AVALIAÇÃO DE EFEITOS NEUROPROTETIVOS DE COMPOSTOS ALCALÓIDES

ASSESSMENT OF NEUROPROTECTIVE EFFECTS OF ALKALOID COMPOUNDS

ОЦЕНКА НЕЙРОПРОТЕКТОРНЫХ ЭФФЕКТОВ АЛКАЛОИДНЫХ СОЕДИНЕНИЙ

SEIDAKHMETOVA, Roza B.^{1*}; ARYSTAN, Leila I.²; MULDAEVA, Gulmira M.³;
HAYDARGALIEVA, Leila S.⁴; NURMAGANBETOV, Zhangel'dy S.⁵;

¹ JSC "International Research and Production Holding "Phytochemistry", Laboratory of Pharmacology, Karaganda – Republic of Kazakhstan

^{2,3,4} Karaganda Medical University, Department of Family Medicine, Karaganda – Republic of Kazakhstan

⁵ Karaganda Medical University, Department of Biochemistry, Karaganda – Republic of Kazakhstan

* Corresponding author
e-mail: rozabat@mail.ru

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RESUMO

Os alcaloides beta-carbolina mostram uma ampla gama de efeitos psicofarmacológicos (por exemplo, alguns alcaloides beta-carbolina facilitam a transmissão dopaminérgica e interagem com os receptores dopaminérgicos D1 e D2 no corpo estriado). Este artigo apresenta dados sobre os efeitos neuroprotetores de compostos alcaloides usando métodos de simulação em computador, triagem virtual baseada em *docking* e farmacologia experimental. O objetivo do estudo foi investigar a ação neuroprotetora / protetora contra o estresse de novos derivados de compostos alcaloides usando os métodos de simulação computacional, triagem virtual baseada em *docking* e farmacologia experimental. Com o auxílio dos programas *ChemDraw* e *MGLTools*, foram utilizados os métodos de modelagem computacional das moléculas de derivados alcaloides, triagem virtual baseada em *docking*, receptor DRD2 e modelos tridimensionais das moléculas de ligantes. A energia de ligação de uma conformação individual foi usada como resultado final, o que mostra a força da interação entre o ligante e a molécula alvo. Foram estudados 22 compostos de alcaloides e seus derivados. A modelagem virtual de moléculas foi realizada para compostos e receptores, a ligação da molécula "ligante-alvo" foi realizada e os compostos candidatos foram selecionados. Estudos experimentais *in vivo* dos efeitos neuroprotetores desses compostos foram conduzidos no modelo de estresse emocional. Foram estudados os efeitos dos alcaloides harmina, norharmane e guanina no tempo de imobilidade no teste de natação forçada em camundongos, um modelo de depressão em animais. Um teste de natação forçada e um labirinto positivo elevado foram utilizados para determinar os efeitos antidepressivos e ansiolíticos da harmina em ratos. De acordo com os resultados do *docking*, as moléculas apresentadas de compostos alcaloides apresentaram interações com o receptor de dopamina D2. Os resultados obtidos no teste "Elevated Plus Maze (labirinto positivo elevado)" mostraram que os animais tratados com 9-metoxi-2-fenil-11H-indolisino [8,7-β] indol, lappaconitina e citisina na dose de 5 mg/kg, comparados em ratos do grupo controle, experimentaram uma ação ansiolítica (anti-ansiedade) no estresse emocional experimental.

Palavras-chave: beta-carbolina, teste de natação forçada, triagem virtual baseada em *docking*, atividade neurotrópica.

ABSTRACT

Beta-carboline alkaloids show a wide range of psychopharmacological effects (for example, some beta-carboline alkaloids facilitate dopaminergic transmission and interact with dopaminergic receptors D1 and D2 in the striatum). This article presents data on neuroprotective effects of alkaloid compounds using computer simulation methods, docking-based virtual screening, and experimental pharmacology. The purpose of the study was to investigate the neuroprotective/stress-protective action of new derivatives of alkaloid compounds using the methods of computer simulation, docking-based virtual screening, and experimental pharmacology. Through *ChemDraw*, *MGLTools* programs, they have used computer modeling of the molecules of alkaloid derivatives, docking-based virtual screening, DRD2 receptor, and three-dimensional models of the ligand molecules. The binding energy of an individual conformation was used as a final result, which shows the strength of the interaction between the ligand and the target molecule. 22 compounds of alkaloids and their derivatives were studied. Virtual

molecule modeling was performed for compounds and receptors, "ligand-target" molecule docking was carried out, and candidate compounds were selected. *In vivo* experimental studies of the neuroprotective effects of these compounds were conducted in the emotional stress model. The effects of harmine, norharmane, and guanine alkaloids on immobility time in the forced swimming test in mice, a model of depression in animals, were studied. A forced swimming test and an elevated plus-maze were used to determine the antidepressant and anxiolytic effects of harmine in rats. According to the docking results, the presented molecules of alkaloid compounds showed interactions with dopamine receptor D2. The results obtained in the "Elevated Plus Maze" test showed that the animals treated with 9-methoxy-2-phenyl-11H-indolizino[8,7-β]indole, lappaconitine and cytisine at a dose of 5 mg/kg, compared to rats in the control group, experienced an anxiolytic (anti-anxiety) action in the experimental emotional stress.

