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Upconversion Nanotheranostic Agent Activated by Hypoxia Combined with NIR Irradiation for Selective Hypoxia Imaging and Tumour Therapy

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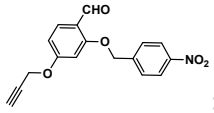
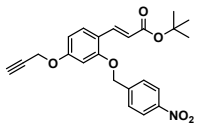
Supplementary Information

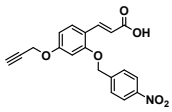
1. The characterization of FDU-CA_E-NO_2 and UCNP-CA_E-FDU/NO_2

2-(4-Nitrobenzyloxy)-4-(prop-2-ynyloxy)benzaldehyde (2) 

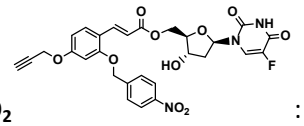
: A yellow solid, Mp: 163.3-164.8 °C; ^{1}H-NMR (600 MHz, DMSO-d_6): δ 10.31 (s, 1 H), 8.28 (d, 2 H, *J* = 8.4 Hz,), 7.80 (d, 2 H, *J* = 8.4 Hz), 7.73 (d, 1 H, *J* = 8.4 Hz), 6.86 (d, 1 H, *J* = 2.4 Hz), 6.76 (d, 1 H, *J* = 8.4 Hz), 5.46 (s, 2 H), 4.94 (d, 2 H, *J* = 2.4 Hz), 3.64 (s, 1 H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm): δ 187.42, 163.66, 161.66, 147.10, 144.15, 130.18, 128.19, 123.68, 118.99, 107.70, 100.66, 78.90, 78.38, 68.67, 56.04. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}NO_5$ $[M+H]^+$ 312.08665, found 312.08673.

(*E*)-*tert*-Butyl-3-(2-(4-nitrobenzyloxy)-4-(prop-2-ynyloxy)phenyl) acrylate (4) 

: A white solid. Mp: 145.7-148.3 °C; ^{1}H-NMR (DMSO-d_6, 600 MHz, ppm): δ 8.29 (d, 2H, *J* = 9.0 Hz), 7.83 (d, 1 H, *J* = 15.6 Hz), 7.74 (d, 2 H, *J* = 9.0 Hz), 7.72 (d, 1H, *J* = 9.0 Hz), 6.76 (d, 1H, *J* = 2.4 Hz), 6.67 (dd, 1H, *J* = 9.0, 2.4 Hz,) 6.42 (d, 1H, *J* = 15.6 Hz) , 5.39 (s, 2H), 4.86 (d, 2H, *J* = 2.4 Hz), 3.60 (s, 1H) , 1.47 (s, 9H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm): δ 166.00, 160.20, 157.53, 147.11, 144.40, 137.70, 129.67, 128.22, 123.67, 117.71, 116.37, 107.27, 100.73, 79.46, 78.74, 78.51, 68.64, 55.73, 27.81. HRMS (ESI) *m/z* calcd for $C_{23}H_{23}NO_6$ $[M+H]^+$ 410.15981, found 410.16003.

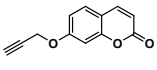
(*E*)-3-(2-(4-Nitrobenzyloxy)-4-(prop-2-ynyloxy)phenyl)acrylic acid (5) 

: A white solid, Mp: 197.6-199.5 °C. ^{1}H-NMR (DMSO-d_6, 600 MHz, ppm): δ 8.28 (d, 2 H, *J* = 8.4 Hz), 7.73 (d, 2 H, *J* = 8.4 Hz), 7.50 (d, 1 H, *J* = 8.4 Hz), 7.47 (d, 1 H, *J* = 15.6 Hz), 6.69 (d, 1 H, *J* = 2.4 Hz), 6.60 (dd, 1 H, *J* = 9.0, 2.4 Hz), 6.30 (d, 1 H, *J* = 15.6 Hz) , 5.34 (s, 2 H), 4.79 (d, 2 H, *J* = 2.4 Hz), 3.56 (s, 1 H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm): δ 167.99, 160.14, 157.54, 147.18, 144.35, 138.22, 128.39, 123.73, 117.22, 116.48, 107.29, 100.76, 78.76, 78.51, 68.64, 55.74. HRMS (ESI) *m/z* calcd for $C_{19}H_{15}NO_6$ $[M+H]^+$ 354.09721, found 354.09723.

FDU-CA_E-NO_2 

: A white solid. Mp: 143.4-146.3 °C. ^{1}H NMR (DMSO-d_6, 600 MHz, ppm): δ 11.88 (s, 1 H), 8.28 (d, 2 H, *J* = 8.7 Hz), 7.92 (d, 1 H, *J* = 16.0 Hz), 7.87 (d, 1 H, *J* = 6.8 Hz), 7.75 (d, 1 H, *J* = 8.8 Hz), 7.72 (d, 2 H, *J* = 8.7 Hz), 6.77 (d, 1 H, *J* = 2.0 Hz), 6.69 (dd, 1 H, *J* = 8.8, 2.0 Hz), 6.60 (d, 1 H, *J* = 16.0 Hz), 6.14 (t, 1 H, *J* = 6.4 Hz), 5.51 (d, 1 H, *J* = 4.4 Hz), 5.40 (d, 2 H, *J* = 3.2 Hz), 4.87 (d, 2 H, *J* = 2.0

Hz), 4.40-4.28 (m, 3 H), 4.01 (s, 1 H), 3.61 (s, 1 H), 2.24-2.09 (m, 2 H). ^{13}C NMR (DMSO-d_6, 150 MHz, ppm): δ 166.47, 160.54, 157.03, 157.03, 156.77, 148.86, 147.09, 144.29, 141.12, 139.43, 138.83, 130.21, 128.26, 124.53, 124.19, 123.71, 116.12, 115.53, 107.34, 100.73, 84.55, 83.97, 78.71, 78.59, 70.00, 68.65, 63.67, 55.77. HRMS (ESI) *m/z* calcd for $C_{28}H_{24}N_3FO_{10}$ $[M+H]^+$ 582.15185, found 582.15216.

7-Propargyloxycoumarin (CM)  : A white solid yield, Mp: 70.3-71.8 °C. ^{1}H NMR ($CDCl_3$, 600 MHz, ppm): δ 7.64 (d, 1 H, J = 9.6 Hz), 7.41 (d, 1 H, J = 8.4 Hz), 6.94 (s, 1 H), 6.92 (d, 1 H, J = 8.4 Hz), 6.29 (d, 1 H, J = 9.6 Hz), 4.77 (d, 2 H, J = 2.4 Hz), 2.56 (s, 1 H). ^{13}C NMR ($CDCl_3$, 150 MHz, ppm): δ 160.98, 160.55, 155.66, 143.27, 128.84, 113.67, 113.20, 113.05, 102.16, 77.38, 76.57, 56.22. HRMS (ESI) *m/z* calcd for $C_{12}H_8O_3$ $[M+H]^+$ 201.05462, found 201.05461.

