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Synthesis and structure of 4-substituted (1*S*,9*aR*)-1-[(1,2,3-triazol-1-yl)methyl]octahydro-1*H*-quinolysines of lupinine

The article presents results on the synthesis and investigation of the structural features of a number of 1,4-disubstituted 1*H*-1,2,3-triazole derivatives of the alkaloid lupinine. Lupinine modification reactions were carried out at the hydroxymethylene group in the C-1 position of the quinolysine backbone. It has been shown that (octahydro-2*H*-quinolysine-1-ylmethyl)methanesulfonate in high yield (93%) is formed by the interaction of lupinine with methanesulfonyl chloride in methylene chloride. Subsequent treatment of this compound with sodium azide in dimethylformamide on heating leads to the formation of 1-(azidomethyl)octahydro-2*H*-quinolysine in 61% yield. It has been found that the reaction of a new azide with terminal alkynes of various nature in the presence of aqueous CuSO₄ and sodium ascorbate in dimethylformamide can form the corresponding 4-substituted (1*S*,9*aR*)-1-[(1,2,3-triazol-1-yl)methyl]octahydro-1*H*-quinolysines. New 1,2,3-triazole derivatives of lupinine containing various aryl substituents at the C-4 position of the triazole ring have been obtained. The high selectivity of the reaction is explained by the action mechanism of the Sharpless catalyst. The spatial structure of the molecules of lupinine methanesulfonate, 4-aryltriazolylmethyl-octahydro-quinolysines has been established by X-ray diffraction analysis. X-ray structural analysis data of new compounds have been deposited in the form of CIF files at the Cambridge Crystallographic Data Center.

Keywords: quinolysine alkaloids, lupinine, azides, triazoles, methanesulfonyl chloride, terminal alkynes, 1,3-dipolar cycloaddition reaction, X-ray structural analysis.

Introduction

The products of secondary plant metabolism, namely alkaloids are promising models for studying the relationship patterns “structure-biological activity”. A wide range of biological properties of their derivatives allows accumulating factual material for a databank of their structural derivatives and using them in the search for new drugs. The development of methods for the chemical modification of alkaloid compounds opens up new possibilities for the creation of original agents with specific biological activity. The alkaloid lupinine obtained from plants of the genera *Lupinus* and *Anabasis* is one of these important compounds in terms of the search for new bioactive substances [1–3]. The presence of a primary alcohol group makes it possible to obtain various modifications of lupinine derivatives [4]. It is also interesting that lupinine, having a transquinolizidine ring with an axial oxymethyl group, is able to change its configuration from trans to cis-junction of the quinolizidine ring upon the nitrogen atom protonation [5, 6]. This leads to the transition of the axial oxymethyl group to the equatorial position with a change in the sign of the angle of rotation, which can lead to the manifestation of new types of activities.

In terms of pharmacological action, lupinine has a bactericidal, sedative effect, and short-term anthelmintic, as well as hypotensive properties [3, 4, 6]. The presence of an active hydroxyl function in the lupinine molecule makes it possible to synthesize a variety of derivatives on its basis. In [4, 5], pharmacological studies of the compound [(4-nitrobenzylidene)-imino]lupinine and [(2,4-dihydroxybenzylidene)-imino]lupinine were carried out, which showed high antibiotic activity against plague and cholera microbes. A number of lupinine esters have shown a local anesthetic effect, as well as anti-tuberculosis and anticholinesterase activity [6]. Compound 11-[(gossypolydene)-imino]lupinine has been shown to have high anti-AIDS activity [7]. Esters of lupinine [8], which have pronounced antiviral, antitumor and hepatoprotective activity, are the most studied ones among the known lupinine derivatives [9]. Therefore, the interest in lupinine and its new derivatives continues unabated.

The synthesis and investigation of lupinine triazole derivatives is one of the poorly studied and promising directions for modifying the lupinine structure. It is known that compounds with triazole moieties have a wide range of applications in the production of pharmaceuticals, photoactive chemicals dyes, and agricultural chemicals [10, 11]. Recently, the search for compounds with antiviral activity is an extremely urgent task due to the global COVID-19 pandemic. Particular importance is attached to the search for broad-spectrum antiviral agents capable of suppressing the replication of various viruses. Compounds with anti-HIV, anti-antiviral, and antihistaminic activity have been identified among 1,2,3-triazole derivatives; it should be noted that they also inhibit β 3-adrenergic receptors selectively [12–14]. The creation of medicines on their basis that will be used in the treatment of socially significant infectious diseases of viral etiology is one of the most important tasks of modern pharmaceutical chemistry.

The aim of this work is to synthesize 4-substituted (1*S*,9*aR*)-1-[(1,2,3-triazol-1-yl)methyl]octahydro-1*H*-quinolysines of lupinine alkaloid using the “click”-reaction technology and study the structure of new synthesized compounds by ^1H -, ^{13}C - and two-dimensional NMR spectra, namely COSY (^1H - ^1H) and HMQC (^1H - ^{13}C), as well as X-ray analysis.

Experimental

IR spectra were recorded on a Vector-22 Fourier spectrometer in KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 (400 and 101 MHz, respectively) and Bruker DRX-500 (500 and 125 MHz, respectively) spectrometers. The compounds spectra were recorded in CDCl_3 , the signal of which ($\delta_{\text{C}}=76.9$ ppm) and the residual signal of CHCl_3 ($\delta_{\text{H}}=7.24$ ppm) were used as an internal standard.