Keywords: *beta-carboline, forced swimming test, docking-based virtual screening, neurotropic activity.*

АННОТАЦИЯ

Бета-карболиновые алкалоиды проявляют широкий спектр психофармакологических эффектов (например, некоторые алкалоиды бета-карболина облегчают дофаминергическую передачу и взаимодействуют с дофаминергическими рецепторами D1 и D2 в полосатом теле). В этой статье представлены данные о нейропротекторном действии алкалоидных соединений с использованием методов компьютерного моделирования, виртуального скрининга на основе докинга и экспериментальной фармакологии. Цель исследования – изучение нейропротекторного/стресс-протекторного действия новых производных алкалоидных соединений с применением методов компьютерного моделирования, виртуального докинга и экспериментальной фармакологии. В ходе исследования использовались следующие методы: компьютерное моделирование молекул производных алкалоидов, виртуальный скрининг на основе докинга, рецептор DRD2, трехмерные модели молекул лигандов, которые были сконструированы с использованием программы ChemDraw с использованием набора программ. Autodock (Исследовательский институт Скриппса, США), MGLTools (Исследовательский институт Скриппса, США). В качестве конечного результата была использована энергия связи индивидуальной конформации, которая показывает силу взаимодействия между лигандом и молекулой-мишенью. Было изучено 22 соединения алкалоидов и их производных. Моделирование виртуальных молекул выполняли для соединений и рецепторов, проводили стыковку молекул «лиганд-мишень» и отбирали соединения-кандидаты. Экспериментальные исследования нейропротекторных эффектов этих соединений в естественных условиях проводились в модели эмоционального стресса. Исследовано влияние алкалоидов гуарена, норхармана и гуанина на время неподвижности в тесте принудительного плавания на мышах, модели депрессии на животных. Тест на принудительное плавание и лабиринт с повышенным уровнем плюс были использованы для определения антидепрессивного и анксиолитического действия гуанина у крыс. По результатам проведенного докинга установлено, что представленные молекулы алкалоидных соединений проявили взаимодействие с рецептором дофамин D2. Результаты, полученные в тесте «Приподнятый крестообразный лабиринт», показали, что в группе животных, получавших вещества 9-Метокси-2-фенил-11Н-индолизин [8,7-β] индол, лаппаконитин и цитизин в дозе 5 мг/кг по сравнению с крысами контрольной группы в условиях экспериментального эмоционального стресса, проявлялось анксиолитическое (противотревожное) действие.

Ключевые слова: *бета-карболин, тест принудительного плавания, виртуальный скрининг на основе докинга, нейротропная активность.*

1. INTRODUCTION:

Beta-carboline alkaloids show a wide range of psychopharmacological effects through binding to benzodiazepine, imidazoline, serotonin and opiate receptors, as well as monoamine oxidase (MAO) inhibition (Herraiz *et al.*, 2010; Liu *et al.*, 2017; Xiong *et al.*, 2018; Costanzi *et al.*, 2019). Neurochemical and behavioral studies have shown that some beta-carboline alkaloids facilitate dopaminergic transmission and interact with dopaminergic receptors D1 and D2 in the striatum (Farzin *et al.*, 2011; Li *et al.*, 2017; Ye *et*

al., 2017; Liu *et al.*, 2019). Most beta-carboline alkaloids are known to be potent inhibitors that metabolize catecholamine neurotransmitters (Yonezawa *et al.*, 2011; Taborskaya *et al.*, 2017; Axen *et al.*, 2017; Moore *et al.*, 2018). Harmine, an indole alkaloid, shows antidepressant activity, interacting with MAO-A and several cell surface receptors, including serotonin 2A receptor (5-hydroxytryptamine receptor 2A, 5-HT2A) (Réus *et al.*, 2010; Nasehi *et al.*, 2018; Kwon *et al.*, 2018; Li *et al.*, 2018; Long *et al.*, 2019; Sun *et al.*, 2019).

