Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supplementary information

Synthesis of sulfonium *N*-chloramines for antibacterial applications

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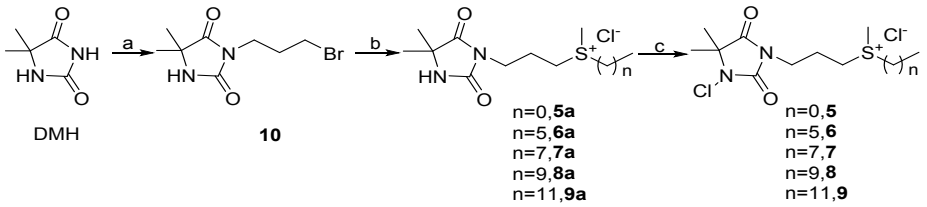
1. Reagents and materials

All reagents and solvents purchased from commercial suppliers (Aladdin Co. China) were used in this research without further purification. All products and intermediates were purified by flash column chromatography and silica gel which received from Qingdao Haiyang Chemical Plant, China. Thin layer chromatography (TLC) was carried out by means of iodine fumigation. *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 25923 were given as a gift from Dalian Medical University and were herein used as model microorganism to challenge all biocides.

DMH-bromide **10**, QA *N*-chloramine **1** and its precursor **1a** were prepared according to our previous procedures, respectively.[1-4] In addition, *t*-butyl hypochlorite, the chlorination agent used in this work, was also synthesized as described.[4] The obtained ^{1}H-NMR and ^{13}C-NMR data of all compounds were identical with those previous literatures.

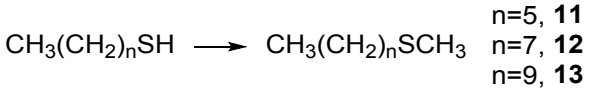
NMR spectra were recorded at room temperature using Bruker DRX 500 instrument at the condition of $CDCl_3$ or D_2O. Mass spectra were conducted on a Q-TOF Micro mass spectrometry (Manchester, UK) equipped with Z-spray ionization source.

2. Synthesis of Sulfonium *N*-chloramines



Scheme 1. Chemical synthesis of **5-9**: (a) $Br(CH_2)_3Br$, K_2CO_3, acetone, reflux; (b) CF_3COOH, $CH_3S(CH_2)_nCH_3$, reflux; Ion-exchange (Amberlite R IRA-900, Cl^-); (c) *t*-BuOCl, H_2O: *t*-BuOH (1:4, v:v), rt.

2.1 General synthesis of theiother **11-13**



Scheme 2. Chemical synthesis of theiother **12-14**: CH_3I, K_2CO_3, *N, N'*-dimethylformamide, reflux.

To a solution of thiol (21.2 mmol) in *N, N'*-dimethylformamide (13.2 mL) was added iodomethane(3.62 g, 1.58 mL, 25.5 mmol, 1.2 equiv.) and potassium carbonate(3.52 g, 25.5 mmol, 1.2 equiv.) to stir for 4 hours. Solvent was removed and the crude product was applied on chromatography column (ether/ethyl acetate, 1:25, v/v) to afford thioethers.

Hexyl-methyl sulfide **11** (2.80 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (t, *J* =7.4 Hz, 2H), 2.03 (s, 3H), 1.56-1.48 (m, 2H), 1.34-1.28 (m, 2H), 1.26-1.19 (m, 4H), 0.82 (t, *J* = 6.9 Hz, 3H). (The NMR data was identical with the published literature).[5]

Octyl-methyl sulfide **12** (2.10 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (t, *J* = 7.5 Hz, 2H), 2.02 (s, 3H), 1.55-1.49 (m, 2H), 1.34-1.28 (m, 2H), 1.25-1.17 (m, 8H), 0.81 (t, *J* = 6.7 Hz, 3H). (The NMR data was identical with the published literature).[5]

Decyl-methyl sulfide **13** (1.70 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (t, *J* = 7.5 Hz, 2H), 2.02

(s, 3H), 1.56-1.48 (m, 2H), 1.34-1.26 (m, 2H), 1.25-1.15 (m, 12H), 0.81 (t, *J* = 6.9 Hz, 3H). (The NMR data was identical with the published literature).[5]

2.2 General synthesis of sulfonium *N*-chloramine precursor **5a-9a**

To a solution of DMH-bromide (1.50 g, 6.40 mmol) in trifluoroacetic acid (2 mL) was added thioether (4.27 mmol, 0.7 equiv.) and then the mixture was heated to gently reflux for 3h. Afterward, adding methyl sulfide (133 μg, 157 μL, 2.14 mmol, 0.3 equiv.) to the mixture continued to reflux for 20 h. The product was precipitated by using diethyl ether and further purification was performed on recrystallization in acetone or flash chromatography to give the sulfonium salts (Br^- form) as white solid. The bromide form salt was dissolved in DI water and passed through anion exchange resin (Amberlite IRA-900, Cl^-), and all the corresponding fractions were collected and concentrated to afford the final sulfonium salts in quantitative yield.

Sulfonium salts **5a** (0.93 g, 49.1%). ^{1}H NMR (500 MHz, D_2O) δ 3.60 (t, *J* = 6.7 Hz, 2H), 3.26 (t, *J* = 1.3 Hz, 2H), 2.86 (s, 6H), 2.10-2.02 (m, 2H), 1.36 (s, 6H); ^{13}C NMR (126 MHz, D_2O) δ 176.9, 155.5, 66.3, 40.5, 37.7, 24.5, 44.0, 36.4, 22.3, 20.9; HRMS calcd. for $C_{10}H_{19}N_2O_2S$ $[M\text{-}Cl]^+$: 231.1158; found: 231.1167.

Sulfonium salts **6a** (1.78 g, 70.0%). ^{1}H NMR (500 MHz, D_2O) δ 3.60 (t, *J* = 6.5 Hz, 2H), 3.33-3.17 (m, 4H), 2.82 (s, 3H), 2.16-2.01 (m, 2H), 1.80-1.65 (m, 2H), 1.46-1.38 (m, 2H), 1.36 (s, 6H), 1.32-1.20 (m, 4H), 0.81 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, D_2O) δ 180.7, 157.1, 59.2, 41.6, 38.7, 36.7, 30.2, 27.1, 23.5, 23.2, 22.6, 22.1, 21.7, 13.3; HRMS calcd. for $C_{15}H_{29}N_2O_2S$ $[M\text{-}Br]^+$: 301.1943, found: 301.1950.

Sulfonium salts **7a** (1.78 g, 70.0%). ^{1}H NMR (500 MHz, D_2O) δ 3.59 (t, *J* = 6.6 Hz, 2H), 3.30-3.18 (m, 4H), 2.82 (s, 2H), 2.13-2.02 (m, 2H), 1.78-1.68 (m, 2H), 1.44-1.33 (m, 8H), 1.31-1.18 (m, 8H), 0.79 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (126 MHz, D_2O) δ 180.6, 157.0, 59.2, 41.6, 38.8, 36.6, 31.0, 28.1, 27.9, 27.5, 23.5, 23.2, 22.6, 22.2, 22.0, 13.5; HRMS calcd. for $C_{17}H_{33}N_2O_2S$ $[M\text{-}Br]^+$: 329.2272, found: 329.2263.

Sulfonium salts **8a** (1.50 g, 65.0%). ^{1}H NMR (500 MHz, D_2O) δ 3.59 (t, *J* = 6.6 Hz, 2H), 3.44-3.29 (m, 4H), 2.91 (s, 3H), 2.17-2.03 (m, 2H), 1.82-1.68 (m, 2H), 1.45-1.38 (m, 2H), 1.36 (s, 6H), 1.33-1.15 (m, 12H), 0.79 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, D_2O) δ 179.9, 156.8, 59.0, 41.7, 39.1, 36.5, 31.8, 29.4, 29.2, 28.8, 28.0, 23.8, 23.7, 23.7, 22.9, 22.6, 22.5, 13.7; HRMS calcd. for $C_{19}H_{37}N_2O_2S$ $[M\text{-}Br]^+$: 357.2568, found: 357.2576.

Sulfonium salts **9a** (0.75 g, 65.0%). ^{1}H NMR (500 MHz, D_2O) δ 3.59 (t, *J* = 6.6 Hz, 2H), 3.37-3.14 (m, 4H), 2.82 (s, 3H), 2.13-2.02 (m, 2H), 1.79-1.68 (m, 2H), 1.44-1.37 (m, 2H), 1.35 (s, 6H), 1.30-1.12 (m, 16H), 0.78 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, D_2O) δ 179.8, 156.8, 58.9, 41.7, 39.2, 36.5, 31.9, 29.8, 29.8, 29.7, 29.4, 28.9, 28.1, 23.9, 23.8, 23.7, 22.9, 22.7, 22.6, 13.8; HRMS calcd. for $C_{21}H_{41}N_2O_2S$ $[M\text{-}Cl]^+$: 385.2891; found: 385.2889.

2.3 General synthesis of sulfonium *N*-chloramine **5-9**

To a solution of sulfonium-DMH (12.0 mmol) in 30mL H_2O/*t*-butanol (1/4) was added *t*-butyl hypochlorite (36.0 mmol, 3 equiv.). The mixture was then sealed in dark for 60 h. After removing excess *t*-butyl hypochlorite and the solvent, the final sulfonium *N*-chloramine was obtained in quantitative amount.

Sulfonium *N*-chloramine **5**. ^{1}H NMR (500 MHz, D_2O) δ 3.67 (t, *J* = 6.7 Hz, 2H), 3.36 (t, *J* = 1.3 Hz, 2H), 2.85 (s, 6H), 2.14-2.04 (m, 2H), 1.42 (s, 6H); ^{13}C NMR (126 MHz, D_2O) δ 176.9, 155.5, 66.3, 44.0, 40.5, 36.4, 37.7, 24.5, 22.3, 20.9; HRMS calcd. for $C_{10}H_{18}N_2O_2ClS$ $[M\text{-}Cl]^+$: 265.0771; found:

265.0778.