2. The size of UCNP-CA$_E$-FDU/NO$_2$ and UCNP analyzed by DLS and TEM

The samples for TEM and DLS were prepared by dispersing UCNP-CA$_E$-FDU/NO$_2$ **(**200 μg/mL**)** in PBS (25 mmol/L, pH 7.4) with intermittent ultrasonic by a needle type ultrasonic instrument. The samples of UCNP were dispersed in cyclohexane (20 μg/mL). The TEM sample was prepared by dropping on the surface of a copper grid and negative staining for 30 s by a droplet of phosphotungstic acid. The DLS of the samples were measured using a Nano-ZS system in disposable cuvettes.

3. HPLC and HRMS analysis

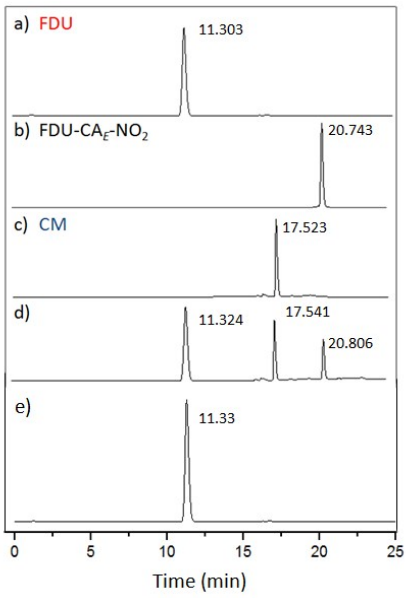


Figure S1. HPLC profiles of a) FDU; b) FDU-CA$_E$-NO$_2$; c) CM; d) solution of FDU-CA$_E$-NO$_2$ incubated with $Na_2S_2O_4$ and then illuminated by UV light at 365 nm; e) UCNP-CA$_E$-FDU/NO$_2$ incubated with $Na_2S_2O_4$ and then illuminated by NIR light at 980 nm

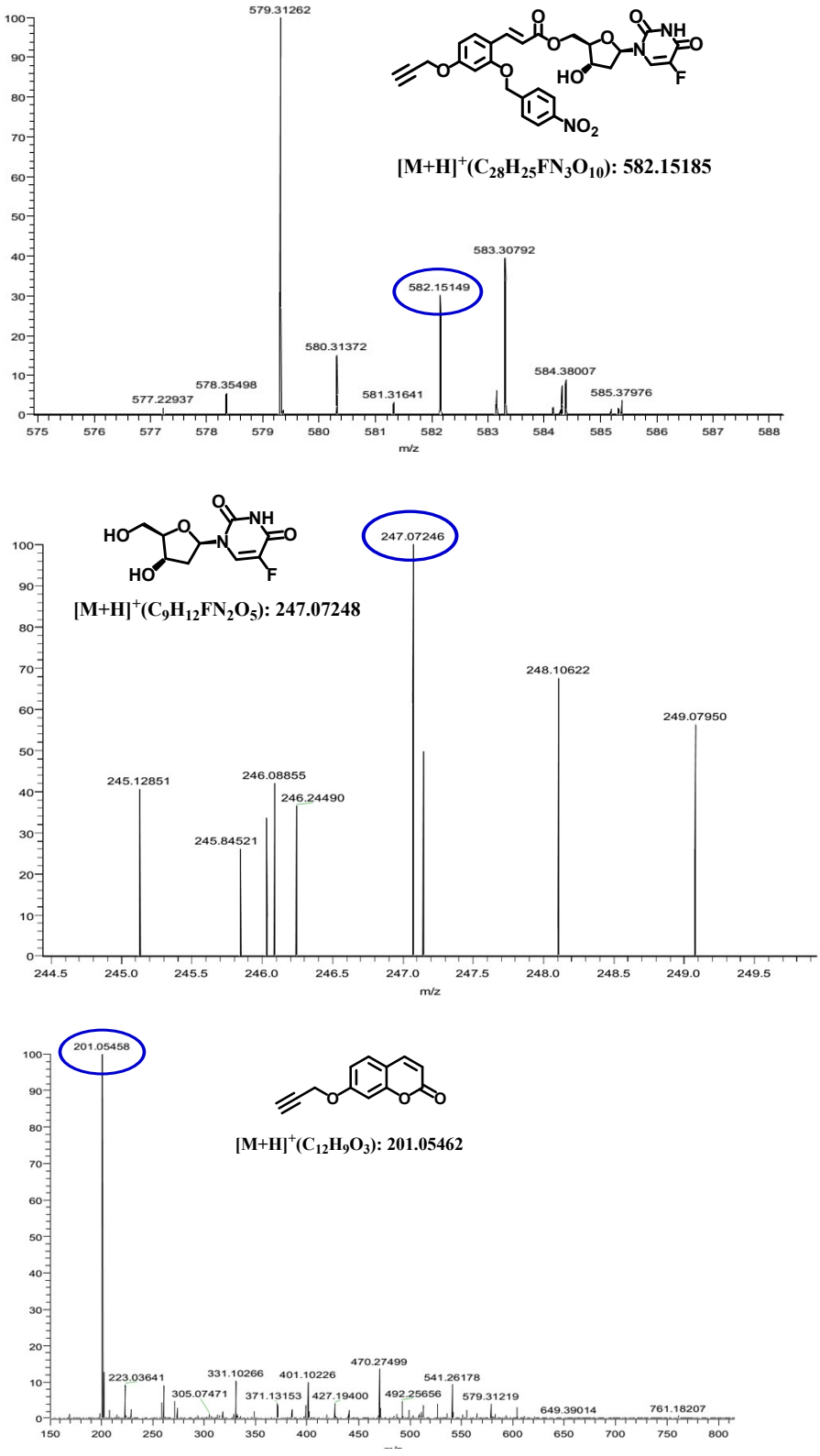


Figure S2. HRMS of the solution of **FDU-CA$_E$-NO$_2$** incubated with $Na_2S_2O_4$ and then illuminated by UV-light at 365 nm

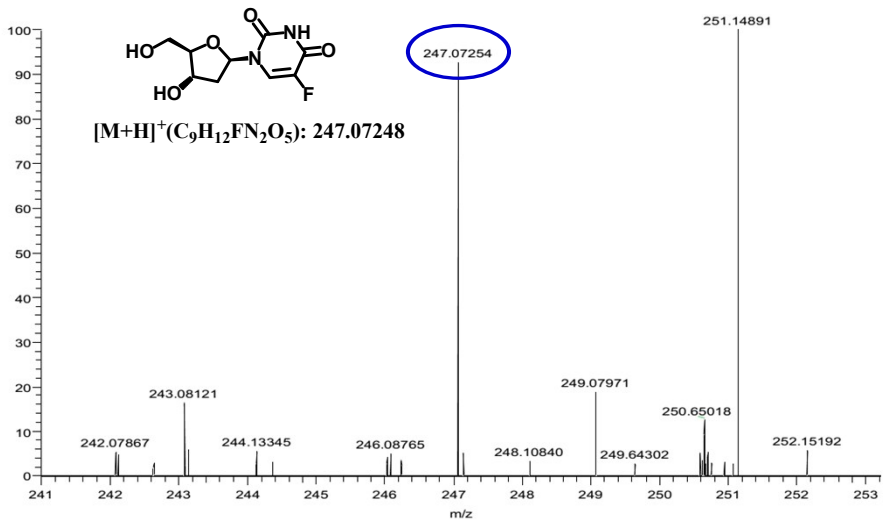


Figure S3. HRMS of the mixture of **UCNP-CA$_F$-FDU/NO$_2$** with $Na_2S_2O_4$ and then illuminated by NIR-light at 980 nm

