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Comparative characteristics of new benzimidazole derivatives with potential analgesic properties

Gleb V. Pridvorov[1, 2], Vyacheslav P. Ganapolsky[2, 3], Aleksandr A. Spasov[1]

[1] Volgograd State Medical University, 1 Ploshchad' Pavshikh Bortsov, Volgograd, 400066, Russian Federation
[2] Military Medical Academy named after S.M. Kirov, 6Zh, Akademika Lebedeva str., Saint Petersburg, 194044, Russian Federation
[3] North-Western State Medical University named after I.I. Mechnikov, 41 Kirochnaya str., Saint Petersburg, 191015, Russian Federation

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Corresponding author:
Gleb V. Pridvorov
E-mail:
gleb.pridvorov@gmail.com

ABSTRACT. ***Introduction***. The development of novel highly effective analgesics represents a critical objective due to the high prevalence of pain syndrome as a component of various pathological conditions, which significantly impairs patients' quality of life. ***Aim.*** The study aimed to investigate the duration of action of two novel opioid analgesics, determine their median lethal (LD_{50}) and median effective (ED_{50}) doses, and calculate their therapeutic indices. ***Materials and methods***. The analgesic activity was assessed using the Tail Flick test. The ED_{50} was determined based on the results of an additional Tail Flick assay. To estimate the LD_{50}, the test compounds were administered at doses exceeding the previously determined ED_{50} by more than 100-fold. The therapeutic index was calculated as the ratio of LD_{50} to ED_{50}. ***Results.*** For compound BIF-70, the ED_{50} was 0.7854 mg/kg, the LD_{50} was 304.3 mg/kg, and the therapeutic index was 387.45. For BIF-72, the ED_{50} was 0.5852 mg/kg, the LD_{50} was 331.4 mg/kg, and the therapeutic index was 566.3. The duration of analgesic action for both compounds was at least 150 minutes at doses ranging from 1 to 10 mg/kg. ***Discussion.*** The duration of action of the studied compounds was comparable to that of classical opioid analgesics. The LD_{50} values for both substances were consistent with those of conventional opioids. Notably, the therapeutic indices of BIF-70 and BIF-72 significantly exceeded that of morphine, though they remained lower than that of butorphanol. ***Conclusions.*** Both compounds demonstrate promising pharmacological profiles as potential opioid analgesics and warrant further preclinical investigation.

Keywords: benzimidazole derivatives, opioid analgesics, behavioral tests, analgesic activity, pharmacokinetic parameters, therapeutic index

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Сравнительная характеристика новых производных бензимидазола с потенциальными анальгетическими свойствами

Глеб Васильевич Придворов[1, 2], Вячеслав Павлович Ганапольский[2, 3], Александр Алексеевич Спасов[1]

[1] Волгоградский государственный медицинский университет, 400066, г. Волгоград, площадь Павших Борцов, д. 1, Российская Федерация
[2] Военно-медицинская академия им. С.М. Кирова, 194044, г. Санкт-Петербург, ул. Академика Лебедева, д. 6, лит. Ж, Российская Федерация
[3] Северо-Западный государственный медицинский университет им. И.И. Мечникова, 191015, г. Санкт-Петербург, ул. Кирочная, д. 41, Российская Федерация

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Автор для корреспонденции:
Глеб Васильевич Придворов
E-mail:
gleb.pridvorov@gmail.com

РЕЗЮМЕ. ***Введение.*** Создание новых высокоэффективных анальгетиков представляется важной задачей в связи с распространенностью болевого синдрома как компонента различных патологий, значительно ухудшающего качество жизни пациентов. ***Цель.*** Изучить длительность действия двух новых опиоидных анальгетиков, определить значения их полулетальной (LD_{50}) и полуэффективной (ED_{50}), доз а также установить условный терапевтический индекс. ***Материалы и методы.*** Исследования анальгетической активности проводились на установке Tail Flick. Определение значения полуэффективной дозы проводилось на основании результатов дополнительного теста Tail Flick. Для расчета полулетальной дозы исследуемые вещества вводились в дозах, превышающих рассчитанную на предыдущем шаге полуэффективную более чем в 100 раз. На основании данных показателей рассчитывался интегральный терапевтический индекс. ***Результаты.*** Для соединения BIF-70 полуэффективная доза составила 0,7854 мг/кг, полулетальная — 304,3 мг/кг, условный терапевтический индекс — 387,45. Для BIF-72 полуэффективная доза составила 0,5852 мг/кг, полулетальная — 331,4 мг/кг, условный терапевтический индекс — 566,3. Длительность действия изученных соединений составляет не менее 150 минут при дозировках от 1 до 10 мг/кг. ***Обсуждение.*** Длительность действия незначительно отличается от классических опиоидных анальгетиков. Величина полулетальной дозы обоих соединений в целом соответствует классическим анальгетикам. Значение терапевтического индекса как BIF-70, так и BIF-72 заметно превосходит аналогичный параметр морфина, но уступает буторфанолу. ***Выводы.*** Оба соединения можно рассматривать в качестве перспективных кандидатов опиоидных анальгетиков и рекомендовать их к дальнейшему доклиническому изучению.

