

Synthesis and in vitro study of the novel borneol derivatives as potent inhibitors of influenza virus.

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1. Experimental section

1.1 General

Reagents and solvents were purchased from commercial suppliers and used as received. Dry solvents were obtained according to the standard procedures. Optical rotation: PolAAR 3005 spectrometer; CHCl₃ soln. ¹H and ¹³C NMR spectra were recorded with a Bruker AV-400 (¹H: 400.13 MHz, ¹³C: 100.78 MHz), DRX-500 (¹H: 500.13 MHz, ¹³C: 125.76 MHz) and AV-600 (¹H: 600.30 MHz, ¹³C: 150.95 MHz) in CDCl₃; chemical shifts δ in ppm relative to residual [$\delta(\underline{\text{CHCl}}_3)$ 7.24, $\delta(\underline{\text{CDCl}}_3)$ 76.90. HR-MS: DFS Thermo Scientific spectrometer in full scan mode (15–500 *m/z*, 70 eV electron impact ionization, direct sample administration) and Agilent 7200 Quadrupole Time-of-Flight GC/MS system. Spectral and analytical investigations were carried out at the Chemical Service Centre of the Siberian Branch of the Russian Academy of Sciences. The purity of the target compounds was determined by gas chromatography methods. All of the target compounds reported in this paper have a purity of no less than 95%. Column chromatography (CC) was performed on silica gel (60–200 μ m, Macherey-Nagel). Numeration of atoms in the compounds is given for assigning the signals in the NMR spectra and does not coincide with that for the names according to the nomenclature of compounds (see [Supplementary data](#)). Specific rotation is expressed as (deg ml) (g dm)⁻¹; concentration is expressed as (g) (100 ml)⁻¹.

1.2 Synthesis of (1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-chloroacetate (2)

To the mixture of (–)-borneol (0.03 mol) and Et₃N (0.03 mol) in 20 ml dry CH₂Cl₂ at 15–18 °C in an Ar atmosphere was added chloroacetyl chloride (0.05 mol), and the mixture was stirred at 23–25 °C for 12 h. The organic layers were washed with brine and extracted with CH₂Cl₂. The combined organic phase was dried over anhydrous Na₂SO₄ and the solvent was removed. The crude product was purified by vacuum distillation (bp 105 °C at 5 mm Hg). Yield: 65%, colourless oil. **¹H NMR (δ , ppm, J/Hz):** 0.81 (3H, s, Me-9), 0.85 (3H, s, Me-10), 0.88 (3H, s, Me-8), 0.98 (1H, dd, ²J=13.7, J_{2endo,1exo}=3.5, H-2endo), 1.17-1.33 (2H, m, H-4endo, H-5exo), 1.67 (1H, dd, J_{3,2exo}=J_{3,4exo}=4.6, H-3), 1.69-1.79 (1H, m, H-4exo), 1.90 (1H, ddd, ²J=12.9, J_{5endo,4endo}=9.3, J_{5endo,4exo}=4.4, H-5endo), 2.30-2.40 (1H, m, H-2exo), 4.03 (2H, s, H-12), 4.94 (1H, ddd, J_{1exo,2exo}=10.0, J_{1exo,2endo}=3.5, J_{1exo,5exo}=2.2, H-1exo). **¹³C NMR (δ , ppm):** 167.30 s (C-11), 81.98 d (C-1), 48.86 s (C-6), 47.81 s (C-7), 44.75 d (C-3), 41.11 d (C-12), 36.50 t (C-2), 27.82 t (C-4), 26.82 t (C-5), 19.57 q (Me-9), 18.69 q (Me-10), 13.32 q (Me-8). This compound was previously obtained.¹ Spectral data agree with those specified in the literature.

1.3 Synthesis of (1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-chloropropanoate (3)

To the solution of 3-chloropropanoic acid in dry CH₂Cl₂, excess oxalyl chloride and N,N-dimethylformamide (one drop) were added. The mixture was stirred at room temperature for 4 h in an Ar atmosphere. The excess oxalyl chloride was removed on a rotary evaporator. The resulting chloroanhydride of 3-chloropropanoic acid was used in a further reaction immediately.

To the solution of (-)-borneol (30 mmol) in CH₂Cl₂ was added the chloroanhydride (30 mmol) in CH₂Cl₂ (5 ml) and Et₃N (30 mmol) at 0–5 °C, and the mixture was stirred at room temperature for 24 h in an atmosphere of Ar. The resulting precipitate was filtrated; the filtrate was washed with brine and extracted with CH₂Cl₂. The combined organic phase was dried over anhydrous Na₂SO₄ and the solvent was removed. The crude product was purified by flash CC (silica gel, eluent: hexane–ethyl acetate). Yield: 59%, yellow oil. ¹H NMR (δ, ppm, J/Hz): 0.80 (3H, s, Me-9), 0.84 (3H, s, Me-10), 0.87 (3H, s, Me-8), 0.97 (1H, dd, ²J=13.7, J_{2endo, 1exo}=3.5, H-2endo), 1.16-1.33 (2H, m, H-4endo, H-5exo), 1.65 (1H, dd, J_{3,2exo}=J_{3,4exo}=4.6, H-3), 1.67-1.77 (1H, m, H-4exo), 1.89 (1H, ddd, ²J=12.9, J_{5endo, 4endo}=9.3, J_{5endo, 4exo}=4.4, H-5endo), 2.33 (1H, m, H-2exo), 2.77 (2H, t, J=6.6, H-12), 3.74 (2H, t, J=6.6, H-13), 4.91 (1H, ddd, J_{1exo, 2exo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). ¹³C NMR (δ, ppm): 170.40 s (C-11), 80.50 d (C-1), 48.69 s (C-6), 47.69 s (C-7), 44.71 d (C-3), 39.18 d (C-13), 37.80 d (C-12), 36.54 t (C-2), 27.85 t (C-4), 26.97 t (C-5), 19.55 q (Me-9), 18.69 q (Me-10), 13.34 q (Me-8). [α]_D²⁷ = -36.2 (CHCl₃, c=0.7). HRMS: calcd for C₁₃H₂₁O₂Cl: 244.1222 found: 244.1225.

1.4 General synthetic procedure for compounds 4–21

A mixture of 1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-chloroacetate (2) or 1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-chloropropanoate (3) (2 mmol), the corresponding amine (2.2 mmol), Et₃N (2.2 mmol) and 15 ml MeOH were stirred at room temperature for 24 h. After completion, the mixture was concentrated in a vacuum. Brine and ethyl acetate were added to the residue, and then the mixture was extracted twice with ethyl acetate. The combined organic phase was dried over Na₂SO₄ and the solvent was removed in vacuo. The crude product was purified by silica gel CC (eluent: hexane–ethyl acetate).

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(pyrrolidin-1-yl)acetate (4)

Yield: 82%, yellow oil. ¹H NMR (δ, ppm, J/Hz): 0.79 (3H, s, Me-9), 0.83 (3H, s, Me-10), 0.87 (3H, s, Me-8), 0.95 (1H, m, H-2endo), 1.15-1.30 (2H, m, H-4endo, H-5exo), 1.64 (1H, m, H-3), 1.64-1.76 (1H, m, H-4exo), 1.79 (4H, m, H-14, H-15), 1.85-1.95 (1H, m, H-5endo), 2.28-2.37 (1H, m, H-2exo), 2.60-2.67 (4H, m, 2H-13, 2H-16), 3.33 (2H, s, H-12), 4.92 (1H, ddd, J_{1exo, 2exo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). ¹³C NMR (δ, ppm): 171.00 s (C-11), 79.97 d (C-1), 56.54 t (C-12), 53.57 t (C-13, S-16), 48.64 s (C-6), 47.72 s (C-7), 44.65 d (C-3),

36.60 t (C-2), 27.99 t (C-4), 27.01 t (C-5), 23.68 t (C-14, C-15), 19.68 q (Me-9), 18.66 q (Me-10), 13.33 q (Me-8). $[\alpha]_D^{25} = -21.0$ (CHCl₃, c=1.02). HRMS: calcd for C₁₆H₂₇NO₂: **265.2036** found: **265.2038**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(piperidin-1-yl)acetate (5)

Yield: 80%, pale yellow oil. ¹H NMR (δ, ppm, J/Hz): 0.80 (3H, s, Me-10), 0.84 (3H, s, Me-8), 0.88 (3H, s, Me-9), 0.95 (1H, dd, ²J=13.7, J_{2endo, 1exo}=3.5, H-2endo), 1.14-1.31 (2H, m, H-4endo, H-5exo), 1.36-1.45 (2H, m, H-15), 1.54-1.62 (4H, m, 2H-14, 2H-16), 1.64 (1H, dd, J_{3,2exo}=J_{3,4exo}=4.6, H-3), 1.66-1.76 (1H, m, H-4exo), 1.89 (1H, ddd, ²J=12.9, J_{5endo,4endo}=9.3, J_{5endo,4exo}=4.4, H-5endo), 2.33 (1H, m, H-2exo), 2.46-2.56 (4H, br. s, 2H-13, 2H-17), 3.18 (2H, s, H-12), 4.90 (1H, ddd, J_{1exo, 2exo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). ¹³C NMR (δ, ppm): 170.68 s (C-11), 79.87 d (C-1), 59.98 t (S-12), 53.81 t (C-13, C-17), 48.55 s (C-6), 47.59 s (C-7), 44.65 d (C-3), 36.60 t (C-2), 27.81 t (C-4), 26.93 t (C-5), 25.62 t (C-14, C-16), 23.68 t (C-15), 19.50 q (Me-9), 18.63 q (Me-10), 13.35 q (Me-8). HRMS: calcd for C₁₇H₂₉O₂N: **279.2193** found: **279.2196**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(4-methylpiperidin-1-yl)acetate (6)

Yield: 85%, pale yellow oil; ¹H NMR (δ, ppm, J/Hz): 0.77 (3H, s, Me-10), 0.81 (3H, s, Me-8), 0.84 (3H, s, Me-9), 0.86 (3H, d, J=5.7, Me-16), 0.92 (1H, dd, ²J=13.7, J_{2endo, 1exo}=3.5, H-2endo), 1.12-1.32 (5H, m, H-4endo, H-5exo, H-14a, H-15, H-17a), 1.52-1.59 (2H, m, H-14e, H-17e), 1.62 (1H, m, J_{3,2exo}=J_{3,4exo}=4.6, H-3), 1.63-1.74 (1H, m, H-4exo), 1.86 (1H, ddd, ²J=12.9, J_{5endo,4endo}=9.3, J_{5endo,4exo}=4.4, H-5endo), 2.08-2.18 (2H, m, H-13a, H-18a), 2.30 (1H, m, H-2exo), 2.78-2.91 (2H, m, H-13e, H-18e), 3.17 (2H, s, H-12), 4.88 (1H, ddd, J_{1exo,2exo}=10.0, J_{1exo,2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). ¹³C NMR (δ, ppm): 170.80 s (C-11), 79.76 d (C-1), 59.71 t (C-12), 53.29 and 53.27 t (C-13, C-18), 48.51 s (C-6), 47.56 s (C-7), 44.62 d (C-3), 36.58 t (C-2), 33.99 t (C-14, C-17), 30.11 d (C-16), 27.79 t (C-4), 26.91 t (C-5), 21.67 q (Me-16), 19.49 q (Me-9), 18.62 q (Me-10), 13.34 q (Me-8). $[\alpha]_D^{26} = -32.4$ (CHCl₃, c=0.92). HRMS: calcd for C₁₈H₃₁NO₂: **293.2349**; found: **293.2150**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-morpholinoacetate (7)

Yield: 62%, yellow oil. ¹H NMR (δ, ppm, J/Hz): 0.79 (3H, s, Me-9), 0.84 (3H, s, Me-10), 0.87 (3H, s, Me-8), 0.93 (1H, dd, ²J=13.7, J_{2endo, 1exo}=3.5, H-2endo), 1.13-1.31 (2H, m, H-4endo, H-5exo), 1.64 (1H, dd, J_{3, 2exo}=J_{3, 4exo}=4.6, H-3), 1.66-1.76 (1H, m, H-4exo), 1.86 (1H, ddd, ²J=12.9, J_{5endo, 4endo}=9.3, J_{5endo, 4exo}=4.4, H-5endo), 2.33 (1H, m, H-2exo), 2.55-2.62 (4H, m, 2H-13, 2H-16), 3.21 (2H, s, H-12), 3.69-3.75 (4H, m, 2H-14, 2H-15), 4.91 (1H, ddd, J_{1exo,2exo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). ¹³C NMR (δ, ppm): 170.25 s (C-11), 70.10 d (C-1), 66.64 t (C-14, C-15), 59.53 t (C-12), 53.04 t (C-13, C-16), 48.56 s (C-6), 47.61 s (C-7), 44.62 d (C-3), 36.58 t (C-2), 27.80 t (C-4), 26.91 t (C-5), 19.49 q (Me-9), 18.62 q (Me-10), 13.35

q (Me-8). $[\alpha]_D^{26} = -30.6$ (CHCl₃, c=1.2). HRMS: calcd for C₁₆H₂₇O₃N: **281.1986**; found: **281.1991**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(4-methylpiperazin-1-yl)acetate (8)

Yield: 60%, pale yellow oil. **¹H NMR (δ, ppm, J/Hz):** 0.77 (3H, s, Me-10), 0.82 (3H, s, Me-8), 0.85 (3H, s, Me-9), 0.94 (1H, dd, ²J=13.7, J_{2endo, 1exo}=3.5, H-2endo), 1.12-1.29 (2H, m, H-4endo, H-5exo), 1.64 (1H, dd, J_{3, 2exo}=J_{3, 4exo}=4.6, H-3), 1.64-1.75 (1H, m, H-4exo), 1.86 (1H, ddd, ²J=12.9, J_{5endo, 4endo}=9.3, J_{5endo, 4exo}=4.4, H-5endo), 2.24 (3H, s, Me-15), 2.26-2.36 (1H, m, H-2exo), 2.36-2.66 (8H, br. s., 2H-13, 2H-14, 2H-16, 2H-17), 3.17 (2H, s, H-12), 4.89 (1H, ddd, J_{1exo, 2exo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). **¹³C NMR (δ, ppm):** 170.45 s (C-11), 80.07 d (C-1), 59.32 t (C-12), 54.73 t (C-13, C-17), 52.82 (C-14, C-16), 48.63 s (C-6), 47.80 s (C-7), 45.86 k (Me-15), 44.70 d (C-3), 36.63 t (C-2), 27.87 t (C-4), 26.95 t (C-5), 19.56 q (Me-9), 18.69 q (Me-10), 13.41 q (Me-8). $[\alpha]_D^{25} = -31.9$ (CHCl₃, c=1.18). HRMS: calcd for C₁₇H₃₀O₂N₂: **294.2302**; found: **294.2303**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(4-ethylpiperazin-1-yl)acetate (9)

Yield: 63%, yellow oil. **¹H NMR (δ, ppm, J/Hz):** 0.77 (3H, s, Me-10), 0.82 (3H, s, Me-8), 0.85 (3H, s, Me-9), 0.94 (1H, dd, ²J=13.7, J_{2endo, 1exo}=3.5, H-2endo), 1.12-1.29 (2H, m, H-4endo, H-5exo), 1.64 (1H, dd, J_{3, 2exo}=J_{3, 4exo}=4.6, H-3), 1.64-1.75 (1H, m, H-4exo), 1.86 (1H, ddd, ²J=12.9, J_{5endo, 4endo}=9.3, J_{5endo, 4exo}=4.4, H-5endo), 2.24 (3H, s, Me-15), 2.26-2.36 (1H, m, H-2exo), 2.36-2.66 (8H, br s., 2H-13, 2H-14, 2H-16, 2H-17), 3.17 (2H, s, H-12), 4.89 (1H, ddd, J_{1exo, 2exo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). **¹³C NMR (δ, ppm):** 170.45 s (C-11), 80.07 d (C-1), 59.32 t (C-12), 54.73 t (C-13, C-17), 52.82 (C-14, C-16), 48.63 s (C-6), 47.80 s (C-7), 45.86 k (Me-15), 44.70 d (C-3), 36.63 t (C-2), 27.87 t (C-4), 26.95 t (C-5), 19.56 q (Me-9), 18.69 q (Me-10), 13.41 q (Me-8). $[\alpha]_D^{28} = -21.4$ (CHCl₃, c=1.02). HRMS: calcd for C₁₈H₃₂O₂N₂: **308.2458**; found: **308.2456**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(piperazin-1-yl)acetate (10)

Yield: 65%, pale yellow oil. **¹H NMR (δ, ppm, J/Hz):** 0.77 (3H, s, Me-10), 0.82 (3H, s, Me-8), 0.85 (3H, s, Me-9), 0.93 (1H, dd, ²J=13.7, J_{2endo, 1exo}=3.5, H-2endo), 1.04 (3H, t, J=7.24, Me-16), 1.13-1.30 (2H, m, H-4endo, H-5exo), 1.62 (1H, dd, J_{3, 2exo}=J_{3, 4exo}=4.6, H-3), 1.65-1.74 (1H, m, H-4exo), 1.86 (1H, ddd, ²J=12.9, J_{5endo, 4endo}=9.3, J_{5endo, 4exo}=4.4, H-5endo), 2.31 (1H, m, H-2exo), 2.39 (2H, t, J=7.2, H-15), 2.42-2.68 (8H, br. s., 2H-13, 2H-14, 2H-17, 2H-18), 3.17 (2H, s, H-12), 4.89 (1H, ddd, J_{1exo, 2exo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). **¹³C NMR (δ, ppm):** 170.40 s (C-11), 80.01 d (C-1), 59.36 t (C-12), 52.87 t (C-13, C-18), 52.36 (C-14, C-17),

52.04 t (C-15), 48.59 s (C-6), 47.67 s (C-7), 44.63 d (C-3), 36.54 t (C-2), 27.78 t (C-4), 26.86 t (C-5), 19.49 q (Me-9), 18.65 q (Me-10), 13.32 q (Me-8), 11.81 q (Me-16). $[\alpha]_D^{26} = -31.5$ (CHCl₃, c=0.82). HRMS: calcd for C₁₆H₂₈N₂O₂: **280.2145**; found: **280.2142**.

