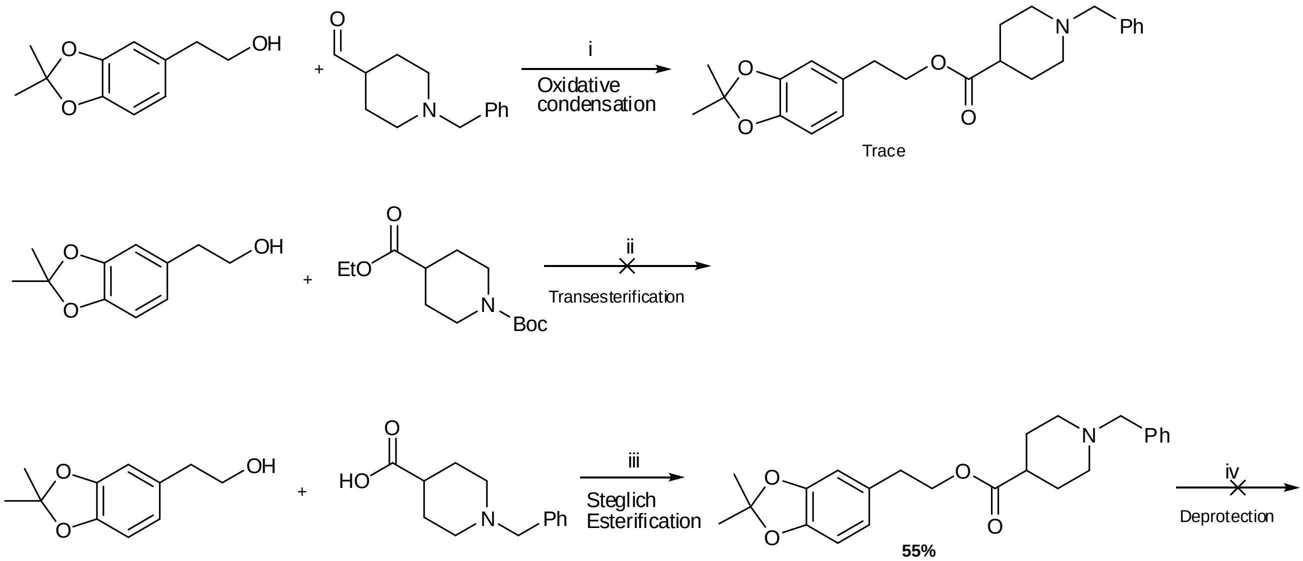
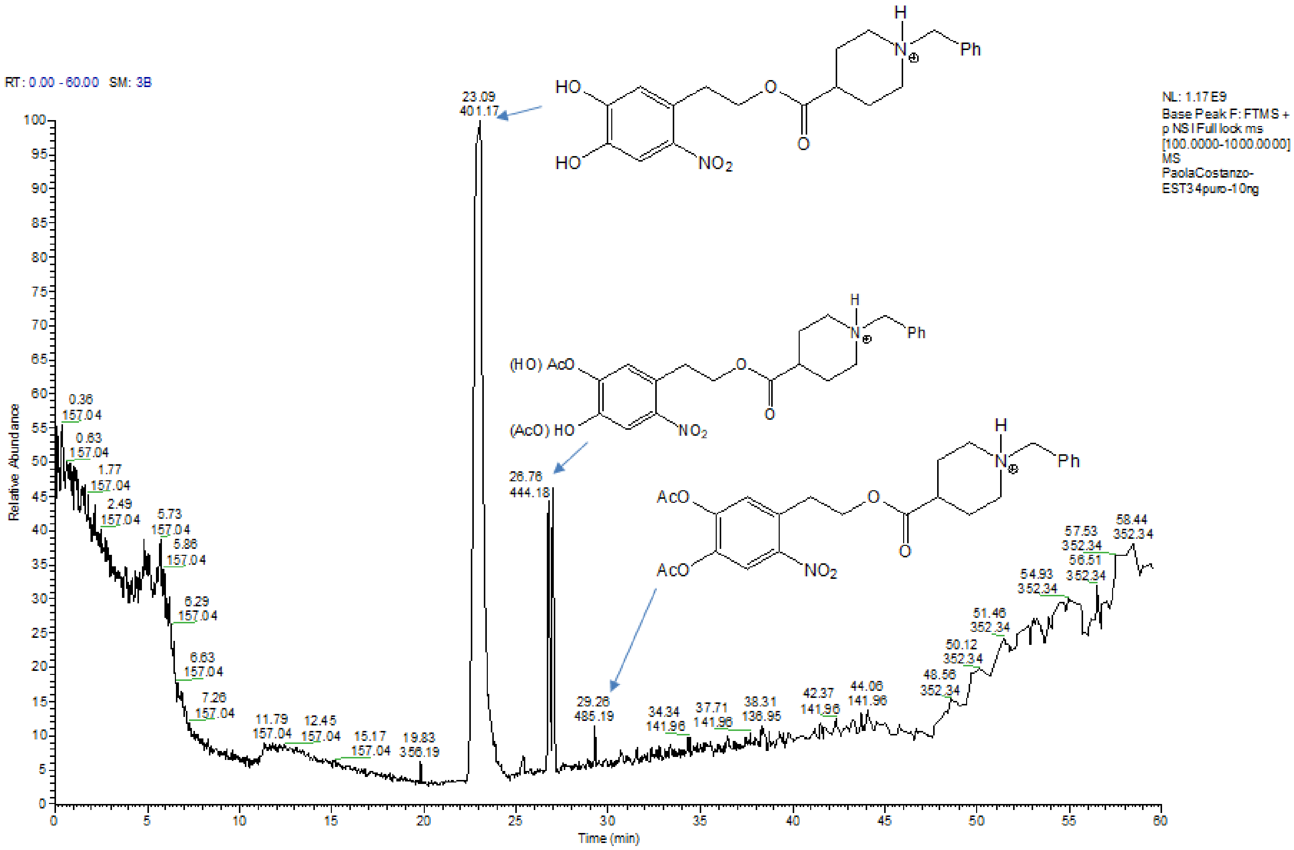
Supplementary Material

1 Synthetic pathways tested for the synthesis of the hydroxytyrosol-donepezil hybrid



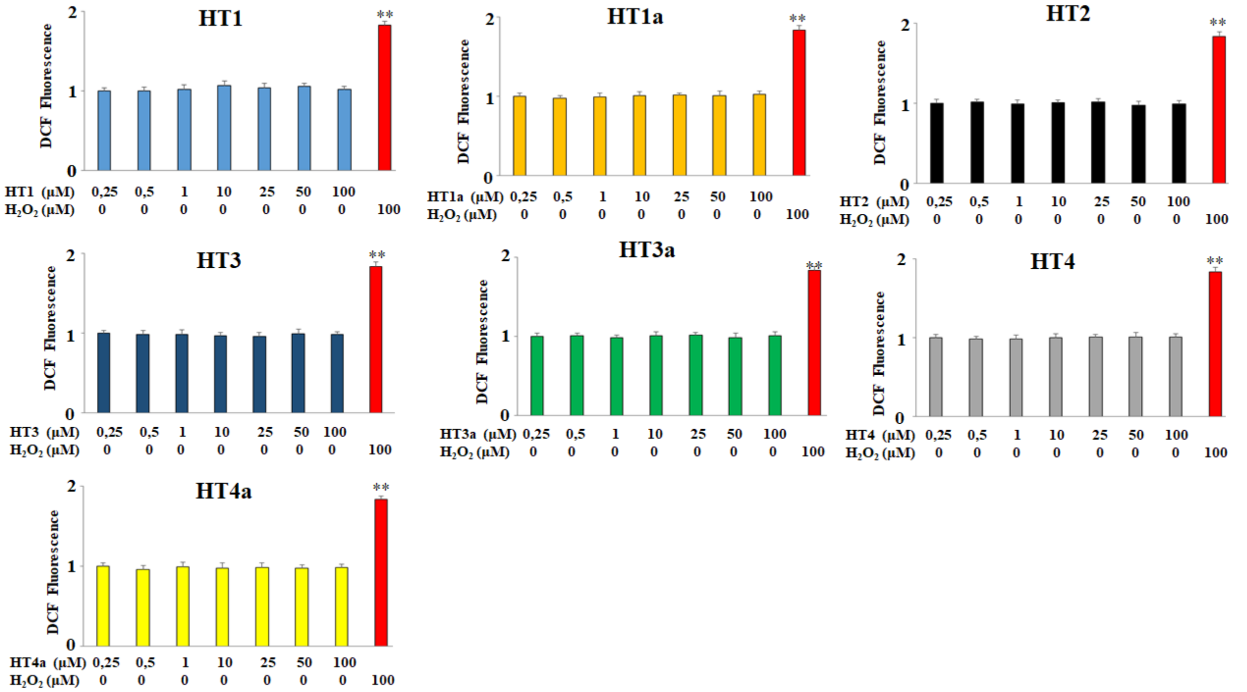
Supplementary Figure 1. Reaction conditions: (i) I_2, K_2CO_3, *t*-BuOH, rt, N_2, 4 days; (ii) $Sc(OTf)_3$, MW, 160 °C, 40 min; or MgO, 70 °C, N_2, o.n.; (iii) DIC, DMAP, CH_2Cl_2 dry / DMF dry (1:1), 0 °C to rt, o.n., N_2; (iv) Amberlist, MeOH, reflux.

