Supporting Information

A pH-triggered polymer degradation or drug delivery system by light-mediated cis / trans isomerization of *o*-hydroxy cinnamates

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1. Material and methods

Unless otherwise specified, all reagents, starting materials, and solvents (p.a. grade) were purchased from commercial suppliers (i.e. ABCR, Acros, Sigma-Aldrich, TCI, or Merck) and used as received without further purification. Synthesis of starting materials requiring oxygen- or moisture-sensitive reagents were carried out using flame-dried glassware, degassed solvents, and Schlenk lines. For the sake of clarity, ^{1}H NMR data for all known compounds as well as a full characterization of new compounds are included in this section. Thin-layer chromatography (TLC) analyses were performed using pre-coated TLC-sheets ALUGRAM® Xtra SIL G/UV$_{254}$. Visualization was accomplished with UV light (λ_{max} = 254 nm). Column chromatography and flash chromatography were performed using silica gel with particle size 63 – 200 µm and 40 – 63 µm, respectively, as the stationary phase. UV/Vis measurements were performed on a Perkin Elmer LAMBDA 35. The molecular weight was estimated by size exclusion chromatography (GPC) using a liquid chromatograph (Shimadzu, model LC-8A, Tokyo, Japan) equipped with an Empower computer program (Waters, Milford, MA, USA). A PL HFIP gel column (Polymer Lab) and a refractive index detector (Shimadzu RID-10A, Tokyo, Japan) were employed. Buffers were adjusted by the pH meter HANNA HI 991001. High-resolution mass spectra (HRMS) were obtained according to the IUPAC recommendations (2013) from the central analytic mass spectrometry facilities of the Faculty of Chemistry and Pharmacy at the University of Regensburg. NMR spectra were recorded with a Bruker Avance 400 (^{1}H NMR: 400 MHz, ^{13}C NMR: 101 MHz, ^{19}F NMR: 376 MHz) or a Bruker Avance 300 (^{1}H NMR: 300 MHz, ^{13}C NMR: 75 MHz, ^{19}F NMR: 282 MHz).

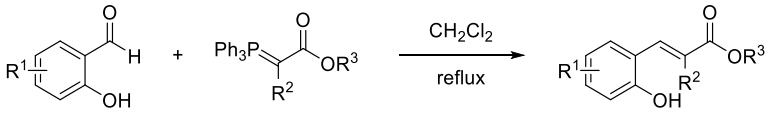
Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peak ($CHCl_3$, 7.26 ppm). Coupling constants (*J*) are given Hertz (Hz). The following notations are used to indicate the multiplicity of the signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Photochemical reactions were performed using a custom-made set-up with an array of suitable LEDs (OSLON SSL 80, GD CS8PM1.14; 1 W, 3.5 V, 700 mA), i.e. λ_{ex} = 455 ± 15 nm, connected to a power supply. The irradiation device was equipped with a stainless-steel jacket to maintain refrigeration of the vials. The distance between the LEDs and the reaction vials was adjusted to 0.9 ± 0.1 cm. The apparatus also allows the magnetic stirring of the reaction mixtures. The reported yields are referred to as the isolated compounds unless otherwise stated. Oxygen- and moisture-free reactions were carried out with dry and degassed solvents, as well as glassware subjected to several evacuations (vacuum)/refill (nitrogen) cycles.

Poly(ethylene glycol) based compounds like poly(ethylene glycol) bis(azide); M_n=200[1], poly(ethylene glycol) bis(azide); M_n=2000[2] and poly(ethylene glycol) methyl ether azide; M_n=2000[2] were synthesized according to the corresponding literature procedures.

2. Synthesis

2.1. Synthesis of cinnamates

General procedure A:

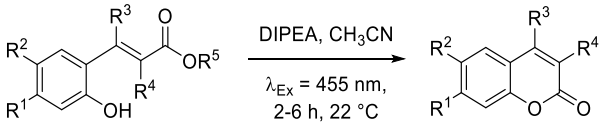


The cinnamate derivatives **1** were synthesized according to the literature[3] with minor differences: To a solution of the *ortho*-hydroxy benzaldehyde derivative (1 equiv) in dry CH_2Cl_2 (45 equiv) was added triphenyl-λ^5-phosphaneylidene derivative (1.3 equiv) and the mixture was refluxed and monitored by TLC. Afterward the solvent was evaporated under

reduced pressure and the residue was purified by chromatography using a mixture of hexanes and ethyl acetate as eluent giving the desired compounds **1**. Spectroscopical data matched the literature.[3]

2.2. Synthesis of coumarins

General procedure B:



In an 8 mL vial equipped with a magnetic stir bar 2-hydroxy cinnamates **1** (0.25 mmol) and 20 mol% DIPEA in acetonitrile (1 mL) were added. The vial was closed with a septum and subjected to three freeze-pump-thaw cycles for degassing and subsequently irradiated with a LED (λ_{Ex} = 455 nm) for 4 h. Evaporation of the solvent and purification on silica (hexanes/EtOAc) gave the desired compounds **2**.

*Coumarin **2a***

The NMR data was matching the literature[4]:

Synthesized according to general procedure A (33.6 mg, 0.230 mmol, 92 %).

R_f 0.18 (hexanes/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.6 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.23 – 7.10 (m, 2H), 6.27 (d, *J* = 9.6 Hz, 1H).

*7-Hydroxycoumarin **2b***

The NMR data was matching the literature[5]:

Synthesized according to general procedure A (37.7 mg, 0.232 mmol, 93 %).

R_f 0.15 (hexanes/EtOAc 7:3); ^{1}H NMR (300 MHz, DMSO) δ 10.59 (s, 1H), 7.93 (d, *J* = 9.5 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 6.78 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.72 (t, *J* = 4.5 Hz, 1H), 6.20 (d, *J* = 9.4 Hz, 1H).

*3-Methylcoumarin **2c***

The NMR data was matching the literature[6]:

Synthesized according to general procedure A (38.4 mg, 0.240 mmol, 96 %).

R_f 0.30 (hexanes/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.49 – 7.39 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.28 – 7.21 (m, 1H), 2.21 (d, *J* = 1.3 Hz, 3H).

*3-Methyl-7-hydroxycoumarin **2d***

The NMR data was matching the literature[7]:

Synthesized according to general procedure A (43.6 mg, 0.248 mmol, 99 %).

R_f 0.23 (hexanes/EtOAc 7:3); ^{1}H NMR (300 MHz, DMSO) δ 10.39 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 6.76 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.69 (d, *J* = 2.3 Hz, 1H), 2.03 (s, 3H).

*4-Methylcoumarin **2e***

The NMR data was matching the literature[4]:

Synthesized according to general procedure A (32.0 mg, 0.200 mmol, 80 %).

R_f 0.18 (hexanes/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.34 – 7.24 (m, 2H), 6.28 (s, 1H), 2.43 (s, 3H).

*3-Allylcoumarin **2f***

The NMR data were matching the literature[8]:

Synthesized according to general procedure A (45.6 mg, 0.245 mmol, 98 %).

R_f 0.30 (hexanes/EtOAc 9:1); ^{1}H NMR (300 MHz, DMSO) δ 7.82 (q, *J* = 1.0 Hz, 1H), 7.67 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.56 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.33 (td, *J* = 7.5, 1.2 Hz, 1H), 5.97 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 1H), 5.25 – 5.10 (m, 2H), 3.23 (dq, *J* = 6.6, 1.4 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 161.04, 153.06, 139.84, 134.85, 131.48, 128.34, 127.49, 124.94, 119.65, 118.07, 116.38, 34.51.

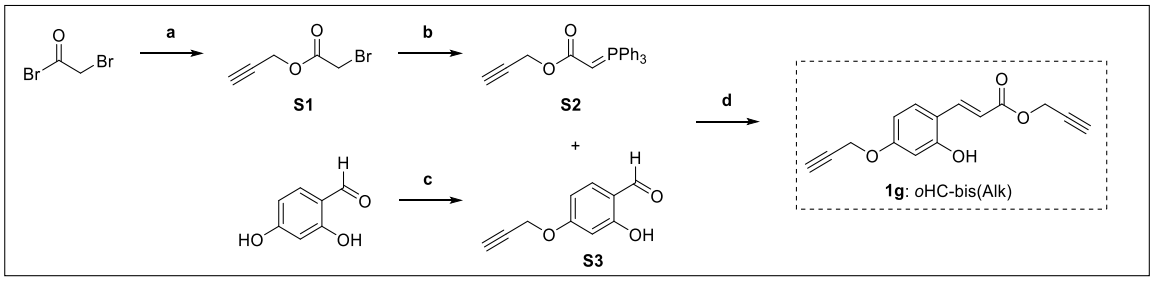
*7-(Propargyloxy)-coumarin **2g***

The NMR data was matching the literature[9]:

Synthesized according to general procedure A (49.0 mg, 0.245 mmol, 98 %).

R_f 0.25 (hexanes/EtOAc 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.5 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.29 (d, *J* = 9.5 Hz, 1H), 4.77 (d, *J* = 2.4 Hz, 2H), 2.58 (t, *J* = 2.4 Hz, 1H); GC-MS (EI) *m/z*: $[M]^{+\bullet}$ calcd for $C_{12}H_8O_3$, 200.05; found 200.0473.

2.3. Synthesis of *o*HC-bis(Alk) 1g



Scheme S1. Synthesis overview of the monomer **1g**; Reaction conditions a) propargyl alcohol pyridine, CH_2Cl_2, 0 to r.t., 1 h. b) 1) PPh_3, C_7H_8, r.t. 16 h 2) NaOH (2M), 30 min. c) K_2CO_3, propargyl bromide, acetone, reflux, 3 h. d) CH_2Cl_2, reflux, 2 h.

*Propargyl bromoacetate **S1***

The compound was synthesized according to the literature procedure[10] with minor differences:

Bromoacetyl bromide (2.61 mL, 30.0 mmol, 1 equiv) was added dropwise to a solution of propargyl alcohol (1.73 mL, 30 mmol, 1 equiv) and pyridine (2.4 mL, 30 mmol, 1 equiv) in CH_2Cl_2 (40 mL) at 0 °C to form a white suspension that was stirred for 20 min at 0 °C and then an additional 30 min at 25 °C. At this time, H_2O (50 mL) was added to the reaction mixture and the organic layer was separated. The aqueous layer was then extracted with CH_2Cl_2 (2 mL x 20). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. The filtrate was then concentrated to give **S1** as a colorless liquid which was used directly without purification for the next step.

Propargyl-(triphenyl-λ^5-phosphaneylidene)acetate ***S2***

The compound was synthesized according to the literature procedure[10] with minor differences:

Propargyl bromoacetate was added dropwise to a toluene solution (100 mL) of triphenylphosphine (7.8 g, 30 mmol, 1 equiv) to form a white precipitate. The resulting slurry was stirred overnight, filtered over a glass fritted filter, and washed with toluene and hexanes to give phosphonium salt as a white solid. The white solid was dissolved in H_2O (100 mL) and NaOH (2 M) was added to keep the aqueous pH > 7. A white solid appeared, and the mixture was stirred for 30 min before CH_2Cl_2 (50 mL) was added. The organic layer was separated and washed with brine (50 mL) and dried over Na_2SO_4. The filtrate was concentrated to give phosphorane **S2** as a white solid which was used directly without further purification for the next step.

2-Hydroxy-4-prop-2-ynyloxy-benzaldehyde ***S3***

The compound was synthesized according to the literature procedure[11] with minor differences:

A flask was charged with dry acetone (50 ml), 2,4-dihydroxybenzaldehyde (5 g, 36 mmol, 1 equiv) and potassium carbonate (5 g, 36 mmol, 1 equiv). The mixture was heated to 50 °C, to this reaction mixture, propargyl bromide solution (3.4 ml, 36 mmol, 1 equiv; 80 wt. % solution in toluene) was slowly added via syringe. Then, the reaction mixture was stirred for 3 h under reflux. After cooling to room temperature, the mixture was concentrated under vacuum and DCM (180 ml) was added. The organic layer was washed four times with water, dried over Na_2SO_4, filtered and concentrated. Purification by silica gel chromatography (hexanes/$CHCl_3$ 1:1) afforded the desired product **S3** as a white solid (1.90 g, 10.8 mmol, 30 %).

The NMR data was matching the literature[11]:

R_f 0.53 (hexanes/$CHCl_3$ 1:1); ^{1}H NMR (300 MHz, DMSO) δ 11.03 (s, 1H), 10.04 (s, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 6.60 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 4.88 (d, *J* = 2.4 Hz, 2H), 3.67 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 191.45, 164.17, 163.26, 132.45, 117.15, 108.30, 102.28, 79.40, 78.95, 56.30; Mp.: 81 °C.

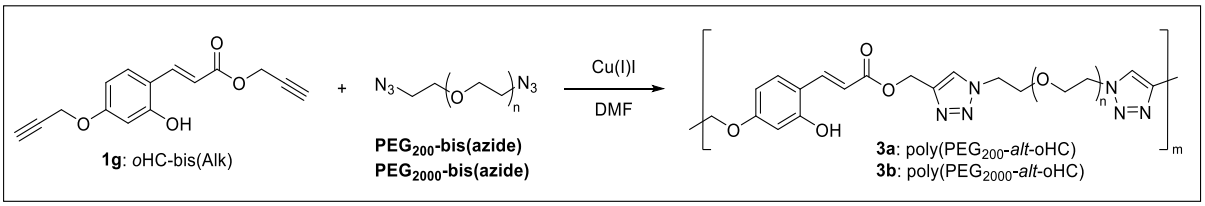
Propargyl-3-(2-hydroxy-4-(propargyloxy)phenyl)acrylate ***1g***

The compound was synthesized according to the literature procedure[3] with minor differences:

To a solution of 2-hydroxy-4-prop-2-ynyloxy-benzaldehyde (500 mg, 2.84 mmol, 1 equiv) in dry CH_2Cl_2 (8 mL) was added propargyl-(triphenyl-λ^5-phosphaneylidene)acetate (1.35 g, 3.7 mmol, 1.3 equiv) and the mixture was refluxed for 2 h. After the reaction completed (monitored by TLC), the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexanes/10 - 30 % EtOAc) eluting the desired compound **1g** as white crystals (630 mg, 2.3 mmol, 86 %).