4. NMR, IR and HRMS spectra

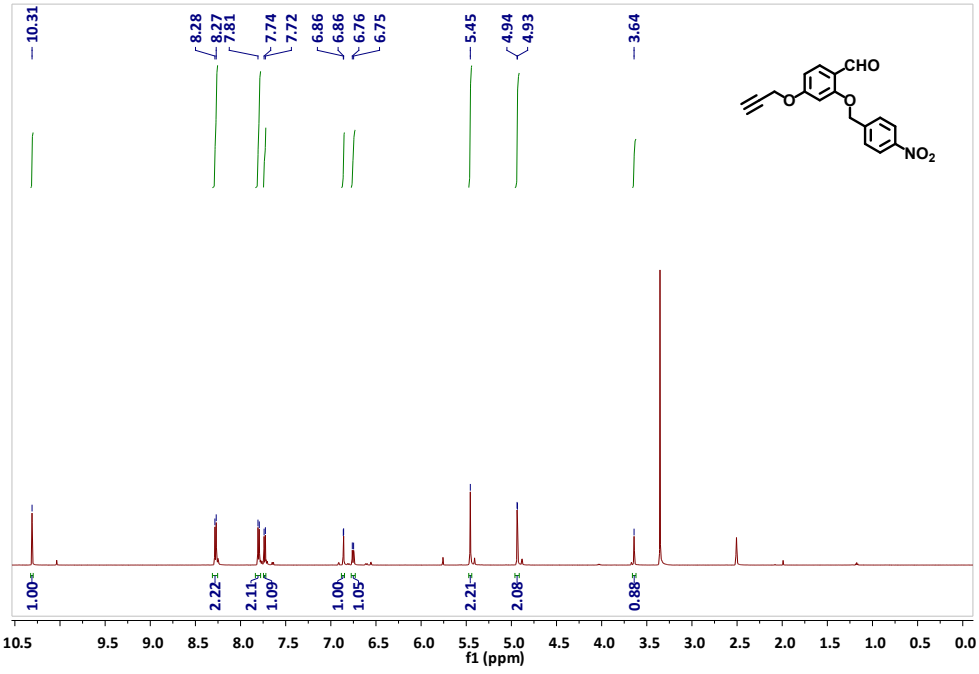


Figure S4. ^{1}H NMR of 2-(4-nitrobenzyloxy)-4-(prop-2-ynyloxy)benzaldehyde **(2)**

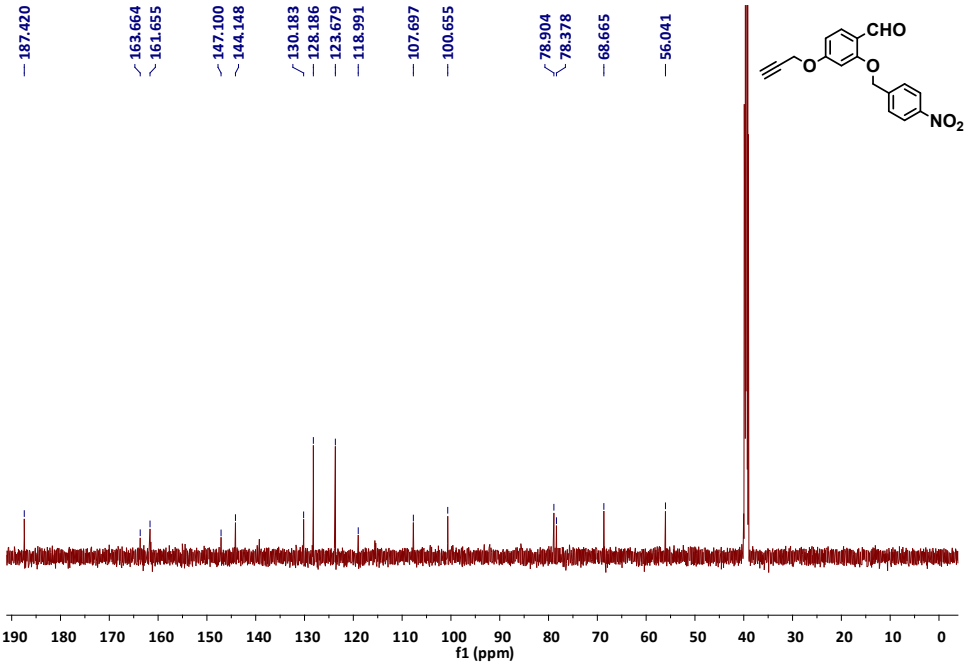


Figure S5. ^{13}C NMR of 2-(4-nitrobenzyloxy)-4-(prop-2-ynyloxy)benzaldehyde **(2)**

