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Журнал «Фармация и фармакология» включен в перечень рецензируемых научных изданий, входящих в международные реферативные базы данных и системы цитирования, и в соответствии с пунктом 5 правил формирования перечня рецензируемых научных изданий, в которых должны быть опубликованы основные научные результаты диссертаций на соискание ученой степени кандидата наук, на соискание ученой степени доктора наук (Перечень ВАК), Scopus, Web of Science (ESCI), РИНЦ, eLibrary, ВИНИТИ, РГБ, Киберленинка, Соционет, EMBASE, Chemical Abstracts (CAS), Directory of Open Access Journals (DOAJ), EBSCO Discovery Service, RNMJ, University of CAMBRIDGE, Ulrich'sWeb, Google Scholar, Biefeld Academic Search Engine (BASE), Directory of Open Access Scholarly Resources (ROAD), Research Bible, Open Archives Initiative, Academic Keys, JournalTOCs, WorldCat, OpenAIRE, University of Oxford, The British Library, Universitait Gent, Université de Montréal, University of Saskatchewan.

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RESEARCH ARTICLE

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Analysis of pharmacy organisation staff awareness of pharmacovigilance

R.I. Yagudina[1], O.L. Listova [2], A.R. Umerova[3], K.A. Kopeyka[1]

[1] Sechenov First Moscow State Medical University,
Bldg. 2, 8, Trubetskaya Str., Moscow, Russia, 119991
[2] Ministry of Health of the Stavropol Territory,
42/311, Marshal Zhukov Str., Stavropol, Russia, 355003
[3] Astrakhan State Medical University,
121, Bakinskaya Str., Astrakhan, Russia, 414000

E-mail: kirillkopeika@gmail.com

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The aim of the study was to investigate the awareness of pharmacists' knowledge of the pharmacovigilance basics in pharmacy organisations (PhOs) of the Russian Federation and to identify the factors influencing their participation in the drug safety monitoring system.

Materials and methods. A single-point survey study was conducted in the form of a single solid group online questionnaire survey of 513 pharmaceutical specialists from different regions of Russia. A specially designed 14-item questionnaire aimed was used to assess their knowledge of the pharmacovigilance system. Retrospective, comparative, statistical, and logical analysis methods were applied.

Results. A comprehensive assessment of the level of pharmaceutical specialists' pharmacovigilance knowledge in Russia was carried out. The factors influencing the specialists' awareness were determined. The necessity of educational activities to increase the involvement of PhOs employees in the drug safety monitoring system was justified. The insufficient level of pharmaceutical specialists' knowledge about the basic concepts and procedures of pharmacovigilance was revealed. Specialists with secondary specialized education and less work experience demonstrated a lower level of awareness. Only 13% of the participants had received training on pharmacovigilance, while the majority (about 80%) considered it necessary to increase the number of training programmes. The influence of education, work experience and job position on the awareness of professionals was established. Most respondents recognize the need to report adverse drug reactions (ADRs) occurring when taking a medicine, but in practice the level of reporting remains low.

Conclusion. Insufficient knowledge of the pharmacovigilance basics among pharmacy workers causes a low level of ADRs reporting by them. A comprehensive approach, including educational initiatives and the development of targeted interventions, is required to improve specialists' engagement in the drug safety monitoring system. Further research is necessary to develop and evaluate the effectiveness of educational programmes and motivational models to increase pharmaceutical specialists' pharmacovigilance activities.

Keywords: pharmacovigilance; pharmaceutical specialists; pharmacy organisations; adverse drug reactions; drug safety

Abbreviations: ADR – adverse drug reaction; HP – health professional.

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Анализ осведомлённости персонала аптечной организации об основах фармаконадзора

Р.И. Ягудина[1], О.Л. Листова[2], А.Р. Умерова[3], К.А. Копейка[1]

[1] Федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет), 119991, Россия, г. Москва, ул. Трубецкая, 8, стр. 2
[2] Министерство здравоохранения Ставропольского края, 355003, Россия, г. Ставрополь, ул. Маршала Жукова, д. 42/311
[3] Федеральное государственное бюджетное образовательное учреждение высшего образования «Астраханский государственный медицинский университет» Министерства здравоохранения Российской Федерации, 414000, Россия, г. Астрахань, ул. Бакинская, д. 121

E-mail: kirillkopeika@gmail.com

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Цель. Исследование осведомлённости знаний фармацевтических работников аптечных организаций (АО) Российской Федерации об основах фармаконадзора и выявление факторов, влияющих на их участие в системе мониторинга безопасности лекарственных средств.

Материалы и методы. Проведено одномоментное опросное исследование в форме однократного сплошного группового онлайн-анкетирования 513 фармацевтических работников из различных регионов России с использованием специально разработанной анкеты из 14 вопросов, направленных на оценку знаний о системе фармаконадзора. Применялись методы ретроспективного, сравнительного, статистического и логического анализа.

Результаты. Проведена комплексная оценка уровня знаний фармацевтических работников России в области фармаконадзора. Определены факторы, влияющие на осведомлённость специалистов. Обоснована необходимость образовательных мероприятий для повышения вовлечённости сотрудников АО в систему мониторинга безопасности лекарственных средств. Выявлен недостаточный уровень знаний фармацевтических работников об основных понятиях и процедурах фармаконадзора. Специалисты со средним специальным образованием и меньшим стажем работы продемонстрировали более низкий уровень осведомлённости. Лишь 13% участников проходили обучение по фармаконадзору, при этом большинство (около 80%) считают необходимым увеличение количества обучающих программ. Установлено влияние образования, стажа работы и должности на осведомлённость специалистов. Большинство респондентов признаёт необходимость в сообщении нежелательных реакций (НР), возникающих при приёме того или иного препарата, однако на практике уровень репортирования остаётся низким.

Заключение. Недостаточные знания основ фармаконадзора среди фармацевтических работников АО обуславливают низкий уровень репортирования ими НР. Для повышения вовлечённости специалистов в систему мониторинга безопасности лекарств необходим комплексный подход, включающий образовательные мероприятия и разработку целевых интервенций. Требуются дальнейшие исследования по разработке и оценке эффективности образовательных программ и мотивационных моделей повышения активности фармацевтических работников в сфере фармаконадзора.

Ключевые слова: фармаконадзор; фармацевтические работники; аптечные организации; нежелательные реакции; безопасность лекарственных средств

Список сокращений: АО — аптечная организация; НР — нежелательная реакция; ЛП — лекарственный препарат; МР — медицинский работник.

INTRODUCTION

Pharmacovigilance plays a key role in ensuring the drug safety. As defined by the World Health Organization (WHO), pharmacovigilance is a set of scientific studies and activities aimed at detecting, analyzing, understanding and preventing adverse effects of pharmacotherapy[1].

The Eurasian Economic Union (EAEU) Rules of Good Pharmacovigilance approved by Decision of the Council of the Eurasian Economic Commission No. 87[2] are in force in our country. The EAEU rules establish common approaches to the organization of drug

[1] World Health Organization. WHO: Pharmacovigilance: ensuring the safe use of medicines; 2004, No. WHO/EDM/2004.8. Available from: https://www.who.int/publications/i/item/WHOEDM2004.8

[2] Decision of the Council of the Eurasian Economic Commission No. 87 dated 03.11.2016 (as amended on 19.05.2022). “On approval of the Rules of good practice of pharmacovigilance of the Eurasian Economic Union”. Russian

safety monitoring, define the procedures for collecting and analyzing information on adverse drug reactions (ADRs) [1, 2]. At the national level, Federal Law No. 61-FZ "On Circulation of Medicines"[3] dated 12.04.2010 obliges all subjects of the pharmaceutical market to report to Roszdravnadzor any identified risks to patient life or health associated with the use drugs [3]. The legislation stipulates liability for a concealment or an untimely transfer of such information. The key role in the functioning of the pharmacovigilance system belongs to the pharmacy organisation (PhO). Professional standards for "Pharmacists", "Pharmacy Technicians" and "Specialists in Pharmacy Management" stipulate the duties of pharmaceutical specialists to collect information on ADRs, inform authorized bodies and advise consumers on the drug safety [5–7]. Pharmacy managers are responsible for a proper organization of pharmacovigilance in their subordinate institutions.

The effectiveness of the pharmacovigilance system aimed at detecting, evaluating and preventing ADRs of medicines depends on the involvement of all subjects of the medicines circulation, including pharmacy staff [4]. In modern conditions, when the availability of primary health care is not always fully ensured [5], and some part of the population (from 18 to 27%) is not satisfied with the quality of medical services [6, 7], the role of pharmaceutical specialists in the health care system is significantly increasing. Pharmacists and pharmacy technicians in pharmacies become the most important link between patients and the drug safety monitoring system, as they have a direct and regular contact with drug consumers. We believe that pharmacists and pharmacy technicians can play a key role in the drug safety monitoring system, as they are the ones who directly interact with consumers and are the primary link for collecting information on safety violations, including ADRs. However, despite a detailed regulation of pharmacovigilance, there remains a practical issue of insufficient awareness and engagement among pharmacy staff in this system [8–10]. This leads to a low level of the ADRs reporting by them and, as a consequence, an incomplete collection of data on the drug safety [11].

Although the pharmacy employees may occupy a key position in the ADRs reporting chainthe studies show that they are not sufficiently involved in the pharmacovigilance system [12]. It has been reported that only a small proportion of pharmacy professionals (about 5%) complete notifications of identified ADRs, while almost 1/5th (19%) of the employees never do so [13]. The established facts indicate the need to find effective ways to increase the participation of pharmacists and pharmacy technicians in drug safety monitoring which is an urgent scientific and practical task.

Similar trends are noted in the works by other authors [14, 15]. They point to significant differences in the level of participation between the representatives of the pharmaceutical industry (registration certificate holders and legal entities with clinical trial approvals), who actively identify ADRs, and PhOs staff, who treat this responsibility rather formally [14, 15]. The key problem in the organization of the ADRs data collection is a low motivation of specialists to fill in relevant notifications. The experts attribute a low activity of health professionals (HPs) in this area to a number of factors. First, it is the difficulty of identifying causal links between the intake of a particular medicine and the occurrence of ADRs. Second, it is an insufficient level of knowledge in the field of drug safety monitoring. Third, these are psychological aspects, including the fear of damaging the reputation of a medical organization or a pharmaceutical company. Finally, the lack of financial incentives to do additional work on pharmacovigilance plays an important role.

Foreign studies also confirm that one of the main reasons for a low ADRs reporting rate is the lack of awareness of pharmacovigilance among medical and pharmaceutical professionals [16–19]. A study conducted in Shiraz, Iran, showed that pharmacists have little knowledge about the process, purpose and importance spontaneous ADR reporting system. The authors concluded that education and training courses would be important to maintain, improve and enhance ADR reporting by pharmacists [20].

A survey among pharmacy students in Romania found out that 92% of future pharmacists planned to report identified ADRs, but only 48% of the final year students and 37% of the fourth-year students considered themselves sufficiently prepared or ready to do so [21]. The same Romanian study indicated that fewer than half (45.7%) of student-pharmacists had studied pharmacovigilance and 95% agreed that pharmacovigilance should be included as a separate course in their curriculum.

A Ghanaian study of doctors, nurses and pharmacists showed that although 82.8% had encountered ADRs, only 52.6% had reported them, with the pharmacists accounting for 66.7% of this population [22]. In the Ghanaian study, 85.8% of the HPs were aware of the ADRs reporting procedure and had a positive attitude, suggesting that other factors besides the awareness may influence under-reporting.

[3] Federal Law No. 61-FZ dated 12.04.2010 (latest edition) "On the Circulation of Medicines". Russian

ОРИГИНАЛЬНАЯ СТАТЬЯ
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A systematic review by V. Paudyal et al. showed that financial incentives and face-to-face educational interventions improved the quality and quantity of ADR reports compared to interventions without a face-to-face interaction [23]. The authors focus on the need to develop and test training programmes based on the principles of behavioural psychology. It is noted that most of the research has been focused primarily on HRs, while the role of patients in pharmacovigilance remains poorly understood.

Thus, the problem of the insufficient involvement of pharmacy workers in the pharmacovigilance system is relevant not only for Russia, but also for many other countries. Consequently, it is critically important to evaluate the knowledge level of pharmacy workers in Russia regarding the safety monitoring of drugs.

THE AIM of the study was assessing the knowledge level of pharmacy workers in the Russian Federation regarding pharmacovigilance fundamentals and to identify factors influencing their awareness and participation in the drug safety monitoring system.

MATERIALS AND METHODS

The authors conducted a single-point survey study in the form of a solid group online questionnaire survey. This method was chosen for a rapid collection of the primary information, as it allows interviewing a large number of respondents in a short period of time and with minimal material costs. To conduct the study, an anonymous online questionnaire was developed to collect and analyze the responses of pharmaceutical specialists. The following is a typical form of the questionnaire, consisting of 14 questions with suggested answer options (Table 1).

The survey was conducted online by Sechenov University between September 13 and 30, 2023. The information about the opportunity to voluntarily participate in the questionnaire, an invitation to participate and a link to the questionnaire were emailed to 700 pharmacy workers (from 18 Russian regions) who had undergone training or certification at Sechenov University. Prior to the main study, a pilot test involving 10 pharmacy workers (5 pharmacists and 5 pharmacy technicians) was conducted. In the course of the pilot test, the following were evaluated: a comprehensibility of the questions wording, an unambiguous interpretation of the terms used, and a logical structure of the questionnaire. Based on the results of preliminary testing, the sequence of questions in the questionnaire was optimized, the validity of the questionnaire and the adequacy of the terms used were confirmed.

This study did not require a submission of a biomedical ethics committee approval or other documents because it contained anonymized data. The questions whose content did not meet ethical standards had not been included in the study. Completed anonymous questionnaires were considered as an informed consent from pharmacy workers to participate in the study and a permission to process the provided data. The anonymity of respondents was a mandatory condition of the survey; no personal information (surname, name, patronymic, gender, age) and contact details were collected in the course of the study.

To determine a statistically representative number of respondents (a number of questionnaires), a random non-repeat sampling method was used. The margin of error was set at 5%. To ensure reliable results, at least 400 questionnaires needed to be processed [24, 25]:

$$n = \frac{22}{(4 \times 0.052)} = 400$$

As a part of the survey, 700 emails were sent to potential respondents. The authors received 550 completed questionnaires, which was 78.6% of the total number of questionnaires sent out. The questionnaires were selected for the analysis according to the following criteria: 1) “completeness” – presence of responses to all mandatory question 2) “correctness” – a logical consistency of answers, the absence of obvious mistakes in filling in. As a result of applying these criteria, 37 questionnaires with incomplete or incorrect answers were excluded. Thus, the final sample for the analysis was 513 questionnaires (73.3% of the initially sent ones).

The non-parametric Pearson’s chi-square test (χ^2) was used to assess the statistical significance of differences between the groups. This method had been chosen as the most appropriate for analyzing the categorical data obtained from the questionnaires. The differences between the responses of different groups were investigated using conjugation tables. For each comparison, null and alternative hypotheses were formulated. The null hypothesis implied the absence of differences between the groups, while the alternative hypothesis implied the presence of statistically significant differences. A significance level of p=0.05 was set for all statistical tests. At p <0.05 the differences were considered statistically significant, which allowed rejecting the null hypothesis about the absence of differences between the groups. The data analysis was performed using MS Excel 2019 software package (Microsoft Corp., USA).

RESULTS AND DISCUSSION

Based on the analysis of the received questionnaires, the characteristics of the study participants were compiled (Table 2). The majority of the respondents (53.0%) had secondary specialized education, 39.8% had higher pharmaceutical education, and 7.2% were students of medical universities and colleges. The average work experience of the survey participants was 13.86 years. The sample of the respondents is represented by various categories of pharmaceutical specialists, including front desk specialists (62.0%), supervisors (32.0%), representatives of other job positions (pharmacy technologists, pharmacy analysts, consultants). More than half of the respondents (56.9%) work in private pharmacies. The vast majority (94.0%) are employees of pharmacy chains, only 6.0% of the respondents work in individual PhOs; 89.0% of the participants work in urban areas, 11.0% in rural settlements.

Approximately half of the respondents, regardless of the level of education, experience, position, or pharmacy type correctly identified that the term "pharmacovigilance" refers to the type of activities aimed at identifying, assessing, understanding and preventing undesirable consequences of the drug (Fig. 1). However, more than 40% of respondents incorrectly believed that pharmacovigilance is a body of a state supervision and control over compliance with the legislation of the Russian Federation in the sphere of drug circulation. Only a small proportion of the respondents chose other answer options, such as: "the science that studies (using epidemiological methods), the efficacy, safety and specifics of the drug use in real-life conditions at the level of a population or large groups of people" (3.43% with higher education and 6.62% with secondary specialized education) and "the research and activities related to the consideration of any problems associated with a medicinal product" (2.45 and 1.84%, respectively).

Herewith, about 55% of specialists with higher education were well acquainted with the term "adverse drug reaction" (Fig. 2), compared to 37.50% of those with secondary specialized education (χ^2=26.28; p <0.05). The analysis of the answers depending on the work experience showed that the level of familiarity with the term "adverse drug reaction" increases as the professional experience is acquired. Among the specialists with the work experience up to 1 year, only 25% indicated that they were well acquainted with the term, whereas among the professionals with more than 10 years of work experience – 52.69% (χ^2=18.09; p <0.05).

This trend indicates that practical experience and the accumulation of knowledge in the course of work contribute to a better understanding of the basic concepts of pharmacovigilance. Pharmacy supervisors demonstrated greater familiarity with the term "adverse drug reaction" (54.88% were well acquainted) than front desk specialists (37.54%, χ^2=27.30; p <0.05). The analysis of responses according to the pharmacy location (urban or rural) showed that the level of familiarity with the term "adverse reaction" was slightly lower among rural pharmacy specialists (38.60% were well familiar) compared to urban pharmacy (44.08% χ^2=6.95; p <0.05). The proportion of those who had never heard of the term was also higher among the specialists in rural pharmacy (8.77 *vs.* 2.41% in urban PhOs).

The level of familiarity with the ADR reporting (Fig. 3) form varies according to the education, experience, position, pharmacy ownership, pharmacy chain affiliation and location. Among the respondents with higher education, 75% were familiar with the form, whereas among those with secondary specialized education the figure was 55.15% (χ^2=20.22, p <0.05). The differences in the level of familiarity with the increasing work experience and between the employees of individual and chain pharmacies were not statistically significant (χ^2=4.783, p >0.05 and χ^2=1.80, p >0.05). Pharmacy supervisors show a higher level of familiarity with the form (76.22%) compared to the front desk specialists (56.47%; χ^2=18.73, p <0.05). In public PhOs, 68.33% of the employees were familiar with the form, while in private PhOs, 58.90% were familiar with the form (χ^2=4.83, p <0.05).

A similar trend was observed with regard to the awareness of where to obtain an adverse drug reaction reporting form (Fig. 4). The level of awareness of where to obtain the adverse drug reaction reporting form is higher among the people with higher education (68.14%) compared to the people with secondary specialized education (41.54%; χ^2=33.50, p <0.05). The percentage of the pharmacy specialists familiar with the reporting form increased with experience, from 55.26% among the specialists with the experience up to 1 year, to 67.31% among those with more than 10 years of experience (χ^2=21.05, p <0.05). The study found out that pharmacy supervisors showed higher awareness than front desk specialists regarding familiarity with the form (76.22 *vs.* 56.47%; χ^2=18.27, p <0.05) and how to obtain it (67.68 *vs.* 43.85%; χ^2=24.66, p <0.05). The employees of public and non-chain pharmacies were more aware of how to obtain an adverse drug reaction reporting form (63.80 and 77.42%) than the employees of private and chain pharmacies (42.47 and 50.00%; χ^2=27.91, p <0.05). Pharmaceutical specialists from the urban pharmacies were more familiar with the form (63.60%) and knew where to obtain it (53.07%) compared to the pharmacy staff from the rural areas (57.89% and

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40.35%, respectively), but the differences were not statistically significant (χ^2=0.6821, p >0.05 and χ^2=3.3095, p >0.05).

The majority of pharmacy professionals recognize the need to report identified ADRs (Fig. 5). Among the respondents with higher education, 61.76% believed that ADRs should be always reported, while among the specialists with secondary specialized education this figure was slightly lower – 58.82% (χ^2=1.739, p >0.05, the differences not significant). The pharmaceutical specialists with 2 to 5 years of work experience showed the highest willingness to always report ADRs – 74% (χ^2=12.70, p <0.05). The pharmacy supervisors and front desk specialists equally recognized the need to report ADRs (60.37 and 60.25%, respectively). No statistically significant difference was found out between the private and public pharmacy employees (χ^2=3.43, p <0.05). However, it was established that in the individual pharmacy chains, 67.74% of employees believed that ADRs should be always reported, while in the chain pharmacies this figure was only 32.16% (χ^2=19.229, p <0.05). At the same time, it should be noted that 34.02% of the employees in the chain pharmacies believe that it is not necessary to report ADRs, which is an alarming signal.

When asked to correctly identify the government body collecting information on ADRs in Russia, the majority of the respondents correctly stated that it was Roszdravnadzor. However, the level of awareness varied depending on several factors. Among the specialists with higher education, 87.25% gave a correct answer, while among the specialists with secondary specialized education this figure was 70.22% (χ^2=20.85, p <0.05). The work experience also influenced their awareness: with the increasing work experience, the percentage of pharmacists who correctly identified Roszdravnadzor, increased (from 63.16% among those with up to 1 year of experience to 81.92% among those with more than 10 years of experience; χ^2=19.96, p <0.05). The Pharmacy supervisors showed higher awareness (85.37%) compared to the front desk specialists, 71.29% (χ^2=12.29, p <0.05).

The level of pharmacy professionals' awareness about the pharmacovigilance regulation at the EAEU level varies depending on different factors (Fig. 6). Specialists with higher education are better informed on this issue – 38.24% are well aware of it, while 37.25% have superficial knowledge. Among the specialists with secondary specialized education, only 25% are well informed, 37.13% have superficial knowledge and 37.87% have no knowledge at all (χ^2=13.10, p <0.05). The work experience has a positive effect on the level of knowledge. While among the employees with up to 1 year of experience only 22.37% have good knowledge of pharmacovigilance regulations at the EAEU level, among the specialists with more than 10 years of experience this indicator reaches 33.46%. At the same time, with the increasing work experience, the share of those who do not know about it at all decreases (χ^2=8.76, p >0.05). The Pharmacy supervisors are significantly better informed (39.02% are well aware) than ordinary first desk specialists – 24.29% (χ^2=13.16, p <0.05). The differences in awareness between public and private, individual and chain, urban and rural pharmacy specialists are not statistically significant (χ^2=5.34, p >0.05; χ^2=4.01, p >0.05; χ^2=2.56, p >0.05).

The results of the study showed that only 13.24% of the respondents with higher education and 14.71% with specialized secondary education had received full-fledged training on pharmacovigilance during their professional career. The majority of the specialists either had not studied pharmacovigilance at all (59.80% with higher education and 62.13% with secondary education) or attended only separate lectures (26.96 and 23.16%, respectively). The analysis of the data according to the work experience revealed that only 11.84% of the staff with up to 1 year of experience had received training in pharmacovigilance. With the increasing work experience, the situation improves somewhat, but even among the specialists with more than 10 years of service, the share of those who have received training is only 13.85%, while the share of those who have not received training is 58.08%. Nevertheless, the differences between the groups by work experience are not statistically significant (χ^2=8.64, p >0.05). Pharmacy supervisors are more likely to be trained in pharmacovigilance (15.85%) than the rank and file first desk specialists (12.93%). However, among the supervisors, more than half (51.83%) had never received training on pharmacovigilance either (χ^2=9.15, p <0.05). A comparison of responses from the employees of public and private PhOs showed that the employees in private PhOs are more likely to be trained in pharmacovigilance (17.81 *vs.* 8.60% in public PhOs; χ^2=9.18, p <0.05). However, the proportion of the untrained employees was higher in public PhOs (66.06%) than in private pharmacies (57.53%). It is worth noting that individual pharmacies had a significantly higher rate of pharmacovigilance training (25.81%) than chain pharmacies (13.07%) (χ^2=4.29, p <0.05). At the same time, the proportion of those who had attended only separate lectures was lower in individual pharmacies (12.90 *vs.* 25.73% in chain pharmacies; χ^2=4.53, p <0.05). The differences in the number of people trained in pharmacovigilance and attending individual lectures between urban and rural pharmacies are not statistically significant (χ^2=1.92, p >0.05). However, the overall situation is about the same – more than half of the workers in both urban and rural PhOs have not been trained in pharmacovigilance at all.

Table 1 – Questionnaire form for respondents' survey

No	Question	Answer options
	First of all, we ask you to tell us a little bit about yourself:	
1	What kind of pharmaceutical education do you have?	☐ Higher; ☐ Secondary specialized; ☐ Medical student: University, college.
2	What is your work experience in the speciality (years)?	Specify: _____
3	What is your "job position" in the pharmacy	☐ Supervisor; ☐ Front desk specialist; Other (specify): _____.
	What pharmacy are you working in?	
4	By ownership form:	☐ Public; ☐ Private.
5	In relation to pharmacy chains:	☐ Chain; ☐ Individual.
6	By location:	☐ City; ☐ Rural settlement.
	Further on, we ask you to answer a number of questions related to pharmacovigilance:	
7	Do you think pharmacovigilance is…	☐ A science that studies the efficacy, safety, and patterns of medicines use in real-world settings at the population or large group level using epidemiological methods; ☐ A type of activity aimed at identifying, assessing, understanding and preventing adverse drug reactions; ☐ Research and activities related to taking into account any concerns about drugs; ☐ The body of state supervision and control over compliance with the legislation of the Russian Federation in the sphere of the drug circulation.
8	How are you familiar with the term "adverse drug reaction"?	☐ Well acquainted – I have a full understanding; ☐ Familiar – I have a basic understanding; ☐ Heard of the term – I can't define it; ☐ Never heard of the term.
9	Are you familiar with the adverse drug reaction reporting form for medical professionals?	☐ Yes; ☐ No.
10	Do you know of a location where this form can be obtained?	☐ Yes; ☐ No.
11	What body collects information on adverse drug reactions in the Russian Federation?	☐ Ministry of Health of Russia; ☐ Rospotrebnadzor; ☐ Roszdravnadzor; ☐ Rosstat.
12	Do you know that pharmacovigilance is regulated at the EAEU level?	☐ Yes; ☐ No. ☐ I know, but only superficially.
13	Have you received training in pharmacovigilance?	☐ Yes; ☐ No; ☐ Attended separate lectures.
14	Do you think there is a need for more training programmes for pharmaceutical specialists in the identification and reporting of adverse drug reactions?	☐ I agree; ☐ I disagree.

Note: PhO – pharmacy organization.

