Electronic Supplementary Information

Molecularly Imprinted Nanoparticles as Tailor-Made Sensors for Small Fluorescent Molecules

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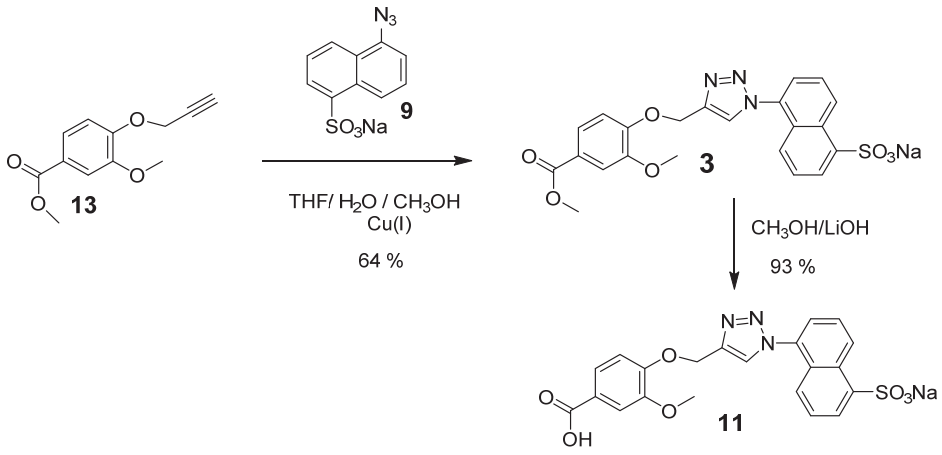
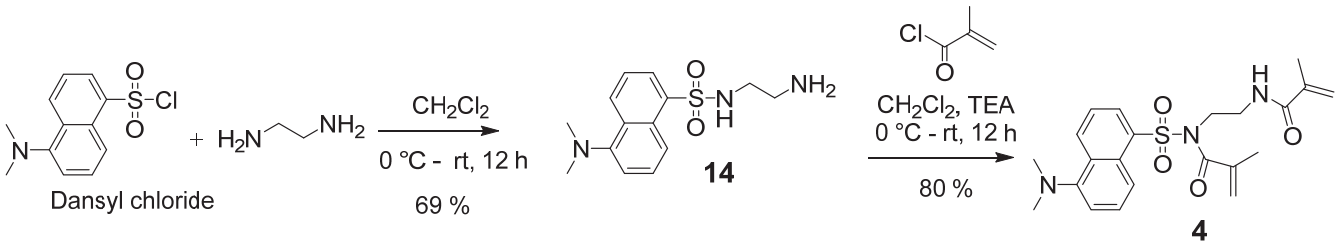
General Method

Methanol, methylene chloride, and ethyl acetate were of HPLC grade and were purchased from Fisher Scientific. All other reagents and solvents were of ACS-certified grade or higher, and were used as received from commercial suppliers. Routine ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 or on a Varian VXR-400 spectrometer. ESI-MS mass was recorded on Shimadzu LCMS-2010 mass spectrometer. Dynamic light scattering (DLS) was performed on a PD2000DLS+ dynamic light scattering detector. Fluorescence spectra were recorded at ambient temperature on a Varian Cary Eclipse Fluorescence spectrophotometer. Isothermal titration calorimetry (ITC) was performed using a MicroCal VP-ITC Microcalorimeter with Origin 7 software and VPViewer2000 (GE Healthcare, Northampton, MA).

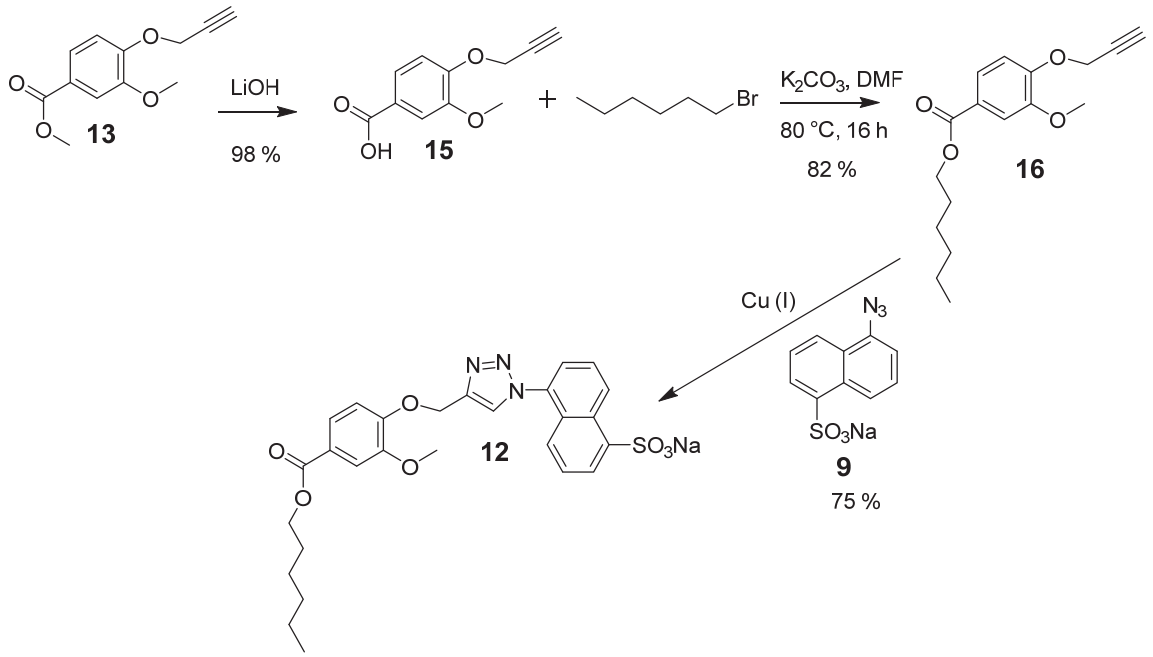
Scheme S1



Scheme S2



Scheme S3



Syntheses

Syntheses of compounds **1**,[1] **5**,[2] **6**,[3] **9**,[4] **10**,[5] **13**,[6] and **14**[7] were previously reported.

Compound 3. To a solution of **9** (0.18 g, 0.66 mmol), copper sulfate hydrate (0.13 g, 0.66 mmol), and sodium ascorbate (0.33 g, 1.32 mmol) in a 2:1:1 THF/H_2O/CH_3OH mixture (20 mL), **13** (0.18 g, 0.80 mmol) in THF (1 mL) was added dropwise. After being stirred at 40 °C for 12 h, the reaction mixture was concentrated. The residue was diluted with THF (10 mL). The solid was filtered off and the filtrate was concentrated in vacuo. The residue was then purified by column chromatography over silica gel using 1:3 methanol/methylene chloride as the eluent to give an off-white powder (0.25 g, 64%). ^{1}H NMR (400 MHz, CD_3OD, δ): 9.16 (d, *J* = 8.4 Hz, 1H), 8.51 (s, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.28(d, *J* = 6.8 Hz, 1H), 7.80 - 7.51 (m, 4H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.13(d, *J* = 8.4 Hz, 1H), 5.45(s, 2H), 3.90 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD = 1:1, δ): 167.7, 152.2, 149.7, 133.9, 130.4, 129.9, 129.8, 127.4, 127.3, 126.8, 126.2, 125.5, 124.5, 123.9, 123.9, 123.8, 113.5, 112.9, 62.8, 56.1, 52.3. ESI-HRMS (*m/z*): $[M-Na]^-$ calcd for $C_{22}H_{18}N_3O_7S$, 468.0860; found, 468.0865.

Compound 4. The compound was synthesized according to a modified literature procedure.[8] Compound **14** (110.0 mg, 0.38 mmol) and triethylamine (TEA, 56.7 mg, 0.56 mmol) were dissolved in dichloromethane (20 mL) and cooled on an ice bath. Methacryloyl chloride (58.8 mg, 0.56 mmol) in dichloromethane (5 mL) was added dropwise to the stirred solution. The ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. The solution was carefully acidified with 1M hydrochloric acid to pH 4 and washed with water (3 × 20 mL). The organic solvent was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography over silica gel using 1:20 methanol/methylene chloride as the eluent to give a yellow powder (102 mg, 63%). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.56 (d, *J* = 8.4 Hz, 1H), 8.27 (d, *J* = 7.2 Hz, 1H), 8.16 (d, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.70 –7.67 (m, 2H) , 7.28 (d, *J* = 5.6 Hz, 1H), 5.76 (s, 1H), 5.35 (d, *J* = 9.2 Hz, 2H), 5.19 (s, 1H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.40 (t, *J* = 6.4 Hz, 2H), 2.83 (s, 6H), 1.86 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 172.3, 168.5, 139.5, 139.3, 132.8, 132.8, 131.9, 129.7, 129.5, 128.8, 123.1, 121.1, 120.5, 120.5, 117.8, 115.4, 46.2, 45.4, 39.5, 29.7, 19.1, 18.5. ESI-HRMS (*m/z*): $[M + H]^+$ calcd for $C_{22}H_{28}N_3O_4S$, 430.1795; found, 430.1803.

