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SYNTHESIS OF THE NEW HETEROCYCLIC DERIVATIVES OF ALKALOIDS

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The aim of the study is the synthesis of heterocyclic derivatives of alkaloids. A convenient method has been developed for obtaining natural alkaloid derivatives of anabazine and cytisine by the acylation reaction of 1,2-azole-3-, pyridine-3-, pyridine-4- and adamantane-1-carbonyl chlorides. A number of N-acyl derivatives of anabazine and cytisine have been obtained for the discovery of new medicines based on natural products. Molecular docking of the studied compounds was carried out on a model of hemagglutinin (1 RAY 1930 Swine H1 Hemagglutinin) and neuraminidase (neuraminidase 3BEQ strain A/Brevig Mission/1/1918 H1N1) proteins. It was found that all the studied compounds are able to bind to hemagglutinin and neuraminidase. Computer modeling was carried out on the basis of the AutoDock Vina 1.1.2 program, as well as external tools such as AutoDock Tools. All synthesized compounds were tested for antiviral activity. Compounds with adamantane fragment showed the greatest antiviral effect. Adamantane derivatives of anabazine and cytisine showed pronounced antiviral properties, even surpassing the commercial drugs Tamiflu and Remantadine in activity. Derivatives of N-acyl anabazine and cytisine are promising for further study of their pharmacological properties.

Keywords: cytisine, amides, quaternary salts of pyridinium, isoxazole, isothiazole, pyridine, antiviral activity

СИНТЕЗ НОВЫХ ГЕТЕРОЦИКЛИЧЕСКИХ ПРОИЗВОДНЫХ АЛКАЛОИДОВ

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Целью исследования является синтез гетероциклических производных алкалоидов. Разработан удобный метод получения природных алкалоидных производных анабазина и цитизина по реакции ацилирования 1,2-азол-3-, пиридин-3-, пиридин-4- и адамантан-1-карбонилхлоридами. Ряд N-ацилпроизводных анабазина и цитизина был получен для открытия новых лекарственных средств на основе натуральных продуктов. Проведен молекулярный докинг исследуемых соединений на модели белков гемагглютинина (1RUY 1930 Swine H1 Hemagglutinin) и нейраминидазы (нейраминидаза 3BEQ штамма A/Brevig Mission/1/1918 H1N1). Установлено, что все исследованные соединения способны связываться с гемагглютинином и нейраминидазой. Компьютерное моделирование проводилось на базе программы AutoDock Vina 1.1.2, а также внешних инструментов, таких как AutoDock Tools. Все синтезированные соединения были протестированы на противовирусную активность. Соединения с адамантановым фрагментом показали наибольший противовирусный эффект. Адамантановые производные анабазина и цитизина проявили выраженные противовирусные свойства, даже превосходящие по активности коммерческие препараты Тамифлю и Ремантадин. Производные N-ациланабазина и цитизина перспективны для дальнейшего изучения их фармакологических свойств.

Ключевые слова: цитизин, амиды, четвертичные соли пиридиния, изоксазол, изотиазол, пиридин, противовирусная активность

ALKALOIDLARNING YANGI GETEROTSIKLIK HOSILALARINI SINTEZI

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Tadqiqot maqsadi alkaloidlarning geterotsiklik hosilalarini sintez qilishdir. 1,2-azol-3-, piridin-3-, piridin-4- va adamantan-1-karbonilxloridlar bilan atsillanish reaksiyasi yo'li bilan anabazin va sitizinning tabiiy alkaloid hosilalarini olishning qulay usuli ishlab chiqilgan. Tabiiy mahsulotlar asosida yangi dori vositalarini ochish uchun anabazin va sitizinning bir qancha N-atsil hosilalari olindi. O'rganilayotgan birikmalarning molekulyar biriktirilishi gemagglutinin oqsillari (1RUY 1930 Swine H1 Gemagglutinin) va neyraminidaza (neyraminidaza 3BEQ shtammi A/Brevig Mission/1/1918 H1N1) modelida amalga oshirildi. O'rganilgan barcha birikmalar gemagglyutinin va neyraminidaza bilan bog'lanish qobiliyatiga ega ekanligi aniqlandi. Kompyuterni modellashtirish AutoDock Vina 1.1.2 dasturi, shuningdek AutoDock Tools kabi tashqi vositalar asosida amalga oshirildi. Barcha sintez qilingan birikmalar virusga qarshi faollik uchun sinovdan o'tkazildi. Adamantan fragmenti bo'lgan birikmalar eng katta antiviral ta'sir ko'rsatdi. Anabazin va sitizinning Adamantan hosilalari aniq antiviral xususiyatlarni ko'rsatdi, hatto faolligi bo'yicha Tamiflu va Remantadin tijorat preparatlaridan ham oshib ketdi. N-atsilanabazin va sitisin hosilalari ularning farmakologik xususiyatlarini yanada o'rganish uchun istiqbolli.

Kalit so'zlar: sitizin, amidlar, to'rtlamchi piridin tuzlari, izoksazol, izotiyazol, piridin, antiviral faoliyat

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Introduction

Currently synthetic transformations of natural compounds have firmly established as a leading area of pharmaceutical science [1, 2]. This is due to the unique structure and biological properties of substances synthesized as a result of complex biochemical processes. Alkaloids are one of the first plant compounds that attracted the attention of pharmacologists for the medicines creation. Many representatives of the alkaloid class have been widely used in clinical practice for several decades, for example, the antitumor drugs Vinblastine, Kolhamin, the antihypertensive Vincamine, *Reserpine*, the analgesic *Morphine*, the antitussive

Codeine, and many others [3]. In addition, some alkaloids are proven to have neuroprotective properties, so they are used in the treatment of Alzheimer's disease [4].

Kazakhstan has large resources of medicinal plants, which are an inexhaustible source for obtaining physiologically active substances. In this regard, the alkaloids cytisine and anabasine, which are rich in wild plant species leafless barnyard (*Anabasis aphylla L.*), russian laburnum (*Cytisus ruthenicus*), lanceolate thermopsis (*Thermopsis lanceolata*), are of particular interest.

For a long time the quinolizidine alkaloid (–)-cytisine did not find wide therapeutic application, besides using as an analeptic and for the treatment of tobacco dependence. However, over the past two decades, it has become a popular initial matrix for the synthesis of substances with potential neurotropic properties [5–9] due to its high affinity for nicotinic acetylcholine receptors (nAChRs), which are associated with an ever-growing list of diseases [10]. It should be noted that besides the presence of a unique physiological effect on the human body, alkaloids at the same time have a side toxic effect [11, 12]. In this regard, the researchers took the path of chemical modification of these substances in order to obtain derivatives that would retain their main physiological effect and would be deprived of unwanted side effects. Although anabasine is used as a hydrochloride to reduce the craving for smoking, in large doses it has an analeptic effect and is a "ganglionic poison", acting similarly to nicotine. In a number of works the substitution of hydrogen at the nitrogen of anabasine or cytisine is shown to lead to a decrease in toxicity and the appearance of interesting biological properties [5, 13-17]. Thus, the analgesic, antihypertensive and inotropic activities were found in some N-substituted cytisines [17].

