# Title One-pot Synthesis of Quaternary Pyridinium Salts of Lupane Triterpenoids and Their Antimicrobial Properties

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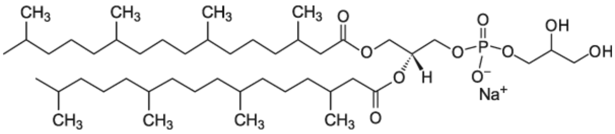
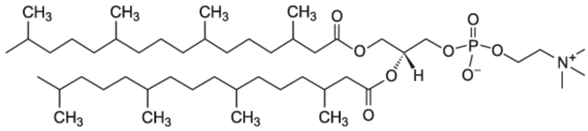
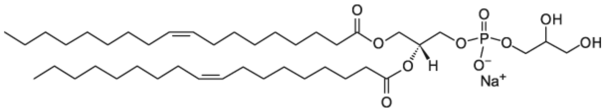
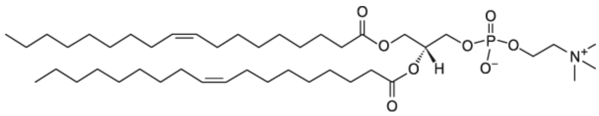
## *Supporting Information*

**Table S1.** Growth inhibition (%) of compounds **1-9, 1a-9a, 1b-7b, 9b, 1c-9c, 1d, 3d, 4d, 1e, 3e, 9e** at concentration 32 μg/mL

| Compound | **Gram-positive bacteria** | **Gram-negative bacteria** | | | | **Fungi** | |
|---|---|---|---|---|---|---|---|
| | *Staphylococcus aureus* | *Escherichia coli* | *Klebsiella pneumoniae* | *Acinetobacter baumannii* | *Pseudomonas aeruginosa* | *Candida albicans* | *Cryptococcus neoformans* |
| **1** | 17.26 | 3.53 | 8.89 | 16.33 | 1.88 | 4.38 | -27.83 |
| **2** | -4.44 | 1.47 | 2.81 | 10.29 | 29.39 | 43.03 | -22.51 |
| **3** | -1.38 | 34.32 | -2.91 | 11.04 | -11.38 | 28.68 | 29.75 |
| **4** | 3.51 | -5.37 | 10.43 | 15.17 | 1.63 | 10.01 | -28.74 |
| **5** | -5.71 | 28.56 | -8.42 | 9.17 | 2.16 | 10.38 | 18.35 |
| **6** | 9.91 | 18.13 | -2.78 | 4.48 | -11.51 | 3.52 | 31.93 |
| **7** | 2.75 | 28.82 | 2.8 | 4.7 | -1.96 | 7.55 | 23.36 |
| **8** | -8.58 | 20.79 | -8.36 | -1.7 | -13.51 | 3.23 | 32.22 |
| **9** | 10.86 | -0.87 | 2.61 | 3.73 | 18.21 | 2.71 | 40.29 |
| **1a** | **96.54** | 14.03 | 13.84 | -3.82 | 29.53 | 8.4 | -68.74 |
| **2a** | **94.27** | 2.94 | 8.91 | 10.84 | 10.79 | 19.36 | 78.51 |
| **3a** | **92.34** | 74.98 | 17.74 | 47.89 | **93.86** | **100.1** | **82.07** |
| **4a** | **87.96** | 16.87 | 23.06 | 5.71 | 34.72 | 8.77 | -42.67 |
| **5a** | -24.62 | 26.9 | 6.33 | 11.86 | -8.73 | 7.83 | 45.33 |
| **6a** | **95.91** | 26.82 | 22.56 | 29.8 | 32.33 | **100.35** | **104.41** |
| **7a** | **95.04** | 32.65 | 14.46 | 29.62 | 32.5 | 20.48 | -37.01 |
| **8a** | **94.23** | 13.23 | 14.77 | 17.83 | 7.01 | **100.64** | **96.89** |
| **9a** | **98.35** | 23.43 | -2.68 | 4.41 | 6.02 | **101.03** | **92.21** |
| **1b** | **90.28** | 0.01 | 6.7 | -3.64 | 22.02 | 3.8 | -95.69 |
| **2b** | -7.73 | 3.48 | 8.91 | 5.5 | 13.65 | 10.96 | -38.28 |
| **3b** | **89.62** | 8.31 | 25.44 | 1.98 | 55.01 | **105.5** | **105.3** |
| **4b** | **91.1** | 49.83 | 24.11 | 27.89 | **90.28** | **103.7** | **90.02** |
| **5b** | -34.11 | 0.66 | 17.31 | -9.69 | 14.81 | 7.25 | 1.25 |
| **6b** | **98.62** | **92.81** | 32.93 | 45.95 | 57.13 | **108.6** | **102.3** |
| **7b** | **90.43** | 41.28 | 22.97 | 40.94 | 57.09 | **104.9** | **104.6** |
| **9b** | -3.95 | 7.19 | 10.41 | -7.67 | 12.78 | 19.41 | **113.1** |
| **1c** | **98.85** | 7.19 | 31.43 | 3.49 | 46.53 | 11.32 | -22.01 |
| **2c** | **97.24** | 3.05 | 10.53 | 8.23 | 9.21 | 2.01 | -22.66 |
| **3c** | **96.64** | 19.43 | 30.49 | 19.59 | 51.15 | **98.85** | **100.3** |
| **4c** | **97.67** | 35.89 | 23.43 | 38.04 | 56.3 | **99** | **107** |
| **5c** | 50.01 | 9.48 | 10.06 | -8.3 | 18.5 | 19.34 | -77.13 |
| **6c** | **99.04** | **93.85** | 36.94 | 51.51 | **96.11** | **108.8** | **128.6** |
| **7c** | **90.84** | 48.63 | 22.6 | 39.24 | 64.19 | **105.1** | **111.4** |
| **8c** | **100.5** | 51.08 | 35.16 | 52.5 | 68.88 | **109.6** | **105.6** |
| **9c** | **98.62** | 5.46 | 17.41 | 10.01 | 29.92 | 16.98 | 108.5 |
| **1d** | **97.49** | 0.58 | 12.78 | 5.61 | 23.26 | 6.88 | -63.2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **3d** | 68.46 | -2.22 | 8.52 | 2.67 | 51.83 | 10.32 | -94.59 |
| **4d** | -14.69 | -0.15 | 4.61 | 11.05 | 1.59 | 20.06 | -26.22 |
| **1e** | **95.79** | 11.22 | 22.45 | -5.94 | 43.65 | 5.4 | -69.67 |
| **3e** | -5.93 | -2.72 | 6.63 | -3.67 | 2 | 22.42 | **100.5** |
| **9e** | **98.69** | 17.16 | 31.46 | 27.77 | 53.97 | 34.48 | 94.35 |

**Table S2.** Structure of lipids and charge at neutral pH.

| DPhPG (the charge is **-1**) | DPhPC (the charge is **0**) |
|---|---|
|  4ME 16:0 PG 1,2-diphytanoyl-sn-glycero-3-phospho-(1'-rac-glycerol) |  4ME 16:0 PC 1,2-diphytanoyl-sn-glycero-3-phosphocholine |
| DOPG (the charge is **-1**) | DOPC (the charge is **0**) |
|  18:1 (Δ9-Cis) PG *1,2-dioleoyl-sn-glycero-3-phospho-(1'-rac-glycerol)* |  18:1 (Δ9-Cis) PC (DOPC) 1,2-dioleoyl-sn-glycero-3-phosphocholine |

## Experimental Section

1-{2-[(*1R,3aS,5aR,5bR,9S,11aR*)-3a-carboxy-9-hydroxy-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}pyridin-1-ium bromide (**5a**).

Yield 94%, m.p. 210-212°C, $[\alpha]_D^{22}$ = -7.4° (c 0.27, $C_2H_5OH$). $^1$H NMR (500 MHz, $CD_3OD$, δ, ppm): 0.68-2.47 (m, 23H, CH, $CH_2$ pentacyclic skeleton), 0.73, 0.83, 0.92, 0.94, 1.01 (all s, 15H, 5$CH_3$), 1.78 (t, 1H, $^3$J= 11.4, H-18), 2.80-2.96 (m, 1H, H-19), 3.13 (dd, 1H, $^3$J= 4.7, $^3$J= 11.2, H-3), 4.76, 5.25 (each s, each H, H-29), 5.30-5.41 (m, 2H, H-30), 8.20 (t, 2H, $^3$J= 6.8, Py), 8.69 (t, 1H, $^3$J = 7.6, Py), 9.04 (d, 2H, $^3$J= 4.2, Py). $^{13}$C NMR (125.5 MHz, $CD_3OD$, δ, ppm): 15.07, 16.08, 16.64, 16.52, 27.88 (all $CH_3$, C23-27), 19.30-56.65 (pentacyclic skeleton), 57.24 (C17), 67.08 (C30), 79.48 (C3), 113.80 (C29), 129.57, 146.55, 147.50 (C-Py), 151.10 (C20), 179.45 (C28). MALDI TOF/TOF (m/z) for $C_{35}H_{52}BrNO_3$: calcd. 614.696, found 534.497 $[M-Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,9S,11aR*)-9-(acetyloxy)-3a-[(acetyloxy)methyl]-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}pyridin-1-ium bromide (**6a**).

Yield 92%, m.p. 160-162°C, $[\alpha]_D^{22}$ = -5.2°(c 0.18, $C_2H_5OH$). $^1$H NMR (500 MHz, $CDC1_3$, δ, ppm): 0.76-1.84 (m, 24H, CH, $CH_2$ pentacyclic skeleton), 0.83 (all s, 9H, 3$CH_3$), 0.96, 1.00 (all s, 6H, 2$CH_3$), 2.03 (s, 3H, C28-OCOC$\underline{H}_3$), 2.05 (s, 3H, C3-OCOC$\underline{H}_3$), 2.19-2.32 (m, 1H, H-19), 3.70, 4.21 (each d, each H, $^3$J= 11.8, $^3$J= 11.8, H-28), 4.45 (dd, 1H, $^3$J= 5.5, $^3$J= 10.3, H-3), 4.81, 5.17 (each br.s, each H, H-29), 5.64, 5.78 (each d, each H, $^3$J= 14.3, $^3$J= 14.3, H-30), 8.15 (t, 2H, $^3$J= 7.4, Py), 8.61 (t, 1H, $^3$J= 7.4, Py), 9.38 (d, 2H, $^3$J= 5.6, Py). $^{13}$C NMR (125.5 MHz, $CDCl_3$, δ, ppm): 14.80, 16.02, 16.15, 16.47, 27.92 (all $CH_3$, C23-27), 16.47-55.31 (pentacyclic skeleton), 20.89 (C28-OCO$\underline{C}H_3$), 21.03 (C3-OCO$\underline{C}H_3$), 62.14 (C28), 66.05 (C30), 80.85 (C3), 113.57 (C29), 128.15, 145.72, 145.85 (C-Py), 149.09 (C20), 170.99 (C3-O$\underline{C}$O$CH_3$), 171.45 (C28-OCO$\underline{C}H_3$). HRMS (ESI, m/z) for $C_{39}H_{58}BrNO_4$: calcd. 684.786, found 604.4354 $[M-Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-acetyl-5a,5b,8,8,11a-pentamethyl-9-oxo-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}pyridin-1-ium bromide (**7a**).

Yield 93%, m.p. 190-192°C, $[\alpha]_D^{22}$ = -0.9° (c 0.28, $C_2H_5OH$). $^1$H NMR (500 MHz, $CD_3OD$, δ, ppm): 0.96, 0.97, 1.04, 1.07, 1.08 (all s, 15H, 5$CH_3$), 0.99-3.36 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 3.68 (s, 3H, C17-COOC$\underline{H}_3$), 4.75, 5.29 (each br.s, each H, H-29), 5.33-5.49 (m, 2H, H-30), 8.23 (t, 2H, $^3$J = 6.6, Py), 8.71 (t, 1H, $^3$J = 7.4, Py), 9.08 (d, 2H, $^3$J = 5.8, Py). $^{13}$C NMR (125.5 MHz, $CD_3OD$, δ, ppm): 13.76, 14.93, 15.22, 20.12, 25.89 (all $CH_3$, C23-27), 19.36-56.41 (pentacyclic skeleton), 50.70 (C17-COO$\underline{C}H_3$), 65.69 (C30), 112.42 (C29), 128.32, 145.35, 146.27 (C-Py), 149.77 (C20), 176.33 (C17-$\underline{C}$OO$CH_3$), 219.34 (C3). MALDI TOF/TOF (m/z) for $C_{36}H_{52}BrNO_3$: calcd. 626.706, found 546.446 $[M-Br]^+$, 626.342 [M].

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-acetyl-9-(acetyloxy)-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}pyridin-1-ium bromide (**8a**).

Yield 93%, m.p. 189-191°C, $[\alpha]_D^{22}$ = -5.3° (c 0.24, $C_2H_5OH$). $^1$H NMR (500 MHz, CDC13, δ, ppm): 0.63 (all s, 6H, 2$CH_3$), 0.67, 0.77, 1.20 (all s, 9H, 3$CH_3$), 0.81-2.66 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 1.85 (s, 3H, C3-OCOC$\underline{H}_3$), 3.46 (s, 3H, C17-COOC$\underline{H}_3$), 4.20-4.28 (m, 1H, H-3), 4.63, 5.02 (each br.s, each H, H-29), 5.26, 5.35 (each d, each H, $^3J$ = 14.6, $^3J$ = 14.6, H-30), 7.99-8.11 (m, 2H, Py), 8.48-8.59 (m, 1H, Py), 8.80-8.89 (m, 2H, Py). $^{13}$C NMR (125.5 MHz, CDC1$_3$, δ, ppm): 14.65, 15.89, 16.14, 16.44, 27.90 (all $CH_3$, C23-27), 20.94-56.50 (pentacyclic skeleton), 21.29 (C3-OCO$\underline{C}H_3$), 51.48 (C17-COO$\underline{C}H_3$), 65.89 (C30), 80.83 (C3), 113.82 (C29), 128.57, 145.77, 146.64 (C-Py), 148.91 (C20), 171.02 (C3-O$\underline{C}$OC$H_3$), 176.23 (C17-$\underline{C}$OOC$H_3$). HRMS (ESI, m/z) for $C_{38}H_{56}BrNO_4$: calcd. 670.759, found 590.8565 $[M-Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-(acetyloxy)-3a-carboxy-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}pyridin-1-ium bromide (**9a**).

Yield 95%, m.p. 181-183°C, $[\alpha]_D^{22}$ = -3.4° (c 0.18, $C_2H_5OH$). $^1$H NMR (500 MHz, CDC1$_3$, δ, ppm): 0.60, 0.63, 0.66, 0.68, 0.79 (all s, 15H, 5$CH_3$), 0.70-2.73 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 1.89 (s, 3H, C3-OCOC$\underline{H}_3$), 4.21-4.35 (m, 1H, H-3), 4.67, 5.03 (each br.s, each H, H-29), 5.42-5.72 (m, 2H, H-30), 7.91-8.10 (m, 2H, Py), 8.40-8.56 (m, 1H, Py), 8.82-9.05 (m, 2H, Py). $^{13}$C NMR (125.5 MHz, $CDCl_3$, δ, ppm): 14.42, 15.78, 15.98, 16.23, 27.68 (all $CH_3$, C23-27), 17.84-57.43 (pentacyclic skeleton), 21.13 (C3-OCOC$H_3$), 66.54 (C30), 80.64 (C3), 112.54 (C29), 128.40, 145.45, 146.12 (C-Py), 149.54 (C20), 170.85 (C3-O$\underline{C}$OC$H_3$), 178.23 (C28). MALDI TOF/TOF (m/z) for $C_{37}H_{54}BrNO_4$: calcd. 656.746, found 576.867 $[M-Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-carboxy-5a,5b,8,8,11a-pentamethyl-9-oxo-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-4-methylpyridin-1-ium bromide (**2b**).

Yield 87%, m.p. 155-157°C, $[\alpha]_D^{22}$ = -0.68° (c 0.29, $C_2H_5OH$). $^1$H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.84, 0.88, 0.92, 0.95, 1.00 (all s, 15H, 5$CH_3$), 1.08-2.76 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 2.67 (s, 3H, Py-$CH_3$), 4.73, 5.12 (each br.s, each H, H-29), 5.19-5.44 (m, 2H, H-30), 7.81-7.98 (m, 2H, Py), 8.72-8.94 (m, 2H, Py). $^{13}$C NMR (125.5 MHz, $CDCl_3$, δ, ppm): 14.58, 15.73, 16.00, 20.99, 26.66 (all $CH_3$, C23-27), 19.61-56.09 (pentacyclic skeleton), 22.41 (Py-$CH_3$), 66.26 (C30), 112.85 (C29), 128.92, 144.31 (C-Py), 149.69 (C20), 160.13 (C-Py), 178.51 (C28), 219.10 (C3). MALDI TOF/TOF (m/z) for $C_{36}H_{52}BrNO_3$: calcd. 626.720, found 546.371 $[M-Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-[(acetyloxy)methyl]-9-hydroxy-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-4-methylpyridin-1-ium bromide (**3b**).

Yield 85%, m.p. 170- 172°C, $[\alpha]_D^{22}$ = -9.6° (c 0.23, $C_2H_5OH$). $^1$H NMR (500 MHz, $CD_3OD$, δ, ppm): 0.78, 0.89, 0.97, 1.06, 1.09 (all s, 15H, 5$CH_3$), 0.84-2.43 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 2.06 (s, 3H, C28-OCOC$\underline{H}_3$), 2.72 (s, 3H, Py-$CH_3$), 3.14 (dd, 1H, $^3J$ = 4.3, $^3J$ = 11.4, H-3), 3.83, 4.38 (each d, each H, $^3J$ = 11.1, $^3J$= 11.1, H-28), 4.68, 5.26 (each br.s, each H, H-29), 5.17-5.32 (m, 2H, H-30), 8.80 (d, 2H, $^2J$ = 6.1, Py), 8.81 (d, 2H, $^2J$ = 6.1, Py). $^{13}$C NMR (125.5 MHz, $CD_3OD$, δ, ppm): 13.05, 13.79, 14.72, 15.13, 27.23 (all $CH_3$, C23-27), 15.28-55.36 (pentacyclic skeleton), 19.40 (C28-OCO$\underline{C}H_3$), 20.71 (Py-$CH_3$), 61.83 (C28), 64.80 (C30), 78.20 (C3), 112.22 (C29), 128.65, 144.18 (C-

Py), 149.66 (C20), 160.79 (C-Py), 171.79 (C28-OCO<u>C</u>H3). HRMS (ESI, m/z) for $C_{38}H_{58}BrNO_3$: calcd. 656.790, found 576.4434 $[M\text{-}Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-hydroxy-3a-(methoxycarbonyl)-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-4-methylpyridin-1-ium bromide (**4b**).

Yield 87%, m.p. 185-187°C, $[\alpha]_D^{22}$ = -4.9° (c 0.10, $C_2H_5OH$). $^1H$ NMR (500 MHz, $CDCl_3$, δ, ppm): 0.66-2.79 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.75, 0.80, 0.86 (all s, 9H, $3CH_3$), 0.95 (both s, 6H, $2CH_3$), 2.70 (s, 3H, Py-$CH_3$), 3.19 (dd, 1H, $^3J$ = 4.2, $^3J$ = 10.8, H-3), 3.65 (s, 3H, C17-COOC$\underline{H}_3$), 4.89, 5.17 (each br.s, each H, H-29), 5.47, 5.61 (each d, each H, $^3J$ = 14.9, $^3J$ = 14.9, H-30), 7.88 (d, 2H, $^2J$ = 5.8, Py), 9.07 (d, 2H, $^3J$ = 5.8, Py). $^{13}C$ NMR (125.5 MHz, $CDCl_3$, δ, ppm): 14.77, 15.40, 15.91, 16.12, 28.00 (all $CH_3$, C23-27), 18.23-56.46 (pentacyclic skeleton), 22.43 (Py-$CH_3$), 51.52 (C17-COO$\underline{C}H_3$), 65.62 (C30), 78.80 (C3), 113.60 (C29), 128.52, 144.65 (C-Py), 149.08 (C20), 159.45 (C-Py), 176.23 (C28). HRMS (ESI, m/z) for $C_{37}H_{56}BrNO_3$: calcd. 642.763, found 562.4275 $[M\text{-}Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-carboxy-9-hydroxy-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-4-methylpyridin-1-ium bromide (**5b**).

Yield 88%, m.p. 201-203°C, $[\alpha]_D^{22}$ = -4.1° (c 0.24, $C_2H_5OH$). $^1H$ NMR (500 MHz, $CD_3OD+CDCl_3$, δ, ppm): 0.54-2.71 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.62, 0.68, 0.78, 0.82, 0.85 (all s, 15H, $5CH_3$), 2.63 (s, 3H, Py-$CH_3$), 3.02-3.13 (m, 1H, H-3), 4.70, 5.15 (each s, each H, H-29), 5.06-5.29 (m, 2H, H-30), 7.79-7.91 (m, 2H, Py), 8.67-8.80 (m, 2H, Py). $^{13}C$ NMR (125.5 MHz, $CD_3OD+CDCl_3$, δ, ppm): 14.34, 15.15, 15.55, 15.77, 27.63 (all $CH_3$, C23-27), 17.94-55.77 (pentacyclic skeleton), 22.08 (Py-$CH_3$), 65.85 (C30), 78.48 (C3), 113.08 (C29), 128.78, 143.98 (C-Py), 149.07 (C20), 160.09 (C-Py), 178.03 (C28). MALDI TOF/TOF (m/z) for $C_{36}H_{54}BrNO_3$: calcd. 628.736, found 548.293 $[M\text{-}Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-(acetyloxy)-3a-[(acetyloxy)methyl]-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-4-methylpyridin-1-ium bromide (**6b**).

Yield 86%, m.p. 135-137°C, $[\alpha]_D^{22}$= -8.5° (c 0.25, $C_2H_5OH$). $^1H$ NMR (500 MHz, $CDCl_3$, δ, ppm): 0.74-2.23 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.81 (all s, 9H, $3CH_3$), 0.95, 0.99 (all s, 6H, $2CH_3$), 2.02 (s, 3H, C28-OCOC$\underline{H}_3$), 2.03 (s, 3H, C3-OCOC$\underline{H}_3$), 2.69 (s, 3H, Py-$CH_3$), 3.68, 4.21 (each d, each H, $^3J$ = 10.2, $^3J$ = 10.2, H-28), 4.43 (dd, 1H, $^3J$ = 5.6, $^3J$ = 10.4, H-3), 4.80, 5.14 (each br.s, each H, H-29), 5.50, 5.65 (each d, each H, $^3J$ = 14.6, $^3J$ = 14.6, H-30), 7.83-7.95 (m, 2H, Py), 9.07-9.20 (m, 2H, Py). $^{13}C$ NMR (125.5 MHz, $CDC1_3$, δ, ppm): 14.78, 16.00, 16.14, 16.46, 27.92 (all $CH_3$, C23-27), 18.09-55.29 (pentacyclic skeleton), 21.02 (C28-OCO$\underline{C}H_3$), 21.30 (C3-OCO$\underline{C}H_3$), 22.44 (Py-$CH_3$), 62.16 (C28), 65.27 (C30), 80.84 (C3), 113.47 (C29), 128.61, 144.70 (C-Py), 149.02 (C20), 159.57 (C-Py), 170.97 (C3-O$\underline{C}OCH_3$), 171.44 (C28-O$\underline{C}OCH_3$). MALDI TOF/TOF (m/z) for $C_{40}H_{60}BrNO_4$: calcd. 698.827, found 618.395 $[M\text{-}Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-(methoxycarbonyl)-5a,5b,8,8,11a-pentamethyl-9-oxo-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-4-methylpyridin-1-ium bromide (**7b**).