Ethyl 4-(2-oxo-2-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)ethyl)piperazine-1-carboxylate (11)

Yield: 69%, yellow solid. ¹H NMR (δ, ppm, J/Hz): 0.77 (3H, s, Me-10), 0.82 (3H, s, Me-8), 0.85 (3H, s, Me-9), 0.92 (1H, dd, ²J=13.7, J_{2endo, 1exo}=3.5, H-2endo), 1.12-1.30 (2H, m, H-4endo, H-5exo), 1.62 (1H, dd, J_{3, 2exo}=J_{3, 4exo}=4.6, H-3), 1.64-1.74 (1H, m, H-4exo), 1.85 (1H, ddd, ²J=12.9, J_{5endo, 4endo}=9.3, J_{5endo, 4exo}=4.4, H-5endo), 1.94 (1H, br. s., N-H), 2.23-2.37 (1H, m, H-2exo), 2.47-2.57 (4H, br. s., 2H-14, 2H-15), 2.84-2.94 (4H, m, 2H-13, 2H-16), 3.17 (2H, s, H-12), 4.88 (1H, ddd, J_{1exo, 2exo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). ¹³C NMR (δ, ppm): 170.51 s (C-11), 80.02 d (C-1), 59.87 t (C-12), 53.91 t (C-13, C-16), 48.62 s (C-6), 47.66 s (C-7), 45.73 t (C-14, C-15), 44.67 d (C-3), 36.64 t (C-2), 27.87 t (C-4), 26.96 t (C-5), 19.57 k (Me-9), 18.70 k (Me-10), 13.43 k (Me-8). $[\alpha]_D^{26} = -23.7$ (CHCl₃, c=1.36). HRMS: calcd for C₁₉H₃₂O₄N₂: **357.2357**; found: **357.2349**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-(dibutylamino)acetate (12)

Yield: 75%, pale yellow oil. ¹H NMR (δ, ppm, J/Hz): 0.80 (3H, s, Me-9), 0.84 (3H, s, Me-10), 0.87 (3H, s, Me-8), 0.88 (6H, t, J=7.26, Me-19, Me-20), 0.94 (1H, dd, ²J=13.8, J_{2endo, 1exo}=3.5, H-2endo), 1.15-1.34 (6H, m, H-4endo, H-5exo, 2H-17, 2H-18), 1.37-1.46 (4H, m, 2H-15, 2H-16), 1.64 (1H, m, H-3), 1.67-1.77 (1H, m, H-4exo), 1.92 (1H, m, H-5endo), 2.33 (1H, m, H-2exo), 2.51-2.58 (4H, m, 2H-13, 2H-14), 3.31 (2H, s, H-12), 4.90 (1H, ddd, J_{1exo, 2exo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). ¹³C NMR (δ, ppm): 172.00 s (C-11), 79.75 d (C-1), 54.95 t (C-12), 54.03 (C-13, C-14), 48.55 s (C-6), 47.62 s (C-7), 44.72 d (C-3), 36.73 t (C-2), 29.72 t (C-15, C-16), 27.88 t (C-4), 27.07 t (C-5), 20.40 t (C-17, C-18), 19.56 q (Me-9), 18.68 q (Me-10), 13.91 q (Me-19, Me-20), 13.38 q (Me-8). $[\alpha]_D^{26} = -30$ (CHCl₃, c=1.28). HRMS: calcd for C₂₀H₃₇O₂N: **323.2819**; found: **323.2823**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-(pyrrolidin-1-yl)propanoate (13)

Yield: 78%, yellow oil. ¹H NMR (δ, ppm, J/Hz): 0.78 (3H, s, Me-9), 0.82 (3H, s, Me-10), 0.86 (3H, s, Me-8), 0.93 (1H, m, H-2endo), 1.13-1.30 (2H, m, H-4endo, H-5exo), 1.63 (1H, m, H-3), 1.64-1.80 (5H, m, H-4exo, H-15, H-16), 1.85-1.95 (1H, m, H-5endo), 2.23-2.37 (1H, m, H-2exo), 2.42-2.53 (6H, m, 2H-12, 2H-14, 2H-17), 2.70-2.79 (2H, m, H-13), 4.86 (1H, ddd, J_{1exo, 2exo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). ¹³C NMR (δ, ppm): 172.72 s (C-11), 79.60 d (C-1), 53.79 t (C-14, C-17), 51.36 t (C-13), 48.60 s (C-6), 47.61 s (C-7), 44.71 d (C-3), 36.53 t (C-2), 34.51 t (C-12), 27.87 t (C-4), 26.96 t (C-5), 23.33 t (C-15, C-16), 19.54 q (Me-9), 18.68 q

(Me-10), 13.29 q (Me-8). $[\alpha]_D^{25} = -42.2$ (CHCl₃, c=0.7). HRMS: calcd for C₁₇H₂₉NO₂: **279.2193**; found: **279.2192**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-(piperidin-1-yl)propanoate (14)

Yield: 74%, pale yellow oil. ¹H NMR (δ, ppm, J/Hz): 0.79 (3H, s, Me-10), 0.83 (3H, s, Me-8), 0.86 (3H, s, Me-9), 0.94 (1H, dd, ²J=13.7, J_{2endo, 1exo}=3.5, H-2endo), 1.15-1.30 (2H, m, H-4endo, H-5exo), 1.33-1.43 (2H, m, H-16), 1.49-1.57 (4H, m, 2H-15, 2H-17), 1.63 (1H, dd, J_{3,2exo}=J_{3,4exo}=4.6, H-3), 1.65-1.76 (1H, m, H-4exo), 1.85-1.94 (1H, ddd, ²J=12.9, J_{5endo, 4endo}=9.3, J_{5endo, 4exo}=4.4, H-5endo), 2.30 (1H, m, H-2exo), 2.31-2.42 (4H, br. s, 2H-14, 2H-18), 2.43-2.53 (2H, m, H-12), 2.57-2.66 (2H, m, H-13), 4.86 (1H, ddd, J_{1exo, 2endo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). ¹³C NMR (δ, ppm): 172.62 s (C-11), 79.28 d (C-1), 54.02 t (C-13), 53.78 t (C-14, C-18), 48.32 s (C-6), 47.32 s (C-7), 44.73 d (C-3), 36.21 t (C-2), 32.33 t (C-12), 27.57 t (C-4), 26.66 t (C-5), 25.52 t (C-15, C-17), 23.87 t (C-16), 19.23 q (Me-9), 18.38 q (Me-10), 13.01 q (Me-8). $[\alpha]_D^{24} = -31.5$ (CHCl₃, c=0.8). HRMS: calcd for C₁₇H₂₉NO₂: **293.2349**; found: **293.2356**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-(4-methylpiperidin-1-yl)propanoate (15)

Yield: 77%, colorless oil. ¹H NMR (δ, ppm, J/Hz): 0.79 (3H, s, Me-10), 0.84 (3H, s, Me-8), 0.87 (3H, s, Me-9), 0.89 (3H, d, J=12.1, Me-17), 0.94 (1H, dd, ²J=13.7, J_{2endo, 1exo}=3.5, H-2endo), 1.15-1.37 (5H, m, H-4endo, H-5exo, H-15a, H-16, H-18a), 1.53-1.61 (2H, m, H-15e, H-18e), 1.63 (1H, dd, J_{3, 2exo}=J_{3, 4exo}=4.6, H-3), 1.65-1.76 (1H, m, H-4exo), 1.84-1.97 (3H, m, H-5endo, H-14a, H-19a), 2.30 (1H, m, H-2exo), 2.45-2.52 (2H, m, H-12), 2.60-2.68 (2H, m, H-13), 2.79-2.86 (2H, m, H-14e, H-19e), 4.86 (1H, ddd, J_{1exo, 2exo}=10.0, J_{1exo, 2endo}=3.5, J_{1exo, 5exo}=2.2, H-1exo). ¹³C NMR (δ, ppm): 172.61 s (C-11), 79.28 d (C-1), 53.67 t (C-13), 53.26 and 53.22 t (C-14, C-19), 48.32 s (C-6), 47.32 s (C-7), 44.43 d (C-3), 36.22 t (C-2), 33.89 and 33.87 t (C-15, C-18), 32.49 t (C-12), 30.25 d (C-16), 27.57 t (C-4), 26.67 t (C-5), 21.42 q (Me-17), 19.24 q (Me-9), 18.38 q (Me-10), 13.01 q (Me-8). $[\alpha]_D^{24} = -30.6$ (CHCl₃, c=0.68). HRMS: calcd for C₁₉H₃₃O₂N: **307.2506**; found: **307.2503**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-morpholinopropanoate (16)

Yield: 58%, pale yellow oil. ¹H NMR (δ, ppm, J/Hz): 0.80 (3H, s, Me-9), 0.83 (3H, s, Me-10), 0.87 (3H, s, Me-8), 0.94 (1H, dd, ²J=13.7, J_{2endo, 1exo}=3.5, H-2endo), 1.13-1.30 (2H, m, H-4endo, H-5exo), 1.65 (1H, dd, J_{3, 2exo}=J_{3, 4exo}=4.6, H-3), 1.71 (1H, ddddd, ²J=J_{4exo, 5exo}=12.0, J_{4exo, 3}=4.6, J_{4exo, 5endo}=4.4, J_{4exo, 2exo}=3.3, H-4exo), 1.88 (1H, ddd, ²J=12.9, J_{5endo, 4endo}=9.3, J_{5endo, 4exo}=4.4, H-5endo), 2.31 (1H, m, H-2exo), 2.38-2.45 (4H, m, 2H-14, 2H-17), 2.45-2.49 (2H, m, H-12), 2.62-

2.68 (2H, m, H-13), 3.60-3.73 (4H, m, 2H-15, 2H-16), 4.87 (1H, ddd, $J_{1\text{exo},2\text{exo}}=10.0$, $J_{1\text{exo},2\text{endo}}=3.5$, $J_{1\text{exo},5\text{exo}}=2.2$, H-1exo). ^{13}C NMR (δ , ppm): 172.56 s (C-11), 79.76 d (C-1), 66.83 t (C-15, C-16), 54.06 t (C-13), 53.26 t (C-14, C-17), 48.69 s (C-6), 47.68 s (C-7), 44.75 d (C-3), 36.55 t (C-2), 32.50 t (C-12), 27.94 t (C-4), 27.02 t (C-5), 19.57 q (Me-9), 18.71 q (Me-10), 13.37 q (Me-8). $[\alpha]_D^{28}=-34$ (CHCl_3 , $c=0.7$). HRMS: calcd for $\text{C}_{17}\text{H}_{29}\text{O}_3\text{N}$: **295.2142**; found: **295.2138**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-(piperazin-1-yl)propanoate (17)

Yield: 52%, pale yellow oil. ^1H NMR (δ , ppm, J/Hz): 0.79 (3H, s, Me-10), 0.83 (3H, s, Me-8), 0.86 (3H, s, Me-9), 0.94 (1H, dd, $^2J=13.7$, $J_{2\text{endo},1\text{exo}}=3.5$, H-2endo), 1.13-1.30 (2H, m, H-4endo, H-5exo), 1.63 (1H, dd, $J_{3,2\text{exo}}=J_{3,4\text{exo}}=4.6$, H-3), 1.66-1.75 (1H, m, H-4exo), 1.85-1.93 (1H, ddd, $^2J=12.9$, $J_{5\text{endo},4\text{endo}}=9.3$, $J_{5\text{endo},4\text{exo}}=4.4$, H-5endo), 2.31 (1H, m, H-2exo), 2.40 (4H, br. s, 2H-15, 2H-16), 2.44-2.50 (2H, m, H-12), 2.61-2.68 (2H, m, H-13), 2.80-2.88 (4H, m, 2H-14, 2H-17) 4.86 (1H, ddd, $J_{1\text{exo},2\text{exo}}=10.0$, $J_{1\text{exo},2\text{endo}}=3.5$, $J_{1\text{exo},5\text{exo}}=2.2$, H-1exo). ^{13}C NMR (δ , ppm): 172.71 s (C-11), 79.69 d (C-1), 54.20 t (C-13), 54.03 t (C-14, C-17), 48.65 s (C-6), 47.65 s (C-7), 45.87 t (C-15, C-16), 44.73 d (C-3), 36.53 t (C-2), 32.50 t (C-12), 27.90 t (C-4), 26.99 t (C-5), 19.55 q (Me-9), 18.70 q (Me-10), 13.35 q (Me-8). $[\alpha]_D^{28}=-23$ (CHCl_3 , $c=0.62$). HRMS: calcd for $\text{C}_{17}\text{H}_{30}\text{O}_2\text{N}_2$: **294.2302**; found: **294.2299**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-(4-methylpiperazin-1-yl)propanoate (18)

Yield: 91%, pale yellow oil. ^1H NMR (δ , ppm, J/Hz): 0.78 (3H, s, Me-10), 0.82 (3H, s, Me-8), 0.85 (3H, s, Me-9), 0.93 (1H, dd, $^2J=13.7$, $J_{2\text{endo},1\text{exo}}=3.5$, H-2endo), 1.10-1.30 (2H, m, H-4endo, H-5exo), 1.62 (1H, dd, $J_{3,2\text{exo}}=J_{3,4\text{exo}}=4.6$, H-3), 1.62-1.74 (1H, m, H-4exo), 1.83-1.91 (1H, ddd, $^2J=12.9$, $J_{5\text{endo},4\text{endo}}=9.3$, $J_{5\text{endo},4\text{exo}}=4.4$, H-5endo), 2.22 (3H, s, Me-16), 2.29 (1H, m, H-2exo), 2.43-2.47 (2H, m, H-12), 2.32-2.57 (8H, br. s., 2H-14, 2H-15, 2H-17, 2H-18), 2.62-2.67 (2H, m, H-13), 4.85 (1H, ddd, $J_{1\text{exo},2\text{exo}}=10.0$, $J_{1\text{exo},2\text{endo}}=3.5$, $J_{1\text{exo},5\text{exo}}=2.2$, H-1exo). ^{13}C NMR (δ , ppm): 172.61 s (C-11), 79.64 d (C-1), 54.94 t (C-14, C-18), 53.56 t (C-13), 52.71 (C-15, C-17), 48.62 s (C-6), 47.62 s (C-7), 45.90 k (Me-16), 44.71 d (C-3), 36.50 t (C-2), 32.66 t (C-12), 27.88 t (C-4), 26.97 t (C-5), 19.54 q (Me-9), 18.68 q (Me-10), 13.35 q (Me-8). $[\alpha]_D^{25}=-30.6$ (CHCl_3 , $c=0.68$). HRMS: calcd for $\text{C}_{18}\text{H}_{32}\text{O}_2\text{N}_2$: **308.2458**; found: **308.2459**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-(4-ethylpiperazin-1-yl)propanoate (19)

Yield: 68%, pale yellow oil. ^1H NMR (δ , ppm, J/Hz): 0.79 (3H, s, Me-10), 0.82 (3H, s, Me-8), 0.86 (3H, s, Me-9), 0.94 (1H, dd, $^2J=13.7$, $J_{2\text{endo},1\text{exo}}=3.5$, H-2endo), 1.03 (3H, t, $J=7.24$,

Me-17), 1.13-1.30 (2H, m, H-4endo, H-5exo), 1.63 (1H, dd, $J_{3,2\text{exo}}=J_{3,4\text{exo}}=4.6$, H-3), 1.64-1.75 (1H, m, H-4exo), 1.83-1.93 (1H, ddd, $^2J=12.9$, $J_{5\text{endo},4\text{endo}}=9.3$, $J_{5\text{endo},4\text{exo}}=4.4$, H-5endo), 2.30 (1H, m, H-2exo), 2.35 (2H, t, $J=7.2$, H-16), 2.44-2.50 (2H, m, H-12), 2.32-2.63 (8H, br. s., 2H-14, 2H-15, 2H-18, 2H-19), 2.63-2.69 (2H, m, H-13), 4.86 (1H, ddd, $J_{1\text{exo},2\text{exo}}=10.0$, $J_{1\text{exo},2\text{endo}}=3.5$, $J_{1\text{exo},5\text{exo}}=2.2$, H-1exo). $^{13}\text{C NMR}$ (δ , ppm): 172.63 s (C-11), 79.64 d (C-1), 53.57 t (C-13), 52.72 t (C-14, C-19), 52.61 (C-15, C-18), 52.11 t (C-16), 48.62 s (C-6), 47.61 s (C-7), 44.71 d (C-3), 36.50 t (C-2), 32.65 t (C-12), 27.87 t (C-4), 26.96 t (C-5), 19.53 k (Me-9), 18.66 q (Me-10). 13.32 q (Me-8), 11.81 q (Me-17). $[\alpha]_D^{25}=-25.5$ (CHCl_3 , $c=0.94$). HRMS: calcd for $\text{C}_{19}\text{H}_{34}\text{O}_2\text{N}_2$: **322.2615**; found: **322.2612**.