Sulfonium *N*-chloramine **6**. ^{1}H NMR (500 MHz, D_2O) δ 3.69 (t, *J* = 6.6 Hz, 2H), 3.36-3.18 (m, 4H), 2.83 (s, 3H), 2.17-2.05 (m, 2H), 1.79-1.70 (m, 2H), 1.43 (s, 6H), 1.33-1.21 (m, 4H), 0.81 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, D_2O) δ 176.9, 66.4, 41.6, 38.6, 37.8, 30.2, 27.1, 23.1, 22.4, 22.1, 21.6, 21.0, 13.2; HRMS calcd. for $C_{15}H_{28}N_2O_2ClS$ $[M\text{-}Cl]^+$: 335.1565; found: 335.1560.

Sulfonium *N*-chloramine **7**. ^{1}H NMR (500 MHz, D_2O) δ 3.69 (t, *J* = 6.6 Hz, 2H), 3.35-3.21 (m, 4H), 2.84 (s, 3H), 2.18-2.05 (m, 2H), 1.79-1.68 (m, 2H), 1.43-1.34 (s, 8H), 1.33-1.18 (m, 8H), 0.80 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, D_2O) δ 176.9, 155.4, 66.4, 41.6, 38.6, 37.8, 31.0, 28.1, 27.9, 23.2, 22.5, 22.1, 22.0, 21.0, 13.5; HRMS calcd. for $C_{17}H_{32}N_2O_2ClS$ $[M\text{-}Cl]^+$: 363.1880; found: 363.1873.

Sulfonium *N*-chloramine **8**. ^{1}H NMR (500 MHz, D_2O) δ 3.70 (t, *J* = 6.5 Hz, 2H), 3.37-3.24 (m, 4H), 2.89 (s, 3H), 2.19-2.07 (m, 2H), 1.81-1.70 (m, 2H), 1.46-1.18 (m, 20H), 0.80 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, D_2O) δ 176.2, 155.2, 66.2, 41.7, 38.7, 37.8, 31.7, 29.2, 29.0, 28.9, 28.6, 27.8, 23.6, 22.6, 22.4, 21.2, 13.8; HRMS calcd. for $C_{19}H_{36}N_2O_2ClS$ $[M\text{-}Cl]^+$: 391.2180; found: 391.2186.

Sulfonium *N*-chloramine **9**. ^{1}H NMR (500 MHz, D_2O) δ 3.68 (t, *J* = 6.5 Hz, 2H), 3.36-3.15 (m, 4H), 2.83 (s, 3H), 2.16-2.05 (m, 2H), 1.79-1.70 (m, 2H), 1.42 (s, 6H), 1.39-1.32 (m, 2H), 1.31-1.13 (m, 16H), 0.78 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, D_2O) δ 179.8, 156.8, 58.9, 41.7, 39.2, 31.9, 29.8, 29.8, 29.7, 29.4, 28.9, 28.1, 23.8, 23.7, 22.9, 22.7, 22.6, 13.8; HRMS calcd. for $C_{21}H_{40}N_2O_2ClS$ $[M\text{-}Cl]^+$: 419.2492; found: 419.2499.

3. ^{1}H NMR spectra analysis of **5a**

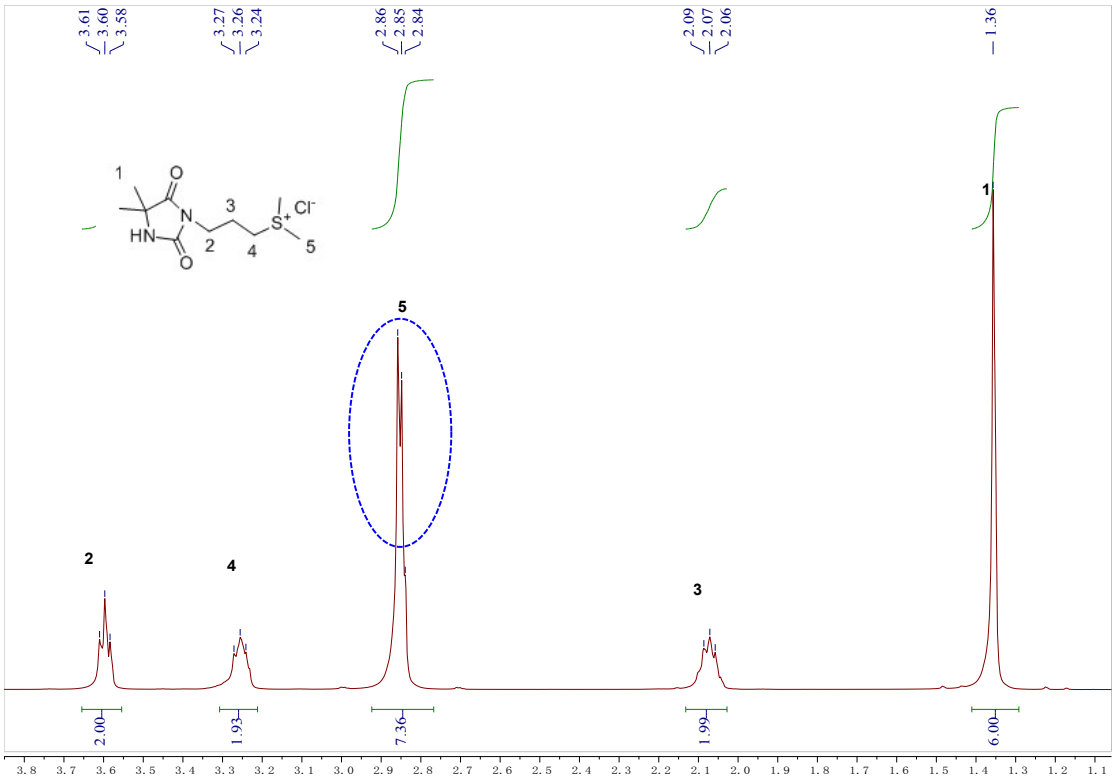


Fig. S1 ^{1}H NMR data of Sulfonium *N*-chloramine precursor **5a** (probably containing oxidized methyl sulfide)

4. ^{13}C NMR spectra analysis of **5a** and **5**

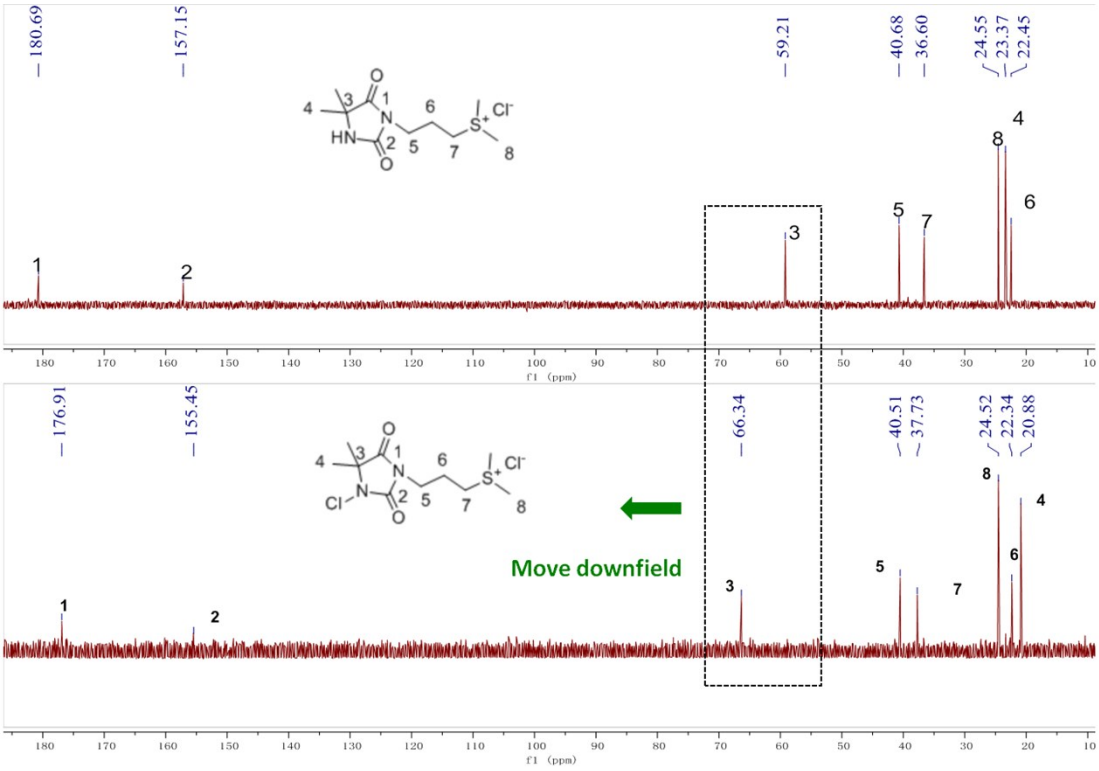


Fig. S2 ^{13}C NMR data of Sulfonium *N*-chloramine **5** and its precursor **5a**

5. Antimicrobial tests

We used tryptone soya agar (TSA) medium for culturing stock bacteria at 37°C for 18-24 h to give logarithmic-phase cultures. Subsequent antimicrobial activity test of *N*-chloramines was performed as followed. To 10 mL of bacterial suspension (10^6~10^7 CFU mL^{-1}) in a centrifuge tube was added to 20 µL of *N*-chloramine **1** solution or 10 µL of *N*-chloramine **5-9** solution (0.28 M stock solution, final 20 ppm [Cl^+]) and timing of exposure to bicide was started immediately. After determined interval of 5 min and 10 min, 1 mL bacterial solution was withdrawn and mixed with 1 mL of sterile 0.02 N sodium thiosulfate ($Na_2S_2O_4$) solution to neutralize all oxidative chlorine of *N*-chloramine. 100 µL of each diluted bacterial suspension was placed on Luria-Bertani plates in triplicate for incubating at 37°C for 18-24 h. The same procedure was also conducted for all *N*-chloramine precursors (**5a-9a**).The viable bacterial colonies on the plates were counted to report the reduction of bacteria by the formula as followed:

$$\text{Percentage reduction of bacteria (\%)} = (A\text{-}B)/A\times 100$$

$$\text{Log reduction} = \text{Log}\,(A/B) \text{ if } B>0;$$

$$= \text{Log}\,A \text{ if } B=0$$

where A is the number of bacteria retrieved from controls (CFU mL^{-1}), and B is the number of bacteria retrieved from *N*-chloramines or its precursors (CFU mL^{-1}).

