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Synthesis and structure-activity relationship (SAR) of novel perfluoroalkyl-containing quaternary ammonium salts

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Abstract

A new series of perfluoroalkyl-containing quaternary ammonium compounds were prepared and examined for their antibacterial activities. The perfluoroalkyl-containing quaternary ammonium salts mainly exhibited excellent antibacterial activity for the Gram-positive strain such as *Staphylococcus aureus*, the MIC (minimal inhibitory concentration) values was between 2.5 and 10 μg/mL and the MBC (minimal bactericidal concentration) values were 20 μg/mL. They all showed weak activity against the Gram-negative strain such as *Escherichia coli*, and against fungi such as *Candida albicans*, the MIC values and MBC values were about 100 μg/mL. Moreover, the relationship between their antimicrobial activities and structures were further discussed.

Keywords: Perfluoroalkyl-containing compounds; Quaternary ammonium salt; Antibacterial activity

1. Introduction

In daily life, people inevitably get in touch with many kinds of microorganisms such as bacteria, fungi (yeasts, molds, mildew) and algae, some of which can bring about unpleasant odor, stain, and discoloration to fabric. One important reason is that textiles are excellent medium for the growth of microbes, which will be easily impregnated if the suitable moisture and enough time are given. Thus, they unassailably pose a threat to human health via breeding on textiles. As the increasing demand for healthy living, it is urgent to develop materials capable of killing harmful microorganisms [1]. Recently, antibacterial finishing has received more and more attention owing to their antibacterial properties, and various antibacterial agents (such as antiobiotics, silver ions, iodine and quarternary ammonium compounds et al.) have been applied to the textiles [2–8]. The long-chain quaternary ammonium salt surfactants were firstly discovered to have marked antimicrobial activity in 1935 [9], which directly caused its wide research and utilization in the past 70 years.

The antibacterial activity of quaternary ammonium compounds is supposed to be due to their surface activity properties. Recently, the perfluoroalkyl-containing compounds and fluoropolymers have been shown to be effective in application as repellent agents in textile finishing, which worked by reducing the critical surface energy of fabrics [10]. In addition, some fluoroalkyl end-capped compounds with cationic segments such as trimethylammonium, pyridinium [11,12], allylammonium [13,14], and diallylammonium groups, were also reported to be valid in reducing the surface tension of water and oil with the cationic surfactants. These fluorinated compounds also exhibited antibacterial activity to some extent [11–14].

Our research group has recently reported on the synthesis and antimicrobial activity of the perfluoroalkyl-containing compound **1** (Fig. 1), which has good antibacterial activity for Gram-positive strain (*Staphylococcus aureus* ATCC 6538) and Gram-negative strain (*Escherichia coli* 8099)

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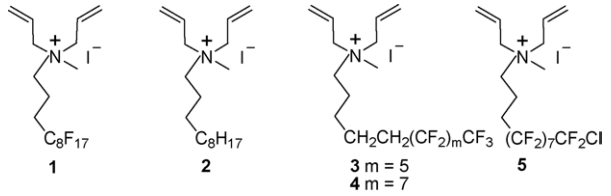


Fig. 1. Structures of compounds **1**–**5**.

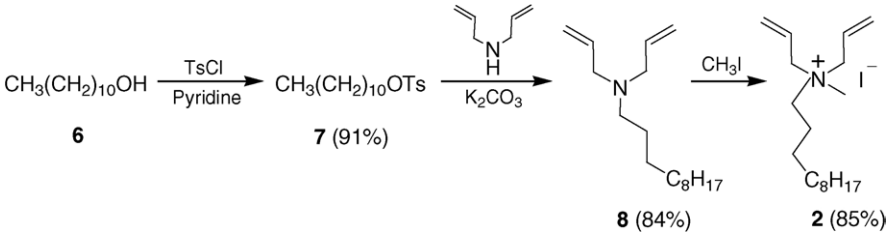
[15]. In connection with our ongoing project about textile finishing, we need to further investigate the structure-activity relationship about some analogues of compound **1**. Here reported is our synthesis and antibacterial activity test of a novel series of perfluoroalkyl-containing quaternary ammonium salts **2**–**5**, all of which are the analogues of our reported compound **1**. We have a preliminary comprehension about the impact of chain-length, halogen atoms and nonfluoroalkyl chain on the antibacterial activity.

