UDC 547.837.2 https://doi.org/10.24959/ophcj.20.193867

E. V. Zaliznaya, S. A. Varenichenko, O. K. Farat, V. I. Markov

Ukrainian State University of Chemical Technology, Ukraine
8, Gagarin Ave., Dnipro, Ukraine, 49005. E-mail: zaliznayaekaterina@gmail.com

The study of the neurotropic activity of the pyrrolopyrimidin-4-ones rearrangement products under the action of phosphorus oxychloride

Aim. To synthesize the annelated 4-aminopyridines and study the biological activity of one of products.

Results and discussion. In the laboratory of the Research Institute of Biomedical Problems of the Dnipropetrovsk Medical Academy the studies of the effect of 2,3,3-trimethyl-2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[3,4-*b*]quinolin-9-amine on the neuroactivity in the "open field" model have been conducted. According to the results of the experiment it has been found that in two hours after the administration of the oil solution of the compound the indices of the motor activity of mice are significantly reduced.

Experimental part. 2,3,3-Trimethyl-2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[3,4-*b*]quinolin-9-amine and 2,3,6,7,7-pentamethyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-4-amine were obtained by the rearrangement of the corresponding pyrrolopyrimidin-4-ones under the action of the excess of phosphorus oxychloride in toluene. The initial pyrrolopyrimidin-4-ones were synthesized by the condensation of 4-amino-1,2,2-trimethyl-2,5-dihydro-1*H*-pyrrole-3-carbonitrile with ketones. The structure of all compounds obtained was confirmed by ^{1}H NMR-spectroscopy, mass spectrometry and elemental analysis.

Conclusions. The neurotropic activity has been detected for the oil solution of 2,3,3-trimethyl-2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[3,4-*b*]quinolin-9-amine on the "open field" model. It has been found that the aqueous solution of this compound does not exhibit the neurotropic activity regardless of the administered dose. Taking into account the presence of the neurotropic activity further research in this field is a promising way to search novel bioactive molecules among 4-aminopyridine derivatives, which are structural analogs of the drug Tacrine.

***Key words*:** rearrangement; pyrrolopyrimidin-4-ones; aminohydroacridines; neurotropic activity; Tacrine

К. В. Залізна, С. А. Вареніченко, О. К. Фарат, В. І. Марков
Український державний хіміко-технологічний університет, Україна

Дослідження нейротропної активності продуктів перегрупування піролопіримідин-4-онів під дією хлорокису фосфору

Мета. Синтезувати анельовані 4-амінопіридини та дослідити біологічну активність одного з продуктів.

Результати та їх обговорення. У лабораторії науково-дослідного інституту медико-біологічних проблем Дніпропетровської медичної академії проведено дослідження впливу 2,3,3-триметил-2,3,5,6,7,8-гексагідро-1*H*-піроло-[3,4-*b*]хінолін-9-аміну на показники нейроактивності на моделі «відкрите поле». За результатами експерименту було встановлено, що через дві години після введення олійного розчину сполуки показники рухової активності були значно знижені.

Експериментальна частина. 2,3,3-Триметил-2,3,5,6,7,8-гексагідро-1*H*-піроло-[3,4-*b*]хінолін-9-амін і 2,3,6,7,7-пентаметил-6,7-дигідро-5*H*-піроло[3,4-*b*]піридин-4-амін одержано у результаті перегрупування відповідних піролопіримідин-4-онів під дією надлишку хлорокису фосфору у толуені. Вихідні піролопіримідин-4-они синтезовано конденсацією 4-аміно-1,2,2-триметил-2,5-дигідро-1*H*-піроло-3-карбонітрилу з кетонами. Будову всіх отриманих сполук доведено за допомогою ^{1}H ЯМР-спектроскопії, мас-спектрометрії та елементного аналізу.

Висновки. Виявлено нейротропну активність для 2,3,3-триметил-2,3,5,6,7,8-гексагідро-1*H*-піроло[3,4-*b*]-хінолин-9-аміну у вигляді олійного розчину на моделі «відкрите поле». Встановлено, що водний розчин даної сполуки не проявляє нейротропну активність незалежно від об'єму введеної дози. Враховуючи наявність нейротропної активності, перспективним є проведення подальших досліджень серед похідних 4-амінопіримідинів, які є структурними аналогами лікарського засобу «Такрин».

Ключові слова: перегрупування; піролопіримідин-4-они; аміногідроакридини; нейротропна активність; Такрин

Е. В. Зализная, С. А. Вареніченко, О. К. Фарат, В. И. Марков
Украинский государственный химико-технологический университет, Украина

Исследование нейротропной активности продуктов перегруппировки пирролопиримидин-4-онов под действием хлорокиси фосфора

Цель. Синтезировать аннелированные 4-аминопиридины и изучить биологическую активность одного из продуктов.

