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SYNTHESIS, STRUCTURE, AND BIOLOGICAL ACTIVITY OF NOVEL BISPIDINE DERIVATIVES

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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-cyclopropanmethyl-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 cyclopropanmethyl- substituted bispidines. In the series of O-benzoyloximes of bispidinones, the isopropoxypropyl- substituted analog is 1.3 times less toxic than ethoxypropyl- one.

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

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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-cyclopropanmethyl-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-Isopropoxypropyl- and 3-ethoxypropyl-)-4-oxopiperidine (1, 2) as starting substrates was used to obtain the target bispidines (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 bispidinone 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 $CDCl_3$ 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 (Al_2O_3) of the third degree of activity, R_f of the compounds is provided for this type of plate. The spots were developed in iodine vapors.

3-Cyclopropanmethyl-7-(3-isopropoxypropyl)-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-isopropoxypropyl)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 alkalinized to pH 12 and the organic part was extracted with chloroform, dried over $MgSO_4$. 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-cyclopropanmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1] nonan-9-one (3) was obtained in the form of a light yellow oil with R_f=0.23 (Al_2O_3, benzene:isopropanol = 6:1).

Found, %: C 69.41, H 10.24, N 9.55. $C_{17}H_{30}N_2O_2$.

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

IR spectrum, cm^{-1}: 1734 ($\nu_{C=O}$), 1122 (ν_{C-O-C}).

^{13}C-NMR spectrum, δ, ppm ($CDCl_3$): 46.6 ($C_{1,5}$), 58.4 ($C_{6,8}$), 58.8 ($C_{2,4}$), 214.4 (C_9), 57.9 (C_{10}), 31.7 (C_{11}), 64.8 (C_{12}), 67.7 (C_{13}), 28.2 (C_{14}). 63.1 (C_{16}), 7.7 (C_{17}), 4.0 (C_{18}).

3-Cyclopropanmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (4)

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 cyclopropanemethylamine, 8.7 g (0.140 mol) of paraform, 3.8 ml of concentrated hydrochloric acid, and 5.6 ml of glacial acetic acid was added and stirred for 15 min under nitrogen atmosphere. A solution of 13.4 g (0.070 mol) of 1-(3-ethoxypropyl)piperidin-4-one (2) and 6.2 ml of glacial acetic acid in 11 ml of methanol was added dropwise. After heating the reaction mixture for 10 h at 60–65°C, the second equivalent of paraform is added and the mixture was held for another 12 h at the same temperature. Throughout the reaction, the reaction mixture is 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 alkalinized to pH 12 and the organic part was extracted with chloroform, dried over $MgSO_4$. 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-cyclopropanmethyl-7-(3-ethoxypropyl)-3,7-diazabicyc-lo[3.3.1]nonan-9-one (4) was obtained in the form of a light yellow oil with R_f=0.50 (Al_2O_3, benzene:isopropanol = 6:1).

Found, %: C 68.38, H 10.12, N 9.92. $C_{16}H_{28}N_2O_2$.

Calculated, %: C 68.57, H 10.00, N 10.00.

IR spectrum, cm^{-1}: 1736 ($\nu_{C=O}$), 1118 (ν_{C-O-C}).

^{13}C-NMR spectrum, δ, ppm ($CDCl_3$): 46.6 ($C_{1,5}$), 58.2 ($C_{6,8}$), 58.7 ($C_{2,4}$), 211.1 (C_9), 58.4 (C_{10}), 27.6 (C_{11}), 66.2 (C_{12}), 68.6 (C_{13}), 15.2 (C_{14}), 67.1 (C_{15}), 9.1 (C_{16}), 4.0 (C_{17}).

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

A mixture of 2.0 g (0.0068 mol) of 3-cyclopropanmethyl-7-(3-isopropoxy-propyl)-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 $MgSO_4$. The solvent was evaporated, the obtained product was purified by column chromatography on Al_2O_3, benzene:dioxane 5:1. 2.1 g (42%) of 3-cyclopropanmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1] nonane (5) is obtained as a pale yellow oil with R_f=0.23 (Al_2O_3, benzene:isopropanol = 7:1).

