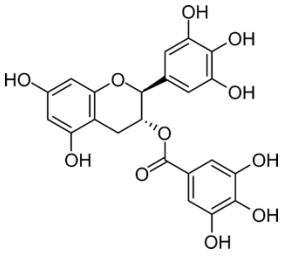
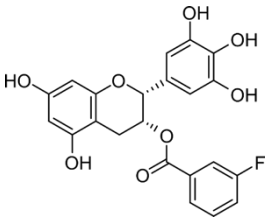
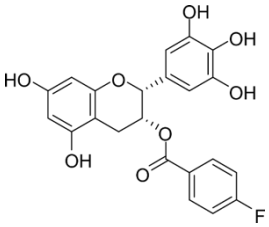
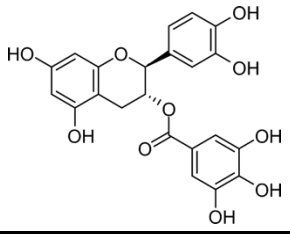


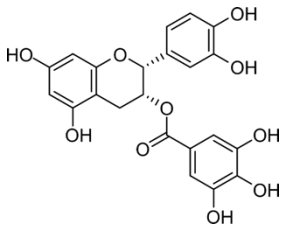
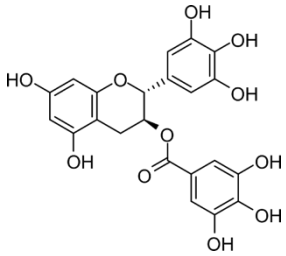
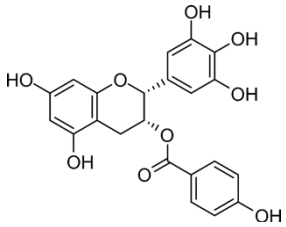
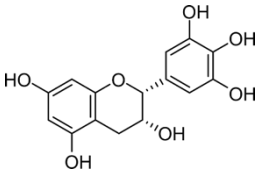
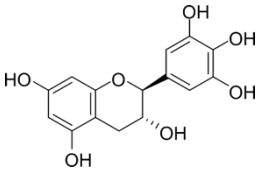
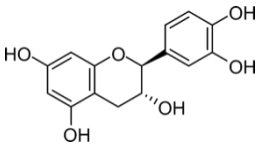
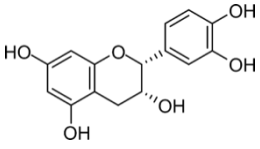
Supplementary Figure 4 (related to Figure 3). (**A**) Effect of screening hits on 5-Carboxytetramethylrhodamine (5-TAMRA) alone. As a negative control, buffer only was analyzed (ctrl). For 5-TAMRA samples, 1 µM 5-TAMRA was incubated with 1 µM hit compound or DMSO or PBS only. No significant reduction of TAMRA fluorescence (Ex/Em 550/580 nm) was detected by compound addition. (**B**) Gating strategy and representative FACS blots from Live/Dead toxicity

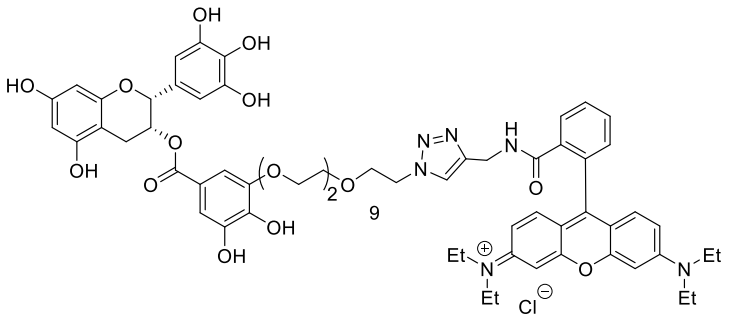
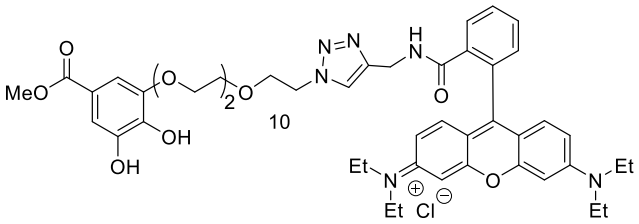
assay. Cells were treated with 1 µM Ab42 aggregates (monomer equivalent) and increasing concentrations of EGCG. As a control, cells without Ab42 (untreated) were incubated with EGCG. For toxicity positive control, cells were treated with Triton-X100 for 15 min and subsequently dead cells alone (Triton-X100) as well as a 1:1 mixture of dead and untreated cells (untreated:Triton-X100 1:1) were analyzed. Prior to analysis, cells were stained with propidium iodide and calcein-AM according to the manufacturer's protocol (see Methods section).



Supplementary Figure 5 (related to Figure 6). (**A**) Synthesis route for azido-functionalized EGCG derivative. a) *p*-TsCl, KOH, CH_2Cl_2, 89%; b) NaN_3, EtOH, 90 °C, 25%; c) $HC(OMe)_3$, IR-120 plus, toluene, 150 °C, 76%; d) **2**, Cs_2CO_3, DMF, 78%; e) *p*-TsOH, MeOH, 31%; f) BnCl, K_2CO_3, DMF, 80 °C, 88%; g) KOH (40 w%), EtOH, 80 °C, 90%; h) **4**, EDC·HCl, DMAP, CH_2Cl_2, 84%; (**B,C**) Alkyne-azide "click" coupling reactions of EGCG derivative and control compound to Rhodamine B. i) $CuSO_4$ (5 mol%), sodium ascorbate (10 mol%), DMSO, 65 °C, 90%; j) $Pd(OH)_2$, THF/MeOH (1:1), H_2 (1 atm), 89%; k) *p*-TsOH, MeOH, 31%; l) $CuSO_4$ (5 mol%), sodium ascorbate (10 mol%), DMSO, 65 °C, 57%.

Compound	Structure
(-)-Epigallocatechin gallate Abbr.: **EGCG** (2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,4,5-trihydroxybenzoate	
(-)-Epigallocatechin 3,5-dihydroxybenzoate Abbr.: **EGC-3,5-DHB (10)** (2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,5-dihydroxybenzoate*	
(-)-Epigallocatechin dihydroxybenzoate Abbr.: **EGC-3,4-DHB (11)** (2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,4-dihydroxybenzoate*	
(-)-Gallocatechin gallate Abbr.: (-)-**GCG** (2S,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,4,5-trihydroxybenzoate	
(-)-Epigallocatechin 3-fluorobenzoate Abbr.: **EGC-3-FB (12)** (2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3-fluorobenzoate*	
(-)-Epigallocatechin 4-fluorobenzoate Abbr.: **EGC-4-FB (13)** (2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 4-fluorobenzoate*	
(-)-Catechin gallate Abbr.: **CG** (2S,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxychroman-3-yl 3,4,5-trihydroxybenzoate	

(-)-Epicatechin gallate Abbr.: **ECG** (2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxychroman-3-yl 3,4,5-trihydroxybenzoate	
(+)-Gallocatechin gallate Abbr.: (+)-**GCG** (2R,3S)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 3,4,5-trihydroxybenzoate*	
(-)-Epigallocatechin 4-hydroxybenzoate Abbr.: **EGC-4-HB (14)** (2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl 4-hydroxybenzoate*	
(-)-Epigallocatechin Abbr.: **EGC** (2R,3R)-2-(3,4,5-trihydroxyphenyl)-chroman-3,5,7-triol	
(-)-Gallocatechin Abbr.: **GC** (2S,3R)-2-(3,4,5-trihydroxyphenyl)-chroman-3,5,7-triol	
(-)-Catechin Abbr.: **C** (2S,3R)-2-(3,4-dihydroxyphenyl)-chroman-3,5,7-triol	
(-)-Epicatechin Abbr.: **EC** (2R,3R)-2-(3,4-dihydroxyphenyl)-chroman-3,5,7-triol	

(-)-Epigallocatechin 3-RhodamineB-4,5-dihydroxybenzoate Abbr.: **EGC-DHB-Rhodamine (8)** *N*-(6-(Diethylamino)-9-(2-(((1-(2-(2-(2-(5-((((2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl) chroman-3-yl)oxy)carbonyl)-2,3-dihydroxyphenoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)carbamoyl)phenyl)-3H-xanthen-3-ylidene)-N-ethylethan-aminium chloride*	
4,5-Dihydroxymethyl-benzoate-Rhodamine B Abbr.: **DHMB-Rhodamine (9)** *N*-(6-(Diethylamino)-9-(2-(((1-(2-(2-(2-(2,3-dihydroxy-5-(methoxycarbonyl)phenoxy) ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)carbamoyl)phenyl)-3H-xanthen-3-ylidene)-N-ethylethanaminium chloride*	

Supplementary Table 1 (related to Figure 4 and Figure 6). Description, abbreviations, systematic names and structures of EGCG derivatives used in this study. Derivatives marked with an asterisk (*) have been newly synthesized (for detailed synthesis description, see below). All other EGCG derivatives were purchased from Sigma-Aldrich. All compounds were at analytical grade (>95% purity or higher) and dissolved in DMSO at 20 mM and stored at -20 °C. Non-fluorescently labeled derivatives are sorted by potency in cellular Aβ42 assay in descending order.

DETAILED SYNTHESIS DESCRIPTION

General

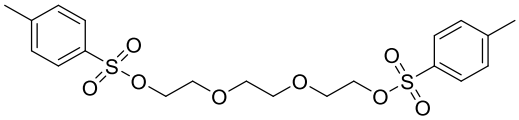
All reagents from Alfa Aeser, Fisher Scientific, Fluka, Sigma-Aldrich and VWR/Merck were used in reagent grade. (−)-Epigallocatechin Gallate (EGCG) was purchased from BLDPharm (purity: 99.81%) and (-)-Catechin gallate (CG) from TargetMol (purity: 100%). The used solvents were purchased purely or purified and/or dried by conventional methods. To dry dimethyl sulfoxide, *N,N*-dimethylformamide 4 Å molecular sieves were used. Methanol *was* distilled over magnesium and stored over 3 Å molecular sieves. Dichloromethane and tetrahydrofuran were purchased from Sigma-Aldrich and were dried with a Solvent Purification System (MBraun, MB-SPS-800). Tetrahydrofuran and methanol as well as deuterated methanol were degassed by using the method “freeze-pump-thaw”. Acetonitrile and water (HPLC quality) were degassed in an ultrasound bath. $NaOD/D_3PO_4$ buffer (+ 0.1% DMSO-d_6) in D_2O was prepared from sodium deuteroxide solution 40 wt. % in D_2O (Acros organics), phosphoric acid-d_3 solution 85 wt. % in D_2O (Carl Roth), deuterium oxide (Sigma Aldrich) and dimethyl sulfoxide-d_6 (Sigma Aldrich). The corresponding pH values were checked using a 744 Metrohm pH meter. The deuterated buffer solution was degassed by using the method “freeze-pump-thaw”. Reactions were monitored by thin-layer chromatography using aluminum foil backed silica gel from Macherey-Nagel (ALUGRAM® Xtra SIL G/U254) with fluorescence indicator or thin-layer chromatography using aluminum foil backed silica gel 60 RP-18 F254s from Merck. For purification by column chromatography silica gel 60 from Fisher Scientific (Acros Organics, ultrapure, 40-60µm, 60 Å) and aluminum oxide (Brockmann act. III) from Macherey-Nagel (50-200µm) were used. All preparations involving air-and moisture-sensitive compounds were carried out inside a glovebox (Vacuum Atmospheres model OMNI-LAB) under N_2-atmosphere (Air Liquide ALPHAGAZ™ 5.0) or under argon atmosphere inside the fume hood using standard Schlenk technique. Glassware was dried for two hours at 120 °C and cooled down in vacuo. To concentrate solutions under reduced pressure, rotary evaporators (Heidolph Instruments) in combination with vacuum pumps of Vakuubrand were used. For purifications by high performance liquid chromatography, an HPLC system equipped with a Merck column (LiChrospher® Si 60 (5 µm)), a HITACHI L-4000 UV detector and a gradient pump (L-6250 Intelligent Pump) with fraction collector (L-7650 Fraction Collector) were used. All samples were filtered with syringe filters (13 mm, 0.2 µm PTFE membrane). ^{1}H- and ^{13}C-NMR-spectra were measured at room temperature using a Bruker Avance III – 300 (300 MHz) or Bruker Avance III – 600 (600 MHz) and decoupled. The chemical shifts were referenced to residual chloroform (^{1}H 7.26 ppm, ^{13}C 77.16 ppm), dimethyl sulfoxide (^{1}H 2.50 ppm, ^{13}C 39.7 ppm), methanol (^{1}H 3.35 or 4.78 ppm, ^{13}C 3.35 or 49.3 ppm), or deuterium

oxide (^{1}H 4.79 ppm) peaks. The coupling constants *J* are given in Hertz (Hz) and the chemical shifts δ in ppm. IR-spectra were measured as thin films on a NaCl single crystal with a JASCO FT/IR-6200 or as solids using a Shimadzu IR Affinity-1 (Fourier Transform infrared spectrophotometer). UV-VIS-measurements were performed on an Agilent Cary 60 UV-Vis spectrometer with a Cary Single Cell Peltier Accessory. Hellma cuvettes with magnetic stirrer (10 x 10 mm, quartz glass) and with PTFE stopper were used. The sample was measured at 37 °C. Specific rotations were measured on a Perkin Elmer 341 polarimeter at the indicated concentration, temperature, and with the specified solvent using a sodium lamp (589 nm). Melting points were determined using a Büchi Melting Point B-540 apparatus and were not corrected. High resolution mass spectra (HRMS) were measured with a UHR-QTOF maXis 4G spectrometer from Bruker Daltonics.

Synthesis of individual compounds

Triethylene glycol di-p-toluenesulfonate

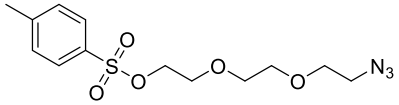
The compound was prepared according to literature following a procedure by Bonger *et al*.[1] Triethylene glycol (**1**) (**Supplementary Figure 2A**) (17.2 g, 0.114 mol, 1.00 eq) was suspended in methylene chloride (114 mL). *p*-Toluenesulfonyl chloride (43.8 g, 0.228 mol, 2.00 eq) was added and the mixture was cooled to 0 °C. Finely crushed KOH (51.6 g, 0.919 mol, 8.06 eq) was added in portions and it was stirred for 3 h at 0 °C, then for nine days at RT. The reaction progress was monitored by TLC (*n*-hexane/EtOAc 1:1, R_f = 0.3). The residue was dissolved in ice water (500 mL) and extracted with methylene chloride (4 x 150 mL). The combined organic layers were washed with water (300 mL) and dried over sodium sulfate. The desiccant was filtered off and the organic layer was concentrated under reduced pressure to afford the product as a white solid (46.3 g, 0.101 mol, 89%).



^{1}H NMR (75 MHz, $CDCl_3$): δ [ppm] = 7.81 – 7.76 (m, 4H), 7.37 – 7.30 (m, 4H), 4.17 – 4.10 (m, 4H), 3.68 – 3.62 (m, 4H), 3.52 (s, 4H), 2.44 (s, 6H).

2-(2-(2-Azidoethoxy)ethoxy)ethyl-4-methylbenzenesulfonate (**2**)

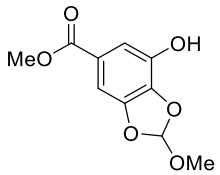
The compound was prepared according to literature following a procedure by Hanson *et al.*[2] Triethylene glycol di-*p*-toluenesulfonate (3.10 g, 6.76 mmol, 1.00 eq) was dissolved in ethanol (20 mL) and sodium azide (0.527 g, 8.11 mmol, 1.20 eq) was added. The solution was heated up to 90 °C over five days. The solvent was evaporated under reduced pressure and the residue was treated with water (40 mL). The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (30 mL) and dried over sodium sulfate. The desiccant was filtered off and the organic layer was concentrated under reduced pressure to afford 1.73 g of a lightly yellow liquid. Column chromatography (SiO_2, *n*-hexane/EtOAc, 3:1, R_f = 0.23) afforded monoazide **2** (0.689 g, 1.71 mmol, 25%) as a lightly yellowish oil.



^{1}H NMR (75 MHz, $CDCl_3$): δ [ppm] = 7.82 – 7.76 (m, 2H), 7.37 – 7.30 (m, 2H), 4.18 – 4.13 (m, 2H), 3.72 – 3.66 (m, 2H), 3.66 – 3.61 (m, 2H), 3.61 – 3.58 (m, 4H), 3.39 – 3.33 (m, 2H), 2.44 (s, 3H).

Methyl 7-hydroxy-2-methoxybenzo[d][1,3]dioxole-5-carboxylate

The compound was prepared according to literature following a procedure by Merz *et al*.[3] To a solution of methyl gallate (**1**) (**Supplementary Figure 2A**) (3.00 g, 16.3 mmol, 1.00 eq) in toluene (54 mL), trimethyl orthoformate (2.59 g, 24.4 mmol, 1.50 eq) and Amberlite® IR-120 plus (0.15 g) were added at RT. The suspension was heated to 150 °C for four hours until methanol began to distill off. The suspension was cooled down to RT, hexane (20 mL) and ethyl acetate (10 mL) were added, and it was heated to 80 °C for 3 h. The precipitated residue was mixed with *n*-hexane (20 mL) and cooled down to RT. The desiccant was filtered off and the organic layer was concentrated under reduced pressure. Drying under vacuum afforded the title compound as a purple solid (2.81 g, 12.4 mmol, 76%).

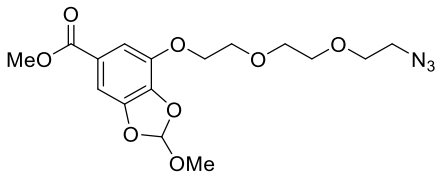


^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.40 (d, *J* = 1.5 Hz, 1H), 7.21 (d, *J* = 1.5 Hz, 1H), 6.95 (s, 1H), 5.49 (s, 1H), 3.89 (s, 3H), 3.44 (s, 3H).

^{13}C NMR (75 MHz, (DMSO): δ [ppm] = 165.53, 146.80, 140.24, 136.58, 123.52, 119.68, 113.22, 100.63, 52.01, 50.38.IR (Film): ν [cm^{-1}] = 3364 (b), 2953 (b), 2849 (b), 2347 (b),1697 (m), 1644 (s), 1617 (m), 1518 (m), 1506 (m), 1441 (s), 1376 (m), 1338 (m), 1285 (m), 1250 (m), 1204 (m), 1146 (m), 1077 (s), 1031 (s), 993 (b), 913 (b), 876 (b), 820 (bw), 768 (m), 748 (m), 726 (b), 665 (b), 614 (w), 524 (w).
HRMS (ESI) m/z: [M+H$^+$] Calc $C_{10}H_{11}O_6$ 227.0556; found 227.0555.
Melting point: 129 °C

Methyl 7-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-2-methoxybenzo[d][1,3]dioxole-5-carboxylate (**3**)

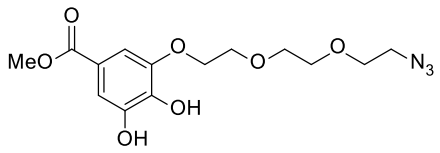
The compound was prepared according to literature following a procedure by Ueno *et al*.[4] Methyl 7-hydroxy-2-methoxybenzo[*d*][1,3]dioxole-5-carboxylate (211 mg, 0.932 mmol, 1.00 eq) was dissolved in DMF (12 mL) at RT. Monoazide **2** (307 mg, 0.932 mmol, 1.00 eq) and cesium carbonate (304 mg, 0.932 mmol, 1.00 eq) were added. The suspension was stirred at RT for two days. The residue was dissolved in water (150 mL) and extracted with methylene chloride (5 x 20 mL). The combined organic layers were washed with water (4 x 5 mL) and with brine (10 mL), then dried over sodium sulfate. The desiccant was filtered off and the organic layer was concentrated under reduced pressure. After purification by column chromatography (SiO_2, *n*-hexane/EtOAc, 2:1) the product was provided as a lightly yellowish oil (280 mg, 0.731 mmol, 78%).



^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.36 (d, 1H, *J* = 1.5 Hz), 7.24 (d, 1H, *J* = 1.5 Hz), 6.91 (s, 1H), 4.32 – 4.27 (m, 2H), 3.89 – 3.84 (m, 5H), 3.76 – 3.70 (m, 2H), 3.70 – 3.64 (m, 4H), 3.42 (s, 3H), 3.40 – 3.34 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 166.28, 147.21, 141.72, 138.21, 124.33, 120.24, 111.69, 103.49, 70.96, 70.71, 70.09, 69.69, 69.17, 52.19, 50.69, 50.17.
HRMS (ESI) m/z: [M+NH_4^+] Calc $C_{16}H_{25}N_4O_8$ 401.1672; found 401.1672.

