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α-Glucosidase Inhibitory Activity of Phenolic Compounds Isolated from the Stems of *Caesalpinia decapetala* var. *japonica*

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Abstract – In our study, sixteen known phenolic compounds, including quercetin (**1**), methyl gallate (**2**), caesalpiniaphenol C (**3**), 8*S*,8′*S*,7′*R*-(–)-lyoniresinol (**4**), 7,3′,5′-trihydroxyflavanone (**5**), sappanchalcone (**6**), sappanone A (**7**), taxifolin (**8**), fisetin (**9**), fustin (**10**), (+)-catechin (**11**), brazilin (**12**), 3,4,5-trimethoxyphenyl *β*-D-glucopyranoside (**13**), 1-(2-methylbutyryl)phloroglucinol-glucopyranoside (**14**), (+)-*epi*-catechin (**15**), and astragalin (**16**) and one mixture of two conformers of protosappanin B (**17/18**) were isolated from the stems of *Caesalpinia decapetala* var. *japonica.* Their structures were elucidated based on a comparison of their physicochemical and spectral data with those of literature. To the best of our knowledge, this represents the first isolation of compounds **3**, **4**, **8**, **9**, and **10** from *C. decapetala* and compounds **13** and **14** from the *Caesalpinia* genus. All the isolated compounds were evaluated for their inhibitory effect against the α-glucosidase enzyme. Among them, two flavonols (**1** and **9**), one chalcone (**6**), and one homoisoflavanone (**7**) exhibited an inhibitory effect on α-glucosidase action with an IC_{50} range value of 5.08 – 15.01 μM, stronger than that of the positive control (acarbose, IC_{50} = 152.22 μM). Kinetic analysis revealed that compounds **1** and **9** showed non-competitive α-glucosidase inhibition, while the inhibition type was mixed for compounds **6** and **7**.
Keywords – *Caesalpinia decapetala* var. *japonica*, Leguminosae, flavonoids, anti-diabetic, α-glucosidase

Introduction

Diabetes, a chronic disease, is a heterogeneous metabolic disorder characterized by elevated blood glucose levels in the body. This disease affects millions of people around the world, causing a variety of life-threatening complications on cardiovascular, neurological, and kidney. Although conventional synthetic medicines are available, they are usually accompanied by serious adverse effects such as gastrointestinal problems disturbances, and metabolic effects.[1] Thus, finding alternative natural medicine is an attractive strategy. The α -glucosidase enzyme hydrolyzes starch and sucrose down to glucose, inducing an increase in postprandial glucose levels in diabetic patients.[2] Hence, inhibiting the activity of this enzyme produces a massive reduction of postprandial hyperglycemia, and decreases the risk of developing diabetes.[3]

The *Caesalpinia* genus (Leguminosae family) comprises approximately 100 species and spreads widely in the tropical and subtropical regions of Southeast Asia. *Caesalpinia decapetala* var. *japonica* is located in China, Korea, India, and Malaysia.[4] Its whole plants had great medicinal values in folk medicine. Seeds of *C. decapetala* var. *japonica* were used for malaria and freckled skin.[5] Flowers of this plant treat infusion in bronchitis, asthma, and malarial fevers.[6] Leaves of *C. decapetala* var. *japonica* were used in the treatment of burns, biliousness, and stomach disorders.[6] Its roots were applied to treat bronchitis, prevent colds, and anti-malarial.[6] Roots and stems were also used for relieving pain.[6] *C. decapetala* var. *japonica* contained various chemical components, including essential oils,[7] flavonoids,[8,9] chalcones,[9] terpenoids,[8,10] and steroids,[9] which showed beneficial bioactivities such as anti-tumor,[9] anti-oxidant,[9] anti-analgesic,[8] anti-inflammatory,[8] anti-pyretic,[8] and anti-virus.[11]

However, most of the previous phytochemical investigations of *C. decapetala* var. *japonica* focused on its root and leaves,[12-14] the number of studies on its stems is still limited. Furthermore, although the blood-glucose-lowering

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effects of leaves and whole plant extract have been demonstrated,[15,16] this effect of *C. decapetala* var. *japonica* stems and its chemical components have not been reported. Therefore, we herein conducted isolation and structural determination of chemical components from *C. japonica* stem extract, and investigation of their α-glucosidase inhibitory effect aimed to explore the anti-diabetic activity of *C. decapetala* var. *japonica* stems.

Experimental

General experiment procedures – Specific optical rotation was measured using a JASCO P-2000 digital polarimeter (JASCO Corporation, Tokyo, Japan). The 1D and 2D-NMR spectra were obtained on a Varian Unity Inova 400 MHz (Varian, Inc., California, USA) spectrometer with tetramethylsilane (TMS) as an internal standard and the chemical shifts were recorded in δ values (ppm). Silica gel (Merck, 0.040-0.063 mm), RPC-18 (Merck, 17 mesh), and Sephadex LH-20 (Pharmacia Company) were used for column chromatography (CC). High-performance liquid chromatography was carried out on a Waters 2487 controller system with a UV detector (UV/VIS-156). RPC-18 F_{254s} and silica gel F_{254} (Merck) plates were used to perform thin-layer chromatography (TLC). Compounds were detected under UV light and then visualized by heating after spraying with H_2SO_4 10%.

Chemical and reagents – Yeast α-glucosidase, *p*-nitrophenyl α-D-glucopyranoside (*p*-NPG), sodium phosphate, sodium carbonate, acarbose, and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich Co. (St. Louis, MO, U.S.A).

Plant materials – The stems of *Caesalpinia decapetala* var. *japonica* were collected at Jeju-do, Republic of Korea, in June 2018 and identified by Professor Byung Sun Min. A voucher specimen (CUD-1857-1) was deposited at the Herbarium of the College of Pharmacy, Daegu Catholic University, Korea.

Extraction and isolation – The dried stems of *C. decapetala* var. *japonica* (16.0 kg) were extracted with MeOH (20 L × 5 times × 4 h) and then evaporated to dryness to obtain the MeOH extract. The MeOH extract (4.0 kg) was suspended in distilled water (3 L) and then partitioned successively with *n*-hexane, CH_2Cl_2, EtOAc, and *n*-butanol to collect *n*-hexane (715.1 g), CH_2Cl_2 (408.5 g), EtOAc (110.1 g), and *n*-butanol (490.2 g) fractions and a water residue, respectively.

The EtOAc fraction (110.1 g) was chromatographed over a silica gel column (CH_2Cl_2:MeOH, stepwise, 25:1→0:1) to collect 4 fractions (E1–E4). E2 (15.5 g) was then separated by a silica gel CC (CH_2Cl_2:MeOH, 20:1) to yield 7 sub-fractions E2.1–E2.7. Fraction E2.4 (3.1 g) was fractionated by a normal phase CC (CH_2Cl_2:MeOH, 25:1) to furnish compound **1** (6.0 mg) and sub-fractions E2.4.1–E3.4.5. E2.4.3 (234.2 mg) was purified by RPC-18 CC (MeOH:H_2O, 1:3) and then Sephadex LH-20 CC (MeOH:H_2O, 1:1) to afford **2** (5.1 mg) and **3** (9.8 mg). By the same method, compounds **4** (9.9 mg), **5** (30.1 mg), and **6** (49.5 mg) were collected from E2.4.4 (345.5 mg), and compounds **7** (6.0 mg) and **8** (50.1 mg) were obtained from E2.4.5 (158.7 mg). Fractionation of E2.6 passed over silica gel CC (CH_2Cl_2:MeOH, 22:1) to yield sub-fractions E2.6.1–E2.6.5. Sub-fraction E2.6.4 (359.7 mg) was subjected to chromatography on a RPC-18 column (MeOH:H_2O, 1:4) and subsequently purified by Sephadex LH-20 CC (MeOH:H_2O, 1:1) to obtain **9** (15.2 mg) and **10** (80.6 mg). Sub-fraction E2.6.5 (390.1 mg) was separated by RPC-18 CC using MeOH: H_2O (1:4) and further purified by a preparative Waters HPLC system (40% MeOH in 5 mL/min, 40 min) to yield **11** (3.0 mg, t_R = 28.4 min). Compound **12** (5.1 mg) was afforded from E2.7 (124.6 mg) under the same conditions. E3 (4.5 g) was divided into 8 sub-fractions E3.1–E3.8 by using a silica gel CC (CH_2Cl_2: MeOH, 12:1). Fraction E3.3 (556.7 mg) was continuously separated by a silica gel CC (CH_2Cl_2: MeOH, 10:1) to give 5 sub-fractions E3.3.1–E3.3.5. Sub-fraction E3.3.5 (159.7 mg) was chromatographed over a RPC-18 CC (MeOH:H_2O, 1:3) and then purified by Sephadex LH-20 CC (MeOH:H_2O, 1:2) to furnish **13** (14.5 mg). Fraction E3.7 (631.4 mg) was divided into 3 sub-fractions E3.7.1–E3.7.3 by a silica gel CC (CH_2Cl_2: MeOH, 9:1). Application the same method in case of sub-fraction E2.6.4 for sub-fraction E3.7.2 (324.2 mg), compounds **14** (80.0 mg) and **15** (9.7 mg) were isolated. Similarly, compound **16** (5.0 mg), and a mixture **17/18** (30.1 mg) were afforded from E3.8.3 (250.4 mg).

Quercetin (1) – Amorphous yellow powder; $C_{15}H_{10}O_7$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.71 (1H, s, H-2′), 7.61 (1H, d, J = 8.4 Hz, H-6′), 6.86 (1H, d, J = 8.4 Hz, H-5′), 6.36 (1H, s, H-6), 6.16 (1H, s, H-8); ^{13}C NMR (100 MHz, CD_3OD): δ_C 175.9 (C-4), 164.2 (C-7), 161.0 (C-5), 156.8 (C-9), 147.3 (C-4′), 146.5 (C-3′), 144.8 (C-2), 135.8 (C-3), 122.7 (C-1′), 120.2 (C-6′), 114.8 (C-5′), 114.6 (C-2′), 103.0 (C-10), 97.8 (C-6), 92.9 (C-8).[17]

Methyl gallate (2) – Amorphous white powder; $C_8H_8O_5$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.02 (2H, s, H-2, 6), 3.79 (3H, s, 7-OCH_3); ^{13}C NMR (100 MHz, CD_3OD): δ_C 167.6 (C-7), 145.0 (C-3, 5), 138.3 (C-4), 119.9 (C-1), 108.6 (C-2, 6), 50.8 (7-OCH_3).[18]

Caesalpiniaphenol C (3) – Yellow needles; $C_{14}H_{10}O_5$;

^{1}H NMR (400 MHz, CD_3OD): δ_H 7.06 (1H, d, J = 8.2 Hz, H-1), 6.68 (2H, s, H-8, 11), 6.66 (1H, dd, J = 8.4, 1.8 Hz, H-2), 6.62 (1H, d, J = 1.8, H-4), 4.42 (2H, s, H-6); ^{13}C NMR (100 MHz, CD_3OD): δ_C 207.7 (C-7), 159.6 (C-3), 159.0 (C-4a), 145.6 (C-9), 145.3 (C-10), 131.8 (C-11a), 130.9 (C-1), 127.1 (C-11b), 124.8 (C-7a), 117.4 (C-8, C-11), 113.3 (C-2), 108.8 (C-4), 78.8 (C-6).[19]

(8*S*,8′*S*,7′*R*)-(–)-lyoniresinol (4) – Amorphous white powder; $C_{22}H_{28}O_8$; α_D^{20} –40 (c = 0.025, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ_H 6.56 (1H, s, H-2), 6.36 (2H, s, H-2′, 6′), 4.29 (1H, d, J = 5.7 Hz, H-7′), 3.83 (3H, s, 3-OCH_3), 3.71 (6H, s, 3′, 5′-OCH_3), 3.64 (1H, d, J = 5.5 Hz, Hb-9′), 3.57 (1H, dd, J = 10.8, 5.0 Hz, Hb-9), 3.48 (2H, m, Ha-9′, Ha-9), 3.35 (3H, s, 5-OCH_3), 2.68 (1H, dd, J = 15.0, 4.8 Hz, Hb-7), 2.55 (1H, dd, J = 15.0, 11.8 Hz, Ha-7), 1.95 (1H, dd, J = 8.1, 5.5 Hz, H-8′), 1.61 (1H, m, H-8); ^{13}C NMR (100 MHz, CD_3OD): δ_C 147.5 (C-3′, 5′), 147.2 (C-3), 146.2 (C-5), 137.8 (C-1′), 137.4 (C-4), 133.0 (C-4′), 128.7 (C-1), 124.8 (C-6), 106.3 (C-2), 105.4 (C-2′, 6′), 65.3 (C-9), 62.7 (C-9′), 58.7 (5-OCH_3), 55.3 (3-OCH_3), 55.2 (3′, 5′-OCH_3), 47.6 (C-8′), 40.9 (C-7′), 39.4 (C-8), 32.1 (C-7).[20]

7,3′,5′-Trihydroxyflavanone (**5**) – Amorphous white powder; $C_{15}H_{14}O_5$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.69 (1H, dd, J = 8.8, 0.8 Hz, H-5), 6.91 (1H, s, H-4′), 6.77 (2H, s, H-2′, 6′), 6.47 (1H, d, J = 8.8 Hz, H-6), 6.33 (1H, d, J = 1.2 Hz, H-8), 5.28 (1H, d, J = 12.8 Hz, H-2), 2.98 (1H, dd, J = 16.8, 12.8 Hz, Ha-3), 2.66 (1H, dd, J = 16.8, 2.4 Hz, Ha-3); ^{13}C NMR (100 MHz, CD_3OD): δ_C 192.2 (C-4), 165.2 (C-7), 164.1 (C-9), 145.3 (C-5′), 145.0 (C-3′), 130.1 (C-1′), 128.4 (C-5), 117.8 (C-2′), 114.8 (C-6′), 113.5 (C-10), 113.3 (C-4′), 110.3 (C-6), 102.4 (C-8), 79.6 (C-2), 43.5 (C-3).[21]

Sappanchalcone (6) – Amorphous yellow powder; $C_{16}H_{14}O_5$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.55 (1H, d, J = 8.5 Hz, H-6′), 7.47 (1H, d, J = 15.6 Hz, H-7), 7.34 (1H, d, J = 15.6 Hz, H-8), 7.09 (1H, s, H-2), 6.96 (1H, d, J = 8.2 Hz, H-6), 6.77 (1H, d. J = 8.2 Hz, H-5), 6.48 (1H, d, J = 1.6 Hz, H-3′), 6.43 (1H, d, J = 8.5, 1.6 Hz, H-5′), 3.86 (3H, s, 2′-OCH_3); ^{13}C NMR (100 MHz, CD_3OD): 191.7 (C-9), 163.1 (C-4′), 161.1 (C-2′), 148.1 (C-4), 145.4 (C-3), 143.1 (C-7), 132.3 (C-6′), 127.2 (C-1), 123.7 (C-8), 121.9 (C-6), 120.3 (C-1′), 115.1 (C-5), 113.8 (C-2), 107.5 (C-5′), 98.7 (C-3′), 54.7 (2′-OCH_3).[22]

Sappanone A (7) – Amorphous yellow powder; $C_{16}H_{12}O_5$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.77 (1H, d, J = 8.7 Hz, H-5), 7.62 (1H, s, H-9), 6.84 (1H, d, J = 8.1 Hz, H-5′), 6.80 (1H, s, H-2′), 6.74 (1H, d, J = 8.1 Hz, H-6′), 6.50 (1H, d, J = 8.7 Hz, H-6), 6.28 (1H, s, H-8), 5.33 (2H, s, H-2); ^{13}C NMR (100 MHz, CD_3OD): 181.6 (C-4), 165.1 (C-7), 163.4 (C-8a), 147.3 (C-3′), 145.1 (C-4′), 137.0 (C-9), 129.2 (C-5), 128.0 (C-1′), 126.2 (C-3), 123.1 (C-6′), 116.9 (C-5′), 115.1 (C-2′), 114.5 (C-4a), 110.7 (C-6), 102.2 (C-8), 67.7 (C-2).[23]

Taxifolin (8) – Amorphous colorless powder; $C_{15}H_{12}O_7$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 6.95 (1H, d, J = 1.5 Hz, H-2), 6.83 (1H, dd, J = 8.1, 1.5 Hz, H-6), 6.78 (1H, d, J = 8.1 Hz, H-5′), 5.90 (1H, d, J = 1.5 Hz, H-8), 5.86 (1H, d, J = 1.5 Hz, H-6), 4.87 (1H, d, J = 11.5 Hz, H-2), 4.48 (1H, d, J = 11.5 Hz, H-3); ^{13}C NMR (100 MHz, CD_3OD): δ_C 196.9 (C-4), 167.3 (C-7), 163.8 (C-5), 163.0 (C-9), 145.7 (C-4′), 144.8 (C-3′), 128.4 (C-1′), 119.6 (C-6′), 114.7 (C-5′), 114.5 (C-2′), 100.4 (C-10), 95.9 (C-6), 94.9 (C-8), 83.6 (C-2), 72.2 (C-3).[24]

Fisetin (9) – Amorphous white powder; $C_{15}H_{10}O_7$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.96 (1H, dd, J = 9.4, 0.5 Hz, H-5), 7.75 (1H, d, J = 2.1 Hz, H-2′), 7.65 (1H, ddd, J = 8.5, 2.1, 0.5 Hz, H-6′), 6.88 (3H, m, H-6, H-8, H-5′); ^{13}C NMR (100 MHz, CD_3OD): δ_C 172.9 (C-4), 162.9 (C-7), 157.1 (C-9), 147.2 (C-4′), 146.0 (C-3′), 144.8 (C-2), 137.1 (C-3), 126.0 (C-5), 122.9 (C-1′), 120.2 (C-6′), 114.8 (C-5′), 114.5 (C-6), 114.5 (C-2′), 113.9 (C-10), 101.5 (C-8).[25]

Fustin (10) – White needles; $C_{15}H_{12}O_6$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.69 (1H, d, J = 8.7 Hz, H-5), 6.97 (1H, d, J = 1.9 Hz, H-2′), 6.84 (1H, dd, J = 8.1, 1.9 Hz, H-6′), 6.79 (1H, d, J = 8.1, H-5′), 6.50 (1H, dd, J = 8.7, 2.2 Hz, H-6), 6.31 (1H, d, J = 2.2 Hz, H-8), 4.92 (1H, d, J = 11.8 Hz, H-2), 4.46 (1H, d, J = 11.8 Hz, H-3); ^{13}C NMR (100 MHz, CD_3OD): δ_C 193.1 (C-4), 165.4 (C-7), 163.6 (C-9), 145.6 (C-3′), 144.8 (C-4′), 128.7 (C-10), 128.6 (C-5), 119.5 (C-6′), 114.7 (C-2′), 114.5 (C-5′), 111.9 (C-10), 110.7 (C-6), 102.3 (C-8), 84.2 (C-2), 73.1 (C-3).[26]

(+)-Catechin (11) – Colorless solid; $C_{15}H_{14}O_6$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 6.83 (1H, d, J = 1.9 Hz, H-2′), 6.75 (1H, d, J = 8.1 Hz, H-5′), 6.70 (1H, dd, J = 8.1, 1.9 Hz, H-6′), 5.93 (1H, d, J = 1.8, H-6), 5.86 (1H, d, J = 1.8 Hz, H-8), 4.56 (1H, d, J = 7.5 Hz, H-2), 3.97 (1H, dd, J = 7.5, 5.5 Hz, H-3), 2.83 (1H, dd, J = 16.1, 5.5 Hz, Ha-4), 2.50 (1H, dd, J = 16.1, 8.1 Hz, Hb-4); ^{13}C NMR (100 MHz, CD_3OD): δ_C 156.3 (C-7), 156.1 (C-5), 155.4 (C-9), 144.8 (C-4′), 144.8 (C-3′), 130.8 (C-1′), 118.7 (C-6′), 114.8 (C-5′), 114.8 (C-2′), 99.5 (C-10), 94.9 (C-6), 94.2 (C-8), 81.4 (C-2), 67.4 (C-3), 27.0 (C-4).[27]

