Supporting Information

Rapid and Scalable Synthesis of Innovative Unnatural α, β or γ–Amino Acids Functionalized with Tertiary Amines on their Side-chain

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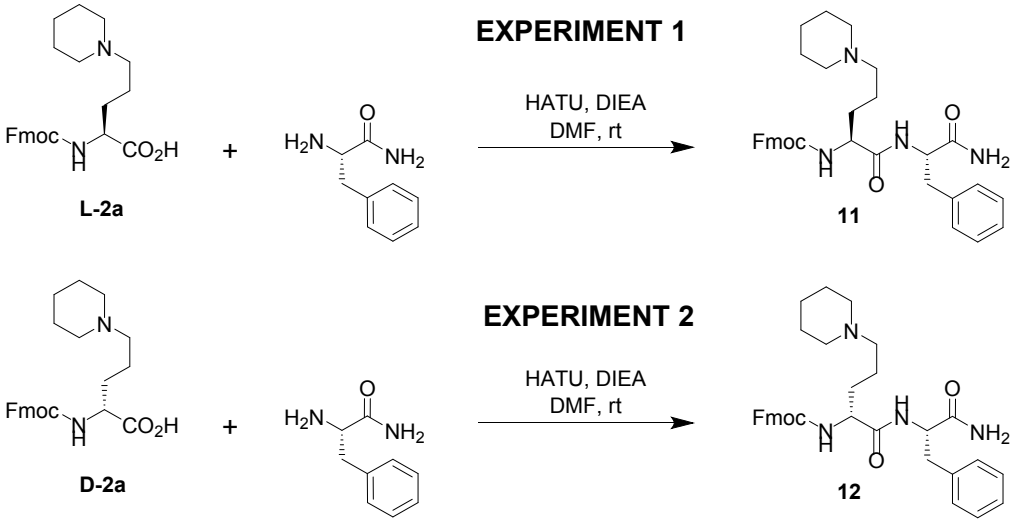
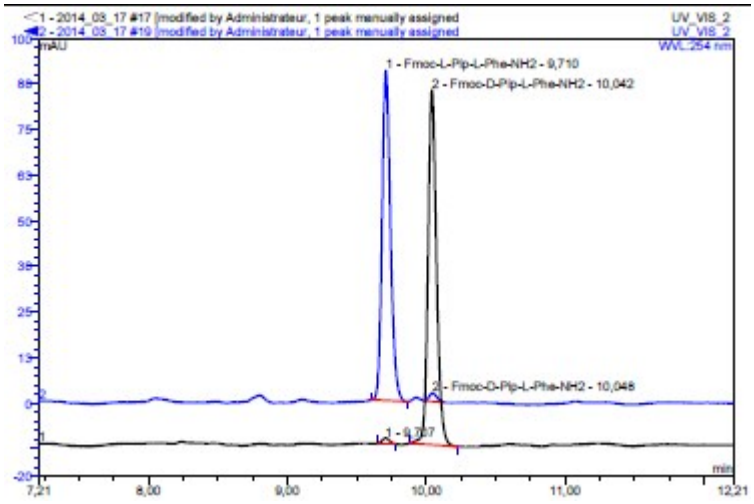
The ruthenium-catalyzed reduction does not affect the chirality of the amino acid

We evaluate whether this ruthenium-catalyzed reduction could affect the chirality of the amino acid. To answer this issue, both enantiomers **L-2a** and **D-2a** were coupled to the commercially available H-L-Phe-NH_2 using HATU as coupling reagent. In both case, HATU was the last reagent to be added.



After 1 hour, each reaction mixture was analyzed by RP-HPLC-UV without any treatment (Figure 1).

Analytical RP-HPLC-DAD was performed with a Dionex Ultimate3000 with a Waters XSelect CSH™ column (150 x 4.6 mm; 5 µm) using the following parameters : Solvent system : A (MeOH) and B (0.05% TFA in H2O); Method : Linear gradient from t = 0 min (80%B) to t = 12 min (0% B); Flow rate : 1 mL/min; Column temperature: 30°C; The ratio of product was determined by integration of UV spectra recorded at 254 nm.



Both diastereoisomers were easily separated: Experiment 1 (blue) led to 99% of compound **11** with 1% of the epimere **12**, while experiment 2 (black) led to 99% of compound **12** with 1% of the epimere **11**. Interestingly, we observed that when compound **2a** was pre-activated with the coupling reagent HATU for one or two minutes before adding phenylalanine, the epimerization ratio increased up to 15%. This observation was also true with other coupling reagents such as BOP or COMU. Consequently, we think that the trace of epimerization we observed in experiments 1 and 2 is more likely due to the coupling reaction, and not to the ruthenium-catalyzed reduction.

The ruthenium-catalyzed reduction described in this work does not affect the chirality of the resulting basic non-natural amino acids. However, these new amino acids are quite sensitive to epimerization during coupling reaction, and pre-activation has to be avoided.

Experimental section:

Materials and apparatus:

Chemical reagents and anhydrous solvents were obtained from commercial sources and used as-is. Analytical thin-layer chromatography was performed using silica gel plates Merck 60F254 and plates were visualized by exposure to ultraviolet light. When required, compounds were purified using Armen Spot flash chromatography on silica gel Merck 60 (particle size 0.040-0.063mm), or on reversed-phase column (AIT Simply Connect C18 columns – 35g - 0.040-0.063mm). Optical rotations were determinated with a Jasco P-2000 polarimeter. 1H and 13C NMR spectra were recorded on Bruker Advance spectrometer operating at 400 MHz or 500 MHz for proton and 100 MHz or 125 MHz for carbon. All chemical shift values and coupling constants J are quoted in ppm and in Hz, respectively. Traces of ruthenium were quantified by ICP-AES (Analytical platform ECPM, Strasbourg).

Abbreviations:

HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate; BOP: (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate. COMU: (1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate ; TMDS: Tetramethyldisiloxane; $Ru_3(CO)_{12}$: dodecakis(methanidyldyneoxidanium)triruthenium; TFA: Trifluoroacetic acid;

General procedure for the synthesis of amides 1:

To a solution of commercially available Fmoc-Glu(OH)-OtBu (2.35 mmol, 1 equiv.) in DMF (20 mL) were added DIEA (3.53 mmol, 1.5 equiv.), amine (2.4 mmol, 1.02 equiv.), and HATU (2.47 mmol, 1.05 equiv.). The reaction mixture was stirred at room temperature for 3 hours, and the mixture was concentrated under reduced pressure. The resulting mixture was solubilized in EtOAc, and treated with aqueous 1N HCl, aqueous saturated $NaHCO_3$, and aqueous saturated NaCl. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford compounds **1** without further purification steps, excepted for compounds **1c**, **1i**, and **1j** which required a purification on silica gel.

tert-butyl (2S)-5-(piperidin-1-yl)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxopentanoate (L-1a). 99% yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 7.86 (d, *J*=7.6 Hz, 2H), 7.62-7.75 (m, 3H), 7.39 (t, *J*=7.5 Hz, 2H), 7.30 (t, *J*=7.4 Hz, 2H), 4.34-4.14 (m, 3H), 3.99-3.92 (m, 1H), 3.39 (br d, *J*=4.3 Hz, 2H), 3.36-3.28 (m, 3H), 2.49 (d, *J*=9.5 Hz, 1H), 2.41-2.28 (m, 2H), 1.98-1.87 (m, 1H), 1.87-1.70 (m, 1H), 1.58-1.46 (m, 2H), 1.41 (br s, 3H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) = 171.5, 169.3, 156.1, 143.8, 140.7, 127.6, 127.0, 125.2, 120.1, 80.5, 65.6, 54.0, 46.7, 45.7, 41.9, 28.7, 27.6, 26.5, 26.0, 25.3, 24.0.

tert-butyl (2S)-5-(azepan-1-yl)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxopentanoate (1b). 99% Yield**;** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.67 (d, *J*= 7.4 Hz, 2H), 7.53 (*t*, *J*= 7.3 Hz, 2H), 7.31 (*t*, *J*= 7.5 Hz, 2H), 7.22 (*t*, *J*= 7.3 Hz, 2H), 5.79 (d, *J*= 7.6 Hz, 1H), 4.33-4.12 (m, 4H), 3.45 (t, *J*= 5.9, 2H), 3.30 (t, *J*= 5.9, 2H), 2.44-2.26 (m, 2H), 2.21-2.11 (m, 1H), 2.04-1.92 (m, 1H), 1.65-1.55 (m, 4H), 1.48-1.43 (m, 4H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.7, 171.5, 156.3, 144.1, 141.4, 127.8, 127.1, 125.4, 120.0, 82.2, 67.1, 54.6, 47.9, 47.3, 46.3 29.5, 29.1, 28.2, 27.8, 27.7, 27.2, 26.9.

tert-butyl (2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-[(2R)-2-methylpyrrolidin-1-yl]-5-oxopentanoate (1c). 77% yield after column chromatography (EtOAc – Heptane, 40/60); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.68 (d, *J*= 7.7 Hz, 2H), 7.54 (*t*, *J*= 6.8 Hz, 2H), 7.32 (*t*, *J*= 7.3 Hz, 2H), 7.23 (*t*, *J*= 7.3 Hz, 2H), 5.89-5.75 (m, 1H), 4.36-4.29 (m, 1H), 4.25-4.18 (m, 1H), 4.16-4.11 (m, 2H), 3.43-3.24 (m, 2H), 2.39-2.10 (m, 3H), 2.04-1.75 (m, 4H), 1.60-1.42 (m, 2H), 1.40 (s, 9H), 1.12-1.07 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.6, 170.5, 156.4, 144.2, , 141.5, 127.8, 127.2, 125.4, 120.1, 82.3, 67.2, 54.8, 53.3, 47.4, 47.0, , 32.0, 31.3, 27.3, 24.0, 22.0, 19.7.

tert-butyl(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxo-5-[(1S,5R)-1,3,3-trimethyl-6-azabicyclo[3.2.1]octan-6-yl]pentanoate (1d). 95 % yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) =7.69 (d, *J*= 7.6 Hz, 2H), 7.54 (*t*, *J*=7.6 Hz, 2H), 7.32 (*t*, *J*= 7.5 Hz, 2H), 7.24 (*t*, *J*= 7.5 Hz, 2H), 5.89-5.73 (m, 1H), 4.43-3.97 (m, 5H), 3.40-3.19 (m, 1H), 3.00-2.95 (m, 1H), 2.46-1.89 (m, 4H), 1.69-1.49 (m, 2H), 1.46-1.18 (m, 12 H), 0.99-0.97 (m, 3H), 0.88-0.75 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.5, 169.6, 158.7, 144.0, 141.4, 127.8, 127.2, 125.5, , 120.1, 82.3, 67.2, 57.3, 56.555.2, 54.7, 52.0, 51.5, 47.3, 44.5, 43.4, 41.4, 40.3, 38.2, 36.6, 31.7, 28.2, 25.2, .

tert-butyl(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-(4-methylpiperazin-1-yl)-5-oxopentanoate (1e). 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.73 (d, *J*= 7.6 Hz, 2H), 7.58 (*t*, *J*= 7.6 Hz, 2H), 7.37 (*t*, *J*= 7.5 Hz, 2H), 7.28 (*t*, *J*= 7.3 Hz, 2H), 5.68 (d, *J*= 7.5 Hz, 1H), 4.35-4.13 (m, 4H), 3.69-3.51 (m, 2H), 3.40-3.32 (m, 2H), 2.40-2.11 (m, 10 H), 1.97-1.90 (m, 1H), 1.4 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.4, 170.5, 156.3, 144.1, 141.4, 127.8, 127.2, 125.3, 120.1, 82.4, 67.2, 55.1, 54.8, 54.4, 47.3, 46.1, 45.4, 41.8, 29.4, 29.1.

tert-butyl(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxo-5-[4-(pyrimidin-2-yl)piperazin-1-yl]pentanoate (1f). 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.25 (d, *J*= 4.8 Hz, 2H), 7.69 (d, *J*= 7.3 Hz, 2H), 7.55-7.52 (m, 2H), 7.32 (*t*, *J*= 7.3 Hz, 2H), 7.24 (*t*, *J*= 7.3 Hz, 2H), 6.47 (*t*, *J*= 4.8 Hz, 1H), 5.59 (d, *J*= 7.9 Hz, 1H), 4.34-4.13 (m, 4H), 3.79-3.73 (m, 4H), 3.66-3.57 (m, 2H), 3.46-3.38 (m, 2H), 2.48-2.31 (m, 2H), 2.24-2.16 (m, 1H), 2.00-1.94 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.4, 170.8, 161.5, 157.9, 156.3, 143.9, 141.5, 127.9, 127.3, 125.4, 120.1, 110.6, 82.5, 67.2, 54.4, 47.3, 45.4, 43.7, 41.7, 29.5, 28.2.

tert-butyl(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxo-5-[4-(piperidin-1-yl)piperidin-1-yl]pentanoate (1g). 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.69 (d, *J*= 7.6 Hz, 2H), 7.56-7.51 (m, 2H), 7.32 (*t*, *J*= 7.6 Hz, 2H), 7.24 (*t*, *J*= 7.3 Hz, 2H), 5.64 (m, 1H), 4.34-4.13 (m, 4H), 3.31-2.71 (m, 5H), 2.65-2.14 (m, 4H), 2.11-1.69 (m, 6H), 1.65-1.35 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.5, 170.2, 156.4, 144.2, 141.4, 127.9, 127.2, 125.4, 120.2, 82.4, 67.2, 62.8, 54.6, 50.3, 47.3, 45.3, 41.8, 28.8, 28.2, 27.7, 26.3, 24.7.

Ethyl-1-[(4S)-5-(tert-butoxy)-4-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxopentanoyl]piperidine-4-carboxylate (1h). 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.74 (d, *J*= 7.5 Hz, 2H), 7.54 (*t*, *J*= 7.4 Hz, 2H), 7.38 (*t*, *J*= 7.4 Hz, 2H), 7.29 (*t*, *J*= 7.4 Hz, 2H), 5.63-5.59 (m, 1H), 4.35-4.13 (m, 5H), 4.11 (q, *J*= 6.9 Hz, 2H), 3.72-3.66 (m, 1H), 3.06-2.95 (m, 1H), 2.79-2.69 (m, 1H), 2.51-2.31 (m, 3H), 2.14-2.27 (m, 1H), 2.06-1.83 (m, 3H), 1.65-1.54 (m, 2H), 1.45 (s, 9H), 1.22 (t, *J*= 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 174.3, 171.5, 170.4, 156.3, 144.2, 127.9, 127.3, 125.4, 120.2, 82.5, 67.2, 60.8, 54.5, 47.3, 44.9, 41.4, 41.2, 29.6, 28.6, 28.2, 28.0, 14.4.

tert-butyl(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-(4-hydroxypiperidin-1-yl)-5-oxopentanoate (1i). 70% yield after column chromatography (DCM – MeOH, 96/4); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.68 (d, *J*= 7.5 Hz, 2H), 7.53 (*t*, *J*= 7.3 Hz, 2H), 7.31 (*t*, *J*= 7.3 Hz, 2H),

7.22 (*t*, *J*= 7.5 Hz, 2H), 5.72 (m, 1H), 4.33-4.12 (m, 4H), 4.03-3.93 (m, 1H), 3.81 (m, 1H), 3.64-3.56 (m, 1H), 3.02-3.24 (m, 2H), 2.43-1.89 (m, 5H), 1.70-1.81 (m, 2H), 1.31-1.52 (m, 11H);^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.5, 170.4, 156.3, 144.1, 141.4, 127.9, 127.3, 127.2, 125.4, 120.1, 82.4, 67.2, 67.1, 54.5, 47.3, 42.9, 39.3, 34.6, 34.0, 29.5, 28.2, 28.1.

tert-butyl(2S)-5-(4-benzylpiperidin-1-yl)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxopentanoate (1j). 70% yield after column chromatography (EtOAc – Heptane, 5/95 to 30/70); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.69 (d, *J*= 7.6 Hz, 2H), 7.53 (*t*, *J*= 7.3 Hz, 2H), 7.32 (*t*, *J*= 7.4 Hz, 2H), 7.25-7.18 (m, 4H), 7.14-7.09 (m, 1H), 7.04-7.01 (m, 2H), 5.66 (d, *J*= 7.1 Hz, 1H), 4.53 (d, *J*= 11.8 Hz, 1H), 4.34-4.13 (m, 4H), 3.69 (d, *J*= 12.5 Hz, 1H), 2.83 (t, *J*= 12.5 Hz, 1H), 2.5-2.25 (m, 5H), 2.18-2.09 (m, 1H), 1.98-1.89 (m, 1H), 1.70-1.58 (m, 4H), 1.39 (s, 9H), 1.27-1.16 (m, 1H), 1.13-0.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.5, 170.3, 156.3, 144.0, 141.5, 140.1, 129.2, 128.5, 127.9, 127.3, 126.3, 125.4, 120.2, 82.4, 67.2, 54.6, 47.4, 46.0, 43.1, 42.4, 38.4, 32.7, 31.9, 29.6, 28.2, 28.1.

tert-butyl(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxo-5-(1,2,3,4-tetrahydroisoquinolin-2-yl)pentanoate (1k). 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.73 (d, *J*= 7.4 Hz, 2H), 7.54-7.52 (m, 2H), 7.37 (*t*, *J*= 7.4 Hz, 2H), 7.28 (*t*, *J*=7.3 Hz, 2H), 7.11-6.98 (m, 4H), 5.63 (m, 1H), 4.65 (s, 1H), 4.50 (s, 1H), 4.40-4.10 (m, 4H), 3.81 (t, *J*= 5.6 Hz, 1H), 3.61 (t, *J*= 5.4 Hz, 1H), 2.81-2.77 (m, 2H), 2.48-2.35 (m, 2H), 2.24-2.14 (m, 1H), 2.08-1.94 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.5, 171.1, 156.3, 144.1, 144.0, 141.5, 135.3, 134.2, 133.6, 132.5, 129.1, 128.4, 127.9, 127.3, 127.2, 126.9, 126.6, 126.3, 125.4, 125.3, 120.2, 82.5, 67.2, 54.6, 47.40, 44.5, 43.4, 40.1, 30.0, 29.6, 28.7, 28.2, 28.1.

tert-butyl (2S)-5-(2,3-dihydro-1H-indol-1-yl)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxopentanoate (1l). 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.17 (d, *J*=8.0 Hz, 1H), 7.67 (d, *J*= 7.3 Hz, 2H), 7.50 (d, *J*= 7.3 Hz, 2H), 7.30 (*t*, *J*= 7.4 Hz, 2H), 7.21-7.16 (m, 2H), 7.13-7.09 (m, 2H), 6.93 (t, *J*= 7.3 Hz, 1H), 5.67 (d, *J*= 7.5 Hz, 1H), 4.28-3.89 (m, 6H), 3.09 (t, *J*= 8.4 Hz, 2H), 2.52-2.01 (m, 4H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.4, 170.4, 156.4, 144.1, 144.0, 143.1, 141.5, 131.2, 127.9, 127.8, 127.2, 125.4, 124.7, 123.9, 120.1, 117.2, 82.5, 67.2, 54.5, 48.1, 47.3, 32.3, 28.2, 28.1, 27.5.

tert-butyl (2S)-5-(1H-1,3-benzodiazol-1-yl)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxopentanoate (1m). 98% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.54-8.24 (m, 1H), 8.14-8.04 (m, 1H), 7.74-7.39 (m, 5H), 7.35-7.05 (m, 6H), 5.63-5.51 (d, J= 8.1 Hz, 1H), 4.36-4.21 (m, 3H), 4.06-3.96 (m, 1H), 3.19-2.65 (m, 2H), 2.45-2.25 (m, 1H), 2.15-1.95 (m, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 170.9, 169.6, 156.3, 151.8, 143.8, 141.4, 141.1, 131.5, 129.6, 127.8, 127.1, 126.1, 125.2, 125.1, 120.6, 120.1, 115.6, 83.0, 67.0, 53.7, 47.2, 32.1, 28.1, 27.4.

tert-butyl-(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-4-[methyl(phenyl)carbamoyl]butanoate (1n). 97% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.69 (d, *J*= 7.4 Hz, 2H), 7.52-7.49 (m, 2H), 7.34-7.18 (m, 7H), 7.07 (d, *J*= 7.5 Hz, 2H), 5.53 (d, *J*= 7.4 Hz, 1H), 4.29-4.19 (m, 2H), 4.13-4.02 (m, 2H), 3.18 (s, 3H), 2.09-1.87 (m, 4H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 172.2, 171.4, 156.1, 144.1, 143.9, 141.4, 130.0, 128.1, 127.9, 127.4, 127.2, 125.4, 120.1, 82.2, 67.2, 54.4, 47.3, 37.6, 30.6, 28.2, 28.1.

tert-butyl (2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-4-[methyl(2-phenylethyl)carbamoyl] butanoate (1o). 94% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.74 (*dd*, *J*= 7.5, 3.4 Hz, 2H), 7.55-7.52 (m, 2H), 7.34-7.29 (m, 2H), 7.25-7.11 (m, 6H), 7.03 (d, *J*= 7.0 Hz, 1H), 5.58 (*dd*, *J*= 76.7, 8.0 Hz, 1H), 4.46-4.10 (m, 4H), 3.63-3.39 (m, 2H), 3.01-2.71 (m, 5H), 2.49-

1.74 (m, 4H), 1.55-1.39 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 172.0, 171.5, 156.4, 144.2, 141.5, 139.5, 138.3, 129.0, 128.9, 127.9, 127.3, 127.0, 126.6, 125.4, 120.2, 82.4, 67.2, 54.6, 51.8, 50.5, 47.4, 36.3, 34.9, 34.0, 33.9, 30.0, 29.1, 28.2, 28.0, 27.8.

