SUPPLEMENTARY MATERIALS

Abietic, Maleopimaric and Quinopimaric Dipeptide Ugi-4CR Derivatives and Their Potency against Influenza A and SARS-CoV-2

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A set of 12 abietane diterpene derivatives have been synthesized by the Ugi-four component reaction (Ugi-4CR) and tested for cytotoxicity and activity against influenza virus A/Puerto Rico/8/34 (H1N1) and SARS-CoV-2 pseudovirus. Five dipeptide derivatives demonstrated a selectivity index (SI) higher than 10 and IC_{50} values from 2 to 32 μM against influenza virus. Compound **11** was found to be a lead with SI of 200, and time-of-addition experiments showed the viral entry into the cell and the binding of the virus to the receptor as a possible target. Compound **7** was the only one showed weak anti-SARS-CoV-2 activity with EC_{50} value of 80.96 μM. Taken together, our data suggest the potency of diterpene acids-Ugi products as new effective anti-influenza compounds.

Keywords: Ugi-4CR; Diterpenes; Abietic acid; Maleopimaric acid; Dihydroquinopimaric acid; Influenza A; SARS-CoV-2

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3. Experimental

Chemistry

General

The spectra were recorded at the Center for the Collective Use "Chemistry" of the Ufa Institute of Chemistry of the UFRC RAS and RCCU "Agidel" of the UFRC RAS. ^{1}H and ^{13}C-NMR spectra were recorded on a "Bruker AM-500" (Bruker, Billerica, MA, USA, 500 and 125.5 MHz respectively, δ, ppm, Hz) in $CDCl_3$, internal standard tetramethylsilane. Melting points were detected on a micro table "Rapido PHMK05" (Nagema, Dresden, Germany). Optical rotations were measured on a polarimeter "Perkin-Elmer 241 MC" (Perkin Elmer, Waltham, MA, USA) in a tube length of 1 dm. Elemental analysis was performed on a Euro EA-3000 CHNS analyzer (Eurovector, Milan, Italy); the main standard is acetanilide. Thin-layer chromatography analyses were performed on Sorbfil plates (Sorbpolimer, Krasnodar, Russian Federation), using the solvent system petroleum ester – ethyl acetate, 1:1. Substances were detected by 10% H_2SO_4 with subsequent heating to 100–120 °C for 2–3 min. Abietic **1**, dihydroquinopimaric **2** and maleopimaric **3** acids were synthesized according (Harris et al. 1952), (Herz et al. 1969), (Zalkov et al. 1962).

General procedure for UGI reactions (GP)

Paraformaldehyde (1 mmol) was suspended in 10-20 mL dry methanol, followed by the addition of amine (1.2 mmol). The suspension was stirred for 2 h at room temperature. The diterpenic acid (1 mmol) and the 2,6-dimethoxyphenylisocyanide (1 mmol) were added, and the solution was stirred for additional 5-7 days. The reaction mixture was poured into aqueous HCl (2M) and the precipitate formed was filtered off, washed until neutral, and dried in air. The residue was purified by column chromatography using petroleum ether: ethyl acetate as eluent.

N-butyl-N-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)-N-(18-oxoabieta-7,13-dien-18-yl)carboxamide (4). Compound **4** was prepared according to GP by reaction of abietic acid **1** (0.30 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), *n*-butylamine (0.09 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether /ethyl acetate, 7:1) afforded compound **4** (0.34 g, 66%) as a white solid; R_f = 0.60 (petroleum ether / ethyl acetate, 1:1); mp = 93–96 °C; $[\alpha]_D$ = - 103° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.93 (s, 3H, H-18), 1.06 (d, ^{2}J = 6.8 Hz, 3H, H-15), 1.07 (d, ^{2}J = 6.8 Hz, 3H, H-16), 1.12-1.31 (m, 4H, H-1, H-3), 1.39 (s, 3H, H-4'), 1.43 (s, 3H, H-19), 1.55-2.12 (m, 13H, H-2, H-5, H-6, H-11, H-12, H-2', H-3'), 2.18 (s, 6H, H-10', H-10''), 2.28-240 (m, 2H, H-9, H-14), 3.61-3.67 (m, 2H, H-1'), 4.11-4.19 (m, 2H, H-5'), 5.37 (br. s., 1H, H-7), 5.79 (br. s., 1H,

H-17), 6.89-7.18 (m, 3H, H-8', H-8'', H-9'), 8.33 (br. s., 1H, NH); δ_C (125.76 MHz, $CDCl_3$) 14.10 (C4'), 14.56 (C18), 18.47 (C2), 18.59 (C12', C12''), 20.32 (C3'), 21.03 (C19), 21.55 (C15, C16), 22.51 (C11), 25.91 (C6), 27.45 (C12), 29.70 (C2'), 34.91 (C14), 36.41 (C3), 37.65 (C1), 45.29 (C1'), 46.70 (C4), 51.34 (C9), 53.48 (C5), 53.74 (C10), 54.20 (C5'), 120.57 (C7), 121.25 (C17), 122.45 (C9'), 128.14 (C7', C7''), 133.82 (C8', C8''), 135.16 (C6'), 135.20 (C8), 145.73 (C13), 168.99 (C21), 179.50 (C20). Analysis calculated for $C_{34}H_{50}N_2O_2$ (518.98): C 78.72, H 9.71, N 5.40; found: C 78.75; H 9.70; N 5.38.

Methyl N-{2-[(2,6-dimethylphenyl)amino]-2-oxoethyl}-N-(18-oxoabieta-7,13-dien-18-yl)glycinate (5). Compound **5** was prepared according to GP by reaction of abietic acid **1** (0.30 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), glycine methyl ester hydrochloride (0.15 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether / ethyl acetate, 7:1) afforded compound **5** (0.37 g, 70%) as a white solid; R_f = 0.60 (petroleum ether /ethyl acetate, 1:1); mp = 112–114 °C; $[\alpha]_D$ = - 37° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.93 (s, 3H, H-18), 1.06 (d, ^2J = 6.8 Hz, 3H, H-15), 1.07 (d, ^2J = 6.8 Hz, 3H, H-16), 1.12-1.31 (m, 4H, H-1, H-3), 1.43 (s, 3H, H-19), 1.55-2.12 (m, 9H, H-2, H-5, H-6, H-11, H-12),-2.17 (s, 6H, H-12', H-12''), 2.28-2.39 (m, 2H, H-9, H-14), 3.75-3.77 (m, 2H, H-1'), 3.78 (s, 3H, H-23), 4.32-4.39 (m, 2H, H-2'), 5.37 (br. s., 1H, H-7), 5.77 (br. s., 1H, H-17), 7.04-7.14 (m, 3H, H-5', H-5'', H-6'), 8.85 (br. s., 1H, NH); δ_C (125.76 MHz, $CDCl_3$) 14.56 (C18), 18.47 (C2), 18.53 (C12', C12''), 21.03 (C19), 21.55 (C15, C16), 22.51 (C11), 25.91 (C6), 27.45 (C12), 34.91 (C14), 36.41 (C3), 37.65 (C1), 45.29 (C1'), 46.70 (C4), 51.26 (C9), 53.50 (C5), 54.97 (C23), 55.29 (C10), 55.32 (C2'), 120.60 (C7), 122.45 (C17), 126.95 (C6'), 127.43 (C5'), 128.28 (C5''), 133.51 (C3'), 135.28 (C9'), 135.32 (C9''), 135.39 (C8), 145.10 (C13), 167.48 (C22), 171.23 (C21), 179.36 (C20). Analysis calculated for $C_{33}H_{46}N_2O_4$ (534.74): C 74.12, H 8.67, N 5.24; found: C 74.23; H 8.65; N 5.28.

Methyl N-{2-[(2,6-dimethylphenyl)amino]-2-oxoethyl}-N-(18-oxoabieta-7,13-dien-18-yl)phenylalaninate (6). Compound **6** was prepared according to GP by reaction of abietic acid **1** (0.30 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), *L*-phenylalanine methyl ester hydrochloride (0.26 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether / ethyl acetate, 5:1) afforded compound **4** (0.51 g, 82%) as a white solid; R_f = 0.60 (petroleum ether / ethyl acetate, 1:1); mp = 118–120 °C; $[\alpha]_D$ = -27° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.92 (s, 3H, H-18), 1.06 (d, ^2J = 6.8 Hz, 3H, H-15), 1.07 (d, ^2J = 6.8 Hz, 3H, H-16), 1.12-1.31 (m, 4H, H-1, H-3), 1.43 (s, 3H, H-19), 1.55-2.12 (m, 9H, H-2, H-5, H-6, H-11, H-12), 2.19 (s, 6H, H-12', H-12''), 2.24-2.32 (m, 2H, H-9, H-14), 3.44-3.48 (m, 2H, H-2'), 3.74-3.76 (m, 1H, H-1'), 3.84 (s, 3H, H-23), 4.42-4.46 (m, 2H, H-

7’), 5.45 (br. s., 1H, H-7),), 5.85 (br. s., 1H, H-17), 7.06-7.31 (m, 8H, H-4’, H-4’’, H-5’, H-5’’, H-6’, H-10’, H-10’’, H-11’), 9.65 (br. s., 1H, NH); δ_C (125.76 MHz, $CDCl_3$) 14.46 (C18), 18.14 (C2), 18.79 (C12’, C12’’), 21.03 (C19), 21.55 (C15, C16), 22.51 (C11), 25.91 (C6), 27.45 (C12), 34.81 (C2’), 34.91 (C14),–36.41 (C3), 37.65 (C1), 46.35 (C4), 51.53 (C9), 53.17 (C5, C23), 53.52 (C10), 55.53 (C7’), 67.74 (C1’), 120.57 (C7), 122.46 (C17), 127.26 (C11’), 127.40 (C6’), 128.41 (C5’, C5’’), 129.05 (C10’, C10’’), 129.34 (C4’, C4’’), 133.63 (C8’), 135.10 (C9’, C9’’), 135.82 (C8), 137.29 (C3’), 145.14 (C13), 167.25 (C22), 172.41 (C21), 178.07 (C20). Analysis calculated for $C_{40}H_{52}N_2O_4$ (624.87): C 76.89, H 8.39, N 4.48; found: C 76.83; H 8.35; N 4.50.

Methyl N-{2-[(2,6-dimethylphenyl)amino]-2-oxoethyl}-N-(18-oxoabieta-7,13-dien-18-yl)tyrosinate (7). Compound **7** was prepared according to GP by reaction of abietic acid **1** (0.30 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), *L*-tyrosine methyl ester hydrochloride (0.28 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether / ethyl acetate, 5:1) afforded compound **7** (0.51 g, 80%) as a white solid; R_f = 0.60 (petroleum ether / ethyl acetate, 1:1); mp = 133–135 °C; $[\alpha]_D$ = - 69° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.92 (s, 3H, H-18), 1.06 (d, ^2J = 6.8 Hz, 3H, H-15),–1.07 (d, ^2J = 6.8 Hz, 3H, H-16), 1.12-1.31 (m, 4H, H-1, H-3), 1.45 (s, 3H, H-19), 1.59-2.10 (m, 9H, H-2, H-5, H-6, H-11, H-12), 2.15 (s, 6H, H-12’, H-12’’), 2.24-2.40 (m, 2H, H-9, H-14), 3.38-3.42 (m, 2H, H-2'), 3.67-3.73 (m, 1H, H-1’), 3.82 (s, 3H, H-23), 4.43-4.47 (m, 2H, H-7’), 5.41 (br. s., 1H, H-7), 5.82 (br. s., 1H, H-17), 6.64-7.28 (m, 7H, H-4’, H-4’’, H-5’, H-5’’, H-10’, H-10’’, H-11’), 9.74 (br. s., 2H, OH, NH); δ_C (125.76 MHz, $CDCl_3$) 14.21 (C18), 18.17 (C2), 18.78 (C12’, C12’’), 20.99 (C19), 21.48 (C15), 21.52 (C16), 22.52 (C11), 25.85 (C6), 27.42 (C12), 33.49 (C14), 34.83 (C2’), 34.91 (C3), 36.89 (C1), 37.67 (C4), 45.21 (C9), 46.24 (C10), 51.46 (C5, C23), 53.13 (C7’), 60.61 (C1’), 116.01 (C5’, C5’’), 120.60 (C7), 122.52 (C17), 127.56 (C11’), 127.98 (C3’), 128.47 (C10’, C10’’), 130.24 (C4’, C4’’), 133.42 (C8’), 135.08 (C8), 135.69 (C9’, C9’’), 145.04 (C13), 155.76 (C6’), 168.15 (C22), 172.67 (C21), 178.31 (C20). Analysis calculated for $C_{40}H_{52}N_2O_5$ (640.87): C 74.97, H 8.18, N 4.37; found: C 74.95; H 8.15; N 4.38.