Brazilin (12) – Amorphous red powder; $C_{16}H_{14}O_5$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 7.17 (1H, d, J = 8.3 Hz, H-5), 6.69 (1H, s, H-2′), 6.58 (1H, s, H-5′), 6.45 (1H, dd, J = 8.3, 2.4 Hz H-6), 6.28 (1H, d, J = 2.4 Hz, H-8), 3.95 (1H, s, H-4), 3.91 (1H, d, J = 11.4 Hz, Ha-2), 3.67 (1H, d, J = 11.4 Hz, Hb-2), 3.00 (1H, d, J = 15.6 Hz, Ha-9), 2.75 (1H, d, J = 15.6 Hz, Hb-9); ^{13}C NMR (100 MHz, CD_3OD):

δ_C 157.8 (C-7), 155.7 (C-8a), 145.6 (C-3′), 145.3 (C-4′), 137.4 (C-6′), 132.2 (C-5), 131.3 (C-1′), 115.5 (C-4a), 112.8 (C-2′), 112.4 (C-5′), 109.9 (C-6), 104.3 (C-8), 78.1 (C-3), 70.8 (C-2), 51.0 (C-4), 42.9 (C-9).[28]

3,4,5-Trimethoxyphenyl *β*-D-glucopyranoside (13) – Amorphous white powder; $C_{15}H_{22}O_9$; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.35 (2H, s, H-2, H-6), 4.74 (1H, d, *J* = 7.4 Hz, H-1′), 3.70 (6H, s, 3,5-OCH_3), 3.55 (3H, s, 4-OCH_3), 3.04–3.41 (m, H-2′–6′); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 154.4 (C-1), 153.5 (C-3, 5), 132.8 (C-4), 101.4 (C-1′), 94.7 (C-2, 6), 77.7 (C-5′), 77.2 (C-3′), 73.7 (C-2′), 70.5 (C-4′), 61.3 (C-6′), 60.5 (4-OCH_3), 56.1 (3, 5-OCH_3).[29]

1-(2-Methylbutyryl)phloroglucinol-glucopyranoside (14) – Amorphous white powder; $C_{17}H_{24}O_9$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 6.16 (1H, d, *J* = 2.0 Hz, H-6), 5.94 (1H, d, *J* = 2.0 Hz, H-4), 5.02 (1H, d, *J* = 7.5 Hz, H-1″), 3.88 (2H, m, H-2′, Ha-6″), 3.70 (1H, dd, *J* = 12.1, 5.4 Hz, Hb-6″), 3.35-3.50 (4H, m, H-2″–5″), 1.79 (1H, dt, *J* = 14.2, 7.4 Hz, Hb-3′), 1.37 (1H, dt, *J* = 14.2, 7.4 Hz, Ha-3′), 1.11 (3H, d, *J* = 6.7 Hz, H-5′), 0.87 (3H, t, *J* = 7.4 Hz, H-4′); ^{13}C NMR (100 MHz, CD_3OD): δ_C 211.7 (C-1′), 167.4 (C-3), 165.8 (C-5), 161.7 (C-1), 106.7 (C-2), 101.6 (C-1″), 98.3 (C-4), 95.4 (C-6), 78.7 (C-5″), 78.4 (C-3″), 74.8 (C-2″), 71.2 (C-4″), 62.5 (C-6″), 46.9 (C-2′), 28.2 (C-3′), 16.8 (C-5′), 12.0 (C-4′).[30]

(+)-*Epi*-catechin (15) – Colorless solid; $C_{15}H_{14}O_6$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 6.95 (1H, d, *J* = 1.9 Hz, H-2′), 6.75 (1H, dd, *J* = 8.1, 1.9 Hz, H-6′), 6.74 (1H, d, *J* = 8.1 Hz, H-5′), 5.92 (1H, d, *J* = 1.9, H-6), 5.90 (1H, d, *J* = 1.9 Hz, H-8), 4.79 (1H, s, H-2), 4.15 (1H, br s, H-3), 2.84 (1H, dd, *J* = 16.7, 4.5 Hz, Ha-4), 2.71 (1H, dd, *J* = 16.7, 2.8 Hz, Hb-4); ^{13}C NMR (100 MHz, CD_3OD): δ_C 156.5 (C-7), 156.2 (C-5), 155.9 (C-9), 144.5 (C-4′), 144.3 (C-3′), 130.8 (C-1′), 117.9 (C-6′), 114.5 (C-5′), 113.9 (C-2′), 99.6 (C-10), 94.9 (C-6), 94.5 (C-8), 78.4 (C-2), 66.0 (C-3), 27.8 (C-4).[27]

Astragalin (16) – Amorphous yellow powder; $C_{21}H_{20}O_{11}$; ^{1}H NMR (400 MHz, CD_3OD): δ_H 8.07 (2H, d, *J* = 8.9 Hz, H-2′, 6′), 6.87 (2H, d, *J* = 8.9 Hz, H-3′, 5′), 6.39 (1H, d, *J* = 2.1 Hz, H-6), 6.19 (1H, d, *J* = 2.1 Hz, H-8), 5.13 (1H, d, *J* = 7.8 Hz, H-1″), 3.42–3.80 (6H, H-2″–6″). ^{13}C NMR (100 MHz, CD_3OD): δ_C 179.7 (C-4), 166.1 (C-7), 163.1 (C-5), 161.6 (C-4′), 159.1 (C-2), 158.5 (C-9), 135.6 (C-3), 132.4 (C-2′, 6′), 122.7 (C-1′), 116.1 (C-3′, 5′), 105.7 (C-10), 104.9 (C-1″), 99.9 (C-6), 94.8 (C-8), 77.1 (C-3″), 75.0 (C-5″), 73.0 (C-2″), 70.0 (C-4″), 61.9 (C-6″).[31]

Mixture of two conformers of protosappanin B (17/18) – Colorless solid; $C_{16}H_{16}O_6$.

Major form of protosappanin B (17): ^{1}H NMR (400 MHz, CD_3OD): δ_H 6.96 (d, *J* = 8.0 Hz, H-1), 6.72 (ovl, H-9, 12), 6.53 (ovl, H-2), 6.44 (s, H-4), 4.14 (d, *J* = 12.4 Hz, Ha-6), 3.85 (d, *J* = 12.4 Hz, Hb-6), 3.53 (ovl, Ha-7a), 3.45 (d, *J* = 11.2 Hz, Hb-7a), 2.54 (d, *J* = 13.6 Hz, Ha-8), 2.48 (d, *J* = 13.6 Hz, Hb-8). ^{13}C NMR (100 MHz, CD_3OD): δ_C 159.3 (C-4a), 158.9 (C-3), 144.9 (C-10, 11), 133.2 (C-1), 132.5 (C-12a), 127.5 (C-8a), 124.1 (C-12b), 119.9 (C-9), 117.5 (C-12), 111.5 (C-2), 108.2 (C-4), 76.7 (C-6), 73.0 (C-7), 68.4 (C-7a), 39.9 (C-8).[32]

Minor form of protosappanin B (18): ^{1}H NMR (400 MHz, CD_3OD): δ_H 6.96 (d, *J* = 8.0 Hz, H-1), 6.72 (ovl, H-9), 6.66 (s, H-12), 6.53 (ovl, H-2), 6.50 (s, H-4), 4.37 (d, *J* = 12.0 Hz, Ha-6), 3.53 (ovl, Hb-6, Ha-7a), 3.39 (d, *J* = 11.2 Hz, Hb-7a), 2.67 (s, H-8). ^{13}C NMR (100 MHz, CD_3OD): δ_C 160.4 (C-4a), 159.0 (C-3), 144.8 (C-10), 144.8 (C-11), 132.7 (C-1), 132.0 (C-12a), 128.1 (C-8a), 125.2 (C-12b), 119.0 (C-9), 117.9 (C-12), 112.1 (C-2), 108.8 (C-4), 76.7 (C-6), 73.3 (C-7), 65.7 (C-7a), 42.7 (C-8).[32]

α-Glucosidase inhibition assay – α-Glucosidase inhibitory assay was conducted spectrophotometrically using *p*-nitrophenyl α-D-glucopyranoside (*p*-NPG) as the substrate, according to the previously published procedure with a slight modification.[33] In brief, 20 µL enzyme α-glucosidase (0.1 unit) was added to 96 well plates, which contained 20 µL samples and 20 µL phosphate buffer (100 mM, pH = 6.8). Subsequently, the enzyme reaction was started by the addition of 20 µL *p*-NPG (2.5 mM) and then incubated for 10 min at 37°C. After 10 min, 80 µL Na_2CO_3 0.2 M was used for each well to finalize the enzyme reaction. The absorbance was measured at 405 nm using a microplate spectrophotometer. Acarbose was used as a positive control. The percentage inhibition (%) is calculated using the following equation:

$$\text{Inhibition (\%)} = (A_c - A_s) / A_c \times 100$$

In which A_c and A_s are the average value of control and sample, respectively.

Enzyme kinetics of α-glucosidase inhibition – To determine the mode of α-glucosidase inhibition of the most active compounds (**1**, **6**, **7**, and **9**), two kinetic methods including Lineweaver-Burk plots and Dixon plots were used.[33] The α-glucosidase inhibition was monitored at various concentrations of substrate *p*-NPG (0.625, 1.25, and 2.5 mM) and different concentrations of tested compounds (1.71, 4.44, and 8.41 µM for **1**; 3.0, 7.0, and 25.0 µM for **6**; 8.0, 16.0, and 26.0 µM for **7**; 5.0, 10.0, and 25.0 µM for **9**). The enzyme reaction was carried out as described above. The obtained results were analyzed by using SigmaPlot 12.0 software (SPCC Inc, Chicago IL, U.S.A). Kinetic constant values (K_i) were calculated due to the Dixon plots.

Statistical analysis – All experimental bioassay data were performed as the mean ± standard error (SE) of the mean from at least three independent experiments. One-way analysis of variance (ANOVA) and Dunnett's test were applied to evaluate statistical significance. *P* values of less than 0.05 were considered to be statistically significant.

Result and Discussion

Phytochemical investigation of *C. decapetala* var. *japonica* stems resulted in the isolation of 16 known compounds (**1**–**16**) (Fig. 1), which were identified as quercetin (**1**),[17] methyl gallate (**2**),[18] caesalpiniaphenol C (**3**),[19] 8*S*,8′*S*,7′*R*-(–)-lyoniresinol (**4**),[20] 7,3′,5′-trihydroxy-flavanone (**5**),[21] sappanchalcone (**6**),[22] sappanone A (**7**),[34] taxifolin (**8**),[24] fisetin (**9**),[25] fustin (**10**),[26] (+)-catechin (**11**),[27] brazilin (**12**),[28] 3,4,5-trimethoxyphenyl *β*-D-glucopyranoside (**13**),[29] 1-(2-methylbutyryl)phloroglucinol-glucopyranoside (**14**),[30] (+)-*epi*-catechin (**15**),[27] and astragalin (**16**)[31], and a mixture of two conformers of protosappanin B (**17**/**18**),[32] by analyzing and comparing their spectroscopic data with those reported in the literature. Among them, caesalpiniaphenol C (**3**), 8*S*,8′*S*,7′*R*- (–)-lyoniresinol (**4**), taxifolin (**8**), fisetin (**9**), and fustin (**10**) were isolated from *C. decapetala* for the first time. In addition, this represents the first isolation of 3,4,5-trimethoxyphenyl *β*-D-glucopyranoside (**13**) and 1-(2-methylbutyryl) phloroglucinol-glucopyranoside (**14**) from the *Caesalpinia* genus.

Compound **3** was obtained as a yellow needle. The ^{1}H and ^{13}C NMR spectra of **3** showed one aromatic ABX system at [δ_H/δ_C 7.06 (1H, d, $J = 8.4$ Hz, H-1)/130.9 (C-1), 6.66 (1H, dd, $J = 8.4$, 1.8 Hz, H-2)/113.3 (C-2), and 6.62 (1H, d, $J = 1.8$ Hz, H-4)/108.8 (C-4)], one 1,2,4,5-tetrasubstituted benzene ring assigned at δ_H/δ_C 6.68 (2H, s, H-8, 11)/117.4 (C-8, 11). It also displayed one methylene group at δ_H/δ_C 4.42 (2H, s, H_2-6)/78.8 (C-6). Besides, the ^{13}C NMR spectrum of **3** exhibited one carbonyl carbon signal at δ_C 207.7 (C-7). The NMR data of **3** closely

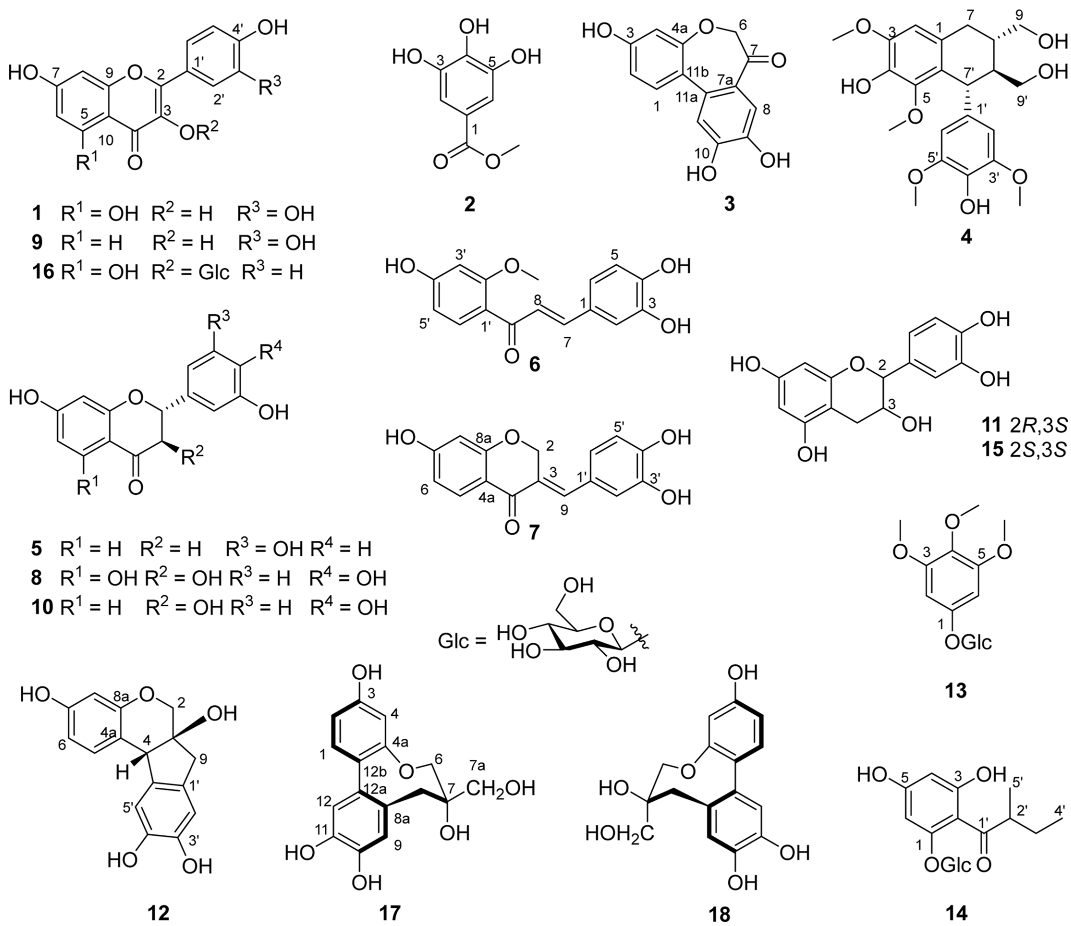
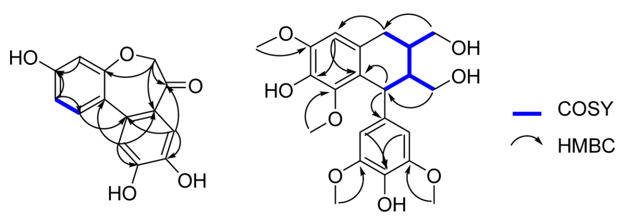


Fig. 1. Chemical structures of the isolated compounds (**1-18**).



3 4

Fig. 2. Key HMBC and ^{1}H-^{1}H COSY correlations of compounds **3** and **4**.

resembled those of caesalpiniaphenol C reported in the literature.[19] The complete structure of **3** was further determined by the key HMBC correlations of H-6/C-4a, H-6/C-7, H-6/C-7a, H-8/C-7, H-1/C-11a, H-11/C-11a, H-2/C-11b, and H-11/C-11b (Fig. 2). Therefore, **3** was determined to be caesalpiniaphenol C.[19]

Compound **4** was obtained as an amorphous, white powder with a negative optical rotation [α_D^{20} –40 (c = 0.025, MeOH)]. The ^{1}H and ^{13}C NMR spectra of **4** displayed typical signals for a 4-aryltetralin type lignan, which revealed one 1,2,3,4,5-pentasubstituted benzene ring at [δ_H/δ_C 6.56 (1H, s, H-2)/106.3 (C-2)], one 1,3,4,5-tetrasubstituted ring at [δ_H/δ_C 6.36 (2H, s, H-2′, 6′)/105.4 (C-2′, 6′)], four aromatic methoxy groups at [δ_H/δ_C 3.83 (3H, s, 3-OCH_3)/55.3 (3-OCH_3), 3.35 (3H, s, 5-OCH_3)/58.7 (5-OCH_3), 3.71 (6H, s, 3′, 5′-OCH_3)/55.2 (3′, 5′-OCH_3)], two oxygenated methylene groups at [δ_H/δ_C 3.48 (2H, m, Ha-9, Ha-9′), 3.57 (1H, dd, J = 10.8, 5.0 Hz, Hb-9), 3.64 (1H, d, J = 5.5 Hz, Hb-9′)/65.3 (C-9), 62.7 (C-9′)], one methylene signal at [δ_H/δ_C 2.55 (1H, dd, J = 15.0, 11.8 Hz, Ha-7), 2.68 (1H, dd, J = 15.0, 4.8 Hz, Hb-7)/32.1 (C-7)], and three methine groups at [δ_H/δ_C 4.29 (1H, d, J = 5.7 Hz, H-7′)/40.9 (C-7′), 1.95 (1H, dd, J = 8.1, 5.5 Hz, H-8′)/47.6 (C-8′), 1.61 (1H, m, H-8)/39.4 (C-8)]. Based on the above 1D NMR data together with the analysis of the HMQC and HMBC data (Fig. 2), **4** was determined to be lyoniresinol.[20] Consequently, the absolute configuration of **4** was identified as 8*S*,8′*S*,7′*R*-(–)-lyoniresinol based on these observations and comparison with its reported literature.[20]

Compound **8** was obtained as an amorphous colorless powder. The ^{1}H and ^{13}C NMR spectra of **8** showed resonances characteristic of a flavanonol with signals of one ABX coupling system at [δ_H 6.95 (1H, d, J = 1.5 Hz, H-2′), 6.78 (1H, d, J = 8.1 Hz, H-5′), 6.83 (1H, dd, J = 8.1, 1.5 Hz, H-6′)], one 1,2,3,5-tetrasubstituted ring, which was supported by two *meta* coupling protons at [δ_H 5.86 (1H, d, J = 1.5 Hz, H-6), 5.90 (1H, d, J = 1.5 Hz, H-8)], two oxygenated methine protons at δ_H 4.87 (1H, d, J = 11.5 Hz, H-2), 4.48 (1H, d, J = 11.5 Hz, H-3), and one carbonyl carbon signal at δ_C 196.9 (C-4). The ^{13}C NMR spectrum of **8** revealed 15 carbon signals corresponding to the predicted structure. Thus, the chemical structure of **8** was established to be taxifolin.[24]

Compound **9** was obtained as an amorphous white powder. The ^{1}H NMR spectrum of **9** displayed signals of two ABX coupling systems at δ_H 7.96 (1H, dd, J = 9.4, 0.5 Hz, H-5), 6.88 (3H, m, H-6, H-8, H-5′), 7.75 (1H, d, J = 2.1 Hz, H-2′), 7.65 (1H, ddd, J = 8.5, 2.1, 0.5 Hz, H-6′). Its ^{13}C NMR spectrum exhibited 15 carbon signals, including 12 carbon signals for two substituted benzene rings at δ_C 126.0 (C-5), 114.5 (C-6), 162.9 (C-7), 101.5 (C-8), 157.1 (C-9), 113.9 (C-10), 122.9 (C-1′), 114.5 (C-2′), 146.0 (C-3′), 147.2 (C-4′), 114.8 (C-5′), 120.2 (C-6′), two oxygenated olefinic carbon signals at δ_C 144.8 (C-2), and 137.1 (C-3), and one carbonyl signal at δ_C 172.9 (C-4). Based on a comparison of the above 1D NMR data with those in the literature,[25] **9** was determined as a flavonol (fisetin).