The effects of harmine, norharmane, and guanine alkaloids on immobility time in the forced

swimming test (FST) in mice, a model of depression in animals, were studied. It was concluded that harmine, norharmane and guanine shorten immobility time in this test, suggesting an antidepressant effect, due to the inverse agonistic mechanism located in benzodiazepine receptors (Farzin and Mansouri, 2006; Dai *et al.*, 2018; Xi *et al.*, 2018). A forced swimming test (FST) and an elevated plus maze (EPM) were used to determine the antidepressant and anxiolytic effects of harmine in rats compared to a known antidepressant, imipramine (30 mg/kg ip). Administration of harmine resulted in a dose-dependent reduction of the immobility time in the FST and increased the time spent in the open arms in the EPM, compared to the group which received saline (dos Santos and Hallak, 2017; Herraiz and Guillén, 2018). Therefore, as an endogenous substance, it has anti-anxiety and anti-depressant effects (Aricioglu and Altunbas, 2003; Chen *et al.*, 2017; Wang *et al.*, 2018; Ferraz *et al.*, 2019).

Several potential molecular targets that have been identified for the central pharmacological effects of harmine include zinc-dependent kinases CDK (CDK1, 2 and 5), MAO-A, 5-HT_{2A} sites, and imidazoline receptors I1 and I2. Harmine is a potent, double specific tyrosine phosphorylation inhibitor regulated by kinase (DYRK) (Song *et al.*, 2004; Egusa *et al.*, 2011; Ueda *et al.*, 2019). Harmine has been reported to show antidepressant effects in rodents (Réus *et al.*, 2012; Deng *et al.*, 2017; Zhang *et al.*, 2019). Harmine has anxiolytic, behavioral effects and antitumor potential both *in vitro* and *in vivo* (Hamsa and Kuttan, 2011; Cui *et al.*, 2019a). Harmine has a high inhibitory affinity to the kinase activity of DYRK1A, which indicates that harmine can modify tau phosphorylation (Frost *et al.*, 2011; Zhao *et al.*, 2019). Harmine also has a dual effect on the upstream potential of the atrial muscle (Carpentier, 1982). Also, a cytotoxic activity against human tumor cell lines has been reported in humans (Cao *et al.*, 2005; Freire *et al.*, 2018).

At the International Research and Production Holding "Phytochemistry" (Karaganda, Kazakhstan), a phytochemical study of an individual compound obtained from the roots of harmel peganum (*Peganum harmala* L.) growing in the southern regions of the Republic of Kazakhstan was carried out. Harmine, an indole alkaloid, was isolated and processed, and a water-soluble form, harmine hydrochloride, was synthesized. Studies of harmine hydrochloride pharmacological activity show edits potential antiparkinsonian activity (Turmukhambetov, 2009;

Turmukhambetov *et al.*, 2009). Further toxicological studies showed that harmine hydrochloride had no toxic effects on the internal organs or brain in a chronic three-month experiment in rats at the studied doses of 2.5 and 5 mg/kg (Lou *et al.*, 2017; Zhanaidarova *et al.*, 2019; Cui *et al.*, 2019b; Krüzselyi *et al.*, 2019).

The antiparkinsonian effects of harmine hydrochloride were studied in the experiments. To achieve this goal, the authors used haloperidol-induced catalepsy and MPTP-induced Parkinson's disease. It was found that harmine hydrochloride at a dose of 2.5 mg/kg eliminated haloperidol-induced catalepsy in rats and reduced hypokinesia and rigidity in the test for parkinsonism in C57BL/6 mice (Nurmaganbetov *et al.*, 2019). Based on the results, the search for new harmine derivatives with neuroprotective activity was continued.

The purpose of the study was to investigate the neuroprotective/stress-protective action of new derivatives of alkaloid compounds using the methods of computer simulation, docking-based virtual screening, and experimental pharmacology.

2. MATERIALS AND METHODS:

The following compounds were presented for the study: harmine N-oxide, 6-bromoharmine; 8-bromoharmine; 6,8-dibromoharmine; 6-iodoharmine; 6,8-dichloroharmine; 9-methoxy-2-phenyl-11*H*-indolisino[8,7- β]indole; 9-methoxy-2-(4-methoxyphenyl)-11*H*-indolisino[8,7- β]indole; 2-(3,4-dichlorophenyl)-9-methoxy-11*H*-indolisino[8,7- β]indole; 2-(4-methoxy-phenyl)-3,10-bis-formyl-11*H*-indolisino[8,7- β]indole; 3-acetyl-9-methoxy-2-phenyl-11*H*-indolisino[8,7- β]indole; 8-acetylharmine; 8-formylharmine; chalcone derivative of harmine; pyrazoline derivative of harmine; 4-methoxychalcone derivative of harmine; 4-methoxy-pyrazoline derivative of harmine; 2,4-dimethoxy-chalcone derivative of harmine; 2,4-dimethoxy-pyrazoline derivative of harmine; 2,3,4-trimethoxy-chalcone derivative of harmine; 2,3,4-trimethoxy-pyrazoline derivative of harmine; 2-F-chalcone derivative of harmine; 2-F-pyrazoline derivative of harmine.