Ключевые слова: производные бензимидазола, опиоидные анальгетики, поведенческие тесты, анальгетическая активность, фармакокинетические показатели, терапевтический индекс

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования

INTRODUCTION

The development of new safe and effective analgesics is a priority for experimental pharmacology [1] due to the large number of conditions accompanied by pain, as well as the sharp rise in opioid abuse and the increase in associated overdose deaths, which have led to the opioid crisis [2]. It is precisely the threat of the continued escalation of the opioid epidemic that makes it urgent to change the strategy and substantially revise the structure of medical use of potent opioid analgesics, such as morphine. These agents are characterized by unfavorable pharmacokinetic properties and a low therapeutic index, necessitating significantly higher therapeutic doses (relative to their high affinity for CNS opioid receptors), exhibit abuse liability, and lead to pronounced adverse effects, including those life-threatening and detrimental to patient health [3].

To overcome the challenge of abuse liability in new analgesics, the search among selective opioid receptor agonists, in particular kappa-agonists — long recognized as analgesics with low abuse potential — appears promising [4]. However, their use may be associated with the development of serious kappa-mediated psychotropic adverse effects, including dysphoria, anhedonia, and hallucinations. The mechanism underlying these effects involves signal transduction via the β-arrestin-2 intracellular signaling cascade with activation of mitogen-activated protein kinase — p38-MAPK, as opposed to analgesia mediated by $G\alpha_{I/O}$ protein activation [5]. This fact suggests the therapeutic potential of G protein-biased kappa-opioid receptor ligands as analgesics devoid of dysphoric side effects.

Previous studies conducted at the Department of Pharmacology and Bioinformatics of Volgograd State Medical University (VolgSMU) included targeted *in vitro* screening of benzimidazole-based polycyclic derivatives synthesized at the Research Institute of Physical and Organic Chemistry of Southern Federal University (RIPOC SFU, Rostov-on-Don) [6]. These efforts identified a number of compounds with high selectivity for kappa-opioid receptors [7]. Analysis of the core scaffolds of the experimentally tested substances demonstrated that 2,9-disubstituted imidazo[1,2-α]benzimidazoles represent a promising class of compounds for the discovery of structurally novel kappa-agonists with potentially high kappa-receptor selectivity. Moreover, the kappa-agonist properties of derivatives in this class largely depend on the nature of the substituent at the key nitrogen atom in position 9 and the structure of the moiety at the second position of the heterocyclic core. In the latter case, the presence of a phenyl ring at the C^2 position of the tricyclic system is decisive, while the introduction of halogen atoms, particularly fluorine, into the phenyl ring statistically significantly increases the efficacy of the studied compounds [8]. The most promising compound — a fluorophenyl derivative of [1,2-α]-imidazobenzimidazole [9] — exhibits pronounced analgesic activity (superior to butorphanol and morphine in *in vivo* experiments), and docking analysis revealed that its binding energy to the catalytic domain of p38-MAPK is high and comparable to that of the reference p38-MAPK inhibitor SB203580. The ability of this compound to inhibit p38-MAPK was assessed in a conditioned place avoidance test following systemic administration [10].

The fact that selective p38-MAPK inhibitors belong to the class of fluorophenyl derivatives of imidazole systems [11, 12] provides a rationale for incorporating these moieties into new molecules in order to develop structurally novel kappa-receptor agonists with p38-MAPK inhibitory properties. These findings prompted further search for compounds with a specified pharmacological activity profile, which led to the identification [13] of two lead compounds exhibiting the most pronounced analgesic effects and selected for evaluation of certain pharmacokinetic and toxicological parameters.

