

PHARMACOLOGY AND PHARMACY

ANTI-INFLAMMATORY AND ANTINOCICEPTIVE ACTIVITY OF INDENOPYRROLES AND INDENOPYRIDAZINES IN THE EXPERIMENT

Gein O.N.³,
Nosova N.V.¹,
Chizhova E.G.²,
Hein V.S.⁴,
Gein V.L.¹

¹ Perm State Pharmaceutical Academy of the Ministry of Health of the Russian Federation (Polevaya St. 2, Perm 614990 Russian Federation)

² Institute of Ecology and Genetics of Microorganisms – branch of the Perm Federal Research Center of the Ural Branch of the Russian Academy of Sciences (Golev Str. 13, Perm 614990 Russian Federation)

³ Perm State Medical University named after Academician E.A. Wagner, Ministry of Health of the Russian Federation (Petropavlovskaya Str. 26, Perm 614990, Russian Federation)

⁴ Perm State National Research University (Bukirev Str. 15, Perm 614068, Russian Federation)

Corresponding author:
Oksana N. Gein
e-mail: heinon77@mail.ru

ABSTRACT

Background. Currently, the main groups of anti-inflammatory drugs used in medical practice are steroidal (glucocorticoids) and non-steroidal agents. However, despite their widespread use, these groups of anti-inflammatory drugs have a fairly wide range of negative side effects, which makes the search for low-toxic substances with anti-inflammatory effects currently relevant.

The aim. To study anti-inflammatory, antinociceptive activity and acute toxicity of individual representatives of indenopyrroles and indenopyridazines.

Methods. The acute toxicity of the studied compounds was studied using the method of Prozorovsky VB. Anti-inflammatory activity was assessed in a carrageenan-induced rat paw edema model. The production of active oxygen radicals by leukocytes was evaluated using luminol-dependent chemiluminescence. The antinociceptive activity of the compounds was assessed using the "writhing" and "hot plate" tests in mice.

Results. The obtained results allowed the studied compounds to be classified as "practically nontoxic" (LD50 > 1000 mg/kg). Compounds 1b of the indenopyrrole series and indenopyridazines 2a-b were found to exhibit anti-inflammatory activity, reducing the severity of exudative inflammation. Compound 2a exhibited the greatest antiexudative activity, reducing edema by more than 60 % ($p < 0.01$). Compounds 2a-b and compound 1b reduced the production of reactive oxygen species by more than 40 % ($p < 0.05$) compared to the control. In the "hot plate" test, the studied compounds 1a, 1b, 2a-b exhibited an antinociceptive effect comparable to nimesulide; in the "acetic acid-induced writhing" test, the effect of compounds 1a, 2b, 2b was comparable to nimesulide, and the effect of compound 2a exceeded the comparison drug by 32.96 % ($p < 0.05$).

Conclusion. The studied compounds of the indenopyrrole series and their indenopyridazine derivatives are virtually non-toxic compounds, exhibit an anti-inflammatory effect and reduce the severity of pain associated with inflammation.

Key words: indenopyrroles, indenopyridazines, anti-inflammatory activity, production of reactive oxygen species, analgesic activity, acute toxicity, mice, rats

Received: 16.11.2025
Accepted: 01.06.2026
Published: 23.07.2026

For citation: Gein O.N., Nosova N.V., Chizhova E.G., Hein V.S., Gein V.L. Anti-inflammatory and antinociceptive activity of indenopyrroles and indenopyridazines in the experiment. *Acta biomedica scientifica*. 2026; 11(3): 138-145. doi: 10.29413/ABS.2026-11.3.17

ПРОТИВОВОСПАЛИТЕЛЬНАЯ И АНТИНОЦИЦЕПТИВНАЯ АКТИВНОСТЬ ИНДЕНОПИРРОЛОВ И ИНДЕНОПИРИДАЗИНОВ В ЭКСПЕРИМЕНТЕ

Гейн О.Н.³,
Носова Н.В.¹,
Чиждова Е.Г.²,
Гейн В.С.⁴,
Гейн В.Л.¹

¹ ФГБОУ ВО Пермская государственная фармацевтическая академия Минздрава России (614990, г. Пермь, ул. Полевая 2, Россия)

² Институт экологии и генетики микроорганизмов – филиал ФГБУН Пермского федерального исследовательского центра Уральского отделения Российской академии наук (614990, г. Пермь, ул. Голева 13, Россия)