Table 2 – Characteristics of study participants

Survey question		Response	Number and proportion of respondents, *n* (%)
What kind of pharmaceutical education do you have?		Higher	204 (39.8%)
		Secondary specialized	272 (53.0%)
		Medical student: University, college	37 (7.2%)
What is your position' in the PhO?		Supervisor	318 (62.0%)
		Front desk specialist	164 (32.0%)
		Other (specify)	31 (6.0%)
What PhO are you working in?	By ownership form:	Public	221 (43.1%)
		Private	292 (56.9%)
	In relation to pharmacy chains:	Chain	482 (94.0%)
		Individual.	31 (6.0%)
	By location:	City	457 (89.0%)
		Rural settlement.	56 (11.0%)

Note: PhO – pharmacy organisation.

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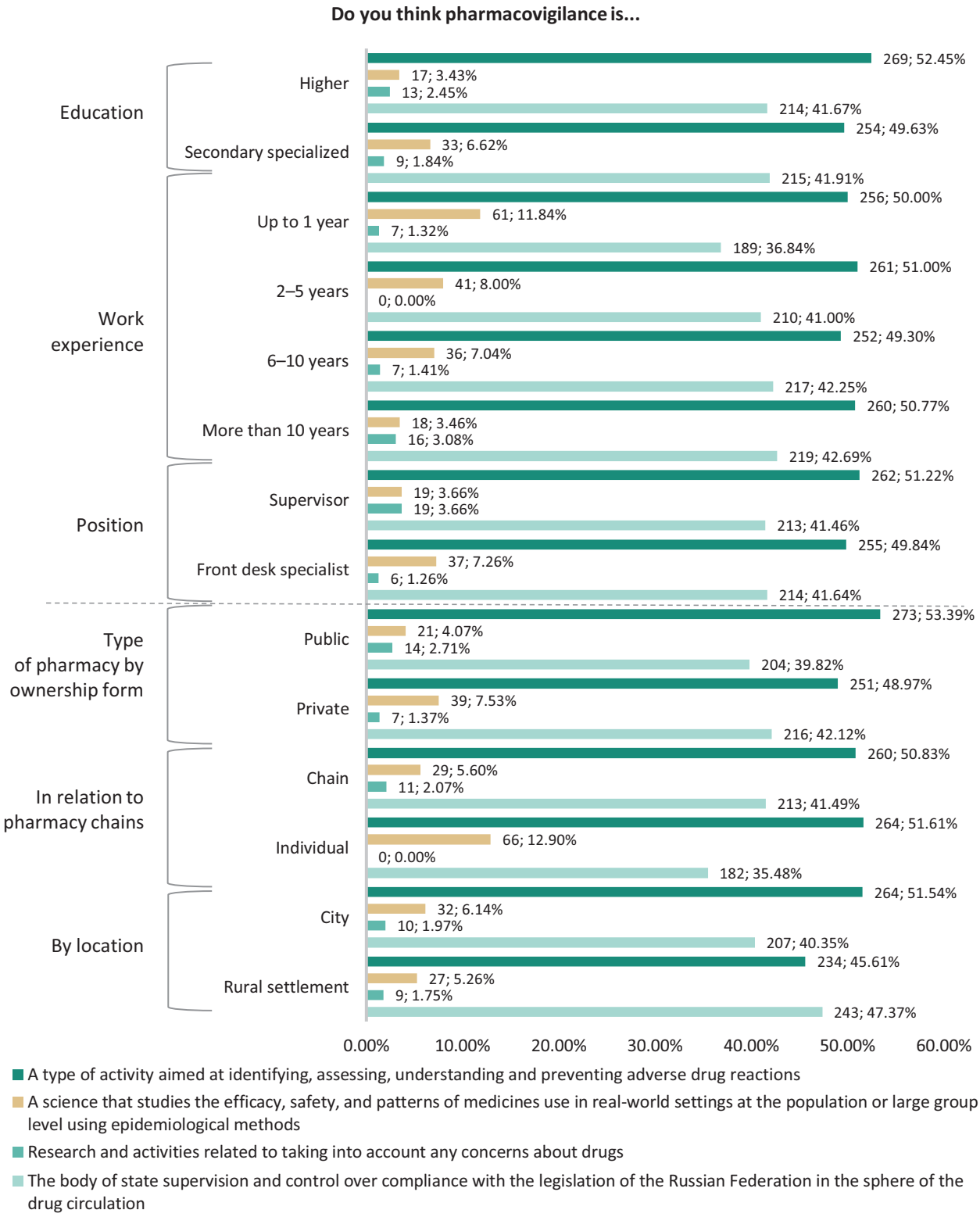

Figure 1 – Distribution of respondents' answers to the question: "Do you think pharmacovigilance is..."

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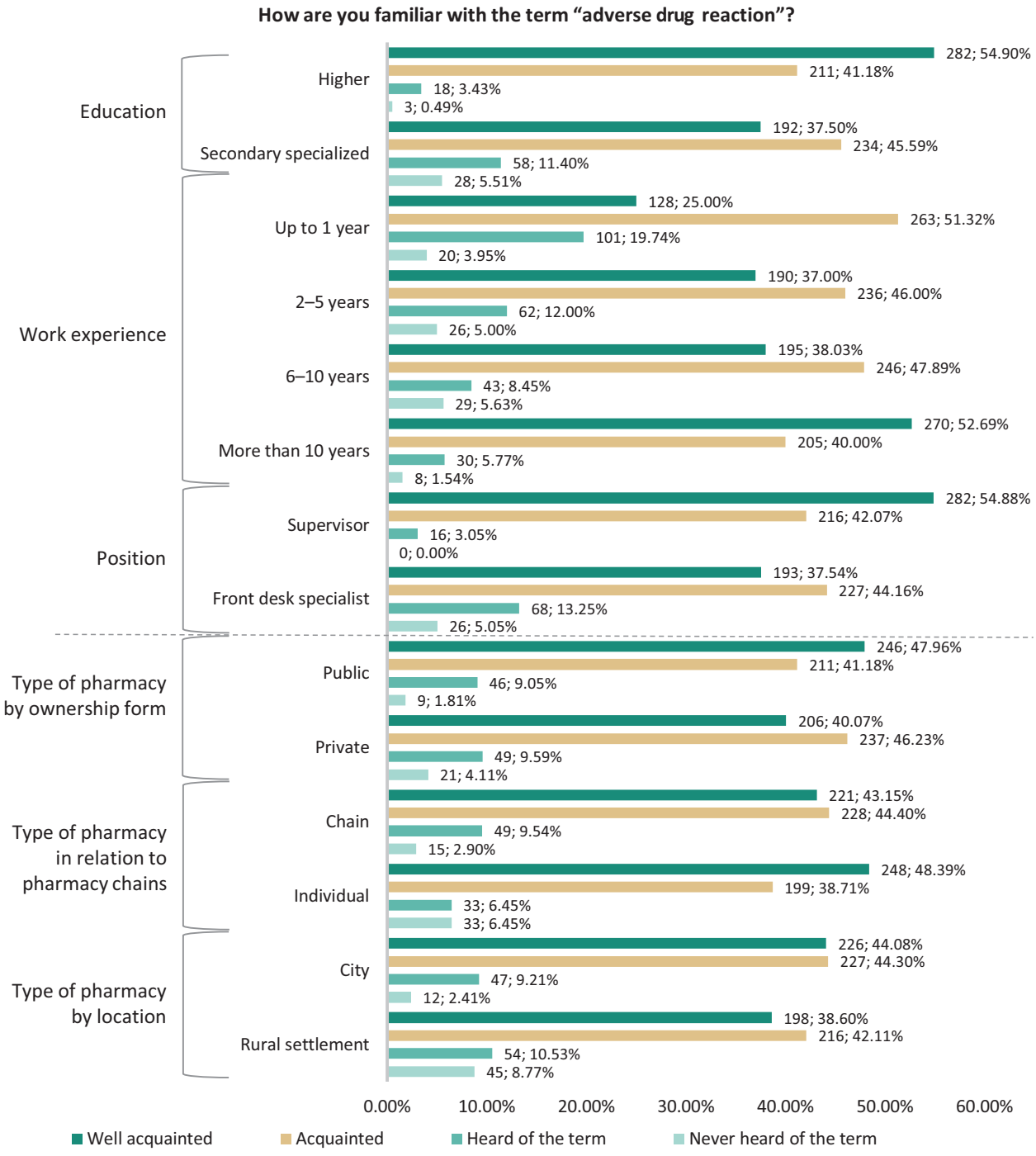

Figure 2 – Distribution of respondents' answers to the question: "How familiar are you with the term "adverse drug reaction"?

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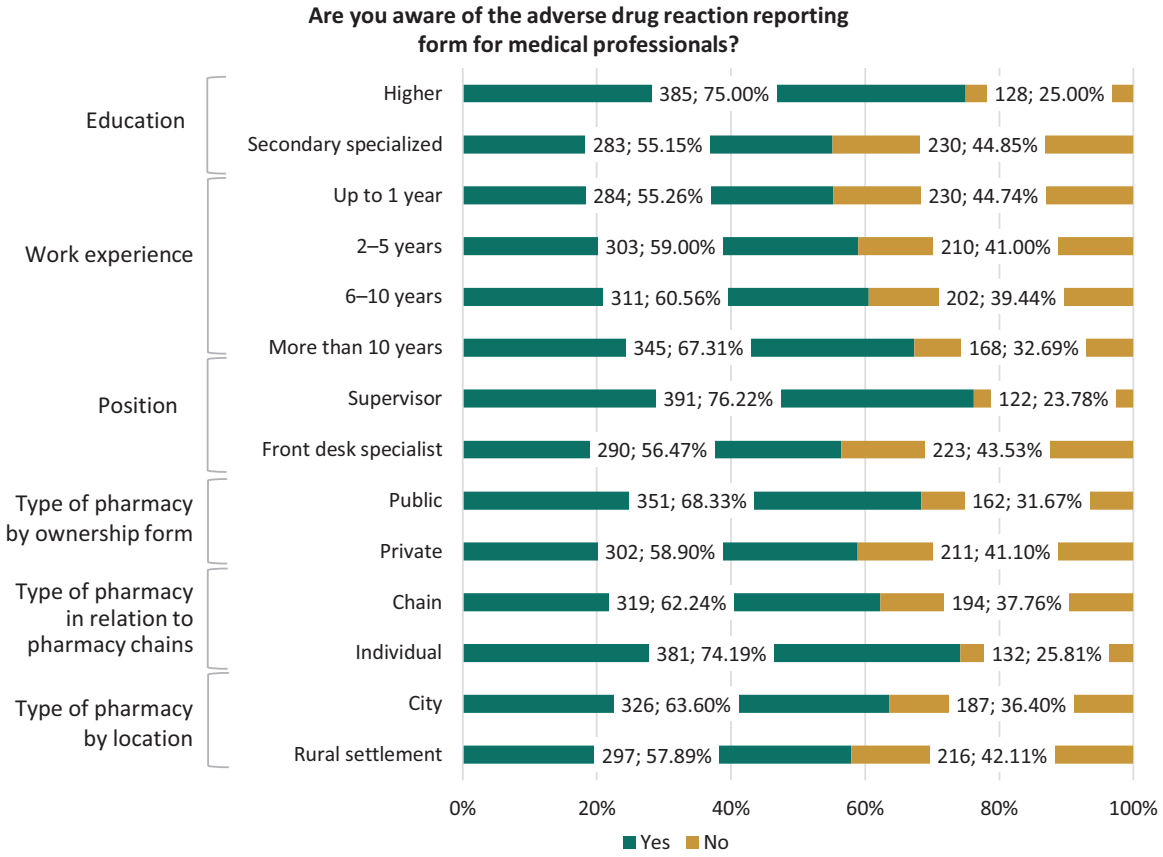

Figure 3 – Distribution of respondents' answers to the question: "Are you aware of the adverse drug reaction reporting form for medical professionals?"

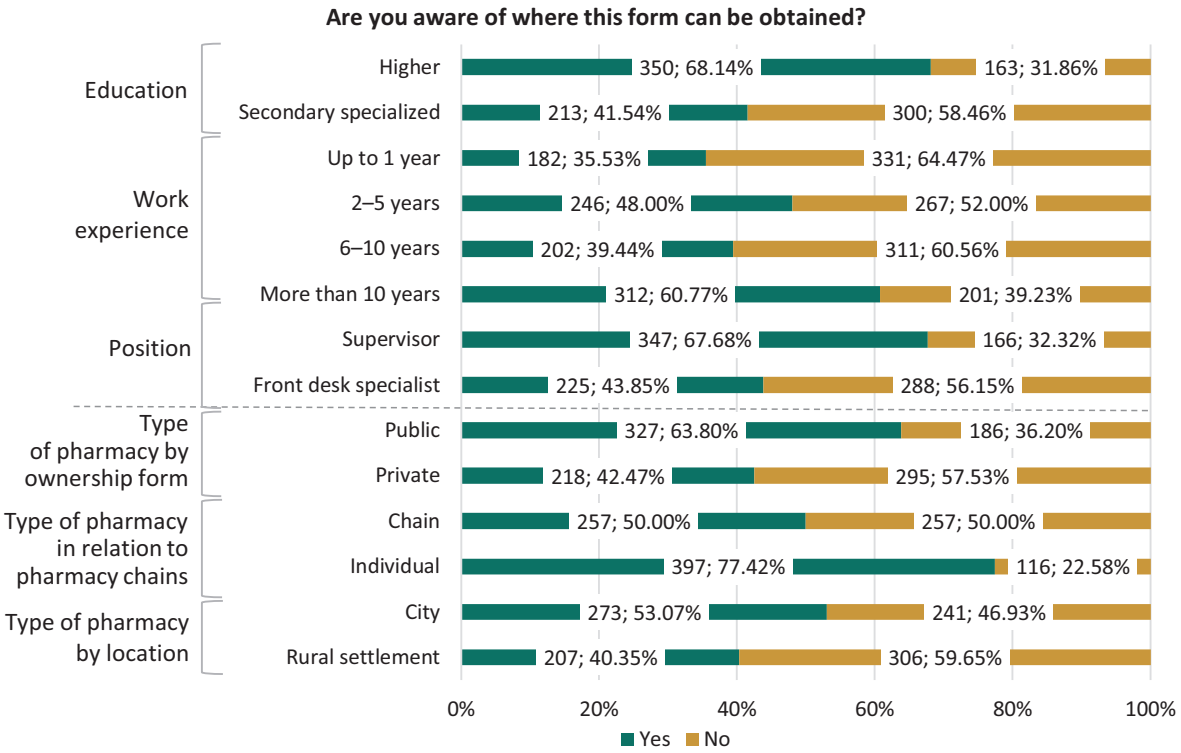

Figure 4 – Distribution of respondents' answers to the question: "Do you know where this form can be obtained?"

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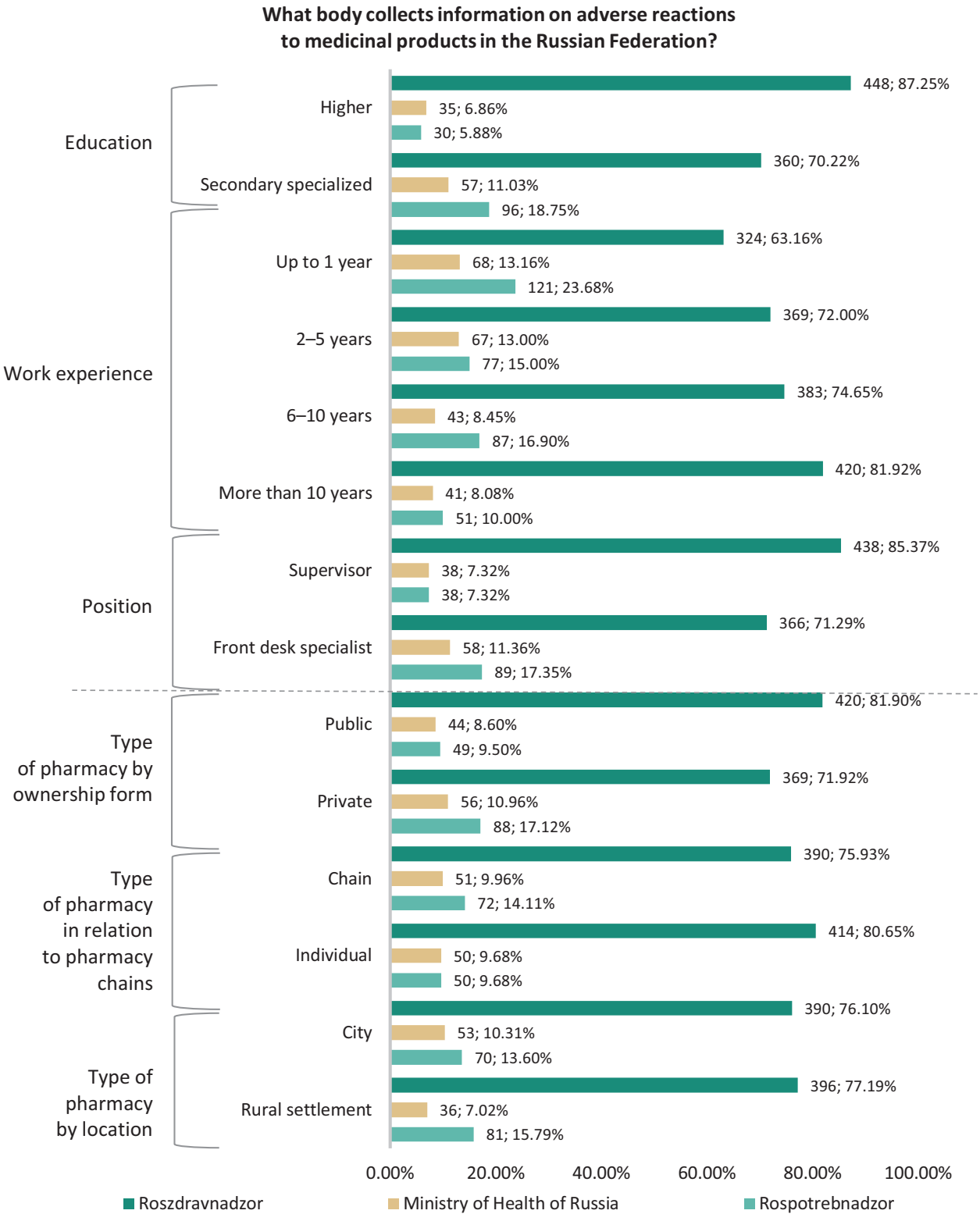

Figure 5 – Distribution of respondents' answers to the question: "What body collects information on adverse drug reactions in the Russian Federation?"

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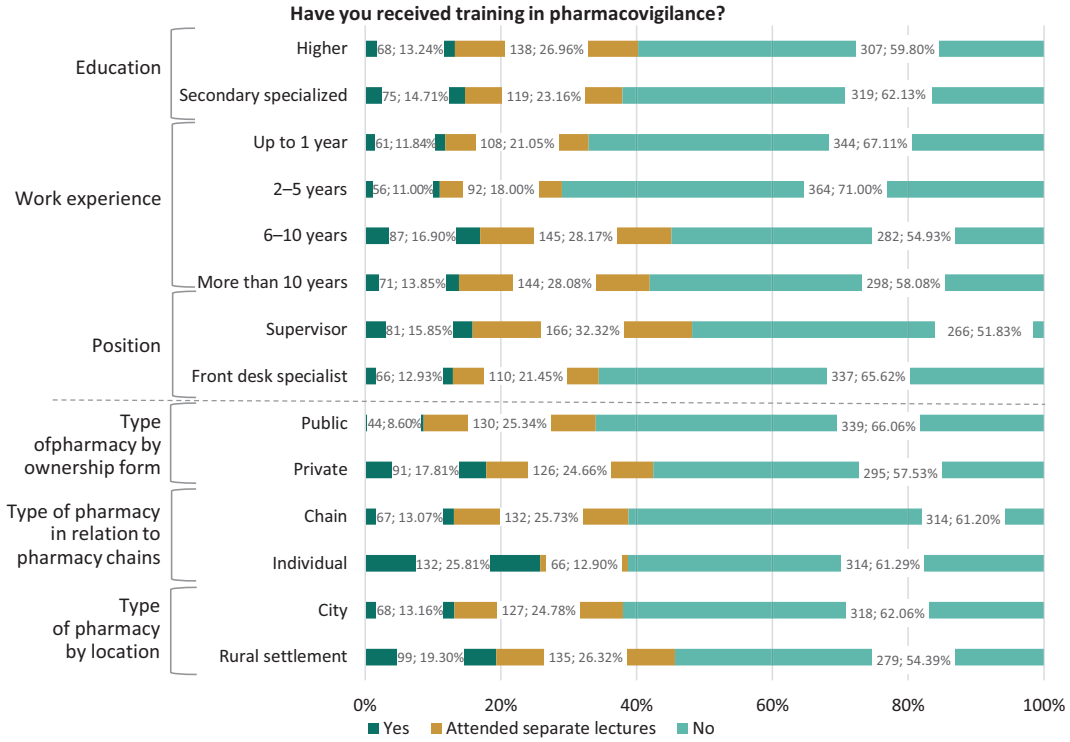

Figure 6 – Distribution of respondents' answers to the question: "Have you received training in pharmacovigilance?"

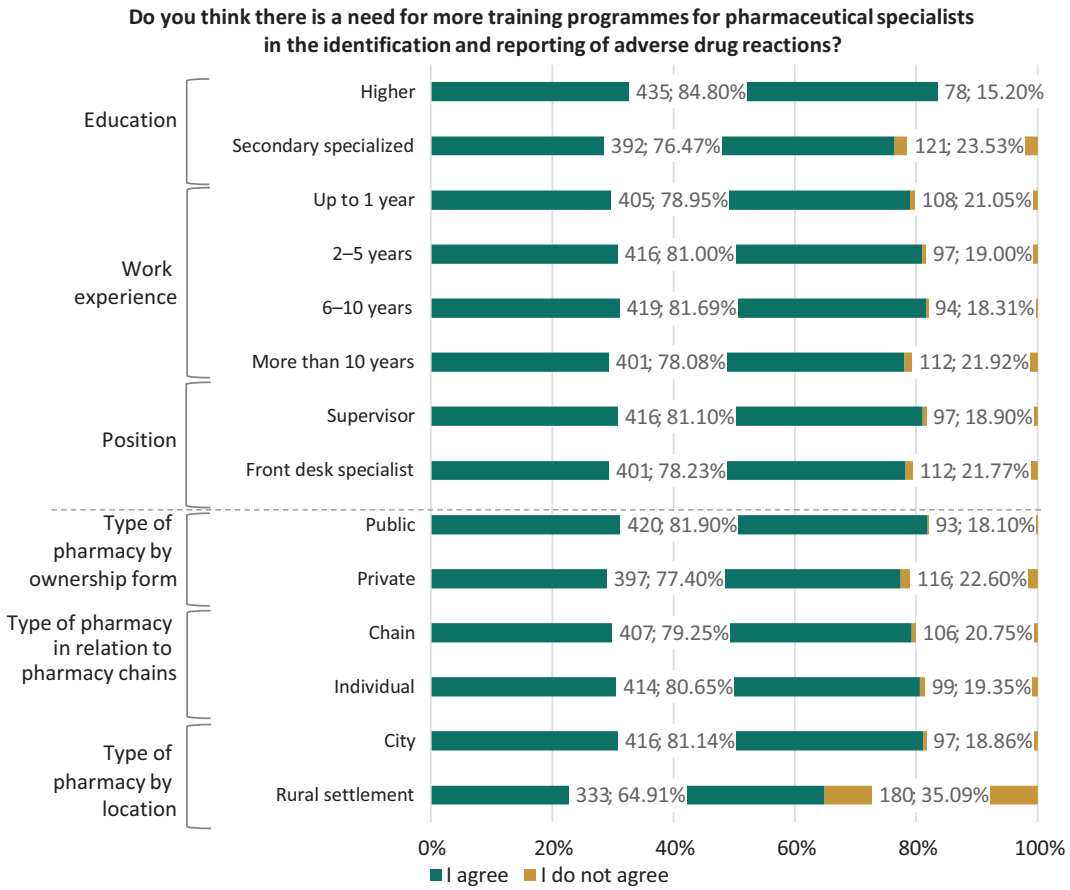

Figure 7 – Distribution of respondents' answers to the question: "Do you think there is a need for more training programs for pharmaceutical specialists on the identification and reporting of adverse drug reactions?"

The vast majority of pharmacy workers, regardless of various factors, believe that an increase in the number of training programmes aiming at the detection and reporting of ADRs is necessary (Fig. 7). Among the professionals with higher education, 84.80% agreed with this statement, and among those with secondary specialized education, 76.47% agreed (χ^2=4.57, p <0.05). The analysis of the answers depending on the work experience shows that the need for training programmes is high in all the groups. The proportion of those who agree varies slightly, from 78.08% among the specialists with more than 10 years of experience to 81.69% among the professionals with 6 to 10 years of work experience. The Pharmacy supervisors are slightly more likely to agree with the need to increase the number of training programmes (81.10%) than first desk specialists (78.23%), but this difference is not statistically significant (χ^2=0.564, p >0.05). The majority of the public and private pharmacy specialists agree on the need for more training programmes (81.90 and 77.40%). No significant differences were found out between the chain and individual pharmacies on this issue. The share of those who agree with the need for an additional training is 79.25% in the chain pharmacies and 80.65% in the individual pharmacies. Among the employees of the urban pharmacies, a support for the idea of increasing the number of training programmes is noticeably higher (81.14%) than among the employees of the rural pharmacies – 64.91% (χ^2=8.38, p <0.05).

The data gained are consistent with other studies in the field, which also show a lack of pharmacovigillance awareness among pharmacists, which negatively affects their participation in the ADRs reporting system. Knowledge of specific aspects of the drug safety monitoring system varies according to the education level, work experience and position. However, even among the specialists with higher education and extensive experience, there are still significant gaps in knowledge of the basics of pharmacovigilance, indicating the need to introduce additional educational programs at the training stage and in the postgraduate education. The availability of a large number of educational programs on pharmacovigilance does not guarantee their coverage of a wide range of specialists. Perhaps the reasons lie in the insufficient motivation, time constraints and lack of information about training opportunities or organizational barriers within pharmacies. Foreign studies show that financial incentives and face-to-face educational activities based on the principles of behavioral psychology are effective measures to increase the activities of specialists in this field. In the future, it is important to conduct additional research aimed at identifying specific barriers and developing targeted interventions for different groups of pharmaceutical professionals. A comprehensive approach combining educational, motivational and organisational measures could significantly improve the quality and quantity of ADRs reporting, which in turn, would improve the pharmacovigilance system as a whole and increase the safety of drug therapy for the public.