AIM

The aim of this study was to assess the duration of action of the novel opioid analgesics with laboratory codes BIF-70 and BIF-72, to determine their median lethal (LD_{50}) and median effective (ED_{50}) doses, and to determine their therapeutic index (TI).

MATERIALS AND METHODS

The study was performed on adult non-inbred male mice weighing 23–28 g, obtained from the Rappolovo Laboratory Animal Breeding Facility of the Russian Academy of Medical Sciences (Saint Petersburg, Russia). During the experimental period, mice were housed

in groups of 10 with unrestricted access to water and food, under a regulated light/dark cycle (12/12 h, lights on at 8:00 AM) and at a temperature of 20–22 °C. All animal procedures were carried out in compliance with national and international legal and ethical regulations. National requirements were met in accordance with Decree No. 51 of August 29, 2014, approving Sanitary Regulations and Standards SP 2.2.1.3218-14 "Sanitary and Epidemiological Requirements for the Design, Equipment, and Maintenance of Experimental Biological Clinics (Vivariums)". International standards were followed as specified in Directive 2010/63/EU of the European Parliament and of the Council of September 22, 2010, on the protection of animals used for scientific purposes. The experiments were approved by the Regional Research Ethics Committee of Volgograd Region (registration number IRB 00005839, IORG 0004900 (OHRP); protocol No. 2077-2018 dated October 30, 2018).

The compounds BIF-70 and BIF-72 are 2-(2'-fluoro-[1,1'-biphenyl]-4-yl)-3-methyl-9-(2-(pyrrolidin-1-yl)ethyl)-9H-benzo[d]imidazo[1,2-a]imidazole and 4-(2-(2-(2'-fluoro-[1,1'-biphenyl]-4-yl)-3-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-9-yl)ethyl)morpholine, respectively. They were used as bulk substances synthesized at the Research Institute of Physical and Organic Chemistry of Southern Federal University, Rostov-on-Don.

Analgesic activity was assessed using a Tail Flick apparatus (Ugo Basile S.r.l., Varese, Italy) at 55 % irradiation intensity in male mice. Group sizes and allocation were determined according to the experimental conditions. Animals were randomly assigned to groups; baseline values were recorded for each animal prior to substance administration.

Analgesic activity was assessed based on the increase in nociceptive response latency to a painful stimulus (infrared irradiation) [14]. Animals were placed in a restraining tube for habituation to the novel environment 5 minutes prior to testing. The nociceptive response was defined as tail withdrawal from the stimulus source. The painful stimulus was applied four times per animal. Response latency was recorded using the built-in software of the apparatus. The maximum exposure time to infrared irradiation was 15 s [15].

The compounds were dissolved in distilled water and administered intraperitoneally.

To study the duration of action of the compounds, the experiment was performed on 40 animals divided into 4 groups according to the dose of the test compound. Measurements were taken 30 minutes after substance administration and then repeated every 30 minutes over a 3-hour period for each animal. For each animal, the mean latency ± standard error of the mean (SEM) was calculated.

To construct time–effect curves, the relative change in response (Δ%) was calculated. The magnitude of the effect was assessed by comparing the absolute response time of animals before substance administration and during the plateau phase, which was determined based on the preceding calculations.

To determine the ED_{50}, an additional Tail Flick test was performed using the same protocol in a group of 40 male mice divided into 4 subgroups according to the dose of the administered compound. The magnitude of the effect was again assessed during the plateau phase, as defined previously.

To calculate the LD_{50} of each compound, 40 animals were randomized into four groups and received the test compounds at doses of 100, 250, 350, and 500 mg/kg. Mortality was assessed 24 hours after administration.

The therapeutic index was calculated based on these parameters using the following formula:

$$\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}}.$$

Data were analyzed using two-way ANOVA followed by Fisher's least significant difference (LSD) test. Graph plotting and statistical calculations, including ED_{50} and LD_{50} estimation, were performed using GraphPad Prism 8 software with its built-in tools.

RESULTS

The study of effect duration demonstrated that a pronounced analgesic effect developed within 30 min, forming a plateau that persisted on average from the 60th to the 90th minute, followed by a steady decline in analgesic activity. Figures 1 and 2 show individual time-effect curves for the tested compounds. Figure 3 presents the distribution of individual effect values during the plateau phase.

