SYNTHESIS, STRUCTURE, AND BIOLOGICAL ACTIVITY OF NOVEL BISPIDINE DERIVATIVES

AIGUL YE. MALMAKOVA1*, VALENTINA K. YU1, KALDYBAY D. PRALIYEVA1, ALTYNAI B. KALDYBAYEVA1, MARZHAN K. AMIRKULOVA2

1Department of of Physiologically Active Substances, A.B. Bekturov Institute of Chemical Sciences/Laboratory of Synthetic and Natural Medicinal Compounds Chemistry, Almaty, Kazakhstan. 2Department of Chemistry, Kazakh National Women’s Teacher Training University/Faculty of Natural Science, Almaty, Kazakhstan. 3Department of Pharmacology, Asfendiyarov Kazakh National Medical University/School of General Medicine, Almaty, Kazakhstan. Email: malmakova@mail.ru

Received: 13 October 2020, Revised and Accepted: 28 November 2020

ABSTRACT

Objective: Derivatives of 3,7-diazabicyclo[3.3.1]nonan-9-one attract considerable attention from pharmacists for the treatment of a wide range of diseases. According to this interest, the novel derivatives of 3-cyclopropanemethyl-7-alkoxyalkyl-3,7-diazabicyclo[3.3.1]nonan-9-one with isopropoxypropyl and ethoxypropyl substituents in the position 7 had been synthesized to study their biological activity and toxicity. The practical significance of the work is in the accumulation and development of scientific representations about diazabicyclic compounds, methods for their synthesis, structure, and properties, which can subsequently be used in a targeted design and identification of even more complex systems, as well as in the development of further research in the field of 3,7-diazabicyclo[3.3.1]nonanes. For this purpose, complexes of the synthesized compounds with β-cyclodextrin are obtained and their biological activity is investigated at the Department of Pharmacology of S.D. Asfendiyarov Kazakh National Medical University with the aid of the pharmacological tests.

Methods: An experimental study of local anesthetic activity on the models of infiltration, conduction anesthesia, and acute toxicity of synthesized molecules was carried out using primary screening methods.

Results: As a result of pharmacological screening, it has been found that the compounds exhibit local anesthetic activity and low toxicity and was recommended for in-depth study of their pharmacological properties.

Conclusion: It turned out that a nature of the N-alkoxyalkyl radical does not affect the toxicity of cyclopropanemethyl-substituted bispindines. In the series of 0-benzoyloximes of bispindines, the isopropoxypropyl-substituted analog is 1.3 times less toxic than ethoxypropyl-one.

Keywords: Bispidine, Synthesis, Structure, Activity, Anesthetics, Acute toxicity.

INTRODUCTION

An analysis of current trends in the medical use of drugs indicates the ongoing gradual replacement of obsolete drugs with more effective and safe drugs of novel generations. Therefore, research on the search for novel potentially biologically active substances is relevant.

The aim of research is the synthesis of novel potentially pharmacologically active derivatives of 3-cyclopropanemethyl-7-alkoxyalkyl-3,7-diazabicyclo[3.3.1]nonan-9-one, as well as the establishment of the structure and evaluation of their biological activity.

The interest of chemists in the study of heteroanalogs of bicyclo[3.3.1]nonane is due to the unique properties of these compounds, which makes them valuable from a theoretical and practical point of view [1-10]. It is also known that methylenecyclopropane residue is a valuable structural unit of bioactive compounds, particularly, opiate antagonists [11,12].

1-(3-Isoproxypropyl)- and 3-ethoxypropyl)-4-oxopiperidine (1, 2) as starting substrates was used to obtain the target bispindines (3-14) according to Fig. 1.

The reaction products were obtained with high yields as viscous oils. Monitoring of the progress of the reaction was carried out by TLC on alumina. The structure of bispidine derivatives (3-10) was determined by nuclear magnetic resonance (NMR) and infrared (IR) spectroscopies.

To study the biological properties of the novel derivatives of 3,7-diazabicyclo[3.3.1]nonan-9-ones, their complexes with β-cyclodextrin had been synthesized [11-14].