Yield 85%, m.p. 180-182°C, $[\alpha]_D^{22}$ = -0.4° (c 0.27, $C_2H_5OH$). $^1$H NMR (500 MHz, $CDC1_3$, δ, ppm): 0.77-2.86 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.91 (all s, 6H, $2CH_3$), 0.93, 1.02, 1.07 (all s, 9H, $3CH_3$), 2.70 (s, 3H, Py-$CH_3$), 3.66 (s, 3H, C17-COOC$\underline{H}_3$), 4.88, 5.18 (each br.s, each H, H-29), 5.52, 5.66 (each d, each H, $^3$J = 15.3, $^3$J = 15.3, H-30), 7.87 (d, 2H, $^2$J = 6.9, Py), 9.12 (d, 2H, $^2$J = 6.9, Py). $^{13}$C NMR (125.5 MHz, $CDCl_3$, δ,ppm): 14.11, 14.72, 15.73, 19.60, 26.68 (all $CH_3$, C23-27), 21.00-56.46 (pentacyclic skeleton), 21.48 (Py-$CH_3$), 51.55 (C17-COO$\underline{C}H_3$), 65.55 (C30), 113.49 (C29), 128.47, 144.70 (C-Py), 149.13 (C20), 159.45 (C-Py), 176.20 (C17-$\underline{C}OOCH_3$), 218.02(C3). HRMS (ESI, m/z) for $C_{37}H_{54}BrNO_3$: calcd. 640.747, found 560.4126 $[M-Br]^+$, 640.3196 [M].

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-(acetyloxy)-3a-carboxy-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-4-methylpyridin-1-ium bromide (**9b**).

Yield 89%, m.p. 210-212°C, $[\alpha]_D^{22}$ = -2.8° (c 0.18, $C_2H_5OH$). $^1$H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.75-2.26 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.81, 0.82, 0.85, 0.87, 0.91 (all s, 15H, $5CH_3$), 2.03 (s, 3H, C3-OCOC$\underline{H}_3$), 2.68 (s, 3H, Py-$CH_3$), 4.43-4.46 (m, 1H, H-3), 4.64, 5.11 (each br.s, each H, H-29), 5.47-5.62 (m, 2H, H-30), 7.87-7.97 (m, 2H, Py), 9.02-9.16 (m, 2H, Py). $^{13}$C NMR (125.5 MHz, $CDC1_3$, δ, ppm): 14.11, 14.57, 16.50, 16.28, 27.94 (all $CH_3$, C23-27), 18.15-55.38 (pentacyclic skeleton), 21.33 (C3-OCO$\underline{C}H_3$), 22.69 (Py-$CH_3$), 66.32 (C30), 80.92 (C3), 112.17 (C29), 128.74, 144.56 (C-Py), 150.42 (C20), 159.52 (C-Py), 171.09 (C3-O$\underline{C}OCH_3$), 178.23 (C28). HRMS (ESI, m/z) for $C_{38}H_{55}BrNO_4$: calcd. 670.759, found 590.4204 $[M-Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-carboxy-5a,5b,8,8,11a-pentamethyl-9-oxo-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-3,5-dimethylpyridin-1-ium bromide (**2c**).

Yield 85%, m.p. 134-136ºC, $[\alpha]_D^{22}$ = -0.4° (c 0.24, $C_2H_5OH$). $^1$H NMR (500 MHz, $CD_3OD+CDCl_3$, δ, ppm): 0.67, 0.72, 0.75, 0.77, 0.82 (all s, 15H, $5CH_3$), 0.87-2.23 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 2.35 (both s, 6H, Py-$CH_3$), 4.52, 5.11 (each br.s, each H, H-29), 4.93-5.06 (m, 2H, H-30), 7.98 (m, 1H, Py), 8.43 (m, 2H, Py). $^{13}$C NMR (125.5 MHz, $CDCl_3$, δ, ppm): 14.07, 15.36, 15.59, 19.30, 26.27 (all $CH_3$, C23-27), 20.50-56.47 (pentacyclic skeleton), 17.80 (Py-$CH_3$), 66.13 (C30), 112.45 (C29), 138.87, 141.65, 146.82 (C-Py), 149.73 (C20), 183.43 (C28), 219.74 (C3). MALDI TOF/TOF (m/z) for $C_{37}H_{54}BrNO_3$: calcd. 640.747, found 560.450 $[M-Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-[(acetyloxy)methyl]-9-hydroxy-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-3,5-dimethylpyridin-1-ium bromide (**3c**).

Yield 83%, m.p. 125-127°C, $[\alpha]_D^{22}$ = -7.2° (c 0.26, $C_2H_5OH$). $^1$H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.56-2.17 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.66, 0.72, 0.87, 0.92, 1.17 (all s, 15H, $5CH_3$), 1.98 (s, 3H, C28-OCOC$\underline{H}_3$), 2.53 (both s, 6H, Py-$CH_3$), 3.04-3.19 (m, 1H, H-3), 3.67, 4.13 (each m, each H, H-28), 4.80, 5.11 (each br.s, each H, H-29), 5.25-5.48 (m, 2H, H-30), 8.07 (m, 1H, Py), 8.74 (m, 2H, Py). $^{13}$C NMR (125.5 MHz, $CDCl_3$, δ, ppm): 14.80, 15.40, 15.90, 16.03, 27.93 (all $CH_3$, C23-27), 18.13-55.11 (pentacyclic skeleton), 20.98 (C28-OCO$\underline{C}H_3$), 18.74 (Py-$CH_3$), 62.26 (C28), 66.07 (C30), 78.62 (C3), 114.08 (C29), 138.75, 142.36, 147.09 (C-Py), 148.63 (C20), 171.66 (C28-O$\underline{C}OCH_3$). MALDI TOF/TOF (m/z) for $C_{39}H_{60}BrNO_3$: calcd. 670.817, found 590.593 $[M-Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-hydroxy-3a-(methoxycarbonyl)-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-3,5-dimethylpyridin-1-ium bromide (**4c**).

Yield 85%, m.p. 177-179°C, $[\alpha]_D^{22}$ = -5.1° (c 0.12, $C_2H_5OH$). $^1$H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.62-2.74 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.73, 0.78, 0.85 (all s, 9H, $3CH_3$), 0.94 (both s, 6H, $2CH_3$), 2.57 (both s, 6H, Py-$CH_3$), 3.11-3.22 (m, 1H, H-3), 3.63 (s, 3H, C17-COOC$\underline{H}_3$), 4.94, 5.18 (each br.s, each H, H-29), 5.42, 5.65 (each d, each H, $^3J$ = 14.8, $^3J$ = 14.8, H-30), 80.7 (m, 1H, Py), 8.91 (m, 2H, Py). $^{13}$C NMR (125.5 MHz, $CDCl_3$, δ, ppm): 14.74, 15.40, 15.90, 16.11, 27.32 (all $CH_3$, C23-27), 18.22-56.50 (pentacyclic skeleton), 18.59 (Py-$CH_3$), 51.48 (C17-COO$\underline{C}H_3$), 65.94 (C30), 78.76 (C3), 114.00 (C29), 138.56, 142.32, 146.62 (C-Py), 148.82 (C20), 176.22 (C28). HRMS (ESI, m/z) for $C_{38}H_{58}BrNO_3$: calcd. 656.790, found 576.4535 $[M-Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-carboxy-9-hydroxy-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-3,5-dimethylpyridin-1-ium bromide (**5c**).

Yield 87%, m.p. 120-122ºC, $[\alpha]_D^{22}$ = -2.3° (c 0.30, $C_2H_5OH$). $^1$H NMR (500 MHz, $CD_3OD$, δ, ppm): 0.71-2.91 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.76, 0.86, 0.95, 0.96, 1.03 (all s, 15H, $5CH_3$), 2.57 (both s, 6H, Py-$CH_3$), 3.14 (dd, 1H, $^3J$ = 4.6, $^3J$ = 11.5, H-3), 4.80, 5.25 (each s, each H, H-29), 5.19-5.30 (m, 2H, H-30), 8.36 (m, 1H, Py), 8.73 (m, 2H, Py). $^{13}$C NMR (125.5 MHz, $CD_3OD$, δ, ppm): 15.06, 16.06, 16.54, 16.65, 27.93 (all $CH_3$, C23-27), 18.32-58.25 (pentacyclic skeleton), 18.25 (Py-$CH_3$), 66.74 (C30), 79.49 (C3), 113.76 (C29), 140.48, 143.32, 148.41 (C-Py), 150.93 (C20), 179.50 (C28). MALDI TOF/TOF (m/z) for $C_{37}H_{56}BrNO_3$: calcd. 642.763, found 562.415 $[M-Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-(acetyloxy)-3a-[(acetyloxy)methyl]-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-3,5-dimethylpyridin-1-ium bromide (**6c**).

Yield 86%, m.p. 129-131°C, $[\alpha]_D^{22}$ = -7.7° (c 0.21, $C_2H_5OH$). $^1$H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.73-2.35 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.79 (all s, 9H, $3CH_3$), 0.96, 0.99 (all s, 6H, $2CH_3$), 2.00 (s, 3H, C28-OCOC$H_3$), 2.01 (s, 3H, C3-OCOC$\underline{H}_3$), 2.55 (both s, 6H, Py-$CH_3$), 3.68, 4.17 (each d, each H, $^3J$ = 10.1, $^3J$ = 10.1, H-28), 4.42 (dd, 1H, $^3J$ = 5.7, $^3J$ = 10.1, H-3), 4.89, 5.14 (each br.s, each H, H-29), 5.41, 5.55 (each d, each H, $^3J$ = 14.4, $^3J$ = 14.4, H-30), 8.06 (m, 1H, Py), 8.93 (m, 2H, Py). $^{13}$C NMR (125.5 MHz, $CDCl_3$, δ, ppm): 14.71, 15.97, 16.12, 16.44, 27.89 (all $CH_3$, C23-27), 18.05-55.27 (pentacyclic skeleton), 18.55 (Py-$CH_3$), 21.00 (C28-OCO$\underline{C}H_3$), 21.29 (C3-OCO$\underline{C}H_3$), 62.16 (C28), 65.69 (C30), 80.82 (C3), 114.01 (C29), 188.63, 142.32, 146.70 (C-Py), 148.71 (C20), 171.00 (C28-O$\underline{C}$OC$H_3$), 171.50 (C3-O$\underline{C}$OC$H_3$). HRMS (ESI, m/z) for $C_{41}H_{62}BrNO_4$: calcd. 712.854, found 632.4768 [M-Br]+.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-(methoxycarbonyl)-5a,5b,8,8,11a-pentamethyl-9-oxo-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-3,5-dimethylpyridin-1-ium bromide (**7c**).

Yield 85%, m.p. 153-155°C, $[\alpha]_D^{22}$ = -1.7° (c 0.14, $C_2H_5OH$). $^1$H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.70-3.36 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.82 (all s, 6H, $2CH_3$), 0.90, 0.93, 0.99 (all s, 9H, $3CH_3$), 2.52 (both s, 6H, Py-$CH_3$), 3.58 (s, 3H, C17-COOC$\underline{H}_3$), 4.85, 5.11 (each br.s, each H, H-29), 5.39, 5.50 (each d, each H, $^3J$ = 14.8, $^3J$ = 14.8, H-30), 8.08 (m, 1H, Py), 8.93 (m, 2H, Py). $^{13}$C NMR (125.5 MHz, CDC13, δ, ppm): 14.63, 15.66, 15.92, 20.95, 26.63 (all $CH_3$, C23-27), 19.53-56.42 (pentacyclic skeleton), 18.53 (Py-$CH_3$), 51.47 (C17-COO$\underline{C}H_3$), 65.61 (C30), 113.68 (C29), 138.56, 142.30, 146.77 (C-Py), 148.81 (C20), 176.12 (C17-$\underline{C}OOCH_3$), 218.04 (C3). MALDI TOF/TOF (m/z) for $C_{38}H_{56}BrNO_3$: calcd. 654.774, found 574.246 $[M\text{-}Br]^+$, 654.071 [M].

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-(acetyloxy)-3a-(methoxycarbonyl)-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-3,5-dimethylpyridin-1-ium bromide (**8c**).

Yield 86%, m.p. 190-192°C, $[\alpha]_D^{22}$= -6.8° (c 0.23, $C_2H_5OH$). $^1H$ NMR (500 MHz, $CDCl_3$, δ, ppm): 0.80 (all s, 6H, 2$CH_3$), 0.81, 0.84, 0.91 (all s, 9H, 3$CH_3$), 1.11-2.23 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 2.01 (s, 3H, C3-OCOC$\underline{H}_3$), 2.56 (both s, 6H, Py-$CH_3$), 3.62 (s, 3H, C17-COOC$\underline{H}_3$), 4.44 (dd, 1H, $^3J$ = 5.1, $^3J$ = 10.2, H-3), 4.89, 5.16 (each br.s, each H, H-29), 5.39, 5.54 (each d, each H, $^3J$ = 14.1, $^3J$ = 14.1, H-30), 8.06 (m, 1H, Py), 8.89 (m, 2H, Py). $^{13}C$ NMR (125.5 MHz, $CDC1_3$, δ, ppm): 14.65, 15.89, 16.14, 16.44, 27.90 (all $CH_3$, C23-27), 20.91-56.51 (pentacyclic skeleton), 18.57 (Py-$CH_3$), 21.29 (C3-OCO$\underline{C}H_3$), 51.48 (C17-COO$\underline{C}H_3$), 65.89 (C30), 80.83 (C3), 113.82 (C29), 138.59, 142.31, 146.64 (C-Py), 148.91 (C20), 171.02 (C3-O$\underline{C}OCH_3$), 176.23 (C17-$\underline{C}OOCH_3$). HRMS (ESI, m/z) for $C_{40}H_{60}BrNO_4$: calcd. 698.827, found 618.4593 $[M\text{-}Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-(acetyloxy)-3a-carboxy-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-3,5-dimethylpyridin-1-ium bromide (**9c**).

Yield 87%, m.p. 209- 211°C, $[\alpha]_D^{22}$ = -3.4° (c 0.21, $C_2H_5OH$). $^1H$ NMR (500 MHz, $CD_3OD$+$CDC1_3$, δ, ppm): 0.60, 0.62, 0.63, 0.71, 0.75 (all s, 15H, 5$CH_3$), 0.72-2.70 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 1.84 (s, 3H, C3-OCOC$\underline{H}_3$), 2.38 (both s, 6H, Py-$CH_3$), 4.47-4.60 (m, 1H, H-3), 4.97-5.10 (m, 2H, H-29), 4.95-5.12 (m, 2H, H-30), 7.98 (m, 1H, Py), 8.47 (m, 2H, Py). $^{13}C$ NMR (125.5 MHz, $CD_3OD$+$CDCl_3$, δ, ppm): 14.14, 15.79, 15.59, 16.05, 27.52 (all $CH_3$, C23-27), 17.79-56.53 (pentacyclic skeleton), 17.90 (Py-$CH_3$), 20.85 (C3-OCO$\underline{C}H_3$), 66.24 (C30), 80.98 (C3), 112.12 (C29), 138.78, 141.62, 146.67 (C-Py), 149.91 (C20), 171.45 (C3-O$\underline{C}OCH_3$), 183.67 (C28). MALDI TOF/TOF (m/z) for $C_{39}H_{58}BrNO_4$: calcd. 684.800, found 604.448 $[M\text{-}Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-hydroxy-3a-(hydroxymethyl)-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-4-methoxypyridin-1-ium bromide (**1d**).

Yield 85%, m.p. 234- 236°C, $[\alpha]_D^{22}$ = -7.29° (c 0.29, $C_2H_5OH$). $^1H$ NMR (500 MHz, $CD_3OD$, δ, ppm): 0.72-2.39 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.77, 0.88, 0.97, 1.05, 1.09 (all s, 15H, 5$CH_3$), 3.14 (dd, 1H, $^3J$ = 4.6, $^3J$ = 11.3, H-3), 3.26, 3.74 (each d, each H, $^3J$ = 11.3, $^3J$= 11.3, H-28), 4.19 (s, 3H, Py-OC$\underline{H}_3$), 4.64, 5.20 (each br.s, each H, H-29), 5.06-5.17 (m, 2H, H-30), 7.60 (d, 2H, $^2J$ = 7.3, Py), 8.74 (d, 2H, $^2J$ = 7.3, Py). $^{13}C$ NMR (125.5 MHz, $CD_3OD_3$, δ, ppm): 13.82, 14.75, 15.16, 15.31, 27.24 (all $CH_3$, C23-27), 18.03-55.37 (pentacyclic skeleton), 57.51 (Py-O$\underline{C}H_3$), 58.69 (C28), 63.46 (C30), 78.20 (C3), 111.51 (C29), 113.36, 146.44 (C-Py), 150.20 (C20), 171.83 (C-Py). MALDI TOF/TOF (m/z) for $C_{36}H_{56}BrNO_3$: calcd. 630.752, found 550.474 $[M\text{-}Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-[(acetyloxy)methyl]-9-hydroxy-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-4-methoxypyridin-1-ium bromide (**3d**).

Yield 84%, m.p. 145-147°C, $[\alpha]_D^{22}$ = -11.8° (c 0.24, $C_2H_5OH$). $^1$H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.64-2.32 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.73, 0.80, 0.94, 0.95, 1.00 (all s, 15H, $5CH_3$), 2.04 (s, 3H, C28-$OCOC\underline{H}_3$), 3.16 (dd, 1H, $^3J$=4.9, $^3J$=10.9, H-3), 3.66 (s, 3H, Py-$OC\underline{H}_3$), 3.75, 4.19 (each d, each H, $^3J$=11.0, $^3J$=11.0, H-28), 4.26-4.38 (m, 2H, H-30), 4.58, 5.02 (each br.s, each H, H-29), 6.37 (d, 2H, $^2J$ = 7.5, Py), 7.21 (d, 2H, $^2J$ = 7.5, Py). $^{13}$C NMR (125.5 MHz, $CDCl_3$, δ, ppm): 14.85, 15.48, 16.09, 16.17, 27.99 (all $CH_3$, C23-27), 15.99-55.36 (pentacyclic skeleton), 20.98 (C28-$OCO\underline{C}H_3$), 43.54 (Py-$O\underline{C}H_3$), 61.01 (C30), 62.26 (C28), 78.83 (C3), 111.35 (C29), 118.80, 140.39 (C-Py), 149.62 (C20), 171.54 (C28-$O\underline{C}OCH_3$), 178.96 (C-Py). MALDI TOF/TOF (m/z) for $C_{38}H_{58}BrNO_4$: calcd. 672.789, found 578.464 $[M\text{-}Br, \text{-}CH_3]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-hydroxy-3a-(methoxycarbonyl)-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-4-methoxypyridin-1-ium bromide (**4d**).

Yield 84%, m.p. 164-166°C, $[\alpha]_D^{22}$ = -15.3° (c 0.27, $C_2H_5OH$). $^1$H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.68-2.86 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.75, 0.81, 0.89 (all s, 9H, $3CH_3$), 0.96 (both s, 6H, $2CH_3$), 3.18 (dd, 1H, $^3J$ = 4.7, $^3J$ = 11.2, H-3), 3.66 (s, 3H, C17-$COOC\underline{H}_3$), 3.72 (s, 3H, Py-$OC\underline{H}_3$), 4.64, 5.06 (each br.s, each H, H-29), 4.24-4.45 (m, 2H, H-30), 6.44 (d, 2H, $^2J$ = 7.2, Py), 7.30 (d, 2H, $^2J$ = 7.2, Py). $^{13}$C NMR (125.5 MHz, $CDCl_3$, δ, ppm): 14.70, 15.39, 15.91, 16.11, 27.99 (all $CH_3$, C23-27), 18.25-56.43 (pentacyclic skeleton), 43.86 (Py-$O\underline{C}H_3$), 51.49 (C17-$COO\underline{C}H_3$), 61.69 (C30), 78.78 (C3), 110.85 (C29), 118.51, 140.57 (C-Py), 150.23 (C20), 176.15 (C28), 178.73 (C-Py). HRMS (ESI, m/z) for $C_{37}H_{56}BrNO_4$: calcd. 658.762, found 564.4023 $[M\text{-}Br, \text{-}CH_3]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-hydroxy-3a-(hydroxymethyl)-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-3-methoxypyridin-1-ium bromide (**1e**).

Yield 85%, m.p. 220-222ºC, $[\alpha]_D^{22}$ = -18.4° (c 0.32, $C_2H_5OH$). $^1$H NMR (500 MHz, $CD_3OD$+$CDCl_3$, δ, ppm): 0.56-2.18 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.65, 0.71, 0.85, 0.87, 0.91 (all s, 15H, $5CH_3$), 3.01-3.12 (m, 1H, H-3), 3.18, 3.55 (each d, each H, $^2J$ = 12.4, $^2J$= 12.4, H-28), 4.02 (s, 3H, Py-$OC\underline{H}_3$), 4.80, 5.12 (each s, each H, H-29), 5.19-5.44 (m, 2H, H-30), 7.96 (d, 1H, $^3J$ = 5.3, Py), 8.00 (d, 1H, $^3J$ = 7.9, Py), 8.52 (d, 1H, $^3J$ = 6.2, Py), 8.70 (m, 1H, Py). $^{13}$C NMR (125.5 MHz, $CD_3OD$+$CDCl_3$, δ, ppm): 14.50, 15.26, 15.76, 15.93, 27.78 (all $CH_3$, C23-27), 18.13-55.16 (pentacyclic skeleton), 57.84 (Py-$O\underline{C}H_3$), 59.56 (C28), 67.02 (C30), 78.54 (C3), 113.64 (C29), 128.62, 131.17, 132.14, 137.43 (C-Py), 149.15 (C20), 158.74 (C-Py), 178.03 (C28). MALDI TOF/TOF (m/z) for $C_{36}H_{56}BrNO_3$: calcd. 630.752, found 550.385 $[M\text{-}Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-3a-[(acetyloxy)methyl]-9-hydroxy-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-3-methoxypyridin-1-ium bromide (**3e**).

Yield 83%, m.p. 230-232°C, $[\alpha]_D^{22}$ = -1.4° (c 0.21, $C_2H_5OH$). $^1$H NMR (500 MHz, $CD_3OD$+$CDCl_3$, δ, ppm): 0.45-2.50 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.53, 0.61, 0.74, 0.78, 0.81 (all s, 15H, $5CH_3$), 1.86 (s, 3H, C28-$OCOC\underline{H}_3$), 2.88-3.00 (m, 1H, H-3), 3.55, 4.02 (each d, each H, $^2J$ = 11.0, $^2J$ = 11.0, H-28), 3.90 (s, 3H, Py-$OC\underline{H}_3$), 4.64, 5.03 (each br.s, each H, H-29), 5.05-5.22 (m, 2H, H-30), 7.91-8.02 (m, 1H, Py), 8.30-8.40 (m, 1H, Py), 8.46-8.56 (m, 1H, Py), 8.73-8.88 (m, 1H, Py). $^{13}$C NMR (125.5 MHz, $CD_3OD$+$CDCl_3$, δ, ppm): 14.37, 15.06, 15.61, 15.70, 27.55 (all $CH_3$, C23-27), 17.95-

55.01 (pentacyclic skeleton), 20.55 (C28-OCO$\underline{C}H_3$), 57.52 (Py-O$\underline{C}H_3$), 62.08 (C28), 66.32 (C30), 78.33 (C3), 113.63 (C29), 128.62, 130.91, 132.26, 137.14 (C-Py), 148.39 (C20), 158.69 (C-Py), 171.95 (C28-O$\underline{C}OCH_3$). MALDI TOF/TOF (m/z) for $C_{38}H_{58}BrNO_4$: calcd. 672.789, found 592.477 $[M-Br]^+$.

1-{2-[(*1R,3aS,5aR,5bR,11aR*)-9-(acetyloxy)-3a-carboxy-5a,5b,8,8,11a-pentamethyl-icosahydro-1H-cyclopenta[a]chrysen-1-yl]prop-2-en-1-yl}-3-methoxypyridin-1-ium bromide (**9e**).