Compound **10** was obtained as a white needle. The proton and carbon spectra of **10** were similar to those of **8** except for the signals belonging to ring A with one ABX coupling system at [δ_H/δ_C 7.69 (1H, d, J = 8.7 Hz, H-5)/128.6 (C-5), 6.50 (1H, dd, J = 8.7, 2.2 Hz, H-6)/110.7 (C-6), 6.31 (1H, d, J = 2.2 Hz, H-8)/102.3 (C-8)], in **10**. In the comparison with the previous report, **10** was identified to be fustin.[26]

Compound **13** was obtained as a white powder. The proton spectrum of **13** showed two singlet proton signals for two symmetric protons belonging to one 1,3,4,5-tetrasubstituted benzene ring at δ_H 6.35 (2H, s, H-2, H-6), and three aromatic methoxy groups at δ_H 3.70 (6H, s, 3, 5-OCH_3), and 3.55 (3H, s, 4-OCH_3). In addition, an anomeric proton signal with a large J coupling constant was observed at δ_H 4.74 (1H, d, J = 7.4 Hz, H-1′). The β-glucose moiety was further confirmed by the ^{13}C NMR spectrum with 6 typical carbon signals at δ_C 101.4 (C-1′), 73.7 (C-2′), 77.2 (C-3′), 70.5 (C-4′), 77.7 (C-5′), and 61.3 (C-6′). The position of glucose moiety was located at C-1 (δ_C 154.4) due to the HMBC correlation between anomeric proton H-1′ and C-1. Therefore, **13** was established as 3,4,5-trimethoxyphenyl β-D-glucopyranoside.[29]

Compound **14** was obtained as an amorphous white powder. The ^{1}H NMR spectrum of **14** showed the aliphatic signals for a 2-methylbutyryl moiety at [δ_H 1.37 (1H, dt, J = 14.2, 7.4 Hz, Ha-3′), 1.79 (1H, dt, J = 14.2, 7.4 Hz, Hb-3′), 0.87 (3H, t, J = 7.4 Hz, H-4′), 1.11 (3H, d, J = 6.7 Hz, H-5′)],[30] and an anomeric proton at δ_H 5.02 (1H, d, J = 7.5 Hz, H-1″). Besides, two *meta*-coupled doublets appeared at δ_H 5.94 (1H, d, J = 2.0 Hz, H-4), 6.16 (1H, d,

$J = 2.0$ Hz, H-6), indicating an asymmetrically substituted ring. The glucose moiety was attached to δ_C 161.7 (C-1), which was confirmed by the HMBC cross-peaks between H-1″ and C-1. Therefore, **14** was determined to be 1-(2-methylbutyryl)phloroglucinol-glucopyranoside.[30]

The isolated compounds were evaluated for their inhibitory effect against α-glucosidase enzyme with acarbose was used as a positive control (IC_{50} = 152.22 ± 1.86 μM). Our results showed that the isolated flavonols, quercetin (**1**), and fisetin (**9**) exhibited a potent inhibitory effect, presenting IC_{50} values of 5.80 ± 0.25 μM and 10.82 ± 0.19 μM, respectively, which were much lower than acarbose (Fig. 3). While astragalin (**16**), a flavonol glycoside suppressed slightly α-glucosidase enzyme action (IC_{50} > 50 μM) (Table 1). The chalcone **6** (sappanchalcone) and homoisoflavanone **7** (sappanone A) showed a significant α-glucosidase inhibitory activity with IC_{50} values of 15.01 ± 0.34 μM and 14.13 ± 0.27 μM, respectively. The isolated flavanone **5** (7,3′,5′-trihydroxyflavanone) and flavan-3-ol **15** (*epi*-catechin) exhibited an inhibitory effect of α-glucosidase with IC_{50} values of 22.56 ± 0.54 μM and 30.85 ± 0.40 μM, respectively. Besides, caesalpiniaphenol C (**3**), and the mixture (**17**/**18**) also suppressed α-glucosidase action with IC_{50} values of 34.82 ± 0.25 μM and 49.51 ± 0.06 μM, respectively. The remaining compounds (**2–4**, **8**, **10–14**) exhibited a weak effect on the inhibition of α-glucosidase (IC_{50} > 50 μM) (Table 1).

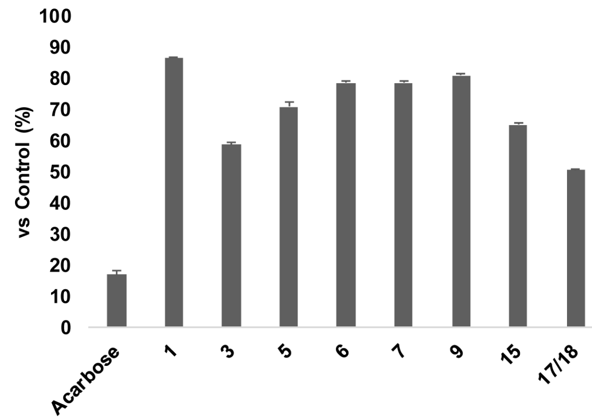


Fig. 3. Inhibitory effects (%) of the active compounds (**1**, **3**, **5**, **6**, **7**, **9**, **15**, and **17**/**18**) and acarbose on the enzymatic activities of α-glucosidase at a concentration of 50 μM. The data are expressed as mean ± SE. The experiments were done in triplicates.

For the potent inhibitors (**1**, **6**, **7**, and **9**), we continuously examined their inhibition kinetics *in vitro*. α-Glucosidase was treated individually with four concentrations of tested compounds, using *p*-NPG as a substrate (0.625 – 2.5 mM). The type of inhibition and inhibition constants (K_i values) of the above compounds was deduced from two kinetic methods: Lineweaver-Buck plots and Dixon plots (Fig. 4). After analysis of these two types of graphs and based on the best fit results and goodness to fit analysis, we concluded that two flavonols (**1** and **9)** (Fig.

Table 1. α-Glucosidase inhibitory activity of compounds (**1**–**18**) and their inhibition type

Compounds	IC_{50} (μM)	Inhibition type	K_i (μM)
1	5.80 ± 0.25	noncompetitive	5.8
2	>50		
3	34.82 ± 0.25		
4	>50		
5	22.56 ± 0.54		
6	15.01 ± 0.34	mixed	11.8
7	14.13 ± 0.27	mixed	8.0
8	>50		
9	10.82 ± 0.19	noncompetitive	10.8
10	>50		
11	>50		
12	>50		
13	>50		
14	>50		
15	30.85 ± 0.40		
16	>50		
17/18	49.51 ± 0.06		
Acarbose[a]	152.22 ± 1.86		

[a]Positive control. These data were expressed as the mean ± SE of triplicate experiments.

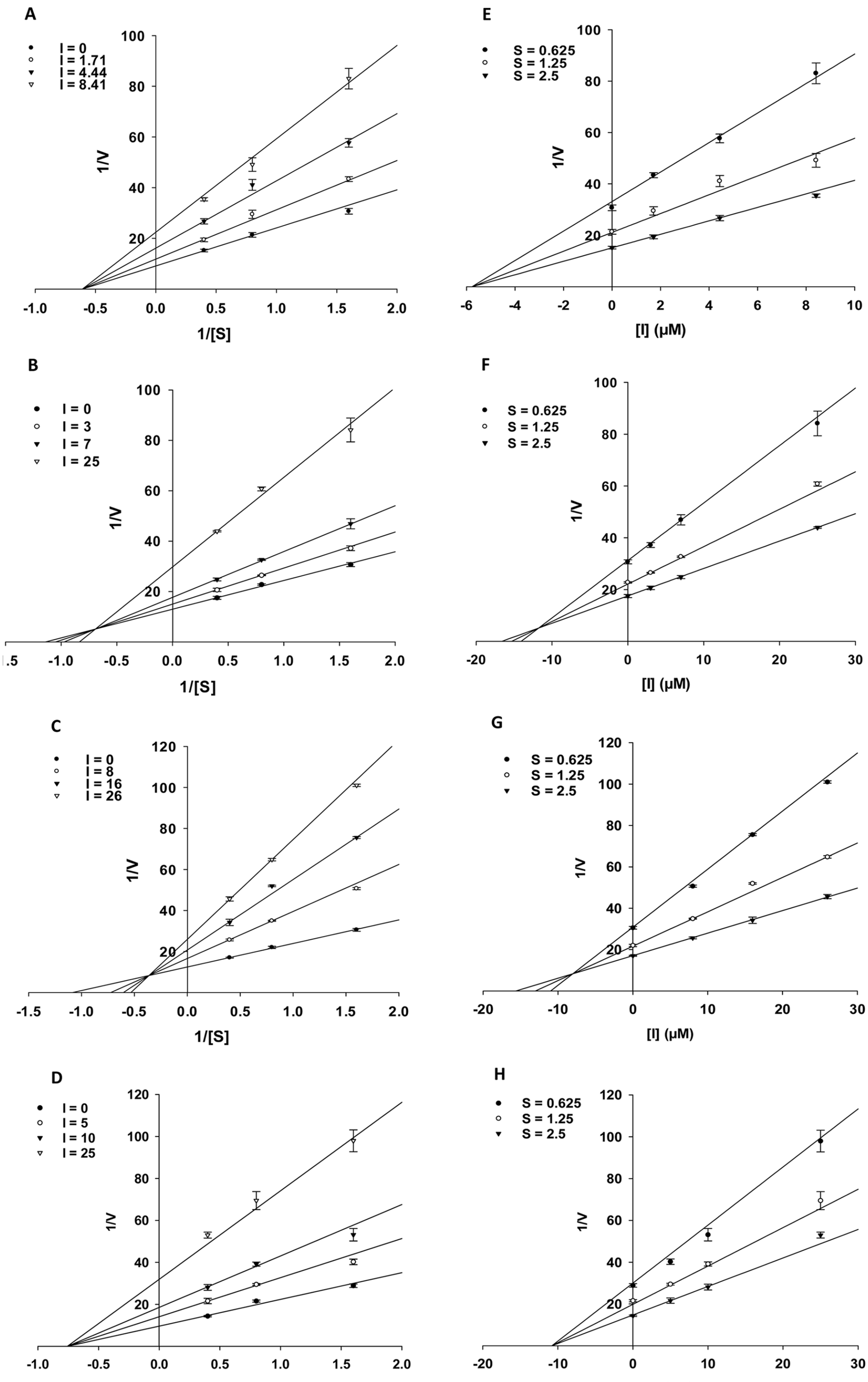


Fig. 4. The inhibition kinetics of compounds **1**, **6**, **7**, and **9** towards α-glucosidase. (A–D) Lineweaver-Burk plots for α-glucosidase inhibition of compounds **1** (A), **6** (B), **7** (C), and **9** (D). (E–H) Dixon plots for α-glucosidase inhibition of compounds **1** (E), **6** (F), **7** (G), and **9** (H).

4A and 4D) showed a non-competitive inhibition type with K_i values of 5.8 and 10.8 μM, respectively, while chalcone (**6**) and homoisoflavanone (**7**) (Fig. 4B and 4C) had shown a mixed inhibition type with K_i values of 11.8 and 8.0 μM, respectively. The K_i values were calculated using Dixon plot by plotting the reciprocal of maximum velocity ($1/V_{max}$) (*y*-axis) against the concentrations (*x*-axis) (Fig. 4E–H).

Interestingly, two flavonols (**1** and **9**), which contained one carbonyl carbon and one double bond at the C-ring inhibited strongly α-glucosidase enzyme action. The absence of both these characteristics at the C-ring in the case of flavan-3-ols (**11** and **15**), or the lack of a double bond at C-2 in the C ring in the case of flavanone (**5**) and flavanonols (**8** and **10**) induced a significant reduction in the level of inhibition. Meanwhile, the addition of one glucose moiety at C-3 in the structure of **16** also decreased dramatically its inhibitory activity. This evidence supported the key role of flavones in anti-diabetic drug research. Our findings for α-glucosidase inhibitory activity of compounds **1**, **5**, **6**, **9**, **15–18** were in accordance with those previously reported.[35,36] On the other hand, this is the first report on inhibiting α-glucosidase action for caesalpiniaphenol C (**3**) and sappanone A (**7**). Furthermore, the α-glucosidase enzyme kinetic inhibition types of sappanchalcone (**6**) and sappanone A (**7**) were also investigated for the first time.

In summary, sixteen known phenolic compounds and one known mixture were isolated from the *C. decapetala* var. *japonica* stems. Five compounds (**3**, **4**, **8**, **9**, and **10**) were reported from this plant for the first time, and two compounds (**13** and **14**) were found in this genus for the first time. Our research concluded that *C. decapetala* var. *japonica* and its flavonoids, especially flavonols, homoisoflavanone, and chalcones were considered to be alternative inhibitors for the regulation of hyperglycemia.

Acknowledgments

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α-Glucosidase Inhibitory Activity of Phenolic Compounds Isolated from the Stems of *Caesalpinia decapetala* var. *japonica*

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Supporting information

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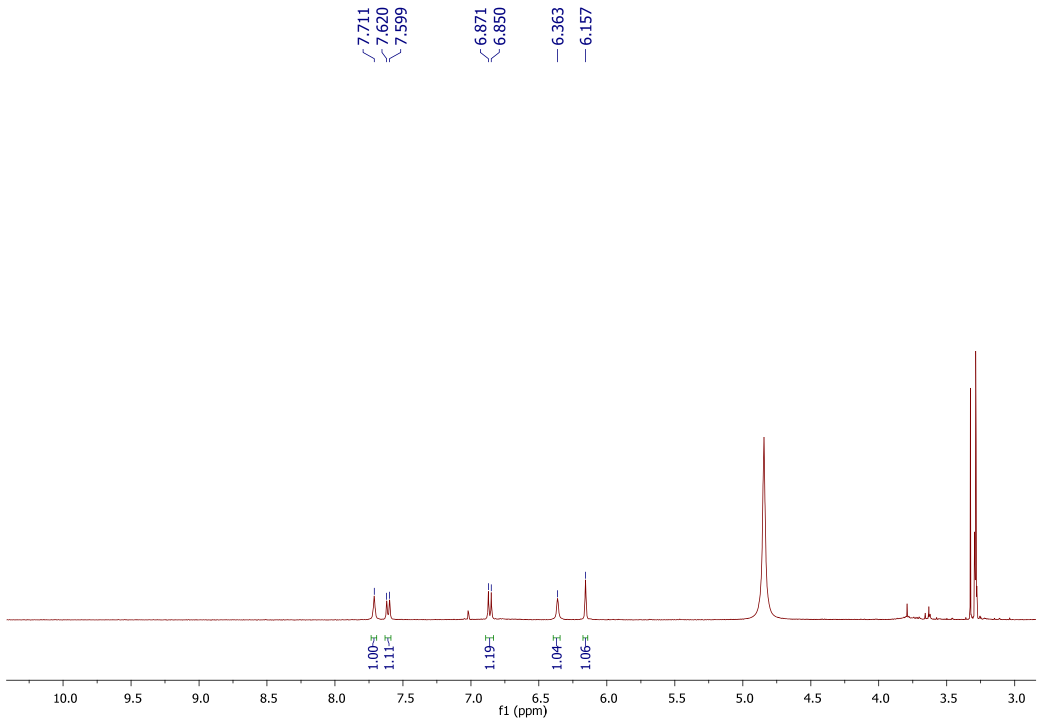
Fig. S39. [13]C NMR spectrum of compound **17/18** (CD_3OD, 100 MHz).

Fig. S1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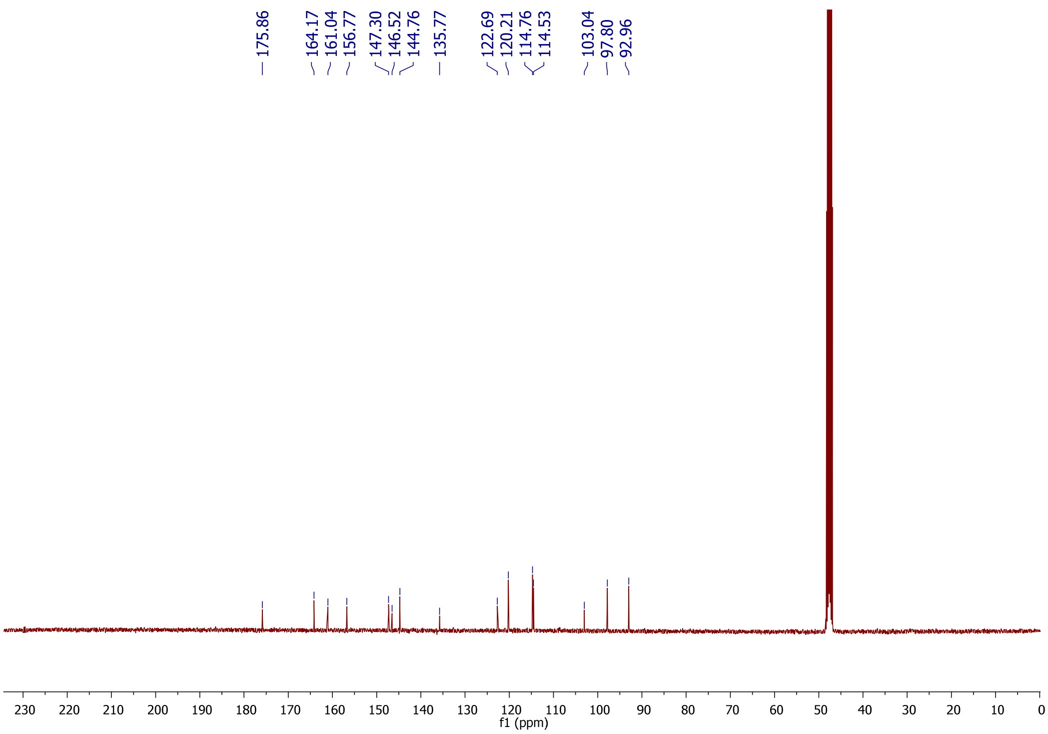
7.620
7.599
6.871
6.850
6.363
6.157
1.00
1.11
1.19
1.04
1.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0
f1 (ppm)