METHODS

Experimental chemical part

NMR spectra of the studied compounds were recorded on a JEOL JNM-ECA400 spectrometer with an operating frequency on carbon nuclei of 100.53 MHz in CDCl3, with hexamethyldisiloxane as internal standard. Elemental analysis data were consistent with calculated values. IR spectra were recorded on a Nicolet 5700 instrument between KBr plates. Column chromatography and thin-layer chromatography were carried out on alumina (Al2O3) of the third degree of activity, R, of the compounds is provided for this type of plate. The spots were developed in iodine vapors.

3-Cyclopropanemethyl-7-(3-isoproxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (3)

In a three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel, 60 ml of methanol was deoxygenated under a stream of nitrogen. After 30 min, a mixture of 4.6 g (0.059 mol) of cyclopropanemethylamine, 7.2 g (0.46 mol) of paraform, 3.1 ml of concentrated hydrochloric acid, and 4.5 ml of glacial acetic acid was added and stirred for 15 min in the atmosphere of nitrogen. A solution of 11.7 g (0.059 mol) of 1-(3-isoproxypropyl)piperidin-4-one (1) and 4.5 ml of glacial acetic acid in 15 ml of methanol was added...
dropwise. After 10 h of heating the reaction mixture at 60–65°C, a second equivalent of paraform was added and held for another 12 h at the same temperature. The solvent was evaporated, the residue was dissolved in 30 ml of water. The extraction of neutral products was carried out with diethyl ether. The aqueous layer was alkalized to pH 12 and the organic part was extracted with chloroform, dried over MgSO₄. The solvent was evaporated, the resulting product was purified on a column of aluminum oxide, benzene:dioxane = 5:1. 9.3 g (73.6%) of 3-cyclopropanemethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (3) was obtained in the form of a light yellow oil with Rf = 0.23 (Al₂O₃, benzene:isopropanol = 6:1).

Found, %: C 69.38, H 10.20, N 9.52.  
Calculated, %: C 69.38, H 10.20, N 9.52.

IR spectrum, cm⁻¹: 1736 (νC=O), 1118 (νC–N).

13C-NMR spectrum, δ ppm (CDCl₃): 46.6 (C₁₅), 58.4 (C₁₂), 58.8 (C₁₃), 214.4 (C₁₄), 57.9 (C₁₀), 31.7 (C₁₁), 64.8 (C₉), 67.7 (C₈), 28.2 (C₆), 63.1 (C₈), 7.7 (C₂), 4.0 (C₃).

3-Cyclopropanemethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (3)

In a three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel, 80 ml of methanol was deoxygenated under a stream of nitrogen. After 30 min, a mixture of 5.2 g (0.070 mol) of 1-(3-ethoxypropyl)piperidin-4-one (2) and 6.2 ml of glacial acetic acid was added, extracted with diethyl ether, and dried over anhydrous MgSO₄. After 10 h of heating the reaction mixture at 60–65°C, a second equivalent of paraform was added and held for another 12 h at the same temperature. Throughout the reaction, the reaction mixture was purged with a stream of nitrogen. The solvent was evaporated, the residue was dissolved in 113 ml of water. The extraction of neutral products was carried out with diethyl ether. The aqueous layer was alkalized to pH 12 and the organic part was extracted with chloroform, dried over MgSO₄. The solvent was evaporated, the resulting product was purified on a column of aluminum oxide, benzene:dioxane = 5:1. 16.1 g (79%) of 3-cyclopropanemethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (4) was obtained in the form of a light yellow oil with Rf = 0.50 (Al₂O₃, benzene:isopropanol = 6:1).

Found, %: C 68.38, H 10.12, N 9.92. C₂₁₂₄H₂₃N₂O₂.  
Calculated, %: C 68.57, H 10.00, N 10.00.

IR spectrum, cm⁻¹: 1736 (νC=O), 1118 (νC–N).

13C-NMR spectrum, δ ppm (CDCl₃): 46.6 (C₁₅), 58.4 (C₁₂), 58.8 (C₁₃), 214.4 (C₁₄), 57.9 (C₁₀), 31.7 (C₁₁), 64.8 (C₉), 67.7 (C₈), 28.2 (C₆), 63.1 (C₈), 7.7 (C₂), 4.0 (C₃).