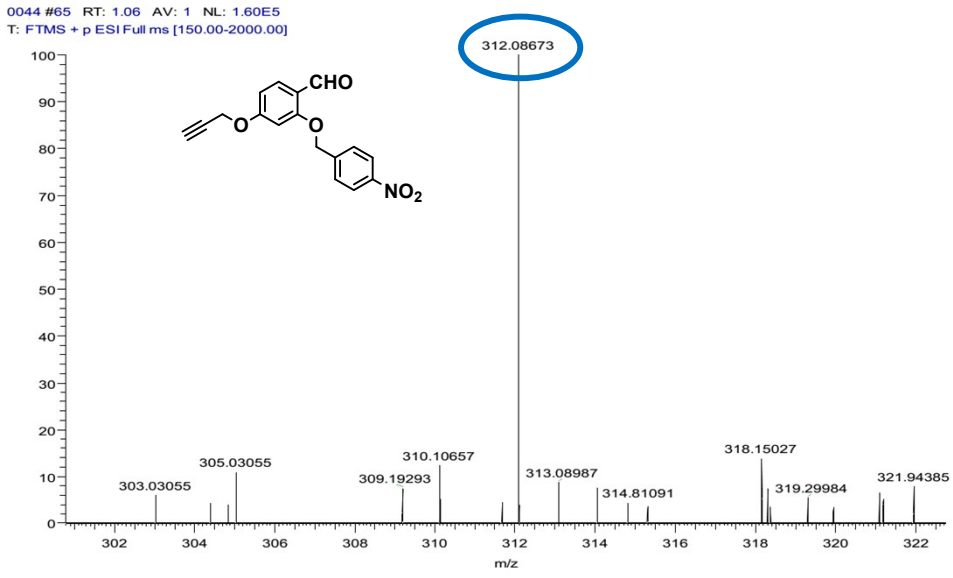


Figure S6. HRMS of 2-(4-nitrobenzyloxy)-4-(prop-2-ynyloxy)benzaldehyde **(2)**

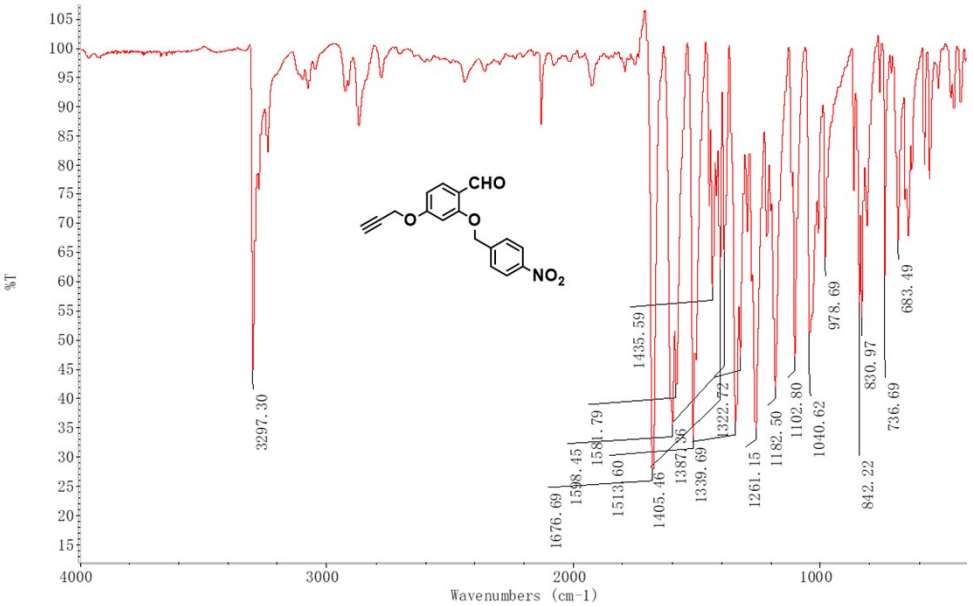


Figure S7. IR of 4-nitrobenzyloxy-4-diethylaminobenzaldehyde (**2**)

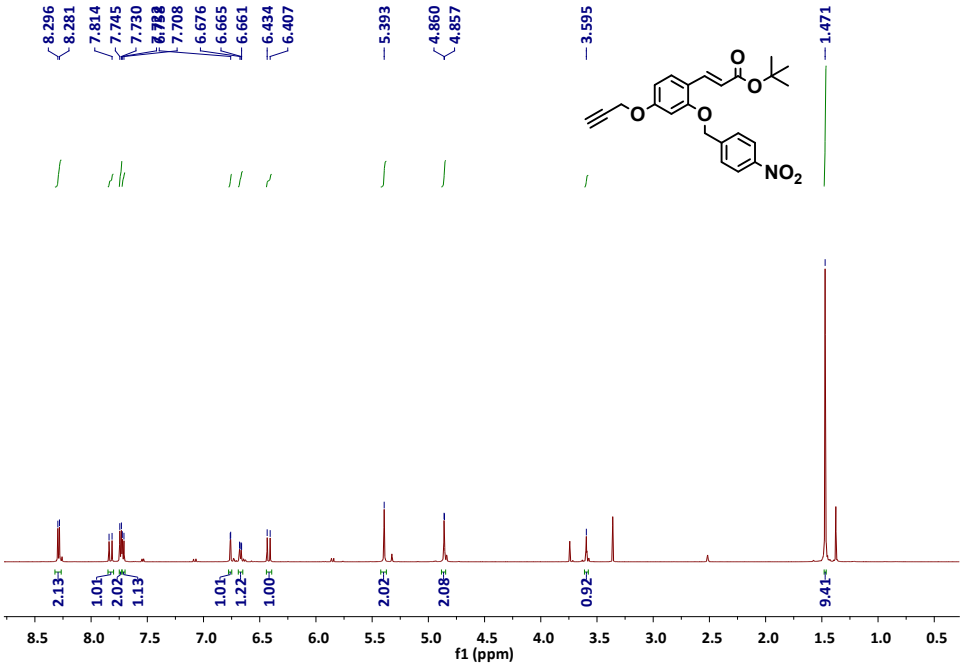


Figure S8. ^{1}H NMR of (*E*)-*tert*-butyl-3-(2-(4-nitrobenzyloxy)-4-(prop-2-ynyloxy)phenyl)acrylate **(4)**

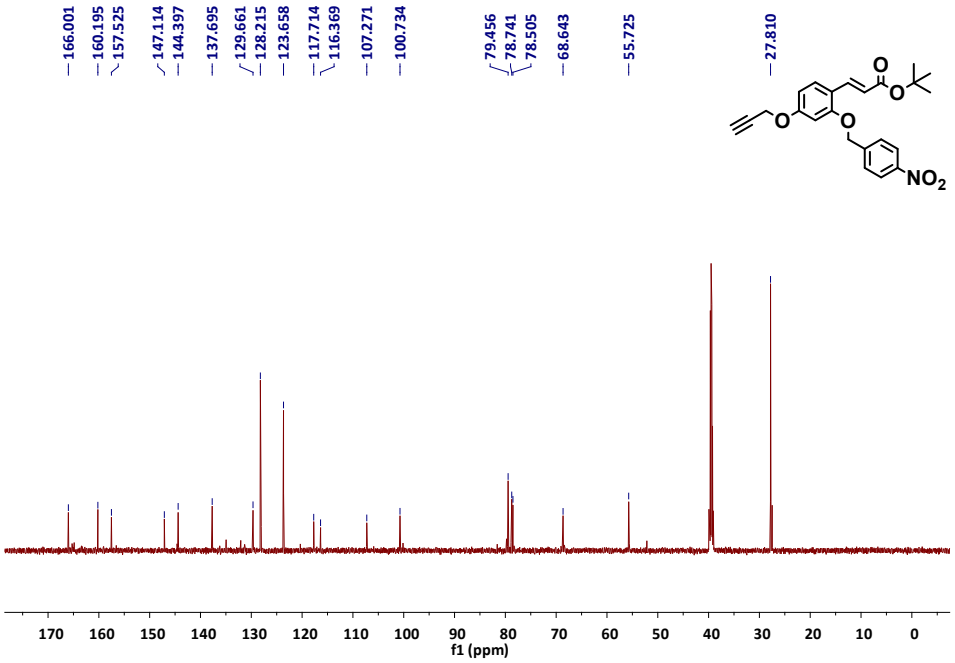


Figure S9. ^{13}C NMR of (*E*)-*tert*-butyl-3-(2-(4-nitrobenzyloxy)-4-(prop-2-ynyloxy)phenyl)acrylate **(4)**

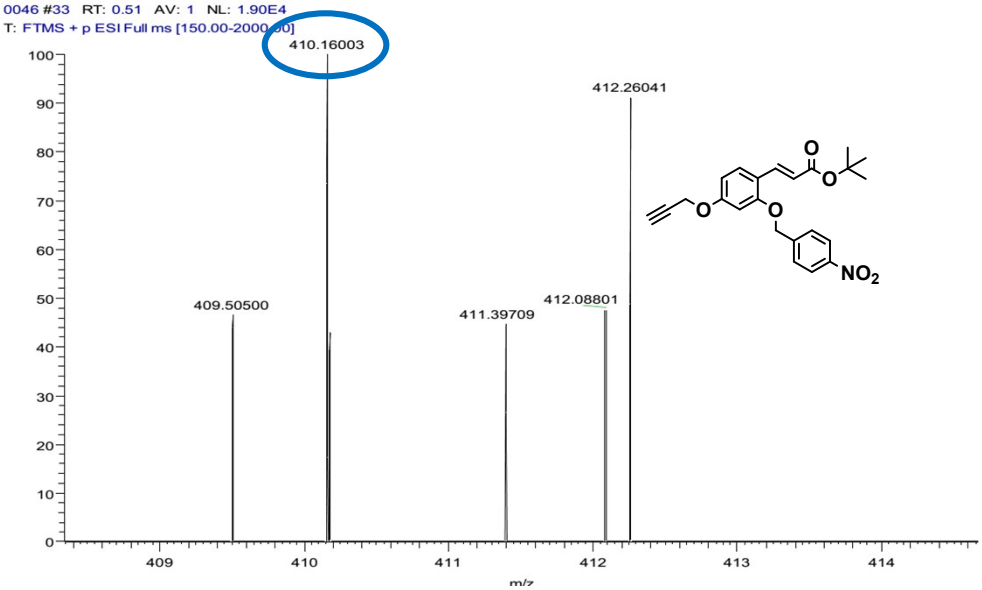


Figure S10. HRMS of (*E*)-*tert*-butyl-3-(2-(4-nitrobenzyloxy)-4-(prop-2-ynyloxy)phenyl)acrylate **(4)**

