Supplementary Information

for

Adhesive ^{19}F MRI chemical probe allows signal off-to-on-type molecular sensing in a biological environment

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1. Figures S1-S2

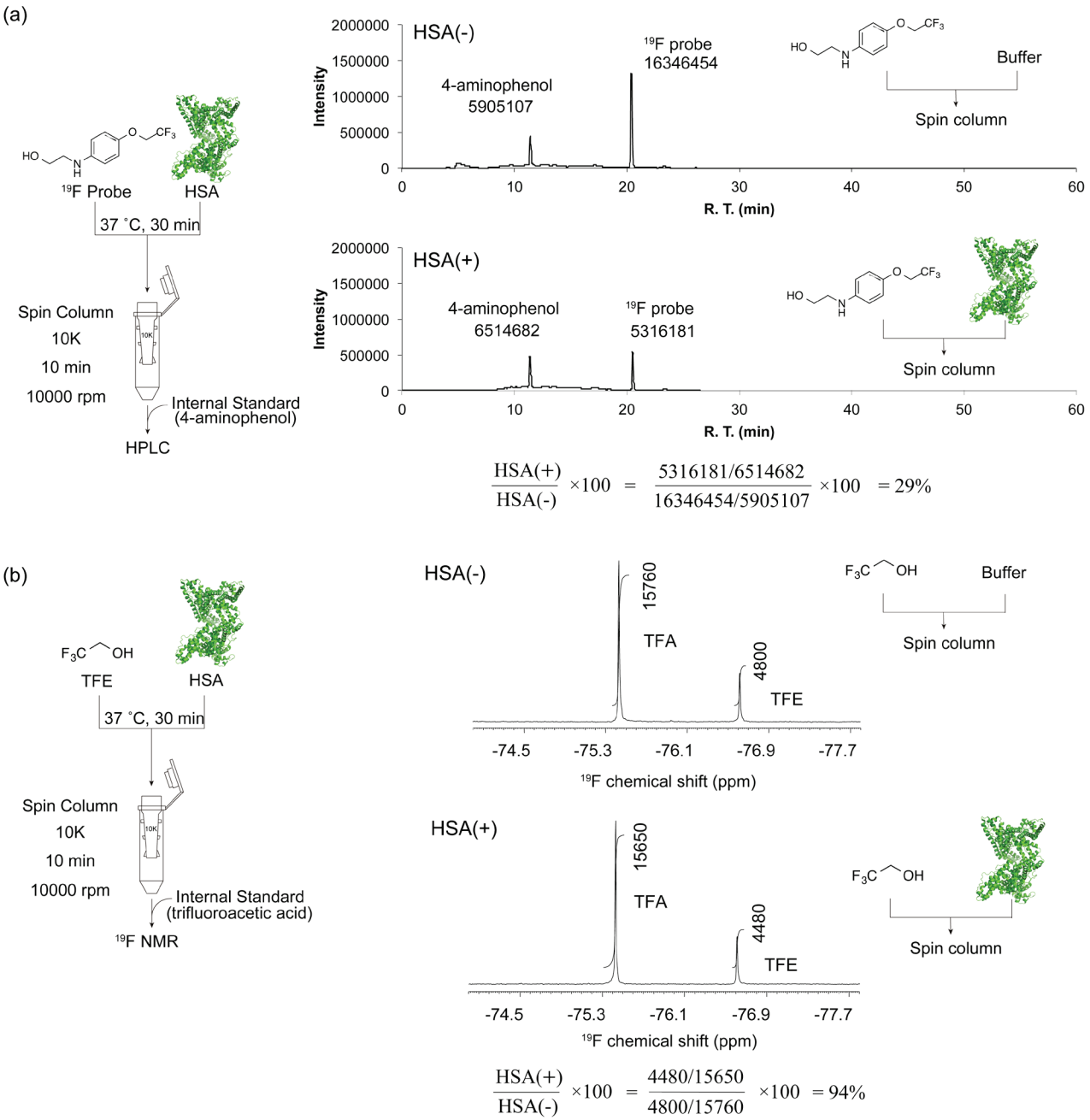


Fig. S1 Evaluation of adhesive property of probe **1** and product trifluoroethanol to HSA. a) Probe **1** (400 μM) or b) product trifluoroethanol (400 μM) was mixed with HSA (50 g L^{-1}) in 100 mM sodium phosphate buffer (pH 7.4) containing 150 mM NaCl. The mixture was filtered through ultrafiltration cartridge (Amicon Ultra MWCO 10 K, 9,300 g, 10 min). a) Probe **1** or b) product trifluoroethanol in filtrate was quantified by HPLC-UV or ^{19}F NMR, respectively. Recovery yields of probe and product were determined as HSA(+)/HSA(–) = 29 and 94%, respectively, suggesting that probe **1** tends to adhere to HSA, while product trifluoroethanol does not.

