SUPPLEMENTARY MATERIAL

A novel and efficient synthesis of 3,4-dihydroxyphenylacetic ester and amide derivatives/conjugates and assessment of their antioxidant activity

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Abstract: Phenolic acids, a sub-class of polyphenols, are widely studied. By contrary, 3,4-dihydroxyphenylacetic acid is scarcely studied. For this purpose, a series of 3,4-dihydroxyphenylacetic acid ester and amide derivatives/conjugates were synthesized for the first time. A systematic study has been performed to quantitatively identify the functional groups present in these compounds using different techniques such as ^{1}H NMR, ^{13}C NMR and ESI MS. The synthesized compounds were evaluated for their *in vitro* antioxidant activity by a DPPH radical-scavenging assay. Their physico-chemical profile is also studied using Molinspiration tool. Among all tested compounds, amidoester **36** showed the best scavenging activity possessing an EC_{50} 17 μM and improved physico-chemical properties compared to the parent compound.

Keywords: polyphenols, phenolic acids, antioxidant, 3,4-dihydroxyphenylacetic acid, molinspiration, conjugates, DPPH

Experimental section

1.General

Reagents were purchased at the highest commercial quality, and were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (silica gel 60F254) and components were visualized by UV light absorbance. Purification of compounds by column chromatography was carried out on silica gel (70-230 mesh) or reversed phase silica gel (Kieselgel 60, RP-18, 40-63 μm) and the indicated solvents. ^{1}H, and ^{13}C spectra were recorded on a 200 MHz Mercury spectrometer. ^{1}H and ^{13}C spectra are referenced according to the residual peak of the solvent based on literature data. ESI mass spectral analyses were performed on a mass spectrometer, using direct sample injection. Negative or positive ion ESI spectra were acquired by adjusting the needle and cone voltages accordingly.

General method for the synthesis of monoesters/diesters A

To a stirred solution of 3,4-dimethoxyphenylacetic acid (0.19 g, 1.00 mmol) and the corresponding alcohol (1.00 mmol)/diol (0.50 mmol) in CH_2Cl_2 (10 mL), 10% DMAP (0.01 g, 0.10 mmol) was added and the mixture was cooled to 0°C. Then EDC (0.19 g, 1.00 mmol) was added and the reaction mixture was stirred at 0°C for 30 min and at room temperature for 24 hours. Then CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the organic phase was successively washed with HCl 0.6 N (10 mL), H_2O (10 mL), $NaHCO_3$ 5% (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The residue was purified with column chromatography using CH_2Cl_2/MeOH: 9.5/0.5 as eluent.

General method for the synthesis of monoamides/diamide B

To a stirred solution of 3,4-dimehtoxyphenylacetic acid (0.19 g, 1.00 mmol) and the corresponding amine (1.00 mmol)/diamine (0.50 mmol) in CH_2Cl_2 (10 mL), HOBt (0.13 g, 1.00 mmol) was added and the mixture was cooled to 0°C. Then EDC (0.19 g, 1.00 mmol) was added and the reaction mixture was stirred at 0°C for 30 min and at room temperature for 2 hours. Then CH_2Cl_2 (20 mL) and H_2O (5 mL) were added and the organic phase was successively washed with H_2O (5 mL) and brine (10 mL), dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The residue was purified with column chromatography using CH_2Cl_2/MeOH: 9/1 as eluent.

General method for the synthesis of amidoalcohols C

To a stirred solution of 3,4-dimethoxyphenylacetic acid (0.19 g, 1.00 mmol) and the corresponding aminoalcohol(1.00 mmol) in CH_2Cl_2 (8 mL), HOBt (0.13 g, 1.00 mmol) was added and the mixture was cooled to 0°C. Then EDC (0.19 g, 1.00 mmol) was added and the reaction mixture was stirred at 0°C for 30 min and at room temperature for 2 hours. Then CH_2Cl_2 (20 mL) and H_2O (5 mL) were added and the organic phase was successively washed with H_2O (5 mL) and brine (10 mL), dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The residue was purified with column chromatography using CH_2Cl_2/MeOH: 9/1 as eluent.

General method for the synthesis of amidoesters D

To a stirred solution of the corresponding amidoalcohol (1.00 mmol in CH_2Cl_2 (10 mL), 3,4-dimethoxyphenylacetic acid (0.19 g, 1.00 mmol) and HOBt (0.13 g, 1.00 mmol) were added and the mixture was cooled to 0°C. Then EDC (0.19 g, 1.00 mmol) was added and the reaction mixture was stirred at 0°C for 30 min and at room temperature for 24 hours Then CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the organic phase was successively washed with HCl 0.6 N (10 mL), H_2O (10 mL), $NaHCO_3$ 5% (10 mL), H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The residue was purified with column chromatography using CH_2Cl_2/MeOH: 9.5/0.5 as eluent.

General method for the phenolic hydroxyl group deprotection E

The methoxy-containing compound (0.50 mmol) was dissolved in 5 mL of dry CH_2Cl_2 and cooled to 0 °C. A solution of $BF_3{\cdot}SMe_2$ (10 mmol/methoxy) was added to the mixture. The solution was allowed to slowly warm to room temperature and stirred for a total of 18 h. The reaction was stopped by the addition of 2 mL of water and 8 mL of methanol. The volatiles were removed *in vacuo*, the residue was taken up in AcOEt (20 mL) and washed with brine (5 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified with column chromatography using CH_2Cl_2/MeOH: 9/1 as eluent in the case of monoesters, diesters and amidoesters or with reversed phase column chromatography using CH_3CN/H_2O 0:10 to 9:1 in the case of monoamides and diamide.

cyclohexyl 2-(3,4-dimethoxyphenyl)acetate (2)

Following the general method **A** using cyclohexanol, monoester **2** was obtained in 78% yield as thick oil. R_f = (CH_2Cl_2/MeOH 9.5:0.5) = 0.79 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.81 (d, *J* = 4.3 Hz, 3H), 4.75 (s, 1H), 3.85 (dd, *J* = 2.7, 1.4 Hz, 6H), 3.52 (s, 2H), 1.71 (dd, *J* = 14.6, 8.6 Hz, 4H), 1.57 – 1.16 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.2, 148.6, 147.8, 126.7, 121.2,

112.1, 110.9, 72.9, 55.7, 55.7, 41.2, 31.4, 25.2, 23.5. MS (ESI) m/z calculated for $C_{16}H_{26}NO_4^+$ $[M+NH_4]^+$ 296.2, found 296.4.

hexadecyl 2-(3,4-dimethoxyphenyl)acetate (3)

Following the general method for the synthesis of monoesters **A** using 1-hexadecanol, compound **3** was obtained in 79% yield as white solid R_f = (CH_2Cl_2/MeOH 9.5:0.5) = 0.88 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.78 (d, *J* = 3.9 Hz, 3H), 4.04 (td, *J* = 6.6, 1.6 Hz, 2H), 3.82 (dd, *J* = 3.7, 1.9 Hz, 6H), 3.50 (d, *J* = 1.6 Hz, 2H), 1.55 (d, *J* = 6.3 Hz, 2H), 1.22 (s, 26H), 0.84 (dd, *J* = 6.6, 4.8 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.6, 148.6, 147.8, 126.4, 121.1, 112.1, 110.8, 64.7, 55.6, 55.5, 40.8, 31.7, 29.5, 29.5, 29.4, 29.3, 29.2, 29.0, 28.4, 25.7, 22.5, 13.9. MS (ESI) m/z calculated for $C_{26}H_{48}NO_4^+[M+NH_4]^+$ 438.4, found 438.3.

octyl 2-(3,4-dimethoxyphenyl)acetate (4)

Following the general method for the synthesis of monoesters **A** using *n*-octanol, compound **4** was obtained in 68% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 9.5:0.5) = 0.89 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.81 (s, 3H), 4.07 (td, *J* = 6.7, 2.1 Hz, 2H), 3.88 – 3.83 (m, 6H), 3.54 (d, *J* = 1.9 Hz, 2H), 1.68 – 1.53 (m, 2H), 1.25 (s, 10H), 0.86 (dd, *J* = 6.6, 4.6 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.9, 148.8, 148.0, 126.6, 121.3, 112.2, 111.0, 65.0, 55.8, 55.7, 40.9, 31.7, 29.1, 28.5, 25.8, 22.6, 14.1. MS (ESI) m/z calculated for $C_{18}H_{32}NO_4^+[M+NH_4]^+$ 326.2, found 326.1.

butyl 2-(3,4-dimethoxyphenyl)acetate (5)

Following the general method for the synthesis of monoesters **A** using *n*-butanol compound **5** was obtained in 91% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 9.5:0.5) = 0.84 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.78 (d, *J* = 2.1 Hz, 3H), 4.06 (td, *J* = 6.6, 2.1 Hz, 2H), 3.83 (dd, *J* = 3.1, 2.2 Hz, 6H), 3.52 (d, *J* = 2.0 Hz, 2H), 1.65 – 1.48 (m, 2H), 1.41 – 1.22 (m, 2H), 0.94 – 0.83 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8, 148.7, 147.9, 126.5, 121.2, 112.1, 110.9, 64.5, 55.7, 55.6, 40.8, 30.5, 18.9, 13.5. MS (ESI) m/z calculated for $C_{14}H_{24}NO_4^+[M+NH_4]^+$ 270.2, found 270.2.

cyclohexyl 2-(3,4-dihydroxyphenyl)acetate (6)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **6** was obtained in 52% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 9:1) = 0.52 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.79 – 6.59 (m, 3H), 6.25 (br s, 2H), 4.77 (dd, *J* = 8.4, 4.6 Hz, 1H), 3.48 (s, 2H), 1.77 (dd, *J* = 25.7, 7.1 Hz, 4H), 1.57 – 1.23 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.1, 143.8, 143.1, 126.2, 121.5, 116.2, 115.3, 73.9, 41.0, 31.4, 25.2, 23.6. MS (ESI) m/z calculated for $C_{14}H_{17}O_4^-$ $[M-H]^-$ 249.1, found 249.1.

hexadecyl 2-(3,4-dihydroxyphenyl)acetate (7)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **7** was obtained in 75% yield as white solid. R_f = (CH_2Cl_2/MeOH 9:1) = 0.67 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.76 – 6.68 (m, 2H), 6.67 – 6.59 (m, 1H), 6.28 (br s, 1H), 5.96 (br s, 1H), 4.10 (t, *J* = 6.7 Hz, 2H), 3.50 (s, 2H), 1.61 (d, *J* = 6.5 Hz, 2H), 1.26 (s, 26H), 0.87 (dd, *J* = 6.5, 5.0 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.6, 143.8, 143.1, 126.0, 121.6, 116.2, 115.3, 65.6, 40.7, 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 28.5, 25.8, 22.7, 14.1. MS (ESI) m/z calculated for $C_{24}H_{39}O_4^-$ $[M-H]^-$ 391.3, found 391.3.

octyl 2-(3,4-dihydroxyphenyl)acetate (8)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **8** was obtained in 77% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 9:1) = 0.72 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.76 – 6.56 (m, 3H), 6.50 (s, 1H), 6.21 (s, 1H), 4.16 – 4.03 (m, 2H), 3.50 (s, 2H), 1.61 (d, *J* = 6.7 Hz, 2H), 1.27 (s, 10H), 0.88 (t, *J* = 5.8 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.7, 143.8, 143.1, 125.9, 121.6, 116.2, 115.3, 65.6, 40.7, 31.7, 29.1, 28.4, 25.8, 22.6, 14.1. MS (ESI) m/z calculated for $C_{16}H_{23}O_4^-$ $[M-H]^-$ 279.2, found 279.3.

butyl 2-(3,4-dihydroxyphenyl)acetate (9)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **9** was obtained in 84% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 9:1) = 0.83 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.74 (t, *J* = 8.0 Hz, 3H), 6.66 – 6.46 (m, 2H), 4.21 – 3.98 (m, 2H), 3.48 (d, *J* = 4.0 Hz, 2H), 1.69 – 1.49 (m, 2H), 1.46 – 1.21 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.7, 143.8, 143.1, 125.9, 121.5, 116.3, 115.4, 65.3, 40.6, 30.4, 19.0, 13.6. MS (ESI) m/z calculated for $C_{12}H_{15}O_4^-$ $[M-H]^-$ 223.1, found 223.2.

***N*-(sec-butyl)-2-(3,4-dimethoxyphenyl)acetamide (10)**

Following the general method for the synthesis of monoamides **B** using *sec*-butylamine, compound **10** was obtained in 85% yield as white solid. R_f = (CH_2Cl_2/MeOH 9:1) = 0.72 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.84 – 6.68 (m, 3H), 5.26 (br s, 1H), 3.92 – 3.73 (m, 7H), 3.45 (s, 2H), 1.33 (dtd, *J* = 14.0, 7.3, 3.4 Hz, 2H), 0.98 (t, *J* = 6.1 Hz, 3H), 0.77 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.5, 149.0, 148.0, 127.5, 121.4, 112.2, 111.3, 55.8, 46.5, 43.4, 29.4, 20.2, 10.2. MS (ESI) m/z calculated for $C_{14}H_{22}NO_3^+$ $[M+H]^+$ 252.1, found 252.2.

***N*-cyclohexyl-2-(3,4-dimethoxyphenyl)acetamide (11)**

Following the general method for the synthesis of monoamides **B** using cyclohexylamine, compound **11** was obtained in 95% yield as white solid R_f = (CH_2Cl_2/MeOH 9:1) = 0.71 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.61 (dd, *J* = 11.3, 4.3 Hz, 3H), 6.02 (t, *J* = 9.4 Hz, 1H), 3.71 – 3.59 (m, 6H), 3.59 – 3.47 (m, 1H), 3.26 (d, *J* = 11.7 Hz, 2H), 1.64 (s, 2H), 1.42 (d, *J* = 10.3 Hz, 3H), 1.21 – 0.78 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.0, 148.5, 147.5, 127.5, 120.9,

111.8, 110.8, 55.3, 55.3, 47.7, 42.7, 32.4, 25.0, 24.4. MS (ESI) m/z calculated for $C_{16}H_{27}N_2O_3^+$[M+NH_4]$^+$ 295.2, found 295.2.

***N*-(sec-butyl)-2-(3,4-dihydroxyphenyl)acetamide (12)**

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **12** was obtained in 80% yield as white solid. R_f = (CH_2Cl_2/MeOH/AcOH 7:2:0.5) = 0.83 ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.78 (br s, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 6.72 – 6.54 (m, 2H), 6.47 (d, *J* = 7.7 Hz, 1H), 3.60 (d, *J* = 7.0 Hz, 1H), 3.17 (s, 2H), 1.34 (dd, *J* = 14.2, 7.3 Hz, 2H), 1.00 (dd, *J* = 6.6, 3.5 Hz, 3H), 0.78 (td, *J* = 7.3, 3.2 Hz, 3H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 169.9, 144.9, 143.7, 127.5, 119.6, 116.3, 115.3, 45.6, 42.0, 29.0, 20.4, 10.6. MS (ESI) m/z calculated for $C_{12}H_{16}NO_3^-$ [M-H]$^-$ 222.1, found 222.1.

***N*-cyclohexyl-2-(3,4-dihydroxyphenyl)acetamide (13)**

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **13** was obtained in 75% yield as white solid. R_f = (CH_2Cl_2/MeOH/AcOH 7:2:0.5) = 0.70 ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.79 (br s, 2H), 7.81 (d, *J* = 7.8 Hz, 1H), 6.67 – 6.55 (m, 2H), 6.47 (dd, *J* = 8.0, 1.8 Hz, 1H), 3.46 (s, 1H), 3.17 (s, 2H), 1.78 – 1.45 (m, 5H), 1.21 (dd, *J* = 35.4, 12.1 Hz, 5H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 169.8, 145.0, 143.8, 127.6, 119.7, 116.4, 115.4, 47.6, 42.0, 32.6, 25.4, 24.7. MS (ESI) m/z calculated for $C_{14}H_{20}NO_3^+$ [M+H]$^+$ 250.1, found 250.2.

butane-1,4-diyl bis(2-(3,4-dimethoxyphenyl)acetate) (14)

Following the general method **A** using 1,4-butanediol, diester **14** was obtained in 88% yield as white solid. R_f = (CH_2Cl_2/MeOH 9.5:0.5) = 0.63. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.78 (s, 6H), 4.06 (s, 4H), 3.83 (d, *J* = 2.7 Hz, 12H), 3.52 (s, 4H), 1.64 (s, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.6, 148.6, 147.9, 126.2, 121.2, 112.1, 110.9, 64.0, 55.6, 55.6, 40.7, 25.0. MS (ESI) m/z calculated for $C_{24}H_{34}NO_8^+$ [M+NH_4]$^+$ 464.2, found 464.2.

propane-1,3-diyl bis(2-(3,4-dimethoxyphenyl)acetate) (15)

Following the general method **A** using 1,3-propanediol, diester **15** was obtained as thick oil in 87% yield. R_f = (CH_2Cl_2/MeOH 9.5:0.5) = 0.76 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.78 (s, 6H), 4.12 (t, *J* = 6.3 Hz, 4H), 3.83 (dd, *J* = 2.6, 0.9 Hz, 12H), 3.52 (s, 4H), 2.00 – 1.86 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.5, 148.7, 147.9, 126.1, 121.2, 112.1, 110.9, 61.1, 55.7, 55.6, 40.6, 27.7. MS (ESI) m/z calculated for $C_{23}H_{32}NO_8^+$ [M+NH_4]$^+$ 450.2, found 450.3.

oxybis(ethane-2,1-diyl) bis(2-(3,4-dimethoxyphenyl)acetate) (16)

Following the general method **A** using diethyleneglycol, diester **16** was obtained as thick oil in 97% yield. R_f = (CH_2Cl_2/MeOH 9.5:0.5) = 0.83 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.75 (d, *J* = 3.0 Hz, 6H), 4.16 (dd, *J* = 5.2, 4.1 Hz, 4H), 3.79 (dd, *J* = 4.9, 1.1 Hz, 12H), 3.58 (dd, *J* = 5.3, 4.1

Hz, 4H), 3.52 (s, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.4, 148.5, 147.7, 125.9, 121.1, 112.0, 110.8, 68.6, 63.5, 55.5, 55.5, 40.3. MS (ESI) m/z calculated for $C_{24}H_{34}NO_9^+$ $[M+NH_4]^+$ 480.2, found 480.2.

decane-1,10-diyl bis(2-(3,4-dimethoxyphenyl)acetate) (17)

Following the general method **A** using 1,10-decanediol, diester **17** was obtained in as white solid in 92% yield. R_f = (CH_2Cl_2/MeOH 9.5:0.5) = 0.89 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.73 (d, *J* = 4.4 Hz, 6H), 3.99 (t, *J* = 6.6 Hz, 4H), 3.81 – 3.71 (m, 12H), 3.46 (s, 4H), 1.51 (d, *J* = 5.9 Hz, 4H), 1.18 (s, 12H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.4, 148.4, 147.6, 126.2, 120.9, 111.9, 110.6, 64.4, 55.3, 55.3, 40.5, 28.9, 28.7, 28.1, 25.4. MS (ESI) m/z calculated for $C_{30}H_{46}NO_8^+$ $[M+NH_4]^+$ 548.3, found 548.3.

cyclohexane-1,4-diyl bis(2-(3,4-dimethoxyphenyl)acetate) (18)

Following the general method **A** using 1,4-cyclohexanediol, diester **18** was obtained as white solid in 84% yield. R_f = (CH_2Cl_2/MeOH 9.5:0.5) = 0.86 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 3.8, 2.8 Hz, 6H), 4.80 (s, 2H), 3.84 (t, *J* = 2.8 Hz, 12H), 3.51 (d, *J* = 5.2 Hz, 4H), 1.65 (ddd, *J* = 28.7, 21.5, 5.3 Hz, 8H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.8, 148.4, 147.6, 126.1, 120.9, 111.8, 110.6, 70.6, 55.4, 55.4, 40.8, 27.1, 26.8. MS (ESI) m/z calculated for $C_{26}H_{36}NO_8^+$ $[M+NH_4]^+$ 490.2, found 490.2.

butane-1,4-diyl bis(2-(3,4-dihydroxyphenyl)acetate) (19)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **19** was obtained in 46% yield as white solid. R_f = (CH_2Cl_2/MeOH 8:2) = 0.64 ^{1}H NMR (200 MHz, Acetone-d_6) δ 7.93 – 7.78 (m, 4H), 6.84 – 6.71 (m, 4H), 6.61 (dd, *J* = 8.1, 2.1 Hz, 2H), 4.09 – 4.00 (m, 4H), 3.46 (s, 4H), 1.74 – 1.53 (m, 4H). ^{13}C NMR (50 MHz, Acetone-d_6) δ 172.2, 145.7, 144.8, 126.9, 121.5, 117.1, 115.9, 64.5, 40.9, 25.9. MS (ESI) m/z calculated for $C_{20}H_{21}O_8^-$ $[M-H]^-$ 389.1, found 389.2.

propane-1,3-diyl bis(2-(3,4-dihydroxyphenyl)acetate) (20)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **20** was obtained in 42% yield as white solid. R_f = (CH_2Cl_2/MeOH 8:2) = 0.59 ^{1}H NMR (200 MHz, Acetone-d_6) δ 7.90 (d, *J* = 7.9 Hz, 4H), 6.77 (dd, *J* = 8.1, 5.1 Hz, 4H), 6.60 (dd, *J* = 8.0, 2.1 Hz, 2H), 4.10 (t, *J* = 6.4 Hz, 4H), 3.46 (s, 4H), 1.97 – 1.86 (m, 4H). ^{13}C NMR (50 MHz, Acetone-d_6) δ 172.5, 145.8, 144.9, 126.8, 121.4, 117.2, 116.0, 61.8, 40.9, 28.8. MS (ESI) m/z calculated for $C_{19}H_{19}O_8^-$ $[M-H]^-$ 375.1, found 375.1.

oxybis(ethane-2,1-diyl) bis(2-(3,4-dihydroxyphenyl)acetate) (21)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **21** was obtained in 33% yield as sticky solid. R_f = (CH_2Cl_2/MeOH 8:2) = 0.67 ^{1}H NMR (200

MHz, Acetone-d_6) δ 8.08 – 7.76 (m, 4H), 6.88 – 6.68 (m, 4H), 6.61 (dd, *J* = 8.0, 2.0 Hz, 2H), 4.17 (dd, *J* = 9.6, 5.0 Hz, 4H), 3.63 (dd, *J* = 5.6, 4.0 Hz, 4H), 3.48 (s, 4H). ^{13}C NMR (50 MHz, Acetone-d_6) δ 172.2, 145.7, 144.8, 126.8, 121.5, 117.2, 115.9, 69.5, 64.4, 40.8. MS (ESI) m/z calculated for $C_{20}H_{21}O_9^-$ $[M-H]^-$ 405.1, found 405.1.

decane-1,10-diyl bis(2-(3,4-dihydroxyphenyl)acetate) (22)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **22** was obtained in 69% yield as white solid. R_f = (CH_2Cl_2/MeOH 8:2) = 0.64 ^{1}H NMR (200 MHz, Acetone-d_6) δ 7.81 (s, 4H), 6.75 (dd, *J* = 8.1, 5.0 Hz, 4H), 6.58 (dd, *J* = 8.0, 1.6 Hz, 2H), 4.00 (t, *J* = 6.5 Hz, 4H), 3.42 (s, 4H), 1.53 (d, *J* = 6.4 Hz, 4H), 1.23 (s, 12H). ^{13}C NMR (50 MHz, Acetone-d_6) δ 172.2, 145.7, 144.7, 127.0, 121.4, 117.1, 115.9, 65.0, 41.0, 30.2, 29.3, 26.5. MS (ESI) m/z calculated for $C_{26}H_{33}O_8^-$ $[M-H]^-$ 473.2, found 473.4.

cyclohexane-1,4-diyl bis(2-(3,4-dihydroxyphenyl)acetate) (23)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **23** was obtained in 26% yield as sticky solid. R_f = (CH_2Cl_2/MeOH 8:2) = 0.61 ^{1}H NMR (200 MHz, Acetone-d_6) δ 7.91 (dd, *J* = 19.0, 13.1 Hz, 4H), 6.83 – 6.70 (m, 4H), 6.66 – 6.54 (m, 2H), 4.75 (s, 2H), 3.45 (d, *J* = 4.8 Hz, 4H), 1.87 (d, *J* = 7.5 Hz, 2H), 1.68 (s, 2H), 1.51 (d, *J* = 5.4 Hz, 4H). ^{13}C NMR (50 MHz, Acetone-d_6) δ 171.6, 145.8, 144.9, 127.0, 121.4, 117.0, 115.9, 71.3, 41.3, 28.0. MS (ESI) m/z calculated for $C_{22}H_{23}O_8^-$ $[M-H]^-$ 415.1, found 415.2.

***N,N'*-(ethane-1,2-diyl)bis(2-(3,4-dimethoxyphenyl)acetamide) (24)**

Following the general method for the synthesis of diamide **B** using ethylenediamine, compound **24** was obtained in 80% yield as white solid. R_f = (CH_2Cl_2/MeOH 9:1) = 0.69. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.84 – 6.68 (m, 6H), 6.13 (br s, 2H), 3.84 (d, *J* = 1.3 Hz, 12H), 3.41 (s, 4H), 3.26 (s, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.5, 149.3, 148.4, 127.2, 121.6, 112.5, 111.5, 56.0, 43.3, 39.9. MS (ESI) m/z calculated for $C_{22}H_{27}N_2O_6^-$ $[M-H]^-$ 415.2, found 415.3.

***N,N'*-(ethane-1,2-diyl)bis(2-(3,4-dihydroxyphenyl)acetamide) (25)**

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **25** was obtained in 21% yield as colorless sticky solid. R_f = (CH_2Cl_2/MeOH/AcOH 9:1:0.5) = 0.14 ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.84 (d, *J* = 1.8 Hz, 2H), 8.74 (d, *J* = 1.8 Hz, 2H), 7.95 (br s, 2H), 6.62 (dd, *J* = 8.1, 1.8 Hz, 4H), 6.46 (dd, *J* = 8.0, 1.9 Hz, 2H), 3.17 (s, 4H), 3.05 (d, *J* = 2.3 Hz, 4H). ^{13}C NMR (50 MHz, DMSO-d_6) δ 171.1, 145.0, 143.9, 127.1, 119.9, 116.5, 115.4, 42.0, 38.6. MS (ESI) m/z calculated for $C_{18}H_{19}N_2O_6^-$ $[M-H]^-$ 359.1, found 359.2.

2-(3,4-dimethoxyphenyl)-*N*-(2-(2-hydroxyethoxy)ethyl)acetamide (26)

Following the general method for the synthesis of amidoalcohols **C** using 2-(2-aminoethoxy)ethanol, compound **26** was obtained in 89% yield as colorless oil. R_f = (CH_2Cl_2/MeOH 9:1) = 0.5 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.74 (d, *J* = 0.9 Hz, 3H), 6.52 (br s, 1H), 3.79 (s, 6H), 3.64 – 3.55 (m, 2H), 3.44 (d, *J* = 7.6 Hz,5H), 3.34 (d, *J* = 5.8 Hz, 3H), 3.07 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8, 148.8, 147.9, 127.2, 121.2, 112.2, 111.1, 72.0, 69.5, 61.3, 55.7, 42.8, 39.2. MS (ESI) m/z calculated for $C_{14}H_{22}NO_5^+$[M+H]$^+$ 284.1, found 284.1.

2-(3,4-dimethoxyphenyl)-*N*-(3-hydroxypropyl)acetamide (27)

Following the general method for the synthesis of amidoalcohols **C** using 3-amino-1-propanol, compound **27** was obtained in 76% yield as white solid. R_f = (CH_2Cl_2/MeOH 9:1) = 0.56 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.80 – 6.66 (m, 3H), 6.32 (br s, 1H), 3.79 (s, 6H), 3.53 – 3.39 (m, 5H), 3.28 (dd, *J* = 12.4, 6.2 Hz, 2H), 1.55 (dt, *J* = 11.5, 5.8 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6, 148.8, 147.9, 127.0, 121.3, 112.1, 111.2, 58.9, 55.6, 42.8, 36.2, 31.8. MS (ESI) m/z calculated for $C_{13}H_{18}NO_4^-$ [M-H]$^-$ 252.1, found 252.2.

2-(3,4-dimethoxyphenyl)-*N*-(5-hydroxypentyl)acetamide (28)

Following the general method for the synthesis of amidoalcohols **C** using 5-amino-1-pentanol, compound **28** was obtained in 69% yield as colorless oil. R_f = (CH_2Cl_2/MeOH 9:1) = 0.49 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.82 – 6.66 (m, 3H), 5.89 (br s, 1H), 3.80 (s, 6H), 3.52 (t, *J* = 6.3 Hz, 2H), 3.43 (s, 2H), 3.14 (dd, *J* = 12.8, 6.5 Hz, 3H), 1.35 (ddt, *J* = 19.1, 15.7, 8.0 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.6, 148.9, 147.9, 127.2, 121.4, 112.2, 111.2, 62.0, 55.7, 43.0, 39.3, 31.8, 28.9, 22.8. MS (ESI) m/z calculated for $C_{15}H_{24}NO_4^+$[M+H]$^+$ 282.2, found 282.2.

2-(3,4-dimethoxyphenyl)-*N*-(4-hydroxybutyl)acetamide (29)

Following the general method for the synthesis of amidoalcohols **C** using 4-amino-1-butanol, compound **29** was obtained in 98% yield as white solid. R_f = (CH_2Cl_2/MeOH 9:1) = 0.56 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.79 – 6.65 (m, 3H), 6.15 (br s, 1H), 3.79 (s, 6H), 3.51 (t, *J* = 5.9 Hz, 2H), 3.41 (s, 2H), 3.14 (d, *J* = 6.0 Hz, 3H), 1.43 (dd, *J* = 6.3, 3.0 Hz, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.7, 148.8, 147.9, 127.2, 121.3, 112.2, 111.2, 61.6, 55.7, 42.9, 39.2, 29.4, 25.7. MS (ESI) m/z calculated for $C_{14}H_{20}NO_4^-$M-H]$^-$ 266.1, found 266.2.

2-(2-(2-(3,4-dimethoxyphenyl)acetamido)ethoxy)ethyl 2-(3,4-dimethoxyphenyl)acetate (30)

Following the general method for the synthesis of amidoesters **D,** compound **30** was obtained in 84% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 9:1) = 0.69 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.80 – 6.67 (m, 6H), 5.93 (br s, 1H), 4.18 – 4.10 (m, 2H), 3.80 (d, *J* = 3.1 Hz, 12H), 3.58 – 3.48 (m, 4H), 3.42 (d, *J* = 4.6 Hz, 4H), 3.39 – 3.27 (m, 2H). ^{13}C NMR (50 MHz,

$CDCl_3$) δ 171.6, 171.2, 148.9, 148.6, 147.9, 127.1, 126.0, 121.2, 121.2, 112.1, 111.1, 110.9, 69.4, 68.6, 63.5, 55.6, 43.0, 40.4, 39.1. MS (ESI) m/z calculated for $C_{24}H_{32}NO_8^+[M+H]^+$ 462.2, found 462.2.

3-(2-(3,4-dimethoxyphenyl)acetamido)propyl 2-(3,4-dimethoxyphenyl)acetate (31)

Following the general method for the synthesis of amidoesters **D,** compound **31** was obtained in 81% yield as white solid. R_f = (CH_2Cl_2/MeOH 9:1) = 0.63 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.72 (d, *J* = 7.3 Hz, 6H), 5.83 (br s, 1H), 4.02 (t, *J* = 6.1 Hz, 2H), 3.80 (d, *J* = 2.3 Hz, 12H), 3.44 (d, *J* = 6.3 Hz, 4H), 3.19 (q, *J* = 6.4 Hz, 2H), 1.72 (p, *J* = 6.4 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8, 171.3, 148.9, 148.5, 147.9, 147.8, 127.0, 126.0, 121.2, 121.1, 112.0, 111.1, 110.8, 61.9, 55.6, 43.0, 40.5, 36.1, 28.3. MS (ESI) m/z calculated for $C_{23}H_{28}NO_7^-[M-H]^-$ 430.2, found 430.3

5-(2-(3,4-dimethoxyphenyl)acetamido)pentyl 2-(3,4-dimethoxyphenyl)acetate (32)

Following the general method for the synthesis of amidoesters **D,** compound **32** was obtained in 83% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 9:1) = 0.69 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.82 – 6.67 (m, 6H), 5.56 (br s, 1H), 4.00 (t, *J* = 6.6 Hz, 2H), 3.82 (d, *J* = 2.9 Hz, 12H), 3.47 (d, *J* = 8.9 Hz, 4H), 3.13 (dd, *J* = 13.0, 6.7 Hz, 2H), 1.56 (dt, *J* = 13.9, 6.8 Hz, 2H), 1.37 (dd, *J* = 14.0, 7.3 Hz, 2H), 1.29 – 1.16 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8, 171.2, 148.9, 148. 6, 148.0, 147.8, 127.1, 126.3, 121.4, 121.2, 112.1, 112.1, 111.2, 110.8, 64.4, 55.7, 43.2, 40.7, 39.2, 28.9, 28.0, 22.9. MS (ESI) m/z calculated for $C_{25}H_{34}NO_7^+[M+H]^+$ 460.2, found 460.3.

4-(2-(3,4-dimethoxyphenyl)acetamido)butyl 2-(3,4-dimethoxyphenyl)acetate (33)

Following the general method for the synthesis of amidoesters **D,** compound **33** was obtained in 79% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 9:1) = 0.67 ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.74 (d, *J* = 4.5 Hz, 6H), 5.61 (br s, 1H), 4.01 (t, *J* = 6.1 Hz, 2H), 3.82 (s, 12H), 3.47 (d, *J* = 7.1 Hz, 4H), 3.24 – 3.09 (m, 2H), 1.60 – 1.35 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.7, 171.2, 148.9, 148.5, 148.0, 147.8, 127.1, 126.2, 121.3, 121.1, 112.0, 111.1, 110.8, 64.1, 55.6, 43.1, 40.6, 38.9, 25.9, 25.7 MS (ESI) m/z calculated for $C_{24}H_{32}NO_7^+[M+H]^+$ 446.2, found 446.2.

2-(2-(2-(3,4-dihydroxyphenyl)acetamido)ethoxy)ethyl 2-(3,4-dihydroxyphenyl)acetate (34)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **34** was obtained in 71% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 8:2) = 0.66 ^{1}H NMR (200 MHz, Acetone-d_6) δ 8.09 (br s, 4H), 7.35 (br s, 1H), 6.88 – 6.68 (m, 4H), 6.68 – 6.53 (m, 2H), 4.21 – 4.04 (m, 2H), 3.61 – 3.29 (m, 10H). ^{13}C NMR (50 MHz, Acetone-d_6) δ 172.9,

172.3, 145. 8, 145.0, 144.8, 128.0, 126.6, 121.4, 121.3, 117.0, 117.0, 116.0, 115.8, 70.1, 69.3, 64.4, 43.1, 40. 9, 40.0. MS (ESI) m/z calculated for $C_{20}H_{22}NO_8^-$[M-H]$^-$ 404.1, found 404.2.

3-(2-(3,4-dihydroxyphenyl)acetamido)propyl 2-(3,4-dihydroxyphenyl)acetate (35)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **35** was obtained in 73% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 8:2) = 0.60 ^{1}H NMR (200 MHz, Acetone-d_6) δ 8.04 (br s, 4H), 7.37 (s, 1H), 6.83 (dd, *J* = 7.4, 2.0 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.59 (ddd, *J* = 8.2, 6.3, 2.1 Hz, 2H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.44 (s, 2H), 3.37 (s, 2H), 3.30 – 3.22 (m, 2H), 1.85 – 1.68 (m, 2H). ^{13}C NMR (50 MHz, Acetone-d_6) δ 172.3, 171.7, 145.8, 145.7, 145.0, 144.8, 128.0, 126.7, 121.4, 121.3, 117.0, 116.9, 116.0, 115.3, 62.0, 42.6, 40.4, 36.4, 28.8. MS (ESI) m/z calculated for $C_{19}H_{20}NO_7^-$[M-H]$^-$ 374.1, found 374.2.

5-(2-(3,4-dihydroxyphenyl)acetamido)pentyl 2-(3,4-dihydroxyphenyl)acetate (36)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **36** was obtained in 50% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 8:2) = 0.65 ^{1}H NMR (200 MHz, Acetone-d_6) δ 8.47 (s, 1H), 8.04 (s, 1H), 7.95 (s, 1H), 7.84 (s, 1H), 7.31 (br s, 1H), 6.77 (ddd, J = 13.3, 7.7, 1.5 Hz, 4H), 6.69 – 6.53 (m, 2H), 4.00 (t, J = 6.3 Hz, 2H), 3.43 (s, 2H), 3.36 (s, 2H), 3.17 (dd, J = 12.7, 6.6 Hz, 2H), 1.64 – 1.23 (m, 6H). ^{13}C NMR (50 MHz, Acetone-d_6) δ 172.7, 172.2, 145.8, 145.0, 144.8, 128.2, 126.9, 121.3, 121.3, 117.0, 116.9, 116.0, 115.8, 64.8, 43.2, 41.1, 39.9, 29.9, 28.9, 23.9. MS (ESI) m/z calculated for $C_{21}H_{24}NO_7^-$ [M-H]$^-$ 402.1, found 402.1.

4-(2-(3,4-dihydroxyphenyl)acetamido)butyl 2-(3,4-dihydroxyphenyl)acetate (37)

Following the general method for the phenolic hydroxyl group deprotection **E,** compound **37** was obtained in 53% yield as colorless thick oil. R_f = (CH_2Cl_2/MeOH 8:2) = 0.58 ^{1}H NMR (200 MHz, Acetone-d_6) δ 8.05 (br s, 4H), 7.36 (s, 1H), 6.85 – 6.66 (m, 4H), 6.60 (td, J = 8.0, 2.0 Hz, 2H), 4.02 (t, J = 5.8 Hz, 2H), 3.43 (s, 2H), 3.36 (s, 2H), 3.19 (q, J = 6.3 Hz, 2H), 1.56 (s, 4H). ^{13}C NMR (50 MHz, Acetone-d_6) δ 172.8, 172.2, 145.8, 145.0, 144.8, 128.1, 126.8, 121.4, 121.3, 117.0, 116.9, 116.0, 115.8, 64.6, 43.2, 41.1, 39.7, 26.6. MS (ESI) m/z calculated for $C_{20}H_{22}NO_7^-$[M-H]$^-$ 388.1, found 388.2.

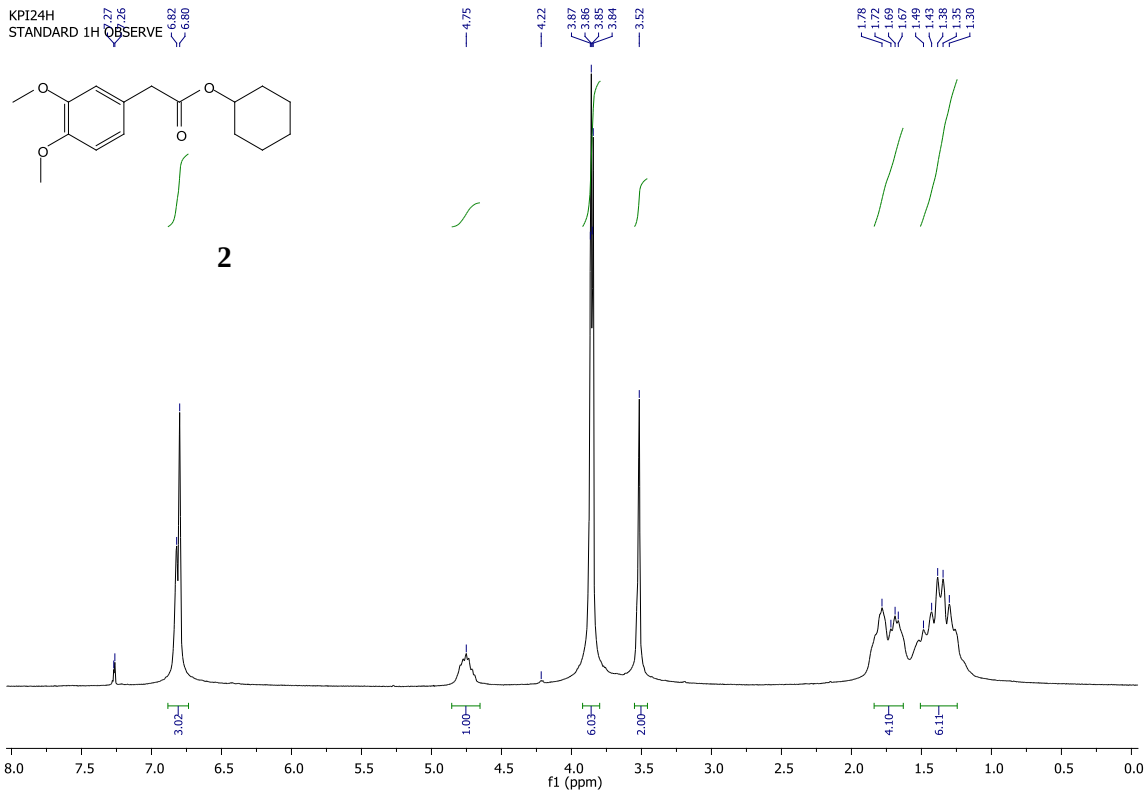


Figure S1: ^{1}H NMR of **2**.

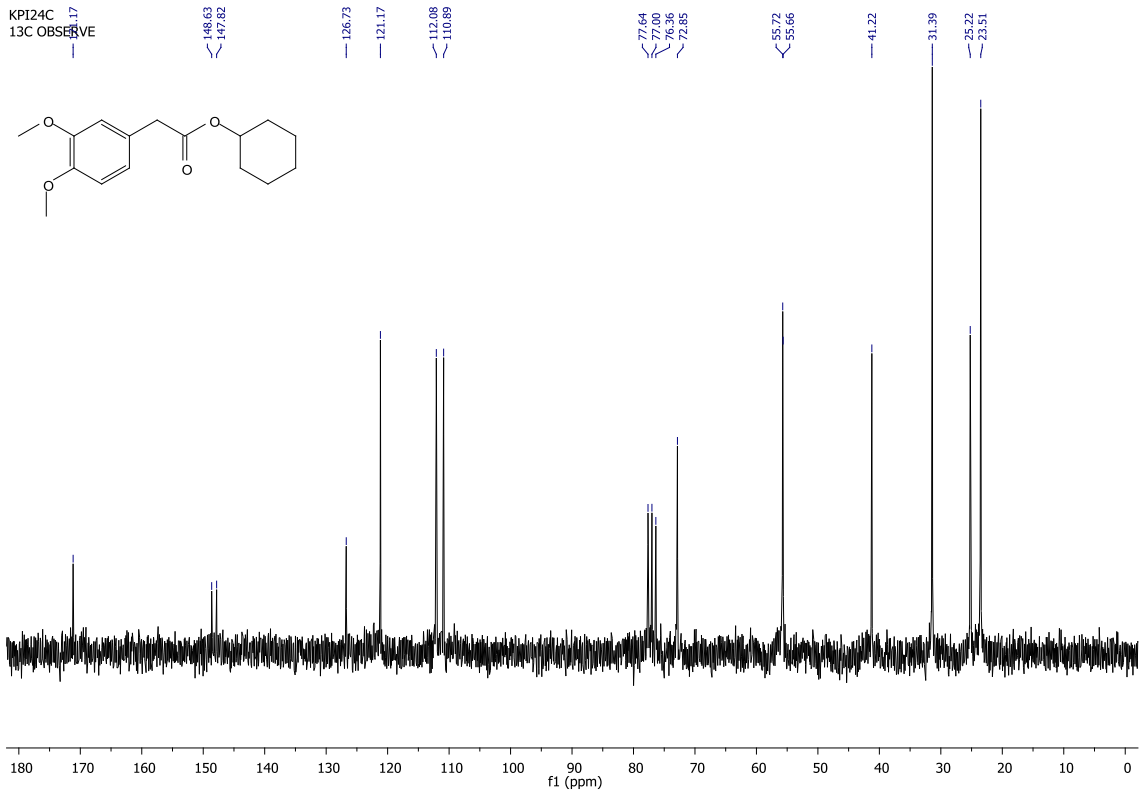


Figure S2: ^{13}C NMR of **2**.

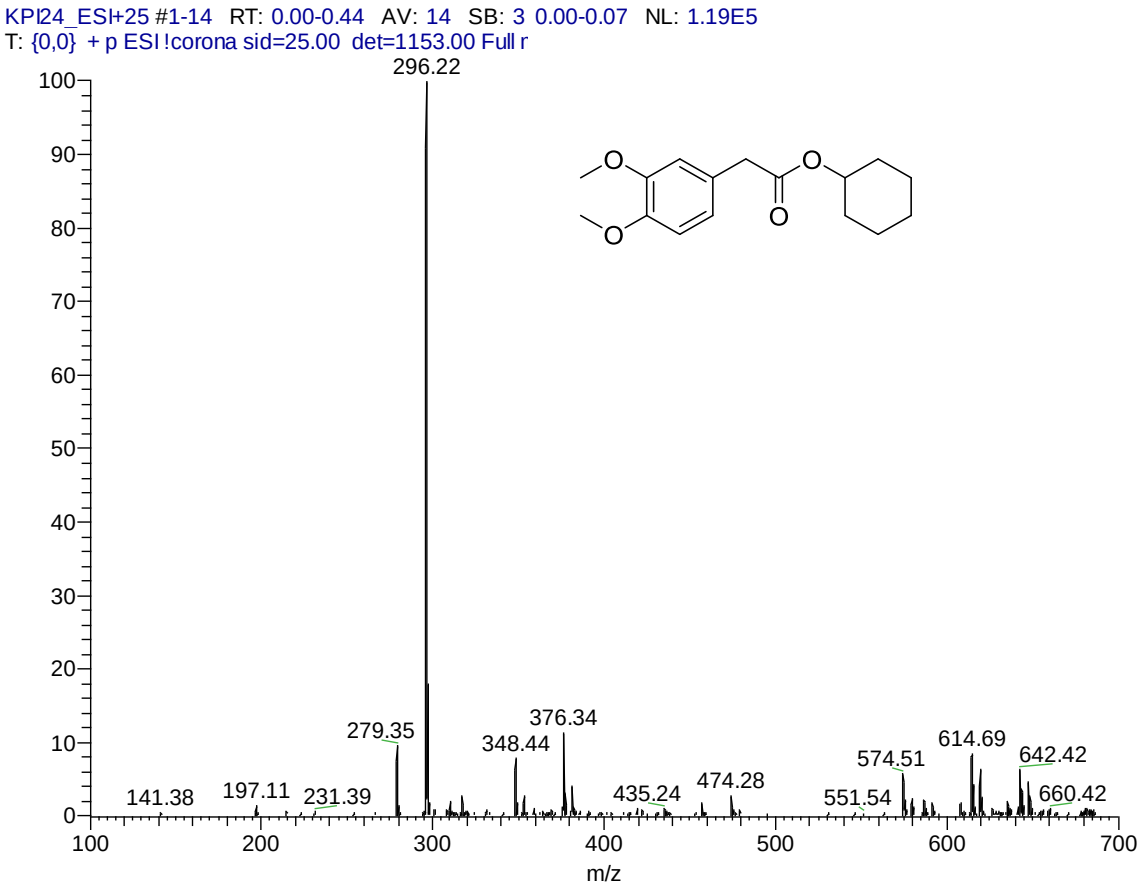


Figure S3: ESI-MS of **2**.

