

The effect of 3,7-diazabicyclo[3.3.1]nonanes containing monoterpenoid moieties on the physical activity of mice

Anastasiya A. KOTLYAROVA ^{3*} , Konstantin Yu. PONOMAREV ¹ , Ekaterina A. MOROZOVA ¹ , Dina V. KORCHAGINA ² , Evgeniy V. SUSLOV ¹ , Alla V. PAVLOVA ¹ , Tatyana G. TOLSTIKOVA ¹ , Konstantin P. VOLCHO ¹ , Nariman F. SALAKHUTDINOV ¹ 

¹ Department of Medicinal Chemistry, Novosibirsk Institute of Organic Chemistry of Siberian Branch of Russian Academy of Sciences, Lavrentjev av. 9, 630090, Novosibirsk, Russia

² Department of Physical Organic Chemistry, Novosibirsk Institute of Organic Chemistry of Siberian Branch of Russian Academy of Sciences, Lavrentjev av. 9, 630090, Novosibirsk, Russia

³ Department of Experimental Pharmacology, Research Institute of Clinical and Experimental Lymphology - a branch of the Institute of Cytology and Genetics of Siberian Branch of Russian Academy of Sciences, Acad. Timakova str., 2, 630060, Novosibirsk, Russia

* Corresponding Author. E-mail: kotlyarova.anastasiya@yandex.ru (A.K.); Tel. +7-913-489 20 02.

1. Synthesis of test compounds and their ¹H and ¹³C NMR spectra, as well as optical rotation and elemental composition	2
1.1 3,7-Bis-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (K1-458)	3
1.2 3,7-Bis-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-carbonyl)-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (K1-456)	7
REFERENCES	11

1. Synthesis of test compounds and their ^1H and ^{13}C NMR spectra, as well as optical rotation and elemental composition

All reagents used in the work had a purity of at least 95%. Solvents were dried and distilled before use according to standard methods. The synthesis of 1,3-diazaadamantane (2) and 1,5-dimethyl-3,7-diazabicyclo [3.3.1]nonan-9-one (3) was carried out according to the procedure [1]. 2-(Bromomethyl)-6,6-dimethylbicyclo [3.1.1]hept-2-ene (4) (Figure 1) was obtained according to the procedure [2]. The acid chloride 5 was synthesized according to [3].

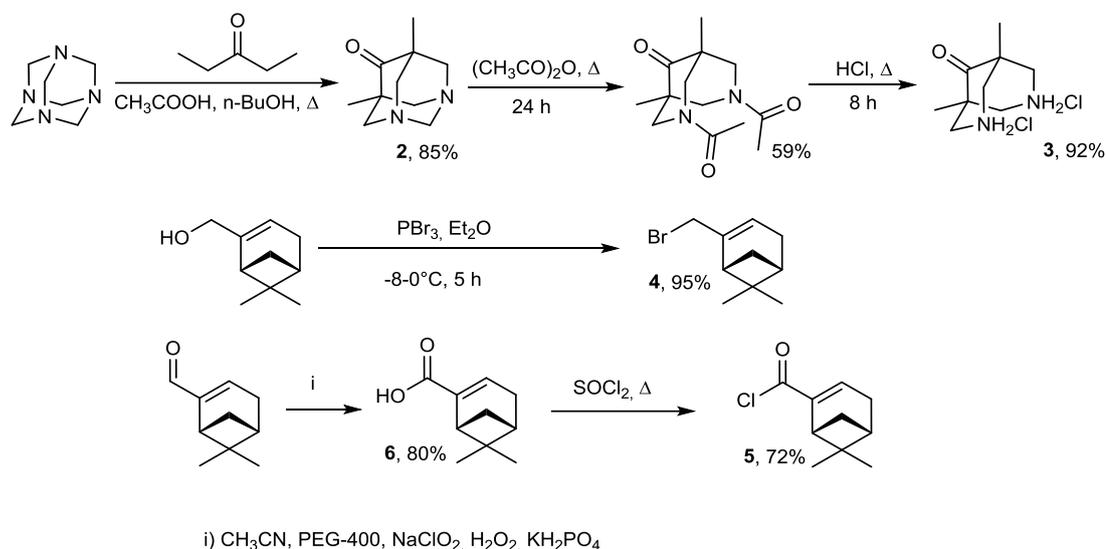


Figure 1. Synthesis of diazaadamantane 2, bispidinone 3 and bromo derivative 4.

Column chromatography: silica gel (SiO_2 ; 60–200 μ ; Macherey–Nagel); hexane/ EtOAc 100/0 \rightarrow 0/100 (increments of 2%).

GC: 7820A gas chromatograph (Agilent Tech., USA); flame ionization detector; HP-5 capillary column (O 0.25 mm \times 30 m \times 0.25 μm); He as a carrier gas (flow rate 2 mL min^{-1} , flow division 99:1).

HRMS: DFS Thermo Scientific spectrometer in a full-scan mode (15–500 m/z , 70 eV electron ionization, direct sample injection).

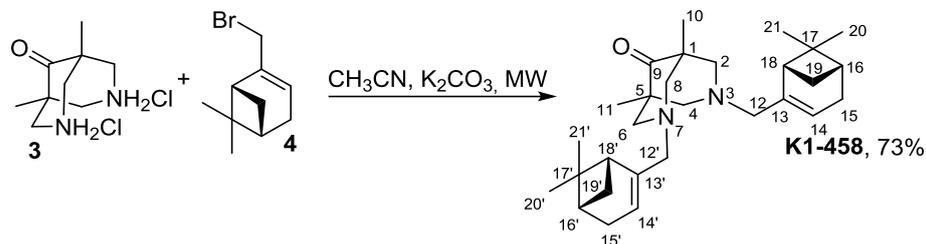
Elemental analysis: Carlo-Erba 1106-Elemental analysis instrument.