2 LC-HRMS identification of HT2 acetylation products



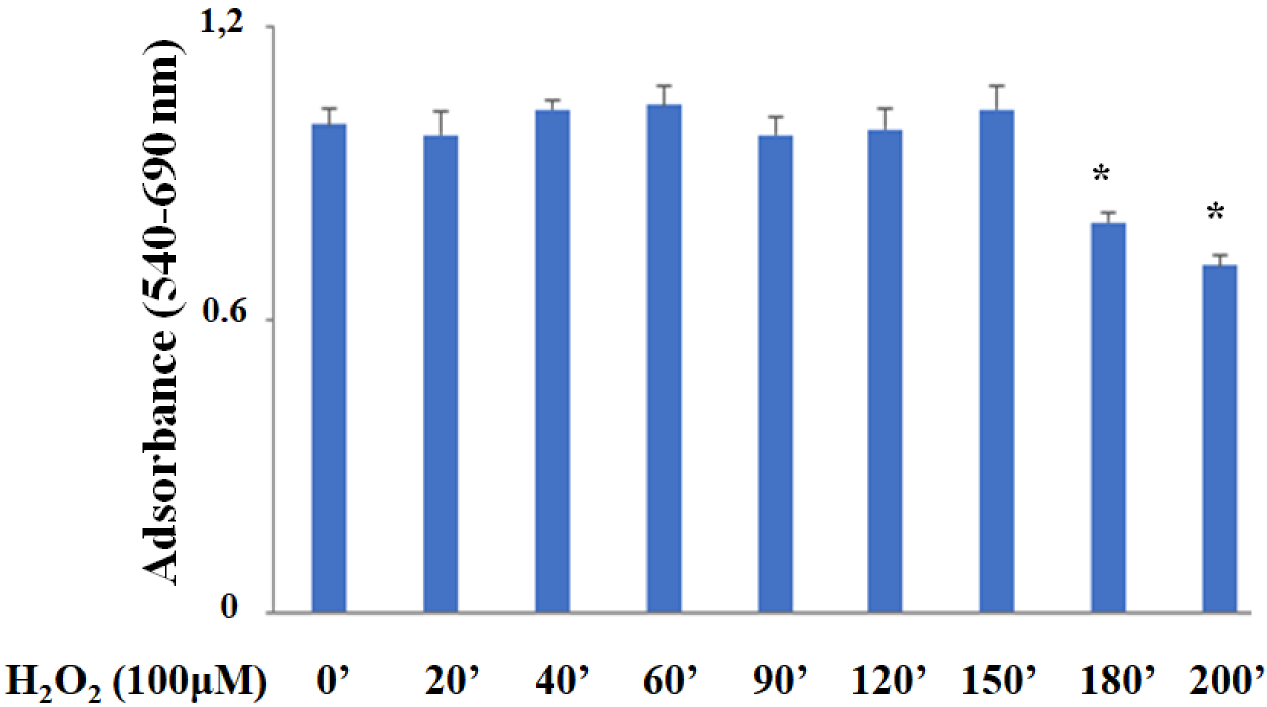
Supplementary Figure 2. Detection of the acetylated and di-acetylated form of **HT2** in the reaction crude. [**HT2-monoacetylated + H]$^+$:** 443.1811 (theoretical [M+H]$^+$ m/z 443.1813); [**HT2-diacetylated + H]$^+$:** 485.1917 (theoretical [M+H]$^+$ m/z 485.1918).

3 Evaluation of pro-oxidant effect for donepezil hybrids



Supplementary Figure 3. Donepezil hybrids have no pro-oxidant effects. Human neuroblastoma (SH-SY5Y) cell line was treated with donepezil hybrids for 24 h at the concentrations shown in the figure. No concentration showed accumulation of ROS. H_2O_2 was used as positive control. Three independent experiments were carried out, with values expressed as the mean ± standard deviation (sd). ** denotes $p < 0.01$ vs. control. Analysis of Variance (ANOVA) was followed by a Tukey–Kramer comparison test.

4 SH-SY5Y Cell viability after treatment with H_2O_2



Supplementary Figure 4. Measurement of cell viability following treatment with H_2O_2. Cell viability following treatment with H_2O_2 100µM was determined for several times (0-200'). The values of three independent experiments are expressed as the means ± standard deviations. * denotes $p < 0.05$ vs. control. Analysis of Variance (ANOVA) was followed by the Tukey–Kramer comparison test.

5 CUPRAC test

The CUPRAC test was performed as reported by Ozyürek et al. (Ozyürek et al., 2008) on the new compounds in the unacetylated form.

Supplementary Table 1. Concentration linearity range for all the unprotected hybrids.

Antioxidant	Linear equation and correlation coefficient	ε (L mol−1 cm−1)	TEAC
Trolox	A= 0,0133, c - 0,0414, r = 0.9979	0,0133	1
HT	A= 0,0375, c - 0,0201, r =0,9991	0,0375	2,82
HT1	A= 0,0447, c - 0,0336, r = 0,9943	0,0447	3,36
HT2	A= 0,0369, c+ 0,0178, r = 0,998	0,0369	2,77
HT3	A= 0,0239, c - 0,0192, r = 0,9945	0,0239	1,80
HT4	A= 0,0132, c - 0,0164, r = 0.9948	0,0132	0,99

6 Characterization of compounds

3,4-dihydroxyphenethyl 1-benzylpiperidine-4-carboxylate (HT1): White power, Yield 65%, R_f= (DCM:MeOH:TEA – 84:13:2) 0.6. HRMS: $[M+H]^+$ m/z 356.1852 (theoretical $[M+H]^+$ m/z 356.1856). ^{1}H NMR δ (ppm) (500 MHz, d_6-DMSO): 8.64-8.71 (m br, 2H, OH), 7.21-7.33 (m, 5H), 6.63 (d, *J*=8 Hz, 1H), 6.59 (d, 1H, *J*=2 Hz, 1H), 6.45 (dd, *J*=8 Hz and 2 Hz, 1H), 4.13 (t, *J*=7.0 Hz, 2H), 3.43 (s, 2H), 2.66-2.72 (m, 4H), 2.22-2.36 (m, 1H), 1.96-2.01 (t, *J*=11.2 Hz, 2H), 1.72-1.76 (m, 2H), 1.49-1.57(m, 2H). ^{13}C NMR (500 MHz, d_6-DMSO): δ 174.16, 144.96, 143.60, 128.46, 128.48, 128.02, 126.73, 119.36, 116.11, 115.34, 64.51, 62.13, 52.03, 45.63, 33.70, 27.81.

4,5-dihydroxy-2-nitrophenethyl 1-benzylpiperidine-4-carboxylate (HT2): Orange powde r, Yield=85%, R_f= ($CHCl_3$:AcOEt:TEA-60:38:2) 0.56. HRMS: $[M+H]^+$ m/z 440,2058 (theoretical $[M+H]^+$ m/z 440.2068). ^{1}H NMR δ (ppm) (300MHz, d_6-DMSO): 7.47 (s, 1H), 7.21-7.33 (m, 6H), 4.23 (t, *J*=6.3 Hz, 2H), 3.42 (s, 2H,), 3.08 (t, *J*=6.3 Hz, 2H), 2.69 (br d, *J*=10.7 Hz, 2H), 2.18-2.25 (m, 1H), 1.96 (br t, *J*=9.3 Hz, 2H), 1.70-1.73 (m, 2H), 1.46-1.53 (m, 2H); ^{13}C NMR (500 MHz, d_6-DMSO). 174.16, 152.53, 144.35, 138.71, 138.34, 128.74, 128.12, 126.83, 126.75, 118.54, 111.85, 63.29, 62.22, 52.15, 32.15, 30.40, 29.22, 27.85.

4-hydroxy-3-methoxyphenethyl 1-benzylpiperidine-4-carboxylate (HT3): White power, Yield=45%, R_f= (CH_2Cl_2:MeOH:TEA – 90:8:2) 0.70. HRMS: $[M+H]^+$ m/z 370.2007 (theoretical $[M+H]^+$ m/z 370.2013). ^{1}H NMR δ (ppm) (500 MHz, $CDCl_3$): 7.20-7.32 (m, 5H), 6.83 (d, *J*=7.8 Hz, 1H), 6.68-6.71 (m, 2H), 4.25 (t, *J*=6.9 Hz, 2H), 3.86 (s, 3H), 3.48 (s, 2H), 2.80-2.87 (m, 2H), 2.24-2.31 (m, 1H), 2.00-2.03 (m, 2H), 1.83-1.86 (m, 2H), 1.70-1.79 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): 175.31, 146.68, 144.53, 129.8, 129.34, 128.5, 127.25, 121.84, 114.58, 111.60, 65.21, 63.41, 56.09, 41.36, 35.04, 32.12, 28.42.

4-hydroxyphenethyl 1-benzylpiperidine-4-carboxylate (HT4): White power, Yield=55%; R_f= (DCM:MeOH:TEA – 90:8:2) 0.37. HRMS: $[M+H]^+$ m/z 340.1898 (theoretical $[M+H]^+$ m/z 340.1907). ^{1}H NMR δ (ppm) (500 MHz, $CDCl_3$): 7.23-7.32 (m, 5H), 7.03 (d, *J*=8.4 Hz, 2H), 6.72 (d, *J*=8.4 Hz, 2H), 4.23 (t, *J*=6.9 Hz, 2H), 3.50 (s, 2H), 2.83 (t, *J*=6.9 Hz, 4H), 2.23-2.33 (m, 1H), 2.00-2.08 (m, 2H), 1.82-1.86 (m, 2H), 1.70-1.79 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$,): δ 175.31, 154.89, 137.84, 130.22, 129.68, 129.57, 128.46, 127.39, 115.68, 65.31, 63.40, 52.95, 41.23, 34.46, 32.12, 28.16.