2. Results and discussion

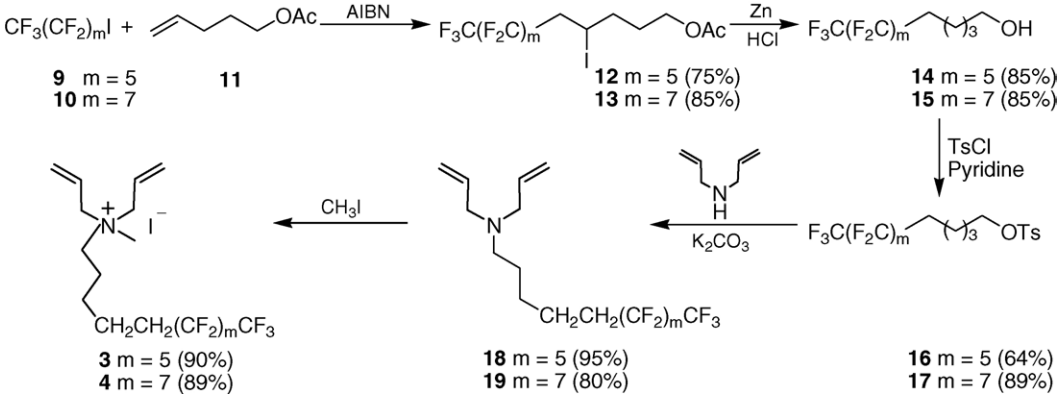
We firstly synthesized out designed target molecules **2**–**5**. The alkyl-containing quaternary ammonium compound **2** was prepared as shown in Scheme 1. Treatment of alcohol **6** with TsCl in the presence of pyridine afforded tosylate **7** in 91% yield. Then, alkylation of diallylamine with **7** in the presence of K_2CO_3 provided the desired compound **8** in 94% yield, which was finally transformed to the desired molecule **2** as ammonium salts in 85% yield.

Syntheses of compounds **3** and **4** started from perfluoroalkylated iodides **9** and **10**, respectively (Scheme 2). The first step proceeded by a free radical addition [16–18] of **9** and **10** to alkene **11** in the initiation of AIBN to provide the fluoroalkylated iodides **12** and **13** in good yield, respectively. Treatment of **12** and **13** with Zn dust and HCl gas [19] resulted in one-step removal of iodine and acetyl group and the desired alcohols **14** and **15** were furnished in 85% yield, respectively. Tosylation of compounds **14** and **15** smoothly gave the products **16** and **17**, which further reacted with diallylamine to produce the tertiary amines **18** and **19** in 95 and 80% yields. Finally, quaternary ammonium compounds **3** and **4** were obtained from the reaction of **18** and **19** with CH_3I in anhydrous CH_3CN in 90 and 89% yields, respectively.

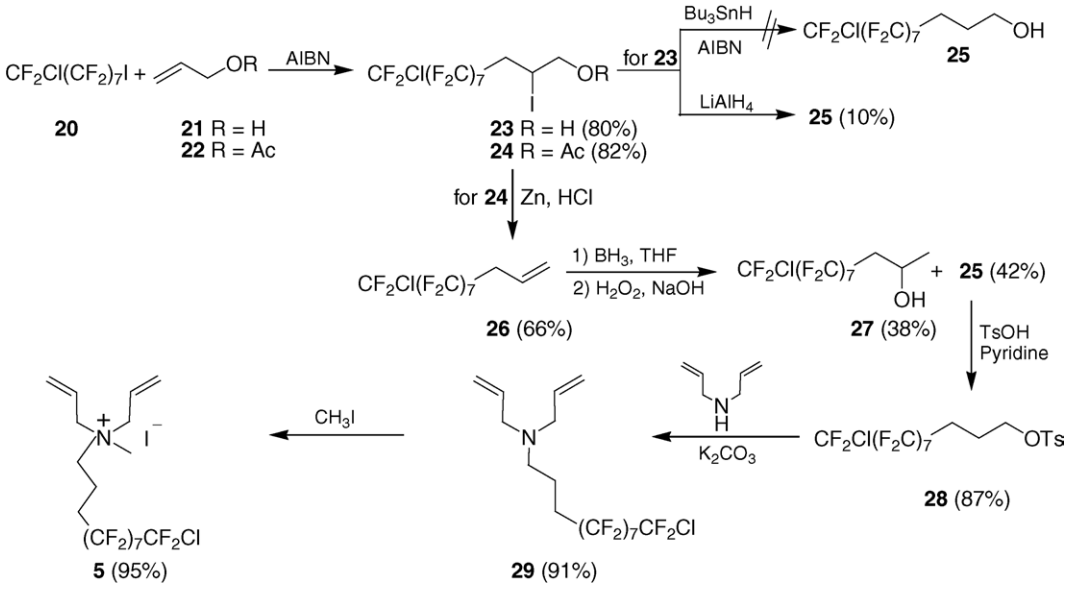
As to the synthesis of target compound **5**, we firstly attempted to prepare the key intermediate **25** from chlorofluoroalkylated iodide **20** and allylic alcohol **21** (Scheme 3). However, treatment of compound **24** with Bu_3SnH/AIBN could not provide the alcohol **25**. The reaction was very complicated and in our opinion, reaction failure was attributed to the existence of chlorine atom, which involved in the free radical reaction. In addition, attempt to remove iodine in **25** via $LiAlH_4$ reduction [20] only gave the desired product **25** in 10% yield. In view of failure and low yield of above reactions, we decided to construct the requisite hydroxyl group in **25** via hydroboration-oxidation of corresponding alkene. Thus, reaction of chlorofluoroalkylated iodide **20** and allyl acetate **22** afforded adduct **24**, which was then converted into desired alkene **26**



