ISSN 1070-3632, Russian Journal of General Chemistry, 2018, Vol. 88, No. 9, pp. 1922–1926. © Pleiades Publishing, Ltd., 2018.
Original Russian Text © V.B. Sokolov, A.Yu. Aksinenko, 2018, published in Zhurnal Obshchei Khimii, 2018, Vol. 88, No. 9, pp. 1554–1558.

LETTERS TO THE EDITOR

Dedicated to the 110th anniversary of M.I. Kabachnik's birth

N-Propargyl-α-aminophosphonates in 1,3-Dipolar Cycloaddition with Azide-Containing Pharmacophores

V. B. Sokolov[a] and A. Yu. Aksinenko[a]*

[a] *Institute of Physiologically Active Substances of the Russian Academy of Sciences, Severnyi proezd 1, Chernogolovka, 142432 Russia*
**e-mail: alaks@ipac.ac.ru*

Received June 28, 2018

Abstract—Some transformations of *N*-propargyl-α-aminophosphonates synthesized by the Kubachnik–Fields reaction were studied in copper-catalyzed 1,3-dipolar cycloaddition with azide-containing pharmacophores (phenothiazine, tetrahydrocarbazole, carbazole, and 3,5-dimethyl-1-aminoadamantane) leading to the formation of the corresponding 1,4-substituted 1,2,3-triazoles and allowing the introduction of a diethoxyphosphoryl fragment into the molecules of potential neuroprotectors.

Keywords: *N*-propargyl-α-aminophosphonates, phenothiazine, carbazole, 3,5-dimethyl-1-amino-adamantane, 1,3-dipolar cycloaddition

DOI: 10.1134/S107036321809027X

Aminophosphoryl compounds, which are mainly synthesized by the three-component Kabachnik–Fields reaction [1, 2], for many decades attract the attention of researchers in the field of medical and agrochemistry [3, 4]. Among these compounds inhibitors of enzymes, for example, protein-tyrosine-phosphatase [5], urokinase [6], as well as compounds exhibiting antitumor activity were detected [7, 8].

