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Synthesis, Structure, and Biological Activity of Cinnamoyl-Containing Cytisine and Anabasine Alkaloids Derivatives

O. A. Nurkenov[a]*, Zh. S. Nurmaganbetov[a, b], T. M. Seilkhanov[c], S. D. Fazylov[a], Zh. B. Satpayeva[a], K. M. Turdybekov[d], S. A. Talipov[e], and R. B. Seydakhmetova[f]

[a] *Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, ul. Alikhanova 1, Karaganda, 100008 Kazakhstan*
**e-mail: nurkenov_oral@mail.ru*
[b] *Karaganda State Medical University, Karaganda, Kazakhstan*
[c] *Sh. Ualikhanov Kokshetau State University, Kokshetau, Kazakhstan*
[d] *E.A. Buketov Karaganda State University, Karaganda, Kazakhstan*
[e] *A.S. Sadykov Institute of Bioorganic Chemistry, Academy of Sciences of the Republic of Uzbekistan, Tashkent, Uzbekistan*
[f] *International Research and Production Holding "Phytochemistry", Karaganda, Kazakhstan*

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Abstract—The reactions of the cytisine and anabasine alkaloids with cinnamic acid chloride have been studied, and hydrazinolysis of the resulting *N*-cinnamoylcytisine and *N*-cinnamoylanabazine has been carried out. The reaction of cinnamoyl isothiocyanate with alkaloids has afforded the corresponding thiourea derivatives. Antimicrobial and cytotoxic activity of cinnamoyl-containing derivatives of these alkaloids has been evaluated.

Keywords: cytisine, anabasine, *N*-cinnamoylcytisine, *N*-cinnamoylanabasine, cinnamoyl chloride

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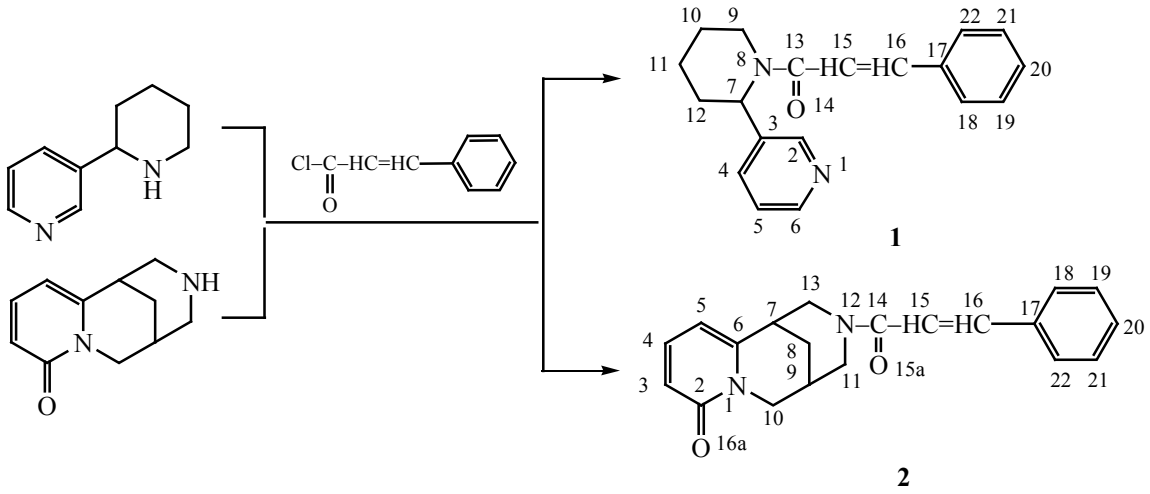
The interest to the study of chemical transformations of alkaloids cytisine and anabasine has been inspired by wide range of biological activity of their derivatives. Many derivatives of cytisine and anabasine bearing different substituents at the nitrogen atom [1–3] including the acryloyl groups [4] have been prepared. It has been shown that the substitution of the N–H hydrogen atom with an acyl group results in the decrease in toxicity and appearance of other peculiar biological properties [5]. Many cinnamoyl derivatives have been recommended as drugs for the treatment or prevention of arterial and/or venous thrombosis, acute coronary syndrome, restenosis, stable pectoris, cardiac rhythm disturbance, myocardial infarction, hypertensia, heart failure, and apoplexy [6, 7]. The interaction of cytisine with cinnamoyl chloride in toluene has been reported [8]; the product has been obtained in low yield (45%). The preparation of a similar derivative of anabasine has not been reported.

To extend the range of reactions on cytisine and anabasine N-acylation, we investigated their interaction with cinnamoyl chloride and further transformations of the formed *N*-cymmanoylcytisine and *N*-cynnamoylanabasine. Acylation of the alkaloids was performed in benzene in the presence of triethylamine at room temperature. The interaction occurred smoothly and afformed the derivatives of anabasine (**1**) and cytisine (**2**) with yield 75 and 95%, respectively (Scheme 1). The synthesized compounds **1** and **2** were white crystalline compounds readily soluble in organic solvents.