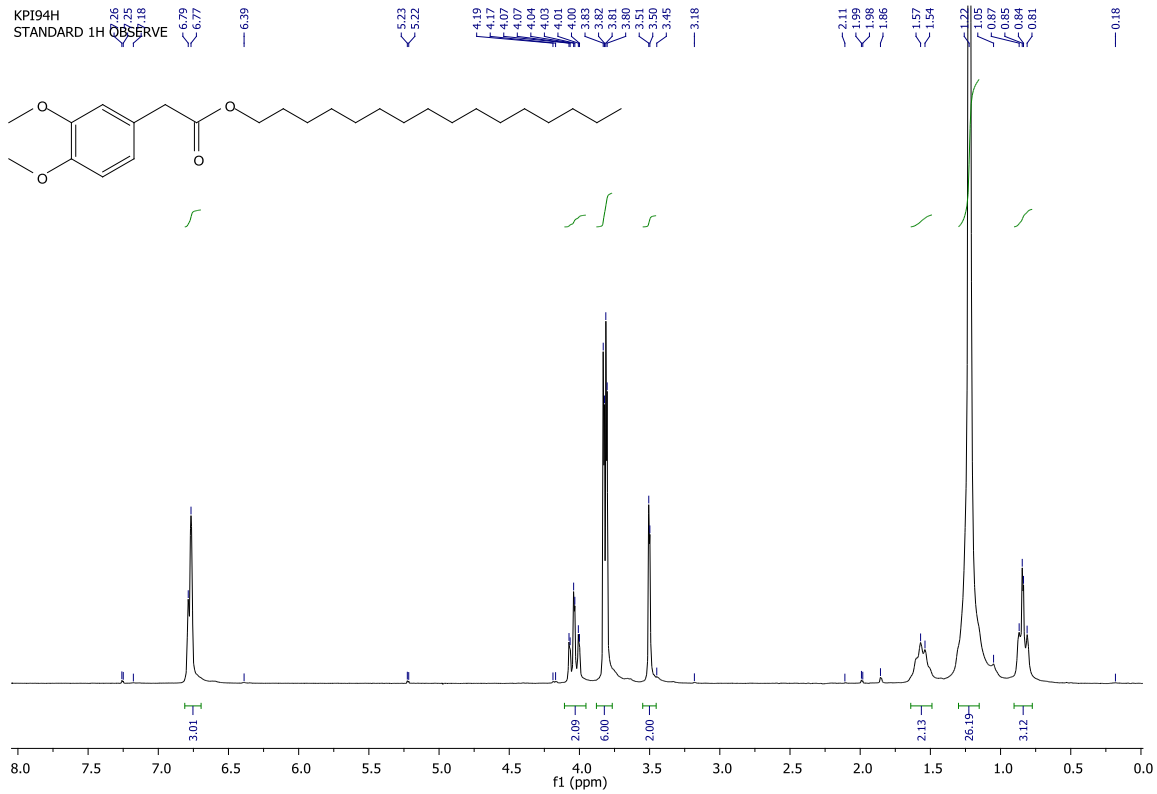


Figure S4: ^{1}H NMR of **3**.

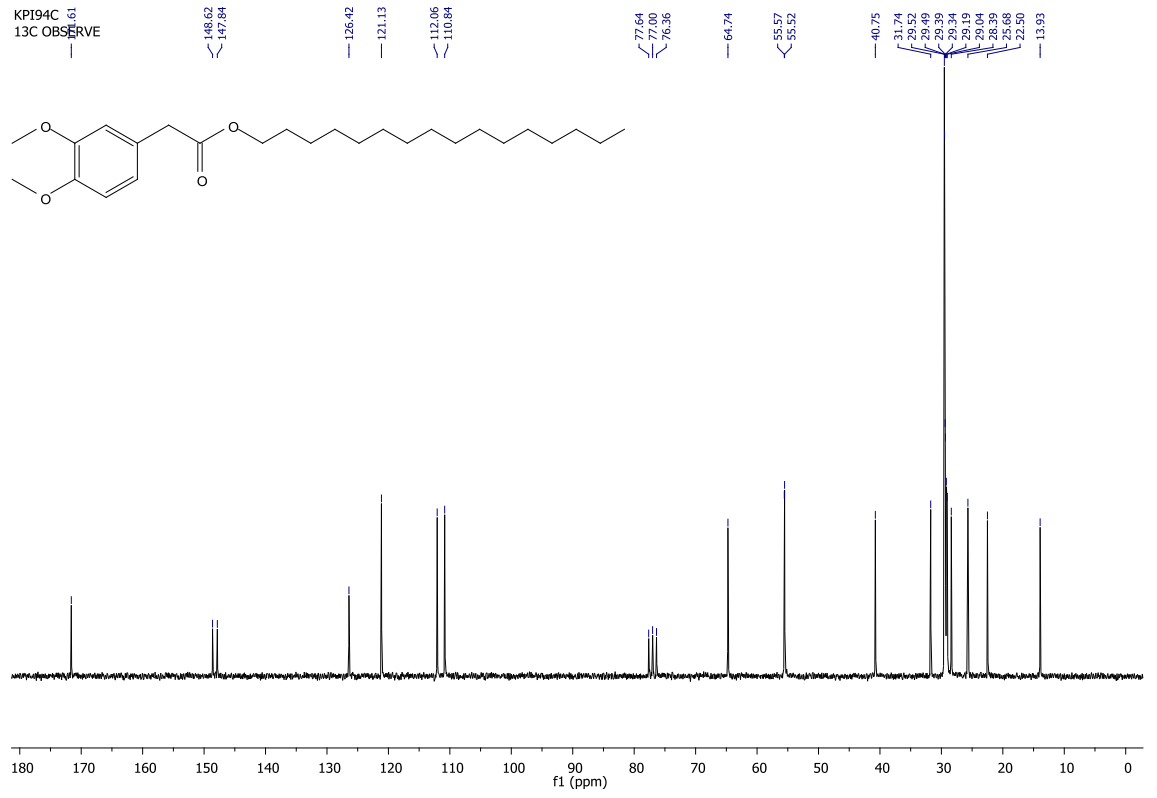


Figure S5: ^{13}C NMR of **3**.

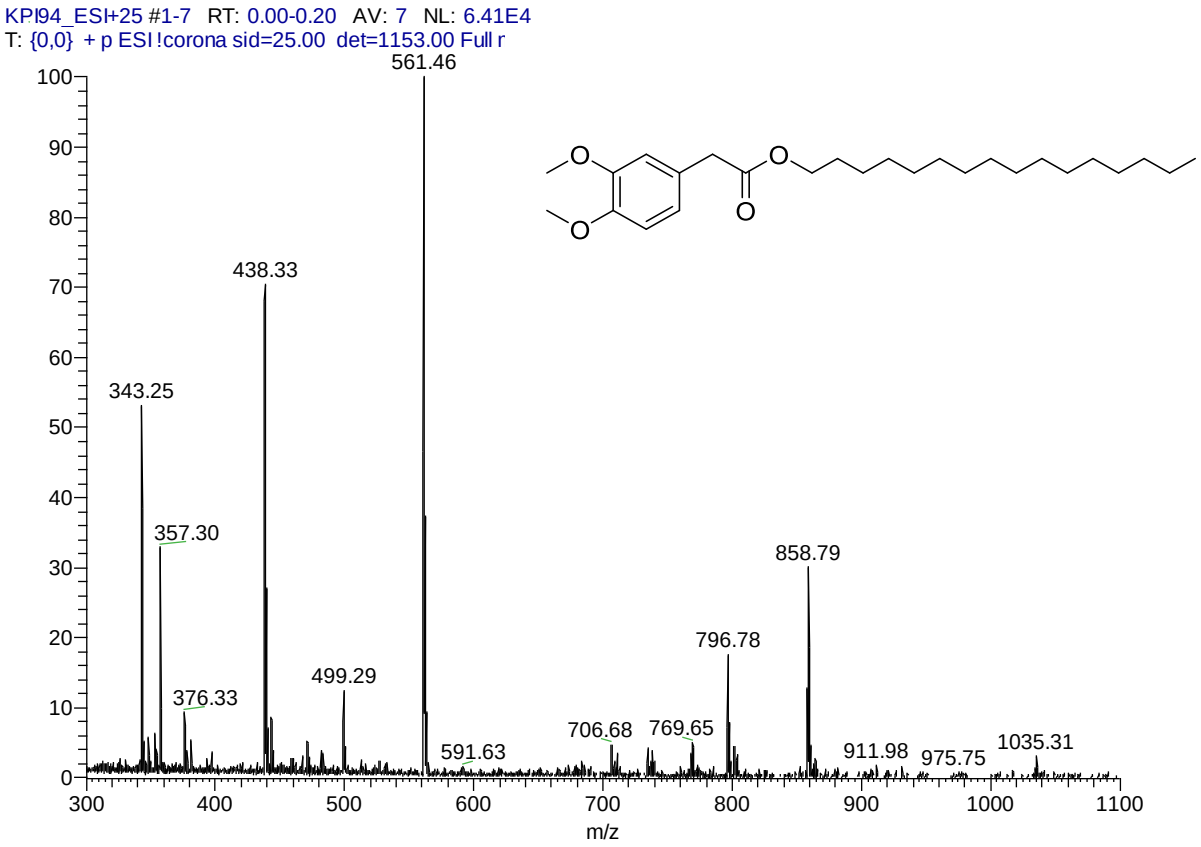


Figure S6: ESI-MS of **3**.

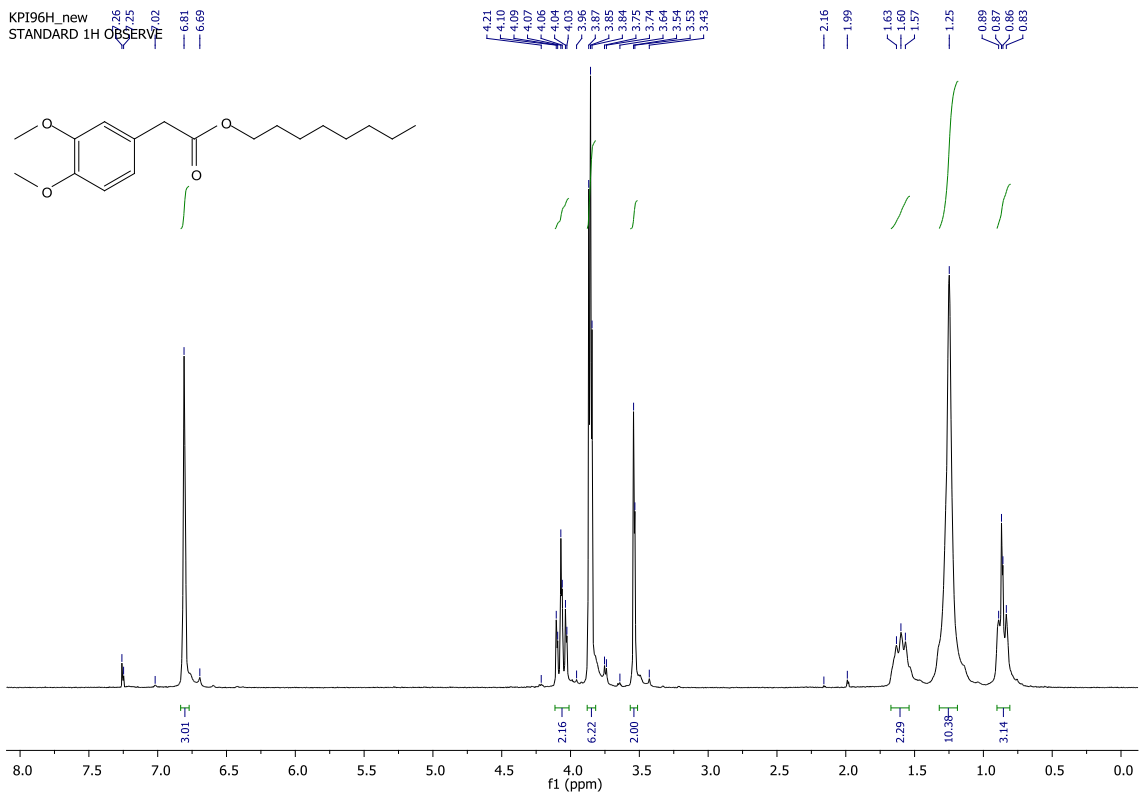


Figure S7: ^{1}H NMR of **4**.

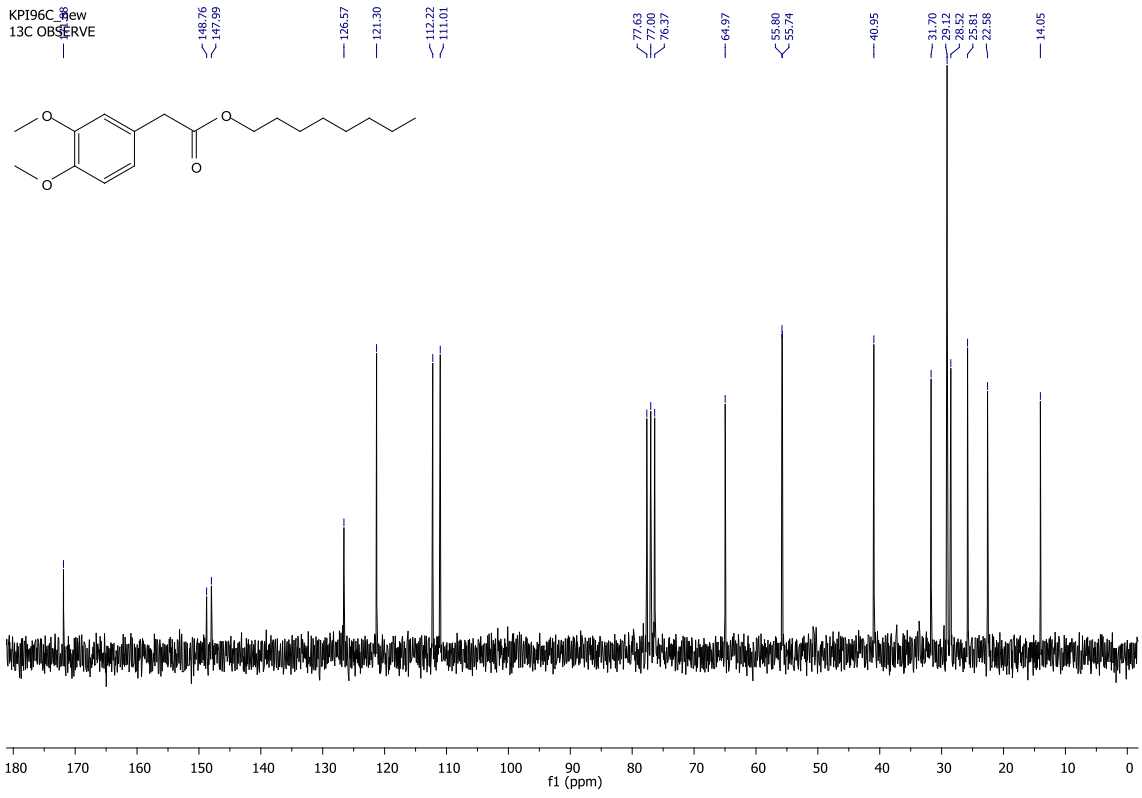


Figure S8: ^{13}C NMR of **4**.

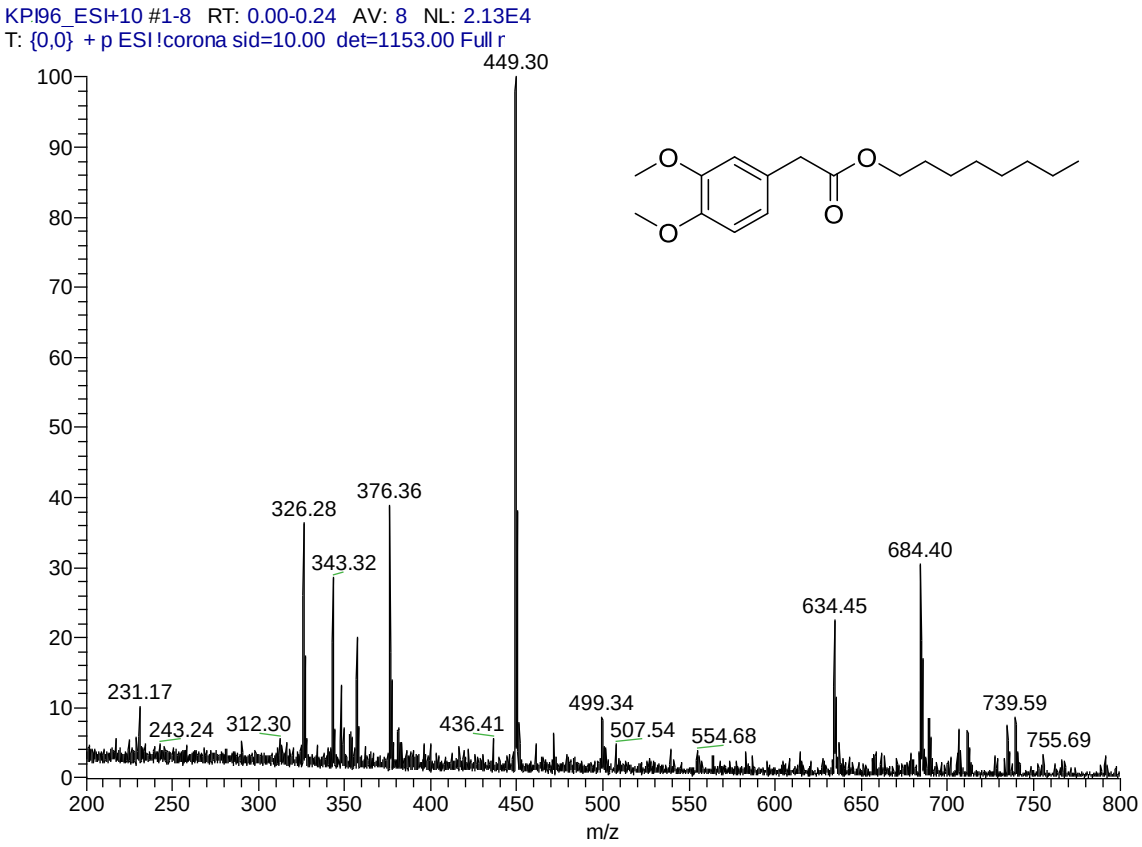


Figure S9: ESI-MS of **4**.

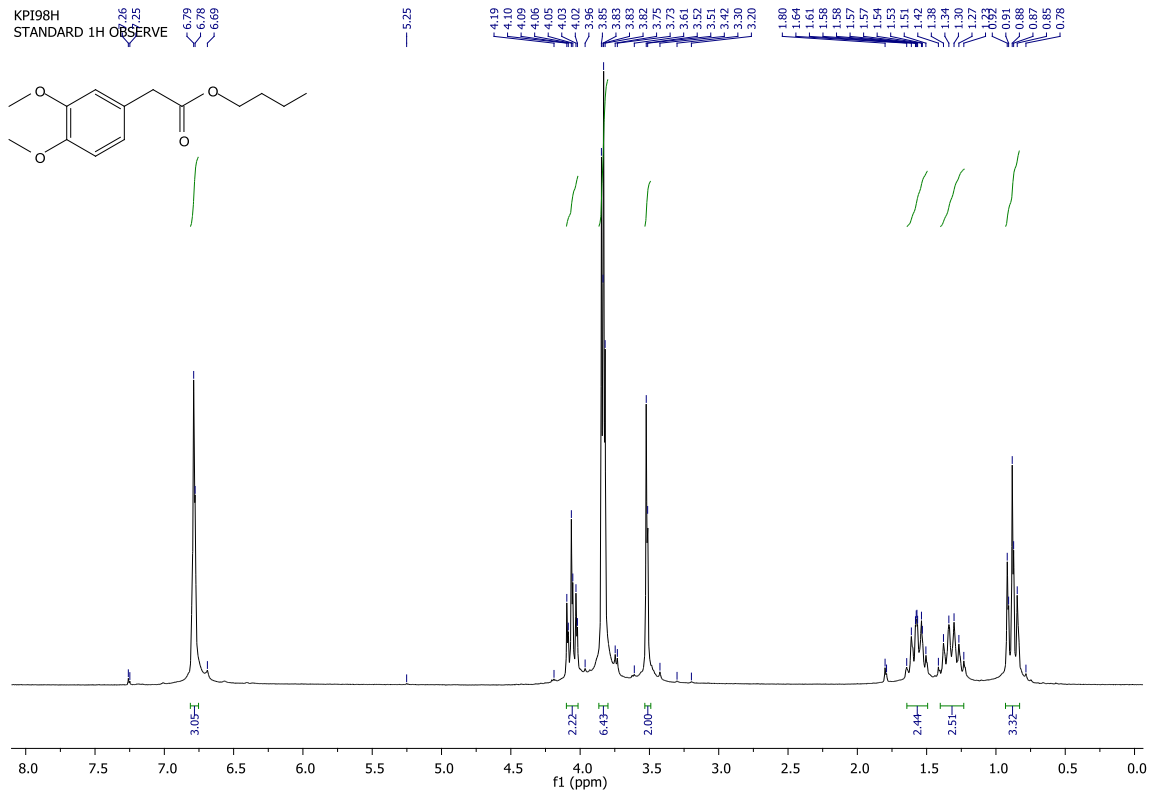


Figure S10: ^{1}H NMR of **5**.

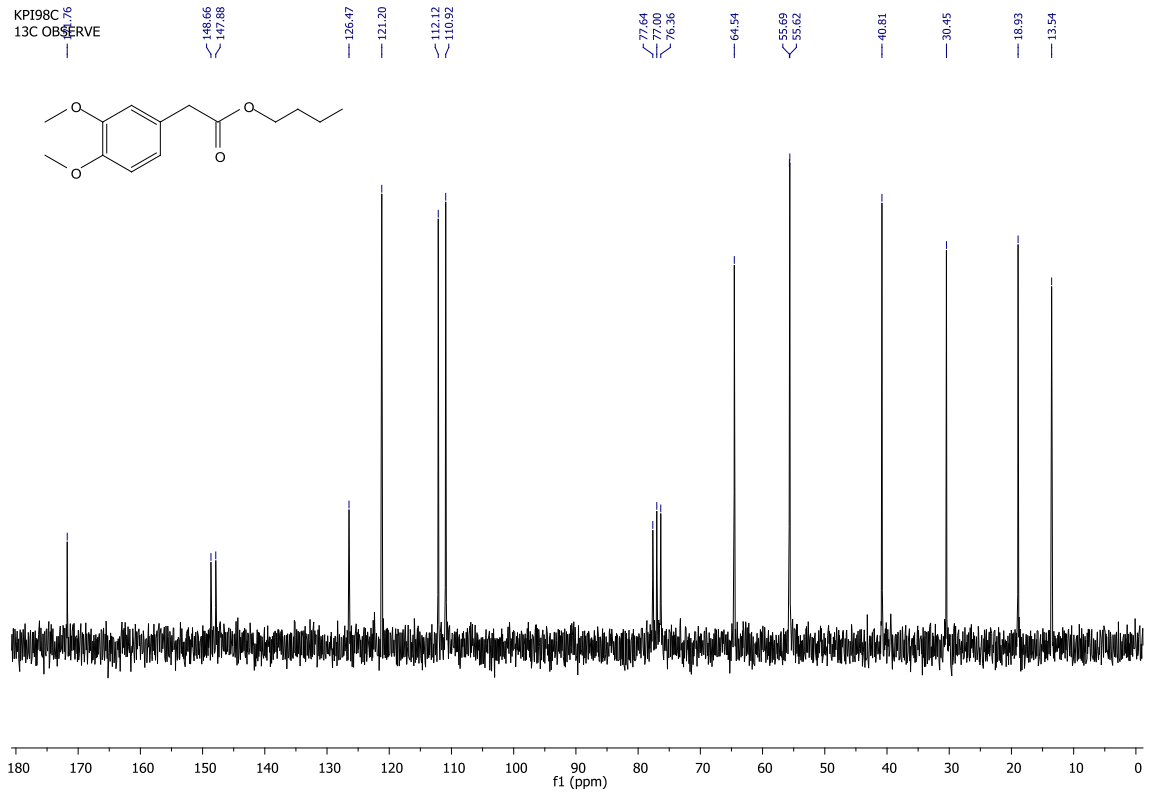


Figure S11: ^{13}C NMR of **5**.

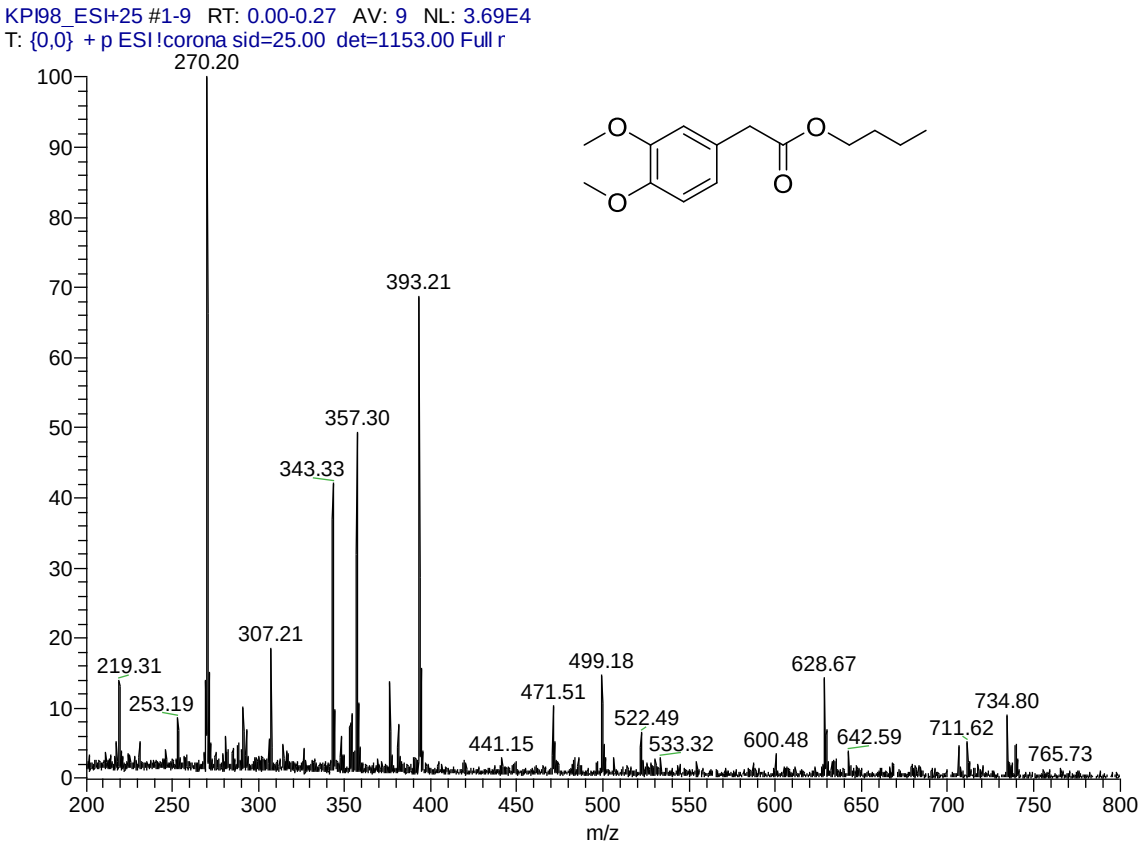


Figure S12: ESI-MS of **5**.

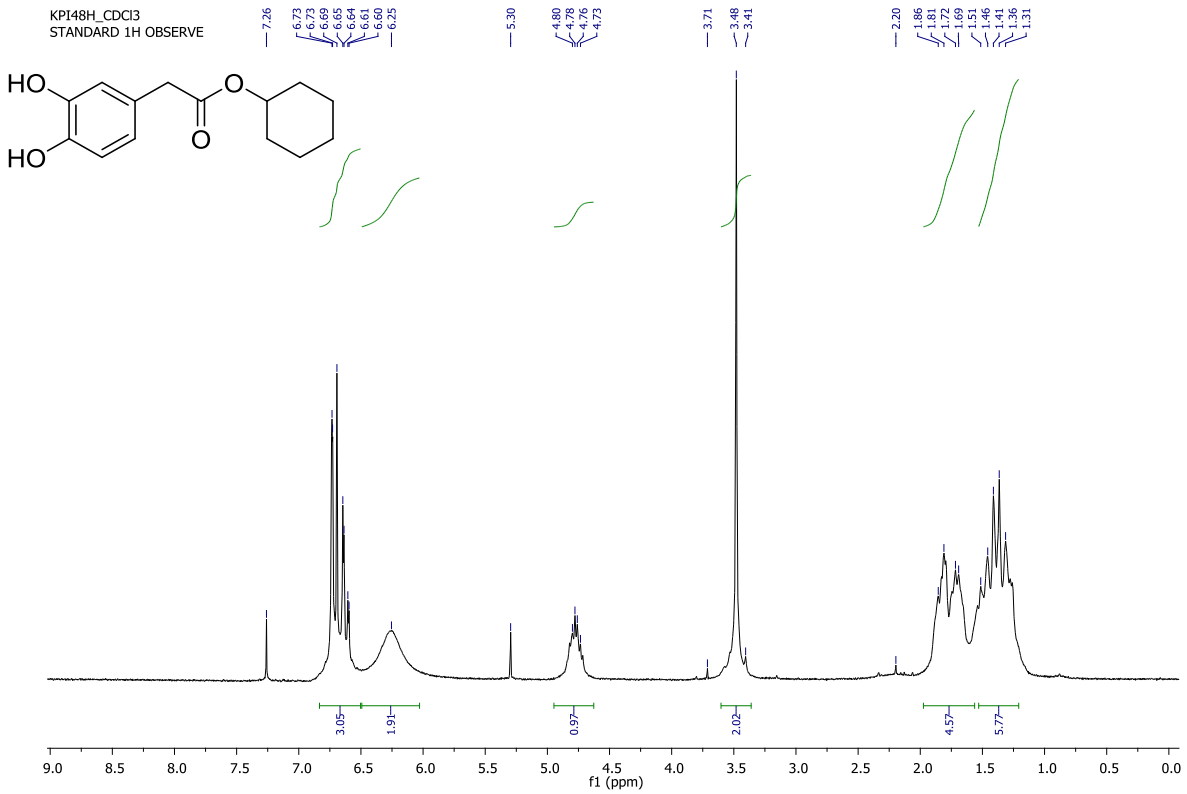


Figure S13: ^{1}H NMR of **6**.

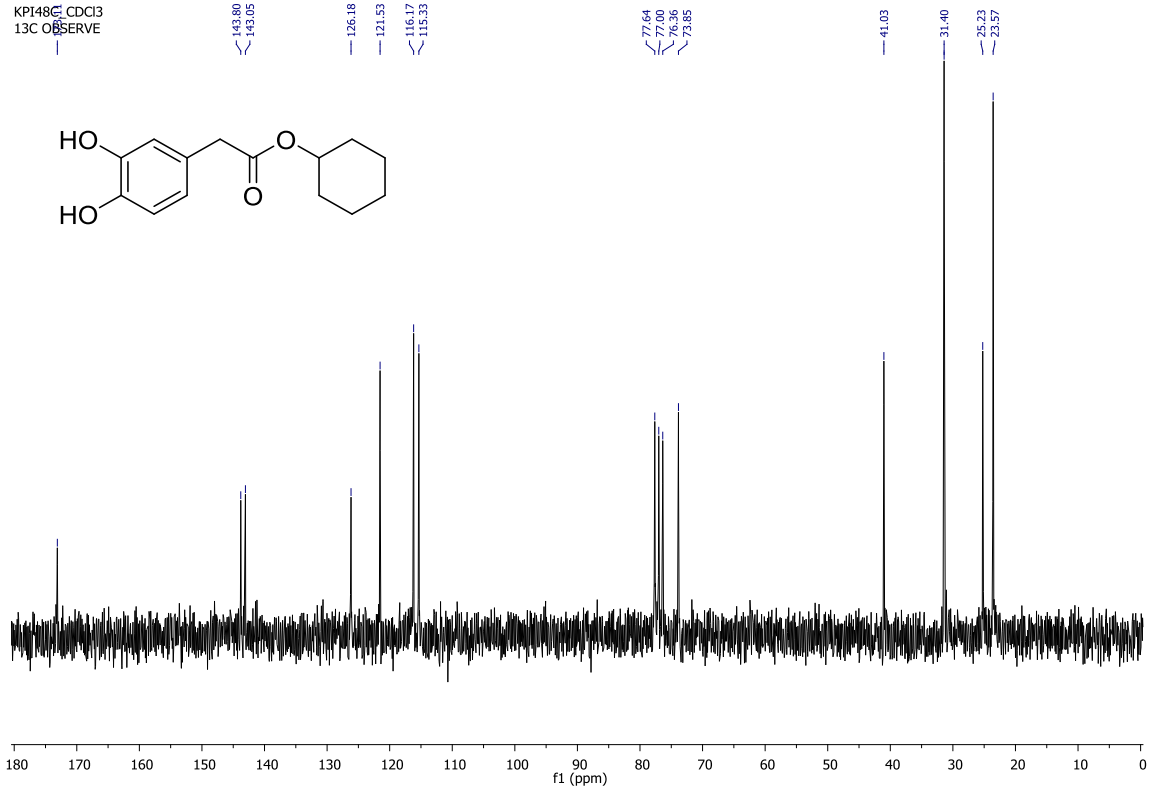


Figure S14: ^{13}C NMR of **6**.

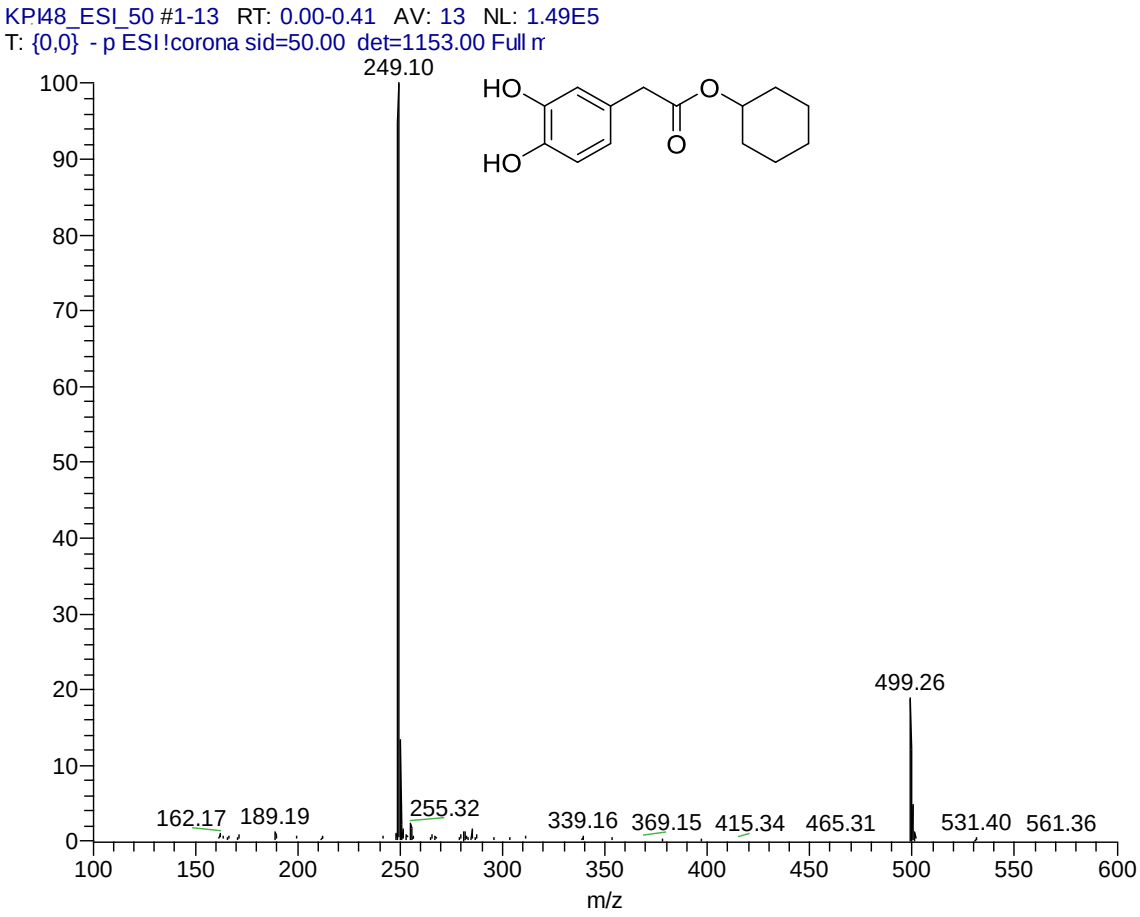


Figure S15: ESI-MS of **6**.

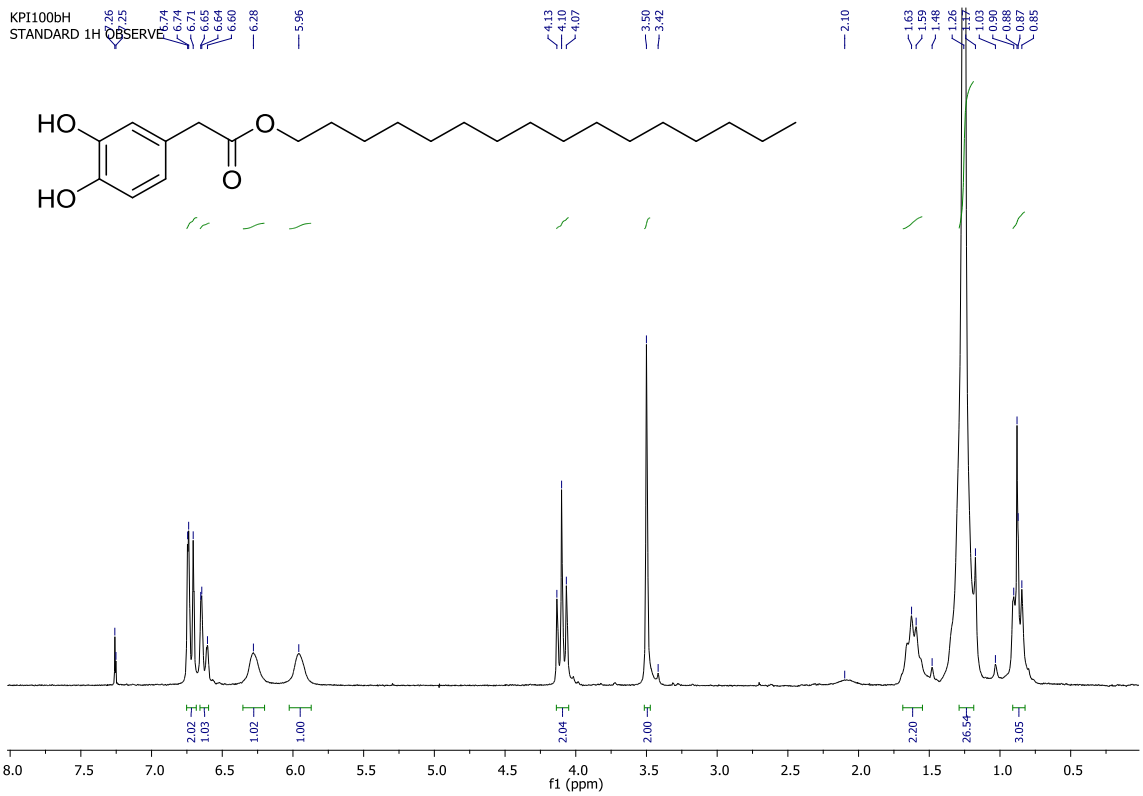


Figure S16: ^{1}H NMR of **7**.

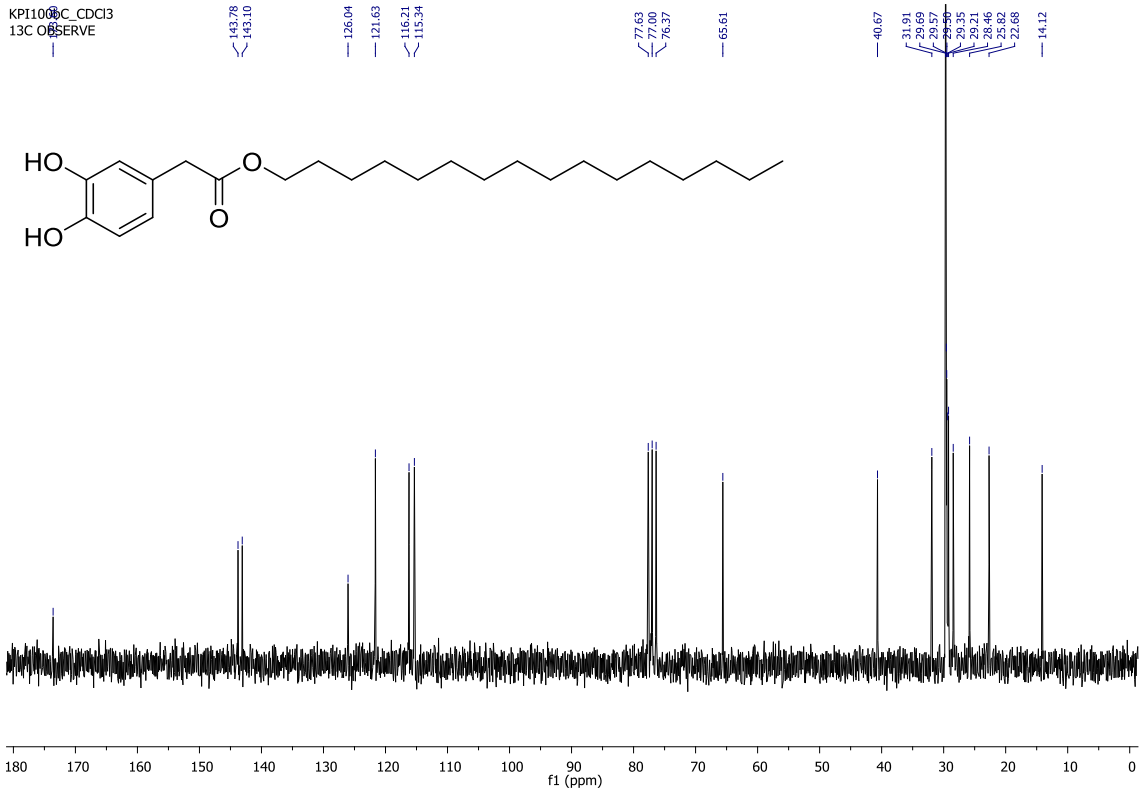


Figure S17: ^{13}C NMR of **7**.

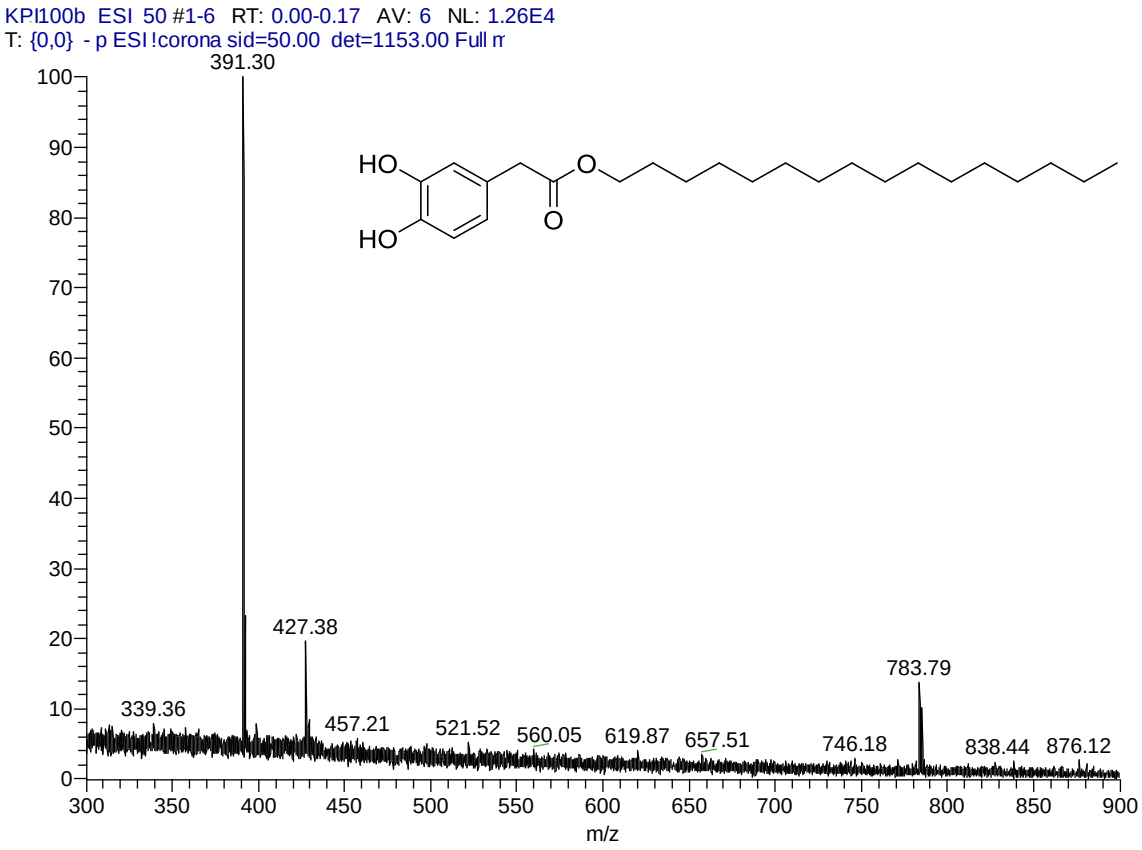


Figure S18: ESI-MS of **7**.