Computer modeling of the molecules of alkaloid derivatives and docking-based virtual screening with an estimated biological target, DRD2 receptor, one of the five known types of dopamine receptors belonging to the class of D₂-like receptors which inhibit adenylate cyclase, were performed (Aricioglu and Altunbas, 2003). Three-dimensional models of the ligand molecules were constructed using the ChemDraw program,

using a set of programs Autodock (The Scripps Research Institute, USA), MGLTools (The Scripps Research Institute, USA). The binding energy of an individual conformation was used as a final result, which shows the strength of the interaction between the ligand and the target molecule.

The experimental part was carried out following the "Rules of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (European Convention..., 1986) and under the requirements for the studies of new pharmacological substances in sexually mature rats (60 animals), equal amounts of females and males, with initial body weight of 240-370 g. The animals were kept in standard vivarium conditions on a regular diet and free access to water and food. Besides, general conditions of the animals were evaluated: changes in the animal's body weight, motor activity, appetite and reaction to external stimuli.

Emotional stress was modeled by placing the rats in tight plastic cylinders with their subsequent immersion in water to the neck level (20-22°C) for 2 hours daily for four days (Razueva *et al.*, 2014). The studied substances were administered to the animals at doses of 5 mg/kg for seven days before modeling emotional stress followed by a daily administration 1 hour before placing the animals in the plastic cylinders. Piracetam (JSC "BZMP", Republic of Belarus) was used as a reference drug, which was administered to the animals according to a similar scheme. All drugs were administered daily orally in the form of an aqueous solution at a dose of 1 ml/kg. The animals of the control and intact groups received purified water in the same volume.

On the fourth day after emotional stress modeling, the behavioral effects of the studied compounds were assessed using generally accepted methods in the following tests: "Open Field" and "Elevated Plus Maze" (Koplik *et al.*, 1995). Statistical processing of the results was carried out using the "Statistica 8.0" software package. The results are presented as "mean values $\pm$ standard error of the mean". The differences were considered significant at a significance level of $p < 0.05$.

3. RESULTS AND DISCUSSION:

According to the docking results, the presented molecules of alkaloid compounds showed interactions with dopamine receptor D2. According to the docking results, the following alkaloid derivatives showed the maximum binding

to dopamine receptor D2: 9-methoxy-2-phenyl-11H-indolisino[8,7- β]indole (BE = -11.6); 2-(3,4-dichlorophenyl)-9-methoxy-11H-indolisino[8,7- β]indole (BE = -10.7); 2-F-chalcone derivative of harmine (BE = -10.7) (Table 1). The spatial structures of the ligands and a schematic representation of the ligand-target interactions are presented in Figures 1-3.

During the experiment to assess an *in vivo* neurotrophic activity, it was noted that body weight data in the rats from all groups remained within baseline parameters; there were no significant changes in body weight gain in the animals from all groups (Table 2).

Administration of the studied compounds, harmine, 8-acetylharminine, delcosine and lappaconitine, to rats reduced the number of entries into the closed arms; administration of 8-acetylharminine and lappaconitine increased the number of peeps. The number of leaning overincreased in the 8-acetylharminine and delcosine groups. The number of defecations and urinations decreased in the groups of 8-acetylharminine, ((E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-on, (E)-1-(7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl)-3-(2-fluorophenyl)prop-2-en-1-on and echinopsine (Tables 3, 4).

According to the docking results, the following alkaloid derivatives showed the maximum binding to dopamine receptor D2: 9-methoxy-2-phenyl-11H-indolisino[8,7- β]indole (BE = -11.6); 2-(3,4-dichlorophenyl)-9-methoxy-11H-indolisino[8,7- β]indole (BE = -10.7); 2-F-chalcone derivative of harmine (BE = -10.7). This experimental study showed that indole alkaloids, 8-acetylharminine, 9-methoxy-2-phenyl-11H-indolisino[8,7- β]indole, diterpene alkaloid lappaconitine and cytosine at a dose of 5 mg/kg exhibit neurotropic effects, increase the levels of orientation and research activity, normalize emotional state and decrease anxiety and fear levels in animals.

4. CONCLUSIONS:

The results obtained in the "Elevated Plus Maze" test showed that the animals treated with 9-methoxy-2-phenyl-11H-indolisino[8,7- β]indole, lappaconitine and cytosine at a dose of 5 mg/kg, compared to rats in the control group, experienced an anxiolytic (anti-anxiety) action in the experimental emotional stress.

In particular, the time spent in the closed

arms was reduced by 23.9% in the lappaconitine group, by 12.5% in the 9-methoxy-2-phenyl-11H-indolisino[8,7- β]indole group, by 12.4% in the 8-acetylarmine group and by 5.6% in the cytosine group, compared to the control group. The time spent by the animals in the open arms increased by 78% in the 9-Methoxy-2-phenyl-11H-indolisino[8,7- β]indole group, by 76.4% in the lappaconitine group, by 76.1% in the 8-acetylarmine group and by 64.1% in the cytosine group, compared to the control group. The time spent on the central site increased by 37.8% in the lappaconitine group, compared to the control group.