The structure of the obtained compounds was established by analyzing the ^1H and ^{13}C NMR spectra, the signal multiplicity in the ^{13}C NMR spectra was determined from the spectra recorded in the J-modulation mode (JMOD). The signals assignment in the spectra was carried out using various correlation spectroscopy ^1H - ^1H (COSY), and ^1H - ^{13}C (HMBC, HSQC) using literature data for the quinolysine backbone. When describing the spectra, we used the numbering of the core atoms given in structure (1). Specific rotation values were measured on a PolAAr 3005 polarimeter. High-resolution mass spectra were recorded on a DFS ThermoScientific mass spectrometer (evaporator temperature 200–250 °C, EI ionization, 70 eV). Melting points were determined on a Mettler Toledo FP900 thermosystem. X-ray structural analysis of compounds (2, 5a, 5b) was carried out on an Xcalibur, Ruby diffractometer with a CCD detector (CuK α radiation, graphite monochromator, λ 1.54184 Å, ω -scanning). Processing of the initial array of measured intensities and the absorption was carried out using the CrysAlisPro software (multi-scan) [15].

The structure was solved by a direct method. The positions of non-hydrogen atoms were refined in the anisotropic approximation using full-matrix least squares. Hydrogen atoms were placed in geometrically calculated positions and their positions were refined in the isotropic approximation with fixed positional and thermal parameters (“rider” model). The structures were determined by a direct method and refined using the SHELXS-2014 and SHELXL-2014 software packages [16]. Spectral-analytical studies were carried out at the Chemical Service Center for Collective Use of the Siberian Branch of the Russian Academy of Sciences.

The reaction progress was monitored by TLC on Sorbfil UV-254 plates using chloroform, chloroform – ethanol, 10:1 systems. Detection was carried out in an iodine chamber and in UV light. The reaction products were isolated by recrystallization or using column chromatography on Acros silicagel (0.035–0.240 mm), eluents CHCl_3 ; CHCl_3 – EtOH, 100:1 \rightarrow 10:1).

The reagents used in the work were sodium azide, 4-methoxyphenylacetylene (4a), *m*-tolylacetylene (4b). They were purchased from Alfa Aesar. Solvents (chloroform, DMF) and Et_3N were purified according to standard methods; DMF was additionally distilled in a stream of argon immediately before carrying out the reactions.

(Octahydro-2*H*-quinolysine-1-ylmethyl)methanesulfonate (2). A solution of methanesulfonyl chloride (4.8 g, 42 mmol) in 20 ml of CH_2Cl_2 was added dropwise to an ice bath-cooled solution of lupinine (1) (3.54 g, 21 mmol) and triethylamine (6.36 g, 63 mmol) in CH_2Cl_2 (200 ml). The reaction mixture was stirred for 30 min while cooling to 0°C and for 6 h at room temperature, then washed with saturated sodium chloride solution (2×20 ml), dried over anhydrous MgSO_4 , the drying agent was filtered off; the solvent was distilled off in a vacuum. The residue was chromatographed on a silicagel column (chloroform, chloroform-ethanol, 50:1). Yield was 4.84 g (93%). Cream crystals are obtained; m.p. is 57–58 °C (from ether). $[\alpha]_{\text{D}}^{25}$ –21.6 (c 1.4, CHCl_3). IR spectrum (KBr), ν , cm^{-1} : 1184, 1336 (OSO₂), 2740, 2757, 2798 (quinolizidine). ^1H NMR spectrum (400 MHz, CDCl_3), δ , ppm (J, Hz): 1.12–1.26 (1H, m, H-2a); 1.28–1.51 (5H, m, H-2e, 8a, 8e, 3a, 7a); 1.54 (1H, m, H-9a); 1.59–1.77 (2H, m, H-3e, 7e); 1.84–2.02 (5H, m, H-1.4a, 6a, 9e, 9a); 2.73–2.80

(2H, m, H-4e, 6e); 2.97 (3H, s, CH₃); 4.37 (1H, dd, J = 10.6, J = 9.8, H-10); 4.47 (1H, dd, J = 10.6, J = 5.3, H-10). ¹³C NMR spectrum (101 MHz, CDCl₃), δ, ppm: 20.6 (C-3); 24.7; 25.4 (C-7.8); 26.3 (C-2); 29.8 (C-9); 37.0 (CH₃); 38.0 (C-1); 56.8; 57.1 (C-4.6); 64.0 (C-9a); 69.5 (C-10). Mass spectrum, m/z (I, %): 248 (1), 247 (7), 153 (10), 152 (100), 150 (3), 98 (6). Found, m/z: 247.1238 [M]⁺. C₁₁H₂₁NO₃S. Calculated, m/z: 247.1237.

X-ray structural study of compound (2). The main crystallographic data and characteristics of the X-ray diffraction experiment are presented in Table 1. The XRD data in the form of a CIF file were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2087144).

