IRSTI 577.1:547.94:547:544.424:547.7/.8:547.9 https://doi.org/10.26577/IJBCh20251811

A. Amanzhan[1, 3]*, E.E. Schultz[2], B.S. Adekenov[1], O.V. Maslova[1], M.K. Ibraev[3], S.M. Adekenov[1]

[1]Research and Production Center "Phytochemistry", Karaganda, Kazakhstan
[2]N.N. Vorozhtsov Novosibirsk Institute of Organic Chemistry of the Siberian Branch of Russian Academy of Sciences, Novosibirsk, Russia
[3]Karaganda Buketov University, Karaganda, Kazakhstan
*e-mail: asel.amanzhan@mail.ru
(Received 05 May 2025; received in revised form 05 June 2025; accepted 16 June 2025)

# Synthesis of new acetylharmine derivatives and their neurotropic activity

**Abstract:** Alkaloids containing a β-carboline fragment are of significant interest as potential new physiologically active agents for the treatment of central nervous system disorders. The roots of *Peganum harmala* L. (family *Zygophyllaceae*) are a promising and readily available raw material for the production of active pharmaceutical substances. The β-carboline alkaloid harmine is a promising compound for the development of novel, original neurotropic drugs based on these alkaloids. The article considers the ways of synthesizing new compounds based on the alkaloid harmine and, simultaneously, studies the neurotropic activity of new harmine derivatives containing various substituents at the C-8 position. Harmine was selectively acetylated at the 8-position using acetyl chloride and tin tetrachloride, yielding 8-acetylharmine. This intermediate was then used to synthesize a series of novel harmine derivatives, including 8-{Z}-1-{Z}-(1-(arylidene)hydrazono)ethyl and 8-cinnamoyl analogs. The evaluation of the neurotropic action of samples of C-8 harmine derivatives was carried out on models of experimental stress using the "Open Field" and "Elevated Plus Maze" tests. Several compounds exhibited marked antidepressant activity with sedative effects comparable to those of amitriptyline. It was demonstrated that structural modifications at the C-8 position of harmine contribute to the generation of new pharmacophores capable of crossing the blood-brain barrier and modulating behavioral responses. In particular, the compounds 8-acetylharmine (2) and {(Z)-1-[(Z)-(2-arylidene)hydrazono]ethyl}-harmines (4–5), at a dose of 10 mg/kg, demonstrated behavioral features indicative of reduced anxiety levels in animals. These findings highlight the potential of β-carboline-based harmine derivatives for the development of novel neurotropic agents.
**Key words:** β-carbolines, harmine, 8-acetylharmine, (Z)-hydrazono-8-acetylharmine, chalcone derivatives of harmine, neurotropic activity.

## Introduction

According to epidemiological data, one in four individuals worldwide will face a neurodegenerative disease during their life, and there is a steady increase in the number of these diseases [1]. Neurodegenerative disorders are multifactorial in origin and have been linked to genetic predispositions, disruptions in cellular signaling pathways, programmed neuronal cell death (apoptosis), inflammatory mechanisms, accumulation of misfolded protein aggregates, mitochondrial impairment, oxidative damage, aging processes, sex-specific factors, genetic mutations, ethnic background, environmental influences, and potentially climate-related conditions [2-4].

There is a broad spectrum of neurotropic (neuroprotective) drugs that reduce anxiety and enhance stress resilience. Modern neuroprotectors are compounds with potential effects on different parts of the nervous system in cases of impaired blood supply and myocardial function disorders: AMPA-receptor antagonists (Zonanpanel, Japan), serotonin agonists (Repinotan, Piclozotan), membrane modulators (Ceraxon, Spain), and others [5].

Plant alkaloids are widely known as a consistent source of drugs for the treatment of chronic diseases, and possessing properties of polypharmacological modulation, they are potentially useful for the further development of targeted drug agents [6-8]. Harmine (1), an alkaloid belonging to the group

of biologically active compounds, exhibits a wide range of pharmacological properties, including vasodilatory, anti-inflammatory, analgesic, antimicrobial, antioxidant, cholinesterase-inhibiting, antiparkinsonian, antitumor, anti-addictive, and antidepressant activities. These diverse effects have been summarized in several systematic reviews [9–13]. Despite its broad spectrum of established biological activities, the molecular mechanisms underlying harmine's pharmacological actions remain insufficiently elucidated. Recent findings indicate that harmine may exert its pharmacological effects by interacting with a variety of molecular targets, such as monoamine oxidases A and B, benzodiazepine receptors, GABA-A receptors, serotonin receptors of the 5-HT2A/C subtypes, glutamatergic receptors including NMDA and GLT-1, imidazoline receptors (I1 and I2), as well as by modulating the expression and activity of neurotrophic factors [14–20]. Moreover, harmine (1) has been reported to suppress Tau protein phosphorylation through the inhibition of DYRK1A kinase activity, a mechanism that correlates with enhanced memory, spatial learning, and overall cognitive performance in APP/PS1 transgenic mice, as well as in rodent models of scopolamine-induced cognitive deficits [21, 22]. Interestingly, in the late 1920s and early 1930s, harmine hydrochloride was used to treat symptoms of Parkinson's disease such as muscle rigidity, depression, memory deficits, apathy, phobias, fatigue, and attention problems [23]. With respect to its therapeutic potential in the central nervous system (CNS), recent preclinical research has validated the antidepressant properties of harmine (1) [14,18]. More basic and clinical research is needed to elucidate the neurochemical mechanisms underlying these effects.

We have previously studied the pharmacological properties of harmine hydrochloride and established its antidepressant activity [24-27]. The alkaloid harmine (1) is an available metabolite of *Peganum harmala* L., which is widespread in the territory of South Kazakhstan, where its industrial reserves are available [28].

The availability of domestic raw materials for the isolation of the β-carboline alkaloid harmine (1), its high biological activity, and the presence of reaction centers in the molecule make it promising for further targeted chemical modifications. To study the effect of various substituents in the indole fragment of the alkaloid on the pharmacological activity, we carried out a chemical modification with the introduction of various substituents in the C-8 position of the alkaloid harmine (1).

## Materials and methods

*Reagents and chemicals*

All used chemicals (analytical grade) were purchased from E. Merck (Darmstadt, Germany) and Sigma Chemical Co. (Sigma-Aldrich Chemie Gmbh, Steinheim, Germany) and were used without further purification. These chemicals are as follows: ethanol ($C_2H_5OH$≥96%), methanol ($CH_3OH$≥99.8%), tin (IV) chloride ($SnCl_4$≥98%), acetyl chloride ($CH_3COCl$), methylene chloride (), hydrazine hydrate ($NH_2NH_2 \cdot H_2O$, 50 v/v %), anisaldehyde ($CH_3OC_6H_4CHO$≥96%), 2-fluorobenzaldehyde ($FC_6H_4CHO$≥97%), sodium hydroxide (NaOH≥98%), hydrochloric acid (HCl≥36%), ethyl acetate ($CH_3COOC_2H_5$≥99.5%), 2,4-dimethoxybenzaldehyde (2.4-$(CH_3O)_2C6H_3CHO$≥97%), 2,3.4-trimethoxybenzaldehyde $(CH_3O)_3C6H_2CHO$≥97%).

The IR spectrum was recorded on the Avatar 360 ESP device from Thermo Nicolet (Madison, WI, USA) in pellets with KBr.

UV spectra were obtained on a Cary 60 UV-Vis spectrometer in EtOH solutions ($10^{-4}$ mol/L).