N-butyl-N-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)-13-isopropyl-7,10a-dimethyl-1,4-dioxo-2,3,4,4a,5,6,6a,7,8,9,10,10a,10b,11,12,12a-hexadecahydro-1H-4b,12-ethenochrysene-7-carboxamide (8). Compound **8** was prepared according to GP by reaction of dihydroquinopimaric acid **2** (0.41 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), butylamine (0.09 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether / ethyl acetate, 5:1) afforded compound **8** (0.47 g, 75%) as a colorless solid; R_f = 0.40 (petroleum ether / ethyl acetate, 1:1); mp = 107–109 °C; $[\alpha]_D$ = - 19° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.66 (s, 3H, H-18), 0.85-0.98 (m, 2H,

H-6), 0.94 (d, ^2J = 6.9 Hz, 3H, H-16), 0.97 (d, ^2J = 6.8 Hz, 3H, H-17), 1.01 (s, 3H, H-4'), 1.26 (s, 3H, H-19), 1.18-1.69 (m, 16H, H-5, H-6b, H-8, H-9, H-10, H-10b, H-11, H-2', H-3'), 2.18 (s, 6H, H-10', H-10''), 2.39 (t, ^2J 6.2 Hz, 1H,H-15), 2.40-2.58 (m, 4H, H-2, H-3), 2.85 (br. s, 1H, H-12), 3.22 (d, ^2J 2.24 Hz, 1H, H-1a), 3.07-3.11 (m, 1H, H4a), 3.55-3.58 (m, 2H, H-1'), 4.06-4.20 (s, 2H, H-5'), 5.54 (br. s., 1H, H-14), 7.03 (br. s., 3H, H-8', H-8'', H-9'), 8.25 (br. s., 1H, NH); δ_C (125.76 MHz, $CDCl_3$) 13.85 (C4'), 14.07 (C17), 15.91 (C16), 17.25 (C18), 18.55 (C12', C12''), 18.91 (C9), 19.56 (C6), 20.18 (C3'), 20.57 (C19), 21.44 (C2'), 29.49 (C11), 32.12 (C15), 35.87 (C5), 38.04 (C8), 40.82 (C4b), 44.61 (C10), 46.73 (C10a), 47.24 (C12), 49.65 (C7), 50.94 (C1'), 53.89 (C5'), 54.58 (C6b), 56.46 (C10b), 58.94 (C1a), 61.21 (C2), 67.67 (C3), 70.47 (C4a), 125.65 (C14), 125.75 (C9'), 127.15 (C7', C7''), 133.75 (C8', C8''), 135.19 (C6'), 149.55 (C13), 168.83 (C21), 180.02 (C20), 205.64 (C4), 212.96 (C1). Analysis calculated for $C_{40}H_{56}N_2O_4$ (628.90): C 76.39, H 8.98, N 4.45; found: C 76.33; H 8.96; N 4.45.

Methyl N-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)-N-13-isopropyl-7,10a-dimethyl-1,4-dioxo-2,3,4,4a,5,6,6a,7,8,9,10,10a,10b,11,12,12a-hexadecahydro-1H-4b,12-ethenochrysene-7-carbonyl)glycinate (9). Compound **9** was prepared according to GP by reaction of dihydroquinopimaric acid **2** (0.41 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), glycine methyl ester hydrochloride (0.15 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether / ethyl acetate, 5:1) afforded compound **9** (0.51 g, 79%) as a colorless solid; R_f = 0.40 (petroleum ether / ethyl acetate, 1:1); mp = 170–172 °C; $[\alpha]_D$ = + 59° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.56 (s, 3H, H-18), 0.85-0.98 (m, 2H, H-6), 0.94 (d, ^2J = 6.9 Hz, 3H, H-16), 0.97 (d, ^2J = 6.8 Hz, 3H, H-17), 1.26 (s, 3H, H-19), 1.18-1.69 (m, 12H, H-5, H-6b, H-8, H-9, H-10, H-10b, H-11), 2.19 (s, 6H, H-12', H-12''), 2.39 (t, ^2J 6.2 Hz, 1H, H-15), 2.40-2.58 (m, 4H, H-2, H-3), 2.85 (br. s, 1H, H-12), 3.22 (d, ^2J 2.24 Hz, 1H, H-1a), 3.07-3.11 (m, 1H, H4a), 3.74-3.79 (m, 2H, H-1'); 3.81 (s, 3H, H-23), 4.16-4.20 (m, 2H, H-2'), 5.56 (br. s., 1H, H-14), 7.07-7.11 (m, 3H, H-5', H-5'', H-6'), 8.75 (br. s., 1H, NH); δ_C (125.76 MHz, $CDCl_3$) 14.07 (C17), 15.91 (C16), 17.25 (C18), 18.56 (C12', C12''), 18.91 (C9), 19.56 (C6), 20.57 (C19), 29.49 (C11), 32.12 (C15), 35.87 (C5), 38.04 (C8), 40.82 (C4b), 44.66 (C10), 46.54 (C1'), 46.73 (C10a), 47.30 (C12), 49.81 (C7), 54.58 (C6b), 54.91 (C23), 55.29 (C2'),–56.46 (C10b), 58.94 (C1a), 59.02 (C2), 60.60 (C3), 66.39 (C4a), 125.61 (C14), 127.49 (C6'), 128.36 (C5', C5''), 133.46 (C3'), 135.24 (C9', C9''), 149.57 (C13), 167.24 (C22), 170.65 (C21), 179.51 (C20), 208.91 (C4), 209.82 (C1). Analysis calculated for $C_{39}H_{52}N_2O_6$ (644.85): C 72.64, H 8.13, N 4.34; found: C 72.61; H 8.15; N 4.35.

Methyl N-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)-N-(13-isopropyl-7,10a-dimethyl-1,4-dioxo-2,3,4,4a,5,6,6a,7,8,9,10,10a,10b,11,12,12a-hexadecahydro-1H-4b,12-ethenochrysene-

7-carbonyl)phenylalaninate (10). Compound **10** was prepared according to GP by reaction of dihydroquinopimaric acid **2** (0.41 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), *L*-phenylalanine methyl ester hydrochloride (0.26 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether / ethyl acetate, 3:1) afforded compound **10** (0.59 g, 80%) as a colorless solid; R_f = 0.40 (petroleum ether / ethyl acetate, 1:1); mp = 101–103 °C; $[\alpha]_D$ = - 23° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.55 (s, 3H, H-18), 0.81-0.98 (m, 2H, H-6), 0.95 (d, ^2J = 6.9 Hz, 3H, H-16), 0.97 (d, ^2J = 6.8 Hz, 3H, H-17), 1.20 (s, 3H, H-19), 1.10-1.69 (m, 12H, H-5, H-6b, H-8, H-9, H-10, H-10b, H-11), 2.17 (s, 3H, H-12'), 2.23 (s, 3H, H-12''), 2.39-2.58 (m, 5H, H-2, H-3, H-15), 2.80 (br. s, 1H, H-12), 3.07-3.11 (m, 1H, H4a), 3.20 (d, ^2J 2.24 Hz, 1H, H-1a), 3.44-3.48 (m, 2H, H-2'), 3.51-3.53 (m, 1H, H-1'), 3.82 (s, 3H, H-23), 4.38-4.46 (m, 2H, H-7'), 5.53 (br. s., 1H, H-14), 7.01-7.28 (m, 8H, H-4', H-4'', H-5', H-5'', H-6', H-10', H-10'', H-11'), 9.41 (br. s., 1H, NH). δ_C (125.76 MHz, $CDCl_3$) 14.08 (C17), 16.79 (C12', C12''), 16.83 (C16), 17.25 (C18), 17.91 (C9), 19.91 (C6), 20.78 (C19), 21.79 (C11), 27.79 (C15), 32.89 (C2'), 34.69 (C5), 36.65 (C8), 37.71 (C4b), 37.87 (C10), 38.29 (C10a), 38.48 (C12), 38.93 (C7), 38.96 (C6b), 41.27 (C10b), 46.75 (C1a), 49.09 (C2), 53.52 (C23), 54.88 (C3), 55.91 (C4a, C7'), 60.46 (C1'), 125.48 (C14), 127.46 (C11'), 127.60 (C6'), 128.12 (C5', C5''), 128.41 (C10', C10''), 129.03 (C4', C4''), 129.29 (C8'), 135.07 (C9', C9''), 135.21 (C3'), 149.48 (C13), 160.11 (C22), 166.31 (C21), 183.87 (C20), 209.03 (C4), 210.22 (C1). Analysis calculated for $C_{46}H_{58}N_2O_6$ (734.98): C 75.17, H 7.95, N 3.81; found: C 75.20; H 7.95; N 3.28.

Methyl N-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)-N-(13-isopropyl-7,10a-dimethyl-1,4-dioxo-2,3,4,4a,5,6,6a,7,8,9,10,10a,10b,11,12,12a-hexadecahydro-1H-4b,12-ethenochrysene-7-carbonyl)tyrosinate (11). Compound **11** was prepared according to GP by reaction of dihydroquinopimaric acid **2** (0.41 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), *L*-tyrosine methyl ester hydrochloride (0.28 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether / ethyl acetate, 2:1) afforded compound **11** (0.64 g, 85%) as a colorless solid; R_f = 0.40 (petroleum ether / ethyl acetate, 1:1); mp = 147–149 °C; $[\alpha]_D$ = - 18° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.59 (s, 3H, H-18), 0.81-0.98 (m, 2H, H-6), 0.95 (d, ^2J = 6.9 Hz, 3H, H-16), 0.97 (d, ^2J = 6.8 Hz, 3H, H-17), 1.23 (s, 3H, H-19), 1.18-1.69 (m, 12H, H-5, H-6b, H-8, H-9, H-10, H-10b, H-11), 2.19 (s, 6H, H-12', H-12''), 2.39-2.60 (m, 5H, H-2, H-3, H-15), 2.80 (d, ^2J 2.24 Hz, 1H, H-1a), 3.18-3.20 (m, 2H, H4a, H-12), 3.33-3.35 (m, 2H, H-2'), 3.65-3.74 (m, 1H, H-1'), 3.79 (s, 3H, H-23), 4.43-4.50 (m, 2H, H-7'), 5.53 (br. s., 1H, H-14), 6.75-6.77 (m, 2H, H-5', H-5''), 6.97-7.07 (m, 5H, H-4', H-4'', H-10', H-10'', H-11'), 9.69 (br. s., 2H, OH, NH); δ_C (125.76 MHz, $CDCl_3$) 16.11 (C17), 17.94 (C16), 17.97 (C18), 18.43 (C12', C12''), 18.75 (C9), 19.93 (C6), 20.78 (C19), 20.81 (C11),

21.87 (C15), 27.58 (C5), 32.89 (C8), 33.42 (C4b), 34.79 (C2'), 34.02 (C10), 37.30 (C10a), 38.51 (C12), 38.89 (C7), 41.32 (C6b), 41.37 (C10b), 46.60 (C1a), 49.34 (C2), 53.19 (C23), 54.97 (C3), 56.19 (C4a), 60.51 (C7'), 67.57 (C1'), 116.14 (C5', C5''), 125.64 (C14), 127.51 (C11'), 125.64 (C3'), 127.51 (C10'), 127.82 (C10''), 128.07 (C4'), 128.43 (C4''), 130.20 (C8'), 133.43 (C9'), 135.01 (C9''), 149.49 (C13), 155.81 (C6'), 167.77 (C22), 172.69 (C21), 178.48 (C20), 209.27 (C4), 210.59 (C1). Analysis calculated for $C_{46}H_{58}N_2O_7$ (750.98): C 73.57, H 7.79, N 3.73; found: C 73.55; H 7.80; N 3.75.