³ ФГБОУ ВО Пермский государственный медицинский университет им. акад. Е.А. Вагнера Минздрава России (614990, г. Пермь, ул. Петропавловская 26, Россия)

⁴ ФГАОУ ВО Пермский государственный национальный исследовательский университет (614068, г. Пермь, ул. Букирева 15, Россия)

Автор, ответственный за переписку:
Гейн Оксана Николаевна
e-mail: heinon77@mail.ru

РЕЗЮМЕ

Обоснование. В настоящее время в медицинской практике в качестве основных групп противовоспалительных средств применяются средства стероидной (глюкокортикоиды) и нестероидной природы. Однако, не смотря на их широкое применение, указанные группы противовоспалительных средств обладают достаточно широким спектром негативных побочных эффектов, что делает поиск малотоксичных субстанций, обладающих противовоспалительным действием, в настоящее время актуальным.

Цель исследования. Изучение противовоспалительной, антиноцицептивной активности и острой токсичности отдельных представителей инденопирролов и инденопиридазинов.

Методы. Острую токсичность исследуемых соединений изучали по методу Прозоровского В.Б. Противовоспалительную активность оценивали в модели каррагенинового отека лапы крысы. С помощью люминолзависимой хемилюминисценции оценивали продукцию активных кислородных радикалов лейкоцитами. Антиноцицептивную активность исследуемых соединений изучали в тесте «корчей» и в тесте «горячая пластина» на мышцах.

Результаты. Полученные результаты позволили отнести исследуемые соединения к «практически нетоксичным» (ЛД₅₀ > 1000 мг/кг). Установлено, что соединение 1в ряда инденопирролов и инденопиридазины 2а-в проявляют противовоспалительную активность, уменьшая выраженность экссудативного воспаления. Наибольшую антиэкссудативную активность проявило соединение 2а, уменьшая отек более, чем на 60 % ($p < 0,01$). Соединения 2а-в и соединение 1в уменьшали продукцию активных форм кислорода более чем на 40 % ($p < 0,05$) по сравнению с контролем. В тесте «горячая пластина» исследуемые соединения 1а, 1в, 2а-в проявляли антиноцицептивный эффект сопоставимый с нимесулидом; в тесте «уксусные корчи» эффект соединений 1а, 2б, 2в был сопоставим с нимесулидом, а эффект соединения 2а превосходил препарат сравнения на 32,96 % ($p < 0,05$).

Заключение. Исследуемые соединения ряда инденопирролов и их производные инденопиридазины являются практически нетоксичными соединениями, проявляют противовоспалительный эффект и уменьшают выраженность боли, связанной с воспалением.

Ключевые слова: инденопирролы, инденопиридазины, противовоспалительная активность, продукция активных форм кислорода, анальгетическая активность, острая токсичность, мышцы, крысы

Статья поступила: 16.11.2025
Статья принята: 01.06.2026
Статья опубликована: 23.07.2026

Для цитирования: Гейн О.Н., Носова Н.В., Чиждова Е.Г., Гейн В.С., Гейн В.Л. Противовоспалительная и антиноцицептивная активность инденопирролов и инденопиридазинов в эксперименте *Acta biomedica scientifica*. 2026; 11(3): 138-145. doi: 10.29413/ABS.2026-11.3.17

INTRODUCTION

Inflammation, as a protective-adaptive reaction of the body, on the one hand, provides a non-specific defense against various pathogens and participates in the elimination of damaged host cells. On the other hand, it can accompany various pathological conditions such as trauma, infections, and autoimmune diseases. Under these circumstances, the endogenous mechanisms aimed at containing the local inflammatory process are often insufficient, leading to generalization of inflammation with the release of inflammatory mediators and pro-inflammatory cytokines into the systemic circulation [1]. Therefore, it is important for potential medications to effectively influence the course of inflammation at all stages of its development. This may be achieved through the multi-component mechanism of their anti-inflammatory action.

Currently, two main groups of anti-inflammatory medications are used in medical practice: steroid and non-steroidal drugs. However, despite their widespread use, these groups of anti-inflammatory drugs have a relatively broad range of adverse effects, making the search for low-toxic substances with anti-inflammatory activity highly significant [2, 3].

Indenopyrroles and their indenopyridazine derivatives, due to their high reactivity, show promise for the synthesis of a wide range of compounds, including those with biological activity. The indenopyrrole and indenopyridazine compounds studied here incorporate nitrogen-containing heterocyclic rings such as pyrrole and pyridazine into their structures. Previously, substances with anti-inflammatory activity have been identified within the class of pyrrole-containing compounds and their derivatives [4]. However, the impact of indenopyrroles and indenopyridazines on inflammatory processes has not yet been investigated.