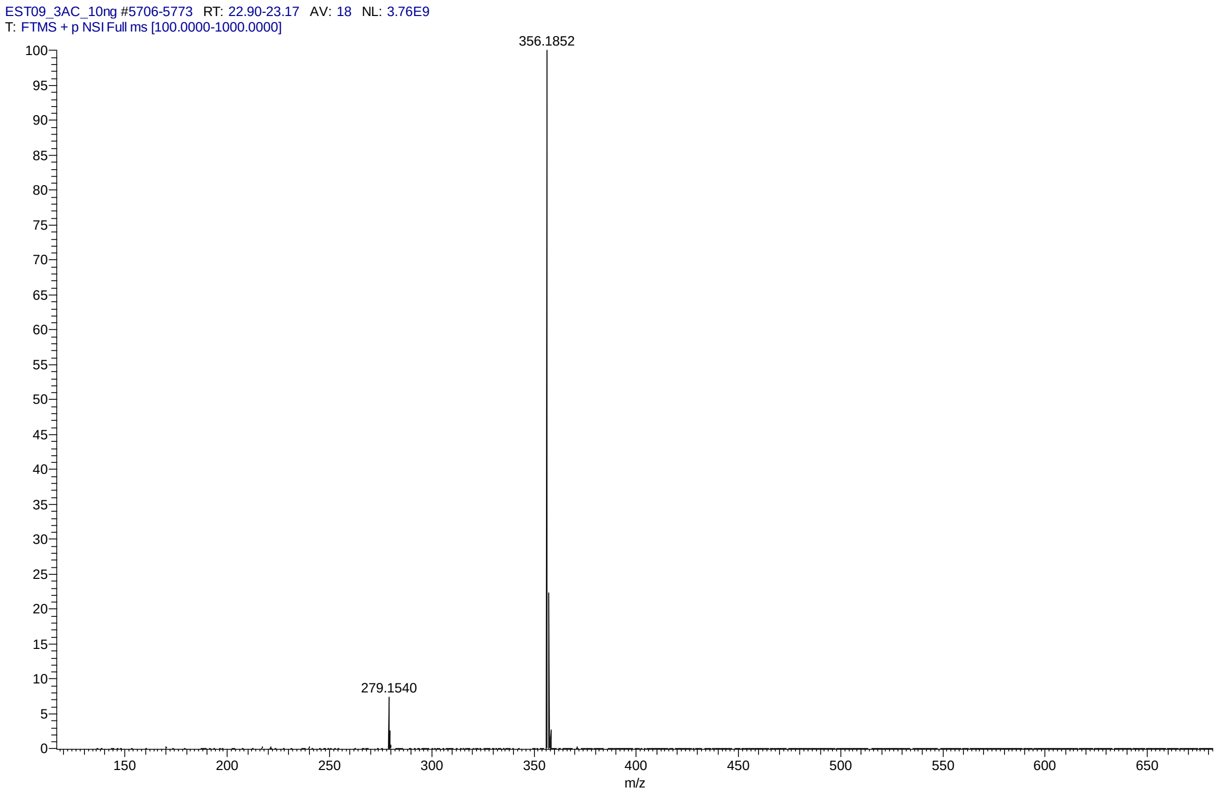
4-(2-(1-benzylpiperidine-4-carbonyloxy)ethyl)-1,2-phenylene diacetate (HT1a): Orange oil, Yield=55%, R_f= (CH_2Cl_2:MeOH:TEA-90:8:2) 0.52. HRMS: $[M+H]^+$ m/z 401.1706 (theoretical $[M+H]^+$ m/z 401.1707). ^{1}H NMR δ (ppm) ($CDCl_3$, 300 MHz): 7.22-7.37 (m, 5H), 7.08-7.18 (m, 2H), 7.00-7.08 (m, 1H), 4.29 (t, *J*=9.9 Hz, 2H), 3.50 (s, 2H), 2.92 (t, *J*=9.9 Hz, 2H), 2.84 (d, *J*=11 Hz, 2H), 2.22-2.38 (m, 7H), 1.92-2.10 (m, 2H), 1.90-1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz). δ: 179.1, 175.2, 168.4, 146.3, 142.5, 137.8, 135.3, 129.9, 128.7, 127.5, 124.3, 65.4, 63.3, 52.4, 41.9, 34.6, 28.1, 20.7.

4-acetoxy-3-methoxyphenethyl 1-benzylpiperidine-4-carboxylate (HT3a): Orange oil, Yield=98%, R_f= (CH_2Cl_2:MeOH:TEA – 90:8:2) 0.77; HRMS: $[M+H]^+$ m/z 412.2111 (theoretical $[M+H]^+$ m/z 412.2118). ^{1}H NMR δ (ppm) (500 MHz, $CDCl_3$): 7.15-7.24 (m, 5H), 6.87 (d, *J*=8.0 Hz, 1H), 6.69-6.75 (td, *J*=8.0 and *J*=1.8 Hz, 2H), 4.22 (t, *J*=7.2 Hz, 2H), 3.74 (s, 3H), 3.41 (s, 2H), 2.84 (t, *J*=7.0 Hz, 2H), 2.75 (br d, *J*=11.0 Hz, 2H), 2.24 (s, 3H), 2.16-2.22 (m, 1H), 1.94 (t br, =11.0 Hz, 2H), 1. 77-1.79 (m, 2H), 1.63-1.73 (m, 2H). ^{13}C NMR ($CDCl_3$, 500 MHz): 175.32, 169.34, 151.13, 138.6, 136.99, 129.28, 128.4, 127.19, 122.88, 121.27, 113.27, 64.76, 63.44, 56.07, 53.07, 41.42, 35.26, 28.49, 20.88.

4-acetoxyphenethyl 1-benzylpiperidine-4-carboxylate (HT4a): Incolor oil; Yield=85%; R_f= ($CHCl_3$:AcOEt:TEA-60:38:2) 0.28. HRMS: $[M+H]^+$ m/z 382.2005 (theoretical $[M+H]^+$ m/z 382.2013); ^{1}H NMR δ (ppm) (500 MHz, $CDCl_3$): 7.15-7.24 (m, 5H), 7.14 (d, *J*=8.4 Hz, 2H), 6.94 (d, *J*=8.5 Hz, 2H), 4.21 (t, *J*=6.8 Hz, 2H), 3.41 (s, 2H), 2.85 (t, *J*=6.9 Hz, 2H), 2.73-2.77 (br d, *J*=11.5 Hz, 2H), 2.16-2.23 (m, 4H), 1.91-1.96 (br t, *J*=10.8 Hz, 2H), 1.74-1.81 (m, 2H), 1.61-1.70 (m, 2H); ^{13}C NMR (500 MHz, $CDCl_3$,): δ 175.31, 169.77, 149.54, 138.58, 135.66, 130.08, 129.32, 128.40, 127.19, 121.75, 64.78, 63.45, 53.08, 41.37, 34.72, 28.1, 21.35.

7 HRMS

HT1



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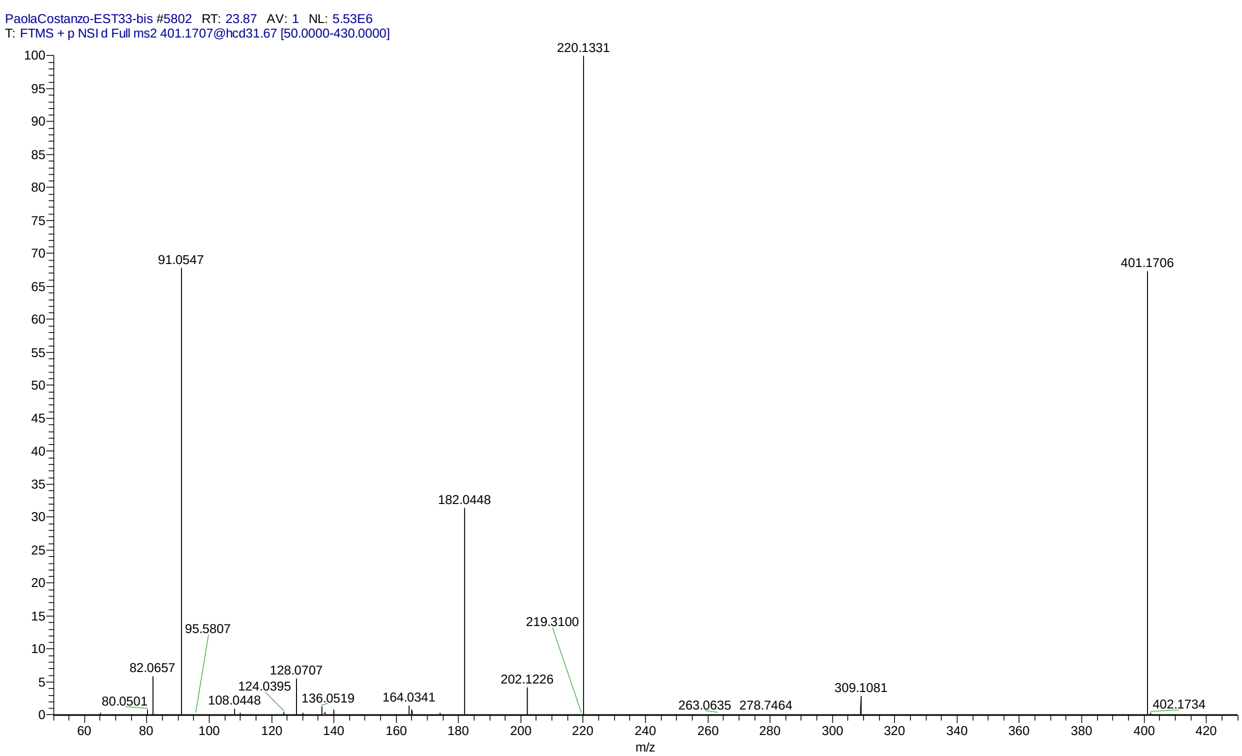