HPLC was performed on an Agilent 1100 Series liquid chromatograph (USA) equipped with a QuatPump G1311A pump, a Rheodyne injection valve with a 20 μl loop, a G1322A column holder, and a G1314A UV detector. For all analyses, a 15 cm × 0.46 cm Zorbax SB-C18 column with 5 μm particles (Agilent, Santa Clara, CA, USA) and the following solvents were used: methanol, acetonitrile, and water (analytical reagents with a purity of at least 99.9% obtained from Sigma-Aldrich (Merck-Millipore, St. Louis, MO, USA).

$^1$H NMR and $^{13}$C NMR spectra were recorded by using JEOL JNM-ECZR 500 MHz (500.16 ($^1$H), 125.76 MHz ($^{13}$C)). The $^{19}$F NMR spectrum of compound 5 was recorded on a JEOL JNM-ECZR 500 MHz spectrometer (282 MHz) in $CDCl_3$.

Silufol TLCP-AI A-UF TLC plates manufactured by Imid (Krasnodar, Russia) were used for thin layer chromatography. The compounds were visualized by developing plates through spraying them with a saturated $KMnO_4$ solution.

Column chromatography was performed on $Al_2O_3$ (II degrees, Acros, The pore diameter is between 0.035 and 0.070 mm and is 6 nm) using a sum of substances-to-sorbent ratio of 1:20. The purity of the synthesized compounds was controlled by thin-layer chromatography (TLC) and HPLC data.

*Plant material*

The object of the study was the roots of *Peganum harmala* L., collected in the surroundings of the village of Akshi, Almaty region, Republic of Kazakhstan. Herbarium samples were stored in the herbarium fund of "Research and Production Center "Phytochemistry" (Karaganda, Kazakhstan). Raw materials of the roots of *Peganum harmala* L. were dried by the air-shadow method and ground. The grinding particle size is 2.5 mm.

Air-dried crushed roots of *Peganum harmala* L. after alkalization, were extracted with 96% ethanol on a P-250 percolator (manufactured by Artlife, Tomsk, Russia) for 3 hours with stirring. Liquid extracts were combined and evaporated on a Pilotvap-50 rotary evaporator (Genser Scientific Instruments, Germany).

In this study were investigated various process parameters influencing the yield of extractive substances. The following variables were considered: the ratio of plant material to solvent ($X_1$), extraction duration per cycle, number of extraction cycles ($X_3$), extraction temperature ($X_2$), particle size of the raw material ($X_4$), and the presence or absence of pre-alkalization ($X_5$). Based on theoretical principles of equilibrium extraction, the experimental ranges were established as follows: $X_1$ – from 1:10 to 1:20; $X_2$ – from 55 to 65 °C; $X_3$ – from 1 to 3; $X_4$ – from 2 to 10 mm; $X_5$ – with or without pre-alkalization. These ranges were determined based on preliminary experimental data. The optimization criterion (Y) was the total yield of extractive compounds.

The quantification of harmine in the extracts was performed using high-performance liquid chromatography (HPLC) on an Agilent 1100 system (Agilent Technologies, USA). This system offers a high level of sensitivity and precision when analyzing complex plant-derived compounds. Chromatographic separation of components was performed using a Zorbax SB-C18 column (geometric parameters: 4.6 × 150 mm) packed with a sorbent with a particle size of 5 µm. The mobile phase, consisting of acetonitrile and 0.1 M aqueous ammonia solution in a volume ratio of 1:1, was eluted at a flow rate of 0.5 mL/min. Analytical signals were recorded at a wavelength of 301 nm. During analysis, the column was maintained at ambient (room) temperature. The injection volume was 20 µL.

Each determination was carried out in triplicate. The resulting set of quantitative data was subjected to statistical analysis. To assess the statistical significance of the observed differences between the study groups, Student's t-test was applied; differences were considered significant at $p \leq 0.05$. Data collection, processing, and graphical representation were carried out using Microsoft Excel.

*Synthesis of 8-acetylharmine (2).* We cooled the solution of harmine (1) (14.5 mmol) to 0 °C, and then we added acetyl chloride (29 mmol) dropwise under stirring to the cooled solution of harmine. We followed this with the gradual addition of tin (IV) chloride (9.5 mmol). So, we left the reaction mixture for 16 hours at room temperature, giving it a good stir every now and then. Once it was finished, the blend was thinned with 100 µL of methylene chloride, rinsed successively with $H_2O$ (3 × 20 µL), and desiccated over anhydrous magnesium sulfate. So, we took the crude product and purified it using column chromatography on aluminium oxide, and we used chloroform as the eluent. A white microcrystalline powder with a melting point of 152–153°C was obtained by recrystallizing the purified compound from ethyl acetate. The yield was 2.21 g (85%).

*Synthesis of Z-hydrazono-8-acetylharmine (3).* A solution of compound 2 (0.5 g, 1.96 mmol) in 25 mL ethanol was treated with excess hydrazine hydrate (2.94 g, 0.06 mol) under stirring. The reaction mixture was heated to 60 °C and stirred for 7–8 h. The resulting precipitate was filtered and recrystallized from ethanol. Yield: 69%, yellow microcrystalline powder, mp 207–209 °C. Molecular formula 8-acetylharmine – $C_{15}H_{16}N_4O$.

*General procedure for the preparation of azines (Z,Z) of configuration (4,5).* A methanolic solution of hydrazone (3) (0.37 mmol) was combined with the corresponding aromatic aldehyde (anisaldehyde or 2-fluorobenzaldehyde). The reaction mixture was stirred at 60–65°C for four hours. Upon completion, the resulting product was purified by recrystallisation from ethanol. Yields of the target compounds ranged from 56% to 82%.

*General procedure for the synthesis of 3-(aryl)-1-(1-methyl-7-methoxy-9H-β-carbolin-8 yl) prop-2-en-1-ones (6,7).* A solution of 2 mmol of compound (2) and 2.1 mmol of the corresponding aromatic aldehyde (2,4-dimethoxybenzaldehyde, 2,3.4-trimethoxybenzaldehyde) in approximately 15µL of ethanol was treated with 5µL of 25% aqueous NaOH at room temperature. The reaction mixture was stirred for 3 hours at a constant temperature of 25°C. The reaction mixture was subjected to agitation for a period of three hours at a temperature of 25°C, followed by a subsequent hour of agitation at 60°C. Then, after it had cooled, we neutralized the mixture with concentrated hydrochloric acid. The resulting solid was then recrystallized using

ethyl acetate. When obtaining chalcones (6, 7), the precipitate formed after neutralization is separated and chromatographed on silica gel using chloroform as the eluent. The part of the substance that we were looking for was separated again from a liquid called ethyl acetate.

*Model of neurotropic action*

Emotional stress was modelled by placing rats in tight plastic cylinders and immersing them up to their necks in water at 20–22 °C for two hours a day for four days. [29]. The studied substances (1,2,4,5,6) at a dose of 10 mg/kg were administered intragastrically through a tube to the animals for seven days before modeling emotional stress, and then daily, 1 hour before placing the animals in the plastic cylinders. The use of amitriptyline (10 mg/kg, p.o.) as a reference drug was according to the same regimen. All compounds were administered as aqueous solutions. The volume was 1 mL/kg body weight. The reference drug was administered in the same way. Four days after the start of the stress protocol, the behavior of the animals was evaluated using the Open Field Test (OFT) and the Elevated Plus Maze (EPM). These are both widely recognized behavioral assays, as described in the literature [30–36]. Experiments were conducted on 80 adult male outbred white rats weighing 240–380 g, randomly divided into 8 groups (n = 10 per group).