1-(Azidomethyl)octahydro-2H-quinolysine (3). A mixture of compound (2) (4.84 g, 20 mmol) and sodium azide 3.44 g (53 mmol) in DMF (50 ml) was stirred at 70 °C for 5 h (TLC control). After the end of the reaction, the solvent was removed from the reaction mixture, the residue was dissolved in CH₂Cl₂, washed with a saturated sodium chloride solution, dried over anhydrous MgSO₄, the desiccant was filtered, the solvent was distilled in vacuum, the residue was chromatographed on a column with silicagel (chloroform-ethanol, 50:1). Yield was 2.33 g (60%). Light yellow mobile liquid was obtained. [α]_D²⁶ -29.85 (s 2.4, chloroform). IR spectrum, ν, cm⁻¹: 1269, 2096 (N≡N), 2744, 2762, 2804 (quinolizidine). ¹H NMR spectrum (400 MHz, CDCl₃), δ, ppm (J, Hz): 1.12–1.26 (1H, m, H-2a); 1.30–1.57 (6H, m, H-8a, 8e, 9a, 9e, 3a, 7a); 1.58–1.76 (3H, m, H-2e, 3e, 7e); 1.80–1.99 (4H, m, H-1.4a, 6a, 9a); 2.72–2.82 (2H, m, H-4e, 6e); 3.42 (1H, dd, J = 12.6, J = 9.6, CH₂-10); 3.54 (1H, dd, J = 12.6, J = 5.3, CH₂-10). ¹³C NMR spectrum (125 MHz, CDCl₃), δ, ppm: 20.7 (C-3); 24.9 (C-8); 25.4 (C-7); 27.3 (C-2); 29.6 (C-9); 38.2 (C-1); 50.4 (C-10); 56.8; 57.2 (C-4.6); 64.3 (C-9a). Mass spectrum, m/z (I, %): 194 (2), 153 (10), 152 (100), 137 (7), 136 (5), 98 (12), 84 (7), 83 (9), 82 (6), 55 (10), 41 (14). Found, m/z: 194.1528 [M]⁺. C₁₀H₁₈N₄. Calculated, m/z: 194.1526.

Synthesis of compounds (5a,b) (General method). A mixture of azide (3) (0.29 g, 1.5 mmol), substituted acetylene (4a,b) (1.35 mmol), CuSO₄·5H₂O (0.017 g, 0.0675 mmol) and sodium ascorbate (0.013 g, 0.0675 mmol) in DMF (4 ml) was stirred at 75 °C for 4–6 h (TLC control). The precipitate formed upon cooling was filtered off, washed with hexane, and dried to obtain triazoles (5a,b). The solvent was distilled off in vacuum to isolate triazoles (5a,b); the residue was chromatographed on a silicagel column (eluent chloroform, mixture of chloroform with ethanol, 100:1 → 10:1).

(1S,9aR)-1-[[4-(4-Methoxyphenyl)-1H-1,2,3-triazole-1-yl]methyl]octahydro-1H-quinolysine (5a). Yield was 0.35 g (83 %). There are obtained white crystals; m.p. was 177–178 °C (from ethyl acetate). [α]_D²⁶ -16.9 (c 0.8, chloroform). IR spectrum, ν, cm⁻¹: 829, 920, 1443, 1458, 1498, 1560, 1618, 3097 (C=C, C=N); 1008, 1132, 1246 (C–O); 2761, 2804 (quinolizidine). ¹H NMR spectrum (400 MHz, CDCl₃), δ, ppm (J, Hz): 1.17–1.40 (3H, m, H-2a, 2e, 8a); 1.40–1.64 (5H, m, H-8e, 9a, 9e, 3a, 7a); 1.73–1.90 (2H, m, H-3e, 7e); 1.92–2.05 (2H, m, H-4a, 6a); 2.06–2.10 (1H, m, H-9a), 2.22–2.26 (1H, m, H-1); 2.83–2.88 (2H, m, H-4e, 6e); 3.81 (3H, s, OCH₃); 4.54 (1H, dd, J = 13.8, J = 5.5, H-10); 4.60 (1H, dd, J = 13.8, J = 12.5, H-10); 6.92 (2H, d, J = 8.6, H-3'', 5''); 7.61 (1H, s, H-5''); 7.73 (2H, d, J = 8.6, H-2'', 6''). ¹³C NMR spectrum (101 MHz, CDCl₃), δ, ppm: 20.5 (C-3); 24.7; 25.4 (C-7.8); 26.1 (C-2); 29.5 (C-9); 39.1 (C-1); 48.4 (C-10); 55.2 (OCH₃); 56.9; 57.2 (C-4.6); 64.3 (C-9a); 114.1 (C-3'', 5''); 119.3 (C-5''); 123.3 (C-1''); 126.8 (C-2'', 6''); 147.2 (C-4''); 159.4 (C-4''). Mass spectrum, m/z (I, %): 328 (1), 327 (12), 226 (49), 152 (42), 151 (100), 150 (66), 138 (18), 137 (14), 136 (33), 111 (18), 96 (17), 83 (25), 41 (150). Found, m/z: 326.2100 [M]⁺. C₁₉H₂₆N₄O. Calculated, m/z: 326.2101.

X-ray structural study of compound (5a). The main crystallographic data and characteristics of the X-ray diffraction experiment are presented in Table 1. The XRD data in the form of a CIF file were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2087145).