Study limitations

The sample was drawn from the professionals who had been trained and certified at Sechenov University (Moscow, Russia). This could lead to the sampling bias, as respondents may be more motivated or informed than the general population of pharmacy professionals in Russia. Conducting the survey in an online format may have limited the participation of professionals who do not have a regular access to the internet. The survey was based on the respondents' self-reports, so, there may be inaccuracies related to the subjective assessment of their own knowledge level. The study was cross-sectional, i.e. the data were collected at one point in time, which makes it impossible to trace the dynamics of changes in the knowledge level of pharmacy professionals over time.

CONCLUSION

The results of this study indicate inadequate knowledge of pharmacovigilance fundamentals among pharmacy workers. Education work experience and position are important factors affecting the level of their pharmacovigilance knowledge. Professionals with higher education, longer work experience and those in supervisor positions show a higher level of knowledge compared to those with secondary specialized education, shorter work experience and those in front desk positions. However, it is the PhOs front desk specialists who are in direct contact with patients and are in a position to be the first to identify ADRs. The lack of awareness of this specialists' category (only 37.54% are familiar with the term "adverse drug reaction") may significantly reduce the effectiveness of the pharmacovigilance system. This may be due to the lack of awareness of the reporting procedure, the lack of motivation and organizational barriers.

Despite the availability of educational programs, most specialists do not have special training in this area, and in practice, the ADRs reporting level remains low. The data obtained show that only 13.24% of respondents with higher education and 14.71% with specialized secondary education have been trained in pharmacovigilance. At the same time, the vast majority of survey participants (84.80% with higher education and 76.47% with secondary specialized education)

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consider it necessary to increase the number of training programs on ADR detection and reporting. The solution to this problem requires a comprehensive approach that includes educational activities, financial incentives, and the development of theoretically grounded interventions targeted at the pharmacy staff. Training should be practice-oriented and take into account the specifics of work in pharmacies of various types (public, private, chain, individual). The use of modern training technologies, including distance and online formats, will make it possible to reach more specialists and increase the effectiveness of training. Support from the pharmacy management plays a key role in creating a favorable environment for the staff training, providing the necessary resources and time to carry out their respective responsibilities. The implementation of a set of educational activities can help to improve the quality of spontaneous reports and increase their number, which will contribute to the improvement of the pharmacovigilance system in the Russian Federation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Roza I. Yagudina – development of the research concept, discussion of results, critical evaluation of the material; Olga L. Listova – development of the research concept, discussion of results, critical evaluation of the material; Adelya R. Umerova – analysis of literature sources, collection and analysis of material; Kirill A. Kopeyka – collection and analysis of material, statistical processing of results, writing and editing of the manuscript.
All the authors confirm that their authorship meets the international ICMJE criteria (all the authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before the publication).

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AUTHORS

Roza I. Yagudina – Doctor of Sciences (Pharmacy), Professor, Head of the Department of Organisation of Drug Supply and Pharmacoeconomics, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-9080-332X. E-mail: yagudina@mail.ru

Olga L. Listova – Candidate of Sciences (Pharmacy), Deputy Minister of Health of the Stavropol Territory (Russia). E-mail: lol@mz26.ru

Adelya R. Umerova – Doctor of Sciences (Medicine), Professor, Head of the Department of Clinical Pharmacology, Astrakhan State Medical University. ORCID ID: 0000-0002-3129-2443. E-mail: klinfarm_agma@mail.ru

Kirill A. Kopeyka – Assistant of the Department of Organization of Drug Supply and Pharmacoeconomics, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0003-3581-0620. E-mail: kirillkopeika@gmail.com

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Analysis of antioxidant properties of dibenzylideneacetone derivatives using quantum chemical parameters of the molecule

E.T. Oganesyan, V.M. Rukovitsyna, D.I. Pozdnyakov, S.L. Adzhiakhmetova

Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University,
11, Kalinin Ave., Pyatigorsk, Russia, 357532

E-mail: rukovitsina.vika@mail.ru

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The antioxidant activity of 10 synthetic dibenzylideneacetone (DBA) derivatives has been studied. Except for the base compound, all other derivatives contain electron-bearing substituents, such as OH and OCH_3, on aromatic fragments. Formally, DBA can be considered a system containing a cinnamoyl moiety linked to a substituted styrene residue.

The aim of the study was to investigate antioxidant properties of the synthesized DBA derivatives and to analyze their quantum chemical parameters revealing the regularities of the «structure–activity» relationship.

Materials and methods. For the carbon atoms of the analyzed compounds, Mulliken charges (AUs), bond numbers (Nms), an unsaturation index (IUA), a free valence index (Fr), a theoretical valence (TV) and the electron density were determined. All calculations were performed on a workstation with an Intel Xeon E5-1620 3.5GHz processor and 20GB RAM using a semi-empirical RM7 method and the WinMopac 2016 software. Ionization energies were calculated using the WinMopac 7.21 software for the studied compounds. The Way2Drug PASS Online predictive program was used to evaluate their possible pharmacological activity. The antioxidant activity was evaluated both *in vitro* (using DPPH and ABTS assays) and *in vivo* (by measuring a superoxide dismutase (SOD) activity and the concentration of products reacting with 2-thiobarbituric acid (TBA-AP) in Wistar rats without pathology).

Results. A preliminary analysis of the possible types of the biological activity of the synthesized DBA derivatives was performed using the Way2Drug PASS Online program. This analysis showed that all the structures have an antitumor activity, which is apparently due to their antioxidant properties. This type of activity was experimentally confirmed by four tests: by DPPH and ABTS *in vitro* and the effect on SOD and by the TBA-AP in animals. The analysis of the data allowed us to determine that the most active antioxidants are compounds 5, 6, and 8, which contain phenolic hydroxyl groups. In these compounds, the 8-hydroxy group is surrounded by OCH_3 radicals on both sides, making it spatially blocked and, therefore, the phenoxyl radical it forms is the most stable. A comparison of the values of the quantum chemical parameters found shows that the most informative for studying the structure–activity relationship are the Mulliken charges (AUs), electron density on carbon atoms, and also their IUA and Fr.

Conclusion. The structural features of the 1,5-diphenylpent-1,4-diene-3-one derivatives and the nature of free radicals formed during biological tests indicate that this class of compounds can be considered promising as antioxidants.

Keywords: quantum chemical parameters, antioxidants, 1,5-diphenylpent-1,4-dien-3-one derivatives, antitumor properties.

Abbreviations: ROS — reactive oxygen species, DPPH — 2,2-diphenyl-1-picrylhydrazyl; ABTS — diammonium salt of 2,2'-azino-bis[3-ethylbenzthiazoline-6-sulfonic acid]; SOD — superoxide dismutase; TBA-AP — thiobarbituric acid active products; IP — ionization potential.

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Анализ антиоксидантных свойств производных дибензилиденацетона с использованием квантовохимических параметров молекул

Э.Т. Оганесян, В.М. Руковицина, Д.И. Поздняков, С.Л. Аджиахметова

Пятигорский медико-фармацевтический институт –
филиал федерального государственного бюджетного образовательного учреждения
высшего образования «Волгоградский государственный медицинский университет»
Министерства здравоохранения России,
357532, Россия, Пятигорск, пр-кт Калинина, д. 11

E-mail: rukovitsina.vika@mail.ru

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Изучена антиоксидантная активность 10 синтетических производных дибензилиденацетона (ДБА), молекула которого представляет собой (1E, 4E)-1,5-дифенилпента-1,4-диен-3-он. За исключением родоначального соединения, остальные содержат в ароматических фрагментах электронодорные заместители — OH, OCH_3. Формально молекулу можно рассматривать как систему, содержащую циннамоильный фрагмент, связанный с остатком замещённого стирола.

Цель. Изучение антиоксидантных свойств синтезированных производных ДБА и их квантовохимических параметров с целью выявления закономерностей взаимосвязи «структура–активность».

Материалы и методы. Для атомов углерода анализируемых соединений определены Малликеновские заряды (а.е.), связевые числа (Nμ), индекс ненасыщенности (IUA), индекс свободной валентности (Fμ), теоретическая валентность (Vμ) и электронная плотность. Все расчёты осуществлены на рабочей станции с процессором IntelXeonE5-1620 3,5 ГГц, 20 Гб оперативной памяти с использованием полуэмпирического метода PM7 (программа WinMopac 2016). Для изучаемых соединений по программе WinMopac 7.21. был рассчитан показатель энергии ионизации. Для оценки возможной фармакологической активности использовалась прогностическая программа Way2Drug PASS Online. Антиоксидантную активность анализируемых соединений оценивали *in vitro* (DPPH и ABTS тесты), а также *in vivo* (определение активности супероксиддисмутазы (СОД) и концентрации активных продуктов, реагирующих с 2-тиобарбитуровой кислотой (ТБК-АП) у крыс линии Wistar без патологии).

Результаты. Предварительно был осуществлён анализ возможных видов биологической активности синтезированных производных ДБА по программе Way2Drug PASS Online который показал, что для всех структур характерна противоопухолевая активность, что, по-видимому, обусловлено в том числе и антиоксидантными свойствами. Данный вид активности экспериментально определялся по 4 тестам — DPPH и ABTS (*in vitro*) и по влиянию на СОД и ТБК-АП (на животных). Анализ полученных данных позволил установить, что наиболее активными антиоксидантами являются соединения 5, 6 и 8, содержащие фенольные гидроксигруппы. В структуре 8 гидроксигруппа с обеих сторон окружена OCH_3-радикалами, то есть она является пространственно затруднённой и, следовательно, образуемый им феноксильный радикал наиболее устойчив. Сопоставление значений найденных квантовохимических параметров показывает, что наиболее информативными с точки зрения изучения взаимосвязи «структура–активность» являются Малликеновские заряды (а.е.), электронная плотность на атомах углерода, а также индексы IUA и Fμ.

Заключение. Структурные особенности полученных производных 1,5-дифенилпента-1,4-диен-3-она, а также природа образуемых свободных радикалов в использованных биологических тестах однозначно свидетельствуют о том, что анализируемый класс соединений можно считать перспективными антиоксидантами.

Ключевые слова: квантовохимические параметры; антиоксиданты; производные 1,5-дифенилпента-1,4-диен-3-она; противоопухолевые свойства

Список сокращений: АФК — активные формы кислорода; DPPH — 2;2-дифенил-1-пикрилгидразил; ABTS — диаммониевая соль 2,2’-азино-бис [3-этилбензтиазолин-6-сульфоновой кислоты; СОД —- супероксиддисмутаза; ТБК-АП – активные продукты тиобарбитуровой кислоты; ИП — ионизационный потенциал.

INTRODUCTION

Currently, extensive experimental data have been accumulated, they clearly indicate a relationship between free radical oxidation processes and metabolic disorders. These processes, as a rule, lead to the suppression of the antioxidant defense mechanisms due to the accumulation of free radicals, including reactive oxygen species (ROS), in the body. Among the latter, the hydroxyl radical (HO•) characterized by electrophilic properties, is the most dangerous. It interacts with the nitrogenous bases of nucleic acids, promoting the formation of numerous mutations [1-4]. The hydroxyl radical simultaneously interacts with phospholipids in the cell membranes, causing tissue damages and various pathological processes in the human body [2, 5–7].

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In the cases of disorders caused by an excessive production of ROS and other free radicals, it is important to search for non-toxic antioxidants. From this perspective, the authors believe that derivatives of 1,5-diphenylpent-1,4-diene-3-one (DBA), which contain two cinnamoyl groups, are of interest. These molecules have the structure shown in Fig. 1.

Previously, the interaction of natural polyphenols, such as cinnamic acid derivatives, with the hydroxyl radical using quantum chemical methods, had been analyzed [8, 9]. A relationship between their biological activity and the presence of a hindered phenol group had also been established [10, 11].

THE AIM of the study was to investigate antioxidant properties of the synthesized DBA derivatives and to analyze their quantum chemical parameters revealing the regularities of the «structure–activity» relationship.

MATERIALS AND METHODS

Study Design

At the first stage of the study, virtual structures for potential target compounds using the Way2Drug PASS Online program (Way2Drug, Russia)[1], were described; that allowed the authors to predict their activity. Then 10 compounds, which had been synthesized by condensing acetone with 2 moles of corresponding aromatic aldehydes in an alkaline environment, were selected. After a five-fold recrystallization, the structures of the compounds were confirmed, and then were studied their antioxidant activity. The study period lasted from 11 November 2023 to 29 May 2024.

Tested compounds

The DBA derivatives were obtained through the alkaline condensation of one mole of acetone and two moles of various aromatic aldehydes, including benzaldehyde, p-hydroxybenzaldehyde, salicylic aldehyde, 4-methoxybenzaldehyde, 2,3-dihydroxybenzaldehyde, vanillin, veratinaldehyde, lilialdehyde, 3,4,5-trimethoxybenzaldehyde, and 2,4,6-trimethoxyphenylacetaldehyde. These compounds contain similarly-named substituents on the aryl fragments. The quantum chemical properties of these target compounds were computed on a workstation equipped with an Intel Xeon E5-1620 processor at a frequency of 3.5 GHz and 20 GB of RAM. The ionization energy of the synthesized molecules was calculated using the WinMOPAC 7.21 software (Russia).

[1] Way2Drug PASS Online. Available from: http:// www. Pharmaexpert.ru/ passonline/

DPPH assay

To assess the ability of the investigated substances to scavenge ингибировать DPPH radicals in a model system, the method proposed by B. Ahmadipour et al., was used [12].

Then 1 ml of the solution (20 mg/mL was the initial solution) of the analyzed substances was incubated in ethanol (Vecton, Russia) at various concentrations in double dilutions, and 0.5 mL of a 0.4 mM solution of DPPH (Sigma-Aldrich, Germany) in methanol (Vecton, Russia) was added for 30 min at room temperature. Then, the optical density change (measured using a PE-5300V spectrophotometer from Ekroschem LLC, Russia at λ=518 nm against pure methanol from Panreac, Spain) of the samples was recorded. The methanol DPPH solution served as a positive control (A_0). The inhibition percentage was calculated using the following formula:

$$\% \text{ ing.} = \frac{A_x}{A_0} \times 100\%,$$

where A_x is the optical density of the sample and A_0 is the optical density of the positive control.

ABTS assay

0.1 mL of the solution (20 mg/mL is the initial concentration) containing the analyzed substances in ethanol (Vecton, Russia), in various concentrations, and 0.19 mL of a 7 mM aqueous solution of ABTS (Sigma-Aldrich, Germany) were incubated for 5 min at room temperature in the dark. After that, the optical density of the samples was measured at λ=734 nm compared to purified water. An aqueous solution of ABTS served as a positive control (A_0). The percentage of the inhibition was calculated using above formula [13].

The *in vivo* study of the antioxidant activity was conducted on 100 male Wistar rats, weighing 200–210 g obtained from the «Rappolovo» laboratory animal nursery (Russia), after a microbiological control and a 2-week quarantine. These animals were kept under standard conditions, including the air temperature between 18–22°C, a relative humidity of 60±5%, with a daily cycle of 12 hours of light and 12 hours of darkness, and a free access to food and water. The design of the study and conditions for the animal care adhered to generally accepted standards for experimental ethics, as outlined in Directive 2010/63/EU, and was approved by the Local Ethics Committee at the Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University (Protocol No. 7 dated 4 April 2024).

For the analysis, the compounds were administered to the animals (*n*=10 per test substance) for a period of 30 days, at a dose of 20 mg/kg, once per day in the form of an *ex tempore* suspension prepared on a water basis, without the use of any additional substances. The experimental groups were: Group 1 — the animals receiving compound 1, Group 2 — the animals receiving compound 2, Group 3 — the animals receiving compound 3, Group 4 — the animals receiving compound 4, Group 5 — the animals receiving compound 5, Group 6 — the animals receiving compound 6, Group 7 — the animals receiving compound 7, Group 8 — the animals receiving compound 8, Group 9 — the animals receiving compound 9, and Group 10 — the animals receiving compound 10.

Afterwards, the blood was collected from the abdominal aorta of rats under chloral hydrate anesthesia (Panreac, Spain; dose 350 mg/kg, intraperitoneally). Then, the blood samples were centrifuged at 3500 rpm for 15 min (Armed centrifuge, Russia) to obtain serum, in which changes in the superoxide dismutase (SOD) activity and concentrations of products reacting with 2-thiobarbituric acid (TBA-AP) were assessed.

Determination of SOD activity

The activity of SOD was estimated using a xanthine oxidase method [14]. The incubation medium consisted of 0.05 mmol/L xanthine, 0.025 mmol/L 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride, 0.94 mmol/L EDTA, 80 U/L xanthine oxidase, and 40 mmol/L CAPS buffer. The extinction of the samples was measured at 505 nm, and the activity of SOD was expressed in U/L.

Determination of TBA-AP concentration

The concentration of TBA-AP was determined using a spectrophotometry at 532 nm. The optical density of the stained product of the reaction between aldehydes and 2-thiobarbituric acid was proportional to the TBA-AP concentration and was expressed in nM/mL [15].

Statistical analysis

A statistical processing of the results obtained was carried out using a software package StatPlus 7.0 (AnalystSoft Inc., USA, license 16887385). The data were expressed as a mean±standard deviation (M±SD). The normality of the data distribution was assessed using the Shapiro–Wilk test. The differences between the groups were determined using ANOVA with the Newman–Keuls post-hoc test (normally distributed data) or the Kruskal–Wallis test with the Dunn post-hoc test (abnormally distributed data) [16].

RESULTS AND DISCUSSION

Endogenous ROS take part in biochemical processes that are regulated by enzymatic and non-enzymatic components in cells. When there is an overproduction of ROS in the body, this disrupts equilibrium processes, leading to uncontrolled chemical reactions that cause damage and death to cells. In these cases, natural and synthetic antioxidants are important [17–19]. Cinnamic acid and its hydroxy and methoxy derivatives are some of the most active natural compounds when it comes to ROS. The hydroxyl radical has significant electrophilic properties and attaches to the C-8 position of cinnamic acid, as this carbon atom has the largest charge and highest electron density among the neighboring carbon atoms [20].

The DBA derivatives analyzed in this report contain two cinnamoyl fragments, or cinnamic acid residues, as their basis. This fact was used to determine the positions in the DBA structure that have electron-donating properties, which neutralize the ROS by donating an electron.

Table 1 shows the structures of the compounds analyzed and their experimentally determined antioxidant activity. It also provides information on the types of the predicted antitumor activities based on the Way2Drug PASS Online program, as well as the manifestation likelihood of these activities.

From the data in Table 1, it can be seen that compounds 5, 6, and 8 have the highest levels of the antioxidant activities.

In the DPPH assay, the IC_{50} value of compound 5 was significantly lower than those of compounds 1–4, 7, 9 and 10, by 79.1, 67.2, 75.3, 70.6, 56.1, and 24.6%, respectively (all *p*-values <0.05). Similarly, in the ABTS assay, the IC_{50} of compound 5 was also significantly lower (p <0.05) than those of the other compounds (Table 1). Additionally, the SOD activities in the rats treated with compound 5 was higher than in those treated with compounds 1–4 and 7, by 41.1, 27.8, 44.9, 23.3, and 41.1% (all *p*-values <0.05), respectively. In these groups, the concentration of TBA-AP was also decreased by 42.3, 37.5, 37.6, 48.3, and 34.8% (all *p*-values <0.05), respectively.

In the DPPH assay, the IC_{50} value of compound 6 was lower than those of compounds 1–4 and 7,9 and 10 by 82.0, 71.8, 78.7, 74.7, 62.2, 34.1, and 33.2%, respectively (all *p*-values <0.05). Similarly, in the ABTS assay, the IC_{50} of compound 6 was lower than the IC_{50} of compounds 1–4, 7, 9, and 10 by 84.2, 71.6, 85.2, 78.1, 63.6, 39.1, and 35.1%, respectively (all *p*-values <0.05). In terms of the animal studies, the activity of SOD was increased in the

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rats treated with compound 6 compared to those treated with compounds 1, 2, and 3 and compound 7, 22.1, 38.4, 17.8, and 34.9%, respectively (all *p*-values <0.05). Additionally, the content of TBA-AP was decreased in the rats treated with compound 6 by 30.8, 25, 25.1, and 21.7%, respectively, compared to the rats treated with the other compounds (all *p*-values <0.05).

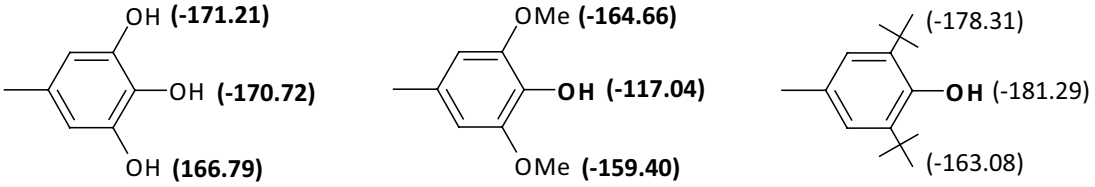
The IC_{50} value of compound 8 in the DPPH and ABTS assays was significantly lower than those of compounds 1 by 84.1 and 87.0% (*p* <0.05); compounds 2 — 75.1 and 76.5% (*p* <0.05); compounds 3 — 81.2 and 87.8% (*p* <0.05); compounds 4 — 77.6 and 81.9% (*p* <0.05); compounds 7 — 66.6 and 69.9% (*p* <0.05); compounds 8 — 42.7 and 49.8% (*p* <.05); compounds 10 — 41.0 and 46.4% (*p* <0.05). It is also worth noting that the activity of serum SOD in rats treated with compound 8 was higher than in animals treated with compounds 1–4 and 7 by 40.6, 27.3, 44.3, 22.8 and 40.6% (all *p*-values <0.05), while the content of TBK-AP decreased by 46.2, 41.7, 41.8, 51.7, and 39.1% (all *p*-values <0.05), respectively.

The analysis of the quantum chemical parameters of the synthesized compounds testifies to the fact that the pentadiene moiety exhibits the highest reactivity. In this moiety, two vinyl groups are separated by a carbonyl carbon atom, indicating the absence of a conjugated double bond.

Free phenolic hydroxyl groups are capable of breaking the H-O bond homolytically and forming phenoxyl radicals. If the hydroxyl group is shielded on both sides, the resulting radical is stabilized and relatively stable [8].

It has been previously experimentally shown that the Gibbs energy of homolytic H-O bond breaking depends not only on the unsaturation index (IUA) and a positive charge of the carbon atom to which the hydroxyl group is attached, but also on the nature of the neighboring substituents. For example, if methoxy groups act as shielding substituents, the Gibbs energy is -117.04. In contrast, if alkyl ditret-butyl groups act as substituents, this energy increases to -181.29.

These results are summarized below:



Bond numbers (Nμ) and free valence indices (Fr)

As it is known, a free valence index is an important tool for analyzing the reactivity of organic compounds. This value, Fr, is typically calculated by subtracting the maximum possible number of bonds (Nm) from the actual number of bonds a carbon atom can form (in this case, 4.732, which corresponds to the maximum "valence" of 4.732) [21–23].

The number of bonds an atom has, Nμ, indicates its saturation level: the more bonds an atom forms, the lower its N value, and vice versa. Table 2 shows the bond numbers (Nm) for the carbon atoms in the aromatic nuclei (positions C-2 to C-3 and C-15 to C-18).

Therefore, if certain atoms do not fully utilize their properties to form bonds, it can be said that they have a certain amount of "free valence". This value indicates a potential for the interaction with reagents lacking a charge dipole.

Fr applies only to sp- and sp^2-hybridized carbon atoms, and not to C atoms that can form σ-bonds. If, for example, the Fr value is 0.732 (for an ethylene carbon atom), this indicates that the atom is highly reactive in reactions involving the addition of neutral particles. Atoms with Fr >1 values are more likely to attach free radicals.

Tables 3 and 4 provide the Fμ values for atoms 7, 8, 11, and 12 in the pentadienone fragment, as well as for aryl-C-2-C-5 and C-15-C-18.

The data presented show the following.

1. The Fr values of carbon atoms (C-7, C-8, C-11, and C-12) in the pentadienone fragment are very similar and range from 0.781 to 0.815.
2. The Fr indices for C2 aromatic nuclei (C-2-C-5 and C-15-C-18) differ depending on the substituent connected to them. In compound 5, with two OH groups connected to atoms C-4, C-5 (ring "A") and C-17, C-18 (ring "B"), the Fμ values are in the range of 0.813-0.830. For the remaining atoms — C-2, C-3, and C-15, C-16 — they are approximately the same and range from 0.780 to 0.790.
3. In compound 6, the phenolic hydroxyl group is bound to C-3 (ring "A"), with an Fr value of 0.830; it is also bound to C-16, with an Fμ of 0.823. The Fr values for C-4 and C-17 are 0.819 and 0.820, respectively.
4. In the most active compound, hydroxyl groups

are associated with C-3 (ring "A") and C-16 (ring "B"). The magnitude of Fr on these atoms is 0.807 and 0.838, respectively.

5. It is characteristic of compounds 4, 6, 7 and 8 to have aryl carbon atoms associated with OCH_3 groups. Atoms C-3 and C-16 (compound 4), C-4 and C-17 (compound 6), C-3, C-4, and C-16 and C-17 (compound 7), and C-2, C-4 and C-15 and C-17 (compound 8) have positive Mulliken charges in the range of 0.1024 to 0.1600. The carbonyl carbon atom (C-9), on the other hand, has the highest positive charge, equal to 0.4600±0.0045 in compounds 5, 6 and 8, and reaching up to 0.4725±0.0025 in compounds 1–4 and 7.

Electron density and electronic effects of substituents

The distribution of the electron density in the analyzed molecules depends on the electronic effects of substituents that are conjugated with the pentadienone fragment in the aromatic nuclei. This unevenness in the electron density distribution suggests the presence of reactive centers in the molecule. These centers determine the direction of the attack by other molecules or agents. If the latter is of a radical nature (the presence of an unpaired electron), then, being highly reactive, it (the agent) has little sensitivity to the electron density distribution.-

When analyzing this parameter for the DBA derivatives, the pentadienone fragment and its associated aryl residues A and B, taking into account the "+mesomeric effect" of electron-donating substituents, were considered. Tables 3 and 4 show the values of the electron density on the carbon atoms of the pentadiene fragment (C-7, C-8 and C-11, C-12), as well as the aromatic fragments "A" (C-2-C-5) and "B" (C-15-C-18).

In the unsubstituted parent structure, the electron density is distributed as follows: C-7 — 4.080; C-8 — 4.279; C-11 — 4.31; C-12 — 4.039. On the carbon atoms of aromatic fragments "A" and "B", the electron densities are almost the same: C-2 and C-15 — 4.154; C-3 and C-16 — 4.134; C-4 and C-17 — 4.156; and C-5 and C-18 — 4.142, with the differences appearing only on the third decimal place.