tert-butyl-(2S)-4-[butyl(methyl)carbamoyl]-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}butanoate (1p). 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.72 (d, *J*= 7.7 Hz, 2H), 7.59 (*t*, *J*= 7.4 Hz, 2H), 7.36 (*t*, *J*= 7.3 Hz, 2H), 7.4 (t, J= 7.4 Hz, 2H), 5.91-5.78 (m, 1H), 4.41-4.09 (m, 4H), 3.34 (t, *J*= 7.5 Hz, 1H), 3.19 (t, *J*=7.5 Hz, 1H), 2.89 (s, 3H), 2.44 (m, 2H), 2.19 (m, 1H), 2.10-1.92 (m, 1H), 1.47-1.42 (m, 2H), 1.39 (s, 9H), 1.32-1.21 (m, 2H), 0.95-0.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 171.8, 171.5, 156.3, 144.1, 141.4, 127.8, 127.2, 125.4, 120.1, 82.2, 67.1, 54.6, 47.8, 47.3, 33.6, 29.9, 29.5, 28.1, 27.7, 20.2, , 13.9.

tert-butyl(2S)-4-[(2-cyanoethyl)(methyl)carbamoyl]-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino} butanoate (1q). 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.65-7.20 (m, 8H), 5.67 (s, 1H), 4.28-4.12 (m, 4H), 3.47-3.35 (m, 2H), 2.95-2.66 (m, 3H), 2.49-1.87 (m, 6H), 1.37 (9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 172.5, 171.3, 156.2, 144.0, 141.3, 127.7, 127.1, 125.2, 120.0, 118.4, 82.3, 67.0, 54.1, 47.2, 45.0, 36.8, 29.5, 28.0, 27.6, 16.2.

tert-butyl (2S)-4-{N-benzyl-N'-[(tert-butoxy)carbonyl]hydrazinecarbonyl}-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}butanoate (1r). 65% yield after column chromatography; ^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) = 7.76 (d, J=7.5 Hz, 2H), 7.58 (d, J=7.3 Hz, 2H), 7.36 (t, J=6.9 Hz, 2H), 7.32-7.18 (m, 7H), 5.70-5.50 (m, 1H), 5.49-5.22 (m, 1H), 4.42-3.92 (m, 5H), 2.72-1.79 (m, 4H), 1.45 (s, 9H), 1.42-1.32 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 174.9, 171.5, 144.3, 141.2, 135.7, 129.2, 128.9, 128.1, 127.9, 127.2, 125.3, 120.6, 82.5, 67.3, 47.3, 28.3, 28.1

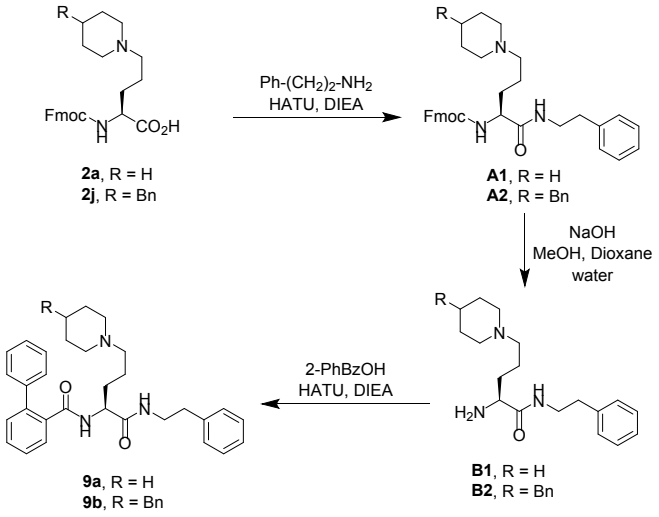
(2S)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-4-oxo-4-(piperidin-1-yl)butanoic acid (3). Same procedure than for compounds **1**, starting from commercially available Fmoc-L-Asp-OtBu. 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.73(d, J=7.5 Hz, 2H), 7.60 (dd, J=7.3, 3.5 Hz, 2H), 7.37 (t, J=7.5, 2H), 7.28 (br tt, J=7.5, 1.0 Hz, 2H), 6.14 (br d, J=9.0 Hz, 1H), 4.55-4.47 (m, 1H), 4.44 (dd, J=9.9, 6.7 Hz, 1H), 4.29-4.16 (m, 2H), 3.59 (br s, 1H), 3.49 (br dd, J=7.0, 4.4 Hz, 1H), 3.44-3.26 (m, 2H), 3.10 (dd, J=16.6, 4.0 Hz, 1H), 2.72 (dd, J=16.6, 3.9 Hz, 1H), 1.70-1.59 (m, 4H), 1.59-1.48 (m, 4H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 170.3, 168.3, 156.4, 144.0, 143.9, 141.3, 127.6, 127.0, 125.3, 120.0, 82.0, 67.3, 51.4, 47.4, 46.8, 42.9, 35.8, 28.1, 26.6, 25.8, 24.6.

tert-butyl (3S)-3-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-4-oxo-4-(piperidin-1-yl)butanoate (5). Same procedure than for compounds **1**, starting from commercially available Fmoc-L-Asp(OtBu)-OH. 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.74 (d, J=7.7 Hz, 2H), 7.58 (t, J=1.0 Hz, 2H), 7.37 (t, J=1.0 Hz, 2H), 7.32-7.26 (m, 2H), 5.83 (d, J=8.2 Hz, 1H), 4.72 (br td, J=3.6 Hz, 1H), 4.33 (d, J=7.2 Hz, 2H), 4.19 (br t, J=7.0 Hz, 1H), 3.64-3.42 (m, 4H), 2.40-2.22 (m, 1H), 2.06-1.94 (m, 1H), 1.79-1.68 (m, J=7.9 Hz, 1H), 1.68-1.49 (m, 7H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 172.1, 169.5, 156.1, 144.0, 141.3, 127.6, 127.0, 125.2, 120.1, 80.5, 67.2, 50.1, 47.4, 46.8, 43.5, 30.9, 28.6, 28.3, 26.7, 25.7, 24.6.

tert-butyl (4S)-4-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-5-oxo-5-(piperidin-1-yl)pentanoate (6). Same procedure than for compounds **1**, starting from commercially available Fmoc-L-GluO(tBu)-OH. 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.73 (d, J=7.5 Hz, 2H), 7.56 (br d, J=7.4 Hz, 2H), 7.37 (t, J=7.4 Hz, 2H), 7.28 (t, J=7.4 Hz, 2H), 5.78 (br d, J=9.2 Hz, 1H), 5.05-4.95 (m, 1H), 4.34 (d, J=7.2

Hz, 2H), 4.19 (t, J=7.1 Hz, 1H), 3.64-3.40 (m, 4H), 2.68 (dd, J=15.4, 6.0 Hz, 1H), 2.49 (dd, J=15.4, 6.5 Hz, 1H), 1.68-1.48 (m, 6H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 169.7, 168.9, 155.8, 144.0, 141.5, 127.9, 127.2, 125.3, 120.1, 81.5, 67.3, 47.9, 47.3, 46.9, 43.5, 39.4, 28.1, 26.6, 25.7, 24.7.

Synthesis of compounds 9a and 9b



To a solution of **2** (1.96 mmol, 1 equiv.) in DMF (10 mL) were added DIEA (4.9 mmol, 2.5 equiv.), phenethylamine (2.05 mmol, 1.05 equiv.), and HATU (2.05 mmol, 1.05 equiv.). The reaction mixture was stirred at room temperature for 1 hour, and the mixture was concentrated under reduced pressure. The resulting mixture was solubilized in EtOAc, and treated with aqueous 1N HCl, aqueous saturated $NaHCO_3$, and aqueous saturated NaCl. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford the expected amide **A** without further purification steps.

A1 : R = H; 91% yield; ^1H NMR (400 MHz, MeOD-d_4) δ (ppm) : 7.81 (d, *J* = 7.5 Hz, 2H), 7.66 (m, 2H), 7.40 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.31 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.28 – 7.15 (m, 5H), 4.41 (m, 2H), 4.21 (m, 1H), 3.97 (m, 1H), 3.41 (m, 2H), 2.79 (m, 2H), 2.72 – 2.38 (m, 6H), 1.83 – 1.51 (m, 10H).

A2 : R = Bn; 87% yield; ^1H NMR (400 MHz, MeOD-d_4) δ (ppm) : 7.78 (d, *J* = 7.5 Hz, 2H), 7.65 (m, 2H), 7.38 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.32 – 7.09 (m, 12H), 4.39 (m, 2H), 4.19 (m, 1H), 4.01 (m, 1H), 3.41 (m, 2H), 2.92 (m, 2H), 2.77 (m, 3H), 2.51 (m, 3H), 2.39 (m, 2H), 1.77 – 1.44 (m, 7H), 1.36 – 1.22 (m, 2H).

To a solution of amide **A** (0.97 mmol, 1 equiv.) in a mixture of methanol (72 mL) and dioxane (19 mL) was added NaOH (4M in water, 4.8 mL, 20 equiv.). The reaction mixture was stirred at room temperature for 45 minutes, and the mixture was concentrated under reduced pressure. Water was added to the resulting mixture to afford a white solid. The precipitate was solubilized in dichloromethane, and the resulting organic layer was dried ($MgSO_4$), filtered and evaporated to afford an oil. HCl 2N in ether (20 mL) was added to afford the amine **B** as a powder (> 80% yield), which was directly used in the next step without further purification steps.

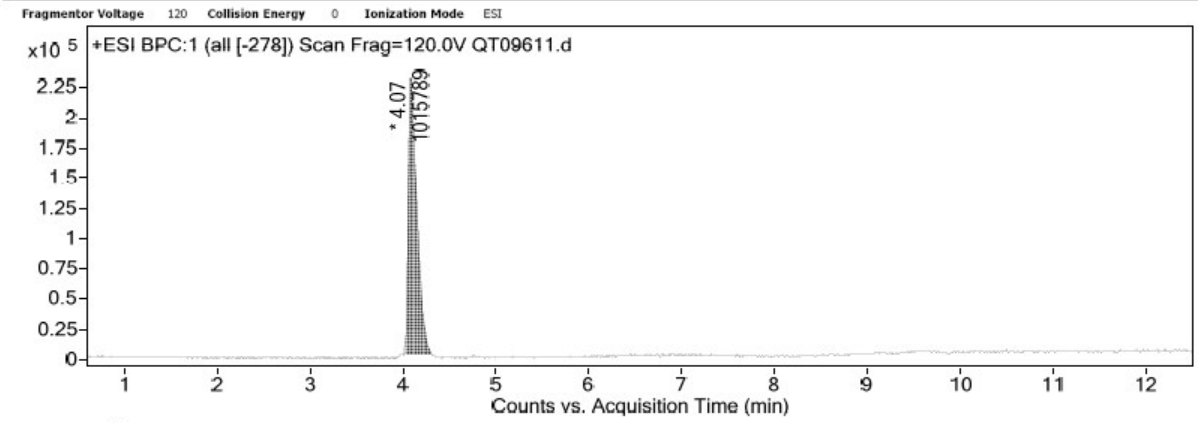
To a solution of 2-biphenylcarboxylic acid (0.19 mmol, 1.05 equiv.) in DMF (1 mL) were added DIEA (0.61 mmol, 2.5 equiv.), **B** (0.176 mmol, 1 equiv.) and HATU (0.19 mmol, 1.05 equiv.). The reaction mixture was stirred at room temperature for 1 hour, and the mixture was concentrated under reduced pressure. The resulting mixture was purified by column chromatography using a reversed-phase C18 column (eluent: MeOH – water containing 0.05% TFA). Compounds **9** were obtained as

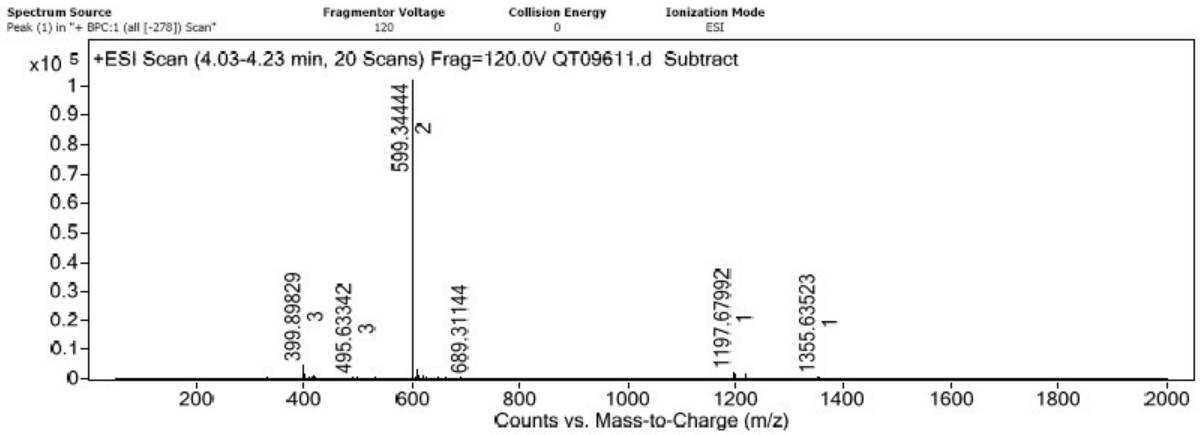
trifluoroacetic acid salts (**9a** : 72% yield; **9b** : 34% yield); Analytical data were in full agreement with those previously published (Bihel et al. *ACS Chem Neurosci* **2015**. DOI: 10.1021/cn500219h).

Synthesis of peptide 10

The peptide chain elongation was carried out manually using a Rink-Amide resin. Typically the coupling was carried out using a solution of the Fmoc-amino acid (3 equiv.), HATU (3.8 equiv.) and DIEA (8 equiv.) in DMF. 1-1.5 h reaction is enough for most amino acids. Non-natural amino acid **2j** was used to replace Arg. In this case, it was important to add HATU as the last reagent to avoid any epimerization. After the coupling reaction the resin was washed with DMF and DCM. The Fmoc group was removed by treatment with 20% piperidine in DMF (twice: 5 min, 10 min). Ninhydrin test may be carried out to check the coupling efficiency. After assembly of peptide chains, the N-terminal Fmoc group was removed. After washing the resin the cleavage/deprotection step was carried out by treating the resin with cleavage cocktail (TFA/TIPS/thiophenol/, 92:3:5) for 1 h. Then the solution was collected and concentrated under reduced pressure. After precipitation with cold Et_2O and centrifugation the crude peptides can be obtained. Analysis and purification was carried out using HPLC and MS. After lyophilisation the desired peptide **10** was obtained. HRMS (ESI+) calcd. for $C_{65}H_{88}N_{12}O_{10}$ [M + 2H]+ 599.3444, found 599.3444.

HRMS (chromatogram and spectrum)





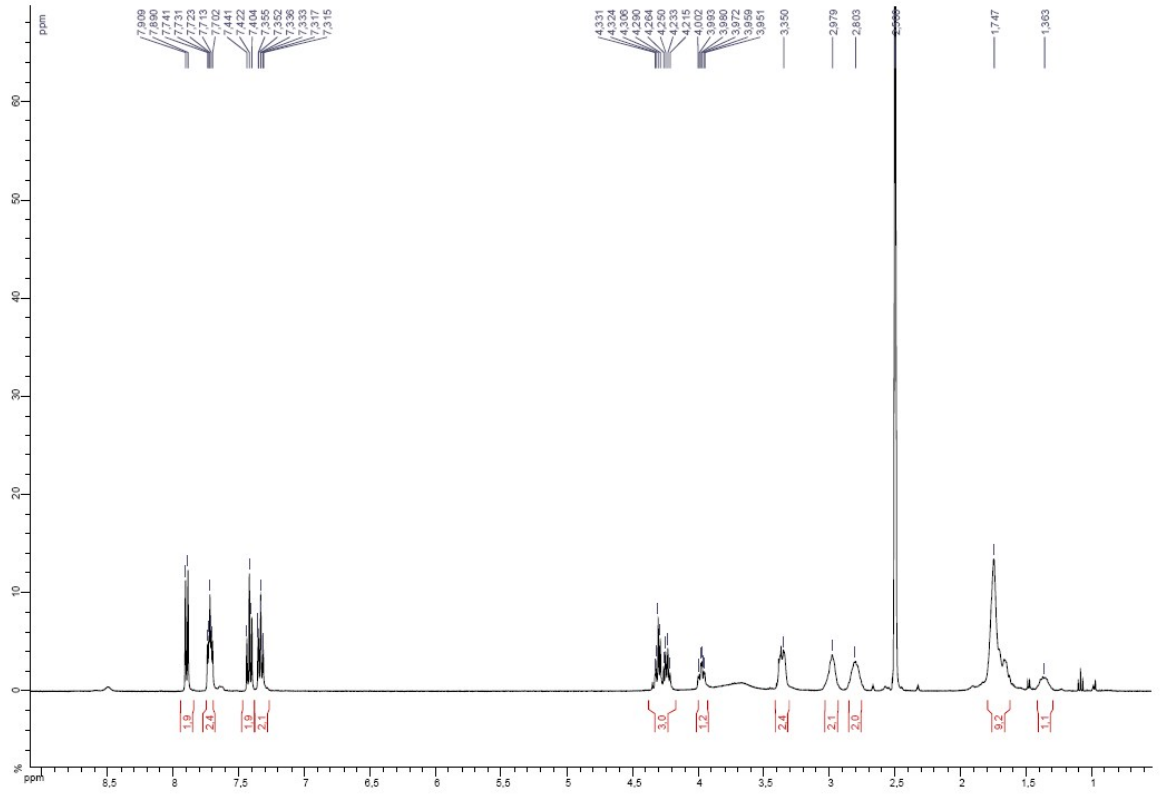
NPFFR1 and NPFFR2 receptor binding assays

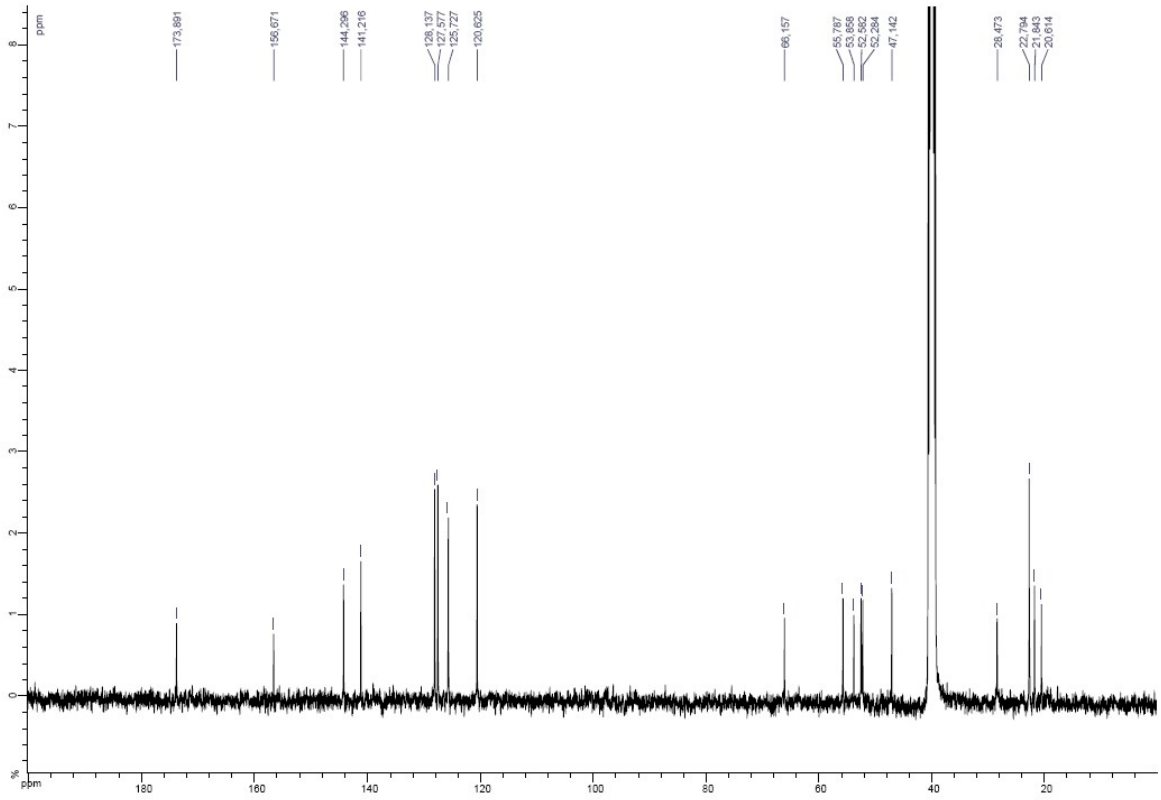
Competition experiments with membranes from CHO cells stably expressing hNPFFR1 and hNPFFR2 were performed essentially as described [1]. Briefly, hNPFFR1 or hNPFFR2 membranes (5 to 10 µg of proteins) were incubated (1 hr at 25°C; 0.25 mL total volume) with 0.015 nM [D-Tyr^1[^{125}I], N-MePhe^3]-NPFF (Hartmann Analytic GmbH) in 50 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% bovine serum albumin. Non-specific binding was determined in the presence of 10 µM RFRP-3. Incubation was terminated by rapid filtration through a 96-well GF/B unifilter apparatus (Perkin Elmer Life and Analytical Sciences, Courtaboeuf, France). Unifilters were washed three times with binding buffer, then dried for 1 h at 65°C. After addition of 40 µL scintillation cocktail (Microscint-O, Perkin Elmer) per well, bound radioactivity was determined on a TopCount scintillation counter (Perkin Elmer).