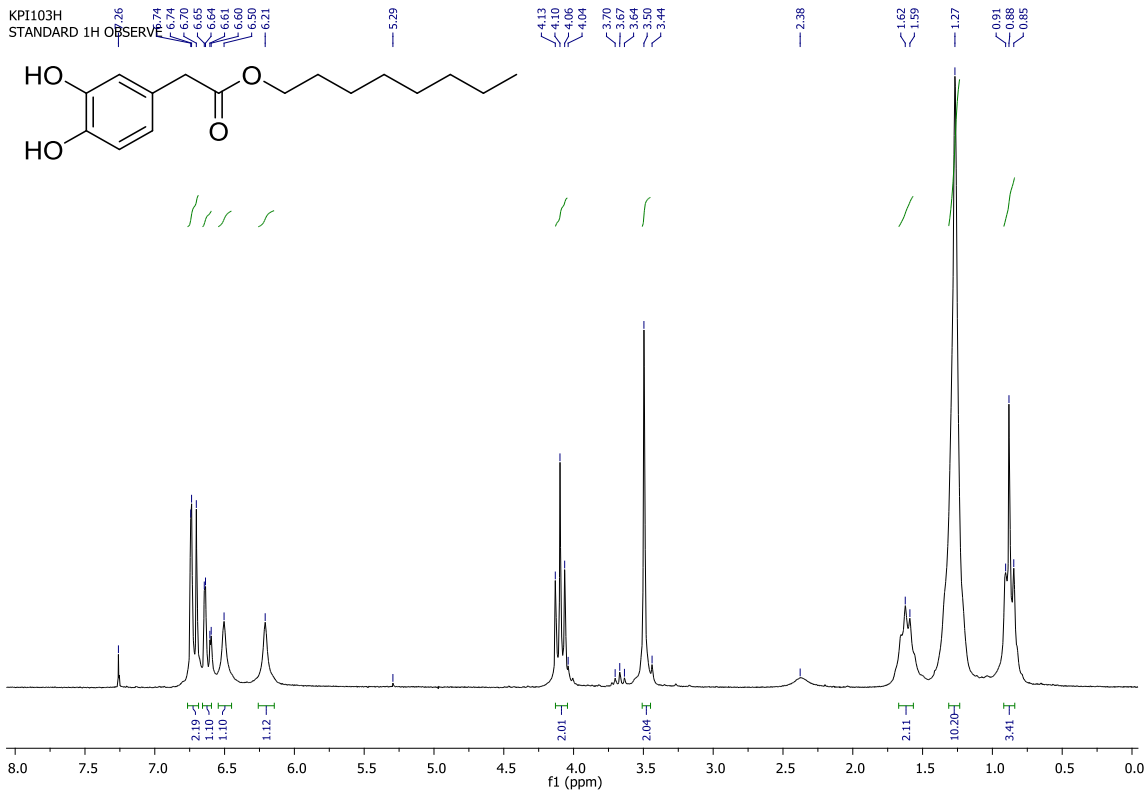


Figure S19: ^{1}H NMR of **8**.

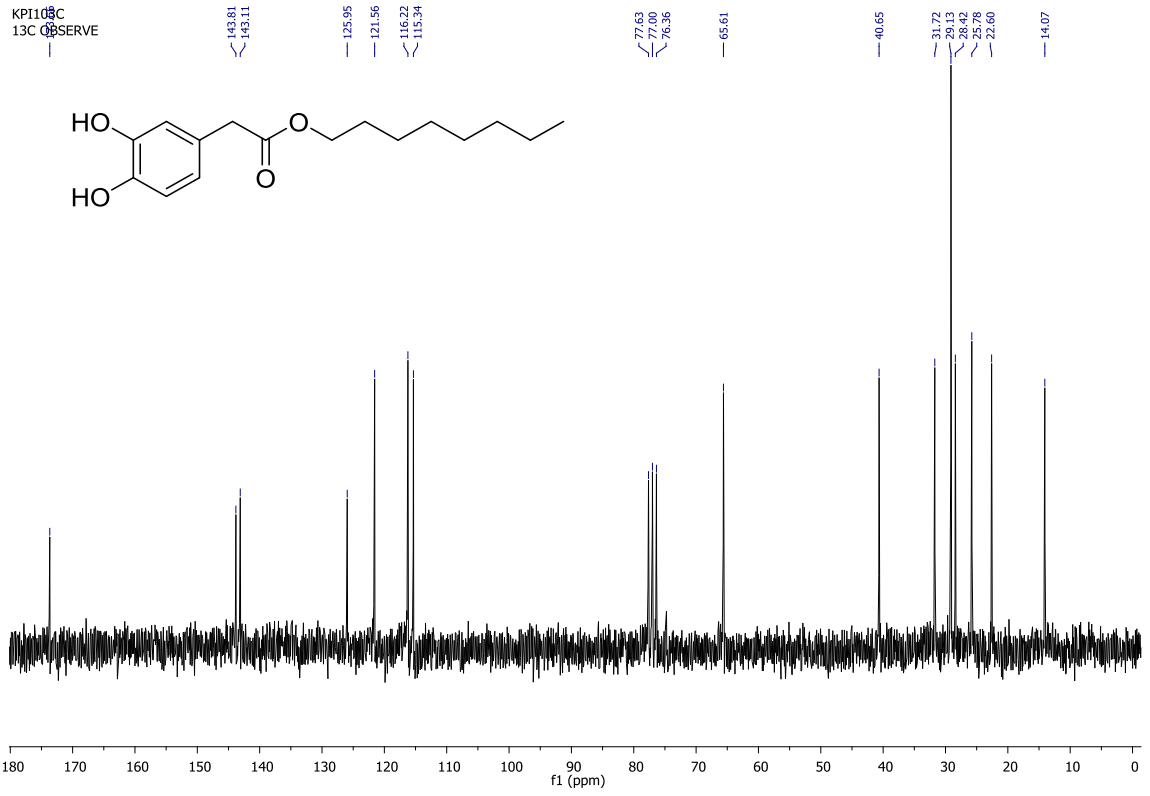


Figure S20: ^{13}C NMR of **8**.

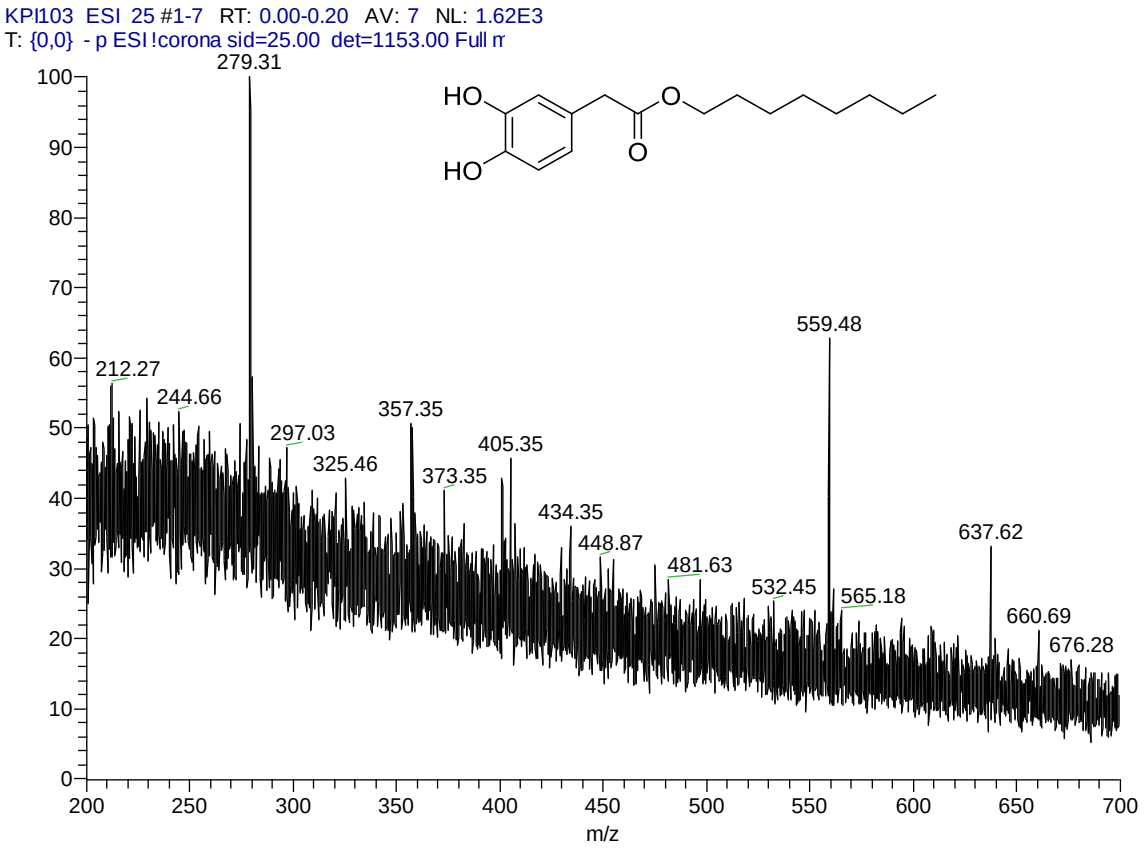


Figure S21: ESI-MS of **8**.

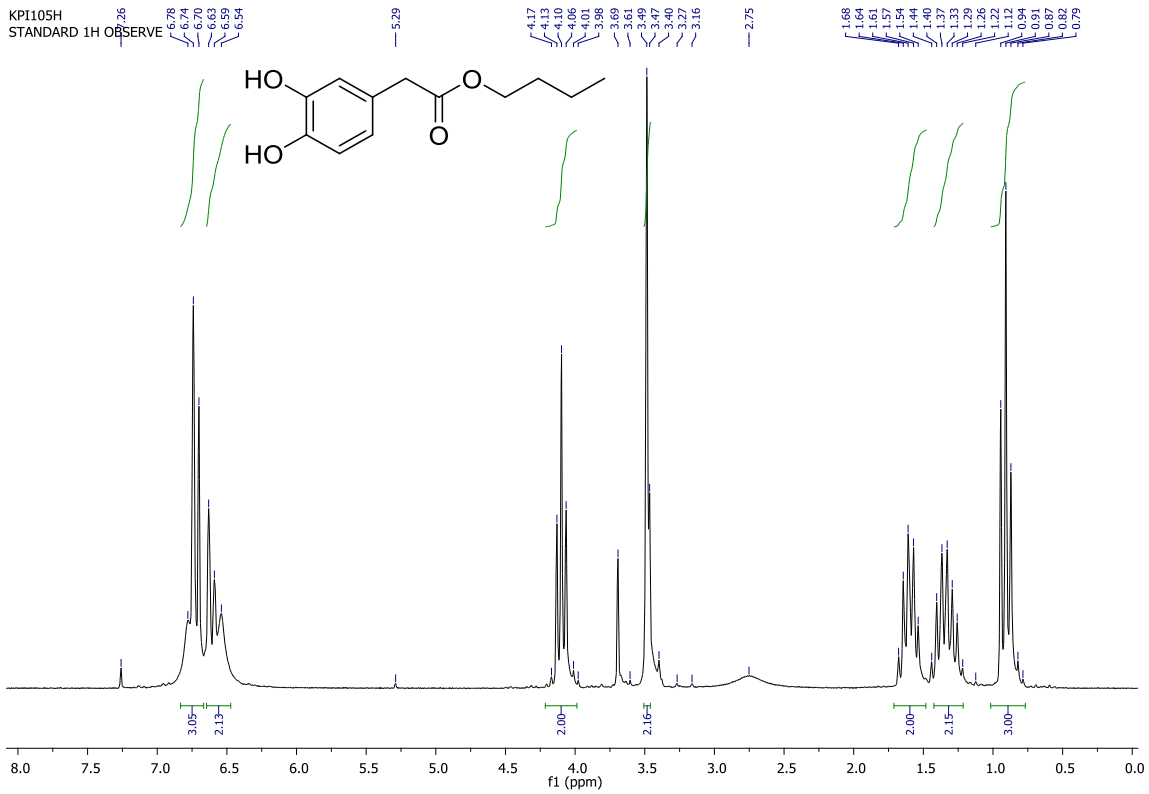


Figure S22: ^{1}H NMR of **9**.

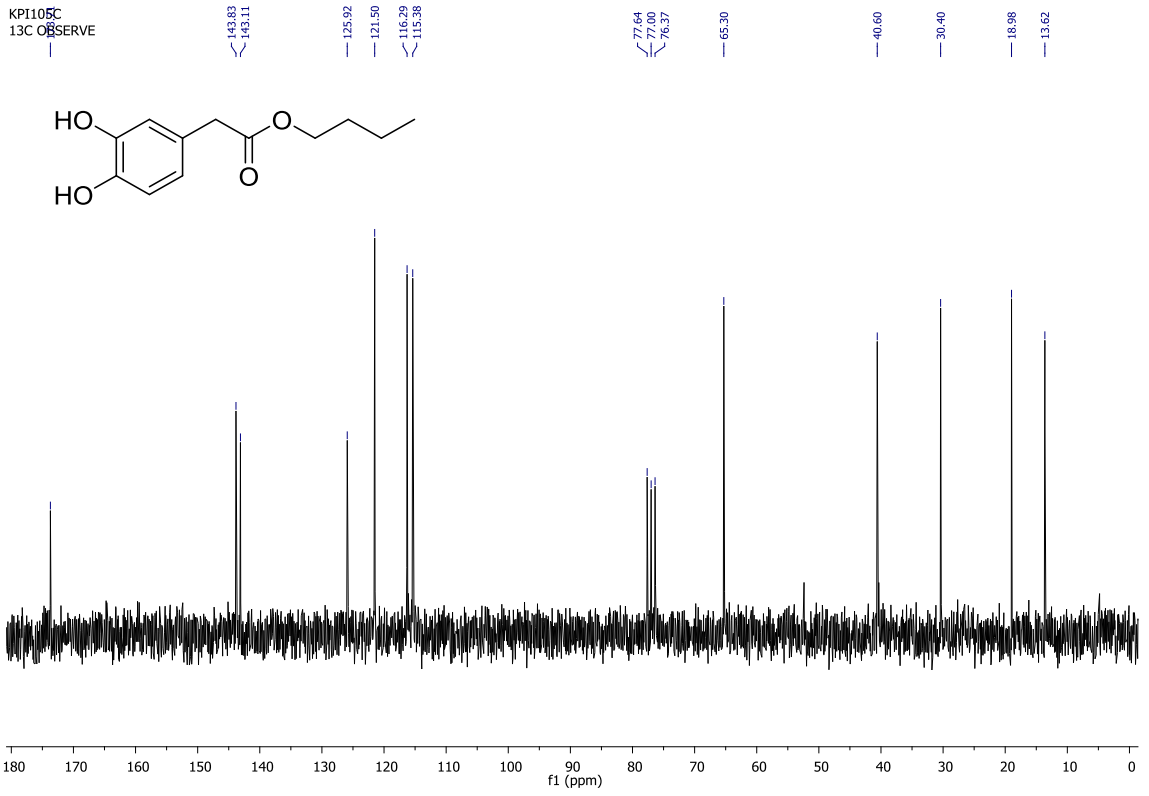


Figure S23: ^{13}C NMR of **9**.

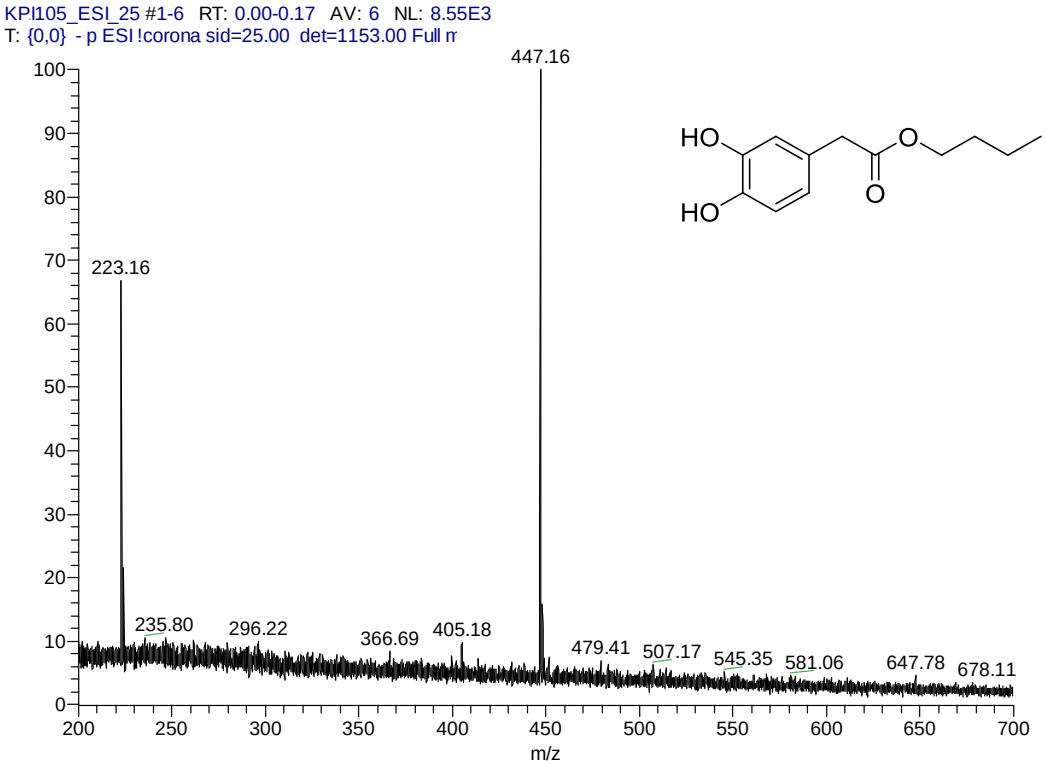


Figure S24: ESI-MS of **9**.

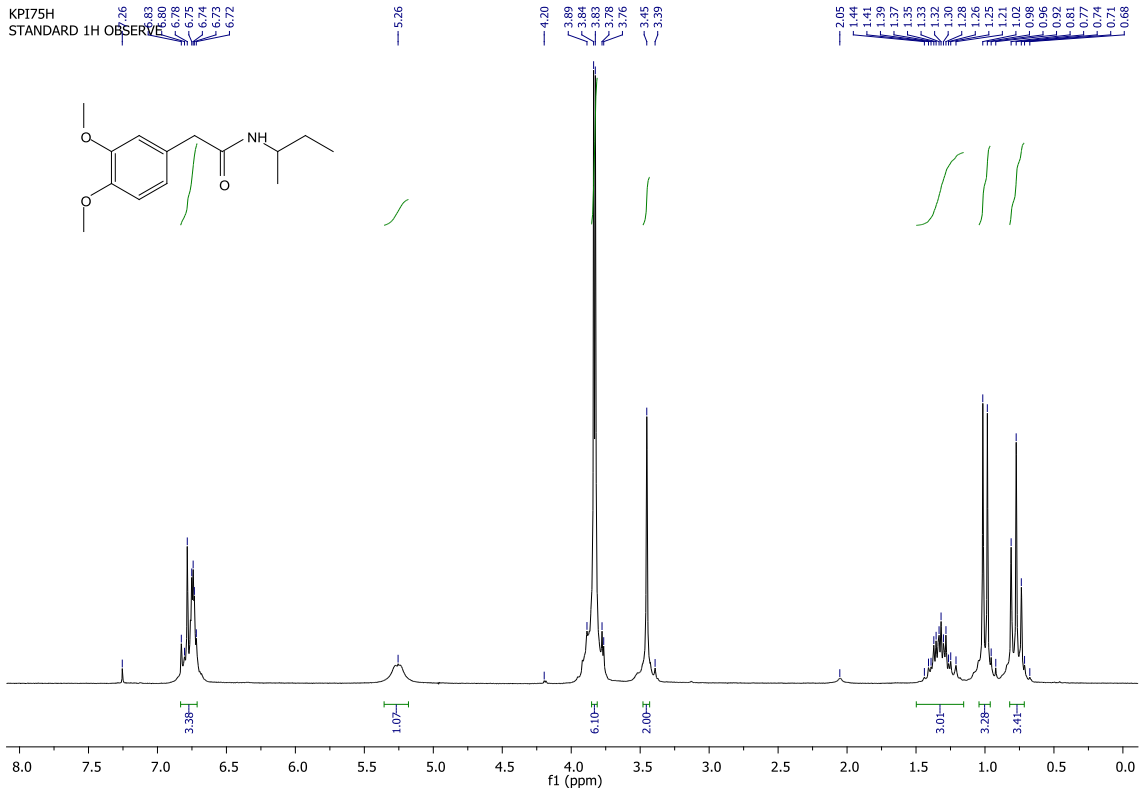


Figure S25: ^{1}H NMR of **10**.

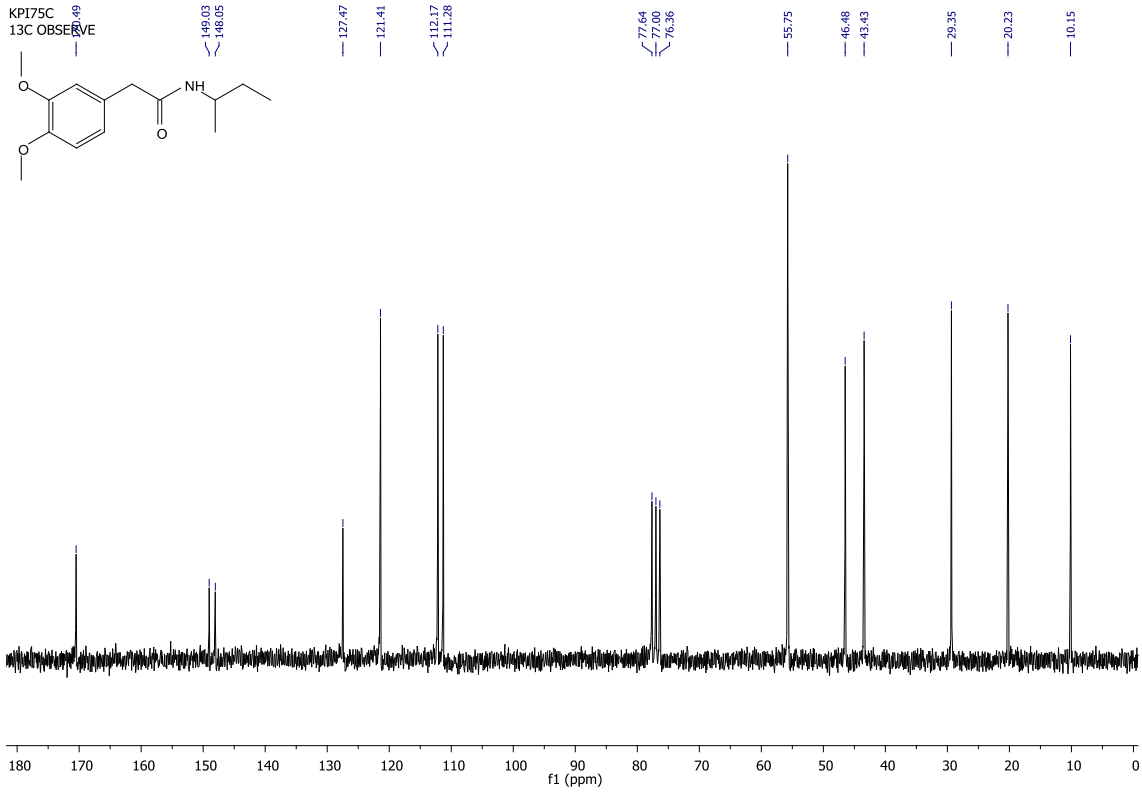


Figure S26: ^{13}C NMR of **10**.

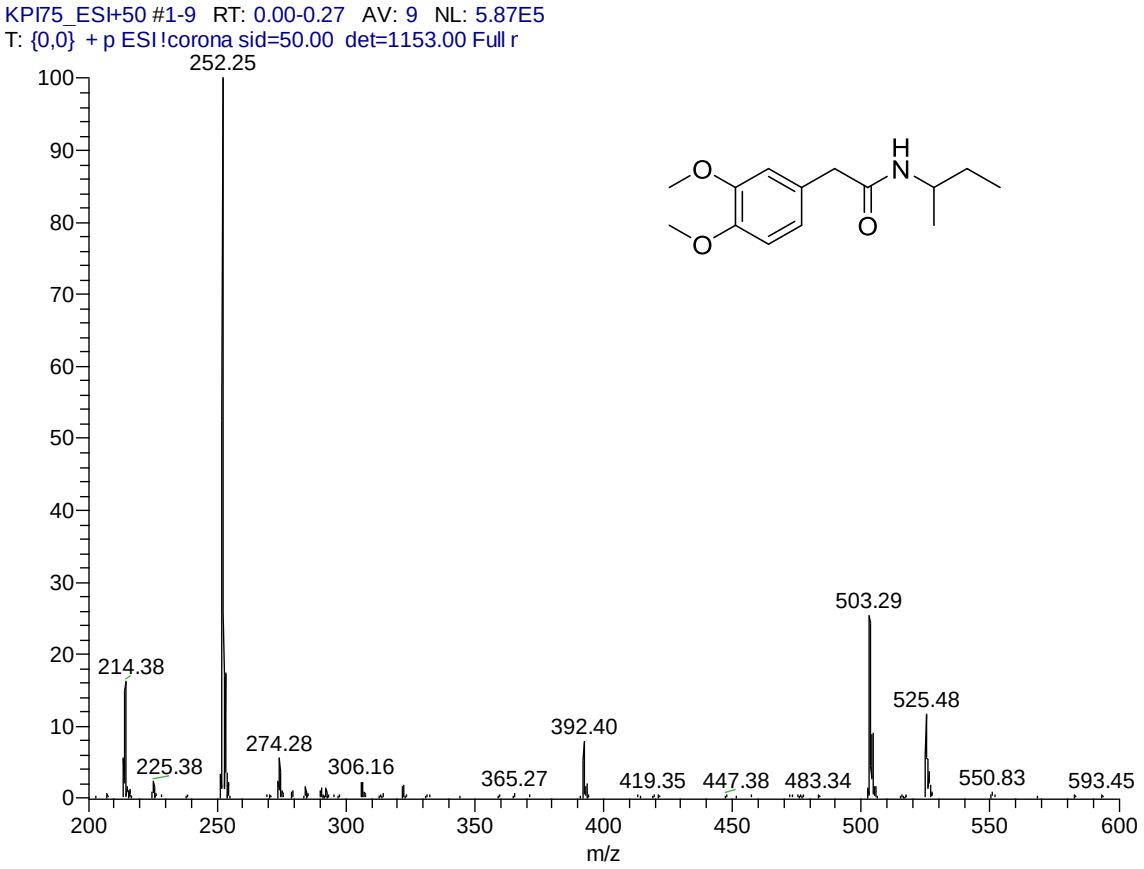


Figure S27: ESI-MS of **10**.

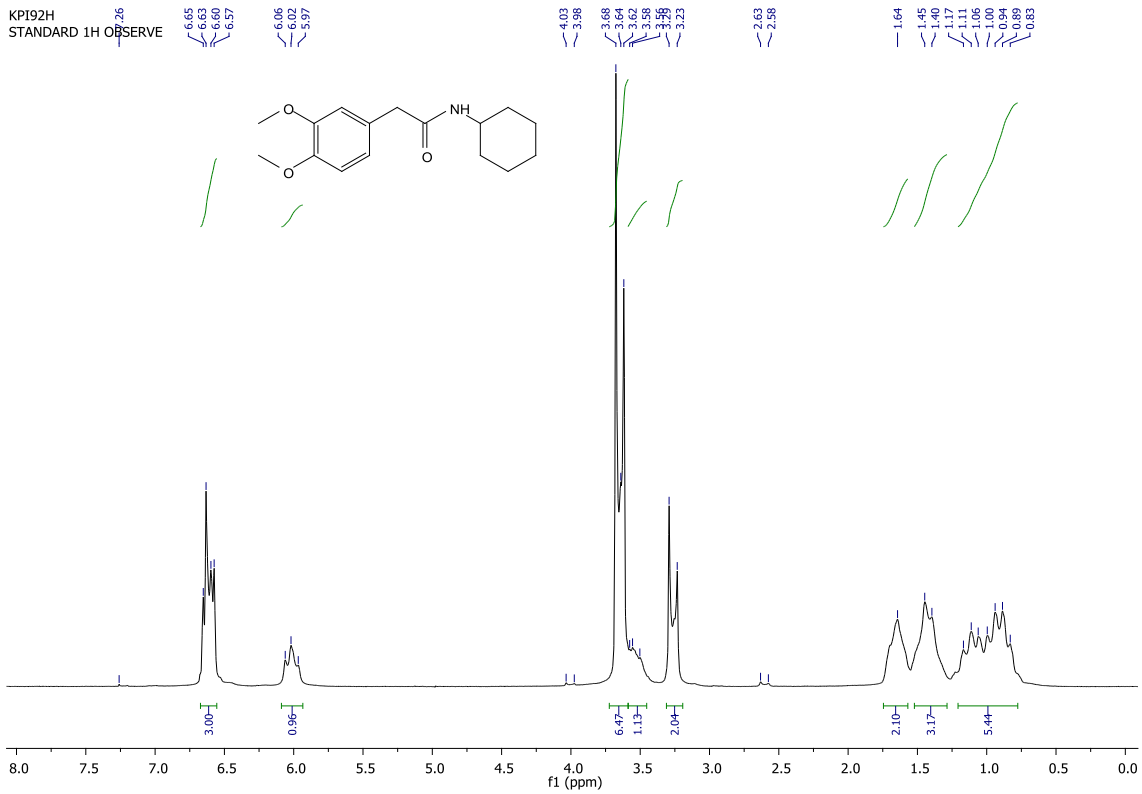


Figure S28: ^{1}H NMR of **11**.

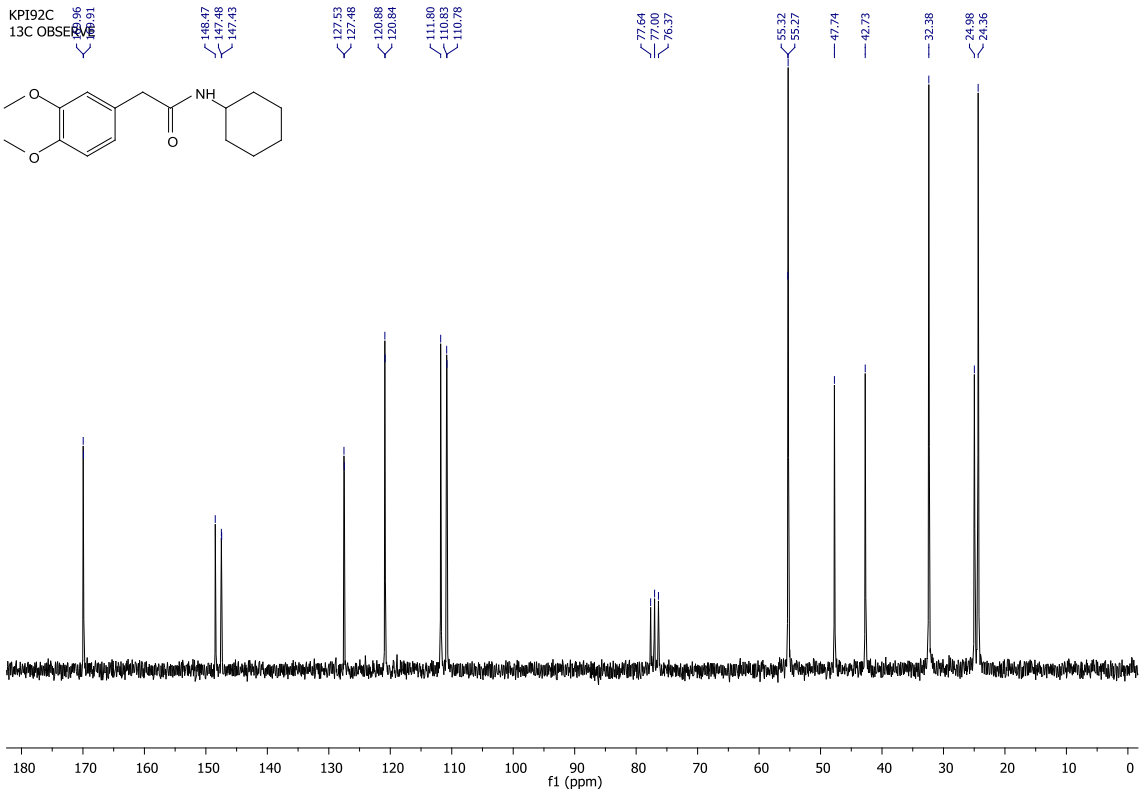


Figure S29: ^{13}C NMR of **11**.

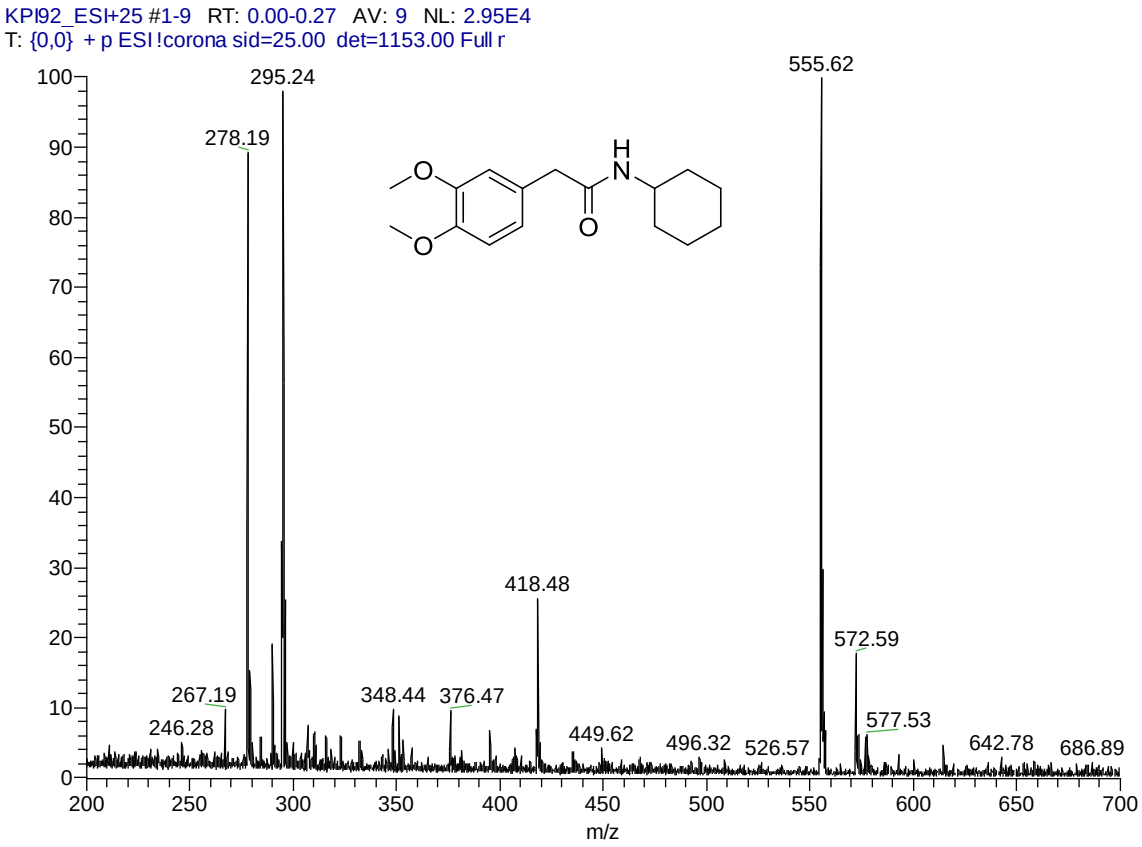


Figure S30: ESI-MS of **11**.

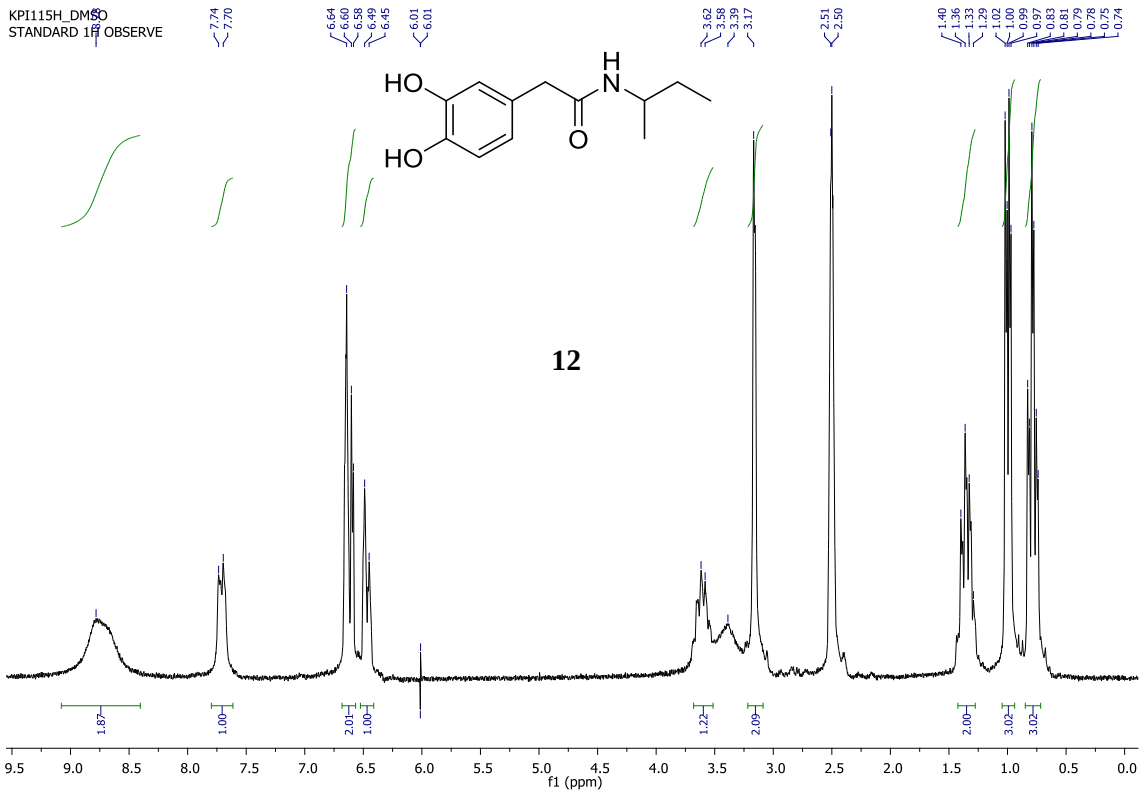


Figure S31: ^{1}H NMR of **12**.

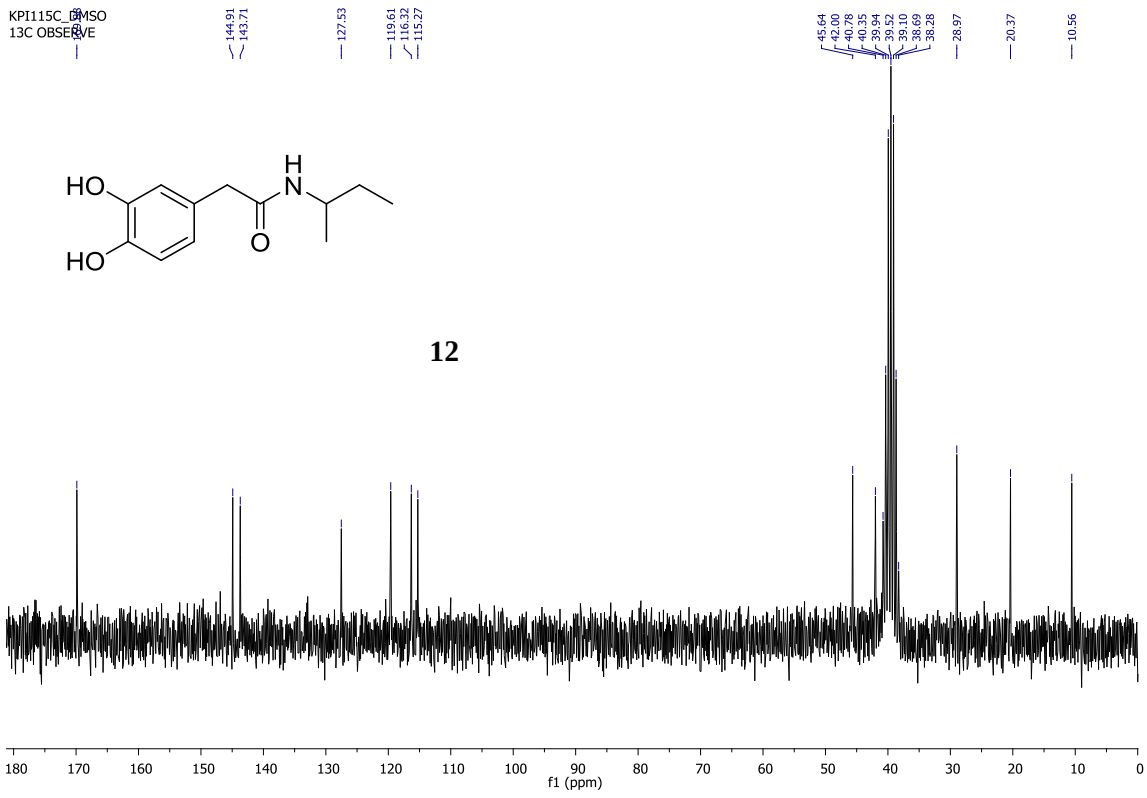


Figure S32: ^{13}C NMR of **12**.

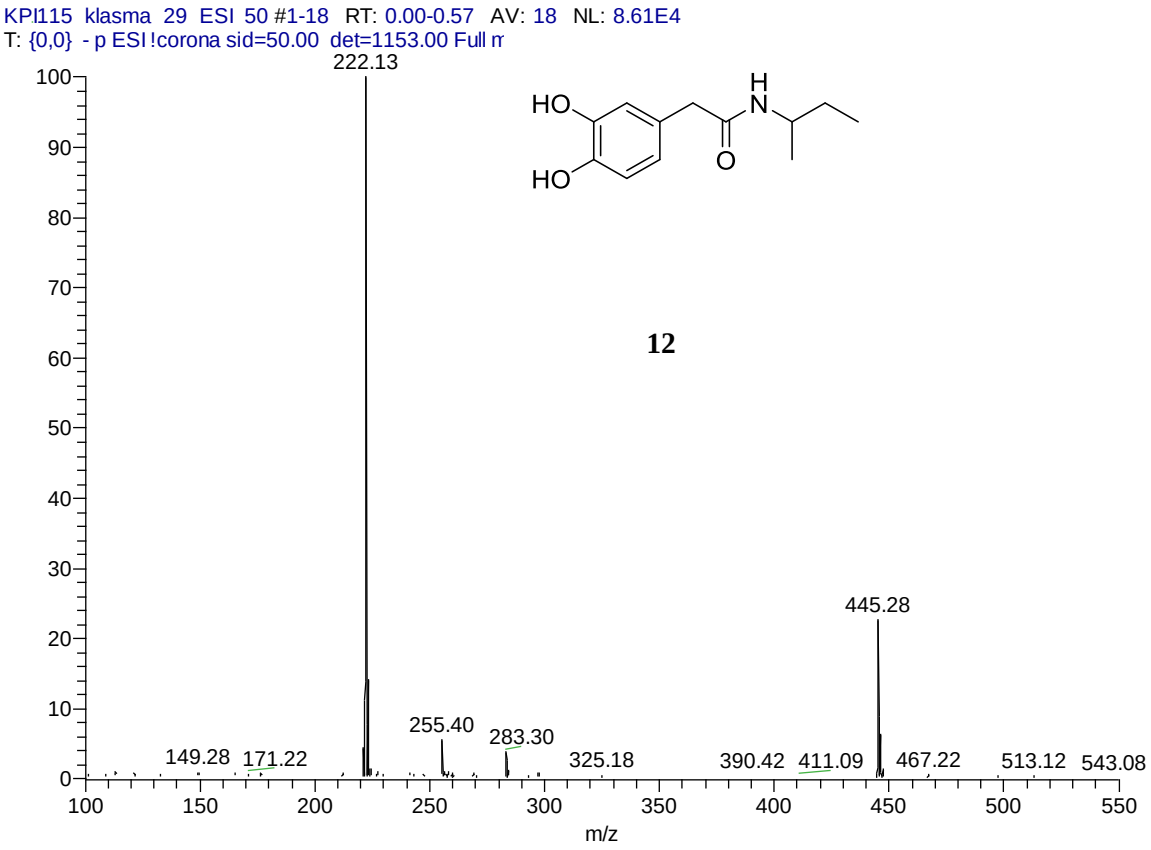


Figure S33: ESI-MS of **12**.

