

SUPPORTING INFORMATION

Sub-picomolar iron sensing platform based on functional lipid monolayer microarrays

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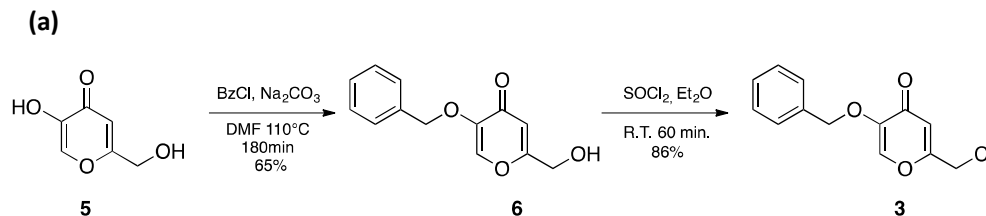
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1. Synthesis of γ -pyrone derivative: Fe^{3+} chelator

γ -pyrone derivative is obtained from commercially available Kojic acid in a two steps synthesis using standard procedures.

Ref for **6**: (a) Ma, Y.; Luo, W.; Quinn, P. J.; Liu, Z.; Hider, R. C. *J. Med. Chem.*, **2004**, *47*, 6349-6362. (b) Beer, P. D.; Gale, P. A.; Chen, G. Z. *Coord. Chem. Rev.* **1999**, *185–186*, 3–36

Ref for **3**: Storr, T.; Mitchell, D.; Buglyo, P.; Thompson, K. H.; Yuen, V. G.; McNeill, J. H.; Orvig, C. *Bioconjugate Chem.*, **2003**, *14*, 212-221.



Compound 6: To a solution of 2.00 g (14.00 mmol) of kojic acid and 3.20 ml (23.00 mmol) of benzyl chloride (BzCl) in 10 mL of dry DMF was added 3.00 g (28.30 mmol) of sodium carbonate. The reaction mixture was heated up to 110°C and was kept at that temperature during 3 hours. The reaction mixture was cooled down to room temperature and 8 mL of water were added dropwise. The organic compound was extracted three times with 15 mL of chloroform. The combined organic phases were dried over MgSO_4 , filtered and the solvent was removed under reduced pressure affording a brownish solid. The latter was recrystallized in chloroform leading to 2.10 g of **6** (65%) as beige solid.

^1H NMR (250 MHz, CD_3OD) δ = 4.43 (s, 2H, CH_2OH); 5.04 (s, 2H, OCH_2); 6.53 (s, 1H, H_5); 7.37 (m, 5H); 8.04 (s, 1H, H_2). ^{13}C NMR (67.5 MHz, CD_3OD) δ = 61.00 (CH_2OH); 72.6 (OCH_2); 112.08 (CH, C_5); 129.1 (CH, C_9C_{13}); 129.4 (CH, C_{11}); 129.6 (CH, $\text{C}_{10}\text{C}_{12}$); 137.3 (C, C_8); 143.2 (CH, C_2); 148.3 (C, C_3); 170.6 (C, C_6); 183.10 (C, C_4).

Compound 3: To a solution of 2.00 g (8.62 mmol) of compound **6** in 20 mL diethyl ether was added dropwise, under Ar atmosphere, 0.8 mL (11.00 mmol) of thionyl chloride. The reaction mixture was stirred at room temperature during 1 hour, then successively were added 30 mL of water and 20 mL of diethyl ether. The organic phases were washed twice with 20 mL of water and dried over MgSO_4 . The solvent was removed under reduced pressure affording 1.90 g (86%) of compound **3** as orange solid.

^1H NMR (250 MHz, CDCl_3) δ = 4.46 (s, 2H, CH_2Cl); 4.92 (s, 2H, OCH_2); 6.38 (s, 1H, H_5); 7.29 (m, 5H); 7.50 (s, 1H, H_2). ^{13}C NMR (67.5 MHz, CDCl_3) δ = 39.9 (CH_2Cl); 70.9 (CH_2O); 113.9 (CH, C_5); 126.7 (CH, C_9C_{13}); 127.5 (CH, C_{11}); 127.7 (CH, $\text{C}_{10}\text{C}_{12}$); 134.4 (C, C_8); 140.6 (CH, C_2); 146.2 (C, C_3); 160.6 (C, C_6); 173.5 (C, C_4).