Methyl 3-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-4,5-dihydroxybenzoate

The compound was prepared according to literature following a procedure by Merz *et al*.[3] Methyl 7-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-2-methoxybenzo[*d*][1,3]dioxole-5-carboxylate (**3**) (280 mg, 0.731 mmol, 1.00 eq) and *p*-toluenesulfonic acid (5.0 mg, 0.029 mmol, 0.04 eq) were dissolved in methanol (4 mL) at RT. The suspension was stirred at RT under N_2-atmosphere overnight. To the reaction mixture was added concentrated hydrochloric acid (four drops), it was diluted with water (10 mL) and extracted with diethyl ether (8 x 5 mL). The combined organic layers were washed with brine (10 mL) and dried over sodium sulfate. The desiccant was filtered off and the organic layer was concentrated under reduced pressure. After purification by column chromatography (SiO_2, *n*-hexane/EtOAc, 2:1, R_f = 0.22) the title compound was provided as a colorless oil (77.1 mg, 0.226 mmol, 31%).

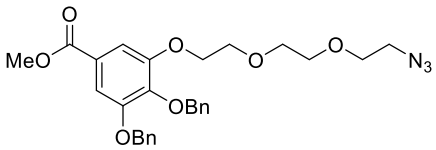


^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.37 (d, *J* = 1.9 Hz, 1H), 7.27 (d, *J* = 1.9 Hz, 1H), 4.23 – 4.18 (m, 2H), 3.86 (s, 3H), 3.85 – 3.81 (m, 2H), 3.79 – 3.75 (m, 2H), 3.74 – 3.66 (m, 4H), 3.45 – 3.39 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 166.90, 145.86, 144.73, 139.53, 121.65, 111.94, 110.48, 70.9, 70.71, 70.57, 70.21, 69.68, 52.16, 50.91.
IR (Film): v [cm^{-1}] = 3375 (b), 2927 (b), 2110 (m), 1713 (s), 1607 (s), 1516 (s), 1438 (s), 1345 (m), 1318 (m), 1227 (m), 1090 (m), 1008 (b), 916 (b), 876 (b), 806 (b), 768 (b), 657 (b), 557 (b), 505 (b).
HRMS (ESI) m/z: [M+H$^+$] Calcd $C_{14}H_{20}N_3O_7$ 342.1301; found 342.1300.

Methyl 3-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-4,5-bis(benzyloxy) benzoate

The compound was prepared according to literature following a procedure by Percec *et al*.[5] Methyl 3-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-4,5-dihydroxybenzoate (76.5 mg, 0.224 mmol, 1.00 eq) was dissolved in DMF (5 mL) at RT. To this solution benzyl chloride (77.0 µL, 0.672 mmol, 3.00 eq) and potassium carbonate (83.6 mg, 0.605 mmol, 2.70 eq) were added. The suspension was stirred at 80 °C for eight hours. The reaction mixture was poured into ice water and extracted with ethyl acetate (4 x 10 mL) and with water (6 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over sodium sulfate. The desiccant was filtered off and the organic layer was concentrated under reduced pressure. After purification by column

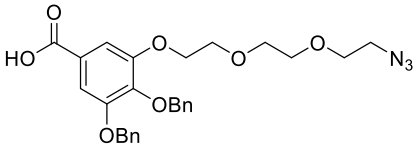
chromatography (SiO_2, *n*-hexane/EtOAc, 3:1, R_f = 0.29) the title compound was provided as a colorless oil (103 mg, 0.197 mmol, 88%).



^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.51 – 7.27 (m, 12H), 5.14 (s, 2H), 5.13 (s, 2H), 4.24 – 4.19 (m, 2H), 3.92 – 3.86 (m, 5H), 3.76 – 3.71 (m, 2H), 3.68 – 3.61 (m, 4H), 3.36 – 3.30 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 166.60, 152.62, 152.48, 142.21, 137.64, 136.69, 128.53, 128.45, 128.18, 128.00, 127.93, 127.52, 125.20, 109.00, 108.74, 77.56, 77.14, 76.71, 74.97, 71.19, 70.94, 70.74, 70.06, 69.75, 68.81, 52.2, 50.64.
IR (Film): v [cm^{-1}] = 3648 (w), 3032 (w), 2961 (s), 2360 (s), 2341 (m), 2104 (m), 1716 (s), 1589 (s), 1499 (s), 1455 (m), 1429 (s), 1335 (s), 1259 (s), 1110 (m), 1014 (m), 912 (w), 865 (w), 800 (m), 759 (m), 698 (s), 560 (w).
HRMS (ESI) m/z: [M+NH_4^+] Calc $C_{28}H_{35}N_4O_7$ 539.2506; found 539.2502.

3-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)-4,5-bis(benzyloxy) benzoic acid (**4**)

Methyl 3-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-4,5-bis(benzyloxy)benzoate (103 mg, 0.197 mmol, 1.00 eq) was dissolved in ethanol (7 mL) at RT. To this solution a potassium hydroxide solution (40 w%, 2.70 mL) was added. The solution was stirred at 100 °C for three hours until TLC (SiO_2, *n*-hexane:EtOAc, 3:1, R_f = 0.29) showed full consumption of the starting material. After cooling down to rt, to this mixture 1 M hydrochloric acid (1 mL) was added and the mixture was extracted with ethyl acetate (4 x 5 mL) and with water (2 x 5 mL). The combined organic layers were washed with brine (30 mL) and dried over sodium sulfate. The desiccant was filtered off and the organic layer was concentrated under reduced pressure, the title compound was provided as a brown oil (90.2 mg, 0.178 mmol, 90%).

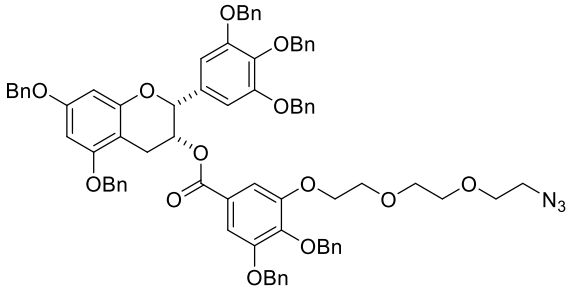


^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 11.13 (broad s, 1H), 7.51 – 7.27 (m, 12H), 5.30 (s, 1H), 5.16 (s, 2H), 5.14 (s, 2H), 4.27 – 4.19 (m, 2H), 3.94 – 3.86 (m, 2H), 3.77 – 3.70 (m, 2H), 3.69 – 3.61 (m, 4H), 3.38 – 3.30 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 171.50, 152.78, 152.61, 143.10, 137.65, 136.68, 128.67, 128.56, 128.32, 128.16, 128.09, 127.65, 124.27, 109.68, 109.48, 75.13, 71.32, 71.07, 70.86, 70.19, 69.88, 68.98, 50.77.
IR (Film): v [cm^{-1}] = 3089 (w), 3064 (m), 3032 (m), 2927 (w), 2871 (w), 2552 (w), 2352 (w), 2318 (w), 2104 (s), 1954 (w), 1812 (w), 1683 (s), 1584 (m), 1503 (s), 1454 (m), 1428 (s), 1371 (m), 1327 (m), 1221 (m), 1120 (m), 1048 (w), 1029 (w), 987 (w), 915 (w), 870 (w), 853 (w), 770 (m), 736 (m), 697 (s), 678 (w), 641 (w), 607 (w), 556 (w).
HRMS (ESI) m/z: [M+NH_4^+] Calc $C_{27}H_{33}N_4O_7$ 525.2349; found 525.2362.

(2R,3R)-5,7-Bis(benzyloxy)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 3-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-4,5-bis(benzyloxy)benzoate (**6**)

The compound was prepared according to literature following a procedure by Khandelwal *et al*.[6] 3-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)-4,5-bis(benzyloxy) benzoic acid (**4**) (0.211 g, 0.416 mmol, 2.00eq), DMAP (25.0 mg, 0.208 mmol, 1.00 eq) and EDC·HCl (79.5 mg, 0.416 mmol, 2.00 eq) were dissolved in CH_2Cl_2 (8 mL) at RT under N_2-atmosphere. The mixture was cooled down to 0 °C and a solution of benzyl protected *cis*-chromanol (**5**) (157 mg, 0.208 mmol, 1.00 eq) in CH_2Cl_2 (2 mL) was added under N_2-atmosphere. The resulting mixture was stirred overnight at RT. The reaction was diluted with CH_2Cl_2 (5 mL), it was washed with 0.5 M HCl (2 mL) and then with saturated $NaHCO_3$ solution (5 mL) and with brine (5 mL). The organic layer was dried over Na_2SO_4, filtered off and it was concentrated under reduced pressure. The residue was purified *via* flash chromatography (aluminum oxide activity level III, 1:3 EtOAc:*n*-hexane, R_f = 0.20) and the ester (**6**) was obtained as a lightly yellow oil (0.218 g, 0.174 mmol, 84%).

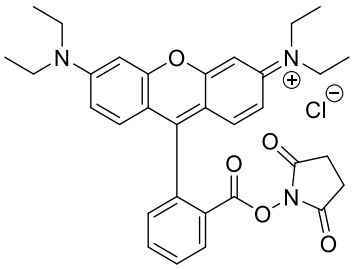


^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.43 – 7.13 (m, 37H), 6.73 (s, 2H), 6.35 (d, *J* = 2.2 Hz, 2H), 5.66 – 5.60 (m, 1H), 5.12 – 4.90 (m, 12H), 4.84 (d, *J* = 11.5 Hz, 2H), 4.71 (m, 2H), 4.08 – 4.01 (m, 2H), 3.75 – 3.69 (m, 2H), 3.61 – 3.58 (m, 2H), 3.62 – 3.56 (m, 4H), 3.25 – 3.19 (m, 2H), 3.15 – 2.99 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 165.01, 158.96, 158.09, 155.69, 152.96, 152.74, 152.33, 142.78, 138.54, 137.87, 137.74, 137.01, 136.92, 136.54, 133.40, 128.71, 128.66, 128.65, 128.59, 128.49, 128.31, 128.28, 128.14, 128.13, 128.05, 127.96, 127.91, 127.83, 127.61, 127.59, 127.32, 125.11, 109.35, 109.22, 106.83, 101.06, 94.80, 94.09, 77.92, 75.23, 75.01, 71.36, 71.16, 70.93, 70.74, 70.27, 70.08, 69.75, 69.03, 68.53, 50.69, 26.22.
IR (Film): ν [cm^{-1}] = 2929 (w), 2869 (w), 2102 (m), 1715 (s), 1618 (s), 1590 (s), 1498 (s), 1372 (m), 1327 (m), 1214 (w), 1147 (m), 1114 (m), 1028 (s), 739 (w), 697 (s).
HRMS (ESI) m/z: [M+NH_4^+] Calc $C_{77}H_{75}N_4O_{13}$ 1263.5331; found 1263.5325.
Specific rotation: $[\alpha]_D^{20}$ -55.8 (*c* 0.35, chloroform).

N-(6-(Diethyamino)-9-(2-(((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)phenyl)-3H-xanthen-3-ylidene)-N-ethylethanaminium chloride

The compound was prepared according to literature following a procedure by Fujisaki *et al*.[7] Rhodamine B (500 mg, 1.04 mmol, 1.00 eq) was dissolved in DMF (15 mL) at RT. To this solution, EDC·HCl (259 mg, 1.36 mmol, 1.30 eq) and *N*-hydroxysuccinimide (156 mg, 1.36 mmol, 1.30 eq) were added. The solution was stirred at RT for 24 hours until TLC (SiO_2, methanol:methylene chloride, 95:5, R_f = 0.43) showed full consumption of the starting material. The lightly red solution was extracted with ethyl acetate (8 x 15 mL) and with water (8 x 15 mL). The combined organic layers were washed with brine (30 mL) and dried over sodium sulfate. The desiccant was filtered off and the organic layer was concentrated under reduced pressure. The product was obtained as a pink solid (602 mg, 1.11 mmol, 88%) and used for the next step without further purification.

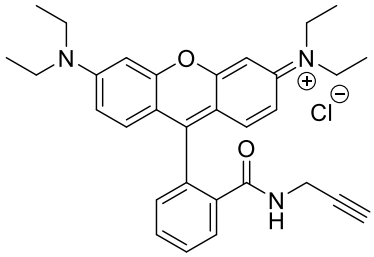


^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 8.41 (dd, *J* = 9.0, 8.0 Hz, 1H), 7.99 – 7.94 (m, 1H), 7.80 (td, *J* = 7.8, 1.3 Hz, 1H), 7.61 (td, *J* = 7.4, 1.4 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.20 – 7.17 (d, *J* = 9.5 Hz, 1H), 7.06 (d, *J* = 9.4 Hz, 1H), 6.85 (dd, *J* = 9.5, 2.5 Hz, 2H), 6.80 (d, *J* = 2.4 Hz, 1H), 2.79 – 2.71 (m, 4H), 3.64 (q, *J* = 7.2 Hz, 8H), 2.77 (s, 4H), 1.32 (t, *J* = 7.1 Hz, 12H).
^{13}C NMR (75 MHz, CD_3OD): δ [ppm] = 169.76, 168.74, 160.82, 157.90, 155.81, 155.73, 153.73, 149.94, 135.04, 134.59, 134.30, 131.87, 131.16, 131.06, 130.08, 129.29, 129.23, 128.36, 125.48,

125.23, 124.59, 114.56, 113.53, 108.45, 106.56, 97.60, 96.70, 46.34, 44.67, 36.61, 31.55, 25.72, 12.79, 12.66.

N-(6-(Diethyamino)-9-(2-(prop-2-yn-1-ylcarbamoyl)phenyl)-3H-xanthen-3-ylidene)-N ethylethanaminium chloride (**7**)

The compound was prepared according to literature following a procedure by Andrade *et al.*[8] Propargyl amine (71.4 µL, 1.11 mmol, 1.00 eq) and triethyl amine (311 µL, 2.22 mmol, 2.00 eq) were dissolved in DMF (45 mL) and cooled down to 0 °C. To this cooled mixture a solution of NHS-rhodamine B (602 mg, 1.11 mmol, 1.00 eq) dissolved in DMF (5 mL) was added dropwise. The resulting mixture was stirred for 30 min at 0 °C. The ice bad was removed and the resulting solution was stirred over night at RT. The solution was extracted with ethyl acetate (8 x 20 mL) and with water (8 x 20 mL). The combined organic layers were washed with brine (30 mL) and dried over sodium sulfate. The desiccant was filtered off and the organic layer was concentrated under reduced pressure. After purification by column chromatography (SiO_2, methanol:dichloromethane, 99:1, R_f = 0.31) the product (**13**) was provided as a pink solid (246 mg, 0.511 mmol, 68%).

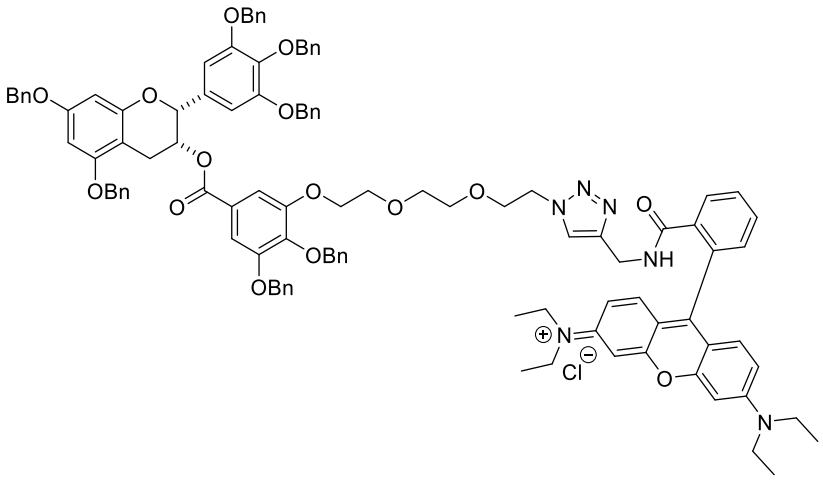


^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.96 - 7.88 (m, 1H), 7.47 – 7.38 (m, 2H), 7.14 – 7.06 (m, 1H), 6.48 (s, 1H), 6.45 (s, 1H), 6.39 (d, *J* = 2.5 Hz, 2H), 6.27 (dd, *J* = 8.9, 2.6 Hz, 2H), 3.95 (d, *J* = 2.5 Hz, 2H), 3.33 (q, *J* = 7.0 Hz, 8H), 1.76 (t, *J* = 2.5 Hz, 1H), 1.16 (t, *J* = 7.0 Hz, 12H).

(2R,3R)-5,7-Bis(benzyloxy)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 3,4-bis(benzyloxy)-5-(2-(2-2-(4-((2-(3-(diethyl-λ4-azaneylidene)-6-(diethylamino)-3H xanthen-9-yl) benzamido) methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy) ethoxy benzoate

The compound was prepared according to literature following a procedure by Kolarovič *et al.*[9] A 10 mL, round-bottomed flask equipped with a magnetic stirring bar was sequentially charged with copper sulfate (0.743 mg, 2.98 µmol, 5 mol%) and sodium ascorbate (1.18 mg, 5.96 µmol, 10 mol%) in DMSO (100 µL). To this green mixture a solution of azide-functionalized EGCG

derivative **6** (74.1 mg, 0.0595 mmol, 1.10 eq) in DMSO (100 µL) followed by a solution of rhodamine B derivative **7** (26.0 mg, 0.0542 mmol, 1.00 eq) in DMSO (100 µL) was added. The brown solution was stirred at 65 °C overnight until TLC (SiO_2, MeOH/CH_2Cl_2, 5:95, R_f = 0.43) showed complete consumption of starting material. The solvent was evaporated and the residue was purified by column chromatography (aluminum oxide, activity level III, MeOH/CH_2Cl_2, 5:95), providing the product (92.3 mg, 0.0534 mmol, 90%) as pink oil.



^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.91 – 7.86 (m, 2H), 7.45 – 7.14 (m, 45H), 7.10 – 7.01 (m, 1H), 6.74 (s, 2H), 6.38 (d, *J* = 2.0 Hz, 2H), 6.33 (d, *J* = 2.2 Hz, 2H), 6.28 (d, *J* = 8.7 Hz, 2H), 6.12 (d, *J* = 8.1 Hz, 2H), 5.67 (s, 1H), , 5.07 – 4.94 (m, 10H), 4.92 (s, 1H), 4.84 (d, *J* = 11.5 Hz, 2H), 4.74 (d, *J* = 11.5 Hz, 2H), 4.46 (s, 2H), 4.16 – 4.09 (m, 2H), 4.05 – 3.99 (m, 2H), 3.70 – 3.64 (m, 2H), 3.61 – 3.55 (m, 2H), 3.54 – 3.49 (m, 2H), 3.43 – 3.38 (m, 2H), 3.32 – 3.20 (m, 8H), 3.14 – 3.01 (m, 1H), 1.14 – 1.06 (m, 12H).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] = 167.81, 164.89, 158.87, 158.00, 155.60, 153.40, 152.86, 152.64, 152.21, 148.64, 142.65, 138.42, 137.77, 136.90, 136.41, 133.32, 132.50, 128.76, 128.62, 128.57, 128.49, 128.40, 128.19, 128.17, 128.10, 128.07, 128.04, 127.96, 127.90, 127.83, 127.75, 127.51, 127.49, 127.22, 125.03, 123.87, 123.20, 122.85, 109.23, 109.08, 107.78, 106.72, 105.36, 100.97, 97.86, 94.73, 94.00, 77.84, 75.14, 74.89, 71.25, 71.06, 70.67, 70.51, 70.18, 70.02, 69.59, 69.36, 68.94, 68.44, 44.33, 41.05, 12.63.

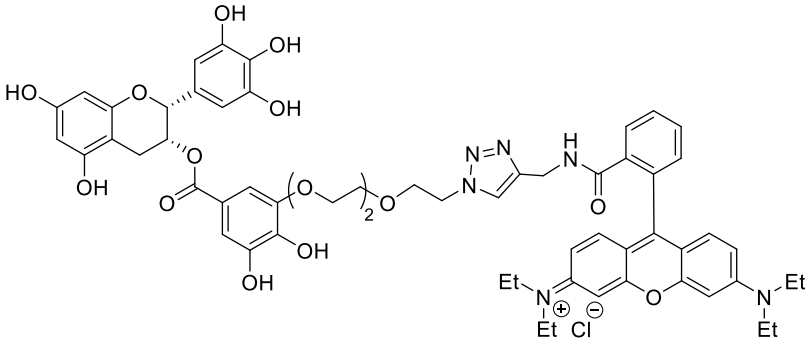
IR (Film): v [cm^{-1}] 2968 (w), 1683.86 (w), 1614.42 (s), 1589.34 (s), 1516.05 (s), 1427.32 (s), 1373.32 (s), 1328.95 (w), 1307.74 (s), 1263.37 (s), 1219.01 (w), 1120.98 (w), 910.40 (w), 813.96 (s), 734.88 (s), 696.30 (s).

