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Water-soluble meroterpenes containing an aminoglyceride fragment with geraniol residues: synthesis and membranotropic properties

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1. Materials and methods

^{1}H NMR spectra were recorded on Bruker Avance-400 spectrometer at 400 MHz and ^{13}C spectra were obtained on the pulse mode spectrometer Bruker Avance-400 at100 MHz. Chemical shifts were determined against the signals of residual protons of deuterated solvent (DMSO-d_6 or $CDCl_3$). The concentration of sample solutions was 3-5 %.

Attenuated total internal reflectance IR spectra were recorded with Spectrum 400 (Perkin Elmer) Fourier spectrometer.

Elemental analysis was performed with Perkin Elmer 2400 Series II instrument.

Mass spectra (MALDI-TOF) were recorded on Ultraflex III mass spectrometer in the 4-nitroaniline matrix. Melting points were determined using Boetius Block apparatus.

Additional control of the purity of compounds and monitoring of the reaction were carried out by thin-layer chromatography using Silica G 200 μm plates, UV 254.

Most chemicals were purchased from Aldrich and used as received without additional purification. Organic solvents were purified in accordance with standard procedures.

2. Synthetic methods and spectral characteristics of the compounds **1**, **2**, **3a-b**, **4a-b**, **5** and **6a-c**.

(2,2-Dimethyl-1,3-dioxolan-4-yl)methanol 1[1]: 10 ml (137 mmol) of glycerol were placed in a 100 ml round-bottom flask, 30 ml (409 mmol) of acetone and 0.1 g (0.6 mmol) of toluene sulfonic acid were added. Molecular sieves (4 Å) were added to this mixture, after which the mixture remained for 2 days at room temperature. Then the liquid was filtered, and the molecular sieves were washed with acetone. Acetone was evaporated in a rotary evaporator, the residue was dried in high vacuum. After vacuum distillation, product **1** was obtained as a colorless liquid. Yield 15.37 g (85%), n_D^{20} 1.4335 (lit. n_D^{20} 1.4338). ^{1}H NMR ($CDCl_3$) δ: 1.37 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.96 (br. s, 1H, OH), 3.59 (dd, 1H, HO–CH–*H*, ^{3}J 5.1 Hz, ^{2}J 11.7 Hz),

3.73 (dd, 1H, HO–C*H*–H, ^3J 3.7 Hz, ^2J 11.7 Hz), 3.79 (dd, 1H, O–CH–*H*, ^3J 6.5 Hz, ^2J 8.2 Hz), 4.03 (dd, 1H, O–C*H*–H, ^3J 6.6 Hz, ^2J 8.2 Hz), 4.24 (m, 1H, CH).

(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl-4-methylbenzenesulfonate 2[2]: 4 g (30 mmol) of compound 1 was dissolved in 20 ml of pyridine. 7 g (37 mmol) of *p*-toluenesulfonyl chloride was added to the solution with constant stirring. The reaction mixture remained for 24 h at room temperature. Then 30-40 ml of water was added to it. The solution was stirred for 30 minutes. Next the mixture is washed with 50 ml of dilute hydrochloric acid. The resulting solution was extracted with diethyl ether (3 × 30 ml). The organic fraction was washed with 50 ml of 2M NaOH solution and 2 × 50 ml of distilled water. The product is obtained as a white crystalline substance. Yield 8.24 g (96%), mp 40-41°C. ^{1}H NMR ($CDCl_3$) δ: 1.32 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.76 (m, 4H, CH_2–CH–CH_2), 4.01 (m, 1H, CH), 7.59 (m, 4H, CH_{ar}).

Compounds **3a-c** were obtained by the method similar to the sources.[3]
5 g (18 mmol) of compound **2** and 30 mmol of amine (pyrrolidine in the case of **3a**, diethylamine in the case of **3b** and piperidine in the case of **3c**) were placed in an ampoule. Then the ampoule was sealed. The reaction mixture was boiled for 8 h. Then the ampoule was opened its content was transferred to a round bottom flask. The amine was evaporated *in vacuo*, the residue was poured into water and extracted with trichloromethane (3 × 30 ml). The organic layer was washed with 50 ml of 2M sodium hydroxide solution, then with distilled water, and evaporated on a rotary evaporator under reduced pressure. The corresponding product **3a-c** was obtained as yellow oil.