So the development of rational methods for synthesis using alkaloids cytisine and anabasine, aimed at obtaining new drugs, is a very urgent task of the synthetic drugs chemistry.

This article focuses on obtaining new N-acyl derivatives of the alkaloids with heterocyclic fragments of 1,2-azoles and pyridine. Isoxazole, isothiazole and pyridine derivatives are widely represented among drugs and can be used to treat a wide variety of diseases [18-20].

The combination of alkaloids fragments, pyridine and 1,2-azoles in one molecule can impart new useful properties to their conjugates, and the high lipophilicity, along with the bulk structure of the adamantane radical, when introduced into the molecules of various biologically active compounds, can significantly promote and modify their pharmacological action, due to the creation of favorable conditions for their transport through biological membranes [21].

Research methods

UV spectra were recorded on a Varian Cary 300 spectrophotometer using quartz cuvettes with l = 1 cm. The concentration of the studied compounds in methanol was $4 \cdot 10^{-5}$–$1 \cdot 10^{-4}$ M. IR spectra were registered on a Thermo Nicolet Protege 460 Fourier transform spectrometer in KBr pellets.

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance 500 spectrometer (500 and 125 MHz, respectively) in DMSO-*d*6 and $CDCl_3$. The residual solvent signals were DMSO-*d*6, δH 2.5, δC 40.1 ppm; $CDCl_3$, δH 7.26, δC 77.2 ppm. TMS was used as an internal standard. The assignment of signals in the ^{13}C NMR spectra was performed using the DEPT technique.

Liquid chromatography-mass spectrometry spectra were recorded on an Agilent 1200 LC-MS system with an Agilent 6410 Triple Quad Mass Selective Detector with electrospray ionization in the positive ion registration mode (MS2 scanning mode). An Agilent ZORBAX Eclipse XDB-C18 (4.6 × 50 mm, 1.8 μm) column was used. The mobile phase was MeCN–H_2O + 0.05% HCO_2H with gradient elution from 40 to 90% MeCN in 10 min. A flow rate of 0.5 mL/min was used.

Elemental analysis was performed on a Vario MICRO cube CHNS-analyzer. The halogen content was determined by classical microanalysis using a modified Pregl's method. Melting points were determined on a Kofler bench.

Reagents and solvents used were of analytical grade with the content of the main component being more than 99.5%. Dichloromethane was preliminarily kept for 1 day over $CaCl_2$ to remove 0.5% of ethanol used for stabilizing dichloromethane. 5-Arylisoxazole-3-carboxylic and 4,5-dichloroisothiazole-3-carboxylic acids and acid chlorides were synthesized according to previously described procedures [22].

General Procedure for the Synthesis of Compounds ***1a-c, 3a-c, 3f***

Anabasine (1.6 g, 10 mmol) or cytisine (1.9 g, 10 mmol) was dissolved in 100 mL of dry dichloromethane. Then, 1.2 g (12 mmol) of triethylamine and 11 mmol of 1,2-azole-3- (**1a-c, 3a-c**) or adamantane- (**1f, 3f**) carbonyl chlorides were successively added to the resulting solution under stirring. The mixture was stirred for 1 h and left for 15 h at 20–23 °C. The mixture was washed with water (2 × 200 mL, 1 h stirring) and 5% sodium bicarbonate solution (2 × 200 mL, 1 h stirring). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was crystallized from a mixture of ether and hexane (1:3).

(4,5-Dichloroisothiazol-3-yl)(2-(pyridin-3-yl)piperidin-1-yl)methanone (**1a**): white solid; yield is 82%; mp is 154–155 °C; UV (MeOH c = $6'10^{-5}$ M) λ_{max} (log ε) 257 (3.95), 263 (4.04), 269 (4.00); IR (KBr) ν 3058, 3041 (C=C-H); 2981, 2950, 2935, 2872 (C–H_{aliph}), 1637 (C=O), 1587, 1572, 1500 (C=C_{arom}); 1448, 1440, 1416, 1346, 1319, 1253, 1245, 1192, 1163, 1129, 1014, 962, 825, 808, 712, 691, 641, 620, 571, 548, 493 cm^{-1}; ^{1}H NMR (DMSO–*d*6, 500 MHz) δ 1.35–1.72 (4H, m, $2CH_2$), 1.81–1.95, 2.40–2.56 (2H, m, CH_2); 2.61–2.73, 2.89–3.01 (1H, m, NCH_2); 3.33–3.44, 4.39–4.49 (1H, m, NCH_2); 4.96–5.04, 5.86–5.93 (1H, m, CH); 7.38–7.49 ($1H_{Py}$, m); 7.67–7.77 ($1H_{Py}$, m); 8.46–8.61 ($2H_{Py}$, m); ^{13}C NMR (DMSO -*d*6, 125 MHz) δ 19.58, 19.65 (CH_2); 25.53, 26.08 (CH_2); 27.45, 28.77 (CH_2); 38.65, 43.72 (NCH_2); 50.12, 55.39 (CH); 124.18, 124.33 ($1CH_{Py}$); 134.92, 135.04 ($1CH_{Py}$); 148.57, 148.70 ($2CH_{Py}$); (121.65, 121.78); (134.24, 134.35); (149.59, 149.73); 160.68; (162.07, 162.17) ($5C_{quater}$); MS *m*/*z* (I_{rel}, %) 342.00 $[M]^+$ (100); Anal. calcd. for $C_{14}H_{13}Cl_2N_3OS$ (342.24): C, 49.13; H, 3.83; Cl, 20.72; N, 12.28; S, 9.37%; Found: C, 49.42; H, 4.01; Cl, 20.41; N, 12.00; S, 9.03%.