HRMS (ESI) m/z: [M+H$^+$] Calc $C_{108}H_{105}N_6O_{15}$ = 1725.7632; found 1725.7618.

Specific rotation: $[\alpha]_D^{20}$ -42.7 (*c* 0.845, chloroform).

N-(6-(Diethylamino)-9-(2-(((1-(2-(2-(2-(5-((((2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-chroman-3-yl)oxy)carbonyl)-2,3-dihydroxyphenoxy) ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)-methyl)carbamoyl)phenyl)-3H-xanthen-3-ylidene)-N-ethylethanaminium chlorid ***(8)***

The compound was prepared according to literature following a procedure by Li *et al.*[10] A 25 mL, two necked round-bottomed flask equipped with a magnetic stirring bar and three way cock, which was equipped with a balloon filled with hydrogen, was sequentially charged with (2R,3R)-5,7-bis(benzyloxy)-2-(3,4,5-tris-(benzyloxy)phenyl)chroman-3-yl 3,4-bis(benzyloxy)-5-(2-(2-2-(4-((2-(3-(diethyl-λ4-azaneylidene)-6-(diethylamino)-3H xanthen-9-yl) benzamido) methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy) ethoxy benzoate (92.3 mg, $5.19 \cdot 10^{-5}$ mol, 1.00 eq) in a mixture of THF/methanol (2 mL, 1:1, v/v). The flask was flowed with argon when one lightly heaped spatula $Pd(OH)_2$ (20% on carbon) was added in one batch to the solution. The resulting mixture was stirred at rt under H_2-atmosphere until TLC (RP 18, acetonitrile/H_2O, 1:1) showed complete consumption of the starting material. The black suspension was filtered through a syringe filter (0.20 µm PTFE) and the filtrate was evaporated. The residue was purified by flash chromatography on RP silica gel with acetonitrile to afford the desired compound **8** (52.7 mg, $4.60 \cdot 10^{-5}$ mol, 89%) as a pink solid.



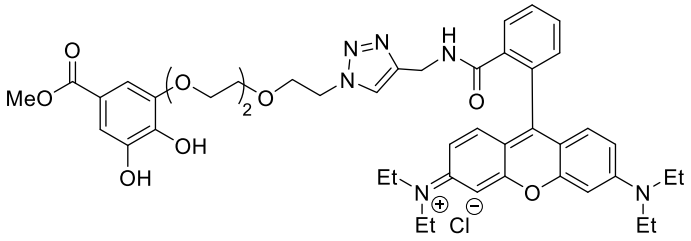
^{1}H NMR (300 MHz, CD_3OD): δ [ppm] = 7.92 – 7.89 (m, 2H, 12-H, 13-H), 7.51 – 7.45 (m, 2H, 26-H, 27-H), 7.08 – 7.03 (m, 2H, 25-H), 7.00 – 6.94 (m, 2H, 28-H), 6.57 (s, 2H, 3-H, 4-H), 6.38 – 6.26 (m, 4H, 29-H, 30-H, 33-H, 34-H), 5.98 (s, 2H, 8-H, 9-H), 5.49 – 5.47 (m, 1H, 6-H), 5.02 – 4.99 (m, 1H, 5-H), 4.42 (br s, 1H, 35-H), 4.27 – 4.24 (m, 1H, 33-H), 4.02 – 3.93 (m, 2H, 23-H), 3.74 – 3.66 (m, 4H, 16-H, 17-H), 3.60 (d, *J* = 4.3 Hz, 2H, 18-H), 3.55 (d, *J* = 4.7 Hz, 2H, 19-H), 3.47 (br s, 2H, 20-H), 3.43 (td, *J* = 6.1, 3.1 Hz, 2H, 21-H), 3.33 (td, *J* = 3.3, 1.7 Hz, 8H, 35-H, 37-H), 3.02 – 2.98 (m, 1H, 7-H), 2.95 – 2.90 (m, 1H, 7-H), 1.10 (t, *J* = 7.0 Hz, 12H, 36-H, 38-H).

^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 167.29, 157.80, 157.69, 156.98, 154.62, 154.30, 147.70, 146.59, 146.16, 144.44, 140.92, 134.29, 133.54, 131.27, 130.79, 130.00, 129.65, 125.24, 124.87, 123.77, 121.44, 112.05, 108.27, 106.65, 99.16, 96.42, 95.69, 78.26, 71.28, 71.12, 70.48, 70.38, 69.91, 69.54, 68.69, 66.38, 50.85, 46.62, 35.55, 26.44, 26.32, 12.38.

IR (Film): ν [cm^{-1}] = 2970 (b), 2900 (b), 2358 (m), 1608 (b), 1514 (m), 1332 (b), 1217 (b), 1078 (b), 1037 (m), 819 (s), 761 (s).
HRMS (ESI) m/z: [M^+] Calc $C_{59}H_{63}N_6O_{15}$ 1095.4346; found 1095.4330.
TLC = RP 18 (methanol), R_f = 0.85.

N-(6-(Diethylamino)-9-(2-(((1-(2-(2-(2-((2-methoxy-6-(methoxycarbonyl)benzo[d][1,3]dioxol-4-yl)oxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)carbamoyl)phenyl)-3H-xanthen-3-ylidene)-N-ethylethanaminium chloride (**9**)

The compound was prepared according to literature following a procedure by Kolarovič *et al.*[9] A 10 mL, round-bottomed flask equipped with a magnetic stirring bar was sequentially charged with copper sulfate (1.69 mg, 6.75 µmol, 5 mol%) and sodium ascorbate (2.68 mg, 0.0135 mmol, 10 mol%) in DMSO (100 µL). To this green mixture a solution of methyl 3-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-4,5-dihydroxybenzoate (46.1 mg, 0.135 mmol, 1.10 eq) in DMSO (100 µL) followed by a solution of rhodamine B derivative **7** (59.0 mg, 0.123 mmol, 1.00 eq) in DMSO (100 µL) were added. The brown solution was stirred at 65 °C overnight until TLC (SiO_2, MeOH/CH_2Cl_2, 2:98) showed complete consumption of starting material. The solvent was evaporated and the residue was purified by column chromatography (aluminum oxide, activity level III, MeOH/CH_2Cl_2, 2:98), providing triazole **9** (57.7 mg, 0.0702 mmol, 57%) as pink oil.



^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 8.85 (br s, 1H, 5-H), 7.96 – 7.90 (m, 1H, 15-H), 7.46 – 7.39 (m, 3H, 18-H, 17-H, 16-H), 7.35 (d, *J* = 1.9 Hz, 1H, 2-H), 7.18 (d, *J* = 2.0 Hz, 1H, 3-H), 7.11 – 7.05 (m, 1H, 12-H), 6.87 (br s, 1H, 4-H), 6.34 (d, *J* = 2.5 Hz, 2H, 20-H, 19-H), 6.26 (d, *J* = 8.8 Hz, 2H, 24-H, 23-H), 6.11 (dd, *J* = 8.9, 2.6 Hz, 2H, 26-H, 25-H), 4.46 (s, 2H, 13-H), 4.28 (t, *J* = 5.1 Hz, 2H, 6-H), 4.14 – 4.08 (m, 2H, 7-H), 3.84 (s, 3H, 1-H), 3.75 (t, *J* = 5.1 Hz, 2H, 8-H), 3.68 – 3.63 (m, 2H, 9-H), 3.60 – 3.53 (m, 4H, 11-H, 10-H), 3.29 (q, *J* = 7.0 Hz, 8H, 27-H, 21-H), 1.13 (t, *J* = 7.0 Hz, 12H, 28-H, 22-H).
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 168.34, 167.08, 153.73, 153.53, 148.83, 146.26, 145.21, 144.10, 139.72, 132.81, 130.75, 128.67, 128.22, 124.01, 123.04, 121.04, 111.73, 108.69, 107.88, 104.96, 98.06, 70.63, 70.44, 69.77, 69.46, 65.52, 49.92, 44.44, 41.08, 35.54, 12.67.

IR (Film): v [cm^{-1}] = 2970 (s), 2929 (s), 2871 (s), 2358 (s), 2337 (s), 2244 (s), 1687 (b), 1633 (s), 1614 (s), 1547 (s), 1515 (m), 1433 (m), 1331 (b), 1266 (s), 1220 (m), 1118 (s), 1090 (s), 1016 (m), 913 (m), 819 (s), 788 (m), 731 (m).

HRMS (ESI) m/z: [M^+] Calc $C_{45}H_{53}N_6O_9$ 821.3869; found 821.3861.

TLC = SiO_2, CH_2Cl_2/MeOH, 98:2, R_f = 0.11.

EGCG derivatives for structure activity relationship (SAR) analysis

Synthesis of protected benzoic acids

The benzoic acid derivatives were introduced as their benzylated or methylated analogues for the formation of EGCG derivatives. The benzylation was realized by the use of benzyl bromide, DMF and K_2CO_3 according to general methodology. The methylation was realized as described previously. The following saponification of the ester to the corresponding acid was completed by the use of potassium hydroxide in a mixture of ethanol and water.

General protocol for the Steglich esterification

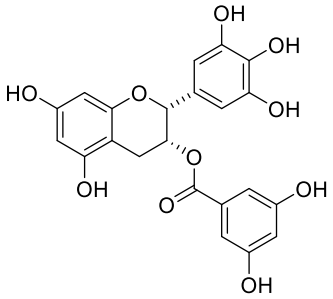
The esterification was done according to literature following a procedure by Khandelwal *et al*.[6] A 100-mL, two necked, round-bottomed flask equipped with a magnetic stirring bar was sequentially charged with the benzoic acid (2.00 eq), EDC·HCl (2.00 eq), and DMAP (2.00 eq) in dry CH_2Cl_2 (8 mL) at 0 °C under N_2-atmosphere. To this mixture a solution of *cis*-chroman-3-ol **5** (1.00 eq) in dry CH_2Cl_2 (2 mL) was added at 0 °C under N_2-atmosphere. The resulting mixture was stirred overnight at rt. Then the reaction was diluted with CH_2Cl_2 (5 mL) and washed with HCl (2 mL, 2.5 M) and sat. $NaHCO_3$ (10 mL) solution. The organic layer was washed with brine (10 mL) and dried (Na_2SO_4), the drying agent was filtered off, and concentrated under reduced pressure. The residue was purified *via* flash chromatography (Alox III, *n*-hexane/EtOAc, 1:5) to give the desired ester.

General protocol for the palladium-catalyzed hydrogenation of benzoate esters

The compounds were prepared according to literature following a procedure by Li *et al.*[10] A 100-mL, two necked round-bottomed flask equipped with a magnetic stirring bar and three-way-cock, equipped with a balloon filled with hydrogen, was charged with the corresponding ester (0.100 mmol,1.00 eq) in a mixture of THF/methanol (5 mL, 1:1, v/v). The head space was purged with N_2, then $Pd(OH)_2$ (0.82 eq, 20% on carbon) was added in one batch to the solution. The resulting mixture was stirred at RT under H_2-atmosphere until TLC (RP 18, acetonitrile/H_2O, 3:2) showed full consumption of the starting material. The black solution was filtered through a syringe filters (0.2 µm PTFE) and the filtrate was evaporated.

(2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-(3,5-dihydroxy)benzoate (**10**)

The compound was prepared following the general procedures for Steglich esterification and catalytic hydrogenation giving the compound as a lightly grey solid (22 mg, 0.0498 mmol, 88%).



^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 6.85 (dd, *J* = 2.4, 0.8 Hz, 2H), 6.54 (s, 2H), 6.44 (td, *J* = 2.3, 0.8 Hz, 1H), 6.00 (s, 2H), 5.60 – 5.98 (br s, 1H), 5.05 – 4.98 (m, 1H), 3.03 (dd, *J* = 17.3, 4.7 Hz, 1H), 2.90 (dd, *J* = 17.5, 2.6 Hz, 1H).

^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 167.28, 159.62, 159.50, 157.85, 157.78, 157.15, 146.66, 133.72, 133.09, 132.88, 130.72, 128.51, 118.14, 116.05, 108.95, 108.86, 108.29, 106.76, 106.34, 99.28, 96.52, 95.86, 78.44, 70.36, 70.19, 26.74, 26.44.

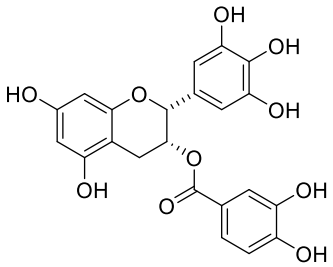
IR (solid): v [cm^{-1}] = 3296 (b), 2474 (b), 1697 (m), 1597 (m), 1448 (m), 1363 (m), 1332 (m), 1238 (m), 1163 (m), 1109 (m), 1033 (s), 997 (s), 964 (m), 848 (s), 763 (s), 731 (s), 673 (s).

HRMS (ESI^+) m/z: [$M+H^+$] Calc $C_{22}H_{19}O_{10}$ 433.0973; found 443.0971.

TLC = RP 18, acetonitrile/H_2O, 3:2, R_f = 0.84.

(2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-(3,4-dihydroxy)benzoate (**11**)

The compound was prepared following the general procedures for Steglich esterification and catalytic hydrogenation giving the compound as a slightly grey solid (50.7 mg, 0.115 mmol, 91%).



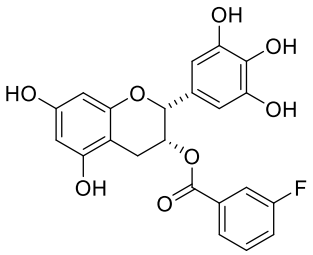
^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.31 – 7.25 (m, 2H), 6.72 – 6.65 (m, 1H), 6.47 (s, 2H), 5.96 – 5.85 (m, 2H), 5.48 (br s, 1H), 4.94 (s, 1H), 3.00 – 2.77 (m, 2H).

^{13}C NMR (600 MHz, CD_3OD): δ [ppm] = 167.27, 157.56, 156.89, 151.36, 146.38, 145.59, 133.42, 130.52, 123.66, 122.34, 117.21, 115.54, 106.52, 99.10, 96.23, 95.54, 78.26, 69.77, 26.46.

IR (solid): v [cm^{-1}] = 3313 (b), 2941 (s), 2463 (b), 2237 (s), 2071 (s), 1689 (b), 1593 (m), 1504 (m), 1440 (m), 1421 (s), 1371 (m), 1336 (s), 1224 (m), 1116 (m), 1035 (s), 968 (s), 871 (s), 819 (s), 763 (s), 630 (s).
HRMS (ESI^+) m/z: [$M+H^+$] Calc$C_{22}H_{19}O_{10}$ 443.0973; found 443.0971.
TLC = RP 18, acetonitrile/H_2O, 3:2) R_f = 0.77.

(2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-(3-fluoro)benzoate (**12**)

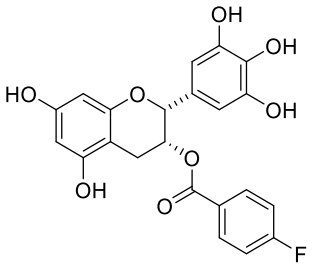
The compound was prepared following the general procedures for Steglich esterification and catalytic hydrogenation giving the compound as a light grey solid (20.8 mg, 0.0486 mmol, 66%).



^{1}H NMR (300 MHz, CD_3OD): δ [ppm] = 7.69 (m, 1H), 7.53 (m, 1H), 7.42 (m, 1H,), 7.28 (m, 1H), 6.51 (s, 2H), 6.05 – 5.91 (m, 2H), 5.98 (br s, 1H), 5.02 (s, 1H), 3.03 (dd, *J* = 17.4, 4.4 Hz, 1H), 2.91 (dd, *J* = 17.6, 2.7 Hz, 1H).
^{13}C NMR (75 MHz, CD_3OD): δ [ppm] = 210.11, 166.06, 166.02, 165.50, 162.25, 158.01, 157.85, 157.12, 146.80, 133.77, 133.73, 133.67, 131.51, 131.41, 130.65, 126.56, 126.52, 121.13, 120.84, 117.23, 116.92, 106.55, 99.08, 96.58, 95.78, 78.33, 71.18, 30.67, 26.63.
^{19}F NMR (600 MHz, CD_3OD): δ [ppm] =-110.55. IR (solid): v [cm^{-1}] = 3176 (b), 2465 (b), 1695 (m), 1593 (m), 1525 (s), 1444 (m), 1359 (m), 1284 (m), 1269 (m), 1205 (s), 1145 (s), 1093 (s), 1070 (s), 1016 (s), 968 (s), 937 (s), 889 (s), 815 (m), 781 (s), 754 (s), 671 (s).HRMS (ESI^+) m/z: [$M+H^+$] Calc $C_{22}H_{18}FO_8$ 429.0980; found 429.0979.
TLC = RP 18, acetonitrile/H_2O, 3:2, R_f = 0.85.

(2R,3R)-5,7-Dihydroxy-2-(3,4,5-tris(hydroxyl)phenyl)chroman-3-yl-(4-fluoro)benzoate (**13**)

The compound was prepared following the general procedures for Steglich esterification and catalytic hydrogenation giving the compound as a colorless oil (23.0 mg, 0.0537 mmol, 48%).



^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.96 – 7.92 (m, 2H), 7.17 – 7.11 (m, 2H,), 6.52 (s, 2H), 6.00 – 5.96 (m, 2H), 5.57 (br s, 1H), 5.02 (s, 1H,), 3.03 (dd, *J* = 17.5, 4.4 Hz, 1H), 2.95 – 2.89 (m, 1H).

^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 168.01, 166.34, 166.29, 158.00, 157.95, 157.86, 157.14, 146.78, 143.79, 133.73, 133.41, 133.35, 130.71, 127.85, 127.83, 116.52, 116.37, 106.61, 99.13, 96.54, 95.77, 78.41, 70.89, 30.67, 26.66.

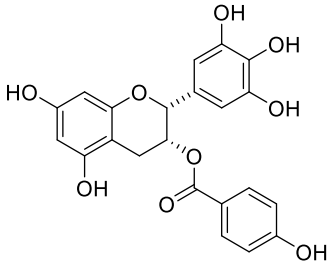
^{19}F NMR (300 MHz, $CDCl_3$): δ [ppm] =-108.09.

IR (film): v [cm^{-1}] = 3176 (b), 2465 (b), 2416 (b), 2225 (s), 1695 (s), 1595 (s), 1525 (m), 1485 (m), 1444 (s), 1359 (m), 1284 (s), 1269 (s), 1205 (s), 1145 (s), 1093 (s), 1070 (s), 1031 (s), 1016 (s), 968 (s), 937 (m), 889 (s), 815 (m), 781 (s), 754 (s).

HRMS (ESI$^+$) m/z: [M+H$^+$] Calc $C_{22}H_{18}FO_8$ 429.0980; found 429.0977.

(2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-(4-hydroxy)benzoate (**14**)

The compound was prepared following the general procedures for Steglich esterification and catalytic hydrogenation giving the compound as a white solid (32.4 mg, 0.07609 mmol, 79%).



^{1}H NMR (600 MHz, CD_3OD): δ [ppm] = 7.79 – 7.74 (m, 2H), 6.80 – 6.74 (m, 2H), 6.54 (s, 2H), 6.03 – 5.97 (m, 2H), 5.55 – 5.49 (m, 1H), 5.02 (s, 1H), 3.02 (dd, *J* = 17.3, 4.6 Hz, 1H), 2.90 (dd, *J* = 17.4, 2.8 Hz, 1H).

^{13}C NMR (151 MHz, CD_3OD): δ [ppm] = 167.49, 163.37, 157.88, 157.84, 157.79, 157.77, 157.72, 157.16, 157.12, 157.10, 146.68, 133.66, 132.90, 132.83, 130.83, 122.27, 118.14, 116.06, 106.73, 99.34, 96.51, 95.77, 78.51, 70.21, 26.67.

IR (solid): v [cm^{-1}] = 3275 (b), 2478 (b), 2073 (s), 1681 (m), 1600 (m), 1512 (s), 1423 (s), 1357 (s), 1265 (m), 1205 (m), 1165 (m), 1101 (b), 1043 (m), 966 (m), 850 (s), 813 (s), 769(s), 694 (s).

HRMS (ESI^+) m/z: [$M+H^+$] Calc $C_{22}H_{19}O_9$ 427.1024; found 427.016.

