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Supplementary Information

A New Approach for the Synthesis of 3-Substituted Cytotoxic *Nor*-β-Lapachones

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Experimental

General information

Reagents were purchased from Sigma Aldrich and were used without further purification. Column chromatography was performed with silica gel 60 (Merck 70-230 mesh). Analytical thin layer chromatography (TLC) was performed with silica gel plates (Merck, TLC silica gel 60 F254), and the plates were visualized using UV light or aqueous solutions of ammonium sulfate. Yields refer to chromatographically and spectroscopically homogeneous materials. Melting points were obtained on a Fischer-Johns apparatus and were uncorrected. Infrared spectra were measured using KBr pellets on a Perkin-Elmer model 1420 FTIR (Fourier transform infrared) spectrophotometer, calibrated relative to the 1601.8 cm^{-1} absorbance of polystyrene. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity Plus VXR (500 MHz) instrument in $CDCl_3$ solutions. The chemical shift data were reported in units of δ (ppm) downfield from tetramethylsilane or the solvent, which were used as an internal standard; coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities. The high resolution mass spectra (electrospray ionization) were obtained using a QTOF Micro (Waters, Manchester, UK) mass spectrometer (high resolution electron spray ionization mass spectroscopy, HRESIMS).

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General procedure for **11** a **17**

To a solution of nor-lapachol (**5**, 228 mg, 1 mmol) in 25 mL of solvent, it was added 2 mL of bromine (6 g, 38 mmol) under an inert atmosphere. The bromo intermediate precipitated immediately as an orange solid. After removal of the bromine under reduced pressure, the nucleophile (2 mmol) was added to this mixture and stirred, after which the crude product was poured into 50 mL of water. The organic phase was separated and washed with sodium bicarbonate solution (3 × 50 mL), dried over sodium sulfate, filtered, and evaporated under reduced pressure. The mixture was purified by column chromatography in silica gel and eluted with an increasing polarity gradient mixture of hexane and ethyl acetate.

3-((2-(1*H*-Indol-3-yl)ethyl)amino)-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**11**): stirred for 5 h in chloroform; yellow solid 6%; mp 239-240 °C; IR (KBr) ν/cm^{-1} 3450, 2968, 2936, 2871, 1701, 1658, 1648, 1617, 1589, 1570, 1493, 1453, 1405, 1372, 1347, 1278, 1262, 1222, 1116, 1084, 1401, 981, 827; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25 ((C2)-C$\underline{H}_3$), 1.59 ((C2)-C$\underline{H}_3$), 2.23 (d, 2H, *J* 5.3 Hz, –NH–CH_2–C$\underline{H}_2$), 2.37 (d, 2H, *J* 5.3 Hz, –NH–C$\underline{H}_2$), 5.01 (s, 1H, H3), 5.81 (s, 1H, H7'), 7.62-7.65 (m, 2H, H3', H4'), 7.66-7.73 (m, 2H, H2', H5'), 8.07 (td, 2H, *J* 7.8, 0.9 Hz, H.7, H8), 8.11-8.13 (m, 2H, H6, H9); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.4 (C2)-C$\underline{H}_3$), 26.6 (C2)-C$\underline{H}_3$), 29.6 (C8'), 53.3 (C9'), 75.0 (C3), 96.6 (C2), 112.4 (C3a), 117.3 (C6'), 122.6 (C.7'), 125.8 (C9a),

127.3 (C5a'), 129.3 (C6), 130.2 (C3', C4'), 131.1 (C5a), 125.1, 132.5, 134.5 (C7, C8, C9), 135.3 (C2', C5'), 147.0 (C1a'), 170.6 (C9b), 176.0 (C4), 181.1 (C5); HRESIMS *m/z* 387.1701 $[M + H]^+$ (Calcd. for $C_{24}H_{23}N_2O_3^+$ 387.1703).

2,2-Dimethyl-3-((2,4-dibromophenyl)amino)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**12**): stirred for 72 h in chloroform; orange solid 75%; mp 300-301 °C; IR (KBr) ν/cm^{-1} 3407, 1664, 1615, 1582, 1489, 1450, 1395, 1322, 1258, 1218, 1083, 792; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.54 (s, 3H, (C2)-C$\underline{H}_3$), 1.66 (s, 3H, (C2)-C$\underline{H}_3$), 4.47 (d, 1H, *J* 6.8 Hz, N$\underline{H}$), 4.83 (d, 1H, *J* 6.8 Hz, H3), 6.55 (d, 1H, *J* 8.8 Hz, H6'), 7.29 (dd, 1H, *J* 8.8, 2.4 Hz, H-5'), 7.56 (d, 1H, *J* 2.4 Hz, H3'), 7.75-7.64 (m, 1H, H7), 7.75-7.64 (m, 1H, H8), 7.75-7.64 (m, 1H, H9), 8.14 (d, 1H, *J* 7.8 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7 (C2)-C$\underline{H}_3$), 27.2 (C2)-C$\underline{H}_3$), 61.5 (C3), 96.9 (C2), 113.0 (C4'), 115.1 (C3a), 118.0 (C6'), 121.2 (C2'), 127.3 (C9a), 129.2 (C6), 129.4 (C3' and C5'), 131.1 (C5a), 125.0, 132.5, 134.6 (C-7, C-8, C-9), 147.2 (C1'), 169.7 (C9b), 175.4 (C4), 180.9 (C5); HRESIMS *m/z* 475.9486 $[M + H]^+$ (Calcd. for $C_{20}H_{16}Br_2NO_3^+$ 475.9491).

3-((1*H*-Benzo[*d*][1,2,3]triazol-1-yl)oxy)-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**13**): stirred for 5 h in chloroform; orange solid 10%; mp 198-199 °C; IR (KBr) ν/cm^{-1} 2965, 2927, 1659, 1623, 1591, 1497, 1461, 1405, 1361, 1254, 1218, 1161, 1110, 1084, 749; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.32 (s, 3H, (C2)-C$\underline{H}_3$), 1.88 (s, 3H, (C2)-C$\underline{H}_3$), 6.50 (s, 1H, H3), 7.62 (t, 2H, *J* 7.8 Hz, H5', H6'), 7.96-7.93 (m, 1H, H4'), 7.96-7.93 (m, 1H, H7'), 8.10-7.99 (m, 1H, H7), 8.10-7.99 (m, 1H, H8), 8.10-7.99 (m, 1H, H9), 8.17 (dd, 1H, *J* 8.3, 1.5 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5 (C2)-C$\underline{H}_3$), 22.9 (C2)-C$\underline{H}_3$), 66.4 (C3), 95.1 (C2), 112.7 (C3a), 115.5 (C4'), 126.1 (C5', C6'), 126.3 (C9a), 128.8 (C6), 129.8 (C7'), 130.4 (C5a), 131.3 (C3a'), 125.1, 133.5, 134.3 (C7, C8, C9), 134.4 (C7a'), 171.6 (C9b), 174.4 (C4), 179.8 (C5); HRESIMS *m/z* 362.1141 $[M + H]^{+\cdot}$ (Calcd. for $C_{20}H_{16}N_3O_4^+$ 362.1135).

2,2-Dimethyl-3-((5-(trifluoromethyl)-1*H*-1,2,4-triazol-3-yl)amino)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**14**): stirred for 5 h in chloroform. Yellow solid 7%; mp 242-243 °C; IR (KBr) ν/cm^{-1} 3388, 2927, 1703, 1646, 1614, 1570, 1493, 1453, 1409, 1345, 1319, 1225, 1166, 1116, 1075, 798, 781; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 (s, 3H, (C2)-C$\underline{H}_3$), 1.62 (s, 3H, (C2)-C$\underline{H}_3$), 3.62-3.72 (m, 1H, N$\underline{H}$), 3.80-3.90 (m, 1H, H2'), 4.55 (s, 1H, H3), 7.57-7.68 (m, 3H, H7), 7.57-7.68 (m, 3H, H8), 7.57-7.68 (m, 3H, H9), 8.09 (dd, 1H, *J* 7.33, 1.4 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.5 ((C2)-C$\underline{H}_3$), 27.0 ((C2)-C$\underline{H}_3$), 66.0 (C3), 95.2 (C.2), 110.9 (C$\underline{F}_3$), 111.3 (C3a), 126.6 (C9a), 128.7 (C6), 131.9 (C5a), 132.7 (C3'), 124.9, 132.9, 134.6 (C7, C8, C9), 148.0 (C5'), 169.7 (C9b), 174.6 (C4), 179.8 (C5).

(*Z*)-3-((4-Bromo-1-(4-bromophenyl)-3-methyl-1*H*-pyrazol-5-yl)imino)-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**15**) and 3-((4-bromo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)amino)-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**16**): stirred for 5 h in chloroform; **15** and **16** were isolated as a red solid 10 and 6%, respectively; **15**: mp 210-212 °C; IR (KBr) ν/cm^{-1} 1655, 1614, 1586, 1568, 1563, 1532, 1493, 1412, 1262, 1218, 1113, 1083; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 3H, (C2)-C$\underline{H}_3$), 1.64 (s, 3H, (C2)-C$\underline{H}_3$), 2.38 (s, 3H, C$\underline{H}_3$), 7.46-7.56 (m, 1H, H7), 7.46-7.56 (m, 1H, H8), 7.46-7.56 (m, 1H, H9), 7.63 (dd, 2H, *J* 8.3, 1.5 Hz, H2", H6"), 7.80 (dd, 2H, *J* 8.3, 1.5 Hz, H3", H5"), 7.94 (d, 1H, *J* 7.8 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.1 (C$\underline{H}_3$), 22.2 (C2)-C$\underline{H}_3$), 29.2 (C2)-C$\underline{H}_3$), 96.6 (C2), 101.3 (C4'), 119.7 (C3a), 123.5 (C2", C6"), 126.8 (C9a), 127.6 (C4"), 128.9 (C3", C5"), 129.8 (C6), 131.8 (C5a), 124.9, 132.3, 134.5 (C7, C8, C9), 137.7 (C1"), 150.4 (C3'), 151.7 (C5'), 165.9 (C3), 169.9 (C9b), 174.7 (C4), 180.4 (C5); HRESIMS *m/z* 553.9733 $[M + H]^+$ (Calcd for $C_{24}H_{18}Br_2N_3O_3^+$ 553.9709). **16**: mp 200-201 °C; IR (KBr) n/cm^{-1} 1655, 1644, 1616, 1566, 1498, 1491, 1449, 1404, 1352, 1217, 1092; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.43 (s, 3H, (C2)-C$\underline{H}_3$), 1.60 (s, 3H, (C2)-C$\underline{H}_3$), 2.24 (s, 3H, C$\underline{H}_3$), 3.52 (d, 1H, *J* 9.8 Hz, N$\underline{H}$), 4.75 (d, 1H, *J* 9.8 Hz, H3), 7.48 (dd, 2H, *J* 9.0, 2.4 Hz, H3", H5"), 7.55 (dd, 2H, *J* 9.0, 2.4 Hz, H2", H6"), 7.68-7.60 (m, 1H, H7), 7.68-7.60 (m, 1H, H8), 7.68-7.60 (m, 1H, H9), 8.11 (dt, 1H, *J* 7.0, 1.4 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.8 (C$\underline{H}_3$), 22.0 (C2)-C$\underline{H}_3$), 26.7 (C2)-C$\underline{H}_3$), 62.0 (C3), 80.4 (C4'), 95.9 (C2), 115.5 (C3a), 124.9 (C2", C6"), 127.2 (C9a), 127.5 (C4"), 128.1 (C3", C5"), 129.5 (C6), 131.1 (C5a), 125.2, 132.5, 134.5 (C7, C8, C9), 138.7 (C1"), 142.5 (C3'), 147.7 (C5'), 169.3 (C9b), 175.1 (C4), 180.6 (C5); HRESIMS *m/z* 555.9854 $[M + H]^+$ (Calcd. for $C_{24}H_{20}Br_2N_3O_3^+$ 555.9866).

3-((4-Bromo-1-(4-bromophenyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**17**): stirred for 5 h in THF; red solid 33%; mp 221-222 °C; (KBr) ν/cm^{-1} 1654, 1623, 1590, 1566, 1562, 1536, 1494, 1450, 1413, 1385, 1377, 1222, 1113; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (s, 3H, (C2)-C$\underline{H}_3$), 1.59 (s, 3H, (C2)-C$\underline{H}_3$), 2.24 (s, 3H, C$\underline{H}_3$), 3.63 (d, 1H, *J* 9.6 Hz, N$\underline{H}$), 4.86 (d, 1H, *J* 9.6 Hz, H3), 7.30 (tt, 1H, *J* 7.3, 2.0 Hz, H4"), 7.43 (td, 2H, *J* 7.3, 2.0 Hz, H3", H5"), 7.55 (dt, 2H, *J* 7.0, 1.4 Hz, H2", H6"), 7.61-7.67 (m, 1H, H7), 7.61-7.67 (m, 1H, H8), 7.61-7.67 (m, 1H, H9), 8.08 (dt, 1H, *J* 7.0, 1.5 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.4 (C$\underline{H}_3$),

21.6 (C2)-C$\underline{H}_3$), 26.3 (C2)-C$\underline{H}_3$), 61.6 (C3), 80.0 (C4'), 95.5 (C2), 115.1 (C3a), 124.5 (C2", C-6"), 126.1 (C6), 126.8 (C9a), 127.7 (C4"), 129.1 (C3", C5"), 130.7 (C5a), 124.8, 132.1, 134.1 (C7, C8, C9), 138.3 (C1"), 142.1 (C3'), 147.3 (C5'), 168.9 (C9b), 174.7 (C4), 180.3 (C5); HRESIMS *m/z* 478.0758 $[M + H]^+$ (Calcd. for $C_{24}H_{20}BrN_3O_3^+$ 478.0761).

General procedure for 3-hydroxy-2,2-dimethyl-2,3-dihydronaphtho[1,2-b]furan-4,5-dione (**18**)

To a solution of nor-lapachol (**5**, 228 mg, 1 mmol) in 25 mL of solvent, it was added 2 mL of bromine (6 g, 38 mmol) under an inert atmosphere. The bromo intermediate precipitate immediately as an orange solid and the mixture was poured into a saturated aqueous solution of sodium bisulfite. After solution was extracted with ethyl acetate and the organic phase was separated and washed with sodium bicarbonate solution (3 × 50 mL), dried over sodium sulfate, filtered and evaporated under reduced pressure. The mixture was purified by column chromatography in silica gel and eluted with an increasing polarity gradient mixture of hexane and ethyl acetate. Orange solid 60%; mp 300 °C; IR (KBr) ν/cm^{-1} 3447, 2985, 1698, 1653, 1615, 1588, 1571, 1222, 1115, 1082, 970, 836; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.51 (s, 3H, (C2)-C$\underline{H}_3$), 1.65 (s, 3H, (C2)-C$\underline{H}_3$), 5.04 (s, 1H, H3), 7.60-7.73 (m, 3H, H7), 7.60-7.73 (m, 3H, H8), 7.60-7.73 (m, 3H, H9), 8.10 (dd, 1H, *J* 7.33, 0.58 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.1 ((C2)-C$\underline{H}_3$), 26.2 ((C2)-C$\underline{H}_3$), 74.7 (C3), 96.4 (C.2), 117.0 (C3a), 127.0 (C9a), 129.0 (C6), 130.8 (C5a), 124.7, 132.2, 134.2 (C7, C8, C9), 170.4 (C9b), 175.7 (C4), 180.8 (C5); HRESIMS *m/z* 245.0811 $[M + H]^+$ (Calcd. for $C_{20}H_{16}Br_2NO_3^+$ 245.0736).

General procedure for **19a-h**

To a solution of 3-hydroxy-*nor*-β-lapachone (**18**, 50 mg, 0.2 mmol) in 2 mL of chloroform, 0.01 mL of methanesulfonic acid (20 mg, 1 mmol) was added under an inert atmosphere. This mixture was stirred for 1 h. Then, 1.2 mmol of 1*H*-pyrazol-5-amine or the alcohol derived of carbohydrate acetonides were added to this mixture and, immediately, this solution was transferred to another flask containing anhydrous sodium sulfate. The reaction was stirred for 5 h and the organic phase was separated and washed with sodium bicarbonate (3 × 50 mL) and distilled water (3 × 50 mL), dried over sodium sulfate, filtered, and evaporated under reduced pressure to yield a solid, which was purified by column chromatography in silica gel and eluted with an increasing polarity gradient mixture of hexane and ethyl acetate.

2,2-Dimethyl-3-((3-methyl-1-phenyl-1*H*-pyrazol-5-yl) amino)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**19a**): orange solid 52%; mp 196-198 ºC; IR (KBr) ν/cm^{-1} 1655, 1620, 1589, 1569, 1560, 1532, 1492, 1451, 1411, 1386, 1373, 1220, 1110; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.53 (s, 3H, (C2)-C$\underline{H}_3$), 1.58 (s, 3H, (C2)-C$\underline{H}_3$), 2.18 (s, 3H, CH_3), 3.97 (d, 1H, *J* 5.7 Hz, N$\underline{H}$), 4.60 (d, 1H, *J* 5.7 Hz, H3), 5.28 (s, 1H, H4'), 7.22 (d, 1H, *J* 7.5 Hz, H4"), 7.35 (t, 2H, *J* 7.5 Hz, H3", H5"), 7.44 (d, 2H, *J* 7.5 Hz, H2", H-6"), 7.55-7.61 (m, 1H, H7), 7.55-7.61 (m, 1H, H8), 7.55-7.61 (m, 1H, H9), 8.04 (d, 1H, *J* 8.0 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.6 (CH_3), 21.1 (C2)-C$\underline{H}_3$), 27.5 (C2)-C$\underline{H}_3$), 63.3 (C3), 87.9 (C4'), 96.0 (C2), 113.6 (C3a), 124.1 (C-2", C6"), 126.7 (C9a), 127.0 (C4"), 129.2 (C3", C5"), 129.2 (C6), 130.7 (C5a), 124.7, 132.2, 134.2 (C7, C8, C9), 137.9 (C1"), 146.6 (C5'), 148.7 (C3'), 169.3 (C9b), 174.9 (C4), 180.3 (C5); HRESIMS *m/z* 400.1661 $[M + H]^{+\cdot}$ (Calcd. for $C_{24}H_{22}N_3O_3^+$ 400.1656).

3-((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl) amino)-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**19b**): orange solid 29%; mp 230-232 °C; IR (KBr) ν/cm^{-1} 3409, 3311, 1613, 1563, 1529, 1502, 1458, 1440, 1412, 1374, 1248, 1149, 1112, 1081, 1051, 1025, 996, 889, 772; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.25 (s, 3H, (C2)-C$\underline{H}_3$), 1.70 (s, 3H, (C2)-C$\underline{H}_3$), 3.83 (s, 3H, OC$\underline{H}_3$), 4.11 (d, 1H, *J* 5.8 Hz, N$\underline{H}$), 4.77 (d, 1H, *J* 5.8 Hz, H3), 5.91 (s, 1H, H4'), 6.92 (dd, 2H, *J* 9.3, 2.4 Hz, H3'", 5'"), 7.31-7.37 (m, 1H, H4"), 7.44-7.50 (m, 2H, H3", H-5"), 7.63 (d, 2H, *J* 7.3 Hz, H2", H-6"), 7.75 (dd, 2H, *J* 9.2, 2.4 Hz, H2'", H6'"), 7.59 (d, 1H, *J* 7.8 Hz, H7), 7.65-7.72 (m, 2H, H-8, H-9), 8.11 (d, 1H, J 7.8 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5 (C$\underline{H}_3$), 27.9 (C2)-C$\underline{H}_3$), 55.2 OC$\underline{H}_3$), 63.7 (C3), 85.3 (C4'), 96.3 (C2), 113.9 (C3a), 124.0 (C2", C6"), 126.8 (C2'", C6'"), 127.0 (C9a), 127.6 (C4"), 129.3 (C6), 129.5 (C3", C5"), 129.6 (C3'", C-5'"), 131.1 (C5a), 124.7, 132.6, 134.5 (C-7, C-8, C-9), 138.2 (C1'"), 145.7 (C4'"), 147.3 (C5'), 151.1 (C3'), 159,4 (C1"), 169.7 (C9b), 175.3 (C4), 180.6 (C5); HRESIMS *m/z* 492.1925 $[M + H]^{+\cdot}$ (Calcd. for $C_{30}H_{26}N_3O_4^+$ 492.1918).

