Research Results in Pharmacology

Research Results in Pharmacology 11(4): 56–65
UDC 615.214.22:547.8
DOI 10.18413/rrpharmacology.11.808

Anti-anxiety properties of new 5H-2,3-benzodiazepine and 5H-[1,2,5]triazepine derivatives

Maria O. Maltseva[1], Dmitriy V. Maltsev[1], Mikhail V. Miroshnikov[2], Luidmila N. Divaeva[3], Anton O. Kharaneko[3], Oleg I. Kharaneko[4], Anatolii S. Morkovnik[3], Alexander A. Spasov[1]

1 Volgograd State Medical University; 1 Pavshikh Bortsov Sq., Volgograd 400137 Russia,
2 St. Petersburg Institute of Pharmacy; 3-245 Zavodskaya St., urban settlement Kuzmolovsky, Leningrad region 188663 Russia,
3 Research Institute of Physical and Organic Chemistry, Southern Federal University; 194/2 Stachki Ave. Rostov-on-Don 344090 Russia,
4 L.M. Litvinenko Institute of Physical Organic and Coal Chemistry; 70 R. Luxemburg St., Donetsk 83114 Russia.

Corresponding author: Maria O. Maltseva (maria.maltseva.volsmu@mail.ru)

Academic editor: Mikhail Korokin ♦ **Received** 21 July 2025 ♦ **Accepted** 11 November 2025 ♦ **Published** 10 December 2025

Citation: Maltseva MO, Maltsev DV, Miroshnikov MV, Divaeva LN, Kharaneko AO, Kharaneko OI, Morkovnik AS, Spasov AA (2025) Anti-anxiety properties of new 5H-2,3-benzodiazepine and 5H-[1,2,5]triazepine derivatives. Research Results in Pharmacology 11(4): 56–65. https://doi.org/10.18413/rrpharmacology.11.808

Abstract

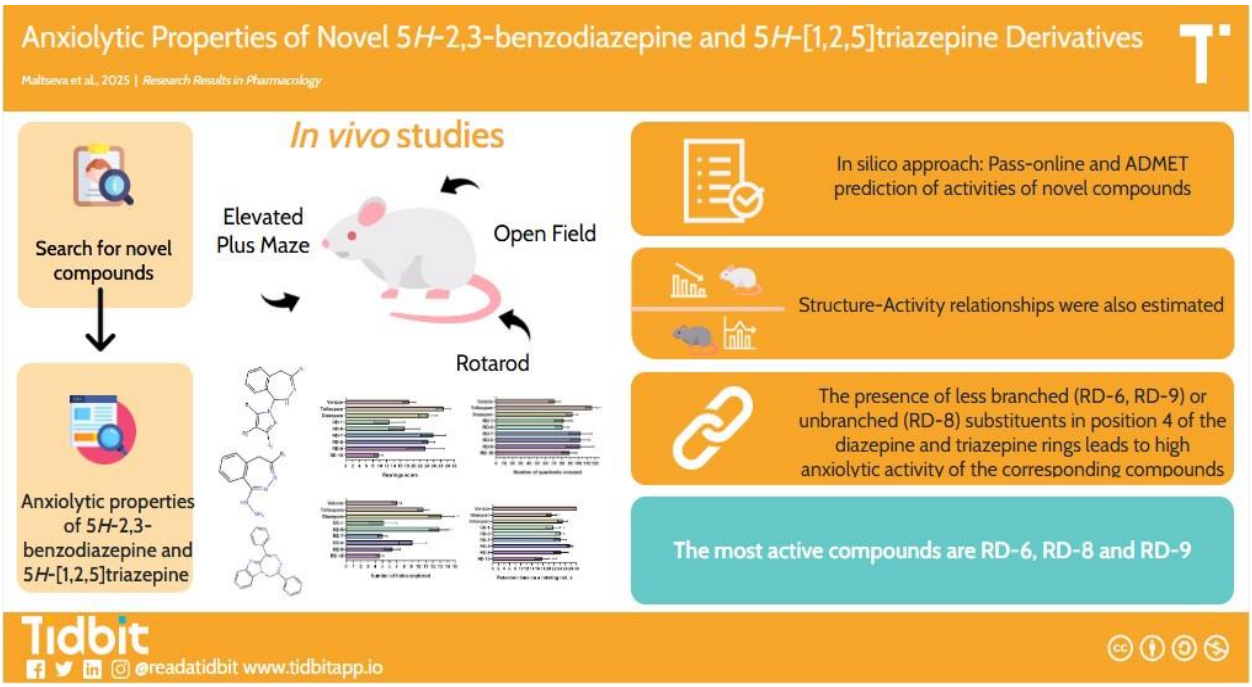
Introduction: Previous studies have examined the anxiolytic properties of compounds containing mutually annulated systems of 5*H*-2,3-benzodiazepine and [1,2,4]triazole, namely 7*H*-[1,2,4]triazolo[3,4-*a*][2,3]benzodiazepine derivatives. In the present work, another group of 5*H*-2,3-benzodiazepine and 5*H*-[1,2,5]triazepine derivatives was examined for psychotropic activity.

Materials and Methods: For *in silico* assay the PASS online test system and ADMET analysis were used. Compounds under study were also tested *in vivo* in Elevated Plus Maze, Open Field and Rotarod tests.