Reference

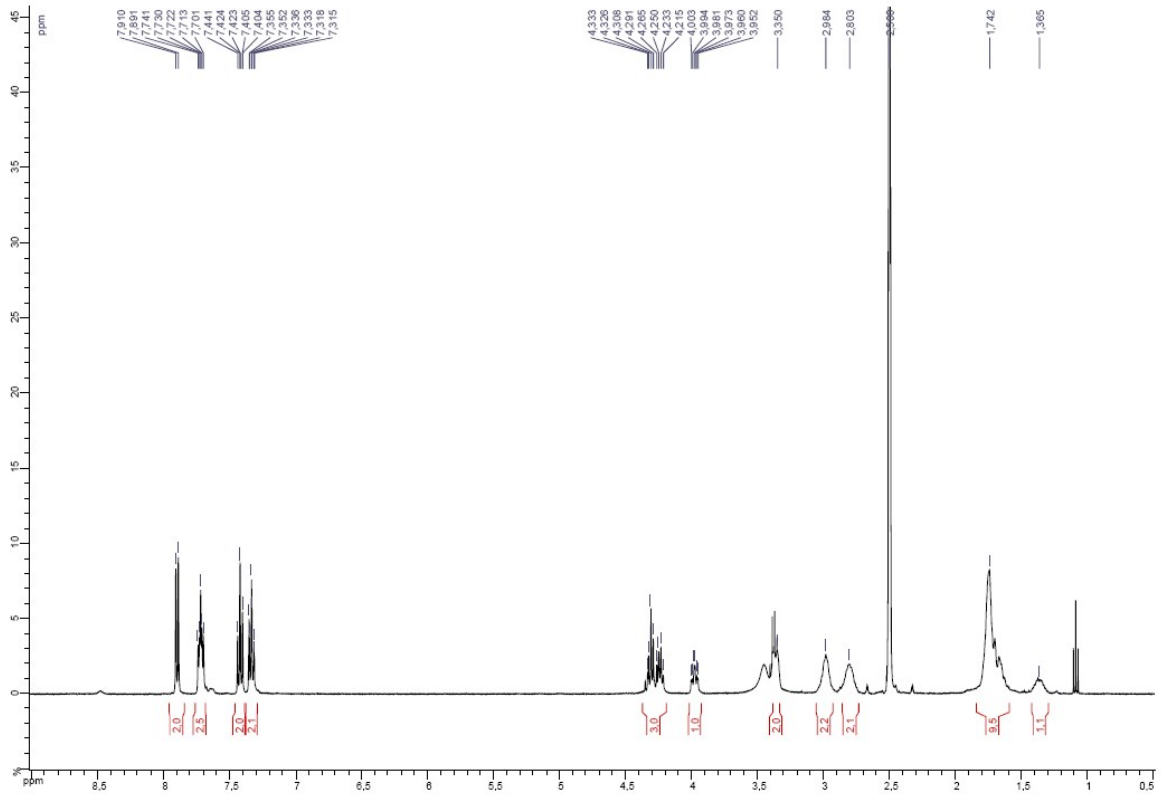
1. Elhabazi, K., J.P. Humbert, I. Bertin, M. Schmitt, F. Bihel, J.J. Bourguignon, B. Bucher, J.A. Becker, T. Sorg, H. Meziane, B. Petit-Demouliere, B. Ilien, and F. Simonin, *Endogenous mammalian RF-amide peptides, including PrRP, kisspeptin and 26RFa, modulate nociception and morphine analgesia via NPFF receptors.* Neuropharmacology, 2013. 75C, 164-171.