Scheme 1.



Scheme 2.



Scheme 3.

upon treatment with Zn/HCl. Hydroboration-oxidation of alkene **26** gave the key intermediate **25** in 42% yield along with the isomer **27** in 38% yield [21,22]. Finally, target compound **5** was smoothly prepared from alcohol **25** via tosylation and amination, followed by treatment of the resulting amine **29** with CH_3I.

With all designed quaternary ammonium compounds **1**–**5** in hand, we examined their antibacterial activity against gram positive (*S. aureus*), gram negative (*Escherichia coli*) and fungi (*Candida albicans*) microorganisms on the basis of MIC (minimal inhibitory concentration) values and MBC (minimal bactericidal concentration) values. The results of antibacterial activity tests were shown in Table 1.

The perfluoroalkyl-containing quaternary ammonium salts (**1**, **3**, **4** and **5**) showed evident antibacterial activities against gram-positive strain, which were even better than their non perfluoroalkyl-containing counterpart **2**. Their antibacterial activities against Gram-negative strain were low, whether these compounds have perfluoroalkyl-containing groups or not. However, the antibacterial activity against the fungi strain of the long alkyl chain compound **2** is superior to the perfluoroalkyl-containing compounds (**1**, **3**, **4**, **5**).

Among these compounds with the same length of the chains, such as **3**, **5**, and **1**, the antibacterial activities of compound **3** showed evident decline against *S. aureus*, the MIC values rose from 2.5–5 μg/mL to 10 μg/mL. If we change the end-capped fluorine atom into chlorine atom (that is, from **1** to **5**), the MIC values showed a little difference. We get the similar result of the MIC values and the MBC values when we kept the perfluoroalkyl-containing groups ($CF_3(CF_2)_n$-, $n = 7$) the same but increased the number of spacer methylene groups from three to five (that is from **1** to **4**). It can be concluded that the influence of the fluoroalkyl group is more effective than that of alkyl group for antibacterial activity. In general, what we designed and synthesized as perfluoroalkyl-containing quaternary ammonium salts exhibit better properties than ecumenical ones. As a kind of multifunctional finishing for textiles, these compounds not only satisfy high demand for water, oil and soil repellency, but also show good antibacterial activities. However, the length of the chains does not have an absolute connection with their antimicrobial activity.

Table 1
The MIC values and the MBC values for the compounds **1**–**5**

Compound	MIC (μg/mL)			MBC (μg/mL)		
	S. aureus ATCC 25923	*E. coli* ATCC 25922	*C. albicans* ATCC 1600	*S. aureus* ATCC 25923	*E. coli* ATCC 25922	*C. albicans* ATCC 1600
1	2.5–5	>100	50–100	20	>100	>100
2	20	>100	50	40	100	50
3	10	100	100	20	100	>100
4	2.5	>100	100	20	>100	100
5	2.5	>100	>100	20	>100	>100

3. Experimental

Melting points were determined on a Pai-ke melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM 400 (400 MHz) spectrometer with Me_4Si as an internal standard. ^{19}F NMR spectra were obtained on Bruker AM 400 (376 MHz) spectrometer in $CDCl_3$ with $CFCl_3$ as an external standard, downfield shifts being designated as negative. All chemical shifts (δ) are expressed in ppm, coupling constants (J) are given in Hz. Mass spectra were recorded on a Finnigan-MAT-8430 instrument using EI ionization at 70 eV. IR spectra were recorded on a Shimadzu IR-440 spectrometer.