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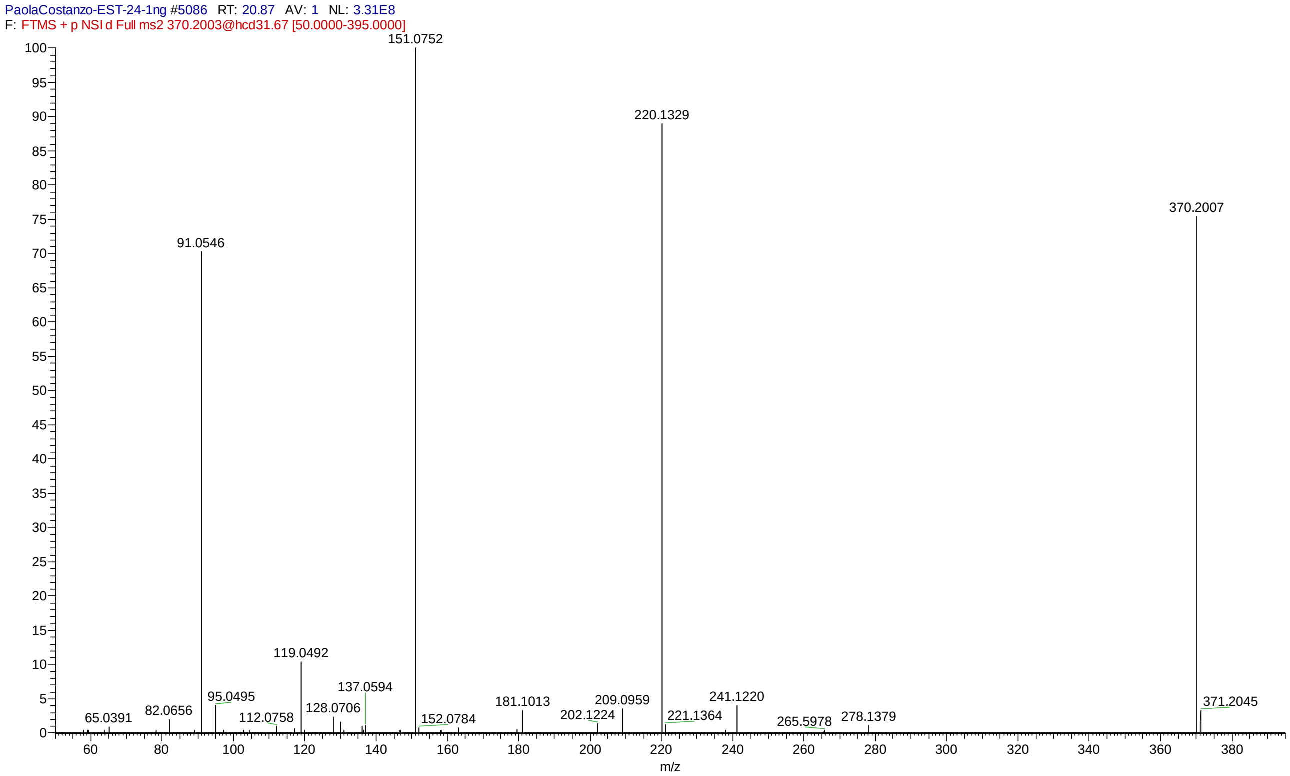
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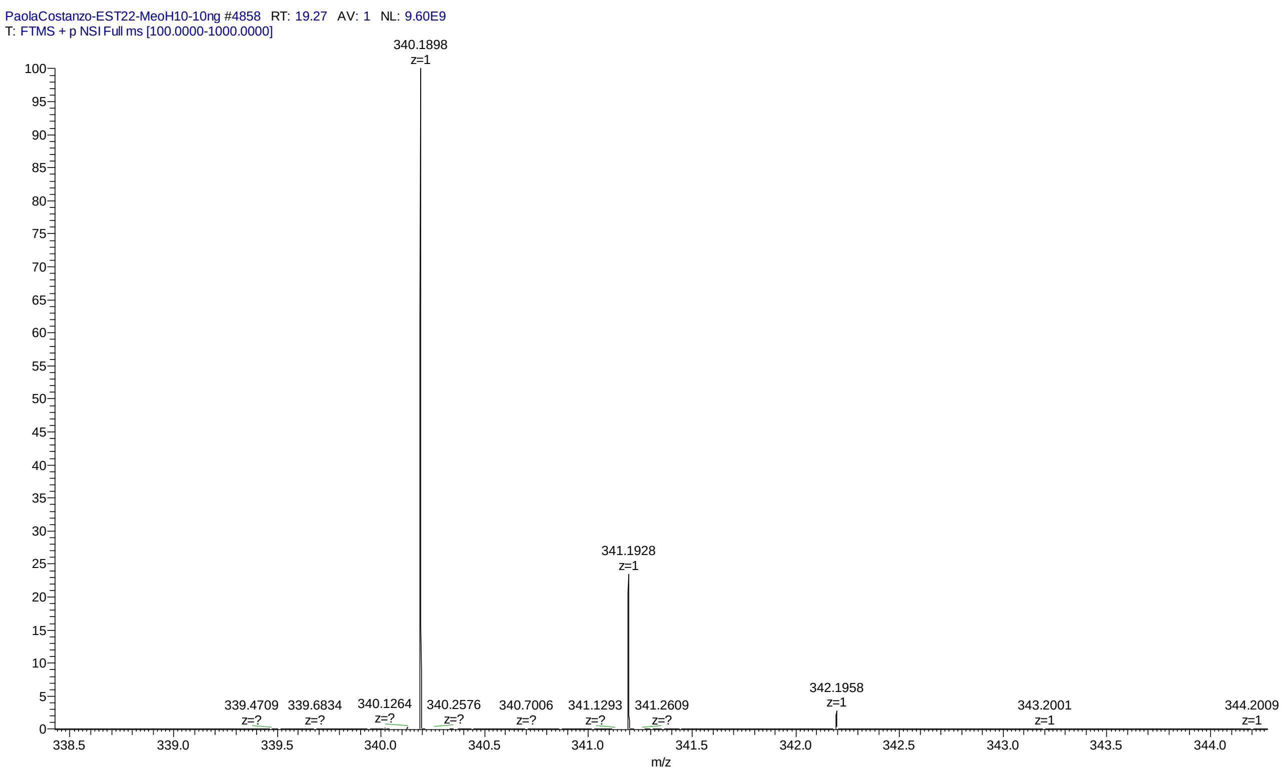
HT4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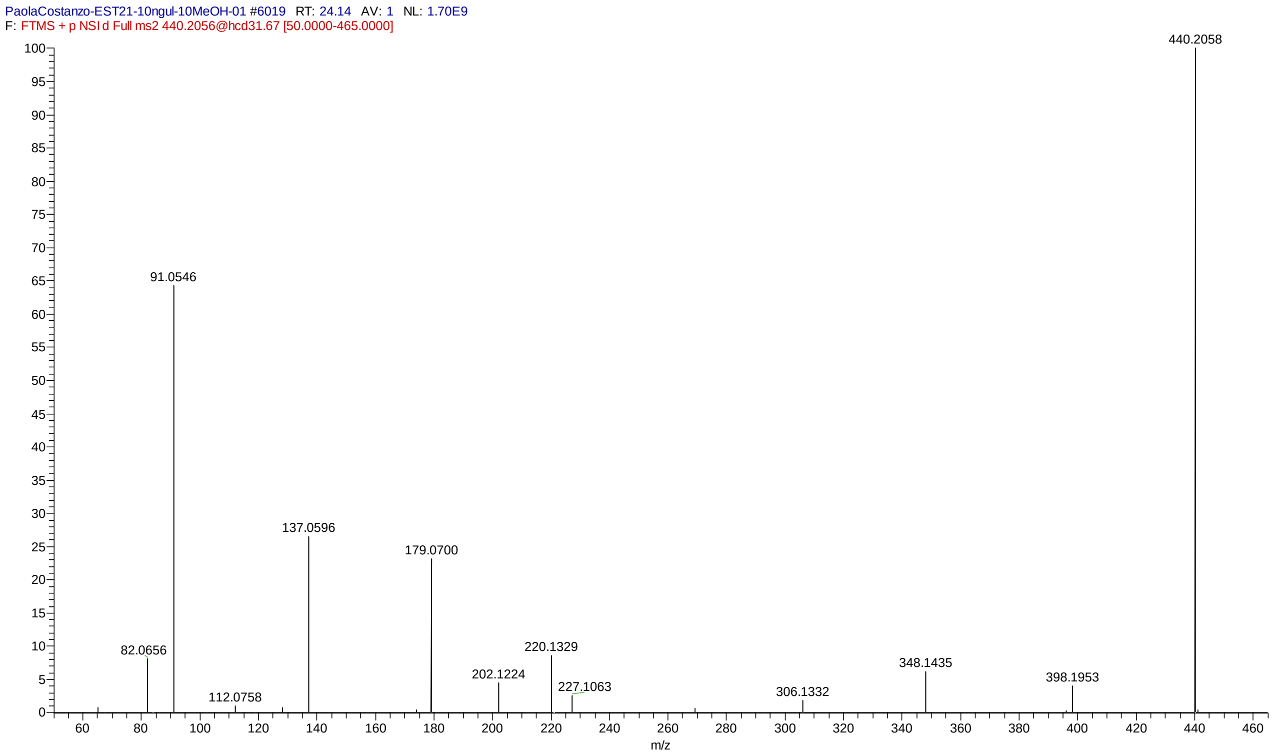
HT1a