R_f 0.19 (hexanes/EtOAc 4:1); ^{1}H NMR (300 MHz, DMSO) δ 10.49 (s, 1H), 7.84 (d, *J* = 16.1 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 6.57 – 6.46 (t, 2H), 6.50 (d, J = 13.2 Hz, 1H), 4.79 (d, *J* = 2.4 Hz, 4H), 3.63 (t, *J* = 2.4 Hz, 1H), 3.56 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 166.62, 160.79, 158.85, 141.34, 130.89, 114.91, 114.05, 107.21, 102.53, 79.39, 79.26, 79.07, 77.98, 55.93, 51.88; IR(neat): 3284, 3247, 2361, 1672, 1601, 1512, 1434 cm^{-1}; HRMS (ESI) *m/z*: $[M-H]^-$ calcd for $C_{15}H_{12}O_4$, 255.07; found 255.0676. Anal. calcd for $C_{15}H_{12}O_4$: C 70.31, H 4.72, O 24.97; found: C 70.68, H 4.81, O 24.51; Mp.: 122 °C.

2.4. Synthesis of the polymer 3a/3b



Scheme S2. Synthesis overview of **3a**/**3b** via CuAAC "click" reaction; Reaction conditions: **1g**, PEG_n-bis(azide), Cu(I)I, DMF, 70 °C, 16 h.

Poly(PEG_{200}-alt-oHC) ***3a***

In a septum sealed vial propargyl-3-(2-hydroxy-4-(propargyloxy)phenyl)acrylate (75 mg, 0.3 mmol, 1 equiv), the corresponding PEG-bis(azide) (0.3 mmol, 1 equiv) and Cu(I)I (6 mg, 0.03 mmol, 0.1 equiv) was dissolved in DMF (1.5 mL) and subjected to ultrasonication for 1 min. The vial was sealed, N_2 was bubbled through the solution for 15 min and the polymerization was carried out in an aluminum heating block for 16 h at 70 °C. Afterward, the solvent was removed in vacuo and the resulting polymer **3a** (145 mg) was used without further purification.

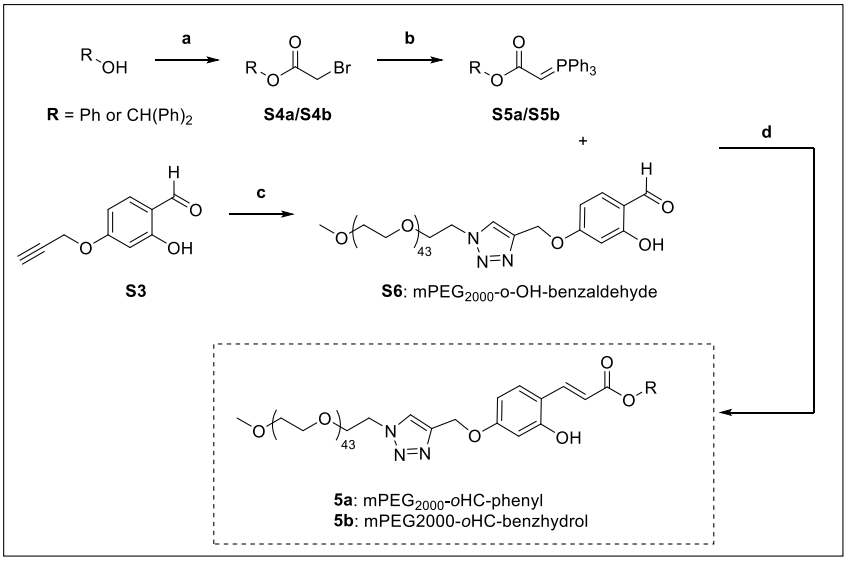
^{1}H NMR (300 MHz, DMSO) δ 10.42 (s, 1H), 8.16 (d, *J* = 12.0 Hz, 2H), 7.81 (d, *J* = 16.0 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 6.57 – 6.41 (m, 3H), 5.22 (s, 2H), 5.12 (s, 2H), 4.51 (t, *J* = 5.2 Hz, 4H), 3.78 (t, *J* = 5.2 Hz, 4H), 3.53 – 3.32 (m, 8H).

Poly(PEG_{2000}-alt-oHC) ***3b***

In a septum sealed vial propargyl-3-(2-hydroxy-4-(propargyloxy)phenyl)acrylate (75 mg, 0.3 mmol, 1 equiv), the corresponding PEG-bis(azide) (0.3 mmol, 1 equiv) and Cu(I)I (6 mg, 0.03 mmol, 0.1 equiv) was dissolved in DMF (1.5 mL) and subjected to ultrasonication for 1 min. The vial was sealed, N_2 was bubbled through the solution for 15 min and the polymerization was carried out in an aluminum heating block for 16 h at 70 °C. Afterward, the polymer mixture was precipitated in 100 mL Et_2O, decanted, dissolved in the least amount of DCM (~1-2 mL) and precipitated in 100 mL Et_2O. This purification method was repeated five times to remove the DMF, then the material was dried in vacuo for 48 h yielding the resulting polymer **3b** (523 mg).

^{1}H NMR (300 MHz, DMSO) δ 10.42 (s, 1H), 8.17 (d, *J* = 11.5 Hz, 2H), 7.81 (d, *J* = 16.1 Hz, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 6.55 (d, *J* = 6.9 Hz, 2H), 6.48 (d, *J* = 16.1 Hz, 1H), 5.22 (s, 2H), 5.12 (s, 2H), 4.54 (t, *J* = 5.0 Hz, 4H), 3.82 (t, *J* = 5.3 Hz, 4H), 3.50 (s, 192H). IR(neat): 2878, 1709, 1609, 1467, 1344, 1281, 1244, 1147, 1100, 1061 cm^{-1}.

2.5. Synthesis of mPEG$_{2000}$-*o*HC-drug 5a/5b



Scheme S3. Synthesis overview of **5a**/**5b**; Reaction conditions a) DCC, DMAP, CH_2Cl_2, r.t., 16 h. b) PPh_3, $NaOH/H_2O$, toluene, r.t., 16 h. c) mPEG$_{2000}$-N_3, Cu(I)I, DMF, 65 °C, 18 h. d) CH_2Cl_2, reflux, 2 h.

*2-(Triphenyl phosphaneylidene)acetates **S5a/S5b***

The compounds were synthesized according to the literature procedure[12] with minor differences:

2-Bromoacetic acid (6 mmol, 1.2 equiv) and the corresponding alcohol (5 mmol, 1.0 equiv) were dissolved in CH_2Cl_2 (40 mL) in a 100 mL round-bottom flask with a stir bar, then DCC (6 mmol, 1.2 equiv) was added to the mixture, followed by adding a catalytic amount of DMAP (0.5 mmol, 0.1 equiv), the mixture was stirred overnight at room temperature. Afterward the mixture was filtered, extracted with brine (3 x 30 mL), dried with Na_2SO_4, and subjected to silica gel column chromatography (hexanes/EtOAc 19:1) to afford the desired bromoacetates **S4a/S4b**.

In a 100 mL round-bottom flask equipped with a magnetic stir bar, triphenylphosphine (4.06 mmol, 1 equiv) was dissolved in toluene (30 mL) and bromoacetate (4.06 mmol, 1 equiv) was added to this solution slowly. The solution was stirred at room temperature and a white precipitate formed. The reaction was monitored by TLC (hexanes/EtOAc 20:1). After

complete consumption of starting material, the precipitate was filtered and washed with EtOAc and dried to afford the phosphonium salt.

The obtained phosphonium salt was dissolved in DCM (30 mL) and H_2O (15 mL) was added. To the stirred two-phase system, NaOH solution (4.06 mmol, 1 equiv) was added until the pH reached stable basic conditions. Afterward, the organic phase was separated, and the water phase was extracted with DCM (2 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered, and dried in vacuo to afford the desired ylide **S5a/S5b** as a white solid powder. The compound was used without further purification.

*$mPEG_{2000}$-o-OH-benzaldehyde **S6***

In a septum sealed vial $mPEG_{2000}$-N_3 (0.5 g, 0.24 mmol, 1 equiv), 2-hydroxy-4-prop-2-ynyloxy-benzaldehyde (51 mg, 0.29 mmol, 1.2 equiv) and Cu(I)I (5 mg, 0.024 mmol, 0.1 equiv) were dissolved in DMF (2 mL) and degassed by bubbling with a stream of N_2 through the solution. The reaction vessel was stirred in a preheated aluminum block at 65 °C for 18 h. After that the Cu(I)I salt was centrifuged and the solution was precipitated into cold Et_2O (5 x 100 mL) from the least amount of DCM (~1-2 mL) to remove all DMF residues. The product **S6** was dried under vacuo and used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.43 (s, 1H), 9.72 (s, 1H), 7.89 (s, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 6.63 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.54 (d, *J* = 2.3 Hz, 1H), 5.24 (s, 2H), 4.56 (t, *J* = 4.9 Hz, 1H), 3.79 – 3.54 (m, 248H), 3.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.50, 165.37, 164.29, 135.41, 115.47, 108.57, 101.76, 71.90, 70.54, 70.42, 69.31, 62.22, 59.02, 50.42; IR(neat): 2882, 1635, 1471, 1344, 1285, 1244, 1147, 1110, 1061 cm^{-1}; Anal. calcd for $C_{15}H_{12}O_4$: C 57.54, H 8.43, N 1.77, O 32.27; found: C 55.51, H 8.37, N 1.36, O 34.76; Mp.: 50 °C.

*mPEG$_{2000}$-oHC-drug **5a**/**5b***

In a 25 mL Schlenk flask mPEG$_{2000}$-*o*-OH-benzaldehyde (0.074 mmol, 1 equiv) and the corresponding phosphonium ylide (0.088 mmol, 1.2 equiv) were dissolved in dry DCM (6 mL) under a stream of N_2 and the solution was refluxed for 16 h. Afterward the solvent was reduced to the least amount (~1-2 mL) and precipitated into cold Et_2O (100 mL), centrifuged, decanted and re-dissolved in the least amount of DCM (~1-2 mL). This procedure was repeated for five times. The material was dissolved in H_2O (1 mL), centrifuged and the supernatant was lyophilized for 24 h. The pure mPEG$_{2000}$-*o*HC-drug was obtained as a slightly yellow solid material **5a** (120 mg, 0.052 mmol, 45 %); **5b** (108 mg, 0.045 mmol, 62 %).

5a: ^{1}H NMR (300 MHz, DMSO) δ 10.56 (s, 1H), 8.23 (d, *J* = 11.8 Hz, 1H), 7.97 (d, *J* = 16.1 Hz, 1H), 7.79 – 7.72 (m, 3H), 7.65 (d, *J* = 9.9 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 16.1 Hz, 1H), 6.64 – 6.56 (m, 1H), 5.21 (d, *J* = 34.0 Hz, 2H), 4.55 (t, *J* = 5.1 Hz, 2H), 3.83 (t, *J* = 4.7 Hz, 2H), 3.79 – 3.37 (m, 218H), 3.24 (s, 3H); IR(neat): 2882, 1720, 1605, 1471, 1344, 1281, 1240, 1195,1151, 1110, 1061 cm^{-1}; Anal. calcd for $C_{107}H_{193}N_3O_{48}$: C 56.13, H 8.5, N 1.84, O 33.54; found: C 55.89, H 8.37, N 1.49, O 34.25; Mp.: 48 °C.

5b: ^{1}H NMR (300 MHz, DMSO) δ 10.56 (s, 1H), 8.23 (d, *J* = 13.6 Hz, 1H), 7.97 (d, *J* = 16.5 Hz, 1H), 7.92 – 7.83 (m, 1H), 7.80 – 7.72 (m, 2H), 7.70 – 7.51 (m, 5H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 2H), 6.71 (d, *J* = 16.2 Hz, 1H), 6.57 (s, 1H), 5.21 (d, *J* = 34.6 Hz, 2H), 4.55 (t, *J* = 5.1 Hz, 2H), 3.82 (t, *J* = 5.2 Hz, 2H), 3.77 – 3.38 (m, 229H), 3.24 (s, 3H); IR(neat): 2882, 1709, 1609, 1471, 1344, 1281, 1244, 1151, 1110, 1061 cm^{-1}; Anal. calcd for $C_{114}H_{199}N_3O_{48}$: C 57.54, H 8.43, N 1.77, O 32.27; found: C 56.01, H 8.40, N 1.46, O 34.14; Mp.: 47 °C.

3.1. Characterization of 3a/3b by ^{1}H NMR

The final polymer **3a** was characterized by NMR analysis. The synthesis of the polymer was confirmed by the triazole peaks at 8.18 and 8.14 ppm (**b**) (see **Figure S1**, B) and the incorporation of the PEG_{200}-bis(azide) monomer at 3.30-3.51 ppm, 3.78 and 4.51 ppm (**j**, **i** and **h**, respectively) and the *o*HC-bis(alkyne) moiety at 6.50, 7.53, and 7.81 ppm (**e**, **f**, **d** and **c**) as well as the phenolic proton at 10.42 ppm (**a**). The CH_2-junctions at the triazole rings can be found grouped at 5.12 and 5.22 ppm ($\mathbf{g_1}$ and $\mathbf{g_2}$) (see **Figure S1**, B).