3-((1,3-Diphenyl-1*H*-pyrazol-5-yl)amino)-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**19c**): orange solid 37%; mp 202-203 °C; IR (KBr) ν/cm^{-1} 1653, 1617, 1590, 1561, 1516, 1494, 1455, 1401, 1384, 1082, 725, 691; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.63 (s, 3H, (C2)-C$\underline{H}_3$), 1.70 (s, 3H, (C2)-C$\underline{H}_3$), 4.12 (d, 1H, *J* 5.8 Hz, N$\underline{H}$), 4.78 (d, 1H, *J* 5.8 Hz, H3), 5.85 (s, 1H, H4'), 7.29-7.34 (m, 2H, H-4" e H-4'"), 7.38 (t, 2H, *J* 7.8 Hz, H3"', H5"'), 7.46 (t, 2H, *J* 7.3 Hz, H3", H5"), 7.60 (d, 2H, *J* 7.3 Hz, H2", H6"), 7.81 (d, 2H, *J* 6.8, 2.0 Hz, H2'", H-6'"), 7.72-7.59 (m, 1H,

H7), 7.72-7.59 (m, 1H, H8), 7.72-7.59 (m, 1H, H9), 8.11 (dd, 1H, *J* 6.8 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6 (C2)-C$\underline{H}_3$), 28.0 (C2)-C$\underline{H}_3$), 63.8 (C3), 85.7 (C4'), 96.4 (C2), 114.0 (C3a), 125.1 (C2", C6"), 125.6 (C3'", C5'"), 127.1 (C9a), 127.8 (C4", C4'"), 128.4 (C3", C5"), 129.6 (C2'", C6'"), 129.7 (C6), 131.2 (C5a), 124.8, 132.7, 134.6 (C7, C8, C9), 133.4 (C1"), 138.3 (C1'"), 147.5 (C5'), 151.4 (C3'), 169.7 (C9b), 175.4 (C4), 180.6 (C5); HRESIMS *m/z* 462.1810 $[M + H]^{+\cdot}$ (Calcd. for $C_{29}H_{24}N_3O_3^+$ 462.1812).

3-((1-(4-Bromophenyl)-3-phenyl-1*H*-pyrazol-5-yl) amino)-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**19d**): orange solid 35%; mp 225-226 °C; IR (KBr) ν/cm^{-1} 3383, 1619, 1588, 1561, 1490, 1385, 1070; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.63 (s, 3H, (C2)-C$\underline{H}_3$), 1.71 (s, 3H, (C2)-C$\underline{H}_3$), 4.05 (d, 1H, *J* 5.7 Hz, N$\underline{H}$), 4.77 (d, 1H, *J* 5.7 Hz, H3), 5.86 (s, 1H, H4'), 7.25 (t, 1H, *J* 7.3 Hz, H4'"), 7.32 (t, 2H, *J* 7.3 Hz, H3'", H-5'"), 7.44 (d, 2H, *J* 8.8 Hz, H2", H-6"), 7.51 (d, 2H, *J* 8.8 Hz, H3", H5"), 7.73 (d, 2H, *J* 7.3 Hz, H2'", H-6'"), 7.66-7.57 (m, 1H, H7), 7.66-7.57 (m, 1H, H8), 7.66-7.57 (m, 1H, H9), 8.06 (d, 1H, *J* 7.3 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6 (C2)-C$\underline{H}_3$), 28.0 (C2)-C$\underline{H}_3$), 63.9 (C3), 86.2 (C4'), 96.3 (C2), 113.8 (C3a), 121.4 (C4"),125.6 (C2", C6"), 126.3 (C2'", C6'"), 127.0 (C9a), 128.0 (C3'", C5'"), 128.5 (C3", C5"), 129.7 (C6), 131.2 (C5a), 133.1 (C1"), 125.2, 132.8, 134.7 (C7, C8, C9), 137.4 (C1'"), 147.5 (C5'), 151.8 (C3'), 169.9 (C9b), 175.5 (C4), 180.6 (C5); HRESIMS *m/z* 540.0926 $[M + H]^+$ (Calcd. for $C_{29}H_{23}BrN_3O_3^+$ 540.0917).

2,2-Dimethyl-3-((1-phenyl-3-(p-tolyl)-1*H*-pyrazol-5-yl) amino)-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**19e**): orange solid 35%; mp 235-236 ºC; IR (KBr) ν/cm^{-1} 1725, 1651, 1618, 1589, 1561, 1495, 1412, 1253, 1232, 1219, 1112; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.63 (s, 3H, (C2)-C$\underline{H}_3$), 1.70 (s, 3H, (C2)-C$\underline{H}_3$), 2.37 (s, 3H, C$\underline{H}_3$), 4.10 (d, 1H, *J* 5.8 Hz, N$\underline{H}$), 4.77 (d, 1H, *J* 5.8 Hz, H3), 5.82 (s, 1H, H4'), 7.19 (d, 2H, *J* 7.8 Hz, H3", H5"), 7.32 (tt, 1H, *J* 8.4, 2.1 Hz, H4"), 7.46 (td, 2H, *J* 8.4, 1.5 Hz, H2", H-6"), 7.60 (d, 2H, *J* 7.8 Hz, H3'", H5'"), 7.71 (d, 2H, *J* 7.8 Hz, H2'", H6'"), 7.69-7.63 (m, 1H, H7), 7.69-7.63 (m, 1H, H8), 7.69-7.63 (m, 1H, H9), 8.11 (dd, 1H, J 7.9, 1.5 Hz, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4 (C$\underline{H}_3$), 21.4 (C2)-C$\underline{H}_3$), 27.9 (C2)-C$\underline{H}_3$), 63.4 (C3), 85.5 (C4'), 96.2 (C2), 113.9 (C3a), 124.0 (C2", C6"), 125.4 (C2'", C6'"), 126.9 (C9a), 127.6 (C4"), 129.0 (C3", C5"), 129.3 (C6), 129.5 (C3'", C5'"), 130.4 (C5a), 124.7, 132.3, 134.5 (C7, C8, C9), 137.4 (C1"), 138.2 (C1'"), 147.3 (C5'), 151.3 (C3'), 169.7 (C9b), 175.2 (C4), 180.5 (C5).

3-(1-*O*-Metil-2,3-*O*-isopropylideno)-β-D-ribofuranosyl-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**19f**): orange solid 62%; mp 130-131 °C; IR (KBr) ν/cm^{-1} 2921, 1644, 1612, 1567, 1491, 1453, 1405, 1372, 1343, 1271, 1218, 1070, 979, 848, 795, 771, 721, 685; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22 and 1.24 (s, 3H, C$\underline{H}_3$), 1.38 and 1.40 (s, 3H, C$\underline{H}_3$), 1.41 and 1.42 (s, 3H, C$\underline{H}_3$), 1.58 and 1.60 (s, 3H, C$\underline{H}_3$), 3.24 and 3.25 (s, 3H, OC$\underline{H}_3$), 3.57-3.82 (m, 1H, H5' two diastereoisomers), 4.13-4.27 (m, 1H, H5" two diastereoisomers), 4.49-4.53 (m, 1H, H4' two diastereoisomers), 4.51 (s, 1H, H3), 4.57 and 4.58 (d, 1H, *J* 6.1 Hz, H2'), 4,62 and 4.63 (d, 1H, *J* 6.1 Hz, H3'), 4.88 (s, 1H, H-1'), 7.53-7.66 (m, 1H, H7), 7.53-7.66 (m, 1H, H8), 7.53-7.66 (m, 1H, H9), 8.04-8.08 (m, 1H, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.6 (C$\underline{H}_3$), 20.7 (C$\underline{H}_3$), 24.9 and 24.8 (C$\underline{H}_3$), 26.3 and 26.4 (C$\underline{H}_3$), 54.6 and 54.7 (OC$\underline{H}_3$), 72.0 and 72.3 (C5'), 81.9 (C3'), 82.5 (C2'), 83.3 (C3), 85.0 and 85.1 (C4'), 95.5 and 95.6 (C2), 109.1 and 109.2 (C1'), 112.2 (C6'), 117.0 (C3a), 125.1 (C7 or C8 or C9), 127.6 (C9a), 129.3 (C7 or C8 or C9), 131.1 (C5a), 132.3 (C7 or C8 or C9), 134.5 (C6), 170.2 (C9b), 175.9 (C4), 181.3 (C5); HRESIMS *m/z* 431.1686 $[M + H]^{+\cdot}$ (Calcd. for $C_{23}H_{27}O_8^+$ 431.1700).

3-(1,2:3,4-di-*O*-Isopropylideno)-α-D-galactopiranosyl-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**19g**): orange solid 14%; mp 235-236 °C; IR (KBr) ν/cm^{-1} 1700, 1644, 1612, 1567, 1490, 1452, 1407, 1372, 1342, 1317, 1272, 1217, 1165, 1115, 1071, 981, 952, 901, 850, 825, 795, 770, 721, 682, 653; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (s, 3H, C$\underline{H}_3$), 1.35 (s, 3H, C$\underline{H}_3$), 1.46 (s, 3H, C$\underline{H}_3$), 1.54 (s, 3H, C$\underline{H}_3$), 1.63 (s, 3H, C$\underline{H}_3$), 1.70 (s, 3H, C$\underline{H}_3$), 3.90-3.81 (m, 1H, H5), 3.90-3.81 (m, 2H, H6'), 4.28 (dd, 1H, *J* 7.8, 1.5 Hz, H4'), 4.34 (dd, 1H, *J* 5.1, 2.4 Hz, H2'), 4.53 (s, 1H, H3), 5.58 (d, 1H, *J* 5.1 Hz, H1'), 7.52-7.65 (m, 1H, H7), 7.52-7.65 (m, 1H, H8), 7.52-7.65 (m, 1H, H9), 8.02-8.07 (m, 1H, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.1 (C$\underline{H}_3$), 24.7 (C$\underline{H}_3$), 25.7 (C$\underline{H}_3$), 25.8 (C$\underline{H}_3$), 26.9 (C$\underline{H}_3$), 27.8 (C$\underline{H}_3$), 62.0 (C6'), 68.0 (C5'), 70.3 (C2'), 70.5 (C3'), 71.3 (C4'), 83.3 (C3), 95.5 (C2), 96.1 (C1'), 108.5 (C8'), 109.2 (C7'), 117.0 (C3a), 125.3 (C7 or C8 or C9), 127.8 (C9a), 129.1 (C7 or C8 or C9), 131.4 (C5a), 132.1 (C7 or C8 or C9), 134.0 (C6), 170.1 (C9b), 176.5 (C4), 181.0 (C5); HRESIMS *m/z* 487.1966 $[M + H]^{+\cdot}$ (Calcd for $C_{26}H_{31}O_9^+$ 487.1963).

3-(3-*O*-Benzil-1,2-*O*-isopropylideno)-α-D-xilofuranose-2,2-dimethyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (**19h**): orange solid 11%; mp 125-126 °C; IR (KBr) ν/cm^{-1} 1699, 1644, 1612, 1566, 1491, 1453, 1407, 1373, 1343, 1272, 1219, 1164, 1115, 850, 795, 770, 720, 610; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.33 (s, 3H, C$\underline{H}_3$); 1.49 (s,

3H, C$\underline{H}_3$), 1.63 (s, 3H, C$\underline{H}_3$), 1.70 (s, 3H, C$\underline{H}_3$), 3.90-3.81 (m, 1H, H5), 3.85 (dd, 1H, *J* 5.1, 12.0 Hz, H5'), 3.94 (dd, 1H, *J* 5.1, 12.0 Hz, H5"), 4.01 (d, 1H, *J* 3.4 Hz, H3'), 4.03 (td, 1H, *J* 3.4, 5.1, H4'), 4.51 (s, 1H, H3), 4.49 (d, 1H, *J* 12.0 Hz, C$\underline{H}_2$Ph), 4.64 (d, 1H, *J* 3.9 Hz, H2'), 4.72 (d, 1H, *J* 12.0 Hz, C$\underline{H}_2$Ph), 5.99 (d, 1H, *J* 3.9 Hz, H1'), 7.28-7.40 (m, 5H, Ph), 7.50-7.62 (m, 1H, H7), 7.50-7.62 (m, 1H, H8), 7.50-7.62 (m, 1H, H9), 8.03-8.08 (m, 1H, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.0 ($\underline{C}H_3$), 26.5 ($\underline{C}H_3$), 26.9 ($\underline{C}H_3$), 27.8 ($\underline{C}H_3$), 60.6 (C5'), 71.6 (O$\underline{C}H_2$Ph), 82.0 (C2'), 80.0 (C3'), 82.4 (C4'), 83.3 (C3), 95.6 (C2), 111.5 (C6'), 117.0 (C3a), 125.3 (C7 or C8 or C9 or CHPh), 127.5 (C7 or C8 or C9 or CHPh), 127.8 (C9a or CHPh), 127.9 (C7 or C8 or C9 or CHPh), 128.4 (C7 or C8 or C9 or CHPh), 129.1 (C7 or C8 or C9 or CHPh), 131.4 (C5a), 132.1 (C7 or C8 or C9 or CHPh), 134.0 (C6), 136.9 (C_0Ph), 170.1 (C9b), 176.5 (C4), 181.0 (C5); HRESIMS *m/z* 507.2009 $[M + H]^+$ (Calcd. for $C_{29}H_{31}O_8^+$ 507.2013).

MTT assay

The cytotoxicity was tested against OVCAR-8 (ovarian), HCT-116 (colorectal), SF-295 (central nervous system) and HL-60 (leukaemia) cancer cells. For all experiments, cells were plated in 96-well plates (10^5 cells *per* well for adherent cells or 0.3×10^5 cells *per* well for suspended cells in 100 µL of medium). After 24 h, all compounds (0.09-62.6 µM) dissolved in 1% DMSO were added to each well using a high-throughput screening system (Biomek 3000-Beckman Coulter, Inc. Fullerton, CA, USA), and the cultures were incubated for 72 h. Doxorubicin (Sigma) was used as a positive control. Control groups received the same amount of DMSO. Tumor cell growth was quantified by the ability of living cells to reduce the yellow dye 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazoliumbromide (MTT) to a purple formazan product (Mosmann, 1983). At the end of the incubation, the plates were centrifuged and the medium was replaced with fresh medium (150 µL) containing MTT (0.5 mg mL^{-1}). After 3 h, the plates were centrifuged, the MTT formazan product was dissolved in 150 µL DMSO, and the absorbance was measured using a multiplate reader (Spectra Count, Packard, Ontario, Canada). The drug effect was quantified as the percentage of the control absorbance of the reduced dye at 595 nm.

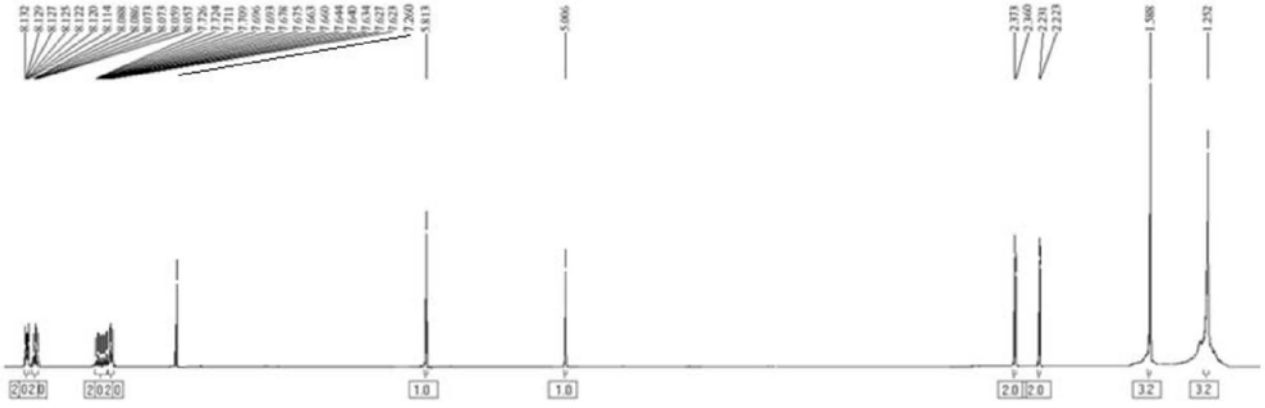

Figure S1. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **11**.

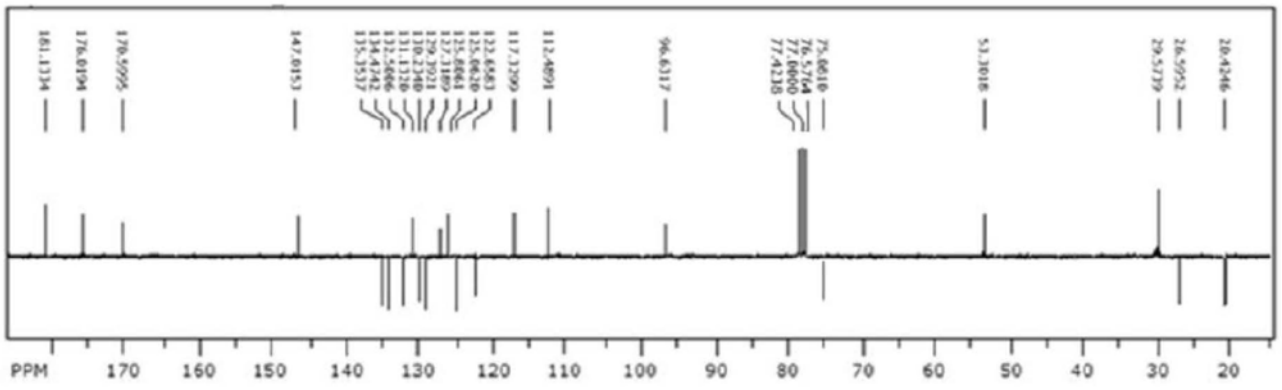

Figure S2. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **11**.

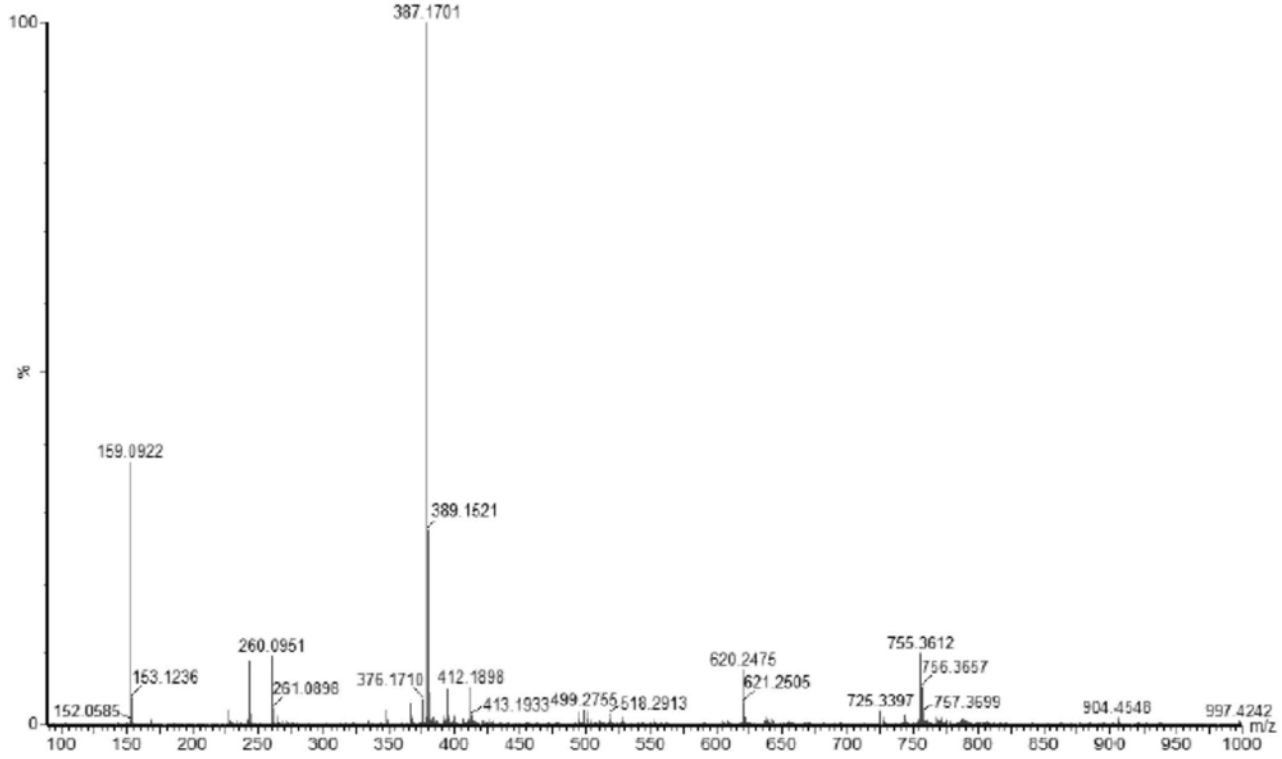

Figure S3. HRESIMS spectrum of **11**.