^1H - and ^{13}C -NMR spectra: Bruker Avance - III 600 spectrometer [600.30 MHz (^1H) and 150.95 MHz (^{13}C) in CDCl_3]; chemical shifts in ppm rel. to residual chloroform [δ_{H} 7.24 ppm, δ_{C} 76.90 ppm], J in Hz. The structures of the products were determined by analyzing their ^1H NMR spectra, J -modulated ^{13}C NMR spectra (JMOC) and ^{13}C - ^1H -type 2D heteronuclear correlation with one bond (HSQC, 1J 145 Hz) and long-range spin-spin coupling constants (HMBC, $^{2,3}J$ 7 Hz) and ^1H - ^1H double-resonance spectra (COSY, NOESY). 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 the compounds.

Optical rotation ($[\alpha]_{\text{D}}$): polAAR 3005 spectrometer; MeOH soln. concentration g/100 mL; specific rotation is expressed as $\text{deg mL g}^{-1} \text{dm}^{-1}$.

Microwave reactor: Monowave 300 from Anton Paar.

1.1 3,7-Bis-(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (K1-458)



A mixture of the hydrochloric acid salt of diamine **3** (0.82 g (3.4 mmol)), 2.5-times excess of bromo-derivative **4** and 6-time excess of potassium carbonate in 6 ml of acetonitrile was heated in a microwave reactor to 70 ° C and held for 60 minutes. After cooling the reaction mixture, the precipitate was separated, washed with ethyl acetate. The organic phases are combined, the solvent is distilled. The yield of the product after chromatography was 1.10 g (73%). $[\alpha]_D^{25.6} = 5.484$ ($C = 0.62$, MeOH).

^1H NMR (600 MHz, CDCl_3 , δ_{H} , J, Hz): 0.81 s (6H, C21H₃, C21'H₃); 0.94 s (6H, C10H₃, C11H₃); 1.08 d (2H, $^2J = 8.6$, H19_{anti}, H19'_{anti}); 1.27 s (6H, C20H₃, C20'H₃); 2.04-2.09 m (2H, H16, H16'); 2.19 dm (2H, $^2J = 17.7$, H15, H15'); 2.22-2.28 m (4H, H'15, H'15', H18, H18'); 2.36 ddd (2H, $^2J = 8.6$, $J_{19\text{sin},16} = J_{19\text{sin},18} = 5.6$, $J_{19'\text{sin},16'} = J_{19'\text{sin},18'} = 5.6$, H19_{sin}, H19'_{sin}); 2.75 d (2H, $^2J = 13.0$, H12, H12'); 2.81 brd (2H, $^2J = 13.0$, H'12, H'12'); 2.24-2.28 m (2H); 2.29 d (2H, $^2J = 10.7$); 2.86 d (2H, $^2J = 10.7$); 2.93 d (2H, $^2J = 10.7$) - 4N-CH₂; 5.31-5.34 m (2H, H14, H14').

^{13}C NMR (151 MHz, CDCl_3 , δ_{C}): 46.56 s (C1, C5); 65.62 t, 65.70 t (C2, C4, C6, C8); 215.88 s (C9), 20.28 q (C10, C11); 62.60 t (C12, C12'); 145.96 s (C13, C13'); 119.54 d (C14, C14'); 31.23 t (C15, C15'); 40.91 d (C16, C16'); 37.84 s (C17, C17'); 44.06 d (C18, C18'); 31.68 t (C19, C19'); 26.24 q (C20, C20'); 21.14 q (C21, C21').

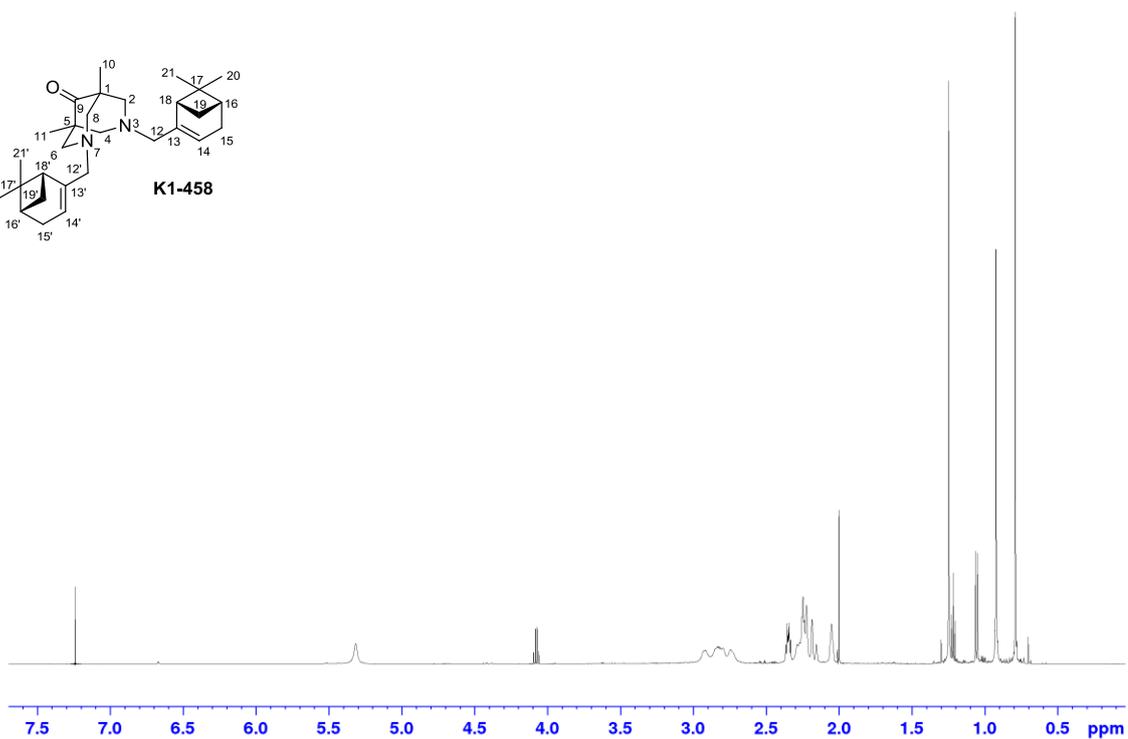
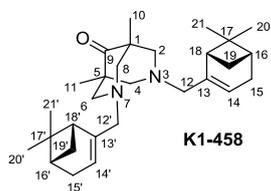
Calcd./Found (m/z): 436.3454/436.3452 (M^+) ($\text{C}_{29}\text{H}_{44}\text{N}_2\text{O}^+$)

Anal. calcd for $\text{C}_{29}\text{H}_{44}\text{N}_2\text{O}$ (%): C 79.76; H 10.16; N 6.42. Found (%): C 78.69; H 10.79; N 6.01.