6. Bactericidal evaluation using **1**, **3** and **5** as control

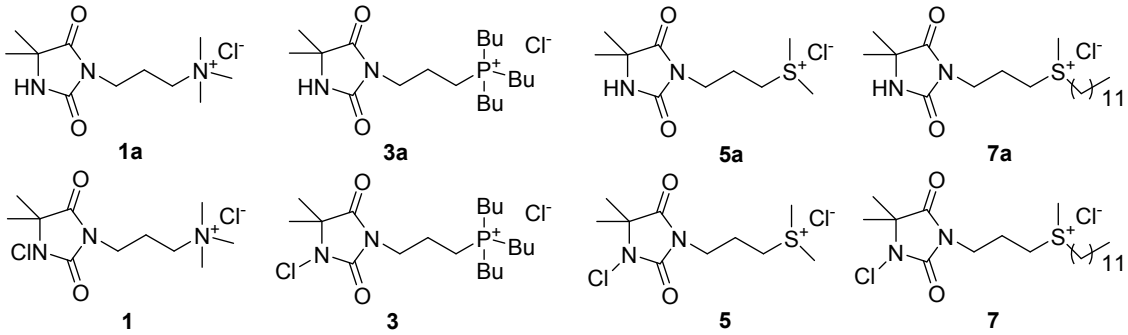


Table S1. Bactericidal data.

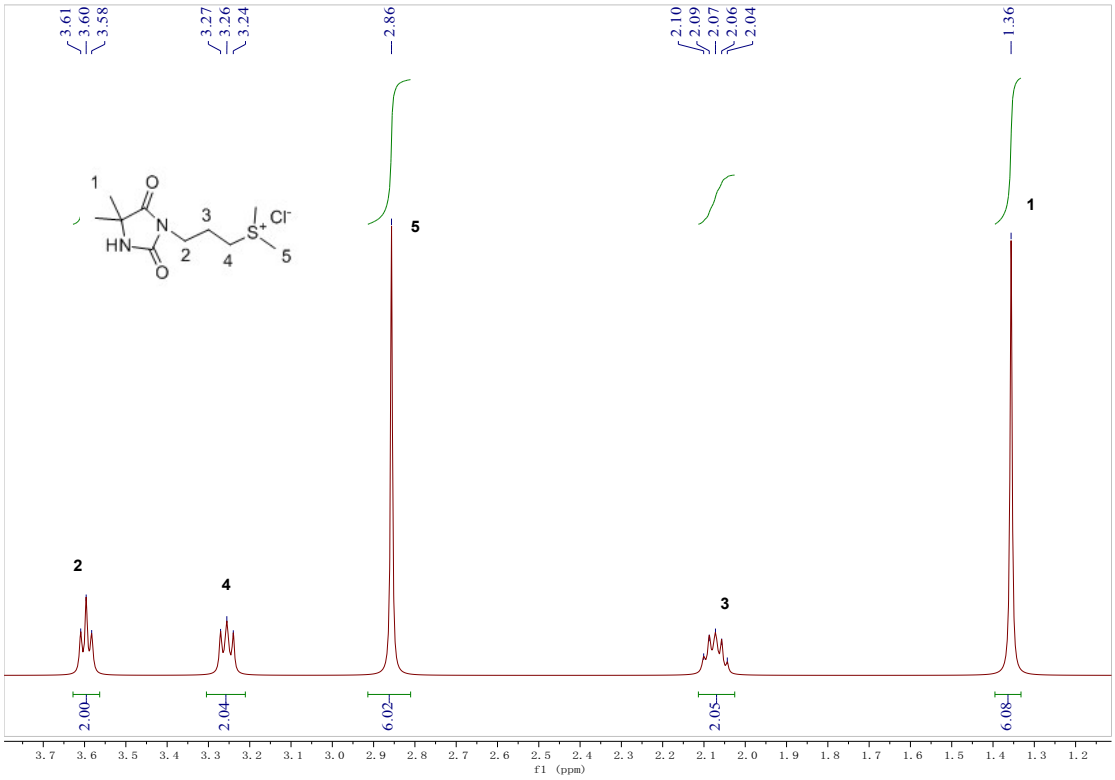
Bacteria	Synthetic compounds	Active chloramine/ppm	Contact time (min)	
			5	
			Percent reduction/%	Log reduction/log
S. aureus[a]	1a	0	0	0
	1	20	19.73±5.18	0.10±0.03
	3a	0	0	0
	3	20	77.53±0.63	0.65±0.01
	5a	0	0	0
	5	20	32.59±1.04	0.17±0.01
	7a	0	46.20±3.48	0.27±0.04
	7	20	100	6.80

[a] Inoculum concentration was 6.32×10^6 CFU/mL (colony-forming Units)

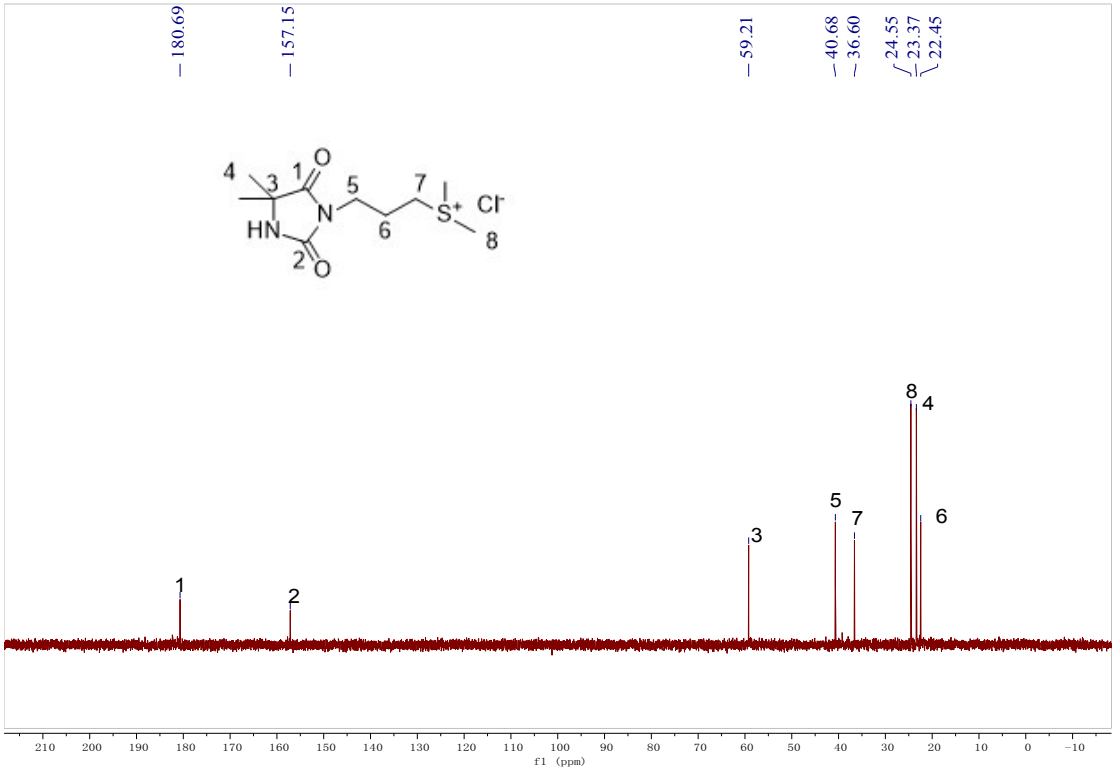
7. References

1. L. Li, H. Zhou, F. Gai, X. Chi, Y. Zhao, F. Zhang and Z. Zhao, *RSC Adv.*, 2017, **7**, 13244-13249.
2. L. Li, Y. Zhao, H. Zhou, A. Ning, F. Zhang and Z. Zhao, *Tetrahedron Lett.*, 2017, **58**, 321-325.
3. L. Li, X. Chi, F. Gai, H. Zhou, F. Zhang and Z. Zhao, *J. Appl. Polym. Sci.*, 2017, **134**, 45323.
4. L. Li, T. Pu, G. Zhanel, N. Zhao, W. Ens and S. Liu, *Adv. Healthc. Mater.*, 2012, **1**, 609-620.
5. S. Ohsugi, K. Nishide, K. Oono, K. Okuyama, M. Fudesaka, S. Kodama and M. Node, *Tetrahedron*, 2003, **59**, 8393-8398.