N-butyl-N-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)-12-isopropyl-6,9a-dimethyl-1,3-dioxo-3,3a,4,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-3b,11-ethenophenanthro[1,2-c]furan-6-carboxamide (12). Compound **12** was prepared according to GP by reaction of maleopimaric acid **3** (0.40 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), butylamine (0.09 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether / ethyl acetate, 5:1) afforded compound **12** (0.44 g, 72%) as a white solid; R_f = 0.50 (petroleum ether / ethyl acetate, 1:1); mp = 117–119 °C; $[\alpha]_D$ = - 48° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.59 (s, 3H, H-20), 0.65-0.90 (m, 3H, H-1_{ax}, H-2), 0.93 (d, ^2J = 6.9 Hz, 3H, H-18), 0.98 (d, ^2J = 7.0 Hz, 3H, H-19), 1.17 (s, 3H, H-21), 1.01 (s, 3H, H-4'), 1.20-1.81 (m, 15H, H-1_{eq}, H-3, H-5, H-6, H-7, H-9, H-11, H-2', H-3'), 2.03 (s, 6H, H-10', H-10''), 2.25 (d, ^2J = 8.4 Hz, 1H, H-17), 2.43 (dt, ^2J = 3.0, ^3J = 14.0 Hz, 1H, H-16), 2.69 (d, ^2J = 8.4 Hz, 1H, H-15), 3.08 (d, ^2J = 8.4 Hz, 1H, H-12), 3.59-3.63 (m, 2H, H-1'), 4.06-4.23 (s, 2H, H-5'), 5.53 (s, 1H, H-14), 7.06 (br. s., 3H, H-8', H-8'', H-9'), 8.22 (br. s., 1H, NH); δ_C (125.76 MHz, $CDCl_3$) 14.71 (C4'), 15.73 (C20), 16.74 (C21), 17.07 (C2), 18.55 (C12', C12''), 19.96 (C18), 20.14 (C3'), 20.56 (C19), 21.65 (C6), 22.09 (C2'), 27.11 (C11), 30.42 (C17), 32.75 (C7), 34.73 (C12), 35.65 (C3), 35.97 (C1), 36.75 (C10), 40.41 (C8), 45.65 (C15), 46.64 (C4), 49.03 (C5), 50.79 (C1'), 52.97 (C16), 53.60 (C9), 60.38 (C5'), 125.11 (C9'), 125.29 (C14), 127.23 (C7', C7''), 133.78 (C6'), 135.26 (C8', C8''), 148.08 (C13), 168.69 (C25), 171.00 (C24), 177.87 (C23), 179.78 (C22); Analysis calculated for $C_{38}H_{52}N_2O_5$ (616.84): C 73.99, H 8.50, N 4.54; found: C 74.00; H 8.52; N 4.51.

Methyl N-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)-N-(12-isopropyl-6,9a-dimethyl-1,3-dioxo-3,3a,4,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-3b,11-ethenophenanthro[1,2-c]furan-6-carbonyl)glycinate (13). Compound **13** was prepared according to GP by reaction of maleopimaric acid 3 (0.40 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), glycine methyl ester hydrochloride (0.15 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether / ethyl acetate, 5:1) afforded compound **13** (0.48 g, 76%) as a white solid; R_f = 0.50 (petroleum ether / ethyl acetate, 1:1); mp = 121–123 °C; $[\alpha]_D$ = -

15° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.69 (s, 3H, H-20), 0.75-0.90 (m, 3H, H-1_{ax}, H-2), 0.93 (d, ^2J = 6.9 Hz, 3H, H-18), 0.98 (d, ^2J = 7.0 Hz, 3H, H-19), 1.28 (s, 3H, H-21), 1.20-1.81 (m, 11H, H-1_{eq}, H-3, H-5, H-6, H-7, H-9, H-11), 1.97 (d, ^2J = 8.4 Hz, 1H, H-17), 2.18 (s, 6H, H-12', H-12''), 2.25 (dt, ^2J = 3.0, ^3J = 14.0 Hz, 1H, H-16), 2.47 (d, ^2J = 8.4 Hz, 1H, H-15), 2.72 (d, ^2J = 8.4 Hz, 1H, H-12), 3.06-3.09 (m, 2H, H-1'); 3.79 (s, 3H, H-26), 4.14-4.18 (m, 2H, H-2'), 5.53 (s, 1H, H-14), 7.05-7.11 (m, 3H, H-5', H-5'', H-6'), 8.62 (br. s., 1H, NH); δ_C (125.76 MHz, $CDCl_3$) 15.73 (C20), 16.74 (C21), 17.07 (C2), 19.81 (C12', C12''), 19.99 (C18), 20.61 (C19), 21.88 (C6), 27.07 (C11), 32.76 (C17), 34.70 (C7), 35.64 (C12), 36.52 (C3), 37.45 (C1), 37.97 (C10), 40.38 (C8), 45.67 (C15, C1'), 46.35 (C4), 9.89 (C5), 52.75 (C16), 53.03 (C9), 53.52 (C26), 55.01 (C2'),-125.29 (C6'), 127.49 (C14), 128.35 (C5', C5''), 133.47 (C3'), 135.26 (C9', C9''), 148.11 (C13), 167.18 (C27), 171.06 (C24), 171.23 (C25), 172.89 (C23), 179.59 (C22); Analysis calculated for $C_{37}H_{48}N_2O_7$ (632.80): C 70.23, H 7.65, N 4.43; found: C 70.20; H 7.66; N 4.45.

Methyl N-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)-N-(12-isopropyl-6,9a-dimethyl-1,3-dioxo-3,3a,4,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-3b,11-ethenophenanthro[1,2-c]furan-6-carbonyl)phenylalaninate (14). Compound **14** was prepared according to GP by reaction of maleopimaric acid **3** (0.40 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), *L*-phenylalanine methyl ester hydrochloride (0.26 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether / ethyl acetate, 3:1) afforded compound **14** (0.61 g, 85%) as a white solid; R_f = 0.50 (petroleum ether / ethyl acetate, 1:1); mp = 125–127 °C; $[\alpha]_D$ = - 28° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.59 (s, 3H, H-20), 0.65-0.90 (m, 3H, H-1_{ax}, H-2), 0.93 (d, ^2J = 6.9 Hz, 3H, H-18), 0.98 (d, ^2J = 7.0 Hz, 3H, H-19), 1.23 (s, 3H, H-21), 1.20-1.81 (m, 11H, H-1_{eq}, H-3, H-5, H-6, H-7, H-9, H-11), 2.23 (s, 6H, H-12', H-12''), 2.25 (d, ^2J = 8.4 Hz, 1H, H-17), 2.43 (dt, ^2J = 3.0, ^3J = 14.0 Hz, 1H, H-16), 2.69 (d, ^2J = 8.4 Hz, 1H, H-15), 3.08 (d, ^2J = 8.4 Hz, 1H, H-12), 3.05-3.09 (m, 2H, H-2'), 3.51-3.53 (m, 1H, H-1'), 3.85 (s, 3H, H-26), 4.38-4.46 (m, 2H, H-7'), 5.53 (s, 1H, H-14), 7.05-7.32 (m, 8H, H-4', H-4'', H-5', H-5'', H-6', H-10', H-10'', H-11'), 9.52 (br. s., 1H, NH); δ_C (125.76 MHz, $CDCl_3$) 15.73 (C20), 16.74 (C21), 16.80 (C12', C12''), 20.00 (C2), 20.62 (C18), 21.60 (C19), 21.81 (C6), 27.00 (C11), 27.16 (C17), 32.75 (C7), 32.77 (C2'), 34.77 (C12), 35.63 (C3), 36.43 (C1), 37.97 (C10), 40.43 (C8), 45.65 (C15), 46.70 (C4), 49.06 (C5), 49.61 (C16), 53.02 (C9), 53.21 (C26), 53.67 (C7'), 67.41 (C1'), 125.13 (C11'), 125.31 (C14), 127.46 (C6'), 128.19 (C5', C5''), 128.45 (C10', C10''), 129.35 (C8'), 129.03 (C4', C4''), 135.03 (C9', C9''), 137.13 (C3'), 148.11 (C13), 167.23 (C25), 171.14 (C24), 172.37 (C27), 172.84 (C23), 178.61 (C22); Analysis calculated for $C_{44}H_{54}N_2O_7$ (722.92): C 73.10, H 7.53, N 3.88; found: C 73.13; H 7.55; N 3.90.

Methyl N-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)-N-(12-isopropyl-6,9a-dimethyl-1,3-dioxo-3,3a,4,5,5a,6,7,8,9,9a,9b,10,11,11a-tetradecahydro-1H-3b,11-ethenophenanthro[1,2-c]furan-6-carbonyl)tyrosinate (15). Compound **15** was prepared according to GP by reaction of maleopimaric acid **3** (0.40 g, 1 mmol), (0.30 g, 1 mmol), paraformaldehyde (0.03 g, 1 mmol), *L*-tyrosine methyl ester hydrochloride (0.28 g, 1.2 mmol) and 2,6-dimethylphenylisocyanide (0.13 g, 1 mmol). Column chromatography (silica gel, petroleum ether /ethyl acetate, 2:1) afforded compound **15** (0.62 g, 84%) as a white solid; R_f = 0.50 (petroleum ether /ethyl acetate, 1:1); mp = 162–164 °C; $[\alpha]_D$ = - 64° (c = 0.001, $CHCl_3$); δ_H (500.13 MHz, $CDCl_3$) 0.59 (s, 3H, H-20), 0.65-0.90 (m, 3H, H-1_{ax}, H-2), 1.02 (d, ^2J = 6.9 Hz, 3H, H-18), 1.04 (d, ^2J = 7.0 Hz, 3H, H-19), 1.17 (s, 3H, H-21), 1.20-1.81 (m, 11H, H-1_{eq}, H-3, H-5, H-6, H-7, H-9, H-11), 2.18 (s, 6H, H-12', H-12''), 2.27 (d, ^2J = 8.4 Hz, 1H, H-17), 2.67 (dt, ^2J = 3.0, ^3J = 14.0 Hz, 1H, H-16), 2.69 (d, ^2J = 8.4 Hz, 1H, H-15), 3.08 (br.s., 1H, H-12), 3.30-3.38 (m, 2H, H-2'), 3.69-3.74 (m, 1H, H-1'), 3.84 (s, 3H, H-26), 4.43-4.50 (m, 2H, H-7'), 5.52 (s, 1H, H-14), 6.70-6.71 (m, 2H, H-5', H-5''), 6.98-7.12 (m, 5H, H-4', H-4'', H-10', H-10'', H-11'), 9.72 (br. s., 2H, OH, NH); δ_C (125.76 MHz, $CDCl_3$) 15.98 (C20), 16.75 (C21), 17.71 (C2), 18.77 (C12', C12''), 20.58 (C18), 20.61 (C19), 21.59 (C6), 21.78 (C11), 26.98 (C17), 32.77 (C7), 34.73 (C12), 34.75 (C2'), 35.62 (C3), 37.33 (C1), 37.93 (C10), 40.41 (C8), 45.67 (C15), 46.34 (C4), 49.51 (C5), 53.21 (C16), 53.27 (C26), 53.67 (C9), 55.51 (C7'), 67.44 (C1'), 116.00 (C5', C5''), 125.26 (C14), 127.60 (C11'), 127.91 (C3'), 128.49 (C8'), 128.66 (C10', C10''), 130.27 (C4', C4''), 133.32 (C9'), 135.63 (C9''), 148.16 (C13), 155.73 (C6'), 167.85 (C25), 171.30 (C27), 172.56 (C24), 172.90 (C23), 178.62 (C22); Analysis calculated for $C_{44}H_{54}N_2O_8$ (738.92): C 71.52, H 7.37, N 3.79; found: C 71.55; H 7.35; N 3.78.

