

Synthesis and Biological Evaluation of Fentanyl Acrylic Derivatives

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Materials and Methods:

N-Phenyl-*N*-piperidin-4-yl-propionamide was purchased from Astatech Inc., 4-bromophenethyl bromide, *N,N*-diisopropylethylamine, *N,N'*-dimethylethylenediamine, sodium azide, sodium ascorbate, tris(2-pyridylmethyl)amine (TPMA), butyl acrylate, *tert*-butyl acrylate, 3-dimethylamino-1-propyne, 3-butyne-1-ol, poly(ethylene glycol) methyl ether acrylate (average M_n 480), palladium acetate, and ethylenebis(diphenylphosphine) were purchased from Sigma-Aldrich. Copper(II) bromide was purchased from Fisher Scientific. All other reagents were purchased from Aldrich and were used without further purification. Forskolin, IBMX, and Ro-20-1724 were purchased from Sigma. CHO cells expressing the Human mu Opioid Receptor were purchased from ChanTest Corporation and cultured according to manufactures instructions. cAMP assay was purchased from Promega and used according to manufactures instructions. Hot plate was purchased from IITC Life Sciences. Polar surface area (PSA), cLogP, and molecular weight were determined using ChemDraw Ultra. ^1H and ^{13}C NMR was measured in CDCl_3 or $\text{DMSO}-d_6$ on a Bruker Avance 500 MHz spectrometer. HPLC spectra were collected using an 1260 Infinity Isocratic Pump with an ZirChrom®-PBD column (50 mm x 2.1 mm i.d., 3 micron). The mobile phase was acetonitrile/10 mM ammonium acetate (v/v = 45/55) with 0.1 mM citrate (pH 4.4) and the temperature was 25 °C. The flow rate was set at 0.3 ml/min. IR spectra were obtained on Thermo Scientific Nicolet iS10. Samples were analyzed by ESI-MS on a LCQ (Thermo Scientific, San Jose, CA) mass spectrometer operated using flow injection analysis (FIA) for sample introduction. The number of microscans was set to 20 for all acquisitions. Data was processed using Xcalibur (Thermo Scientific, San Jose, CA).

Synthesis of Fentanyl Derivatives:

Synthesis of Fen-Br. *N*-phenyl-*N*-piperidin-4-yl-propionamide (Norfentanyl, 0.93 g, 4.0 mmol) and 4-bromophenethyl bromide (1.58 g, 6.0 mmol) was dissolved in 15 mL DMF, followed by addition of *N,N*-diisopropylethylamine (0.78 g, 6.0 mmol). The reaction was kept stirring at 60 °C for 24 h. The reaction mixture was cooled to room temperature before ethyl ether (100 mL) was added, and the organics were washed with 1 N NaOH (30 mL×3), water (30 mL×3) and brine (30 mL×3). The organics were then dried over MgSO_4 and concentrated under vacuum. The organics were redissolved in ethyl ether, and pure Fen-Br were precipitated as HCl salt by addition of HCl in ethanol solution (95%): UV-Vis (λ_{abs}): 227 nm; IR (ATR): 2933, 2464, 1647,

1490, 1394, 1271, 1072, 1044, 1011, 939, 812, 701, cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.41–7.35 (m, 5H), 7.08 (dd, $J = 8.5, 8.5$ Hz, 2H), 7.02 (d, $J = 8.5$ Hz, 2H), 4.68 (tt, $J = 12.0, 4.0$ Hz, 1H), 3.00 (d, $J = 12.0$ Hz, 2H), 2.70 (m, 2H), 2.53 (m, 2H), 1.93 (dd, $J = 15.0, 7.5$ Hz, 2H), 1.85 (d, $J = 13.0$ Hz, 2H), 1.6–1.4 (m, 4H), 1.01 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz; $\text{DMSO}-d_6$): δ 172.2, 140.4, 139.3, 131.45, 131.27, 130.8, 129.7, 128.6, 119.3, 59.6, 53.0, 52.3, 32.7, 30.6, 28.3, 10.0; MS: m/z 417.07 $[\text{M}+\text{H}]^+$.

Synthesis of Fen-Acrylates by Heck Coupling. Fen-Br (270 mg, 0.6 mmol) and acrylates (3 mmol, 5 eq) were dissolved in Et_3N (2 mL) and DMF (3 mL). Palladium acetate (6.7 mg, 0.03 mmol) and ethylenebis(diphenylphosphine) (12.0 mg, 0.03 mmol) was added, and the reaction was kept stirring at 140 °C under N_2 overnight. The reaction mixture was cooled to room temperature before dichloromethane (100 mL) was added, and the solution was passed through a neutral alumina column to remove the Pd catalyst. The mixture was washed with 1 M NaOH, water and brine, and was dried over MgSO_4 . The organics were concentrated under vacuum, and redissolved in ether. Crude product was precipitated by addition of HCl in ethanol, and the precipitate was further purified by column chromatography (1:2 Hexane/ethyl acetate) to afford the desired product.

Fen-Acry-EtOH (85%): UV-Vis (λ_{abs}): 216, 278 nm; IR (ATR): 2932, 2447, 1713, 1642, 1495, 1402, 1266, 1042, 740, 707, cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.69 (d, $J = 16.0$ Hz, 1H), 7.45–7.39 (m, 5H), 7.24 (d, $J = 7.0$ Hz, 2H), 7.11 (dd, $J = 8.5, 8.5$ Hz, 2H), 6.44 (d, $J = 16.0$ Hz, 1H), 4.81 (tt, $J = 12.0, 4.0$ Hz, 1H), 4.35 (t, $J = 5.0$ Hz, 2H), 3.90 (t, $J = 5.0$ Hz, 2H), 3.63 (d, $J = 12.0$ Hz, 2H), 3.23 (m, 2H), 3.14 (m, 2H), 2.84 (td, $J = 12.0, 1.5$ Hz, 2H), 2.2–1.9 (m, 6H), 1.02 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz; $\text{DMSO}-d_6$): δ 172.6, 172.0, 166.8, 144.6, 138.6, 137.7, 133.1, 130.8, 129.92, 129.73, 129.10, 129.06, 128.96, 127.2, 118.3, 66.3, 59.5, 56.9, 49.7, 46.69, 46.53, 29.8, 28.7, 28.2, 27.8, 9.9; MS: m/z 451.13 $[\text{M}+\text{H}]^+$.

Fen-Acry-Bu (90%): UV-Vis (λ_{abs}): 217, 281 nm; IR (ATR): 2976, 2599, 2495, 1474, 1296, 1171, 1035, 806 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.66 (d, $J = 16.0$ Hz, 1H), 7.45–7.39 (m, 5H), 7.18 (d, $J = 7.0$ Hz, 2H), 7.10 (dd, $J = 8.5, 8.5$ Hz, 2H), 6.40 (d, $J = 16.0$ Hz, 1H), 4.70 (tt, $J = 12.0, 4.0$ Hz, 1H), 4.22 (t, $J = 5.0$ Hz, 2H), 3.00 (d, $J = 12.0$ Hz, 2H), 2.76–2.60 (m, 2H), 2.52 (td, $J = 12.0, 1.5$ Hz, 2H), 2.19–2.15 (m, 2H), 1.96 (dd, $J = 15.0, 7.5$ Hz, 2H), 1.82 (d, $J = 13.0$ Hz, 2H), 1.70 (q, $J = 7.0$ Hz, 2H), 1.45 (m, 2H), 1.46 (q, $J = 12.0$ Hz, 2H), 1.03 (t, $J = 7.5$ Hz, 3H), 0.96 (t, $J = 7.0$, 3H); ^{13}C NMR (125 MHz; $\text{DMSO}-d_6$): δ 172.6, 166.7, 144.5, 140.2, 138.6, 133.1, 130.8, 130.0, 129.7, 129.12, 129.10, 128.99, 118.4, 64.2, 56.5, 51.4, 49.5, 46.6, 30.8, 29.7, 28.2, 27.8, 19.1, 14.0, 9.9; MS: m/z 463.20 $[\text{M}+\text{H}]^+$.

Fen-Acry-tBu (75%): UV-Vis (λ_{abs}): 216, 272 nm; IR (ATR): 2978, 2929, 2598, 2496, 1702, 1652, 1368, 1278, 1148, 975, 830, 713 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.66 (d, $J = 16.0$ Hz, 1H), 7.45–7.39 (m, 5H), 7.18 (d, $J = 7.0$ Hz, 2H), 7.10 (dd, $J = 8.5, 8.5$ Hz, 2H), 6.40 (d, $J = 16.0$ Hz, 1H), 4.71 (tt, $J = 12.0, 4.0$ Hz, 1H),), 3.00 (d, $J = 12.0$ Hz, 2H), 2.76–2.60 (m, 2H), 2.52 (td,

$J = 12.0, 1.5$ Hz, 2H), 2.19 – 2.15 (m, 2 H), 1.96 (dd, $J = 15.0, 7.5$ Hz, 2H), 1.82 (d, $J = 13.0$ Hz, 2H), 1.55 (s, 9H), 1.46 (q, $J = 12.0$ Hz, 2H), 1.03 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz; DMSO- d_6): δ 172.6, 171.97, 171.89, 166.0, 143.6, 140.0, 138.6, 133.2, 130.8, 129.9, 129.7, 129.10, 129.07, 128.97, 128.93, 120.0, 80.4, 56.5, 53.6, 51.3, 46.6, 45.7, 42.4, 34.4, 28.3, 18.4, 17.2, 9.9, 8.8; MS: m/z 463.20 $[\text{M}+\text{H}]^+$.

Fen-Acry-PEO₉ (70%): UV-Vis (λ_{abs}): 217, 283 nm; IR (ATR): 3292, 2928, 2628, 1643, 1560, 1464, 1376, 1265, 1101, 706 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.68 (d, $J = 16.0$ Hz, 1H), 7.45–7.39 (m, 5H), 7.18 (d, $J = 7.0$ Hz, 2H), 7.10 (dd, $J = 8.5, 8.5$ Hz, 2H), 6.44 (d, $J = 16.0$ Hz, 1H), 4.70 (tt, $J = 12.0, 4.0$ Hz, 1H), 4.37 (t, $J = 5.0$ Hz, 2H), 3.8 – 3.4 (m, 36H), 3.00 (d, $J = 12.0$ Hz, 2H), 2.76 – 2.60 (m, 2H), 2.52 (td, $J = 12.0, 1.5$ Hz, 2H), 2.19 – 2.15 (m, 2 H), 1.96 (dd, $J = 15.0, 7.5$ Hz, 2H), 1.82 (d, $J = 13.0$ Hz, 2H), 1.46 (q, $J = 12.0$ Hz, 2H), 1.03 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz; DMSO- d_6): δ 172.6, 166.7, 158.8, 157.4, 144.8, 140.3, 139.4, 138.6, 133.0, 130.8, 129.9, 129.7, 129.15, 128.97, 118.1, 107.4, 71.7, 70.0, 68.8, 63.9, 60.6, 58.5, 56.5, 54.9, 54.4, 51.3, 49.6, 49.0, 42.36, 42.30, 40.48, 40.41, 40.31, 40.24, 40.09, 39.73, 39.65, 39.48, 36.8, 35.5, 34.6, 29.7, 28.2, 27.7, 25.6, 16.1, 15.1, 9.9; MS: m/z 817.40 $[\text{M}+\text{H}]^+$.

Synthesis of Fen-Acry-OH. Fen-Acry-tBu (270 mg, 0.6 mmol) was dissolved in dichloromethane (20 mL) with slow addition of trifluoroacetic acid (1 mL). The solution was stirred at room temperature for 24 h. 1 N HCl (40 mL) was added, and the reaction mixture was extracted with dichloromethane (20 mL) three times. The organics were combined, washed with water and brine, and was evaporated under high vacuum to afford pure Fen-Acry-OH (95%): UV-Vis (λ_{abs}) 216, 279 nm; IR (ATR): 2924, 2469, 1659, 1649, 1455, 1366, 1271, 1146, 829, 812, 708, cm^{-1} ; ^1H NMR: (500 MHz, CDCl_3): δ 7.58 (d, $J = 16.0$ Hz, 1H), 7.5–7.4 (m, 5H), 7.22 (d, $J = 7.0$ Hz, 2H), 7.09 (dd, $J = 8.5, 8.5$ Hz, 2H), 6.34 (d, $J = 16.0$ Hz, 1H), 4.82 (tt, $J = 12.0, 4.0$ Hz, 1H), 3.57 (m, 2H), 3.02 (m, 4H), 2.69 (m, 2H), 2.2–1.9 (m, 6H), 1.04 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz; DMSO- d_6): δ 172.6, 168.0, 158.8, 158.5, 143.9, 139.7, 138.6, 133.4, 130.9, 130.0, 129.7, 129.00, 128.96, 119.5, 56.6, 55.4, 51.6, 49.2, 29.8, 28.2, 27.8, 9.9; MS: m/z 407.20 $[\text{M}+\text{H}]^+$.

Synthesis of Fen-Acrylates or Fen-Acrylamides by EDC/DMAP coupling reaction. Fen-Acry-OH (160 mg, 0.4 mmol) and the desired alcohol or amine (0.6 mmol) was dissolved in dichloromethane. EDC (191 mg, 1 mmol) and DMAP (6.1 mg, 0.05 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. Additional dichloromethane (50 mL) was added to the reaction mixture, which was then washed with 1 N NaOH, water and brine. The organics was dried over MgSO_4 , filtered and the solvent was evaporated under vacuum. The crude product was redissolved in ether, and the product was precipitated by dropwise addition of HCl in ethanol.

Fen-Acry-PEO₇ (60%): UV-Vis (λ_{abs}) 217, 281 nm; IR (ATR): 3394, 2863, 2514, 1706, 1651, 1454, 1377, 1257, 1103, 951, 831, 711, cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.67 (d, $J = 16.0$

Hz, 1H), 7.52–7.45 (m, 5H), 7.28 (d, J = 7.0 Hz, 2H), 7.11 (dd, J = 8.5, 8.5 Hz, 2H), 6.46 (d, J = 16.0 Hz, 1H), 4.82 (tt, J = 12.0, 4.0 Hz, 1H), 4.38 (t, J = 5.0 Hz, 2H), 3.68 (t, J = 5.0 Hz, 2H), 3.65 – 3.60 (m, 24H), 3.56 (m, 2H), 3.40 (s, 3H), 3.27 (d, J = 12.0 Hz, 2H), 3.12 (s, 2H), 2.84 (td, J = 12.0, 1.5 Hz, 2H), 2.19 (m, 2 H), 2.00 (dd, J = 15.0, 7.5 Hz, 2H), 1.96 (d, J = 13.0 Hz, 2H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz; DMSO- d_6): δ 172.6, 166.7, 144.8, 138.7, 133.1, 130.8, 130.0, 129.7, 129.15, 128.98, 118.1, 71.7, 68.8, 63.9, 60.7, 58.5, 56.64, 56.61, 56.57, 51.55, 51.47, 49.56, 49.54, 49.52, 49.48, 42.5, 28.2, 27.87, 27.83, 9.9; MS: m/z 729.33 $[\text{M}+\text{H}]^+$.

Fen-Acmd-PEO₈ (54%): UV-Vis (λ_{abs}) 217, 279 nm; IR (ATR): 3346, 2868, 1621, 1449, 1237, 1091, 930, 829, 705, cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.76 (d, J = 15.0 Hz, 1H), 7.59–7.42 (m, 5H), 7.28 (d, J = 7.0 Hz, 2H), 7.12 (dd, J = 8.5, 8.5 Hz, 2H), 6.68 (d, J = 12.0 Hz, 1H), 4.80 (tt, J = 12.0, 4.0 Hz, 1H), 3.8 – 3.5 (m, 28H), 3.38 (s, 3H), 3.27 (s, 2H), 3.12 (s, 2H), 2.84 (s, 2H), 2.19 (m, 2 H), 2.00 (dd, J = 15.0, 7.5 Hz, 2H), 1.96 (d, J = 13.0 Hz, 2H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz; DMSO- d_6): δ 165.5, 139.0, 138.62, 138.59, 134.0, 130.8, 130.0, 129.7, 129.0, 128.2, 122.5, 71.7, 70.4, 70.07, 70.04, 69.6, 58.5, 56.6, 51.4, 49.5, 42.4, 29.7, 28.2, 27.8, 9.9; MS: m/z 772.40 $[\text{M}+\text{H}]^+$.

Mu Opioid Receptor Activation:

CHO cells expressing the Human mu Opioid Receptor were cultured according to manufactures instructions. Cells were plated at 90% confluency in black 96 well plates. Prior to the cAMP assay forskolin was added to each well for a final concentration of 100 μM followed by an induction buffer of IBMX (final concentration 500 μM) and Ro-20-1724 (100 μM). 30 minutes after the addition of induction buffer fentanyl derivatives were added. Cells were incubated for 30 min and a cAMP assay was conducted according to instructions provided by Promega.