Spectral data K1-458

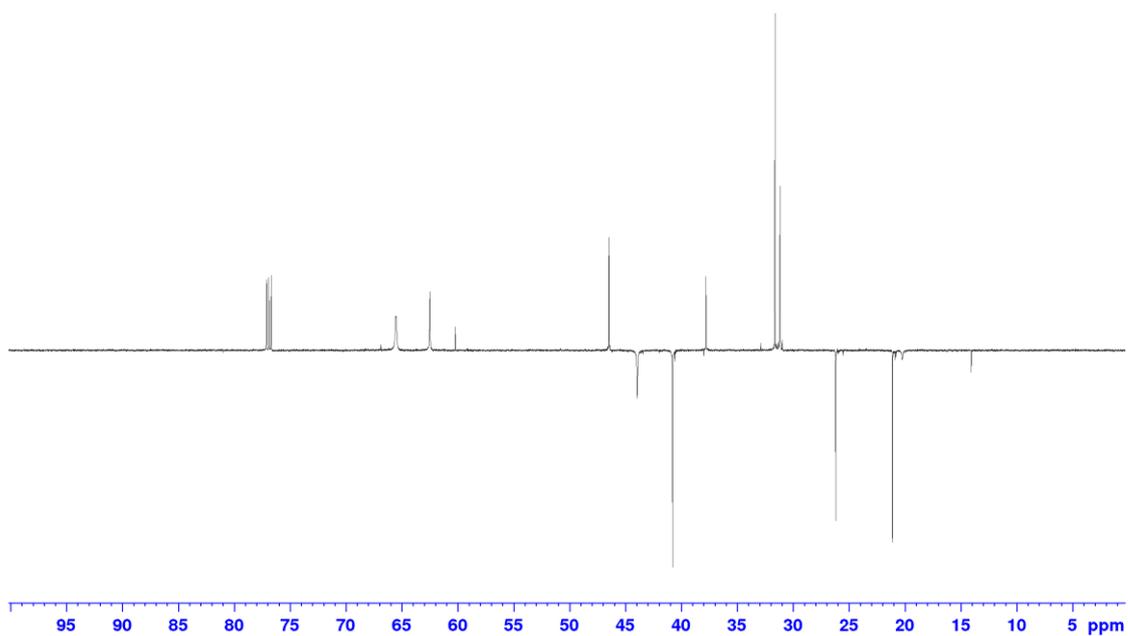
^1H NMR

in CDCl_3 , 60mg



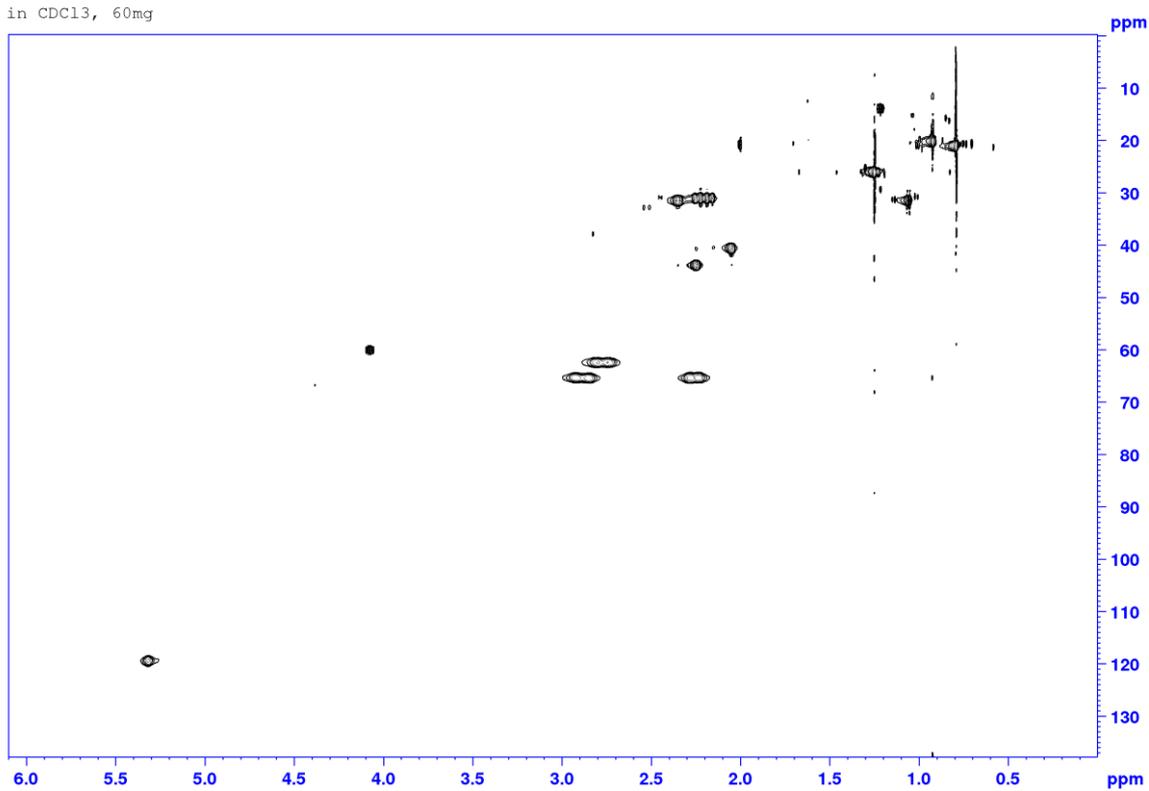
J-modulated ^{13}C NMR

in CDCl_3 , 60mg