Compound 16. To compound **15** (0.20 g, 0.97 mmol) in anhydrous DMF (30 mL), potassium carbonate (0.34 g, 2.43 mmol) and 1-bromohexane (0.24 mg, 1.46 mmol) were added. After being stirred at 80 ˚C for 16 h, the reaction mixture was cooled to room temperature and the solid was removed by vacuum filtration. The DMF solution was combined with water (50 mL) and the resulting solution was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography over silica gel using 1:6 ethyl acetate/hexane as the eluent to afford a colorless oil (0.23 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.68 (m, 1H), 7.56 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 4.82 (s, 2H), 4.30 (t, J = 6.8 Hz, 2H), 3.90 (s, 3H), 2.53 (s, 1H), 1.77 (m, 2H), 1.34–1.31 (m, 6H), 0.91 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 166.3, 150.5, 149.1, 124.2, 123.0, 123.0, 112.5, 77.8, 76.3, 65.1, 56.5, 56.0, 31.5, 28.7, 25.7, 22.5, 14.0. ESI-HRMS (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{23}O_4$, 291.1596; found, 291.1598.

Compound 12. To a solution of **9** (90 mg, 0.33 mmol), copper sulfate hydrate (66 mg, 0.33 mmol), and sodium ascorbate (165 mg, 0.66 mmol) in a 2:1:1 THF/H_2O/CH_3OH mixture (20 mL), **16** (116 mg, 0.4 mmol) in THF (1 mL) was added dropwise. After being stirred at 40 °C for 24 h, the reaction mixture was concentrated. The residue was diluted with THF (10 mL). The solid was filtered off and the filtrate was concentrated in vacuo. The residue was then purified by column chromatography over silica gel using 1:3 methanol/methylene chloride as the eluent to give an off-white powder (146 mg, 75%). ^{1}H NMR (400 MHz, CD_3OD /DMSO-d_6), δ: 8.04 (s, 1H), 7.65 (m, 2H), 7.63 (m, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.92 (s, 1H), 6.85 (t, J = 8.4 Hz, 1H), 6.60 (s, 1H), 4.83 (s, 2H), 4.30 (t, J = 8.4 Hz, 1H), 3.90 (s, 3H), 1.77 (m, 2H), 1.34–1.31 (m, 6H), 0.91 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 166.3, 150.5, 149.9, 149.1, 146.1, 124.2, 124.0, 123.0, 123.0, 123.0, 123.0, 114.0, 112.5, 112.5, 112.5, 112.4, 112.4, 112.4, 111.7, 65.1, 56.5, 56.0, 31.5, 28.7, 25.7, 22.5, 14.0. ESI-HRMS (*m/z*): $[M\text{-}Na]^-$ calcd for $C_{27}H_{28}N_3O_7S$, 538.1653; found, 538.1648.

Preparation of Molecularly Imprinted Nanoparticles (MINPs)

MINP(2). To a micellar solution of **1** (9.3 mg, 0.02 mmol) in D_2O (2.0 mL), divinylbenzene (DVB, 2.8 μL, 0.02 mmol), **2** in D_2O (10 μL of 7.8 mg/mL, 0.0004 mmol), **4** in dimethyl sulfoxide (DMSO, 10 μL 34.4 mg/mL, 0.0008 mmol), and 2,2-dimethoxy-2-phenylacetophenone (DMPA,10 μL of a 12.8 mg/mL solution in DMSO, 0.0005 mmol) were added. The mixture was subjected to ultrasonication for 10 min before compound **5** (4.1 mg, 0.024 mmol), $CuCl_2$ (10 μL of a 6.7 mg/mL solution in D_2O, 0.0005 mmol), and sodium ascorbate (10 μL of a 99 mg/mL solution in D_2O, 0.005 mmol) were added. After the reaction mixture was stirred slowly at room temperature for 12 h, compound **6** (10.6 mg, 0.04 mmol), $CuCl_2$ (10 μL of a 6.7 mg/mL solution in D_2O, 0.0005 mmol), and sodium ascorbate (10 μL of a 99 mg/mL solution in D_2O, 0.005 mmol) were added. After being stirred for another 6 h at room temperature, the reaction mixture was transferred to a glass vial, purged with nitrogen for 15 min, sealed with a rubber stopper, and irradiated in a Rayonet reactor for 12 h. ^1H NMR spectroscopy was used to monitor the progress of reaction. The reaction mixture was poured into acetone (8 mL). The precipitate was collected by centrifugation and washed with a mixture of acetone/water (5 mL/1 mL) three times. The crude produce was washed by methanol/acetic acid (5 mL/0.1 mL) three times until no fluorescence could be observed in the residual wash, and then with excess acetone. The off white powder was dried in air to afford the final MINPs (17 mg, 85%).

MINP(3). To a micellar solution of **1** (9.3 mg, 0.02 mmol) in D_2O (2.0 mL), divinylbenzene (DVB, 2.8 μL, 0.02 mmol), **3** in D_2O (10 μL of 18 mg/mL in D_2O, 0.0004 mmol), **4** in dimethyl sulfoxide (DMSO, 10 μL 34.4 mg/mL, 0.0008 mmol), and 2,2-dimethoxy-2-phenylacetophenone (DMPA,10 μL of a 12.8 mg/mL solution in DMSO, 0.0005 mmol) were added. The mixture was subjected to ultrasonication for 10 min before compound **5** (4.1 mg, 0.024 mmol), $CuCl_2$ (10 μL of a 6.7 mg/mL solution in D_2O, 0.0005 mmol), and sodium ascorbate (10 μL of a 99 mg/mL solution in D_2O, 0.005 mmol) were added. After the reaction mixture was stirred slowly at room temperature for 12 h, compound **6** (10.6 mg, 0.04 mmol), $CuCl_2$ (10 μL of a 6.7 mg/mL solution in D_2O, 0.0005 mmol), and sodium ascorbate (10 μL of a 99 mg/mL solution in D_2O, 0.005 mmol) were added. After being stirred for another 6 h at room temperature, the reaction mixture was transferred to a glass vial, purged with nitrogen for 15 min, sealed with a rubber stopper, and irradiated in a Rayonet reactor for 12 h. ^1H NMR spectroscopy was used to monitor the progress of reaction. The reaction mixture was poured into acetone (8 mL). The precipitate was collected by centrifugation and washed with a

mixture of acetone/water (5 mL/1 mL) three times. The crude produce was washed by methanol/acetic acid (5 mL/0.1 mL) three times until no fluorescence could be observed in the residual wash, and then with excess acetone. The off white powder was dried in air to afford the final MINPs (17 mg, 85%).

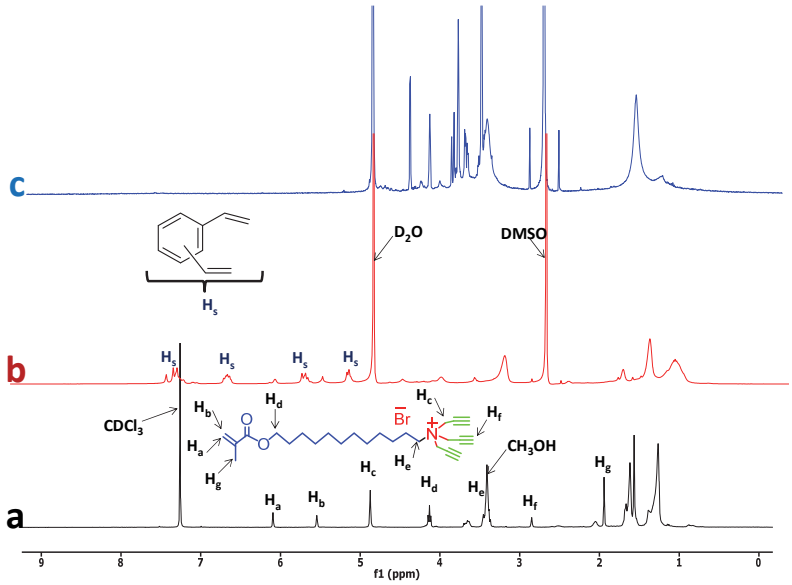


Figure S1. ^{1}H NMR spectra of **1** in $CDCl_3$ (black), alkynyl-SCM in D_2O (red), and fluoro-MINP(**2**) (blue) in D_2O

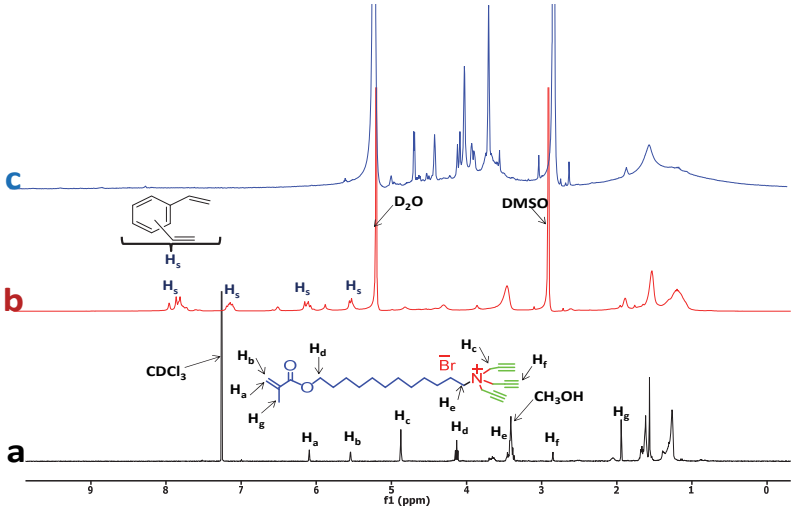


Figure S2. ^{1}H NMR spectra of **1** in $CDCl_3$ (black), alkynyl-SCM in D_2O (red), and fluoro-MINP(**3**) (blue) in D_2O