*Statistical Analysis*

All calculations were carried out using Statistica 8.0. Results were presented as mean±standard error of the mean (SEM). Differences between groups were evaluated with the nonparametric Mann–Whitney U test [37].

*Ethical approvals*

The study adhered to the European Convention for the Protection of Animals Used for Experimental and Other Scientific Purposes, as well as institutional and national regulations governing research with new pharmaceuticals. There is a conclusion from the ethical committee of the NJSC "Karaganda Medical University" № 13, Protocol No. 2 dated 05/08/19. Experimental animals were obtained from the animal facility of the Research and Production Center "Phytochemistry" and maintained under standard conditions with ad libitum access to food and water.

## Results and discussion

Previously, the extraction of alkaloids from *Peganum harmala* L. for the production of harmine (1) was primarily carried out using maceration. However, this method presents several limitations, the most significant of which is the extended duration of the process. [38-40]. To enhance the efficiency of alkaloid extraction, we designed an experimental matrix incorporating variation of the key extraction parameters (Table 1). The selection of factor ranges for the extraction process was based on preliminary experimental data. The optimization criterion (Y) was defined as the total yield of extractive substances.

**Table 1** – Planning matrix and experimental part

| № | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $X_5$ | $Y_{mean}$, % (n=3) |
|---|---|---|---|---|---|---|
| 1 | 1:10 | 65 | 1 | 2-3 | Treatment with 5% $Na_2CO_3$ solution | 10.25 |
| 2 | 1:15 | 65 | 1 | 7-8 | | 10.6 |
| 3 | 1:20 | 65 | 1 | 7-8 | | 11.0 |
| 4 | 1:20 | 65 | 1 | 2-3 | | 12.0 |
| 5 | 1:10 | 65 | 2 | 7-8 | | 12.9 |
| 6 | 1:20 | 65 | 2 | 7-8 | No treatment | 9.55 |
| 7 | 1:20 | 60 | 2 | 7-8 | | 7.27 |
| 8 | 1:20 | 55 | 3 | 7-8 | | 7.22 |

As shown in Table 1, pretreatment of the plant material with a saturated sodium carbonate solution significantly improved the extraction efficiency. This step facilitates the conversion of target alkaloids into their free base forms, thereby enhancing their solubility in the extraction solvent. Even under otherwise optimized conditions (e.g., solvent-to-material ratio of 3:1), the total yield of extractive substances did not exceed 9.55% in the absence of pretreatment. Furthermore, due to the dense structure of *Peganum harmala* L. roots, the degree of material pulverization was identified as another critical

parameter affecting extraction efficiency. When the raw material was milled to a particle size of 2–3 mm, the overall yield of extractive substances reached 12.9% (in relation to the air-dried plant mass).

Using the experimental data, three mathematical models were developed based on second-order polynomial equations to represent the effects of the chosen variables on extraction efficiency:

$$Y= -11.03+0.74X_1 +0.456X_2 -133.8X_3 + +0.7375X_4+2.995X_5 -0.255*X_1 *X_4 \quad (1)$$

$$Y= -21.6975+2.051X_1 +0.456X_2 -36.6X_3 + + 0.7375X_4 +3.905X_5 -12.96*X_1*X_3 - -0.225*X_1*X_4 \quad (2)$$

$$Y= -8.7375+0.755X_1 +0.456X_2 -166.2X_3 + + 2.5025X_4 +3.905X_5 -0.225*X_1*X_4 + +32.4*X_3*X_4 \quad (3)$$

The experimental and calculated data were compared based on the calculated models (Table 2).

As can be seen from Table 2, models 2 and 3 show the greatest convergence with the experimental data, compared with model 1 (Figure 1). This improved agreement is attributed to the inclusion of additional interaction terms: $+k\cdot X_1\cdot X_3$ in Model 2 and $+k\cdot X_3\cdot X_4$ in Model 3, which enhance the models' predictive accuracy by accounting for synergistic effects between the respective variables.

**Table 2** – Comparison of experimental and calculated data on the yield of total extractive substances from *Peganum harmala* L.

| № of experiment | Experimental values, % | Mathematical model 1, % | Mathematical model 2, % | Mathematical model 3, % |
|---|---|---|---|---|
| 1 | 10.25 | 10.25 | 10.25 | 10.25 |
| 2 | 10.6 | 10.6 | 10.6 | 10.6 |
| 3 | 11.0 | 10.925 | 11.0 | 11.0 |
| 4 | 12.9 | 12.825 | 12.9 | 12.9 |
| 5 | 12.9 | 15.06 | 12.9 | 12.9 |
| 6 | 9.55 | 9.395 | 9.55 | 9.55 |
| 7 | 7.27 | 7.115 | 7.27 | 7.27 |
| 8 | 7.22 | 7.065 | 7.22 | 7.22 |

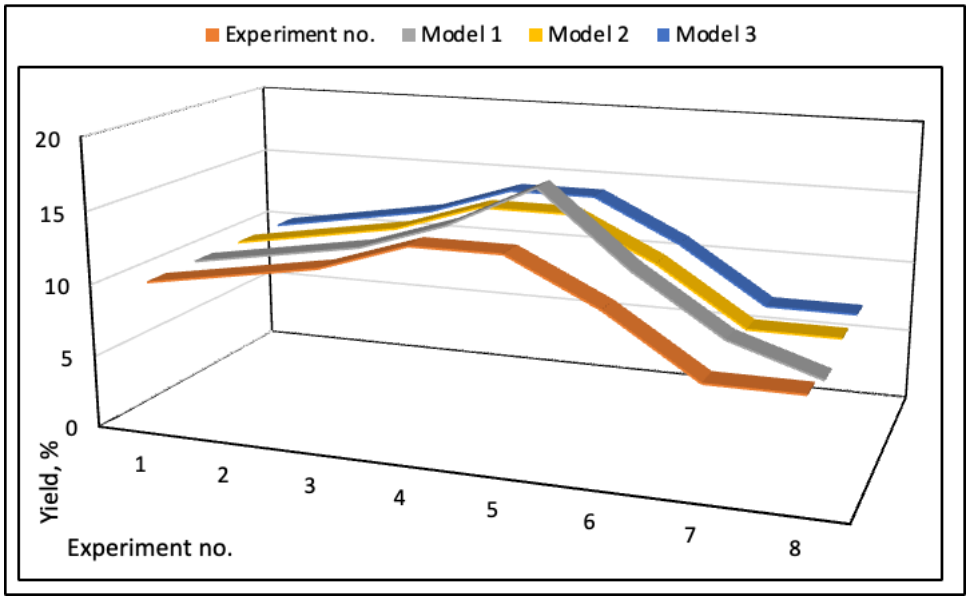



**Figure 1** – Comparison of calculated and experimental data

It can therefore be concluded that the optimal extraction mode was represented by the conditions of Experiments № 4 and № 5 (Figure 2).

As can be seen from the data presented in Figure 2, the quantitative extraction of harmine (1) (up to 97% of the content in air-dried raw materials), as well as the number of extractive substances from the roots of *Peganum harmala* L., is observed with double percolation at a temperature of 65°C for 3 hours; the degree of grinding of the raw material is 2-3 mm, the ratio of raw material to extractant is 1:10 (experiment No. 5).