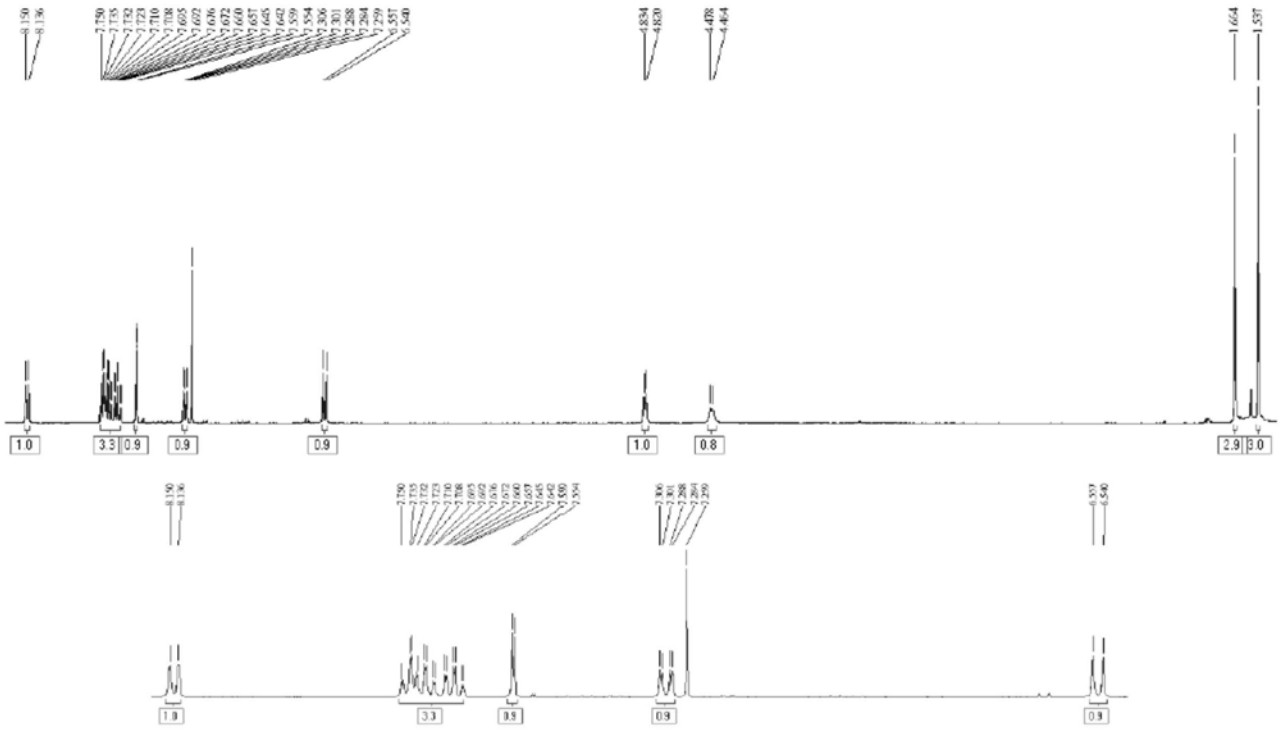

Figure S4. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **12**.

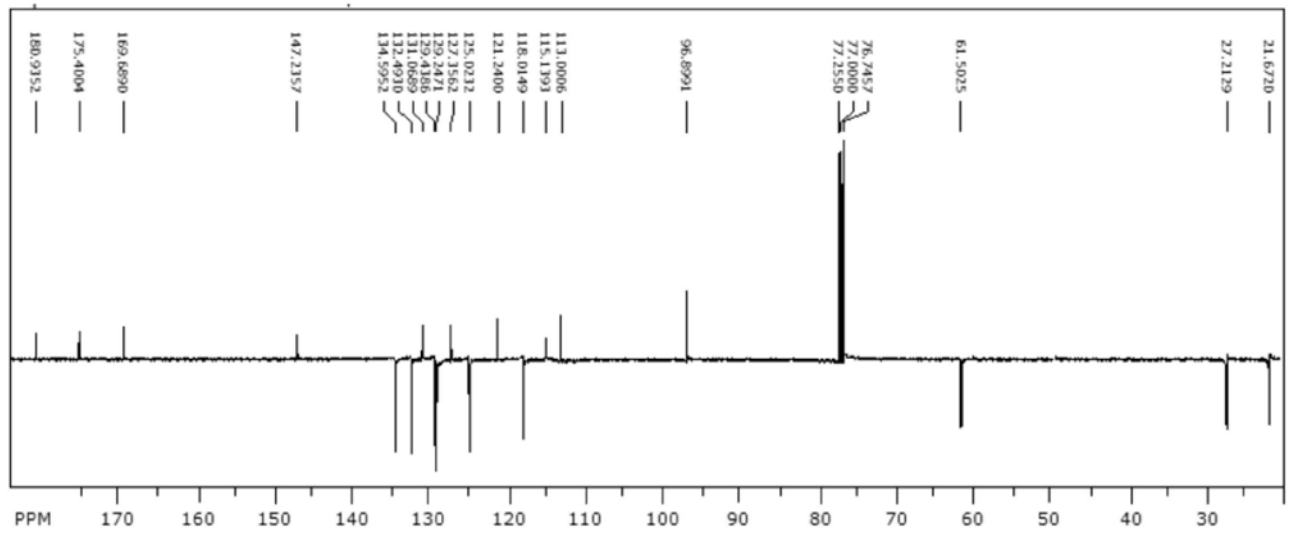

Figure S5. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **12**.

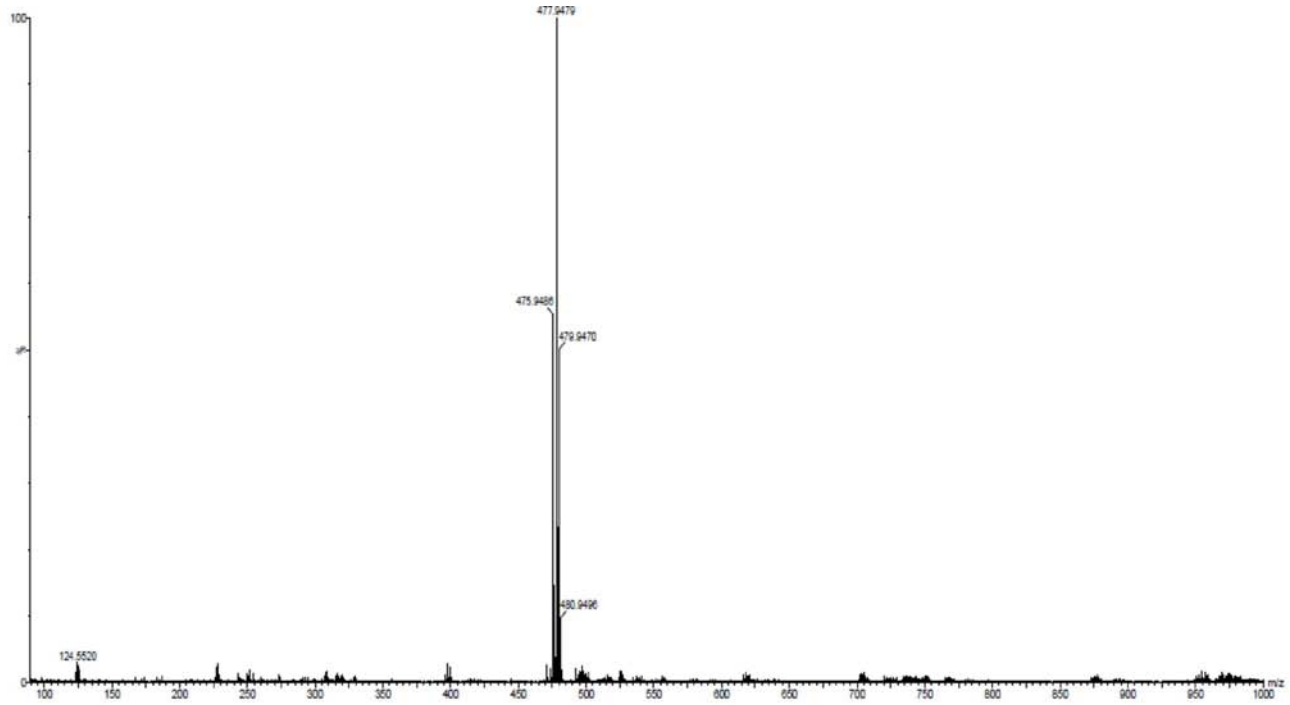

Figure S6. HRESIMS spectrum of **12**.

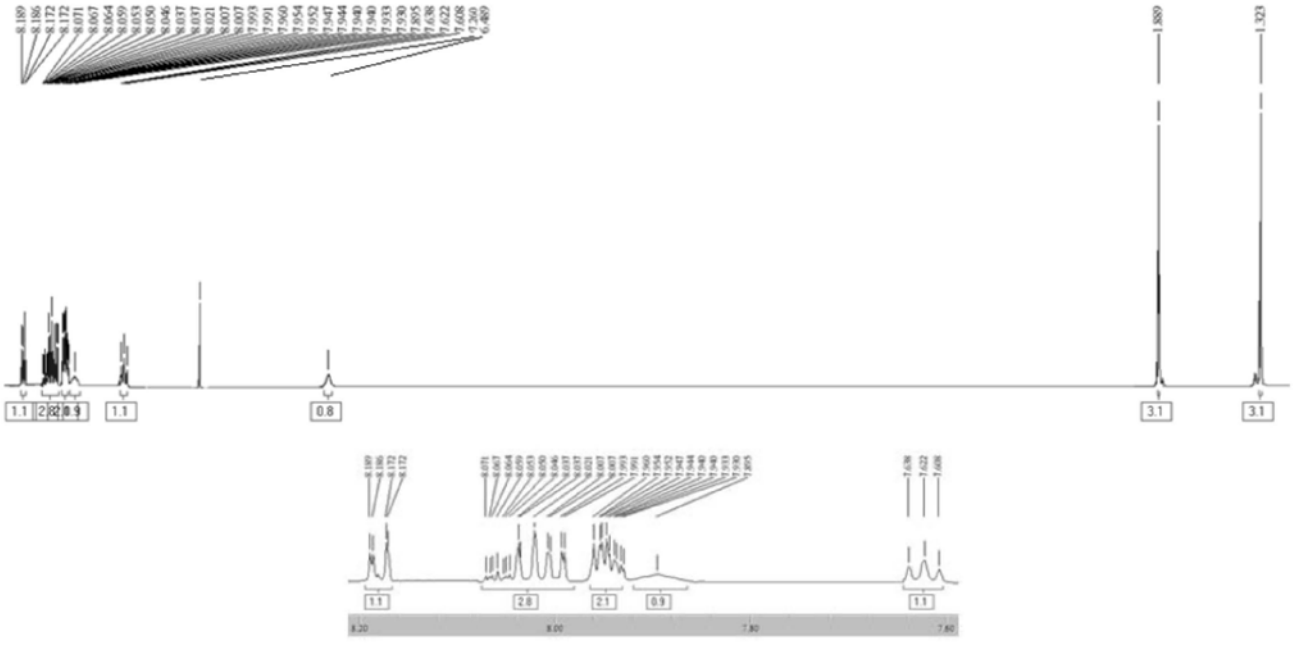

Figure S7. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **13**.

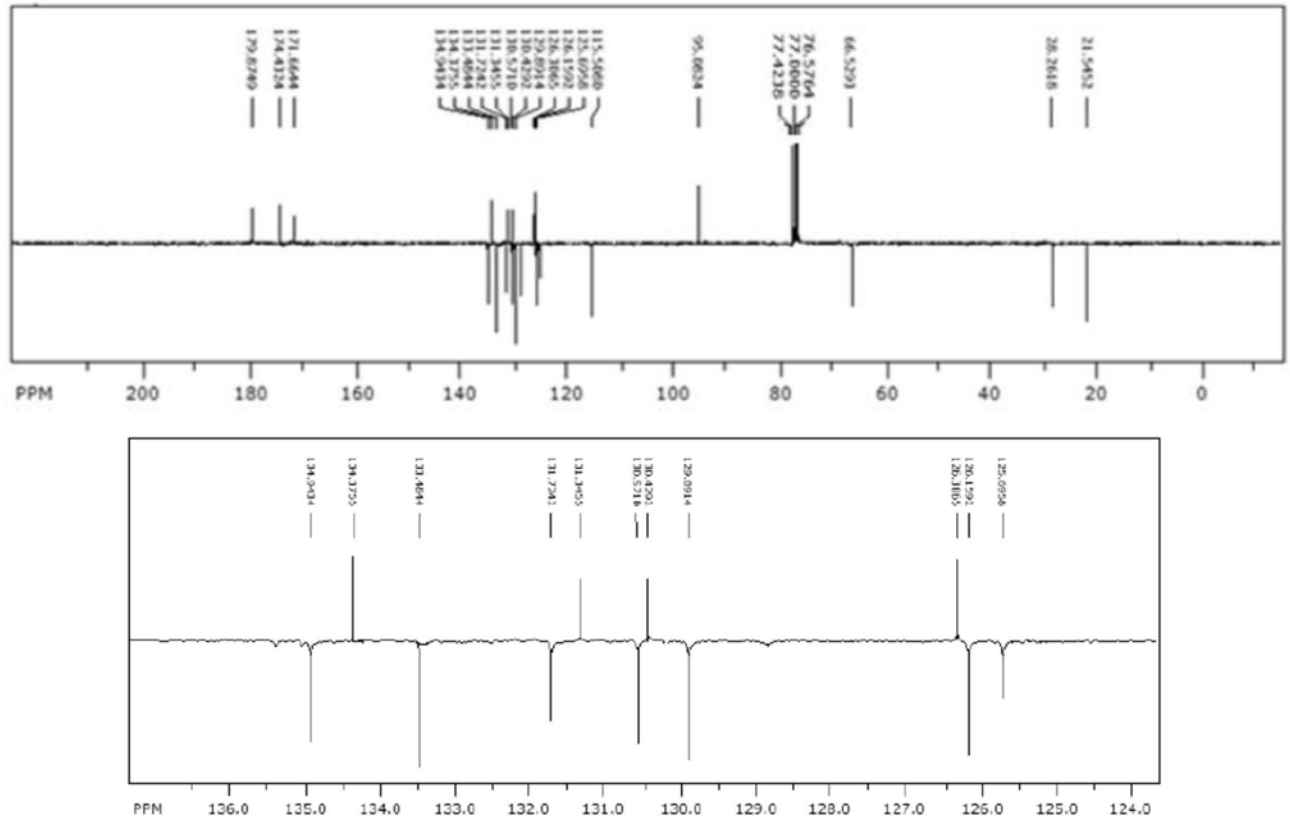

Figure S8. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **13**.

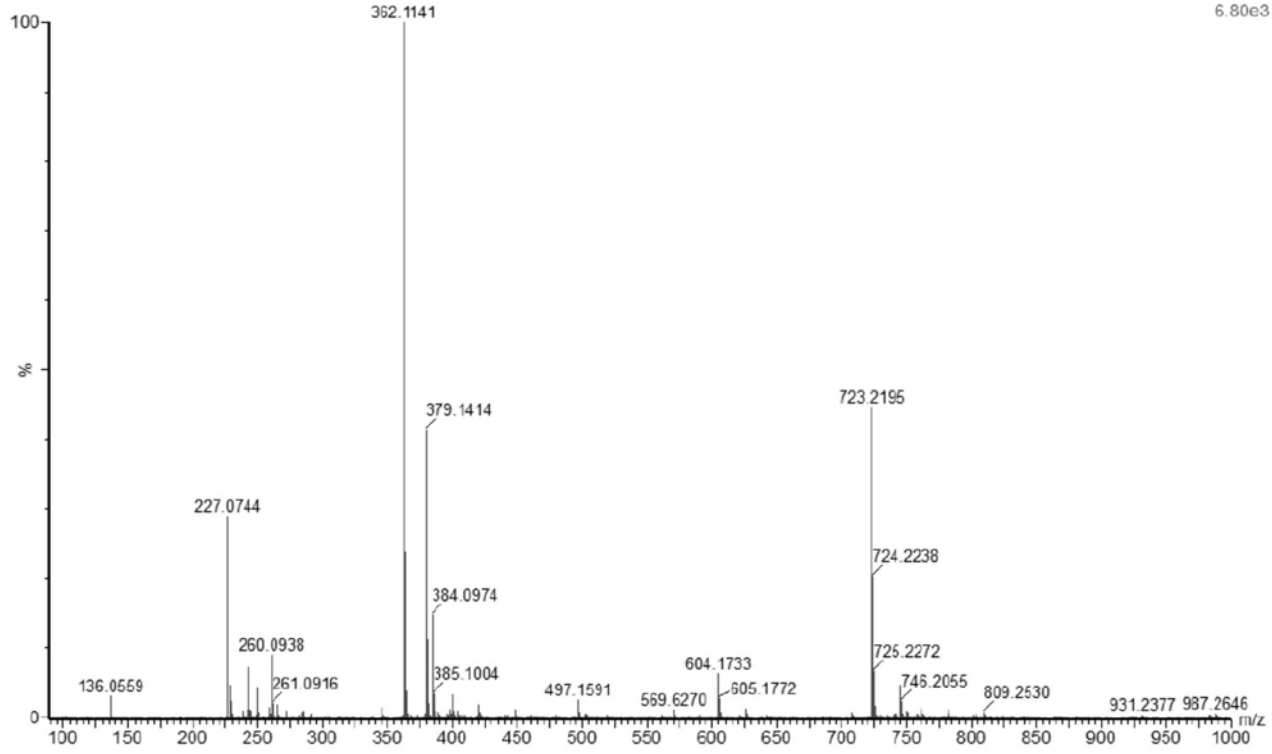

Figure S9. HRESIMS spectrum of **13**.