Результаты и их обсуждение. В лаборатории научно-исследовательского института медико-биологических проблем Днепропетровской медицинской академии проведены исследования влияния 2,3,3-триметил-2,3,5,6,7,8-гексагидро-1*H*-пирроло[3,4-*b*]хинолин-9-амина на показатели нейротропной активности на модели «открытое поле». По результатам эксперимента было установлено, что через два часа после введения масляного раствора соединения показатели двигательной активности были существенно снижены.

Экспериментальная часть. 2,3,3-Триметил-2,3,5,6,7,8-гексагидро-1*H*-пирроло[3,4-*b*]хинолин-9-амин и 2,3,6,7,7-пентаметил-6,7-дигидро-5*H*-пирроло[3,4-*b*]пиридин-4-амин получены в результате перегруппировки соответствующих пирролопиримидин-4-онов под действием избытка хлорокиси фосфора в толуоле. Исходные пирролопиримидин-4-оны синтезированы конденсацией 4-амино-1,2,2-триметил-2,5-дигидро-1*H*-пирроло-3-карбонитрила с кетонами. Структура всех полученных соединений установлена с помощью ^{1}H ЯМР-спектроскопии, масс-спектрометрии и элементного анализа.

Выводы. Выявлена нейротропная активность для 2,3,3-триметил-2,3,5,6,7,8-гексагидро-1*H*-пирроло[3,4-*b*]-хинолин-9-амина в виде масляного раствора на модели «открытое поле». Установлено, что водный раствор данного соединения не проявляет нейтротропную активность независимо от объема введенной дозы. Учитывая наличие нейротропной активности перспективно проведение дальнейших исследований среди производных 4-аминопиримидина, которые являются структурными аналогами лекарственного препарата «Такрин».

Ключевые слова: перегруппировка; пирролопиримидин-4-оны; аминогидроакридины; нейротропная активность; Такрин

One of the most promising approaches to the creation of new drugs is the synthesis of molecules close in structure to those natural compounds that play a key role in certain biochemical processes. To a large extent, this applies to various condensed systems with a pyridine nucleus, for example, such as derivatives of acridine and quinoline. Research in this area is carried out mainly in two directions: modification of the pyridine skeleton with pharmacophore fragments or annulation of new heteronuclei to the pyridine ring. In medical practice, for the treatment of Alzheimer's disease, 1,2,3,4-tetrahydroacridine-9-amine is used, a vivid representative of the condensed system with the pyridine core, it is better known as the drug Tacrine [1]. However, along with the effectiveness of the drug a strongly pronounced hepatotoxic effect is observed, which forces us to conduct new studies in this area. In neurology, more attention is paid to the concept of mixed dementia, according to which both the neurodegenerative and ischemic components are present in the development of vascular and neurodegenerative cognitive impairment. In Alzheimer's disease, concomitant vascular pathology leads to the formation of a more pronounced cognitive deficiency and intensification of the degenerative process. One of the directions of the treatment may be a decrease in the presence of these metabolic cerebral disorders [2]. In this regard, the efforts of many researchers are aimed at finding analogs of Tacrine among derivatives of acridines, which would have a higher pharmacological activity with low toxicity [3–5].

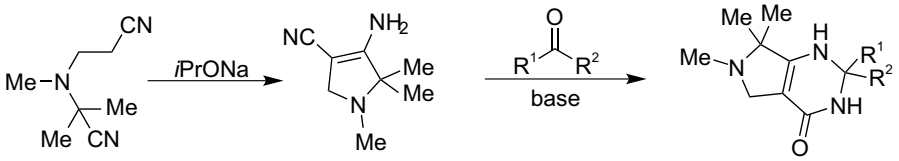
Earlier, we proposed the one-stage method for the synthesis of hard-to-reach derivatives of hydroacridines [6] – structural analogs of Tacrine, and also studied their reactivity [7–10]. Taking into account the prospects of this area the aim of our work is the synthesis of compounds that are structural analogs of Tacrine and the study of the biological activity of one of them.

2,2-Disubstituted pyrimidin-4-ones **3a–d** were selected as model compounds. Compounds **3a–d** were synthesized by condensation of 4-amino-1,2,2-trimethyl-2,5-dihydro-1*H*-pyrrole-3-carbonitrile **2** with ketones. Enaminonitrile **2** was obtained by Torp–Ziegler cyclization of dinitrile **1** [11] with a good yield when using sodium isopropylate as a catalyst, in contrast to the published data where stronger bases were used for such cyclizations (Scheme 1) [12–15].

