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THE STUDY OF NEUROTROPIC ACTION OF ALKALOIDS AND THEIR DERIVATIVES

Abstract. The article presents the results of a study of the neurotropic action of alkaloids and their derivatives. It was established that the studied compounds 8-acetylharmine, ((E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indol-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one, lappaconitine and cytisine at a dose of 5 mg/kg have a neurotropic effect, increasing the level of the orienting reaction of animals in the «Open field» test; they also normalize the emotional state, reducing the level of anxiety and fear of animals in the test "Elevated plus maze".

Keywords: alkaloids, neurotropic action, emotional stress, alkaloid derivatives.

Introduction. Currently in the world there is an increase in the number of neurological patients, an increase in the morbidity of the nervous system. Among the main causes of the spread of diseases of the central nervous system can be called stress, psycho-emotional stress, which results in anxiety, depression, develop of addictions [2]. In this regard, there is a significant interest of researchers to neurotropic drugs [1]. Among the promising in the study of the neurotropic action of natural compounds alkaloid compounds and their derivatives should be noted.

Alkaloids are a group of natural organic compounds that are synthesized by plants [3]. Alkaloids can affect the central nervous system, including the nerve cells of the brain and spinal cord, which control many of the functions of the human body and its behavior [4,5]. Experimental evidence has been obtained that alkaloids have a broad spectrum of pharmacological properties, including neurotropic effects and can selectively bind to receptors of nerve cells [4-11].

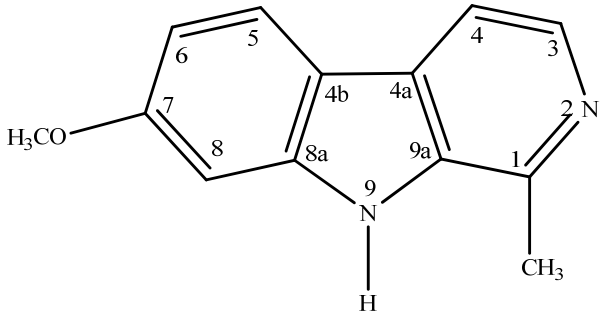
The most interesting in their chemical structure are the indole, isoquinoline, diterpene and pyrrolidine alkaloids, among which there are substances with various combinations of methoxy, hydroxy, amino, carboxy and heterocycles, as well as conformational and optical isomers, which can serve as a source for obtaining various drugs, including neurotropic drugs.

Thus, the indole alkaloid, harmine, has an effect on the central nervous system (CNS), showing its effect in neurological diseases [12, 13]. Diterpene alkaloids have a broad spectrum of biological activity, which allows them to be considered as a source of promising pharmacological compounds [14, 15].

Objective: to study the neurotropic action of alkaloid compounds and their derivatives on experimental stress models.

Material and Methods: The following compounds were presented for the study: harmine (1), 8-acetylharmine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4- b] indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4), delkozin (5), lappaconitine (6), cytisine (7), echinopsine (8).

Previously a computer simulation of the molecules of the substances and virtual docking with the proposed biological target dopamine receptor D2 were carried out. The ligand-target interaction strength was evaluated by the binding energy index.



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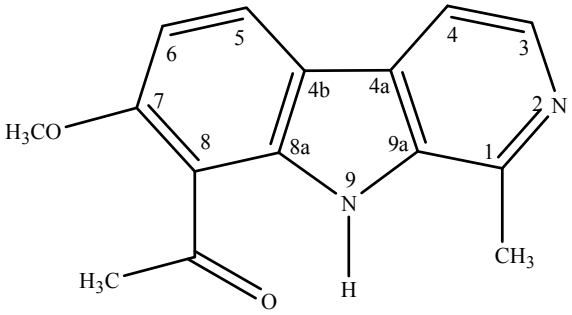

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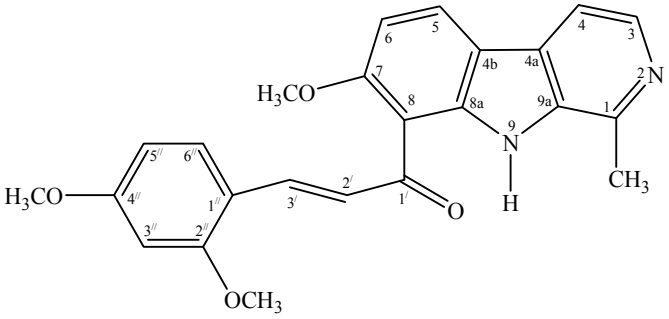

