

## Exploring carbonic anhydrase inhibition with multimeric coumarins displayed on a fullerene scaffold

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## Supplementary Information

All reactions were carried out under an argon atmosphere. Yields refer to chromatographically and spectroscopically homogeneous materials. All reagents were purchased from commercial suppliers (Aldrich, Fisher or TCI) and used without further purification.

All reactions were performed using purified and dried solvents: tetrahydrofuran (THF) was refluxed over sodium-benzophenone, dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), triethylamine (NEt<sub>3</sub>), and pyridine were refluxed over calcium hydride (CaH<sub>2</sub>).

All reactions were monitored by thin-layer chromatography (TLC) carried out on Merck aluminum roll silica gel 60-F254 using UV light and a molybdate-sulfuric acid solution or potassium permanganate as revelator. Merck silica gel (60, particle size 0.040–0.063 mm) was employed for flash column chromatography and preparative thin layer chromatography using technically solvent distilled prior to use as eluting solvents.

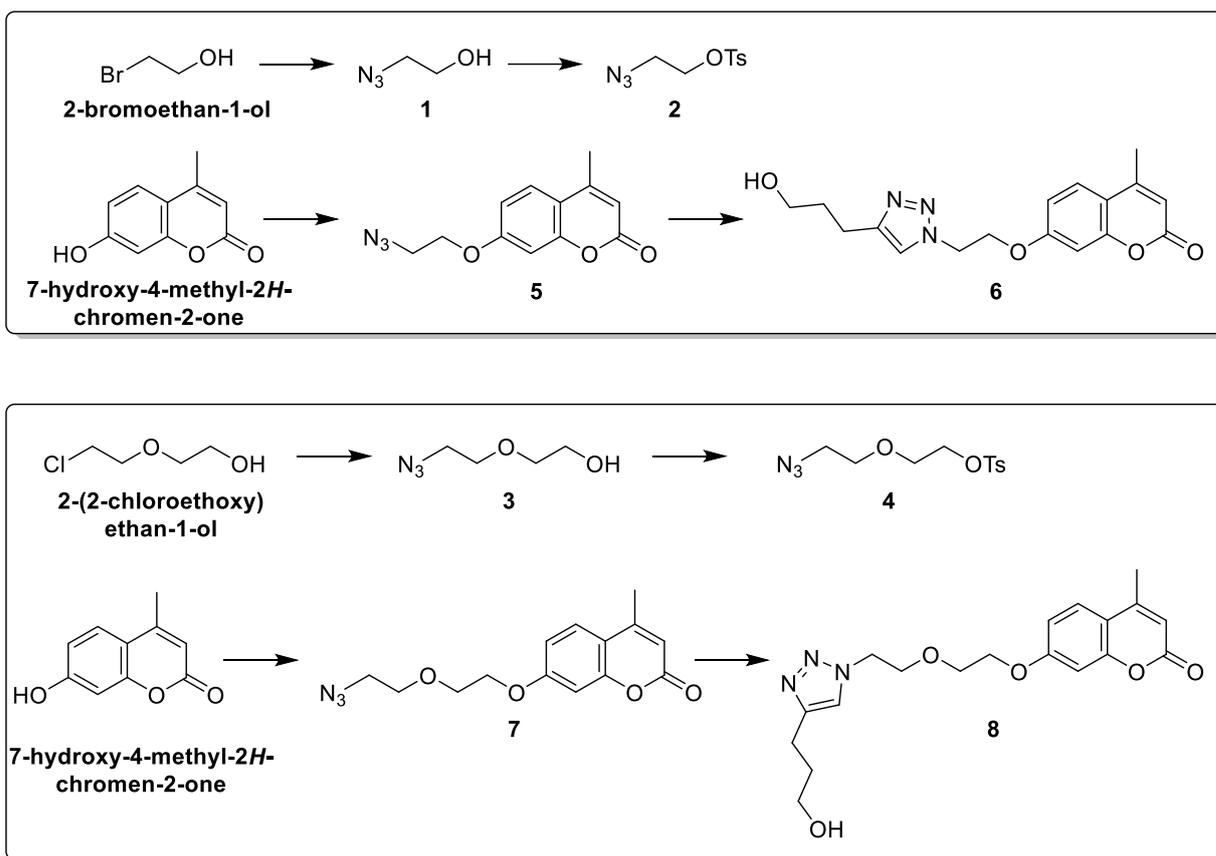
IR spectra (cm<sup>-1</sup>) were recorded on a Perkin–Elmer Spectrum One Spectrophotometer.

UV/Vis spectra ( $\lambda_{\max}$  in nm) were recorded on a Hitachi U-3000 spectrophotometer. Melting points were recorded on an Electrothermal 9100 instrument in open capillary tubes and are uncorrected.

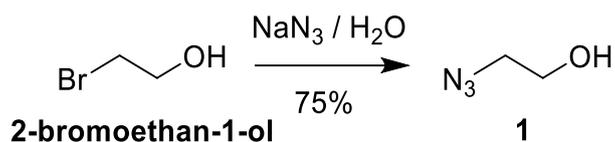
All compounds were characterized by  $^1\text{H}$  and  $^{13}\text{C}$  nuclear magnetic resonance (NMR) as well as by  $^1\text{H}$ - $^1\text{H}$  and  $^1\text{H}$ - $^{13}\text{C}$  correlation experiment when necessary. Spectra were recorded at 25 °C on JNM EX-400, at 400 MHz for  $^1\text{H}$  and at 100.4 MHz for  $^{13}\text{C}$ . All chemical shifts are quoted in ppm, relative to tetramethylsilane, using the residual solvent peak as a reference standard. The following abbreviations are used to describe the multiplicities: s= singlet, d= doublet, t= triplet, m= multiplet, br= broad, br s= broad singlet. The numbering of the protons and carbons is analogous to the proton numbers resulting from the name of the compound. Aromatic, acetyl and methyl (carbons and protons) are respectively labeled with “Ar”, “Ac” and “Me” subscript, quaternary carbons are indicated with a “q” subscript. Chemical shifts ( $\delta$ ) are reported in ppm and referenced indirectly to TMS *via* the solvent (or residual solvent) signals.

MALDI-MS mass spectra were recorded in University of Mons (UMH, Mass Spectrometry Research Group - CISM) using a Waters QToF Premier mass spectrometer equipped with a nitrogen laser, operating at 337 nm with a maximum output of 500 J.m<sup>-2</sup> delivered to the sample in 4 ns pulses at 20 Hz repeating rate. Time-of-flight mass analyses were performed in the reflectron mode at a resolution of about 10,000. All the samples were analyzed using dihydroxybenzoic acid (DHB), that matrix was prepared as 20 mg/mL solution in acetone. The matrix solution (1  $\mu\text{L}$ ) was applied to a stainless steel target and air dried. Samples were dissolved in water to obtain 1 mg/mL solutions. 1  $\mu\text{L}$  aliquots of those solutions were applied onto the target area already bearing the matrix crystals, and air-dried. For the recording of the single-stage MS spectra, the quadrupole (rf-only mode) was set to pass all the ions of the distribution, and they were transmitted into the pusher region of the time-of-flight analyzer where they were mass analyzed with 1 s integration time. Data were acquired in continuum mode until acceptable averaged data were obtained.

## 1. Synthesis of the monovalent compounds



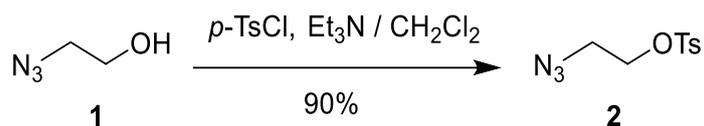
**Scheme 1.** Synthesis of the monovalent coumarin derivatives **5**, **6**, **7** and **8**.



**2-azidoethan-1-ol (1).** 2-bromoethan-1-ol (10 mL, 94.70 mmol) was dissolved in H<sub>2</sub>O (20 mL) and sodium azide (4.36 g, 67.010 mmol, 2.5 eq) was added. The reaction mixture was stirred at 80°C under Ar for 18 h and then poured into sodium hydroxide (5%, 100 mL) and extracted with diethyl ether (100 mL x 3). The organic layer was dried over MgSO<sub>4</sub> and evaporated to dryness to afford **1** (1.74 g, 75%) as a yellow oil. The analytical data of **1** were in complete agreement with literature data.<sup>1</sup>

- **Formula:** C<sub>2</sub>H<sub>5</sub>N<sub>3</sub>O
- **Mw:** 87.08 g/mol
- **R<sub>f</sub>:** 0.69 (Cy/EtOAc 4:6)
- **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 3.78 (t, *J* = 5.2 Hz, 2H, CH<sub>2</sub>OH), 3.45 (t, *J* = 4.8 Hz, 2H, CH<sub>2</sub>N<sub>3</sub>), 1.96 (s, 1H, OH).
- **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ = 61.6 (CH<sub>2</sub>OH), 53.6 (CH<sub>2</sub> N<sub>3</sub>)

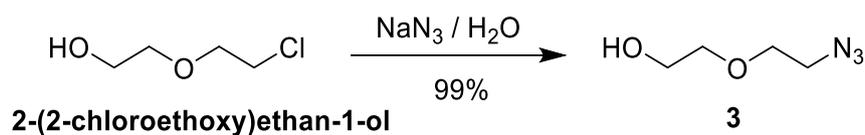
<sup>1</sup> A. Haslop, A. Gee, C. Plisson, N. Long, *J. Labelled Comp. Radiopharm.* **2013**, 56, 313–316.



**2-azidoethyl 4-methylbenzenesulfonate (2).** Compound **1** (1.05 g, 13.502 mmol, 1 eq) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and triethylamine (2.82 mL, 20.253 mmol, 1.5 eq) was added. The solution was cooled down to 0°C and *p*-TsCl (3.09 g, 16.203 mmol, 1.2 eq) was added. The reaction mixture was stirred at this temperature for 1 h and then was allowed to warm to room temperature and stirred under Ar for 16 h. Then, the mixture was washed with NaHCO<sub>3</sub> (50 mL), water (50 mL) and brine (50 mL). The organic layer was dried over MgSO<sub>4</sub> and evaporated to dryness. The crude was purified by column chromatography (Cy/AcOEt 95:5 to 7:3) to afford **2** (2.94 g, 90%) of as a yellow oil. The analytical data of **2** were in complete agreement with literature data.<sup>2</sup>

- **Formula:** C<sub>9</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S
- **Mw:** 241.26 g/mol
- **R<sub>f</sub>:** 0.86 (Cy/AcOEt 4:6)
- **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 7.80 (d, *J* = 8.4 Hz, 2H, CH<sub>Ar</sub>), 7.36 (d, *J* = 8.0 Hz, 2H, CH<sub>Ar</sub>), 4.15 (t, *J* = 5.2 Hz, 2H, CH<sub>2</sub>O), 3.48 (t, *J* = 5.6 Hz, 2H, CH<sub>2</sub>N<sub>3</sub>), 2.45 (s, 3H, CH<sub>3</sub>).
- **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ = 145.4 (C<sub>Ar</sub>), 132.6 (C<sub>Ar</sub>), 130.1 (CH<sub>Ar</sub>), 128.1 (CH<sub>Ar</sub>), 68.2 (CH<sub>2</sub>O), 49.7 (CH<sub>2</sub> N<sub>3</sub>), 21.8 (CH<sub>3</sub>).