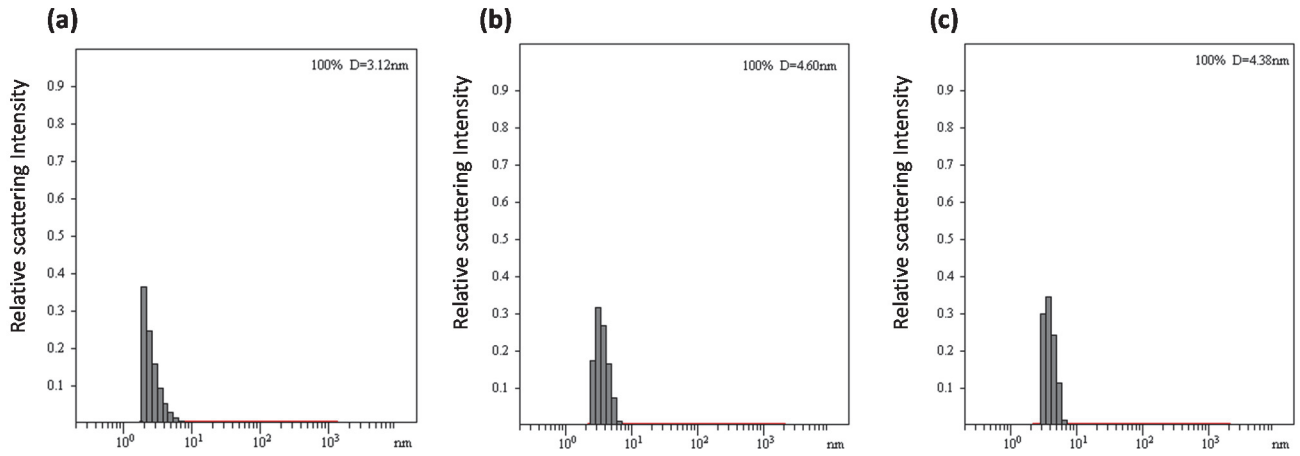


Figure S3. Distribution of the hydrodynamic diameters of the nanoparticles in water as determined by DLS for (a) alkynyl-SCM, (b) surface-functionalized SCM and (c) MINP(**2**) after purification.

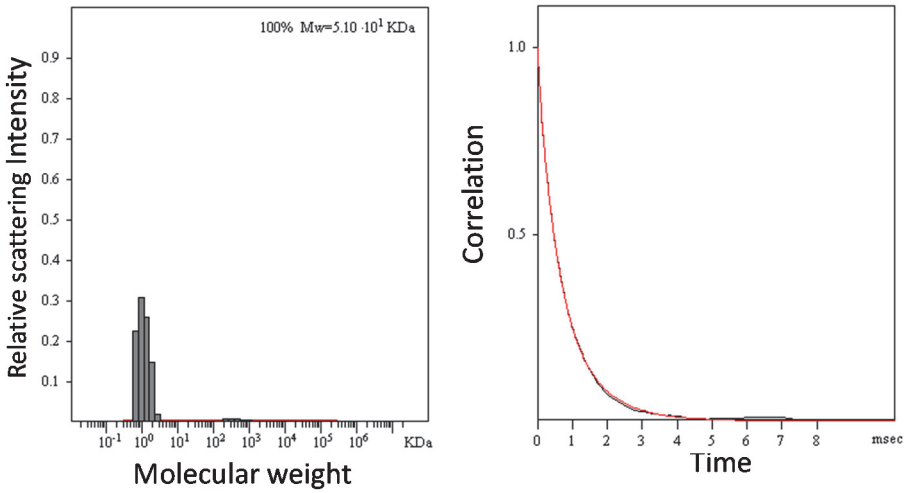


Figure S4. Distribution of the molecular weights of fluoro-MINP(**2**) and the correlation curves for DLS. The PRECISION DECONVOLVE program assumes the intensity of scattering is proportional to the mass of the particle squared. If each unit of building block for the fluoro-MINP(**2**) is assumed to contain one molecule of compound **1** (MW = 465 g/mol), 0.04 molecules of compound **4** (MW = 430 g/mol), 1.2 molecules of compound **5** (MW = 172 g/mol), one molecule of DVB (MW = 130 g/mol), and 0.8 molecules of compound **6** (MW = 264 g/mol), the molecular weight of fluoro-MINP(**3**) translates to 50 [= 51000/(465+0.04×430+1.2×172+130+0.8×264)] of such units.

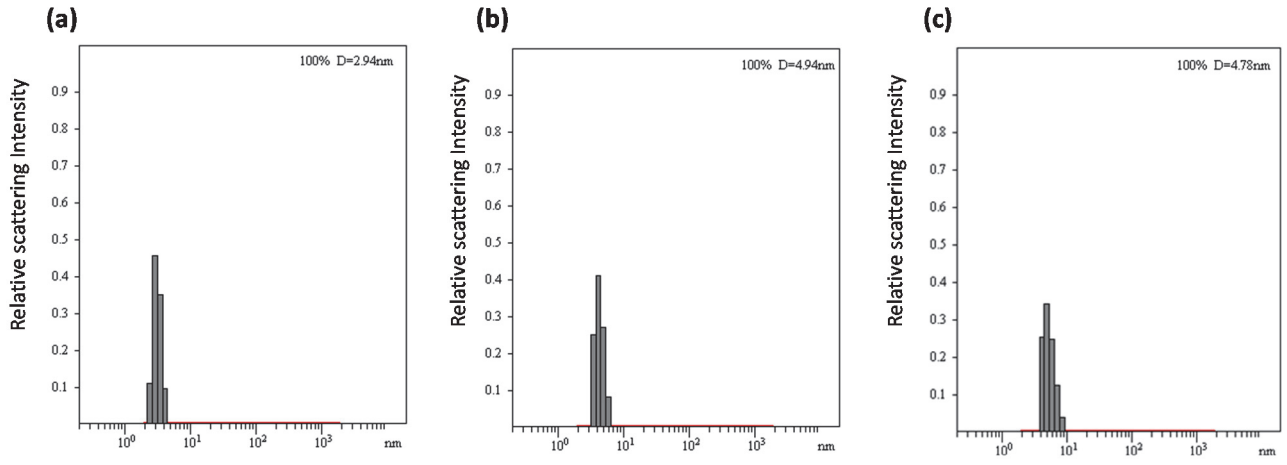


Figure S5. Distribution of the hydrodynamic diameters of the nanoparticles in water as determined by DLS for (a) alkynyl-SCM, (b) surface-functionalized SCM and (c) MINP(**3**) after purification.

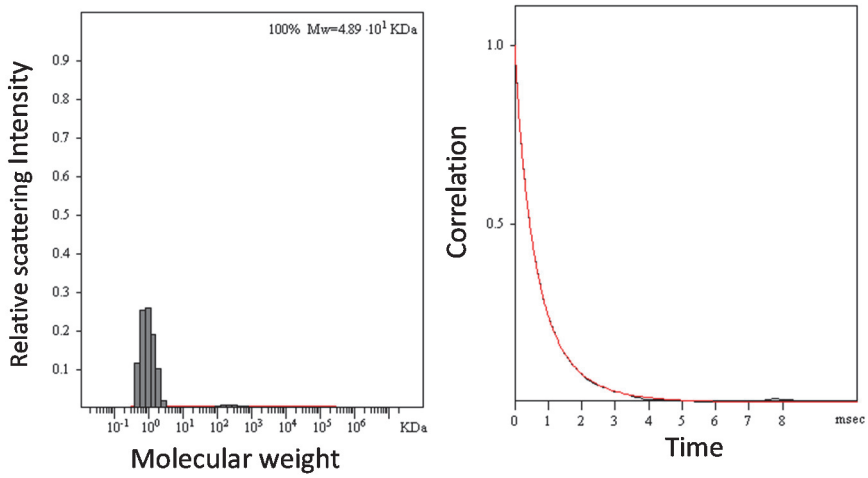


Figure S6. Distribution of the molecular weights of fluoro-MINP(**3**) and the correlation curves for DLS. The PRECISION DECONVOLVE program assumes the intensity of scattering is proportional to the mass of the particle squared. If each unit of building block for the fluoro-MINP(**3**) is assumed to contain one molecule of compound **1** (MW = 465 g/mol), 0.04 molecules of compound **4** (MW = 430 g/mol), 1.2 molecules of compound **5** (MW = 172 g/mol), one molecule of DVB (MW = 130 g/mol), and 0.8 molecules of compound **6** (MW = 264 g/mol), the molecular weight of fluoro-MINP(**3**) translates to 47 [= 48900/(465+0.04×430+1.2×172+130+0.8×264)] of such units.

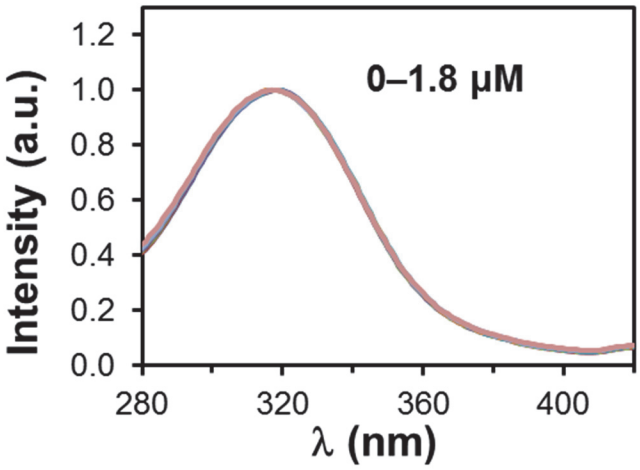


Figure S7. Normalized excitation spectra of Fluoro-MINP(**2**) in the presence of different concentrations of **3**. The emission for the dansyl acceptor at 500 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.25 μM in 50 mM Tris buffer (pH 7.4).