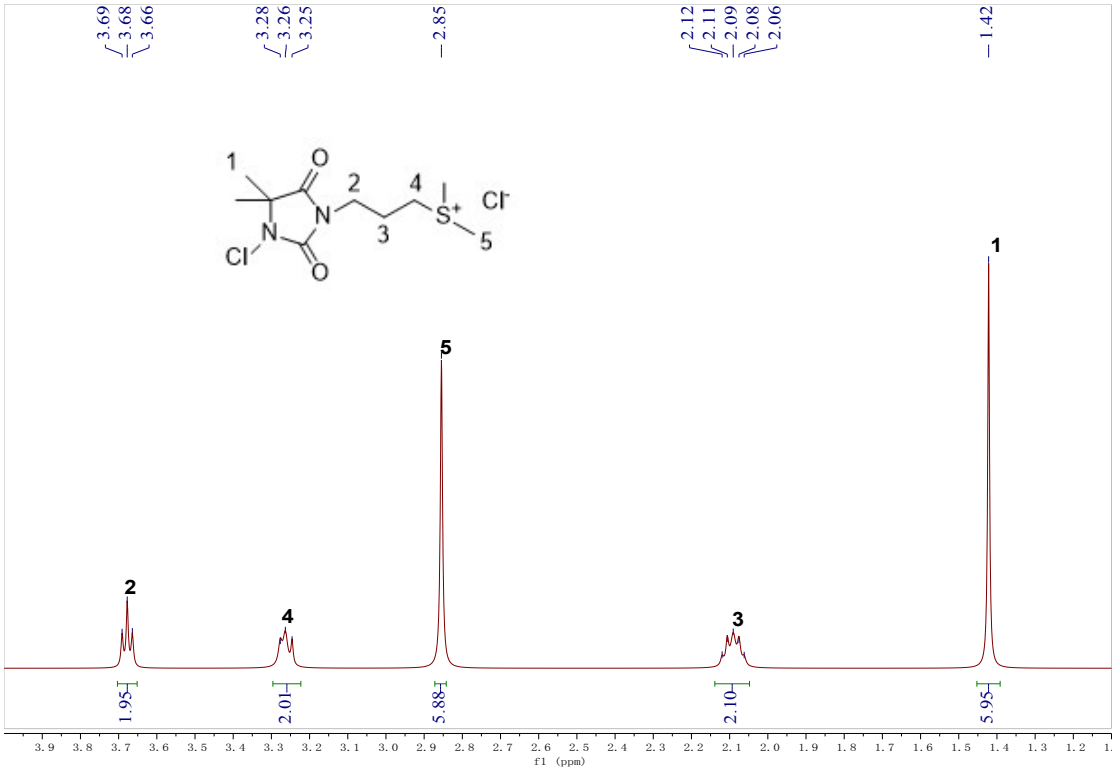
8. Original NMR spectra data



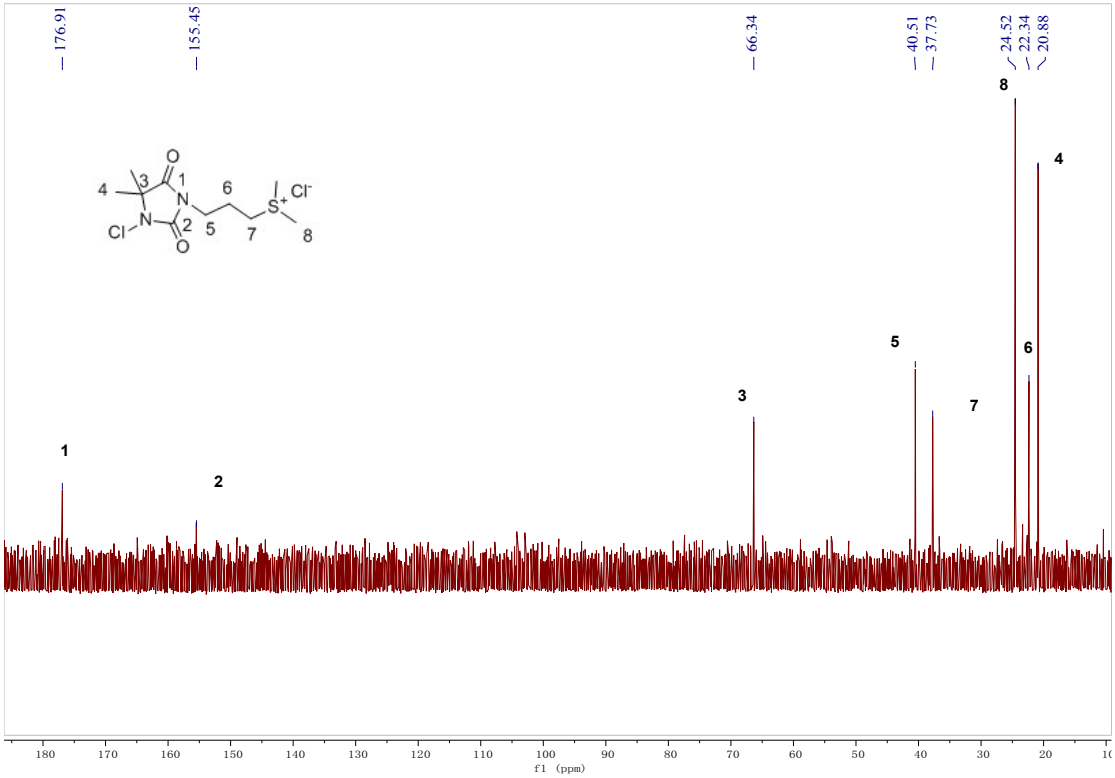
The ^{1}H NMR spectrum of compound **5a**



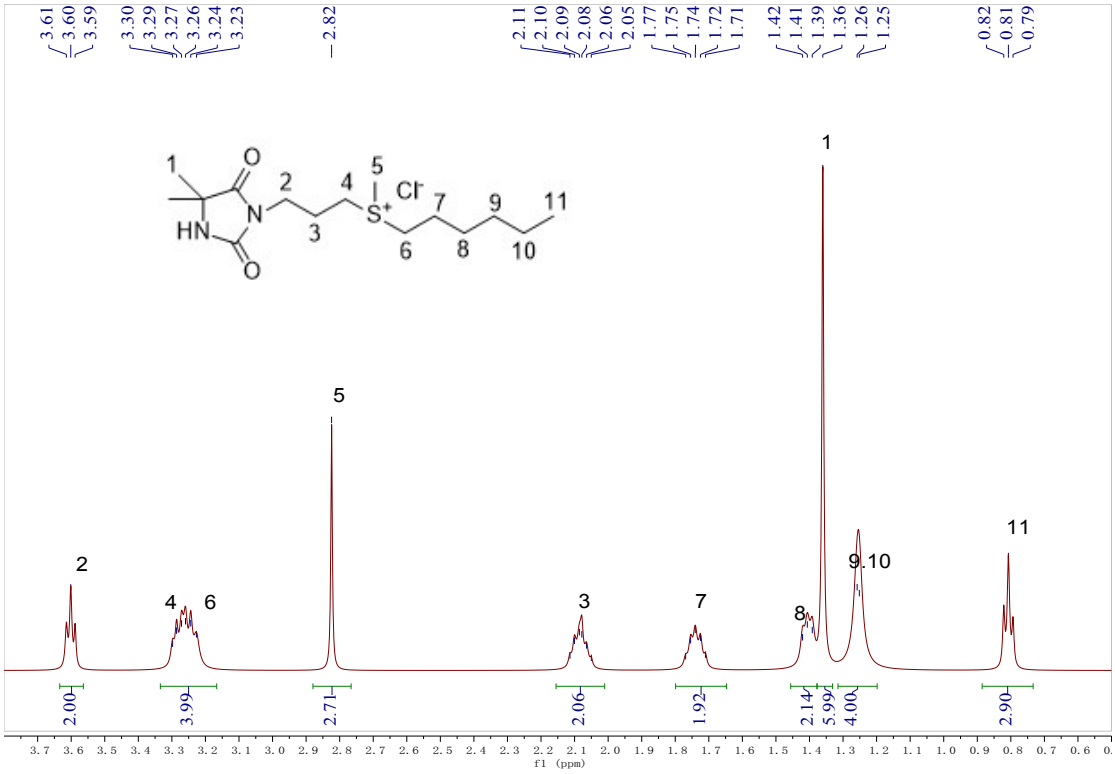
The ^{13}C NMR spectrum of compound **5a**



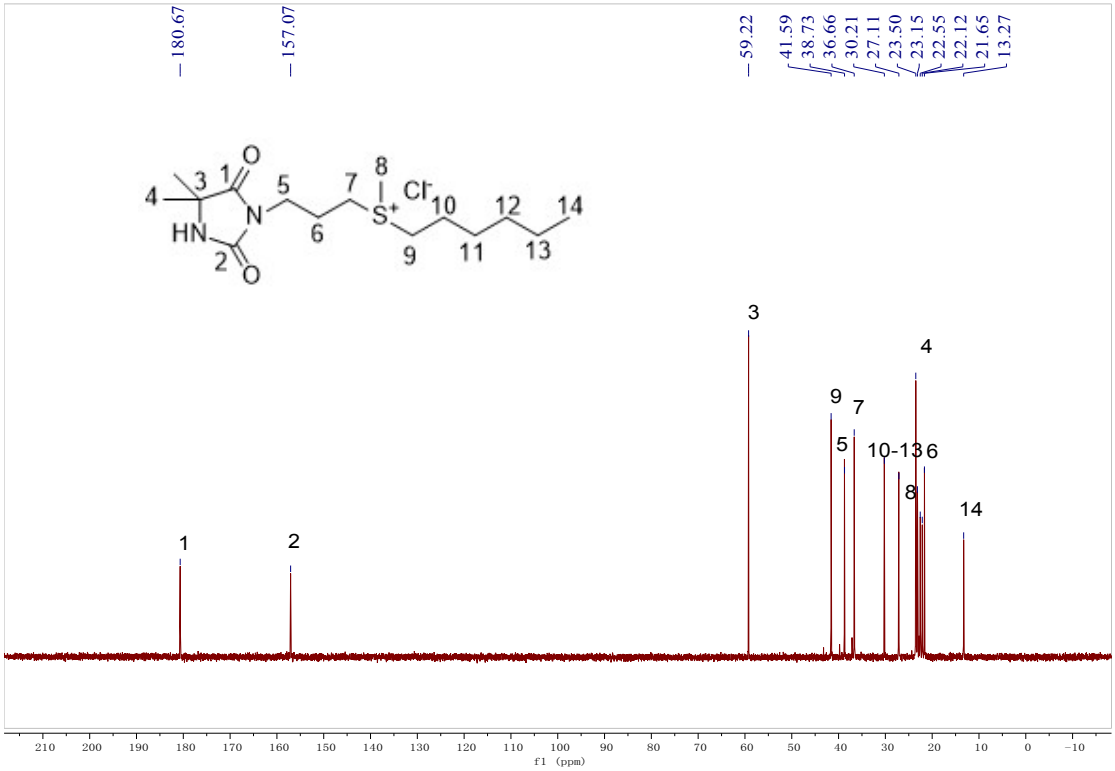
The ^{1}H NMR spectrum of compound **5**