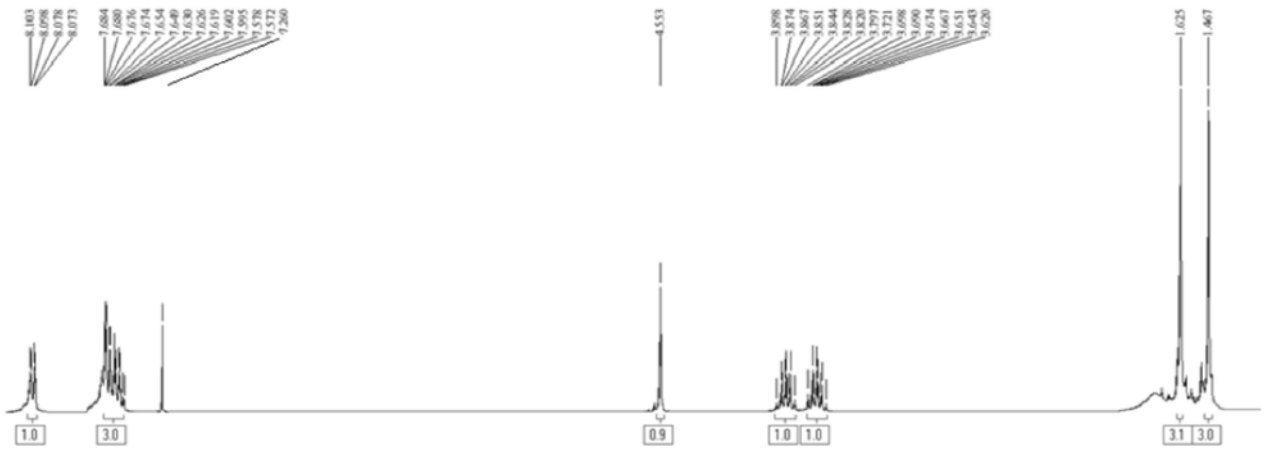

Figure S10. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **14**.

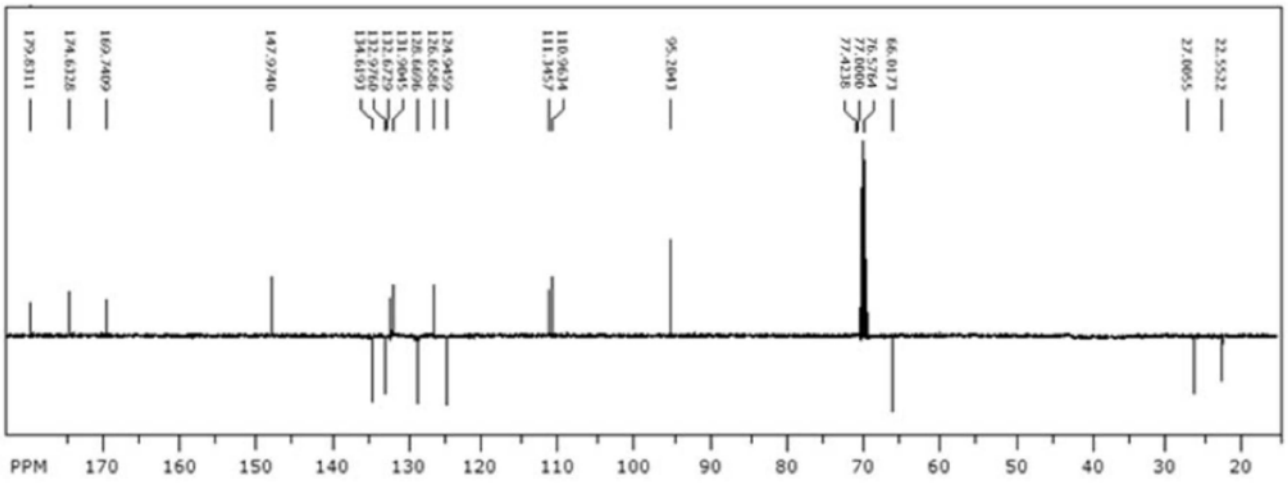

Figure S11. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **14**.

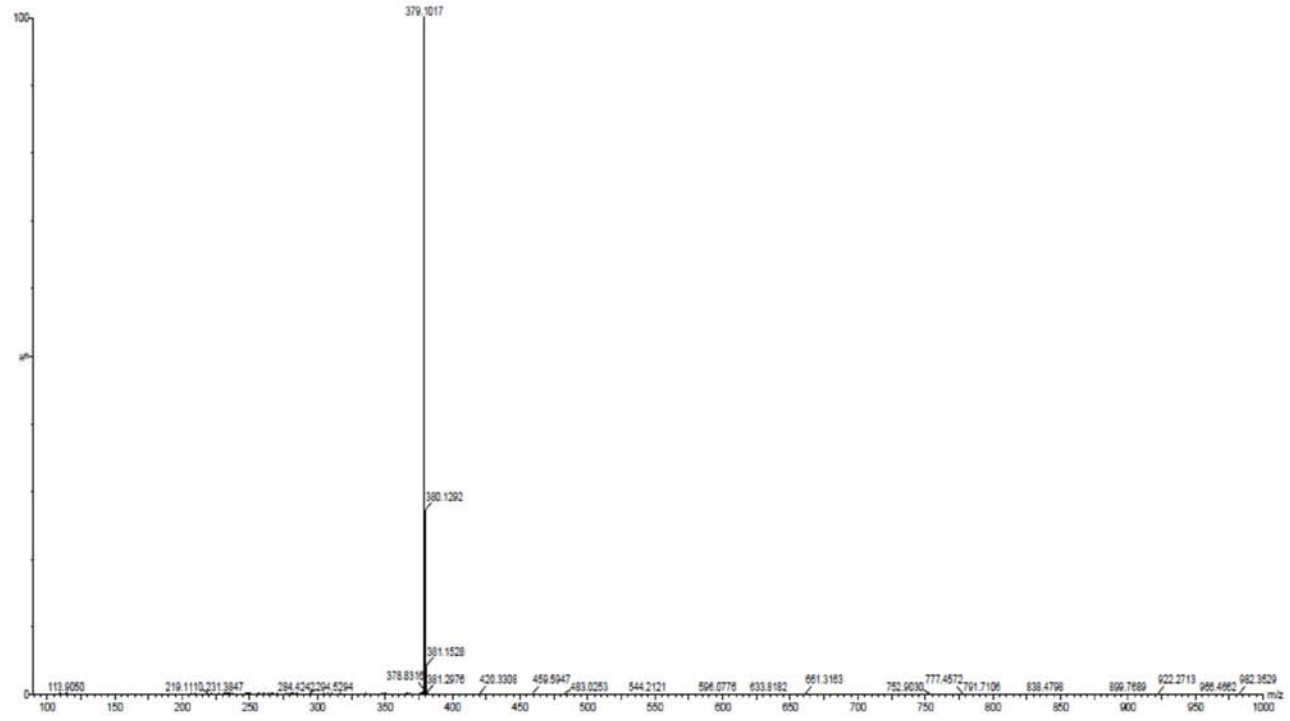

Figure S12. HRESIMS spectrum of **14**.

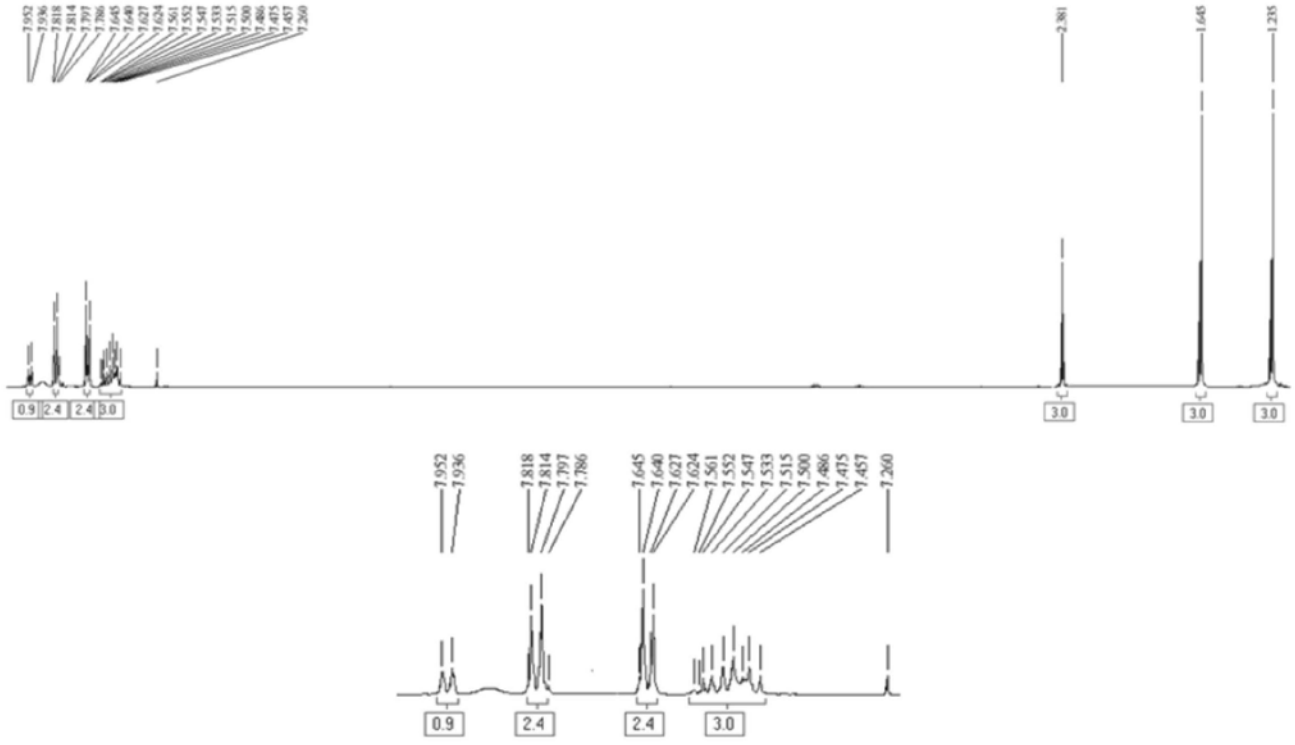

Figure S13. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **15**.

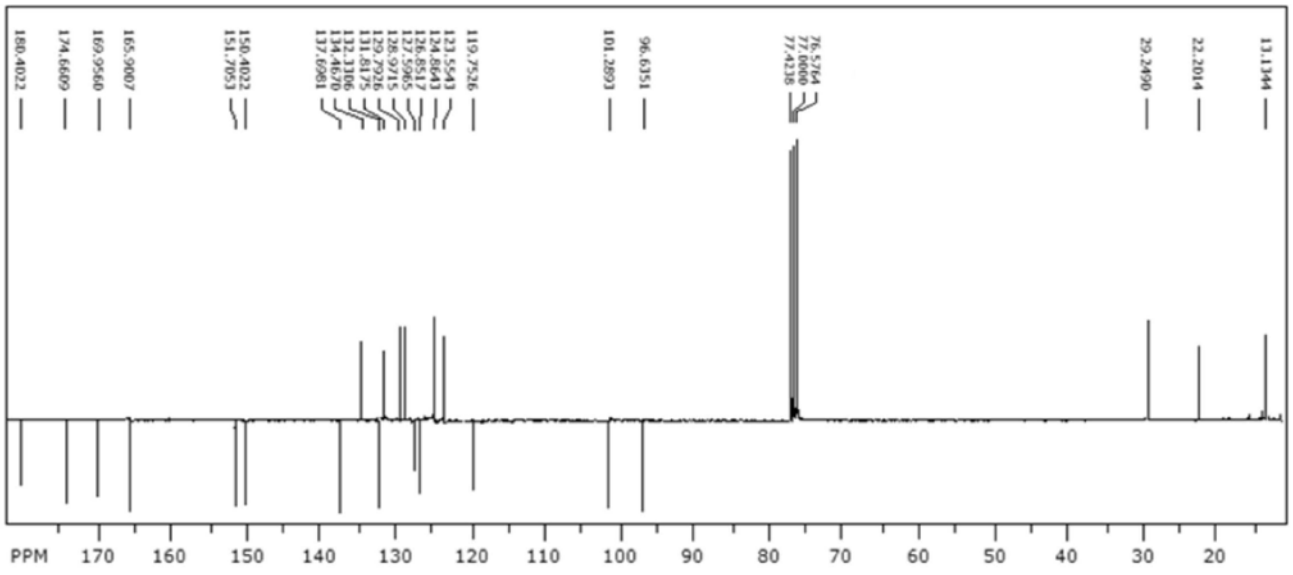

Figure S14. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **15**.

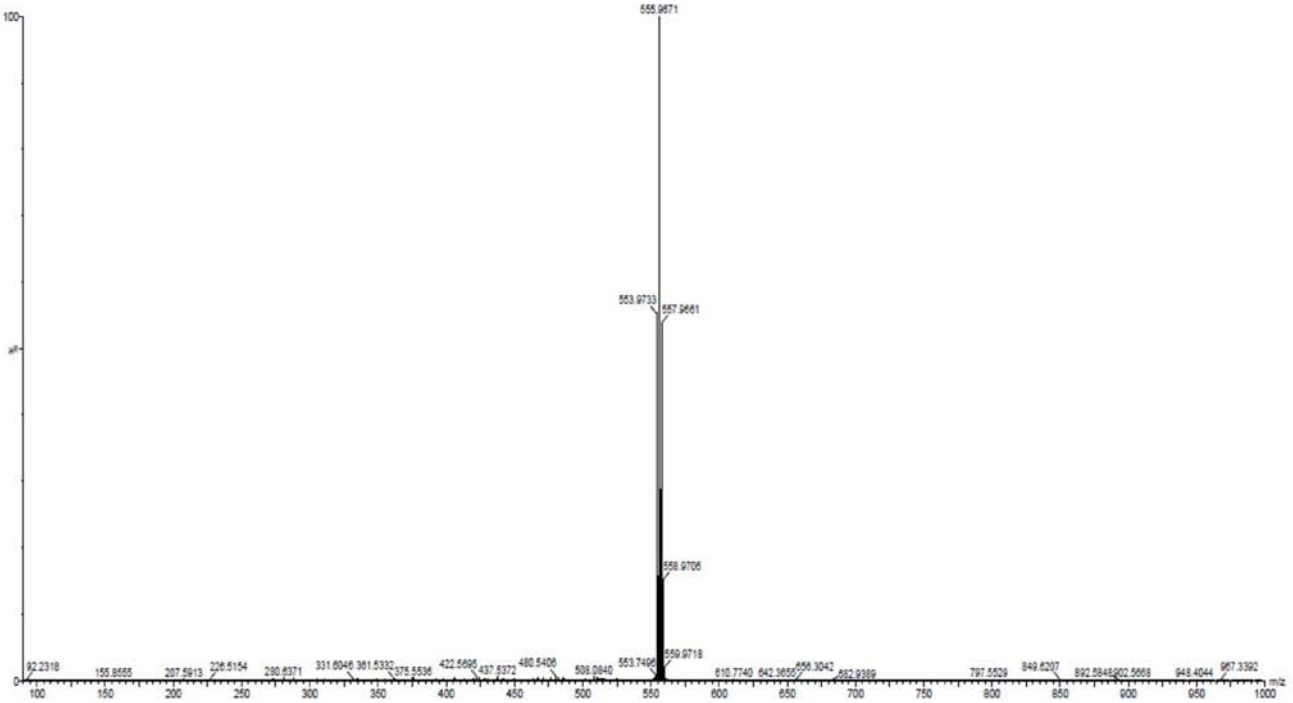

Figure S15. HRESIMS spectrum of **15**.

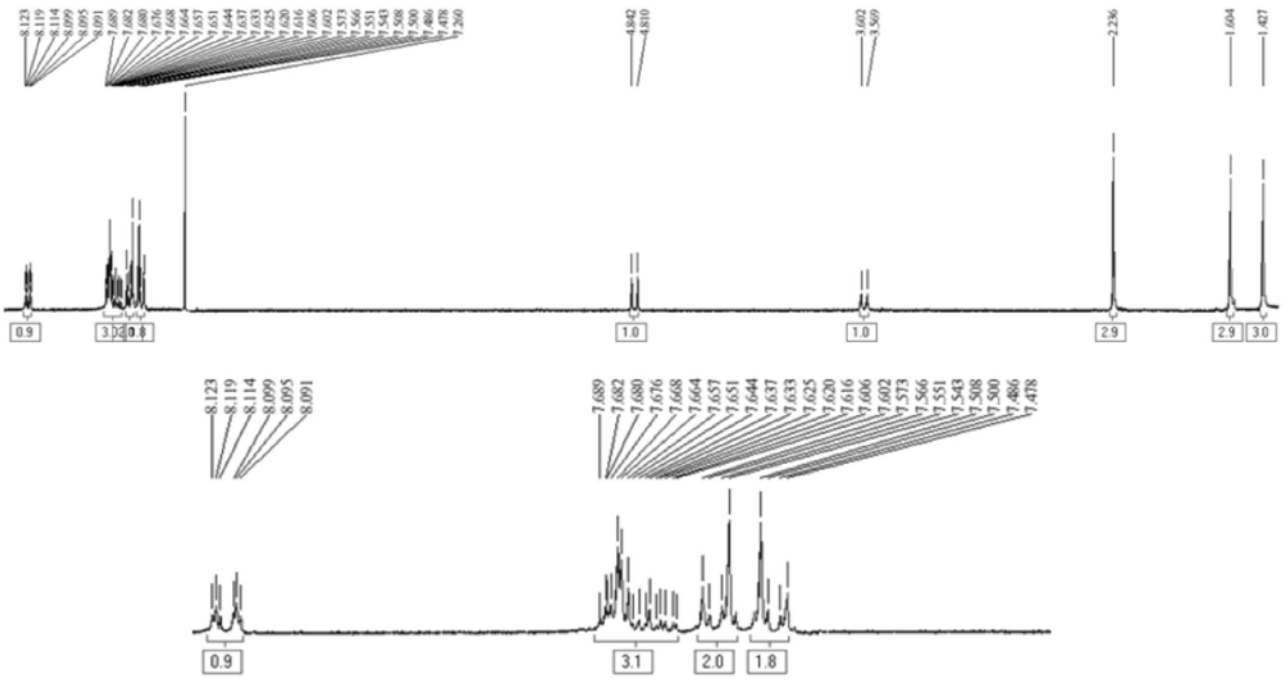

Figure S16. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **16**.

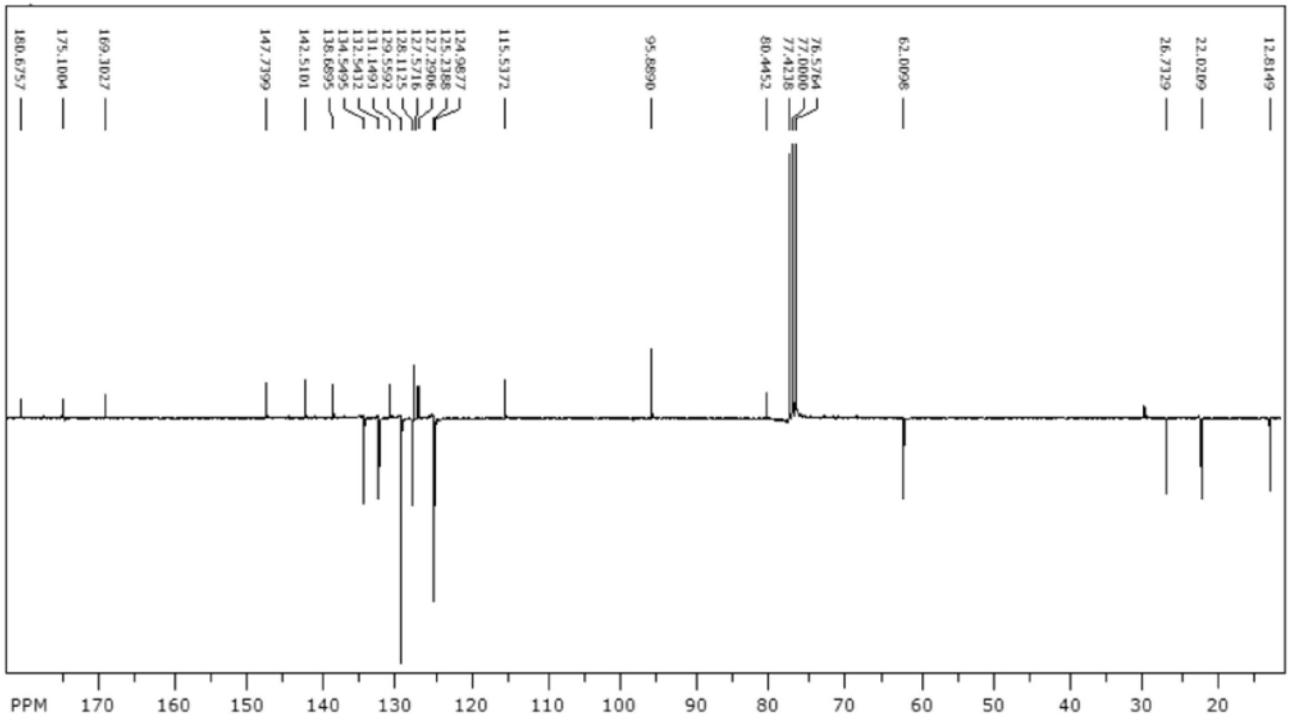

Figure S17. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **16**.