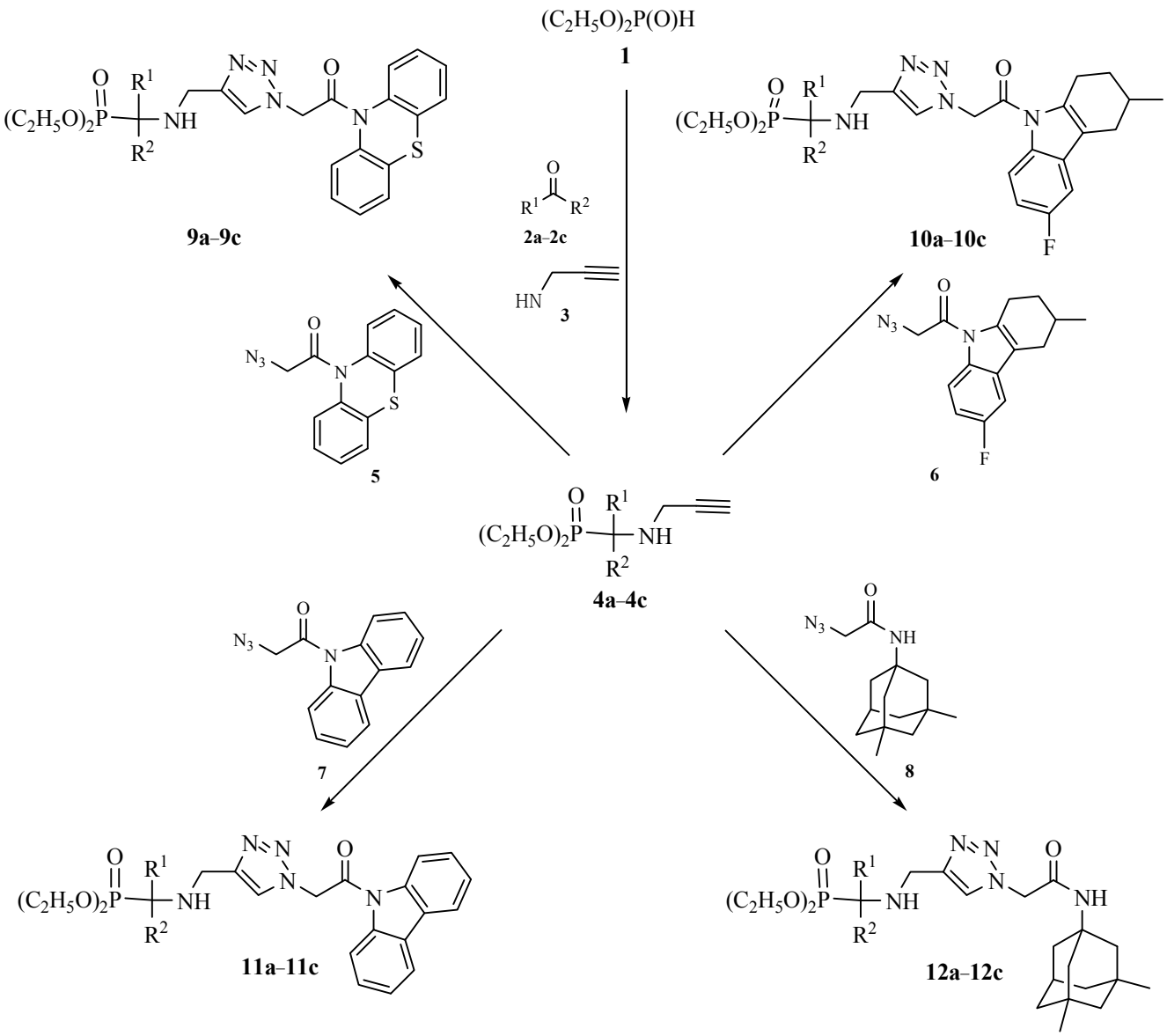
Apparently one of the most promising trends in the development of aminophosphonate synthesis is further development of approaches to the introduction of reactive functional groups into their molecules that allow targeted synthesis of substances with useful properties to be performed. In this regard here we reported on a method of functionalization of pharmacophore ligands with a diethoxyphosphorylalkyl fragment based on alkyne-azide copper-catalyzed 1,3-dipolar cycloaddition of previously unknown *N*-propargyl-α-aminophosphonates and azide-containing pharmacophores. The choice of pharmacophore was due to the data on biological activity of phenothiazine [9, 10], carbazole [11, 12], tetrahydrocarbazole [13, 14], and aminoadamantane derivatives [15].

N-Propargylaminophosphonates **4a–4c** were synthesized by Kubachnik–Fields reaction by heating (60°C) an alcohol solution of equimolar amounts of diethyl phosphite **1**, carbonyl compound **2a–2c,** and propargylamine **3**.

The functionalization of phosphonates **4a–4c** was performed by the reaction of alkyne-azide 1,3-dipolar cycloaddition (Huisgen reaction) [16] in its copper-catalyzed version [17]. Phosphonates **4a–4c** reacted with *N*-substituted azidoacetamides **5–8** in the presence of catalytic amounts of Cu(I) to form the corresponding 1,4-substituted 1,2,3-triazoles **9–12** in a 81–89% yield.

The composition and the structure of compounds **4**, **9–12** were confirmed by elemental analysis and NMR spectroscopy data. The signals of the phosphorus atom of these compounds are registered in the 24–32 ppm region characteristic of the 1-aminophosphonic acids derivatives. In the ^{1}H NMR spectra the proton signals with characteristic spin-spin coupling constants are observed. Thus, the signal of the methyl group at the position 1 relative to the phosphorus atom appears as a doublet with $^3J_{PH}$ = 16 Hz. The α-proton signal is also recorded as a doublet with $^2J_{PH}$ = 19 Hz. For compounds **9–12** (Scheme 1), the singlet signal of the 1,2,3-triazole ring at 7.6–7.8 ppm is characteristic.

Scheme 1.



$R^1 = R^2 = CH_3$ (**a**); $R^1 = CH_3$, $R^2 = C_2H_5$ (**b**); $R^1 = H$, $R^2 = C_6H_5$ (**c**).