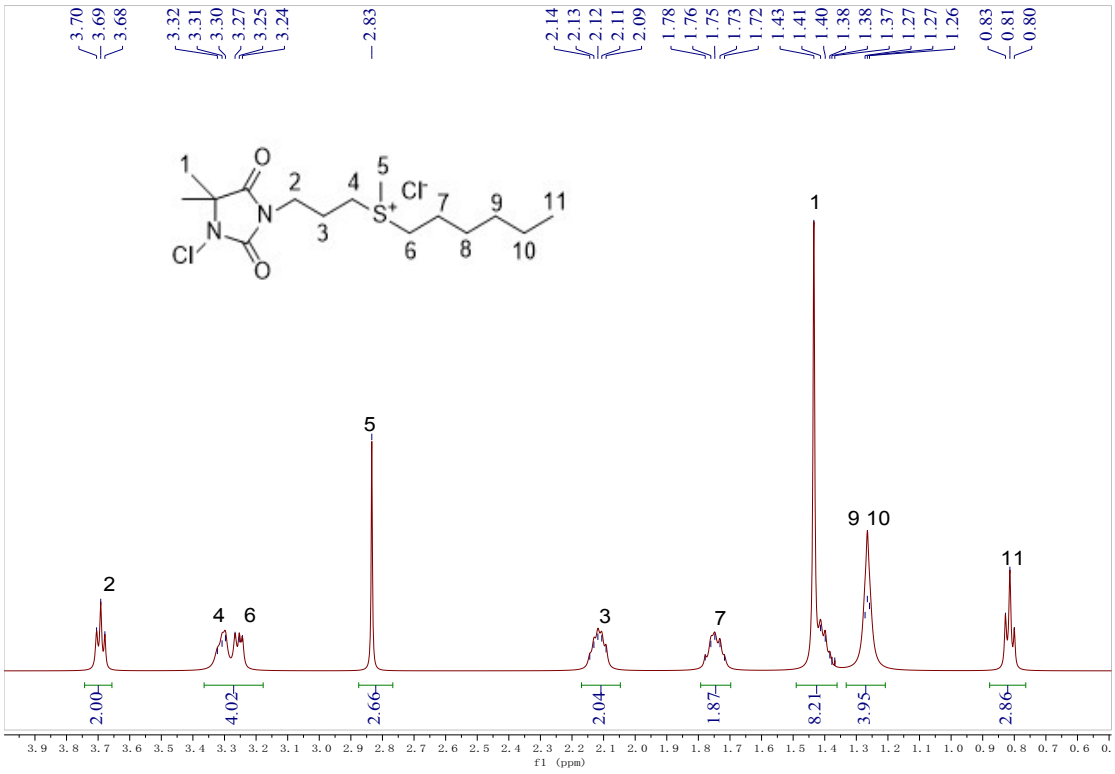
The ^{13}C NMR spectrum of compound **5**



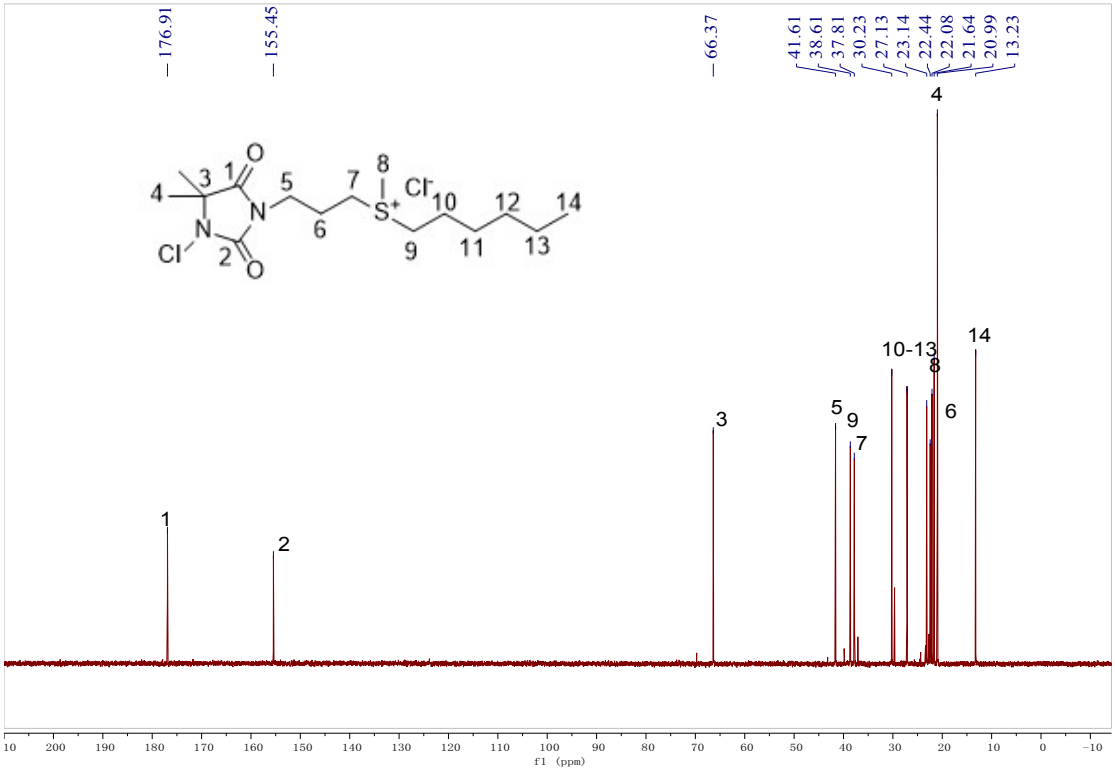
The ^{1}H NMR spectrum of compound **6a**



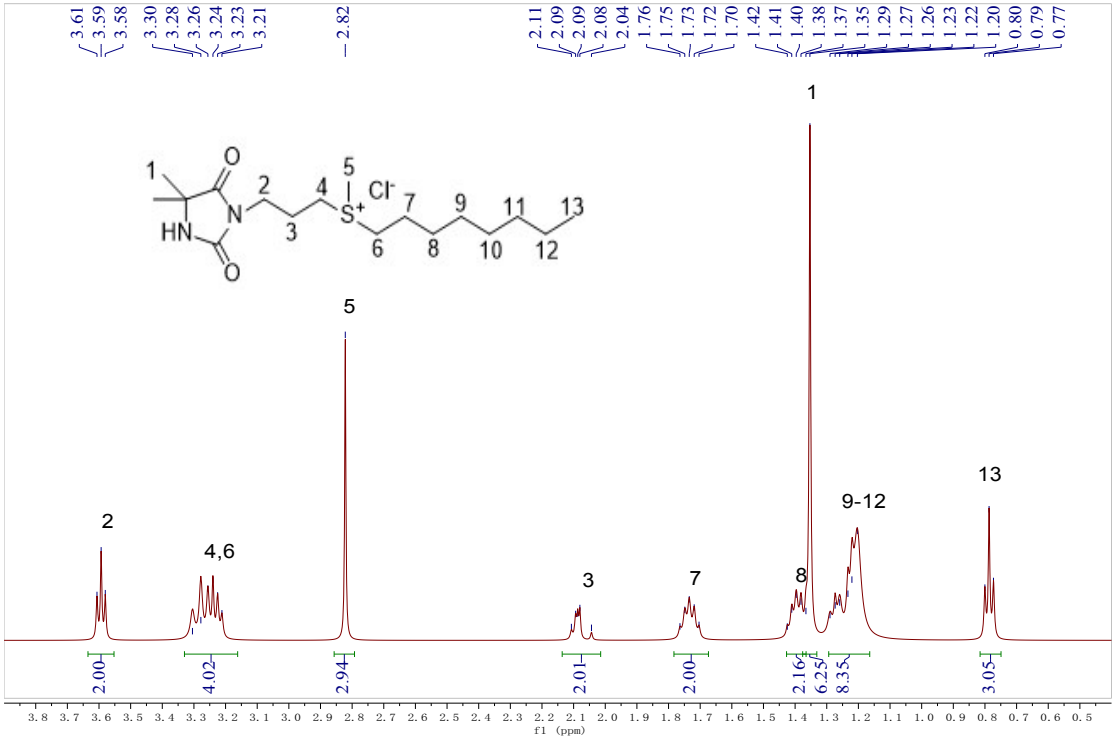
The ^{13}C NMR spectrum of compound **6a**