Yield 83%, m.p. 120-122ºC, $[\alpha]_D^{22}$ = -6.3° (c 0.26, $C_2H_5OH$). $^1$H NMR (500 MHz, $CD_3OD$, δ, ppm): 0.82-2.95 (m, 25H, CH, $CH_2$ pentacyclic skeleton), 0.87 (all s, 6H, $2CH_3$), 0.89, 0.98, 1.04 (all s, 9H, $3CH_3$), 2.04 (s, 3H, C3-OCOC$\underline{H}_3$), 4.11 (s, 3H, Py-OC$\underline{H}_3$), 4.40-4.53 (m, 1H, H-3), 4.88, 5.27 (each br.s, each H, H-29), 5.19-5.42 (m, 2H, H-30), 8.05-8.13 (m, 1H, Py), 8.25-8.31 (m, 1H, Py), 8.59-8.65 (m, 1H, Py), 8.78-8.83 (m, 1H, Py). $^{13}$C NMR (125.5 MHz, $CD_3OD$, δ, ppm): 15.07, 16.69, 16.72, 16.89, 28.42 (all $CH_3$, C23-27), 19.19-51.81 (pentacyclic skeleton), 21.35 (C3-OCO$\underline{C}H_3$), 56.76 (Py-O$\underline{C}H_3$), 67.51 (C30), 82.47 (C3), 108.43 (C29), 124.37, 126.54, 128.76, 133.24 (C-Py), 145.76 (C20), 160.38 (C-Py), 172.97 (C3-O$\underline{C}OCH_3$), 182.66 (C28). MALDI TOF/TOF (m/z) for $C_{38}H_{56}BrNO_5$: calcd. 686.772, found 606.440 $[M-Br]^+$.

## Biological activity studies

### Antimicrobial screening, cytotoxicity and haemolysis

Antimicrobial screening was conducted at the University of Queensland (Australia) as part of the CO-ADD (The Community for Antimicrobial Drug Discovery) program, https://www.co-add.org), financed by the Wellcome Trust (UK) on five bacterial strains: Escherichia coli ATCC 25922, Klebsiella pneumoniae ATCC 700603, Acinetobacter baumannii ATCC 19606, Pseudomonas aeruginosa ATCC 27853 and Staphylococcus aureus ATCC 43300. Antifungal activity was assayed on two fungal strains: Candida albicans ATCC 90028 and Cryptococcus neoformans ATCC 208821. Solutions of compounds **5**–**7** in DMSO were used for assays. DMSO solvent does not adversely affect the development of the studied bacteria and fungi. The growth inhibition ratio was calculated for each well using a negative control (medium only) and a positive control (bacteria without inhibitors). All tests were duplicated. Complete growth inhibition was determined at <= 20% growth (or > 80% inhibition) and concentrations were only chosen if the next highest concentration exhibited complete inhibition (ie 80-100%).

### Sample preparation

Samples were provided by the collaborator and stored frozen at -20°C. Samples were prepared in DMSO and water to a final testing concentration of 32μg/mL or 20μM (unless otherwise indicated in the data sheet) and serially diluted 1:2 fold for 8 times. Each sample concentration was prepared in 384-well plates, non-binding surface plate (**NBS;** Corning 3640) for each bacterial/fungal strain, tissue-culture treated (**TC-treated;** Corning 3712/3764) black for mammalian cell types and polypropylene 384-well (**PP**; Corning 3657) for haemolysis assays, all in duplicate (n=2), and keeping the final DMSO concentration to a maximum of 0.5%. All the sample preparation was done using liquid handling robots.

### Antibacterial assay

**Procedure**

All bacteria were cultured in Cation-adjusted Mueller Hinton broth (**CAMHB**) at 37°C overnight. A sample of each culture was then diluted 40-fold in fresh broth and incubated at 37°C for 1.5-3 h. The resultant mid-log phase cultures were diluted (CFU/mL measured by $OD_{600}$), then added to each well of the compound containing plates, giving a cell density of $5x10^5$ CFU/mL and a total volume of 50µL. All the plates were covered and incubated at 37°C for 18 h without shaking.

**Analysis**

Inhibition of bacterial growth was determined measuring absorbance at 600 nm ($OD_{600}$), using a Tecan M1000 Pro monochromator plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate. The MIC was determined as the lowest concentration at which the growth was fully inhibited, defined by an inhibition ≥ 80%. In addition, the maximal percentage of growth inhibition is reported as DMax, indicating any compounds with partial activity. Hits were classified by MIC ≤ 16µg/mL or MIC ≤ 10µM in either replicate (n=2 on different plates).

**Antifungal assay**

**Procedure**

Fungi strains were cultured for 3 days on Yeast Extract-Peptone Dextrose (**YPD**) agar at 30°C. A yeast suspension of $1x10^6$ to $5x10^6$ CFU/mL (as determined by $OD_{530}$) was prepared from five colonies. The suspension was subsequently diluted and added to each well of the compound-containing plates giving a final cell density of fungi suspension of $2.5x10^3$ CFU/mL and a total volume of 50µL. All plates were covered and incubated at 35°C for 36 h without shaking.

**Analysis**

Growth inhibition of C. albicans was determined measuring absorbance at 630nm ($OD_{630}$), while the growth inhibition of C. neoformans was determined measuring the difference in absorbance between 600 and 570nm ($OD_{600-570}$), after the addition of resazurin (0.001% final concentration) and incubation at 35°C for 2 h. The absorbance was measured using a Biotek Multiflo Synergy HTX plate reader. In both cases, the percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (fungi without inhibitors) on the same plate. The MIC was determined as the lowest concentration at which the growth was fully inhibited, defined by an inhibition ≥ 80% for C. albicans and an inhibition ≥ 70% for C. neoformans. Due to a higher variance in growth and inhibition, a lower threshold was applied to the data for C. neoformans. In addition, the maximal percentage of growth inhibition is reported as DMax, indicating any compounds with marginal activity. Hits were classified by MIC ≤ 16µg/mL or MIC ≤ 10µM in either replicate (n=2 on different plates).

**Cytotoxicity assay**

**Procedure**

HEK293 cells were counted manually in a Neubauer haemocytometer and then plated in the 384-well plates containing the compounds to give a density of 5000 cells/well in a final volume of 50µL. **DMEM** supplemented with 10% FBS was used as growth media and the cells were incubated together with the compounds for 20 h at 37°C in 5% $CO_2$.

**Analysis**

Cytotoxicity (or cell viability) was measured by fluorescence, ex: 560/10nm, em: 590/10nm ($F_{560/590}$), after addition of 5µL of 25µg/mL resazurin (2.3µg/mL final concentration) and after incubation for further 3 h at 37°C in 5% $CO_2$. The fluorescence intensity was measured using a Tecan M1000 Pro monochromator plate reader, using automatic gain calculation.

$CC_{50}$ (concentration at 50% cytotoxicity) were calculated by curve fitting the inhibition values vs. log(concentration) using a sigmoidal dose-response function, with variable fitting values for bottom, top and slope. In addition, the maximal percentage of cytotoxicity is reported as $D_{Max}$, indicating any compounds with partial cytotoxicity. The curve fitting was implemented using Pipeline Pilot's dose-response component, resulting in similar values to curve fitting tools such as GraphPad's Prism and IDBS's XIFit. Any value with > indicate sample with no activity (low $D_{Max}$ value) or samples with $CC_{50}$ values above the maximum tested concentration (higher $D_{Max}$ value). Cytotoxic samples were classified by $CC_{50}$ ≤ 32µg/mL or $CC_{50}$ ≤ 10µM in either replicate (n=2 on different plates). In addition, samples were flagged as partial cytotoxic if $D_{Max}$ ≥ 50%, even with $CC_{50}$ > the maximum tested concentration.

**Haemolysis assay**

**Procedure**

Human whole blood was washed three times with 3 volumes of 0.9% NaCl and then resuspended in same to a concentration of 0.5 x 108 cells/mL, as determined by manual cell count in a Neubauer haemocytometer. The washed cells were then added to the 384-well compound-containing plates for a final volume of 50µL. After a 10 min shake on a plate shaker the plates were then incubated for 1 h at 37°C. After incubation, the plates were centrifuged at 1000g for 10 min to pellet cells and debris, 25µL of the supernatant was then transferred to a polystyrene 384-well assay plate.

**Analysis**

Haemolysis was determined by measuring the supernatant absorbance at 405 mm ($OD_{405}$). The absorbance was measured using a Tecan M1000 Pro monochromator plate reader. $HC_{10}$ and $HC_{50}$ (concentration at 10% and 50% haemolysis, respectively) were calculated by curve fitting the inhibition values vs. log(concentration) using a sigmoidal dose-response function with variable fitting values for top, bottom and slope. In addition, the maximal percentage of haemolysis is reported as $D_{Max}$, indicating any compounds with partial haemolysis. The curve fitting was implemented using Pipeline Pilot's dose-response component, resulting in similar values to curve fitting tools such as GraphPad's Prism and IDBS's XIFit. Any value with > indicate sample with no activity (low $D_{Max}$ value) or samples with $HC_{10}$ values above the maximum tested concentration (higher $D_{Max}$ value). Haemolysis samples were classified by $HC_{10}$ ≤ 32µg/mL or $HC_{10}$ ≤ 10µM in either replicate (n=2 on different plates). In addition, samples were flagged as partial haemolytic if $D_{Max}$ ≥ 50%, even with $HC_{10}$ > the maximum tested concentration.

**Antibiotic, cytotoxic and haemolytic standards preparation and quality control**

Colistin and Vancomycin were used as positive bacterial inhibitor standards for Gram-negative and Gram-positive bacteria, respectively. Fluconazole was used as a positive fungal inhibitor standard for

C. albicans and C. neoformans. Tamoxifen was used as a positive cytotoxicity standard. Melittin was used as a positive haemolytic standard.

Each antibiotic standard was provided in 4 concentrations, with 2 above and 2 below its MIC or $CC_{50}$ value, and plated into the first 8 wells of column 23 of the 384-well NBS plates. Tamoxifen and melittin was used in 8 concentrations in 2 fold serial dilutions with 50µg/mL highest concentration.

The quality control (QC) of the assays was determined by Z'-Factor, calculated from the Negative (media only) and Positive Controls (bacterial, fungal or cell culture without inhibitor), and the Standards. Plates with a Z'-Factor of ≥ 0.4 and Standards active at the highest and inactive at the lowest concentration, were accepted for further data analysis.

**Membrane activity study**

**Bilayer setup, recording system, and mode of calculations**

Synthetic 1,2-diphytanoyl-sn-glycero-3-phosphocholine (DPhPC) and 1,2-diphytanoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (DPhPG) were obtained from Avanti® Polar Lipids. Bilayer lipid membranes were prepared from DPhPC or DPhPG using a monolayer-opposition technique [M. Montal, P. Muller, *Proc. Nat. Acad. Sci. USA*. **1972**, *65*, 3561–3566.] on a 50 µm-diameter aperture in a 10 µm-thick Teflon film separating cis- and trans- compartments of the Teflon chamber. Experiments were performed in the chambers containing 0.1 M KCl, 5 mM Hepes-KOH pH 7.4.

Tasting derivatives (**1a**, **3a**, **6c**) from 10 mg/ml solutions in ethanol were added to the cis-chamber to mimic the physiologically relevant conditions to the final concentration indicated in the Table 7 and were observed the changes in the ion permeability of the model membranes. Ag/AgCl electrodes with 1.5% agarose/2 M KCl bridges were used to apply the transmembrane voltage (V) and measure the transmembrane current (I). 'Positive voltage' refers to the case in which the cis-side compartment is positive with respect to the trans-side. All experiments were performed at room temperature.

The changes in the ion permeability of the model membranes for the defined experimental conditions were averaged from 3 to 4 bilayers mean ± standard error ($p \leq 0.05$).

Current was measured using an Axopatch 200B amplifier (Molecular Devices, LLC, Orlean, CA, USA) in the voltage clamp mode. Data were digitized using a Digidata 1440A and analyzed using pClamp 10.0 (Molecular Devices, LLC, Orlean, CA, USA) and Origin 8.0 (OriginLab Corporation, Northampton, MA, USA). Data were acquired at a sampling frequency of 5 kHz using low-pass filtering at 200 Hz.

**4.3.3. Measurement of the membrane boundary potential**

Virtually solvent-free planar lipid bilayers were prepared using a monolayer-opposition technique [42]. Lipid bilayers were made from DPhPC or DPhPG. After the membrane was completely formed and stabilized and its stability was assessed by applying voltages in the range from -200 to 200 mV with 50 mV-step for 5-10 minutes, stock solutions of nonactin A (7 µg/ml in ethanol) were added to the bathing solution (0.1 M KCl, 5 mM HEPES, pH 7.4) in both compartments to obtain a final concentration ranging from 0.1 to 1 µM.

Tasting derivatives (**1a**, **3a**, **6c**) from 10 mg/ml solutions in ethanol were added to the both compartments in the concentration range from 5 µg/ml to the limiting concentration that causes destabilization and destruction of the bilayer in increments of 25 µg/ml. The changes in the membrane boundary potential for the defined experimental conditions were averaged from 4 bilayers mean ± standard deviation ($p \leq 0.05$).

The conductance of the bilayers was determined by measuring membrane conductance (*G*) at a constant transmembrane voltage (*V* = 50 mV). In the subsequent calculations, the membrane conductance was assumed to be related to the membrane boundary potential ($\varphi_b$), the potential drop between the aqueous solution and the membrane hydrophobic core, by the Boltzmann distribution [O.S. Andersen, A. Finkelstein, I. Katz, A. Cass, *J. Gen. Physiol*. **1976**, *67*, 749–771.]

$$\frac{G_m}{G_m^0} = \exp(\frac{e\Delta\varphi_b}{kT}), \quad (1)$$

where $G_m$ and $G_m^0$ are the steady-state membrane conductances induced by $K^+$-nonactin in the presence and absence of derivatives, respectively; e, k, and T have their usual meanings.

4.3.4. Calcein release assay

Large unilamellar vesicles were made from 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) or 1,2-dioleoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (DOPG) and loaded with the fluorescent dye calcein (35 mM) using a mini-extruder (Avanti® Polar Lipids).At this concentration calcein fluorescence inside the liposomes is self-quenched. The increase of fluorescence of free calcein in the surrounding media is a measure of the disturbance of membrane integrity in the absence and presence of derivatives (**1a**, **3a**, **6c**). The control samples were not modified. Experimental samples were addition of the derivatives (**1a**, **3a**, **6c**) to a concentration in the range from 5 to 50 μg/ml. Fluorescence of released calcein was determined on a Fluorat-02-Panorama spectrofluorimeter **(**Lumex, Saint-Petersburg, Russia) (at excitation wavelength of 490 nm, emission wavelength of 520 nm). The detergent triton X-100 (at final concentration of 1%) was added at the end of experiments for complete disruption of liposomes (referred to full disengagement of the marker from vesicles).

The relative intensity of calcein fluorescence (*IF*, %) was calculated as:

$$IF = \frac{I - I_0}{I_{\max}/0.9 - I_0} \cdot 100\%, \quad (2)$$

where I and $I_0$ are the calcein fluorescence intensities in the presence and absence of derivatives, respectively, and $I_{max}$ is the maximal fluorescence after treatment of liposomes with triton X-100 (a factor of 0.9 was introduced to account for sample dilution by triton X-100).

**Figure S1.** $^{1}$H and $^{13}$C NMR of compound **5a**

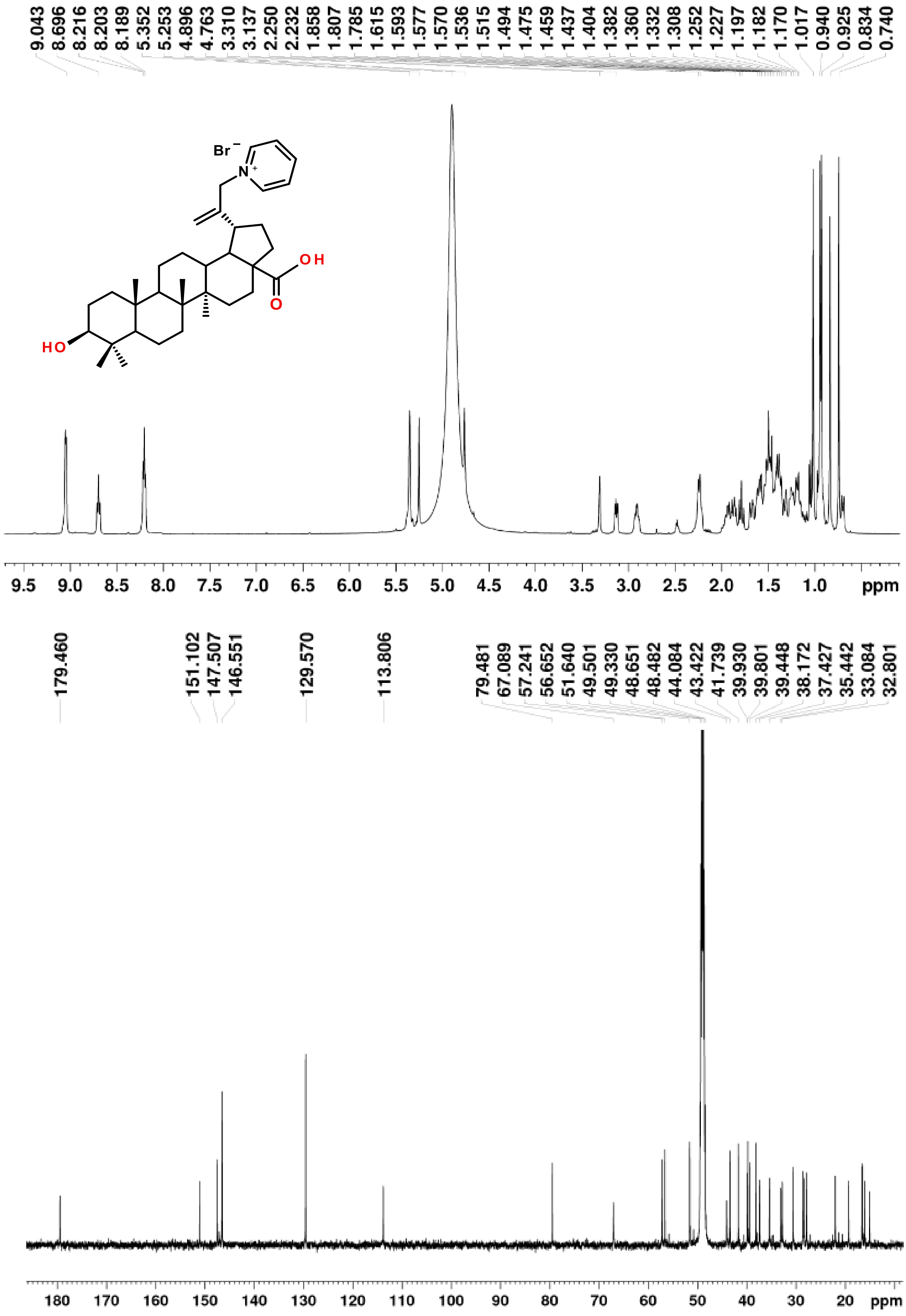
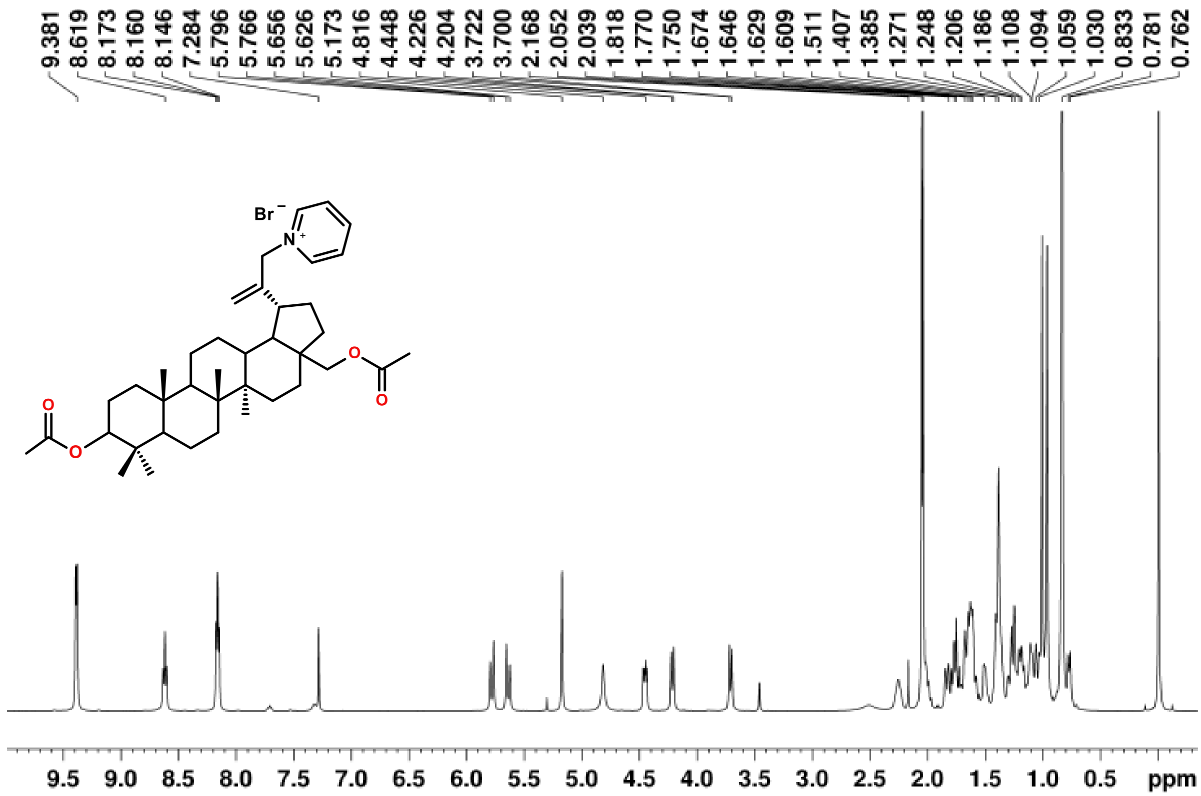