The structure of the compounds synthesized was confirmed by ^{1}H NMR-spectroscopy and mass spectrometry, as well as by elemental analysis. The signals of amide NH (6.68 ppm) and amine NH (6.53 ppm) protons in ^{1}H NMR-spectra of compounds **3a–d** were characteristic for the derivatives of 2,2-disubstituted pyrimidin-4-ones [16].

The rearrangement of substituted pyrimidin-4-ones under the action of acid agents leading to the formation of bisannelated ones was previously described in literature [17–21]. The compounds containing the 4-aminopyridine cycle, like 4-aminopyridine itself, are modulators of ion channels. These compounds stimulate the formation of acetylcholine, its synthesis in the body is necessary for the treatment of Alzheimer's disease [22].

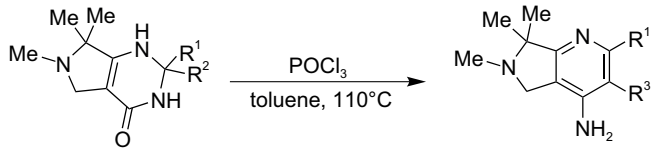
From the analysis of the published data, it follows that overcoming the energy barrier to the opening of



1 **2** **3a–d**

3a $R^1 + R^2 = (CH_2)_5$; **3b** $R^1 = R^2 = CH_3$;
3c $R^1 = CH_3$, $R^2 = C_2H_5$; **3d** $R^1 = CH_3$, $R^2 = n$Bu

Scheme 1. The synthesis of 2,2-disubstituted pyrimidin-4-ones **3a–d**



3a,c **4a,c** (45–67%)

3a $R^1 + R^2 = (CH_2)_5$; **3b** $R^1 = R^2 = CH_3$;
4a $R^1 + R^3 = (CH_2)_4$; **4c** $R^1 = R^3 = CH_3$

Scheme 2. The synthesis of substituted 4-aminopyridines **4a,c**

the pyrimidine cycle occurs at high temperatures in the strong acid medium [21]. Similar reaction conditions became the basis of our synthetic procedure. To expand the range of bisannelated 4-aminopyridines and study their biological activity pyrrolopyrimidin-4-ones **3a**,**c** were rearranged with an excess of $POCl_3$ by boiling in toluene. As a result of the reaction, the expected annelated 4-aminopyridines **4a,c** were isolated (Scheme 2).

In the case of compound **4a** we proposed the following scheme for the mechanism of this reaction (Scheme 3).

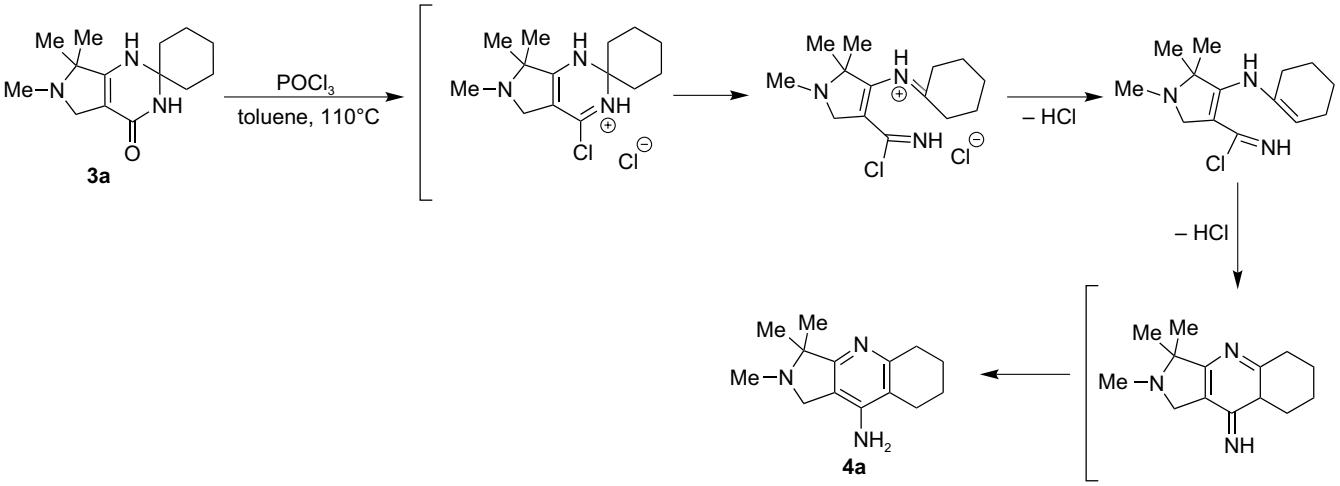
The prospect of substituted 4-aminopyridines as biologically active substances prompted us to test compounds **4a** for the presence of the neuroactivity. In the laboratory of the Research Institute of Biomedical Problems of the Dnipropetrovsk Medical Academy under the supervision of prof. Drozdov O. L. the studies of the effect of compound **4a** on the neuroactivity in the "open field" model were conducted. The experiment was carried out on 20 white adult mice weighing 150.0–200.0 g. The substance was administered in the form of the oil solution in the doses of 10, 20, 100 mg/kg. Compound **4a** was administered to mice intraperitoneally on an empty stomach. Before the introduction of the compound solution the "open field" test was performed for each group of mice to determine the baseline. After that mice were injected with the oil solution of compound **4a** in an equivalent dose, and the "open field" test was performed in 2 hours after the administration. A day later, the group of mice was re-tested to record the dynamics of the indicators. The behavior indicators of mice were changed on a setup of 100×100 cm in size with a distance between false burrows of 10 cm. The data obtained were mathematically processed using Student's *t*-test.