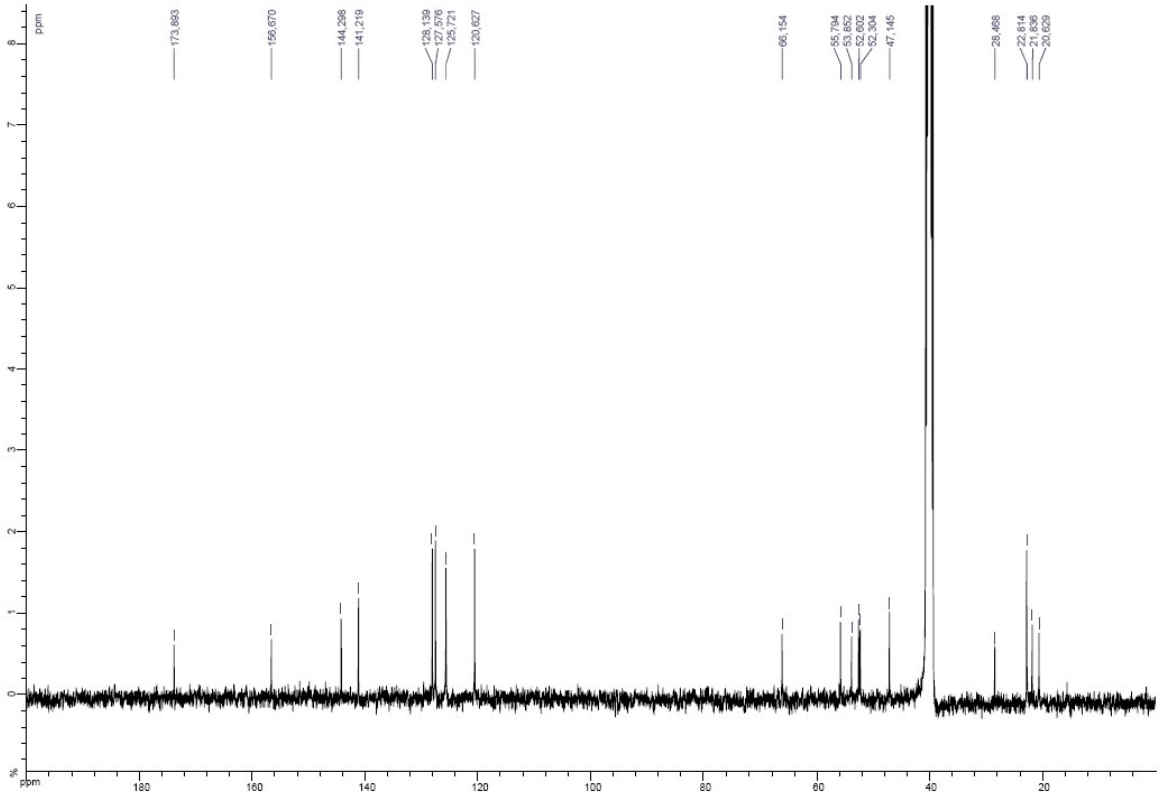
Compound L-2a



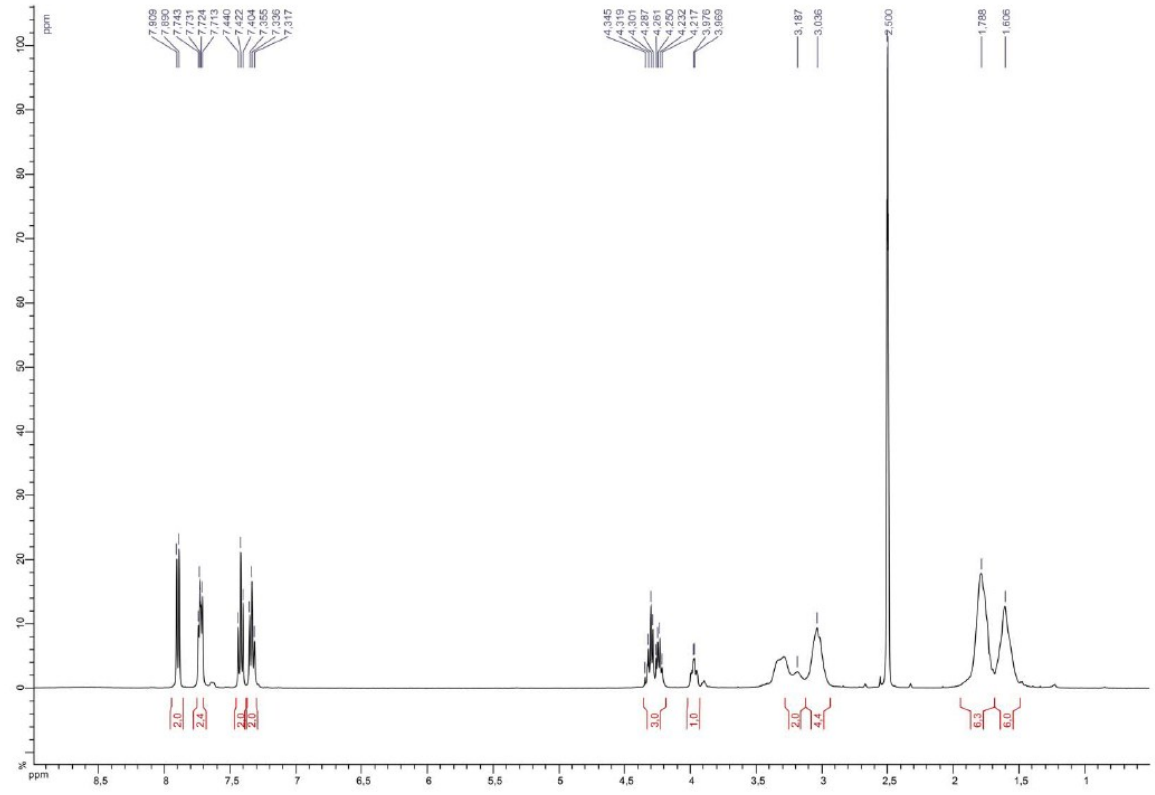


Compound D-2a





Compound 2b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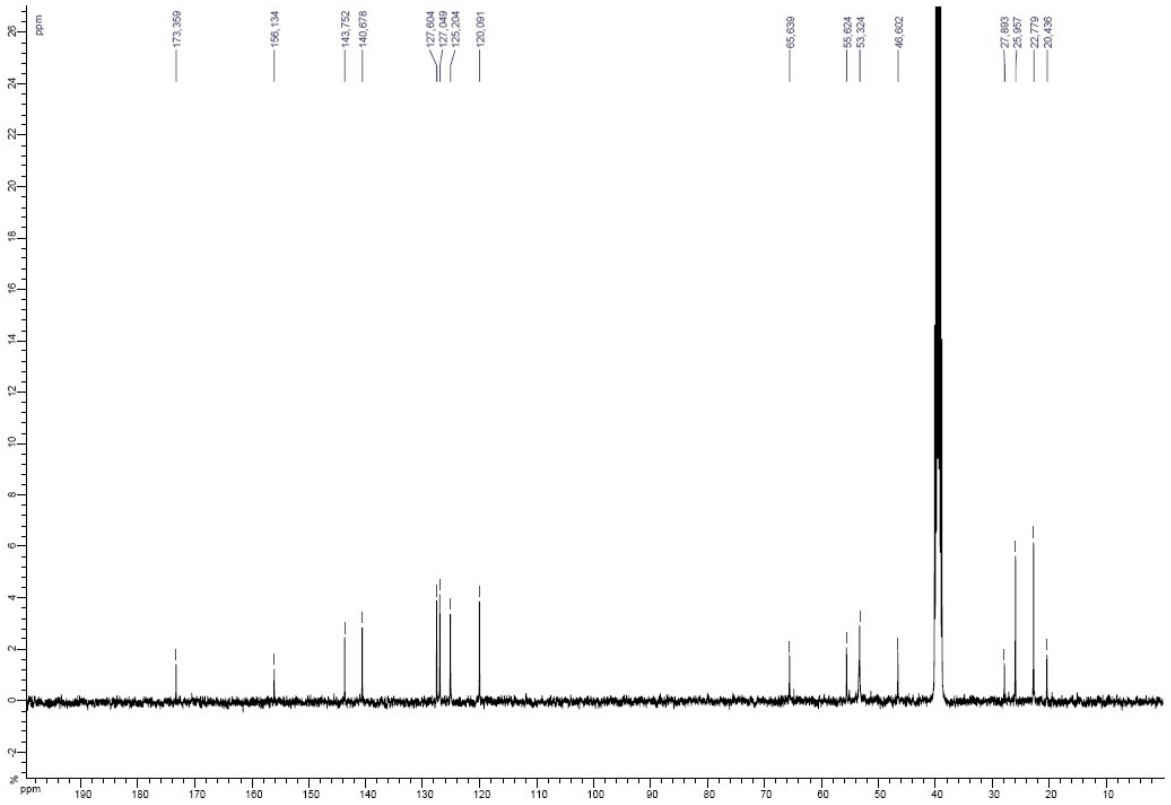
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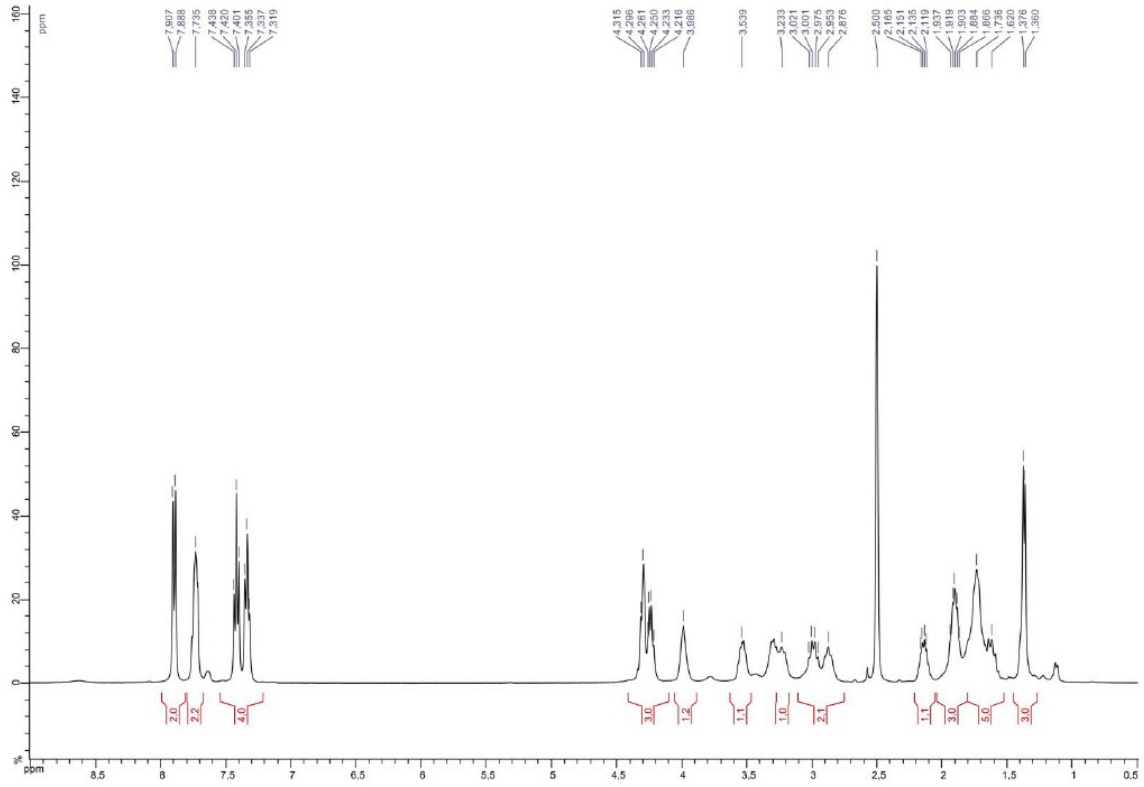
Compound 2c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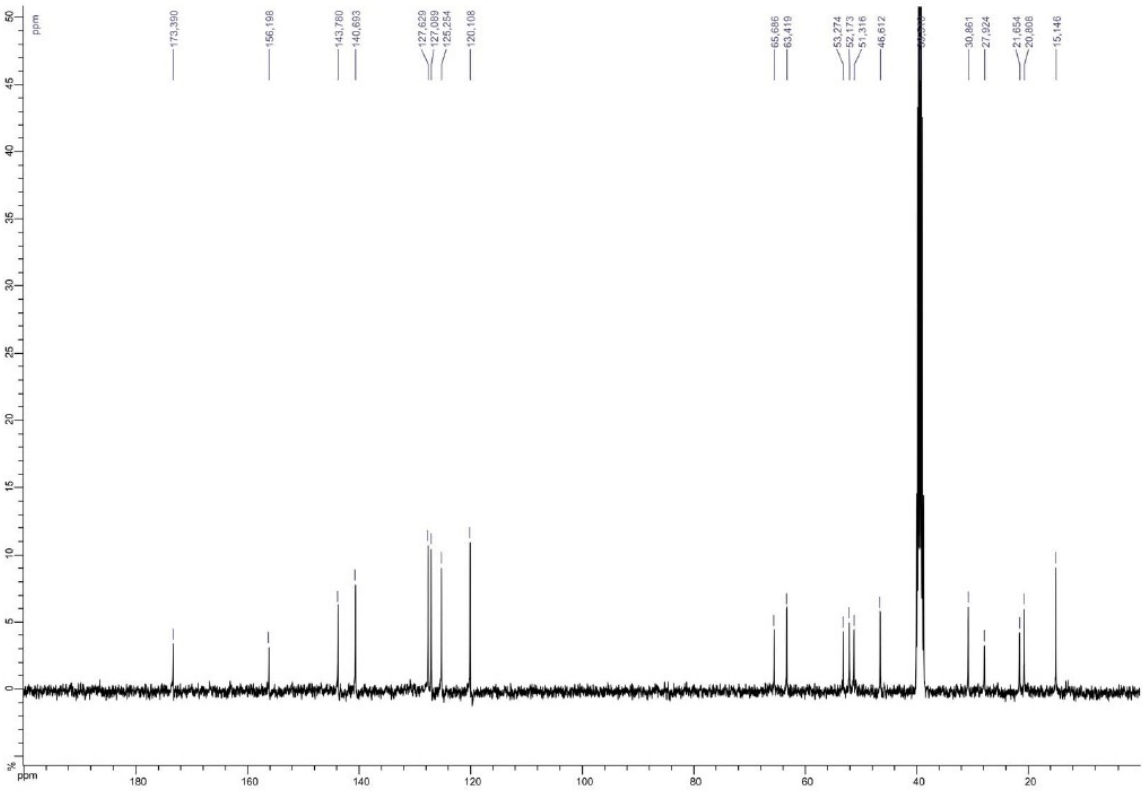
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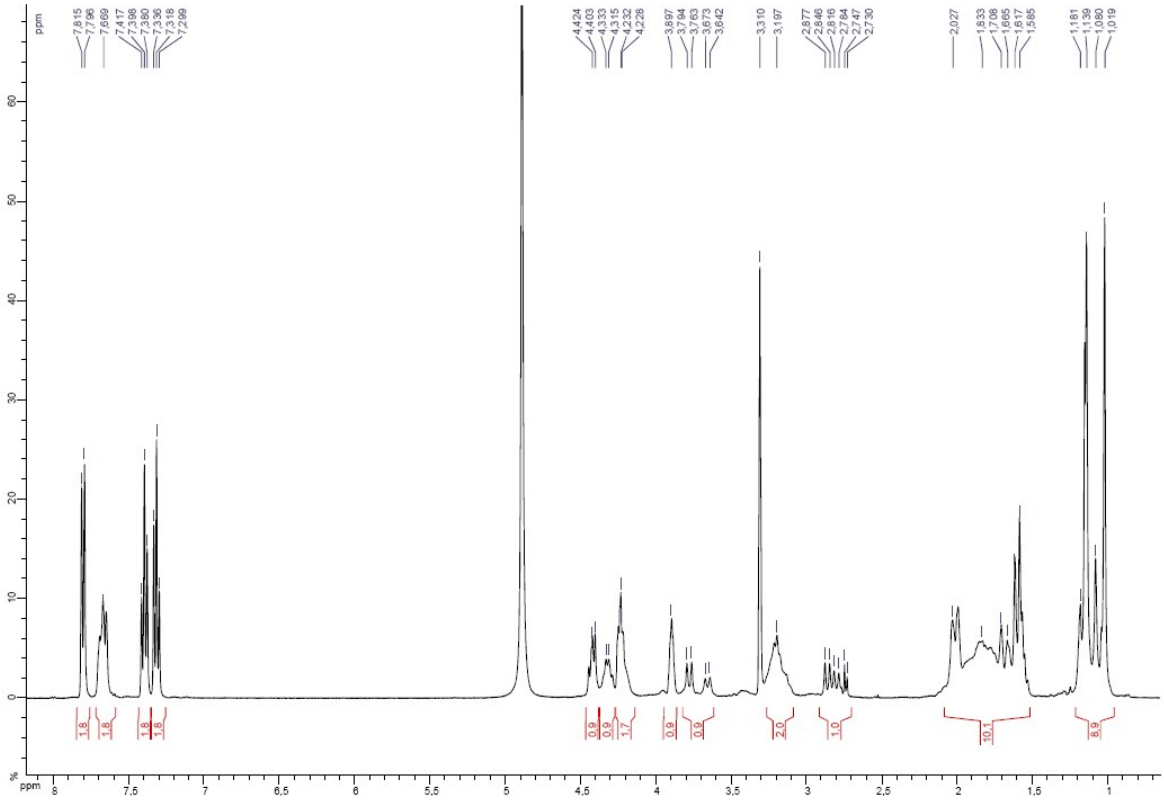
Compound 2d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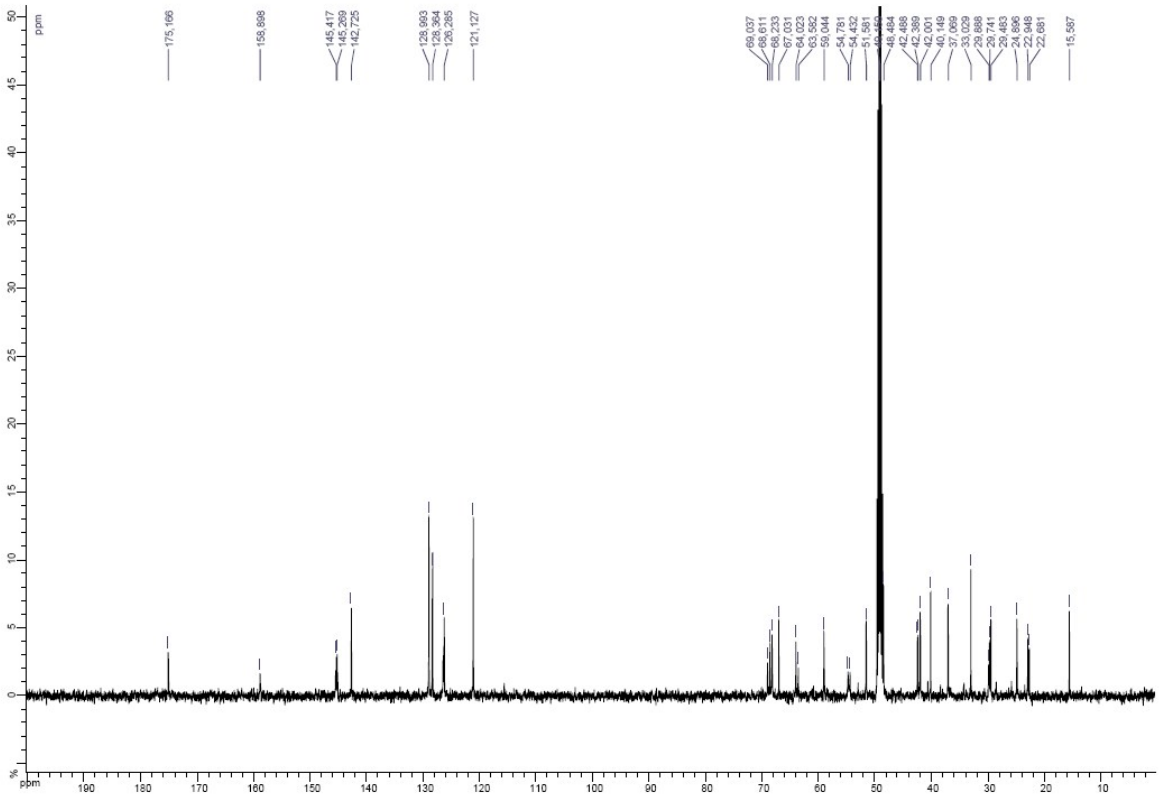
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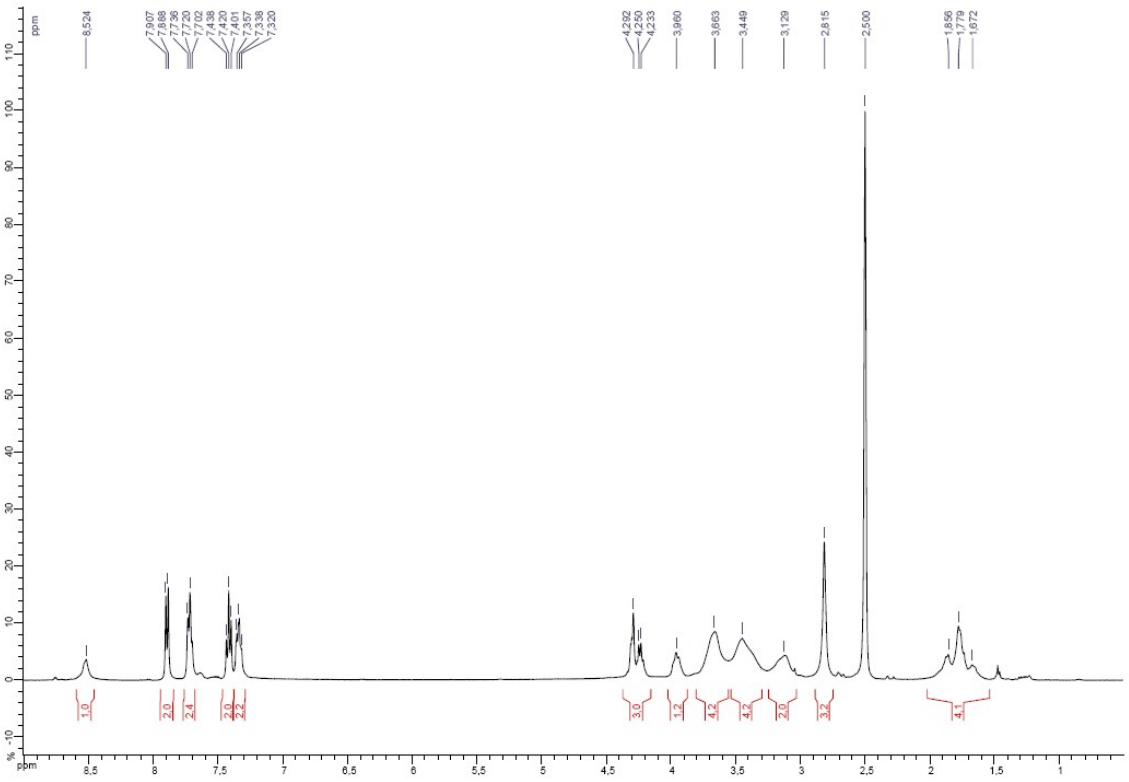
Compound 2e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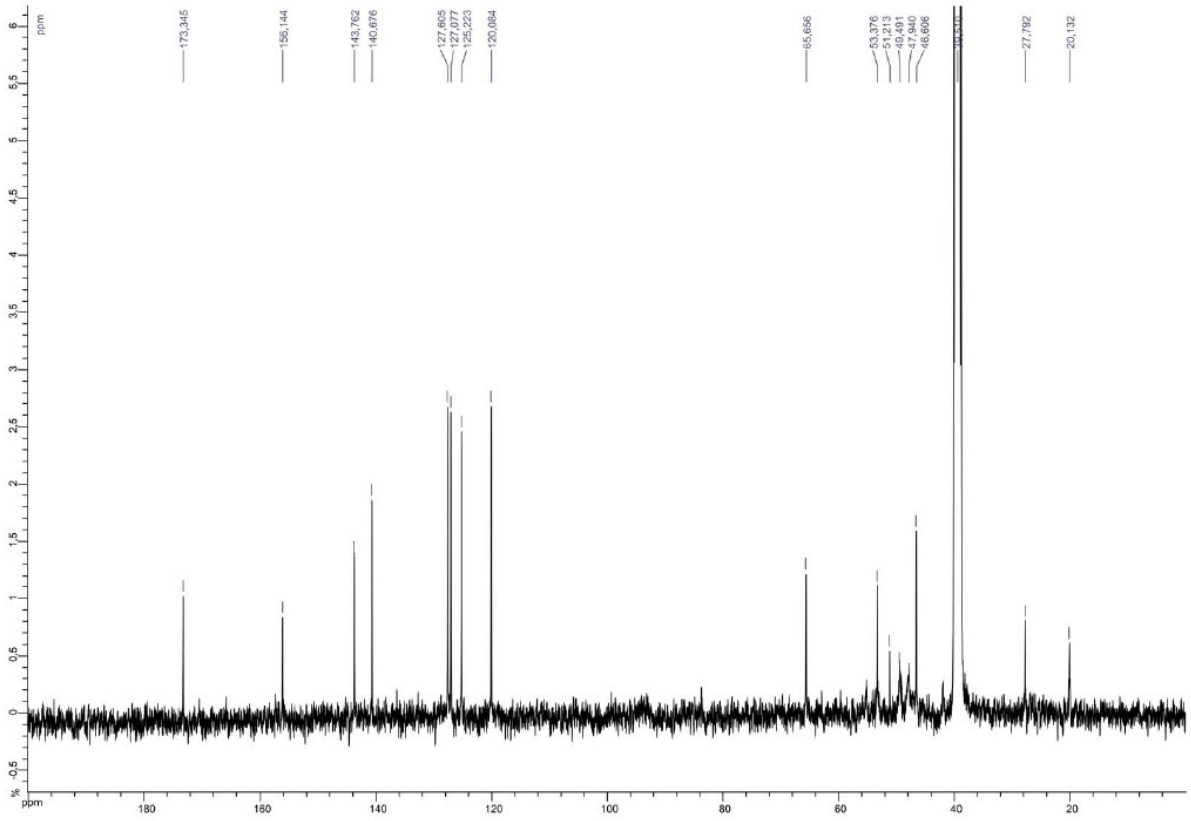
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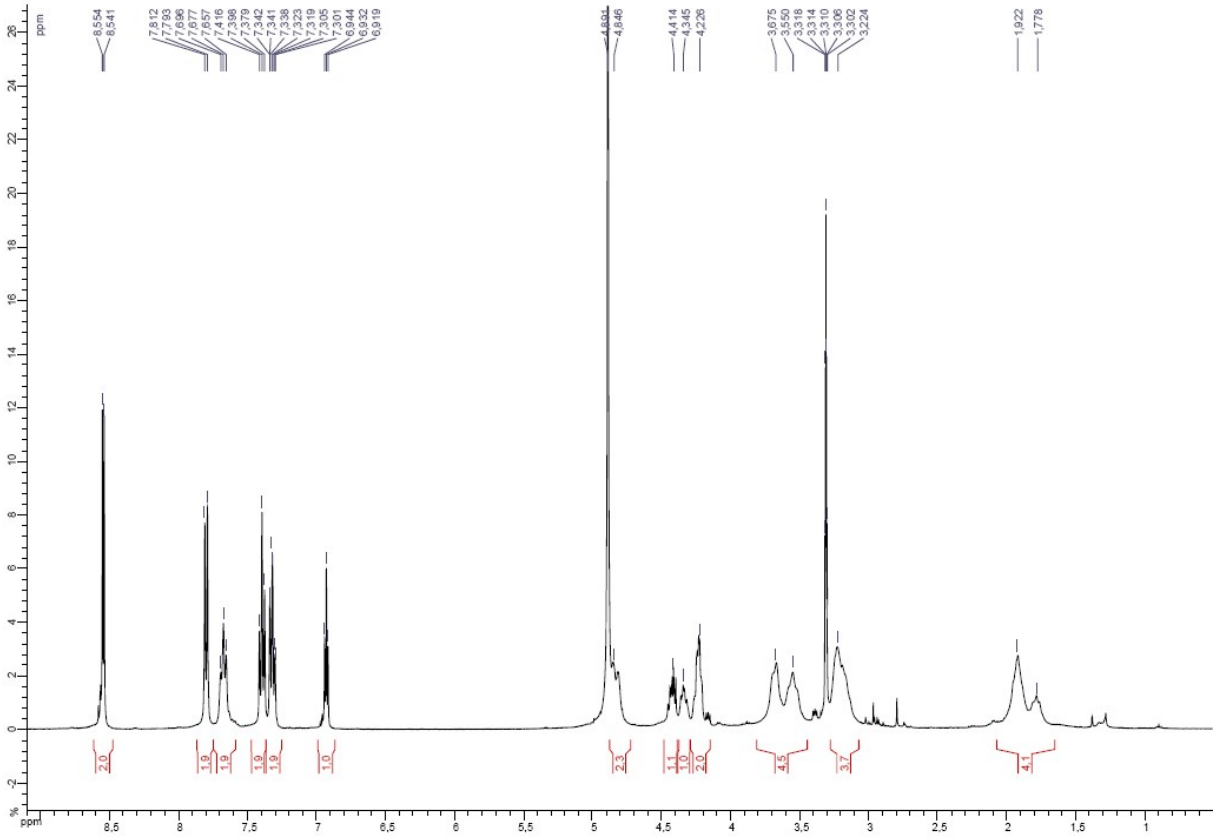
Compound 2f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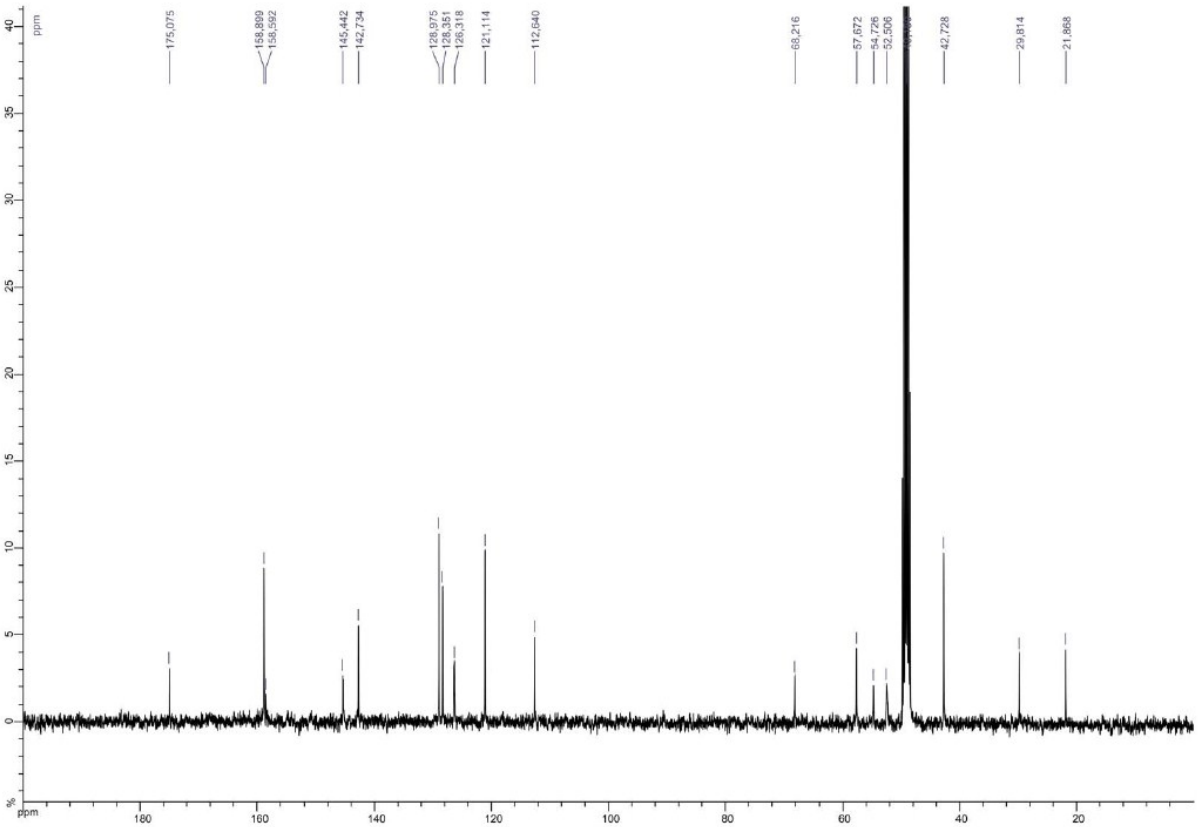
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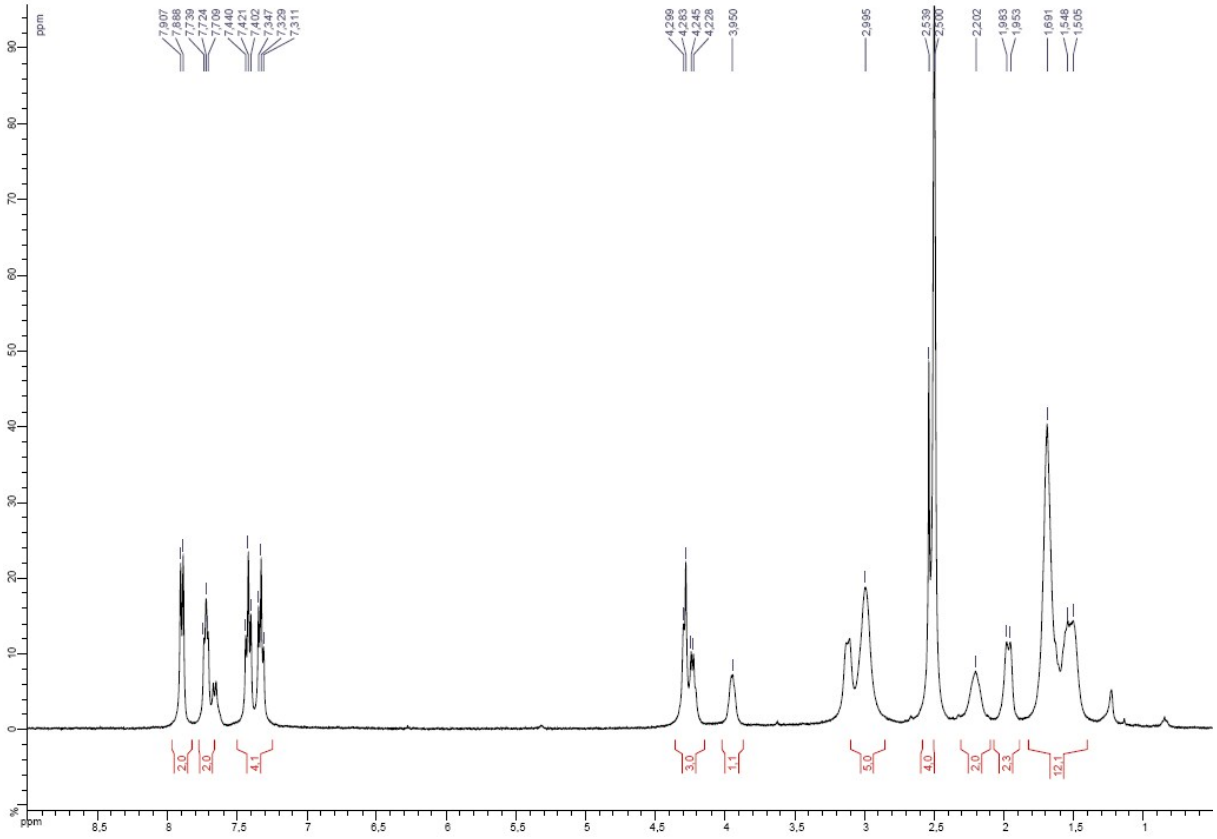
Compound 2g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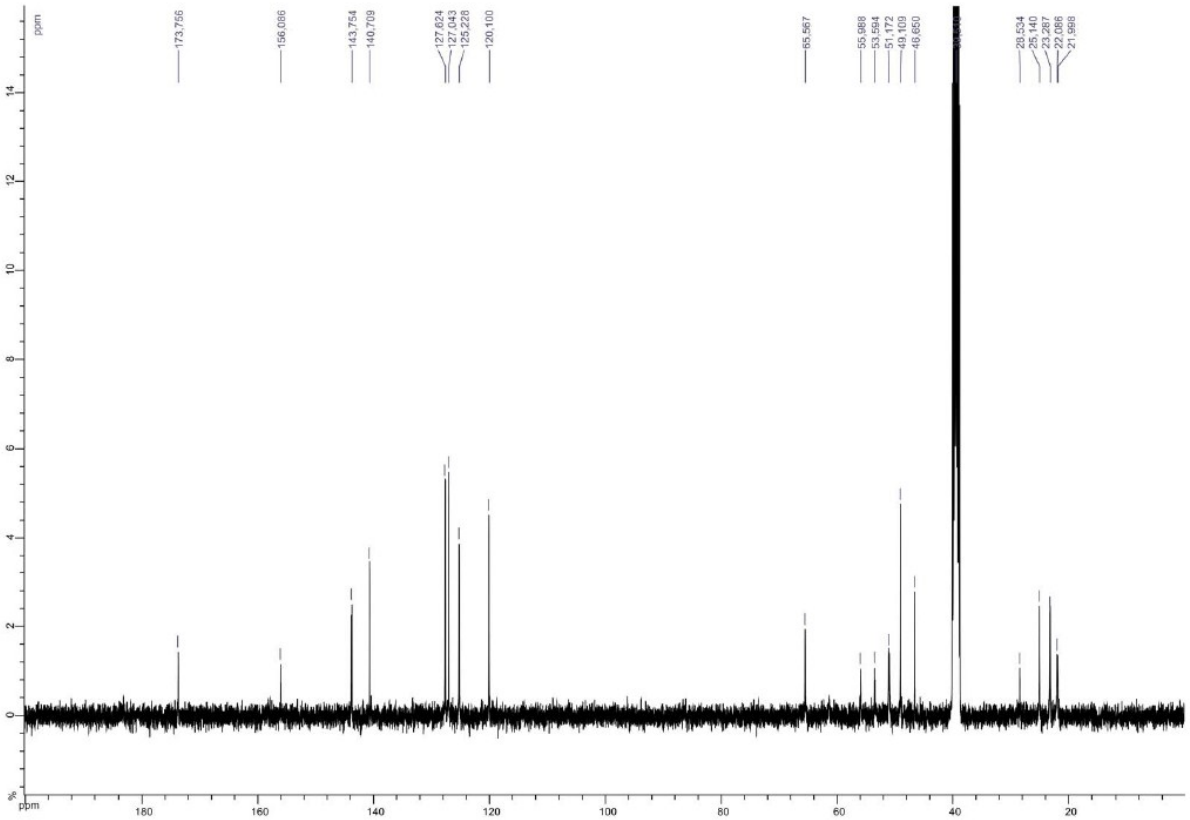
12.1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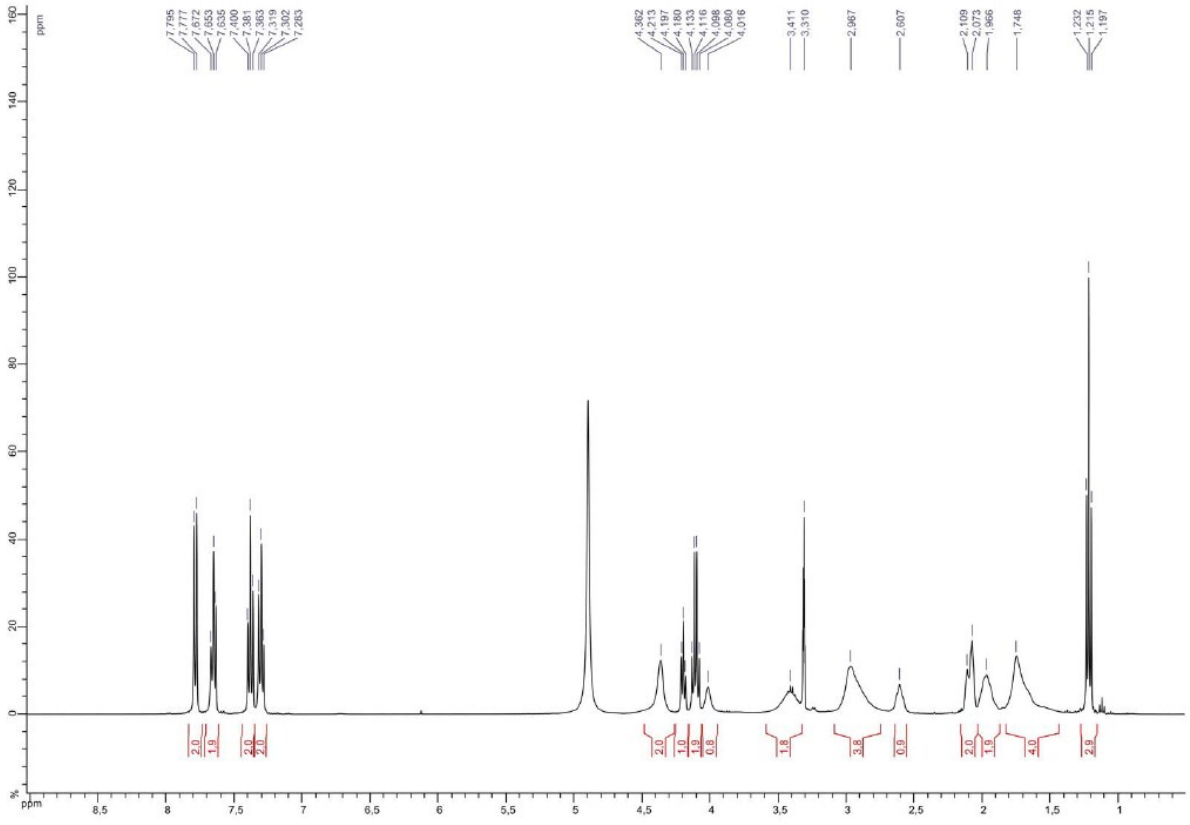
143.754
140.709
127.624
127.043
125.228
120.100
65.567
55.988
53.594
51.172
49.109
48.650
28.534
25.140
23.367
22.086
21.998