Ethyl 4-(3-oxo-3-((1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yloxy)propyl)piperazine-1-carboxylate (20)

Yield: 67%, pale yellow oil. $^1\text{H NMR}$ (δ , ppm, J/Hz): 0.80 (3H, s, Me-10), 0.84 (3H, s, Me-8), 0.87 (3H, s, Me-9), 0.95 (1H, dd, $^2J=13.7$, $J_{2\text{endo},1\text{exo}}=3.5$, H-2endo), 1.22 (3H, t, $J=7.2$, Me-18), 1.14-1.31 (2H, m, H-4endo, H-5exo), 1.65 (1H, dd, $J_{3,2\text{exo}}=J_{3,4\text{exo}}=4.6$, H-3), 1.67-1.79 (1H, m, H-4exo), 1.78-1.93 (1H, ddd, $^2J=12.9$, $J_{5\text{endo},4\text{endo}}=9.3$, $J_{5\text{endo},4\text{exo}}=4.4$, H-5endo), 2.30 (1H, m, H-2exo), 2.36-2.43 (4H, m, 2H-14, 2H-20), 2.44-2.50 (2H, m, H-12), 2.64-2.70 (2H, m, H-13), 3.35-3.50 (4H, m, 2H-15, 2H-19), 4.10 (2H, t, $J=7.1$, H-17), 4.88 (1H, ddd, $J_{1\text{exo},2\text{exo}}=10.0$, $J_{1\text{exo},2\text{endo}}=3.5$, $J_{1\text{exo},5\text{exo}}=2.2$, H-1exo). $^{13}\text{C NMR}$ (δ , ppm): 172.18 s (C-11), 155.03 c (C-16), 79.46 d (C-1), 60.86 t (C-17), 53.34 t (C-13), 52.15 t (C-15, C-19), 48.35 s (C-6), 47.34 s (C-7), 44.41 d (C-3), 43.16 (C-14, C-20), 36.21 t (C-2), 32.33 t (C-12), 27.61 t (C-4), 26.68 t (C-5), 19.23 q (Me-9), 18.37 q (Me-10). 14.21 q (Me-18), 13.04 q (Me-8). $[\alpha]_D^{25}=-23.6$ (CHCl_3 , $c=0.56$). HRMS: calcd for $\text{C}_{20}\text{H}_{34}\text{O}_4\text{N}_2$: **366.2513**; found: **366.2520**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-(dibutylamino)propanoate (21)
Yield: 69%, yellow oil. $^1\text{H NMR}$ (δ , ppm, J/Hz): 0.79 (3H, s, Me-9), 0.83 (3H, s, Me-10), 0.86 (3H, s, Me-8), 0.87 (6H, t, $J=7.2$, Me-20, Me-21), 0.93 (1H, m, H-2endo), 1.14-1.43 (10H, m, H-4endo, H-5exo, 2H-16, 2H-17, 2H-18, 2H-19), 1.63 (1H, m, H-3), 1.65-1.75 (1H, m, H-4exo), 1.86-1.95 (1H, m, H-5endo), 2.25-2.34 (1H, m, H-2exo), 2.32-2.44 (6H, m, 2H-12, 2H-14, 2H-15), 2.72-2.79 (2H, m, H-13), 4.84 (1H, ddd, $J_{1\text{exo},2\text{exo}}=10.0$, $J_{1\text{exo},2\text{endo}}=3.5$, $J_{1\text{exo},5\text{exo}}=2.2$, H-1exo). $^{13}\text{C NMR}$ (δ , ppm): 173.18 s (C-11), 79.57 d (C-1), 53.45 t (C-14, S-15), 49.48 t (C-13), 48.57 s (C-6), 47.63 s (C-7), 44.74 d (C-3), 36.59 t (C-2), 32.48 t (C-12), 29.23 t (C-16, C-17), 27.88 t (C-4), 26.98 t (C-5), 20.53 t (C-18, C-19), 19.56 q (Me-9), 18.69 q (Me-10), 13.94 q (Me-20, Me-21), 13.35 q (Me-8). $[\alpha]_D^{25}=-28.8$ (CHCl_3 , $c=0.82$). HRMS: calcd for $\text{C}_{21}\text{H}_{39}\text{O}_2\text{N}$: **337.2975**; found: **337.2970**.

1.5 Synthesis of derivatives based on (-)-isoborneol 23–26

(1S,2S,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-chloroacetate (23)

Compound **23** was prepared similarly to compound **2** and purified by flash silica gel column chromatography (hexane-ethyl acetate eluent). Yield: 87%, pale yellow oil. **¹H NMR (400 MHz, CDCl₃, δ, ppm, J/Hz):** 0.81 (3H, s, Me-9), 0.85 (3H, s, Me-10), 0.88 (3H, s, Me-8), 0.99 (1H, dd, ²J=13.6, J_{2endo,1endo}=3.4, H-2endo), 1.17-1.34 (2H, m, H-4endo, H-5exo), 1.65-1.78 (2H, m, H-3, H-4exo), 1.90 (1H, m, H-5endo), 2.35 (1H, m, H-2exo), 4.05 (2H, s, H-12), 4.94 (1H, m, H-1endo). **¹³C NMR (100 MHz, CDCl₃, δ, ppm):** 167.46 s (C-11), 81.98 d (C-1), 48.81 s (C-6), 47.79 s (C-7), 44.65 d (C-3), 41.06 d (C-12), 36.38 t (C-2), 27.81 t (C-4), 26.80 t (C-5), 19.52 q (Me-9), 18.67 q (Me-10), 13.32 q (Me-8). [α]_D²⁸ = -37.5 (CHCl₃, c=0.8). HRMS: calcd for C₁₂H₁₉O₂Cl: 230.1068; found: 230.1066.

(1S,2S,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-chloropropanoate (24)

Compound **24** was prepared similarly compound to **3**. Yield: 65%, colorless oil. **¹H NMR (400 MHz, CDCl₃, δ, ppm, J/Hz):** 0.81 (3H, s, Me-9), 0.85 (3H, s, Me-10), 0.88 (3H, s, Me-8), 0.97 (1H, dd, ²J=13.9, J_{2endo,1endo}=3.8, H-2endo), 1.17-1.33 (2H, m, H-4endo, H-5exo), 1.63-1.77 (2H, m, H-3, H-4exo), 1.90 (1H, m, H-5endo), 2.34 (1H, m, H-2exo), 2.79 (2H, t, J=6.6, H-12), 3.75 (2H, t, J=6.6, H-13), 4.92 (1H, m, H-1endo). **¹³C NMR (125 MHz, CDCl₃, δ, ppm):** 170.36 s (C-11), 80.45 d (C-1), 48.62 s (C-6), 47.63 s (C-7), 44.63 d (C-3), 39.12 d (C-13), 37.74 d (C-12), 36.48 t (C-2), 27.79 t (C-4), 26.91 t (C-5), 19.49 q (Me-9), 18.63 q (Me-10), 13.28 q (Me-8). [α]_D²⁹ = -32.7 (CHCl₃, c=0.4). HRMS: calcd for C₁₃H₂₁O₂Cl: **244.1222** found: **244.1223**.

(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-morpholinoacetate (25)

Compound **25** was prepared similarly to compound **7**. Yield: 67%, pale yellow oil. **¹H NMR (400 MHz, CDCl₃, δ, ppm, J/Hz):** 0.79 (3H, s, Me-9), 0.84 (3H, s, Me-10), 0.87 (3H, s, Me-8), 0.94 (1H, dd, ²J=13.9, J_{2endo,1endo}=3.5, H-2endo), 1.15-1.31 (2H, m, H-4endo, H-5exo), 1.62-1.77 (2H, m, H-3, H-4exo), 1.86 (1H, m, H-5endo), 2.33 (1H, m, H-2exo), 2.57 (4H, m, 2H-13, 2H-16), 3.20 (2H, s, H-12), 3.72 (4H, m, 2H-14, 2H-15), 4.90 (1H, m, H-1endo). **¹³C NMR (100 MHz, CDCl₃, δ, ppm):** 169.97 s (C-11), 79.89 d (C-1), 66.35 t (C-14, C-15), 59.25 t (C-12), 52.76 t (C-13, C-16), 48.32 s (C-6), 47.37 s (C-7), 44.39 d (C-3), 36.33 t (C-2), 27.56 t (C-4), 26.67 t (C-5), 19.24 q (Me-9), 18.37 q (Me-10), 13.10 q (Me-8). [α]_D²⁸ = -23.8 (CHCl₃, c=0.68). HRMS: calcd for C₁₆H₂₇NO₃: 281.1985; found: 281.1985.

(1S,2S,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 3-morpholinopropanoate (26)

Compound **26** was prepared similarly to compound **16**. Yield: 49%, pale yellow oil. **¹H NMR (400 MHz, CDCl₃, δ, ppm, J/Hz):** 0.79 (3H, s, Me-9), 0.83 (3H, s, Me-10), 0.86 (3H, s, Me-8), 0.94 (1H, dd, ²J=13.7, J_{2endo,1endo}=3.5, H-2endo), 1.13-1.30 (2H, m, H-4endo, H-5exo), 1.63 (1H, dd, J_{3,2exo}=J_{3,4exo}=4.6, H-3), 1.71 (1H, m, H-4exo), 1.87 (1H, m, H-5endo), 2.30 (1H,

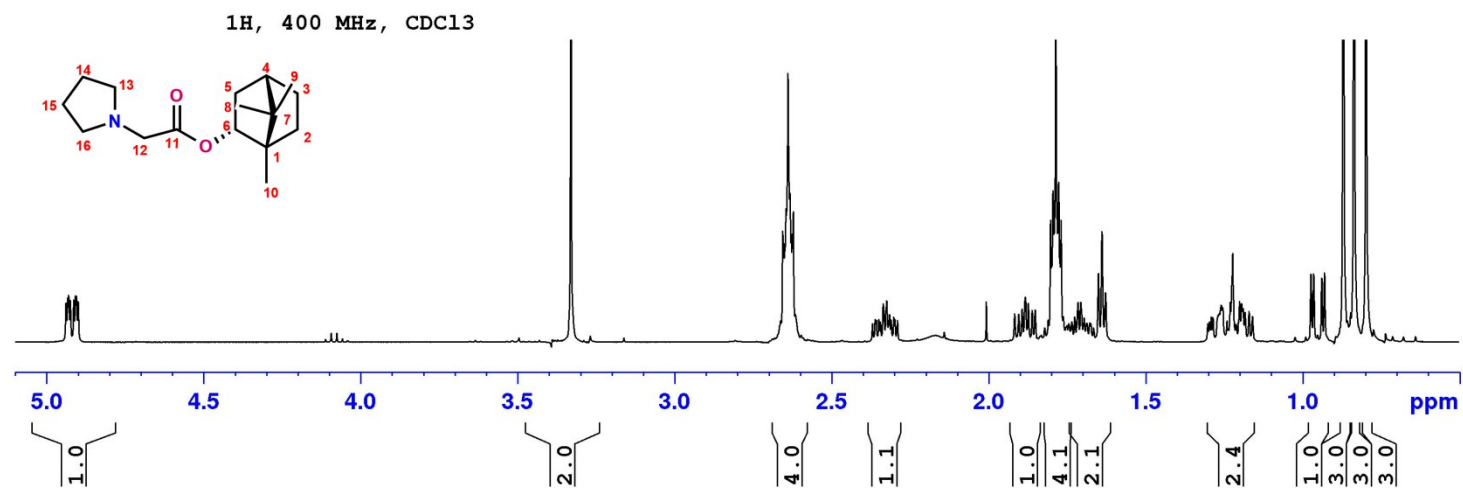
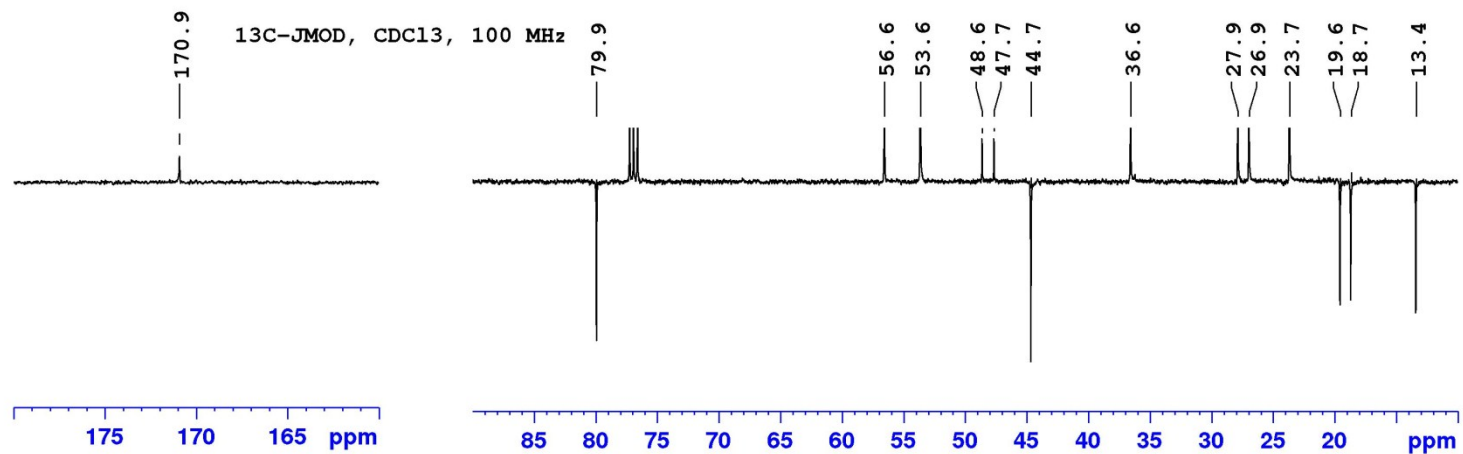
m, H-2exo), 2.39-2.45 (4H, m, 2H-14, 2H-17), 2.45-2.49 (2H, m, H-12), 2.59-2.68 (2H, m, H-13), 3.53-3.73 (4H, m, 2H-15, 2H-16), 4.86 (1H, m, H-1exo). ¹³C NMR (125 MHz, CDCl₃, δ, ppm): 172.5 s (C-11), 79.7 d (C-1), 66.7 t (C-15, C-16), 53.9 t (C-13), 53.1 t (C-14, C-17), 48.6 s (C-6), 47.6 s (C-7), 44.6 d (C-3), 36.5 t (C-2), 32.3 t (C-12), 27.8 t (C-4), 26.9 t (C-5), 19.5 q (Me-9), 18.6 q (Me-10), 13.3 q (Me-8). $[\alpha]_D^{28} = -27$ (CHCl₃, c=0.7). HRMS: calcd for C₁₇H₂₉O₃N: **295.2142**; found: **295.2140**.