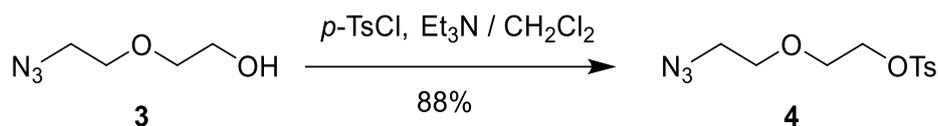
<sup>2</sup> A. Haslop, A. Gee, C. Plisson, N. Long, *J. Labelled Comp. Radiopharm.* **2013**, *56*, 313–316.



**2-(2-azidoethoxy)ethan-1-ol (3).** 2-(2-chloroethoxy)ethan-1-ol (10 mL, 94.70 mmol) was dissolved in H<sub>2</sub>O (60 mL) and sodium azide (15.4 g, 236.75 mmol, 2.5 eq) was added. The reaction mixture was stirred at 80°C under Ar for 16 h and then poured into sodium hydroxide (5%, 100 mL) and extracted with diethyl ether (100 mL x 3). The organic layer was dried over MgSO<sub>4</sub> and evaporated to dryness to afford **3** (12.4 g, 99%) as a clear oil. The analytical data of **3** were in complete agreement with literature data.<sup>3</sup>

- **Formula:** C<sub>4</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>
- **Mw:** 131.16 g/mol
- **R<sub>f</sub>:** 0.49 (EtOAc/MeOH 9:1)
- **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 3.76 (t, *J* = 4.0 Hz, 2H, CH<sub>2</sub>O), 3.70 (t, *J* = 4.4 Hz, 2H, CH<sub>2</sub>O), 3.61 (t, *J* = 4.8 Hz, 2H, CH<sub>2</sub>O), 3.41 (t, *J* = 4.8 Hz, 2H, CH<sub>2</sub>O), 2.01 (s, 1H, OH)
- **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ = 72.5 (CH<sub>2</sub>O), 70.2 (CH<sub>2</sub>O), 61.9 (CH<sub>2</sub>O), 50.8 (CH<sub>2</sub>N<sub>3</sub>).
- **MS ESI+:** [M+H]<sup>+</sup> 132.1, [M+Na]<sup>+</sup> 154.1.
- **HRMS:** (ESI<sup>+</sup>-MS, *m/z*) calcd for C<sub>4</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 154.0587, found: 154.0587.

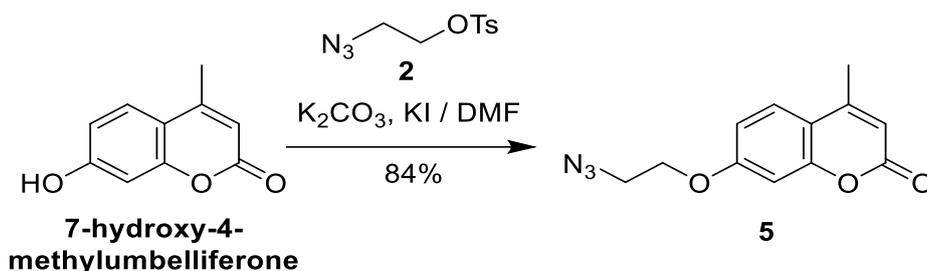
<sup>3</sup> J. Sinha, R. Sahoo, A. Kumar, *Macromolecules* **2009**, *42*, 2015–2022.



**2-(2-azidoethoxy)ethyl 4-methylbenzenesulfonate (4).** To a solution of 2-(2-azidoethoxy)ethan-1-ol (1 g, 7.624 mmol, 1 eq) in dry  $\text{CH}_2\text{Cl}_2$  (30 mL) was added  $\text{Et}_3\text{N}$  (1.359 mL, 11.436 mmol, 1.5 eq) and the mixture was cooled to  $0^\circ\text{C}$ . Then  $p\text{-TsCl}$  (1.74 g, 9.149 mmol, 1.2 eq) was added and this solution stirred under Ar atm. at  $0^\circ\text{C}$  for 1 h. Then it was allowed to warm to room temperature and the reaction mixture was stirred at room temperature under Ar for 16 h. The solution was washed with  $\text{NaHCO}_3$  (3 x 50 mL),  $\text{H}_2\text{O}$  (1 x 50 mL) and brine (1 x 50 mL), dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Cy/EtOAc 95:5) affording the desired linker **4** (1.92, 88%) as a clear oil. The analytical data of **4** were in complete agreement with literature data.<sup>4</sup>

- **Formula:**  $\text{C}_{11}\text{H}_{15}\text{SN}_3\text{O}_4$
- **Mw:** 285.33 g/mol
- **Rf:** 0.70 (Cy/EtOAc 4:6)
- **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.80 (d,  $J$  = 8.4 Hz, 2 H,  $\text{CH}_{\text{Ar}}$ ), 7.34 (d,  $J$  = 8.0 Hz, 2 H,  $\text{CH}_{\text{Ar}}$ ), 4.17 (t,  $J$  = 4.8 Hz, 2 H,  $\text{CH}_2\text{O}$ ), 3.70 (t,  $J$  = 4.4 Hz, 2 H,  $\text{CH}_2\text{O}$ ), 3.60 (t,  $J$  = 4.8 Hz, 2 H,  $\text{CH}_2\text{O}$ ), 3.32 (t,  $J$  = 4.8 Hz, 2 H,  $\text{CH}_2\text{N}$ ), 2.45 (s, 3 H,  $\text{CH}_3$ ).
- **$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 145.1 ( $\text{C-Ar}$ ), 133.0 ( $\text{C-Ar}$ ), 130.0 ( $\text{CH-Ar}$ ), 128.1 ( $\text{CH-Ar}$ ), 70.3 ( $\text{CH}_2\text{O}$ ), 69.3 ( $\text{CH}_2\text{O}$ ), 68.1 ( $\text{CH}_2\text{O}$ ), 50.7 ( $\text{CH}_2\text{N}$ ), 21.8 ( $\text{CH}_3$ ).
- **MS ESI+:**  $[\text{M}+\text{Na}]^+$  308.1,  $[\text{M}+\text{K}]^+$  324.0.
- **HRMS:** (ESI<sup>+</sup>-MS,  $m/z$ ) calcd for  $\text{C}_{11}\text{H}_{15}\text{N}_3\text{NaO}_4\text{S}^+$   $[\text{M}+\text{Na}]^+$ : 308.0675, found: 308.0675.

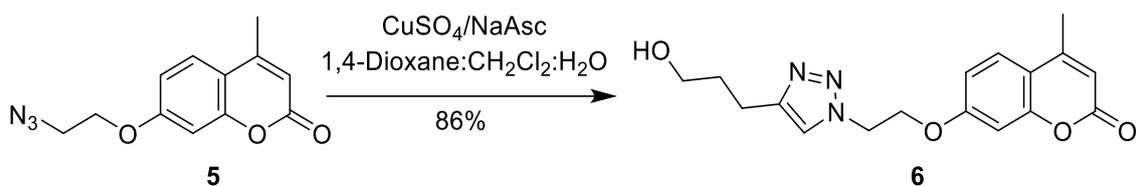
<sup>4</sup> A. Banerjee, S. Maschauer, H. Hübner, P. Gmeiner, O. Prante, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6079–6082.



**7-(2-azidoethoxy)-4-methyl-2H-chromen-2-one (5).** Tosylate **2** (282 mg, 1.168 mmol, 1.1 eq) was dissolved in dry DMF (7 mL) together with 7-hydroxy-4-umbelliferone (187 mg, 1.061 mmol, 1 eq), then  $\text{K}_2\text{CO}_3$  (733 mg, 5.305 mmol, 5 eq) and KI (176 mg, 1.061 mmol, 1 eq) were added and the mixture was stirred at  $60^\circ\text{C}$  under Ar for 6h. The solution was cooled down to  $0^\circ\text{C}$  and quenched with HCl (1 M, 25 mL), extracted with AcOEt (25 mL x 3) and the organic layer was washed with water (50 mL), dried over  $\text{MgSO}_4$  and evaporated to dryness. The crude was purified by column chromatography (Cy/EtOAc 8:2) to afford **5** (229 mg, 84%) as a white powder. The analytical data of **5** were in complete agreement with literature data.<sup>5</sup>

- **Formula:**  $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_3$
- **Mw:** 245.24 g/mol
- **R<sub>f</sub>:** 0.68 (Cy/EtOAc 4:6)
- **ATR-IR:** 2924 (C-H), 2104 ( $\text{N}_3$ ), 1716 (C=O), 1613 (C=C), 1266 (O-CO)  $\text{cm}^{-1}$
- **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.51 (d,  $J$  = 8.8 Hz, 1H,  $\text{CH}_{Ar}$ ), 6.89 (dd,  $J$  = 2.4 Hz,  $J$  = 8.4 Hz, 1H,  $\text{CH}_{Ar}$ ), 6.82 (d,  $J$  = 2.4 Hz, 1H,  $\text{CH}_{Ar}$ ), 6.14 (d,  $J$  = 1.2 Hz, 1H, CH), 4.20 (t,  $J$  = 4.8 Hz, 2H,  $\text{CH}_2\text{O}$ ), 3.65 (t,  $J$  = 5.2 Hz, 2H,  $\text{CH}_2\text{N}_3$ ), 2.40 (s, 3H,  $\text{CH}_3$ ).
- **$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 161.3 (CO,  $\text{C}_{Ar}$ ), 155.3 (C), 152.6 (C), 125.9 ( $\text{C}_{Ar}$ ), 114.2 ( $\text{C}_{Ar}$ ), 112.8 ( $\text{C}_{Ar}$ ), 112.4 (CH), 101.6 ( $\text{C}_{Ar}$ ), 67.5 ( $\text{CH}_2\text{O}$ ), 50.0 ( $\text{CH}_2\text{N}_3$ ), 18.8 ( $\text{CH}_3$ ).

<sup>5</sup> Y.-C. Duan, Y.-C. Ma, E. Zhang, X.-J. Shi, M.-M. Wang, X.-W. Ye, H.-M. Liu, *Eur. J. Med. Chem.* **2013**, 62, 11–19.

