Electronic Supplementary Material (ESI) for Chemical Communications.

Tuning the Solubility of Ionophores: Glutathione-Mediated Transport of Chloride Ions across Hydrophobic Membranes

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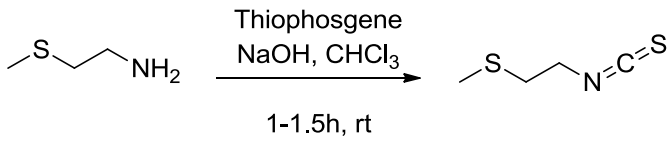
Supporting Information

1. General Information:

All the reagents and solvents were purchased from commercial sources like Sigma-Aldrich, Alfa Aesar, Merck and directly used without further purification, unless otherwise stated. Thin-layer chromatography (TLC) on silica gel 60 F254 (0.25 mm) was used to monitor the reactions. The column chromatography was performed using the silica gel of 120-200 mesh. The ^{1}H NMR and ^{13}C NMR were recorded at 400 and 100 MHz respectively by Bruker spectrometer. The chemical shifts were reported in parts per million (δ) using DMSO-d_6, $CDCl_3$ as internal solvent. The coupling constant (*J*) values were reported in hertz and the abbreviation were stated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiple), and br (broadened). The high-resolution mass spectra (HRMS) were recorded at Agilent Q-TOF mass spectrometer with Z-spray source using built-in software for the analysis of the recorded mass data. Egg yolk phosphatidylcholine (EYPC) and cholesterol were purchased from Sigma Aldrich. Dipalmitoylphosphatidylcholine (DPPC) was purchased from Avanti Polar Lipids. HEPES buffer, 8-hydroxypyrene-1, 3, 6-trisulfonic acid (HPTS), lucigenin, calcein, Triton X-100 and inorganic salts and their corresponding hydroxide bases were also purchased from Sigma Aldrich. Ultrapure water (Milli-Q system, Millipore, Billerica, MA) was used for the preparation of all the buffers. The stock solutions of compounds were prepared in gas chromatographic grade DMSO which also purchased from Sigma.

2. Synthesis of the Compounds:

2.1. ***Synthesis of 1-isothiocyanato-2-(methylthio)ethane***[1] **—** To a stirring solution of 2-(methylthio)ethan-1-amine (830 mg, 7.90 mmol) in chloroform (10 mL) and water (10 mL) at 0 °C was added a solution of thiophosgene (0.9 ml, 11.86 mmol) and NaOH (948 mg, 23.7

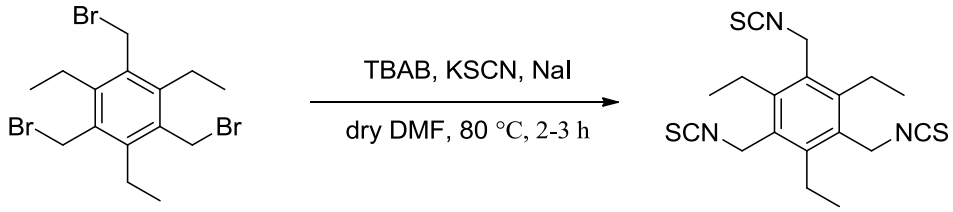


Scheme 1. Synthesis of 1-isothiocyanato-2-(methylthio)ethane.

mmol) in chloroform (10 mL). After 10 minutes the reaction mixture was allowed to warm up to room temperate and the stirring was continued for 1-1.5 hours. The progress of reaction was monitored by TLC analysis. After completion of the reaction, the organic layer was extracted with chloroform (2 × 50 mL). The combined organic layers was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was

purified through the column chromatography with a solvent gradient system using methanol/chloroform to give a light yellow liquid compound with 70% yield.

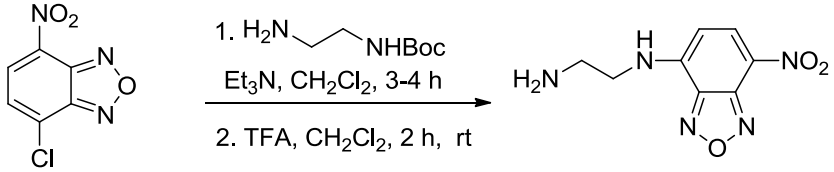
2.2. ***Synthesis of 1, 3, 5-triethyl-2, 4, 6-tris(isothiocyanatomethyl)benzene***[1-3] **—** To a stirring solution of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (200 mg, 0.45 mmol) in dry DMF solvent, were added tetrabutyl ammonium bromide (585 mg, 1.81 mmol), potassium thiocyante (308 mg, 3.17 mmol) and sodium iodide (55 mg, 0.36 mmol) at room temperature



Scheme 2. Synthesis of 1, 3, 5-triethyl-2, 4, 6-tris(isothiocyanatomethyl)benzene.

under N_2 atmosphere. Then the reaction mixture was continued to stir for 2-3hours at 80 ^{0}C temperature. The progress of reaction was monitored by TLC analysis. After completion of the reaction the unwanted salts were filtered through the filter paper. The filtrate was diluted with water (50 mL) and the organic layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was purified through the column chromatography with a solvent gradient system using ethyl acetate/hexane to give a white solid compound with 60% yield.

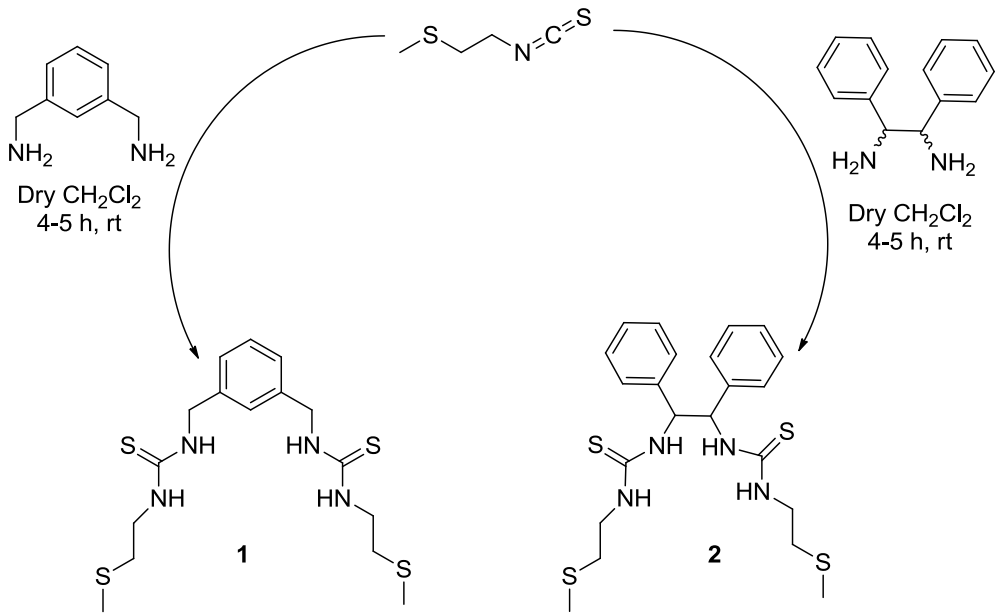
2.3. ***Synthesis of N-(2-aminoethyl)-7-nitrobenzo[c][1,2,5]oxadiazol-4-amine***[4] **—** To a stirring solution of NBD-Cl (250 mg, 1.252 mmol) in CH_2Cl_2 was added *N*-Boc-1,2-diaminoethane (221 mg, 1.378 mmol) and triethylamine (2 mL, 1.378 mmol) in CH_2Cl_2 (10 mL). The resulting dark-brown colour solution was continued to stirred until the disappearance of the



Scheme 3. Synthesis of *N*-(2-aminoethyl)-7-nitrobenzo[c][1,2,5]oxadiazol-4-amine.

starting materials. The progress of the reaction was monitored by the TLC analysis. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and the organic layer was washed with $NaHCO_3$ solution in water (2 × 10 mL). The collected organic layers were dried over the anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then, the crude reaction mixture was dissolved in CH_2Cl_2 (5 mL) and 30% trifluoroacetic acid solution in CH_2Cl_2 (2 mL, 1:9 (v/v)) was slowly added at room temperature. After 2 hours, diethyl ether (30 mL) was added and the precipitated product was collected through filtration, washed with cold diethyl ether to give the brown colour product with 70% yield.

2.4. ***Synthesis of bis(thiourea) derivatives*** ─ To a stirring solution of 1, 3-phenylenedimethanamine (100 mg, 0.734 mmol) or 1, 2-diphenylethane-1, 2-diamine (100 mg, 0.4710 mmol) in CH_2Cl_2 (15 mL) was added a solution of 1-isothiocyanato-2-(methylthio)ethane (1.615 mmol for compound **1** and 1.036 mmol for **2**)) in CH_2Cl_2 and the

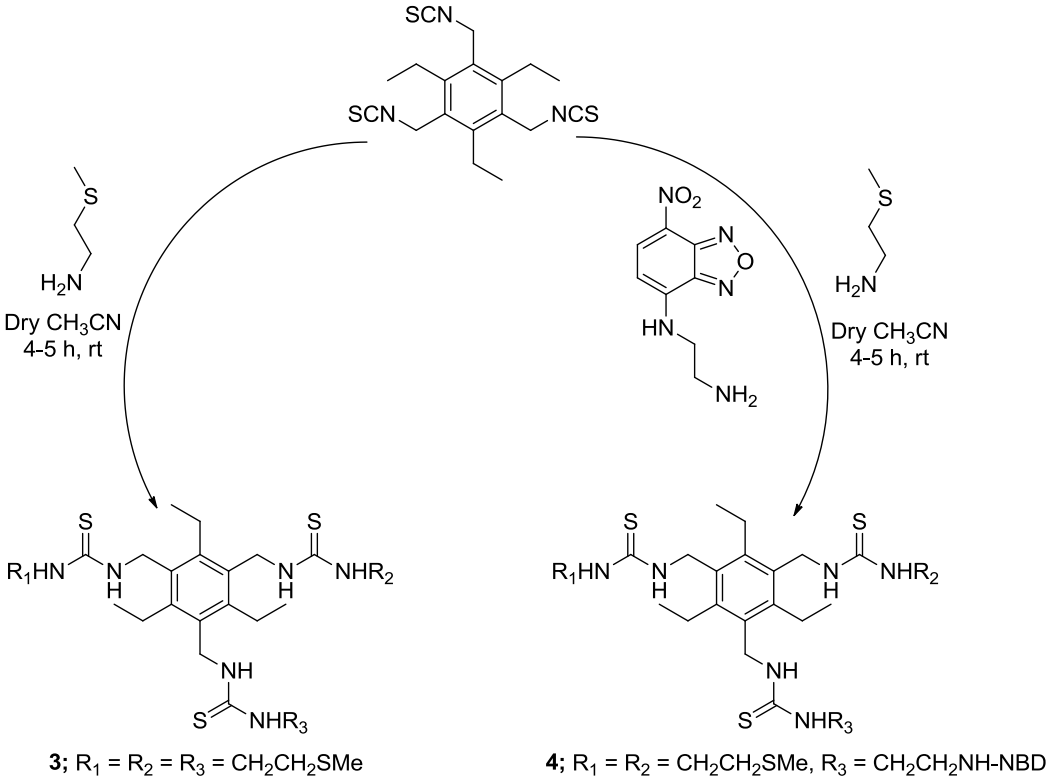


Scheme 4. Synthesis of bis(thiourea) derivatives.

whole reaction mixture was allowed to stir for 4-5 hours at room temperature. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure. The crude reaction mixture was purified through the column chromatography with a

solvent gradient system using MeOH/ CH_2Cl_2 to give the targeted compounds **1** and **2** with 70 and 75% yield respectively.

2.5. ***Synthesis of tris(thiourea) derivatives***[3] **—** To a stirring solution of N^1-(7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)ethane-1,2-diamine (62 mg, 0.266 mmol) in CH_3CN and/or 2-(methylthio)ethan-1-amine (97 mg, 1.065 mmol for compound **3** or 46 mg, 0.5054

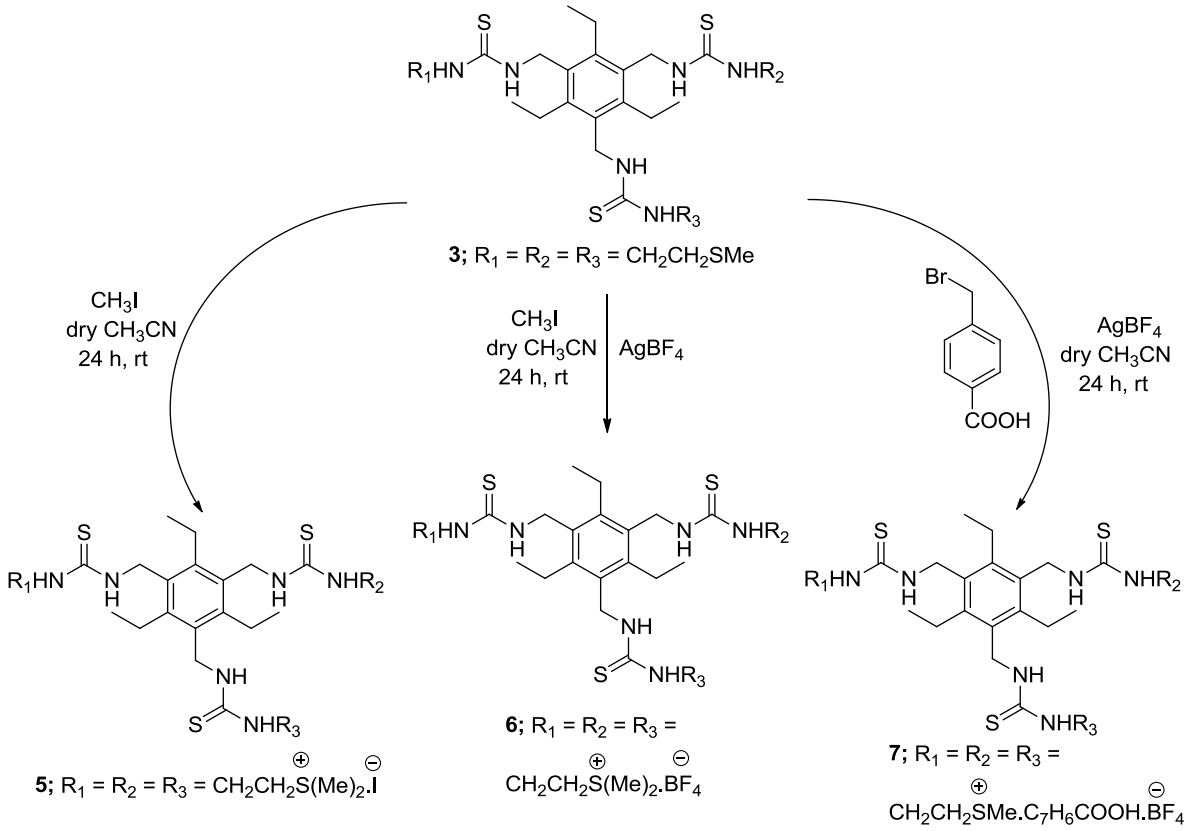


Scheme 5. Synthesis of tris(thiourea) derivatives.

mmol for compound **4**) was added a solution of 1,3,5-triethyl-2,4,6-tris(isothiocyanatomethyl)benzene (100 mg, 0.266 mmol for both compounds **3** and **4**) in CH_3CN. The reaction mixture was then allowed to stir for 4-5 hours at room temperature. The progress of the reaction was monitored by the TLC analysis. A white precipitation was observed (for the compound **3)** and the precipitate was filtered and washed with CH_2Cl_2 and CH_3CN to get the pure compound **3** as white solid with 90% yield. However, there was no precipitation for compound **4.** After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over anhydrous Na_2SO_4. The organic solvent was removed under reduced pressure and the purification was done by the column chromatography using a gradient

solvent system of MeOH/CH_2Cl_2. The targeted compound **4** was obtained as white solid with 50% yield.

2.6. ***Synthesis of sulfonium derivatives***[5] **—** To a stirring solution of 1,1',1''-((2,4,6-triethylbenzene-1,3,5-triyl)tris(methylene))tris(3-(2-(methylthio)ethyl)thiourea) (compound **3**; 1 equiv.) in CH_3CN was added a solution of iodomethane (3.2 euiv. for compound **5** and **6**) or 4-(bromomethyl)benzoic acid (3.2 equiv. for compound **7**) in CH_3CN. To this reaction mixture a trace amount of dry DMF was added and the mixture was heated (at 40-50 °C) to

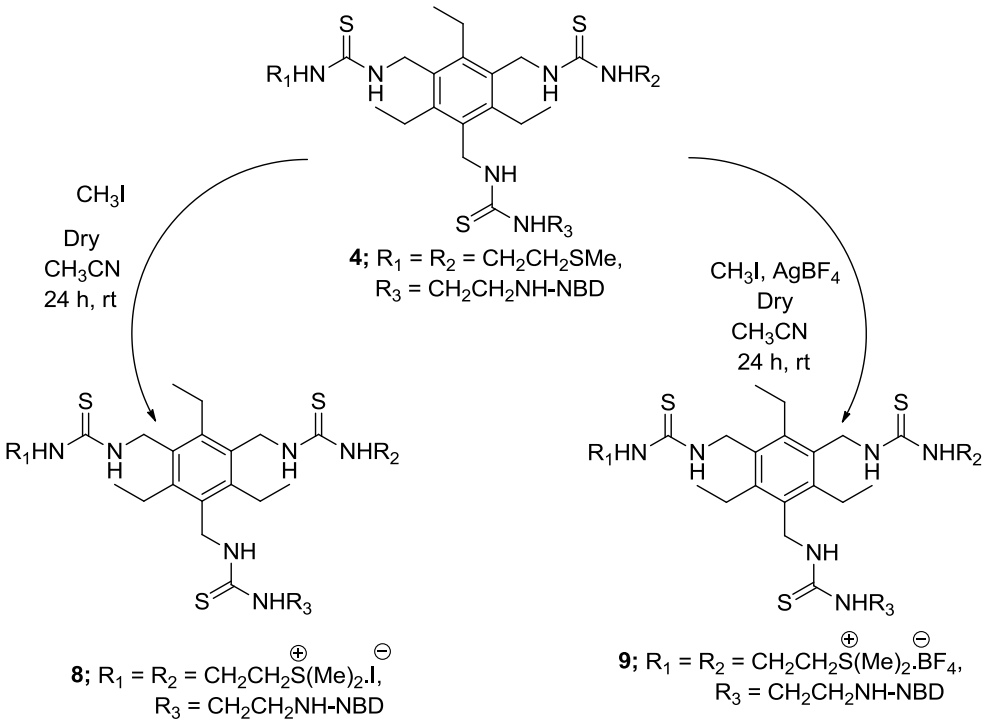


Scheme 6. Synthesis of sulphonium based compound.

solubilize the whole reaction mixture, and was allowed to stir for 24 hours at room temperature. For the synthesis of the compound **6** and **7**, 20 mol% of $AgBF_4$ were also added to prepare their respective tetrafluroborate salts for making them as a better water soluble compounds. The progress of the reaction was monitored by TLC analysis. The precipitation due to the silver salt was filtered and the filtrate part was washed with diethyl ether, CH_2Cl_2 and CH_3CN to obtain the pure product **6** and **7** as sticky liquid with 60% and 70% yields, respectively. As $AgBF_4$ was not used for the preparation of compound **5**, so there was not any precipitation under the experimental conditions and after the completion of the reaction, the

reaction mixture was simply washed with the diethyl ether, CH_2Cl_2 and CH_3CN to get the pure product as sticky liquid with 90% yield.

2.7. ***Synthesis of NBD-labeled sulfonium derivatives***[5, 6] ― To a stirring solution of compound **4** in CH_3CN (10 mL) was added a solution of iodomethane in CH_3CN and the whole reaction mixture was allowed to stir for 24 hours at room temperature. After completion of the

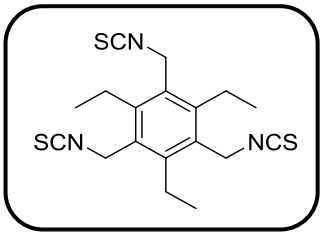


Scheme 7. Synthesis of NBD-labeled sulfonium derivatives.

reaction the reaction mixture was washed with diethyl ether, CH_2Cl_2 and CH_3CN to obtain a sticky compound **8** with 90% yield. For the synthesis of the compound **9**, 20 mol% of $AgBF_4$ was added to the solution of compound **4** in CH_3CN. The precipitate due to the presence of excess silver salt was filtered off and the filtrate part was washed with diethyl ether, CH_2Cl_2 and CH_3CN to get the pure product **9** as sticky compounds with 50% yield.

3. Characterization of the Synthesized Compounds:

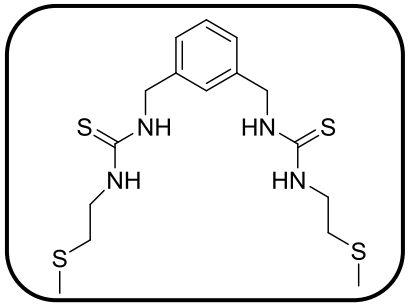
3.1. ***1,3,5-triethyl-2,4,6-tris(isothiocyanatomethyl)benzene*** ― Following the general procedure as mentioned in section 2.2, using 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene (200 mg,0.45 mmol), tetrabutyl ammonium bromide (585 mg,1.81 mmol), potassium



thiocyante (308 mg, 3.17 mmol) and the sodium iodide(55 mg, 0.36 mmol) provided the colourless solid compound as 70% yield. The product was characterized by the ES-MS, ^{1}H NMR and ^{13}C NMR analyses. ^{1}H NMR (600 MHz, **$CDCl_3$**) δ 4.68 (s, 6H), 2.79 (q, *J* = 7.7 Hz, 6H), 1.21 (t, *J* = 7.7 Hz, 9H). ^{13}C NMR (151 MHz, **$CDCl_3$**) δ 144.1, 132.1, 129.9, 42.8, 23.1, 15.7. **ES-MS (ESI+) m/z**: 376.098. **HRMS (ESI)** calcd. for $C_{18}H_{21}N_3S_3$ $(M+H)^+$: 376.0970, found: 376.0981.

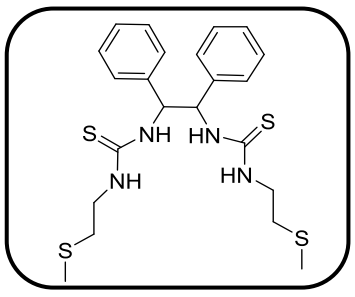
3.2. ***N^1-(7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)ethane-1,2-diamine[4]*** **—** This compound was synthesized according to the reported procedure using NBD-Cl (250 mg, 1.252 mmol) in CH_2Cl_2 and N-Boc-1,2-diaminoethane (221 mg, 1.378 mmol). All the characterization data were matched with the reported literature.

3.3. ***1,1'-(1,3-phenylenebis(methylene))bis(3-(2-(methylthio)ethyl)thiourea)(1)*** **—** Following



the general procedure as mentioned in section 2.4, using 1,3-phenylenedimethanamine (100mg, 0.734 mmol)and (2-isothiocyanatoethyl)(methyl)sulfane (215 mg, 1.615 mmol) provided the colorless solid compound as 70% yield. The product was characterized by the ES-MS, ^{1}H NMR and ^{13}C NMR analyses**. ^{1}H NMR (600 MHz, DMSO-d_6)** δ 7.97 (s, 2H), 7.60 (s, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.19 – 7.16 (m, 3H), 4.64 (s, 4H), 3.62 (s, 4H), 2.63 (t, *J* = 7.0 Hz, 4H), 2.08 (s, 6H). **^{13}C NMR (151 MHz, DMSO-d_6)** δ 183.6, 139.8, 128.7, 126.7, 126.3, 47.5, 43.3, 32.9, 15.1. **ES-MS (ESI+) m/z**: 403.1119. **HRMS (ESI)** calcd. for $C_{16}H_{26}N_4S_4$ $(M+H)^+$: 403.1113, found: 403.1119.

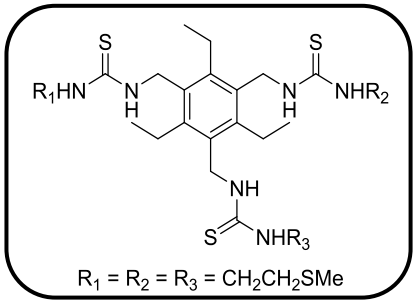
3.4. ***1,1'-(1,2-diphenylethane-1,2-diyl)bis(3-(2-(methylthio)ethyl)thiourea) (2)*** **—** Following



the general procedure as mentioned in section 2.4, using 1,2-diphenylethane-1,2-diamine (100 mg, 0.471 mmol) and (2-isothiocyanatoethyl)(methyl)sulfane (138 mg, 1.036 mmol) provided the brownish solid compound as 75% yield. The product was characterized by the ES-MS, ^{1}H NMR and ^{13}C NMR analyses. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 7.91 (brs, 2H), 7.61 (brs, 2H), 7.29-7.27 (m, 6H), 7.24-7.22 (m, 4H), 6.03 (brs, 2H), 3.51 (brs, 4H), 2.01 (s, 6H). **^{13}C NMR (151 MHz, DMSO-d_6)** δ 182.9, 157.6, 140.4, 128.3, 128.0, 127.5,

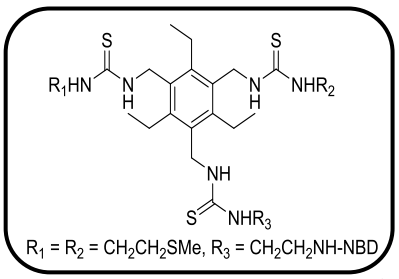
61.1, 43.2, 32.7, 15.0. **ES-MS (ESI+) m/z**: 479.1429. **HRMS (ESI)** calcd. for $C_{22}H_{30}N_4S_4$ $(M+H)^+$: 479.1426, found: 479.1429.

3.5. ***1,1',1''-((2,4,6-triethylbenzene-1,3,5-triyl)tris(methylene))tris(3-(2-(methylthio)ethyl)thiourea)(3)*** **—** Following the general procedure as mentioned in section 2.5, using 1,3,5-triethyl-2,4,6-tris(isothiocyanatomethyl)benzene (100 mg, 0.266 mmol) and

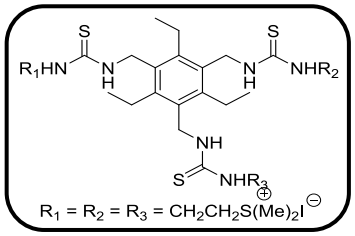


2-(methylthio)ethan-1-amine (97 mg, 1.065 mmol) provided the white solid compound as 90% yield. The compound was simply purified by the washing with the CH_3CN and DCM solvent. The product was characterized by the ES-MS, ^{1}H NMR and ^{13}C NMR analyses. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 7.40 (brs, 6H), 4.61 (s, 6H), 3.64-3.61 (s, 6H), 2.67-2.61 (m, 12H), 2.08 (s, 9H), 1.11 (t, J = 7.4 Hz, 9H). **^{13}C NMR (151 MHz, DMSO-d_6)** δ 182.6, 143.9, 132.7, 43.0, 42.5, 32.9, 23.2, 16.8, 14.9. **ES-MS (ESI+) m/z**: 649.2336. **HRMS (ESI)** calcd. for $C_{27}H_{48}N_6S_6$ $(M+H)^+$: 649.2337, found: 649.2336.