1-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)pyrrolidine (3a).
Yield: 2.23 g (83%). ^{1}H NMR ($CDCl_3$) δ: 1.38 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.79 (m, 4H, CH_2–CH_2), 2,54 (m, 1H, N–CH–H), 2.57 (m, 4H, N–CH_2), 2.70 (dd, 1H, N–CH–H, 3J 6.9 Hz, ^2J 12.4 Hz), 3.62 (t, 1H, O–CH–H, ^3J 7.6 Hz), 4.10 (dd, 1H, O–CH–H, ^3J 6.2 Hz, ^2J 8.0 Hz), 4.27 (m, 1H, CH).

***N*-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-*N*-ethylethanamine (3b)**.
Yield: 3 g (89%). ^{1}H NMR ($CDCl_3$) δ: 1.03 (t, 6H, $\underline{CH_3}$–CH_2–N, ^3J 7.1 Hz), 1.37 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.50 (dd, 1H, N–CH–$\underline{H}$, ^3J 6.1 Hz, ^2J 13.2 Hz), 2.57 (m, 4H, CH_3–$\underline{CH_2}$–N), 2.64 (dd, 1H, N–C$\underline{H}$–H, ^3J 6.1 Hz, ^2J 13.4 Hz), 3.64 (m, 1H, O–CH–$\underline{H}$), 4.08 (dd, 1H, O–C$\underline{H}$–H, ^3J 6.3 Hz, ^2J 7.9 Hz), 4.22 (p, 1H, CH, ^3J 6.3 Hz).

Compounds **4a-c** were obtained by the method similar to the published one.[3]

15 mmol of amine (**3a**, **3b** or **3c**) was dissolved in 20 ml of 1M HCl, the reaction mixture was kept at 20 ºC for 24 h. Then the water was evaporated *in vacuo*. A solution of sodium methoxide (15 mmol) in methanol was added to the residue. The reaction mixture was stirred for 30 minutes. The precipitated NaCl was filtered. The filtrate was evaporated on a rotary evaporator under reduced pressure, product **4a-c** was obtained as yellow oil.

3-(Pyrrolidin-1-yl)propane-1,2-diol (4a).

Yield: 1.74 g (80%). ^{1}H NMR ($CDCl_3$) δ: 1.77 (m, 4H, CH_2–CH_2), 2.43 (dd, 1H, N–CH–H, ^3J 3.9 Hz, ^2J 12.3 Hz), 2.56 (dd, 2H, N–CH_2, ^3J 2.1 Hz, ^2J 7.0 Hz), 2.69 (dd, 2H, N–CH_2, ^3J 2.1 Hz, ^2J 7.0 Hz), 2.77 (dd, 1H, N–CH–H, ^3J 9.0 Hz, ^2J 12.2 Hz), 3.48 (dd, 1H, O–CH–H, ^3J 4.9 Hz, ^3J 11.4 Hz), 3.63 (dd, 1H, O–CH–H, ^3J 4.0 Hz, ^2J 11.4 Hz), 3.78 (m, 1H, CH), 4.20 (s, 2H, OH).

3-(Diethylamino)propane-1,2-diol (4b).

Yield 1.83 g (83%). ^{1}H NMR ($CDCl_3$) δ: 1.13 (t, 6H, $\underline{CH_3}$–CH_2–N, ^3J 7.2 Hz), 2.67 (dd, 1H, N–CH–$\underline{H}$, ^3J 4.0 Hz, ^2J 13.0 Hz), 2.76 (m, 4H, CH_3–$\underline{CH_2}$–N), 2.83 (dd, 1H, N–C$\underline{H}$–H, ^3J 7.1 Hz, ^2J 13.2 Hz), 3.56 (dd, 1H, O–CH–$\underline{H}$, ^3J 4.6 Hz, ^2J 11.4 Hz), 3.70 (dd, 1H, O–C$\underline{H}$–H, ^3J 4.4 Hz, ^2J 11.4 Hz), 3.89 (m, 1H, CH), 4.56 (s, 2H, OH).

Geranylchloride (5). Lit.[4]

Yield 13.09 g (88%). n_D^{20} 1.412 (lit. n_D^{20} 1.4794). ^{1}H NMR ($CDCl_3$) δ: 1.45 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.93 (m, 4H, CH_2–CH_2), 3.95 (d, 2H, CH_2–Cl, ^3J 8.0 Hz), 4.93 (m, 1H, =CH), 5.29 (m, 1H, =CH).

1-(2,3-Bisgeranyloxypropyl)pyrrolidine (6a).