In summary, an algorithm for the functionalization of biologically active substances (phenothiazine, carbazole, tetrahydrocarbazole and 3,5-dimethyl-1-aminoadamantane) with a diethoxyphosphorylalkyl group using two standard Kabachnik–Fields and Huisgen reactions was developed. It allows the preparation of a wide range of potential biologically active substances.

Azides **5–8** were prepared by azidation of the corresponding chloroacetyl derivatives according to the procedure [18]. Diethyl phosphite **1**, carbonyl compounds **2a–3c**, and propargylamine **3** (Aldrich) were used without preliminary purification.

Diethyl 2-(prop-2-yn-1-ylamino)propane-2-phosphonate (4a). A mixture of 10 mmol of diethyl phosphite **1**, 10.5 mmol of acetone **2a**, 10.5 mmol of propargylamine, and 50 mL of ethanol was stirred at 60°C for 8 h. After removal of the solvent the residue was chromatographed on silica gel (60 mesh, methanol–chloroform, 1 : 20). Yield 1.9 g (81%), oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.31 d (6H, CH_3CP,

$^3J_{PH}$ = 15.5), 1.32 t (6H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.6), 1.73 br. s (1H, PCNH), 2.21 t (1H, HC≡C, $^4J_{HH}$ = 2.5), 3.57 d (1H, CH_2N, $^4J_{HH}$ = 2.5), 3.58 d (1H, CH_2N, $^4J_{HH}$ = 2.5), 4.05–4.24 m (4H, $CH_3\underline{CH_2}O$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.2 ppm. Found, %: C 51.68; H 8.42; N 5.82. $C_{10}H_{20}NO_3P$. Calculated, %: C 51.49; H 8.64; N 6.01.

Diethyl 2-(prop-2-yn-1-ylamino)butane-2-phosphonate (4b) was prepared similarly. Yield 1.9 g (77%), oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.97 t (3H, $\underline{CH_3}CH_2C$, $^3J_{HH}$ = 7.6), 1.26 d (3H, CH_3CP, $^3J_{PH}$ = 15.6), 1.34 t (6H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.6), 1.53–1.92 m (3H, $CH_3\underline{CH_2}C$ + PCNH), 2.23 t (1H, HC≡C, $^4J_{HH}$ = 2.4), 3.51 (1H, CH_2N, AB-system, $^2J_{AB}$ = 16.0, $^3J_{HH}$ = $^4J_{HH}$ = 2.4), 3.62 (1H, CH_2N, AB-system, $^2J_{AB}$ = 16.0, $^3J_{HH}$ = 2.1, $^4J_{HH}$ = 2.4), 4.06–4.25 m (4H, $CH_3\underline{CH_2}O$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.3 ppm. Found, %: C 53.68; H 8.72; N 5.82. $C_{11}H_{22}NO_3P$. Calculated, %: C 53.43; H 8.97; N 5.66.

Diethyl phenyl(prop-2-yn-1-ylamino)methanephosphonate (4c) was prepared similarly. Yield 2.3 g (82%), oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.20 t (3H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.6), 1.27 t (3H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.6), 2.24 t (1H, HC≡C, $^4J_{HH}$ = 2.4), 2.35 br. s (1H, PCNH), 3.17 (1H, CH_2N, AB-system, $^2J_{AB}$ = 17.0, $^4J_{HH}$ = 2.4), 3.62 (1H, CH_2N, AB-system, $^2J_{AB}$ = 17.0, $^3J_{HH}$ = 2.1, $^4J_{HH}$ = 2.4), 3.82–4.25 m (4H, $CH_3\underline{CH_2}O$), 4.38 d (1H, CHP, $^2J_{PH}$ = 18.0), 7.26–7.42 m (3H, CH_{Ar}), 7.42–7.55 m (2H, CH_{Ar}). ^{31}P NMR spectrum ($CDCl_3$): δ_P 24.5 ppm. Found, %: C 53.68; H 8.72; N 5.82. $C_{14}H_{20}NO_3P$. Calculated, %: C 59.78; H 7.17; N 4.98.