**Figure S2.** $^{1}H$ and $^{13}C$ NMR of compound **6a**



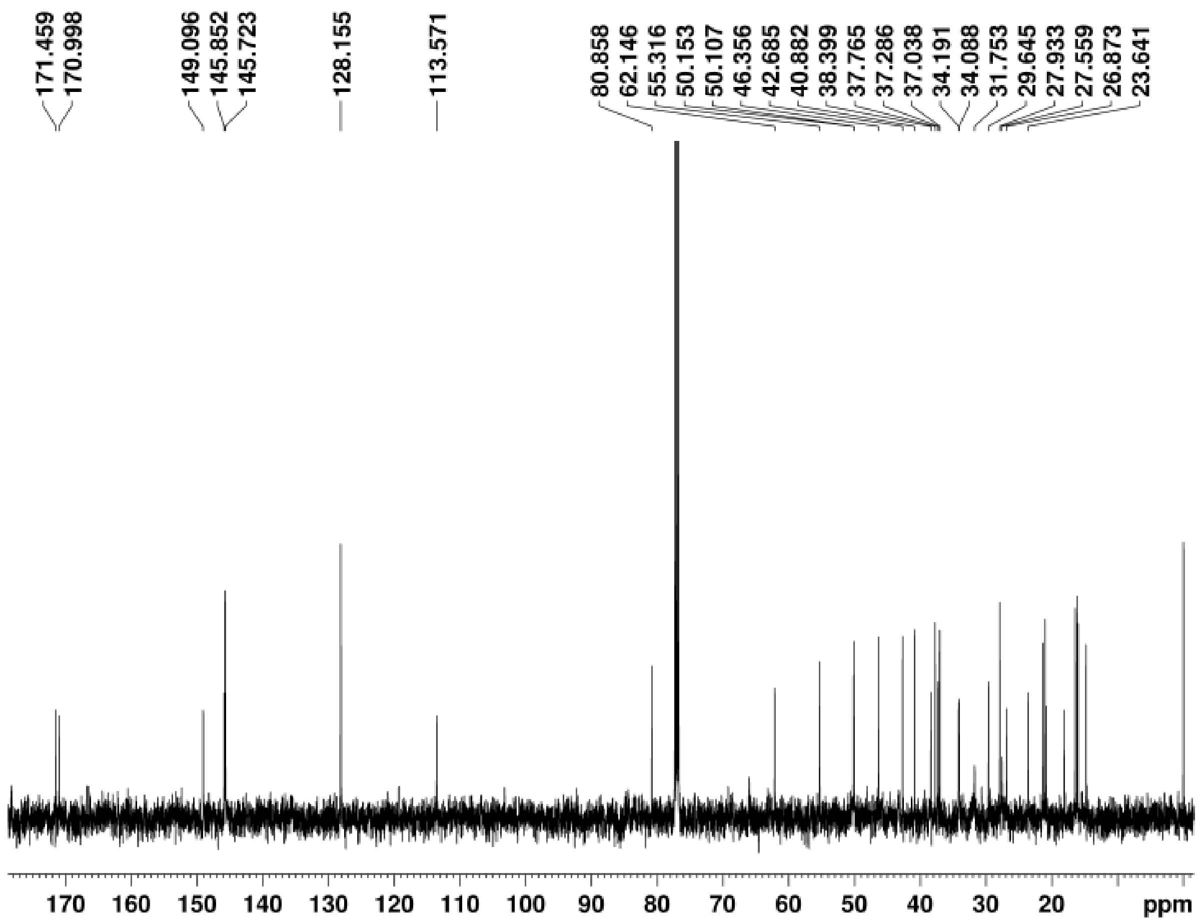
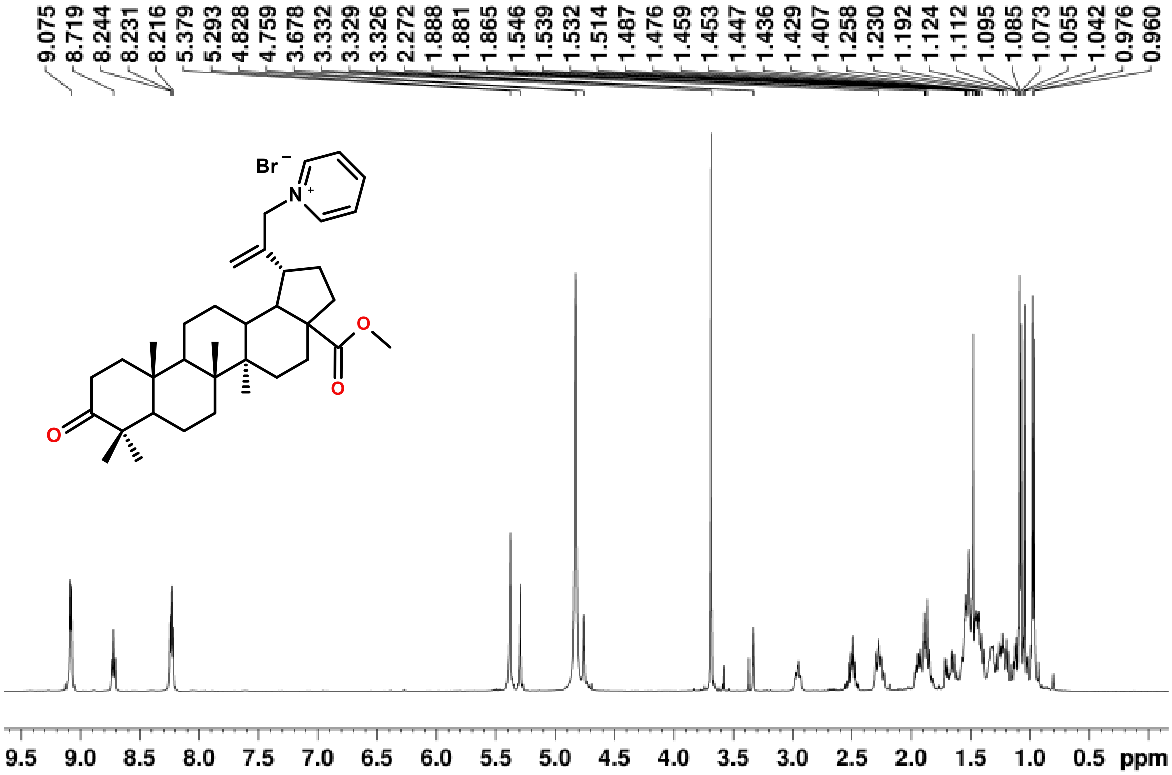
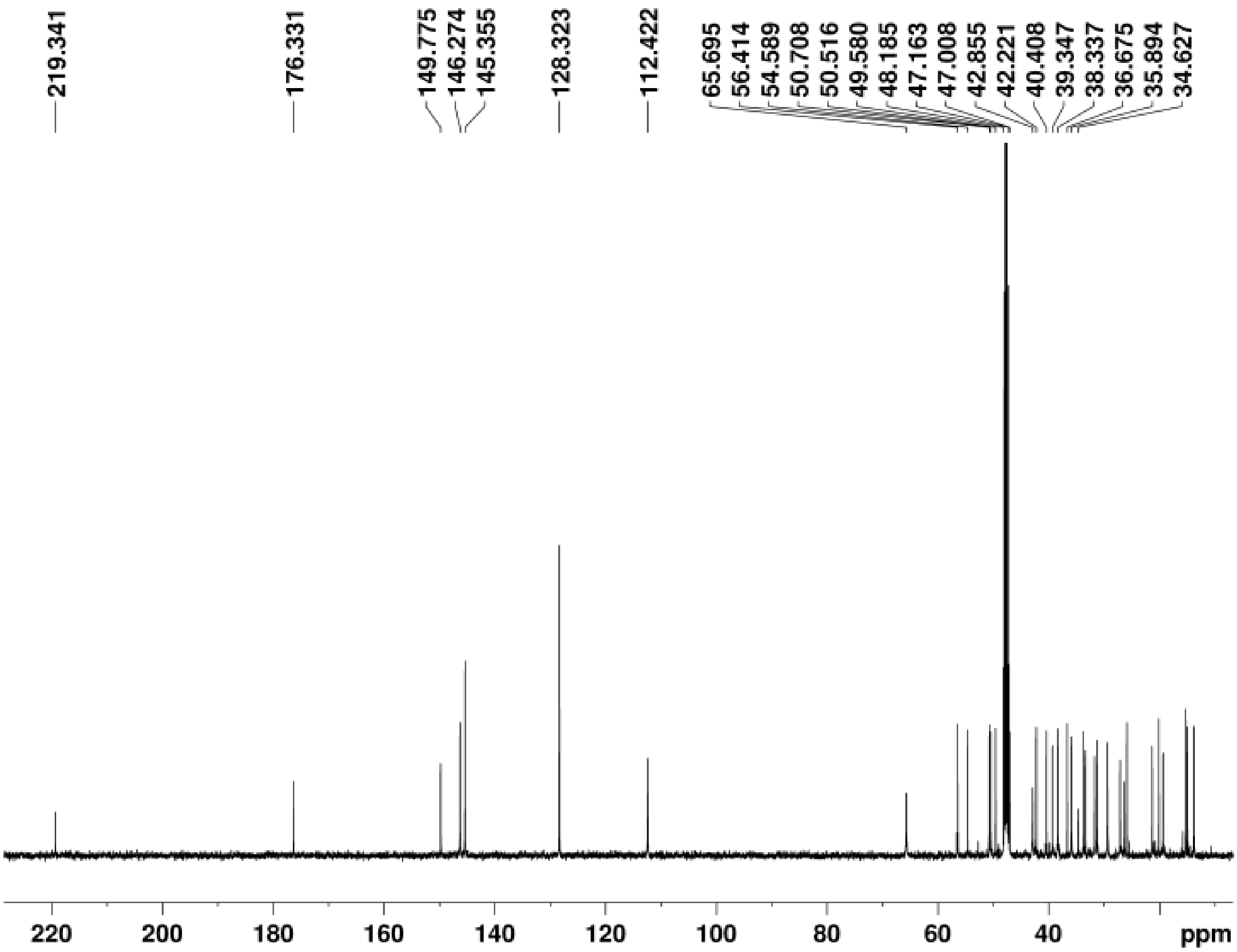
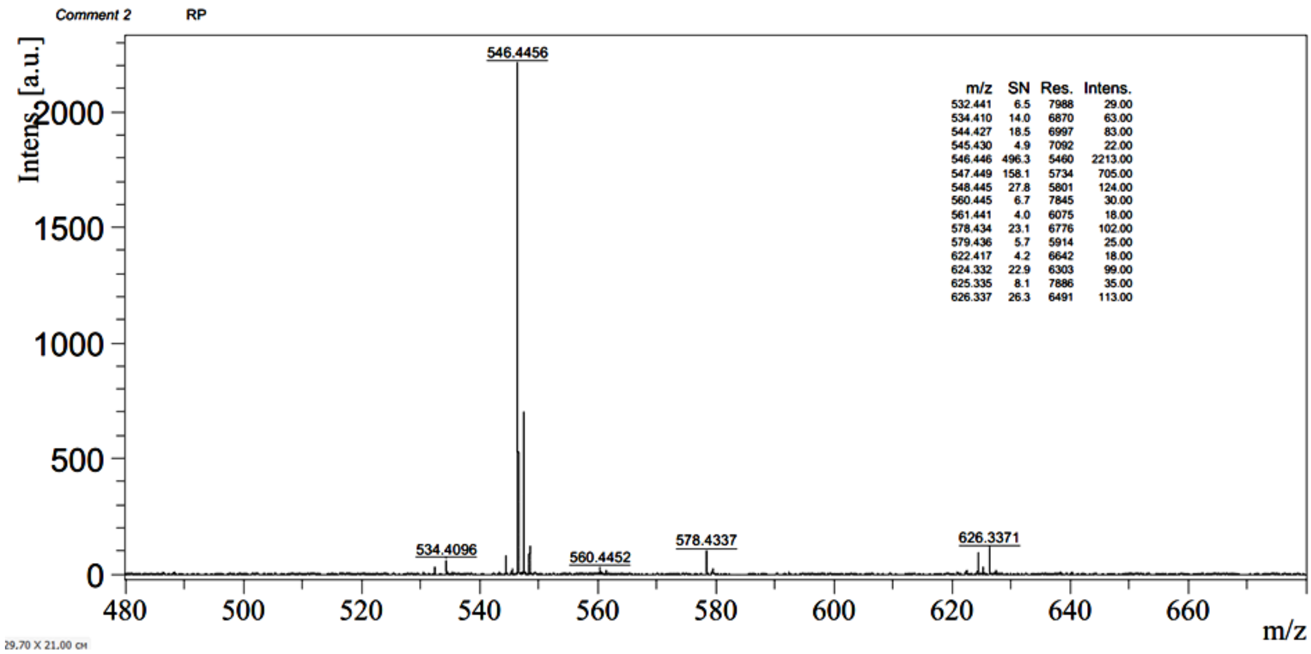



**Figure S3.** $^{1}$H, $^{13}$C NMR and MALDI TOF/TOF of compound **7a**

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m/z SN Res. Intens.
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546.446 496.3 5460 2213.00
547.449 158.1 5734 705.00
548.445 27.8 5801 124.00
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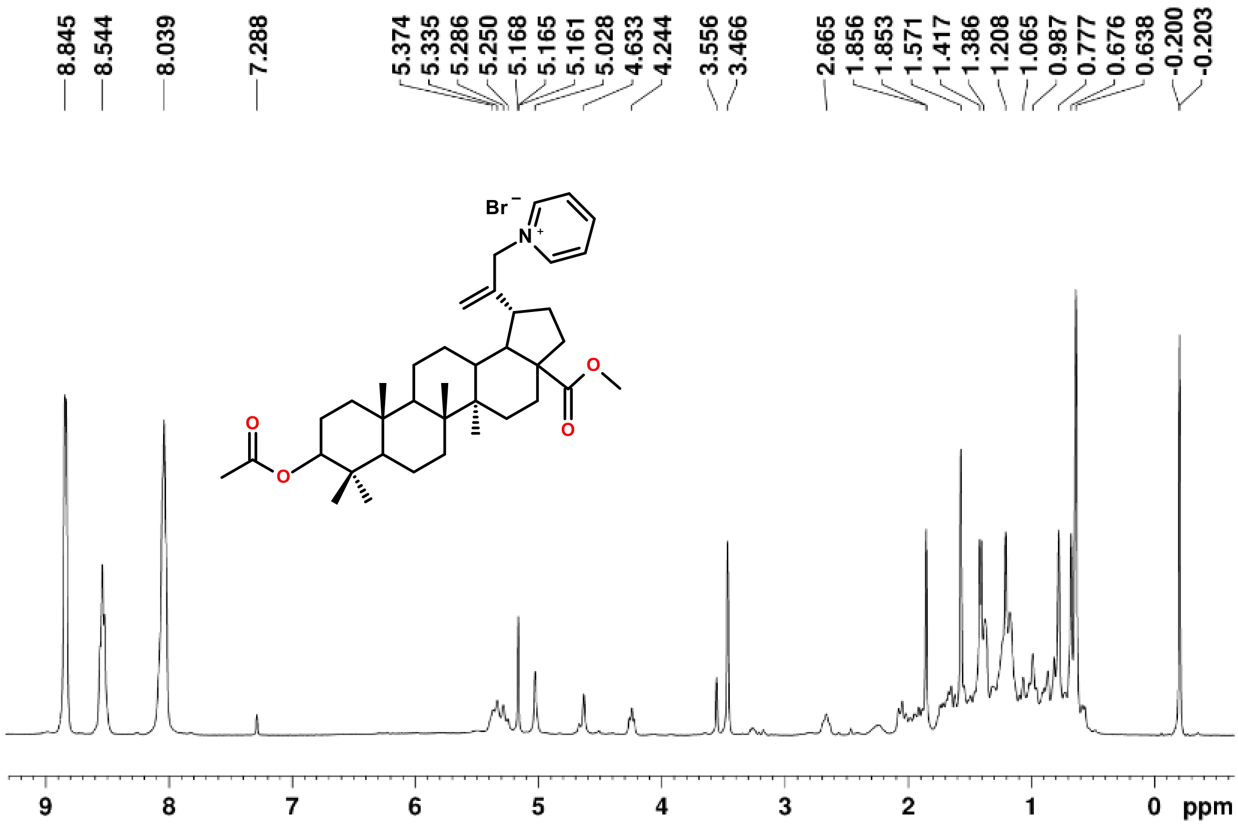
561.441 4.0 6075 18.00
578.434 23.1 6776 102.00
579.436 5.7 5914 25.00
622.417 4.2 6642 18.00
624.332 22.9 6303 99.00
625.335 8.1 7886 35.00
626.337 26.3 6491 113.00
29.70 X 21.00 cm