The number of crossed squares for 2 minutes was indicative of the horizontal motor activity (HMA), the number of lifts on the hind legs was indicative of the vertical motor activity (VMA), the number of acts of defecation boluses (ADB) was indicative of the emotional reactivity, the number of burrows examined (NBE) was indicative of the unconditioned reflex activity. Along with these indicators, the continuation of grooming (Gr.) in seconds was recorded during testing. The test results are presented in Table and Fig.

According to the results of the experiment it was found that in two hours after the administration of the oil solution of compound **4a** the indices of the motor activity of mice, namely horizontal and vertical, were significantly reduced. The percent changes in the parameters were the same, regardless of the dose used. It was found that an hour after the administration of the aqueous solution of compound **4a** the indices of the motor activity did not change.

Experimental part

^{1}H NMR-spectra were obtained on a Bruker Avance II 400 spectrometer in DMSO-d_6 with TMS as an internal standard. Mass spectra (FAB ionization) were registered on a VG-7070 spectrometer. Ion desorption from *m*-nitrobenzyl alcohol was done by a beam of argon atoms with an energy of 8 keV. Mass spectra (EI ionization, 70 eV) for compounds **3c** and **4a** were recorded on a MX1321 apparatus with direct sample injection at 200°C of ionization chamber temperature. Elemental analysis was performed on a LECO CHN-900 elemental analyzer. Melting points were determined on an Electrothermal 9100 digital apparatus. Monitoring of the reaction progress and assessment of



Scheme 3

Table

The effect of compound **4a** in the form of the oil solution on mice

	Series of observations	Static indicators	HMA	VMA	Gr.	NBE	ADB
1	The study background	M	40.40	7.40	0.20	4.33	1.20
		±m	7.65	0.51	0.20	0.61	0.80
2	Two hours after injection; the dose of 10 mg/kg	M	14.40	2.60	6.60	1.00	0.40
		±m	4.85	1.03	3.74	0.32	0.40
		% measurement	–64.36%	–64.87%	32.00%	–76.91%	–66.67%
3	The study background	M	39.40	8.00	2.80	3.20	1.60
		±m	4.87	1.14	0.86	0.80	0.51
4	Two hours after injection; the dose of 20 mg/kg	M	21.20	4.40	0.40	1.60	0.80
		±m	5.88	1.21	0.40	0.51	0.00
		% measurement	–46.19%	–45.00%	–85.71%	–50.00%	–50.00%
5	The study background	M	29.60	6.50	6.20	2.80	0.90
		±m	4.17	1.15	2.38	1.06	0.28
6	Two hours after injection; the dose of 100 mg/kg	M	12.90	2.10	4.30	1.80	0.30
		±m	2.23	0.57	2.59	0.61	0.15
		% measurement	–56.42%	–67.69%	–30.65%	–35.71%	–66.67%

the purity of the compounds synthesized was done by TLC on Silica gel 60 F254 plates (Merck), the eluent – $CHCl_3$–*i*PrOH (10:1), visualization in the iodine chamber. Compounds **1** and **2** were obtained according to the literature methods [11].