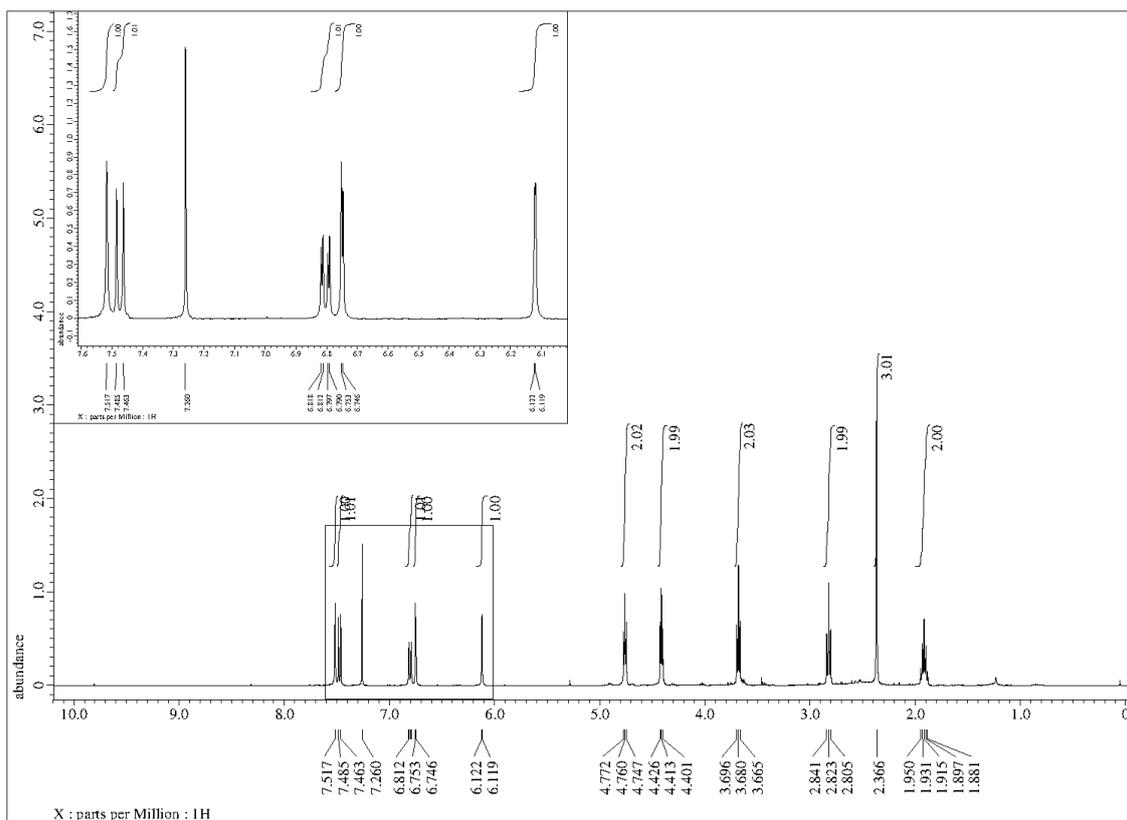


**7-(2-(4-(3-hydroxypropyl)-1H-1,2,3-triazol-1-yl)ethoxy)-4-methyl-2H-chromen-2-one**

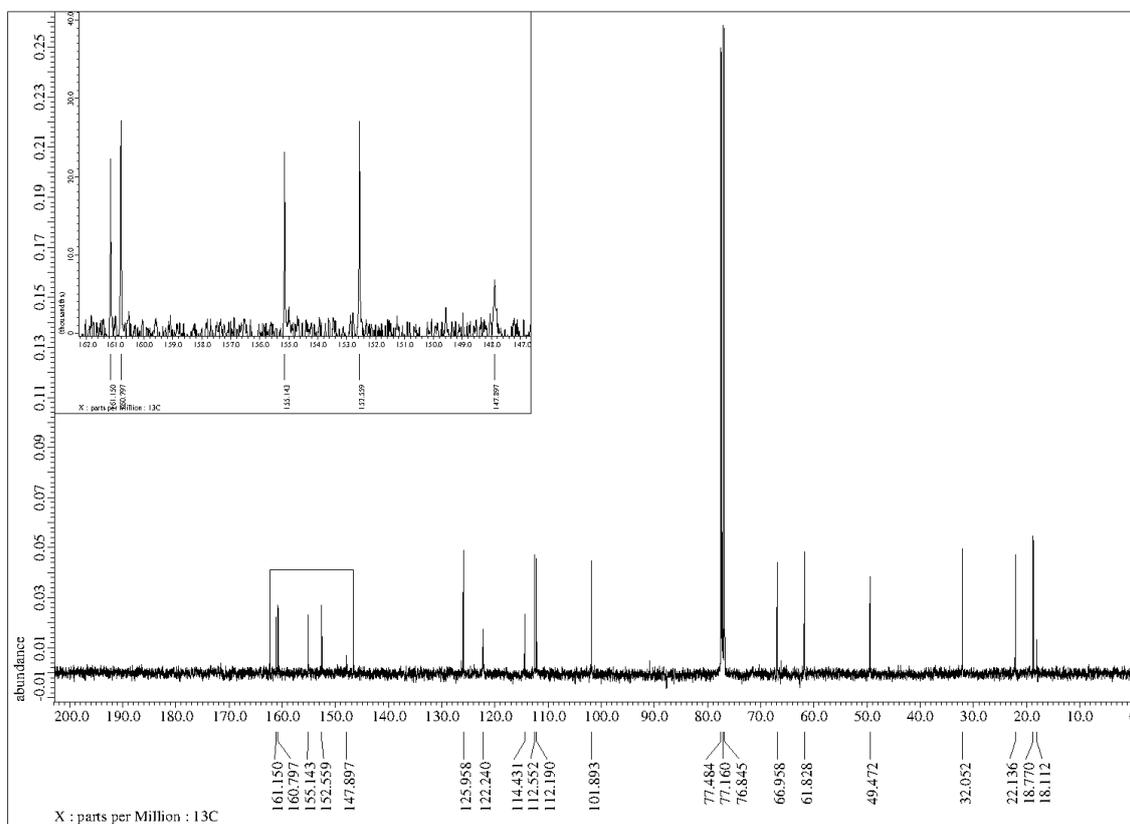
(**6**). Azide **5** (50 mg, 0.204 mmol, 1.2 eq) and 4-pentyn-1-ol (14.3 mg, 0.170 mmol, 1 eq) were dissolved in 1, 4-dioxane (0.3 mL) and CH<sub>2</sub>Cl<sub>2</sub> (0.3 mL), then CuSO<sub>4</sub> (2.7 mg, 0.017 mmol, 0.1 eq) and NaAsc (9.7 mg, 0.051 mmol, 0.3 eq) were added in H<sub>2</sub>O (0.1 mL) and the mixture was stirred at 60°C under Ar for 5h. The solution was cooled down to room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and washed with H<sub>2</sub>O (2 x 10 mL). The organic layers were combined, dried over MgSO<sub>4</sub> and evaporated to dryness. The crude was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5) to afford **6** (48 mg, 86%) as a yellow powder.

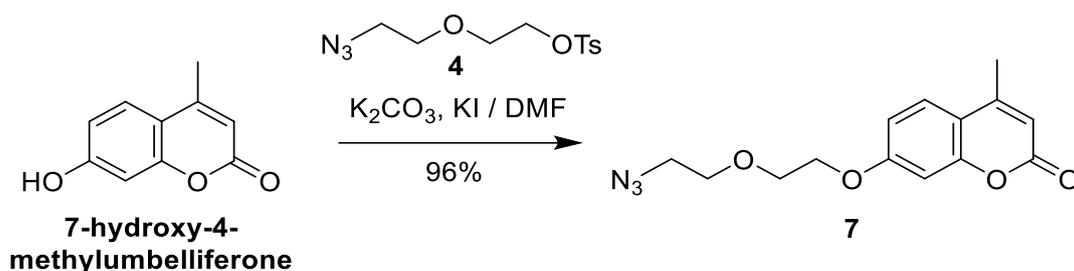
- **Formula:** C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>
- **Mw:** 329.36 g/mol
- **R<sub>f</sub>:** 0.53 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1)
- **ATR-IR:** 3323 (O-H), 2943 (C-H), 1718 (C=O), 1617 (C=C), 1294 (O-C=O) cm<sup>-1</sup>
- **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 7.52 (s, 1H, CH<sub>triazole</sub>), 7.47 (d, *J* = 8.8 Hz, 1H, CH<sub>Ar</sub>), 6.80 (dd, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H, CH<sub>Ar</sub>), 6.75 (d, *J* = 2.8 Hz, 1H, CH<sub>Ar</sub>), 6.12 (d, *J* = 1.2 Hz, 1H, CH), 4.76 (t, *J* = 4.8 Hz, 2H, CH<sub>2</sub>N), 4.41 (t, *J* = 5.2 Hz, 2H, CH<sub>2</sub>O), 3.68 (t, *J* = 6.4 Hz, 2H, CH<sub>2</sub>OH), 2.82 (t, *J* = 7.2 Hz, 2H, CH<sub>2</sub>C), 2.37 (s, 3H, CH<sub>3</sub>), 1.92 (dt, *J* = 6.4 Hz, 2H, CH<sub>2</sub>).
- **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ = 161.2, 160.8 (CO, C<sub>Ar</sub>), 155.3 (C), 152.6 (C), 147.9 (C<sub>triazole</sub>), 126.0 (C<sub>Ar</sub>), 122.2 (CH<sub>triazole</sub>), 114.4 (C<sub>Ar</sub>), 112.6 (C<sub>Ar</sub>), 112.2 (CH), 101.9 (C<sub>Ar</sub>), 67.0 (CH<sub>2</sub>O), 61.8 (CH<sub>2</sub>OH), 49.5 (CH<sub>2</sub> N<sub>3</sub>), 32.1 (CH<sub>2</sub>), 22.1 (CH<sub>2</sub>C), 18.8 (CH<sub>3</sub>).
- **HRMS:** (ESI<sup>+</sup>-MS, m/z) calcd for C<sub>17</sub>H<sub>20</sub>N<sub>3</sub>O<sub>4</sub><sup>+</sup> [M+H]<sup>+</sup>: 330.1448, found: 330.1448.