1.6 Biological studies

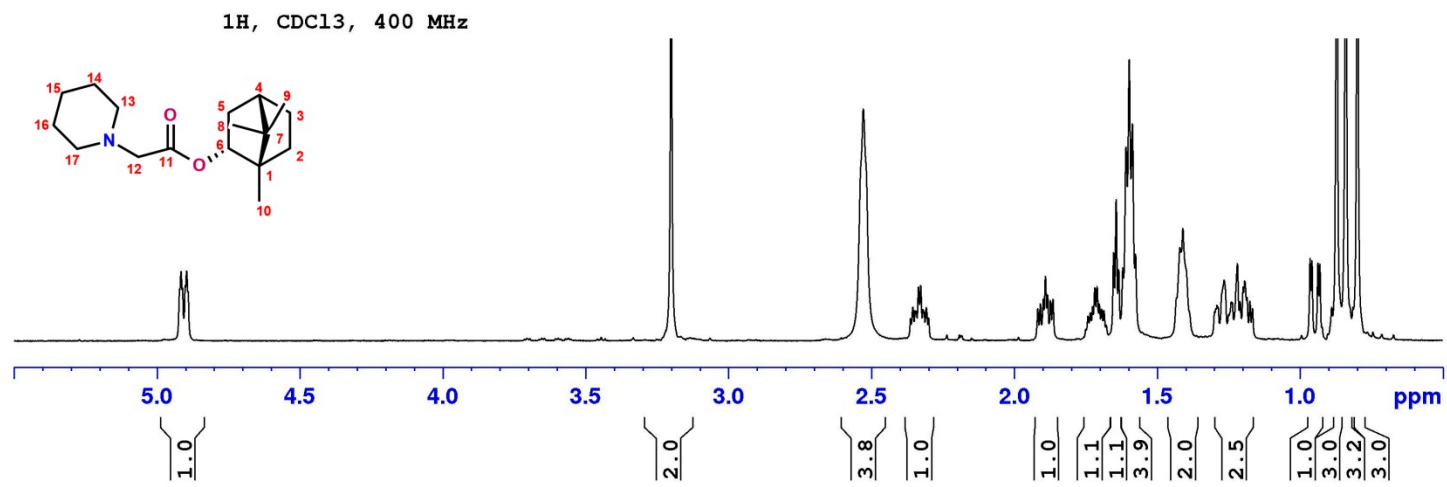
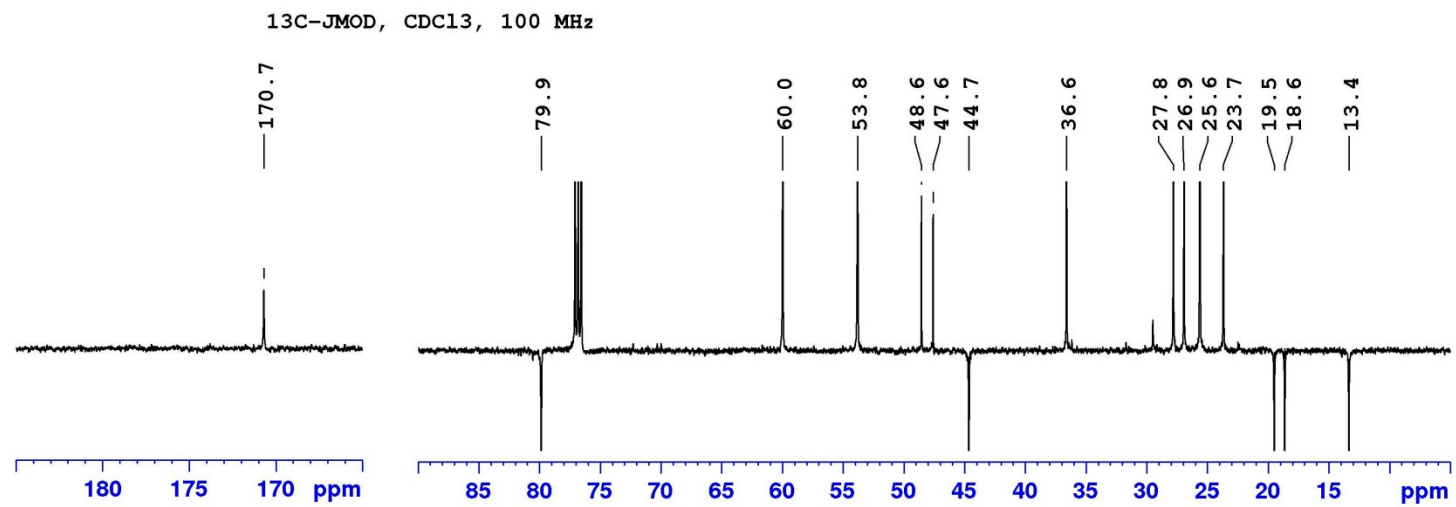
Each compound was tested for its toxicity against MDCK cells and for virus-inhibiting activity as described previously². Briefly, compounds were dissolved in 0.1 mL DMSO, and 0.9 mL of MEM medium was added. Then three-fold dilutions of compounds starting from 0.3 mg/mL were prepared and applied to an MDCK cell monolayer. Cell viability was further evaluated by MTT test.³ To assess antiviral activity, cells were infected with either rimantadine-resistant, oseltamivir-sensitive influenza virus A/Puerto/Rico/8/34 (H1N1) in the presence of three-fold dilutions of compounds. Virus titer was further measured by TCID₅₀ titration. Based on the data obtained, the 50% cytotoxic concentration (concentration resulting in the death of 50% of cells, CC₅₀), 50% inhibition concentration (concentration resulting in a decrease of virus titer by 50%, IC₅₀) and selectivity index (SI, ratio of CC₅₀ to IC₅₀) were calculated.

NMR ¹H and ¹³C spectra of the compounds **4-21**

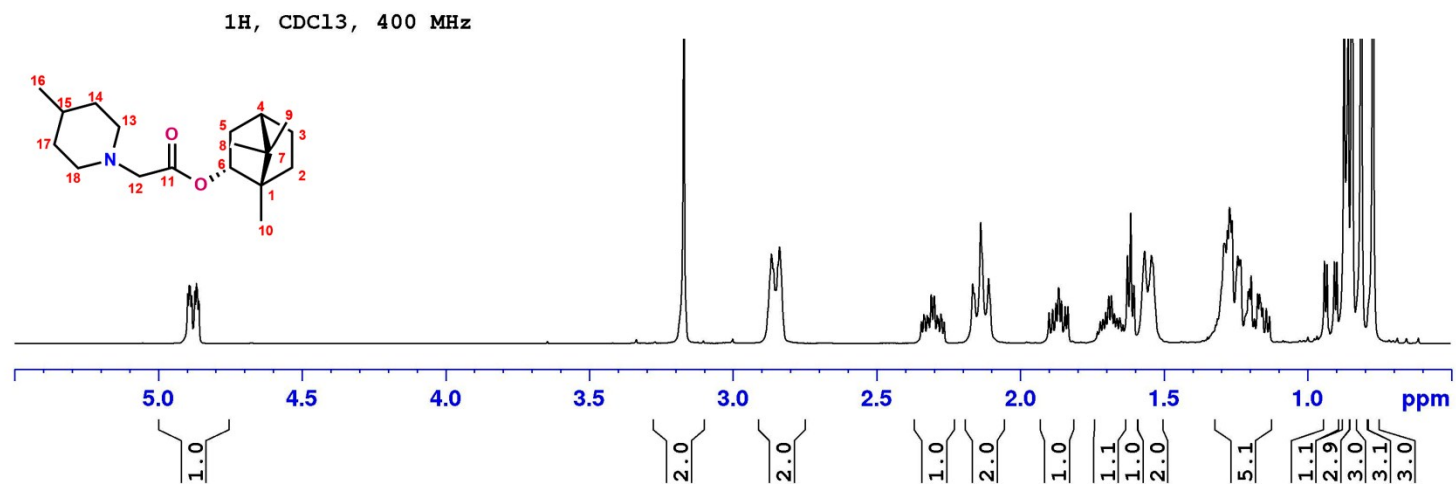
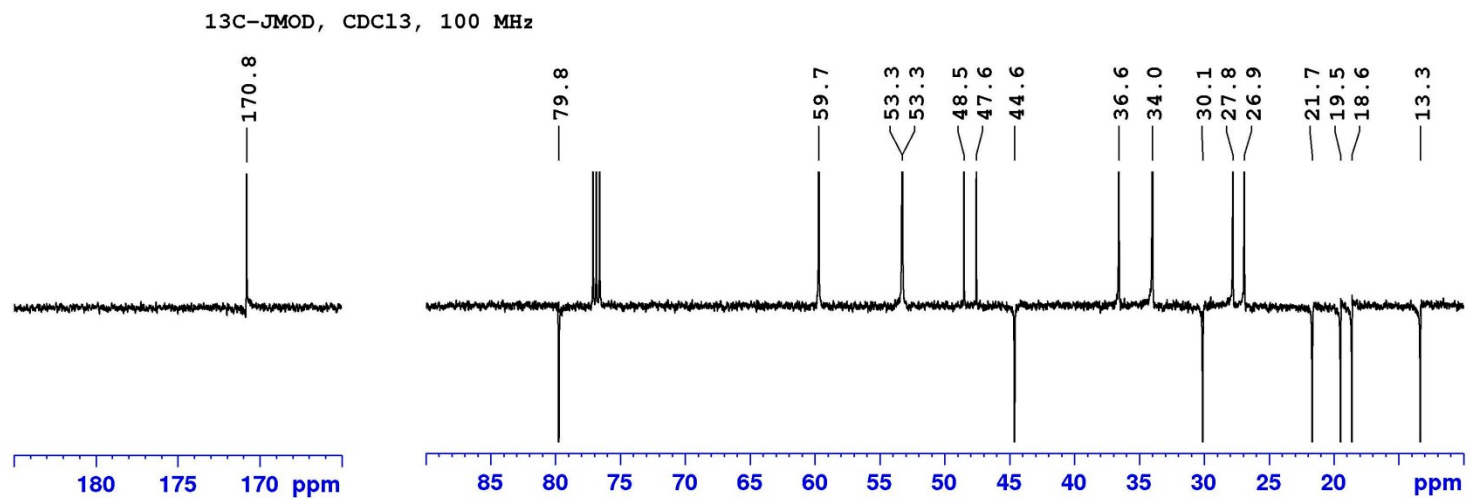
Compound 4



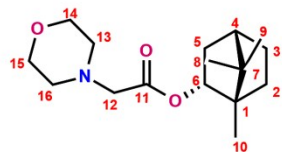
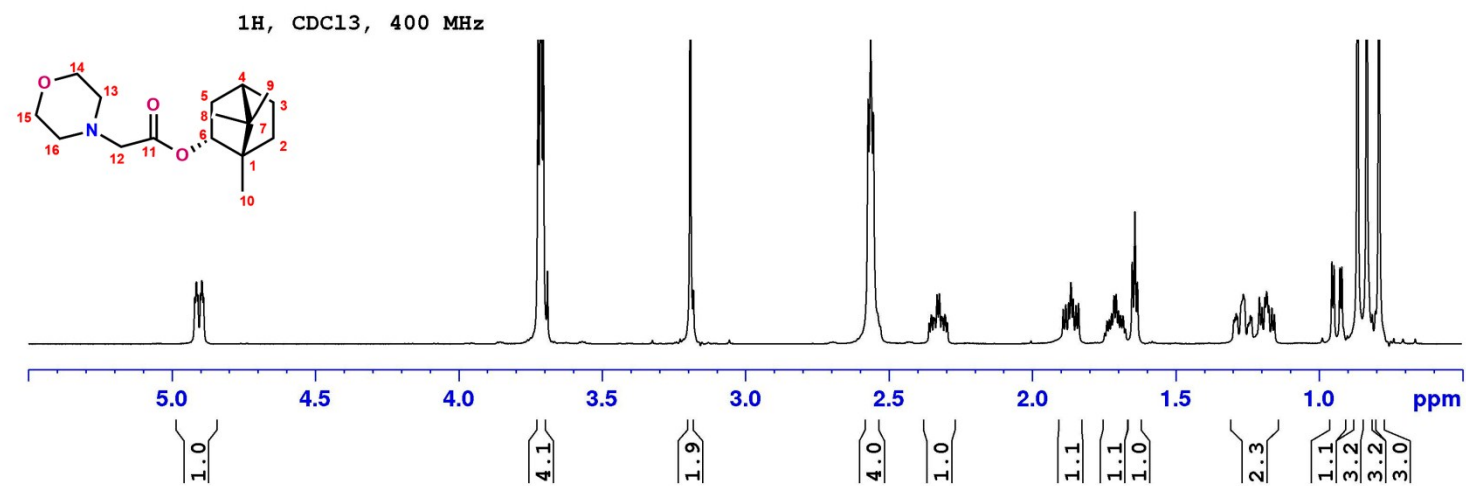
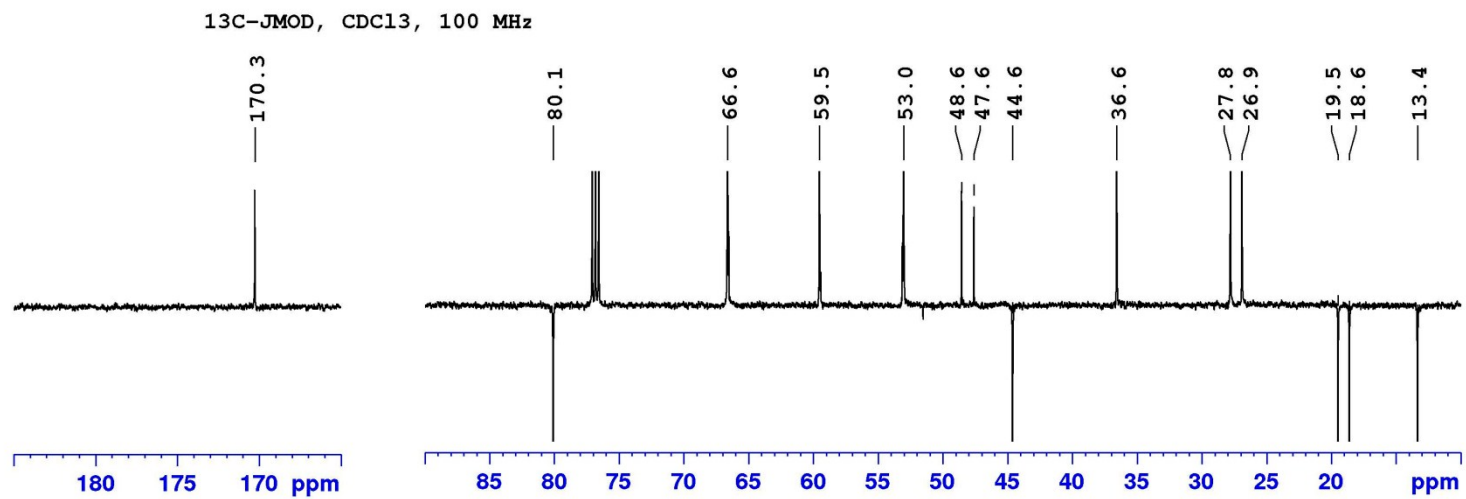
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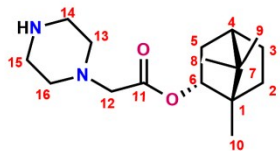
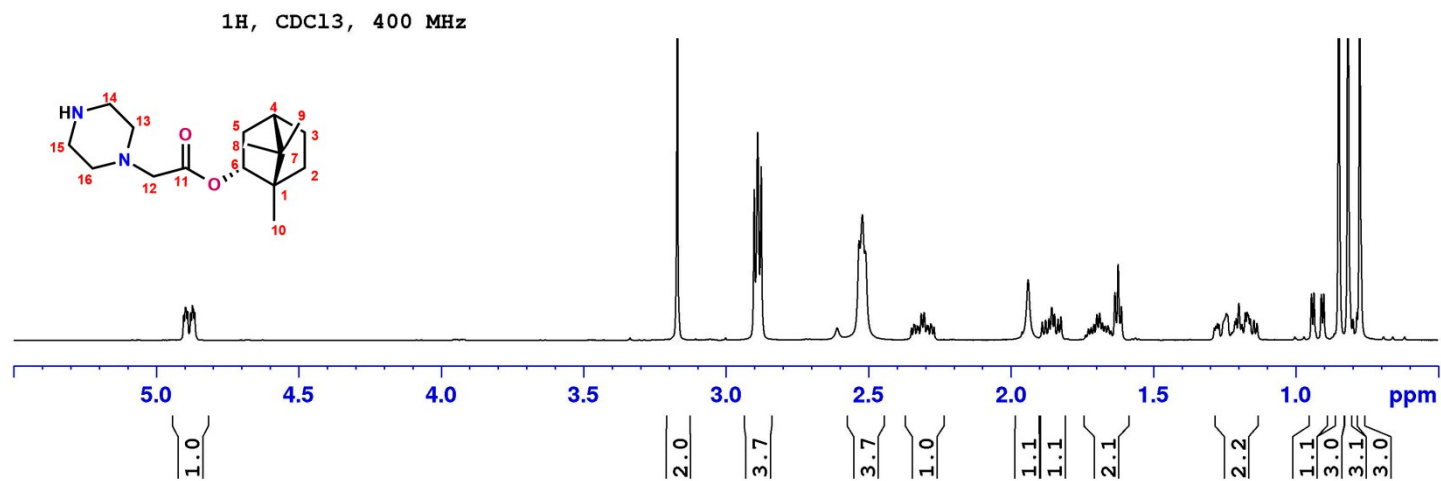
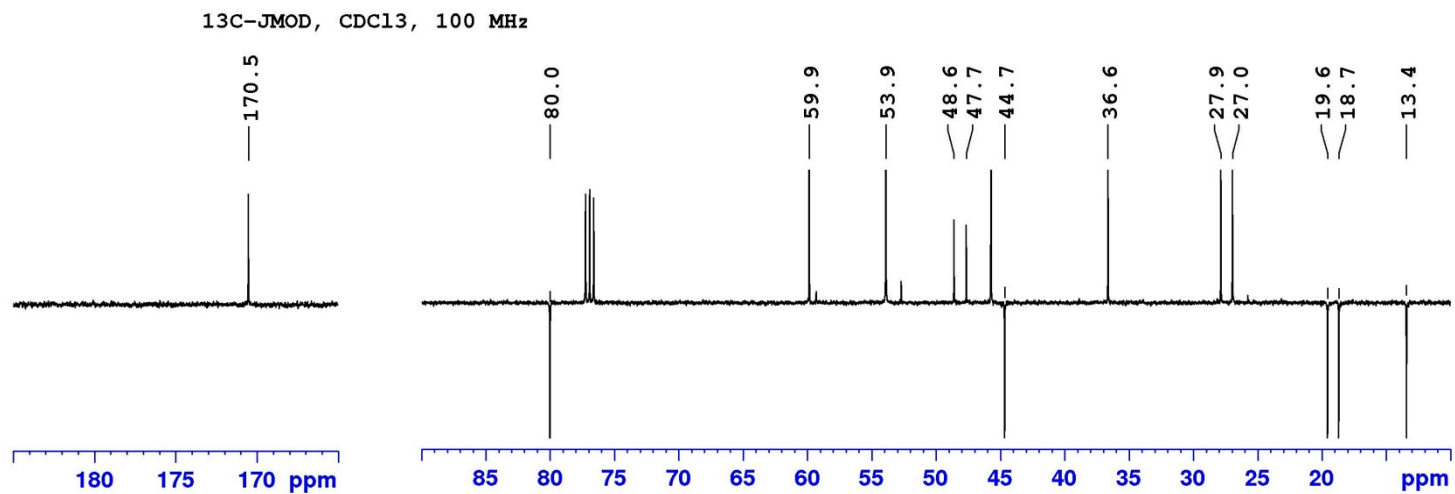
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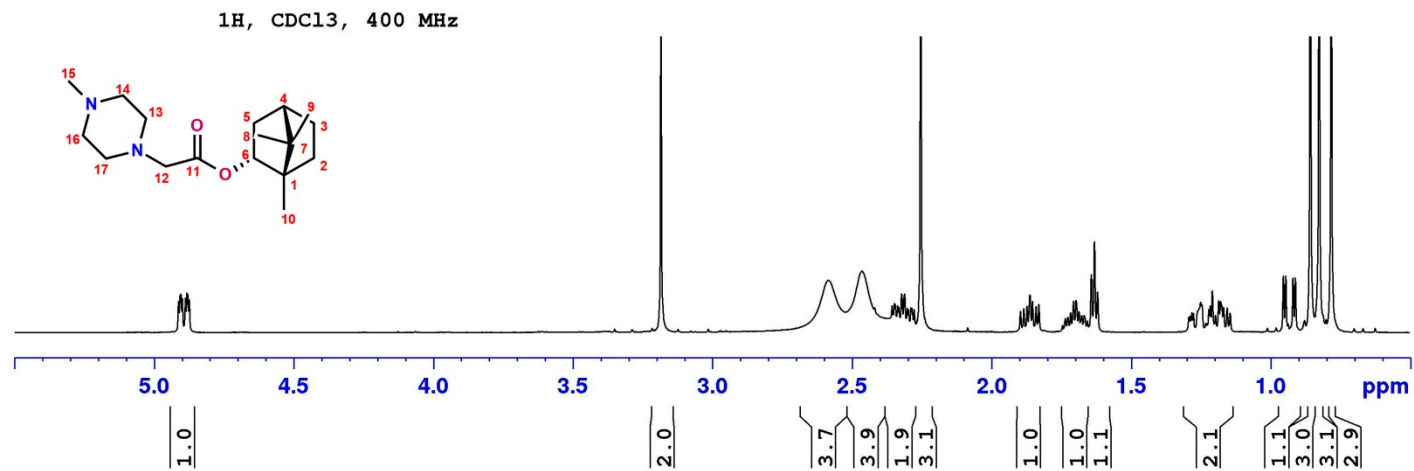
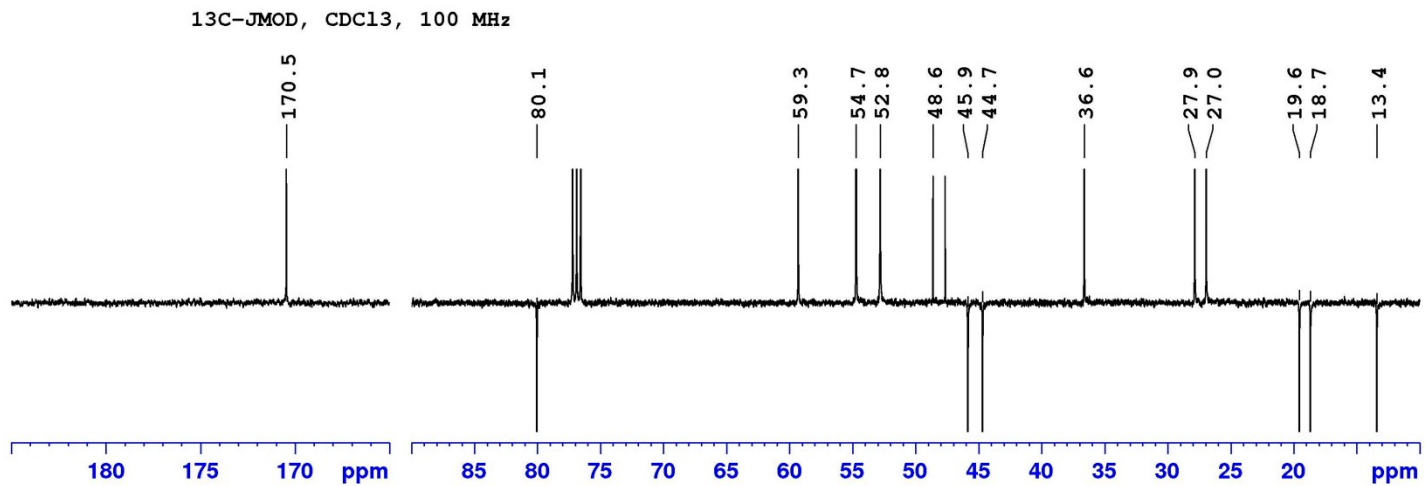
Compound 7