The structure of compounds **1** and **2** was confirmed by the data of IR spectroscopy, NMR spectroscopy [^{1}H, ^{13}C, COSY (^{1}H–^{1}H), and HMQC (^{1}H–^{13}C)], and X-ray diffraction analysis (for *N*-cynnamoylanabasine **1**). IR spectra of compounds **1** and **2** contained the absorption band of the amide carbonyl at 1648 and 1643 cm^{-1}, respectively. The ^{1}H NMR data suggested the presence of several rotamers (with respect to the N–CO и CO–CH=CH–C_6H_5 bonds) in solutions of *N*-cynnamoylanabasine **1** and *N*-cynnamoylcytisine **2**. Since the rotation barriers were low, they could result either to the appearance of the spectra signals assignable to several conformers or to the lines broadening. In certain cases, that did not allow unambiguous assignment of the signals.

Scheme 1.



Let us consider the ^{1}H NMR spectrum of compound **1** in more detail. It contained the signals of piperidine ring as multiplets at 1.30–1.42 (1H, H^{11ax}), 1.54–1.57 (2H, $H^{11eq,10ax}$), 2.36–2.46 (1H, H^{12ax}), and 3.43–3.46 (1H, H^{9ax}) ppm and broadened singlets at 1.79 (1H, H^{10eq}), 2.87 (1H, H^{12eq}), 4.22 (1H, H^{9eq}), and 5.87 (1H, H^{7}) ppm. The unsaturated aliphatic protons H^{15} and H^{16} were manifested as a multiplet at 7.56–7.69 ppm. The aromatic phenyl and pyridine protons resonated as multiplets at 7.30–7.34 (5H, $H^{5,18,19,21,22}$), 7.56–7.69 (2H, $H^{4,20}$), and 8.44–8.47 (2H, $H^{2,6}$) ppm.

^{13}C NMR spectrum of compound **1** contained the signals of the piperidine ring atoms at 19.72 (C^{11}), 26.19 (C^{10}), 27.61 (C^{12}), 48.23 (C^{9}), and 49.84 (C^{7}) ppm. The atoms of the phenyl and pyridine fragments were observed at 124.13 (C^{5}), 128.58 (C^{3}), 128.80 (C^{20}), 129.23 ($C^{19,21}$), 130.05 ($C^{18,22}$), 134.92 (C^{4}), 135.68 (C^{17}), 148.28 (C^{6}), and 148.65 (C^{2}) ppm. The signals at 118.83 and 142.68 ppm were assigned to the carbon atoms at the double bond: C^{15} and C^{16}, respectively. A weak-field signal at 166.27 ppm was assigned to the carbonyl group carbon (C^{13}).

The structure of compound **1** was further confirmed by means of two-dimensional ^{1}H–^{13}C HMQC NMR spectroscopy revealing the heteronuclear spin-spin interactions. The observed correlations are shown in Fig. 1. Heteronuclear interactions of the protons with the adjacent carbon atoms were revealed for the following atoms: H^{11}/C^{11} (1.56, 20.37), H^{10}/C^{10} (1.60, 26.65), H^{12}/C^{12} (2.34, 28.02), H^{9}/C^{9} (4.24, 42.78), H^{7}/C^{7} (5.90, 50.36), H^{5}/C^{5} (7.31, 124.58), $H^{18,19,20,21,22}/C^{18,19,20,21,22}$ (7.28, 129.33), H^{15}/C^{15} (7.60, 119.22), H^{4}/C^{4} (7.55, 135.27), H^{16}/C^{16} (7.56, 143.13), and $H^{2,6}/C^{2,6}$ (8.45, 148.86).

Spatial structure of *N*-cymmanoylanabasine **1** was elucidated by means of X-ray diffraction analysis. General view of the molecule is shown in Fig. 2. Bond lengths and bond angles in the compound **1** were close to usual ones [11]. As is seen from Fig. 2, the pyridine ring in the molecule of compound **1** was in axial orientation with respect to the piperidine one. The X-ray diffraction analysis data for anabasine hydroiodite [12] have shown that anabasine cation takes a single conformation: the piperidine cycle in the *chair* conformation with equatorial orientation of the pyridine ring. This has been confirmed by means of molecular mechanics simulation. The substitution of the N–H hydrogen of the piperidine ring with bulkier methyl group has not changed the conformation of N^{7}-methylanabasine [13].

At the same time, the conformation of the piperidine ring in compound **1** was close to the ideal *chair* [ΔC_S^9 = 1.1° and $\Delta C_2^{7,8}$ = 1.1° (max)], whereas it was somewhat distorted in compound **3** due to the presence of a bulkier substituent [ΔC_S^8 = 2.7° (max) и $\Delta C_2^{8,9}$ = 2.8° (max)]. The N^{7} atom in the molecule of compound **3** took pyramidal configuration (sum of bond angles 328.2°).

The unusual orientation of the pyridine ring with respect to the piperidine one revealed in compound **1** has been earlier observed in the structure of anabasino-*N*-ethylthiocarbamide and has been ascribed to the steric hindrance between the ethylaminothiocarbonyl group and the pyridine ring [14]. Fairly strong van der Waals interaction was observed in compound **1** as well (the $H^{8}\cdots H^{14}$ contact 1.88 Å, sum of the van der Waals radii being 2.32 Å [15]). However, the rotation about the N^{7}–C^{13} bond did not lead to more favorable conformation, due

Fig. 1. Correlations in the HMQC spectrum of compound **1**.