(5-Phenylisoxazol-3-yl)(2-(pyridin-3-yl) piperidin-1-yl)methanone (**1b**): oil; yield is 87%; UV (MeOH c = $1'10^{-4}$ M) λ_{max} (log ε) 264 (4.36); IR (KBr) ν 3121 (CH_{isox}), 3037 (C=C–H); 2942, 2865 (C–H_{aliph}); 1640 (C=O), 1590, 1573, 1479 (C=C_{arom}); 1447, 1420, 1395, 1261, 1237, 1148, 1127, 1021, 981, 949, 851, 767, 708, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) 1.35–1.81 (4H, m, $2CH_2$), 2.00–2.11, 2.44–2.52 (2H, m, CH_2); 2.66–2.76, 2.99–3.12 (1H, m, NCH_2); 4.29–4.42, 4.61–4.73 (1H, m, NCH_2); 5.88–5.98, 6.06–6.18 (1H, m, CH); 6.84, 6.86 (CH_{isox}, s); 7.29–7.34 ($1H_{Py}$, m); 7.40–7.51 ($3H_{Ar}$, m); 7.61–7.68 ($1H_{Py}$, m); 7.70–7.84 ($2H_{Ar}$, m); 8.52 ($1H_{Py}$, d, *J* = 4.5 Hz); 8.55–8.66 ($1H_{Py}$, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.62 (CH_2); 25.55, 26.41 (CH_2); 27.07, 28.39 (CH_2); 39.06, 43.89 (NCH_2); 50.36, 55.37 (CH); 100.73, 100.77 (CH_{isox}); 123.77 ($1CH_{Py}$); 126.05 ($2CH_{Ar}$); 129.24 ($1CH_{Ar}$); 130.81 ($2CH_{Ar}$); 134.84, 134.93 ($1CH_{Py}$); 148.39, 148.43 ($1CH_{Py}$); 148.53, 148.60 ($1CH_{Py}$); (126.73, 126.82); (134.15, 134.28); (159.21, 159.29); (160.80, 160.98); 170.63 ($5C_{quater}$); MS *m*/*z* (I_{rel}, %) 334.20 $[M+H]^+$ (100), 356.10. $[M+Na]^+$ (6.0), 667.30. $[2M+H]^+$ (34.3), 689.30. $[2M+Na]^+$ (34.2); Anal. calcd. for $C_{20}H_{19}N_3O_2$ (333.39): C, 72.05; H, 5.74; N, 12.60%; Found: C, 72.35; H, 5.81; N, 12.44%.

(2-(Pyridin-3-yl)piperidin-1-yl)(5-(p-tolyl) isoxazol-3-yl)methanone (**1c**): oil; yield is 78%; UV (MeOH c = $1'10^{-4}$ M) λ_{max} (log ε) 270 (4.40); IR (KBr) ν 3128 (CH_{isox}), 3128, 3032 (C=C–H), 2925, 2857 (C–H_{aliph}), 1635 (C=O), 1594, 1573, 1510, 1478 (C=C_{arom}), 1442, 1418, 1392, 1258, 1019, 980, 820, 706, 503 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.52–1.82 (4H, m, $2CH_2$); 1.98–2.11, 2.43–2.51 (2H, m, CH_2); 2.31–2.43 (3H, m, Me); 2.64–2.77, 2.97–3.13 (1H, m, NCH_2); 4.29–4.42, 4.61–4.73 (1H, m, NCH_2); 5.88–5.98, 6.08–6.18 (1H, m, CH); 6.78, 6.80 (CH_{isox}, s); 7.19–7.28 ($2H_{Ar}$, m); 7.28–7.35 ($2H_{Py}$, m); 7.57–7.66 ($2H_{Ar}$, m); 7.67–7.72 ($1H_{Py}$, m); 8.52 ($1H_{Py}$, d, *J* = 4.5 Hz); 8.58–8.62 ($1H_{Py}$, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.62 (CH_2); 21.63 (Me); 25.55, 26.41 (CH_2); 27.07, 28.37 (CH_2); 39.02, 43.87 (NCH_2); 50.32, 55.35 (CH); 100.09 (CH_{isox}); 123.75 ($1CH_{Py}$); 125.81, 125.99 ($2CH_{Ar}$); 129.91, 130.18 ($2CH_{Ar}$); 134.90 ($1CH_{Py}$); 148.44, 148.52 ($1CH_{Py}$); 148.65 ($1CH_{Py}$); 124.13, (134.15, 134.30); 141.20, 159.15; 161.08; 170.82 ($6C_{quater}$); MS *m*/*z* (I_{rel}, %) 348.20 $[M]^+$ (100), 695.30 [2M] (6.0), 717.30 $[2M+Na]^+$ (12.1); Anal. calcd. for $C_{21}H_{21}N_3O_2$ (347.41): C, 72.60; H, 6.09; N, 12.10%; Found: C, 72.98; H, 6.22; N, 11.95%.

Adamantan-1-yl(2-(pyridin-3-yl)piperidin-1-yl)methanone (**1f**): oil; yield is 79%; UV (MeOH c = $1'10^{-4}$ M) λ_{max} (log ε) 255 (4.51), 263 (3.40), 269 (3.30); IR (KBr) ν 3083, 3034, 2938, 2906, 2852, 1621 (C=O), 1573, 1478, 1453, 1401, 1266, 1243, 1157, 1102, 1005, 973, 936, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.46–1.62 (2H, m, CH_2), 1.64–1.78 (6H, m, CH_{2adam}); 1.85–1.93 (3H, m, $3CH_{adam}$), 1.97–2.14 (10H, m, $3CH_{2adam}$+$2CH_2$); 2.33–2.43 (1H, m, CH_2); 4.27–

4.38 (1H, m, CH_2); 5.88–6.02 (1H, m, CH); 7.22–7.29 (1H_{Py}, m); 7.43–7.51 (1H_{Py}, m); 8.41–8.52 (2H_{Py}, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.70 (CH_2); 26.39, 27.27 (CH_2); 27.80 (CH); 28.66 (3CH_{adam}); 36.43 (CH_2); 36,77 (3CH_{2adam}); 38.40 (CH_2); 39.30 (3CH_{2adam}); 123.64 (1CH_{Py}); 134.90 (1CH_{Py}); 147.94 (1CH_{Py}); 148.73 (1CH_{Py}); 42.23, 135.24, 176.73 (3C_{quater}); MS *m/z* (I_{rel}, %) 325.30 $[M+H]^+$ (100), 671.40 $[2M+Na]^+$ (10.0); Anal. calcd. for $C_{21}H_{28}N_2O$ (324.47): C, 77.74; H, 8.70; N, 8.63%; Found: C, 77.98; H, 8.76; N, 8.52%.