A statistically significant difference from the control group was maintained:

- for BIF-70 at 1 mg/kg — until the end of the observation period;
- for BIF-70 at 10 mg/kg — until the 150th minute;

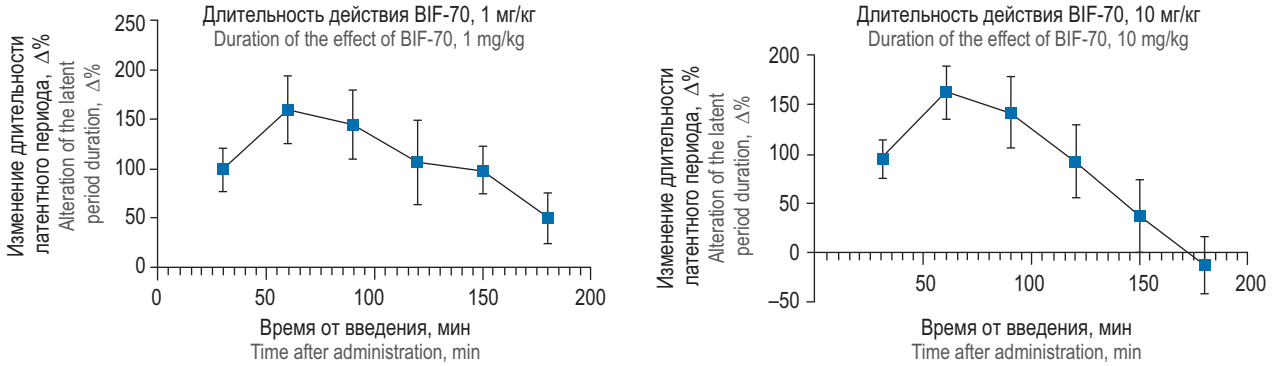

Fig. 1. **Time-dependent changes in the effect intensity of BIF-70 (1 and 10 mg/kg, intraperitoneal) (drawing by the authors)**

Рис. 1. Изменение выраженности эффекта соединения BIF-70 (1 и 10 мг/кг, внутрибрюшинно) во времени (рисунок авторов)

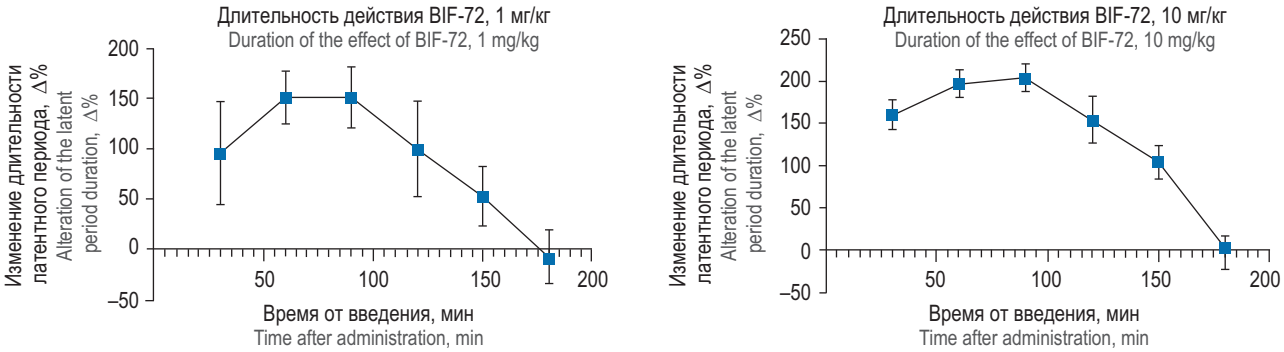

Fig. 2. **Time-dependent changes in the effect intensity of BIF-72 (1 and 10 mg/kg, intraperitoneal) (drawing by the authors)**

Рис. 2. Изменение выраженности эффекта соединения BIF-72 (1 и 10 мг/кг, внутрибрюшинно) во времени (рисунок авторов)

