An Efficient Synthesis of Methyl 2-Cyano-3,12-dioxoursol-1,9-dien-28-oate (CDDU-Methyl Ester), Analogues, Biological Activities, and Comparison with Oleanolic Acid Derivatives

Liangfeng Fu, Qi-Xian Lin, Karen T. Liby,[§] Michael B. Sporn,*[,§] and Gordon W. Gribble*

Department of Chemistry, Dartmouth College, Hanover, NH 03755, United States

[§]Department of Pharmacology and Toxicology, Geisel School of Medicine, Hanover, NH 03755, United States

Organic and Biomolecular Chemistry

Supporting Information

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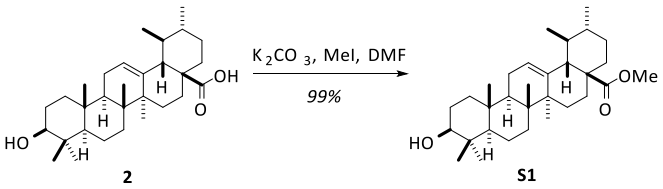
General Experimental Procedures. All reactions were performed in a single-neck, round-bottomed flask fitted with rubber septa under a positive pressure of nitrogen, unless otherwise noted. Organic solutions were concentrated by rotary evaporation below 30 ^{o}C. Flash-column chromatography was performed using silica gel (0.04-0.063 mm, 230-400 mesh ASTM) purchased from DAWN RUSSUP Macherey-Nagel INC. (Bethlehem, PA). Analytical thin-layered chromatography (TLC) was performed using glass backed TLC extra hard layer pre-coated with silica gel (0.25 mm, 60Å pore size) impregnated with a fluorescent indicator. TLC plates were visualized by exposure to ultraviolet light (UV) or/and submersion in PAA or CAM stains followed by brief heating on a hot plate (120 ^{o}C, 10-15 s).Commercial solvents and reagents were used as received. Iodoxybeozoic acid (IBX) was prepared according to the procedure of Frigerio, Santagostino, and Sputore.[1]

Instrumentation. Proton nuclear magnetic spectra (^{1}H NMR) were recorded at 500 MHz at 24 ^{o}C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, coupling constant in Hertz, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 500 MHz at 24 ^{o}C unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ 77.0). IR spectra were recorded on a Jasco FT-IR 4100 Series spectrophotometer, γ_{max} (cm^{-1}) are partially reported. High resolution mass spectra were acquired from the Mass Spectrometry Laboratory of the University of Illinois (Urbana-Champaign, IL).

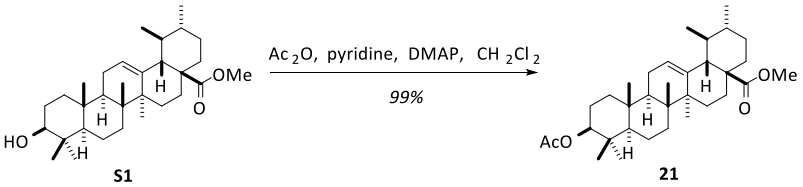
Biological Evaluation. ***NO Assay.*** RAW264.7 cells ($5x10^5$ cells per well) were plated in 96-well plates. The next day, cells were incubated with TP and 10 ng/ml IFNγ (R & D Systems) for 24 h. NO was measured as nitrite by the Griess reaction.

Synthetic Procedure.

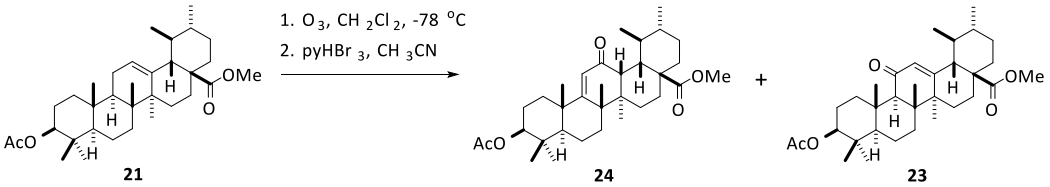


2 **S1**

To a stirred solution of oleanolic acid (**2**) (456 mg, 1.0 mmol, 1.0 equiv) in dimethyl formamide (5 mL) was added powdered potassium carbonate (414 mg, 3.0 mmol, 3.0 equiv) followed by slow addition of iodomethane (0.06 mL, 1.0 mmol, 1.0 equiv) at 0 ^{o}C. After completion of addition, the reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched by slow addition of water followed by extraction with ethyl acetate (5 x mL). The combined organic extracts were washed with water (4 x mL), brine (1 x mL), and dried over Na_2SO_4. Filtration followed by removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1) gave the desired product **S1** (469 mg, 99%) as a white solid.[2]

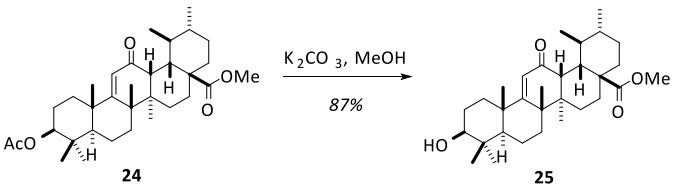


To a stirred solution of ester **S1** (469 mg, 1.0 mmol, 1.0 equiv) in methylene chloride (10 mL) at 0 ^{o}C was added pyridine (0.26 mL, 3.0 mmol, 3.0 equiv) and catalytic amount of dimethylaminopyridine, followed by slow addition of acetic anhydride (0.20 mL, 2.0 mmol, 2.0 equiv). The resulting mixture was allowed to stir at room temperature for 24 h. After the completion of reaction, it was diluted with methylene chloride (50 mL), washed with 1 N aqueous HCl (3 x 10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1) gave **21** (510 mg, 99%) as a white solid.[2]



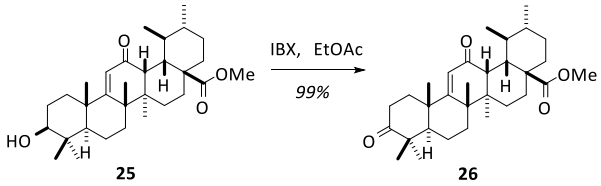
To a stirred solution of ester **21** (500 mg, 0.98 mmol, 1.0 equiv) in methylene chloride (10 mL) was subjected to ozonolysis at -78 ^{o}C. Upon completion of the reaction, it was allowed to slowly warm to room temperature and kept at room temperature for 3 h. The solvent was then removed to give crude inseparable reaction mixtures with the desired ketone **22** and **23** (~8:1). The crude mixture was dissolved in acetonitrile (10 mL) and pyridinium perbromide (416 mg, 1.30 mmol, 1.3 equiv) was added. The resulting mixture was then heated to 50 ^{o}C for 18 h. After the completion of reaction, it was allowed to cool to room temperature and quenched with 20% aqueous sodium thiosulfate (20 mL). It was then extracted with methylene chloride (3 x 20 mL), the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL), brine (20 mL), and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1 & 2:1) gave **23** (52 mg, 10%) and **24**[2] (365 mg, 71%) as white solids, respectively.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 4.47 (dd, 1H, J_1 = 11.7 Hz, J_2 = 4.6 Hz), 3.63 (s, 3H), 2.91 (dd, 1H, J_1= 11.5 Hz, J_2 = 3.2 Hz), 2.39 (d, 1H, J = 3.7 Hz), 2.04 (s, 3H), 1.87-2.00 (m, 2H), 1.72-1.80 (m, 4H), 1.36-1.70 (m, 10H), 1.14-1.29 (m, 2H), 1.21 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.83-0.90 (m, 1H), 0.87 (d, 3H, J = 5.6 Hz), 0.73 (d, 3H, J = 6.6 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 201.0, 179.3, 178.5, 171.1, 123.3, 80.0, 52.1, 51.2, 50.3, 50.2, 45.4, 42.4, 40.9, 40.1, 39.6, 38.9, 38.3, 37.0, 36.2, 33.0, 31.3, 28.4, 28.3, 24.6, 24.4, 24.1, 24.0, 21.5, 20.9, 19.9, 19.7, 17.7, 16.9; IR (solution, $CHCl_3$): 3019, 2366, 2340, 1717, 1652, 1558, 1540, 1520, 1507, 1456, 1217, 772, 669, 463; HRMS-ESI (calcd for $C_{33}H_{50}O_5$ $[M+H]^+$) 526.3658, found 526.3622.



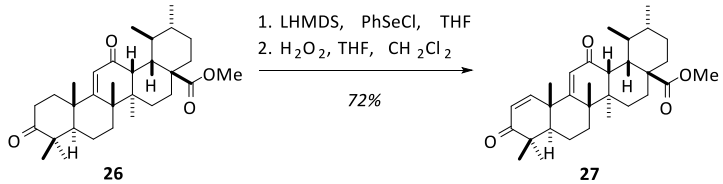
To a stirred solution of enone **24** (7.0 g, 13.3 mmol, 1.0 equiv) in methanol (100 mL) was added potassium carbonate (7.0 g, 40.0 mmol, 3.0 equiv). The reaction mixture was allowed stir at room temperature for 24 h. After completion of the reaction, it was quenched with water (200 mL) and extracted with methylene chloride (4 x 100 mL). The combined organic extracts were washed with brine (80 mL) and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (2:1) gave alcohol **25** (5.6 g, 87%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (s, 1H), 3.56 (s, 3H), 3.13 (dd, 1H, J_1 = 11.6 Hz, J_2 = 4.5 Hz), 2.83 (dd, 1H, J_1= 11.4 Hz, J_2 = 3.0 Hz), 2.32 (d, 1H, J = 3.8 Hz), 2.25 (brs, 1H), 1.78-1.91 (m, 2H), 1.37-1.72 (m, 12H), 1.24-1.35 (m, 2H), 1.03-1.20 (m, 2H), 1.09 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.95 (s, 3H), 0.79 (d, 3H, J = 6.1 Hz), 0.73 (s, 3H), 0.65 (d, 3H, J = 6.6 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 201.0, 179.9, 178.4, 123.0, 77.9, 52.0, 51.1, 50.1, 45.4, 42.3, 40.8, 40.2, 39.5, 39.4, 38.8, 36.9, 36.4, 33.0, 31.3, 28.4, 27.6, 24.5, 24.4, 23.9, 20.9, 19.9, 19.7, 18.0, 15.9; IR (solution, $CHCl_3$): 3019, 2410, 2360, 2340, 1716, 1652, 1558, 1539, 1520, 1507, 1217, 772, 669, 624, 432; HRMS-ESI (calcd for $C_{31}H_{49}O_4$ $[M+H]^+$) 485.3631, found 485.3633.



To a stirred solution of alcohol **25** (4.9 g, 10.1mmol, 1.0 equiv) in ethyl acetate (80 mL) was added iodoxybenzoic acid (3.7 mg, 13.1 mmol, 1.3 equiv) in one portion. The resulting suspension was heated to reflux for 24 h. After completion of the reaction, it was cooled in ice bath and was then filtered through Celite. The resulting filtrate was concentrated and flash column chromatography over silica gel using hexanes:EtOAc (2:1) gave ketone **26** (4.8 g, 99%) as a yellowish solid.

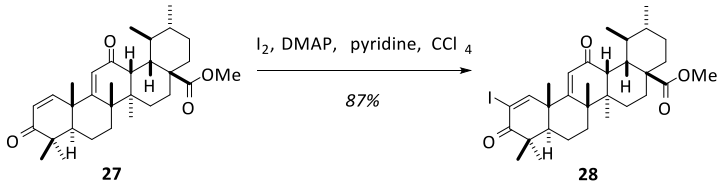
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (s, 1H), 3.60 (s, 3H), 2.86 (dd, 1H, J_1 = 11.2 Hz, J_2 = 2.7 Hz), 2.57 (m, 1H), 2.45 (m, 2H), 2.18 (m, 1H), 1.35-1.95 (m, 14H), 1.00-1.30 (m, 2H), 1.24 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.83 (d, 3H, J = 6.1 Hz), 0.67 (d, 3H, J = 6.3 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ215.4, 199.9, 177.9, 177.6, 124.2, 51.8, 50.9, 50.5, 49.9, 47.3, 45.3, 42.2, 40.7, 39.4, 39.3, 38.7, 36.8, 36.7, 34.1, 32.0, 31.1, 28.3, 26.5, 24.3, 24.2, 23.8, 21.4, 20.8, 19.7, 19.5, 19.0; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1698, 1684, 1652, 1558, 1540, 1507, 1217, 772, 668; HRMS-ESI (calcd for $C_{31}H_{47}O_4$ $[M+H]^+$) 483.3474, found 483.3471.



To a stirred solution of ketone **26** (4.8 g, 10.0 mmol, 1.0 equiv) in anhydrous THF (150 mL) at -78 ^{o}C was slowly added LHMDS (20 mL, 1.0 M solution, 20.0 mmol, 2.0 equiv), it was kept stirring at -78 ^{o}C for 30 min and then allowed to warm to 0 ^{o}C and kept at 0 ^{o}C for 30 min. It was then cooled back to -78 ^{o}C and phenylselenium chloride (3.8 g, 20.0 mmol, 2.0 equiv) in anhydrous THF (10 mL) was added slowly. After the completion of the reaction, it was quenched with saturated aqueous ammonium chloride, and extracted with methylene chloride (3 x 100 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed to give crude product, which was used directly for next step without further purifications.

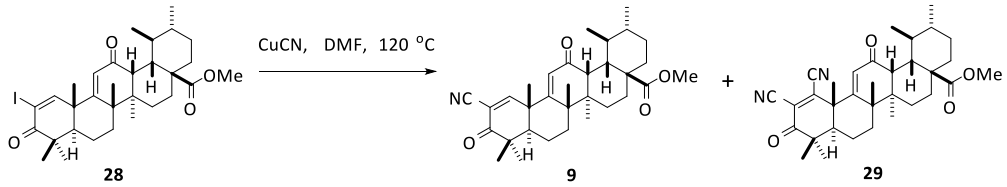
The selenite obtained above was dissolved in a 1:1 mixture of THF and methylene chloride (100 mL), and 30% aqueous hydrogen peroxide (5 mL) was added at 0 ^{o}C. The reaction mixture was allowed to warm to room temperature and stirred until disappearance of starting selenite. The reaction mixture was then diluted with ethyl acetate (100 mL) and washed with 20% aqueous sodium thiosulfate (10 mL), brine (10 mL), and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1 & 2:1) gave bis-enone **27** (3.44 g, 72%) as a yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, 1H, *J* = 10.7 Hz), 6.14 (s, 1H), 5.93 (d, 1H, *J* = 10.3 Hz), 3.66 (s, 3H), 2.95 (dd, 1H, J_1 = 11.2 Hz, J_2 = 3.2 Hz), 2.48 (d, 1H, *J* = 3.7 Hz), 1.89-1.98 (m, 1H), 1.70-1.84 (m, 7H), 1.44-1.65 (m, 4H), 1.40 (s, 3H), 1.10-1.29 (m, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H), 1.11 (s, 3H), 0.88 (d, 3H, *J* = 6.1 Hz), 0.73 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ203.8, 200.0, 178.4, 173.0, 155.4, 126.5, 124.4, 52.1, 51.4, 50.2, 48.4, 45.8, 44.9, 42.5, 42.1, 41.1, 39.6, 38.9, 36.9, 32.2, 31.3, 28.5, 28.0, 27.5, 25.3, 24.0, 21.8, 20.9, 20.0, 19.6, 18.5; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1716, 1699, 1652, 1558, 1540, 1520, 1507, 1216, 770, 668, 451; HRMS-ESI (calcd for $C_{31}H_{45}O_4$ $[M+H]^+$) 481.3318, found 481.3306.



To a stirred solution of bis-enone **27** (1.07 g, 2.3 mmol, 1.0 equiv) in a 1:1 mixture of pyridine and carbon tetrachloride (10 mL) was added dimethylaminopyridine (56 mg, 0.46 mmol, 0.2 equiv) and iodine (1.75 g, 6.9 mmol, 3.0 equiv), and the resulting mixture was allowed to heat to 90 ^{o}C for 24 h without light. After the completion of the reaction, the solvent was removed under vacuum, and the residue was diluted with ethyl acetate (100 mL). The resulting solution was successively washed with 20% aqueous sodium thiosulfate (3 x 10 mL), 1 N aqueous HCl (3 x 10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1 & 2:1) gave iodoenone **28** (1.18 g, 87%) as a yellowish solid.

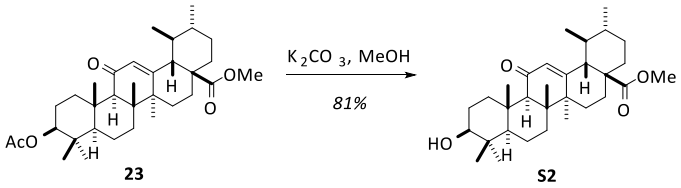
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 6.11 (s, 1H), 3.66 (s, 3H), 2.95 (dd, 1H, J_1 = 11.3 Hz, J_2 = 3.0 Hz), 2.48 (d, 1H, *J* = 3.7 Hz), 1.90-1.99 (m, 1H), 1.70-1.87 (m, 7H), 1.59-1.65 (m, 1H), 1.44-1.57 (m, 3H), 1.41 (s, 3H), 1.15-1.26 (m, 3H), 1.18 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H), 0.89 (d, 3H, *J* = 6.1 Hz), 0.75 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.8, 197.0, 178.3, 171.5, 163.8, 124.6, 102.4, 52.2, 51.3, 50.2, 38.3, 36.5, 45.9, 45.4, 42.5, 41.2, 39.6, 38.9, 36.9, 31.9, 31.3, 28.6, 28.5, 28.0, 25.3, 24.0, 22.4, 20.9, 20.0, 19.7, 18.7; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1717, 1652, 1540, 1520, 1507, 1217, 770, 669; HRMS-ESI (calcd for $C_{31}H_{44}IO_4$ $[M+H]^+$) 607.2284, found 607.2280.



To a stirred solution of iodoenone **28** (322 mg, 0.5 mmol, 1.0 equiv) in anhydrous dimethylformamide (5 mL) was added copper (I) cyanide (54 mg, 0.6 mmol, 1.2 equiv), and the resulting mixture was allowed to heat to 120 °C for 12 hours. After the completion of the reaction, it was cooled to room temperature, diluted with ethyl acetate (100 mL). The resulting solution was washed with water (3 x 10 mL), brine (3 x 10 mL), and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1 & 2:1) gave cyanoenone **9** (142 mg, 53%) and bis-cyanoenone **29** (76 mg, 27%) as yellowish solids, respectively.

For **9**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.11 (s, 1H), 3.67 (s, 3H), 2.96 (dd, 1H, J_1= 11.5 Hz, J_2 = 2.7 Hz), 2.51 (d, 1H, J = 3.7 Hz), 1.91-1.99 (m, 1H), 1.72-1.85 (m, 7H), 1.60-1.68 (m, 1H), 1.47-1.58 (m, 3H),1.48 (s, 3H), 1.16-1.30 (m, 2H),1.26 (s, 3H), 1.21 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H),0.90 (d, 3H, J = 6.1 Hz), 0.83-0.90 (m, 1H), 0.74 (d, 3H, J = 6.6 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.3, 196.9, 178.3, 169.8, 166.4, 124.9, 115.1, 114.7, 52.2, 51.4, 50.2, 47.9, 46.0, 45.3, 42.9, 42.6, 41.2, 39.6, 38.9, 36.9, 31.9, 31.3, 28.5, 27.6, 27.5, 25.4, 23.9, 21.8, 20.9, 20.0, 19.6, 18.4; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1716, 1652, 1558, 1540, 1520, 1507, 1217, 772, 669, 464; HRMS-ESI (calcd for $C_{32}H_{44}NO_4$ $[M+H]^+$) 506.3270, found 506.3267.

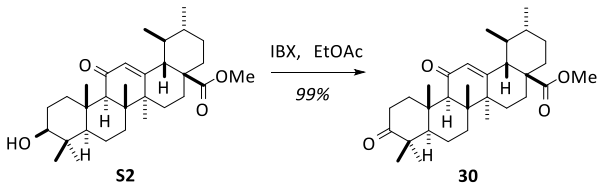
For **29**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (s, 1H), 3.68 (s, 3H), 3.02 (dd, 1H, J_1 = 11.6 Hz, J_2 = 2.0 Hz),2.51 (d, 1H, J = 3.4 Hz), 1.74-2.02(m, 7H), 1.40-1.67 (m, 4H), 1.62 (s, 3H), 1.18-1.34 (m, 2H), 1.26 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H),1.17 (s, 3H), 0.83-0.97 (m, 1H), 0.90 (d, 3H, J = 5.9 Hz), 0.74 (d, 3H, J = 6.6 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 198.0, 195.2, 178.3, 166.3, 146.8, 126.9, 124.6, 113.9, 112.1, 52.3, 51.6, 50.3, 47.3, 46.4, 46.2, 46.1, 42.7, 42.1, 39.8, 38.8, 36.8, 31.4, 29.1, 28.8, 26.6, 26.2, 26.1, 24.1, 21.0, 20.9, 20.0, 19.3, 19.2; IR (solution, $CHCl_3$): 3019, 2929, 2360, 2340, 1732, 1716, 1683, 1668, 1653, 1558, 1540, 1520, 1507, 1472, 1456, 1217, 772, 669, 473; HRMS-ESI (calcd for $C_{33}H_{43}N_2O_4$ $[M+H]^+$) 531.3474, found 531.3468.



To a stirred solution of enone **23** (2.0 g, 3.8mmol, 1.0 equiv) in methanol (40 mL) was added potassium carbonate (2.0 g, 11.4 mmol, 3.0 equiv). The reaction mixture was allowed stir at room temperature for 24 h. After completion of the reaction, it was quenched with water (100 mL) and extracted with methylene chloride (4 x 60 mL). The combined organic extracts were washed with brine (30 mL) and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (2:1) gave alcohol **S2** (1.5 g, 81%) as a white solid.

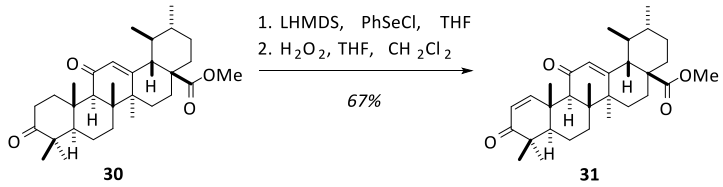
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (s, 1H), 3.55 (s, 3H), 3.15 (dd, 1H, J_1 = 11.2 Hz, J_2 = 4.9 Hz), 2.73 (dd, 1H, J_1= 10.1 Hz, J_2 = 3.3 Hz), 2.36 (d, 1H, J = 11.2 Hz), 2.25 (s, 1H), 2.01 (m, 2H), 1.66-1.78 (m, 3H), 1.46-1.64 (m, 6H), 1.17-1.38 (m, 7H), 1.25

(s, 3H), 1.06 (s, 3H), 0.94 (s, 3H), 0.91 (d, 3H, *J* = 6.4 Hz),0.85 (s, 3H), 0.81 (d, 3H, *J* = 6.6 Hz),0.74 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.1, 117.4, 163.0, 130.9, 78.8, 61.6, 55.2, 52.9, 52.0, 47.8, 44.8, 43.9, 39.4, 39.3, 38.8, 38.7, 37.3, 36.2, 33.2, 30.5, 28.6, 28.3, 27.4, 24.1, 21.3, 21.2, 19.0, 17.6, 17.3, 16.4, 15.9; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1698, 1652, 1558, 1540, 1520, 1507, 1217, 771, 669, 436; HRMS-ESI (calcd for $C_{31}H_{49}O_4$ $[M+H]^+$) 485.3631, found 485.3633.



To a stirred solution of alcohol **S2** (1.4 g, 2.9 mmol, 1.0 equiv) in ethyl acetate (30 mL) was added iodoxybenzoic acid (1.2 mg, 3.9 mmol, 1.3 equiv) in one portion. The resulting suspension was heated to reflux for 24 h. After completion of the reaction, it was cooled in ice bath and was then filtered through Celite. The resulting filtrate was concentrated and flash column chromatography over silica gel using hexanes:EtOAc (2:1) gave ketone **30** (1.38 g, 99%) as a yellowish solid.

