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Research Article

Anxiolytic, antidepressant and analgesic activities of novel derivatives of 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2H-benzimidazol-2-one

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Abstract

Introduction: Benzimidazole (1,3-benzodiazole) derivatives hold an important place in the field of medicinal chemistry, since they have a wide spectrum of pharmacological activity, as well as high variability of the mechanisms of action: GABA-, serotonin-, dopamine-, adrenaline-, angiotensin-, adenosine-, and glutamatergic. In view of the diversity of the ways of influence of benzimidazole derivatives on neurotransmitter systems, as well as the pharmacological effects of these compounds, the synthesis of highly effective neurotropic drugs with an improved safety profile on their basis is of interest for study. **The aim of this study** was to investigate the neuropsychotropic potential of new derivatives of 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2H-benzimidazole-2-one *in vivo*.

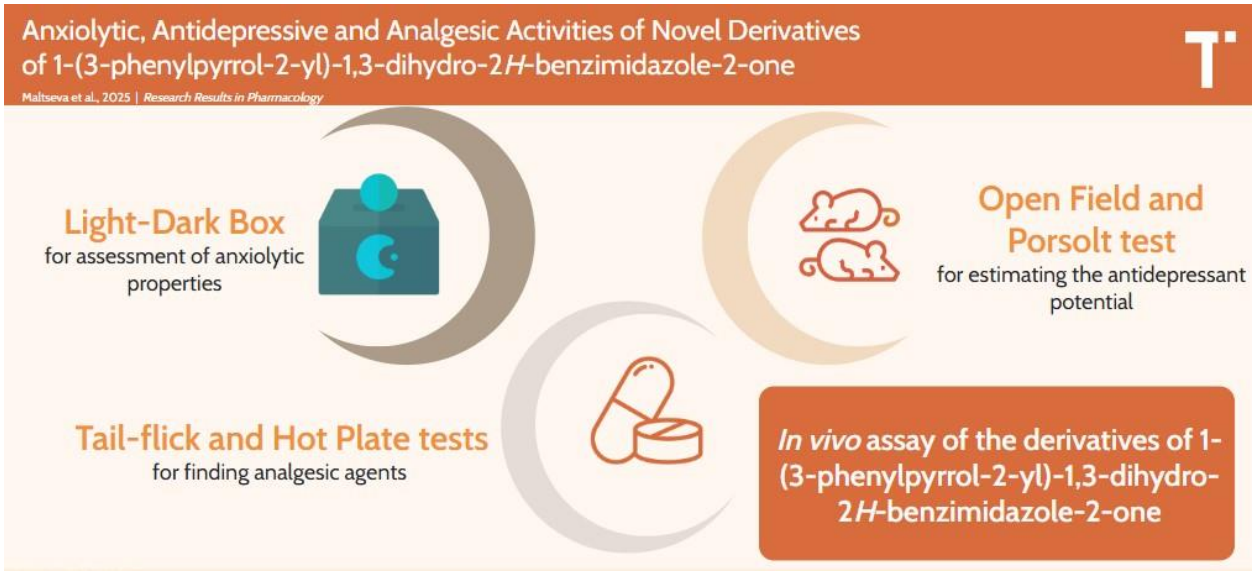
Materials and Methods: The study was conducted on 258 white outbred male mice weighing 25-30 g. The work was carried out in several stages. At the first stage, the safety of the compounds was studied by *in silico* methods using the PASS-online program with a preliminary calculation of LD_{50}. At the second stage, animals were tested under the influence of the compounds in the Open Field and Light-Dark Box tests. Etifoxine (50 mg/kg) and phenazepam (0.1 mg/kg) were chosen as comparison drugs. At the third stage, the behavior of rodents was studied in Porsolt test, with amitriptyline (10 mg/kg) and fluoxetine (10 mg/kg) used as reference drugs. At the fourth stage, the analgesic properties of the compounds were assessed in the Tail-flick and Hot Plate tests in comparison with morphine (5 mg/kg).