Diethyl 2-[({1-[2-oxo-2-(10*H*-phenothiazin-10-yl)-ethyl]-1*H*-1,2,3-triazol-4-yl}methyl)amino]propane-2-phosphonate (9a). To a solution of 0.5 mmol of phosphonate **4a** in 20 mL of methylene chloride were added 0.5 mmol of azide **5**, 0.1 mmol of $CuSO_4$ in 1 mL of H_2O, and 0.1 mmol of sodium ascorbate in 1 mL of H_2O. The reaction mixture was stirred for 6 h at 40°C, then washed with 10 mL of a 1% aqueous ammonia solution. The organic layer was separated, the methylene chloride was evaporated, the residue was chromatographed on silica gel (60 mesh, methanol–chloroform, 1 : 10). Yield 0.22 g (85%), mp 223–225°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.14–1.64 m (12H, CH_3CP + $\underline{CH_3}CH_2O$), 2.23 br. s (1H, PCNH), 4.06 s (2H, CH_2N), 4.07–4.34 m (4H, $CH_3\underline{CH_2}O$), 5.30 br. s [2H, $CH_2C(O)$], 7.13–7.45 m (4H, CH_{Ar}), 7.48 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.3), 7.59 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.3), 7.67 s (1H, =CHNN). ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.8 ppm. Found, %: C 55.68; H 5.70; N 13.40. $C_{24}H_{30}N_5O_4PS$. Calculated, %: C 55.91; H 5.87; N 13.58.

Diethyl 2-[({1-[2-oxo-2-(10*H*-phenothiazin-10-yl)-ethyl]-1*H*-1,2,3-triazol-4-yl}methyl)amino]butane-2-phosphonate (9b) was prepared similarly. Yield 0.22 g (83%), mp 223–225°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.96 t (3H, $\underline{CH_3}CH_2C$, $^3J_{HH}$ = 7.3), 1.26 d (3H, CH_3CP, $^3J_{PH}$ = 15.6), 1.32 t (6H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.6), 1.57–1.97 m (2H, $CH_3\underline{CH_2}C$), 2.20 br. s (1H, PCNH), 3.98 (1H, CH_2N, AB-system, $^2J_{AB}$ = 13.4), 4.07 (1H, CH_2N, AB-system, $^2J_{AB}$ = 13.4), 4.07–4.27 m (4H, $CH_3\underline{CH_2}O$), 5.30 br. s [2H, $CH_2C(O)$], 7.22–7.42 m (4H, CH_{Ar}), 7.48 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.6), 7.60 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.6), 7.67 s (1H, =CHNN). ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.9 ppm. Found, %: C 56.58; H 5.90; N 13.40. $C_{25}H_{32}N_5O_4PS$. Calculated, %: C 56.70; H 6.09; N 13.22.

Diethyl {[({1-[2-oxo-2-(10*H*-phenothiazin-10-yl)-ethyl]-1*H*-1,2,3-triazol-4-yl}methyl)amino](phenyl)-methyl}phosphonate (9c) was obtained similarly. Yield 0.25 g (89%), mp 90–91°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.17 t (3H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.0), 1.26 t (3H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.0), 2.51 br. s (1H, PCNH), 3.76 (1H, CH_2N, AB-system, $^2J_{AB}$ = 14.0), 3.93 (1H, CH_2N, AB-system, $^2J_{AB}$ = 14.0), 3.87–4.14 m (4H, $CH_3\underline{CH_2}O$), 4.12 d (1H, CHP, $^2J_{PH}$ = 19.0), 5.30 br. s [2H, $CH_2C(O)$], 7.23–7.62 m (13H, CH_{Ar}), 7.64 s (1H, =CHNN). ^{31}P NMR spectrum ($CDCl_3$): δ_P 24.3 ppm. Found, %: C 59.48; H 5.58; N 12.60. $C_{28}H_{30}N_5O_4PS$. Calculated, %: C 59.67; H 5.37; N 12.43.