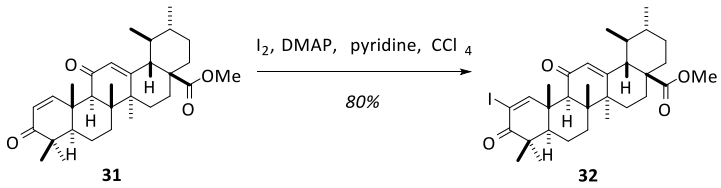
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (s, 1H), 3.55 (s, 3H), 2.88 (m, 1H), 2.55 (m, 1H), 2.25-2.40 (m, 3H), 2.03 (m, 1H), 1.67-1.80 (m, 3H), 1.30-1.64 (m, 9H), 1.16-1.30 (m, 3H), 1.24 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H), 0.90 (d, 3H, *J* = 6.3 Hz), 0.88 (s, 3H), 0.80 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 217.3, 199.2, 177.3, 163.5, 130.7, 60.9, 55.5, 52.9, 52.0, 47.9, 47.8, 44.6, 44.0, 39.9, 38.8, 38.7, 36.9, 36.1, 34.4, 32.5, 30.5, 28.6, 26.7, 24.0, 21.6, 21.2, 21.1, 18.9, 18.8, 17.3, 15.7; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1717, 1653, 1539, 1507, 1456, 1214, 669; HRMS-ESI (calcd for $C_{31}H_{47}O_4$ $[M+H]^+$) 483.3474, found 483.3476.



To a stirred solution of ketone **30** (1.3 g, 2.7mmol, 1.0 equiv) in anhydrous THF (50 mL) at -78 ^{o}C was slowly added LHMDS (5.4 mL, 1.0 M solution, 5.4 mmol, 2.0 equiv), it was kept stirring at -78 ^{o}C for 30 min and then allowed to warm to 0 ^{o}C and kept at 0 ^{o}C for 30 min. It was then cooled back to -78 ^{o}C and phenylselenium chloride (1.1 g, 5.4 mmol, 2.0 equiv) in anhydrous THF (5 mL) was added slowly. After the completion of the reaction, it was quenched with saturated aqueous ammonium chloride, and extracted with methylene chloride (3 x 50 mL). The combined organic extracts were washed with brine (20 mL) and dried over Na_2SO_4. The solvent was removed to give crude product, which was used directly for next step without further purifications.

The selenite obtained above was dissolved in a 1:1 mixture of THF and methylene chloride (20 mL), and 30% aqueous hydrogen peroxide (2 mL) was added at 0 ^{o}C. The reaction mixture was allowed to warm to room temperature and stirred until disappearance of starting selenite. The reaction mixture was then diluted with ethyl acetate (100 mL) and washed with 20% aqueous sodium thiosulfate (10 mL), brine (10 mL), and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1 & 2:1) gave bis-enone **31** (0.88 g, 67%) as a yellowish solid.

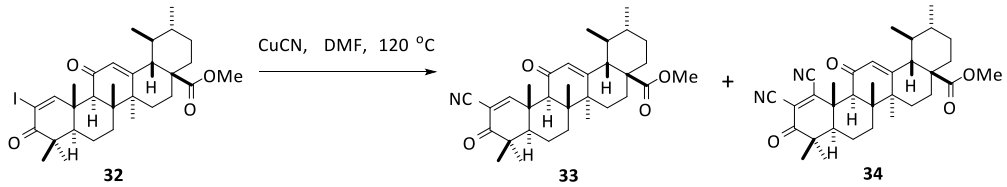
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, 1H, *J* = 10.3 Hz), 5.77 (d, 1H, *J* = 10.3 Hz), 5.67 (s, 1H), 3.60 (s, 3H), 2.61 (s, 1H), 2.44 (d, 1H, *J* = 11.2 Hz), 2.06 (m, 1H), 1.72-1.84 (m, 3H), 1.46-1.68 (m, 7H), 1.25-1.44 (m, 4H), 1.37 (s, 3H),1.30 (s, 3H),1.12 (s, 3H), 1.08 (s, 3H),0.95 (d, 3H, *J* = 6.4 Hz), 0.94 (s, 3H),0.85 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.8, 198.8, 177.3, 164.5, 161.9, 130.5, 124.8, 55.5, 53.1, 53.0, 52.1, 47.9, 45.0, 44.9, 44.3, 39.1, 38.8, 38.7, 36.1, 32.6, 30.5, 28.7, 27.9, 24.1, 21.8, 21.3, 21.2, 20.2, 19.4, 18.3, 17.3; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1716, 1699, 1652, 1558, 1540, 1520, 1507, 1216, 770, 668; HRMS-ESI (calcd for $C_{31}H_{45}O_4$ $[M+H]^+$) 481.3318, found 481.3316.



31 **32**

To a stirred solution of bisenone **31** (0.47 g, 1.0 mmol, 1.0 equiv) in a 1:1 mixture of pyridine and carbon tetrachloride (6 mL) was added dimethylaminopyridine (25 mg, 0.2mmol, 0.2 equiv) and iodine (0.76 g, 3.0mmol, 3.0 equiv), and the resulting mixture was allowed to heat to 90 ^{o}C for 24 h without light. After the completion of the reaction, the solvent was removed under vacuum, and the residue was diluted with ethyl acetate (50 mL). The resulting solution was successively washed with 20% aqueous sodium thiosulfate (3 x 5 mL), 1 N aqueous HCl (3 x 5 mL), saturated $NaHCO_3$ (5 mL), brine (5 mL), and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1 & 2:1) to give iodoenone **32** (0.47 g, 80%) as a yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 5.70 (s, 1H), 3.62 (s, 3H), 2.67 (s, 1H), 2.46 (d, 1H, *J* = 11.2 Hz), 2.10 (m, 1H), 1.74-1.86 (m, 3H), 1.48-1.70 (m, 7H), 1.22-1.46 (m, 4H), 1.40 (s, 3H),1.33 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H), 0.98 (d, 3H, *J* = 6.3 Hz), 0.94 (s, 3H), 0.88 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 198.3, 197.6, 177.3, 169.9, 164.9, 130.3, 101.0, 55.1, 53.1, 52.8, 52.2, 47.9, 45.7, 45.0, 44.4, 43.8, 38.9, 38.8, 36.1, 32.4, 30.5, 29.0, 28.7, 24.1, 22.4, 21.3, 21.2, 20.0, 19.4, 18.5, 17.3; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1717, 1652, 1540, 1520, 1507, 1217, 770, 669; HRMS-ESI (calcd for $C_{31}H_{44}IO_4$ $[M+H]^+$) 607.2284, found 607.2231.



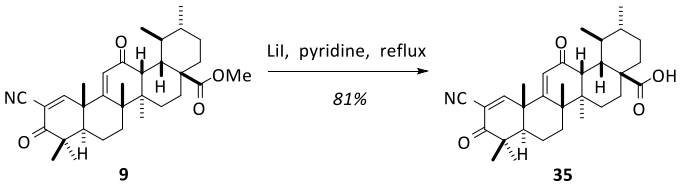
32 **33** **34**

To a stirred solution of iodoenone **32** (286 mg, 0.47 mmol, 1.0 equiv) in anhydrous dimethylformamide (5 mL) was added copper (I) cyanide (51 mg, 0.57 mmol, 1.2 equiv), and the resulting mixture was allowed to heat to 120 ^{o}C for 12 h. After the completion of the reaction, it was cooled to room temperature, diluted with ethyl acetate (100 mL). The resulting solution was washed with water (3 x 10 mL), brine (3 x 10 mL), and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1 & 2:1) gave cyanoenone **33** (111 mg, 47%) and biscyanoenone **34** (56 mg, 23%) as yellowish solids, respectively.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 5.72 (s, 1H), 3.62 (s, 3H), 2.67 (s, 1H), 2.47 (d, 1H, *J* = 11.2 Hz), 2.12 (m, 1H), 1.74-1.87 (m, 3H), 1.52-1.70 (m, 6H), 1.24-1.48 (m, 2H), 1.42 (s, 3H),1.32 (s, 3H), 1.11-1.23 (m, 2H), 1.19 (s, 3H), 1.13 (s,

3H), 0.97 (d, 3H, *J* = 6.6 Hz), 0.96 (s, 3H), 0.87 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 198.0, 197.8, 177.3, 173.0, 165.6, 130.1, 115.1, 113.5, 54.3, 53.2, 52.2, 52.1, 47.9, 45.3, 45.1, 44.4, 40.0, 38.9, 38.8, 36.0, 32.1, 30.4, 28.7, 27.8, 24.0, 21.8, 21.3, 21.2, 19.7, 19.4, 18.2, 17.3; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1717, 1683, 1652, 1558, 1540, 1520, 1507, 1456, 1217, 772, 669; HRMS-ESI (calcd for $C_{32}H_{44}NO_4$ $[M+H]^+$) 506.3270, found 506.3230.

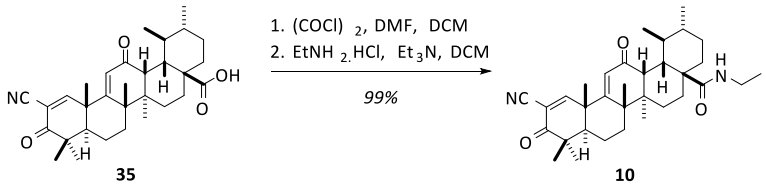
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (s, 1H), 3.62 (s, 3H), 2.99 (s, 1H), 2.50 (d, 1H, *J* = 11.2 Hz), 2.13 (m, 1H), 1.74-1.88(m, 3H), 1.46-1.70 (m, 6H), 1.54 (s, 3H), 1.24-1.46 (m, 3H), 1.40 (s, 3H), 1.30 (s, 3H), 1.18 (s, 3H),1.04-1.14 (m, 1H), 0.98 (d, 3H, *J* = 6.4 Hz), 0.96 (s, 3H), 0.91 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 196.7, 196.3, 177.3, 165.2, 153.4, 129.9, 123.4, 114.3, 112.5, 53.4, 53.3, 52.2, 51.8, 47.9, 46.2, 45.1, 44.7, 41.9, 38.9, 38.8, 36.0, 31.4, 30.5, 30.1, 28.6, 24.0, 21.9, 21.6, 21.2, 21.1, 19.2, 19.0, 17.4; IR (solution, $CHCl_3$): 3019, 2929, 2360, 2340, 1732, 1716, 1683, 1668, 1653, 1558, 1540, 1520, 1507, 1472, 1456, 1217, 772, 669, 473.



9 **35**

To a stirred solution of CDDU-methyl ester (**9**) (6.0 g, 11.9 mmol, 1.0 equiv) in pyridine (50 mL) was added LiI (16.0 g, 0.12 mol, 10.0 equiv) and the resulting suspension was heated to reflux for 16 hours. Additional LiI (3.2 g, 23.8 mmol, 2.0 equiv) was added and the heating was continued for another 8 hours. After the completion of the reaction, it was cooled to room temperature, and the solvent was removed by vacuum. The reaction was quenched with 2 N HCl (200 mL), and extracted with ethyl acetate (4 x 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (2:1 & 1:1) gave acid **35** (4.7 g, 81%) as a yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 6.12 (s, 1H), 2.95 (dd, 1H, J_1= 11.0 Hz, J_2 = 2.5 Hz), 2.59 (d, 1H, *J* = 3.4 Hz), 1.66-2.00 (m, 9H), 1.43-1.62 (m, 2H),1.47 (s, 3H), 1.18-1.34 (m, 3H),1.26 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.13 (s, 3H), 0.82-0.94 (m, 1H), 0.90 (d, 3H, *J* = 5.8 Hz),0.75 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.3, 196.8, 170.0, 166.3, 124.8, 115.2, 114.6, 51.4, 47.9, 46.0, 45.3, 42.8, 42.6, 41.2, 39.5, 38.8, 37.0, 31.8, 31.2, 28.5, 27.6, 25.5, 23.8, 21.8, 20.9, 20.0, 19.6, 18.4; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1716, 1698, 1684, 1652, 1558, 1540, 1520, 1507, 1456, 1217, 772, 669; HRMS-ESI (calcd for $C_{31}H_{42}NO_4$ $[M+H]^+$) 492.3114, found 492.3108.

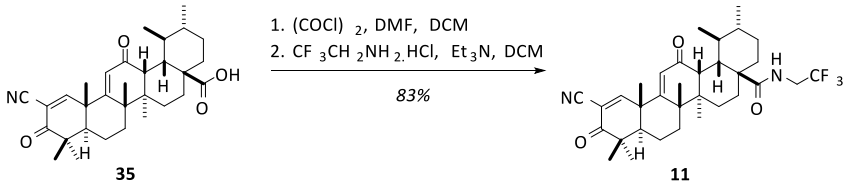


35 **10**

To a stirred solution of acid **35** (400 mg, 0.81 mmol, 1.0 equiv) in methylene chloride (15 mL) was added oxalyl chloride (0.35 mL, 4.05 mmol, 5.0 equiv) and anhydrous dimethylformamide (0.11 µL, 2.0 µmol, catalytic) slowly at 0 ^{o}C, and it was allowed to warm to room temperature for 2 h. The solvent was removed, and toluene (10 mL) was added and removed by vacuum, which was repeated for three times to provide the corresponding acyl chloride.

To a stirred solution of the resulting acyl chloride obtained above in methylene chloride (10 mL) was added triethylamine (0.58 mL, 4.05 mmol, 5.0 equiv) followed by slow addition of ethylamine hydrochloride (340 mg, 4.05 mmol, 5.0 equiv) at 0 ^{o}C. After the addition, the resulting mixture was allowed to warm to room temperature and kept stirring until the disappearance of acyl chloride. After the completion of the reaction, the solvent was removed and it was diluted with methylene chloride (80 mL), washed with 1 N HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (2:1 & 1:1) g ethylve amide **10** (418 mg, 99%) as a yellowish solid.

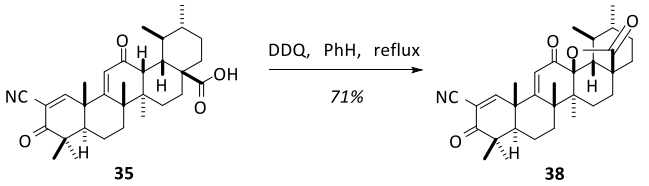
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 6.36 (s, 1H), 6.16 (t, 1H, *J* = 5.5 Hz), 3.33 (m, 1H), 3.21 (m, 1H), 2.68 (dd, 1H, J_1= 10.7 Hz, J_2 = 2.2 Hz), 2.62 (d, 1H, *J* = 3.4 Hz), 1.60-1.99 (m, 9H), 1.46-1.60 (m, 2H), 1.44 (s, 3H), 1.05-1.30 (m, 3H), 1.28 (s, 3H), 1.24 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H), 0.85-0.95 (m, 1H), 0.90 (d, 3H, *J* = 6.1 Hz), 0.68 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.5, 197.1, 177.4, 171.1, 168.1, 124.9, 115.1, 114.8, 51.0, 49.3, 47.8, 46.2, 45.3, 43.8, 43.2, 41.2, 39.9, 39.0, 37.9, 34.6, 31.9, 31.4, 29.6, 28.2, 27.4, 27.3, 25.8, 23.7, 21.8, 21.0, 19.5, 19.4, 15.2; IR (solution, $CHCl_3$): 3019, 2979, 2360, 2340, 1698, 1684, 1652, 1636, 1558, 1540, 1520, 1507, 1456, 1217, 771, 669, 444; HRMS-ESI (calcd for $C_{33}H_{47}N_2O_3$ $[M+H]^+$) 519.3587, found 519.3585.



To a stirred solution of acid **35** (400 mg, 0.81 mmol, 1.0 equiv) in methylene chloride (15 mL) was added oxalyl chloride (0.35 mL, 4.05 mmol, 5.0 equiv) and anhydrous dimethylformamide (0.11 µL, 2.0 µmol, catalytic) slowly at 0 ^{o}C, and it was allowed to warm to room temperature for 2 h. The solvent was removed, and toluene (10 mL) was added and removed by vacuum, which was repeated for three times to provide the corresponding acyl chloride.

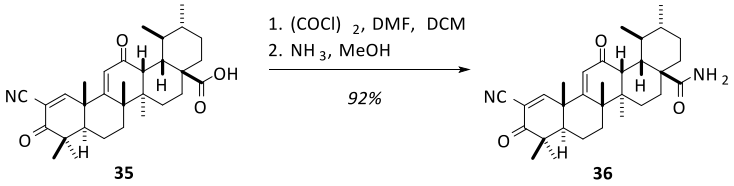
To a stirred solution of the resulting acyl chloride obtained above in methylene chloride (10 mL) was added triethylamine (0.58 mL, 4.05 mmol, 5.0 equiv) followed by slow addition of ethylamine hydrochloride (340 mg, 4.05 mmol, 5.0 equiv) at 0 ^{o}C. After the addition, the resulting mixture was allowed to warm to room temperature and kept stirring until the disappearance of acyl chloride. After the completion of the reaction, the solvent was removed and it was diluted with methylene chloride (80 mL), washed with 1 N HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (2:1 & 1:1) gave trifluoroethyl amide **11** (387 mg, 83%) as a yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H), 6.92 (t, 1H, *J* = 6.5 Hz), 6.74 (t, 1H, *J* = 5.5 Hz), 4.20 (m, 1H), 3.55 (m, 1H), 2.89 (dd, 1H, J_1= 9.9 Hz, J_2 = 2.8 Hz), 2.48 (d, 1H, *J* = 3.2 Hz), 1.93-2.15 (m, 1H), 1.69-1.92 (m, 6H), 1.47-1.65 (m, 4H), 1.55 (s, 3H), 1.05-1.30 (m, 3H), 1.29 (s, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 1.05 (s, 3H), 0.85-0.95 (m, 1H), 0.87 (d, 3H, *J* = 6.6 Hz), 0.57 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.3, 197.2, 178.2, 171.2, 169.4, 125.0, 124.5 (q), 115.6, 114.4, 51.1, 49.8, 47.7, 46.1, 45.3, 43.4, 43.3, 41.1, 40.5 (s), 39.7, 38.7, 37.4, 31.9, 31.3, 29.6, 27.9, 27.1, 27.0, 25.9, 23.7, 21.8, 20.9, 19.4, 18.3; ^{19}F NMR (500 MHz, $CDCl_3$) δ 72.8; IR (solution, $CHCl_3$): 3019, 2957, 2869, 2360, 2340, 1652, 1558, 1539, 1520, 1507, 1465, 1436, 1376, 1364, 1217, 772, 669; HRMS-ESI (calcd for $C_{33}H_{44}N_2F_3O_3$ $[M+H]^+$) 573.3304, found 573.3307.



To a stirred solution of acid **35** (250 mg, 0.51 mmol, 1.0 equiv) in benzene (15 mL) was added DDQ (136 mg, 0.61 mmol, 1.2 equiv) and the resulting mixture was heated to reflux for 24 h. After the completion of the reaction, it was cooled to room temperature and filtered through celite. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1 & 2:1) gave the desired product **38** (175.5 mg, 71%) as a reddish solid.

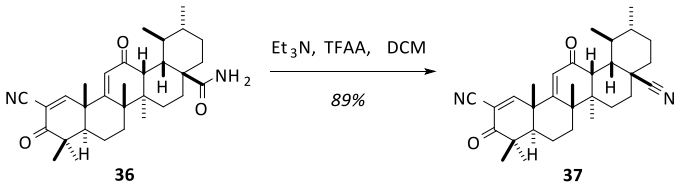
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 6.28 (s, 1H), 2.56 (d, 1H, *J* = 11.7 Hz), 2.12 (m, 1H), 1.71-1.92 (m, 4H), 1.60-1.70 (m, 3H), 1.57 (s, 3H), 1.50 (s, 3H), 1.39-1.50 (m, 2H), 1.22-1.44 (m, 1H), 1.28 (s, 3H), 1.21 (s, 3H), 1.18 (s, 3H), 1.00-1.10 (m, 1H), 0.95 (d, 3H, *J* = 6.3 Hz), 0.82-0.90 (m, 1H), 0.82 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 196.6, 192.2, 178.3, 174.3, 165.7, 123.4, 115.4, 114.5, 87.8, 55.1, 48.1, 46.4, 45.3, 45.1, 43.2, 42.9, 39.8, 37.5, 32.8, 31.3, 31.2, 30.8, 28.0, 27.6, 26.3, 21.9, 21.8, 20.3, 19.5, 18.6, 17.8; IR (solution, $CHCl_3$): 3019, 2969, 2936, 2360, 2340, 1772, 1715, 1697, 1675, 1652, 1558, 1540, 1520, 1507, 1456, 1215, 909, 749, 669; HRMS-ESI (calcd for $C_{31}H_{40}NO_4$ $[M+H]^+$) 490.2957, found 490.2961.



To a stirred solution of acid **35** (860 mg, 1.75 mmol, 1.0 equiv) in methylene chloride (15 mL) was added oxalyl chloride (0.50 mL, 5.72 mmol, 3.3 equiv) and anhydrous dimethylformamide (0.15 µL, 2.7 µmol, catalytic) slowly at 0 °C, and it was allowed to warm to room temperature for 2 h. The solvent was removed, and toluene (10 mL) was added and removed by vacuum, which was repeated for three times to provide the corresponding acyl chloride.

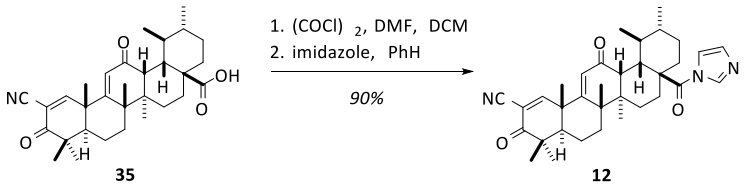
To a stirred solution of the resulting acyl chloride obtained above in methylene chloride (20 mL) was added ammonia (8.75 mL, 1.0 M in MeOH, 8.75 mmol, 5.0 equiv), and the resulting mixture was stirred at room temperature until the disappearance of acyl chloride. After the completion of the reaction, the solvent was removed and flash column chromatography over silica gel using hexanes:EtOAc (1:1 & 1:2) gave ethyl amide **36** (791 mg, 92%) as a yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 6.28 (s, 1H), 2.51 (d, 1H, *J* = 11.7 Hz), 2.10 (m, 1H), 1.69-1.90 (m, 6H), 1.51-1.67 (m, 4H), 1.54 (s, 3H), 1.34-1.50 (m, 2H), 1.46 (s, 3H), 1.10-1.30 (m, 2H), 1.23 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 0.82-0.92 (m, 1H), 0.91 (d, 3H, *J* = 6.3 Hz), 0.78 (d, 3H, *J* = 6.1 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.3, 197.0, 180.4, 171.1, 167.7, 124.9, 115.0, 114.9, 51.2, 49.8, 47.8, 46.2, 45.3, 43.9, 43.1, 41.2, 39.9, 39.0, 37.9, 31.9, 31.4, 28.2, 27.5, 25.9, 23.7, 21.8, 20.9, 20.1, 19.5, 18.4; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1652, 1558, 1540, 1507, 1217, 771, 669, 429; HRMS-ESI (calcd for $C_{31}H_{43}N_2O_3$ $[M+H]^+$) 491.3114, found 491.3105.



To a stirred solution of amide **36** (600 mg, 1.22 mmol, 1.0 equiv) in methylene chloride (40 mL) at 0 ^{o}C was added triethylamine (0.44 mL, 3.13 mmol, 2.5 equiv) and trifluoroacetic anhydride (0.26 mL), and the resulting mixture was stirred at 0 ^{o}C until the disappearance of starting material. After the completion of the reaction, it was quenched with saturated aqueous $NaHCO_3$ (20 mL), and extracted with methylene chloride (3 x 20 mL). The combined organic extracts were washed with brine (10 mL) and dried over Na_2SO_4. Removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1 & 2:1) gave the desired product **37** (407 mg, 89%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 6.16 (s, 1H), 3.17 (d, 1H, *J* = 3.7 Hz), 2.72 (dd, 1H, J_1 = 11.2 Hz, J_2 = 3.2 Hz), 1.95-2.18 (m, 4H), 1.74-1.86 (m, 3H), 1.55-1.66 (m, 3H), 1.53 (s, 3H), 1.34-1.50 (m, 2H), 1.45 (s, 3H), 1.27 (s, 3H), 1.16-1.26 (m, 2H), 1.20 (s, 3H), 1.12 (s, 3H), 0.92 (d, 3H, *J* = 5.6 Hz), 0.82-0.92 (m, 1H), 0.76 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 198.1, 196.8, 170.4, 166.1, 125.0, 124.8, 115.2, 114.6, 51.5, 48.0, 46.1, 45.3, 44.3, 43.0, 41.5, 41.2, 39.0, 38.7, 36.7, 32.0, 30.6, 28.8, 27.6, 27.5, 25.8, 25.6, 21.8, 20.6, 19.8, 19.6, 18.4; IR (solution, $CHCl_3$): 3019, 2360, 2340, 1697, 1684, 1662, 1653, 1558, 1540, 1520, 1507, 1473, 1456, 1217, 909, 772, 669, 450; HRMS-ESI (calcd for $C_{31}H_{41}N_2O_2$ $[M+H]^+$) 473.3168, found 473.3165.