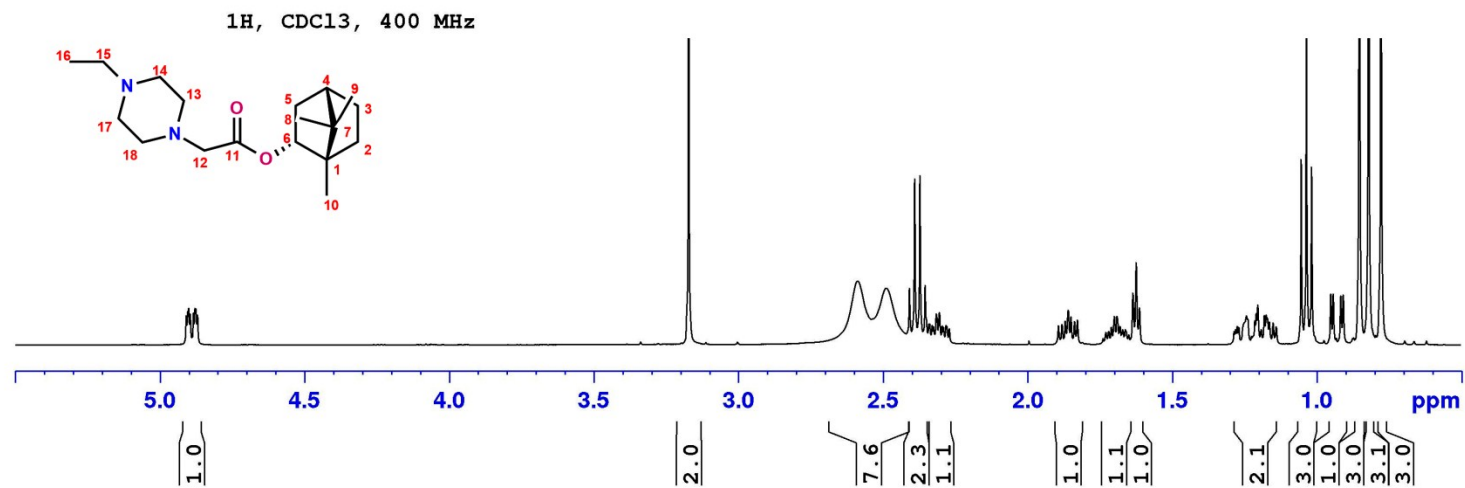
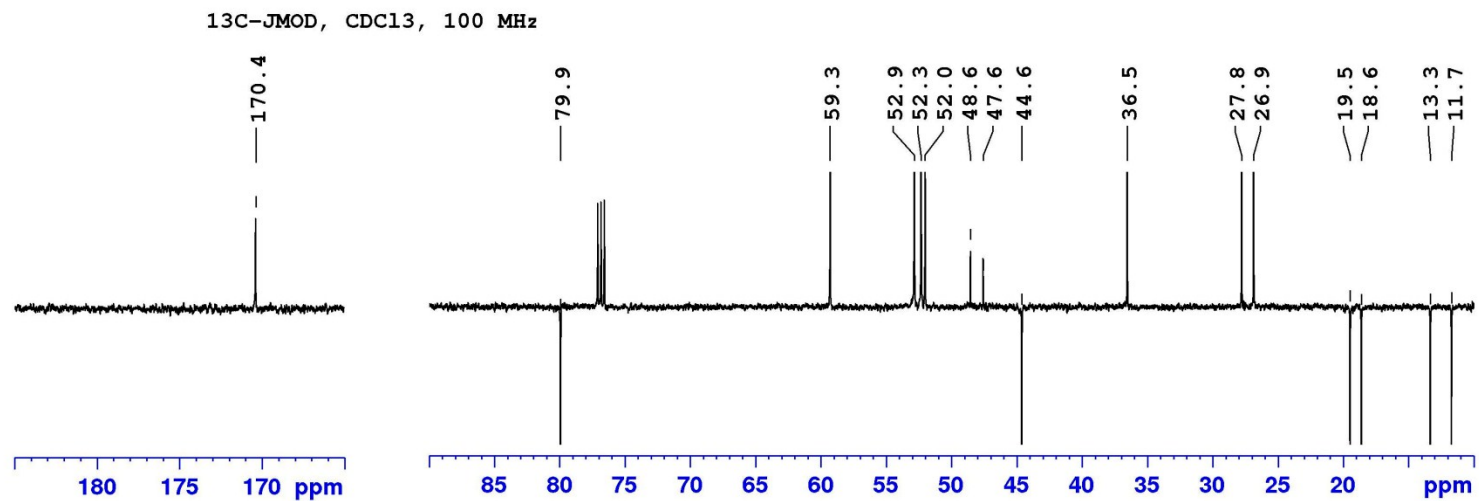
Compound 8



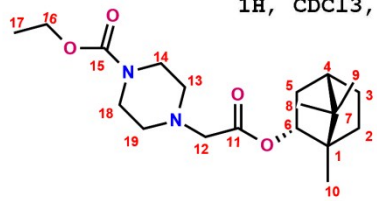
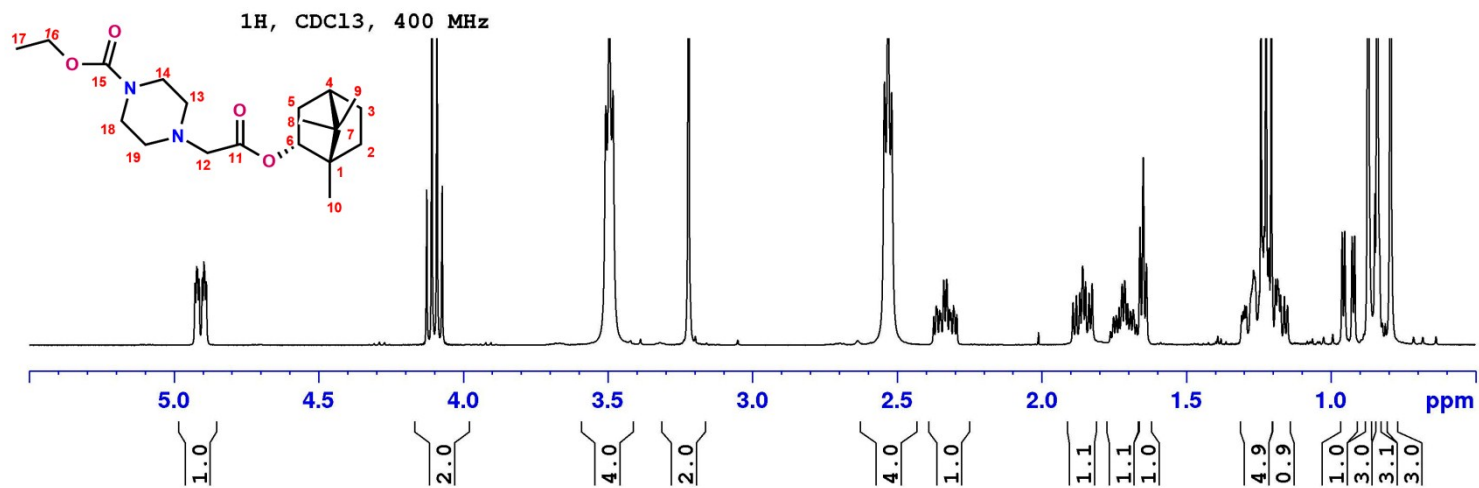
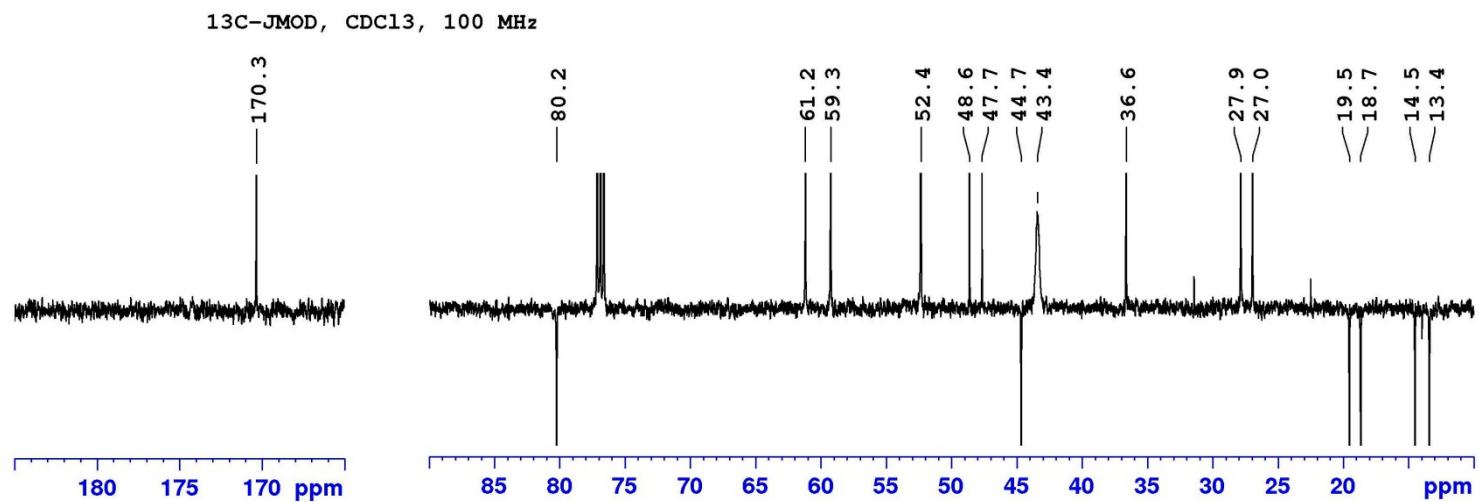
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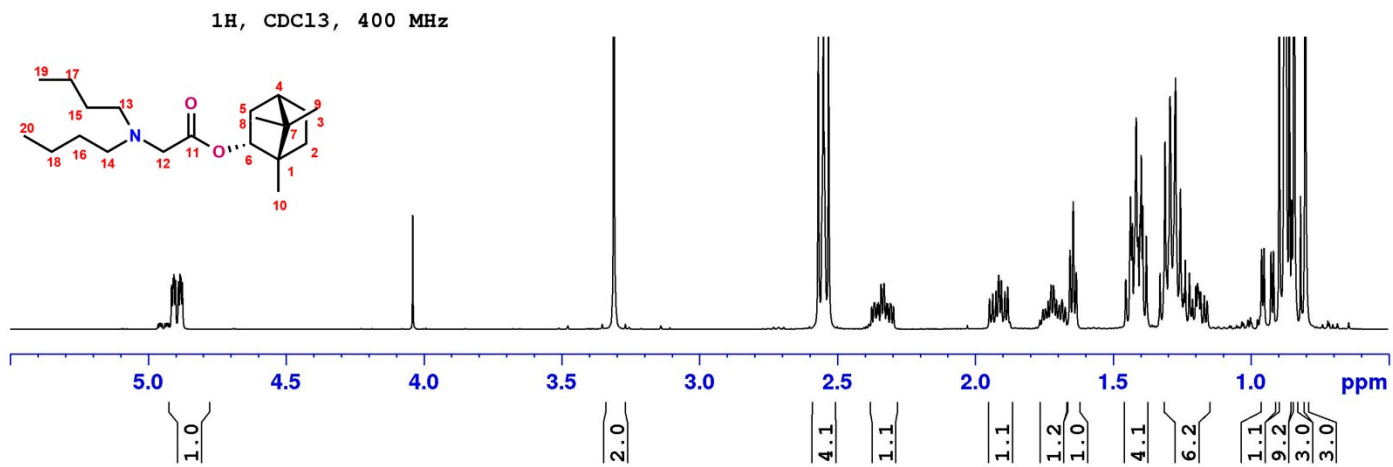
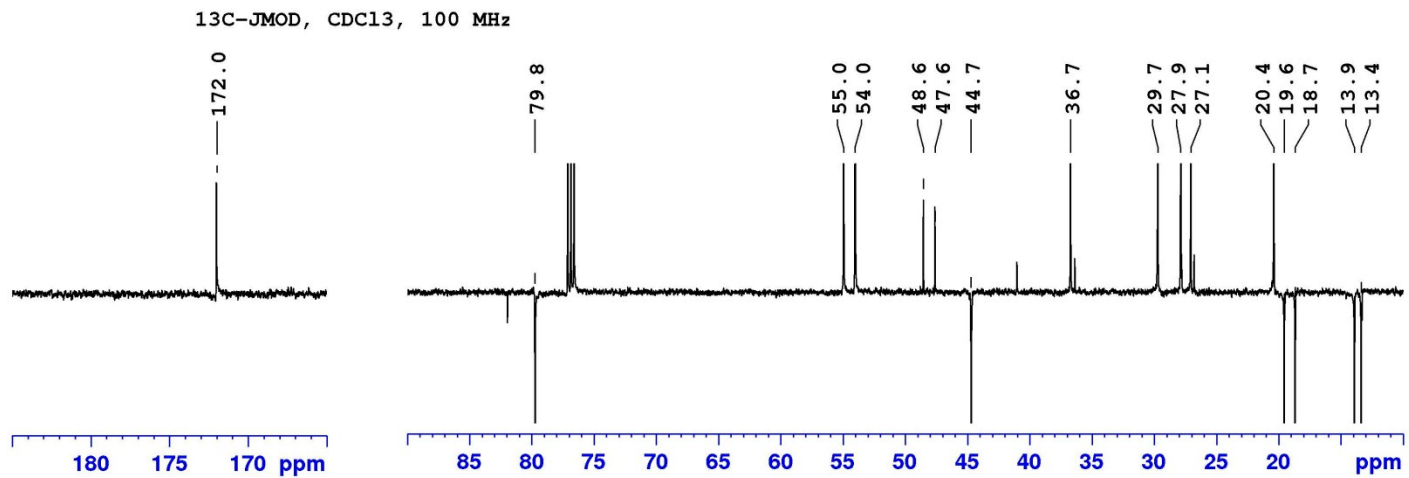
Compound 10