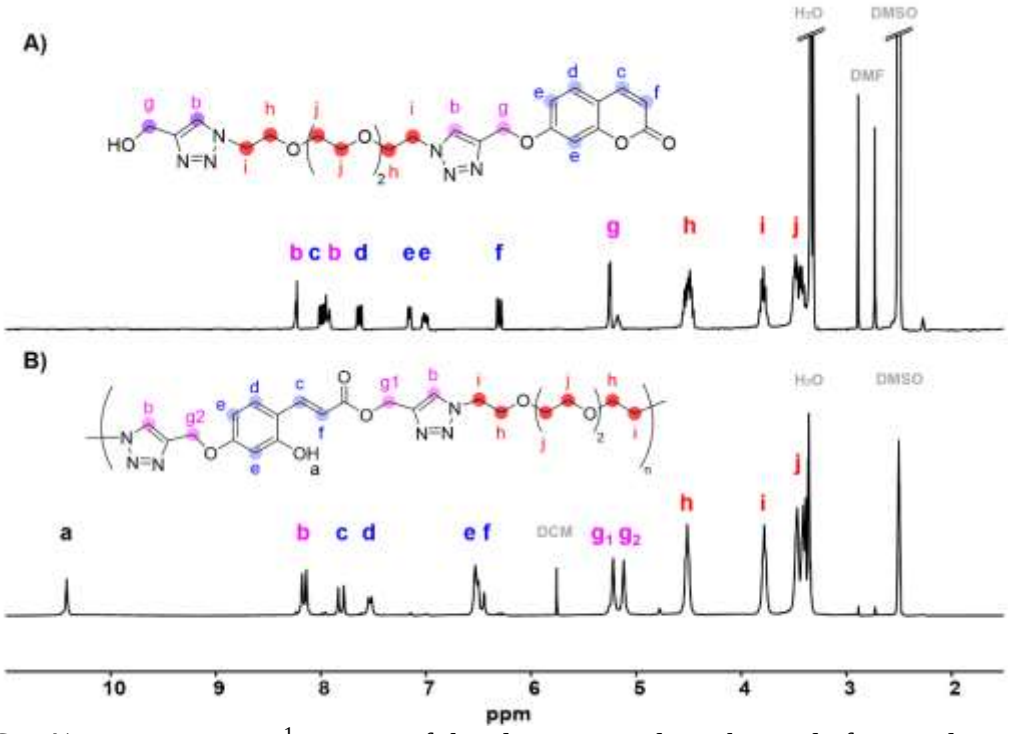


Figure S1. A) Representative ^{1}H NMR of the cleaving product obtained after irradiation of **3a** in DMF, measured in DMSO-*d6*. B) Representative ^{1}H NMR of the polymer material **3a** measured in DMSO-*d6*.

3.2. Photocleavage experiments

Figure S2. 1.5 mM solutions of **3b** in 0.1M Britton-Robinson buffer (left) pH=2.1, (mid) pH=7.4 and (right) pH=11.8.

*Photocleavage of **1g** monitored by ^{1}H NMR*

In a septum-sealed vial equipped with a magnetic stirrer, a 0.25 mM solution of **1g** in dry MeCN was degassed by bubbling with a stream of N_2 for 15 min. Afterward 20 mol% DIPEA was added by syringe through the septum and the vessel was irradiated (λ_{Ex} = 455 nm) for 2 h under stirring, while 20 µL samples were taken in a 10 min interval for 60 min and one last sample at 120 min. The collected samples were dried under vacuum for 48 h, dissolved in 0.6 mL of $CDCl_3$ and subjected to ^{1}H NMR spectroscopy. The doublet from the (CH_2)-allylene group at 4.81 ppm was monitored in comparison to the doublet-peak from the newly formed (CH_2)-allylene of the aryl ether at 4.77 ppm, which shifted downfield during this process from 4.67 ppm (see **Figure S3**).

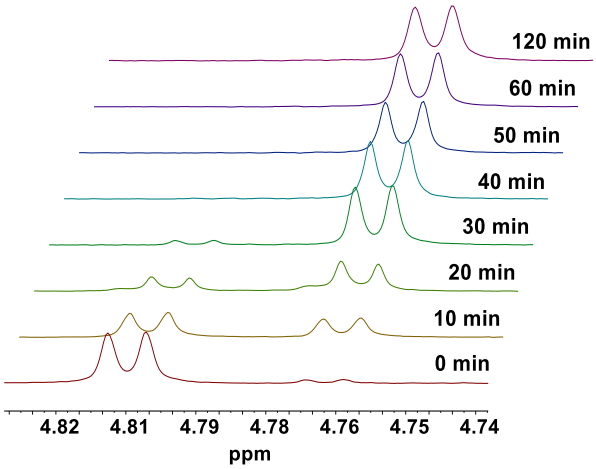


Figure S3. Time-dependent photocleavage of **1g** followed by ^{1}H NMR spectroscopy in $CDCl_3$.

*Photocleavage of **3a** to **4a** monitored by ^{1}H NMR*

In a septum-sealed vial equipped with a magnetic stirrer 50 mg of **3a** in dry DMF (1 mL) was degassed by bubbling with a stream of N_2 for 15 min. Afterward, DIPEA (40 µL) was added by syringe through the septum and the vessel was irradiated (λ_{Ex} = 455 nm) for 2 h, while 20 µL samples were taken in a 10 min interval for 60 min and one last sample at 120 min, if necessary. The collected samples were dried under vacuum for 48 h, dissolved in 0.6 mL of deuterated DMSO and subjected to ^{1}H NMR spectroscopy. The shift of $\mathbf{g_1}$ and $\mathbf{g_2}$ peaks (**Figure S1** and **Figure S4**) was monitored over time.

^{1}H NMR of the corresponding degradation product **4a** after irradiation: ^{1}H NMR (300 MHz, DMSO) δ 8.23 (d, *J* = 3.3 Hz, 1H), 7.99 (dd, *J* = 9.5, 4.1 Hz, 1H), 7.92 (s, 1H), 7.63 (dd, *J* = 8.7, 4.4 Hz, 1H), 7.16 (dd, *J* = 5.1, 2.4 Hz, 1H), 7.01 (ddd, *J* = 8.6, 4.7, 2.4 Hz, 1H), 6.30 (dd, *J* = 9.5, 3.0 Hz, 1H), 5.25 (d, *J* = 3.4 Hz, 2H), 5.17 (d, *J* = 6.2 Hz, 1H), 4.51 (dq, *J* = 15.7, 5.0 Hz, 5H), 3.79 (p, *J* = 5.3 Hz, 4H), 3.53 – 3.39 (m, 8H).

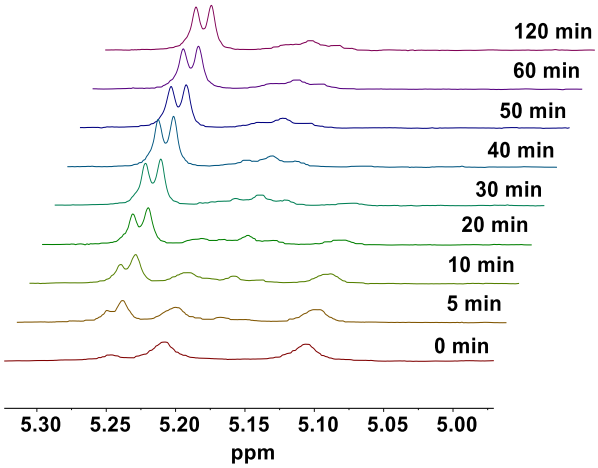


Figure S4. Time-dependent photocleavage of **3a** to **4a** followed by H NMR spectroscopy measured in $CDCl_3$.

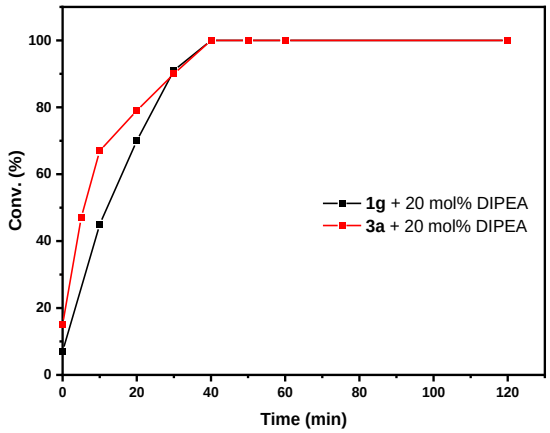


Figure S5. Photocleavage of **1g** and **3a** with 20 mol% DIPEA in MeCN followed by ^{1}H NMR spectroscopy in $CDCl_3$ and DMSO-*d6*, respectively.

*Photocleavage of **3b** to **4b** monitored by ^{1}H NMR*

In a septum-sealed vial equipped with a magnetic stirrer **3b** (100 mg) in a suitable buffer (2 mL) was degassed by bubbling with a stream of N_2 for 15 min. Afterward, the vessel was irradiated (λ_{Ex} = 455 nm) for 2 h, while 0.2 mL samples were collected into Eppendorf cups during a given time interval. The collected samples were freeze-dried until complete removal of water, dissolved in 0.6 mL of $CDCl_3$ and the soluble part was subjected to ^{1}H NMR spectroscopy. The shift of $\mathbf{g_1}$ and $\mathbf{g_2}$ peaks (**Figure S1** and **Figure S6**) was monitored over time.

^{1}H NMR of the corresponding degradation product **4b** after irradiation: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.83 (s, 1H), 7.64 (d, *J* = 9.5 Hz, 1H), 7.39 (d, *J* = 9.2 Hz, 1H), 7.00 – 6.85 (m, 2H), 6.26 (d, *J* = 9.5 Hz, 1H), 5.26 (s, 2H), 4.78 (s, 2H), 4.56 (dt, *J* = 8.1, 5.0 Hz, 4H), 3.94 – 3.81 (m, 4H), 3.77 – 3.45 (m, 186H).

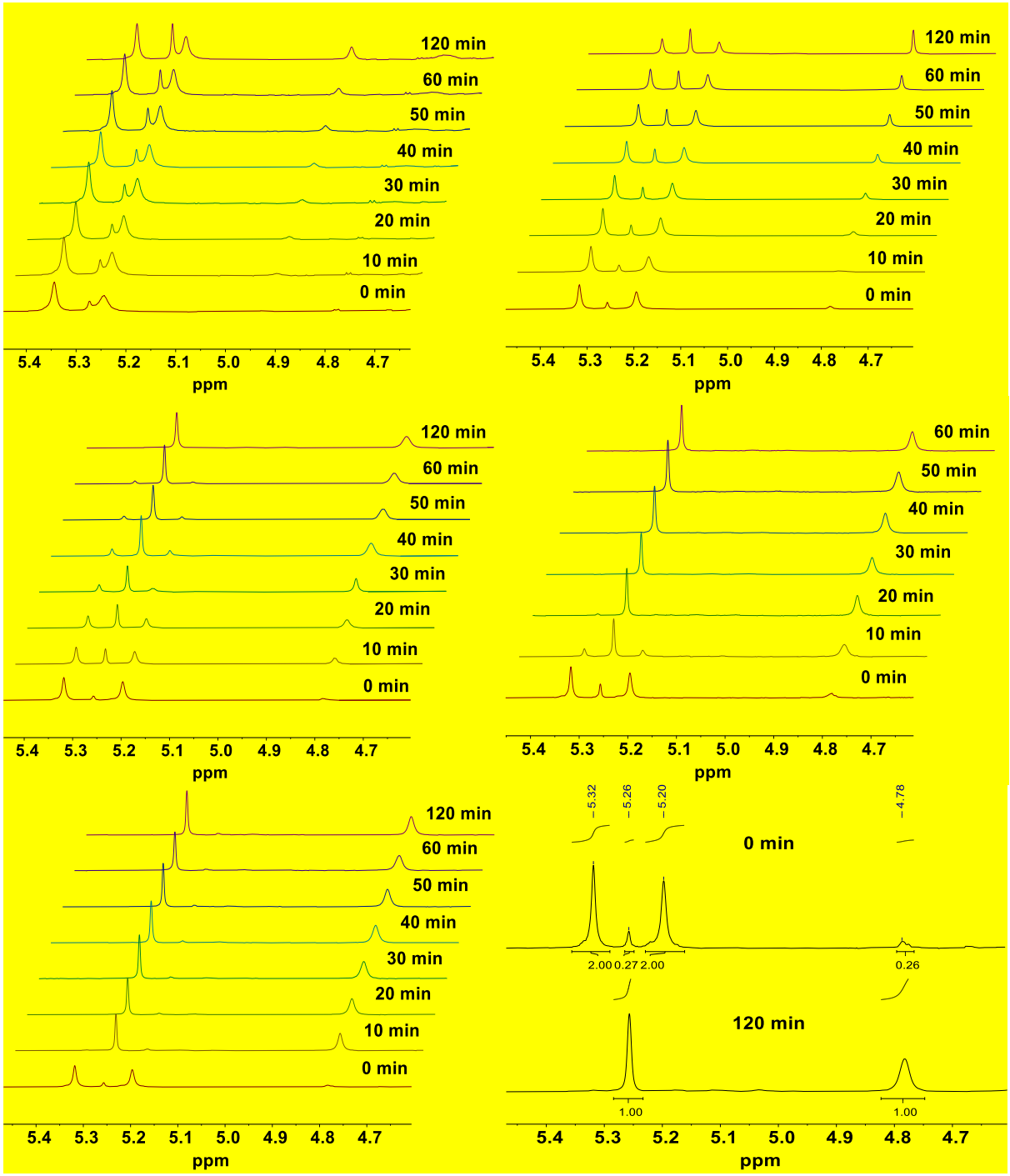


Figure S1. Time dependent photodegradation of **3b** to **4b** followed by H NMR in (top, left) 0.1M HCl/KCl buffer (pH=2.1) (top, right) 0.01 M PBS buffer (pH = 5.5), (center, left) 0.01 M PBS buffer (pH = 6.5), (center, right) 0.01 M PBS buffer (pH = 7.4) and (bottom, left) 0.1 M carbonate buffer (pH = 9.2) measured in $CDCl_3$. (Bottom, right) 0.01 M PBS buffer (pH = 6.5) integration of $\mathbf{g_1}$/$\mathbf{g_2}$ at 0 min and 120 min.

