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Synthesis, quantum-chemical calculations and virtual screening of the alkaloid cytisine derivatives

The synthesis of some cytisine derivatives was carried out in the work. The article provides the data of quantum-chemical calculation and virtual screening of the alkaloid cytisine derivatives synthesized. At the same time, the reaction centers of the cytisine derivatives molecules were determined. In order to study the reactivity of the derivatives obtained (namely cinnamoylcytisine, lipoylcytisine, and cytisinylisoalantholactone) the quantum-chemical calculations were conducted to determine the energy and charge characteristics of the molecules. The results indicate a sufficient thermodynamic stability of the cinnamoylcytisine and lipoylcytisine molecules. The cytisinylisoalantholactone molecule is not stable according to the results of quantum chemical calculations. The data on the energy values of the frontier molecular orbitals show that, in general, all molecules exhibit electrophilic properties. A bioprediction was implemented using PASS (Prediction of Activity Spectra for Substances) as one of the most efficient and well-known computer program with the aim of detailed study and the probable establishment of the biological activity of the synthesized cytisine derivatives. Based on the results of virtual screening, promising types of alkaloid cytisine derivatives were identified, which are potential sources of original drugs.

Keywords: alkaloids, cytisine, synthesis, physicochemical properties, derivatives, quantum-chemical calculation, virtual screening, prediction of activity spectra for substances.

Introduction

Carrying out directed synthetic transformations of available substances of plant origin in order to create new biologically active compounds is an actively developing area of fine organic synthesis and medicinal chemistry [1–4]. Taking into account the valuable biological properties of alkaloids and their derivatives, the search for new ways of chemical modification of alkaloids is undoubtedly relevant, and the attention of researchers is attracted by the obtaining of more complexly constructed heterocyclic systems. Interest in research on the chemical transformation of the alkaloid cytisine is due to the wide spectrum of biological activity of its derivatives. To date, a large number of derivatives of the cytisine alkaloid with various groups at the nitrogen atom have been synthesized [5–6]. Research on the transformation of available alkaloids, the use of which in medicine is not possible due to significant side effects, is being successfully developed.

It should be noted that compounds with other types of biological activity, not typical for cytisine itself, namely antispasmodic, antiarrhythmic, hepatoprotective, analgesic, cholinergic, insecticidal, fungicidal etc., are constantly found among the various cytisine derivatives, which attracts attention and encourages the implementation of syntheses and its new derivatives investigation [7–12]. Recently, a new class of heterocyclic compounds with a fundamental 1,4-dihydropyridine base, possessing high antihypertensive and nootropic activity, has begun to be widely used in medical practice [13–14]. The aim of this work is to synthesize and develop derivatives of the cytisine alkaloid with various functionally substituted fragments in terms of further obtaining new modified structures applying quantum-chemical calculations and pharmacological activity evaluation.

Experimental

^{1}H and ^{13}C NMR spectra of compounds (2-4) were recorded on a JNN-ECA Jeol 400 spectrometer (frequencies 399.78 and 100.53 MHz, respectively) using a DMSO-d_6 solvent. Chemical shifts were measured relative to the signals of residual protons or carbon atoms of DMSO-d_6. The reaction progress and the ob-

tained purity of compounds were monitored by thin layer chromatography on Silufol UV-254 plates in isopropyl alcohol-ammonia-water 7:2:1, ethanol-chloroform 1:4 systems. The plates were developed with iodine vapors. The reaction products were isolated by recrystallization or by column chromatography on alumina. All solvents used in this work were purified and absolutized according to standard methods.

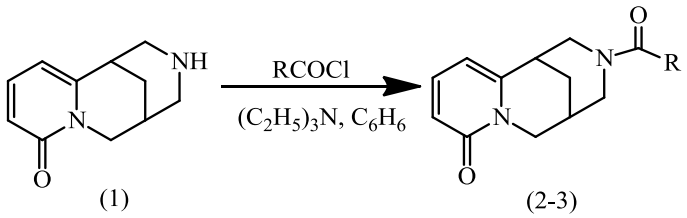
N-Cinnamoylcytisine (2). 9 g (6.0 mmol) of triethylamine and a solution of 15 g (6.0 mmol) of cinnamoyl chloride in 200 ml of benzene were added with stirring to a solution of 17.1 g (6.0 mmol) of cytisine in 500 ml of benzene. The reaction mixture was stirred for 3.3 hours at room temperature until a precipitate formed. The formed precipitate of triethylamine hydrochloride was filtered off, the mother liquor was evaporated, and the residue was treated with diethyl ether. There was obtained 14.25 g (95 %) of N-cinnamoylcytisine (2) in the form of a white powder with a yellowish tint, m.p. 130-134°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.86-1.97 m (2H, H8.8), 2.44 br.s. (1H, H9), 2.90-3.40 m (3H. H7.11ax, 13ax), 3.63-3.97 m (2H, H10ax, 10eq), 4.24-4.65 m (2H, H11eq, 13eq, 6.14 d (2H, H3, 5. 3J 6.1), 6.49-6.75 m (1H, H15), 7.16-7.64 m (7H, H4, 15, 18-22). ^{13}C NMR spectrum, δC, ppm: 25.95 (C8), 27.86 (C9), 35.13 (C7), 49.05 (C10), 51.31 (C11), 53.04 (C13), 105.29 (C5), 116.40 (C3), 128.85 (C15), 129.24 (C18, 19, 21, 22), 129.99 (C20), 135.55 (C4), 139.09 (C16), 141.32 (C17), 150.47 (C6), 162.66 (C2), 165.65 (C14) ppm HMQC (^{1}H-^{13}C) NMR cross peaks, ppm: H8-C8 (1.96, 26.60), H9-C9 (2.44, 28.48), H7-C7 (3.13, 35.65), H10ax-C10ax (3.59, 49.56), H10ax-C10ax (3.98, 49.58), H5-C5 (6.14, 105.76), H3-C3 (6.12, 116.82) and H18,19,21,22-C18,19,21,22 (7.37, 129.52).