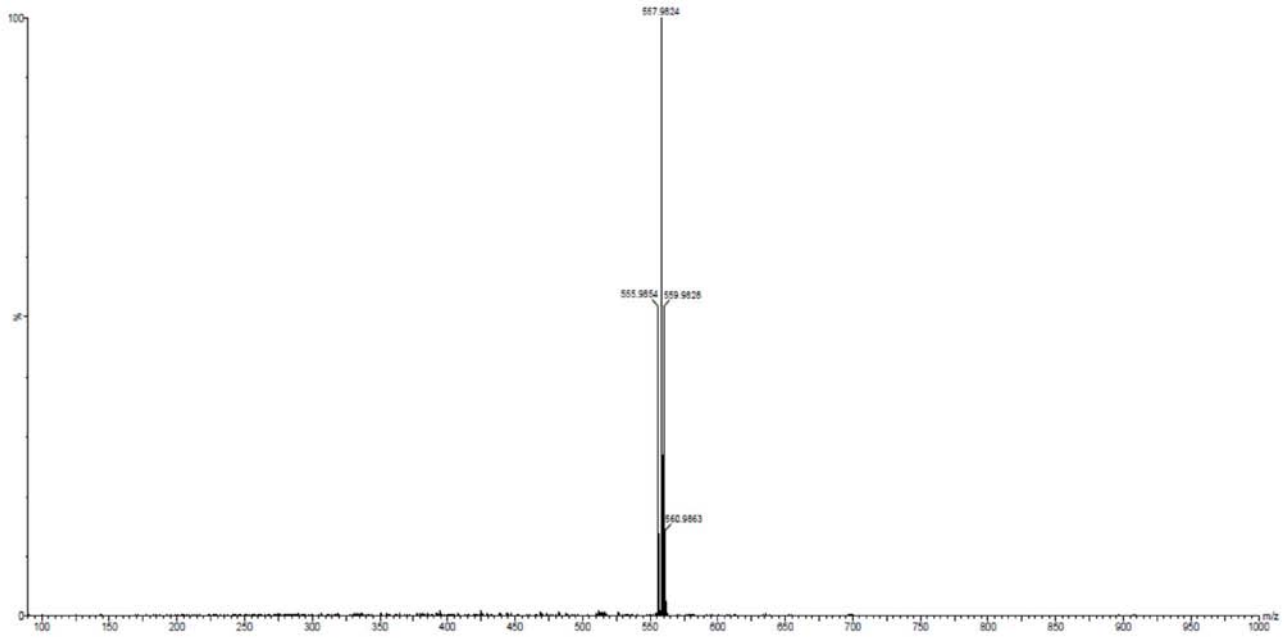

Figure S18. HRESIMS spectrum of **16**.

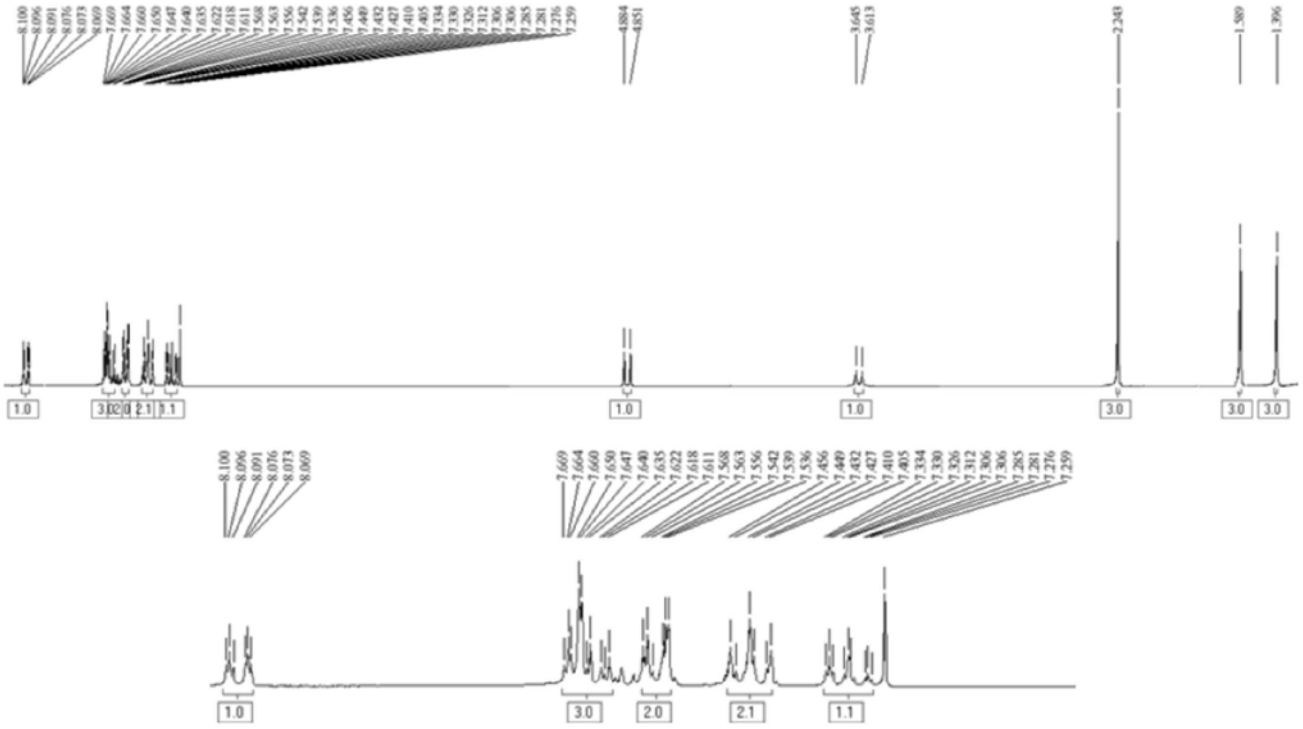

Figure S19. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **17**.

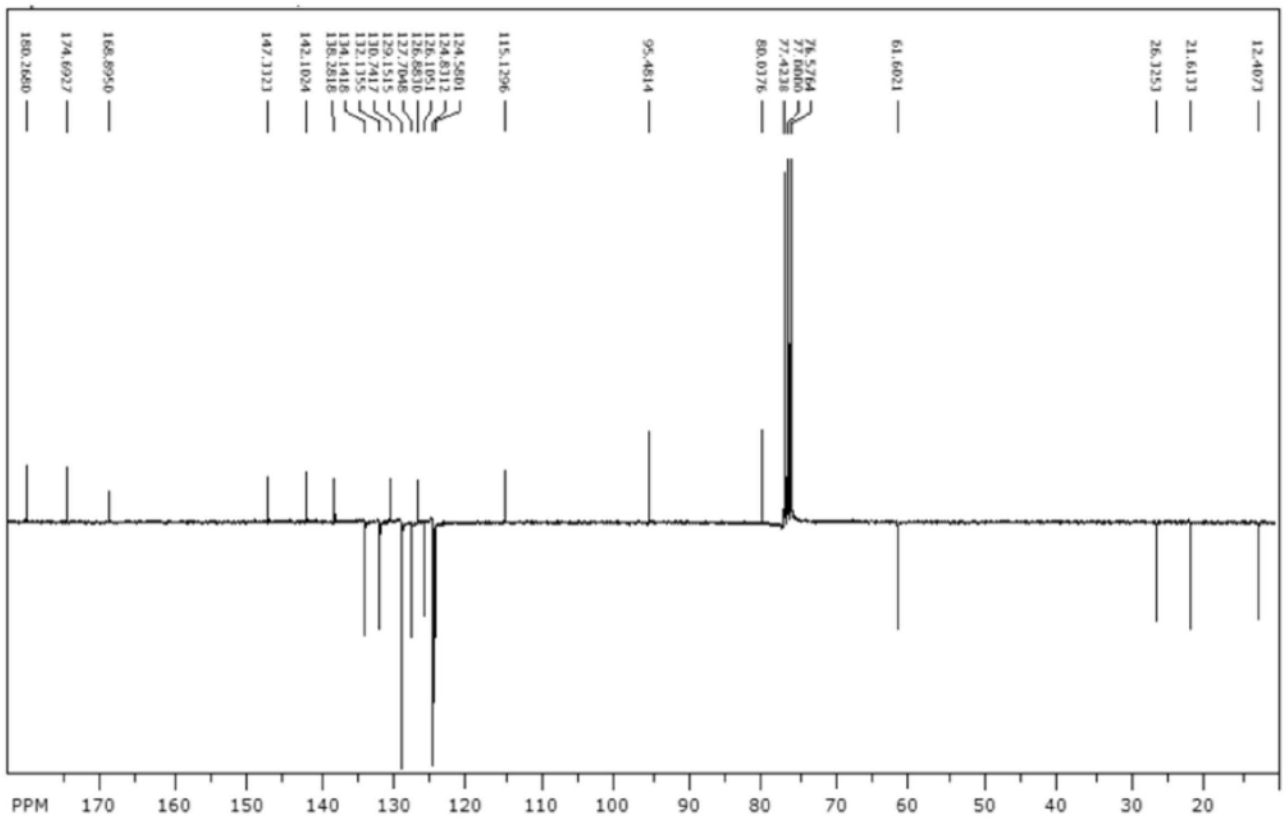

Figure S20. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **17**.

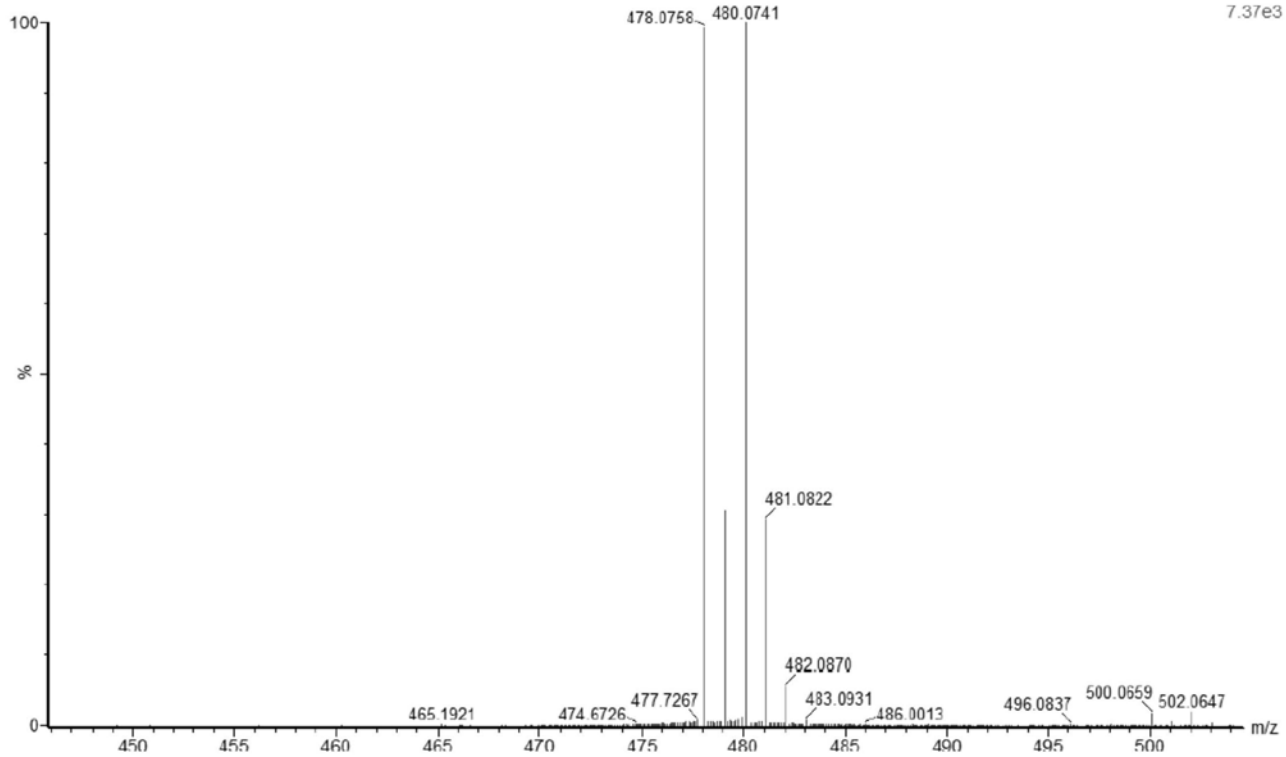

Figure S21. HRESIMS spectrum of **17**.

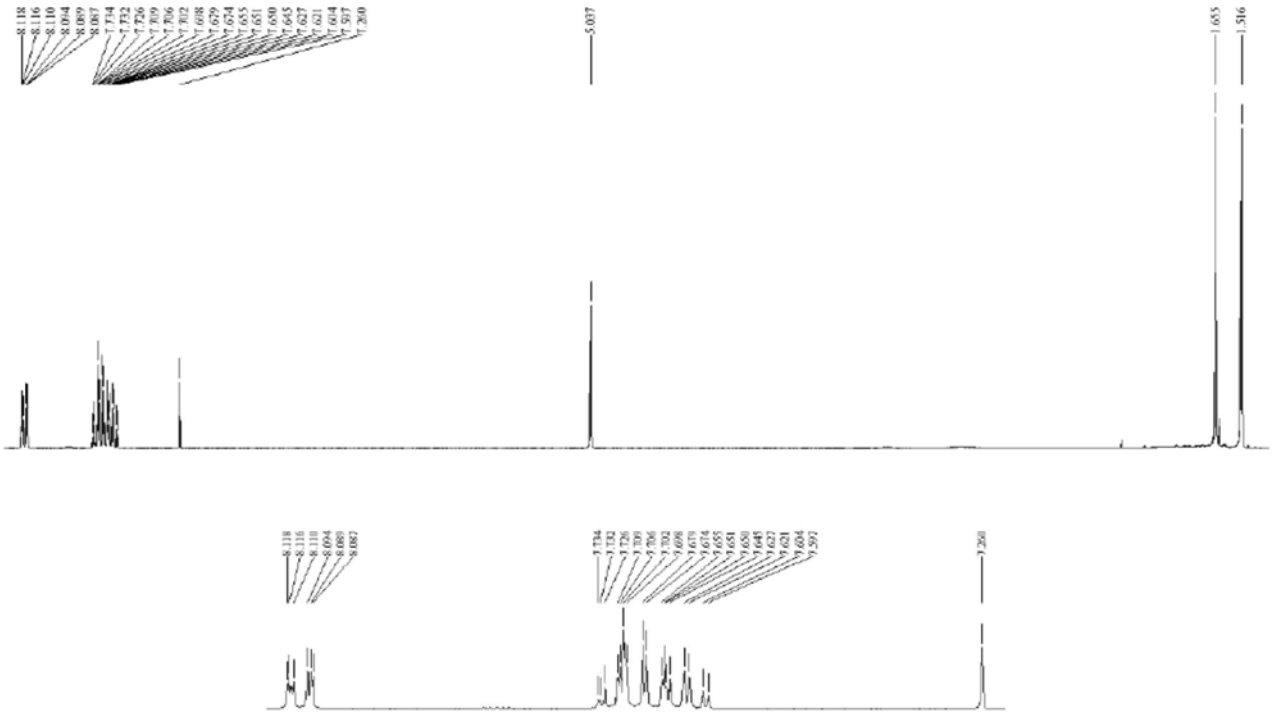

Figure S22. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **18**.

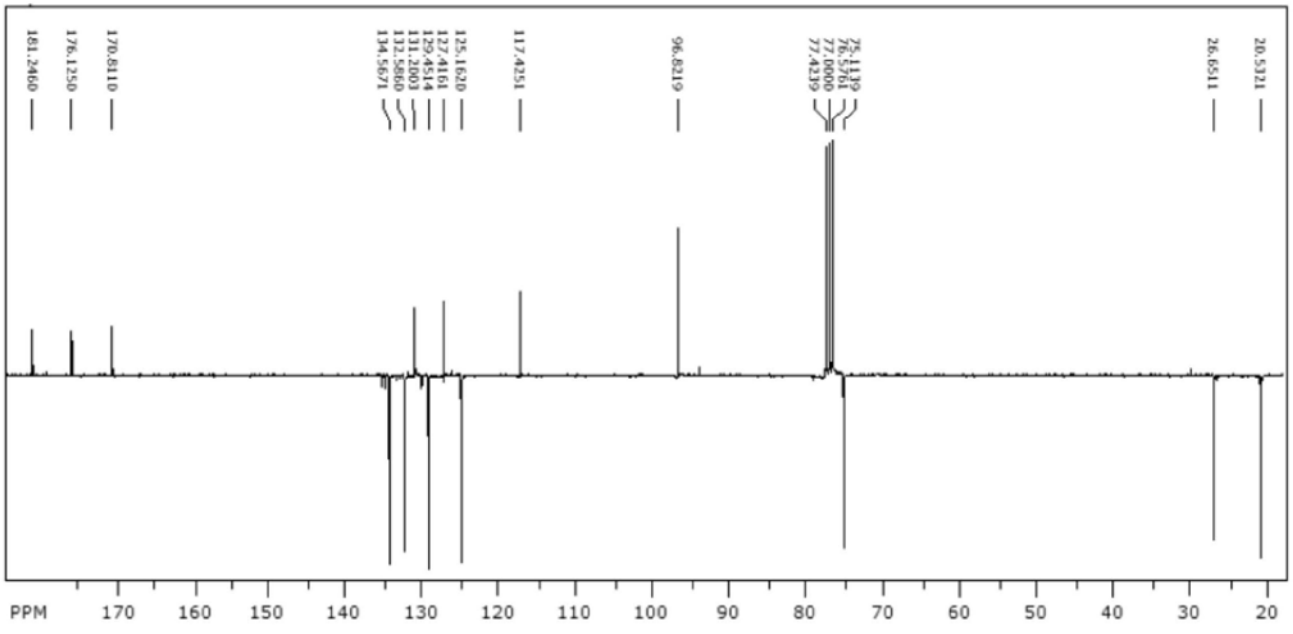

Figure S23. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **18**.