3.6. Compound 4 — Following the general procedure as mentioned in section 2.5, using



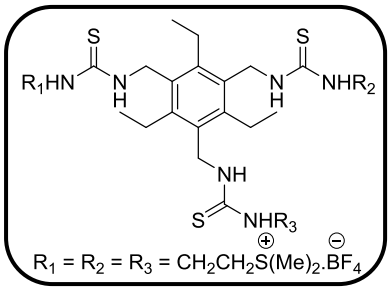
1,3,5-triethyl-2,4,6-tris(isothiocyanatomethyl)benzene (100 mg, 0.266 mmol), 2-(methylthio)ethan-1-amine (46 mg, 0.5059 mmol) and N^1-(7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)ethane-1,2-diamine(59 mg, 0.266 mmol) provided the brownish solid compound as 70% yield. The product was characterized by the ES-MS, ^{1}H NMR and ^{13}C NMR analyses. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.36 (brs, 1H), 7.57-7.49 (m, 4H), 6.44 (brs, 2H), 6.35 (s, 1H), 4.57 (s, 6H), 3.05 (s, 4H), 2.79 (s, 2H), 2.60 (s, 6H), 2.06 (s, 6H), 1.88 (s, 6H), 1.29-1.07 (m, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.0, 152.9, 147.6, 144.8, 143.9, 136.9, 100.7, 45.1, 32.9, 23.2, 22.6, 22.0, 16.8, 15.0. **ES-MS (ESI+) m/z**: $(M+3H)^+$: 783.2679 $(M+4H)^+$ 784.2703, $(M+5H)^+$ 785.2652.



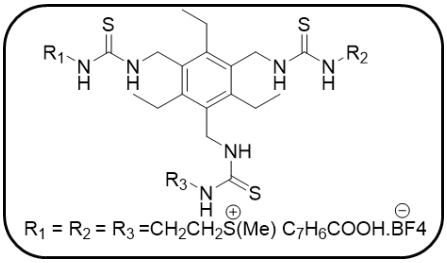
3.7. Compound 5 — Following the general procedure as mentioned in section 2.6, using 1,1',1''-((2,4,6-triethylbenzene-1,3,5-triyl)tris(methylene))tris(3-(2-(methylthio)ethyl)thiourea (50mg, 0.077 mmol), and methyl iodide (16 µL, 0.2465 mmol) provided the white solid compound as 70% yield. The product was confirmed by the ES-MS,

^{1}H NMR and ^{13}C NMR data. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.53-9.43 (m, 1H), 9.22-8.75 (m, 3H), 7.57-7.32 (m, 2H), 4.70-4.48 (m, 6H), 4.04-3.99 (m, 1H), 3.77 (s, 2H), 3.63-3.61 (m, 3H), 2.83-2.76 (m, 4H), 2.69-2.63 (m, 8H), 2.18 (s, 8H), 2.15 (s, 4H), 2.09-2.05 (m, 6H), 1.13-1.11 (m, 9H). The product was characterized by the ES-MS, ^{1}H NMR and ^{13}C NMR analyses. ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.9, 146.7, 129.5, 128.8, 62.8, 55.5, 49.1, 44.7, 42.6, 26.7, 25.5, 25.3, 24.0, 16.7, 15.5. **ES-MS (ESI+) m/z**: $[M - 2I^{-} + H]^{+}$ 821.2031.

3.8. Compound 6 ─ Following the general procedure as mentioned in section 2.6, using 1,1',1"-((2,4,6-triethylbenzene-1,3,5-triyl)tris(methylene))tris(3-(2-(methylthio)ethyl)thiourea) (50mg, 0.077 mmol), methyl iodide (16 µL, 0.2465 mmol) and $AgBF_4$ (20 mol%) provided the brownish colour sticky compound as 65% yield. . The product was characterized by the ES-MS, ^{1}H NMR and ^{13}C NMR analyses. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.52 -9.49 (m, 1H), 9.14-8.98 (m, 2H), 8.79-8.75 (m, 1H), 7.48-7.31 (brs, 2H), 4.64-4.51 (m, 6H), 4.04-3.98 (m, 1H), 3.77 (brs, 2H), 3.62-3.60 (m, 3H), 2.98-2.96 (m, 1H), 2.82-2.81 (m, 3H), 2.68-2.62 (m, 8H), 2.18 (s, 8H),2.15 (s, 4H), 2.08-2.04 (m, 6H), 1.12-1.10 (m, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.9, 146.6, 129.4, 128.7, 62.7, 55.4, 49.0, 44.6, 42.5, 26.6, 25.2, 23.9, 16.6, 15.5. **ES-MS (ESI+) m/z**: $[M/3 + NH_4^{+}]$ 337.1539. **MALDI-TOF m/z**: $[M/2 + 1H]^{+}$ 478.5.

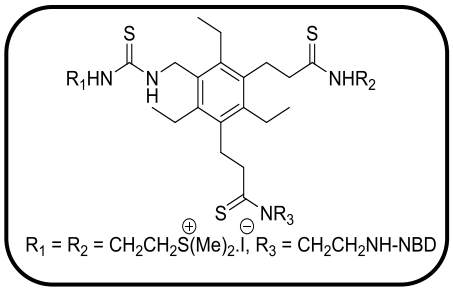


3.9. Compound 7 ─ Following the general procedure as mentioned in section 2.6, using 1,1',1"-((2,4,6-triethylbenzene-1,3,5-triyl)tris(methylene))tris(3-(2-(methylthio)ethyl)thiourea) (50mg, 0.077 mmol), 4-(bromomethyl)benzoic acid (53mg, 0.2464 mmol) and $AgBF_4$ (20 mol%) provided the brownish color sticky compound as 65% yield. The product was characterized by the ES-MS, ^{1}H NMR and ^{13}C NMR analyses. **^{1}H NMR (600 MHz, DMSO-d_6)** δ 13.07 (brs, 3H), 9.81-9.21 (m, 4H), 7.99-7.97 (m, 1H), 7.93-7.90 (m, 4H), 7.63 (s, 1H), 7.61 (m, 2H), 7.58-7.42 (m, 4H), 4.76 (s, 1H), 4.61-4.45 (m, 11H), 3.76 (s, 3H), 3.63 (s, 3H), 2.72 (s, 4H), 2.62 (s, 8H), 2.08 (s, 9H), 1.12-1.06 (m, 9H). **^{13}C NMR (151 MHz, DMSO-d_6)** δ 183.1, 167.6, 165.3, 144.5, 144.3, 143.3, 140.7,131.0, 130.3, 130.1, 129.9, 129.8, 129.7, 129.4, 44.9, 43.3, 42.6, 37.2, 33.8, 33.0, 23.5,



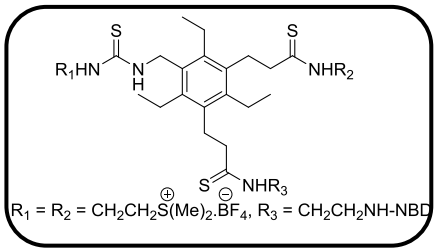
23.4, 23.2, 16.9, 16.8, 16.6, 15.3, 15.0, 14.8. **ES-MS (ESI+) m/z**: [M - $2BF_4^-$ +NH_4^+] 1159.7907, [M - $2BF_4^-$ - 2Me + H]$^+$ 1111.7909. **MALDI-TOF m/z**: [(M- BF_4)/3 + 1H]$^+$ 410.1.

3.10. Compound 8 ─ Following the general procedure as mentioned in section 2.7, using



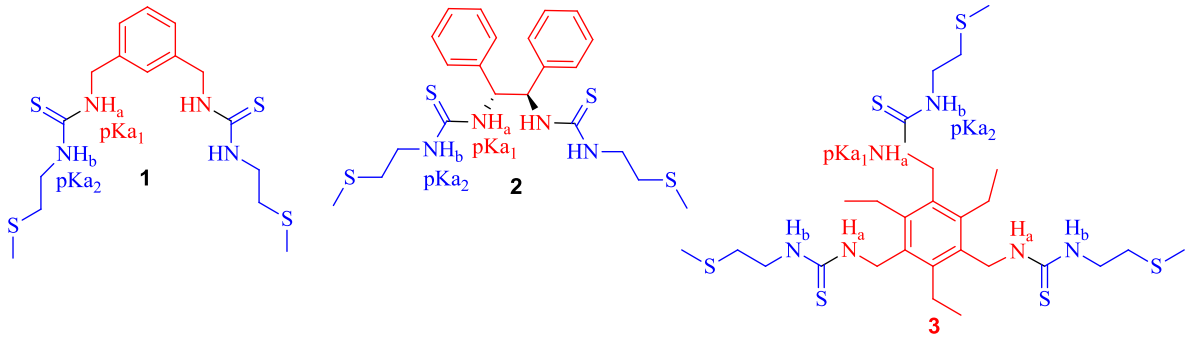
compound **4** (100 mg, 0.128 mmol) and methyl iodide (17 µL, 0.2691 mmol) provided the solid compound as 70% yield. The product was characterized by the ES-MS, ^{1}H NMR and ^{13}C NMR analyses. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.35-8.34 (m, 1H), 7.61-7.49 (m, 4H), 6.50 (s, 2H), 6.45-6.34 (m, 1H), 4.57 (s, 6H), 3.84 (s, 2H), 3.05 (s, 2H), 2.79 (s, 4H), 2.59 (s, 4H), 2.06 (s, 6H), 1.88 (s, 12H), 1.22 (s, 3H), 1.08-1.07 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.0, 145.5, 144.8, 143.9, 137.0, 100.7, 100.4, 63.5, 44.8, 43.2, 32.9, 31.7, 30.3, 29.5, 23.2, 22.6, 21.9, 16.8, 15.0, 14.4. **ES-MS (ESI+) m/z**: [M + Br^- + H] $^+$ 1145.5355, [M + Br^- + 2H] $^+$ 1146.5326, [M + Br^- + 2H] $^+$ 1147.5347. **MALDI-TOF m/z**: [M/2 + 2H]$^+$ 534.6, [M/2 + 3H]$^+$ 535.3, [M/2 + 4H]$^+$ 536.6.

3.11. Compound 9 ─ Following the general procedure as mentioned in section 2.7, using



compound **4** (100 mg, 0.128 mmol) and methyl iodide (17 µL, 0.2691 mmol) and $AgBF_4$ (20 mol%) provided the sticky compound as 70% yield. The product was characterized by the ES-MS, ^{1}H NMR and ^{13}C NMR analyses. **^{1}H NMR (600 MHz, DMSO-d_6)** δ_{ppm} 8.45-8.42 (m, 1H), 8.34-8.33 (m, 1H), 7.75-7.49 (m, 4H), 6.50-6.43 (m, 2H), 6.35-6.33 (m, 1H), 4.57 (s, 6H), 3.83 (s, 2H), 3.04 (s, 2H), 2.78 (m, 4H), 2.59 (s, 4H), 2.06 (s, 6H), 1.87 (s, 12H), 1.22 (s, 3H), 1.09-1.06 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.2, 145.6, 144.9, 144.1, 137.1, 100.8, 100.5, 63.6, 44.9, 43.3, 33.1, 31.9, 30.4, 29.6, 23.3, 22.7, 22.1, 16.9, 15.1, 14.5. **ES-MS (ESI+) m/z**: [M + Br^-] 1063.5571. **MALDI-TOF m/z**: [M-$2BF_4$] 810.5, : [M-$2BF_4$ + 2H]$^+$ 812.5, [M-$2BF_4$ + 4H]$^+$ 814.5.

Table S1. Chemical properties of the compounds.



Compound	LogP[a]	pK_{a1} (N-H)[b]	pK_{a2} (N-H)[b]	K_d (mM)[c]
1	3.01	13.93	14.53	68.84
2	4.83	14.37	13.73	-
3	6.40	13.74	14.22	81.84 (N-H_a) 47.65 (N-H_b)

LogP[a], [b]pK_{a1} and pK_{a2} were calculated using the MarvinSketch 17.27 program.

[c]K_d values of the compounds were calculated using ^{1}H NMR titration.

4. ^{1}H-NMR Titrations:

4.1. ***Anion binding analysis by ^{1}H-NMR titrations***[7, 8] **—** The ^{1}H NMR titration was performed for compound **1** and **3** in DMSO-d_6. The stock solutions of the compound (8.4 mM) and tetrabutyl ammonium chloride (TBACl; 6 M) were prepared in DMSO-d_6. The TBACl was used as the source of Cl^- ion. ^{1}H-NMR titrations of the compounds in DMSO-d_6 were performed by the subsequent addition of TBACl (0-35 equiv.). The changes in chemical shift ($\Delta\delta$) values of the N-H protons of the compounds were analysed. MestReNova software was used for the stacking of all the titration spectra. The changes in chemical shift against the concentration of chloride ion were fitted by the WinEQNMR2 program using 1:1 binding model.[8] The dissociation constant (K_d) values were determined by taking the reciprocal of binding constant (K_a; as mentioned in WinEQNMR2 program). The following equation (Eq.-S1) was used to calculate the binding constant-

$$\delta_{cal} = \sum_{m=1}^{m=i} \sum_{n=0}^{n=j} \frac{\delta_{mn}\beta_{mn}m[M]^m[L]^n}{[M]_{total}} \quad \text{.....Eq.-S1}$$

Where, *M* represents the free, uncomplexed receptor and *L* is the ligand; δ_{calc}, is the weighted average of the chemical shifts of the various *M*-containing species present, M_mL_n, and i and j represent the maximum values of m and n respectively.[8]

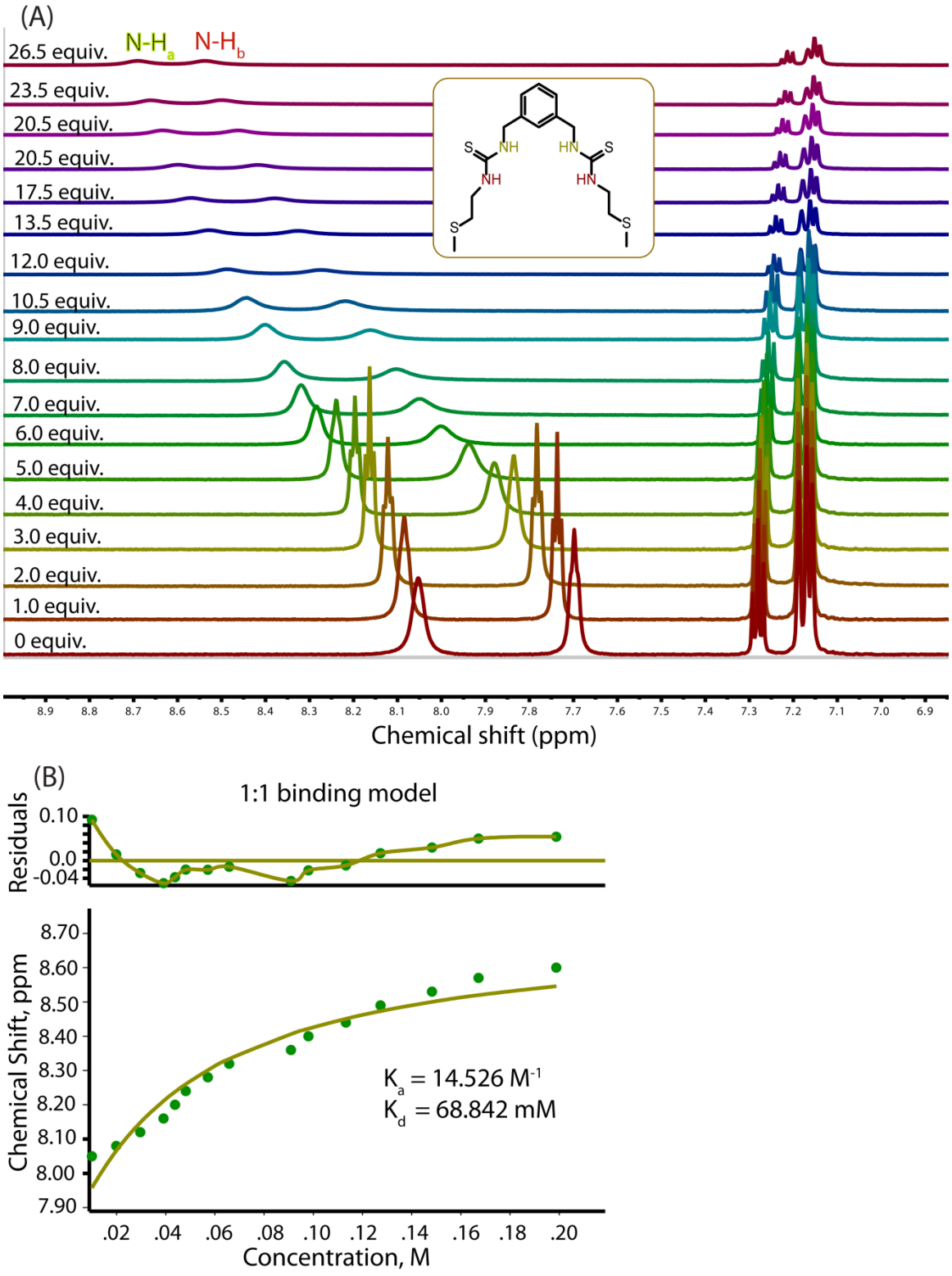


Figure S1: ^{1}H-NMR (600MHz) titration spectra for compound **1** with sequential addition of TBACl in DMSO-d_6 solvent. The amounts of added TBACl are shown on the spectra (**A**). Plot of concentration of TBACl verses chemical shift of ^{1}H signal, fitted to 1:1 binding model of WinEQNMR2 program (**B**).

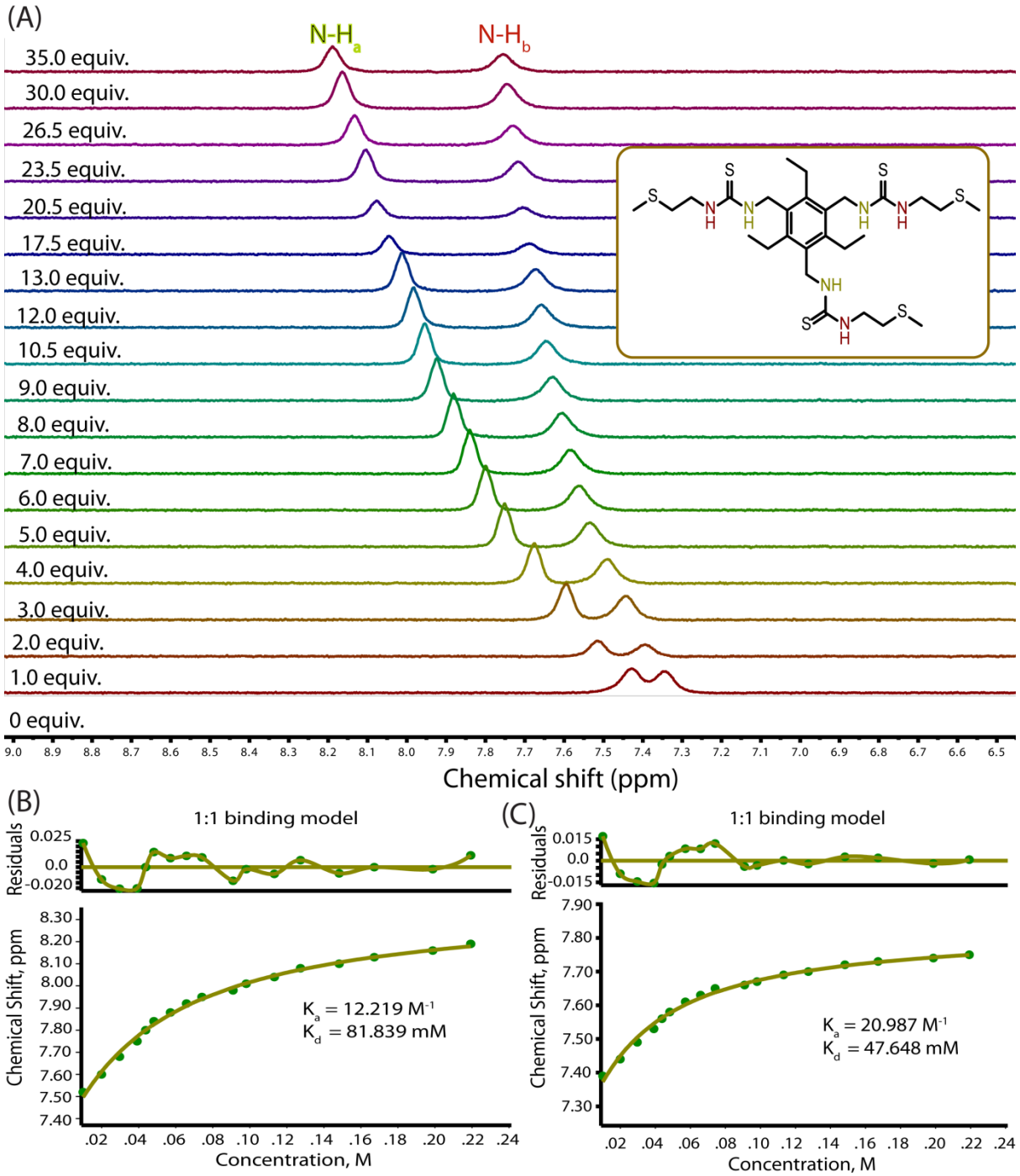


Figure S2: ^{1}H-NMR (600MHz) titration spectra for compound **3** with sequential addition of TBACl in DMSO-d$_6$ solvent. The amounts of added TBACl are shown on the spectra (**A**). Plot of concentration of TBACl verses chemical shift of ^{1}H signal (for N-H$_a$), fitted to 1:1 binding model of WinEQNMR2 program (**B**). Plot of concentration of TBACl verses chemical shift of ^{1}H signal (for N-H$_b$), fitted to 1:1 binding model of WinEQNMR2 program (**C**).

4.2. ***Determination of anion binding stoichiometry by Job's plot***[3, 7, 9] **—** A continuous variation method of Job's plot was used to determine the binding stoichiometry of the complex which was formed during the titration of compound **3** in the presence of Cl^- ion (TBACl). The DMSO-d_6 solvent was used to prepare the stock solutions of host (compound) and the guest (TBACl). During the titration experiments total 10 separate NMR tubes containing the required amount of host and guest concentrations were taken to keep the final concentration fixed to be at 10 mM. The chemical shift values were recorded and the changes of chemical shift of N-H proton at different mole fraction of the Cl^- ion were tabulated (Table S2). The Job's plot of compound **3** specifies a 1:1 binding stoichiometry of the complex.[7]

Table S2: Calculation and result table for the Job's plot analysis**.**

Sample No.	Host conc. ([H], mM)	Guest conc. ([G], mM)	[H] + [G] (mM)	[H]/ ([H]+[G])	δ of proton	Δδ	{[H] / ([H] +[G])}*Δδ
JB-1-1d	1.0	9.0	10	0.1	7.66	0.25	0.025
JB-2-1d	2.0	8.0	10	0.2	7.65	0.24	0.048
JB-3-1d	3.0	7.0	10	0.3	7.62	0.21	0.063
JB-4-1d	4.0	6.0	10	0.4	7.6	0.19	0.076
JB-5-1d	5.0	5.0	10	0.5	7.57	0.16	0.08
JB-6-1d	6.0	4.0	10	0.6	7.54	0.13	0.078
JB-7-1d	7.0	3.0	10	0.7	7.51	0.1	0.07
JB-8-1d	8.0	2.0	10	0.8	7.48	0.07	0.056
JB-9-1d	9.0	1.0	10	0.9	7.44	0.03	0.027
JB-10-1d	10	0.0	10	1	7.41	0	0

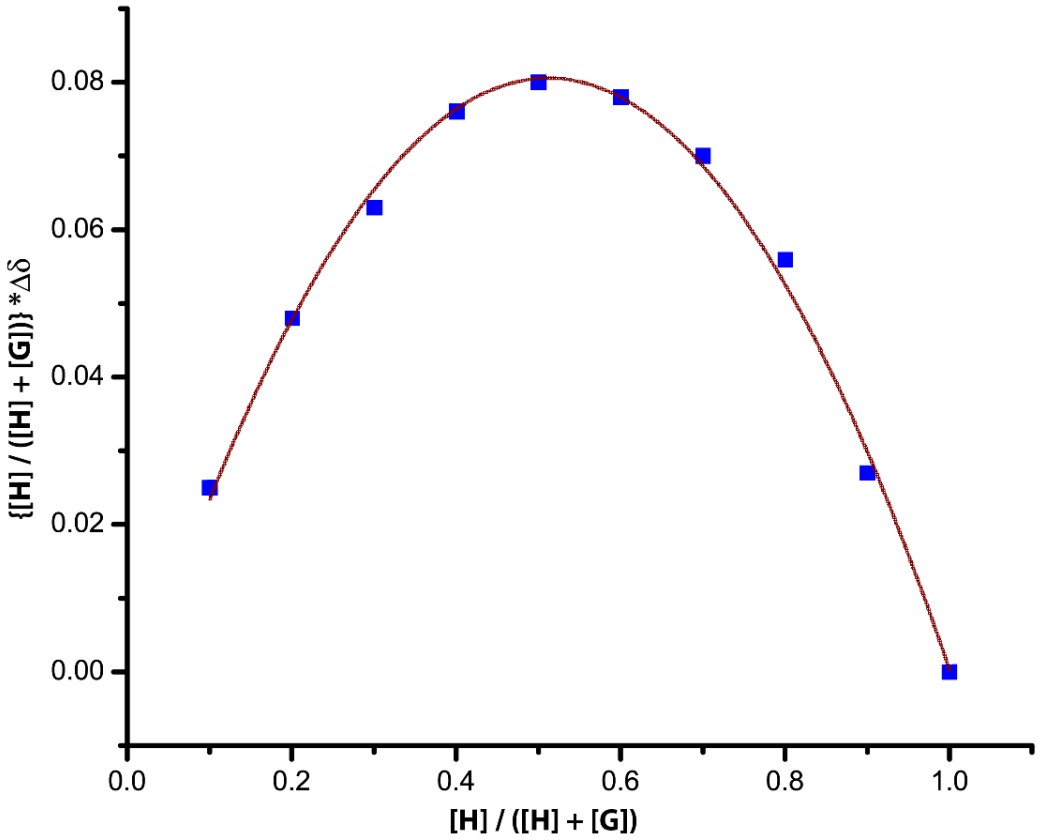


Figure S3: Job's plot for the compound **3** (according to Table S2).

