Drug Delivery

Monitoring Fluorinated Dendrimer-Based Self-Assembled Drug-Delivery Systems with $^{19}$F Magnetic Resonance


Abstract: Monitoring a drug-delivery system with an imaging modality is of great importance for detailed understanding of drug-delivery processes and for achieving optimal therapeutic effects. Here, novel fluorinated self-assembled dendrimers with a single $^{19}$F NMR signal were conveniently synthesized on multi-gram scales, and $^{19}$F magnetic resonance, including spectroscopy ($^{19}$F NMR) and imaging ($^{19}$F MRI), was used to monitor the fluorinated dendrimer-based self-assembled drug-delivery systems. It was found that $^{19}$F NMR and $^{19}$F MRI were convenient and sensitive tools to monitor the self-assembly and drug-loading processes and to detect weak interactions between the drug and the drug-delivery vehicle because changes in the self-assembly profile sensitively induced corresponding $^{19}$F magnetic resonance responses.

Introduction

Self-assembly is an important phenomenon that plays a crucial role in many drug-delivery systems.[1] For example, liposome- and micelle-based drug-delivery systems are mainly based on the self-assembly of amphiphiles to encapsulate, stabilize, and deliver drugs. Therefore, novel strategies to study self-assembly are of great importance for the design of novel self-assembled systems that can be used to monitor the drug-delivery process and to optimize drug therapy.

$^{19}$F Magnetic resonance imaging ($^{19}$F MRI) and $^{19}$F nuclear magnetic resonance ($^{19}$F NMR) spectroscopy are powerful tools in monitoring chemical and biochemical reactions,[2] drug–target interactions,[3] protein dynamics and interactions,[4] nucleic-acid recognition,[5] and biodistribution of targets.[6] Besides the inherent advantages of magnetic resonance, for example, no tissue depth limit or ionizing radiation, $^{19}$F MRI and $^{19}$F NMR spectroscopy provide not only quantitative images and spectra with high sensitivity and negligible background, but also sensitive responses to microenvironments.[7] These features make $^{19}$F MRI/NMR appropriate tools for monitoring self-assembly in drug-delivery systems.

Self-assembled fluorinated amphiphiles are promising drug-delivery vehicles, because the in vivo drug-delivery process can be conveniently monitored by $^{19}$F MRI and $^{19}$F NMR, which may facilitate personalized drug therapy.[8] However, as far as we know, there are only a few reports on the $^{19}$F-MRI- and $^{19}$F-NMR-monitored self-assembly of fluorinated amphiphiles.[6d,9] Therefore, it is of great importance to develop novel self-assembled fluorinated amphiphiles as $^{19}$F-MRI- and $^{19}$F-NMR-traceable drug-delivery vehicles and to perform comprehensive $^{19}$F MRI and $^{19}$F NMR studies on their self-assembly behaviors and drug–vehicle interactions.

The design of fluorinated self-assembled dendrimers is crucial for efficient encapsulation and delivery of drugs as well as for sensitive detection of the process by $^{19}$F MRI and $^{19}$F NMR spectroscopy. Fluorinated Janus dendrimers 1b and 2b were then designed as self-assembled amphiphiles in which weak interactions, that is, $\pi$–$\pi$ stacking and hydrophobic effects of the phenyl and trifluoromethyl groups, were employed as the driving force for self-assembly (Figure 1). In amphiphiles 1b and 2b, each moiety plays a certain role, that is, the fluorinated benzyl group serves as a hydrophobic head, monodispersed oligoethylene glycol units act as hydrophilic tails, and 12 symmetrical fluorine atoms together serve as a sensitive $^{19}$F MRI/NMR signal emitter without chemical-shift artefacts.[10] A thiol group was introduced in 1a for further modification, such as their attachment to gold nanoparticles, biomolecules, and drugs. It is noteworthy that the hydrophilic–hydrophobic balance can be monitored by the length of the monodisperse oligoethylene glycol units and the number of phenyl groups. Besides tuning the hydrophilic–hydrophobic balance, the two additional phenyl groups in 1a–c were also used to evaluate their hydrophobic effects and $\pi$–$\pi$ interactions in the self-assembly drug-delivery system.
Results and Discussion