**Figure S4.** $^{1}$H and $^{13}$C NMR of compound **8a**



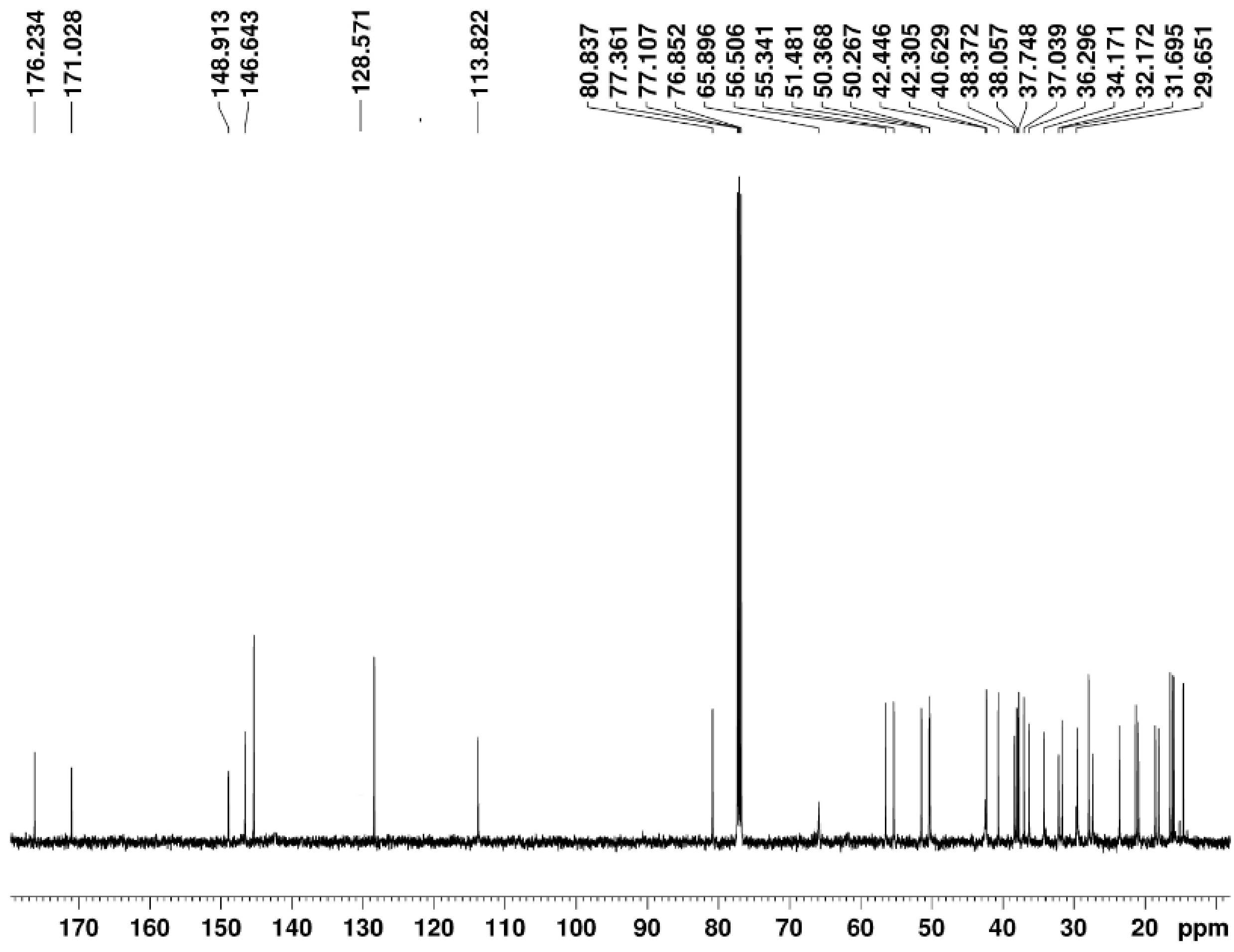



**Figure S5.** $^{1}H$ and $^{13}C$ NMR of compound **9a**

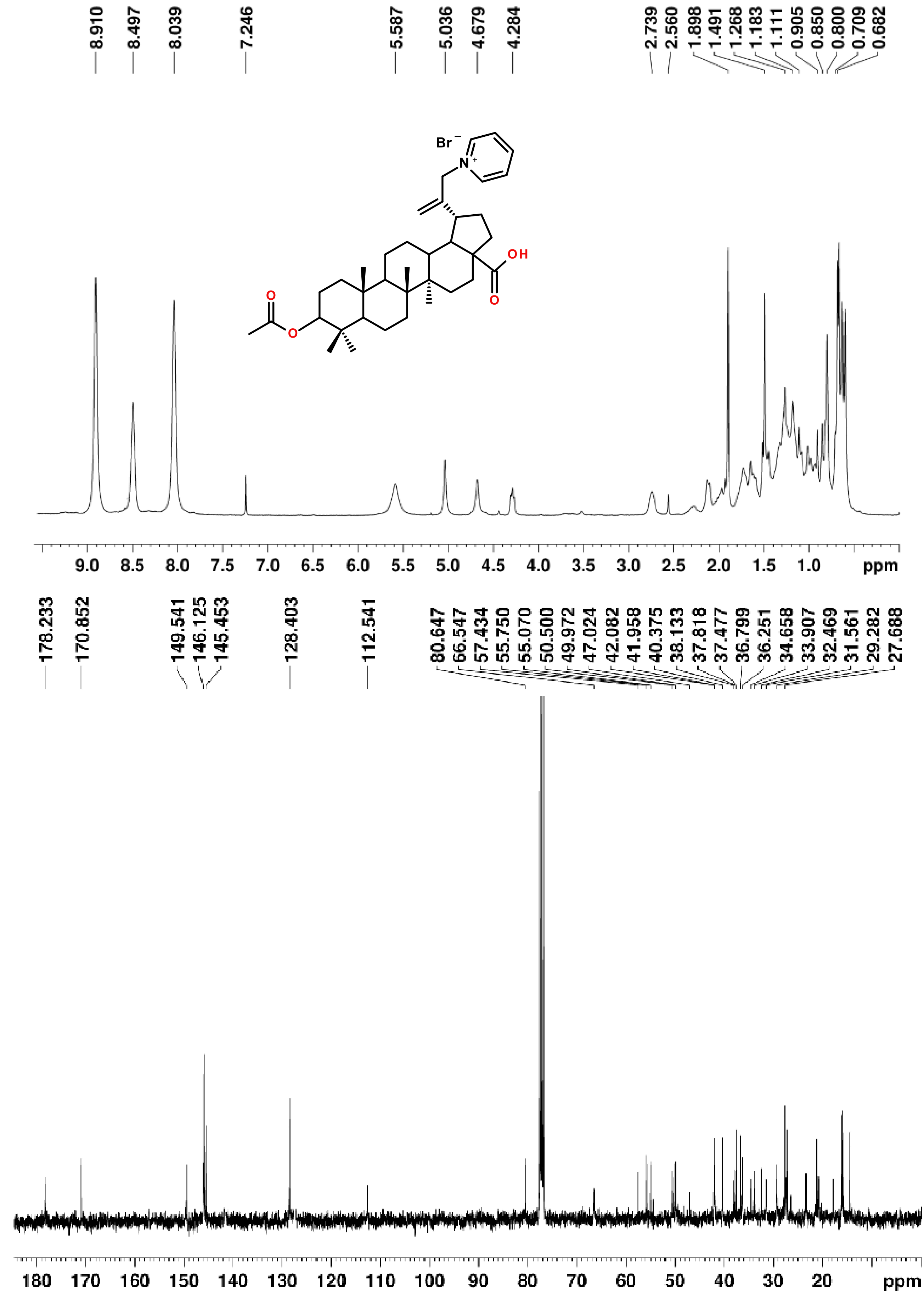


**Figure S6.** $^{1}H$ and $^{13}C$ NMR of compound **2b**

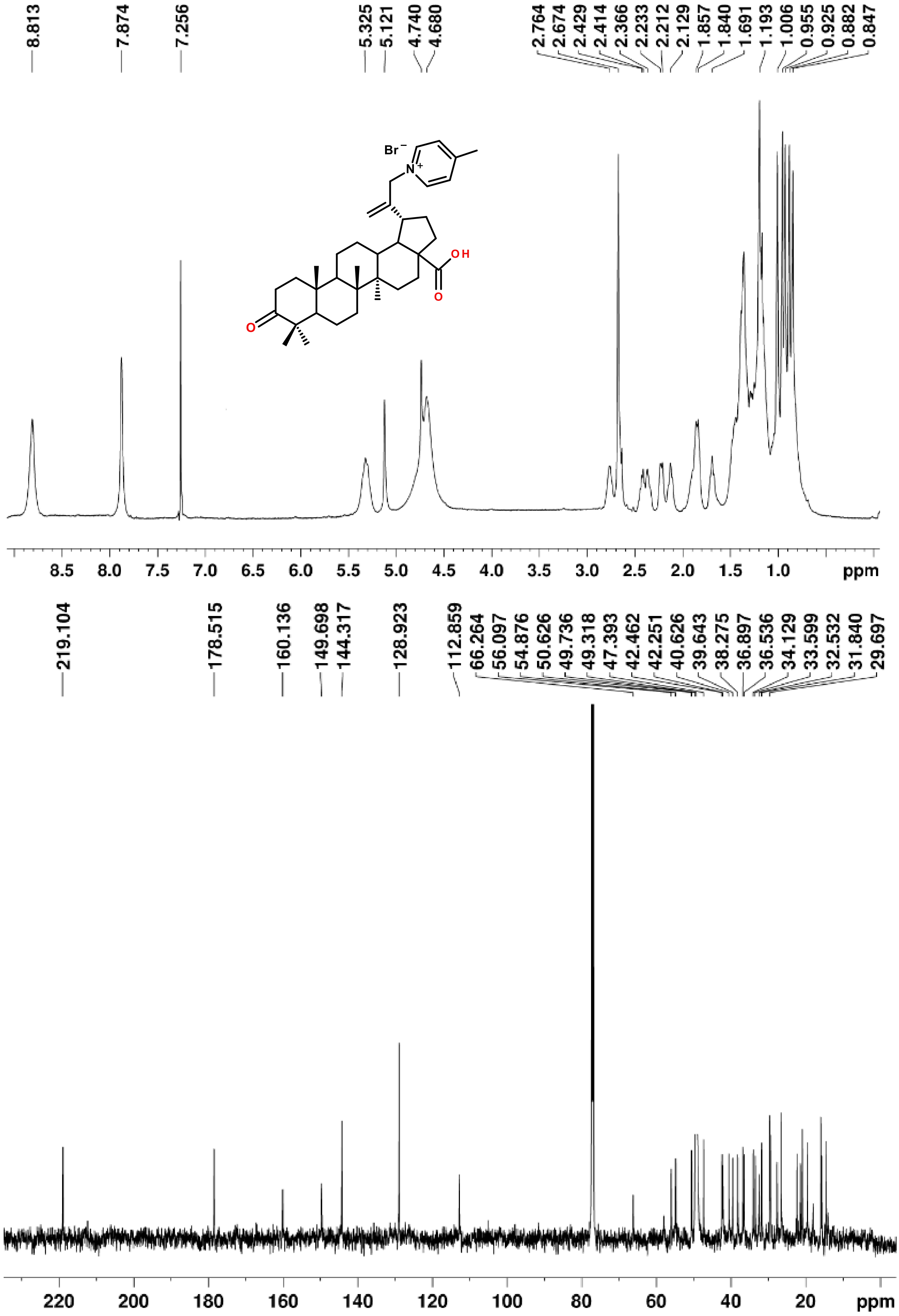


**Figure S7.** $^{1}H$ and $^{13}C$ NMR of compound **3b**

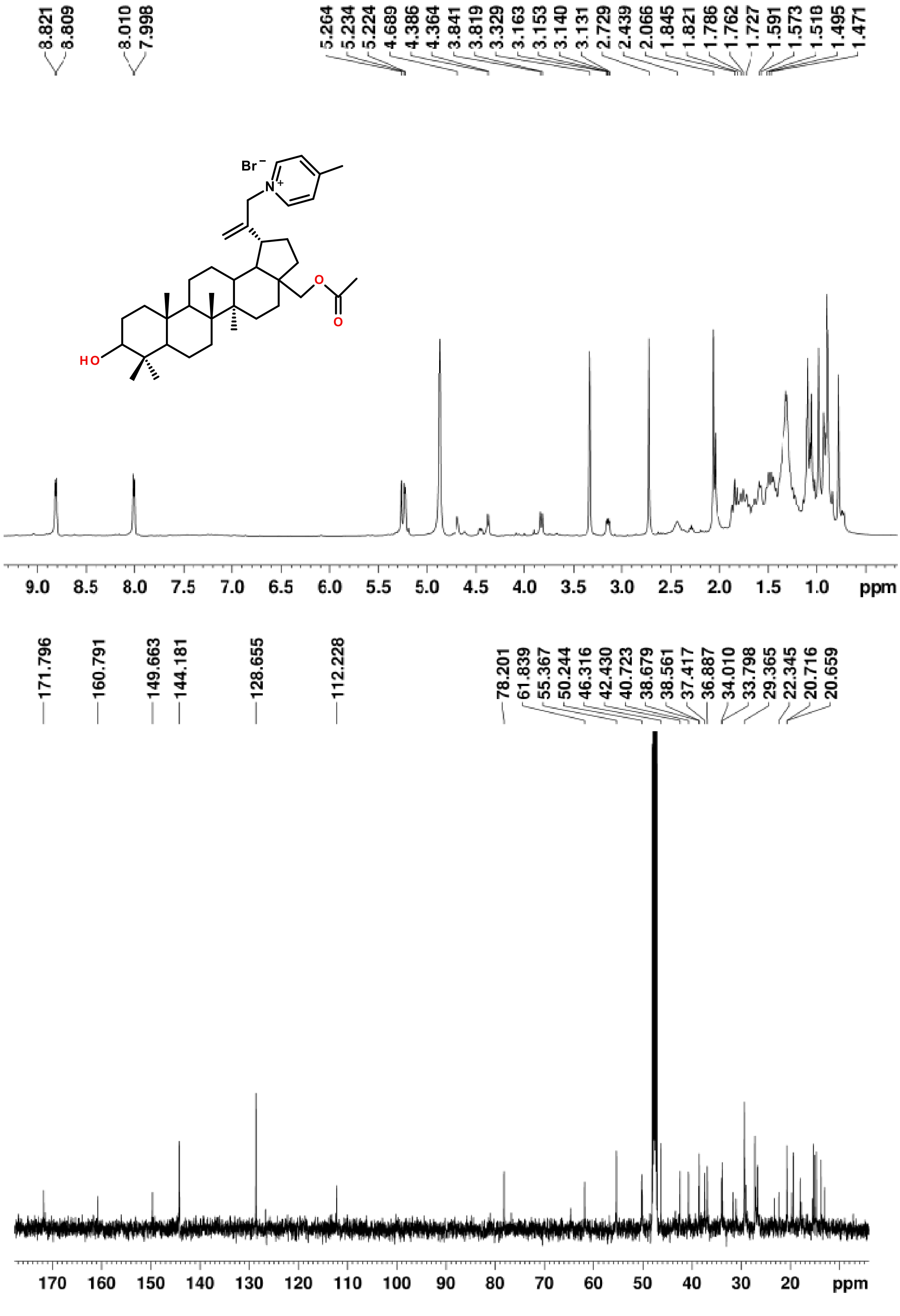


**Figure S8.** $^{1}H$ and $^{13}C$ NMR of compound **4b.**

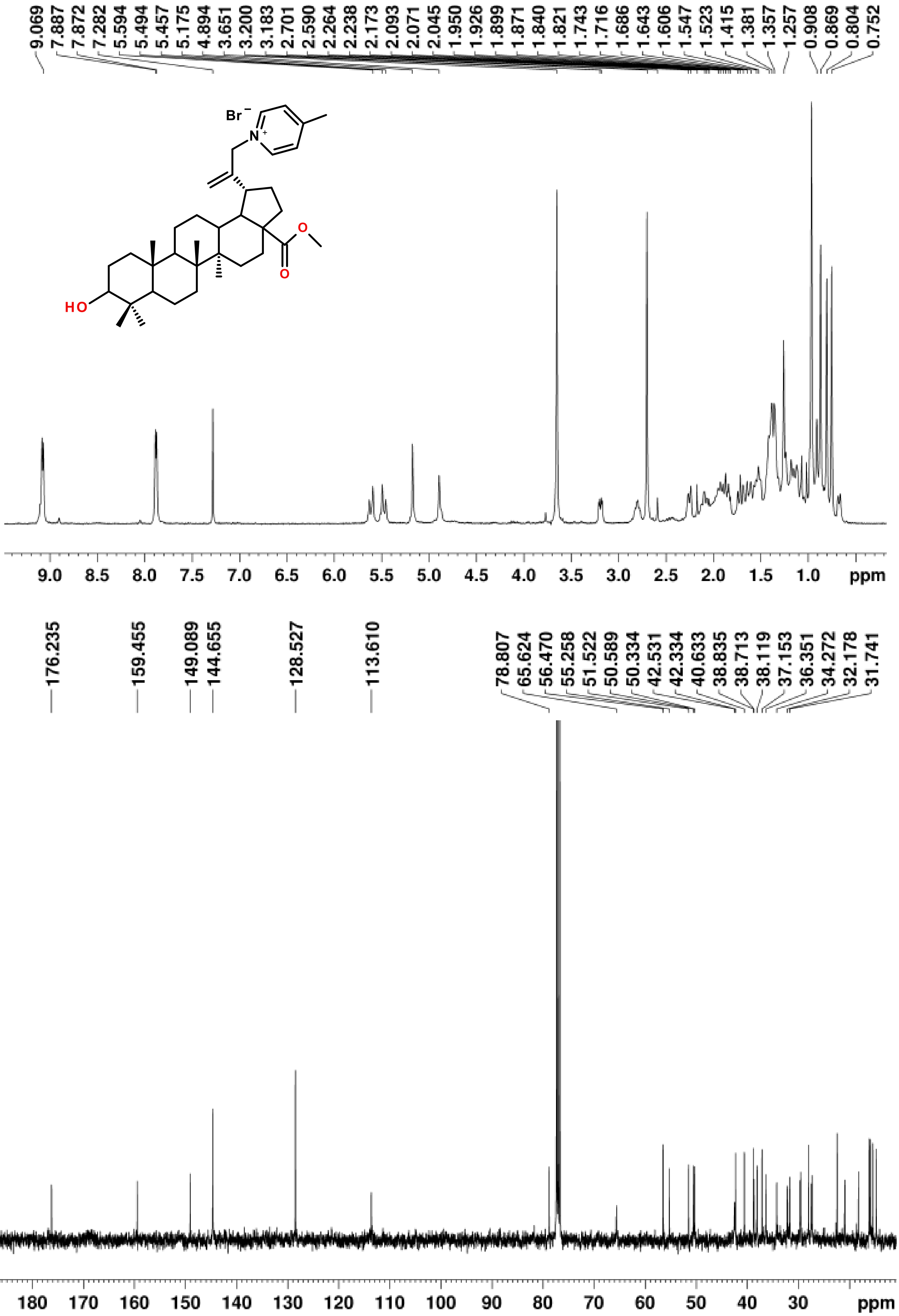


**Figure S9.** $^{1}$H and $^{13}$C NMR of compound **5b**

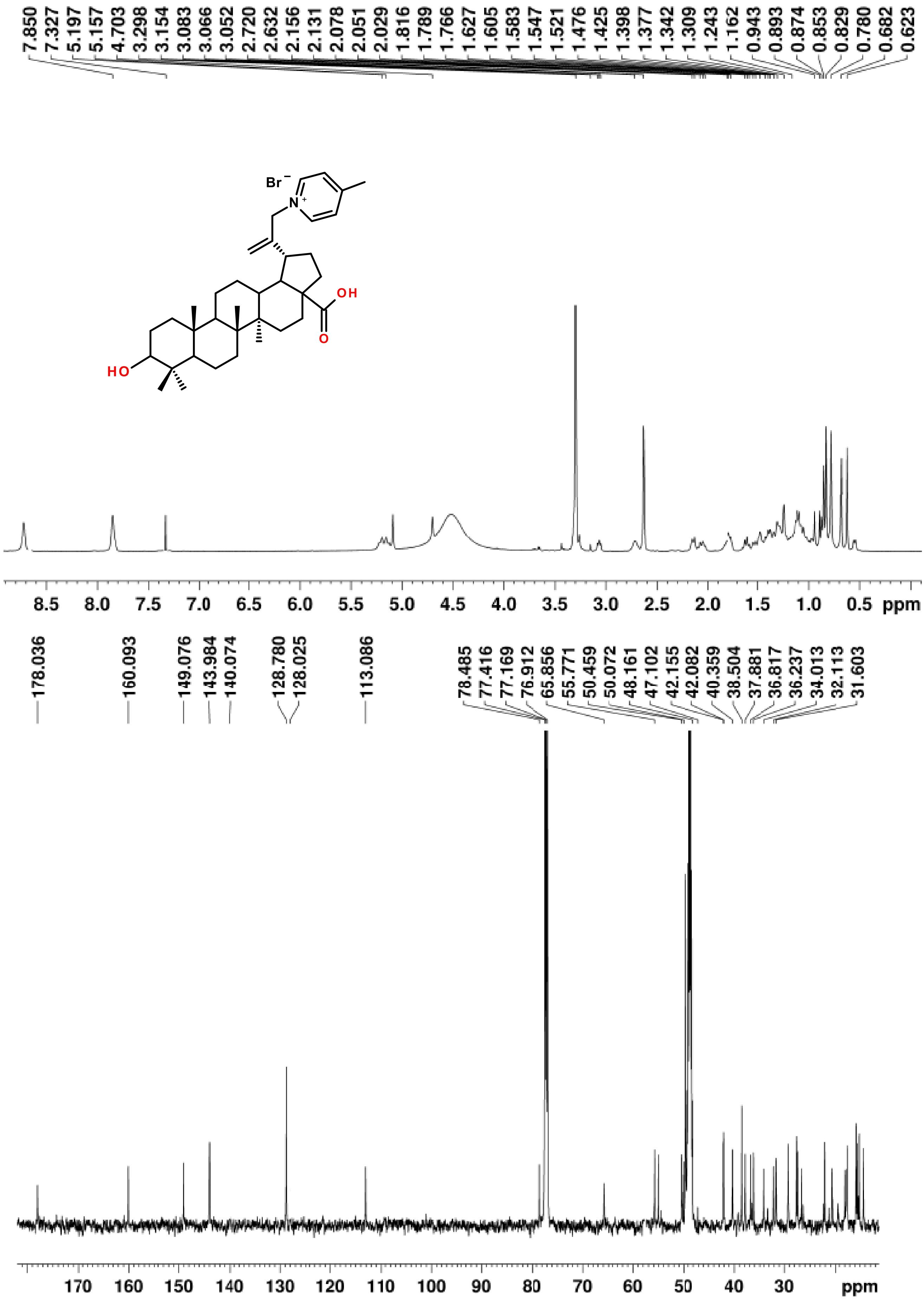


**Figure S10.** $^{1}$H and $^{13}$C NMR of compound **6b**

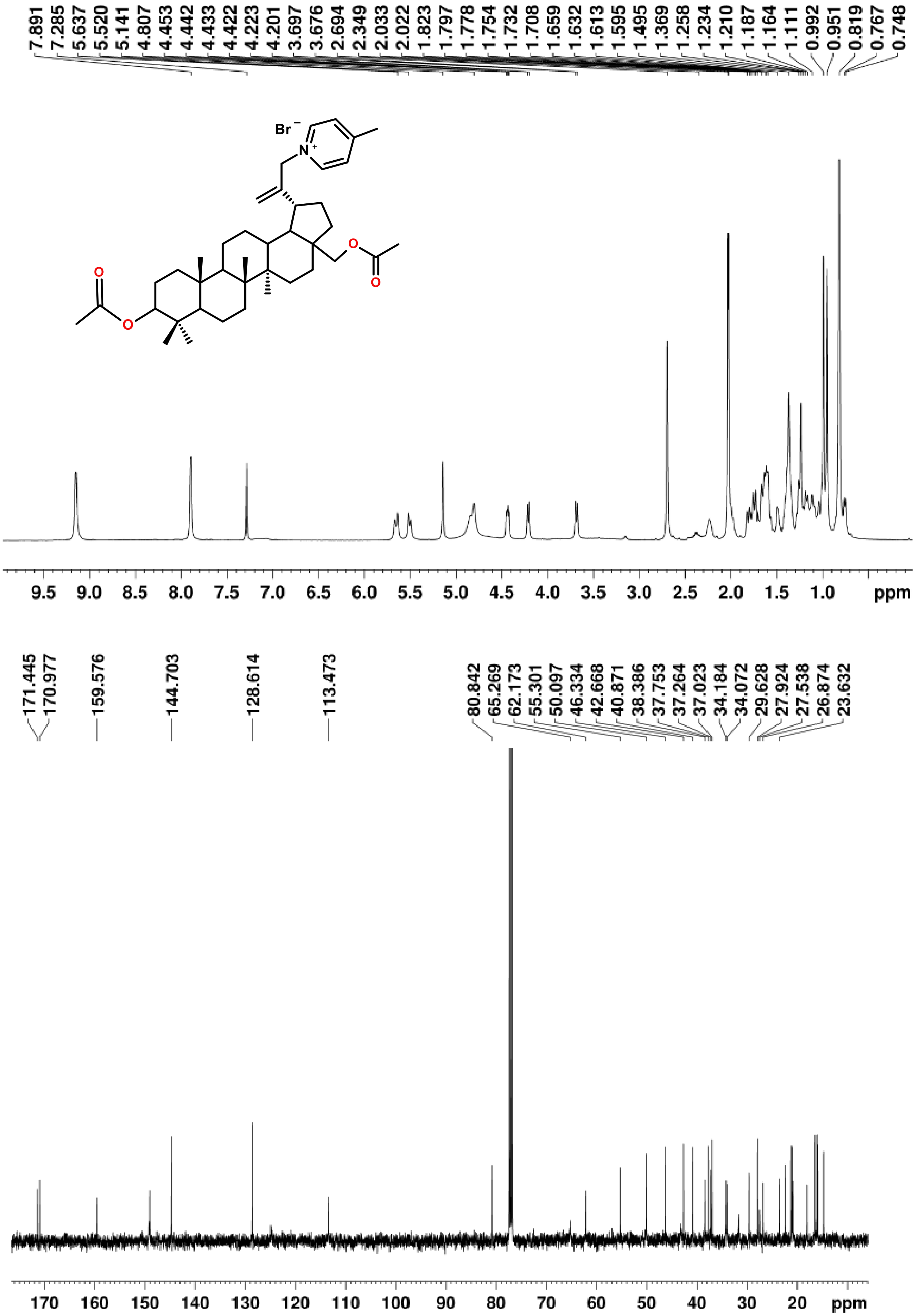
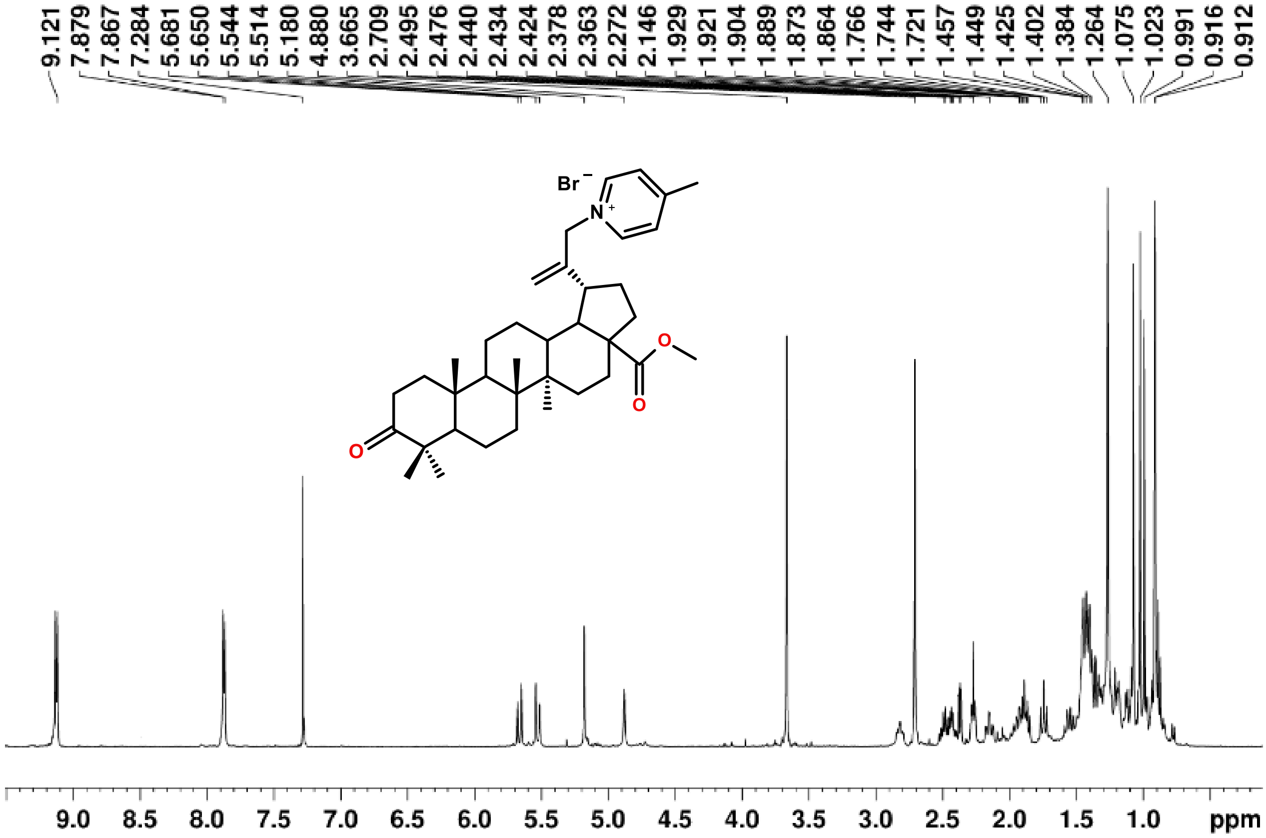
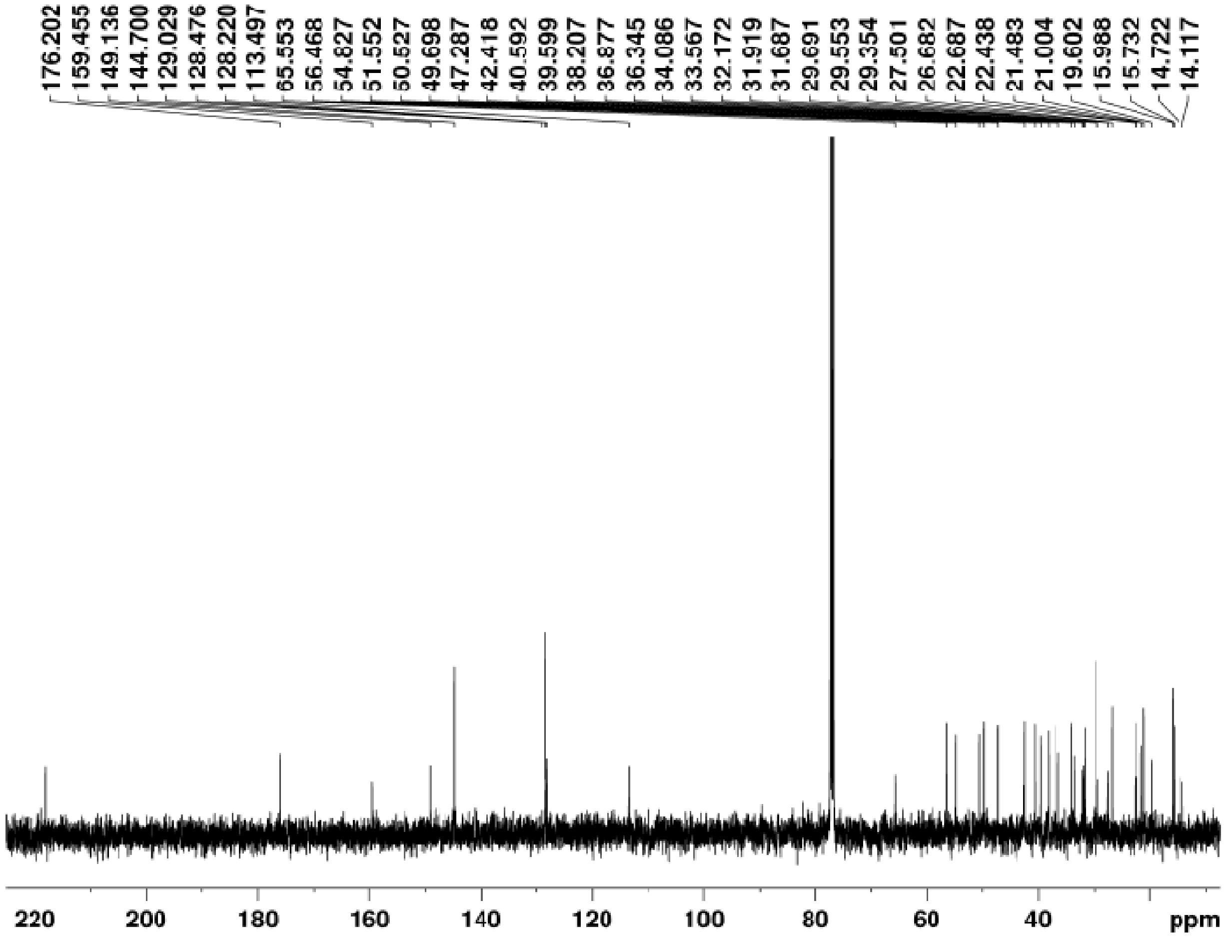
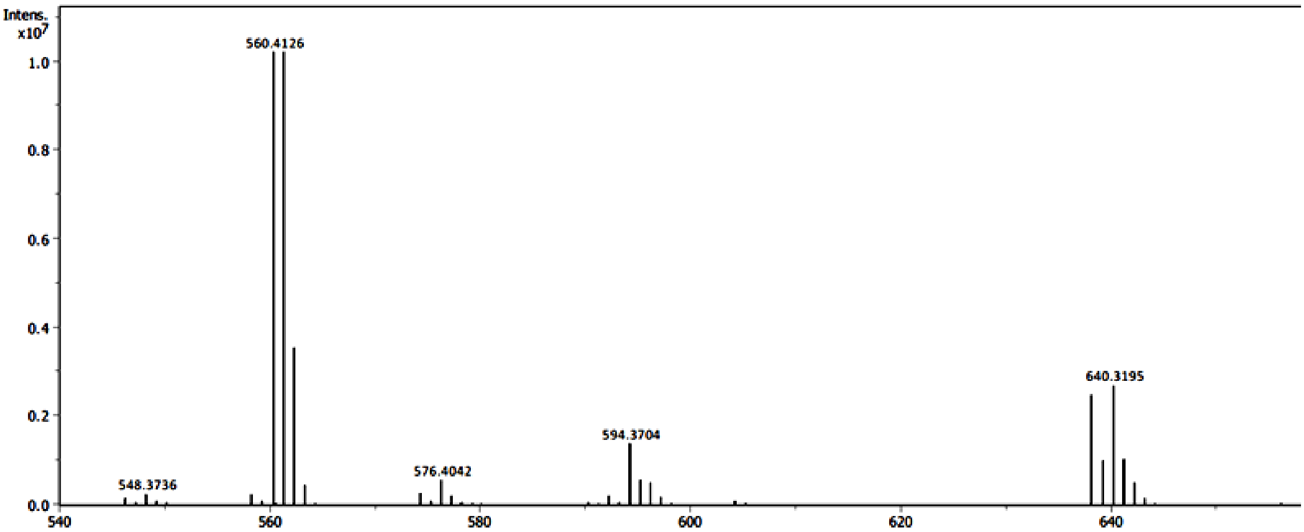