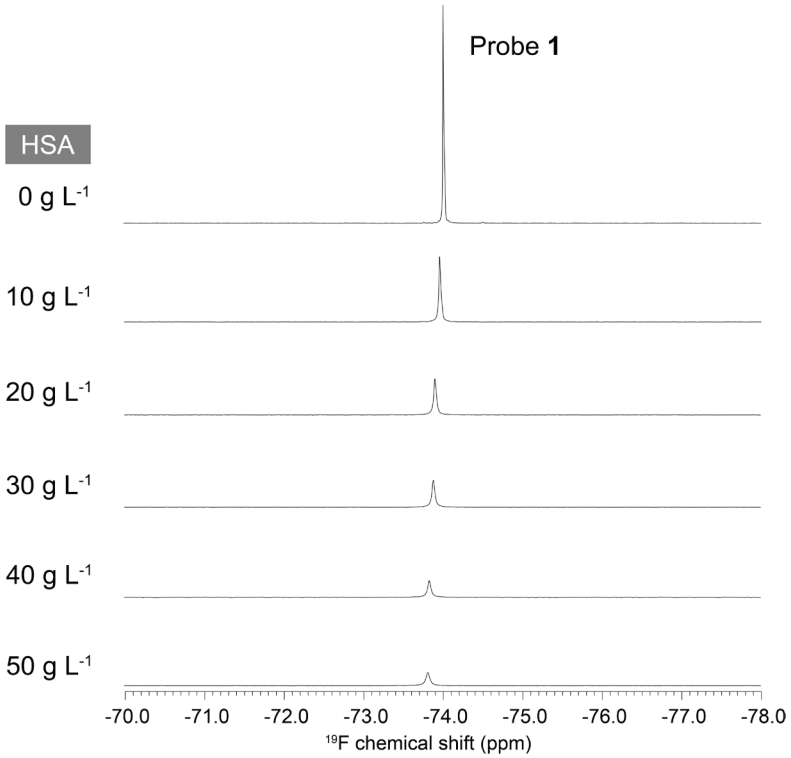


Fig. S2 ^{19}F NMR (long spin echo time, TE = 20 ms) of probe **1** solution (5 mM) in 100 mM sodium phosphate buffer (pH 7.4) containing 150 mM NaCl in the presence of HSA (0, 10, 20, 30, 40, and 50 g L^{-1}).

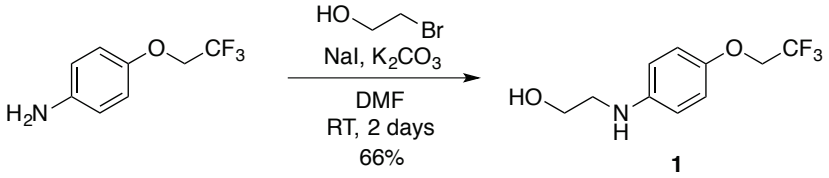
2. Methods

2.1. Synthesis

General

Reagents and solvents were purchased from standard suppliers and used without further purification. ^{1}H NMR (2.50 ppm for DMSO-d_6 as an internal standard) and ^{13}C NMR (39.5 ppm for DMSO-d_6 as an internal standard) spectra were acquired using a Bruker Avance III spectrometer (400 MHz for ^{1}H NMR). Mass spectra (MS) were measured using a JEOL JMS-HX110A (FAB).