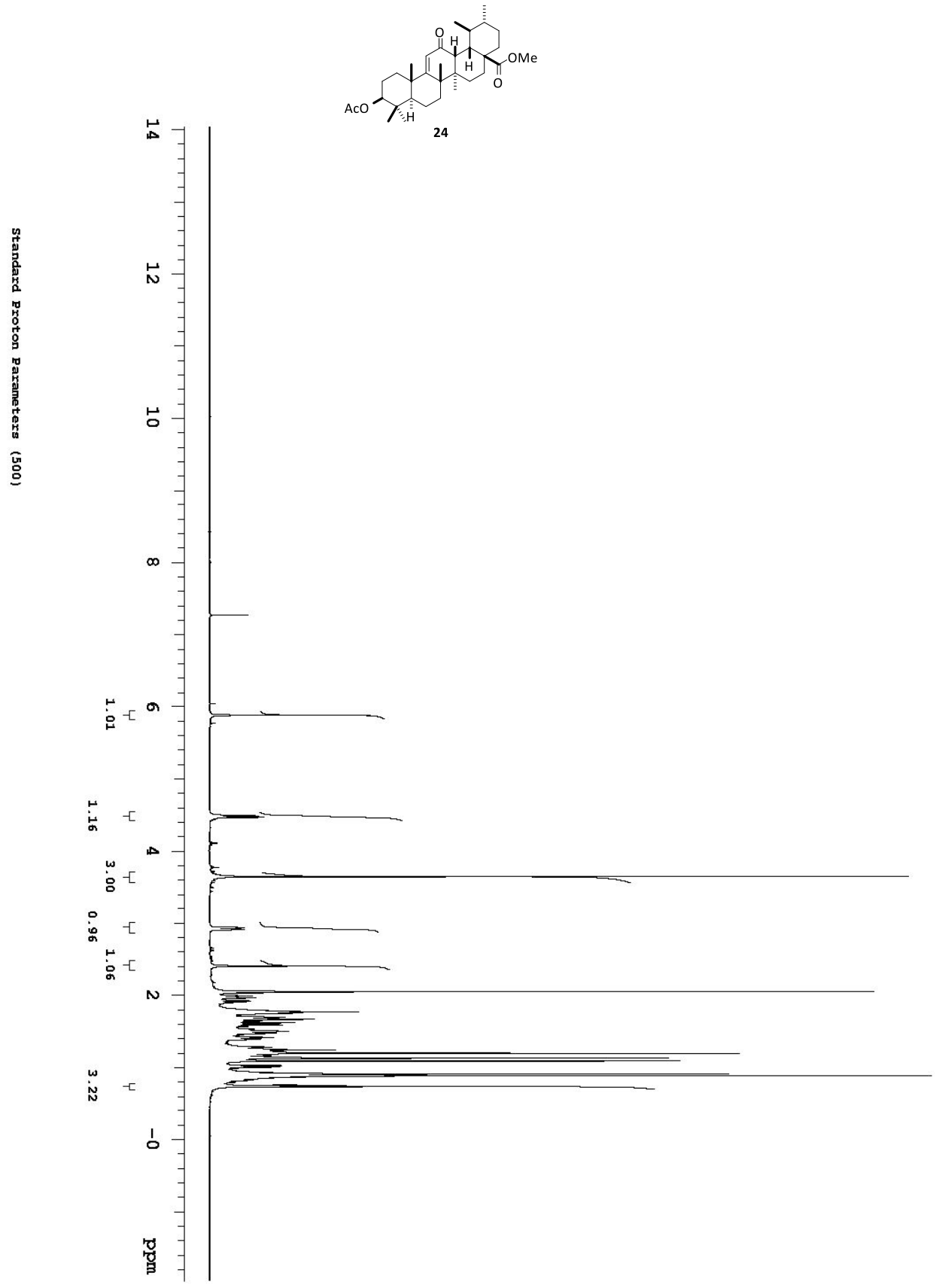
To a stirred solution of acid **35** (460 mg, 1.0 mmol, 1.0 equiv) in methylene chloride (20 mL) was added oxalyl chloride (0.50 mL, 5.8 mmol, 5.8 equiv) and anhydrous dimethylformamide (0.15 µL, 2.0 µmol, catalytic) slowly at 0 ^{o}C, and it was allowed to warm to room temperature for 2 h. The solvent was removed, and toluene (10 mL) was added and removed by vacuum, which was repeated for three times to provide the corresponding acyl chloride.

To a stirred solution of the resulting acyl chloride obtained above in benzene (10 mL) was added imidazole (350 mg, 5.0 mmol, 5.0 equiv) and the resulting mixture was stirred at room temperature until the disappearance of acyl chloride. After the completion of the reaction, removal of solvent and flash column chromatography over silica gel using hexanes:EtOAc (4:1 & 2:1) gave ethyl amide **12** (458 mg, 90%) as a yellowish solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.05 (s, 1H), 7.66 (s, 1H), 7.06 (s, 1H), 6.10 (s, 1H), 3.27 (d, 1H, *J* = 9.8 Hz), 2.43 (s, 1H), 0.98-2.06 (m, 11H), 1.44 (s, 3H), 1.23 (s, 3H), 1.16 (s, 9H), 0.96 (d, 3H, *J* = 5.1 Hz), 0.78 (d, 3H, *J* = 5.9 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 197.9, 196.8, 175.5, 170.2, 166.3, 137.8, 130.6, 124.6, 117.9, 115.1, 114.6, 52.6, 51.1, 47.9, 46.0, 45.2, 43.1, 42.9, 41.3, 39.9, 38.8, 35.8, 31.7, 31.0, 28.1, 27.5, 27.5, 25.4, 21.8, 20.8, 20.0, 19.7, 18.3; IR (solution, $CHCl_3$): IR (solution, CHCl3): 3019, 2360, 2340, 1716, 1698, 1652, 1558, 1540, 1520, 1507, 1214, 909, 773, 669, 438; HRMS-ESI (calcd for $C_{34}H_{44}N_3O_3$ $[M+H]^+$) 542.3383, found 542.3377.

Bibliography.

1. M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* 1999, **64**, 4537.
2. C.-M. Ma, S.-Q. Cai, J.-R. Cui, R.-Q. Wang, P.-F. Tu, M. Hattori, M. Daneshtalab, *Eur. J. Med. Chem.* **2005**, *40*, 582-589.


O
H
H
OMe
O
AcO
H
24
Standard Proton Parameters (500)
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8
6
4
2
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ppm
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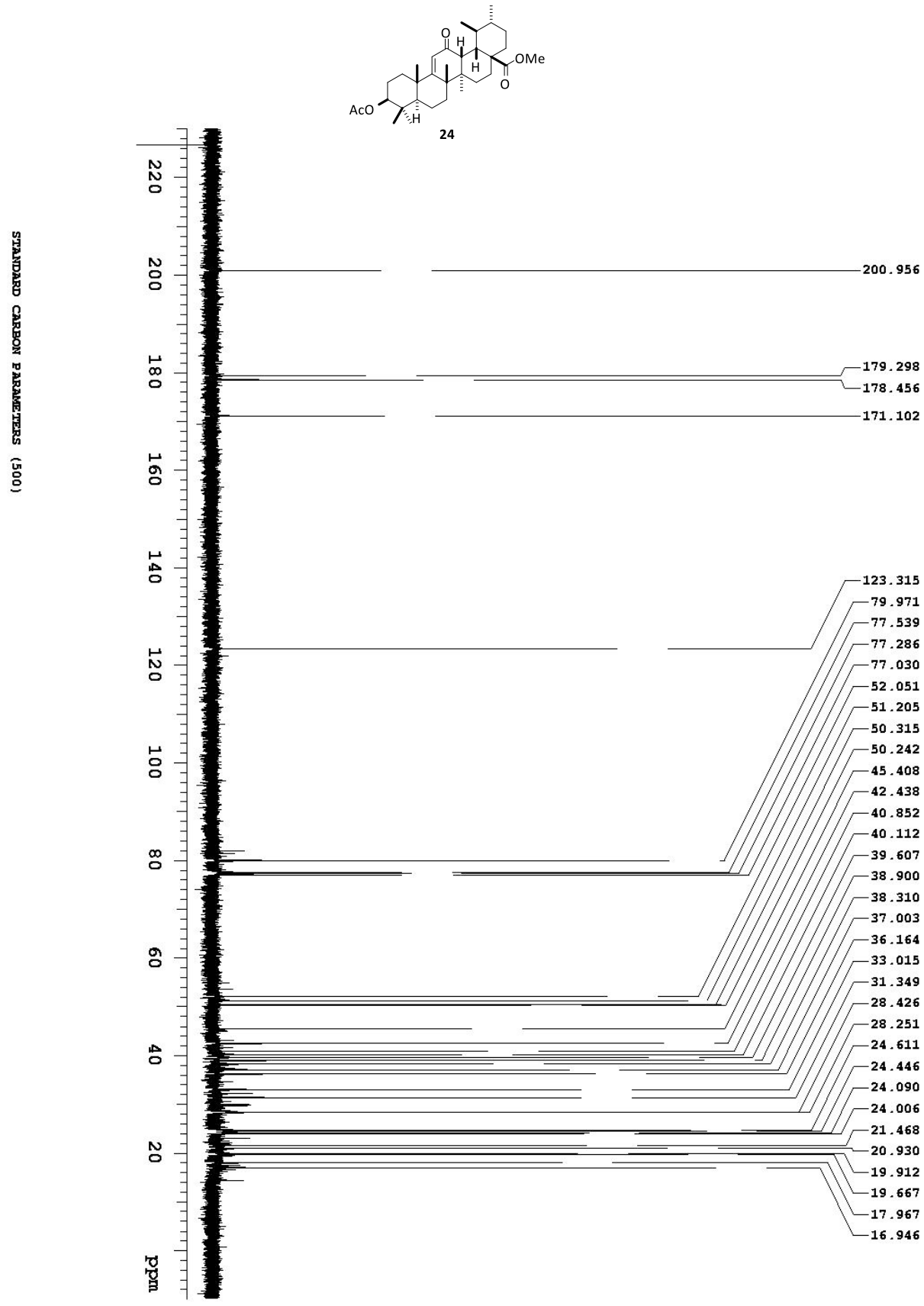
1.16
3.00
0.96
1.06
3.22


O
H
H
OMe
O
AcO
H
24
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140
120
100
80
60
40
20
ppm
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178.456
171.102
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79.971
77.539
77.286
77.030
52.051
51.205
50.315
50.242
45.408
42.438
40.852
40.112
39.607
38.900
38.310
37.003
36.164
33.015
31.349
28.426
28.251
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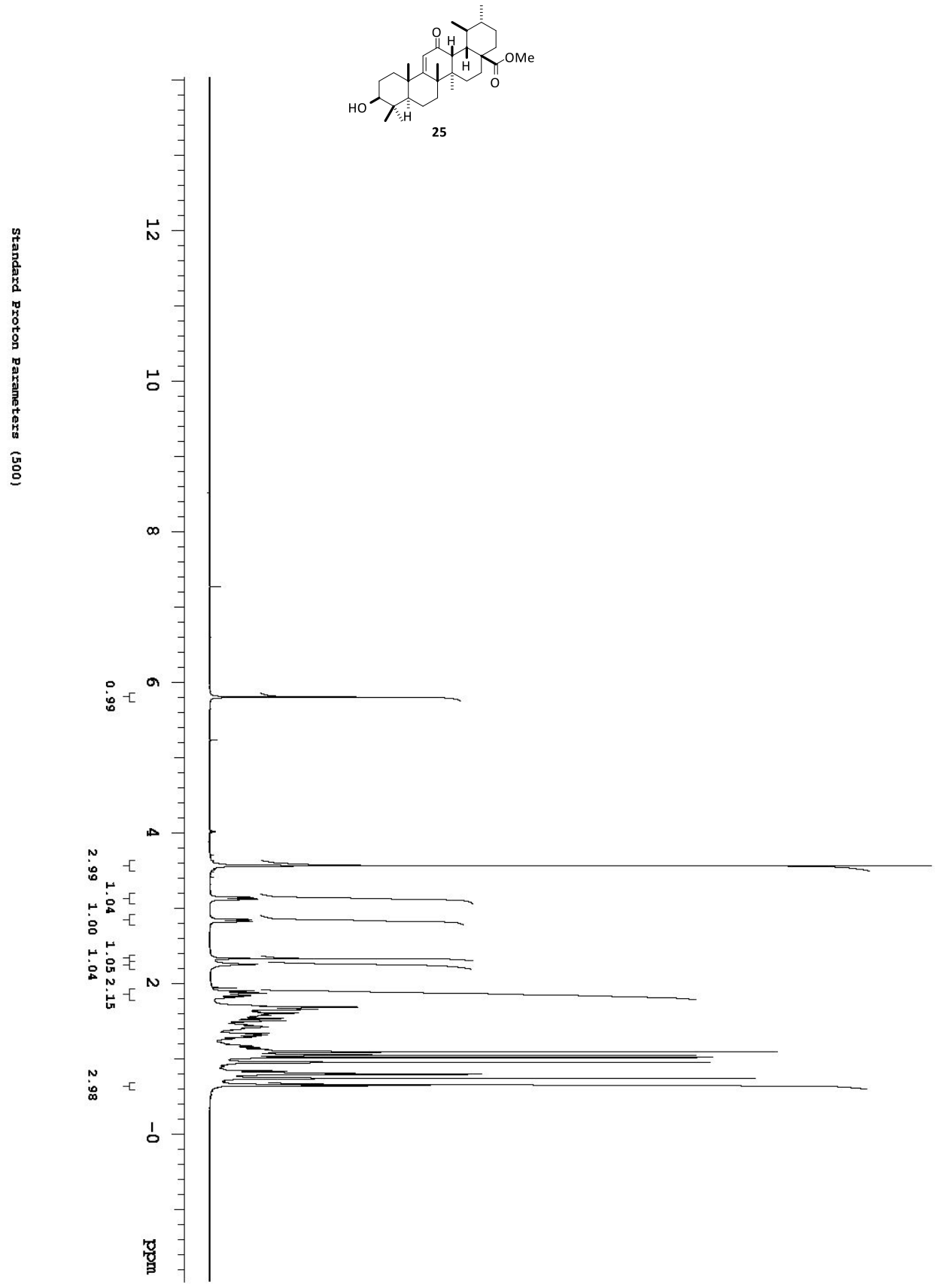
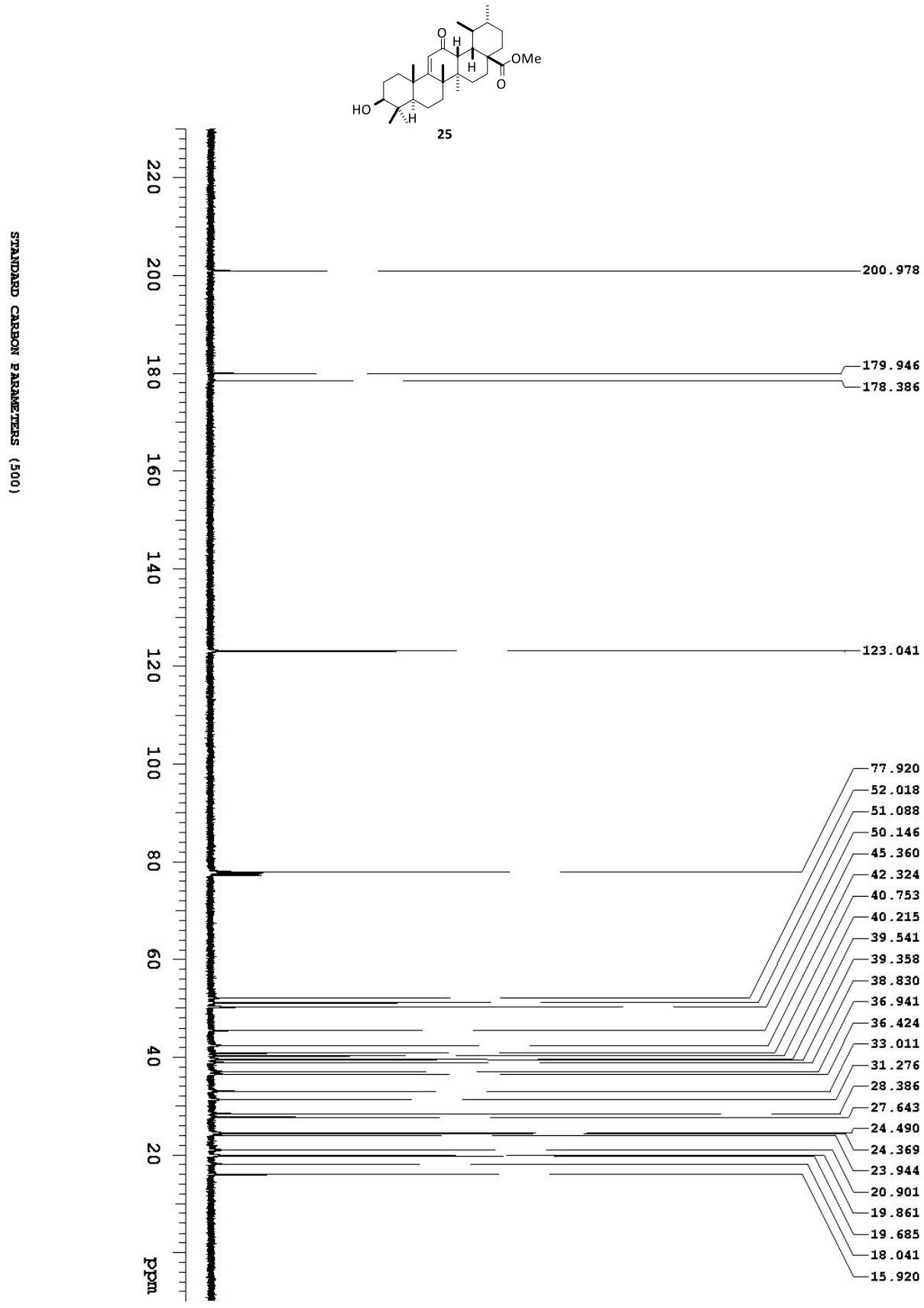
20.930
19.912
19.667
17.967
16.946



25

Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*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80
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40
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52.018
51.088
50.146
45.360
42.324
40.753
40.215
39.541
39.358
38.830
36.941
36.424
33.011
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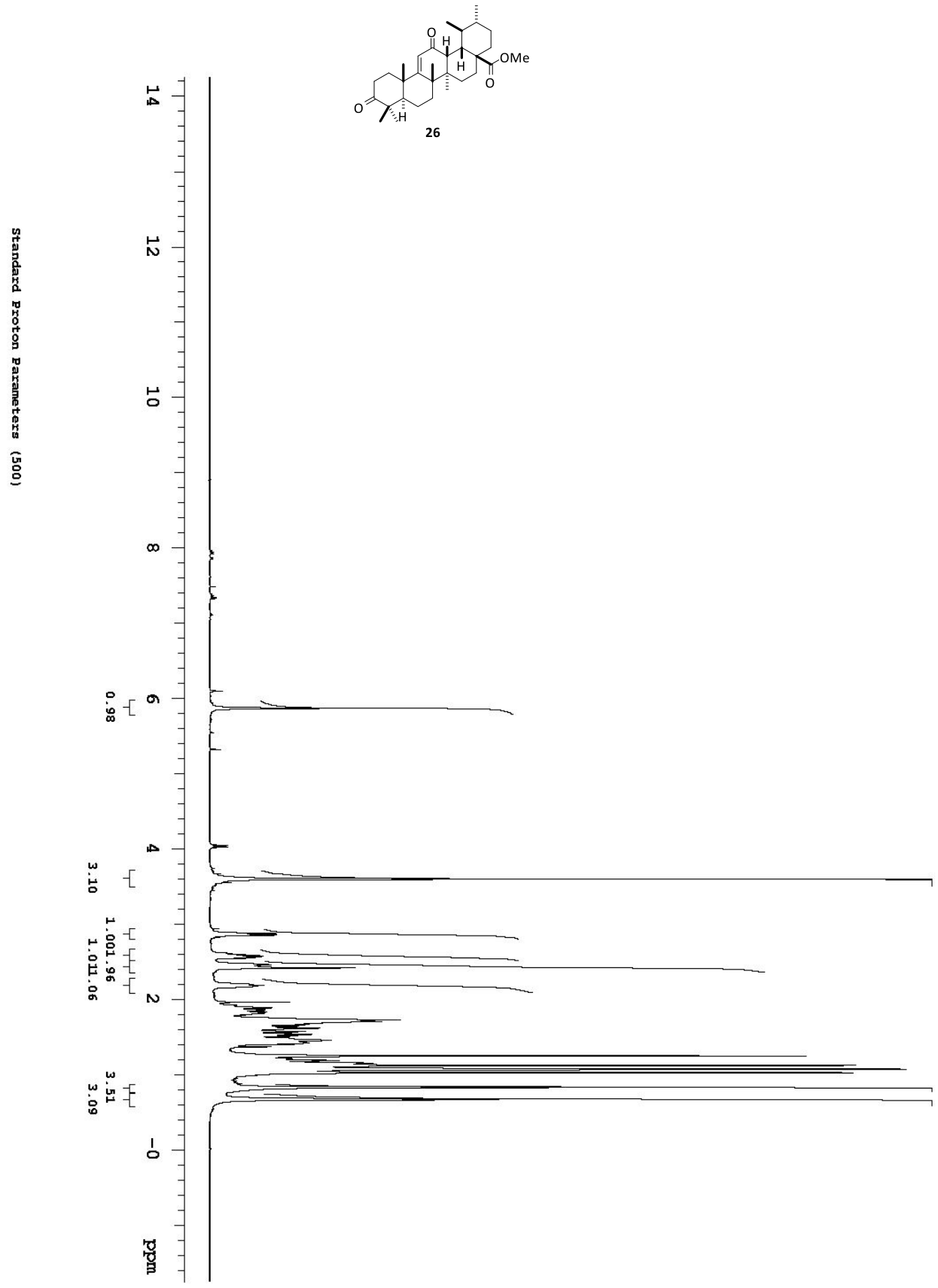
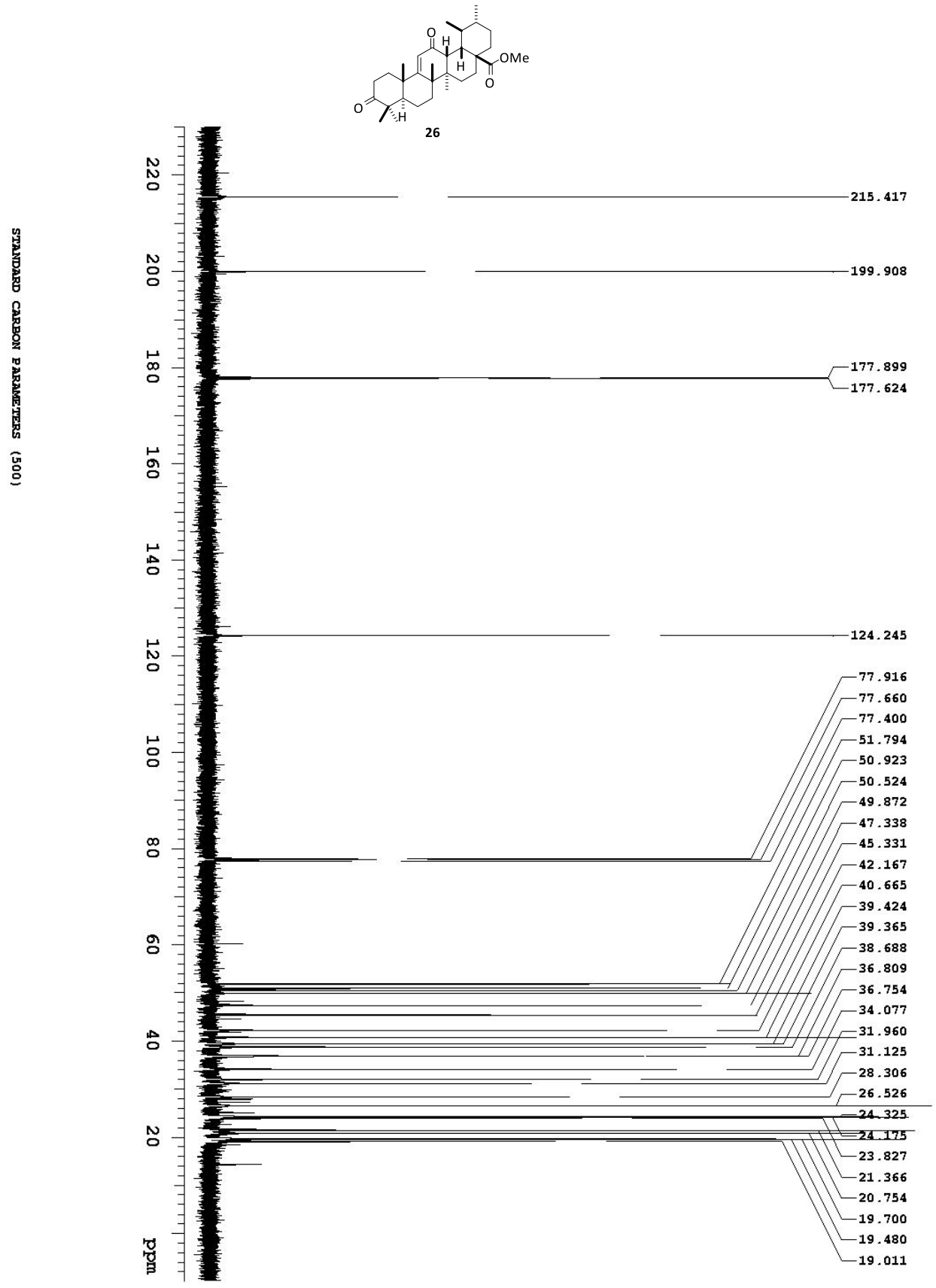
27.643
24.490
24.369
23.944
20.901
19.861
19.685
18.041
15.920