AIM

To study anti-inflammatory, antinociceptive activity and acute toxicity of selected representatives of indenopyrroles and indenopyridazines.

MATERIALS AND METHODS

In vivo experiments were conducted using sexually mature white Wistar rats weighing 180–220 g and sexually mature white outbred CD-1 mice weighing 22–25 g.

All research procedures involving laboratory animals were performed in accordance with generally accepted ethical standards for animal care, as outlined in the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes [5] and recommendations from the Board of the Eurasian Economic Commission dated November 14, 2023 No. 33 "On the Guidelines for the Care and Use of Laboratory (Experimental) Animals in Preclinical (Non-clinical)

Studies" [6]. These studies were approved by the Bioethics Committee of the Perm State Pharmaceutical Academy of the Ministry of Health of the Russian Federation (Protocol No. 2-н-ж, dated January 16, 2024, Perm, Russia).

The compounds selected for this study were representatives of the indenopyrrole series (1a-c) and their indenopyridazine derivatives (2a-c), which differ in terms of the presence of various substituents within their molecular structures (Fig. 1). These compounds were synthesized at the Department of General and Organic Chemistry of the Perm State Pharmaceutical Academy of the Ministry of Health of the Russian Federation. The structure and purity of these indenopyrroles and indenopyridazines were confirmed through IR, ^1H NMR, and ^{13}C NMR spectroscopy [7].

The acute toxicity of the studied compounds was assessed using the method proposed by Prozorovsky V.B. [8]. The substances were administered via intraperitoneal injection in a 2 % starch mucilage at increasing doses of 500, 631, 794 and 1000 mg/kg. Based on the data obtained, the toxicity classification of the compounds was determined using the classification system proposed by Sidorov K.K. [9].

Acute inflammation was induced by administering 0.1 mL of a 1 % carrageenan solution to the plantar surface of the rat hind paw. Paw volume was measured using an oncometer before carrageenan injection (control) and then at 3 and 5 hours after carrageenan administration. The tested compounds were administered intraperitoneally at a dose of 50 mg/kg in a 2 % starch mucilage 30 minutes prior to carrageenan injection. The anti-inflammatory effect was assessed based on the reduction in paw edema [10].

Reactive oxygen species production was assessed using a luminol-dependent chemiluminescence (LDCL) assay. The reaction was carried out in 96-well flat-bottom plates (Greiner, Germany). Each well contained 10^5 cells (peritoneal leukocytes from mice) in 100 μL of Hank's solution. Opsonized zymosan at a concentration of 150 $\mu\text{g/mL}$ was used as the LDCL inducer. Luminol at a concentration of 10^{-5} M was used as a marker of the LDCL reaction intensity [9]. Results were recorded over 1 hour at 5-minute intervals using a luminometer (Tecan Trading AG, Switzerland).

The analgesic activity of the tested compounds was evaluated using the acetic acid-induced writhing test

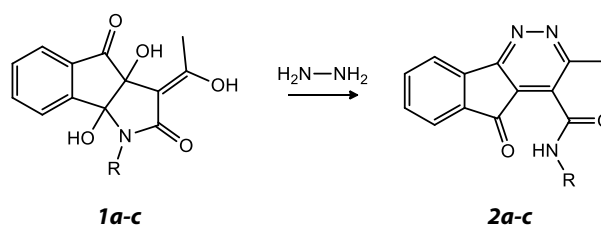


FIG. 1.

Structural formulas of the studied compounds

$R=2\text{-ClC}_6\text{H}_4$ (1a, 2a), $R=\text{H}$ (1b, 2b), $R=2\text{-CH}_3\text{OC}_6\text{H}_4$ (1c, 2c)

and the hot plate test in mice [10]. The tested compounds were administered intraperitoneally at a dose of 50 mg/kg in a 2 % starch mucilage. The control group of animals received an equal volume of a 2 % starch mucilage. Writhing was induced by intraperitoneal injection of a 0.75 % acetic acid solution (0.1 mL per 10 g of body weight) 30 minutes after administration of the tested compounds. The number of abdominal contractions (writhing episodes) was recorded for each animal over a 20-minute period following acetic acid administration. The criterion for analgesic activity was defined as a decrease in the number of writhing episodes relative to the control group.