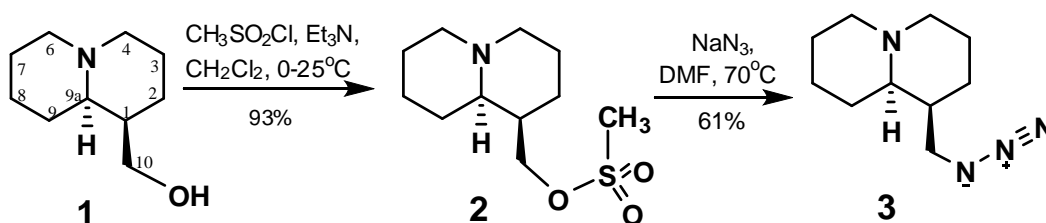
(1S,9aR)-1-[[4-(m-Tolyl)-1H-1,2,3-triazole-1-yl]methyl]octahydro-1H-quinolysine (5b). Yield was 0.52 g (80 %). There were obtained white crystals; m.p. was 141–142 °C (from ethyl acetate). [α]_D²⁶ -13.8 (c 1.0, chloroform). IR spectrum, ν, cm⁻¹: 694, 791, 846, 1443, 1464, 1487, 1614, 3122 (C=C, C=N); 2763, 2804 (quinolizidine). ¹H NMR spectrum (500 MHz, CDCl₃), δ, ppm (J, Hz): 1.20–1.40 (3H, m, H-2a, e, 8a); 1.41–1.63 (5H, m, H-8 e, 9a, 9e, 3a, 7a); 1.74–1.91 (2H, m, H-3e, 7e); 1.94–2.02 (2H, m, H-4a, 6a); 2.06–2.09 (1H, m, H-9a), 2.22–2.26 (1H, m, H-1); 2.37 (3H, s, CH₃); 2.83–2.88 (2H, m, H-4e, 6e); 4.56 (1H, dd, J = 13.8, J = 5.8, H-10); 4.61 (1H, dd, J = 13.8, J = 11.2, H-10); 7.11 (1H, d, J = 7.5, H-4''); 7.27 (1H, t, J = 7.5, H-5''); 7.58 (1H, dd, J = 7.5, J = 1.6, H-6''); 7.66 (1H, s, H-5''); 7.72 (1H, d, J = 1.6, H-2''). ¹³C NMR spectrum (125 MHz, CDCl₃), δ, ppm: 20.5 (C-3); 21.3 (CH₃); 24.7; 25.4 (C-7.8); 26.2 (C-2); 29.6 (C-9); 39.1 (C-1); 48.5 (C-10); 56.91; 57.2 (C-4.6); 64.3 (C-9a); 120.0 (C-5''); 122.7; 126.2; 128.5; 128.6 (C-2'', 4'', 5'', 6''); 130.5 (C-1''); 138.3 (C-3''); 147.5 (C-4''). Mass spectrum, m/z (I, %): 312 (1), 311 (9), 310 (42), 152

(28), 151 (100), 150 (52), 138 (15), 136 (35), 83 (20). Found, m/z : 310.2155 $[M]^+$. $C_{19}H_{26}N_4$. Calculated, m/z : 310.2152.

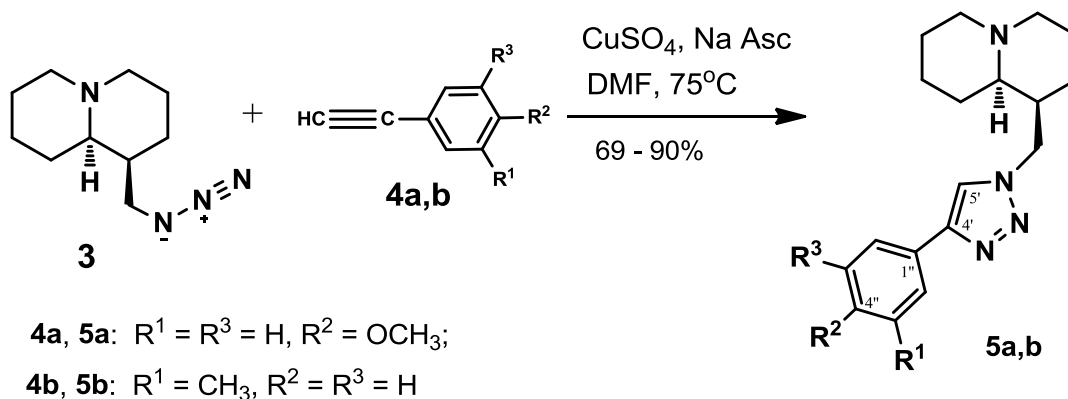
Results and Discussion

In this work, we describe the synthesis of lupinyl azide (**3**) and an unknown group of quinolysine alkaloids derivatives, containing a 1,2,3-triazole substituent. The synthesis of triazoles (**5a**) and (**5b**) was carried out by the reaction of 1,3-dipolar addition according to Huesgen in the presence of a Sharpless catalyst, which is a sodium ascorbate – copper (II) sulfate system. This method is convenient due to the fact that the addition of acetylene to an azide leads to the formation of 1,4-substituted triazoles, while a mixture of 1,4- and 1,5-isomers is formed during thermal cyclization [17].

When lupinine (**1**) interacts with methanesulfonyl chloride in the presence of triethylamine in methylene chloride, (octahydro-2*H*-quinolysine-1-ylmethyl)methanesulfonate (**2**) is formed smoothly upon cooling (yield is 93 %). Treatment of compound (**2**) with NaN_3 in DMF medium upon heating led to the formation of 1-(azidomethyl)octahydro-2*H*-quinolysine (**3**), which was isolated in 61 % yield as a result of column chromatography on silicagel.