*Photocleavage of **3b** to **4b** monitored by UV/Vis spectroscopy*

In a septum-sealed vial equipped with a magnetic stirrer 100 mg of **3b** in 2 mL 0.1M Britton-Robinson buffer (pH = 6.50) was degassed by bubbling with a stream of N_2 for 15 min.

Afterward, the vessel was irradiated (λ_{Ex} = 455 nm) for 2 h, while 0.20 mL samples were taken in a 10 min interval for 60 min and one last sample at 120 min and filled up to 1 mL with 0.1M Britton-Robinson buffer (pH = 11.8) and used as stock solutions. The samples were diluted with 0.1M Britton-Robinson buffer (pH = 11.8) to 62 µM and measured.

*Photocleavage of **3b** to **4b** monitored by fluorescence spectroscopy*

In a septum-sealed vial equipped with a magnetic stirrer 100 mg of **3b** in 2 mL 0.1M Britton-Robinson buffer (pH = 6.5) was degassed by bubbling with a stream of N_2 for 15 min. Afterward, the vessel was irradiated (λ_{Ex} = 455 nm) for 2 h, while 0.20 mL samples were taken in a 10 min interval for 60 min and one last sample at 120 min and filled up to 1 mL with 0.1M Britton-Robinson buffer (pH = 11.8) and used as stock solutions. The samples were diluted with 0.1M Britton-Robinson buffer (pH = 11.8) to 1.55 nM and measured.

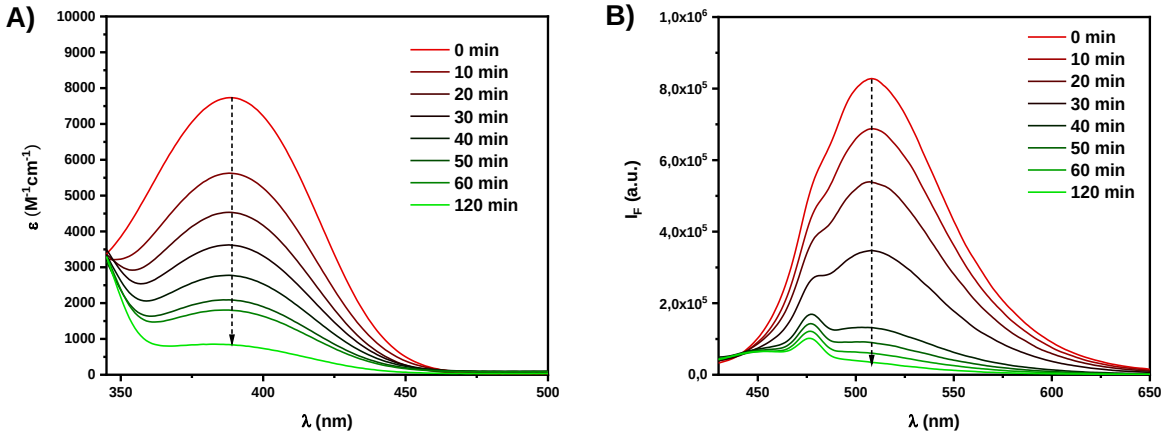


Figure S7. A) Time-dependent photocleavage process of **3b** in 0.01M PBS buffer (pH 6.5) monitored by UV/Vis spectroscopy. B) Time-dependent photocleavage process of **3b** in 0.01M PBS buffer (pH 6.5) monitored by fluorescence spectroscopy exciting at 410 nm.

*Photocleavage of **3b** to **4b** monitored by GPC*

In a septum-sealed vial equipped with a magnetic stirrer 100 mg of **3b** in 2 mL 0.1M Britton-Robinson buffer (pH = 6.50) was degassed by bubbling with a stream of N_2 for 15 min. Afterward, the vessel was irradiated (λ_{Ex} = 455 nm) for 2 h, while 0.20 mL samples were taken in a 10 min interval for 60 min and one last sample at 120 min. The samples were

freeze-dried until complete removal of water. The polymer was dissolved and eluted in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) containing CF_3COONa (0.05 M) at a flow rate of 1 mL/min (injected volume 20 μL, sample concentration 15.0 mg/mL). The number and weight average molecular weights were calculated using polymethyl methacrylate standards.

*Determination of pK_a of **3b** by UV/Vis spectroscopy*

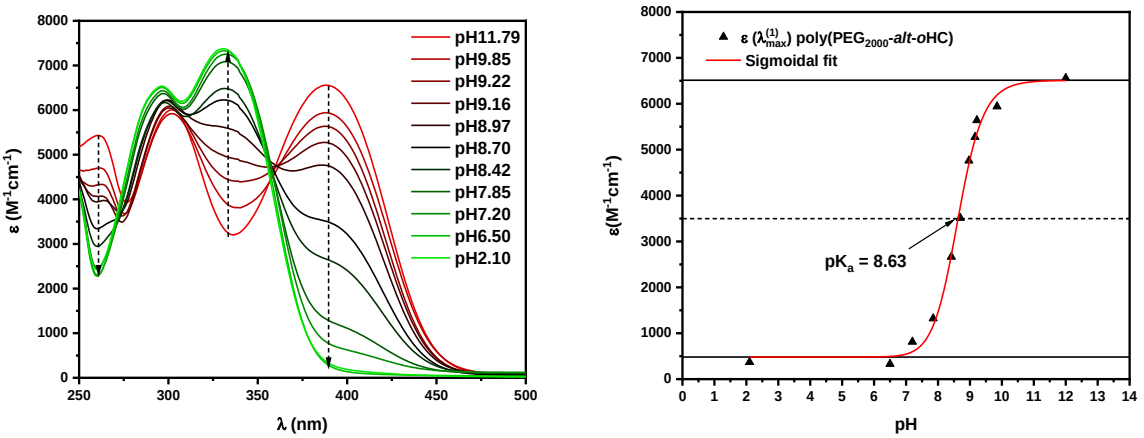


Figure S8. *Left:* Dependence on pH of the absorption spectra of 62 µM solution of **3b** from basic to acidic in 0.1M Britton-Robinson buffers. *Right:* Determination of pK_a value of **3b** by the sigmoidal fitting.

*Photocleavage / drug delivery of **5a**/**5b** monitored by UV/Vis spectroscopy*

In a septum-sealed vial equipped with a magnetic stirrer 2.5 µmol of **5a**/**5b** was dissolved in PBS buffer (2 mL, 0.01M, pH = 7.4) and the vessel was irradiated (λ_{Ex} = 455 nm) in an intermittent manner while the LED was switched on/off every 2.5 min and 50 µL samples were taken in a 0.5 min interval for 13 min, filled up to 1 mL with 0.1M Britton-Robinson buffer (pH = 11.8) (63 µM) and measured.

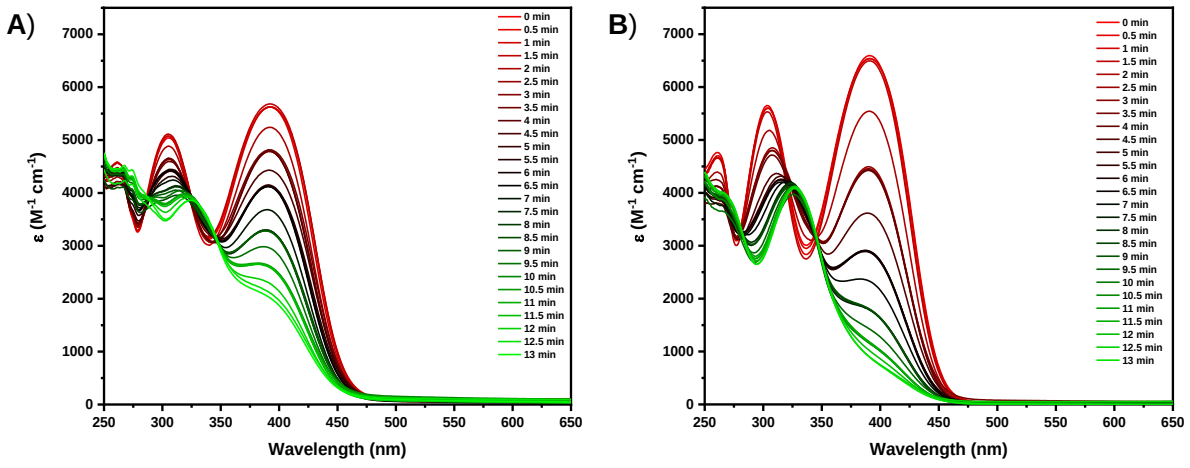


Figure S9. Confirmation of drug delivery by UV absorption spectra of A) **5a** and B) **5b** after irradiation with visible light (λ_{Ex} = 455 nm) in an off and on intermittent manner.

4. UV/Vis spectroscopy

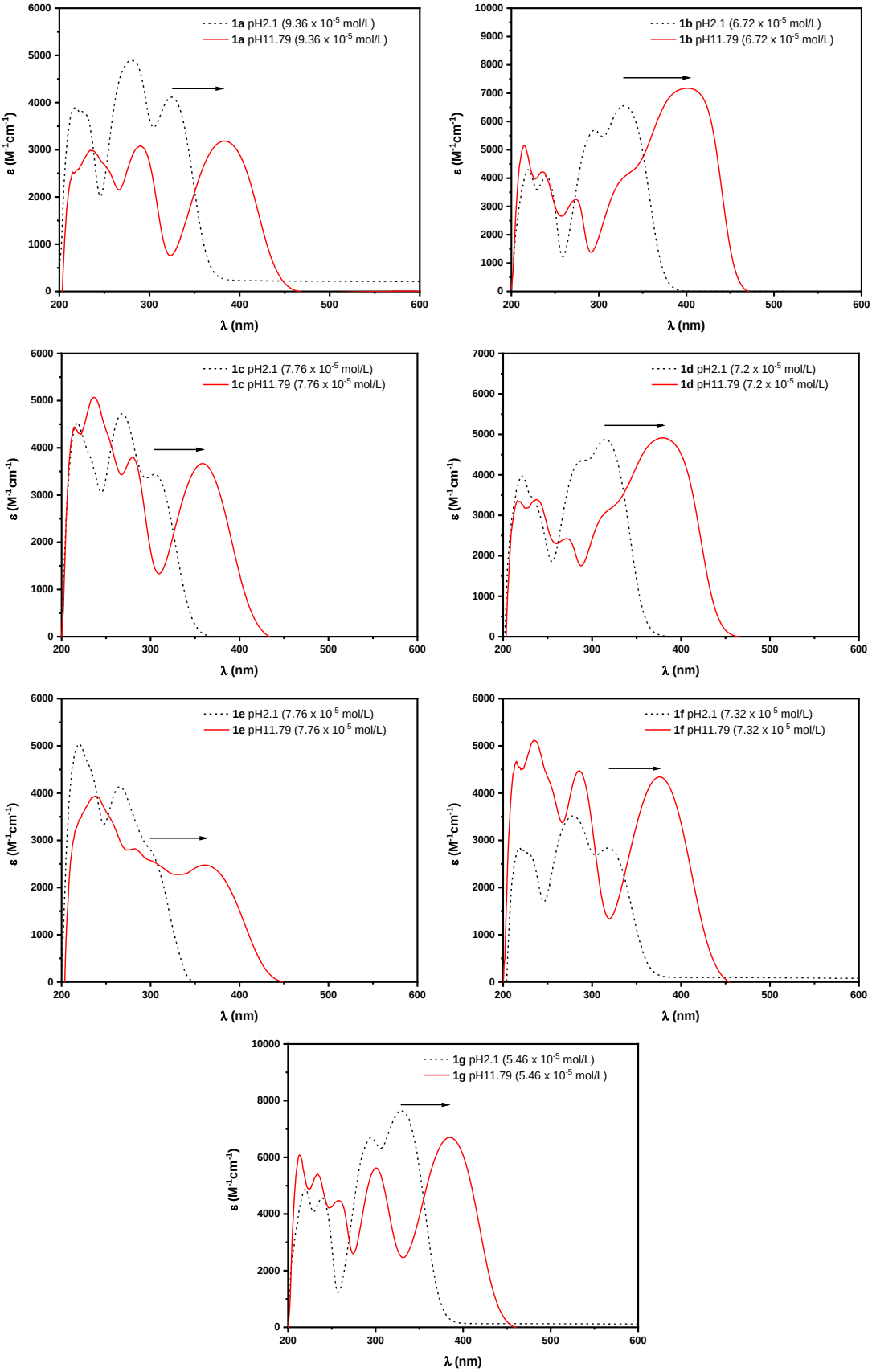


Figure S10. UV/Vis spectra of the substrates **1a – g** in 0.1M HCl/KCl buffer pH=2.1 and MeCN 9/1 (v/v) and 0.1M Britton-Robinson buffer pH=11.8 and MeCN 9/1 (v/v).