5. Crystallographic Study:

The crystal was obtained by crystallisation of compound **3** in the presence of $Me_4N^+Cl^-$ in DMSO solvent at room temperature.[3] The crystallographic data were recorded by the Bruker Nonius SMART APEX CCD diffractometer equipped with a graphite monochromator and Apex CCD camera using SMART software. All crystallographic data were refined using the software SHELXL-2014/7 and or Olex2 1.2-alpha. The ORTEP diagram was obtained with the help of ORTEP software with 50% thermal ellipsoid. The tetrabutylammonium chloride salt was used as a chloride ion source for co-crystallization with the compound **3** in presence of DMSO solvent. The crystallographic parameters and refinement data were listed in Table S3. All H-atoms are omitted from the ORTEP diagram for clarity.

Table S3: Crystal parameters and refinement data of the anion complex.

Parameters	Compound **3**
Formula	C27 H48 N6 S6, C16 H36 N, Cl, O
Fw	942.98
Crystal system	triclinic
Space group	'P -1'
a/Å	12.8015(8)
b/Å	13.8204(8)
c/Å	16.5396(7)
α/°	67.517(5)
β/°	87.324(4)
γ/°	85.158(5)
V/Å3	2693.8(3)
Z	2
Dc/g cm−3	1.163
μ Mo Kα mm−1	0.341
F000	1024.0
T/K	293(2)
θ max.	25.00
Total no. of reflections	18456
Independent reflections	9485
Parameters refined	557
R1, I > 2σ(I	0.0739
wR2, I > 2σ(I	0.1708
GOF (F2)	1.020
CCDC	1900065

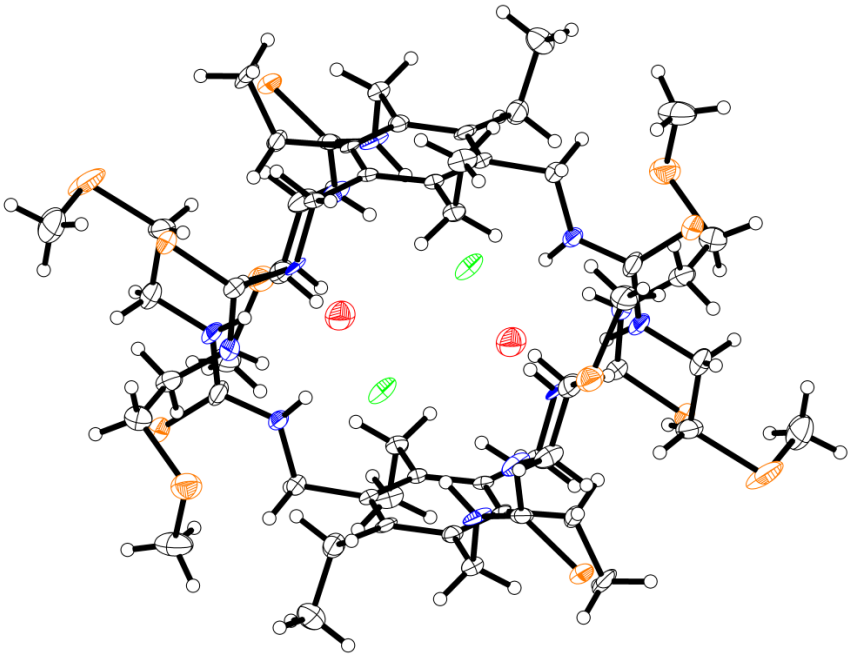


Figure S4: ORTEP diagram of complex **3** (50% thermal ellipsoid plot, H-atoms are omitted for clarity). The TBA^+ cations outside the cavity were omitted for clarity.

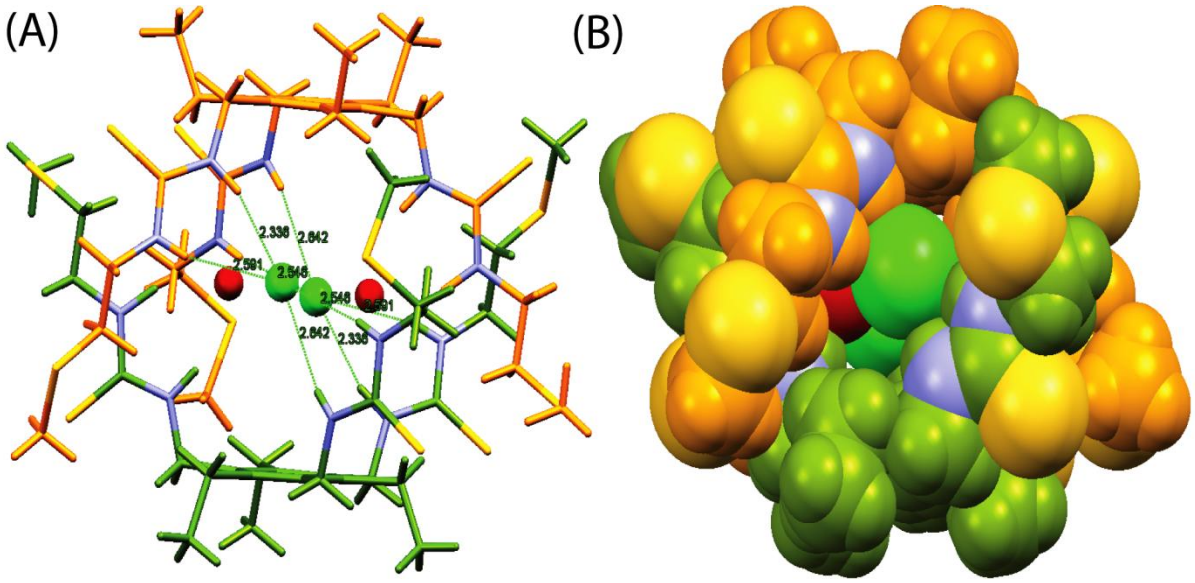


Figure S5: X-ray crystal structure depicting the non-covalent interactions involved in 2 : 2 Cl^- ion encapsulation (capped sticks and spacefill model) by compound **3** ((**3**·Cl^-·$H_2O)_2$), where the green ball represents the chloride ion, red ball represents the water molecules, the purple colour represents the nitrogen atom and yellow colour represents sulphur atom. One molecule of compound **3** is coloured orange and the other is coloured the grey. The TBA^+ cations outside the cavity were omitted for clarity.

6. Ion Transport Activity Studies:

6.1. Ion transport activity studies using fluorescence based assay[7, 9, 10]

6.1.1. ***Preparation of EYPC/CHOL-LUV⊃HPTS*** **—** An appropriate amount of EYPC (stock solution, 50 mg/mL in deacidified $CHCl_3$) and cholesterol (stock solution, 25 mg/mL in deacidified $CHCl_3$) were taken in a clean and dry glass vial so that the molar ratio of EYPC and cholesterol would be 6:4. The solution was then dried under vacuum for minimum 6 hours to remove any remnants of $CHCl_3$ to form a transparent thin film. The dry film was then hydrated with 500 µL of 20 mM HEPES buffer, pH 7.2 containing 100 mM NaCl and 1 mM HPTS. The solution was then kept at room temperature for 1 hour with occasional vortexing (6-7 times). The suspension was further passed through 12-13 cycles of freeze-thaw (freezing with liquid N_2 and melting with lukewarm water respectively) to break up the multilamellar vesicles. After this the suspension was vortexed for the next 15 minutes. The vesicle solution was extruded through a polycarbonate membrane (using a mini-extruder from Avanti Polar Lipids) having pore size of 200 nm (size of LUVs are > 200 nm) for 19/21-times (as it must be an odd number), to give LUVs with a mean diameter of ~200 nm. All the unencapsulated dye from the extravesicular solution was removed using gel filtration technique (Sephadex G-50) and 20 mM HEPES buffer, pH 7.2 containing 100 mM NaCl as the eluting solvent. The final lipid concentration was 25 mM (assuming 100 % lipid regeneration).

6.1.2. ***Ion transport activity across EYPC/CHOL-LUV⊃HPTS***[7, 9, 10] **—**The HPTS fluorescence assay was performed according to the reported procedure. Briefly, in a clean and dry 3 mL fluorescence cuvette, 2890 µL of buffer solution (20 mM HEPES buffer, pH 7.2 containing 100 mM NaCl), 50 µL of 25 mM EYPC/CHOL-LUV⊃HPTS and 50 µL of 0.75 M NaOH were taken and the cuvette was placed in the fluorescence spectrophotometer (Fluoromax-4 spectrofluorometer) under slow stirring condition for approximately 3 minutes. During this time a pH gradient of ~ 0.6 gets generated between the extra and intra-vesicular system. The HPTS fluorescence intensity was monitored (at t = 0 s) at λ_{em} = 510 nm (λ_{ex} = 450 nm). After addition of 10 µL of the compound at t = 50 s, the Cl^- ion transport kinetics was recorded and finally at t = 450 s, the vesicles were lysed by adding 20 µL of 20% Triton X-100 solution. The fluorescence intensity measurement was continued for further 50 s (i.e. up to t = 500 sec).

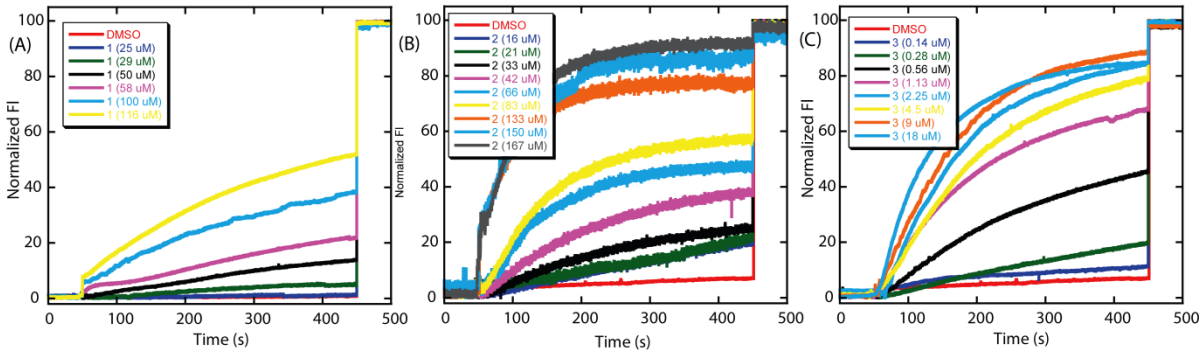


Figure S6. Concentration dependent curves for the compounds **1** (A), **2** (B) and **3**(C). The Cl^- ion transport activity of the compounds were measured across the EYPC/CHOL-LUV⊃HPTS.

6.1.3. ***Quantitative measurement of transport activity from HPTS assay*** [7, 9, 10] **—**The fluorescence emission intensities of the HPTS dye were normalized and the intensities appearing at t = 0 and t = 500 s were taken as 0 and 100 units, respectively. The normalized fluorescent intensities (FI) at t = 450 s (prior to the addition of Triton X-100 solution) were considered to measure the transport activity of the compounds.

$$i.e.\ Transport\ activity,\ \ T_{HPTS} = \frac{F_t - F_0}{(F_\infty - F_0)} \times 100\ \% \qquad \text{..... Eq.-S2}$$

Where, F_t = fluorescence intensity at time t = 450 s, F_0 = fluorescence intensity immediately before the addition of the compound (t = 0 s) and F_∞ = fluorescence intensity after addition of Triton X-100 solution (i.e. at saturation after complete saturation at t = 500 s).

6.1.4. ***Measurement of half maximal effective concentrations (EC_{50}) of compound from HPTS assay*** [7, 9, 10] **—** The fluorescence signals from the HPTS dye were normalized between 0 to 100 units (t = 0 to t = 400 s). The normalized fluorescent intensity (FI) values at t = 450 s (prior to the addition of Triton X-100 solution) were considered as the transport activity of the compound. The transport activity (T) of a compound at a particular concentration was determined by using previous Eq.-S2. To get the effective concentration (EC_{50}) of the compound, the transport activity values were plotted against concentration and fitted using the Hill equation (Eq.-S3).

$$T = T_{\infty} + \frac{T_0 - T_{\infty}}{\left[1 + \left(\frac{c}{EC_{50}}\right)^n\right]} \quad \ldots\ldots \text{Eq.} -\text{S3}$$

Here, T_0 and T_∞ correspond to the transport activity obtained in the absence and at excess concentration of the compound, respectively. *c* = Concentration of the compound. EC_{50} value corresponds to the concentration of compound required to obtain half of the maximum transport activity. The number of molecules required for the transportation of a single ion is given by 'n' and it is the Hill coefficient for the compound.

6.2. *Ion transport activity studies using ion selective electrode based assay*

6.2.1. *Chloride ion efflux studies using chloride ion selective electrode (chloride-ISE)* —

The extent of chloride ion efflux by the compounds from the LUVs was measured using a chloride ion selective electrode (chloride ISE from Thermo Scientific™ Orion™). The chloride–ISE was calibrated prior to each experiment with standard 1 ppm, 10 ppm and 100 ppm of aqueous NaCl solution. The Cl^- ion concentration (ppm) appearing in the display of the ion meter was set in the continuous mode for the time-dependent measurements.

6.2.2. ***Preparation of EYPC/CHOL-LUV*** — The large unilamellar vesicles (LUVs) were prepared by mixing appropriate amount of EYPC (stock solution, 50 mg/mL in deacidified $CHCl_3$) and cholesterol (stock solution, 25 mg/mL in deacidified $CHCl_3$) in a clean and dry glass vial in the molar ratio of 6:4. The solution was dried under vacuum for minimum 6 hours to remove any remnants of $CHCl_3$ and to form a transparent thin film. The dry film was then hydrated with 500 µL buffer (5 mM phosphate and 100 mM NaCl, pH 7.2). It was then kept at room temperature for 1 hour with occasional vortexing (6-7 times). The suspension was further passed through 12-13 cycles of freeze-thaw (freezing with liquid N_2 and melting with lukewarm water respectively) to break up the multilamellar vesicles. After this the suspension was vortexed for the next 15 minutes. The vesicle solution was extruded through a polycarbonate membrane (using a mini-extruder from Avanti Polar Lipids) having pore size of 200 nm (size of LUVs are > 200 nm) for 19/21-times (as it must be an odd number), to give LUVs with a mean diameter of ~200 nm. The unilamellar vesicles were dialyzed with 5 mM phosphate buffer at pH 7.2 containing 100 mM $NaNO_3$ (iso-osmolar with 100 mM NaCl buffer) to remove the extravesicular NaCl solution. The LUVs were then collected and the

final volume adjusted to 500 µL with 5 mM phosphate buffer at pH 7.2 containing 100 mM $NaNO_3$. The final lipid concentration was 25 mM (assuming 100 % lipid regeneration).

6.2.3. ***Chloride efflux study across EYPC/CHOL-LUVs*** **—** To measure the extent of chloride efflux using ISE, the EYPC/CHOL-LUVs (50 µL) and 5 mM phosphate buffer at pH 7.2, containing 100 mM $NaNO_3$ (3940 µL) were taken in a clean and dry glass vial and kept under mild stirring condition while the glass electrode was immersed into the solution. To initiate the Cl^- ion transport kinetics at t = 50 s, 10 µL of the synthetic compound was added into the stirring solution and the readings were noted from the ion meter. After 5 minutes, the vesicles were lysed using 50 µL of 20% Triton X-100 solution. The total Cl^- ion efflux reading was taken at 7 minutes (allowing complete disruption of the LUVs). The initial reading was considered as 0% Cl^- ion efflux and the final reading at 7 min was considered as 100% Cl^- ion efflux.

6.2.4. ***Quantitative measurement of transport activity from chloride-ISE assay*** **—** The Cl^- ion efflux efficiency of the compounds were normalized and the Cl^- ion efflux appearing at t = 0 and t = 700 s were taken as 0 and 100 units, respectively. The normalized chloride efflux efficiencies (EE) at t = 500 s (prior to the addition of Triton X-100 solution) were considered for the measurement of chloride transport efficiency of the compounds-

$$i.e.\ Chloride\ efflux\ efficiency,\ \ EE_{Chloride} = \frac{EE_t - EE_0}{(EE_\infty - EE_0)} \times 100\ \% \qquad \text{..... Eq.-S1}$$

Where, EE_t = Cl^- ion efflux efficiency at t = 500 s (prior to the addition of Triton X-100 solution), EE_0 = Cl^- ion efflux efficiency immediately before the addition of the compounds (t = 0 s) and EE_∞ = Cl^- ion efflux efficiency after addition of Triton X-100 solution (i.e. at saturation after complete leakage at t = 700 s).

The differences in the Cl^- ion transport activities of the compounds between the HPTS and ISE based assays could be due to the concentration differences of the compounds used for both the assay.

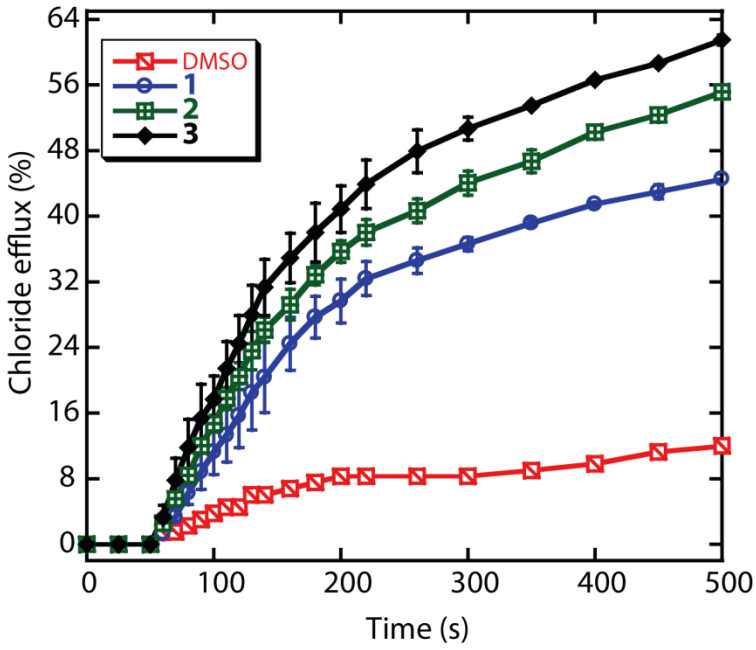


Figure S7. Transmembrane Cl^- ion transport activity of the compounds (**1-3**, Compound concentration = 18 μM) across the EYPC/CHOL-LUVs as measured by chloride-ion selective electrode at pH 7.2.

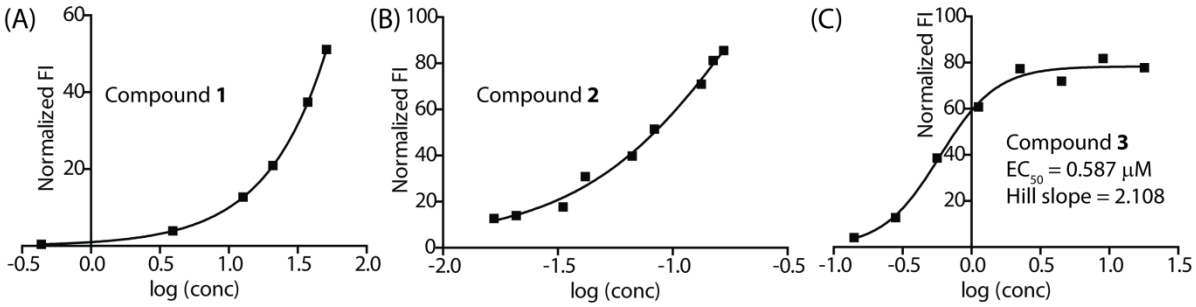


Figure S8. Concentration dependent Cl^- ion transport activity of the compounds across the EYPC/CHOL-LUV⊃HPTS. Dose-response plot of Cl^- ion transport activity of the compounds at 450 sec (after the addition of the compounds). The effect solvent on the transport activities was corrected. The EC_{50} values of compounds **1** and **2** cannot be measured because of the aggregation formation at higher concentrations.

7. Ion Selectivity Studies using HPTS Assay with Applied pH Gradient:

7.1. ***Buffer and stock solution preparation*** **—** Required amount of HEPES buffer and MCl or Na_xA salt (LiCl, NaCl, KCl, $CaCl_2$, $MgCl_2$, NaBr, NaI, $NaNO_3$, and $NaClO_4$) were added and dissolved in Milli-Q water to attain a buffer composition of 20 mM HEPES buffer pH 7.2, containing 100 mM of the respective salt (MCl or Na_xA).

7.2. ***EYPC/CHOL-LUV⊃HPTS preparation*** **—** The EYPC/CHOL-LUV⊃HPTS were prepared following a similar procedure as in section 6.1.1.

7.3. ***Anion selectivity studies***[7, 9, 10] **—** For the HPTS fluorescence assay, in a clean and dry 3 mL fluorescence cuvette buffer solution (2890 µL of 20 mM HEPES buffer pH 7.2, containing 100 mM Na_xA, pH = 7.2, where A = Cl^-, Br^-, I^-, NO_3^-, and ClO_4^-), 50 µL of 25 mM EYPC/CHOL-LUV⊃HPTS and 50 µL of 0.75 M NaOH were taken and the cuvette was placed in the fluorescence spectrophotometer under slow stirring condition for approximately 3 minutes. During this time period a pH gradient of ~ 0.6 gets generated between the extra and intra-vesicular system. The HPTS fluorescence intensity was monitored (at t = 0 s) at λ_{em} = 510 nm (λ_{ex} = 450 nm). After addition of 10 µL of the respective compound at t = 50 s, the Cl^- ion transport kinetics was recorded and finally at t = 450 s, the vesicles were lysed by adding 20 µL of 20% Triton X-100 solution. The fluorescence intensity measurement was continued for further 50 s.

7.4. ***Cation selectivity studies***[7, 9, 10] **—** For cation selectivity assay a similar procedure was followed as reported in section 7.3. Here, 20 mM HEPES buffer pH 7.2, containing 100 mM MCl (where M = Li^+, Na^+, K^+, Ca^{2+}, and Mg^{2+}) was used. In this experimental condition no difference in Cl^- ion transport activity was observed for the cations.

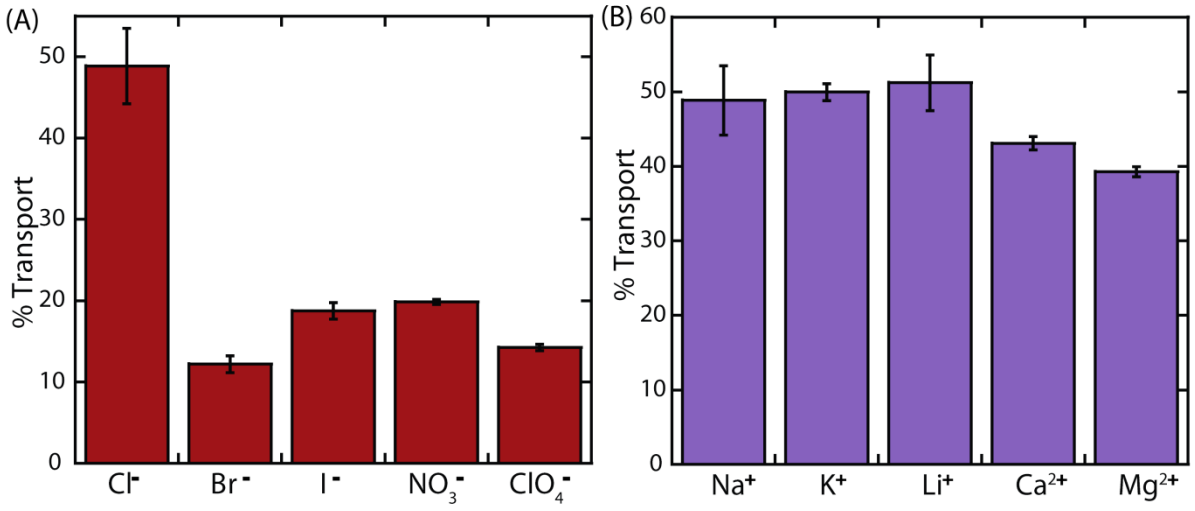


Figure S9. Anion (A) and cation (B) selectivity of compound **3** as measured by HPTS-based fluorescence assay in the presence of a pH gradient of ~0.6.

8. Evidence for the Mechanistic Pathway for Chloride Ion Transport[7, 9, 10]

8.1. ***Preferential ion selectivity assay using FCCP*** **—** The LUVs were prepared by following a similar procedure as discussed in the section 6.1.1. For this assay, 2890 µL of buffer solution (20 mM HEPES buffer, pH 7.2 containing 100 mM NaCl), 50 µL of 25 mM EYPC/CHOL-LUV⊃HPTS and 50 µL of 0.75 M NaOH were taken in a clean and dry fluorescence cuvette and the cuvette was placed in the fluorescence spectrophotometer under slow stirring condition for approximately 3 minutes. During this time a pH gradient of ~ 0.6 gets generated between the extra and intra-vesicular system. The HPTS fluorescence intensity was monitored (at t = 0 s) at λ_{em} = 510 nm (λ_{ex} = 450 nm). The time-dependent Cl^- ion transport activities were measured in the presence of compound (8 µL), and/or FCCP (2 µL from 1.5 µM stock solution). The kinetics measurements were initiated at t = 50 s and finally at t = 450 s, the vesicles were lysed by adding 20 µL of 20% Triton X-100 solution. The fluorescence intensity measurement was continued for further 50 s. To investigate whether the anionophore is transporting H^+ the assay was done both in presence and in absence of FCCP (2 µL of DMSO was used in place of 2 µL of FCCP in the latter case).

8.2. ***Preferential ion selectivity assay using valinomycin*** **—** The LUVs were prepared by following a similar procedure as discussed in the section 6.1.1. In this assay 20 mM HEPES buffer, pH 7.2 containing 100 mM KCl was used as the extravesicular buffer. To investigate the preferential ion selectivity, 2890 µL of buffer solution (20 mM HEPES buffer, pH 7.2 containing 100 mM KCl), 50 µL of 25 mM EYPC/CHOL-LUV⊃HPTS and 50 µL of 0.75 M NaOH were taken in a clean and dry fluorescence cuvette and the cuvette was placed in the fluorescence spectrophotometer under slow stirring condition for approximately 3 minutes. During this time a pH gradient of ~ 0.6 gets generated between the extra and intra-vesicular system. The HPTS fluorescence intensity was monitored (at t = 0 s) at λ_{em} = 510 nm (λ_{ex} = 450 nm). After addition of 8 µL of the compound and 2 µL of valinomycin (2.0 pM) at t = 50 s, the kinetics was initiated and finally at t = 450 s, the vesicles were lysed by adding 20 µL of 20% Triton X-100 solution. The fluorescence intensity measurement was continued for further 50 s. The data was recorded once using valinomycin and again in absence of valinomycin (2 µL of valinomycin was replaced with 2 µL of DMSO in the latter case).

8.3. ***Evidence for mobile carrier mechanism***

8.3.1. Cholesterol dependency assay[7] **—** The LUVs were prepared according to the procedure mentioned in 5.1.2. by varying the molar ratios of EYPC and cholesterol as 6:4, 8:2 and 10:0 to delve into the fact whether increasing the cholesterol concentration in preparing the vesicles (cholesterol is known to increase the rigidity of the lipid bilayer) has any effect on the Cl^- ion transport activity of the compound. The chloride transport activity of the compound was measured using ISE. In case of a mobile carrier the transport activity was anticipated to decrease on increasing the molar ratio of cholesterol (increasing cholesterol slows the diffusion process) while for an ion channel mechanistic pathway no difference in transport activity should be there. For this assay similar procedure as described in section 6.2.3 was followed using three compositions of liposomes. No significant change was observed in the chloride ion transport activity indicating mobile carrier mechanism being followed by the compound.