3.1. Toluene-4-sulfonic acid undecyl ester (7)

n-Undecanol (4.05 g, 23.5 mmol) and toluene-4-sulfonyl chloride (6.22 g, 32.9 mmol) were dissolved in $CHCl_3$ (50 mL), pyridine (4 mL) was then added, and the mixture was stirred at room temperature until no alcohol was detected remaining by TLC. The reaction mixture was washed with water (20 mL), 2 M hydrochloric acid (20 mL) and saturated $NaHCO_3$ solution and brine. After drying (Na_2SO_4) and filtrating, the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 10:1) to give **3** as a white sheet solid (6.99 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, J = 9.5 Hz 3H), 1.24 (s, 16H), 1.59–1.66 (m, 2H), 2.45 (s, 3H), 4.02 (t, J = 6.5 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H).

3.2. N-(Undecyl)-N,N-diallylamine (8)

A suspension of toluene-4-sulfonate **7** (6.55 g, 20.1 mmol), diallylamine (2.39 g, 24.6 mmol), and potassium carbonate (3.40 g, 24.6 mmol) in anhydrous CH_3CN (30 mL) was heated to refluxing for 24 h under nitrogen. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 20:1) to give compound **8** (4.24 g, 84%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, J = 6.6 Hz 3H), 1.26 (s, 16H), 1.43–1.49 (m, 2H), 2.40 (t, J = 6.8 Hz, 2H), 3.09 (d, J = 6.5 Hz, 4H), 5.12–5.19 (m, 4H), 5.81–5.91 (m, 2H).

3.3. N-(Undecyl)-N,N-diallylmethyl ammonium iodide (2)

A mixture of compound **8** (3.27 g, 13.0 mmol), CH_3I (3.69 g, 26.0 mmol) and anhydrous CH_3CN (10 mL) were stirred at 50 °C under nitrogen until no raw material was detected remaining by TLC. The solvent was removed in vacuo. The residue was washed with anhydrous ether (3 × 10 mL) to give the quaternary ammonium salt **2** (4.86 g, 95%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, J = 6.6 Hz 3H), 1.26 (s, 12H), 1.32 (s, 4H), 1.80–1.87 (m, 2H), 3.27 (s, 3H), 3.39 (t, J = 6.8 Hz 2H), 4.27 (d, J = 6.5 Hz, 4H), 5.75–5.91 (m, 4H), 6.00–6.10 (m, 2H).

3.4. 5-(Perfluorohexyl)-4-iodopentyl acetate (12)

Heating 4-pentenyl acetate **11** (0.44 g, 3.4 mmol) with perfluorohexyl iodide **9** (3.02 g, 6.1 mmol) and AIBN (50 mg) overnight at 95 °C under nitrogen until no raw material was detected remaining by TLC. The gross product was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 20:1) to give compound **12** (1.47 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65–1.79 (m, 4H), 2.05 (s, 3H), 2.78–2.89 (m, 2H), 4.11–4.14 (m, 2H), 4.33–4.38 (m,1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −80.83 (s, 3F), −112.04 to −111.25 (m, 2F), −121.81 (s, 2F), −122.89 (s, 2F), −123.63 (s, 2F), −126.19 (s, 2F).

3.5. 5-(Perfluorooctyl)-4-iodopentyl acetate (13)

Compound **13** (8.73 g, 85%) was prepared from 4-pentenyl acetate **11** (1.96 g, 15.3 mmol), perfluorooctanyl iodide **10** (10.44 g, 19.1 mmol) and AIBN (80 mg) using the same conditions as described for compounds **12**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.74–1.93 (m, 4H), 2.08 (s, 3H), 2.76–3.00 (m, 2H), 4.13–4.16 (m, 2H), 4.37–4.39 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.34 (s, 3F), −111.65 to −115.65 (m, 2F), −122.07 to −122.41 (m, 6F), −123.24 (s, 2F), −124.04 (s, 2F), −126.67 (s, 2F).

3.6. 5-(Perfluorohexyl) pentanol (14)

A HCl gas was bubbled through a suspension of Zn powder (1.29 g, 19.7 mmol) and 5-(perfluorohexyl)-4-iodopentyl acetate (3.77 g, 6.6 mmol) in ethanol (10 mL), until the Zn powder was totally consumed. The mixture was then refluxed until no compound **12** was detected by TLC. After the removal of ethanol, the crude product was dissolved in diethyl ether (25 mL), washed with brine, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 10:1) to give compound **14** (2.28 g, 85%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45–1.50 (m, 2H), 1.58–1.67 (m, 4H), 1.79 (s, 1H), 2.05–2.09 (m, 2H), 3.69 (t, J = 6.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −80.81 (s, 3F), −114.41 (m, 2F), −121.96 (s, 2F), −121.90 (s, 2F), −123.56 (s, 2F), −126.16 (s, 2F).