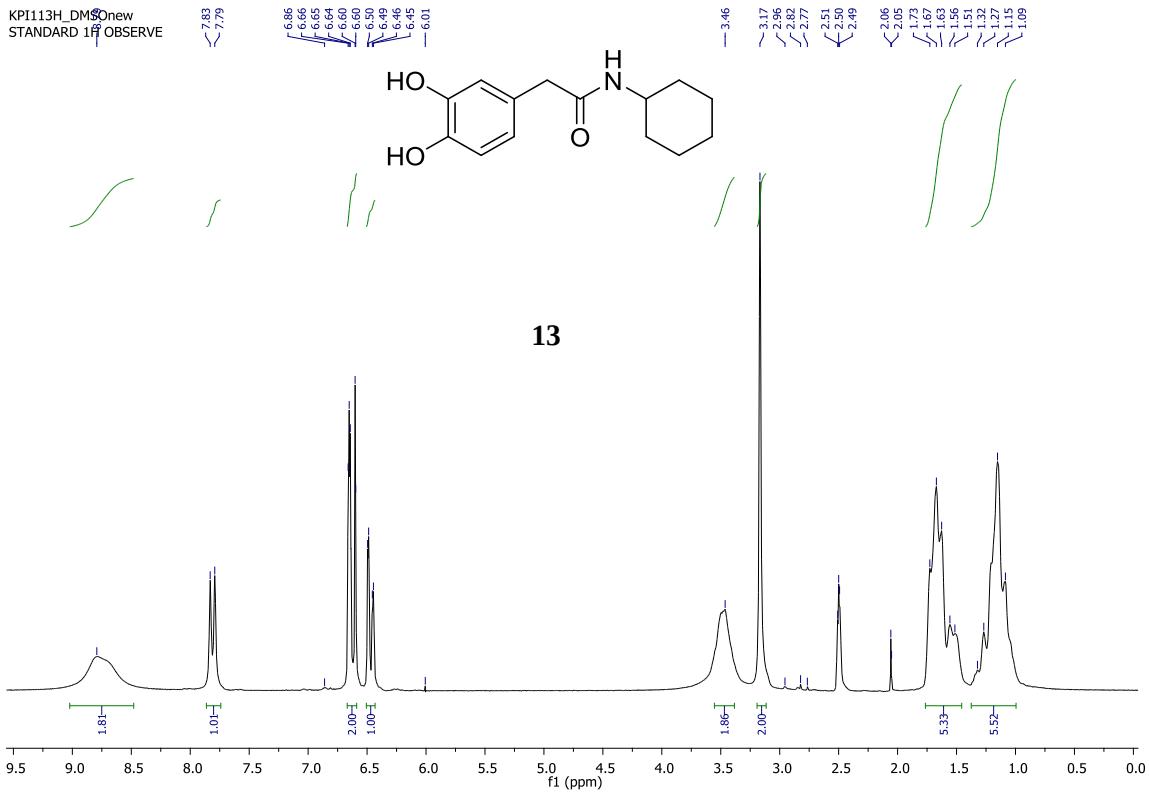


Figure S34: ^{1}H NMR of **13**.

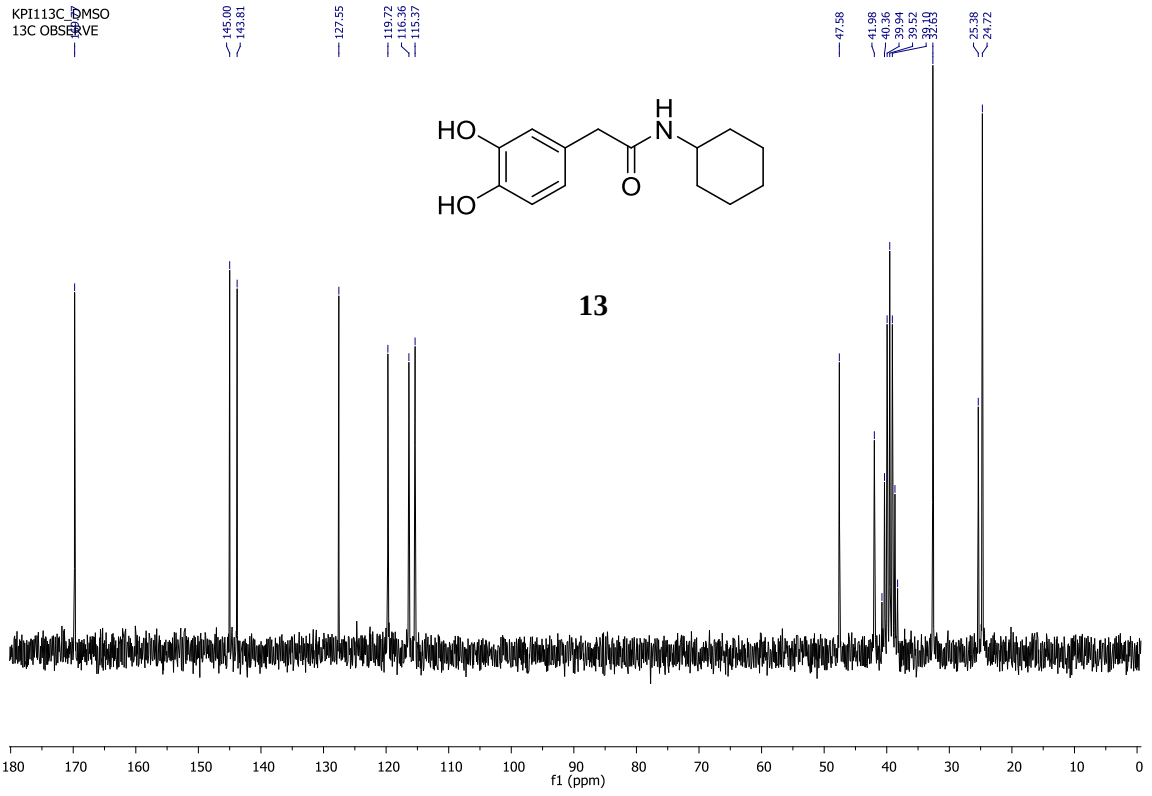
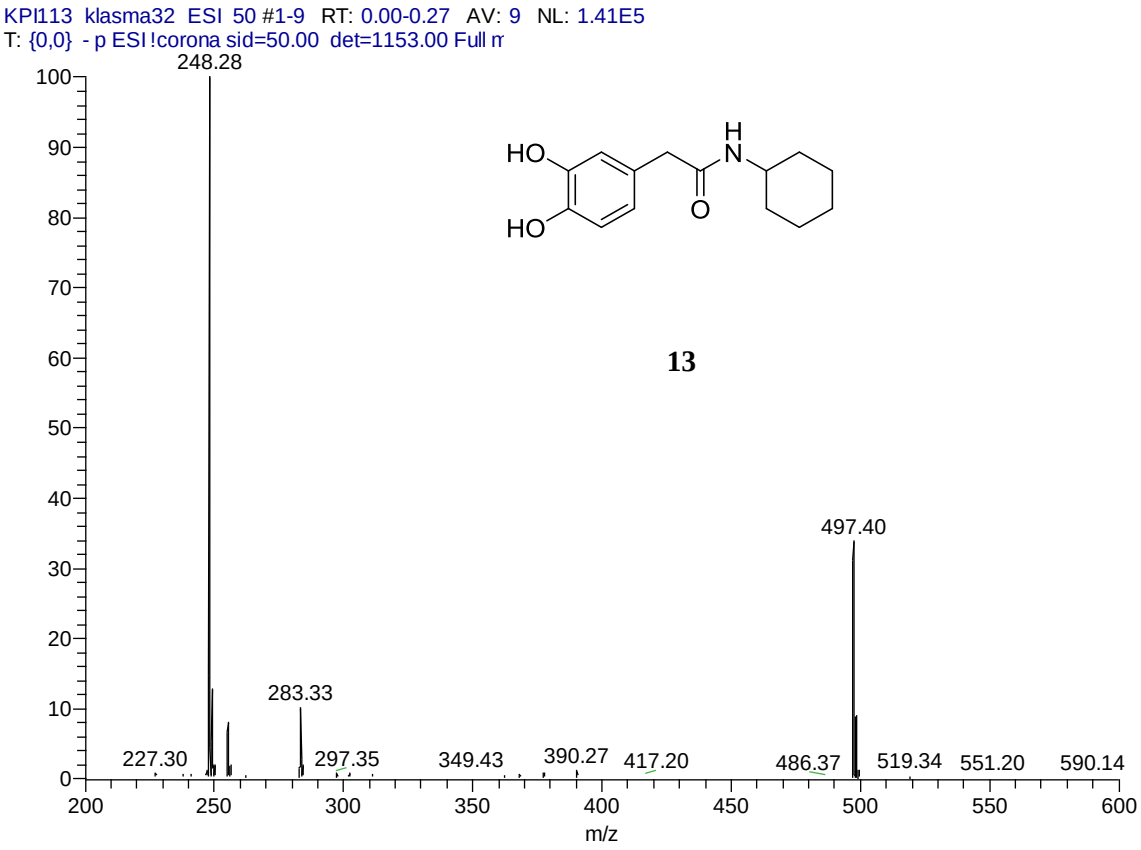


Figure S35: ^{13}C NMR of **13**.



13

Figure S36: ESI-MS of **13**.

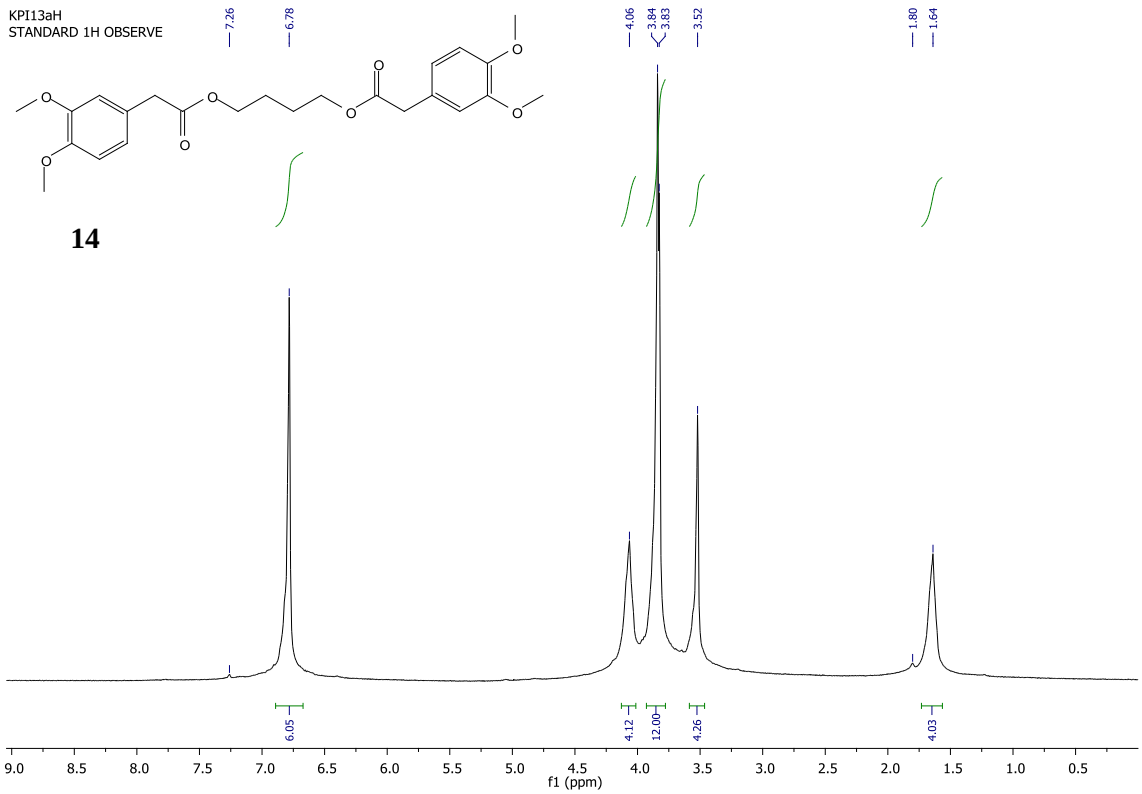


Figure S37: ^{1}H NMR of **14**.

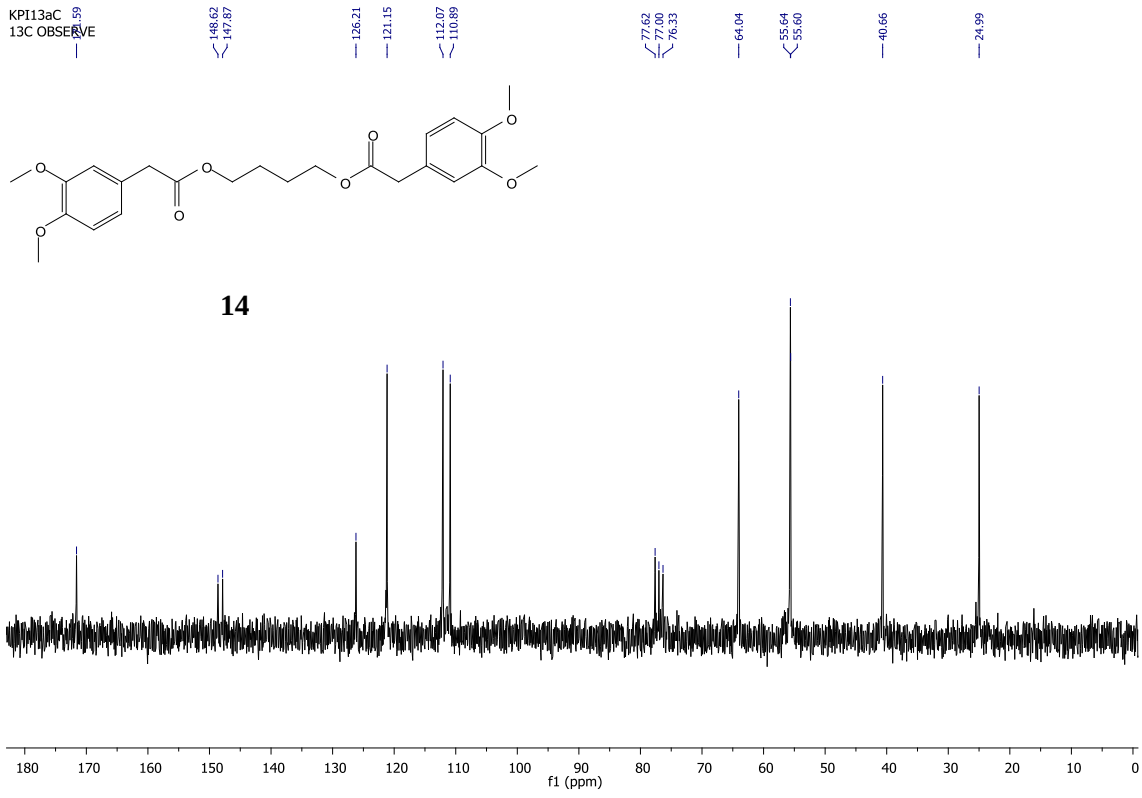


Figure S38: ^{13}C NMR of **14**.

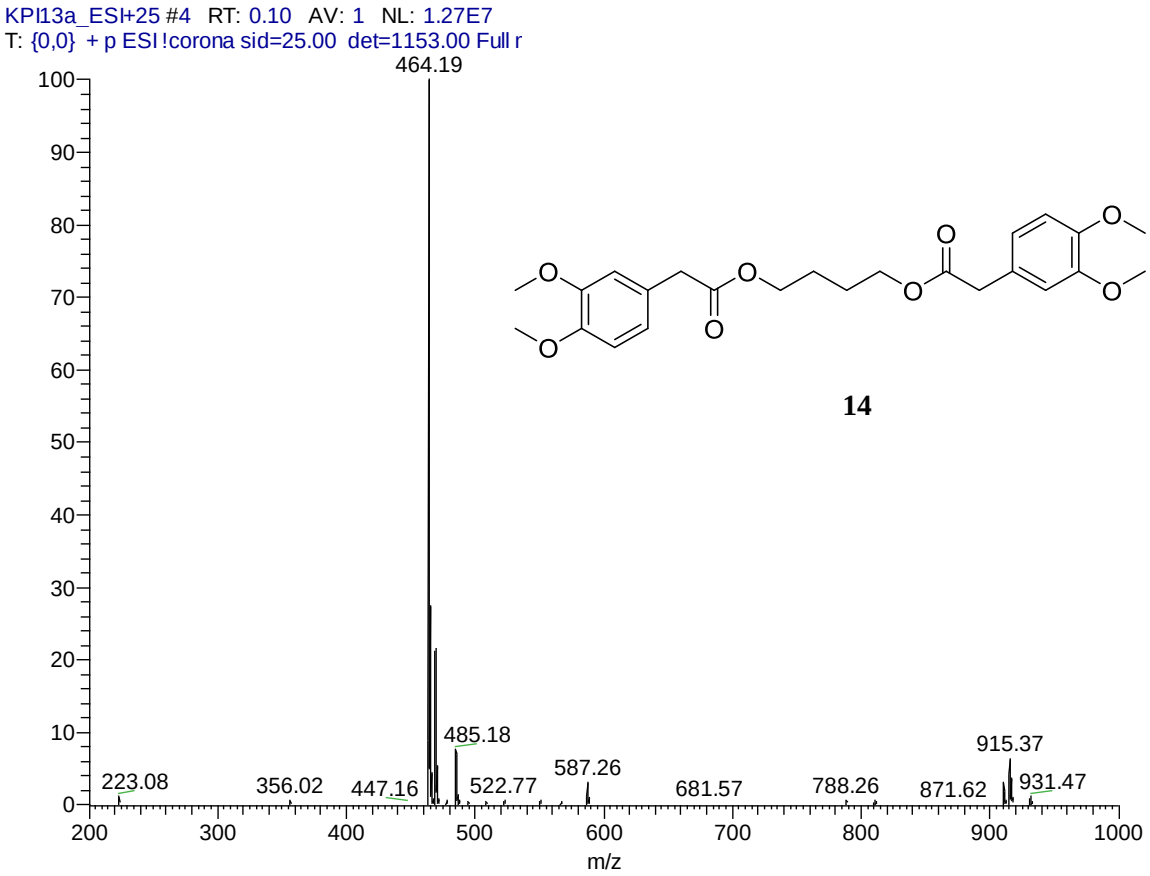


Figure S39: ESI-MS of **14**.

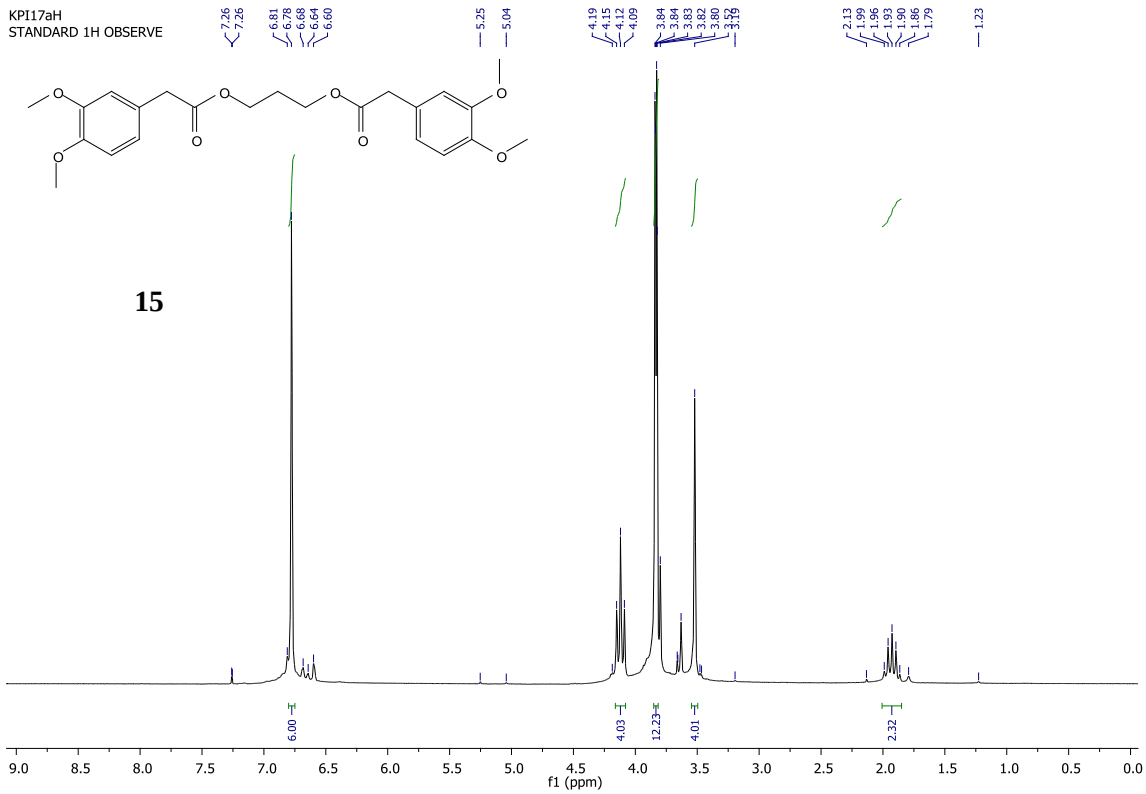


Figure S40: ^{1}H NMR of **15**.

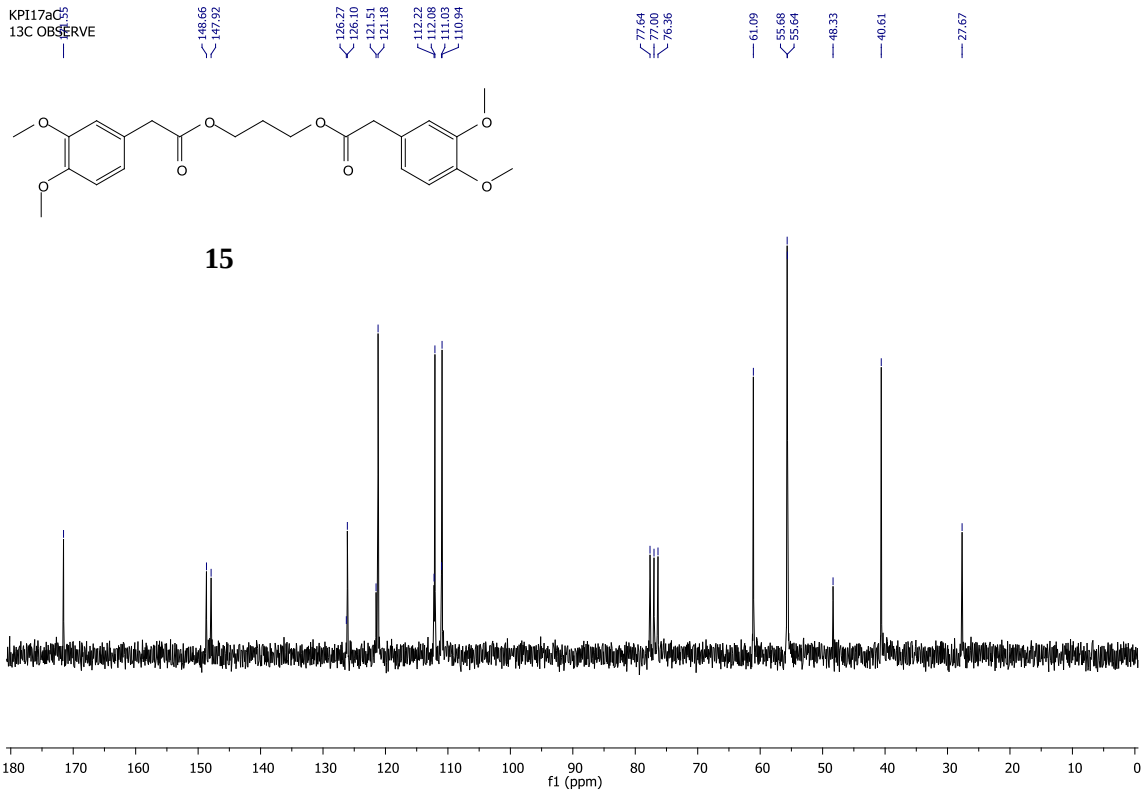


Figure S41: ^{13}C NMR of **15**.

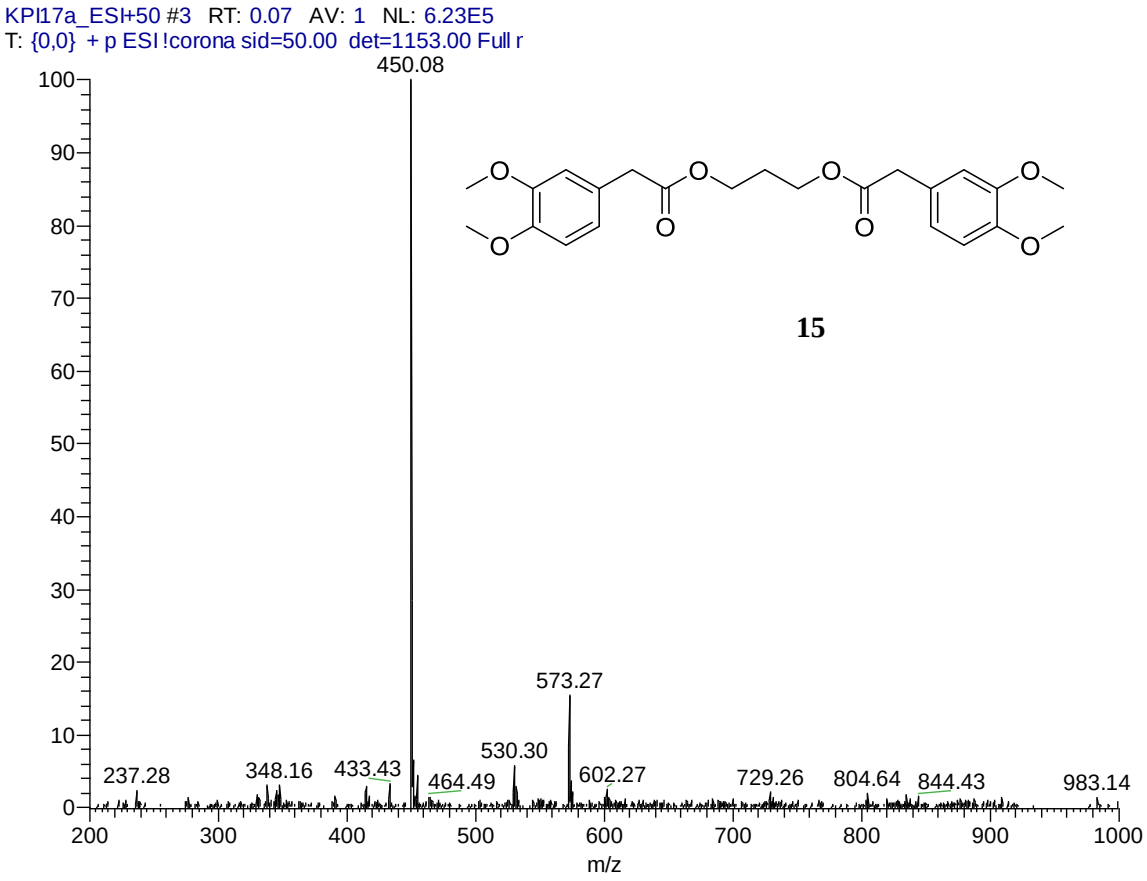


Figure S42: ESI-MS of **15**.

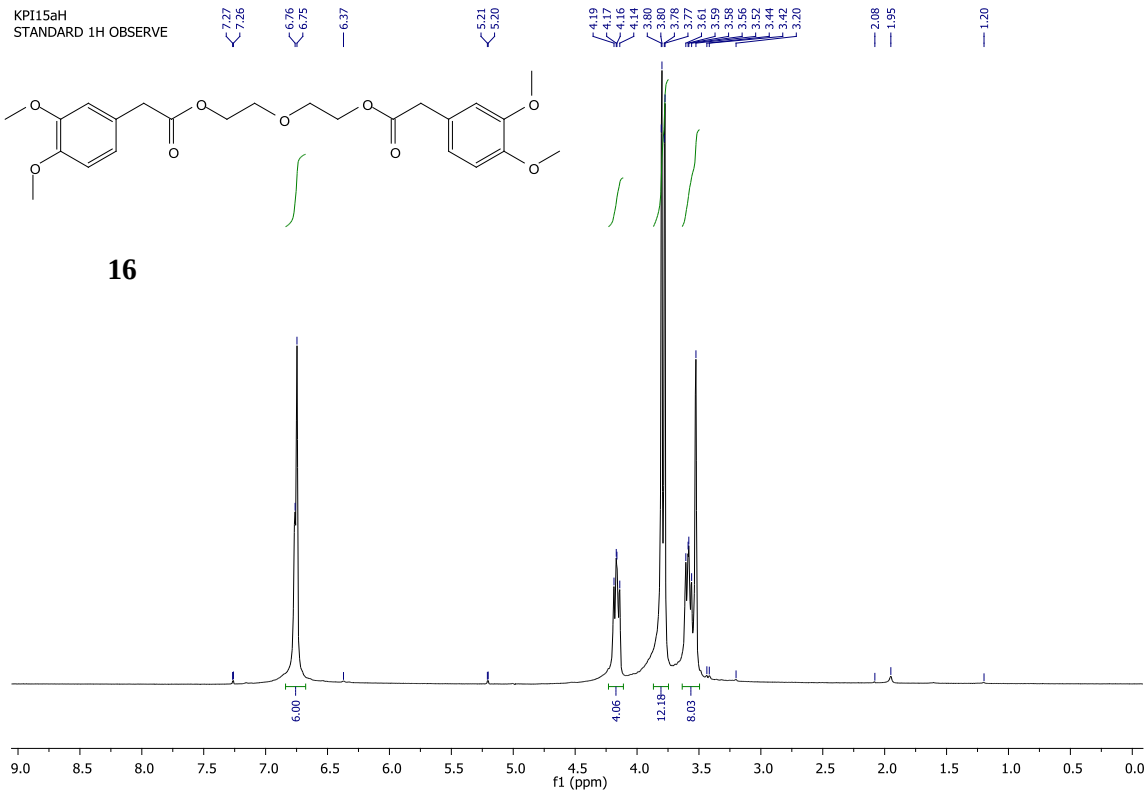


Figure S43: ^{1}H NMR of **16**.

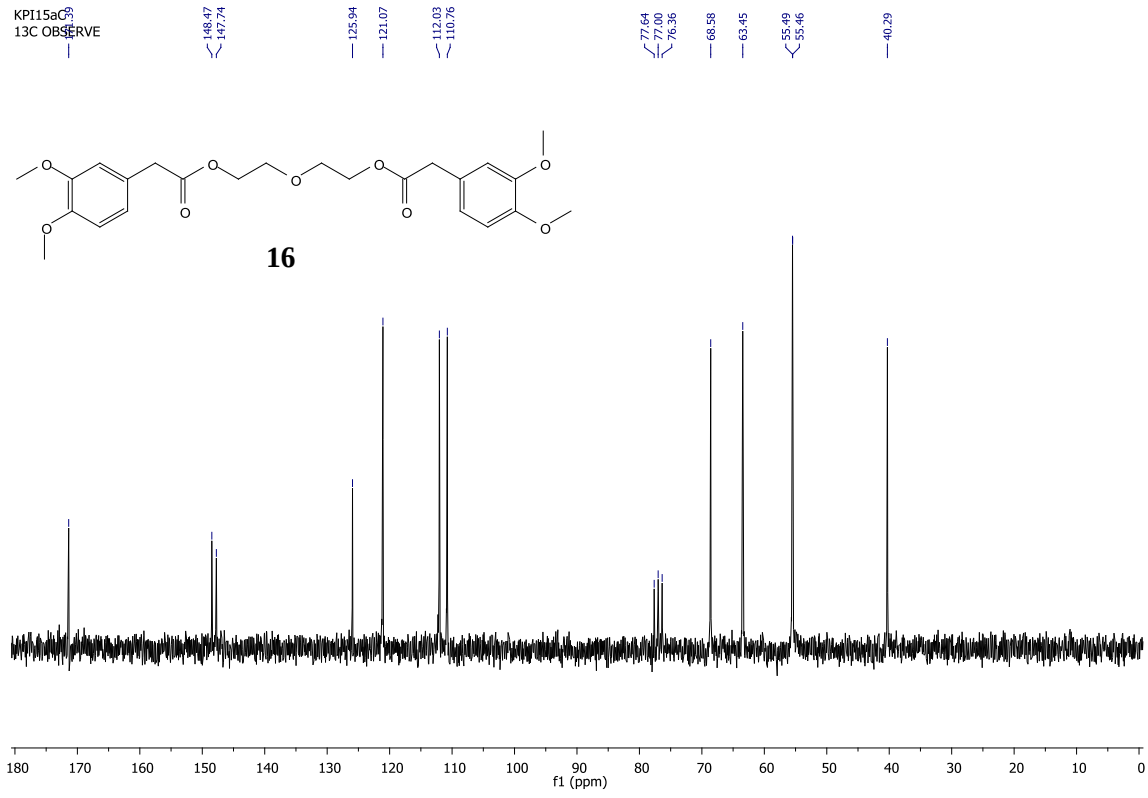


Figure S44: ^{13}C NMR of **16**.

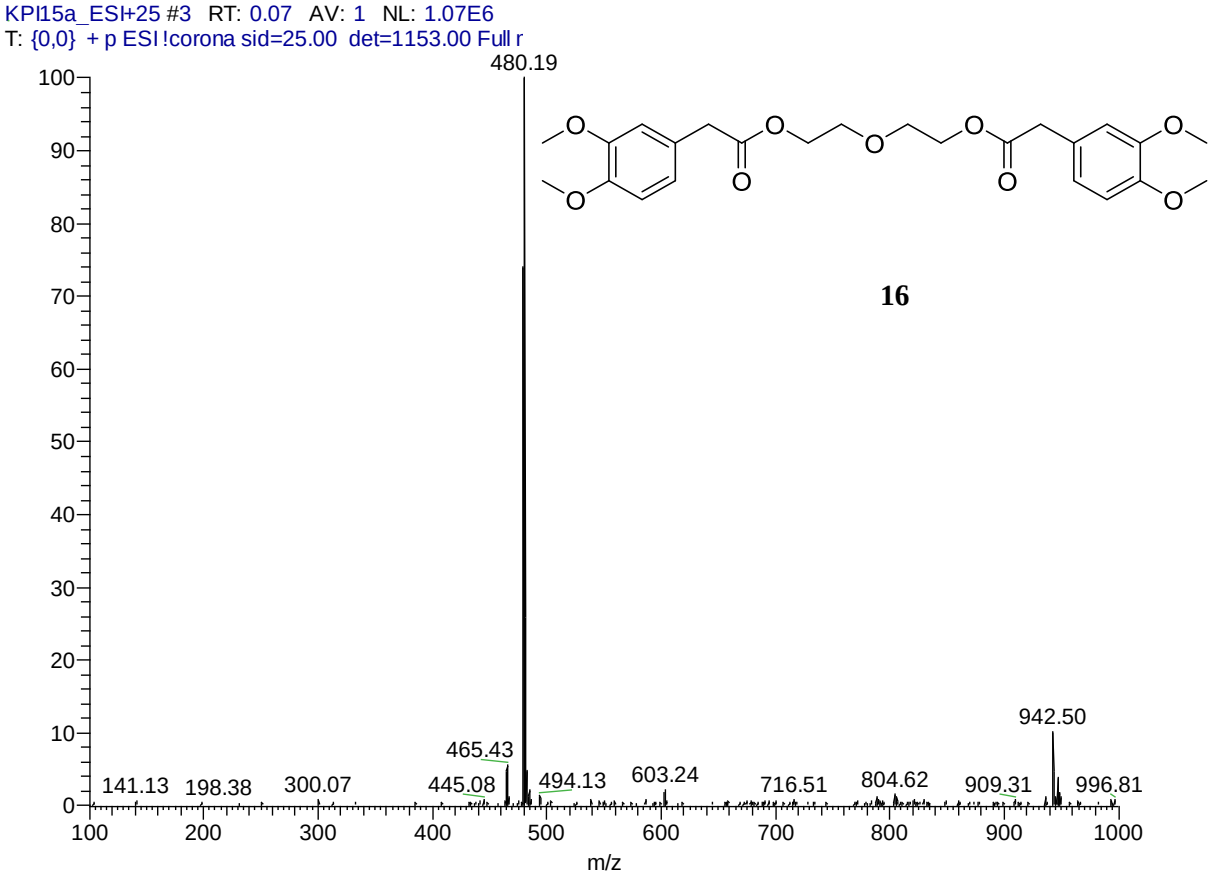


Figure S45: ESI-MS of **16**.

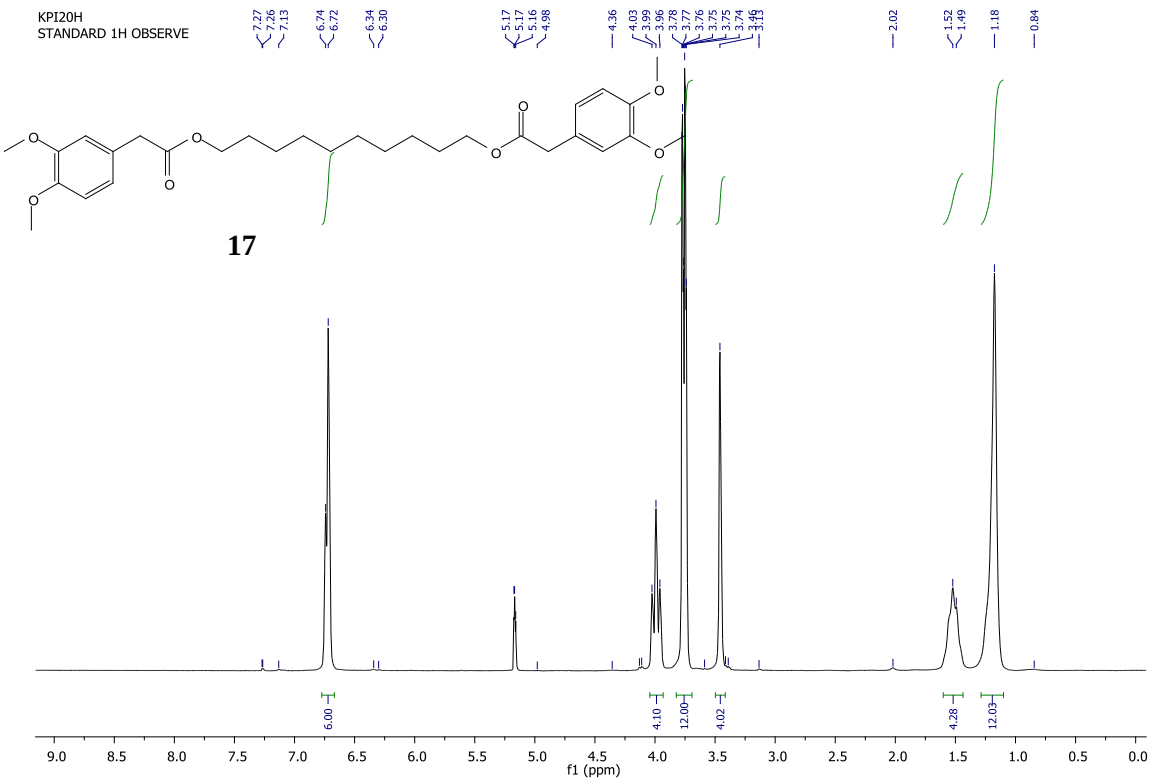


Figure S46: ^{1}H NMR of **17**.

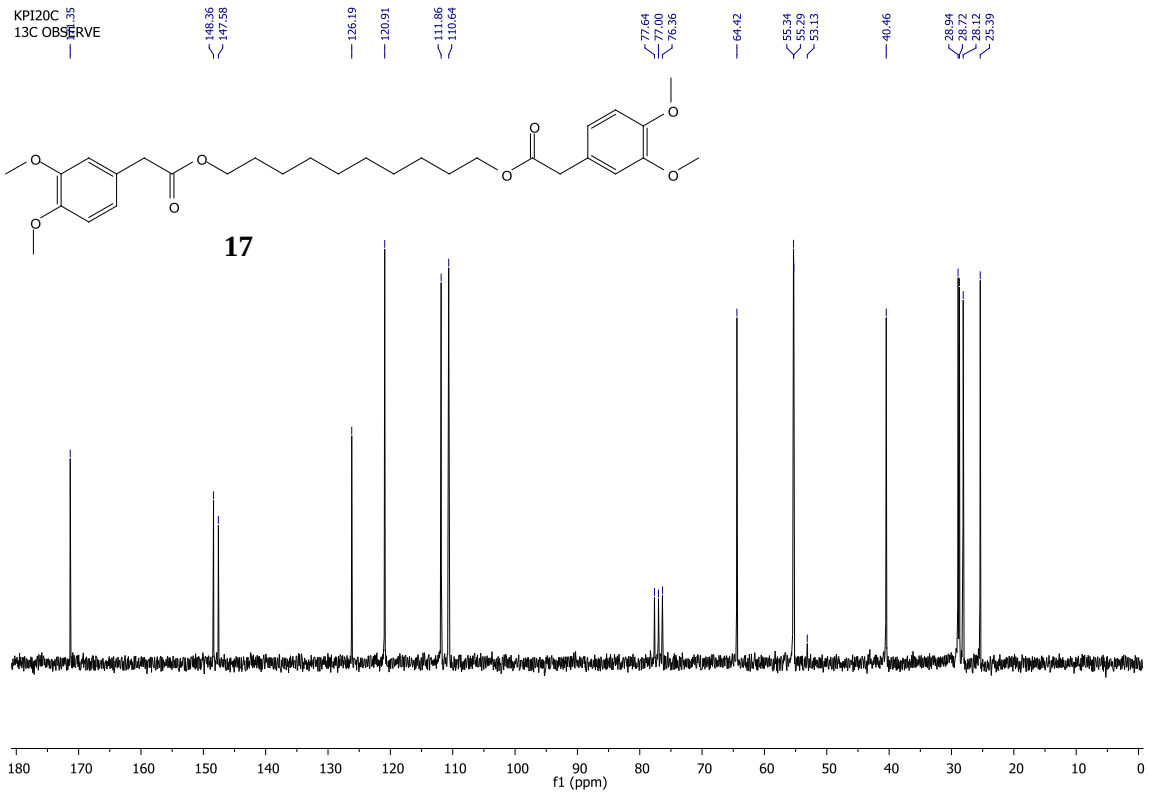


Figure S47: ^{13}C NMR of **17**.

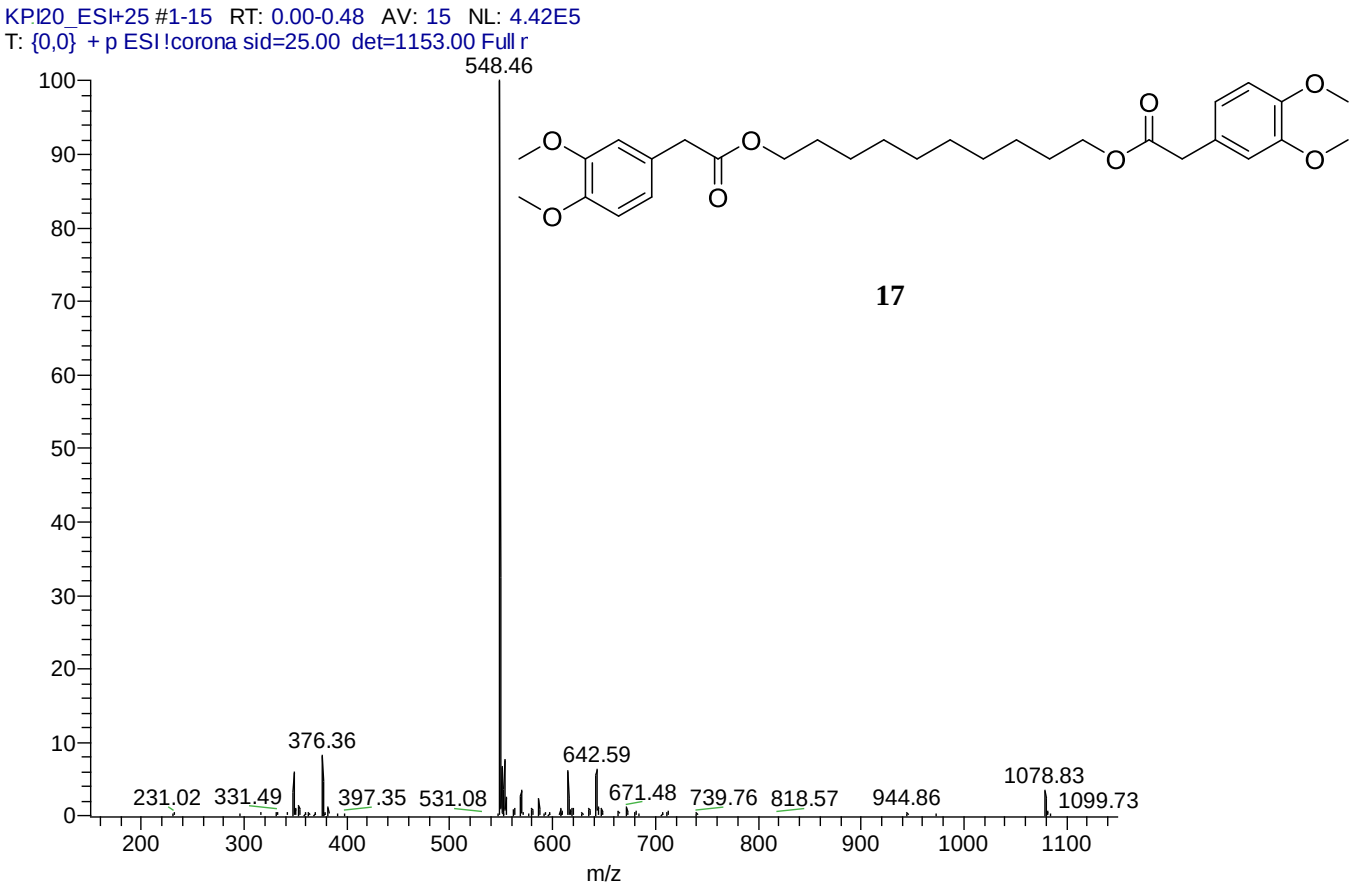


Figure S48: ESI-MS of **17**.

