Supporting Information

Redox-Responsive Macrocyclic Based on Crown Ether C7Te for Enhanced Bacterial Inhibition

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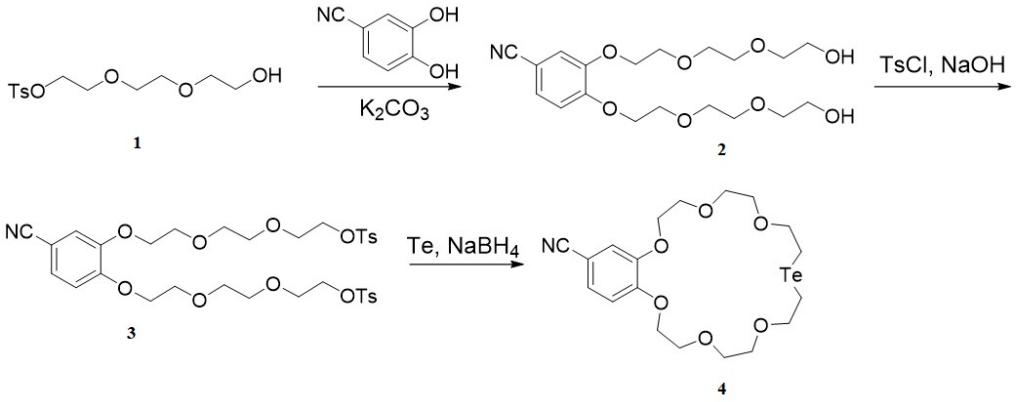
1. Synthesis and Characterization of Compounds

1.1 Preparation of Crown Ether C7Te



Scheme S1. The synthetic route of compounds **C7Te**.

Preparation of Compound 1

Triethylamine (2.01 g, 66.6 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a solution of *p*-toluenesulfonyl chloride (3.17 g, 16.7 mmol) and triethylene glycol (10 g, 66.6 mmol) in CH_2Cl_2 (200 mL) at 0℃. The suspension was stirred for 2 h at 0℃ and then at room temperature for another 16 h. The finish of the reaction was monitored by TLC. Afterwards, ice water (100 mL) was poured into the reaction mixture and 0.1 M HCl was added to adjust the pH to 2~3. The organic layer was washed by water (100 mL × 2) and brine (100 mL) respectively. After drying over Na_2SO_4 and removal of the solvents, the residue was purified by silica gel column chromatography to provide triethylene glycol monotosylate (4 g, 79 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.80 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 4.19 – 4.14 (m, 2H), 3.71 (dd, J = 8.6, 3.8 Hz, 4H), 3.63 – 3.55 (m, 6H), 2.45 (s, 2H).

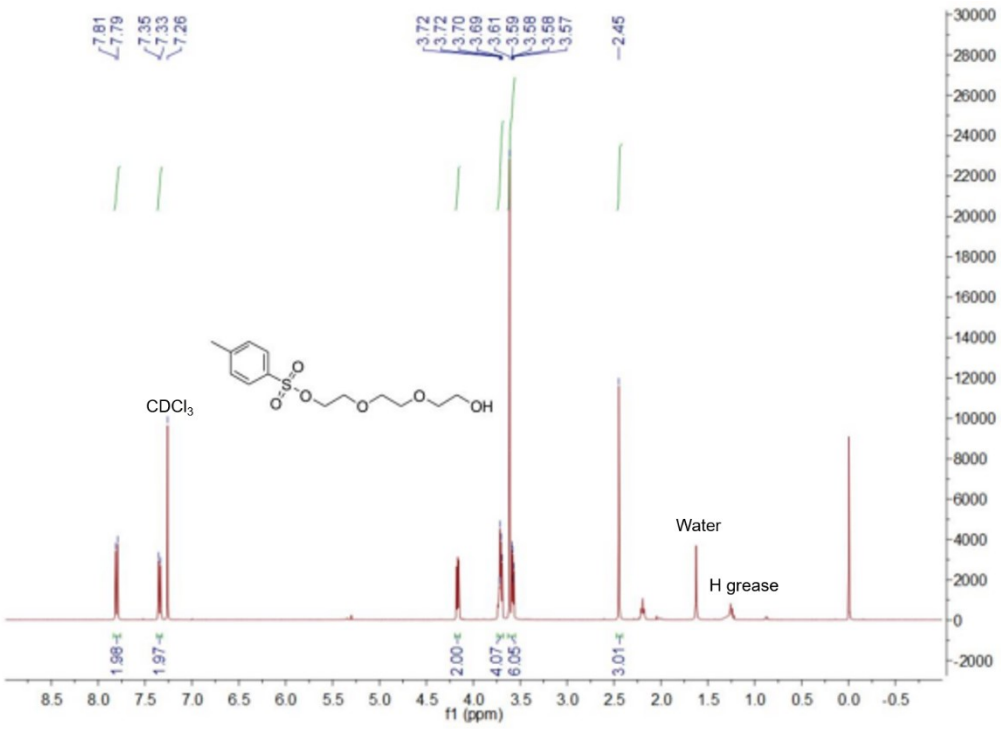


Figure S1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298K) of compound **1**.