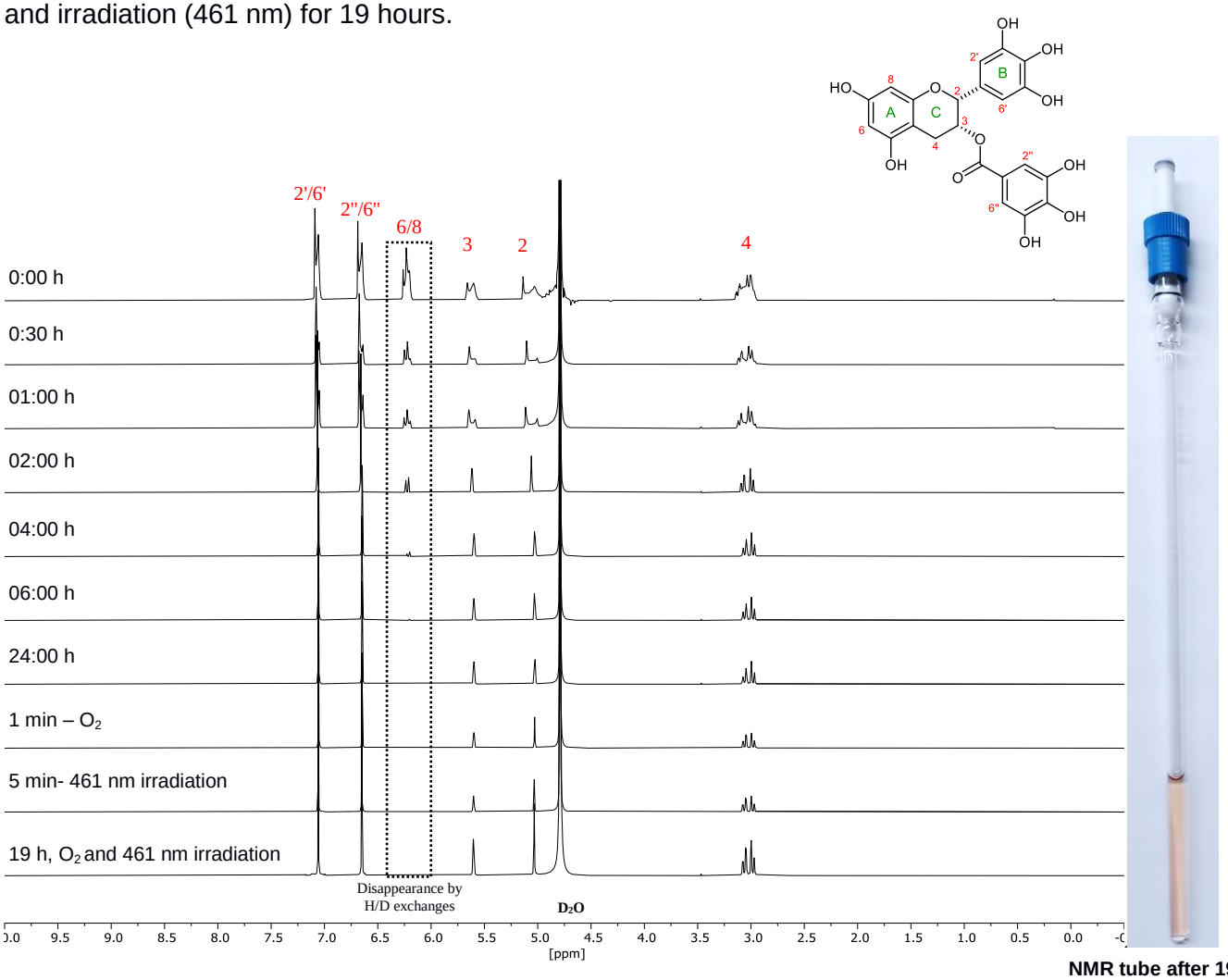
TLC = RP 18, acetonitrile/H_2O, 3:2, R_f = 0.82.

Stability studies of gallocatechin and catechin derivatives

I) NMR-Studies

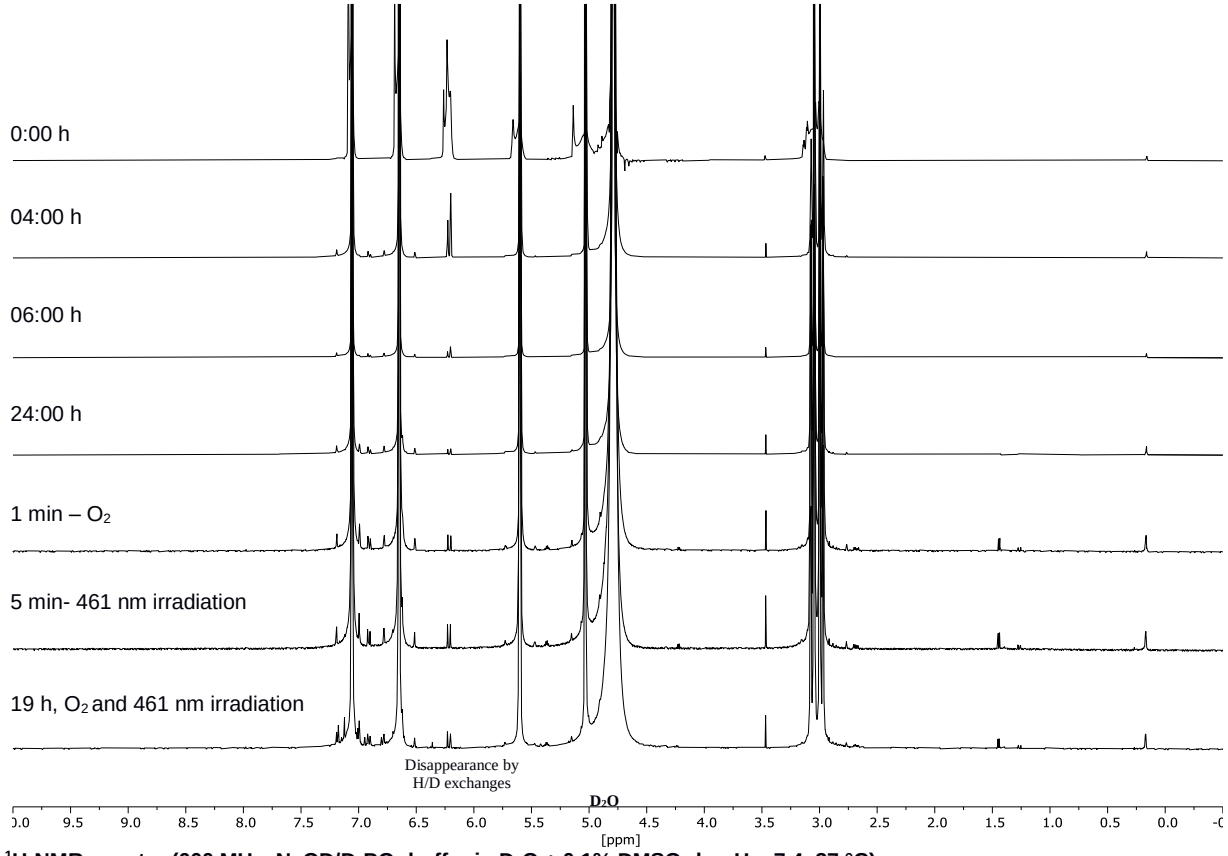
(−)-Epigallocatechin Gallate (EGCG)

Inside the glovebox EGCG (11.3 mg, 0.0247 mmol) was weighed into a Young-NMR tube. Outside the glovebox and under argon atmosphere, the degassed phosphate buffer (0.7 mL) was added to the sample. The Young-NMR tube was tempered in a water bath (37 °C) and measured at 37 °C for the indicated times. The signals of the first measurements are broader than those of the later ones, since the sample was completely dissolved only at elevated temperature. After 24 h air was bubbled through the sample with a Teflon tube for the indicated time. Irradiation was performed in a photoreactor[11]. The clear and colorless sample became colored after being exposed to oxygen and irradiation (461 nm) for 19 hours.

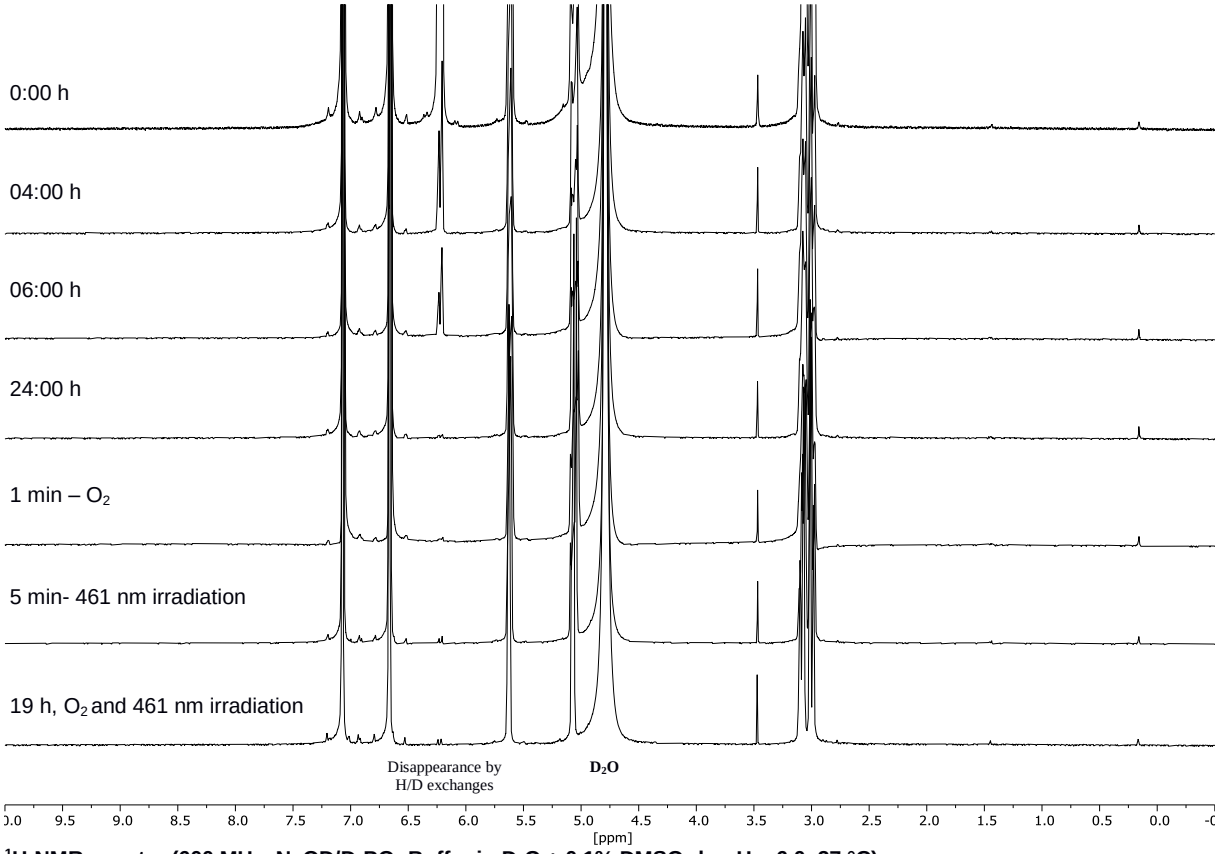


NMR spectra (600 MHz, NaOD/D_3PO_4 buffer in D_2O + 0.1% DMSO-d_6, pH = 7.4, 37 °C)

NMR tube after 19 h of air exposure and irradiation at 461 nm



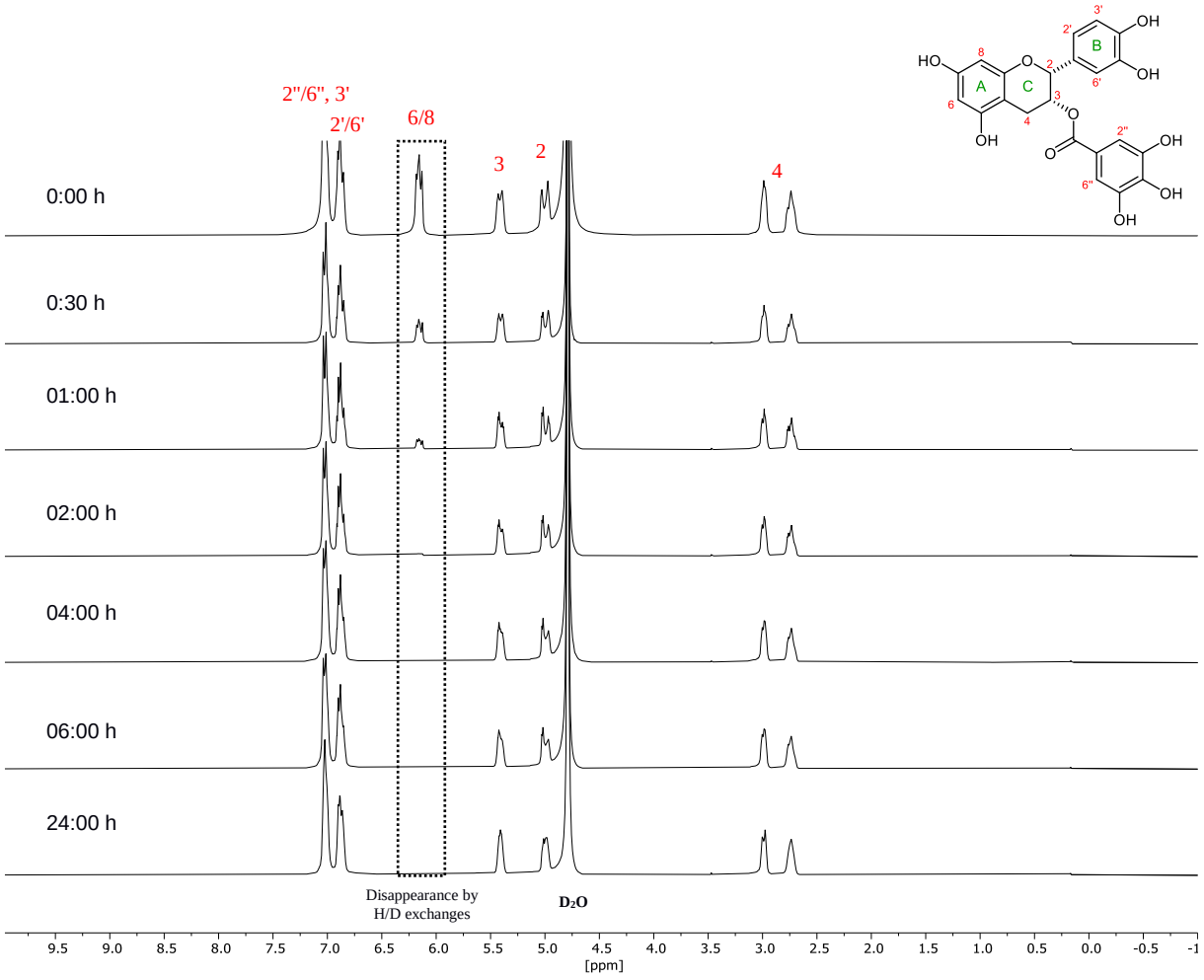
^{1}H-NMR spectra (600 MHz, NaOD/D_3PO_4 buffer in D_2O + 0.1% DMSO-d_6, pH = 7.4, 37 °C)



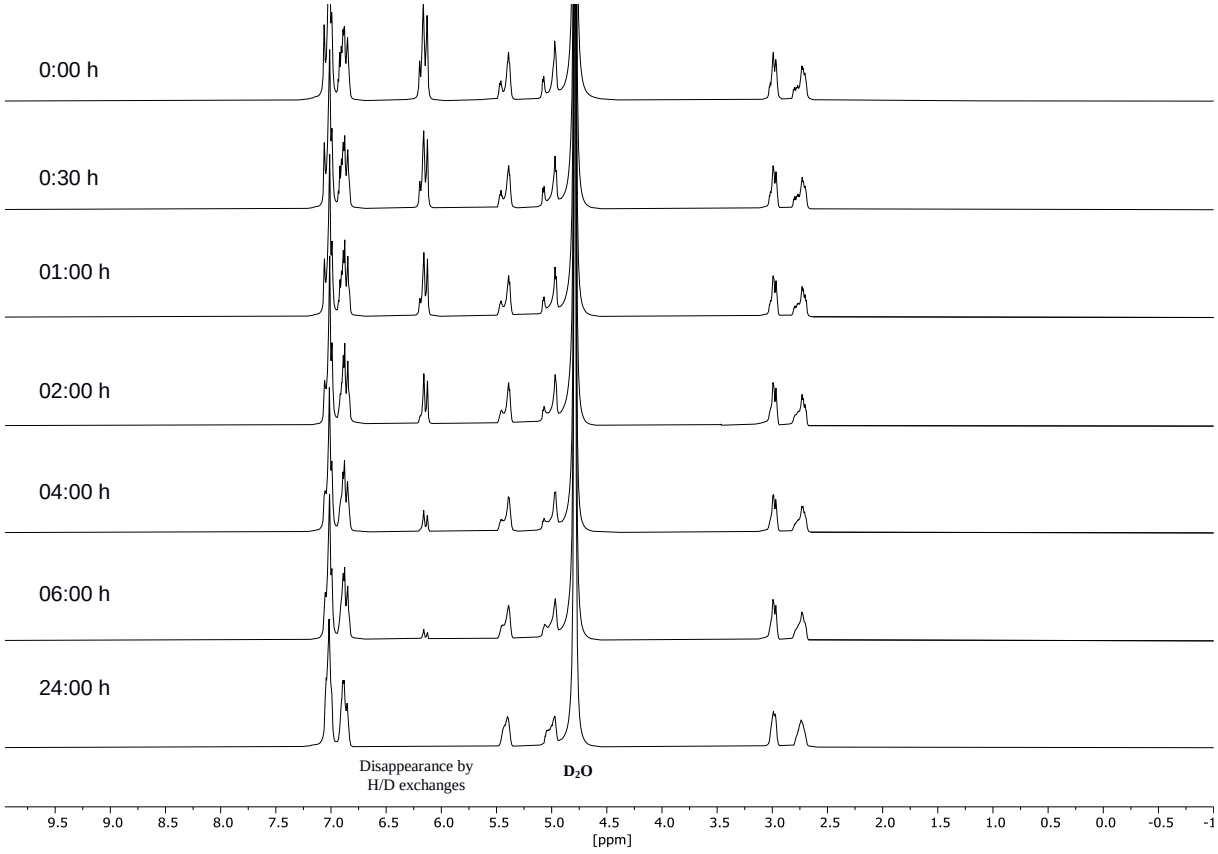
^{1}H-NMR spectra (600 MHz, NaOD/D_3PO_4 Buffer in D_2O + 0.1% DMSO-d_6, pH = 6.0, 37 °C)

(-)-Catechin gallate (CG)

Inside the glovebox CG (10 mg, 0.022 mmol) was weighed into a Young-NMR tube. Outside the glovebox and under argon atmosphere, the degassed phosphate buffer (0.7 mL) was added to the sample. The Young-NMR tube was tempered in a water bath (37 °C) and measured at 37 °C for the indicated times. The signals of the first measurements are broader than those of the later ones, since the sample was completely dissolved only at elevated temperature.