Results and Discussion: Of note is that the presence of a 3,4-dimethoxyphenyl substituent at position 4 of the diazepine ring (RD-1, RD-7) leads to a decrease in anxiolytic activity compared to 4-methoxyphenyl derivatives (RD-6, RD-9). Among the derivatives of condensed 5*H*-[1,2,5]triazepines, a more pronounced anti-anxiety effect was exerted by compound RD-8 with an annelated benzimidazole bicycle compared to its analog RD-15 with a pyrrole cycle. The high anxiolytic activity of the compounds is facilitated by the presence of slightly branched (RD-6, RD-9) or unbranched (RD-8) substituents in position 4 of the diazepine or triazepine cycle. In the Rotarod test, it was noted that 4-(3,4-dimethoxyphenyl)-1-hydrazino-5*H*-2,3-benzodiazepine (RD-1) and 4-hydrazino-7,8,9-trimethyl-1-phenyl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine (RD-15) have a negative effect on muscle tone in mice due to the presence of a hydrazino group in their composition. According to ADMET analysis, compounds RD-6, RD-8 and RD-9 are low toxic; however, a specific toxicity study among these derivatives is recommended.

Conclusion: The most active and safe compound for further studies among the studied derivatives with a single administration is 1,4-diphenyl-5*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole (RD-8) at a dose of 1.3 mg/kg.

Graphical Abstract



Keywords

5*H*-2,3-benzodiazepine, 5*H*-[1,2,5]triazepine, ADMET, PASS online, SAR, anxiolytic, open field

Introduction

Polycyclic derivatives of diazepine and triazepine have been of interest for their psychotropic properties for many decades (Stefancich et al. 1991). The well-known 2,3-benzodiazepine derivative tofisopam has the prominent anxiolytic effect without classic benzodiazepine side effects such as movement impairment, cognitive deficit, and addiction (Üçel et al. 2020). According to the literature, hydrogenated derivatives of 2,3-benzodiazepine, such as 4-(4-methoxyphenyl)-2,3,4,5-tetrahydro-2,3-benzodiazepin-1-one (compound VBZ102), exert anxiolytic effects at various doses (Amaghnouje et al. 2021). In the pharmacological screening, 2-thioxo-1*H*-2,3,4,5-tetrahydropyrido[2,3-*e*]-1,3,4-triazepin-5-ones and 2-thioxo-1*H*-2,3,4,-5-tetrahydro-1,3,4-benzotriazepin-5-ones showed an antianxiety activity in the four plate test. The replacement of the benzene ring by the pyridine one in triazepines is accompanied by the enhancement of anxiolytic activity as well as toxicity (Nawrocka et al. 1994). Among the central effects, the triazepine ring in the form of pyridazino[1,2-*a*]1,2,5-triazepine has been studied for sedative properties (Groszkowski et al. 1978), and in the form of benzo[*f*][1,3,5]triazepine the structure is characterized by antipsychotic properties (Abu-Hashem et al. 2024).

We have previously published a study on the anxiolytic properties of new compounds with a similar structure, based on mutually annulated systems of 5*H*-2,3-benzodiazepine and [1,2,4]triazole, 7*H*-[1,2,4]triazolo[3,4-*a*][2,3]benzodiazepines (Skripka et al. 2021).

The aim of this study was to investigate another group of new derivatives of condensed systems based on 5*H*-2,3-benzodiazepine and 5*H*-[1,2,5]triazepine for the presence of psychotropic activity.

Materials and Methods

Experimental animals

The experiments were conducted on 54 white outbred male mice m=20±2 g (n=6). The animals were kept in the vivarium of the Department of Pharmacology and Bioinformatics of the Scientific Center of Drug Research of Volgograd State Medical University, Russia, with a

natural light regimen at a relative air humidity of 40-50% and a temperature of 22-24°C on a standard complete diet for laboratory animals (GOST R 50258-92). All studies were approved for implementation by the Biomedical Ethics Committee of Volgograd State Medical University IRB 00005839 IORG 0004900 (OHRP) No. 2023/191 dated June 2, 2023.

Drugs and treatment

Synthesis of 5*H*-2,3-benzodiazepine derivatives RD-6 (1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(4-methoxyphenyl)-5*H*-2,3-benzodiazepine), RD-7 (1-[4-(3,4-dimethoxyphenyl)-5*H*-2,3-benzodiazepin-1-yl]-3-ethyl-4-methyl-1*H*-pyrazol-5-amine) and RD-9 (1-hydrazino-4-(4-methoxyphenyl)-5*H*-2,3-benzodiazepine) was described by Khabarov et al. (2009). Synthesis of 5*H*-[1,2,5]triazepine derivatives RD-8 (1,4-diphenyl-5*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole) and RD-15 (4-hydrazino-7,8,9-trimethyl-1-phenyl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine) was also described previously (Kharaneko 2017; Kharaneko 2019). Diazepam (Relanium™, Polfa, Poland, 1 mg/kg) and tofisopam (Grandaxin™, EGIS ZAO Pharmaceutical Factory, Russia, 2 mg/kg) were selected as comparison drugs based on their structural and qualitative characteristics. The compounds were tested at a dose equimolar to diazepam (1 mg/kg). All substances were administered to animals *per os* using an atraumatic probe 30 minutes before testing. The control group was administered an equivalent volume of solvent (distilled water).