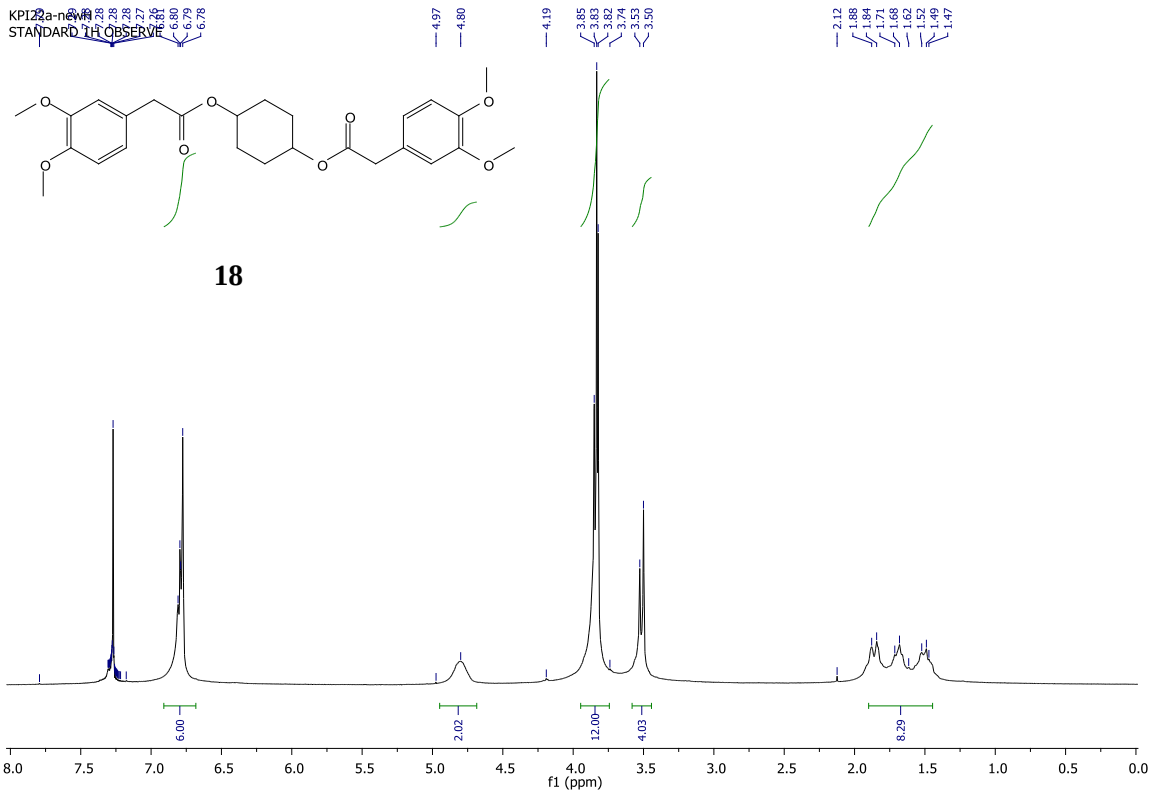


Figure S49: ^{1}H NMR of **18**.

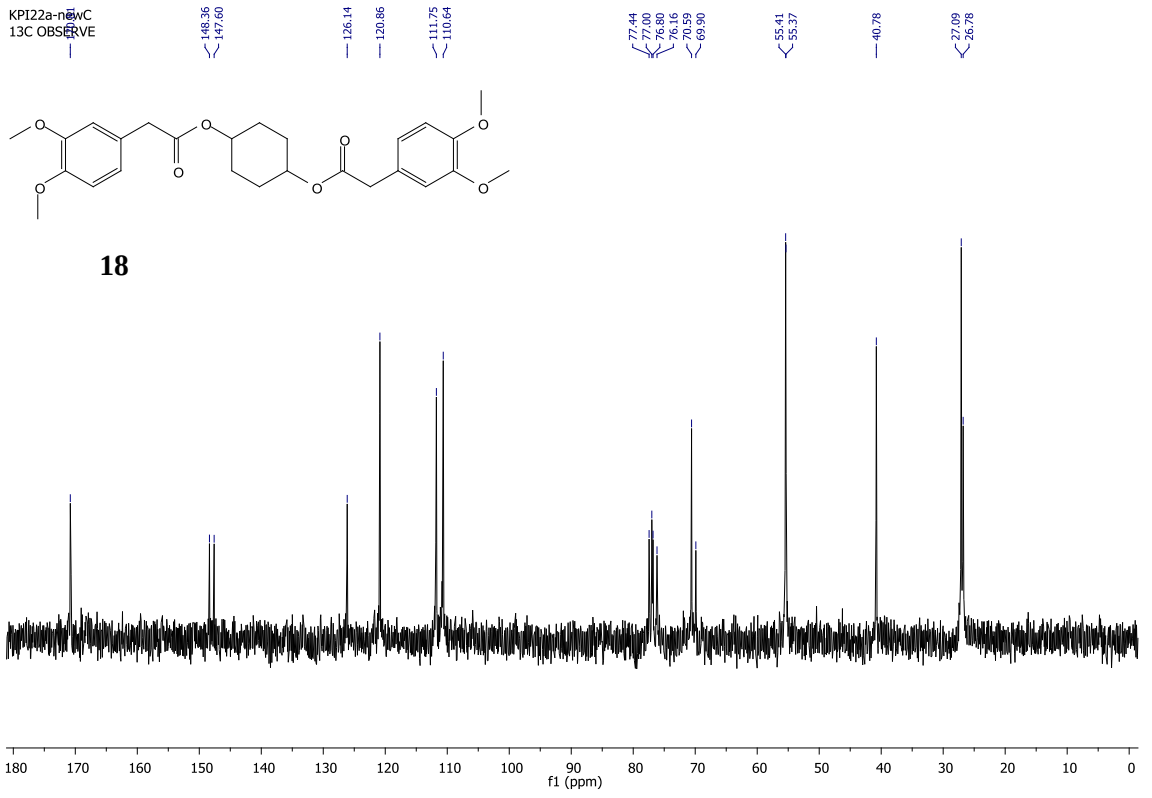


Figure S50: ^{13}C NMR of **18**.

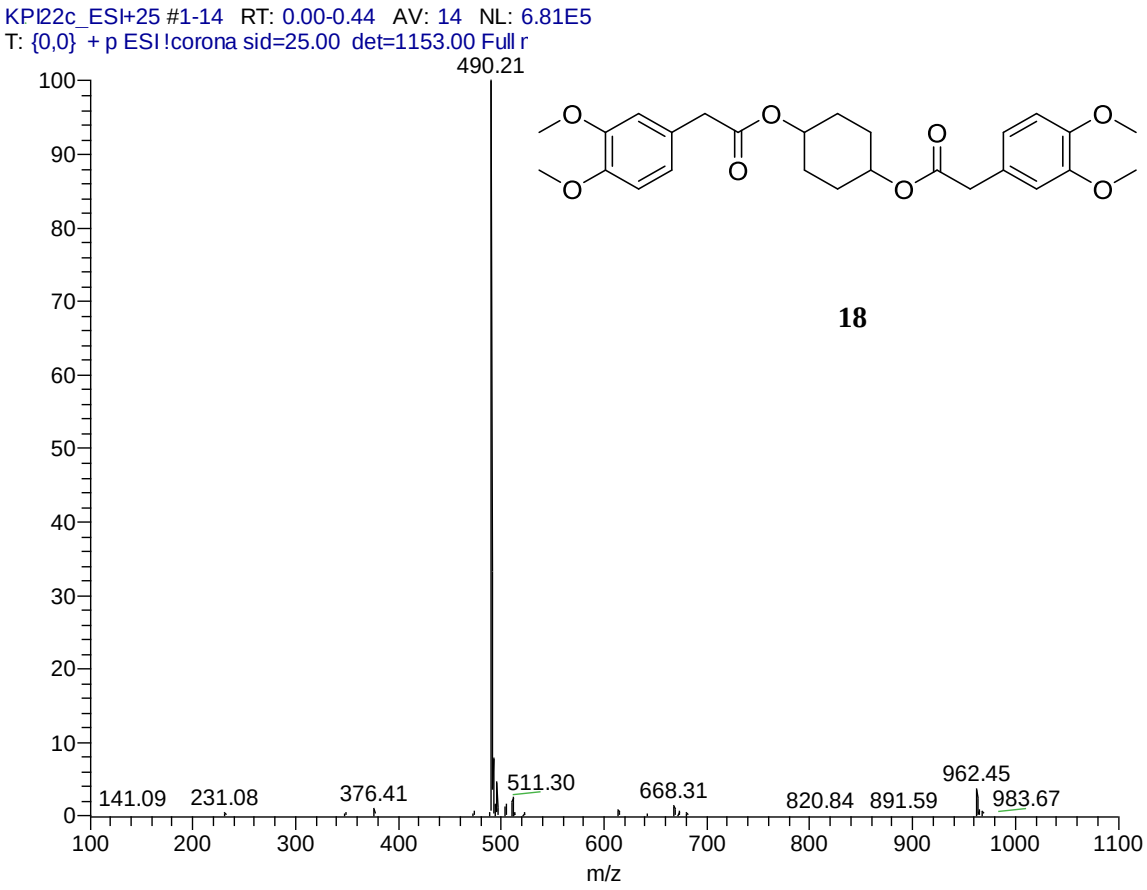


Figure S51: ESI-MS of **18**.

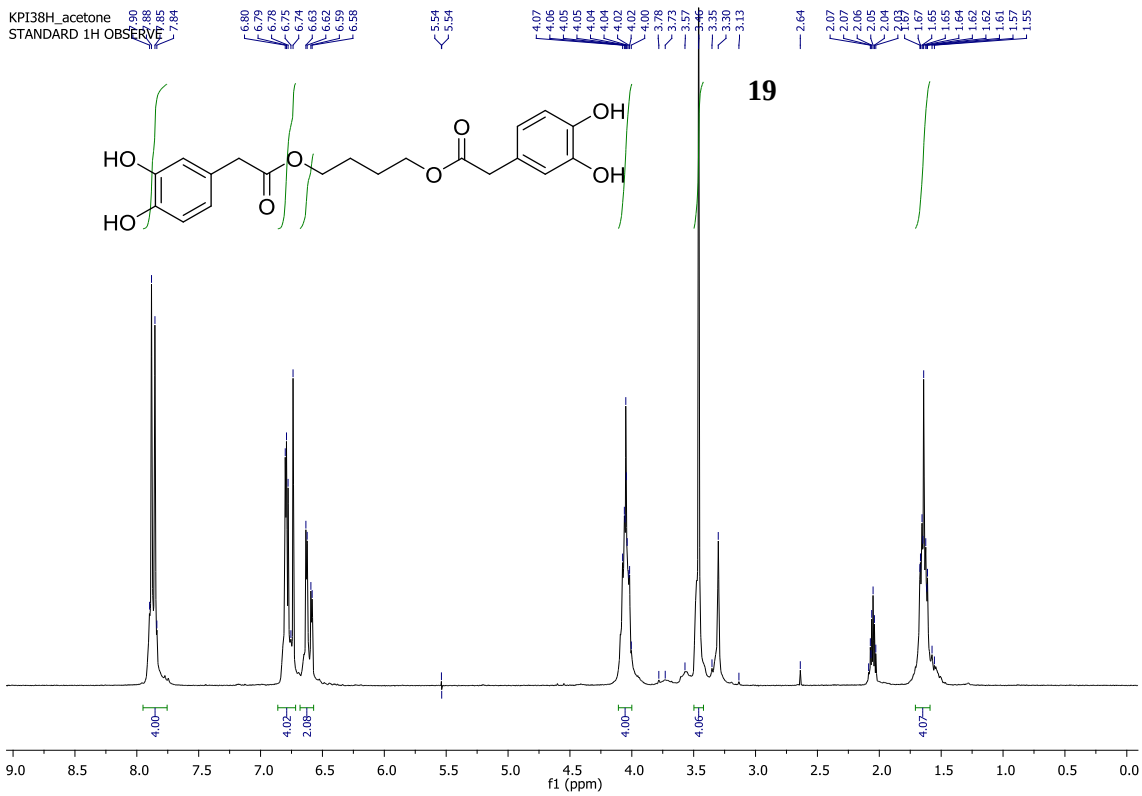


Figure S52: ^{1}H NMR of **19**.

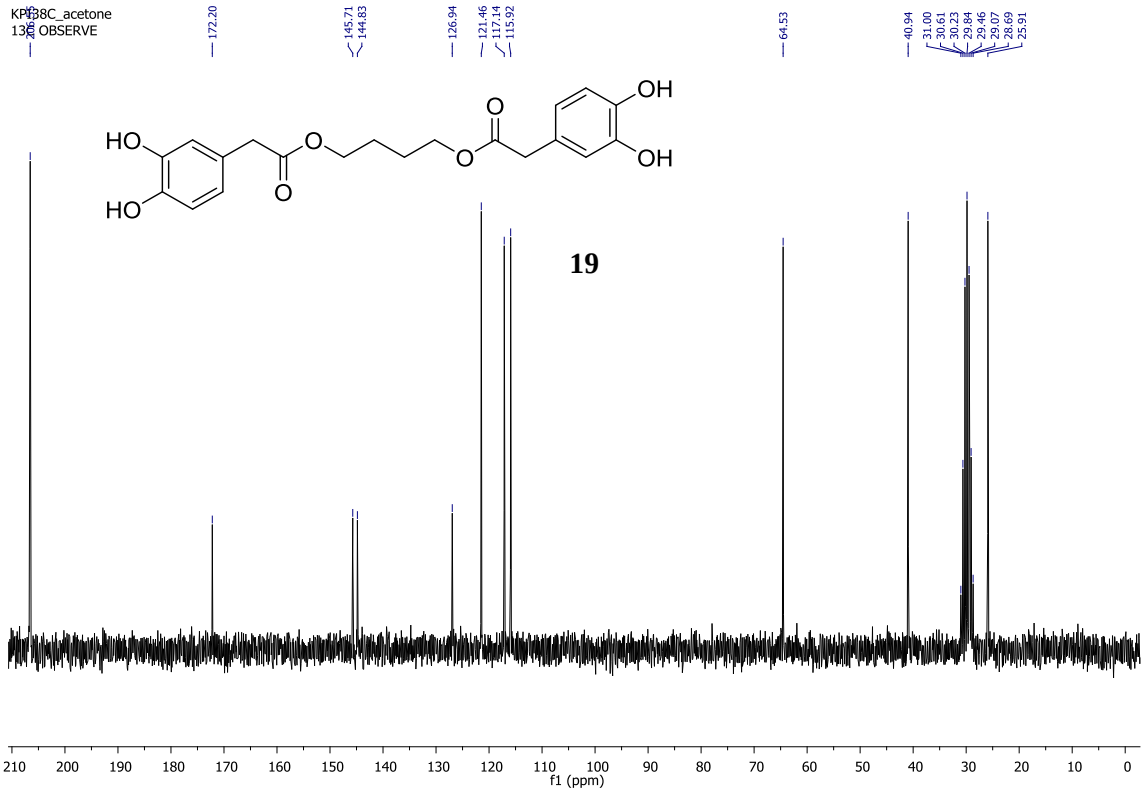


Figure S53: ^{13}C NMR of **19**.

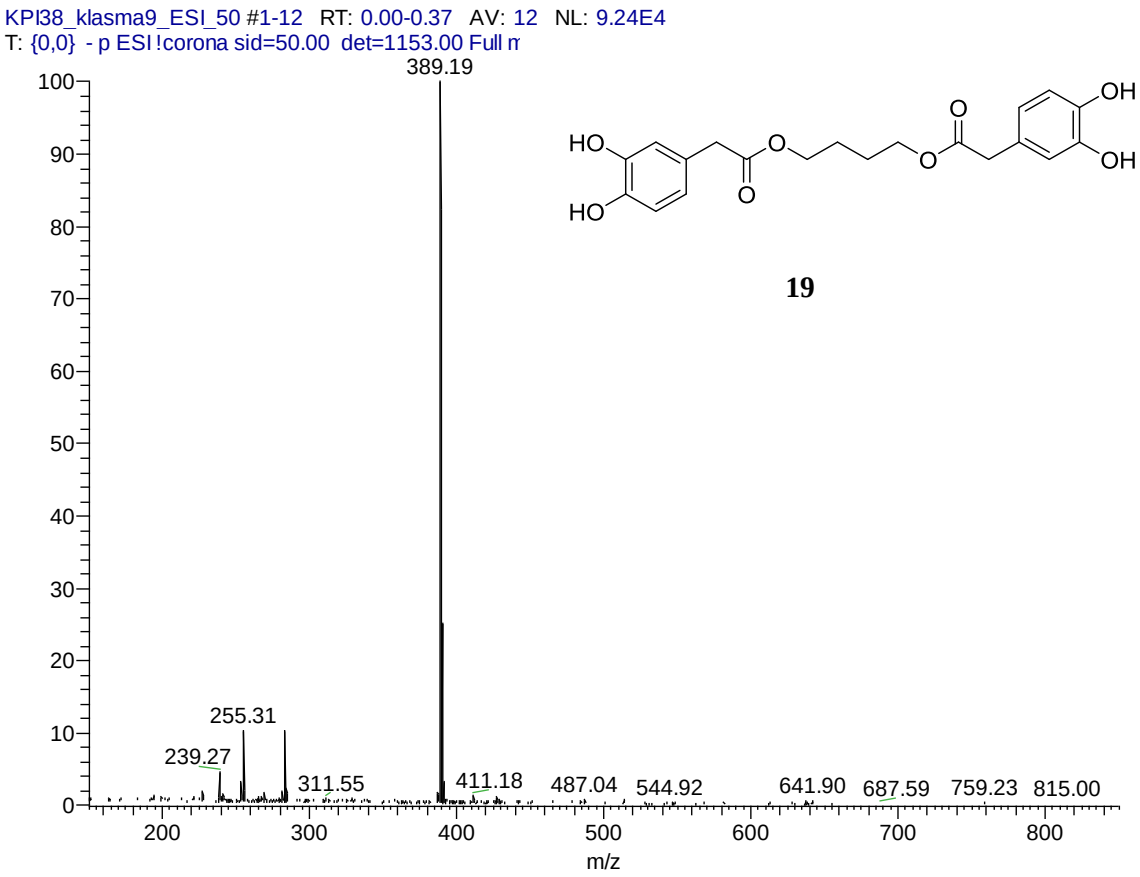


Figure S54: ESI-MS of **19**.

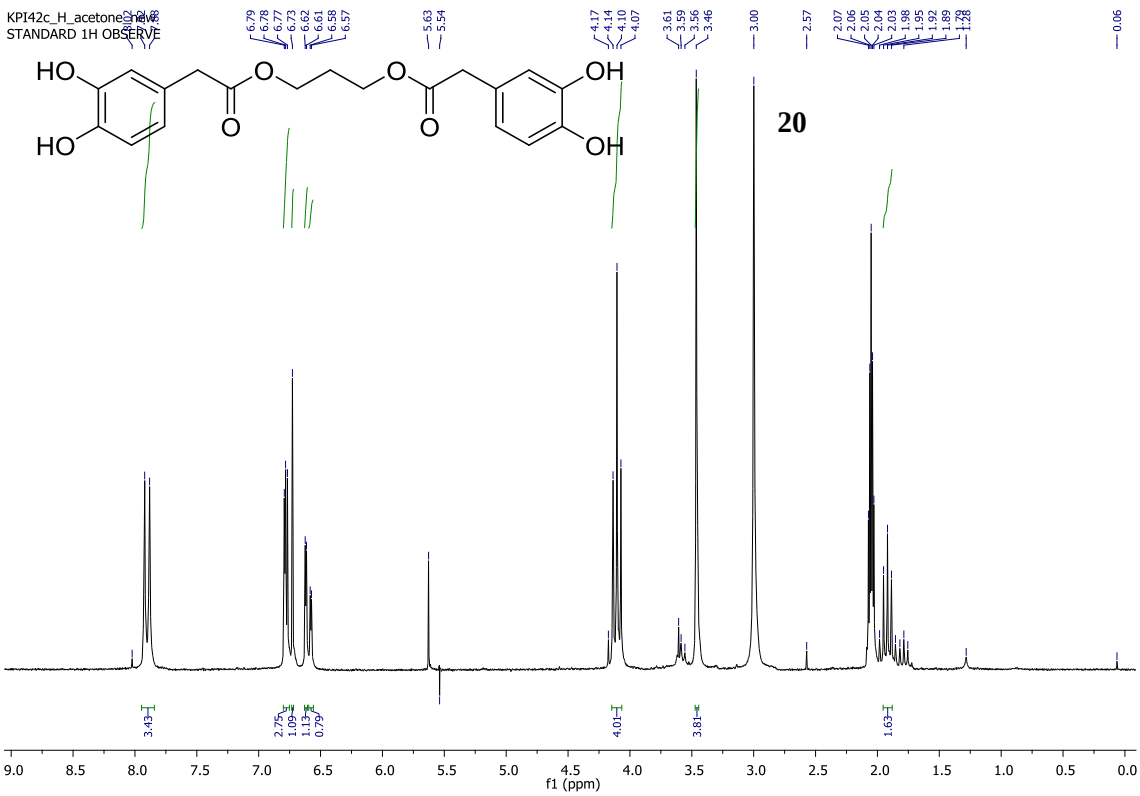


Figure S55: ^{1}H NMR of **20**.

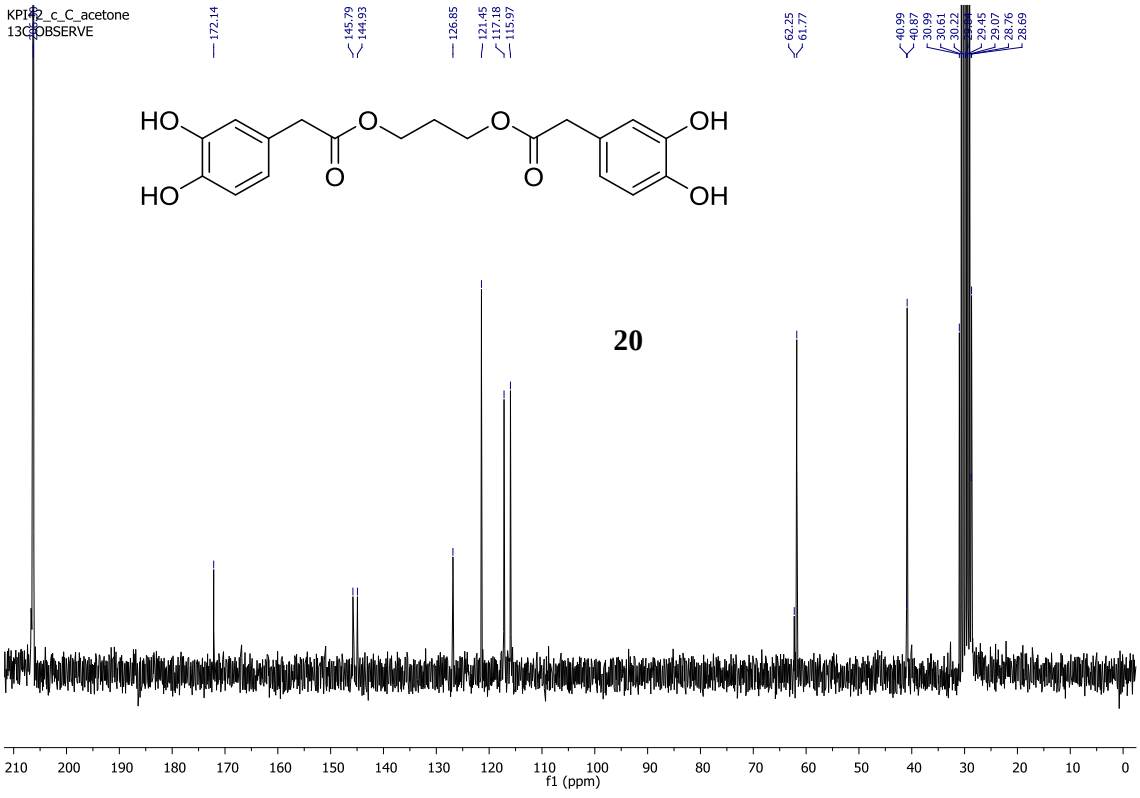


Figure S56: ^{13}C NMR of **20**.

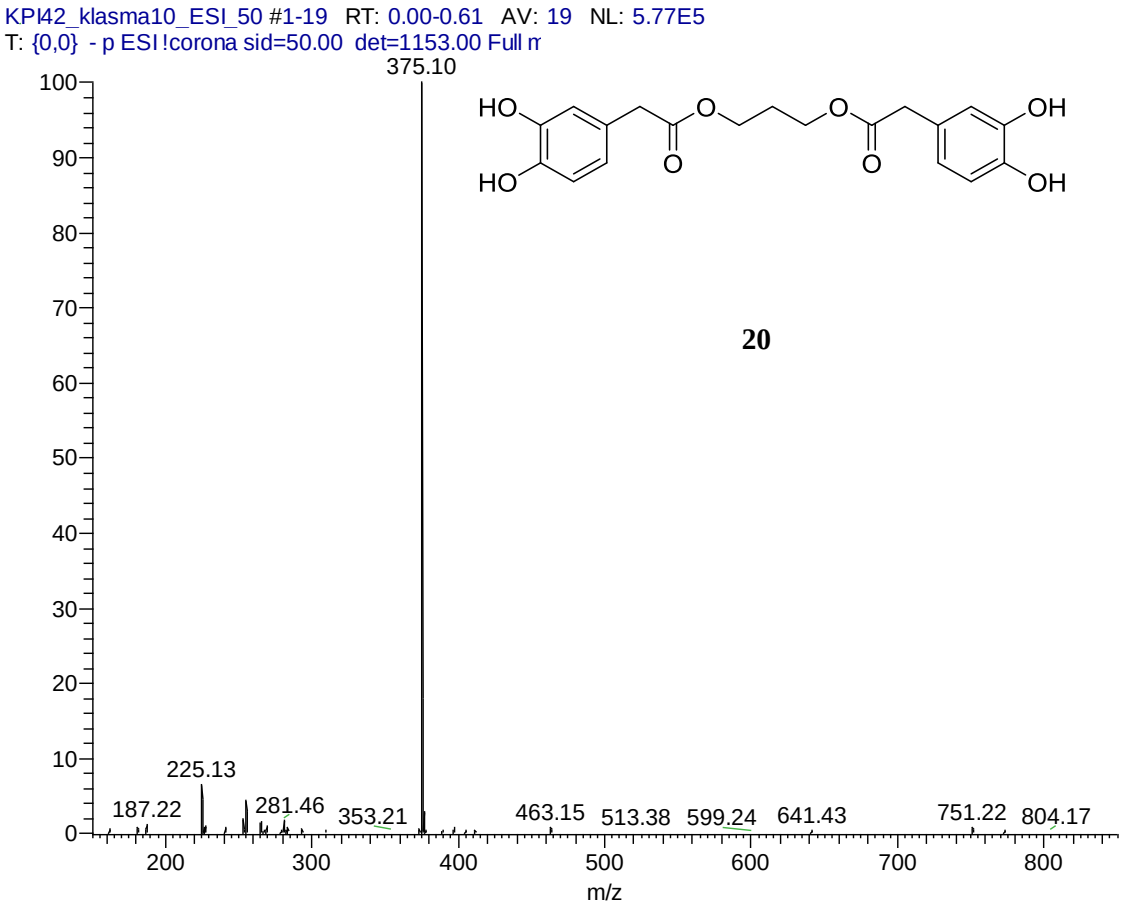


Figure S57: ESI-MS of **20**.

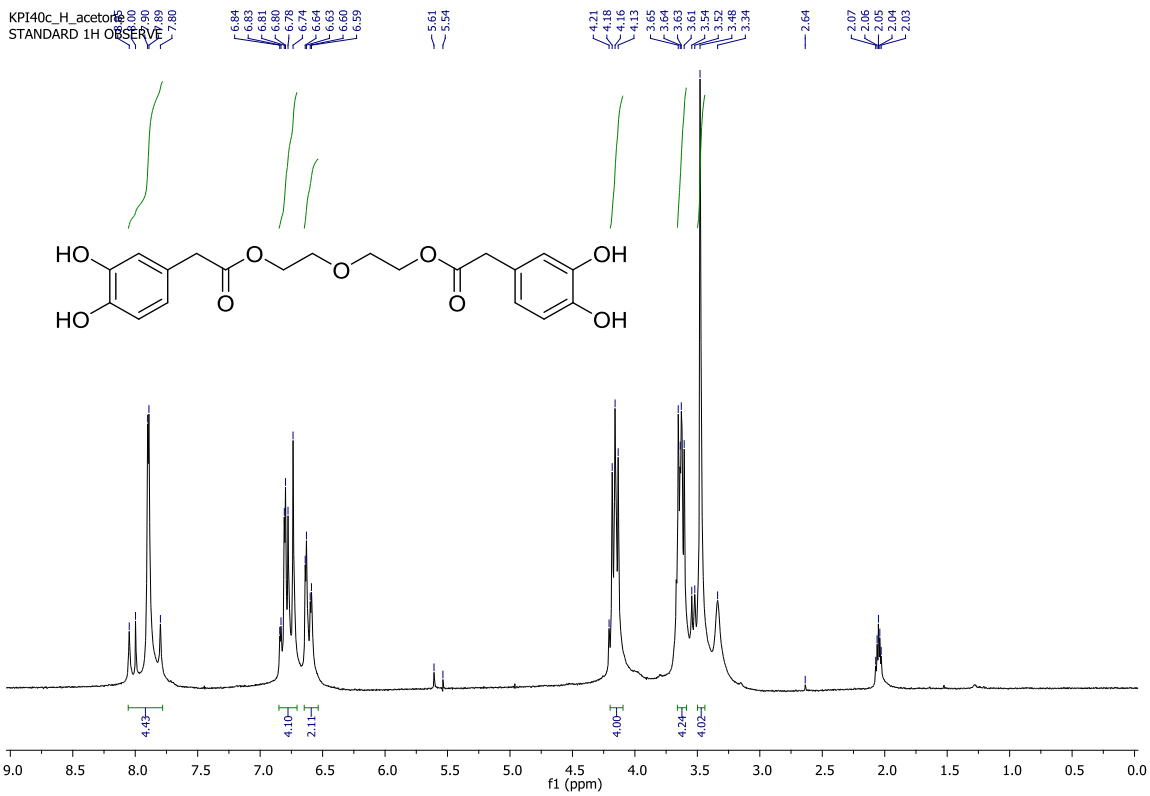


Figure S58: ^{1}H NMR of **21**.

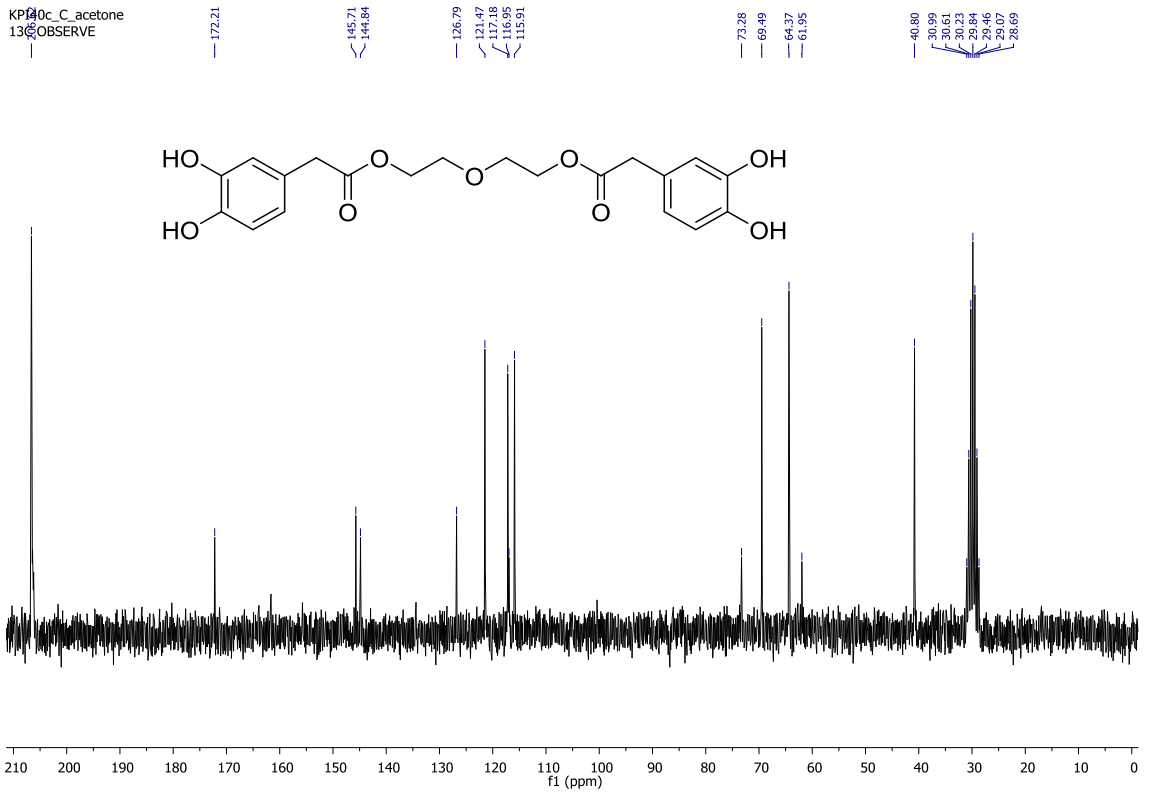


Figure S59: ^{13}C NMR of **21**.

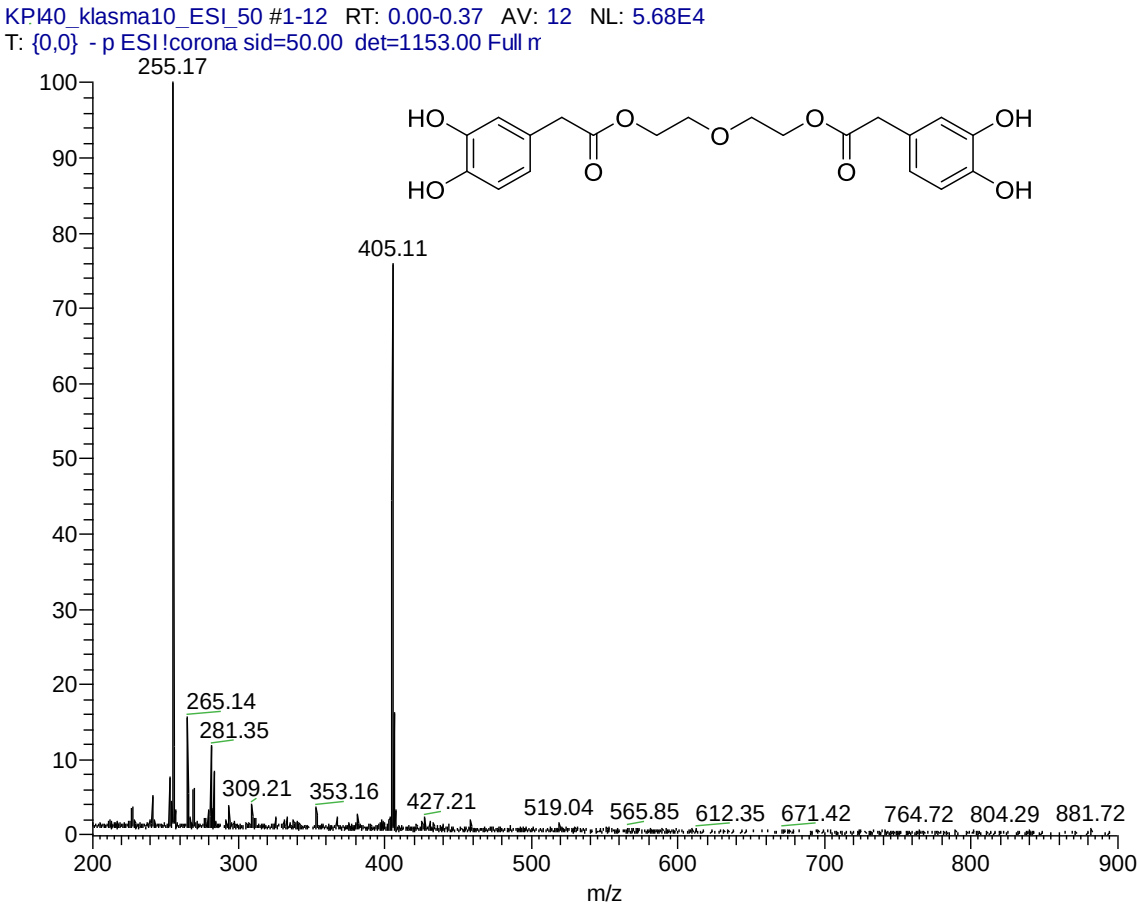


Figure S60: ESI-MS of **21**.

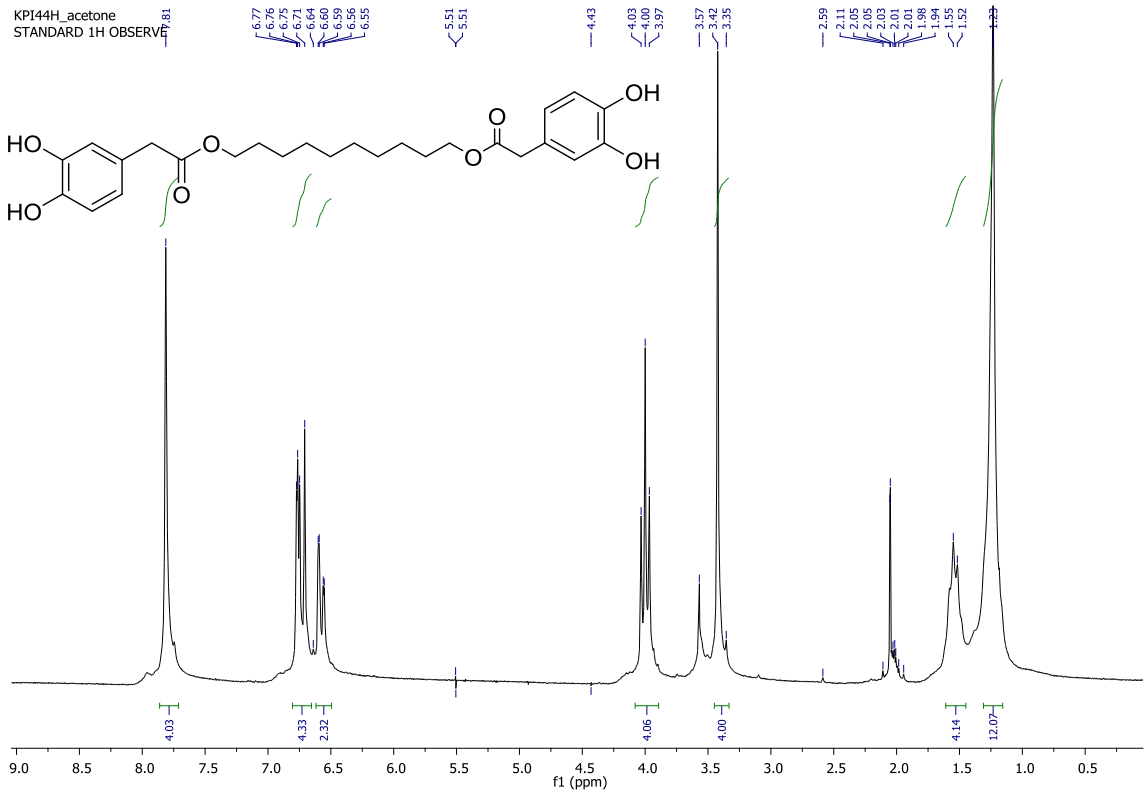


Figure S61: ^{1}H NMR of **22**.

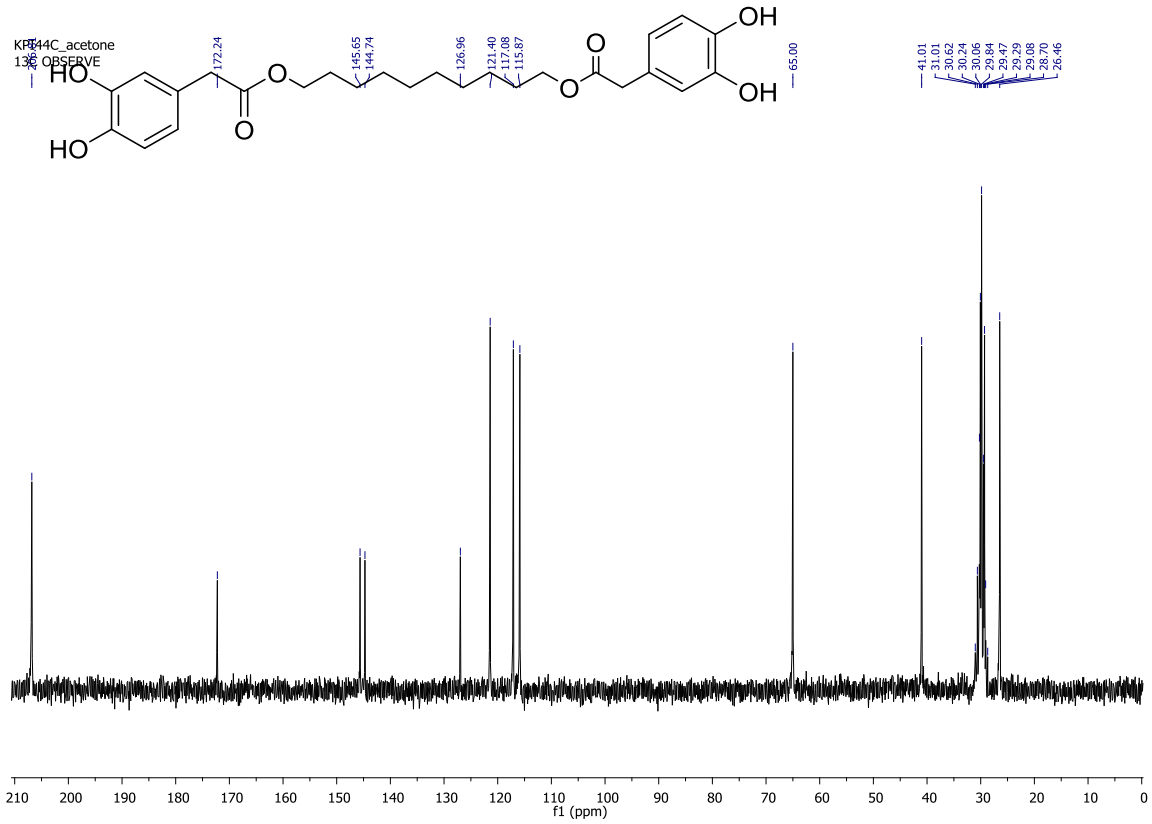


Figure S62: ^{13}C NMR of **22**.

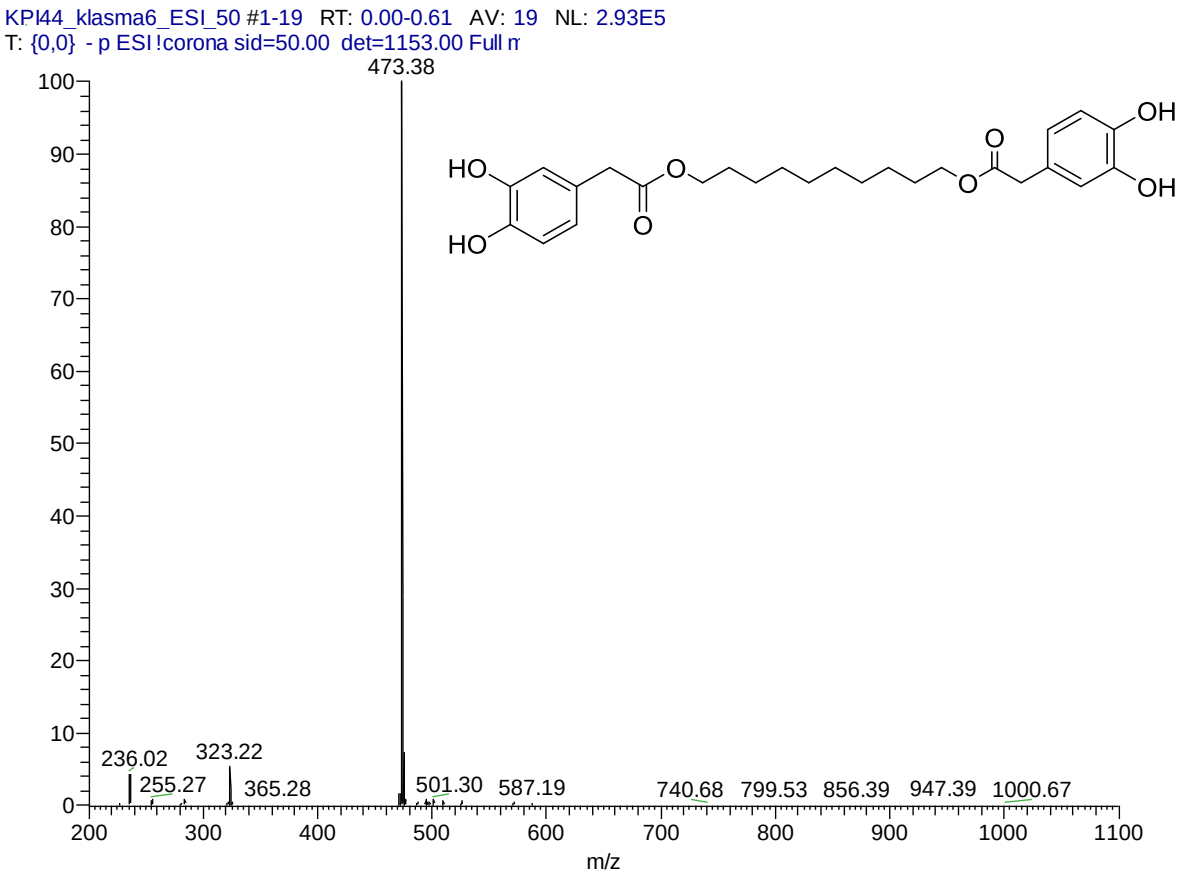


Figure S63: ESI-MS of **22**.

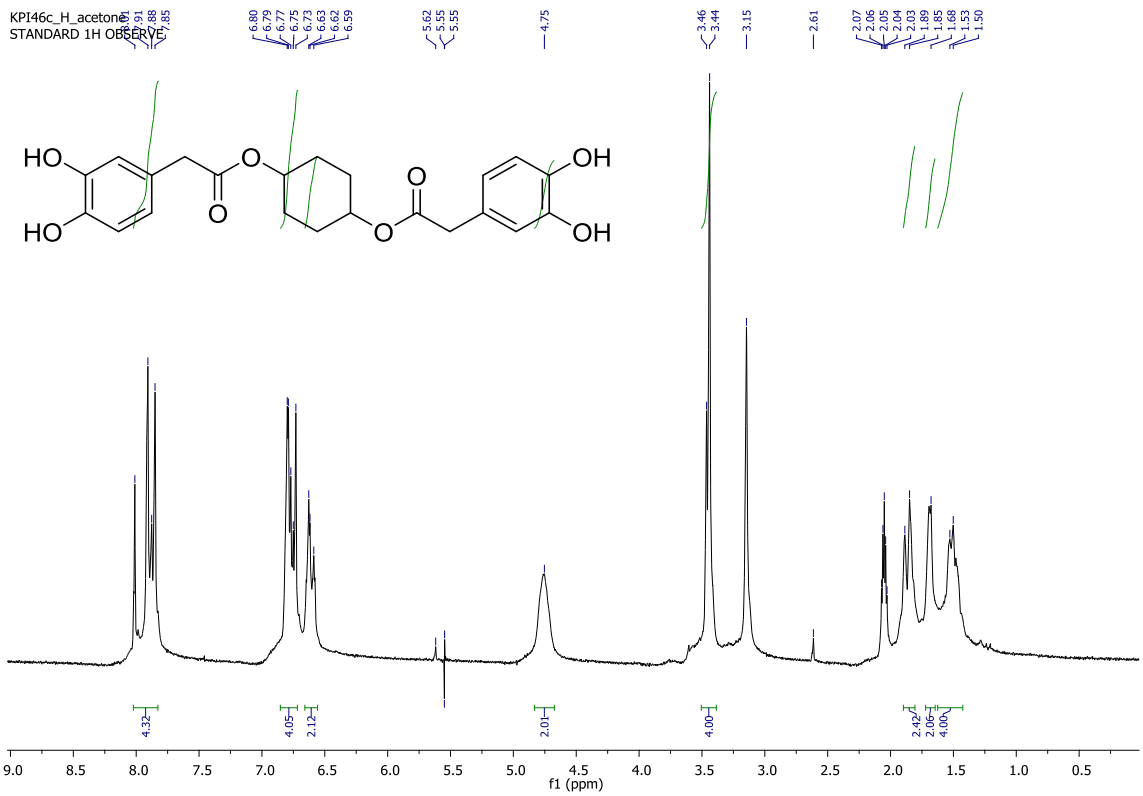


Figure S64: ^{1}H NMR of **23**.