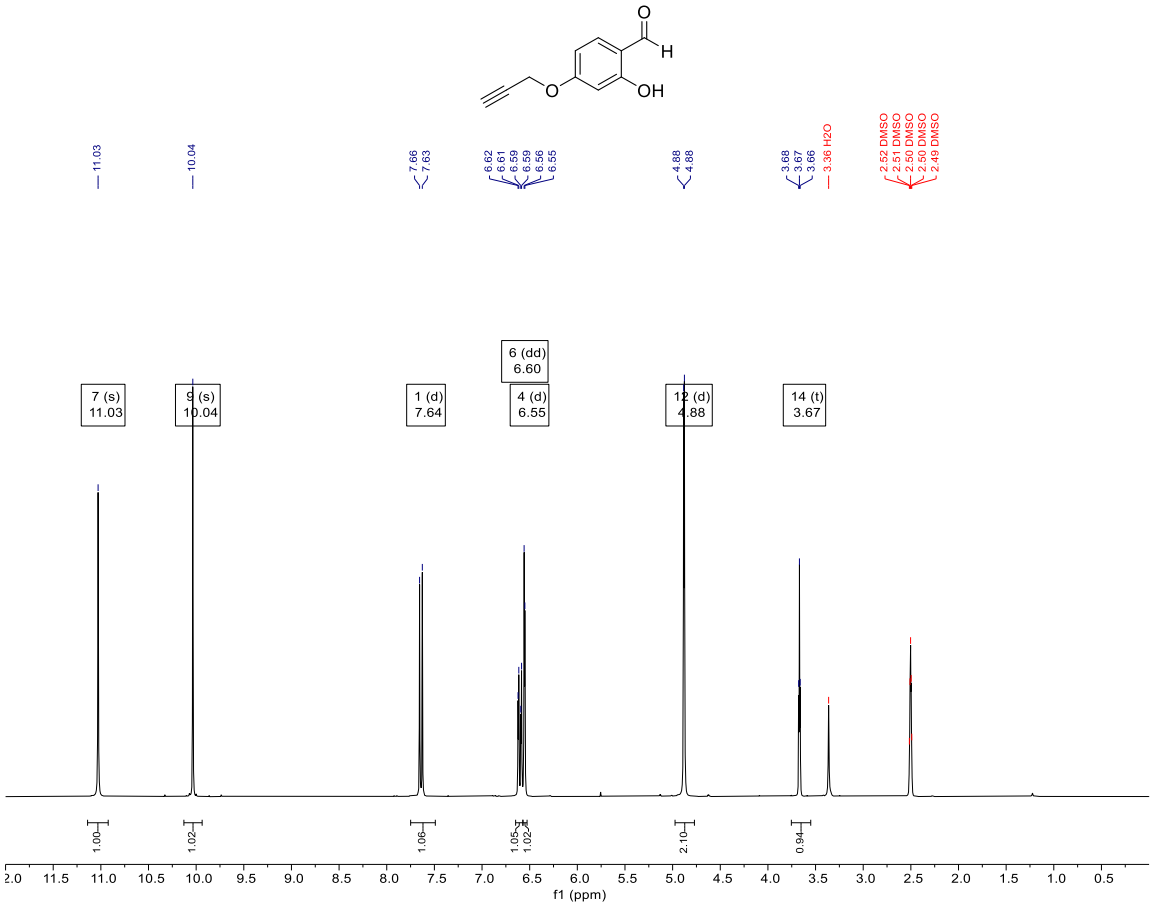
Table S1. Bathochromic shifts and molar attenuation coefficients of the substrates at different pH values.

	$\lambda^{(1)}_{max}$ [nm]		$\varepsilon(\lambda^{(1)}_{max})$ [$M^{-1}cm^{-1}$]	
Substrate	pH = 2.1[a)]	pH = 11.8[b)]	pH = 2.1[a)]	pH = 11.8[b)]
1a	325	385	4115	3184
1b	329	400	6555	7173
1c	304	359	3441	3667
1d	315	380	4877	4913
1e	300	362	2734	2475
1f	318	377	2840	4339
1g	330	384	7643	6701

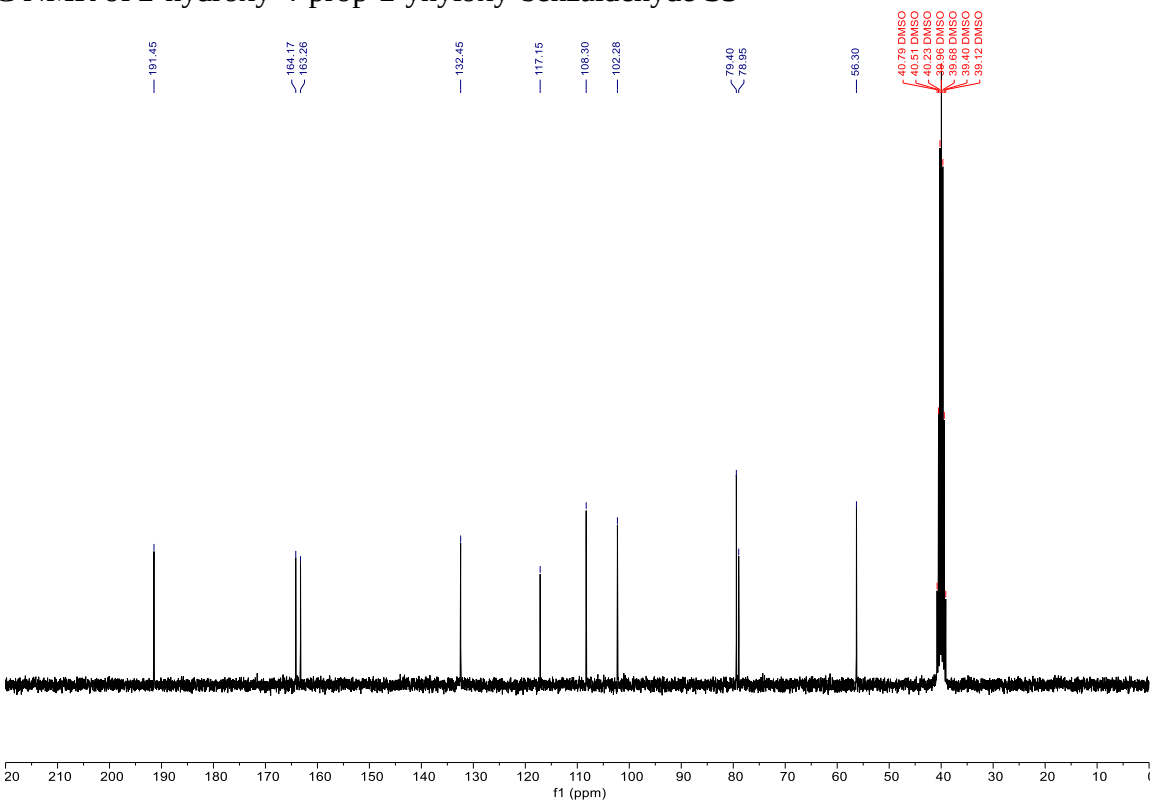
UV/Vis spectra of **1a-g** in [a)] 0.1M HCl/KCl buffer pH=2.1 and MeCN 9/1 (v/v) and [b)] 0.1M Britton-Robinson buffer pH=11.8 and MeCN 9/1 (v/v).

5. NMR Data

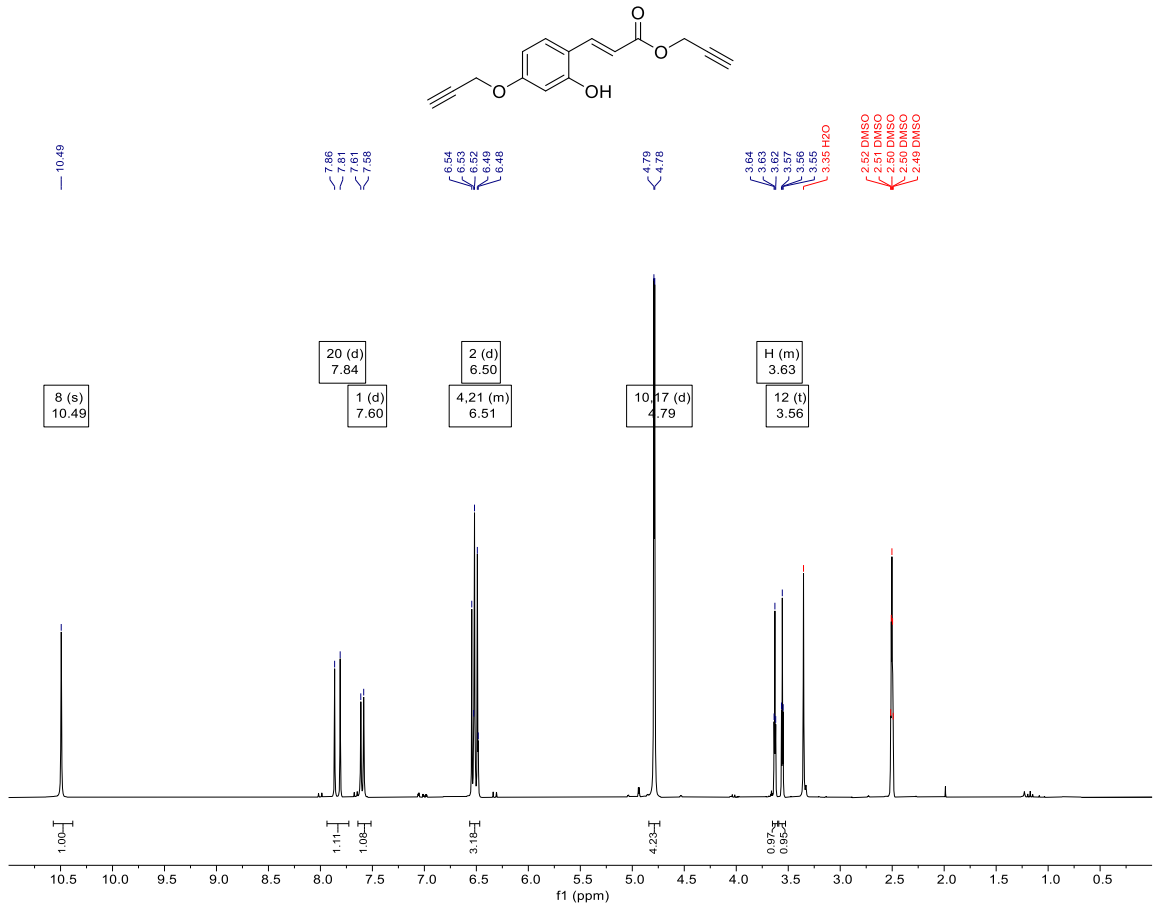
^{1}H NMR of 2-hydroxy-4-prop-2-ynyloxy-benzaldehyde **S3**



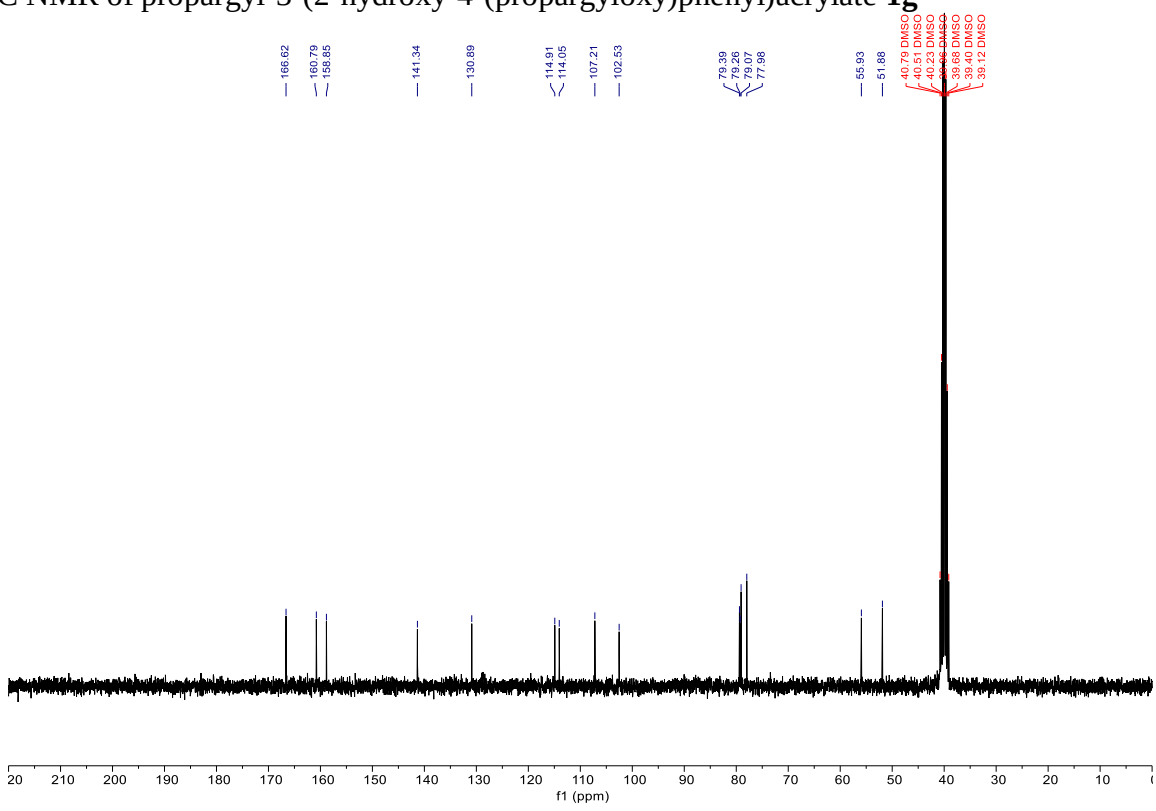
^{13}C NMR of 2-hydroxy-4-prop-2-ynyloxy-benzaldehyde **S3**