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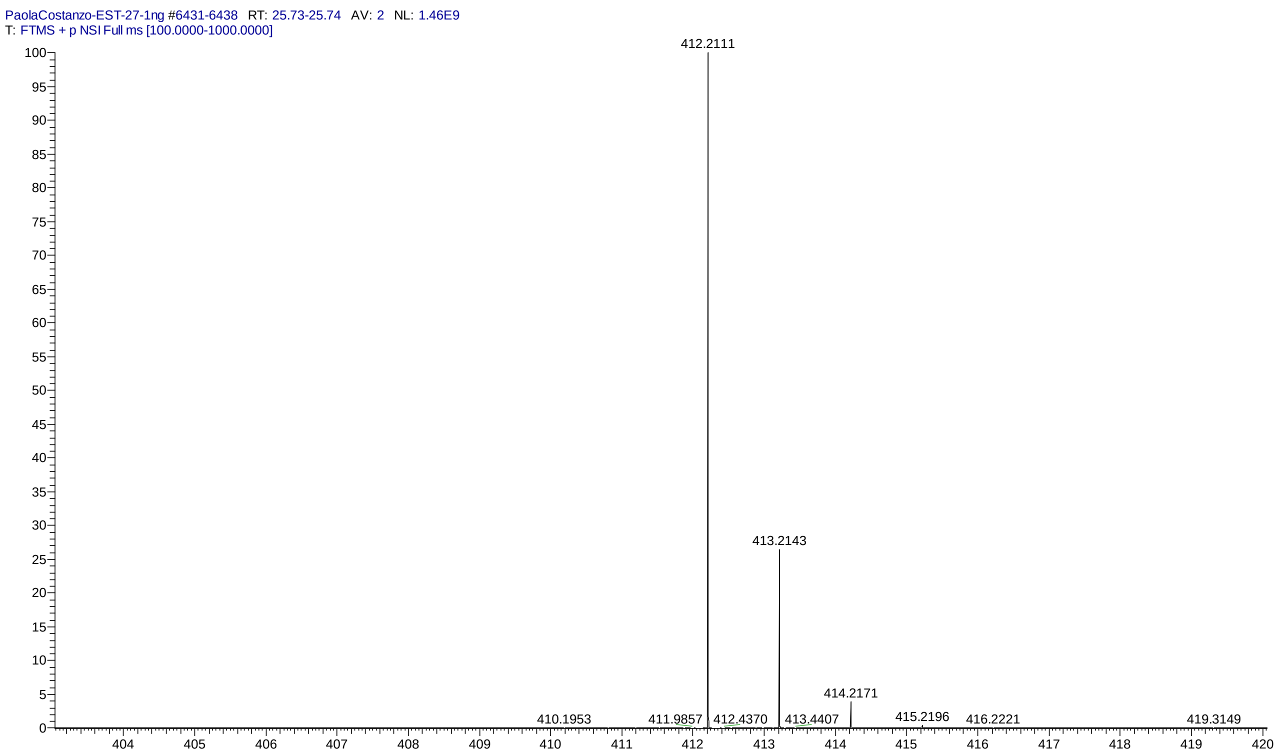
HT3a



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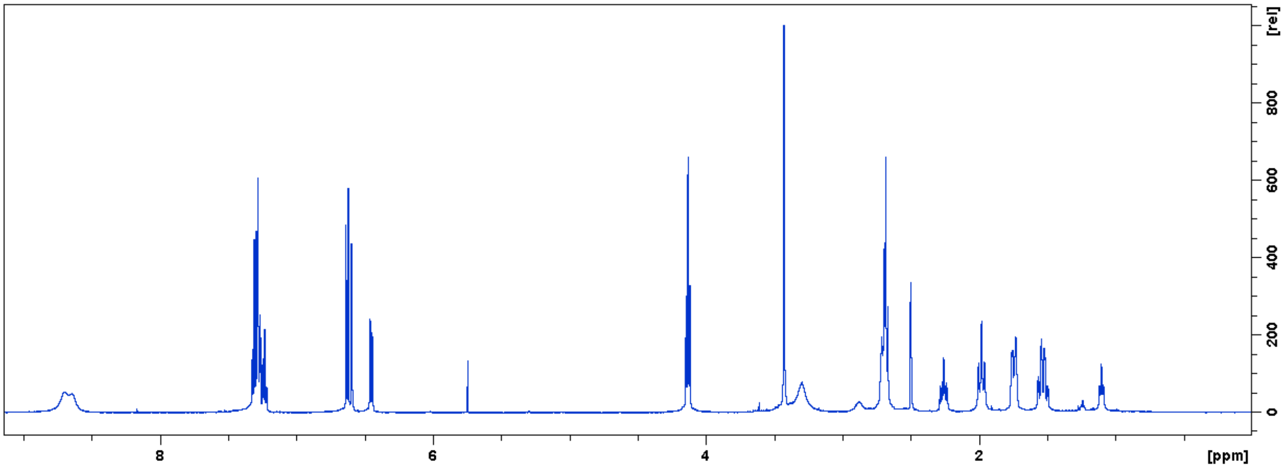
8 ^{1}H-NMR

HT1



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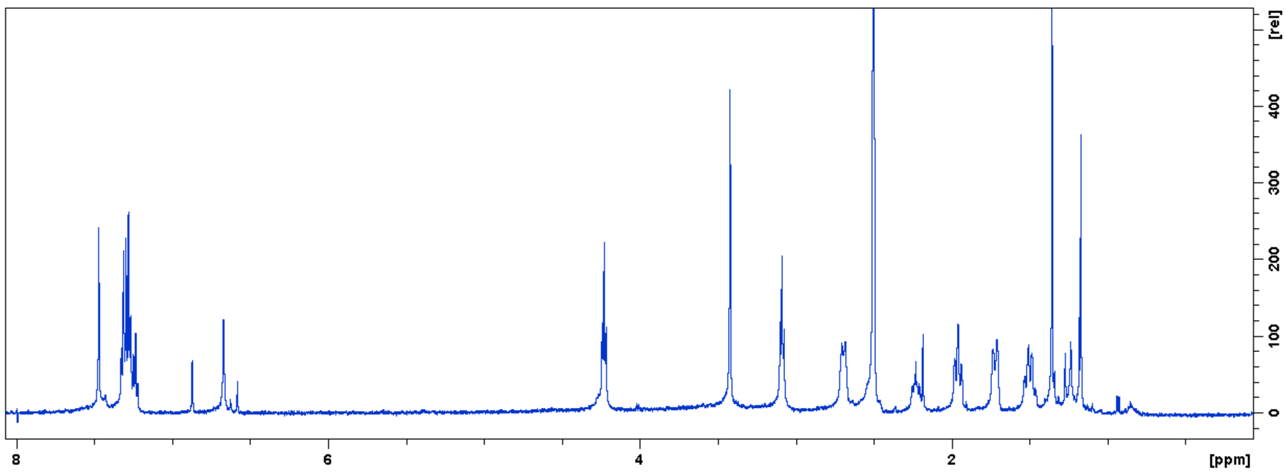

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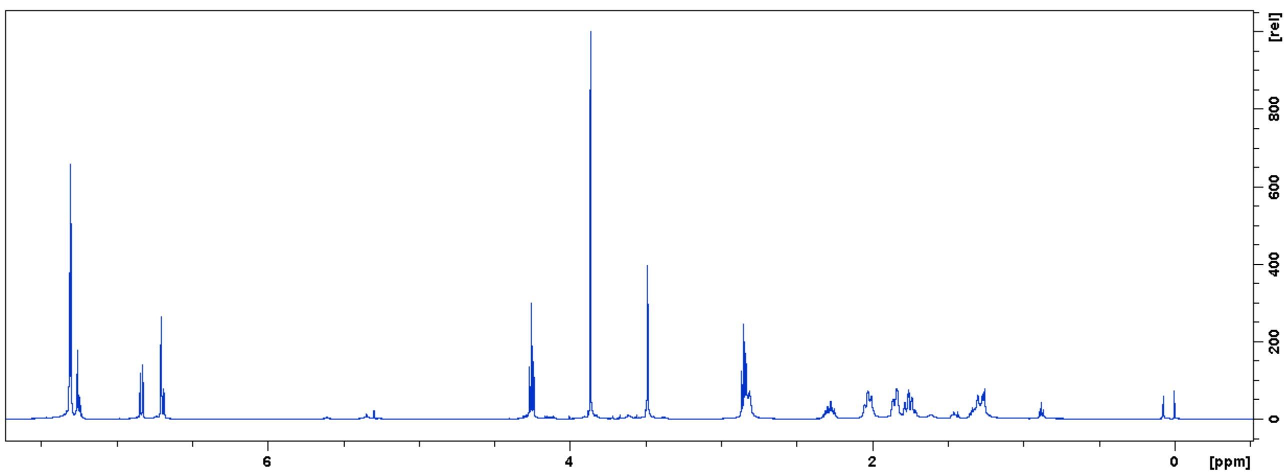