6',7',7'-Trimethyl-1',5',6',7'-tetrahydrospiro-[cyclohexane-1,2'-pyrrolo[3,4-*d*]pyrimidin]-4'-(3'*H*)-one 3a. Dissolve enaminonitrile **2** (0.01 mol) in cyclohexanone (0.015 mol), and add 5 mL of 2 M solution of NaOH/MeOH. Heat the reaction mixture

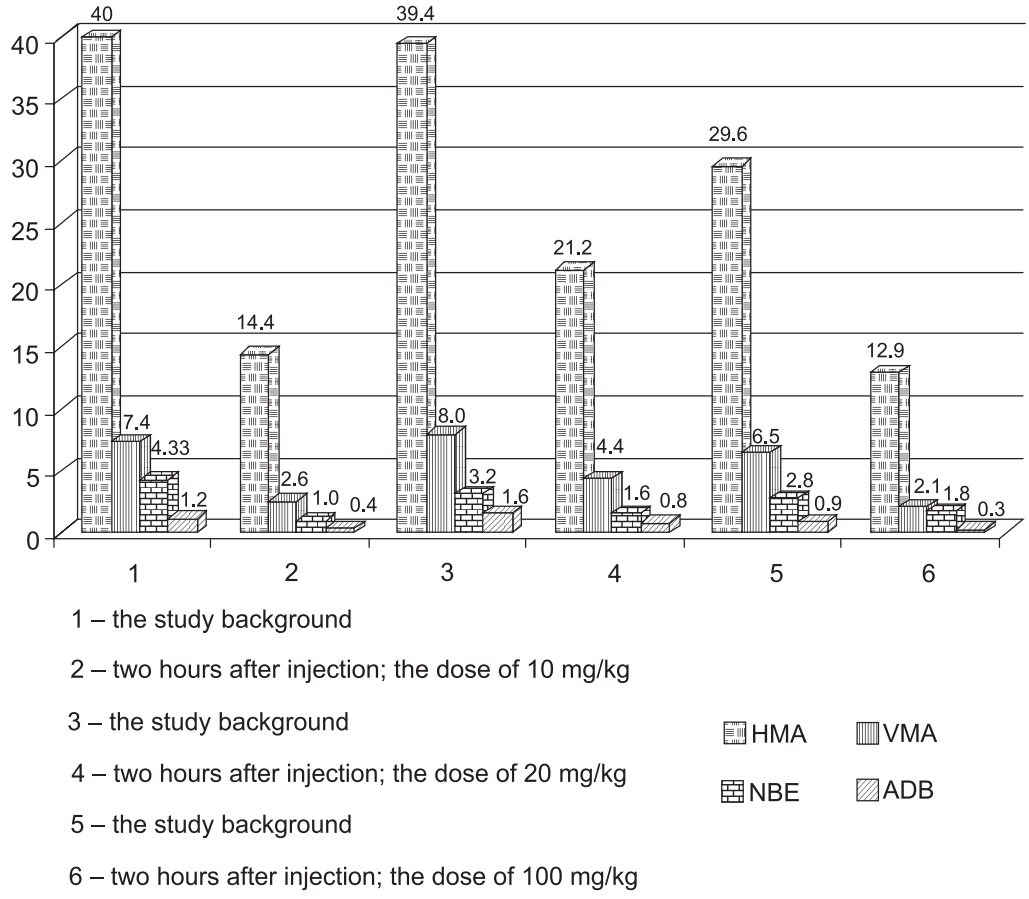


Fig. The plot of the effect of compound **4a** in the form of the oil solution on mice

under reflux for 20 min. Then pour the reaction mixture onto ice, filter the precipitate and recrystallize from acetonitrile. A colorless powder. Yield – 78%. M. p. 185–190°C. Anal. Calcd. for $C_{14}H_{23}N_3O$, %: C 67.43, H 9.30, N 16.85. Found, %: C 67.61, H 9.19, N 16.98. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.68 (1H, s, CONH), 6.53 (1H, s, NH), 3.26 (2H, s, CH_2), 2.18 (3H, s, N–CH_3), 1.25–1.72 (9H, m, 4CH_2, CH_{eq}), 1.06 (6H, s, 2CH_3), 0.97–1.04 (1H, m, CH_{ax}). Mass spectrum (FAB), m/z (*I*, %): 250[M+H]$^+$ (100).

2,2,6,7,7-Pentamethyl-1,2,3,5,6,7-hexahydro-4*H*-pyrrolo[3,4-*d*]pyrimidin-4-one 3b. Dissolve enaminonitrile **2** (0.01 mol) in an excess of acetone (15 mL), then add a catalyst – 5 mL of 2 M NaOH aqueous solution. Allow the mixture to stand at room temperature for 3–4 days, filter the crystals formed and recrystallize from methanol or acetonitrile. A white powder. Yield – 74%. M. p. 265–267°C. Anal. Calcd. for $C_{11}H_{19}N_3O$, %: C 63.13, H 9.15, N 20.08. Found, %: C 63.24, H 9.02, N 20.21. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.81 (1H, s, CONH), 6.69 (1H, s, NH), 3.27 (2H, s, CH_2), 2.19 (3H, s, N–CH_3), 1.31 (6H, s, 2CH_3), 1.03 (6H, s, 2CH_3). Mass spectrum (FAB), m/z (*I*, %): 210 [M+H]$^+$ (100).