Biological assays

Antiviral activity against influenza virus A

Viruses and cells

The A/Puerto Rico/8/34 (H1N1) influenza virus was obtained from the Smorodintsev Research Institute of Influenza viral collection. Being prepared to the experiments, virus was propagated in the allantoic cavities of 9–11 day old chicken embryos for 48 h at 36 °C. MDCK (Madin-Darby canine kidney) cells were obtained from Smorodintsev Research Institute of Influenza cell collection. 293T cell line was purchased from Stem Cell Bank, Chinese Academy of Sciences (China). Human ACE2-overexpressed baby hamster kidney cells (BHK-21-hACE2 cells) secrete Gaussia luciferase (Gluc) were provided by State Key Laboratory of Virology, Wuhan

University (China). 293T cells were cultured in DMEM (Gibco) supplemented with 10% fetal bovine serum (FBS) (Gibco) at 37°C with 5% CO_2. BHK-21-hACE2 cells were cultured in the above medium supplemented with 1 μg/mL puromycin (Beijing leagene biotech, Cat. CA0070) under the same conditions.

Virus inhibition assay

The compounds were dissolved in 0.1 mL DMSO to prepare stock solutions, and final solutions were prepared by adding MEM with 1 μg/mL trypsin. Compounds were incubated with MDCK cells for 1 h at 36°C. The cell culture was then infected with influenza virus A/Puerto Rico/8/34 (H1N1) (MOI 0.01) for 24 h at 36°C in the presence of 5% CO_2. A virus titer in the supernatant was determined by hemagglutination assay after cultivating of the virus in MDCK cells for 48 h at 36°C in the presence of 5% CO_2. Oseltamivir was used as a reference drug. For calculations, virus titer was expressed as per cent of the titer in control wells without compounds. The 50% inhibiting concentrations (IC_{50}) and the selectivity index (SI, the ratio of CC_{50} to IC_{50}) were calculated from the data obtained.

Cytotoxicity assay

The MTT-test and CCK-8-test was used to study the cytotoxicity of the compounds.

For CCK-8-test, cell-counting kit (cck-8, Topscience) containing a highly watersoluble tetrazolium salt (WST-8) [2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium, monosodium salt] was used to evaluate the vitality of BHK-21-ACE2. After seeding 96-well plates and culturing overnight, the BHK-21-ACE2 cells were incubated with twofold serial dilutions of compounds (final concentrations ranging from 0 to 200 μM and diluted with culture media) for 24 hs before being washed with PBS. Following incubation, 10 μl CCK-8 reagent was added to each well, followed by further incubation at 37°C for 1-4 hs. Absorbance values at 450 nm were measured using a microplate reader (TECAN, Spark®). GraphPad Prism 8 was used to determine the CC_{50} values.

For MTT-test, series of threefold dilutions of each compound in DMEM were prepared. MDCK cells were incubated for 48 hs at 36°C in 5% CO_2 in the presence of the dissolved substances. The cells were washed twice with phosphate-buffered saline (PBS), and a solution of 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide (0.5 μg/mL) in PBS was added to the wells. After 1 h incubation, the wells were washed and the formazan residue was dissolved in DMSO (0.1 mL per well). The optical density in the wells was then measured on a multifunctional reader at wavelength of 535 nm and plotted against the concentration of

compounds. The 50% cytotoxic concentration (CC_{50}) of each compound was calculated from the data obtained.

Time-of-addition experiments

Compounds were added at different time points before, after or simultaneously with the introduction of the virus. The time of addition of the compound was counted from point 0 - the time of entry of the virus into the cell. During the period (-1) - 0, the cells together with the virus were incubated at 4 ^{o}C. All other experiments were carried out at 37 ^{o}C. Virus was added to the cells at a time that was conventionally designated as point -1, after which the cells were kept for an hour at a temperature of 4^{o}C. Then, at point 0, the virus was unbound. The cells were transferred to a thermostat at 37 ^{o}C, where they were incubated for 10 hours. After this period, the medium was taken from each well and a series of ten-fold dilutions were made on a fresh cell culture and incubated for 3 days. For each compound, 2 repetitions were made by different operators. The virus titer was estimated by standart haemagglutination assay. The compounds were added at the following times relative to the addition of the virus: point -2 - the compound was introduced one hour before cell infection (prophylactic regimen). point 0 - at the moment of temperature change, point 1, 2, 4, 6, 24 - after 1, 2, 4, 6 and 24 hours after the temperature change, respectively. In the wells marked (-2) - (10), the compound was kept throughout the experiment, starting from point -2 and until the end of the experiment - 10 hours. No compound was added to the control wells; instead, a similar volume of medium was added.

Primary Screening against SARS-CoV-2 pseudovirus protocol

Pseudovirus propagation

293T cells were seeded at 30% density in 150 mm dish at 12-15 hs before transfection. Cells were then transfected with 225 µg of polyethylenimine (PEI) Max 40,000 (Polysciences) in complex with 15 µg of plasmid encoding a coronavirus spike protein, 15 µg of plasmid encoding murine leukemia virus (MLV) Gag and Pol proteins, and 45 µg of a pQCXIP based EGFP/Firefly luciferase reporter plasmid. 8 hs after transfection, cell culture medium was refreshed and changed to growth medium (Opti-MEM, Gibco). Cell culture supernatants were collected at 36-48 hs post transfection, spun down at 3,000 × g for 10 min, and filtered through 0.45 µm filter units to remove cell debris. Coronavirus spike pseudotyped viruses were then concentrated 10 times at 2,000 × g using 10 kDa Vivaspin® Turbo 15 (MWCO PES, VS15T02).

Anti-SARS-CoV-2 pseudovirus assay

For compounds screening, BHK-21-hACE2 cells (5×10^4/well) were seeded into 96-well white opaque plate (Corning) in DMEM with 10% FBS. After culturing 24 hs, cells in each well were added with 1 μL of compounds (dissolved in dimethyl sulfoxide at a stock concentration of 20 mM) with the final concentration of 20 μM, then infected with 10 μL of SARS-CoV-2 pseudovirus (10 × concentrated). 48 hs after infection, images of infected cells with EGFP expression were acquired with the Opera Phenix® Plus High Content Screening System and the values of EGFP (which reflect relative inhibition) were calculated with the same instrument.

For the determine of EC_{50}, BHK-21-hACE2 cells (5×10^4/well) were seeded into 96-well white opaque plate (Corning) in DMEM with 10% FBS. After culturing 24 hs, cells in each well were incubated with threefold serial dilutions of compounds (final concentrations ranging from 0 to 80 μM and diluted with culture media), then infected with 10 μL of SARS-CoV-2 pseudovirus (10 × concentrated, express Firefly luciferase). 48 hs after infection, Firefly luciferase expression were measured using a microplate reader (TECAN, Spark®). GraphPad Prism 8.0 was used to determine the EC_{50} values.

Luciferase luminescence flash assay.

For compounds screening, the cell viability of BHK-21-hACE2 cells after incubation with the tested compounds for 48 h was measured by Gaussia luciferase (Gluc) reporter assay to evaluate their cytotoxicity. To measure Gaussia luciferase expression secreted by cells (which reflect relative cell viability), 20 μL of cell culture supernatant of each well of 96-well plate and 100 μL of assay buffer containing 4 μM coelenterazine native (Biosynth Chemistry & Biology) were added to one well of a new 96-well white opaque assay plate (Corning), and measured with the Tristar 5 multimode microplate reader (Berthold Technologies) for 0.1 second/well.

To measure Firefly luciferase expression, the growth medium was carefully removed from 96-well plate, after a rinse with PBS, cells were lysed with 100 μL passive lysis and 20 μL of cell lysates transferred to a 96-well white opaque assay plate (Corning). Dispense 100 μL Luciferase assay buffer containing Firefly luciferase substrate and measure with the Tristar 5 multimode microplate reader (Berthold Technologies) for 10 second/well.

References

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^{1}H NMR and ^{13}C NMR spectra

Figure S1.Compound **4**.

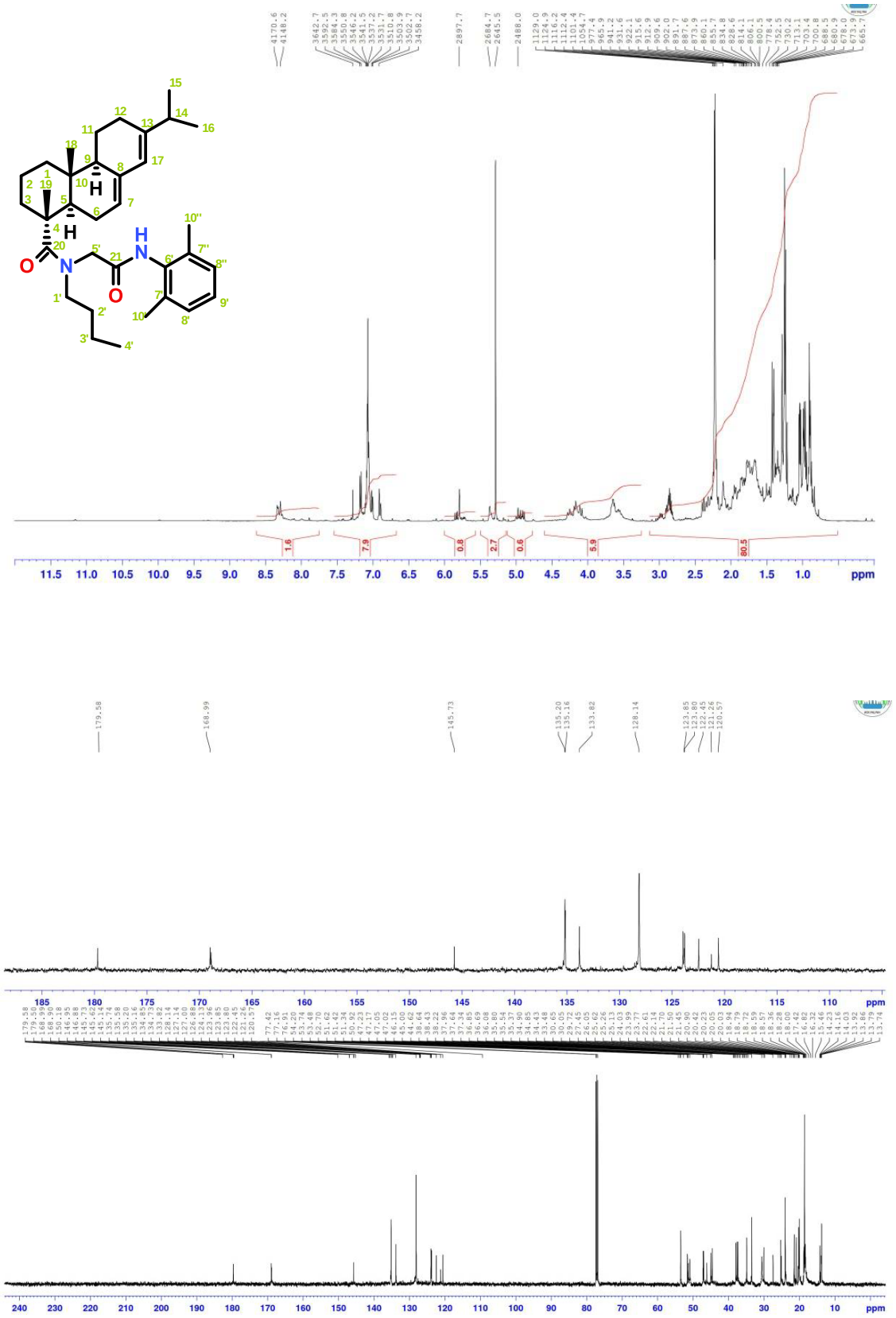

Figure S2.Compound **5**.