8.3.2. U-tube experiment **—** The 'U-tube' experiment was performed to confirm the mechanistic pathway for the Cl^- ion transport. The lipid bilayer was mimicked here by using nitrobenzene as the organic layer. First, compound (0.2 mM) and $TBA^+PF_6^-$ (2 mM) were dissolved in nitrobenzene (16 mL) and placed in a U-tube (1.5 cm cone with 15 cm arm length). The $TBA^+PF_6^-$ (2 mM) was used to provide a counter anion for the transportation of Cl^- ion. In the source end 8 mL of 5 mM phosphate buffer at pH 7.2 containing 489 mM NaCl was used. In the receiver end 10 mL of 5 mM phosphate buffer at pH 7.2 containing 489 mM $NaNO_3$ was used. The organic phase was stirred gently using a magnetic stirrer and the Cl^- ion concentration of the receiver end was monitored using a chloride ion selective electrode.

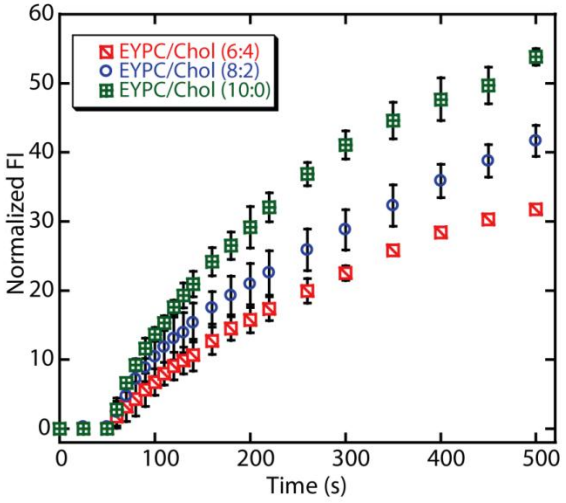


Figure S10. Effect of the concentration of cholesterol in the EYPC/cholesterol membrane on Cl^- ion transport activity of compound **3**.

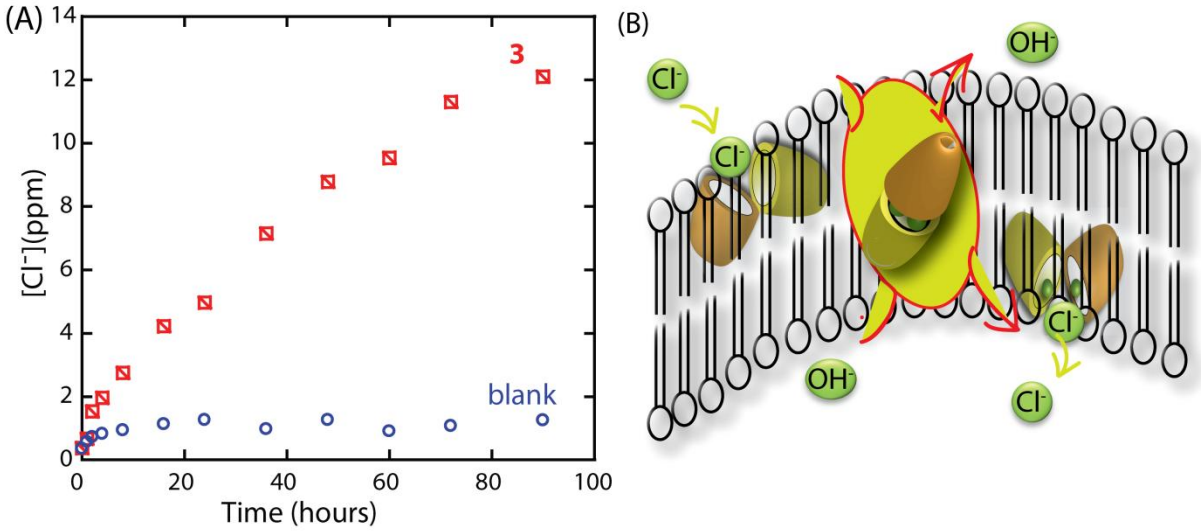


Figure S11. Measurement of the Cl^- ion transport efficacy by U-tube assay in the presence of compound **3**, using a chloride ISE and NaCl gradient (A). Schematic representation to illustrate the transport of Cl^- ion via carrier mechanism (B).

8.4. ***Test for the leaching-out of the compounds from the membrane bilayer environment*** [7]**—** To confirm that these synthetic compounds reside in the EYPV/CHOL membrane bilayer and do not come out in the aqueous solution over the period of time, leaching test was performed. It is hypothesized that if the compounds leached out from the membrane bilayer environment to the aqueous medium then transport rate of the compounds will be greatly affected (reduced) by the dilution of the vesicular solution. Whereas dilution factor will not affect the transport rate if the compounds are localized inside the bilayer environment. For

this assay, various concentrations of EYPC/CHOL-LUV⊃HPTS and the buffer solution (20 mM HEPES and 100 mM NaCl, pH 7.2, final concentration of the vesicles were 300 µM, 400 µM, 500 µM and 600 µM respectively in each case) and 50 µL of 0.75 M NaOH were taken in a clean and dry 3 mL fluorescence cuvette which was placed in a slow stirring condition for about 3 minutes followed by addition of the compound (10 µL from the DMSO stock solution to maintain a fixed anionophore/lipid ratio in all cases) at t = 50 s. The HPTS fluorescence intensity was monitored (at t = 0 s) at λ_{em} = 510 nm (λ_{ex} = 450 nm). Finally at t = 450 s, the vesicles were lysed by adding 20 µL of 20% Triton X-100 solution. The fluorescence intensity measurement was continued for further 50 s. The results confirm that the compound remains in the lipid bilayer during the course of all our experiments.

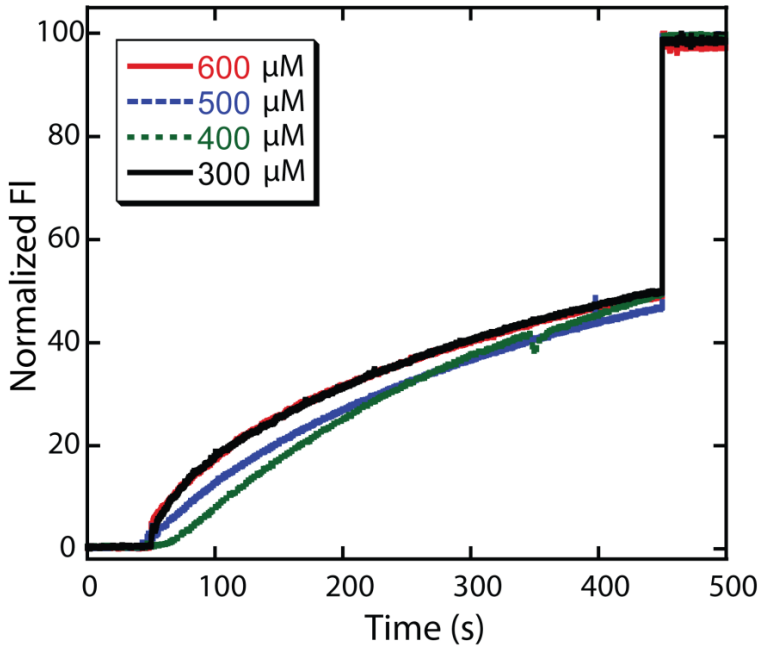


Figure S12. Leaching experiment of compound **3** (at compound to lipid ratio of 0.142 mol%).

9. Evidence of Vesicle Stability in the Presence of the Compounds:

Calcein leakage assay[7] **—** The vesicles were prepared according to the method described in section 6.1.1, with the exception that in this assay 50 mM calcein was used for the vesicle preparation (instead of 1 mM HPTS). For this assay, 2940 µL of buffer (20 mM HEPES buffer and 34 mM Na_2SO_4) and 50 µL of 25 mM EYPC/CHOL-LUV⊃calcein were taken in a clean and dry fluorescence cuvette and kept under a slow stirring condition for about 3 minutes. The calcein fluorescence intensity was monitored (t = 0 s) at 520 nm (λ_{ex} = 490 nm).

After t = 50 s, compound (4 mol%) was added and the change in calcein fluorescence intensity were monitored using the fluorescence spectrophotometer. Finally the vesicles were lysed by adding 50 µL of 20% Triton X-100 solution to the cuvette and the fluorescence measurement was carried out for further 50 s. The result shows that the synthetic compound didn't cause any disruption of the vesicles during the various assays performed (the vesicles were stable during the experimental conditions) and that no large channels were being formed in the EYPC/CHOL membrane, hence our transporter behave as a mobile carrier.

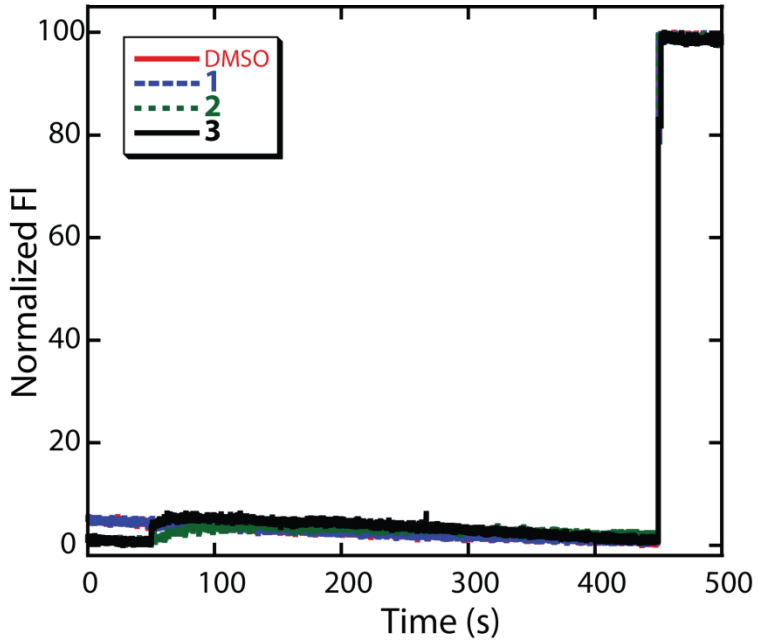


Figure S13. Extent of calcein leakage from the EYPC/CHOL-LUV⊃calcein in the presence of compounds. After time t = 50, DMSO solutions of compound or DMSO (blank) was added and the fluorescence intensity (λ_{ex} = 490 nm, λ_{em} = 520 nm) was recorded. After t = 450 sec the LUVs were lysed using triton X-100.

The leaching test confirmed the membrane localization of the compound (Figure S12). The non-leaky property of the calcein dye from the vesicles in the absence or presence of compounds confirms the integrity of the vesicles (Figure S13).

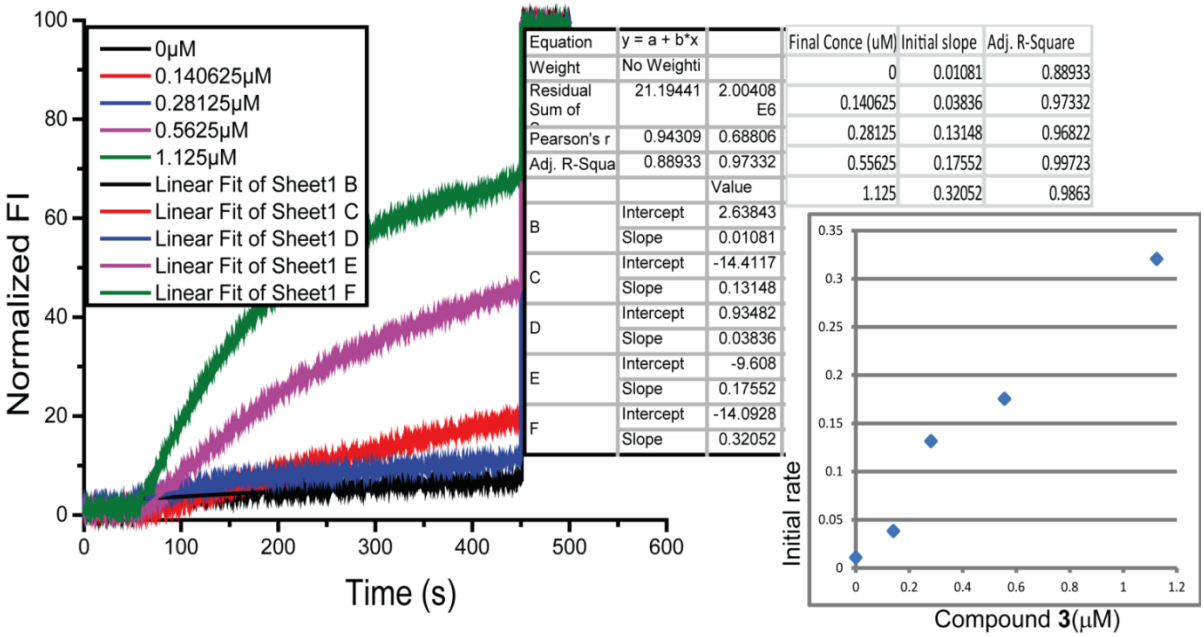


Figure S14. Calculation of the initial slope from the concentration dependent transport activities of compound **3.** Plot of the initial rates of Cl^- ion transport activities at different concentrations of compound **3.**

Table S4. Aqueous solubility of the selected compounds.

Compound Code	Aqueous solubility (mg/mL)
3	insoluble[a]
5	2.0
6	3.3
7	4.0
8	2.5
9	3.3

[a]insoluble in 1 mL water.

10. Regeneration of the Active Transporter by Dealkyation of the Proanionophores:

The tetrafluoroboratesulfonium salt **7** (1 mM) was dissolved in 10 mM PBS, pH 7.4 containing 10 mM reduced glutathione (GSH) and the mixture was incubated in 37 °C. At different time points, an aliquot of the reaction solution was removed and monitored by HPLC analysis. The aliquot was dissolved in methanol before its injection to the analytical HPLC (Waters 600E HPLC) system. The Hypersil GOLD™ C18 Selectivity LC Column and a UV-detector (214 nm) was used for the analysis. Methanol/water gradient (70%

methanol and 30% water) was used as the mobile phase at a flow rate of 1.0 mL/minute for 20 minutes run time. Regeneration of lead compound and reduction of sulfonium compound were analysed by inbuilt software and confirmed by ES-MS (ESI+).

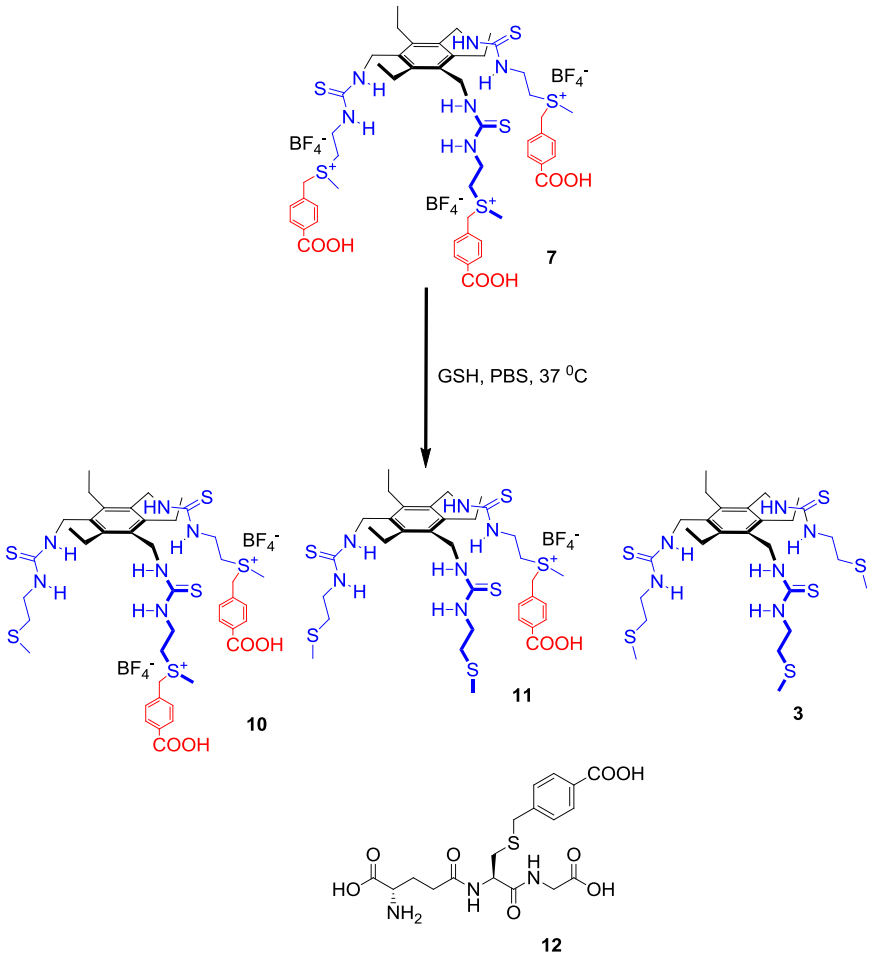


Figure S15. Reaction of compound **7** in the presence of GSH in PBS at 37 ºC. Regeneration of compound **3** and formation of mono- (**10**) and di-dealkylated (**11**) intermediates and GSH derivative (**12**).

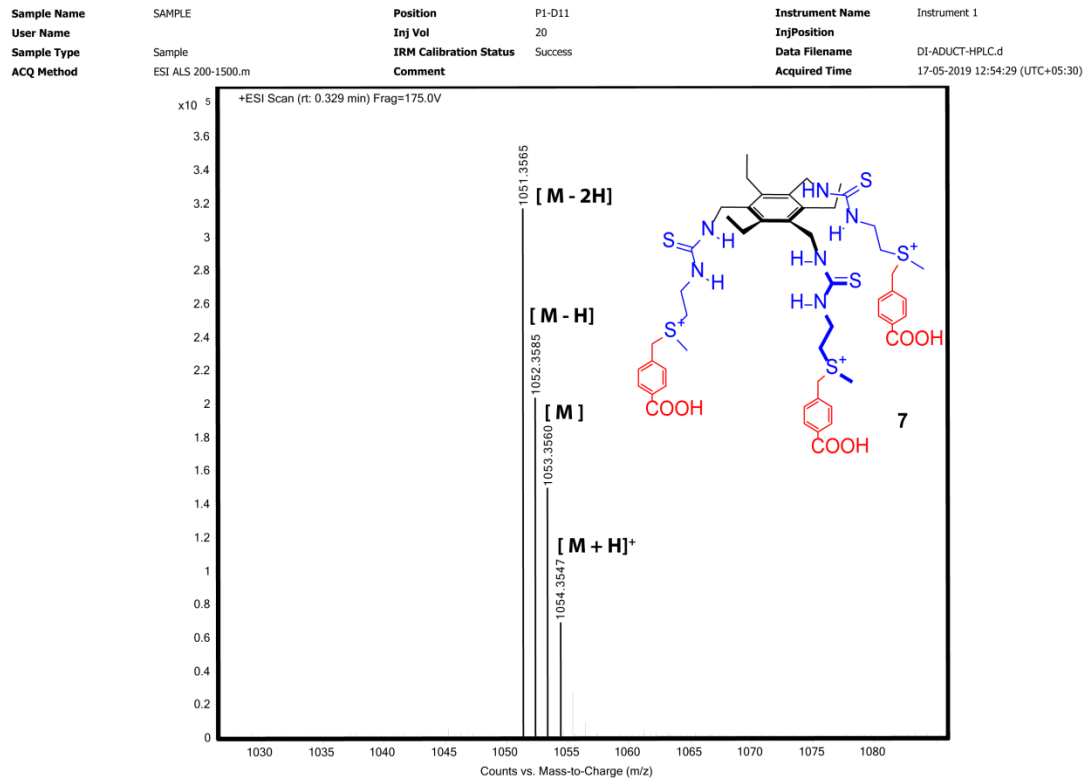
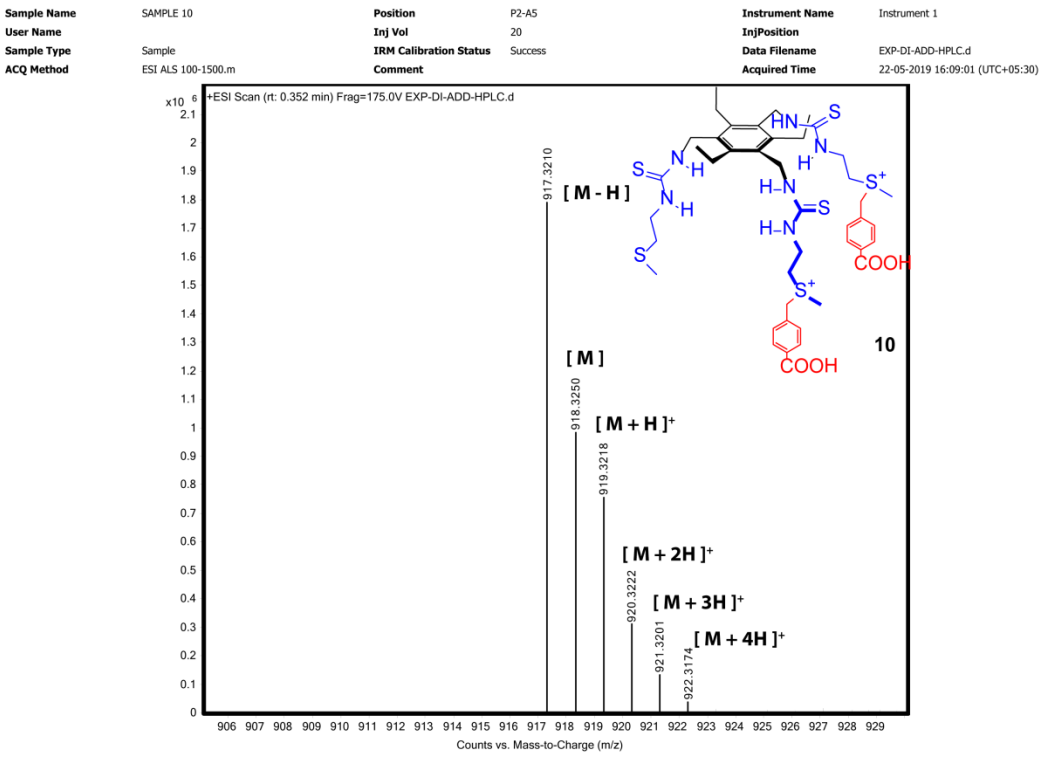


Figure S16. Mass spectral signals of compounds **7** and **11** (in water) after separation by HPLC analyses.



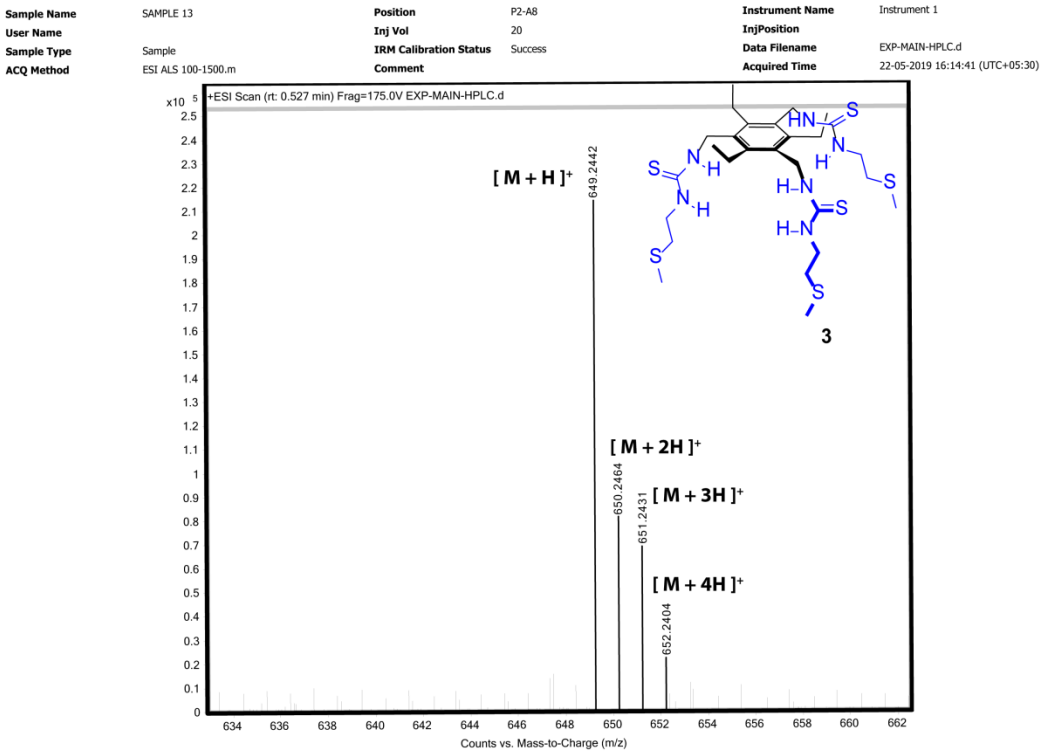


Figure S17. Mass spectral signals of compounds **10** and **3** (in water) after separation by HPLC analyses.