In the hot plate test, animals were placed on a metal plate that was heated to 52°C for 60 minutes after administration of the tested compounds. The analgesic effect was assessed based on the latency time until a behavioral response to a thermal stimulus, which was manifested as licking, shaking of the hind paws, or jumping. The latency time was measured in seconds.

Nimesulide substance (Sigma-Aldrich) was administered intraperitoneally at a dose of 50 mg/kg in a 2 % starch mucilage and served as the reference drug in the study.

The data obtained were tested for normal distribution using the Kolmogorov–Smirnov test. The *p*-value from the Kolmogorov–Smirnov test was > 0.05, supporting the null hypothesis that the distribution is close to normal. Subsequently, the data were analyzed using an unpaired Student's *t*-test. Differences between groups were considered statistically significant at *p* < 0.05.

RESULTS

As a result of the acute toxicity study following a single intraperitoneal administration of the indenopyrroles

and their indenopyridazine derivatives, the tested organic compounds were classified as belonging to class 5, “practically non-toxic compounds”, according to the classification of Sidorov K.K. [9].

All tested compounds, except for compound 1b, demonstrated a reduction in the severity of the inflammatory response when compared to the control group of animals, both at 3 hours and 5 hours after carrageenan administration. Compound 2a exhibited an effect that was comparable to that of the reference drug (Table 1).

The course of an inflammatory reaction is often accompanied by pain caused by irritation of nociceptors by inflammatory mediators such as exudates, including prostaglandins, kinins, and others. This has led to the investigation of the antinociceptive effects of certain compounds.

It was found that the studied indenopyridazines (2a-c) and indenopyrrole 1a reduced the number of involuntary contractions of abdominal muscles (writhing) when injected intraperitoneally with acetic acid (Table 2). An antinociceptive effect exceeding that of nimesulide was observed only for compound 2a.

In the hot plate test, which evaluates the effect of the studied compounds on the central mechanisms of pain perception, nearly all of the studied indenopyrroles and their indenopyridazine derivatives, with the exception of compound 1b, prolonged the time that animals spent on a heated plate (Table 3). The observation of antinociceptive activity in the hot plate assay suggests a potential impact on supraspinal mechanisms of pain regulation [10].

As is known, neutrophils, monocytes, and macrophages are the main players in the inflammatory response, as they are able to secrete not only inflammatory mediators, but also reactive oxygen species (ROS). These ROS can not only help eliminate pathogens, but also sustain the inflammatory response. In this context, the effect

TABLE 1

THE EFFECT OF INDENOPYRROLES (1A-C) AND INDENOPYRIDAZINES (2A-C) ON THE SEVERITY OF EXUDATIVE INFLAMMATION INDUCED BY CARRAGEENAN IN RATS

Compound	Increase in paw volume, %	Inhibition of paw edema, %	Increase in paw volume, %	Inhibition of paw edema, %
	at 3 h		at 5 h	
Control (n=8)	42.89 ± 6.83	-	30.96 ± 4.18	-
Nimesulide (n=8)	11.39 ± 2.88*	73.42 ± 6.72	5.77 ± 1.64*	81.36 ± 5.29
1a (n=7)	19.47 ± 2.21*	54.59 ± 5.15	13.68 ± 1.70*	55.79 ± 5.50
1b (n=6)	25.02 ± 3.79	41.67 ± 8.85	15.99 ± 4.04	48.36 ± 13.05
1c (n=7)	24.40 ± 3.44*	43.09 ± 8.02	16.56 ± 3.37*	46.49 ± 10.88
2a (n=7)	15.26 ± 2.37*	64.43 ± 5.54	9.35 ± 2.06*	69.81 ± 6.64
2b (n=7)	20.86 ± 3.53*	51.35 ± 8.23	17.66 ± 3.03*	42.95 ± 9.79
2c (n=7)	16.24 ± 2.49*	62.12 ± 5.83	11.79 ± 2.57*	61.90 ± 8.31

Note. Data are presented as mean and standard error of the mean (M ± m). * – *p* < 0.05 compared to the control group (Student's *t*-test). # – *p* < 0.05 compared to nimesulide (Student's *t*-test). *n* – number of animals per group.

of the studied compounds on ROS production by peritoneal leukocytes was evaluated using the LDCL assay.

As shown in Figure 2, indenopyrroles (1a-c) did not affect the spontaneous production of ROS by leukocytes in the LDCL assay. In the stimulated version of the assay, these compounds exhibited diverse effects on ROS production: compounds 1a and 1b enhanced ROS production, while compound 1c reduced ROS production from 5 to 30 minutes of observation (Fig. 2).