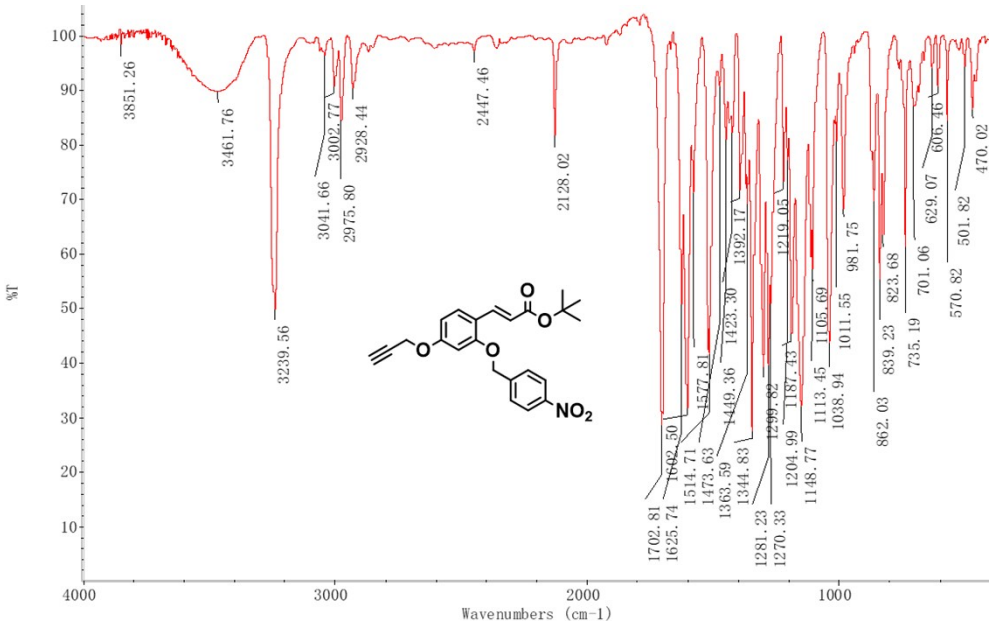


Figure S11. IR of (*E*)-*tert*-butyl-3-(2-(4-nitrobenzyloxy)-4-(prop-2-ynyloxy)phenyl)acrylate **(4)**

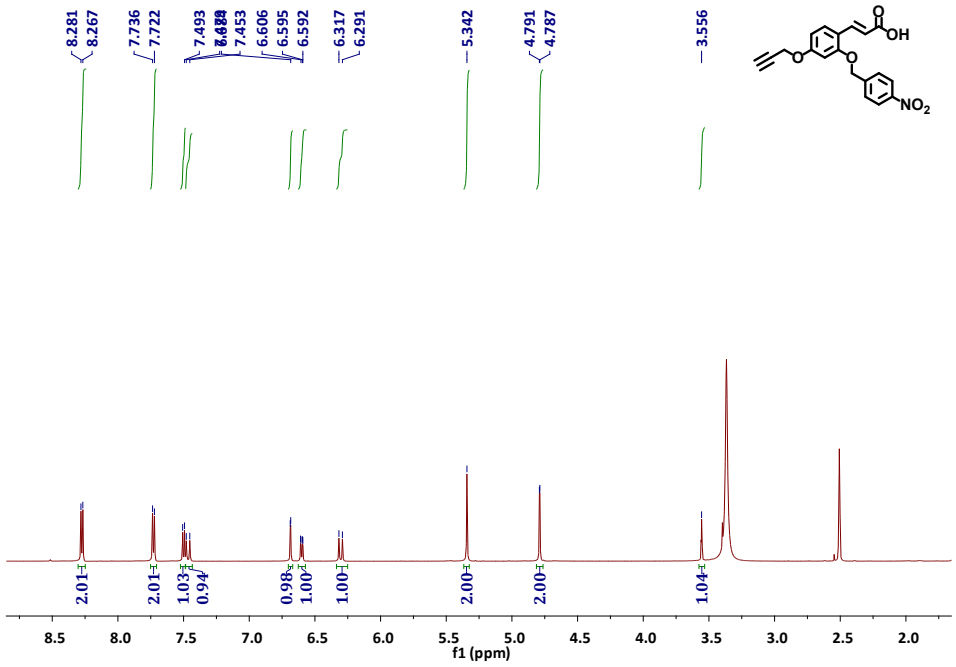


Figure S12. ^{1}H NMR of (*E*)-3-(2-(4-nitrobenzyloxy)-4-(prop-2-ynyloxy)phenyl)acrylic acid **(5)**

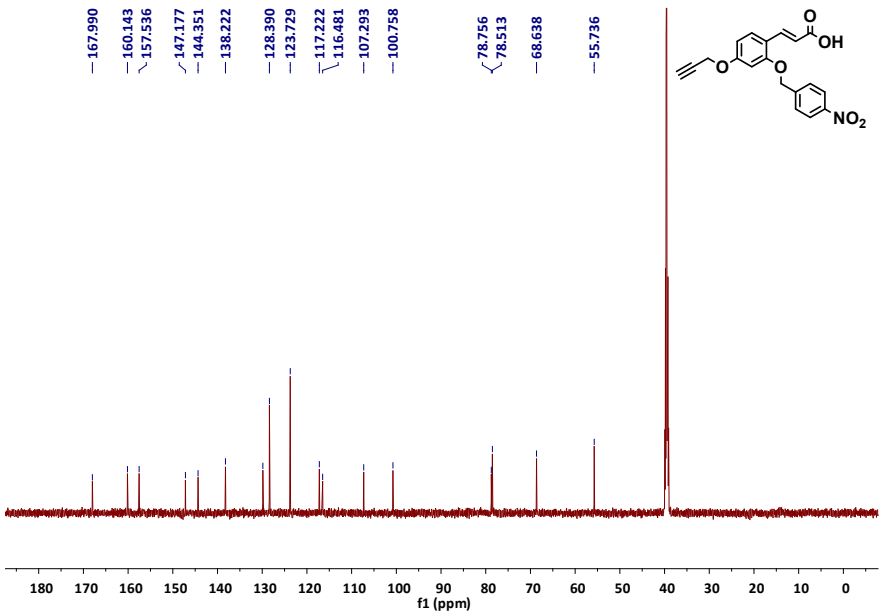


Figure S13. ^{13}C NMR of (*E*)-3-(2-(4-nitrobenzyloxy)-4-(prop-2-ynyloxy)phenyl)acrylic acid **(5)**