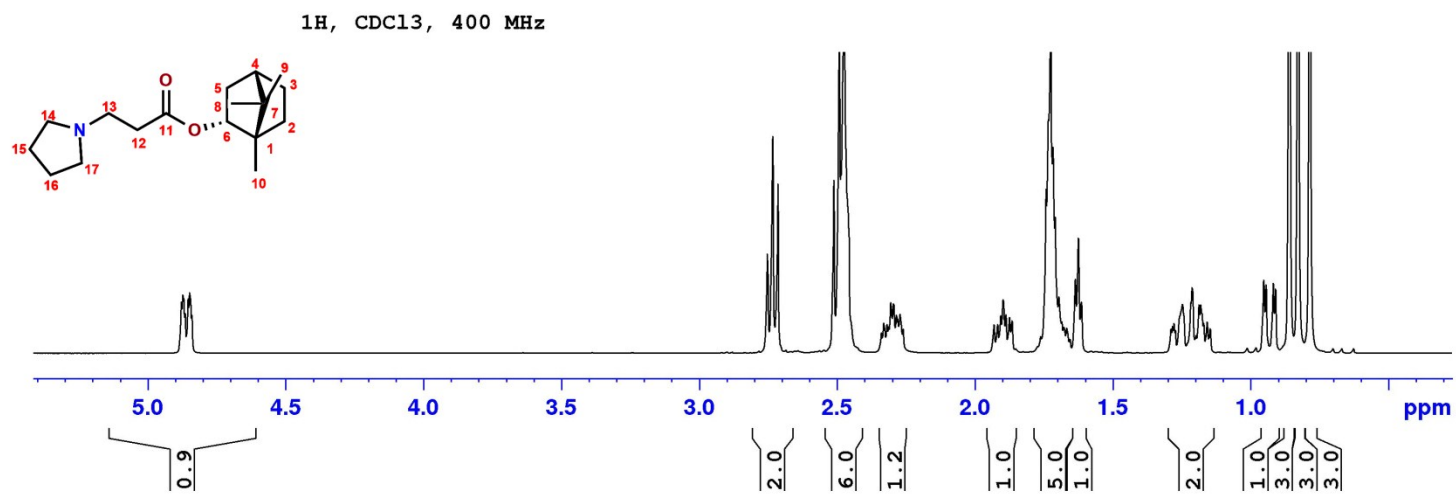
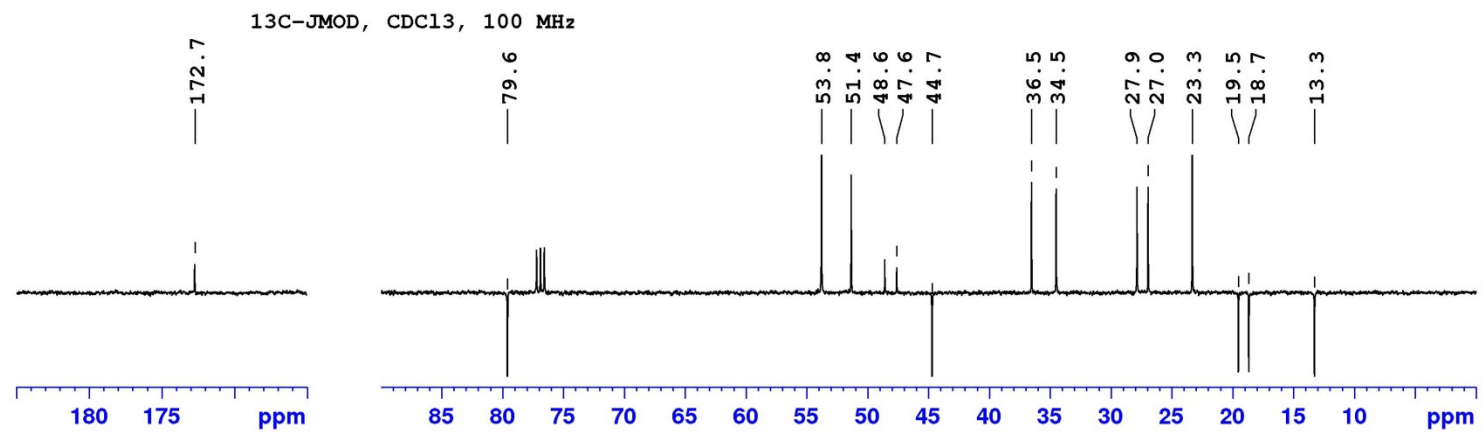
Compound 11



