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Screening Study of the Anxiolytic Activity of New Triazole Compounds

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Resume. The article presents data on the study of the anxiolytic activity of compounds representing new triazole derivatives – combinations of two privileged structures. At the "Raised Cruciform labyrinth" installation, such indicators of the studied compounds, the time of exit into the open sleeve, the number of exits and the total time spent in it were studied that the D-389 compounds are not inferior to the comparison drug, which indicates the presence of high anxiolytic activity.

Key words: triazole compounds, seduxene, anxiolytic, raised cruciform labyrinth.

Introduction. Pharmacological correction of anxiety-depressive disorders is of indisputable importance for modern medicine [1], which has a large number of various drugs for the prevention and treatment of neuropsychiatric diseases. In clinical practice, benzodiazepine derivatives (diazepam, phenazepam, lorazepam, medazepam, nitrazepam, etc.) are most often used [3], but most of these drugs have adverse side effects consisting in central nervous system depression: daytime drowsiness, lethargy, muscle weakness, dulling of emotions, headache, dizziness, ataxia, etc. it may be a violation of cognitive functions, and with prolonged use – addiction and drug dependence [2]. Currently, the search for new drugs with anxiolytic and

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anticonvulsant activity and a low risk of side effects among triazole, pyrimidine, and pyrazole derivatives is actively underway [4, 6, 7].

Experimental studies conducted earlier on the basis of the ICPS of the Academy of Sciences of the Republic of Uzbekistan revealed various types of activities in triazole and oxadiazole derivatives: psychoactivating [8] antiepileptic, as well as anxiolytic, along with a low risk of undesirable effects. In this regard, it is promising to study new compounds synthesized on the basis of new triazole compounds as part of the search and development of potential anxiolytics.

Objective. Screening study of the anxiolytic activity of new derivatives of triazole 2-(6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-3 yl) benzenamine (D-389).

Research methodology. The experiments were carried out on mature male mice weighing 18-23 g. The animals were kept in a vivarium with a natural light regime on a standard diet of laboratory animals, without restricting access to food and water in compliance with International Recommendations for the Protection of Vertebrates used in experimental studies (1997). The animals were divided into groups of 10 animals each. The studied substances were orally administered 60 minutes before the start of the test, control groups of mice were injected with isotonic sodium chloride solution. The method of studying anxiolytic activity in the "Raised Cruciform Labyrinth" (RCL) test was based on the natural preference of rodents for dark burrows, as well as on the fear of being in open areas and falling from a height [2]. The animals were placed in an elevated cruciform labyrinth and the following indicators of anxiolytic activity were recorded for 2 minutes: the latent time of exit into the open sleeve (c), the number of exits into the open sleeve and the total time spent in the open sleeves of the labyrinth (c) [2, 5]. An additional study of anxiolytic activity was carried out in the "Dark Light Chamber" installation [9], within 2 minutes, the following indicators were recorded: the time spent in the dark compartment, and the time spent in the light compartment and the number of transitions between compartments. And also the action in the "open field" test was studied [10]. Statistical processing of the results was carried out by the tabular method proposed by R.B. Strelkov.

Results. As a result of the study, it was revealed that the animals injected with the D-389 compound retained a sense of fear of open space, therefore, the latent time of the animals entering the open sleeve of the RCL does not differ from the values of the control group. In the experimental groups that were injected with D-389 compounds, the indicator of the latent exit time into the light sleeve decreased by 2 times relative to the control group and was not inferior to the indicator in the control group, which indicates the suppression of anxiety in animals. D-389 compounds after administration to animals led to a significant decrease in the latent time of entry into the light sleeve by 5 times relative to the control, surpassing the control group. The total number of animal exits into the light sleeve of the PCL was also studied (see Tab-1).

Table - 1
The effect of compounds under the code D-389 on the behavior of mice in the " Raised Cruciform Labyrinth" test

№	Groups and doses in mg/kg	Time spent in the light compartment (in seconds)	Time spent in the dark sleeve (in seconds)	Number of transitions	K= S(light)/ T(dark)
1	Control	32±1,44	88±1,93	2,2±0,24	0,36
2	D-389 10 mg/kg	57±1,93*	63±2,4*	4,5±0,96*	0,9*
3	D-389 30 mg/kg	64,4±1,69*	55,6±2,2*	5,2±0,24*	1,16*
4	D-389 60 mg/kg	44±1,2*	76±1,44*	2,8±0,24*	0,58*

Note.*P≤0.05 comparison with the control group.

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As indicated, when mice are placed in a 5-chamber maze, mice prefer to be in dark chambers and, to a lesser extent, in light ones. With an increased sense of anxiety, mice prefer dark cells even more and move from one chamber to another less often.

One of the most significant evaluation criteria in the study of anxiolytic activity in the "Dark Light Chamber" installation is the time spent by animals in the light compartment, which indicates the presence or absence of natural phobias of open and illuminated spaces in laboratory animals. In the experiment, D-389 administered in doses of 10, 30 and 60 mg/kg were used. The results obtained are presented in Table. 2, it is said that all doses of D-389 increase the K index from 3 to 9 times, but the most active dose was 30 mg / kg, and doses of 10 and 60 mg/kg according to the results respectively 4 and 3 times increase the K index compared with the control group.