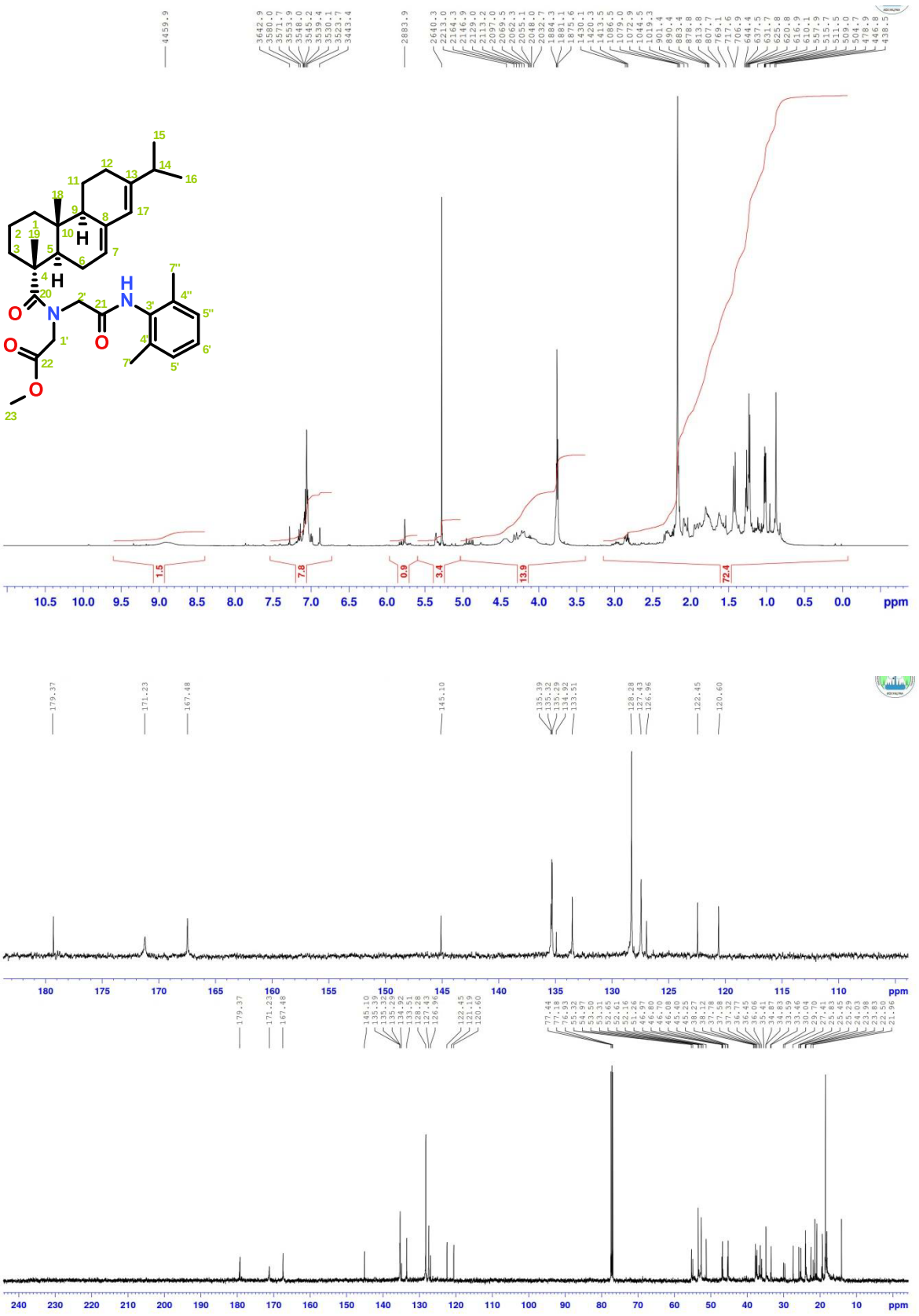

Figure S3.Compound **6**.

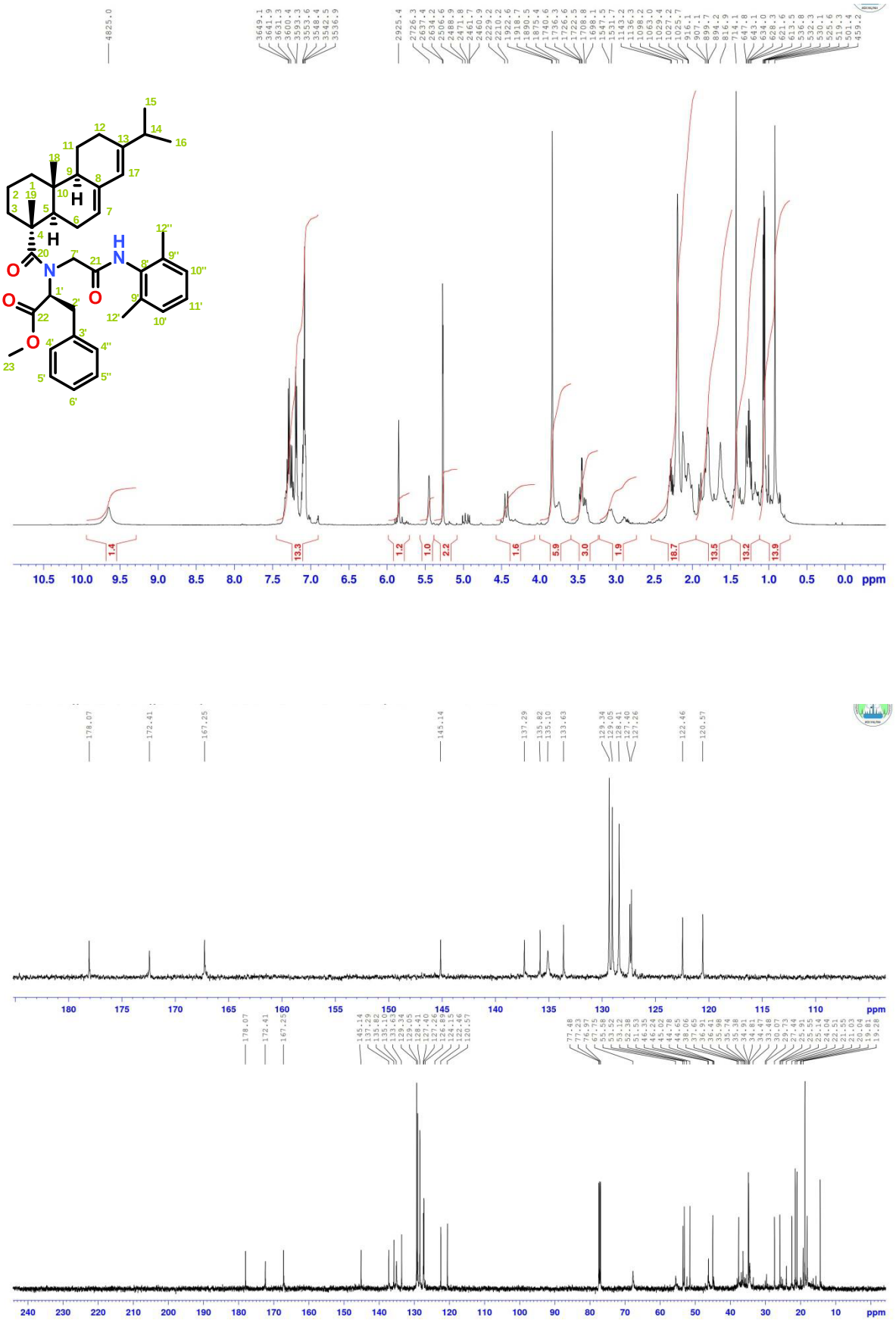

Figure S4.Compound **7**.

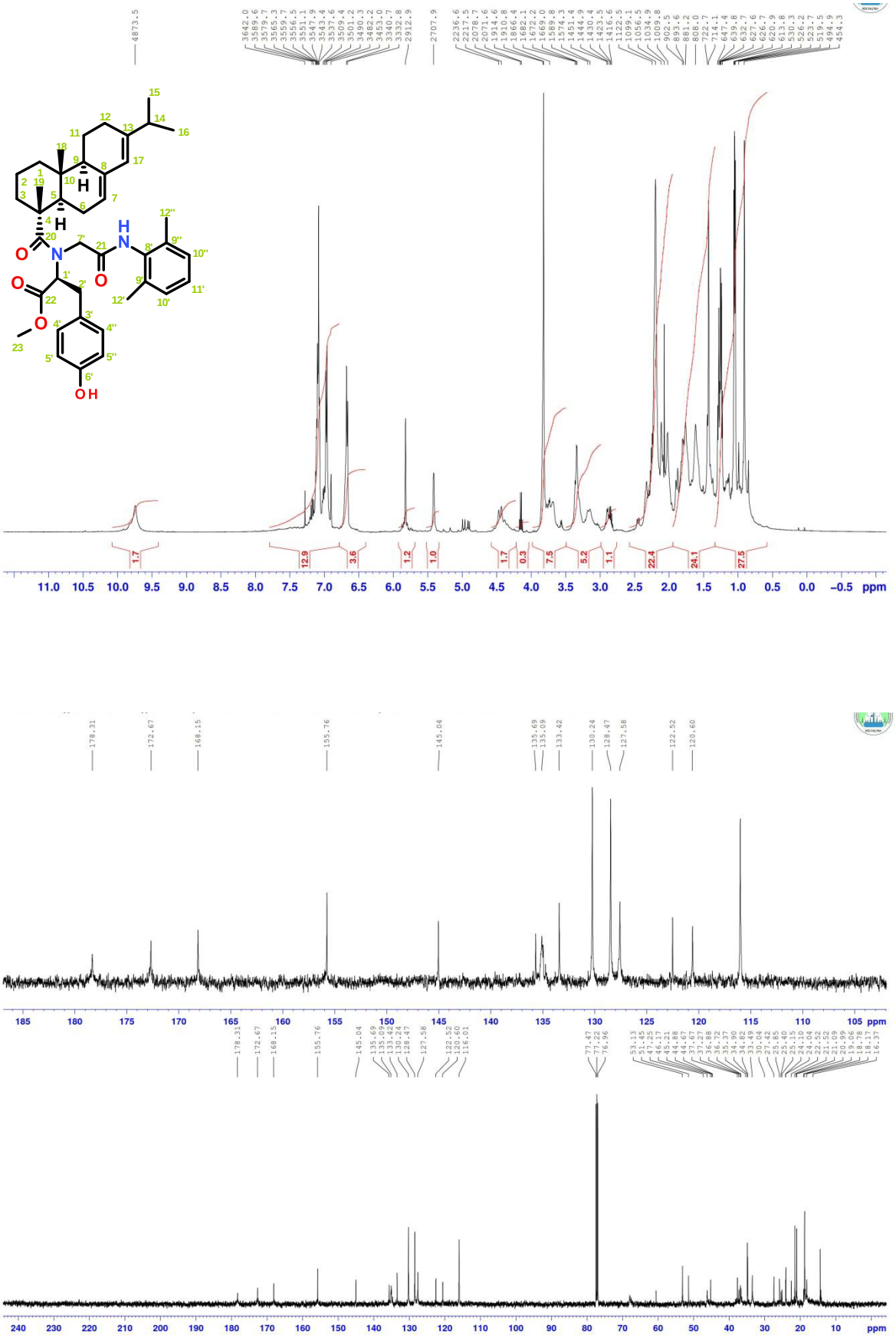

Figure S5.Compound **8**.