(1R,5S)-3-(4,5-Dichloroisothiazole-3-carbonyl)-1,2,3,4,5,6-hexahydro-8H-1, methanopyrido [1,2-a][1,5] diazocin-8-one (3a): white solid; yield is 81%; mp is 232–233 °C; UV (MeOH c = 1′10−4 M) λmax (log ε) 232 (4.08), 267 (3.90), 311 (3.85); IR (KBr) ν 3022, 2995, 2960, 2945, 2924, 2873, 1656 (C=O), 1636 (C=O), 1577, 1547, 1501, 1465, 1453, 1356, 1335, 1258, 1230, 1218, 1186, 1143, 1109, 1061, 968, 798, 742, 735, 694, 644 cm−1; 1H NMR (CDCl3, 500 MHz) δ 1.99–2.09 (2H, m, CH2), 2.42–2.49, 2.59–2.67 (1H, m, CH); 2.93–3.01, 3.16–3.22 (1H, m, CH2); 3.05–3.11, 3.37–3.44 (1H, m, CH2); 3.08–3.14, 3.45–3.51 (1H, m, CH2); 3.57–3.64, 3.77–3.83 (1H, m, CH); 3.81–3.94 (1H, m, CH2); 4.11–4.23 (1H, m, CH2); 4.74–4.82, 4.84–4.92 (1H, m, CH2); 5.81, 6.11 (1HPy, dd, J = 6.8, 0.9 Hz); 6.39 –6.49 (1HPy, m); 7.19, 7.28 (1HPy, dd, J = 9.1, 6.8 Hz); 13C NMR (CDCl3, 125 MHz) δ 26.21, 26.29 (CH2); 27.44, 27.68 (CH); 34.51, 34.89 (CH); 48.22, 48.68 (CH2); 48.83, 49.19 (CH2); 52.72, 53.92 (CH2); 105.23, 106.00 (1CHPy); 117.87, 118.40 (1CHPy); 138.65, 139.13 (1CHPy); (123.24, 123.31); (147.80, 147.84); (149.07, 149.72); (159.35, 159.46); (161.61, 161.74); (163.44, 163.51) (6Cquater); MS m/z (Irel, %) 370.00 [M]+ (100), 392.00 [M+Na]+ (43.2), 763.00 [2M+Na]+ (25.1); Anal. calcd. for C15H13Cl2N3O2S (370.25): C, 48.66; H, 3.54; Cl, 19.15; N, 11.35; S, 8.66%; Found: C, 48.89; H, 3.66; Cl, 19.01; N, 11.13; S, 8.58%.

*(*1R,5S)-3-(5-Phenylisoxazole-3-carbonyl)-1,2,3,4,5,6-hexahydro-8H-1,5-methanopyrido [1,2-a] [1,5] diazocin-8-one (3b): white solid; yield is 77%; mp is 74–76 °C; UV (MeOH c = 1′10−4 M) λmax (log ε) 239 (4.15), 267 (4.32), 311 (3.78); IR (KBr) ν 3113 (CHisox), 3055, 2924, 2865, 1656 (C=O), 1574, 1545, 1479, 1446, 1393, 1342, 1258, 1229, 1139, 1070, 983, 797, 767, 689 cm−1; 1H NMR (CDCl3, 500 MHz) δ 2.06–2.13 (2H, m, CH2), 2.49–2.55, 2.59–2.64 (1H, m, CH); 3.03–3.08, 3.16–3.22 (1H, m, CH2); 3.08–3.11, 3.45–3.50 (1H, m, CH2); 3.11–3.15, 3.52–3.57 (1H, m, CH2); 3.80–3.91 (1H, m, CH); 4.22–4.30 (1H, m, CH2); 4.53–4.60, 4.66–4.72 (1H, m, CH2); 4.78–4.85, 4.92–4.98 (1H, m, CH2); 5.90, 6.13 (1HPy, dd, J = 6.8, 0.8 Hz); 6.37, 6.65 (1Hisox, s); 6.46 (1HPy, dt, J = 9.1, 1.5 Hz); 7.16, 7.29 (1HPy, dd, J = 9.1, 6.8 Hz); 7.42–7.49 (3HAr, m); 7.66–7.71, 7.74–7.78 (2HAr, m); 13C NMR (CDCl3, 125 MHz) δ 26.51, 26.60 (CH2); 27.88, 28.03 (CH); 34.91, 35.30 (CH); 48.49, 48.59 (CH2); 49.00, 49.67 (CH2); 53.07, 54.14 (CH2); 100.45, 100.78 (CHisox); 105.69, 106.10 (1CHPy); 117.80 (1CHPy); 125.96, 126.18 (2CHAr); 129.22, 129.27 (2CHAr); 130.81 (1CHAr); 138.69, 139.20 (1CHPy); 126.75; (148.09, 148.13); (158.56, 158.65); (160.43, 160.51); (163.46, 163.52); (170.25, 170.83) (6Cquater); MS m/z (Irel, %) 362.10 [M+H] + (100), 384.10 [M+Na]+ (50.2), 723.30 [2M+H]+ (5.3), 745.20 [2M+Na]+ (32.6); Anal. calcd. for C21H19N3O3 (361.40): C, 69.79; H, 5.30; N, 11.63%; Found: C, 70.05; H, 5.47; N, 11.49%.

(1R,5S)-3-(5-(p-tolyl)isoxazole-3-carbonyl)-1,2,3,4,5,6-hexahydro-8H-1,5-methanopyrido [1,2-a][1,5]diazocin-8-one (**3c**): oil; yield is 84%; UV (MeOH c = 1′10^{-4} M) λ_{max} (log ε) 237 (4.04, 275 (4.32), 313 (3.70); IR (KBr) ν 3125 (CH_{isox}), 3090, 3055, 3030, 2922, 2853, 1657 (C=O), 1610, 1577, 1545, 1479, 1441, 1258, 1230, 1138, 1091, 1070, 983, 795, 678 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.01–2.11 (2H, m, CH_2), 2.37 (3H, s, Me), 2.46–2.53, 2.56–2.64 (1H, m, CH); 2.99–3.09 (1H, m, CH_2); 3.09–3.13, 3.49 –3.55 (1H, m, CH_2); 3.13–3.21, 3.39–3.48 (1H, m, CH_2); 3.76–3.90 (1H, m, CH); 4.25 (1H, m, CH_2); 4.45–4.53, 4.59–4.68 (1H, m, CH_2); 4.73–4.83, 4.87–4.96 (1H, m, CH_2); 5.89, 6.12 (1H_{Py}, d, *J* = 6.3 Hz); 6.27, 6.57 (1H_{isox}, s); 6.44 (1H_{Py}, d, *J* = 9.1 Hz); 7.15, 7.28 (1H_{Py}, dd, *J* = 9.0, 6.9 Hz); 7.23 (2H_{Ar}, d, *J* = 8.0 Hz); 7.55, 7.63 (2H_{Ar}, d, *J* = 8.1 Гц); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.51, 21.52 (Me); 26.26, 26.35 (CH_2); 27.70, 27.84 (CH), 34.72, 35.10 (CH); 48.35, 48.38 (CH_2); 48.87, 49.46 (CH_2); 52.87, 53.99 (CH_2); 99.54, 99.93 (CH_{isox}); 105.64, 105.99 (1CH_{Py}); 117.60 (1CH_{Py}); 125.72, 125.94 (2CH_{Ar}); 129.76, 129.80 (2CH_{Ar}); 138.62, 139.09 (1CH_{Py}); 123.88; 141.06; (148.04, 148.12); (158.32, 158.45); (160.37, 160.53); (163.32, 163.37); (170.28, 170.83) (7C_{quater}); MS m/z (I_{rel}, %) 376.20 $[M+H]^+$ (100), 398.10 $[M+Na]^+$ (30.4), 751.30 $[2M+H]^+$ (40.8),

773.30 $[2M+Na]^+$ (65.1); Anal. calcd. for $C_{22}H_{21}N_3O_3$ (375.43): C, 70.38; H, 5.64; N, 11.19%; Found: C, 70.61; H, 5.88; N, 11.01%.