# <sup>1</sup>H NMR



# <sup>13</sup>C NMR

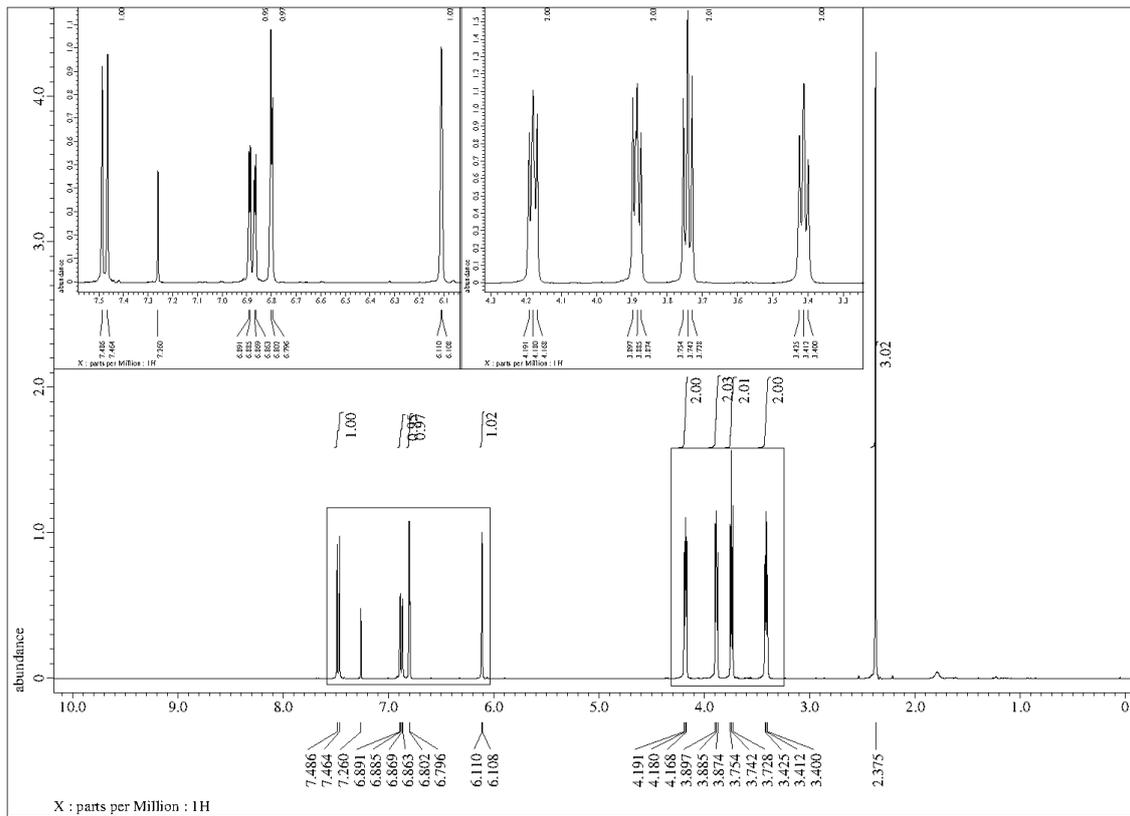




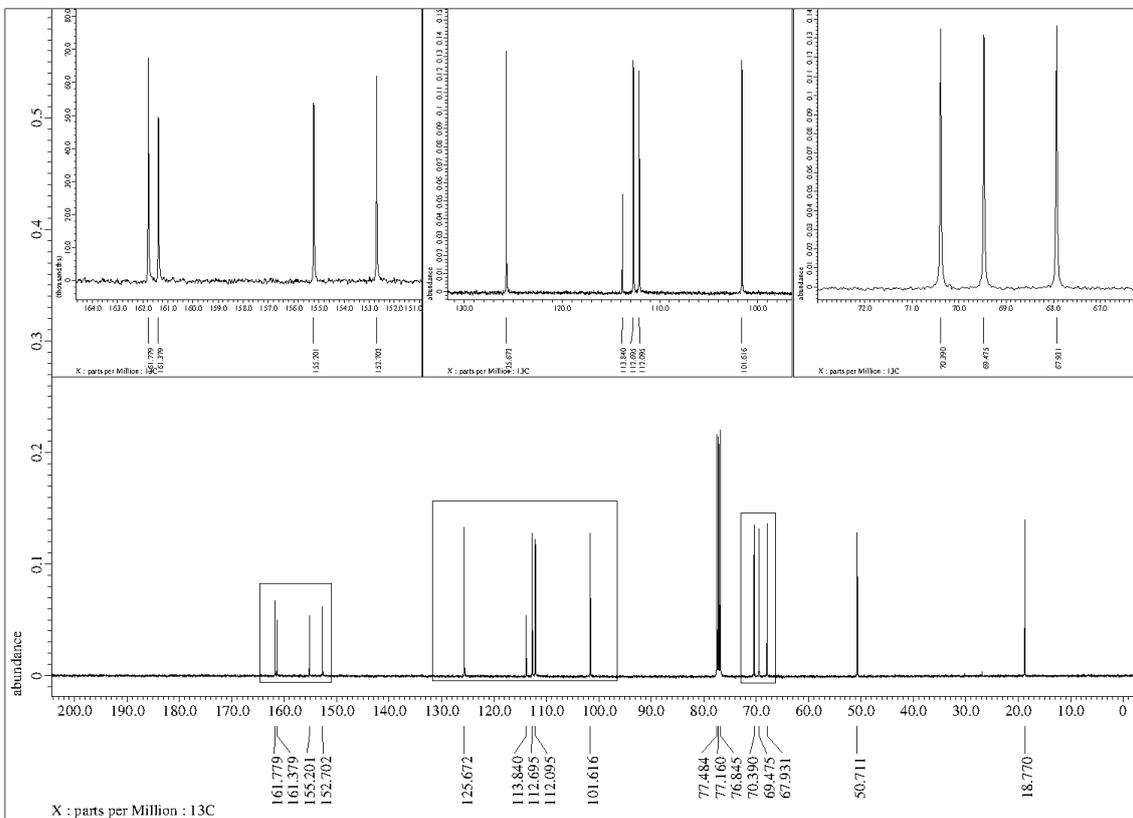
**7-(2-(2-azidoethoxy)ethoxy)-4-methyl-2H-chromen-2-one (7).** Tosylate **4** (650 mg, 2.278 mmol, 1.1 eq) was dissolved in dry DMF (7 mL) together with 7-hydroxy-4-umbelliferone (365 mg, 2.071 mmol, 1 eq), then  $\text{K}_2\text{CO}_3$  (1.43 g, 10.355 mmol, 5 eq) and KI (344 mg, 2.071 mmol, 1 eq) were added and the mixture was stirred at 60°C under Ar for 6 h. The solution was cooled down to 0°C and quenched with HCl (1 M, 50 mL), extracted with EtOAc (50 mL x 3) and the organic layer was washed with water (50 mL), dried over  $\text{MgSO}_4$  and evaporated to dryness. The crude was purified by column chromatography (Cy/EtOAc 8:2) to afford **7** (573 mg, 96%) as a light yellow powder.

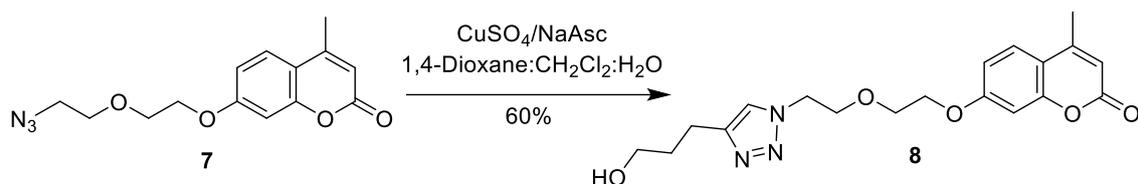
- **Formula:**  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_4$
- **Mw:** 289.29 g/mol
- **R<sub>f</sub>:** 0.67 (Cy/EtOAc 4:6)
- **ATR-IR:** 2901 (C-H), 2117 ( $\text{N}_3$ ), 1719 (C=O), 1608 (C=C), 1281 (O-CO)  $\text{cm}^{-1}$
- **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.47 (d,  $J$  = 8.8 Hz, 1H,  $\text{CH}_{Ar}$ ), 6.87 (dd,  $J$  = 2.4 Hz,  $J$  = 8.8 Hz, 1H,  $\text{CH}_{Ar}$ ), 6.80 (d,  $J$  = 2.4 Hz, 1H,  $\text{CH}_{Ar}$ ), 6.11 (d,  $J$  = 0.8 Hz, 1H, CH), 4.18 (t,  $J$  = 4.8 Hz, 2H,  $\text{CH}_2\text{O}$ ), 3.89 (t,  $J$  = 4.8 Hz, 2H,  $\text{CH}_2\text{O}$ ), 3.74 (t,  $J$  = 4.8 Hz, 2H,  $\text{CH}_2\text{O}$ ), 3.41 (t,  $J$  = 5.2 Hz, 2H,  $\text{CH}_2\text{N}_3$ ), 2.38 (s, 3H,  $\text{CH}_3$ ).
- **<sup>13</sup>C NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 161.8 (CO), 161.4 ( $\text{C}_{Ar}$ ), 155.2 (C), 152.7 (C), 125.7 ( $\text{C}_{Ar}$ ), 113.8 ( $\text{C}_{Ar}$ ), 112.7 ( $\text{C}_{Ar}$ ), 112.1 (CH), 101.6 ( $\text{C}_{Ar}$ ), 70.4 ( $\text{CH}_2\text{O}$ ), 69.5 ( $\text{CH}_2\text{O}$ ), 67.9 ( $\text{CH}_2\text{O}$ ), 50.7 ( $\text{CH}_2\text{N}_3$ ), 18.8 ( $\text{CH}_3$ ).
- **MS ESI+:**  $[\text{M}+\text{H}]^+$  290.1,  $[\text{M}+\text{Na}]^+$  312.1.
- **HRMS:** (ESI<sup>+</sup>-MS,  $m/z$ ) calcd for  $\text{C}_{14}\text{H}_{16}\text{N}_3\text{O}_4^+$   $[\text{M}+\text{H}]^+$ : 290.1135, found: 290.1138.