Preparation of Compound 2

While stirring vigorously under N_2 atmosphere, 3, 4-dihydroxybenzonitrile (0.68 g, 5 mmol) and K_2CO_3 (2.76 g, 20 mmol) were added to the solution of **1** (3.04 g, 10 mmol) dissolved in CH_3CN 40 mL. Then the mixture was heated to 75 ^{o}C and stirred for 18 h. The mixture was cooled to room temperature and filtered. The cake was washed by CH_2Cl_2 40 mL twice and all the filtrate was concentrated under reduced pressure. Then the residue was purified directly by silicon column ($MeOH/CH_2Cl_2$ = 1/300 ~ 6/300) to obtain product as oil 1.82 g with the yield of 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27~7.24 (m, 1H), 7.15 (s, 1H), 6.92 (d, J = 8.4 Hz, 1H), 4.23~4.17 (m, 4H), 3.92~3.88 (m, 4H), 3.76~3.69 (m, 12H), 3.62~3.59 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.80, 148.81, 126.86, 119.14, 117.07, 114.53, 113.46, 104.27, 77.36, 77.25, 77.04, 76.93, 76.72, 76.62, 72.70, 70.95, 70.39, 69.56, 69.39, 69.13, 68.71, 61.73. HR-MS (ESI) *m/z* ($M+Na^+$) *calcd.* for $C_{19}H_{29}NNaO_8Na^+$:422.1791. *Found:* 422.1789.

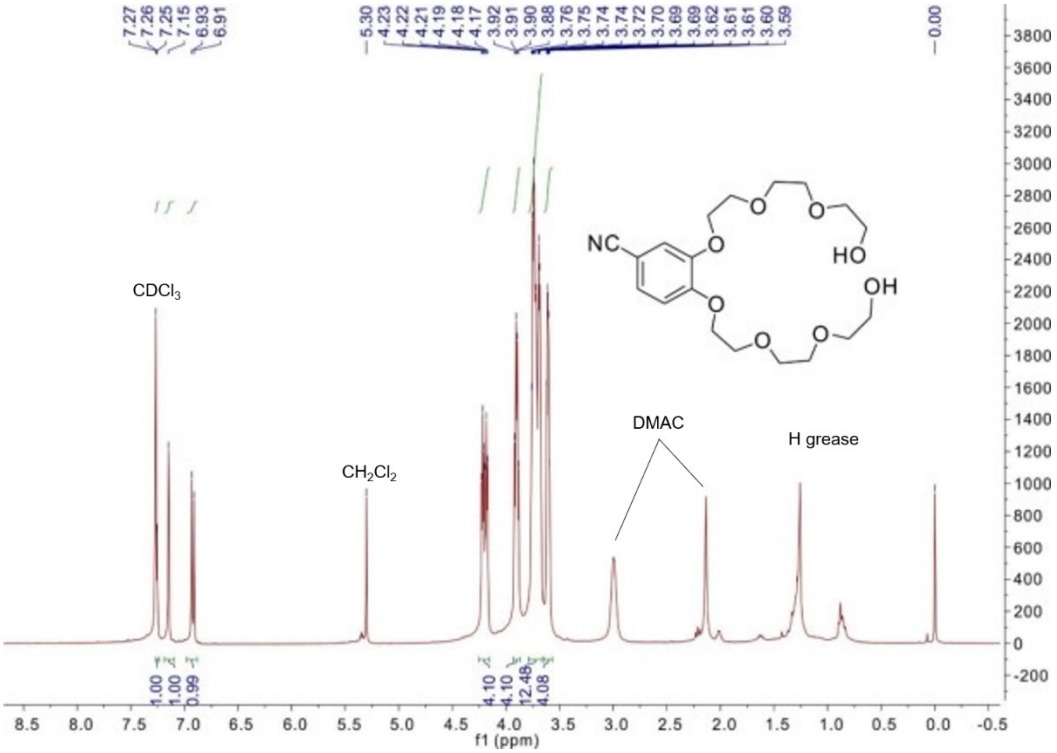


Figure S2. ^{1}H NMR spectrum (400MHz, $CDCl_3$, 298K) of compound **2**.