These fluorinated amphiphiles were synthesized in a convergent way with high efficacy (Scheme 1). Strategies previously developed in this group were applied to manipulate the mono-disperse oligoethylene glycols. Sonogashira coupling and Williamson ether synthesis were employed to conjugate the hydrophilic tails to the hydrophobic head in high yields. Disulfide 1c and 2c were then directly transformed into 1b and 2b, respectively, because thiols 1a and 2a were very unstable in air. Finally, target fluorinated amphiphiles 1b and 2b were synthesized over 11 steps on multigram scales. As expected, each fluorinated amphiphile gives only one 19F NMR signal from its 12 symmetric fluorine atoms (Figure 2), which dramatically increases the 19F NMR/MRI sensitivity of these amphiphiles.

The self-assembly of fluorinated amphiphiles 1b and 2b was then studied by 19F NMR spectroscopy. First, the solvent-dependent 19F NMR spectra show line broadening and chemical-shift changes upon increasing the water content of the solvent (Figure 3a, c), which is a result of increased molecular interactions due to self-assembly of 1b and 2b. Second, the solvent isotope effect indicates that changes in the chemical shift (Δδ) are mainly induced by self-assembly and that the trifluoromethyl groups have limited exposure to water (Figure S1 in the Supporting Information). Third, the temperature-dependent 19F NMR spectra show line broadening at elevated temperatures as a result of faster molecular tumbling (Figure S1). Finally, the self-assembly of 1b and 2b was further confirmed by concentration-dependent 19F NMR spectroscopy, for which a self-assembly-induced Δδ break point corresponds to the critical micelle concentration (CMC, Figure 2b, d). The CMC of 1b in D2O was calculated from the concentration-dependent 19F NMR and 1H NMR spectra as 4.45 and 2.42 mM, respectively (Figure 3e, f; the two symmetric protons on ring A were selected for 1H NMR spectroscopy). The difference in the CMC values from the 19F NMR and 1H NMR spectra probably originates from the different microenvironments of the fluorine and hydrogen atoms. Amphiphile 2b exhibits a higher CMC of 7.35 mM, as determined by 19F NMR spectroscopy, as a result of its higher hydrophilicity (Figure S2).

Structurally, relative to 2b, the two phenyl groups in 1b promote self-assembly through hydrophobic effects and π–π interactions.

Scheme 1. Synthesis of fluorinated amphiphiles 1a–c and 2a–c. Tos = tosyl, DCM = dichloromethane, Trt = trityl (triphenylmethyl), DMAP = 4-(dimethylamino)pyridine.

Figure 1. Structures of fluorinated amphiphiles 1a–c and 2a–c.
actions. Therefore, 1b is more sensitive than 2b to changes in the microenvironment, such as solvent, concentration, and temperature. Interestingly, the difference can be sensitively detected by the $\Delta \delta$ value determined by $^{19}$F NMR spectroscopy. Besides the fact that the $\Delta \delta$ value of 2b ($\Delta \delta = 0.04$ ppm) is much smaller than that of 1b ($\Delta \delta = 0.28$ ppm), as determined by the concentration-dependent $^{19}$F NMR spectra, a smaller $\Delta \delta$ value in the solvent-dependent $^{19}$F NMR spectra was also found for 2b (solve changed from 100 % MeOH to 100 % H$_2$O: 1b $\Delta \delta = 0.65$ ppm, 2b $\Delta \delta = 0.41$ ppm; solve changed from 100 % MeOH to 100 % D$_2$O: 1b $\Delta \delta = 0.56$ ppm, 2b $\Delta \delta = 0.34$ ppm). The difference was further confirmed by dynamic light scattering (DLS), which indicated that 1b aggregated into spherical nanoparticles with a diameter of 6.3 nm, whereas the size of 2b was too small to be measured by DLS. On the basis of the above observation, it is clear that $^{19}$F NMR spectroscopy is a sensitive and convenient tool to monitor self-assembly processes, to detect changes in the microenvironment, and to reveal structural differences in amphiphiles.