Table -2

The influence of D-389 on the feeling of anxiety by "Dark light camera"

№	Groups and doses in mg/kg	Time spent in the light compartment (in seconds)	Time spent in the dark sleeve (in seconds)	Number of transitions	K= S(light)/ T(dark)
1	Control	38±1,44	82±1,93	4,2±1,24	0,46
2	D-389 10 mg/kg	79±7,96*	41±4,8*	7,6±2,48*	1,92*
3	D-389 30 mg/kg	95,8±8,4*	24,2±5,89*	9,8±3,24*	3,96*
4	D-389 60 mg/kg	69±4,69*	51±4,93*	6,1±1,8*	1,35*
5	Seduxen 0,1 мг/кг	83,2±6,8*	36,8±6,8*	25,2±10,75*	2,3*

Note.*P≤0.05 comparison with the control group.

Thus, when D-389 compounds were administered to animals, the indicator of the time spent in the light compartment significantly differed from the indicators of control animals (Table 2). When D-389 was administered, the manifestation of anxiety in animals decreased. Thus, the time spent in the light compartment significantly increased by 9 times relative to the control group, not inferior to the indicators of the comparison drug group – seduxen at a dose of 0.1 mg/kg [11].

The influence of D-389 on motor and research activity in the ”open field" test. With a single injection, D-389 was tested at doses of 10, 30 and 60 mg/ kg. YES was estimated by the number of intersections of square lines, and research activity – by the number of peeks into the gaps of minks. As shown in tab. 3. D-389 increased DA from 1.5 to 3 times in all doses used, and the dose of 30 mg/kg was the most active and did not affect research activity.

Table - 3

The effect of D-389 on the motor and research activity of white mice with a single injection

№	Groups and doses in mg/kg	Motor activity	Effects in %	Research activity	Effects in %
1	Control	7,2±0,24		9,2±0,72	
2	D-389 10 mg/kg	9,6±0,24*	+33,3	7,0±0,96*	-24
3	D-389 30 mg/kg	13,0±0,48*	+81	8,8±0,96*	-8,3
4	D-389 60 mg/kg	9,6±0,96*	+33,3	7,0±0,48*	-24

Note.*P≤0.05 comparison with the control group.

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Conclusion. Thus, the new derivatives of triazole 2-(6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine-3-yl)benzylamino (D-389) exhibit anxiolytic properties. Different levels of antiphobic action were revealed for the studied compounds. The most active doses are 30 mg/ kg, which are not inferior to the seduxen effect.

References

1. Гурович И. Я., Шмуклер А. Б. // Социальная и клиническая психиатрия. – 2011. – Т. 21, № 4. – С. 51–57.
2. Воронина Т. А. // Руководство по проведению доклинических исследований лекарственных средств: под ред. А. Н. Миронова. – 2012. – Ч. 1. – С. 264–275.
3. Морковник А. С., Спасов А. А., Кузьменко Т. А., с соавт. // Известия Академии наук. Серия химическая. – 2015. – № 11. – С. 2622.
4. Чепляева Н. И., Кузнецова В. А., Спасов А. А., с соавт. // Волгоградский научно-медицинский журнал. – 2014. – № 3 (43). – С. 21–24.
5. Хабриев Р.У. // Руководство по экспериментальному изучению новых фармакологических веществ. – 2005. – С. 78-80.
6. X.Q. Deng, L.N. Quan, M.X. Song, C.X. Wei, Z.S. Quan, Zhe-Shan Quan, Synthesis and anticonvulsant activity of 7-phenyl-6,7-dihydro-[1,2,4] triazolo [1,5-*a*] pyrimidin-5(4*H*)-ones and their derivatives, Eur. J. Med. Chem. 46 (2011) 2955-2963.
7. M. Faizi, S. Dabirian, H. Tajali, F. Ahmadi, E.R. Zavareh, S. Shahhosseini, S.A. Tabatabai, Novel agonists of benzodiazepine receptors: design, synthesis, binding assay and pharmacological evaluation of 1,2,4-triazolo[1,5-*a*]pyrimidinone and 3-amino-1,2,4-triazole derivatives, Bioorg. Med. Chem. 23 (2015) 480-487.
8. Rashidov S.Z., Rakhimboev S.D., Sanoev Z.I., Abdinazarov I.T., Khamroev T.T., Ismailova D.S., & Elmuradov B.J. (2022). Study of psychoactive activity potassium salt 5-(o-aminophenyl)-1,3,4- oxadiazole-2-thion (D-361). International Journal of Medical Sciences And Clinical Research, 2(09), 1–5. https://doi.org/10.37547/ijmscr/Volume02Issue09-01
9. Sanoev Z.I., Mirzaev Yu.R. Pharmacological Activity Of The Possessing New Atypical Neuroleptics 1-Phenyltetrahydroisoquinoline Structure. The American Journal of Medical Sciences and Pharmaceutical Research Published: 2020|Pages:18-26 https://doi.org/10.37547/TAJMSPR/Volume02Issue08-03
10. Sanoev, Z.I., Mirzaev, Y.R. Research of a new atypical neuroleptic 1-(3,4,-methylenedioxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline on the central nervous system. Annals of the Romanian Society for Cell Biology, 2021,25(2), 2363–2369
11. 11. Саноев З.И., Мирзаев Ю.Р., Якубова Л.К. Сравнительного фармакологического свойства производного тетрагидроизохинолина и седуксена. Новый день в медицине. Научно – реферативный, духовно-просветительский журнал. 2 (30/2) 2020, с. 365-368