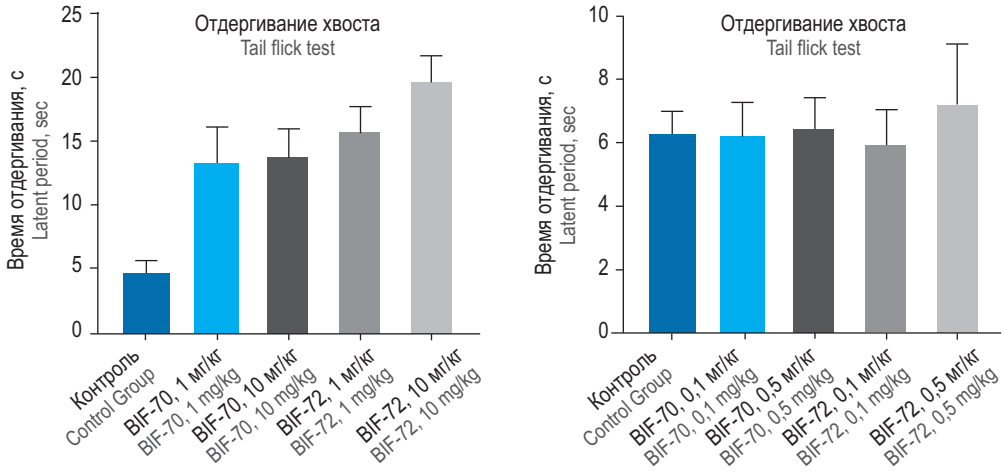

Fig. 3. **Comparison of the effect magnitude of the studied compounds at different concentrations during the plateau phase (60–90 min post-administration) (drawing by the authors)**

Рис. 3. Сравнение выраженности эффекта изучаемых соединений в различных концентрациях в фазе «плато» (60–90 минут от введения) (рисунок авторов)

- for BIF-72 at 1 mg/kg — until the 150th minute;
- for BIF-72 at 10 mg/kg — until the 150th minute.

The analgesic activity of the studied compounds at different doses was then assessed during the plateau phase. The results are shown in Figure 3 (left).

It should be noted that the differences between BIF-70 (1 and 10 mg/kg) and BIF-72 (1 mg/kg) were not statistically significant. At the same time, BIF-72 (10 mg/kg) showed a modest but statistically significant superiority over the other groups..

Thus, the prolongation of reaction time during the plateau phase for these doses was as follows:

- for BIF-70 at 1 mg/kg — 162±38.58%;
- for BIF-70 at 10 mg/kg — 153.75±27.69%;

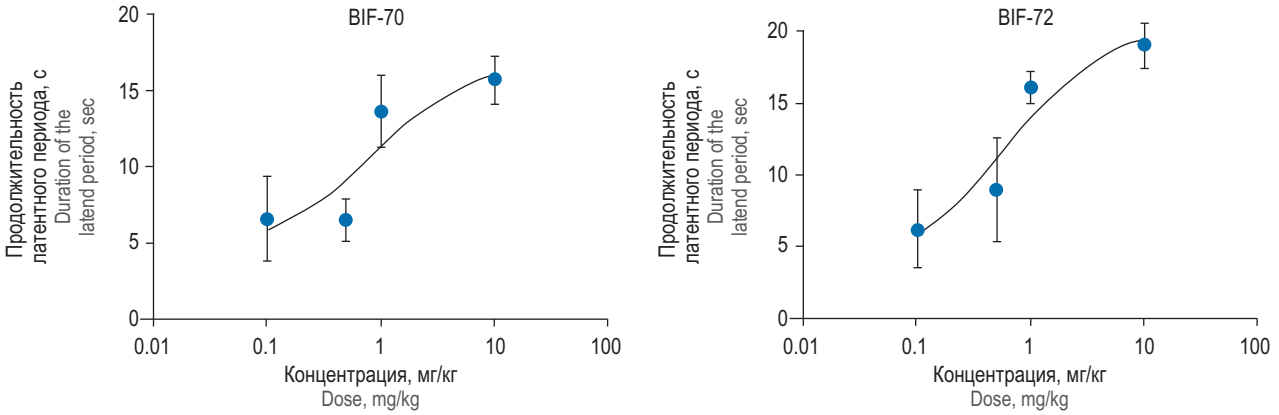

Fig. 4. **Dose-response curves for compounds BIF-70 (left; ED50=0.7854 mg/kg, 95% CI 0.4544–1.383, R^2=0.64) and BIF-72 (right; ED50=0.5852 mg/kg, 95% CI 0.3793–0.8878, R^2=0.77): CI — Confidence interval; ED_{50} — median effective dose; R^2 — coefficient of determination (drawing by the authors)**