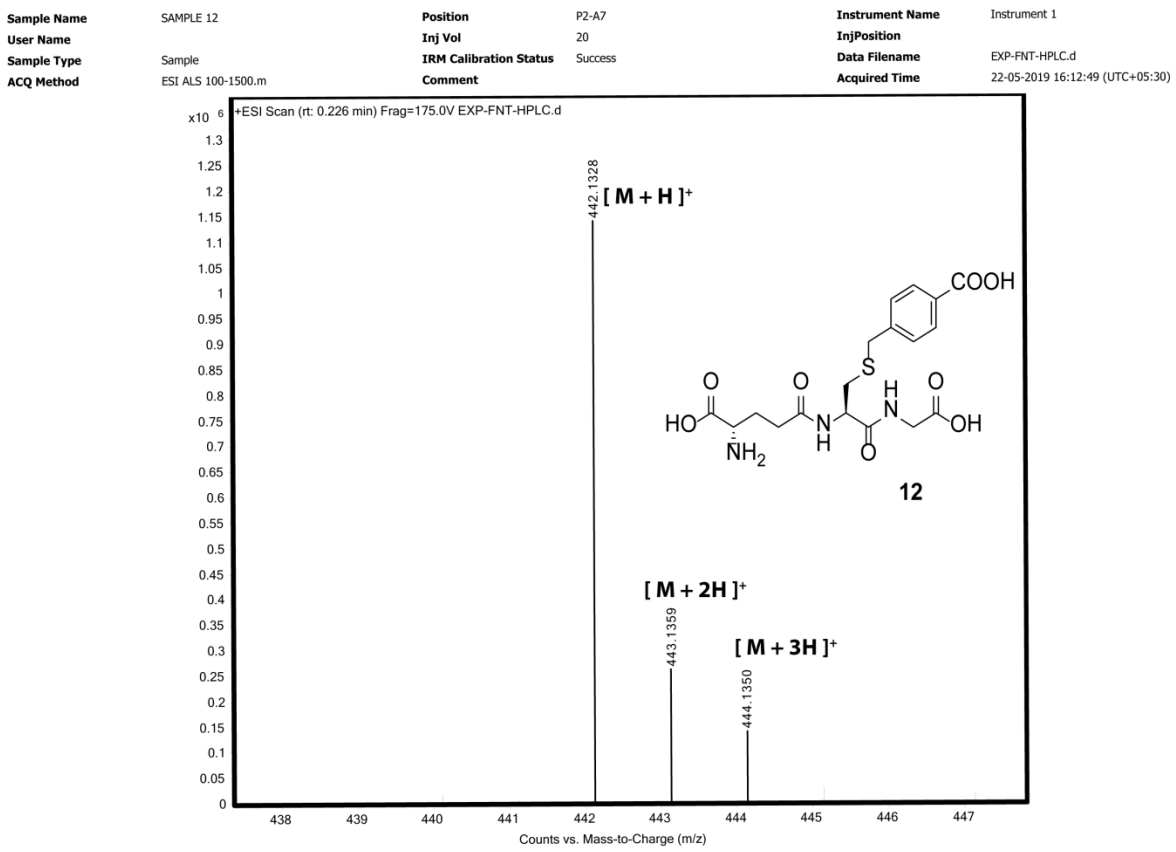


Figure S18. Mass spectral signals of GSH derivative, **12** in water (from reaction mixture).

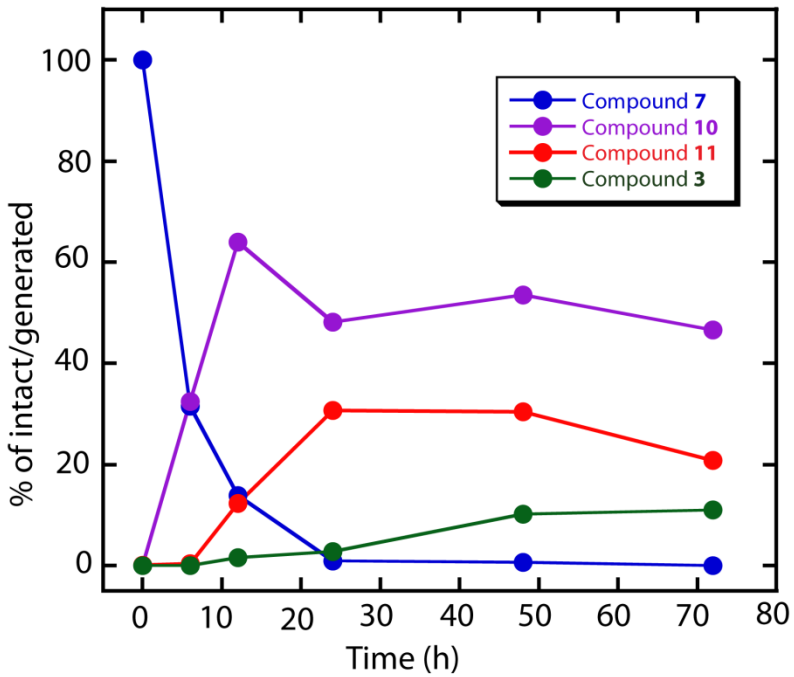


Figure S19. Plot of dealkylated compounds at different time intervals.

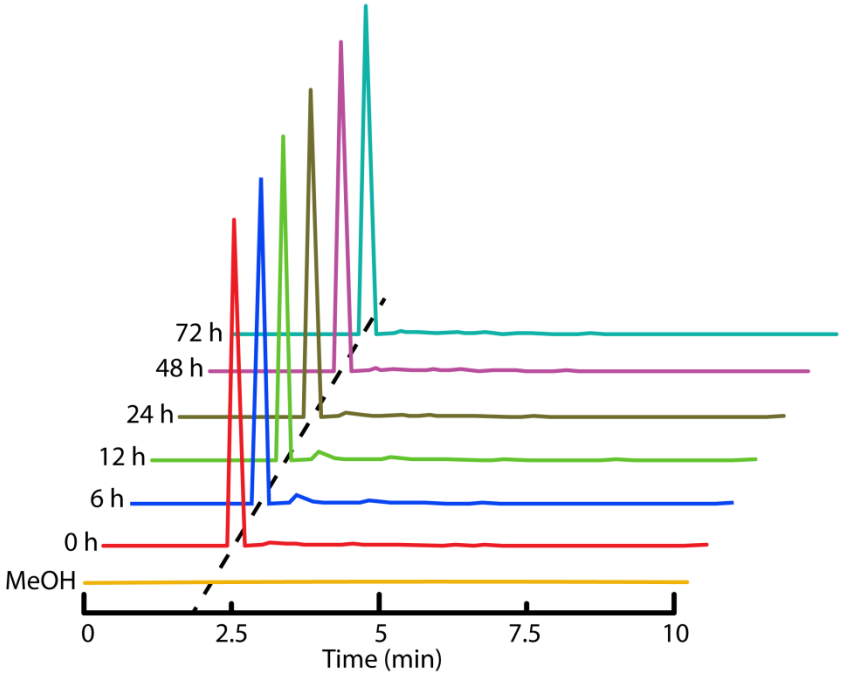


Figure S20. HPLC traces of compound **7** at different time intervals in the absence of GSH.

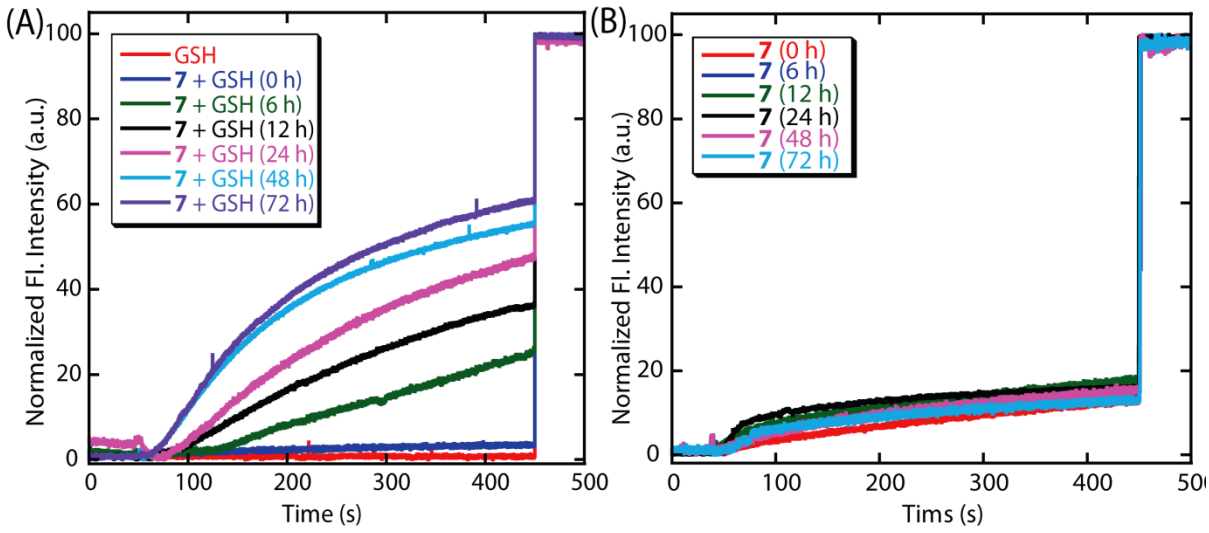


Figure S21. Transport of Cl^- ion by the regenerated compound **3** in the presence of GSH at different time intervals (A). Transport of Cl^- ion by the compound **7** in the absence of GSH at different time intervals (B).

11. Biological Activities of the Compounds:

11.1. MTT-based cytotoxicity assay[7] – HeLa, BHK-21 and MDCK cells were seeded in a 96-well flat bottom tissue culture plates at a density of 10^4 cells/well (per 100 µL) in Dulbecco's modified Eagle medium (DMEM) containing 10% fetal bovine serum (FBS). The cells were incubated in three different plate at 37 °C and 5% CO_2 for 16 h. The media was discarded and

each well was washed with PBS. The compounds were added with media to each well in different concentrations (0, 5, 10, 20, 40, and 80 µM) and incubated. At every 24 hours intervals, MTT solution (10 µL of 5 mg MTT/mL of PBS) was added in each plate and cells were incubated for 4 hours. MTT containing media was removed from each well and 100 µL of DMSO was added (in each well) to dissolve the formazan crystals. The absorbance was recorded in a microplate reader (Multiskan™ GO) at the wavelength of 570 nm. All experiments were performed in triplicate, and the relative cell viability (%) was expressed as a percentage relative to the untreated cells.

11.2. Measurement Cl^- transport in the presence of the compounds[9] **–** Transport of Cl^- ion in presence of compound into the HeLa cell was measured by using chloride selective cell permeable fluorescent dye *N*- (ethoxycarbonylmethyl)-6 methoxyquinolinium bromide (MQAE). Cells were seeded in a 96-well flat bottom tissue culture treated plates at density of 10^4 cells/well (per 100 µL) and incubated at 37 °C, and 5% CO_2 for 16 hours. The plain DMEM with MQAE dye added to each well by maintaining final concentration as 5 mM for 4 hours. Cells were washed with PBS to remove the extracellular dye and compound was added in plain DMEM at three different concentrations (10 and 20 µM) and incubate for 4 hours then visualized a fluorescence microscope (Thermo Fisher Scientific) using a blue channel.

***11.3. Cellular uptake of the compounds* –** The uptake of NBD-tagged compounds was also investigated under the cellular environment. The HeLa cells were seeded on cover slip and incubate for 16 hours at 37 °C and 5% CO_2. After the incubation period the media was removed and washed three-times with PBS. The NBD-tagged compounds were added at 50 and 100 µM concentrations, and incubated for additional 4 hours. The cells were then washed three-times with PBS and fixation was performed with 4% formaldehyde at room temperature for 10 minutes. After that, cells were washed 3-4 times and the slides were prepared for microscopic (both confocal and fluorescence) analyses

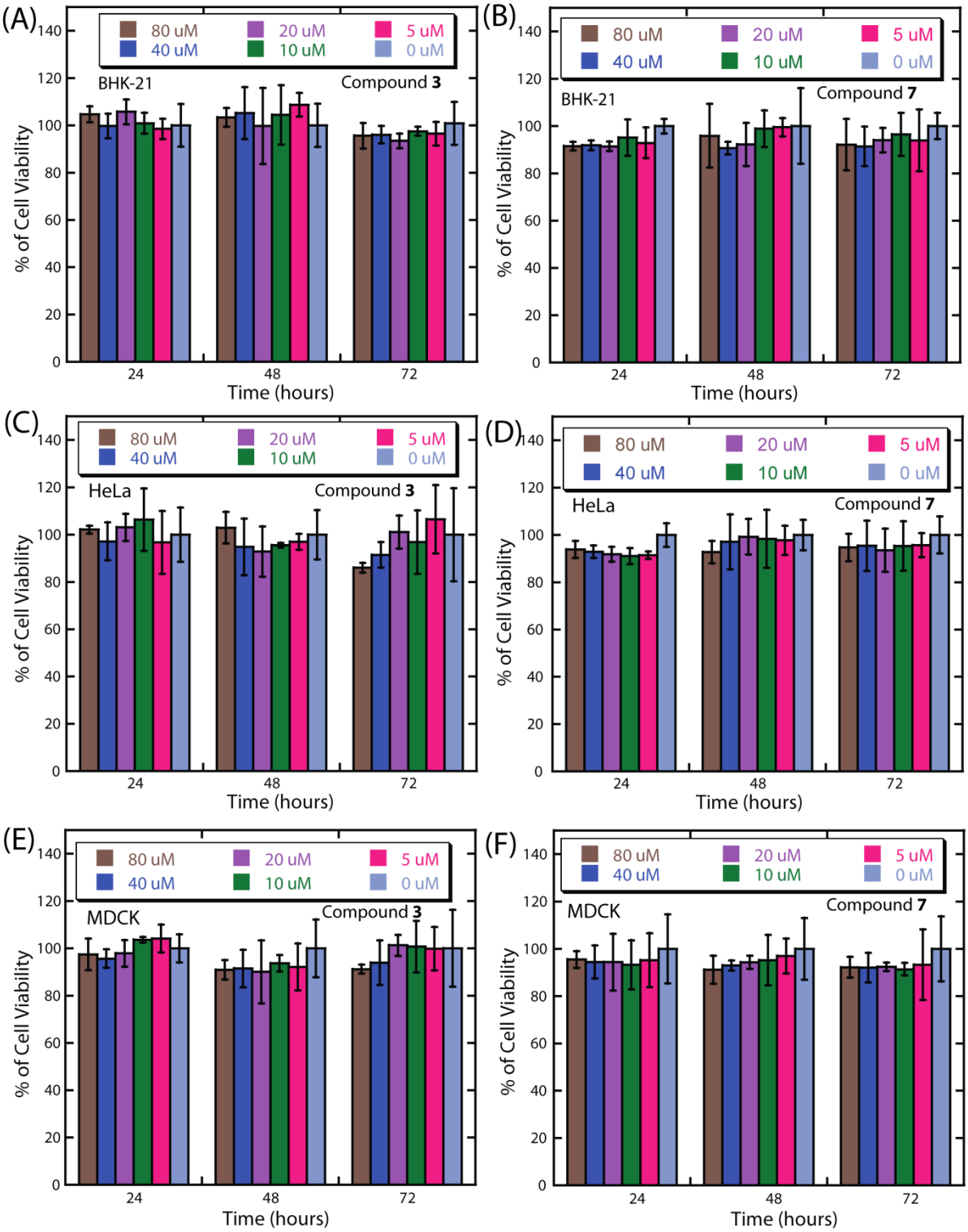


Figure S22. Cell viability of the compounds **3** and **7** was measured at different concentrations of 0-80 µM. Cell viability was measured in BHK-21, HeLa and MDCK cells after 24, 48 and 72 hours of compound treatment. All experiments were performed in triplicates.

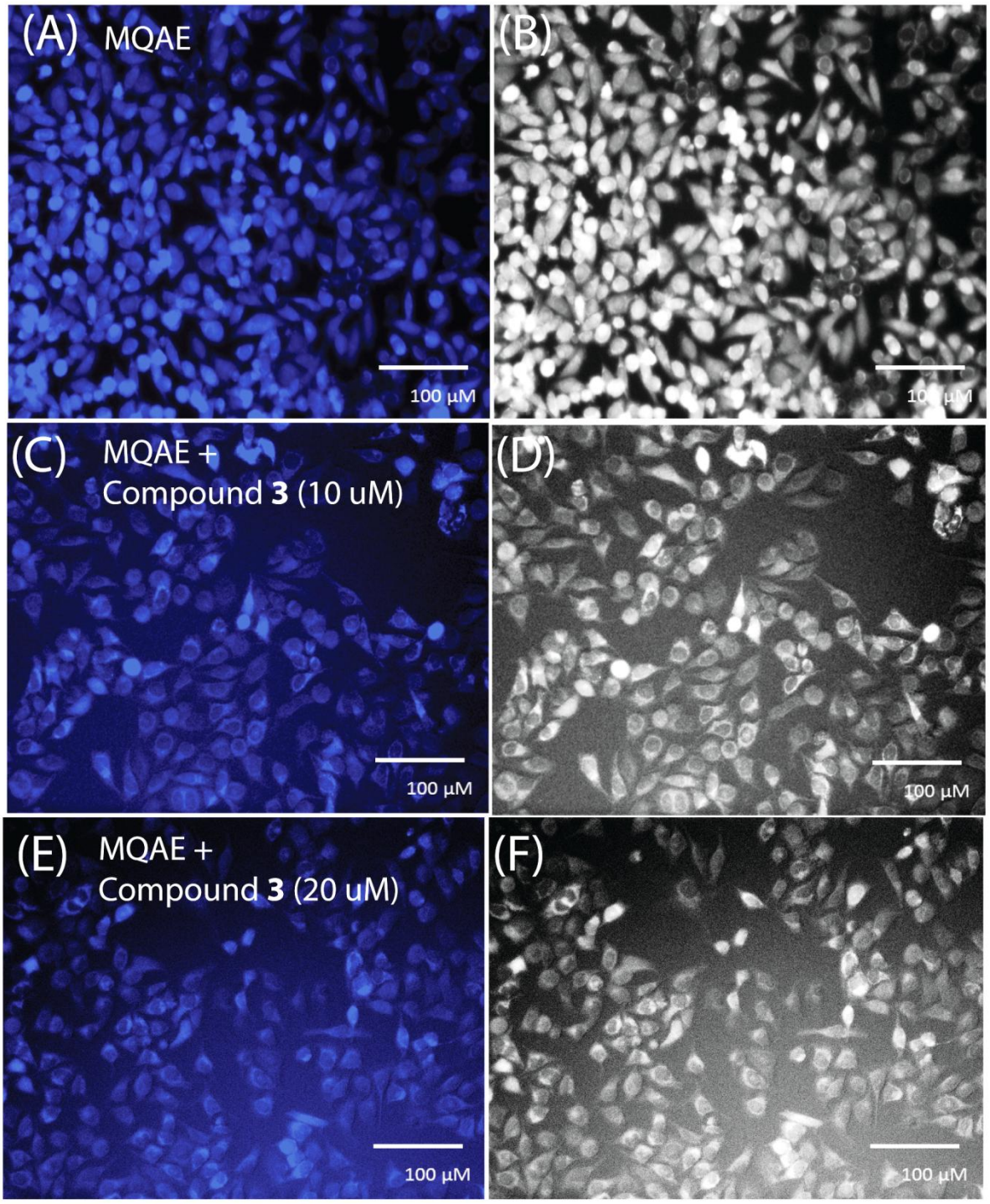


Figure S23. Fluorescence microscopic images of the MQAE dye (λ_{ex} = 350 nm and λ_{em} = 460 nm) labelled HeLa cells in the absence and presence of the compound **3**. Both blue channel (A, C and E) and grey channel (B, D and F) illustrate the fluorescence intensity of the MQAE dye in the absence and presence of the compound **3**.

12. Transport of Chloride Ion across Giant Unilamellar Vesicles (GUVs):

12.1. Preparation of GUVs[11] ─ In a clean and dry glass vial EYPC, cholesterol and DPPS (from the respective stock solution) were taken in the molar ratio of 6:3.5:0.5 and dried under vacuum for 6 hours. To that lipid film, 200 µL of light liquid paraffin oil was added and the mixture was sonicated for 30 minutes; until the lipid film gets fully dissolved in the paraffin oil. After that, 20 µL of the upper buffer (100 mM HEPES, 200 mM sucrose, 1 mM 8-hydroxypyrene-1,3,6-trisulfonic acid (HPTS) in H_2O, pH = 7.4) was added and the solution was mixed thoroughly to form an emulsion. The emulsion was then carefully added to 500 µL of lower buffer (100 mM HEPES, 200 mM glucose in H_2O, pH = 7.4) in a centrifuge tube and the whole mixture was pipetted up and down thoroughly to mix everything. The emulsion was centrifuged for 15 minutes at 10000 rpm to remove the oil as well as the extravehicular free dye. This process was repeated for 4-5 times to remove maximum amount of the paraffin oil from the solution. The final pellet (dense solution containing the GUVs) was mixed with 100 µL of lower buffer (final vesicle conc. of 15 mM).

12.2. Ion transport measurements using GUVs coated on the glass surface ─ The coated glass surface was prepared by following the reported method with minor modifications. In an acid washed glass vial, *N*-(3,4-dihydroxyphenethyl)palmitamide and DPPS solutions were taken in the molar ratio of 1:4 and dried under reduced pressure for 6 hours to remove any traces of organic solvents. The lipid mixture was then dissolved in 0.1 mL of THF/water (9:1 v/v) and the solution was added to 0.9 mL of 5 mM PBS buffer, pH 5.6 (final conc. of 0.2 mM). The solution was then sonicated for 5 minutes. The prepared vesicle solution was directly used for the glass coating. The vesicle solution was drop casted on the surface of a glass bottom disk and incubated for overnight at 37 °C. Finally, the substrate was washed by HEPES buffer thoroughly.

The prepared GUV solution (100 µL) and compound **3** were added on the hydrophobic coated glass bottom dish**.** The GUVs were allowed to settle down for 5 hours. After that, NaCl solution (0.1 M) was added. The images were recorded (in a Nikon ECLIPSE Ts2R fluorescence microscope) before and after the addition of NaCl in the green as well as in the bright field channel to ensure the integrity of the GUVs and quenching of HPTS fluorescence intensity. Here the decay of the HPTS fluorescence intensity is due to Cl^- influx and consequently OH^- efflux (as compound follow OH^-/Cl^- antiport mechanism for its chloride transport activity).

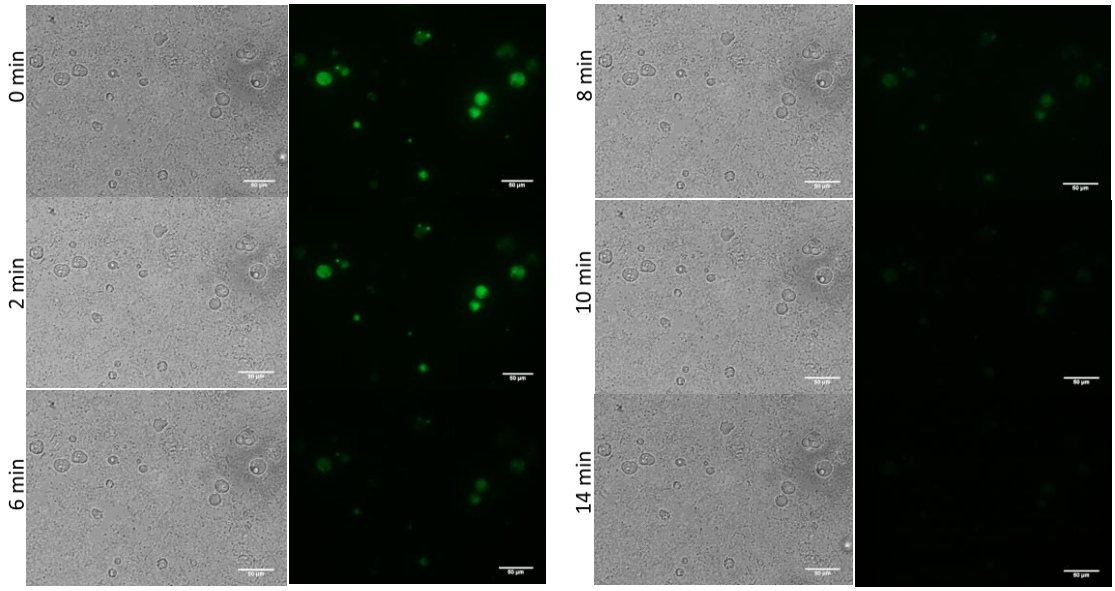


Figure S24. Fluorescence microscopic images of the HPTS loaded GUVs were recorded at different time intervals (0, 2, 10, 20, and 30 minutes), after the addition of compound **3** and NaCl (0.1 M). The change in integrity of the GUVs and encapsulated HPTS fluorescence intensity were monitored using bright-field and green channels, respectively.

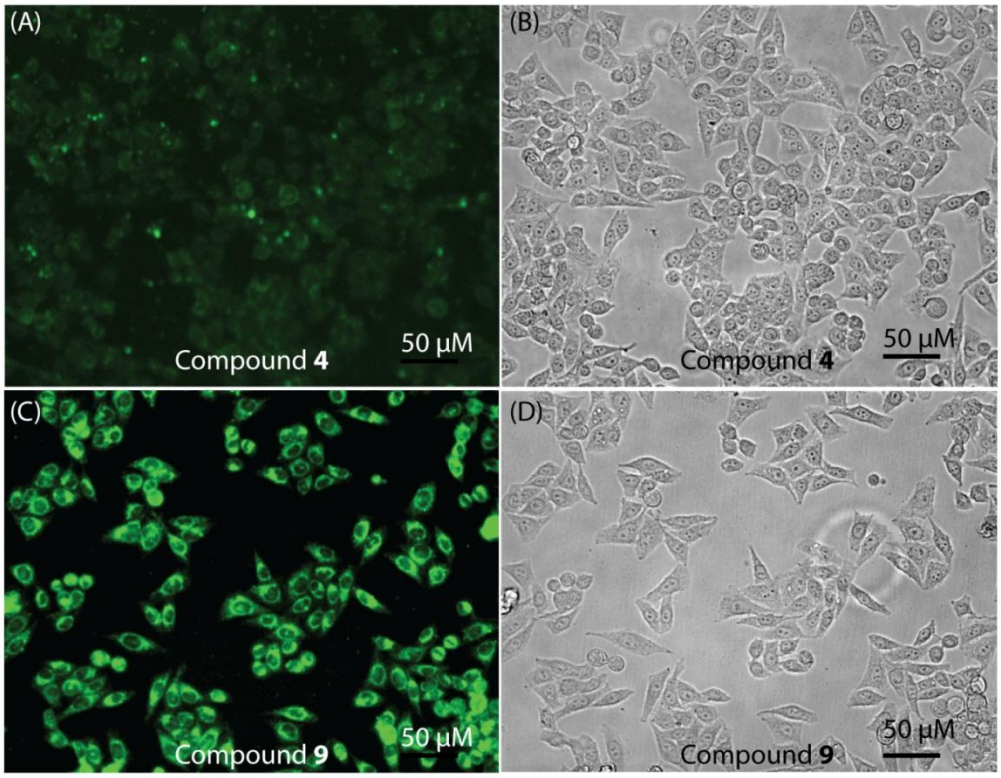


Figure S25. Fluorescence microscopic images of the HeLa cells treated with NBD-labelled compounds **4** and **9**. Green channel illustrating compound uptake, bright field illustrating the cell morphology.