To study drug–amphiphile interactions in micelle- and liposome-based drug-delivery systems, $^{19}$F NMR spectroscopy was employed to monitor the co-self-assembly of 1b and 2b with drugs. A total of 15 small molecules with structural diversity, such as (R)-carvone (C), cholesterol (O), the anesthetic propofol (I), and the anticancer drug doxorubicin (N), were selected as representative “drugs” (Figure 4a). Relative to aqueous solutions of 1b and 2b, the co-self-assembled solutions of 1b and 2b with “drugs” showed very slight changes in the $^{19}$F NMR chemical shift, $\Delta \delta < 0.05$ ppm. This phenomenon promoted us to study the $^1$H NOESY spectra of 1b and 2b in the presence of G in D$_2$O to detect the occurrence of co-self-assembly. Indeed, NOE effects were found between 1b and G and between 2b and G, which indicated that the amphiphile and drug were close to each other as a result of co-self-assembly (Figure 4b, c). However, the co-self-assembly had no effect on the exposure of fluorine to water, because fluorine–water interactions are a major promoter of $\Delta \delta$ (Figure 3). Therefore, the $^{19}$F NMR $\Delta \delta$ value is actually not a sensitive parameter to detect structural differences in the encapsulated “drugs”. However, marked changes in the signal intensity ($\Delta SI$), which is another observable parameter of the “drug”–amphiphile interactions in co-self-assembly systems, were detected by $^{19}$F NMR spectroscopy (Figure 4e). The patterns of the $^{19}$F NMR $\Delta SI$ values for the 1b and 2b co-self-assembly systems are quite different. For systems with 2b, “drugs” A–O all decreased the $^{19}$F NMR $SI$ value, and 1-octanol (A) gave a maximum $\Delta SI$ value of $-33$ %. The all-negative $\Delta SI$ value suggests that 2b and “drugs” co-self-assemble through similar modes of interactions. For systems with 1b, the “drugs” gave more complicated $^{19}$F NMR $\Delta SI$ values. “Drugs” L, N, and K decreased the $^{19}$F NMR $SI$ value, and others increased the $^{19}$F NMR $SI$ values. This phenomenon is a result of more complex modes of interaction and self-assembly between 1b and A–O owing to the presence of two additional phenyl groups in 1b. The $^1$H NOESY spectra of 1b and 2b in the presence of G (Figure 4b, c) also indicate that the interaction between 1b and G is much stronger than that between 2b and G. Therefore, the drug–amphiphile interaction can be visualized by the $^{19}$F NMR $\Delta SI$ value, which is sensitive to the mode and strength of the interaction between the drug and amphiphile used in the drug-delivery system.

The co-self-assembly systems of amphiphiles 1b and 2b with selected “drugs” A, C, H, K, and N were then studied with transverse relaxation time ($T_2$)-weighted $^{19}$F MRI on a 9.4 T scanner.
Figure 4. Co-self-assembly of fluorinated amphiphiles 1b and 2b with “drugs” A–O. (a) Structures of selected “drugs”. $^1$H NOESY spectra of (b) 1b and (c) 2b in the presence of G in D$_2$O, and (d) the $^{19}$F NMR ΔSI values of co-self-assembly solutions. Amphiphile 1b or 2b (8.68 mM) was mixed with each “drug” in a 1:1 ratio, and the mixture was stirred for 12 h before $^{19}$F NMR/MRI measurements. ΔSI = [SI(co-assembly) – SI(1b/2b)]/SI(1b/2b) × 100 %.