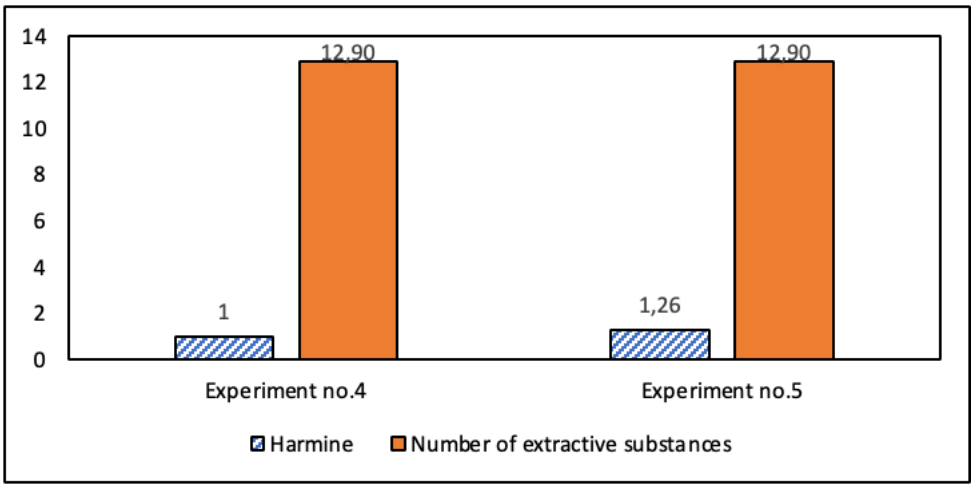



**Figure 2** – Relationship between the extraction method and both the yield of harmine (1) and the quantity of extractive substances

Harmine (1) is a widely used renewable material – a substrate for the synthesis of new biologically active compounds [41-42].

β-Carboline alkaloid harmine (1) is easily acylated with acetyl chloride in the presence of $SnCl_4$ to form 8-acetylharmine (2) (yield 81%), which was used as a starting compound for the synthesis of derivatives (3-7).

We have studied the interaction of 8-acetylharmine (2) with hydrazine hydrate. Hydrazinolysis of 8-acetylharmine (2) in an alcohol medium at a reaction mixture temperature of 60°C proceeds stereoselectively with the formation of (Z)-8-(1-hydrazono)ethylharmine (3) (yield 69%). It has been shown that (Z)-8-(1-hydrazono)ethylharmine (3) readily enters into a condensation reaction with aromatic aldehydes (2-fluorobenzaldehyde and anisaldehyde) with the formation of the corresponding unsymmetrical disubstituted hydrazines (Z,Z) of the (4,5) configuration (yield 56 and 82%, respectively) (Figure 3).

The structure of all compounds was established based on elemental analysis and spectral data (UV, IR, $^1H$, $^{13}C$, $^{19}F$ NMR- spectrum).

The $^1H$ NMR spectrum has shown a singlet signal for the acetyl group protons ($CH_3CO$) at around 2.42 ppm. The $^{13}C$ NMR spectrum of compound (2) has shown the signals of the carbon atom of the C=O group at δ 200.5 ppm and the methyl group $CH_3CO$ at 20.4 ppm, which are characteristic of the specified substituent.

The characteristic signals of the $NH_2$ group of (Z)-8-(1-hydrazono)ethylharmine (3) were observed in a weak field in the region of δ 8.03 and 8.05 ppm as a singlet. The signals of the carbon atoms of (Z)-8-(1-hydrazono)ethylharmine (3), belonging to the $CH_3C=N$, $-CH_3$, $-OCH_3$ groups, appear in the region of δ 18.51, 21.94, 55.55 as quartets, the carbon atom C=N was represented by a singlet at δ 145.95 ppm. The structures of azine derivatives (4, 5) were assigned as (Z,Z)-configured isomers based on analysis of their PMR and $^{13}C$-NMR spectra. A notable high-field shift of the benzylidene proton signal in the PMR spectra (δ = 8.43–8.73 ppm) supported the assignment of an asymmetric 2,3-diazine structure in the (Z,Z) configuration. In contrast, the corresponding (Z,E)-isomers typically exhibit this proton signal at δ ≈ 9.26 ppm, further corroborating the (Z,Z) configuration of

compounds 4 and 5. The doublet of the carbon atom CH=N was located at δ 150.43-157.20 ppm, the singlet of the -C=N group in the substituent at the C-8 atom is shifted downfield relative to the location in the spectrum of hydrazone (3) and was detected at δ 163.59-167.68 ppm.

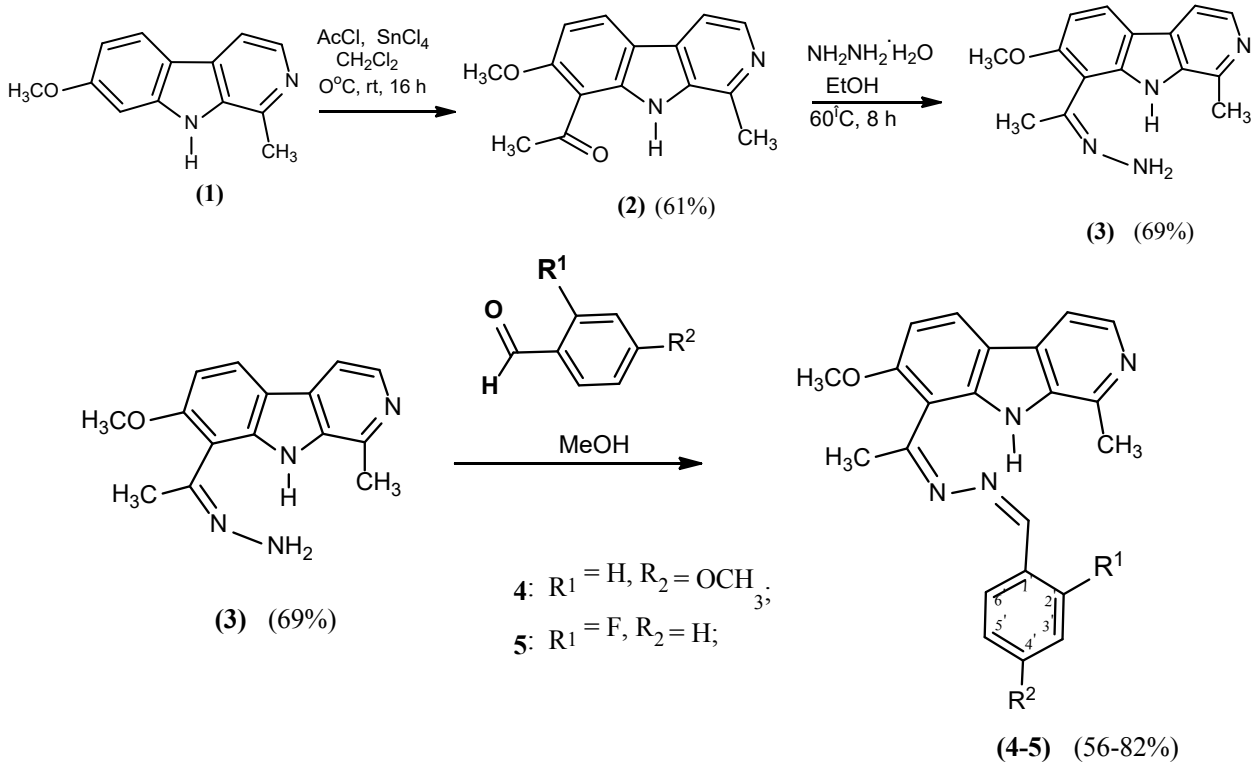
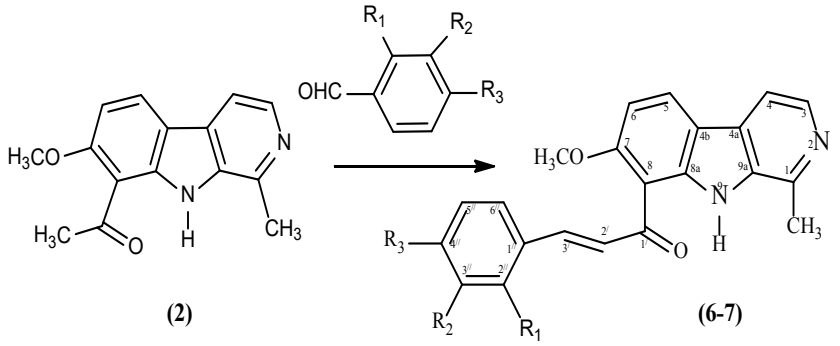