Hot Plate Withdrawal Assay:

All experiments were performed in compliance with the relevant laws and institutional guidelines and conducted with the approval of the Institutional Animal Care and Use Committee at the Allegheny Health Network. CD-1 Mice were purchased from Charels Rivers Laboratories (Male, 30 g) and housed for 1 week prior to initiation of experiments. 30 min prior to placement on a 55 °C Hotplate (IITC Life Sciences), mice were dosed subcutaneously with fentanyl, saline or Fentanyl derivatives (10 $\mu\text{L/g}$). Mice were placed on the hot plate and monitored for hind paw licking or jumping. At the first sign of these symptoms the time was marked and animals were removed from the hot plate and euthanized. Animals that did not show a response after 30 seconds were removed and euthanized.

^1H and ^{13}C NMR spectra:

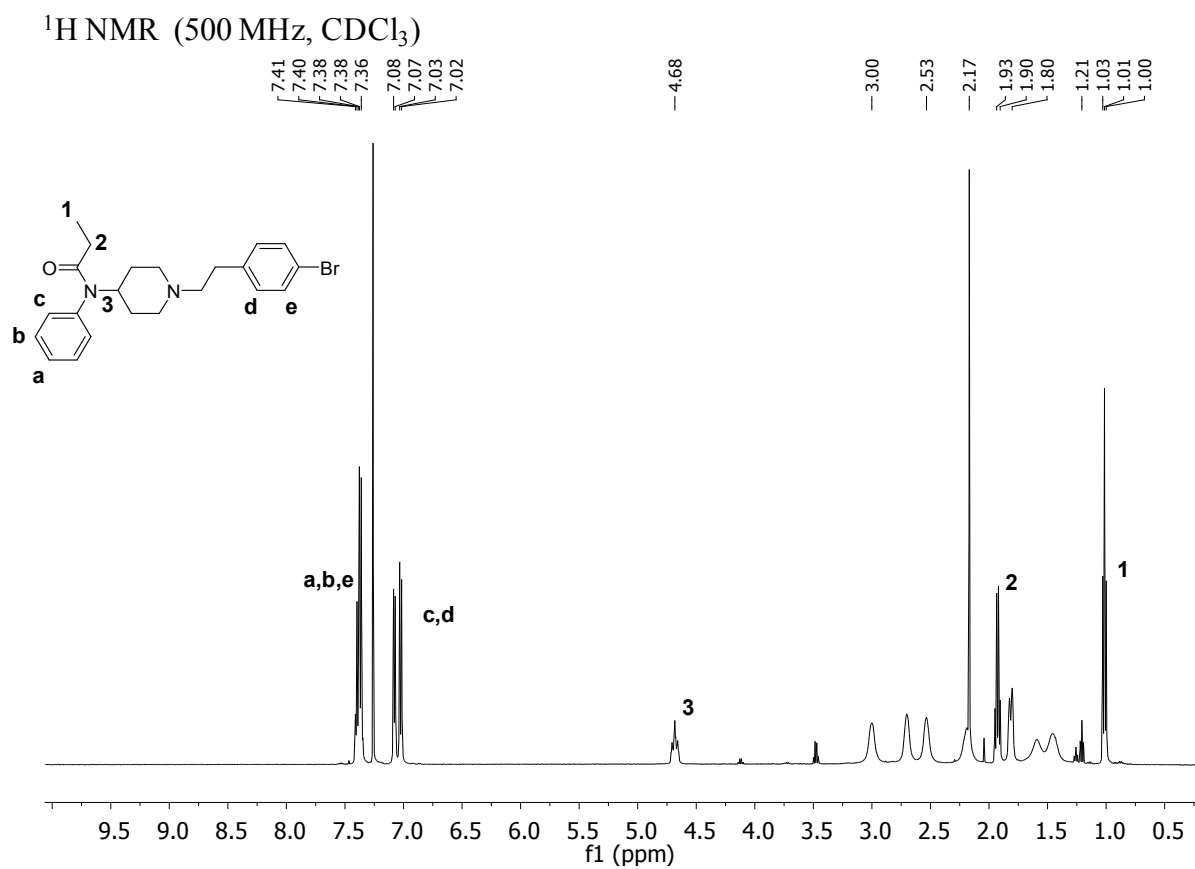


Fig. S1 ^1H NMR spectrum of **Fen-Br**.

^{13}C -NMR (125 MHz, $\text{DMSO-}d_6$)

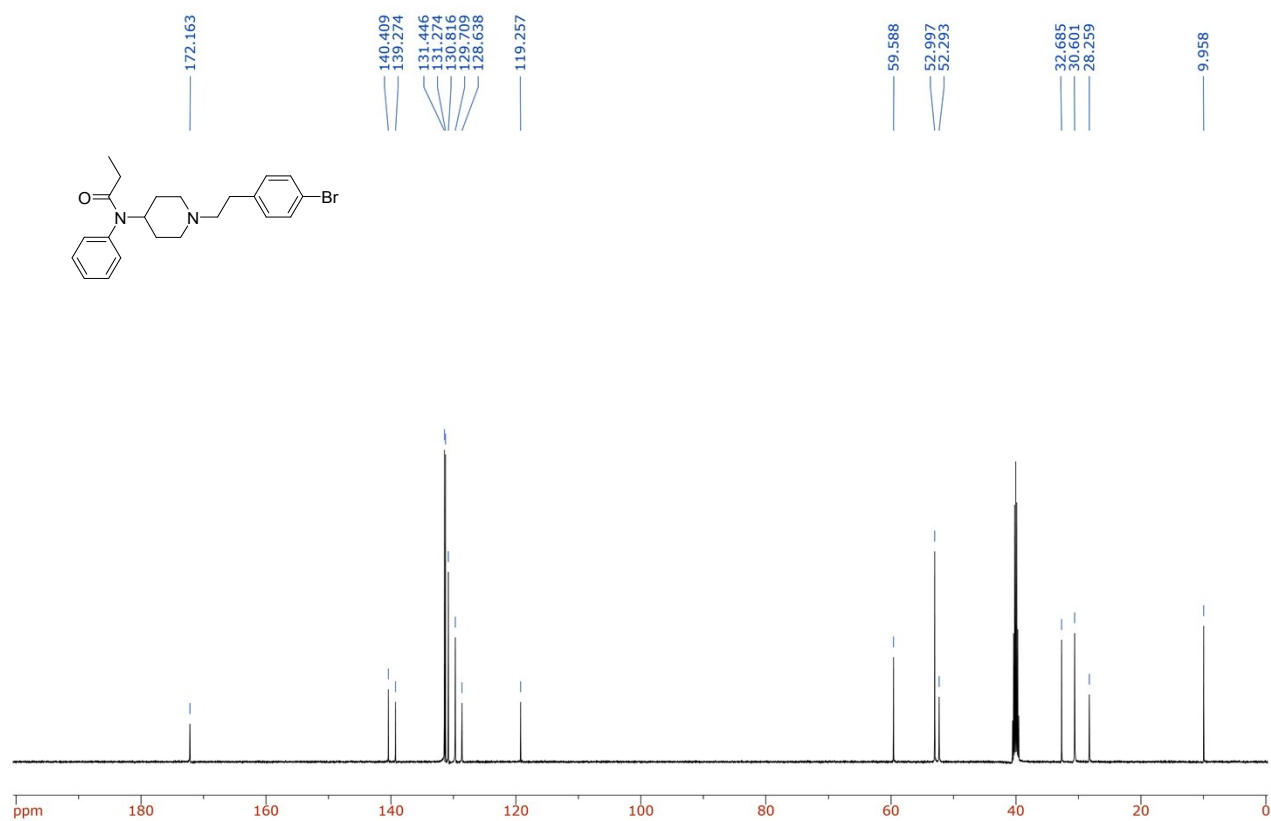


Fig. S2 ^{13}C NMR spectrum of **Fen-Br**.

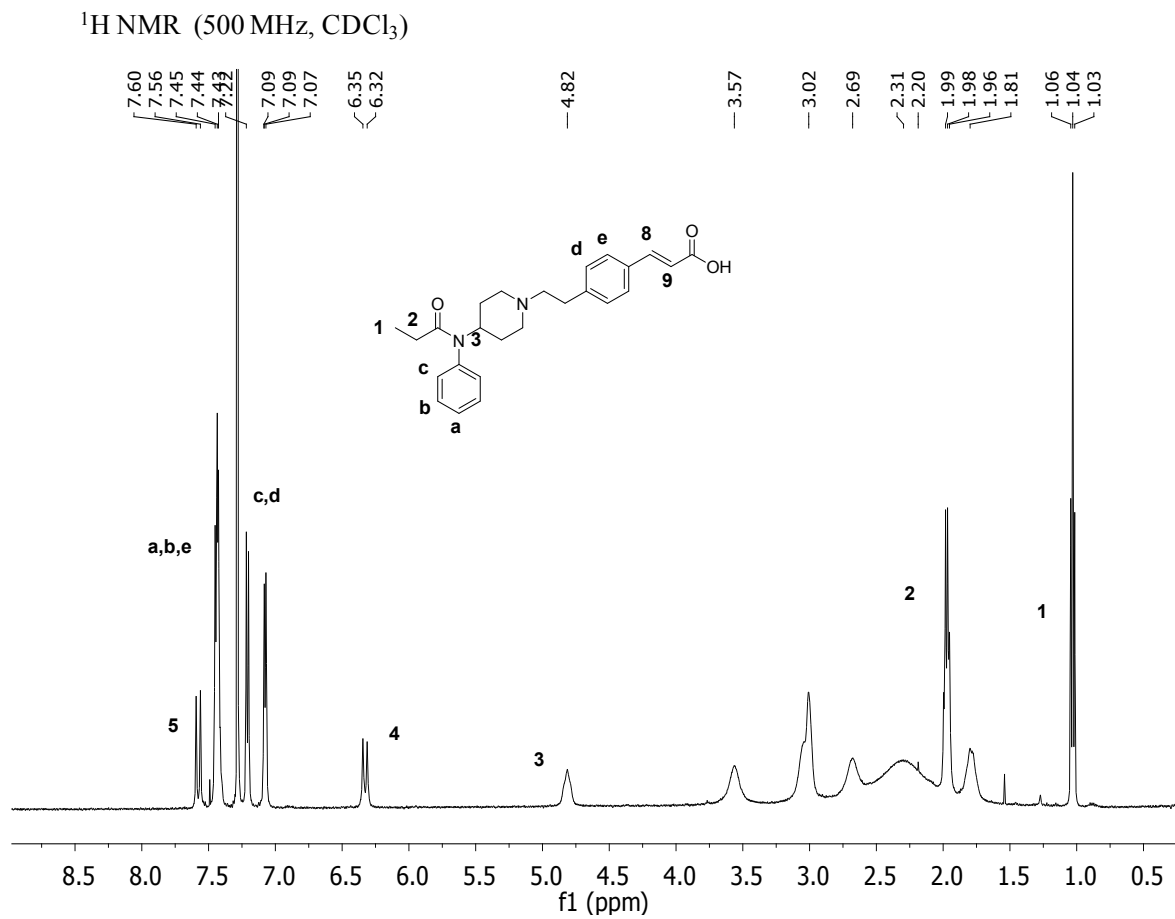


Fig. S3 ^1H NMR spectrum of Fen-Acry-OH.

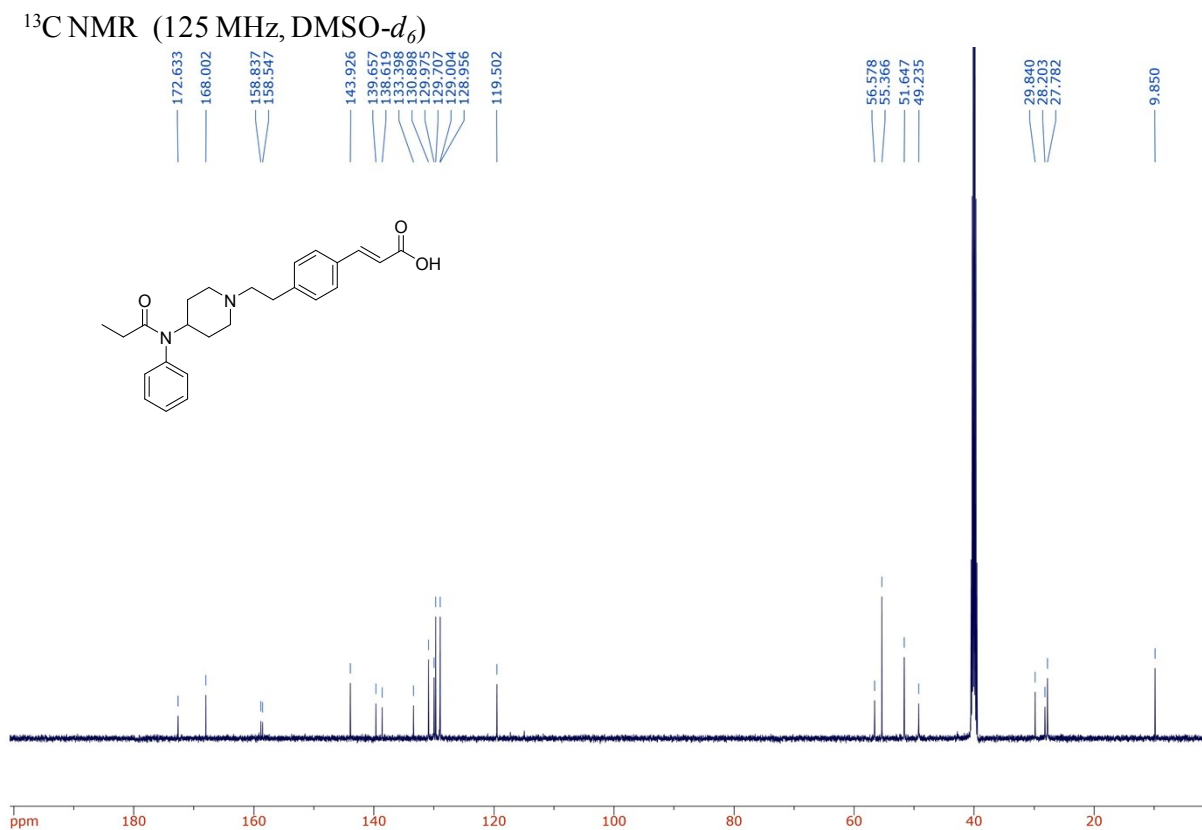


Fig. S4 ^{13}C NMR spectrum of Fen-Acry-OH.

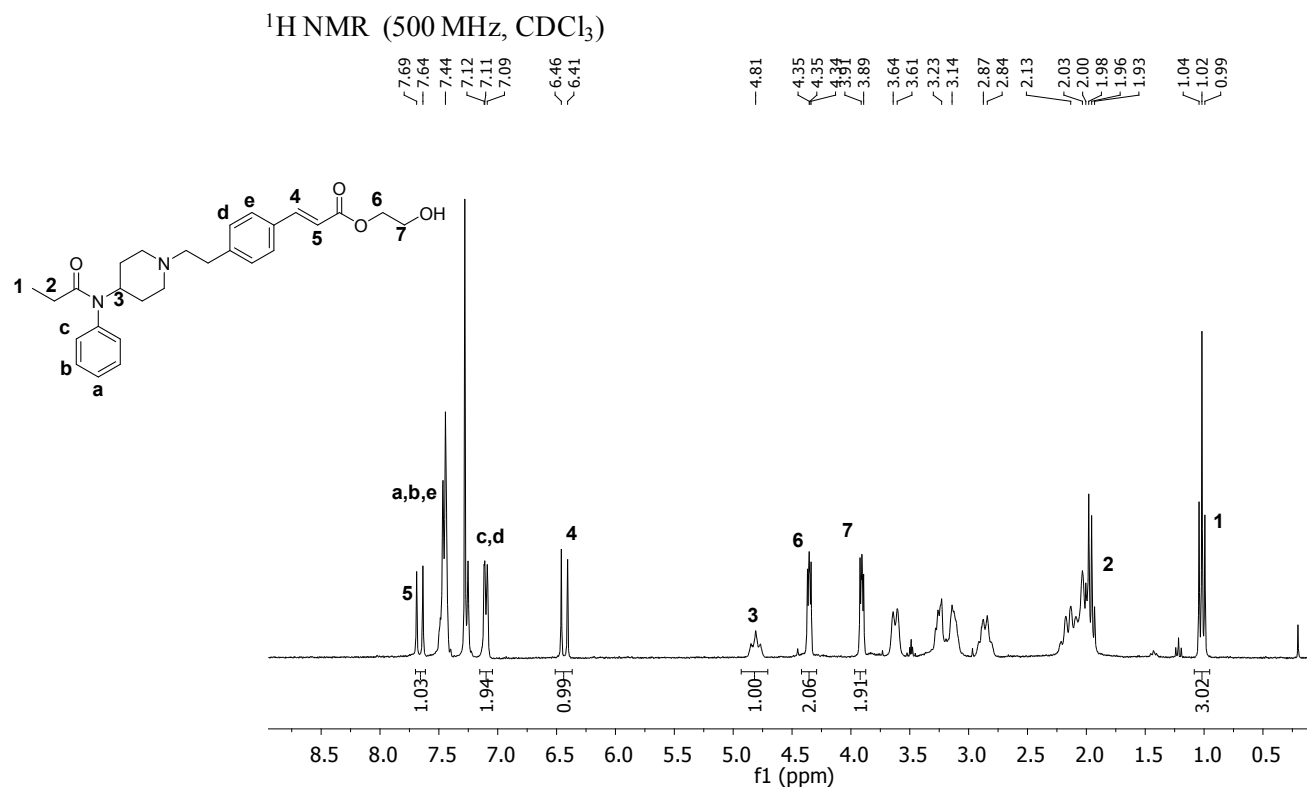


Fig. S5 ¹H NMR spectrum of **Fen-Acry-EtOH**.