(Figure 5). First, solvent-dependent $^{19}$F MRI of 1b and 2b showed a much higher signal-to-noise ratio (S/N) in methanol than in water because the self-assembly in water dramatically shortens $T_2$ and reduces their diffusion, which is consistent with our previous results.$^{[10a]}$ It is noteworthy that the structural difference between 1b and 2b can be visualized by $^{19}$F MRI upon changing the solvent from methanol to water. In the solvent-dependent experiments, the $T_2$, S/N, and diffusion coefficient ($D$) of hydrophobic 1b were significantly reduced by 85, 81, and 37 %, respectively, whereas limited reductions were found for hydrophilic 2b. Second, additive-dependent $^{19}$F MRI of 1b and 2b showed considerable S/N changes in the presence of the “drug”. The S/N of 1b was dramatically increased in the presence of 1-octanol (A), (R)-carvone (C), and 4-phenylphenol (H) by 35, 38, and 31 %, respectively, whereas 4,4',4''-(ethane-1,1,1-triyl)triphenol (K) and doxorubicin (N) severely decreased the S/N by 48 and 40 %, respectively (Figure 5a). It is important to point out that this trend is consistent with the trend of their $T_2$ and additive-dependent $^{19}$F NMR ΔSI values. In contrast, the presence of the “drug” had a much smaller influence on the S/N for 2b (up to 19 %, Figure 5b), which is probably due to the facts that 2b has higher hydrophilicity than 1b, the “drug”–2b interactions are weaker than the “drug”–1b interactions, and 2b forms much smaller co-self-assembled nanoparticles than 1b. Thus, $^{19}$F MRI can not only provide images of the co-self-assembled amphiphile–drug systems for drug tracking and dosing optimization, but it can also show amphiphile–drug interactions by revealing structural differences among the drugs, which should be very useful for monitoring drug-loading and drug-release processes.
Finally, fluorinated amphiphiles 1a and 2a were employed to investigate their self-assembly on gold nanoparticles (GNPs). After modifying GNPs with in situ generated thiols 1a and 2a from corresponding disulfides 1c and 2c, the GNPs were covered with a highly ordered layer of 1a or 2a, because monodisperse oligoethylene glycol units were used as anchors on the GNPs. DLS indicated the average diameter of the GNPs was expanded from 20 to 24 nm after 1a modification. However, there was only a slight size change, ≈0.5 nm in diameter, in the GNPs modified with 2a. The difference is probably because 1a has a larger molecular size than 2a, and therefore, there is a denser layer of monodisperse oligoethylene glycol units on the 2a-modified GNPs. Because the order and dense arrangement of 1a and 2a on the GNPs would enhance intermolecular π–π stacking and hydrophobic interactions and because the Au–S bond would further reduce the molecular movement of 1a and 2a, molecular tumbling of 1a and 2a on the GNPs was severely reduced. It was reported that restricting the mobility of fluorine atoms on GNPs dramatically broadened the 19F NMR signal or even quenched the 19F NMR signal. Therefore, very weak singlets in the 19F NMR spectra of the 1a- and 2a-modified GNPs are detected, which indicates that 1a and 2a are homogeneously distributed on the GNPs and that all of the fluorine atoms have similar environments. For 1a- and 2a-modified GNPs solutions at the same fluorine concentration, the lower 19F NMR S/N of the 1a-modified GNPs is also an indication that additional π–π stacking and hydrophobic interactions from the B rings further restrict the mobility of the fluorine atoms on the GNPs. However, the 19F NMR signal is too weak to obtain a decent image from 19F MRI within a reasonable scanning time at this concentration. So, the molecular movement is also an important factor in the design of 19F NMR/MRI-sensitive drug-delivery systems, especially for nanoparticle-based systems. Thus, 19F NMR spectroscopy is able to detect weak interactions in self-assembly even on GNPs (Figure 6).

Conclusions

In conclusion, 19F NMR/MRI are appropriate tools for monitoring self-assembled drug-delivery systems. Besides images and spectra, the plentiful parameters of 19F NMR/MRI, such as chemical shift, which is sensitive to solvent; signal intensity, which is sensitive to the structure of the encapsulated drug; and relaxation time, which is sensitive to molecular tumbling, provide insightful understanding about the self-assembly process, drug–delivery vehicle interactions, drug structural features, and so on. Fluorinated self-assembled amphiphiles are promising 19F NMR/MRI-traceable drug-delivery vehicles for in vivo tracing and quantifying drugs and detecting drug microenvironments and weak interactions and, therefore, developing 19F NMR/MRI-guided drug therapy. Although this study illustrated the feasibility of using 19F NMR/MRI to monitor drug-delivery systems sensitively and to provide principles for rational 19F NMR/MRI-sensitive drug-delivery vehicles, novel fluorinated drug-delivery vehicles based on this work to improve drug loading ability, targeted delivery, and 19F NMR/MRI sensitivity are necessary to translate these in vitro studied into in vivo 19F NMR/MRI-guided drug therapy. Currently, these works are actively ongoing in this laboratory.