Experimental design

The present study is aimed at the investigation of 5*H*-2,3-benzodiazepine derivatives RD-6, RD-7, RD-9 and 5*H*-[1,2,5]triazepine derivatives RD-8 and RD-15. At the first stage of the study, possible types of psychotropic activity and mechanisms of its implementation among these derivatives were assessed *in silico,* using the PASS online test system (Rudik et al. 2019). Since, according to the prediction, the compounds are characterized by anxiolytic activity, at the second stage, the specified compounds were screened *in vivo* under the conditions of the Elevated Plus Maze test. At the third stage, the effect of substances on the behavior of rodents in the Open Field test was observed, and the muscle relaxant potential characteristic of diazepine derivatives was assessed in the Rotarod test. At the fourth stage, the structural-functional relationships among the studied substances were analyzed. At the last stage, the toxicological properties of the most active substances were assessed using ADMET analysis. As a result of the study, compounds with anxiolytic action were identified, pharmacophores responsible for the manifestation of the effect were isolated, and their safety for further studies was preliminarily assessed.

Elevated plus maze

The EPM technique is based on the natural preference of rodents for dark burrows, as well as their fear of being in open areas and falling from a height (Kraeuter et al. 2019). Animals were placed in the center of the setup, and the time the mice spent in the open arm (s) and the number of exits into the open arm were recorded for 5 min.

Open field

The Open Field setup was a circular arena with a radius of 40 cm and sides of 30 cm. The central area of the arena was illuminated with white fluorescent light, the floor was divided into squares, at the junctions of which there were holes for counting acts of search activity (da Silva et al. 2018). The mouse was placed on the central area, and for 5 minutes of observation, the main parameters, such as number of quadrants crossed and rearings score, as well as search activity, were counted.

Rotarod

The Rotarod is a 2.5 cm diameter rod rotating at a constant speed of 10 rpm (Lubrich et al. 2022). The animal was placed on the rod, after which the time spent on it was recorded for 30 s. Each animal was given no more than three attempts to complete the test, with the best result recorded.

Assessment of the prospects for studying 5H-2,3-benzodiazepine and 5H-[1,2,5]triazepine derivatives in the ADMET prediction system

For the most active derivatives of 5*H*-2,3-benzodiazepine and 5*H*-[1,2,5]triazepine, *in silico* prediction of their general toxicological, pharmacokinetic, and metabolic properties was performed using ADMET analysis using the ProTox-III (Alwaili et al. 2024), SwissADME (Daina et al. 2017), pkCSM (Pires et al. 2015), admetSAR (Yang et al. 2019), and ADMETlab (Dong et al. 2017) Internet services.

Statistical analysis

Statistical processing of the obtained results was performed in the GraphPad Prism 8.0 program using the Kolmogorov-Smirnov test to assess the normality of data distribution, as well as using one-way ANOVA and post-processing with Dunnett's test for parametric distribution in multiple comparisons. The data are presented in the mean ± standard error of the mean (M±SEM) format. Values of $p<0.05$ were considered statistically significant.

Results and Discussion

Predictive assessment of compound activity in the PASS online program

At the first stage of the study, possible types of pharmacological activity and mechanisms of its implementation among the specified derivatives were assessed *in silico* using the PASS online test system. Indicators with Pa of at least 0.3 for at least one compound were selected as the threshold activity. Among the psychotropic types of activity, anxiolytic and antineurodegenerative properties are most characteristic of the compounds. Since the presence of anxiolytic properties had a stronger correlation with the chemical structure, it was decided to evaluate the compounds for this type of activity *in vivo*. According to the forecast, the most probable mechanisms of action for the specified groups of compounds are inhibition of MAO_A and MAP_3K_5, agonistic interaction with the $GABA_A$ receptor, and activation of calcium channels (Table 1). However, the most likely mechanism of action for the 5*H*-2,3-benzodiazepines remains GABAergic due to their diazepine structure. More targeted studies are needed to clarify this.

Table 1. Results of the predictive assessment of psychotropic activity and mechanisms of action of the studied derivatives of 5*H*-2,3-benzodiazepine and 5*H*-[1,2,5]triazepine

Type of activity/mechanism of action	Code of compound					
	RD-1	RD-6	RD-7	RD-8	RD-9	RD-15
	Pa/Pi	Pa/Pi	Pa/Pi	Pa/Pi	Pa/Pi	Pa/Pi
Anxiolytic activity	0.344/0.205	-	-	0.652/0.011	0.362/0.190	0.664/0.010
Treatment of neurodegenerative diseases	0.266/0.194	0.316/0.123	-	0.623/0.014	0.304/0.137	-
Inhibitor MAO_A	0.291/0.004	-	-	-	0.326/0.004	0.137/0.012
Inhibitor MAP_3K_5	-	0.461/0.010	0.335/0.067	0.287/0.117	-	0.248/0.175
Agonist $GABA_A$	-	-	-	0.427/0.005	-	0.128/0.097
Calcium channel activator	0.235/0.097	0.300/0.043	0.255/0.075	0.243/0.089	0.227/0.107	0.322/0.273