^{1}H-NMR spectra (600 MHz, NaOD/D_3PO_4 Buffer in D_2O + 0.1% DMSO-d_6, pH = 7.4, 37 °C)

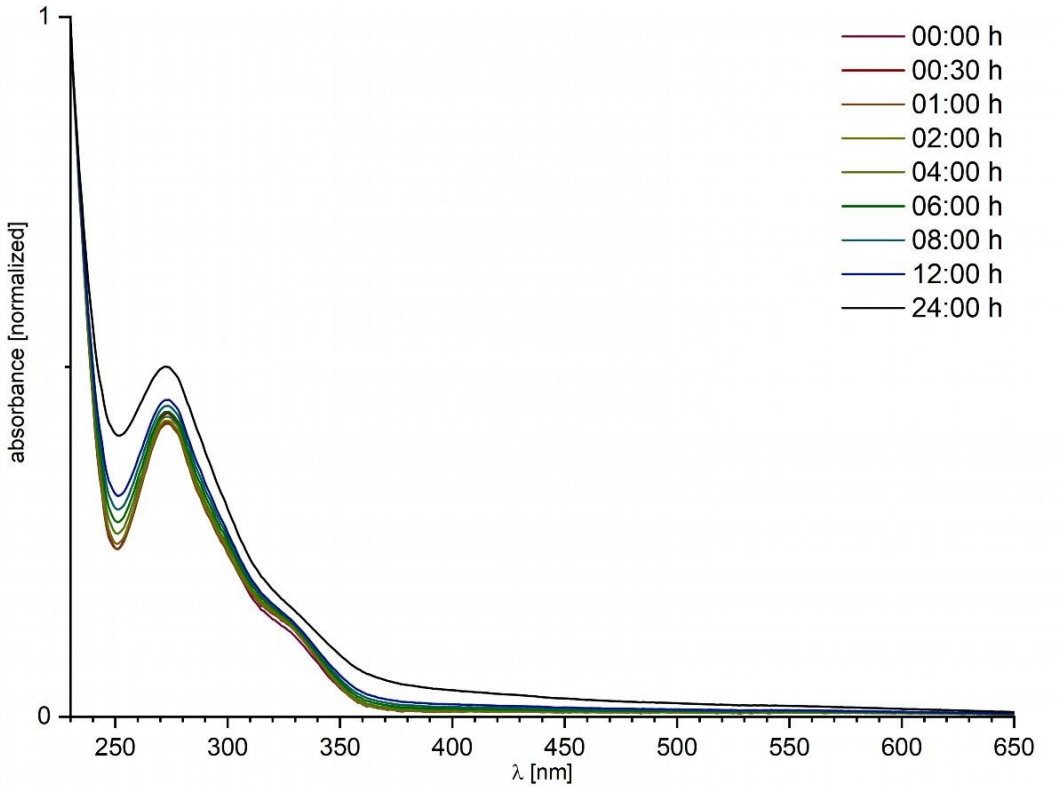


^{1}H-NMR spectra (600 MHz, NaOD/D_3PO_4 Buffer in D_2O + 0.1% DMSO-d_6, pH = 6.0, 37 °C)

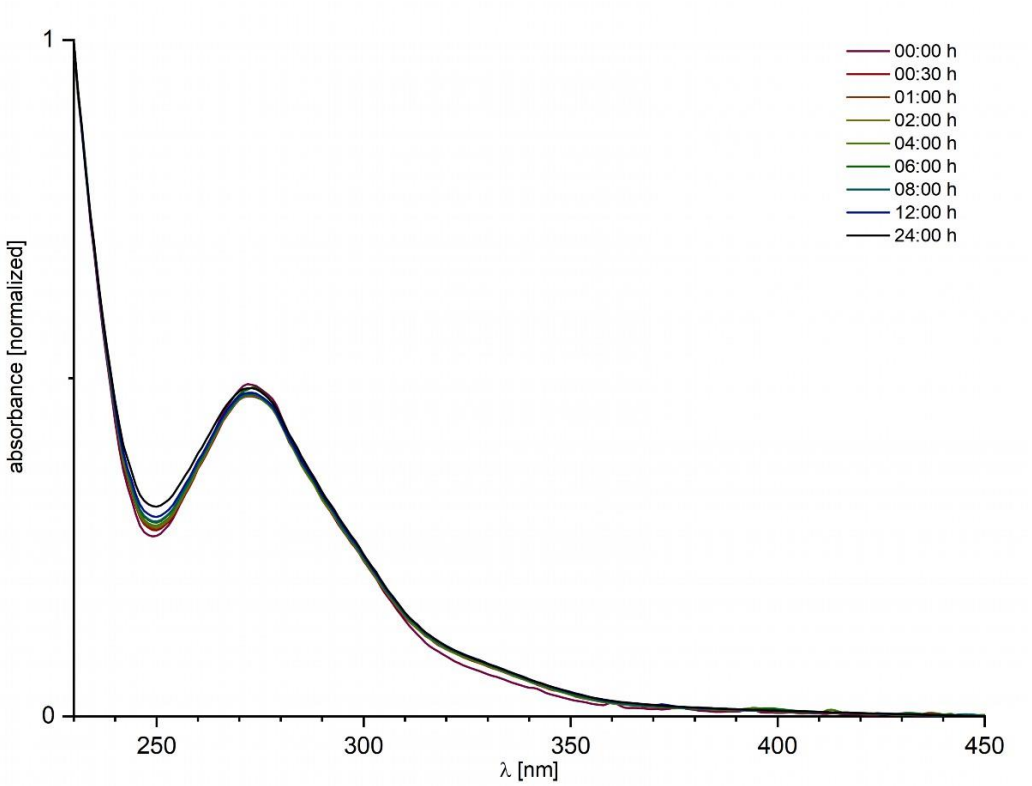
II) UV-Vis-Studies

(−)-Epigallocatechin Gallate (EGCG)

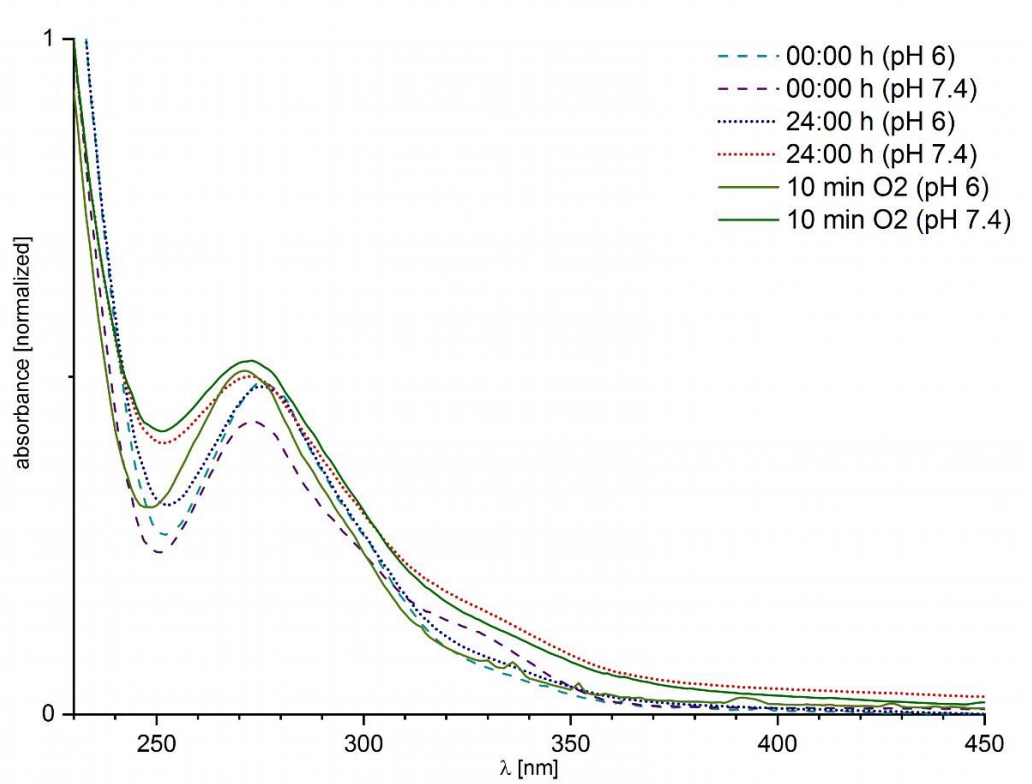
EGCG (1.3 mg, 0.0028 mmol) was weighed in a small vial inside the glovebox. The vial was placed inside a pointed flask with a stopcock and closed with a septum. Outside the glovebox and under argon atmosphere, the degassed buffer (3.0 mL) was added to the sample. From this sample, 0.3 mL was taken and diluted with another 3.0 mL of the buffer. A concentration of 0.090 mM was used. After 24 h air was bubbled through the sample with a Teflon tube for the indicated time. Irradiation was performed in a photoreactor[11].



UV-Vis spectra of EGCG [0.090 mM] (37 °C, NaOD/D_3PO_4 Buffer in D_2O + 0.1% DMSO-d_6, pH = 7.4) (λ_{Max} = 272 nm)



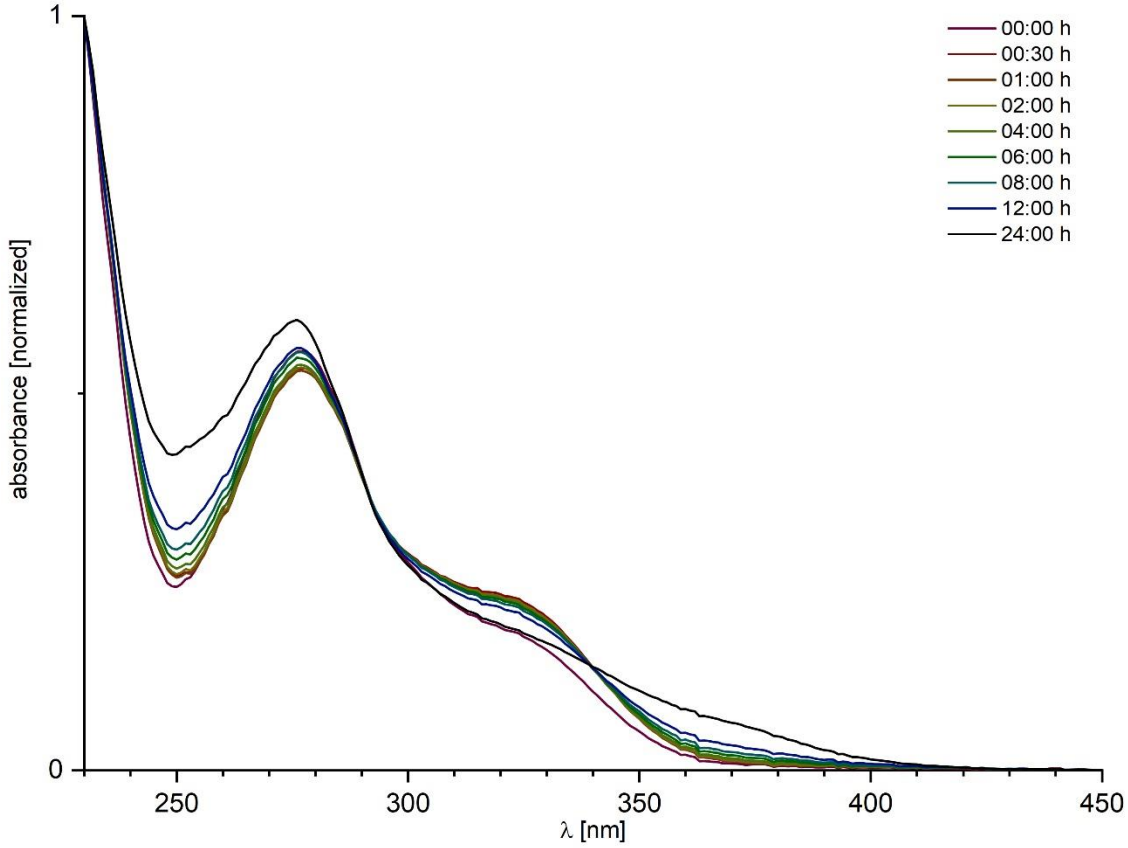
UV-Vis spectra of EGCG [0.090 mM] (37 °C, NaOD/D_3PO_4 Buffer in D_2O + 0.1% DMSO-d_6, pH = 6.0) (λ_{Max} = 272nm)



UV-Vis spectra of EGCG [0.090 mM] (37 °C, NaOD/D_3PO_4 Buffer in D_2O + 0.1% DMSO-d_6, pH = 6.0 and pH = 7.4)

(-)-Catechin gallate, CG

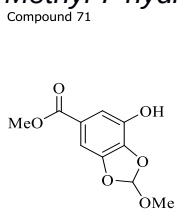
CG (1.0 mg, 0.0023 mmol) was weighed in a small vial inside the glovebox. The vial was placed inside a pointed flask with a stopcock and closed with a septum. Outside the glovebox and under argon atmosphere, the degassed buffer (3.0 mL) was added to the sample. From this sample, 0.4 mL was taken out and diluted with another 3.0 mL of the buffer. A concentration of 0.10 mM was used.



UV-Vis spectra of CG [0.10 mM] (37 °C, NaOD/D_3PO_4 Buffer in D_2O + 0.1% DMSO-d_6, pH = 7.4) (λ_{Max} = 276 nm)

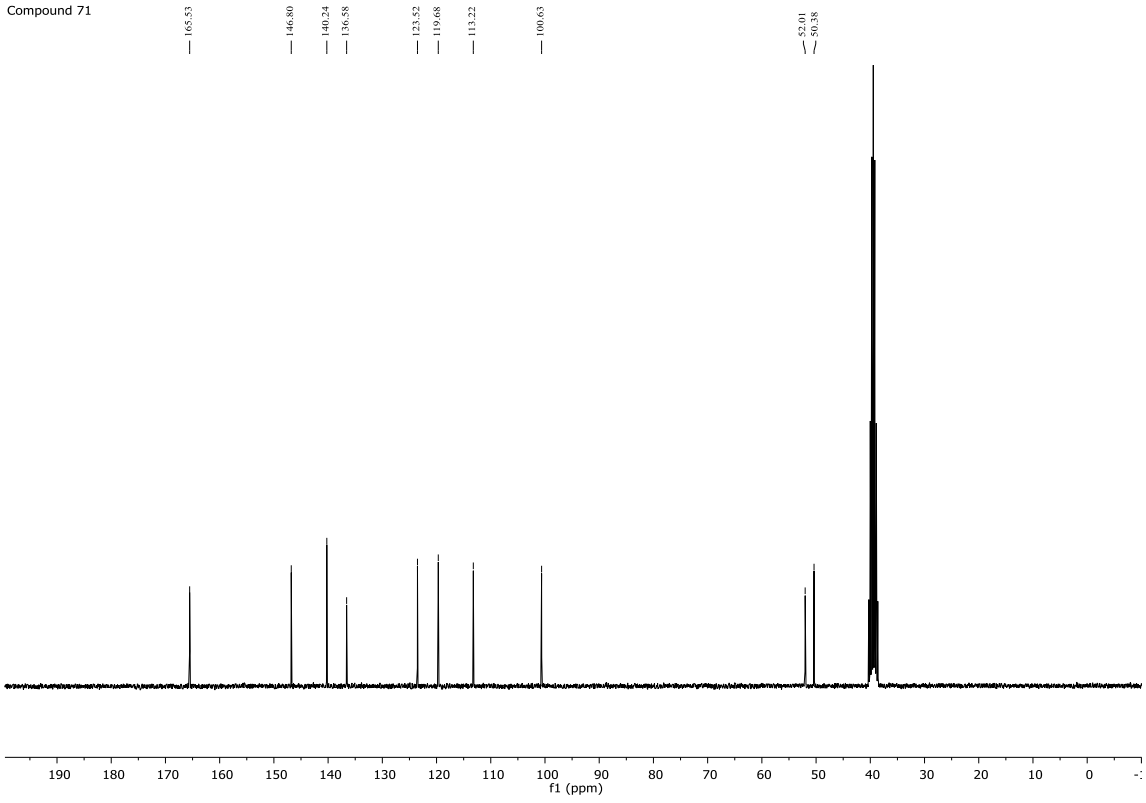
NMR Spectra

Methyl 7-hydroxy-2-methoxybenzo[d][1,3]dioxole-5-carboxylate



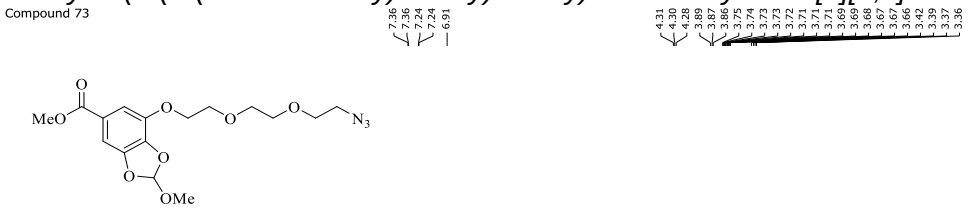
Compound 71

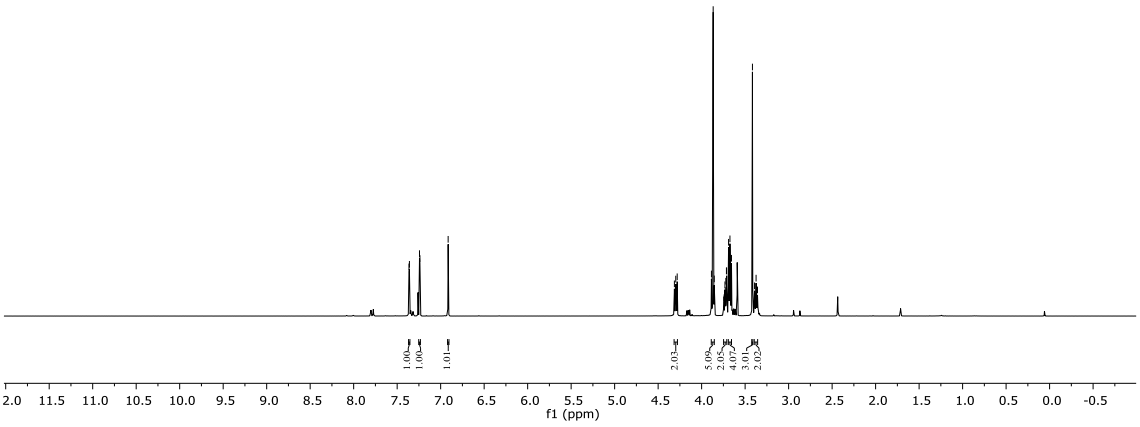
Compound 71



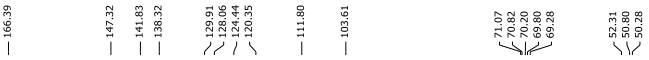
Methyl 7-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-2-methoxybenzo[d][1,3]dioxole-5-carboxylate (**3**)

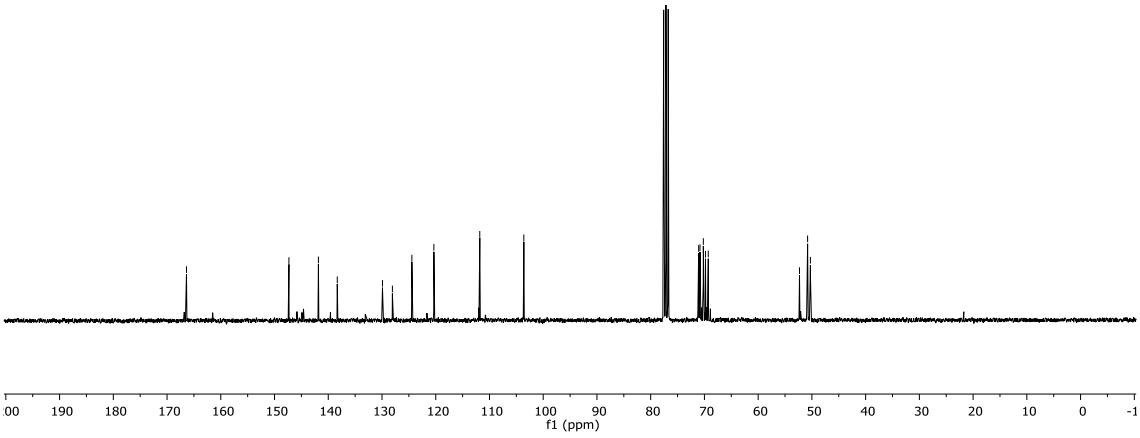
Compound 73





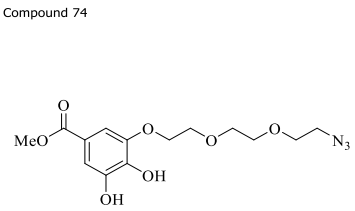
Compound 73

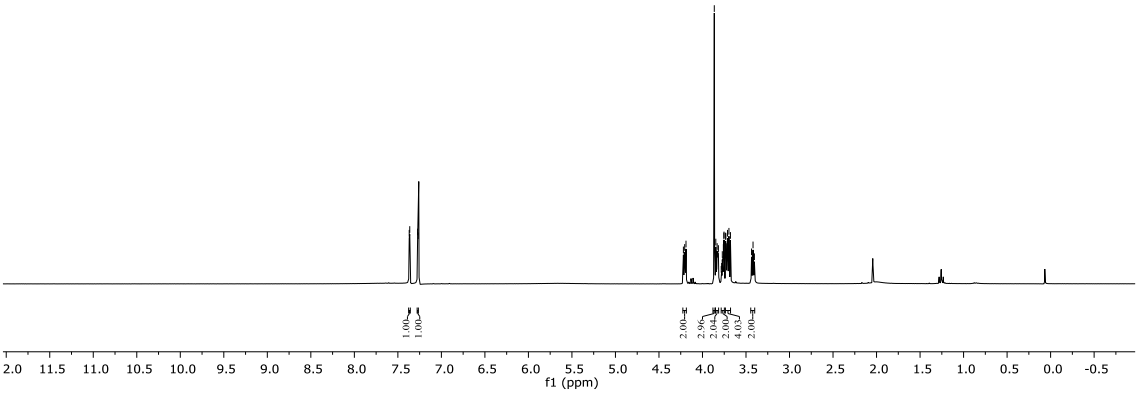




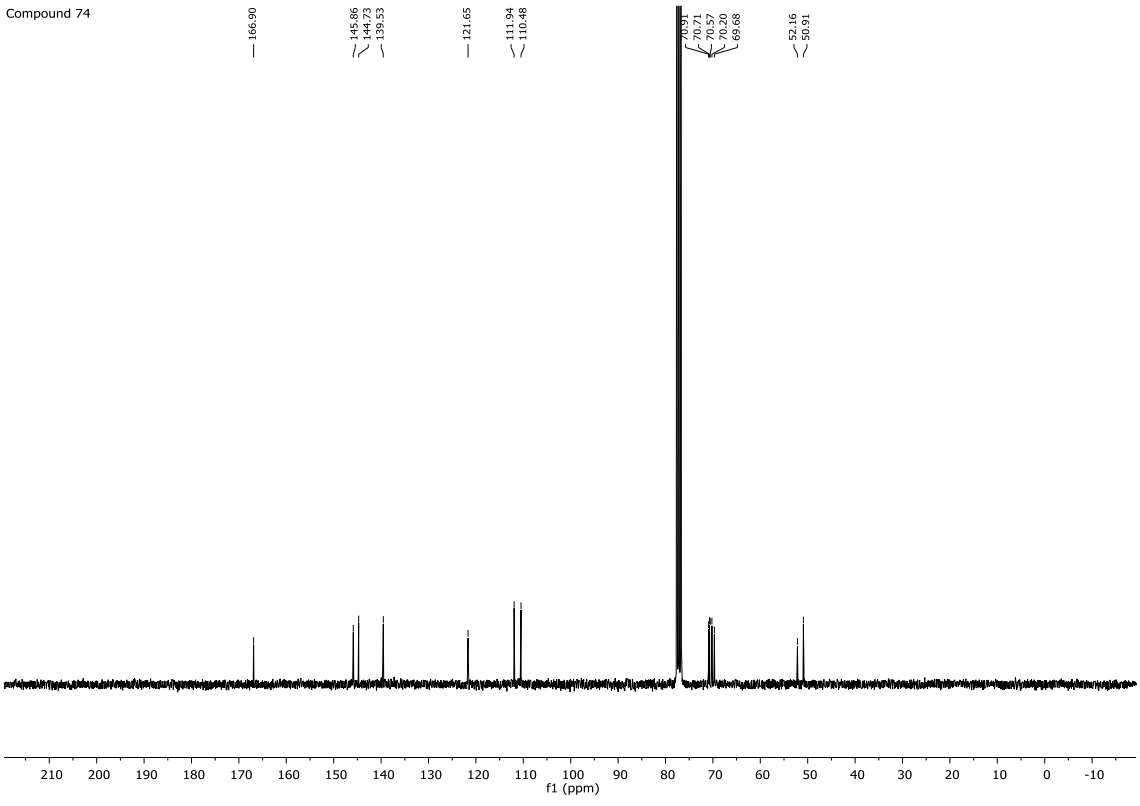
Methyl 3-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-4,5-dihydroxybenzoate