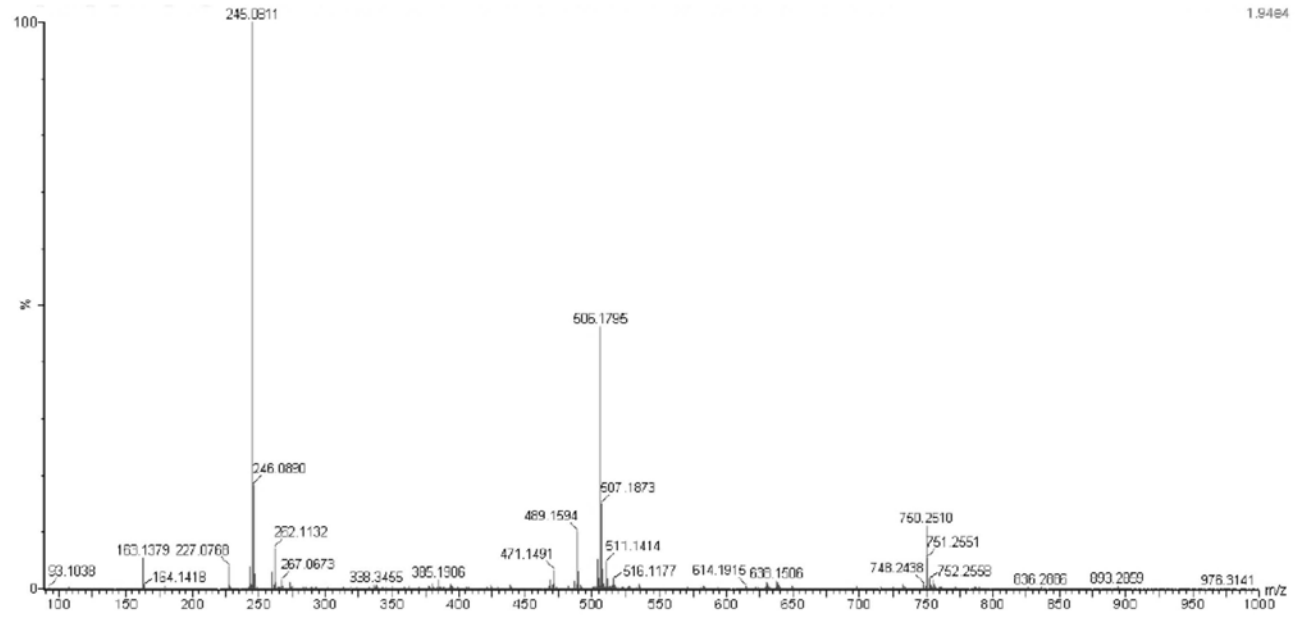

Figure S24. HRESIMS spectrum of **18**.

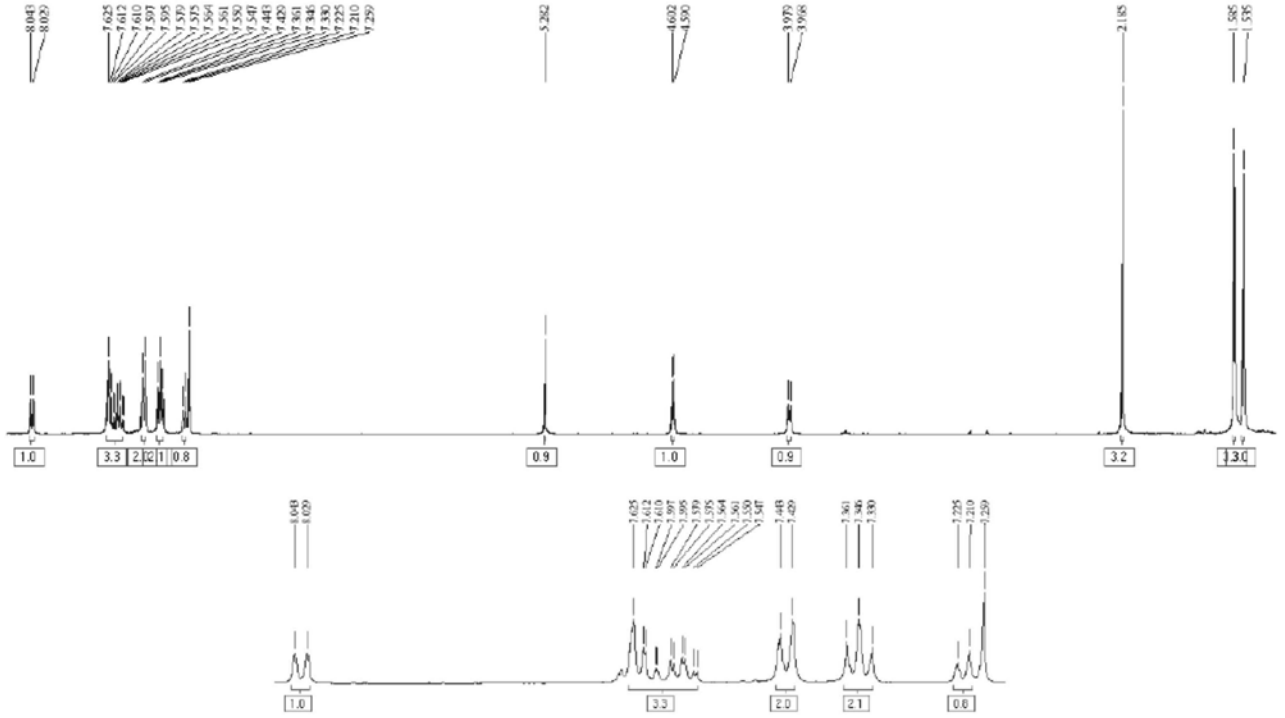

Figure S25. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **19a**.

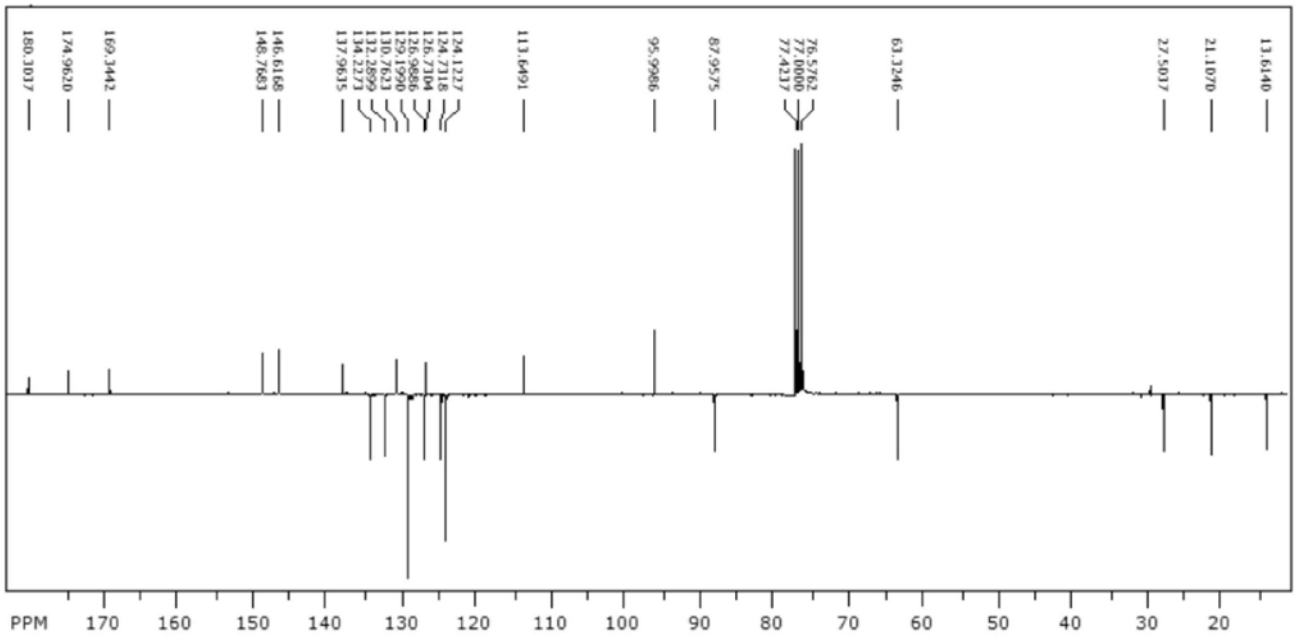

Figure S26. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **19a**.

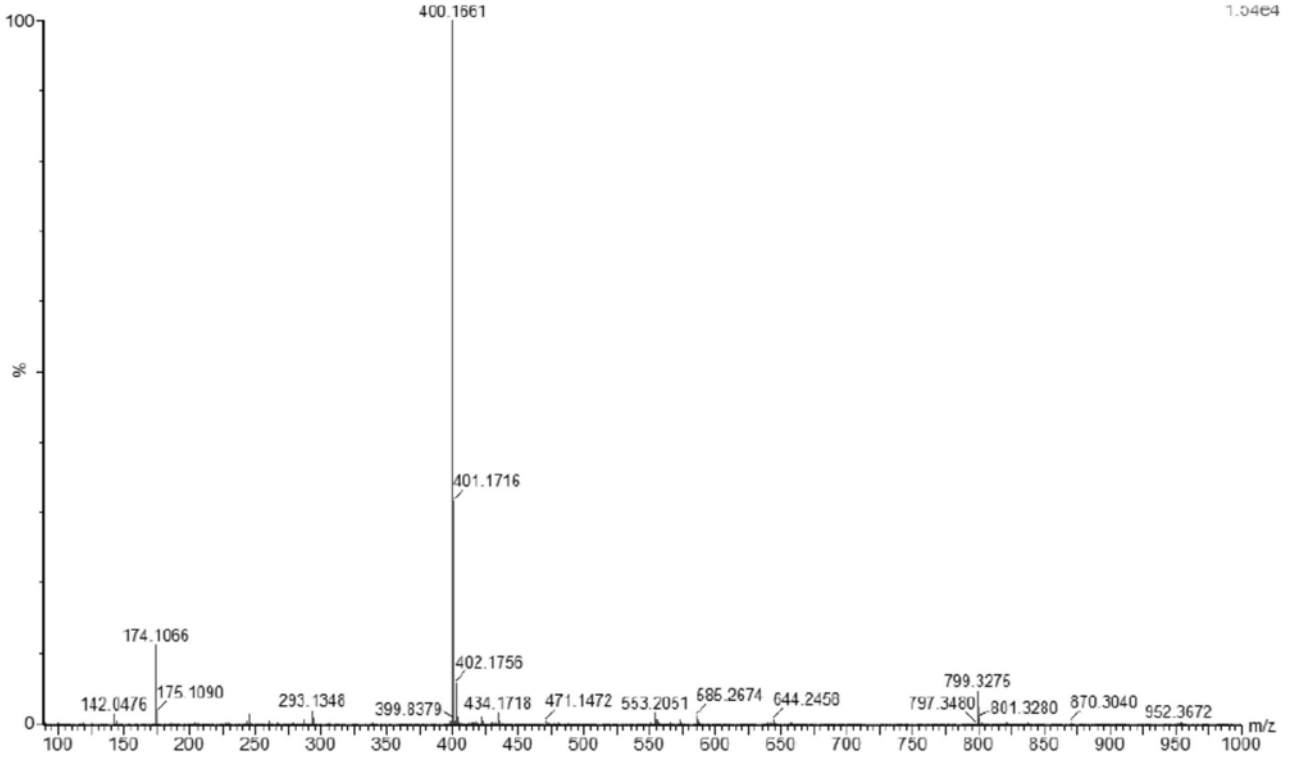

Figure S27. HRESIMS spectrum of **19a**.

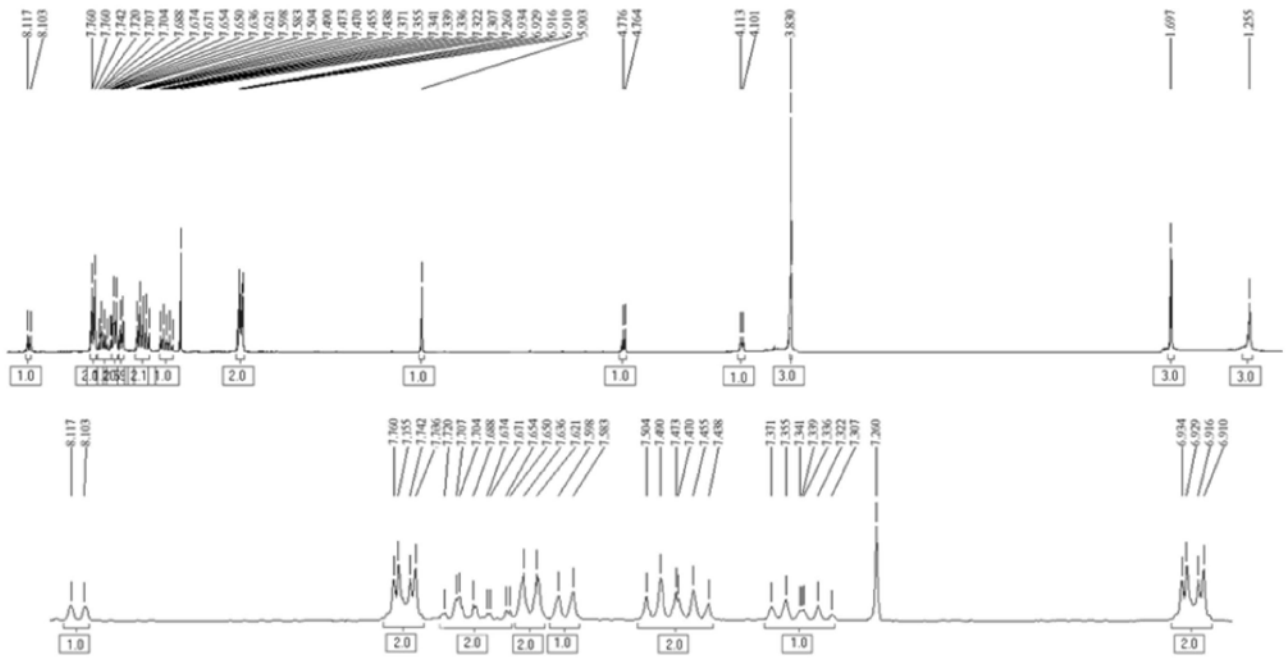

Figure S28. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **19b**.

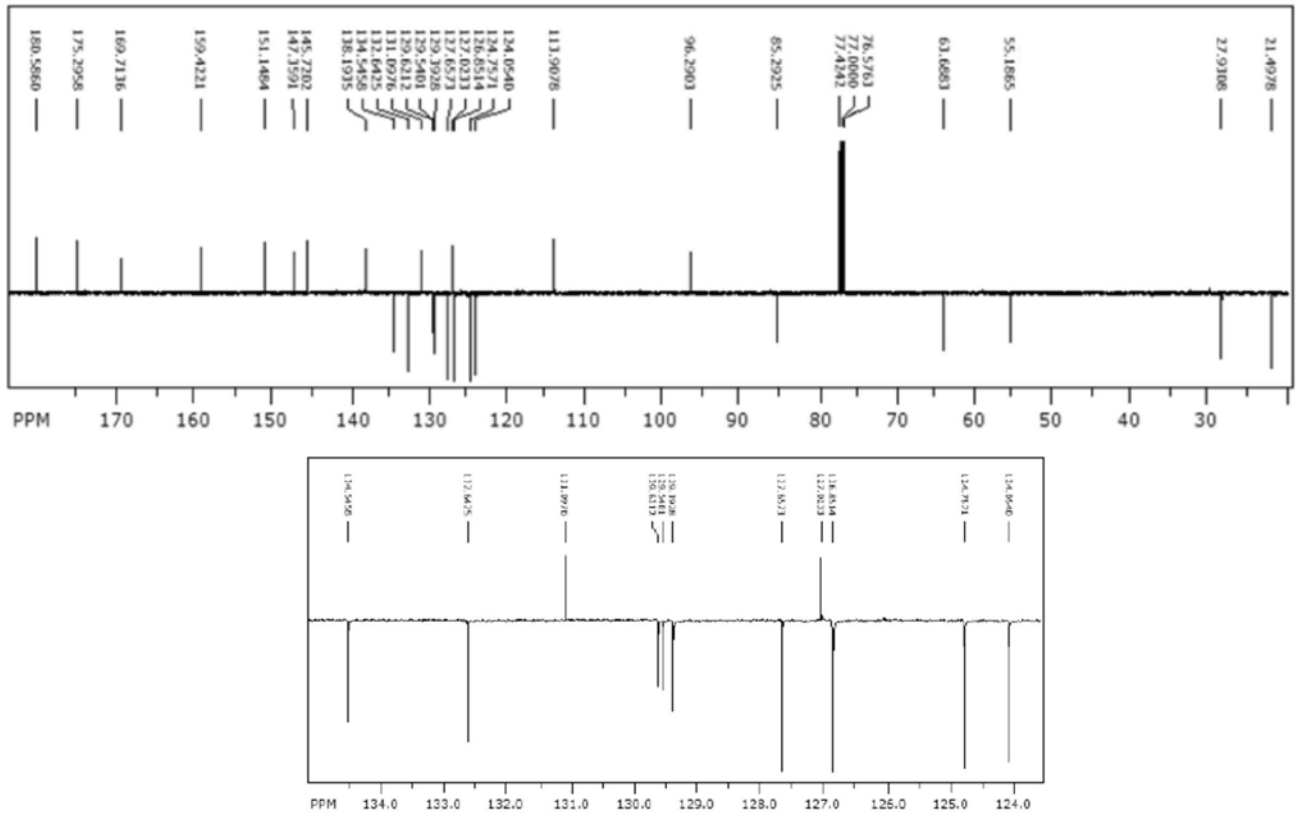

Figure S29. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **19b**.

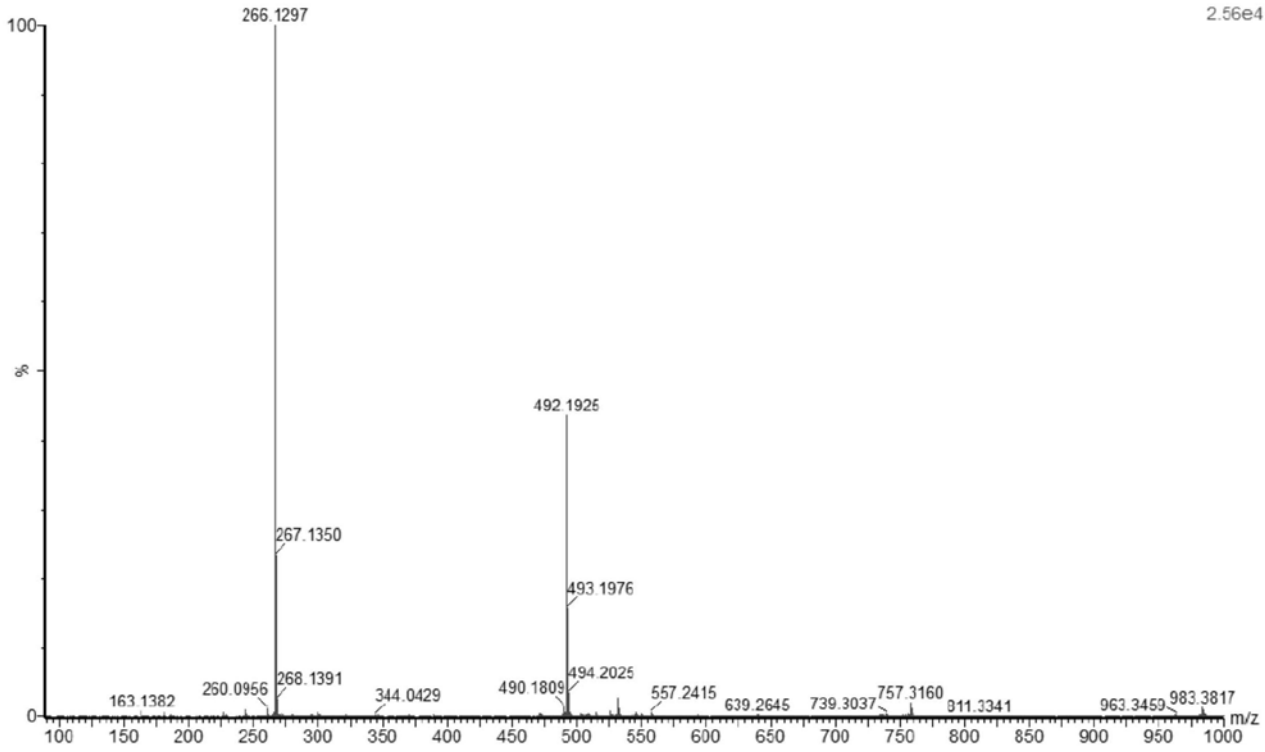

Figure S30. HRESIMS spectrum of **19b**.