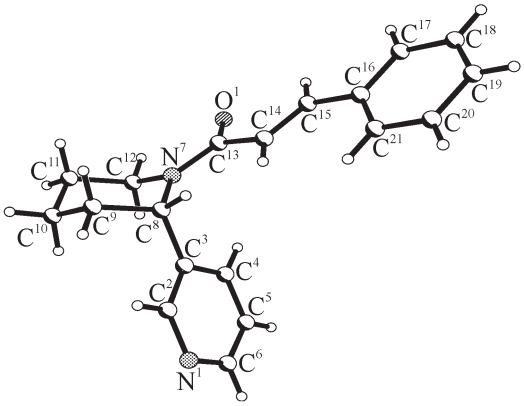
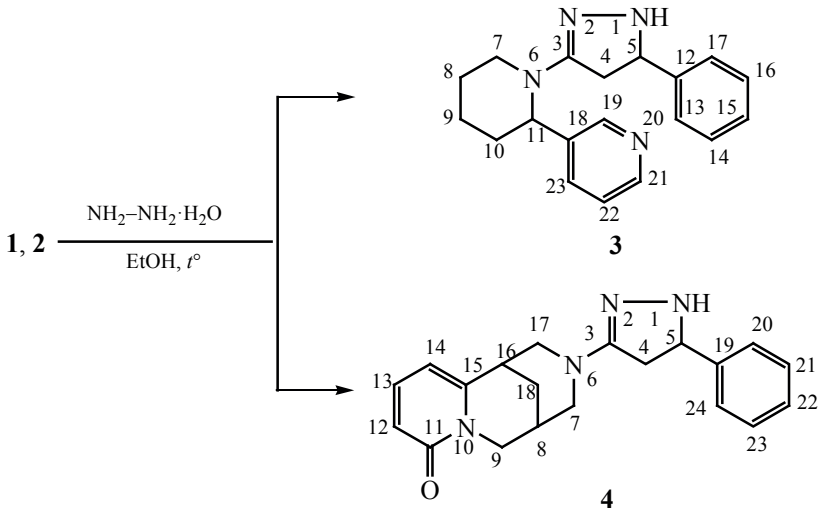


Fig. 2. General view of compound **1** molecule in the crystal.

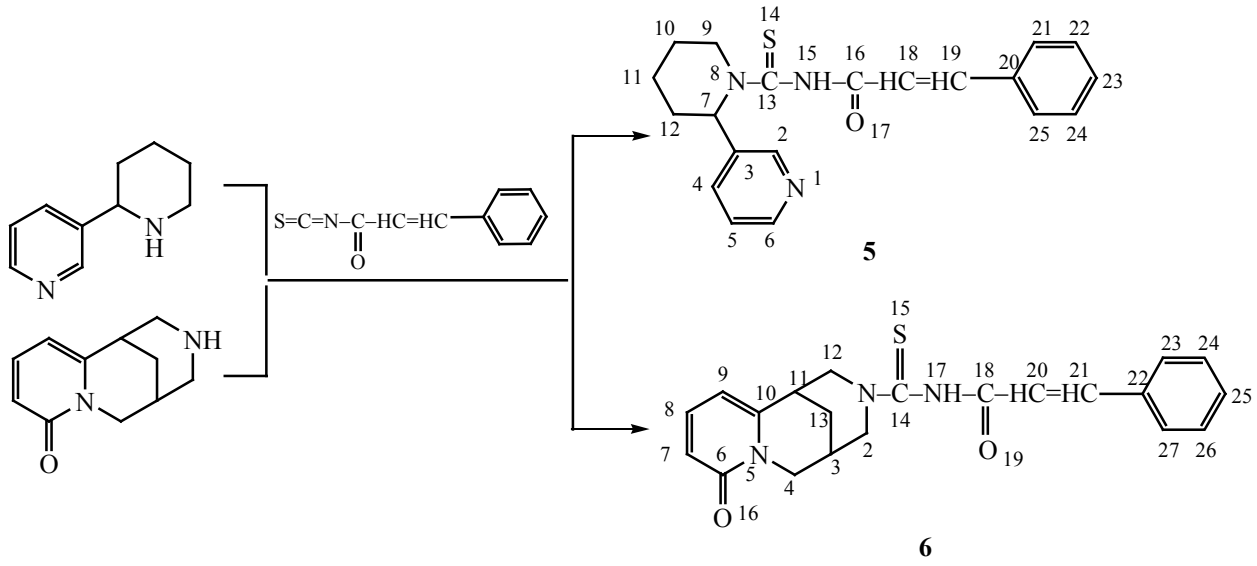
to conjugation of the *p*-orbitals of the C^{13}=C and C^{13}=O^1 double bonds. Moreover, the conjugation of the C^{13}=O^1 double bond and the lone-electron pair of the N^7 atom was observed (mesomeric effect). The latter interaction led to the change in the pyramidal configuration of the N^7 atom into the planar-trigonal one (sun of bond angles 359.8°), and the piperidine ring conformation was significantly distorted [$\Delta C_S^9 = 3.9°$ (max) and $\Delta C_2^{8,9} = 4.1°$ (max)]. It should be noted that the O^1, C^{13}, N^7, C^8, C^{12}, C^{14}, and C^{15} atoms in compound **1** were located almost in the same plane (±0.02 Å) due to the π-conjugation and mesomeric effect.