**Figure 3** – Chemical modification scheme of (Z)-8-(1-hydrazono) ethylharmine and its (Z,Z)-disubstituted hydrazines

The synthesis of the corresponding chalcones – (E)-arylacryloylharmines or cinnamoyl-substituted harmine derivatives (6-7) – the synthesis (yield 90–95%) was performed via the Claisen–Schmidt condensation of compound 2 with aromatic aldehydes in ethanol, using an aqueous NaOH solution (Figure 4).




6: $R_1$=$R_2$=$R_3$=OMe, 7: $R_2$=H, $R_1$=$R_3$=OMe

**Figure 4** – Synthesis of new 8-arylacryloyl derivatives of harmine

The signals characteristic of the protons of the trans-substituted double bond (CH=CH) were observed as two doublets in the region of 7.42–7.96 and 7.87–8.17 ppm and overlap with the signals of the protons of the aromatic system, the chemical shifts of which are observed in the region of 6.90–8.32 ppm. The values of the spin-spin interaction constants of the protons belonging to the 2`, 3` multiple bond in the PMR spectrum (JHα-Hβ = 15–16 Hz) indicated that the chalcones were formed in the form of geometrically pure trans isomers.

Consequently, in terms of searching for new pharmacologically active compounds based on the β-carboline alkaloid harmine, a synthesis of harmine derivatives containing various substituents at position C-8 was carried out.

The neurotropic activity of newly synthesized harmine derivatives was evaluated *in vivo*. Experimental groups 1–5 received harmine (1), 8-acetylharmine (2), {(Z)-1-[(Z)-(2-arylidene) hydrazono]ethyl}-7-methoxy-1-methyl-9H-pyrido[3,4-b]indoles (4, 5), and (E)-3-aryl-1-(1-methyl-7-methoxy-9H-β-carbolin-8-yl)prop-2-en-1-one (6), each at a dose of 10 mg/kg. Group 6 served as the comparison group and received the reference drug amitriptyline at 10 mg/kg under the same administration schedule, 7 control group – animals that received the solvent, and Group 8 included intact animals maintained on a standard diet without experimental intervention. All substances, including the reference drug, were administered orally as aqueous solutions.

The animals were kept in standard vivarium conditions, with free access to food and water, and fed a normal diet. In addition, the general condition of the animals was observed, including changes in body weight, motor activity, appetite and response to external stimuli [29–36].

Throughout the experiment, the animals' general condition, behavioral characteristics, motor activity intensity and nature, hair and mucous membrane condition, and food and water consumption were regularly recorded. Table 3 shows the dynamics of the increase in body weight of the animals in all groups.

**Table 3** – Variability in rat weight gain during for seven days

| Group | Number of animals | Weight, g | |
|---|---|---|---|
| | | Before | After |
| Intact rats | 10 | 262.9 ± 33.2 | 275.9±34.8 |
| Control (No treatment) | 10 | 260.8 ± 29.7 | 278.8±29.7 |
| Comparison group (amitriptyline) | 10 | 252.5 ± 62.8 | 265.5±61.8 |
| (1) | 10 | 303.3 ± 53.0* | 307.3±49.6* |
| (2) | 10 | 287.5±18.6 | 291.3±24.3 |
| (4) | 10 | 355.3±24.2 | 365.3±34.2 |
| (5) | 10 | 382.5±36.5 | 371.5±46.1 |
| (6) | 10 | 371.8±50.6 | 379.8±49.6 |
| Note: * indicates statistically significant differences ($p<0.05$) compared with the control group | | | |

No significant deviations in weight gain were observed across the experimental groups, indicating that the tested compounds did not induce adverse systemic effects or metabolic disturbances.

*Changes in behavioral responses in the "Open Field" test.*

It was found that the animals that received compounds (1-6) had changes in the indices of motor activity (horizontal and vertical movements). At the same time, the motor activity of animals that received harmine (1) significantly decreased in both tests compared to the control group of animals, the group of intact rats and the group that received amitriptyline. The orientation-exploratory activity of compounds containing arylidenehydrazone substituents (5,6) remained at the level of the amitriptyline group. For 8-acetylharmine (2) and its chalcone (6), a reliable (3-fold) decrease in vertical motor activity was observed while maintaining activity in horizontal movement. In animals receiving amitriptyline and compounds containing an arylidenehydrazone substituent at position C-8 of harmine, the anxiety level in terms of grooming episodes (number of washings) decreased, however,

in terms of the number of acts of bowel movements and urination, the anxiety level indicator was at the level of the control group animals. A reliable change in the anxiety level was observed for animals receiving the chalcone derivative of harmine (6); the number of grooming episodes significantly increased by an order of magnitude, compared with the group of animals receiving amitriptyline and 4 times compared with the control group), which can serve as an indirect criterion for an increase in anxiety in the group of animals receiving the chalcone derivative of harmine (6) (Table 4).

**Table 4** – Effect of the test compounds on rat behavior in the Open Field test

| Group | Number of animals | Spectrum of exploratory and research activity | | The spectrum of anxiety | | |
|---|---|---|---|---|---|---|
| | | Number of horizontal movements | Vertical motor activity | Number of grooming episodes | Number of bowel movements | Number of urinations |
| Intact rats | 10 | 28.3±6.58* | 10.7±3.1 | 1.8±1.6 | 0.8±0.8 | 0.6±0.8 |
| Control (no treatment) | 10 | 19.7±4.66* | 12.3±3.65* | 1.5±1.2 | 0.3±0.7 | 0.4±0.5* |
| Comparison group (amitriptyline) | 10 | 22.6±3.1 | 14.0±3.0 | 0.4±0.7* | 0.9±1.4 | 0.5±0.7 |
| (1) | 10 | 8.0±3.2 | 5.8±2.1 | 3.8±1.7 | 2.7±1.4 | 0.2±0.5 |
| (2) | 10 | 17.0±5.9 | 4.5±2.5 | 1.0±0.8 | 0.3±0.5 | 0.3±0.5 |
| (4) | 10 | 25.0±11.6* | 11.3±3.9 | 0.3±0.5* | 2.0±1.7 | 1.3±1.3 |
| (5) | 10 | 24.0±6.5* | 9.0±3.9 | 0.0±0.0 | 0.8±1.5 | 1.0±1.2 |
| (6) | 10 | 17.8±5.1 | 4,3±3.3* | 5.3±1.3* | 2.5±1.6 | 0.5±0.6 |
| Note: * $p<0.05$ compared to values in animals of the control group | | | | | | |

*Assessment of Exploratory Behavior Using the Elevated Plus Maze Test*

To further evaluate the exploratory behavior and anxiety-related responses of rats, the elevated plus maze (EPM) test was employed. We recorded how long the rats spent in the open and closed arms, how long they spent on the middle platform, how many times they went into the open and closed arms, how many times they moved their heads up and down, how many times they stretched (rose up on their backs), and how many times they pooed and peed. The results are summarized in Table 5.