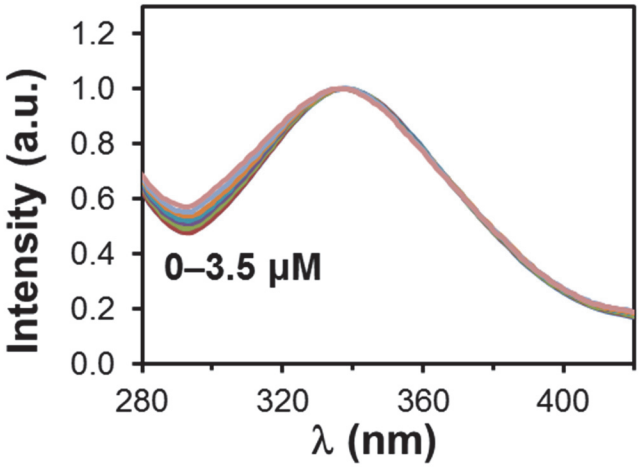


Figure S8. Normalized excitation spectra of Fluoro-MINP(**3**) in the presence of different concentrations of **2**. The emission for the dansyl acceptor at 500 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.25 μM in 50 mM Tris buffer (pH 7.4). *Weak FRET was observed.*

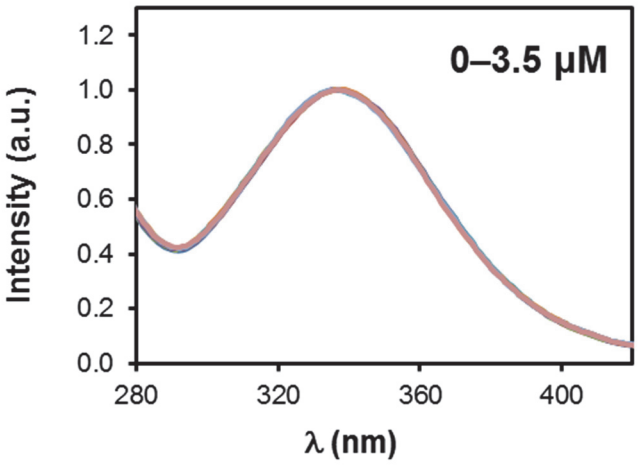


Figure S9. Normalized excitation spectra of Fluoro-MINP(**2**) in the presence of different concentrations of **7**. The emission for the dansyl acceptor at 500 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.25 μM in 50 mM Tris buffer (pH 7.4).

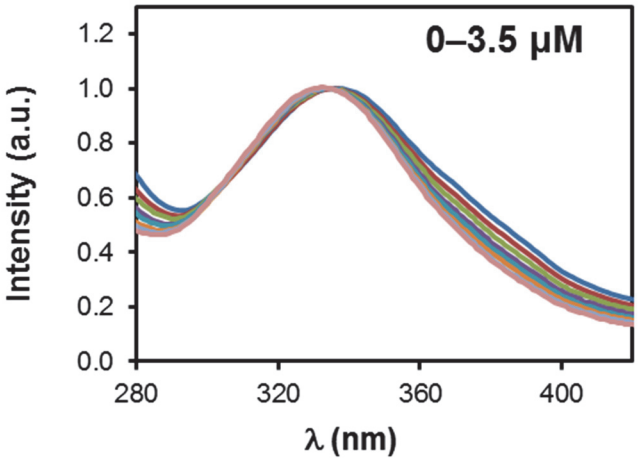


Figure S10. Normalized excitation spectra of Fluoro-MINP(**2**) in the presence of different concentrations of **8**. The emission for the dansyl acceptor at 500 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.25 μM in 50 mM Tris buffer (pH 7.4). *The emission had a gradual shift to the red upon titration with **8**. The intensity near 300–310 nm decreased rather than increased as in the case of FRET.*

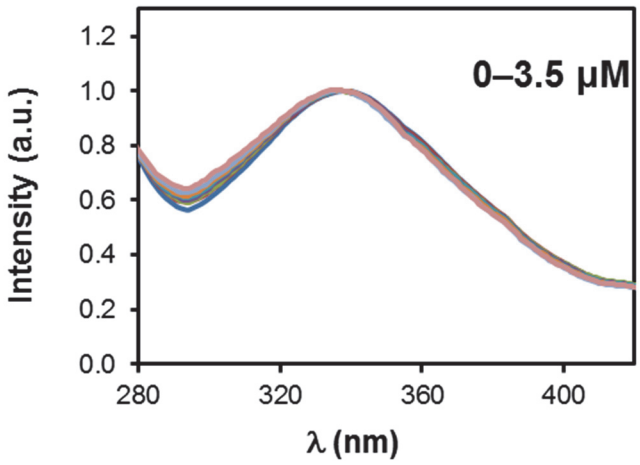


Figure S11. Normalized excitation spectra of Fluoro-MINP(**2**) in the presence of different concentrations of **9**. The emission for the dansyl acceptor at 500 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.25 μM in 50 mM Tris buffer (pH 7.4). *Weak FRET was observed.*

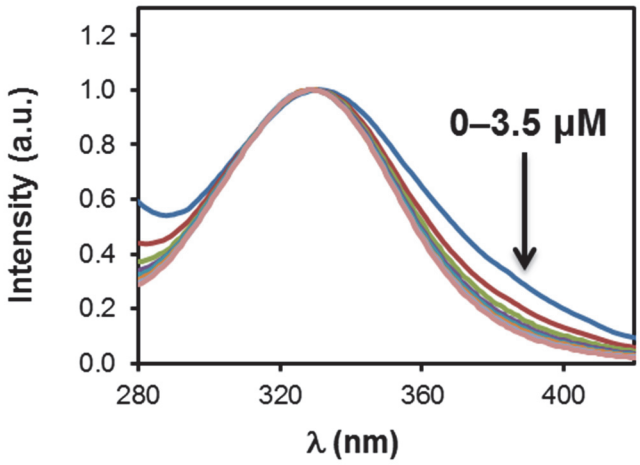


Figure S12. Normalized excitation spectra of Fluoro-MINP(**2**) in the presence of different concentrations of **10**. The emission for the dansyl acceptor at 500 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.25 μM in 50 mM Tris buffer (pH 7.4). *Compound **10** had the same dansyl as the acceptors on the MINP and thus the excitation spectrum toward higher concentration of **10** mainly was from compound **10** itself.*

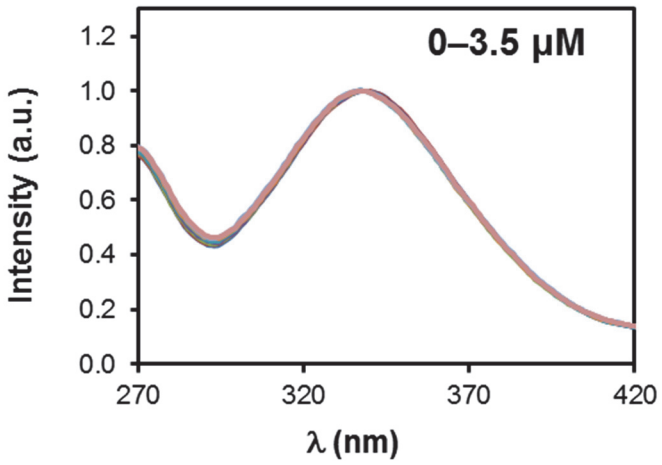


Figure S13. Normalized excitation spectra of Fluoro-MINP(**3**) in the presence of different concentrations of **7**. The emission for the dansyl acceptor at 500 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.25 µM in 50 mM Tris buffer (pH 7.4).

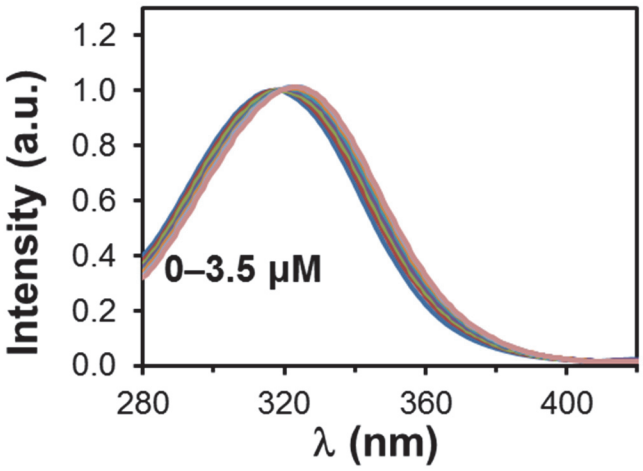


Figure S14. Normalized excitation spectra of Fluoro-MINP(**3**) in the presence of different concentrations of **8**. The emission for the dansyl acceptor at 500 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.25 µM in 50 mM Tris buffer (pH 7.4).