Fig. S2.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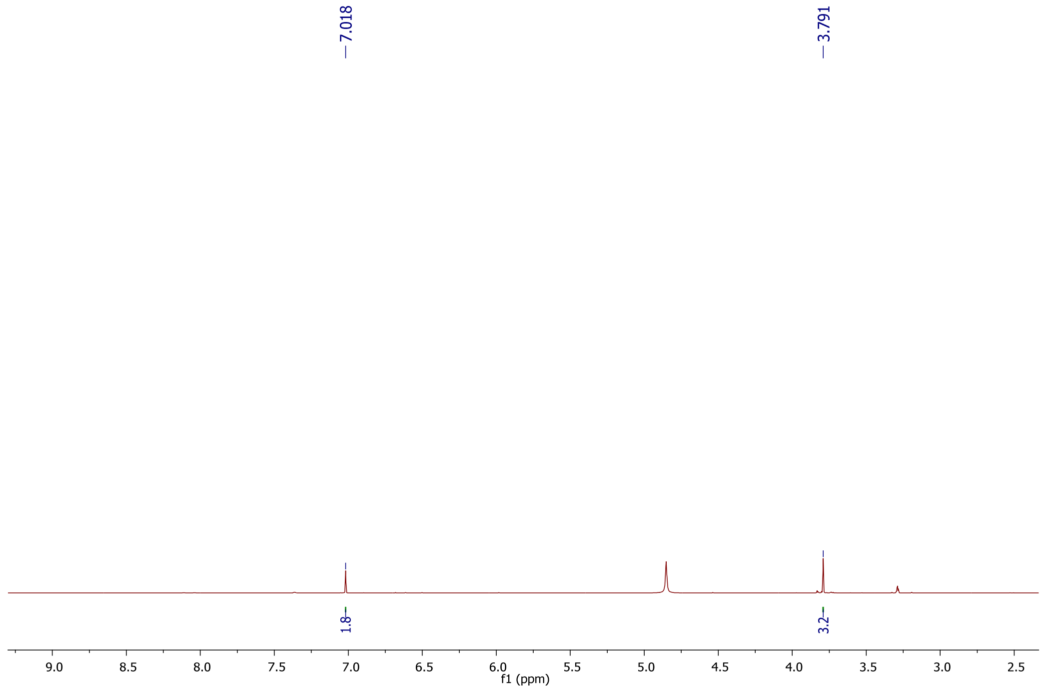
161.04
156.77
147.30
146.52
144.76
135.77
122.69
120.21
114.76
114.53
103.04
97.80
92.96
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Fig. S3.



a

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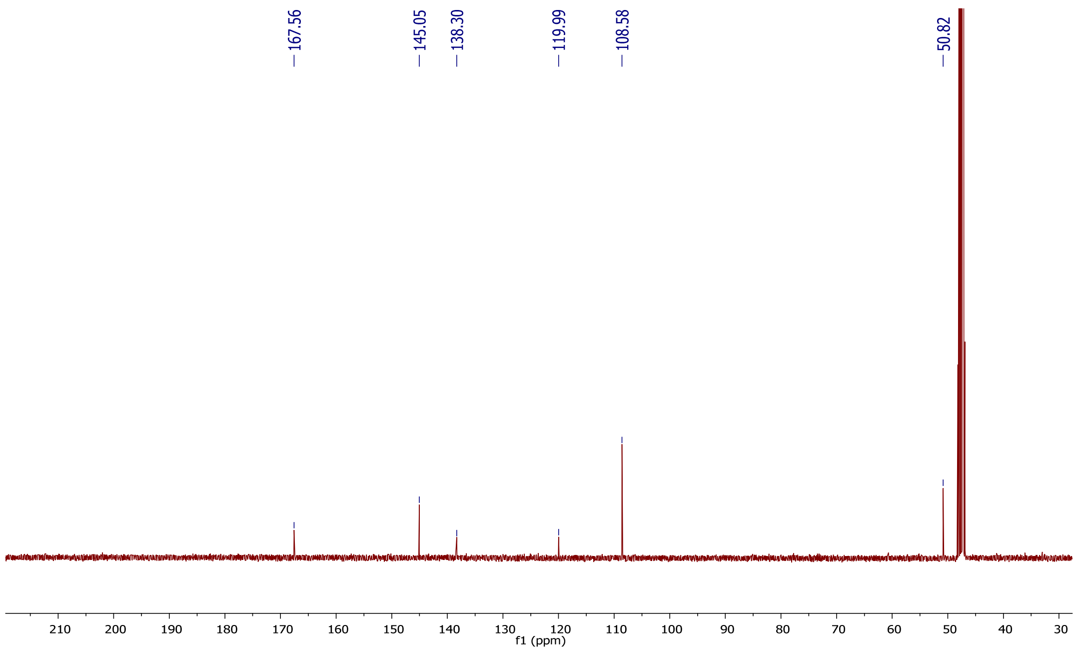

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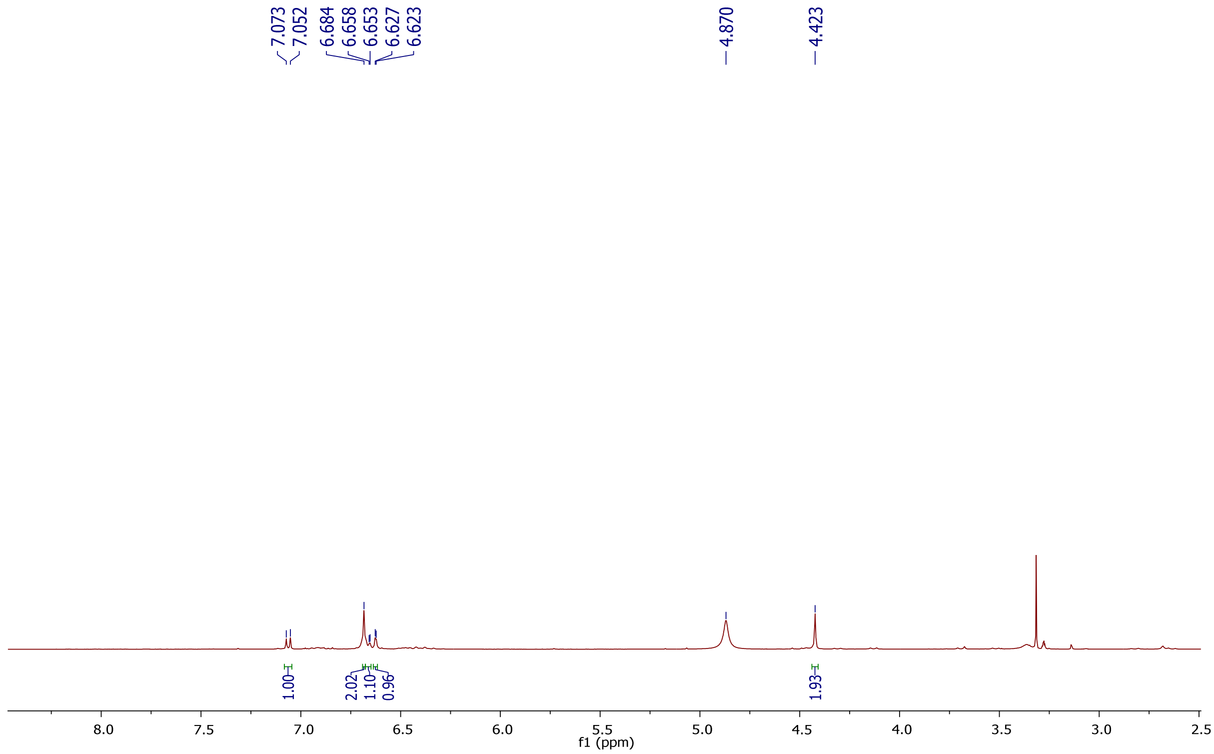
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6.658
6.653
6.627
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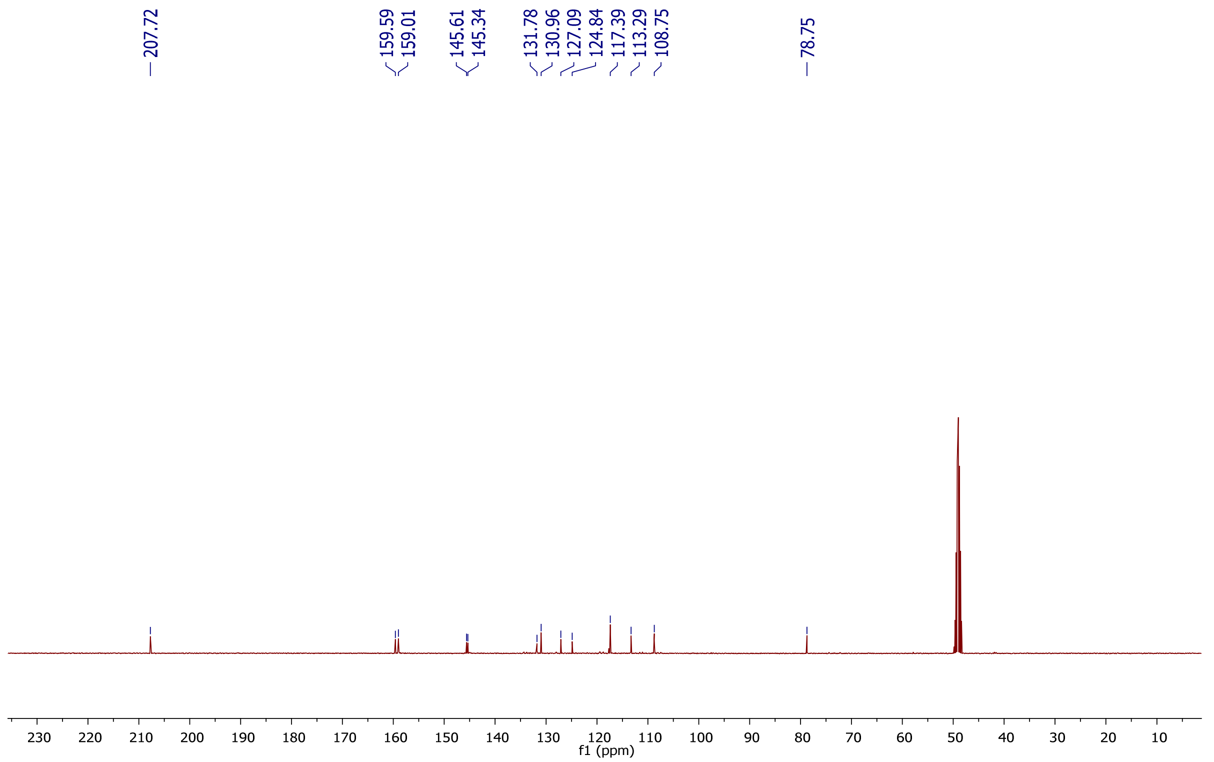
4.870
4.423
1.00
2.02
1.10
0.96
1.93
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)

Fig. S6.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130.96
127.09
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117.39
113.29
108.75
78.75
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Fig. S7.

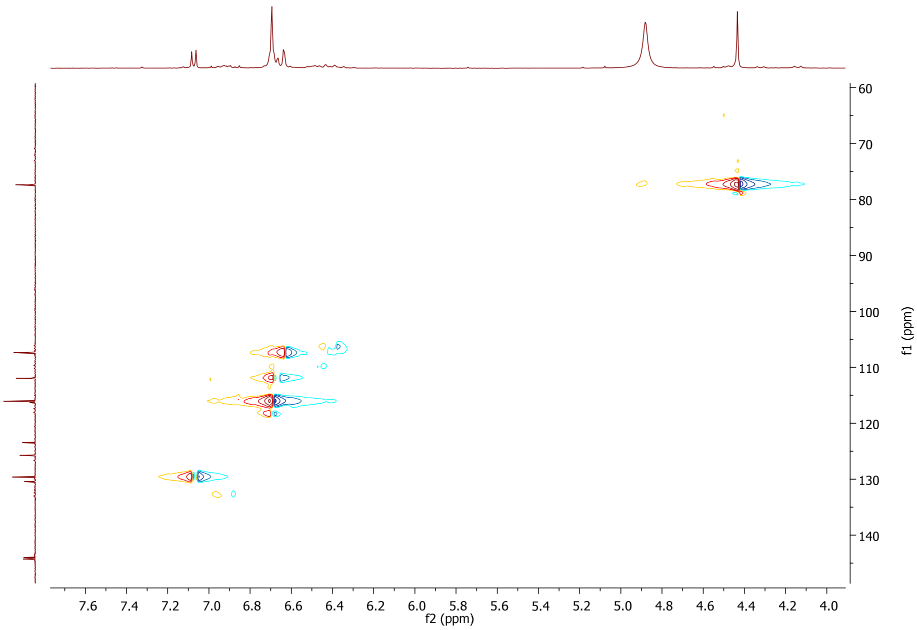
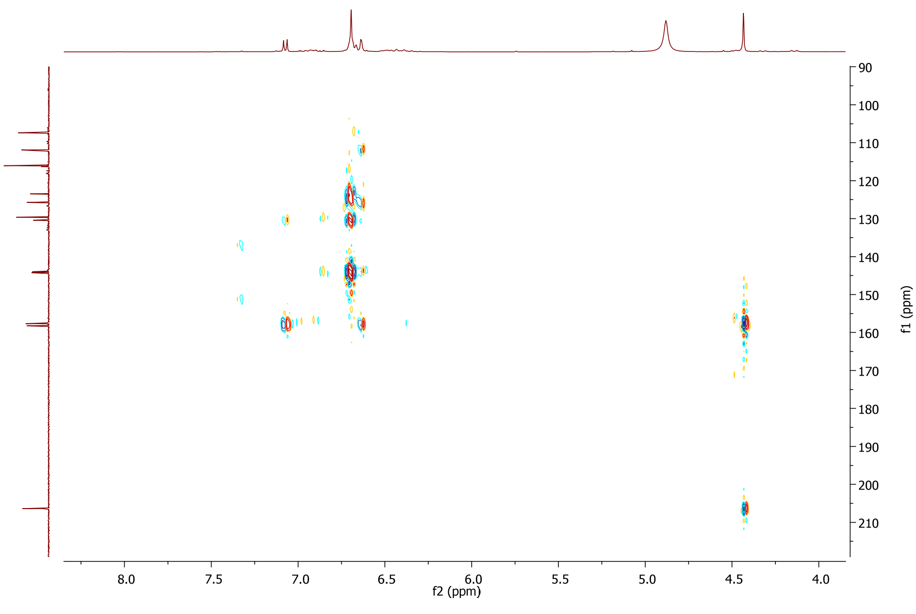

7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0
f2 (ppm)
60 70 80 90 100 110 120 130 140
f1 (ppm)

Fig. S8.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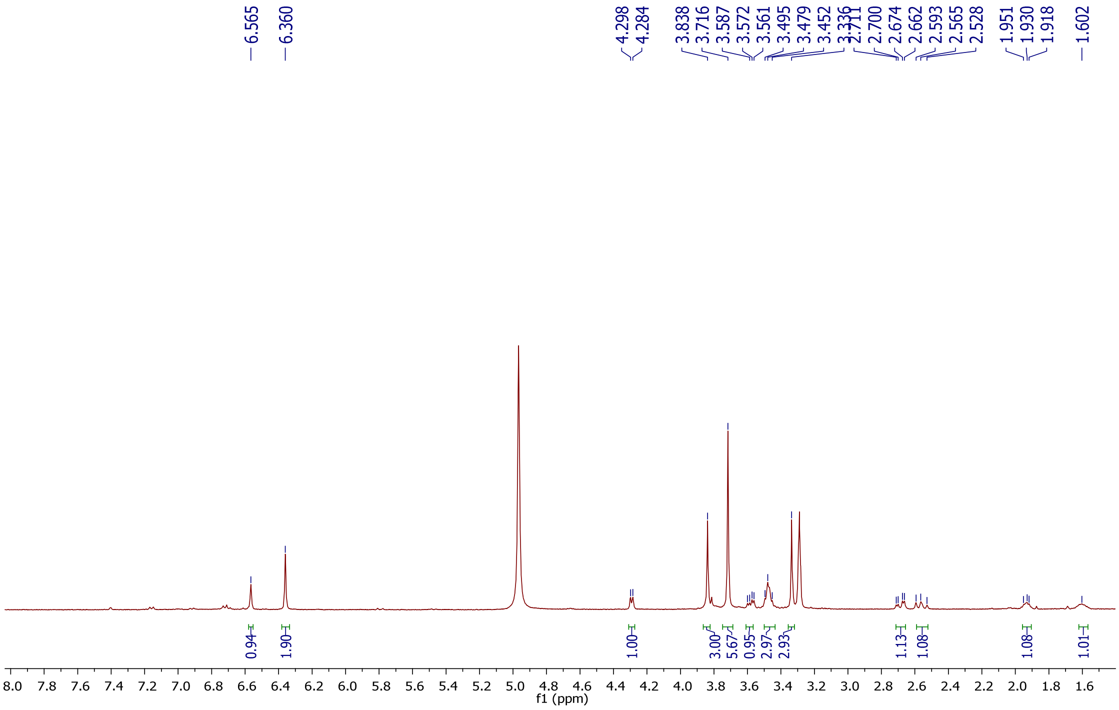
f1 (ppm)

Fig. S9.



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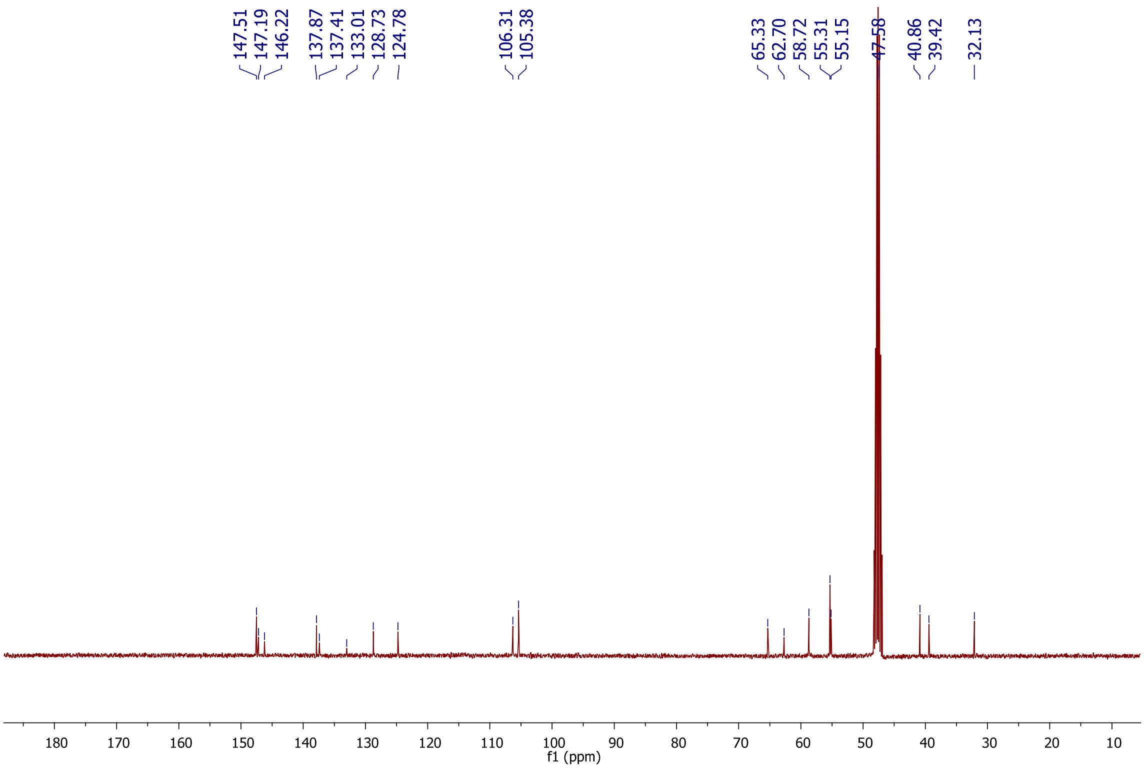