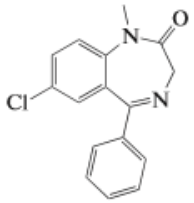
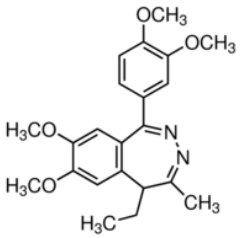
Results of testing substances in the Elevated Plus Maze, Open Field, and Rotarod devices

At the second stage, the anti-anxiety properties of the compounds were studied in the Elevated Plus Maze test. The most active in absolute values was compound 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(4-methoxyphenyl)-5*H*-2,3-benzodiazepine (RD-6), high anxiolytic activity was also observed under the influence of 1,4-diphenyl-5*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole (RD-8) and 1-hydrazino-4-(4-methoxyphenyl)-5*H*-2,3-benzodiazepine (RD-9). It can be noted that the indicated substances belong to different chemical groups: 1-hydrazino-5*H*-2,3-benzodiazepines, 1-(1*H*-pyrazol-1-yl)-5*H*-2,3-benzodiazepines, and 5*H*-[1,2,5]triazepines (Table 2).

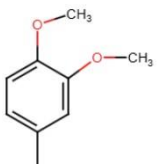
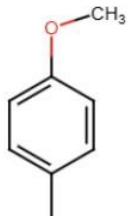
At the third stage, the effect of the studied compounds on the behavior of mice in the Open Field test was studied. It was noted that the compounds did not change the profile of spontaneous motor activity of mice, reflecting a combination of the number of quadrants crossed and rearings score, compared to the control group. Under the influence of 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(4-methoxyphenyl)-5*H*-2,3-benzodiazepine (RD-6), a statistically significant ($p<0.05$) increase in the search activity of rodents was recorded compared to the control (Fig. 1).

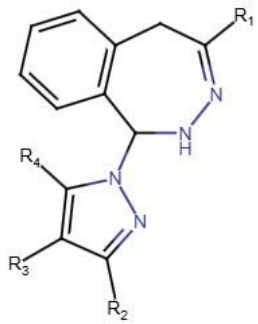
When studying the muscle relaxant potential of 5*H*-2,3-benzodiazepine and 5*H*-[1,2,5]triazepine derivatives in the Rotarod test, it was noted that 4-(3,4-dimethoxyphenyl)-1-hydrazino-5*H*-2,3-benzodiazepine (RD-1, $p<0.05$) and 4-hydrazino-7,8,9-trimethyl-1-phenyl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine (RD-15, $p<0.001$) had a negative effect on the muscle tone of mice. The test results are presented in Figure 2.

Table 2. Anxiolytic effect of 5*H*-2,3-benzodiazepine and 5*H*-[1,2,5]triazepine derivatives in the Elevated Plus Maze test compared with diazepam (1 mg/kg) and tofisopam (2 mg/kg), mice, *per os*, M±SEM

Compound	Structure	Time spent in open arms of EPM (s)	Number of entries to open arms
Vehicle	-	12.3±3.24	1.8±0.47
Diazepam		94.8±15.24*	4.8±0.60*
Tofisopam		102.2±3.62****	5.3±0.49*

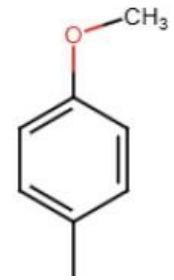
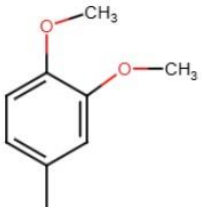
1-hydrazino-5*H*-2,3-benzodiazepine derivatives

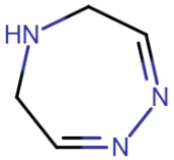
Compound	R_1	HX	Time spent in open arms of EPM (s)	Number of entries to open arms
RD-1 (1.21 mg/kg) 4-(3,4-dimethoxyphenyl)-1-hydrazino-5*H*-2,3-benzodiazepine	 3,4- dimethoxyphenyl	HCl	36.2±2.94	3.5±0.88
RD-9 (1.1 mg/kg) 1-hydrazino-4-(4-methoxyphenyl)-5*H*-2,3-benzodiazepine	 4-methoxyphenyl	HCl	75.2±14.96**	2.3±0.95



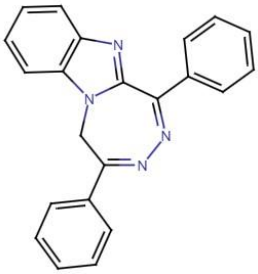
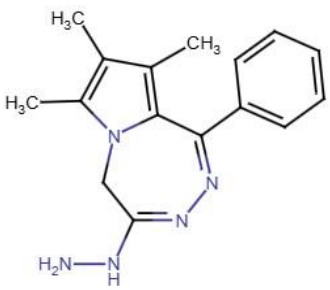
1-(1*H*-pyrazol-1-yl)-5*H*-2,3-benzodiazepine derivatives

end of the table 2

Compound	R_1	R_2	R_3	R_4	HX	Time spent in open arms of EPM (s)	Number of entries to open arms
RD-6 (1.34 mg/kg) 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(4-methoxyphenyl)-5*H*-2,3-benzodiazepine	 4- methoxyphenyl	CH_3 methyl	H	CH_3 methyl	HCl	116.8±13.83 ****	4.3±1.02
RD-7 (1.55 mg/kg) 1-[4-(3,4-dimethoxyphenyl)-5*H*-2,3-benzodiazepin-1-yl]-3-ethyl-4-methyl-1*H*-pyrazol-5-amine	 3,4- dimethoxyphenyl	CH_3-CH_2- ethyl	CH_3 methyl	NH_2 amine	HCl	49.5± 14.43	3.8±0.90