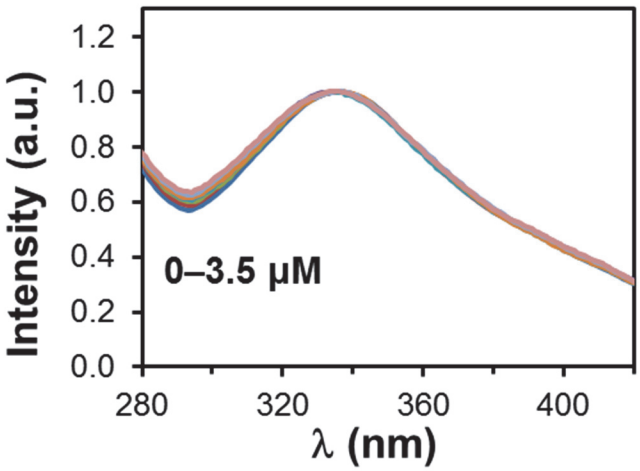


Figure S15. Normalized excitation spectra of Fluoro-MINP(**3**) in the presence of different concentrations of **9**. The emission for the dansyl acceptor at 500 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.25 μM in 50 mM Tris buffer (pH 7.4). *Very weak FRET was observed.*

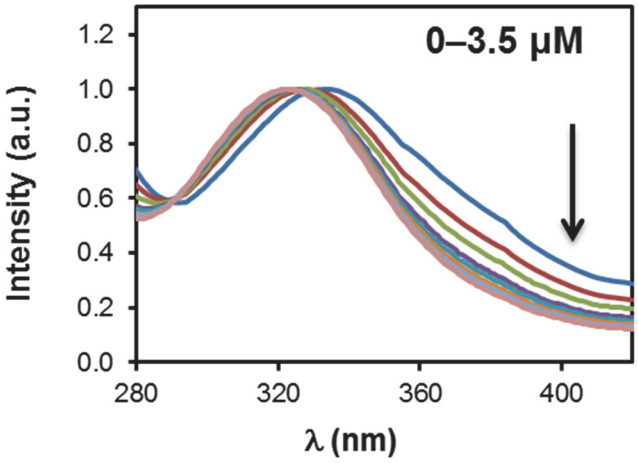


Figure S16. Normalized excitation spectra of Fluoro-MINP(**3**) in the presence of different concentrations of **10**. The emission for the dansyl acceptor at 500 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.25 μM in 50 mM Tris buffer (pH 7.4). *The emission had a gradual shift to the blue upon titration with **10**. Compound **10** had the same dansyl as the acceptors on the MINP and thus the excitation spectrum toward higher concentration of **10** mainly was from compound **10** itself.*

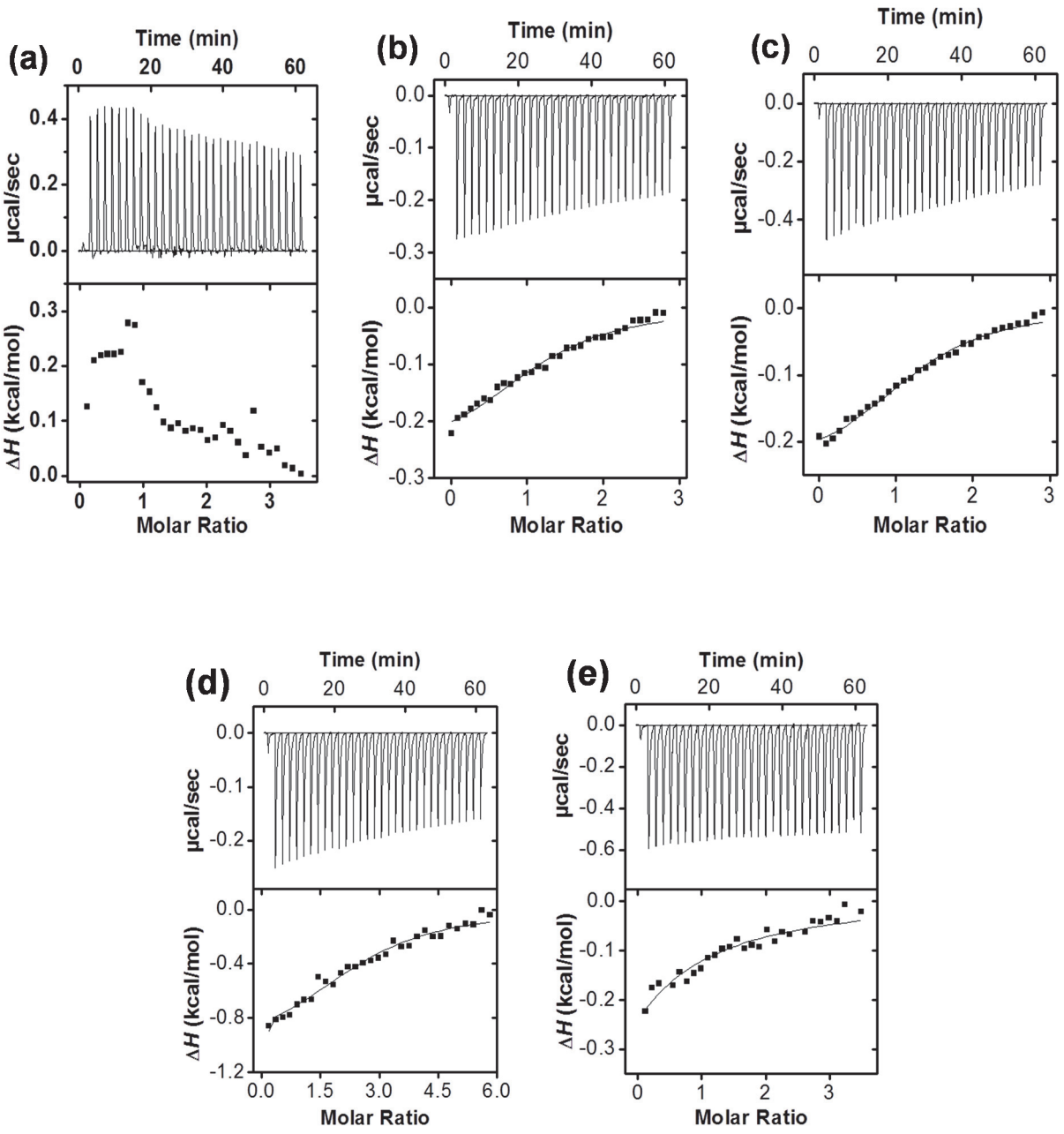


Figure S17. ITC titration curves obtained at 298 K for the titration of fluoro-MINP(**2**) with **3** (a), **7** (b), **8** (c), **9** (d), and **10** (e) in 50 mM Tris buffer (pH 7.4). The data correspond to entries 2–6, respectively, in Table 1. The top panel shows the raw calorimetric data. The area under each peak represents the amount of heat generated at each ejection and is plotted against the molar ratio of MINP to the substrate. The solid line is the best fit of the experimental data to the sequential binding of N equal and independent binding sites on the MINP. The heat of dilution for the substrate, obtained by adding the substrate to the buffer, was subtracted from the heat released during the binding. Binding parameters were auto-generated after curve fitting using Microcal Origin 7.

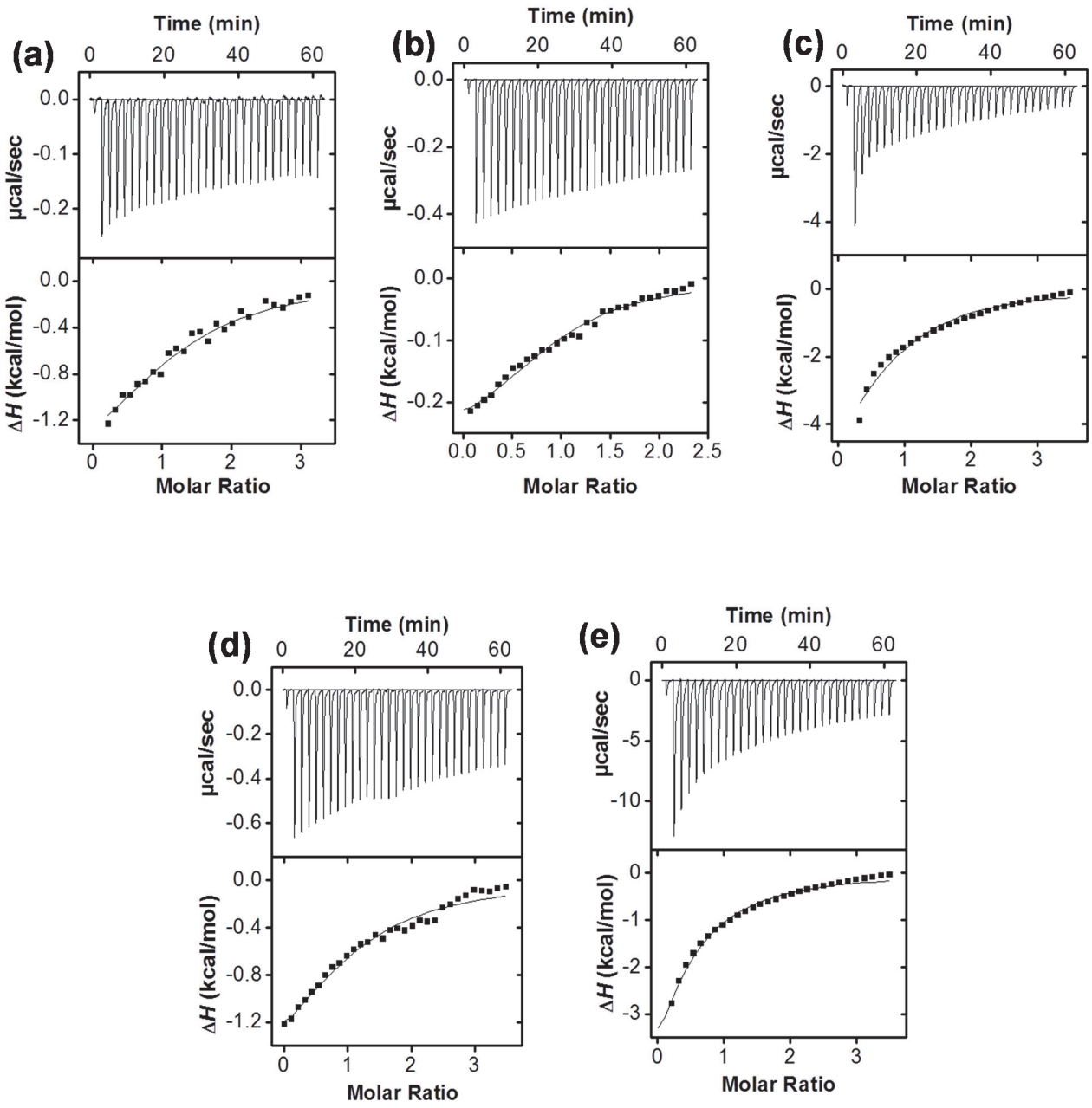


Figure S18. ITC titration curves obtained at 298 K for the titration of fluoro-MINP(**3**) with **2** (a), **7** (b), **8** (c), **9** (d), and **10** (e) in 50 mM Tris buffer (pH 7.4). The data correspond to entries 7 and 9–12, respectively, in Table 1. The top panel shows the raw calorimetric data. The area under each peak represents the amount of heat generated at each ejection and is plotted against the molar ratio of MINP to the substrate. The solid line is the best fit of the experimental data to the sequential binding of N equal and independent binding sites on the MINP. The heat of dilution for the substrate, obtained by adding the substrate to the buffer, was subtracted from the heat released during the binding. Binding parameters were auto-generated after curve fitting using Microcal Origin 7.