^{1}H and ^{13}C chemical shifts of the cinnamoyl fragments bound to the anabasine and cytisine moieties were similar. Slight predominance of the mesomeric effect of the cytisine fragment led to small downfield shift of the signals of compound **2** in comparison with derivative **1**. For example, the H^{15} and H^{16} olefinic protons of the cinnamoyl moiety appeared at 6.49–6.75 and 7.16–7.64 ppm, respectively, in the spectrum of compound **2**, whereas the spectrum of compound **1** contained those signals at 7.56–7.69 ppm. The same effect was observed for the C^{13} carbonyl atoms: they were assigned to the signals at 166.27 ppm (compound **1**) and 165.65 ppm (compound **2**).

Scheme 2.



Scheme 3.



Cyclocondensation of hydrazines with α,β-unsaturated ketones is an important synthetic route to 1,2-azoles. Certain derivatives of pyrazoles can serve as analgesics and inhibitors of platelet aggregation [16] and exhibit strong antibacterial [17] or anaesthetic [18] effect.

Further investigation of synthesis and biological activity of the obtained N-cinnamoyl derivatives **1** and **2** involved their interaction with hydrazine hydrate (Scheme 2). It was found that the interaction of compounds **1** and **2** with hydrazine hydrate in ethanol resulted in the formation of the respective pyrazole derivatives **3** and **4**, likely due to intramolecular cyclocondensation of the hydrazones.

To extend the capacity of cytisine and anabasine functionalization, it was interesting to obtain their novel acyl derivatives via the interaction with cinnamoyl isothiocyanate. The latter was synthesized via the reaction between cinnamoyl chloride with potassium thiocyanate in acetone at heating. The prepared cinnamoyl isothiocyanate reacted with anabasine and cytisine to afford the respective derivatives **5** and **6** (Scheme 3).

Compounds **5** and **6** were white crystalline solids exhibiting moderate solubility in organic solvents. Structure and purity of compounds **5** and **6** were confirmed by means of IR and ^{1}H NMR spectroscopy as well as thin-layer chromatography. IR spectra of compounds **5** and **6** contained an absorption band at 1465 and 1550 cm^{-1}, characteristic of the C=S group. Absorption bands of the amide group were observed at 1691 and 1689 cm^{-1}. IR spectrum of compound **6** contained a strong band of the cytisine amide group (N–C=O) at 1648 cm^{-1}. ^{1}H NMR spectra of compounds **5** and **6** contained the typical signals of the fragments in their suggested structures.

To reveal the biological activity of the prepared alkaloids derivatives, we performed primary screening of antimicrobial (Table 1) and cytotoxic (Table 2) effects of compounds **1**–**6** (Table 1). The antimicrobial activity with respect to Gram-positive (*Staphylococus aureus, Bacillus subtilis*) and Gram-negative (*Escherichia coli*) strains as well as *Candida ablicans* yeast fungus was assessed by diffusion in agar. The reference drugs were Gentamycin for the bacteria and Nystatin for *C. ablicans*. Antimicrobial activity of compounds **1**–**6** was determined from the diameter of the growth suppression zones; each experiment was performed in triplicate [19]. The cytotoxic activity was determined during the *in vitro* cultivation of the *Artemia salina* (*Leach*) larva [20, 21] (Table 2).

The performed primary screening revealed moderate antimicrobial activity of compounds **1** and **3** against Gram-positive *Staphylococcus aureus,* Gram-negative *Escherichia coli*, and *Candida albicans* yeast fungus. Compound **2** revealed moderate antibacterial activity against the Gram-negative *Escherichia coli* strain. Compounds **4**–**6** revealed weak antimicrobial activity against the tested strains. Compounds **1** and **3** revealed moderate cytotoxicity against *Artemia salina* (*Leach*) larva.

In summary, we prepared novel N-cinnamoyl and pyrazole derivatives of anabasine and cytisine and investigated their further chemical transformations into potentially biologically active compounds.

Table 1. Antimicrobial activity of compounds **1–6**[a]

Compound	*S. aureus*	*B. subtilis*	*E. coli*	*C. Albicans*
1	18±0.2	14±0.2	20±0.1	20±0.2
2	12 ±0.2	–	16 ±0.1	14±0.1
3	17±0.1	13±0.2	18±0.2	20±0.1
4	14±0.1	–	13±0.2	–
5	–	–	11±0.1	13±0.2
6	–	–	12±0.2	–
Gentamycin	24 ± 0.1	21± 0.1	26± 0.1	–
Nystatin	–	–	–	21 ± 0.2

[a] "–" denotes the absence of the growth suppression zone. Diameter of the growth suppression zone less than 10 mm or its absence was considered no antibacterial activity, diameter of the growth suppression zone of 10–15 mm was considered weak activity, diameter of the growth suppression zone of 15–20 mm was considered moderate activity, diameter of the growth suppression zone more than 20 mm was considered pronounced activity.

Table 2. Cytotoxicity of compounds **1–6**

Compound	*c*, μg/mL	Number of alive larva, run			LD_{50}, μg/mL
		1	2	3	
1	1	9	9	9	62.18
	10	7	6	8	
	100	4	4	5	
2	1	10	8	9	–
	10	9	7	7	
	100	4	5	5	
3	1	9	8	8	59.36
	10	6	6	7	
	100	4	4	5	
4	1	10	8	8	–
	10	6	7	7	
	100	6	4	4	
5	1	10	10	10	–
	10	10	9	9	
	100	8	8	7	
6	1	9	9	9	–
	10	8	7	8	
	100	8	7	8	
DMSO	1	10	10	10	930.27
	10	10	9	9	
	100	8	8	9	

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded using a JNN-ECA Jeol 400 spectrometer (399.78 and 100.53 MHz, respectively) in DMSO-d_6. The reaction progress and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates [isopropanol–ammonia–water (7 : 2 : 1) or ethanol–chloroform (1 : 4); development in iodine vapor]. The products were isolated via recrystallization or column chromatography on alumina. The solvents were purified and dried via conventional procedures [22].