Compound 74

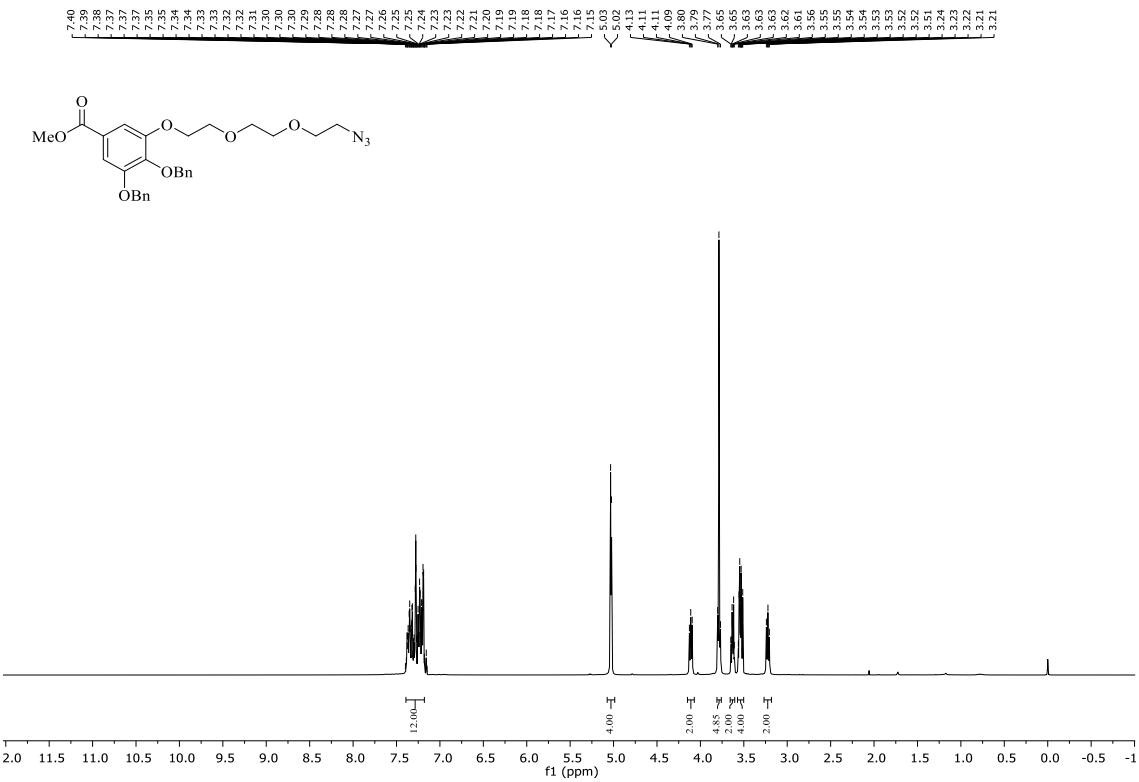




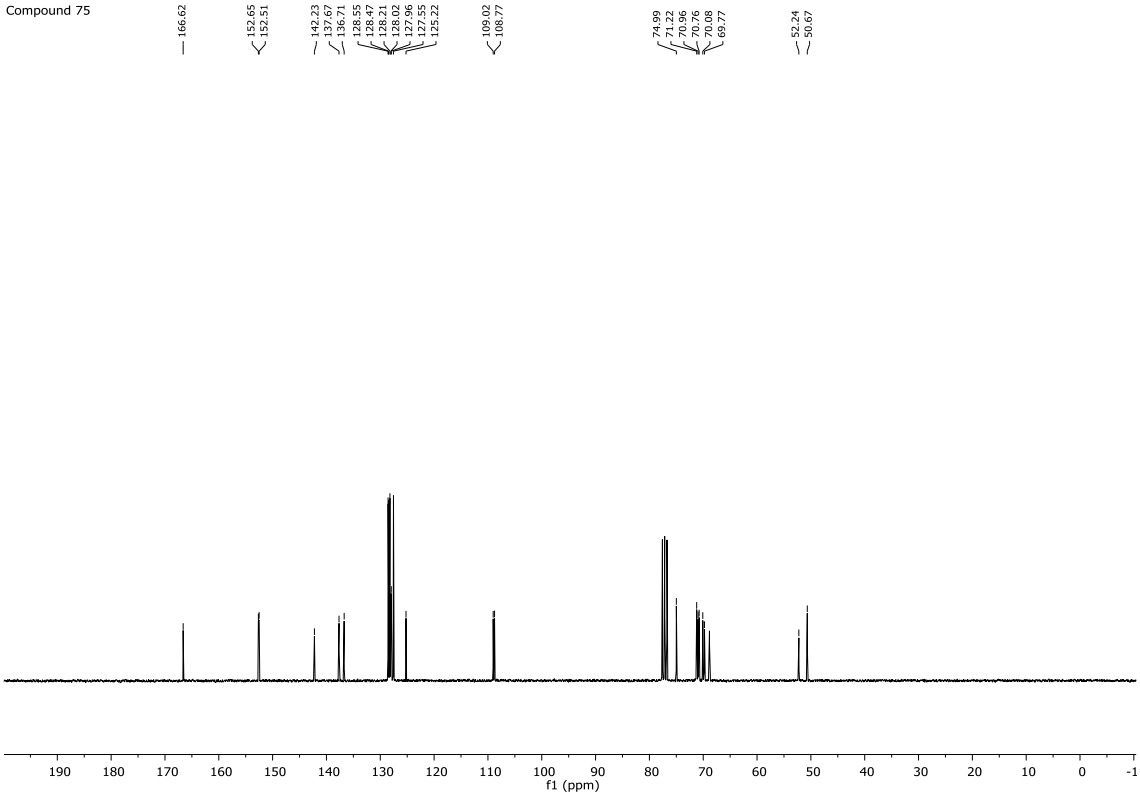
Compound 74



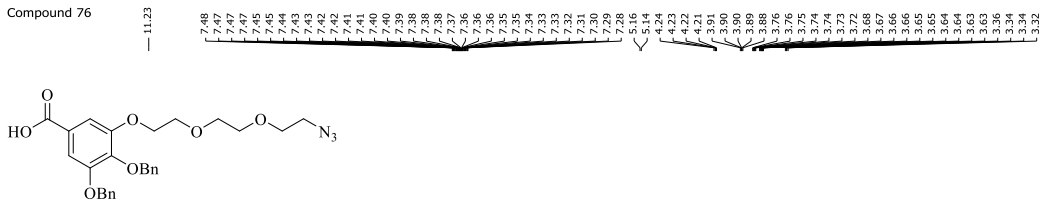
Methyl 3-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-4,5-bis(benzyloxy) benzoate

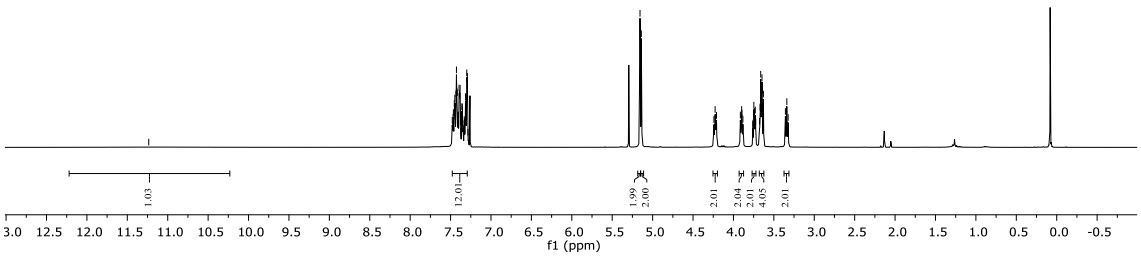


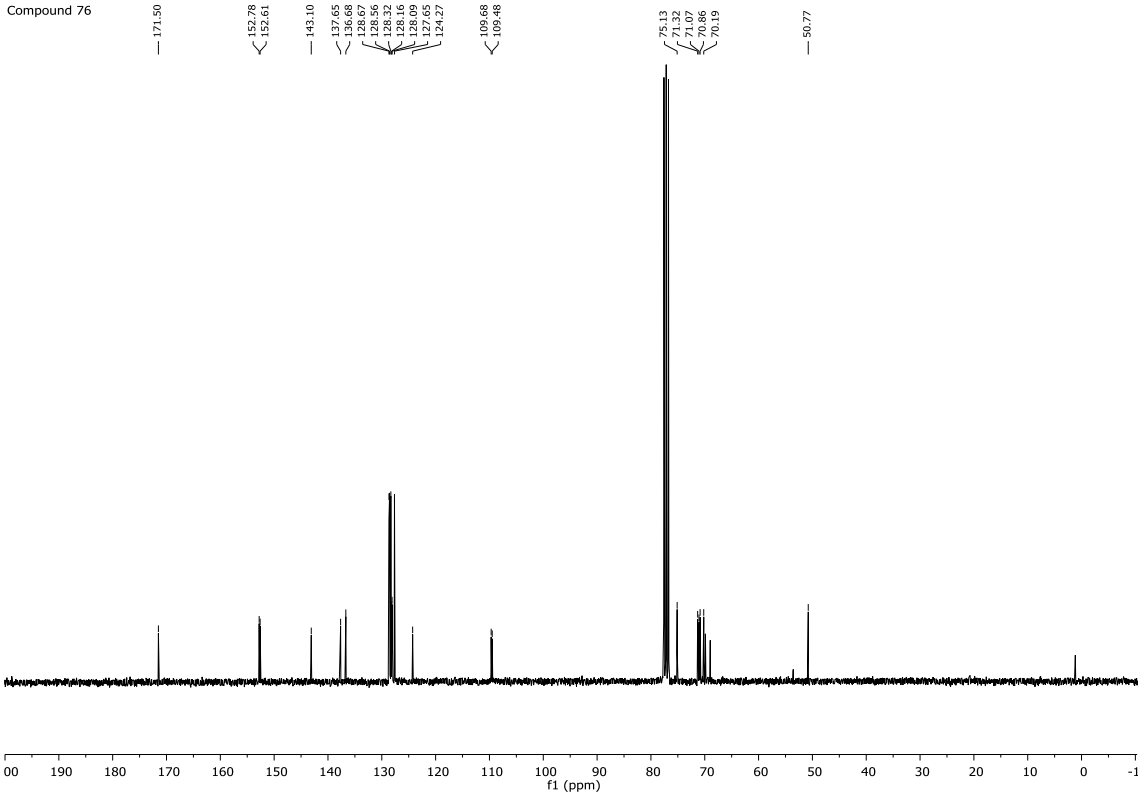
Compound 75



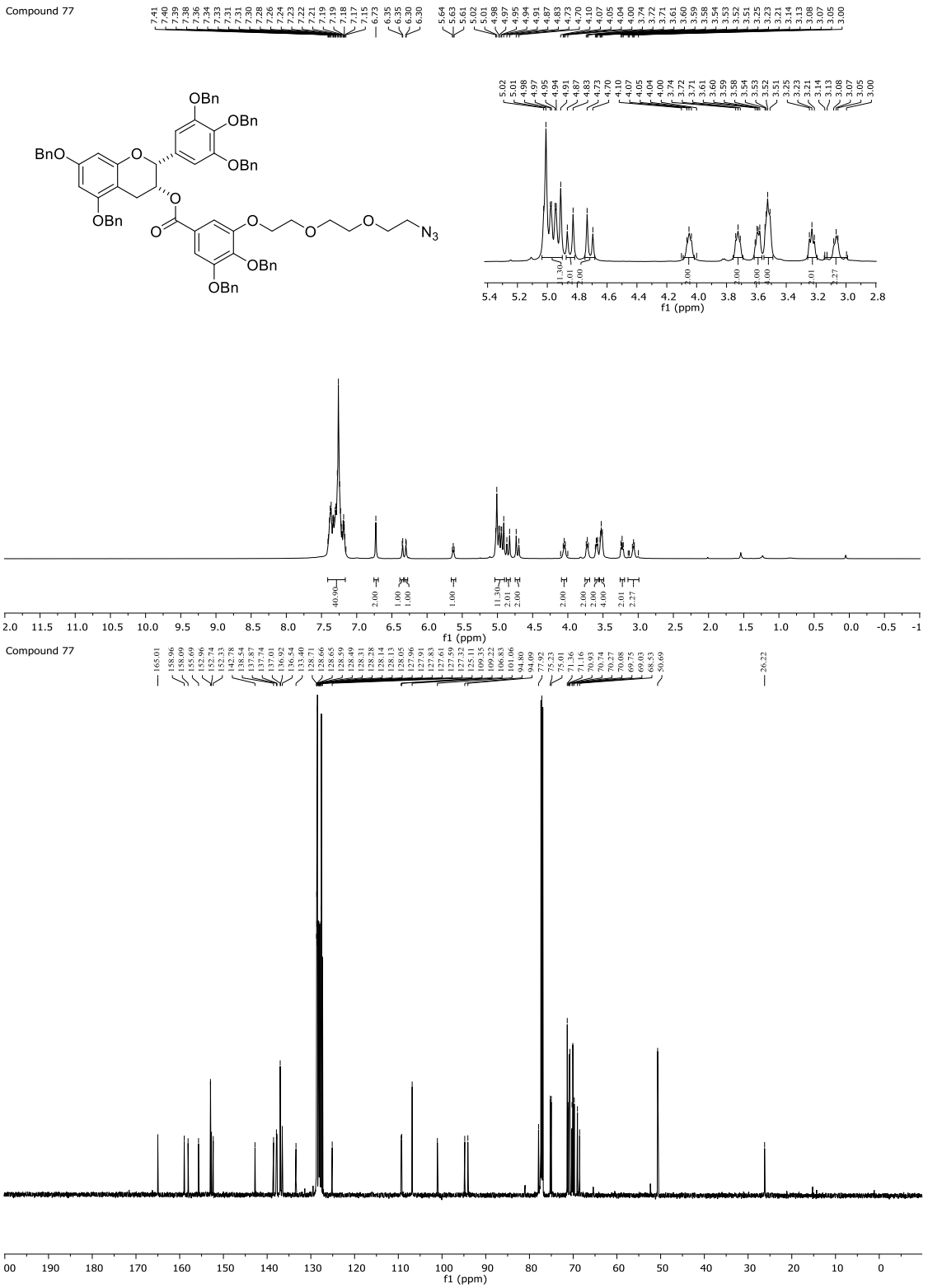
3-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)-4,5-bis(benzyloxy) benzoic acid (**4**)



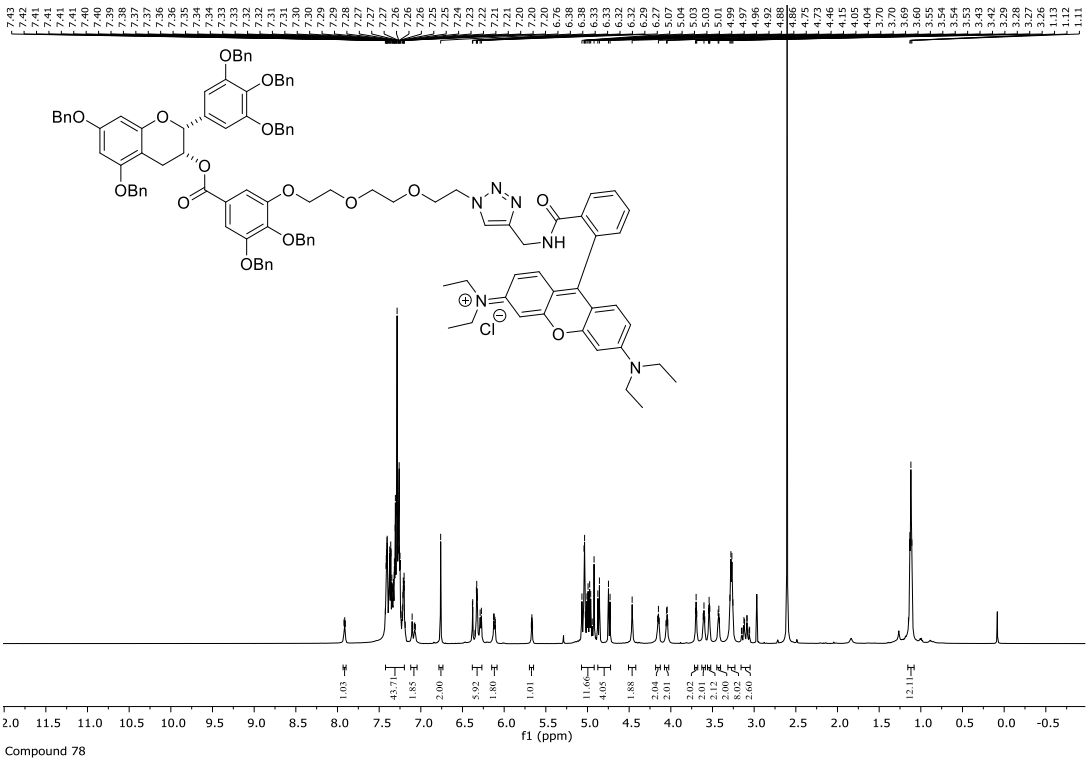




(2R,3R)-5,7-Bis(benzyloxy)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 3-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-4,5-bis(benzyloxy)benzoate (**6**)