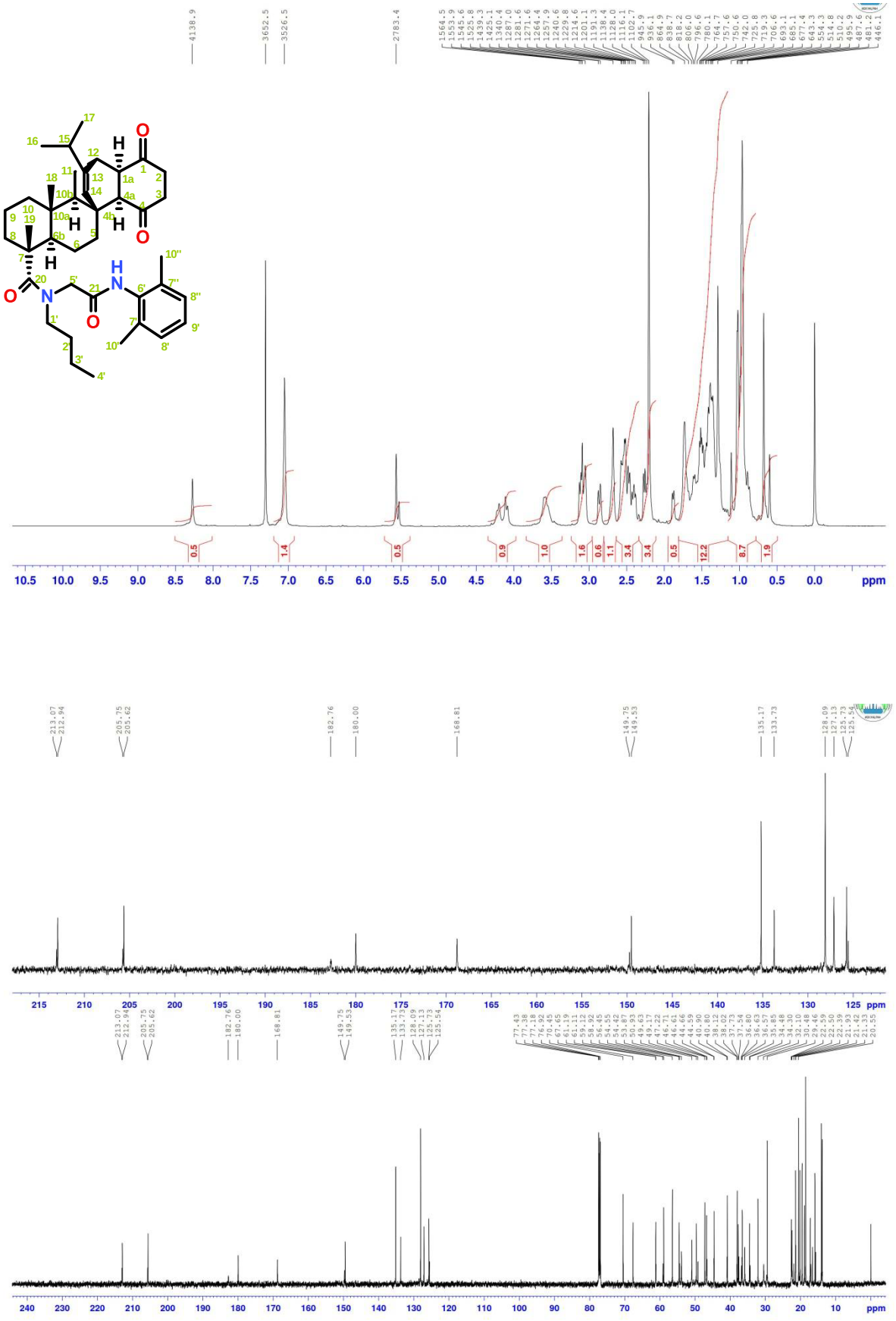

Figure S6.Compound **9**.

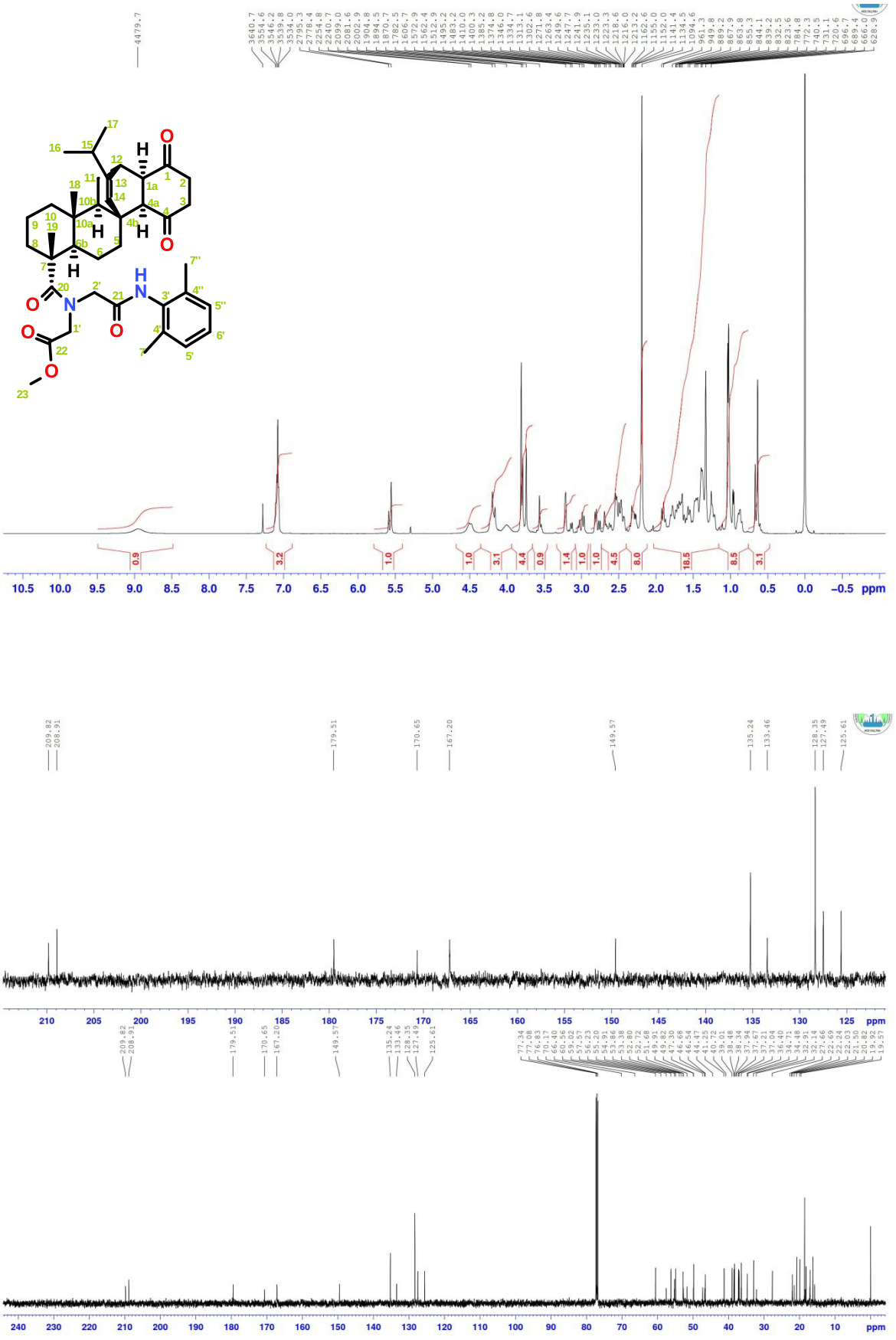

Figure S7. Compound **10**.

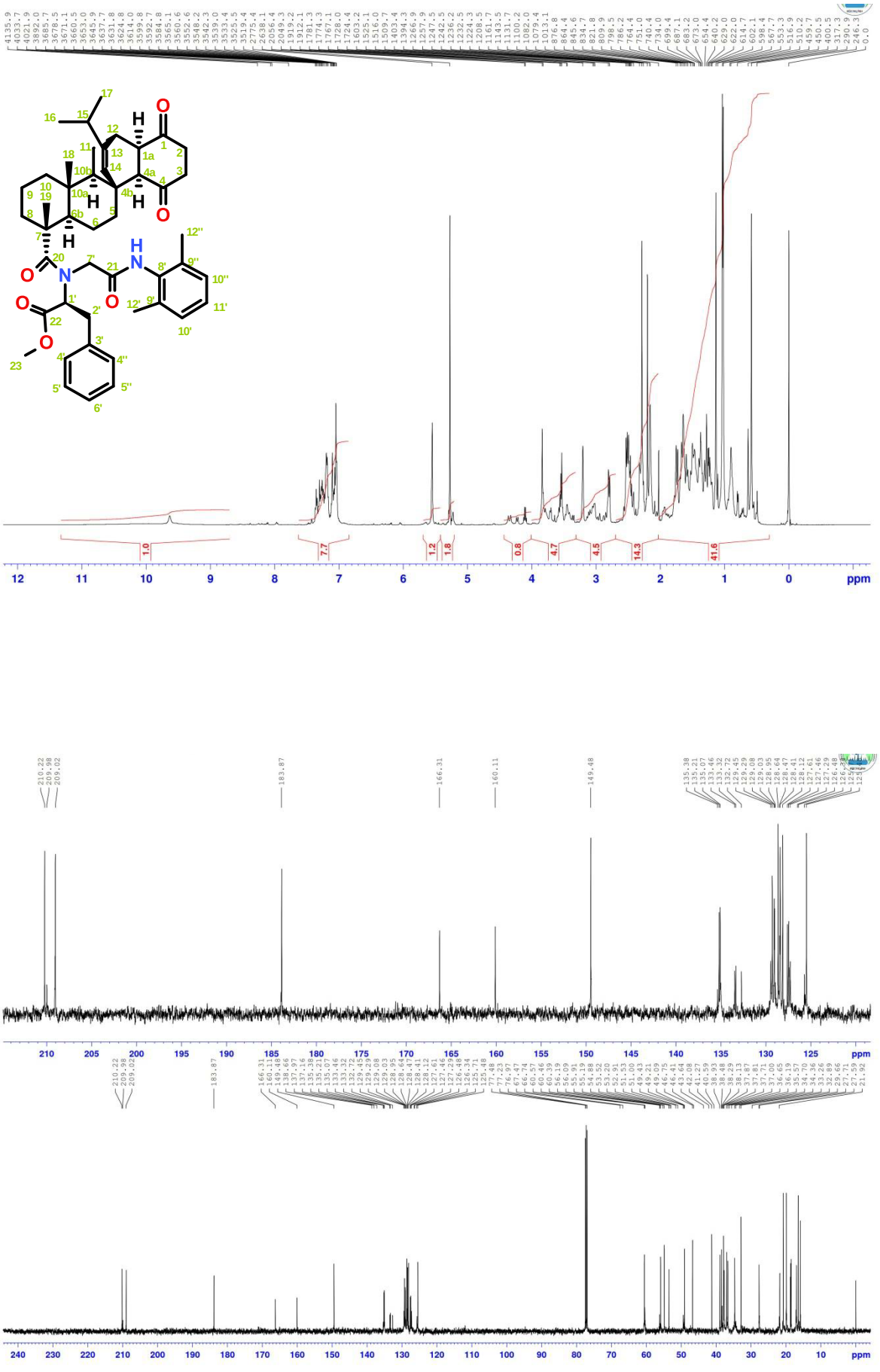

Figure S8. Compound **11**.