N-Lipoylcytisine (3). A solution of 29.61 g (8.78 mmol) of lipoyl chloride [obtained from 67.5 g (21.95 mmol) of lipoic acid and 48.96 g (27.43 mmol) of thionyl chloride], dissolved in 250 ml of benzene was added with stirring to a solution of 25.05 g (8.78 mmol) of cytisine and 18.3 ml (8.78 mmol) of triethylamine in 500 ml of benzene. The reaction mixture was stirred for 3 hours at room temperature until a precipitate formed. The precipitate was filtered off, the mother liquor was evaporated, and the residue was chromatographed on silica gel (eluent: benzene-chloroform). 13.8 g (64.56%) lipoylcytisine (3) was isolated as yellowish thick oil.

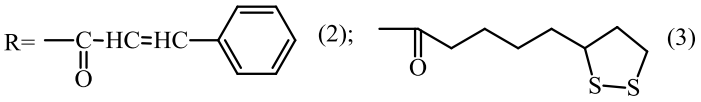
In order to study the reactivity of the derivatives obtained, quantum-chemical calculations were conducted to determine the energy and charge characteristics of molecules, namely cinnamoylcytisine (2), lipoylcytisine (3), and cytisinylisoalantholactone (4). The semiempirical methods AM1 and PM6 were applied quantum-chemical calculations. In addition, we can note the following: in *ab initio* methods, all integrals included in the system of Hartree-Fock equations are calculated explicitly and no experimentally determined parameters are used, except for fundamental physical constants, while the PM6 method combines experimental data as well as ab initio data. The AM1 method was applied to compare hydrogen bonds. The calculations were carried out with the help of MOPAC2009 [15]. The ChemOffice software made it possible to construct the geometry of the studied molecules.

Results and Discussion

The cytisine source availability and the analysis of its structure designate a significance of carrying out its synthetic transformations with the compounds, which are structurally similar to a number of natural metabolites and other practically significant compounds. Thus, the acylation of cytisine with acid chlorides and anhydrides is the simplest and most convenient method for the preparation of its acyl derivatives [16]. Continuing studies of the transformation of cytisine (1) and in order to search for pharmacologically active compounds in this series, we have synthesized acyl derivatives by the interaction of cytisine with carboxylic acid chlorides, where cinnamoyl chloride and lipoyl chloride were used as acylating agents [17–18]. The acylation of cytisine with carboxylic acid chlorides was implemented in benzene in the presence of triethylamine at room temperature. The reactions proceeded smoothly and led to the production of N-acyl derivatives of cytisine (2-3) with a yield of 64-95 %. The synthesized compounds (2, 3) are white crystalline substances, readily soluble in organic solvents.

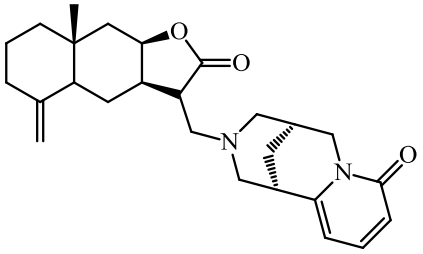


(1) (2-3)



The ^{1}H NMR spectrum of compound (2) is characterized by the presence of multiplet in the upfield region at 1.86-1.97 ppm with the 2H intensity of two H8 protons of the heterocyclic nucleus. The H9 proton resonates as a broadened singlet at 2.44 by the integral 1H. Then, a multiplet appeared in the region of 2.90-3.40 ppm with an integrated intensity of 3H, corresponding to the H7 proton and the axial protons H^{11ax} and H^{13ax}. Equatorial protons H^{11eq} and H^{13eq} appeared as a multiplet signal at 4.24-4.65 ppm with an integral intensity of 2H. Two protons H^{10ax}, 10^{eq} as a result of spin-spin coupling, as well as spin-spin splitting through three bonds with the proton H9 appeared as a multiplet in the region of 3.63-3.97 ppm with integral 2H. Doublet at 6.14 ppm with integral 2H and 3J, 6.1 Hz corresponds to protons H3 and H5. An unsaturated proton H15 (1H) appeared in the region of olefinic protons resonance with a multiplet at 6.49-6.75 ppm, while the adjacent unsaturated proton H16 was detected together with aromatic protons H18-22 and a proton H4 multiplet in the lowest-field part of the spectrum with an integrated intensity of 7H at 7.16-7.64 ppm.