Therefore, 9-methoxy-2-phenyl-11H-indolisino[8,7- β]indole, which had the highest binding energy during ligand-target docking, is a candidate substance as a stress-protective agent for further in-depth studies, as well as indole alkaloids, 8-acetylarmine, 9-methoxy-2-phenyl-11H-indolisino[8,7- β]indole, and diterpene alkaloid lappaconitine, which showed an anxiolytic effect in the stress test.

5. REFERENCES:

1. Aricioglu, F., Altunbas, H. *Annals of the New York Academy of Sciences*, **2003**, 1009, 196–201.
2. Axen, S.D., Huang, X.-P., Cáceres, E.L., Gendele, L., Roth, B.L., Keiser, M.J. *Journal of Medicinal Chemistry*, **2017**, 60(17), 7393–7409.
3. Cao, R., Peng, W., Chen, H., Ma, Y., Liu, X., Hou, X., Guan, H., Xu, A. *Biochemical and Biophysical Research Communications*, **2005**, 338(3), 1557–1563.
4. Carpentier, R.G. *British Journal of Pharmacology*, **1982**, 75(1), 207–212.
5. Costanzi, S., Cohen, A., Danfora, A., Dolatmoradi, M. *Journal of Chemical Information and Modeling*, **2019**, 59(7), 3177–3190.
6. Cui, G., Shu, B., Veeran, S., Yuan, H., Yi, X., Zhong, G. *Pesticide Biochemistry and Physiology*, **2019a**, 154, 67–77.
7. Cui, Y., Jiang, L., Yu, R., Shao, Y., Mei, L., Tao, Y. *Journal of Ethnopharmacology*, **2019b**, 243, article number 112096.
8. Chen, S., Feng, Z., Wang, Y., Ma, S., Hu, Z., Yang, P., Chai, Y., Xie, X. *Journal of Chemical Information and Modeling*, **2017**, 57(5), 1101–1111.
9. Dai, J., Dan, W., Schneider, U., Wang, J. *European Journal of Medicinal Chemistry*, **2018**, 157, 622–656.
10. Deng, Y., Wang, Q.-R., Wang, J.-H., Li, C.-H., Wang, X.-Z. *Chinese Traditional and Herbal Drugs*, **2017**, 48(11), 2353–2364.
11. dos Santos, R.G., Hallak, J.E.C. *Journal of Psychoactive Drugs*, **2017**, 49(1), 1–10.
12. Egusa, H., Doi, M., Saeki, M., Fukuyasu, S., Akashi, Y., Yokota, Y., Yatani, H., Kamisaki, Y. *Bone*, **2011**, 49(2), 264–274.
13. European Convention for the Protection of Vertebrate Animals Used for Experiments or for Other Scientific Purposes. **1986**. <https://rm.coe.int/168007a6a8>, accessed 20 December 2019.
14. Farzin, D., Haghparast, A., Motaman, S., Baryar, F., Mansouri, N. *Pharmacology Biochemistry and Behavior*, **2011**, 98(2), 215–219.
15. Farzin, D., Mansouri, N. *European Neuropsychopharmacology*, **2006**, 16(5), 324–328.
16. Ferraz, C.A.A., de Oliveira Júnior, R.G., Picot, L., da Silva Almeida, J.R.G., Nunes, X.P. *Fitoterapia*, **2019**, 137, article number 104196.
17. Freire, V.F., Silva, G.R., Yariwake, J.H. *Journal of the Brazilian Chemical Society*, **2018**, 29(4), 775–781.
18. Frost, D., Meechoovet, B., Wang, T., Gately, S., Giorgetti, M., Shcherbakova, I., Dunckley, T. *PLoS One*, **2011**, 6(5), article number e19264.
19. Hamsa, T.P., Kuttan, G. *Chinese Medicine*, **2011**, 6(1), 11.
20. Herraiz, T., González, D., Ancín-Azpilicueta, C., Arán, V.J., Guillén, H. *Food and Chemical Toxicology*, **2010**, 48(3), 839–845.
21. Herraiz, T., Guillén, H. *BioMed Research International*, **2018**, 2018, article number 4810394.
22. Koplik, E.V., Salieva, R.M., Gorbunova, A.V. *Journal of Higher Nervous Activity*, **1995**, 45(4), 775–781.
23. Krüzselyi, D., Vetter, J., Ott, P.G., Darcsi, A., Béni, S., Gömöry, Á., Drahos, L., Zsila, F., Móricz, Á.M. *Fitoterapia*, **2019**, 137, article number 104180.