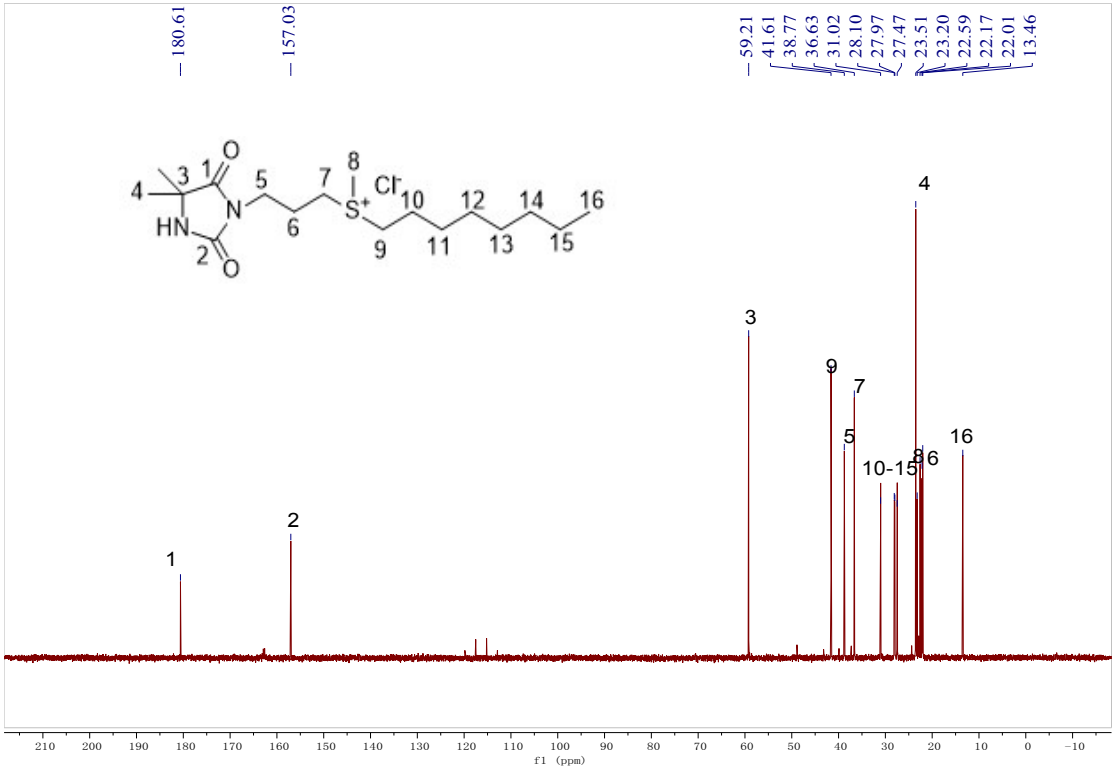
The ^{1}H NMR spectrum of compound **6**



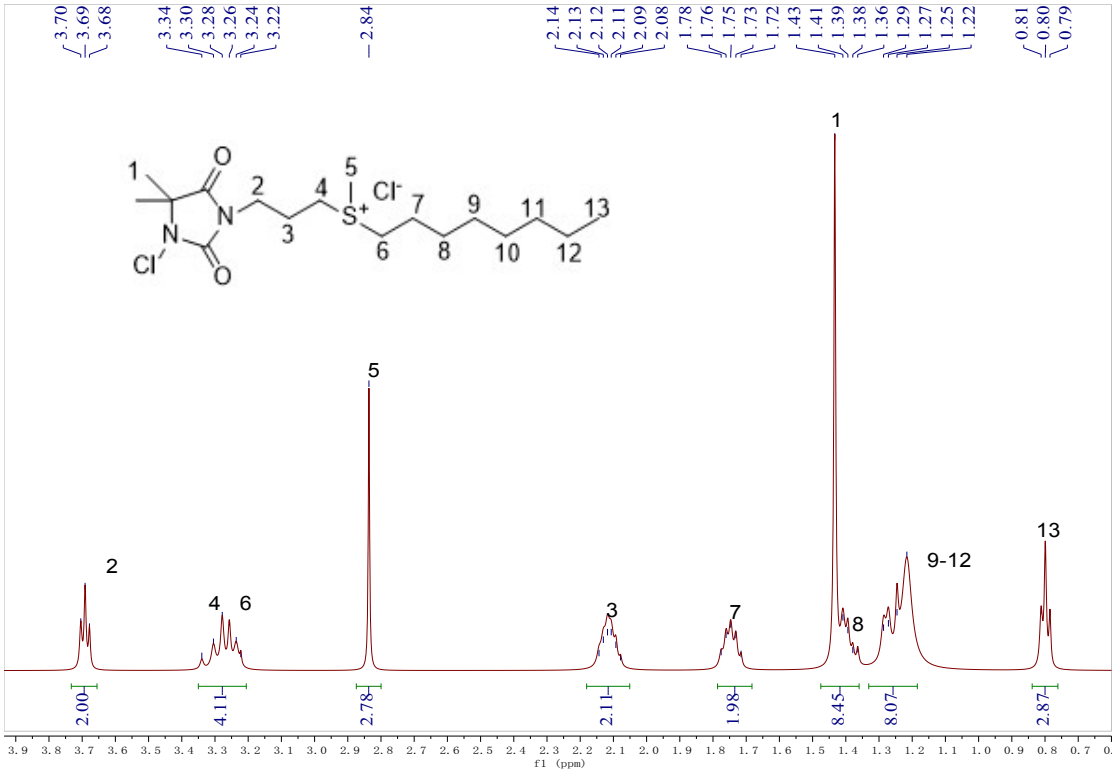
The ^{13}C NMR spectrum of compound **6**



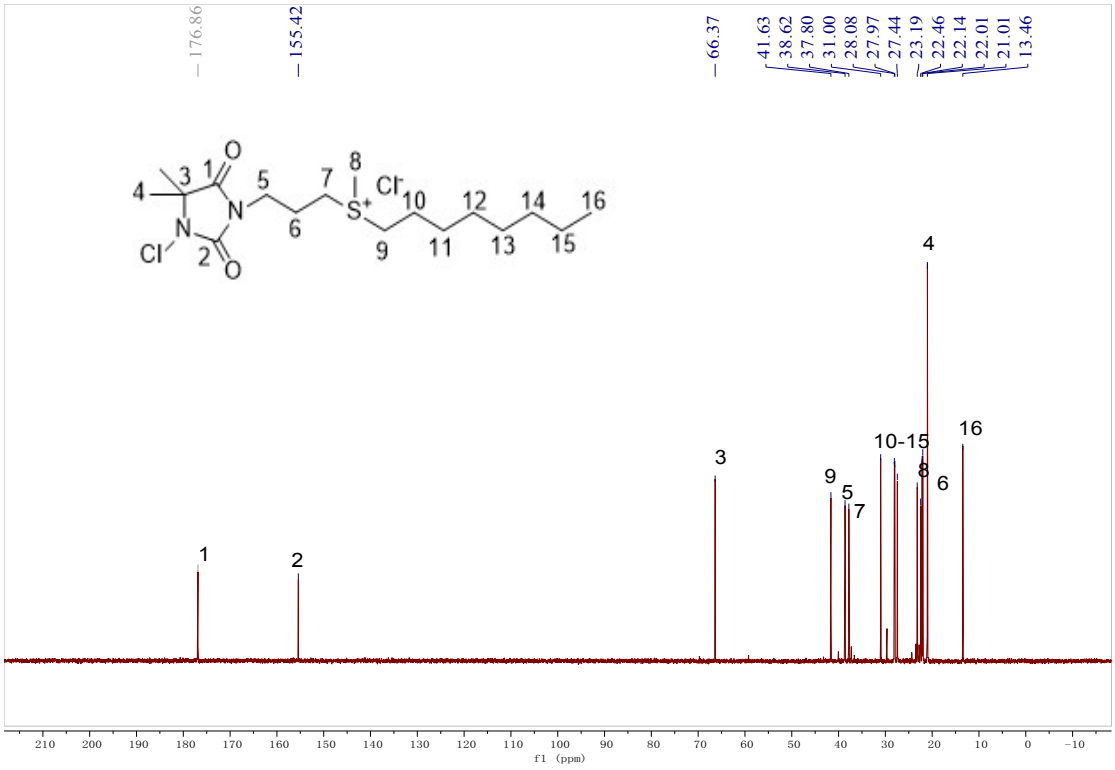
The ^{1}H NMR spectrum of compound **7a**



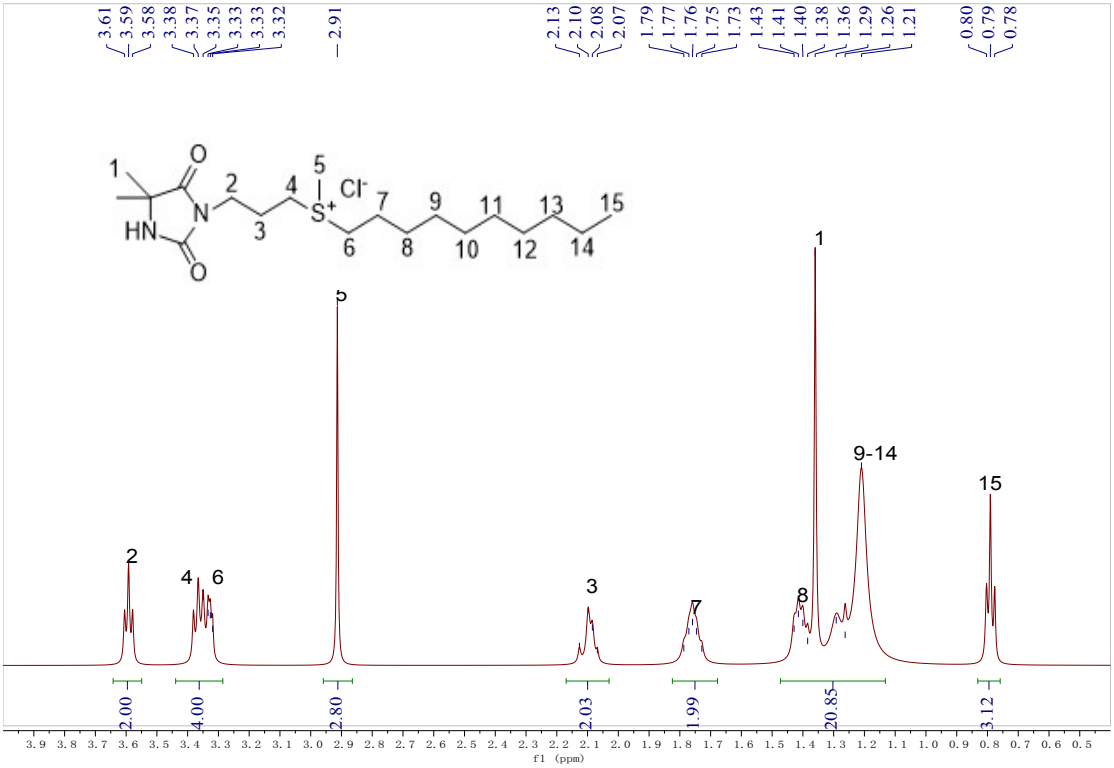
The ^{13}C NMR spectrum of compound **7a**