The introduction of hydroxyl groups in positions C-3 and C-16 (which are para-positions relative to C-7 and C-12, respectively) increases the electron density on atoms C-8 and C-11 of the pentadienone fragment (compound 2). A similar pattern is observed when OH groups are located in positions 5 and 18 (compound 3). However, if the OCH_3 group replaces OH in positions C-3 and C-16 (para-positions to C-7 and C-12), the values of the electron density on C-8 and C-12 remain practically unchanged.

The $\bar{\sigma}$-Taft substituent constants are presented in Table 5 [24].

In compound 5, dihydroxy groups are located in positions C-4 and C-5 (core "A"), as well as in C-17 and C-18 (core "B"). In C-5 and C-18, the OH groups with respect to the pentadienones C-7 and C-12, occupy ortho positions and the σ constant is 0.370; and the OH groups in C-4 and C-17 are located in meta positions with respect to C-7 and C-12 of the pentadienone fragments and their $\bar{\sigma}$ =+0.127. Thus, the total contribution of phenolic hydroxy groups (2 in each core) is:

$$\sum\bar{\sigma} = 2 \times (-0.370) + 2 \times (+0.127) = -0.486$$

Compound 6 has OH groups in the para-positions to C-7 and C-12. C-3 and C-16 have OH groups; but in the meta-positions to C-7 and C-12, there are methoxy groups, so, here the total contribution of two meta-OCH_3 and two para-OH is equal to:

$$\sum\bar{\sigma} = 2 \times (-0.370) + 2 \times (+0.115) = -0.510$$

The most antioxidant active compound 8 contains two shielded hydroxy groups in positions C-3 (core "A") and C-16 (core "B"). In addition to these OH groups, there are two methoxy groups in ortho positions to C-2, C-4 (core "A") and C-15, C-17 (core "B") atoms. These substituents are located in meta positions with respect to the C-7 and C-12 atoms of the pentadienone fragment. The total contribution of the two shielded OH groups in C-3 and C-16 and four methoxy groups in positions 2,4 (core "A") and 15,17 (core "B") is:

$$\sum\bar{\sigma} = 2 \times (-0.370) + 4 \times (+0.115) = -0.280$$

Ionization potential

In the analyzed DBA derivatives, the pentadienone fragment contains electron-redundant centers at C-7, C-8, C-11, and C-12 atoms, which can become electron donors in redox reactions. The energy that is used to detach one electron from a molecule is called the first ionization potential (IP). The lower the IP, the easier it is for the molecule to release an electron, turning into a positively charged ion, i.e., it transitions to an excited state. Table 3 shows the ionization potentials for all 10 synthesized DBA derivatives, which means that the most antioxidant active compounds (5, 6, and 8) are characterized by IP values of 8 987, 8 714, and 8 639, respectively.

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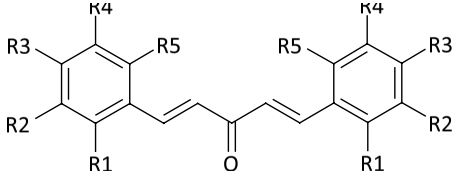
Table 1 – Structures of synthesized derivatives of (5E, 8E) 7,12 (bisphenyl) penta-7,11-diene-3-one* and their biological activities



Compounds, No. in sequence	R mean	Antioxidant activities				Probability of antitumor activities according to Way2Drug PASS Online, %			
		in vitro	*in vitro*	*in vivo*	*in vivo*	Breast cancer	Lung cancer	Cervical cancer	Free radical scavengers
		DPPH, IC_{50} mM/mL	ABTS, IC_{50} mM/mL	SOD, U/L	TBA-AP, nM/mL				
1	$R_1=R_2=R_3=R_4=R_5=H$	76.1±0.29*#Δ	79.8±0.21*#Δ	262.7±10.9*#Δ	2.6±0.5*#Δ	70.3	71.6	–	–
2	$R_1=R_2=R_4=R_5=H$ $R_3=OH$	48.5±1.2*#Δ	44.3±0.31*#Δ	290±9.2*#Δ	2.4±0.2*#Δ	67.3	55.7	–	55.2
3	$R_1=R_2=R_3=R_4=H$ $R_5=OH$	64.3±0.9*#Δ	85.1±0.5*#Δ	255.9±26.4*#Δ	2.4±0.4*#Δ	63.9	–	–	54.0
4	$R_1=R_2=R_4=R_5=H$ $R_3=OCH_3$	54.1±0.3*#Δ	57.6±0.6*#Δ	300.7±8.4*	2.9±0.9*	68.1	65.2	–	50.1
5	$R_1=R_2=R_3=H$ $R_4=R_5=OH$	15.9±0.4	16.7±0.8	370.7±9.4	1.5±0.2	66.1	54.7	53.9	58.2
6	$R_1=R_2=R_4=H$ $R_3=OH$; $R_4=OCH_3$	13.7±0.1	12.6±0.5	354.2±7.2	1.8±0.1	66.9	56.6	53.6	68.4
7	$R_1=R_2=R_5=H$ $R_3=R_4=OCH_3$	36.2±0.7*#Δ	34.6±0.9*#Δ	262.7±10.9*#Δ	2.3±0.2*#Δ	69.8	64.5	59.9	54.9
8	$R_1=R_5=H$ $R_2=R_4=OCH_3$; $R_3=OH$	12.1±0.2	10.4±0.6	369.3±14.5	1.4±0.1	67.6	65.0	55.9	66.9
9	$R_1=R_5=H$ $R_2=R_3=R_4=OCH_3$	21.1±0.64*#Δ	20.7±0.27*#Δ	326.9±12.5	1.7±0.1	79.1	79.1	70.1	55.5
10	$R_2=R_4=H$ $R_1=R_3=R_5=OCH_3$	20.5±0.5*#Δ	19.4±0.42*#Δ	354.7±11.7	1.5±0.1	69.9	57.6	–	–

Note: DPPH — 2,2-diphenyl-1-picrylhydrazyl; ABTS — diammonium salt of 2,2'-azino-bis [3-ethylbenzthiazoline-6-sulfonic acid; SOD — superoxide dismutase; TBA-AP — active products reacting with 2-thiobarbituric acid; * reliably relative to compound 5 (Newman-Keuls test, p <0.05); # reliable relative to compound 6 (Newman-Keuls test, p <0.05); Δ reliable relative to compound 8 (Newman-Keuls test, p <0.05). When forming the structures of molecules for computer calculations, the program itself numbered the positions of the atoms. All compounds were obtained by an alkaline condensation of acetone with 2 mol substituted benzaldehydes, and therefore, the R values in the aromatic nuclei are the same.

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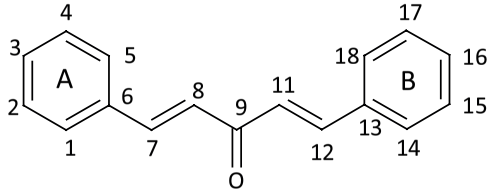
Table 2 – Mulliken charges (AU) and bond numbers (Nμ) on carbon atoms of aromatic nuclei with which OH groups are associated



Compounds, No. in sequence	Position of hydroxyl group								Mulliken charges on carbon atom								Bond numbers (Nμ)							
	2	3	4	5	15	16	17	18	C-2	C-3	C-4	C-5	C-15	C-16	C-17	C-18	C-2	C-3	C-4	C-5	C-15	C-16	C-17	C-18
1	–	–	–	–	–	–	–	–	-0.154	-0.134	-0.156	-0.142	-0.155	-0.131	-0.159	-0.128	3.962	3.961	3.961	3.957	3.962	3.960	3.962	3.952
2	–	+	–	–	–	+	–	–	-0.256	0.308	-0.322	-0.059	-0.256	0.312	-0.327	-0.045	3.935	3.882	3.925	3.945	3.934	3.881	3.925	3.940
3	–	–	–	+	–	–	–	+	-0.231	-0.060	-0.259	0.303	-0.238	-0.06	-0.258	0.314	3.943	3.943	3.938	3.879	3.945	3.941	3.938	3.878
5	–	–	+	+	–	–	+	+	-0.148	-0.183	0.196	0.144	-0.155	-0.180	0.196	0.158	3.952	3.947	3.918	3.961	3.953	3.938	3.919	3.905
6	–	+	–	–	–	+	–	–	-0.201	0.206	0.102	-0.229	0.206	0.215	0.095	-0.209	3.936	3.902	3.913	3.936	3.935	3.909	3.912	3.930
8	–	+	–	–	–	–	–	–	-0.199	0.081	0.159	-0.299	0.214	0.054	0.168	-0.290	3.925	3.911	3.916	3.923	3.964	3.894	3.909	3.918

Table 3 – Ionization potentials of dibenzylidenacetone derivatives, values of unsaturation indices (IUA), electron density, and free valence indices (Fr) on atoms of C-7, C-8, C-11, and C-12 of the pentadienone fragment of compounds 1–10

Compounds, No. in sequence	R	IUA				Electronic density				Fμ				Ionization potential
		C-7	C-8	C-11	C-12	C-7	C-8	C-11	C-12	C-7	C-8	C-11	C-12	
1	$R_1=R_2=R_3=R_4=R_5=H$	0.028	0.01	0.012	0.029	4.080	4.279	4.313	4.039	0.791	0.779	0.784	0.81	9.457
2	$R_1=R_2=R_4=R_5=H$ $R_3=OH$	0.028	0.015	0.018	0.031	4.061	4.294	4.332	4.017	0.791	0.786	0.793	0.814	9.022
3	$R_1=R_2=R_3=R_4=H$ $R_5=OH$	0.038	0.019	0.021	0.032	4.057	4.283	4.323	4.012	0.794	0.79	0.796	0.805	9.195
4	$R_1=R_2=R_4=R_5=H$ $R_3=OCH_3$	0.029	0.014	0.017	0.031	4.057	4.297	4.336	4.013	0.792	0.785	0.793	0.815	8.791
5	$R_1=R_2=R_3=H$ $R_4=R_5=OH$	0.037	0.014	0.019	0.042	4.069	4.268	4.308	4.022	0.792	0.784	0.79	0.813	8.987
6	$R_1=R_2=R_4=H$ $R_3=OH$; $R_4=OCH_3$	0.035	0.021	0.015	0.029	4.093	4.273	4.326	4.025	0.795	0.789	0.789	0.81	8.714
7	$R_1=R_2=R_5=H$ $R_3=R_4=OCH_3$	0.03	0.013	0.017	0.033	4.065	4.287	4.329	4.017	0.792	0.783	0.791	0.817	8.570
8	$R_1=R_5=H$ $R_2=R_4=OCH_3$; $R_3=OH$	0.035	0.017	0.021	0.029	4.100	4.269	4.3152	4.029	0.796	0.784	0.794	0.81	8.639
9	$R_1=R_5=H$ $R_2=R_3=R_4=OCH_3$	0.036	0.018	0.022	0.03	4.105	4.258	4.304	4.044	0.796	0.785	0.793	0.807	8.779
10	$R_2=R_4=H$ $R_1=R_3=R_5=OCH_3$	0.03	0.033	0.035	0.033	4.021	4.302	4.331	3.980	0.8	0.806	0.812	0.815	8.629

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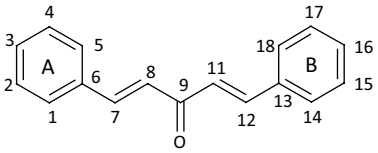
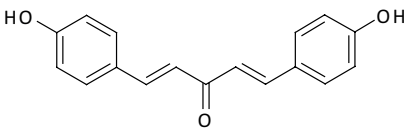
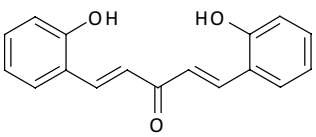
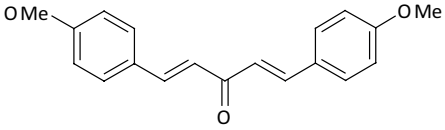
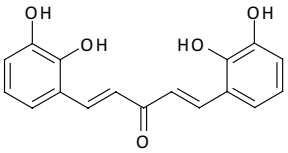
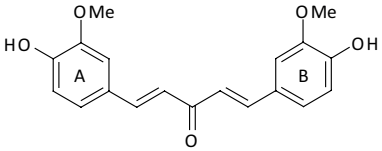
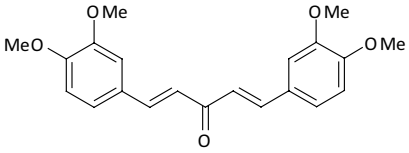
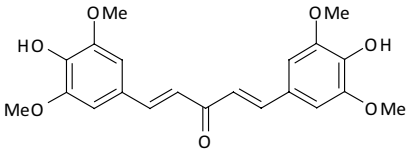
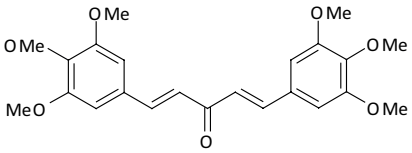
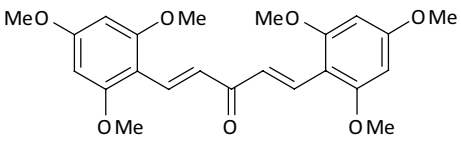
Table 4 – Values of unsaturation indices (IUA), electron density, and free valence indices (Fr) of carbon atoms of aromatic nuclei A and B

Compounds, No. in sequence	Nucleus A										Nucleus B									
	IUA				Electronic density				Fμ				IUA				Electronic density				Fμ	
	C-2	C-3	C-4	C-5	C-2	C-3	C-4	C-5	C-2	C-3	C-4	C-5	C-15	C-16	C-17	C-18	C-15	C-16	C-17	C-18	C-15	C-16	C-17	C-18
1	0.014	0.015	0.015	0.019	4.154	4.134	4.156	4.142	0.77	0.771	0.771	0.775	0.014	0.016	0.014	0.023	4.155	4.130	4.159	4.128	0.77	0.772	0.77	0.78
2	0.022	0.027	0.027	0.025	4.256	3.692	4.322	4.059	0.797	0.85	0.807	0.787	0.023	0.027	0.025	0.027	4.256	3.688	4.326	4.045	0.798	0.851	0.807	0.792
3	0.022	0.025	0.02	0.03	4.231	4.060	4.258	3.696	0.785	0.789	0.794	0.853	0.023	0.027	0.019	0.03	4.238	4.055	4.258	3.686	0.787	0.791	0.794	0.854
4	0.023	0.03	0.031	0.023	4.263	3.732	4.313	4.064	0.798	0.836	0.811	0.785	0.024	0.031	0.029	0.028	4.262	3.728	4.317	4.049	0.799	0.838	0.81	0.792
5	0.022	0.019	0.021	0.029	4.148	4.183	3.804	3.856	0.78	0.785	0.814	0.831	0.021	0.029	0.021	0.028	4.155	4.179	3.803	3.842	0.779	0.794	0.813	0.827
6	0.028	0.034	0.035	0.031	4.201	3.794	3.897	4.228	0.796	0.83	0.819	0.796	0.028	0.026	0.036	0.039	4.205	3.785	3.905	4.209	0.797	0.823	0.82	0.802
7	0.031	0.032	0.04	0.036	4.217	3.821	3.893	4.227	0.80	0.815	0.822	0.799	0.031	0.034	0.04	0.041	4.217	3.817	3.899	4.208	0.8	0.818	0.823	0.803
8	0.027	0.032	0.031	0.026	3.801	3.919	3.841	4.299	0.807	0.821	0.816	0.809	0.044	0.039	0.036	0.032	3.786	3.946	3.832	4.291	0.828	0.838	0.823	0.814
9	0.037	0.037	0.042	0.028	3.751	4.050	3.763	4.358	0.833	0.839	0.839	0.830	0.036	0.041	0.044	0.033	3.753	4.043	3.768	4.342	0.831	0.84	0.84	0.83
10	0.024	0.049	0.024	0.045	4.471	3.626	4.511	3.639	0.886	0.883	0.899	0.875	0.025	0.049	0.032	0.049	4.470	3.624	4.512	3.635	0.887	0.884	0.908	0.877

Table 5 – Constant substituents for substituted phenyls

Compounds		σ̄-Taft substituent constants						∑σ̄ calculated
No.	Structure	OH-П -0.370	OH–O -0.370	OH–M +0.127	OCH_3–П -0.268	OCH_3–O -0.268	OCH_3-M +0.115	
1		–	–	–	–	–	–	–
2		C-3.16	–	–	–	–	–	-0.740
3		–	C-5.18	–	–	–	–	-0.746
4		–	–	–	C-3.16	–	–	-0.536
5		–	–	C-4.17	–	–	–	-0.486
6		C-3.16	–	–	–	–	C-4.17	-0.510
7		–	–	–	C-3.16	–	C-4.17	-0.306
8		C-3.16	–	–	–	–	C-2.15 C-4.17	-0.280
9		–	–	–	C-3.16	–	–	-0.076
10		–	–	–	C-3.16	C-1.14 C-5.18	–	-1.608

Note: * The term “constants” and the values of the σ̄-Taft constants are given in accordance with [24]. They take into account the polar conjugation with the electron-donor reaction center.

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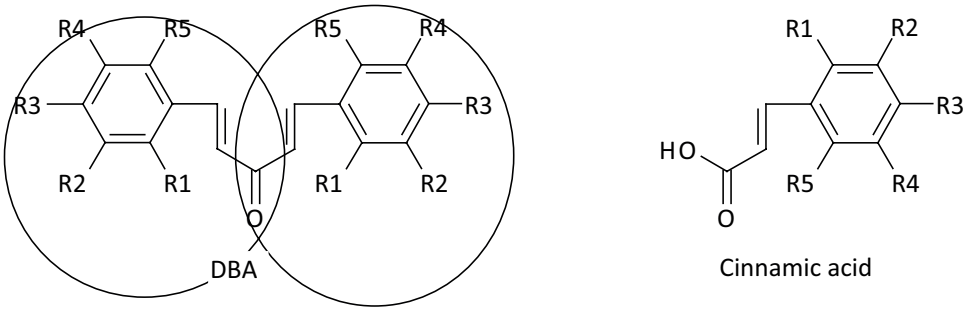

Figure 1 – Structural fragments of dibenzylidenacetone and cinnamic acid
Note: DBA — dibenzylidenacetone.

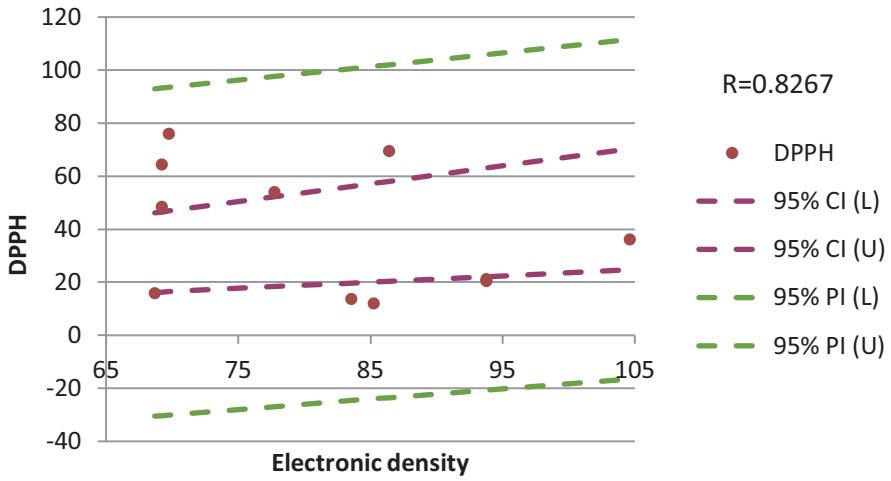

Figure 2 – Correlation relationship between DPPH and electronic density

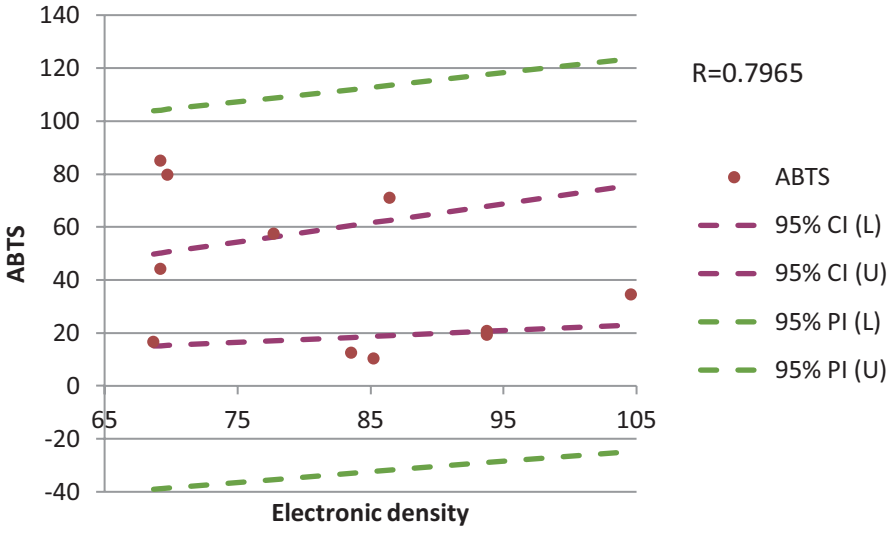

Figure 3 – Correlation relationship between ABTS and electronic density

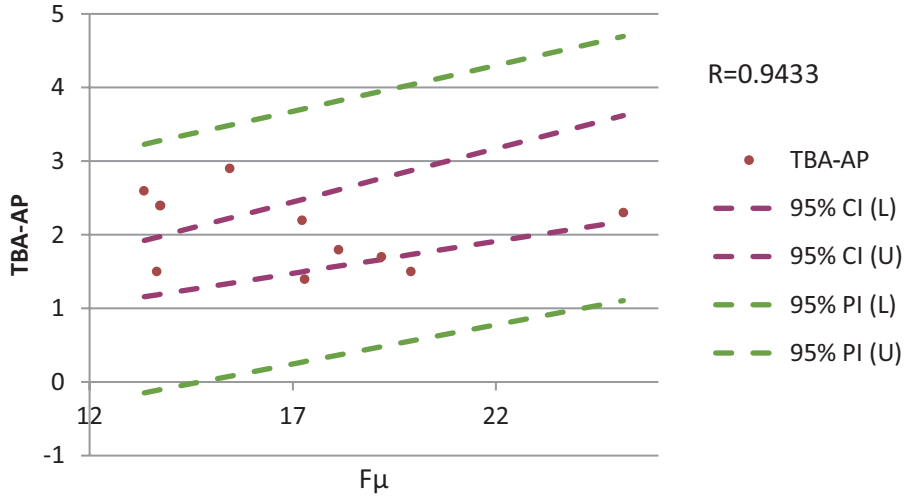

Figure 4 – Correlation relationship between TBA-AP and free valence index

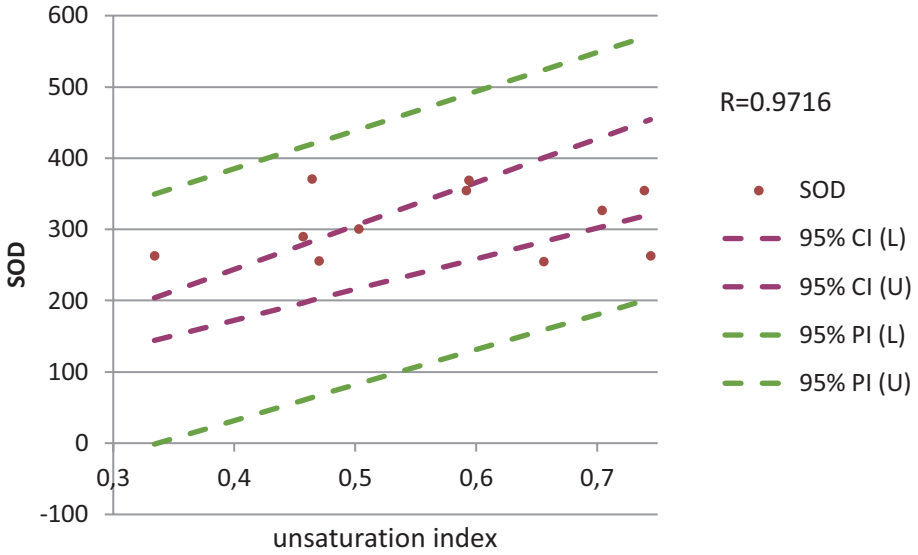

Figure 5 – Correlation between SOD and unsaturation index

When interpreting the biological activity of organic molecules, the problem should be considered taking into account the structural features of the molecules, as well as all physico-chemical parameters, so that the results and conclusions are reliable. So, if the antioxidant activity of the compounds under study is judged only by the IP magnitude, then an error will inevitably arise: compounds 4, 7, 9, and 10 have significantly lower IP values than the most active compounds 5, 6, and 8. In order to avoid such errors, all structural features of the molecules should be taken into account in combination with the other parameters. For example, compounds 4, 7, 9, and 10 lack hydroxy groups in aromatic fragments "A" and "B", and the existing methoxy groups are not able of forming phenoxyl radicals. Compounds 5, 6 and 8, on the contrary, contain free hydroxy groups and, therefore, their antioxidant activity is higher.

Correlation dependencies

In order to identify the relationship between a specific type of activity and the objective parameters of the analyzed molecules, the functional dependences between the level of the antioxidant action and the electron density, the unsaturation index, and the free valence index were determined. The obtained data from the corresponding correlation equations indicate the degree of reliability of the experimental data obtained. Fig. 2–5 show graphs of the functional relationship between the listed quantum chemical parameters and the activity in the corresponding tests.

It should be noted that compounds 4, 7, 9, 10, in which phenolic hydroxy groups are methylated, exhibit their antioxidant activity, in the authors' opinion, only due to the 1,4-diene fragment and therefore, their activity is significantly lower, which is consistent with the previously obtained data for chromone derivatives [25].

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Study limitations

If there are available domestic aldehydes containing, for example, tret-butyl radicals and a hydroxy group between them, it is possible to obtain reliably active antioxidants, the activity of which will be comparable to tocopherols.

CONCLUSION

This article is devoted to the analysis of the quantum chemical parameters of (1E,4E)-1,5-diphenylpent-1,4-diene-3-one derivatives in relation to their antioxidant activity. It has been established that the most informative and reliable are the unsaturation index (IUA), the electron density and the free valence index (Fr). In the experiment using the tests such as DPPH, ABTS, SOD and TBA-AP, it has been found out that the most active compounds are the derivatives containing free hydroxy groups. The most active among them is characterized by the derivative that contains a spatially hindered phenolic hydroxyl, due to which a stable phenoxyl radical is formed. The study of the correlations between the biological activity and quantum chemical parameters indicates that the values of the electron density, free valence indices and unsaturation indices give the most reliable results.