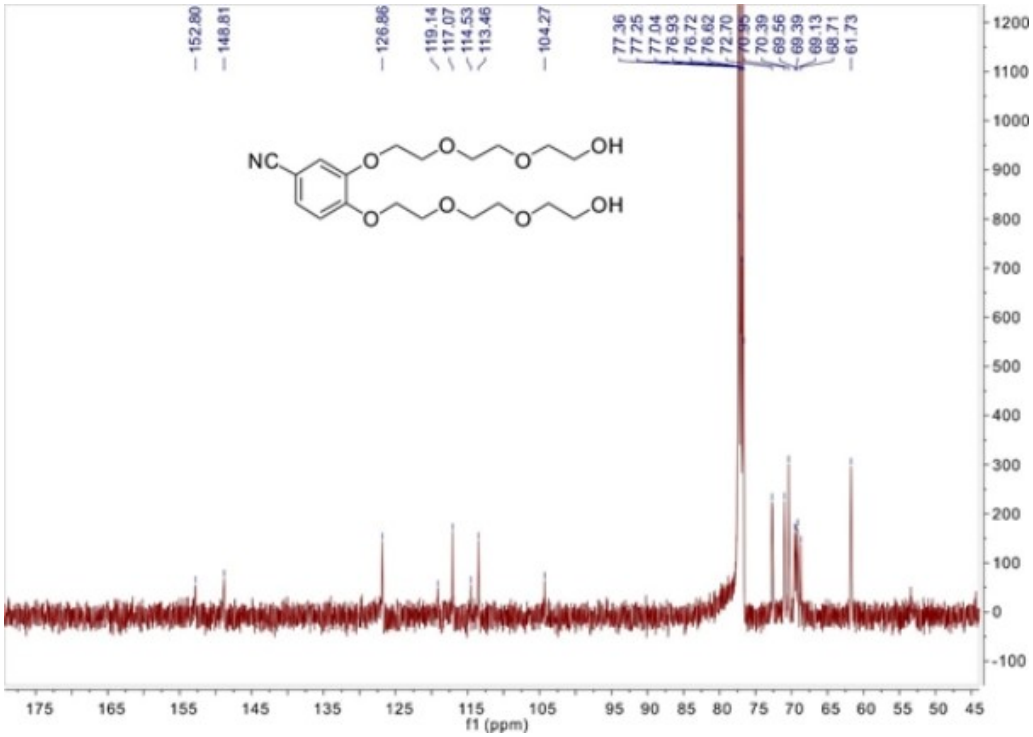


Figure S3. ^{13}C NMR spectrum (100 MHz, $CDCl_3$, 298K) of compound **2**.

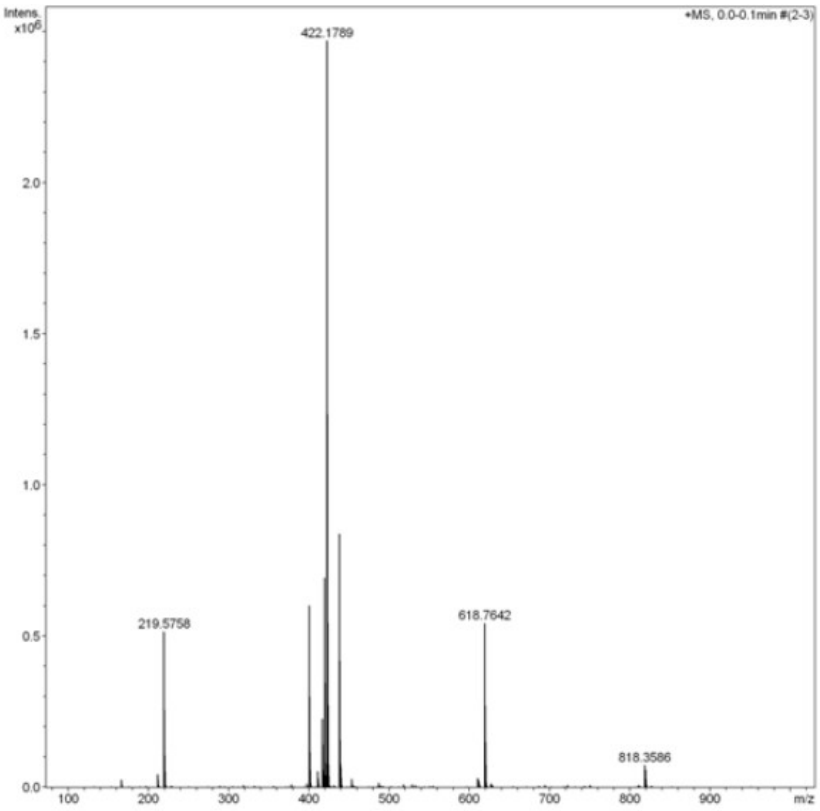


Figure S4. HR-MS characterization of compound **2**.

Preparation of Compound 3

The solution of 2 (1.0 g, 2.5 mmol) dissolved in THF (10 mL) and H_2O (5 mL), NaOH (0.5 g, 12.5 mmol) dissolved in H_2O (5 mL) was added into 250 mL flask. Subsequently, the mixture was cooled to 0℃ and TsCl (1.44 g, 7.5 mmol) dissolved in THF (10 mL) was dropwise added. The finish of reaction was monitored by TLC. Afterwards, ice water 50 mL was added into flask and the mixture was extracted by CH_2Cl_2 50 mL three times. The organic layer was washed by brine 50 mL twice and dried over Na_2SO_4. After removal of the solvents, the residue was purified directly by silicon column with MeOH/CH_2Cl_2 = 1/300 ~ 6/300 *v/v* as eluent to give product 1.63 g as oil with the yield of 92 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, J = 8.2 Hz, 4H), 7.33 (d, J = 8.0 Hz, 4H), 7.24 (d, J = 1.7 Hz, 1H), 7.14 (d, J = 1.6 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 4.20~4.18 (m, 2H), 4.16~4.13 (m, 6H), 3.87~3.82 (m, 4H), 3.71~3.66 (m, 8H), 3.61~3.59 (m, 4H), 2.43 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.92, 152.23, 148.90, 148.32, 144.86, 134.85, 133.01, 131.34, 129.86, 127.98, 127.32, 126.81, 124.18, 117.17, 113.57, 104.94, 104.16, 77.35, 77.03, 76.71, 70.85,

69.66, 69.48, 69.31, 69.25, 69.19, 68.77, 68.72, 53.43, 21.65. HR-MS (ESI) *m/z* ($M+K^+$) *calcd.* for $C_{33}H_{41}NO_{12}S_2K^+$: 746.1707. *Found:* 746.1695.