Diethyl 2-({[1-(2-(6-fluoro-3-methyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl]methyl}amino)propane-2-phosphonate (10a) was obtained similarly. Yield 0.22 g (85%), mp 79–80°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.16 d (3H, CH_3C_{ring}, $^3J_{HH}$ = 6.4), 1.36 t (6H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.0), 1.41 d (6H, CH_3CP, $^3J_{PH}$ = 16.0), 1.35–1.72 m (1H, CH), 1.86–2.30 m (4H, PCNH + CH_2), 2.74 d. d (1H, CH_2, $^2J_{HH}$ = 16.4, $^3J_{HH}$ = 4.0), 2.93–3.16 m (2H, CH_2), 4.05–4.357 m (6H, CH_2N + $CH_3\underline{CH_2}O$), 5.67 and 5.78 [2H, $CH_2C(O)$, AB-system, $^2J_{AB}$ = 17.5), 6.89–7.09 m (2H, CH_{Ar}), 7.77 s (1H, =CHNN), 8.08 d. d (1H, CH_{Ar}, $^3J_{HH}$ = 9.0). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: –42.6 t. d (1F, $^3J_{HF}$ = 8.0, $^4J_{HF}$ = 4.6). ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.5 ppm. Found, %: C 57.58; H 6.95; N 13.60. $C_{25}H_{35}FN_5O_4P$. Calculated, %: C 57.79; H 6.79; N 13.48.

Diethyl 2-({[1-(2-(6-fluoro-3-methyl-3,4-dihydro-1*H*-carbazol-9(2H)-yl-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl]methyl}amino)butane-2-phosphonate (10b) was obtained similarly. Yield 0.23 g (86%), oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.01 t (3H, $\underline{CH_3}CH_2C$, $^3J_{HH}$ = 7.3), 1.17 d (3H, CH_3C_{ring}, $^3J_{PH}$ = 6.4), 1.33 d (3H, CH_3CP, $^3J_{PH}$ = 15.6), 1.37 t (6H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.6), 1.51–2.40 m (7H, PCNH + $CH_3\underline{CH_2}C$ + CH_{2ring}), 2.76 d. d (1H, CH_2C_{ring}, $^2J_{HH}$ = 15.6, $^3J_{HH}$ = 4.0), 3.05 br. s (2H, CH_2C_{ring}), 4.04–4.30 m (6H, CH_2N + $CH_3\underline{CH_2}O$), 5.67 (1H, CH_2N, AB-system, $^2J_{AB}$ = 17.0), 5.80 (1H, AB-system, CH_2N, $^2J_{AB}$ = 17.0), 6.89–7.11 m (2H, CH_{Ar}), 7.77 s (1H, =CHNN), 8.10 d. d (1H, CH_{Ar}, $^3J_{HH}$ = 8.8, $^4J_{HF}$ = 4.4). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: –42.9 t. d (1F, $^3J_{HF}$ = 8.0, $^4J_{HF}$ = 4.6). ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.7 ppm. Found, %: C 58.38; H 6.75; N 13.31. $C_{26}H_{37}FN_5O_4P$. Calculated, %: C 58.53; H 6.99; N 13.13.

Diethyl {[({1-[2-(6-fluoro-3-methyl-1,2,3,4-tetrahydro-9*H*-carbazol-9-yl)-2-oxoethyl]-1*H*-1,2,3-triazol-4-yl}methyl)amino](phenyl)methyl}phosphonate (10c) was obtained similarly. Yield 0.23 g (81%), mp 67–68°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.09–1.38 m (6H, CH_3C_{ring} + $\underline{CH_3}CH_2O$), 1.50–1.72 m (1H, CH_{ring}), 1.87–2.35 m (2H, PCNH + CH_{2ring}), 2.79 d. d (1H, CH_2C_{ring}, $^2J_{HH}$ = 16.0, $^3J_{HH}$ = 4.0), 3.07 br. s (2H, CH_2C_{ring}), 3.73–4.20 m (6H, CH_2N + $CH_3\underline{CH_2}O$), 4.16 d (1H, CHP, $^2J_{PH}$ = 19.2), 5.70 (1H, CH_2N, AB-system, $^2J_{AB}$ = 17.0), 5.81 (1H, CH_2N, AB-system, $^2J_{AB}$ = 17.0), 6.94–7.14 m (4H, CH_{Ar}), 7.24–7.58 m (8H, CH_{Ar}), 7.71 s (1H, =CHNN), 8.14 d. d (1H, CH_{Ar}, $^3J_{HH}$ = 8.8, $^4J_{HF}$ = 4.4). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: –42.4 t. d (1F, $^3J_{HF}$ = 8.8, $^4J_{HF}$ = 4.4). ^{31}P NMR spectrum ($CDCl_3$): δ_P 24.4 ppm. Found, %: C 61.58; H 6.45; N 12.11. $C_{29}H_{35}FN_5O_4P$. Calculated, %: C 61.37; H 6.22; N 12.34.