Experimental Section

Synthesis of 4: At 0 °C, under an atmosphere of argon, a solution of triethylene glycol monomethyl ether (29.90 g, 182.10 mmol) in
THF (150 mL) was added to a suspension of NaH (60 % dispersed in mineral oil, 10.93 g, 273.15 mmol in 500 mL of THF). The mixture was stirred for 30 min and a solution of 3-11 (70 g, 273.15 mmol) in THF (250 mL) was added. The resulting mixture was stirred overnight at room temperature. Then, water (4.92 mL, 273.15 mmol) was added to the mixture, and H₂SO₄ was added to adjust the pH to about 3. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with saturated Na₂CO₃ to adjust the pH to about 7. After removal of the solvent under vacuum, the solution was washed with water and extracted with CH₂Cl₂ (4 x 500 mL). The organic layers were combined, and the solution was concentrated under vacuum. The residue was purified by column chromatography (MeOH/CH₂Cl₂ = 3:100) to give 4 (52.07 g, 84 %) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 3.38 (s, 3 H), 3.52–3.79 (m, 28 H) ppm.

Synthesis of 5: To a stirring solution of ethanol 4 (52.07 g, 152.96 mmol) in THF (500 mL) was added aqueous sodium hydroxide (24.47 g of NaOH in 73.41 mL of water). After stirring for 10 min and cooling to 0 °C, p-toluene sulfonyl chloride (58.32 g, 305.93 mmol) in THF (200 mL) was slowly added to the mixture. After the addition was complete, the mixture was warmed to room temperature and was stirred overnight. The resulting mixture was extracted with EtOAc (3 x 400 mL). The organic layers were combined, and the solution was concentrated under vacuum. The residue was purified by column chromatography (MeOH/CH₂Cl₂ = 3:100) to give 5 (52.07 g, 84 %) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 3.38 (s, 3 H), 3.52–3.79 (m, 28 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 25.5, 52.1, 58.9, 67.8, 68.7, 69.5, 70.3, 70.4, 70.5, 70.6, 70.7, 70.8, 71.2, 72.3, 108.7, 124.8, 142.2, 152.1, 166.4 ppm. HRMS (ESI): calcd. for C₃H₁₀O₂Na⁺ [M + Na]⁺ 116.8685; found 116.8692.

Synthesis of 6: Under an argon atmosphere, a mixture of methyl gallate (6.52 g, 35.4 mmol) and K₂CO₃ (44.03 g, 318.6 mmol) in dry CH₂Cl₂ (150 mL) was slowly added to a solution of LiAlH₄ (3.83 g, 100.89 mmol) in dry THF (100 mL) at 0 °C. After addition was complete, the mixture was warmed to room temperature and was stirred overnight. The resulting mixture was extracted with EtOAc (3 x 400 mL). The organic layers were combined, and the solution was concentrated under vacuum. The residue was purified by column chromatography (MeOH/CH₂Cl₂ = 1:50) to give 6 as a colorless oil (37.02 g, 98 %). ¹H NMR (400 MHz, CDCl₃): δ = 3.38 (s, 9 H), 3.51–3.91 (m, 83 H), 4.16 (t, J = 8.0 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.80 (d, J = 8.0 Hz, 2 H) ppm.
Synthesis of 1c: A solution of I2 (2.05 g, 8.07 mmol) in CH2Cl2 (20 mL) was added to a solution of 14 (25.10 g, 8.07 mmol) in CH2Cl2 (50 mL) in portions over 30 min. The mixture was stirred at room temperature for 4 h and then was quenched with 10% aqueous sodium thiosulfate (20 mL). The mixture was washed with brine, dried with Na2SO4, and concentrated under vacuum to provide a pale-yellow oil. Purification by column chromatography (MeOH/CH2Cl2 = 1:25) gave desired product 1c (18.99 g, 82%) as a pale-yellow oil. 1H NMR (400 MHz, CDCl3): δ = 2.87 (t, J = 4.0 Hz, 4 H), 3.37 (s, 36 H), 3.50–3.59 (m, 2 H), 3.60–4.08 (m, 26 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 38.3, 53.6, 58.9, 66.5, 70.2, 70.3, 71.7, 72.1, 83.8, 106.9, 122.0, 124.9, 126.0, 128.3, 129.4, 130.3, 130.8, 133.2, 136.9, 138.1, 138.2, 152.5, 152.6 ppm. HRMS (ESI): calcd. for C17H34BrNaNO8 [M + Na]+ 482.1352; found 482.1360.