X-ray diffraction analysis. Unit cell parameters and intensity of 2745 reflections (2148 of them being independent, $R_{int} = 0.0285$) were measured using an Xcalibur Ruby diffractometer (Oxford Diffraction) (CuK_α, graphite monochromator, ω-scanning, $5.60° \le \theta \le 76.05°$) at 293 K. Crystals of compound **1** were monoclinic, $C_{19}H_{20}N_2O$, unit cell parameters: a = 8.213(1) Å, b = 9.895(1) Å, c = 10.4238(9) Å, β = 106.03(1)°, V = 814.3(2) Å^3, Z = 2, space group $P2_1$, d_{calc} = 1.192 g/cm^3, μ = 0.582 mm^{-1}. The raw data processing (including accounting for absorbance) was performed using CrysAlisPro software [23]. The structure was solved via direct method. The positions of non-hydrogen atoms were refined via full-matrix least squares method under anisotropic approximation. The hydrogen atoms were placed in the geometry-calculated positions and refined under isotropic approximation with fixed position and heat parameters (the *rider* model). Configuration of the molecule was correlated with the known absolute configuration of anabasine hydrochloride and hydroiodite [14]. The calculations used 1229 independent reflections with $I \ge 2\sigma(I)$, refining 200 parameters. Final divergence factors: R_1 = 0.0535, wR_2 = 0.1051 [over reflections with $I \ge 2\sigma(I)$], R_1 = 0.1020, wR_2 = 0.1347 (over all reflections), GooF = 1.015. Residual electron density peaks: Δρ = 0.101 and –0.100 e/Å^3. The structure was solved and refined using SHELXS [24] and SHELXL-2018.3 [25] software. The X-ray diffraction data were deposited at the Cambridge Crystallographic Data Centre (CCDC 1905735).

***N*-Cinnamoylanabasine (1).** 1.81 g (0.018 mol) of triethylamine and a solution of 3.0 g (0.018 mol) of cinnamoyl chloride in 50 mL of benzene were added at stirring to a solution of 3 g (0.018 mol) of anabasine in 150 mL of benzene. The reaction mixture was stirred during 3 h at room temperature until the precipitate formation. Precipitate of triethylammonium chloride was filtered off, the filtrate was evaporated, and the residue was purified by chromatography on alumina (eluents: benzene or 100 : 1 benzene–ethyl acetate). Yield 3.9 g (75%), white crystals, mp 96–98°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.30–1.42 m (1H, H^{11ax}), 1.54–1.57 (2H, H^{11eq,10ax}), 1.79 br. s (1H, H^{10eq}), 2.36–2.46 m (1H, H^{12ax}), 2.87 br. s (1H, H^{12eq}), 3.43-3.46 m (1H, H^{9ax}), 4.22 br. s (1H, H^{9eq}), 5.87 br. s (1H, H^7), 7.30–7.34 m (5H, H^{5,18,19,21,22}), 7.56–7.69 m (4H, H^{4,15,16,20}), 8.4–8.47 m (2H, H^{2,6}). ^{13}C NMR spectrum, δ_C, ppm: 19.72 (C^{11}), 26.19 (C^{10}), 27.61 (C^{12}), 48.23 (C^9), 49.84 (C^7), 118.83 (C^{15}), 124.13 (C^5), 128.58 (C^3), 128.80 (C^{20}), 129.23 (C^{19,23}), 130.05 (C^{18,22}), 134.92 (C^4), 135.68 (C^{17}), 142.68 (C^{16}), 148.28 (C^6), 148.65 (C^2), 166.7 (C^{13}).

***N*-Cinnamoylcytisine (2)** was prepared similarly from 1.14 g (0.006 mol) of cytisine, 0.6 g (0.006 mol) of triethylamine, and 1 g (0.006 моль) of cinnamoyl chloride. Yield 1.82 g (95%), white powder, mp 132–134°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.86–1.97 m (2H, H^{8,8}), 2.44 br. s (1H, H^9), 2.90–3.40 m (3H. H^{7,11ax,13ax}), 3.63–3.97 m (2H, H^{10ax,10eq}), 4.24–4.65 m (2H, H^{11eq,13eq}), 6.14 d (2H, H^{3,5}, ^3J = 6.1), 6.49–6.75 m (1H, H^{15}), 7.16–7.64 m (7H, H$^{4,15,18–22}$). ^{13}C NMR spectrum, δ_C, ppm: 25.95 (C^8), 27.86 (C^9), 35.13 (C^7), 49.05 (C^{10}), 51.31 (C^{11}), 53.04 (C^{13}), 105.29 (C^5), 116.40 (C^3), 128.85 (C^{15}), 129.24 (C^{18,19,21,22}), 129.99 (C^{20}), 135.55 (C^4), 139.09 (C^{16}), 141.32 (C^{17}), 150.47 (C^6), 162.66 (C^2), 165.65 (C^{14}). ^{1}H–^{13}C HMQC NMR spectrum, ppm: H^8/C^8 1.96/26.60, H^9/C^9 2.44/28.48, H^7/C^7 3.13/35.65, H^{10ax}/C^{10ax} 3.59/49.56, H^{10ax}/C^{10ax} 3.98/49.58, H^5/C^5 6.14/105.76, H^3/C^3 6.12/116.82, H^{18,19,21,22}/C^{18,19,21,22} 7.37/129.52).