Found, %: C 72.89, H 11.41, N 10.05. $C_{17}H_{32}N_2O$

Calculated, %: C 72.85, H 11.43, N 10.00.

IR spectrum, cm^{-1}: 1112 (ν_{C-O-C}).

^{13}C-NMR spectrum, δ, ppm ($CDCl_3$): 29.8 ($C_{1,5}$), 58.4 ($C_{6,8}$), 58,8 ($C_{2,4}$), 31,4 (C_9), 57.7 (C_{10}), 28.1 (C_{11}), 66.5 (C_{12}), 73.3 (C_{13}), 22.3 (C_{14}), 67.0 (C_{16}), 8.6 (C_{17}), 4.1 (C_{18}).

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

A mixture of 5.0 g (0.018 mol) 3-cyclopropanmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (4) and 2.88 g (0.090 mol) hydrazine

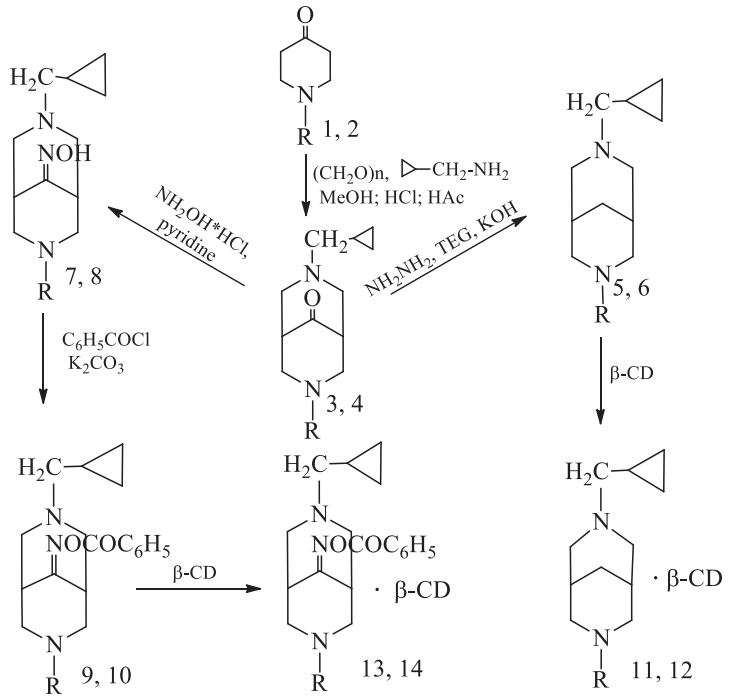

Fig. 1: Synthetic routes to the target bispidines

hydrate (99% solution) in 52.5 ml of triethylene glycol at 60°C add 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 $MgSO_4$. The solvent was evaporated, the obtained product was purified by column chromatography on Al_2O_3, benzene:dioxane 5:1. 2.1 g (42% of theory) of 3-cyclopropanmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonane (6) was obtained in the form of a light yellow oil with R_f=0.34 (Al_2O_3, benzene:isopropanol = 7:1).

Found, %: C 72.32, H 11.12, N 10.65. $C_{16}H_{30}N_2O$.

Calculated, %: C 72.18; H 11.27; N 10.52.

IR spectrum, ν, cm^{-1}: 1111 ($\nu_{C\text{-}O\text{-}C}$).

^{13}C-NMR spectrum, δ, ppm ($CDCl_3$): 30.6 ($C_{1,5}$), 58.6 ($C_{6,8}$), 58.0 ($C_{2,4}$), 31.8 (C_9), 57.4 (C_{10}), 27.9 (C_{11}), 66.1 (C_{12}), 69.6 (C_{13}), 15.2 (C_{14}), 67.2 (C_{15}), 54.1 (C_{17}), 9.5 (C_{16}), 4.2 (C_{17}).