3.7. 5-(Perfluorooctyl) pentanol (15)

Compound **15** (4.33 g, 85%) was prepared as a white solid from compound **13** (6.79 g, 10.1 mmol) and Zn powder (1.88 g, 28.7 mmol) using the same conditions as described for compounds **14**. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.44–1.52 (m, 2H), 1.57–1.70 (m, 2H), 2.05–2.11 (m, 2H), 3.68 (t, J = 6.3 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.2 (s,

3F), −114.9 (m, 2F), −122.4 (s, 2F), −123.21 (s, 2F), −124.0 (s, 2F), −126.6 (s, 2F).

3.8. Toluene-4-sulfonic acid 6,6,7,7,8,8,9,9,10,10, 11,11,11-tridecanfluoro-undecyl ester (**16**)

Alcohol **14** (2.72 g, 6.7 mmol) and toluene-4-sulfonyl chloride (1.95 g, 10.2 mmol) were dissolved in $CHCl_3$ (10 mL). Anhydrous pyridine (5 mL) was then added, and the reaction mixture was stirred at room temperature until no compound **14** was detected by TLC. The suspension was decanted. The organic phase was washed three times with water (30 mL), brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 10:1) to give compound **16** (2.40 g, 64%) as a white solid. M.p. 42.5–43.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.45 (m, 2H), 1.57 (m, 2H), 1.72 (m, 2H), 2.03 (m, 2H), 2.47 (s, 3H), 4.07 (t, J = 6.6 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.1 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −81.66 (s, 3F), −115.32 (s, 2F), −122.84 (s, 2F), −123.79 (s, 2F), −124.43 (s, 2F), 127.01 (s,2F). IR(thin film) 2962, 1599, 1479, 1360, 1260, 1174, 1142, 1047, 959, 840, 816, 698, 653 cm^{-1}. MS *m/z* 173 (100), 172 (49), 155 (68), 91 (92), 65(34), 55 (23), 41 (20). Anal. Calcd. for $C_{18}H_{17}F_{13}SO_3$: C, 38.58; H, 3.06. Found: C, 38.45; H, 3.21%.

3.9. Toluene-4-sulfonic acid 6, 6, 7, 7, 8, 8, 9, 9, 10, 10, 11, 11, 12, 12, 13, 13, 13-heptadecanfluoro tridecyl ester (**17**)

Compound **17** (1.75 g, 89%) was prepared as a white solid from compound **15** (1.51 g, 3.0 mmol), TsCl (1.14 g, 6.0 mmol) and pyridine (3 mL) using the same conditions as described for compounds **16**. M.p. 50–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (m, 2H), 1.55 (m, 2H), 1.68 (m, 2H), 2.03 (m, 2H), 2.45 (s, 3H), 4.05 (t, J = 3.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −80.72 (t, J = 7.5 Hz, 3F), −114.41 (m, 2F), −121.73 (m, 6F), −122.69 (s, 2F), −123.50 (s, 2F), −126.08 (s, 2F). IR (thin film) 2961, 2876, 1598, 1476, 1359, 1256, 1214, 1150, 1046, 961, 838, 814, 702, 656 cm^{-1}. MS *m/z* 173 (82), 172 (48), 155 (62), 91 (100), 69 (22), 65 (38), 55 (24), 41 (24). Anal. Calcd. for $C_{20}H_{17}F_{17}SO_3$: C, 36.38; H, 2.59. Found: C, 36.46; H, 2.81%.

3.10. N-(6,6,7,7,8,8,9,9,10,10,11,11,11-Tridecanfluoroundecyl)-N,N-diallylamine (**18**)

A suspension of toluene-4-sulfonate **16** (0.70 g, 1.3 mmol), diallylamine (0.27 g, 2.7 mmol), and potassium carbonate (0.35 g, 2.6 mmol) in anhydrous CH_3CN (10 mL) was heated to reflux for 24 h under nitrogen. The reaction mixture was filtered. The filtrates were concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 12:1) to give compound **18** (0.6 g, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (m, 2H), 1.51 (m, 2H), 1.61 (m, 2H), 2.05 (m, 2H), 2.44 (t, J = 3.2 Hz, 2H), 3.08 (d, J = 6.8 Hz, 4H), 5.13–5.20 (m, 4H), 5.81–5.91 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −80.78 (s, 3F), −114.36 (m, 2F), −121.92 (m, 2F), −122.88 (m, 2F), −123.53 (s, 2F), −126.14 (s, 2F). IR (thin film) 3080, 2947, 2800, 1644, 1419, 1240, 1145, 995, 920, 811, 707, 653 cm^{-1}. MR *m/z* 100 (100), 41 (36), 42 (11), 68 (8), 69 (5), 55 (4). Anal. Calcd. for $C_{17}H_{20}F_{13}N$: C, 42.07; H, 4.15; N, 2.89. Found: C, 42.04; H, 4.12; N, 2.85%.