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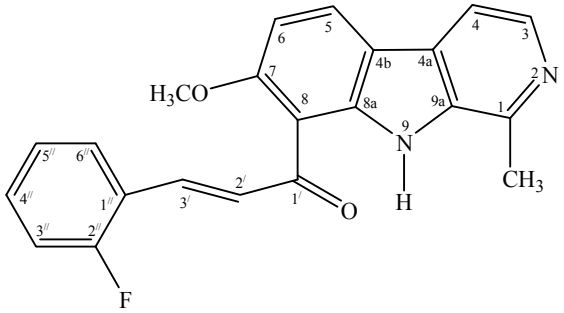

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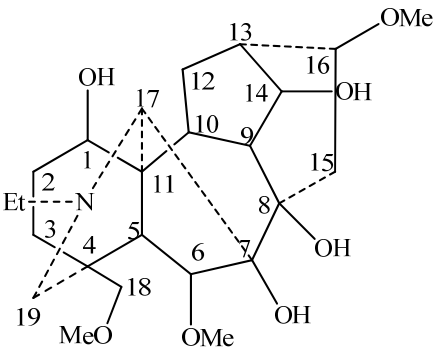

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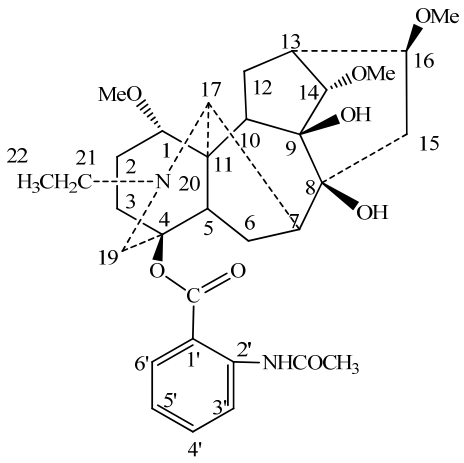

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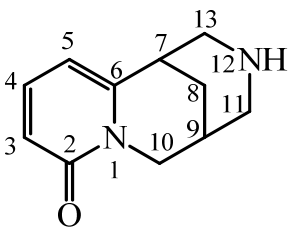

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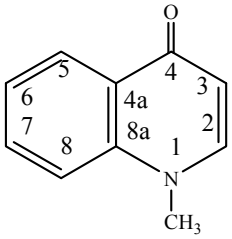

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The experimental part was carried out in accordance with the “Rules of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes” and according to the requirements for the study of new pharmacological substances in adult rats (60 animals) equally males and females, the initial body weight is 240 - 370g. Rats are from own vivarium of International research and production holding "Phytochemistry" (Karaganda). The animals were in standard vivarium conditions on the usual diet and free access to water and food. In addition, observations of the general state of the animals were made: changes in the body weight of animals, motor activity, appetite and response to external stimuli.

Emotional stress was modeled by placing the rats in tight plastic cylinders with their subsequent immersion in water up to the neck level (20-22^{0}C) for 2 hours daily for four days [16]. The test substances at a dose of 5 mg/kg were injected to animals for seven days before emotional stress modeling and then daily 1 hour before placing the animals in plastic cylinders. As the comparison drug, the drug “Piracetam” (OJSC “Borisov Medical Preparations Plant” Republic of Belarus) [17] was used, which was administered to animals in a similar pattern. All drugs were injected daily by mouth as an aqueous solution in a volume of 1 ml/kg. The animals of the control and intact groups received purified water in an appropriate volume.

On the fourth day after emotional stress modeling, the behavioral effect of the studied compounds was assessed using standard methods in the following tests: “Open field” [18] and “Elevated plus-maze” [19].

The “Open Field” test represents a field with a diameter of 100 cm, bounded by 40 cm high sides. The pad is laid out on 16 squares. The animal was placed in the center of the field and within two minutes the number of stances (vertical locomotor activity) and locomotion (horizontal locomotor activity), as well as grooming and the number of defecation (bolus) and urination were visually recorded. The measurements were carried out in silence and under the light of a lamp.