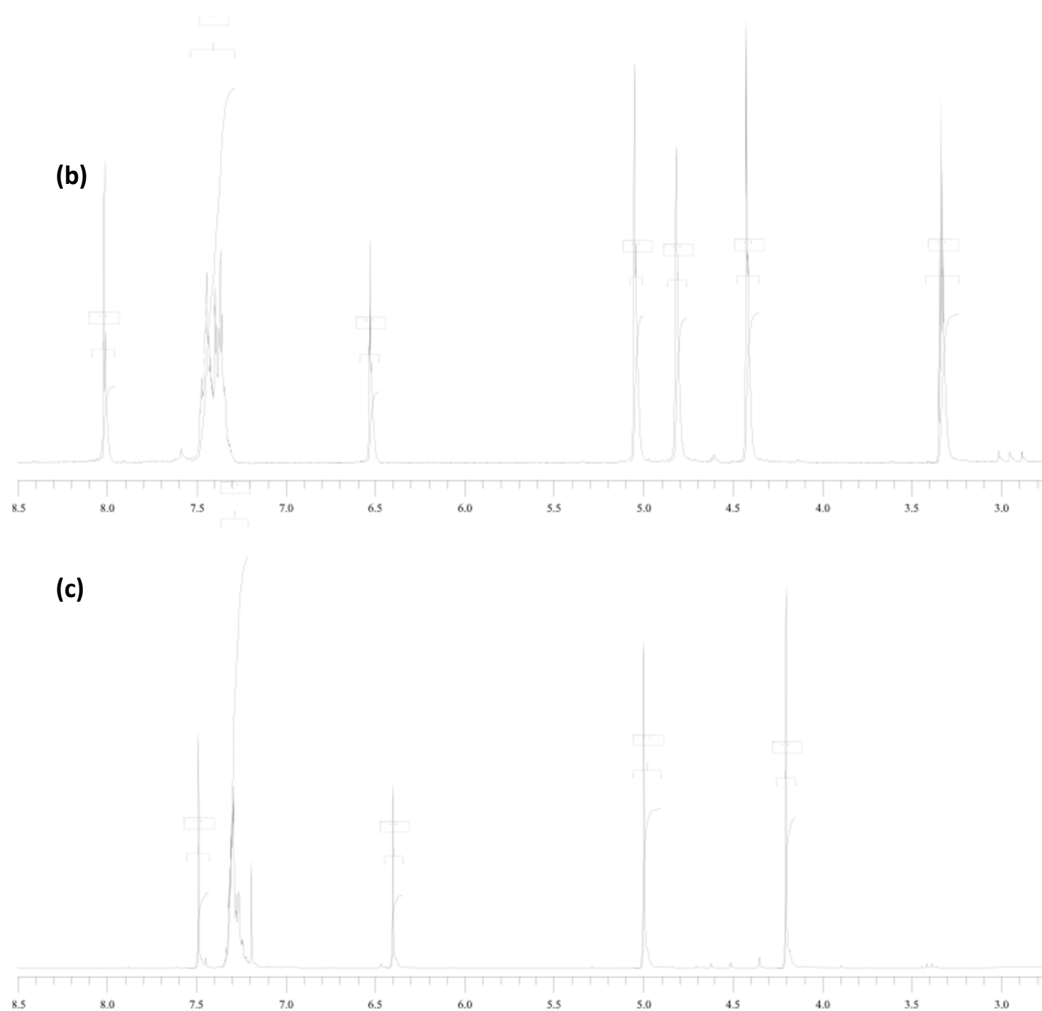


Figure S1: (a) Synthesis of the γ -pyrone derivative. ^1H NMR spectra of products **6 (b) and **3** (c)**

2. Engineered lipid with γ -pyrone **3**

Commercially available 1,2-bis-(10,12-tricosadiynoyl)-*sn*-glycero-3-phosphocholine was selected due to the presence of diyne groups in their aliphatic chains, therefore allowing reticulation between lipids. Modification of lipid head-groups starts with cleaving the phosphocholine group with a phospholipase C leaving an alcohol group instead. The latter is then used to graft the γ -pyrone derivative.