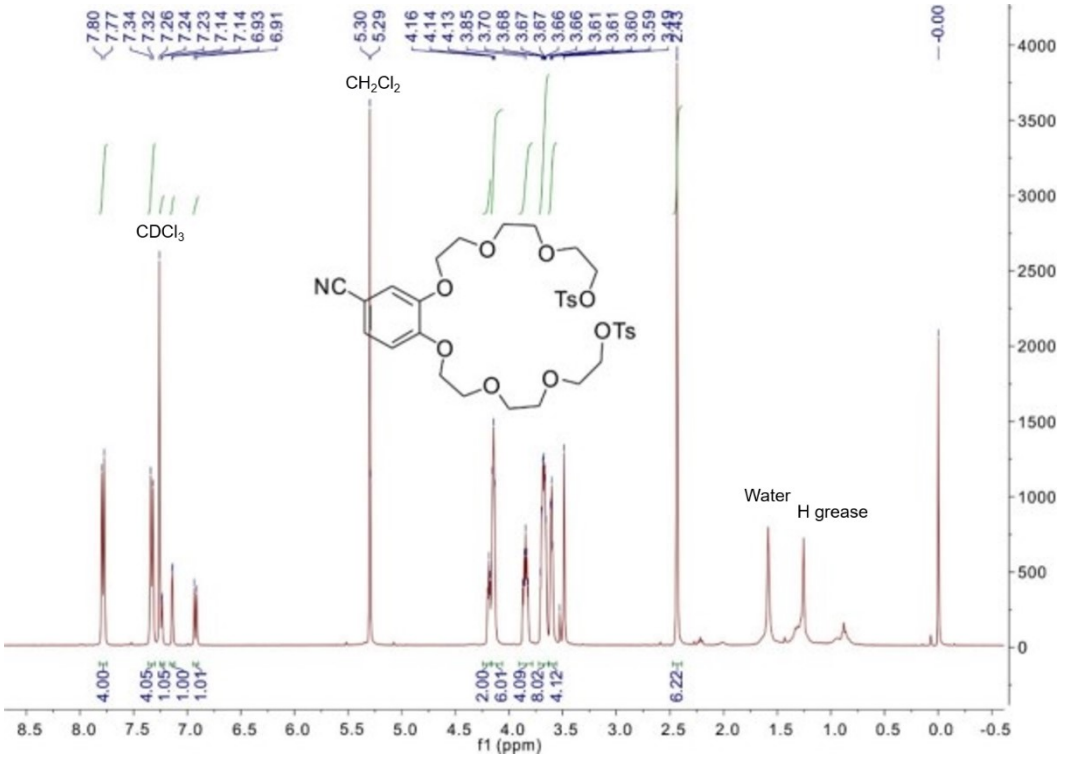


Figure S5. ^{1}H NMR spectrum (400MHz, $CDCl_3$, 298K) of compound **3**.

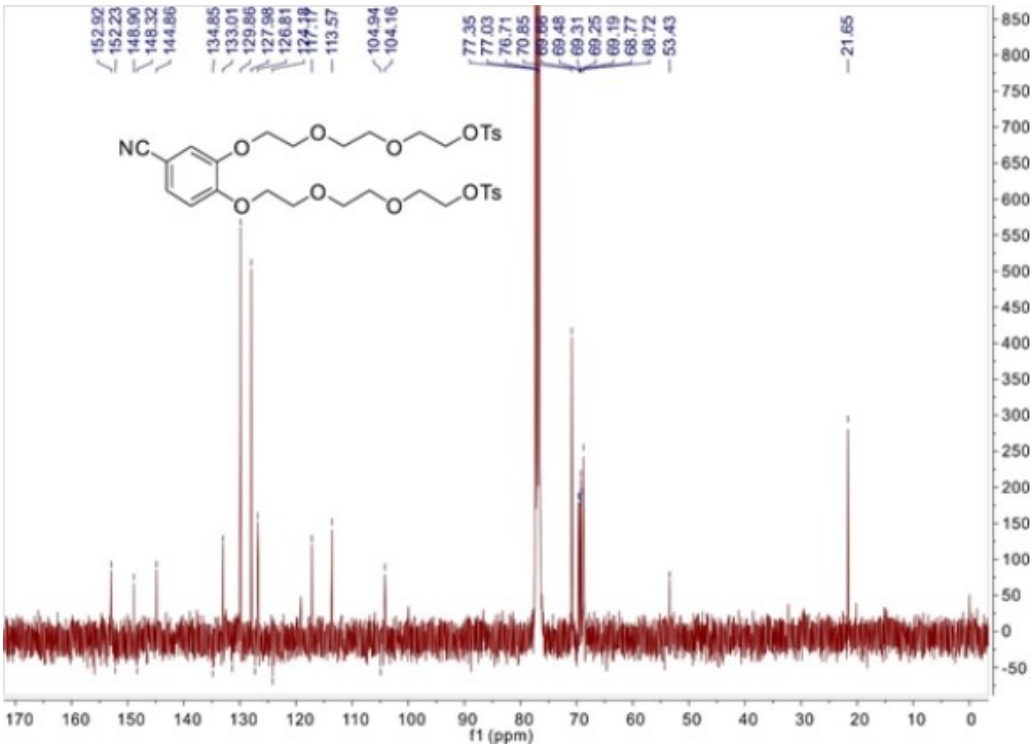


Figure S6. ^{13}C NMR spectrum (100 MHz, $CDCl_3$, 298K) of compound **3**.