Compound 12

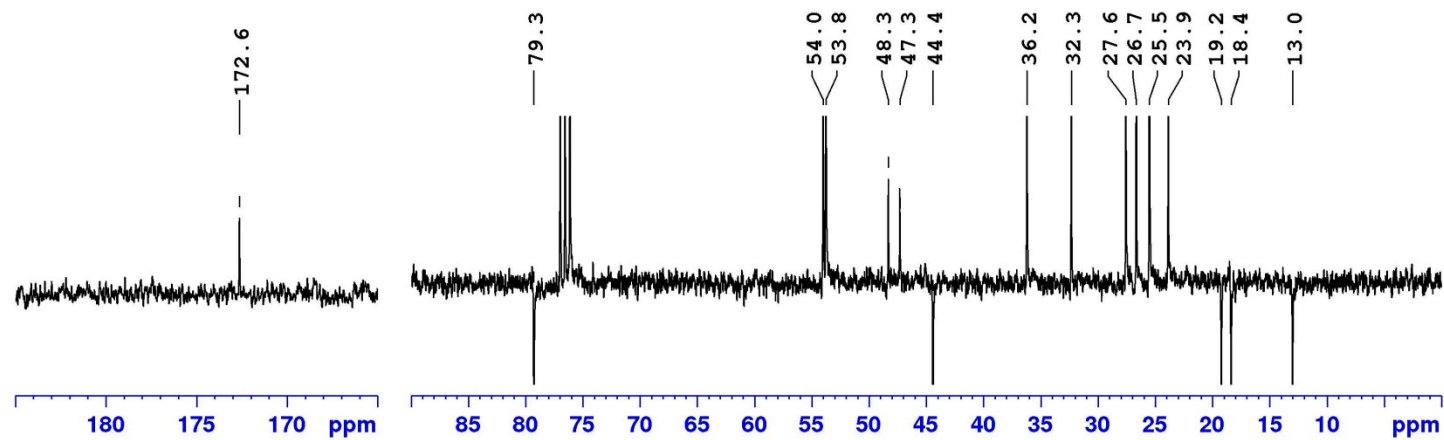


Compound 13

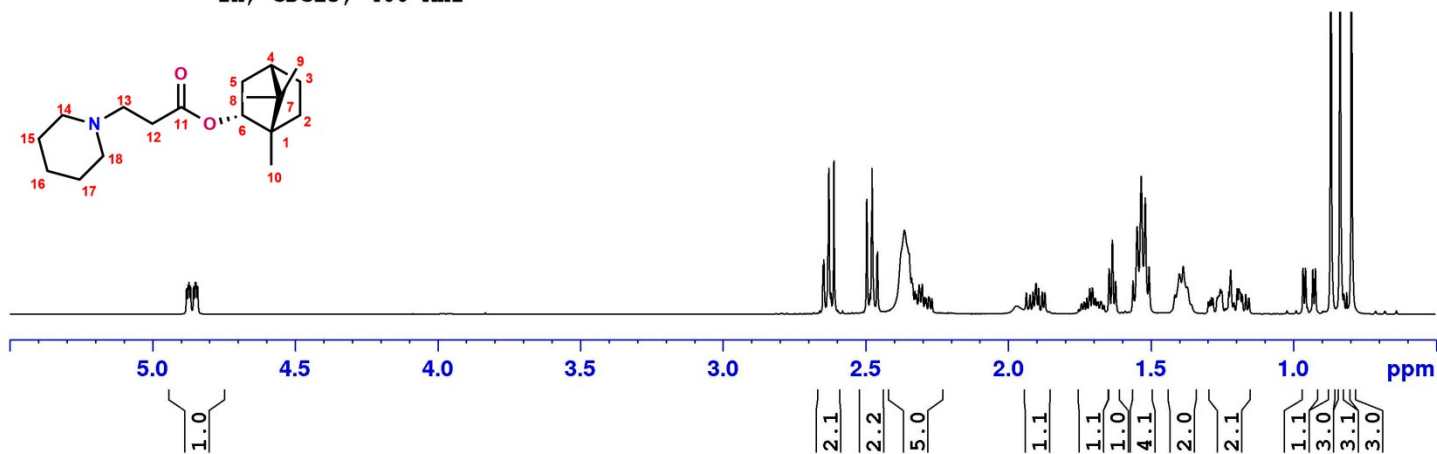


Compound 14

^{13}C -JMOD, CDCl_3 , 100 MHz

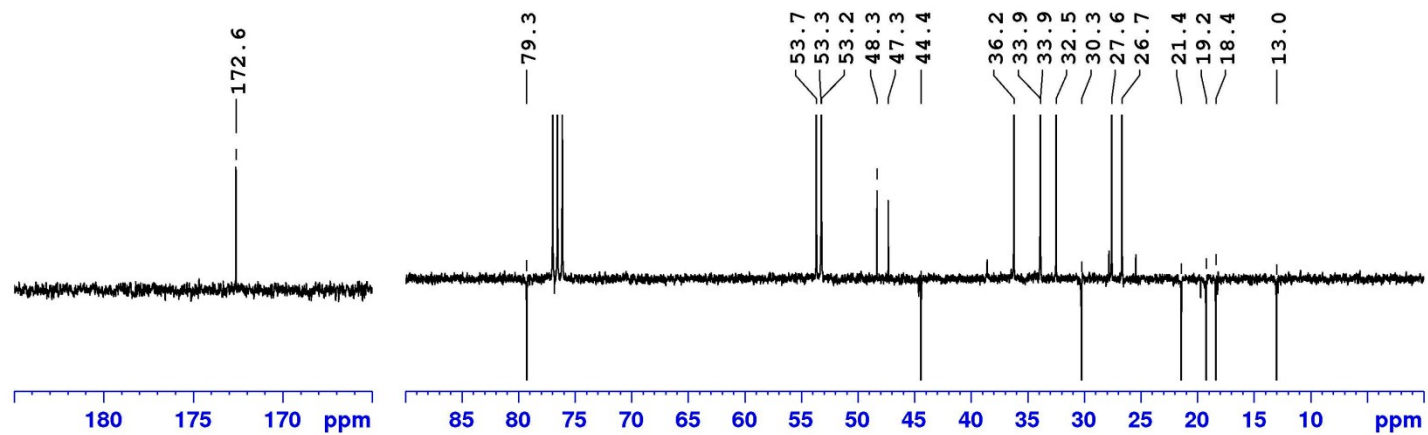


^1H , CDCl_3 , 400 MHz

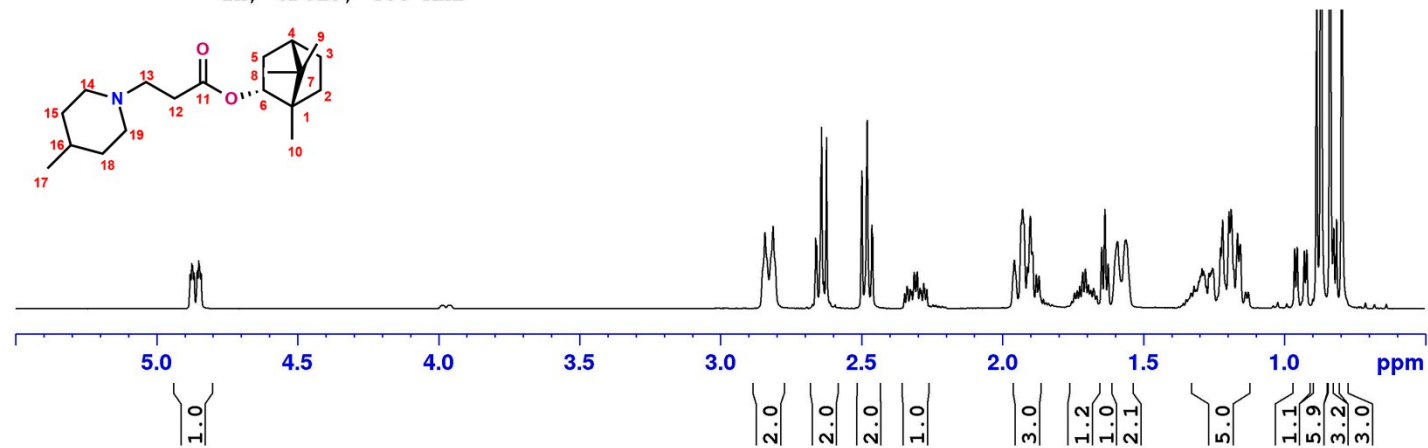


Compound 15

¹³C-JMOD, CDC13, 100 MHz

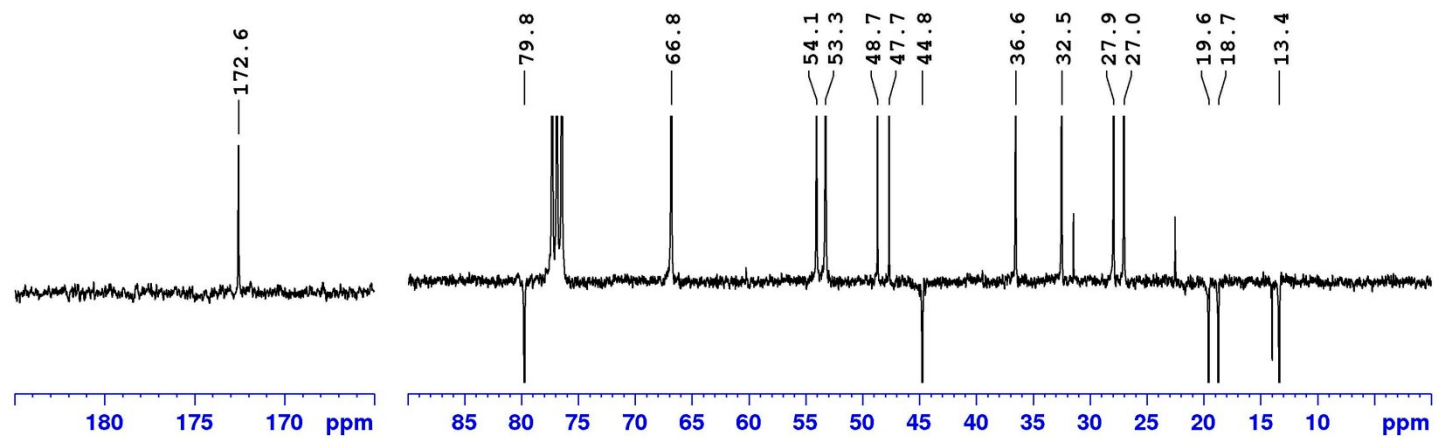


¹H, CDC13, 400 MHz

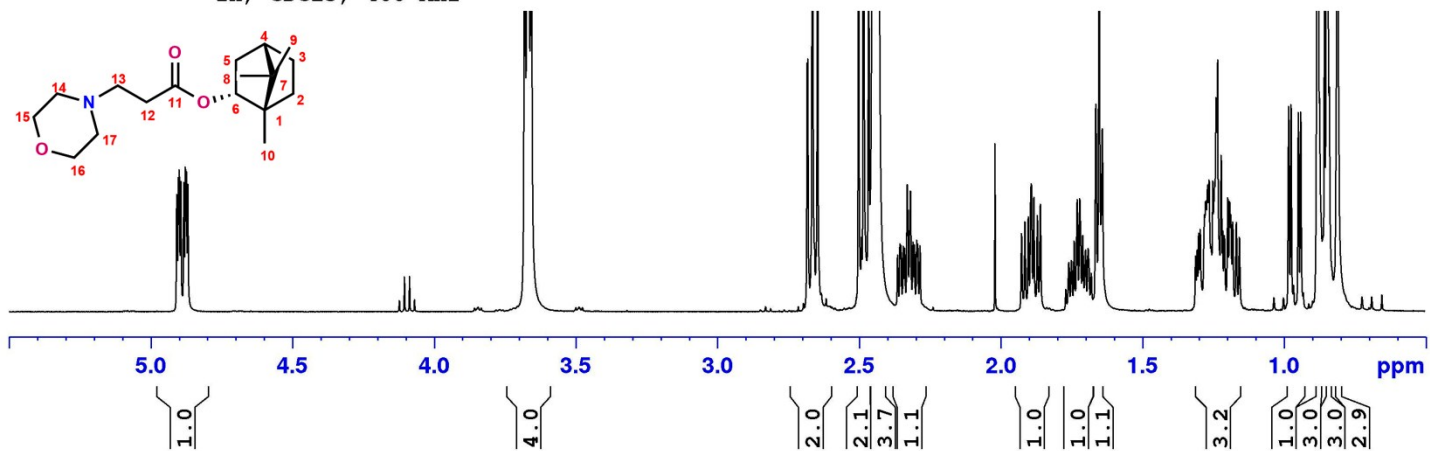


Compound 16

^{13}C -JMOD, CDCl_3 , 100 MHz

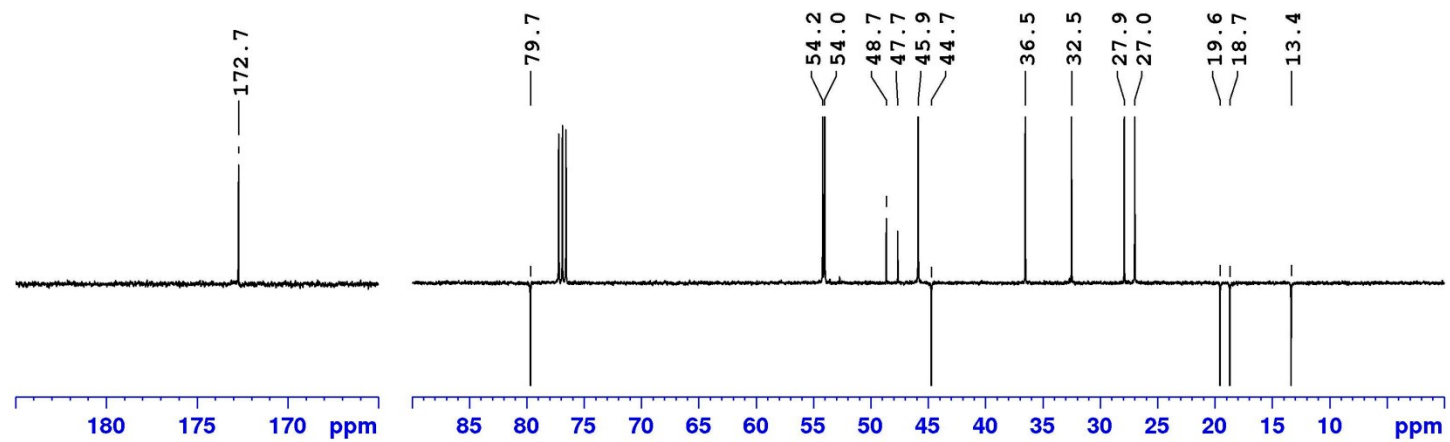


^1H , CDCl_3 , 400 MHz

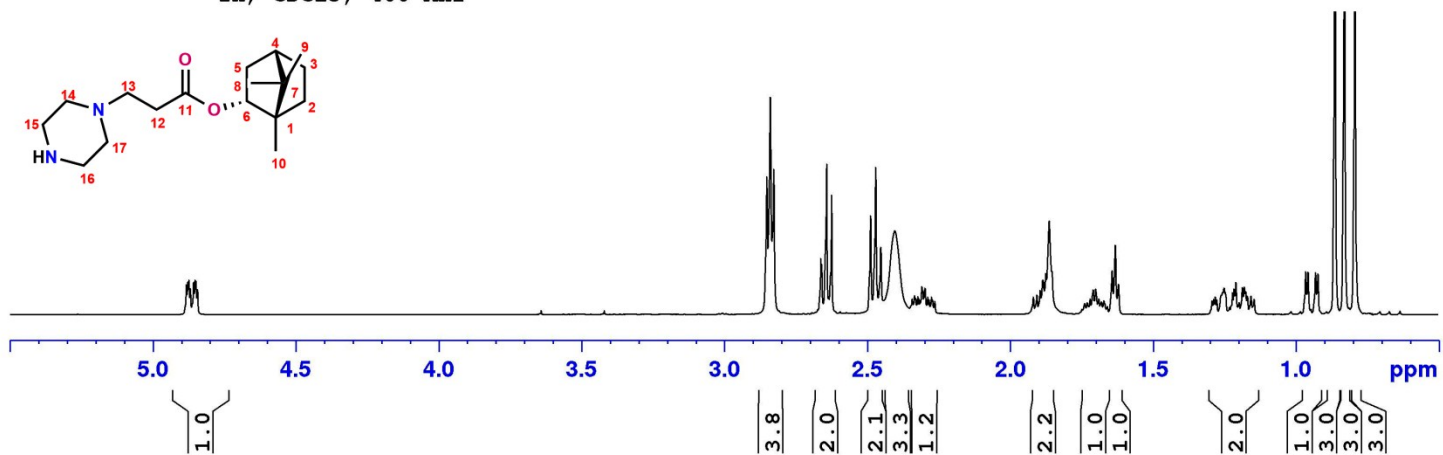


Compound 17

¹³C-JMOD, CDCl₃, 100 MHz

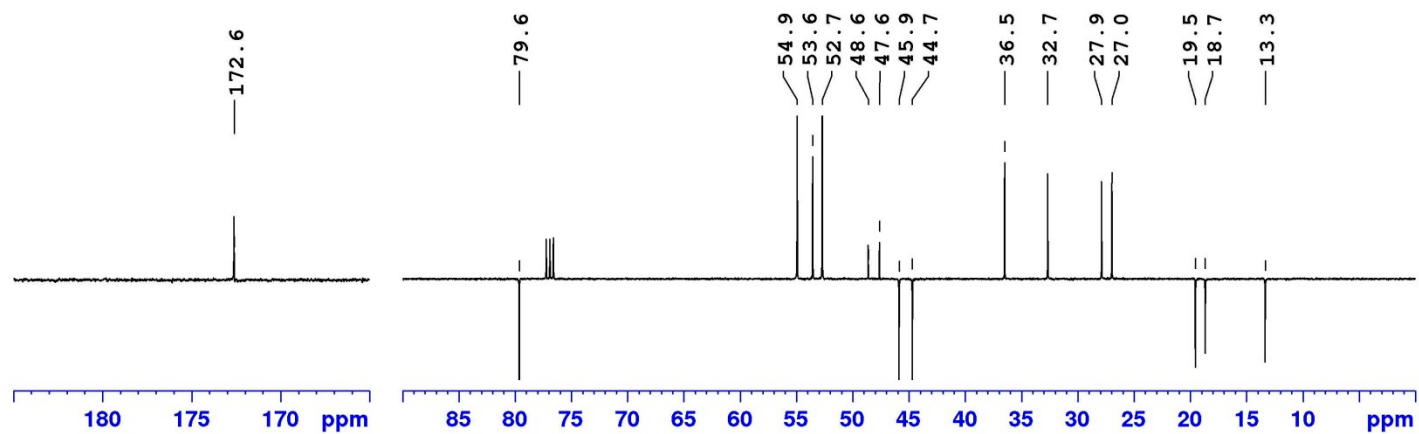


¹H, CDCl₃, 400 MHz

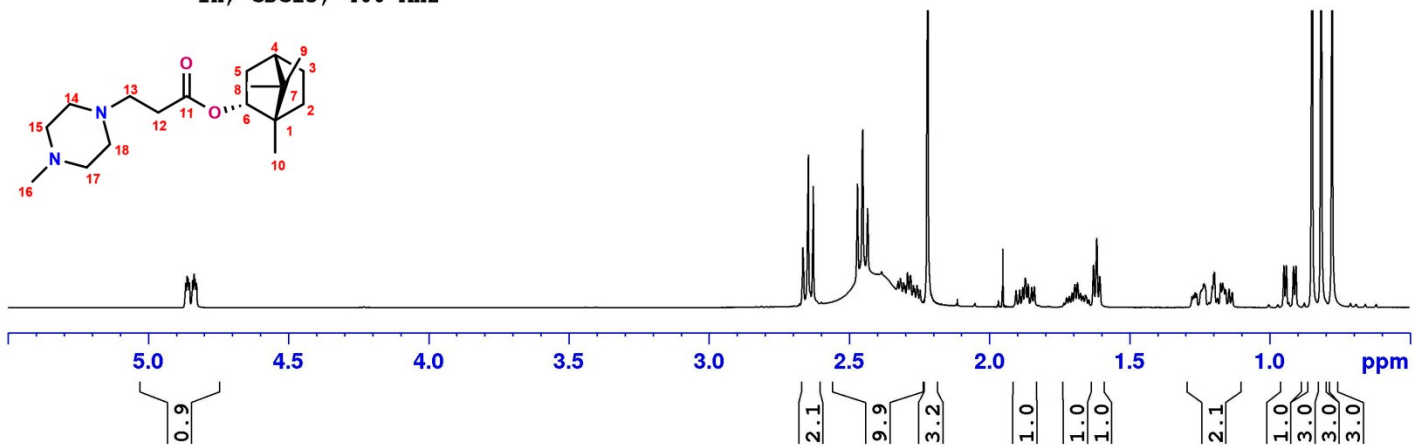


Compound 18

¹³C-JMOD, CDC13, 100 MHz

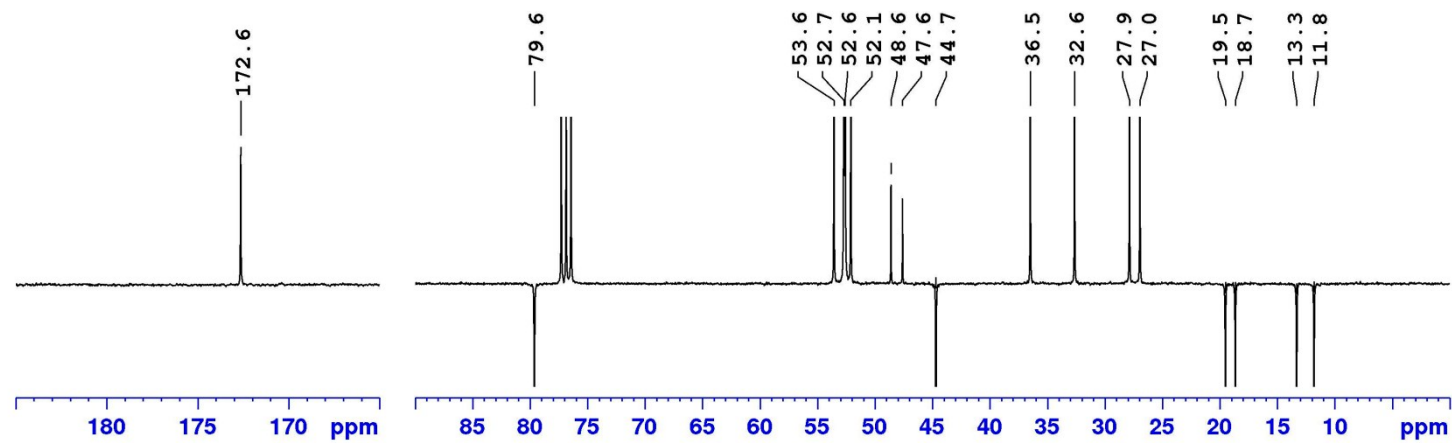


¹H, CDC13, 400 MHz

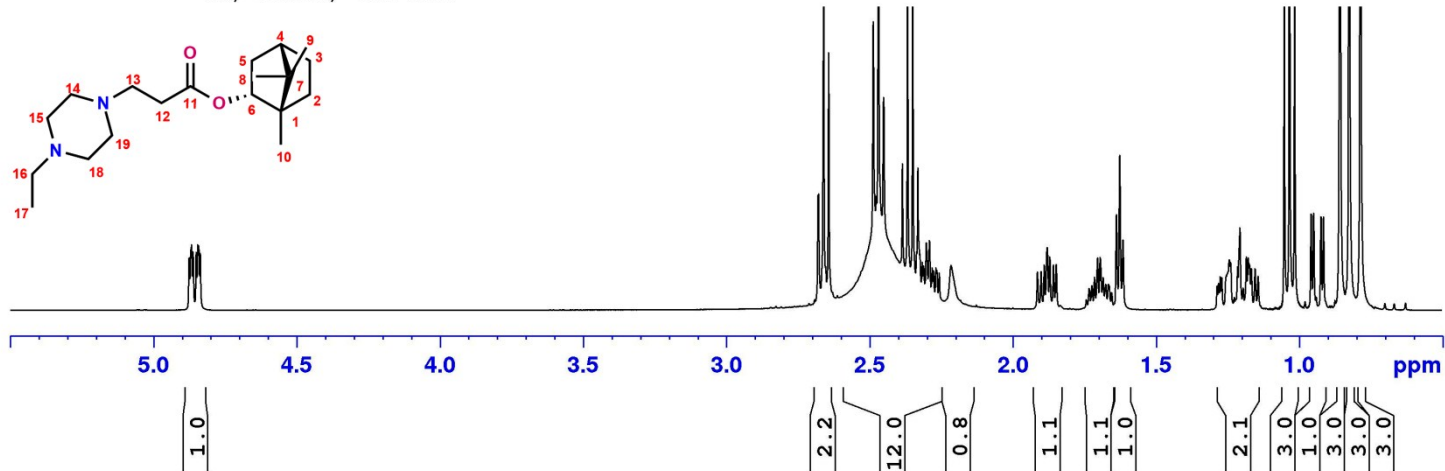


Compound 19

^{13}C -JMOD, CDCl_3 , 100 MHz

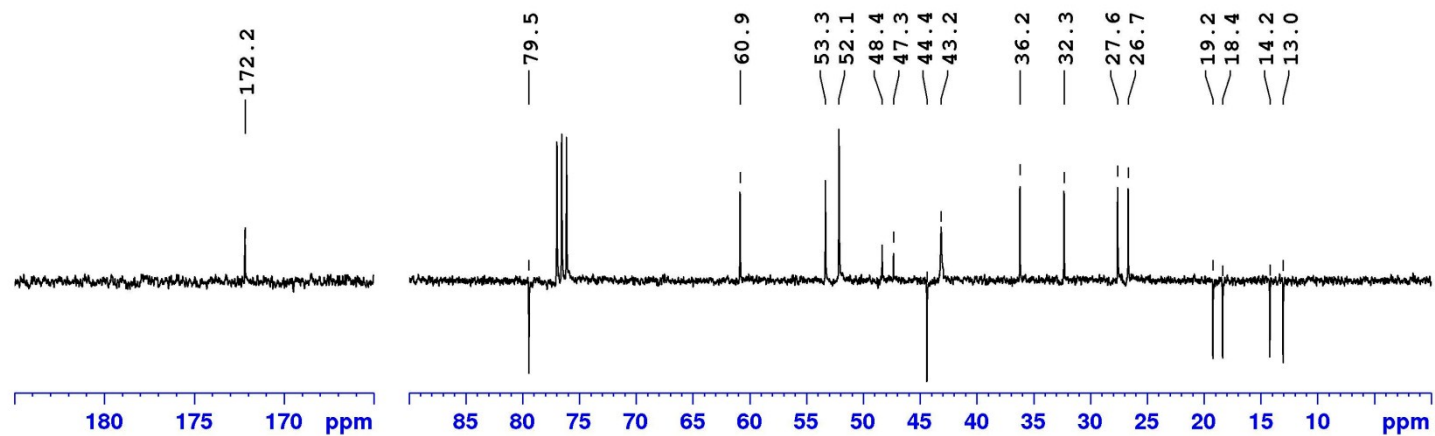


^1H , CDCl_3 , 400 MHz

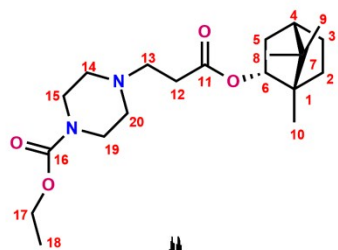
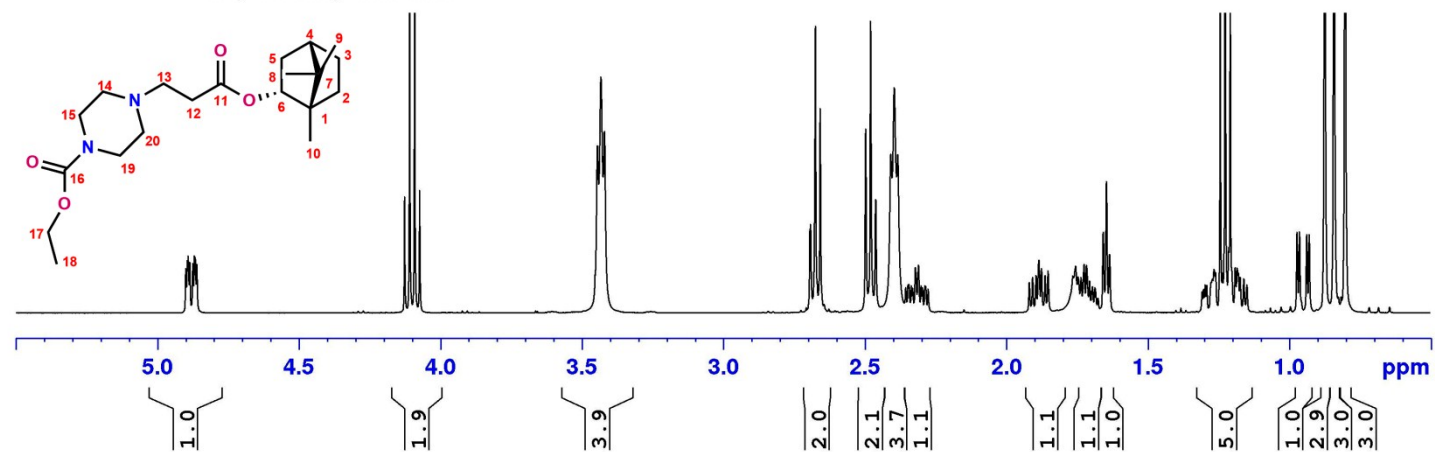