The effect of indenopyridazines (2a-c) on ROS production in the LDCL assay showed a similar trend in both the unstimulated and stimulated versions (Fig. 3). In unstimulated leukocytes, ROS production after treatment

with compounds 2a and 2b was lower compared to the control at 10–20 minutes after treatment, and at 35 minutes, a decrease in ROS production was seen for compounds 2a-c (Fig. 3A). In the stimulated version of the assay, ROS production following administration of compounds 2a-c decreased during the first 10 minutes but did not differ significantly from control values thereafter (Fig. 3B).

DISCUSSION

The development of carrageenan-induced paw edema in rats at the evaluated time points (3 and 5 hours after

TABLE 2

ANTINOCICEPTIVE ACTIVITY OF INDENOPYRROLES (1A-C) AND INDENOPYRIDAZINES (2A-C) IN THE VINEGAR WRITHE TEST IN MICE

Compound	Number of writhes				Total number
	Observation period				
	0-5 min	5-10 min	10-15 min	15-20 min	
Control (n=7)	9.28 ± 2.13	18.57 ± 2.21	17.86 ± 2.30	10.71 ± 0.52	56.43 ± 4.73
Nimesulide (n=7)	5.14 ± 1.08	12.43 ± 0.61*	11.57 ± 1.02	8.14 ± 0.70*	37.29 ± 1.87*
1a (n=6)	4.0 ± 1.15	13.33 ± 1.76	11.83 ± 1.64	10.0 ± 1.86	39.17 ± 4.78*
1b (n=7)	8.71 ± 1.59	15.14 ± 0.96	13.14 ± 0.59	7.29 ± 0.47*	44.29 ± 1.96
1c (n=7)	8.14 ± 1.64	18.43 ± 3.55	13.00 ± 2.32	10.0 ± 1.90	49.57 ± 8.55
2a (n=6)	4.67 ± 1.48	11.67 ± 1.47*	5.33 ± 0.92 ^{*H}	3.33 ± 1.17 ^{*H}	25.0 ± 3.25 ^{*H}
2b (n=7)	6.29 ± 1.76	15.14 ± 1.89	12.00 ± 1.29	8.14 ± 1.39	41.57 ± 3.06*
2c (n=7)	8.00 ± 1.93	12.71 ± 1.96	9.57 ± 1.21*	7.71 ± 1.25	38.00 ± 5.17*

Note. Data are presented as mean and standard error of the mean ($M \pm m$). n – number of animals per group. * – $p < 0.05$ compared to the control group (Student's t -test). H – $p < 0.05$ compared to nimesulide (Student's t -test).

TABLE 3

ANTINOCICEPTIVE ACTIVITY OF INDENOPYRROLES (1A-C) AND INDENOPYRIDAZINES (2A-C) IN MICE IN THE HOT PLATE TEST

No.	Compound	Latency time, s	p vs. control
1	Control (n=7)	13.46 ± 0.75	-
2	Nimesulide (n=8)	17.52 ± 1.02	< 0.02
3	1a (n=8)	19.58 ± 1.53	< 0.01
4	1b (n=8)	13.79 ± 1.58	> 0.05
5	1c (n=7)	18.72 ± 1.14	< 0.01
6	2a (n=8)	20.93 ± 2.05	< 0.02
7	2b (n=8)	19.76 ± 1.24	< 0.01
8	2c (n=8)	20.32 ± 2.10	< 0.02

Note. Data are presented as mean and standard error of the mean ($M \pm m$). H – $p < 0.05$ compared to the reference drug nimesulide (Student's t -test). n – number of animals per group.

phlogogen administration) is associated with the active infiltration of the inflammatory focus by leukocytes, predominantly neutrophils and macrophages, which secrete pro-inflammatory cytokines as well as inflammatory mediators. Carrageenan can directly activate the migratory and secretory activity of macrophages through Toll-like receptor 4 (TLR-4). The stimulation of macrophage secretion leads to an increase in the synthesis of mediators, such as prostaglandins, leukotrienes, and pro-inflammatory cytokines (IL-1, IL-6, TNF- α), which contribute to the development and maintenance of the inflammatory response [11]. Therefore, based on the results of our study, it can be hypothesized that the anti-inflammatory activity of the tested compounds is mediated by inhibition of leukocyte migration, the synthesis of pro-inflammatory cytokines and mediators, and also through an effect on TLR-4.