3-[1-(5-Phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-piperidin-2-yl]pyridine (3). 1.9 mL (39 mmol) of hydrazine hydrate was added dropwise to a solution of 2.33 g (7.9 mol) of compound **1** in 100 mL of ethanol. The reaction mixture was stirred during 1 h at 25°C and 7 h at 70–75°C, cooled to ambient, and evaporated. The residue was dissolved in 300 mL of $CHCl_3$, washed with water (3×60 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on alumina (eluents: benzene and 100 : 1 benzene–chloroform). Yield 2.1 g (87%), yellow-green oil. ^{1}H NMR spectrum, δ, ppm: 1.31–1.52 m (1H, H^{9ax}), 1.53–1.61 m (3H, H^{8ax,10ax,9eq}), 1.70–1.88 m (1H, H^{8eq}), 2.18–2.40 m (1H, H^{10eq}), 2.76–2.84 m (2H, H^{4ax,7ax}), 2.96–2.98 m (1H, H^{7eq}), 3.58–3.65 m (2H, H^{4eq,11}), 4.58 br. s (1H, H^1), 5.12–5.21 m (1H, H^5), 7.18–7.22 m (3H, H$^{14–16}$), 7.25–7.37 m (4H, H^{13,17,22,23}),

8.40–8.50 m (2H, $H^{19,21}$). ^{13}C NMR spectrum, δ_C, ppm: 19.43 (C^9), 25.93 (C^8), 26.96 (C^{10}), 42.12 (C^{11}), 42.14 (C^4), 49.01 (C^7), 70.49 (C^5), 126.29 ($C^{14–16}$), 127.58 ($C^{15,21}$), 128.61 ($C^{13,17,19,23}$), 134.60 ($C^{13,17,22,23}$), 141.20 (C^{18}), 141.22 (C^{12}), 148.61 ($C^{19,21}$). ^1H–^1H COSY NMR spectrum, ppm: H^{4ax}/H^5 2.76/5.16 and 5.16/2.75, $H^{13,17}/H^{14,16}$ 7.34/7.16 and 7.16/7.34, $H^{21,23}/H^{22}$ 8.39/7.34 and 7.34/8.39. ^1H–^{13}C HMQC NMR spectrum, ppm: H^{4ax}/C^4 2.75/42.19, H^{4eq}/C^4 3.64/42.19, H^5/C^5 5.20/70.38, H^{8ax}/C^8 1.53/25.86, H^{8eq}/C^8 1.73/25.86, H^{9ax}/C^9 1.37/ 19.54, H^{9eq}/C^9 1.61/19.54, H^{10eq}/C^{10} 2.25/26.85, H^{11}/C^{11} 3.58/42.12, H^{22}/C^{22} 7.34/134.83.

3-(5-Phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-3,4,5,6-tetrahydro-1*H*-1,5-methanopyrido[1,2-*a*][1,5]diazocinn-8(2*H*)-one (4) was prepared similarly from 0.33 g (1 mmol) of compound **2** and 0.50 mL (10 mmol) of hydrazine hydrate. Yield 0.28 g (85.7%), yellow crystals, mp 123–125°C. ^1H NMR spectrum, δ, ppm: 1.87–1.99 m (2H, H^{18}), 2.25–3.33 m (6H, $H^{4,7,8,16}$), 3.58–4.63 m (5H, $H^{5,9,17}$), 6.11–6.20 m (2H, $H^{12,14}$), 6.97–7.64 m (7H, $H^{1,13,20–24}$). ^{13}C NMR spectrum, δ_C, ppm: 25.80 (C^{18}), 27.52 (C^8), 33.76 (C^{16}), 34.79 (C^4), 48.75 (C^9), 49.18 (C^7), 51.21 (C^{17}), 52.82 (C^5), 105.27 (C^{14}), 116.31 (C^{12}), 126.32 (C^{22}), 128.51 ($C^{21,23}$), 129.25 ($C^{20,24}$), 139.30 (C^{13}), 141.62 (C^{19}), 150.19 (C^{15}), 162.64 (C^3), 170.85 (C^{11}). ^1H–^{13}C NMR spectrum HMQC, ppm: H^{18}/C^{18} 1.88/26.44, H^8/C^8 2.44/28.40, H^{16}/C^{16} 2.52/34.62, H^7/C^7 2.74/48.79, H^4/C^4 3.10/34.89, H^5/C^5 4.22/53.55, H^{17}/C^{17} 4.43/51.92, H^9/C^9 4.53/48.45, H^{14}/C^{14} 6.15/105.77, H^{12}/C^{12} 6.21/117.00, $H^{21,23}/C^{21,23}$ 7.09/129.08, H^{22}/C^{22} 7.12/126.67, $H^{20,24}/C^{20,24}$ 7.32/129.32, H^{13}/C^{13} 7.28/139.80.