Yield: 3.14 g (75%).^{1}H NMR ($CDCl_3$) δ: 1.59 (br. s, 4H, CH_2–CH_2–CH_2–N), 1.63 (s, 6H, CH_3), 1.71 (s, 12H, CH_3), 2.04 (m, 8H, CH_2–CH_2), 2.14 (m, 4H, CH_2–N), 2.20 (m, 2H, CH_2–N), 3.54 (d, 2H, O–CH–$\underline{CH_2}$–O, ^3J 5.2 Hz), 3.68 (m, 1H, O–$\underline{CH}$–CH_2–O), 4.00 (d, 1H, O–CH–H, ^3J 6.1 Hz), 4.07 (d, 1H, O–CH–H, ^3J 6.8 Hz), 4.18 (br. s, 2H, O–CH_2), 5.11 (m, 2H, =CH), 5.44 (m, 2H, =CH). ^{13}C NMR ($CDCl_3$) δ: 25.71, 26.39, 28.95, 29.72, 31.40, 32.45, 39.63, 44.47, 45.50, 45.87, 59.42, 66.40, 115.70, 121.06, 124.06, 138.99. IR,(ν/cm-1): 3405 (=CH), 2967 (CH_3), 2924 (CH_3), 2855 (CH_2), 1723 (=CH), 1671 (C=C), 1449 (=CH), 1376 (CH_3), 1211 (C–N), 992, 924 (C–O–C), 896 (=CH), 567 (=CH). MS (MALDI): calc. [M+] m/z 417.3, found [M+] m/z 416.5, $[M+Na]^+$ m/z 439.5, $[M+K]^+$ m/z 455.5. Found (%): C, 76.90; H, 10.58; N, 3.17. Calc. for $C_{27}H_{47}NO_2$ (%): C, 77.64; H, 11.54; N, 3.35.

2,3-Bisgeranyloxy-*N*,*N*-diethylpropane-1-amine (6b).

Yield: 2.9 g (69%). ^{1}H NMR ($CDCl_3$) δ: 1.19 (m, 3H, $\underline{CH_3}$–CH_2–N), 1.34 (m, 3H, $\underline{CH_3}$–CH_2–N), 1.53 (s, 6H, CH_3), 1.59 (s, 6H, CH_3), 1.61 (s, 6H, CH_3), 1.93 (m, 2H, CH_2), 1.97 (m, 4H, CH_3–$\underline{CH_2}$–N), 2.03 (m, 10H, CH_2), 2.07 (m, 1H, O–CH–$\underline{H}$), 3.91 (d, 2H, O–CH_2, ^{3}J 6.8 Hz), 3.96 (d, 1H, O–C$\underline{H}$–H, ^{3}J 7.0 Hz), 4.03 (m, 1H, CH), 5.02 (m, 2H, =CH), 5.20 (m, 2H, =CH). ^{13}C NMR ($CDCl_3$) δ: 17.66, 23.79, 25.67, 26.39, 28.95, 39.61, 44.47, 53.45, 66.39, 67.96, 68.31, 73.30, 113.26, 121.08, 123.28, 124.05, 143.01. IR (ν/cm^{-1}): 3329 (=CH), 2968 (CH_3), 2925 (CH_3), 2856 (CH_2), 1721 (=CH), 1669 (C=C), 1447 (=CH), 1376 (CH_3), 1255 (C–N), 1139, 1107, 1070, 923 (C–O–C), 987 (=CH), 829 (=CH). MS (MALDI): calc. [M^{+}] *m/z* 419.4, found [M^{+}] *m/z* 420.5, [M+Na]$^{+}$ *m/z* 443.5, [M+K]$^{+}$ *m/z* 460.5. Found (%): C, 76.92; H, 11.58; N, 3.70. Calc. for $C_{27}H_{49}NO_2$ (%): C, 77.27; H, 11.77; N, 3.34.

1-(2,3-Bisgeranyloxypropyl)piperidine (6c).