Involuntary contractions of the abdominal muscles during the acetic acid-induced writhing test are caused by the stimulation of nociceptors in serous membranes through acetic acid injection. This stimulation is also thought to lead to the release of biologically active substances, such as bradykinins, prostaglandins, and leukotrienes, during the early stage of primary hyperalgesia. Prostaglandins and leukotrienes are products of arachidonic

acid metabolism through the cyclooxygenase pathway. Previous studies have demonstrated the ability of compounds with a pyrrole ring structure to inhibit the expression and activity of COX-2 during inflammation [12]. This suggests that these compounds may also inhibit the expression or activity of the COX enzyme, thereby reducing the synthesis of prostaglandin E₂, a primary sensitizer for nociceptors.

The results of the study on leukocyte-derived reactive radical production in the LDCL assay indicate that the mechanism by which indenopyridazine compounds exert their anti-inflammatory effects may be due to their inhibitory effect on radical production.

CONCLUSION

Our data suggest that certain indenopyrrole and indenopyridazine derivatives exhibit anti-inflammatory and antinociceptive activity combined with low toxicity.

In the carrageenan-induced rat paw edema model, the studied indenopyridazines showed comparable anti-inflammatory effects to the reference drug, nimesulide. Additionally, they significantly reduced reactive oxygen species production in the LDCL assay by more than 40 %

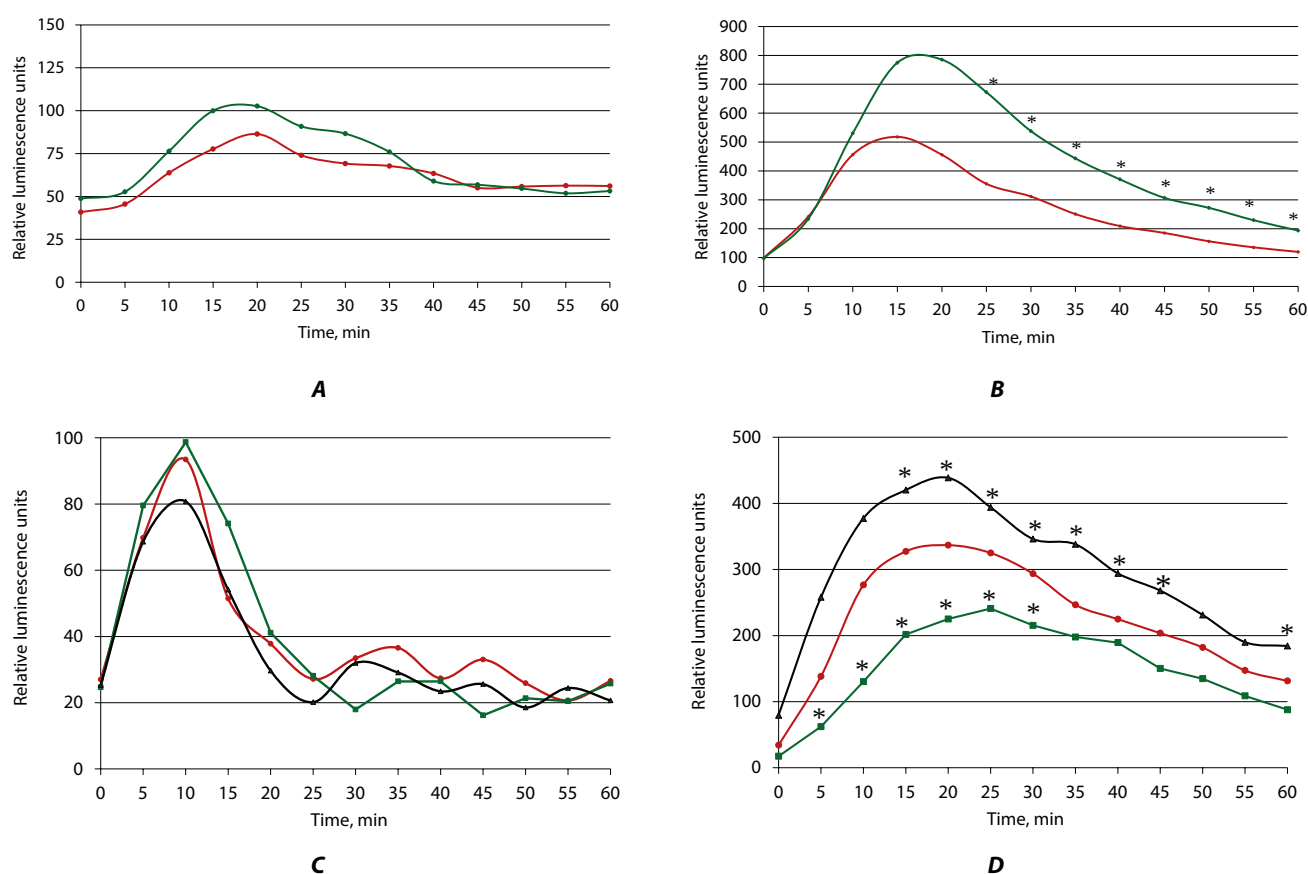


FIG. 2.