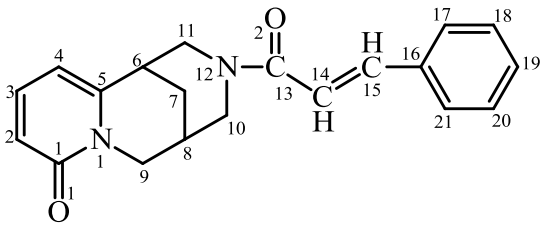
On the basis of the alkaloid cytisine and isoalantholactone, cytisinylisoalantholactone (4) was synthesized with m.p. 196–198 °C, formula $C_{26}H_{34}N_2O_3$, M=422.256 g/mol.



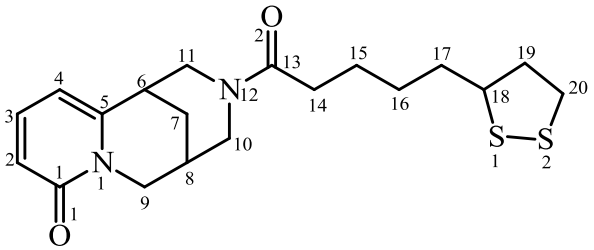
(4)

The structure was established and confirmed using spectral methods and comparison of the literature data [19].

In order to study the reactivity of the molecules of cinnamoylcytisine (2), lipoylcytisine (3), and cytisinylisoalantholactone (4), determine their energy and charge characteristics quantum-chemical calculations were carried out. The calculations were conducted by semiempirical quantum-chemical methods in the AM1 and PM6 parametrization.



(2)



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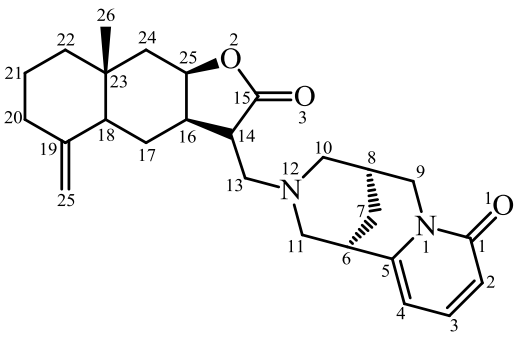


(4)

A quantum-chemical calculations of molecules main energy characteristics were performed to study the thermodynamic stability. The obtained results are illustrated in Table 1.

Table 1

Energy characteristics of molecules (2-4)

Energy characteristics	Method	Molecules		
		(2)	(3)	(4)
Heat of formation, kJ / mol	AM1	32.922	-243.137	623.483
	PM6	-114.86	-379.245	412.703
Total energy, eV	AM1	-3889.28	-4235.07	-5094
	PM6	-3662.65	-3973.06	-4804.12
Ionization potential, eV	AM1	8.774	8.163	8.597
	PM6	8.996	8.414	8.704
HOMO, eV	AM1	-8.775	-8.163	-8.597
	PM6	-8.996	-8.414	-8.704
LUMO, eV	AM1	-0.550	-1.454	-0.812
	PM6	-0.547	-1.094	-0.330

The results presented in the Table 1 indicate a sufficient thermodynamic stability of molecules (2-3). Molecule (4) is not stable according to the results of quantum-chemical calculations. The data on the energy values of the frontier orbitals demonstrate that the molecules (2-4) exhibit electrophilic properties. The Mulliken charge distribution on non-hydrogen atoms was calculated to determine the position of the reaction centers in molecules (2-4). The results are shown in Figure 1.