# <sup>1</sup>H NMR



# <sup>13</sup>C NMR

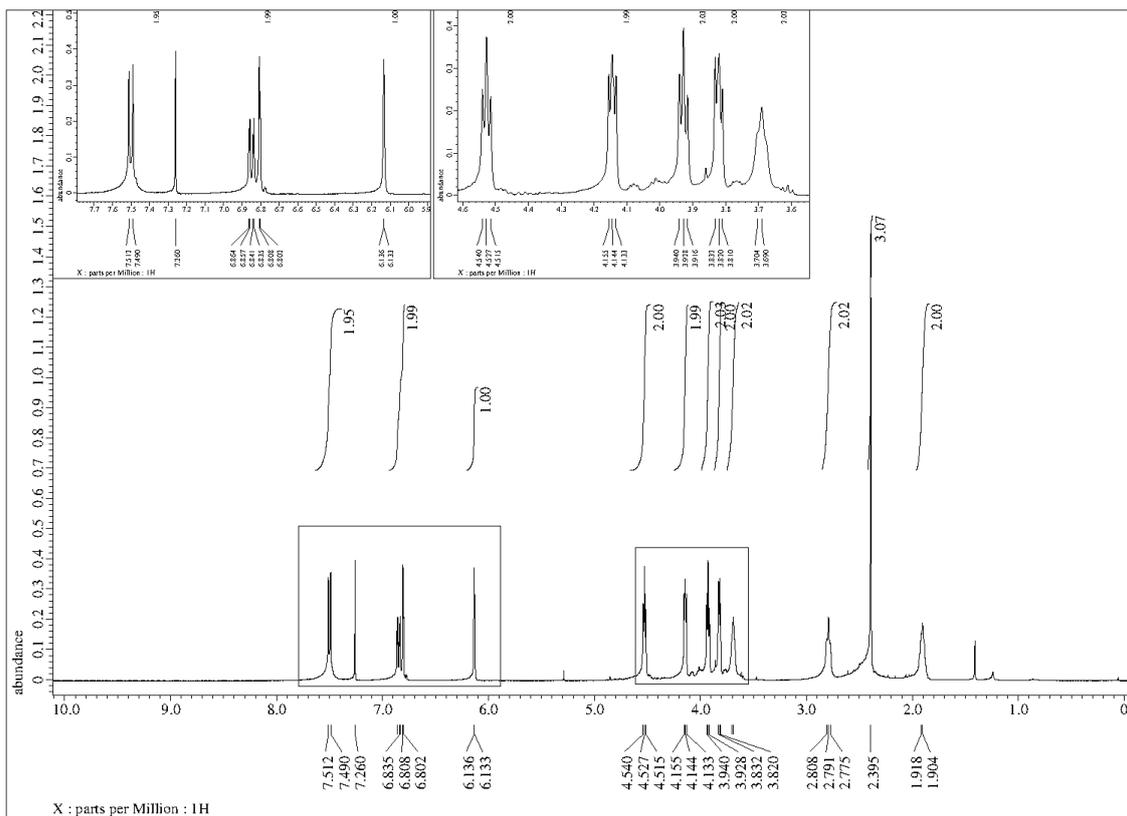




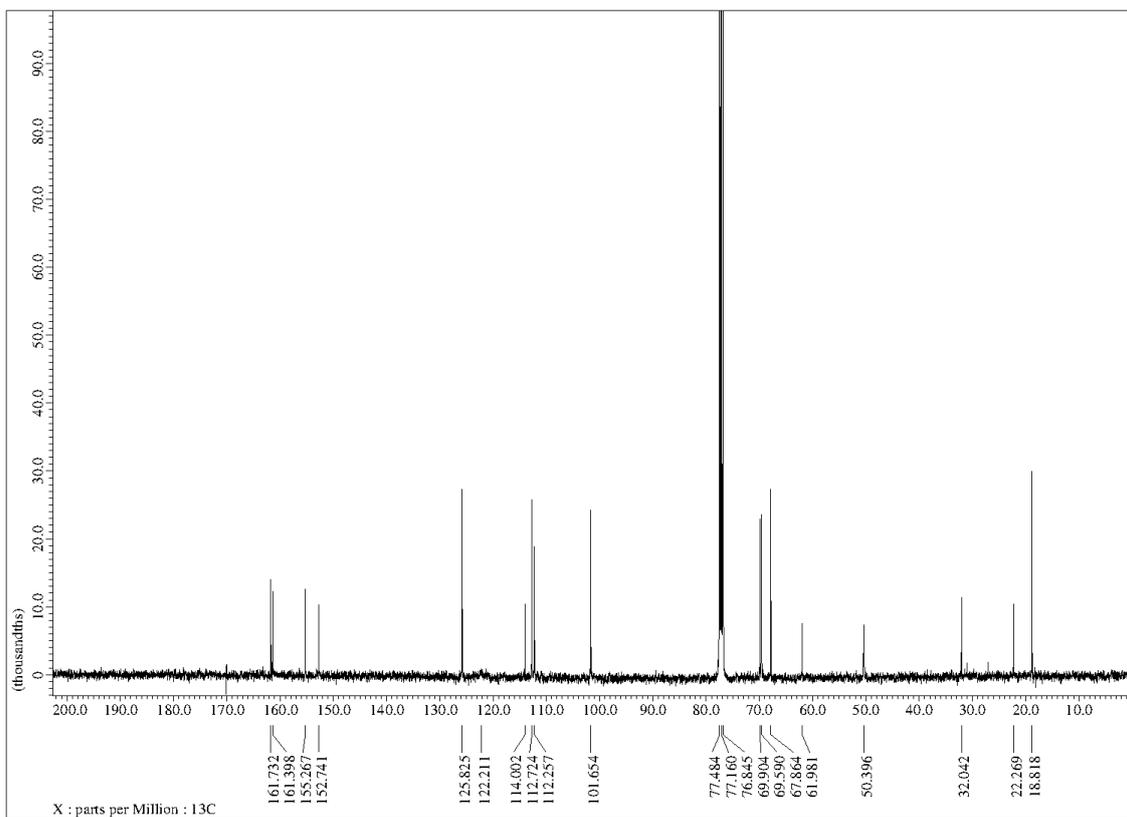
**7-(2-(2-(4-(3-hydroxypropyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)-4-methyl-2H-chromen-2-one (8).** Azide **7** (50 mg, 0.173 mmol, 1.2 eq) and 4-pentyn-1-ol (12.1 mg, 0.144 mmol, 1 eq) were dissolved in 1, 4-dioxane (0.3 mL) and CH<sub>2</sub>Cl<sub>2</sub> (0.3 mL), then CuSO<sub>4</sub> (2.3 mg, 0.014 mmol, 0.1 eq) and NaAsc (8.2 mg, 0.043 mmol, 0.3 eq) were added in H<sub>2</sub>O (0.1 mL) and the mixture was stirred at 60°C under Ar for 5 h. The solution was cooled down to room temperature, diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and washed with H<sub>2</sub>O (2 x 10 mL). The organic layers were combined, dried over MgSO<sub>4</sub> and evaporated to dryness. The crude was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5) to afford **8** (39 mg, 60%) as a white powder.

- **Formula:** C<sub>19</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub>
- **Mw:** 373.41 g/mol
- **R<sub>f</sub>:** 0.51 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1)
- **ATR-IR:** 3386 (O-H), 2949 (C-H), 1711 (C=O), 1611 (C=C) cm<sup>-1</sup>
- **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 7.50 (m, 3H, CH<sub>Ar</sub>, CH<sub>triazole</sub>), 6.86 (dd, *J* = 2.8 Hz, *J* = 8.8 Hz, 1H, CH<sub>Ar</sub>), 6.80 (d, *J* = 2.4 Hz, 1H, CH<sub>Ar</sub>), 6.13 (d, *J* = 1.2 Hz, 1H, CH), 4.53 (t, *J* = 4.8 Hz, 2H, CH<sub>2</sub>N), 4.14 (t, *J* = 4.4 Hz, 2H, CH<sub>2</sub>O), 3.93 (t, *J* = 4.8 Hz, 2H, CH<sub>2</sub>O), 3.82 (t, *J* = 4.8 Hz, 2H, CH<sub>2</sub>O), 3.69 (t, *J* = 4.8 Hz, 2H, CH<sub>2</sub>OH), 2.79 (t, *J* = 6.8 Hz, 2H, CH<sub>2</sub>C), 2.40 (s, 3H, CH<sub>3</sub>), 1.90 (t, *J* = 5.6 Hz, 2H, CH<sub>2</sub>).
- **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ = 161.7 (CO), 161.4 (C<sub>Ar</sub>), 155.3 (C), 152.7 (C), 147.9 (C<sub>triazole</sub>), 125.8 (C<sub>Ar</sub>), 122.2 (CH<sub>triazole</sub>), 114.0 (C<sub>Ar</sub>), 112.7 (C<sub>Ar</sub>), 112.2 (CH), 101.6 (C<sub>Ar</sub>), 69.9 (CH<sub>2</sub>O), 69.6 (CH<sub>2</sub>O), 67.9 (CH<sub>2</sub>O), 62.0 (CH<sub>2</sub>OH), 50.4 (CH<sub>2</sub>N), 32.0 (CH<sub>2</sub>), 22.3 (CH<sub>2</sub>C), 18.8 (CH<sub>3</sub>).
- **HRMS:** (ESI<sup>+</sup>-MS, *m/z*) calcd for C<sub>19</sub>H<sub>24</sub>N<sub>3</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup>: 374.1710, found: 374.1710.