The reaction of lupinylazide (**3**) with arylalkynes [4-methoxyphenylacetylene (**4a**), *m*-tolylacetylene (**4b**)] proceeded smoothly in DMF in the presence of copper sulfate $CuSO_4 \times 5H_2O$ and sodium ascorbate (NaAsc) upon heating to 75 °C (TLC control). (1*S*,9*aR*)-1-[(1,2,3-triazole-1-yl)methyl]octahydro-2*H*-quinolysines (**5a**, **b**), containing aryl substituents at C-4 position of 1,2,3-triazole ring, were isolated by the column chromatography on silicagel.



The high selectivity can be explained by the mechanism of this addition. The principle of the Sharpless catalyst operation is that the resulting monovalent copper, when reacted with acidic terminal acetylene, gives an acetylenide, which selectively coordinates with azides to form 1,4-substituted triazole (“click” reaction technology) [17, 18].

The composition and structure of the synthesized compounds were confirmed by IR, 1H and ^{13}C NMR spectroscopy, mass spectrometry, and X-ray diffraction data. The presence of an azide substituent in structure (**3**) was confirmed by the IR spectrum data (an intense absorption band at 2096 cm^{-1} , corresponding to the stretching vibrations of the azide group).

The 1H and ^{13}C NMR spectra of the synthesized quinolysine 1,2,3-triazoles contain a characteristic set of signals from the quinolysine backbone and the corresponding substituent. In the high-field region (δ 1.17–1.70 ppm), there are broad multiplet signals with an integrated intensity of 8H, which include protons of the lupinine core of both axial and equatorial orientations (H-2*a,e*, 8*a,e*, 9*a,e*, 3*a*, 7*a*).

The multiplet signal (δ 1.70–1.92 ppm) belongs to the equatorially oriented protons H-3,7. Then the axial protons 4, 6 (δ 1.88–2.08 ppm), the nodal proton 9a (δ 2.05–2.18 ppm) and the C-1 proton (δ 2.18–2.30 ppm) resonate. Equatorial protons 4, 6 are represented by a narrow multiplet in the range of δ 2.80–2.88 ppm. The protons of the H-10 methylene group resonate in the form of two doublets of doublets in the range of δ 4.51–4.65 ppm. The proton of 1,2,3-triazole rings in the ^1H NMR spectra of compounds (**5a,b**) corresponds to a singlet signal located in the range of δ 7.37–7.71 ppm. The carbon atoms of the triazole ring in the ^{13}C NMR spectra correspond to signals at 119.3–122.4 (C-5) and 146.2–156.8 ppm (C-4) doublet and singlet, respectively (recording of the spectra in the JMOD mode). These data confirm the formation of 1,4-disubstituted 1*H*-1,2,3-triazoles as a result of the CuAAC reaction.

The mass spectra of all compounds contain peaks of molecular ions of various intensities. In the spectra of all synthesized quinolizidinotriazoles (**5a,b**), there is a peak of the fragmentary $\text{C}_{10}\text{H}_{17}\text{N}$ ion (150–151 a.u.), corresponding to the cleavage of the molecule at the C-10 atom of the quinolizidine backbone.

The spatial structure of (octahydro-2*H*-quinolysine-1-ylmethyl)methanesulfonate (**2**) and 1-[(4-aryl-1,2,3-triazole-1-yl)methyl]octahydro-1*H*-quinolysines (**5a**) and (**5b**) established by the X-ray diffraction method is shown in Fig. 1–3, respectively.

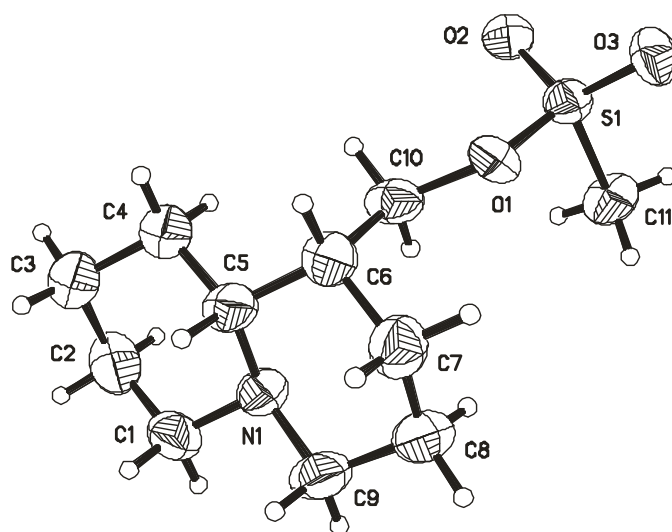


Figure 1. Structure of (octahydro-2*H*-quinolysine-1-ylmethyl)methanesulfonate (**2**) (thermal vibration ellipsoids are shown with a probability of 30%)