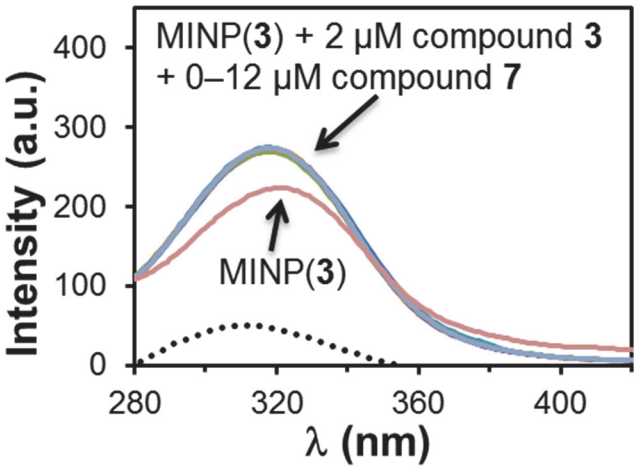


Figure S19. Excitation spectra of MINP(**3**) with 2 μM of compound **3**, titrated with 0–12 μM of compound **7**. The dotted spectrum in black was obtained by subtracting the MINP spectrum from that of the MINP plus compound **3**. The emission for the dansyl acceptor at 520 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.50 μM in 50 mM Tris buffer (pH 7.4).

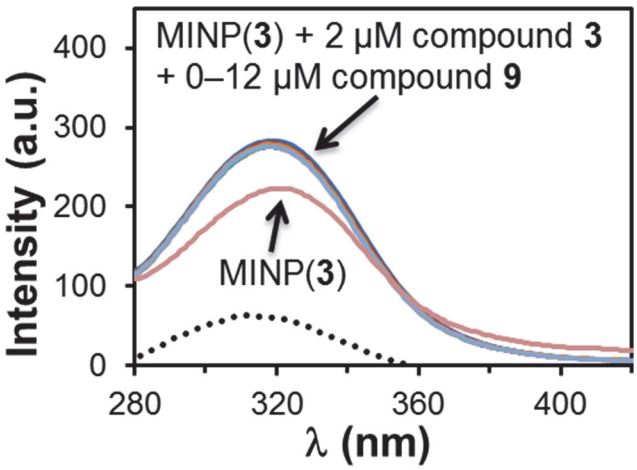


Figure S20. Excitation spectra of MINP(**3**) with 2 μM of compound **3**, titrated with 0–12 μM of compound **9**. The dotted spectrum in black was obtained by subtracting the MINP spectrum from that of the MINP plus compound **3**. The emission for the dansyl acceptor at 520 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.50 μM in 50 mM Tris buffer (pH 7.4).

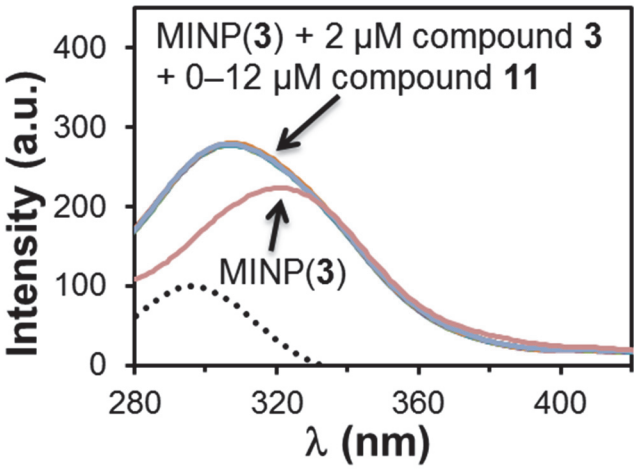


Figure S21. Excitation spectra of MINP(**3**) with 2 μM of compound **3**, titrated with 0–12 μM of compound **11**. The dotted spectrum in black was obtained by subtracting the MINP spectrum from that of the MINP plus compound **3**. The emission for the dansyl acceptor at 520 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.50 μM in 50 mM Tris buffer (pH 7.4).

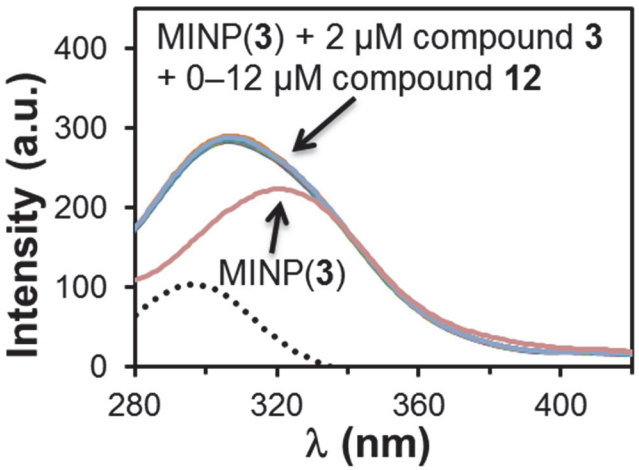
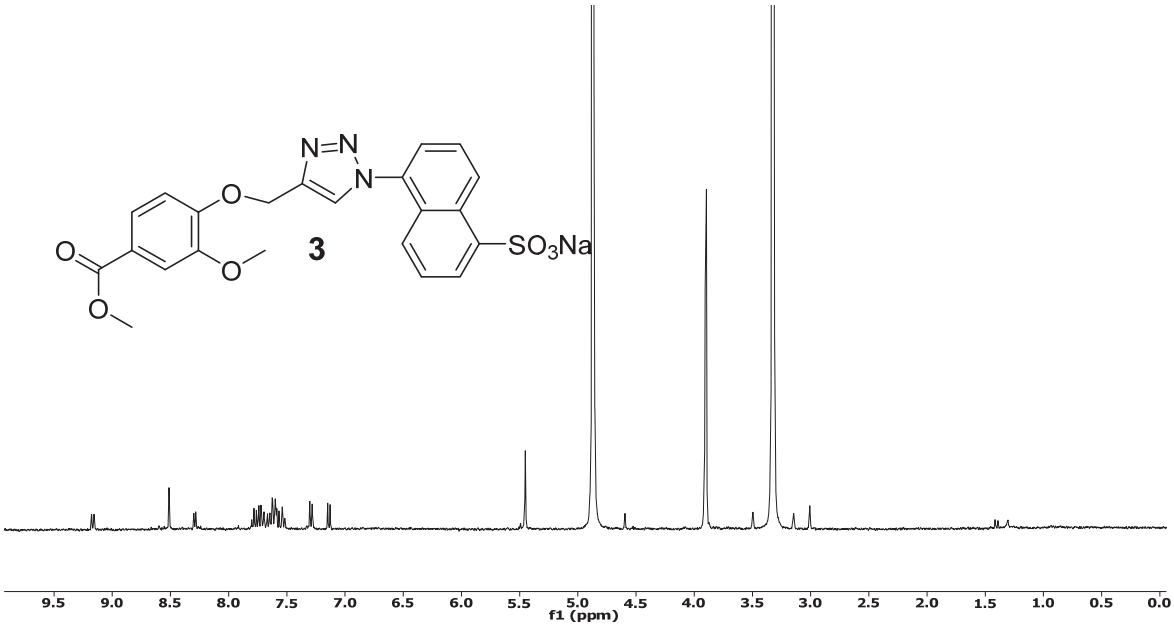
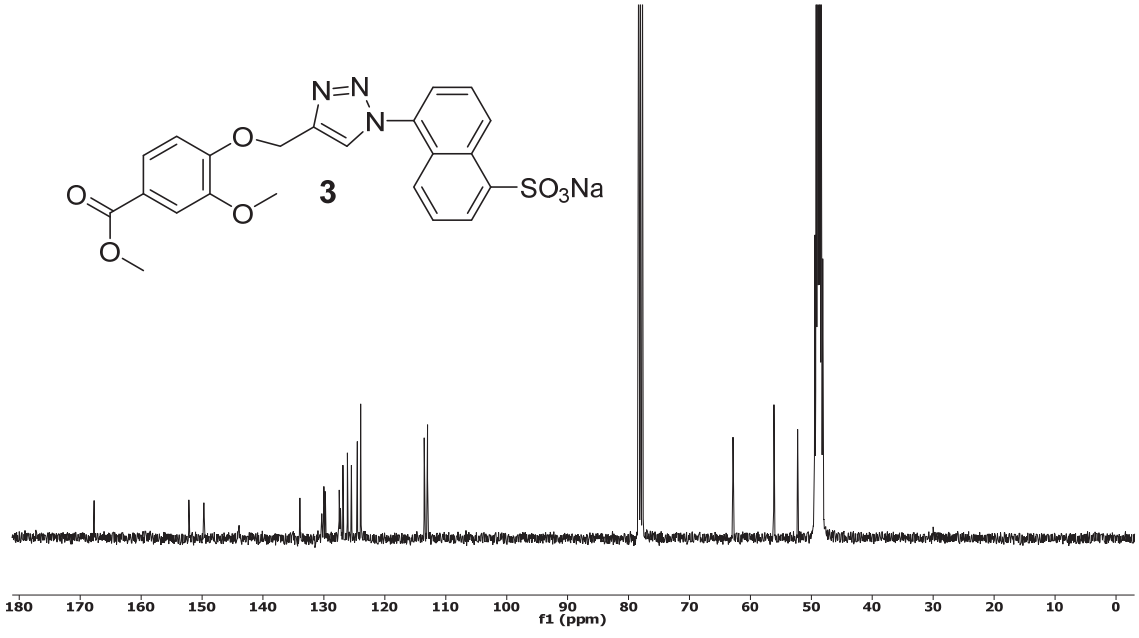
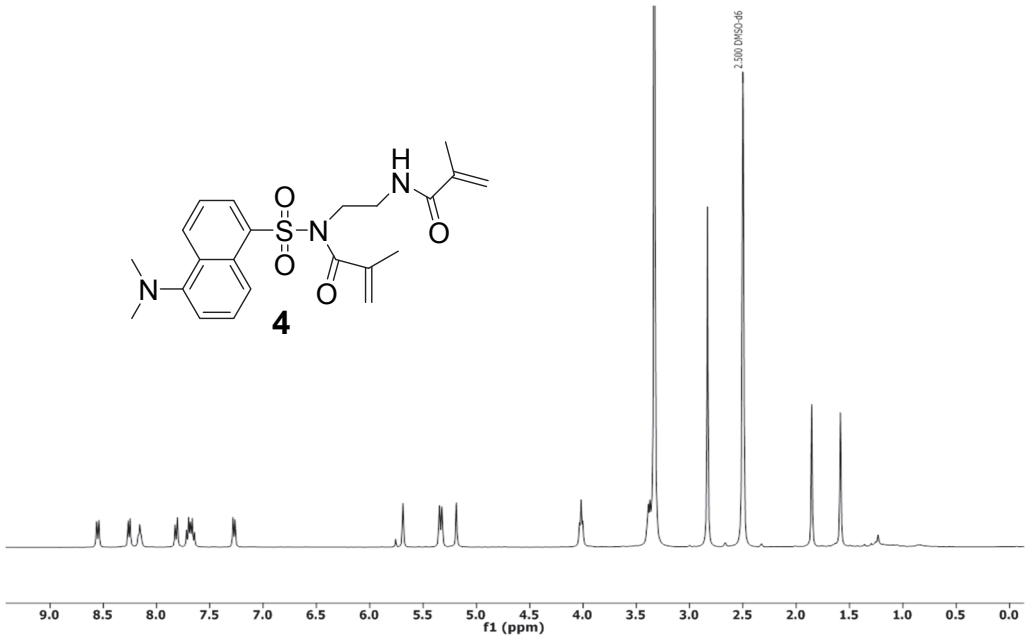