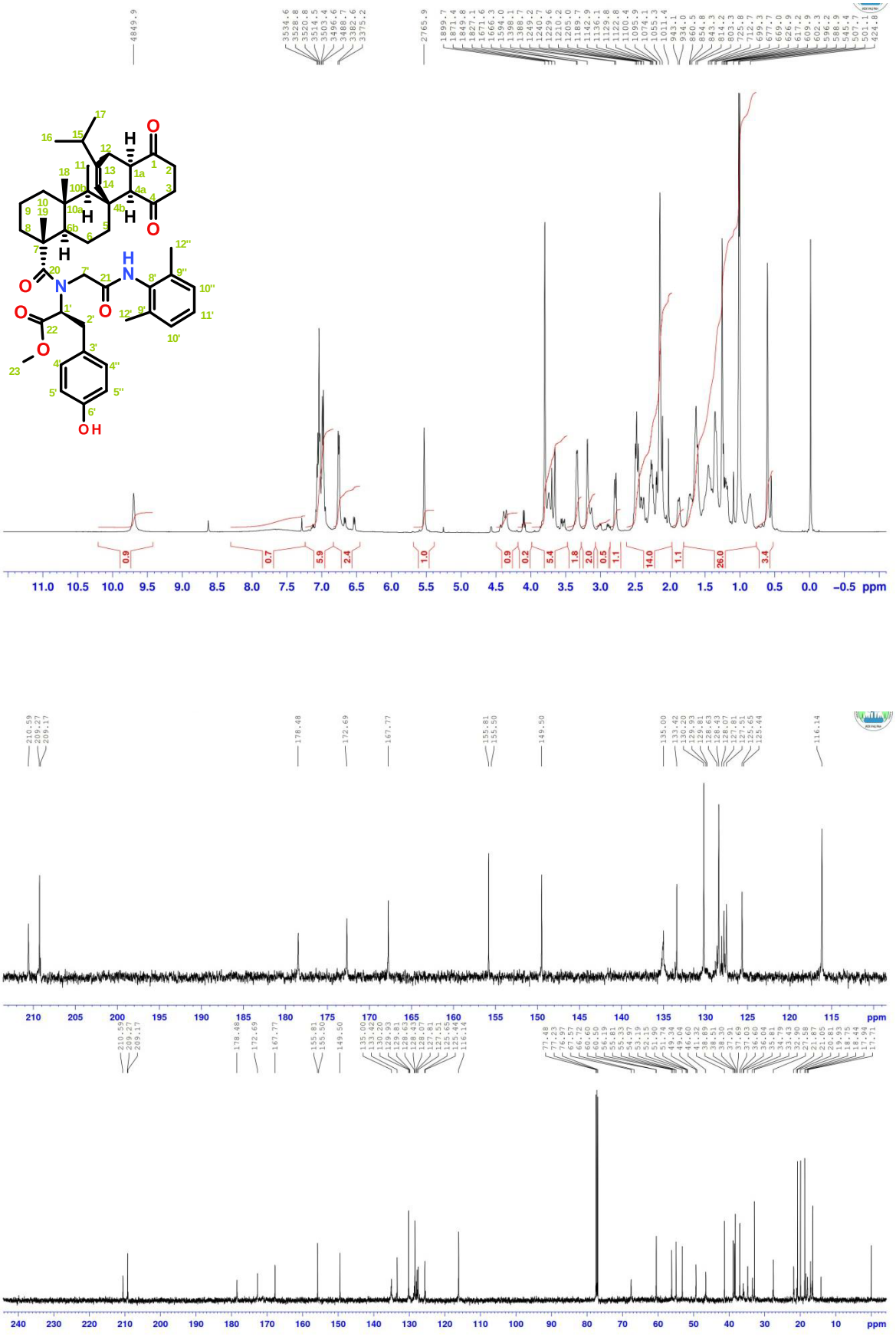

Figure S9. Compound **12**.

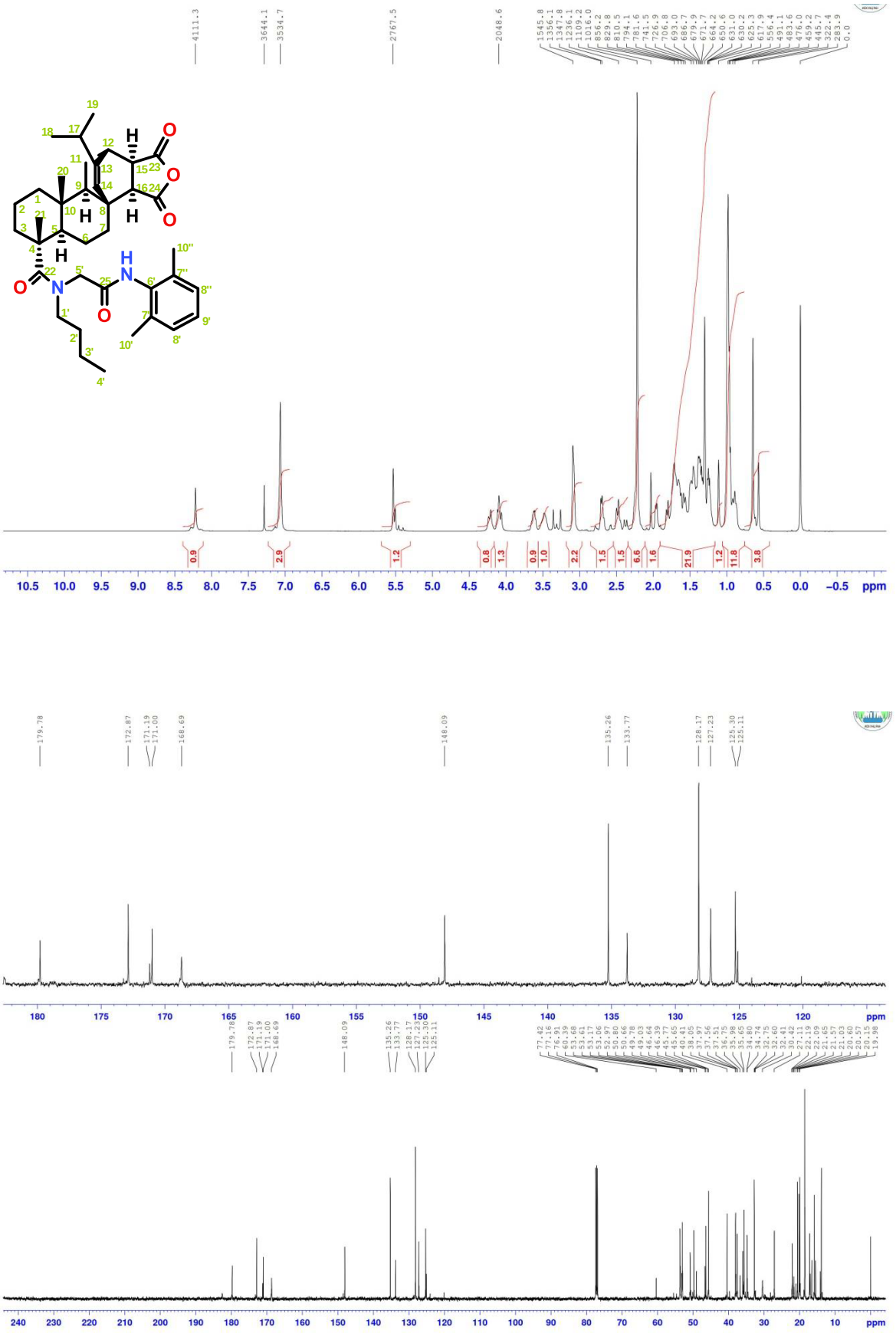

Figure S10. Compound **13**.

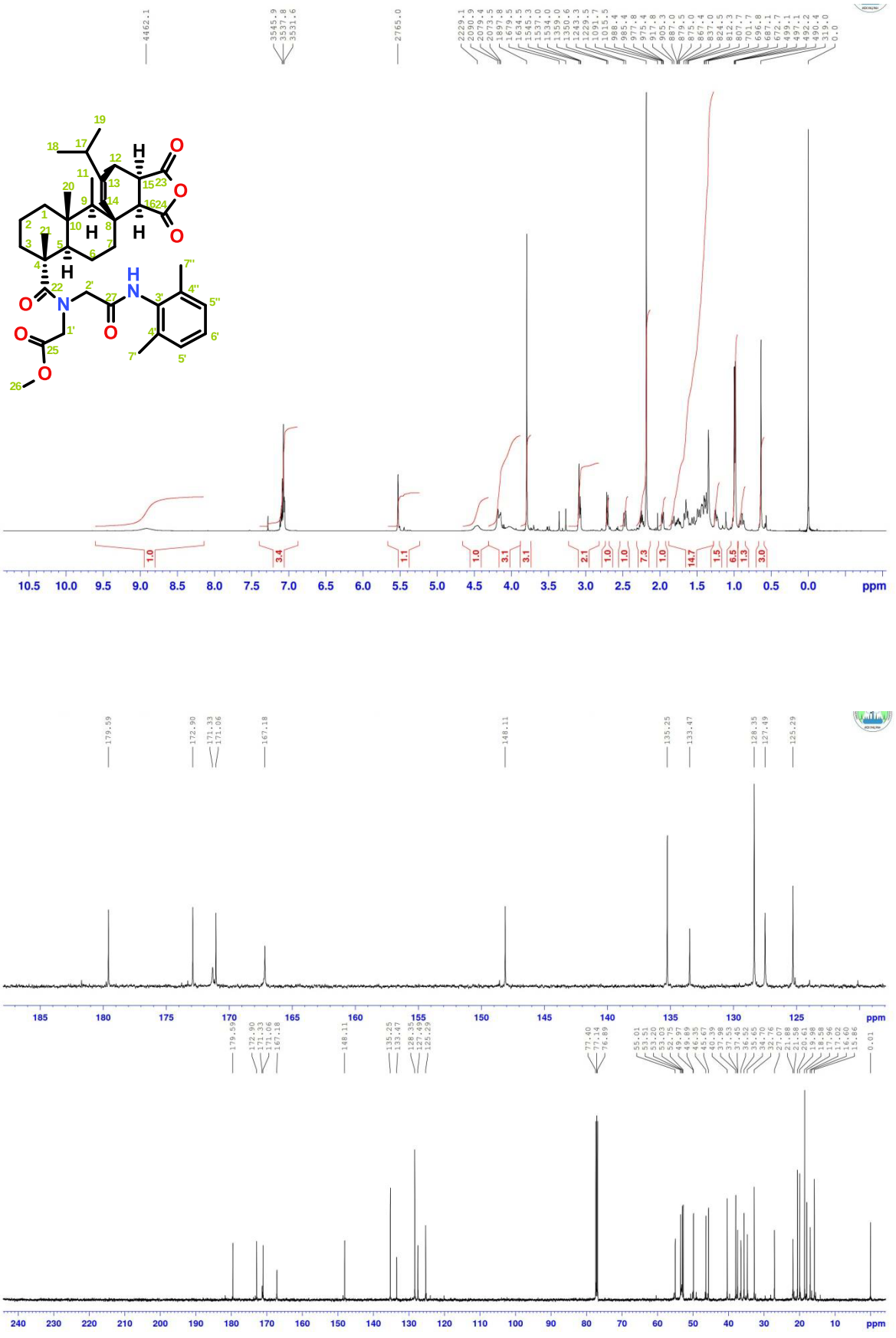

Figure S11. Compound **14**.