^{13}C NMR (125 MHz, $\text{DMSO}-d_6$)

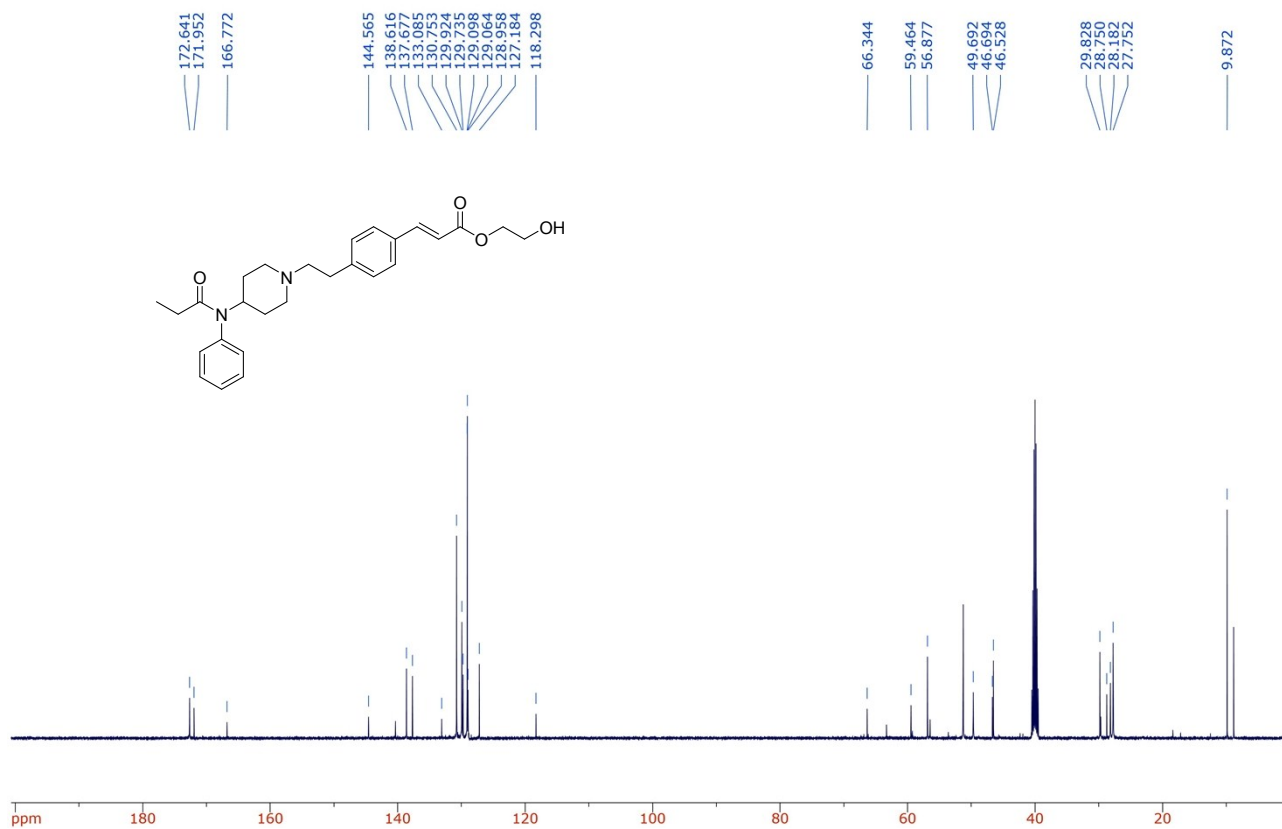


Fig. S6 ^{13}C NMR spectrum of Fen-Acry-EtOH.

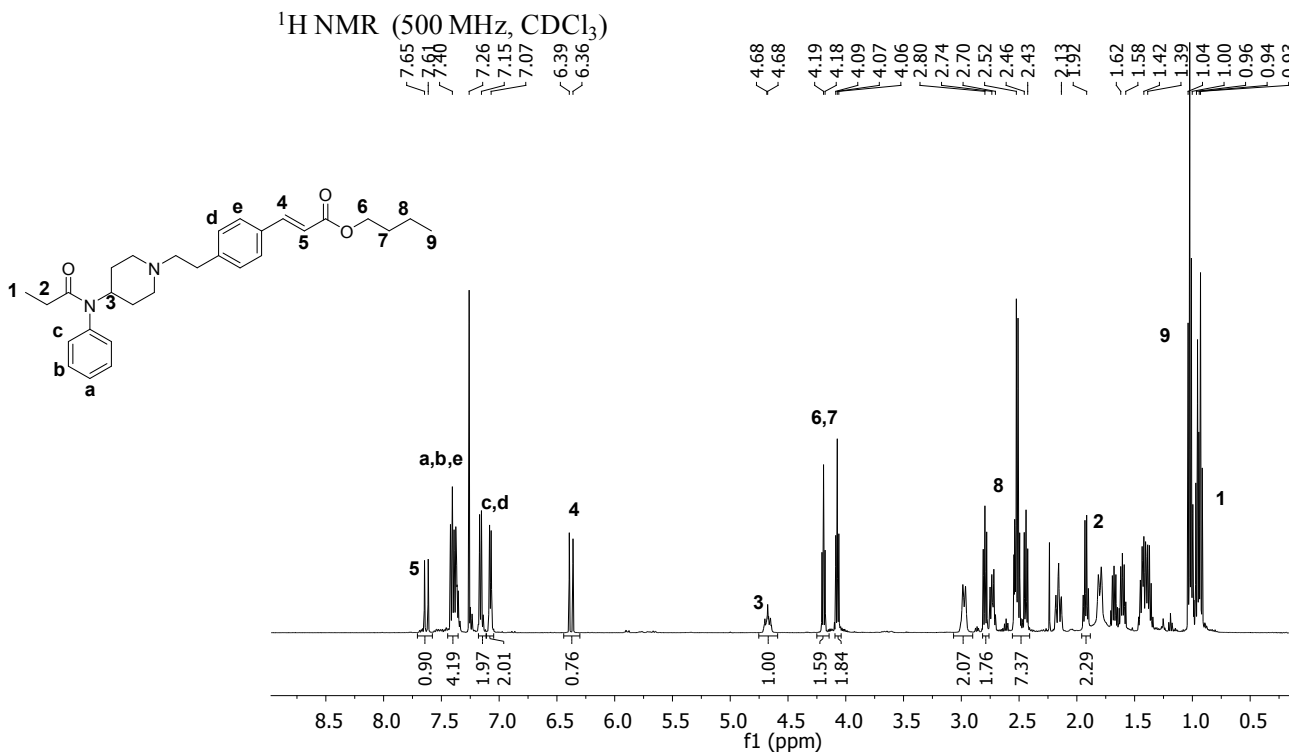


Fig. S7 ^1H NMR spectrum of **Fen-Acry-Bu**.

^{13}C NMR (125 MHz, $\text{DMSO}-d_6$)

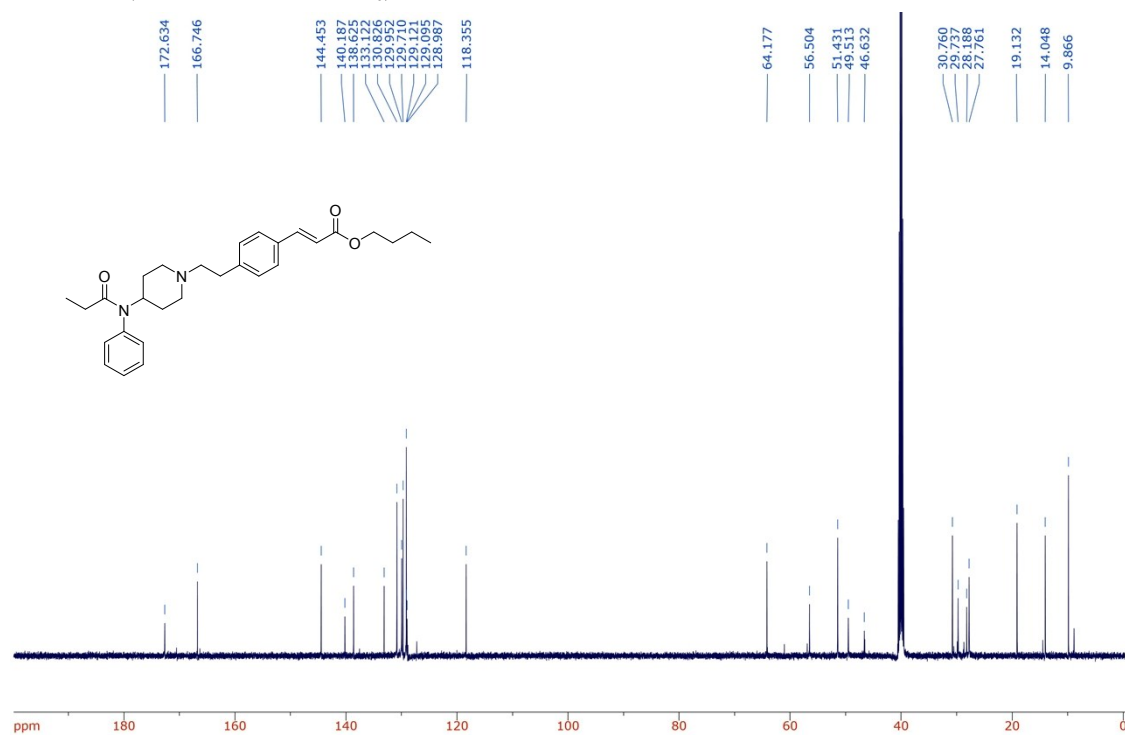


Fig. S8 ^{13}C NMR spectrum of **Fen-Acry-Bu**.

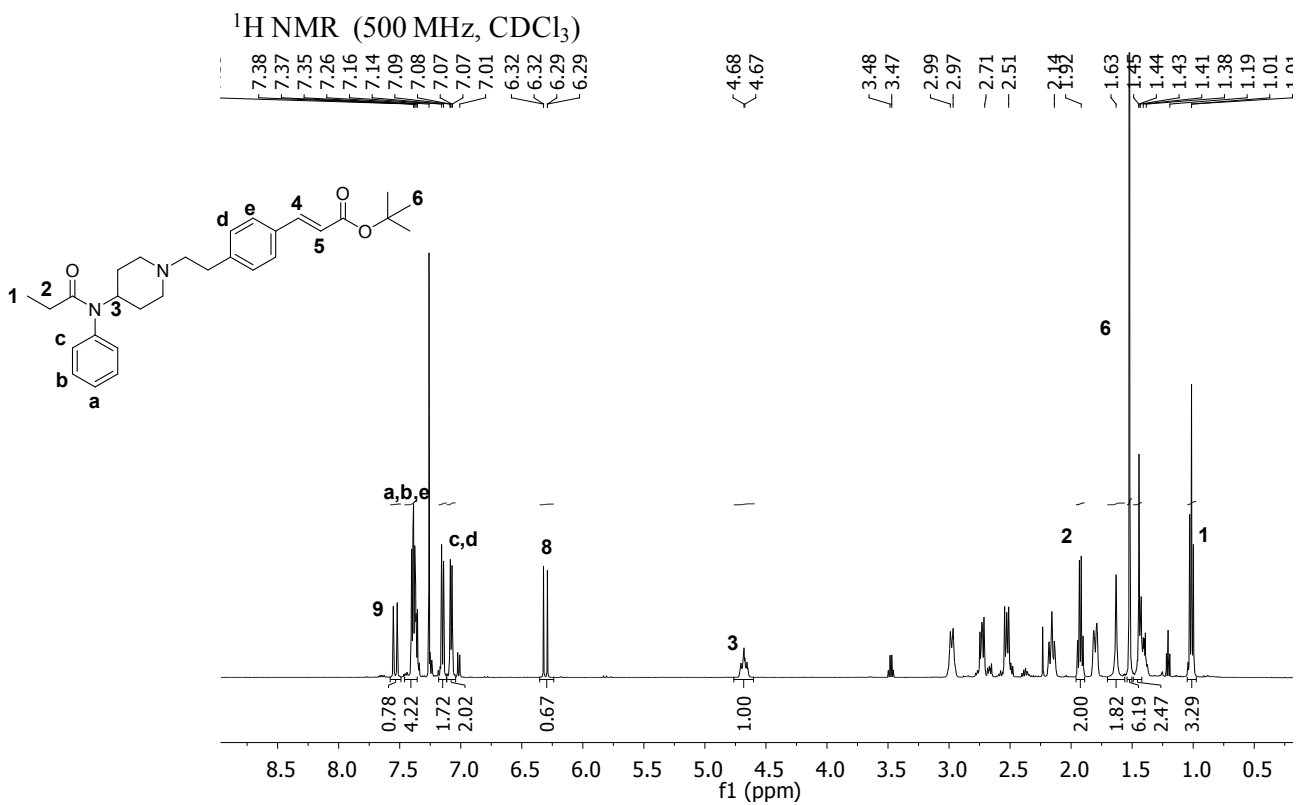


Fig. S9 ¹H NMR spectrum of **Fen-Acry-tBu**.

^{13}C NMR (125 MHz, $\text{DMSO}-d_6$)

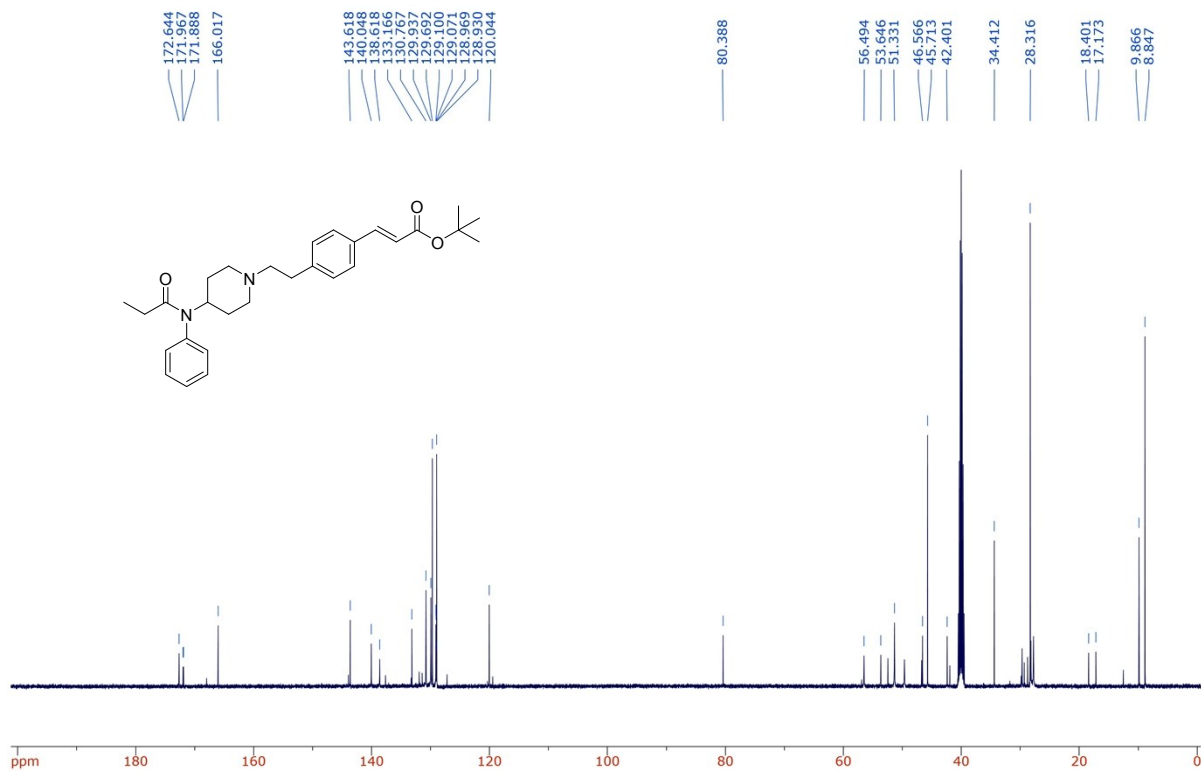


Fig. S10 ^{13}C NMR spectrum of Fen-Acry-tBu.