3-Cyclopropanemethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan (5)

A mixture of 2.0 g (0.0068 mol) of 3-cyclopropanemethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (3) and 1.09 g (0.034 mol) of hydrazine hydrate (99% solution) in 20 ml of triethylene glycol at 60°C was added. 4.7 g (0.084 mol) of KOH. The reaction mixture was heated to 150°C and stirred at this temperature for 4 h. At a temperature of 190–200°C, water and excess hydrazine were removed by evaporation. After cooling, 33 ml of distilled water was added, extracted with diethyl ether, and dried over anhydrous MgSO₄. The solvent was evaporated, the obtained product was purified by column chromatography on Al₂O₃, benzene:isopropanol = 5:1. 2.1 g (42%) of 3-cyclopropanemethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan (5) is obtained as a pale yellow oil with Rf = 0.23 (Al₂O₃, benzene:isopropanol = 7:1).

Found, %: C 72.89, H 11.41, N 10.05. C₁₅₂₀H₁₇₂N₂O₂.  
Calculated, %: C 72.85, H 11.43, N 10.00.

IR spectrum, cm⁻¹: 1112 (νC=O).

13C-NMR spectrum, δ ppm (CDCl₃): 29.8 (C₁₁), 58.4 (C₁₂), 58.8 (C₁₃), 31.4 (C₁₄), 57.7 (C₁₀), 66.5 (C₉), 73.3 (C₈), 22.3 (C₆), 67.0 (C₈), 8.6 (C₂), 4.1 (C₃).

3-Cyclopropanemethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan (6)

A mixture of 5.0 g (0.018 mol) of 3-cyclopropanemethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (4) and 2.88 g (0.090 mol) hydrazine hydrate (99% solution) in 20 ml of triethylene glycol at 60°C was added. 4.7 g (0.084 mol) of KOH. The reaction mixture was heated to 150°C and stirred at this temperature for 4 h. At a temperature of 190–200°C, water and excess hydrazine were removed by evaporation. After cooling, 33 ml of distilled water was added, extracted with diethyl ether, and dried over anhydrous MgSO₄. The solvent was evaporated, the obtained product was purified by column chromatography on Al₂O₃, benzene:isopropanol = 5:1. 2.1 g (42%) of 3-cyclopropanemethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan (5) is obtained as a pale yellow oil with Rf = 0.23 (Al₂O₃, benzene:isopropanol = 7:1).

Found, %: C 72.89, H 11.41, N 10.05. C₁₅₂₀H₁₇₂N₂O₂.  
Calculated, %: C 72.85, H 11.43, N 10.00.

IR spectrum, cm⁻¹: 1112 (νC=O).

13C-NMR spectrum, δ ppm (CDCl₃): 29.8 (C₁₁), 58.4 (C₁₂), 58.8 (C₁₃), 31.4 (C₁₄), 57.7 (C₁₀), 66.5 (C₉), 73.3 (C₈), 22.3 (C₆), 67.0 (C₈), 8.6 (C₂), 4.1 (C₃).

Fig. 1: Synthetic routes to the target bispidines
hydrate (99% solution) in 52.5 ml of triethylenglycol at 60°C and 12.5 g (0.22 mol) of KOH. The reaction mixture was heated to 150°C and stirred at this temperature for 4 h. At a temperature of 190–200°C, water and excess hydrazine were removed by evaporation. After cooling, 64 ml of distilled water was added, extracted with diethyl ether, and dried over anhydrous MgSO₄. The solvent was evaporated, the obtained product was purified by column chromatography on Al₂O₃ benzene: dichloromethane 5:1. 2.1 g (42% of theory) of 3-cyclopropenylmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonane (6) was obtained in the form of a light yellow oil with Rf=0.34 (Al₂O₃ benzene: isopropyl alcohol = 7:1). Found, %: C 72.32, H 11.12, N 10.65. Calculated, %: C 72.18, H 11.27, N 10.52.

IR spectrum, cm⁻¹: 1111 (ν₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋عكس


Oxime of 3-cyclopropenylmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonane-9-one (7)

3.0 g (0.0102 mol) of 3-cyclopropenylmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonane-9-one (9), Rf=0.77 (Al₂O₃ benzene: isopropyl alcohol = 7:1). Found, %: C 69.64, H 8.24, N 10.20. Calculated, %: C 69.73, H 8.48, N 10.17.