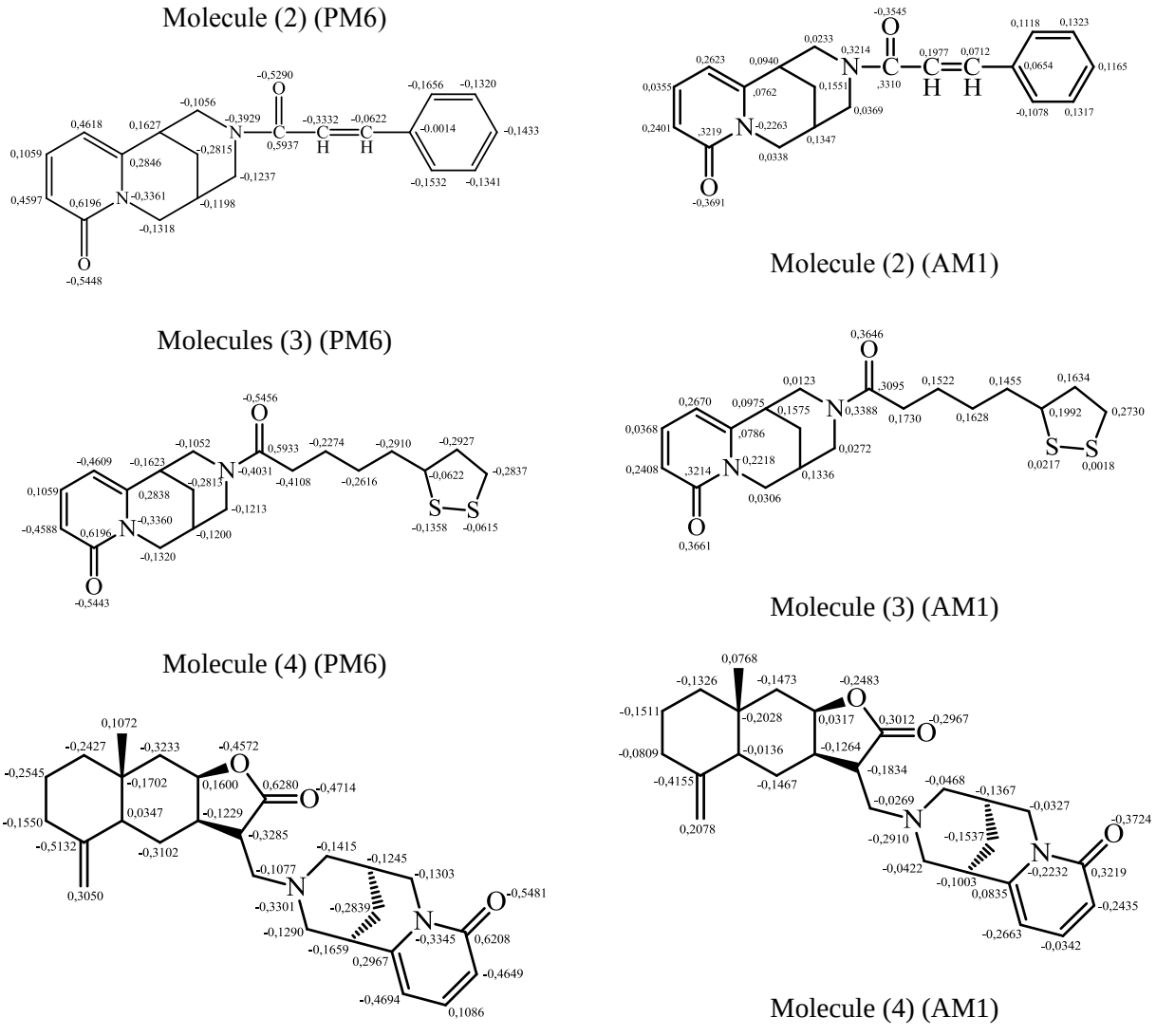


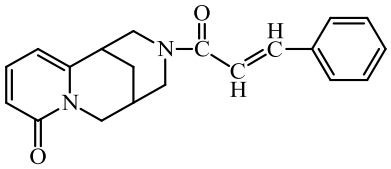
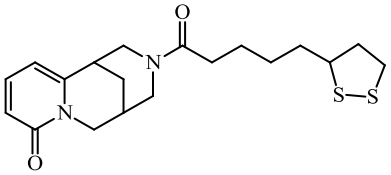
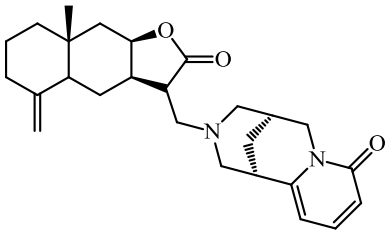
Figure 1. Mulliken charge distribution on non-hydrogen atoms in molecules (2-4)

Based on the data presented above, it can be concluded that the preferred centers for attack by nucleophilic reagents in molecule (2) are C1, C2, C4, and C13 atoms, in molecule (3) — C1, C5, and C13, and in molecule (4) — C1, C5, C15 and C25, which is explained by the presence of an aromatic ring and the adjacent position of keto groups in the structures of the molecules studied.

In terms of a detailed study and establishment of the probable biological activity of synthesized cytisine derivatives, we performed a bioprediction using PASS (Prediction of Activity Spectra for Substances) as one of the most effective and well-known computer programs to date [20]. The results of the bioprediction of the compounds synthesized are presented in the Table 2, in the form of the proposed activity name and the coefficients of the probability of the presence (P_a) and absence (P_i), of each type of activity, which have values from 0 to 1. In this analysis of the predicted list of activities, the conditions were selected, where P_a>70 %.