Yield: 3.02 g (70%). ^{1}H NMR ($CDCl_3$) δ: 1.60 (m, 6H, CH_2–CH_2–CH_2), 1.66 (s, 6H, CH_3), 1.68 (m, 16H, CH_3, CH_2–N), 1.83 (m, 2H, CH–$\underline{CH_2}$–O), 2.09 (m, 10H, CH_2–CH_2 and N–CH_2), 3.98 (d, 4H, O–CH_2, ^{3}J 6.8 Hz) 5.08 (m, 2H, =CH), 5.26 (m, 1H, CH), 5.44 (m, 2H, =CH). ^{13}C NMR ($CDCl_3$) δ: 16.48, 17.70, 23.03, 25.72, 26.39, 32.46, 39.63, 44.47, 45.50, 66.41, 113. 30, 120.99, 121.54, 124.06, 131.63, 140.03. IR (ν/cm-1): 3365 (=CH), 2967 (CH_3), 2928 (CH_3), 2857 (CH_2), 1720 (=CH), 1670 (C=C), 1446 (=CH), 1376 (CH_3), 1256 (C–N), 1140, 1065, 928 (C–O–C), 902 (=CH), 570 (=CH). MS (MALDI): calc. [M^{+}] m/z 431.4, found [M+H]$^{+}$ m/z 432.5, [M+Na]$^{+}$ m/z 456.5, [M+K]$^{+}$ m/z 469.5. Found (%): C, 77.02; H, 10.98; N, 3.56. Calc. for $C_{28}H_{49}NO_2$ (%): C, 77.90; H, 11.44; N, 3.24.

Turbidimetry.

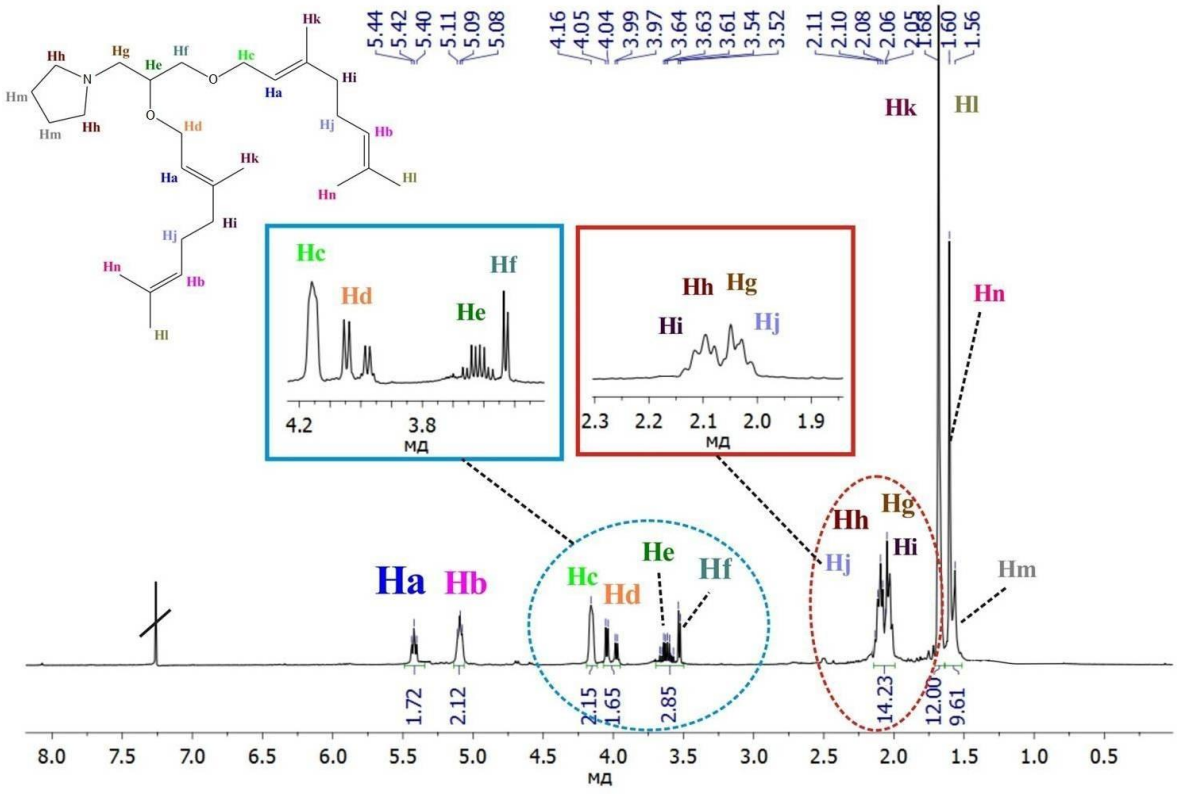
Experiments to determine the temperature of the phase transition were carried out by measuring the turbidity of a dilute lipid suspension (0.7 mM) on Shimadzu UV-3600 spectrophotometer equipped with Peltier temperature control unit, the thickness of the transmission layer was 1 cm, the slit width was 1 nm, and the wavelength was 400 nm. Titration of the lipid by the test compounds was carried out in quartz cells. To reduce the experimental error, the obtained compounds **6a-c** were added to 3 ml of a lipid suspension (0.7 mmol) as their concentrated solutions into a buffer (50 mM Tris-HCl, 150 mM NaCl, pH 7.4). To determine the temperature of the lipid phase transition, we measured the optical density of the samples in the temperature range 38-43°C in steps of 0.1 °C per minute. Experimental data on the dependence of the optical density of the emulsion of the vesicles were mathematically processed in the software package

Origin 8.1 (OriginLab Corporation, Northampton, USA) by the Vant-Hoff 2-state model giving the phase transition temperature (T_m) of the system.