25



26

Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*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140
120
100
80
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20
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177.624
124.245
77.916
77.660
77.400
51.794
50.923
50.524
49.872
47.338
45.331
42.167
40.665
39.424
39.365
38.688
36.809
36.754
34.077
31.960
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20.754
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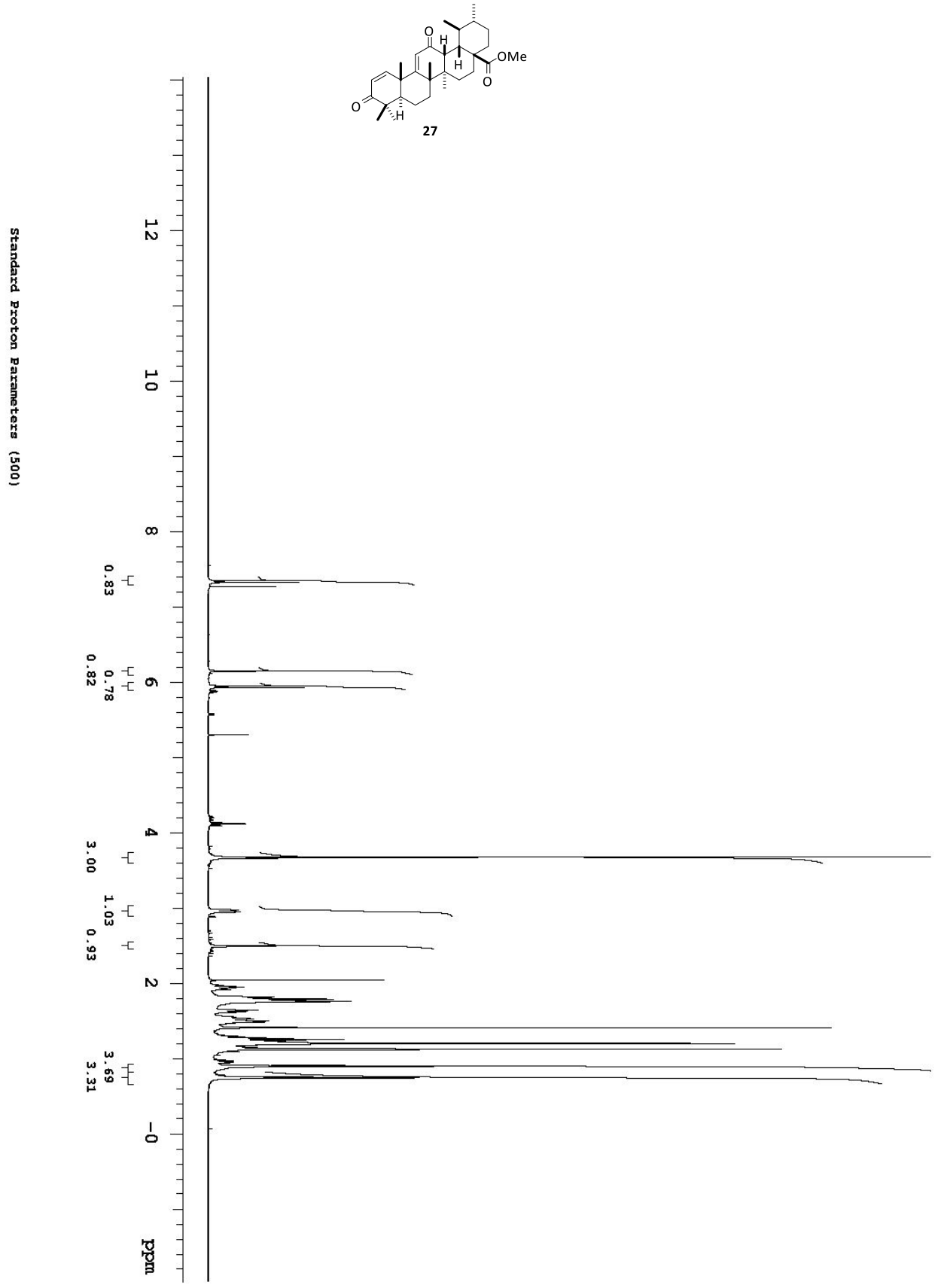
19.480
19.011

26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6
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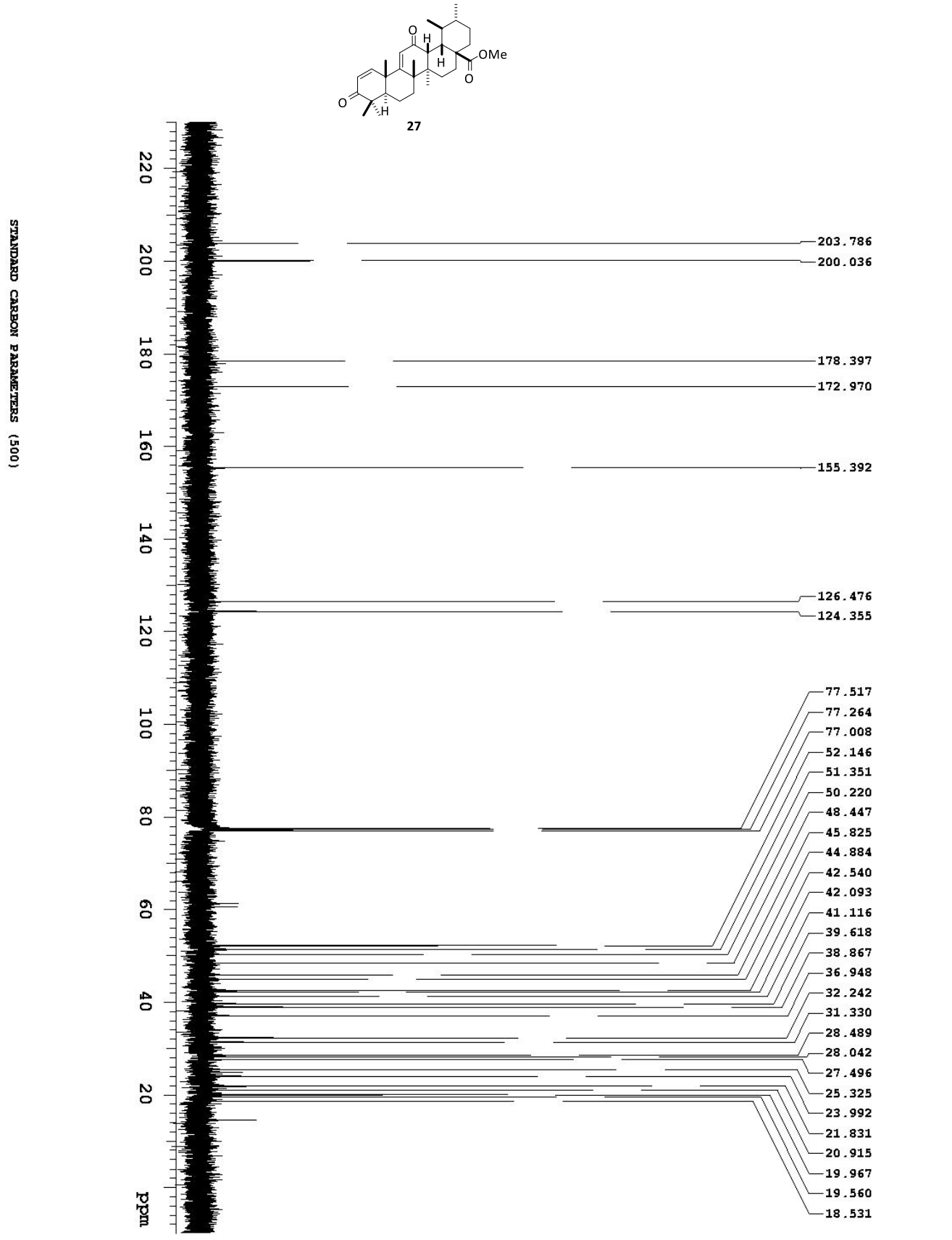
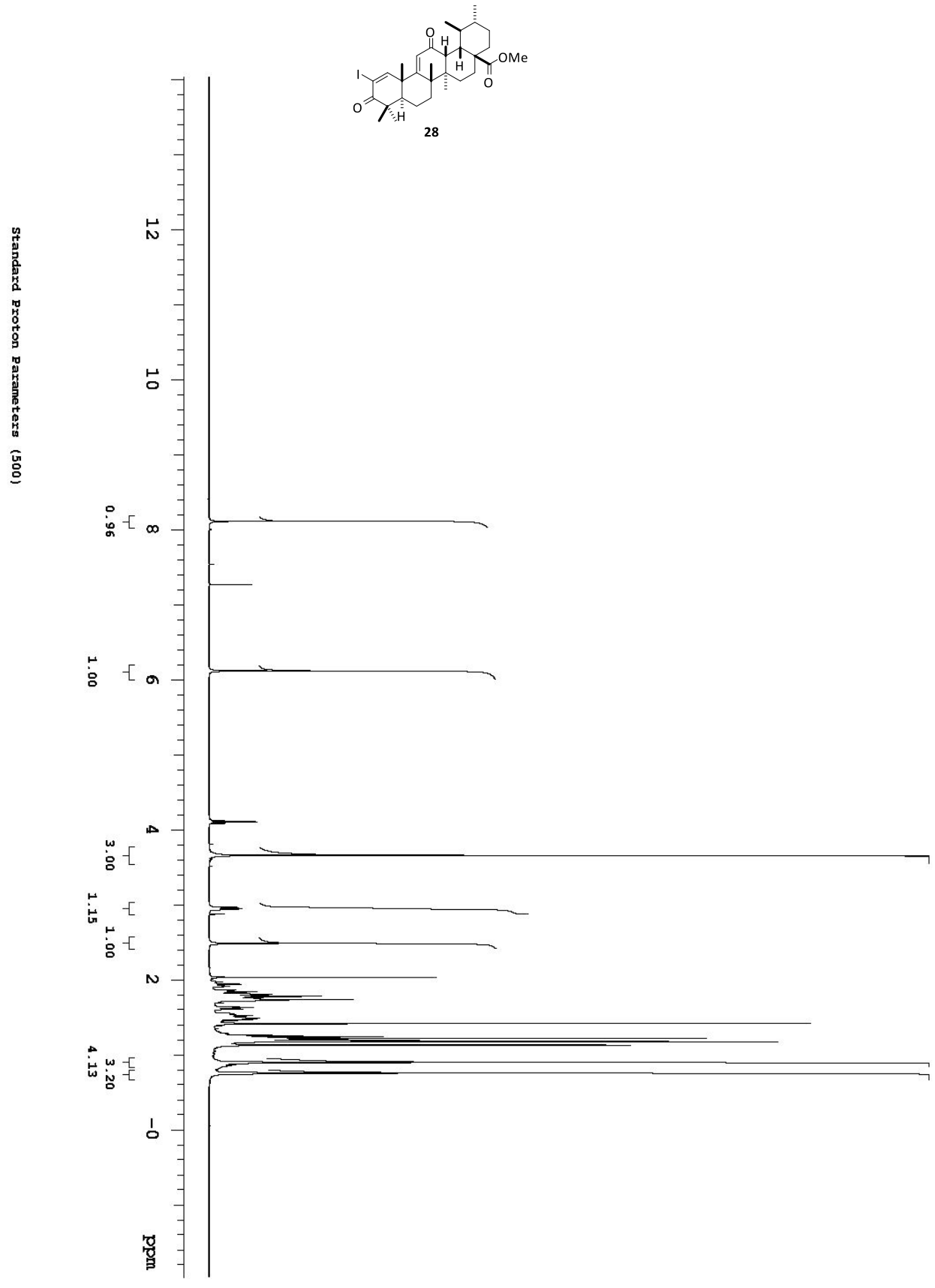
3.31
O
H
H
OMe
O
O
H

27

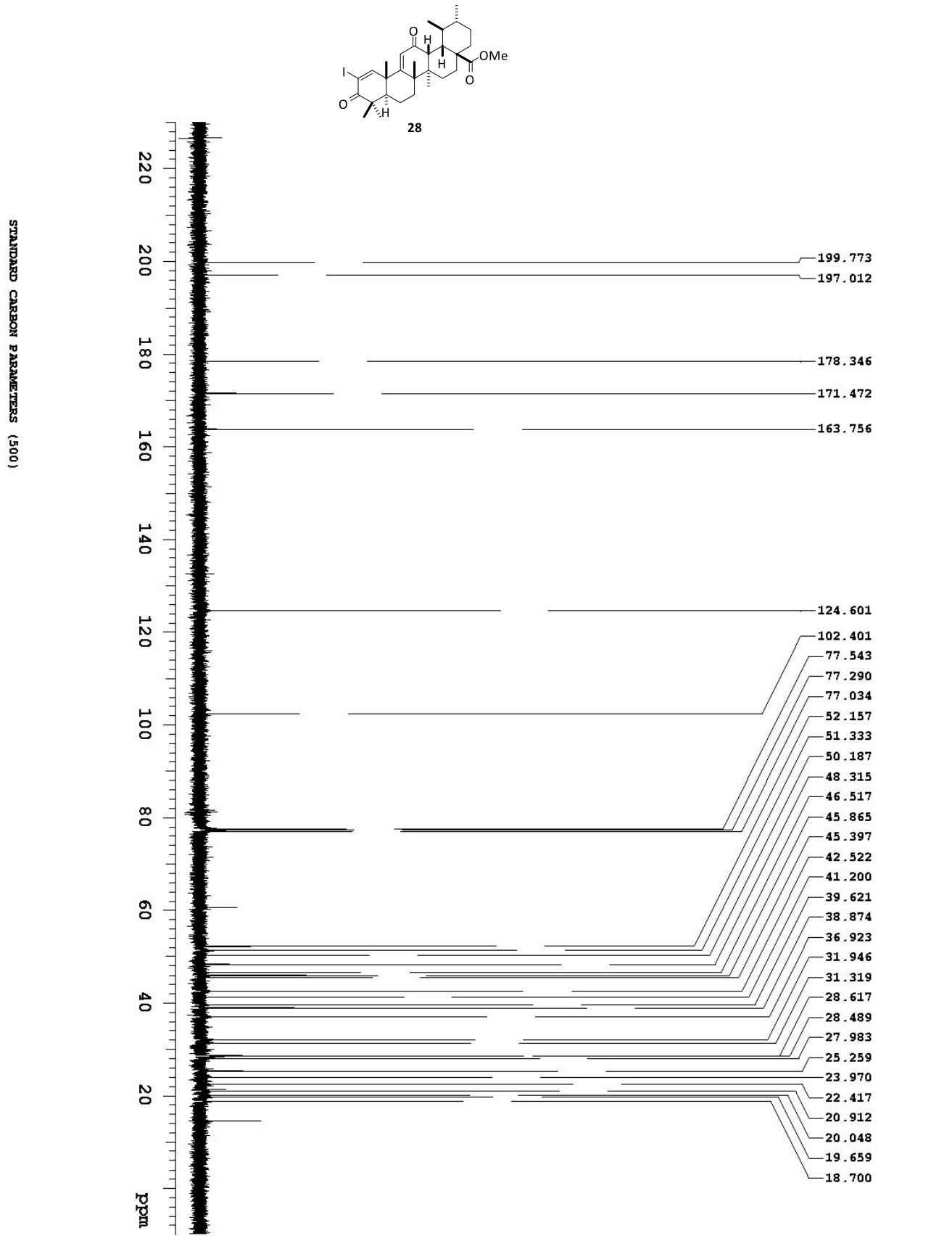


Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*

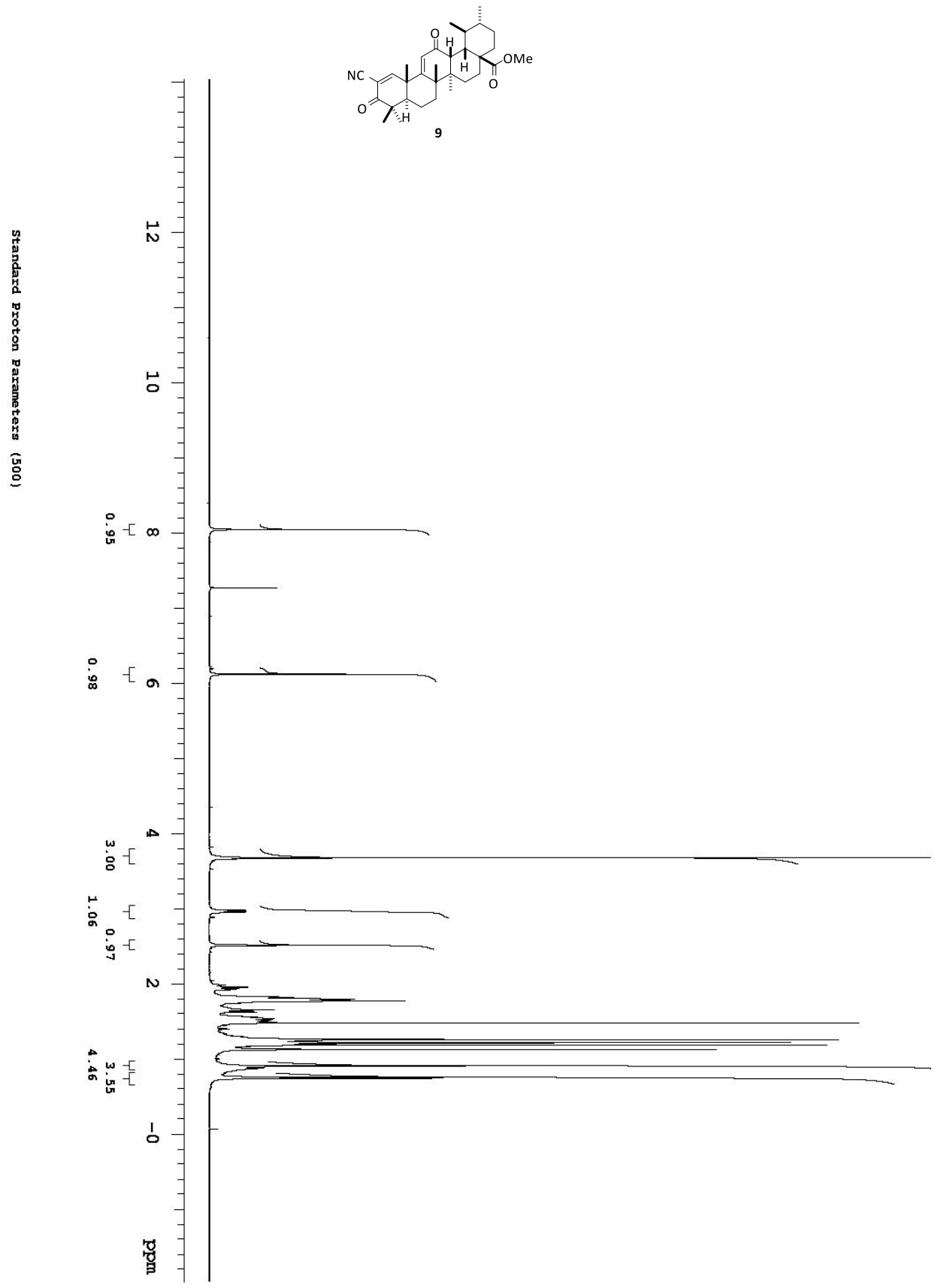


28

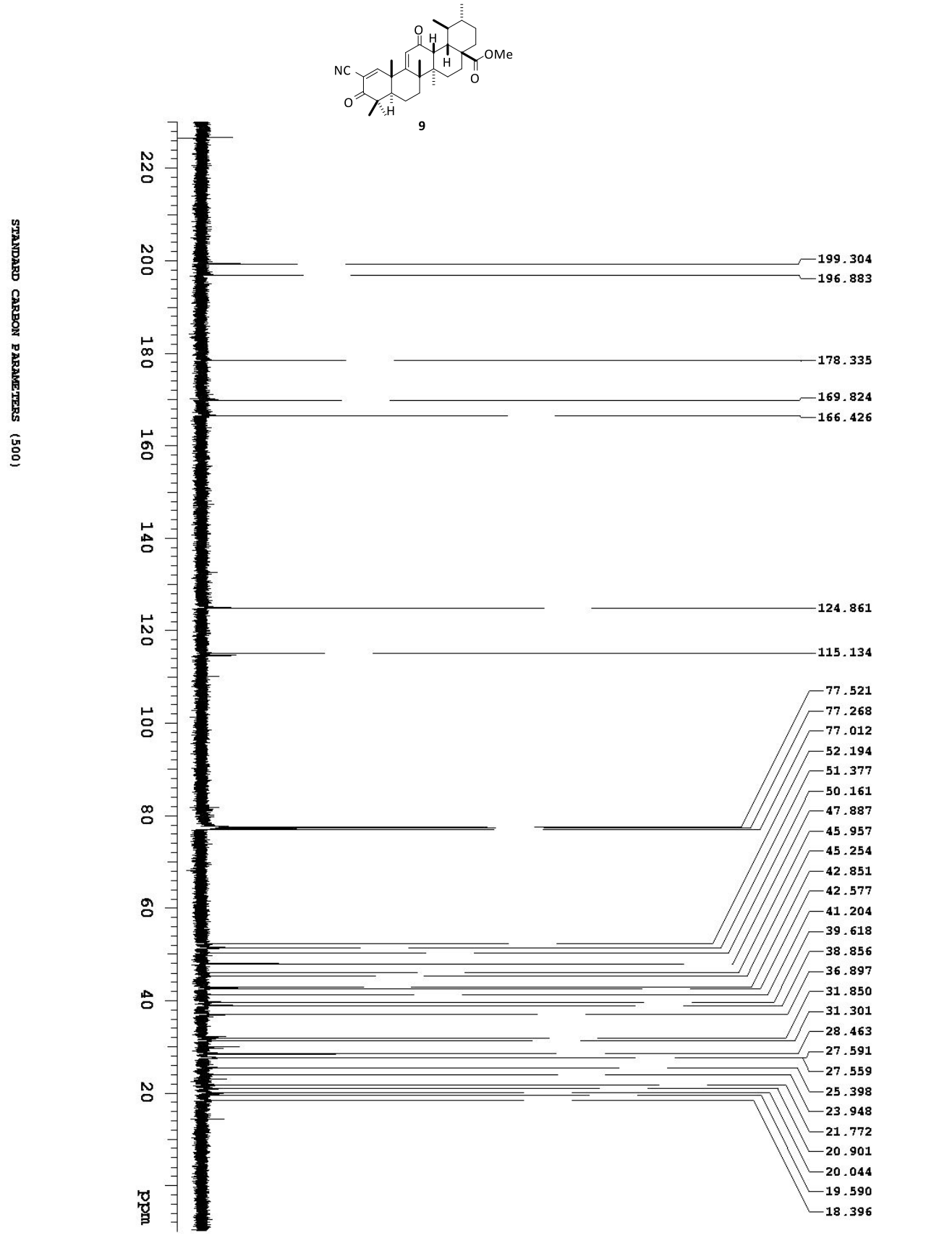
Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*



Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*



Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*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H
H
OMe
O
O
H
9
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120
100
80
60
40
20
ppm
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169.824
166.426
124.861
115.134
77.521
77.268
77.012
52.194
51.377
50.161
47.887
45.957
45.254
42.851
42.577
41.204
39.618
38.856
36.897
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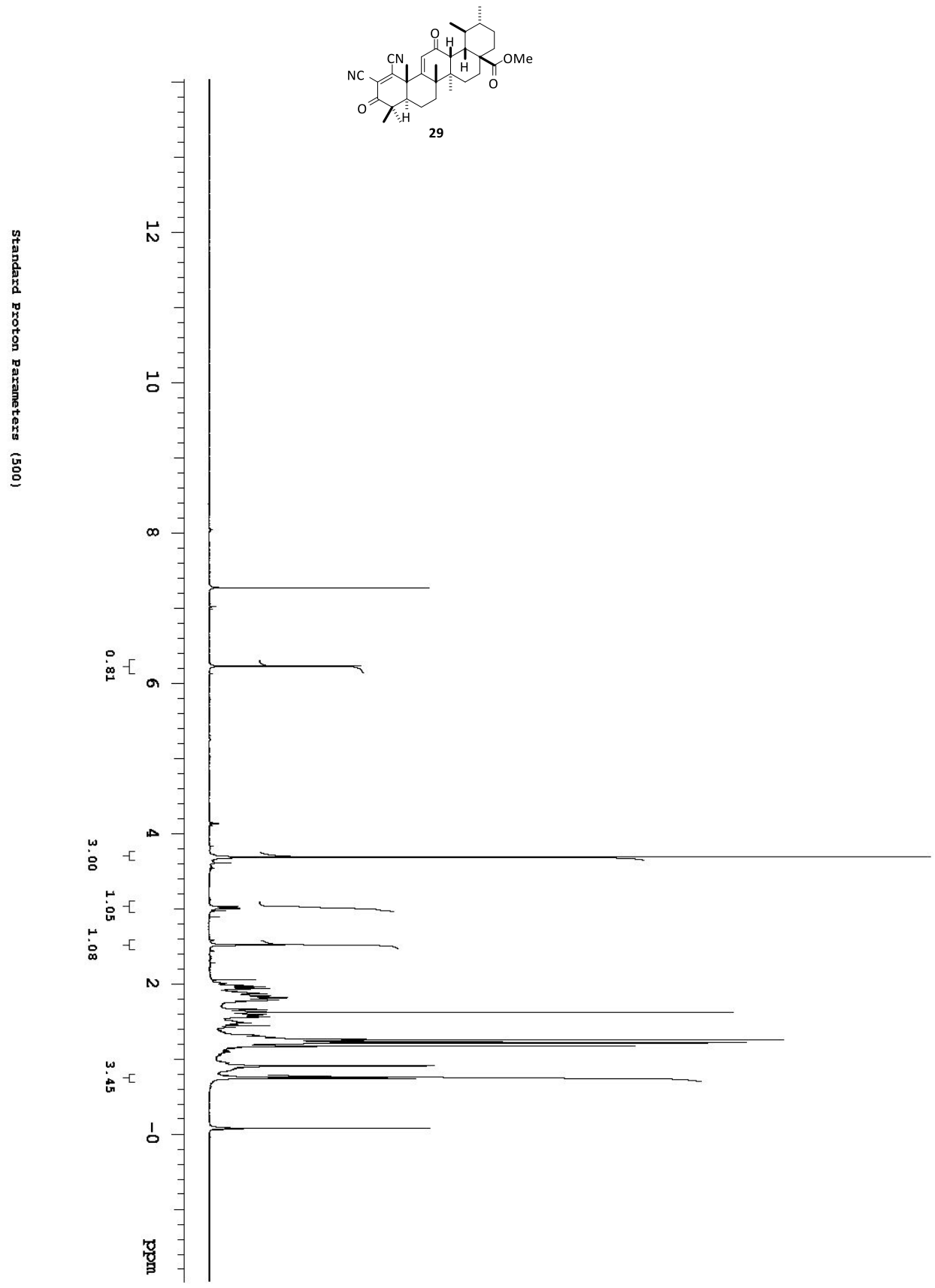
19.590
18.396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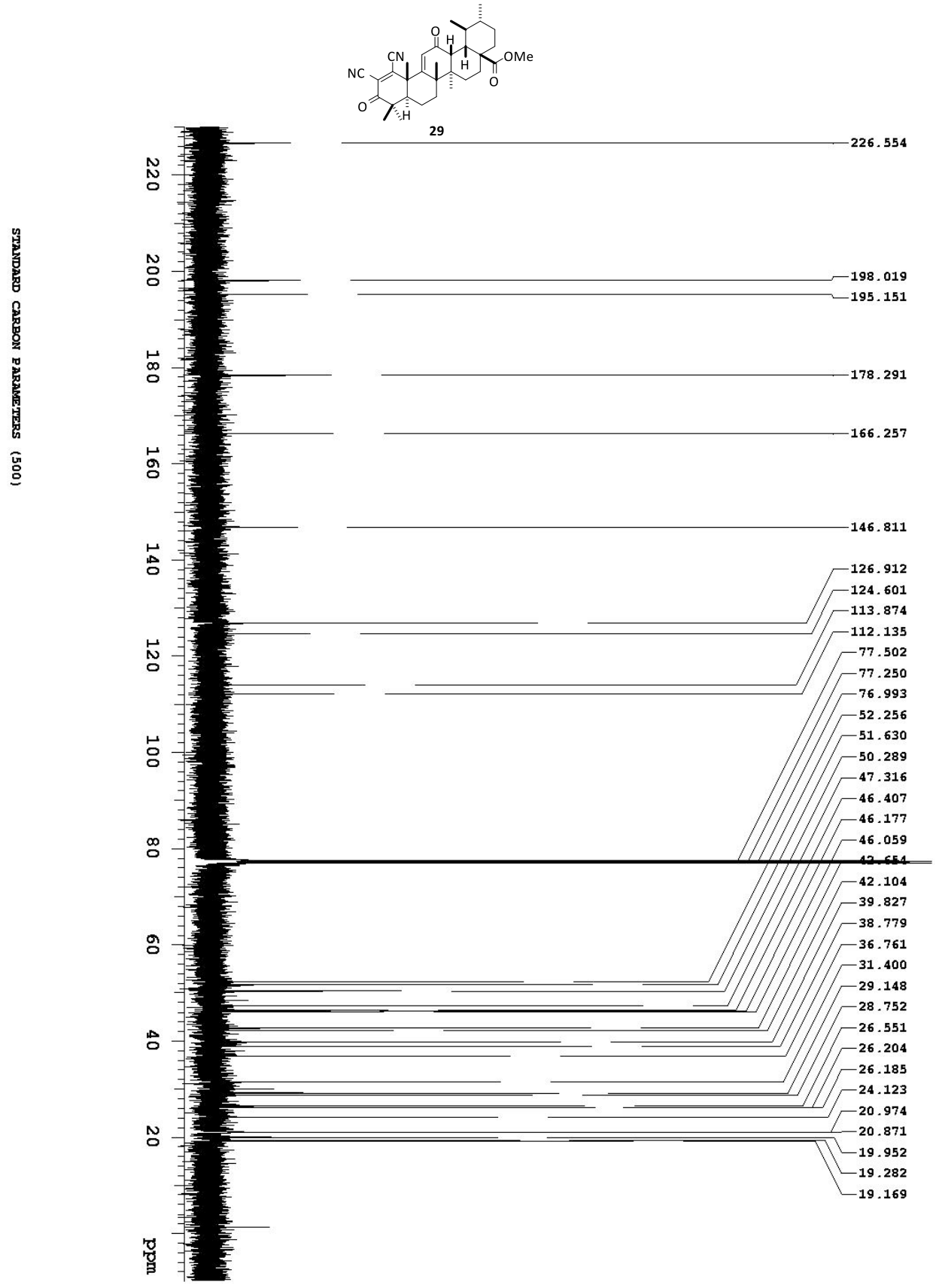
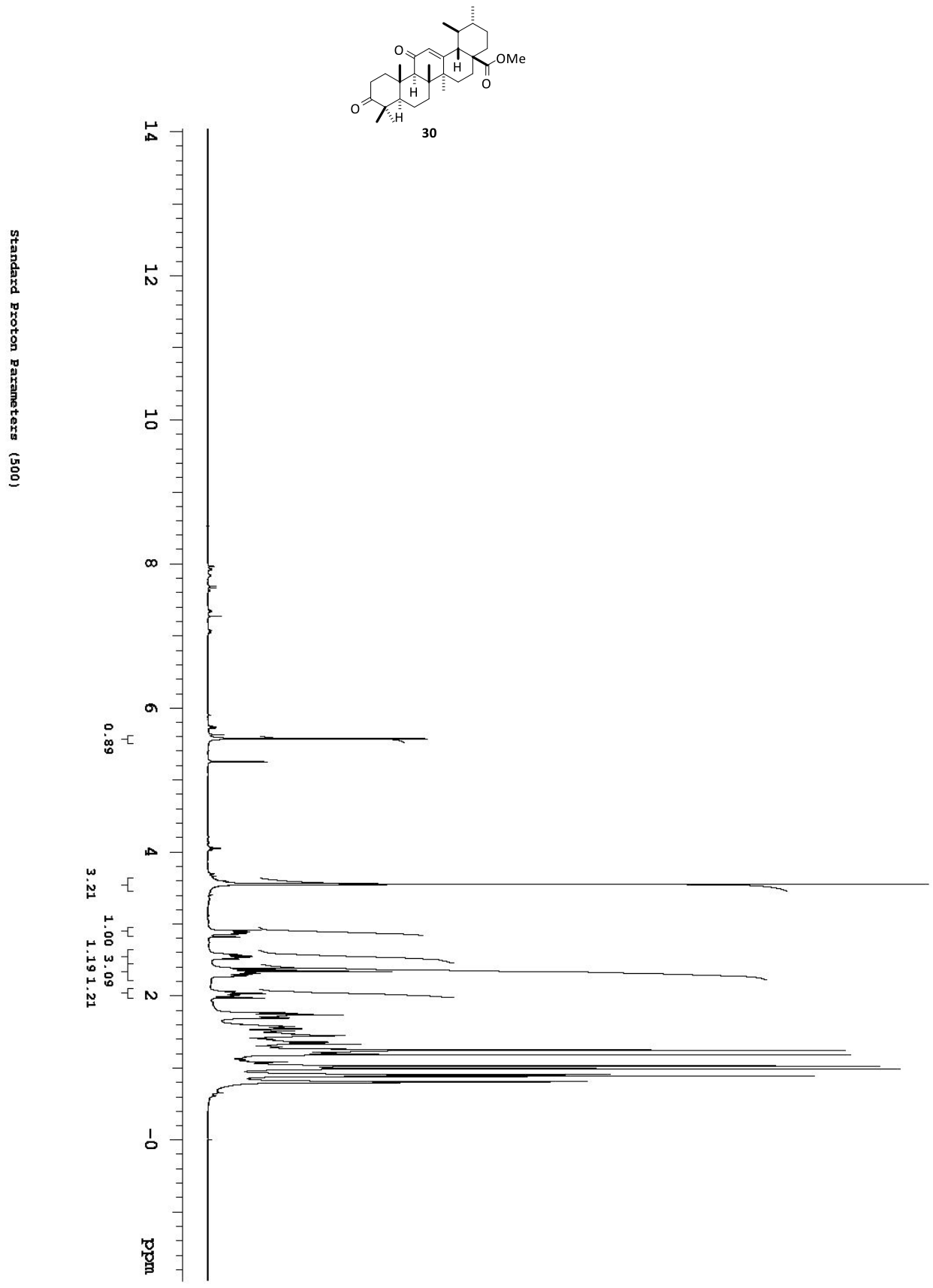
CN
NC
OMe
H
O
O
H

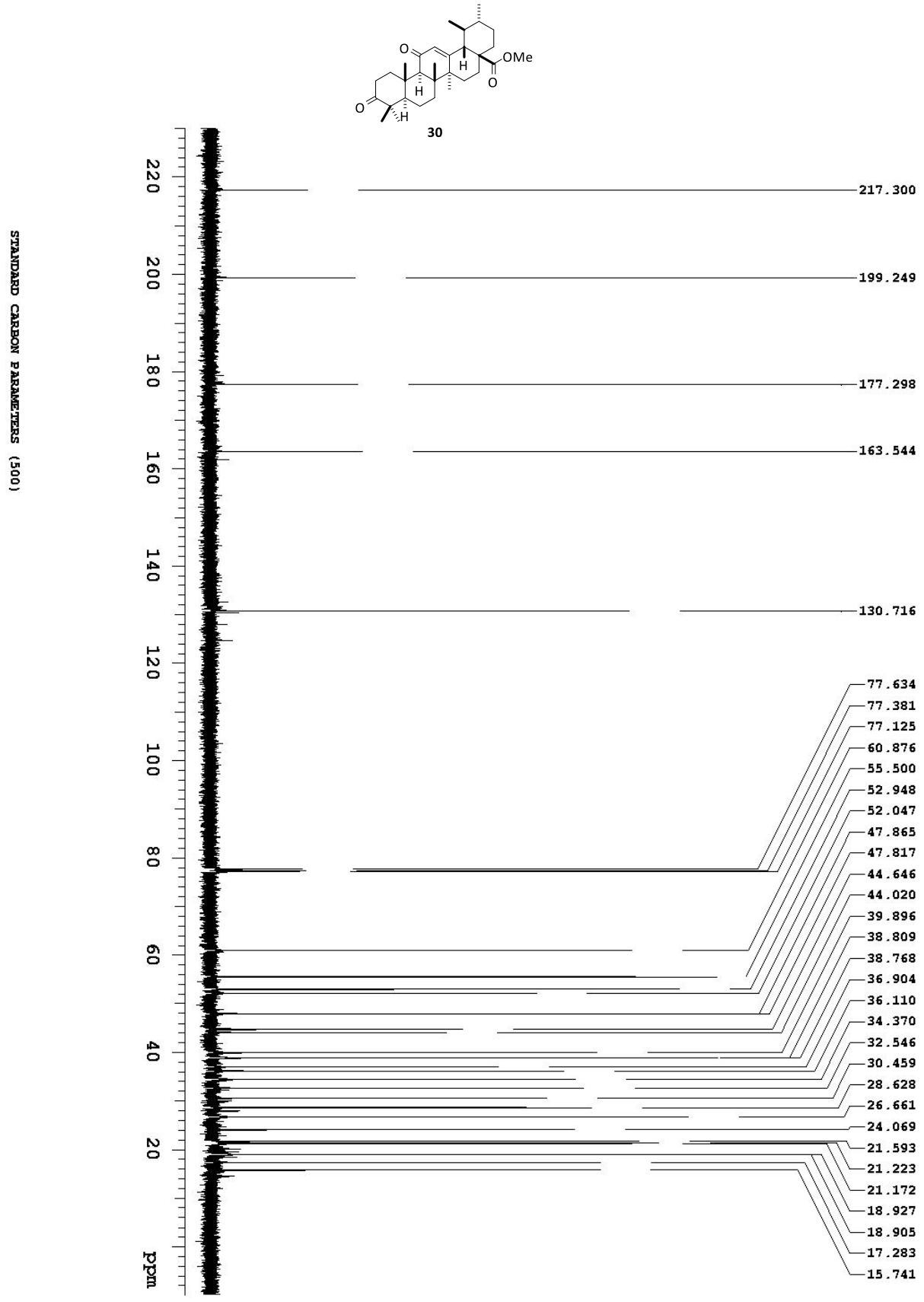
29



Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*



Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*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OMe
H
H
O
O
H
30
STANDARD CARBON PARAMETERS (500)
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200
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160
140
120
100
80
60
40
20
ppm
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199.249
177.298
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77.381
77.125
60.876
55.500
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52.047
47.865
47.817
44.646
44.020
39.896
38.809
38.768
36.904
36.110
34.370
32.546
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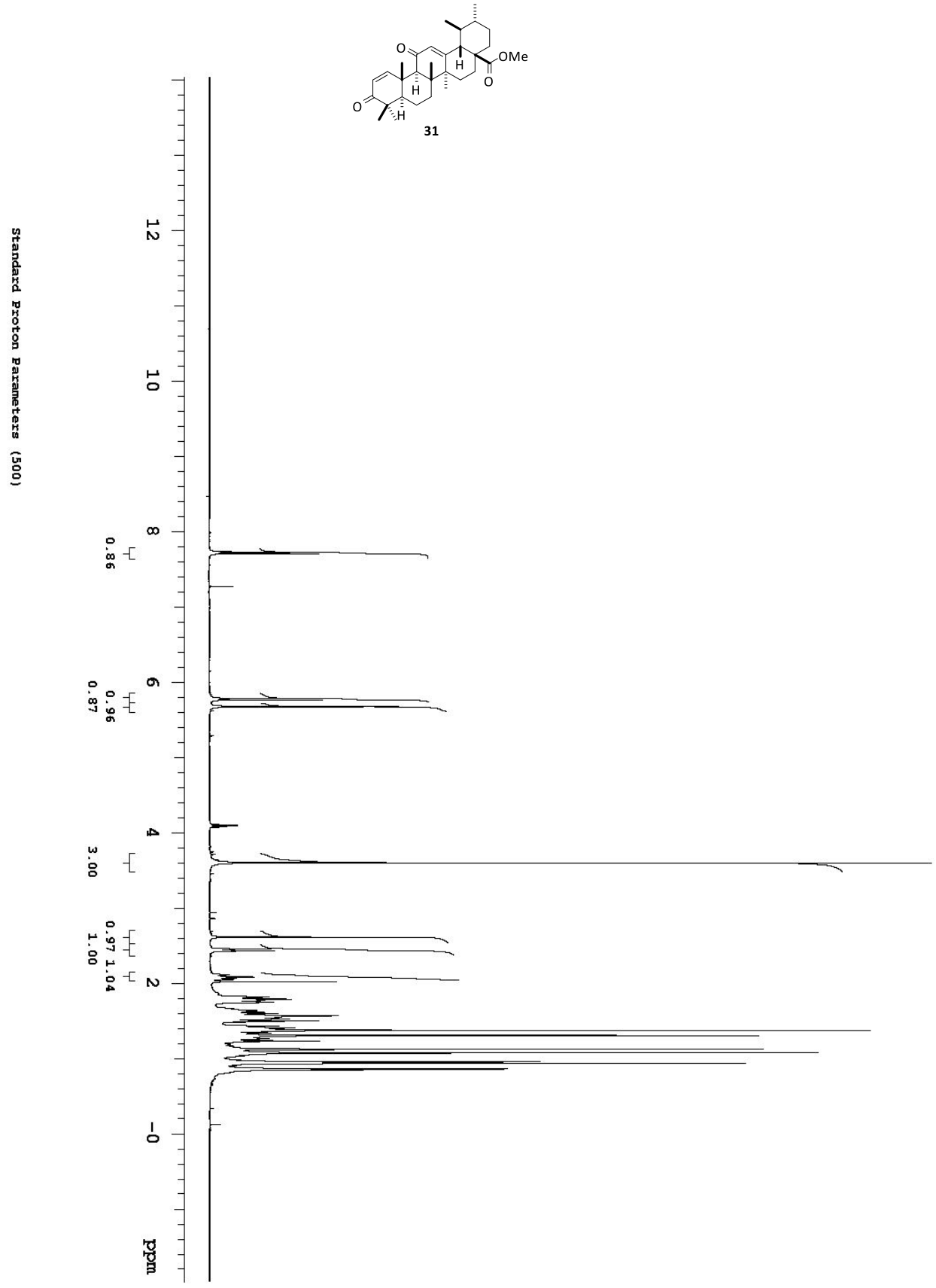
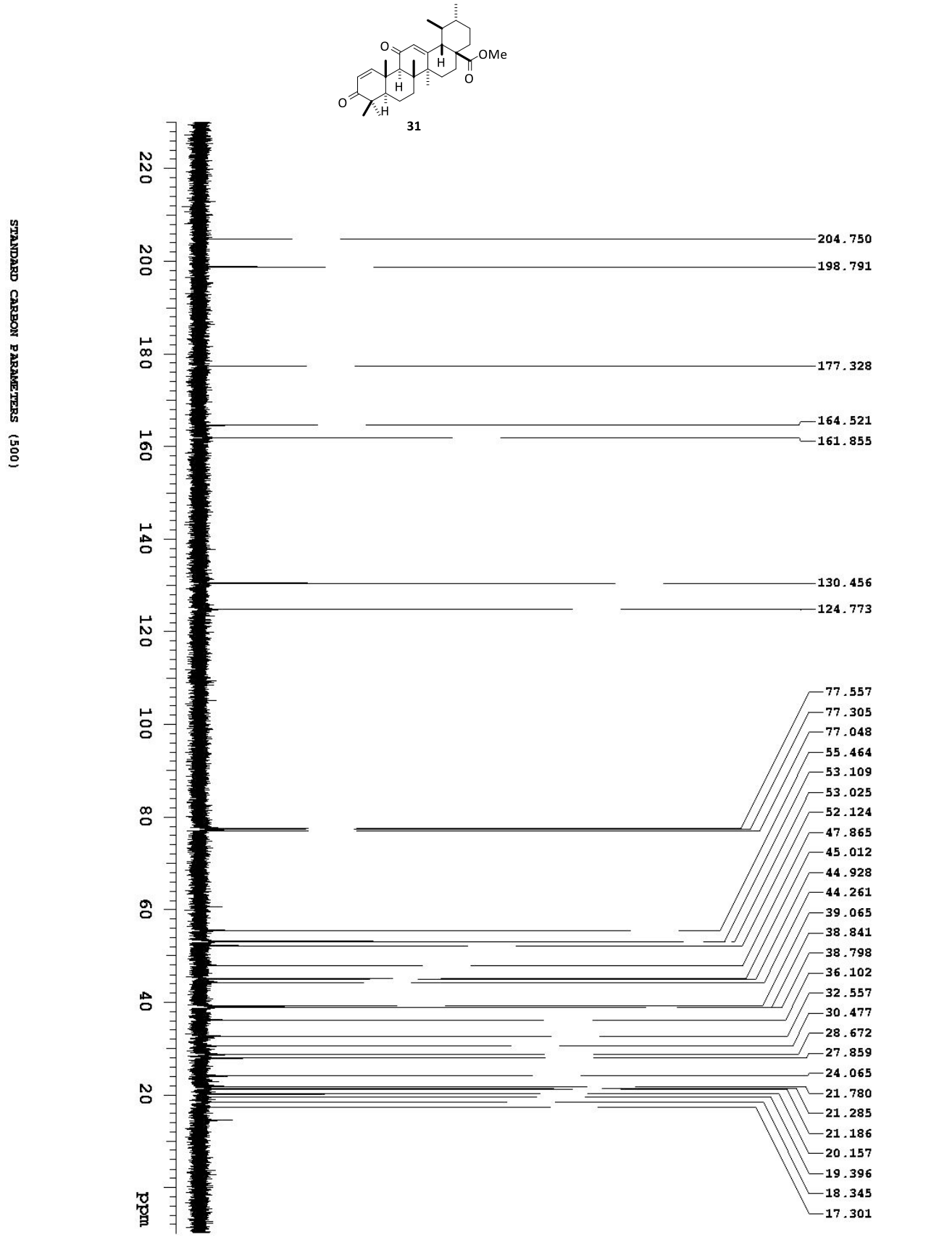