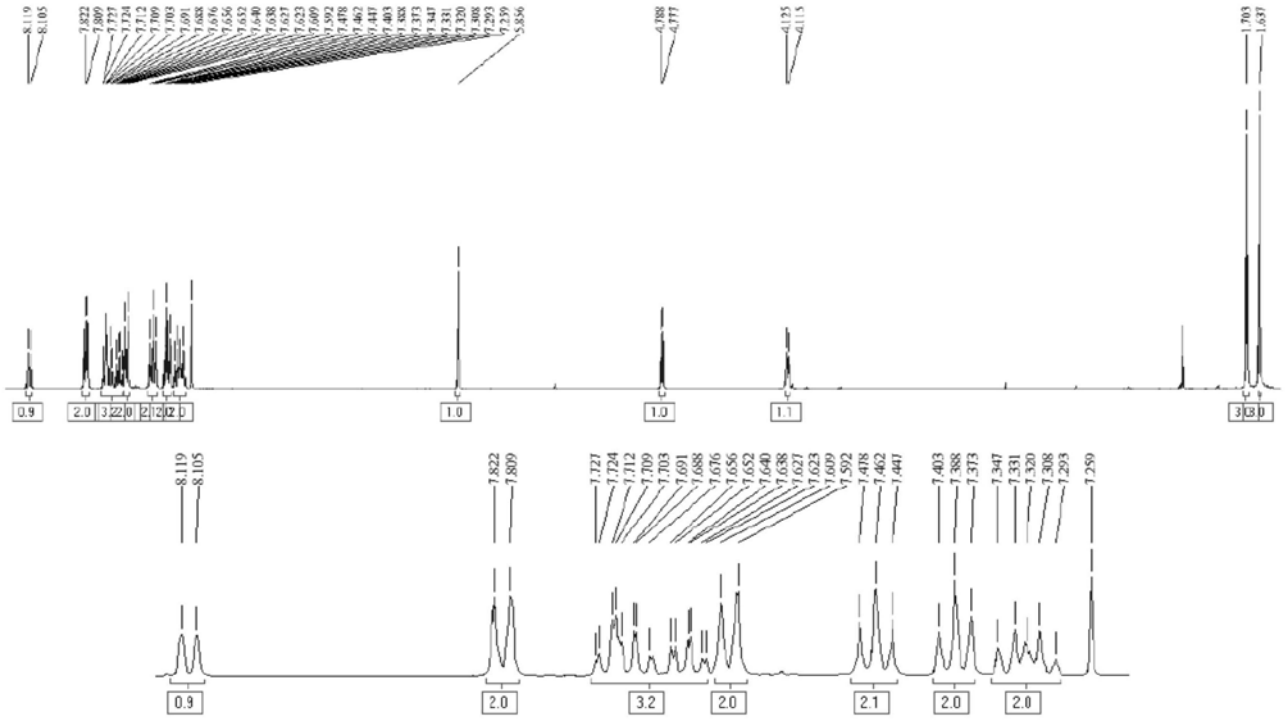

Figure S31. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **19c**.

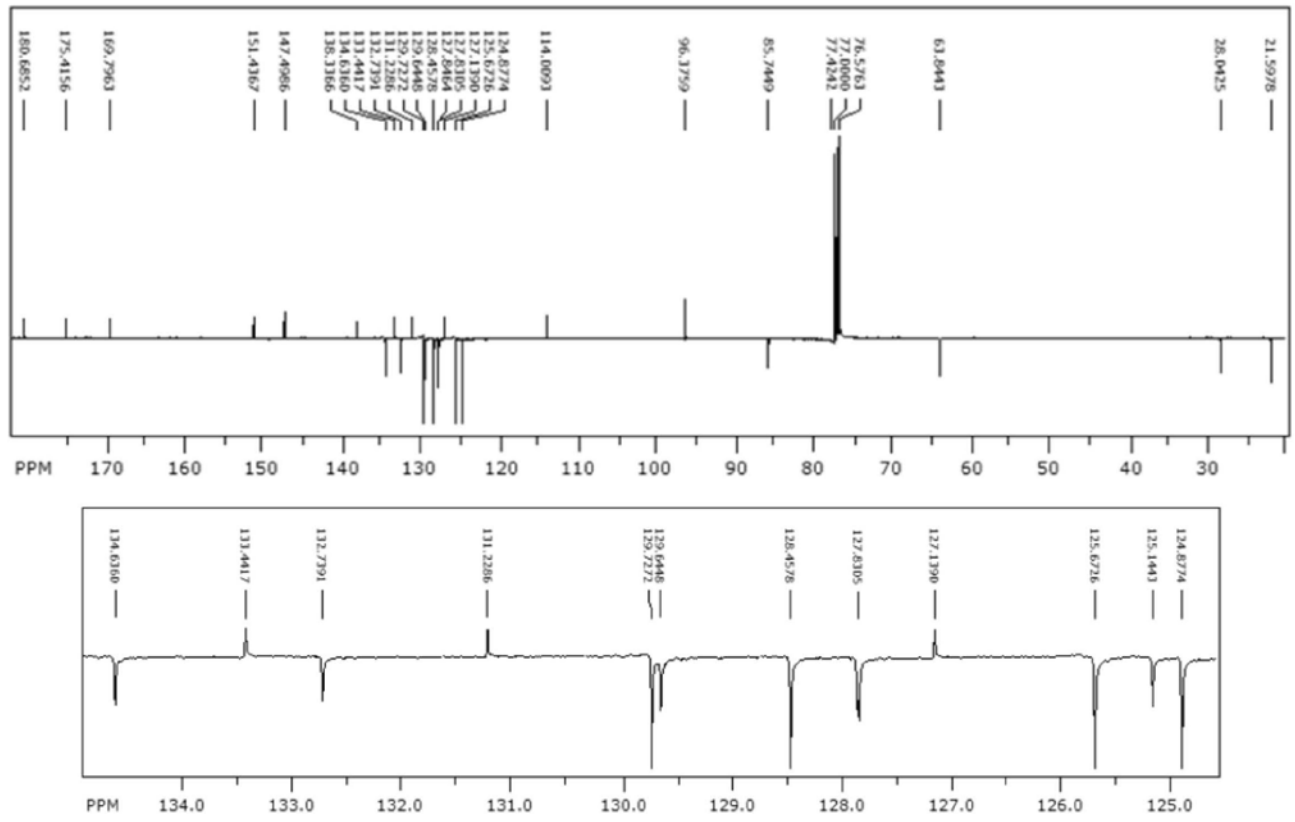

Figure S32. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **19c**.

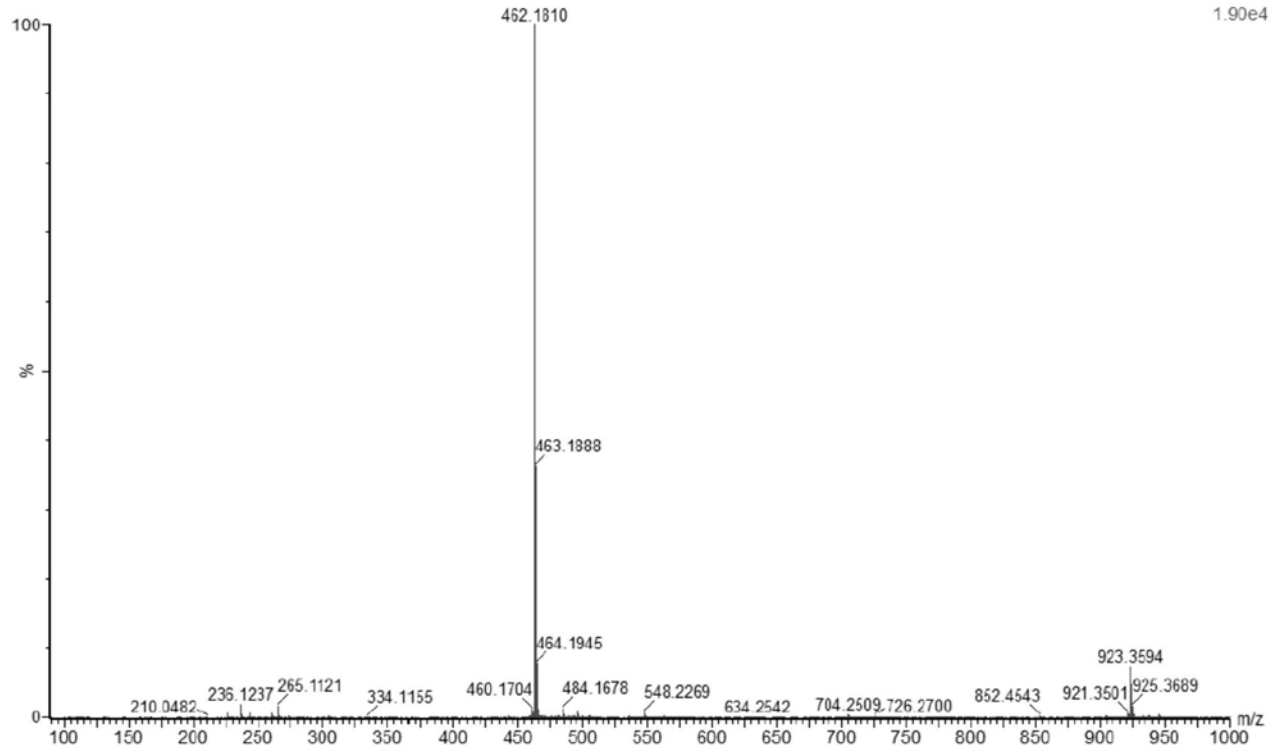

Figure S33. HRESIMS spectrum of **19c**.

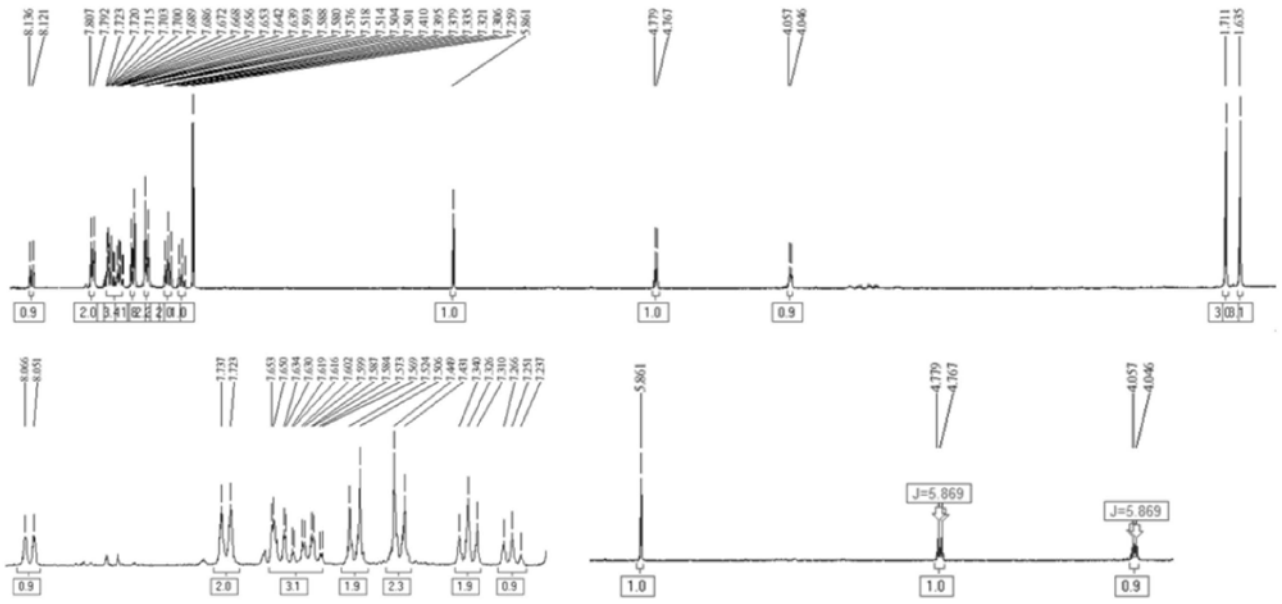

Figure S34. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **19d**.

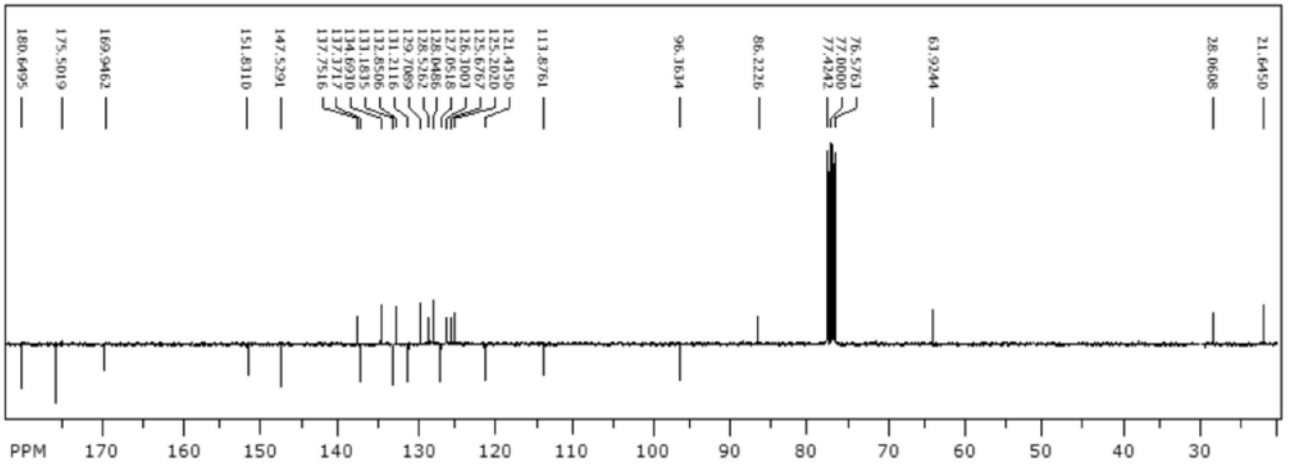

Figure S35. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **19d**.

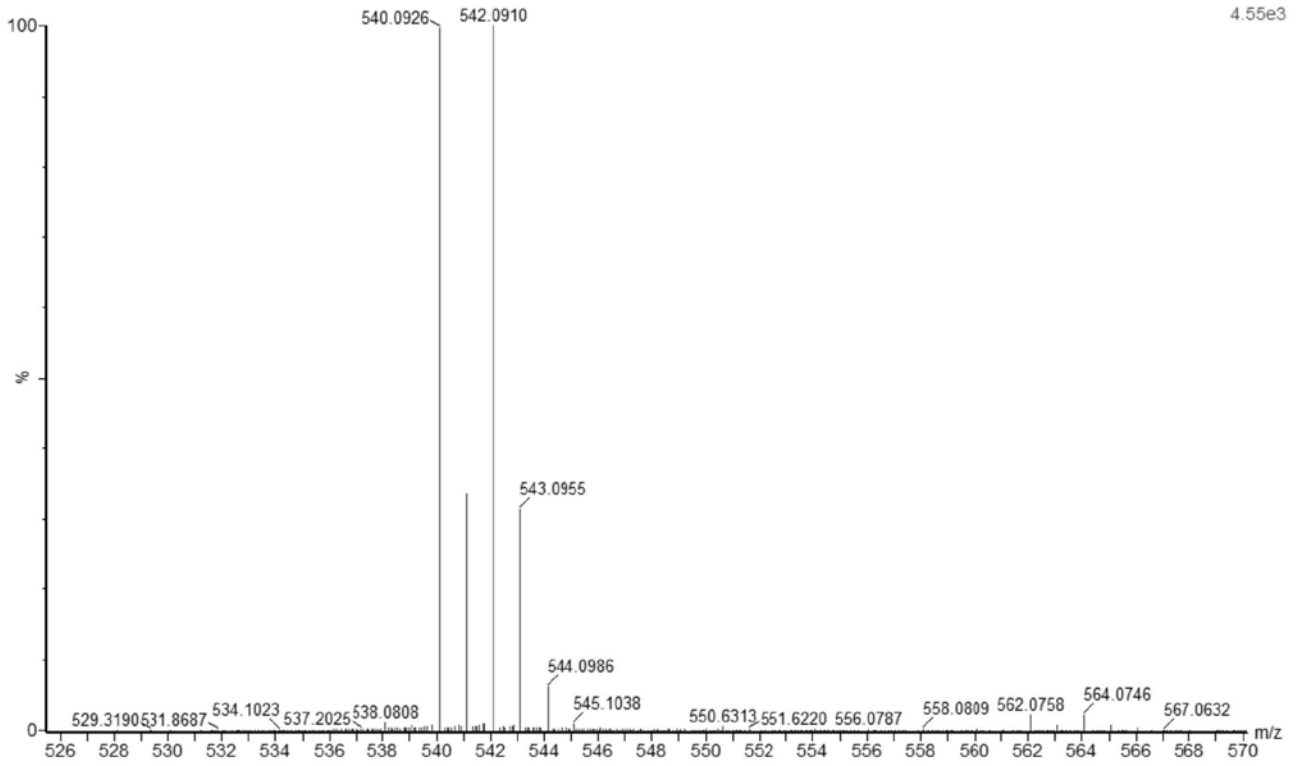

Figure S36. HRESIMS spectrum of **19d**.

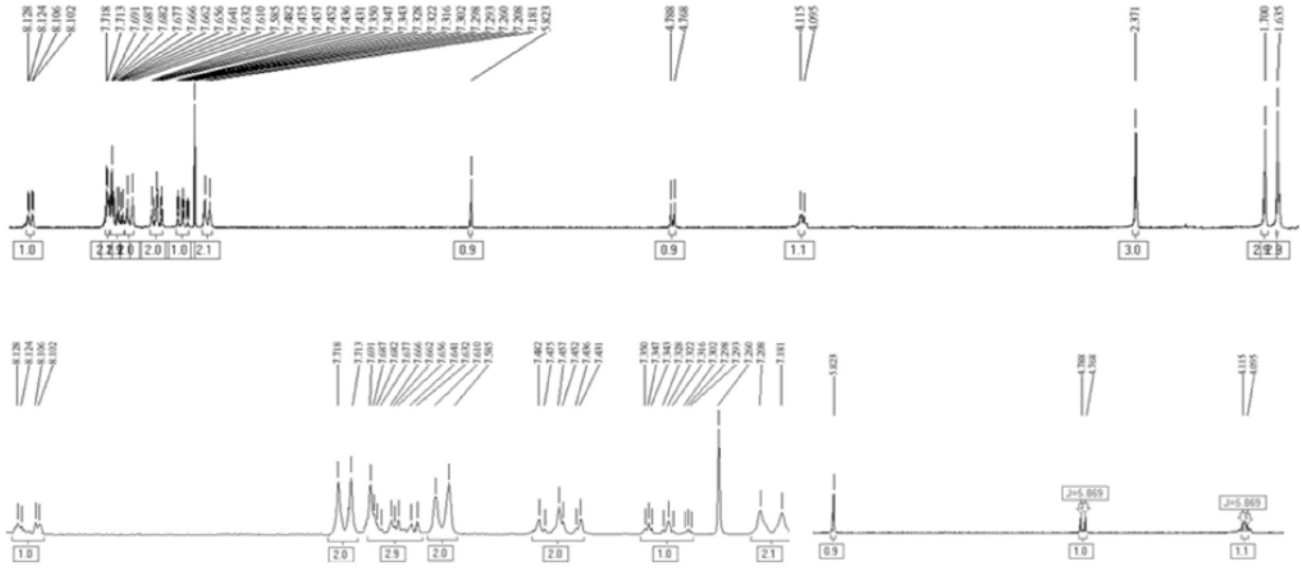

Figure S37. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **19e**.