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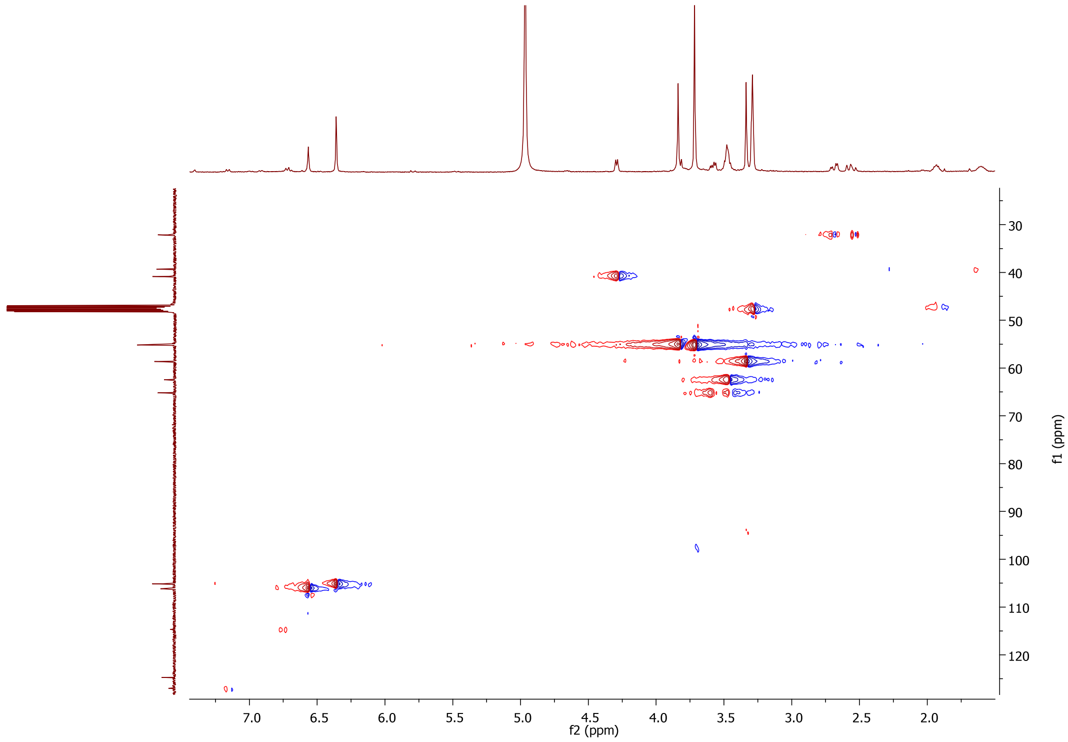

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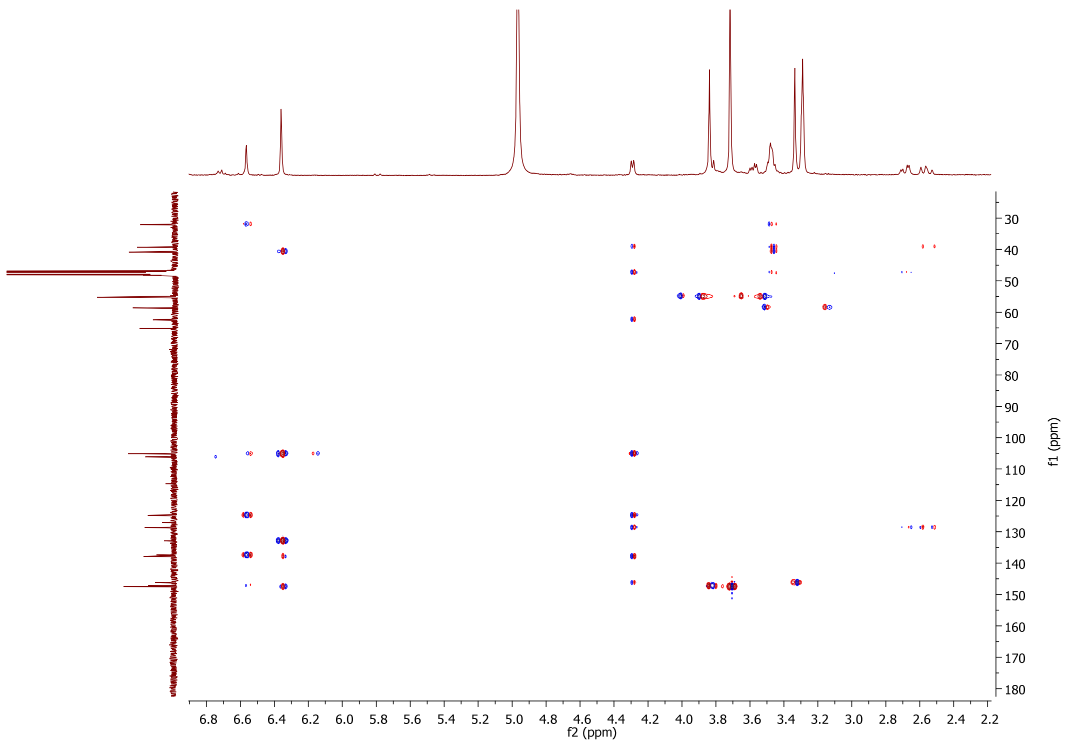

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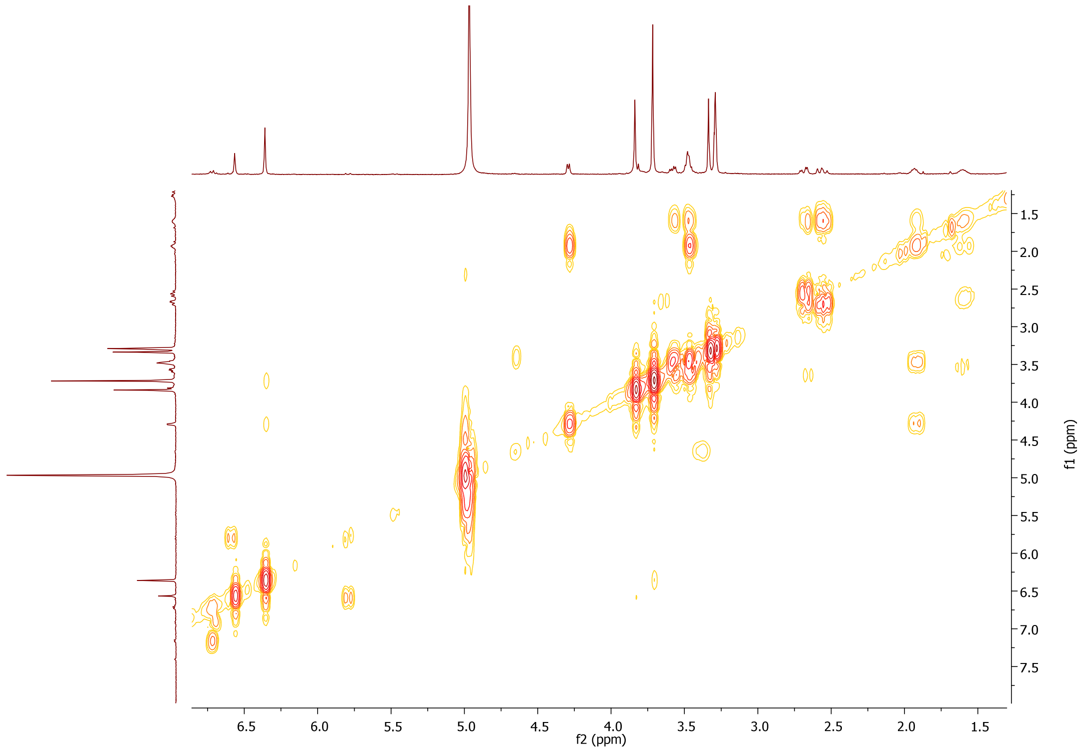

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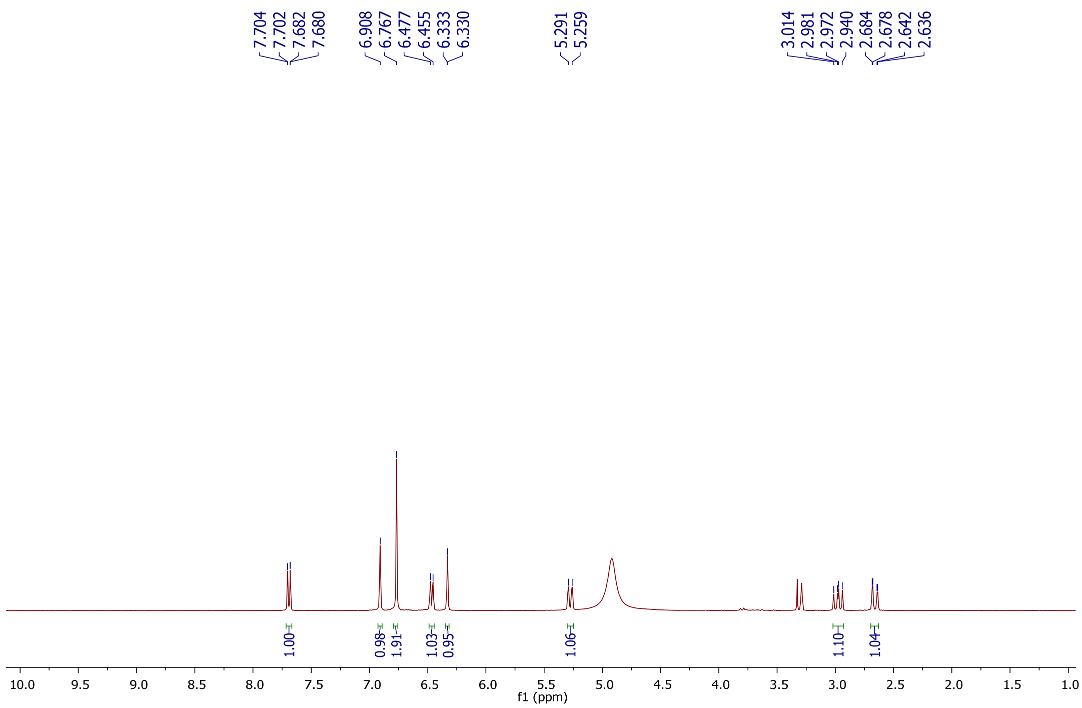

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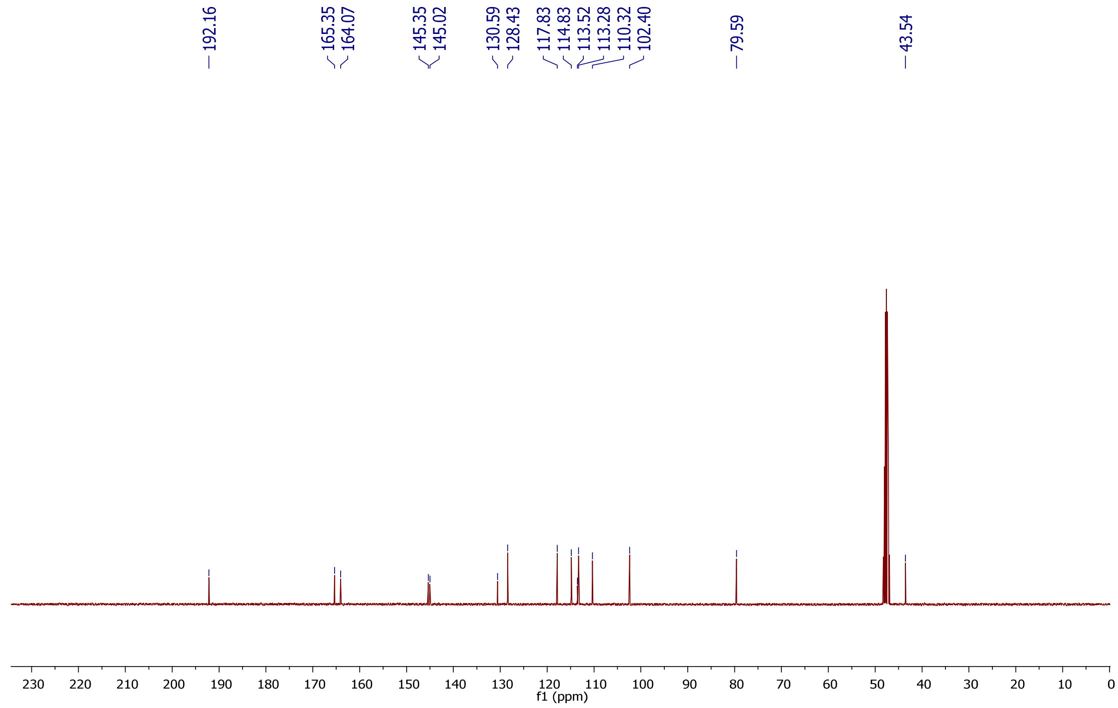

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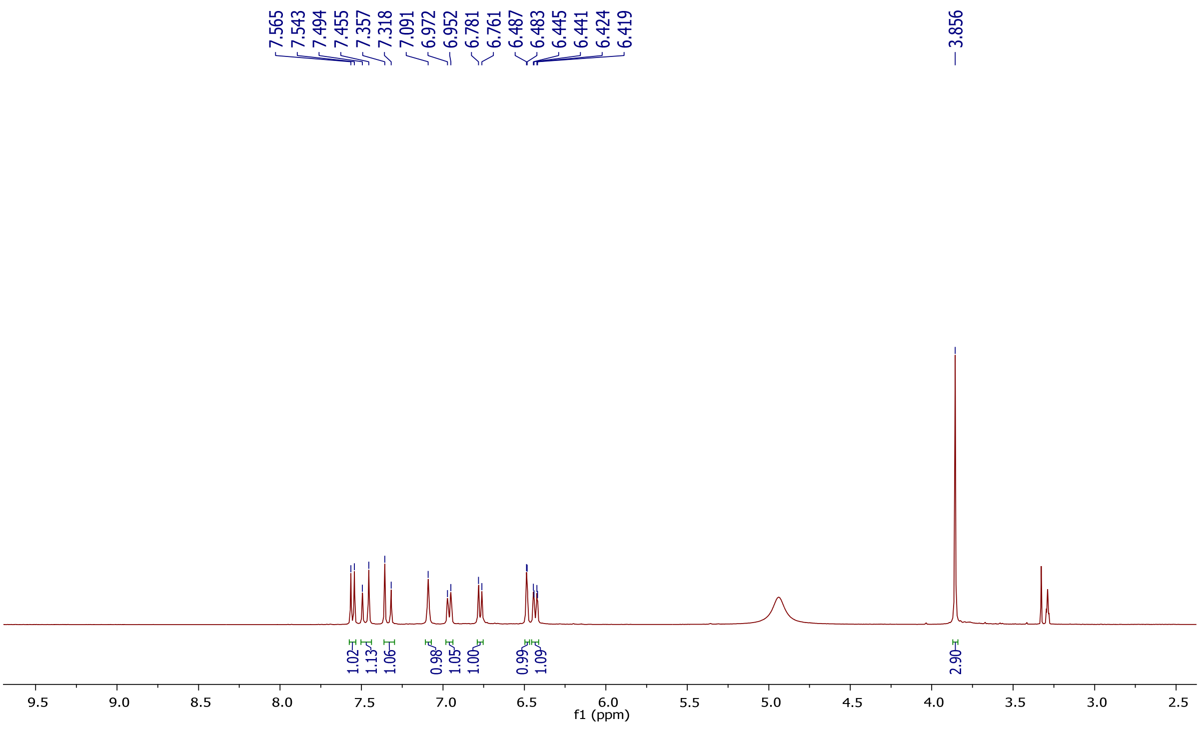

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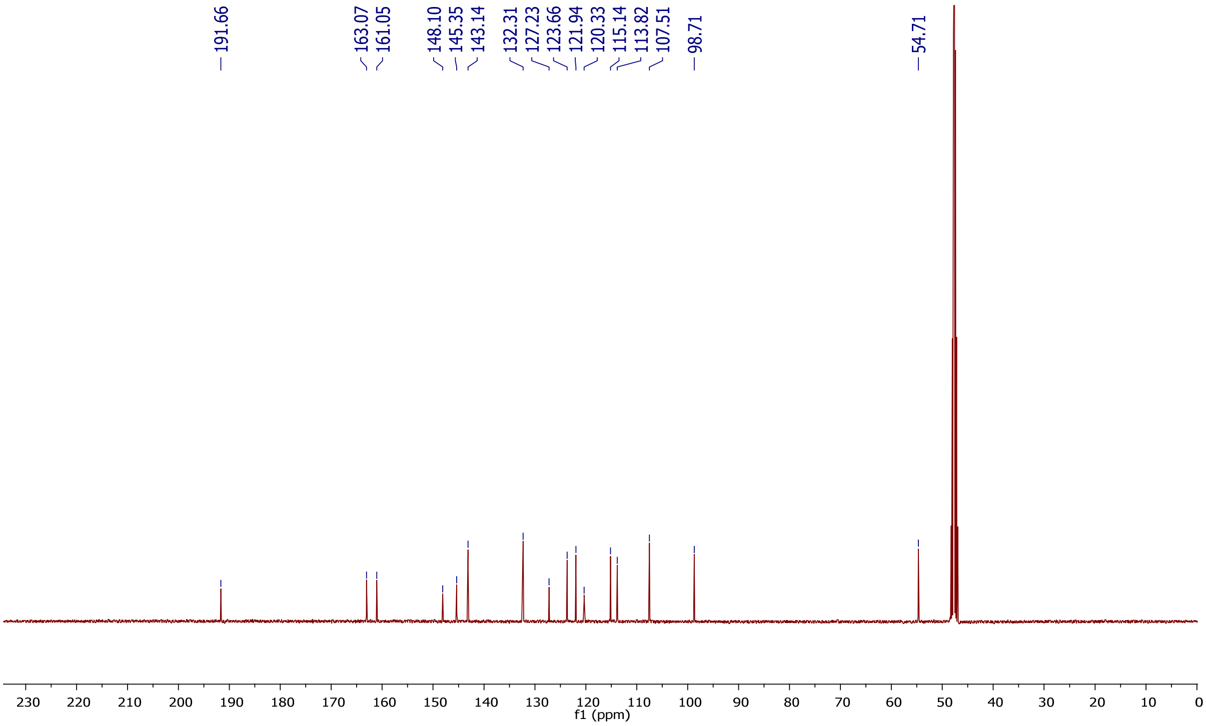

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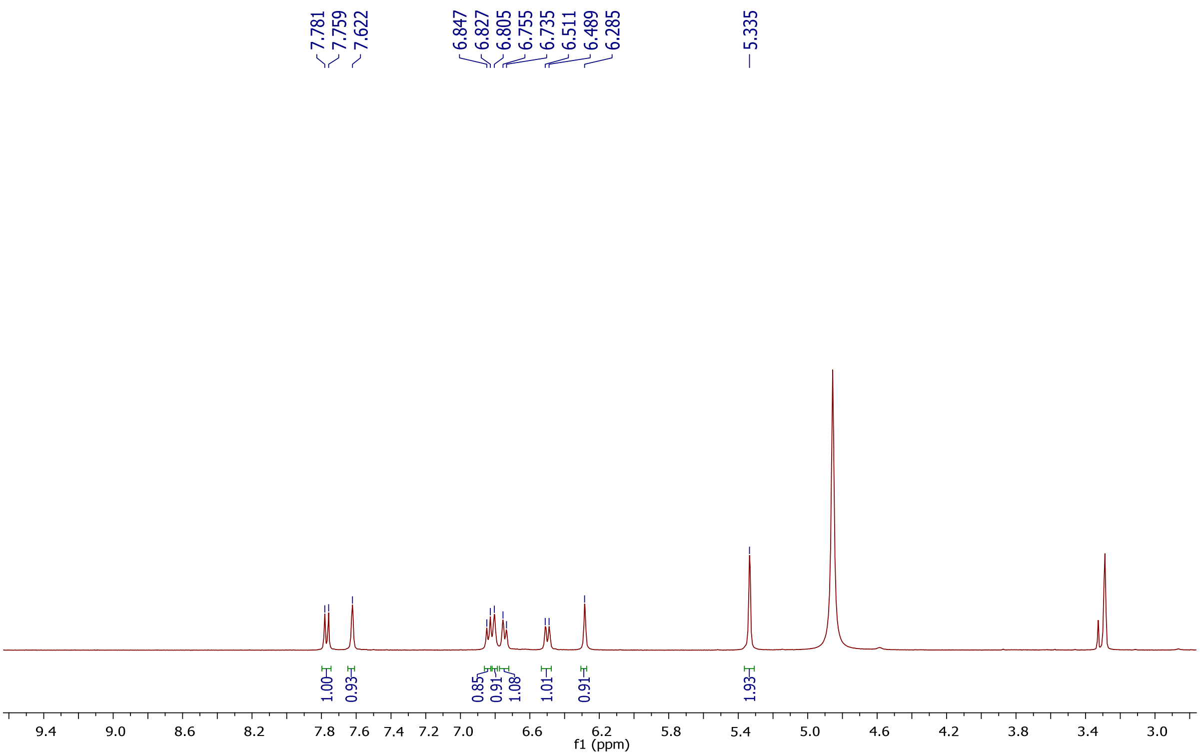