The synthesis of compounds 3c,d. Dissolve enaminonitrile **2** (0.01 mol) in an excess of 15 mL of the appropriate ketone, then add a catalyst – 5 mL of 2 M KOH solution in methyl alcohol. Boil the mixture for 3 h and pour onto ice, filter the crystals formed and recrystallize from methanol.

2-Ethyl-2,6,7,7-tetramethyl-1,2,3,5,6,7-hexahydro-4*H*-pyrrolo[3,4-*d*]pyrimidin-4-one 3c. A white powder. Yield – 89%. M. p. 200–202°C. Anal. Calcd. for $C_{12}H_{21}N_3O$, %: C 64.54, H 9.48, N 18.82. Found, %: C 64.67, H 9.60, N 18.65. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.70 (1H, s, CONH), 6.59 (1H, s, NH), 3.26 (2H, s, CH_2), 2.19 (3H, s, N–CH_3), 1.59 (2H, q, ^3J = 7.0 Hz, C$\underline{H}_2$CH$_3$), 1.26 (3H, s, CH_3), 1.04 (6H, s, 2CH_3), 0.81 (3H, t, ^3J = 7.0 Hz, $CH_2C\underline{H}_3$). Mass spectrum (EI), m/z (*I*, %): 223 [M]$^+$ (20).

2-Butyl-2,6,7,7-tetramethyl-1,2,3,5,6,7-hexahydro-4*H*-pyrrolo[3,4-*b*]pyrimidin-4-one 3d. A white powder. Yield – 20%. M. p. 200–202°C. Anal. Calcd. for $C_{14}H_{25}N_3O$, %: C 66.89, H 10.02, N 16.72. Found, %: C 66.93, H 10.22, N 16.53. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.73 (1H, s, CONH), 6.58 (1H, s, NH), 3.27 (2H, s, N–CH_2), 2.21 (3H, s, N–CH_3), 1.22–1.64 (6H, m, 3CH_2), 1.25 (3H, s, CH_3), 1.04 (6H, s, 2CH_3), 0.82 (3H, t, ^3J = 7.0 Hz, CH_3). Mass spectrum (FAB), m/z (*I*, %): 252 [M+H]$^+$ (100).

The general procedure for preparation of compounds 4a,c. In a round bottom flask mix 0.01 mol of the corresponding pyrrolopyrimidin-4-one **3** and 0.04 mol of $POCl_3$ in 50 mL of toluene. Heat the reaction mixture for 3 h. After cooling decant the toluene layer and add aqueous methanol to dissolve the precipitate. After neutralizing the aqueous 15% NaOH solution to pH = 9–10, a white precipitate is formed, which is further recrystallized from methanol.

2,3,3-Trimethyl-2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[3,4-*b*]quinolin-9-amine 4a. A white powder. Yield – 67%. M. p. 155–157°C. Anal. Calcd. for $C_{14}H_{21}N_3$, %: C 72.69, H 9.15, N 18.16. Found, %: C 72.83, H 9.28, N 18.05. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 5.43 (2H, br s, NH_2), 3.57 (2H, s, N–CH_2), 2.61 (3H, s, N–CH_3), 2.22–2.42 (4H, m, 2CH_2), 1.55–1.83 (4H, m, 2CH_2), 1.04 (6H, s, 2CH_3). Mass spectrum (EI), m/z (*I*, %): 231[M]$^+$ (2), 216 [M–CH_3]$^+$ (100).

2,3,6,7,7-Pentamethyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-4-amine 4c. A white powder. Yield – 45%. M. p. 170–172°C. Anal. Calcd. for $C_{12}H_{19}N_3$, %: C 70.20, H 9.33, N 20.47. Found, %: C 70.32, H 9.19, N 20.38. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 5.52 (2H, br s, NH_2), 3.64 (2H, s, CH_2), 2.37 (3H, s, N-CH_3), 2.34 (3H, s, CH_3), 1.97 (3H, s, CH_3), 1.15 (6H, s, 2CH_3). Mass spectrum (FAB), m/z (*I*, %): 206 [M+H]$^+$ (100).