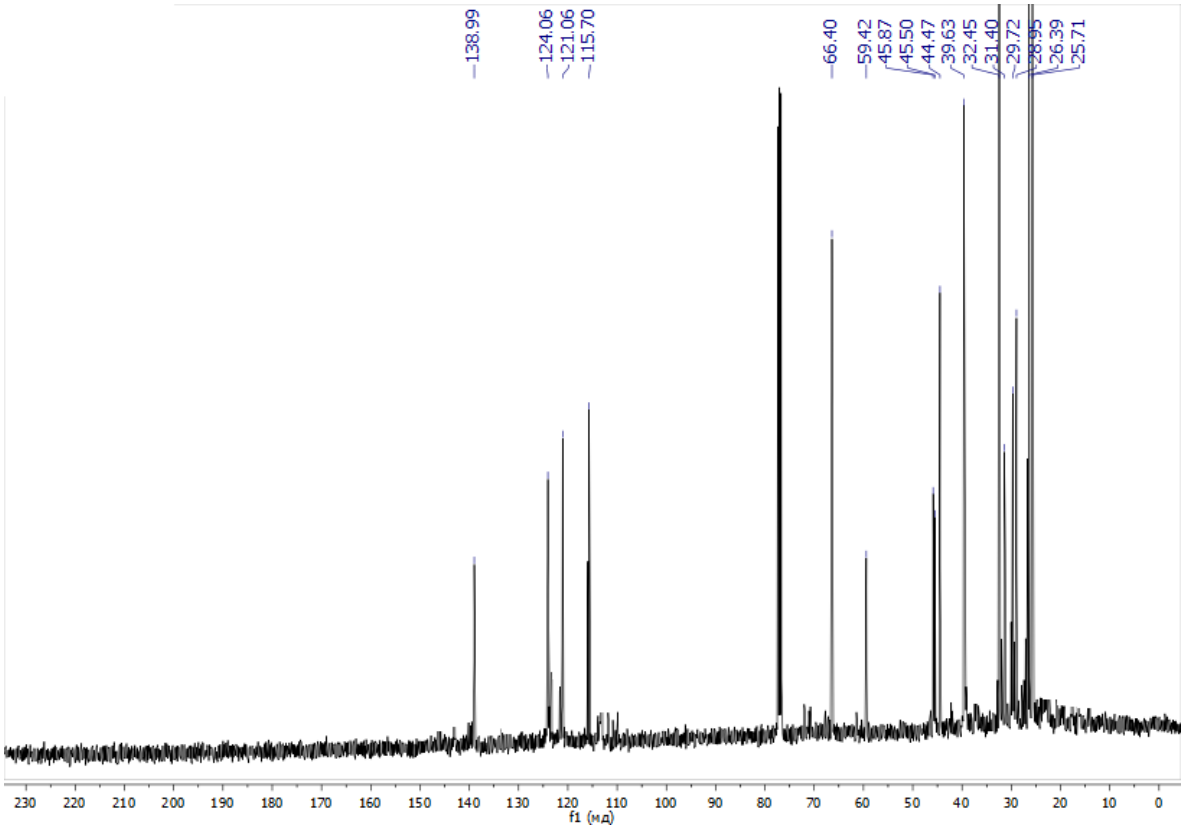
ζ-Potential measurements.

The ζ potential of the DPPC vesicles (0.7 mM) with and without substances **6a-c** in buffer solution was measured by Zetasizer Nano ZS instrument at 50°C. The instrument was equipped with a 4 mW He-Ne laser operating at a wavelength of 633 nm and incorporates noninvasive backscatter optics. The measurements were performed at detection angle of 173°, and the measurement position within the quartz cuvette was automatically determined by the software. The results were processed with the DTS (Dispersion Technology Software 4.20) package.