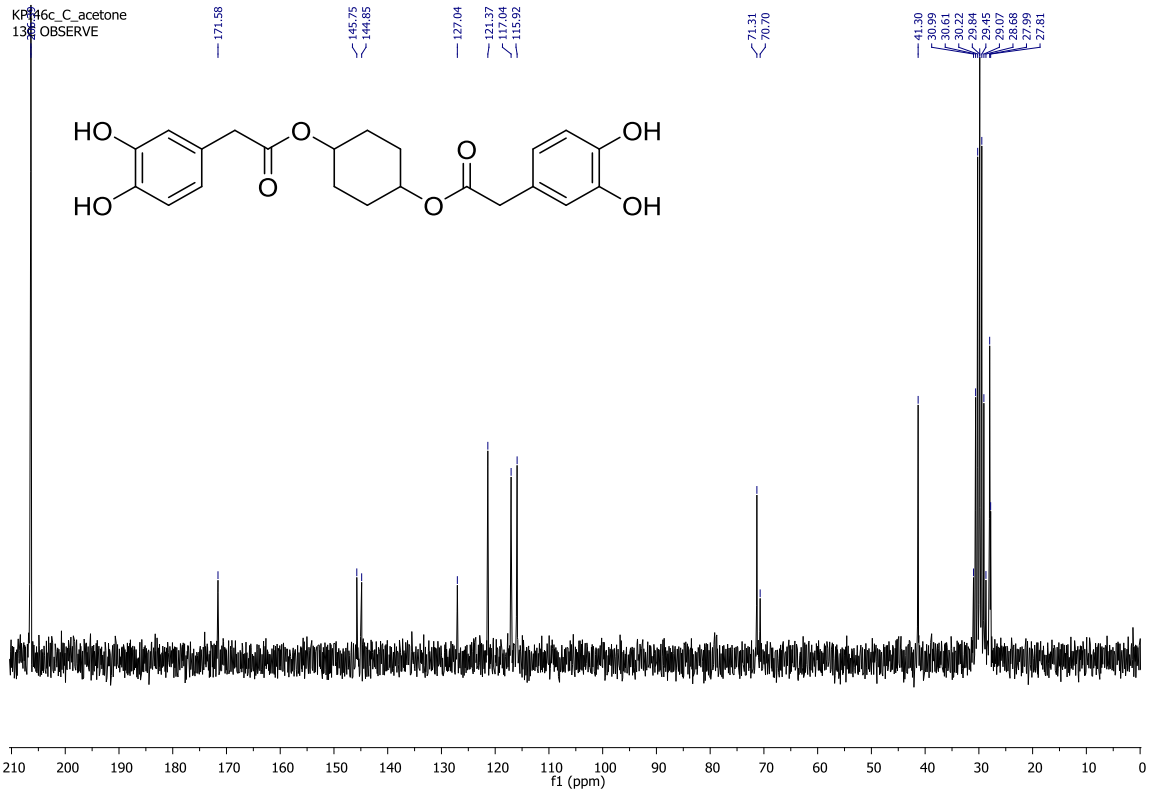


Figure S65: ^{13}C NMR of **23**.

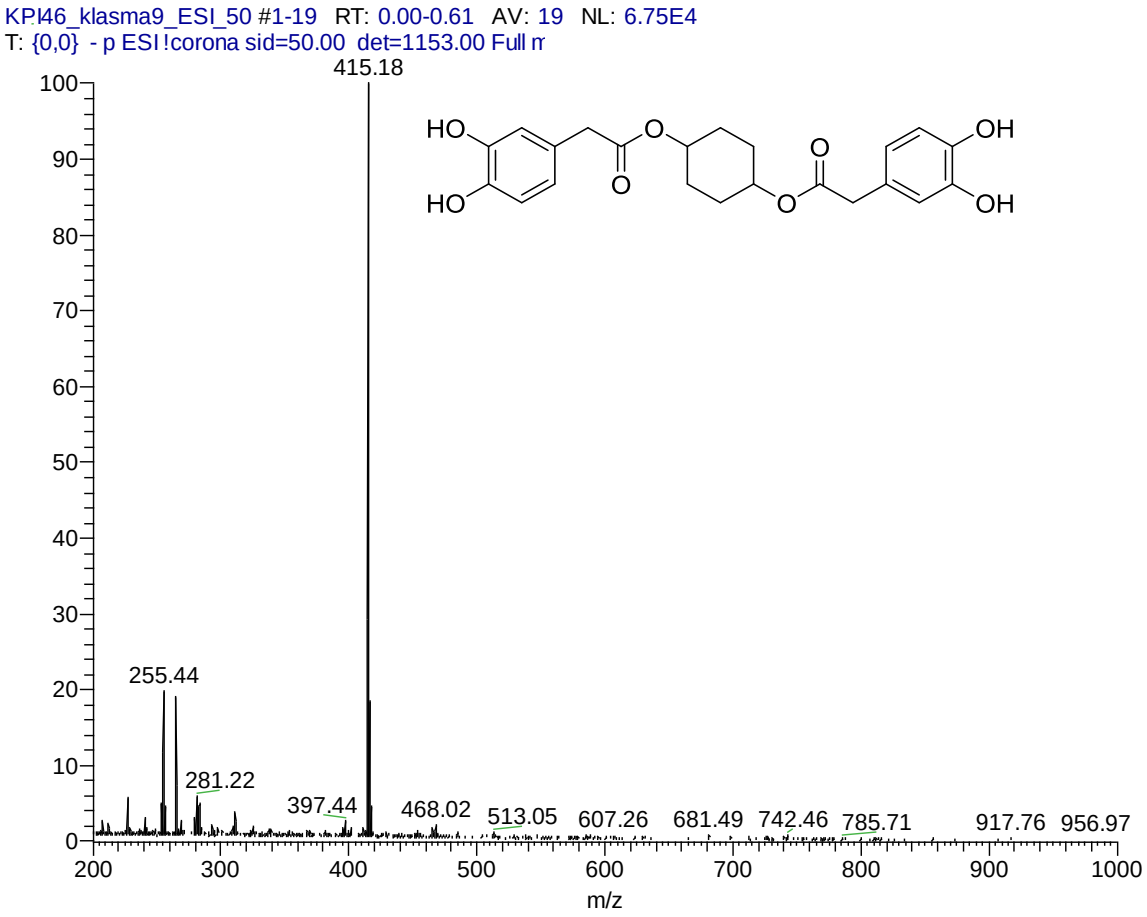


Figure S66: ESI-MS of **23**.

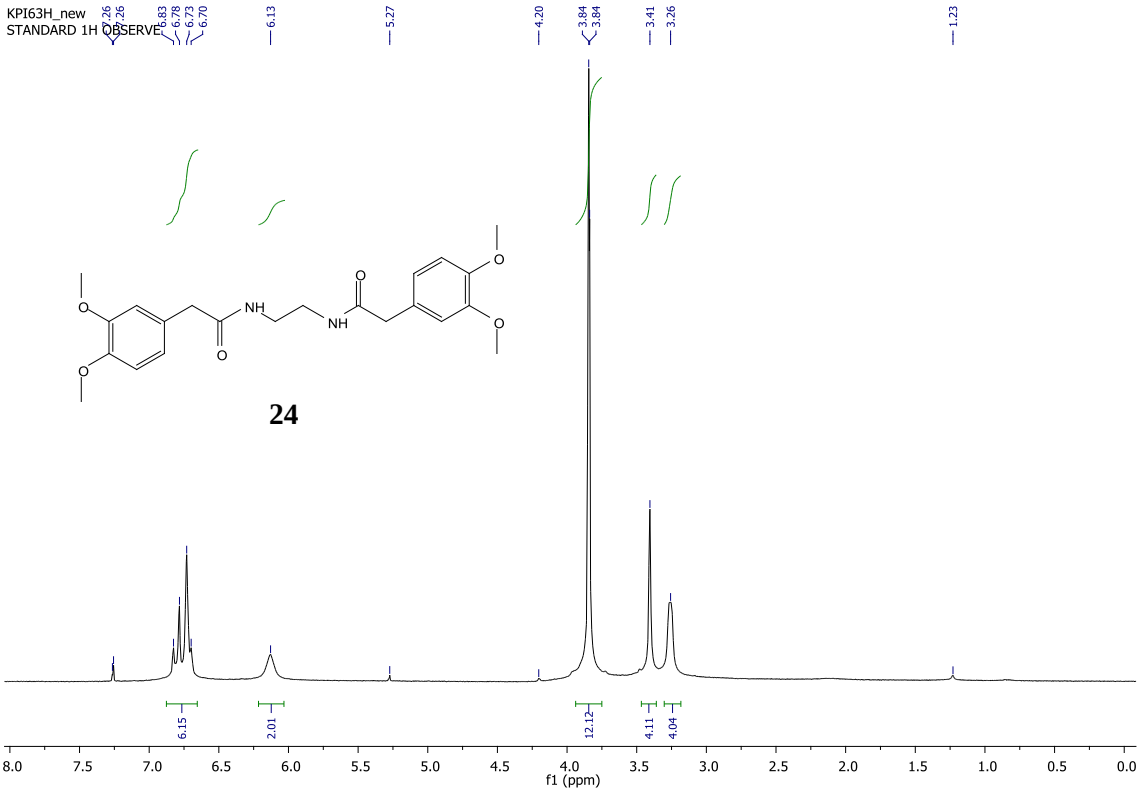


Figure S67: ^{1}H NMR of **24**.

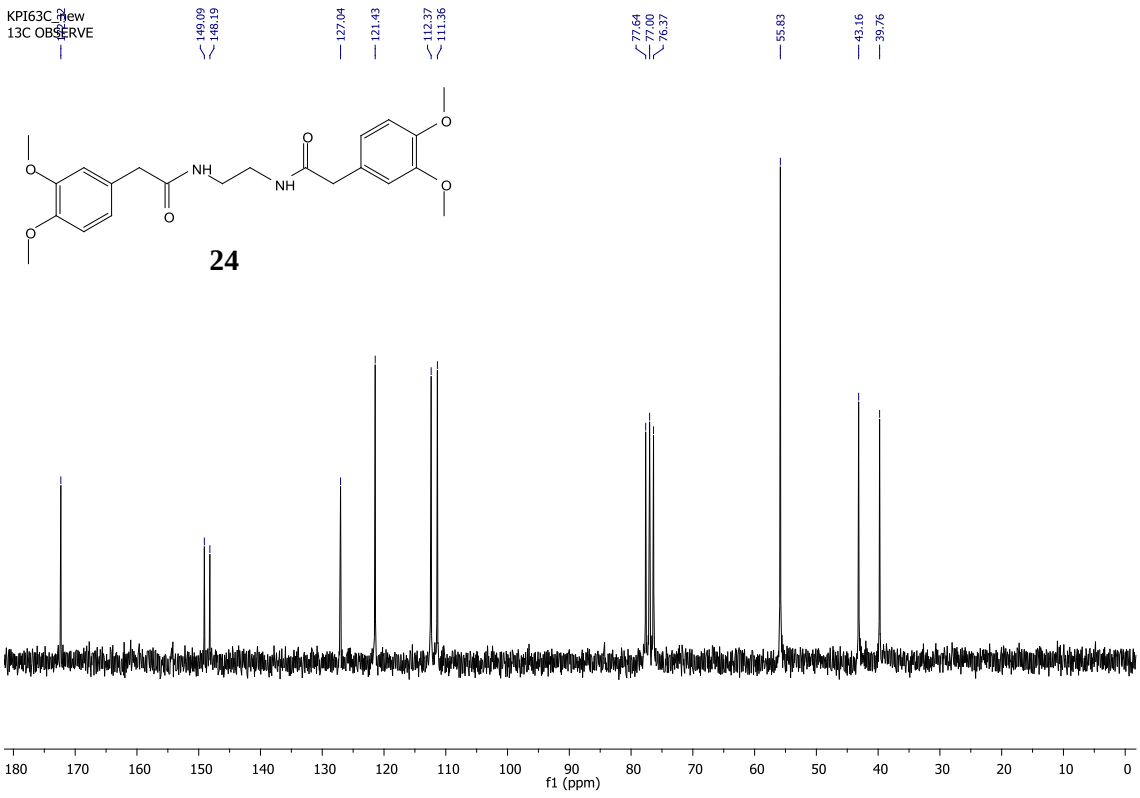


Figure S68: ^{13}C NMR of **24**.

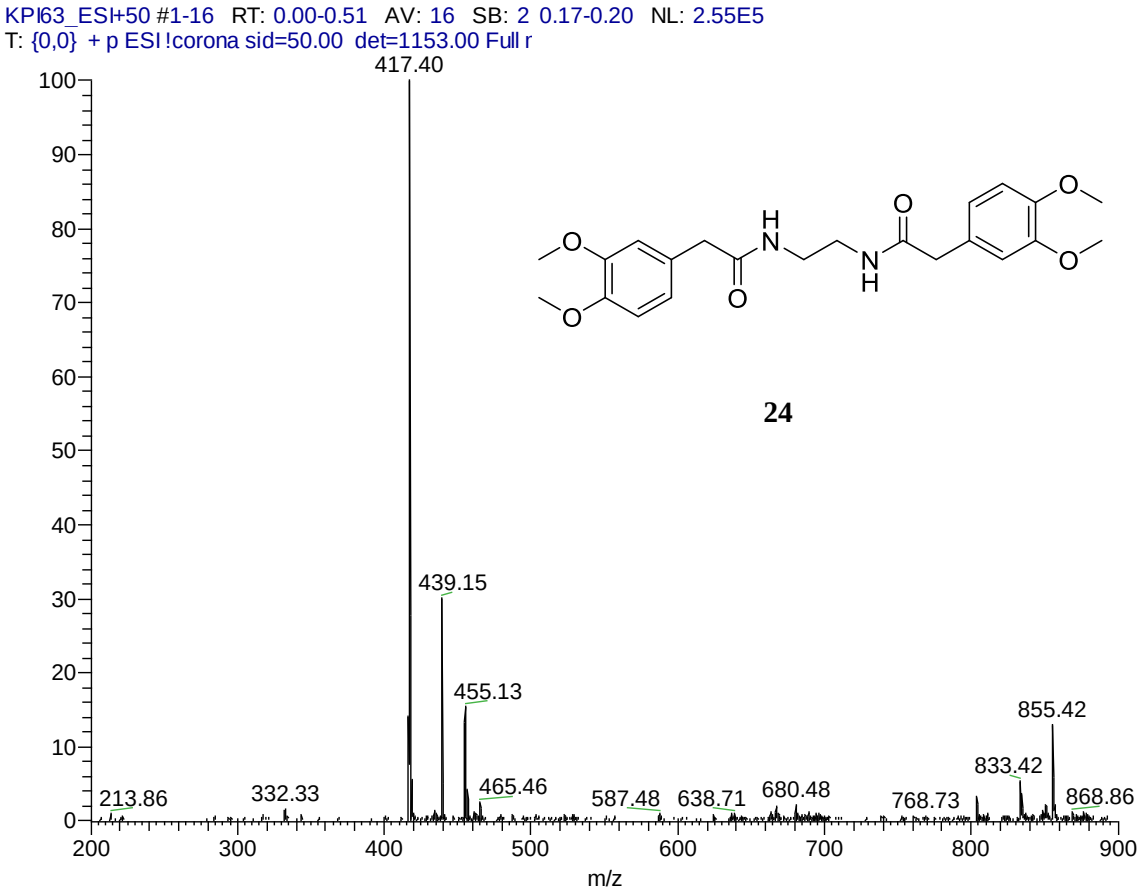


Figure S69: ESI-MS of **24**.

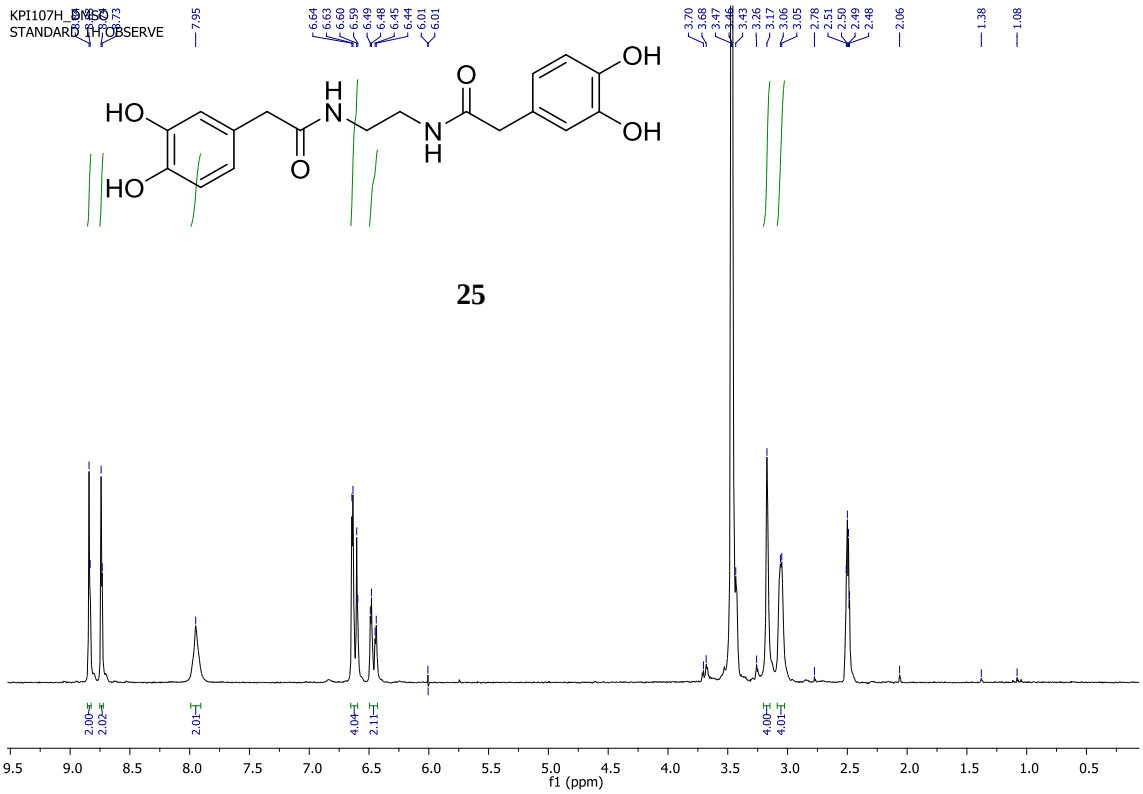


Figure S70: ^{1}H NMR of **25**.

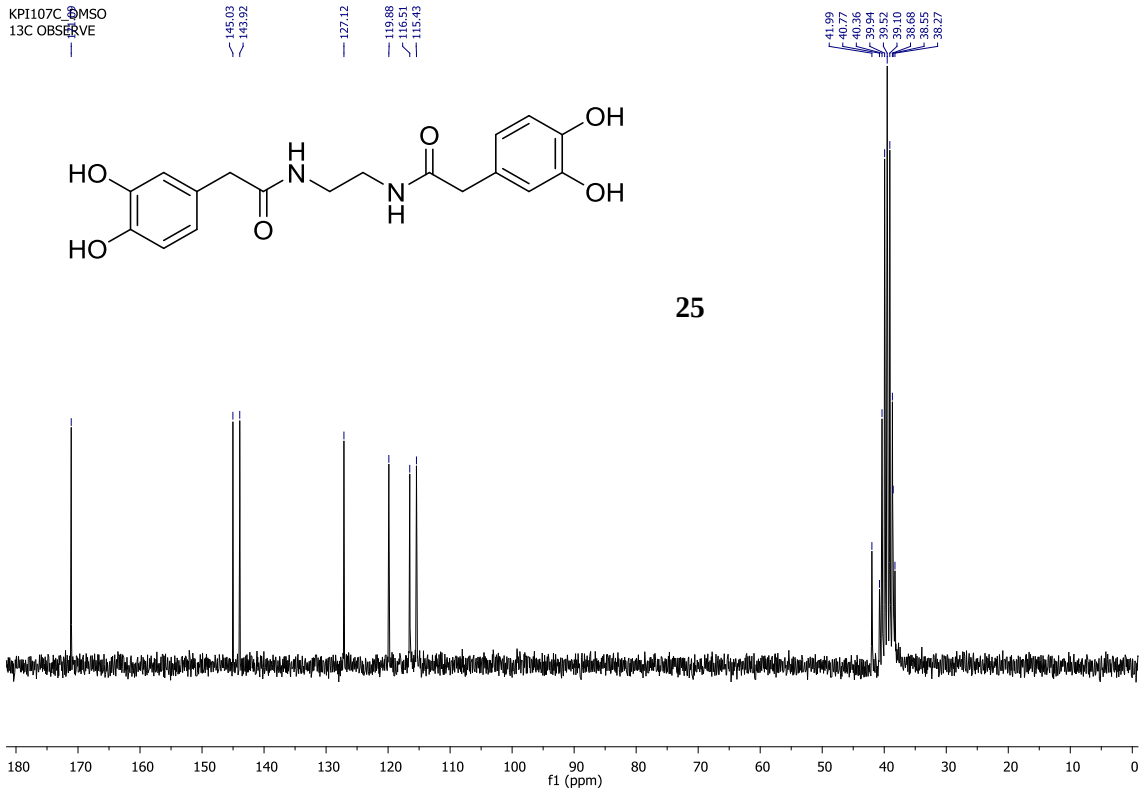


Figure S71: ^{13}C NMR of **25**.

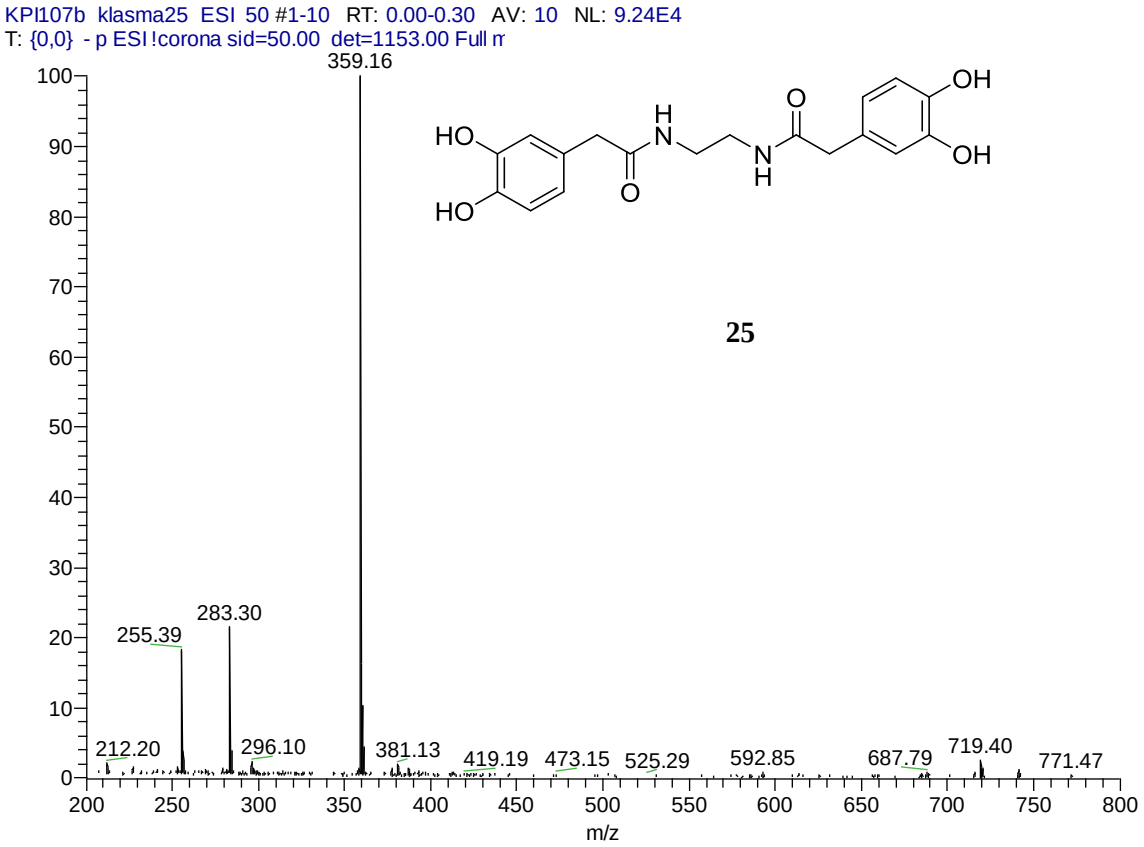


Figure S72: ESI-MS of **25**.

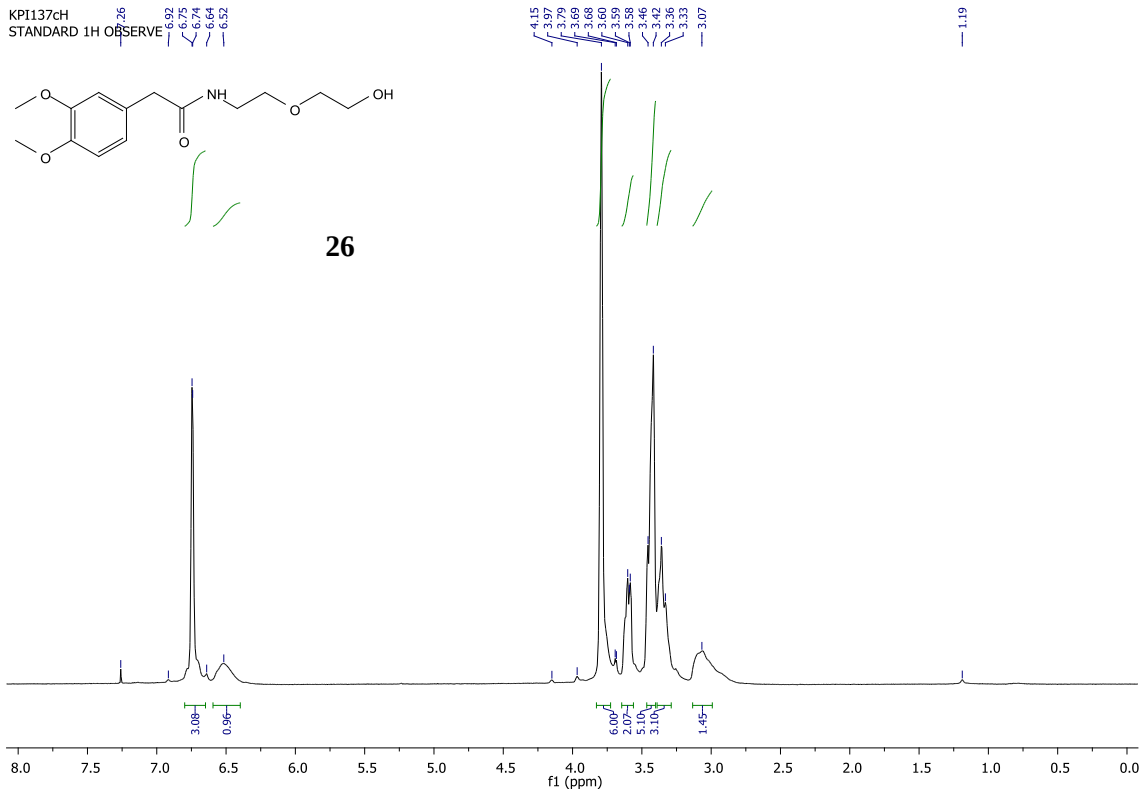


Figure S73: ^{1}H NMR of **26**.

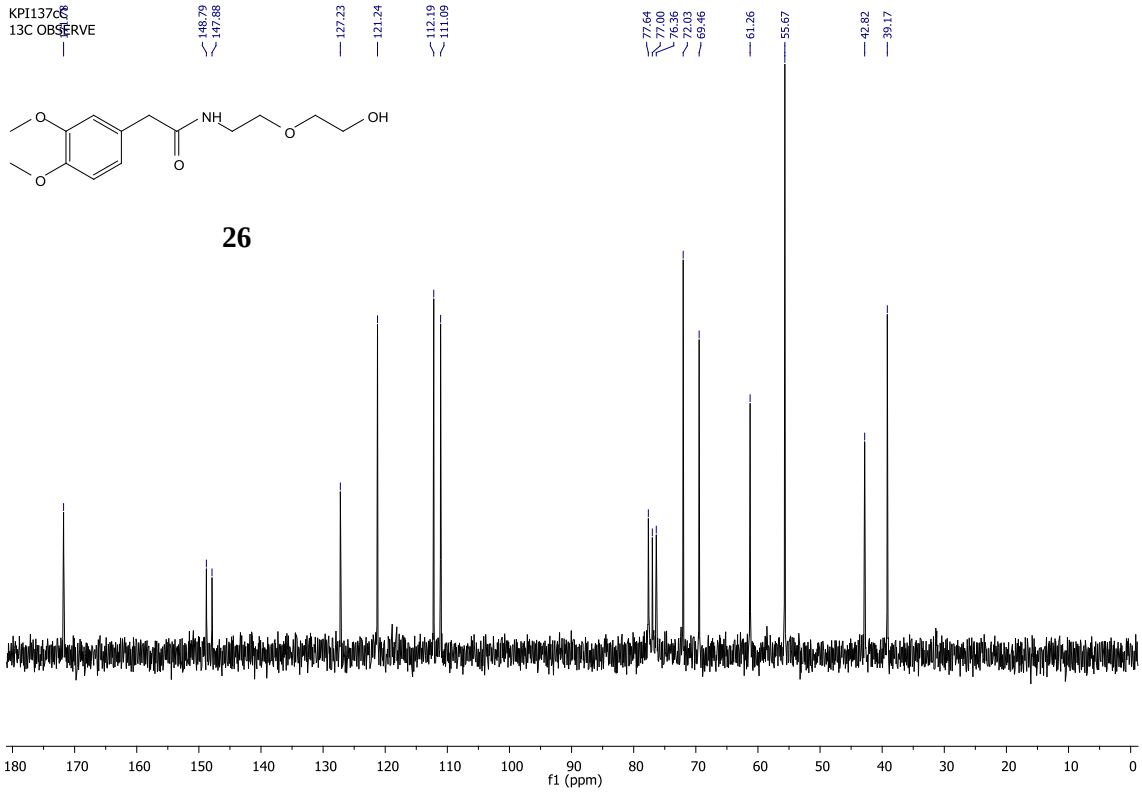


Figure S74: ^{13}C NMR of **26**.

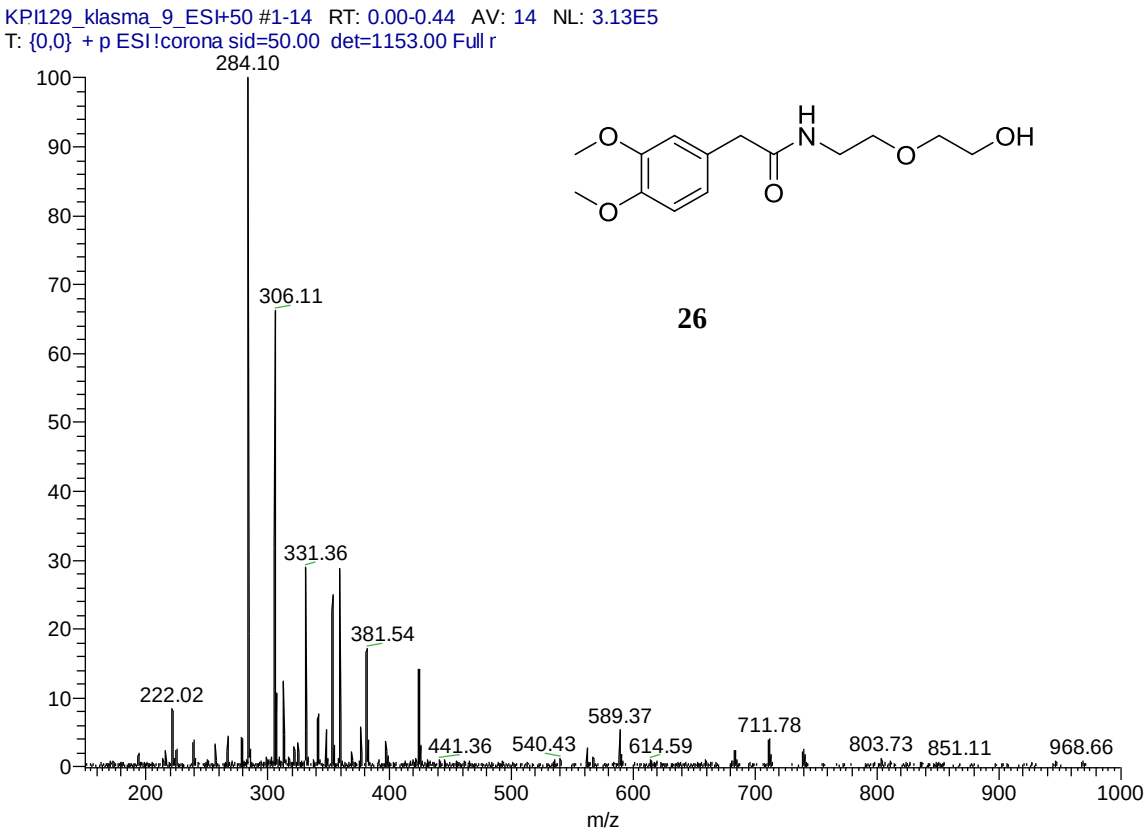


Figure S75: ESI-MS of **26**.

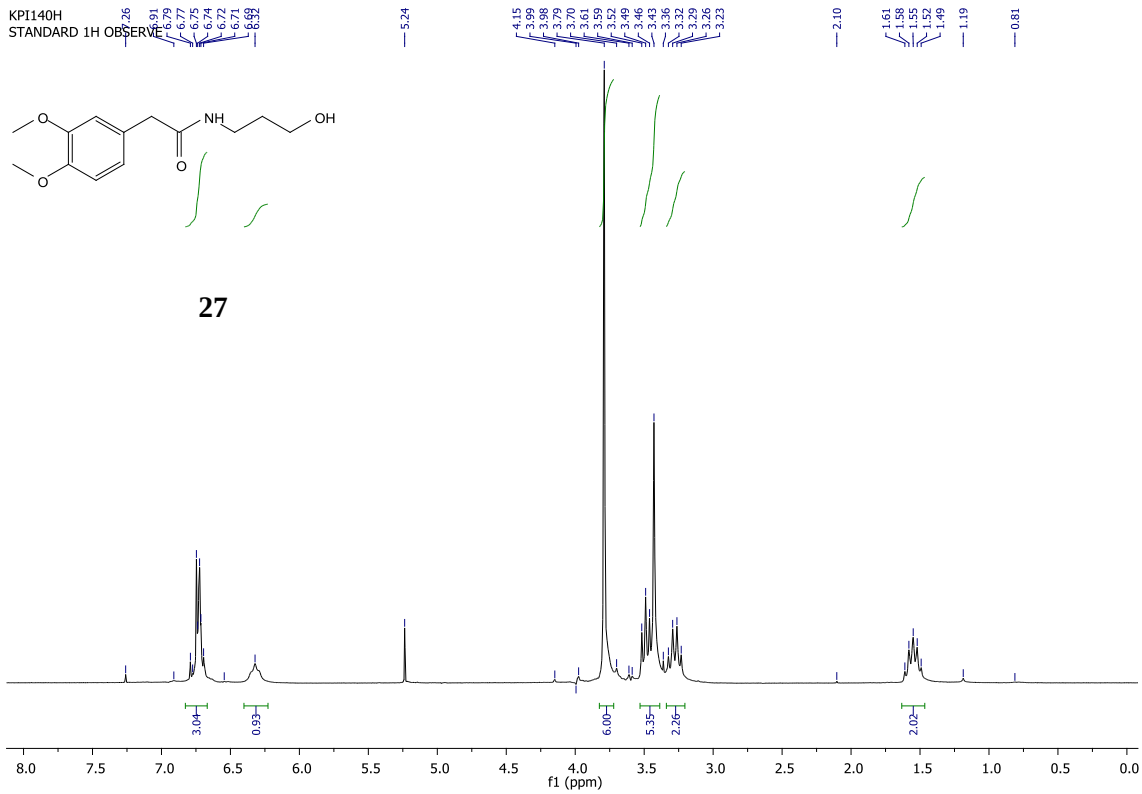


Figure S76: ^{1}H NMR of **27**.

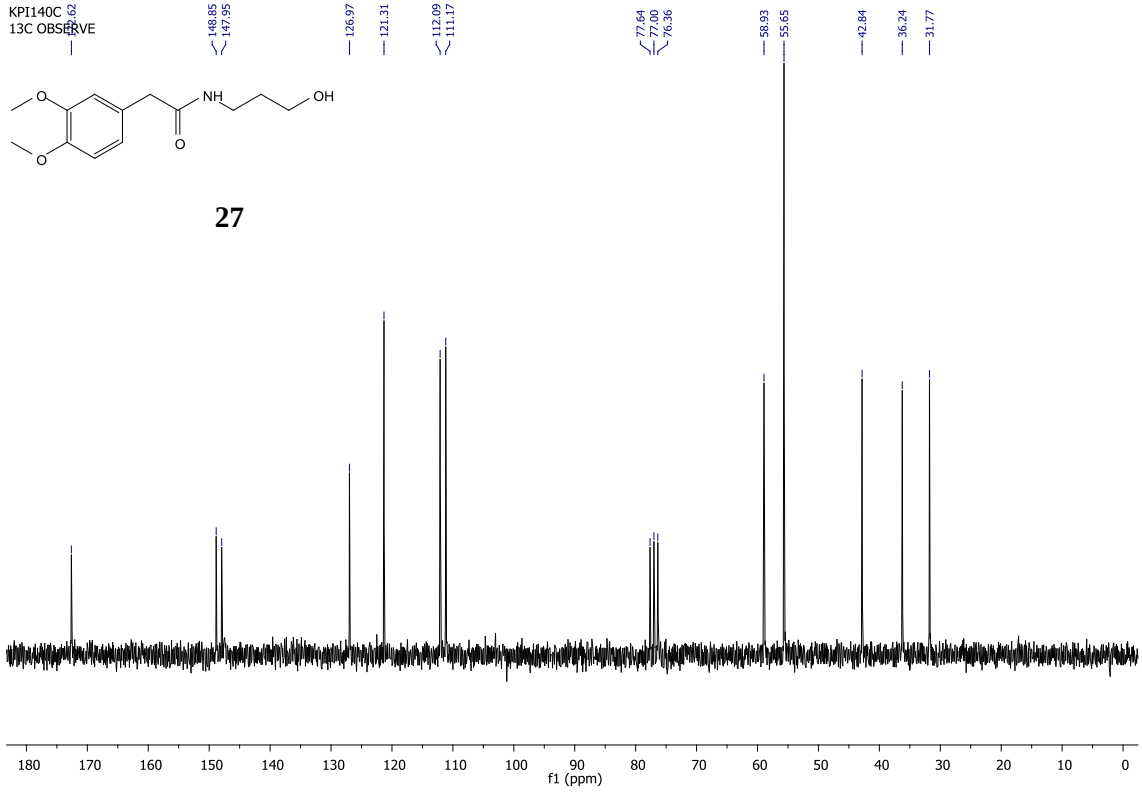


Figure S77: ^{13}C NMR of **27**.

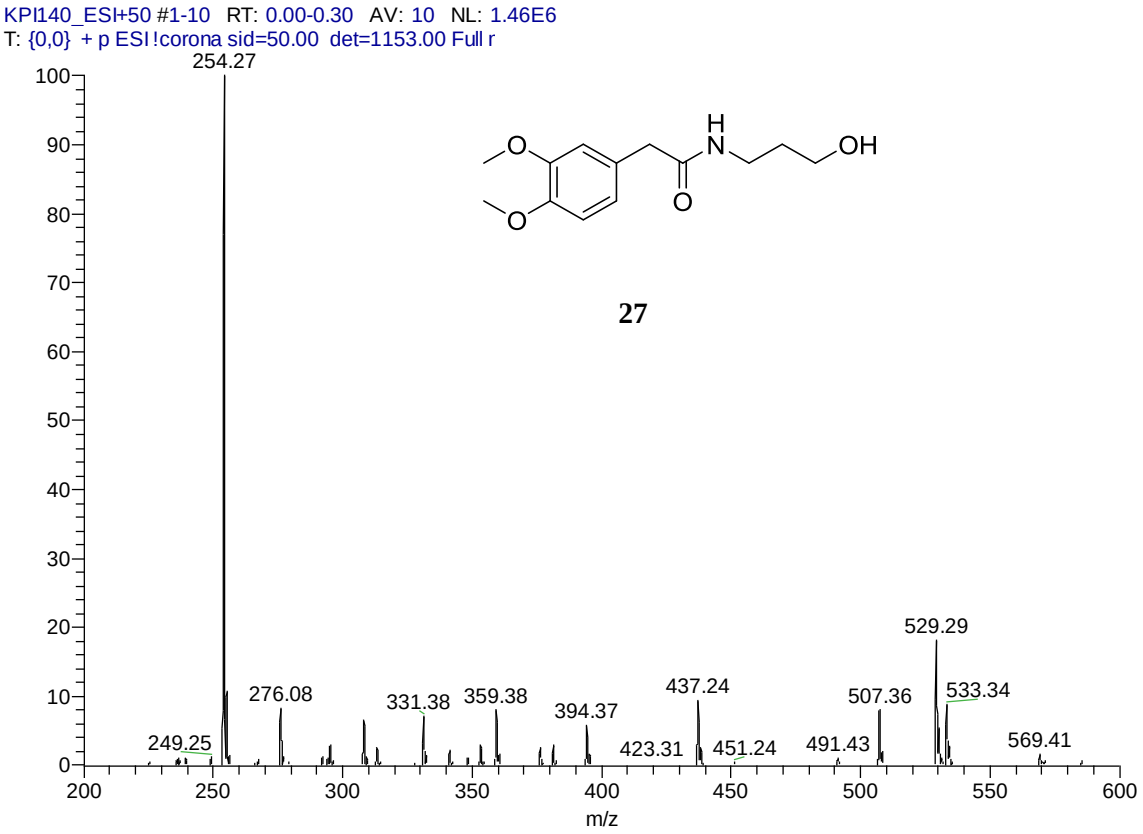


Figure S78: ESI-MS of **27**.

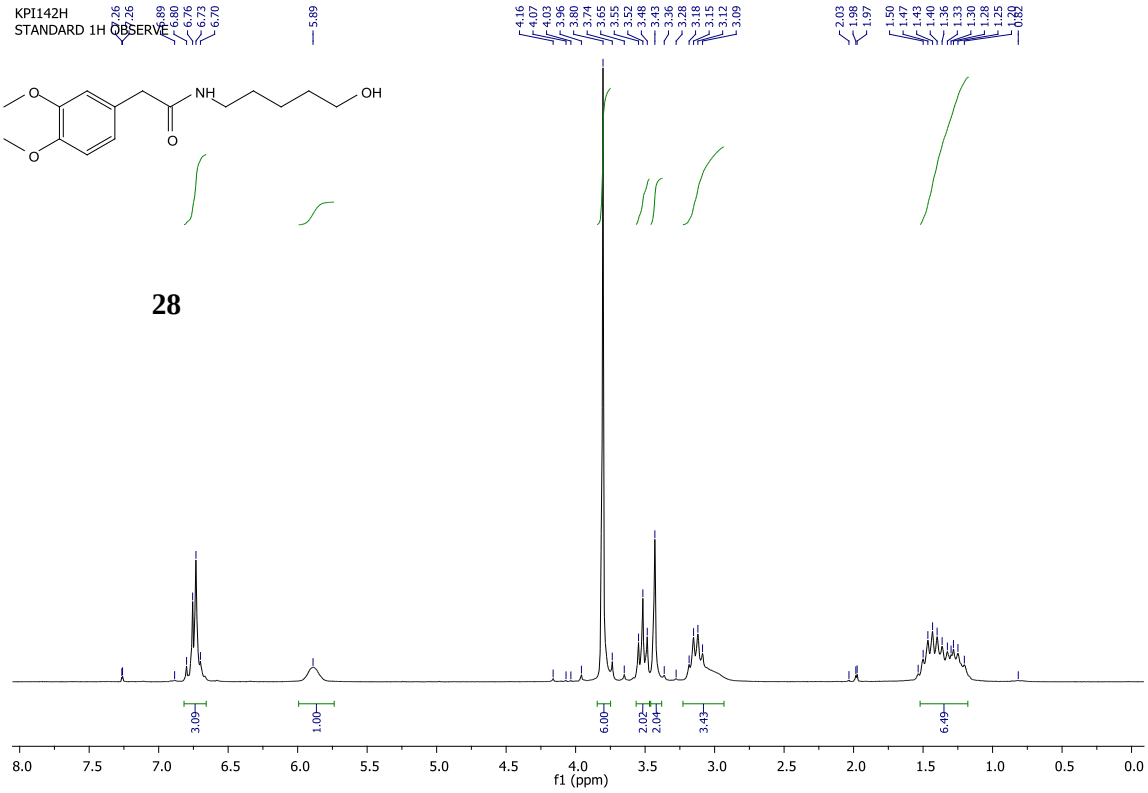


Figure S79: ^{1}H NMR of **28**.