Results and Discussion: Based on the obtained results, it can be noted that the phenyl-containing compound CHS-Bi-46 has anxiolytic activity with an antidepressant component. Compounds containing pyridin-3-yl (CHS-Bi-48) and 2-bromophenyl (CHS-Bi-52) are characterized by antidepressant properties, and CHS-Bi-52 also showed a weak analgesic effect in the Hot plate test. For the substance with a pyridin-4-yl fragment CHS-Bi-47, no significant effects were registered according to the results of the tests, but this substance may have other pharmacological activities.

4-Chlorophenyl substance coded CHS-Bi-50 exhibits antinociceptive activity at the spinal level, which is equal to the reference drug morphine at a dose of 5 mg/kg. The 4-bromophenyl-containing compound CHS-Bi-51 is characterized by a moderate combined spinal and supraspinal analgesic property. It can be noted that the most suitable structure for the manifestation of anxiolytic and antidepressant properties of compounds is the presence of a phenyl substituent in the 5 position of the pyrrole ring, and the severity of the analgesic effects of substances is affected by the presence of Cl atoms in the phenyl radical in position 4 for spinal effects and Br – in positions 2 and 4 for supraspinal effects.

Conclusion: The obtained data indicate the prospects of further study of 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one derivatives in order to search for substances with neuropsychotropic activity.

Graphical abstract



Keywords

amitriptyline; analgesic; anxiolytic; antidepressant; benzimidazoles; phenazepam; fluoxetine; CHS; etifoxine; Porsolt

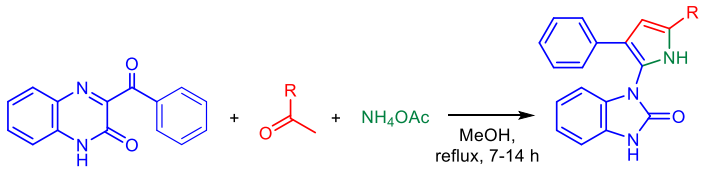
Introduction

Benzimidazole, also known as 1,3-benzodiazole, is a bicyclic heterocyclic aromatic system in which the benzene ring is fused to the 4- and 5-positions of the imidazole ring and the nitrogen atoms are at the 1- and 3-positions (Chung et al. 2023). Benzimidazole derivatives hold an important place in the field of medicinal chemistry, as they have a wide range of pharmacological activities: anthelmintic (albendazole, cyclobendazole, thiabendazole), antitumor (bendamustine, galeterone, pracinostat), antifungal (fuberidazole, carbendazim), antiviral (enviradine, maribavir), antihypertensive (candesartan, mifebradil), antihistamine (mizolastine, astemizole, emedastine), anxiolytic (fabomotizole), and many others (Hernández-López et al. 2022). The mechanism of action of the derivatives of this scaffold is also highly variable: GABA, serotonin, dopamine, adrenaline, angiotensin, adenosine, glutamatergic, etc. (Guo et al. 2021). The initial interest in the neuropsychotropic activity of benzimidazoles was stimulated by the development of the first antipsychotics, such as droperidol (Khokhar and Rathbone 2016). However, the identification of significant side effects associated with its use, in particular extrapyramidal disorders (Siegel et al. 2023), prompted the search for safer compounds. In this regard, optimization of the benzimidazole structure, characterized by pleiotropism of pharmacological action and a variety of neurochemical pathways for implementing the effect, is of considerable interest for the creation of more advanced drugs with neurotropic activity (Maltsev et al. 2020). In this regard, **the aim of the present study** was to investigate the neuropsychotropic potential of new derivatives of 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2H-benzimidazol-2-one *in vivo*.