(1R,5S)-3-(Adamantane-1-carbonyl)-1,2,3,4,5,6-hexahydro-8H-1,5-methanopyrido[1,2-a] [1,5] diazocin-8-one (**3f**): white solid; yield is 81%; mp is 203–204 °C; UV (MeOH c = 1′10^{-4} M) λ_{max} (log ε) 233 (3.90), 312 (3.85); IR (KBr) ν 3052, 2941, 2913, 2898, 2863, 2846, 1657 (C=O), 1619 (C=O), 157011,3 ($1H_{Py}$, m); ^{13}C NMR (DMSO-*d6*, 125 MHz) δ 26.13 (CH_2), 27.68 (CH), 28.38 ($1CH+3CH_{adam}$), 34.75 (CH), 36.49 ($3CH_{2adam}$), 38.74 ($3CH_{2adam}$), 48.85 (CH_2), 50.39 (CH_2), 51.94 (CH_2), 105.48, 116.49 ($1CH_{Py}$), 139.29 ($1CH_{Py}$), 41.67, 150.10, 162.61, 175.95 ($4C_{quater}$); MS m/z (I_{rel}, %) 353.20 $[M+H]^+$ (100), 375.20 $[M+Na]^+$ (42.5), 705.40 $[2M+H]^+$ (21.3), 727.40 $[2M+Na]^+$ (58.0); Anal. calcd. for $C_{22}H_{28}N_2O_2$ (352.48): C, 74.97; H, 8.01; N, 7.95%; Found: C, 75.33; H, 8.15; N, 7.79%.

*General Procedure for the Synthesis of Compounds **1d, e***

Anabasine (1.6 g, 10 mmol) was dissolved in 100 mL of dry dichloromethane. Then, 1.2 g (12 mmol) of triethylamine and 2.5 g (25 mmol) of Et_3N and 1.8 g (11 mmol) of hydrochloride of nicotinic or isonicotinic carbonyl chlorides were successively added to the resulting solution under stirring. The mixture was stirred for 1 h and left for 15 h at 20–23 °C. The mixture was washed with 5% sodium bicarbonate solution (1 × 100 mL, 0.5 h stirring). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed, and the residue was crystallized from a mixture of ether and hexane (1:3).

Pyridin-3-yl(2-(pyridin-3-yl)piperidin-1-yl)methanone (**1d**): white solid; yield is 53%; mp is 93–94 °C; UV (MeOH c = 7×10^{-5} M) λ_{max} (log ε) 248 (3.77), 257 (3.85), 262 (3.85), 270 (3.77); IR (KBr) ν 3221, 3090, 3020 (C=C-H), 2919, 2850 ($C\text{-}H_{aliph}$), 1613 (C=O), 1588, 1570 ($C=C_{arom}$), 1439, 1413, 1324, 1274, 1111, 1025, 998, 828, 812, 737, 712, 627 cm^{-1}; ^1H NMR (DMSO–*d*6, 500 MHz) δ 1.26–1.42 (1H, m, CH_2), 1.48–1.58 (2H, m, CH_2), 1.60–1.68 (1H, m, CH_2), 1.90–1.99 (1H, m, CH_2), 2.40–2.48 (1H, m, CH_2), 2.74–3.20 (1H, m, CH_2), 3.40–3.58 (1H, m, CH_2), 3.58–5.30, 5.30–6.20 (1H, m, CH); 7.42 ($1H_{Py}$, dd, *J* = 8.0, 4.8 Hz), 7.45–7.52 ($1H_{Py}$, m), 7.75 ($1H_{Py}$, d, *J* = 8.0 Hz), 7.92 ($1H_{Py}$, d, *J* = 5.8 Hz), 8.48–8.52 ($1H_{Py}$, d), 8.54–8.60 ($1H_{Py}$, m), 8.65 ($1H_{Py}$, d, *J* = 8.0 Hz), 8.66–8.73 ($1H_{Py}$, m); MS *m/z* (I_{rel}, %) 268.20 $[M+H]^+$ (100); Anal. calcd. for $C_{16}H_{17}N_3O$ (267.33): C, 71.89; H, 6.41; N, 15.72%; Found: C, 72.18; H, 6.53; N, 15.38%.

(2-(Pyridin-3-yl)piperidin-1-yl)(pyridin-4-yl)methanone (**1e**): white solid; yield is 52%; mp is 96–97°C; UV (MeOH c = 7×10^{-5} M) λ_{max} (log ε) 256 (3.78), 262 (3.81), 269 (3.70); IR (KBr) ν 3043, 3020, 2940, 2855, 1623 (C=O), 1594, 1570, 1546, 1460, 1434, 1410, 1407, 1323, 1272, 1024, 1000, 834, 710, 627, 595 cm^{-1}; ^1H NMR (DMSO–*d*6, 500 MHz) δ 1.28–1.43 (1H, m, CH_2), 1.43–1.60 (2H, m, CH_2), 1.60–1.71 (1H, m, CH_2), 1.89–1.99 (1H, m, CH_2), 2.34–2.49 (1H, m, CH_2), 2.60–3.10 (1H, m, CH_2), 3.20–3.45 (1H, m, CH_2), 4.40–5.00, 5.80–6.00 (1H, m, CH); 7.43 ($1H_{Py}$, dd, *J* = 8.0, 4.7 Hz), 7.45–7.54 ($2H_{Py}$, m), 7.71–7.77 ($1H_{Py}$, m), 8.51 ($1H_{Py}$, d, *J* = 4.4 Hz), 8.53–8.59 ($1H_{Py}$, m), 8.62–8.73 ($2H_{Py}$, m); MS *m/z* (I_{rel}, %) 268.20 $[M+H]^+$ (100); Anal. calcd. for $C_{16}H_{17}N_3O$ (267.33): C, 71.89; H, 6.41; N, 15.72%; Found: C, 72.15; H, 6.51; N, 15.34%.

*General Procedure for the Synthesis of Compounds **2a-e***

A mixture of 6 mmol of amides **1a-e** in 30 mL of dry dichloromethane and 18 mmol (1 ml) of dry methyl iodide was kept for 14 days in the dark. Then, the precipitated product was filtered off, washed with 2 × 5 mL of methylene chloride and dried in a vacuum.