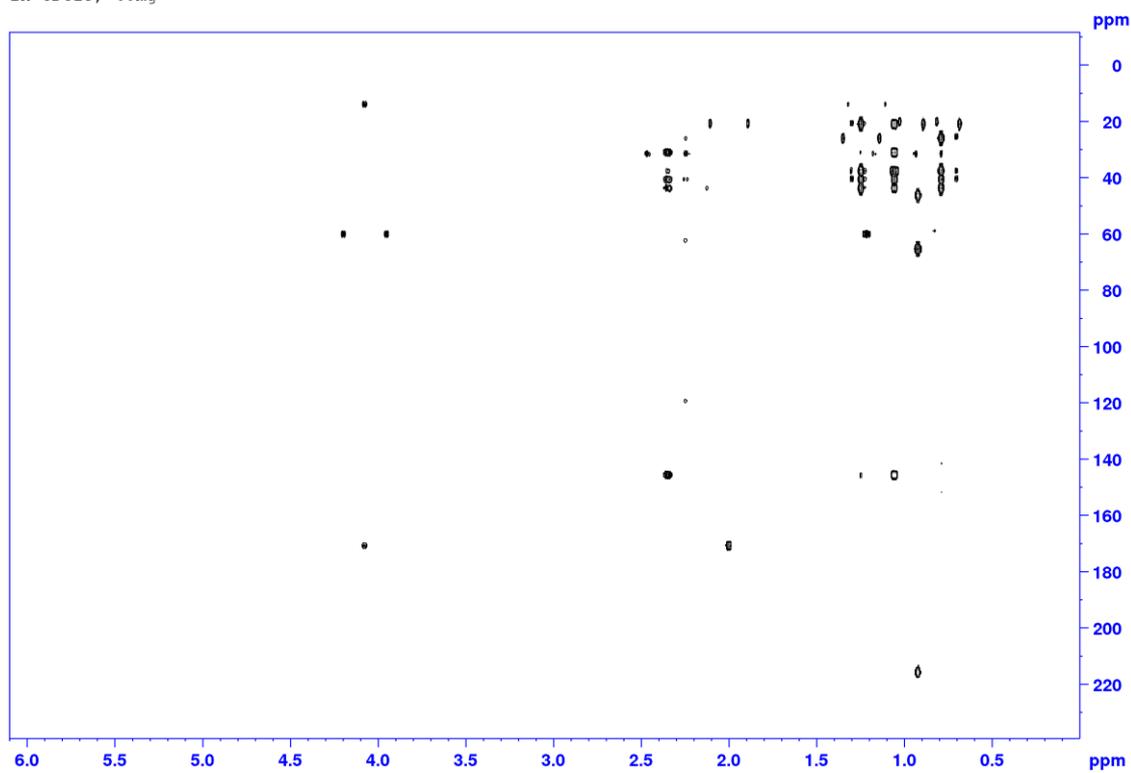
^{13}C - ^1H (HSQC, 1J 145 Hz)

in CDCl_3 , 60mg



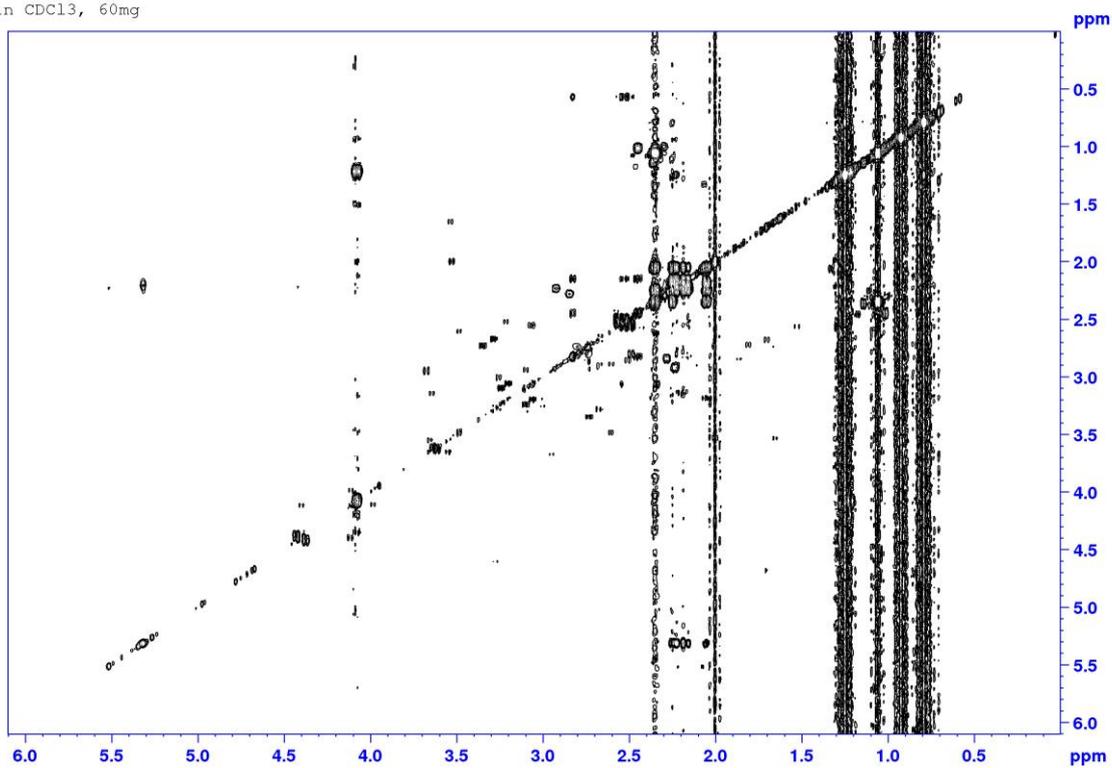
^{13}C - ^1H (HMBC, $^{2,3}J$ 7 Hz)