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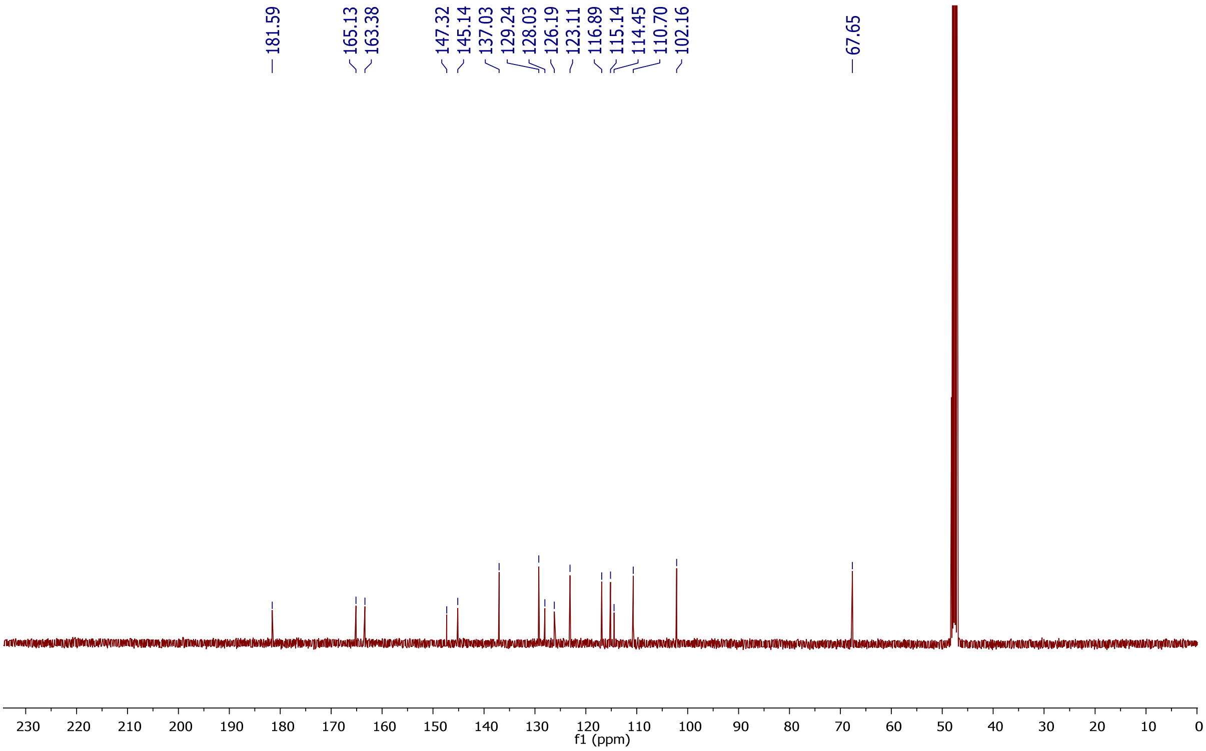

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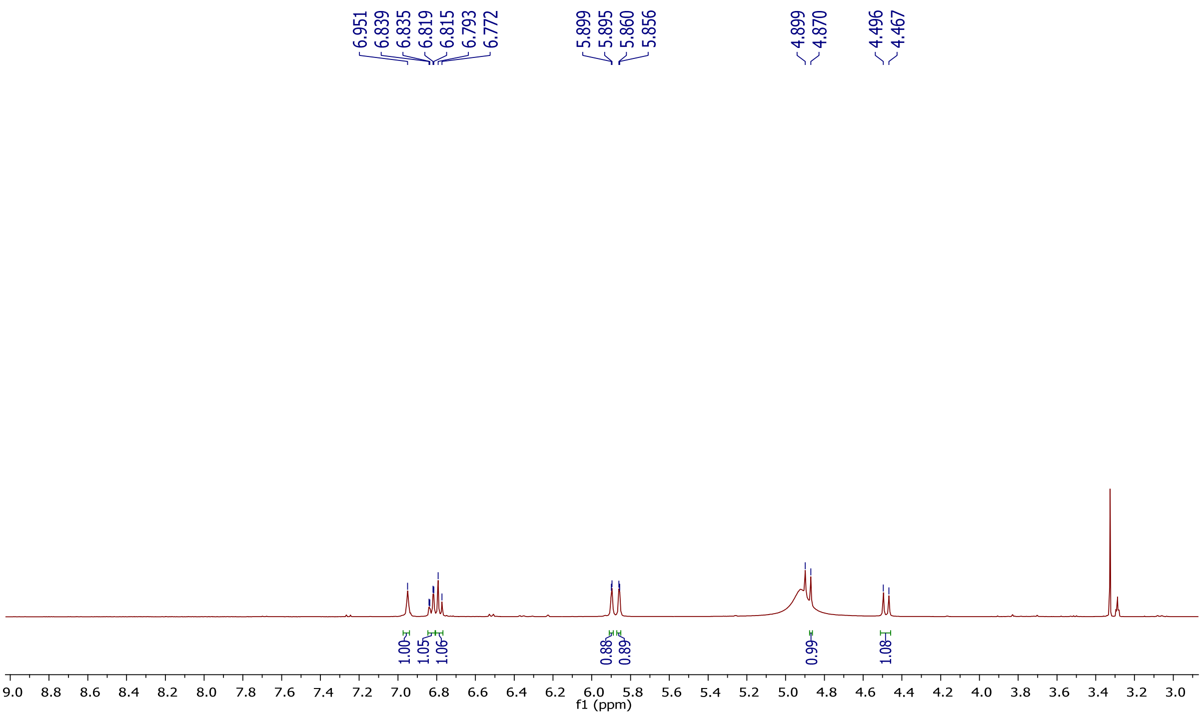

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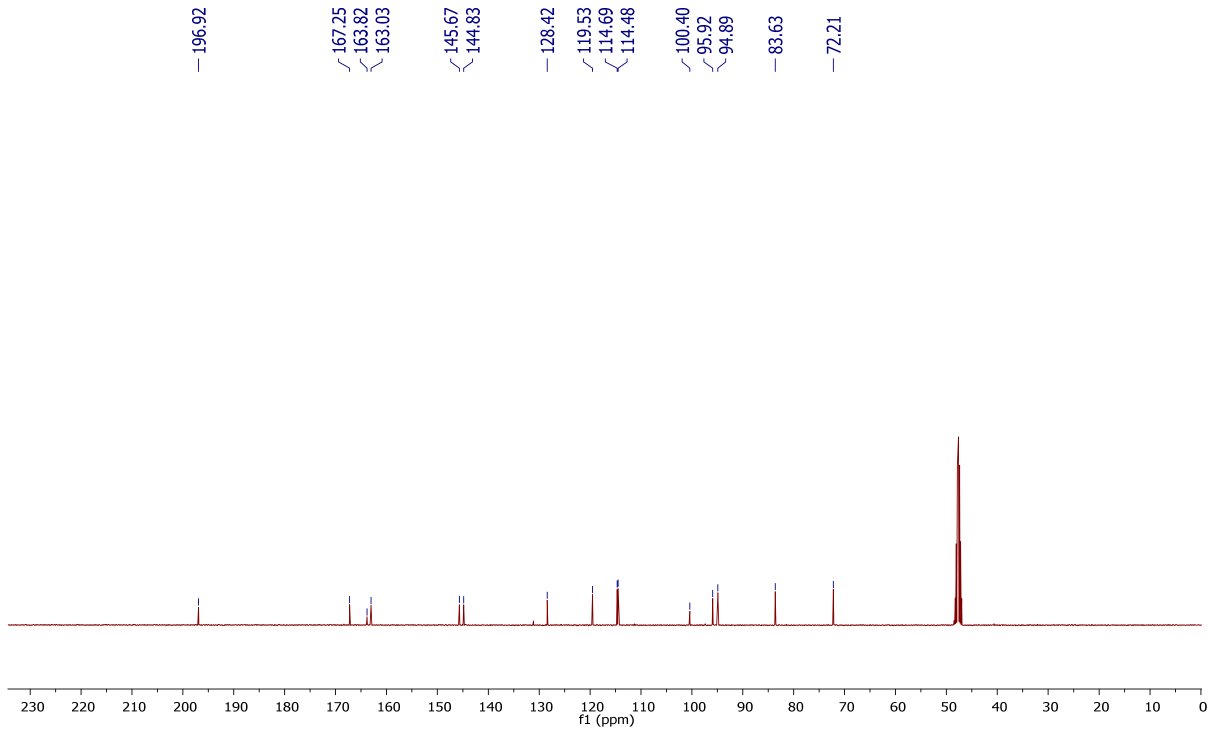

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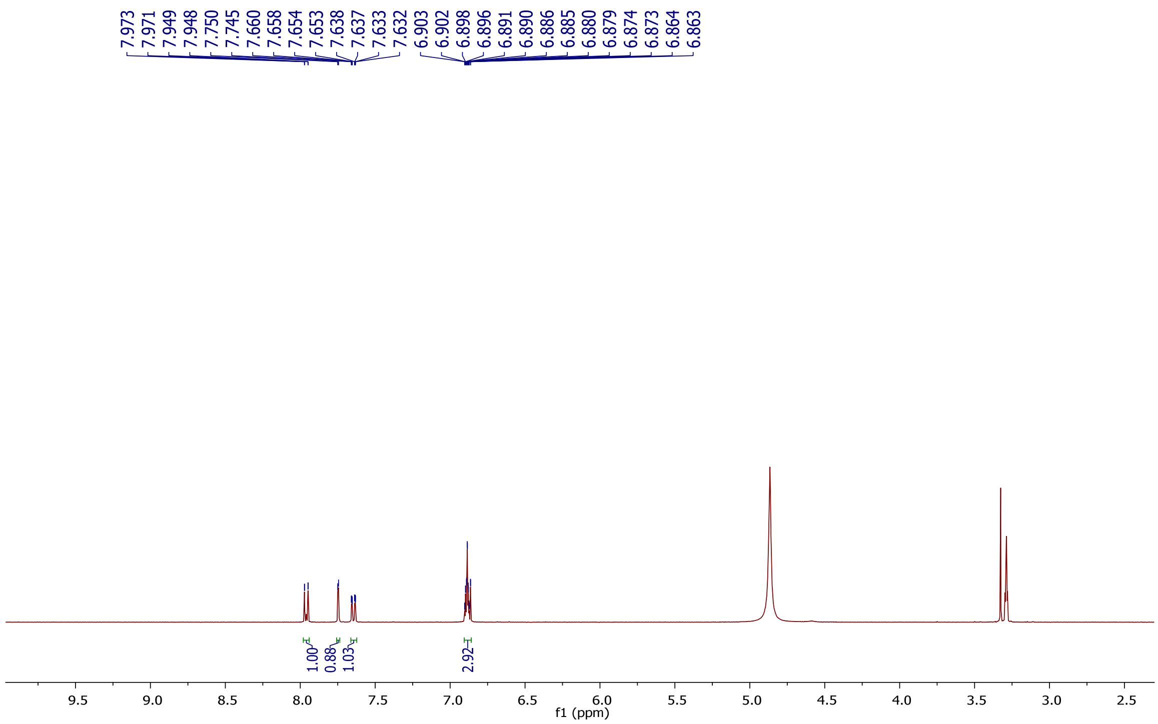

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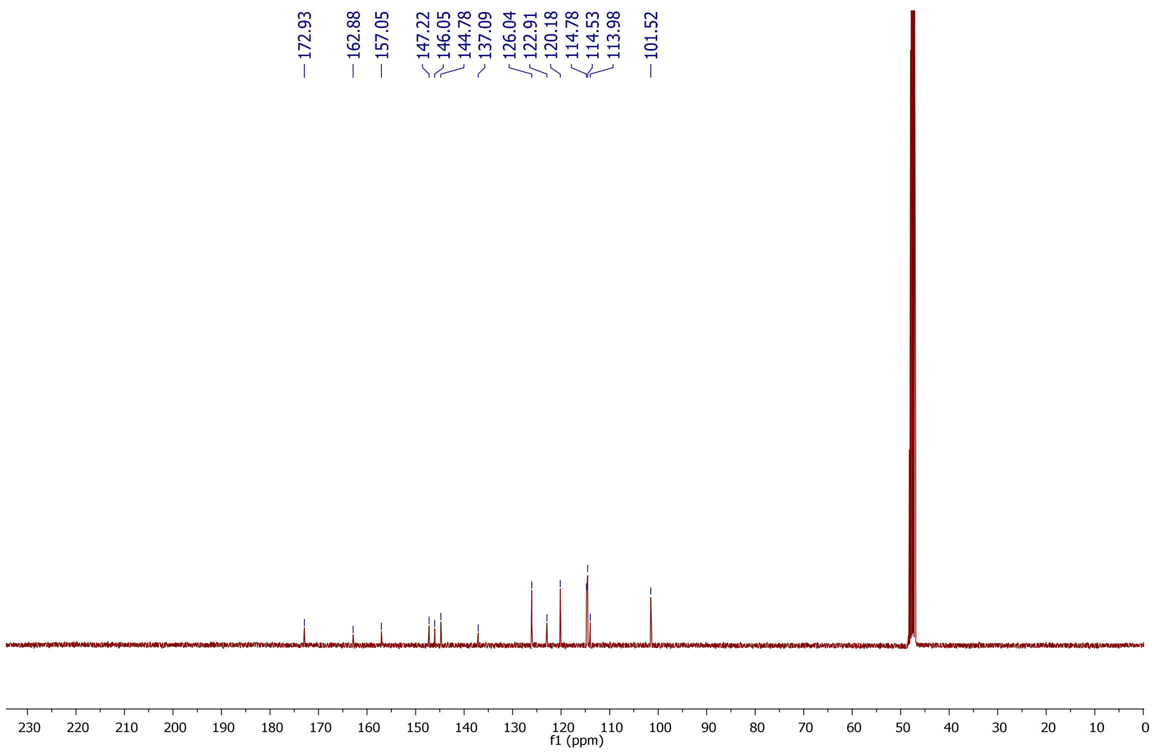

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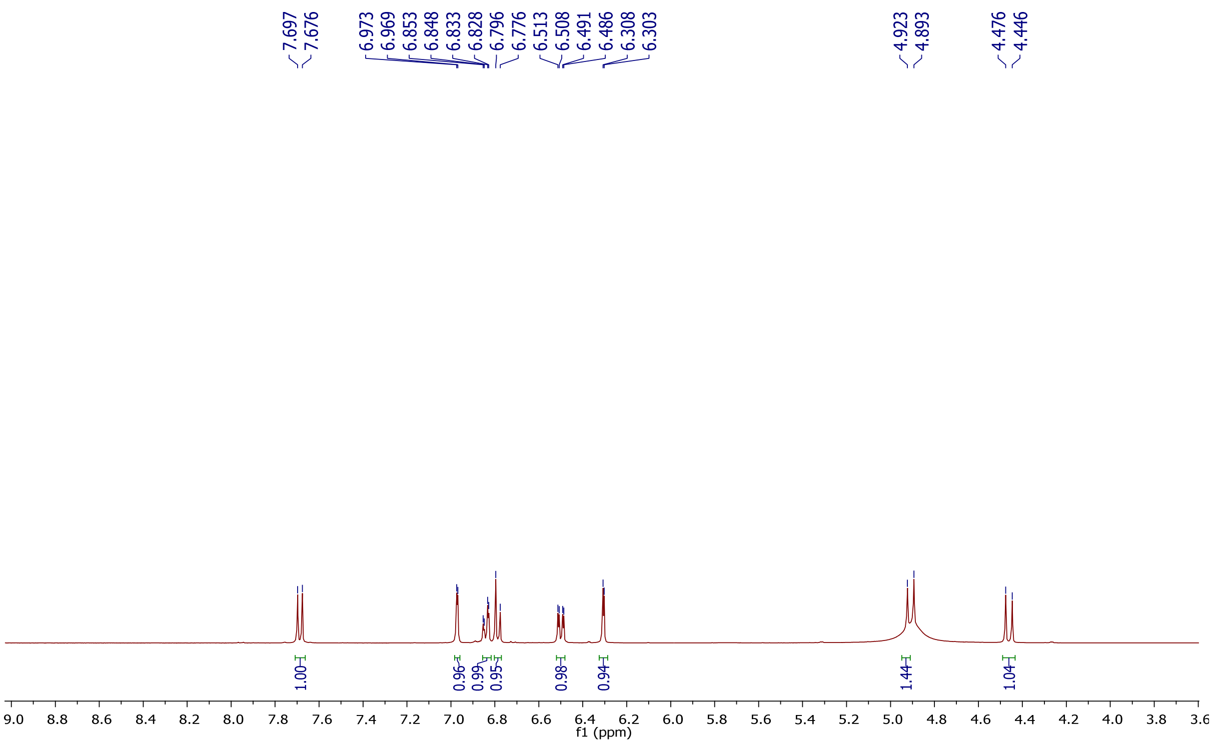

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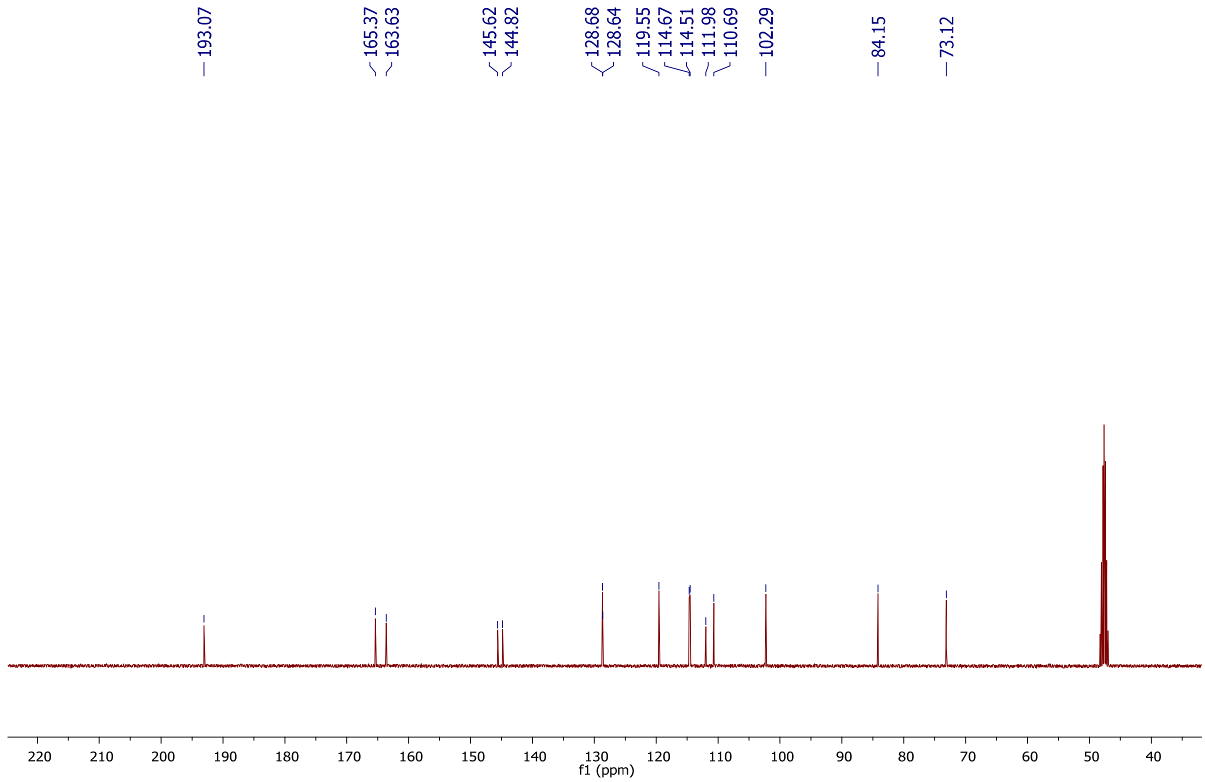