Diethyl 2-[({1-[2-(9*H*-carbazol-9-yl)-2-oxoethyl]-1*H*-1,2,3-triazol-4-yl}methyl)amino]propane-2-phosphonate (11a) was obtained similarly. Yield 0.21 g (87%), oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.20–1.57 m (12H, CH_3CP + $\underline{CH_3}CH_2O$), 2.30 br. s (1H, PCNH), 4.02–4.30 m (6H, CH_2N + $CH_3\underline{CH_2}O$), 5.87 s [2H, $CH_2C(O)$], 7.29–7.50 m (4H, CH_{Ar}), 7.77 s (1H, =CHNN), 7.89 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.0), 8.03 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.9). ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.6 ppm. Found, %: C 59.41; H 6.44; N 14.31. $C_{24}H_{30}N_5O_4P$. Calculated, %: C 59.62; H 6.25; N 14.48.

Diethyl 2-[({1-[2-(9*H*-carbazol-9-yl)-2-oxoethyl]-1*H*-1,2,3-triazol-4-yl}methyl)amino]butane-2-phosphonate (11b) was obtained similarly. Yield 0.21 g (84%), oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.99 t (3H, $\underline{CH_3}CH_2C$, $^3J_{HH}$ = 7.6), 1.31 d (3H, CH_3CP, $^3J_{PH}$ = 16.2), 1.34 t (6H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.6), 1.60–1.99 m (2H, $CH_3\underline{CH_2}C$), 2.30 br. s (1H, PCNH), 3.97–4.27 m (6H, CH_2N + $CH_3\underline{CH_2}O$), 5.88 s [2H, $CH_2C(O)$], 7.32–7.51 m (4H, CH_{Ar}), 7.78 s (1H, =CHNN), 7.91 d. d (2H, CH_{Ar}, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.8), 8.04 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.6). ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.8 ppm. Found, %: C 60.52; H 6.29; N 14.30. $C_{25}H_{32}N_5O_4P$. Calculated, %: C 60.35; H 6.48; N 14.08.

Diethyl {[({1-[2-(9*H*-carbazol-9-yl)-2-oxoethyl]-1*H*-1,2,3-triazol-4-yl}methyl)amino](phenyl)methyl}phosphonate (11c) was obtained similarly. Yield 0.22 g (83%), 105–107°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.19 t (3H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.0), 1.30 t (3H, $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.0), 2.62 br. s (1H, PCNH), 3.77–4.20 m (6H, CH_2N + $CH_3\underline{CH_2}O$), 4.20 d (1H, CHP, $^2J_{PH}$ = 19.0), 6.00 s [2H, $CH_2C(O)$], 7.32–7.64 m (9H, CH_{Ar}), 7.77 s (1H, =CHNN), 8.03 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.0), 8.16 d (2H, CH_{Ar}, $^3J_{HH}$ = 7.9). ^{31}P NMR spectrum ($CDCl_3$): δ_P 24.3 ppm. Found, %: C 63.32; H 5.90; N 13.40. $C_{28}H_{30}N_5O_4P$. Calculated, %: C 63.27; H 5.69; N 13.18.

Diethyl 2-{[(1-(2-{[(3,5-dimethyladamantan-1-yl)-amino]-2-oxoethyl}-1*H*-1,2,3-triazol-4-yl)methyl]-amino}propane-2-phosphonate (12a) was obtained similarly. Yield 0.21 g (85%), 113–115°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.85 s (6H, CH_{3Ad}), 1.15 br. s (2H, CH_{2Ad}), 1.36 t (10H, CH_{2Ad} + $\underline{CH_3}CH_2O$, $^3J_{HH}$ = 7.0), 1.40 d (6H, CH_3CP, $^3J_{PH}$ = 15.6), 1.53–1.69 m (4H, CH_{2Ad}), 1.76–1.86 m (2H, CH_{2Ad}), 2.09–2.20 m (1H, CH_{Ad}), 2.28 br. s (1H, PCNH), 4.11 s (2H, CH_2N), 4.12–4.31 m (4H, $CH_3\underline{CH_2}O$), 4.95 s [2H, $CH_2C(O)$], 6.18 br. s (1H, NH), 7.65 s (1H, =CHNN). ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.5 ppm. Found, %: C 58.37; H 8.71; N 14.38. $C_{24}H_{42}N_5O_4P$. Calculated, %: C 58.16; H 8.54; N 14.13.