in CDCl_3 , 60mg



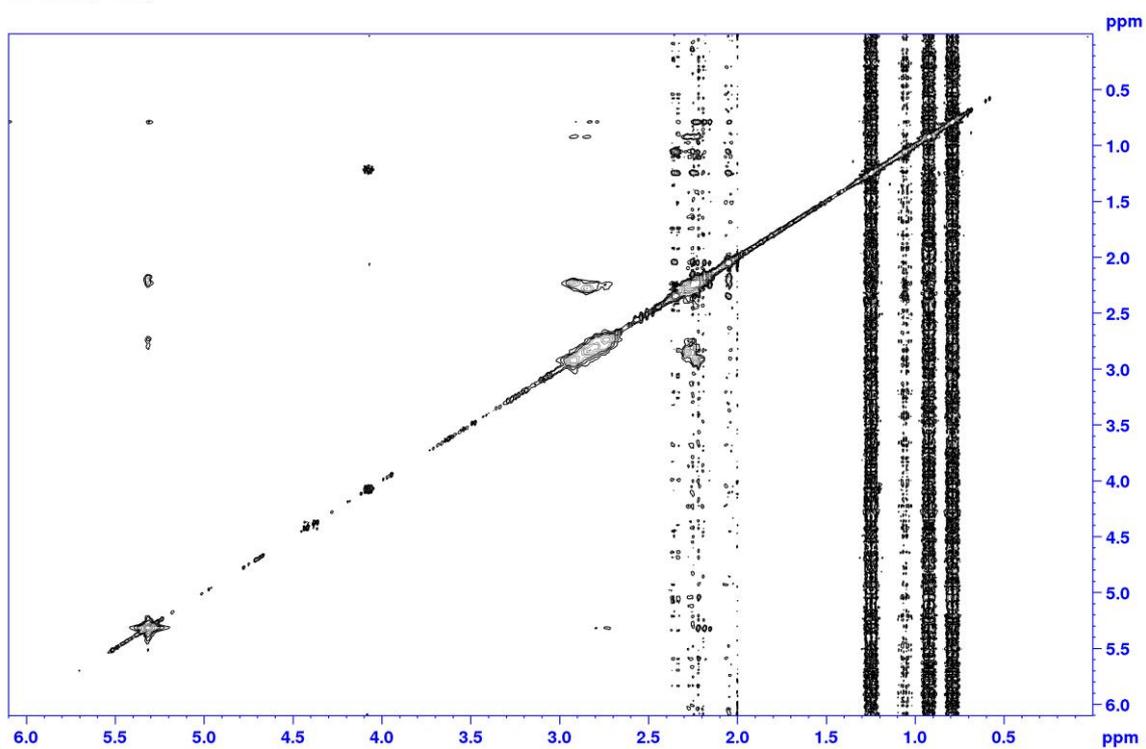
^1H - ^1H (COSY)

in CDCl_3 , 60mg

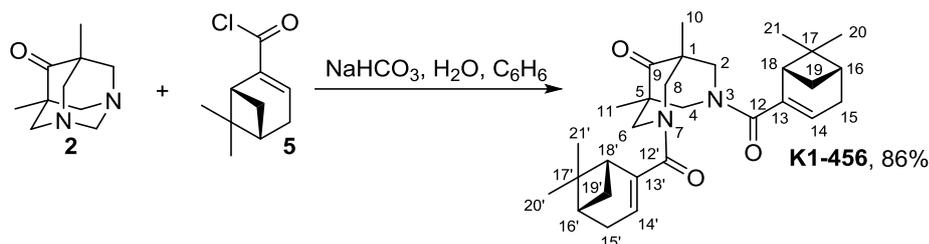


^1H - ^1H (NOESY)

in CDCl_3 , 60mg



1.2 3,7-Bis-((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-ene-2-carbonyl)-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (K1-456)



To a mixture of 0.36 g (1.98 mmol) of diazadamantane 2 and 0.42 g (4.95 mmol) of NaHCO_3 in 14 ml of benzene and 4 ml of water was added 0.91 g (4.95 mmol) of acid chloride (5) over 10 minutes. The mixture was stirred for 6 hours at room temperature. The aqueous phase was separated, washed with benzene; the organic phases are combined, the solvent is distilled off. After chromatography, 0.79 g of product was obtained (86%). $[\alpha]_D^{25.0} = -26.829$ ($C = 0.41$, MeOH).

$^1\text{H NMR}$ (600 MHz, CDCl_3 , δ_{H} , Hz): 0.91 s (6H, C21H₃, C21'H₃); 1.00 s (6H, C10H₃, C11H₃); 1.23 brd (2H, $^2J \sim 8.0$, H19_{anti}, H19'_{anti}); 1.30 s (6H, C20H₃, C20'H₃); 2.07-2.12 m (2H, H16, H16'); 2.34 dm (2H, $^2J = 18.8$, H15, H15'); 2.40 dm (2H, $^2J = 18.8$, H15, H15'); 2.44-2.51 m (2H, H19_{sin}, H19'_{sin}); 2.31-2.38 brm (2H, H18, H18'); 2.72-2.93 brm (2H); 3.05-3.27 brm (2H); 4.08-4.38 brm (2H); 4.65-4.88 brm (2H) - 4N-CH₂; 5.87-5.93 brm (2H, H14, H14').

$^{13}\text{C NMR}$ (151 MHz, CDCl_3 , δ_{C}): 46.09 s (C1, C5); 53.79 brt, 58.36 brt (C2, C4, C6, C8); 212.80 s (C9), 16.83 q (C10, C11); 169.82 brs (C12, C12'); 142.49 brs (C13, C13'); 127.37 brd (C14, C14'); 31.64 t, 31.65 t (C15, C15', C19, C19'); 40.26 d (C16, C16'); 37.77 brs (C17, C17'); 44.14 d (C18, C18'); 25.86 q (C20, C20'); 21.07 q (C21, C21').