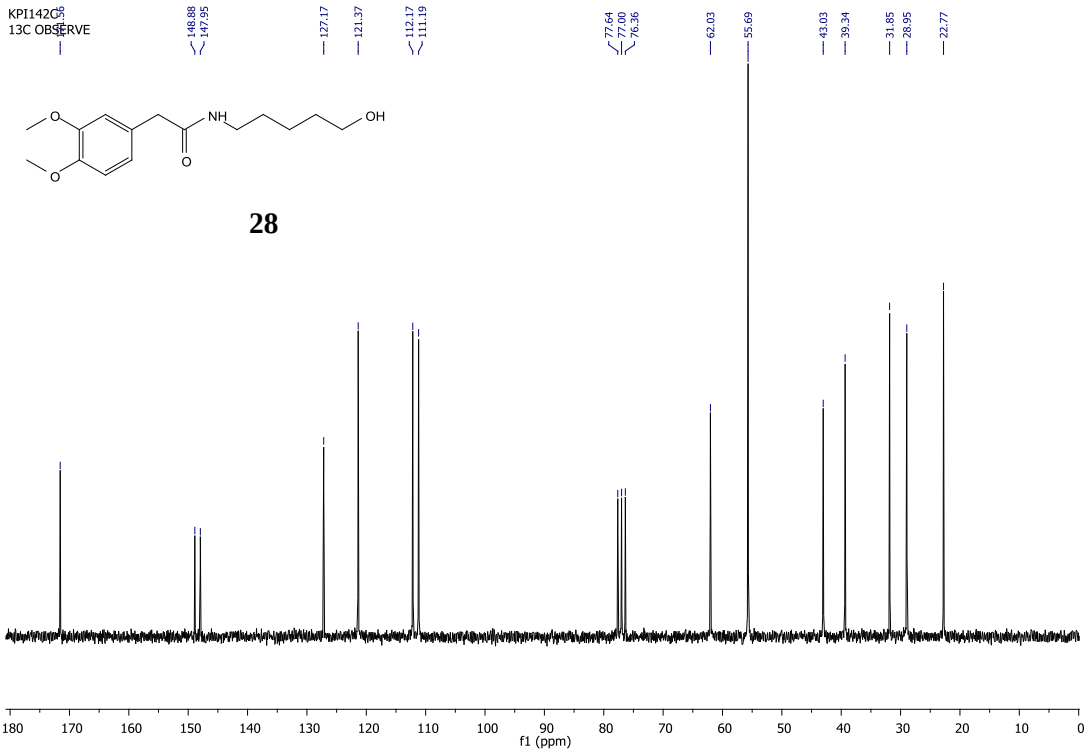


Figure S80: ^{13}C NMR of **28**.

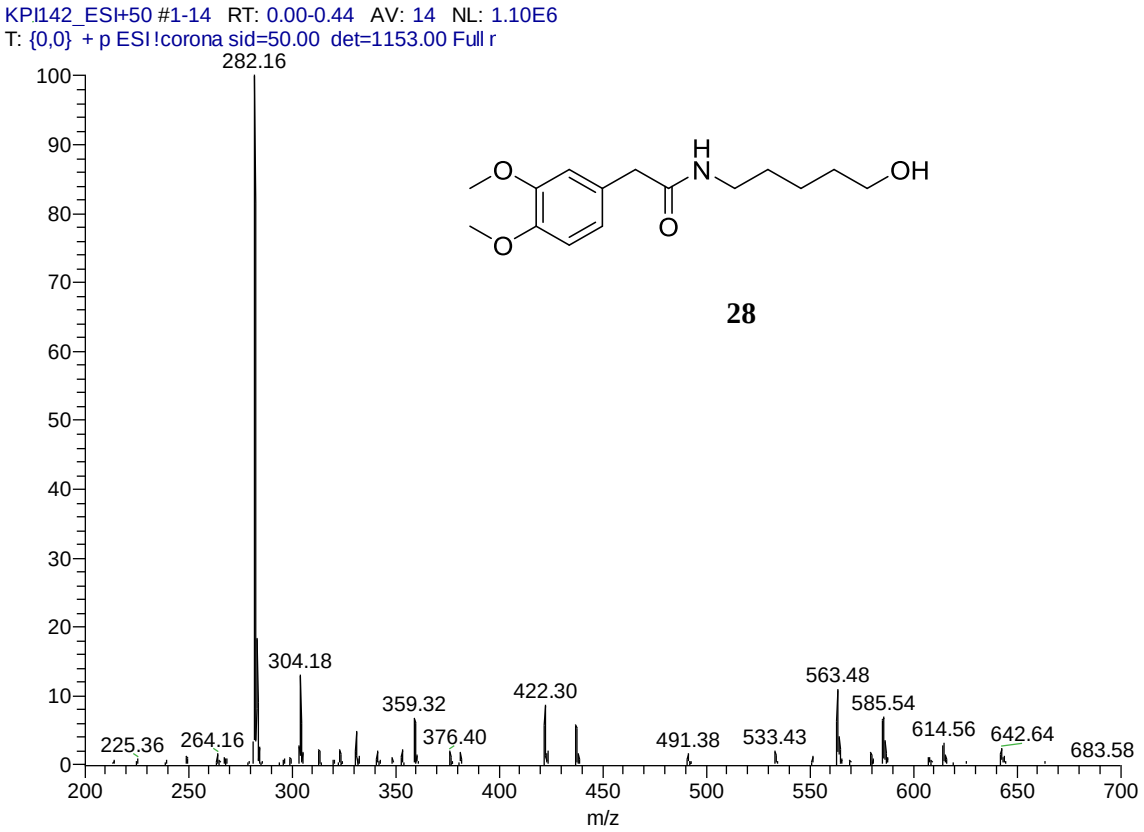


Figure S81: ESI-MS of **28**.

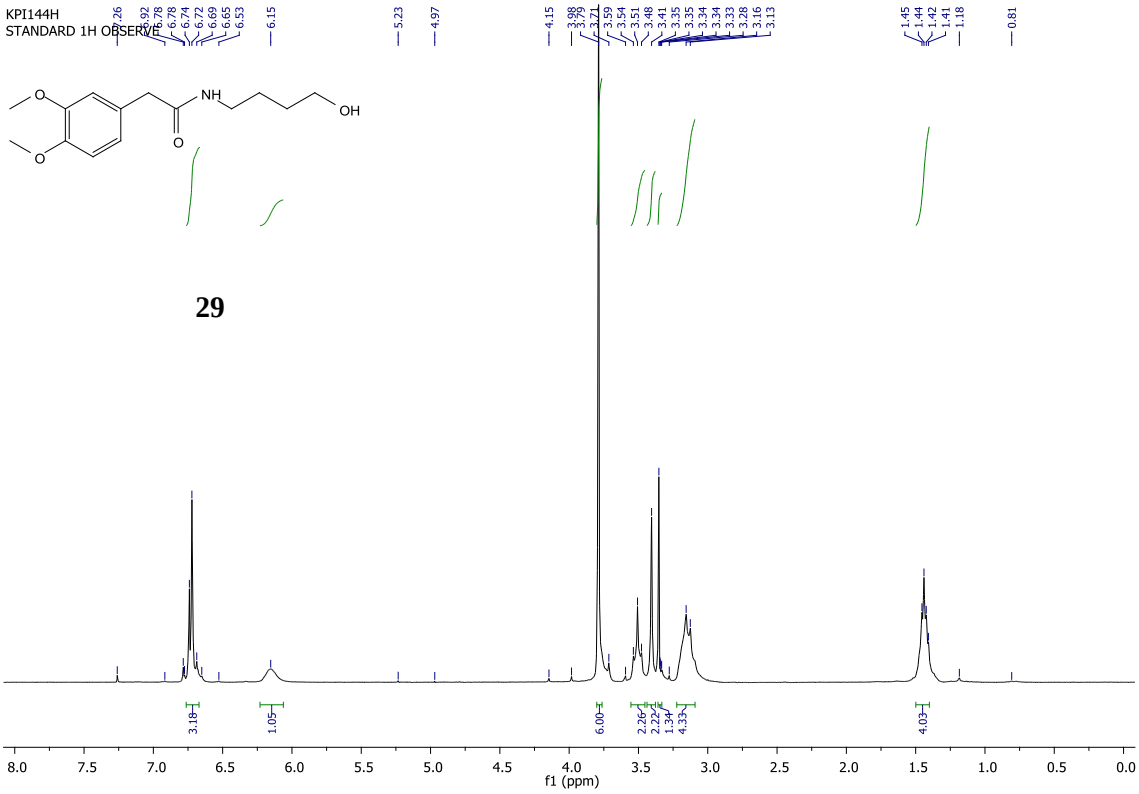


Figure S82: ^{1}H NMR of **29**.

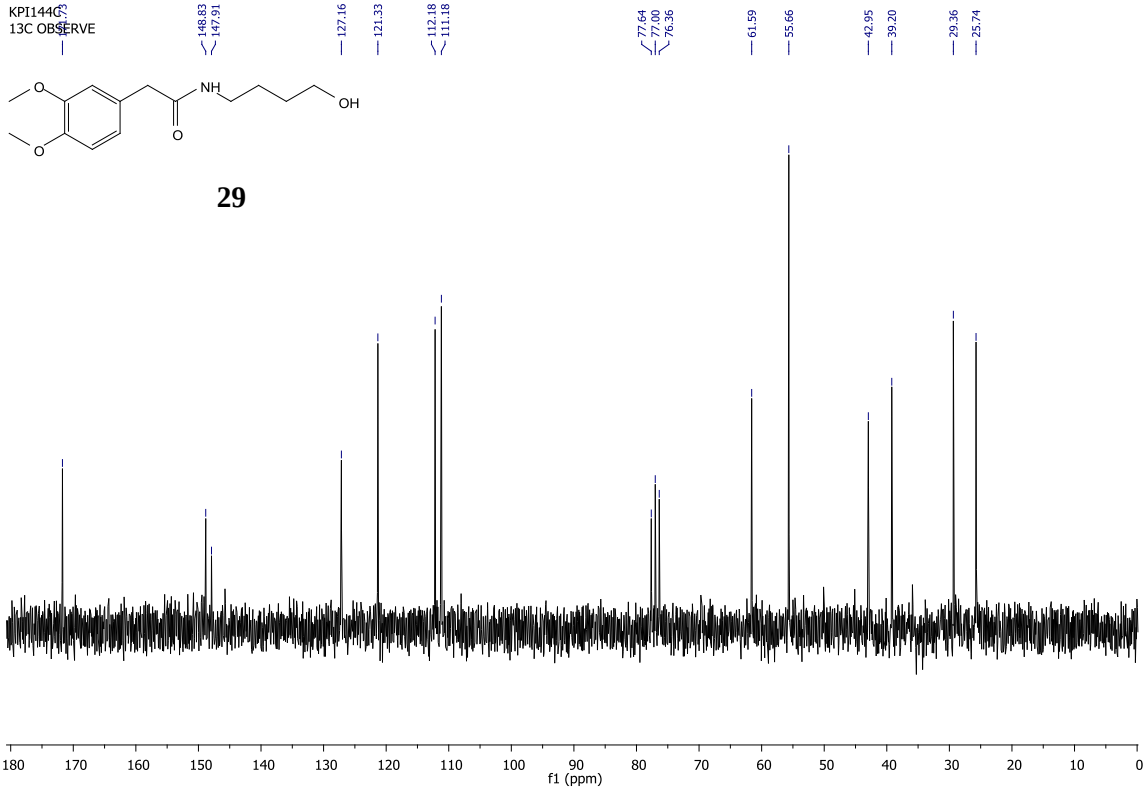


Figure S83: ^{13}C NMR of **29**.

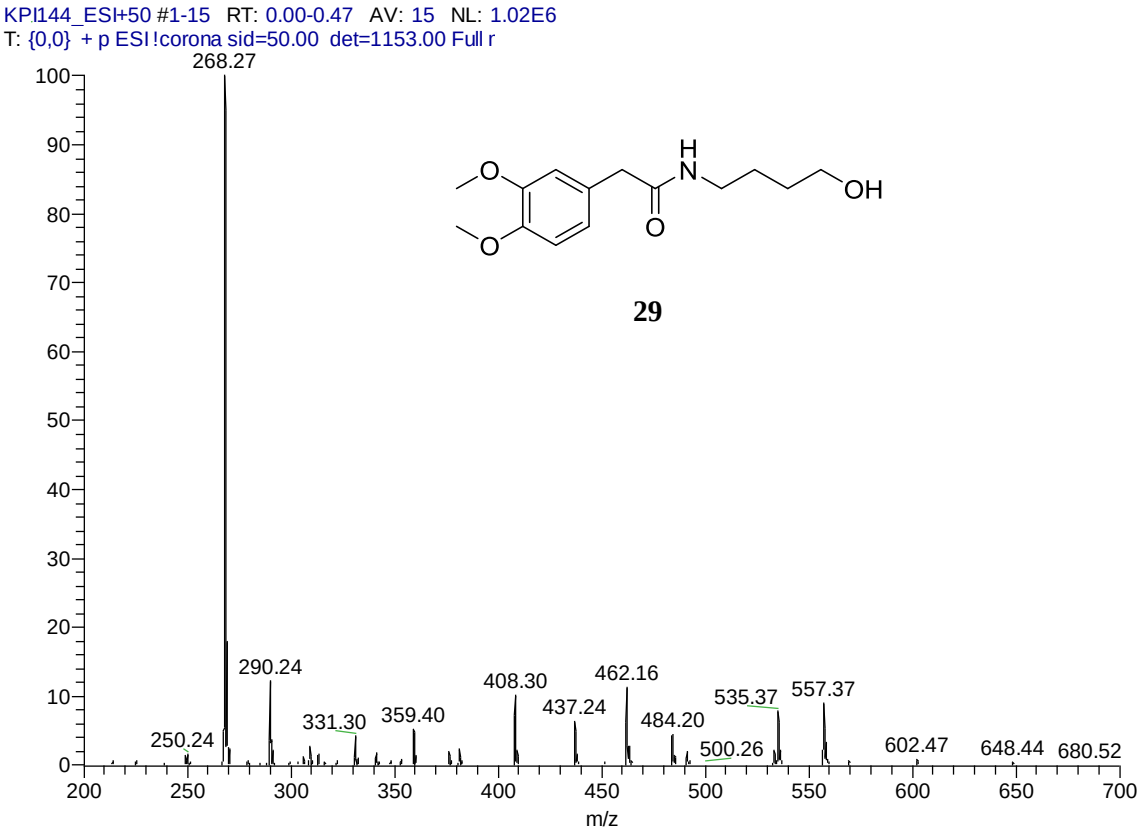


Figure S84: ESI-MS of **29**.

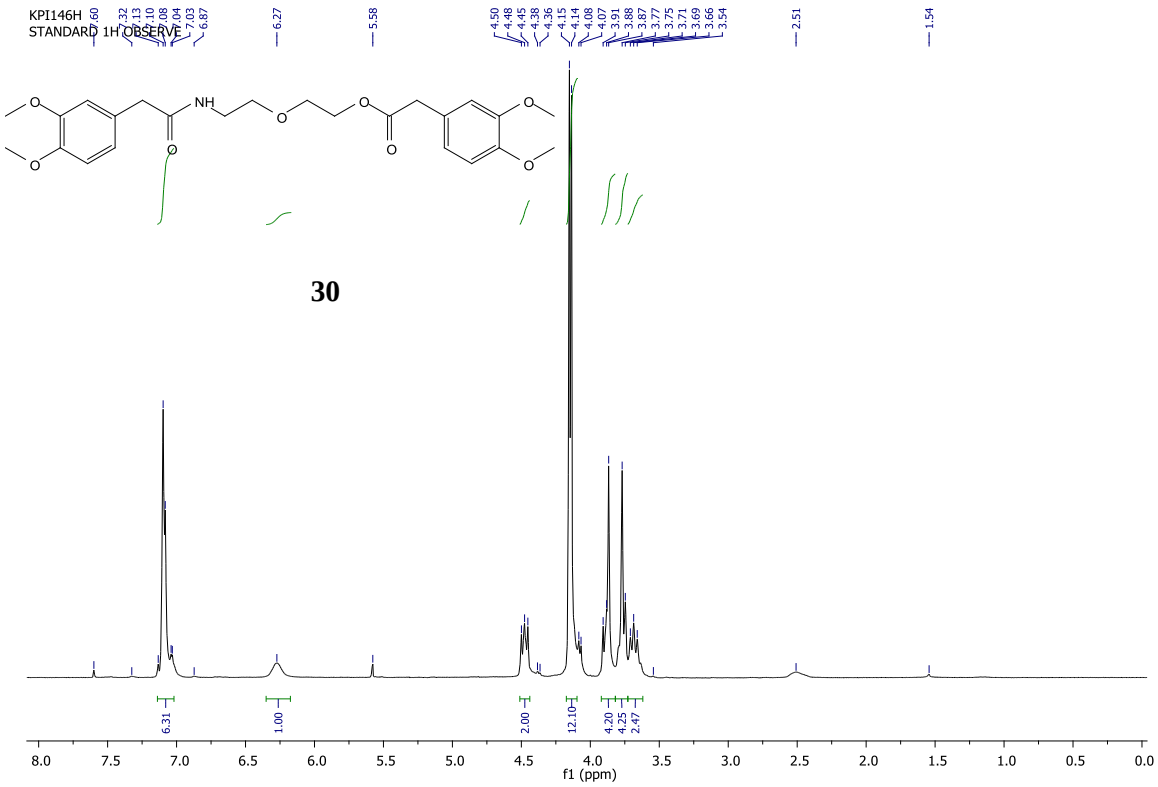


Figure S85: ^{1}H NMR of **30**.

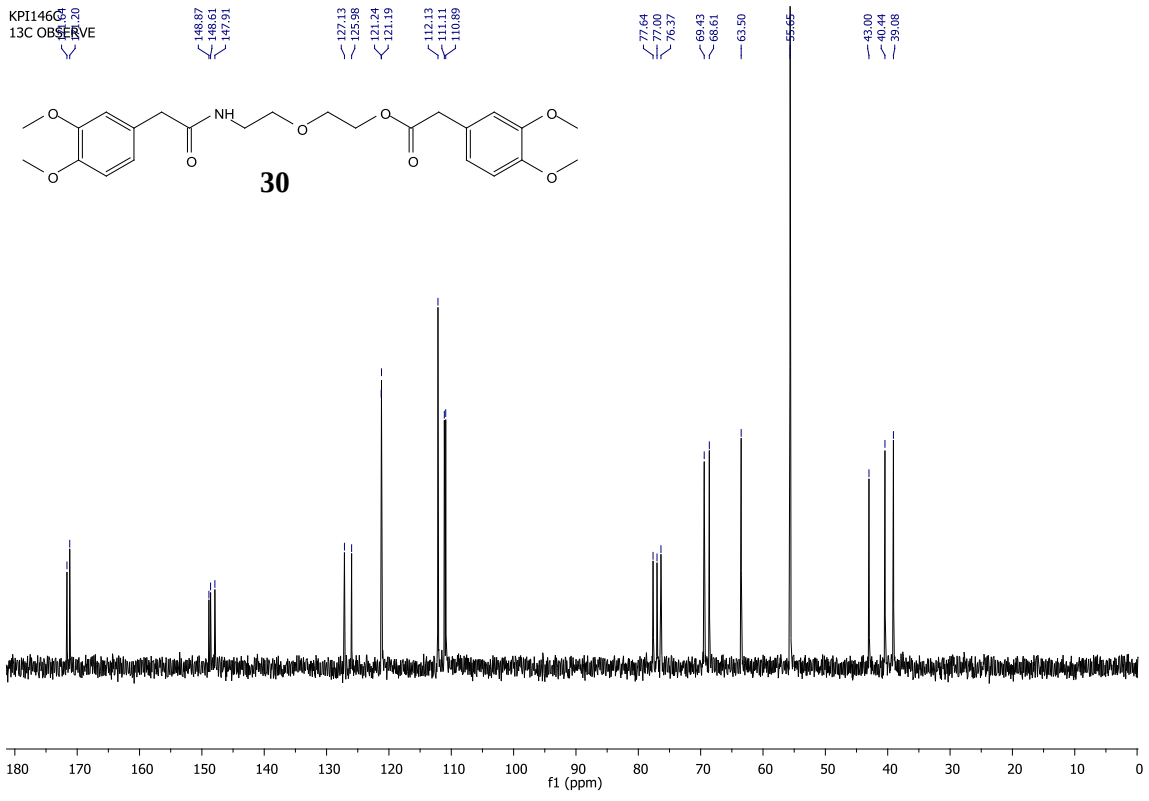


Figure S86: ^{13}C NMR of **30**.

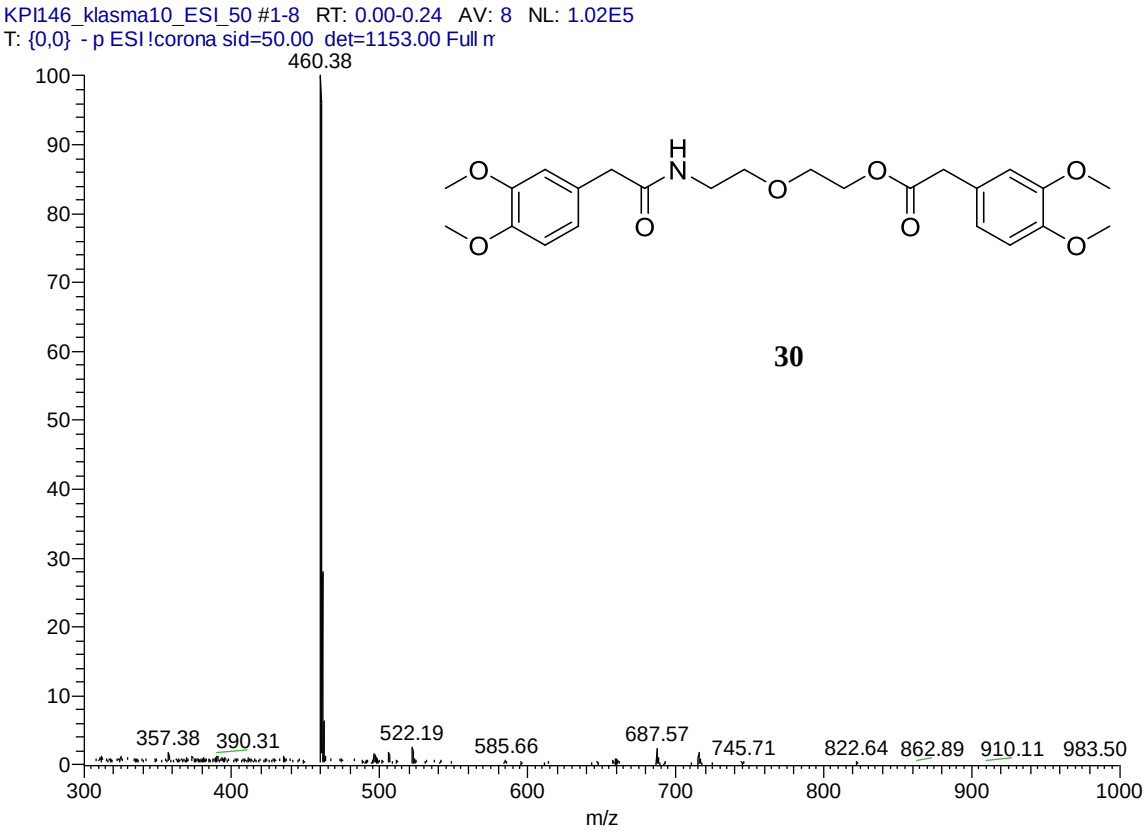


Figure S87: ESI-MS of **30**.

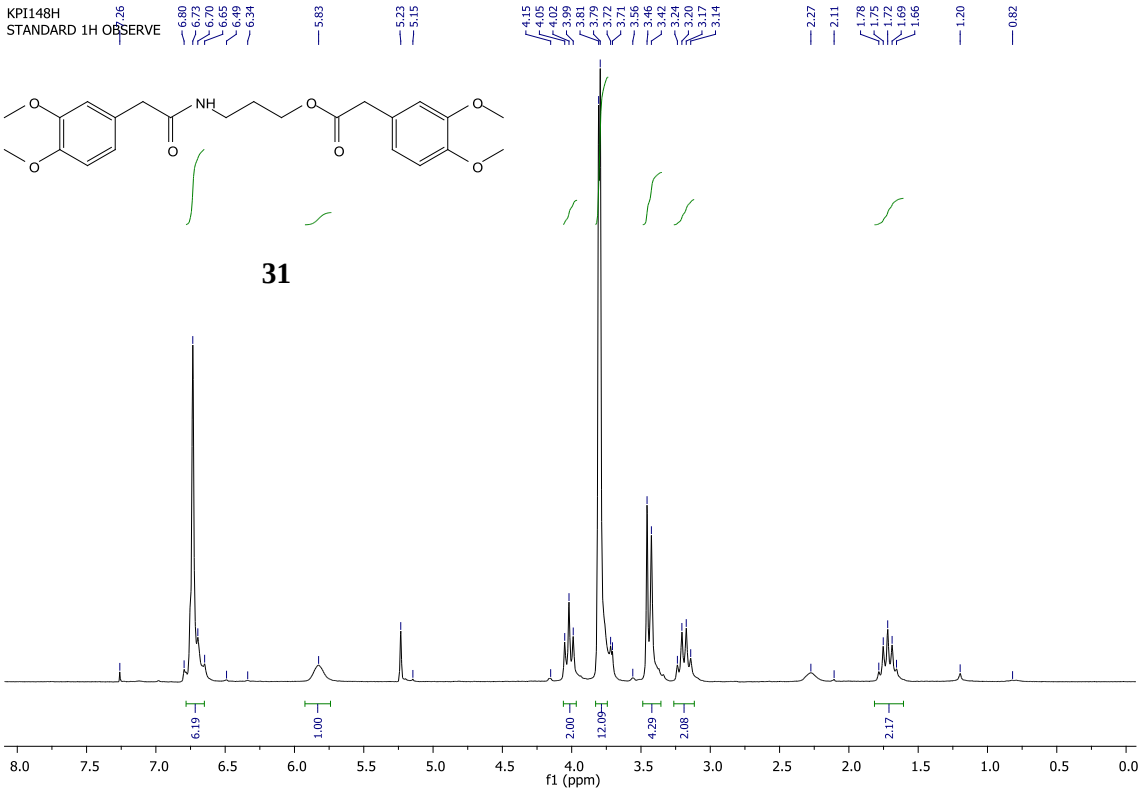


Figure S88: ^{1}H NMR of **31**.

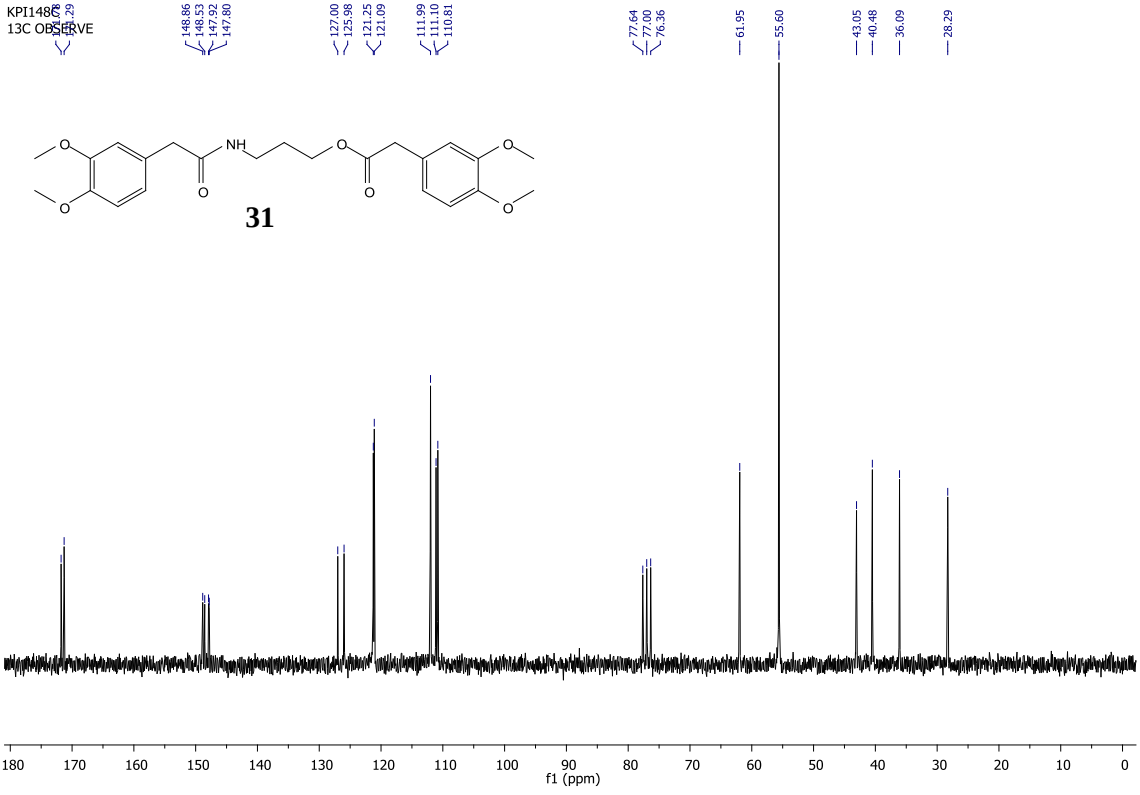
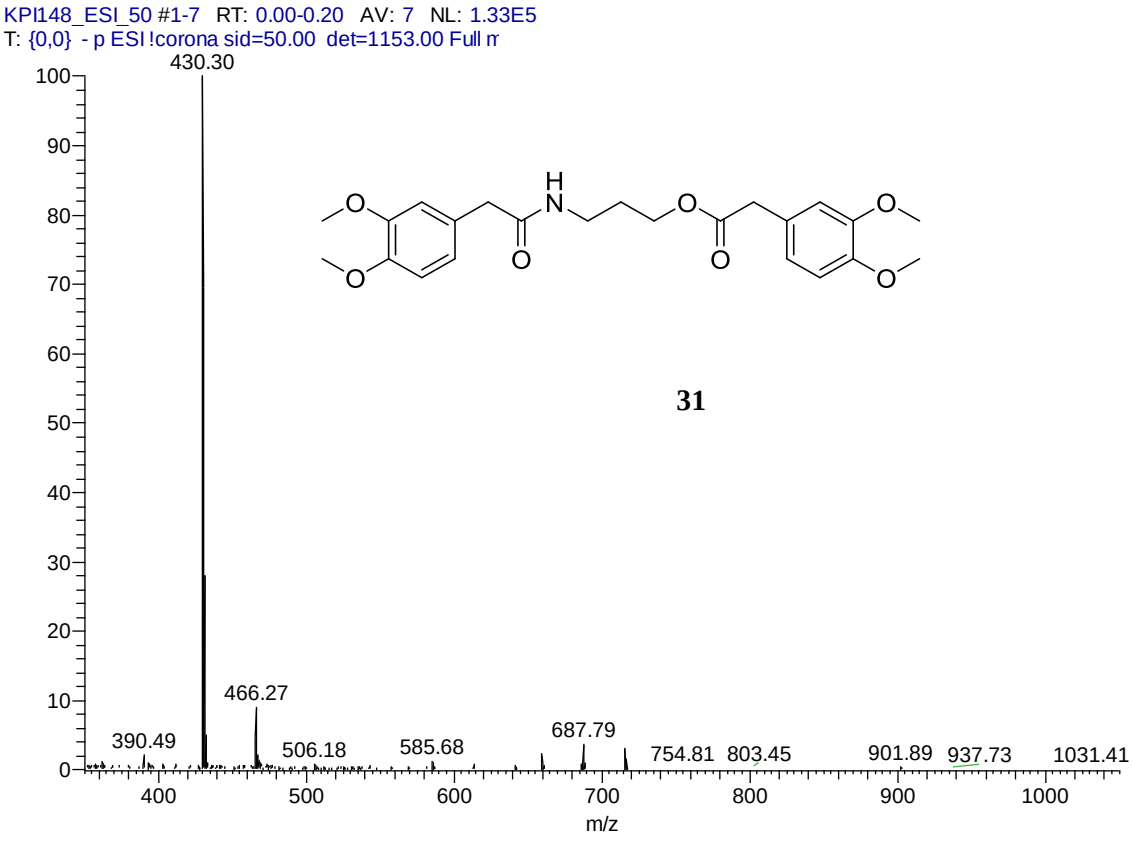


Figure S89: ^{13}C NMR of **31**.



31

Figure S90: ESI-MS of **31**.

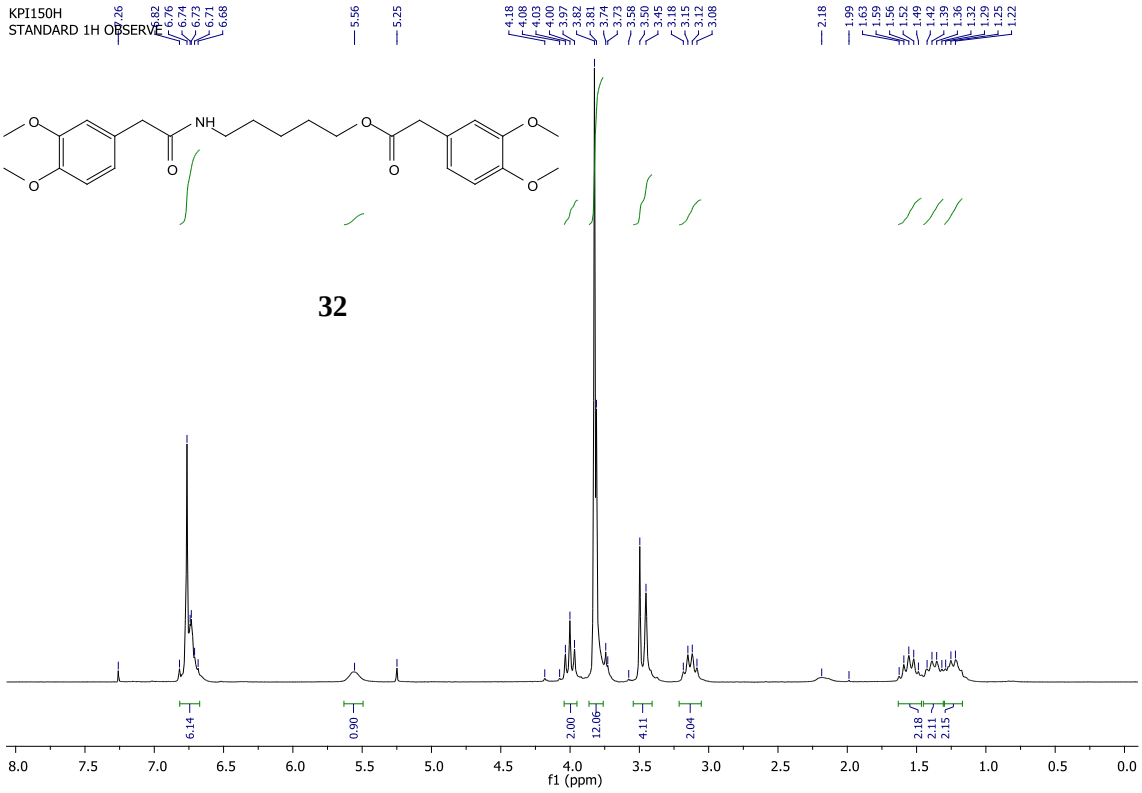


Figure S91: ^{1}H NMR of **32**.

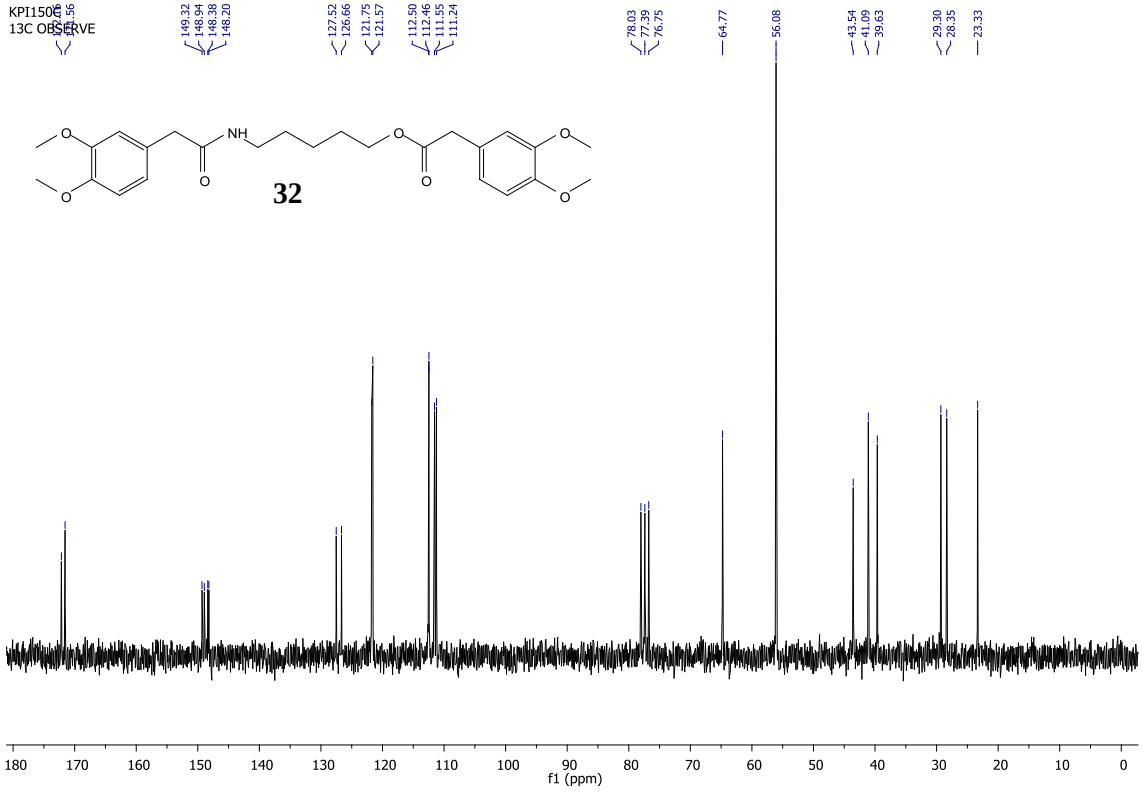


Figure S92: ^{13}C NMR of **32**.

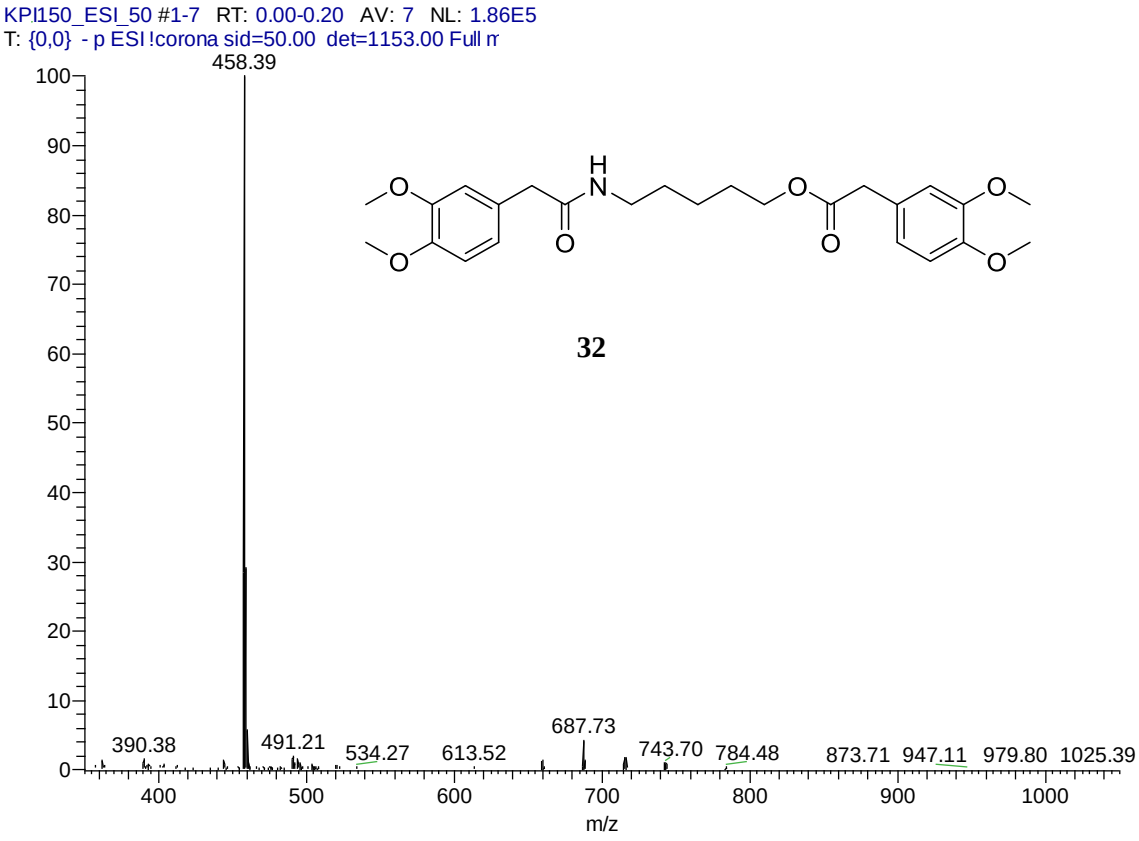


Figure S93: ESI-MS of **32**.

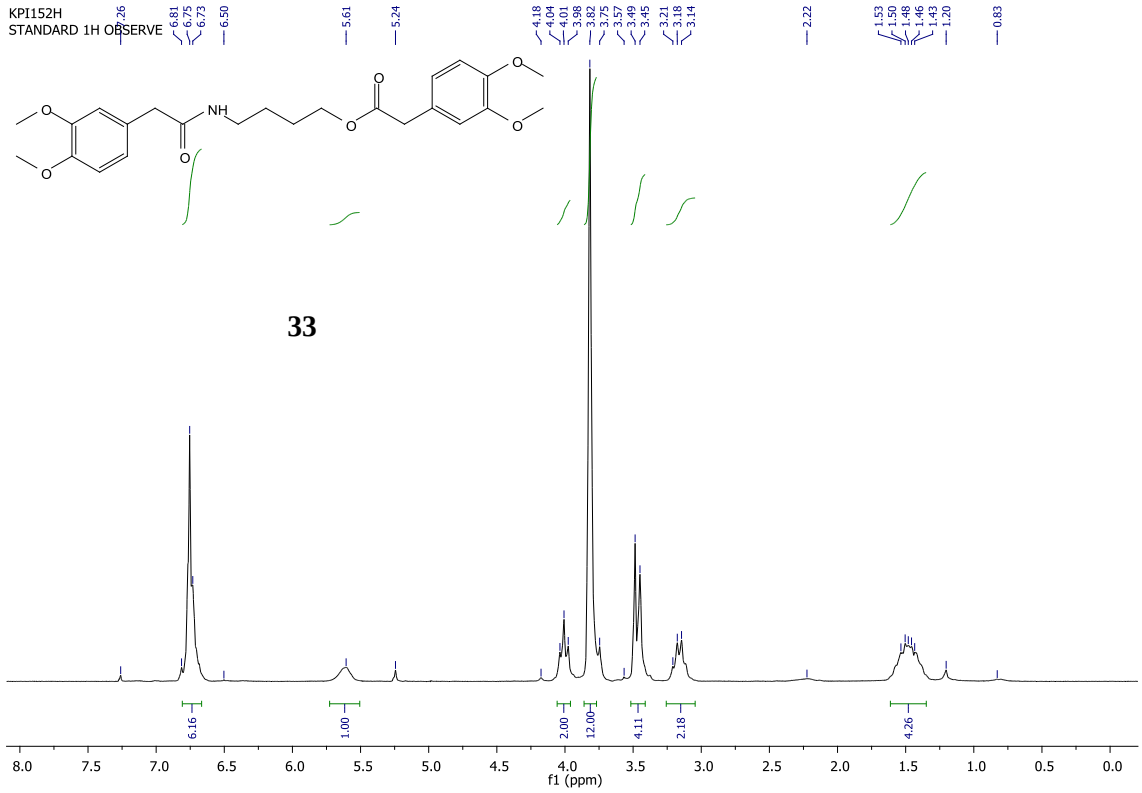


Figure S94: ^{1}H NMR of **33**.

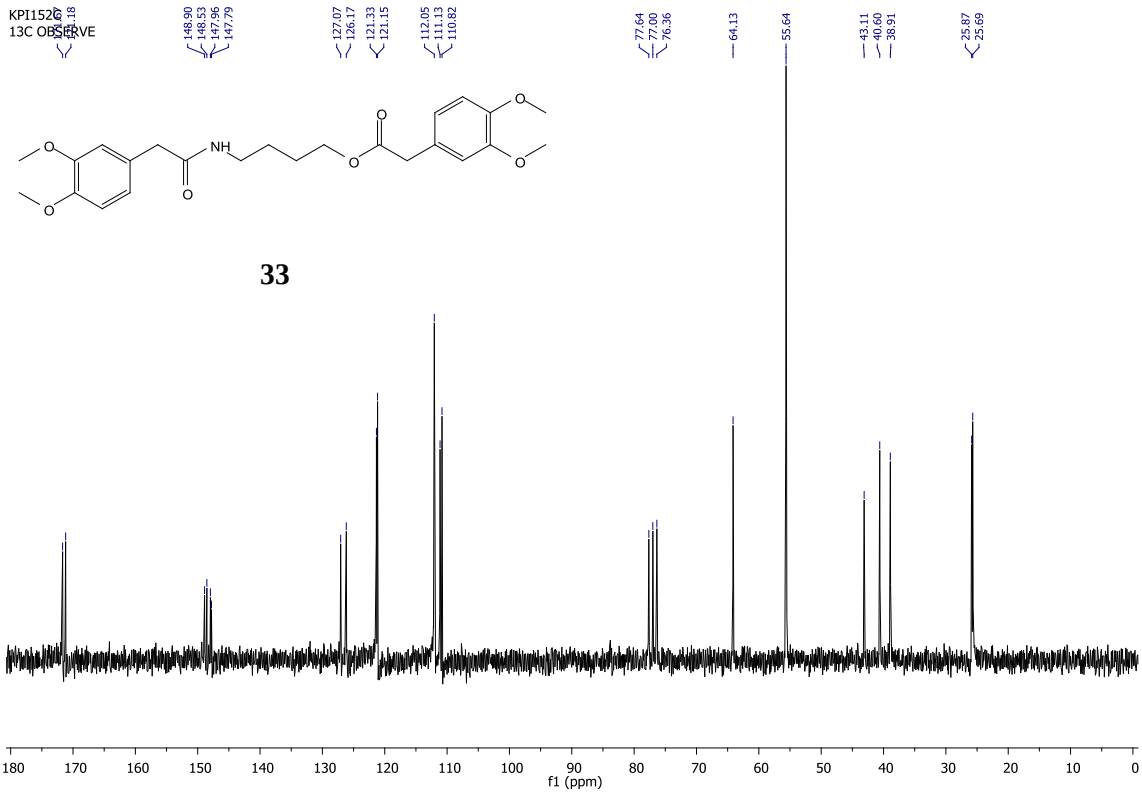


Figure S95: ^{13}C NMR of **33**.