Compound 2h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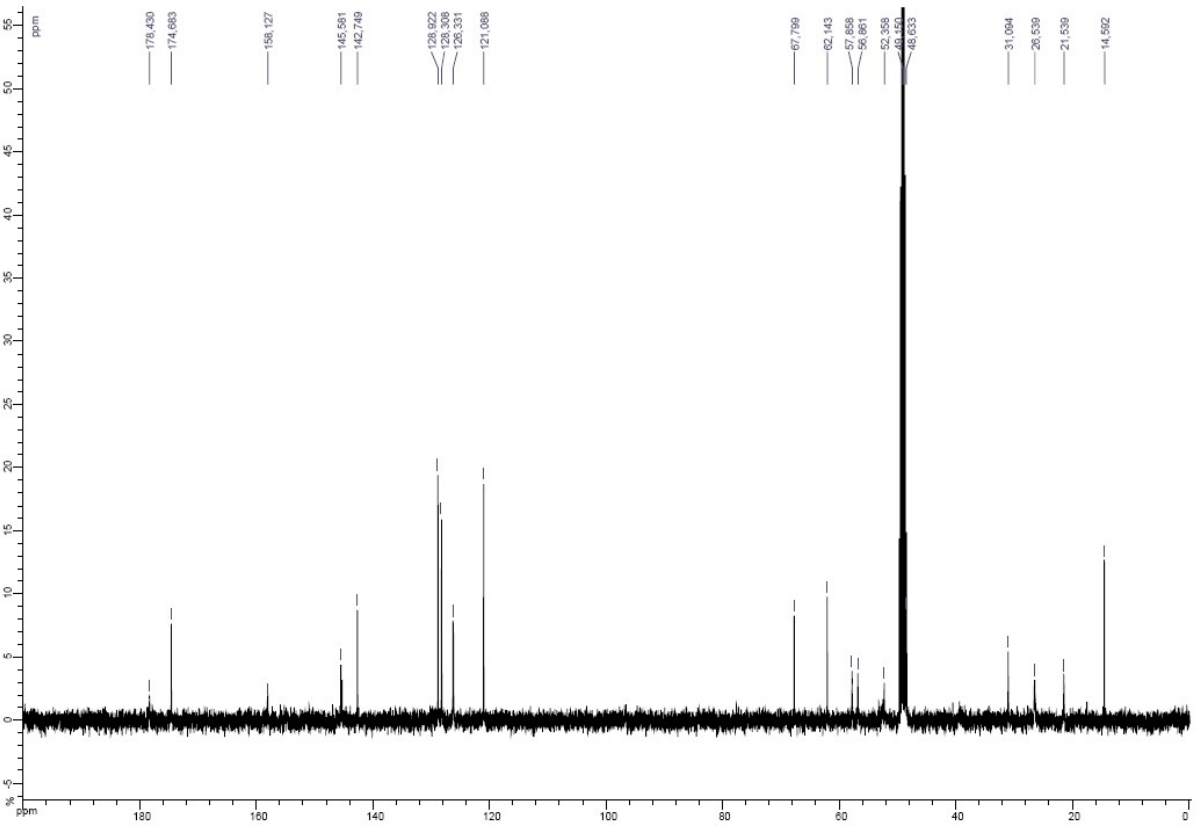
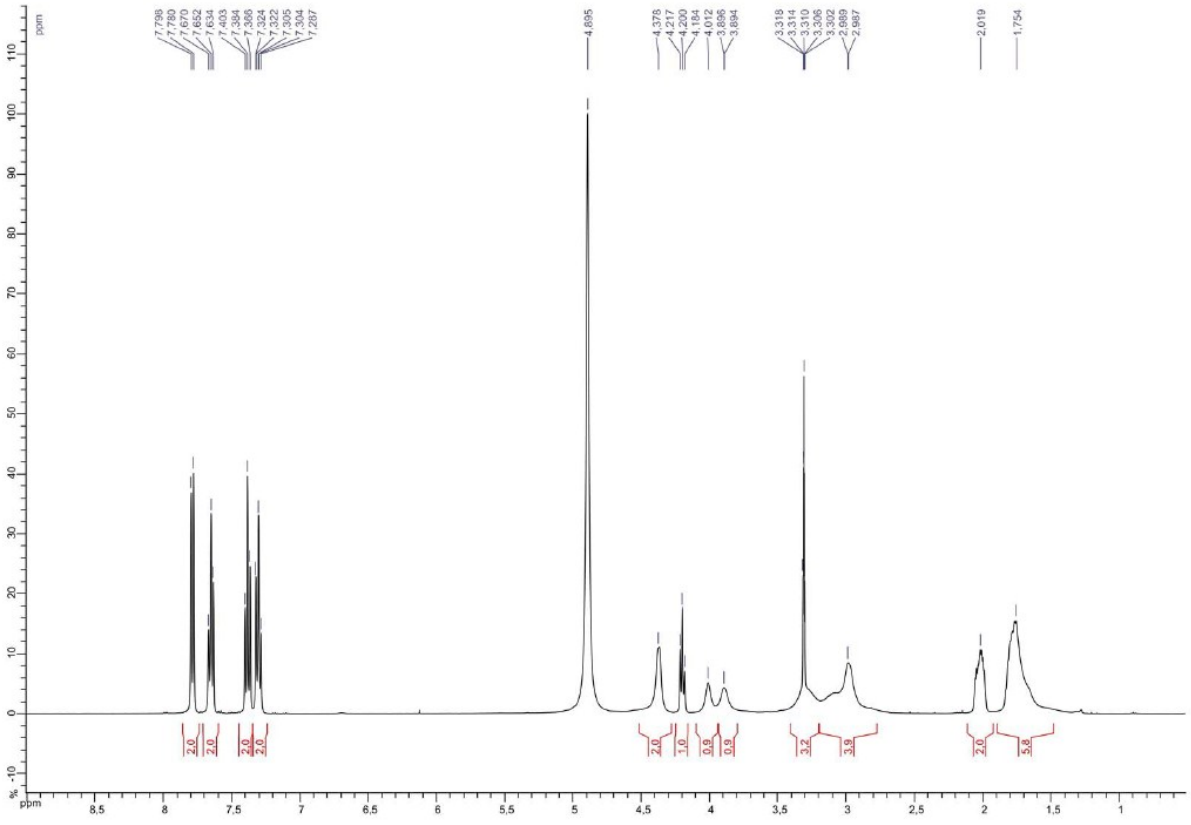
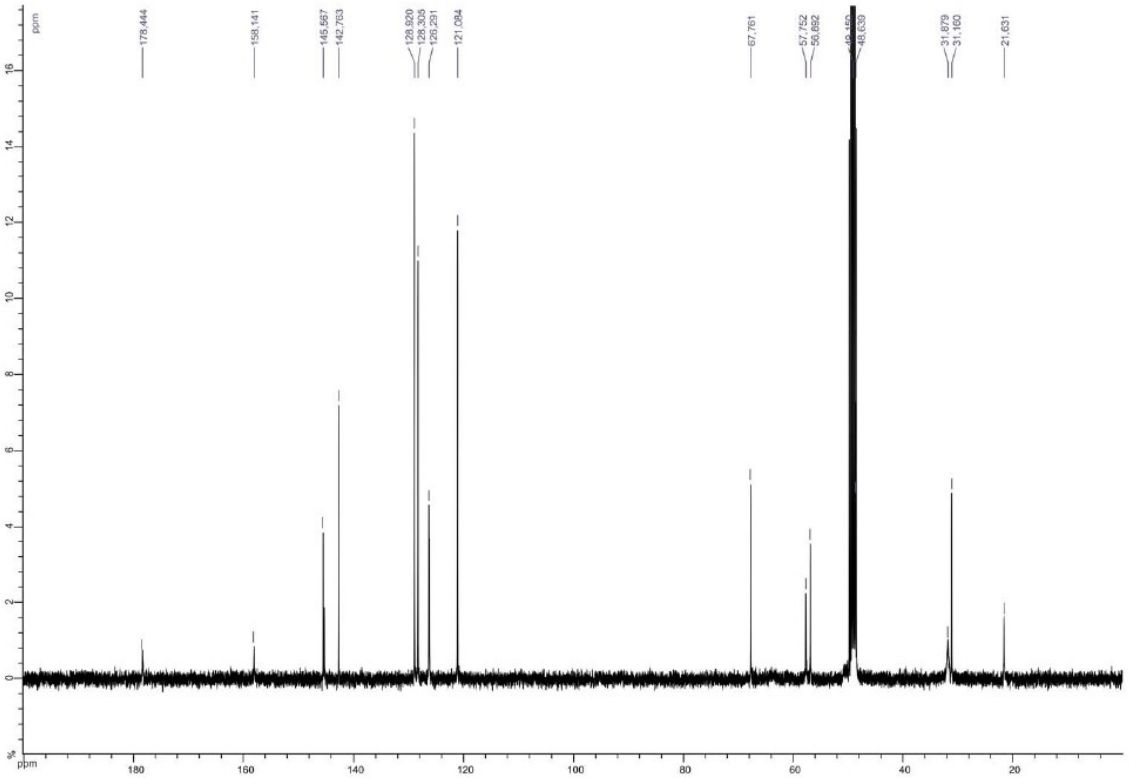
7,672
7,653
7,635
7,400
7,381
7,363
7,319
7,302
7,283
4,362
4,213
4,197
4,180
4,133
4,116
4,098
4,080
4,016
3,411
3,310
2,967
2,607
2,109
2,073
1,966
1,748
1,232
1,215
1,197
ppm

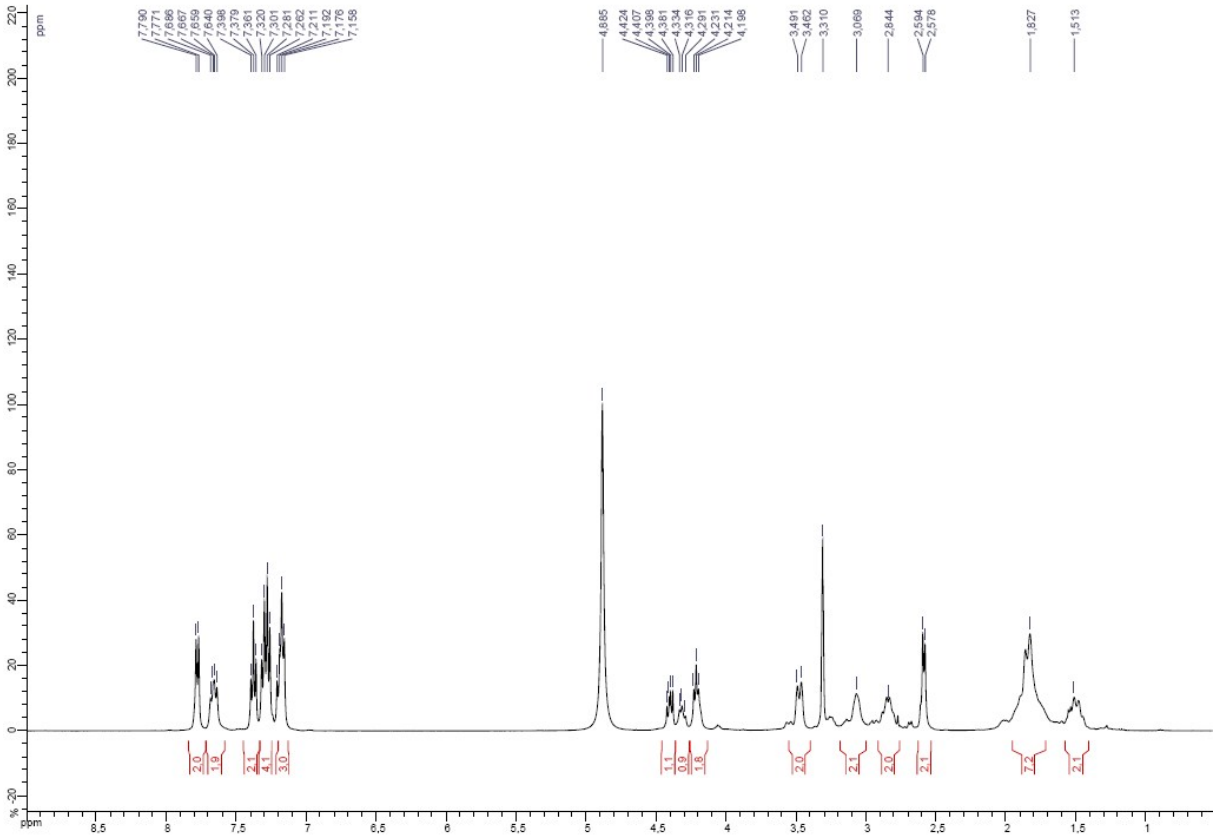

178,430
174,683
158,127
145,581
142,749
128,922
128,308
126,331
121,088
67,799
62,143
57,858
56,661
52,358
48,633
31,084
26,539
21,539
14,592
ppm

Compound 2i


7.798
7.780
7.670
7.652
7.634
7.403
7.384
7.386
7.324
7.322
7.305
7.304
7.287
4.895
4.378
4.217
4.200
4.184
4.012
3.896
3.894
3.315
3.314
3.310
3.306
3.302
2.989
2.967
2.019
1.754
2.0
2.0
2.0
2.0
2.0
1.0
0.9
0.9
3.2
3.9
2.0
5.8


178.444
158.141
145.567
142.763
129.920
128.306
126.291
121.084
67.761
57.752
56.892
48.639
31.879
31.160
21.631

Compound 2j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7,686
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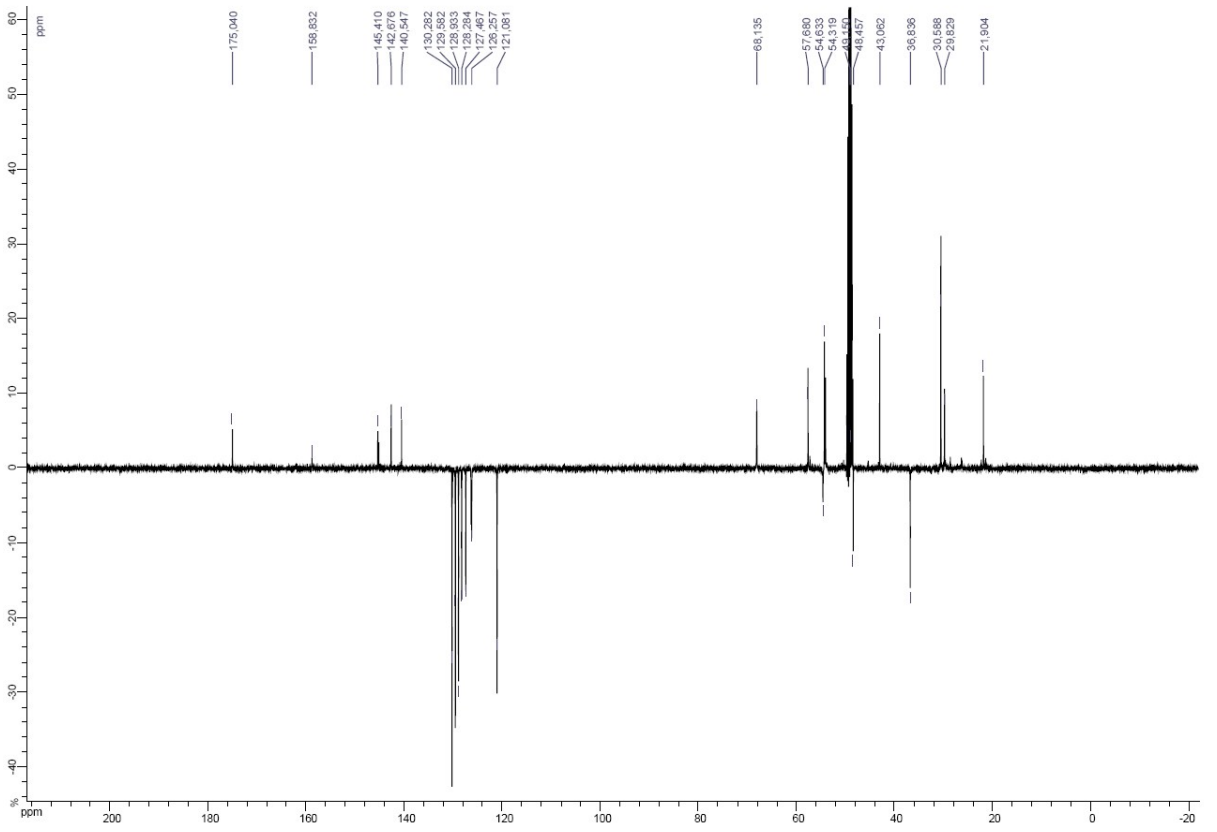
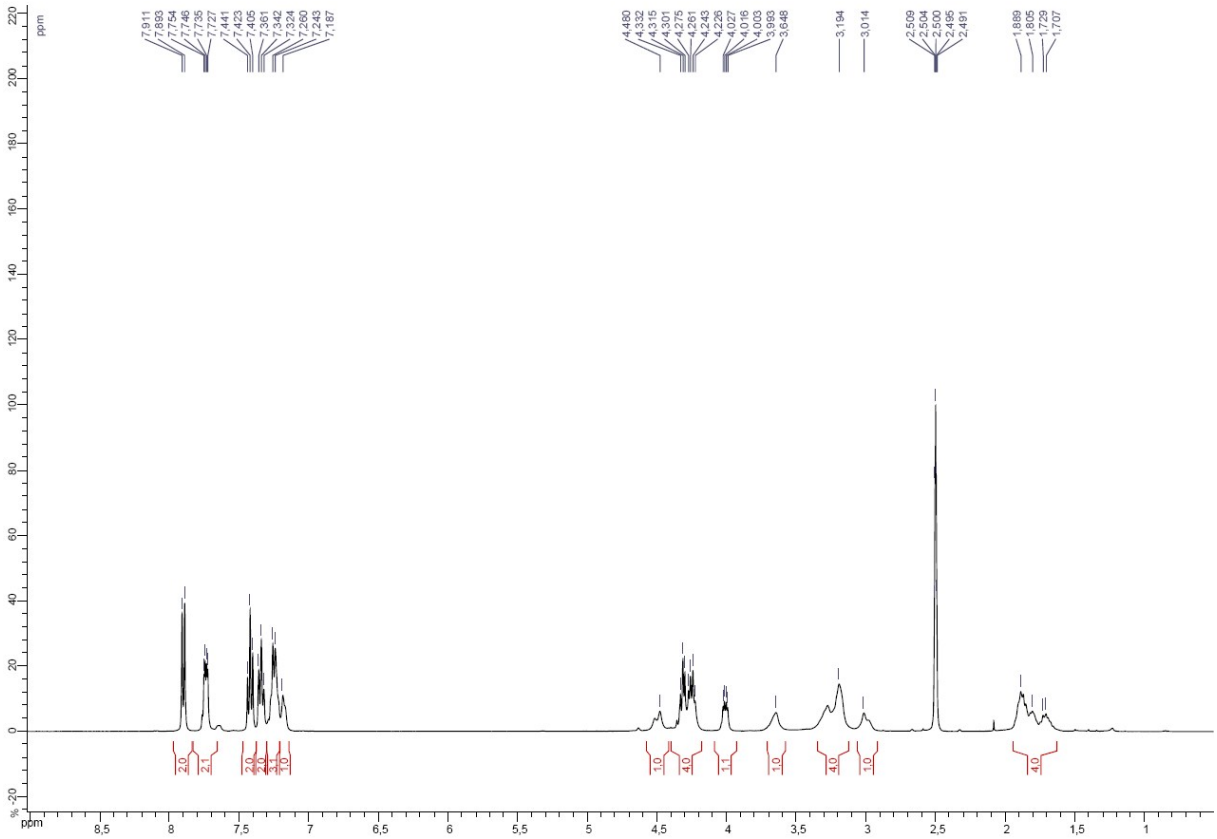
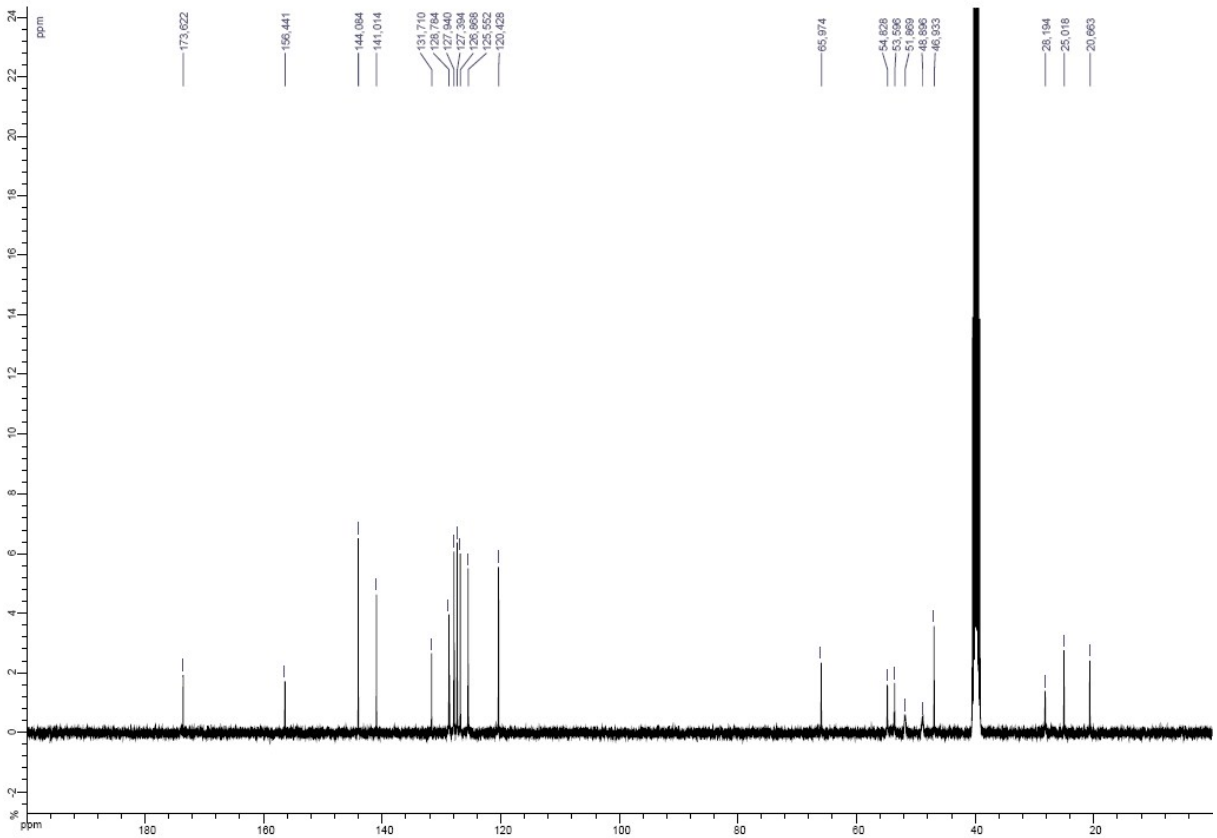
7,659
7,640
7,398
7,379
7,361
7,320
7,301
7,281
7,262
7,211
7,192
7,176
7,158
4,885
4,424
4,407
4,398
4,381
4,334
4,316
4,291
4,231
4,214
4,196
3,491
3,462
3,310
3,069
2,844
2,594
2,578
1,827
1,513
2,0
1,9
2,1
4,1
3,0
1,1
0,9
1,6
2,0
2,1
2,0
2,1
7,2
2,1
ppm