The relationship between the distribution of the electron density on the carbon atoms of the pentadiene fragment and the ionization potential has been shown. The correlation analysis of the functional relationship between the antioxidant activity and IUA, Fr and electron density showed a high reliability of the study data, as evidenced by the correlation coefficients. The authors of the article believe that based on the basic structure of (1E,4E)-1,5-diphenylpent-1,4-diene-3-one, by selecting appropriate substituents in the aromatic fragments, it is possible to significantly increase an antioxidant activity and create pharmacologically promising therapeutic and prophylactic agents.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Eduard T. Oganesyan — development of the research concept, preparation of the manuscript;
Victoriya M. Rukovitsina, Simillа L. Adzhiakhmetova — experiment, statistical analysis of the data;
Dmitry I. Pozdnyakov — development of the research concept, experiment, preparation of the manuscript.
All the authors have made equial and equivalent contributions to the preparation of the publication.
All the authors confirm that their authorship meets the international ICMJE criteria (all the authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before the publication).

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AUTHORS

Eduard T. Oganesyan – Doctor of Sciences (Pharmacy), Professor, Head of the Department of Organic Chemistry, Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0000-0002-2756-9382. E-mail: edwardov@mail.ru

Victoriya M. Rukovitsina – Candidate of Sciences (Pharmacy), Senior lecturer at the Department of Organic Chemistry, Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0000-0003-4104-9217. E-mail: rukovitsina.vika@mail.ru

Dmitry I. Pozdnyakov – Candidate of Sciences (Pharmacy), Associate Professor, Head of the Department of Pharmacology with a course in Clinical Pharmacology, Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0000-0002-5595-8182. E-mail: pozdniackow.dmitry@yandex.ru

Similla L. Adzhiakhmetova – Candidate of Sciences (Pharmacy), Senior lecturer at the Department of Organic Chemistry, Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University. ORCID ID: 0000-0001-9685-1384. E-mail: simillа503@mail.ru

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ОРИГИНАЛЬНАЯ СТАТЬЯ
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Psychotropic activity evaluation of bromantane — *N*-(camphan-2-yl)anilines new structural analogues in *in vivo* tests

A.A. Vernigora[1], L.L. Brunilina[1], A.V. Kazhberov[1], N.S. Bolokhov[2], A.A. Pokhlebin[2], A.A. Sokolova[2], V.E. Pustynnikov[2], I.N. Tyurenkov[2], I.A. Novakov[1], V.I. Krasnov[3], D.N. Polovyanenko[3]

[1] Volgograd State Technical University,
28, Lenin Ave., Volgograd, Russia, 400005
[2] Volgograd State Medical University,
1, Pashykh Bortsov Sq., Volgograd, Russia, 400066
[3] Vorozhtsov Novosibirsk Institute of Organic Chemistry,
9, Academician Lavrentiev Ave., Novosibirsk, Russia, 630090

E-mail: nikita.bolokhov@volgmed.ru

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The aim of the work was the synthesis of bromantane — *N*-(camphan-2-yl)anilines new structural analogues and the study of their psychotropic properties.

Materials and methods. The synthesized compounds were identified using the NMR spectroscopy. The purity of the compounds was confirmed by a GC-MS analysis. Psychotropic properties of N-(camphan-2-yl)anilines were studied in the experiments on the Wistar rats aged 18-20 weeks, the mice (12 weeks old) obtained from the "Stolbovaya" nursery using the following tests: the "Open Field", the "Elevated Plus Maze", the "Novel Object Recognition", the "Vogel Conflict", the "Tail Suspension", the "Tightrope suspension", the "Extrapolation" test.

Results. A series of new camphor aromatic amines, structural analogues of bromantane, were obtained and their psychotropic effects were evaluated by *in vivo* biological studies. Based on the results, it was possible to identify a leader compound, i.e. (1*R*,2*R*,4*R*)-1,7,7-trimethyl-*N*-(4-ethylphenyl)bicyclo[2.2.1.1]heptan-2-amine (4e), which had a pronounced anxiolytic effect. Substance 4f showed cognitive properties in the "Novel Object Recognition" and the "Extrapolation" tests. The fact was established by the indices of the time of learning a novel object and the time of diving.

Conclusion. The obtained data testify to the prospect of searching for substances with a psychotropic action in the range of aromatic camphor amines. Substance 4f, which deserves an in-depth study of the spectrum and mechanism of its psychotropic action, should be singled out separately.

Keywords: bromantane; arylamines of monoterpenoid ketones; camphor; anxiolytic action; antidepressant action; cognitive action

Abbreviations: NMR — nuclear magnetic resonance; GC-MS — gas chromatography-mass spectrometry; TLC — thin layer chromatography; OF — the "Open field" test; EPM — the "Elevated plus maze" test; NOR — the" Novel Object Recognition" test; EP — the "Extrapolation" test; TS — the "Tail suspension" test; TRS — "Tightrope suspension" test.

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Оценка психотропной активности новых структурных аналогов бромантана — *N*-(камфан-2-ил)анилинов — в тестах *in vivo*

А.А. Вернигора[1], Л.Л. Брунилина[1], А.В. Кажберов[1], Н.С. Болохов[2], А.А. Похлебин[2], А.А. Соколова[2], В.Э. Пустынников[2], И.Н. Тюренков[2], И.А. Новаков[1], В.И. Краснов[3], Д.Н. Половяненко[3]

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Волгоградский государственный технический университет», Россия, 400005, г. Волгоград, пр. имени Ленина, д. 28

[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, 400066, г. Волгоград, пл. Павших Борцов, д. 1

[3] Федеральное государственное бюджетное учреждение науки «Новосибирский институт органической химии имени Н.Н. Ворожцова» Сибирского отделения Российской академии наук, Россия, 630090, г. Новосибирск, пр-кт им. Академика Лаврентьева, д. 9

E-mail: nikita.bolokhov@volgmed.ru

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Цель. Синтез новых структурных аналогов бромантана — *N*-(камфан-2-ил)анилинов и изучение их психотропных свойств.

Материалы и методы. Синтезированные соединения идентифицировали с применением ЯМР-спектроскопии. Чистота соединений подтверждалась ГЖХ-МС анализом. Психотропные свойства *N*-(камфан-2-ил)анилинов изучены в экспериментах на крысах линии Wistar в возрасте 18–20 нед., мышах (12 нед.), полученных из питомника «Столбовая» с использованием тестов: «Открытое поле», «Приподнятый крестообразный лабиринт» (ПКЛ), «Тест Распознавание нового объекта», «Питьевой конфликтный тест Фогеля», «Подвешивание мышей за хвост», «Удержание на канатике», «Тест экстраполяционного избавления».

Результаты. Был получен ряд новых ароматических аминов камфоры — структурных аналогов бромантана, и в ходе биологических исследований *in vivo* оценено их психотропное действие. По итогам исследований удалось выделить соединение-лидер, а именно (1*R*,2*R*,4*R*)-1,7,7-триметил-*N*-(4-этилфенил)бицикло[2.2.1]гептан-2-амин (4е), которое оказывало выраженное анксиолитическое действие. Вещество 4е в тестах «Распознавание нового объекта» и в «Тесте экстраполяционного избавления» проявило когнитивные свойства, что было установлено по показателям времени изучения нового объекта и по времени подныривания.

Заключение. Полученные данные свидетельствуют о перспективности поиска веществ с психотропным действием в ряду ароматических аминов камфоры. Отдельно стоит выделить вещество 4е, которое заслуживает углублённого изучения спектра и механизма его психотропного действия.

Ключевые слова: бромантан; ариламины монотерпеноидных кетонов; камфора; анксиолитическое действие; антидепрессивное действие; когнитивное действие

Список сокращений: ЯМР — ядерный магнитный резонанс; ГЖХ-МС — газовая хромато-масс-спектрометрия; ТСХ — тонкослойная хроматография; ОП — тест «Открытое поле»; ПКЛ — тест «Приподнятый крестообразный лабиринт»; РНО — тест «Распознавание нового объекта»; ТЭИ — тест экстраполяционного избавления; ПМХ — тест «Подвешивание мышей за хвост».

INTRODUCTION

A high pace of modern life, psycho-emotional stresses, consequences of viral and somatic diseases are the reasons for the growth of anxiety and depression, and the decrease in the quality of life. According to the world health organization (WHO)[1], about half of the population experience feelings of anxiety and worry at certain intervals in their lives. About 970 million people worldwide suffer from mental disorders [2]. Anxiety and depressive pathologies are the most common types of mental disorders. More than 300 million people in the world are estimated as suffering from anxiety. Cardiovascular, metabolic, respiratory and many other diseases are often associated with anxiety and depression [1].

[1] When an anxious state requires special attention. Available from: https://rg.ru/2024/04/10/kogda-trevozhnoe-sostoianie-trebuet-osobogo-vnimaniia.html

[2] About 4 million Russians suffer from mental illnesses. Available from: https://www.interfax.ru/russia/945840

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Therefore, despite the availability of more than 160 neuropsychotropic drugs in circulation according to the DrugBank[3] database [2–4], the search for the substances aimed at the correction of psychoemotional (anxiety-depressive) states is an urgent task for synthetic chemists and pharmacologists [2–4]. But the problem of the effective and safe treatment of patients with such pathologies is still unsolved [5–7], so the search for the substances with anxiolytic, antiphobic and antidepressant effects continues [8–10].

A drug derivative of adamantane, bromantane, has been used in domestic medical practice for quite a long period of time [11–13]. It has a wide spectrum of action: it increases a physical and mental performance, has an anti-asthenic effect, and has anxiolytic and antidepressant effects [14–16]. The literature also describes bromantan related experimental preparations — ADK-910 (chlodantane), ADK-918 [17]. Unlike bromantan, these compounds belong to amides of carboxylic acids by their chemical structure. In this regard, the spectrum of their pharmacological action is somewhat different. It should be noted that the presence of adamantane fragment in their structure remains unchanged.

Guided by the general idea of creating bioisosteric structural analogues of bromantane, different variants of replacing the adamantane fragment with other hydrocarbon radicals were taken into account. In particular, by a bioisosteric replacement of the adamantane framework fragment with a fragment of norcamphan, for some antiviral agents, the problem of hepatotoxicity of functional adamantane derivatives and their ability to cause Reye's syndrome was solved [18]. A specific example of this kind is the transition from the rimantadine molecule to the deutiforin molecule [18] (Fig. 1).

In the authors' opinion, this approach is also justified for the directed modification of the bromantane molecule. From the total number of the considered variants of hydrocarbon radicals, a special attention was drawn by camphane. Camphane, like adamantane, is a ten-carbon carbocyclic radical of the framework structure and contains 3 methyl groups in its structure, which undergo hydroxylation in the course of a microsomal oxidation, which leads to a decrease in the level of a potential hepatotoxicity of the obtained substances. At the same time, a rapid hydroxylation and a subsequent conjugation may provide a higher level of the obtained substances clearance compared to bromantane. Finally, the availability of the starting compound plays an important role: camphor is of a natural origin and is a component of essential oils [19]. Thus, new structural analogues of bromantane — *N*-(camphan-2-yl)anilines (see Fig. 1) became the objects of the research in this work.

THE AIM of the work was the synthesis of bromantane — *N*-(camphan-2-yl)anilines new structural analogues and the study of their psychophysiological effect on animals

MATERIALS AND METHODS

Methods of preparation and analysis

Reagents from "Alfa Aesar" (UK) and solvents from "Komponent-Reactiv" (Russia) were used for the synthesis. The starting camphor anils had been synthesized as described before [20].

The target compounds were synthesized from the corresponding camphor anils (6b, d-z) by their reduction with a combination of sodium borohydride ($NaBH_4$) and nickel (II) chloride hexahydrate ($NiCl_2{\times}6H_2O$) in 95% ethanol according to the known procedure [21, 22] (Fig. 2).

4.75 g (20 mmol) of $NiCl_2{\times}6H_2O$ dissolved in 70 mL of 95% EtOH was added to the solution of the starting anil 6a-i (10 mmol) in 30 mL of 95% ethanol (EtOH) in one step. The resulting mixture was stirred until a clear solution was formed, and then cooled in a bath of dry ice and 95% EtOH to -40°C. 3.78 g (100 mmol) of $NaBH_4$ was added to the resulting solution in several steps while stirring and maintaining the temperature to -30°C under the argon atmosphere. Upon the completion of the addition, the reaction mixture was stirred for another 60 min under the same conditions and then left overnight at room temperature. The next day, the resulting mixture was treated with 15 mL of a 3N sodium hydroxide aqueous solution, filtered and distilled off with EtOH under the reduced pressure. The cube residue was extracted with diethyl ether (Et_2O); the combined organic extracts were dried in anhydrous sodium sulfate (Na_2SO_4), filtered and evaporated. The technical product remaining in the cube was purified by column chromatography with a gravity isocratic elution with a mixture of cyclohexane: methyl tertiary butyl ether (MTBE) (13:1 by volume) on the silica gel. To obtain analytical samples, cyclohexane was used as an eluent.

The NMR spectroscopy, gas chromatography-mass spectrometry, and thin-layer chromatography (TLC) were used to identify the obtained compounds.

The ^1H and ^{13}C NMR spectra of the compounds were recorded on an AVANCE 600 NMR spectrometer (BRUKER, Germany) (operating frequencies of 600 and 150 MHz, respectively) in deuterobenzene (C_6D_6). The chemical shifts of the ^1H and ^{13}C nuclei are given relative to Me_4Si or solvent signals (C_6D_6: δ_H 7.16 ppm, δC 128.0

[3] DrugBank. Available from: https://go.drugbank.com/drugs

ppm). Two-dimensional NMR spectra (^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC) were recorded using the Z-gradient pulse technique (mixing time — 700 ms). Signals in the ^{1}H and ^{13}C NMR spectra of the products were attributed using 2D experiments ^{1}H–^{1}H COSY, ^{1}H–^{1}H NOESY, ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC.

Macherey-Nagel Alugram Xtra Sil G/UV$_{254}$ plates (Germany) were used for TLC. The spots were visualized in the UV light. R_f values of the substances are given for the eluent (cyclohexane : MTBE=13 : 1 vol.).

A GC-MS analysis was performed on a Chromatech-Crystal 5000 instrument (Russia) under conditions of the electron impact ionisation with an intensity of 70 eV.

It should be noted that the reduction of 4-bromo-*N*-[(1*R*,4*R*)-camphan-2-ylidene]aniline under these conditions leads to the formation of product 4a due to the hydrogenolysis of the C-Br bond [21]. That is why in this work, there is no study of the psychotropic activity of the product, which is the closest to bromantane in the structure.

In vivo studies

All biological activity studies were performed in accordance with the requirements of the current guidelines and in accordance with Article 11 of Federal Law 61 dated 12.04.2010 and according to the requirements of the EAEU.

The study of a psychotropic activity was performed on 69 male Wistar rats aged 20–22 weeks, weighing 300–350 g, and on 18 12-week-old mice weighing 24–28 g. The laboratory animals were obtained from the specialized nursery “Stolbovaya” of Russia (Moscow region, Chekhov district, Stolbovaya settlement). The conditions of the laboratory animals were in accordance with all the requirements of laboratory practice for preclinical studies in the Russian Federation (Order of the Ministry of Health of the Russian Federation No. 199n “On approval of the rules of good laboratory practice” dated 01 Apr 2016, GOST 33044-2014; Interstate Standard Principles of Good Laboratory Practice, and in accordance with the Decree of the Chief State Sanitary Doctor of the Russian Federation No. 51 “On approval of SR 2.2.1.3218-14 “Sanitary and Epidemiological Requirements for the Establishment of the Laboratory Animal Facility” dated 29 Aug 2014.

After the animals had been admitted to the vivarium of the Scientific Centre for Innovative Medicines of Volgograd State Medical University, they were quarantined for 14 days. The animals had a free access to food (standard rodent pellet diet GOST R 51849-2001, LLC “Laboratoryfodder”, Moscow, Russia) and water (GOST “Drinking water” 2874-82 and SanPiN 2.1.4.1074-01 “Drinking water. Hygienic requirements for water quality of centralized drinking water supply systems”). The rats were kept in plastic cages (545×395×200 mm, Type: T/4B, LLC “MEST”, Moscow), at the temperature regime of 20–22°C and the relative humidity of 40–60%. Soft wood chips were used as bedding. The light regime was 12 h of light and 12 h of darkness. The compounds were tested on the animals in equivalent doses taken in proportion to the molecular weight of the substance: 1/100, 1/30 and 1/10 of the molecular weight (Table 1).

Ethics approval

The study was approved by the Local Ethical Committee of the Volgograd State Medical University (IRB registration number 00005839 IORG 0004900 [OHRP]). Minutes of the committee meeting No. 88 dated 06 Oct 2023.

Assessment of psychophysiological state of animals

To assess the psychophysiological state of the animals, the following tests were used: the Open Field (OF) test, the Elevated Plus Maze (EPM) test, the Novel Object Recognition (NOR) test, the Extrapolation (EP) test, the Vogel conflict (VC) test, the Tail suspension (TS) test, the Tightrope suspension (TRS) test.

The animals (rats) were divided into 22 groups of 3 individuals each, except for the control group, which had 6. In the study of the anxiolytic activity, diazepam widely used in clinical practice, was used as a reference drug. Fluoxetine was used as a reference drug in the study of antidepressant properties. Phenotropil was chosen as a reference drug in the study of physical endurance and a cognitive function. The study substances were administered in two equimolar doses of 1/10 and 1/30 of their molecular weight (MW), and the substances that showed their psychotropic activity were studied at a dose of 1/100 of MW. The animals in the control group received a 0.9% sodium chloride (NaCl) solution. The mice were divided into 3 groups of 6 individuals each for the TS test.

Motor and exploratory activities of the animals were evaluated in the OF test. The setup for the “Open Field” test for rats is a circular area 97 cm in diameter, bounded by 40 cm high boards, divided by markings into 25 equal sectors, at the intersection of which, there are 16 holes (2 cm in diameter). The installation is illuminated with steady light (400 lux). To clean the setup and reduce the influence of foreign odours on behaviour (due to the presence of the previous animal), before each test, the setup is wiped with a cloth moistened with water, followed by a cloth moistened with a 5% alcohol solution and a dry rag. The next animal is tested after a complete drying of the unit surface.

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After placing a test animal in the centre of the setup, the following parameters were recorded for 3 minutes: the number of squares crossed (a spontaneous motor activity), the total number of posts and surveyed foot-holes (an approximate exploratory activity), and the number of crossings of the setup central squares [23].

To assess the anxiolytic activity of the compounds under study, the Elevated plus Maze (EPM) test is used to evaluate the level of anxiety in the animals.

The EPM installation consists of 4 (50×14 cm) arms, diverging cross-shaped from the central platform (10×10 cm) at right angles: two opposite, open, without walls (the height of the edge is 1 cm) and two closed, dark, fenced on the sides with walls 30 cm high. The cross-shaped arena of the maze is mounted on a trolley with stoppers, which provides lifting the arena to a height of 55 cm. The installation is illuminated with steady light (400 lux). Before landing the next animal, the installation was treated in the same way as the "Open Field" had been treated.

When the animals land on the central, brightly lit, elevated platform, an aversive environment for them is created; and they tend to move to a more comfortable closed arm from it. After the familiarization with the closed arm, which is not dangerous for them, the reflex of curiosity and assessment of a possible danger in other zones of the EPM is triggered.

The tested animal is placed on the central EPM platform with its head towards the open arm. And during 3 minutes, the parameters of the rodent behaviour in the conditions of a variable stressogenicity (under a free choice of comfortable conditions) are recorded: a latent period of the exit from the central platform to any arm, a number of visits and time of stay in the open arms (a potentially stressful zone of the installation), a frequency of visits and time of stay of the animals in closed arms, a sum of transitions between the arms of the installation. The time of the exit from the central site (a latent period) can be interpreted as an indicator of the speed of decision making, in addition, the central EPM zone is also a lighted space, and the time spent in it is summed up with the time in the open arms [24].

A cognitive function was assessed using the Novel Object Recognition (NOR) test. The test is based on the novelty and curiosity of animals and consists of two sessions: training and reproduction. In the training session, two identical objects are placed in a home cage without a top netting, 10 cm apart and 10 cm from each of the crate walls, and the animal explores the crate and the objects in it for 3 min. The time associated with the exploration of each object is recorded. After training, the animals are placed in home cages. In the playback session, 1 h after training, the animals were re-housed in a home cage without the top net, but one of the objects was replaced with a new one. The objects are different in shape, colour and texture but are approximately the same size. The caged animal freely explores the objects and the environment for 3 min. The animal finds the new object more interesting than the old one, the memory trace of which allows it to pay more attention to the new object (a novelty preference). The time spent exploring each object is recorded. After each test, the box is alcoholized with a 5% alcohol solution. The time spent examining the objects is presented in seconds. The NOR test reflects the state of episodic memory [25].

To assess cognitive functions under stress conditions, the Extrapolation (EP) test was used. The EP test setup is a cylindrical container (height 40 cm, diameter 35 cm) into which water with a temperature of 18–19°C is poured up to a certain level. In the centre of the container, a cylinder is vertically fixed, the lower part of which is lowered into the water by 2.5 cm. The test is conducted in 3 stages: training, the first reproduction and the second reproduction. At the stage of 'training', the animal is placed with its tail down into the inner cylinder, and within 3 min, it has to solve the following task: to dive under the edge of the cylinder, after which it is removed from the installation. After 24 h, the animals that failed to solve the "extrapolation task" within 3 min, are excluded during the first reproduction. The second reproduction is carried out 24 h after the first reproduction, i.e. 48 h after training.

The following indices are recorded in the EP test: a latent period (LP) of diving, immobilization time, a number of jumps (rapid upward body movements). Shorter time spent on the EP task of the animals of the same group receiving the investigated substance, compared to the animals of the control group, is considered as better memorization and execution of the strategy of getting rid of the aversive environment. The increase in the latent period of diving is interpreted as a loss (forgetting) of the animal's skill of active escape from the aversive environment.

The presence of the myorelaxant effect was assessed by the results of the Tightrope suspension test. To perform the test, a 0.5 cm diameter nylon rope is placed horizontally at a height of 95 cm from the cage tray filled with a 5 cm layer of wood chips. The forelegs of the animal are placed on the rope and the hind limbs are released. The time of keeping the rat on the rope is recorded. For each rat, 3 repeated landings were performed 10 sec apart. The duration of the retention was summed. A longer holding time on the rope compared to that of the control animals is considered as an increase in strength and absence of the myorelaxant

action, and *vice versa***,** a shorter holding time on the rope indicates a decrease in strength and/or a myorelaxant action of the tested substance.

The Vogel Conflict test is based on the conflict between the instinct to the quench thirst and the avoidance of punishment. It is used to determine the anxiolytic effect of the tested substances. The animal is deprived of water intake for 18 h. After 18 h, a drinker is placed in the chamber and the animals' approach to take water, but receive a weak electric shock. The number of approaches of the animals in the control group that received a physiological solution or test substances 60 min prior to testing, is recorded. Under the influence of anxiolytic substances, the animals make more approaches to the water drinker.

The Tail Suspension test is a classic test for determining the antidepressant effect of substances. The test setup was a rectangular chamber 46 cm high and 30 cm wide. During the test, the animal was suspended by 1/3 of the tail at a height of 10-15 cm from the ground with an adhesive tape. The duration of the observation is 6 min. The duration of the immobilization (desperation behaviour, the animal does not make any movement, just hangs down) is evaluated in seconds. The total duration of the immobilization during the 6 minutes of testing is taken into account. If the animal climbs on its tail, it is excluded from the experiment. During the test, a video recording of the test was used, which makes it possible to observe the animal while it is out of sight, as well as the possibility to perform an additional analysis of the animal's behaviour based on the video recording.

Statistical processing

The results were processed and analyzed using Microsoft Excel 2021 (Microsoft Corporation, USA).

Statistical processing of the obtained results was carried out by methods of descriptive and analytical statistics. The distribution of quantitative indicators was evaluated using the Shapiro-Wilk and Dunn criteria. Numerical values were presented as an arithmetic mean and a standard error of the mean. The differences between the indicators in the group were considered statistically significant at p **<0.05.**

RESULTS

Characterization of target products

The structures of the studied compounds were confirmed by NMR spectroscopy, thin layer chromatography and gas chromatography-mass spectrometry.

(1*R,*2*R,*4*R*)-1,7,7-Trimethyl-N-phenylbicyclo[2.2.1] heptane-2-amine (4a). The yield is 80%; according to the GC-MS data, the content of the target product is 99.6%. Physicochemical and NMR spectra data of the obtained sample correspond to those published before [21, 26].

(1*R*,2*R*,4*R*)-1,7,7-Trimethyl-*N*-(4-methylphenyl) bicyclo[2.2.1]heptan-2-amine (4b). The yield is 88%, the target product content (as determined by GC-MS) is 100%, the diastereomeric composition (as determined by GC-MS) is 99:1% (*ekzo-/endo-*). The mass spectrum is: (*ekzo*-form) (Eu, 70 eV), m/z (Iotn (%)): 243 [M] (100), 172 (71), 133 (62), 120 (54), 107 (40), 95 (35), 91 (18). The mass spectrum is: (*endo*-form) (Eu, 70 eV), *m/z* (Iotn (%)): 243 [M] (100), 172 (82), 133 (65), 120 (65), 107 (58), 95 (57), 91 (26). The ^{1}H NMR spectrum is: (C_6D_6, δ, m.d.): 0.73 (s, 3 H, C(7)Me camphan), 0.82 (s, 3 H, C(1) Me camphan), 0.91 (s, 3 H, C(7)Me camphan), 0.99–1. 04 (m, 1 H, C(5)H_{endo} camphan), 1.06–1.10 (m, 1 H, C(6) H_{endo} camphan), 1.42–1.47 (m, 1 H, C(6)H_{ekzo} camphan), 1.52–1.65 (m, 3 H, C(3)H_{ekzo}, C(4)H, C(5)H_{ekzo} camphan), 1.68–1.71 (m, 1 H, C(3)H_{endo} camphan), 2.23 (s, 3 H, C(4) $_{Ar}CH_3$), 3.16–3. 19 (m, 1 H, C(2)H_{endo} camphan), 3.38 (s, 1 H, NH), 6.47–6.49 (m, 2 H, C(2)$_{Ar}$H, C(6)$_{Ar}$H), 6.99–7.01 (m, 2 H, C(3)$_{Ar}$H, C(5)ArH). The ^{13}C NMR spectrum is: (C_6D_6, δ, m.d.): 12.67 (C(1)Me camphane), 20.89 (C(7) Me camphane), 20.97 (C(7)Me camphane), 20.98 (C(4)$_{Ar}$CH3), 28.01 (C(5) camphan), 37.18 (C(6) camphan), 41.30 (C(3) camphan), 45. 82 (C(4) camphan), 47.57 (C(1) camphan), 49.29 (C(7) camphan), 62.32 (C(2) camphan), 113.82 (C(2)$_{Ar}$, C(6)$_{Ar}$), 126.12 (C(4)$_{Ar}$), 130.33 (C(3)$_{Ar}$, C(5)$_{Ar}$), 146.84 (C(1)$_{Ar}$). R_f=0.86.