As it is well known, emotional stress is characterized by a manifestation of fear and anxiety, therefore, the assessment of neurotropic activity was performed using the “Elevated plus-maze” test (anxiolytic activity). The test method "Elevated plus maze" allows to identify the anxiolytic activity of drugs. It is based on the ability of animals under the action of drugs to overcome the natural fear of falling from a height and open areas [2]. The rat was placed in the center of the installation, which consisted of 4 arms, crosswise diverging from the central platform at a right angle, 45 cm long and 10 cm wide (wall height of closed arms is 10 cm): two opposite open, without walls, and two closed, dark. In the center of the labyrinth's criss-cross arms there is an open area measuring 10 by 10 cm. Experiments were carried out under normal lighting for 3 minutes. The test allows to assess the level of anxiety of animals under the influence of pharmacological agents. During the experiment, the time spent by animals in open and closed arms, the number of entries in open and closed arms, the number of hanging and peeping from an open rm, the number of stances, grooming, time spent on the central site, the latent period of the first entry into an open arm, urination and defecation number were obtained.

Statistical processing of the results was carried out using the “Statistica 8.0” software package. The results are presented as “mean ± standard error of the mean”. Intergroup differences were assessed by the non-parametric Mann-Whitney U-test. For pairwise related groups, the nonparametric Wilcoxon test was used.

The results of the study. During the experiment, it was noted that the body weight of the rats in all groups remained within the limits of the initial data; no significant changes in the weight gain of the animals of all groups were observed (table 1).

Investigation of the effects of the studied compounds on the orienting-exploratory behavior of animals using the “Elevated plus maze” method. According to a study it was found that emotional stress increases a sense of fear and anxiety in animals. Thus, when checking the behavioral reactions in the “Elevated plus maze” test, it was revealed that the rats of the control group had lower number of entries into open arms and the time spent in them than those of animals of the intact group by 54.5% and 89.7%, respectively . An increase in the number of entries into the labyrinth's closed arms in the control group of animals by 25% also indicated a low emotional level. A decrease in the number of peekings and the number of hanging of the control group rats compared with the indices of animals in the intact group was recorded. The number of stances of the control group rats was absent.

Table 1 – Data on weight gain of rats

Group	Weight, g	
	Before	After
Intact rats n=6	296.3 ± 20.3*	297.0 ± 20.8
Control (without treatment) n=6	367.8 ± 8.5	373.3 ± 10.2
The comparison group (Piracetam) n=6	328.0 ± 12.0	324.5 ± 22.7
Harmine (Gar) (1),n=6	303,3 ± 53,0*	307,3 ± 49,6*
8-acetylharmine (2) n=6	287.5 ± 18.6	291.3 ± 24.3
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl) -3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) n=6	243.0± 10.2	241.8 ± 6.0*
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4- b] indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4) n=6	287.5 ± 18.6	258.0 ± 32.3
Delkozin (5) n=6	295.3 ± 45.5	298.0± 47.6
Lappaconitine (6) n=6	298.0± 6.5	301.0 ± 7.7
Cytisine (7) n=6	245.0 ± 8.4*	243.3± 6.7*
Echinopsine (8) n=6	264.3± 26.2	262.3 ± 27.9
*p <0.05 compared with the values of the control group, n is the number of animals in the group.		

In the group of animals treated with 8-acetylharmine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3), lappaconitine (6) and cytisine (7) at a dose of 5 mg/kg compared with the rats of the control group under conditions of experimental emotional stress showed an anxiolytic (anti-anxiety) effect.

In particular, the time spent in a closed arm in groups of animals using lappaconitine (6) decreased by 23.9%, (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) by 12.5%, cytisine (7) by 5.6% compared with the control group. The time spent by animals in open arms in groups using (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) increased by 78%, lappaconitine (6) by 76.4%, 8-acetylharmine (2) by 76.1%, cytisine (7) by 64.1% compared to control. Time of staying on the central platform in the group of animals that used lappaconitine (6) increased by 37.8% compared with the control. The administration of the harmine (1), 8-acetylharmine (2), delkozin (5), lappaconitine (6) to rats reduced the number of closed arms, as well as with the introduction of 8-acetylharmine (2) and lappaconitine (6), increased the number of peekings. The number of hanging in groups of animals with the use of 8-acetylharmine (2) and delkozin (5) increased. The number of defecation and urenations decreased in groups of animals using 8-acetylharmine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)-prop-2-en-1-one (3), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4- b] indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4) and echinopsine (8) (table 2).