Table 2

Results of computer screening of compounds synthesized (2-4)

No.	Structural formula	P_a (Pharmacological Active)	P_i (Pharmacological Inactive)	Intended type of activity
1	Cinnamoylcytisine 	0.927	0.002	Nicotinic alpha-2-beta-2 receptor antagonist
		0.844	0.001	Alpha-4-beta-2 nicotinic receptor antagonist
		0.766	0.010	Respiratory analeptic
		0.653	0.014	Analeptic
		0.559	0.025	Anticonvulsant
		0.532	0.003	Alpha-6 nicotinic receptor agonist
		0.545	0.039	Phosphatidylcholine retinol-O-acyltransferase inhibitor
		0.476	0.019	Cognitive disorders treatment
		0.503	0.060	Neurotransmitter uptake inhibitor
		0.472	0.035	All-trans retinyl palmitate hydrolase inhibitor
2	Lipoylcytisine 	0.783	0.002	Alpha-4-beta-2 nicotinic receptor antagonist
		0.753	0.017	Nicotinic alpha-2-beta-2 receptor antagonist
		0.718	0.025	Antiischemic, cerebral
		0.659	0.010	Treatment of neurodegenerative diseases
		0.648	0.004	Growth stimulant
		0.633	0.004	Chemoprotective
		0.612	0.006	Treatment of liver diseases
		0.573	0.010	Cognitive disorders treatment
		0.525	0.010	Antiparkinsonian
		0.530	0.029	Anticonvulsant
		0.462	0.005	Growth hormone agonist
		0.454	0.025	Muscular dystrophy treatment
		0.447	0.019	Alzheimer's disease treatment
3	Cytisinylisoalantholactone 	0.830	0.004	Analeptic
		0.829	0.007	Respiratory analeptic
		0.796	0.019	Anti-eczematic
		0.738	0.002	Alpha-4-beta-2 nicotinic receptor antagonist
		0.733	0.021	Antineoplastic
		0.678	0.018	Phosphatase inhibitor
		0.583	0.004	Antineoplastic drugs (pancreatic cancer)
		0.591	0.013	Polarization stimulator
		0.579	0.016	Cardiovascular analeptic
		0.556	0.010	Antimetastatic
		0.575	0.036	Neurotransmitter uptake inhibitor
		0.514	0.029	Dermatological
		0.532	0.048	Anti-inflammatory agent

Computer prognosis demonstrated that cinnamoylcytisine probably (P_a>0.5) has antidepressant and nootropic properties, and also revealed the possibility of its using in the treatment of nicotine addiction in the future.

As a result of predicting the spectrum of biological activity in the PASS online system, the presence of hepatoprotective, antiparkinsonian, neurotropic, nootropic, anabolic actions for lipoylcytisine with a proba-

bility of $P_a > 0.5$ were revealed; and for cytisinylisoalantholactone antitumor, anti-inflammatory, neurotropic effects with a probability of $P_a > 0.5$, as well as the possibility of its use as an analeptic agent in chronic heart failure were predicted.

Thus, the bioscreening of synthesized cytisine derivatives showed the promising use of such compounds in medicine as inhibitors of neurotransmitters uptake, an inhibitor of phosphatidylcholine-retinol-O-acyltransferase, an inhibitor of all-trans-retinyl palmitate hydrolase, etc. This circumstance is significant, since medicines can be obtained on the basis of these compounds.

Conclusions

On the basis of the cytisine molecule, samples of cinnamoylcytisine (2), lipoylcytisine (3), and cytisinylisoalantholactone were synthesized. According to the results of quantum-chemical calculations of these molecules, it was established that the preferred centers for attack by nucleophilic reagents in molecule (2) are C1, C2, C4, and C13 atoms, in molecule (3) — C1, C5, and C13, and in molecule (4) — C1, C5, C15 and C25, which can be explained by the presence of an aromatic ring and the adjacent position of keto groups in the structures of the molecules studied. In addition to it, data of virtual bioscreening of cytisine alkaloid derivatives are provided.

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References

1 Юнусов С.Ю. Алкалоиды: моногр. / С.Ю. Юнусов. — Ташкент: ФАН, 1972. — 270 с.

2 Нуркенов О.А. Синтетические трансформации алкалоида цитизина: моногр. / О.А. Нуркенов, И.В. Кулаков, С.Д. Фазылов. — Караганда: Гласир, 2012. — 210 с.

3 Тлегенов Р. Синтез, строение и свойства производных лупинина, анабазина, цитизина и ряда азотсодержащих гетероциклов: автореф. дис. … д-ра хим. наук / Р. Тлегенов. — 2008. — 54 с.

4 Takagi K. Synthesis of new 3(5)-(2-hydroxyphenyl)pyrazoles as potential analgesic agents and platelet aggregation inhibitors / K. Takagi, M. Tanaka, Y. Murakami, H. Morita, T. Aotsuka // Eur. J. Med. Chem. Chim. Ther. — 1986. — Vol. 21. — P. 65–68. https://doi.org/10.1002/chin.198627339

5 Садыков А.С. Алкалоиды хинолизидинового ряда: моногр. / А.С. Садыков, Х.А. Асланов, Ю.К. Кушмурадов. — М.: Наука, 1975. — 292 с.

6 Нуркенов О.А. Алкалоид анабазин и его производные: моногр. / О.А. Нуркенов, С.Д. Фазылов, И.В. Кулаков, Л.А. Мусина. — Караганда: Гласир, 2010. — 224 с.