Materials and Methods

Drugs and treatment

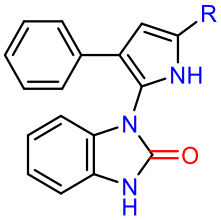
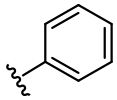
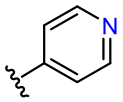
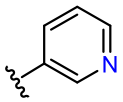
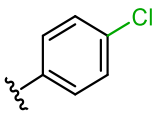
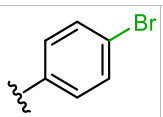
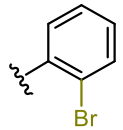
Six compounds were studied under the laboratory codes CHS-Bi-46, CHS-Bi-47, CHS-Bi-48, CHS-Bi-50, CHS-Bi-51, and CHS-Bi-52, which are 5-substituted derivatives of 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2H-benzimidazol-2-one, which were synthesized by the Mamedov rearrangement (Hassner and Namboothiri 2012) using a previously described method developed by the authors (Scheme 1) (Mamedov et al. 2015; Mamedov and Zhukova 2021).



Scheme 1. Synthesis of 1-(pyrrol-2-yl)benzimidazol-2-ones.

The structures of the compounds are presented in Table 1. The doses for the study of benzimidazole derivatives were 1/100 of the pre-calculated LD_{50}. All compounds were administered to animals orally with an atraumatic metal probe at a rate of 0.1 mL of solution per 10 g of body weight. Etifoxine at a dose of 50 mg/kg (Owen et al. 2022) and phenazepam at a dose of 0.01 mg/kg (Voronina et al. 2003) were chosen as reference drugs for the Open Field and Light-Dark Box tests; the compounds were administered 30 minutes before the start of the experiment. In the behavioral despair test according to the Porsolt method, the studied compounds were administered three times 24, 6, and 1 hour before the experiment.

Table 1. Chemical structure of the studied compounds

Basic structure **1-(5-(R)-3-phenylpyrrol-2-yl)-1,3-dihydro-2H-benzimidazol-2-one**			
			
Code of substance	**Chemical name**	**Radical**	**Name of radical**
CHS-Bi-46	1-(3,5-diphenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one		phenyl
CHS-Bi-47	1-(3-phenyl-5-(pyridin-4-yl)pyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one		pyridin-4-yl
CHS-Bi-48	1-(3-phenyl-5-(pyridin-3-yl)pyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one		pyridin-3-yl
CHS-Bi-50	1-(5-(4-chlorophenyl)-3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one		4-chlorophenyl
			End of the table 1
CHS-Bi-51	1-(5-(4-bromophenyl)-3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one		4-bromophenyl
CHS-Bi-52	1-(5-(2-bromophenyl)-3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one		2- bromophenyl

The comparison groups received amitriptyline at a dose of 10 mg/kg and fluoxetine at a dose of 10 mg/kg. For the Tail-flick and Hot plate experiments, the substances were administered 40 min before the experiment, and the reference drug morphine was administered at a dose of 5 mg/kg. Control animals were administered purified water in an equivalent volume.

Experimental animals

The study was conducted on 258 white outbred male mice weighing 25-30 g (n=6). The animals were kept in the vivarium of the Department of Pharmacology and Bioinformatics in Scientific Center for Innovative Medicines of Volgograd State Medical University, 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 02.06.2023.

Experimental procedure

Initially, a virtual prediction of the preliminary toxicity of compounds and their LD_{50} values was carried out using the *in silico* method based on the PASS online software (Rudik et al. 2019). The pharmacological activity of experimental compounds was searched for using the Open Field, Light-Dark Box, Tail-flick, and Hot Plate methods, as well as the Porsolt test. A video camera and the RealTimer program in video recording mode were used to record the indicators.

To determine the effect of a number of 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one derivatives on the behavior of animals, the Open Field method was used (da Silva et al. 2018). The setup was a circular area with fences along the perimeter of the arena, divided into segments and a circular center. Blind holes were located at the intersection of the segments. During 5 minutes of observation, the number of quadrants crossed, rearings score, the latent period of leaving the center of OF (s), the number of long self-grooming acts, the number of holes examined and the number of exits to the center of the arena were recorded.

The anxiolytic activity of the compounds was studied in the Light-Dark Box test, a classic method for assessing emotional reactivity and stress levels in laboratory mice (Campos-Cardoso et al. 2023). The experiment was conducted in a special setup consisting of two compartments, dark and lighted, separated by a partition with a door. Each animal was placed in the dark compartment to freely explore the space, after which the door was opened and the time (s) spent by the animal in the light compartment during 5 minutes of observation was recorded.