# <sup>1</sup>H NMR

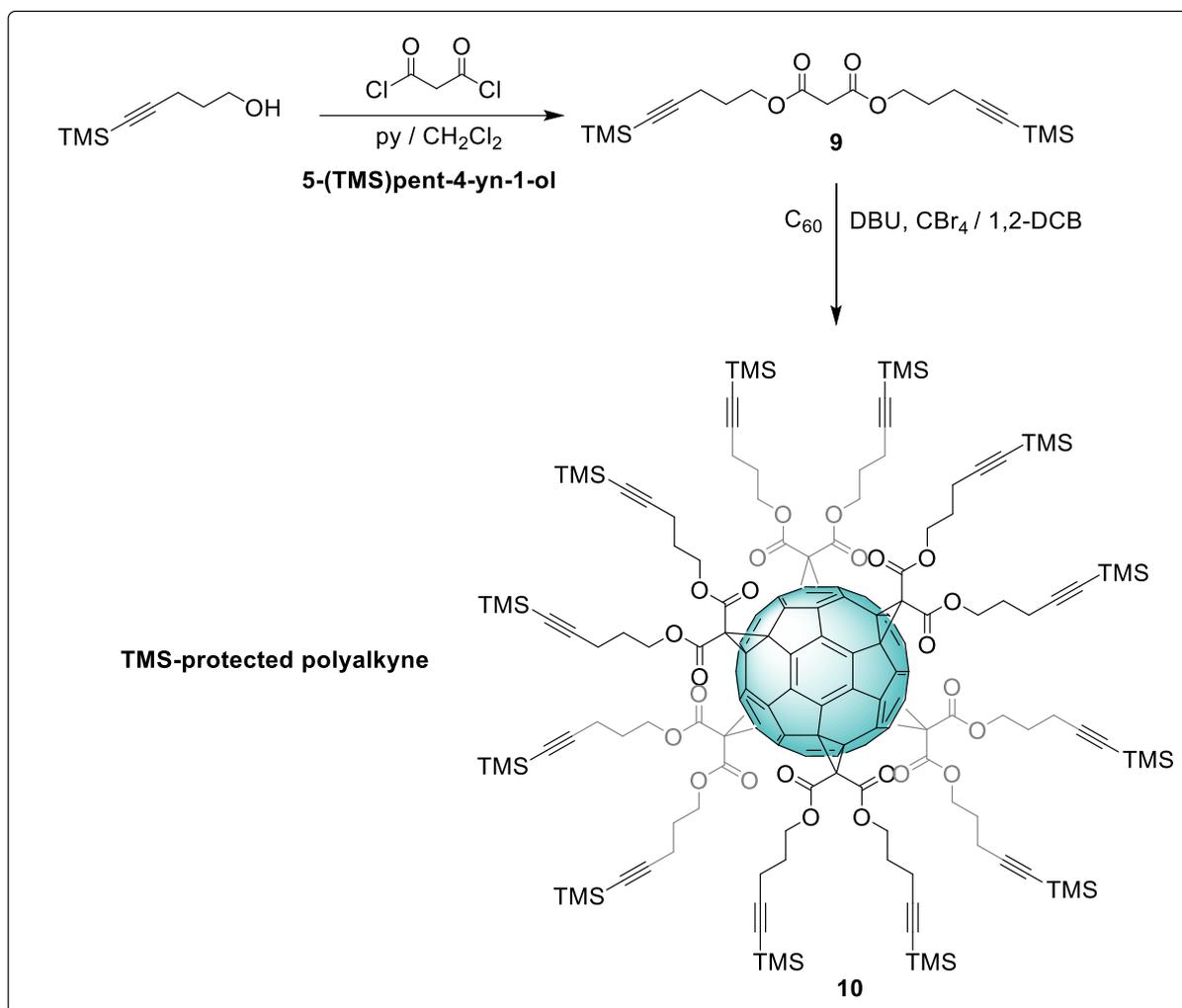


# <sup>13</sup>C NMR

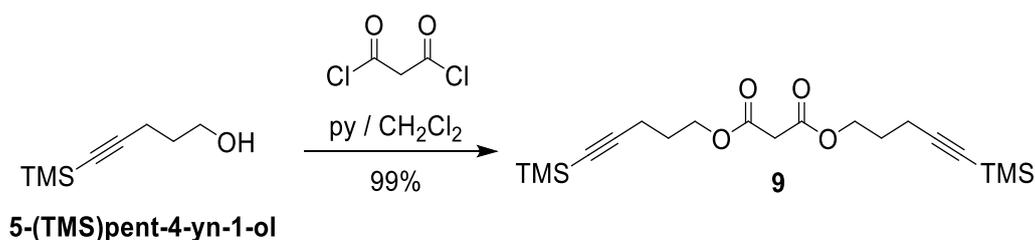


## 2. Synthesis of the multivalent compounds

### 2.1. Synthesis of TMS-protected polyalkyne scaffold



**Scheme 2.** Synthesis of the trimethylsilyl-protected Polyalkyne **10**

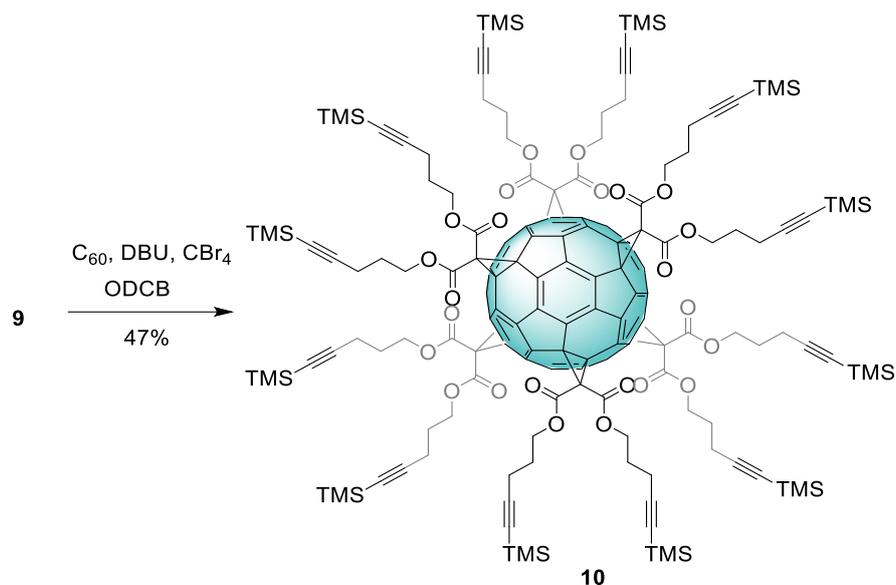


**Bis(5-(trimethylsilyl)pent-4-yn-1-yl) malonate (9).** 5-(trimethylsilyl)pent-4-yn-1-ol (5 g, 32.0 mmol, 2.3 eq) and pyridine (2.58 mL, 32.0 mmol, 2.3 eq) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (75 mL) and malonyl dichloride (1.35 mL, 13.9 mmol) was added to this solution at 0°C under Ar. The mixture was stirred for 1 h and then was allowed to warm to room temperature and stirred for 18 h, filtered through SiO<sub>2</sub> pad and evaporated. Column chromatography (Cy/EtOAc 8:2) gave **9** (5.24 g, 99%) as a colourless oil. The analytical data of **9** were in complete agreement with literature data.<sup>6</sup>

- **Formula:** C<sub>19</sub>H<sub>32</sub>O<sub>4</sub>Si<sub>2</sub>
- **Mw:** 380.58 g/mol
- **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 4.15 (t, *J* = 6.4 Hz, 4H, CH<sub>2</sub>O), 3.29 (s, 2H, CH<sub>2</sub>), 2.23 (t, *J* = 7.2 Hz, 4H, CH<sub>2</sub>C), 1.77 (dt, *J* = 6.8 Hz, 4H, CH<sub>2</sub>), 0.05 (s, 18H, CH<sub>3</sub>).
- **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ = 166.3 (CO), 105.4 (C-Si), 85.3 (C≡C-Si), 64.0 (OCH<sub>2</sub>), 41.4 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 16.4 (CH<sub>2</sub>C≡C), 0.0 (CH<sub>3</sub>).

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<sup>6</sup> J.-F. Nierengarten and J. Iehl, *Chem. Eur. J.* **2009**, *15*, 7306–7309.

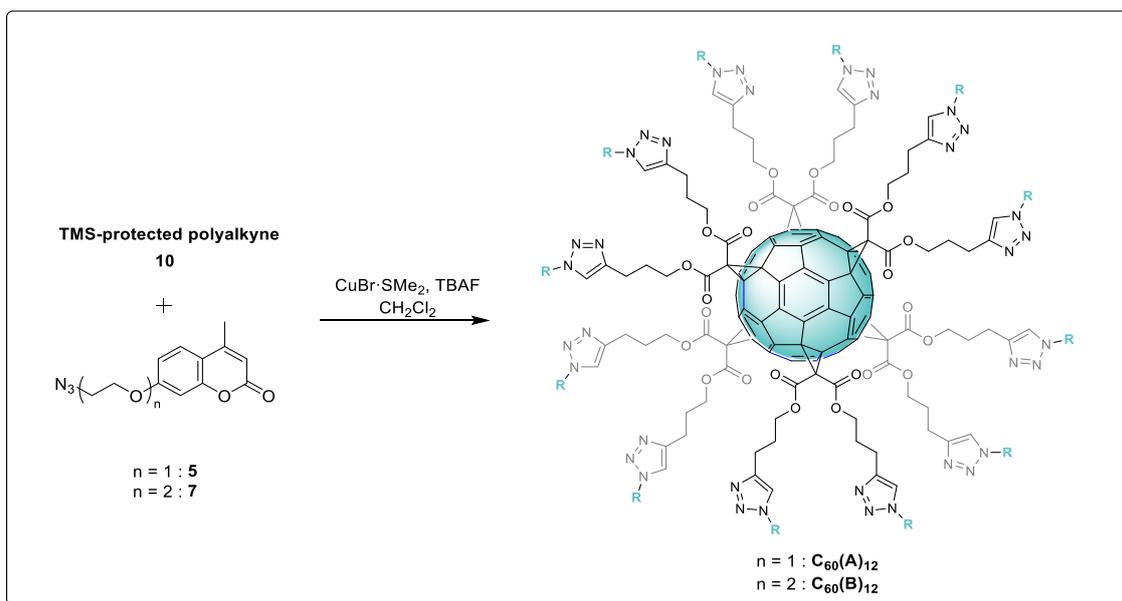


**Trimethylsilyl-protected polyalkyne (10).** Fullerene  $C_{60}$  (0.60 g, 0.833 mmol, 1 eq) was dissolved in 1,2-dichlorobenzene (160 mL) and  $CBr_4$  (27.61 g, 83.26 mmol, 100 eq), **9** (3.17 g, 8.326 mmol, 10 eq), and DBU (1.58 mL, 10.51 mmol) were added successively. The mixture was stirred for 72 h at room temperature and concentrated. Column chromatography (Cy/ $CH_2Cl_2$  3:7) gave **10** (1.44 g, 47%) as an orange glassy product. The analytical data of **10** were in complete agreement with literature data.<sup>7</sup>

- **Formula:**  $C_{174}H_{180}O_{24}Si_{12}$
- **Mw:** 2992.30 g/mol
- **$^1H$  NMR** (400 MHz,  $CDCl_3$ )  $\delta$  = 4.20 (t,  $J$  = 6.4 Hz, 24H,  $CH_2O$ ), 2.32 (t,  $J$  = 6.8 Hz, 24H,  $CH_2C$ ), 1.85 (dt,  $J$  = 6.8 Hz, 24H,  $CH_2$ ), 0.11 (s, 108H,  $CH_3$ ).
- **$^{13}C$  NMR** (100 MHz,  $CDCl_3$ )  $\delta$  = 163.6 (CO), 145.9 ( $C_{sp^2}$ ), 141.1 ( $C_{sp^2}$ ), 105.1 (C-Si), 85.7 ( $C\equiv C-Si$ ), 69.1, 65.6 ( $OCH_2$ ), 45.2 ( $CH_2$ ), 27.5 ( $CH_2$ ), 16.5 ( $CH_2C\equiv C$ ), 0.1 ( $CH_3$ ).

<sup>7</sup> J.-F. Nierengarten and J. Iehl, *Chem. Eur. J.* **2009**, *15*, 7306–7309.