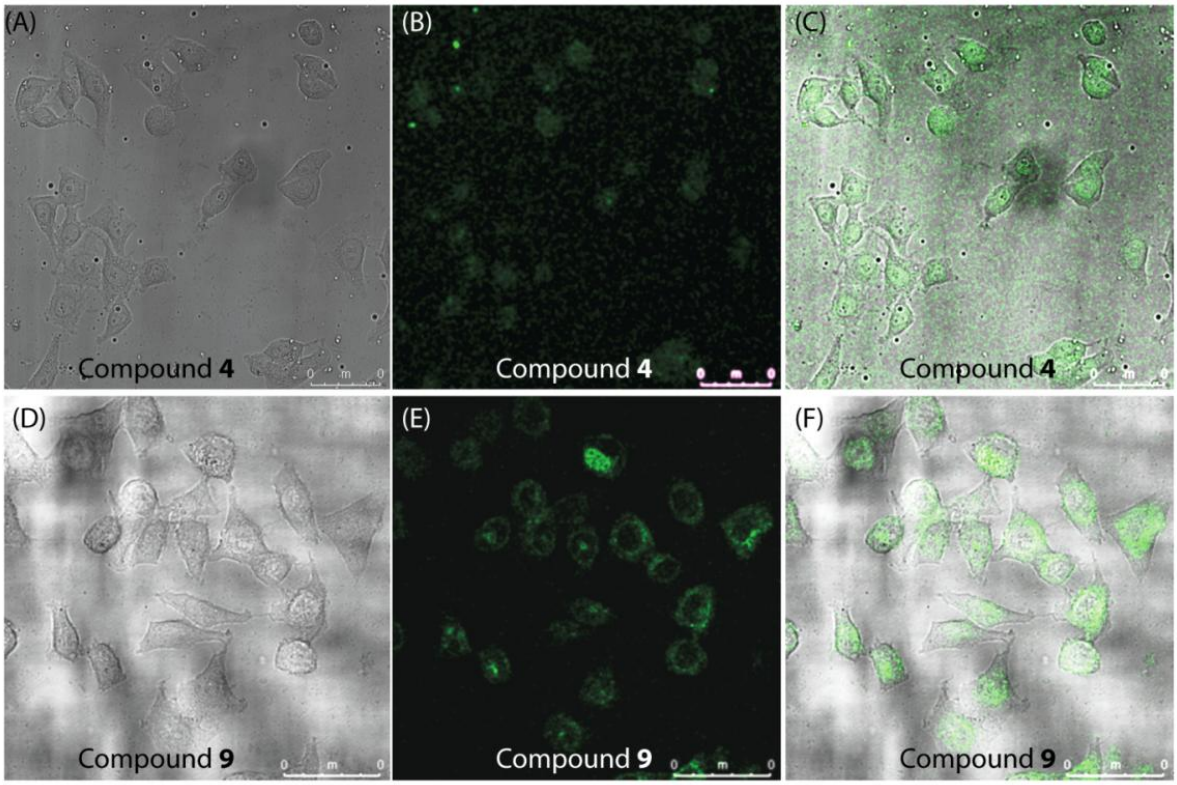
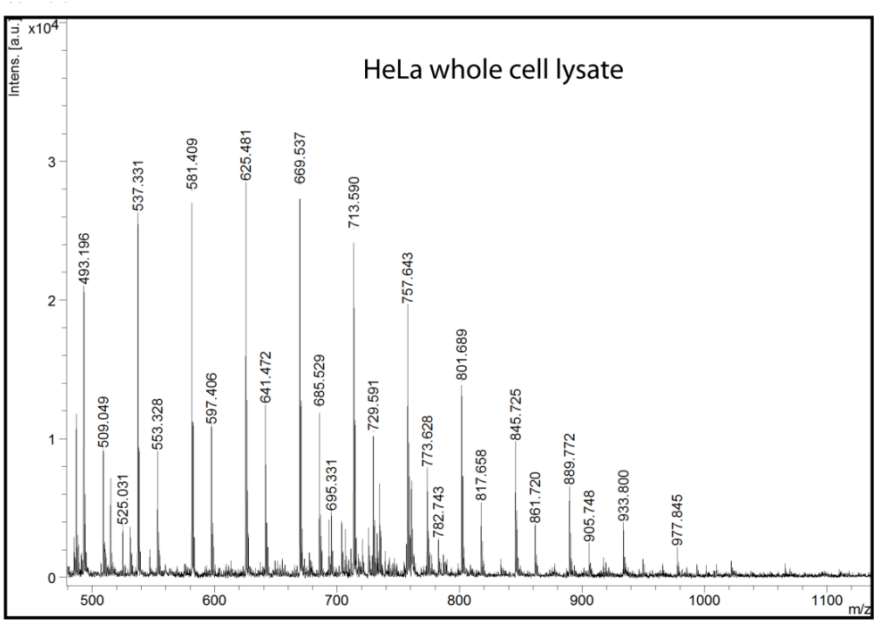


Figure S26. Confocal microscopic images of the HeLa cells treated with NBD-labelled compounds **4** and **9**. Green channel illustrating compound uptake, bright field illustrating the cell morphology, merge of green and bright field channels illustrating cell morphology in the presence of NBD-labelled compounds.

13. Regeneration of Anionophore from Proanionophore under Cellular Environments: HeLa cells were been cultured in T25 culture flasks containing Dulbecco's Modified Eagle's Medium (DMEM) (Gibco) along with 10% fetal bovine serum (FBS), 1% L-glutamine, 1% penicillin/streptomycin, and 1% pyruvate (Gibco), maintaining at 37 °C in a humidified atmosphere with 5% CO_2. Cells were re-cultured and maintained for further study. The cells are counted using trypan blue stain using Countess II FL Automated Cell counter (Thermo Fisher Scientific). In order to examine the effect of GSH and GSH inhibitor, 5×10^6 cells/well were seeded onto six well plate and maintained in DMEM media containing 10% FBS. After 12 h the cells were washed twice with PBS and treated with external GSH (10 mM) and GSH inhibitor (1 mM) in serum free media for 12 h, after incubation period GSH and GSH inhibitor were aspirated and replaced with media containing 2%FBS. After 72 h the media was aspirated and washed twice with PBS. The cells were harvested by centrifugation at 480g for 10 min. The cell pellet were washed twice with ice-cold PBS and kept on ice. The pellets

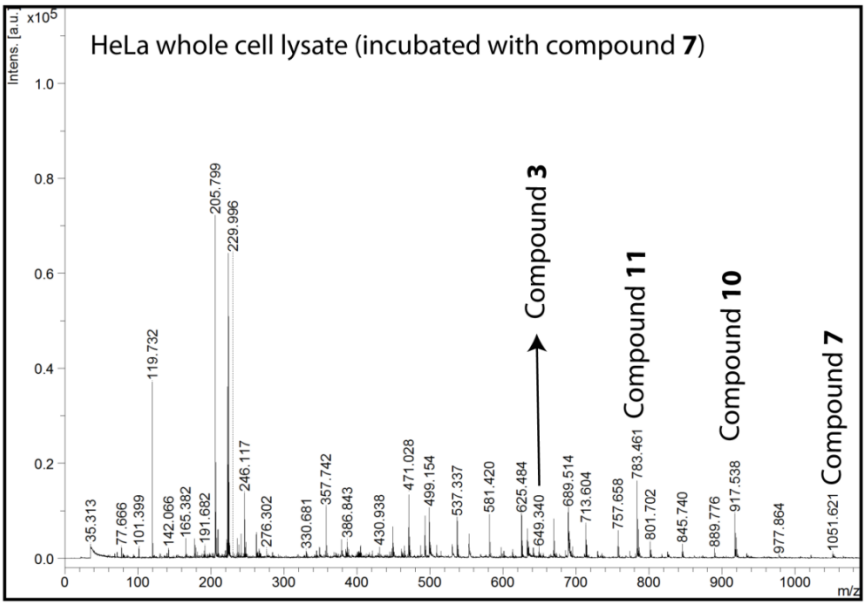
were re-suspended in 1 mL of the lysis buffer (150 mM NaCl + 50mM Tris-Cl (pH 7.4) and incubated in ice for 15 min. The lysate was centrifuged at 20,000g for 10 min at 4^0C. The supernatant was removed carefully in a fresh tube and the samples were used for further experiments.

Later, matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry (Autoflex speed, Bruker, Germany) analysis was carried out to conform the formation of aninophore and intermediates. The HeLa cell lysates were mixed with matrix (Sinapinic acid) as 1:1 ratio for the MALDI-TOF analysis.



m/z	S/N	Quality Fac.	Res.	Intens.	Area
485.016	8	302	2873	2825	716
487.025	32	1797	3249	11467	2556
493.196	48	883	1484	17277	8038
509.049	26	824	2042	9219	3877
515.053	19	3403	2626	6915	2072
525.031	9	1005	3036	3182	896
531.064	11	1641	2418	3815	1361
537.331	73	25420	3120	26031	6917
553.328	25	2796	3263	9008	2350
581.409	78	81170	3105	27822	8241
597.406	31	2325	3371	10945	2984
625.481	81	93332	3165	28572	9161
641.472	36	8349	3667	12546	3551
669.537	83	33897	3440	28278	9265
685.529	36	11289	3758	12226	3686
693.325	12	2301	3793	4191	1262
695.331	13	1593	3665	4373	1359
703.722	12	3622	3237	4054	1485
706.698	10	4045	3495	3443	1141
711.297	6	274	3532	2103	783
713.590	75	47064	3544	25049	8726
720.735	8	1778	3508	2639	966
725.703	11	639	3836	3636	1234
729.591	32	11961	3851	10447	3333
732.711	9	473	3068	2866	1190
734.736	20	2560	3707	6555	2221
756.682	6	39.3	4345	1995	677
757.643	60	13964	3715	19227	7072
760.750	20	764	2927	6282	3099
773.628	25	8510	4153	7825	2623
782.743	8	621	4096	2433	856
801.689	46	28599	4007	14069	5181
817.658	18	3445	4760	5294	1718
845.725	33	17357	4256	9381	3604
861.720	12	1659	4488	3400	1225
889.772	24	7609	4526	6375	2459
905.748	8	798	4999	2058	728
933.800	14	972	4528	3346	1461
977.845	9	874	4485	2030	938

Figure S27. MALDI-TOF mass spectral analysis of HeLa whole cell lysate.



m/z	S/N	Quality Fac.	Res.	Intens.	Area
35.313	26	169	95.5	2624	1142
36.861	17	298	29.2	2173	2470
38.678	9	144	58.4	1328	657
39.683	7	190	41.7	1220	841
71.592	9	845	900	1155	111
77.666	16	3539	1019	2028	181
101.399	17	3807	1767	2225	156
119.732	282	77594	1982	37225	2717
129.786	6	267	1513	841	88.7
140.031	7	303	1296	954	141
142.066	13	325	1996	1784	147
165.382	26	1982	2401	3861	333
177.524	25	4050	2379	3838	340
178.541	12	317	2483	1956	161
179.563	12	352	2682	1944	149
181.572	7	274	3302	1129	83.4
190.679	7	377	1310	1206	232
191.682	15	943	2321	2398	240
205.799	434	173230	2107	71376	9125
206.818	78	15871	3158	12963	1091
209.616	35	14158	1543	5923	1049
219.945	9	144	3166	1528	122
221.935	22	274	2709	3682	373
222.948	212	30792	2457	35737	4144
223.964	359	129645	2314	60571	7622
224.988	58	6581	3280	9847	883
229.996	6	359	2167	1104	152
236.059	23	1536	2683	3971	439
238.092	15	703	2502	2636	306
241.304	29	7702	3087	5057	505
246.117	77	29118	2818	13406	1528
248.138	17	1550	2717	3037	378
262.190	32	12260	2746	5579	743
264.247	7	302	2318	1208	175
266.261	10	181	3282	1892	201
276.302	6	207	1622	1135	268
330.681	6	80.7	2164	1207	227
344.692	8	310	4160	1576	182
348.766	11	301	2913	2221	369

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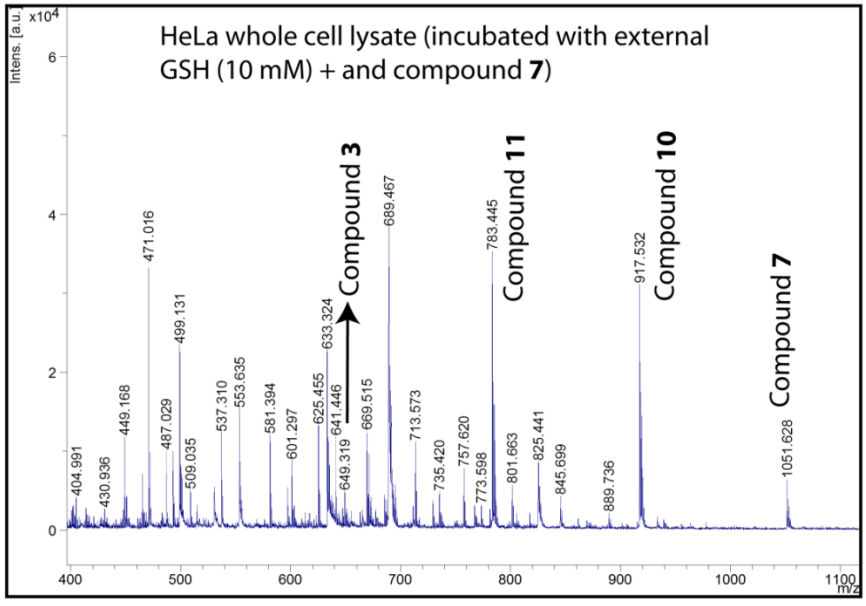
Figure S28. MALDI-TOF mass spectral analysis of HeLa whole cell lysate. The HeLa cells were incubated with compound **7** (50 μM).



m/z	S/N	Quality Fac.	Res.	Intens.	Area
71.588	67	12465	1467	6243	372
77.670	57	8840	1703	5447	285
94.047	53	6553	1928	5599	308
96.083	23	6745	2075	2455	136
110.359	19	3232	2210	2299	130
119.721	77	42935	2002	9792	704
122.608	20	10037	1740	2579	222
138.833	20	5829	1716	3093	305
142.056	12	2545	2222	1903	151
149.122	14	2366	2188	2360	208
155.040	11	1248	1897	1964	192
165.368	22	6742	2063	4105	424
177.509	24	5622	2012	5167	584
179.543	9	265	1834	2029	247
181.578	10	282	2239	2163	208
191.670	13	895	2566	3009	283
197.794	31	1911	2442	7435	790
199.823	10	322	2601	2394	239
205.789	336	174602	1823	83490	12559
206.802	68	14958	2361	16980	1952
209.610	26	6270	1412	6653	1279
209.879	41	10222	3007	10310	890
210.902	13	729	4131	3475	224
212.938	9	1538	2770	2504	245
214.977	19	1710	2403	5076	602
221.914	18	891	2342	4877	636
222.932	162	42123	2259	42827	5647
223.950	248	84337	2061	65480	9590
224.969	45	5711	2474	11909	1483
236.049	13	2619	2368	3618	460
238.073	14	1042	2909	3962	406
241.288	581	184050	3180	161208	16244
246.103	82	30973	2430	23199	3191
248.129	13	1526	1973	3841	657
252.243	6	433	4599	1976	134
262.179	38	25615	2867	11231	1415
267.369	65	24593	4042	19456	1644
284.340	12	880	1916	3796	698
330.694	8	98.8	3766	2698	289

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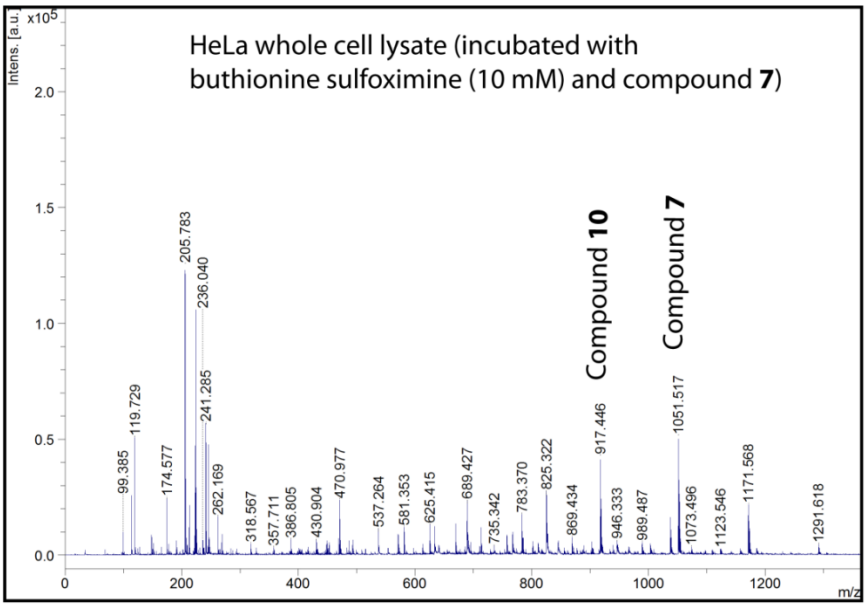
Figure S29. MALDI-TOF mass spectral analysis of HeLa whole cell lysate. The HeLa cells were incubated with external GSH (10 mM) and compound **7** (50 μM).



m/z	S/N	Quality Fac.	Res.	Intens.	Area
99.385	92	85418	1615	10076	727
113.685	202	46563	1890	25234	1806
119.729	384	102444	1832	50722	3922
124.864	19	3967	1775	2604	215
127.945	24	4396	2071	3380	253
148.195	53	13836	2236	8601	686
150.218	15	644	1942	2429	216
151.266	29	6337	1820	4754	479
165.374	17	1477	1848	3019	358
174.577	125	36452	2493	24014	2042
177.564	24	437	1130	4610	841
190.757	29	6692	2055	5902	666
191.669	16	1793	2267	3293	373
201.897	10	187	2103	2208	254
205.783	571	189999	2064	125576	16223
206.805	98	17521	2786	21590	2002
209.600	17	2497	1363	3922	802
212.964	94	25963	2492	20975	2237
221.912	36	3283	2684	8398	899
222.928	196	29159	2603	45366	4948
223.945	439	105728	2344	101336	12506
224.964	81	15743	3176	18904	1797
231.103	12	877	1909	2863	433
236.040	29	2643	2574	6847	805
238.066	14	835	2186	3275	469
241.285	235	170884	2742	56202	6486
245.067	16	742	2633	3987	515
246.089	197	111856	2684	47371	5754
262.169	67	55770	3116	16570	1759
266.255	9	329	3149	2199	219
268.213	23	6656	2779	5698	719
269.348	36	6279	2822	9053	1091
284.305	11	991	2057	2696	493
294.401	10	815	2329	2443	439
318.567	19	3858	3096	5009	690
327.610	10	409	2924	2742	388
357.711	12	1652	2990	3246	529
386.805	23	8993	3310	6575	1054
400.833	9	1481	3741	2597	398

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Figure S30. MALDI-TOF mass spectral analysis of HeLa whole cell lysate. The HeLa cells were incubated with buthionine sulfoximine (BSO; 1 mM) and compound **7** (50 μM).

14. **NMR- Spectra of the Synthesized Compounds**

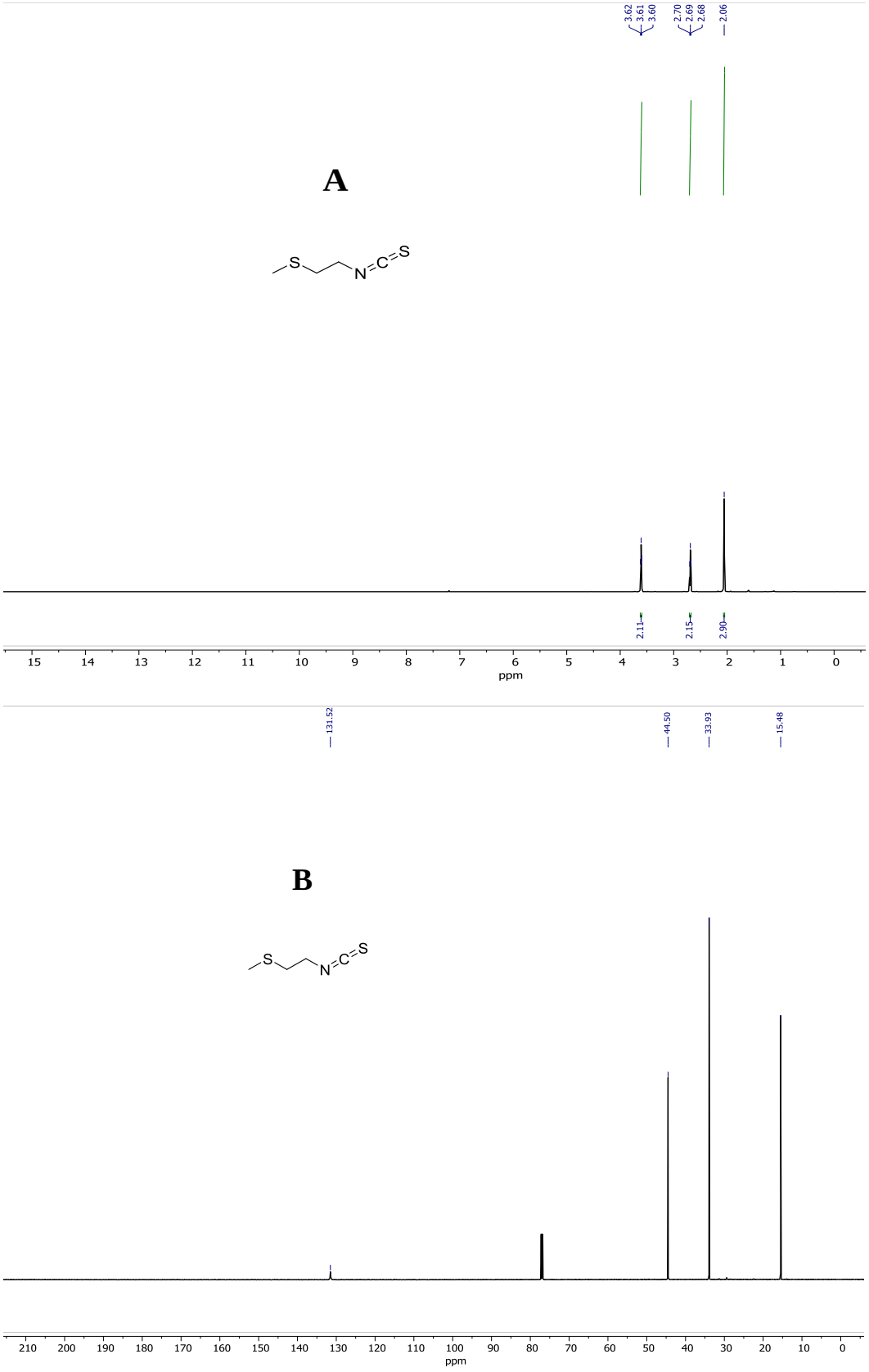


Figure S31: ^{1}H NMR (A) and ^{13}C NMR (B) spectra of (2-isothiocyanatoethyl)(methyl)sulfane.

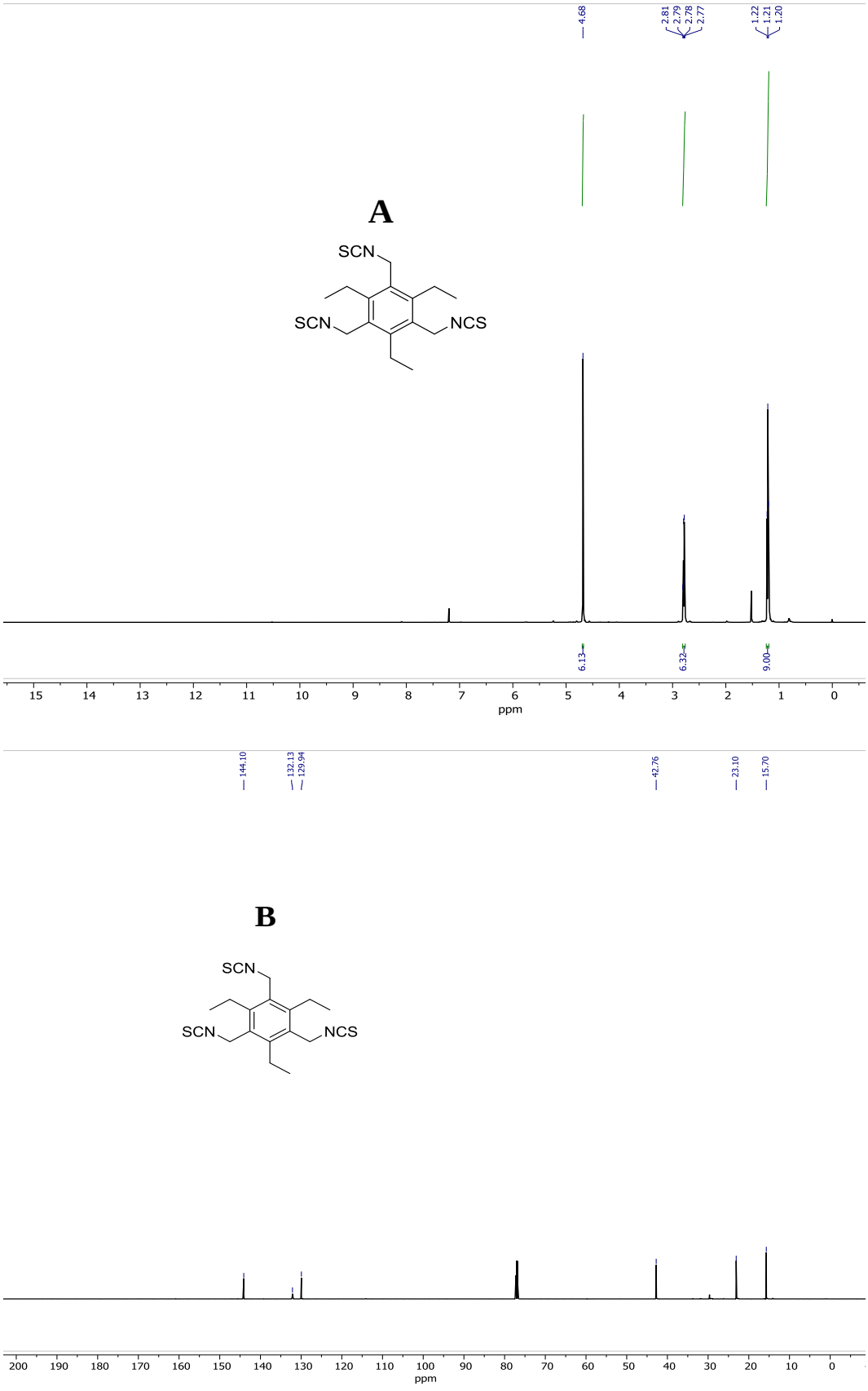


Figure S32: ^{1}H NMR (A) and ^{13}C NMR (B) spectra of 1,3,5-triethyl-2,4,6-tris(isothiocyanatomethyl)benzene.