To study the antidepressant activity, the Porsolt test (Porsolt 1979) was used, based on the animals' search for a way out of an aversive situation when they fall into water. After active escape attempts, the animals entered an immobilization stage, accompanied by minor movements necessary to keep their heads above the surface of the water. The cylinder diameter was 12 cm; the water temperature was maintained at 20ºC. The total test time, taking into account the adaptation period, was 360 s. The duration of immobility of the animals during 240 s of observation was an indicator of the severity of the depressive-like state.

In the study of analgesic activity, methods for assessing thermal somatic pain were used involving the Tail-flick and Hot plate devices (Ugo Basile, Italy). The Tail Flick test is based on the spinal flexor reflex that occurs when infrared radiation (55°C) is applied to the skin surface of the distal third of the animal's tail. In the Hot Plate test, when the animal was placed on a hot surface (55°C), a nociceptive reaction controlled by supraspinal structures was observed – licking of the paw pads (Mwobobia et al. 2021). The maximum exposure time was considered as 100% analgesia – 15 s for the Tail-flick test and 30 s for the Hot Plate test. The latent period of time for getting rid of the pain stimulus was recorded. The level of analgesic effect was assessed by a reliable increase in the latent period of the reaction against the background of the introduction of substances compared to the control group.

Statistical analysis

The obtained data were processed in the GraphPad Prism 8.0 program using the Kolmogorov-Smirnov test to determine the compliance of the data pool with the Gaussian curve. For the case of parametric distribution, one-way ANOVA with Dunnett's posthoc test was used, for nonparametric ones – the Kruskall-Wallis test and Dunn's posthoc. The value $p<0.05$ was considered the criterion of statistical significance.

Results

According to the calculation of the toxicity of substances by the *in silico* method based on the PASS online software, all compounds belong to toxicity class 4. The predicted LD_{50} value for the studied compounds was 1000 mg/kg; the prediction accuracy was 67.38%. The dose for the

studies was selected by calculating 1/100 of the LD_{50} (Gonzalez et al. 2022), and therefore the compounds in the series of experiments were used at a dose of 10 mg/kg.

While studying the derivatives of 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one in the Open Field test, it was found that compounds neither had any statistically significant effect on the number of quadrants crossed by the animals compared to the control group, nor differed significantly from each other in the parameter of the latent time of exit from the illuminated center of the installation (Figs 1A, 1C). Under the influence of 2-bromophenyl derivative CHS-Bi-52, the reactivity of the animals was significantly reduced ($p<0.05$, Fig. 1C). The number of vertical rearings after the introduction of phenazepam and etifoxine was significantly higher ($p<0.001$) than in the control group. The introduction of etifoxine and phenazepam to the animals stimulated the searching activity of the animals ($p<0.001$, Fig. 1D). The number of animal exits to the center of the installation was significantly higher under the influence of etifoxine ($p<0.001$), phenazepam ($p<0.01$), and the phenyl-containing compound CHS-Bi-46 ($p<0.001$), which is typical for substances with anxiolytic action (Fig. 1E). The number of acts of long self-grooming, as an additional anxiolytic parameter, was higher in phenazepam, etifoxine and CHS-Bi-46 groups, although it did not reach the threshold of statistical difference (Fig. 1F).