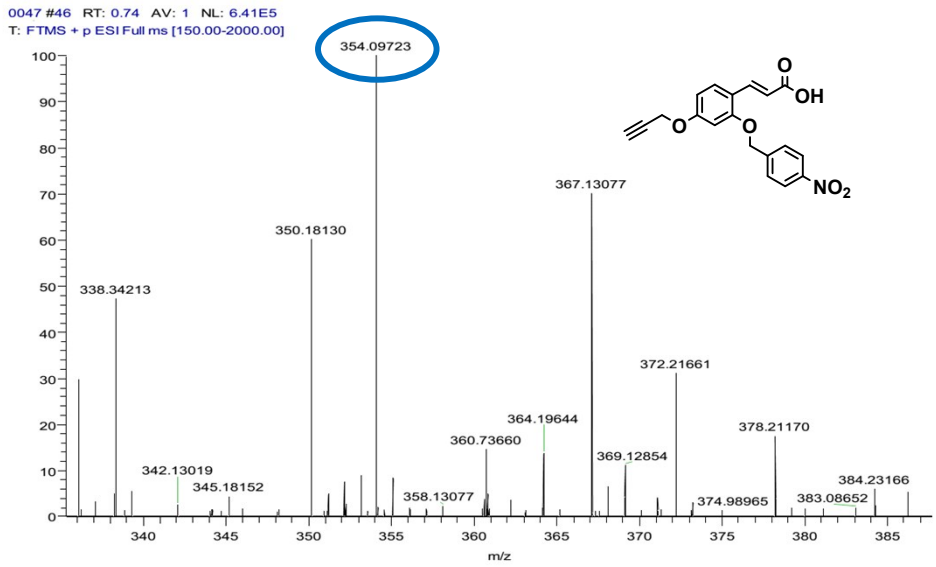


Figure S14. HRMS of (*E*)-3-(2-(4-nitrobenzyloxy)-4-(prop-2-ynyloxy)phenyl)acrylic acid **(5)**