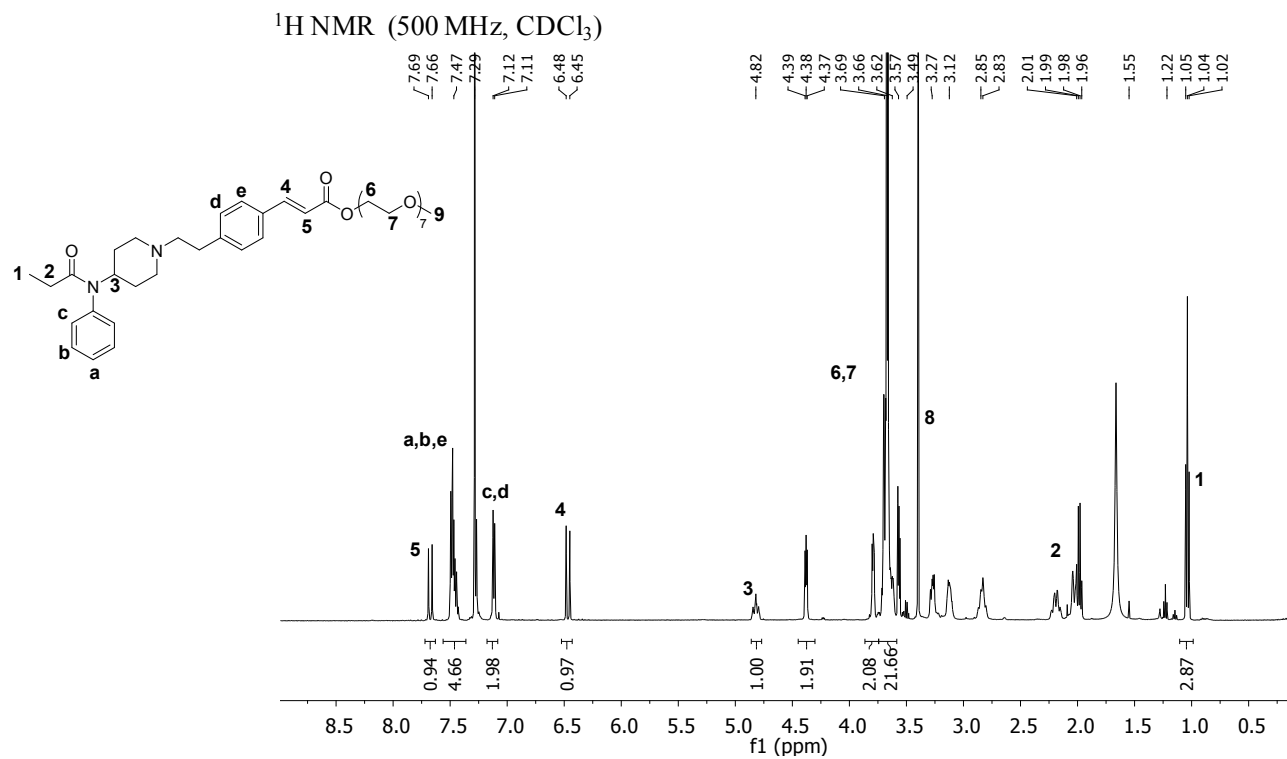


Fig. S11 ¹H NMR spectrum of **Fen-Acry-PEO₇**.

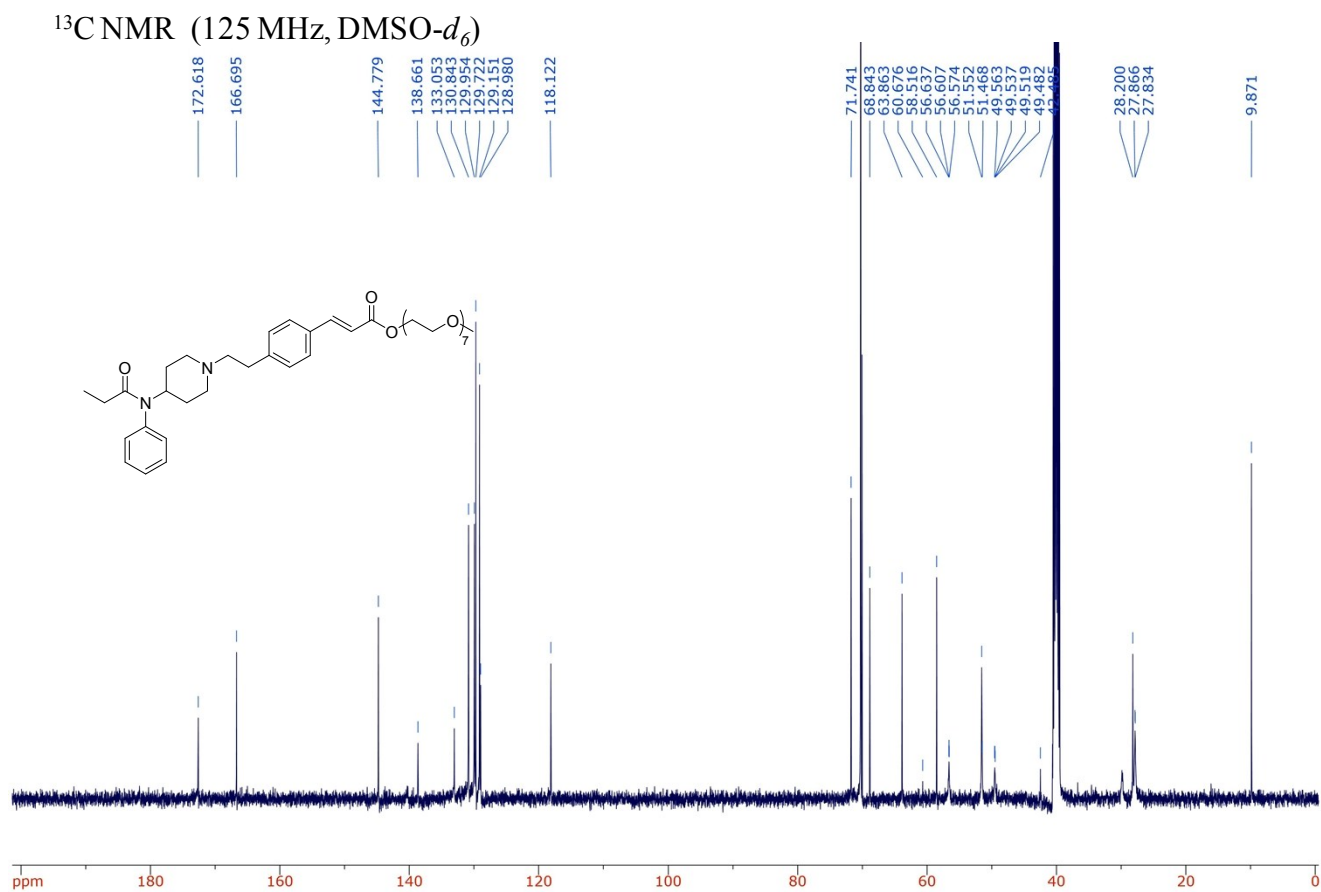


Fig. S12 ^{13}C NMR spectrum of Fen-Acry-PEO₇.

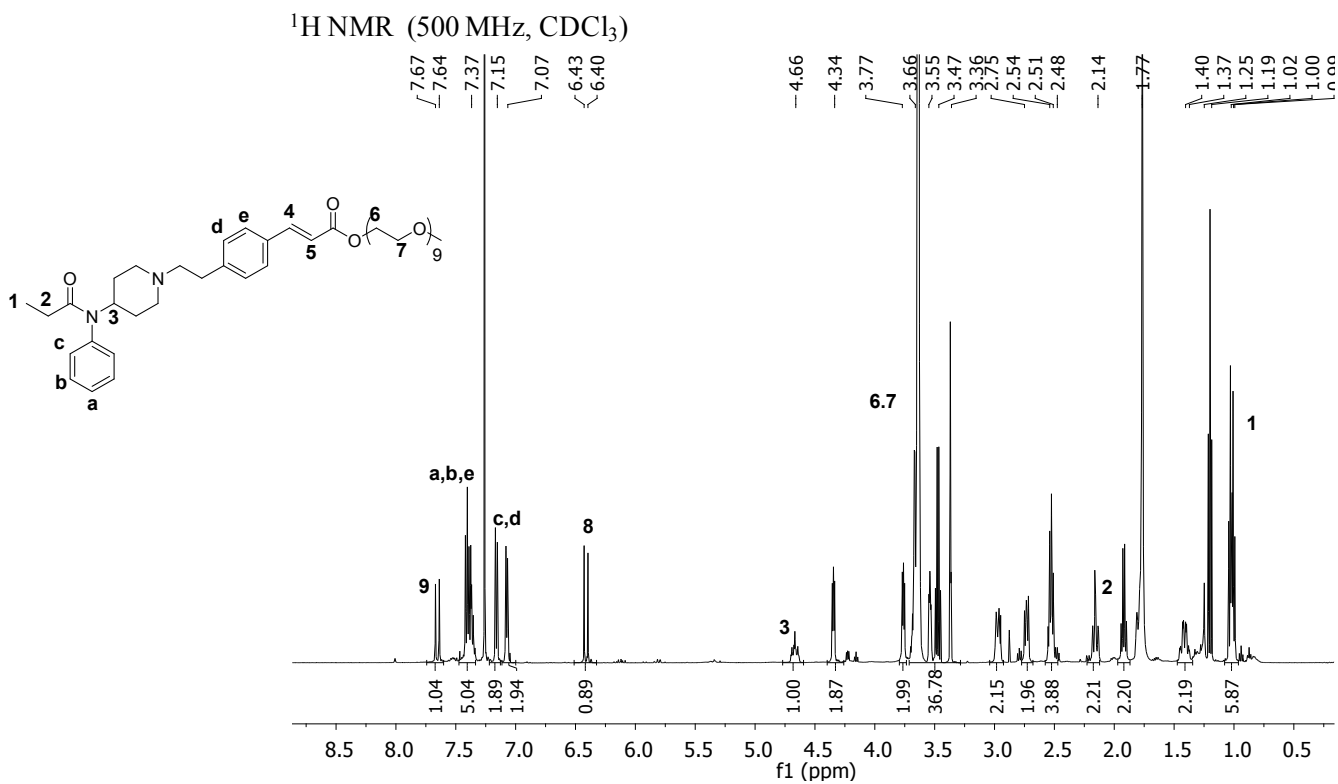


Fig. S13 ¹H NMR spectrum of **Fen-Acry-PEO₉**.

^{13}C NMR (125 MHz, $\text{DMSO-}d_6$)

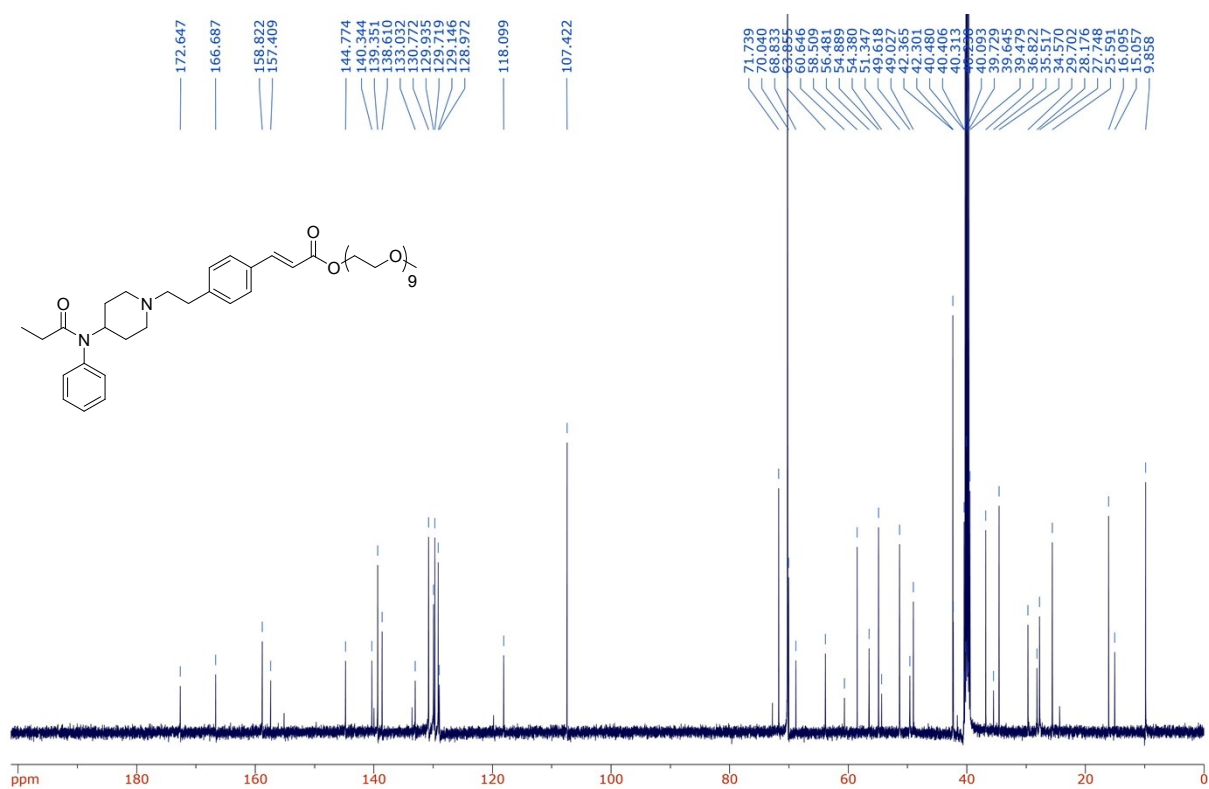


Fig. S14 ^{13}C NMR spectrum of Fen-Acry-PEO₉.

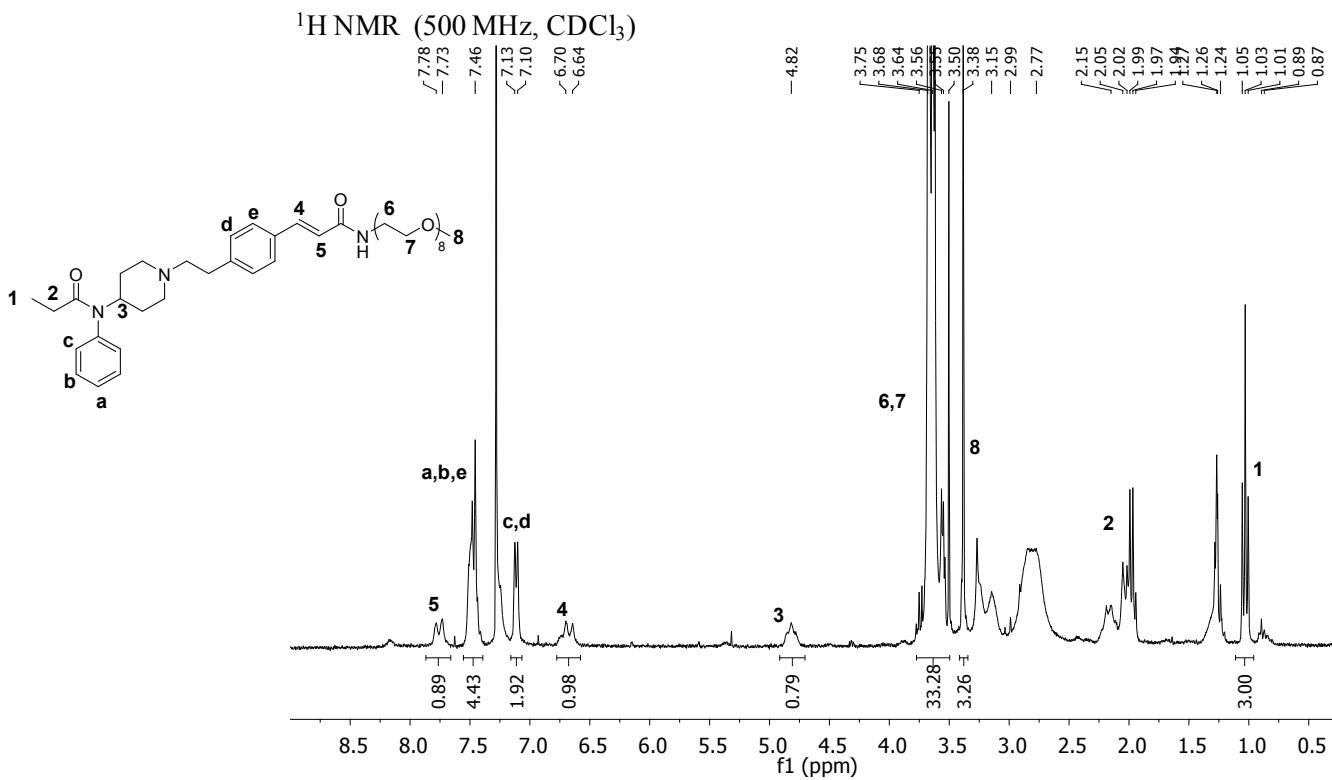


Fig. S15 ¹H NMR spectrum of **Fen-Acmd-PEO₈**.