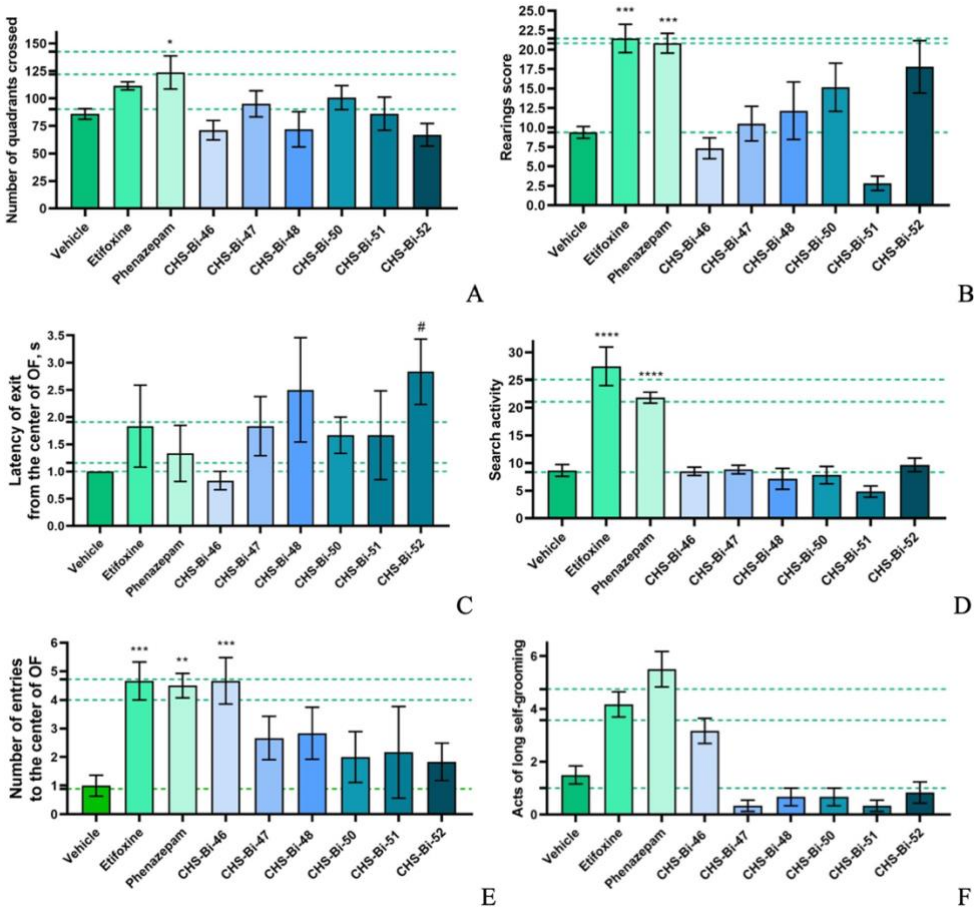


Figure 1. Effect of etifoxine (50 mg/kg), phenazepam (0.01 mg/kg) and 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-one derivatives (1/100 of LD_{50}) on the behavior of male mice in the Open Field test, M±m. ***Note:*** **A** – number of quadrants crossed; **B** – rearings score; **C** – latent period of exiting the center (s); **D** – number of holes examined; **E** – number of exits to the center of the open field; **F** – the number of long self-grooming acts; # – data are significant in comparison with the control group, Kruskall-Wallis test and Dunn's posthoc ($p<0.05$); * – data are reliable in comparison with the control group, one-way ANOVA with Dunnett's posthoc: ** – $p<0.01$, *** – $p<0.001$,**** – $p<0.0001$.

The results of the Light-Dark Box test showed that the mice in the control group spent on average 45.2±5.21 s in the light compartment, in the etifoxine group – 96.8±18.27 s, and in the phenazepam group – 155.0±7.06 s. A difference with the control group was noted for the groups of etifoxine ($p<0.05$) and phenazepam ($p<0.0001$). The phenyl derivative coded CHS-Bi-46 exhibited anxiolytic activity significantly exceeding the control group indicators ($p<0.05$) and corresponding to the etifoxine level, but not reaching the level of phenazepam effect. No significant differences with the control group were shown for the other studied compounds (Fig. 2).