5*H*-[1,2,5]triazepine derivatives

Compound	Structure	HX	Time spent in open arms of EPM (s)	Number of entries to open arms
RD-8 (1.3 mg/kg) 1,4-diphenyl-5*H*-[1,2,5]triazepino[5,4-a]benzimidazole		HCl	99.5±19.90****	3.3±0.76
RD-15 (1.11 mg/kg) 4-hydrazino-7,8,9-trimethyl-1-phenyl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine		HCl	31.7±7.34	1.0±0.44

Note: data are significant in relation to the control group, one-way ANOVA with Dunnett's posttest, * – $p<0.05$, ** – $p<0.01$, **** – $p<0.0001$.

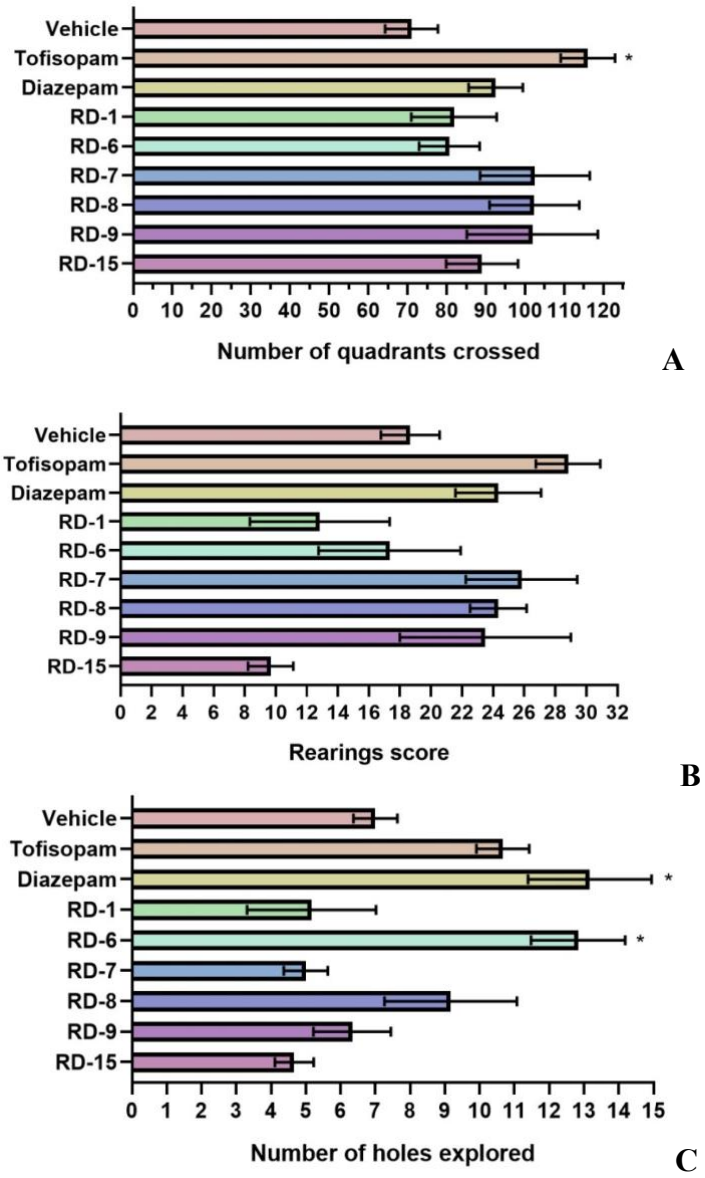


Figure 1. Study of the effect of 5*H*-2,3-benzodiazepine and 5*H*-[1,2,5]triazepine derivatives on the behavior of mice in the Open Field test in comparison with diazepam (1 mg/kg) and tofisopam (2 mg/kg), *per os*, M±SEM. **A** – number of quadrants crossed, **B** – rearings score, **C** – exploratory (search) activity. ***Note:*** data are reliable in relation to the control group, one-way ANOVA with Dunnett's posttest, * – $p<0.05$.

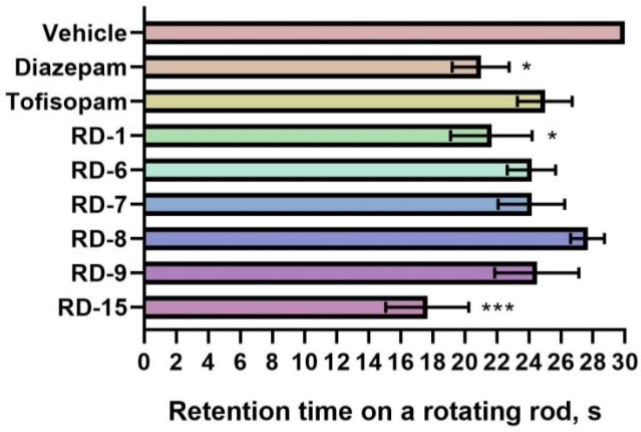


Figure 2. Retention time of mice treated with 5*H*-2,3-benzodiazepine and 5*H*-[1,2,5]triazepine derivatives in the Rotarod test compared to diazepam (1 mg/kg) and tofisopam (2 mg/kg), *per os*, M±SEM. ***Note:*** data are significant relative to the control group, one-way ANOVA with Dunnett's posttest, * – $p<0.05$, *** – $p<0.001$.