## 2.2. CuAAC between C<sub>60</sub> hexakis-adducts and monovalent compounds



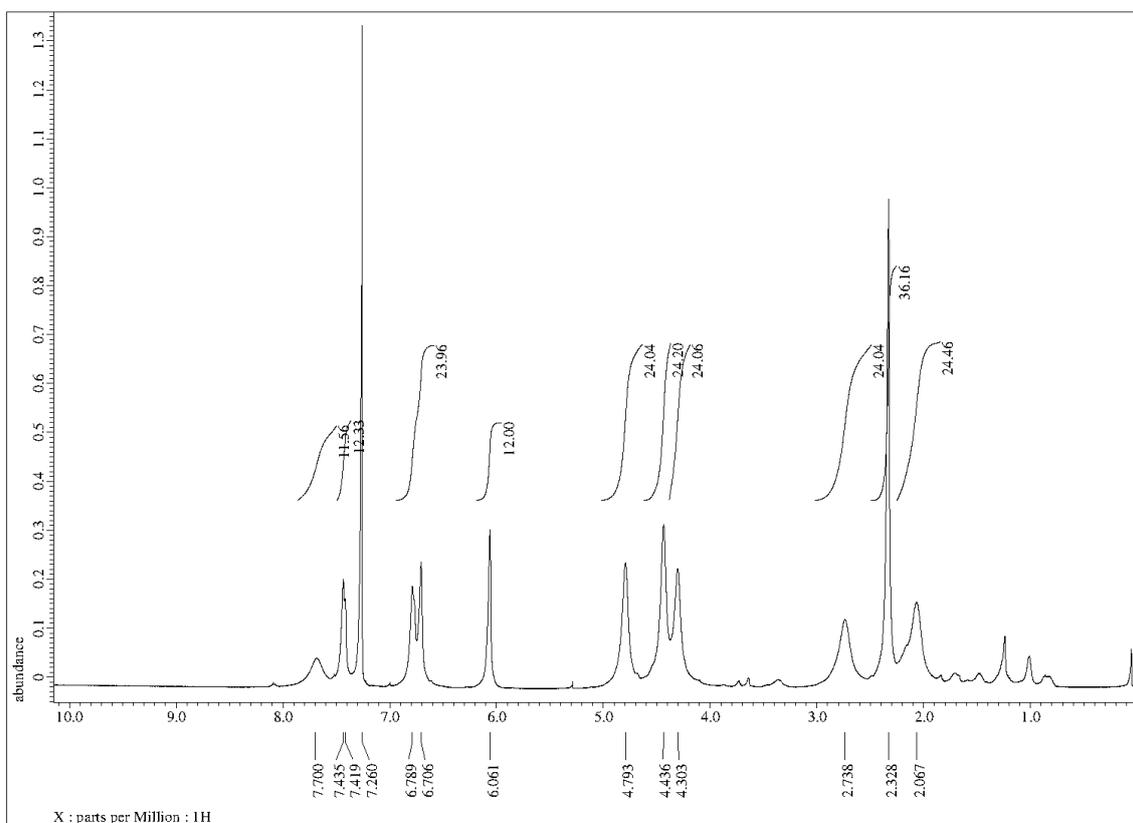
**Scheme 3.** Click chemistry on trimethylsilyl-protected Polyalkyne **10**.

**General procedure for the click reaction.** TMS-protected polyalkyne **10** (40 mg, 0.0134 mmol, 1 eq) and the azide (15 eq) were dissolved in 0.2 mL of CH<sub>2</sub>Cl<sub>2</sub>. TBAF 1M in THF (0.20 mL, 0.2005 mmol, 15 eq) was added and then CuBr·SMe<sub>2</sub> (2.75 mg, 0.0134 mmol, 1 eq). The reaction mixture was stirred at room temperature under Ar for 20h and was diluted in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and washed with H<sub>2</sub>O (5 mL x 3). The organic layer was dried over MgSO<sub>4</sub> and the solvent evaporated under vacuum. Purification of the crude by column chromatography (CH<sub>2</sub>Cl<sub>2</sub> to CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) followed by size exclusion chromatography on Sephadex-LH20 (CH<sub>2</sub>Cl<sub>2</sub>) provided the compounds as glassy orange powders (C<sub>60</sub>(A)<sub>12</sub>: 49%, C<sub>60</sub>(B)<sub>12</sub>: 88%).

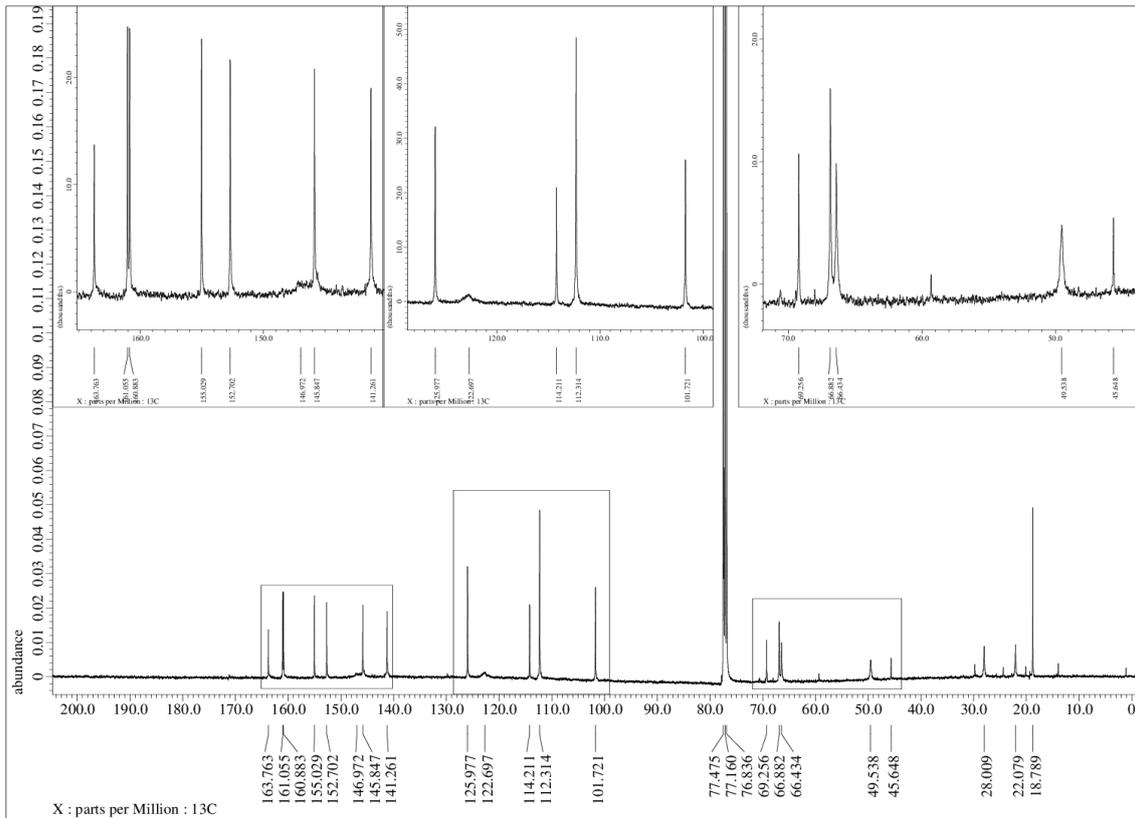
## Fullerene C<sub>60</sub>(A)<sub>12</sub>

- **Formula:** C<sub>282</sub>H<sub>216</sub>N<sub>36</sub>O<sub>60</sub>, **Mw:** 5068.94 g/mol
- **ATR-IR:** 2957 (C-H), 1713 (C=O), 1612 (C=C) cm<sup>-1</sup>
- **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 7.65 (s, 12H, CH<sub>triazole</sub>), 7.42 (bs, 12H, CH<sub>Ar</sub>), 6.78 (bs, 12H, CH<sub>Ar</sub>), 6.70 (bs, 12H, CH<sub>Ar</sub>), 6.07 (bs, 12H, CH), 4.77 (bs, 24H, CH<sub>2</sub>N), 4.42 (bs, 24H, CH<sub>2</sub>O), 4.29 (bs, 24H, CH<sub>2</sub>O), 2.73 (bs, 24H, CH<sub>2</sub>C), 2.32 (s, 36H, CH<sub>3</sub>), 2.02 (m, 24H, CH<sub>2</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ = 163.8 (CO), 161.1 (CO), 160.9 (C<sub>Ar</sub>), 155.0 (C), 152.7 (C), 147.0 (C<sub>triazole</sub>), 145.8 (C<sub>sp2</sub>), 141.3 (C<sub>sp2</sub>), 126.0 (C<sub>Ar</sub>), 122.7 (CH<sub>triazole</sub>), 114.2 (C<sub>Ar</sub>), 112.3 (C<sub>Ar</sub>), 112.3 (CH), 101.7 (C<sub>Ar</sub>), 69.3 (C<sub>C60</sub>), 66.9 (CH<sub>2</sub>O), 66.4 (CH<sub>2</sub>O), 49.5 (CH<sub>2</sub>N), 45.6 (C), 28.0 (CH<sub>2</sub>), 22.1 (CH<sub>2</sub>C), 18.8 (CH<sub>3</sub>).
- **MS ESI+:** [M+3Na]<sup>+</sup> 1712.5, [M+4Na]<sup>+</sup> 1289.9, [M+6Na]<sup>+</sup> 877.6. **HRMS:** (ESI<sup>+</sup>-MS, m/z) calcd for C<sub>282</sub>H<sub>216</sub>N<sub>36</sub>O<sub>60</sub>Na<sub>3</sub><sup>+</sup> [M+4Na]<sup>+</sup> 1289.8636, found: 1289.8638.