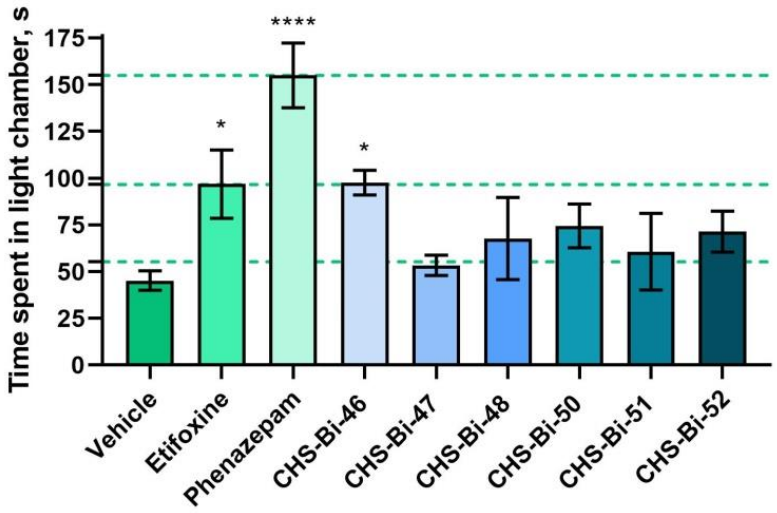


Figure 2. Effect of etifoxine (50 mg/kg), phenazepam (0.01 mg/kg) and 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-one derivatives (1/100 of LD50) on the time (s) spent by male mice in the light compartment of the Light-Dark Box setup, M±m. ***Note:**** – Data are reliable in comparison with the control group, one-way ANOVA with Dunnett's posthoc: * – $p<0.05$, **** – $p<0.0001$.

In a study to identify the antidepressant activity of new derivatives of 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one using the Porsolt method, the freezing time in the control group averaged 201.9±8.49 s, in the amitriptyline group – 81.0±10.38 s, and in the fluoxetine group – 86.0±6.42 s. A significant difference with the control was shown for the amitriptyline ($p<0.0001$) and fluoxetine ($p<0.0001$) groups. Under the influence of the substance CHS-Bi-46, containing a phenyl radical, the freezing time was reduced relative to the control group by 30% ($p<0.001$), the pyridin-3-yl derivative CHS-Bi-48 – by 40% ($p<0.0001$), and the 2-bromophenyl substance CHS-Bi-52 – by 50%, which significantly differs from the control values ($p<0.0001$). For the other studied compounds, no significant differences with the control group were shown (Fig. 3).

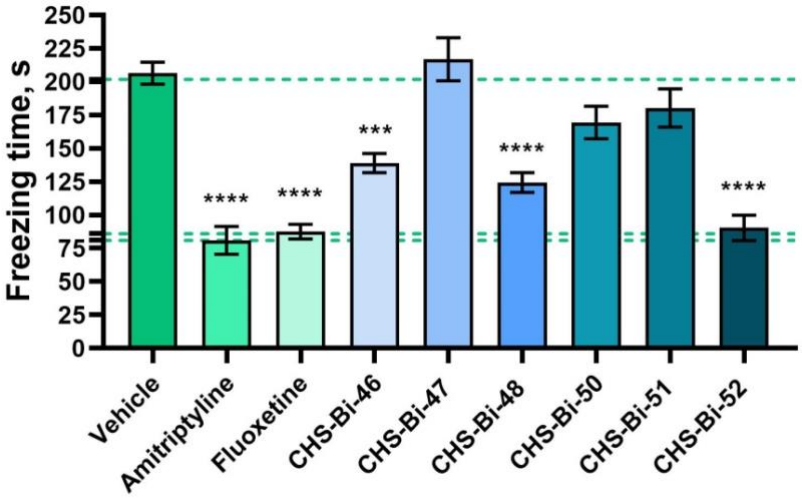


Figure 3. Effect of amitriptyline (10 mg/kg), fluoxetine (10 mg/kg) and 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-one derivatives (1/100 of LD_{50}) on the freezing time of male mice (s) in the Porsolt test, M±m. ***Note:**** – Data are significant in comparison with the control group, one-way ANOVA with Dunnett's posthoc: *** – $p<0.001$, **** – $p<0.0001$.