The effect of indenopyrroles on spontaneous (A, C) and stimulated (B, D) production of reactive oxygen species by mouse leukocytes

• – control, ▲ – compound 1a, ◆ – compound 1b, ■ – compound 1c;

* – $p < 0.05$ compared to control, number of animals in each group $n=9$.

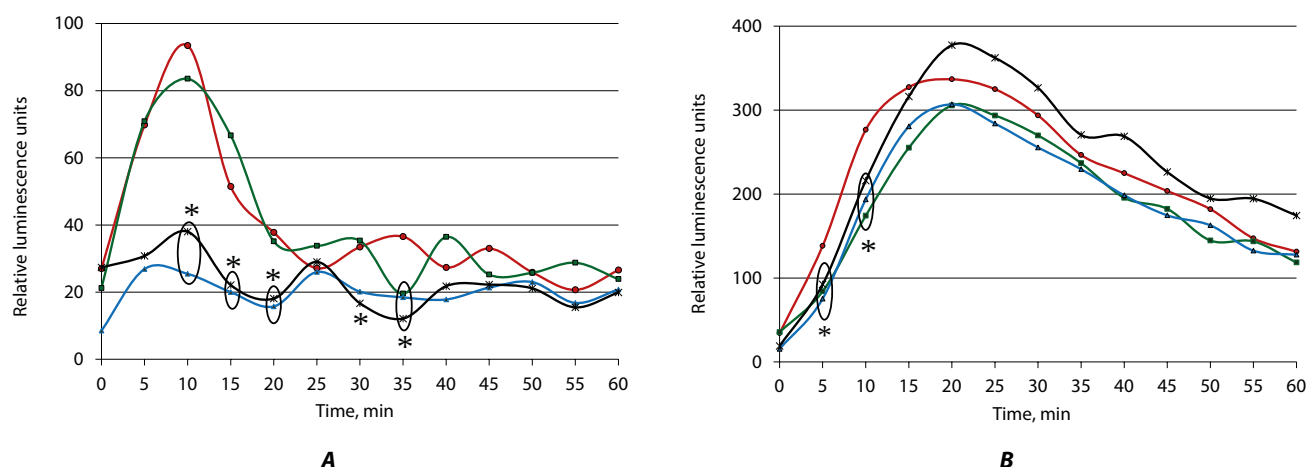


FIG. 3.

The effect of indenopyridazines (2a-c) on spontaneous (A) and stimulated (B) production of reactive oxygen species by mouse leukocytes
 • – control, × – compound 2a, ▲ – compound 2b, ■ – compound 2c, * – $p < 0.05$ compared to control, number of animals in each group $n=9$.

($p < 0.01$) compared to the control group. Furthermore, compound 2a exceeded the reference drug by 32.96 % in the acetic acid-induced writhing assay, compared to the reference compound ($p < 0.05$).

These results suggest that indenopyrroles and their derivatives may be promising candidates for further development as potential anti-inflammatory agents with analgesic properties.

Funding

The study was carried out as part of a government assignment, state registration number of the topic is 124020500027-7.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