31

Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*


O
OMe
H
O
H
O
H
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80
60
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20
ppm
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45.012
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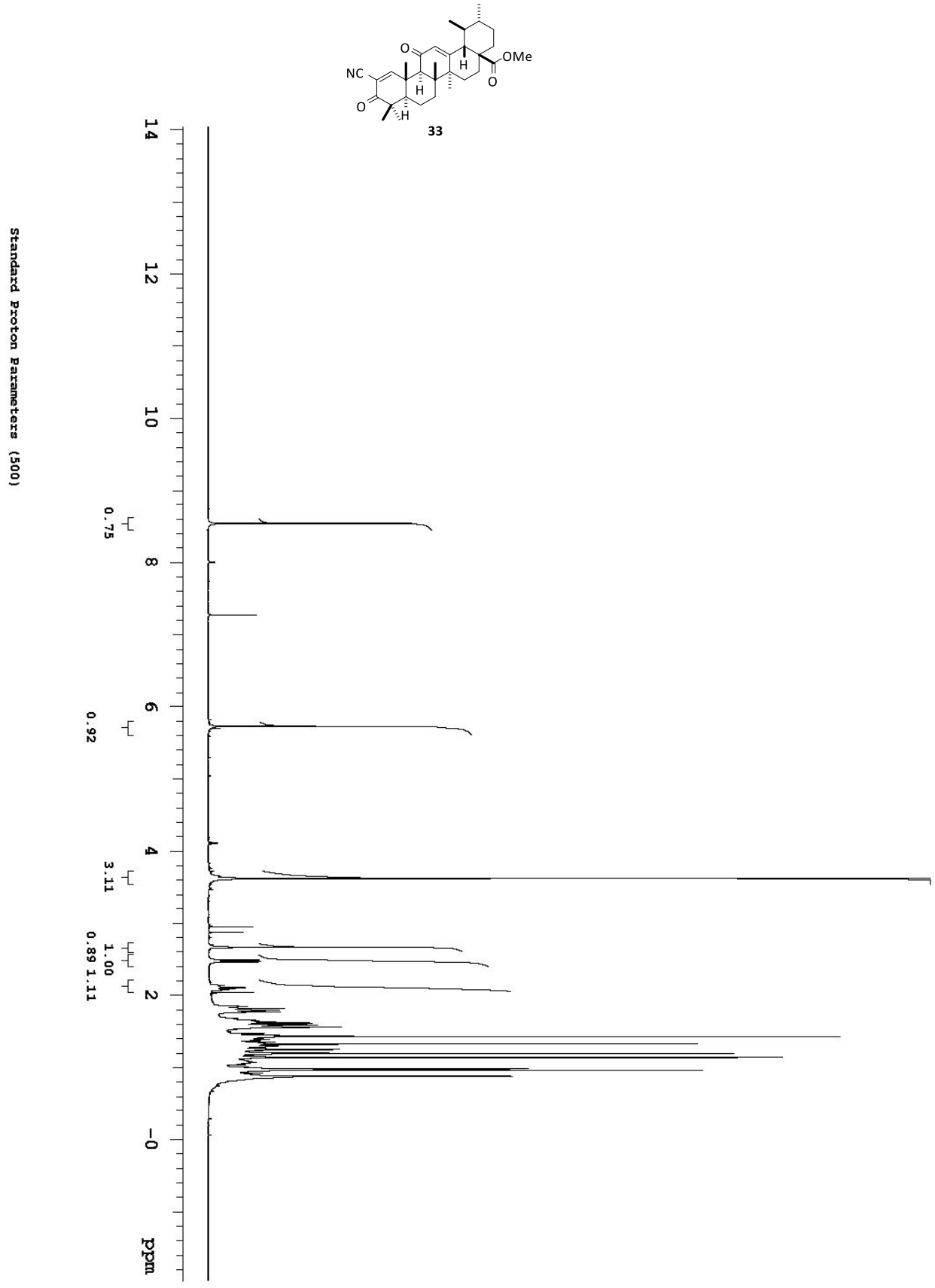
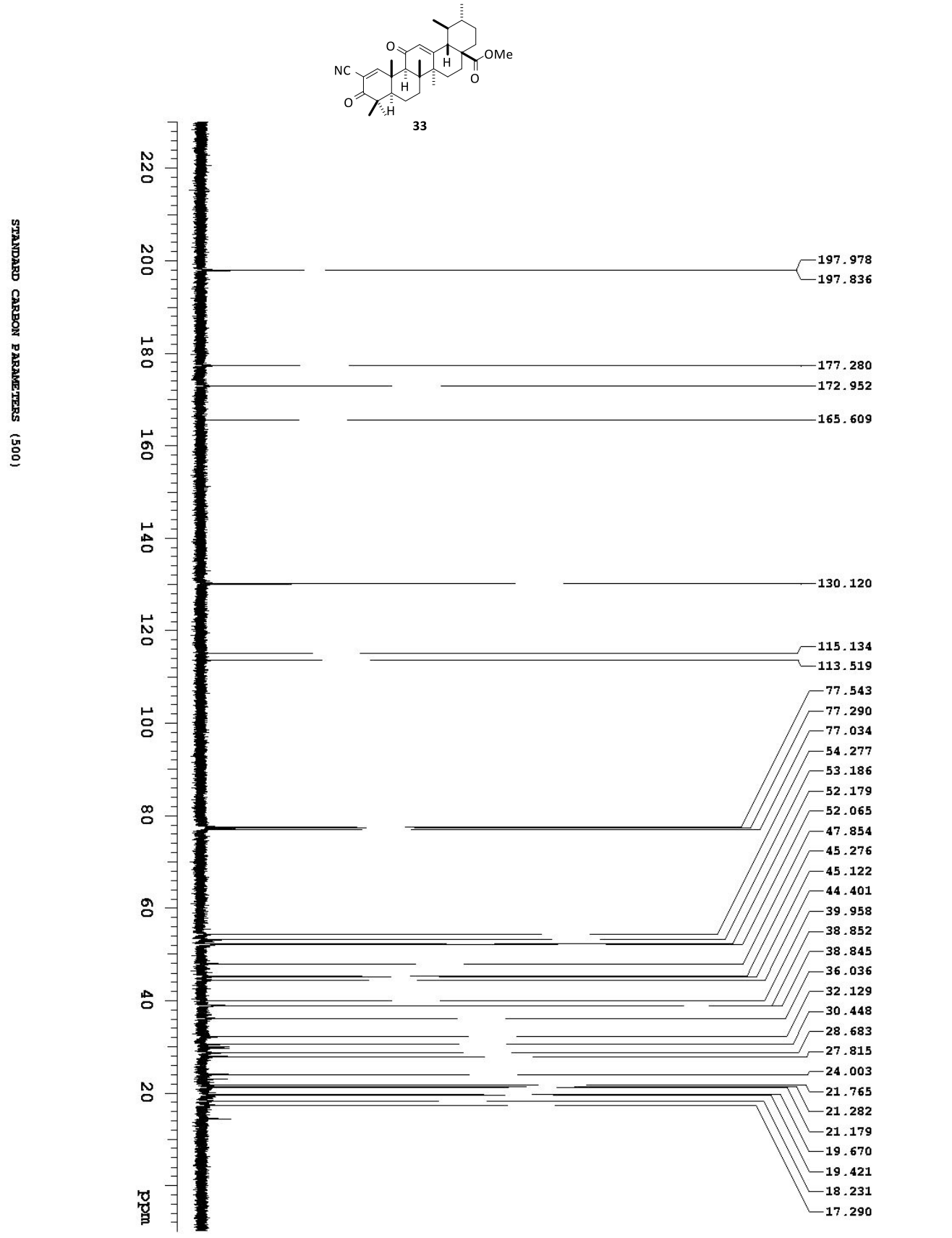


Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*


33
STANDARD CARBON PARAMETERS (500)
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180
160
140
120
100
80
60
40
20
ppm
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177.280
172.952
165.609
130.120
115.134
113.519
77.543
77.290
77.034
54.277
53.186
52.179
52.065
47.854
45.276
45.122
44.401
39.958
38.852
38.845
36.036
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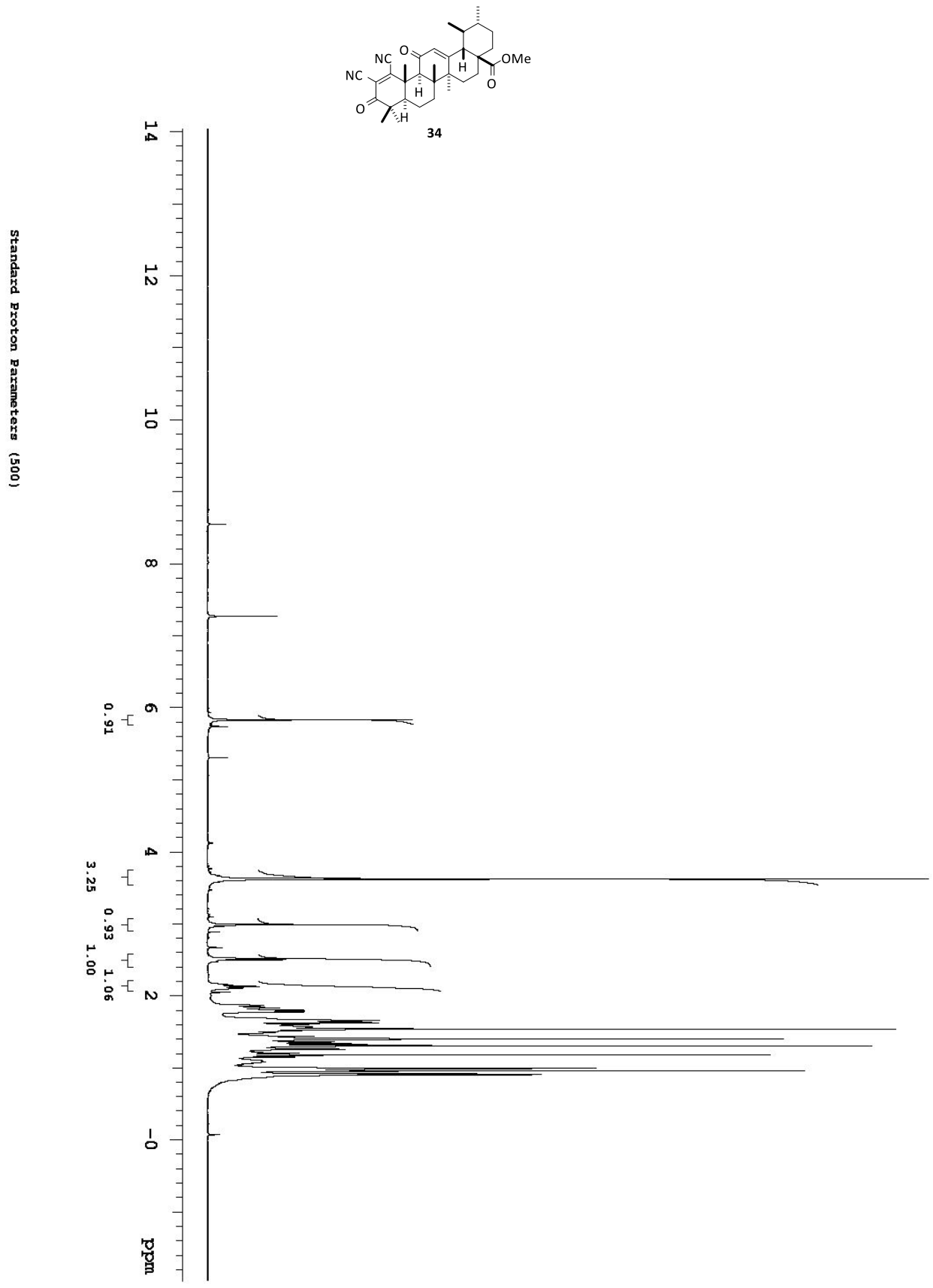
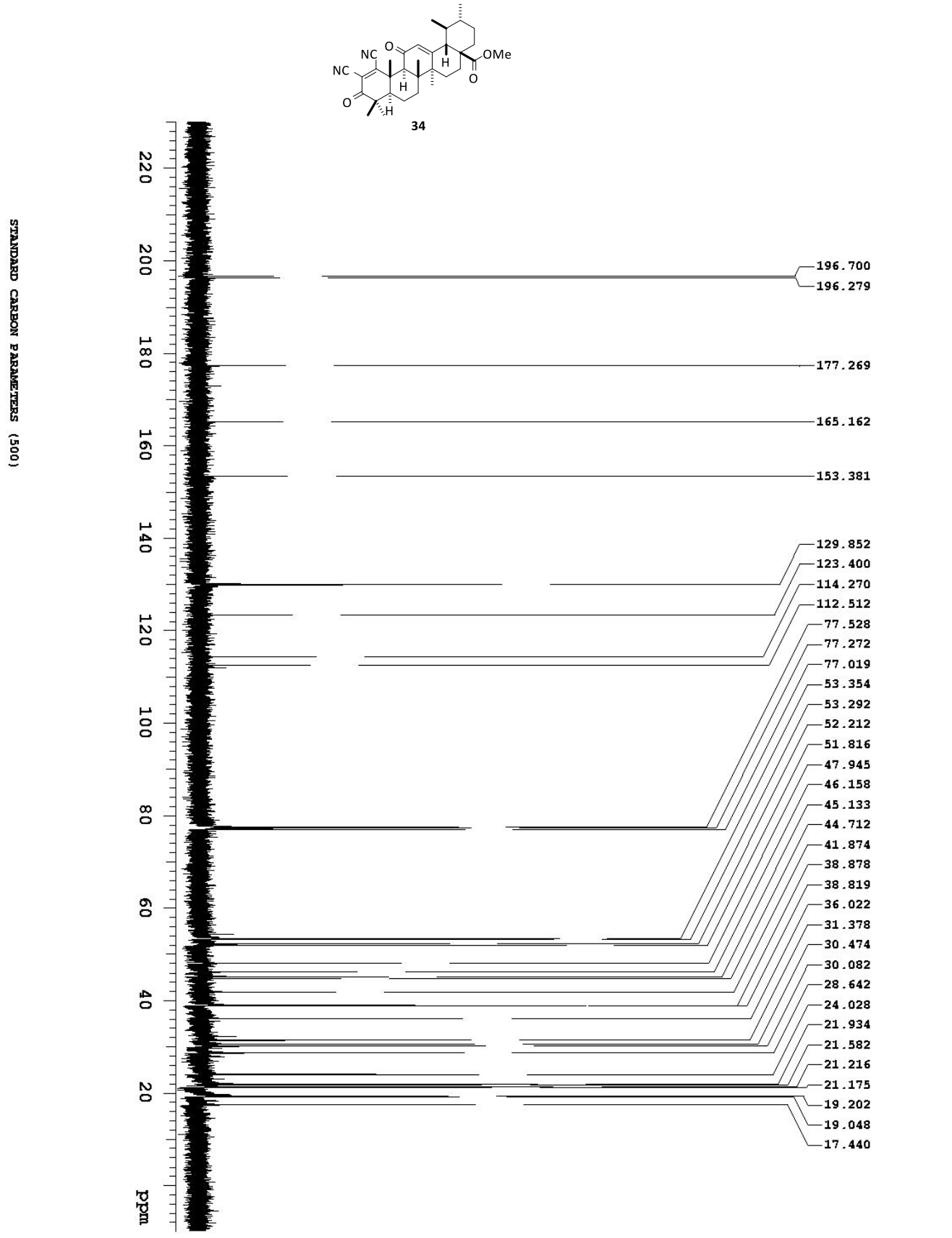


Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*


NC
NC
O
O
H
H
OMe
O
34
STANDARD CARBON PARAMETERS (500)
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200
180
160
140
120
100
80
60
40
20
ppm
196.700
196.279
177.269
165.162
153.381
129.852
123.400
114.270
112.512
77.528
77.272
77.019
53.354
53.292
52.212
51.816
47.945
46.158
45.133
44.712
41.874
38.878
38.819
36.022
31.378
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21.216
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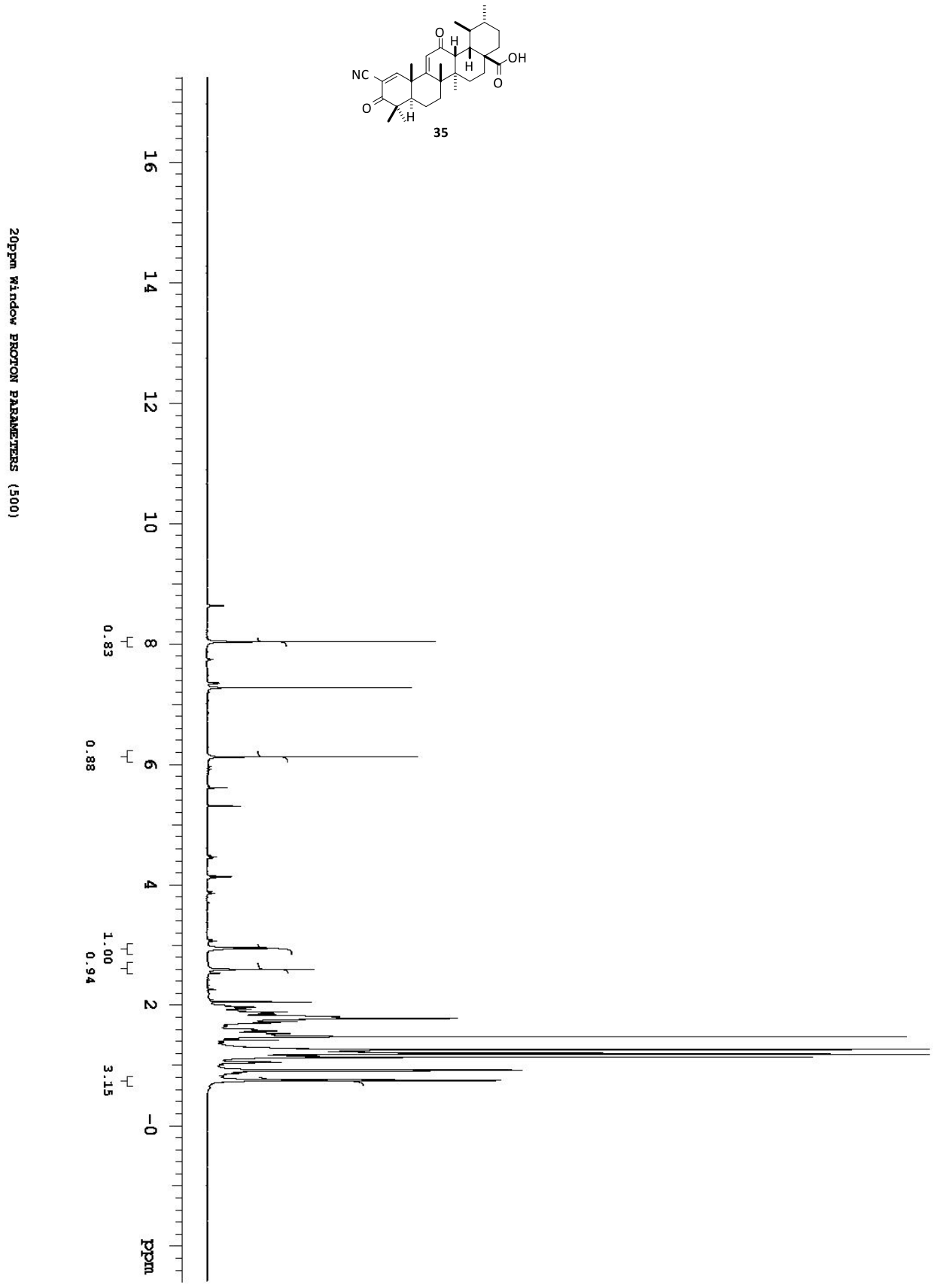
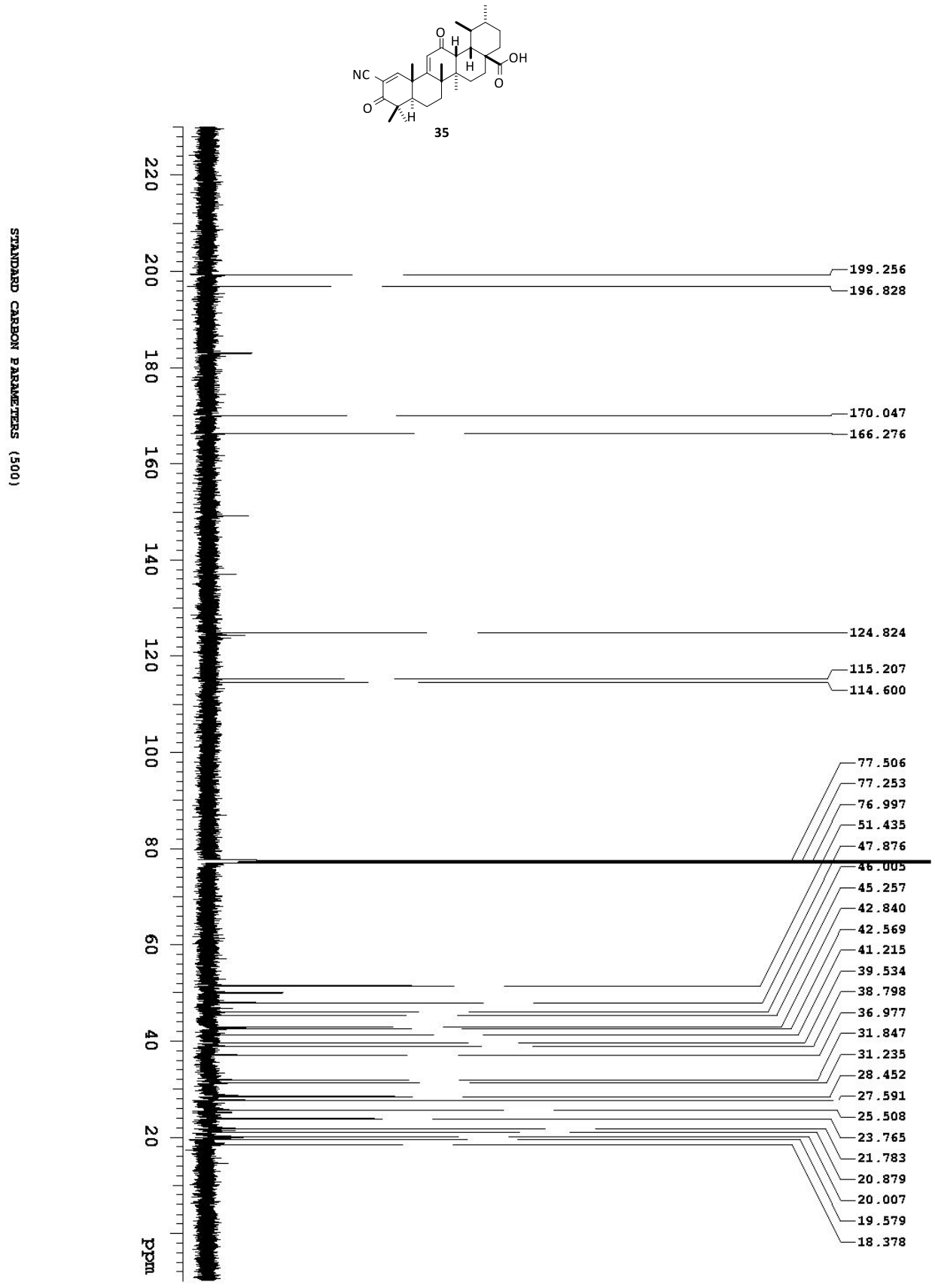


Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*


35
STANDARD CARBON PARAMETERS (500)
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180
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140
120
100
80
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40
20
ppm
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47.876
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42.840
42.569
41.215
39.534
38.798
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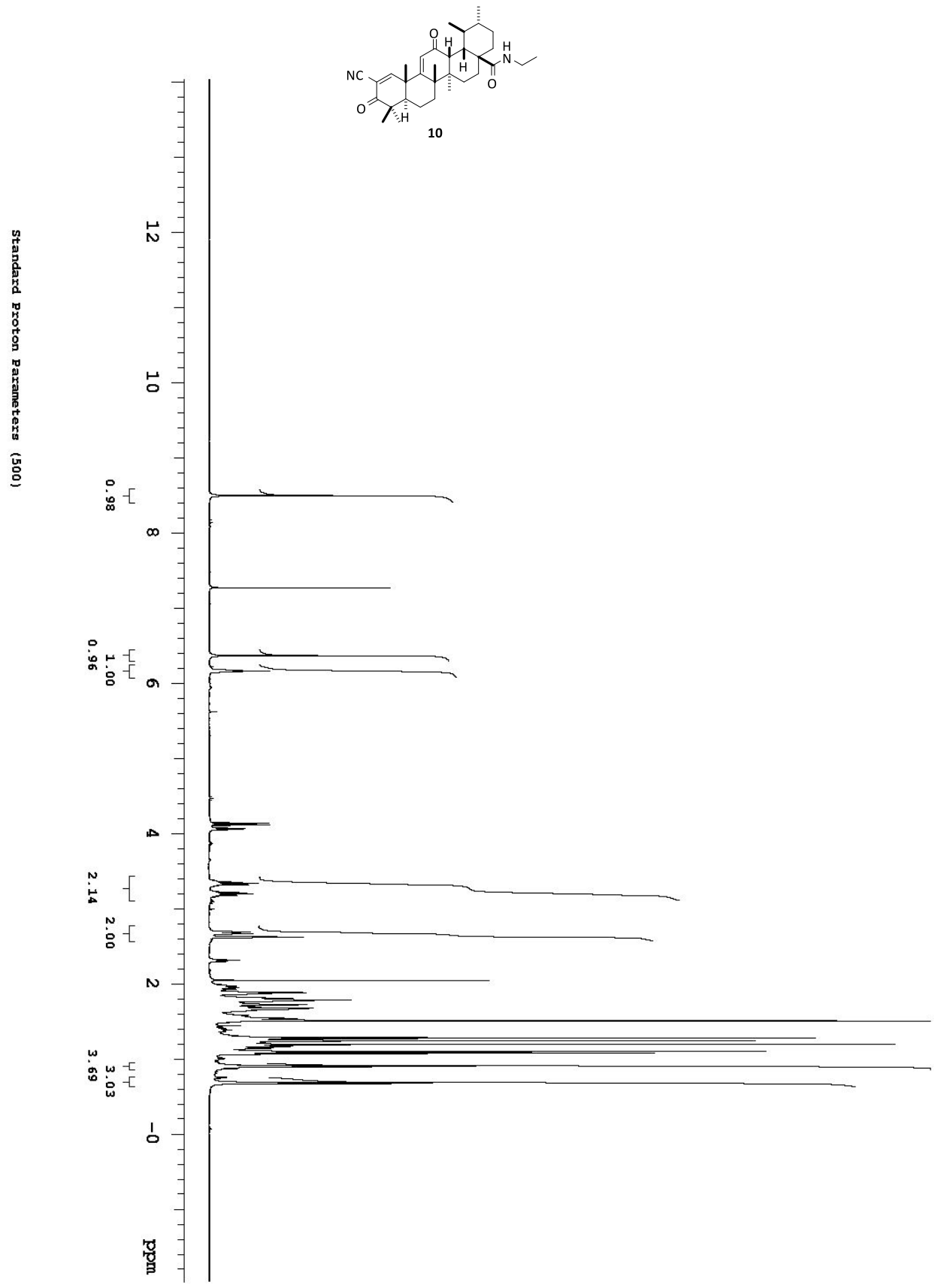
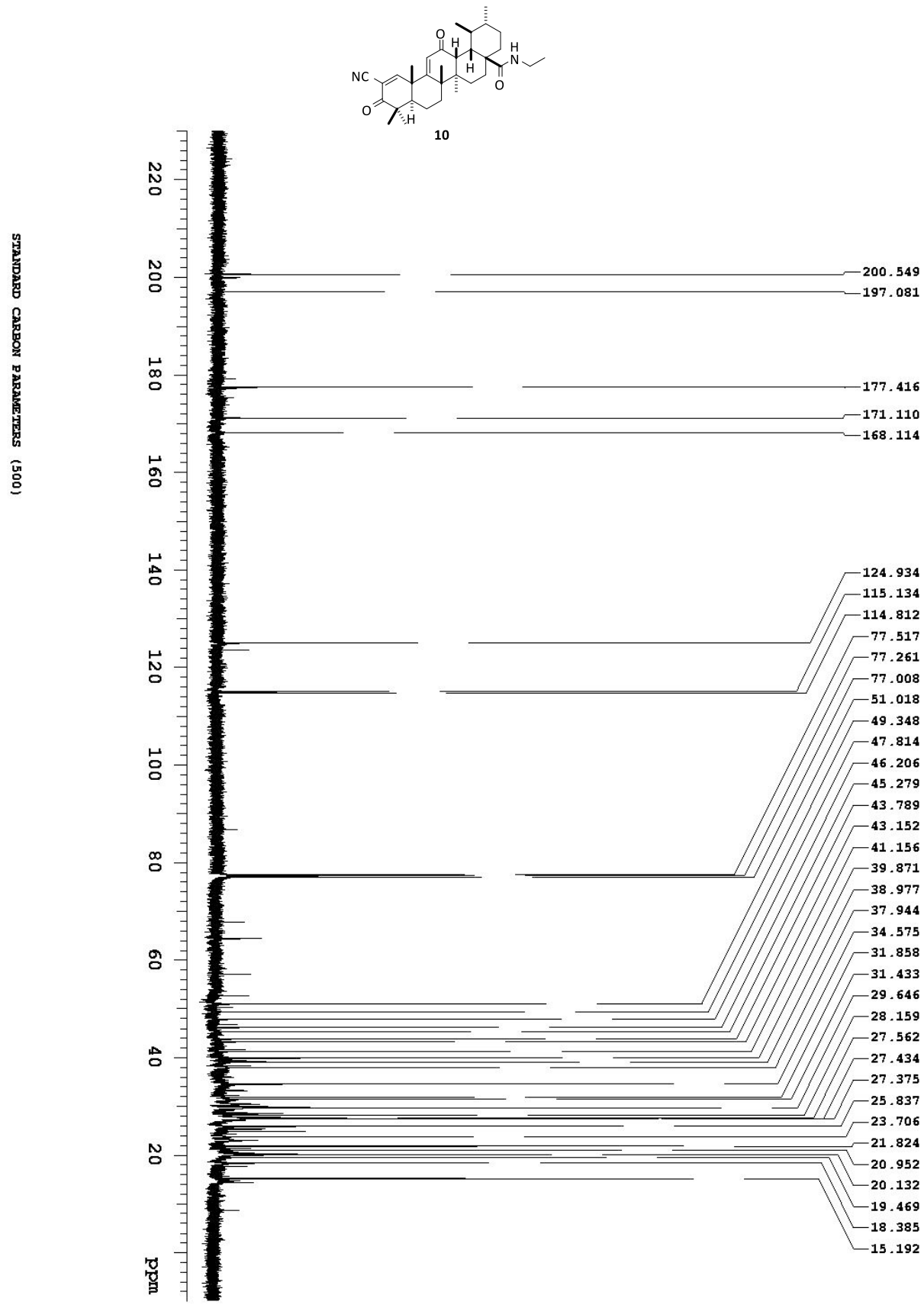
18.378

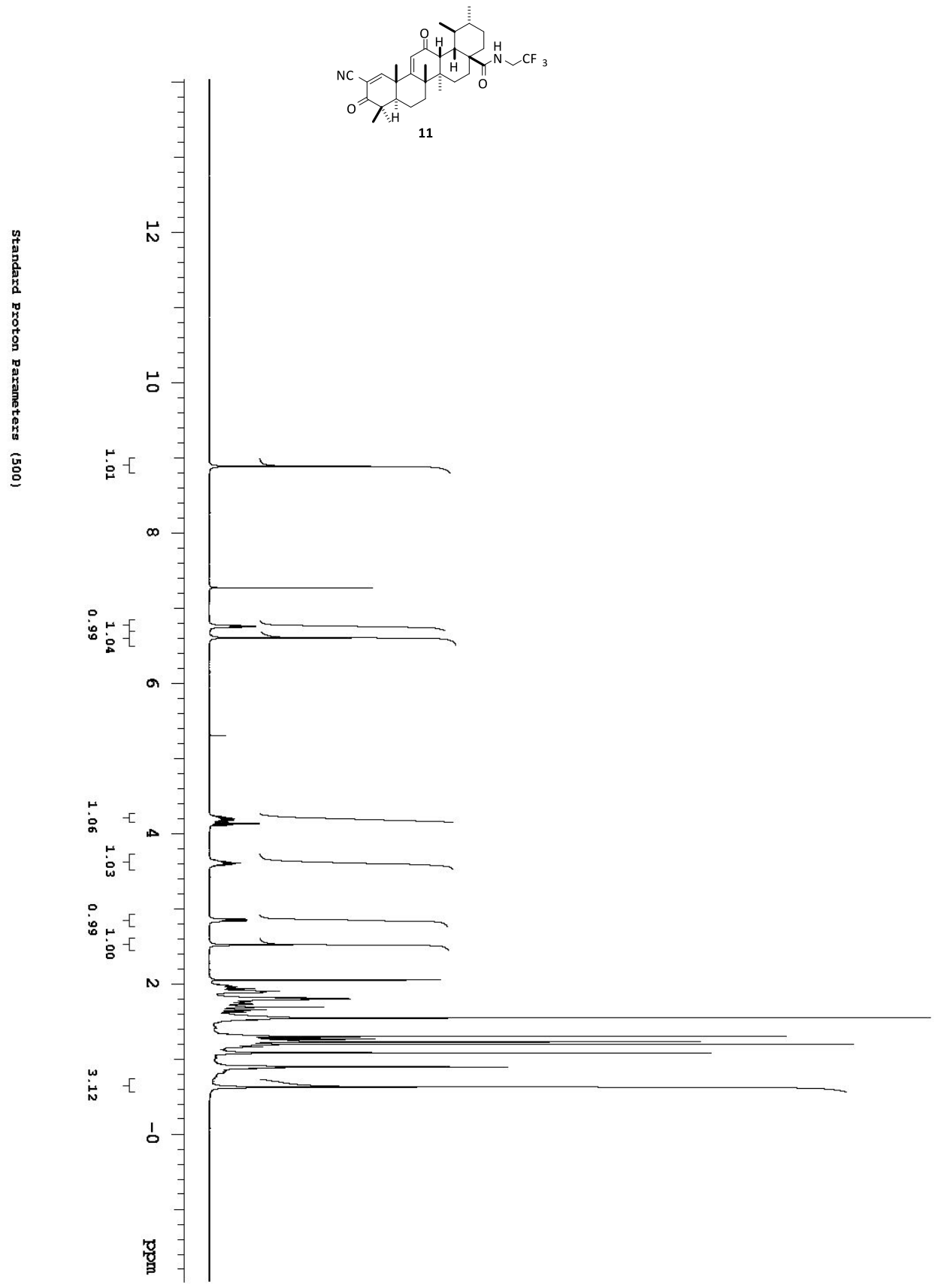


10

Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*

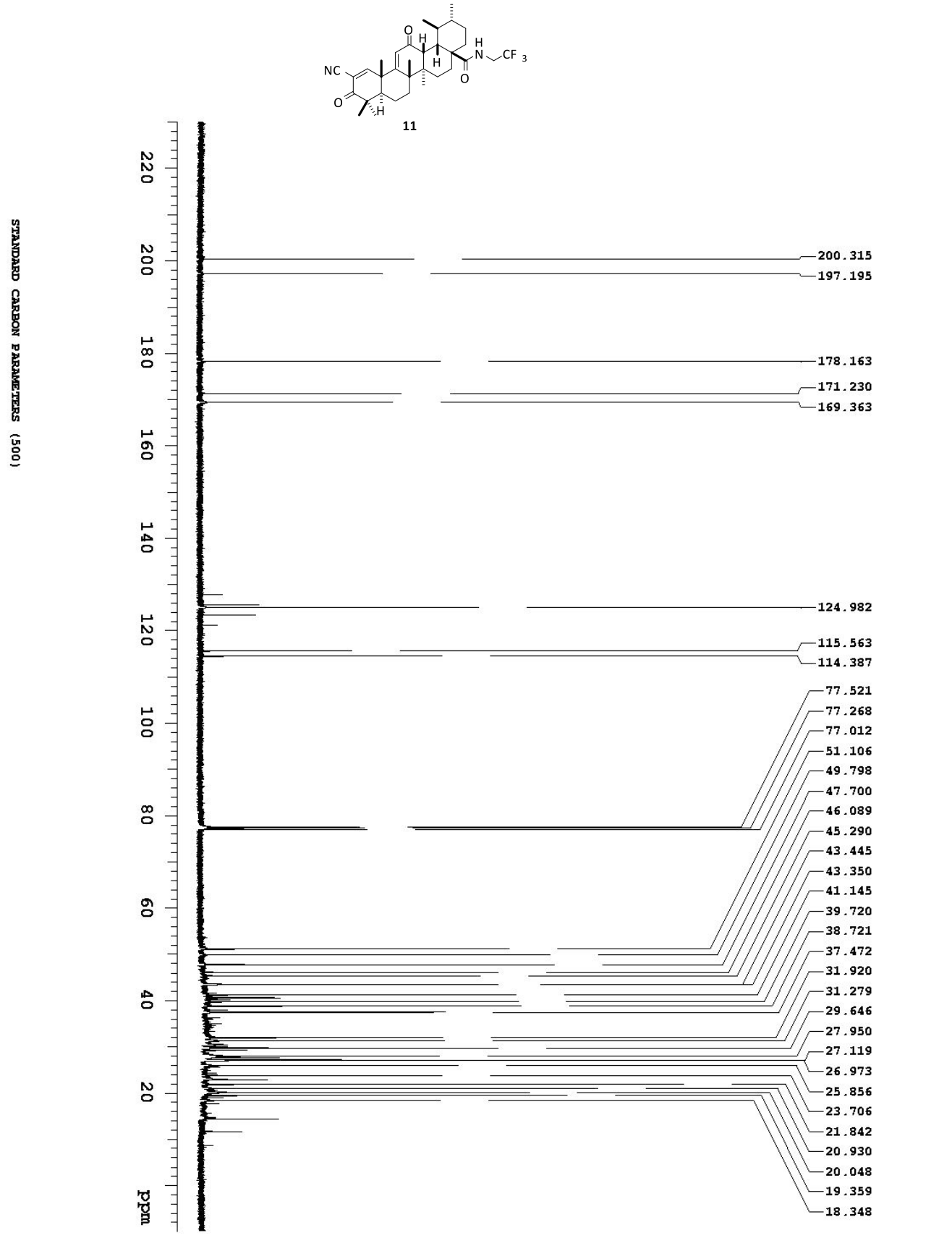


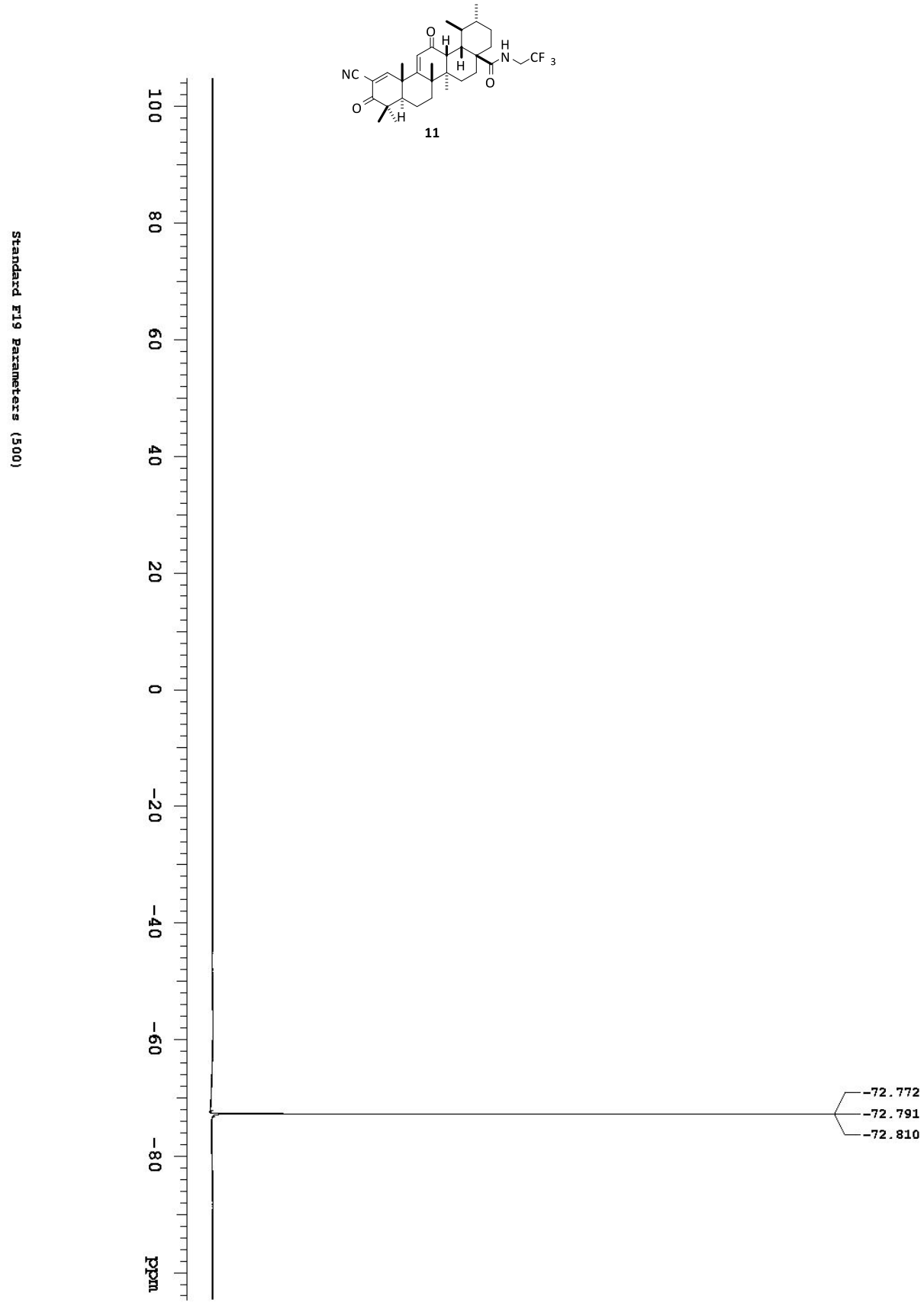
Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*



11

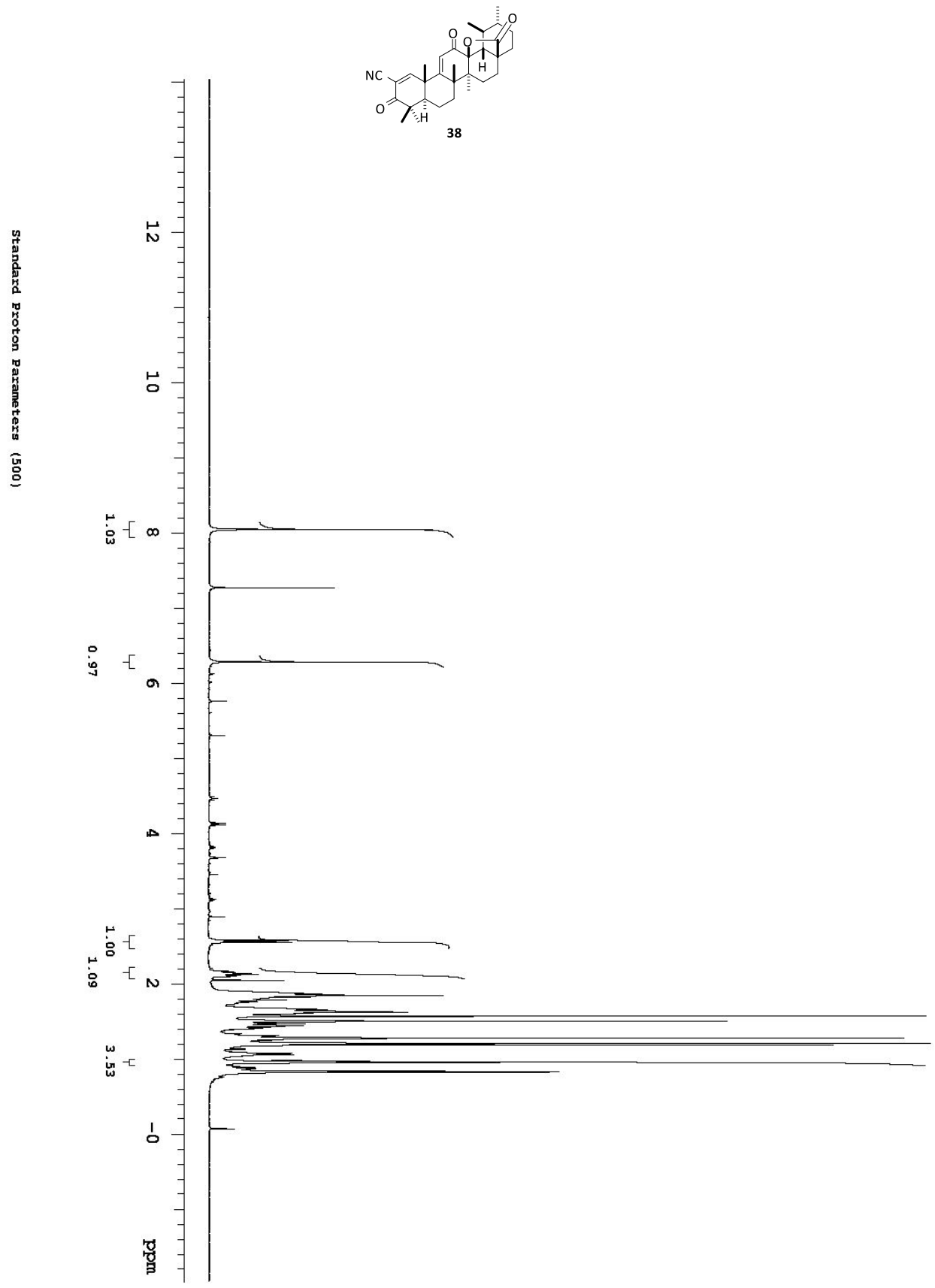
Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*


11
STANDARD CARBON PARAMETERS (500)
200.315
197.195
178.163
171.230
169.363
124.982
115.563
114.387
77.521
77.268
77.012
51.106
49.798
47.700
46.089
45.290
43.445
43.350
41.145
39.720
38.721
37.472
31.920
31.279
29.646
27.950
27.119
26.973
25.856
23.706
21.842
20.930
20.048
19.359
18.348
ppm