Investigation of the effects of the studied compounds on the orientational-exploratory behavior of animals using «The open field» method. As a result of «The open field» test, it was found that animals from groups using 8-acetylharmine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl) -3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3), lappaconitine (6), cytisine (7) and echinopsine (8) at a dose of 5 mg/kg demonstrated a higher level of orientation reaction in «the open field» test, since the number of horizontal and vertical movements is greater than the result of control group and is close to the value of the reference drug group. In animal groups using 8-acetylharmine (2), lappaconitine (6) , cytisine (7) and echinopsine (8) at a dose of 5 mg/kg, the number of urination and defecation is lower than in the control group, the latency of exit from the center of the “open field” is higher (table 4).

Table 2 – The effect of the studied compounds
on the behavior of rats in the test "Elevated plus maze"

Group	Time spent in a closed arm, (s)	Time spent in a open arm, (s)	Number of entries in open arms, (times)	Number of entries in closed arms, (times)	Number of peekings, (times)
Intact rats n=6	59.5±11.8*	77.3±19.3	3.3±1.9	1.5±1.3	3.0±2.4
Control (without treatment) n=6	161.0±15.6	8.0±1.2	1.5±0.6	2.0±1.4	2.0±2.3
The comparison group (Piracetam) n=6	152.0±32.0	20.5±9.8	0.8±1.0	1.5±0.6	5.0±2.2
Harmine (Gar) (1),n=6	167,0±8,7*	13,0±8,7	1,5±0,6	1,5±0,6	0,3±0,5
8-acetylharmine (2) n=6	141.3±40.1	33.5±15.4	1.0±0.8	1.3±0.5	3.0±3.2
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl) -3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) n=6	140.8±32.3*	36.3±17.9	1.5±0.6	2.0±1.2	1.8±1.0
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4- b] indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4) n=6	167.5±5.6*	9.5±3.9	1.0±0.0	1.3±0.5	0.8±1.0
Delkozin (5) n=6	164.5±11.5	9.8±4.2	1.3±0.5	1.3±1.0	1.8±2.4
Lappaconitine (6) n=6	125.5±80.4	35.4±10.8	1.3±0.5	1.5±1.0	2.5±1.3
Cytisine (7) n=6	152.0±23.6*	22.3±6.3	1.3±0.5	2.0±0.8	1.3±0.5
Echinopsine (8) n=6	167.3±12.2*	12.0±2.0	0.8±0.5	1.3±0.5	0.5±0.6
*p <0.05 compared with values of the control group animals, n is the number of animals in the group.					

Table 3 – The effect of the studied compounds
on the behavior of rats in the test "Elevated plus maze"

Group	Number of hangings, (times)	Number of stances, (times)	Time spent in the central platform, (s)	Number of defecation	Number of urination
Intact rats n=6	9.0±2.1	2.5±1.3	34.5±12.1	1.3±0.5*	0.5±0.6
Control (without treatment) n=6	2.5±2.1	0	11.5±8.3	3.3±1.2	0.3±0.6
The comparison group (Piracetam) n=6	2.5±1.0	0.3±0.5	6.3±2.3	0	0.3±0.5
Harmine (Gar) (1),n=6	1,8±1,7	8,0±3,2	0,5±1,0	0,3±0,5	0,3±0,5
8-acetylharmine (2) n=6	4.3±1.5	0	3.5±1.9	0	0.3±0.5
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl) -3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) n=6	1.0±0.2	0	5.0±3.1	0	0.3±0.5
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4- b] indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4) n=6	0.8±0.5	0	3.0±1.6	0	0
Delkozin (5) n=6	3.0±2.2	0	5.3±2.2	0.8±0.5	0.5±0.6
Lappaconitine (6) n=6	2.8±1.5	0	18.5±9.7	0.3±0.5	0.3±0.5
Cytisine (7) n=6	2.5±1.7	0	1.3±0.10	0.3±0.5	0.3±0.5
Echinopsine (8) n=6	3.3±1.8	0	0.8±0.10	0	0.3±0.5
*p <0.05 compared with values of the control group animals, n is the number of animals in the group.					

