Electronic Supplementary Material (ESI) for Polymer Chemistry.

Electronic Supplementary Information

Hyaluronan-Coated Polybenzofulvene Brushes as Biomimetic Materials

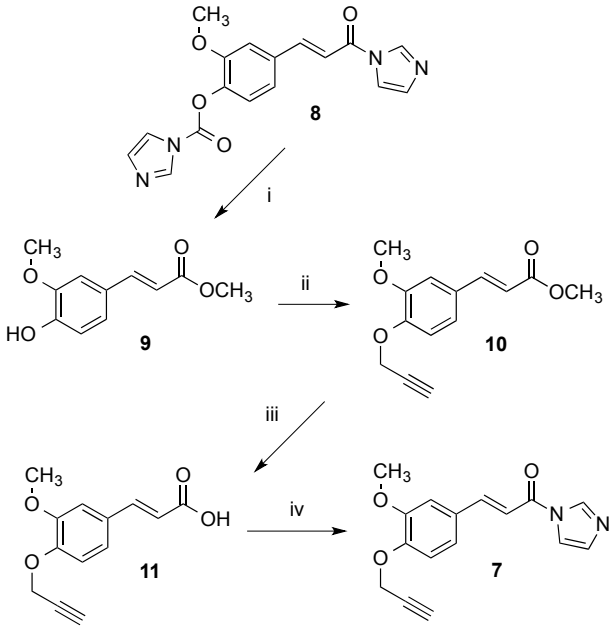
Andrea Cappelli,[*,a] Marco Paolino,[a] Giorgio Grisci,[a] Vincenzo Razzano,[a] Germano Giuliani,[a] Alessandro Donati,[a] Claudia Bonechi,[a] Raniero Mendichi,[b] Salvatore Battiato,[c] Filippo Samperi,[c] Cinzia Scialabba,[d] Gaetano Giammona,[d] Francesco Makovec,[e] Mariano Licciardi.[d]

Content:

Chemistry

The preparation of imidazolide intermediate **7** was carried out by the multistep sequence shown in Scheme ESI-1.

Scheme ESI-1. Synthesis of imidazolide intermediate **7**.



Reagents: (i) CH_3OH, TEA; (ii) $BrCH_2CCH$, K_2CO_3, NaI, DMF; (iii) NaOH, C_2H_5OH, H_2O; (iv) CDI, THF.

Imidazolide derivative **8**[1] was easily converted in methyl ferulate **9**[2] by reaction with methanol in presence of TEA as the base. Phenol group of **9** was alkylated with propargyl bromide in the presence of potassium carbonate as the base and sodium iodide as the catalyst in DMF to obtain propargyloxy derivative **10**,[3] which was promptly hydrolyzed in basic conditions to afford ferulic acid derivative **11**.[4] The activation of **11** with one equivalent of 1,1'-carbonyldiimidazole (CDI) in THF gave imidazolide **7**.

Synthetic procedures

***Methods*.** Melting points were determined in open capillaries in a Gallenkamp apparatus and are uncorrected. Merck silica gel 60 (230-400 mesh) was used for column chromatography. Merck TLC aluminum sheets, silica gel 60 F_{254} were used for TLC. NMR spectra were recorded with a Bruker DRX-400 AVANCE or a Bruker DRX-500 AVANCE spectrometer in the indicated solvents (TMS as internal standard): the values of the chemical shifts are expressed in ppm and the coupling constants (*J*) in Hz. An Agilent 1100 LC/MSD operating with an electrospray source was used in mass spectrometry experiments.

(*E*)-Methyl 3-(4-hydroxy-3-methoxyphenyl)acrylate (9).

To a mixture of compound **8**[1] (4.5 g, 13.3 mmol) in methanol (130 mL), TEA (7.4 mL, 53.1 mmol) was added and the resulting yellow solution was stirred overnight at room temperature in an inert atmosphere. The reaction mixture was then partitioned between a saturated solution of ammonium chloride and dichloromethane. The organic layer was dried over sodium sulfate and concentred under reduced pressure to obtain compound **9**[2] as a pale yellow oil (2.7 g, yield 98%). ^{1}H NMR (400 MHz, $CDCl_3$): 3.78 (s, 3H), 3.89 (s, 3H), 5.82 (br s, 1H), 6.27 (d, *J* = 15.9, 1H), 6.90 (d, *J* = 8.2, 1H), 7.00 (d, *J* = 1.9, 1H), 7.04 (dd, *J* = 8.1, 2.0, 1H), 7.60 (d, *J* = 15.9, 1H). MS (ESI, negative ions): m/z 207 (M - H^+).