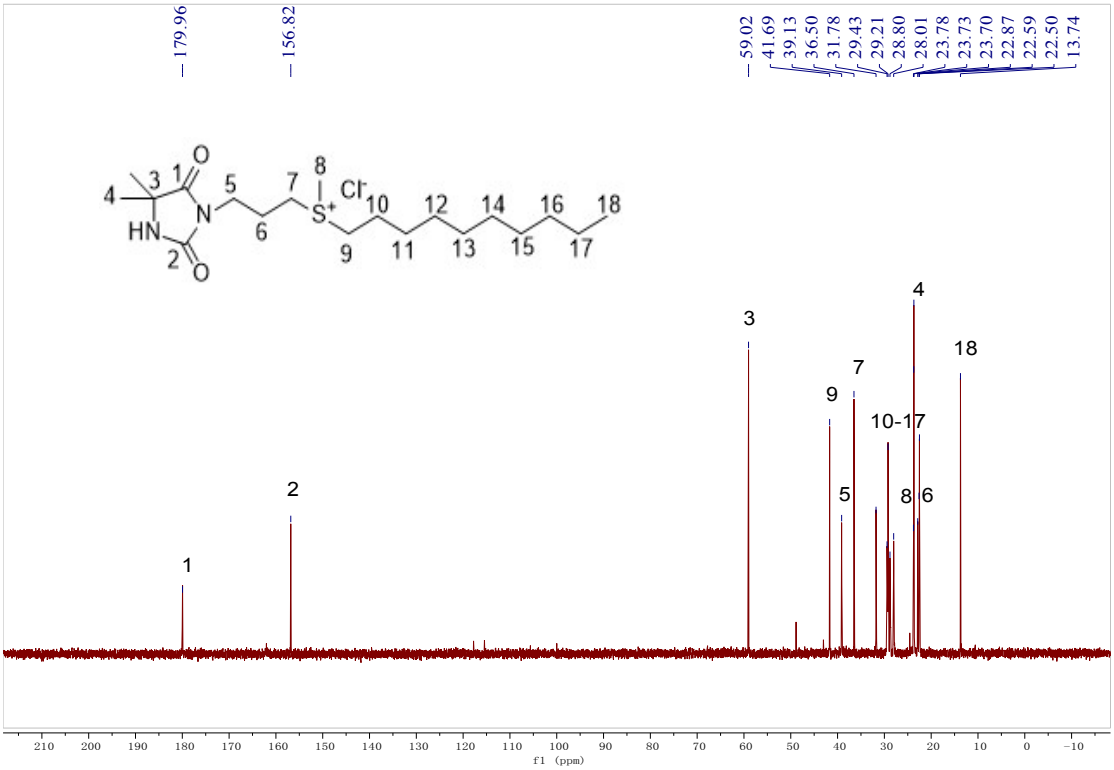
The ^{1}H NMR spectrum of compound **7**



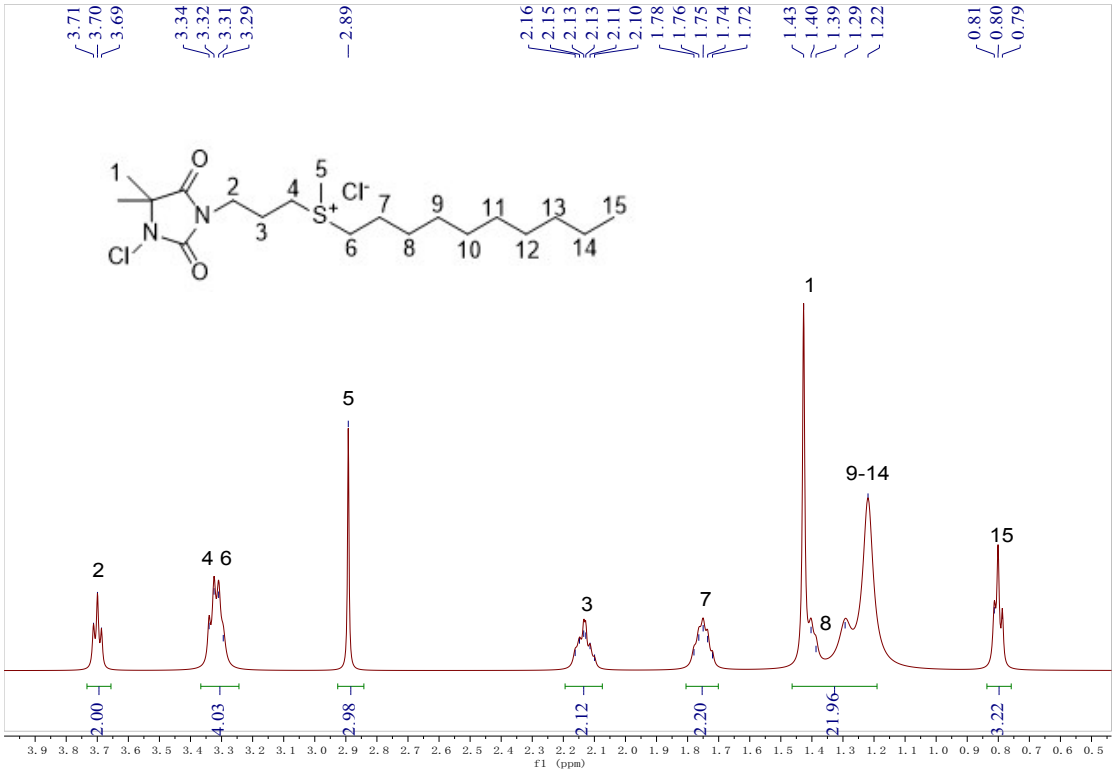
The ^{13}C NMR spectrum of compound **7**



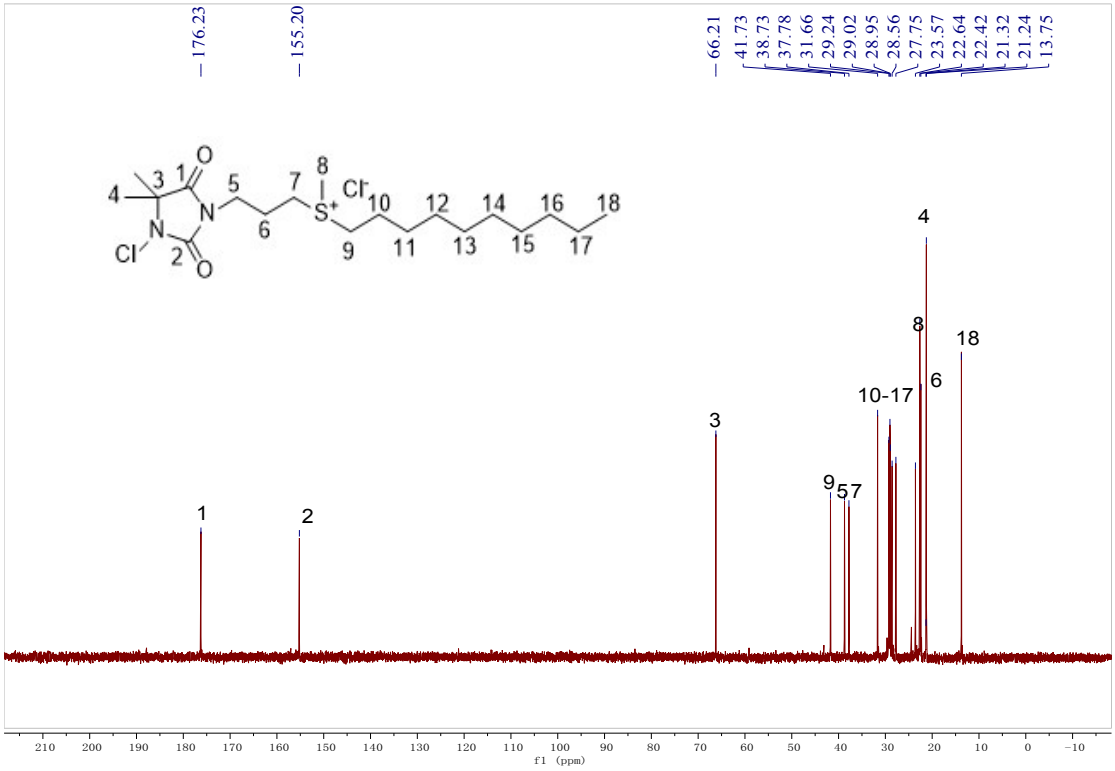
The ^{1}H NMR spectrum of compound **8a**



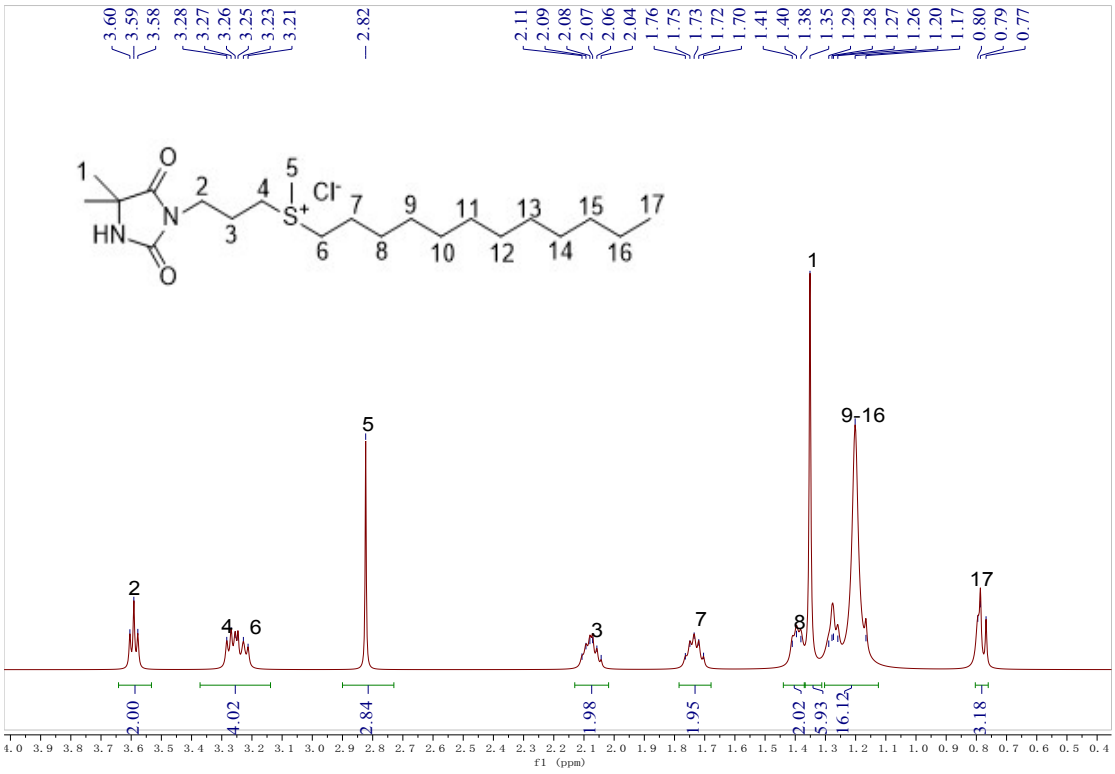
The ^{13}C NMR spectrum of compound **8a**