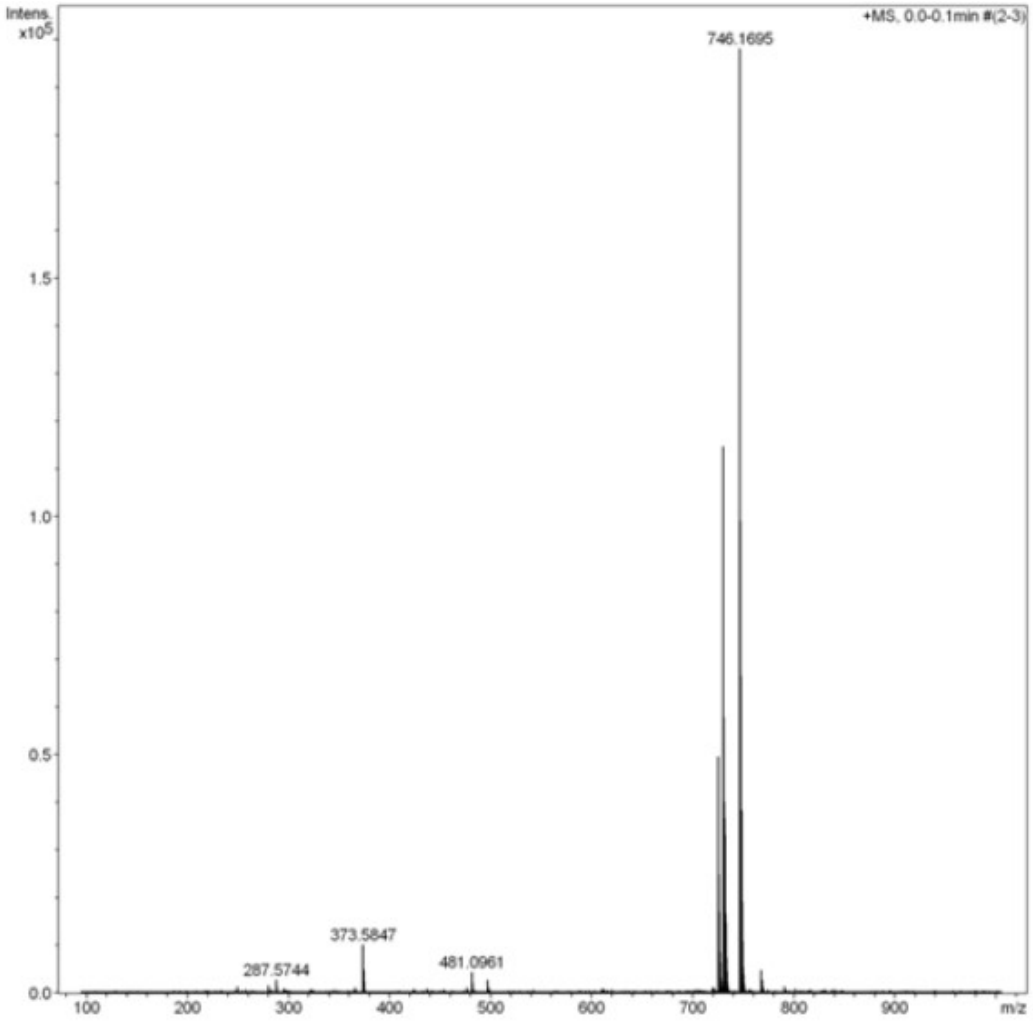


Figure S7. HR-MS characterization of compound **3**.

Preparation of Compound C7Te

To the mixture of Te powder (127.6 mg, 1 mmol) and $NaBH_4$ (302 mg, 8 mmol) was added 30 mL anhydrous ethanol under N_2 atmosphere. The mixture was heated to 50℃. After 2 h, the reaction mass became clear pink solution to give TeHNa solution. It was cool to room temperature. K_2CO_3 and KBF_4 was suspended in 100 mL CH_3CN and was heated to reflux under N_2 protection. Compound **3** (0.71 g, 1 mmol) was dissolved in 30 mL CH_3CN and the solution was homogeneously mixed with TeHNa solution. The mixture was charged slowly to the suspension liquid. The reaction mixture was stirred for 24 h. It was cooled to room temperature. The mixture was filtered and the filtrate was concentrated under reduce pressure. The residue was dissolved in 60 mL CH_2Cl_2 and the solution was washed by brine 50 mL. The solution was dried over Na_2SO_4. Concentrate the solution and the residue was purified by silicon column to give **C7Te** 0.21 g (43%) as slightly yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 (d, J = 1.9 Hz, 1H), 7.25 (d, J = 1.8 Hz, 1H), 7.11 (d, J = 1.8 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.24 ~ 4.18 (m, 2H), 4.18 ~ 4.14 (m, 2H), 3.98 ~ 3.83 (m, 8H), 3.80 ~ 3.72 (m, 4H), 3.70 ~ 3.61 (m, 4H), 2.87 (td, J = 6.8, 2.4 Hz, 4H). ^{13}C NMR (100 MHz, CD_3CN) δ = 152.60, 148.60, 126.56, 119.11, 116.17, 110.43, 73.55, 70.56, 70.54, 69.92, 69.88, 69.12, 69.00, 68.90, 68.72. HR-MS (ESI) *m/z* ($M+K^+$) *calcd.* for $C_{19}H_{27}NO_6TeNa^+$: 518.0798. *Found:* 518.0796.