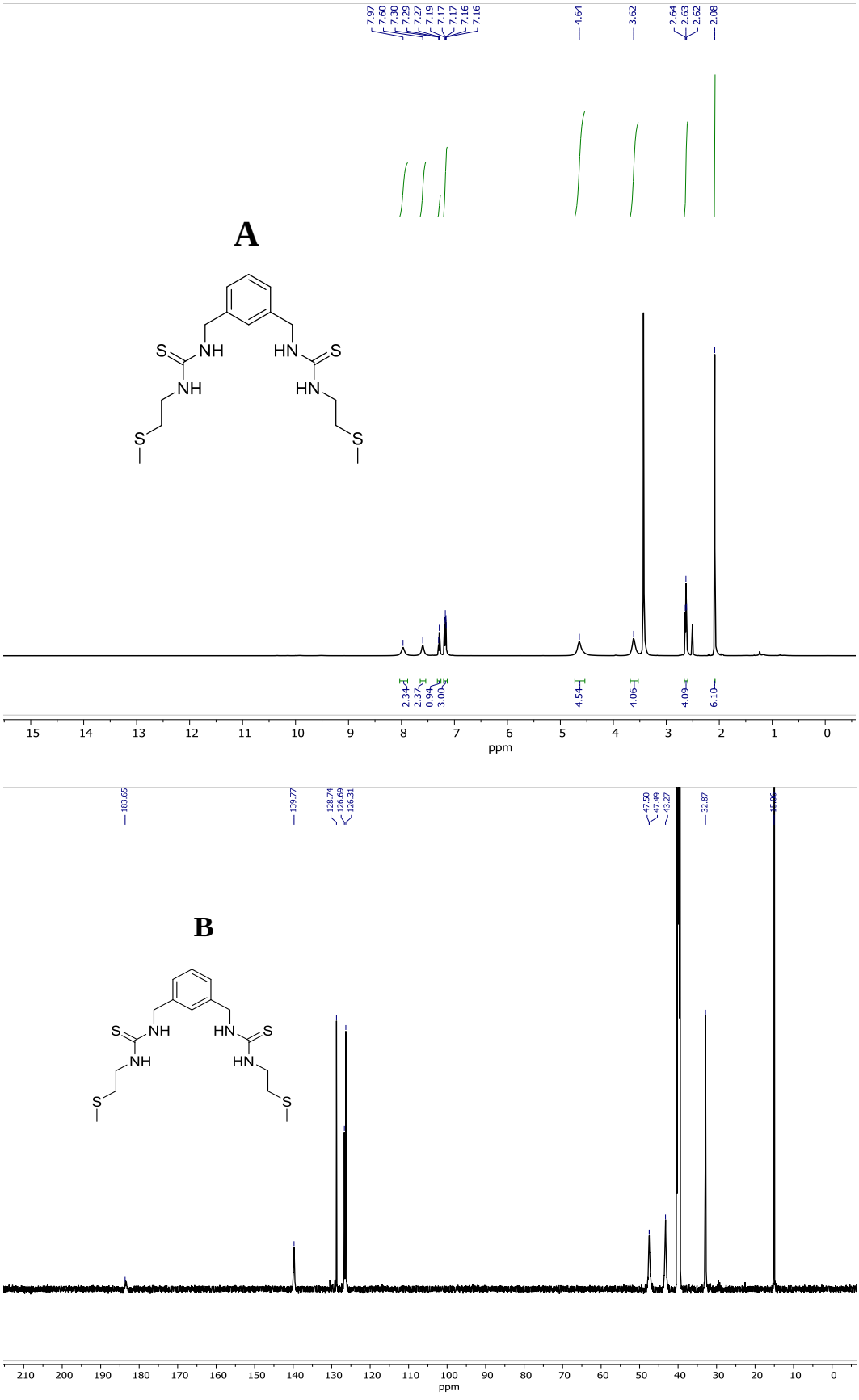


Figure S33: ^{1}H NMR (A) and ^{13}C NMR (B) spectra of compound **1**.