(*E*)-Methyl 3-[3-methoxy-4-(prop-2-ynyloxy)phenyl]acrylate (10).

A mixture of compound **9** (1.8 g, 8.65 mmol), K_2CO_3 (3.6 g, 26.0 mmol) and NaI (2.0 g, 13.3 mmol) in DMF (15 mL) was stirred at room temperature for 15 minutes, and then propargyl bromide (0.86 mL, 9.6 mmol) was added. After stirring overnight at room temperature under an argon atmosphere, the reaction mixture was treated with a saturated solution of NH_4Cl and extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain compound **10**[3] as an off-white solid (2.1 g, yield 99%). An

analytical sample was obtained by recrystallization from methanol by slow evaporation (mp 128-129 °C). ^{1}H NMR (500 MHz, $CDCl_3$): 2.52 (t, *J* = 2.4, 1H), 3.79 (s, 3H), 3.89 (s, 3H), 4.79 (d, *J* = 2.4, 2H), 6.32 (d, *J* = 15.9, 1H), 7.01 (d, *J* = 8.3, 1H), 7.05 (d, *J* = 2.0, 1H), 7.09 (dd, *J* = 8.3, 2.0, 1H), 7.62 (d, *J* = 15.9, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 51.7, 55.9, 56.6, 76.3, 78.0, 110.2, 113.6, 116.1, 122.1, 128.5, 144.6, 148.7, 149.7, 167.6. MS (ESI): *m/z* 269 ($M + Na^+$).

(*E*)-3-[3-Methoxy-4-(prop-2-ynyloxy)phenyl]acrylic acid (11).

A mixture of ester derivative **10** (2.16 g, 8.77 mmol) in ethanol (40 mL) containing a 2N water solution of NaOH (25 mL) was refluxed for 1.5 h under a nitrogen atmosphere. Then, the reaction mixture was cooled at 0 °C and 3N HCl was added dropwise to obtain a white precipitate. The precipitate was collected by filtration and dried under reduced pressure to obtain **11**[4] as a white solid (1.3 g, yield 64%). An analytical sample was obtained by recrystallization from dichloromethane by slow evaporation (mp 196-197 °C). ^{1}H NMR (400 MHz, $CDCl_3$): 2.53 (t, *J* = 2.4, 1H), 3.91 (s, 3H), 4.80 (d, *J* = 2.4, 2H), 6.33 (d, *J* = 15.9, 1H), 7.04 (d, *J* = 8.3, 1H), 7.08 (d, *J* = 2.0, 1H), 7.13 (dd, *J* = 8.3, 2.0, 1H), 7.72 (d, *J* = 15.9, 1H). MS (ESI, negative ions): m/z 231 ($M-H^+$).

(*E*)-1-(1*H*-Imidazol-1-yl-3-[3-methoxy-4-(prop-2-ynyloxy)phenyl]prop-2-en-1-one (7).

A mixture of acid **11** (0.22 g, 0.947 mmol) in dry THF (5.0 mL) containing CDI (0.15 g, 0.93 mmol) was refluxed for 3 h and then concentrated under reduced pressure. Purification of the residue by flash chromatography with dichloromethane-ethyl acetate (2:1) gave **7** as a white solid (0.23 g, yield 86%, mp 146-148 °C). ^{1}H NMR (400 MHz, $CDCl_3$): 2.55 (t, *J* = 2.4, 1H), 3.95 (s, 3H), 4.83 (d, *J* = 2.4, 2H), 6.93 (d, *J* = 15.3, 1H), 7.08 (d, *J* = 8.3, 1H), 7.15 (d, *J* = 2.1, 1H), 7.16 (s, 1H), 7.22-7.30 (m, 1H), 7.63 (s, 1H), 8.01 (d, *J* = 15.3, 1H), 8.34 (s, 1H). MS (ESI): m/z 305 ($M + Na^+$).