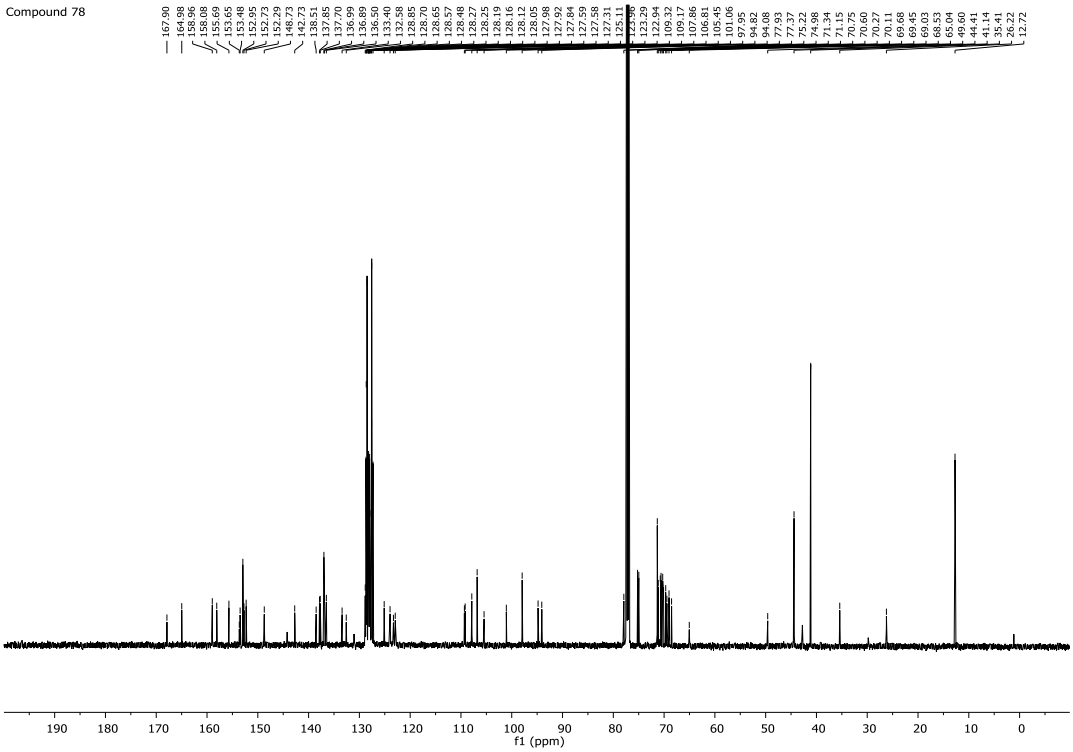


(2R,3R)-5,7-Bis(benzyloxy)-2-(3,4,5-tris(benzyloxy)phenyl)chroman-3-yl 3,4-bis(benzyloxy)-5-(2-(2-2-(4-((2-(3-(diethyl-λ4-azaneylidene)-6-(diethylamino)-3H xanthen-9-yl) benzamido) methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy) ethoxy benzoate

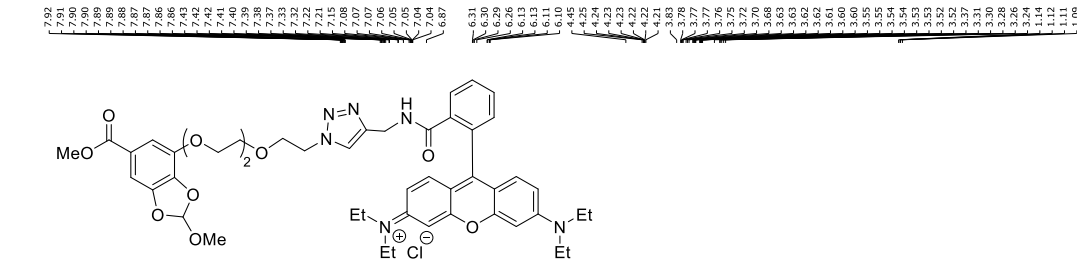


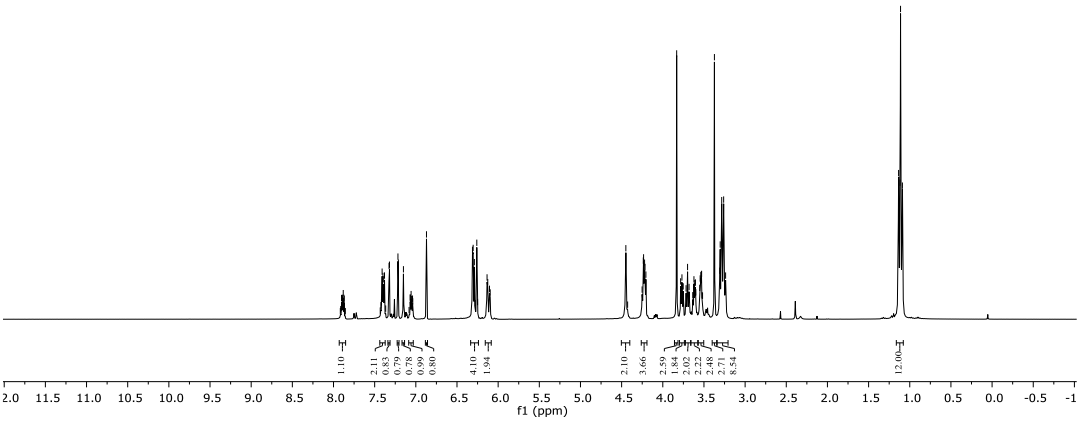
Compound 78

Compound 78

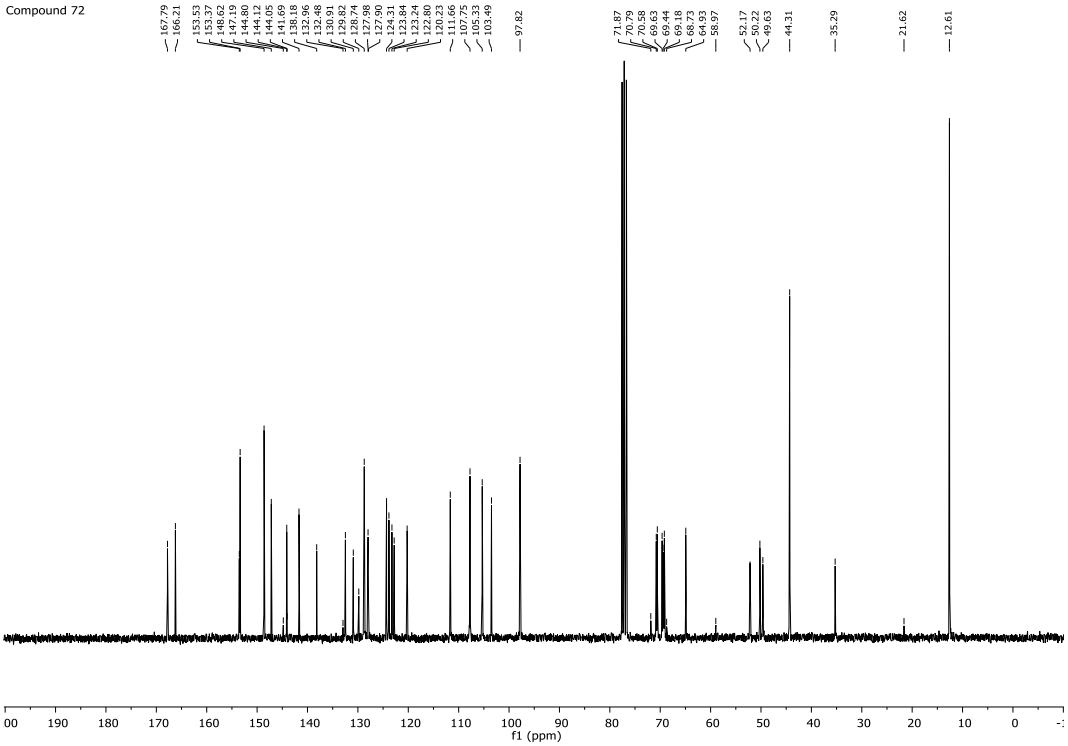


N-(6-(Diethylamino)-9-(2-(((1-(2-(2-(2-((2-methoxy-6-(methoxycarbonyl)benzo[d][1,3]dioxol-4-yl)oxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)carbamoyl)phenyl)-3H-xanthen-3-ylidene)-N-ethylethanaminium chloride

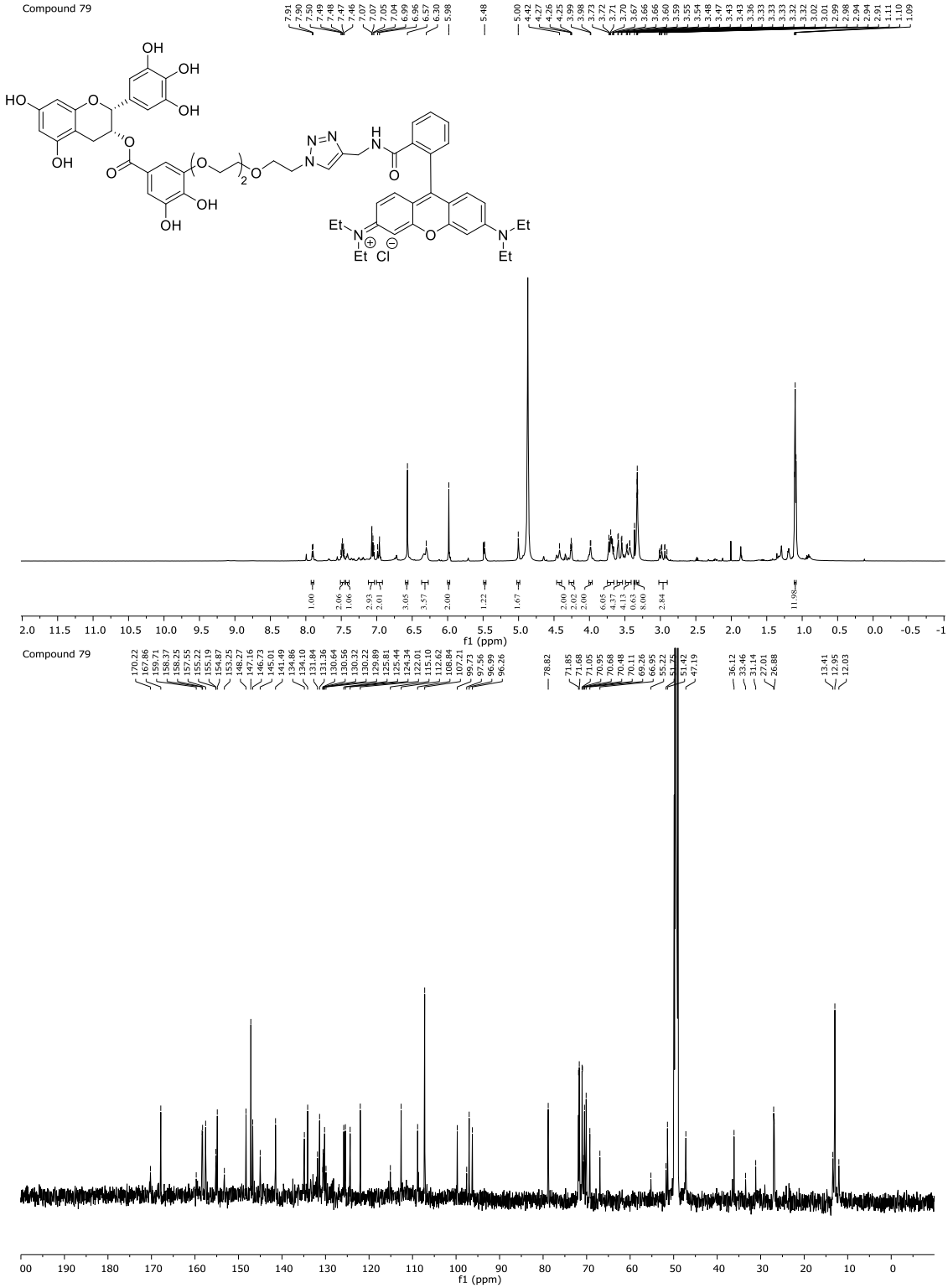




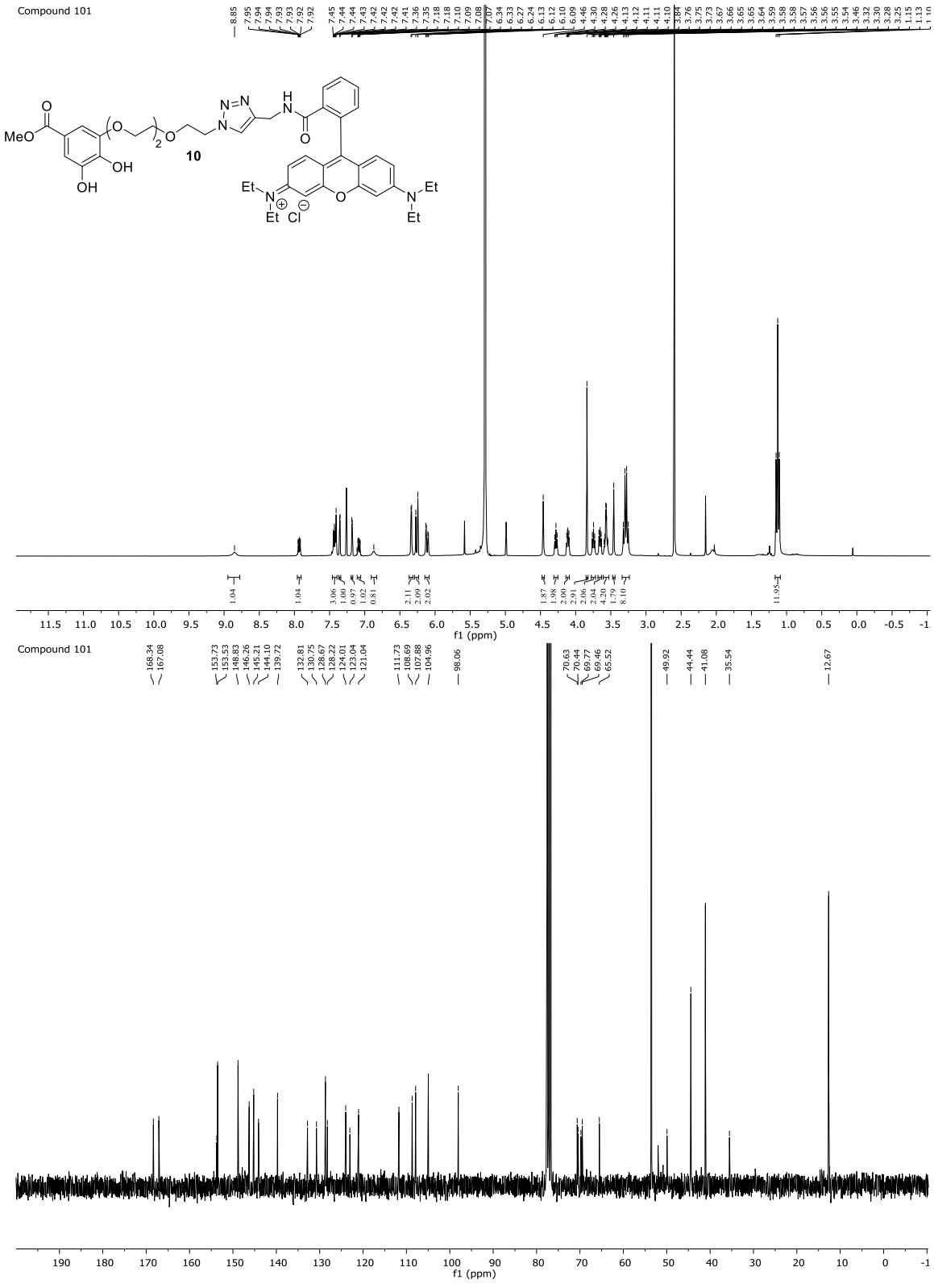
Compound 72



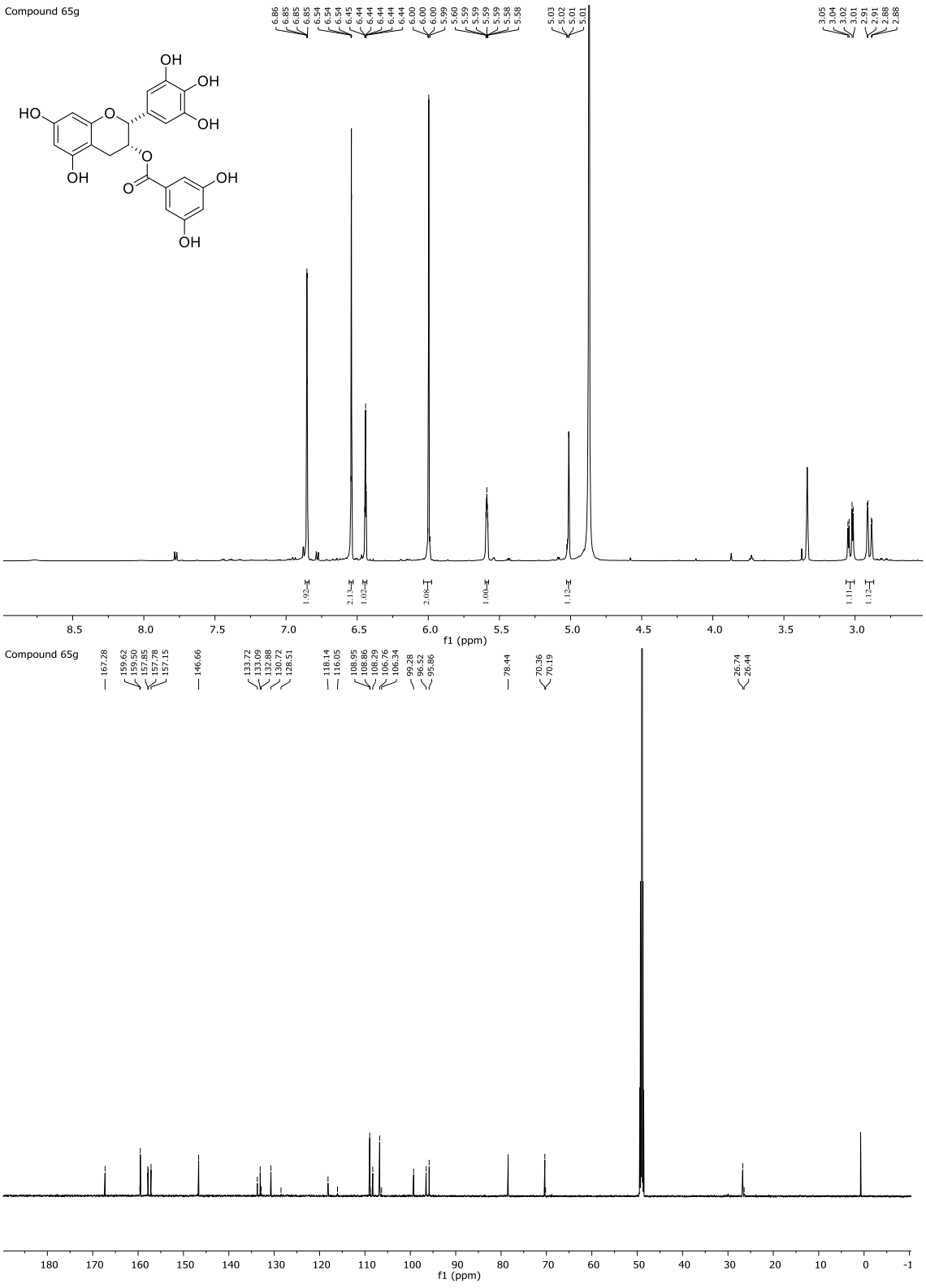
N-(6-(Diethylamino)-9-(2-(((1-(2-(2-(2-(5-((((2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-chroman-3-yl)oxy)carbonyl)-2,3-dihydroxyphenoxy) ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)-methyl)carbamoyl)phenyl)-3H-xanthen-3-ylidene)-N-ethylethanaminium chlorid (**8**)



N-(6-(Diethylamino)-9-(2-(((1-(2-(2-(2-((2-methoxy-6-(methoxycarbonyl)benzo[d][1,3]dioxol-4-yl)oxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methyl)carbamoyl)phenyl)-3H-xanthen-3-ylidene)-N-ethylethanaminium chloride (**9**)

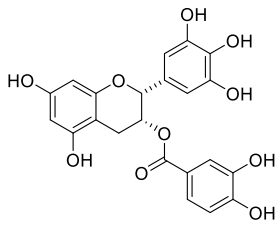


(2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-(3,5-dihydroxy)benzoate (**10**)