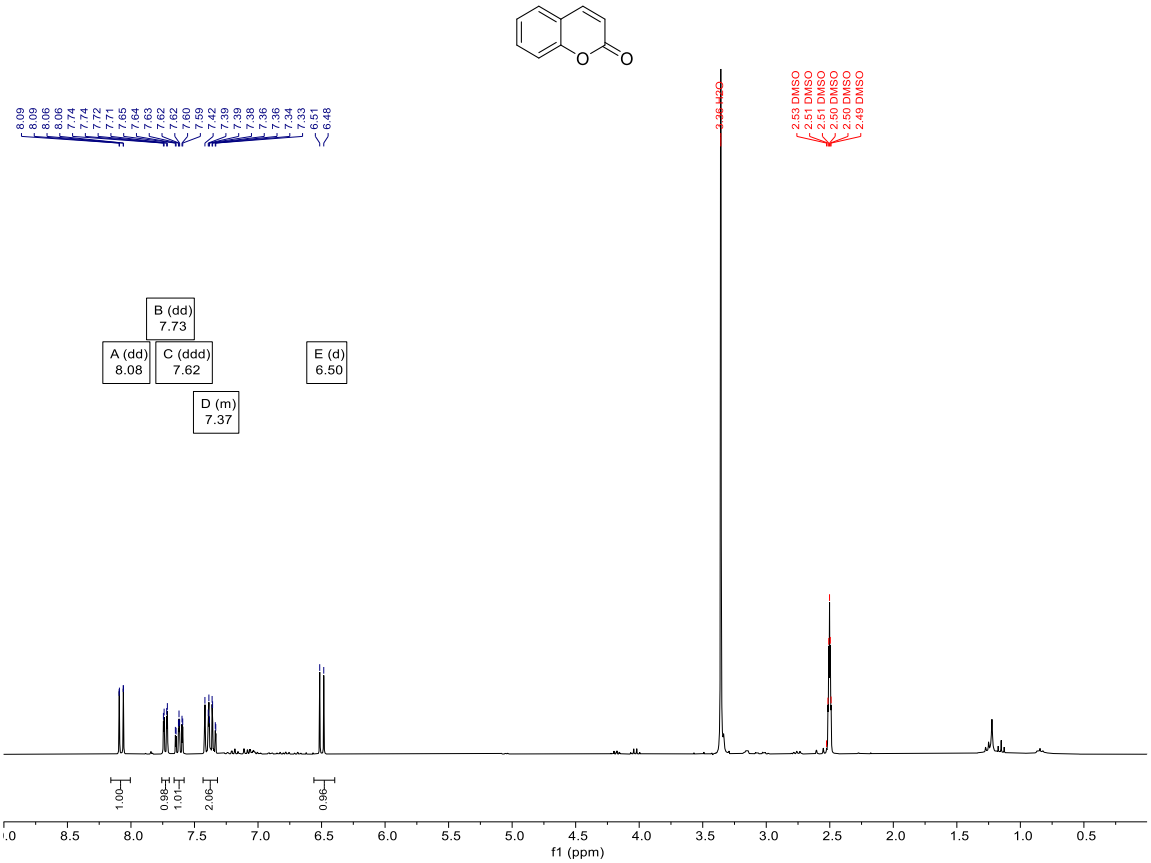
^{1}H NMR of propargyl-3-(2-hydroxy-4-(propargyloxy)phenyl)acrylate **1g**



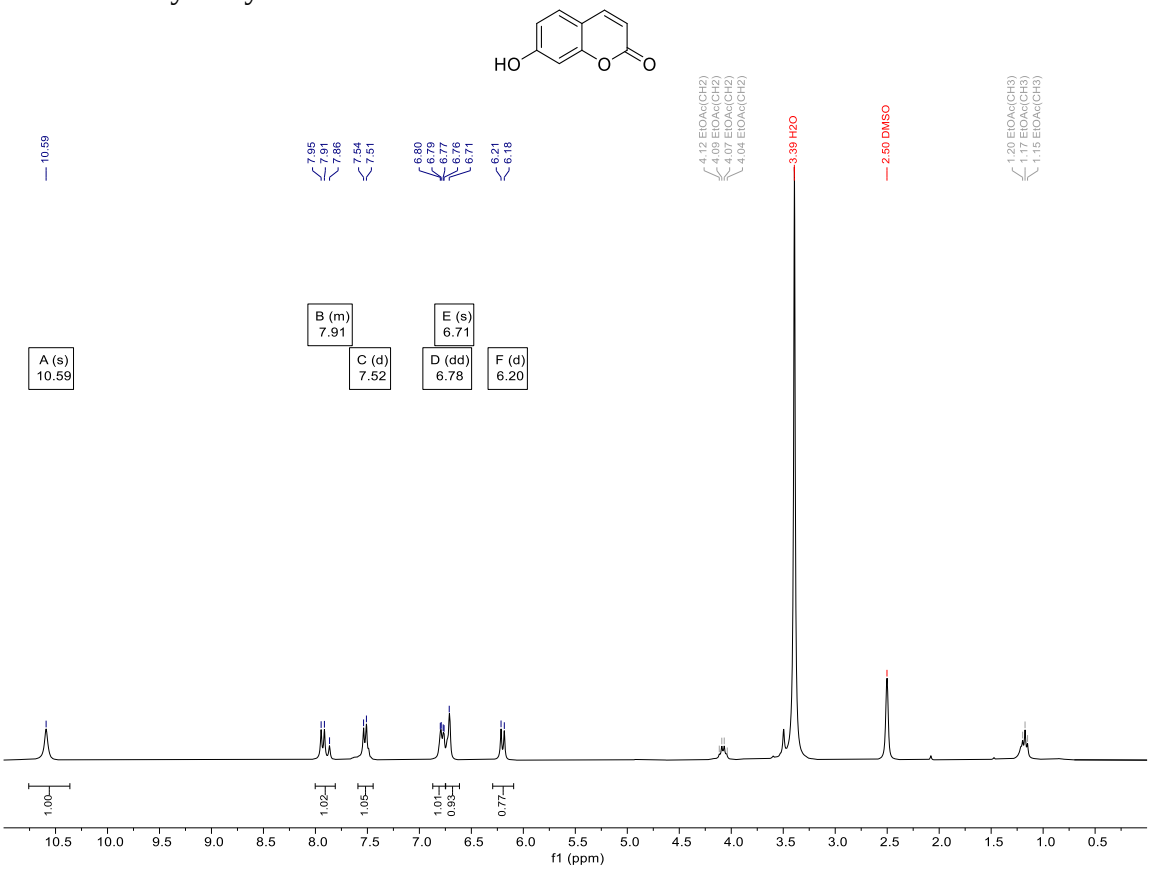
^{13}C NMR of propargyl-3-(2-hydroxy-4-(propargyloxy)phenyl)acrylate **1g**