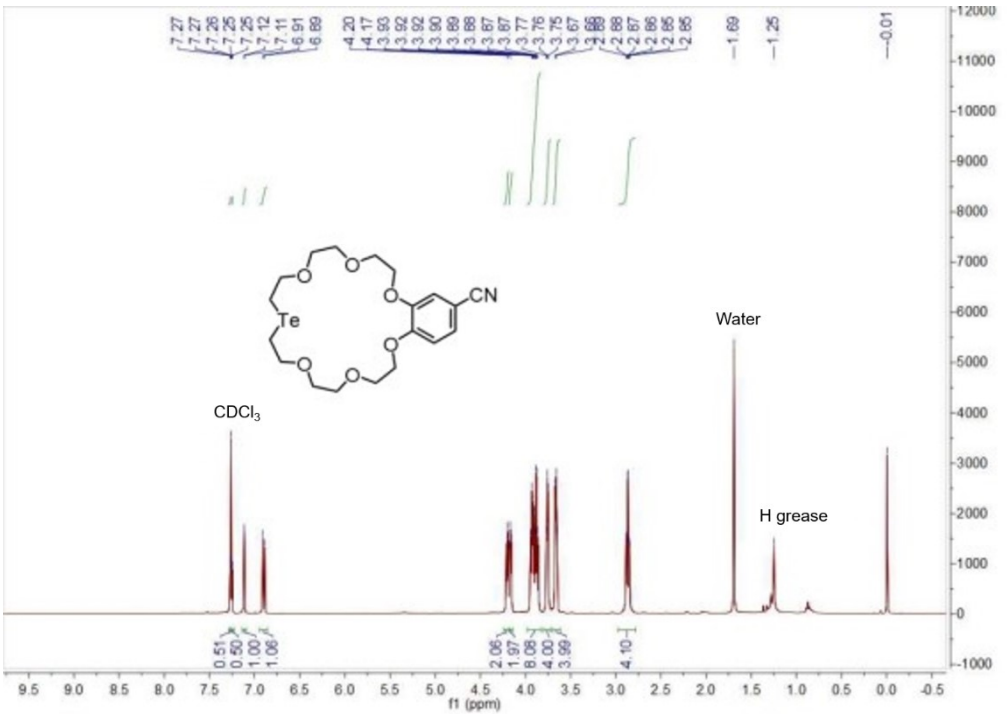


Figure S8. ^{1}H NMR spectrum (400MHz, $CDCl_3$, 298K) of **C7Te**.

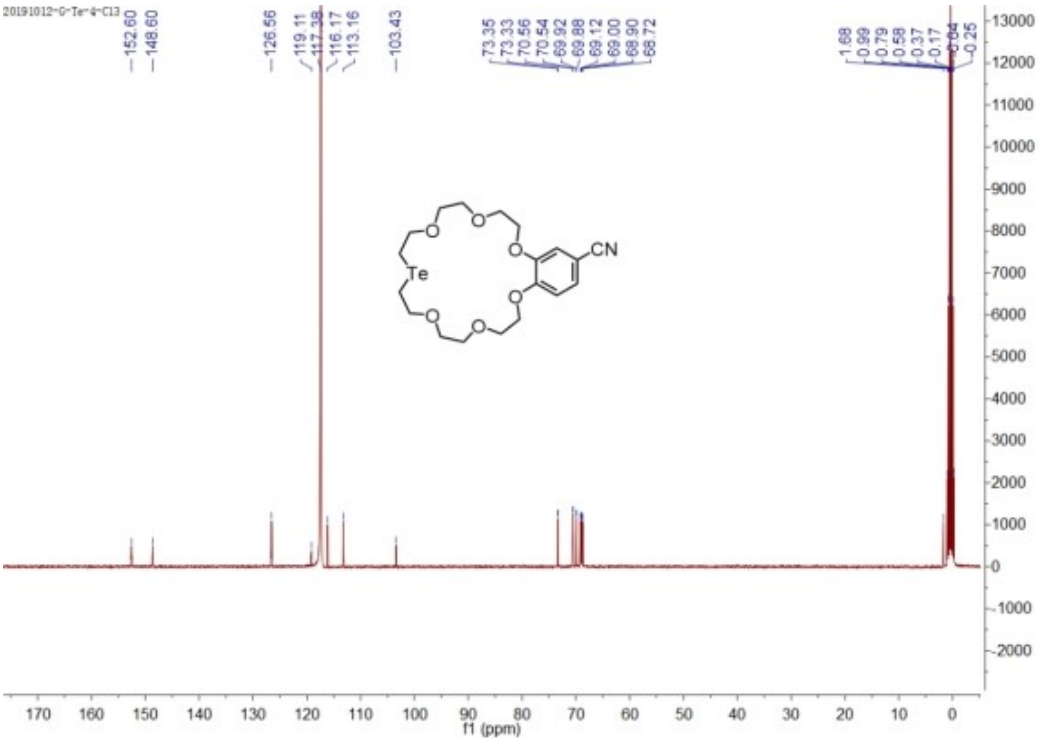


Figure S9. ^{13}C NMR spectrum (100 MHz, CD_3CN, 298K) of **C7Te**.