CC(=O)N1CCN(CC1Cc2ccc(/C=C/C(=O)NCCO)cc2)c3ccccc3

Chemical structure of the compound is shown above the spectrum.

¹³C NMR peaks (ppm):

- 165.483
- 138.958
- 138.618
- 138.590
- 134.039
- 130.821
- 129.766
- 129.701
- 128.992
- 128.221
- 122.510
- 71.742
- 70.423
- 70.043
- 69.595
- 58.514
- 56.605
- 51.425
- 49.511
- 42.427
- 29.686
- 28.187
- 27.759
- 9.865

Fig. S16 ^1H NMR spectrum of **Fen-Acmd-PEO₈**.

HPLC spectra

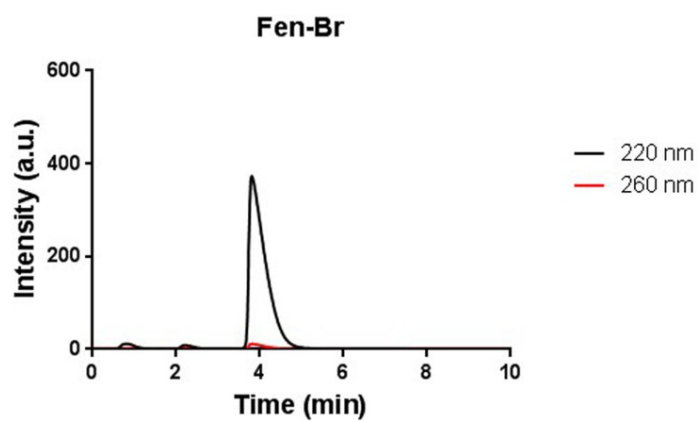


Fig. S17 Chromatographic profile of **Fen-Br**.

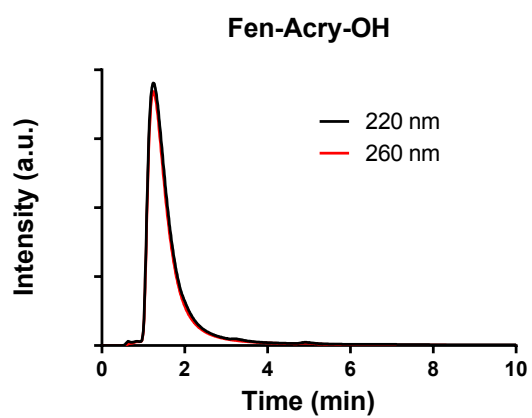


Fig. S18 Chromatographic profile of **Fen-Acry-OH**.

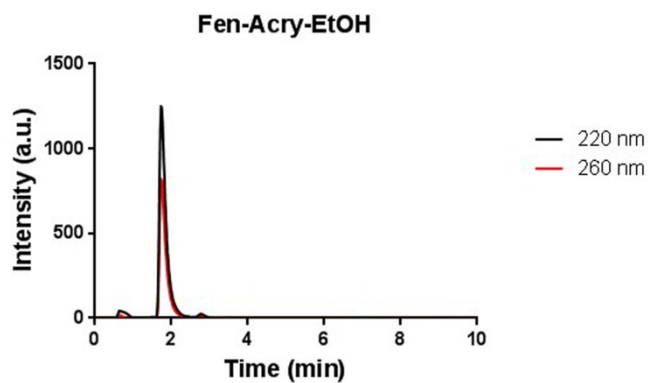


Fig. S19 Chromatographic profile of **Fen-Acry-EtOH**.

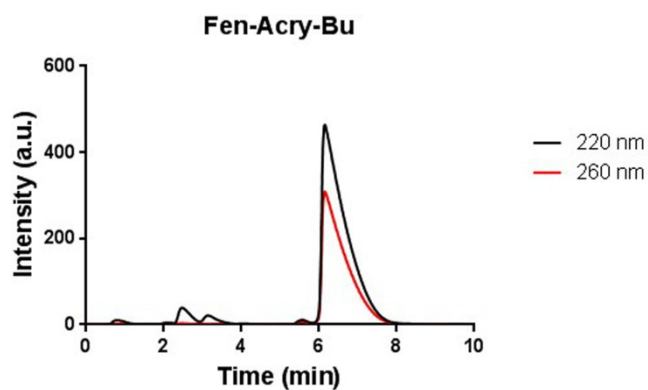


Fig. S20 Chromatographic profile of **Fen-Acry-Bu**.

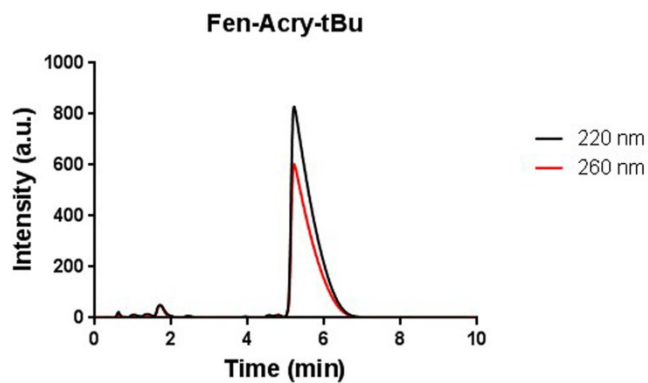


Fig. S21 Chromatographic profile of **Fen-Acry-tBu**.

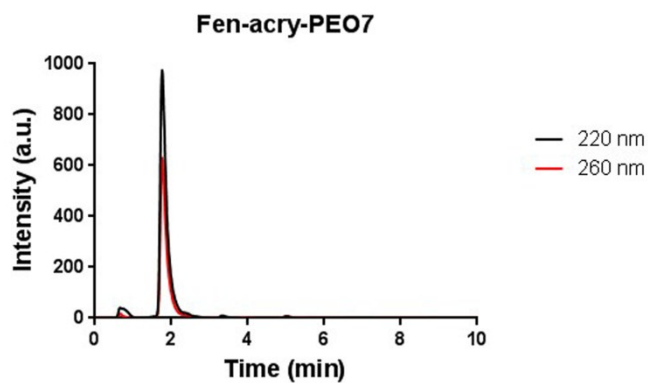


Fig. S22 Chromatographic profile of **Fen-Acry-PEO₇**.

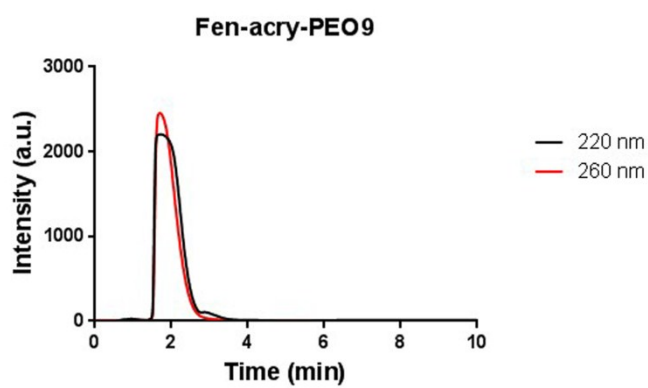


Fig. S23 Chromatographic profile of **Fen-Acry-PEO₉**.

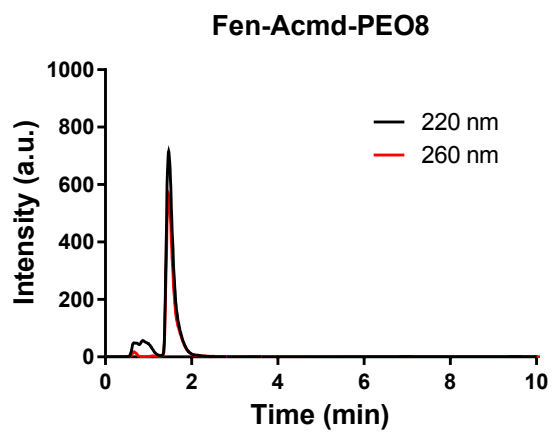


Fig. S24 Chromatographic profile of **Fen-Acmd-PEO₈**.

UV-Vis spectra in MeOH ($\sim 0.1 \mu\text{M}$)

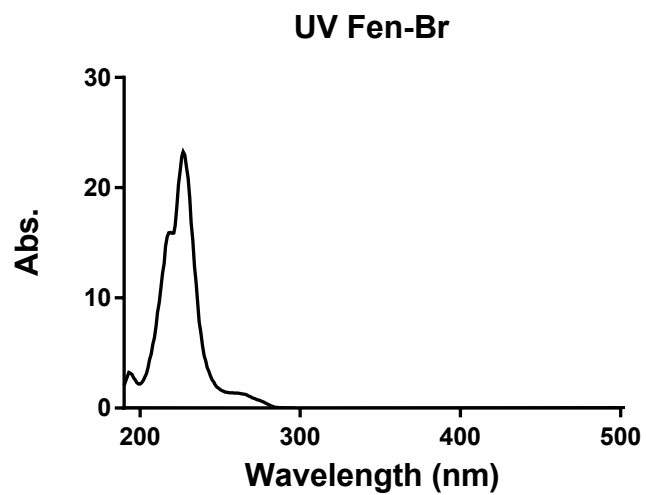


Fig. S25 UV-Vis spectrum of **Fen-Br**.

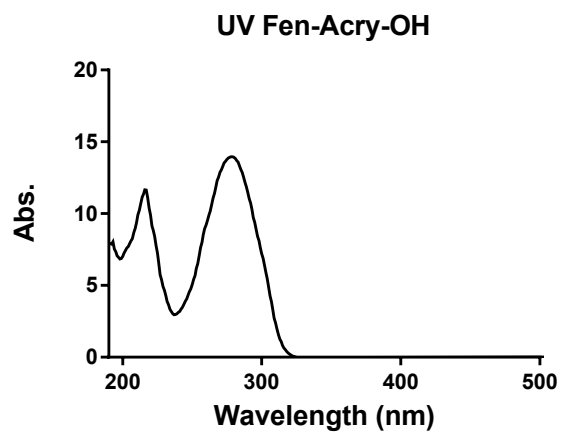


Fig. S26 UV-Vis spectrum of **Fen-Acry-OH**.

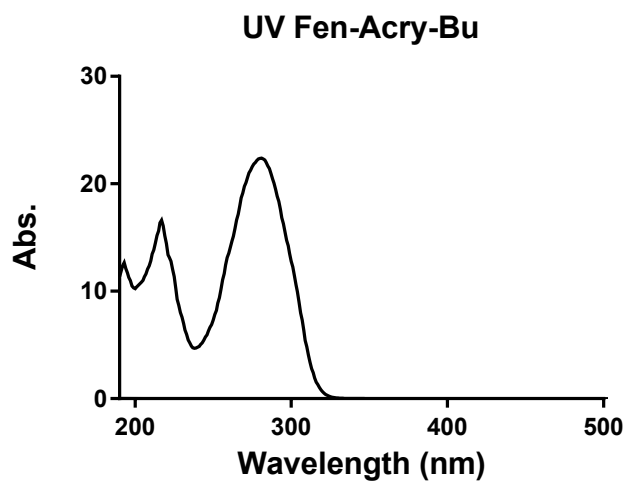


Fig. S27 UV-Vis spectrum of **Fen-Acry-Bu**.

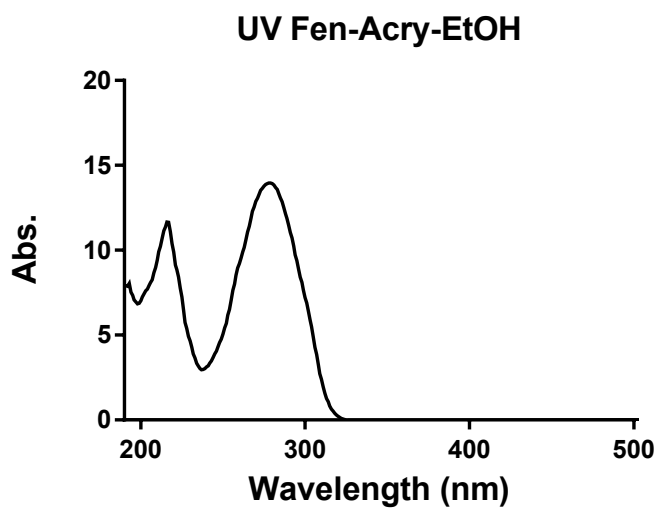


Fig. S28 UV-Vis spectrum of **Fen-Acry-EtOH**.

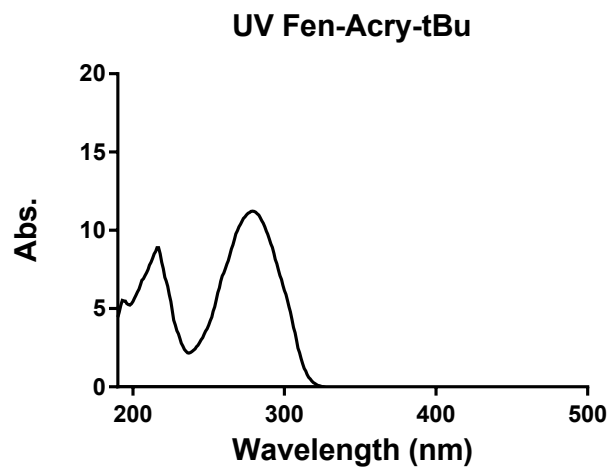


Fig. S29 UV-Vis spectrum of **Fen-Acry-tBu**.

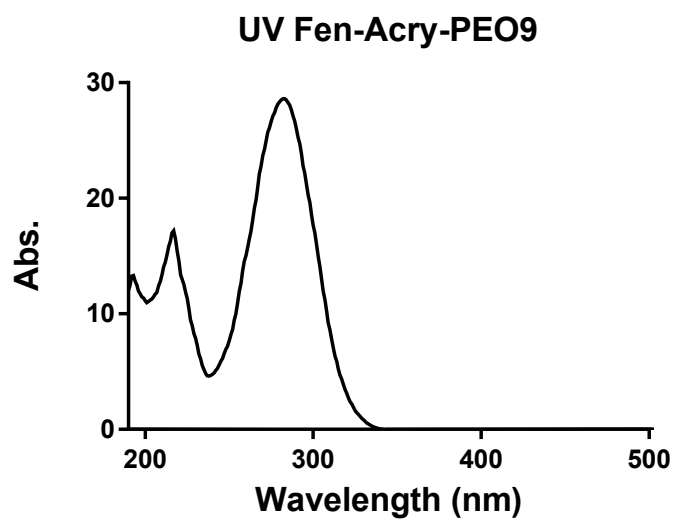


Fig. S30 UV-Vis spectrum of **Fen-Acry-PEO₉**.

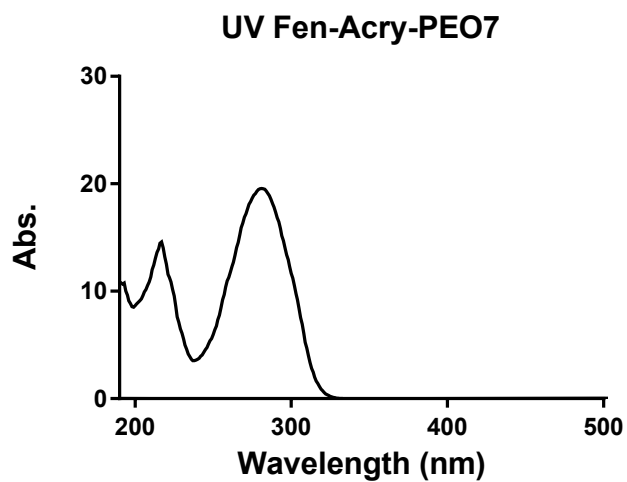


Fig. S31 UV-Vis spectrum of **Fen-Acry-PEO₇**.