175,040
158,832
145,410
142,676
140,547
130,282
129,582
128,933
128,284
127,467
126,257
121,081
68,135
57,680
54,633
54,319
49,150
48,457
43,062
36,836
30,588
29,829
21,904
ppm

Compound 2k


7,911
7,893
7,754
7,746
7,735
7,727
7,441
7,423
7,405
7,361
7,342
7,324
7,260
7,243
7,187
4,480
4,332
4,315
4,301
4,275
4,261
4,243
4,226
4,027
4,016
4,003
3,993
3,648
3,194
3,014
2,509
2,504
2,500
2,495
2,491
1,889
1,805
1,729
1,707
ppm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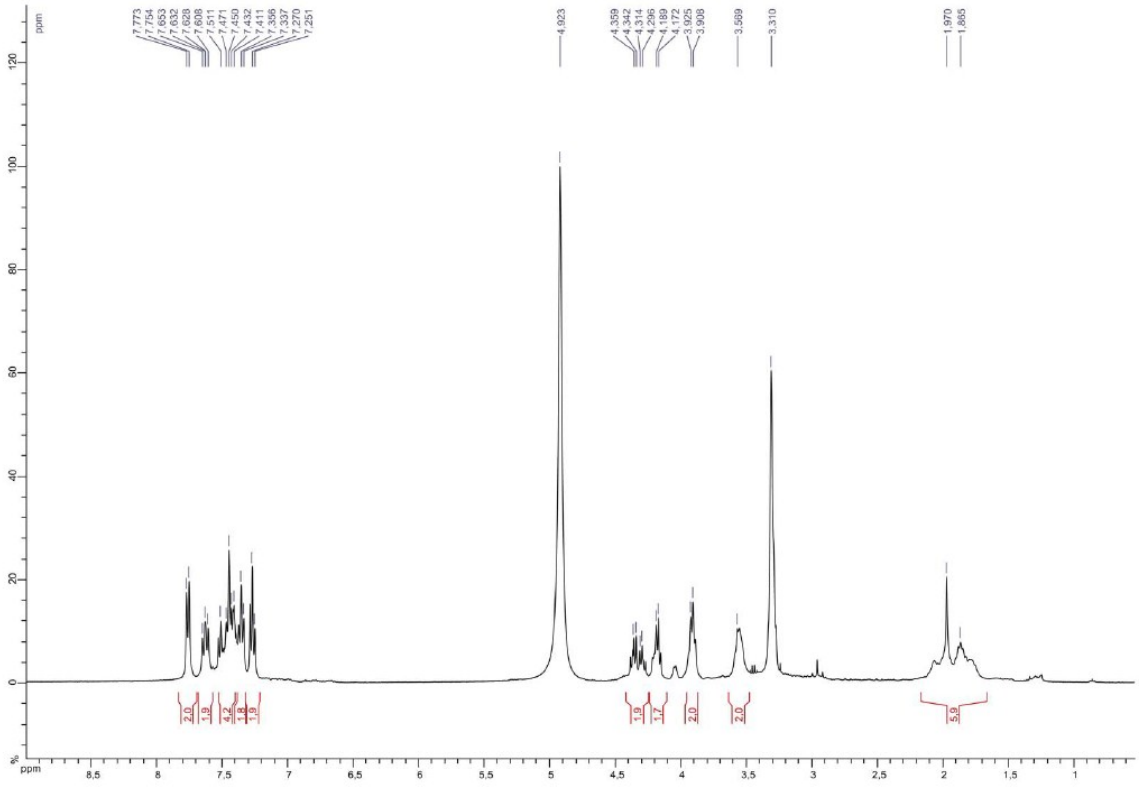
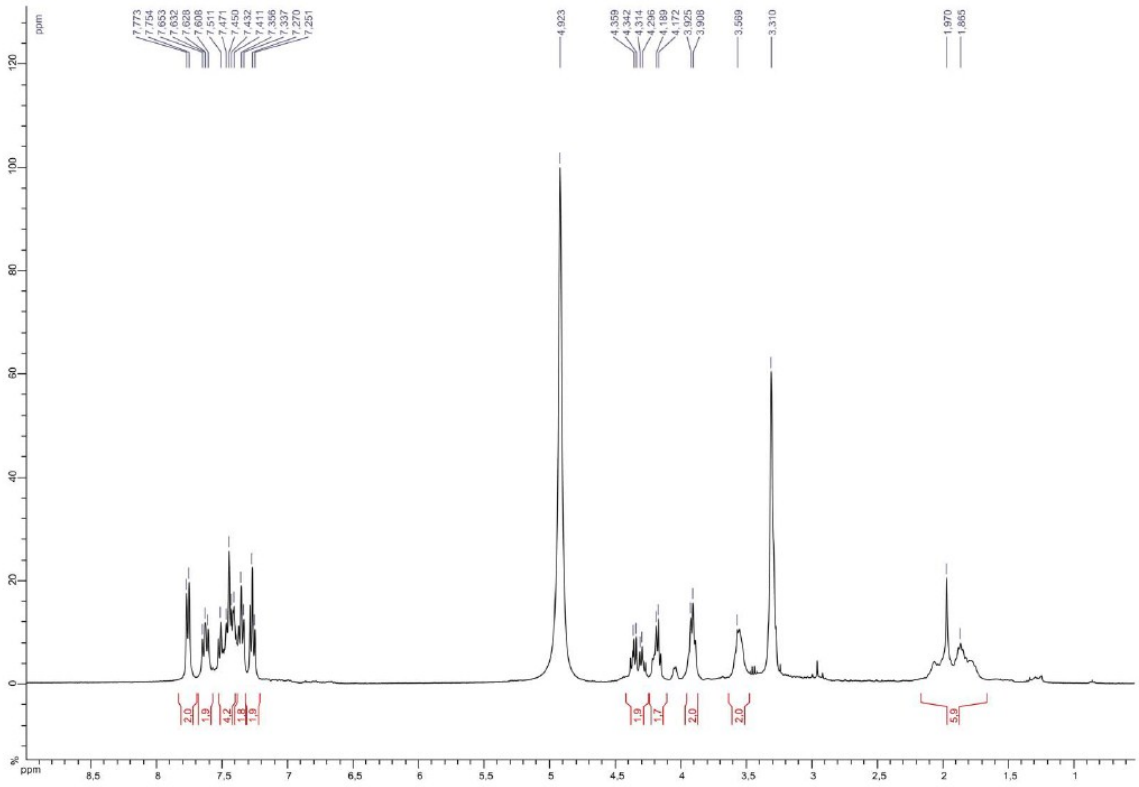
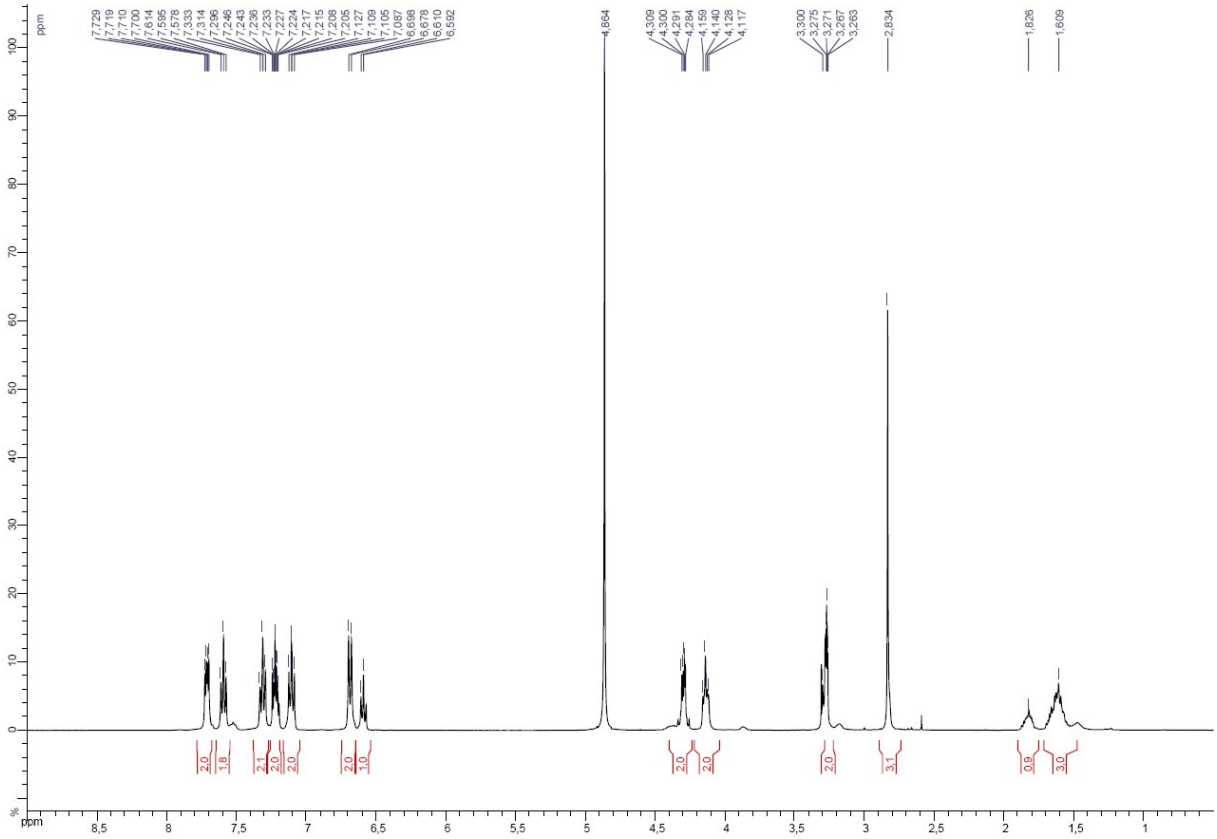
156,441
144,084
141,014
131,710
128,784
127,940
127,394
126,868
125,552
120,428
65,974
54,828
53,596
51,869
48,896
46,933
29,194
25,018
20,663
ppm

Compound 2l


7.773
7.754
7.653
7.632
7.628
7.608
7.511
7.471
7.450
7.432
7.411
7.356
7.337
7.270
7.251
4.923
4.359
4.342
4.314
4.296
4.189
4.172
3.925
3.908
3.569
3.310
1.970
1.865
ppm


7.773
7.754
7.653
7.632
7.628
7.608
7.511
7.471
7.450
7.432
7.411
7.356
7.337
7.270
7.251
4.923
4.359
4.342
4.314
4.296
4.189
4.172
3.925
3.908
3.569
3.310
1.970
1.865
ppm

Compound 2n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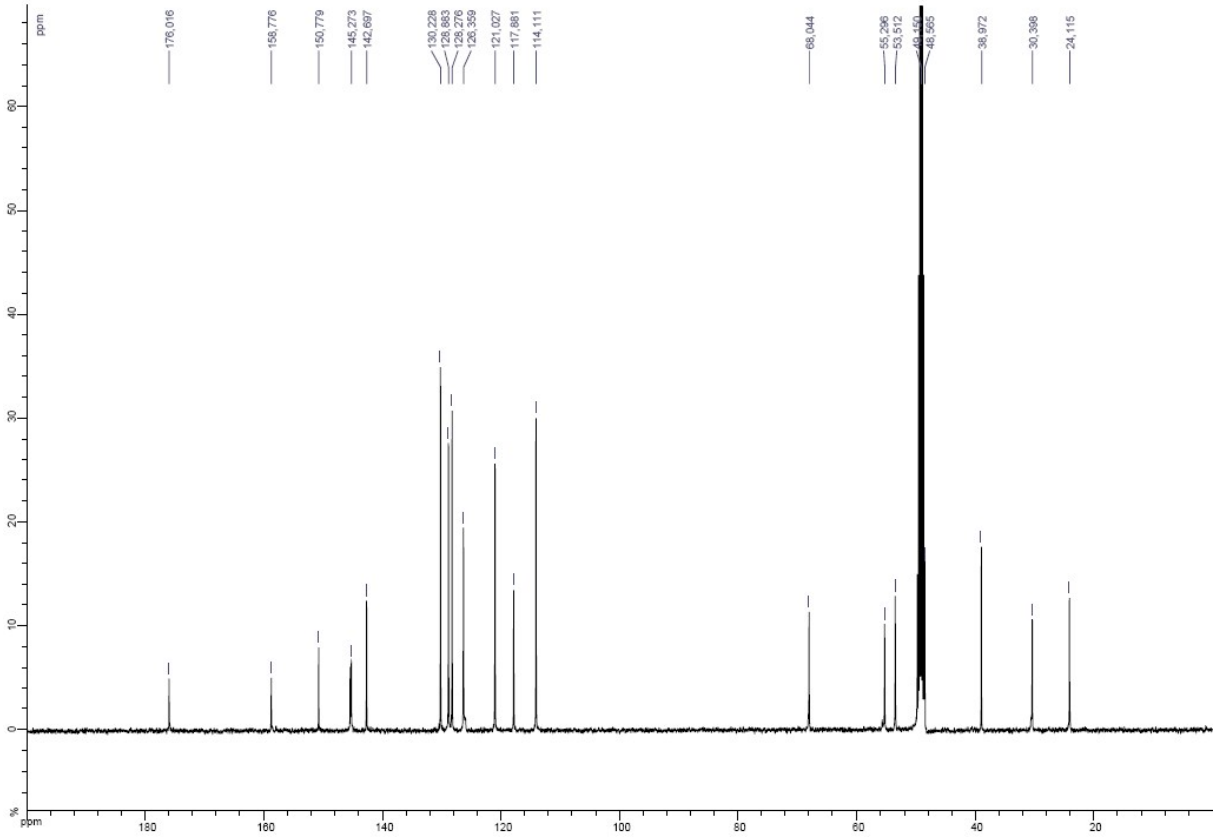
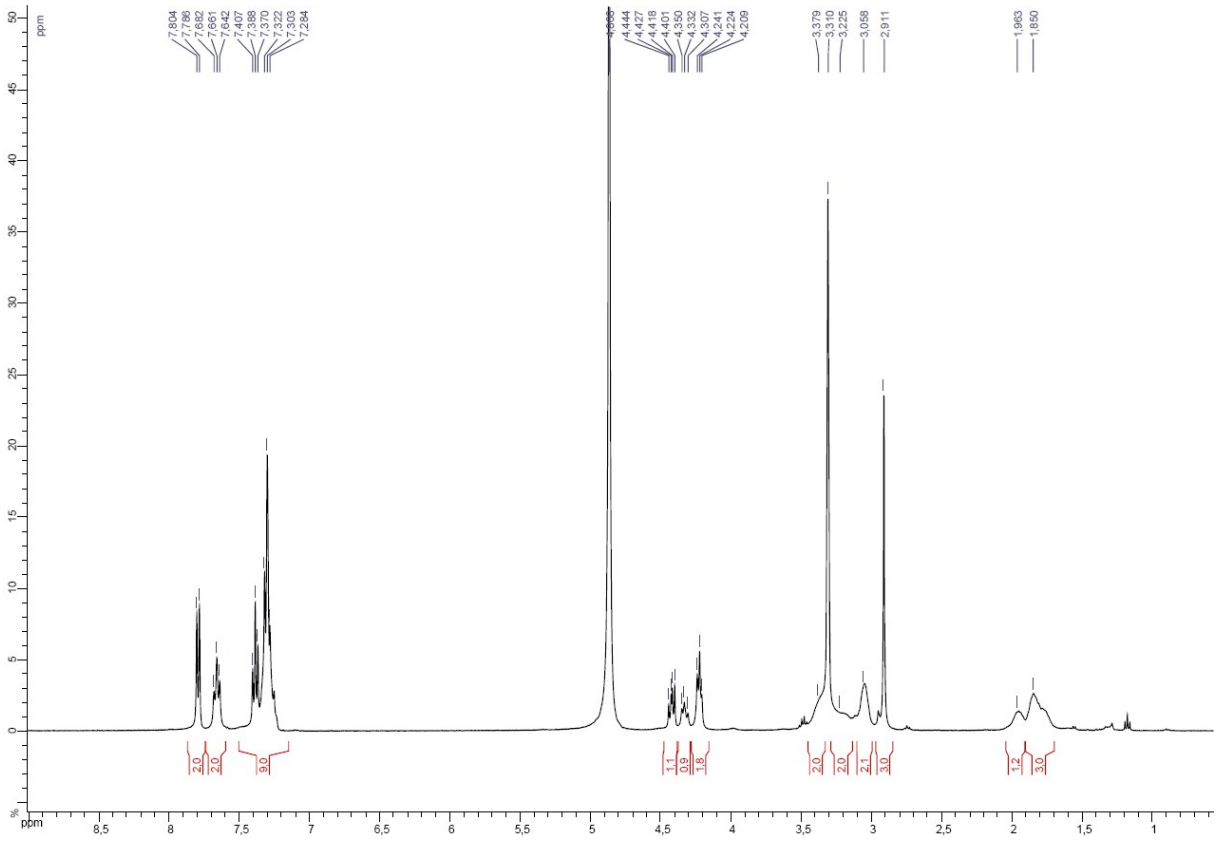
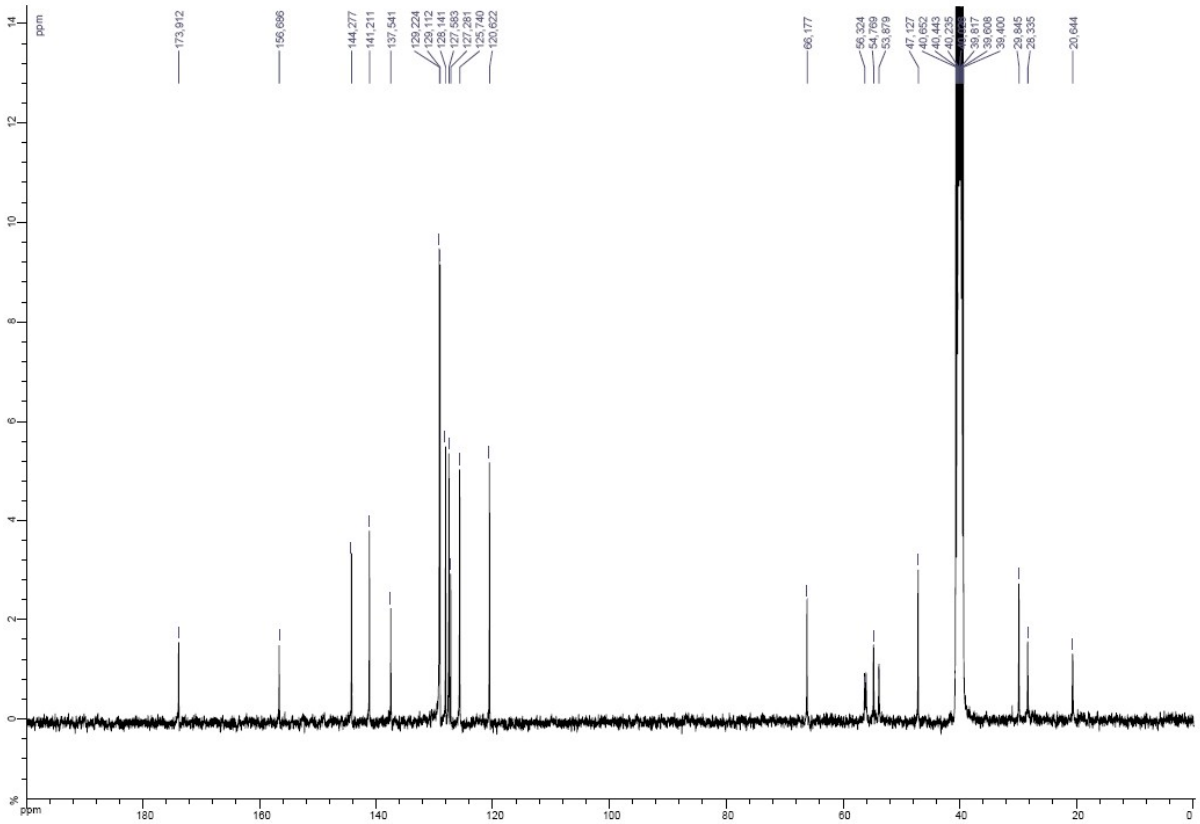
7,719
7,710
7,700
7,614
7,595
7,578
7,333
7,314
7,296
7,246
7,243
7,236
7,233
7,227
7,224
7,217
7,215
7,208
7,205
7,127
7,109
7,105
7,087
6,698
6,678
6,610
6,592
4,864
4,309
4,300
4,291
4,284
4,159
4,140
4,128
4,117
3,300
3,275
3,271
3,267
3,263
2,834
1,826
1,609
2,0
1,8
2,1
2,0
2,0
2,0
1,0
2,0
2,0
2,0
3,1
0,9
3,0
ppm