**Figure S11.** $^{1}$H, $^{13}$C NMR and ESI-MS of compound **7b**

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548.3736
540
560
580
600
620
640

**Figure S12.** $^{1}H$ and $^{13}C$ NMR of compound **9b**

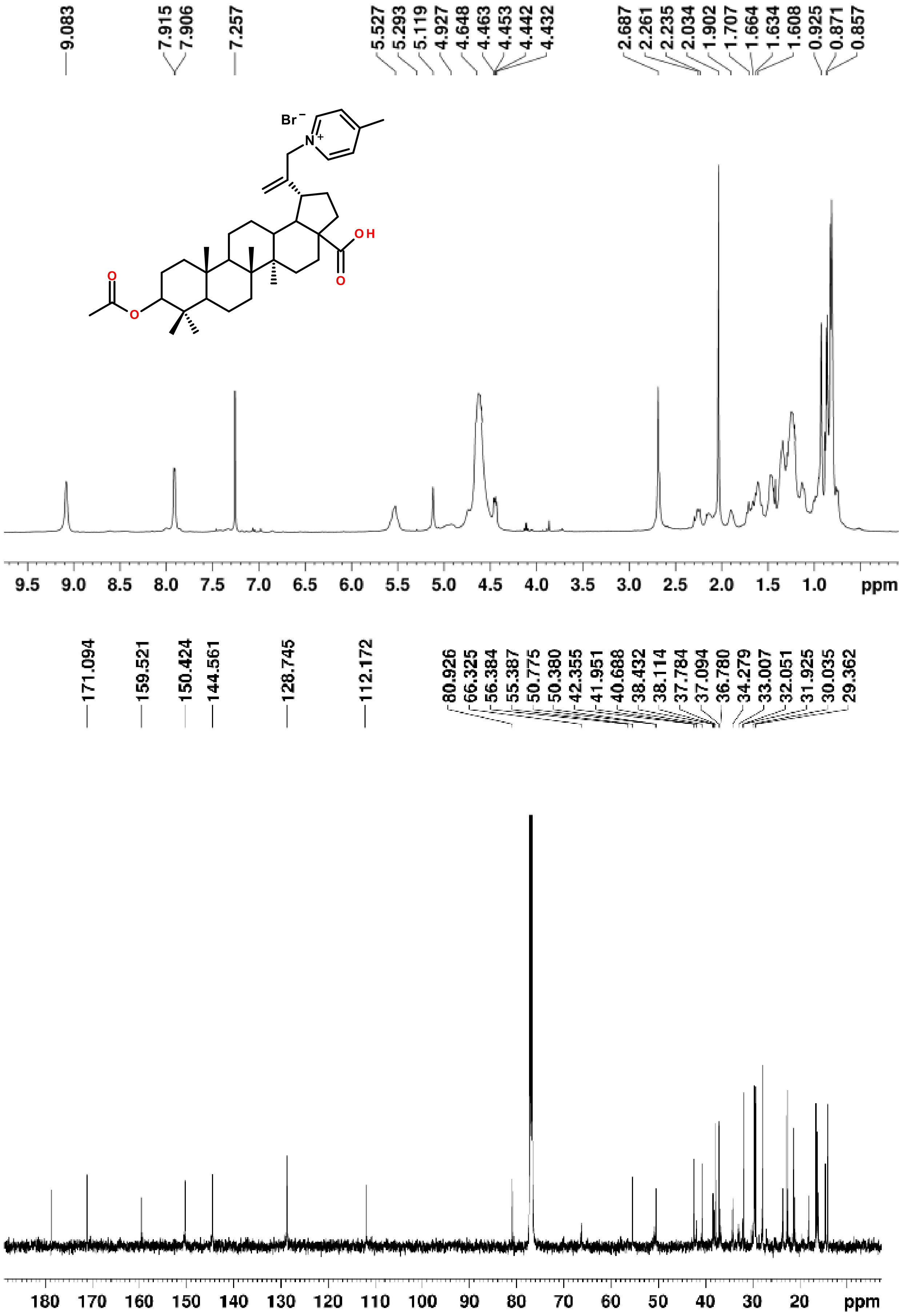


**Figure S13.** $^1$H and $^{13}$C NMR of compound **2c**

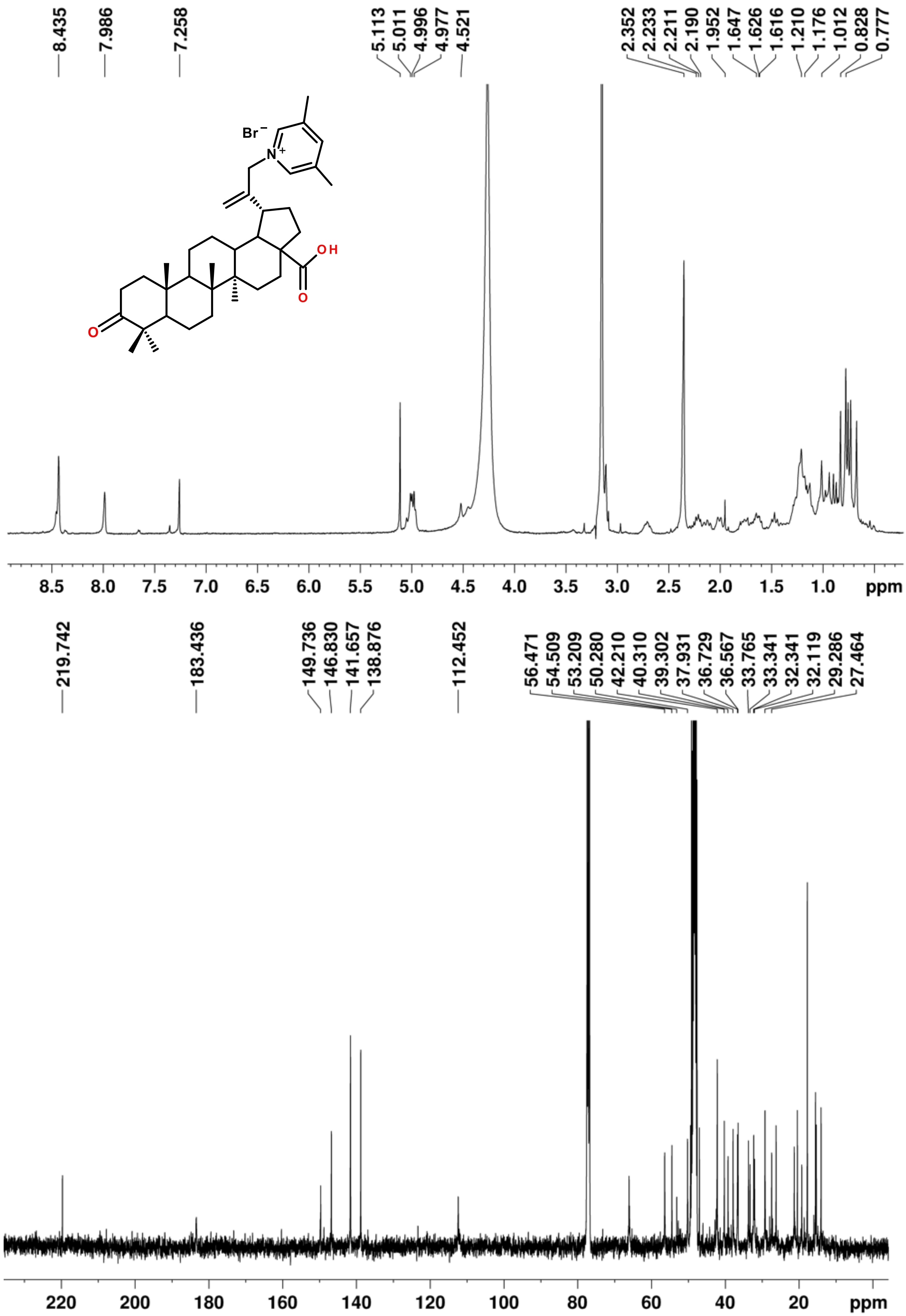


**Figure S14.** $^{1}H$ and $^{13}C$ NMR of compound **3c**

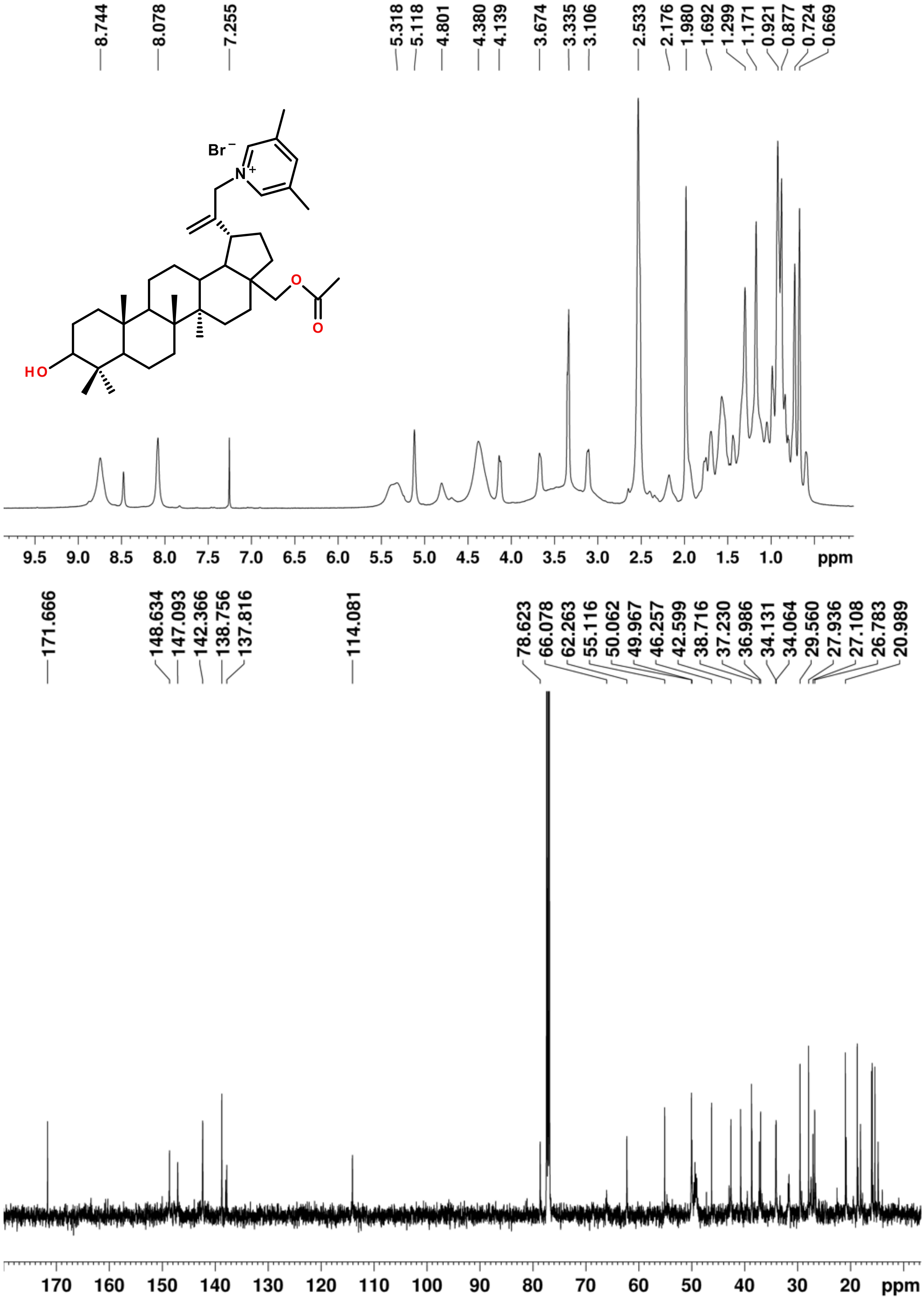


**Figure S15.** $^{1}H$ and $^{13}C$ NMR of compound **4c**

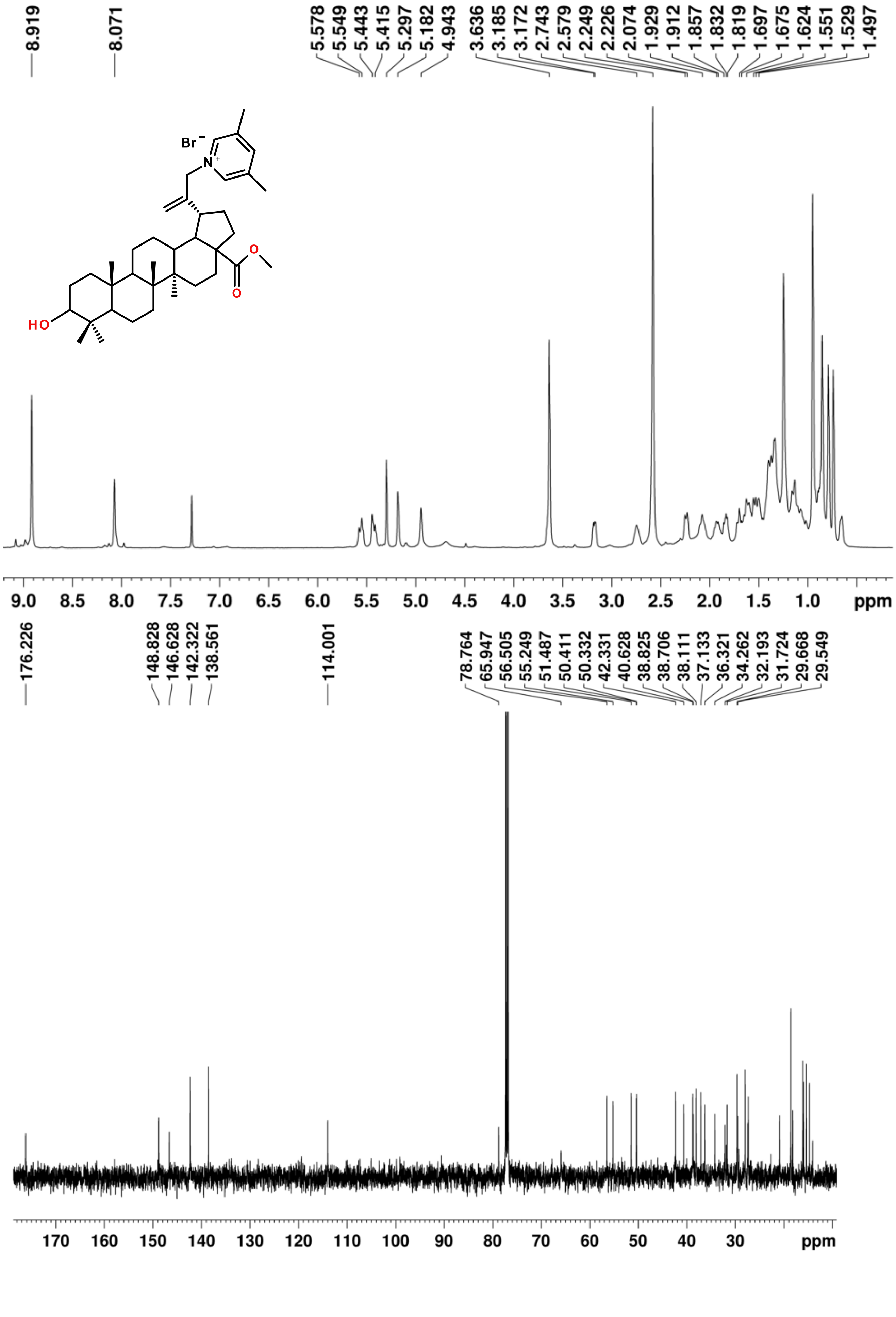


**Figure S16.** $^{1}H$ and $^{13}C$ NMR of compound **5c**

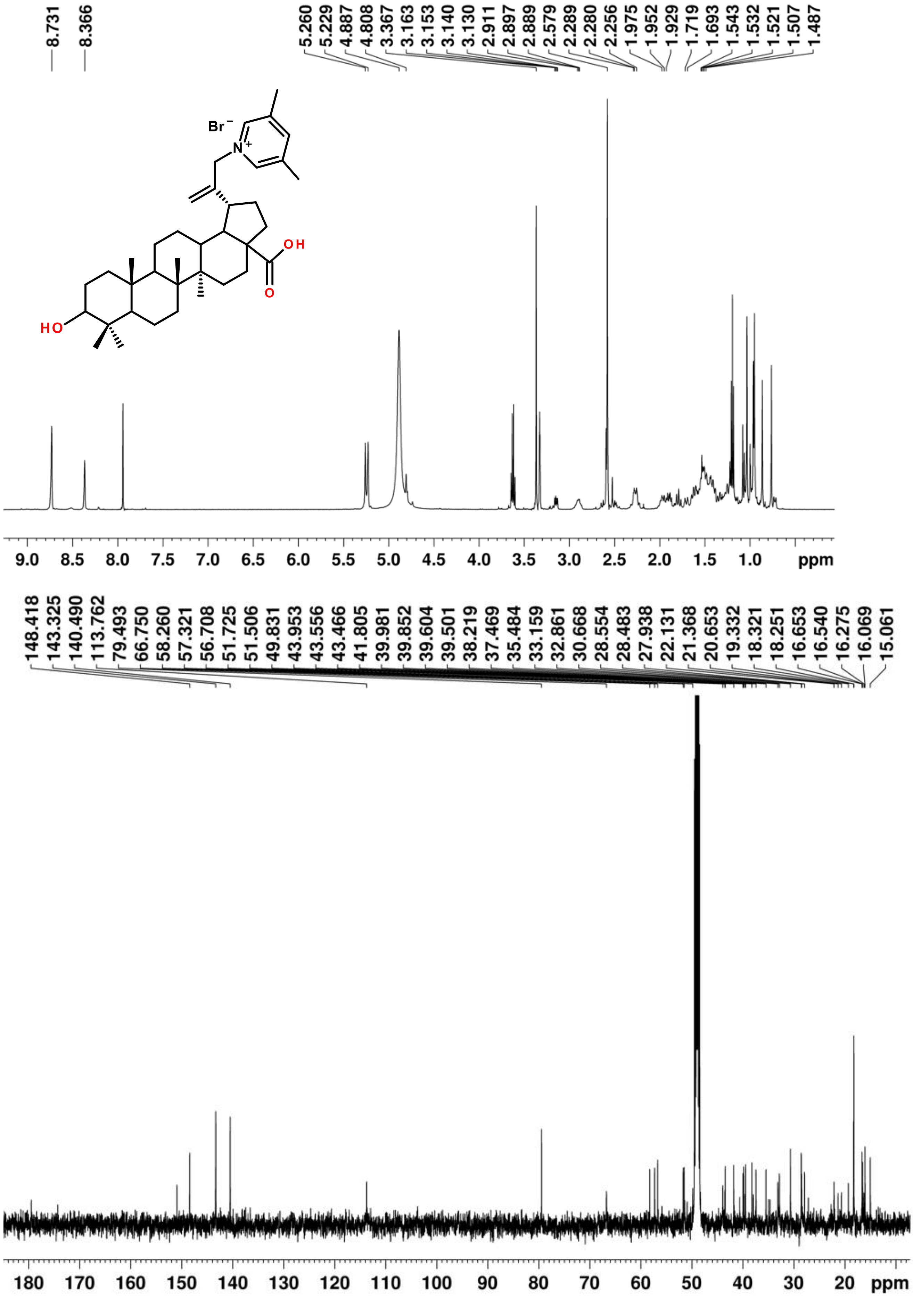
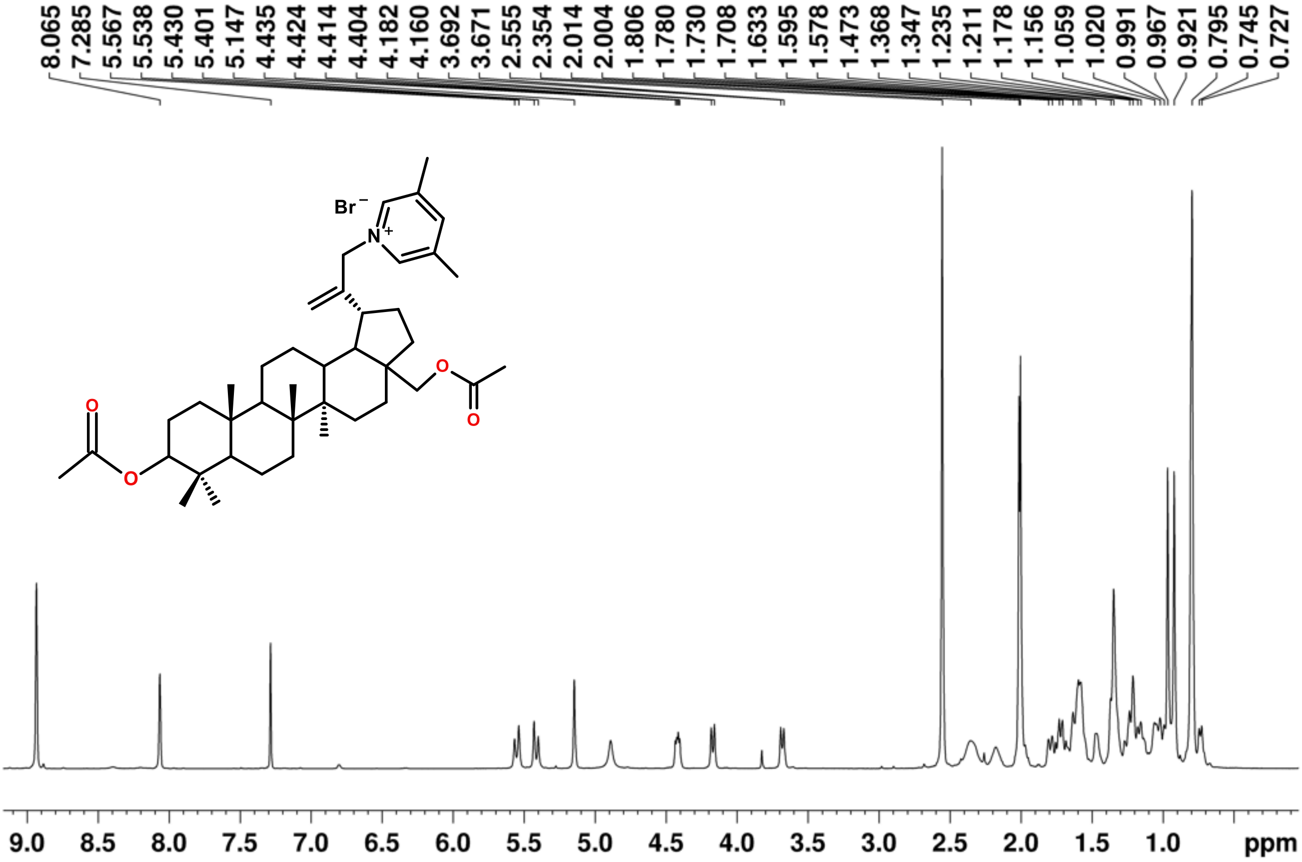