7 Kulakov I.V. Synthesis of N-aminoglycosides derived from alkaloid cytisine, their biological activity and crystal structure of N-(β-D-galactopyranosyl)cytisine / I.V. Kulakov, O.A. Nurkenov, D.M. Turdybekov, R.B. Sejdahmetova, K.M. Turdybekov // Chemistry of Heterocyclic Compounds. — 2010. — Vol. 46, No. 2. — P. 240–244. https://doi.org/10.1002/chin.201049202

8 Gazaliev A.M. Synthesis and fungicidal activity of alkaloid-containing carbohydrates / A.M. Gazaliev, O.A. Nurkenov, I.V. Kulakov, A.A. Ainabaev, D.V. Bessonov // Russian Journal of Applied Chemistry. — 2006. — Vol. 79, No. 3. — P. 508–510. https://doi.org/10.1134/S1070427206030402

9 Kulakov I.V. Synthesis and biological activity of 3,4-dihydropyrimidin-2-thione aminomethylene derivatives based on the alkaloid cytisine / I.V. Kulakov // Chemistry of Natural Compounds. — 2011. — Vol. 47, No. 4. — P. 597–599.

10 Kulakov I.V. Synthesis and biological activity of aminoacyl phenothiazine derivatives based on the alkaloids cytisine, anabasine, and d-pseudoephedrine / I.V. Kulakov // Chemistry of Natural Compounds. — 2010. — Vol. 46, No. 1. — P. 68–71.

11 Yazlovitskii A.V. Synthesis of N-Acylamino-Acid Derivatives of Cytisine / A.V. Yazlovitskii, M.M. Garazd, V.G. Kartsev // Chemistry of Natural Compounds. — 2016. — Vol. 52. — P. 272–275.

12 Rouden J. (–)-Cytisine and and derivatives: synthesis, reactivity, and applications / J. Rouden, M.C. Lasne, J. Blanchet, J. Baudoux // Chem. Rev. — 2014. — Vol. 114, No. 1. — P. 712–778. https://doi.org/10.1021/cr400307e

13 Tsypysheva I.P. Synthesis and Nootropic Activity of new 3-Amino-12-N-Methylcytisine Derivatives / I.P. Tsypysheva, A.V. Koval'skaya, A.N. Lobov, N.S. Makara, P.R. Petrova, E.I. Farafontova, L.F. Zainullina, Yu.V. Vakhitova, F.S. Zarudii // Chem. Nat. Compd. — 2015. — Vol. 51. — P. 910–915. https://doi.org/10.1007/s10600-015-1446-x

14 Tsypysheva I.P. Synthesis and specific nootropic activity of (–)-cytisine derivatives with carbamide and thiocarbamide moieties in their structure / I.P. Tsypysheva, A.V. Koval'skaya, N.S. Makara, A.N. Lobov, I.A. Petrenko, E.G. Galkin, T.A. Sapozhnikova, F.S. Zarudii, M.S. Yunusov // Chem. Nat. Compd. — 2012. Vol. 48. — P. 629-634. https://doi.org/10.1007/s10600-012-0329-7

15 James J.P. Stewart, MOPAC 2009, Stewart Computational Chemistry / J.P. James. — Colorado Springs, CO, USA, 2008. http://OpenMOPAC.net.

16 Тлегенов Р. Синтез N-ацильных производных алкалоида цитизина / Р. Тлегенов // Химия раст. сырья. — 2007. — №1. — С. 49–52.

17 Нуркенов О.А. Синтез, строение и биологическая активность циннамоилсодержащих производных алкалоидов цитизина и анабазина / О.А. Нуркенов, Ж.С. Нурмаганбетов, Т.М. Сейлханов, С.Д. Фазылов, Ж.Б. Сатпаева, К.М. Турдыбеков, С.А. Талипов, Р.Б. Сейдахметова // Журн. общ. хим. — 2019. — Т. 89, № 10. — С. 1550–1559. https://doi.org/10.1134/S0044460X19100093

18 Nurkenov O.A. Synthesis and structured N-acyl and thiourea derivatives citizine and anabazine / O.A. Nurkenov, Zh.S. Nurmaganbetov, T.M. Seilkhanov, S.D. Fazylov, V.M. Manasheva, A.R. Zhasymbekova, A.S. Serikbolov // News of the academy of sciences of the Republic of Kazakhstan. — 2020. — No. 1(439). — P. 37–46. https://doi.org/10.32014/2020.2518-1491.5

19 Klochkov S.G. Modification of alantolactones by natural alkaloids / S.G. Klochkov, S.V. Afanas'eva, A.B. Ermatova, A.V. Chudinov // Chemistry of natural compounds. — 2011. — Vol. 47, No. 5. — P. 716–725. https://doi.org/10.1007/s10600-011-0043-x