24. Kwon, H.S., Lee, H., Lee, J.S., Lee, K., Choi, J.-H. *Archives of Pharmacal Research*, **2018**, 41(5), 513-518.
25. Li, S., Zhang, Y., Deng, G., Wang, Y., Qi, S., Cheng, X., Ma, Y., Xie, Y., Wang, C. *Frontiers in Pharmacology*, **2017**, 8(AUG), article number 541.
26. 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., Cheng, X.-M., Wang, C.-H. *Frontiers in Pharmacology*, **2018**, 9(APR), article number 346.
27. Liu, F., Wu, J., Gong, Y., Wang, P., Zhu, L., Tong, L., Chen, X., Ling, Y., Huang, C. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **2017**, 79, 258-267.
28. Liu, Y.-P., Guo, J.-M., Wang, X.-P., Liu, Y.-Y., Zhang, W., Wang, T., Qiang, L., Fu, Y.-H. *Bioorganic Chemistry*, **2019**, 92, article number 103278.
29. Long, S., Resende, D.I.S.P., Kijjoa, A., Silva, A.M.S., Fernandes, R., Xavier, C.P.R., Vasconcelos, M.H., Sousa, E., Pinto, M.M.M. *Molecules*, **2019**, 24(3), <https://www.mdpi.com/1420-3049/24/3/534>, accessed 21 December 2019.
30. Lou, L.-L., Liu, S., Yan, Z.-Y., Lin, B., Wang, X.-B., Huang, X.-X., Song, S.-J. *Phytochemistry Letters*, **2017**, 22, 107-112.
31. Moore, A., Beidler, J., Hong, M.Y. *Molecules*, **2018**, 23(9), article number 2197.
32. Nasehi, M., Shahini, F., Ebrahimi-Ghiri, M., Azarbayjani, M., Zarrindast, M.-R. *Physiology and Behavior*, **2018**, 194, 239-245.
33. Nurmaganbetov, Zh.S., Arystan, L.I., Muldaeva, G.M., Haydargalieva, L.S., Adekenov, S.M. *Pharmacological Reports*, **2019**, 71(6), 1050-1058.
34. Razueva, Ya.G., Kukharensko, N.S., Ivanova, Yu.L., Nikolaev, S.M., Verlan, N.V., Ubeeva, I.P. *Medical Journal*, **2014**, 6, 125-127.
35. Réus, G.Z., Stringari, R.B., de Souza, B., Petronilho, F., Dal-Pizzol, F., Hallak, J.E., Zuardi, A.W., Crippa, J.A., Quevedo, J. *Oxidative Medicine and Cellular Longevity*, **2010**, 3(5), 325-331.
36. Réus, G.Z., Stringari, R.B., Gonçalves, C.L., Scaini, G., Carvalho-Silva, M., Jeremias, G.C., Jeremias, I.C., Ferreira, G.K., Streck, E.L., Hallak, J.E., Zuardi, A.W., Crippa, J.A., Quevedo, J. *Depression Research and Treatment*, **2012**, 2012, article number 987397.
37. Song, Y., Kesuma, D., Wang, J., Deng, Y., Duan, J., Wang, J.H., Qi, R.Z. *Biochemical and Biophysical Research Communications*, **2004**, 317(1), 128-132.
38. Sun, Q., Liu, F., Sang, J., Lin, M., Ma, J., Xiao, X., Yan, S., Benjamin Naman, C., Wang, N., He, S., Yan, X., Cui, W., Liang, H. *Marine Drugs*, **2019**, 17(2), article number 121.
39. Taborskaya, K.I., Belinskaya, D.A., Avdonin, P.V., Goncharov, N.V. *Journal of Evolutionary Biochemistry and Physiology*, **2017**, 53(5), 384-393.
40. Turmukhambetov, A.Zh. *Alkaloids of plants of Kazakhstan. Isolation, chemical modification and biological activity*. Karaganda: Glasir, **2009**.
41. Turmukhambetov, A.Zh., Agedilova, M.T., Nurmaganbetov, J.S. *Chemistry of Natural Compounds*, **2009**, 4, 504-507.
42. Ueda, S., Ikeda, H., Namba, T., Ikejiri, Y., Nishimoto, Y., Arai, M., Nihira, T., Kitani, S. *Journal of Industrial Microbiology and Biotechnology*, **2019**, 46(5), 739-750.
43. Wang, Z.-X., Xiang, J.-C., Cheng, Y., Ma, J.-T., Wu, Y.-D., Wu, A.-X. *Journal of Organic Chemistry*, **2018**, 83(19), 12247-12254.
44. Xi, J., Zhang, Z., Zhu, Q., Zhong, G. *International Journal of Molecular Sciences*, **2018**, 19(12), article number 4044.
45. Xiong, H., Li, R.-R., Liu, S.-Y., Wu, F.-X., Yang, W.-C., Yang, G.-F. *ACS Applied Bio Materials*, **2018**, 1(2), 310-317.
46. Ye, Y., Zhang, B., Mao, R., Zhang, C., Wang, Y., Xing, J., Liu, Y.-C., Luo, X., Ding, H., Yang, Y., Zhou, B., Jiang, H., Chen, K., Luo, C., Zheng, M. *Organic and Biomolecular Chemistry*, **2017**, 15(17), 3648-3661.
47. Yonezawa, T., Hasegawa, S., Asai, M., Ninomiya, T., Sasaki, T., Cha, B.Y., Teruya, T., Ozawa, H., Yagasaki, K., Nagai, K., Woo, J.T. *European Journal of Pharmacology*, **2011**, 650(2-3), 511-518.
48. Zhanaidarova, G.U., Yessimova, R.Zh., Nurseitova, K.T., Seidakhmetova, R.B., Arystan, L.I., Adekenov, S.M., Nauryzov, N.N., Berikbaeva, B.Kh. *Bangladesh Journal of Medical Science*, **2019**, 18, 598-606.
49. Zhang, J., Wang, C.-X., Song, X.-J., Li, S., Fan, C.-L., Chen, G.-D., Hu, D., Yao, X.-S.,