Conclusions

As a result of the interaction of 4-amino-1,2,2-trimethyl-2,5-dihydro-1*H*-pyrrole-3-carbonitrile and ketones, 2,2-disubstituted 6,7,7-trimethyl-1,2-pyrolo-[3,4-*d*]pyrimidin-4(3*H*)-ones have been synthesized. It has been found that 6,7,7-trimethylpyrrolo[3,4-*d*]-pyrimidin-4(3*H*)-ones undergo the rearrangement under the action of $POCl_3$ to form pyrrolo[3,4-*b*]quinolin (pyridine) derivatives. The results of the "open field" test have shown that the oil solution of acridine **4a** exhibits the neurotropic activity, which is independent of the volume of the administered dose.

Conflict of interests: authors have no conflict of interests to declare.

References

1. Keri, R. S.; Quintanova, C.; Marques, S. M.; Esteves, A. R.; Cardoso, S. M.; Santos, M. A. Design, synthesis and neuroprotective evaluation of novel tacrine–benzothiazole hybrids as multi-targeted compounds against Alzheimer's disease. *Bioorg. Med. Chem.* **2013,** *21* (15), 4559-4569. https://doi.org/10.1016/j.bmc.2013.05.028.
2. Савельєва, О. В.; Шумова, Г. С.; Владимирова, І. М. Аналіз фармацевтичного ринку ноотропних засобів в Україні. *ScienceRise* **2015,** *11* (4), 30-36. https://doi.org/10.15587/2313-8416.2015.54873.
3. Chao, X.; He, X.; Yang, Y.; Zhou, X.; Jin, M.; Liu, S.; Cheng, Z.; Liu, P.; Wang, Y.; Yu, J.; Tan, Y.; Huang, Y.; Qin, J.; Rapposelli, S.; Pi, R. Design, synthesis and pharmacological evaluation of novel tacrine–caffeic acid hybrids as multi-targeted compounds against Alzheimer's disease. *Bioorg. Med. Chem. Lett.* **2012,** *22* (20), 6498-6502. https://doi.org/10.1016/j.bmcl.2012.08.036.
4. Hebda, M.; Bajda, M.; Więckowska, A.; Szałaj, N.; Pasieka, A.; Panek, D.; Godyń, J.; Wichur, T.; Knez, D.; Gobec, S.; Malawska, B. Synthesis, Molecular Modelling and Biological Evaluation of Novel Heterodimeric, Multiple Ligands Targeting Cholinesterases and Amyloid Beta. *Molecules* **2016,** *21* (4), 410-434. https://doi.org/10.3390/molecules21040410.