Structure-activity relationship analysis among the studied compounds

The presented compounds can be divided into several groups by chemical structure (Table 2), including derivatives of 1-hydrazino-5*H*-2,3-benzodiazepine (RD-1, RD-9), 1-(1*H*-pyrazol-1-yl)-5*H*-2,3-benzodiazepine (RD-6, RD-7), and some derivatives of 5*H*-[1,2,5]triazepine (RD-8, RD-15). In the first group of substances, anxiolytic action equal to that of the reference drugs diazepam and tofisopam was noted under the influence of substance RD-9, which contains a 4-methoxyphenyl substituent at position 4 of the benzodiazepine system. When switching to its 3,4-dimethoxyphenyl analogue (compound RD-1), the anxiolytic activity was significantly reduced, almost to the level of control values. A similar pattern was noted in the structural analysis of the number of 1-(1*H*-pyrazol-1-yl)-5*H*-2,3-benzodiazepine derivatives, among which the RD-6 compound, also containing a 4-methoxyphenyl group in position 4 of the benzodiazepine scaffold, was more active than the RD-7 compound with a 3,4-dimethoxyphenyl radical. When examining the bicyclic 5*H*-[1,2,5]triazepine derivatives RD-8 and RD-15, it can be noted that the condensed triazepinobenzimidazole derivative (RD-8), according to the tests, has a significantly higher anxiolytic activity compared to that of the pyrrolodiazepine compound (RD-15).

Thus, the results of the study of new derivatives of condensed systems based on 5*H*-2,3-benzodiazepine and 5*H*-[1,2,5]triazepine indicate a pronounced difference in the effect on the anxiolytic activity of two structurally related substituents, 4-methoxyphenyl and 3,4-dimethoxyphenyl, in position 4 of the diazepine ring: positive – for the first of them (RD-6, RD-9) and negative – for the second (RD-1, RD-7). Among the derivatives of 5*H*-[1,2,5]triazepine, its condensed derivative with benzimidazole (RD-8) had a more pronounced anti-anxiety effect compared to that of pyrrole (RD-15). The low degree of branching of the substituents in position 4 of the diazepine and triazepine cycles (RD-6, RD-9) or the absence thereof (RD-8) contributes to the high anxiolytic activity of the corresponding compounds.

Assessment of general toxicological properties of compounds with high anxiolytic potential using ADMET analysis

Based on the results of the predictive assessment of compounds with high anxiolytic activity, it was noted that all three compounds are characterized by a high degree of permeability through the blood-brain barrier (BBB), good absorption in the gastrointestinal tract, slow clearance, and do not have cardiotoxicity.

The compound 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(4-methoxyphenyl)-5*H*-2,3-benzodiazepine (RD-6) is characterized by an LD_{50} value of 2000-2500 mg/kg, which allows classifying the substance as toxicity class 5. The compound does not have nephro-, immunotoxicity, or AMES mutagenicity. According to the forecast, the substance may be characterized by hepatotoxicity and respiratory toxicity, which requires additional studies of specific toxicity. Metabolic pathways of RD-6 may involve cytochromes CYP1A2, CYP2C19, and CYP3A4.

The substance 1,4-diphenyl-5*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole (RD-8) can be classified as toxicity class 4 with an LD_{50} value of 880-1000 mg/kg. According to the data obtained, the compound is not characterized by organotoxicity. During metabolism, the substance inhibits cytochromes CYP1A2, CYP2C19, CYP2C9 and is a substrate for CYP3A4.

1-Hydrazino-4-(4-methoxyphenyl)-5*H*-2,3-benzodiazepine (RD-9) is low toxic, despite the presence of a hydrazino group in the molecule, and the calculated LD_{50} value is 725-825 mg/kg. The substance is not characterized by hepato-, nephro-, immuno- and respiratory toxicity. At the same time, AMES mutagenicity has been demonstrated for the substance, which must be confirmed by experimental specific toxicity data. The compound must have the properties of a CYP1A2 and CYP2D6 inhibitor, and a CYP2D6 substrate.

Conclusion

Six compounds, derivatives of 5*H*-2,3-benzodiazepine and 5*H*-[1,2,5]triazepine, were studied with a single administration. Among the derivatives, 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-(4-methoxyphenyl)-5*H*-2,3-benzodiazepine (RD-6, 1.34 mg/kg), 1,4-diphenyl-5*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole (RD-8, 1.3 mg/kg), and 1-hydrazino-4-(4-methoxyphenyl)-5*H*-2,3-benzodiazepine (RD-9, 1.1 mg/kg), belonging to different chemical classes, exerted high anxiolytic activity. It is noted that the presence of a 3,4-dimethoxyphenyl substituent at position 4 of the diazepine ring (RD-1, RD-7) leads to reduced anxiolytic activity compared to 4-methoxyphenyl derivatives (RD-6, RD-9). The presence of less branched (RD-6, RD-9) or unbranched (RD-8) substituents at position 4 of the diazepine and triazepine rings leads to high anxiolytic activity of the corresponding compounds. It is noted that the compounds do