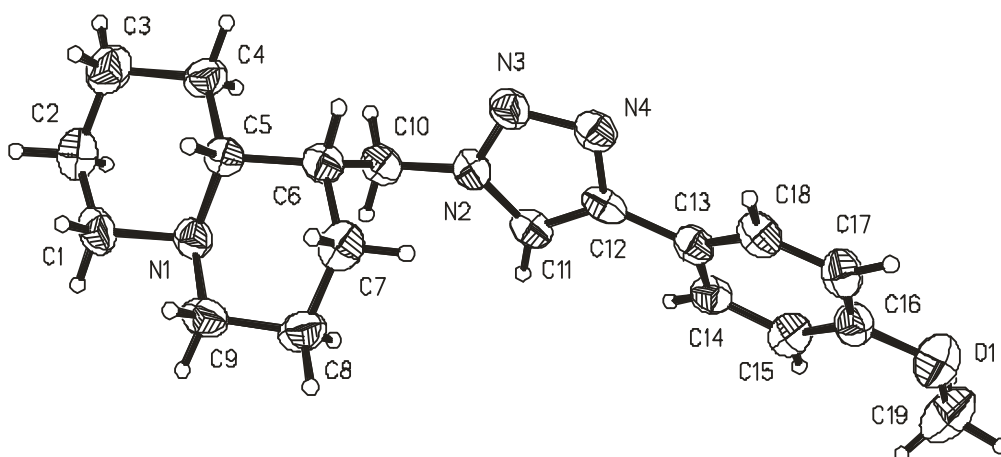


Figure 2. The structure of (1*S*,9*aR*)-1-[[4-(4-methoxyphenyl)-1*H*-1,2,3-triazole-1-yl]methyl]octahydro-2*H*-quinolysine (**5a**) (thermal vibration ellipsoids are shown with a probability of 30%)

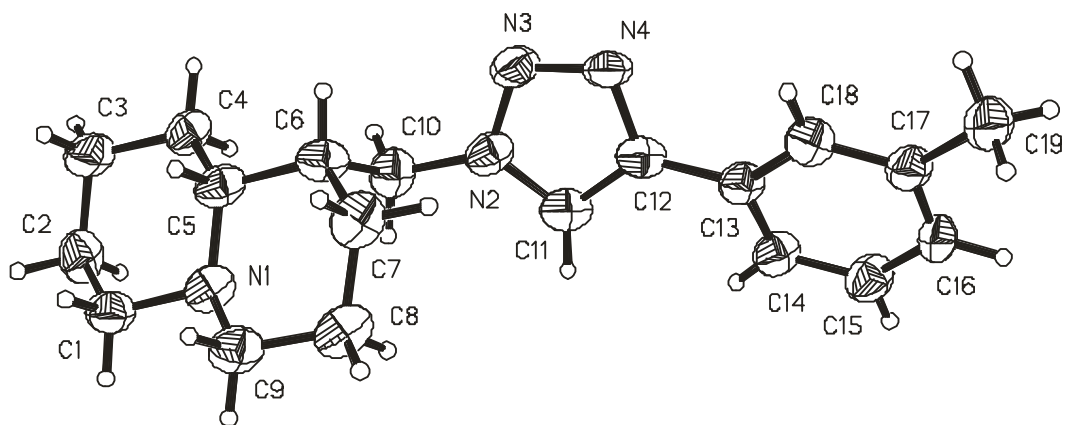


Figure 3. The structure of (1*S*,9*aR*)-1-[[4-(*m*-tolyl)-1*H*-1,2,3-triazole-1-yl]methyl]octahydro-1*H*-quinolizidine (**5b**) (thermal vibration ellipsoids are shown with a probability of 30%)

The configurations of the C5 and C6 chiral centers are correlated with the absolute one in the crystal structure of lupinine chloride [19]. It follows from the data obtained that the bond lengths and bond angles in compounds (**2**), (**5a**), and (**5b**) are close to the usual ones [20]. The conformations of the six-membered rings N1, C1... C5 (A) and N1, C5... C9 (B) in the quinolizidine framework in compounds (**2**), (**5a**), and (**5b**) are close to those in the crystal structure of lupinine [19, 20]. Data on intracyclic torsion angles and parameters of asymmetry of cycles [19] are given in Table 1. Cycles A and B in two crystallographically independent molecules (**2-1**) and (**2-2**) of compound (**2**) as well as (**5a-1**) and (**5a-2**) of compound (**5a**), as well as in molecule (**5b**), are in a conformation close to a somewhat distorted chair.

In crystal (**2**), molecules (**2-1**) and (**2-2**) have different orientations of the sulfonyl group, namely the C5-C6-C10-O1 torsion angles are 177 and 76°, respectively. In two independent crystal molecules (**5a**) and in crystal (**5b**), the orientation of the 1,2,3-triazole ring is the same, namely the C6-C10-N2-N3 torsion angles are 53, 63, and 58°, respectively. The 1,2,3-triazole and phenyl rings in the molecules of compounds (**5a**) and (**5b**) are planar with an accuracy of no more than ± 0.013 Å. The angles between the planes of the triazole and aryl substituents are 23 and 21° in crystal (**5a**) and 27° in crystal (**5b**).

Table 1

Intracyclic torsion angles (τ , deg.) in compounds (**2**), (**5a**) and (**5b**)