20 Садым А.В. Интернет-система прогноза спектра биологической активности химических соединений / А.В. Садым, А.А. Лагунин, Д.А. Филимонов, В.В. Поройков // Хим. фарм. журн. — 2002. — Т. 36, № 10. — С. 21–26. https://doi.org/10.30906/0023-1134-2002-36-10-21-26

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Цитизин алкалоиды туындыларының синтезі, кванттық-химиялық есептеулері және олардың виртуалды скринингі

Мақалада цитизиннің кейбір туындыларына синтез жүргізілген. Цитизин алкалоидының синтезделген туындыларын кванттық-химиялық есептеу және виртуалды скрининг тің деректері алынды. Бұл ретте цитизин туындыларының молекулаларындағы реакция орталықтары анықталды. Алынған туындылардың реакцияға қабілеттілігін зерттеу мақсатында молекулалардың энергиялық және зарядтық сипаттамаларын анықтау үшін циннамоилцитизин, липпоилцитизин, цитизинилизоалантолактон молекулаларына кванттық-химиялық есептеулер жүргізілді. Ұсынылған нәтижелер циннамоилцитизин, липпоилцитизин молекулаларының жеткілікті термодинамикалық тұрақтылығын көрсетеді. Кванттық химиялық есептеулердің нәтижелері бойынша цитизинилизоалантолактон молекуласы онша тұрақты емес екендігі байқалды. Шектік молекулалық орбитальдардың мәндері туралы мәліметтер, жалпы алғанда, барлық молекулалардың электрофильді қасиетке ие екендігін растайды. Синтезделген цитизин туындыларының биологиялық белсенділігін анықтау мақсатымен ең тиімді және танымал компьютерлік бағдарламалардың бірі — PASS (Prediction of Activity Spectra for Substances) көмегімен биоболжамдау жүргізілді. Виртуалды скрининг нәтижелері бойынша бастапқы препараттардың әлеуетті көздері болып табылатын цитизин алкалоидының туындыларының перспективалы түрлері анықталды.

Кілт сөздер: алкалоидтар, цитизин, синтез, физикалық-химиялық қасиеттері, туындылар, кванттық-химиялық есептеулер, виртуалдық скрининг, заттардың биологиялық белсенділігін болжамдау.

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Синтез, квантово-химические расчеты производных алкалоида цитизина и их виртуальный скрининг

В статье проведен синтез некоторых производных цитизина. Получены данные квантово-химического расчета и виртуального скрининга синтезированных производных алкалоида цитизина. Определены реакционные центры в молекулах производных цитизина. С целью изучения реакционной способности полученных производных авторами проведены квантово-химические расчеты определения энергетических и зарядовых характеристик молекул: циннамоилцитизина, липпоилцитизина, цитизинилизоалантолактона. Представленные результаты свидетельствуют о достаточной термодинамической стабильности молекул циннамоилцитизина и липпоилцитизина. Молекула цитизинилизоалантолактона, по результатам квантово-химических расчетов, малостабильна. Данные значений граничных молекулярных орбиталей показывают, что, в целом, все молекулы проявляют электрофильные свойства. В плане детального изучения и вероятного установления биологической активности синтезированных производных цитизина был сделан биопрогноз с использованием одной из наиболее эффективных и

известных на сегодняшний день компьютерных программ – PASS (Prediction of Activity Spectra for Substances). По результатам виртуального скрининга выявлены перспективные типы производных алкалоида цитизина, являющиеся потенциальными источниками оригинальных препаратов.

Ключевые слова: алкалоиды, цитизин, синтез, физико-химические свойства, производные, квантово-химический расчет, виртуальный скрининг, прогнозирование спектров активности веществ.

References

1 Yunussov, S.Yu. (1972). *Alkaloidy [Alkaloids]*. Tashkent: FAN [in Russian].

2 Nurkenov, O.A., Kulakov, I.V., & Fazylov, S.D. (2012). *Sinteticheskiie transformatsii alkaloida tsitizina [Synthetic transformations of cytisine alkaloid]*. Karaganda: Glasir [in Russian].

3 Tlegenov, R. (2008). Sintez, stroieniie, i svoistva proizvodnykh lupinina, anabazina, tsitizina i riada azotsoderzhashchikh heterotsiklov [Synthesis, structure and properties of derivatives of lupinine, anabasine, cytisine and a number of nitrogen-containing heterocycles]. *Extended abstract of Doctor's thesis* [in Russian].

4 Takagi, K., Tanaka, M., Murakami, Y., Morita, H., & Aotsuka T. (1986). Synthesis of new 3(5)-(2-hydroxyphenyl)pyrazoles as potential analgesic agents and platelet aggregation inhibitors. *Eur. J. Med. Chem. Chim. Ther.* 21, 65-68. https://doi.org/10.1002/chin.198627339

5 Sadykov, A.S., Aslanov, Kh.A., & Kushmuradov, Yu.K. (1975). *Alkaloidy khinolizidinovoho riada [Quinolizidine alkaloids]*. Moscow: Nauka [in Russian].

6 Nurkenov, O.A., Fazylov, S.D., Kulakov, I.V., & Musina, L.A. (2010). *Alkaloid anabazin i eho proizvodnyie [The alkaloid anabazine and its derivatives]*. Karaganda: Glasir [in Russian].