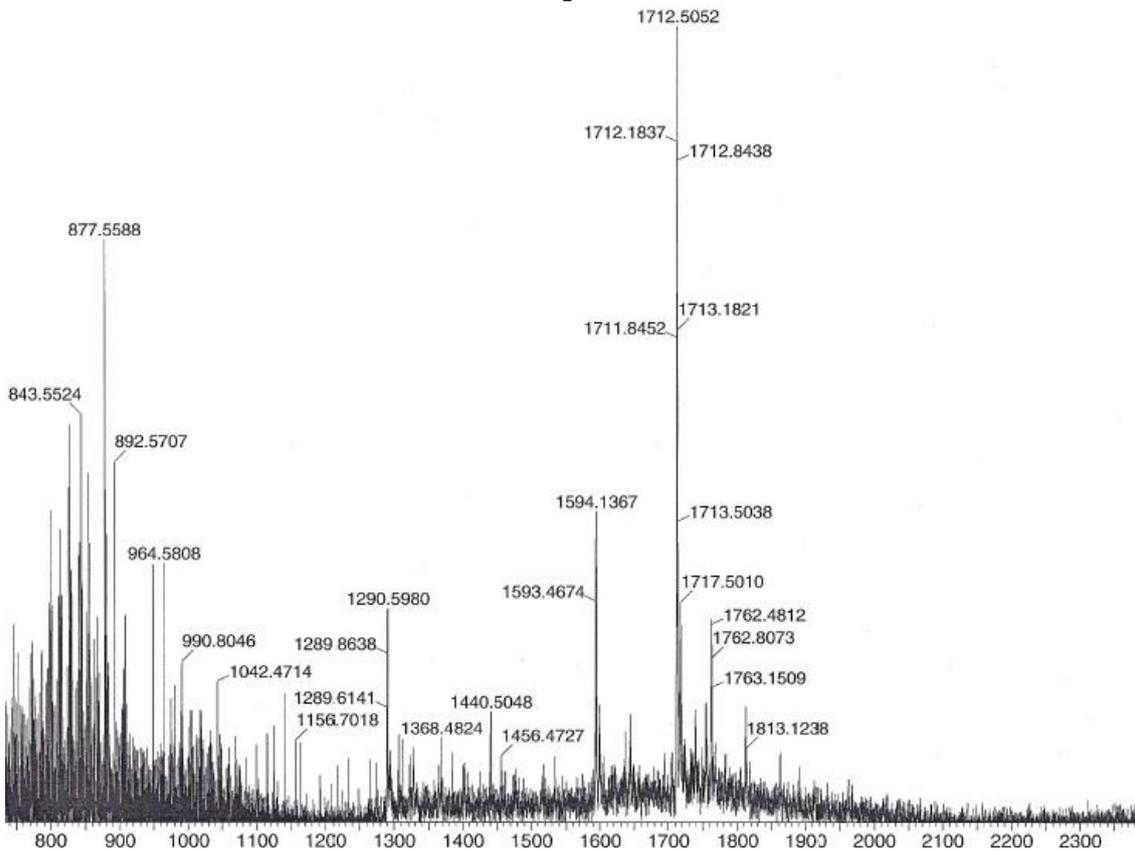
### <sup>1</sup>H NMR



# <sup>13</sup>C NMR



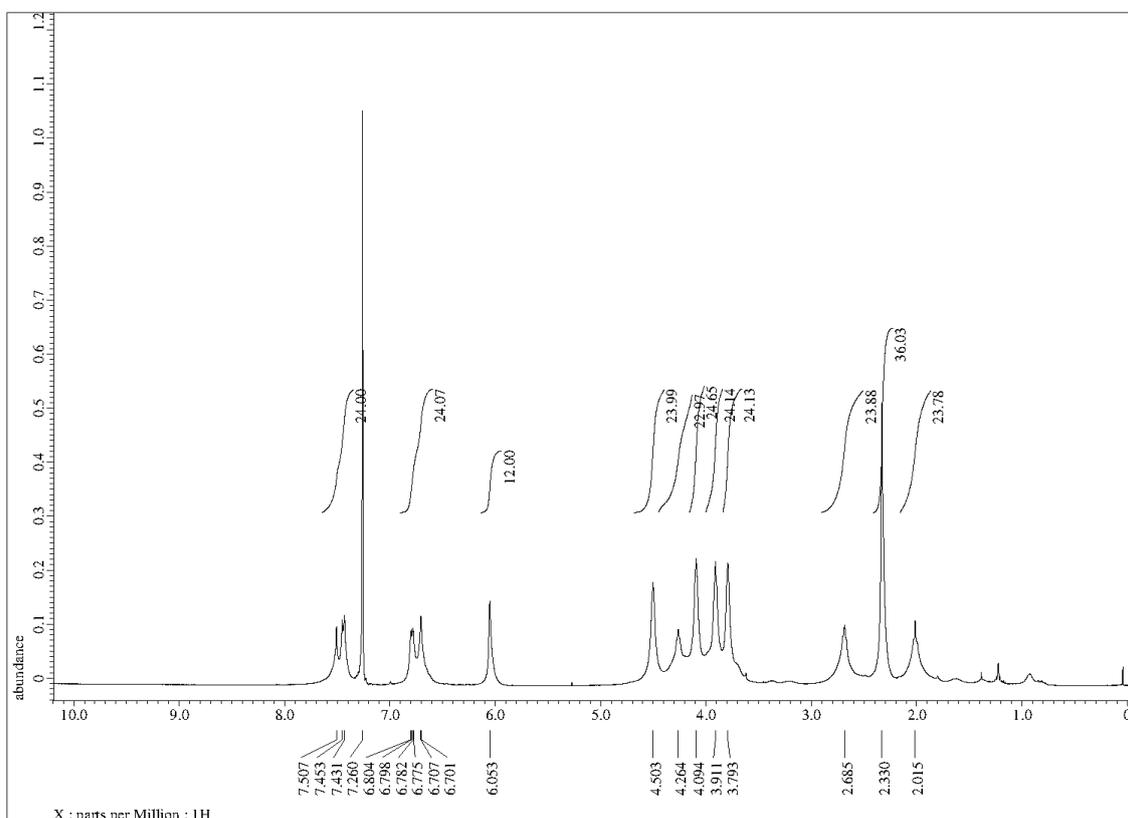
# Mass Spectrum



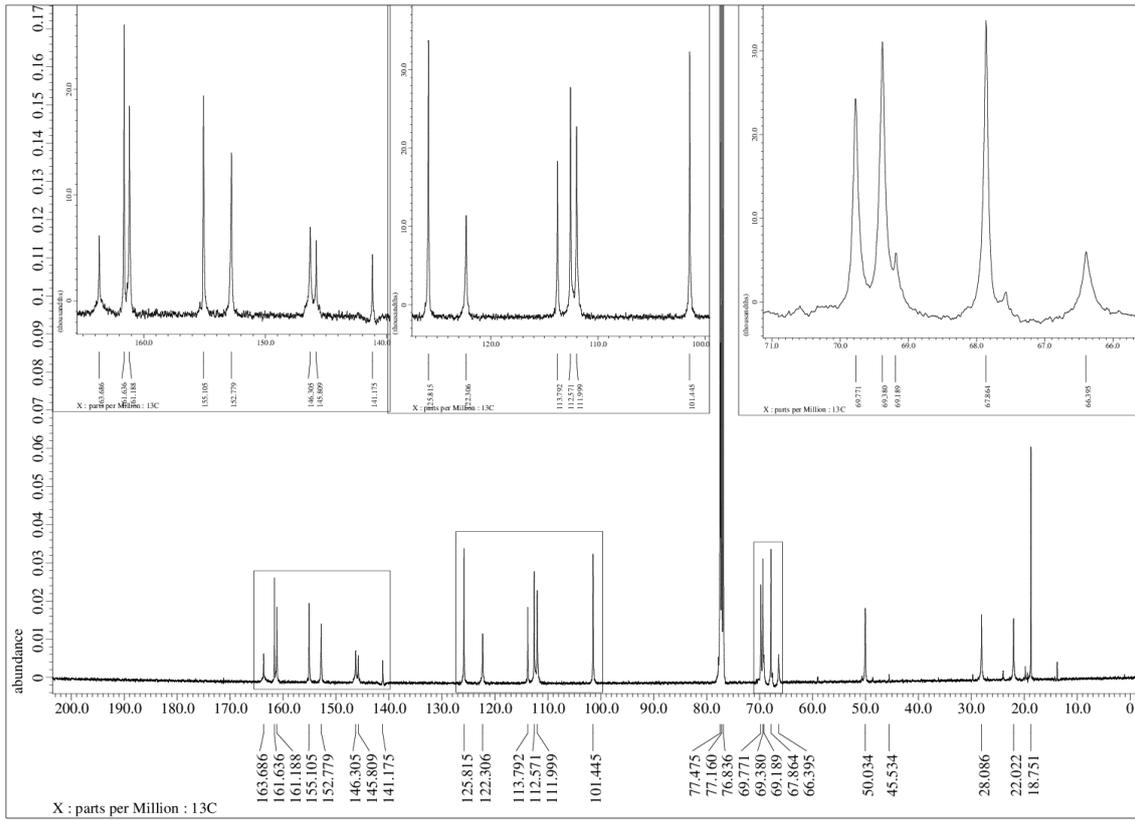
## Fullerene C<sub>60</sub>(B)<sub>12</sub>

- **Formula:** C<sub>306</sub>H<sub>264</sub>N<sub>36</sub>O<sub>72</sub>, **Mw:** 5597.57 g/mol
- **ATR-IR:** 2924 (C-H), 1713 (C=O), 1611 (C=C) cm<sup>-1</sup>
- **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 7.51 (s, 12H, CH<sub>triazole</sub>), 7.44 (d, J = 8.8 Hz, 12H, CH<sub>Ar</sub>), 6.80 (dd, J = 2.4 Hz, J = 8.8 Hz, 12H, CH<sub>Ar</sub>), 6.70 (d, J = 2.4 Hz, 12H, CH<sub>Ar</sub>), 6.05 (bs, 12H, CH), 4.50 (bs, 24H, CH<sub>2</sub>N), 4.26 (bs, 24H, CH<sub>2</sub>O), 4.09 (bs, 24H, CH<sub>2</sub>O), 3.91 (bs, 24H, CH<sub>2</sub>O), 3.79 (bs, 24H, CH<sub>2</sub>O), 2.69 (bs, 24H, CH<sub>2</sub>C), 2.33 (s, 36H, CH<sub>3</sub>), 2.02 (m, 24H, CH<sub>2</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ = 163.7 (CO), 161.6 (CO), 161.2 (C<sub>Ar</sub>), 155.1 (C), 152.8 (C), 146.3 (C<sub>triazole</sub>), 145.8 (C<sub>sp2</sub>), 141.2 (C<sub>sp2</sub>), 125.8 (C<sub>Ar</sub>), 122.3 (CH<sub>triazole</sub>), 113.8 (C<sub>Ar</sub>), 112.6 (C<sub>Ar</sub>), 112.0 (CH), 101.4 (C<sub>Ar</sub>), 69.8 (CH<sub>2</sub>O), 69.4 (CH<sub>2</sub>O), 69.2 (C<sub>C60</sub>), 67.9 (CH<sub>2</sub>O), 66.4 (CH<sub>2</sub>O), 50.0 (CH<sub>2</sub>N), 45.5 (C), 28.1 (CH<sub>2</sub>), 22.0 (CH<sub>2</sub>C), 18.8 (CH<sub>3</sub>).
- **MS ESI+:** [M+Na+2H]<sup>+3</sup> 1873.6, [M+2Na+H]<sup>+3</sup> 1881.2, [M+3Na]<sup>+3</sup> 1888.6, [M+4Na-H]<sup>+3</sup> 1893.9, [M+3K]<sup>+3</sup> 1902.2. **HRMS:** (ESI<sup>+</sup>-MS, m/z) calcd for C<sub>306</sub>H<sub>264</sub>N<sub>36</sub>O<sub>72</sub>Na<sub>3</sub><sup>+3</sup> [M+3Na]<sup>+3</sup> 1888.5958, found: 1888.5730.

### <sup>1</sup>H NMR



# <sup>13</sup>C NMR



# Mass Spectrum