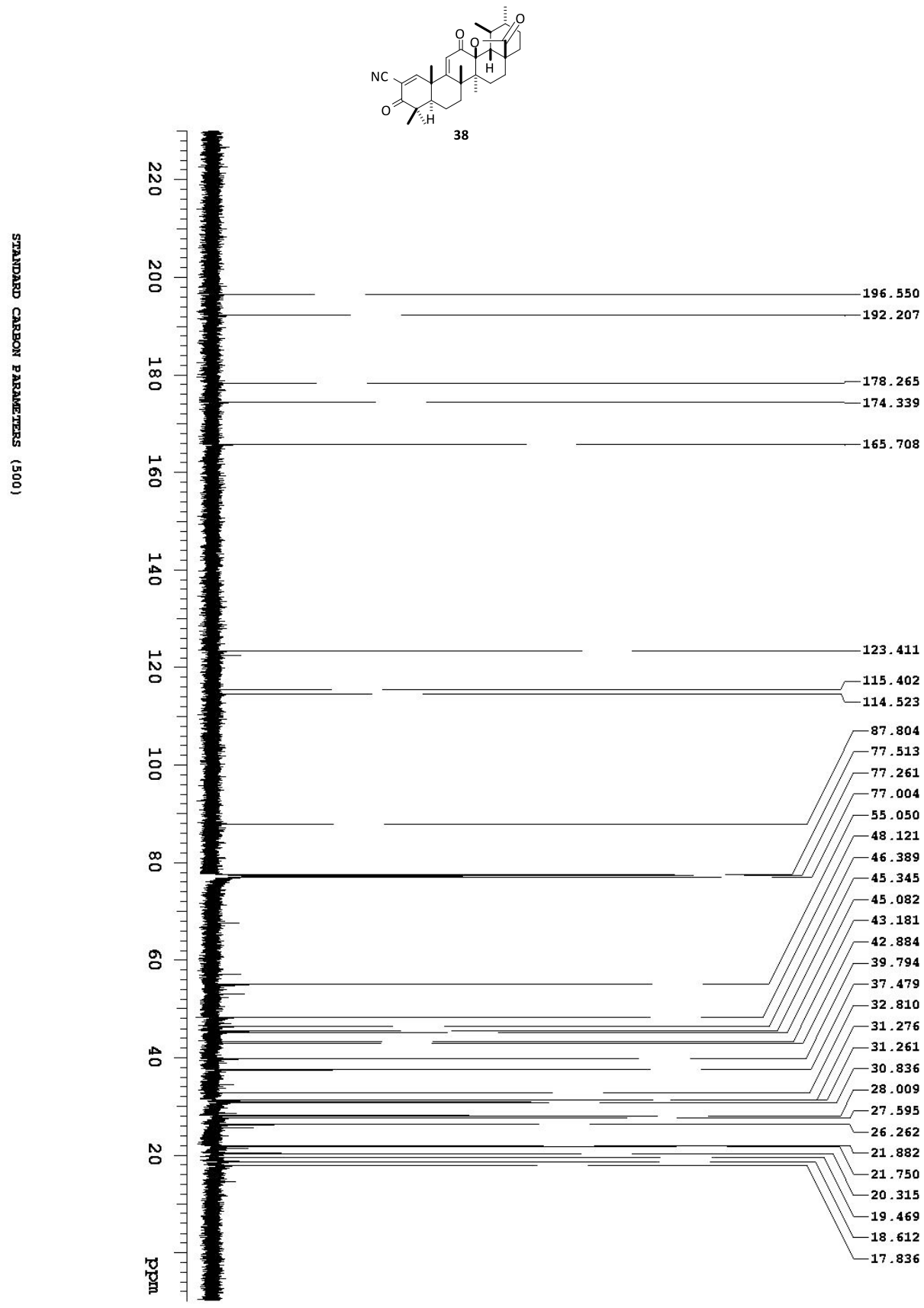


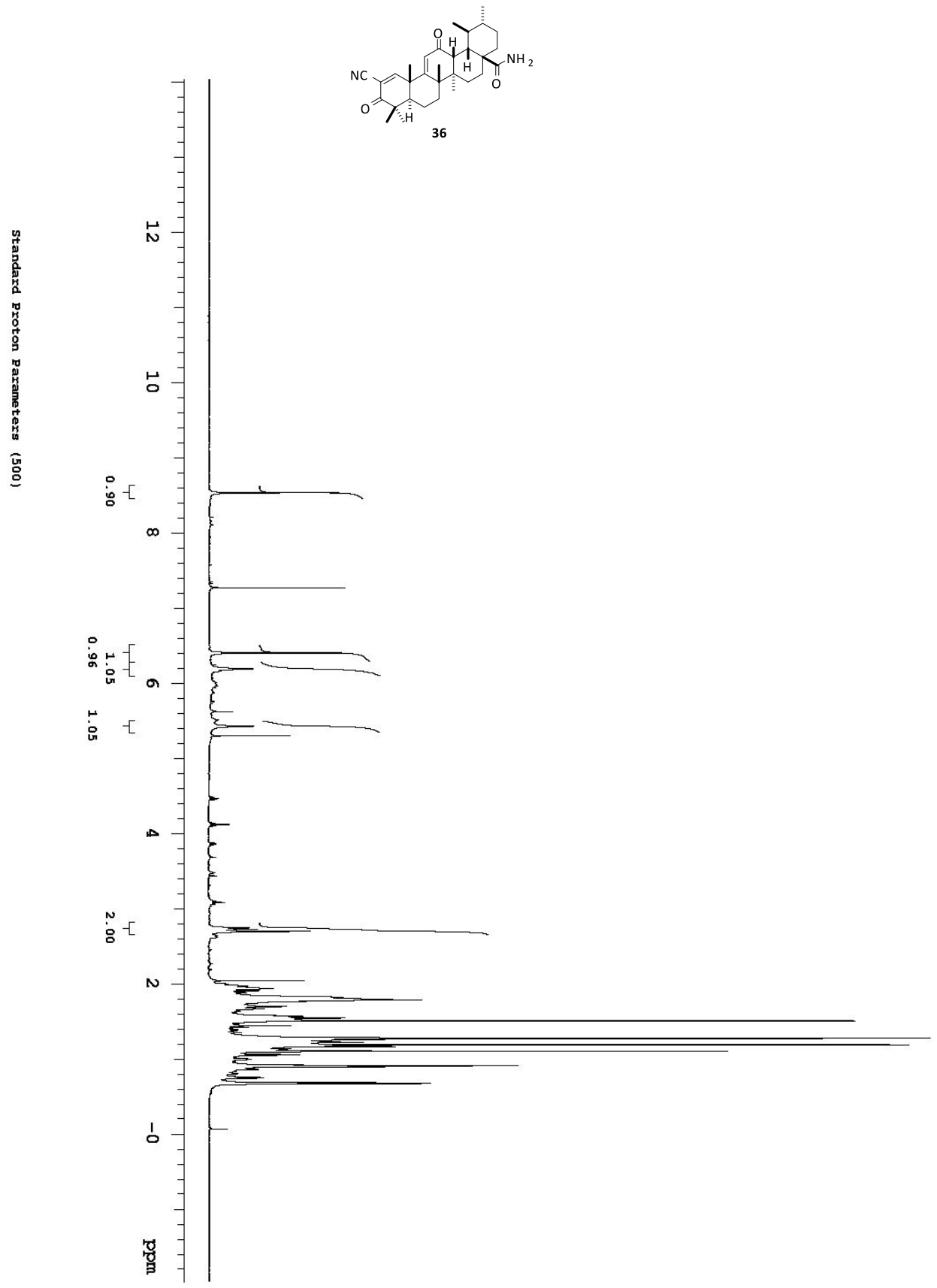
11

Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*



Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*


38
STANDARD CARBON PARAMETERS (500)
220
200
180
160
140
120
100
80
60
40
20
ppm
196.550
192.207
178.265
174.339
165.708
123.411
115.402
114.523
87.804
77.513
77.261
77.004
55.050
48.121
46.389
45.345
45.082
43.181
42.884
39.794
37.479
32.810
31.276
31.261
30.836
28.009
27.595
26.262
21.882
21.750
20.315
19.469
18.612
17.836



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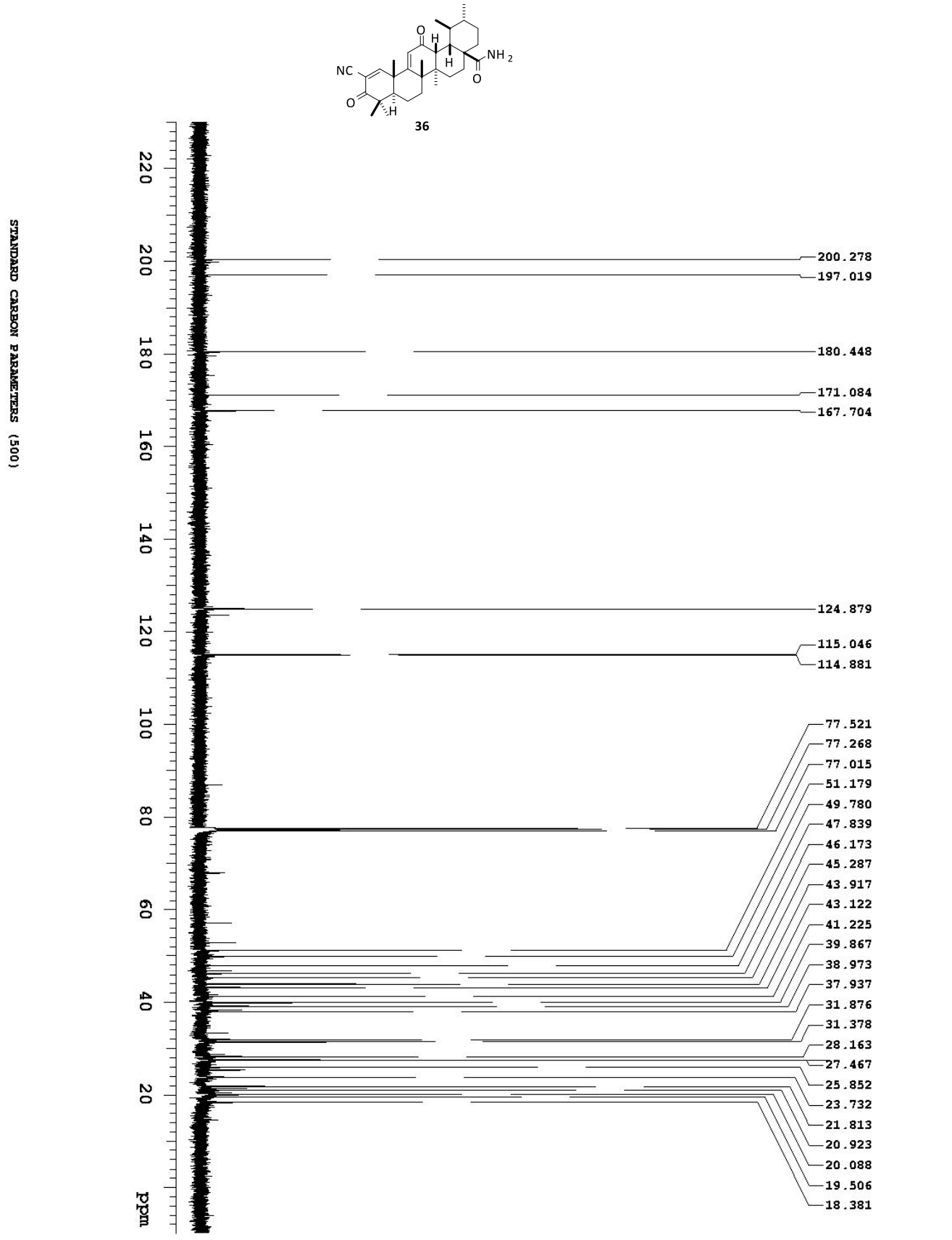
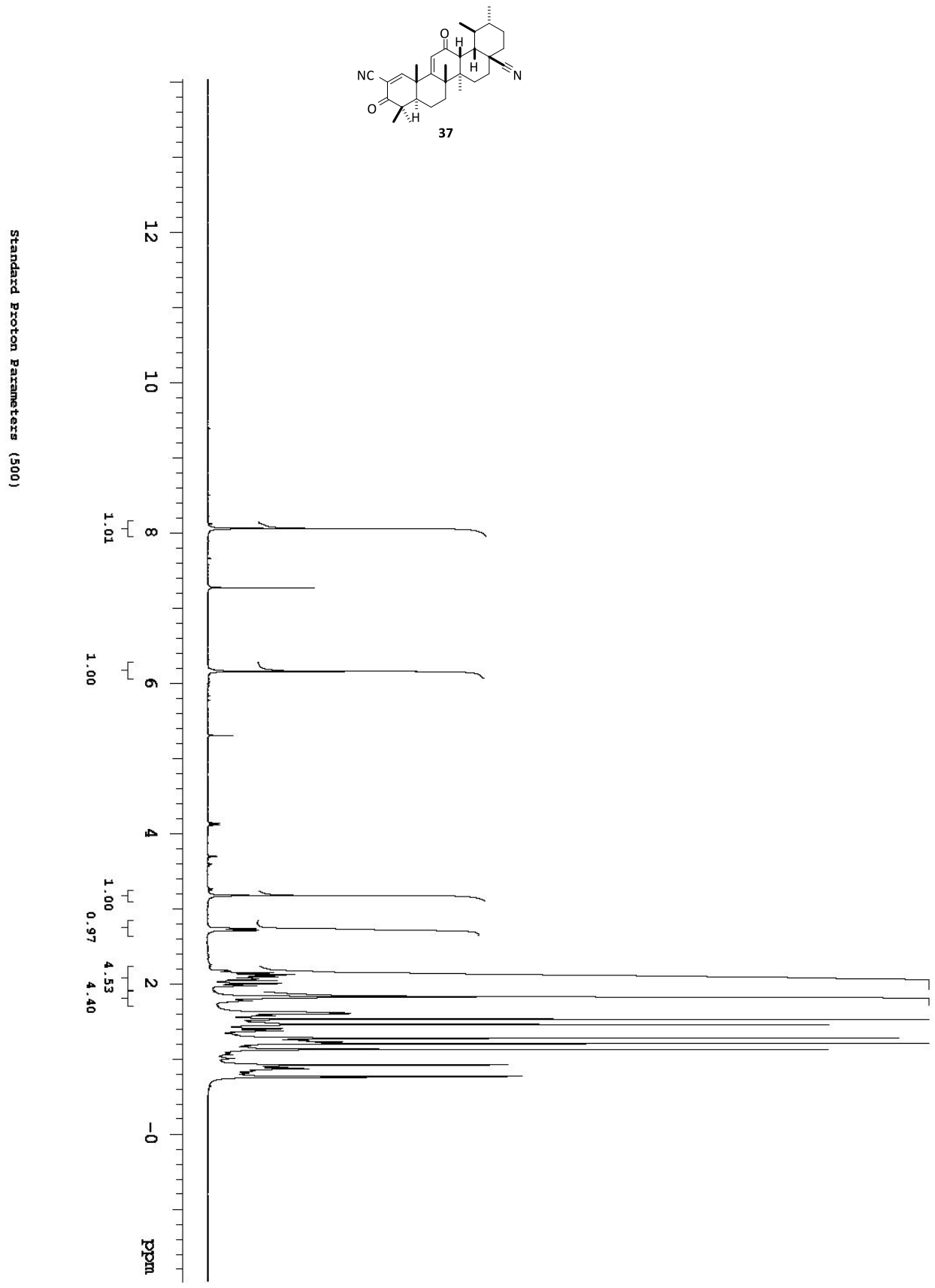
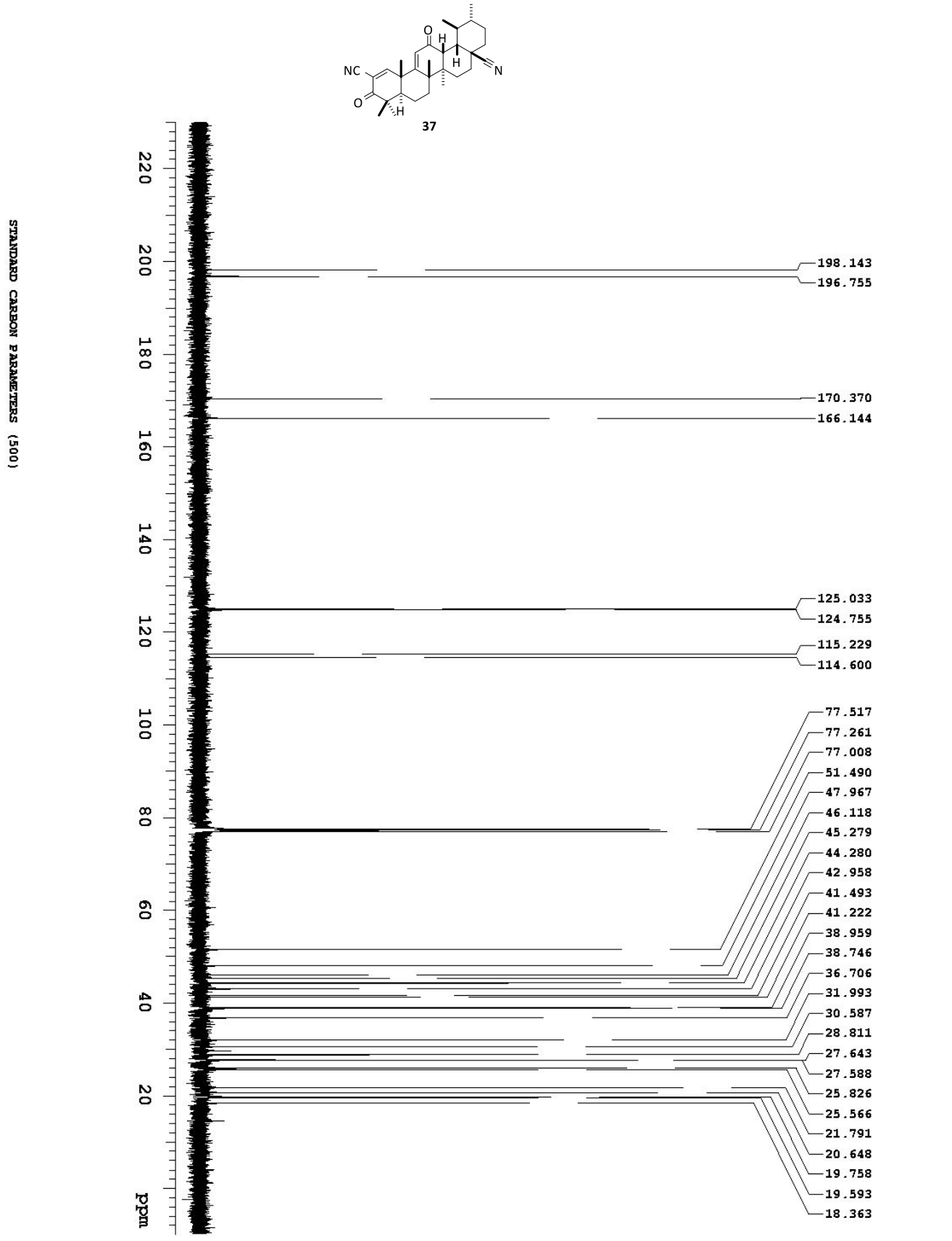
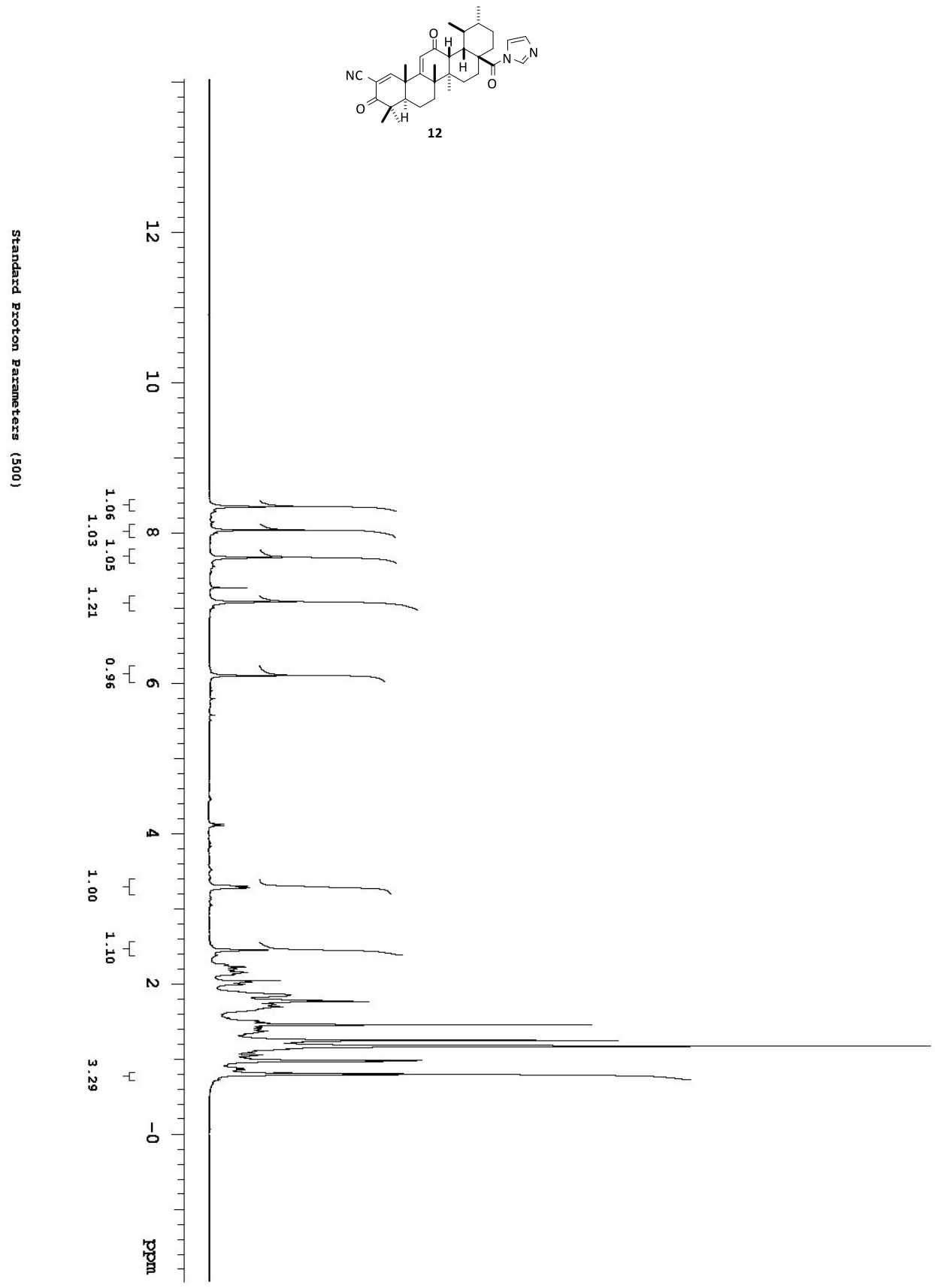

36
STANDARD CARBON PARAMETERS (500)
220
200
180
160
140
120
100
80
60
40
20
ppm
200.278
197.019
180.448
171.084
167.704
124.879
115.046
114.881
77.521
77.268
77.015
51.179
49.780
47.839
46.173
45.287
43.917
43.122
41.225
39.867
38.973
37.937
31.876
31.378
28.163
27.467
25.852
23.732
21.813
20.923
20.088
19.506
18.381



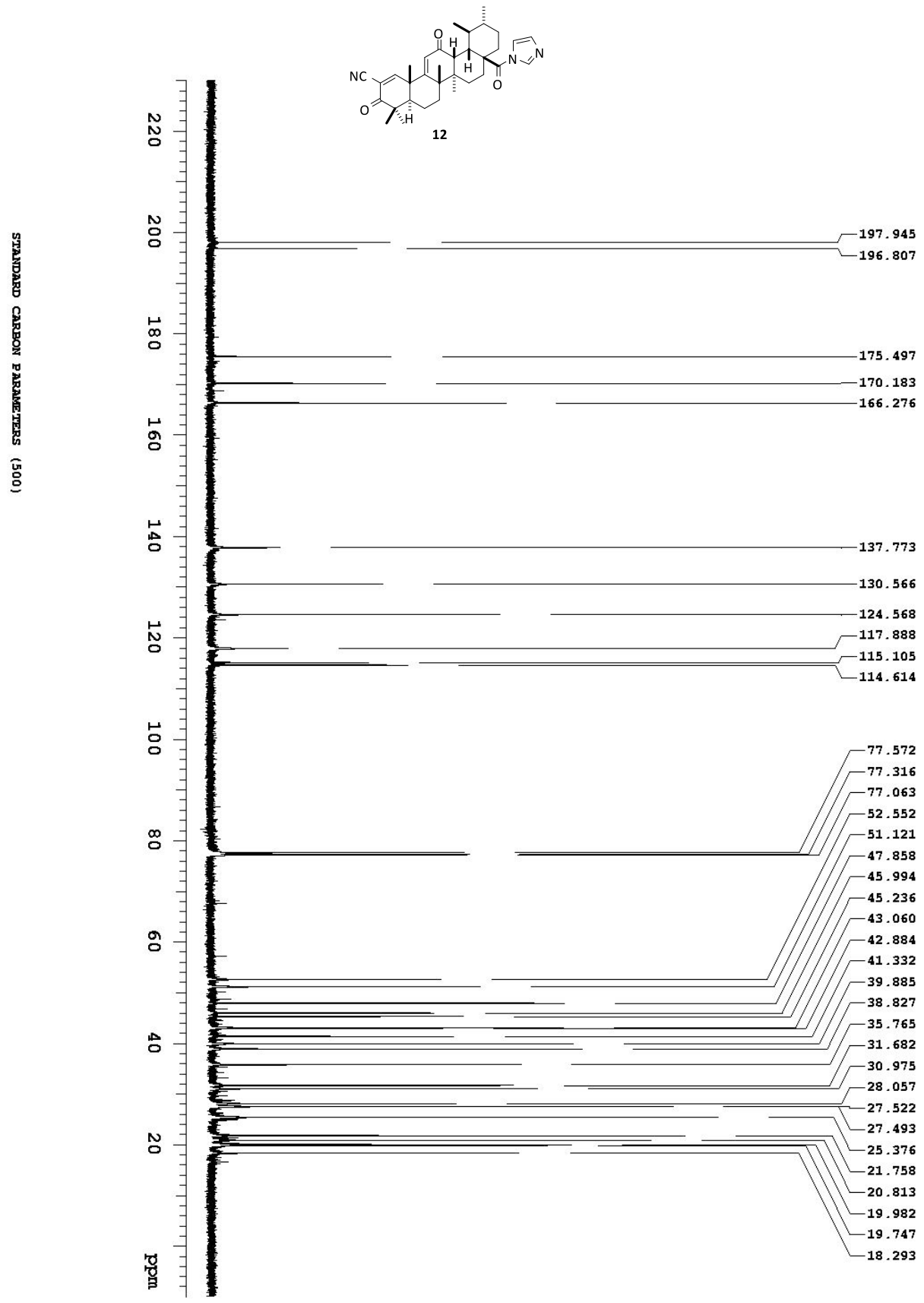
37

Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*


37
STANDARD CARBON PARAMETERS (500)
220
200
180
160
140
120
100
80
60
40
20
ppm
198.143
196.755
170.370
166.144
125.033
124.755
115.229
114.600
77.517
77.261
77.008
51.490
47.967
46.118
45.279
44.280
42.958
41.493
41.222
38.959
38.746
36.706
31.993
30.587
28.811
27.643
27.588
25.826
25.566
21.791
20.648
19.758
19.593
18.363



Biological Activities, and Comparison with Oleanolic Acid Derivatives" *Org. Biomol. Chem.*


12
STANDARD CARBON PARAMETERS (500)
220
200
180
160
140
120
100
80
60
40
20
ppm
197.945
196.807
175.497
170.183
166.276
137.773
130.566
124.568
117.888
115.105
114.614
77.572
77.316
77.063
52.552
51.121
47.858
45.994
45.236
43.060
42.884
41.332
39.885
38.827
35.765
31.682
30.975
28.057
27.522
27.493
25.376
21.758
20.813
19.982
19.747
18.293