3-(1-(4,5-Dichloroisothiazole-3-carbonyl) piperidin-2-yl)-1-methylpyridin-1-ium iodide (**2a**): orange solid; yield is 99%; mp is 161–162 °C; UV (MeOH c = 7′10^{-5} M) λ_{max} (log ε) 218 (4.40), 266 (4.08); IR (KBr) ν 3036, 2933, 2870, 1631 (C=O), 1590, 1504, 1464, 1446, 1355, 1328, 1289, 1250, 1171, 1010, 964, 899, 828, 738, 670 cm^{-1}; ^1H NMR (DMSO–*d*6, 500 MHz) δ 1.34–1.75 (4H, m, $2CH_2$), 1.82–1.94, 1.95–2.06 (1H, m, CH_2); 2.43–2.56 (1H, m, CH_2); 2.71–2.81, 3.04–3.14 (1H, m, NCH_2); 3.46–3.55, 4.44–4.52 (1H, m, NCH_2); 4.38–4.43 (3H, m, MeN), 5.20–5.25, 5.93–5.99 (1H, m, CH); 8.13–8.18, 8.19–8.25 ($1H_{Py}$, m); 8.36–8.42, 8.43–8.49 ($1H_{Py}$, m); 8.92–9.01 ($2H_{Py}$, m); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 19.25, 19.45 (CH_2); 25.34, 25.62 (CH_2); 27.42, 29.03 (CH_2); 38.86, 43.85 (NCH_2); 48.83, 48.91 (NMe); 50.38, 55.27 (CH); 128.11, 128.40 ($1CH_{Py}$); 143.42, 143.83 ($1CH_{Py}$); 144.54, 144.84 ($2CH_{Py}$); (122.05, 122.15); (134.24, 134.35); 149.82; (159.93, 160.03); (161.98, 162.49) ($5C_{quater}$); MS

m/z (I_{rel}, %) 357.10 $[M–I]^+$ (17.1); Anal. calcd. for $C_{15}H_{16}Cl_2IN_3OS$ (484.18): C, 37.21; H, 3.33; Cl, 14.64; I, 26.21; N, 8.68; S,8.97%; Found: C, 37.55; H, 3.61; Cl+I, 40.43; N, 8.39; S, 8.67%.

*1-Methyl-3-(1-(5-phenylisoxazole-3-carbonyl)piperidin-2-yl)pyridin-1-ium iodide (**2b**):* orange solid; yield is 95%; mp is 64–65 °C; UV (MeOH c = 7′10^{-5} M) λ_{max} (log ε) 222 (4.45), 267 (4.40); IR (KBr) ν 3030, 2926, 2855, 1633 (C=O), 1589, 1571, 1500, 1472, 1445, 1391, 1254, 1129, 982, 767, 687, 672 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 1.49–1.75 (4H, m, $2CH_2$), 1.77–1.83, 1.93–2.11 (2H, m, CH_2); 2.52–2.72 (1H, m, NCH_2); 3.15–3.25, 4.19–4.24 (1H, m, NCH_2); 4.65 (3H, s, NMe); 5.84–6.01 (1H, m, CH); 6.84, 6.94 ($1H_{isox}$, s); 7.33–7.41 ($3H_{Ar}$, m); 7.62–7.76 ($2H_{Ar}$, m); 8.07 ($1H_{Py}$, t, *J* = 6.9 Hz); 8.27–8.46 ($1H_{Py}$, m); 9.03–9.20 ($2H_{Py}$, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.63 (CH_2); 25.07, 25.40 (CH_2); 27.39, 28.32 (CH_2); 39.43, 44.64 (NCH_2); 50.25 (NMe); 51.10 (CH); 100.99 (CH_{isox}); 126.16 ($2CH_{Ar}$); 128.54 ($1CH_{Ar}$); 129.31 ($2CH_{Ar}$); 130.96 ($1CH_{Py}$); 144.01 ($1CH_{Py}$); 144.27 ($1CH_{Py}$); 144.37 ($1CH_{Py}$); 126.64; 141.57; 158.81; 161.92; 170.85 ($5C_{quater}$); MS m/z (I_{rel}, %) 348.20 $[M-I]^+$ (100); Anal. calcd. for $C_{21}H_{22}IN_3O_2$ (475.33): C, 53.06; H, 4.67; I, 26.70; N, 8.84%; Found: C, 53.44; H, 4.81; I, 26.55; N, 8.74%.

1-Methyl-3-(1-(5-(p-tolyl)isoxazole-3-carbonyl)piperidin-2-yl)pyridin-1-ium iodide (**2c**): orange solid; yield is 99%; mp is 101–102 °C; UV (MeOH c = 6×10^{-5} M) λ_{max} (log ε) 219 (4.46), 273 (4.40); IR (KBr) ν 3031, 2931, 2856, 1636 (C=O), 1595, 1506, 1486, 1453, 1439, 1392, 1253, 1218, 1156, 1023, 983, 823, 807, 673, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 1.52–1.82 (4H, m, $2CH_2$); 1.98–2.11, 2.43–2.51 (2H, m, CH_2); 2.31-2.43 (3H, m, Me); 2.64–2.77, 2.97–3.13 (1H, m, NCH_2); 4.29–4.42, 4.61–4.73 (1H, m, NCH_2); 5.88–5.98, 6.08–6.18 (1H, m, CH); 6.78, 6.80 ($1H_{isox}$, s); 7.19–7.28 ($2H_{Ar}$, m); 7.28–7.35 ($2H_{Py}$, m); 7.57–7.66 ($2H_{Ar}$, m); 7.67–7.72 ($1H_{Py}$, m); 8.52 ($1H_{Py}$, d, *J* = 4.5 Hz); 8.58–8.62 ($1H_{Py}$, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.62 (CH_2); 21.63 (Me); 25.55, 26.41 (CH_2); 27.07, 28.37 (CH_2); 39.02, 43.87 (NCH_2); 50.32, 55.35 (CH); 100.09 (CH_{isox}); 123.75 ($1CH_{Py}$); 125.81, 125.99 ($2CH_{Ar}$); 129.91, 130.18 ($2CH_{Ar}$); 134.90 ($1CH_{Py}$); 148.44, 148.52 ($1CH_{Py}$); 148.65 ($1CH_{Py}$); 124.13, (134.15, 134.30); 141.20, 159.15; 161.08; 170.82 ($6C_{quater}$); MS m/z (I_{rel}, %) 362.20 $[M-I]^+$ (100), 353.20 $[M+H-I]^+$ (22.0); Anal. calcd. for $C_{22}H_{24}IN_3O_2$ (489.35): C, 54.00; H, 4.94; I, 25.93; N, 8.59%; Found: C, 54.41; H, 5.05; I, 25.74; N, 8.25%.