(1*R*,2*R*,4*R*)-1,7,7-Trimethyl-N-(2-ethylphenyl) bicyclo[2.2.1]heptan-2-amine (4c). The yield is 70%; according to the GC-MS data, the content of the target product is 99.7%. Physicochemical and NMR data of the obtained sample correspond to those published before [21].

(1*R*,2*R*,4*R*)-1,7,7-Trimethyl-N-(4-methoxyphenyl) bicyclo[2.2.1.1]heptan-2-amine (4d). The yield is 85%; and according to GC-MS, the target product content is 99.5%. Physicochemical and NMR data of the obtained sample correspond to those published before [21].

(1*R*,2*R*,4*R*)-1,7,7-Trimethyl-N-(4-ethoxyphenyl) bicyclo[2.2.1]heptan-2-amine (4e). The yield is 83%, the target product content (as determined by GC-MS) is 100%, the diastereomeric composition (as determined by GC-MS) is 100:0% (*ekzo-/endo-*). The mass spectrum (*ekzo*-form) (Eu, 70 eV), *m/z* (Iotn (%)) is: 273 [M] (100), 202 (31), 163 (50), 150 (30), 137 (23), 95 (29). The ^{1}H NMR spectrum (C_6D_6, δ, m.d.) is: 0.74 (s, 3 H, C(7)Me camphan), 0.84 (s, 3 H, C(1)Me camphan), 0.95 (s, 3 H, C(7)Me camphan), 1.01-1.05 (m, 1 H, C(5)N_{endo} camphan), 1. 08-1.12 (m, 1 H, C(6)H_{endo} camphan), 1.20 (t, 3 H, C(4)$_{Ar}$OSH2CH3, J=7.0 Hz), 1.44–1.49 (m, 1 H, C(6) H_{ekzo} camphan), 1.56–1.66 (m, 3 H, C(3)H_{ekzo}, C(4)H, C(5)

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H_{ekzo} camphan), 1.68–1.73 (m, 1 H, C(3)H_{endo} camphan), 3.13–3.15 (m, 1 H, C(2)H_{endo} caffman), 3. 26 (s, 1 H, NH), 3.37 (k, 2 H, C(4)$_{Ar}$OSH2CH3, J=7.0 Hz), 6.47–6.49 (m, 2 H, C(2)$_{Ar}$H, C(6)$_{Ar}$H), 6.86–6.89 (m, 2 H, C(3)$_{Ar}$H, C(5)$_{Ar}$H). The ^{13}C NMR spectrum (C6D6, δ, m.d.): 12.70 (C(1)Me camphan), 15.55 (C(4)$_{Ar}$OSH$_2$CH$_3$), 20.93 (C(7) Me camphan), 20.99 (C(7)Me camphan), 28.05 (C(5) camphan), 37.25 (C(6) camphan), 41.38 (C(3) camphan), 45. 87 (C(4) camphan), 47.60 (C(1) camphan), 49.27 (C(7) camphan), 62.99 (C(2) camphan), 64.28 (C(4)$_{Ar}$OSH$_2$CH$_3$), 114.81 (C(2)$_{Ar}$, C(6)$_{Ar}$), 116.39 (C(3)$_{Ar}$, C(5)$_{Ar}$), 143.34 (C(1)$_{Ar}$), 152.17 (C(4)$_{Ar}$). R_f=0.58.

((1*R*,2*R*,4*R*)-1,7,7-Trimethyl-N-(4-ethylphenyl) bicycle[2.2.1]heptane-2-amine (4e). The yield is 78%, the target product content (as determined by GC-MS) is 99.1%, the diastereomeric composition (as determined by GC-MS) is 100:0% (*ekzo-/endo-*). The mass spectrum (*ekzo*-form) (Eu, 70 eV), *m/z* (Iotn (%)) is: 243 [M] (100), 158 (87), 93 (76), 41 (30). The ^{1}H NMR spectrum (C_6D_6, δ, m.d.) is: 0.72 (s, 3 H, C(7)Me camphan), 0.83 (s, 3 H, C(1) Me camphan), 0.91 (s, 3 H, C(7)Me camphan), 0.99-1.03 (m, 1 H, C(5)H_{endo} camphan), 1.06–1.11 (m, 1 H, C(6)H_{endo} camphan), 1.20 (t, 3 H, C(4)$_{Ar}$CH$_2$CH$_3$, J=7.6 Hz), 1.43–1.47 (m, 1 H, C(6)H_{ekzo} camphan), 1.54–1.65 (m, 3 H, C(3)H_{ekzo}, C(4)H, C(5)H_{ekzo} camphan), 1.69–1.72 (m, 1 H, C(3)H_{endo} camphan), 2. 55 (k, 2 H, C(4)$_{Ar}$CH2CH3, J=7.6 Hz), 3.18–3.20 (m, 1 H, C(2)H_{endo} camphan), 3.43 (widespread s, 1 H, NH), 6.50–6.53 (m, 2 H, C(2)$_{Ar}$H, C(6)$_{Ar}$H), 7.04–7.06 (m, 2 H, C(3)$_{Ar}$H, C(5)$_{Ar}$H). The ^{13}C NMR spectrum (C_6D_6, δ, m.d.): 12.67 (C(1)Me camphane), 16.88 (C(4)$_{Ar}$CH$_2$CH$_3$), 20.88 (C(7)Me camphane), 20.96 (C(7)Me camphane), 28.01 (C(5) camphan), 28.86 (C(4)$_{Ar}$CH2CH3), 37.19 (C(6) camphan), 41. 35 (C(3) camphan), 45.83 (C(4) camphan), 47.59 (C(1) camphan), 49.28 (C(7) camphan), 62.37 (C(2) camphan), 113.86 (C(2)$_{Ar}$, C(6)Ar), 129.16 (C(3)$_{Ar}$, C(5)$_{Ar}$), 133.04 (C(4)$_{Ar}$), 147.07 (C(1)$_{Ar}$). R_f =0.87.

(1*R*,2*R*,4*R*)-1,7,7-Trimethyl-N-(2-methoxyphenyl) bicyclo[2.2.1.1]heptan-2-amine (4f). The yield is 72%, the target product content (as determined by GC-MS) is 100%, the diastereomeric composition (as determined by GC-MS) is 100:0% (*ekzo-/endo-*). The mass spectrum (*ekzo*-form) (Eu, 70 eV), *m/z* (Iotn (%)) is: 259 [M] (100), 188 (89), 136 (83), 95 (70), 41 (20). The ^{1}H NMR spectrum (C_6D_6, δ, m.d.): 0.73 (c, 3 H, C(7)Me camphan), 0.93 (c, 3 H, C(1)Me camphan), 1.03 (ddd, 1 H, C(5)H_{endo} camphan, J=12.5, 9.4, 4.4 Hz), 1.05 (c, 3 H, C(7)Me camphan), 1.11 (ddd, 1 H, C(6)H_{endo} camphan, J=12.5, 9.4, 3.8 Hz), 1. 47 (dd, 1 H, C(6)H_{ekzo} camphan, J=12.5, 11.6, 4.4 Hz), 1.58 (dd, 1 H, C(4)H camphan, *J*=4.3 Hz), 1.59-1. 70 (m, 2 H, C(3)H_{ekzo}, C(5)H_{ekzo} camphan), 1.75 (dd, 1 H, C(3)H_{endo}, *J*=12.8, 8.3 Hz), 3.25 (dd, 1 H, C(2)N_{endo} cafman, J=8.3, 6.1, 4.8 Hz), 3.34 (s, 3 H, C(2)$_{Ar}$OCH3), 4.54 (e, 1 H, NH J=6.1), 6.59 (dd, 1 H, C(3)$_{Ar}$H, J=7.9, 1.4 Hz), 6. 70 (dd, 1 H, C(6)$_{Ar}$H, J=7.9, 1.4 Hz), 6.73 (ddd, 1 H, C(4)$_{Ar}$H, J=7.9, 7.5, 1.5 Hz), 7.01 (ddd, 1 H, C(5)$_{Ar}$H, J=7.9, 7.5, 1.5 Hz). 13C NMR spectrum (C_6D_6, δ, m.d.): 12.74 (C(1)Me camphan), 20.95 (C(7)Me camphan), 20.99 (C(7)Me camphan), 28.05 (C(5)caffman), 37.21 (C(6)camphan), 41.52 (C(3) camphan), 45.92 (C(4)camphan), 47.64 (C(1)camphan), 49.40 (C(7)camphan), 55.46 (C(2)$_{Ar}$OCH3), 61. 91 (C(2) camphan), 110.16 (C(3)$_{Ar}$), 110.68 (C(6)$_{Ar}$), 116.35 (C(4)$_{Ar}$), 122.16 (C(5)$_{Ar}$), 122.16 (C(5)$_{Ar}$), 139.12 (C(1)$_{Ar}$), 147.41 (C(2)$_{Ar}$). R_f =0.82.

(1*R*,2*R*,4*R*)-1,7,7-Trimethyl-N-(2,5-dimethoxyphenyl) bicyclo[2.2.1.1]heptan-2-amine (4z). The yield is 64%, the target product content (as measured by GC-MS) is 99.8%, and the diastereomeric composition (as measured by GC-MS) is 100:0% (*ekzo-/endo-*). The mass spectrum of (*ekzo*-form) (Eu, 70 eV), *m/z* (Iotn (%)) is: 289 [M] (100), 274 (23), 218 (36), 179 (31), 166 (33), 153 (29), 138 (23), 95 (50), 41 (21). The ^{1}H NMR spectrum of (C_6D_6, δ, m.d.) is: 0.70 (s, 3 H, C(7)Me camphan), 0.92 (s, 3 H, C(1)Me camphan), 0.94-0.98 (m, 1 H, C(5)H_{endo} camphan), 1.02-1.07 (m, 1 H, C(6)H_{endo} camphan), 1.03 (s, 3 H, C(7)Me camphan), 1. 40-1.45 (m, 1 H, C(6)H_{ekzo} camphan), 1.54-1.61 (m, 2 H, C(4)H caffman, C(5)H_{ekzo} camphan), 1.64-1.68 (m, 1 H, C(3)H_{ekzo}), 1.73 (dd, 1 H, C(3)H_{endo}, *J*=12.9, 8.3 Hz), 3.23 (ddd, 1 H, C(2)H_{endo} camphan, J=8.3, 6.2, 4.7 Hz), 3.39 (c, 3 H, C(2)$_{Ar}$OCH3), 3. 53 (c, 3 H, C(5)$_{Ar}$OCH3), 4.59 (e, 1 H, NH J=6.2), 6.18 (dd, 1 H, C(4)$_{Ar}$H, J=8.6, 2.9 Hz), 6.55 (e, 1 H, C(6)$_{Ar}$H, J=2.9). The 13C NMR spectrum (C_6D_6, δ, m.d.) is: 12.73 (C(1)Me camphan), 20.90 (C(7) Me camphan), 20.95 (C(7)Me camphan), 27.96 (C(5) camphan), 37.12 (C(6) camphan), 41.35 (C(3) camphan), 45.89 (C(4)camphan), 47.61 (C(1)camphan), 49.38 (C(7) camphan), 55.49 (C(5)$_{Ar}$OCH3), 56.09 (C(2)$_{Ar}$OCH3), 61. 82 (C(2)camphan), 98.50 (C(4)$_{Ar}$), 99.39 (C(6)$_{Ar}$), 110.55 (C(3)$_{Ar}$), 140.13 (C(1)$_{Ar}$), 142.27 (C(2)$_{Ar}$), 156.20 (C(5)$_{Ar}$). R_f=0.65.

Results of *in vivo* studies

In the OF test, the animals administered with substances 4c and 4h had a higher (53.7±1.6 and 52.3±2.0, respectively) motor activity (a number of crossed squares) compared to the control group (38.5±0.8), they were more in the central squares of the setup than others. A higher exploratory activity was registered in the animals injected with substance 4h in all doses, while substances 4c, 4d and 4e increased an exploratory activity only in low (1\100 of MW) doses (Fig. 3).

In the EPM test, i.e. under the conditions of stressogenicity, the behaviour of animals receiving compounds 4c and 4f was particularly different from

the control group (Fig. 4). It is possible to note a decrease in the LP of leaving the central site in the animals receiving compounds 4c (1.3±0.3) and 4g (1.7±0.7), which may indicate a rapid decision making and an increased exploratory activity. There was an increase in the frequency of going into the open arm and the time spent in the open arm, especially for compound 4f (26 mg/kg; 130±10). The animals receiving compounds 4c (9 mg/kg; 5±1), 4f (2.5±1.5) at all doses, 4g (9 and 26 mg/kg; 4.3±1.6 and 3.5±0.9), and 4h (10 and 29 mg/kg; 4.5±2 and 2.8±1.6) were less likely to move between the arms, also indicating a reduced anxiety.

The recording of transitions between the arms, especially the exits to and stays in the open arms, makes it possible to judge the depressant (diazepam) or anxiolytic, antiphobic action (compound 4e).

All the animals, except those receiving diazepam and compound 4e, quickly left the central site. A pre-injection of the investigated substances did not interfere with the decision to leave the central site quickly under the conditions of variable aversiveness. The animals under the influence of compound 4e stayed in the open arms longer than others (130±10), and the animals receiving compound 4c repeatedly moved from one arm to another without lingering on the open surfaces of the EPM. Under the influence of diazepam, the animals moved little both in the OF and in the EPM tests, but after entering the central area or after crossing it, they stayed longer on the open surface.

The anxiolytic properties of the camphor derivative — compound 4e ((1*R*,2*R*,4*R*)-1,7,7-trimethyl-*N*-(4-ethylphenyl)bicyclo[2.2.1]heptan-2-amine), which had the most pronounced anxiolytic effect in the EPM test, were evaluated in the Vogel conflict test. The substance increased the number of attempted punished water draws compared to the animals that received a NaCl solution 60 min before testing (control group), but statistically significantly less than the reference drug diazepam (Fig. 5A).

These data, together with the results obtained in the OF and EPM tests, indicate the anxiolytic properties of substance 4f.

Depressive disorders are not rare in persons with anxiety disorders. Therefore, the presence (or absence) of antidepressant properties of compound 4f was assessed by the duration of the immobilization in the EPM test. Compared to the control animals, the immobilization time was statistically significantly shorter in the mice treated with compound 4f (Fig. 5B).

Amnesic and myorelaxant actions are characteristic for the substances with anxiolytic effects similar to benzodiazepines [27, 28]. For this purpose, cognitive effects were studied in the Novel Object Recognition and Extrapolation tests, as well as in the Tightrope suspension test, and the effect of the substance on the physical strength was tested.

The examination of the compound 4f effect on the attention and short-term memory in the Novel Object Recognition test showed that the animals in the control group learnt the objects more (A1: 9.3±0.3; A2: 7.7±1.8) than the animals receiving compound 4f in the first phase of testing (Fig. 5C). However, after 1 hour in the second stage of testing, most animals that had been administered the compound in all three dosages (1/100: 9±0.3, 1/30: 7.7±2.9 and 1/10: 7.5±2.5 of molecular weight) studied the novel object more, suggesting that the compound under study enhances the animals' attention and short-term memory (Fig. 5D).

In the Extrapolation test, the animals receiving compound 4f at a dose of 9 mg/kg were faster in the extrapolation escape task on day 2 (3.3±2.3) than on day 1 (13.3±10.8), and also faster compared to the control group (9.7±4.1) (Fig. 5E). Taken together, the compound in the Novel Object Recognition and Extrapolation tests indicated an improvement in the cognitive function.

In the course of the experiment on the Tightrope suspension, it was found out that the animals receiving compound 4f at a dose of 26 mg/kg were keping on the rope longer (89.7±14.3) than the animals of the control group (47.7±12.7), which indicates the absence of myorelaxing properties in this substance.

DISCUSSION

The structural features of camphor, a typical representative of natural monoterpenoids, in combination with its low toxicity, were the basis for the choice of this compound as a starting material for a directed structural modification to obtain pharmacologically active monoterpenoid aromatic amines with low toxicity.

The modification was carried out by obtaining intermediates — substituted camphor anils, by the reduction of which the studied compounds had been obtained. Herewith, the known methods of the anil synthesis, involving the use of catalytic systems and condensing agents, lead to obtaining difficult to isolate and, often, contaminated products, which reduces the yield of pure substances. To solve this problem, an original method of synthesis in the presence of an *in situ* obtained catalytic complex was developed. That provides a technological approach to the preparation of intermediates [29], where the catalytic system performs an additional function of an acceptor of the water released during the condensation.

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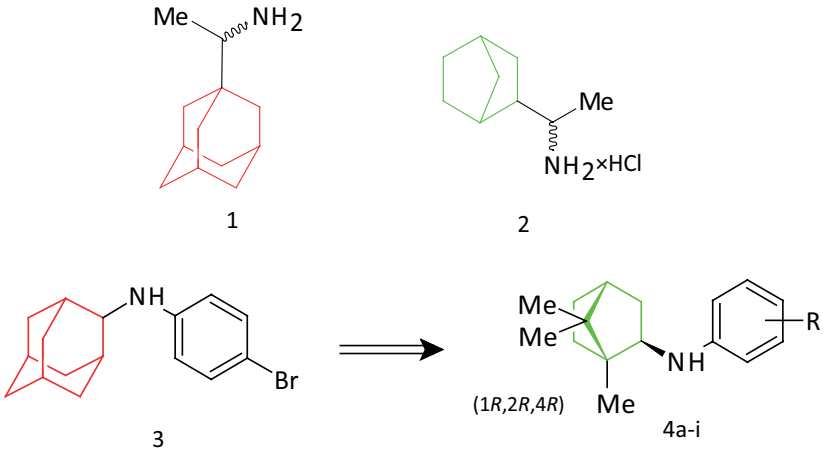

Figure 1 – Chemical structure of rimantadine (1), deutiforin (2), bromantane (3) and the investigated compounds (4 a–z — N-(camphan-2-yl)anilines)

Note: R=H (4a), 4-Me (4b), 2-Et (4c), 4-OMe (4d), 4-OEt (4d), 4-Et (4e), 2-OMe (4j), 2,5-(OMe)2 (4h).

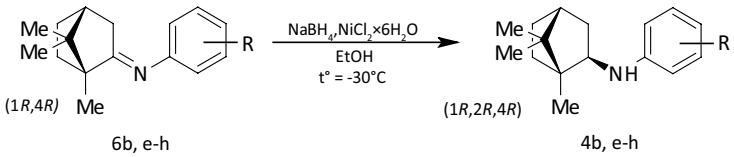

Figure 2 – Reaction of target compounds formation

Note: 4b — 88%, 4e — 83%, 4f — 78%, 4g — 72%, 4i — 64%.

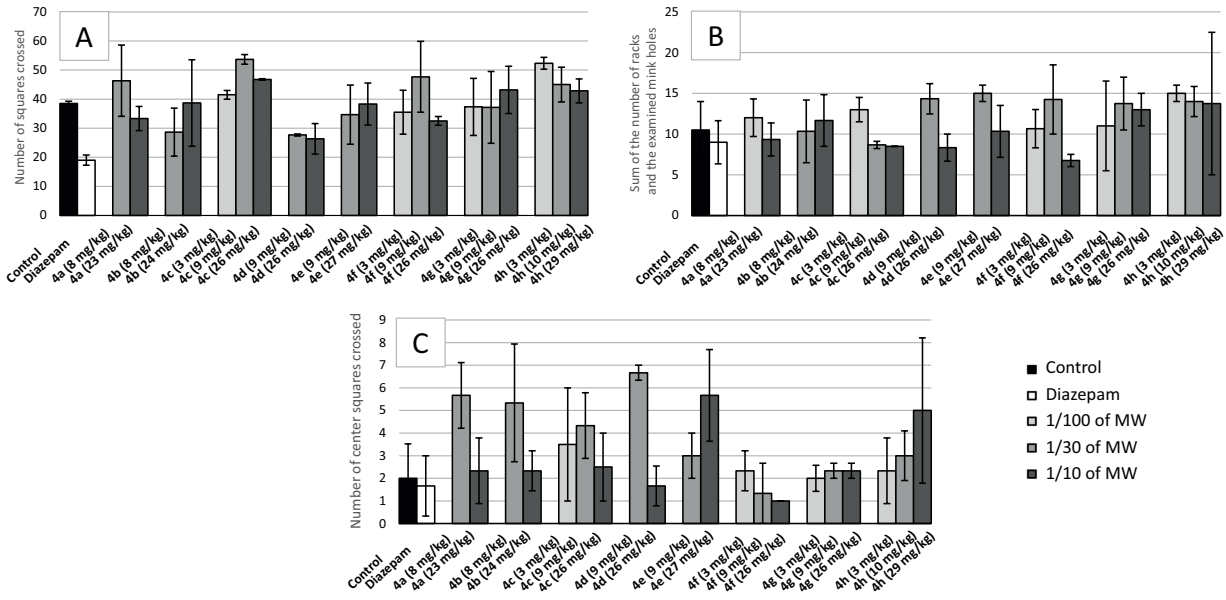

Figure 3 – Effect of the tested substances on animal behaviour in the "Open Field" test

Notes: A) a number of crossed squares; B) total exploratory activities (a total number of peeks into holes, unsupported stands and supported stands); C) a number of crossings of central sectors. * — differences are statistically significant compared to control group animals.

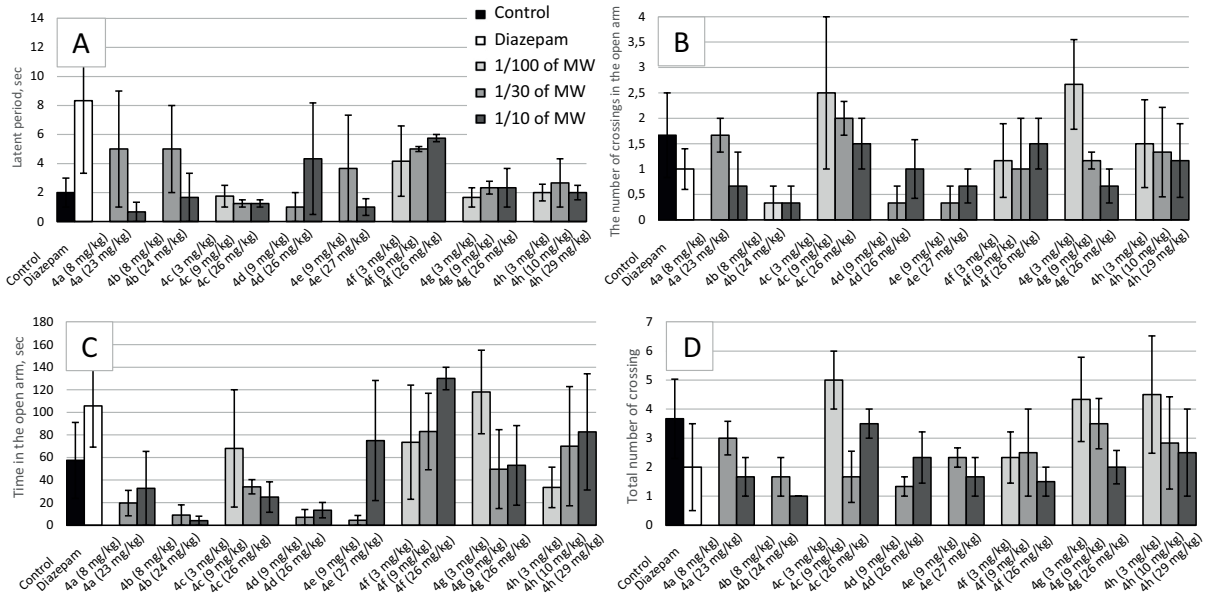

Figure 4 – Effect of the investigated substances on animal behaviour in the Elevated Plus Maze test

Note: A) a latent period of leaving the central site; B) frequency of animal exits to the open arm of the facility; C) time of animal stay in the open arm of the facility; D) a total number of transitions between the arms of the facility (the sum of transitions, entrances to the open arm and entrances to the closed arm). * — the differences are statistically significant compared to the animals of the control group.

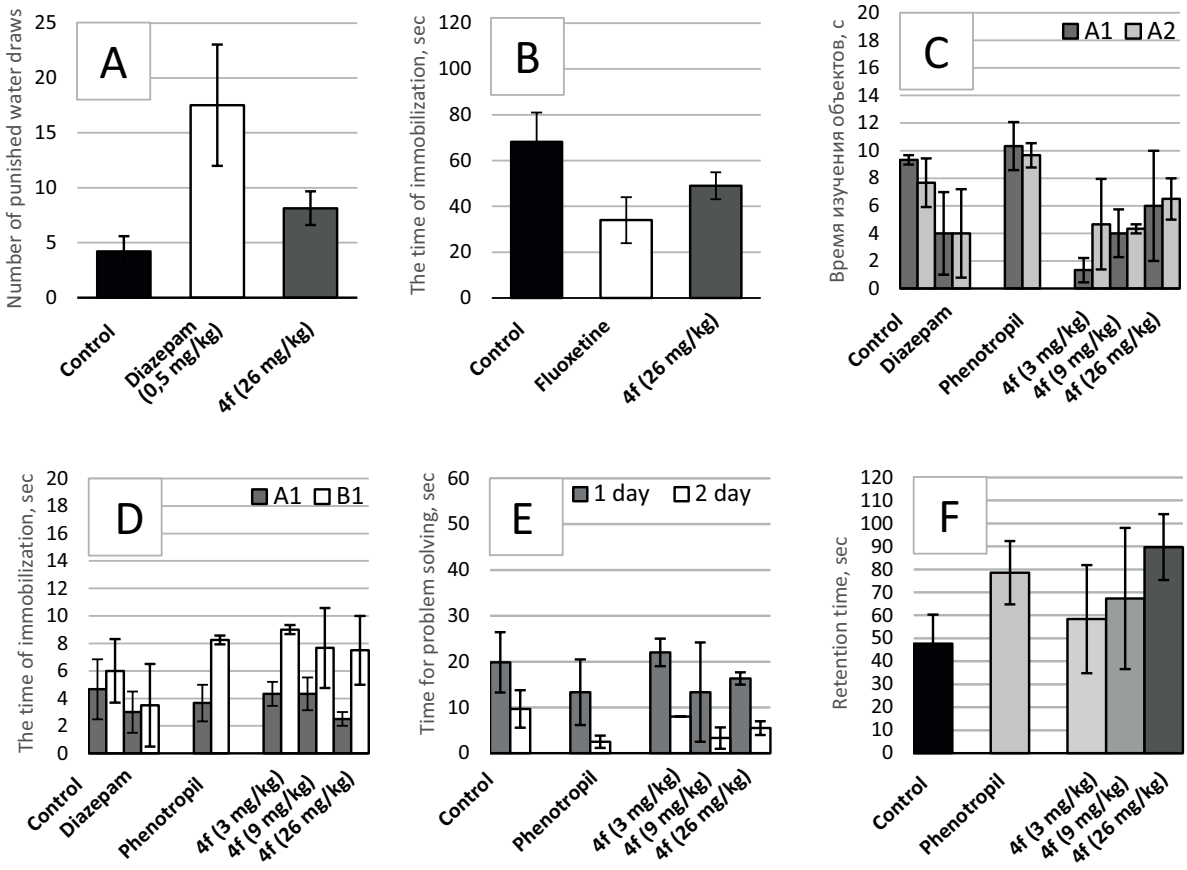

Figure 5 — Behaviour of animals in the tests studied

Note: A) The Vogel conflict test; B) The Tail suspension test; C) The Novel Object Recognition test; the training session; D) The RNO test; the reproduction session; E) The Extrapolation test; F) The tightrope suspension test. * — the differences are statistically significant compared to the group of animals. # — the differences are statistically significant in comparison with the time of learning the object A1 in the NOR test and in comparison with the time of solving the extrapolation task on day 1 in the Extrapolation test.