3.11. N-(6, 6, 7, 7, 8, 8, 9, 9, 10, 10, 11, 11, 12, 12, 13, 13, 13-Heptadecanfluorotridecyl)-N, N-diallylamine (**19**)

Compound **19** (1.10 g, 80%) was prepared as a colorless oil from compound **17** (1.55 g, 2.3 mmol), diallylamine (0.54 g, 5.5 mmol) and potassium carbonate (0.68 g, 4.9 mmol) using the same conditions as described for compound **18**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38 (m, 2H), 1.49 (m, 2H), 1.60 (m, 2H), 2.05 (m, 2H), 2.43 (t, J = 7.5 Hz, 2H), 3.08 (d, J = 6.5 Hz, 4H), 5.12–5.19 (m, 4H), 5.84 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −80.76 (t, J = 11.3 Hz, 3F), −114.93 (m, 2F), −121.92 (m, 6F), −122.71 (s, 2F), −123.53 (s, 2F), −126.10 (s, 2F). IR (thin film) 3080, 2946, 2801, 1643, 1419, 1241, 1208, 1149, 995, 920, 704, 655 cm^{-1}. MS *m/z* 586 (M^+ + 1, 4), 110 (100), 69 (3), 68 (4), 41 (28), 42 (8), 39 (6). Anal. Calcd. for $C_{19}H_{20}F_{17}N$: C, 38.99; H, 3.44; N, 2.39. Found: C, 39.11; H, 3.42; N, 2.68%.

3.12. N-(6,6,7,7,8,8,9,9,10,10,11,11,11-Tridecanfluoroundecyl)-N,N-diallylmethyl ammonium iodide (**3**)

A mixture of compound **18** (1.52 g 3.1 mmol), CH_3I (0.89 g, 6.3 mmol) and anhydrous CH_3CN (8 mL) was refluxed for 24 h under nitrogen. The solvent was removed in vacuo. The residue was washed with anhydrous ether (3 × 10 mL) to give quaternary ammonium salt **3** (1.77 g, 90%) as a pale yellow dope. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53 (m, 2H). 1.72 (m, 2H), 1.94 (m, 2H), 2.10 (m, 2H), 3.30 (s, 3H), 3.50 (m, 2H), 4.29 (m, 4H), 5.75–5.92 (m, 4H), 6.11–6.10 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −80.83 (t, J = 9.8 Hz, 3F), −114.22 (s, 2F), −121.93 (m, 2F), −122.90 (m, 2F), −123.46 (s, 2F), −126.15 (s, 2F). MS *m/z* 110 (9), 84 (100), 69 (6), 42 (23), 41 (51), 39 (22). IR (thin film) 2954, 1640, 1467, 1203, 1145, 1050, 953, 732, 696, 653 cm^{-1}. Anal. Calcd. for $C_{18}H_{23}F_{13}NI$: C, 34.47; H, 3.70; N, 2.23. Found: C, 34.27; H, 3.76, N, 2.21%.

3.13. N-(6, 6, 7, 7, 8, 8, 9, 9, 10, 10, 11, 11, 12, 12, 13, 13, 13-Heptadecanfluorotridecyl)-N, N-diallylmethyl ammonium iodide (**4**)

Compound **4** (0.95 g, 89%) was prepared from compound **19** (0.87 g, 1.5 mmol) and CH_3I (1.20 g, 8.5 mmol) using the

same conditions as described for compound **3**. M.p. 61–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (m, 2H), 1.71 (m, 2H), 1.90 (m, 2H), 2.11 (m, 2H), 3.30 (s, 3H), 3.50 (m, 2H), 4.27 (m, 4H), 5.77–5.90 (m, 4H), 5.60 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −80.74 (t, J = 7.5 Hz, 3F), −114.22 (t, J = 15.0 Hz, 2F), −121.89 (m, 6F), −122.70 (s, 2F), −123.41 (s, 2F), −126.08 (s, 2F). IR (thin film) 2954, 1640, 1476, 1204, 1150, 1051, 956, 871, 705, 657 cm^{-1}. MS *m/z* 168 (4), 110 (7), 85 (7), 84 (100), 69 (6). Anal. Calcd. for $C_{20}H_{23}F_{17}NI$: C, 33.03; H, 3.19; N, 1.93. Found: C, 33.20; H, 3.12; N, 1.91%.