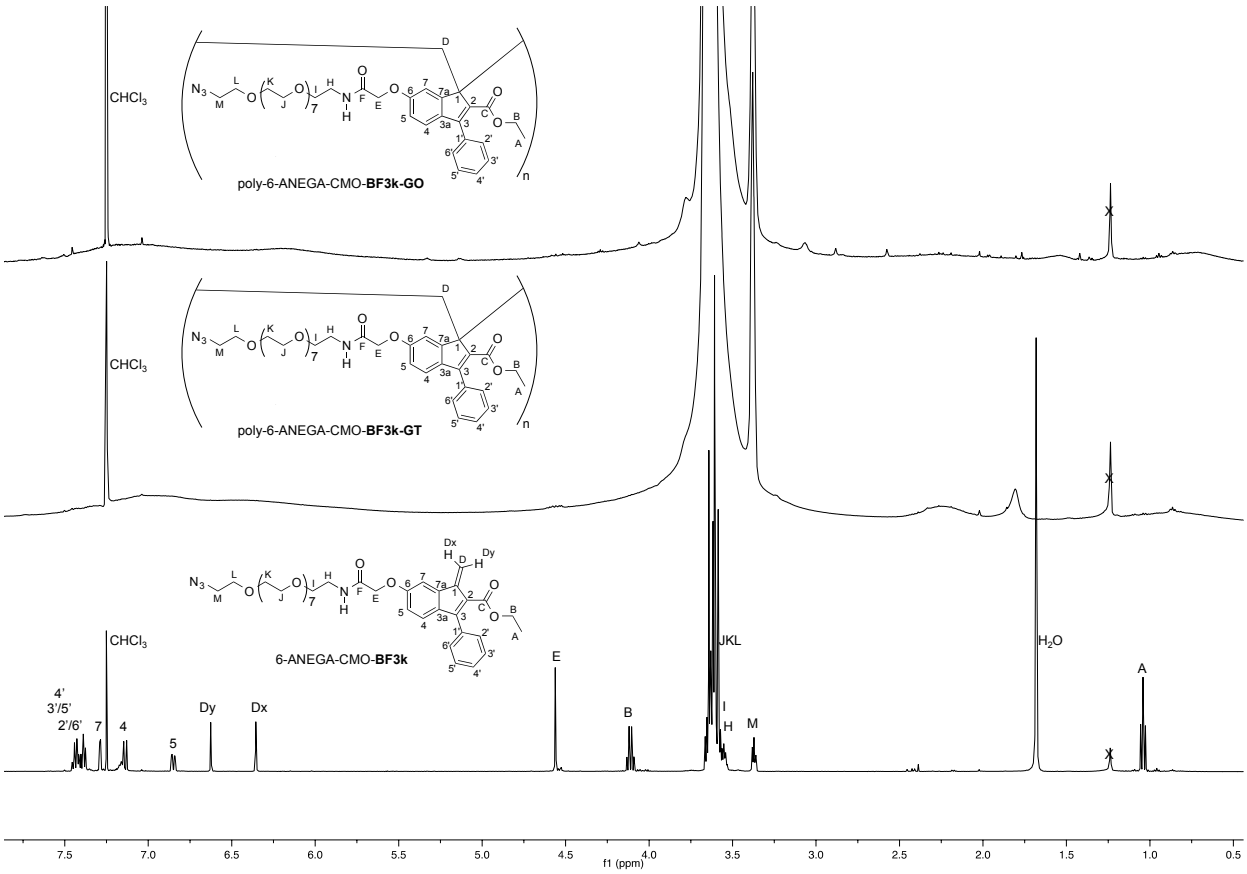


Figure ESI-1. ^{1}H NMR spectra ($CDCl_3$) of newly-synthesized poly-6-ANEGA-CMO-**BF3k-GT** and poly-6-ANEGA-CMO-**BF3k-GO** compared with that of macromonomer 6-ANEGA-CMO-**BF3k**.