3-Phenyl-*N*-(anabasinocarbonothioyl)acrylamide (5). A solution of 2.07 g (0.011 mol) of cinnamoyl thiocyanate in 10 mL of acetone was added dropwise at vigorous stirring to a solution of 1.62 g (0.01 mol) of anabasine in 5 mL of acetone. The mixture was stirred during 1 h at 30°C. The reaction progress was monitored by TLC. After the reaction was complete, the mixture was cooled; fine precipitate was filtered off, washed with small amount of diethyl ether, and recrystallized from isopropanol. Yield 2.82 g (80.4%), white powder, mp 150–151°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.99–1.00 m (1H, H^{10ax}), 1.31–1.34 m (1H, H^{11ax}), 1.44–1.65 m (2H, $H^{10eq,11eq}$), 1.88–2.00 m (1H, H^{12ax}), 2.52–2.55 m (1H, H^{12eq}), 3.00–3.05 m (1H, H^{9ax}), 3.73–3.87 m (1H, H^{9eq}), 6.72 br. s (1H, H^7), 6.87 d (1H, H^{18}, ^3J = 16.0), 7.39 br. s (4H, $H^{5,22–24}$), 7.58 d (2H, $H^{21,25}$, ^3J = 6.4), 7.65 d (1H, H^{19}, ^3J = 15.6), 7.86 br. s (1H, H^4), 8.47 d (1H, H^6, ^3J = 4.1), 8.66 br. s (1H, H^2), 10.85 br. s (1H, H^{15}). ^{13}C NMR spectrum, δ_C, ppm: 18.99 (C^{11}), 26.02 (C^{10}), 27.49 (C^{12}), 48.27 (C^9), 59.00 (C^7), 120.80 (C^{18}), 124.11 (C^5), 128.49 ($C^{21,25}$), 129.60 ($C^{22,24}$), 130.83 (C^{23}), 133.35 (C^{20}), 134.89 (C^4), 134.93 (C^3), 143.27 (C^{19}), 148.52 (C^2), 148.65 (C^6), 162.64 (C^{16}), 181.61 (C^{13}). ^1H–^{13}C NMR spectrum HMQC, ppm: H^{10ax}/C^{10} 1.00/26.67, H^{11ax}/C^{11} 1.28/19.67, H^{11eq}/C^{11} 1.55/19.70, H^{10eq}/C^{10} 1.55/26.80, H^{12ax}/C^{12} 1.90/28.20, H^{12eq}/C^{12} 2.57/28.11, H^{9ax}/C^9 3.03/48.86, H^{9eq}/C^9 3.91/48.87, H^7/C^7 6.74/59.48, H^{18}/C^{18} 6.90/121.09, H^5/C^5 7.39/124.50, $H^{22–24}/C^{22–24}$ 7.40/130.11, $H^{21,25}/C^{21,25}$ 7.58/128.91, H^4/C^4 7.87/135.37, H^{19}/C^{19} 7.68/143.50, H^6/C^6 8.47/148.93, H^2/C^2 8.54/148.93.