*3.14. 11-Chloro-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-Cetanfluoro-2-iodo-1-undecanol (**23**)*

Compound **23** (12.35 g, 80%) was prepared from allyl alcohol **21** (2.07 g, 35.7 mmol), iodide **20** (14.01 g, 24.9 mmol) and AIBN (100 mg) using the same conditions as described for compounds **12**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.02 (s, 1H), 2.73–3.05 (m, 2H), 3.77–3.87 (m, 2H), 4.42–4.46 (m, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −68.01 (s, 2F), −112.91 to −113.4 (m, 2F), −120.08 (s, 2F), −121.13 (s, 2F), −121.52 to −121.74 (m, 6F), −123.46(s, 2F).

*3.15. [3-(8-Chloro-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-Cetanfluoro octyl)-2-iodo]propyl acetate (**24**)*

Compound **24** (10.20 g, 82%) was prepared from allyl acetate **22** (3.17 g, 31.3 mmol), iodide **20** (10.17 g, 22.0 mmol) and AIBN (80 mg) using the same conditions as described for compounds **12**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.12 (s, 3H), 2.75–2.97 (m, 2H), 4.28–4.37 (m, 1H), 4.38–4.47 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −68.31 (s, 2F), −113.32–114.03 (m, 2F), −121.36 (s, 2F), −121.54 to −122.03 (m, 8F), −123.74(s, 2F).

*3.16. 11-Chloro-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-cetanfluoro-hendecane-1-ene (**26**)*

The activated Zn powder (1.29 g, 19.7 mmol) was suspended in isopropanol (15 mL). After the mixture was heated to 70 °C, the mixture of **24** (9.26 g, 14.0 mL), isopropanol (10 mL) and acetic acid (3 mL) were slowly added dropwise. The resulting mixture was heated at 85 °C with stirring for 2 h. Aqueous HCl (2.5 mL) was added and the mixture was stirred for further 4 h at 80 °C to destroy excess zinc. The resulting two phases were separated. After removal of solvent in the organic phase, the residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 100:0) to give compound **26** (4.38 g, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.81–2.93 (m, 2H), 5.31–5.38 (m, 2H), 5.81–5.83 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −68.03 (s, 2F), −121.29 (s, 2F), −128.22 (s, 2F), −129.23(s, 2F), −129.88 (s, 6F), −131.20(s, 2F).

*3.17. 11-Chloro-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-cetanfluoro-1-hendecanol (**25**) and 11-Chloro-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-cetanfluoro-2-hendecanol (**27**)*

*3.17.1. Synthesis of compound **25** from alcohol **23***

A solution of **23** (5.05 g, 8.1 mmol) in anhydrous ether (10 mL) was slowly added dropwise to a suspension of $LiAlH_4$ (0.45 g, 11.8 mmol) in anhydrous ether (15 mL) during a 0.5 h at 35 °C, and the resulting mixture was stirred for 20 h in reflux. Then ethyl acetate (5 mL) were added to destroy excess $LiAlH_4$ and diluent vitriol (2 mL, pH 6) were added. After filtration, the mixture was extracted with ether (3 × 20 mL). After drying (Mg_2SO_4) and filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 10:1) to give compound **25** (0.41 g, 10%).

*3.17.2. Synthesis of compounds **25** and **27** from the alkene **26***

A solution of **26** (5.75 g, 12.1 mmol) in anhydrous THF (15 mL) was slowly added dropwise to a solution of $BH_3{\cdot}(CH_3)_2S$ (1 mL, 10 M in $(CH_3)_2S$) in THF (20 mL) at 10 °C under nitrogen atmosphere. After stirring at room temperature for 3 h, 3 M NaOH (50 mL) and then 30% H_2O_2 (5 mL) were added to the mixture at 20 °C. After further stirring for 2 h, water (80 mL) was added to the mixture. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). After drying (Mg_2SO_4) and filtrating, the solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 5:1) to give compound **25** (2.51 g, 42%) and compound **27** (2.29 g, 38%). Compound **25**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.54 (s, 1H), 1.82–1.91 (m, 2H), 2.13–2.28 (m, 2H), 3.75 (t, J = 12.0 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −68.37 (s, 2F), −114.67 (s, 2F), −120.46 (s, 2F), −121.81 (m, 8F), −122.85(s, 2F). Compound **27**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (d, J = 6.6 Hz, 3H), 2.03 (s, 1H), 2.19–2.37 (m, 2H), 4.32–4.38 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −68.41 (s, 2F), −113.60 (s, 2F), −120.49 (s, 2F), −122.17 to −121.56(m, 8F), −124.01 (s, 2F).