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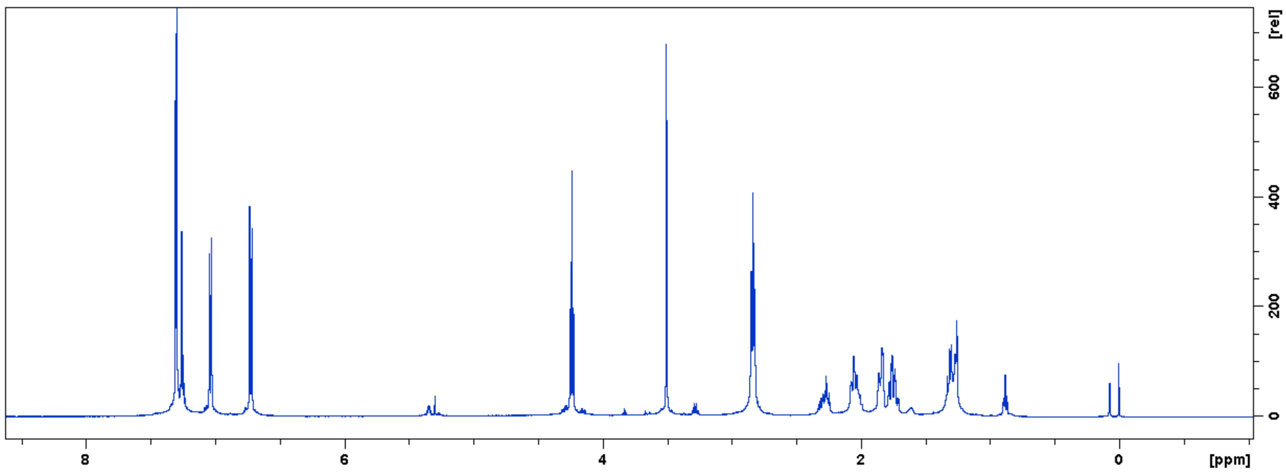

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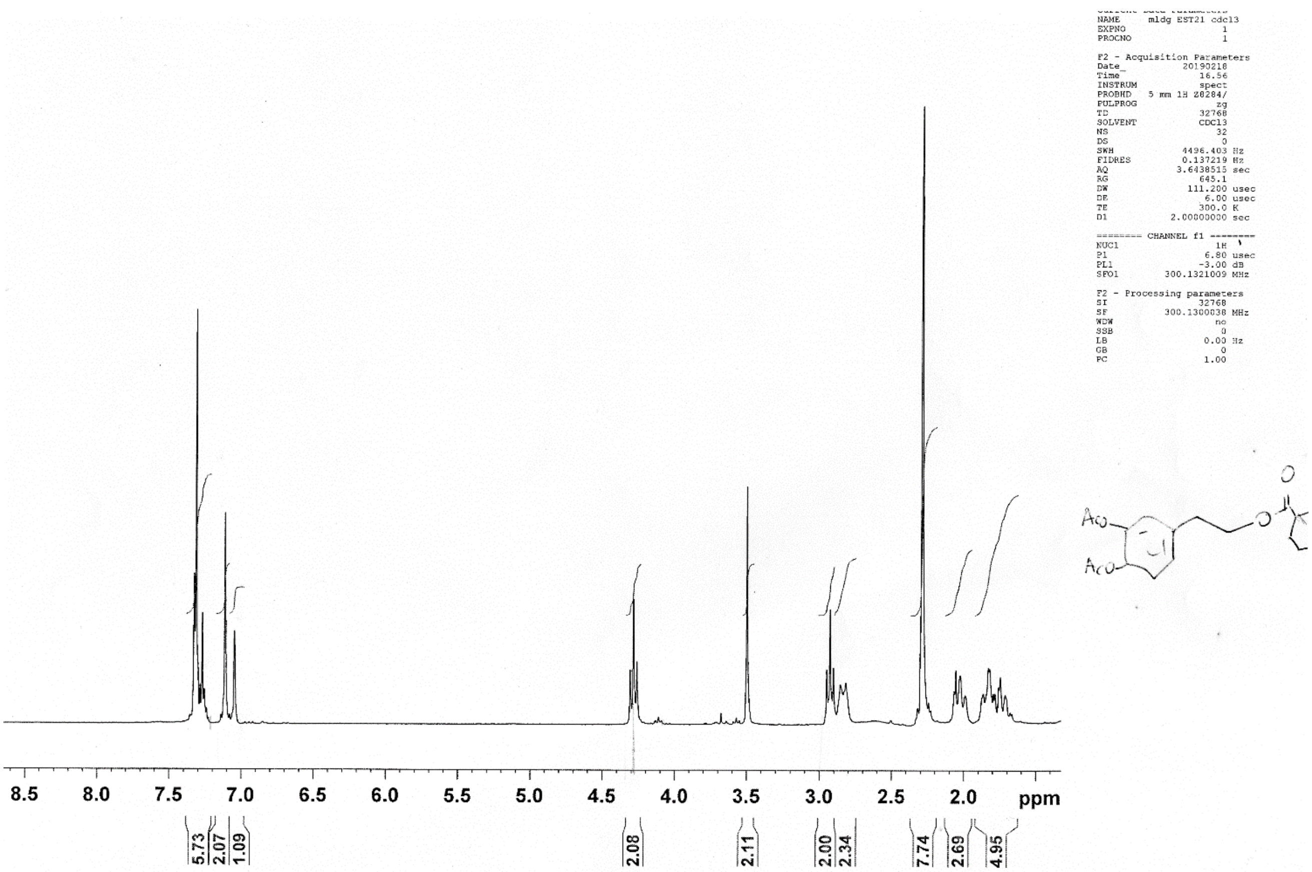

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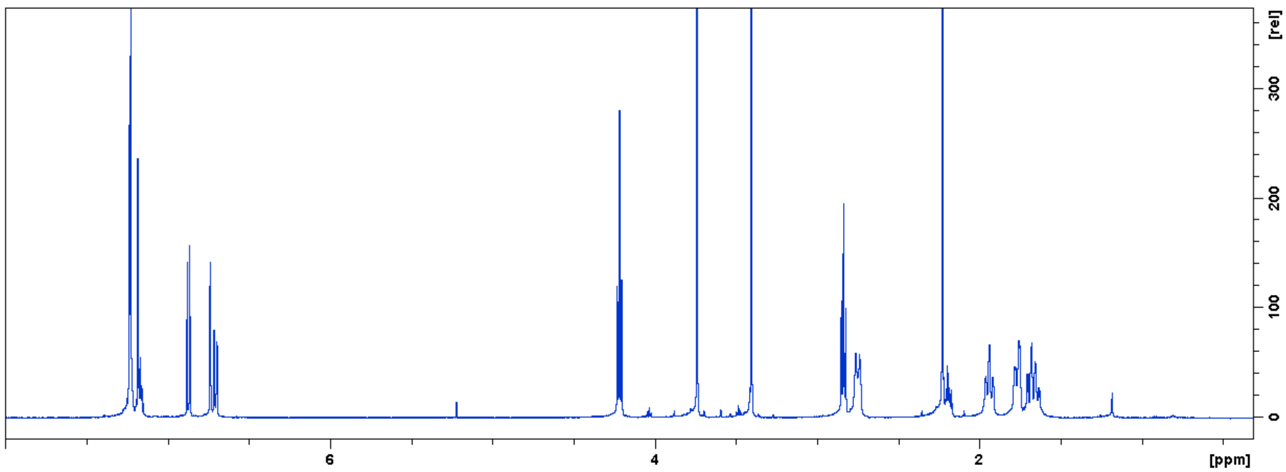

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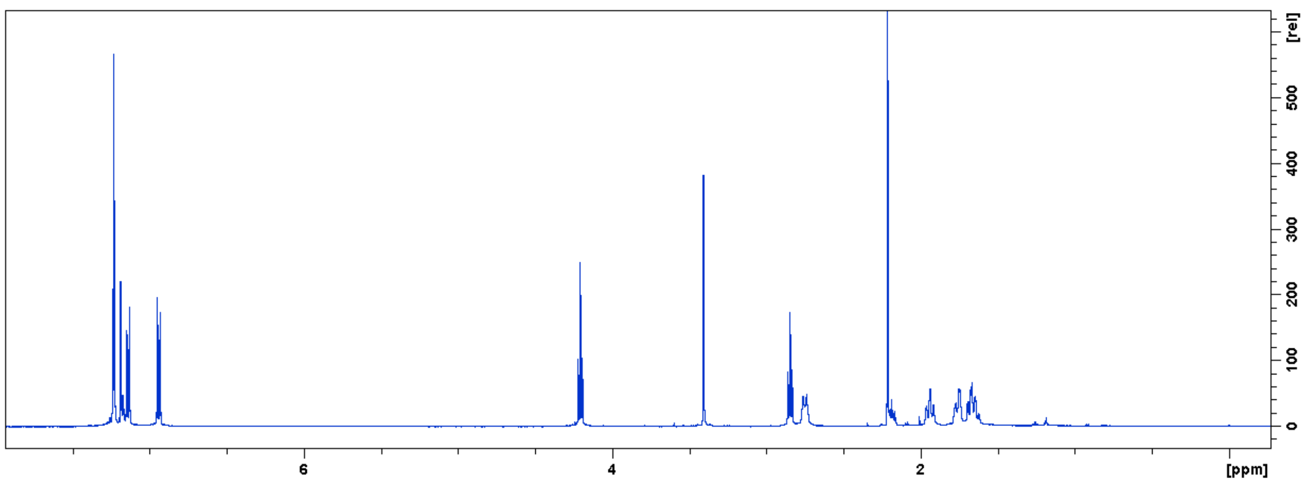