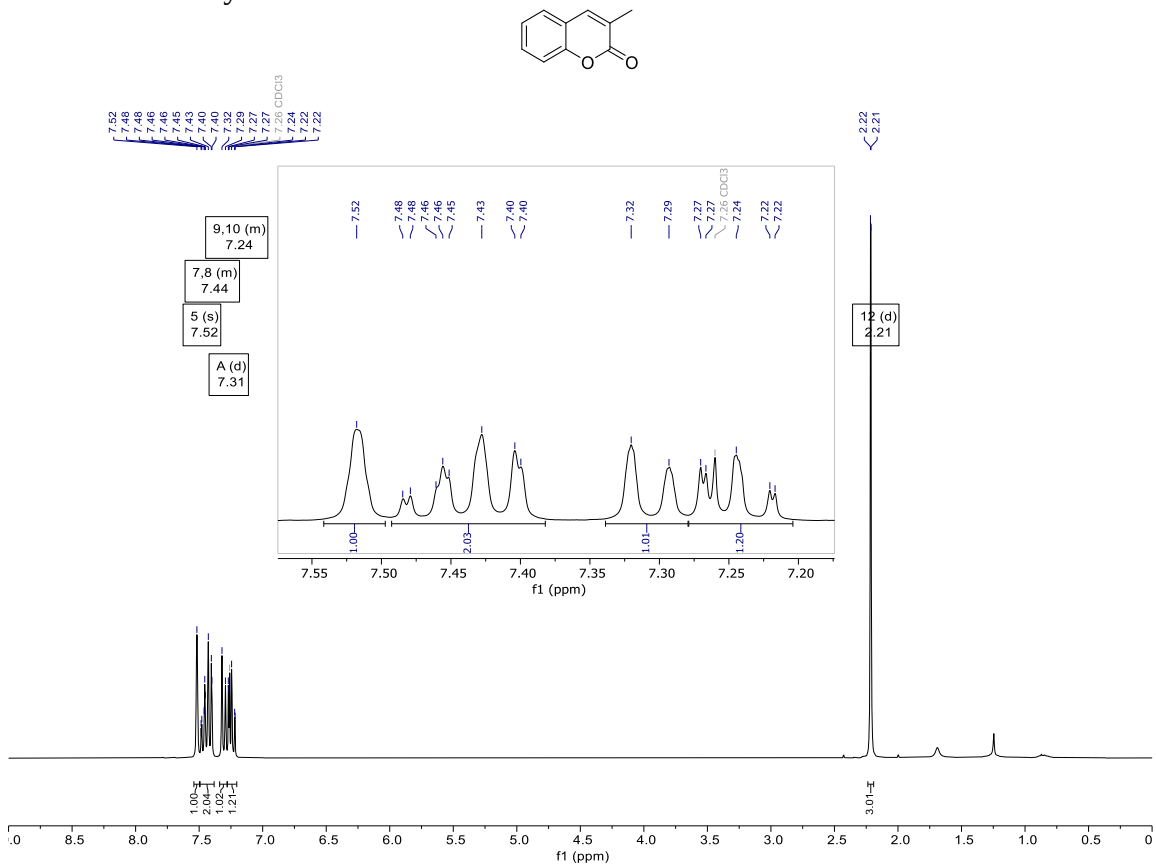
^{1}H NMR of coumarin **2a**



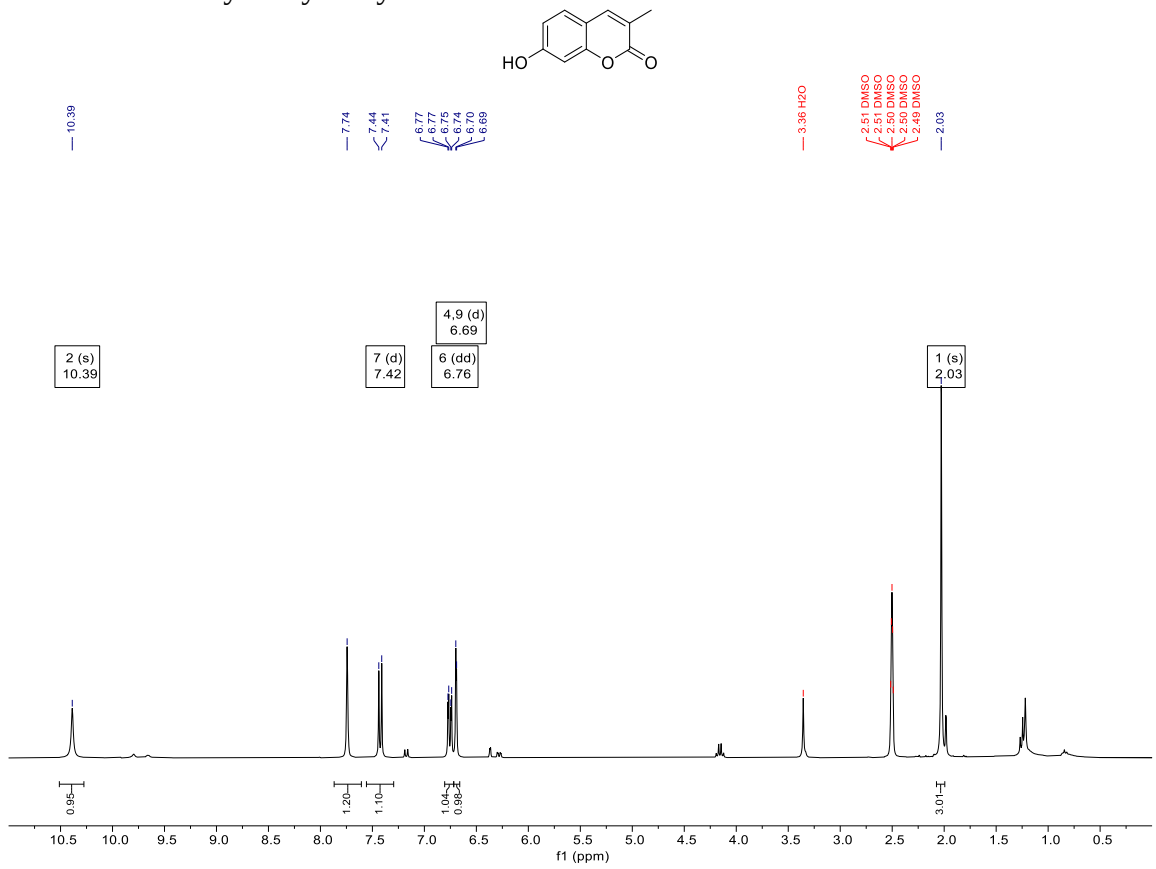
^{1}H NMR of 7-hydroxycoumarin **2b**



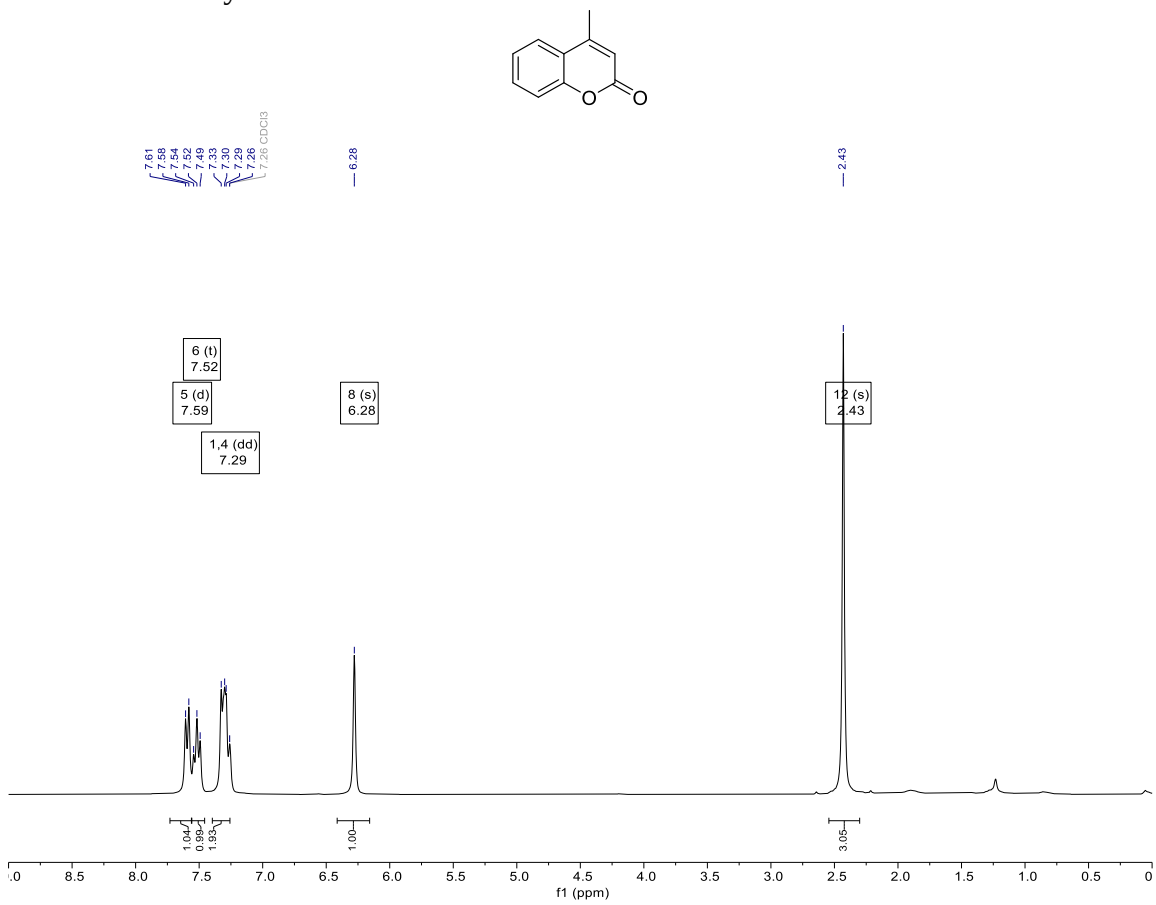
^{1}H NMR of 3-methylcoumarin **2c**



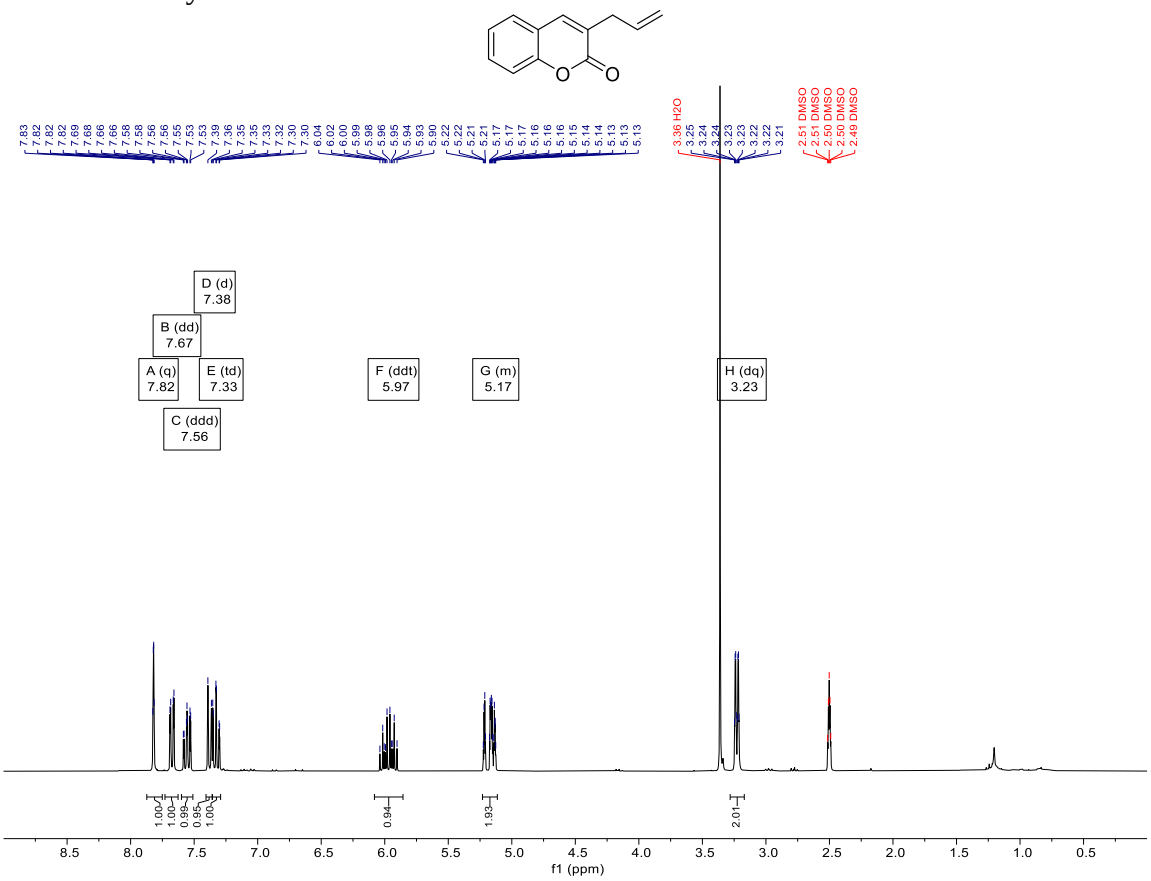
^{1}H NMR of 3-methyl-7-hydroxycoumarin **2d**