As per the statistics displayed, creatures administered harmine (1) demonstrated a considerably elevated quantity of entries into the closed arms ($p>0.05$) in comparison to the time spent in the open arms. In addition, the number of head dips and the duration of time spent on the central platform were markedly reduced. A statistically significant threefold increase was observed in the time spent in the closed arms, indicating enhanced anxiety-like behavior in this group. Thus, the introduction of harmine (1) contributed to a significant increase in the anxiety of animals, compared with the animals of the intact group. The introduction of an acetyl, 4-fluorobenzylidenehydrazone substituent (compounds 2, 4) at the C-8 position of harmine significantly reduced the anxiety activity of animals and significantly increased their activity by increasing the time spent in the open arms and on the central platform. It should also be noted that the orientation-exploratory activity of animals receiving 8-substituted harmine derivatives (time spent in the closed and open sleeve and on the central platform, number of defecations and urinations) was at the level of activity of animals receiving amitriptyline. However, the activity of experimental animals was lower than that of intact animals, and significantly depended on the nature of the substituent in the hydrazone and chalcone fragments (comparison of groups receiving compounds 4 and 5 or 6).

**Table 5** – Effect of the studied compounds on the behavior of rats in the elevated plus maze test

| Group | Time spent in closed sleeve, (sec.) | Time spent in open sleeve, (sec.) | Number of entries into open sleeves (times) | Number of entries into closed sleeves (times) | Number of peeks, (times) | Number of hangings (times) | Number of rearings (times) | Time spent on the central platform, (sec.) | Number of bowel movements | Number of urinations |
|---|---|---|---|---|---|---|---|---|---|---|
| Intact rats | 12,5±19,8* | 116,8±23,1* | 4,0±2,2 | 0,8±0,7 | 3.0±2.4 | 5,5±1,7 | 0,3±0,5 | 50,8±37,8* | 0 | 1,0±0,2 |
| Control (no treatment) | 108,7±32,1 | 21,1±29,1 | 0,9±0,87* | 4,3±1,3 | 2.0±2.3 | 4,0±3,5* | 0,8±1,75 | 50,2±27,7 | 0 | 0,3±0,48 |
| Comparison group (amitriptyline) | 107,3±26,3* | 26,7±25,28* | 1,2±0,78 | 3,2±1,4 | 5.0±2.2 | 2,9±1,85 | 0,6±1,3 | 46,0±19,4* | 0,2±0,6 | 0,1±0,3 |
| (**1**) | 167.0±8.7* | 13.0±8.7 | 1.5±0.6 | 1.5±0.6 | 0.3±0.5 | 1.8±1.7 | 8.0±3.2 | 0.5±1.0 | 0.3±0.5 | 0.3±0.5 |
| (**2**) | 141.3±40.1 | 33.5±15.4 | 1.0±0.8 | 1.3±0.5 | 3.0±3.2 | 4.3±1.5 | 0 | 3.5±1.9 | 0 | 0.3±0.5 |
| (**4**) | 127.0±5.3* | 51.5±18.0 | 0,9±0,6 | 1.3±0.5 | 3.0±1.2 | 1.5±1.0 | 0 | 18.5±8.5 | 0.5±1.0 | 0 |
| (**5**) | 135.3±12.8 | 15.0±2.9 | 0,3±0,5 | 2.5±0.6 | 1.8±2.4 | 2.0±2.4* | 0.3±0.5 | 10.8±6.9 | 1.3±1.9 | 0.3±0.5 |
| (**6**) | 155.0±16.5 | 9.0±3.7 | 1,0±0,8 | 2.5±0.6 | 2.5±1.3 | 1.3±1.5 | 0 | 6.3±3.3* | 0.5±0.6 | 1.0±1.4 |

Note: * $p<0.05$ versus control group; n denotes the number of animals in each group

The anxiolytic activity of the samples in the experimental rat groups was evaluated based on the data presented in Table 5. The anxiety index calculation formula was used to assess the anxiolytic effect. The anxiety index values range from 0 to 1, with an increase in the index indicating increased anxiety-like behavior [27].

An anxiolytic effect was demonstrated in the group of animals that received substances (1), (2), (4), (5) and (6) at a dose of 10 mg/kg, when compared with the control group, under conditions of experimental emotional stress.

In particular, the time spent in the closed arm in group (2) decreased by 12.4%, in group (5) by 17.3%, in group (4) by 12.4% compared to the control group. Administration of the studied compounds, harmine (1) and (2), to rats reduced the number of entries into the closed arms. Introducing compound (2) also increased the number of peeks. The number of hangings increased in group 2. The number of defecations and urinations decreased in group 2.

The average time that the animals spent in the open arms of the apparatus in group 5 was 51.5 ± 18.0 seconds, in group 2 was 33.5±15.4 seconds. The number of entries into the open arms in group 5 was slightly higher than in the control group. Administering the studied compounds (4), (5) and (6) to the animals reduced entries into the closed arms by 41.9%, 69.8% and 41.9% respectively. Group (5) spent an average of 18.5±8.5 seconds on the central platform. For the other groups using the studied compounds, the indicators were lower.

## Conclusions

This study implemented an integrated approach encompassing extraction optimization, synthetic development, and pharmacological evaluation to design and investigate novel neurotropic agents derived from the β-carboline alkaloid harmine. A second-order polynomial model effectively optimized the extraction conditions from *Peganum harmala* L. roots, with the best yield (up to 97%) achieved using double percolation at 65 °C for 3 hours, a 1:10 solvent-to-material ratio, and a particle size of 2–3 mm.

The β-carboline alkaloid harmine served as a versatile scaffold for the synthesis of novel C-8-substituted derivatives, including 8-acetylharmine, (Z)-hydrazono analogs, and cinnamoyl derivatives, with high yields and structural clarity confirmed through spectroscopic.

*In vivo* pharmacological testing revealed that compounds 2, 4, 5 and 6 exhibited significant anxiolytic and antidepressant activity at a dose of 10 mg/kg. In the Open Field Test, these compounds reduced anxiety-related behaviors, such as vertical activity, grooming, defecation and urination, while encouraging horizontal exploration. In the Elevated Plus Maze, compounds 2 and 4 notably increased the time spent in the open arms and on the central platform, which are markers of anxiolytic efficacy comparable to the reference antidepressant amitriptyline.

Of the compounds tested, 8-{(Z)-1-[(Z)-(2-arylidene)hydrazono]ethyl}harmine (compound 4) exhibited the most pronounced anxiolytic properties and was well tolerated. These findings emphasize the important role that C-8 substitution plays in modulating the neuropharmacological activity of harmine, and demonstrate the potential of β-carboline derivatives in the development of multi-target CNS therapeutics.

Consequently, *Peganum harmala* L. should be regarded not only as a renewable source of the biologically active compound harmine, but also as a valuable foundation for designing new neurotropic agents to treat anxiety and depressive disorders.

## Acknowledgments

The work is funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan within the framework of the project No. AP23489904 “Phytosome development – an effective form of targeted transport of original medical compounds in the human body”.