9 ^{13}C-NMR

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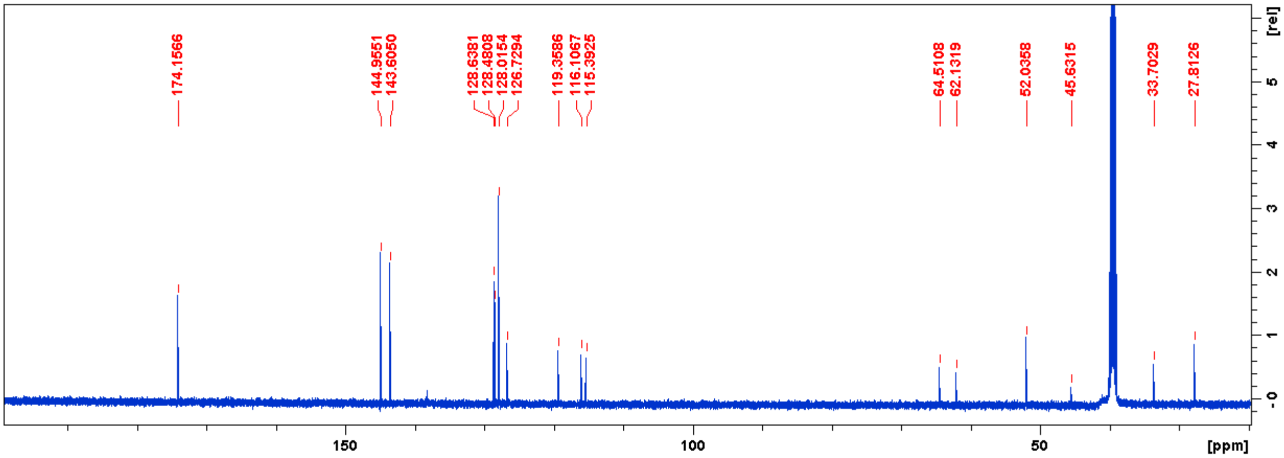

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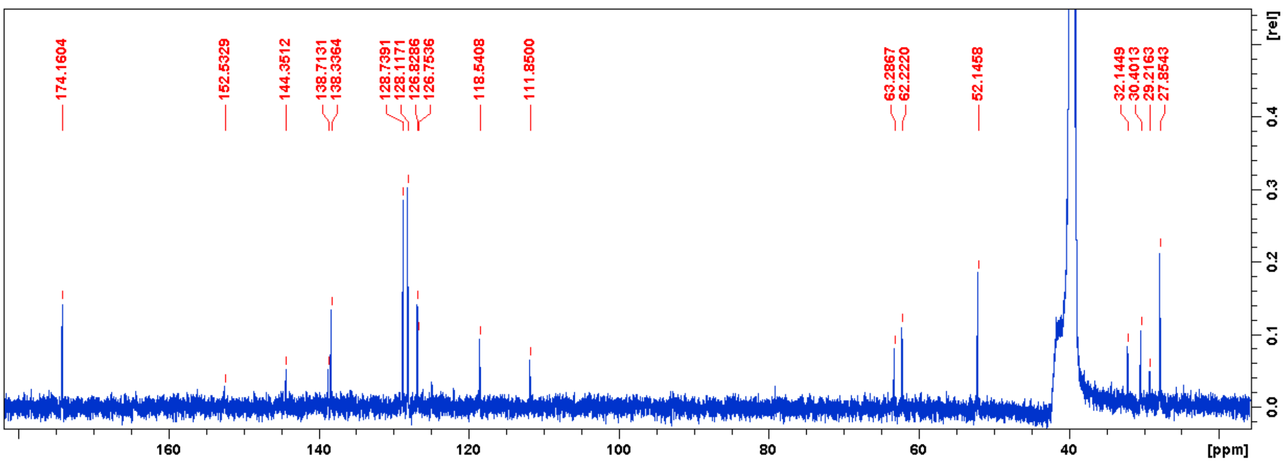

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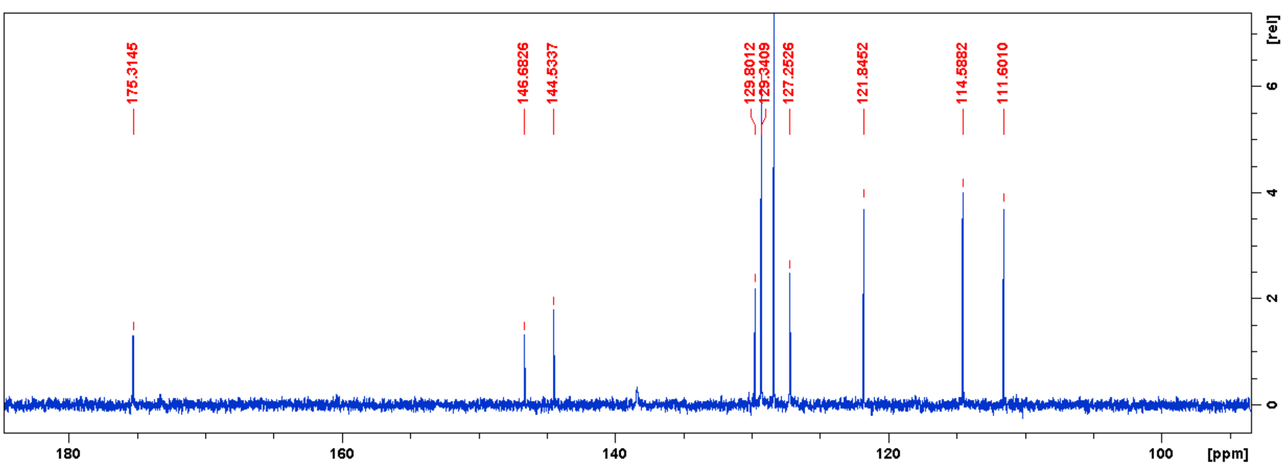