Preparation of 1a-Modified GNPs: To stirring first-grade water (100 mL) was added aqueous trisodium citrate (0.034 M, 6 mL). After the solution had boiled for 3 min, aqueous H2AuCl4 (0.024 M, 2 mL) was added rapidly, and the resulting solution was boiled for another 6 min. Then, the mixture was cooled to room temperature, and the solution was stored in the dark at 4 °C. DLS: diameter = 19.56 nm and polydispersity index (PDI) = 0.049. UV/Vis: λmax = 518 nm. Under an argon atmosphere, a solution of 1a (2.0 g, 0.07 mol) in MeOH (10 mL) was added to the solution of colloidal gold nanoparticles (GNPs), and the mixture was stirred for 24 h at room temperature. The resulting mixture was centrifuged at 16000 xg for 20 min, and the supernatant was carefully removed. The 1a-stabilized GNPs were washed with Milli-Q water (3x). The concentration of the functionalized gold nanoparticles was determined by visible absorbance at 525.50 nm. DLS: diameter = 24.33 nm and PDI = 0.306.

Synthesis of 15: A mixture of 5 (61.28 g, 123.90 mmol) and NaH (24.16 g, 371.70 mmol) in dry DMF (600 mL) was stirred at 80 °C for 5 h. The resulting mixture was filtered to remove the excess amount of NaH. After removing H2O by vacuum distillation, the residue was washed with water and extracted with CH2Cl2 (4 × 300 mL). The organic layers were combined, and the solution was concentrated under vacuum. The residue was purified by column chromatography (EtOAc/petroleum ether = 1:4) to afford 15 as a colorless oil (44.37 g, 98%). 1H NMR (400 MHz, CDCl3): δ = 3.38 (s, 3 H), 3.39–3.43 (m, 2 H), 3.52–3.58 (m, 2 H), 3.63–3.69 (m, 24 H) ppm.

Synthesis of 16: PPh3 (44.84 g, 170.97 mmol) was added to a stirring solution of 15 (41.65 g, 113.98 mmol) in THF (550 mL) at room temperature. After the addition, the mixture was stirred for 30 min and H2O (10.27 mL, 569.90 mmol) was added. The resulting mixture was stirred at this temperature overnight. The mixture was extracted with H2O (2 × 300 mL). The combined aqueous layer was concentrated under vacuum, and the residue was purified by column chromatography (MeOH/CH2Cl2 = 1:25) to afford 16 as a colorless oil (36.75 g, 95%). 1H NMR (400 MHz, CDCl3): δ = 3.39 (s, 3 H), 3.33–3.39 (m, 2 H), 3.60–4.08 (m, 26 H) ppm.

Synthesis of 17: Under an argon atmosphere, a solution of 16 (36.75 g, 108.27 mmol), DMAP (0.66 g, 5.41 mmol), and Et3N (13.15 g, 129.92 mmol) in dry CH2Cl2 (300 mL) was stirred for 10 min at 0 °C. Bromoacetyl bromide (18.84 mL, 216.54 mmol) was then added dropwise to the mixture over a period of 30 min at 0 °C. The mixture was stirred at ambient temperature overnight. The solvent was evaporated under reduced pressure, and then ethyl acetate was added for dissolution. The resulting mixture was filtered to remove a white insoluble solid, and the residue was purified by column chromatography (CH2Cl2/MeOH = 100:1) to afford 17 as a pale-yellow oil (30.90 g, 62%). 1H NMR (400 MHz, CDCl3): δ = 3.38 (s, 3 H), 3.45–3.62 (m, 6 H), 3.62–3.72 (m, 22 H), 3.88 (s, 1 H), 4.06 (s, 1 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 29.0, 39.5, 39.8, 42.5, 58.8, 69.2, 70.1, 70.3, 70.4, 71.7, 166.2 ppm. HRMS (ESI): calcd. for C17H34BrNaNO8+[M + Na]+ 482.1360; found 482.1352.