Diethyl 2-{[(1-(2-{[(3,5-dimethyladamantan-1-yl)-amino]-2-oxoethyl}-1*H*-1,2,3-triazol-4-yl)methyl]-amino}but-2-yl)phosphonate (12b) was obtained similarly. Yield 0.21 g (82%), 107–109°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.83 s (6H, CH_{3Ad}), 0.99 t (3H, $\underline{CH_3}CH_2C$, $^3J_{HH}$ = 7.3), 1.20 d (3H, CH_3CP, $^3J_{PH}$ = 15.6), 1.21–1.48 m (12H, CH_{2Ad} + $\underline{CH_3}CH_2O$), 1.50–1.97 m (8H, CH_{2Ad} + $CH_3\underline{CH_2}C$), 2.04–2.21 m (1H, CH_{Ad}), 2.28 br. s (1H, PCNH), 3.90–4.36 m (6H, CH_2N + $CH_3\underline{CH_2}O$), 4.95 br. s [2H, $CH_2C(O)$], 6.38 s

(1H, NH), 7.67 s (1H, =CHNN). ^{31}P NMR spectrum ($CDCl_3$): δ_P 31.6 ppm. Found, %: C 59.11; H 8.92; N 13.58. $C_{25}H_{44}N_5O_4P$. Calculated, %: C 58.92; H 8.70; N 13.74.

Diethyl [{[(1-{2-[(3,5-dimethyladamantan-1-yl)-amino]-2-oxoethyl}-1*H*-1,2,3-triazol-4-yl)methyl]-amino}(phenyl)methyl]phosphonate (12c) was obtained similarly. Yield 0.22 g (81%), oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.80 s (6H, CH_{3Ad}), 1.00–1.44 (12H, CH_{2Ad} + $\underline{CH_3}CH_2O$), 1.47–1.71 m (4H, CH_{2Ad}), 1.70–1.92 m (2H, CH_{2Ad}), 2.03–2.20 m (1H, $C_{Ad}H$), 2.60 br. s (1H, PCNH), 3.67–4.20 m (6H, CH_2N + $CH_3\underline{CH_2}O$), 4.14 d (1H, CHP, $^2J_{PH}$ = 19.4), 4.94 s [2H, $CH_2C(O)$], 6.28 s (1H, NH), 7.21–7.54 m (5H, CH_{Ar}), 7.61 s (1H, =CHNN). ^{31}P NMR spectrum ($CDCl_3$): δ_P 24.3 ppm. Found, %: C 61.65; H 7.96; N 12.66. $C_{28}H_{42}N_5O_4P$. Calculated, %: C 61.86; H 7.79; N 12.88.

^{1}H, ^{19}F, and ^{31}P NMR spectra were recorded on a Bruker DPX 200 spectrometer at 200.13, 188.0 and 81.0 MHz, respectively. Melting points were determined in a glass capillary.

ACKNOWLEDGMENTS

This work was supported by the Ministry of Education and Science of Russia in the framework of the governmental task for 2018 (no. 0090-2017-0023).

CONFLICT OF INTERESTS

No conflict of interests was declared by the authors.