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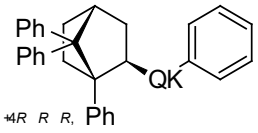
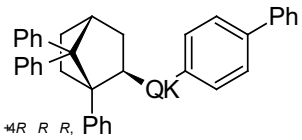
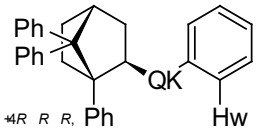
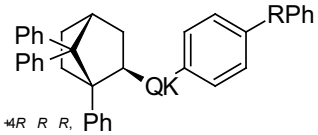
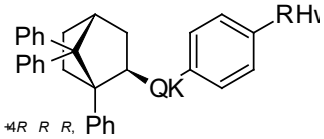
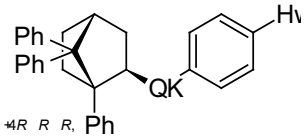
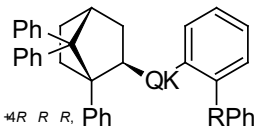
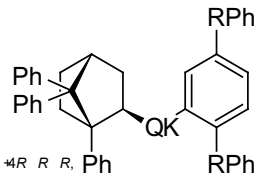
Table 1 – Obtained compounds, their names, structural formulas, molecular weight and doses for *in vivo* study

Sequence number	Name Molecular weight, g/mol; equimolar doses (mg/kg)	Structural formula	Molecular weight, g/mol; equimolar doses (mg/kg)
4a	(1*R*,2*R*,4*R*)-1,7,7-trimethyl-*N*-(phenyl) bicycle[2.2.1]heptane-2-amine		229.36 1/30 (8) 1/10 (23)
4b	(1*R*,2*R*,4*R*)-1,7,7-trimethyl-*N*-(4-methylphenyl) bicycle[2.2.1]heptane-2-amine		243.39 1/30 (8) 1/10 (24)
4c	(1*R*,2*R*,4*R*)-1,7,7-trimethyl-*N*-(2-ethylphenyl) bicycle[2.2.1]heptane-2-amine		257.41 1/100 (3) 1/30 (8) 1/10 (24)
4f	(1*R*,2*R*,4*R*)-1,7,7-trimethyl-*N*-(4-methoxyphenyl) bicyclo[2.2.1.1]heptan-2-amine		259.39 1/30 (8) 1/10 (26)
4g	(1*R*,2*R*,4*R*)-1,7,7-trimethyl-*N*-(4-ethoxyphenyl) bicyclo[2.2.1.1]heptan-2-amine		273.42 1/30 (9) 1/10 (27)
4h	(1*R*,2*R*,4*R*)-1,7,7-trimethyl-*N*-(4-ethylphenyl) bicycle[2.2.1]heptane-2-amine		257.41 1/100 (3) 1/30 (9) 1/10 (26)
4i	(1*R*,2*R*,4*R*)-1,7,7-trimethyl-*N*-(2-methoxyphenyl) bicyclo[2.2.1.1]heptan-2-amine		259.39 1/100 (3) 1/30 (9) 1/10 (26)
4j	(1*R*,2*R*,4*R*)-1,7,7-trimethyl-*N*-(2,5-dimethoxyphenyl)bicyclo[2.2.1.1]heptan-2-amine		289.41 1/100 (3) 1/30 (10) 1/10 (29)

In the reduction process of the obtained intermediates, a special attention was paid to the proper selection of the hydrogenating agent and to the identification of limitations to the application of the technique in terms of steric factors hindering hydrogenation. The competition manifests itself in the form of an activating action of donor substituents in the aromatic ring depending on their structure, amount and location relative to the exocyclic nitrogen atom. A high yield of the target compounds was accompanied by obtaining a by-product of the aromatic ring reduction, so the most effective method of the target compounds isolation was the method of column chromatography. The nature and location of the substituent in the aromatic ring also influenced the activity of the compounds. All the studied camphor aromatic amines, except for substance 4a, contained donor substituents represented by lower alkyl and alkoxyl groups. A high activity expected from

alkoxy-substituted aromatic amines was not justified, and the substituted derivatives 4c and 4f were the most active. In both cases, the ethyl substituent located in positions providing a coordinated orientation with the exocyclic nitrogen, led to an increase in the activity of the substances. However, the shielding effect of the ethyl substituent in the ortho-position slightly reduced the activity of the amine, whereas the para-ethyl substituted product showed the highest activity.

According to the results of the biological activity study, compound 4f should be singled out in the Elevated plus maze (EPM) test (significantly longer dwell time in the open arms compared to the animals of other groups, including the control group). In the Vogel conflict test, the animals receiving the same compound made more approaches to punished water draws than the animals of the control group. In the Tail suspension test, the animals administered with compound 4f recorded a shorter period of immobilization, and in the Extrapolation test, active behaviour and a rapid task solution of getting rid of the aversive environment indicated an antidepressant effect. The animals receiving compound 4f performed better in the Novel Object Recognition and the Extrapolation tests and, respectively, in the first and second tests, learnt more about the novel object and were quicker to dive under the lower edge of the cylinder and get rid of the aversive environment, reflecting good attention, short-term memory and quick decision making. In the Tightrope suspension test, the animals held on longer in comparison with the animals of the control group, and at a dose of 26 mg/kg, and longer than the animals receiving the reference drug phenotropil. Thus, the performed study made it possible to obtain substance 4f ((1*R*,2*R*,4*R*)-1,7,7-trimethyl-N-(4-ethylphenyl)bicyclo[2.2.1.1]heptan-2-amine) with pronounced anxiolytic, antidepressant and nootropic actions in a series of camphan derivatives and possibly increasing physical performance. Compound 4f is promising for a further in-depth study of its psychotropic properties.

Study limitations

The study was conducted on a relatively small group of animals, which can reduce a statistical power and make it difficult to identify rare or weak effects. The experiment covered a limited period of time, which makes it impossible to assess long-term effects of the substances.

CONCLUSION

In the OF test, compounds 4c with an ethyl substituent in the second position of the phenyl ring and 4i, having two methoxy groups in the phenyl ring, increased a motor activity, and in the Elevated plus maze (EPM) test, the animals made more transitions between the arms, indicating their psychostimulant effect.

Compound 4f in the Elevated plus maze (EPM) test increased the time spent in the open arms, and in the Vogel conflict test, there was a greater number of attempts of punished water draws than in the animals of the control group, but fewer than in the animals receiving the comparison drug diazepam.

The 4f substance insignificantly decreased the immobilization time in the Tail suspension and Extrapolation tests compared to the control. When assessing the effects of the substance on the cognitive function, an increase in the time to explore an unknown object and a decrease in the time to solve an extrapolative escape were noted, which can be regarded as an improvement in the cognitive function. In the Tightrope suspension test, a significantly longer retention of the animals was observed.

The presented data indicate that compound 4f had a moderate anxiolytic effect without myorelaxant, amnesic and, at the same time, antidepressant effects. The presented data indicate the prospect of a further search for substances with psychotropic properties in the range of camphan derivatives and the expediency of in-depth study of specific activities and an action mechanism of the compound (1R,2R,4R)-1,7,7trimethyl-N-(4-ethylphenyl)bicyclo(2,2,1,1)heptan-2-amine (4e).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

Andrey A. Vernigora — implementation of the research process, synthesis of chemicals; Leila L. Brunilina — creation and preparation of the manuscript; Andrey V. Kazhberov — implementation of the research process, including isolation and purification of chemical structures; Nikita S. Bolokhov — implementation of the research process, including experiments with animals, creation and preparation of the manuscript, application of statistical methods for the analysis of research data; Aleksander A. Pokhlebin — implementation of the scientific research process, including experiments with animals; Alina A. Sokolova — implementation of the research process, including performing experiments with animals; Vladislav E. Pustynnikov — implementation of the research process, including performing experiments with animals; Ivan N. Tyurenkov — control, leadership and mentoring in the process of planning and conducting research; Ivan A. Novakov — control, leadership and mentoring in the planning process; Vyacheslav I. Krasnov, Dmitry N. Polovyanenko — implementation of the scientific research process, including identification of chemical structures.

All the authors confirm their authorship compliance with the ICMJE international criteria (all the authors made significant contributions to the conceptualization, research and preparation of the article, read and approved the final version before the publication).

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AUTHORS

Andrey A. Vernigora — Senior Lecturer of Department of Organic Chemistry of Volgograd State Technical University. ORCID ID: 0000-0001-6456-0910. E-mail: vernigoraa@vstu.ru

Leila L. Brunilina — Candidate of Sciences (Chemistry), Associate Professor, Associate Professor of the Department of Organic Chemistry of Volgograd State Technical University. ORCID ID: 0000-0001-9956-5412. E-mail: leila_1974@mail.ru

Andrey V. Kazhberov — student (group XT-341) of Volgograd State Technical University. ORCID ID: 0009-0002-4544-3393. E-mail: andejkazberov37042@gmail.com.

Nikita S. Bolokhov — postgraduate student of the Department of Pharmacology, Clinical Pharmacology and Pharmacy of Institute of Continuing Medical and Pharmaceutical Education, Volgograd State Medical University. ORCID ID: 0000-0002-2458-5731. E-mail: nikita.bolokhov@volgmed.ru.

Aleksander A. Pokhlebin — postgraduate student of the Department of Pharmacology, Clinical Pharmacology and Pharmacy of Institute of Continuing Medical and Pharmaceutical Education, Volgograd State Medical University. ORCID ID: 0000-0002-0474-5005. E-mail: spohlebin12340@mail.ru

Alina A. Sokolova — postgraduate student of the Department of Pharmacology, Clinical Pharmacology and Pharmacy of Institute of Continuing Medical and Pharmaceutical Education, Volgograd State Medical University. ORCID ID: 0000-0002-5116-8458. E-mail: sokolovaaa.volgmed@gmail.co

Vladislav E. Pustynnikov — postgraduate student, the Department of Pharmacology, Clinical Pharmacology and Pharmacy of Institute of Continuing Medical and Pharmaceutical Education, Volgograd State Medical University. ORCID ID: 0000-0001-9561-5320. E-mail: Pustynnikov.volgmed@gmail.com

Ivan N. Tyurenkov — Doctor of Sciences (Medicine), Professor, Head of the Laboratory of Pharmacology of Cardiovascular Pharmacology of Institute of Continuing Medical and Pharmaceutical Education, Volgograd State Medical University; Corresponding Member of the Russian Academy of Sciences. ORCID ID: 0000-0001-7574-3923. E-mail: fibfuv@mail.ru

Ivan A. Novakov — Doctor of Sciences (Chemistry), Professor, Head of the Department of Analytical, Physical Chemistry and Physical Chemistry of Polymers of Volgograd State Technical University; Academician of the Russian Academy of Sciences. ORCID ID: 0000-0002-0980-6591. E-mail: phanchem@vstu.ru

Vyacheslav I. Krasnov — Candidate of Sciences (Chemistry), Senior Researcher, Head of the Laboratory of Vorozhtsov Novosibirsk Institute of Organic Chemistry. ORCID ID: 0000-0002-5387-8365. E-mail: krasnov@nioch.nsc.ru

Dmitry N. Polovyanenko — Candidate of Sciences (Physics and Mathematics), Senior Researcher, Head of the Laboratory of Vorozhtsov Novosibirsk Institute of Organic Chemistry. ORCID ID: 0009-0000-3835-825X. E-mail: dpolo@nioch.nsc.ru

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The work of compounding pharmacies and the possible risks of violating the exclusive rights to original medicines

A.V. Alekhin[1,2], T.N. Erivantseva[3], V.O. Kalyatin[4, 5], R.A. Ivanov[6], N.A. Alekhina[7]

[1] Farmaklon Group,
12 Krasnopresnenskaya Emb., room 1542B, Moscow, Russia, 123610
[2] Bauman Moscow State Technical University (National Research University),
10 Presnenskaya Emb., bldg 2, Moscow, 125039, Russia
[3] Eurasian Patent Office of the Eurasian Patent Organization,
2 Cherkassky Lane, Moscow, Russia, 109012
[4] Private Law Research Centre under the President of the Russian Federation named after S.S. Alexeev,
8 Ilyinka Str., Moscow, Russia, 103132
[5] Higher School of Economics,
11 Pokrovsky Blvd, Moscow, Russia, 109028
[6] Sirius University,
1 Triumfalny Ave., Krasnodar Territory, Federal Territory "Sirius", Russia, 354340
[7] Sechenov First Moscow State Medical University (Sechenov University),
8 Trubetskaya Str., bldg 2, Moscow, Russia, 119991

E-mail: ru-patent@mail.ru

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The revival of production pharmacies in Russia began in 2022. To effectively use the capabilities of compounding pharmacies, it is necessary to take into account the importance of eliminating the risk of infringement of intellectual property rights.

The aim. The study of the foreign practice of compounding pharmacies in terms of infringement of exclusive rights, as well as the position of foreign patent offices and the World Intellectual Property Organization (WIPO).

Materials and methods. A key aspect of the research was the study of the foreign practice of violating the exclusive rights to original medicines. An information search was conducted for publications related to the activities of compounding pharmacies in the world, as well as issues related to the regulation of the relationship between their activities and legislation in the field of intellectual property.

Results. The article analyzes foreign judicial practices and positions of patent offices, summarized by WIPO, on this issue. The results and discussion are based on the consideration of foreign court cases and legislative norms related to the production of patented drugs in compounding pharmacies. The examples of court cases that raise issues of violations of exclusive rights are given.

Conclusion. In Russia, the possibility of one-time compounding of drugs using the invention in pharmacies according to doctors' prescriptions is fixed at the legislative level. However, this permission only applies to a "specific recipe". One possible way to reduce the severity of the problem may be to directly allow pharmacies to use contractors to fulfill a specific request. The concept of "one-time compounding" also requires disclosure, which may expand the capabilities of pharmacies. The results obtained can be used in the framework of legislative regulation of the compounding of medicines in a pharmacy.

Keywords: drugs; compounding pharmacies; patent; invention; intellectual property; exclusive right

Abbreviations: CC RF — Civil Code of the Russian Federation; EAPC — Eurasian Patent Convention; EAPO — Eurasian Patent Office; WIPO — World Intellectual Property Organization; WTO — World Trade Organization; NCBI — National Center for Biotechnological Information; FDA — US Food and Drug Administration; SCP — Standing Committee on the Law of Patents; EPO — European Patent Organization.

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Деятельность производственных аптек и возможные риски нарушения исключительных прав на оригинальные лекарственные средства

А.В. Алехин[1,2], Т.Н. Эриванцева[3], В.О. Калятин[4, 5], Р.А. Иванов[6], Н.А. Алехина[7]

[1] Общество с ограниченной ответственностью «УК Фармаклон»,
Россия, 123610, г. Москва, наб. Краснопресненская, д. 12, помещение 1542В
[2] Федеральное государственное автономное образовательное учреждение высшего образования
«Московский государственный технический университет имени Н.Э. Баумана
(Национальный исследовательский университет)»,
Россия, 125039, г. Москва, Пресненская наб., д. 10, стр. 2
[3] Евразийское патентное ведомство Евразийской патентной организации,
109012, Россия, г. Москва, М. Черкасский пер., д. 2
[4] Федеральное государственное бюджетное научное учреждение
«Исследовательский центр частного права имени С.С. Алексеева при Президенте Российской Федерации»,
Россия, 103132, г. Москва, ул. Ильинка, д. 8, стр. 2
[5] Федеральное государственное автономное образовательное учреждение высшего образования
«Национальный исследовательский университет «Высшая школа экономики»,
Россия, 109028, г. Москва, Покровский бульвар, д. 11
[6] Автономная некоммерческая образовательная организация высшего образования
«Научно-технологический университет «Сириус»,
354340, Россия, Краснодарский край, федеральная территория «Сириус», Триумфальный пр-д, д. 1
[7] Федеральное государственное автономное образовательное учреждение высшего образования
«Первый Московский государственный медицинский университет имени И.М. Сеченова»
Министерства здравоохранения Российской Федерации (Сеченовский Университет),
Россия, 119991, Россия, г. Москва, ул. Трубецкая, д. 8, стр. 2

E-mail: ru-patent@mail.ru

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В России с 2022 года началось возрождение производственных аптек. Для эффективного использования возможностей таких аптек требуется учесть важность исключения риска нарушения прав на результаты интеллектуальной деятельности.

Цель. Изучение зарубежной практики производственных аптек с точки зрения нарушения исключительных прав, а также позиции зарубежных патентных ведомств и Всемирной организации интеллектуальной собственности (ВОИС).

Материалы и методы. Ключевым аспектом исследования стало изучение зарубежной практики нарушений исключительных прав на оригинальные лекарственные препараты. Проведён информационный поиск публикаций, касающихся деятельности производственных аптек в мире, а также вопросов регулирования взаимосвязи их деятельности и законодательства в области интеллектуальной собственности.

Результаты. В статье проанализированы зарубежные судебные практики и позиции патентных ведомств, обобщенные ВОИС, относительно данного вопроса. Результаты и обсуждение основаны на рассмотрении зарубежных судебных дел и законодательных норм, касающихся производства запатентованных лекарственных препаратов в производственных аптеках. Представлены примеры судебных дел, поднимающих вопросы нарушений исключительных прав.

Заключение. В России на законодательном уровне закреплена возможность разового изготовления в аптеках по рецептам врачей препаратов с использованием изобретения. Однако это разрешение касается только «конкретного рецепта». Одним из возможных вариантов снижения остроты проблемы может быть прямое разрешение аптекам использовать подрядчиков для выполнения конкретного запроса. Также требует раскрытия понятие «разового изготовления», что может расширить возможности аптек. Полученные результаты могут быть использованы в рамках законодательного регулирования изготовления лекарственных средств в аптечной организации.

Ключевые слова: лекарственные средства; производственные аптеки; патент; изобретение; интеллектуальная собственность; исключительное право

Список сокращений: ЛС — лекарственное средство; ГК РФ — Гражданский Кодекс Российской Федерации; ЕАПК — Евразийская Патентная Конвенция; ЕАПВ — Евразийское патентное ведомство; ВОИС — Всемирная организация интеллектуальной собственности; ВТО — Всемирной торговой организации; NCBI — Национальный центр биотехнологической информации, FDA — Управление по контролю качества пищевых продуктов и лекарственных средств США; ПКПП — Постоянный комитет по патентному праву, EPO — Европейская патентная организация.

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INTRODUCTION

In 2022, Federal Law No. 502-FZ of December 5, 2022, "On Amendments to Article 56 of the Federal Law «On the Circulation of Medicines»[1]," regulating the revival of compounding pharmacies in Russia (RF), was adopted. This initiative is not a novelty introduced exclusively in the Russian Federation. Compounding medicines in a pharmacy is an integral part of providing prompt individual pharmaceutical care to patients when there are no suitable medicines on the market or when a specific dosage form is required [1–3]. Since 2023, pharmacies have been able to produce medicines according to individual prescriptions from doctors, using existing medications in the necessary dosages [4–6]. Due to the lack of a register of compounding pharmacies, it is difficult to reliably assess the dynamics of their opening since the adoption of legislative changes. According to expert estimates[2], there are currently about 460 compounding pharmacies operating in the Russian Federation, and about 2 000 pharmacies have licenses for production activities. A large-scale project within the framework of the revival of compounding pharmacies was the creation of a pilot industrial production facility for the manufacture of "orphan" drugs, announced in 2024. It will operate on the principle of a compounding pharmacy. The project is being implemented on the Federal Territory of Sirius (Russia)[3]. Its opening is scheduled for 2025[4].

The activities of compounding pharmacies, which allow for the prompt replacement of emerging drug shortages, taking into account the individual needs of patients, are closely related to intellectual property, with the turnover of rights to the results of intellectual activity in the area under consideration, namely, with exclusive rights to the original (or reference) drug that is reproduced by pharmacies. In the Russian Federation, compounding pharmacies are only beginning to develop, while similar pharmacies have been operating in European countries [7–9] and the USA [10] for decades. In order to minimize the risks associated with the operation of such pharmacies, the authors of the article decided to study the foreign practice of such pharmacies from the point of view of violations of exclusive rights, as well as the position of foreign patent offices and the World Intellectual Property Organization (WIPO). The importance of understanding this aspect is explained by the fact that the production of medicines is closely related to the existence of exclusive rights to them and their components, granted by a patent. Violation of exclusive rights entails lawsuits from the manufacturer of the original drug against the infringer, which in this case may be a compounding pharmacy.

THE AIM. Analysis of the development of compounding pharmacies in the prism of possible risks of infringement of exclusive rights to original medicines protected by a patent for invention and a trademark certificate.

MATERIALS AND METHODS

An information search of publications was conducted regarding the presence of compounding pharmacies in various countries, as well as issues of regulating the relationship between their activities and legislation in the field of intellectual property. The search was conducted in databases such as: World Intellectual Property Organization (WIPO), National Center for Biotechnology Information (NCBI), ScienceDirect, U.S. Food and Drug Administration (FDA), elibrary.ru. The search results also included publications found through the Google Scholar service. In addition, the scope of the search included regulatory legal bases of the Russian Federation, foreign countries and international communities related to the manufacture and introduction of drugs into civil circulation.

The search was carried out using the following keywords and phrases: "intellectual property", "compounding pharmacy", "law", "patent", "drugs", "extemporaneous compounding", as well as their Russian-language analogues: "интеллектуальная собственность", "производственные аптеки", "закон", "патент", "препарат", "лекарственное средство", "экстемпоральное производство".

The period of studied publications was from November 2024 to January 2025; the search period was 20 years.

A search conducted using keywords in English in the ScienceDirect database revealed 954 thematic works. After screening out publications related to the patenting of pharmaceutical inventions and the activities of compounding pharmacies (*n*=895), as well as articles similar in content (*n*=31), 28 scientific articles were included in the review.

A search conducted using keywords in Russian in the scientific elibrary.ru revealed 213 works; after excluding

[1] Federal Law No. 502-FZ dated 05.12.2022 "On Amendments to Article 56 of the Federal Law "On the Circulation of Medicines". Available from: http://publication.pravo.gov.ru/Document/View/0001202212050043. Russian

[2] Nevinnaya I. The expert explained the importance of manufacturing pharmacies for orphan patients. Projects of Russia. Available from: https://rg.ru/2024/08/17/ekspert-obiasnila-vazhnost-proizvodstvennyh-aptek-dlia-orfannyh-pacientov.html. Russian

[3] An innovative pharmacy for the manufacture of orphan drugs will appear in Sirius in 2024. Available from: https://sirius.gov.ru/tpost/innovatsionnaya-apteka-dlya-izgotovleniya-orfannykh-preparatov-poyavitsya-v-siriuse-v-2024-godu?ysclid=m38lwj36gi311746142

[4] A pharmacy for the creation of rare medicines will be launched in Sirius in 2025. Kommersant. Available from: https://www.kommersant.ru/doc/7283342?ysclid=m38ouy6ksd859117313

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articles similar in content (*n*=191), 22 scientific articles were included in the review.

RESULTS

Problem statement

Pharmacies appeared many centuries ago and have since played an important role in society. The first pharmacy is believed to have opened in the 8th century in Baghdad, and in Russia only in 1581 [11], and since its creation, the state has always paid great attention to them. For a long time, pharmacies were the main institution for the manufacture of medicines, and only with the development of mass industrial pharmaceutical production they began to pay less attention to them. Currently, pharmacy institutions, in addition to retail trade also provide the compounding of drugs for their clients. It is the individual orientation of the production activities of pharmacies that characterizes it in the system of providing society with drugs [12–14]. Until recently this meant that pharmacies were practically not engaged in the compounding of complex modern drugs, today the situation is changing significantly. Pharmacies are able to fill the shortage of certain medicines on the market, ensure the compounding of drugs focused on rare diseases, etc. It is quite clear that the legislator cannot leave this area unattended.

The most important arising problem is the need to protect intellectual property while ensuring the interests of society in the production of medicines. The general rule established by intellectual property law is that the use of an object of protection is allowed only with the consent of the copyright holder, except in *cases provided for by law*[5]. Obviously, a pharmacy institution cannot obtain a license from the copyright holder for a one-off production of medicines, therefore, national laws, as a rule, provide for the permission of such actions without the consent of the copyright holder and without payment of remuneration. However, the widespread use of this opportunity by pharmacies (for example, with the development of the concept of compounding pharmacies) can cause certain problems for copyright holders. In this regard, it is important to assess how real these problems are and whether the current legislation needs adjustments.

International aspects of regulation of the drugs' compounding by pharmacy institution

At the 36th session of WIPO, held in Geneva on October 14–18, 2024, within the work of the Standing Committee on Patent Law (SCP), the issue of the attitude of national and regional patent offices to the one-time preparation of medicines in pharmacies, including in judicial practice, was discussed[6].

The legislation of 85 countries (including the Russian Federation, Canada, Brazil, Japan, France, the Republic of Korea, Spain, Sweden, Switzerland, the United Kingdom, etc.) related to the circulation of rights to the results of intellectual activity provides for an exception regarding the one-off (extemporaneous) production of drugs. This complies with international law. Thus, Article 30 of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) lists the principles that govern exceptions to rights established by members of the World Trade Organization (WTO). In particular, the article states that WTO members may introduce limited exceptions to the rights granted by a patent *if "such exceptions do not unreasonably conflict with the normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking into account the legitimate interests of third parties*."[7]

This formula allows the introduction of new rules on the drugs' compounding by pharmacies into national legislation, expanding their capabilities, but up to a level where copyright holders will be infringed in their commercial plans and cause damage to the possibility of selling their products.