IR spectrum, cm⁻¹: 1745 (ν₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋个百分


Oxime of 3-cyclopropenylmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonane-9-one (7)

6.0 g (0.0155 mol) of 3-cyclopropenylmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonane-9-one (9) was mixed with 40 ml of absolute benzene and a mixture of 12 ml of absolute benzene and 1.9 ml (0.0135 mol of benzoyl chloride was added dropwise. Reaction took place at room temperature. At the end, 15 ml of distilled water was added to the reaction mixture and neutralized with potash to pH 10–11. The product was extracted with chloroform, the combined extracts were dried over anhydrous MgSO₄. The solvent was evaporated and residual was distilled in vacuo. 4.2 g (46% of theory) 0-benzoyloxime of 3-cyclopropenylmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonane-9-one (10) was obtained in the form of a yellow oil (10). Rf=0.3 (Al₂O₃ benzene: isopropyl alcohol = 7:1).

Found, %: C 69.12, H 8.34, N 10.65. Calculated, %: C 69.17, H 8.27, N 10.52.

IR spectrum, cm⁻¹: 1675.4 (ν₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋عكس


Complex of 3-cyclopropenylmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonane-9-one with β-cyclodextrin (11)

Hot solutions of 0.9 g (0.0033 mol) of 3-cyclopropenylmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonane-9-one (5) in 25 ml of ethyl alcohol and 3.7 g (0.0033 mol) of β-cyclodextrin in 35 ml of distilled water were mixed together. The mixture was placed in a drying cupboard, ethanol and water were evaporated at 50–55°C to produce 4.5 g of compound (11).

Found, %: C 50.14, H 7.15, N 1.93. Calculated, %: C 50.07, H 7.21, N 1.98.

Complex of 3-cyclopropenylmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonane-9-one with β-cyclodextrin (12)

Hot solutions of 1.7 g (0.0064 mol) of 3-cyclopropenylmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonane-9-one (6) in 25 ml of ethyl alcohol and 7.2 g (0.0064 mol) of β-cyclodextrin in 45 ml of distilled water were mixed together. The mixture was placed in a drying cupboard, ethanol and water were evaporated at 50–55°C to produce 8.7 g of compound (12).

Found, %: C 59.61, H 7.26, N 1.93. Calculated, %: C 59.71, H 7.14, N 2.00.

Complex of 0-benzoyloxime of 3-cyclopropenylmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonane-9-one with β-cyclodextrin (13)

Hot solutions of 1.9 g (0.004 mol) of 0-benzoyloxime of 3-cyclopropenylmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonane-9-one (9) in 25 ml of ethyl alcohol and 4.8 g (0.004 mol) of β-cyclodextrin in 30 ml of distilled water were mixed together. The mixture was placed in a drying cupboard, ethanol and water were evaporated at 50–55°C to produce 5.4 g of compound (13).
Complex of O-benzoyloxime of 3-cyclopropa n methyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1] nonan-9-one with β-cyclodextrin (14)

Hot solutions of 1.4 g (0.00366 mol) of O-benzoyloxime of 3-cyclopropamethyl-7-[3-ethoxypropyl]-3,7-diazabicyclo[3.3.1] nonan-9-one (10) in 20 ml of ethyl alcohol and 4.15 g (0.00366 mol) of β-cyclodextrin in 30 ml of distilled water were mixed together. The mixture was placed in a drying cupboard; ethanol and water were evaporated at 50–55°C to produce 4.2 g of compound (14).

Found, %: C 51.16, H 6.69, N 2.66. \( C_{16}H_{18}N_{2}O_{5} \).
Calculated, %: C 51.20, H 6.79, N 2.71.

Experimental biological part

An experimental study of local anesthetic activity on the models of infiltration, conduction anesthesia, and acute toxicity of the synthesized molecules was carried out using primary screening methods in six animals in each series at the Department of Pharmacology of S.D. Asfendiyarov Kazakh National Medical University in accordance with the “Rules for the use of experimental animals” (European Convention No. 123, 1986, Helsinki Declaration 2000) and the State Standard of the Republic of Kazakhstan “Good Laboratory Practice” (the main provisions of ST RK 1613-2006) and the “Rules of Good Laboratory Practice of the Customs Union” (Attachment to the Decision of the Commission of the Customs Union, No. 564, dated March 2, 2011). Besides, the team has a positive opinion from the LEC (local expert commission) of S.D. Asfendiyarov Kazakh National Medical University (Minutes No. 7 (58) dated September 12, 2017) on the compliance of work with experimental animals.