5. Boulebd, H.; Ismaili, L.; Bartolini, M.; Bouraiou, A.; Andrisano, V.; Martin, H.; Bonet, A.; Moraleda, I.; Iriepa, I.; Chioua, M.; Belfaitah, A.; Marco-Contelles, J. Imidazopyranotacrines as Non-Hepatotoxic, Selective Acetylcholinesterase Inhibitors, and Antioxidant Agents for Alzheimer's Disease Therapy. *Molecules* **2016,** *21* (4), 400-416. https://doi.org/10.3390/molecules21040400.
6. Markov, V. I.; Farat, O. K.; Varenichenko, S. A.; Velikaya, E. V. Rearrangement of 5',6',7',8'-tetrahydro-1'*H*-spiro(cyclohexane-1,2'-quinazolin)-4'(3'H)-one during the Vilsmeier reaction. *Mendeleev Commun.* **2012,** *22* (2), 101-102. https://doi.org/10.1016/j.mencom.2012.03.017.
7. Zaliznaya, E. V.; Farat, O. K.; Gorobets, N. Y.; Markov, V. I.; Zubatyuk, R. I.; Mazepa, A. V.; Vashchenko, E. V. Reactions of octahydroacridine-4-carbonitrile (carboxamide) with electrophilic reagents. *Chem. Heterocycl. Comp.* **2015,** *51* (4), 327-333. https://doi.org/10.1007/s10593-015-1703-8.
8. Zaliznaya, E. V.; Farat, O. K.; Varenichenko, S. A.; Mazepa, A. V.; Markov, V. I. Functionalization of tetra- and octahydroacridine derivatives through Michael addition. *Tetrahedron Lett.* **2016,** *57* (31), 3485-3487. https://doi.org/10.1016/j.tetlet.2016.06.096.
9. Zalizna, E. V.; Polishuk, T. P.; Varenichenko, S. A.; Farat, O. K.; Markov, V. I. The interreaction of 4,5-diformyl-2,3,6,7,8,10-hexahydroacridine-8a(1*H*)-carbonitrile with *n*-nucleophiles. *Journal of Organic and Pharmaceutical Chemistry* **2016,** *14* (3), 38-42. 10.24959/ophcj.16.888.
10. Zaliznaya, E. V.; Smetanin, N. V.; Varenichenko, S. A.; Mazepa, A. V.; Farat, O. K.; Markov, V. I. Synthesis of new hexahydro-5*H*-indolo[3,2-c]acridines and indolylbutanoic acids by Fischer cyclization of arylhydrazones. *Chem. Heterocycl. Comp.* **2018,** *54* (2), 138-145. https://doi.org/10.1007/s10593-018-2245-7.
11. Dimroth, K.; Aurich, H. G. Zur Cyanmethylierung schwach basischer Amine. *Chem. Ber.* **1965,** *98* (12), 3902-3906. https://doi.org/10.1002/cber.19650981217.
12. Schramm, S.; Schmitz, E.; Gründemann, E. Einfache Darstellung von 4-Oxo-tetrahydropyrimidinen. *Journal für Praktische Chemie* **1984,** *326* (2), 279-286. https://doi.org/10.1002/prac.19843260213.
13. Cavalla, J. F. 899. 3-Amino-4-cyano-3-pyrrolines: their hydrolysis to 3-pyrrolidones and their reaction with hydrogen sulphide. *Journal of the Chemical Society (Resumed)* **1962,** (0), 4664-4672. https://doi.org/10.1039/JR9620004664.
14. Cavalla, J. F. 3-amino-4-cyano-3-pyrrolines: Their conversion to pyrrolo[3,4-*d*]pyrimidines. *Tetrahedron Lett.* **1964,** *5* (39), 2807-2808. https://doi.org/10.1016/S0040-4039(00)70425-4.
15. Cavalla, J. F.; Willis, J. A. D. Substituted pyrrolo[3,4-d]pyrimidines: their preparation from 3-amino-4-cyano-3-pyrrolines. *Journal of the Chemical Society C: Organic* **1967,** (0), 693-697. https://doi.org/10.1039/J39670000693.
16. Pretsch, E.; Bühlmann, P.; Badertscher, M. *Structure Determination of Organic Compounds*. 4th ed.; Springer-Verlag Berlin Heidelberg: Berlin, 2009; p 433.
17. Varenichenko, S. A.; Farat, O. K.; Markov, V. I. Reactivity of Substituted 2-Spiropyrimidin-4-Ones Under Vilsmeier–Haack Conditions. *Chem. Heterocycl. Comp.* **2015,** *50* (11), 1602-1607. https://doi.org/10.1007/s10593-014-1626-9.
18. Zigeuner, G.; Gübitz, G. Über das Tetrahydrospiro[cyclohexan-1,2'(1'H)-chinazolin]-4'(3'H)-on. *Monatsh Chem* **1970,** *101* (5), 1547-1558. https://doi.org/10.1007/BF00911421.
19. Upadysheva, A. V.; Grigor'eva, N. D.; Ryabokobylko, Y. S.; Znamenskaya, A. P. Recyclization of 2,2-disubstituted 4(3*H*)-oxo- and 4-chloro-1,2-dihydropyrimidines to 4-aminopyridine derivatives. *Chem. Heterocycl. Comp.* **1983,** *19* (1), 95-100. https://doi.org/10.1007/BF00512825.
20. Bischoff, C.; Herma, H. Eine einfache Synthese des Cyclohexanon-2-carbonsäure-amids sowie dessen Reaktionen. *Journal für Praktische Chemie* **1976,** *318* (5), 773-778. https://doi.org/10.1002/prac.19763180508.
21. Upadysheva, A. V.; Grigor'eva, N. D.; Znamenskaya, A. P. Intramolecular rearrangement of two-ring 2,2-disubstituted 4-oxo-1,2,3,4-tetrahydropyrimidines under the influence of polyphosphoric acid. *Chem. Heterocycl. Comp.* **1977,** *13* (11), 1240-1243. https://doi.org/10.1007/BF00475956.
22. Andreani, A.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Pietra, C.; Villetti, G. 4-Aminopyridine derivatives with antiamnesic activity. *Eur. J. Med. Chem.* **2000,** *35* (1), 77-82. https://doi.org/10.1016/S0223-5234(00)00103-3.

Received: 26. 12. 2019
Revised: 20. 01. 2020
Accepted: 27. 02. 2020

Acknowledgements
The authors thank prof. O. L. Drozdov and K. O. Suprunenko for the help in organization of biochemical tests.
The research was carried out according to the budget theme of the Ministry of Education and Science of Ukraine "New synthetic methods for the design of nitrogen- and sulfur-containing biologically active compounds" (the state registration No. 0115U003159; the research period 2015–2020).