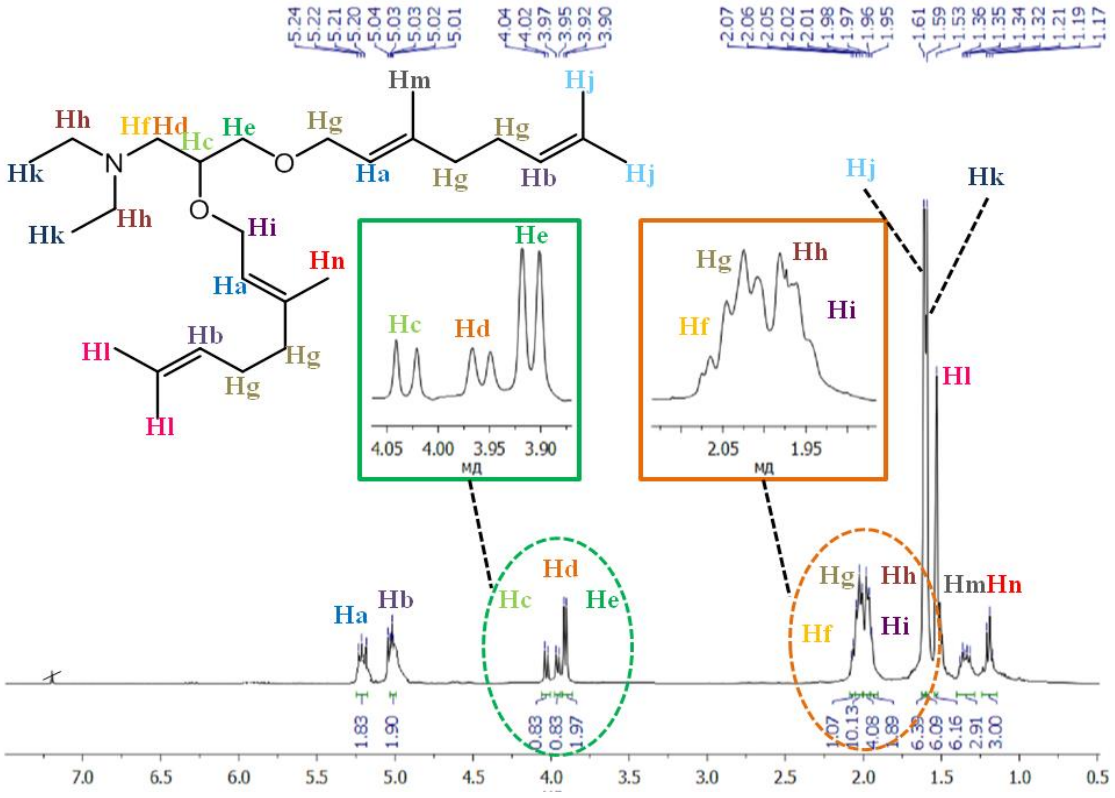
^{1}H NMR spectrum of 1-(2,3-bisgeranyloxypropyl)pyrrolidine (6a), $CDCl_3$, 298 K, 400 MHz