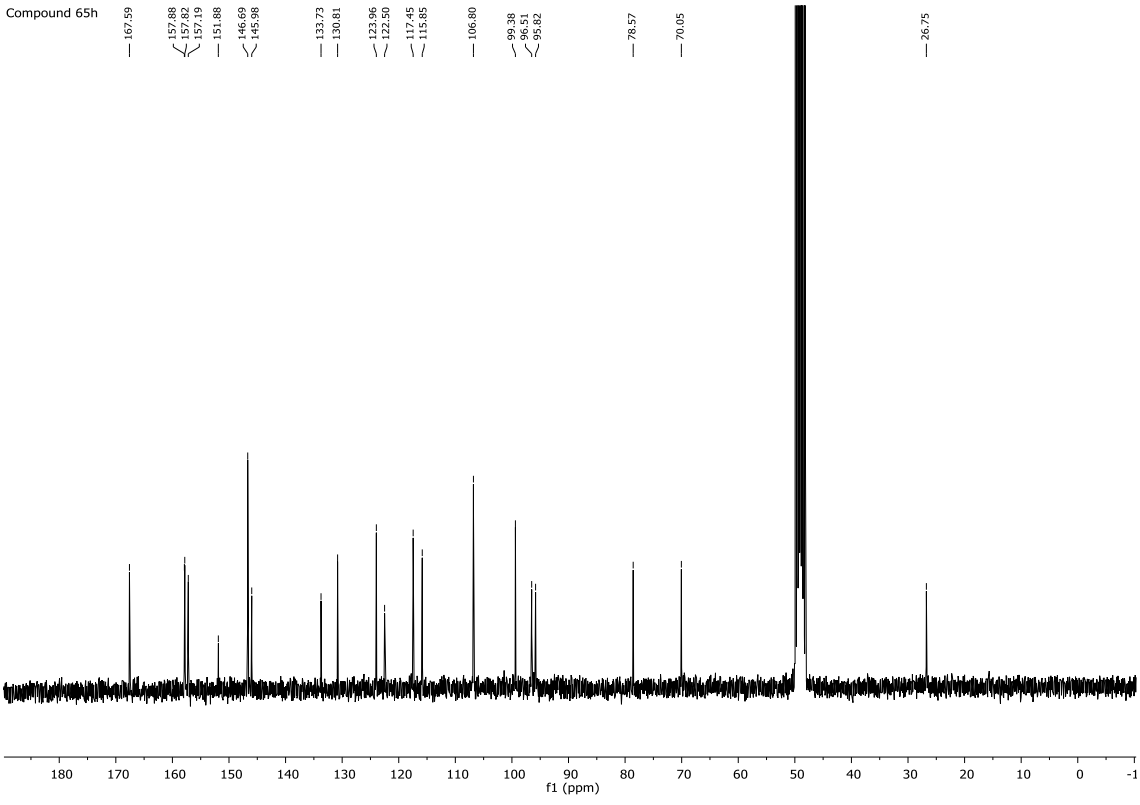


(2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-(3,4-dihydroxy)benzoate (**11**)

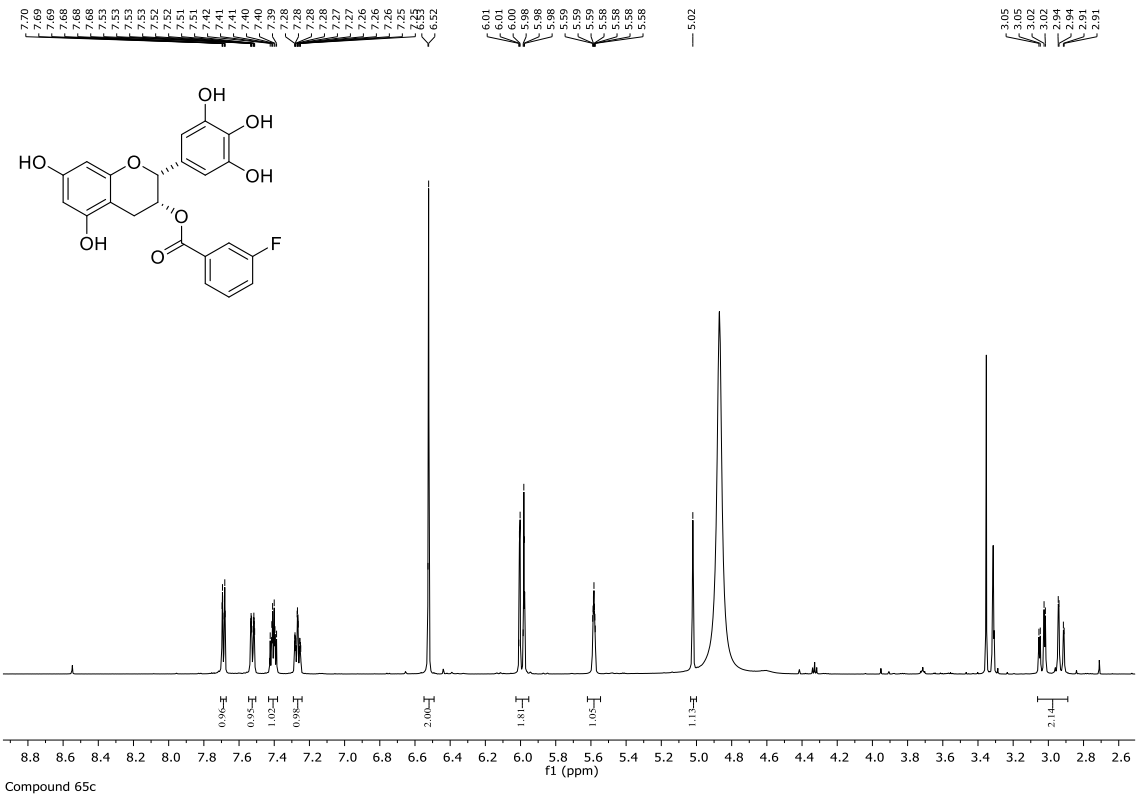
Compound 65h



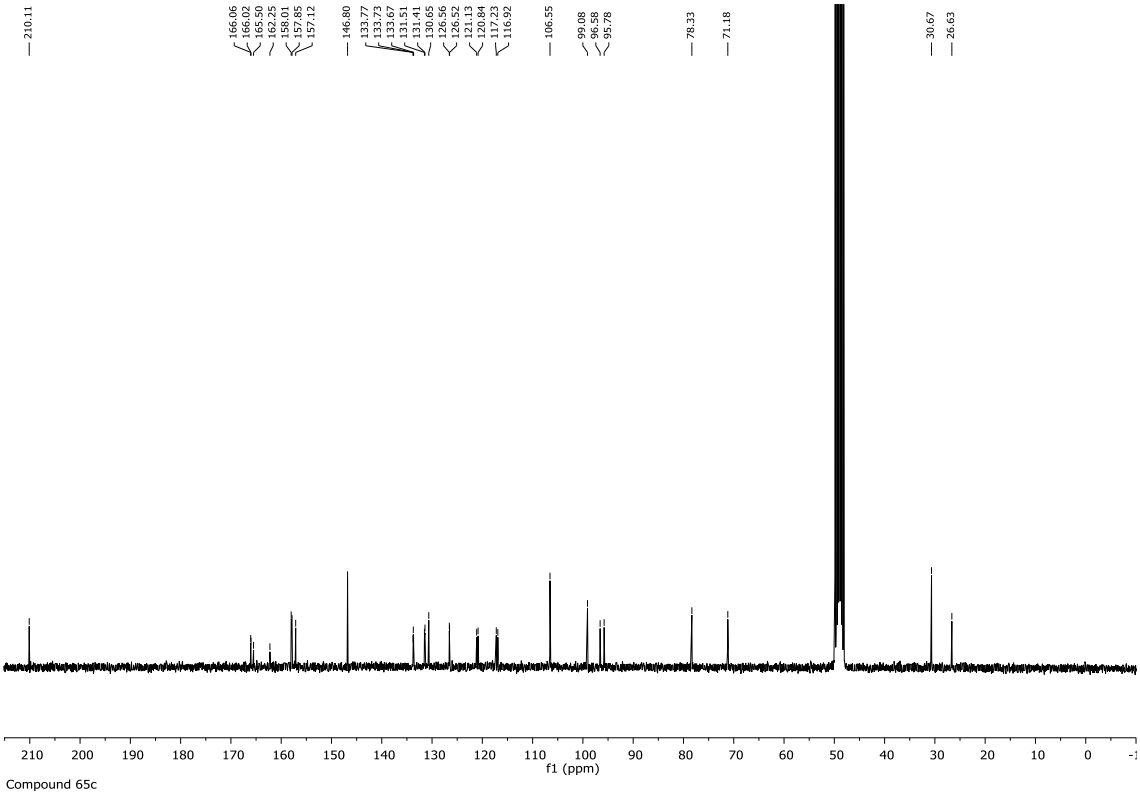
Compound 65h



(2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-(3-fluoro)benzoate (**12**)

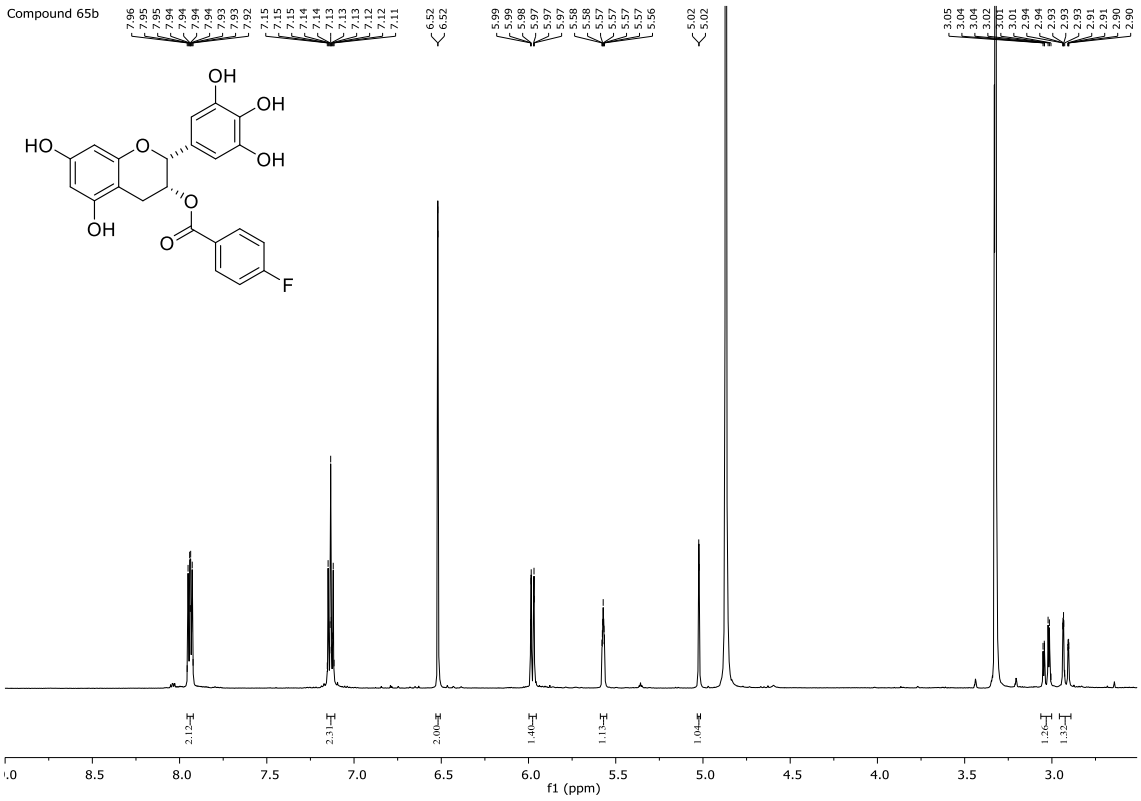


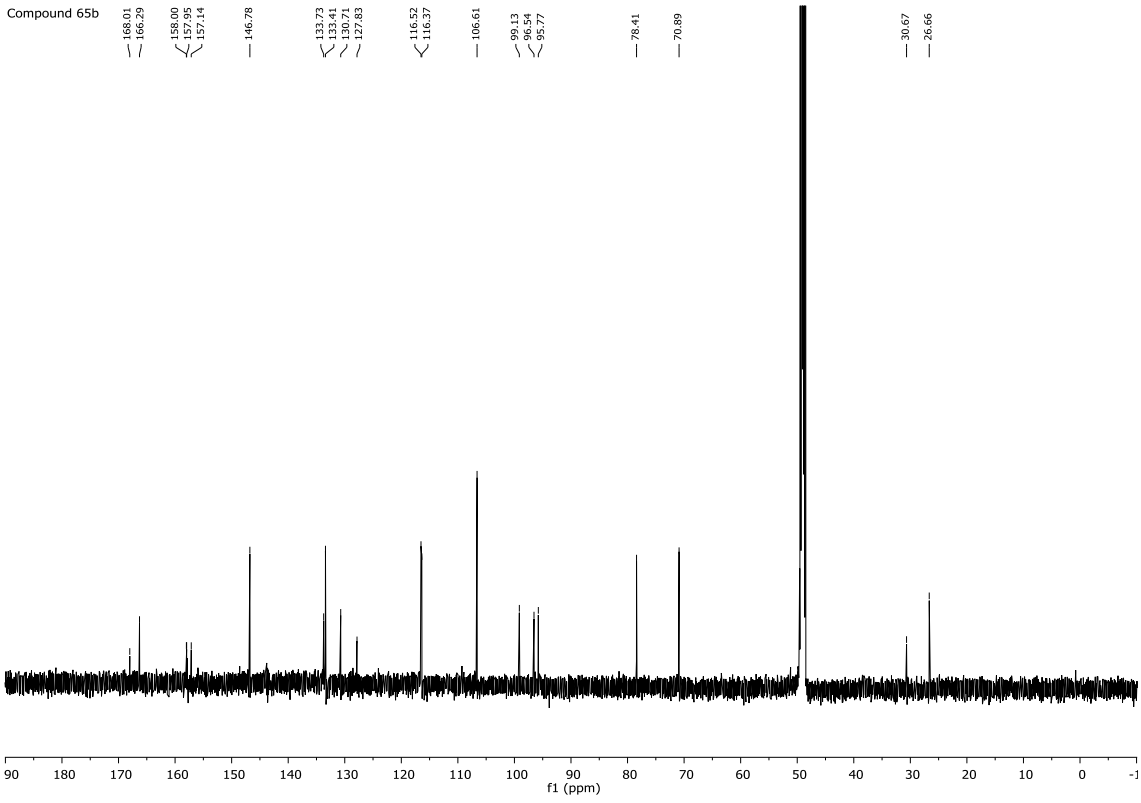
Compound 65c



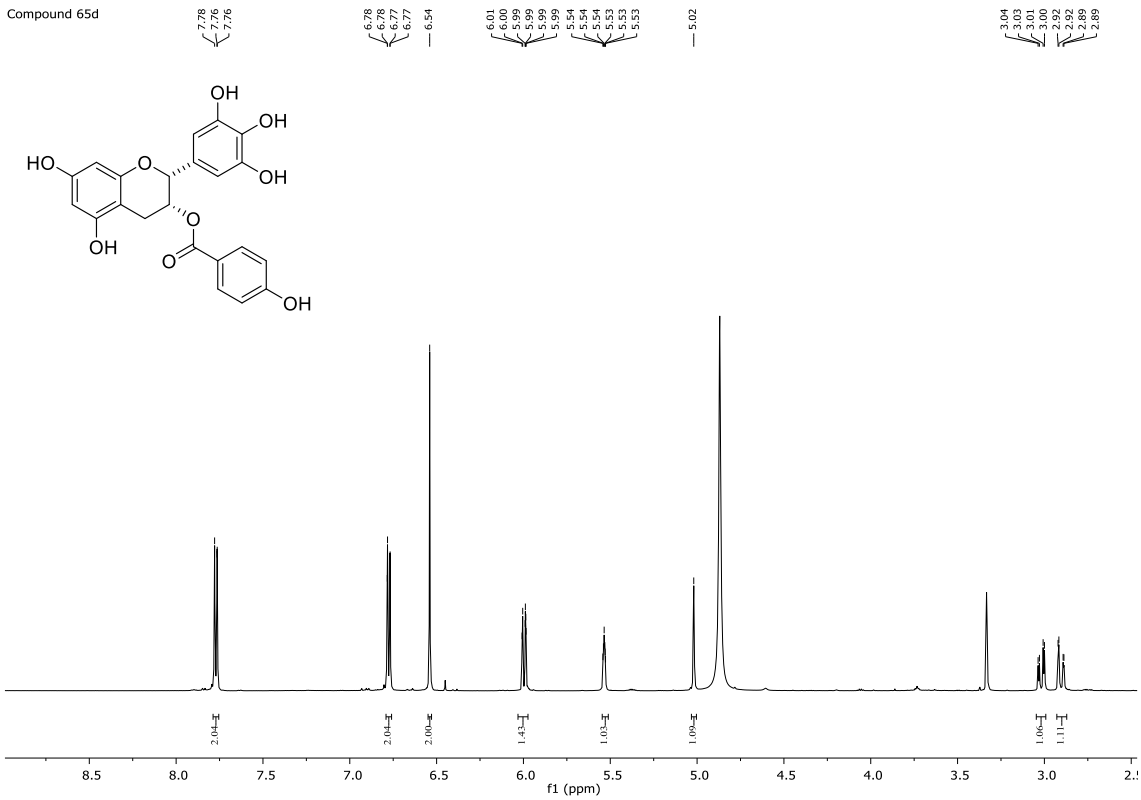
Compound 65c

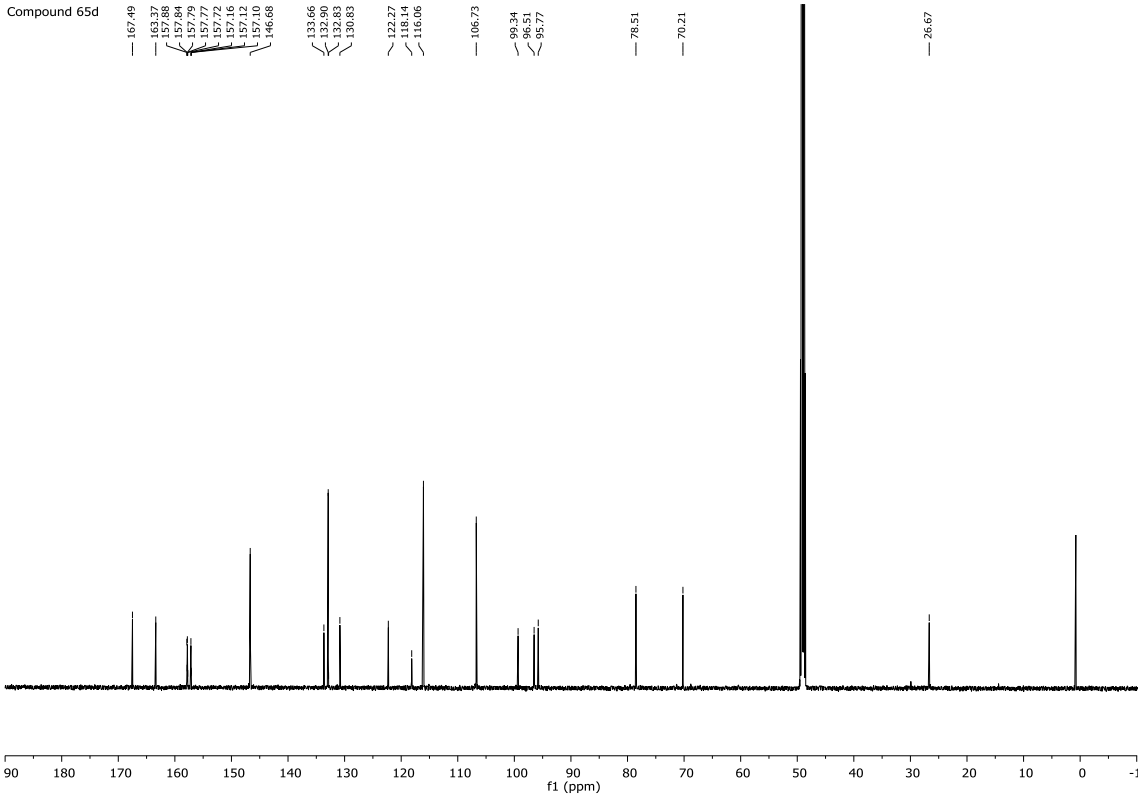
(2R,3R)-5,7-Dihydroxy-2-(3,4,5-tris(hydroxyl)phenyl)chroman-3-yl-(4-fluoro)benzoate (**13**)


Compound 65b
7.96 7.95 7.95 7.94 7.94 7.94 7.94 7.94 7.93 7.93 7.92
7.15 7.15 7.15 7.14 7.14 7.13 7.13 7.13 7.12 7.12 7.11
6.52 6.52
5.99 5.99 5.98 5.97 5.97 5.97 5.58 5.58 5.57 5.57 5.57 5.57 5.56
5.02 5.02
3.05 3.04 3.04 3.02 3.01 3.01 2.94 2.94 2.93 2.93 2.91 2.91 2.90 2.90
OH
OH
HO
O
OH
O
OH
O
F
2.12
2.31
2.00
1.40
1.13
1.04
1.26
1.32
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0
f1 (ppm)


Compound 65b
168.01
166.29
158.00
157.95
157.14
146.78
133.73
133.41
130.71
127.83
116.52
116.37
106.61
99.13
96.54
95.77
78.41
70.89
30.67
26.66
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

(2R,3R)-5,7-Dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl-(4-hydroxy)benzoate (**14**)





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