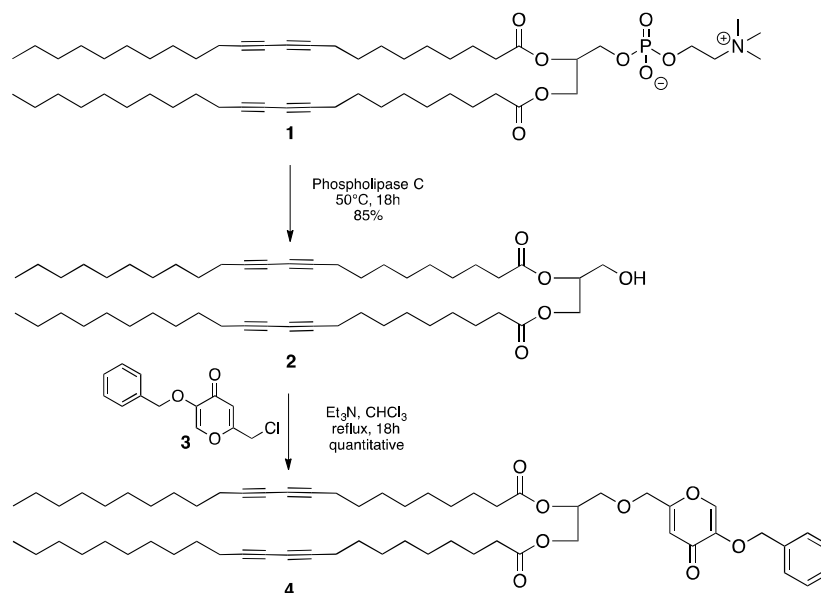


Figure S2: Cleavage of the lipid head-group with a phospholipase C and grafting of the γ -pyrone derivative **3**

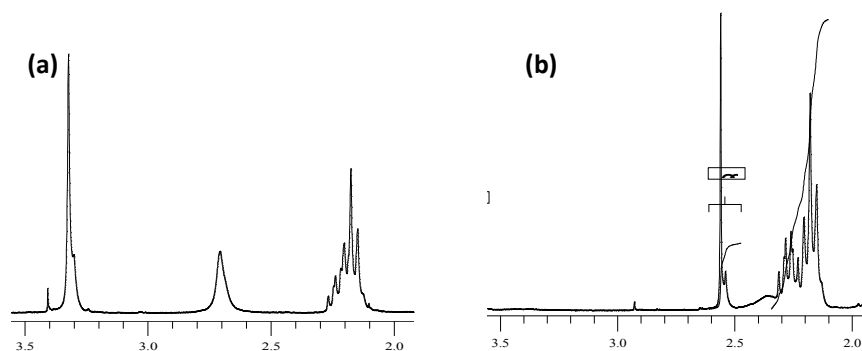


Figure S3 : ^1H NMR spectra of products **1** (a) and **2** (b)

Compound 2: To a solution of 20 mg (21.9 μmol) of 1,2-bis-(10,12-tricosadiynoyl)-*sn*-glycero-3-phosphocholine (from Avanti Polar lipids Inc.) in 5 mL of deionized water was added 14 μg of Phospholipase C (from *Bacillus Cereus*, Sigma Aldrich) and sonicated with an ultrasonic bath for 15 min. The reaction was then left overnight at 50°C and cooled down to room temperature. 50 mL of deionized water was added and the organic compound was extracted twice with 20 mL of chloroform. The organic phases were dried over MgSO_4 , filtrated and the solvent was removed under reduced pressure yielding 14 mg (85%) of compound **2** as a white solid.

^1H NMR (250 MHz, CDCl_3) δ : 4.2 (qd, 1H); 3.65 (d, 2H); 2.55 (d, 2H); 2.1-2.3 (m, 12H); 1.4-1.6 (m, 12H); 1.25 (d, 44H); 0.8 (t, 6H). MS (ESI) m/z : 771.6 $[\text{M}+\text{Na}^+]$

Compound 4: To a solution of 14 mg (18.70 μmol) of **2** in 1 mL of dry chloroform was added 5.62 mg (22.47 μmol) of compound **3** followed by the dropwise addition of 3 μL of triethylamine. The reaction mixture was refluxed overnight (18h). After cooling down to room temperature 50 mL of water were added and the compound was extracted 10 mL of chloroform. The aqueous solution was extracted twice by 10 mL of chloroform. The organic phases were dried over MgSO_4 , filtrated and the solvent was removed under reduced pressure leading to a quantitative yield of **4** as yellowish oil.

^1H NMR (250 MHz, CDCl_3) δ : 0.8 (t, 6H); 1.21 (d, 44H); 1.40-1.60 (m, 12H); 2.10-2.40 (m, 12H); 2.55 (d, 2H); 3.60 (d, 2H); 4.20 (qd, 1H); 4.30 (s, 2H); 5.10 (s, 2H); 6.50 (s, 1H); 7.35 (m, 5H); 7.60 (s, 1H).