1-methyl-3-(1-(1-methylpyridin-1-ium-3-carbonyl)piperidin-2-yl)pyridin-1-ium diiodide (**2d**): orange solid; yield is 95%; mp is 260–262 °C; UV (MeOH c = 4×10^{-5} M) λ_{max} (log ε) 219 (4.59), 267 (4.00); IR (KBr) ν 3026, 2995, 2930, 2972; 1642, 1626 (C=O); 1589, 1509, 1468, 1440, 1325, 1282, 1220, 1175, 1131, 1007, 831, 680, 671 cm^{-1}; ^1H NMR (DMSO-*d6*, 500 MHz) 1.31–1.60 (2H, m, CH_2); 1.61–1.78 (2H, m, CH_2); 2.02–2.16 (1H, m, CH_2); 2.34–2.45, 2.50–2.61 (1H, m, CH_2); 2.78–2.96, 3.07–3.23 (1H, m, CH_2); 3.49–3.67, 4.35–4.41 (1H, m, CH_2); 4.45 (3H, s, Me); 4.46 (3H, s, Me); 5.17–5.30, 5.88–6.00 (1H, m, CH), 8.12–8.24, 8.25–8.36 ($2H_{Py}$, m); 8.60–8.70, 8.80–8.90 ($2H_{Py}$, m), 8.97–9.15, 9.02–9.06 ($2H_{Py}$, m), 9.10–9.17, 9.35–9.43 ($2H_{Py}$, m); MS m/z (I_{rel}, %) 296.20 $[M-2I]^+$ (24.3); Anal. calcd. for $C_{18}H_{23}I_2N_3O$ (551.21): C, 39.22; H, 4.21; I, 46.05; N, 7.62%; Found: C, 39.54; H, 4.51; I, 45.89; N, 7.22%.

1-methyl-3-(1-(1-methylpyridin-1-ium-4-carbonyl)piperidin-2-yl)pyridin-1-ium diiodide(**2e**): orange solid; yield is 91%; mp is 255–257 °C; UV (MeOH c = 4×10^{-5} M) λ_{max} (log ε) 219 (4.56), 266 (4.08); IR (KBr) ν 3118, 3039, 3016, 2930, 2866; 1640, 1624 (C=O); 1511, 1462, 1439, 1320, 1278, 1218, 1157, 1001, 676, 573 cm^{-1}; ^1H NMR (DMSO-*d6*, 500 MHz) 1.27–1.40, 1.40–1.54 (2H, m, CH_2); 1.54–1.71 (2H, m, CH_2); 1.96–2.15 (1H, m, CH_2); 2.30–2.39, 2.45–2.55 (1H, m, CH_2); 2.80–2.92, 3.03–3.14 (1H, m, CH_2); 3.27–3.35, 4.45–4.53 (1H, m, CH_2); 4.30, 4.39 (3H, s, Me); 4.42, 4.44 (3H, s, Me); 4.95–5.01, 5.87–5.95 (1H, m, CH), 8.10–8.21 ($1H_{Py}$, m); 8.25, 8.40 ($2H_{Py}$, d, *J* = 6.2 Hz), 8.51, 8.63 ($1H_{Py}$, d, *J* = 8.0 Hz), 8.94–9.02 ($2H_{Py}$, m); 9.03, 9.18 ($2H_{Py}$, d, *J* = 6.2 Hz); MS m/z (I_{rel}, %) 296.2 $[M-2I]^+$ (9.9), 297.3 $[M-2I+H]^+$ (8.5); Anal. calcd. for $C_{18}H_{23}I_2N_3O$ (551.21): C, 39.22; H, 4.21; I, 46.05; N, 7.62%; Found: C, 39.71; H, 4.33; I, 45.88; N, 7.55%.

Results and Discussion

In the framework of this work new acyl derivatives of anabasine and cytisine by reaction with 1,2-azole-3-, pyridine-3-, pyridine-4- and adamantane-1-carbonyl chlorides were synthesized (Fig. 1). The reaction proceeded in dichloromethane at room temperature in the presence of triethylamine with satisfactory yields (52-87%).

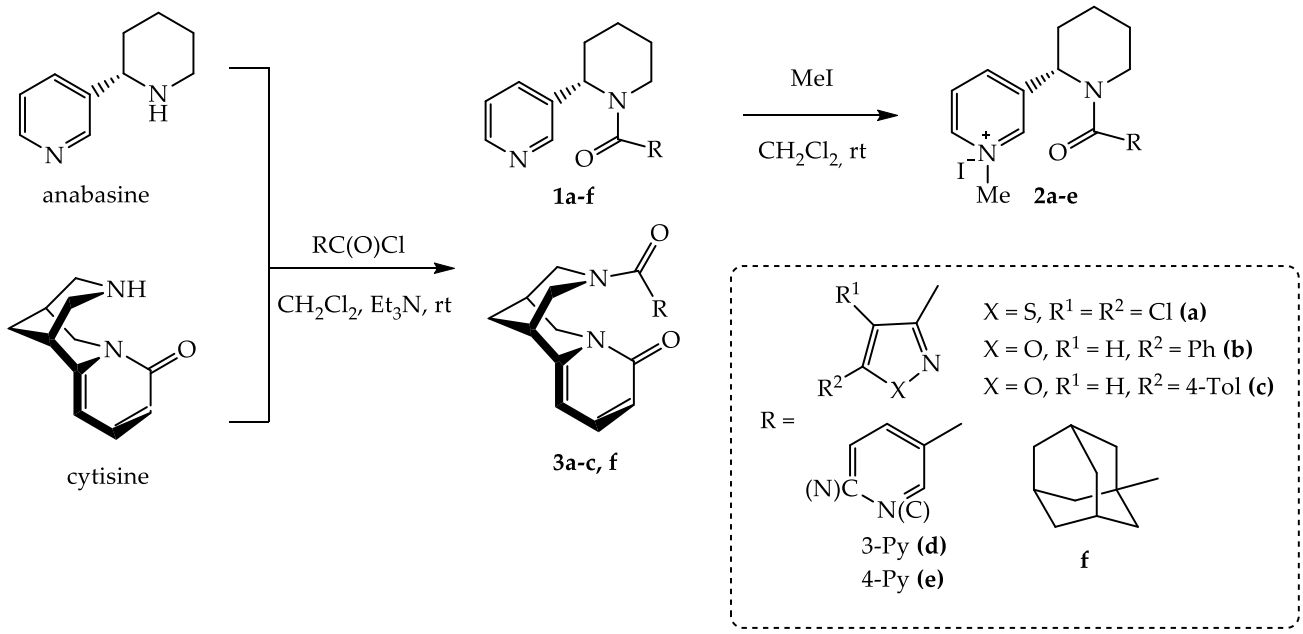

Figure 1. Synthesis of anabasine and cytisine amides with 1,2-azole, pyridine and adamantane fragments.