The anesthetic activity of the synthesized compounds was compared with those of widely used anesthetics – trimecaine, lidocaine, and novocaine.

The evaluation of infiltration anesthesia was studied on guinea pigs according to the Bulbring-Wade method. The following values were determined: The depth of anesthesia (anesthesia index), the duration of deep anesthesia, and the total duration of the anesthetic effect.

The conduction anesthesia was examined through the modified tail flick method on rats. It allows to measure the duration of deep anesthesia and the total duration of the anesthetic effect of the compound.

The study of acute toxicity was carried out on mice of the same species, sex, age, and weighing 18–22 g. Acute toxicity (LD\(_{50}\)) was determined by a single subcutaneous injection of aqueous solutions of the compounds.

The local anesthetic effect and acute toxicity of novel derivatives of 3,7-diazabicyclo[3.3.1]nonan-9-one in the form of complexes with β-cyclodextrin were studied under laboratory codes LA 1-4:

**LA-2**

Complex of 3-cyclopropan methyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonane with β-cyclodextrin

**LA-3**

Complex of O-benzoyloxime of 3-cyclopropan methyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one with β-cyclodextrin

**LA-4**

Complex of O-benzoyloxime of 3-cyclopropan methyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one with β-cyclodextrin

**RESULTS AND DISCUSSION**

The infiltration anesthesia

It turned out that on the model of infiltration anesthesia in a bispidine family, the most active is LA-2, the anesthesia index of which is 35.60±0.19 (Table 1). In addition, it caused a longer complete anesthesia of 34.00±1.26 min, while the total duration of action was 43.00±1.84 min. Replacing the ethoxypropyl radical in the LA-2 compound with an isopropoxypropyl one led to a three-fold decrease in activity.

Among the two of O-benzoyl oximes of 3,7-diazabicyclo[3.3.1]nonan-9-ones, LA-3 with cyclopropamethyl and isopropoxypropyl radicals at nitrogen atoms was active, its anesthesia index was 35.60±1.18, and the duration of deep anesthesia was equal to 34.00±0.98 min. The total duration of action was 43.10±1.17 min. Replacing the isopropoxypropyl radical with a ethoxypropyl one led to a decrease in activity (LA-4) (anesthesia index was 29.16±1.45; the duration of deep anesthesia was 36.00±2.90 min; and the total analgesic effect lasted (29.16±2.06 min).

However, it should be noted that it was weaker than comparison preparations (не знаю, говорят ли так, я предлагаю взамен) for the reference compounds.

Conduction anesthesia

It should be noted that bispidines and O-benzoyl oximes on the model of conduction anesthesia did not show any significant effect. However, LA-1 can be distinguished, which in terms of total duration of action is comparable to novocaine and inferior to trimecaine and lidocaine.

In the group of O-benzoyl oximes, according to the duration of total anesthesia, LA-4 exceeded trimecaine and novocaine (Table 2).

Acute toxicity

The acute toxicity of bispidine derivatives is presented in Table 3.
In this research, derivatives of 3,7-diazabicyclo[3.3.1]nonane-9-one are low toxic compounds. The most harmless is LA-3 [complex of O-benzoyloxy-3-cyclopropylmethyl-7-[3-isoproxypropyl]-3,7-diazabicyclo[3.3.1]nonan-9-one with β-CD], where the LD₅₀ is 825 mg/kg.

It turned out that a nature of the N-alkoxyalkyl radical does not affect the toxicity of cyclopropamethyl-substituted bispidines (LA-1 and LA-2). In the series of O-benzoyloxyamines of bispidines, the isoproxypropyl-substituted analog is 1.3 times less toxic than ethoxypropyl-one.

**CONCLUSION**

In this research, derivatives of 3,7-diazabicyclo[3.3.1]nonan-9-one were synthesized and the biological properties were studied for their complexes with β-cycodextrin.