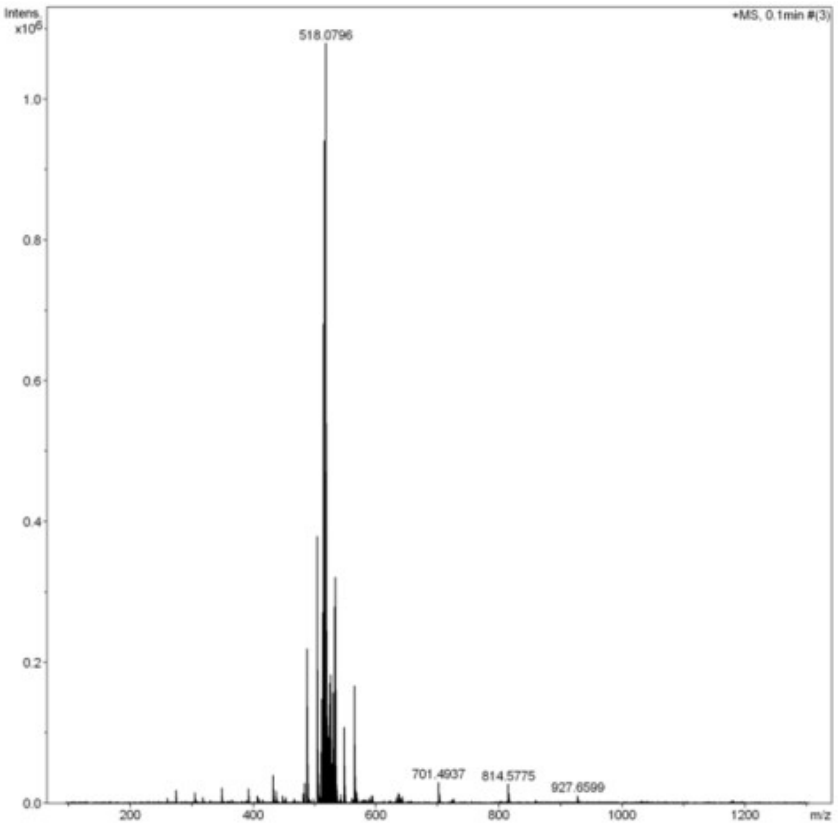
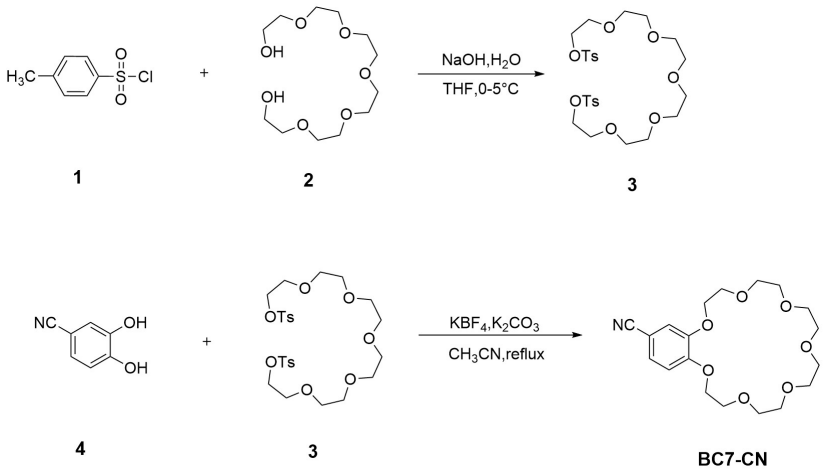


Figure S10. HR-MS characterization of **C7Te**.

1.2 Preparation of Control *Crown Ether C7*



Scheme S2. The synthetic route of compounds **C7**.

The synthesis of compound **C7** was based on previously reported reference.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 1.9 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.22 – 4.14 (m, 4H), 3.93 (dd, J = 8.9, 4.3 Hz, 4H), 3.79 (ddd, J = 5.2, 3.5, 1.7 Hz, 4H), 3.76 – 3.70 (m, 4H), 3.69 – 3.64 (m, 8H).