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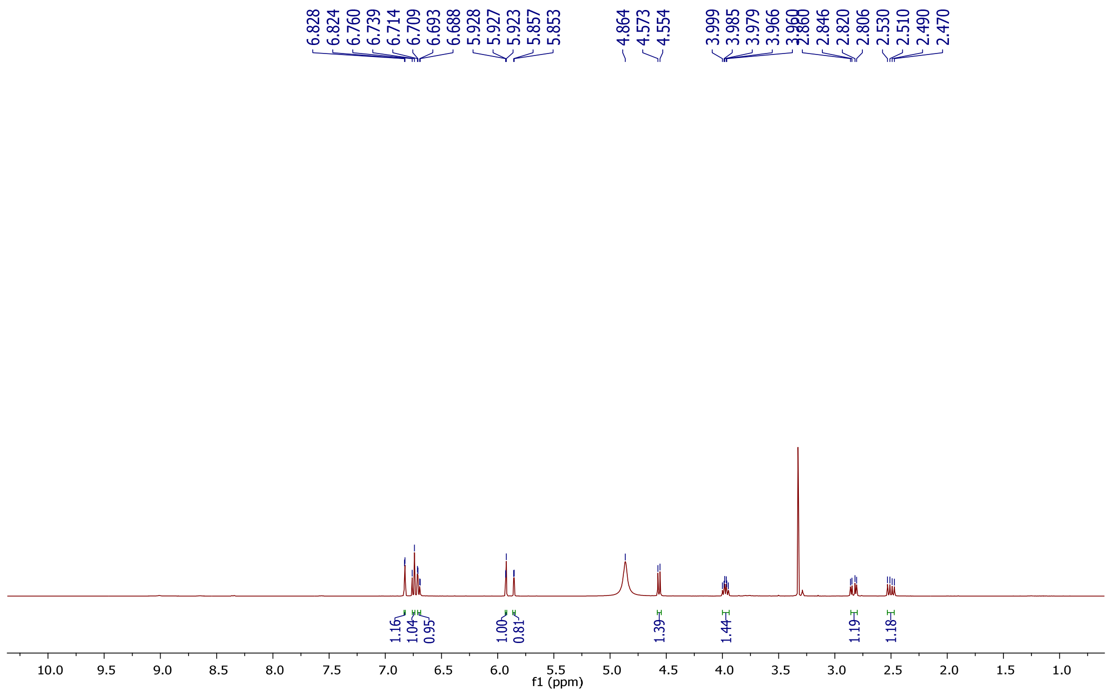

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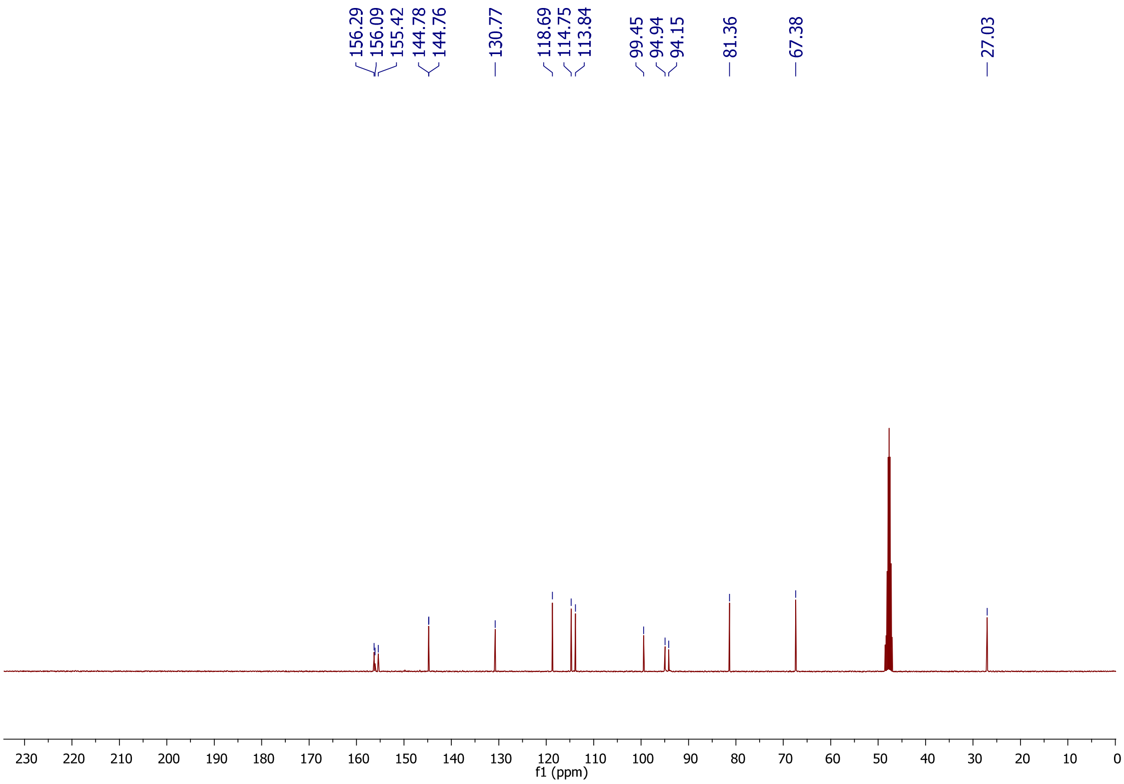

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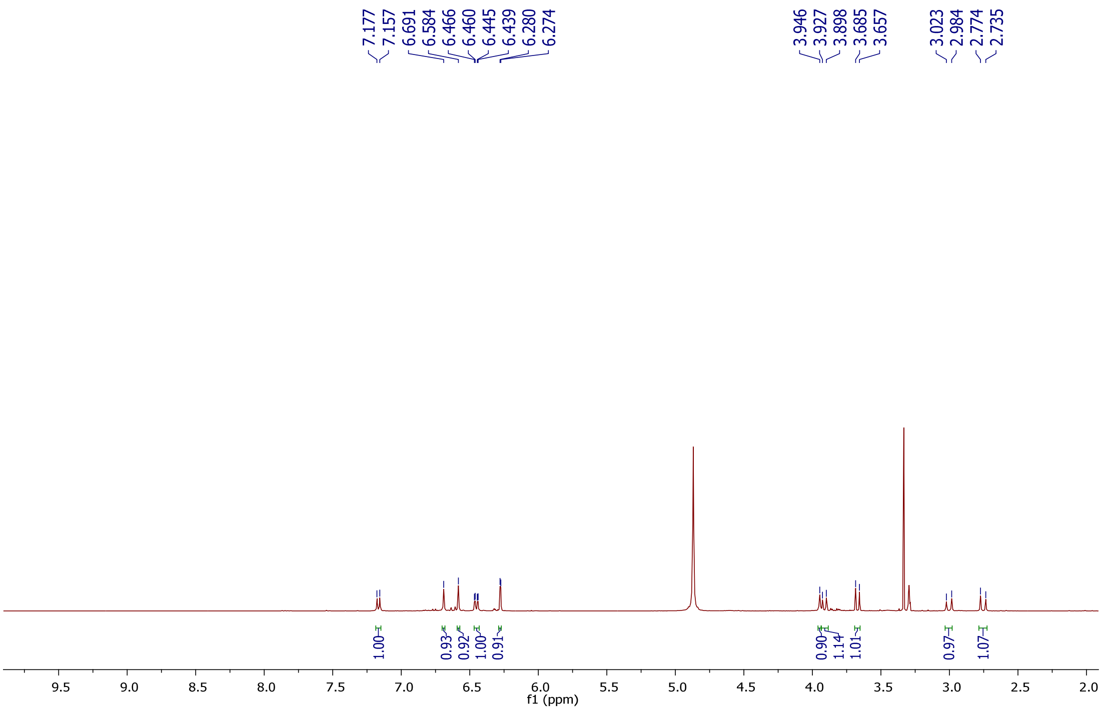

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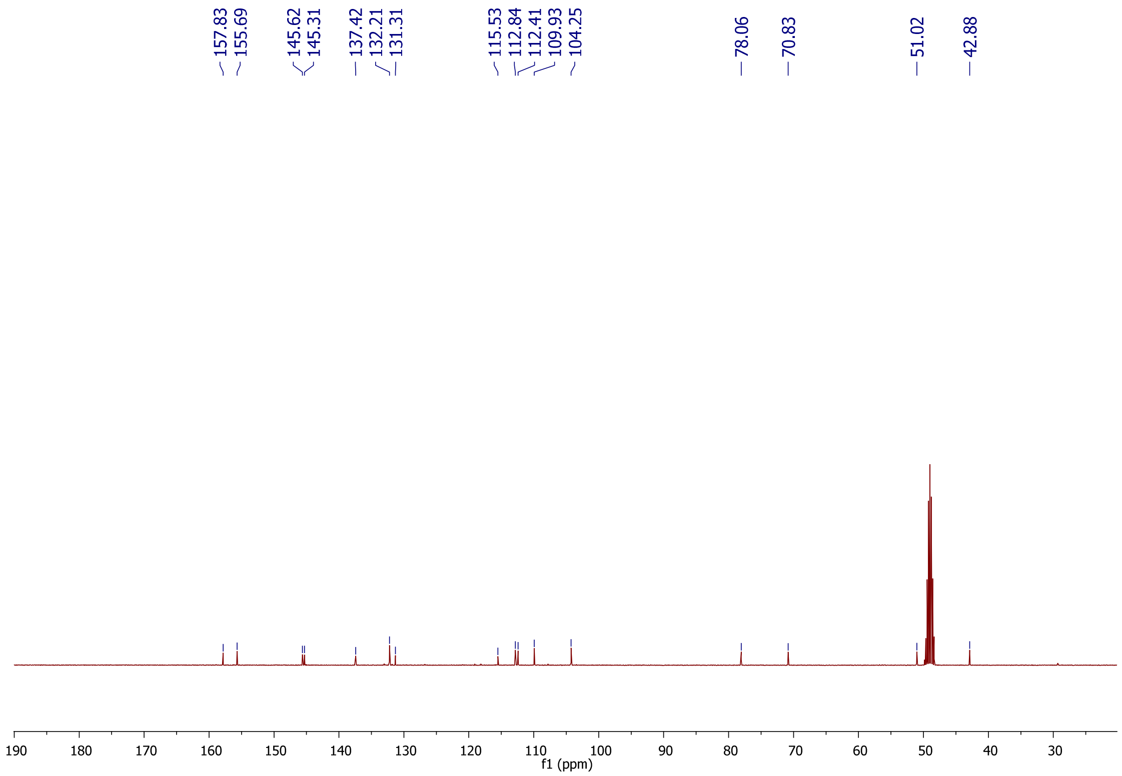

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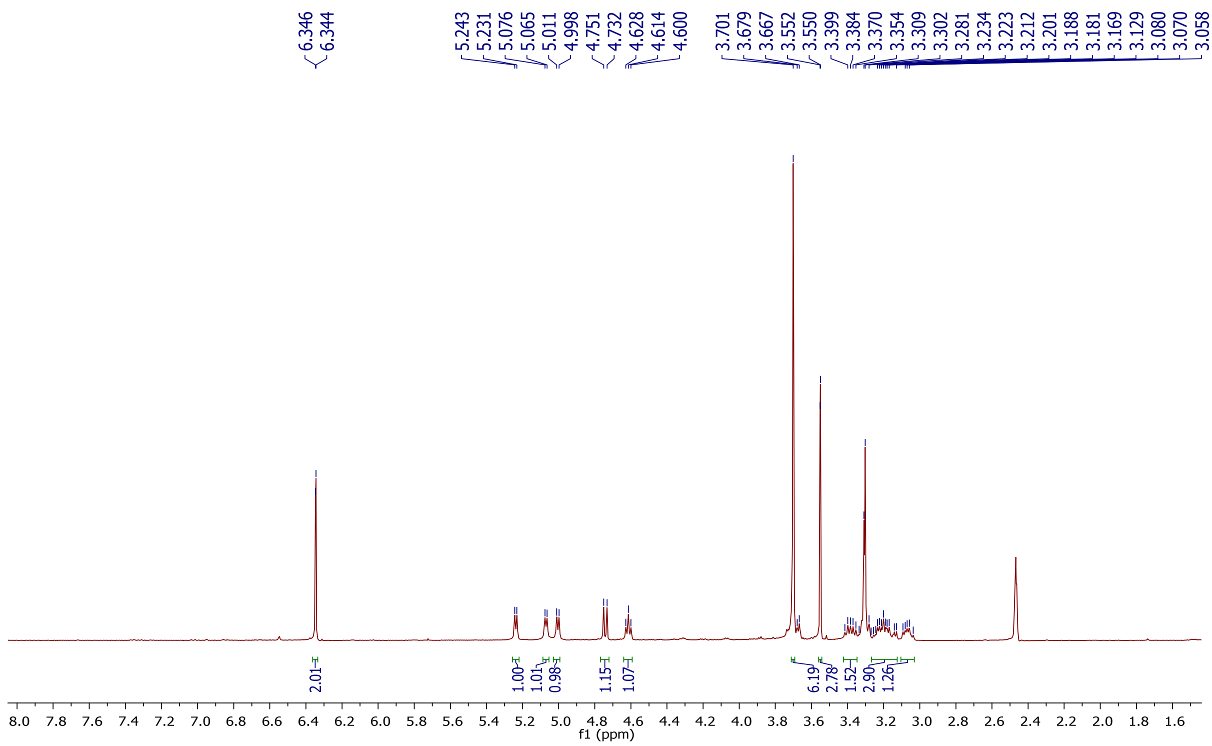

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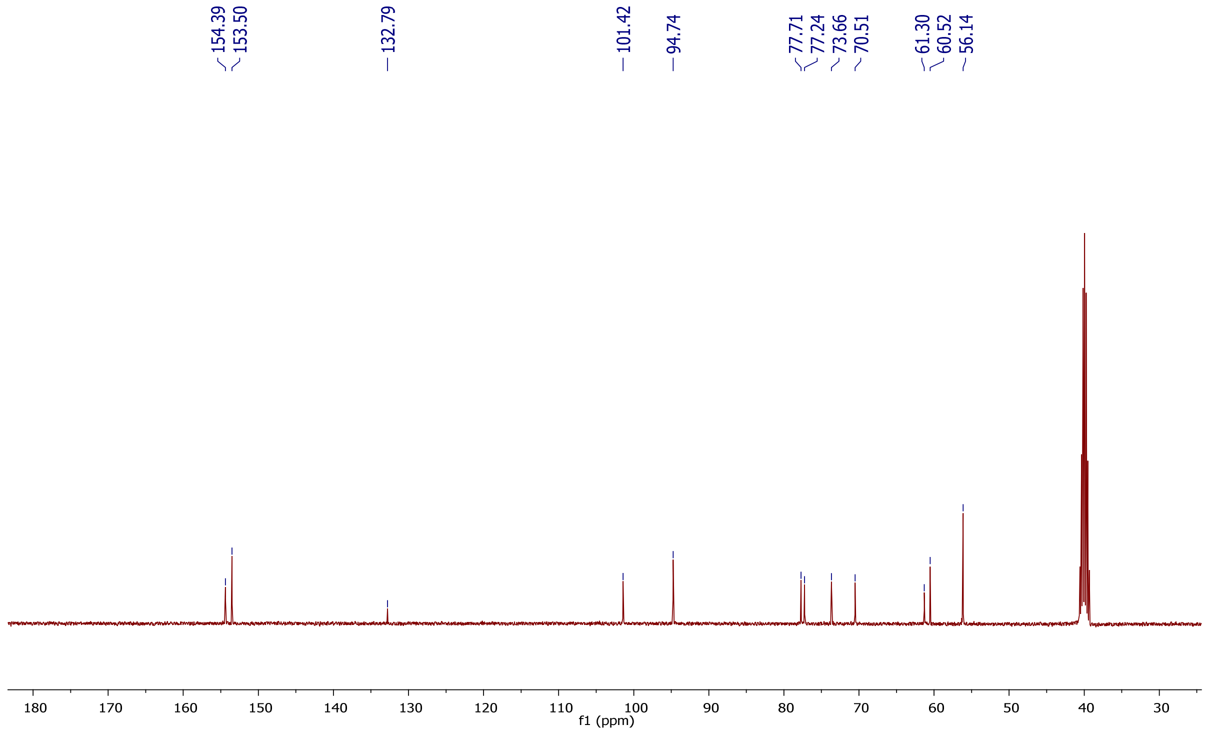

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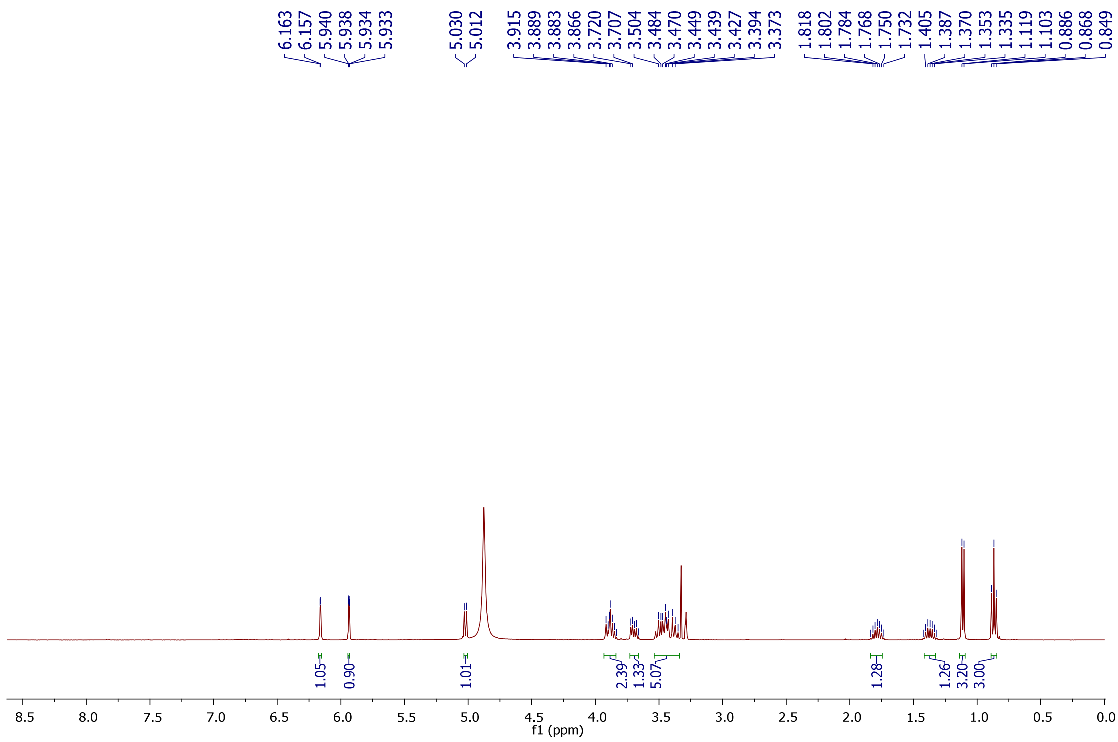