Synthesis of 18: Under an argon atmosphere, a solution of benzylamine (3.27 g, 30.51 mmol) and 17 (30.90 g, 67.12 mmol), and K2CO3 (6.33 g, 45.76 mmol) in dry THF/DMF (1:1, 200 mL) was stirred at 45 °C overnight. DMF was removed by vacuum distillation, and the residue was washed with water and extracted with CH2Cl2 (4 × 200 mL). The organic layers were combined, and the solution was concentrated under vacuum. The residue was purified by column chromatography (MeOH/CH2Cl2 = 1:50) to give 18 as a colorless oil (24.57 g, 93%). 1H NMR (400 MHz, CDCl3): δ = 3.21 (s, 4 H), 3.38 (s, 6 H), 3.42–3.51 (m, 4 H), 3.52–3.58 (m, 8 H), 3.58–3.69 (m, 45 H), 3.73 (s, 2 H), 7.27–7.33 (m, 2 H), 7.34–7.37 (m, 3 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 38.8, 57.8, 58.9, 59.2, 69.6, 70.1, 70.3, 70.4, 70.5, 70.6, 70.8, 71.0, 71.2, 71.8, 72.2, 74.6, 82.4, 82.7, 83.8, 88.3, 106.8, 107.1, 114.5, 122.2 (q, J = 288 Hz), 124.9, 126.0, 128.3, 129.4, 130.3, 130.8, 133.2, 136.9, 138.0, 138.2, 152.55, 152.62 ppm. 19F NMR (376 MHz, CDCl3): δ = –73.66 ppm. HRMS (MALDI-TOP): calcd. 2902.3734 [M + Na]+; found 2902.2285.

Synthesis of 20: Compound 20 was prepared by following the same procedure as that outlined for 17 from 16 as a clear oil
(14.51 g, 62 %). 1H NMR (400 MHz, CDCl3): δ = 3.38 (s, 6 H), 3.42–3.51 (m, 4 H), 3.53–3.60 (m, 8 H), 3.61–3.73 (m, 46 H), 4.01–4.19 (m, 6 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 39.4, 39.5, 41.0, 53.5, 54.0, 59.0, 69.2, 69.4, 70.1, 70.2, 70.4, 70.47, 70.53, 71.9, 167.8, 168.5, 169.0 ppm. HRMS (ESI): calcd. for C68H2BrN2O2S2+ [M + 2H]2+ 448.7017; found 448.7082.

Synthesis of 2b: Compound 2b was prepared by following the same procedure as that outlined for 14 from 13 as a clear oil (12.28 g, 90 %). 1H NMR (400 MHz, CDCl3): δ = 2.40 (t, J = 8.0 Hz, 2 H), 3.27 (t, J = 8.0 Hz, 2 H), 3.35 (s, 12 H), 3.39–3.48 (m, 10 H), 3.49–3.83 (m, 116 H), 4.06 (s, 4 H), 4.27 (s, 4 H), 4.40 (s, 2 H), 4.61 (s, 4 H), 7.13–7.24 (m, 6 H), 7.26–7.31 (m, 2 H), 7.36–7.43 (m, 6 H), 7.72 (s, 2 H), 7.97–8.11 (m, 3 H), 9.35 (s, 2 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 31.5, 39.2, 39.3, 52.9, 53.1, 53.7, 58.7, 64.9, 66.3, 68.9, 69.3, 69.4, 69.9, 70.0, 70.29, 70.30, 71.7, 82.5, 82.8, 83.1, 83.6, 88.3, 121.7 (q, J = 288 Hz), 125.1, 126.5, 127.7, 129.0, 129.9, 133.1, 144.6, 167.1, 168.7, 169.3 ppm. HRMS (ESI): calcd. for C114H176F12N6Na2O40S2+ [M + 2Na]2+ 1254.0083; found 1254.0085.

Preparation of 2a-Modified GNPs: To stirring first-grade water (100 mL) was added aqueous trisodium citrate (0.024 M, 2 mL) at 80 %. The solution had boiled for 3 min, aqueous HAuCl4 (0.024 M, 2 mL) was added rapidly, and the resulting solution was boiled for another 6 min. Then, the mixture was cooled to room temperature, and the solution was stored in the dark at 4 °C. DLS: diameter = 21.94 nm and PDI = 0.131.

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