**REFERENCES**

1. Haridas V, Rajgokul KS, Sadanandan S, Agrawai T, Sharvani V. Bispidine-amino acid conjugates act as a novel scaffold for the design of novel cyclophosphamide derivatives.

**ACKNOWLEDGMENT**

This research is funded by the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan (Grant No. AP08856051).

**AUTHORS’ CONTRIBUTIONS**

All the authors have contributed equally.

**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.
of antivirals that block Japanese encephalitis virus replication. PLOS Negl Trop Dis 2013;7:e2005.

2. Kuhl U, Cambareri A, Sauber C, Störgel F, Hartmann R, Euler H, et al. Synthesis, X-ray analysis and spectroscopic characterization of the hemiaminal cyclization product from 2,4-dipyridine substituted 3,7-diazabicyclo[3.3.1]nonane 1,5-diesters. J Chem Soc 1999:2:2083-8.

3. Smith GS, Thompson MD, Berlin KD, Holt EM, Scherlag BJ, Patterson E, et al. A study of the synthesis and antiarrhythmic properties of selected 3,7-diheterabicyclo[3.3.1]nonan-9-ols with substituents at the 2,4-positions and at the 9-position. Eur J Med Chem 1990;25:1-8.

4. Klepikova SG, Solomin VA, Iskakova TK, Yu VK. Spatial structure of isomers of 3,7-bis(alkoxyalkyl)-3,7-diazabicyclo[3.3.1]nonan-9-ols. Chem Heterocycl Compd 2003;39:504-10.

5. Tran K, Berlin KD, Eastman MA, Holt EM. Synthesis, stereochemical, and conformational studies of selected 3,7-diheterabicyclo[3.3.1]nonan-9-ols: X-ray diffraction analyses of 7-benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol and 7-benzyl-9-(4-N,N’-dimethylaminophenyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol, a rare stable chair-boat form with trigonal nitrogen. Phosphorus Sulfur Silicon Relat Elem 2007;182:99-119.

6. Klepikova SG, Yu VK, Fomicheva EE, Mukhasheva RD, Praliyev KD, Berlin KD. 1H NMR spectroscopy in the study of the three-dimensional structure of 7-alkoxyalkyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ones and some of their derivatives. Chem Heterocycl Compd 2008;44:1398-403.

7. Berlin KD, Iskakova TK, Faskhudinov MF, Praliyev KD, Lee CP. Unusual conformational behavior of 3,7-dihetera(N,N,N,O,N,S-)bicyclo[3.3.1]nonan-9-ols in CDCl₃. Phosphorus Sulfur Silicon Relat Elem 2014;189:864-72.

8. Pichkhadze GM, Smagulova GS, Kadyrova DM, Praliyev KD, Yu VK. Local anesthetic activity of a promising piperidine derivative (LAS-54) in combination with epinephrine. Pharm Chem J 2016;50:600-2.

9. Malmakova AE, Praliyev KD, Welch JT, Iskakova TK, Ibraeva SS. Synthesis of novel 3,7-diazabicyclo[3.3.1]nonane derivatives. Eur Chem Technol J 2014;16:85-9.

10. Praliyev KD, Iskakova TK, Baktybaeva LK, Malmakova AE. Synthesis and myelostimulatory activity of a number of 3,7-diazabicyclo[3.3.1]nonane derivatives. Pharm Chem J 2015;49:292-5.

11. Zheng Y, Oheng S, Wang H, Jali AM, Peddibhotla B, Williams DA, et al. Design, synthesis, and biological evaluation of the third generation 17-cyclopropanmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(4′-pyridyl)carboxamido]morphinan (NAP) derivatives as μ/κ opioid receptor dual selective ligands. J Med Chem 2019;62:561-74.

12. Yuan Y, Elbegdorj O, Chen J, Akubathini SK, Beletskaia IO, Selley DE, et al. Structure selectivity relationship studies of 17-cyclopropanmethyl-3,14β-dihydroxy-4,5α-epoxy-6β-[(4′-pyridyl)carboxamido]morphinan derivatives toward the development of the mu opioid receptor antagonists. Bioorg Med Chem Lett 2011;21:5625-9.