not change the profile of spontaneous motor activity of mice compared to that of the control group in the Open Field. When studying the muscle relaxant potential of compounds in the Rotarod test, it was noted that 4-(3,4-dimethoxyphenyl)-1-hydrazino-5*H*-2,3-benzodiazepine (RD-1) and 4-hydrazino-7,8,9-trimethyl-1-phenyl-5*H*-pyrrolo[2,1-*d*][1,2,5]triazepine (RD-15) had a negative effect on the muscle tone of mice. According to ADMET analysis, compounds RD-6, RD-8 and RD-9 are low-toxic, but a further study of specific toxicity among these derivatives is recommended to confirm or exclude data on mutagenicity and hepatotoxicity. Based on the totality of the obtained results, the most active and safe compound for further research among the studied derivatives is 1,4-diphenyl-5*H*-[1,2,5]triazepino[5,4-*a*]benzimidazole (RD-8).

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

Funding

The study was carried out within the framework of a state assignment, registration number 1024022800309-1-3.5.2;3.1.5;3.1.6.

Ethics statement

All studies were approved for implementation by the Biomedical Ethics Committee of Volgograd State Medical University IRB 00005839 IORG 0004900 (OHRP) No. 2023/191 dated June 2, 2023.

Data availability

Data corroborating the results of this study may be acquired by the corresponding author upon reasonable request.

References

- Abu-Hashem AA, Hakami O, Amri N, Mukhrish YE, Abdelgawad AAM (2024) Synthesis of 1,3,5-triazepines and benzo[f][1,3,5]triazepines and their biological activity: recent advances and new approaches. Molecules 29(3): 632. https://doi.org/10.3390/molecules29030632 [PubMed] [PMC]
- Alwaili MA, Abu-Almakarem AS, Aljohani S, Alkhodair SA, Al-Bazi MM, Eid TM, Alamri J, Mobasher MA, Algarzae NK, A Khayyat AI, Alshaygy LS, El-Said KS (2024) Avenanthramide-C ameliorate doxorubicin-induced hepatotoxicity via modulating Akt/GSK-3β and Wnt-4/β-Catenin pathways in male rats. Frontiers in Molecular Biosciences 11: 1507786. https://doi.org/10.3389/fmolb.2024.1507786 [PubMed] [PMC]
- Amaghnouje A, Bohza S, Bohdan N, Es-Safi I, Kyrylchuk A, Achour S, El Fatemi H, Bousta D, Grafov A (2021) New 2,3-benzodiazepine derivative: synthesis, activity on central nervous system, and toxicity study in mice. Pharmaceuticals 14(8): 814. https://doi.org/10.3390/ph14080814 [PubMed] [PMC]
- da Silva DM, Sanz G, Vaz BG, de Carvalho FS, Lião LM, de Oliveira DR, da Silva Moreira LK, Cardoso CS, de Brito AF, da Silva DPB, da Rocha FF, Santana IGC, Galdino PM, Costa EA, Menegatti R (2018) Tert-butyl 4-((1-phenyl-1H-pyrazol-4-yl) methyl) piperazine-1-carboxylate (LQFM104) – New piperazine derivative with antianxiety and antidepressant-like effects: Putative role of serotonergic system. Biomedicine & Pharmacotherapy 103: 546–552. https://doi.org/10.1016/j.biopha.2018.04.077 [PubMed]
- Daina A, Michielin O, Zoete V (2017) SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports 7(1): 1–13. https://doi.org/10.1038/srep42717 [PubMed] [PMC]
- Dong J (2018) ADMETlab: a platform for systematic ADMET evaluation based on a comprehensively collected ADMET database. Journal of Cheminformatics 10(1): 1–11. [PubMed] [PMC]
- Groszkowski S, Wrona J (1978) Pyridazino[1,2-a]1,2,5-triazepines. Polish Journal of Pharmacology and Pharmacy 30(5): 713–715. [PubMed]
- Khabarov KM, Kharaneko OI, Bogza SL (2009) 2,3-Benzodiazepine-1-thione in the synthesis of substituted and hetero-annelated 2,3-benzodiazepines. Chemistry of Heterocyclic Compounds 45: 468–474.
- Kharaneko AO (2017) 7,8,9-trimethyl-1-phenyl-3H-pyrrolo[2,1-d][1,2,5]triazepin-4(5H)-one. Synthesis and reactions. Russian Journal of Organic Chemistry 53(5): 738–745. https://doi.org/10.1134/S1070428017050153
- Kharaneko AO (2019) 1,4-Diphenyl-5H-[1,2,5]triazepino[5,4-a]benzimidazole – a new heterocyclic system. Synthesis and Properties. Russian Journal of Organic Chemistry 55(1): 115–117. https://doi.org/0.1134/S1070428019010147
- Kraeuter AK, Guest PC, Sarnyai Z (2019) The elevated plus maze test for measuring anxiety-like behavior in rodents. Methods in Molecular Biology 1916: 69–74. https://doi.org/10.1007/978-1-4939-8994-2_4 [PubMed]
- Lubrich C, Giesler P, Kipp M (2022) Motor behavioral deficits in the cuprizone model: validity of the rotarod test paradigm. International Journal of Molecular Sciences 23(19): 11342. [PubMed] [PMC]
- Nawrocka W, Liszkiewicz H, Wilimowski M, Rutkowska M, Barczyńska J, Kedzierska-Goździk L, Wojewódzki W, Szelag A (1994) Carboxylic esters derivatives of 2-thioxo-1H-2,3,4,5-tetrahydropyrido-[2,3-e]-1,3,4-triazepin-5-ones and 2-thioxo-1H-2,3,4,5-tetrahydro-1,3,4-benzotriazepin-5-ones. Acta Poloniae Pharmaceutica 51(3): 243–248. [PubMed]