Table 4 – The effect of the studied compounds on the behavior of rats in the test "Open field"

Group	Spectrum of indicative research activity		Spectrum of anxiety		
	Number of horizontal movements	Vertical movement activity	Grooming	Number of defecation	Number of urination
Intact rats n=6	21.0±2.7	6.8±1.3	1.5±1.3	1.3±2.5	0.5±0.6
Control (without treatment) n=6	5.3±5.3	4.8±1.0	2.0±0.8	2.8±2.1	1.0±0.8
The comparison group (Piracetam) n=6	13.0±4.5*	6.8±2.9	1.0±0.8	2.5±1.9	0.5±0.6
Harmine (Gar) (1),n=6	8,0±3,2	5,8±2,1	3,8±1,7	2,7±1,4	0,2±0,5
8-acetylharmine (2) n=6	17.0±5.9	4.5±2.5	1.0±0.8	0.3±0.5	0.3±0.5
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl) -3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) n=6	13.8±6.3	9.0±2.9	1.5±1.7	2.2±0.9	0.0±0.0
(E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4- b] indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-one (4) n=6	9.5±2.6*	5.3±1.0	0.75±0.9	3.0±1.4	0.3±0.5
Delkozin (5) n=6	8.9±4.9*	4.8±2.8	4.0±0.8*	4.0±3.2	0.5±0.6
Lappaconitine (6) n=6	13.3±3.5*	4.0±2.2	2.3±1.3	0.3±0.5	0.3±0.5
Cytisine (7) n=6	24.8±7.0	7.8±2.9	1.25±0.50	0.0±0.0*	0.3±0.5
Echinopsine (8) n=6	31.8±2.5	11.0±2.6	2.5±1.3	0.0±0.0*	0.3±0.5
*p <0.05 compared with values of the control group animals, n is the number of animals in the group.					

Findings. As a result of the experiments, it was found that the alkaloids of the indole series 8-acetylharmine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl) -3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3), diterpenic alkaloid lappaconitine (6), and also cytisine (7) at a dose of 5 mg/kg show a neurotropic effect, increasing the level of the orienting reaction, normalize the emotional state, lowering the level of anxiety and fear in animals.

According to the results of molecular docking, it was established that the studied molecules of the alkaloid compounds of the indole series interact with the dopamine receptor D2. According to the results of docking, the maximum indicators of binding are: (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl) -3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) (G-score = -10.2), 8-acetylharmine (2) (G-score = = -7.5), which indicates a good ability of these compounds to bind to the dopamine receptor D2.

Thus, it was established that alkaloid compounds 8-acetylharmine (2), (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (3) have a comparatively strong bond with the dopamine receptor D2. The prospects for the development of new neurotropic drugs based on alkaloid compounds have been identified.

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АЛКАЛОИДТАР МЕН ОЛАРДЫҢ ТУЫНДЫЛАРЫНЫҢ НЕЙРОТРОПТЫҚ ӘСЕРІН ЗЕРТТЕУ

Аннотация. Мақалада алкалоидтар мен олардың туындыларының нейротроптық әсерін зерттеу нәтижелері ұсынылады. 5 мг/кг дозадағы 8-ацетилгармин, ((E)-1-(7-Метокси-1-метил-9H-пиридо[3,4-b]индол-8-ил)-3-(2,4-диметоксифенил) проп-2-ен-1-он, лаппаконитин және цитизин қосылыстары «Ашық алаң» тестінде жануарлардың бағдарлау реакциясының деңгейін көтеретін нейротроптық әсерге ие екендігі және «Көтеріңкі крест тәрізді лабиринт» тестінде олардың мазасыздық деңгейі мен қорқыныш сезімін төмендетіп, эмоциялық жағдайын ретке келтіретіні анықталды.

Түйін сөздер: алкалоидтар, нейротроптық әсер, эмоциялық күйзеліс, алкалоидтардың туындылары.

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ИЗУЧЕНИЕ НЕЙРОТРОПНОГО ДЕЙСТВИЯ АЛКАЛОИДОВ И ИХ ПРОИЗВОДНЫХ

Аннотация. В статье представлены результаты исследования нейротропного действия алкалоидов и их производных. Установлено, что изучаемые соединения 8-ацетилгармин, ((*E*)-1-(7-Метокси-1-метил-9*H*-пиридо[3,4-b]индол-8-ил)-3-(2,4-диметоксифенил)проп-2-ен-1-он,лаппако-нитини цитизин в дозе 5 мг/кг обладают нейротропным действием, повышая уровень ориентировочной реакции животных в тесте «Открытое поле», также нормализуют эмоциональное состояние, понижая уровень тревожности и чувства страха у животных в тесте «Приподнятый крестообразный лабиринт».

Ключевые слова: алкалоиды, нейротропное действие, эмоциональный стресс, производные алкалоидов.

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