Compound	(2-1)	(2-2)	(5a-1)	(5a-2)	(5b)	Lupinine
Angle	τ					
Cycle N1-C1-C2-C3-C4-C5 (A)						
N1-C1-C2-C3	-58(2)	-59(2)	-57(1)	-58(1)	-58(2)	-56.2
C1-C2-C3-C4	55(2)	58(2)	56(1)	55(1)	56(2)	52.9
C2-C3-C4-C5	-55(2)	-57(2)	-57(1)	-57(1)	-57(2)	-54.3
C3-C4-C5-N1	56(2)	54(1)	59(1)	60(1)	58(2)	56.7
C4-C5-N1-C1	-54(2)	-52(1)	-58(1)	-60(1)	-59(1)	-57.8
C5-N1-C1-C2	57(2)	55(2)	58(1)	60(1)	60(1)	58.9
Asymmetry parameter (ΔC_{\min} , deg.)	$\Delta C_s^1=1.0$ $\Delta C_2^{1,2}=1.5$	$\Delta C_s^2=1.7$ $\Delta C_2^{2,3}=1.6$	$\Delta C_s^2=1.0$ $\Delta C_2^{2,3}=0.7$	$\Delta C_s^3=1.6$ $\Delta C_2^{2,3}=0.7$	$\Delta C_s^3=0.8$ $\Delta C_2^{3,4}=1.6$	$\Delta C_s^3=1.1$ $\Delta C_2^{2,3}=2.1$
Cycle N1-C5-C6-C7-C8-C9 (B)						
C9-N1-C5-C6	55(2)	58(1)	57(1)	60(1)	59(1)	56.5
N1-C5-C6-C7	-54(2)	-59(1)	-55(1)	-56(1)	-57(1)	-54.5
C5-C6-C7-C8	54(2)	57(2)	54(1)	55(1)	54(2)	53.6
C6-C7-C8-C9	-55(2)	-53(2)	-57(1)	-57(1)	-53(2)	-54.9
C7-C8-C9-N1	58(2)	55(2)	59(1)	61(1)	56(2)	58.1
C5-N1-C9-C8	-58(2)	-59(2)	-60(1)	-62(1)	-59(2)	-58.9
Asymmetry parameter (ΔC_{\min})	$\Delta C_s^6=0.0$ $\Delta C_2^{5,6}=2.2$	$\Delta C_s^5=1.7$ $\Delta C_2^{7,8}=1.4$	$\Delta C_s^6=0.8$ $\Delta C_2^{6,7}=2.0$	$\Delta C_s^6=1.9$ $\Delta C_2^{6,7}=1.0$	$\Delta C_s^7=0.8$ $\Delta C_2^{7,8}=2.0$	$\Delta C_s^6=1.2$ $\Delta C_2^{6,7}=1.2$

The main crystallographic data and characteristics of the X-ray diffraction experiment of compounds (**2**), (**5a**) and (**5b**) are presented in Table 2. The X-ray structural analysis data were deposited in the form of a CIF file at the Cambridge Crystallographic Data Center (deposit CCDC 2087146).

Table 2

Crystallographic data and characteristics of an X-ray diffraction experiment for compounds (**2**), (**5a**) and (**5b**)

Compound	(2)	(5a)	(5b)
Molecular formula	C ₁₁ H ₂₁ NO ₃ S	C ₃₈ H ₅₂ N ₈ O ₂	C ₁₉ H ₂₆ N ₄
<i>M</i>	247.35	652.87	309.43
Syngonia	Triclinic	Monoclinic	Monoclinic
<i>T</i> , K	293	293	293
<i>a</i> , Å	5.435(3)	5.5545(5)	19.692(4)
<i>b</i> , Å	8.766(3)	17.804(2)	5.6186(9)
<i>c</i> , Å	14.395(5)	17.840(2)	16.185(3)
α , degrees	97.90(3)	90	90
β , degrees	98.95(4)	98.95(4)	104.80(2)
γ , degrees	103.60(4)	90	90
<i>V</i> , Å ³ ; <i>Z</i>	647.6(5); 2	1762.6(3); 2	1731.4(6); 4
Space group	P1	P2 ₁	I2
<i>D</i> _{calc.} , g/cm ³	1.268	1.230	1.191
μ , mm ⁻¹	2.180	0.618	0.558
Number of measured reflections	3594	7368	7134
Number of independent reflections	2746 R(int) = 0.0826)	5281 (R(int) = 0.0939)	3358 (R(int) = 0.0203)
Reflections observed (<i>I</i> ≥ 2σ(<i>I</i>))	1493	3088	1225
Number of refined parameters	292	436	210
<i>T</i> _{min} , <i>T</i> _{max} (multiscan)	0.38568, 1.00000	0.92224, 1.00000	0.37817, 1.00000
<i>F</i> (000)	268	704	284
Area θ , degrees	5.279 ≤ θ ≤ 76.035	3.509 ≤ θ ≤ 76.092	2.916 ≤ θ ≤ 27.934
<i>R</i> ₁ , <i>wR</i> ₂ (<i>I</i> ≥ 2σ(<i>I</i>))	0.0826, 0.1956	0.0935, 0.2264	0.1080, 0.2861
<i>R</i> ₁ , <i>wR</i> ₂ (whole array)	0.1269, 0.2444	0.1333, 0.2786	0.1968, 0.3817
Goof	0.963	1.057	0.983
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$, e/Å ³	0.298, -0.624	0.411, -0.209	0.261, -0.226

Conclusion

In this work, the optimal conditions for the modification of the structure of the alkaloid lupinine at the hydroxymethylene group C-1 of the quinolizidine backbone have been proposed and developed. As a result of these studies, potentially bioactive 1,2,3-triazole derivatives of lupinine have been obtained for the first time in high yields. The application of the “click”-reaction technique allowed the synthesis of lupinine azide and its 1,3-dipolar [3+2]-cycloaddition to various alkynes.