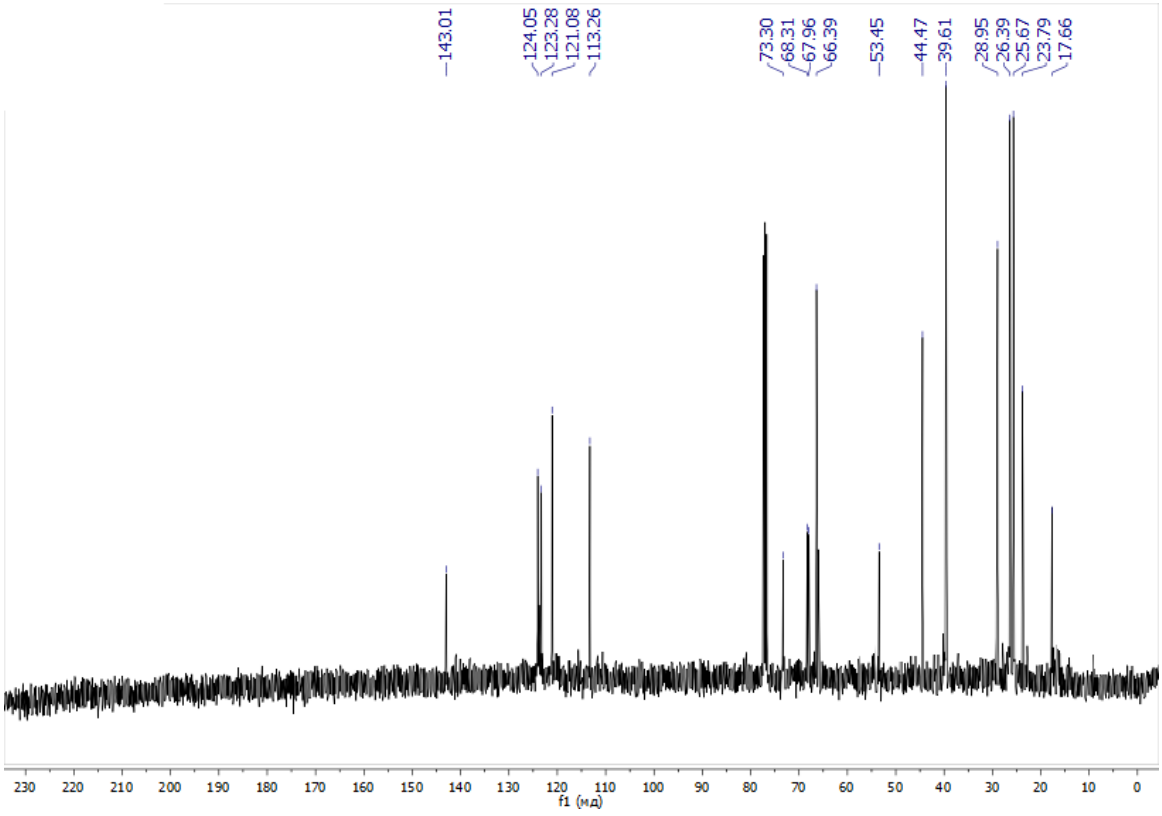
^{13}C NMR spectrum of 1-(2,3-bisgeranyloxypropyl)pyrrolidine (6a), $CDCl_3$, 298 K, 100 MHz



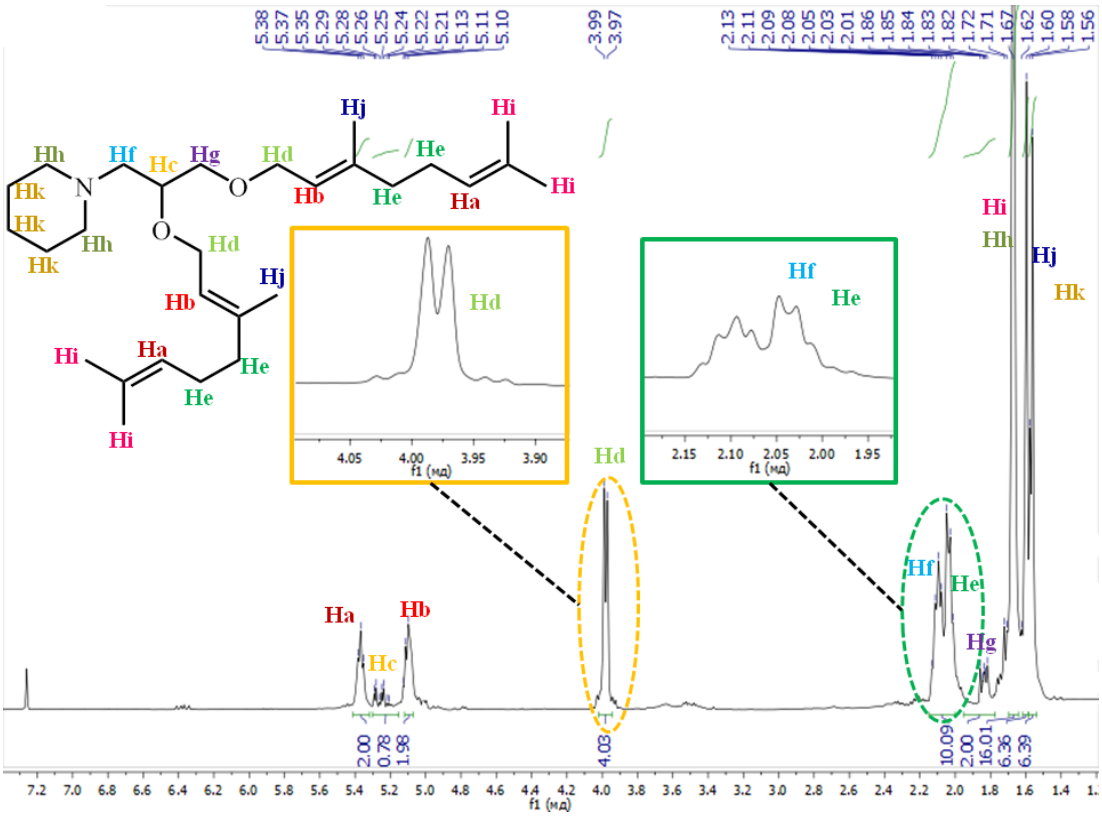
^{1}H NMR spectrum of 2,3-bisgeranyloxy-*N*,*N*-diethylpropane-1-amine (6b), $CDCl_3$, 298 K, 400 MHz