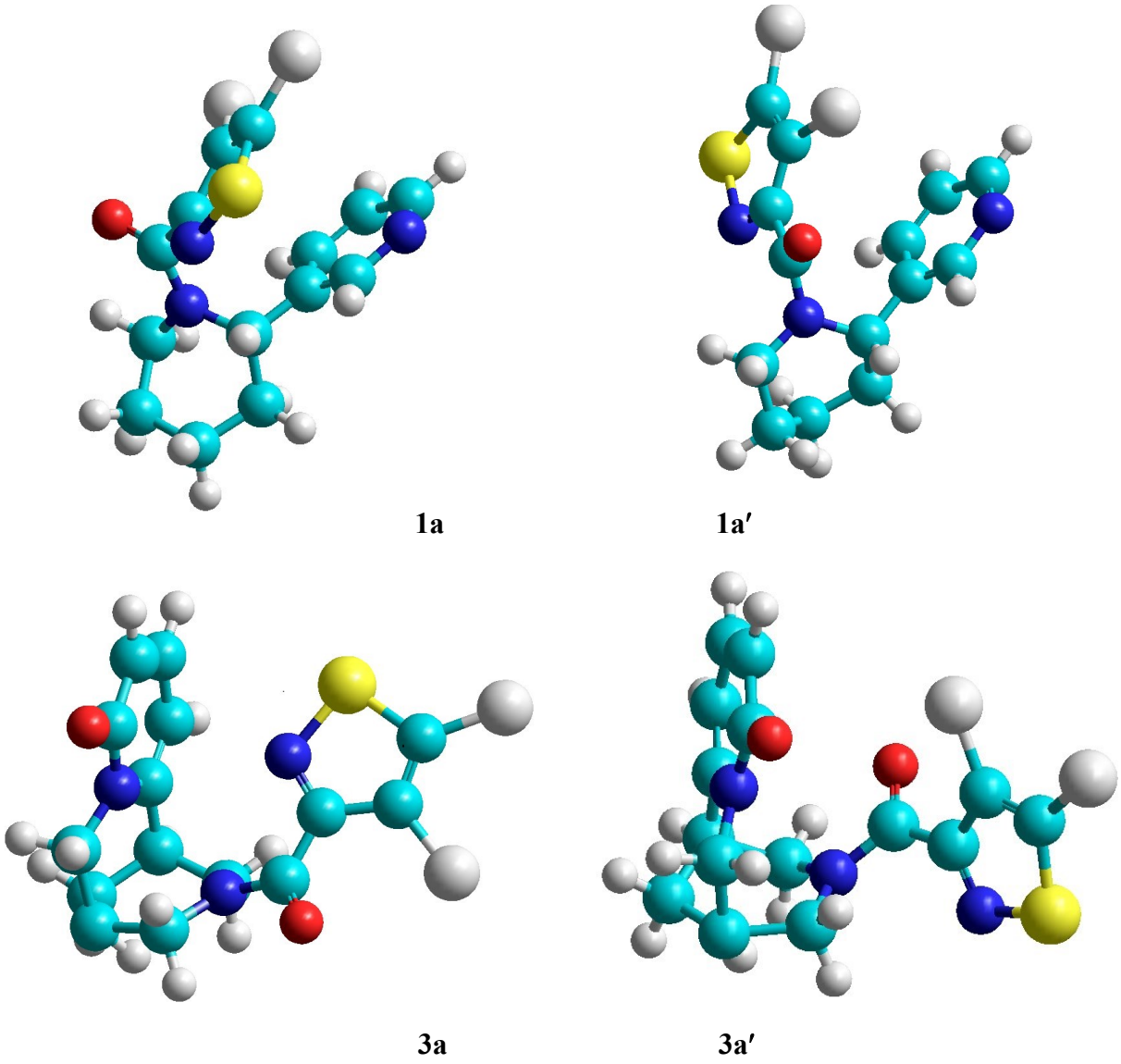

Figure 2. Rotamers of the isothiazole derivatives of anabasine 1a and cytisine 3a.

Enthalpy of transition between two energy states of some alkaloid derivatives

Compound	E_{tot1}, a.e.	E_{tot2}, a.e.	DH, kJ/mol
1a	−2088.4064475735	−2088.3980505218	22.05
1b	−1081.8459454116	−1081.8465730531	1.65
1c	−1120.9340754442	−1120.9406860121	17.35
1f	−995.9839497508	−995.9839012747	0.13
3a	−2201.0972381247	−2201.0973439503	0.27
3b	−1194.5402013015	−1194.5402363646	0.09
3c	−1233.6283876889	−1233.6283950807	0.02
3f	−1108.6840108051	−1108.6773643453	17.45

From an analysis of ^{1}H and ^{13}C NMR spectra of **1a-d**, **2a-d**, **3a-c** we can assume the presence of two rotational isomers of cytisine and anabasine amides with fragments of 1,2-azoles and pyridine (Fig. 2). Since the barriers of these rotations are not large (Table), it leads to registration of spectra from both conformers and to broadening of the spectrum lines.

This phenomenon is not observed in the NMR spectra for alkaloids derivatives with adamantane fragment, since the adamantane fragment is symmetrical relative to the N-C(O) bond.

Based on the synthesized derivatives **1a-f**, quaternary pyridinium salts (iodomethylates) were obtained. Quaternization led to the formation of monoidomethylates **1a-c** in 95–99% yield and diiodomethylates **2d,e** in 91–95% yield. The quaternization reaction proceeds completely with a 3-fold excess of the alkylating agent, and the resulting salts precipitate out of the solution.

Quaternization of alkaloids amides makes it possible to increase the water solubility of compounds, which is important for choosing the most rational ways of introducing drugs into the body. Pyridinium salts are also known to inhibit the growth of various microorganisms such as bacteria, viruses and fungi [23].

The obtained compounds were identified on the basis of IR, UV, mass and NMR spectra (^{1}H and ^{13}C), as well as elemental analysis.

All synthesized compounds were tested for antiviral activity.

Conclusion

A convenient method has been developed for obtaining natural derivatives of anabazine and cytisine alkaloids by the acylation reaction of 1,2-azole-3-, pyridine-3-, pyridine-4- and adamantane-1-carbonyl chlorides. According to biotesting data, adamantane derivatives of anabazine and cytisine showed pronounced antiviral properties, even surpassing commercial drugs Tamiflu and Remantadine in activity. In some cases, the quaternization of compounds has a positive effect on their antimicrobial activity. The above facts allow us to consider the derivatives of N-acyl anabazine and cytisine promising for further study of their pharmacological properties

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