**Figure S17.** $^{1}H$ and $^{13}C$ NMR of compound **6c**



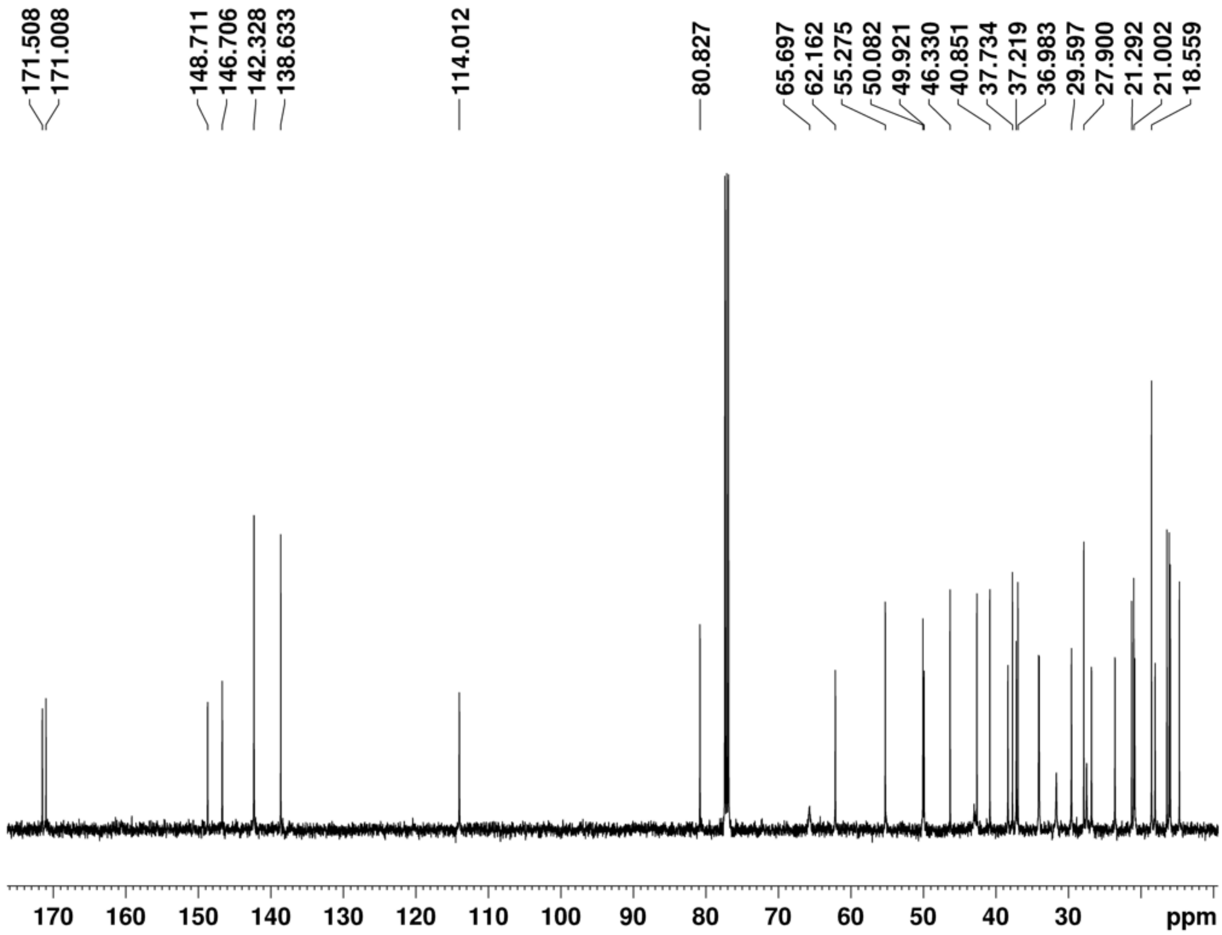
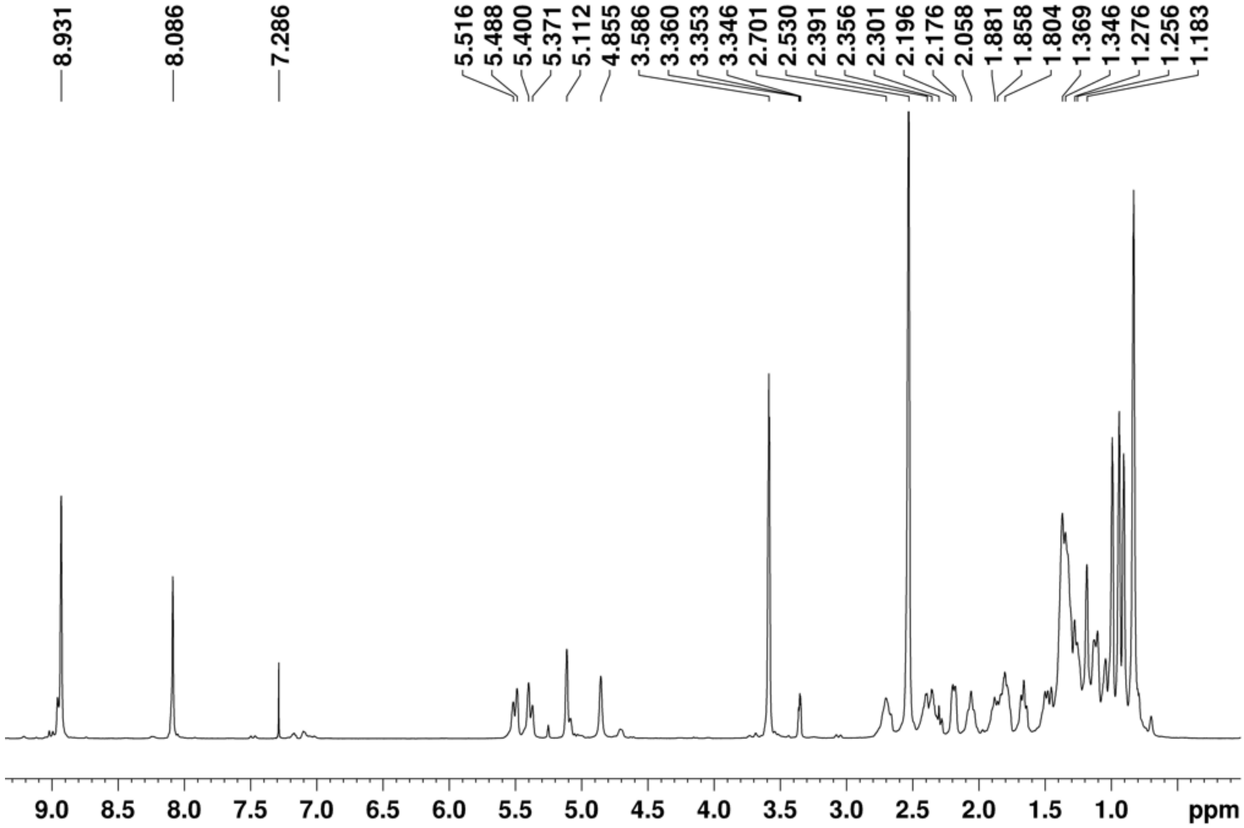
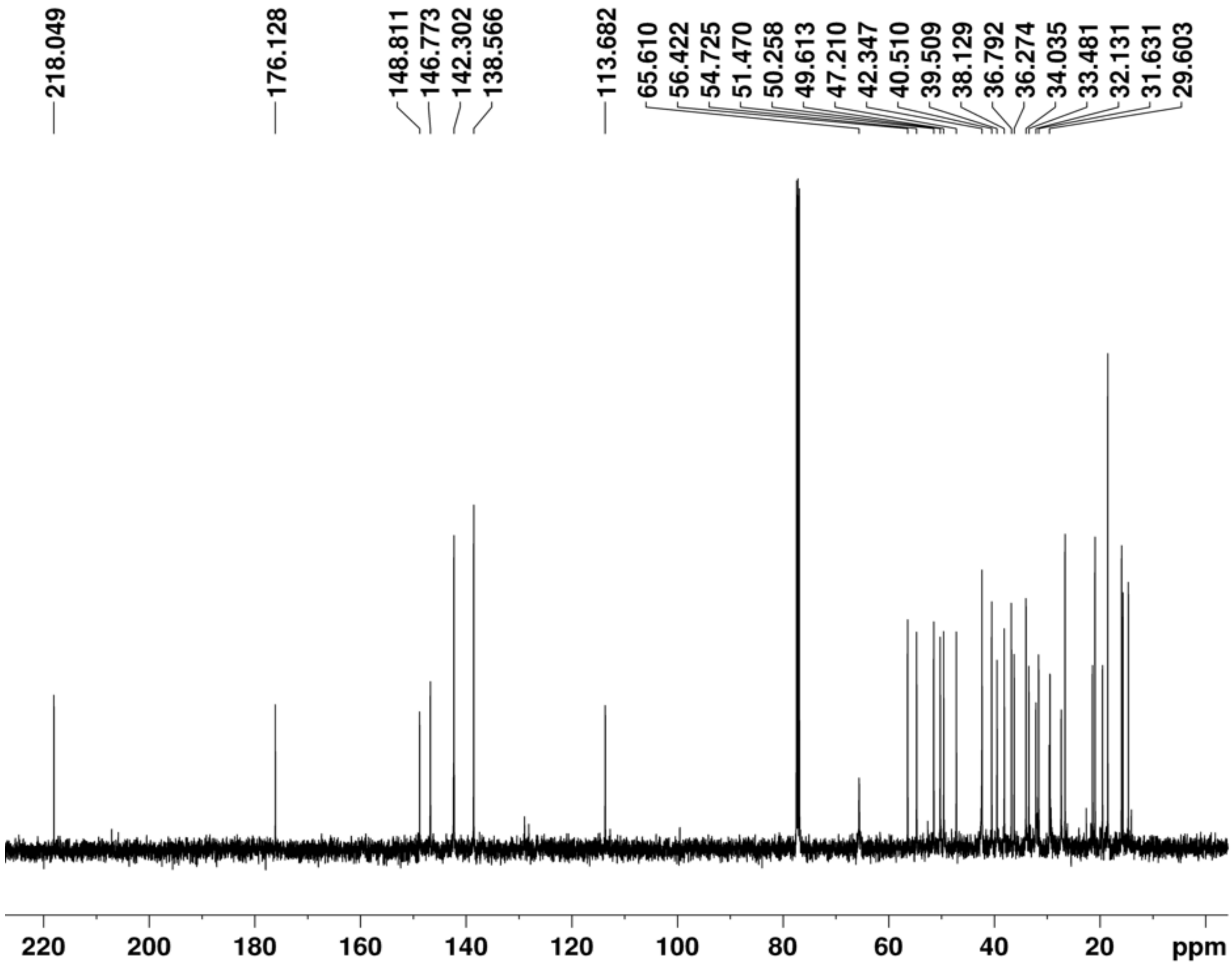
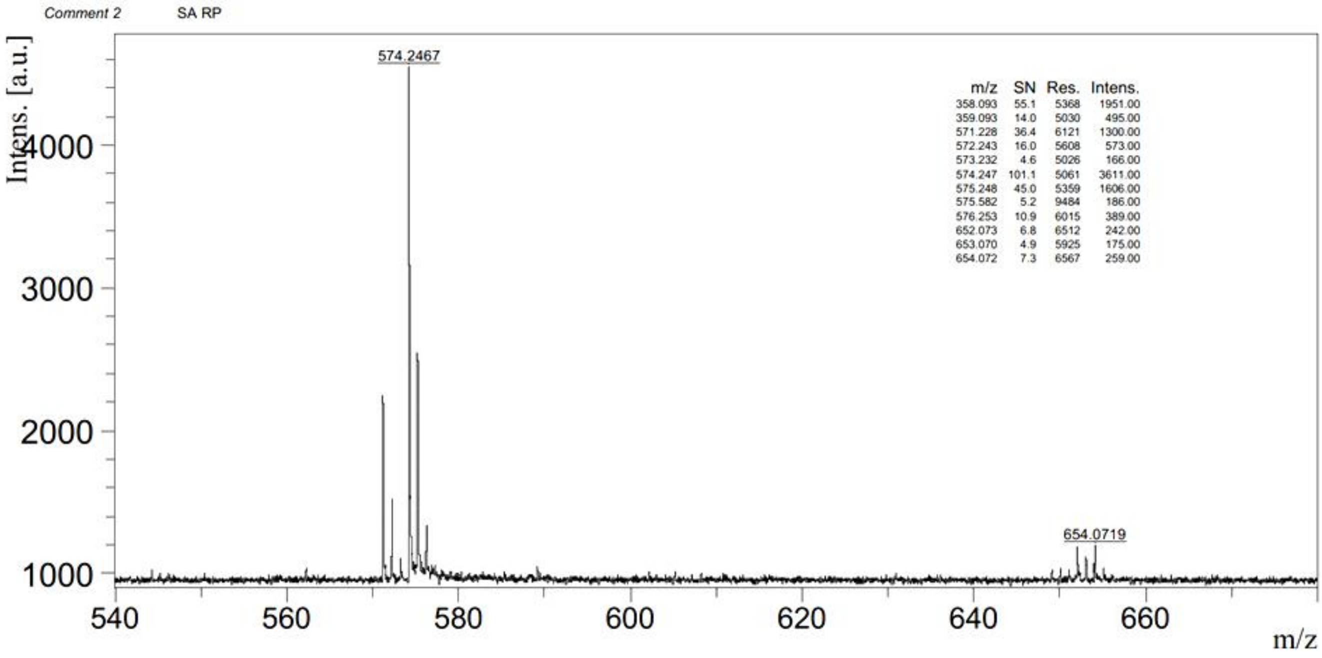



**Figure S18.** $^{1}H$, $^{13}C$ NMR and MALDI TOF/TOF of compound **7c**

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m/z
m/z SN Res. Intens.
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572.243 16.0 5608 573.00
573.232 4.6 5026 166.00
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575.248 45.0 5359 1606.00
575.582 5.2 9484 186.00
576.253 10.9 6015 389.00
652.073 6.8 6512 242.00
653.070 4.9 5925 175.00
654.072 7.3 6567 259.00