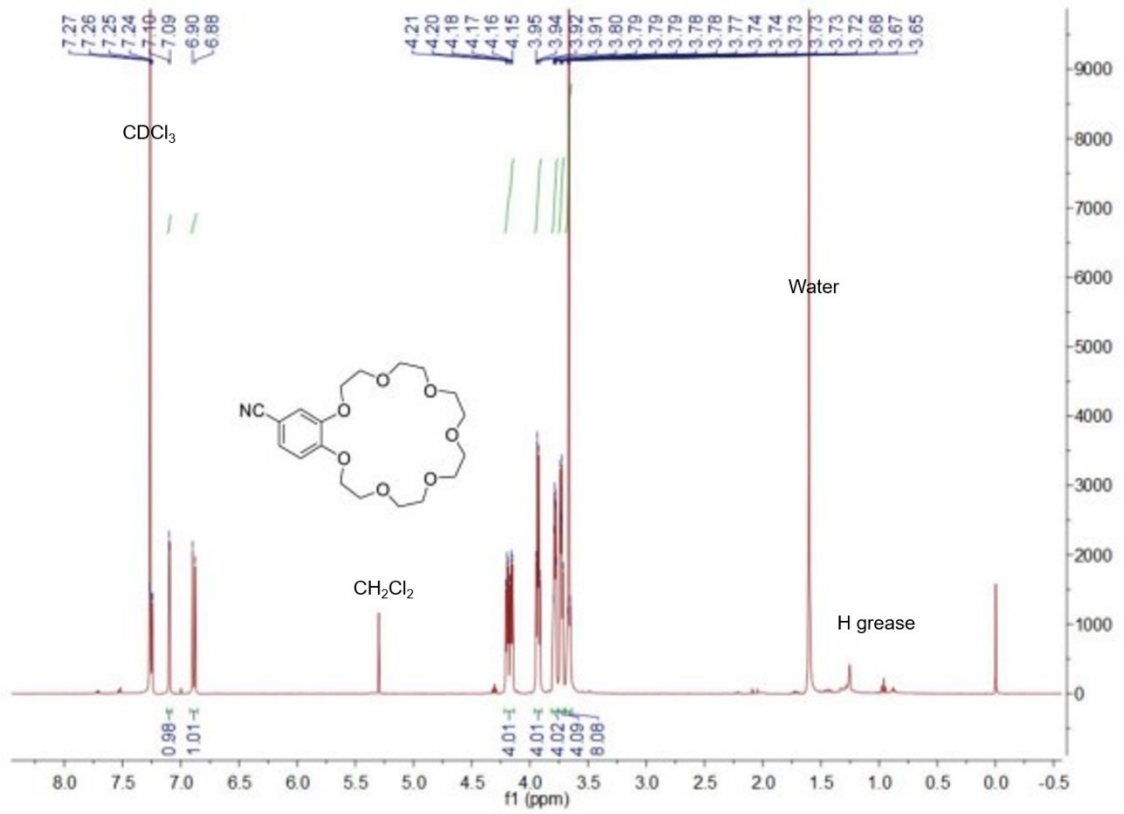


Figure S11. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298K) of **C7**.

2. MTT assay of C7TeO, C7Te

L929 cells at the logarithmic growth stage were taken for cell counting and cell concentration adjustment. The number of cells inoculated in each well was 4×10^3 and inoculated into 96-well plates at 10 μg/mL、25 μg/mL、50 μg/mL and 100 μg/mL of each compound. Add complete medium at 100 μL/ well in Control. Six parallel group were made for each treatment group.The culture medium was discarded for a total of 24 h and each well was cleaned three times with PBS. Add 100 μL 10% MTT to each well, incubate in 37℃，5% CO_2 constant temperature incubator for 4 h, discard the supernatant, add 100 μL DMSO to each well and gently stir for 10 min, then remove the sample and detect the absorbance at 570 nm[2].

MTT was used to assess the cytotoxicity of the C7Te/C7TeO (Figure S25). L929 cells were treated with the solutions of C7Te/C7TeO at different concentrations of 10、25、50 and 100 μg/mL and the incubation time was 24 hours. On the one hand, the

viability of cells incubated with C7Te/C7TeO decreased with the increasing concentration. On the other hand, compared with C7Te the toxic effect on cells changed less in different concentration of C7TeO. These results demonstrated C7TeO not only maintained the bioactivity of sterilization but also biocompatible.

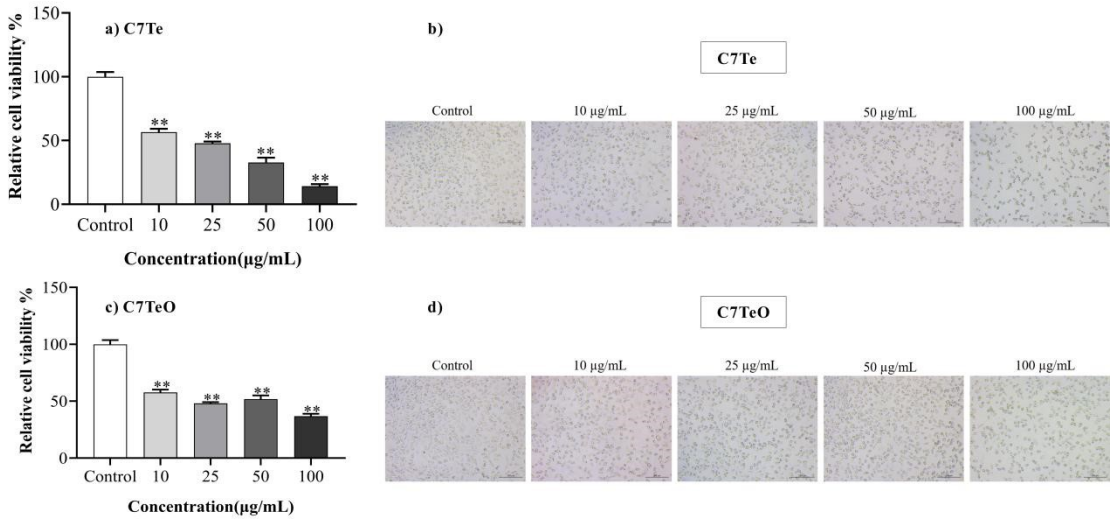


Figure S12 Graph showing percentage viability versus concentration of C7Te (a,b)/C7TeO (c,d) using MTT assay.

3. Reference

[1] Jin, L., Li, B., Cui, Z., Shang, J., Wang, Y., Shao, C., Pan, T., Ge, Y., & Qi, Z. (2019). Selenium Substitution-Induced Hydration Changes of Crown Ethers As Tools for Probing Water Interactions with Supramolecular Macrocycles in Aqueous Solutions. The journal of physical chemistry. B, 123(45), 9692–9698.

[2] Ling S , Yang X , Li C , et al. Tumor Microenvironment-Activated NIR-II Nanotheranostic System for Precise Diagnosis and Treatment of Peritoneal Metastasis[J]. Angewandte Chemie International Edition, 2020, 59.