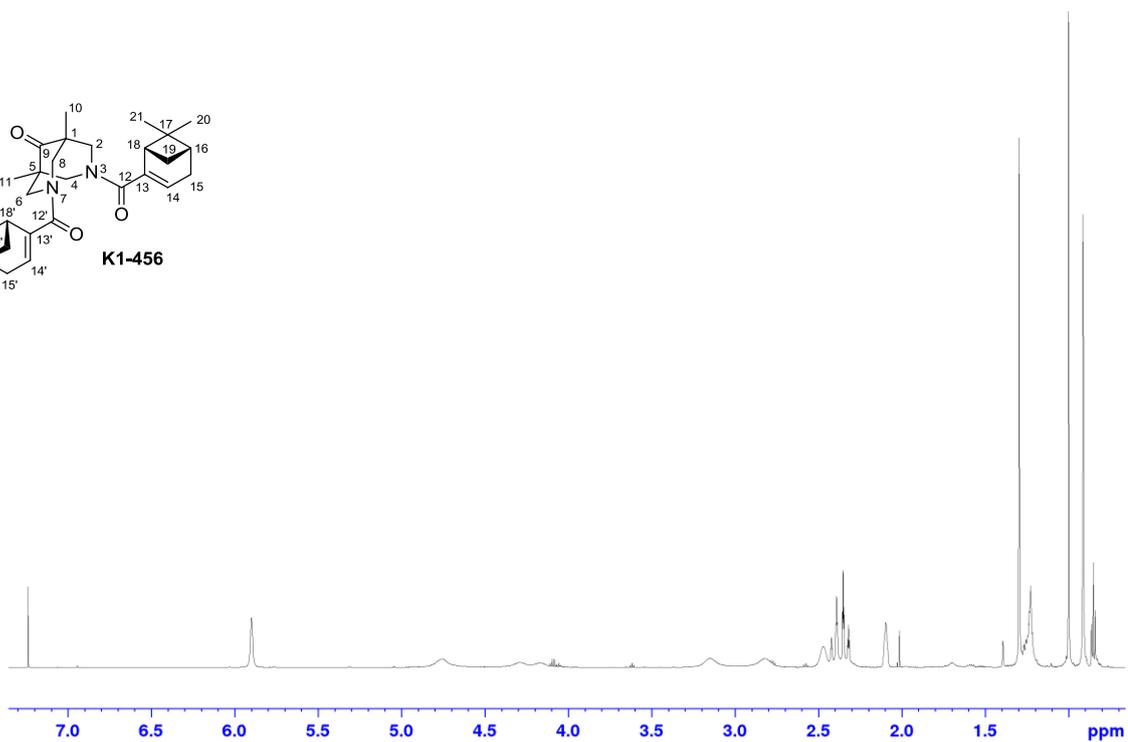
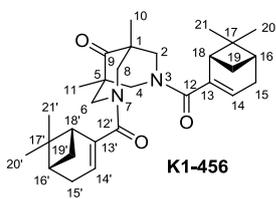
Calcd./Found (m/z): 464.3039 / 464.3040 (M^+) ($\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_3^+$)

Anal. calcd for $\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_3$ (%): C 74.96; H 8.68; N 6.03. Found (%): C 74.98; H 9.85; N 5.73.