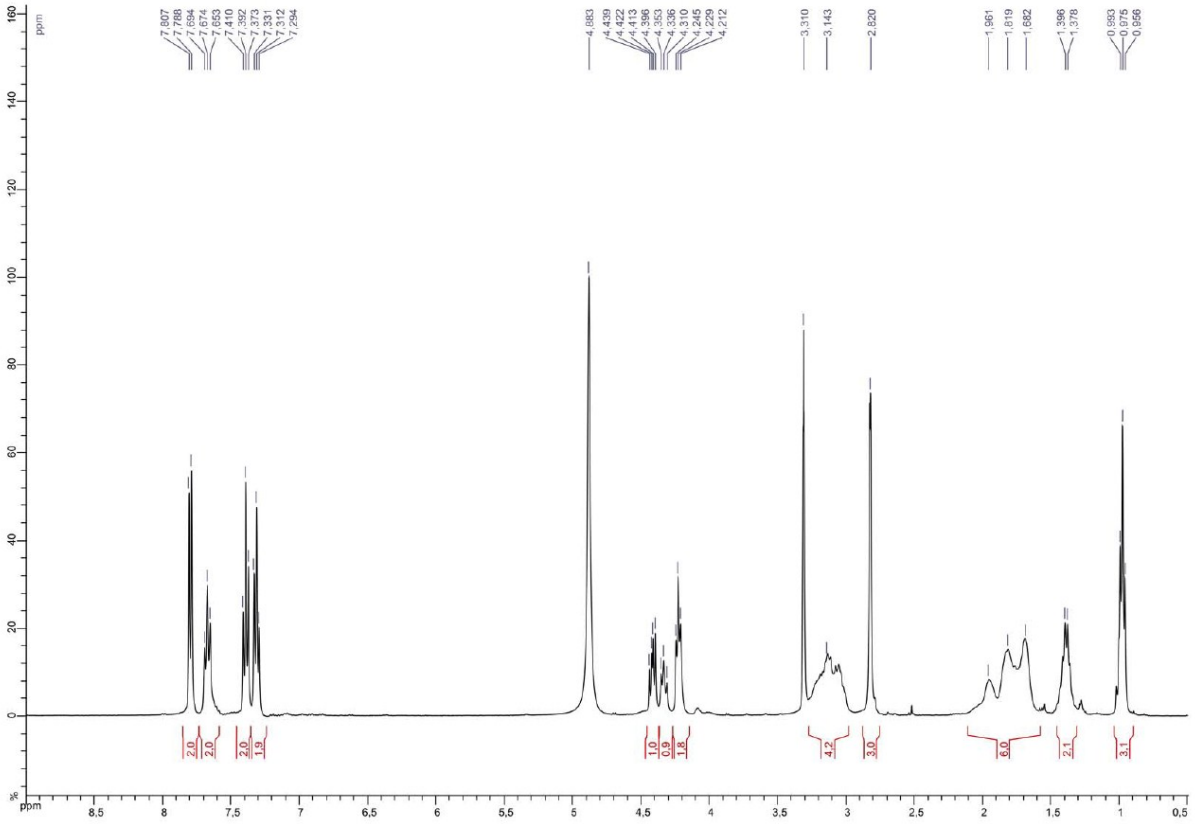

176,016
158,776
150,779
145,273
142,697
130,228
128,883
128,376
125,359
121,027
117,881
114,111
68,044
55,296
53,512
48,565
38,972
30,398
24,115
ppm

Compound 2o


7.804
7.786
7.682
7.661
7.642
7.407
7.388
7.370
7.322
7.303
7.284
4.444
4.427
4.418
4.401
4.350
4.332
4.307
4.241
4.224
4.209
3.379
3.310
3.225
3.058
2.911
1.963
1.850
2.0
2.0
3.0
1.1
0.9
1.8
2.0
2.0
2.1
3.0
1.2
3.0
ppm


173.912
156.686
144.277
141.211
137.541
129.224
129.112
128.141
127.583
127.281
125.740
120.622
66.177
56.324
54.769
53.879
47.127
40.652
40.443
39.817
39.608
39.400
29.845
28.335
20.644
ppm

Compound 2p


7.807
7.788
7.694
7.674
7.653
7.410
7.392
7.373
7.331
7.312
7.284
4.883
4.439
4.422
4.413
4.396
4.353
4.336
4.310
4.245
4.229
4.212
3.310
3.143
2.820
1.961
1.819
1.682
1.396
1.378
0.983
0.975
0.956
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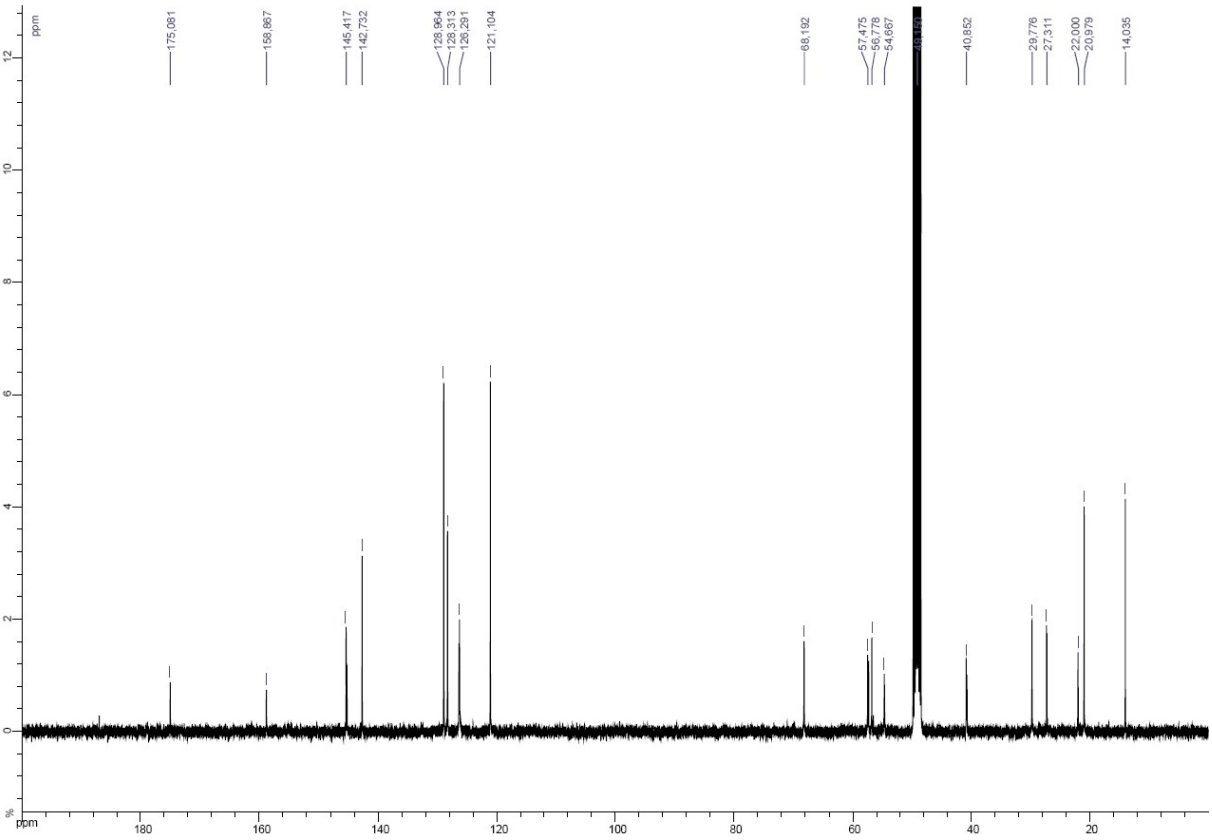
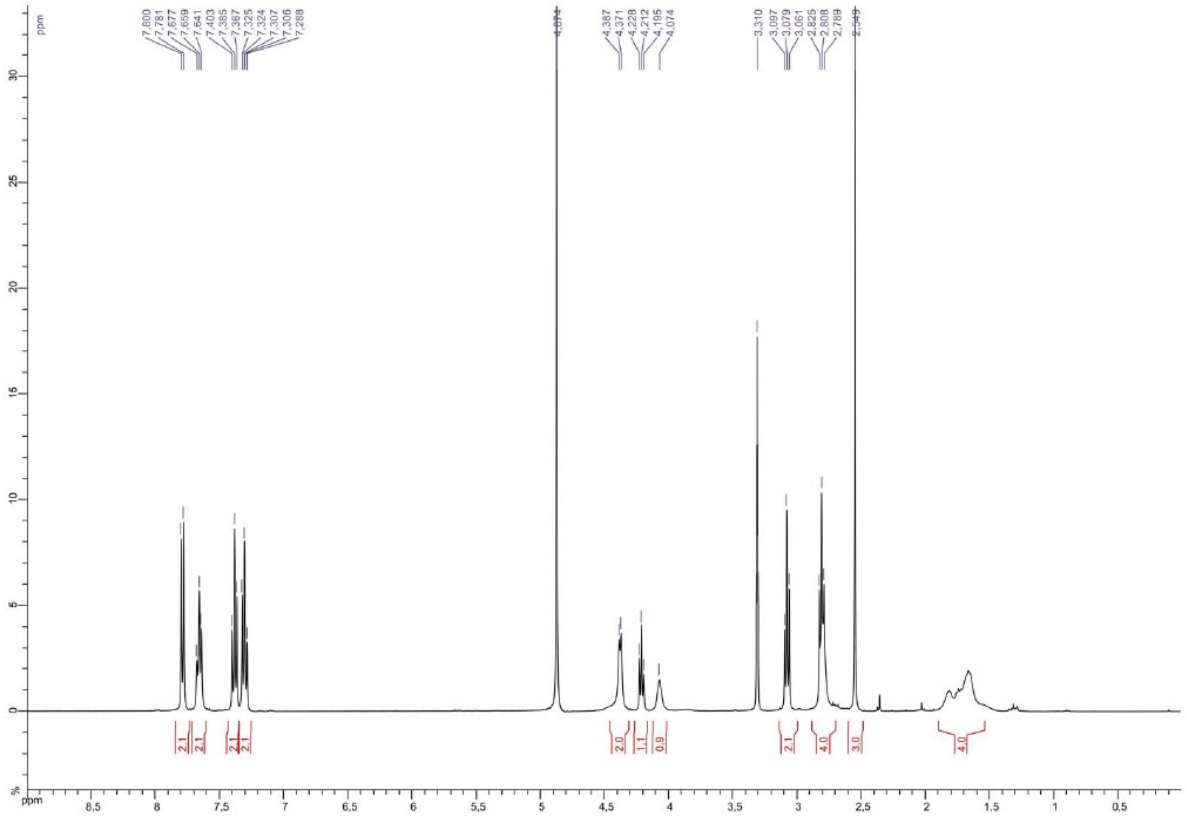
2.0
2.0
1.9
1.0
0.9
1.8
4.2
3.0
6.0
2.1
3.1
ppm


175.081
158.867
145.417
142.732
128.964
128.313
126.291
121.104
68.192
57.475
56.778
54.667
40.852
29.776
27.311
22.000
20.979
14.035
ppm

Compound 2q


7,800
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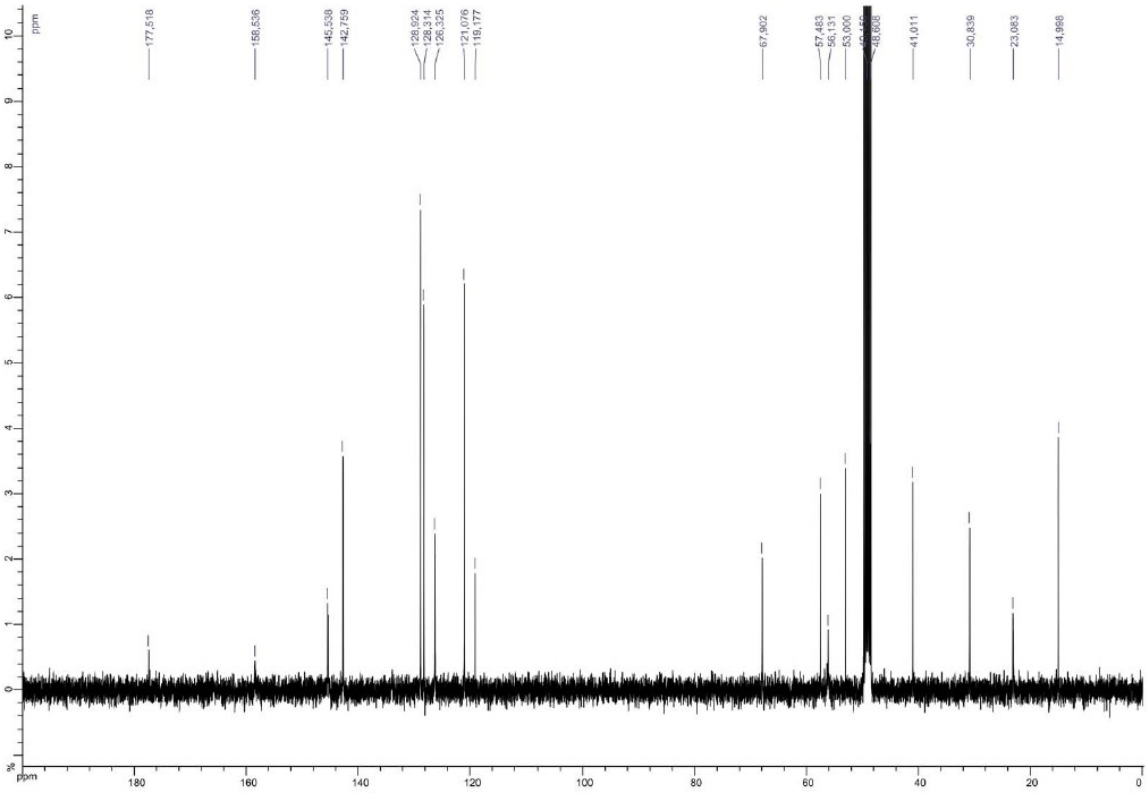
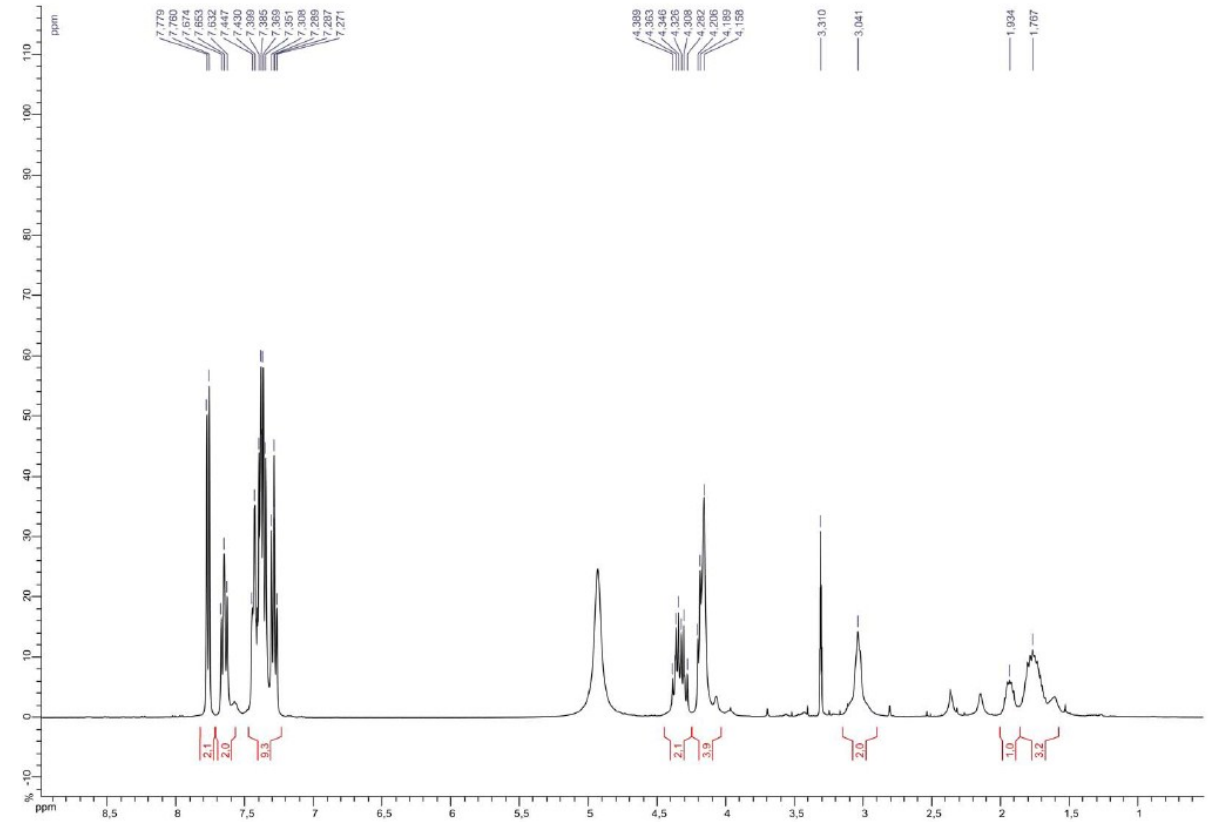
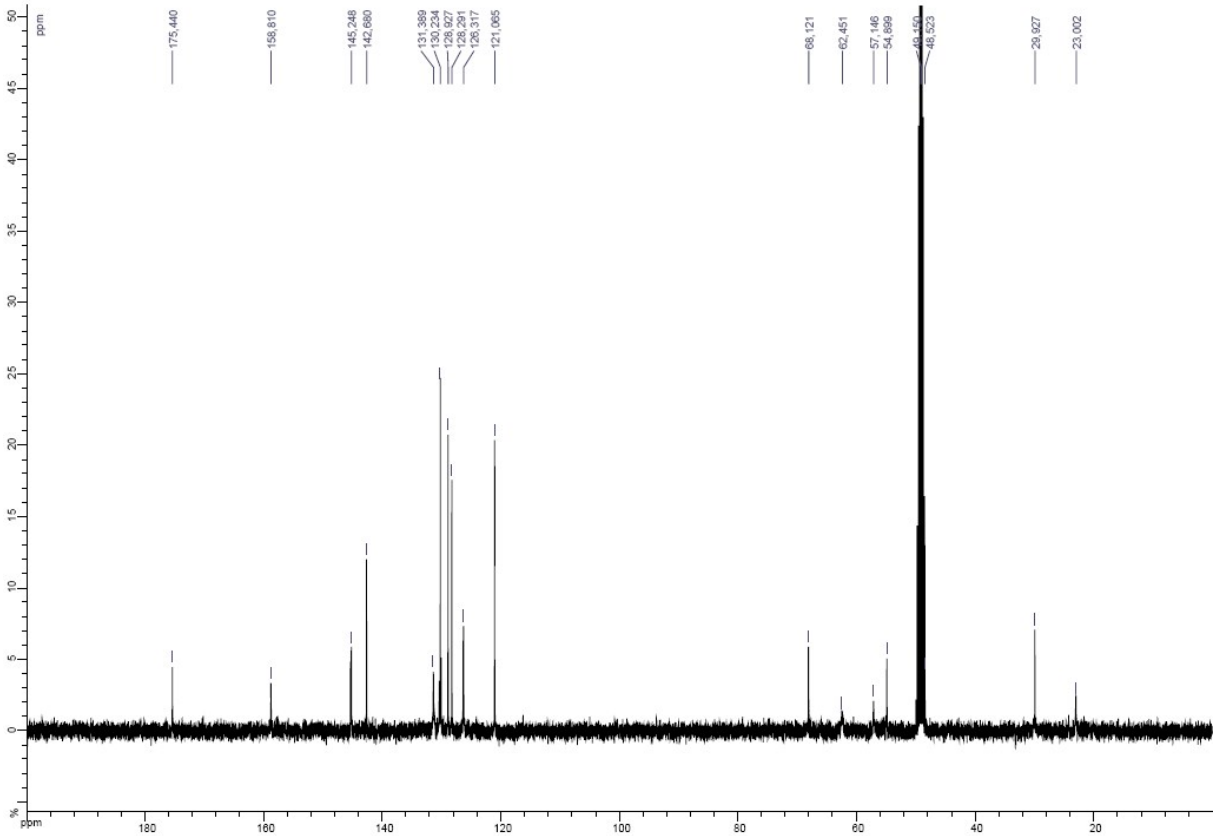
7,677
7,659
7,641
7,403
7,385
7,387
7,325
7,324
7,307
7,306
7,288
4,387
4,371
4,228
4,212
4,195
4,074
3,310
3,097
3,079
3,061
2,825
2,808
2,789
2,543
2,1
2,1
2,1
2,1
2,0
1,1
0,9
2,1
4,0
3,0
4,0
ppm