***N*-Cytisino-3-carbonothioylphenylacrylamide (6)** was prepared similarly from 1.9 g (0.01 mol) of cytisine and 2.07 g (0.011 mol) of cinnamoyl thiocyanate. Yield 2.32 g (61.3%), white crystals, mp 177–178°C (benzene). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.84–1.87 m (1H, H^3), 2.47 br. s (1H, H^{13ax}), 2.65 br. s (1H, H^{13eq}), 3.12 br. s (1H, H^{11}), 3.28 br. s (1H, H^{2ax}), 3.36–3.38 m (1H, H^{2eq}), 3.57–3.61 m (1H, H^{12ax}), 3.79–3.88 m (1H, H^{4ax}), 3.98–4.01 m (1H, H^{12eq}), 4.22–4.25 m (1H, H^{4eq}), 6.08–6.10 m (1H, H^9), 6.18–6.20 m (1H, H^7), 6.68–6.79 m (1H, H^{20}), 7.32–7.53 m (7H, $H^{8,21,23–26}$), 10.53 br. s (1H, H^{17}). ^{13}C NMR spectrum, δ_C, ppm: 25.31 (C^3), 28.90 (C^{13}), 35.47 (C^{11}), 48.41 (C^4), 55.45 (C^2), 58.68 (C^{12}), 105.08 (C^9), 116.95 (C^7), 120.86 (C^{20}), 128.43 ($C^{23,27}$), 128.85 ($C^{24,26}$), 129.57 (C^{25}), 130.79 (C^{22}), 139.36 (C^8), 142.85 (C^{21}), 149.42 (C^{10}), 161.97 (C^6), 162.70 (C^{18}), 180.65 (C^{14}). ^1H–^{13}C HMQC NMR spectrum, ppm: H^3/C^3 1.87/25.98, H^{13ax}/C^{13} 2.47/29.50, H^{13eq}/C^{13} 2.66/29.50, H^{11}/C^{11} 3.12/36.12, H^2/C^2 3.36/56.72, H^{12ax}/C^{12} 3.53/59.30, H^{4ax}/C^4 3.84/49.34, H^{12eq}/C^{12} 3.98/57.98, H^{4eq}/C^4 4.24/49.34, H^9/C^9 6.09/105.49, H^7/C^7 6.20/117.26, H^{20}/C^{20} 6.74/121.45, H^8/C^8 7.26/139.76, $H^{23–27}/C^{23–27}$ 7.32/129.27, H^{21}/C^{21} 7.52/142.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Tlegenov, R., *Doctoral (Chem.) Dissertation*, Tashkent, 2008. 54 s.
2. Primuhamedov, Z.I. and Tillyaev, K.S., *Uzb. Khim. Zh*., 1981, no. 1, p. 52.
3. Primuhamedov, Z.I., Tillyaev, K.S., and Zaidova, R.A., *Uzb. Khim. Zh*., 1982, no. 3, p. 63; Saprikina, V.A., Vinogradova, V.I., Ambartsumova, R.F., Ibragimov, T.F., and Shakhidoyatov, Kh.M., *Chem. Nat. Compd*., 2004, no. 4, p. 276. https://doi.org/10.1007/s10600-006-0182-7
4. Abduvakhabov, A.A., Sadykov, A.A., Dalimov, D.N., and Aslanov, H.A., *Alkaloidy i ikh proizvodnye kak instrument dlya izucheniya kholinergicheskoi sistemy* (Alkaloids and Their Derivatives as a Tool for Studying the Cholinergic System), Tashkent: Fan, 1984.
5. RF Patent 2440997, 2012; *Buyll. Izobret.*, 2012, no. 3.
6. Saprikina, V.A., Vinogradova, V.I., Ambartsumova, R.F., Ibragimov, T.F., Sultankulova, A., and Shakhidoyatov, Kh.M., *Chem. Nat. Compd*., 2004, no. 6, p. 582. https://doi.org/10.1007/s10600-005-0042-x
7. Abdullaev, N.P., Makhmudov, U.S., Tashkhodzhaev, B., Genzhemuratova, G., Levkovich, M.G., and Shakhidoyatov, Kh.M., *Chem. Nat. Compd*., 2009, no. 6, p. 837. https://doi.org/10.1007/s10600-010-9495-7
8. Nurkenov, O.A., Kulakov, I.V., and Fazylov, S.D,. *Sinteticheskie transformatsii alkaloida tsitizina* (Synthetic Transformations of Cytisine Alkaloid), Karaganda: Glasir, 2012.
9. Nurkenov, O.A., Fazylov, S.D., Kulakov, I.V., and Musina, L.A., *Alkaloid anabazin i ego proizvodnye* (Anabazine Alkaloid and Its Derivatives), Karaganda: Glasir, 2010.
10. Allen, F.H., Kennard, O., Watson, D.G., Brammer, L., Orpen, A.G., and Taylor, R., *J. Chem. Soc. Perkin Trans. 2*, 1987, vol. 2, no. 12, p. 1. https://doi.org/10.1039/P298700000S1
11. Wojciechowska-Nowak, M., Boczon, W., Rychlewska, U., and Warzajtis, B., *J. Mol. Struct*., 2007. 840, p. 44. https://doi.org/10.1016/j.molstruc.2006.11.037
12. Wojciechowska-Nowak, M., Jasiewicz, B., Boczon, W., and Rychlewska, U., *J. Mol. Struct*., 2011. 997, p. 15. https://doi.org/10.1016/j.molstruc.2011.04.015
13. Nurkenov, O.A., Satpaeva, Zh.B., Fazylov, S.D., Seilkhanov, T.M., Turdybekov, K.M., Turdybekov, D.M., Akhmetova, S.B., Makhmutova, A.S., and Gazaliev, A.M., *Chem. Nat. Compd*., 2016, vol. 52, no. 2, p. 276. https://doi.org/10.1007/s10600-016-1613-8
14. Zefirov, Yu.V. and Zorkii, P.M., *Zh. Strukt. Khim*., 1974, vol. 15, no. 1, p. 118.
15. Takagi, K., Tanaka, M., Murakami, Y., Morita, H., and Aotsuka, T., *Eur. J. Med. Chem. Chim. Ther*., 1986, vol. 21, p. 65.
16. Ankhiwala, M.D. and Naik, H.B., *J. Indian Chem. Soc*., 1990, vol. 67, no. 3, p. 258. https://doi.org/10.1002/chin.199049179
17. Kaname, T., Masaaki, T., Hikari, M., Kuniyoshi, O., Katsuyuki, I., Naoki, N., and Masayuki, O., *Eur. J. Med. Chem*., 1987, vol. 22, p. 239. https://doi.org/10.1016/0223-5234(87)90055-9
18. Navashin, S.M. and Fomina, I.P., *Ratsional'naya antibiotikoterapiya. Spravochnik* (Rational Antibiotic Therapy. Handbook), Moscow: Meditsina, 1982.
19. Meyer, B.N., Ferrigni, N.R., Putnam, J.E., Jacobsen, L.B., Nicholsand, D.E., and McLaughlin, J.L., *Planta Medica*, 1982, vol. 45, p. 31.
20. McLaughlin, J.L., *Methods Plant Boichem*., 1991, vol. 6, p. 1.
21. Gordon, A.J. and Ford, R.A., *The Chemist's Companion. A Handbook of Practical Data, Techniques and References*, New York: Wiley, 1972..
22. *CrysAlisPro*, Aligent Technologies, Version 1.171.37.34 (release 2014).
23. Sheldrick, G.M., *Acta Crystallogr. (A)*, 2008, vol. 64, p. 112. https://doi.org/10.1107/s0108767307043930
24. Sheldrick, G.M., *Acta Crystallogr. (C)*, 2015, vol. 71, p. 3. https://doi.org/10.1107/S2053229614024218