Spectral data K1-456

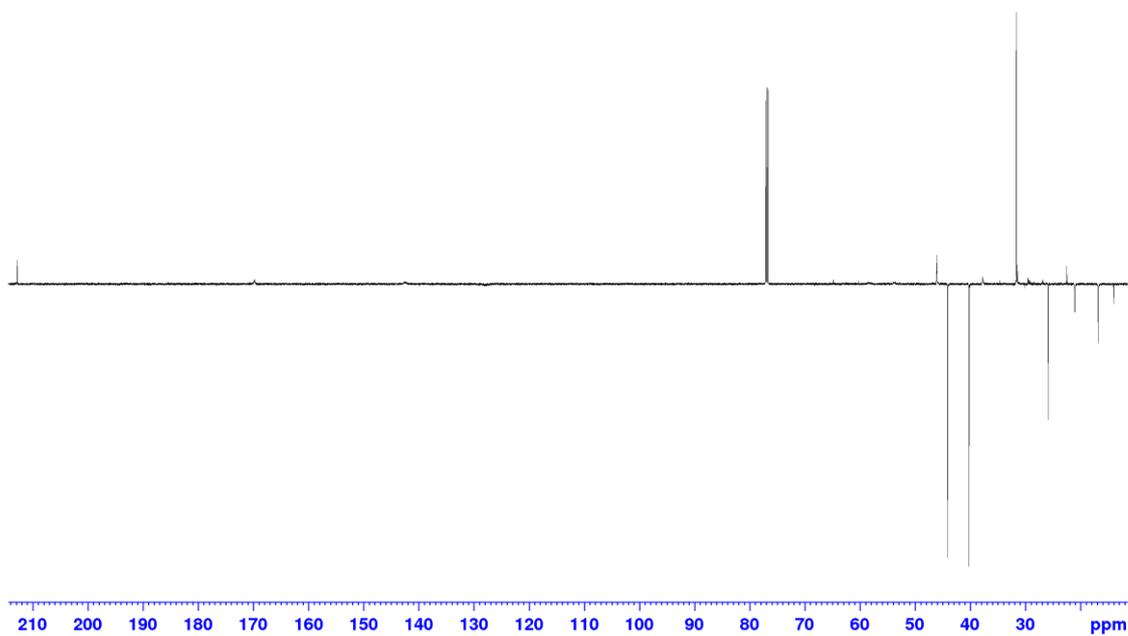
^1H NMR

in CDCl_3 , ~20mg



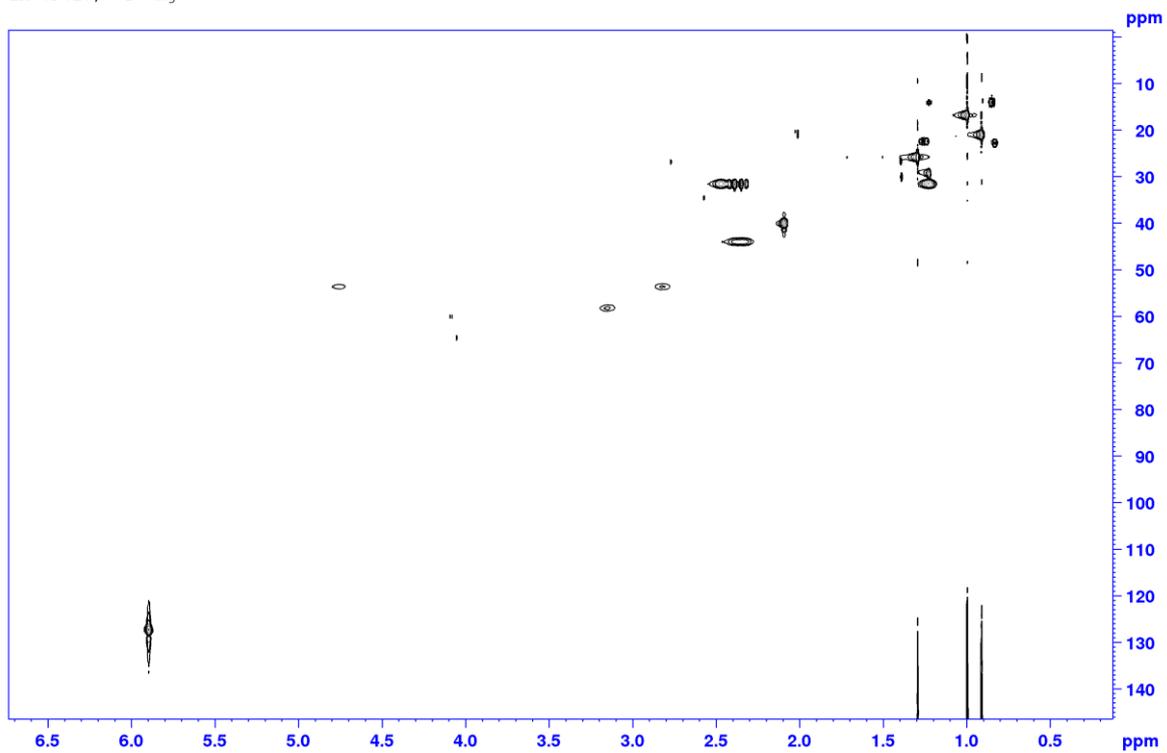
J-modulated ^{13}C NMR

in CDCl_3 , 20mg



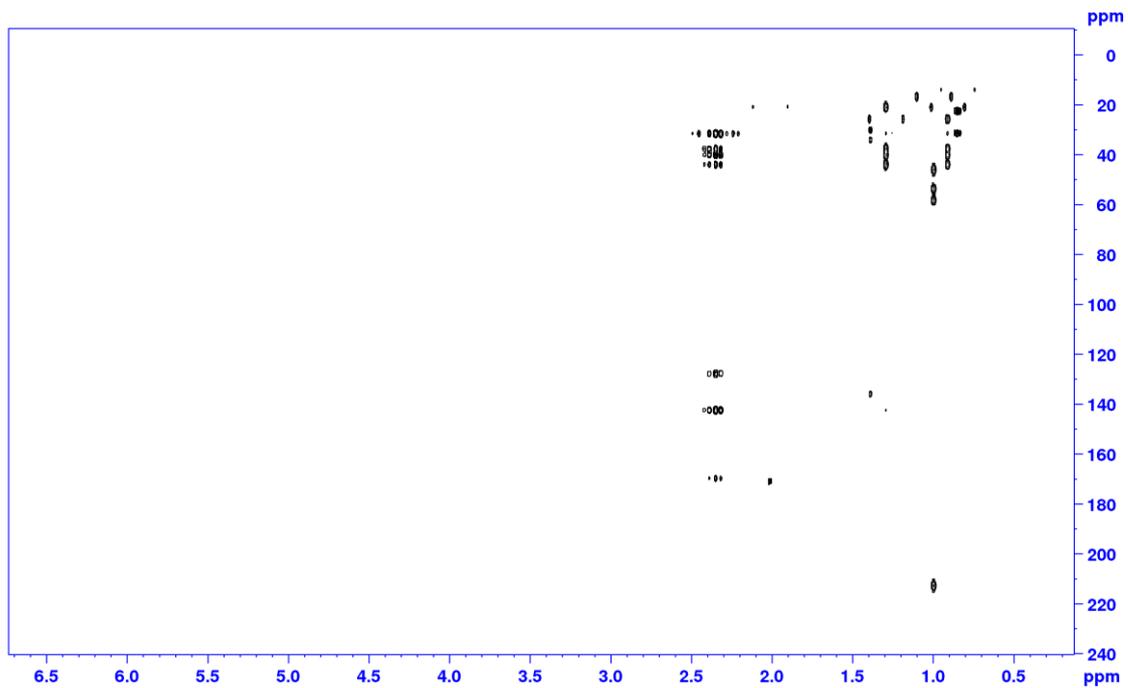
^{13}C - ^1H (HSQC, 1J 145 Hz)