7 Kulakov, I.V., Nurkenov, O.A., Turdybekov, D.M., Sejdahmetova, R.B., & Turdybekov, K.M. (2010). Synthesis of N-aminoglycosides derived from alkaloid cytisine, their biological activity and crystal structure of N-(β-D-galactopyranosyl)cytisine. *Chemistry of Heterocyclic Compounds, 46(2)*, 240–244. https://doi.org/10.1002/chin.201049202

8 Gazaliev, A.M., Nurkenov, O.A., Kulakov, I.V., Ainabaev, A.A., & Bessonov, D.V. (2006). Synthesis and fungicidal activity of alkaloid-containing carbohydrates. *Russian Journal of Applied Chemistry, 9(3)*, 508–510. https://doi.org/10.1134/S1070427206030402

9 Kulakov, I.V. (2011). Synthesis and biological activity of 3,4-dihydropyrimidin-2-thione aminomethylene derivatives based on the alkaloid cytisine. *Chemistry of Natural Compounds, 47(4)*, 597–599.

10 Kulakov, I.V. (2010). Synthesis and biological activity of aminoacyl phenothiazine derivatives based on the alkaloids cytisine, anabasine, and d-pseudoephedrine. *Chemistry of Natural Compounds, 46(1)*, 68–71.

11 Yazlovitskii, A.V., Garazd, M.M., & Kartsev, V.G. (2016). Synthesis of N-Acylamino-Acid Derivatives of Cytisine. *Chemistry of Natural Compounds*, 52, 272–275.

12 Rouden, J., Lasne, M.C., Blanchet, J. & Baudoux, J. (2014). (–)-Cytisine and and derivatives: synthesis, reactivity, and applications. *Chem. Rev., 114*, 712. https://doi.org/10.1021/cr400307e

13 Tsypysheva, I.P., Koval'skaya, A.V., Lobov, A.N., Makara, N.S., Petrova, P.R., & Farafontova, E.I., et al. (2015). Synthesis and Nootropic Activity of new 3-Amino-12-N-Methylcytisine Derivatives. Chem. Nat. Compd., 51, 910-915. https://doi.org/10.1007/s10600-015-1446-x

14 Tsypysheva, I.P., Koval'skaya, A.V., Makara, N.S., Lobov, A.N., Petrenko, I.A., & Galkin, E.G., et al. (2012). Synthesis and specific nootropic activity of (–)-cytisine derivatives with carbamide and thiocarbamide moieties in their structure. *Chem. Nat. Compd., 48*, 629-634. https://doi.org/10.1007/s10600-012-0329-7

15 James J.P. (2008). *Stewart, MOPAC 2009*, *Stewart Computational Chemistry*. Colorado Springs, CO, USA, http://OpenMOPAC.net.

16 Tlegenov, R. (2007). Sintez N-atsilnykh proizvodnykh alkaloida tsitizina [Synthesis of N-acyl derivatives of the alkaloid cytisine]. *Khimiia rastitelnogo syria — Chemistry of plant raw materials*, 1, 49–52 [in Russian].

17 Nurkenov, O.A., Nurmaganbetov, Zh.S., Seilkhanov, T.M., Fazylov, S.D., Satpayeva, Zh.B., & Turdybekov, K.M., et al. (2019). Sintez, stroenie i biologicheskaia aktivnost tsinnamoilsoderzhashchikh proizvodnykh alkaloidov tsitizina i anabazina [Synthesis, structure and biological activity of cinnamoyl-containing derivatives of cytisine and anabasine alkaloids]. *Zhurnal obshchei khimii — Journal of General Chemistry*, 89(10), 1550–1559 [in Russian]. https://doi.org/10.1134/S0044460X19100093

18 Nurkenov, O.A., Nurmaganbetov, Zh.S., Seilkhanov, T.M., Fazylov, S.D., Manasheva, V.M., & Zhasymbekova, A.R., et al.. (2020). Synthesis and structured N-acyl and thiourea derivatives citizine and anabazine *News of the academy of sciences of the Republic of Kazakhstan*, 1(439), 37–46. https://doi.org/10.32014/2020.2518-1491.5

19 Klochkov, S.G., Afanas'eva, S.V., Ermatova, A.B., & Chudinov, A.V. (2011). Modification of alantolactones by natural alkaloids *Chemistry of natural compounds*, 47(5), 716-725. https://doi.org/10.1007/s10600-011-0043-x

20 Sadym, A.V., Lagunin, A.A., Filimonov, D.A., & Poroikov, V.V. (2002). Internet-sistema prognoza spectra biologicheskoi aktivnosti khimicheskikh soedinenii [Internet-system for prediction of the spectrum of biological activity of chemical compounds]. *Khimiko-farmatsevticheskii zhurnal — Chem. pharm. journal*, 36(10), 21–26 [in Russian]. https://doi.org/10.30906/0023-1134-2002-36-10-21-26

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