Рис. 4. График эффективности соединений BIF-70 (слева; ED_{50}=0,7854 (95% ДИ 0,4544–1,383) мг/кг, R^2=0,64) и BIF-72 (справа; ED_{50}=0,5852 (95% ДИ 0,3793–0,8878) мг/кг, R^2=0,77): ДИ — доверительный интервал; ED_{50} — полуэффективная доза, R^2 — коэффициент детерминации (рисунок авторов)

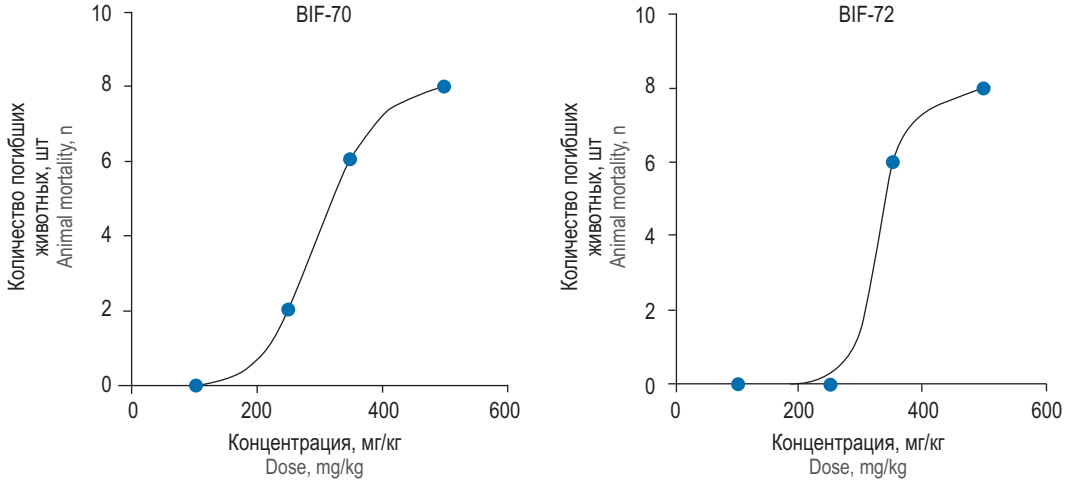

Fig. 5. **Dose-response toxicity curves for compounds BIF-70 (LD_{50}=304.3 mg/kg, R^2=0.86, TI=387.45) and BIF-72 (LD_{50}=331.4 mg/kg, R^2=0.76, TI=566.3): TI — therapeutic index; LD_{50} — median lethal dose; R^2 — coefficient of determination (drawing by the authors)**

Рис. 5. Токсичность соединений BIF-70 (LD_{50}=304,3 мг/кг, R^2=0,86, ТИ=387,45) и BIF-72 (LD_{50}=331,4 мг/кг, R^2=0,76, ТИ=566,3): ТИ — терапевтический индекс, LD_{50} — полулетальная доза; R^2 — коэффициент детерминации (рисунок авторов)

- for BIF-72 at 1 mg/kg — 159.45±23.8%;
- for BIF-72 at 10 mg/kg — 206.02±16.67%.

Regarding the activity of BIF-70 and BIF-72 at lower doses (0.1 and 0.5 mg/kg), no statistically significant differences were observed between any of the groups, including the control group (Fig. 3, right).

Based on the obtained data, dose–response curves were plotted (Fig. 4), and the ED_{50} values were calculated.

Subsequently, the LD_{50} and therapeutic index were determined for the compounds. The results are presented in Figure 5. None of the doses used resulted in complete lethality in any experimental group; however, an LD_{50} was achieved, which was interpreted as a satisfactory level of lethality.

DISCUSSION

The present study demonstrated that the duration of action of the tested compounds is approximately 150 min at doses ranging from 1 to 10 mg/kg. In comparison, butorphanol at similar doses exhibits its most pronounced effect within 60 to 120 min [16]. This time frame closely corresponds to the plateau phase observed for BIF-70 and BIF-72. The magnitude of the analgesic effect

is not discussed here, as it was the subject of a separate publication [13].

Regarding median effective and median lethal doses, previous studies have reported LD_{50} values for classical analgesics in mice after intraperitoneal administration. For butorphanol, the LD_{50} is 192 mg/kg (therapeutic index 192,000 in the tail-flick test) [17]. For morphine, the LD_{50} is 400 mg/kg [18] (therapeutic index 100) [19].