- Pires DEV, Blundell TL, Ascher DB (2015) pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. Journal of Medicinal Chemistry 58(9): 4066–4072. [PubMed] [PMC]
- Rudik AV, Dmitriev AV, Lagunin AA, Filimonov DA, Poroikov VV (2019) PASS-based prediction of metabolites detection in biological systems. SAR and QSAR in Environmental Research 30(10): 751–758. https://doi.org/10.1080/1062936X.2019.1665099 [PubMed]
- Skripka MO, Spasov AA, Maltsev DV (2021) Screening of anxiolytic properties and analysis of structure-activity relationship of new derivatives of 6-(4-methoxy)-7H-[1,2,4]triazolo[3,4-a][2,3]benzodiazepine under the code RD. Research Results in Pharmacology 7(2): 31–37. https://doi.org/10.3897/rrpharmacology.7.67499
- Stefancich G, Massa S, Artico M (1991) Polycyclic diazepine and triazepine derivatives of pharmacological interest. Farmaco 46(1 Suppl): 297–306. [PubMed]
- Üçel Uİ, Can ÖD, Demir Özkay Ü, Ulupinar E (2020) Antiamnesic effects of tofisopam against scopolamine-induced cognitive impairments in rats. Pharmacology, Biochemistry, and Behavior 190: 172858. https://doi.org/10.1016/j.pbb.2020.172858 [PubMed]
- Yang H, Lou C, Sun L, Li J, Cai Y, Wang Z, Li W, Liu G, Tang Y (2019) AdmetSAR 2.0: web-service for prediction and optimization of chemical ADMET properties. Bioinformatics (Oxford, England) 35(6): 1067–1069. https://doi.org/10.1093/bioinformatics/bty707 [PubMed]

Author Contribution

- **Maria O. Maltseva**, PhD in Medicine, Assistant Professor of the Department of Surgical Dentistry and Maxillofacial Surgery, Volgograd State Medical University, Volgograd, Russia; email: maria.maltseva.volsmu@mail.ru; **ORCID ID:** https://orcid.org/0000-0002-4173-7143. The author carried out the experimental part and participated in writing the manuscript.
- **Dmitry V. Maltsev**, Doctor Habil. of Biological Sciences, Professor of the Department of Pharmacology and Bioinformatics, Volgograd State Medical University, Volgograd, Russia; email: maltsevdmitriy@rambler.ru; **ORCID ID:** https://orcid.org/0000-0002-2005-6621. The author carried out the experimental part and participated in writing the manuscript.
- **Mikhail V. Miroshnikov**, PhD in Medicine, Head of the Laboratory Diagnostics Department, St. Petersburg Institute of Pharmacy, St. Petersburg, Russia; email: miroshnikov.mv@doclinika.ru; **ORCID ID:** https://orcid.org/0000-0002-9828-3242. The author carried out the experimental part.
- **Lyudmila N. Divaeva**, PhD in Chemistry, Leading researcher, Laboratory of Organic Synthesis of the Research Institute of the Southern Federal University, Rostov-on-Don, Russia; email: divaevaln@mail.ru; **ORCID ID:** https://orcid.org/0000-0002-7275-0797. The author carried out statistical processing of the data.
- **Anton O. Kharaneko**, PhD in Chemistry, Research fellow, Department of Chemistry of Heterocyclic Compounds of the Research Institute, Southern Federal University, Rostov-on-Don, Russia; email: antonhar08@rambler.ru; **ORCID ID:** https://orcid.org/0000-0002-8677-2647. The author took part in the synthesis of substances.
- **Oleg I. Kharaneko**, PhD in Chemistry, Researcher of the Department of Radical Reactions Research, L.M. Litvinenko Institute of Physical Organic and Coal Chemistry, Donetsk, Russia; email: o_kharaneko@mail.ru; **ORCID ID:** https://orcid.org/0000-0003-1105-8227. The author took part in the synthesis of substances.
- **Anatolii S. Morkovnik**, Doctor Habil. of Chemical Sciences, Chief Researcher, Head of the Department of Heterocyclic Compounds Chemistry of the Research Institute, Southern Federal University, Rostov-on-Don, Russia; email: asmorkovnik@sfedu.ru; **ORCID ID:** https://orcid.org/0000-0002-7275-0797. The author took part in the synthesis of substances.
- **Alexander A. Spasov**, Honored Researcher, Member of the Russian Academy of Sciences, Doctor Habil. of Medical Sciences, Professor, Head of the Department of Pharmacology and Bioinformatics of Volgograd State Medical University, Volgograd, Russia; email: aspasov@mail.ru; **ORCID ID:** https://orcid.org/0000-0002-7185-4826. The author developed the study design.