Figure S22. Excitation spectra of MINP(**3**) with 2 μM of compound **3**, titrated with 0–12 μM of compound **12**. The dotted spectrum in black was obtained by subtracting the MINP spectrum from that of the MINP plus compound **3**. The emission for the dansyl acceptor at 520 nm (λ_{em}) was monitored as the excitation wavelength (λ_{ex}) was scanned from 250 to 450 nm was scanned. [MINP] = 0.50 μM in 50 mM Tris buffer (pH 7.4).

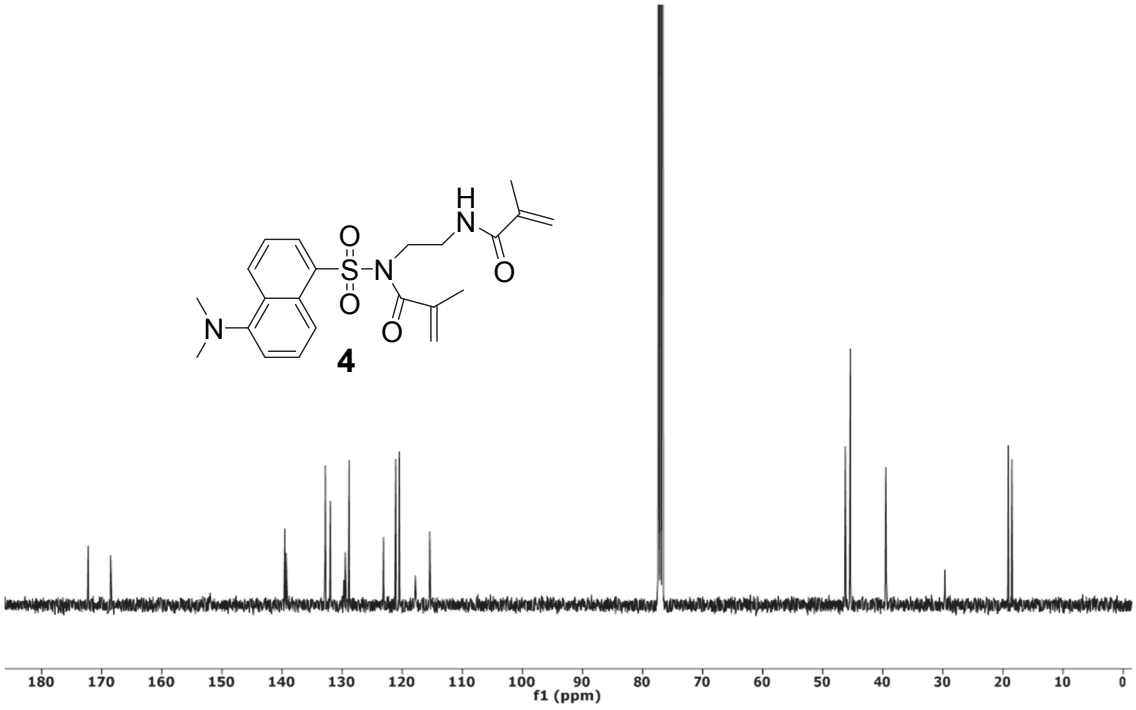
^{1}H and ^{13}C NMR spectra



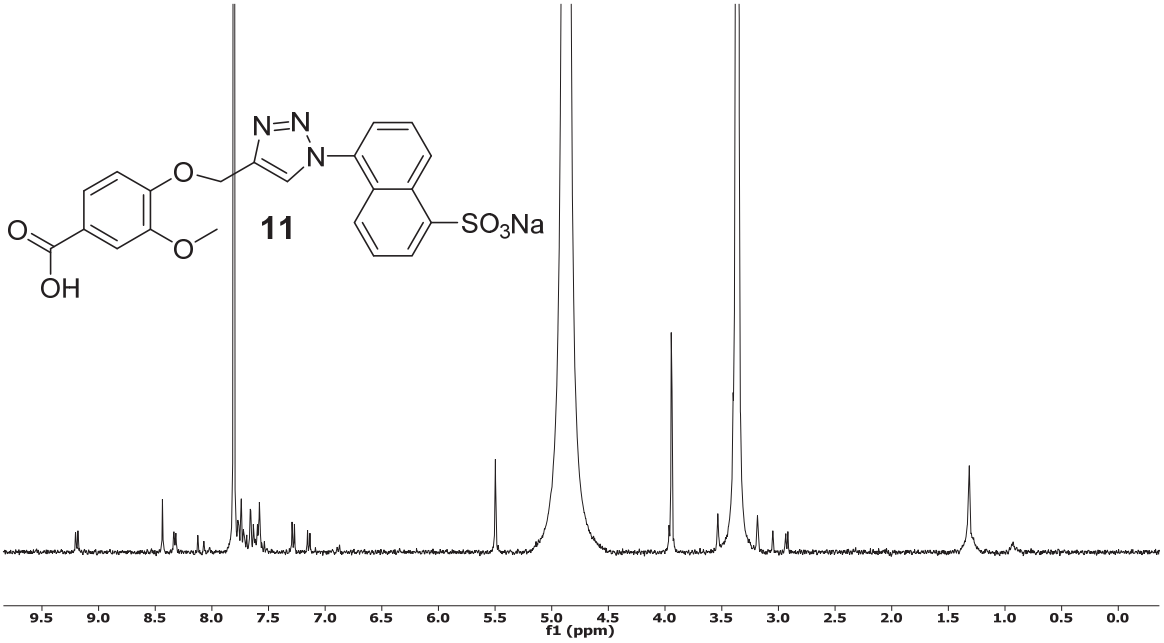


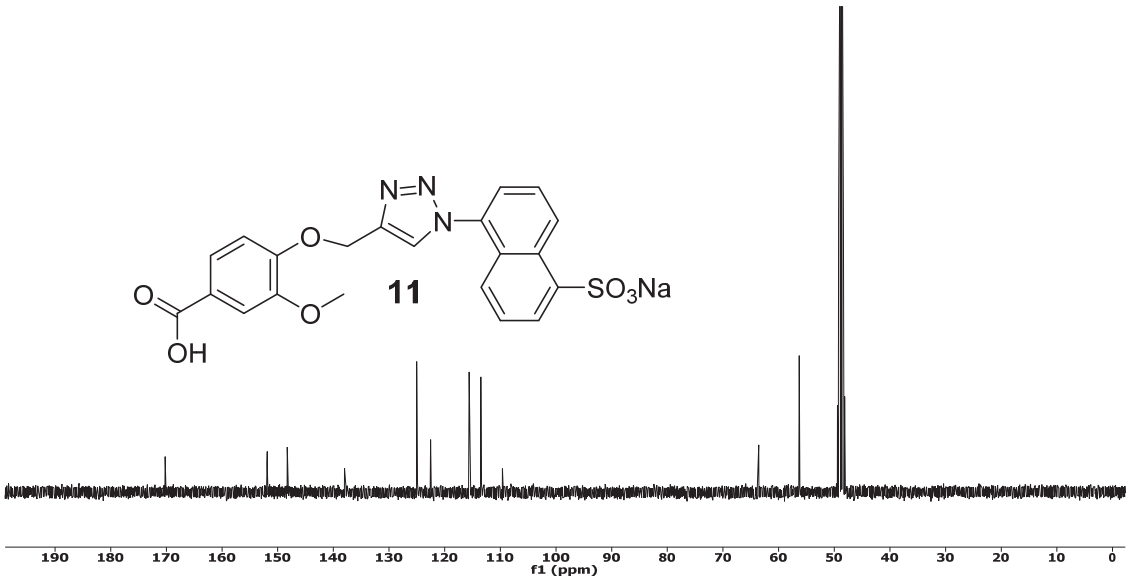

2.500 DMSO-d6