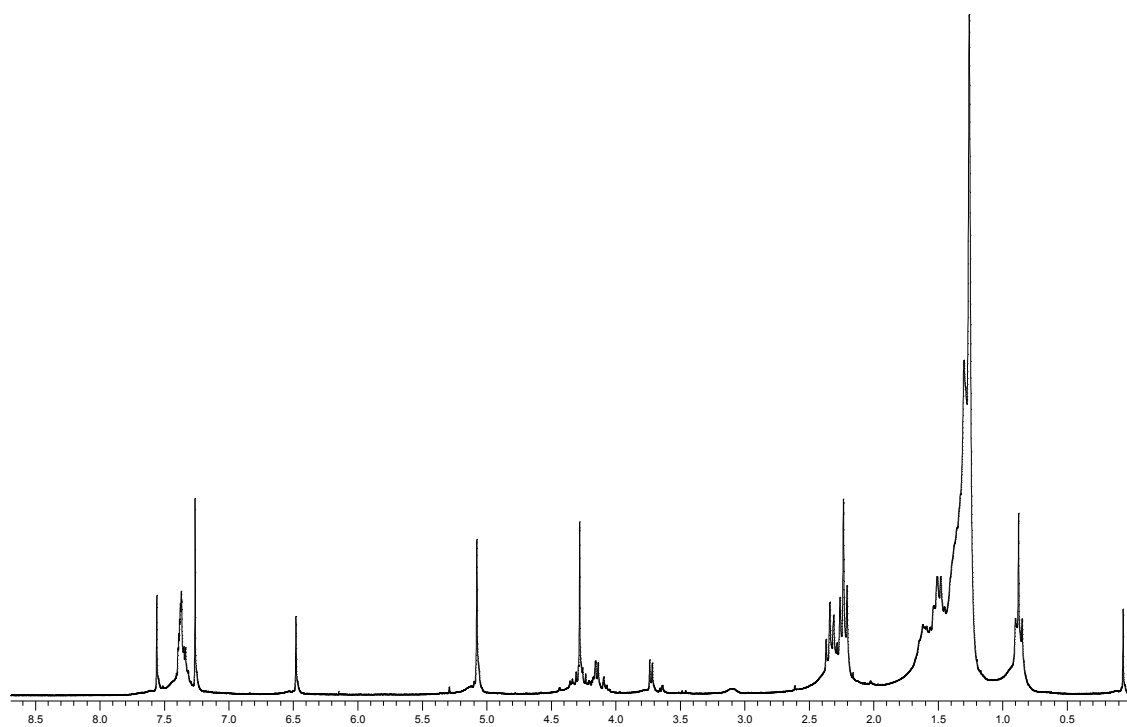


Figure S4: ^1H NMR spectra of product **4**

3. Specificity measurements

Specificity of the lipid probe towards Fe^{3+} was demonstrated earlier as well as its resistance to non-specific adsorption [Nguyen2014]. To confirm these points, Array 3 sensor was exposed to highly concentrated solutions (1 mM) of putative competitive ions, including ferrous ions, Fe^{2+} . For each type of ions, the values of Ψ are reported in Figure S4. Except for Fe^{2+} , the low values of Ψ for the other ions demonstrate the high specificity of our chelator for ferric ions and the good passivity of both lipid and silicon areas against non-specific adsorption. To explain the higher value of Ψ for Fe^{2+} , we assume that a portion of ferrous ions were oxidized in aqueous medium into ferric ions.

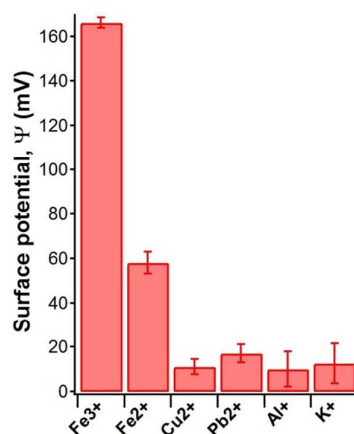


Figure S5: Kelvin probe detection of 1mM Fe^{3+} , Fe^{2+} , Cu^{2+} , Pb^{2+} , Al^{3+} and K^{+} ions using Array3 sensor. The sensor shows very high specificity towards Fe^{3+} with a maximum change in surface potential of 20 mV after exposure to Cu^{2+} , Pb^{2+} , Al^{3+} and K^{+} . For Fe^{2+} , most of the measured potential change most certainly arises from the oxidation of Fe^{2+} into Fe^{3+} in aqueous solution.