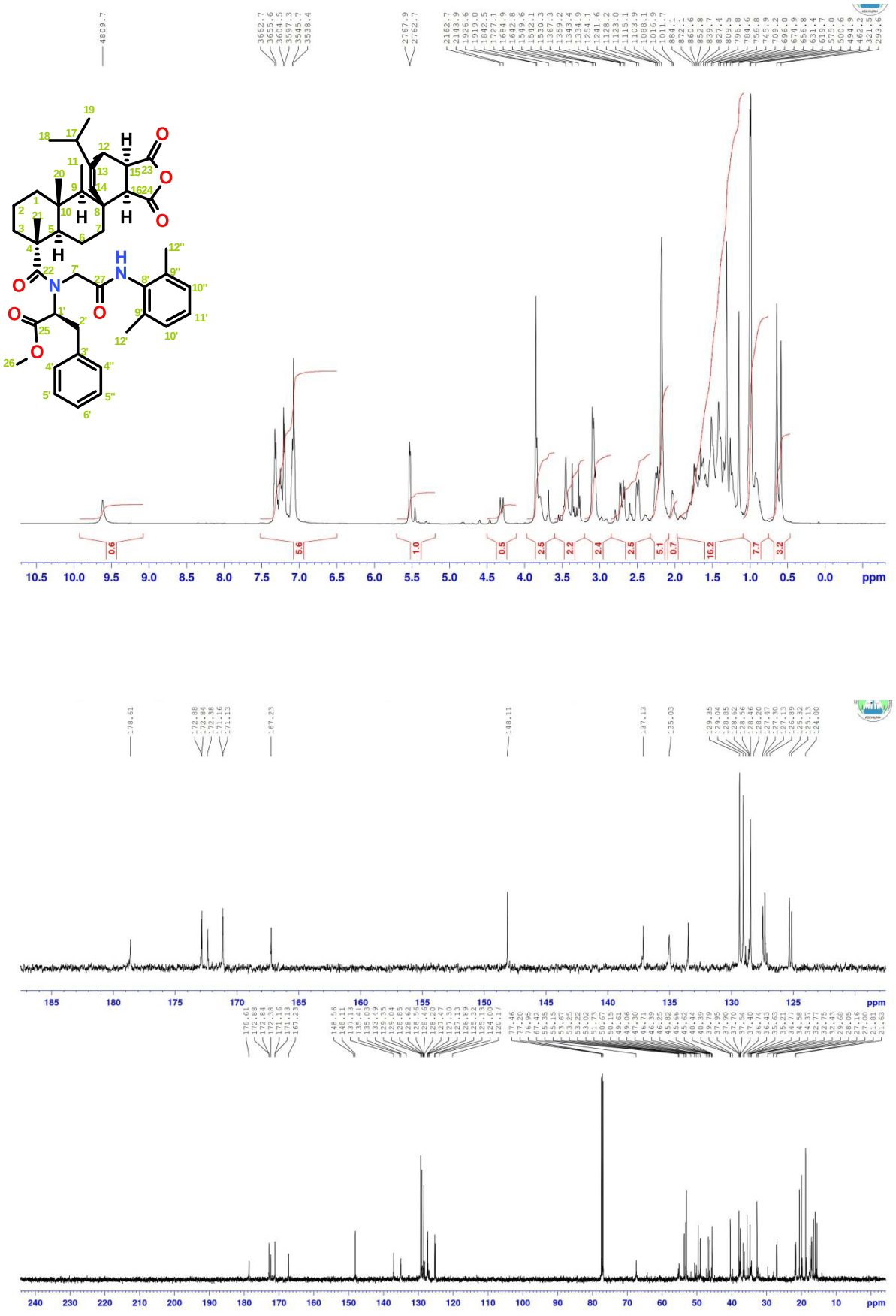

Figure S12. Compound **15**.

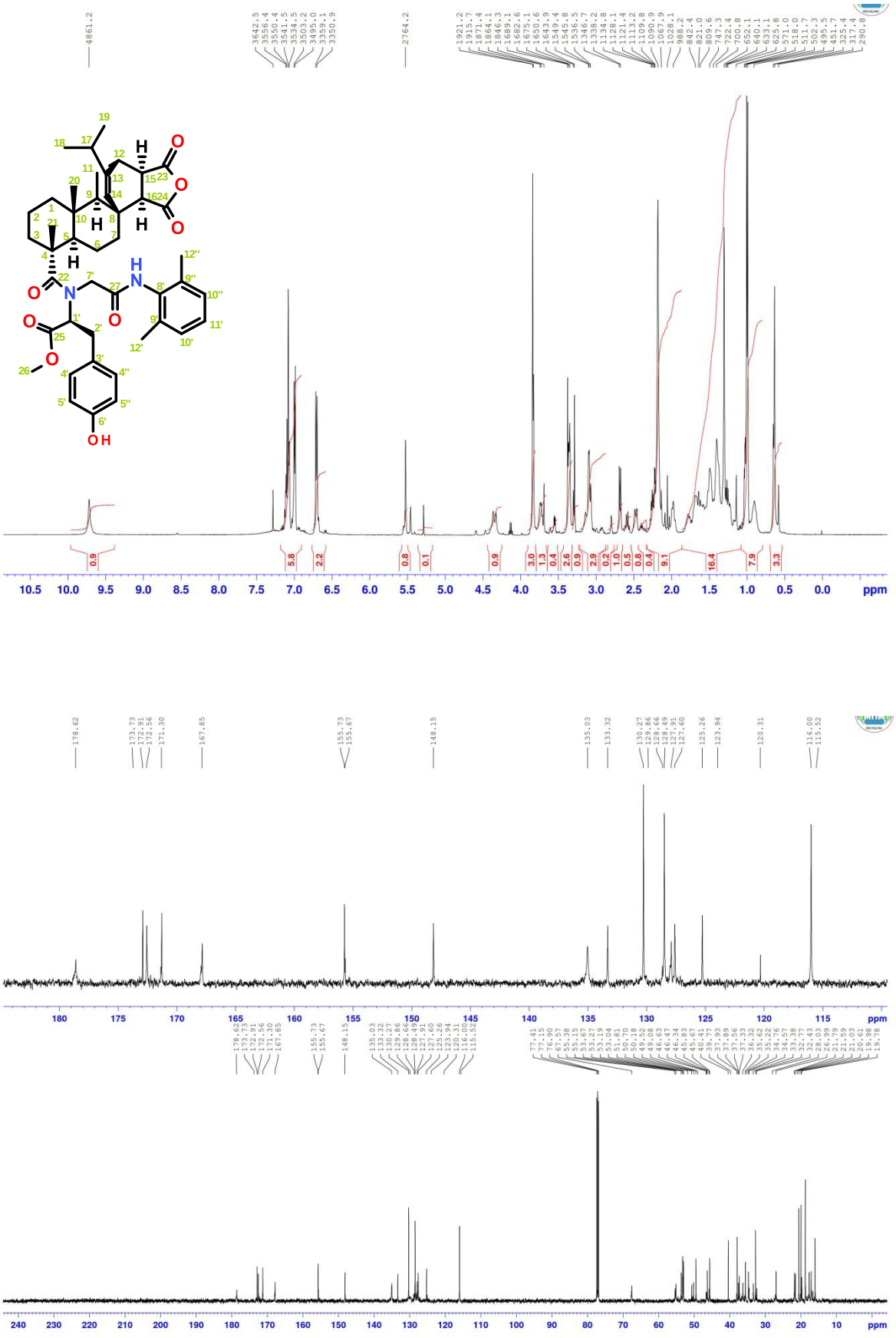

Figure S13. Results of time-of-addition experiments of compound **11**

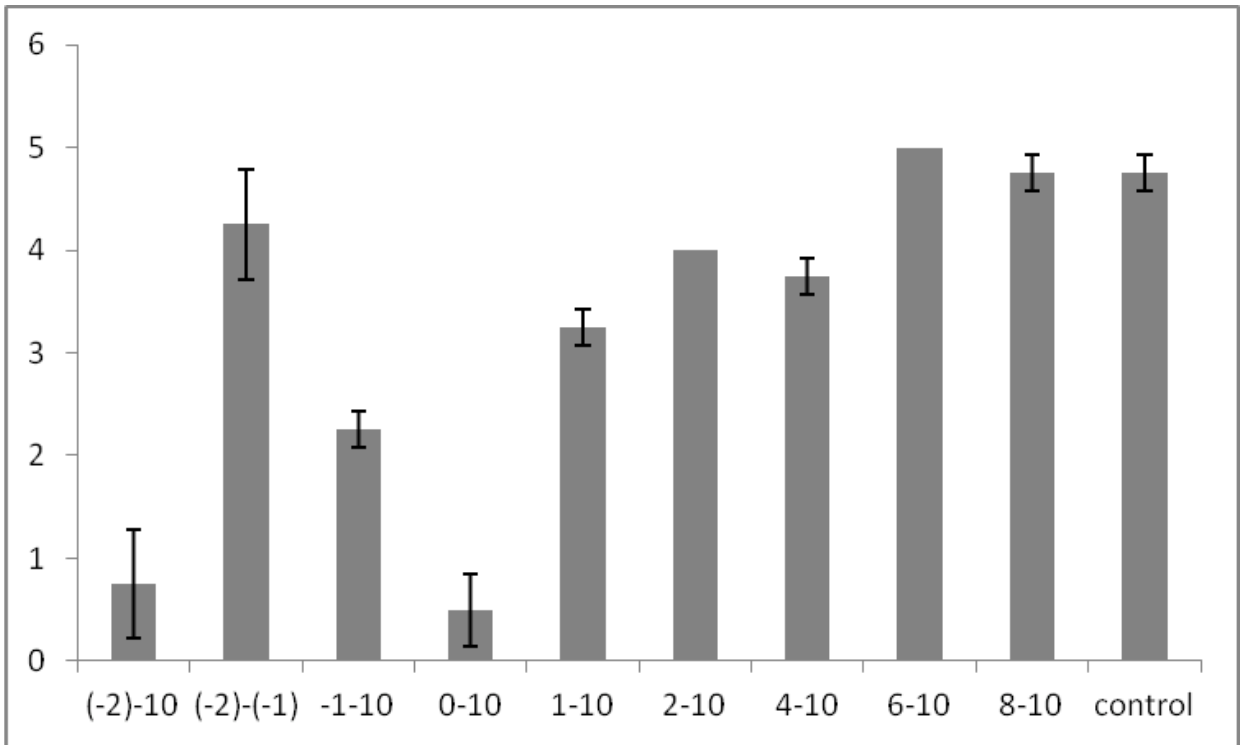

Figure S14. Cytotoxicity and antiviral activity of compound **7** against SARS-CoV-2 pseudovirus in BHK-21-hACE2 cells. (A): Antiviral activity of compound **7** against SARS-CoV-2 by Firefly luciferase assay. (B): Cytotoxicity of compound **7** in BHK-21-hACE2 cells was determined by CCK-8 Assay.