## Conflict of interest

The authors declare that they have no conflicts of interest.

**References**

1. Ayeni E.A., Aldossary A.M., Ayejoto D.A., Gbadegesin L.A., Alshehri A.A., Alfassam H.A., Afewerky H.K., Almughem F.A., Bello S.M., Tawfik E.A. (2022) Neurodegenerative Diseases: Implications of Environmental and Climatic Influences on Neurotransmitters and Neuronal Hormones Activities. *Int. J. Environ. Res. Public Health*, vol. 19(19), pp. 12495-12518. https://doi.org/10.3390/ijerph191912495

2. Ball N., Teo W.P., Chandra S., Chapman J. (2019) Parkinson's Disease and the Environment. *Front. Neurol.* vol. 10, pp. 218-225. https://doi.org/10.3389/fneur.2019.00218

3. Feigin V.L., Nichols E., Alam T., Bannick M.S., Beghi E., Blake N., Culpepper W.J., Dorsey E.R., Elbaz A., Ellenbogen R.G. et al. (2019) Global, regional, and national burden of neurological disorders, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.*, vol.18, pp. 459–480. https://doi.org/10.1016/S1474-4422(18)30499-X

4. Piscopo P., Bellenghi M., Manzini V., Crestini A., Pontecorvi G., Corbo M., Ortona E., Carè A., Confaloni A. (2021) A Sex Perspective in Neurodegenerative Diseases: MicroRNAs as Possible Peripheral Biomarkers. *Int. J. Mol. Sci.* vol. 22, pp. 4423-4437. https://doi.org/10.3390/ijms22094423

5. Durães F., Pinto M., Sousa E. (2018) Old Drugs as New Treatments for Neurodegenerative Diseases. *Pharmaceuticals,* vol. 11(2), pp. 44-65. https://doi.org/10.3390/ph11020044

6. Azimova S.S., Yunusov M.S. (2013). Natural compounds. Alkaloids. New York: Springer- Reference. 821 p. ISBN-10:1461405599, ISBN-13:‎978-1461405597

7. Chaachouay N., Zidane L. (2024) Plant-Derived Natural Products: A Source for Drug Discovery and Development. *Drugs Drug Candidates,* vol. 3, pp. 184–207. https://doi.org/10.3390/ddc3010011

8. Bhambhani S., Kondhare K.R., Giri A.P. (2021) Diversity in Chemical Structures and Biological Properties of Plant Alkaloids. *Molecules*, vol. 26(11), pp. 3374-3402. https://doi.org/10.3390/molecules26113374

9. Javeed M., Rasul A., Hussain G., Jabeen F., Rasool B., Shafiq N., Riaz A., Kaukab G., Ali M. (2018) Harmine and its derivatives: Biological activities and therapeutic potential in human diseases. *Bangladesh J. Pharmacol*, vol. 13, p. 203-213. https://doi.org/10.3329/bjp.v13i3.34990

10. Li Sh., Zhang Q., Wang Y., Lin B., Li Dahong, Hua H., Hu X. (2024) β-Carboline alkaloids from the roots of *Peganum harmala* L. *Chinese Journal of Natural Medicines*, vol. 22(2), pp. 171-177. https://doi.org/10.1016/S1875-5364(24)60583-2

11. Li S., Cheng X., Wang C. (2017) A review on traditional uses, phytochemistry, pharmacology, pharmacokinetics and toxicology of the genus *Peganum*. *J. Ethnopharmacol,* vol. 203, pp. 127-162. https://doi.org/10.1016/j.jep.2017.03.049

12. Doskaliyev A., Seidakhmetova R.B., Tutai D.S., Galdaeva K., Surov V.K., Adekenov S.M. (2021) Alkaloids of *Peganum harmala* L. and their pharmacological activity. *Open Access Macedonian Journal of Medicinal Science*, vol. 9A, pp. 765-775. https://doi.org/10.3889/oamjms.2021.6654

13. Patel K., Gadewar M., Tripathi R., Prasad S.K., Patel D.K. (2012). A review on medicinal importance, pharmacological activity and bioanalytical aspects of beta-carboline alkaloid "harmine." *Asian Pacific Journal of Tropical Biomedicine,* vol. 2(8), pp. 660–664. https://doi.org/10.1016/S2221-1691(12)60116-6

14. Dos Santos R. G., Osório F. L., Crippa J. A., and Hallak J. E. (2016). Antidepressive and anxiolytic effects of ayahuasca: A systematic literature review of animal and human studies. *Revista Brasileira de Psiquiatria,* vol. 38 (1), pp. 65–72. https://doi.org/10.1590/1516-4446-2015-1701.

15. Nunes A. A., Dos Santos R G., Osório F. L., Sanches R. F., Crippa J. A., and Hallak J. E. (2016). Effects of ayahuasca and its alkaloids on drug dependence: A systematic literature review of quantitative studies in animals and humans. *Journal of Psychoactive Drugs,* vol. 48(3), pp. 195–205. https://doi.org/10.1080/02791072.2016.1188225.

16. Glennon R.A., Dukat M., Grella B., Hong S., Costantino L., Teitler M., Smith C., Egan C., Davis K., Mattson M.V. (2000) Binding of β-carbolines and related agents at serotonin (5-HT2 and 5-HT1A), dopamine (D2) and benzodiazepine receptors. *Drug and Alcohol Dependence*, vol. 60(2), pp. 121–132. https://doi.org/10.1016/S0376-8716(99)00148-9.

17. Li Y., Sattler R., Yang E.J., Nunes A., Ayukawa Y., Akhtar S., Ji G., Zhang P.W., Rothstein J.D. (2011). Harmine, a natural beta-carboline alkaloid, upregulates astroglial glutamate transporter expression. *Neuropharmacology,* vol. 60(7–8), pp. 1168–1175. https://doi.org/10.1016/j.neuropharm.2010.10.016.

18. Fortunato J.J., Réus G.Z., Kirsch T.R., Stringari R.B., Fries G.R., Kapczinski F., Hallak J. E., Zuardi A.W., Crippa J.A., and Quevedo J. (2010). Effects of β-carboline harmine on behavioral and physiological parameters observed in the chronic mild stress model: Further evidence of antidepressant properties. *Brain Research Bulletin*, vol. 81(4–5), pp. 491–496. https://doi.org/10.1016/j.brainresbull.2009.09.008.

19. Sun P., Zhang S., Li Y., Wang L. (2014). Harmine mediated neuroprotection via evaluation of glutamate transporter 1 in a rat model of global cerebral ischemia. *Neuroscience Letters*, vol. 583, pp. 32–36. doi:10.1016/j.neulet.2014.09.023.

20. Göckler N., Jofre G., Papadopoulos C., Soppa U., Tejedor F. J., Becker W. (2009). Harmine specifically inhibits protein kinase DYRK1A and interferes with neurite formation. *FEBS Journal*, vol. 276 (21), pp. 6324–6337. https://doi.org/10.1111/ j.1742-4658.2009.07346.x.