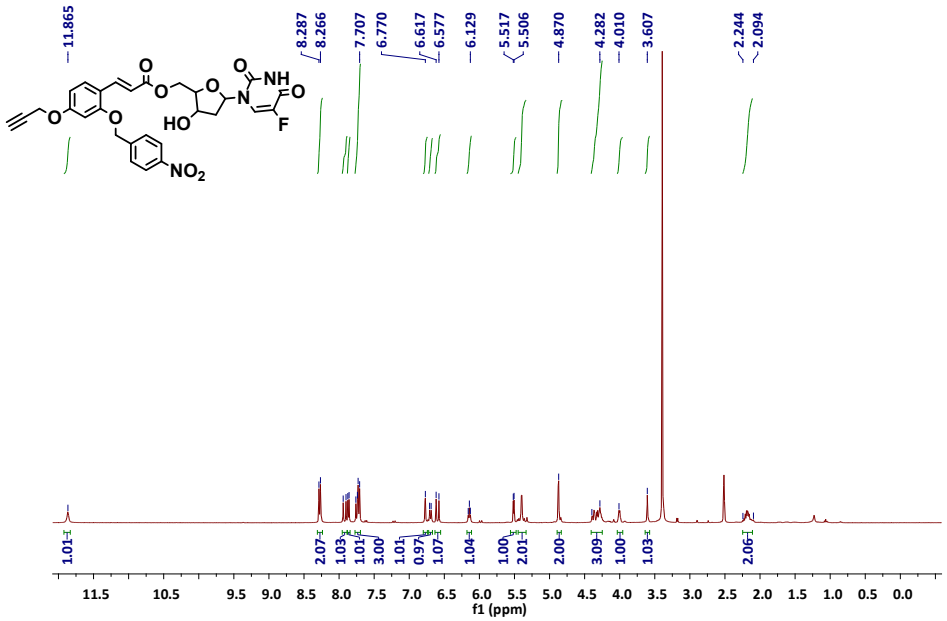


Figure S15. ^{1}H NMR of **FDU-CA$_E$-NO$_2$**

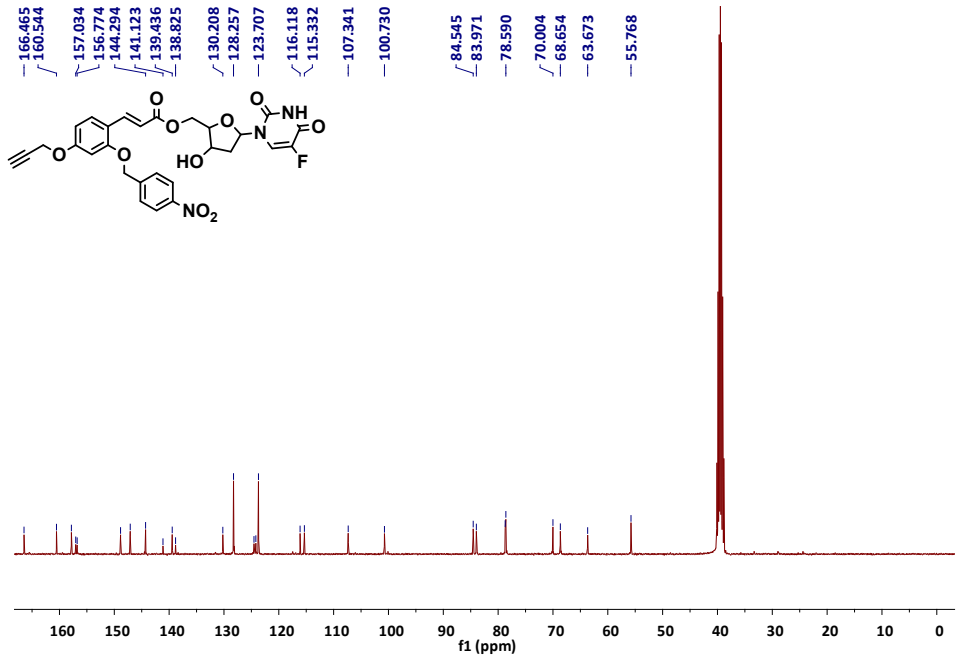


Figure S16. ^{13}C NMR of **FDU-CA$_E$-NO$_2$**

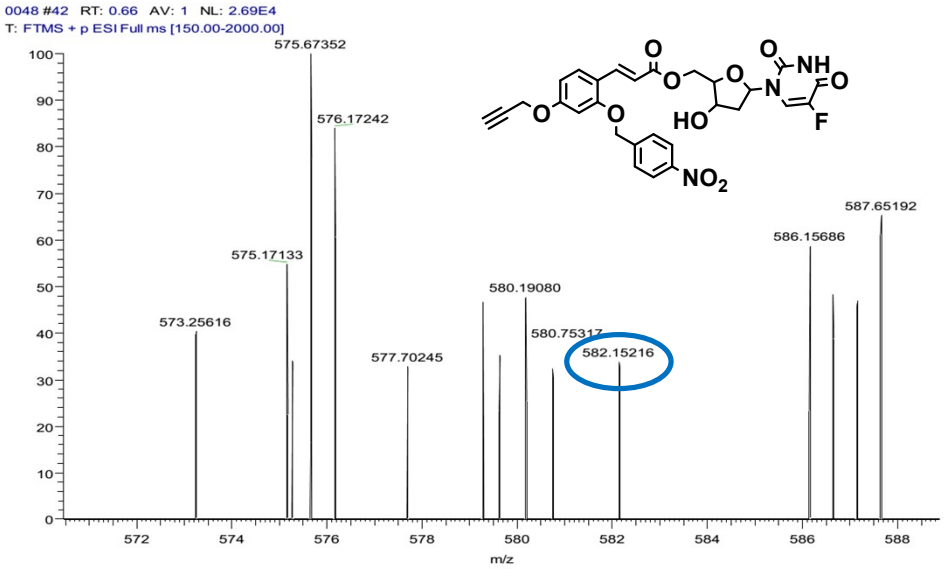


Figure S17. HRMS of **FDU-CA$_E$-NO$_2$**

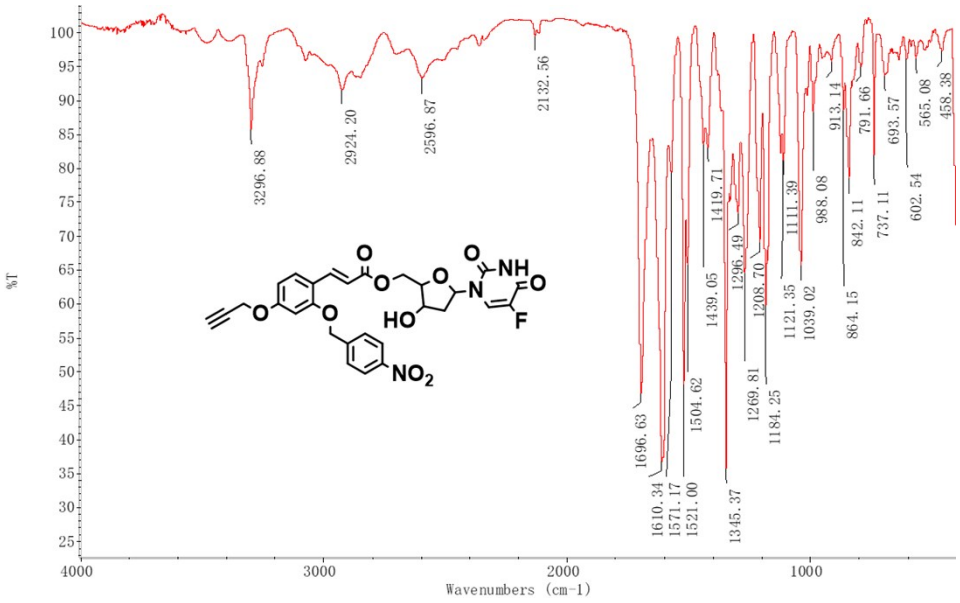


Figure S18. IR of **FDU-CA$_E$-NO$_2$**

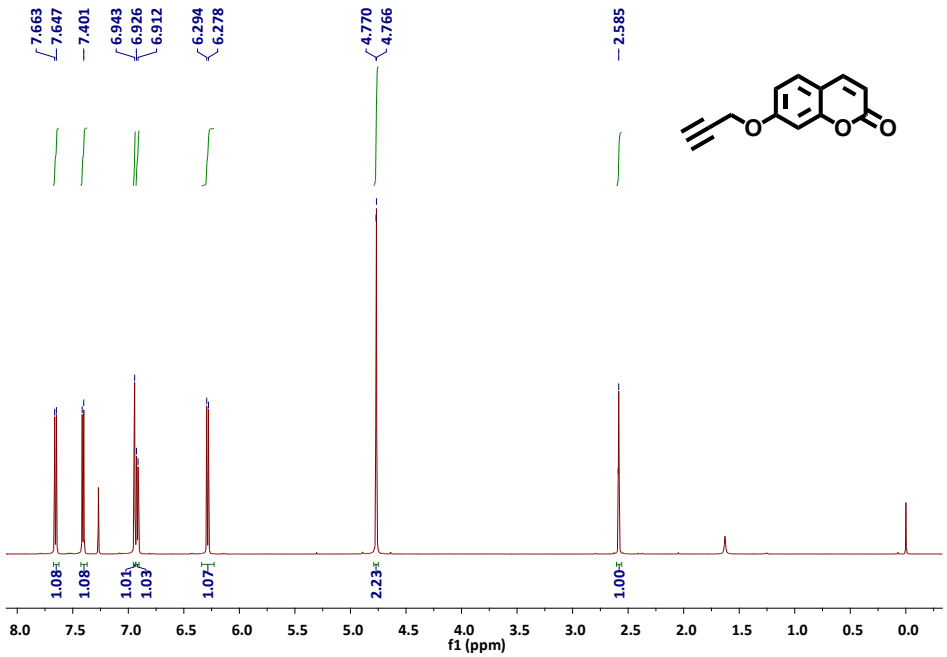