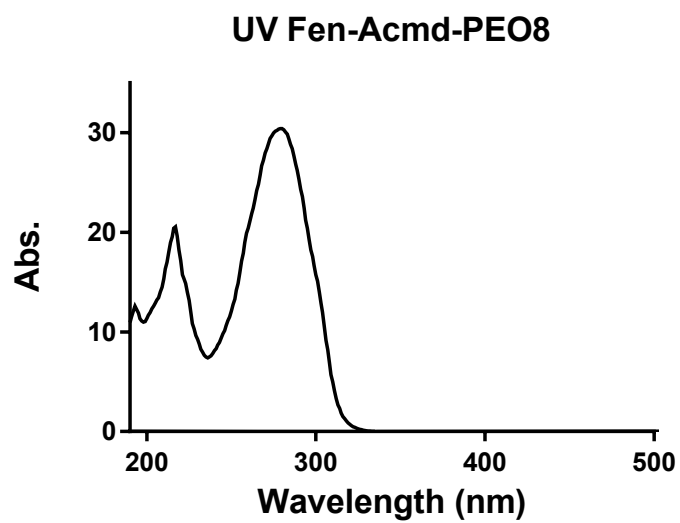


Fig. S32 UV-Vis spectrum of **Fen-Acmd-PEO₈**.

IR (ATR) spectra neat

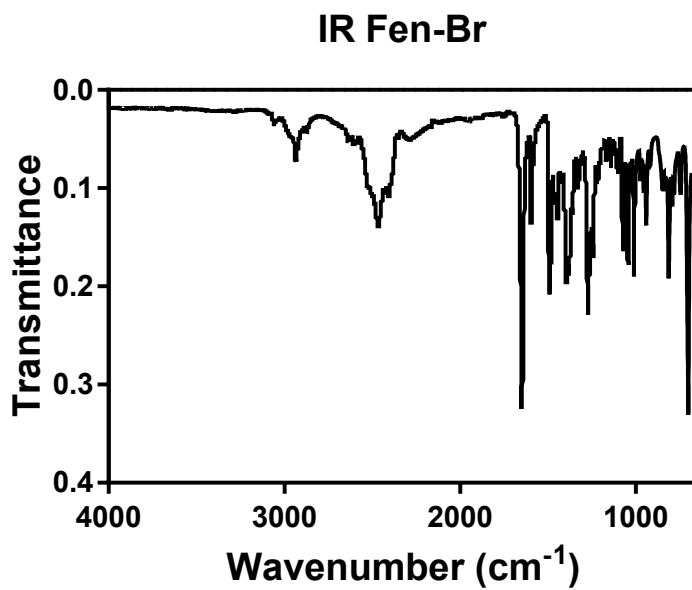


Fig. S33 IR spectrum of Fen-Br.

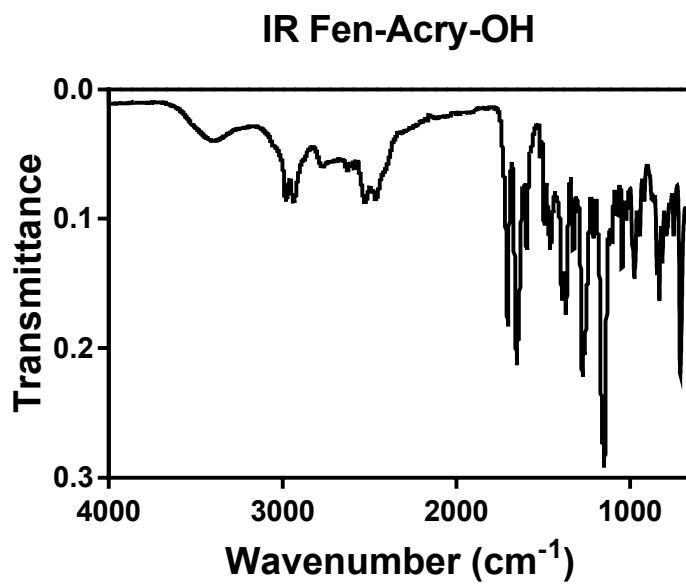


Fig. S34 IR spectrum of Fen-Acry-OH.

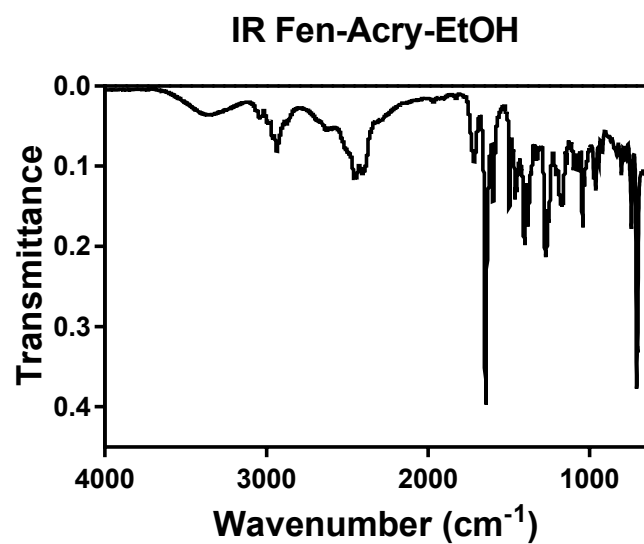


Fig. S35 IR spectrum of **Fen-Acry-EtOH**.

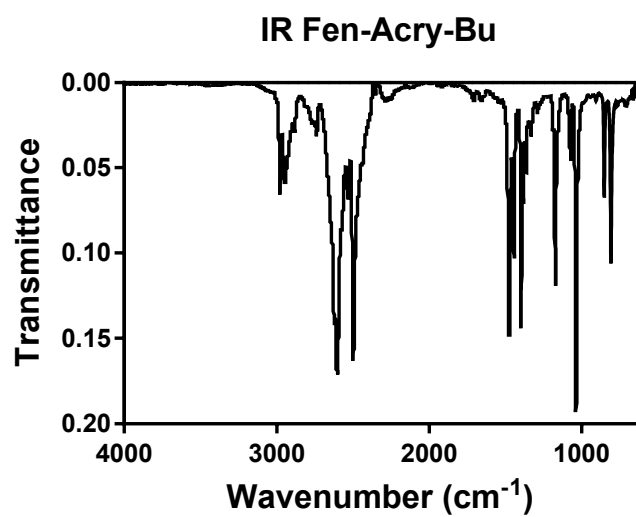


Fig. S36 IR spectrum of **Fen-Acry-Bu**.

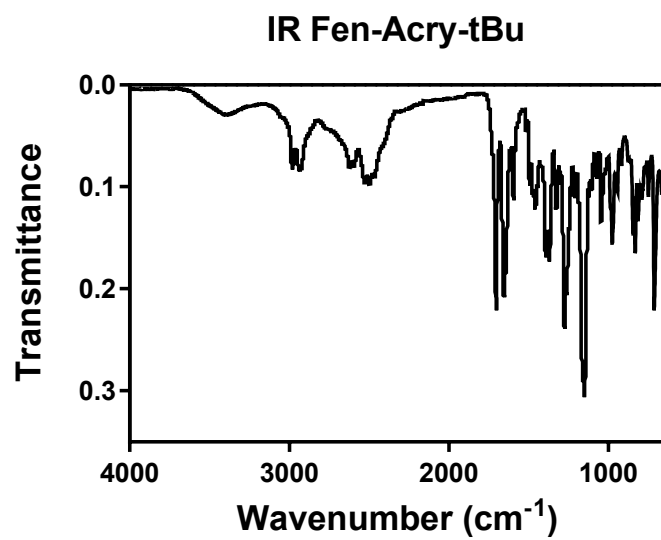


Fig. S37 IR spectrum of **Fen-Acry-tBu**.

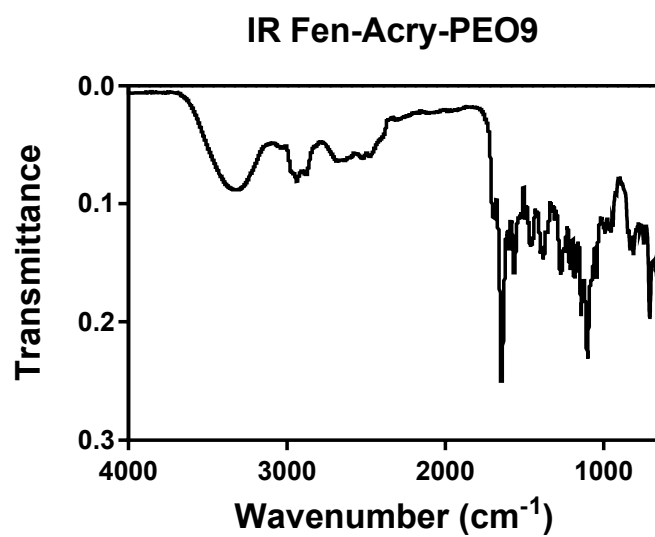


Fig. S38 IR spectrum of **Fen-Acry-PEO9**.

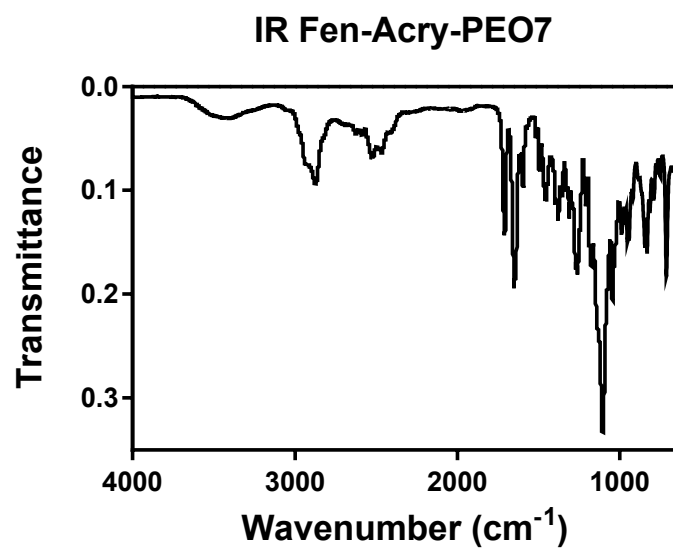


Fig. S39 IR spectrum of **Fen-Acry-PEO7**.

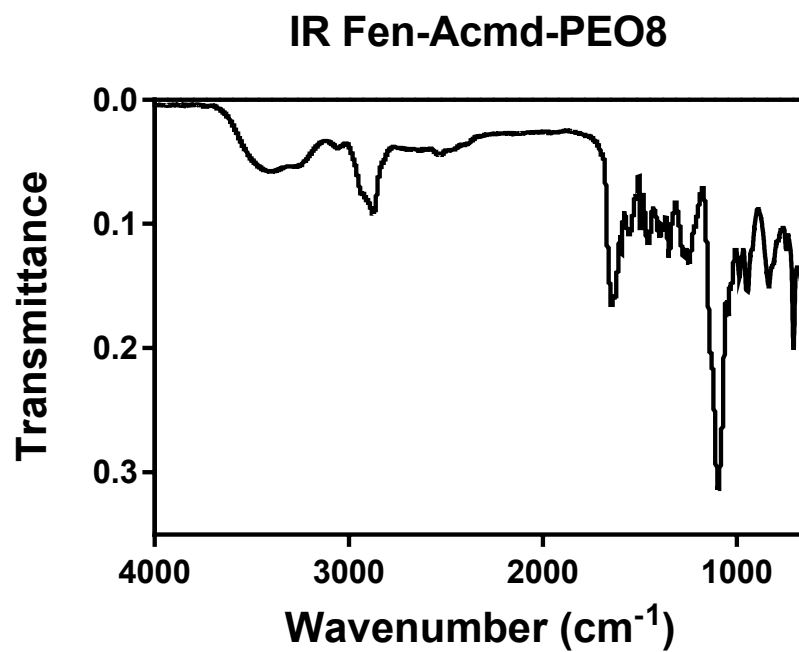


Fig. S40 IR spectrum of **Fen-Acmd-PEO8**.

ESI-MS spectra

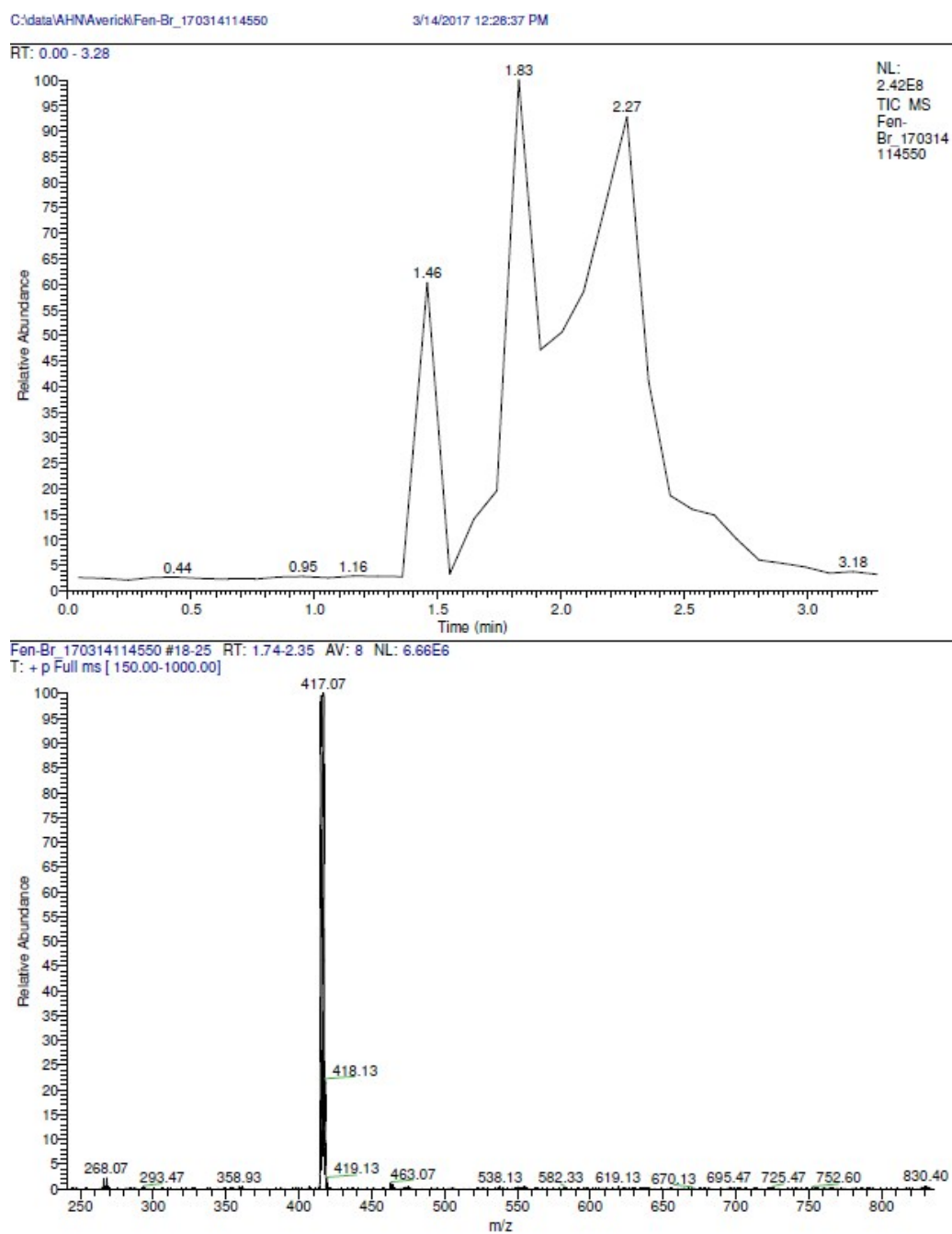


Fig. S41 ESI-MS spectrum of **Fen-Br**.