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

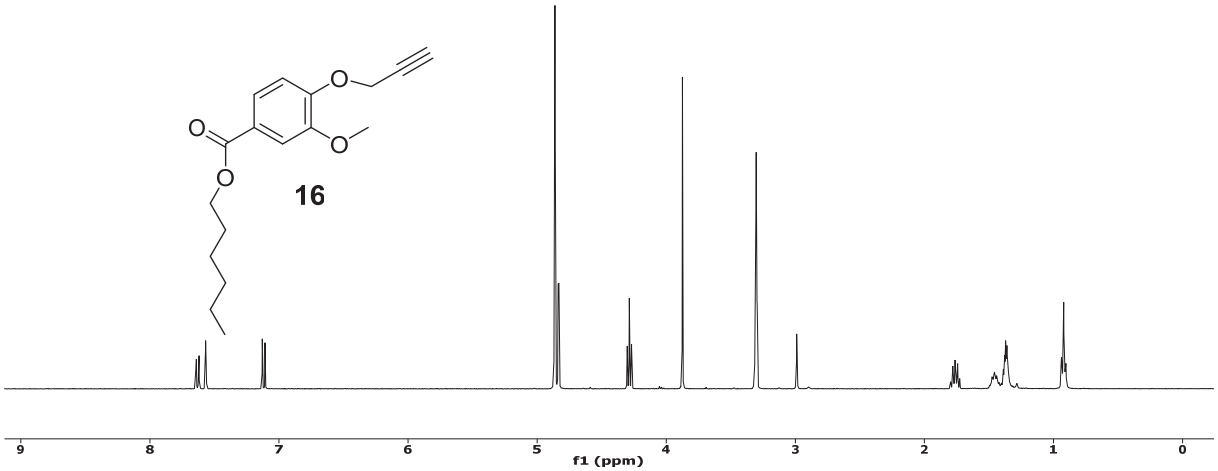
4

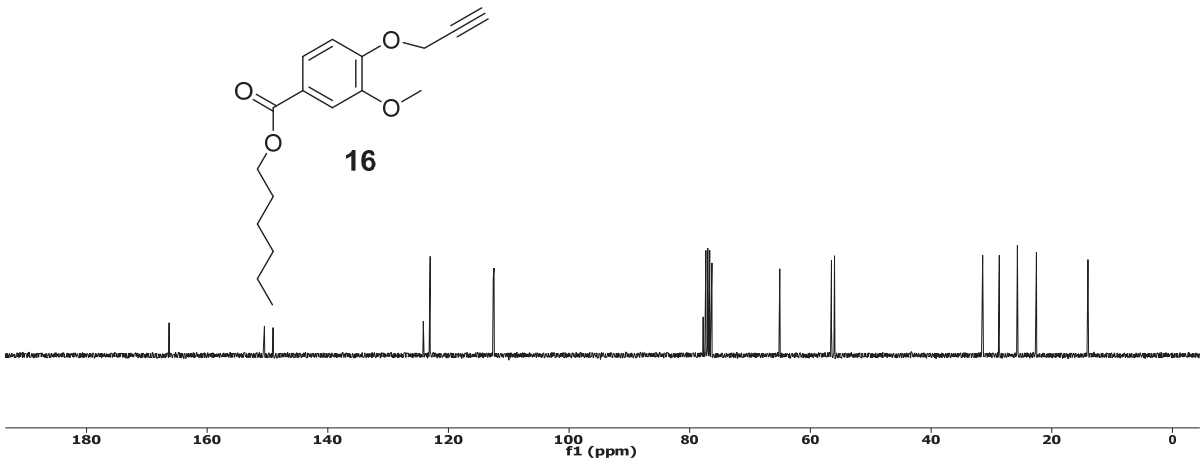

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

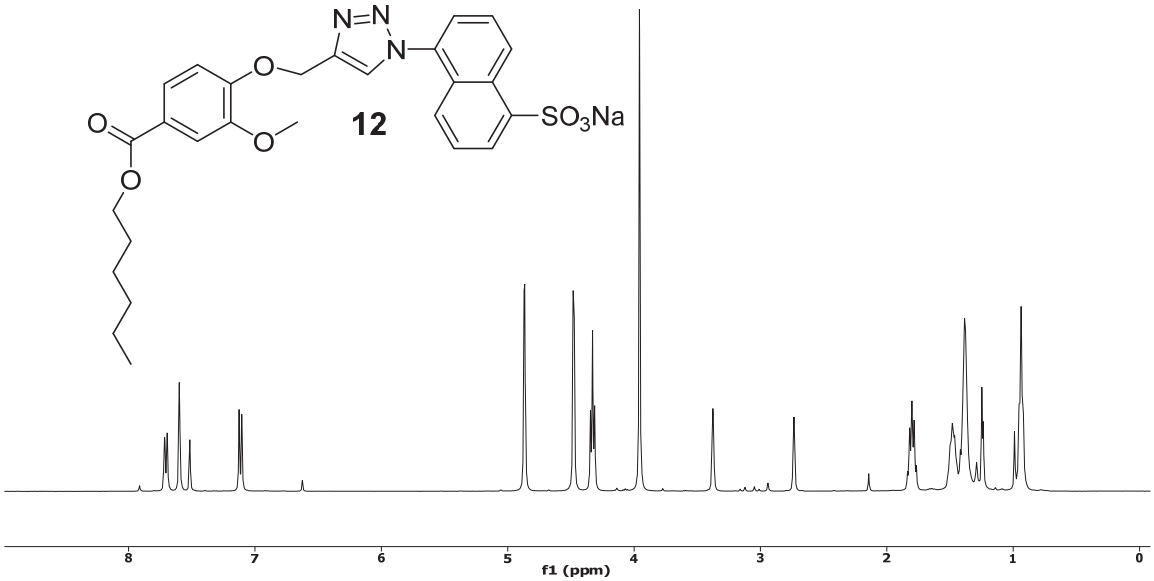
4

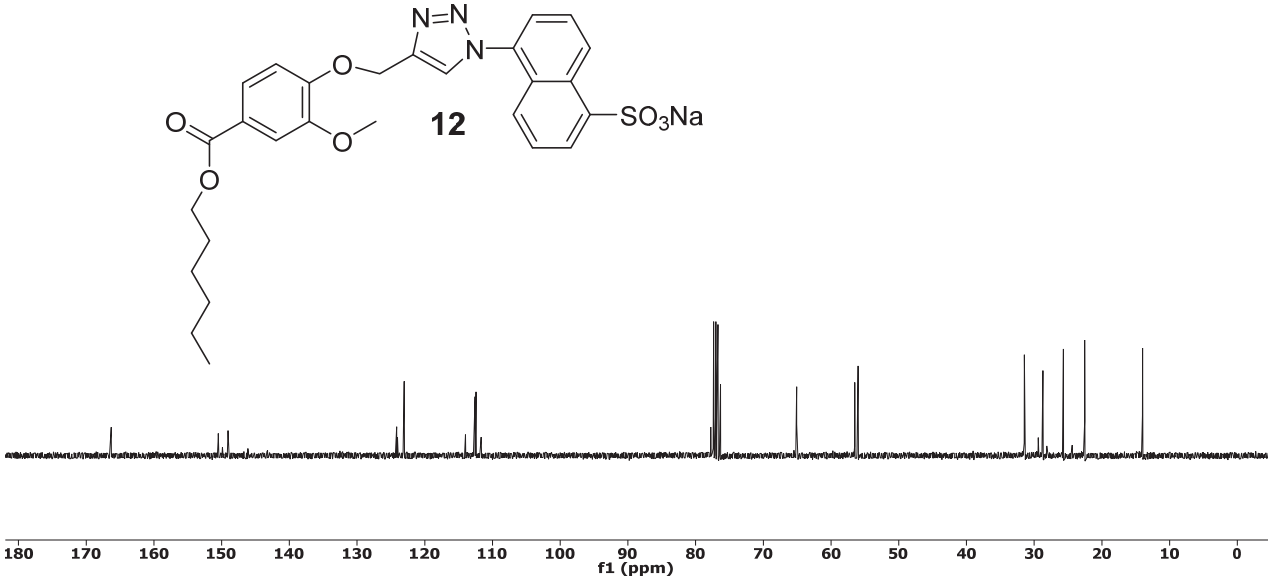

N=N
N
O
O
O
OH
11
SO3Na
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


N=N
N
O
O
O
OH
11
SO3Na
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
O
O
16
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


O
O
O
O
16
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


12
SO3Na
f1 (ppm)


12
SO3Na
f1 (ppm)

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