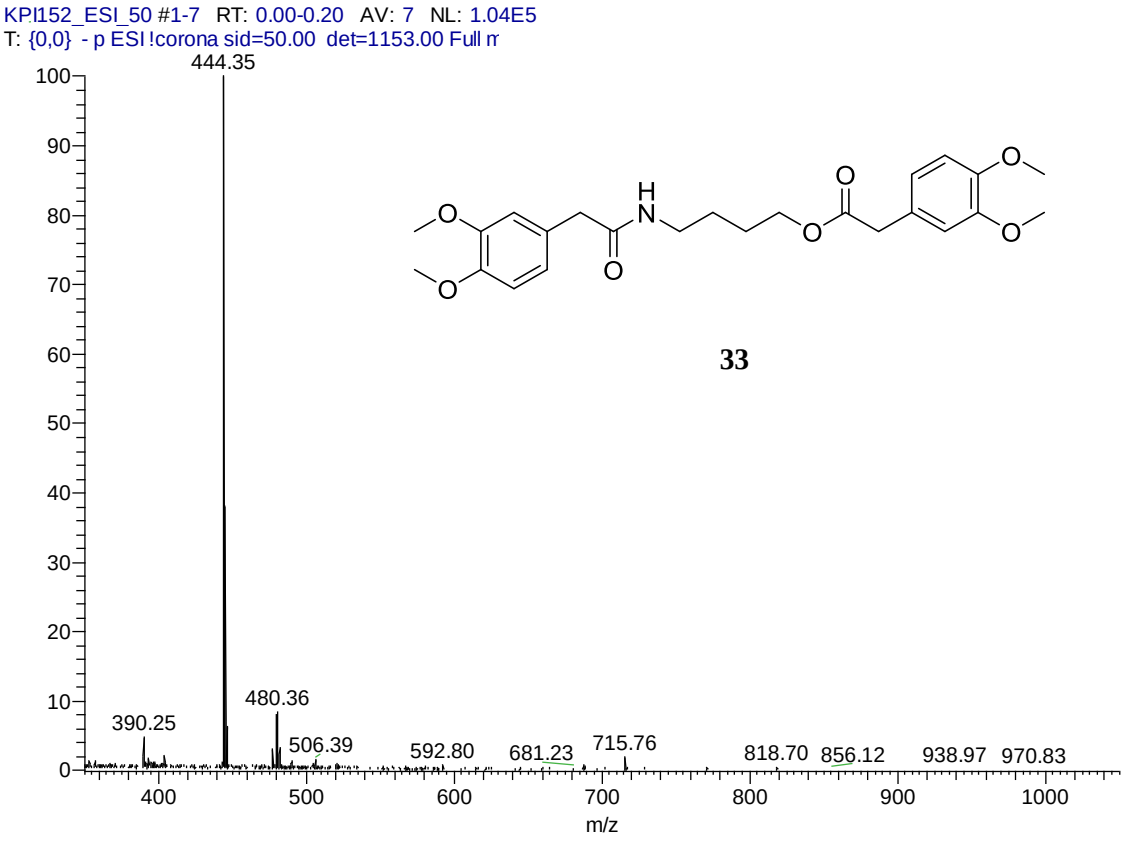


Figure S96: ESI-MS of **33**.

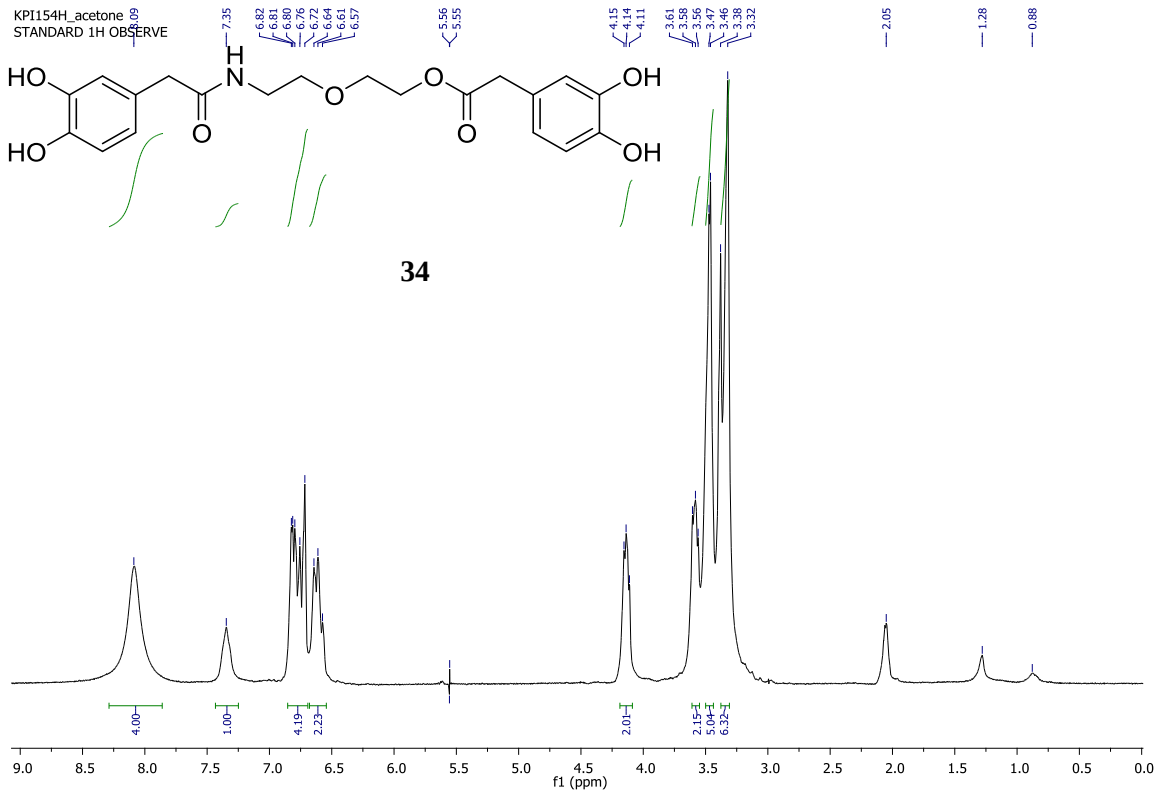


Figure S97: ^{1}H NMR of **34**.

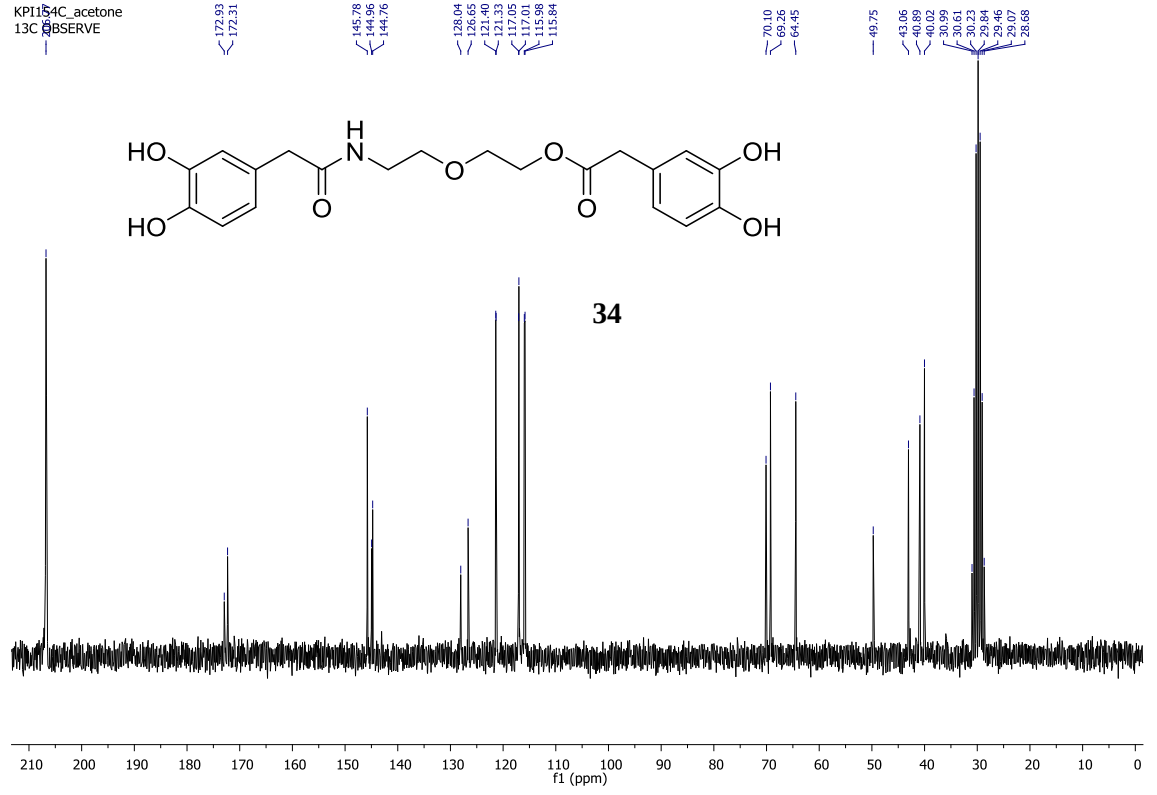


Figure S98: ^{13}C NMR of **34**.

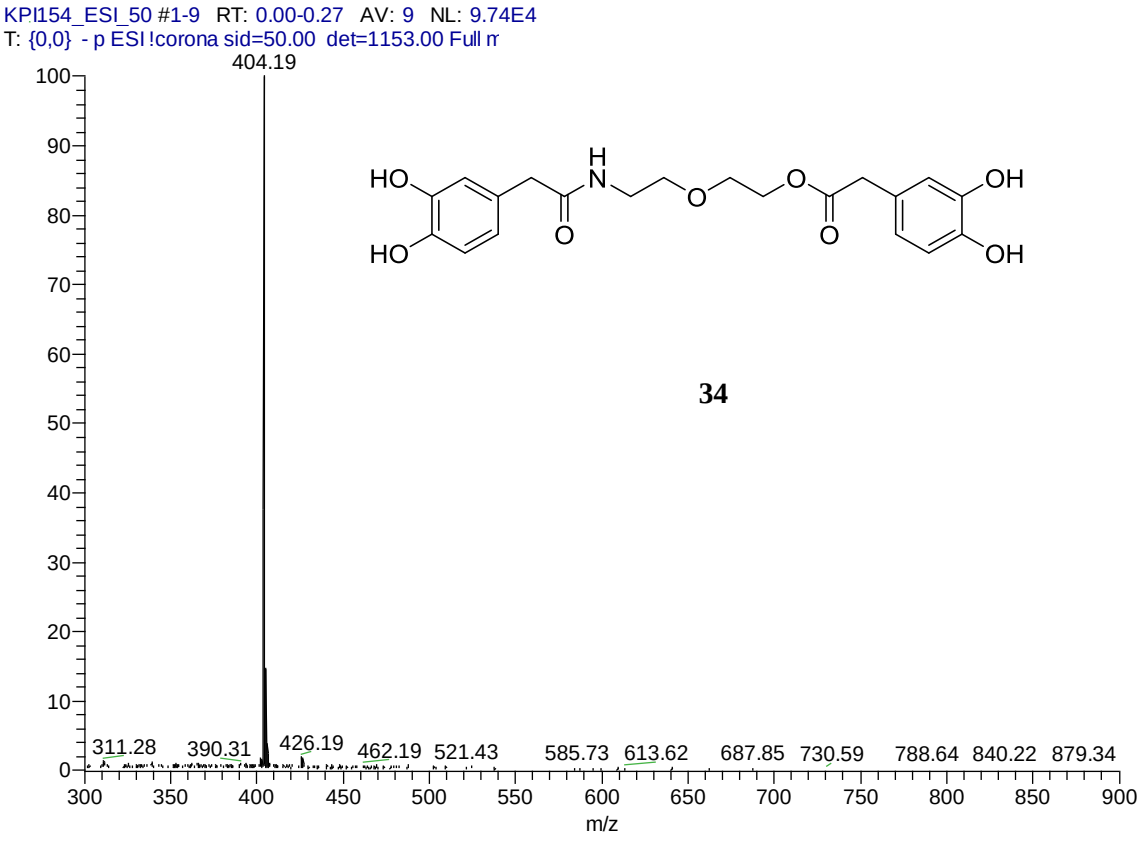


Figure S99: ESI-MS of **34**.

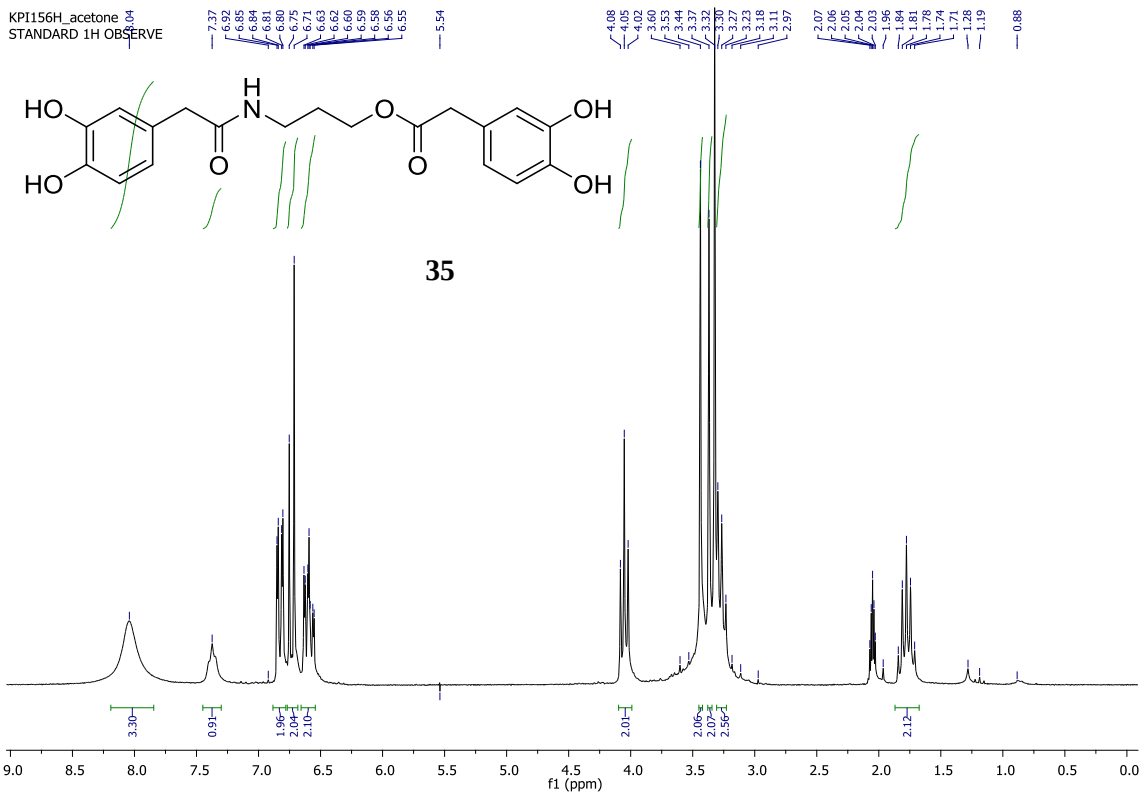


Figure S100: ^{1}H NMR of **35**.

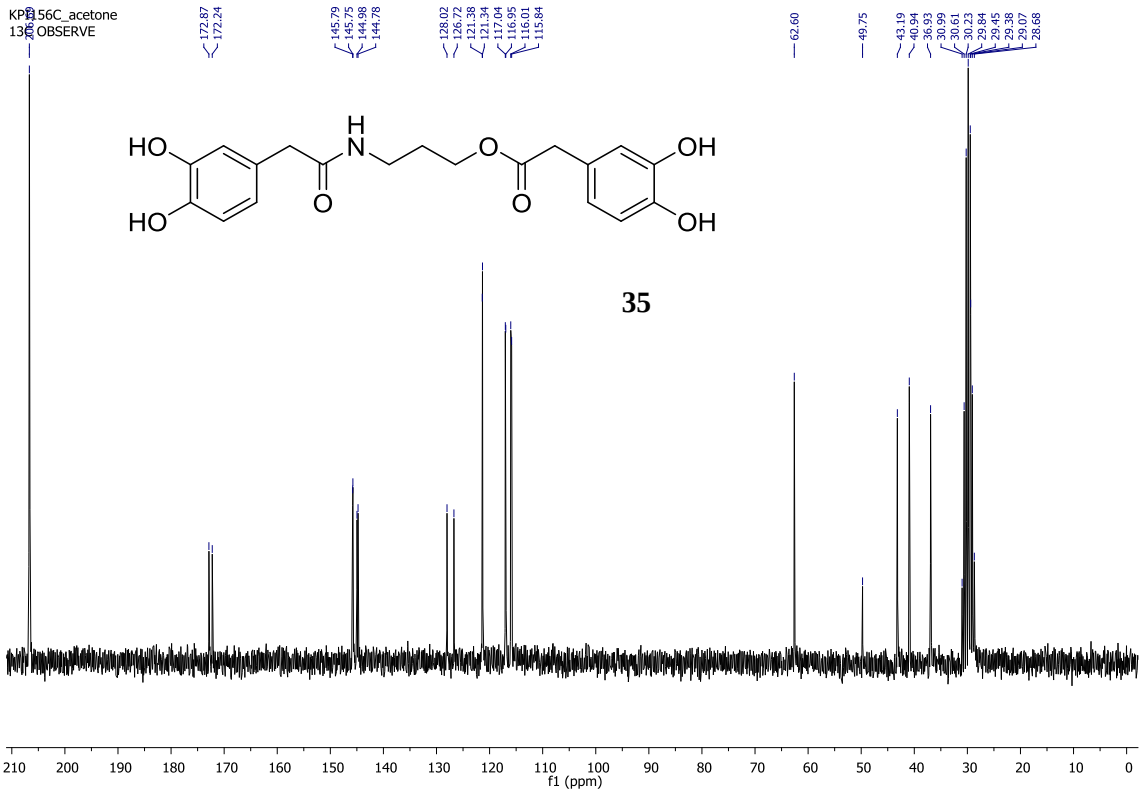


Figure S101: ^{13}C NMR of **35**.

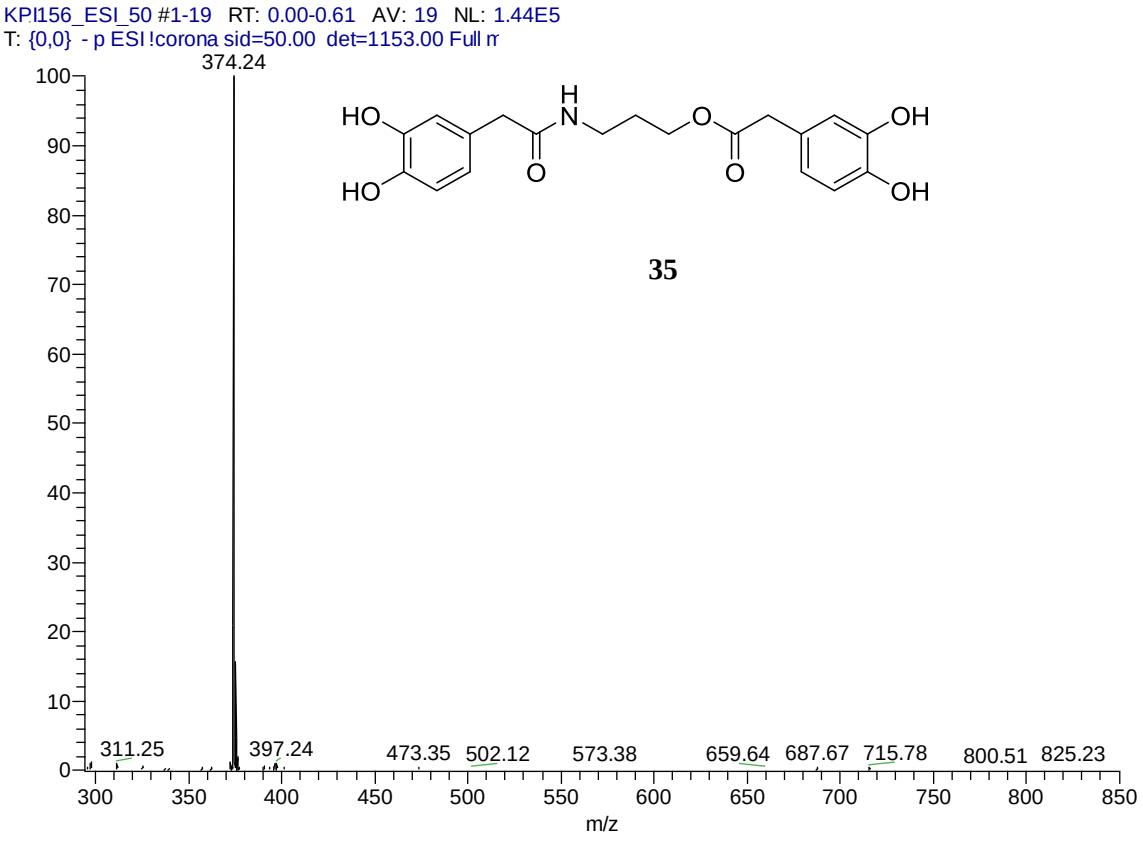


Figure S102: ESI-MS of **35**.

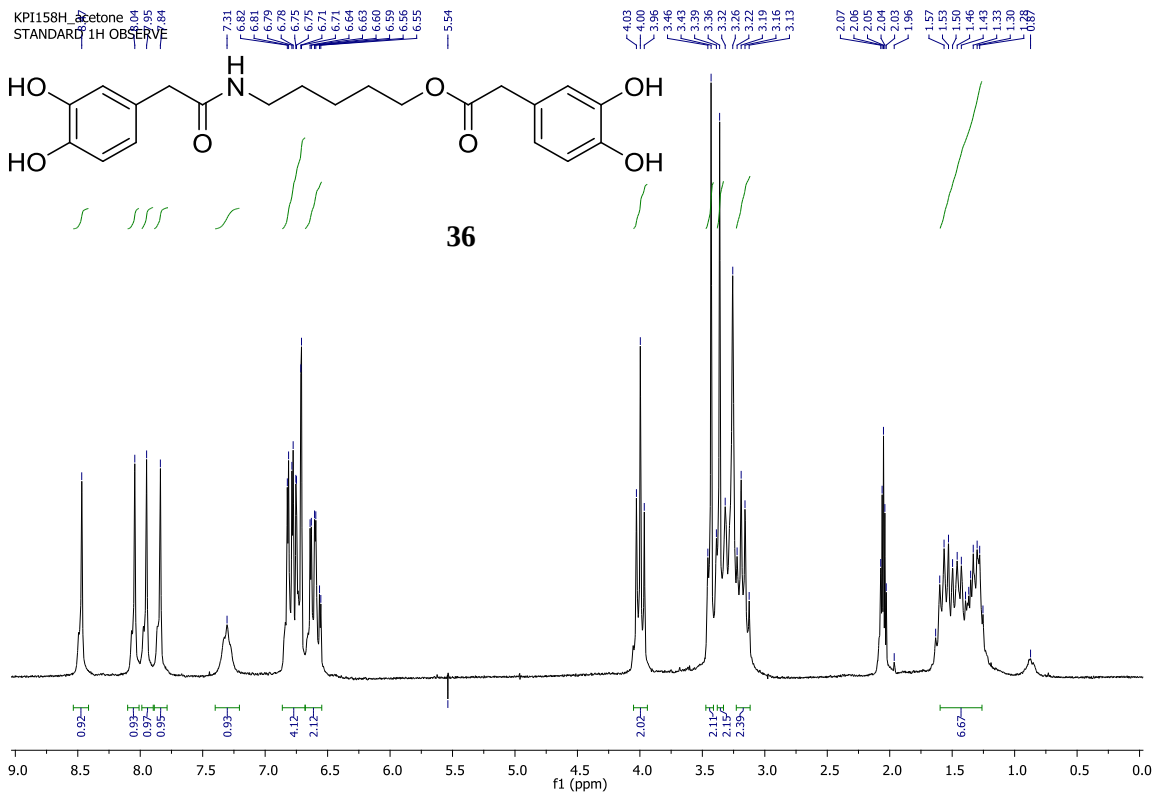


Figure S103: ^{1}H NMR of **36**.

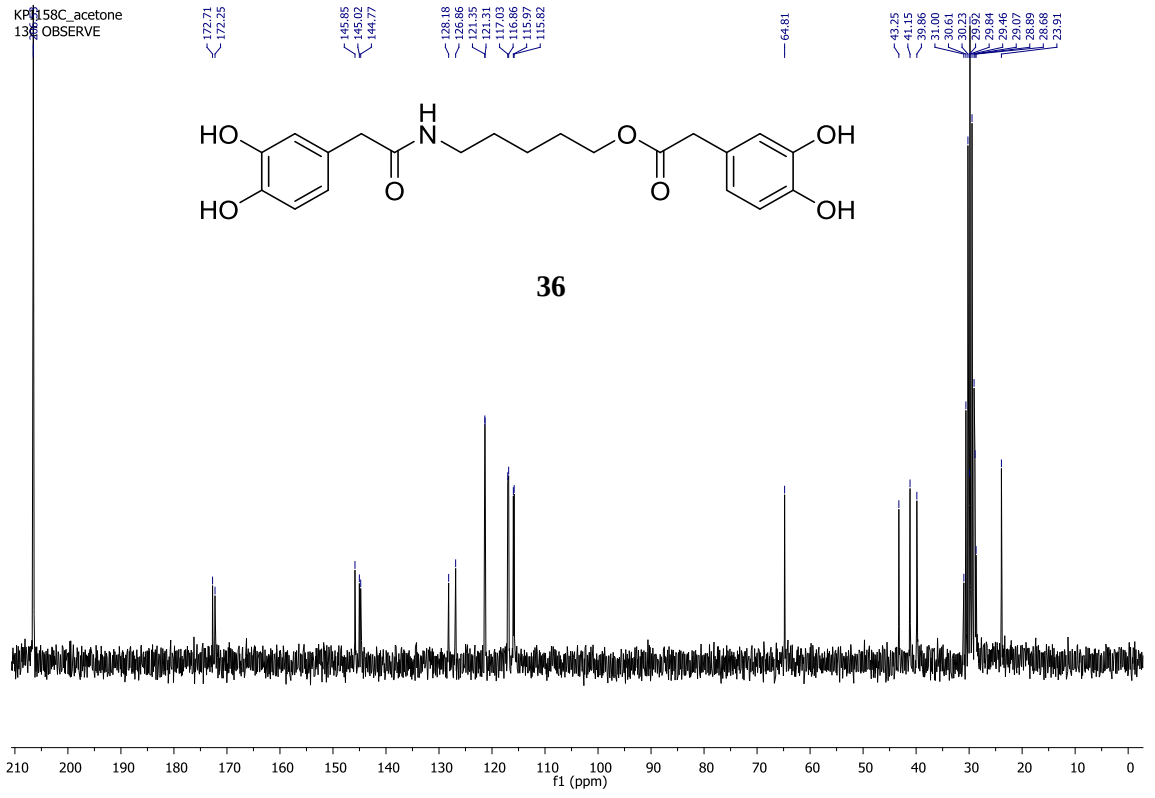
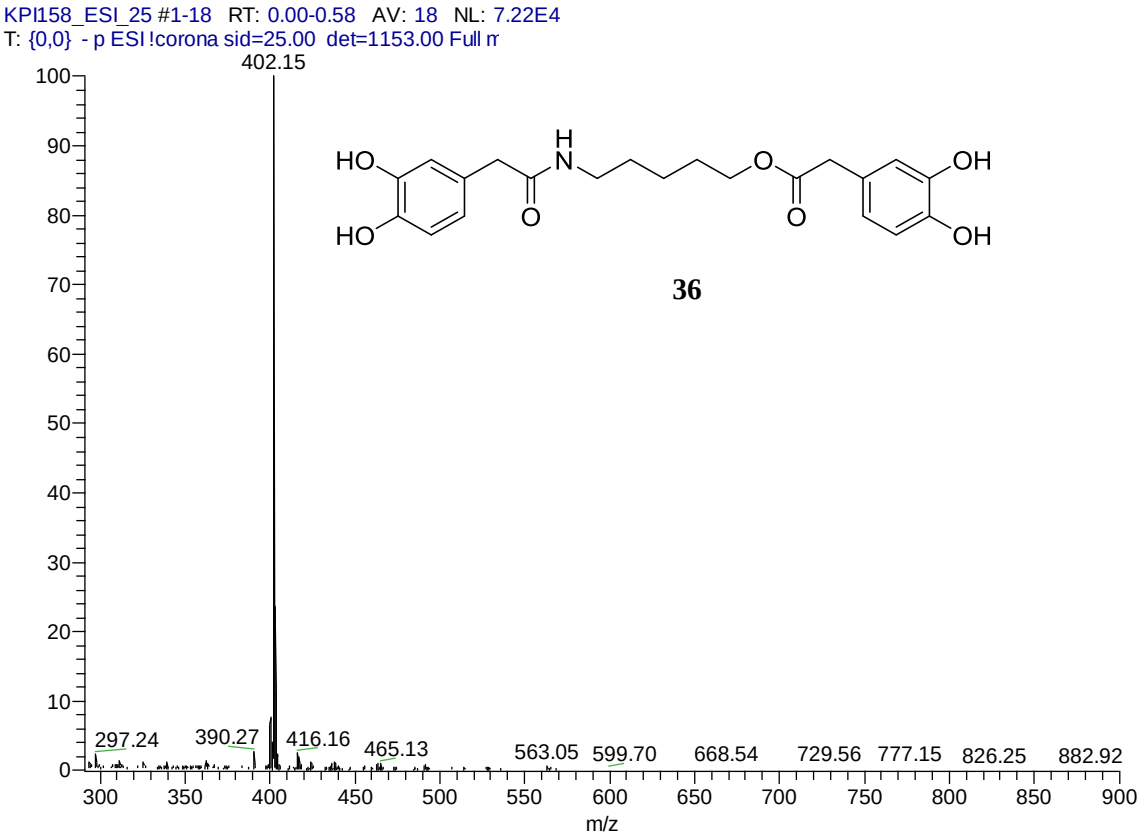


Figure S104: ^{13}C NMR of **36**.



36

Figure S105: ESI-MS of **36**.

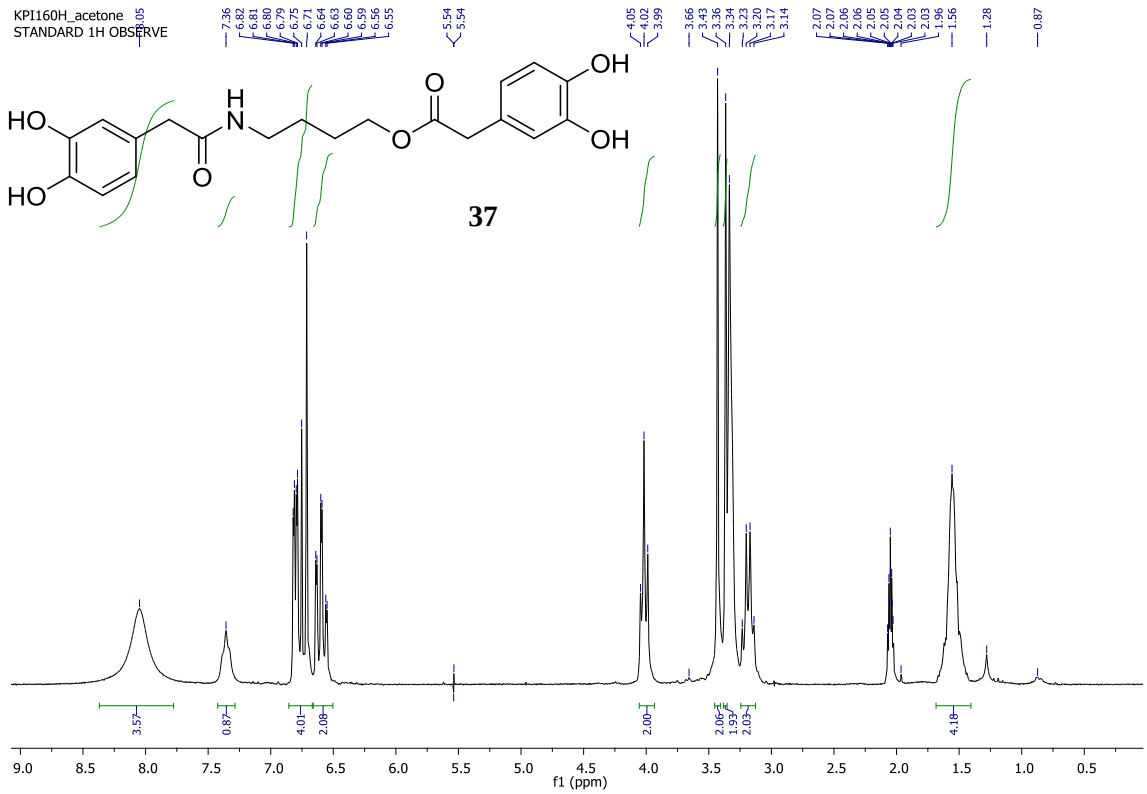


Figure S106: ^{1}H NMR of **37**.

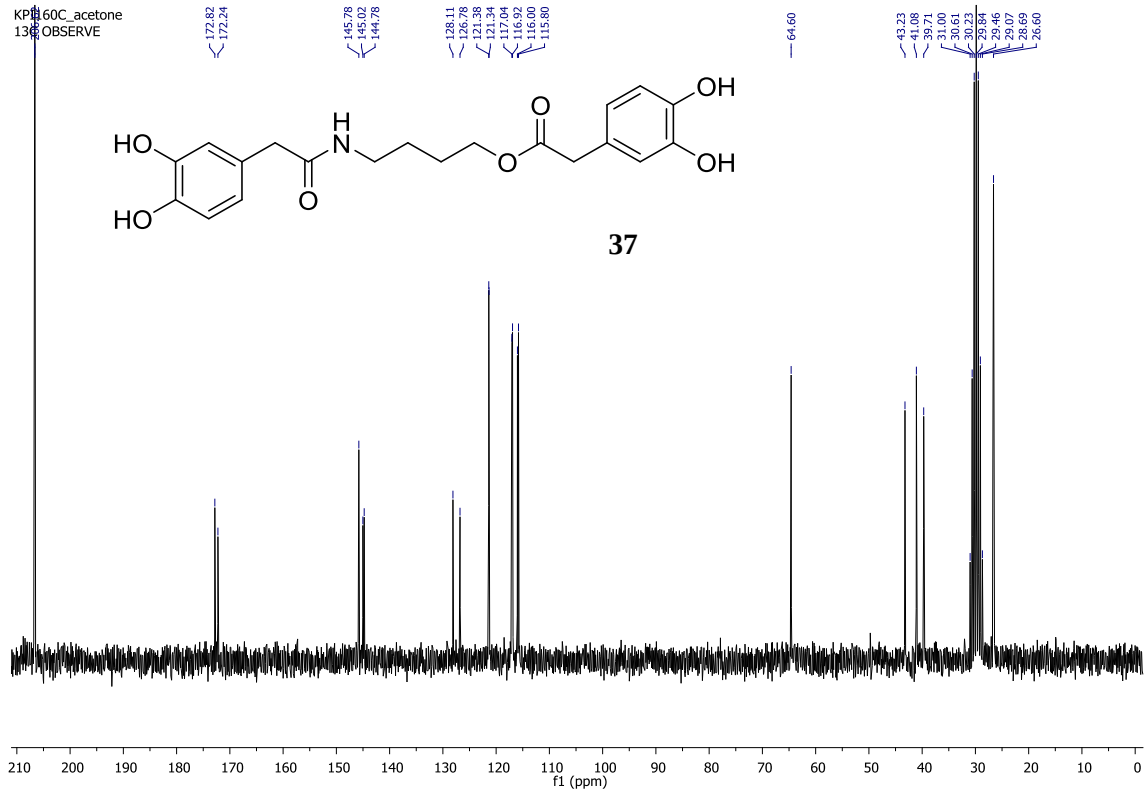
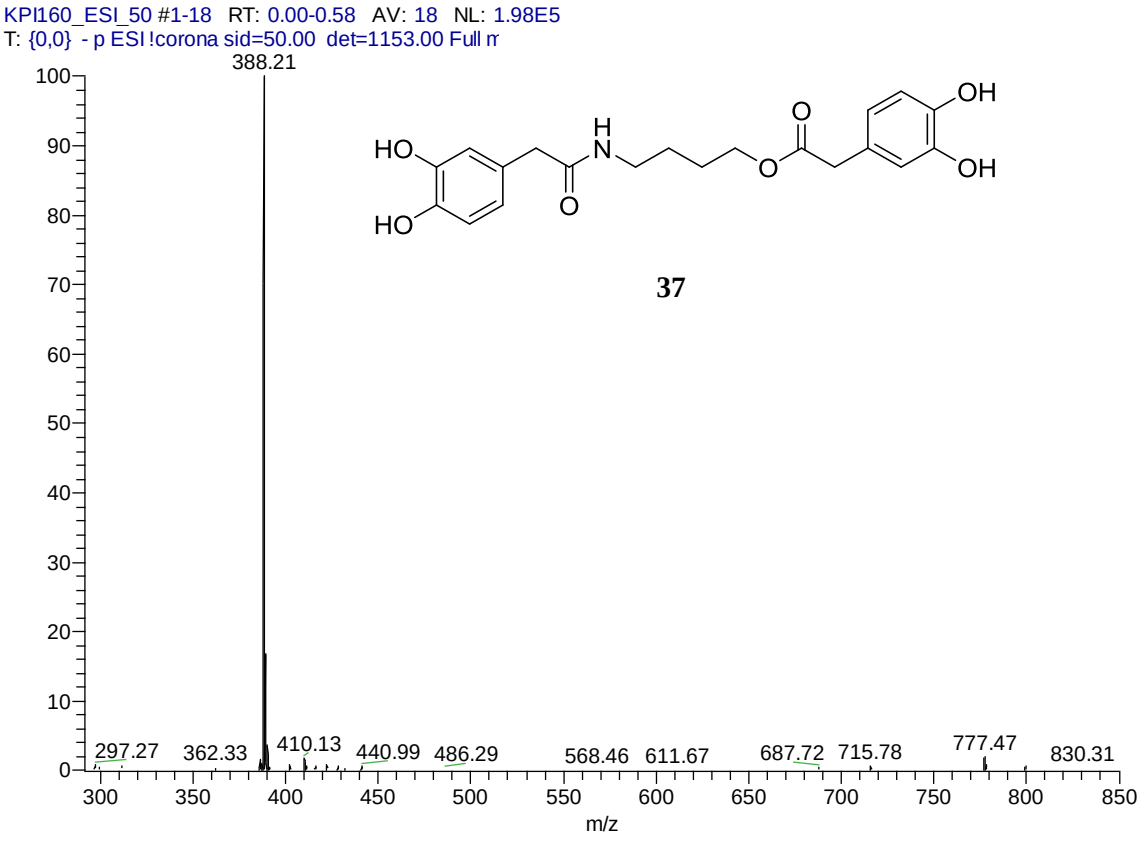


Figure S107: ^{13}C NMR of **37**.



37

Figure S108: ESI-MS of **37**.

2. DPPH Assays

Radical scavenging activity of derivatives/conjugates was determined according to a recently modified literature procedure (Tassano et al. 2015). A 80.14 μm solution of DPPH (2.90 mL, 232 nmol) was placed in a cuvette. A solution of the polyphenol compound (with a known concentration from 100 to 500 μM; 100 μL, from 10 to 50 nmol) was added, and the UV absorbance was monitored versus time at λ = 516 nm with a UV/Vis spectrophotometer. Absorbance values were taken every 0.1 min. The end of the first fast reaction was determined by observation of the second-order derivative: when it approached 0, the first reaction was considered ended. The end of the second slow reaction was determined by reaching the steady state. The EC_{50} value was obtained by plotting the steady-state (t_2) values of the %RSA for the various concentrations, obtaining the best straight line and deducting the concentration at which %RSA was = 50. Experiments were performed at six different concentrations of the antioxidant in triplicate.

Table S1.Results of DPPH assay on selected concentrations.

Compound	C(μM)	MR	t_1(min)	t_2(min)	%RSA$_1$	%RSA$_2$
19	375	0.06	8.5	8.5	76.4	76.4
	250	0.04	2.5	120	36.2	68.2
	125	0.02	2	120	14.9	33.4
20	500	0.08	25	25	76.7	76.7
	375	0.06	10	120	52.4	64.1
	250	0.04	6	120	32.4	42.3
	125	0.02	1	15	21.8	25.5
21	375	0.06	20	20	78.3	78.3
	250	0.04	3	80	38.0	75.5
	175	0.03	2	120	29.0	57.6
	125	0.02	1.6	25	18.5	26.3
22	500	0.08	0.3	0.3	77.0	77.0
	250	0.04	1.6	60	42.6	73.9
	125	0.02	1.3	120	17.2	59.8
	62.5	0.01	0.7	110	14.5	30.4
23	500	0.08	6	43	52.7	78.5
	375	0.06	1.5	30	52.6	72.9

	125	0.02	1.2	120	6.3	42.1
	500	0.08	7	60	47.3	77.4
6	375	0.06	5	120	32.9	65.4
	250	0.04	3	87	16.1	32.5
	500	0.08	1.66	85	35.1	79.0
7	375	0.06	0.7	83	34.5	73.1
	250	0.04	0.49	120	17.5	38.7
	500	0.08	1.6	46	44.9	72.3
	375	0.06	0.6	70	35.1	71.6
8	250	0.04	0.3	120	23.0	65.3
	125	0.02	0.5	120	4.4	25.4
	500	0.08	2	33	56.7	72.3
	375	0.06	0.3	120	34.4	68.4
9	250	0.04	0.5	120	20.2	55.7
	125	0.02	0.2	120	9.8	27.2
	500	0.08	0.3	0.3	72.2	72.2
25	250	0.04	0.22	16	29.3	70.8
	125	0.02	0.4	113	16.7	48.6
	750	0.12	1.66	45	59.5	76.0
	500	0.08	0.6	120	46.2	78.3
	375	0.06	0.5	120	44.1	72.6
12	300	0.048	0.45	120	11.7	37.0
	250	0.04	0.2	120	21.7	31.7
	125	0.02	0.15	60	19.6	25.1
	750	0.12	1.66	50	59.3	78.6
13	500	0.08	1	68	52.9	77.8
	250	0.04	0.6	120	29.1	45.5
	500	0.08	3.7	3.7	80.0	80.0
34	250	0.04	3	70	40.7	60.8
	125	0.02	1	100	27.9	49.4
	500	0.08	3	3	80.5	80.5
35	250	0.04	2.6	56	39.8	76.1
	125	0.02	1	88	26.6	45.1

	500	0.08	5	5	78.1	78.1
	250	0.04	1.6	21	41.6	76.2
36	175	0.028	1.3	95	34.7	68.8
	125	0.02	1.4	120	18.7	43.2
	500	0.08	4.5	4.5	79.4	79.4
37	375	0.06	4	4	74.1	74.1
	125	0.02	1	66	22.3	38.1
	500	0.08	3	3	76.3	76.3
DHPAA	375	0.06	1.66	120	49.8	65.2
	250	0.04	0.8	120	33.4	42.8

Table S2. EC_{50} of 3,4-dihydroxyphenylacetic derivatives/conjugates

Compd	EC_{50}[a]	EC_{50}[b]	Compd	EC_{50}[a]	EC_{50}[b]	Compd	EC_{50}[a]	EC_{50}[b]
6	328	52	**13**	239	38	**25**	39	6
7	291	46	**19**	196	31	**34**	126	20
8	239	38	**20**	297	48	**35**	73	12
9	263	42	**21**	181	29	**36**	17	3
12	347	55	**22**	117	19	**37**	239	38
Ascorbic acid	25	4	**23**	190	30	DHPAA	290	46

[a] (μM)

[b] ($nmol_{compound}/\mu mol_{DPPH}$)

Table S3. Physico-chemical properties of 3,4-dihydroxyphenylacetic derivatives/ conjugates

Compd	miLog*P*[a]	MW[b]	N_{ON}[c]	N_{OHNH}[d]	*N*viol.[e]	*N*rotb.[f]	TPSA[g]
Rule	<5, >1	<500	<10	<5		(<10)	$^{<}$140 Å^2
6	2.92	250	4	2	0	4	67
7	8.41	392	4	2	1	18	67
8	4.47	280	4	2	0	10	67
9	2.45	224	4	2	0	6	67
12	1.46	223	4	3	0	4	70
13	2.16	249	4	3	0	3	70

19	2.25	390	8	4	0	11	133
20	1.98	376	8	4	0	10	133
21	1.32	406	9	4	0	12	143
22	5.28	474	8	4	1	17	133
23	2.63	416	8	4	0	8	133
25	0.20	360	8	6	1	7	139
34	0.75	405	9	5	1	11	145
35	1.22	375	8	5	0	9	136
36	2.00	403	8	5	0	11	136
37	1.49	389	8	5	0	10	136
DHPAA	0.39	168	4	3	1	2	78

[a] Octanol–water partition coefficient, calculated by the methodology developed by Molinspiration.

[b] Molecular weight.

[c] Number of hydrogen-bond acceptors (O and N atoms).

[d] Number of hydrogen-bond donors (OH and NH groups).

[e] Number of 'Rule of five' violations.

[f] Number of rotatable bonds.

[g] Polar surface area.

Reference

Tassano E, Alama A, Basso A, Dondo G, Galatini A, Riva R, Banfi L. 2015. Conjugation of Hydroxytyrosol with Other Natural Phenolic Fragments: From Waste to Antioxidants and Antitumour Compounds. Eur. J. Org. Chem. 6710–6726