Oxime of 3-cyclopropanmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (7)

3.0 g (0.0102 mol) of 3-cyclopropanmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (3) in 60 ml of ethyl alcohol and 1.23 g (0.0153 mol) of pyridine were placed in a three-necked flask equipped with a mechanical stirrer, reflux condenser with a calcium chloride tube, and dropping funnel. While stirring, 1.84 g (0.0265 mol) of hydroxylamine hydrochloride was added. The reaction mixture was heated at 110–120°C for 20 h, the solvent was evaporated, and the residue was dissolved in 15 ml of water, alkalized with NaOH to pH 12, extracted with chloroform, and dried over anhydrous $MgSO_4$. The solvent was evaporated, the residue was purified by column chromatography on Al_2O_3, benzene:dioxane =5:1. 1.83 g (59%) of oxime of 3-cyclopropanmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (7) was obtained in the form of light yellow oils with R_f=0.016 (Al_2O_3, benzene:isopropanol = 20:1).

Found, %: C 66.05, H 10.65, N 13.63. $C_{17}H_{31}N_3O_2$.

Calculated, %: C 66.02, H 10.67, N 13.59.

IR spectrum, cm^{-1}: 1668 ($\nu_{C=N}$), 3074 ($\nu_{O\text{-}H}$).

^{13}C-NMR spectrum, δ, ppm ($CDCl_3$): 38.1 (C_1), 32.0 (C_5), 59.5; 59.7 ($C_{2,4}$), 57.9, 58.0 ($C_{6,8}$), 162.0 (C_9), 57.6 (C_{10}), 31.7 (C_{11}), 64.8 (C_{12}), 67.7 (C_{13}), 28.2 (C_{14}), 63,1 (C_{15}), 7.7 (C_{16}), 4.0 (C_{17}).

Oxime of 3-cyclopropanmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (8)

6.0 g (0.0155 mol) of 3-cyclopropanmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (4) in 160 ml of ethyl alcohol and 3 ml (0.0375 mol) of pyridine were placed in a three-necked flask equipped with a mechanical stirrer, reflux condenser with a calcium chloride tube, and dropping funnel. With stirring, 4.5 g (0.065 mol) of hydroxylamine hydrochloride was added. The reaction mixture was heated at 110–120°C for 20 h, the solvent was evaporated, and the residue was dissolved in 10 ml of water, alkalized with NaOH to pH 12, extracted with chloroform, and dried over anhydrous MgSO4. The solvent was evaporated, the residue was purified by column chromatography on Al_2O_3, benzene:isopropanol-20:1. 5.4 g (85%) of oxime of 3-cyclopropanmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (8) was obtained in the form of light yellow oils with Rf=0.06 (Al_2O_3, benzene:isopropanol = 20:1).

Found, %: C 65.22, H 9.89, N 14.36. $C_{16}H_{29}N_3O_2$.

Calculated, %: C 65.08, H 9.83, N 14.24.

IR spectrum, cm^{-1}: 1643 ($\nu_{C=N}$), 3291 ($\nu_{O\text{-}H}$).

^{13}C-NMR spectrum, δ, ppm ($CDCl_3$): 37.0 (C_1), 32.5 (C_5), 58.5, 58.3 ($C_{2,4}$), 58.5, 58.4 ($C_{6,8}$), 165.8 (C_9), 58.7 (C_{10}), 27.3 (C_{11}), 69.1 (C_{12}), 70.8 (C_{13}), 27.3 (C_{14}), 54.0 (C_{16}), 8.4 (C_{17}), 4.0 (C_{18}).

O-Benzoyloxime of 3-cyclopropanmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (9)

1.5 g (0.0048 mol) of oxime of 3-cyclopropanmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (7) was mixed with 15 ml of absolute benzene and a mixture of 2 ml of absolute benzene and 0.6 ml (0.0048 mol) of benzoyl chloride was added dropwise. Reaction took place at room temperature. At the end, 10 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 $MgSO_4$. The solvent was evaporated and residue was distilled *in vacuo*. 1.9 g (91 % of theory) of O-benzoyloxime of 3-cyclopropanmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one was obtained in the form of a yellow oil (9), R_f=0.77 (Al_2O_3, benzene:isopropanol = 7:1).