Figure S19. ^{1}H NMR of **CM**

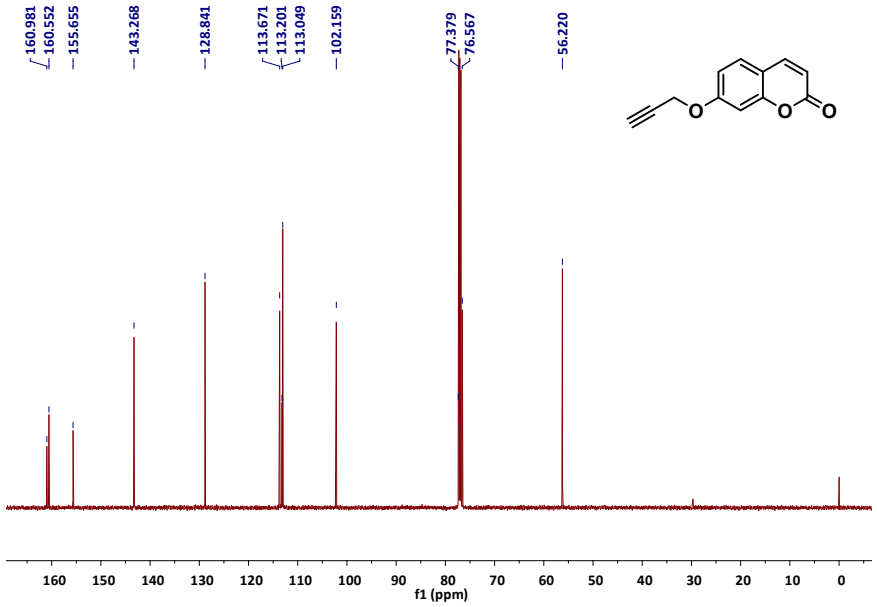


Figure S20. ^{13}C NMR of **CM**

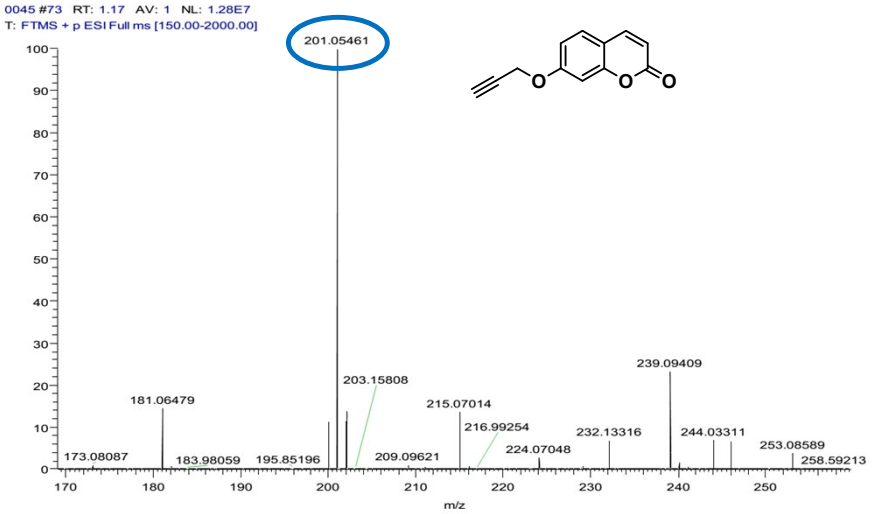


Figure S21. HRMS of **CM**

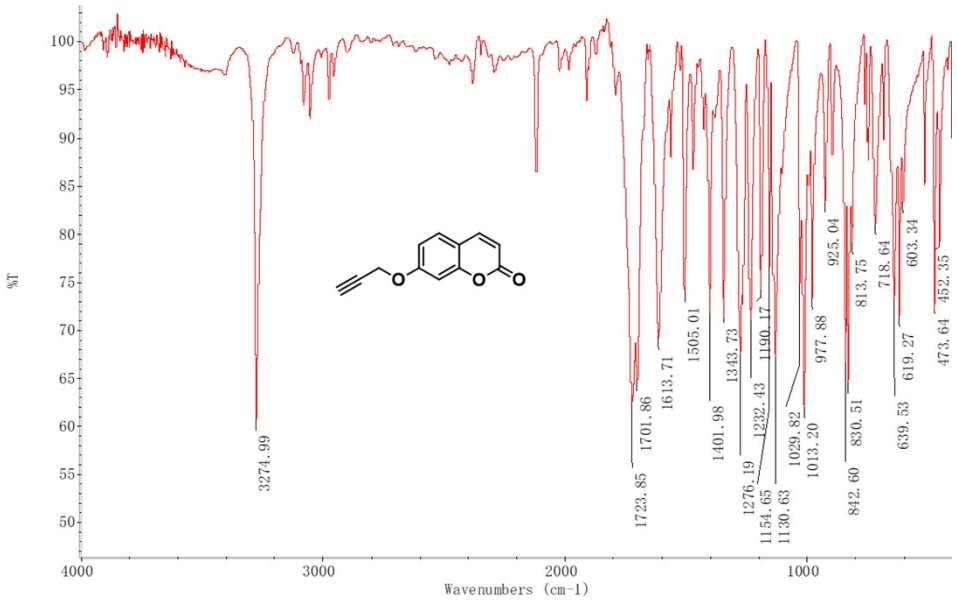


Figure S22. IR of **CM**

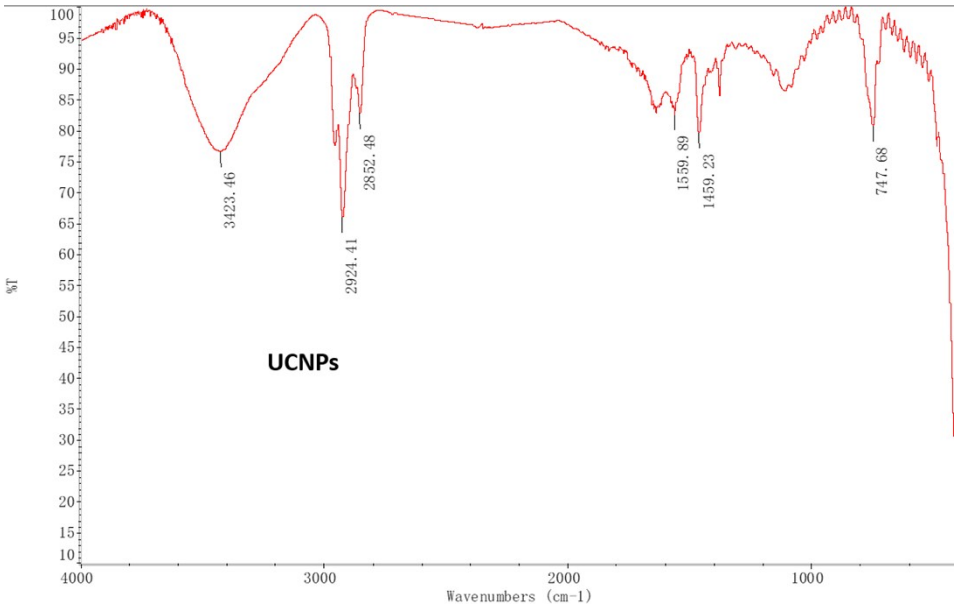


Figure S23. IR of **UCNPs**

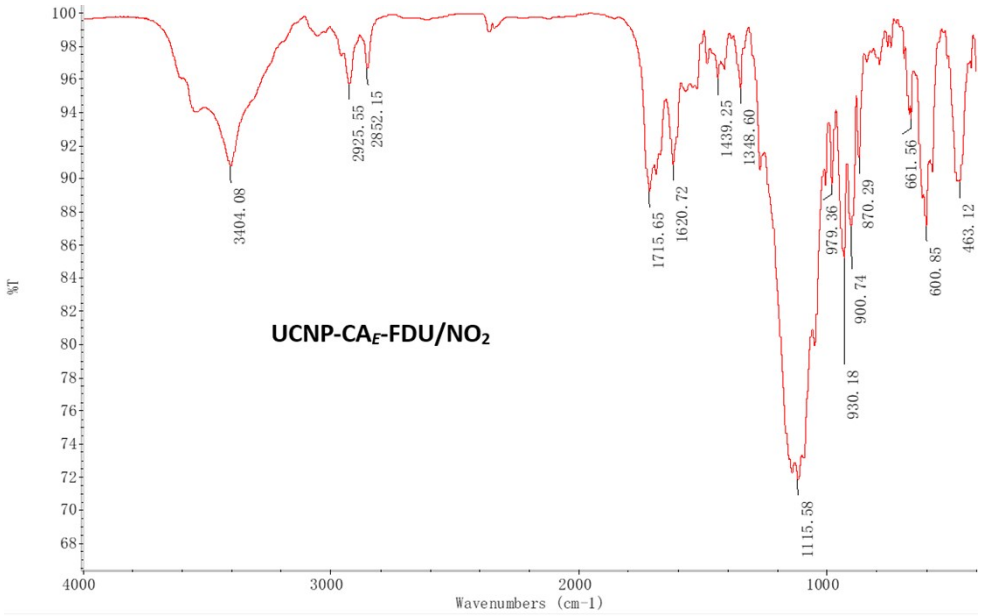


Figure S24. IR of **UCNP-CA$_E$-FDU/NO$_2$**