**Figure S19.** $^{1}H$ and $^{13}C$ NMR of compound **8c**

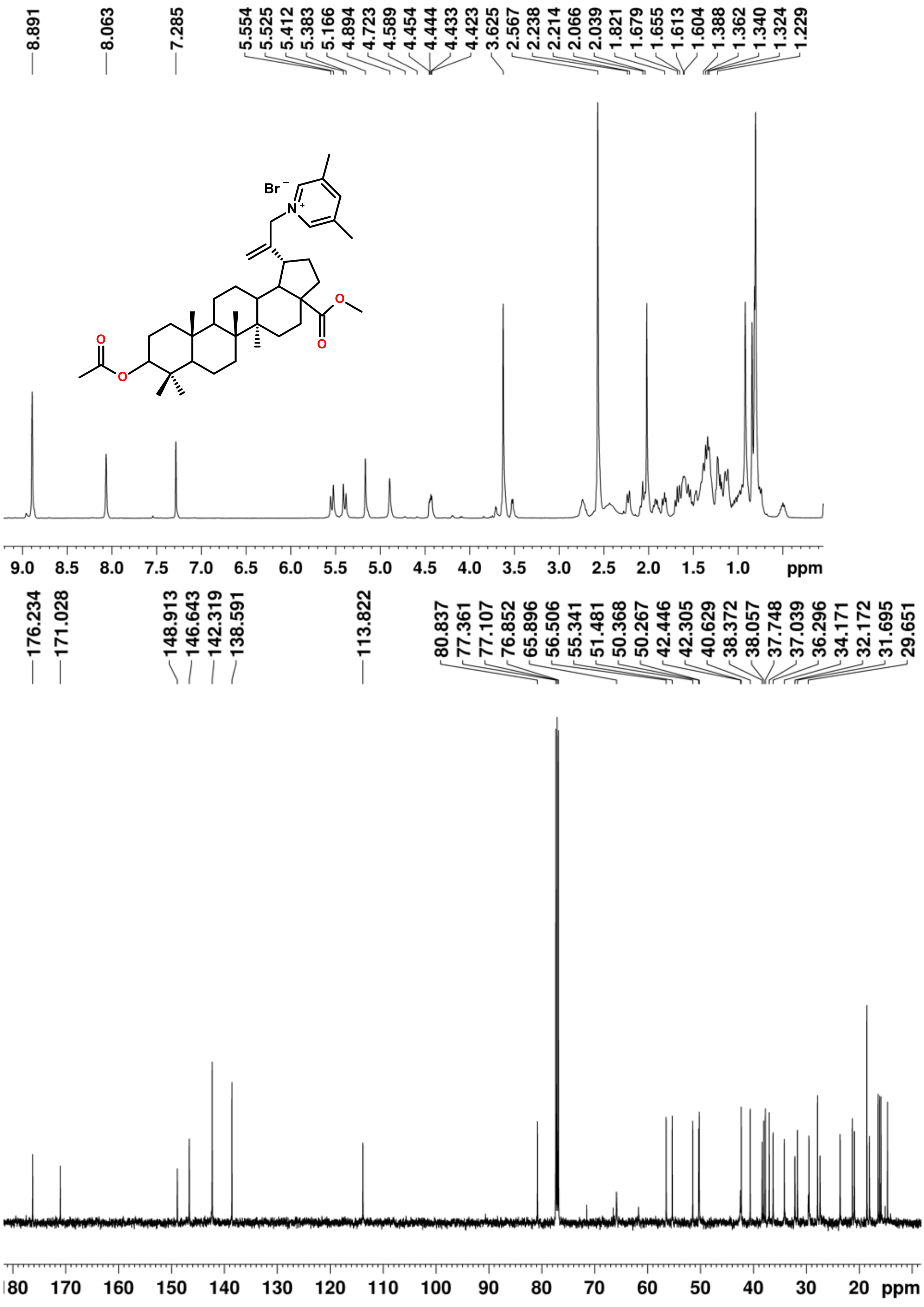


**Figure S20.** $^{1}$H and $^{13}$C NMR of compound **9c**

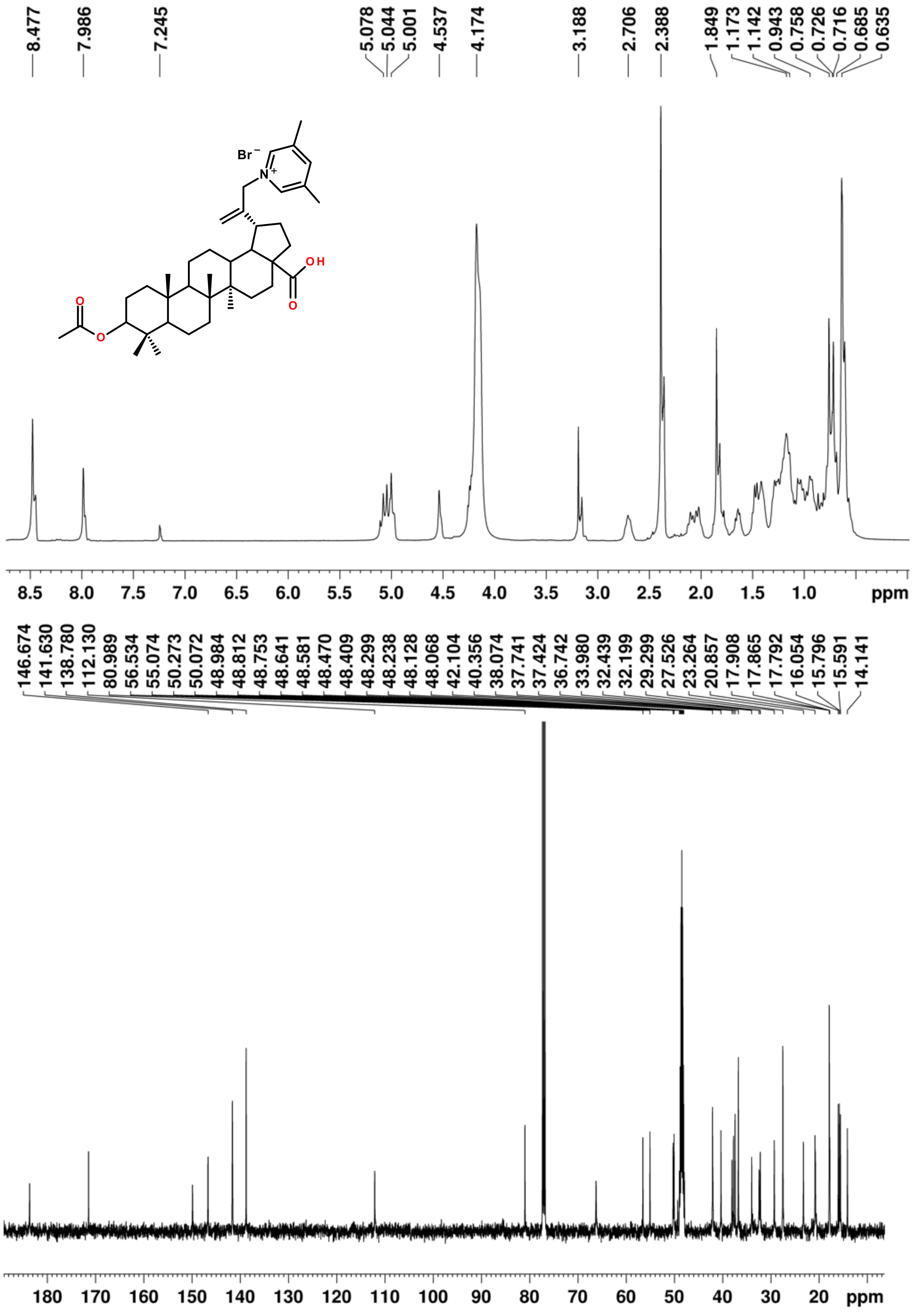


**Figure S21.** $^1H$ and $^{13}C$ NMR of compound **1d**

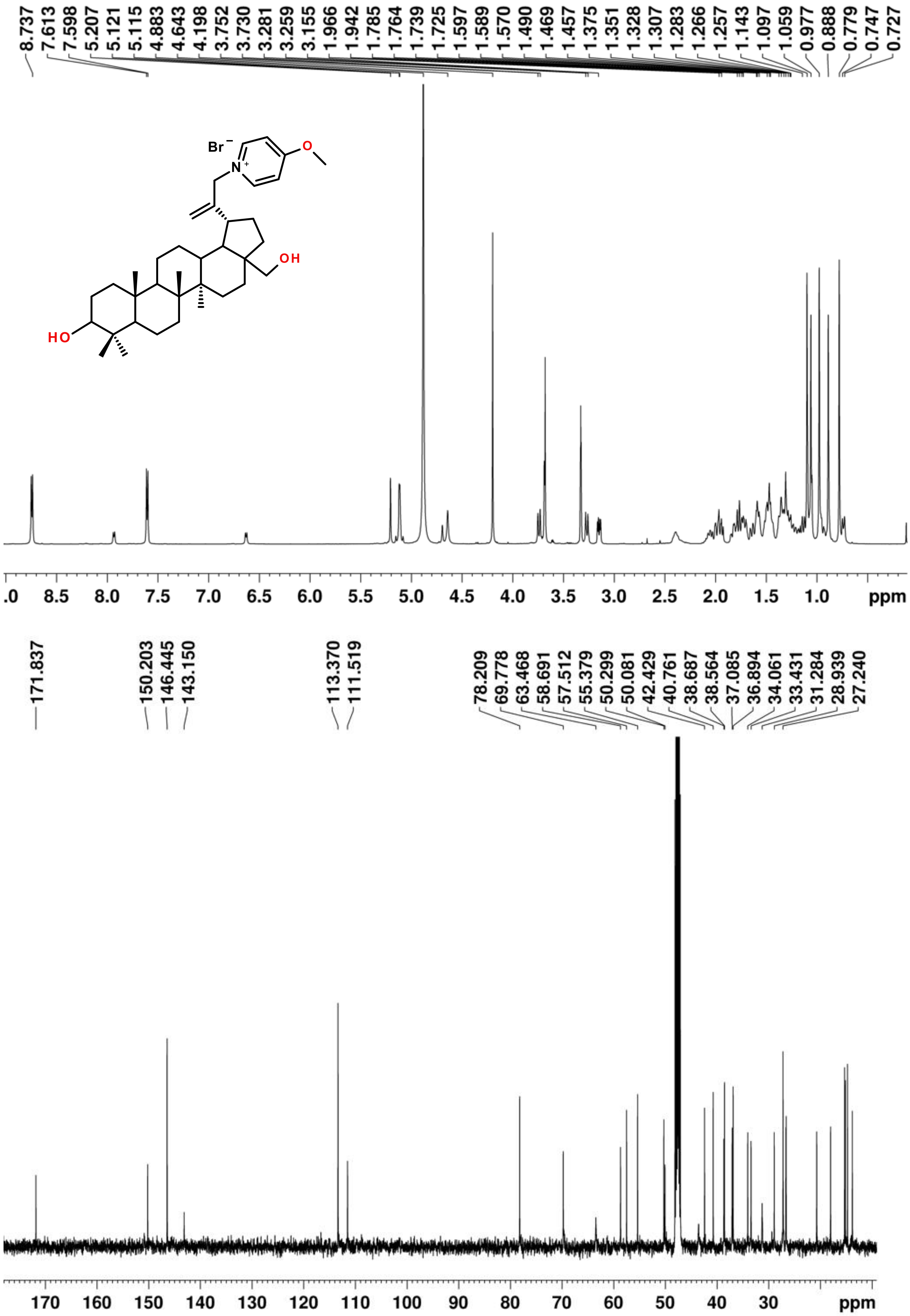


**Figure S22.** $^{1}H$ and $^{13}C$ NMR of compound **3d**

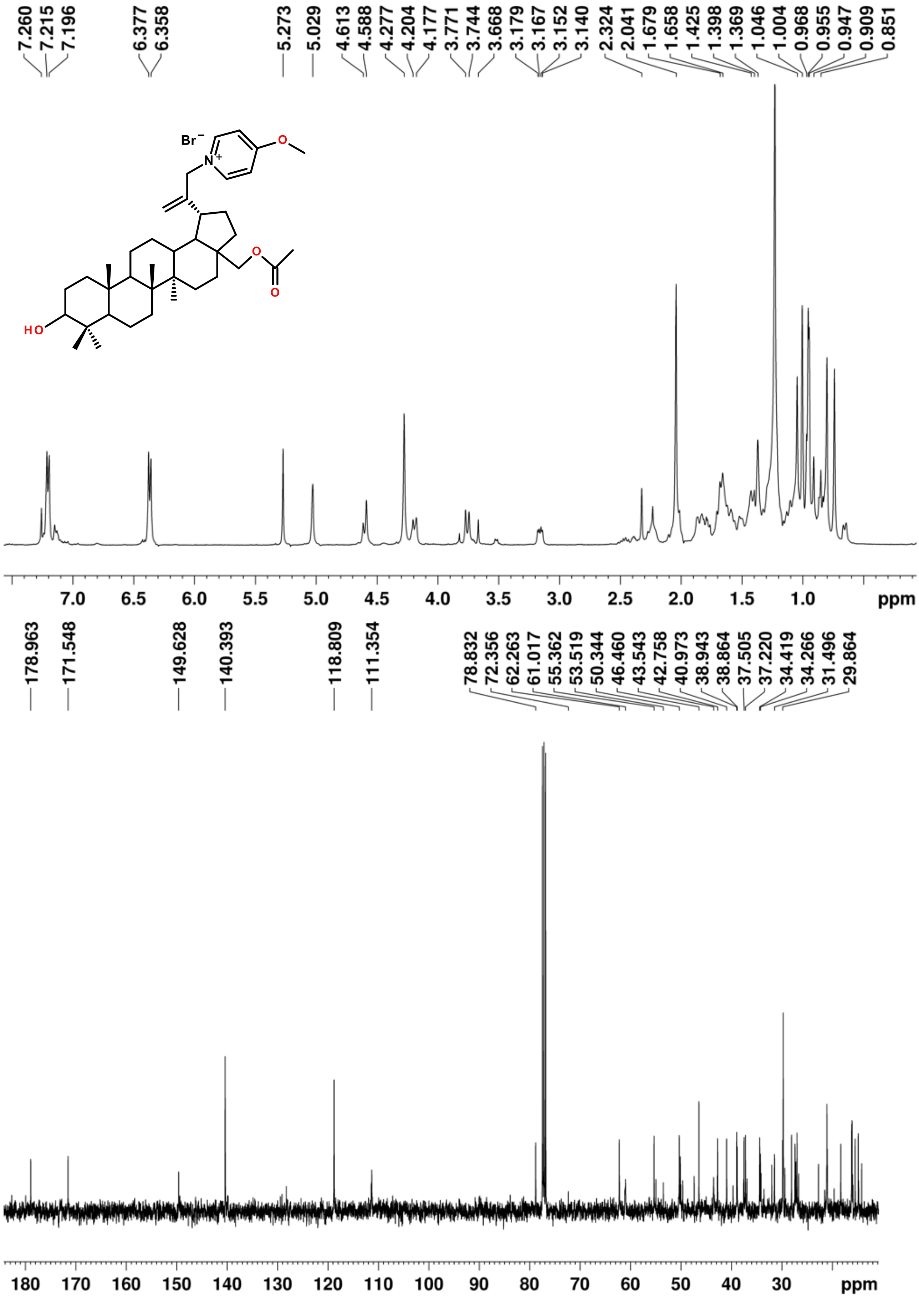
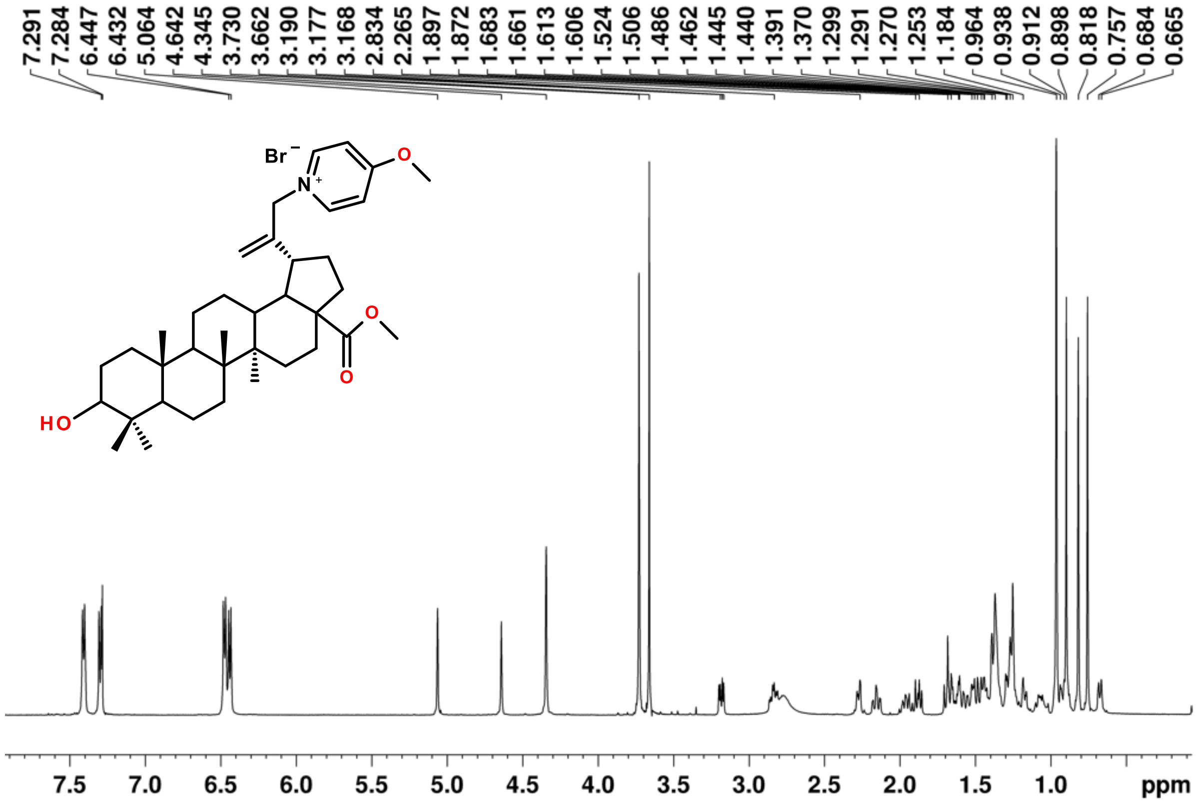


**Figure S23.** $^{1}H$ and $^{13}C$ NMR of compound **4d**



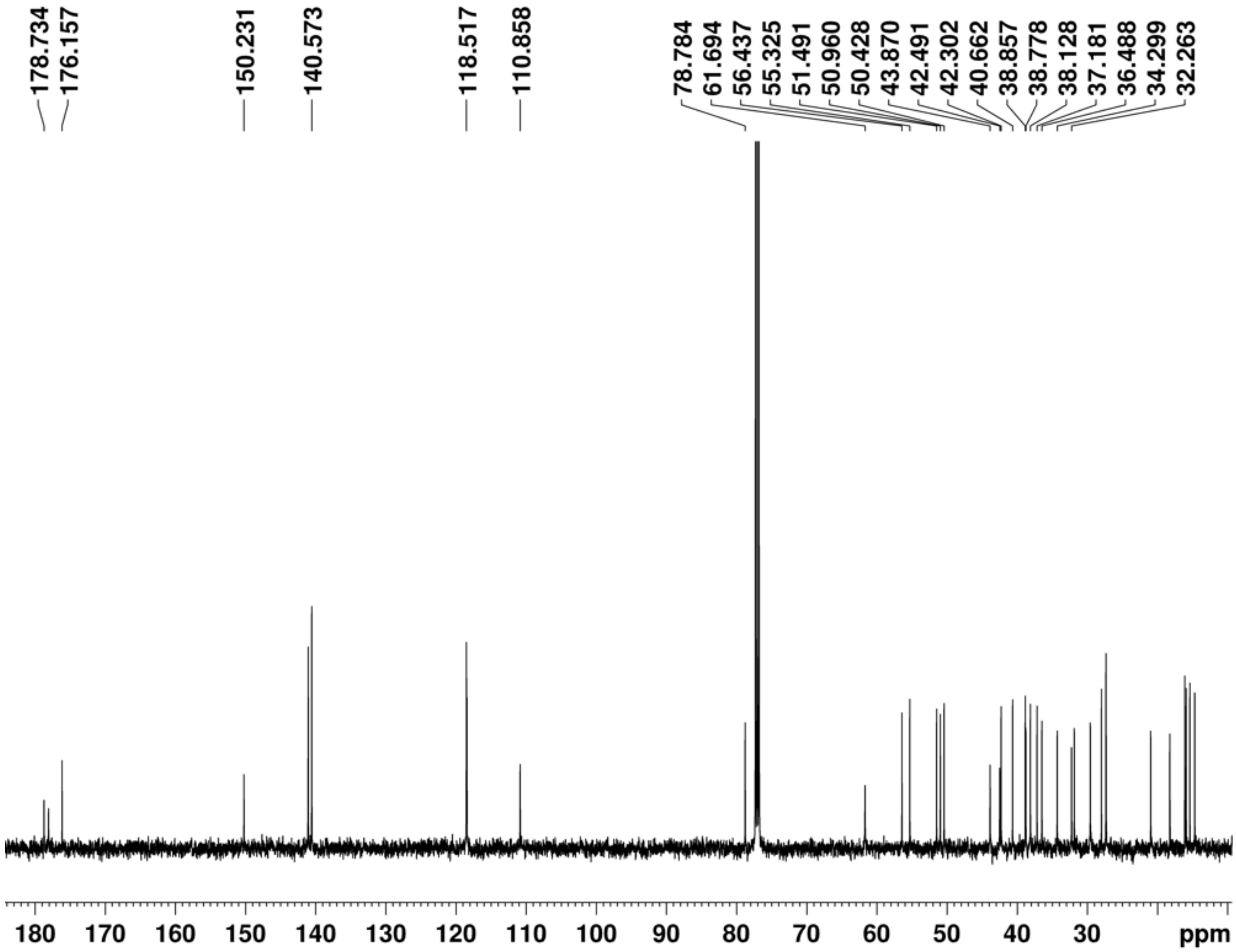
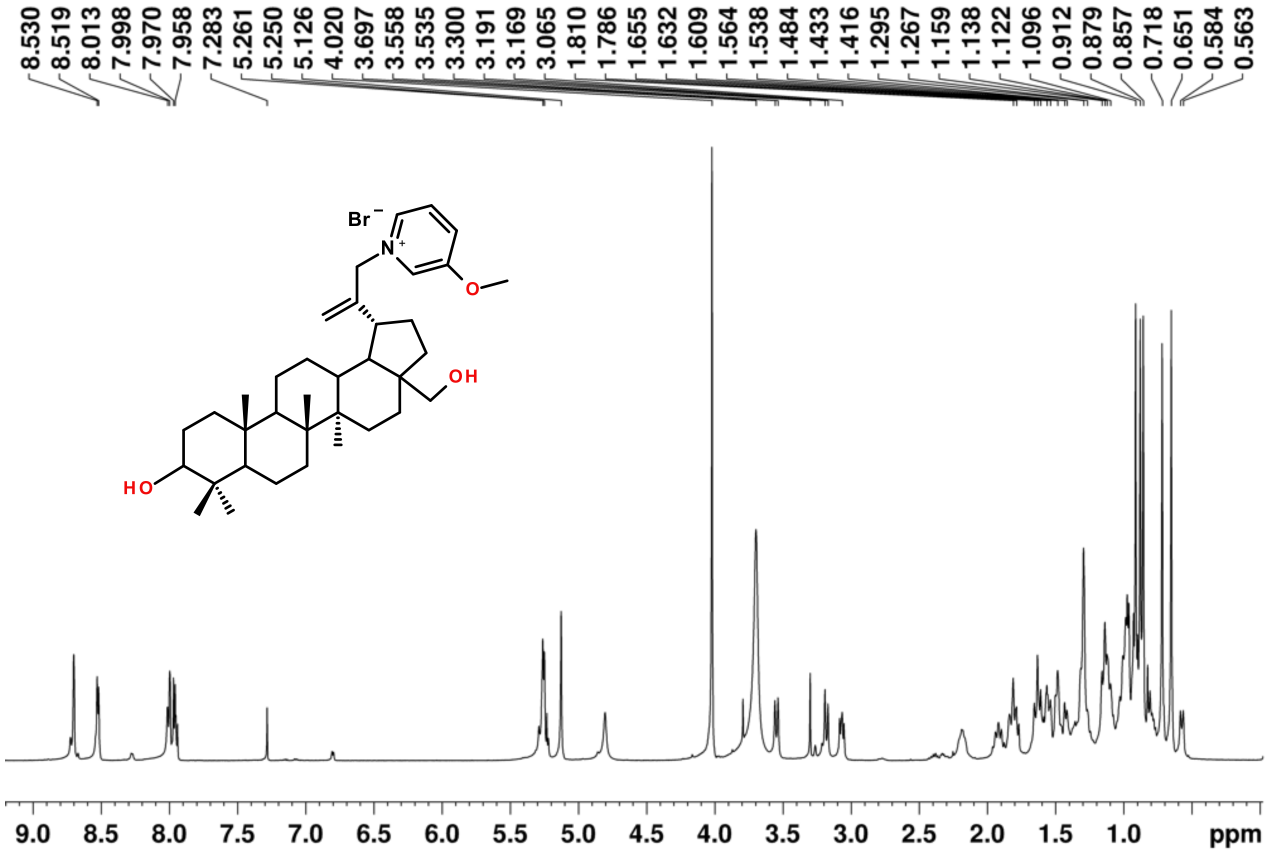



**Figure S24.** $^1$H and $^{13}$C NMR of compound **1e**



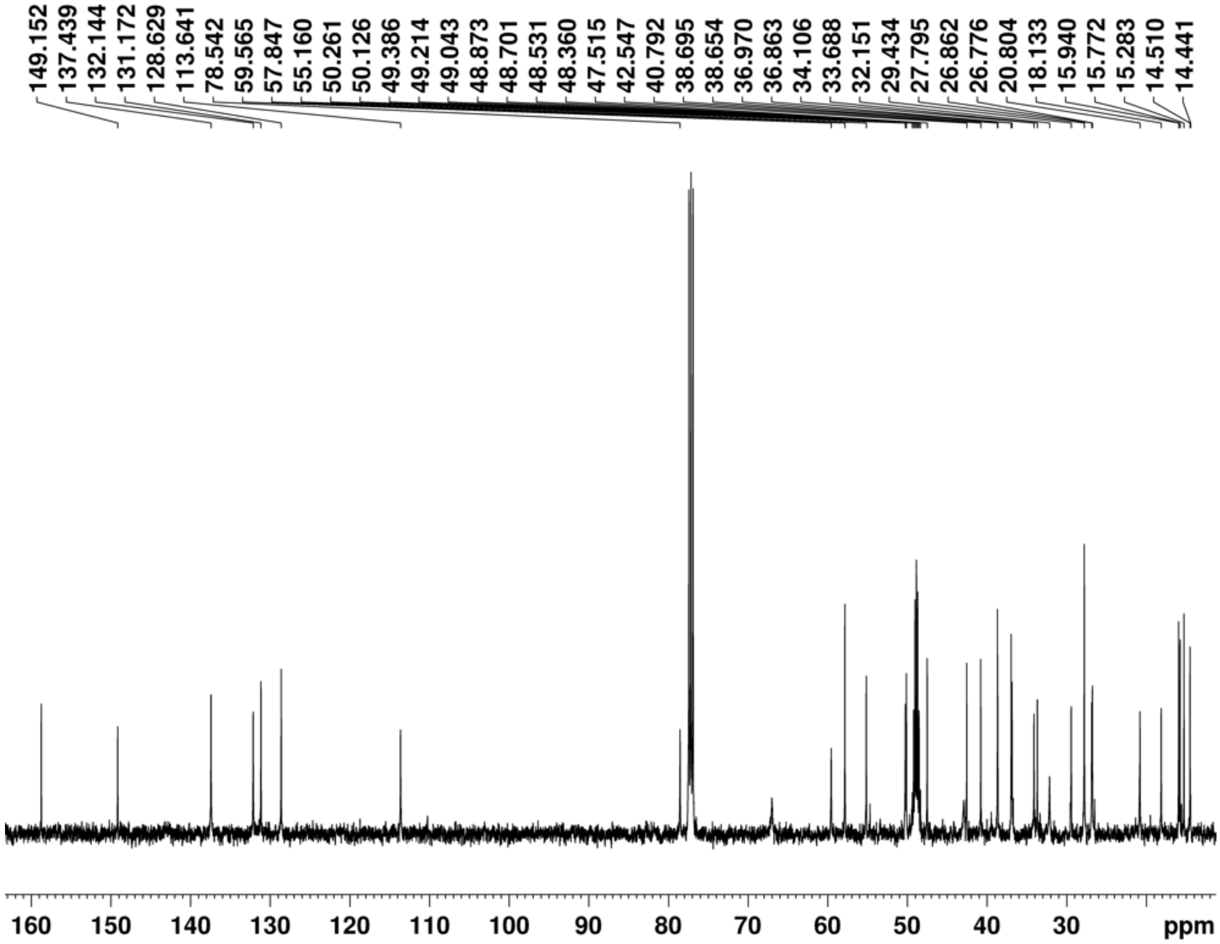



**Figure S25.** $^{1}H$ and $^{13}C$ NMR of compound **3e**

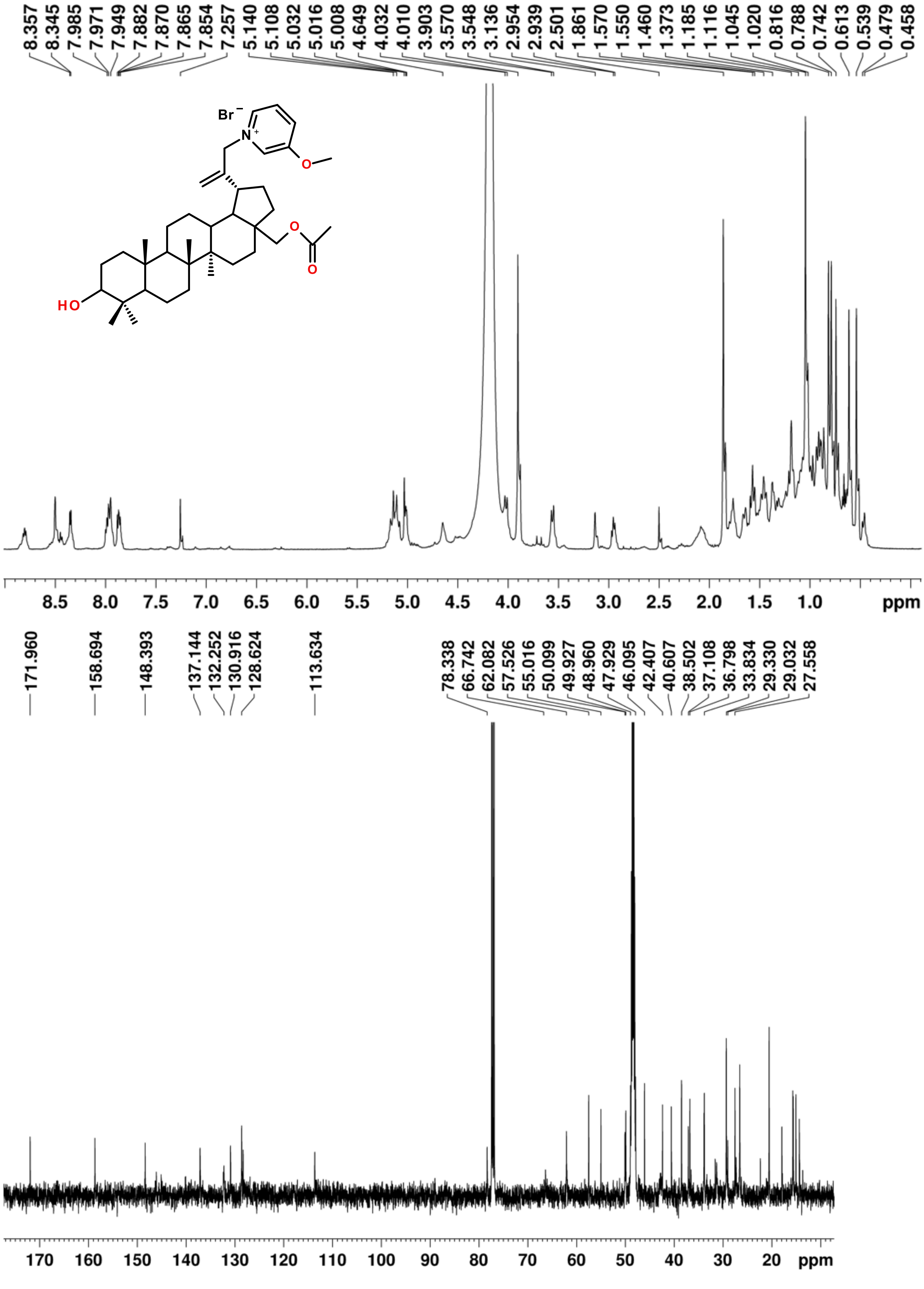


**Figure S26.** $^{1}H$ and $^{13}C$ NMR of compound **9e**