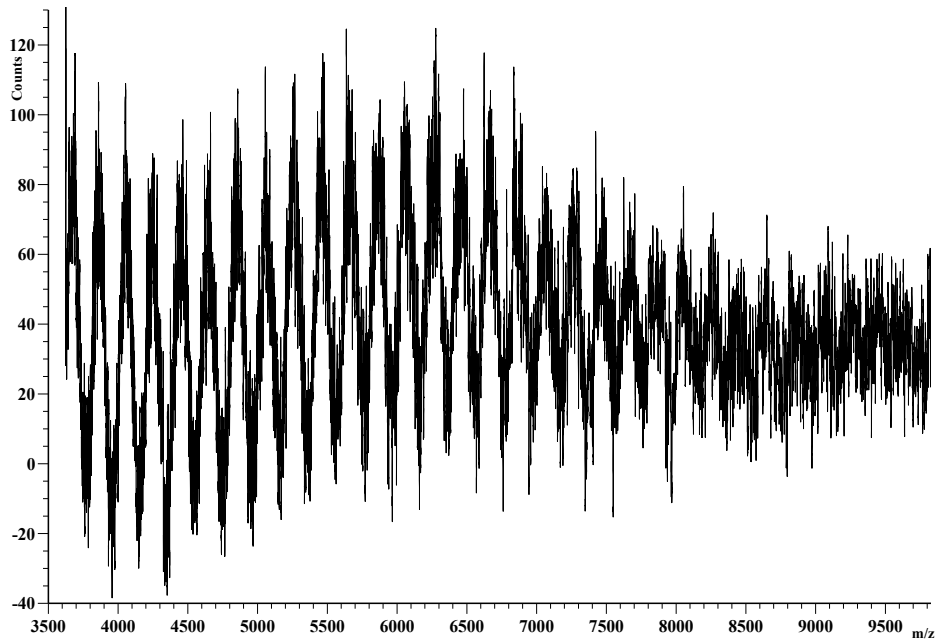


Figure ESI-2. MALDI-TOF mass spectrum (negative-ion mode) of **HA-FA-Pg**.