According to the results of the Tail-flick test, the compounds coded CHS-Bi-50 (4-chlorophenyl) and CHS-Bi-51 (4-bromophenyl) demonstrated activity equal to the reference drug morphine, differing from the control values at the level of $p<0.0001$. In the Hot plate test, the indices of the compounds CHS-Bi-51 (4-bromophenyl) and CHS-Bi-52 (2-bromophenyl) also differed significantly from the control group ($p<0.05$). For the other compounds studied, no significant effects were registered under the conditions of the tests (Fig. 4).

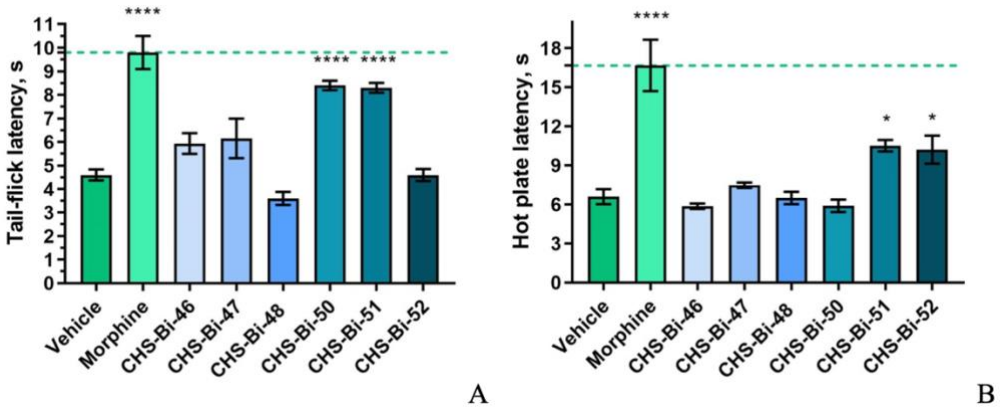


Figure 4. Antinociceptive effects of morphine (5 mg/kg) and 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-one derivatives (1/100 of LD_{50}) in the Tail-flick (**A**) and Hot plate (**B**) tests, M±m. ***Note:*** * – Data are significant in comparison with the control group, one-way ANOVA with Dunnett's posthoc: * – $p<0.05$, **** – $p<0.0001$.

Discussion

In the first stage of the study, the acute toxicity of 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one derivatives was assessed using *in silico* methods to determine the screening dose of the substances under study. Based on the results obtained using the PASS online program, an initial dose of 10 mg/kg was selected, which is 1/100 of the calculated LD_{50}. Next, the behavioral activity of laboratory animals *in vivo* was assessed in the Open Field test, as well as the level of their anxiety behavior in the Light-Dark Box setup. As a rule, mice tend to be in dark and sheltered places and avoid open, lighted spaces. Under the influence of substances with anxiolytic action, the exploratory reflex of rodents begins to prevail over the burrowing reflex, and animals begin to more actively explore illuminated areas (Campos-Cardoso et al. 2023). Therefore, if an animal spends most of its time in a dark chamber, this may indicate a high level of anxiety, which was typical for the control group of animals (da Silva et al. 2018). Under the influence of the phenyl compound coded CHS-Bi-46, the number of exits to the center of the Open Field, as well as the time spent by mice in the light compartment of the Light-Dark Box was statistically significantly higher than in the control group, which may indicate the anxiolytic potential of this compound. Of scientific interest is the presence of antidepressant-like effects in the Porsolt test in the compound with anxiolytic activity CHS-Bi-46, since, according to modern approaches, anxiety-depressive disorders have a common origin, and similar groups of drugs are used to treat them (Choi et al. 2020). The compound CHS-Bi-48, containing pyridin-3-yl fragment, also exhibits antidepressant properties under the conditions of this technique. Considering the absence of stimulation of the motor activity of animals in the Open Field upon the introduction of substances CHS-Bi-46 and CHS-Bi-48 (Figs 1A, 1B), it is possible to exclude the pseudo-antidepressant effect of the studied compounds, which is undoubtedly a positive factor for an in-depth study of these substances.