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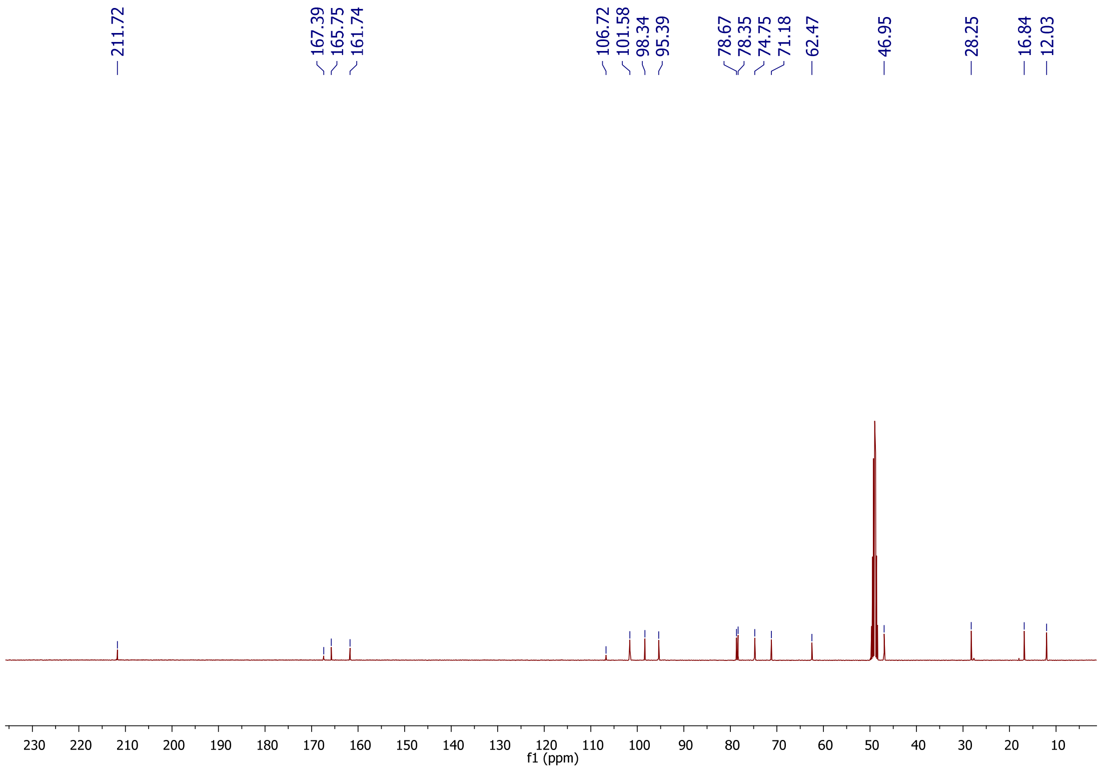

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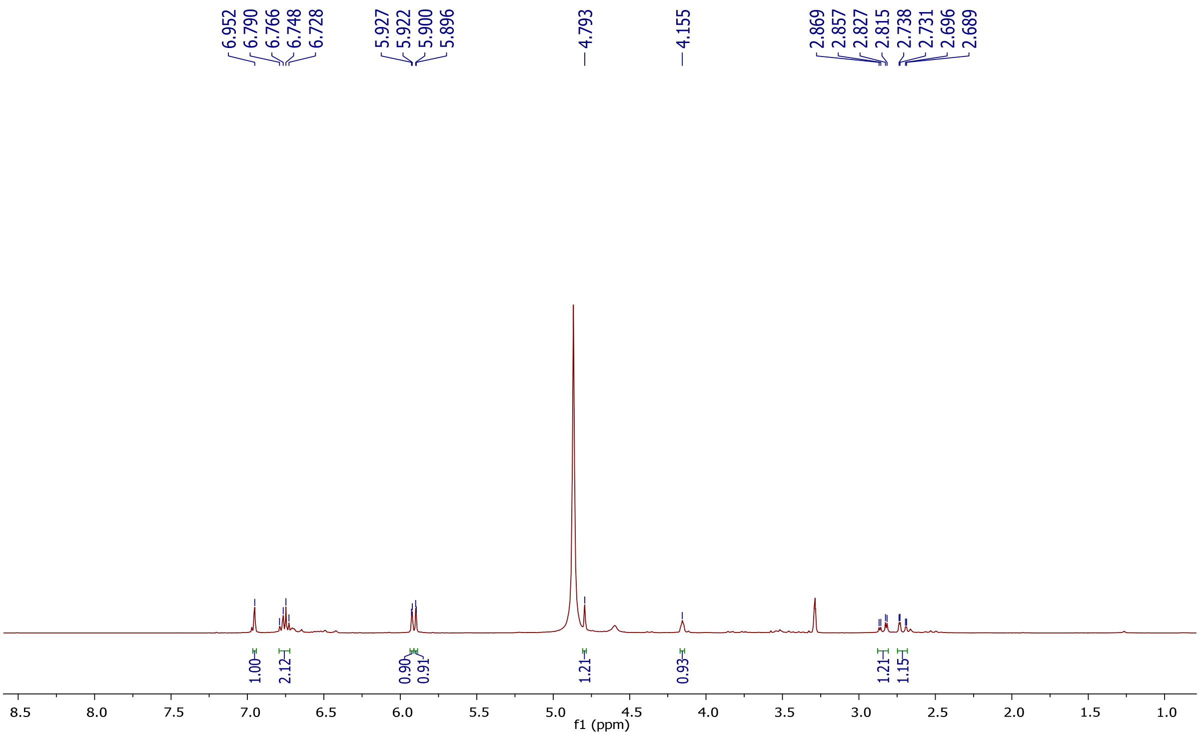

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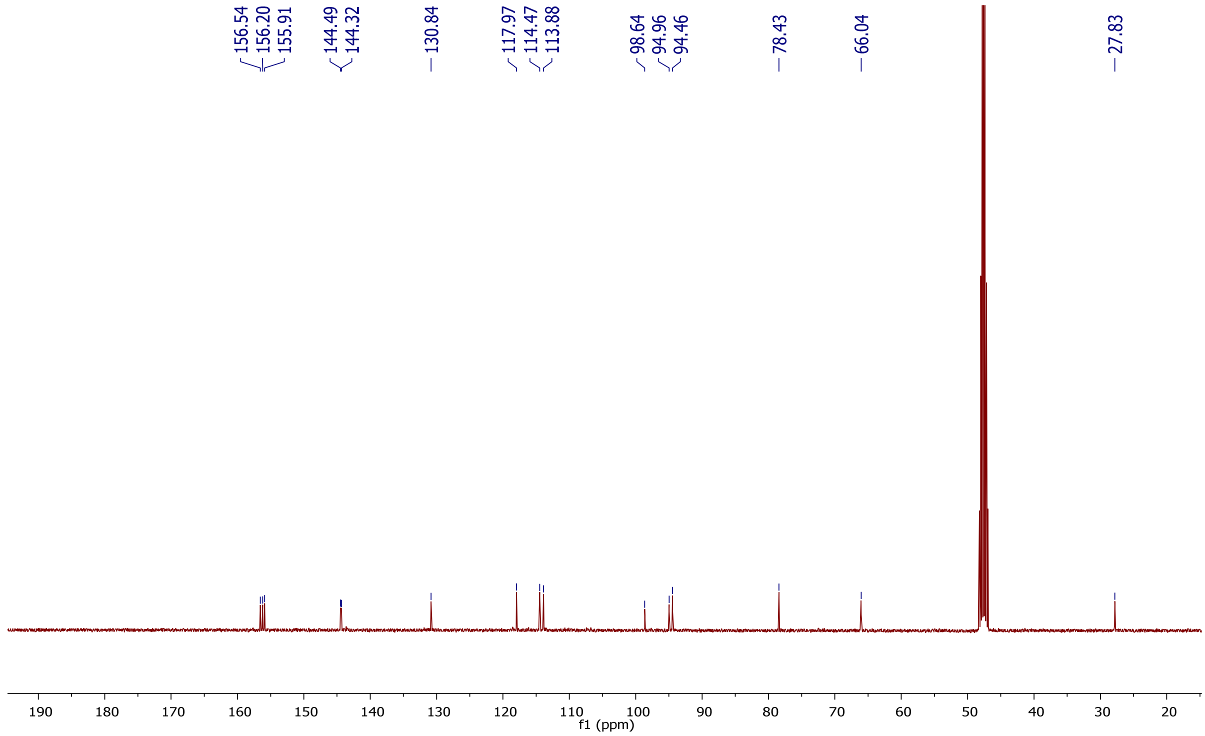

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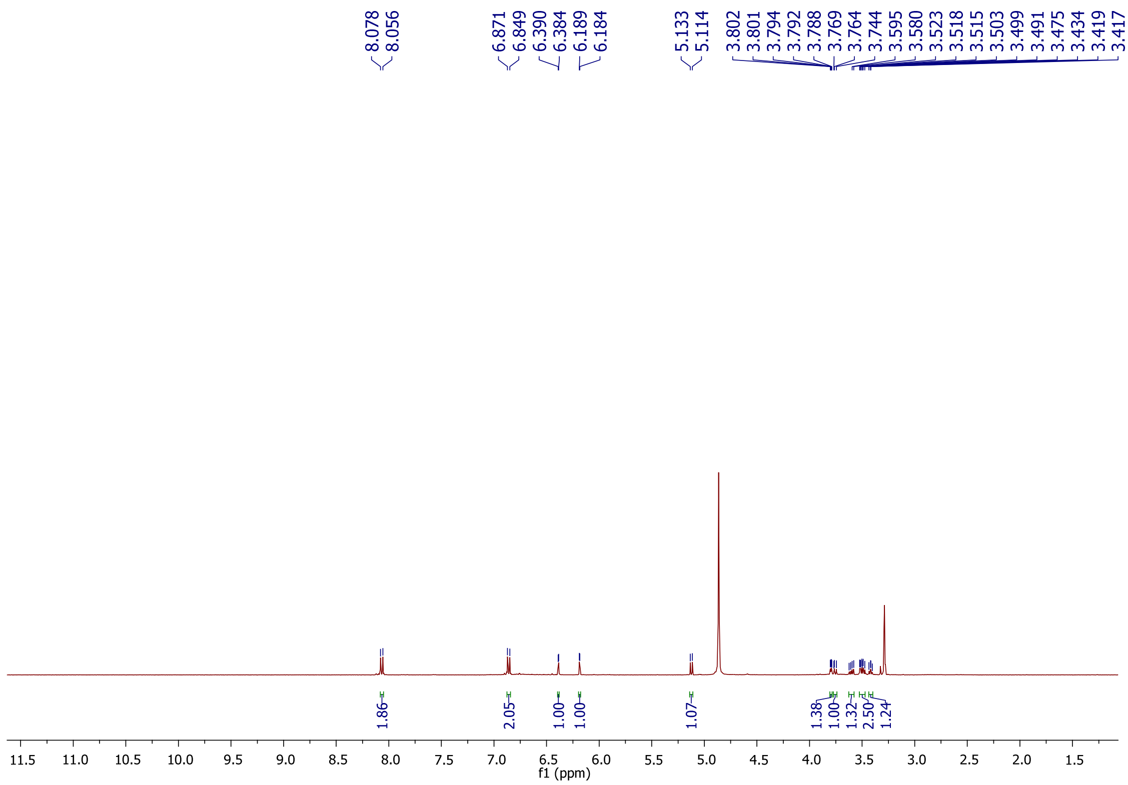

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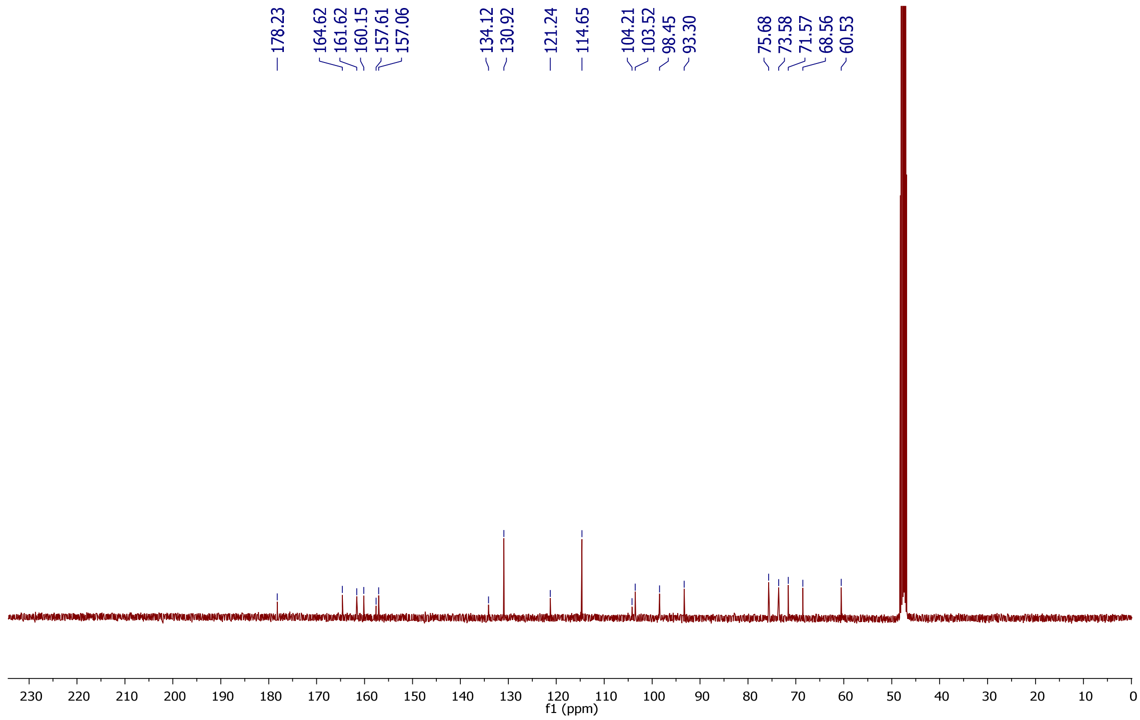

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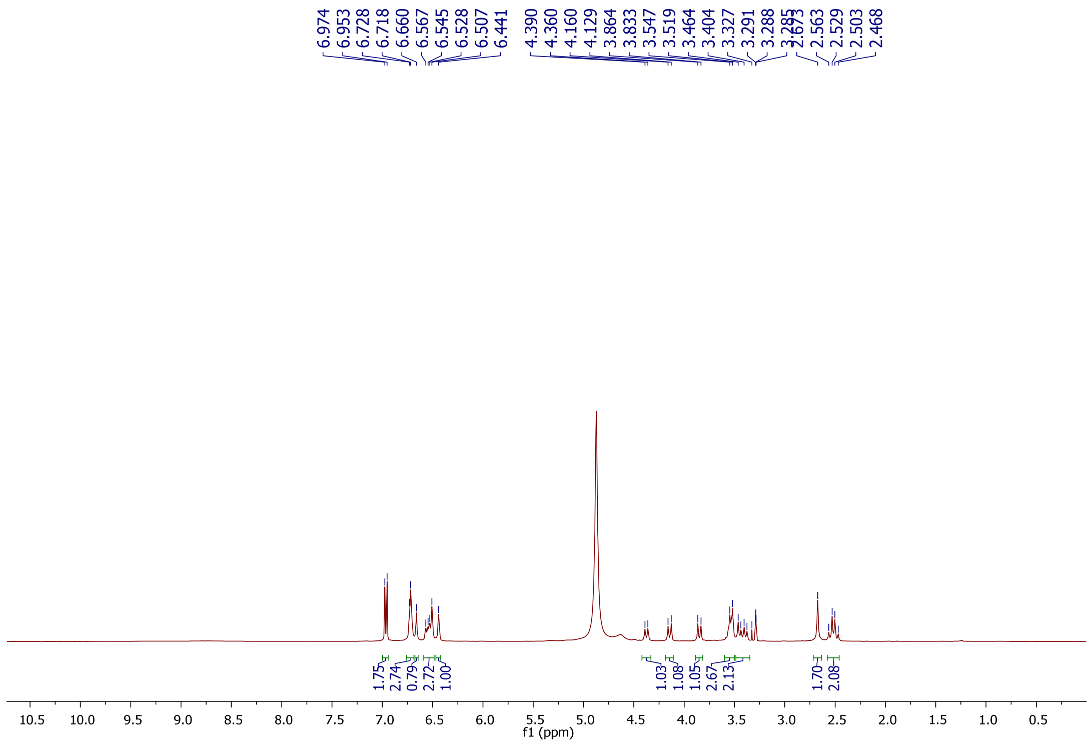

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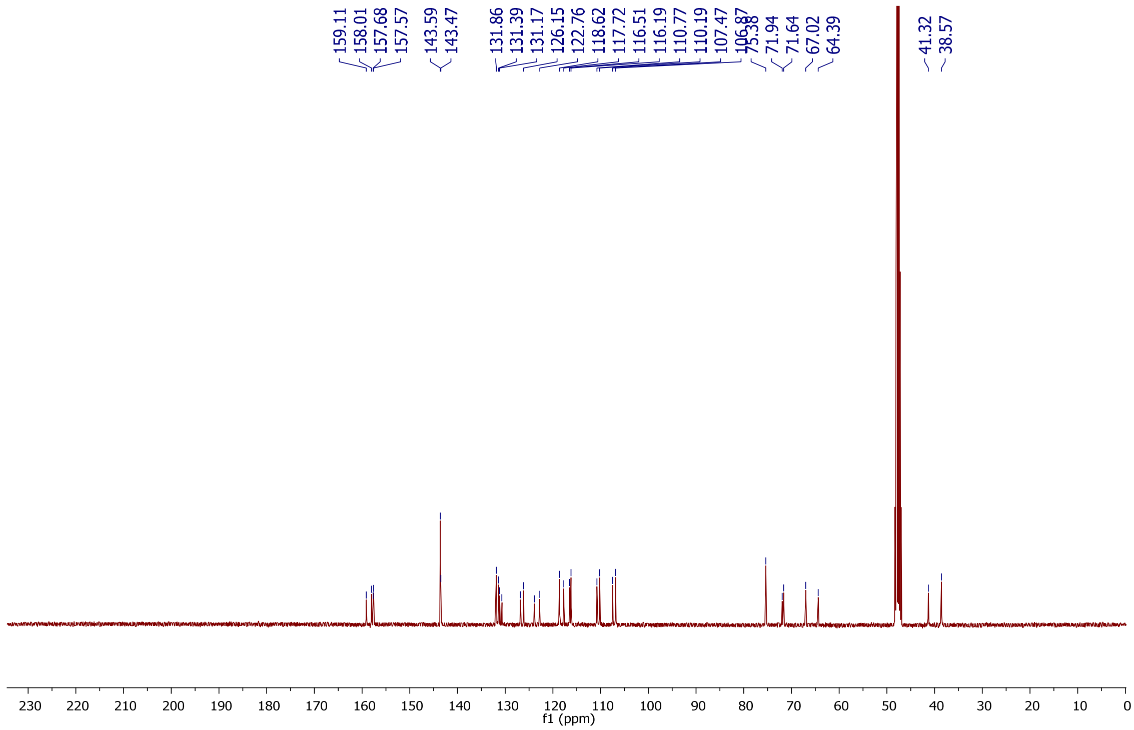
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f1 (ppm)