REFERENCES

1. Kabachnik, M.I. and Medved, T.Ya., *Doklady Akad. Nauk SSSR*, 1952, vol. 83, p. 689.
2. Fields, E.K., *J. Am. Chem. Soc*., 1952, vol. 74, no. 6, p. 1528. doi 10.1021/ja01126a054
3. Kukhar, V.P. and Hudson, H.R., *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, London: John Wiley & Sons, Inc., 2000.
4. Mucha, A., Kafarski, P., and Berlicki, Ł., *J. Med. Chem*. 2011, vol. 54, no. 17, p. 5955. doi 10.1021/jm200587f
5. Wang, Q., Zhu, M., Zhu, R., Lu, L., Yuan, C., Xing, S., Fu, X., Mei, Y., and Hang, Q., *Eur. J. Med. Chem*., 2012, vol. 49, no. 3, p. 354. doi 10.1016/j.ejmech.2012.01.038
6. Joossens, J., Van der Veken, P., Surpateanu, G., Lambeir, A.-M., El-Sayed, I., Ali O.M., Augustyns, K., and Haemers, A., *J. Med. Chem*., 2006, vol. 49, no. 19, p. 5785. doi 10.1021/jm060622g
7. Bhattacharya, A.K., Raut, D.S., Rana, K.C., Polanki, I.K., Khan, M.S., and Iram, S., *Eur. J. Med. Chem*., 2013, vol. 66, no. 8, p. 146. doi 10.1016/j.ejmech.2013.05.036
8. Rezaei, Z., Firouzabadi, H., Iranpoor, N., Ghaderi, A., Jafari, M.R., Jafari, A.A., and Zare, H.R., *Eur. J. Med. Chem.*, 2009, vol. 44, no. 11, p. 4266. doi 10.1016/j.ejmech.2009.07.009
9. Bachurin, S.O., Sokolov, V.B., Aksinenko, A.Yu., Epishina, T.A., Goreva, T.V., Gabrel'yan, A.V., and Grigor'ev, V.V., *Russ. Chem. Bull*., 2015, vol. 64, no. 6, p. 1354. doi 10.1007/s11172-015-1017-0
10. Bandgar, B.P., Adsul, L.K., Chavan, H.V., Jalde, S.S., Shringare, S.N., Shaikh, R., Meshram, R.J., Nacche, G.R., and Masand, V., *Bioorg. Med. Chem. Lett*., 2012, vol. 22, no. 18, p. 5839. doi 10.1016/j.bmcl.2012.07.080
11. Zhu, D., Chen, M., Li, M., Luo, B., Zhao, Y., Huang, P., Xue, F., Rapposelli, S., Pi, R., and Wen, S., *Eur. J. Med. Chem*., 2013, vol. 68, no. 10, p. 81. doi 10.1016/j.ejmech.2013.07.029
12. MacMillan, K.S., Naidoo, J., Liang, J., Melito, L., Williams, N.S., Morlock, L., Huntington, P.J., Estill, S.J., Longgood, J., Becker, G.L., McKnight, S.L., Pieper, A.A., De Brabander, J.K., and Ready, J.M., *J. Am. Chem. Soc*., 2011, vol. 133, no. 5, p. 1428. doi 10.1021/ja108211m
13. Sokolov, V.B., Aksinenko, A.Yu., Goreva, T.V., Epishina, T.A., Grigor'ev, V.V., Gabrel'yan, A.V., Vinogradova, D.V., Dubova, L.G., Schevtsov, P.N., Schevtsova, E.F., and Bachurin, S.O., *Russ. Chem. Bull*., 2016, vol. 65, no. 5, p. 1346. doi 10.1007/s11172-016-1460-6
14. Yoon, H.J., Kong, S.-Y., Park, M.-H., Cho, Y., Kim, S.-E., Shin, J.-Y., Jung, S., Lee, J., Farhanullah, Kim, H.-J., and Lee, J., *Bioorg. Med. Chem*., 2013, vol. 21, no. 22, p. 7165. doi 10.1016/j.bmc.2013.08.066
15. Doody, R.S., Tariot, P.N., Pfeiffer, E., Olin, J.T., and Graham, S.M., *Alzheimer's Dement*., 2007, vol. 3, no. 1, p. 7. doi 10.1016/j.jalz.2006.10.004
16. Huisgen, R., *Angew. Chem. Int. Ed*., 1963, vol. 2, no. 10, p. 565. doi 10.1002/anie.196305651
17. Rostovtsev, V.V., Green, L.G., Fokin, V.V., and Sharpless, K.B., *Angew. Chem. Int. Ed*., 2002, vol. 41, no. 14, p. 2596. doi 10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4
18. Rusu, R., Szumna, A., Rosu, N., Dumea, C., and Danac, R., *Tetrahedron*, 2015, vol. 71, no. 19, p. 2922. doi 10.1016/j.tet.2015.03.060