*3.18. Toluene-4-sulfonic acid 11-chloro-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-cetanfluorohendecyl ester (**28**)*

Compound **28** (2.61 g, 87%) was prepared as a white solid from compound **25** (2.30 g, 4.7 mmol), TsCl (1.38 g, 7.2 mmol) and pyridine (5 mL) using the same conditions as described for compounds **16**. M.p. 49–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.97 (m, 2H), 2.13 (m, 2H), 2.46 (s, 3H), 4.12 (t, J = 5.9 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 6.8 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −68.00 (t, J = 15.0Hz, 2F), −114.46 (s, 2F), −120.08 (s, 2F), −121.14 (s, 2F), −121.72 (s, 6F), −123.43 (s, 2F). IR (thin film) 2958, 1627, 1599, 1449, 1361, 1210, 1191, 1150, 1043, 994, 841, 816, 696, 663 cm^{-1}. MS *m/z* 173 (10), 172 (25), 155 (100), 91

(81), 65 (19). Anal. Calcd. for $C_{18}H_{13}F_{16}ClSO_3$: C,33.32; H, 2.02. Found: C, 33.34; H, 2.04%.

*3.19. N-(11-Chloro-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-cetanfluoro hendecyl) -N, N- diallylamine (**29**)*

Compound **29** (1.96 g, 91%) was prepared as a colorless oil from compound **28** (2.43 g, 3.7 mmol), diallylamine (0.83 g, 8.5 mmol) and potassium carbonate (1.01 g, 7.3 mmol) using the same conditions as described for compound **18**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.75 (m, 2H), 2.11 (m, 2H), 2.50 (t, J = 7.2 Hz, 2H), 3.08 (d, J = 6.4 Hz, 4H), 5.13–5.20 (m, 4H), 5.83 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −68.01 (t, J = 12.0 Hz, 2F), −114.12 (s, 2F), −120.11 (s, 2F), −121.17 (s, 2F), −121.75 (s, 6F), −123.44 (s, 2F). IR (thin film) 3081, 2981, 2809, 1643, 1420, 1380, 1216, 1153, 996, 922, 734, 701, 648, 556cm^{-1}. MS *m*/*z* 110 (100), 91 (8), 85 (9), 69 (9), 41 (29). Anal. Calcd. for $C_{17}H_{16}F_{16}ClN$: C, 35.59; H, 2.81; N, 2.44. Found: C, 35.30; H, 2.71, N, 2.61%.

*3.20. N-(11-Chloro-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11-cetanfluoro hendecyl)-N, N-diallylmethyl ammonium iodide (**5**)*

Compound **5** (2.17 g, 95%) was prepared from compound **29** (1.82 g, 3.2 mmol) and CH_3I (1.57 g, 11.1 mmol) using the same conditions as described for compound **3**. M.p. 98.5–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.21–2.37 (m, 4H), 3.34 (s, 3H), 3.71 (m, 2H), 4.30 (m, 4H), 5.78–5.91 (m, 4H), 6.05 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −68.04 (t, J = 11.3 Hz, 2F), −113.41 (t, J = 15.0 Hz, 2F), −120.08 (s, 2F), −121.11 (s, 2F), −121.72 (m, 6F), −123.09 (s, 2F). IR (thin film) 2967, 1632, 1476, 1438, 1384, 1204, 1149, 1113, 1094, 998, 954, 850, 702, 656 cm^{-1}. MS *m*/*z* 168(5), 110 (5), 84 (100), 42 (11), 39 (9). Anal. Calcd. for $C_{18}H^{19}F_{16}ClNI$: C, 30.21; H,2.68; N, 1.96. Found: C, 29.97; H, 2.76; N, 1.84%.

3.21. Antimicrobial assessment

The antimicrobial activities were evaluated against *S. aureus* ATCC 25923, *E. coli* ATCC 25922 and another yeast strain of *C. albicans* ATCC 1600 by viable cell counting method.

MIC values and MBC values were determined by a standard microdilution method. Common bacterial suspension were incubated for 16–18 h at 37 °C in the presence of each compound in different concentrations, the fungi bacterial suspensions were incubated for 24 h at 35 °C. MIC was the lowest concentration of antibacterial agent inhibiting the development of visible growth. MBC was the lowest concentration of antibacterial agent bactericing the development of visible growth.

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