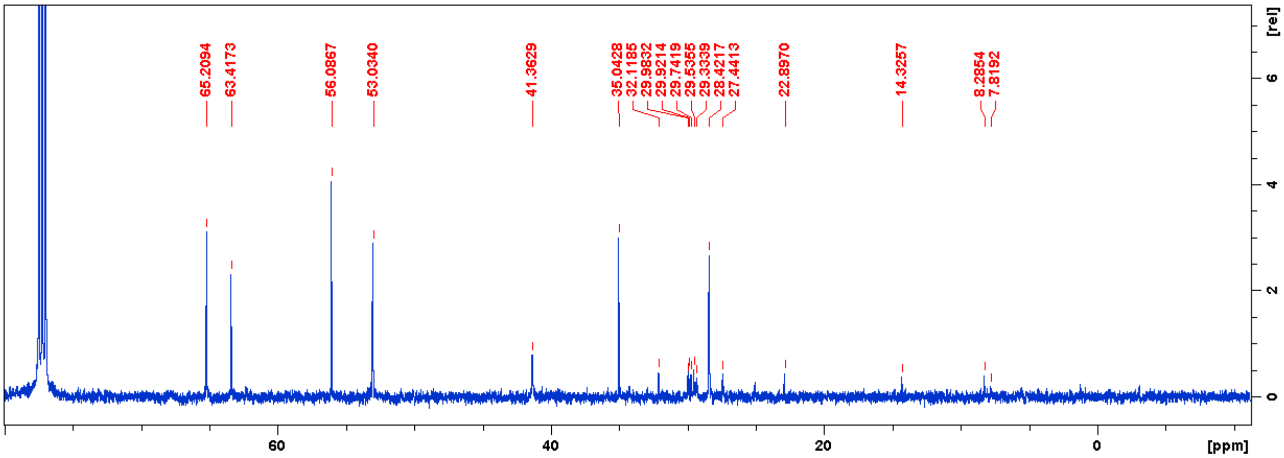
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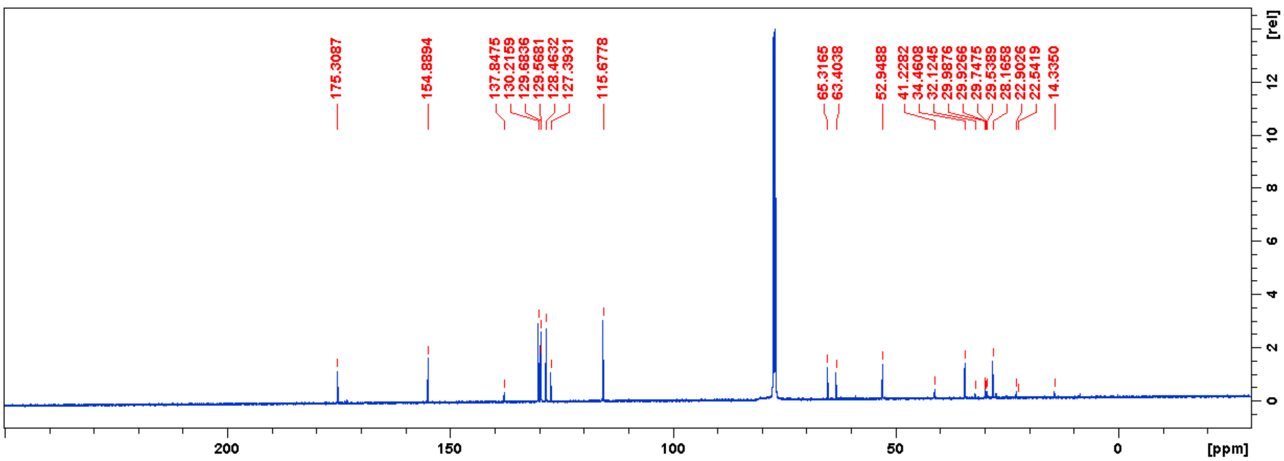
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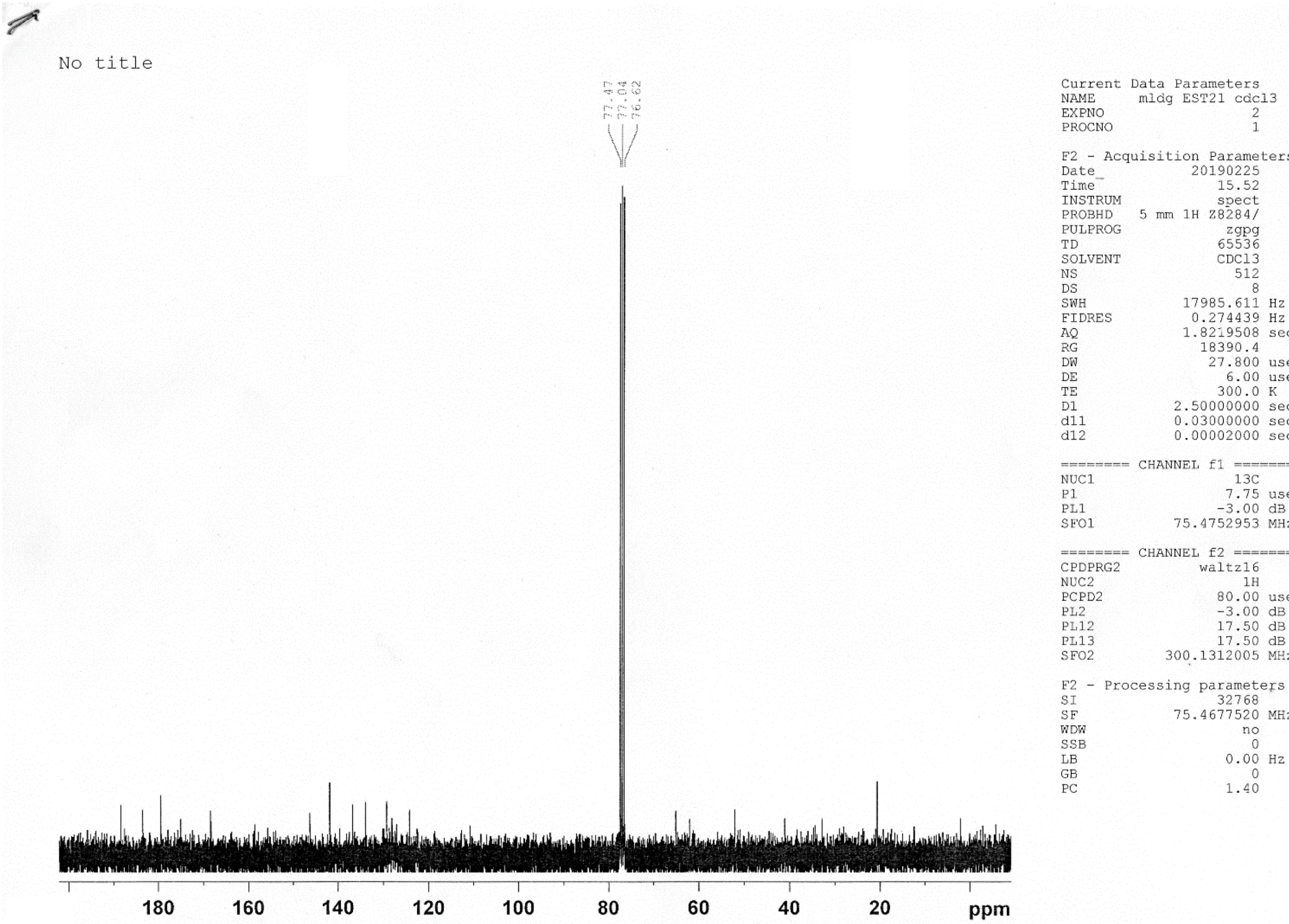
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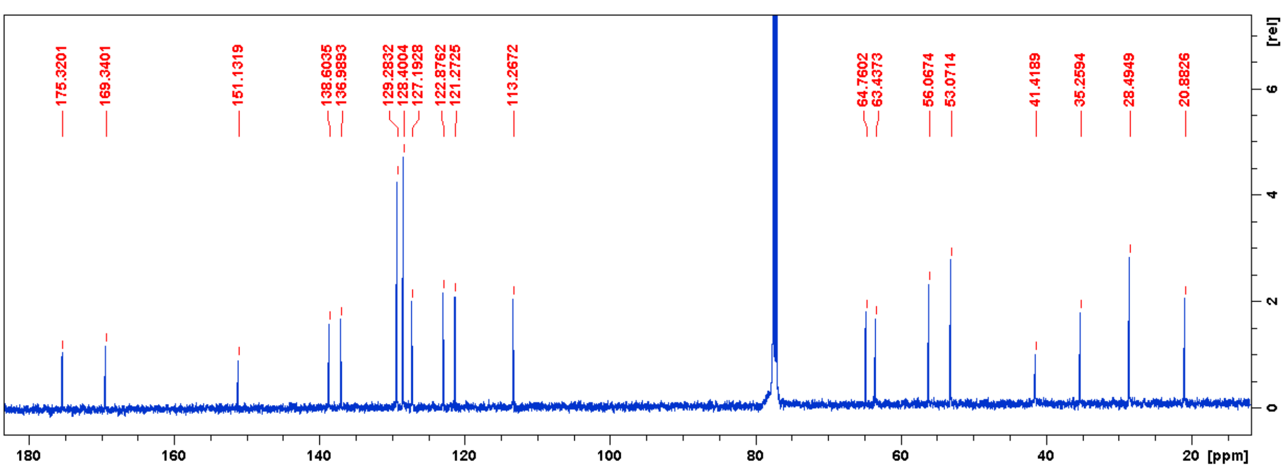
HT3a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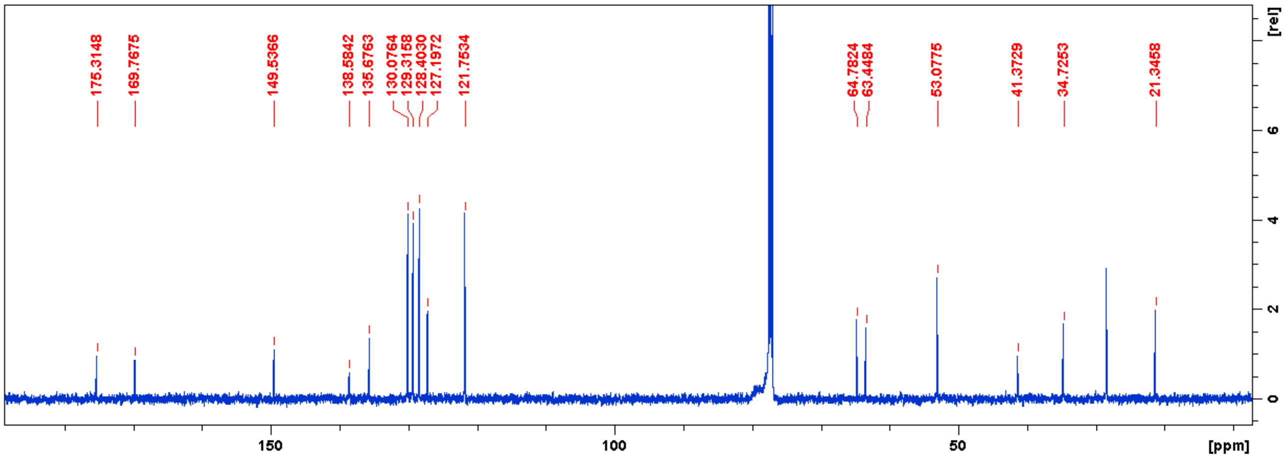

10 References

Ou, B., Hampsch-Woodill, M., and Prior, R. L. (2001). Development and validation of an improved oxygen radical absorbance capacity assay using fluorescein as the fluorescent probe, *J. Agric. Food Chem*. 49, 4619–4626. doi: 10.1021/jf010586o.

Ozyürek, M., Bektaşoğlu, B., Güçlü, K., Güngör, N., and Apak, R. (2008). Simultaneous total antioxidant capacity assay of lipophilic and hydrophilic antioxidants in the same acetone-water solution containing 2% methyl-beta-cyclodextrin using the cupric reducing antioxidant capacity (CUPRAC) method. *Anal. Chim. Acta*. 630(1), 28-39. doi: 10.1016/j.aca.2008.09.057.