50. Zhao, W.-Y., Chen, J.-J., Zou, C.-X., Zhou, W.-Y., Yao, G.-D., Wang, X.-B., Lin, B.,

Figure 1. Interaction between 9-methoxy-2-phenyl-11H-indolizino[8,7-β]indole (Gar-13) and DRD2 receptor; BE = -11.6 kcal/mol¹

Figure 2. Interaction between 2-(3,4-dichlorophenyl)-9-methoxy-11H-indolizino[8,7-β]indole (Gar-17) and DRD2 receptor; BE = -10.7 kcal/mol¹

Figure 3. Interaction between 2-F-chalcone derivative of harmine (Gar-116) and DRD2 receptor; BE = -10.5 kcal/mol¹

Table 1. The results of the interaction between the molecules of alkaloid compounds and DRD2 receptor

Position	Name	Code	Chemical formula	Binding Energy – kcal/mol ⁻¹
1	9-methoxy-2-phenyl-11H-indolisino[8,7-β]indole C ₂₁ H ₁₆ N ₂ O	Gar-13		-11.6
2	2-(3,4-dichlorophenyl)-9-methoxy-11H-indolisino[8,7-β]indole C ₂₁ H ₁₄ Cl ₂ N ₂ O	Gar-17		-10.7
3	2-F-chalcone derivative of harmine C ₂₂ H ₁₇ FN ₂ O ₂	Gar-116		-10.5
4	9-methoxy-2-(4-methoxyphenyl)-11H-indolisino[8,7-β]indole C ₂₂ H ₁₈ N ₂ O ₂	Gar-15		-10.4
5	Chalcone derivative of harmine C ₂₂ H ₁₈ N ₂ O ₂	Gar-105		-10.3
6	4-methoxychalcone derivative of harmine C ₂₃ H ₂₀ N ₂ O ₃	Gar-107		-10.3
7	2-F-pyrazoline derivative of harmine C ₂₄ H ₂₁ FN ₄ O ₂	Gar-117		-10.3
8	3-acetyl-9-methoxy-2-phenyl-11H-indolisino[8,7-β]indole C ₂₃ H ₁₈ N ₂ O ₂	Gar-24		-10.2
9	4-methoxy-pyrazoline derivative of harmine C ₂₅ H ₂₄ N ₄ O ₃	Gar-108		-10.2
10	2,4-dimethoxy-chalcone derivative of harmine C ₂₄ H ₂₂ N ₂ O ₄	Gar-113		-10.2

11	Pyrazoline derivative of harmine $C_{24}H_{22}N_4O_2$	Gar-106		-9.9
12	2,4-dimethoxy-pyrazoline derivative of harmine $C_{26}H_{26}N_4O_4$	Gar-115		-9.6
13	2,3,4-trimethoxy-chalcone derivative of harmine $C_{25}H_{24}N_2O_5$	Gar-110		-9.4
14	2,3,4-trimethoxy- pyrazoline derivative of harmine $C_{27}H_{28}N_4O_5$	Gar-111		-8.6
15	2-(4-methoxy-phenyl)- 3,10-bis-formyl-11H- indolisino[8,7-β]indole $C_{24}H_{18}N_2O_4$	Gar-23		-8.5
16	Harmine N-oxide $C_{13}H_{12}N_2O_2$	Gar-N-O		-8.1
17	8-Formylharmine	8-FGar		-7.5
18	8-Acetylharmine $C_{15}H_{14}N_2O_2$	8-AcGar		-7.4
19	6,8-Dichloroharmine $C_{13}H_{10}Cl_2N_2O$	Gar-6,8Cl		-7.4
20	6,8-Dibromoharmine $C_{13}H_{10}Br_2N_2O$	Gar-6,8Br		-7.3