Compound 20

¹³C-JMOD, CDC13, 100 MHz

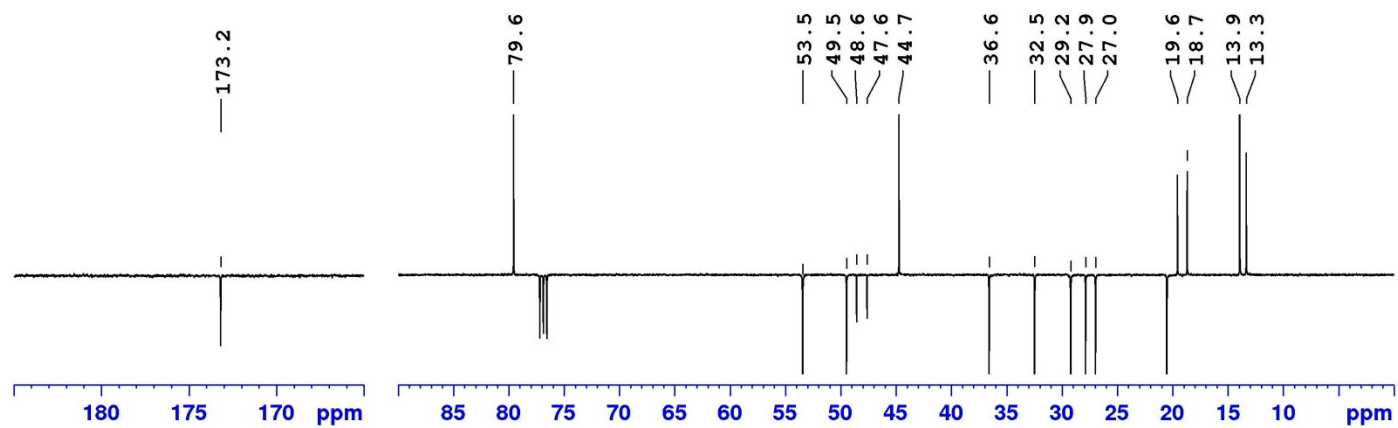


¹H, CDC13, 400 MHz

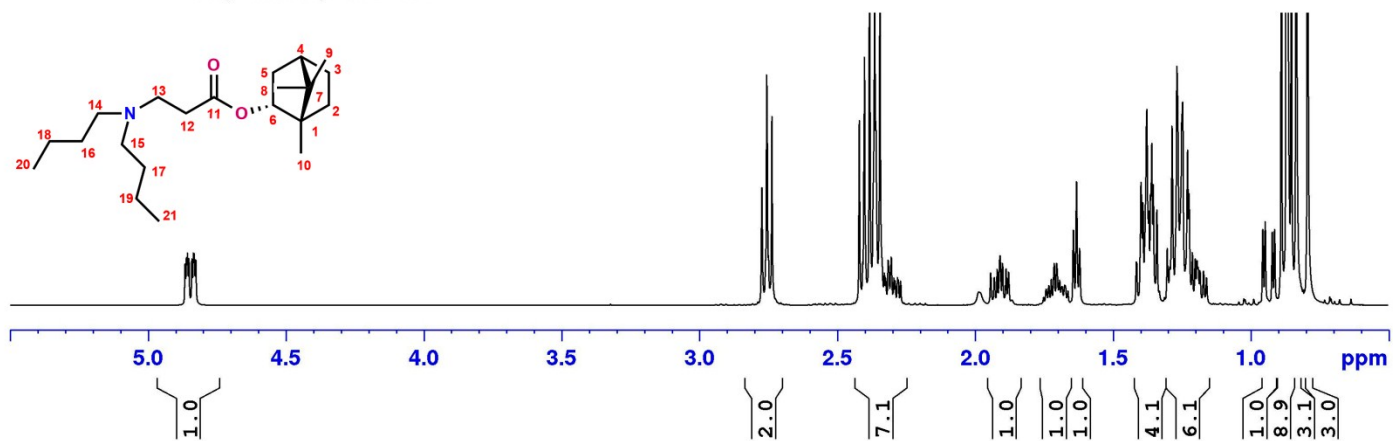


Compound 21

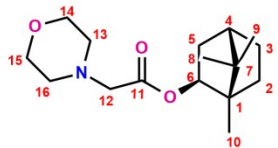
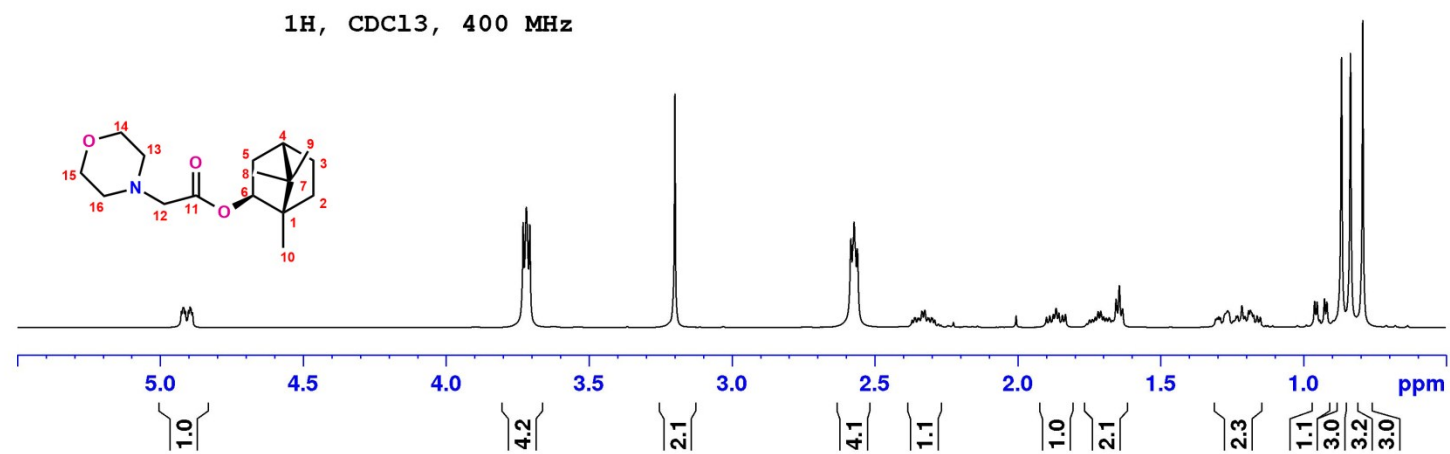
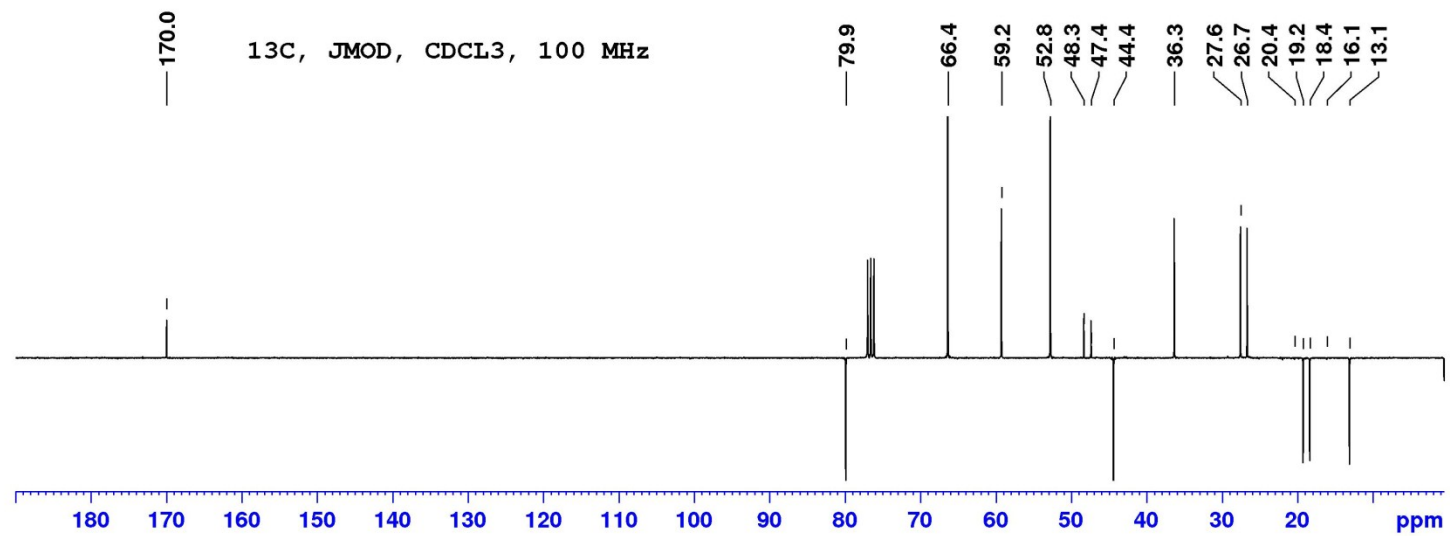
¹³C-JMOD, CDCl₃, 100 MHz



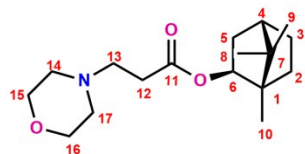
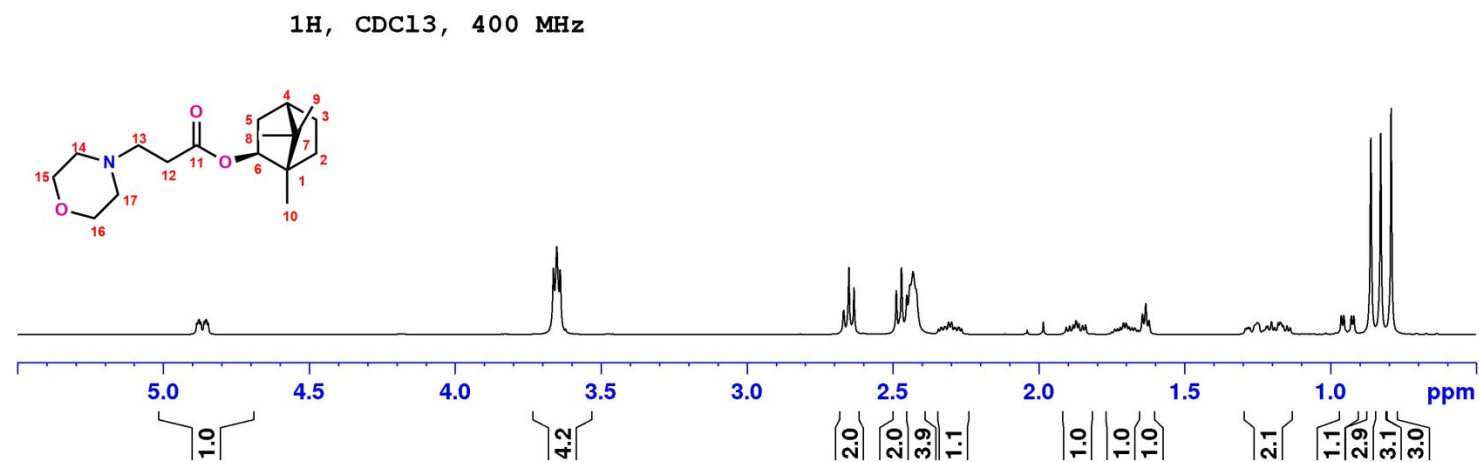
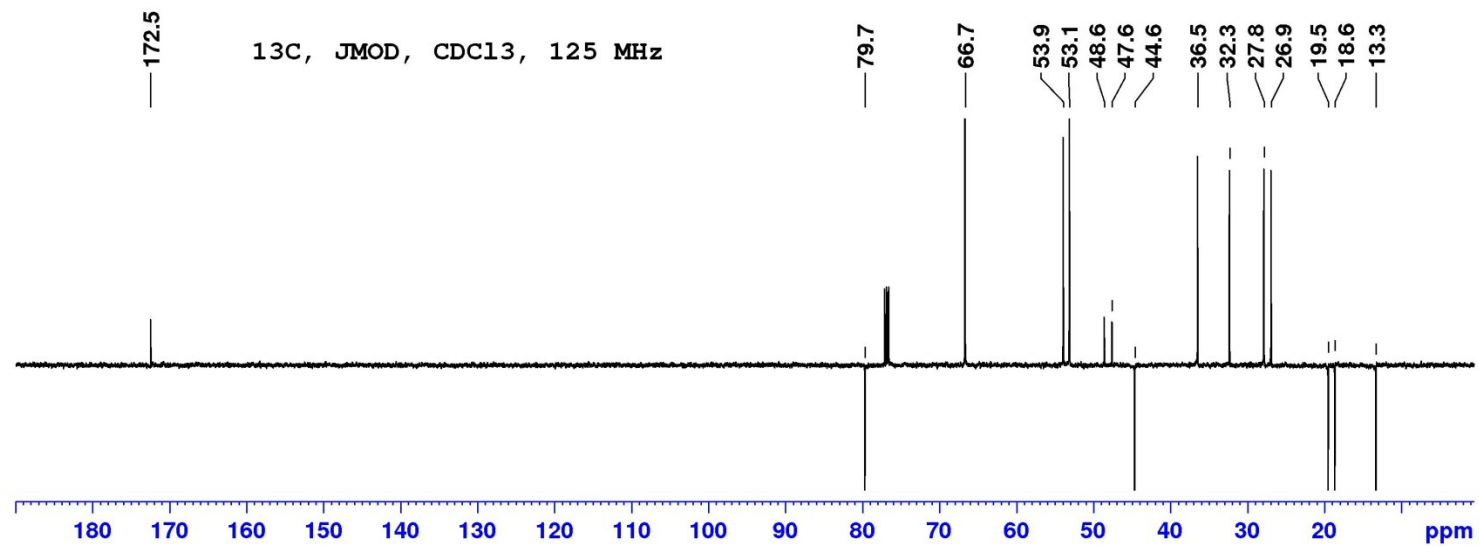
¹H, CDCl₃, 400 MHz



Compound 26



Compound 27



¹ H. Dentel, I. Chataigner, J. Lohier, M. Gulea, *Tetrahedron*, 2012, **68**, 2326.

² A. S. Sokolova, O. I. Yarovaya, A. V. Shernyukov, Yu. V. Gatilov, Yu. V. Razumova, V. V. Zarubaev, T. S. Tretiak, A. G. Pokrovsky, O. I. Kiselev, N. F. Salakhutdinov, *Eur. J. Med. Chem.*, 2015, **105**, 263.

³ T. Mosmann, *J. Immunol. Methods* 1983, **65**, 55.