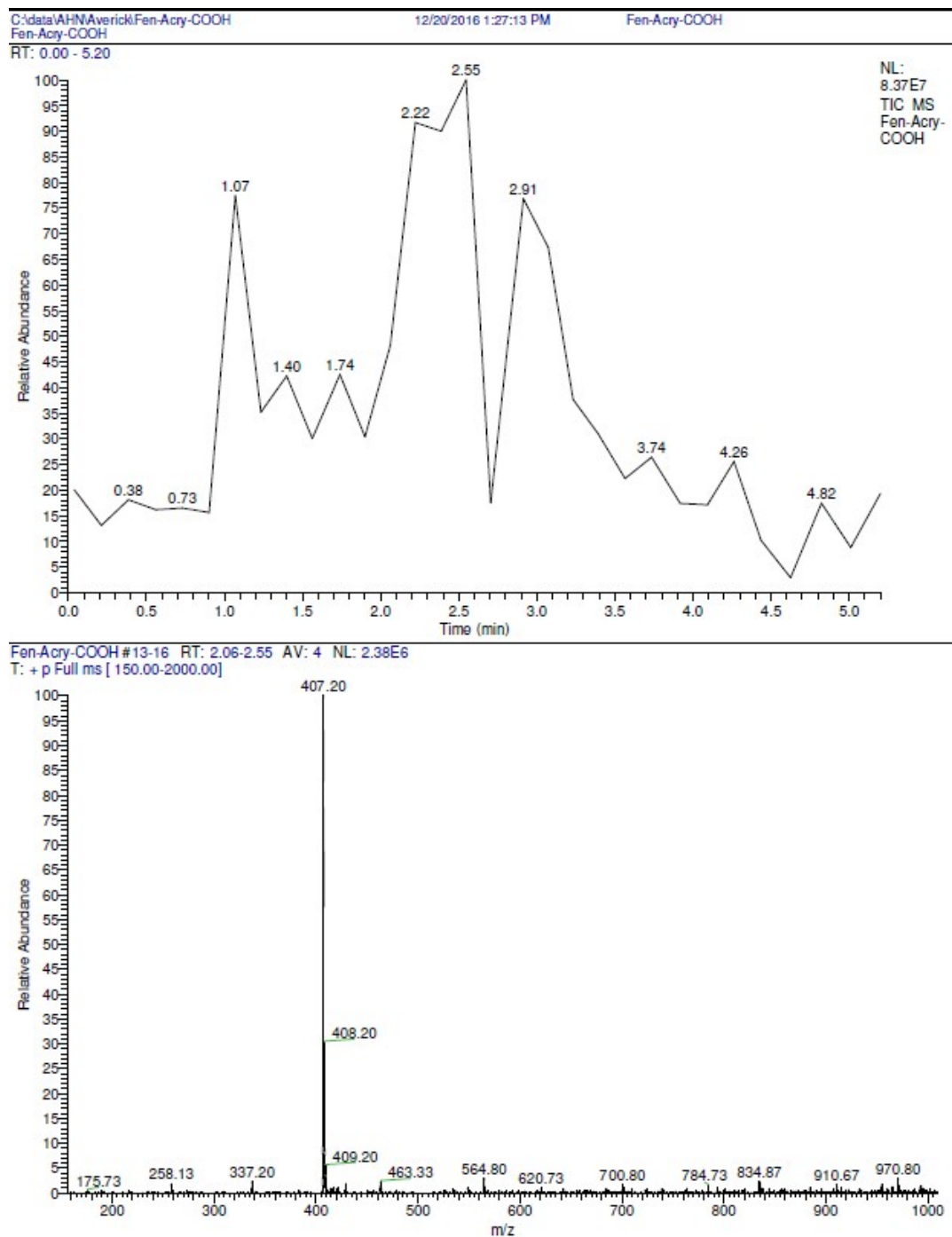
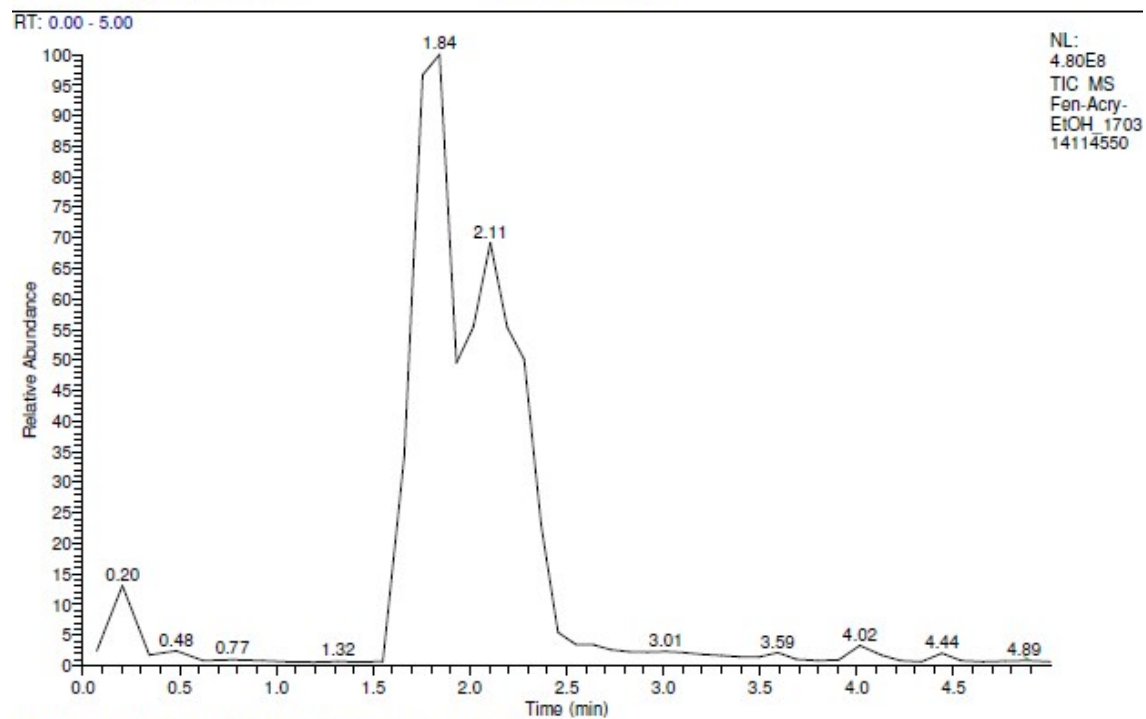


Fig. S42 ESI-MS spectrum of Fen-Acry-OH.



Fen-Acry-EtOH_170314114550 #27 RT: 2.92 AV: 1 NL: 2.77E5
T: + p Full ms [150.00-1000.00]

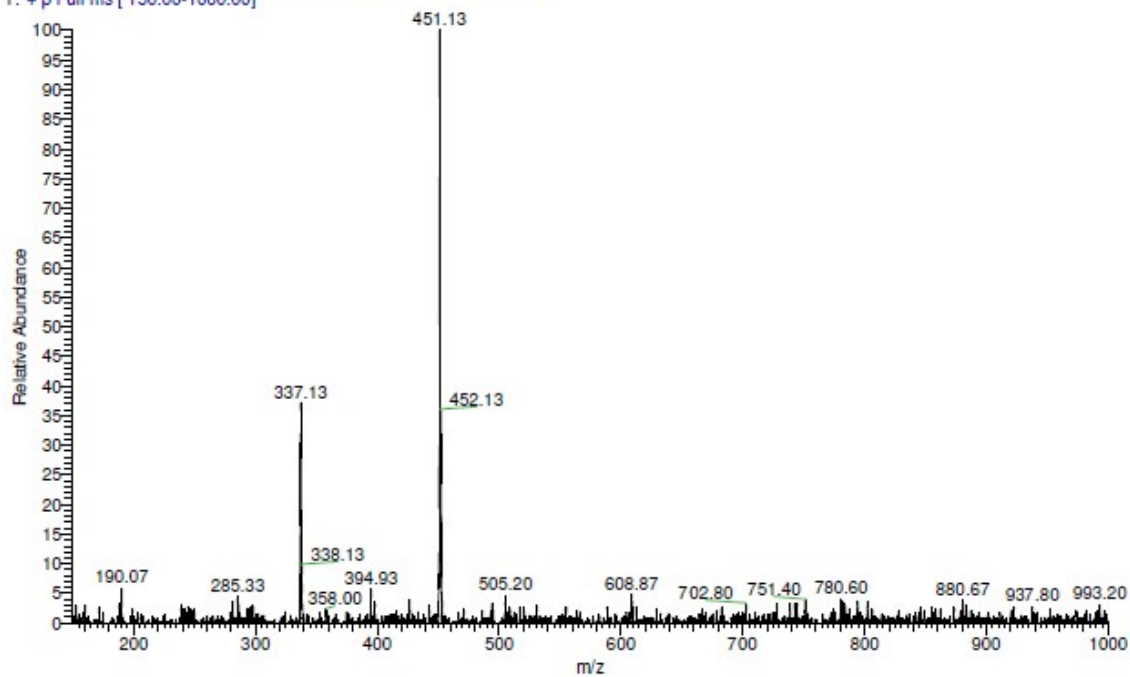
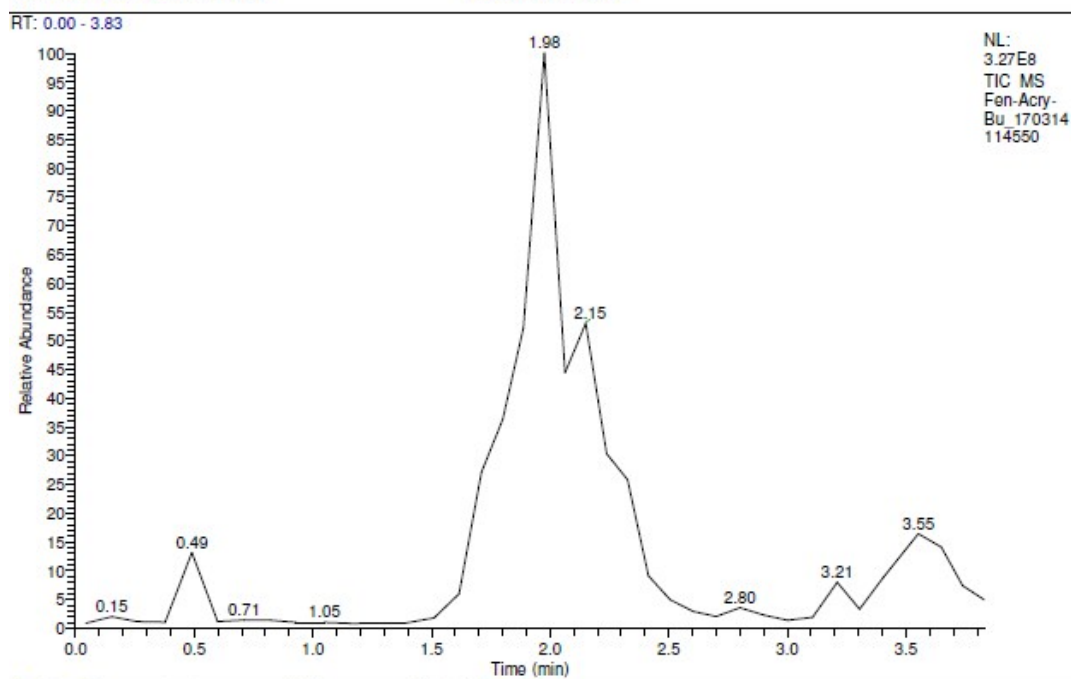


Fig. S43 ESI-MS spectrum of **Fen-Acry-EtOH**.



Fen-Acry-Bu_170314114550 #17-20 RT: 1.80-2.06 AV: 4 NL: 1.22E7
T: + p Full ms [150.00-1000.00]

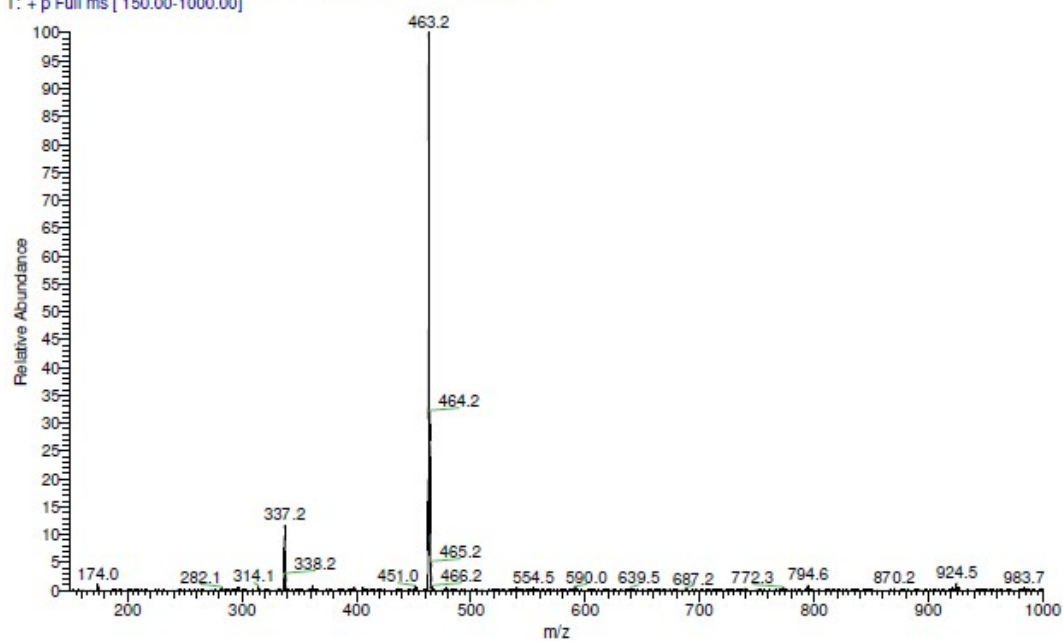
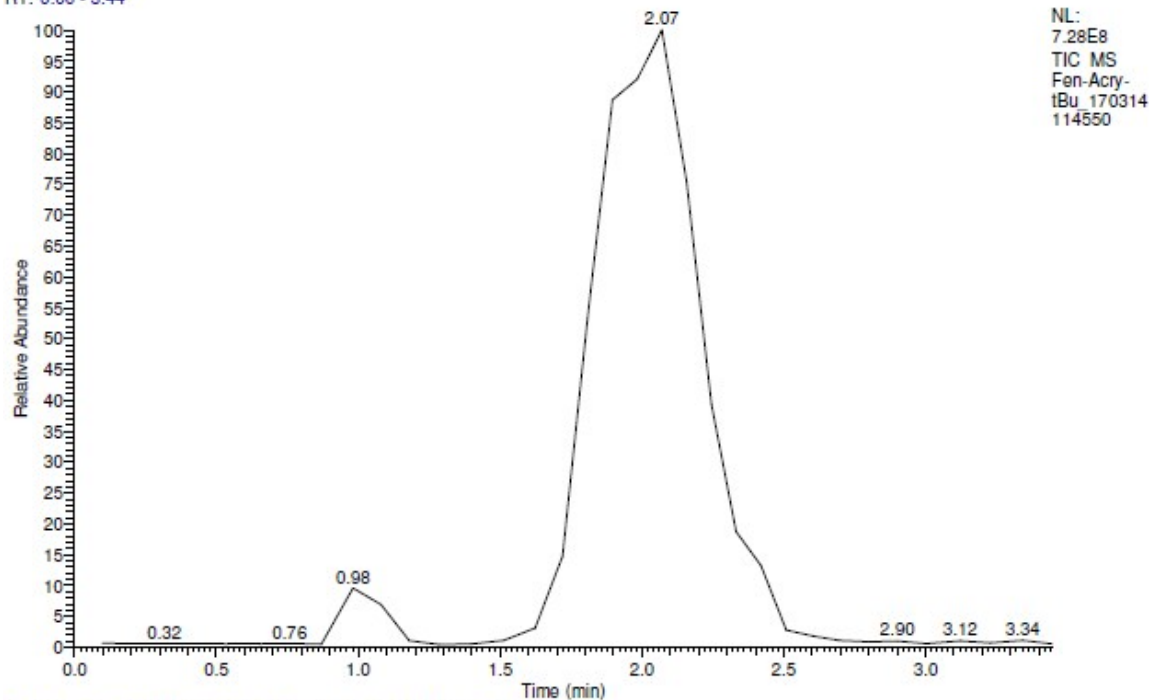


Fig. S44 ESI-MS spectrum of Fen-Acry-Bu.