21	6-Iodoharmine $C_{13}H_{11}IN_2O$	Gar-6I		-7.2
22	8-Bromoharmine $C_{13}H_{11}BrN_2O$	Gar-8Br		-7.2
23	6-Bromoharmine $C_{13}H_{11}BrN_2O$	Gar-6Br		-7.1

Table 2. Weight gain in rats

Group	Weight, g	
	Before	After
Intact rats, n=6	296.3 ± 20.3*	297.0 ± 20.8
Control (no treatment) n=6	367.8 ± 8.5	373.3 ± 10.2
Reference group (Piracetam) n=6	328.0 ± 12.0	324.5 ± 22.7
Harmine (Gar), n=6	303.3 ± 53.0*	307.3 ± 49.6*
8-Acetylharminen=6	287.5 ± 18.6	291.3 ± 24.3
9-Methoxy-2-phenyl-11H-indolisino[8,7-β]indole	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-onn=6	287.5 ± 18.6	258.0 ± 32.3
Delcosinen=6	295.3 ± 45.5	298.0 ± 47.6
Lappaconitinen=6	298.0 ± 6.5	301.0 ± 7.7
Cytisinen=6	245.0 ± 8.4*	243.3 ± 6.7*
Echinopsinen=6	264.3 ± 26.2	262.3 ± 27.9

Note: * – p < 0.05 compared to the control group, n – number of animals in the group.

Table 3. Effects of the studied compounds on behavior of the rats in the "Elevated Plus Maze" test

Group	Time spent in the closed arms, (sec.)	Time spent in the open arms, (sec.)	Number of entries into the closed arms, (n)	Number of entries into the open arms, (n)	Number of peeps, (n)
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 (no treatment) n=6	161.0 ± 15.6	8.0 ± 1.2	1.5 ± 0.6	2.0 ± 1.4	2.0 ± 2.3
Reference 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), n=6	167.0 ± 8.7*	13.0 ± 8.7	1.5 ± 0.6	1.5 ± 0.6	0.3 ± 0.5
8-Acetylharminen=6	141.3 ± 40.1	33.5 ± 15.4	1.0 ± 0.8	1.3 ± 0.5	3.0 ± 3.2
9-Methoxy-2-phenyl-11H-indolisino[8,7-β]indole	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-on n=6	167.5 ± 5.6*	9.5 ± 3.9	1.0 ± 0.0	1.3 ± 0.5	0.8 ± 1.0
Delcosinen=6	164.5 ± 11.5	9.8 ± 4.2	1.3 ± 0.5	1.3 ± 1.0	1.8 ± 2.4
Lappaconitinen=6	125.5 ± 80.4	35.4 ± 10.8	1.3 ± 0.5	1.5 ± 1.0	2.5 ± 1.3
Cytisinen=6	152.0 ± 23.6*	22.3 ± 6.3	1.3 ± 0.5	2.0 ± 0.8	1.3 ± 0.5

Echinopsinen=6	167.3±12.2*	12.0±2.0	0.8±0.5	1.3±0.5	0.5±0.6
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Note: * – p <0.05 compared to the animals in the control group, n – number of animals in the group.

Table 4. Effects of the studied compounds on behavior of the rats in the "Elevated Plus Maze" test

Group	Number of leaning over, (n)	Number of stands, (n)	Time spent on the central site, (sec.)	Number of defecations	Number of urinations
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 (no treatment) n=6	2.5±2.1	0	11.5±8.3	3.3±1.2	0.3±0.6
Reference group (Piracetam) n=6	2.5±1.0	0.3±0.5	6.3±2.3	0	0.3±0.5
Harmine (Gar), n=6	1.8±1.7	8.0±3.2	0.5±1.0	0.3±0.5	0.3±0.5
8-Acetylharmin n=6	4.3±1.5	0	3.5±1.9	0	0.3±0.5
9-Methoxy-2-phenyl-11H-indolizino[8,7-β]indole	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-on n=6	0.8±0.5	0	3.0±1.6	0	0
Delcosinen=6	3.0±2.2	0	5.3±2.2	0.8±0.5	0.5±0.6
Lappaconitinen=6	2.8±1.5	0	18.5±9.7	0.3±0.5	0.3±0.5
Cytisinen=6	2.5±1.7	0	1.3±0.10	0.3±0.5	0.3±0.5
Echinopsinen=6	3.3±1.8	0	0.8±0.10	0	0.3±0.5

Note: * – p <0.05 compared to the animals of the control group, n – number of animals in the group.