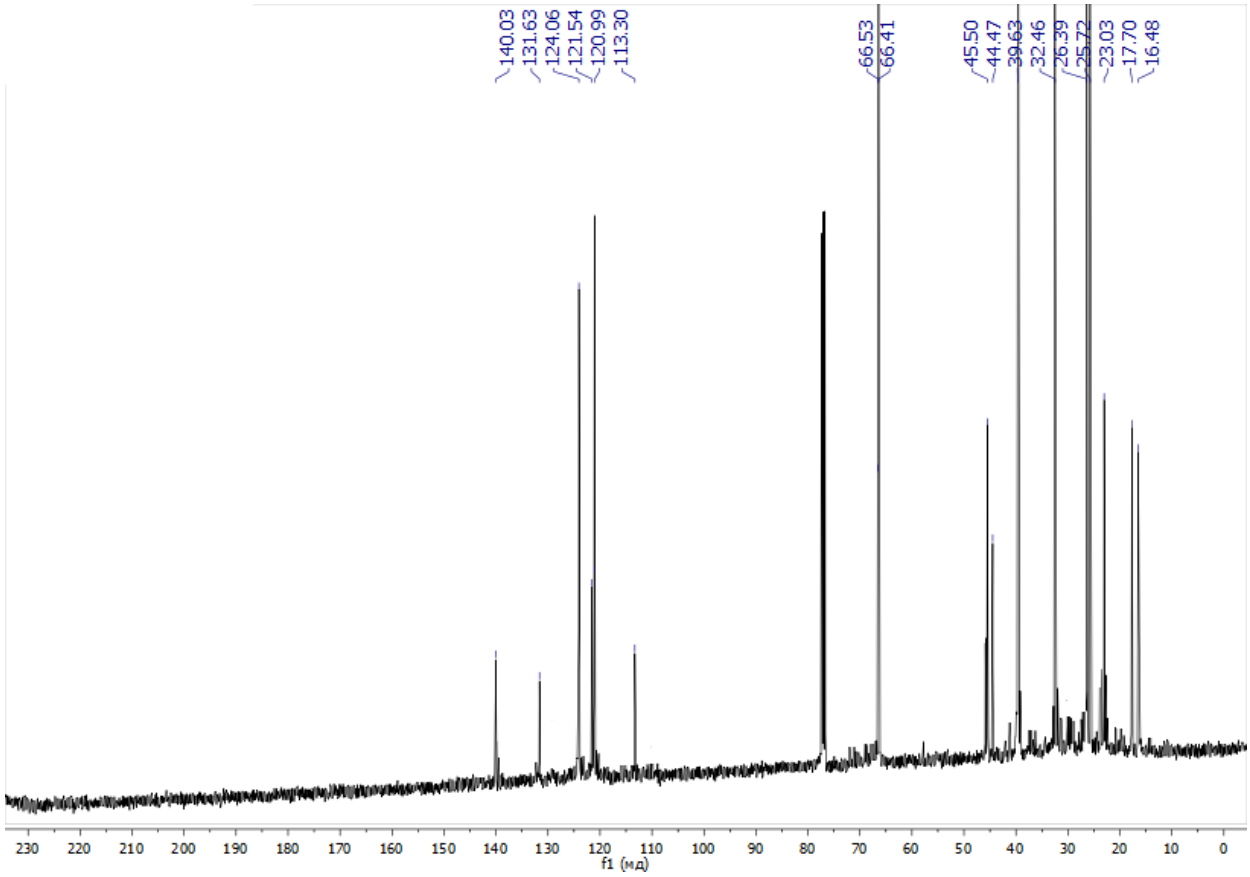
^{13}C NMR spectrum of 2,3-bisgeranyloxy-*N*,*N*-diethylpropane-1-amine (6b), $CDCl_3$, 298 K, 100 MHz



^{1}H NMR spectrum of 1-(2,3-bisgeranyloxypropyl)piperidine (6c), $CDCl_3$, 298 K, 400 MHz



^{13}C NMR spectrum of 1-(2,3-bisgeranyloxypropyl)piperidine (6c), $CDCl_3$, 298 K, 100 MHz



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