Found, %: C 69.64, H 8.24, N 10,20. $C_{24}H_{35}N_3O_3$.

Calculated, %: C 69.73, H 8.48, N 10.17.

IR spectrum, cm^{-1}: 1745 ($\nu_{C=O}$), 1641 ($\nu_{C=N}$).

^{13}C-NMR spectrum, δ, ppm ($CDCl_3$): 38.7, 34.6 ($C_{1,5}$), 57.6, 59.3, 59.6, 59.7 ($C_{2,4,6,8}$), 161.2 (C_9), 57.8 (C_{10}), 28.1 (C_{11}), 64.8 (C_{12}), 70.8 (C_{13}), 28.2 (C_{14}), 63,1 (C_{15}), 7.9 (C_{16}), 4.0 (C_{17}), 171.4 (C_{18}), 129.2 (C_{19}), 129.7 (C_{20}), 128.4 (C_{21}), 133.4 (C_{22}).

O-Benzoyloxime of 3-cyclopropanmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (10)

4.0 g (0.01356 mol) of oxime of 3-cyclopropanmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonan-9-one (8) was mixed with 40 ml of absolute benzene and a mixture of 12 ml of absolute benzene and 1.9 ml (0.01356 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 is extracted with chloroform, the combined extracts were dried over anhydrous $MgSO_4$. The solvent was evaporated and residue was distilled *in vacuo*. 2.4 g (46% of theory) of O-benzoyloxime of 3-cyclopropanmethyl-7-(3-ethoxy-propyl)-3,7-diazabicyclo[3.3.1]nonan-9-one was obtained in the form of a yellow oil (10), R_f=0.30 (Al_2O_3, benzene:isopropanol = 7:1).

Found, %: C 69.12, H 8.34, N 10.65. $C_{23}H_{33}N_3O_3$.

Calculated, %: C 69.17, H 8.27, N 10.52.

IR spectrum, cm^{-1}: 3300.4 ($\nu_{O\text{-}H}$), 1675.4 ($\nu_{C=N}$).

^{13}C-NMR spectrum, δ, ppm ($CDCl_3$): 37.2, 33.6 ($C_{1,5}$), 57.0, 57.4, 57.9, 58.4 ($C_{2,4,6,8}$), 164.4 (C_9), 58.7 (C_{10}), 27.4 (C_{11}), 67.1 (C_{12}), 68.9 (C_{13}), 31.9 (C_{14}), 62.1 (C_{15}), 8.4 (C_{16}), 3.9 (C_{17}), 171.6 (C_{18}), 128.4 (C_{19}), 129.7 (C_{20}), 128.5 (C_{21}), 133.2 (C_{22}).

Complex of 3-cyclopropanmethyl-7-(3-isopropoxy-propyl)-3,7-diazabicyclo[3.3.1]nonane with β-cyclodextrin (11)

Hot solutions of 0.9 g (0.0033 mol) of 3-cyclopropanmethyl-7-(3-isopropoxypropyl)-3,7-diazabicyclo[3.3.1]nonane (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. $C_{59}H_{102}N_2O_{36}$.

Calculated, %: C 50.07, H 7.21, N 1.98.

Complex of 3-cyclopropanmethyl-7-(3-ethoxypropyl)-3,7-diazabicyclo[3.3.1]nonane with β-cyclodextrin (12)

Hot solutions of 1.7 g (0.0064 mol) of 3-cyclopropanmethyl-7-(3-ethoxypropyl)-3,7-diazabi-cyclo[3.3.1]nonane (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. $C_{58}H_{100}N_2O_{36}$.

Calculated, %: C 59.71, H 7.14, N 2.00.

Complex of O-benzoyloxime of 3-cyclopropanmethyl-7-(3-isopropoxypropyl)-3,7-diazabi-cyclo[3.3.1]nonan-9-one with β-cyclodextrin (13)

Hot solutions of 1.9 g (0.004 mol) of O-benzoyloxime of 3-cyclopropanmethyl-7-(3-isopropoxypro-pyl)-3,7-diazabicyclo[3.3.1] nonan-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).