in CDCl_3 , 20 mg



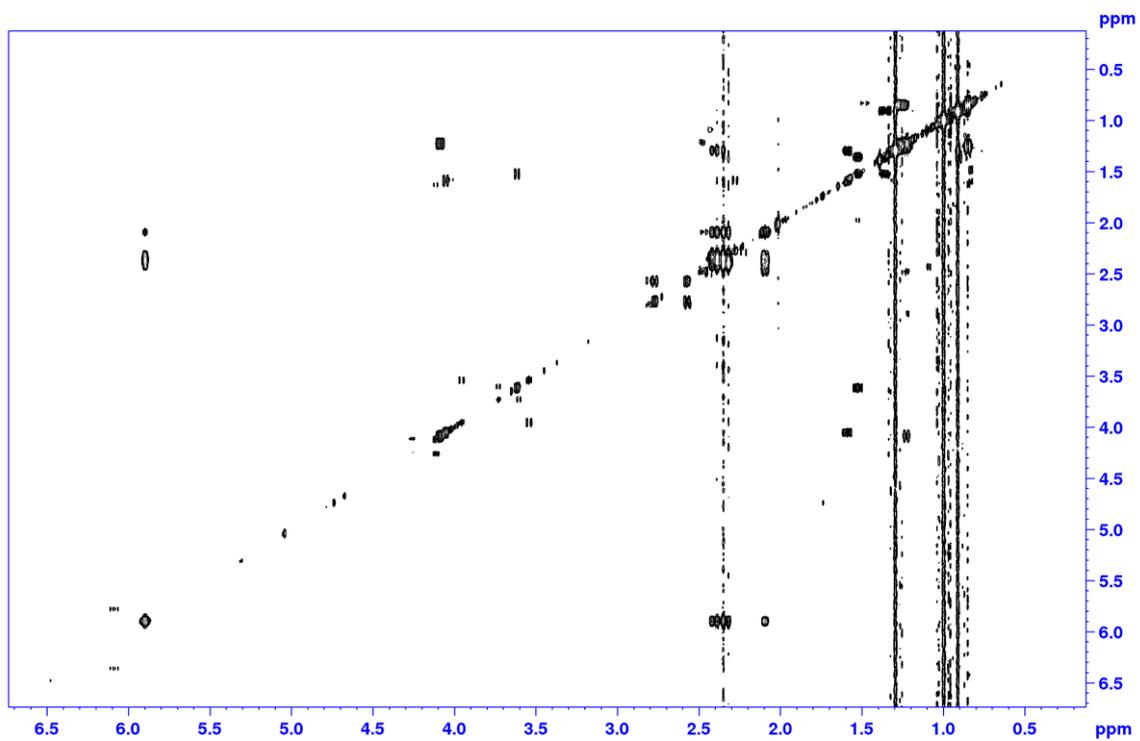
^{13}C - ^1H (HMBC, $^{2,3}J$ 7 Hz)

in CDCl_3 , 20 mg



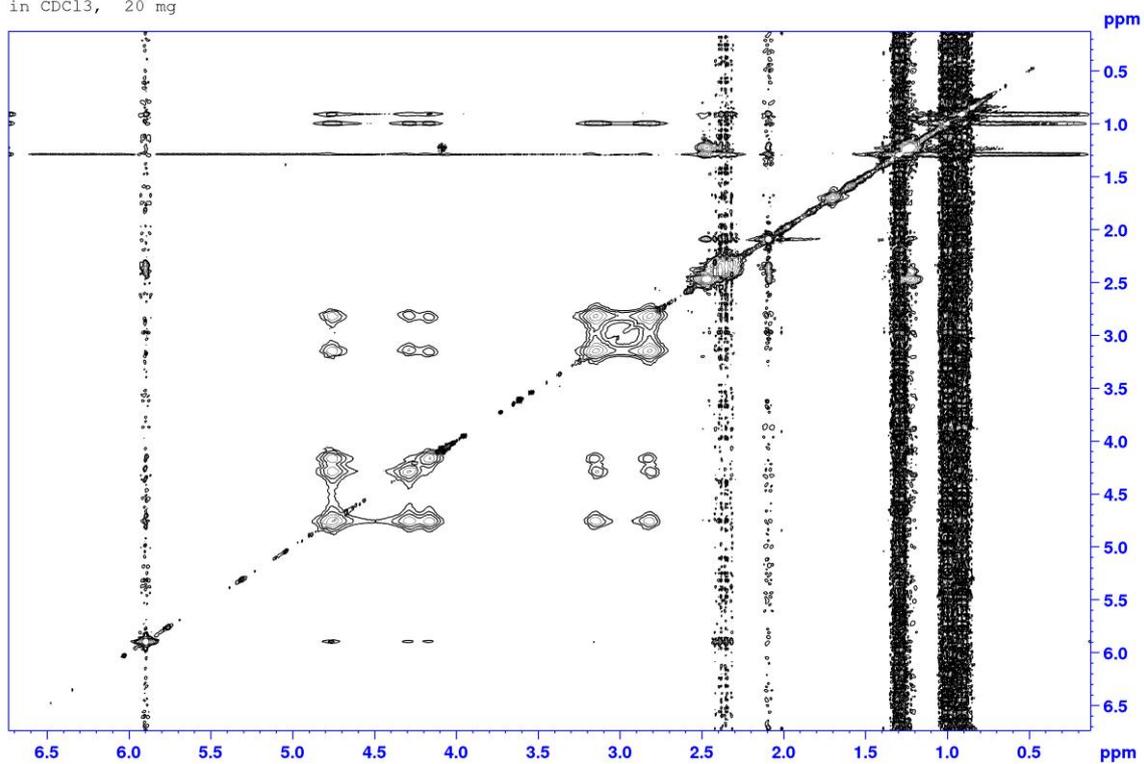
^1H - ^1H (COSY)

in CDCl_3 , 20 mg



^1H - ^1H (NOESY)

in CDCl_3 , 20 mg



REFERENCES

- [1] Ponomarev K, Pavlova A, Suslov E, et al. Synthesis and analgesic activity of new compounds combining azaadamantane and monoterpene moieties. *Med Chem Res* 2015; 24: 4146–4156. [\[CrossRef\]](#)
- [2] Khomenko TM, Zarubaev VV, Orshanskaya IR, et al. Anti-influenza activity of monoterpene-containing substituted coumarins. *Bioorg Med Chem Lett* 2017; 27: 2920–2925. [\[CrossRef\]](#)
- [3] Lin G, Duan W, Liu H, et al. Synthesis and Bioactivity of N-(4-(N'-Substituted Sulfamoyl)Phenyl)Myrtenamides Containing a Heterocycle. *Chem Nat Compd* 2018; 54: 56–62. [\[CrossRef\]](#)