According to the countries positions presented in WIPO regarding the issue, the aims of the exclusion from the list of actions qualifying as a violation of the exclusive rights of the copyright holder are:

1. Ensure a balance of rights, which is necessary when respecting the rights of patients to health protection and free access to medicines while respecting the rights of the patent holder of pharmaceutical innovations (for example, this is the point of view of Brazil)8.
2. Maintenance of public awareness of protecting people's health. Thus, pharmacists should be able to produce prescription drugs, guarantee medical care to patients and being fearless of violating patent rights (these are the positions of the Republic of Korea and the Czech Republic)9.
3. Facilitate the work of doctors and pharmacists. Doctors should prescribe medicines without

[5] Paragraph 1 of Article 1229 of the Civil Code of the Russian Federation. "Exclusive right." Available from: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102110716

[6] WIPO. Standing Committee on the Law of Patents. Available from: https://www.wipo.int/meetings/en/details.jsp?meeting_id=80917

[7] WIPO. World Trade Organization (WTO). Agreement on Trade-Related Aspects of Intellectual Property Rights. Available from: https://www.wipo.int/wipolex/en/text/379915

[8] WIPO. Questionnaire on Exceptions and Limitations to Patent Rights. Available from: https://www.wipo.int/scp/en/exceptions

[9] WIPO. SCP Electronic Forum: Comments and Documents (SCP/36). Available from: https://www.wipo.int/scp/en/meetings/session_36/comments_received.html

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regard to restrictions that may arise due to the exercise of exclusive rights.

The WIPO concept supports objectives encouraging innovation in various fields, including medicine, and does not restrict ways to meet the needs of patients using personalized medicines according to individual prescriptions from doctors.

As part of the work of the Standing Committee on the Law of Patents, issues of interpretation of the exception in question were discussed, namely, which specific pharmacies can use this rule, and who should prepare the drug according to an individual prescription. It is interesting to note that the surveyed states interpret the rule very broadly in terms of the type of place where and by whom the drug will be prepared. In particular, according to the position of the European Patent Office (EPO), the preparation should be carried out in pharmacies, including hospital pharmacies, and not only a pharmacist, but also support personnel can prepare the drug. EPO representatives also believe that this exception also applies to the veterinary field.

In addition, it was mentioned that the exception does not apply to the production of drugs for storage, but only applies to the compounding of a drug for a specific patient.

As mentioned above, the issue of the manufacture of prescription drugs by pharmacists was discussed by representatives of the patent offices of 85 countries, as well as experts from the Eurasian Patent Office (EAPO) and the EPO. They came to the conclusion that in the field of drug manufacturing in pharmacies, there is still no stable judicial practice regarding violations of the exclusive rights of manufacturers of original drug. Only a few court cases were noted.

Thus, one of such cases was a dispute between the corporations Sanofi-Aventis Farmaceutica Ltda and Farma Ltda. It concerned the patented active substance “rimonabant”, used for the treatment of obesity and cardiovascular diseases (Sanofi-Aventis Farmaceutica Ltda v. Sp Farma Ltda, Court of the State of São Paulo, April 18, 2013, case No. 0158190-77.2008.8.26.0100, Brazil). A representative of Sanofi-Aventis Farmaceutica Ltda argued that the defendant was violating the company’s rights to the patented invention by importing and selling rimonabant in Brazil. According to the plaintiff, the defendant’s actions do not fall under the exceptions, since Farma Ltda does not manufacture medicines according to individual prescriptions, but only supplies the substance to pharmacies. In turn, compounding pharmacies without having the appropriate permission to do so, which violates the plaintiff’s rights. As a result, on April 18, 2013, the court in São Paulo decided that the supply of rimonabant to pharmacies that manufacture medicines based on it falls under paragraph III of Art. 43 of the Law on Industrial Property of Brazil[10]. The document states: «43. The provisions of the previous article do not apply: [...] III. to the preparation of a drug according to a doctor’s prescription for individual cases, performed by a qualified specialist, as well as to a drug prepared by this way». Thus, the court considered that the defendant acted in the interests of specific patients, importing rimonabant for pharmacies, which is used for the preparation of individual prescription drugs. In this regard, the court did not see a patent infringement. It also concluded that the defendant’s advertising aimed at attracting new customers is not a violation of patent rights. This case is important because it showed the need for a broad interpretation of the usual restriction of the exclusive right provided for pharmaceutical institutions.

It is important to note that the document published by the Secretariat of the Standing Committee on the Law of Patents (WIPO, Geneva) following the discussion on October 14–18, 2024 of exceptions — does not contain the position of the United States. Though it is in the United States that compounding pharmacies (in the United States they are called compounding pharmacies) have been developing in recent decades and there is extensive judicial practice.

Attitude of drug manufacturers to the activities of compounding pharmacies in the USA and the position of the FDA

According to the FDA[11], doctors in hospitals and other medical facilities have the right to give a prescription for a compounded drug that has not been approved by the FDA [15]. It is possible in two cases:

1. An FDA-approved drug cannot be used for a specific patient in case of possible allergic reaction to certain components or due to the unavailability of the required form of the drug, as in the case when a patient cannot swallow a tablet or capsule due to age and needs to take the drug in another form, for example, as a suspension.
2. The drug is on the shortage list at the time of prescription to the patient.

The fact that a compounded drug is not FDA-approved, meaning it has not been tested for safety and efficacy, is the most common primary argument used by

[10] Article 43 (III) of Law No. 9.279 of May 14, 1996, Industrial Property Law as amended by Law No. 14.200 of September 2, 2021, Brazil. Available from: https://www.wipo.int/wipolex/ru/legislation/details/515

[11] U.S. Food and Drug Administration. Compounding and the FDA: Questions and Answers. Available from: https://www.fda.gov/drugs/human-drug-compounding/compounding-and-fda-questions-and-answers#:~:text=What%20is%20compounding%3F,drugs%20are%20not%20FDA%2Dapproved

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pharmaceutical manufacturers of original drugs against the activities of compounding pharmacies. In their opinion, prescription drugs compounded in a pharmacy put patients at risk of health loss [16–18], as the lack of control over the compounding process of such a drug can lead, for example, to a low or, conversely, excessively high dose of the active substance [8, 19, 20].

However, in the United States, the FDA regulatory document contains rules governing the compounding of drugs in compounding pharmacies[12] (in Russian legislation, the analogue of the concept of "compounding pharmacies" is manufacturing pharmacies). Thus, sections 503A and 503B of the FDA mainly concern the compounding of drugs. Section 503A[13] applies to the compounding of drugs for humans by a licensed pharmacist in a state-licensed pharmacy or federal facility, or by a licensed physician who is not registered with the FDA as an outsourcing facility[14]. Section 503B applies to the compounding of drugs for patients in an outsourcing facility. Outsourcing institutions are a category of drug manufacturers created in 2013 by the Drug Quality and Security Act. Outsourcing facilities are inspected by the FDA[15].

Thus, the activities of both licensed pharmacies and outsourcing facilities are regularly monitored and inspected.

It is worth noting that biologicals cannot be compounded according to sections 503A and 503B of the Drug Act[16]. The term "biologicals" is explained in section 351(i)(1) of the Public Health Service Act (PHS). The definition of this term includes a vaccine, virus, toxin and antitoxin, therapeutic serum, blood and its components, allergenics, as well as a protein (excluding a chemically synthesized polypeptide) or similar product, or arsphenamine, or arsphenamine derivative (any other trivalent organic arsenic compound) used for the prevention and treatment of a patient's disease or condition. Section 351(a)(1) of the PHS Act prohibits the introduction into commerce of any biologicals unless "a license... is not valid for the biologicals." In order that the FDA approve such a product, it must contain data demonstrating safety, purity and efficacy, as well as data that the facility in which the biologicals will be manufactured, processed, packaged or stored meets standards developed to ensure that the biological product continues to be safe, pure and effective (section 351(a)(2)(C) of the PHS Act). All this is quite difficult to comply with in the context of compounding drugs [21–23].

Although American law regulates attentively the activities of institutions entitled to dispense drugs by prescription, there are many publications about litigation concerning the dispensing of drugs compounded this way.

In particular, the increase of lawsuits[17] is noted, which is due to the prevalence of the practice of compounding drugs by prescription. Lawsuits are filed by pharmaceutical companies and related to the area of violation of exclusive rights. Lawsuits mainly contain claims based on:

1. Violation of laws on fraudulent and unfair trade practices, violation of patent rights, violation of the Lanham Act (US Federal Trademark Act[18]) due to false statements in product advertising, as well as violation of trademark rights.
2. Violation of the principles of patient safety due to the fact that compounded drugs do not undergo pre-sale testing for safety, efficacy or quality. Drugs compounded in pharmacies are not evaluated by the FDA for safety or efficacy, do not have standard labelling or information on use, and are not required to report side effects to the FDA, unlike FDA-approved drugs. Product quality is assessed inconsistently, and testing is carried out inconsistently.
3. Patent violation, as they confirm exclusive rights to manufacture, use, and sell a patented product. According to pharmaceutical manufacturers[19], only pharmacies engaged in compounding drugs by prescription, and not their suppliers (i.e., manufacturers of substances), are exempt from patent infringement.

According to the analysed articles, patent infringement may be recognized if the compounded

[12] U.S. Food and Drug Administration. FD&C Act Provisions that Apply to Human Drug Compounding. Available from: https://www.fda.gov/drugs/human-drug-compounding/fdc-act-provisions-apply-human-drug-compounding

[13] U.S. Food and Drug Administration. Section 503A of the Federal Food, Drug, and Cosmetic Act. Available from: https://www.fda.gov/drugs/human-drug-compounding/section-503a-federal-food-drug-and-cosmetic-act

[14] U.S. Food and Drug Administration. Text of Compounding Quality Act. Available from: https://www.fda.gov/drugs/human-drug-compounding/text-compounding-quality-act

[15] U.S. Food and Drug Administration. Compounding and the FDA: Questions and Answers.

[16] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License. Application Guidance for Industry. Available from: https://www.fda.gov/media/90986/download?attachment

[17] Compounding Pharmacies in the US — Market Research Report (2014-2029). Available from: https://www.ibisworld.com/united-states/industry/compounding-pharmacies/5706/

[18] Intellectual Property Challenges for 503A Pharmacy Compounding. Available from: https://www.frierlevitt.com/articles/intellectual-property-challenges-for-503a-pharmacy-compounding/

[19] U.S. Food and Drug Administration. Compounding and the FDA: Questions and Answers.

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drug is “essentially a copy” of a commercially available drug at the time it is prescribed to the patient[20].

Regarding trademark infringement, most cases against pharmacies are initiated due to the compounding of semaglutide[21]. Pharmacies are accused of trademark infringement and unfair competition, as well as false and misleading advertising. The main argument in lawsuits is that pharmacies “substitute” their unapproved compounded drugs, containing semaglutide, as “Ozempic” or “Wegovy,” or in some cases promote their products under the guise of these branded products (Novo Nordisk v. A/S v. Effinger Health PA Tallahassee Clinic, Case No. 4:23-cv-00265 (D.C. N. D. June 21, 2023). Specifically, the allegations are that compounding manufacturers use the brand name drug in their advertising and promotion on their website, and that when viewing it, patients wishing to obtain the original drug are misled by the use of the trademark on such a site. Another accusation against pharmacies compounding semaglutide is the production of unsafe counterfeit “Ozempic”[22] [20]. Bloomberg[23] describes cases where in Louisiana, one pharmacy produced nearly 300 vials of injectable weight loss drug without proper testing for ontaminants, and in Arizona, a pharmacy mixed drugs in non-sterile conditions. It led to the development of side effects in patients.

The problems outlined here show that granting pharmacies the right to compound drugs entails very diverse, though very related, issues.

Despite the existence of litigation in foreign jurisdictions regarding the activities of compounding pharmacies, numerous articles of foreign authors, it is noted that dispensing drugs according to doctors’ prescriptions is one of the effective ways to address the acute drugs shortages[24]. Licensed pharmacists can create drugs that are not commercially available due to production shutdowns, shortages, or other supply chain issues. Compounding pharmacies serve small local groups of patients and doctors, locally addressing shortage issues. Another advantage of compounding drugs prescription is a personalized approach to patient treatment[25] — compounding an individual dose of the drug, an individual compounding of the drug, an individual dose form of the drug [24, 25].

Development of compounding pharmacies in Russia as of 2024 in the context of patent law

The legal status of pharmacies in our country is defined by Federal Law No. 61-FZ of April 12, 2010 “On the Circulation of Medicines,” which establishes that a pharmacy organization (pharmacy) is “an organization, a structural subdivision of a medical organization, engaged in retail trade of medicines, including remote sale, storage, transportation, compounding and selling of medicines for medical use in accordance with the requirements of this Federal Law[26].” Thus, the possibility of pharmacies compounding drugs initially stems from the functional characteristics of this organization. However, carrying out their functions, pharmacies must act in compliance with intellectual property law.

The general principle established by the Civil Code of the Russian Federation is that persons other than the right holder may not use the relevant result of intellectual activity or means of individualization without the consent of the right holder, except in cases provided for by this law[27].

It is worth noting that a drug consists of pharmaceutical substances, which may be separately protected by a patent. According to Article 1358 of the Civil Code of the Russian Federation, the patent holder has the exclusive right to use the invention any way that does not contradict the law. Use of the invention means — importation into the territory of Russia, manufacture, further use, including offering for sale, the sale itself and other introduction into civil circulation or storage of the product in the creation of which the invention, utility model or industrial design was used. Accordingly, to manufacture a drug, it is necessary either to obtain the consent of the right holder or to take advantage of one of the exceptions established by the Civil Code of the Russian Federation.

In Russia, the possibility of one-time compounding of drugs in pharmacies according to doctors’ prescriptions using an invention is enshrined at the legislative level

[20] Ibid.

[21] Why millions are trying FDA-authorized alternatives to Big Pharma’s weight loss drugs // Popular Science. Available from: https://www.popsci.com/health/glp1-compounding-pharmacies-wegovy-zepbound-copycat-drugs-shortages/

[22] Unsafe Ozempic Knockoffs Are Flooding the Market // Bloomberg. Available from: https://www.bloomberg.com/news/articles/2024-07-22/ozempic-wegovy-knockoffs-for-weight-loss-are-flooding-market

[23] Unsafe Ozempic knockoffs are flooding the market // BNN Bloomberg. Available from: https://www.bnnbloomberg.ca/business/2024/07/22/unsafe-ozempic-knockoffs-are-flooding-the-market/

[24] Kumar S. Compounding Inequities Through Drug IP and Unfair Competition (February 26, 2024). Shweta K., Compounding Inequities Through Drug IP and Unfair Competition, 102 Wash. U. L. Rev. (forthcoming 2024), Available from: https://ssrn.com/abstract=4739356

[25] Health Dimensions Clinical Pharmacy. Compounding pharmacy vs retail pharmacy: Top 5 ways they’re different. Available from: https://www.hdrx.com/general/compounding-pharmacy-vs-retail-pharmacy-top-five-ways-theyre-different/

[26] Clause 35 of Article 4 of Federal Law No. 61-FZ dated April 12, 2010 “On the Circulation of Medicines”. Available from: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102137440&ysclid=m720ikunte627102595

[27] Paragraph 1 of Article 1229 of the Civil Code of the Russian Federation. “Exclusive right.” Russian

(subparagraph 5, paragraph 1, Article 1359 of the Civil Code of the Russian Federation[28]). Such action is not considered a violation of patent rights. It is worth noting that the resurgence of compounding pharmacies in Russia began in 2022. Since 2023, pharmacies have again begun to compound drugs according to doctor's prescriptions with individual dosages. However, to date, the practice of litigation concerning violations of the exclusive rights of substance or drug owners has not yet been developed.

There are very few articles on the objective, interpretations of the specified norm of the Civil Code of the Russian Federation. At the same time, it is worth mentioning the following comment of Russian specialists in the field of patent law[29]: "...5. Subparagraph 4 of paragraph 1 of the commented article further limits the scope of the exclusive right of the patent holder, preventing its extension to personal, family, household or other needs not related to entrepreneurial activity, if the purpose of such use is not to obtain profit (income). *On the one hand, this approach reflects the legislator's desire to establish a balance of interests between both the patent holder and society. On the other hand, we are talking about a sphere in which the number of persons using an invention, utility model, industrial design can be so large, and the scale of use by each of them is so small that the realization of the patent holder's rights and the protection of his interests by the state become practically impossible.* 6. The provision contained in subparagraph 5 of paragraph 1 of Article 1359 is due to reasons similar to those listed in the commentary to subparagraph 4.".

Thus, one of the reasons for the existence of this rights' limitation is the practical impossibility of prohibiting such a variant of using the relevant objects of patent law.

At the same time, it is very important that there is no introduction of the obtained products into civil circulation in this case: "Contrary to popular belief, in this case there is no need for a special indication that for the free use of medicines it is not enough to manufacture it, it is also necessary to sell it, i.e. put it into circulation. There is no "sale" here: the medicine is made for a fee, but at the request of the person presenting the prescription, i.e. there is a contract. So, the mentioned process does not allow the introduction of the compounded drug into circulation (the sale of the manufactured drug by the customer will be a violation of the exclusive right)[30]."

Thus, the danger of such actions is minimal for the interests of the right holder, and the social significance is very high. It should be noted that this norm of the Civil Code of the Russian Federation concerns only the direct compounding of drugs, but not preparatory actions. This means that the pharmacy must purchase pharmaceutical substances that have been put into civil circulation.

At the same time, the storage of drugs compounded in accordance with this norm of the Civil Code of the Russian Federation does not require the author's permission. This general rule, which operates in the field of intellectual property [26], was clearly expressed by the Supreme Court of the Russian Federation in relation to copyright objects: "The storage of a material carrier in which a copyright object is expressed, without the purpose of introducing it into civil circulation, is not an independent way of using the work, and therefore such storage does not require special consent of the copyright holder[31]."

It is obvious that a drug compounded on the basis of a prescription can be used repeatedly by one patient. Or a doctor can use the same prescription for several patients. But it is important to note that "it is not the production of drug by the pharmacy in advance for sale, but the compounding of drugs in each individual case — upon receipt of a doctor's prescription from the buyer. At the same time, the indication "one-off production" refers only to the actions of the pharmacy; the doctor's prescriptions are not limited in their number." Therefore, the pharmacy cannot produce the drug in advance - in anticipation of a request from potential customers, it must always respond to a specific prescription.

It is obvious that pharmacists should have possibility to compound specific drugs according to doctors' prescriptions without risking being accused of infringing the rights of patent holders. This will facilitate access of the population to drugs, especially in critical situations (for example, temporary absence of a certain form or dosage of the medicine on the market) [27–29].

Russian legislation generally allows pharmacies to carry out their functions, but limiting the permit to only a "specific prescription" makes it difficult to compound drugs that require a long and complex process. Since "make-to-stock" is not allowed for pharmacies, the

[28] Paragraph 1 of Article 1229 of the Civil Code of the Russian Federation. "Exclusive right." Russian

[29] Gorlenko SA, Kalyatin VO, Kiriy LL, Kozyr OM, Korchagin AD, Orlova VV, Pavlova EA, Sinelnikova VN, Stepanov PV, Trakhtenherts LA, Shilokhvost OYu. "Commentary to the Civil Code of the Russian Federation (Part four) (article-by-article)". Moscow: Infra-M Publishing House, 2016. Russian

[30] Article-by-article commentary to the Civil Code of the Russian Federation, Part Four; Valeeva NG, Vsevolozhsky KV, Gongalo BM, et al.; edited by Krasheninnikov PV; Moscow: Statute; 2011. Russian

[31] Paragraph 92 of the Resolution of the Plenum of the Supreme Court of the Russian Federation dated 04/23/2019 No. 10 "On the application of Part Four of the Civil Code of the Russian Federation". Available from: https://www.consultant.ru/document/cons_doc_LAW_323470/?ysclid=m72140z5gy36622264. Russian

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production process must begin only after receiving a prescription from the client, which means that the client may receive the required drug very soon. One possible way to reduce the severity of this problem could be to allow pharmacies directly use contractors to fulfill a specific request (and not just produce drugs themselves). However, this will not completely eliminate the issue; it is clear that it requires discussion in order to find a mutually acceptable option for regulating the activities of pharmacies. It also requires disclosure (for example, at the level of documents of the Supreme Court of the Russian Federation) of the concept of one-time manufacturing, which may expand the capabilities of pharmacies. Perhaps some completely new solution is also needed.

DISCUSSION

The article provides an overview of modern approaches to the operation of compounding pharmacies and the connection of their activities with the violation of the exclusive rights of manufacturers of original drugs. This analysis examines the advantages of compounding pharmacies for doctors, patients, and the state. The current trend regarding the development of compounding pharmacies in Russia is highlighted. The key aspect of pharmaceutical compounding is the possibility of an individualized approach to treatment, as well as a quick response to drug shortages [29–31].

The review of foreign practices, on one hand, demonstrates a neutral attitude towards the activities of compounding pharmacies in most countries (according to the position described in the WIPO final document), and, on the other hand, shows that the active development of such institutions, for example, in the USA, correlates with the growth of litigation related both to violation of patent rights and trademarks [29, 32, 33]. Due to the fact that the stage of formation of compounding pharmacies is currently taking place in the Russian Federation, it is advisable to take into account in detail the judicial practice of foreign countries in which such pharmacies are widespread when forming Russian legislation [34–36]. This will allow to neutralize the risks of violating both patient rights and the exclusive rights of copyright holders of original drugs [37]. In the context of discussing the risks of drug shortages, the experience of Dutch scientists [38] is of interest, who in 2022, in the context of a shortage of pilocarpine solution on the market (used to diagnose such an orphan disease as cystic fibrosis), conducted a comparative study of the prepared solution in a compounding pharmacy and the original drug. Thus, the study showed similar levels in the concentrations of chloride obtained in the two pilocarpine solutions. This allowed the authors of the article to conclude that the use of compounding pharmacies for the rapid replacement of drugs unavailable on the market is promising and effective. The issue of manufacturing specifically orphan drugs within the framework of compounding pharmacies and hospital pharmacies is increasingly being raised in various countries [39–41]. The need for the availability of such drugs for patients, the number of which is very small, is being discussed. Compounding pharmacies can meet this demand. However, this issue is closely related to the interests of developers of original drugs, whose exclusive rights, on one hand, should not be a barrier to saving patients with orphan diseases, and, on the other hand, should not prevent the creation of new drugs as a result of the loss of a stimulating factor for manufacturers [42, 43]. The last aspect is related to the fact that the development of new drugs is a long research process requiring financial costs. Often the result of such research can be unpredictable. Granting exclusive rights to manufacturers of original drugs is an important incentive, allowing developers to be motivated and, thanks to a temporary monopoly, to compensate for their costs[32] [44–46].

It should be noted that issues related to the activities of compounding pharmacies in other countries [47, 48] do not differ significantly from those arising in Russia. In this regard, it is advisable to take into account the above problems.

The rise of compounding pharmacies in the Russia may lead to an increase in litigation relating, inter alia, to infringement of the exclusive rights of copyright holders. In this regard, it is advisable to pay attention to the formation of regulatory legal acts governing the activities of such pharmacies. On the one hand, they should regulate the procedure for the activities of such pharmacies that are permissible in terms of the production of drugs according to a doctor's prescription, and, on the other hand, in the event of a legal dispute, clarify the legal aspects of such activities.

CONCLUSION

In conclusion of this article, it can be noted that due to the adoption of legislative changes in Russia, which became an important step in the development of drug compounding in pharmacies, it became necessary to study foreign practice in this area, especially judicial practice. The study of the development of compounding pharmacies and possible risks of violation of exclusive rights to drugs made it possible to better understand

[32] The Role of Patents and Regulatory Exclusivities in Drug Pricing (R46679). Available from: https://crsreports.congress.gov/search/#/?termsToSearch=The%20Role%20of%20Patents%20and%20Regulatory%20Exclusivities%20in%20Drug%20Pricing&orderBy=Relevance

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the positions of foreign patent offices, courts of various jurisdictions, as well as WIPO.

The study also showed that the concept of WIPO and most countries supports objectives aimed to encourage innovation and does not limit ways to meet the needs of patients through the use of personalized drugs according to individual prescriptions. Conceptually, in most countries, the law regarding intellectual property in terms of the possibility of compounding a patented drug in a pharmacy according to a doctor's prescription is formulated the same way — this is not a violation of the exclusive rights of the patent holder of the original drug. At the same time, according to practice, for example, in the USA there is a number of legislative norms regulating the control over the activities of such pharmacies. However, the study revealed the existence of lawsuits in this country regarding violations of the exclusive rights of manufacturers of original drugs in the field of their manufacture.

The resurgence of the practice of drugs manufacturing in compounding pharmacies is a very promising area, especially in the context of a constantly emerging shortage. However, taking into account foreign experience, in particular the experience of the United States, it is advisable to work out in detail the issue of legislative regulation of the activities of such pharmacies and mechanisms for monitoring their activities, as well as to work out the issue of measures to prevent pharmacies from violating the exclusive rights of manufacturers of original drugs. It is important to maintain a balance — on the one hand, pharmaceutical patents should not restrict the doctor's freedom to prescribe drugs in the interests of the patient's health. On the other hand, thanks to intellectual property, namely exclusive rights, which are granted to developers, the creation of the very drugs that support or restore the health of the population is stimulated, subject to temporary compensation to developers for costs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Alexey V. Alekhin — problem statement, concept, making comments of intellectual content, final approval of the manuscript; Tatiana N. Erivantseva — collection of material, critical analysis of literary sources, writing the text of the manuscript; Vitaly O. Kalyatin — scientific editing of the text, interpretation of materials; Natalya A. Alekhina — critical analysis of literary sources, editing and formatting the text of the manuscript; Roman A. Ivanov — critical analysis of literary sources, editing the text of the manuscript. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conducting research and preparing the article, read and approved the final version before publication).

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AUTHORS

Alexey V. Alekhin – CEO of Farmaklon Group; assistant of department BMT-3 Bauman Moscow State Technical University (National Research University). ORCID ID: 0009-0003-5882-8994. E-mail: alexey@alekhin.net

Tatiana N. Erivantseva – Candidate of Sciences (Medicine), Advisor to the Organizational and Legal Department of Eurasian Patent Office of the Eurasian Patent Organization. ORCID ID: 0000-0002-7891-9776. E-mail: ru-patent@mail.ru

Vitaly O. Kalyatin – Candidate of Sciences (Law), Associate Professor, Professor of Private Law Research Centre under the President of the Russian Federation named after S.S. Alexeev; Associate Professor Department of Digital Technologies and Bio-Law of the Faculty of Law of Higher School of Economics. ORCID ID: 0000-0002-2927-6591. E-mail: kalvit@yandex.ru

Roman A. Ivanov – Ph.D., Chairman of the Academic Council, Director of Sirius University. ORCID ID: 0000-0002-9573-4183. E-mail: Ivanov.ra@talantiuspeh.ru

Natalya A. Alekhina – Candidate of Sciences (Economics), Associate Professor of the Department of Regulatory Relations in the Field of Circulation of Medicines and Medical Devices, Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-0356-9275. E-mail: romakinan@gmail.com

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