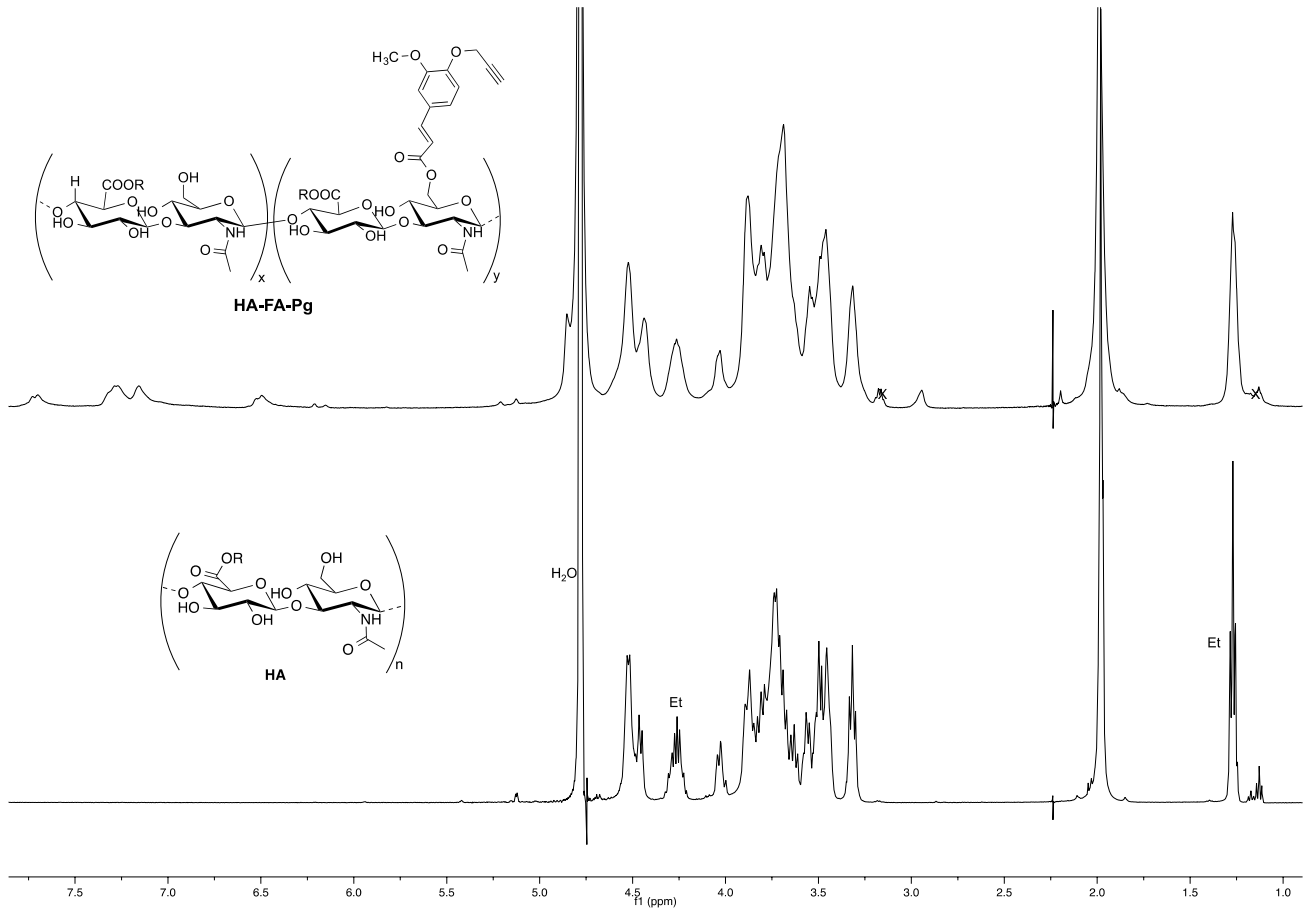


Figure ESI-3. ^{1}H NMR spectrum (D_2O) of **HA-FA-Pg** compared with that of starting low weight **HA** (D_2O). In the spectrum of **HA**, Et labels indicate the signals of ethyl groups of the monomeric units showing R = C_2H_5.

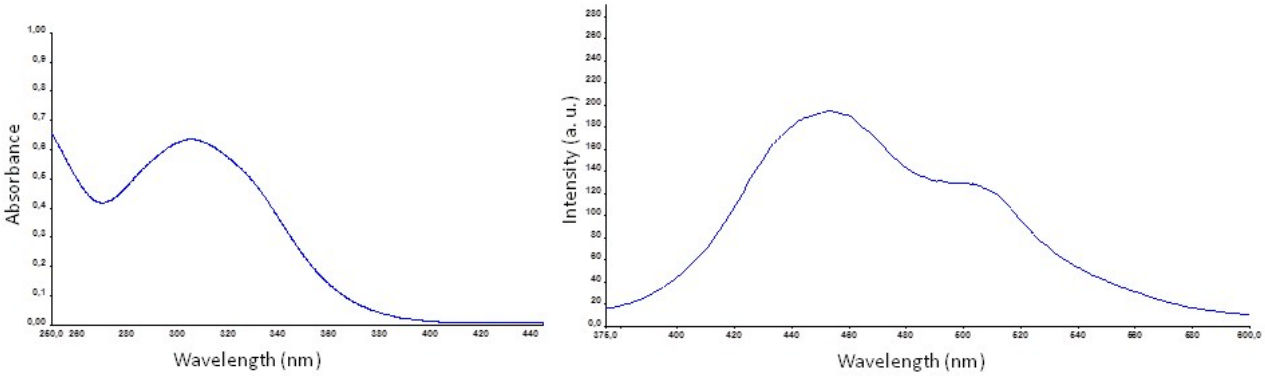


Figure ESI-4. Absorption (left panel) and emission (right panel) spectra of **TCPB** in water. The concentrations were about 100 μg/mL for the absorption spectrum and about 1 μg/mL for the emission spectrum.

References

(1) Cappelli, A.; Grisci, G.; Paolino, M.; Giuliani, G.; Donati, A.; Mendichi, R.; Artusi, R.; Demiranda, M.; Zanardi, A.; Giorgi G.; Vomero, S. Hyaloronan derivatives bearing variable densities of ferulic acid residues. *J. Mater. Chem. B*, **2014**, *2*, 4489-4499.

(2) Putt, K. S.; Nesterenko, V.; Dothager, R. S.; Hergenrother, P. J. The compound 13-D selectively induces apoptosis in white blood cancer versus other cancer cell types. *ChemBioChem*, **2006**, *7*, 1916-1922.

(3) Cai, M.; Hu, J.; Tian, J.-L.; Yan, H.; Zheng, C.-G.; Hu, W.-L. Novel hybrids from *N*-hydroxyarylamide and indole ring through click chemistry as histone deacetylase inhibitors with potent antitumor activities. *Chinese Chem. Lett*. **2015**, *26*, 675-680.

(4) Irfan, M.; Aneja, B.; Yadava, U.; Khan, S. I.; Manzoor, N.; Daniliuc, C. G.; Abid, M. Synthesis, QSAR and anticandidal evaluation of 1,2,3-triazoles derived from naturally bioactive scaffolds. *Eur. J. Med. Chem.* **2015**, *93*, 246-254.