Thus, the median lethal dose of both compounds is generally comparable to that of classical analgesics. However, their therapeutic index is considerably lower than that of butorphanol, which may raise concerns regarding their further clinical prospects. Nevertheless, it should be noted that the therapeutic index of the studied compounds is 4–5 times higher than that of morphine — a drug that remains clinically relevant.

Furthermore, previously reported findings [13] indicate that the analgesic activity of BIF-70 and BIF-72 in various experimental models is comparable to that of butorphanol, with BIF-72 exhibiting neither reinforcing nor dysphoric effects. Moreover, this compound markedly suppressed inflammatory pain responses in specific tests.

The differences in the properties of the studied compounds, as well as in their analgesic activity levels, may result from distinct degrees of affinity for kappa-opioid receptors and possible differences in their effects on post-receptor signaling pathways. Indeed, BIF-72 has previously been shown to exhibit more pronounced agonistic activity at kappa-opioid receptors, which was abolished by a specific antagonist [20]. This mechanism of action may presumably be related to the presence of a hydrogenated six-membered heterocycle linked to the N^9 atom in the compound structure. In the above-cited publication, researchers from the Research Institute of Physical and Organic Chemistry of Southern Federal University proposed further investigation of the properties of 2-arylimidazo[1,2-a]benzimidazoles, with the ultimate goal of developing more effective analgesics.

CONCLUSIONS

In summary, the obtained data collectively suggest that BIF-70 and BIF-72 represent promising opioid analgesics and warrant further preclinical evaluation. Such studies should include docking analysis to elucidate their mechanism of action, as well as investigation of their metabolism and chronic (including organ-specific) toxicity to enable a more refined safety assessment.

With regard to further investigation of analgesic properties per se, the most promising direction involves studies assessing the effects of the compounds on somatic pain — a modality for which effective relief is characteristic of opioidergic agents. Additionally, as noted in a previous report [13], BIF-72 exerted a pronounced effect during the second phase of the formalin-induced pain model, which may be interpreted as evidence of anti-inflammatory activity; however, this finding requires more detailed investigation and independent confirmation.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Animal manipulations were carried out in compliance with legal and ethical standards (Resolution of 29.08.2014 No. 51 “On approval of SP 2.2.1.3218-14 “Sanitary and epidemiological requirements for the design, equipment and maintenance of experimental biological clinics (vivariums)”; Directive of the European Parliament and of the Council of the European Union 2010/63/EU of 22 September 2010 “On the protection of animals used for scientific purposes”).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Манипуляции над животными проводили с соблюдением правовых и этических норм (Постановление от 29.08.2014 г. № 51 «Об утверждении СП 2.2.1.3218-14 “Санитарно-эпидемиологические

требования к устройству, оборудованию и содержанию экспериментально-биологических клиник (вивариев)"»; директива Европейского парламента и Совета Европейского Союза 2010/63/EC от 22 сентября 2010 г. «О защите животных, использующихся для научных целей»).

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Authors' info

*** Gleb V. Pridvorov** — Lecturer of the Department of Pharmacology. E-mail: gleb.pridvorov@gmail.com; https:.orcid.org/0000-0002-8070-693X; SPIN: 7998-0743
Vyacheslav P. Ganapolsky — Dr. Sci. (Med.), Associate Professor; Acting Head of the Department of Pharmacology. E-mail: ganvp@mail.ru; https://orcid.org/0000-0001-7685-5126; SPIN: 9872-8841
Alexander A. Spasov — Dr. Sci. (Med.), Professor, Academician of the Russian Academy of Sciences; Head of the Department of Pharmacology and Bioinformatics. E-mail: aspasov@mail.ru; https://orcid.org/0000-0002-7185-4826; SPIN: 8777-1303

* Corresponding author.
Автор, ответственный за переписку.

Об авторах

*** Глеб Васильевич Придворов** — преподаватель кафедры фармакологии. E-mail: gleb.pridvorov@gmail.com; https://orcid.org/0000-0002-8070-693X; SPIN: 7998-0743
Вячеслав Павлович Ганапольский — д.м.н., доцент, ВРИО заведующего кафедрой фармакологии. E-mail: ganvp@mail.ru; https://orcid.org/0000-0001-7685-5126; SPIN: 9872-8841
Александр Алексеевич Спасов — д.м.н., профессор, академик РАН; заведующий кафедрой фармакологии и биоинформатики. E-mail: aspasov@mail.ru; https://orcid.org/0000-0002-7185-4826; SPIN: 8777-1303