The reactions were carried out in the presence of an aqueous solution of CuSO₄ and sodium ascorbate in DMF. The developed conditions allowed the corresponding 4-substituted (1*S*,9*aR*)-1-[(1,2,3-triazol-1-yl)methyl]octahydro-2*H*-quinolysines to be synthesized in good yields. New synthesized lupinine derivatives with a 1,2,3-triazole fragment can provide additional ligand-receptor interactions of a biologically active substrate, and thereby change the selectivity of the substrate biological action. The complex use of modern physicochemical methods, namely one-dimensional ¹H-, ¹³C- NMR spectra and two-dimensional COSY (¹H-¹H) and HMQC (¹H-¹³C) spectra, as well as XRD analysis made it possible to unambiguously establish the structure of the new 4-substituted (1*S*,9*aR*)-1-[(1,2,3-triazol-1-yl)methyl]octahydro-1*H*-quinolysines of lupinine. X-ray structural analysis data for synthesized compounds were deposited in the form of CIF files at the Cambridge Crystallographic Data Center (CCDC deposit for **2** is 2087144, for **5a** is 2087145, for **5b** is 2087146).

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Лупининнің 4-орынбасылған (1*S*,9*aR*)-1-[(1,2,3-триазол-1-ил)метил]- октагидро-1*H*-хинолизиндерінің синтезі және құрылысы

Мақалада лупинин алкалоидының 1,4-алмастырылған 1*H*-1,2,3-триазол туындылары қатарының синтездеу және рентгендік құрылымдық ерекшеліктерін зерттеу нәтижелері келтірілген. Лупинин алкалоидының химиялық модификациясы хинолизин қаңқасының С-1 орналасқан гидроксиметилден тобы бойынша жүзеге асырылды. Реакциялар бірнеше кезеңде жүргізілді. Лупининнің метансульфохлаоридпен хлорлы метилденде триэтиламин қатысуымен өзара әрекеттесуі кезінде жоғары шығымдылығы бар (93 %) (октагидро-2*H*-хинолизин-1-илметил)метансульфонат оңай түзілетіні көрсетілген. Осы қосылысты диметилформаид ерітіндісінде натрий азидімен ары қарай қыздырып өңдеу нәтижесінде 61% шығыммен 1-(азидометр)октагидро-2*H*-хинолизиннің түзілуі жүреді. Жаңа азидтің сулы CuSO₄ және натрий аскорбаты қатысуымен диметилформаид ерітіндісінде әртүрлі сипаттағы терминалды алкиндермен өзара әрекеттесуі кезінде сәйкес 4-алмастырылған (1*S*,9*aR*)-1-[(1,2,3-триазол-1-ил)метил]октагидро-1*H*-хинолизиндер түзілуі мүмкін екендігі анықталды. Триазол циклінің С-4 жағдайында әртүрлі арил алмастырғыштары бар лупининнің жаңа 1,2,3-триазол туындылары алынды. Реакцияның жоғары селективтілігі Шарплес катализаторының әсер ету механизмімен түсіндіріледі. Рентгенқұрылымдық талдау әдісімен лупинин метансульфонаты, 4-арилтриазолилметил-октагидрохинолизиндер молекулаларының кеңістіктік құрылымы анықталды. CIF файлдары түріндегі жаңа қосылыстарды рентгенқұрылымдық талдау деректері Кембридждегі кристаллқұрылымдық деректер орталығында сақталған.

Кілт сөздері: хинолизинді алкалоидтар, лупинин, азидтер, триазолдар, метансульфонил хлориді, терминалды алкиндер, 1,3-диполярлы циклоқосылу реакциясы, РҚА.

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Синтез и строение 4-замещенных (1*S*,9*aR*)-1-[(1,2,3-триазол- 1-ил)метил]октагидро-1*H*-хинолизинов лупинина

В статье приведены результаты исследований синтеза и рентгеноструктурному исследованию особенностей строения ряда 1,4-дизамещенных 1*H*-1,2,3-триазоловых производных алкалоида лупинина. Химическая модификация алкалоида лупинина осуществлялась по гидроксиметиленовой группе в положении С-1 хинолизинового остова. Реакции проводились в несколько стадий. Показано, что при взаимодействии лупинина с метансульфохлаоридом в присутствии триэтиламина в хлористом метиле не гладко образуется (октагидро-2*H*-хинолизин-1-илметил)метансульфонат с высоким выходом (93 %). Последующая обработка данного соединения действием азидата натрия в среде диметилформаиды при нагревании приводит к образованию 1-(азидометил)октагидро-2*H*-хинолизина с выходом 61 %. Установлено, что при взаимодействии нового азидата с терминальными алкинами различной природы в присутствии водного CuSO₄ и аскорбата натрия в диметилформаиде могут быть образованы соответствующие 4-замещенные (1*S*,9*aR*)-1-[(1,2,3-триазол-1-ил)метил]октагидро-1*H*-хинолизины. Получены новые 1,2,3-триазоловые производных лупинина, содержащие различные арильные заместители в положении С-4 триазольного цикла. Высокая селективность реакции объяснена механизмом действия катализатора Шарплеса. Методом рентгеноструктурного анализа установлено пространственное строение молекул метансульфоната лупинина, 4-арилтриазолилметил-октагидрохинолизинов. Данные рентгеноструктурного анализа новых соединений в виде CIF файлов депонированы в Кембриджском центре кристаллоструктурных данных.

Ключевые слова: хинолизиновые алкалоиды, лупинин, азиды, триазолы, метансульфонил хлорид, терминальные алкины, реакция 1,3-диполярного циклоприсоединения, РСА.

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