At the next stage, the antinociceptive activity of 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one derivatives was assessed. In the context of the increasing prevalence of pathologies accompanied by pain syndrome and the insufficient efficacy and safety of existing analgesics, the study of new compounds for analgesic activity is characterized by scientific relevance (Simon et al. 2017; Reinecke et al. 2015). As is known, the Tail-flick test allows us to draw a conclusion about the effect of the tested substances at the level of the spinal cord, and in the Hot plate test, the involvement of cortical and subcortical formations is required to implement the paw licking reflex, which indicates the effect of the studied compounds on the structures of the thalamus and cerebral cortex (Mwobobia et al. 2021). The results of the studies of the analgesic properties of these compounds revealed that the 4-chlorophenyl derivative coded CHS-Bi-50 demonstrated antinociceptive activity at the spinal level, which was equal to the reference drug morphine at a dose of 5 mg/kg. It is worth paying attention to the profile of the 4-bromophenyl compound CHS-Bi-51, which is characterized by a combined spinal and supraspinal analgesic property. This substance does not have an anti-anxiety effect. However, the rearings score in the Open Field under the influence of compound CHS-Bi-51 was slightly lower than in the control group, which may indirectly indicate the effect of the substance on the muscle tone of animals, which requires more thorough study. Finally, the compound coded CHS-Bi-52 with a 2-bromophenyl fragment is characterized by a moderate antidepressant effect with some supraspinal analgesic effect.

Based on the results of the empirical analysis of the structures of the studied compounds, comparing the data with the experimental results, it can be noted that the presence of 4-chlorophenyl, 4-bromophenyl and 2-bromophenyl substituents in position 5 of the pyrrole ring (CHS-Bi-50, CHS-Bi-51, CHS-Bi-52) leads to the manifestation of analgesic activity of the compounds. In this case, the presence of a Cl atom leads mainly to spinal effects (CHS-Bi-50), and Br – to supraspinal (CHS-Bi-51, CHS-Bi-52). The presence of a phenyl substituent leads to the appearance of antidepressant and anxiolytic properties of this compound. Replacement of the phenyl ring with a pyridine ring in the structure of CHS-Bi-48 leads to a decrease in the anxiolytic effect compared to CHS-Bi-46, while the antidepressant effect is preserved. The displacement of the nitrogen atom from position 3 (CHS-Bi-48) to position 4 (CHS-Bi-47) of the pyridine part results in the loss of psychotropic effects under the conditions of the tests. Thus, the most suitable structure for the manifestation of the anxiolytic and antidepressant properties of the compounds is the presence of a phenyl substituent in position 5 of the pyrrole ring, and the severity of the analgesic effects of the substances is affected by the presence of Cl atoms in position 4 and Br atoms in positions 2 and 4 in the phenyl radical.

Conclusion

Based on the obtained results, it can be concluded that the phenyl-containing compound CHS-Bi-46 has anxiolytic activity with an antidepressant component. Substances containing pyridin-3-yl (CHS-Bi-48) and 2-bromophenyl (CHS-Bi-52) are characterized by antidepressant properties, and CHS-Bi-52 also showed a weak analgesic effect in the Hot plate test. For the substance with a pyridin-4-yl fragment (CHS-Bi-47), no significant effects were registered according to the results of the tests, which does not exclude the possibility of its having other pharmacological activities. The compound with a 4-chlorophenyl substituent in the pyrrole fragment (CHS-Bi-50) exhibits antinociceptive activity at the spinal level, which is equal to the reference drug morphine at a dose of 5 mg/kg. Compound CHS-Bi-51, containing a 4-bromophenyl substituent, is characterized by a moderate combined spinal and supraspinal analgesic property. The obtained data indicate the prospects for further study of 1-(3-phenylpyrrol-2-yl)-1,3-dihydro-2*H*-benzimidazole-2-one derivatives in order to search for substances with neuropsychotropic activity.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

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Data availability

All of the data that support the findings of this study are available in the main text.

Ethics Statements

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 02.06.2023.

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