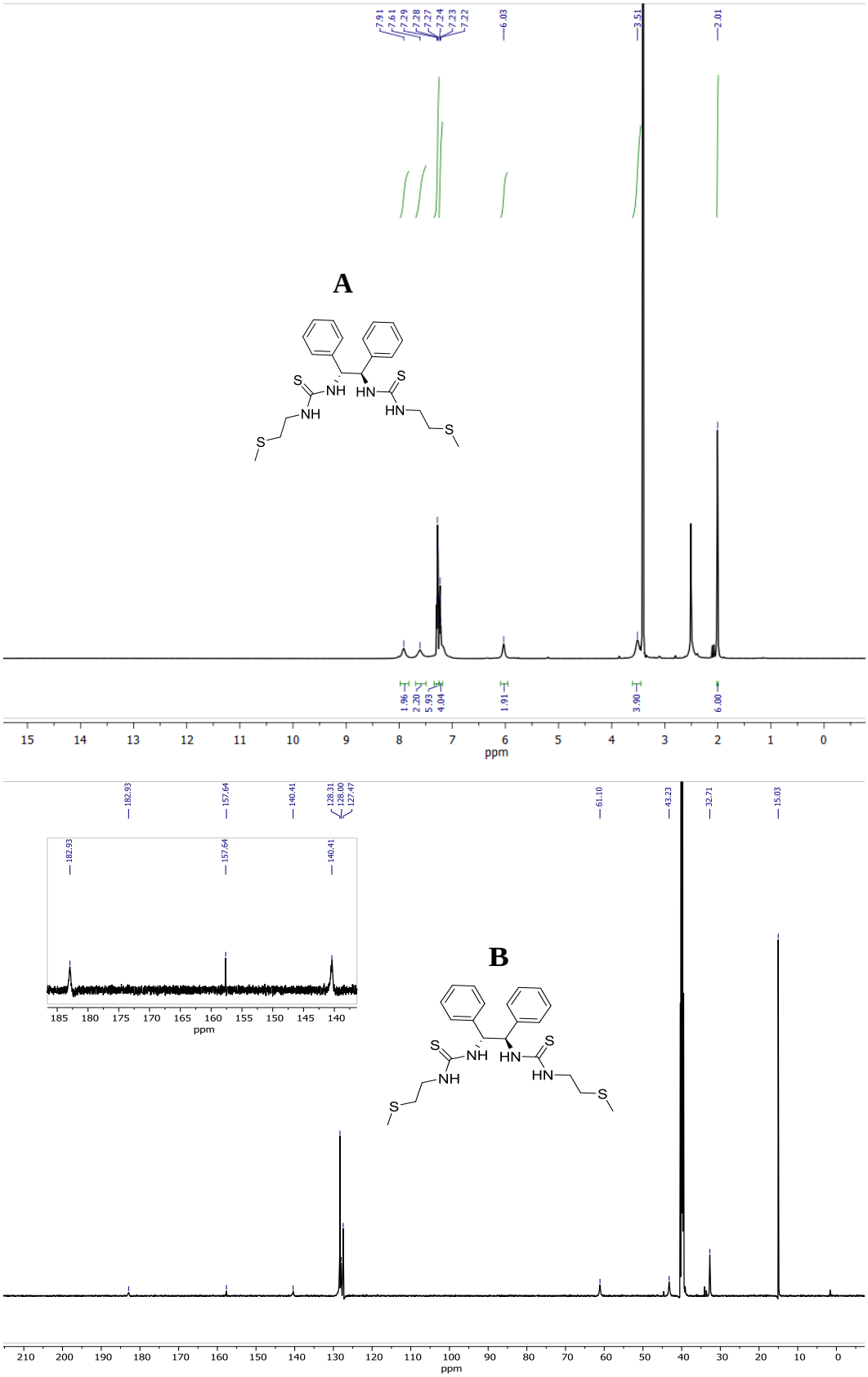


Figure S34: ^{1}H NMR (A) and ^{13}C NMR (B) spectra of compound **2.**

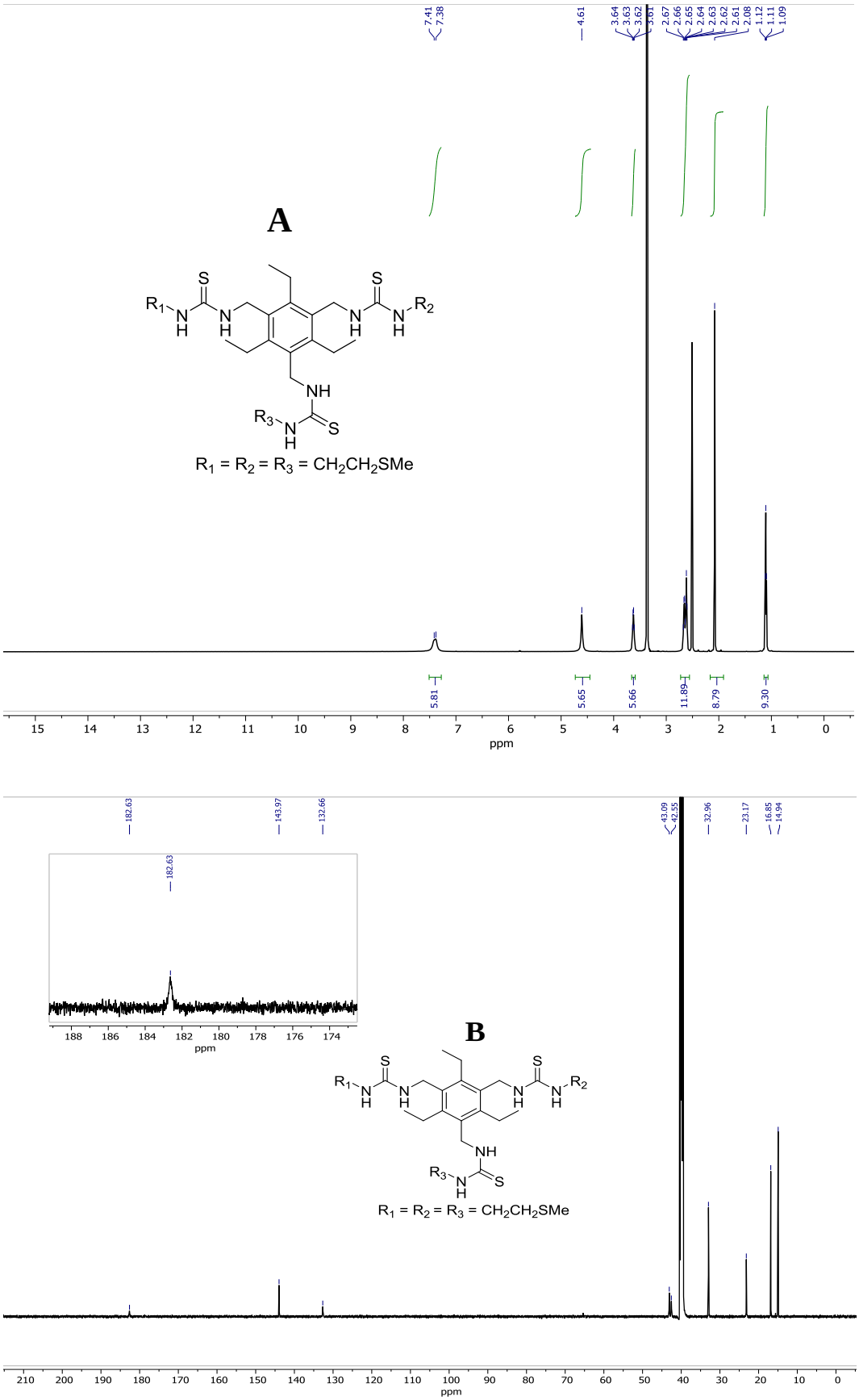


Figure S35: ^{1}H NMR (A) and ^{13}C NMR (B) spectra of compound **3.**

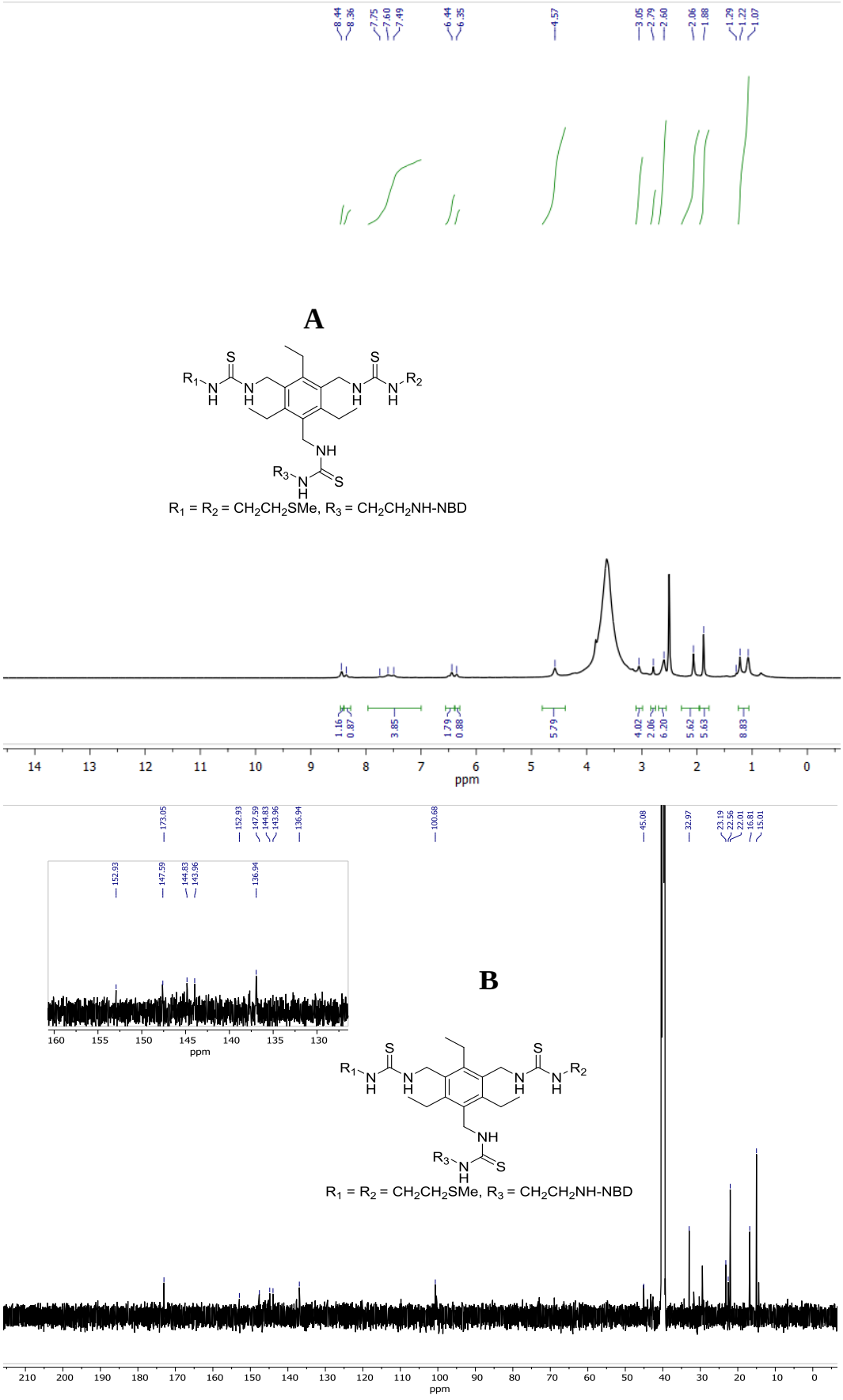


Figure S36: ^{1}H NMR (A) and ^{13}C NMR (B) spectra of compound **4.**

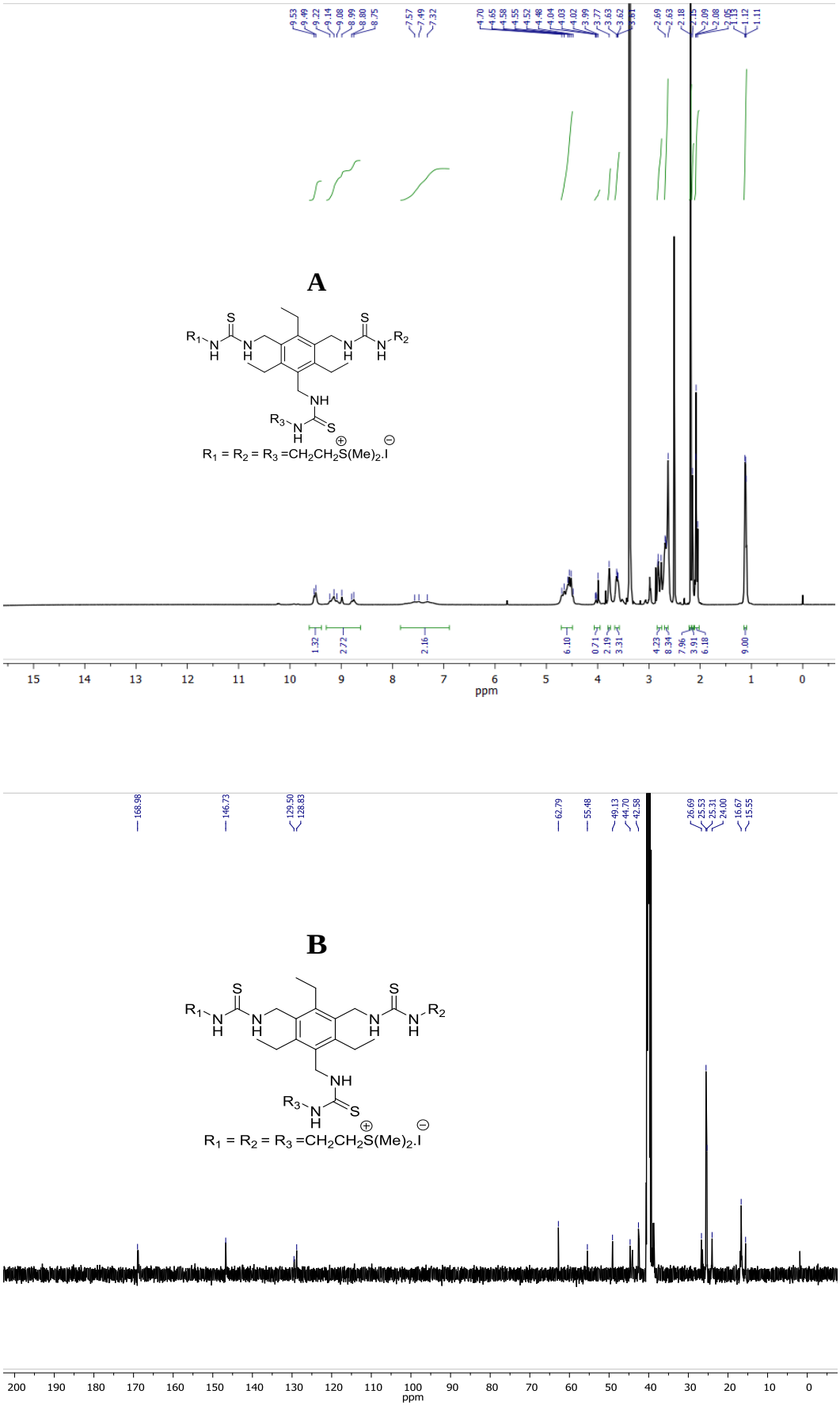


Figure S37: ^{1}H NMR (A) and ^{13}C NMR (B) spectra of compound **5.**

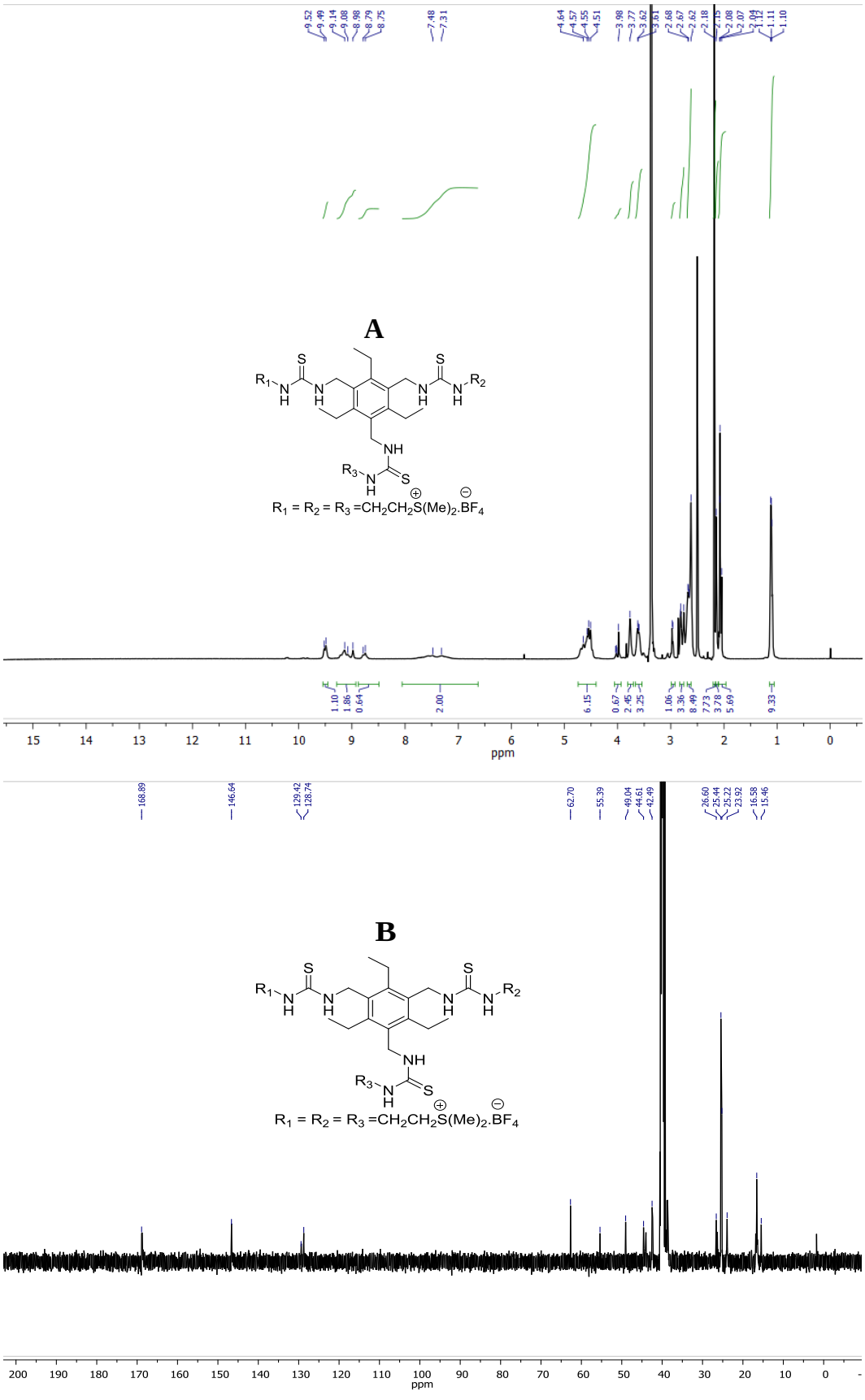


Figure S38: ^{1}H NMR (A) and ^{13}C NMR (B) spectra of compound **6.**

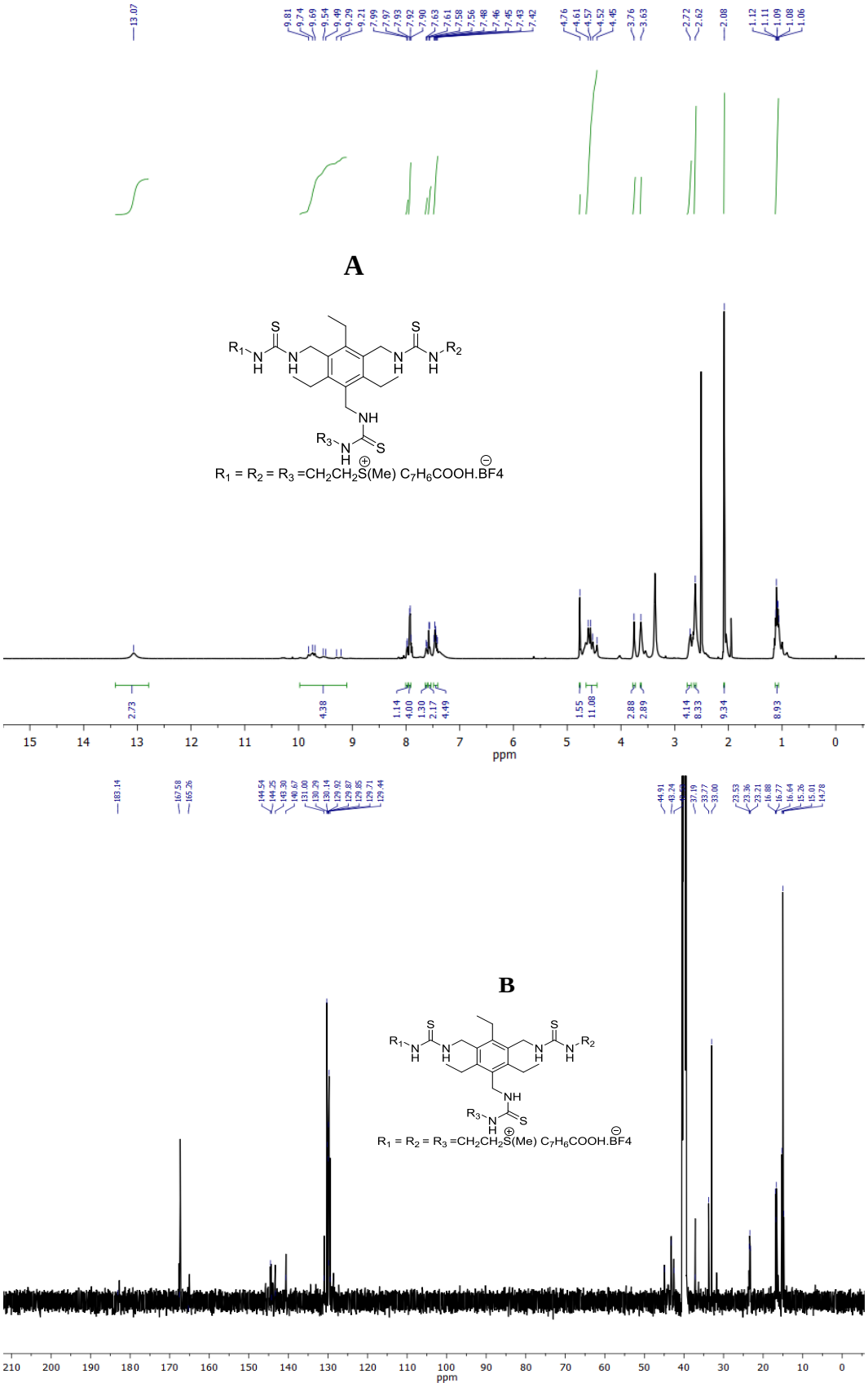


Figure S39: ^{1}H NMR (A) and ^{13}C NMR (B) spectra of compound **7.**

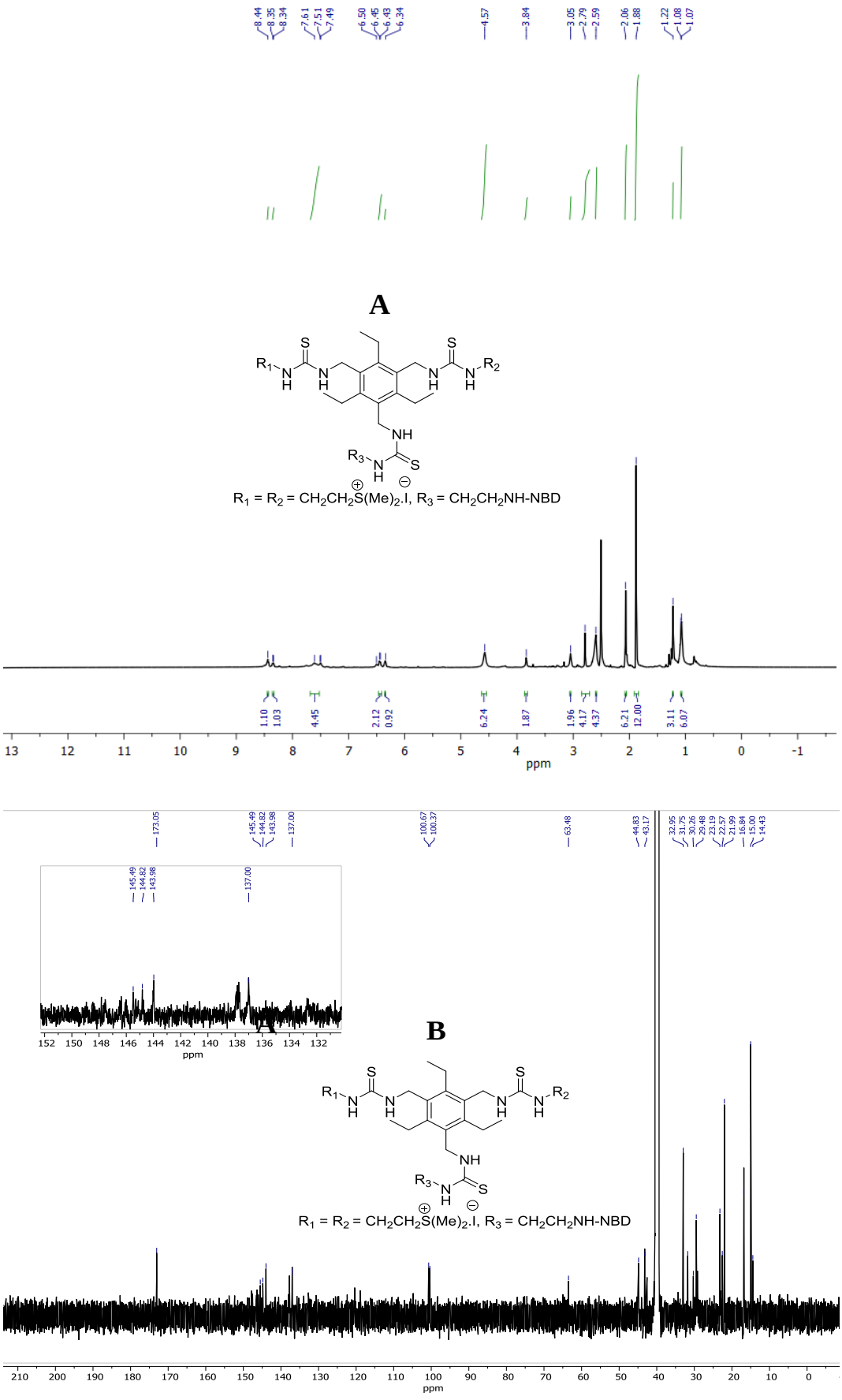


Figure S40: ^{1}H NMR (A) and ^{13}C NMR (B) spectra of compound **8.**

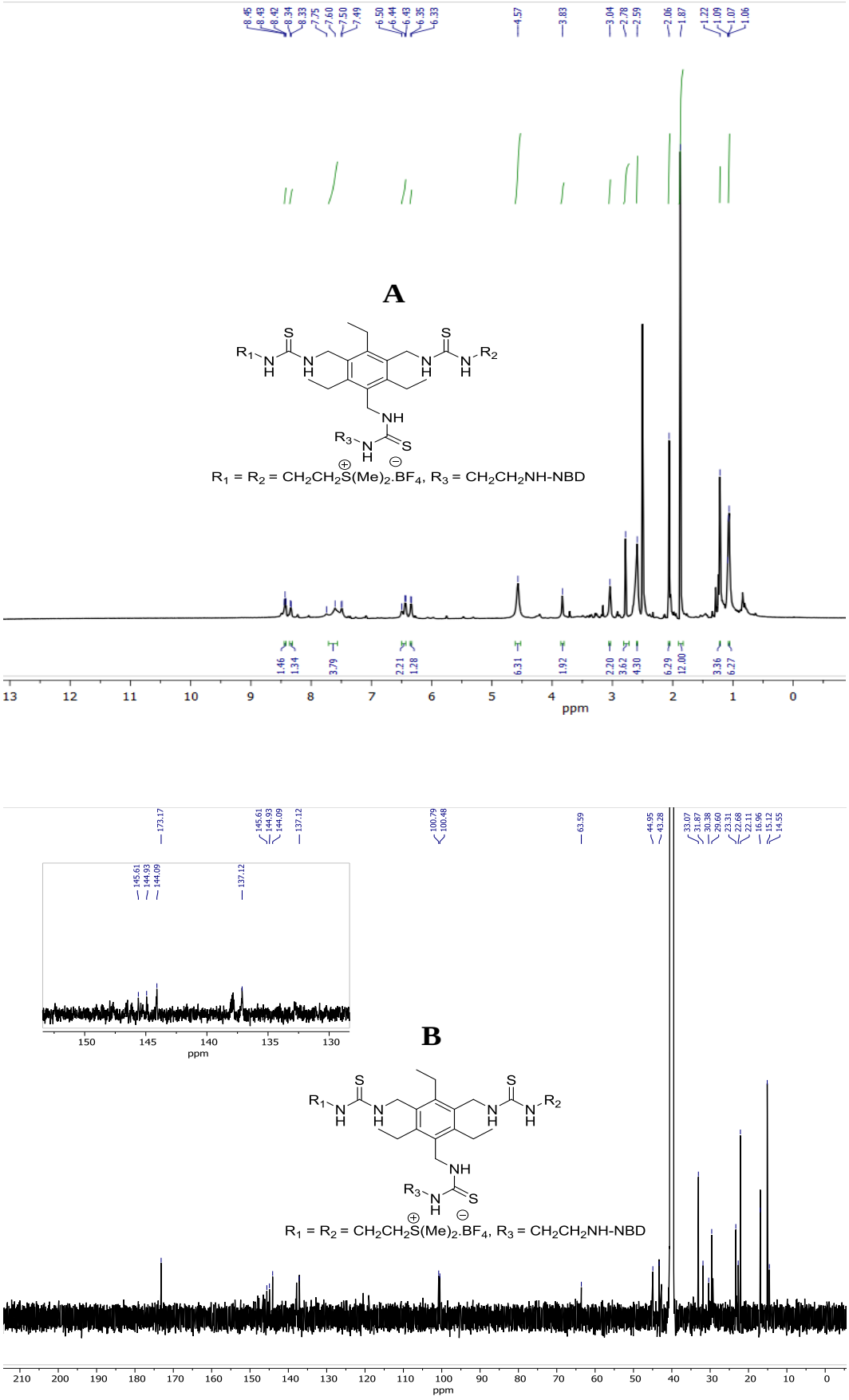


Figure S41: ^{1}H NMR (A) and ^{13}C NMR (B) spectra of compound **9.**

15. ES-MS Spectra of the Synthesized Compounds:

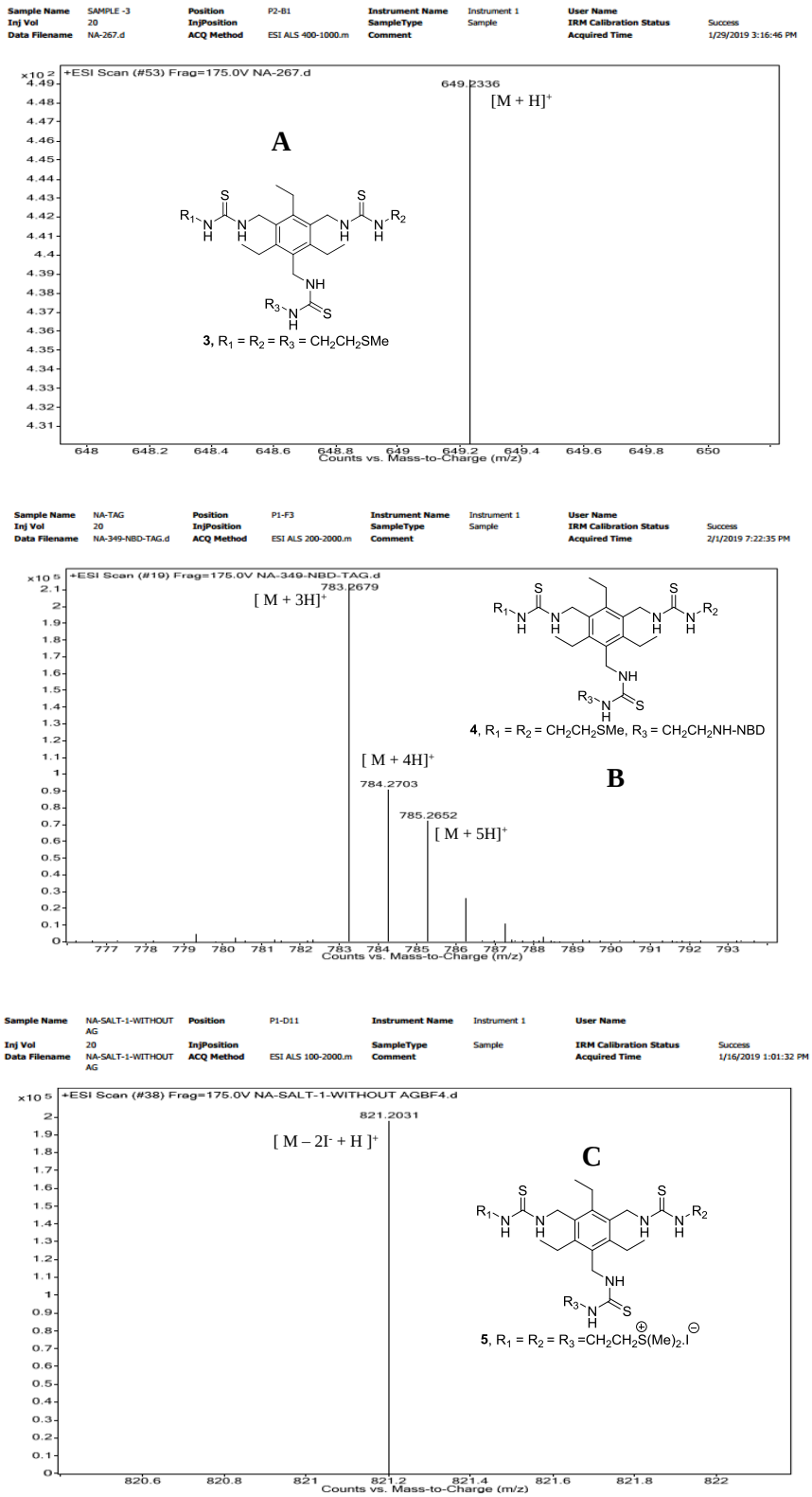


Figure S42: ES-MS spectra of compound **3** (A), **4** (B) and **5** (C).

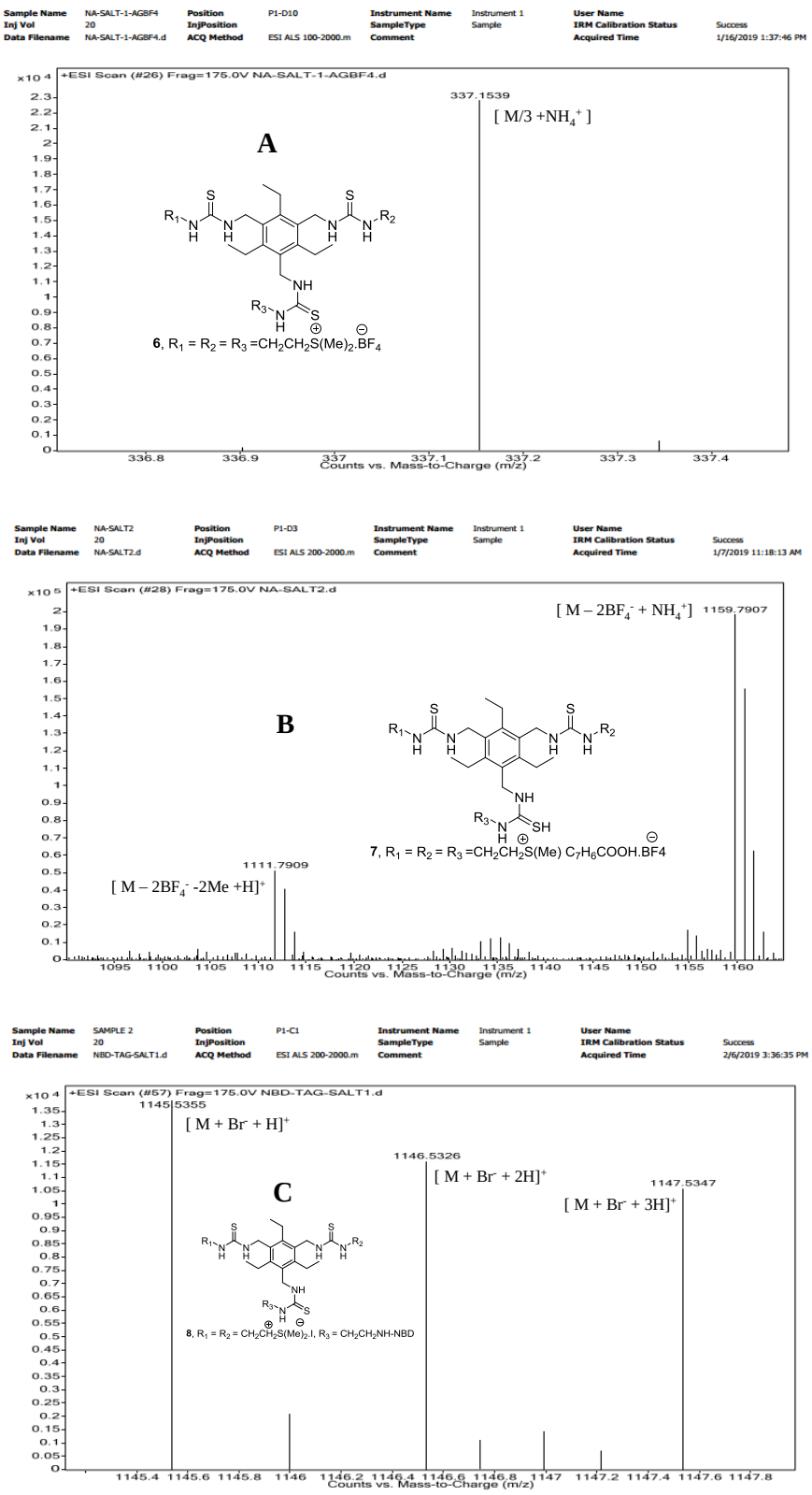


Figure S43: ES-MS spectra of compound **6** (A), **7** (B) and **8** (C).

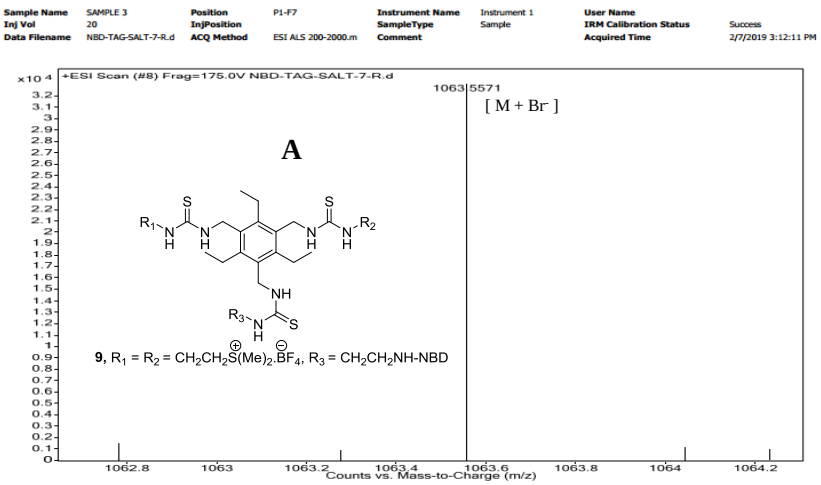
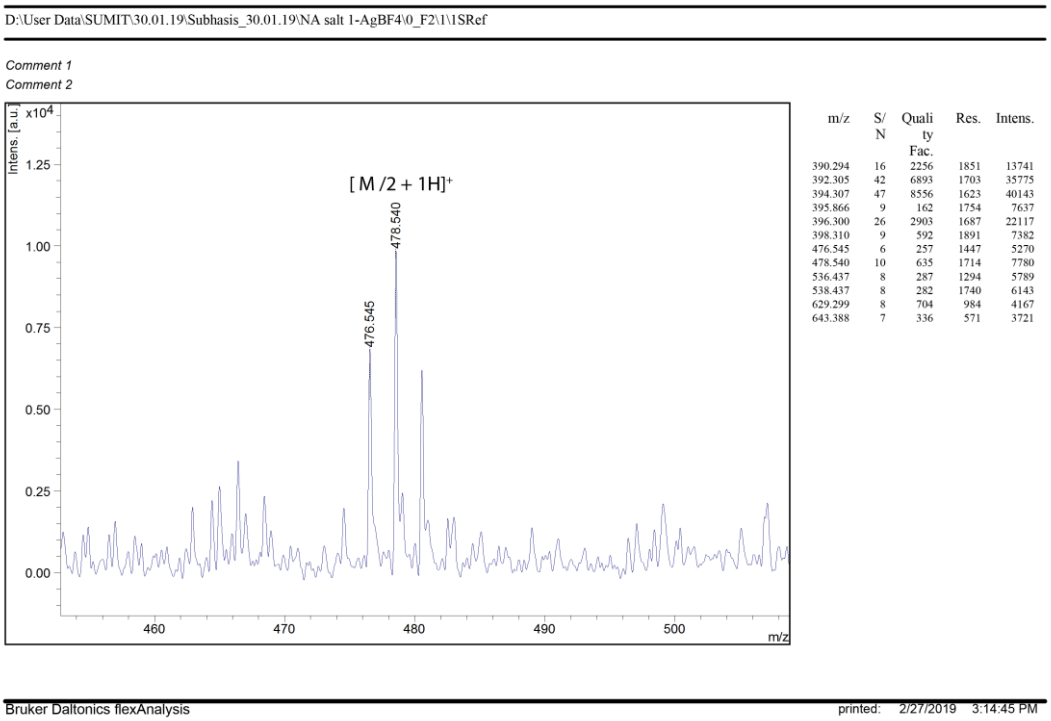


Figure S44: ES-MS spectra of compound **9.**

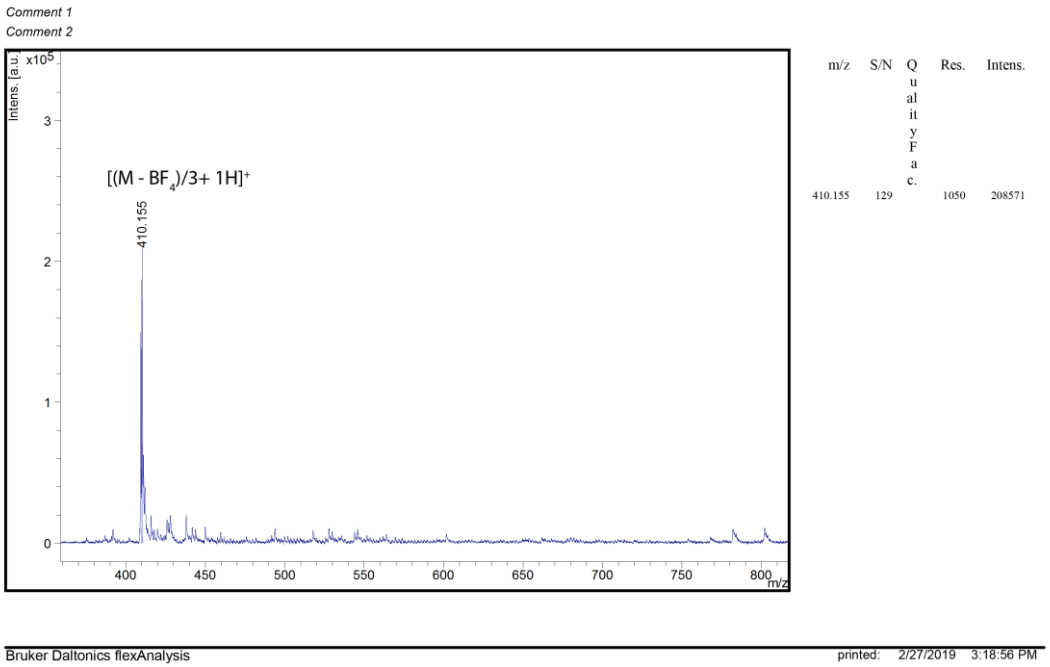
16. MALDI-TOF Analysis of the Compounds

(A)



m/z	S/N	Quality Fac.	Res.	Intens.	Area
390.294	16	2256	1851	13741	4087
392.305	42	6893	1703	35775	11648
394.307	47	8556	1623	40143	14096
395.866	9	162	1754	7637	2321
396.300	26	2903	1687	22117	7932
398.310	9	592	1891	7382	2272
476.545	6	257	1447	5270	2822
478.540	10	635	1714	7780	3520
536.437	8	287	1294	5789	3937
538.437	8	282	1740	6143	3121
629.299	8	704	984	4167	4940
643.388	7	336	571	3721	7223

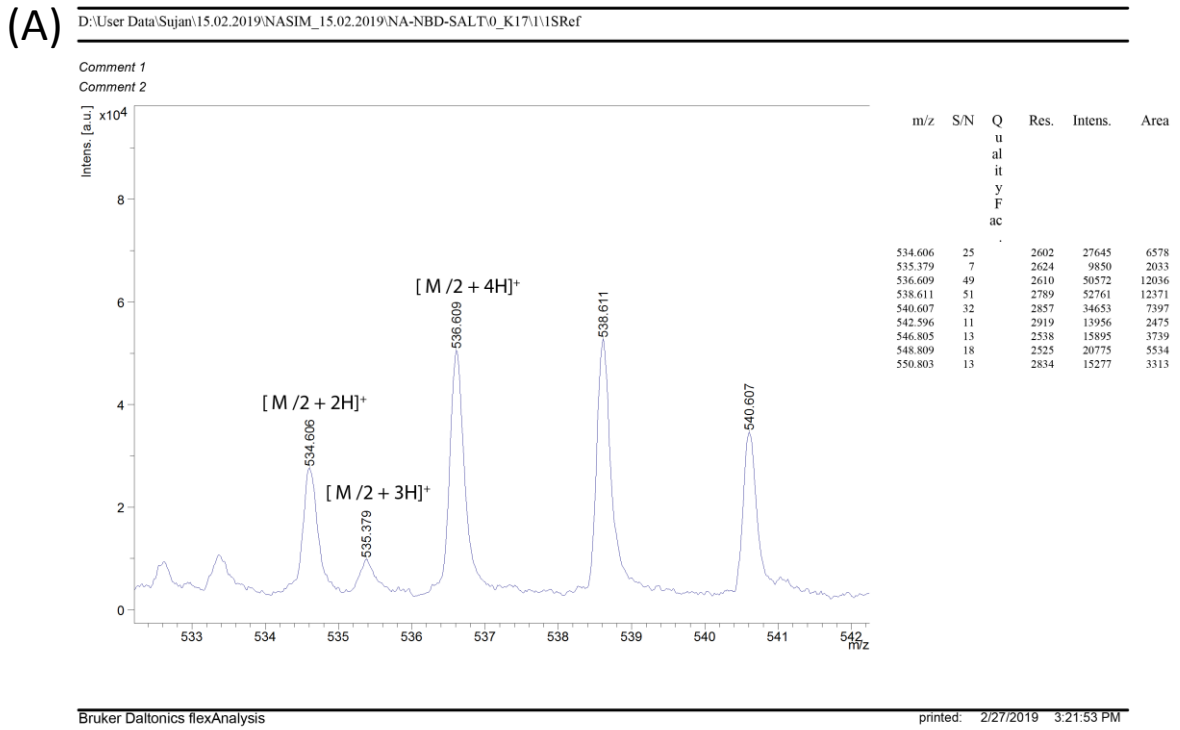
(B)



m/z	S/N	Quality Fac.	Res.	Intens.	Area
410.155	129		1050	208571	108541

Figure S45: MALDI-TOF analysis of compound **6** (A) and **7** (B).

(A)



(B)

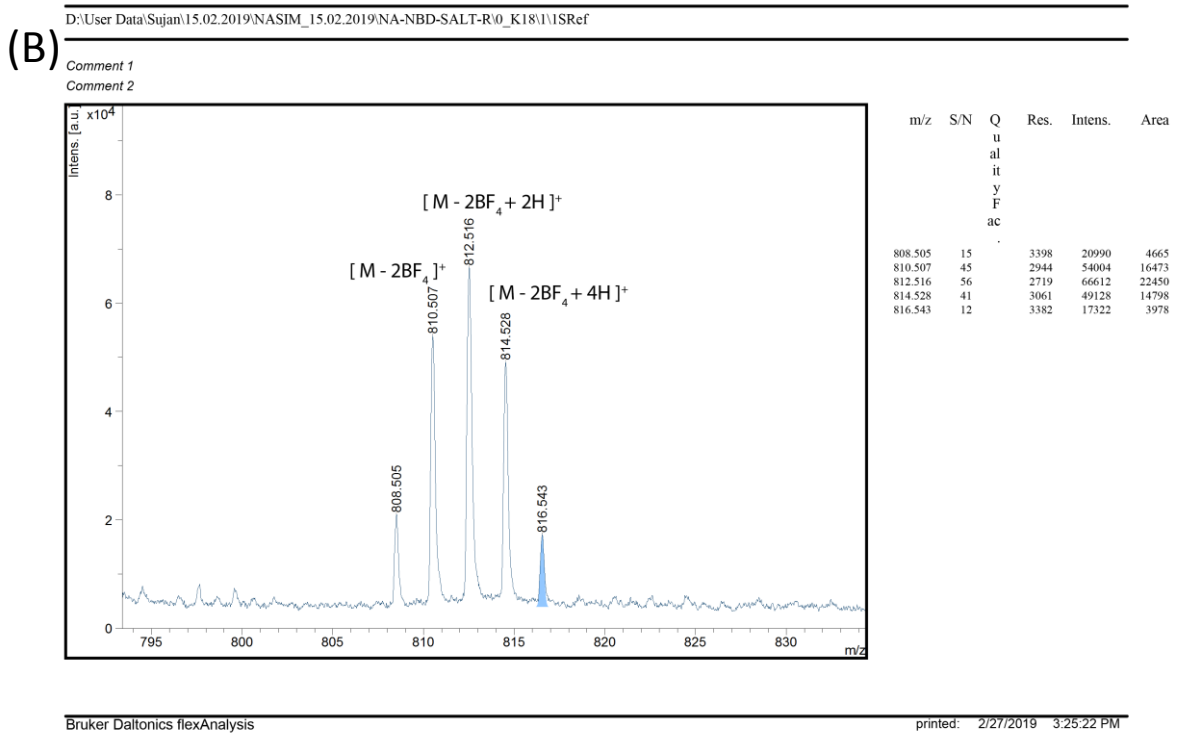


Figure S46: MALDI-TOF analysis of compound **8** (A) and **9** (B).

17. References

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