2-((4-(2,2,2-Trifluoroethoxy)phenyl)amino)ethanol (1)



1

2-Bromoethanol (746 mg, 5.97 mmol), sodium iodide (603 mg, 4.02 mmol) and potassium carbonate (603 mg, 4.36 mmol) were added to a solution of 4-(2,2,2-trifluoroethoxy)aniline (645 mg, 3.37 mmol)[S1] in DMF (1.5 mL) and stirred for 2 days at room temperature. Saturated NH_4Cl aqueous solution was added to the reaction mixture and the mixture was extracted with $CHCl_3$ three times. The organic layer was evaporated to dryness. The resulting residue was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 1/1) twice to give **1** as a pale yellow solid (520 mg, 2.21 mmol, 66%). ^{1}H NMR (DMSO-d_6): δ. 6.82 (d, J = 8.8 Hz, 2H), 6.54 (d, J = 8.8 Hz, 2H), 5.20 (t, J = 5.9 Hz, 1H), 4.63 (t, J = 5.9 Hz, 1H), 4.55 (q, J = 8.9 Hz, 2H), 3.53 (m, 2H), 3.03 (m, 2H). ^{13}C NMR (DMSO-d_6): δ. 148.8, 145.0, 124.7 (q, J = 276 Hz), 116.7, 113.3, 66.2 (q, J = 33.5 Hz), 60.2, 46.7. HRMS (FAB$^+$): calculated for $C_{10}H_{12}O_2NF_3$ (M^+) = 235.0815, observed = 235.0824.

2-2. ^{19}F NMR measurements

General

^{19}F NMR spectra were measured on a Bruker Avance III spectrometer (376 MHz for ^{19}F NMR). Chemical shifts are reported in ppm (trifluorotoluene $\delta = -62.7$ ppm).

^{19}F NMR measurements of ^{19}F chemical probe 1 reacted with HOCl in phosphate buffer (Fig. 2b)

HOCl (final concentration, 0-10 mM) was added to an aqueous solution of ^{19}F chemical probe **1** (final concentration, 5 mM) in 100 mM sodium phosphate buffer (pH 7.4) containing 150 mM NaCl with or without human serum albumin (50 g L^{-1}). The solutions were incubated for 10 min at 37 °C. An aliquot of the solution (450 μL) was mixed with D_2O (50 μL) and subjected to a ^{19}F NMR analysis. Twenty ms of spin echo time (TE) was used.

2-3. T_2-weighted ^{19}F MRI measurements

General

^{19}F MRI images were acquired on a Bruker Avance II spectrometer (470 MHz for ^{19}F), equipped Micro2.5 imaging probe with 25 mm inner diameter ^{19}F coil. ^{19}F images were acquired by RARE (Rapid Acquisition with Relation Enhancement) method. The imaging parameters for Fig. 2b: TR/TE=4000/11.1 ms, matrix = 32×32 (zero-filled to 64×64 for analysis), field of view = 50 mm×50 mm, slice thickness = 30 mm, 32 transients were recorded for each phase step and for Fig. 3: TR/TE=1000/135 ms, matrix = 32×32 (zero-filled to 64×64 for analysis), field of view = 50 mm×50 mm, slice thickness = 30 mm, 256 transients were recorded for each phase step. The **1** or trifluoroethanol selective images were acquired by setting each peak at the center of acquisition frequency and using Gaussian selective pulse for excitation and refocusing. Samples were filled into 5 mm outer diameter NMR tube and placed as shown in each figure.

T_2-weighted ^{19}F MRI measurements ^{19}F chemical probe 1 reacted with HOCl in phosphate buffer (Fig. 2b)

HOCl (final concentration, 0-10 mM) was added to an aqueous solution of ^{19}F chemical probe **1** (final concentration, 5 mM) in 100 mM sodium phosphate buffer (pH 7.4) containing 150 mM NaCl with or without human serum albumin (50 g L^{-1}). The solutions were incubated for 10 min at 37 °C. An aliquot of the solution (450 μL) was mixed with D_2O (50 μL) and subjected to a T_2-weighted ^{19}F MRI analysis.

T_2-weighted ^{19}F MRI measurements of ^{19}F chemical probes reacted with MPO in phosphate buffer containing blood plasma (Fig. 3)

H_2O_2 (final concentration, 4 mM), MPO (final concentration, 0 or 470 nM), and human plasma (final 40% v/v) were added to a solution of **1** (final concentration, 5 mM) in sodium phosphate solution (final concentration, 60 mM, pH 7.4) containing NaCl (final concentration, 90 mM). The reaction solution was incubated for 4 h at 37 °C.

3. Reference

S1) T. Doura, Q. An, F. Sugihara, T. Matsuda, S. Sando, *Chem. Lett*. 2011, **40**, 1357.