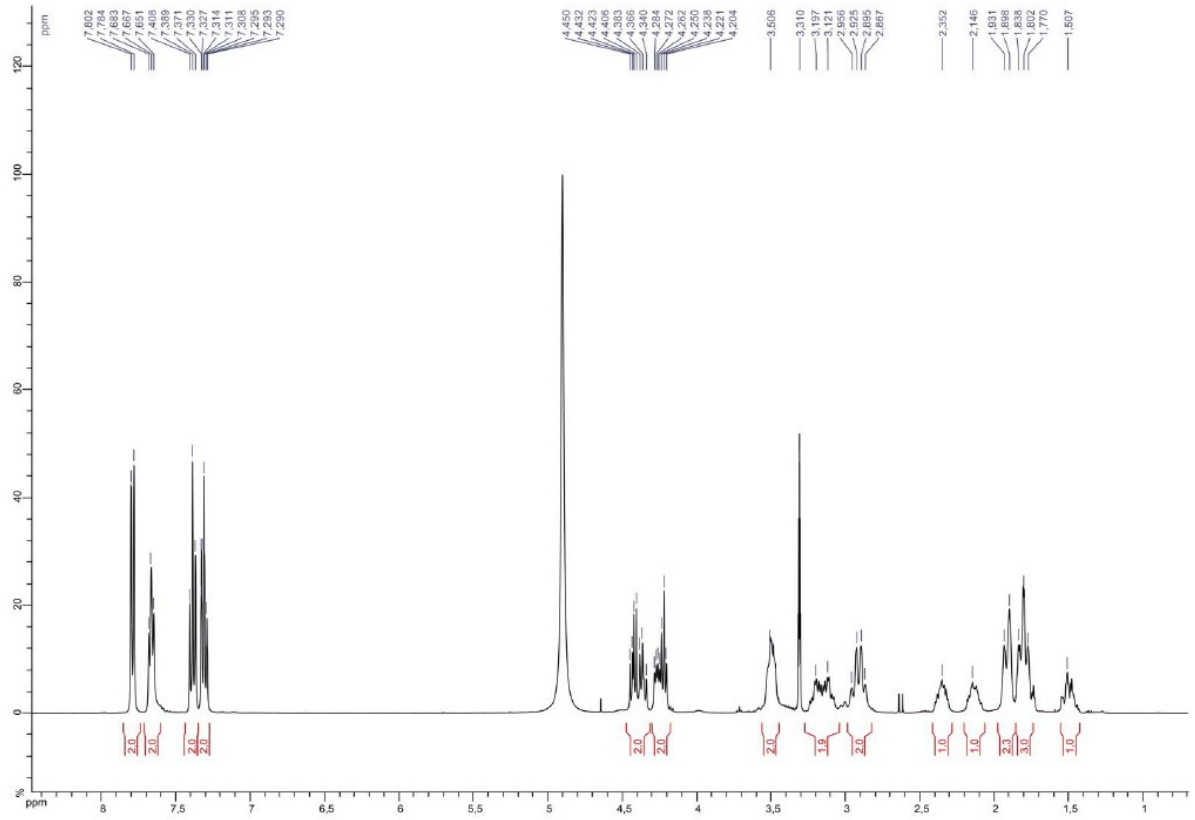

177,518
158,636
145,538
142,759
128,624
128,314
126,325
121,076
119,177
67,902
57,483
56,131
53,000
48,608
41,011
30,839
23,083
14,988
ppm

Compound 2r


7.779
7.760
7.674
7.653
7.632
7.447
7.430
7.389
7.385
7.369
7.351
7.308
7.289
7.287
7.271
4.389
4.383
4.346
4.326
4.308
4.282
4.206
4.189
4.158
3.310
3.041
1.934
1.767
2.1
2.0
3.3
2.1
3.9
2.0
1.0
3.2


175,440
158,810
145,248
142,680
131,389
130,234
128,927
128,291
126,317
121,065
68,121
62,451
57,146
54,899
49,150
48,523
29,927
23,002

Compound 4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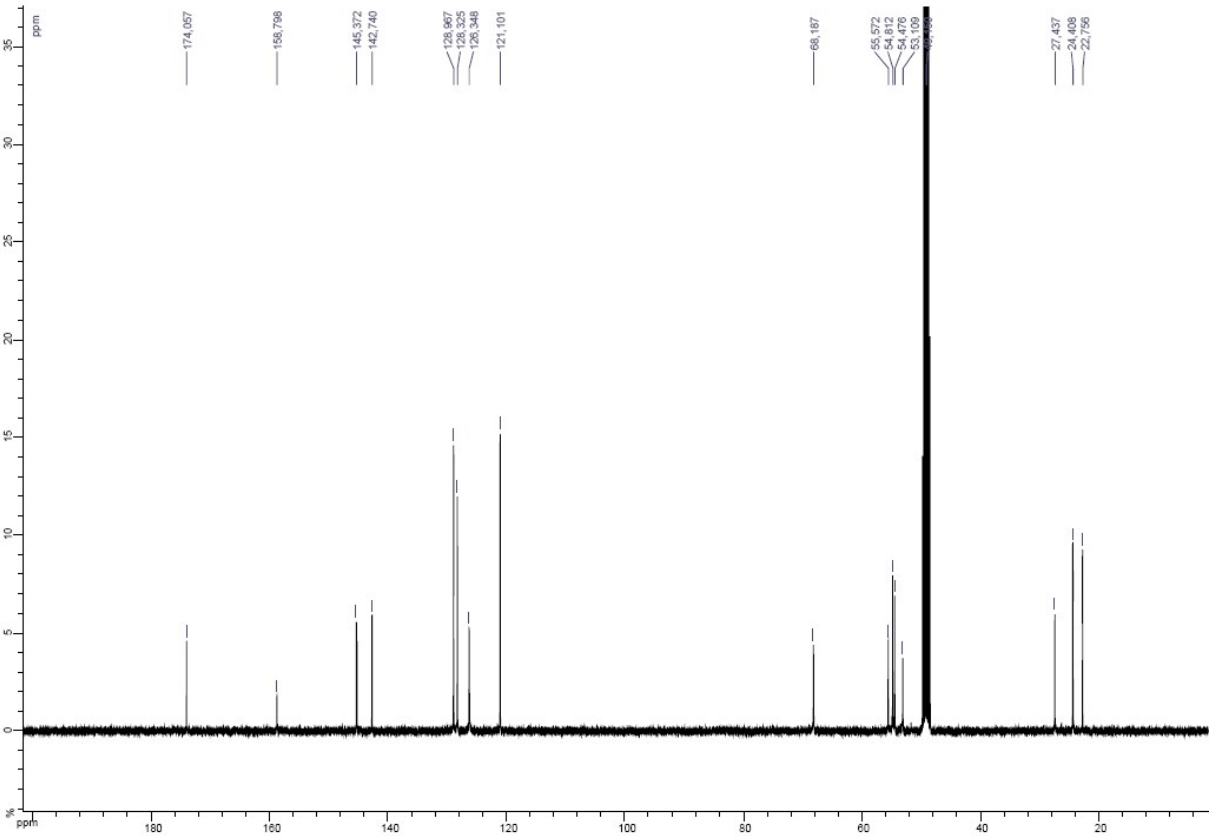
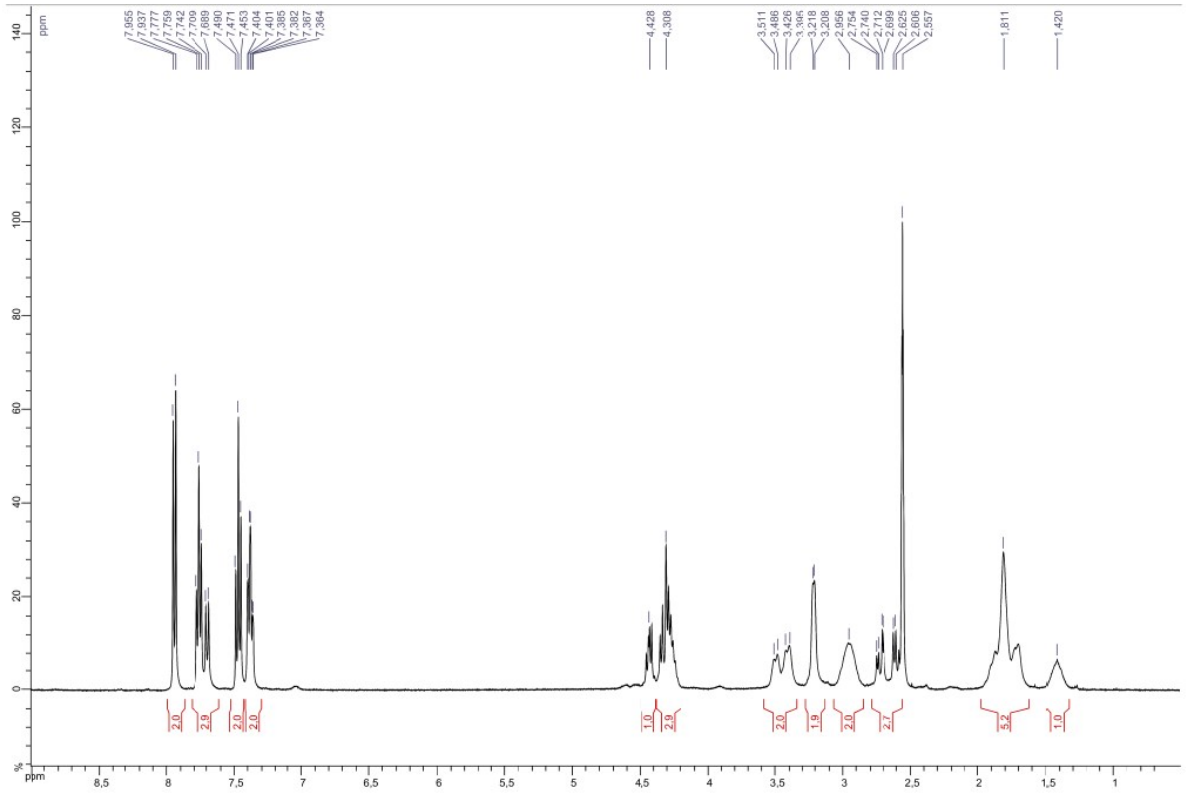
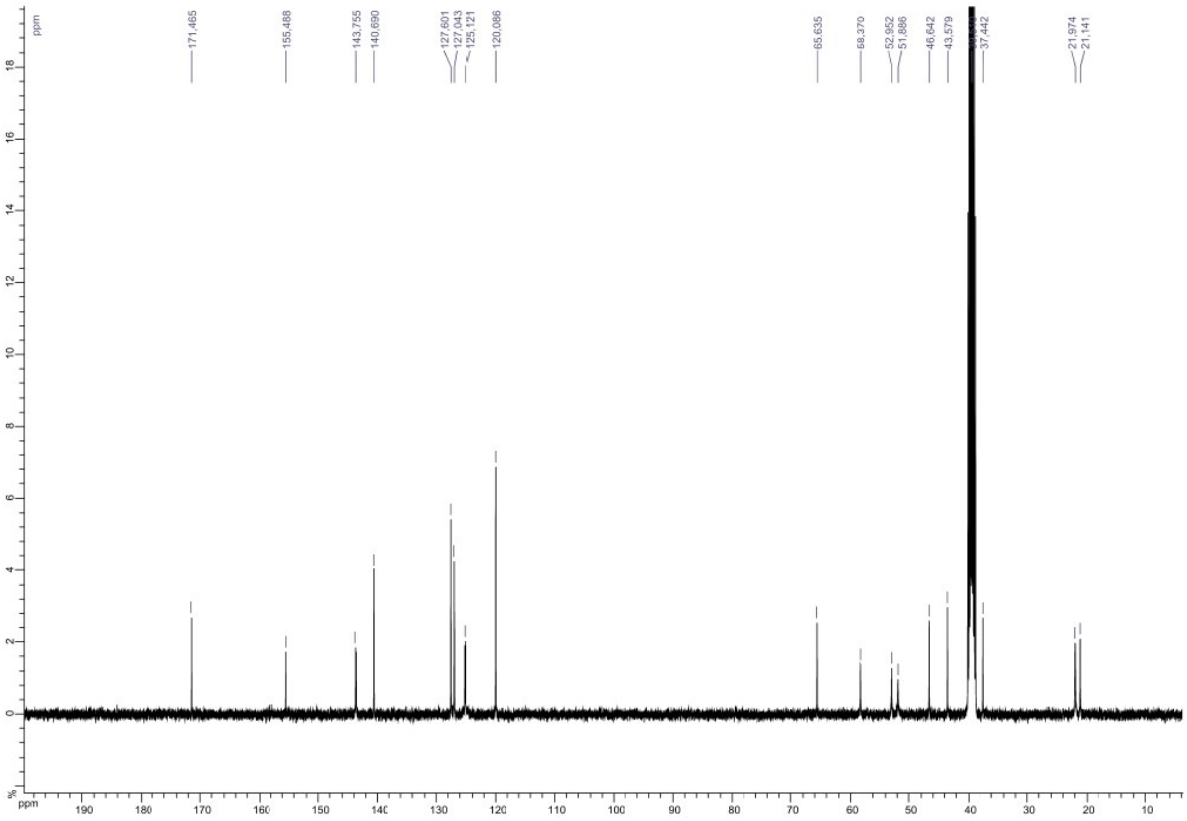
7,784
7,683
7,667
7,651
7,408
7,389
7,371
7,330
7,327
7,314
7,311
7,308
7,295
7,283
7,290
4,450
4,432
4,423
4,406
4,383
4,366
4,340
4,284
4,272
4,262
4,250
4,238
4,221
4,204
3,506
3,310
3,197
3,121
2,956
2,925
2,895
2,867
2,352
2,146
1,931
1,898
1,838
1,802
1,770
1,507
ppm

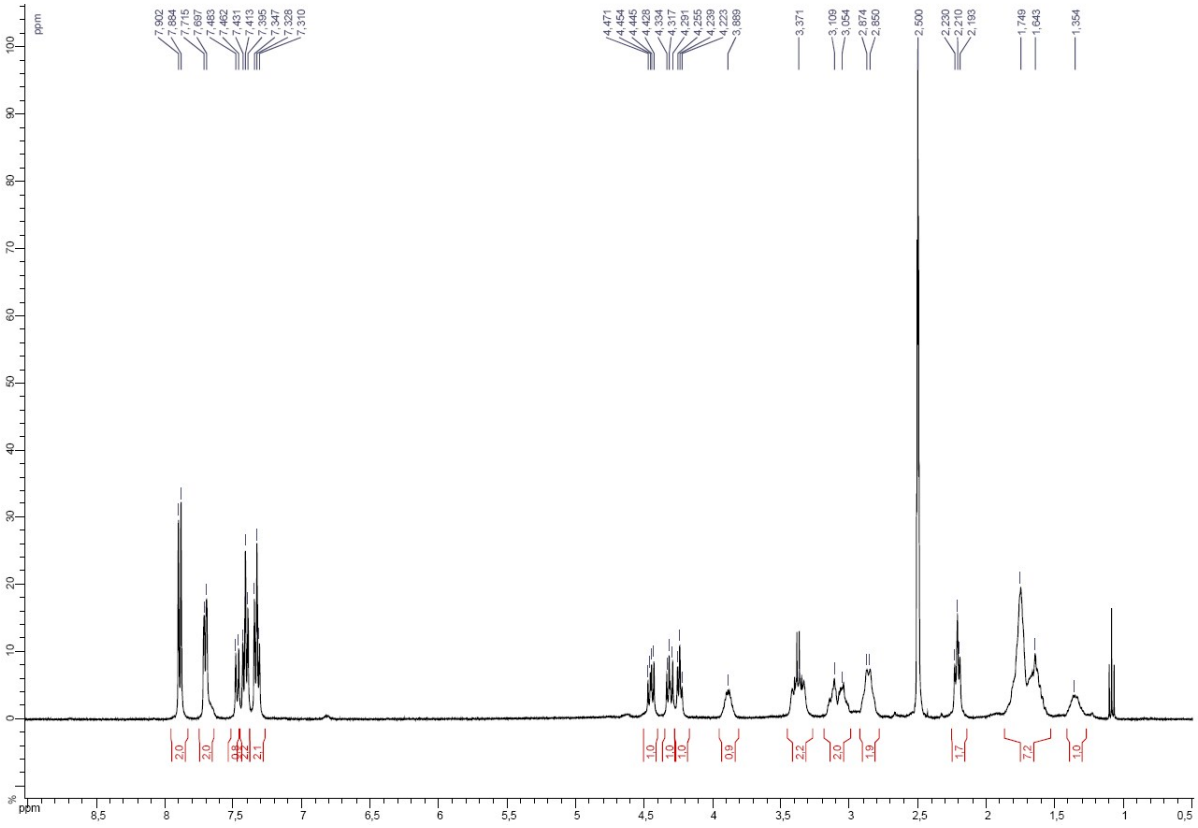

174,057
158,798
145,372
142,740
128,967
128,325
126,348
121,101
68,187
55,572
54,912
54,476
53,109
27,437
24,408
22,756
ppm

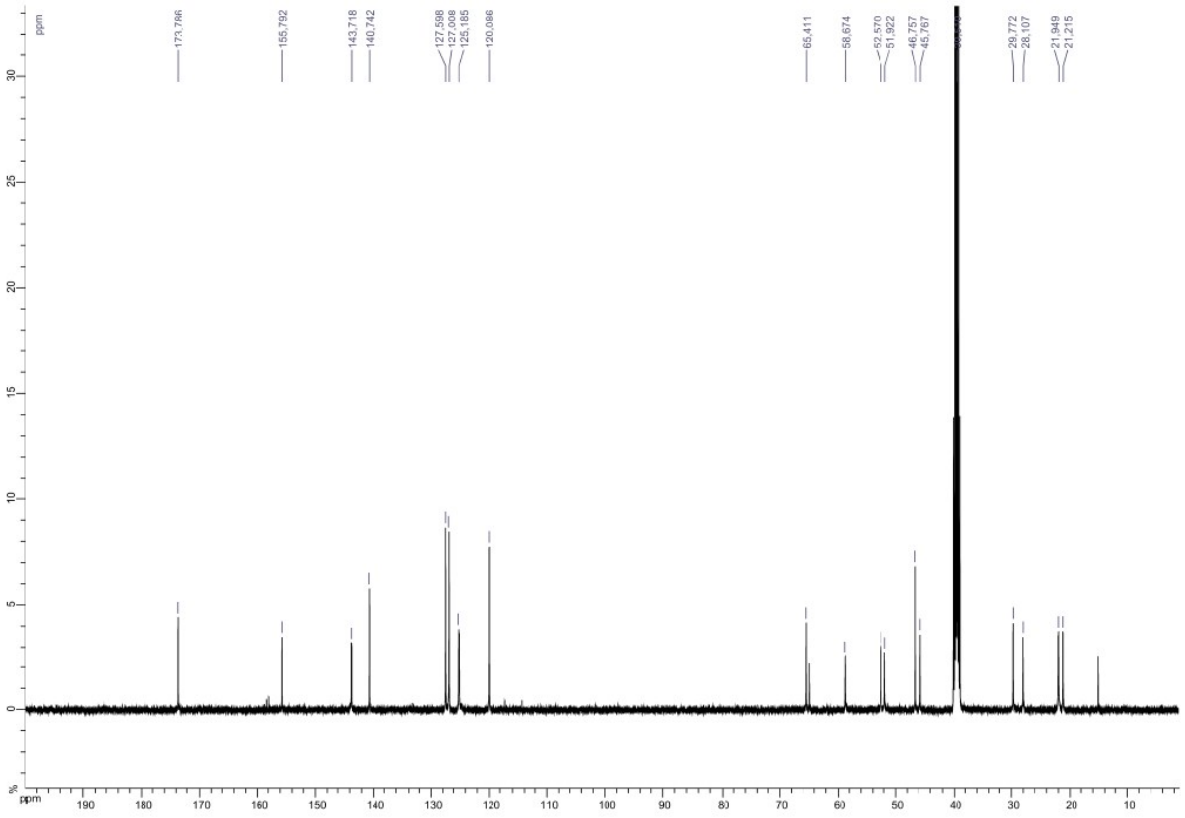
Compound 7


7.955
7.937
7.777
7.759
7.742
7.709
7.689
7.490
7.471
7.453
7.404
7.401
7.385
7.382
7.367
7.364
4.428
4.308
3.511
3.486
3.426
3.346
3.218
3.208
2.956
2.754
2.740
2.712
2.699
2.625
2.606
2.557
1.811
1.420
2.0
2.9
2.0
2.0
1.0
2.9
2.0
1.9
2.0
2.7
5.2
1.0


171.465
155.488
143.755
140.690
127.601
127.043
125.121
120.086
65.635
58.370
52.952
51.886
46.642
43.579
37.442
21.974
21.141

Compound 8


7,902
7,884
7,715
7,697
7,483
7,462
7,431
7,413
7,395
7,347
7,328
7,310
4,471
4,454
4,445
4,428
4,334
4,317
4,291
4,255
4,239
4,223
3,869
3,371
3,109
3,054
2,874
2,850
2,500
2,230
2,210
2,193
1,749
1,643
1,354
ppm


173,766
155,792
143,718
140,742
127,598
127,008
125,185
120,086
65,411
58,674
52,570
51,922
46,757
45,767
29,772
28,107
21,949
21,215
ppm