RT: 0.00 - 3.44



Fen-Acry-tBu_170314114550 #17-21 RT: 1.81-2.16 AV: 5 NL: 3.68E7
T: + p Full ms [150.00-1000.00]

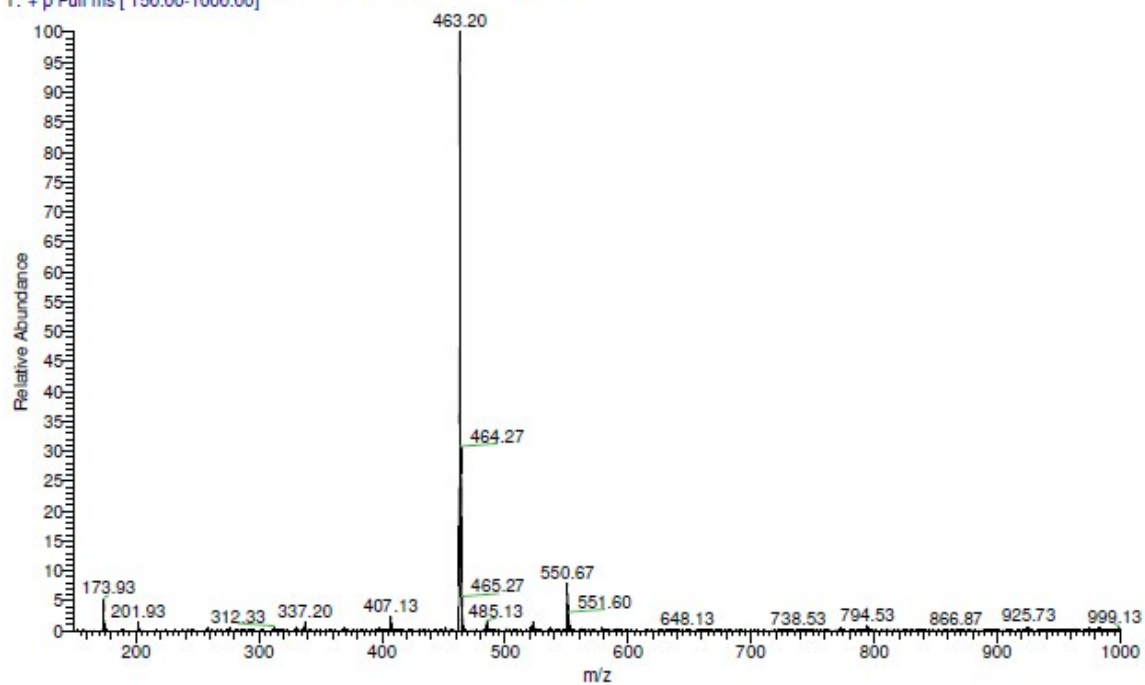
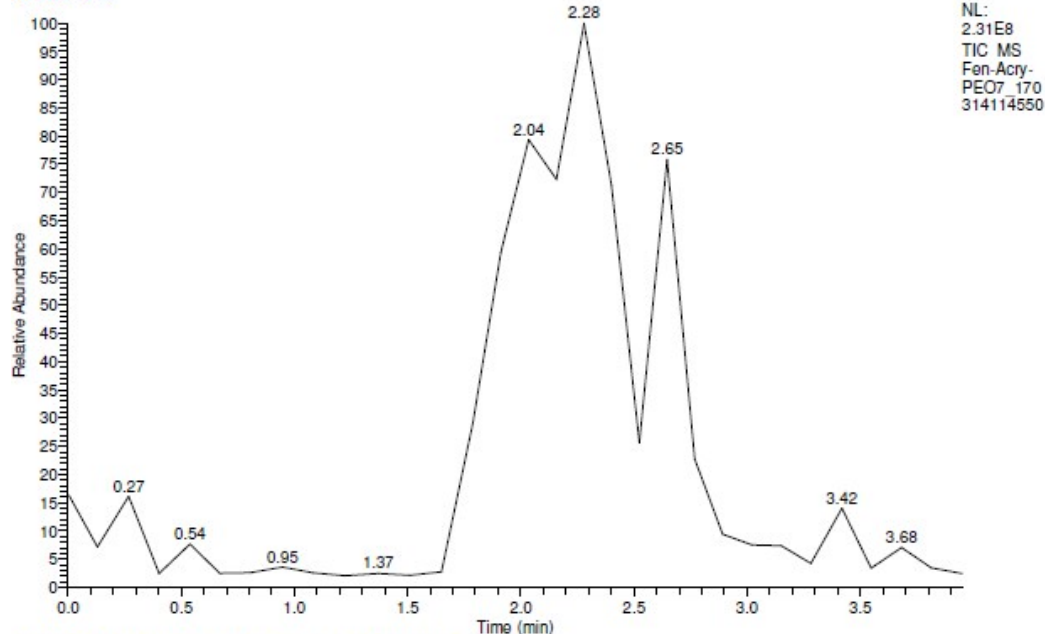


Fig. S45 ESI-MS spectrum of Fen-Acry-tBu.

RT: 0.00 - 3.95



Fen-Acry-PEO7_170314114550 #16-22 RT: 2.04-2.77 AV: 7 NL: 4.16E6

+ p Full ms [150.00-1500.00]

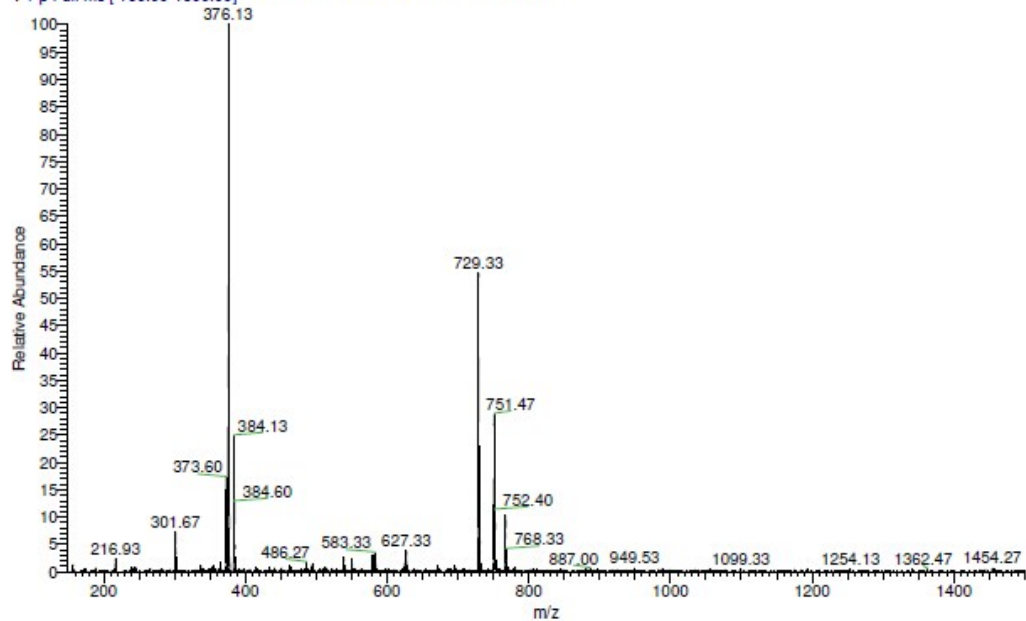
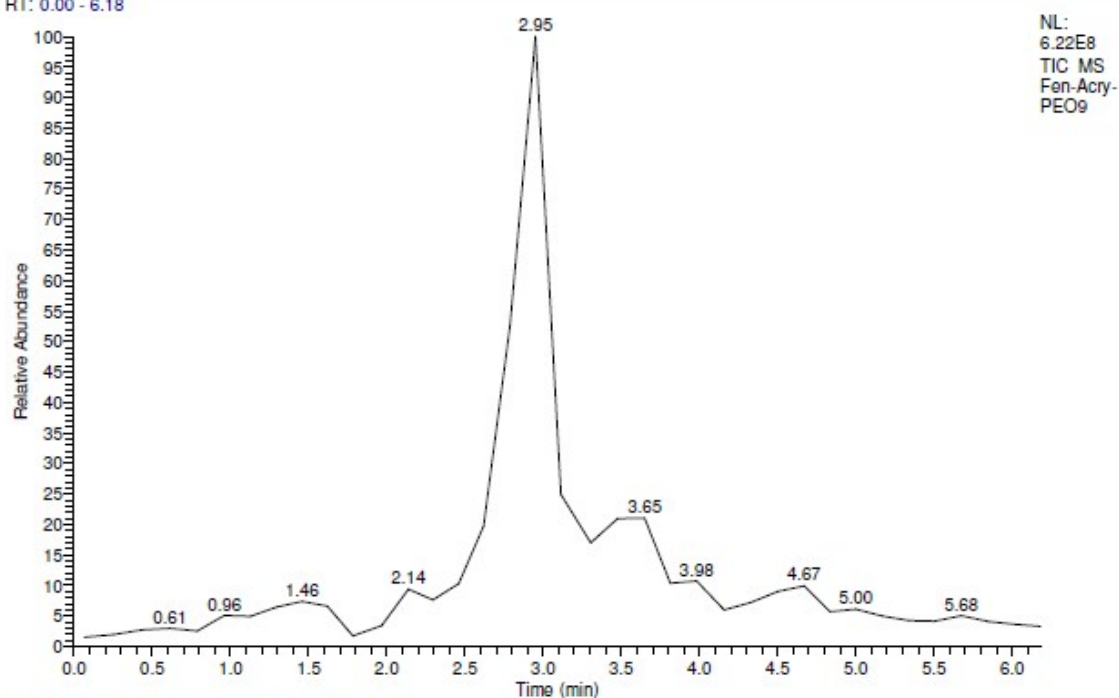


Fig. S46 ESI-MS spectrum of Fen-Acry-PEO₇.

U:\data\AHN\Averick\Fen-Acry-PEO9
Fen-Acry-PEO9
RT: 0.00 - 6.18

12/20/2016 1:33:03 PM

Fen-Acry-PEO9



Fen-Acry-PEO9 #21 RT: 3.48 AV: 1 NL: 7.18E5
T: + p Full ms [150.00-2000.00]

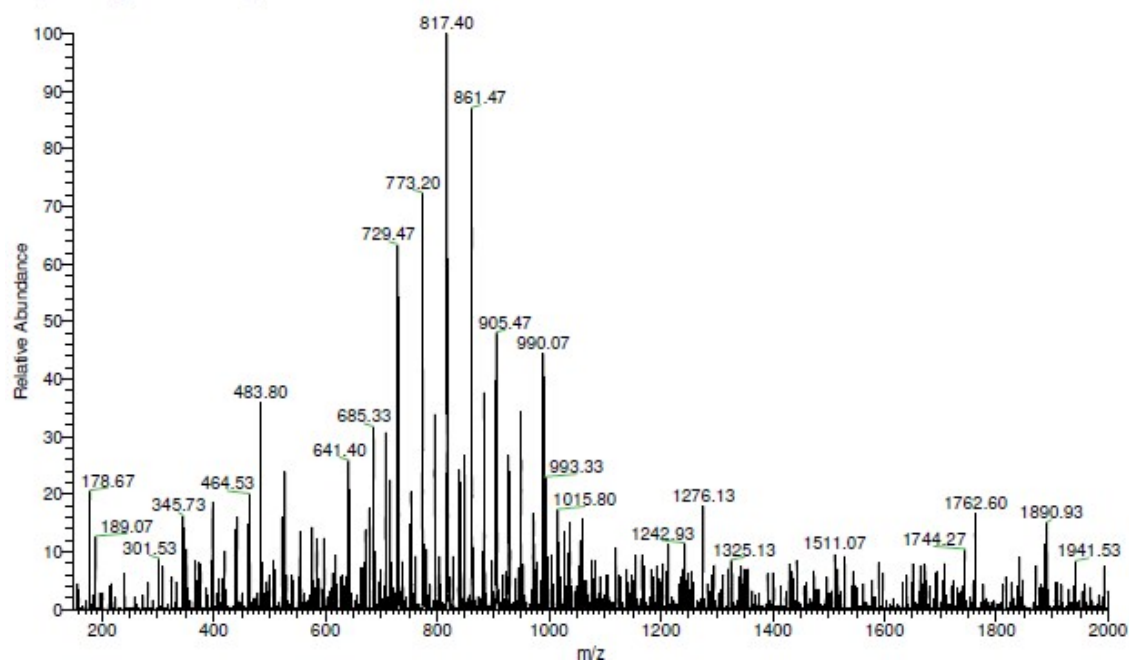
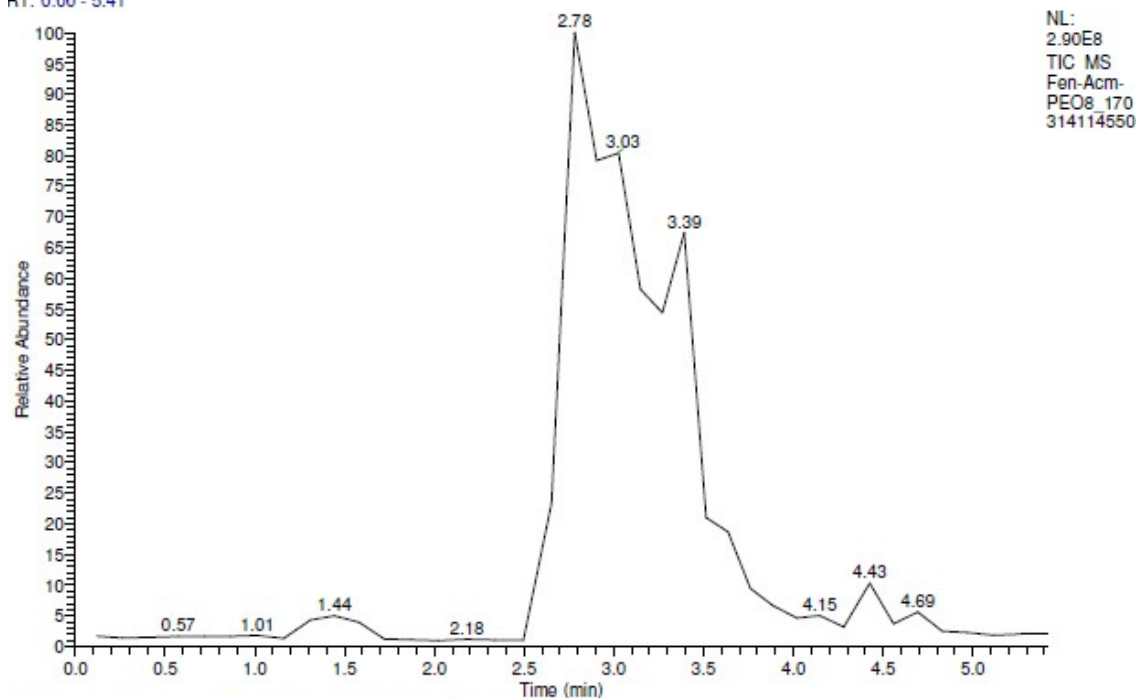
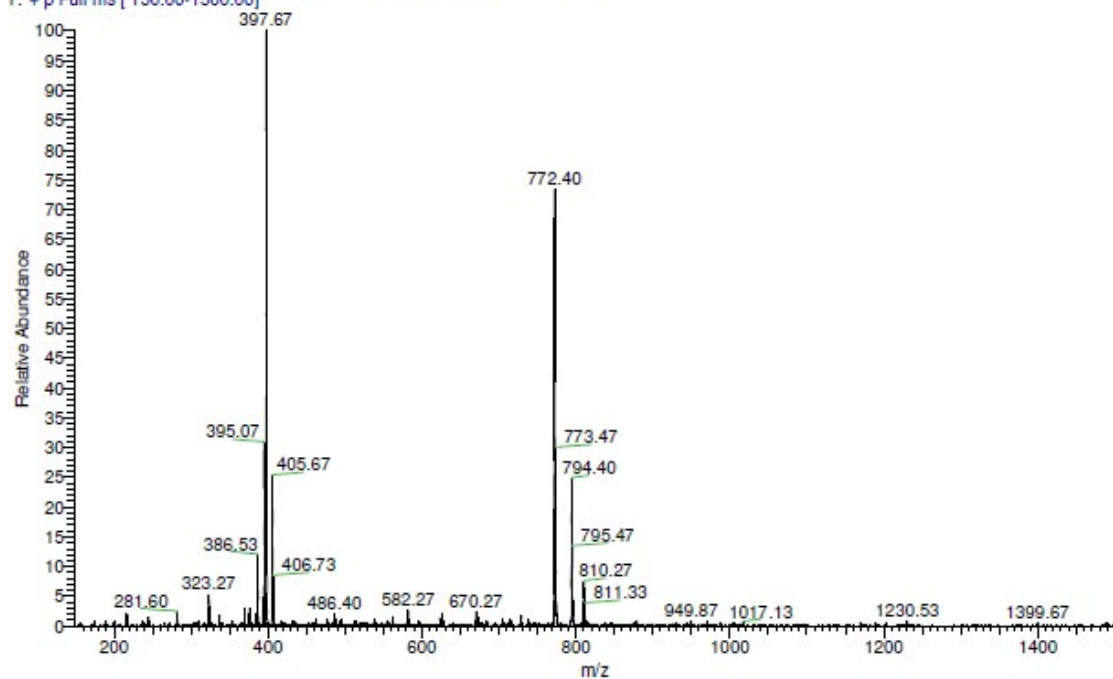


Fig. S47 ESI-MS spectrum of Fen-Acry-PEO₉.

RT: 0.00 - 5.41

Fen-Acm-PEO8_170314114550 #19-24 RT: 2.78-3.39 AV: 6 NL: 5.31E6
T: + p Full ms [150.00-1500.00]Fig. S48 ESI-MS spectrum of Fen-Acmd-PEO₈.