21. He D., Wu H., Wei Y., Liu W., Huang F., Shi H., Zhang B., Wu X., Wang C. (2015) Effects of harmine, an acetylcholinesterase inhibitor, on spatial learning and memory of APP/PS1 transgenic mice and scopolamine-induced memory impairment mice. *Eur. J. Pharmacol,* vol. 768, pp. 96-107. https://doi.org/10.1016/j.ejphar.2015.10.037

22. Li S.P., Wang Y.W., Qi S.L., Zhang Y.P., Deng G., Ding W.Z., Ma C., Lin Q.Y., Guan H.D., Liu W. (2018) Analogous b-carboline alkaloids harmaline and harmine ameliorate scopolamine-induced cognition dysfunction by attenuating acetylcholinesterase activity, oxidative stress, and inflammation in mice. *Front. Pharmacol*, vol. 9, pp. 346-361. https://doi.org/10.3389/fphar.2018.00346

23. Costa O.A., and Faria L.A. (1936). A planta que faz sonhar: O yagê [The plant that induces dreams: The yage]. *Revista da Flora Medicinal*, vol. 2, pp. 575–624.

24. Adekenov S.M., Salimov R.M., Abaimov D.A., Sariev A.K., Kovalev G.I. (2020). Psychopharmacological properties of harmine hydrochloride in the experiment. *Experimental and clinical pharmacology*, vol. 83, no. 3, pp. 3-6. https://doi.org/10.30906/0869-2092-2020-83-3-3-6

25. Nurmaganbetov Zh.S., Arystan L.I., Turmukhambetov A.Zh., et al. (2014) Antidepressant effect of harmine hydrochloride. *Pharmacy and pharmacology*, vol. 2, no. 6-7, pp. 96-98. https://doi.org/10.19163/2307-9266-2014-2-6(7)-96-98

26. Epifantseva E.V., Romanova M.A., Seidakhmetova R.B., Adekenov S.M. (2020) Effect of harmine hydrochloride on behavioral responses of rats with a model of stress-induced disorder. *Medicine and Ecology*, No. 1(94), pp. 77-88. UDC: 616.89, 615.214

27. Seidakhmetova R.B., Rakhimov K.D., Tutay D.S., Mukhanova T.T., Zholbarys A.A., Amanzhan A., Adekenov S.M. (2021) Neurotropic activity of plant alkaloids. *Bulletin of KazNU (experimental biology series)*, No. 3(88), pp. 142-153. https://doi.org/10.26577/eb.2021.v88.i3.14

28. Adekenov S. M., Baitulin I. O., Egeubaeva R. A., Saparbaeva N. A. (2010) The current state of natural thickets of common harmala in the territory of Southern Kazakhstan. *Izv. NAN Rep. Kazakhstan* (Ser. Biol. Med.), No. 5, pp. 55-61.

29. Willner P. (2017) Reliability of the chronic mild stress model of depression: a user survey. *Neurobiol. Stress*, vol. 6, pp. 68–77. https://doi.org/10.1016/j.ynstr.2016.08.001

30. Romanenko E.B., Levitskaya N.G., Kamensky A.A. (2007) Study of the nootropic activity of Betamecine. *Experimental and Clinical Pharmacology*, vol. 70, no. 4, pp. 7 – 10.

31. Voronina T.A., Seredenin S.B. (2000) Guidelines for the study of tranquilizing (anxiolytic) action of pharmacological substances. Guide to experimental (preclinical) study of new pharmacological substances. Moscow: Remedium, pp. 126-136.

32. Koplik E.V., Salieva R.M., Gorbunova A.V. (1995) Open field test as a prognostic criterion for resistance to emotional stress in Wistar rats. *J. of higher nervous activity*, vol. 45, no. 4, pp. 775-781.

33. Walf A. A., Frye C. A. (2007). The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. *Nature Protocols*, vol. 2(2), pp. 322–328. https://doi.org/10.1038/nprot.2007.44

34. Seibenhener M. L., Wooten M. C. (2015). Use of the Open Field Maze to measure locomotor and anxiety-like behavior in mice. *Journal of Visualized Experiments*, vol. 96, e52434. https://doi.org/10.3791/52434

35. Bystrova M.N., Demidova M.A., Galchinskaya I.L., Zholobov I.S. (2012) Research of influence of various medicinal forms of soothing gathering on behaviour of mice in the test «Raised crosswise labyrinth». *Modern Problems of Science and Education*, no. 2, pp. 25-28. UDC: 615.214.22:615.322

36. Khabriev R.U. (2005) Guide to experimental (preclinical) study of new pharmacological substances / edited by Corresponding Member of the Russian Academy of Medical Sciences, Professor R.U. Khabriev. 2nd ed., revised and enlarged. Moscow: OJSC "Izdatelstvo" Medicine ", 832 p. ISBN 5-225-04219-8 (in translation)

37. Nachar N. (2008) The Mann-Whitney U: A Test for Assessing Whether Two Independent Samples Come from the Same Distribution. *Tutorials in Quantitative Methods for Psychology*, vol. 4(1), pp. 13–20.

38. Vachnadze V., Suladze T., Vachnadze N., Kintsurashvili L., Novikova J. (2015) Alkaloids of *Peganum harmala* L. and their biological activity. *Georgian medical news*, N 6, pp. 79–81.

39. Shang X., Pan H., Miao X., Wang D., Wang X., Wang Y., Zhang J. (2017) Method for extracting *Peganum harmala* L. alkaloid under microwave assistance. Patent 104628731B (CN).

40. Khan F.A., Maalik A., Iqbal Z., Malik I. (2013) Recent pharmacological developments in β-carboline alkaloid harmaline. *Eur. J. Pharmacol.,* vol. 721(1-3), pp. 391–394. https://doi.org/10.1016/j.ejphar.2013.05.003

41. Liu W., Liu X., Tian L., Gao Y., Liu W., Chen H., Jiang X., Xu Z., Ding H., Zhao Q. (2021) Design, synthesis and biological evaluation of harmine derivatives as potent GSK-3b/DYRK1A dual inhibitors for the treatment of Alzheimer's disease. *European Journal of Medicinal Chemistry,* vol. 222, pp. 113554-113572. https://doi.org/10.1016/j.ejmech.2021.113554.

42. Kumar K., Wang P., Wilson J., Zlatanic V., Berrouet C., Khamrui S., Secor C., Swartz E.A., Lazarus M., Sanchez R., Stewart A.F., Garcia-Ocana A., DeVita R.J. (2020) Synthesis and biological validation of a harmine-based, central nervous system (CNS)-avoidant, selective, human β-cell regenerative dual-specificity tyrosine phosphorylation-regulated kinase A (DYRK1A) inhibitor. *J. Med. Chem.*, vol. 63(6), pp. 2986-3003. https://doi.org/10.1021/acs.jmedchem.9b01379.

***Information about authors***

*Asel Amanzhan – PhD, JSC Scientific and Production Center "Phytochemistry" (Karaganda, Kazakhstan, e-mail: asel.amanzhan@mail.ru)*

*Elvira Schultz – Doctor of Chemical Sciences, Professor, N.N. Vorozhtsov Novosibirsk Institute of Organic Chemistry of SB RAS (Novosibirsk, Russia, e-mail: schultz@nioch.nsc.ru)*

*Bekbolat Adekenov – JSC Scientific and Production Center "Phytochemistry" (Karaganda, Kazakhstan, e-mail: adekenovbekbolat@gmail.com)*

*Olga Maslova – JSC Scientific and Production Center "Phytochemistry" (Karaganda, Kazakhstan, e-mail: m.olga.84@mail.ru)*

*Marat Ibrayev – Doctor of Chemical Sciences, Professor, Karaganda Buketov University (Karaganda, Kazakhstan, e-mail: mkibr@mail.ru)*

*Sergazy Adekenov – Doctor of Chemical Sciences, Professor, JSC Scientific and Production Center "Phytochemistry" (Karaganda, Kazakhstan, e-mail: arglabin@phyto.kz)*