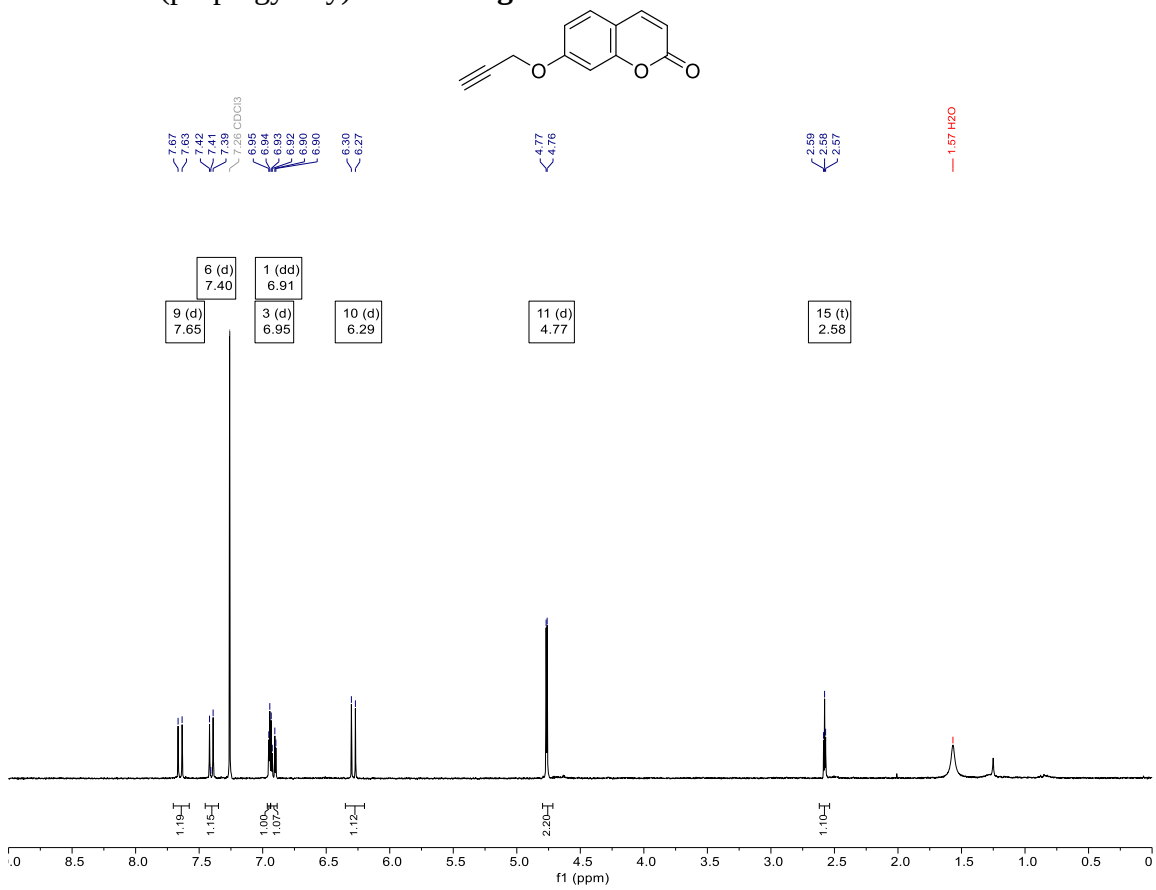
^{1}H NMR of 4-methylcoumarin **2e**



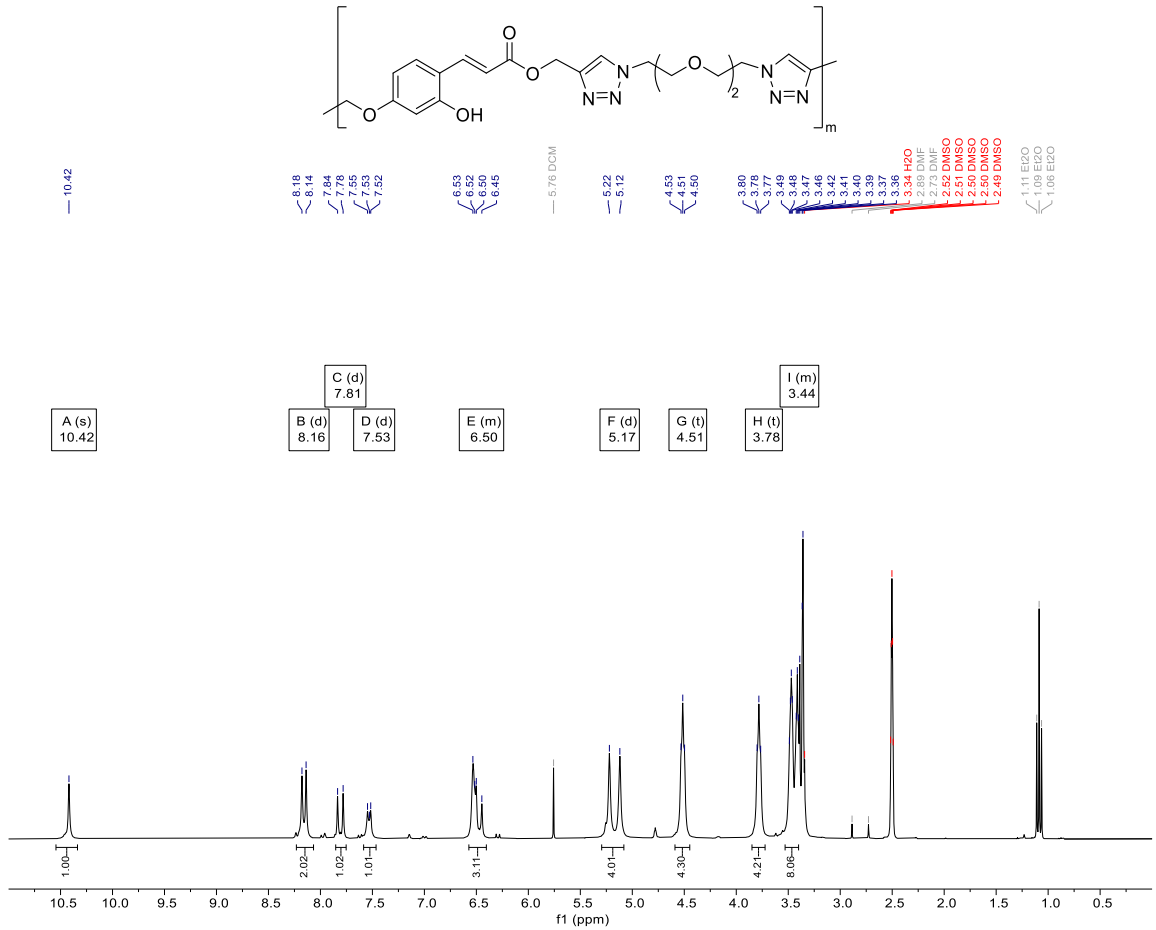
^{1}H NMR of 3-allylcoumarin **2f**



^{1}H NMR of 7-(propargyloxy)coumarin **2g**



^{1}H NMR of **3a**

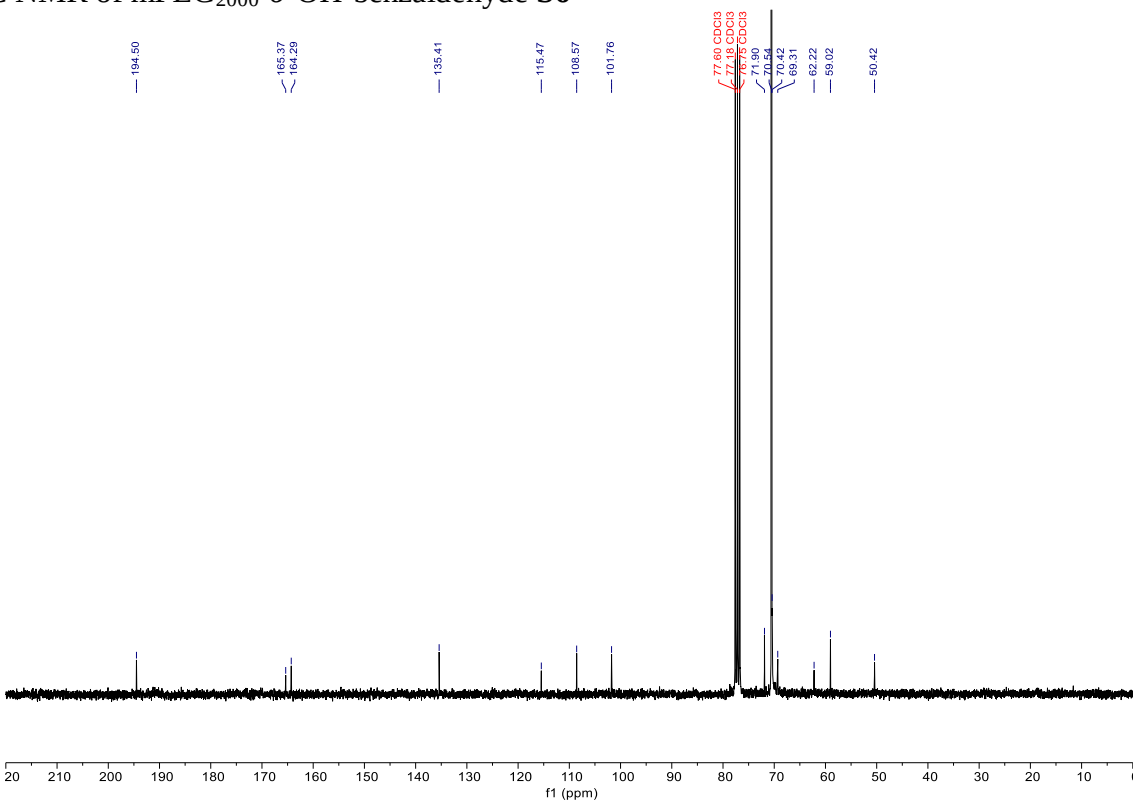

A (s) 10.42
B (d) 8.16
C (d) 7.81
D (d) 7.53
E (m) 6.50
F (d) 5.17
G (t) 4.51
H (t) 3.78
I (m) 3.44
f1 (ppm)

^{1}H NMR of **3b**

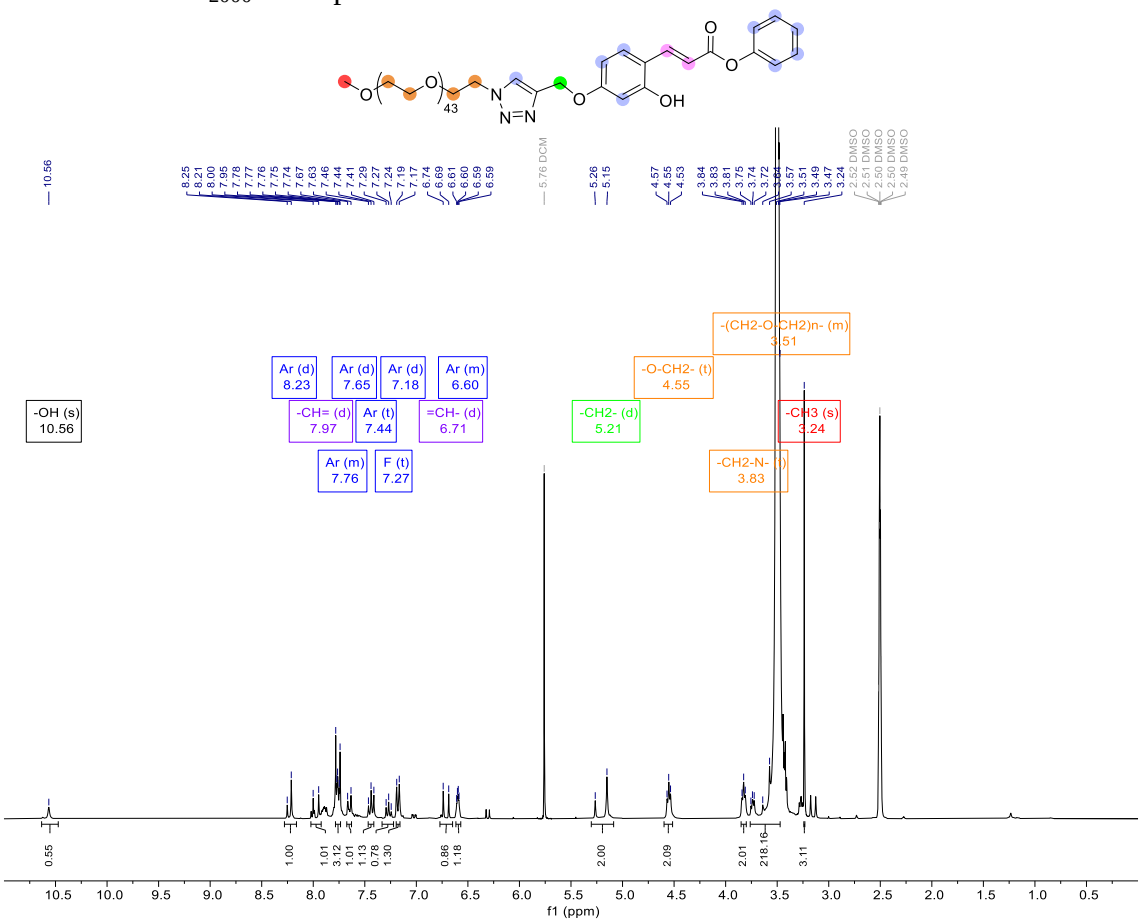

A (s) 10.42
B (d) 8.17
C (d) 7.81
D (d) 7.55
E (d) 6.48
F (d) 6.55
G (s) 5.22
H (s) 5.12
I (t) 4.54
J (t) 3.82
K (s) 3.50
f1 (ppm)

^{1}H NMR of mPEG$_{2000}$-*o*-OH-benzaldehyde **S6**

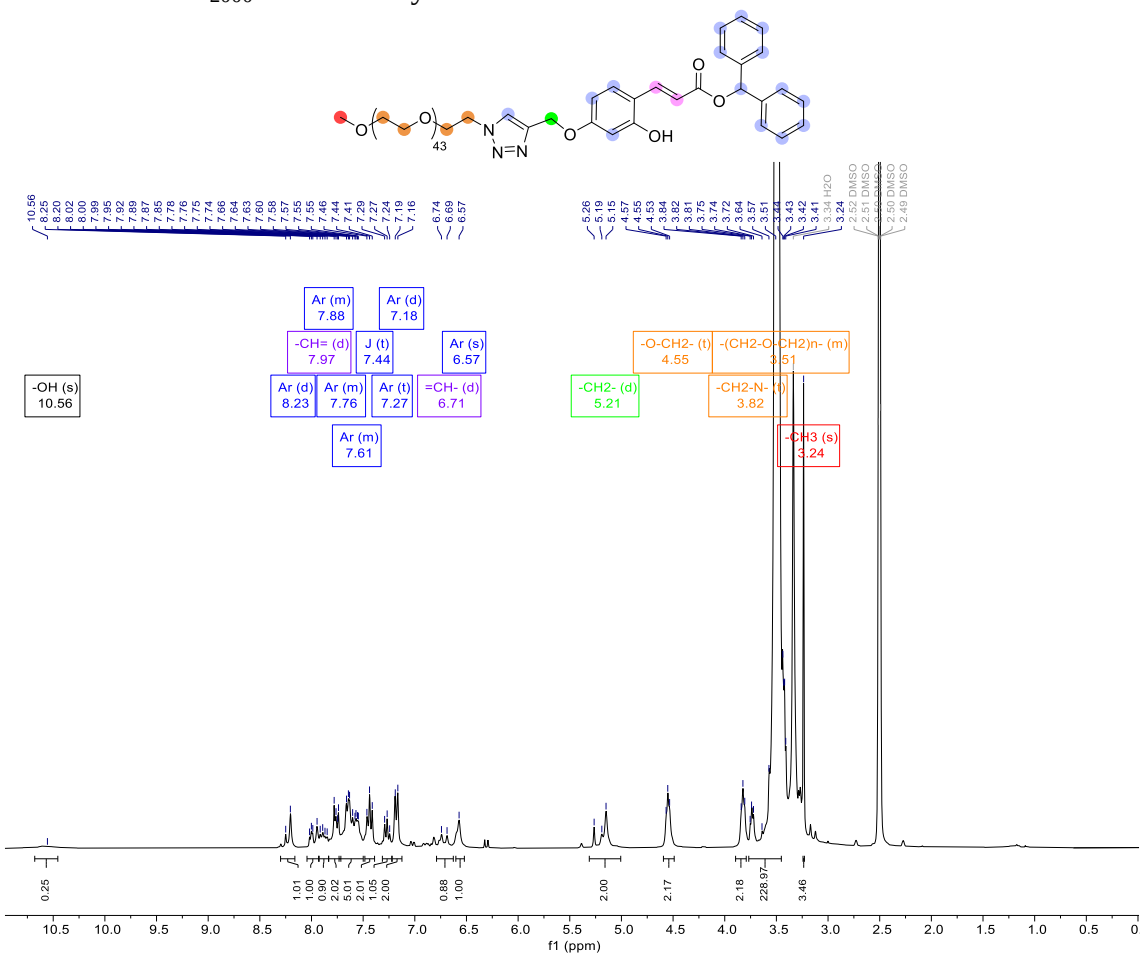
^{13}C NMR of mPEG$_{2000}$-*o*-OH-benzaldehyde **S6**



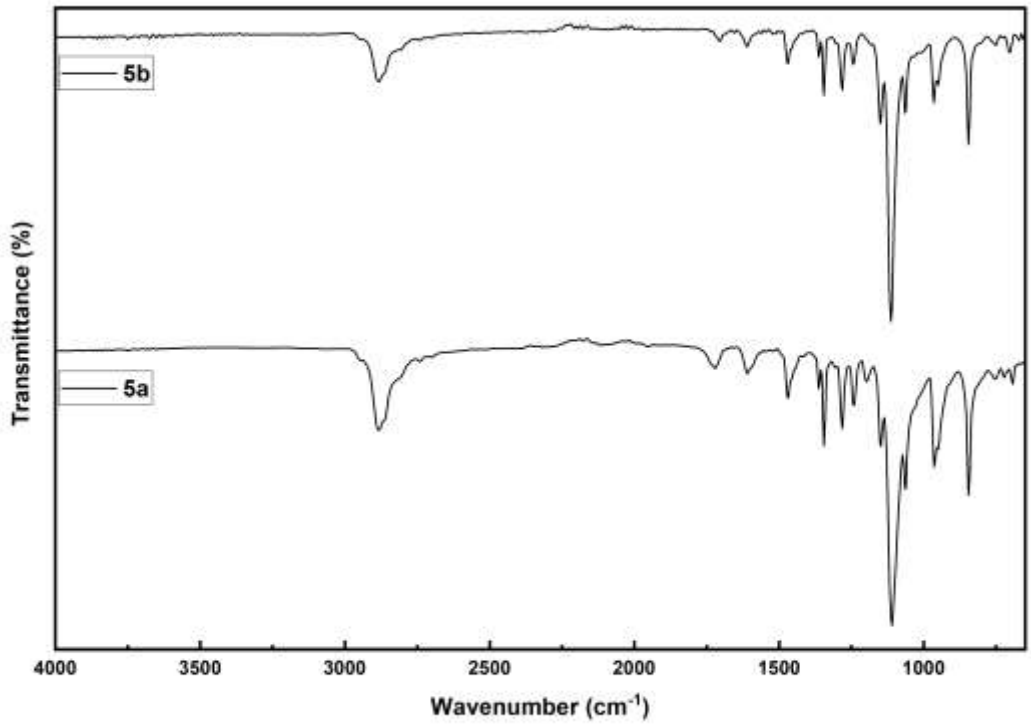
^{1}H NMR of mPEG$_{2000}$-*o*HC-phenol **5a**



^{1}H NMR of mPEG$_{2000}$-*o*HC-benzhydrol **5b**



6. FTIR Data of 5a/5b



7. References

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