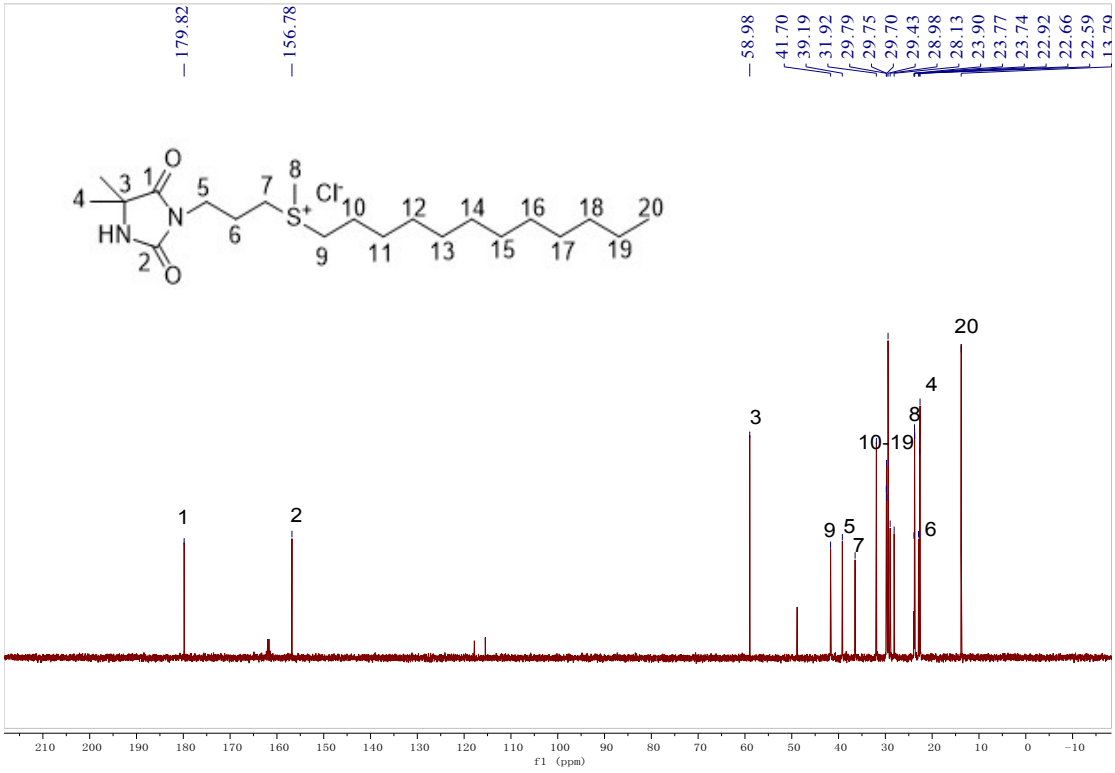
The ^{1}H NMR spectrum of compound **8**



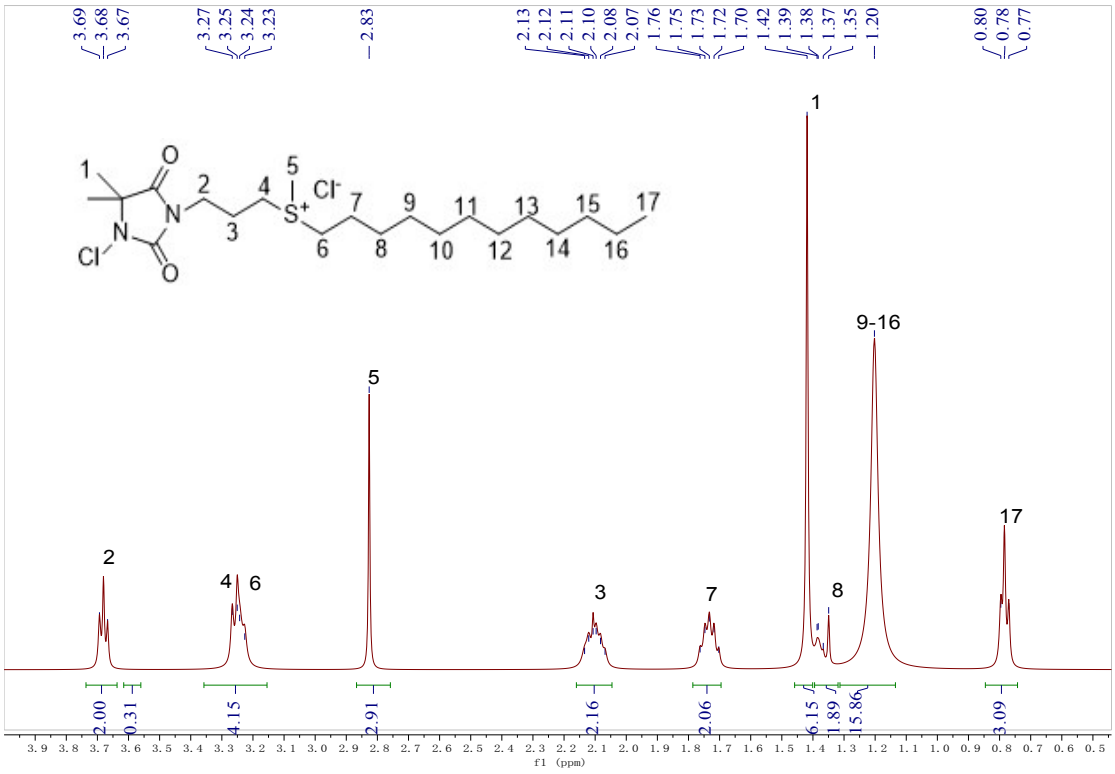
The ^{13}C NMR spectrum of compound **8**



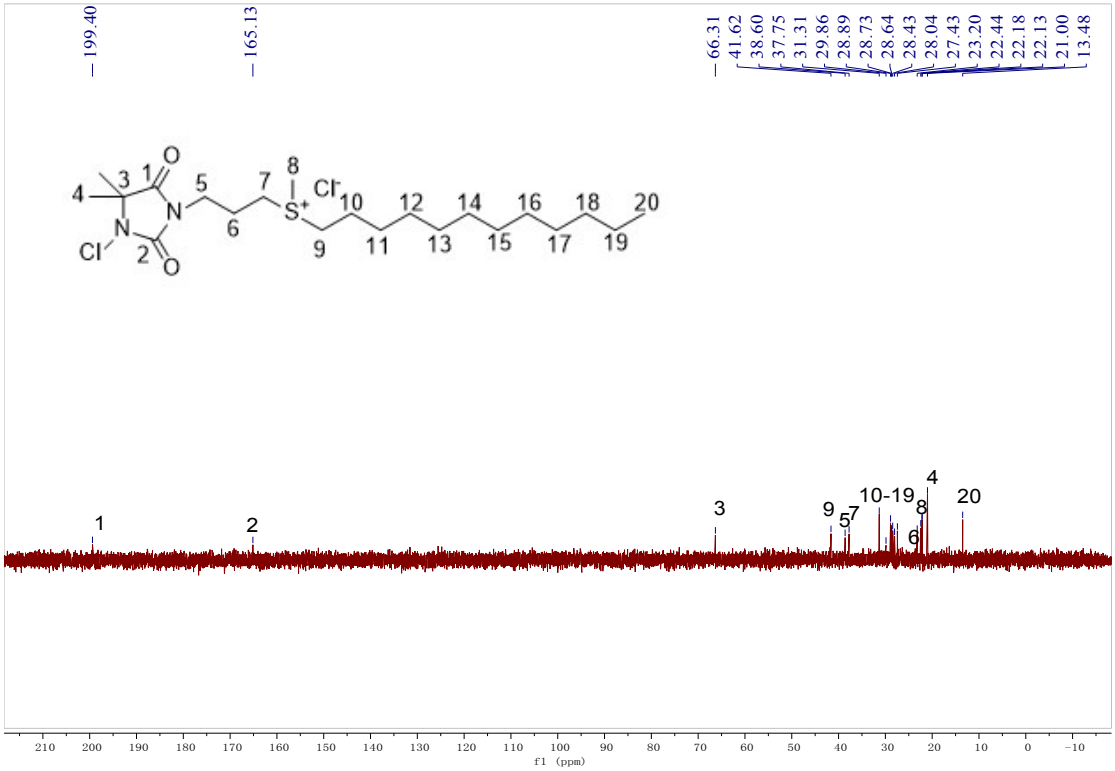
The ^{1}H NMR spectrum of compound **9a**



The ^{13}C NMR spectrum of compound **9a**



The ^{1}H NMR spectrum of compound **9**



The ^{13}C NMR spectrum of compound **9**