- Gusev E, Zhuravleva Y. Inflammation: a new look at an old problem. *International Journal of Molecular Sciences*. 2022; 23(9): 4596. doi: 10.3390/ijms23094596
- Shostak NA, Klimenko AA, Demidova NA, Anichkov DA. Nonsteroidal anti-inflammatory drugs: current aspects of their use. *Klinicist*. 2020; 1-2: 91-99. (In Russ.). [Шостак Н.А., Клименко А.А., Демидова Н.А., Аничков Д.А. Нестероидные противовоспалительные препараты – современные аспекты их применения. *Клиницист*. 2020; 1-2: 91-99.]. doi: 10.17650 / 1818-8338-2020-14-1-2-91-99
- Pofi R, Caratti G, Ray DW, Tomlinson JW. Treating the Side Effects of Exogenous Glucocorticoids; Can We Separate the Good from the Bad? *Endocr Rev*. 2023; 44(6): 975-1011. doi: 10.1210/edrev/bnad016
- Li Petri G, Spanò V, Spatola R, Holl R, Raimondi MV, Barraja P, et al. Bioactive pyrrole-based compounds with target selectivity. *Eur J Med Chem*. 2020; 208: 112783. doi: 10.1016/j.ejmech.2020.112783
- European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes. Strasbourg, (1986). (In Russ.). [Европейская конвенция по защите позвоночных животных, используемых в экспериментальных и других научных целях. Страсбург, (1986)].
- Recommendation of the EEC Board No. 33. «On the Guidelines for Working with Laboratory (Experimental) Animals in Preclinical (Non-Clinical) Studies». (2023). (In Russ.). [Рекомендация Коллегии ЕЭК № 33. «О Руководстве по работе с лабораторными (экспериментальными) животными при проведении доклинических (неклинических) исследований». 2023.].
- Gein VL, Nosova NV, Yankin AN, Bazhina AY, Dmitriev MV. An eco-friendly stereoselective synthesis of novel derivatives of indeno[1,2-b]Pyrrole and Indeno[1,2-c]pyridazine. *Polycyclic Aromatic Compounds*. 2019; 41(3): 540-552. doi: 10.1080/10406638.2019.1602061
- Prozorovskii VB. Statistic processing of data of pharmacological investigations. *Psychopharmacol. Biol. Narkol*. 2007; 7(3-4): 2090–2120. (In Russ.). [Прозоровский В.Б. Статистическая обработка результатов фармакологических исследований. *Психофармакология и биологическая наркология*. 2007; 7(3-4): 2090–2120.].
- Berezovskaya IV. Prognosis of drug safety in preclinical toxicological studies. *The Toxicological bulletin*. 2010; 5(104): 17–22. (In Russ.). [Березовская И.В. Прогноз безопасности лекарственных средств в доклинических токсикологических исследованиях. *Токсикологический вестник*. 2010; 5(104): 17–22.].
- Mironov AN. *Guidelines for conducting preclinical studies of medicinal products. Part one*. M.: Fingerboard and K; 2012. (In Russ.). [Миронов А.Н. *Руководство по проведению доклинических исследований лекарственных средств. Часть первая*. М.: Гриф и К; 2012.].
- Cicinskas E, Begun MA, Vikhareva VV, Karetin YA, Kalitnik AA. Immunological effects of Chondrus armatus carrageenans and their low molecular weight degradation

products. *J Biomed Mater Res A*. 2021; 109(7): 1136-1146. doi: 10.1002/jbm.a.37106

12. Xu XT, Mou XQ, Xi QM, Liu WT, Liu WF, Sheng ZJ, et al. Anti-inflammatory activity effect of 2-substi-

tuted-1,4,5,6-tetrahydrocyclopenta[b]pyrrole on TPA-induced skin inflammation in mice. *Bioorg Med Chem Lett*. 2016; 26(21): 5334-5339. doi: 10.1016/j.bmcl.2016.09.034

Information about the authors

Oksana N. Gein – Cand. Sc. (Biol.), associate professor of the Department of Pharmacology of the Perm State Medical University named after Academician E.A. Wagner of the Ministry of Health of the Russian Federation; e-mail: heinon77@mail.ru, <https://orcid.org/0000-0002-1327-6685>

Natalya V. Nosova – Cand. Sc. (Chem.), associate professor of the Department of General and Organic Chemistry of the Perm Pharmaceutical Academy of the Ministry of Health of the Russian Federation; e-mail: natalia.v.nosova@mail.ru, <https://orcid.org/0000-0001-6380-2543>

Ekaterina G. Chizhova – engineer at the Laboratory of biochemistry of microorganism development at the Institute of Ecology and Genetics of the Ural Branch of the Russian Academy of Sciences; e-mail: dama_74.ru@mail.ru, <https://orcid.org/0009-0007-1977-6609>

Vladimir S. Gein – laboratory assistant at the Organic synthesis laboratory of Perm State National Research University; e-mail: vovagein@gmail.com, <https://orcid.org/0009-0007-7807-9686>

Vladimir L. Gein – Dr. Sc. (Chem.), professor, head of the Department of General and Organic Chemistry, Perm Pharmaceutical Academy of the Ministry of Health of the Russian Federation; e-mail: geinvl48@mail.ru, <https://orcid.org/0000-0002-8512-0399>