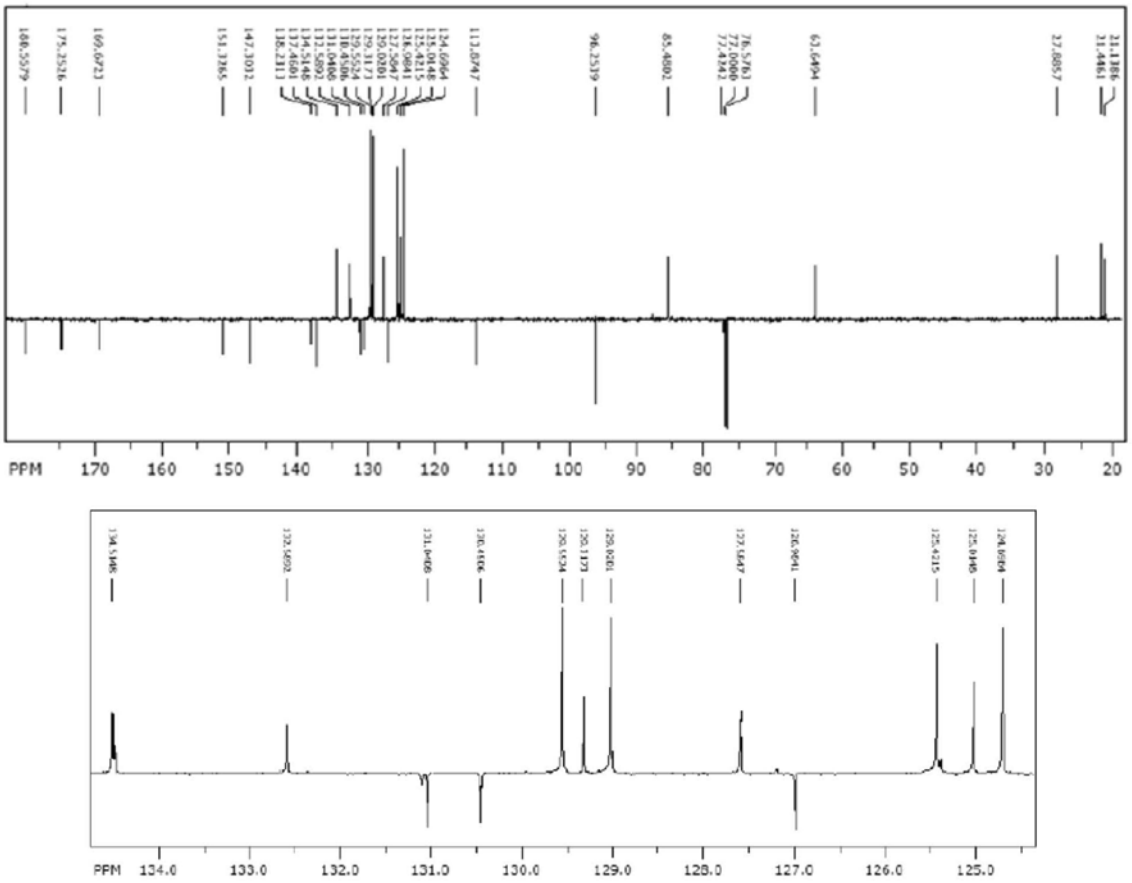

Figure S38. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **19e**.

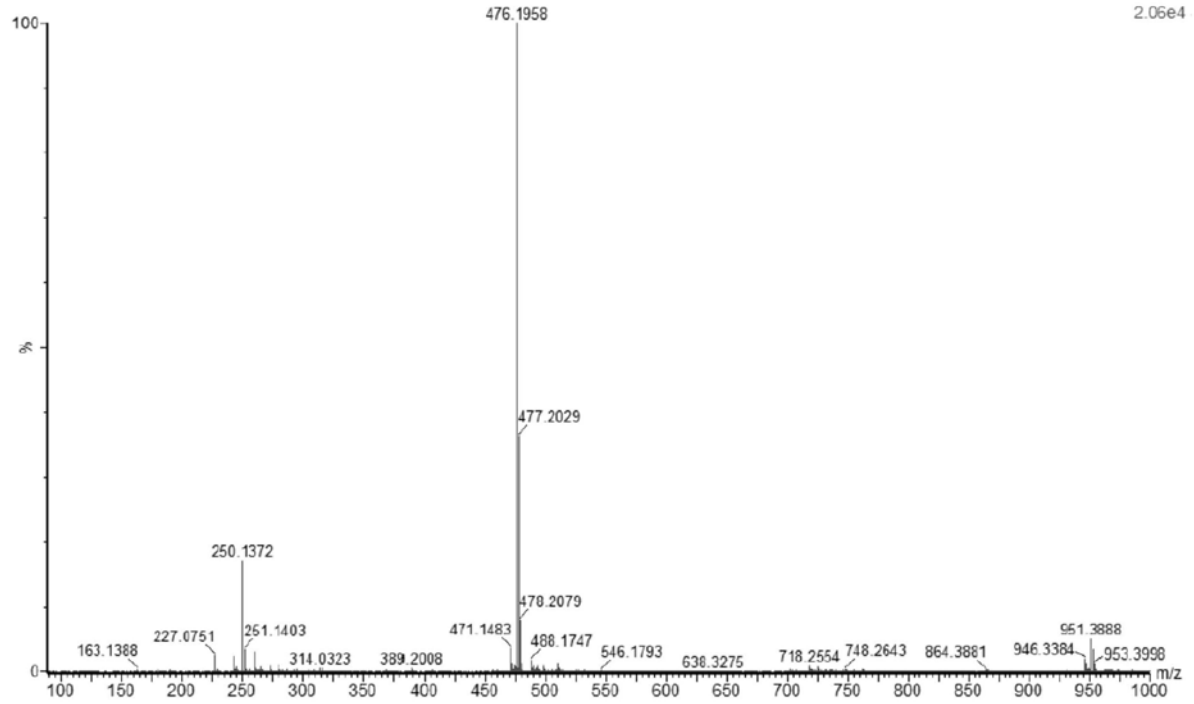

Figure S39. HRESIMS spectrum of **19e**.

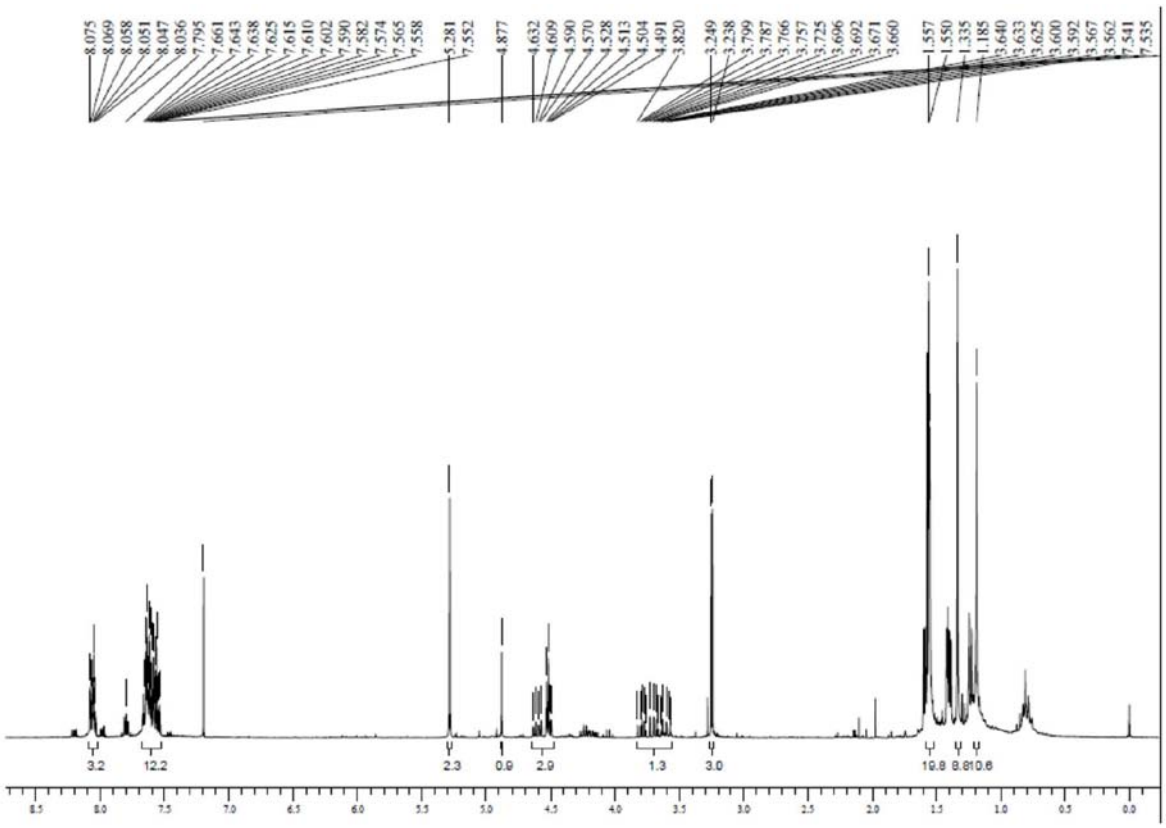

Figure S40. ^{1}H NMR ($CDCl_3$, 125 MHz) spectrum of **19f**.

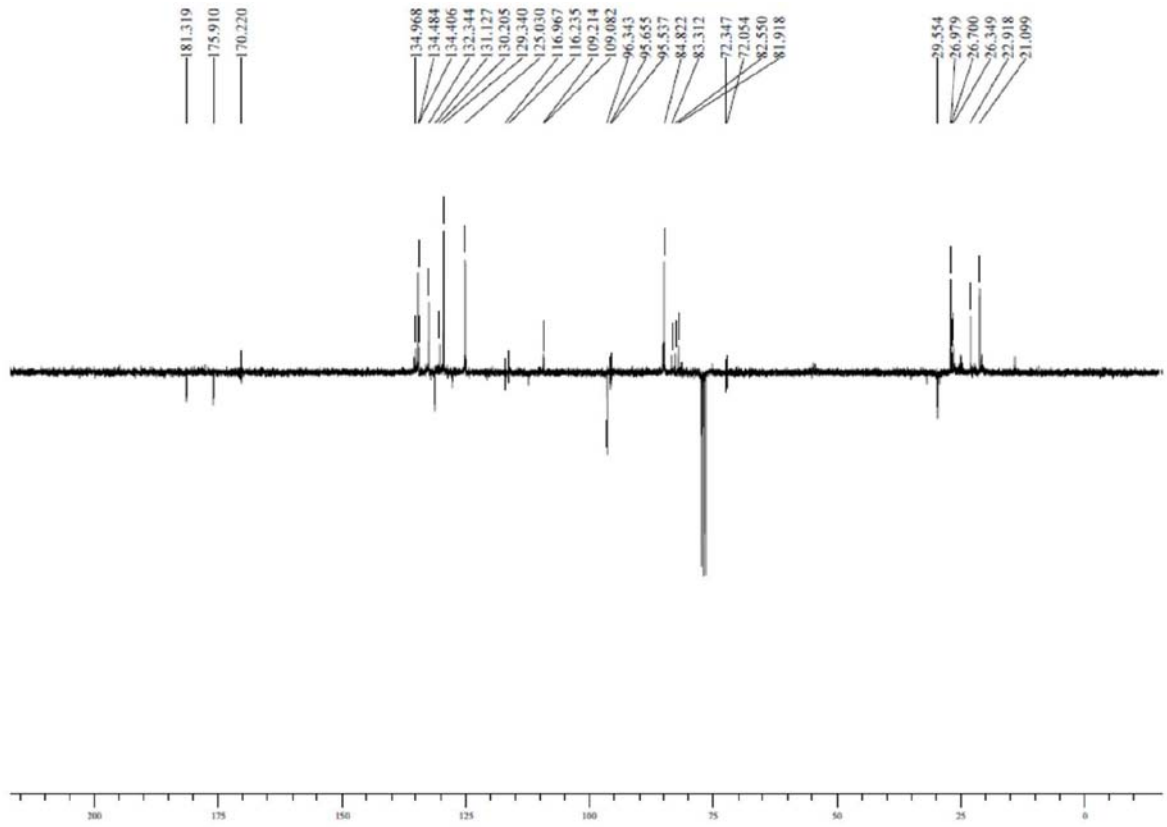

Figure S41. ^{13}C APT NMR ($CDCl_3$, 125 MHz) spectrum of **19f**.

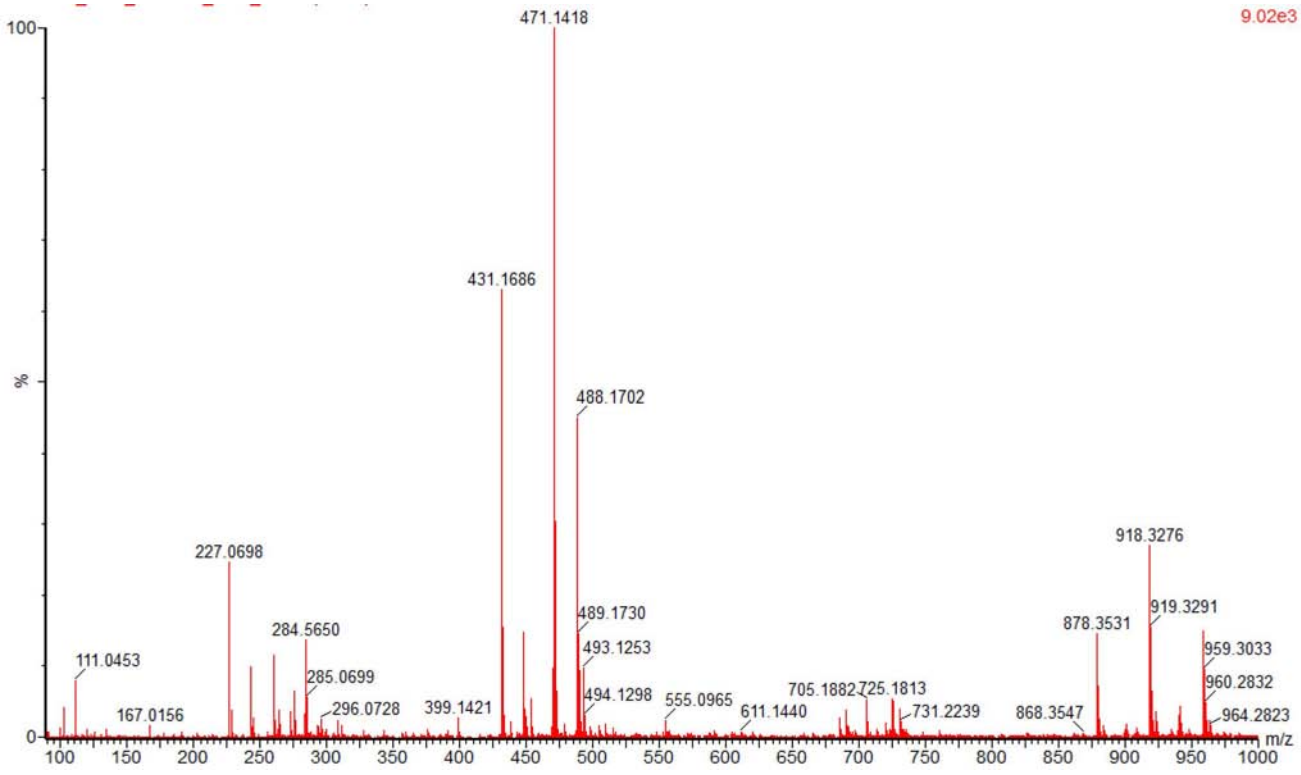

Figure S42. HRESIMS spectrum of **19f**.

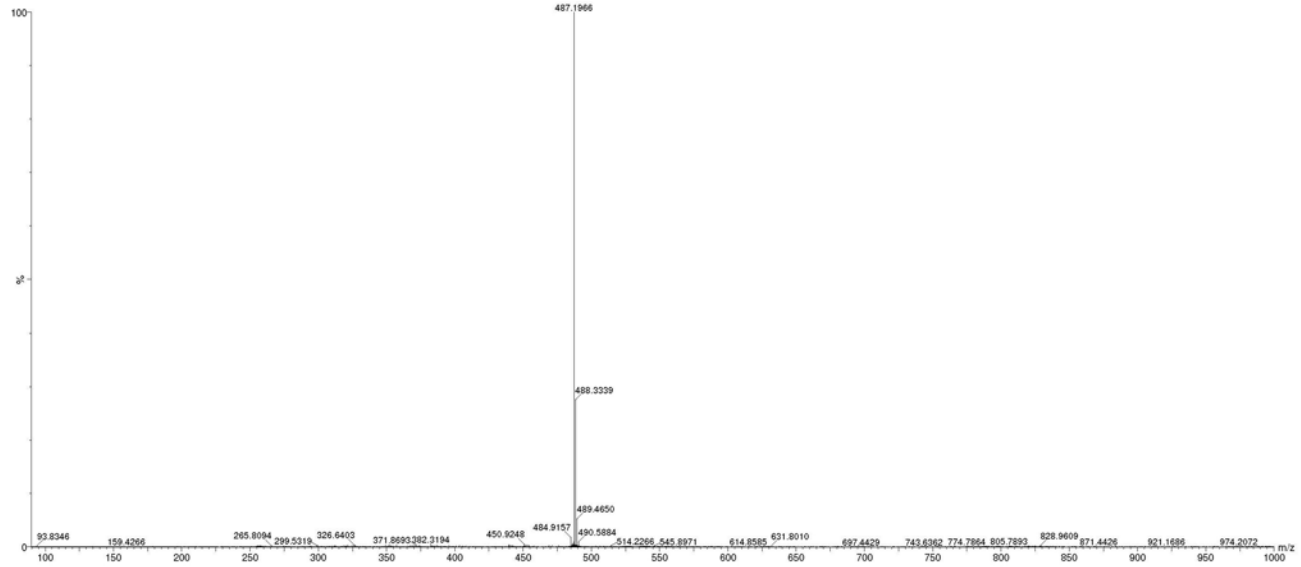

Figure S43. HRESIMS spectrum of **19g**.

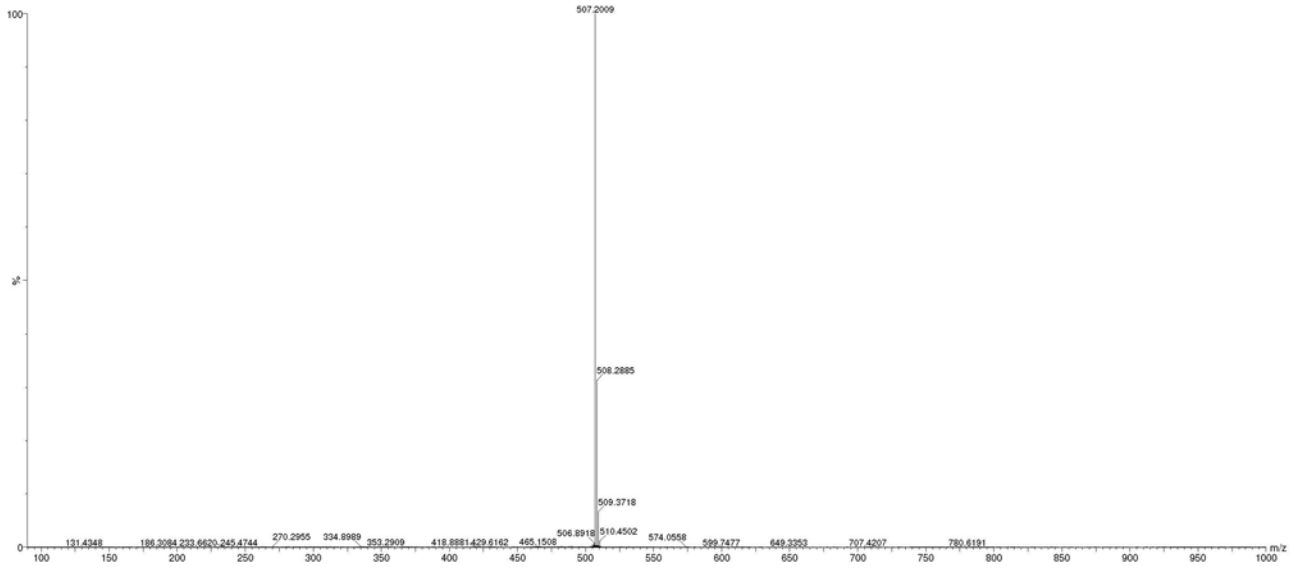

Figure S44. HRESIMS spectrum of **19h**.