SYNTHESIS OF A NOVEL AMIDE DERIVATIVE OF VALPROIC ACID AND 1,3,4-THIADIAZOLE WITH ANTIEPILEPTIC ACTIVITY

Malygin AS[1]✉, Demidova MA[1], Skachilova SYa[2], Shilova EV[2]

[1] Tver State Medical University, Tver, Russia

[2] All-Russian Research Center for the Safety of Bioactive Substances, Staraya Kupavna, Moscow region, Russia

Valproates are commonly used to treat various forms of epilepsy. Problems accompanying their clinical application include drug resistance, adverse effects, acute and chronic toxicity. Safer anticonvulsants with improved efficacy can be obtained through the chemical modification of valproic acid structure. Thiadiazole-linked amide derivatives of valproates hold great promise because 1,3,4-thiadiazole can improve the drug's bioavailability and reduce its toxicity. The aim of this work was to synthesize a novel amide derivative of valproic acid and 1,3,4-thiadiazole exerting antiepileptic activity. The chemical structure of the synthesized valproate was studied by IR, proton NMR and 13C-NMR-spectroscopy, mass spectroscopy and elemental analysis. The purity and individuality of the compound was confirmed by thin-layer and high-performance liquid chromatography. Its antiepileptic activity was assessed in the test with intraperitoneally injected 250 mg/kg isoniazid and subsequent Probit analysis. The synthesized N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide (valprazolamide) had the following characteristics. ESI$^+$MS: *m/z* 256.1 $[M + H]^+$; MRM transitions: *m/z* 256.1 — *m/z* 81.0 and *m/z* 130.1. The valproate exerted antiepileptic activity against isoniazid-induced seizures in mice. In the test with isoniazid, ED_{50} of intraperitoneally injected VPZ was 126.8 mg/kg (95% CI: 65.5–245.4). Its therapeutic index was 7.3.

Keywords: antiepileptic drugs, valproic acid, 1,3,4-thiadiazole

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Compliance with ethical standards: the study was approved by the Ethics Committee of Tver State Medical University (Protocol № 4 dated March 26, 2018). The animals were treated in compliance with the guidelines for laboratory practice in preclinical trials (Order 199n of the Russian Ministry of Healthcare dated April 1, 2016, on the *Good laboratory practice*). All tests were carried out in accordance with the guidelines for preclinical trials of medicinal drugs and in compliance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes (Directive 2010/63/EU).

✉ **Correspondence should be addressed:** Alexandr S. Malygin
Sovetskaya, 4, Tver, 170100; dr.a.s.m@yandex.ru

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СИНТЕЗ НОВОГО АМИДНОГО ПРОИЗВОДНОГО ВАЛЬПРОЕВОЙ КИСЛОТЫ И 1,3,4-ТИАДИАЗОЛА С ПРОТИВОЭПИЛЕПТИЧЕСКОЙ АКТИВНОСТЬЮ

А. С. Малыгин[1]✉, М. А. Демидова[1], С. Я. Скачилова[2], Е. В. Шилова[2]

[1] Тверской государственный медицинский университет, Тверь, Россия

[2] Всесоюзный научный центр по безопасности биологически активных веществ, Старая Купавна, Московская область, Россия

Вальпроаты являются основными препаратами для лечения эпилепсии различных форм. Среди проблем, возникающих при их клиническом использовании, — фармакорезистентность, нежелательные побочные реакции, а также проявления острой и хронической интоксикации. Путем модификации химической структуры вальпроевой кислоты возможно создание более эффективных и безопасных антиконвульсантов. Перспективно получение тиадиазолиламидных производных вальпроатов, так как 1,3,4-тиадиазол может повышать биодоступность и снижать токсичность лекарственных средств. Целью работы был синтез нового амидного производного вальпроевой кислоты и 1,3,4-тиадиазола с противоэпилептической активностью. Химическую структуру синтезированного вальпроата исследовали методами ИК-спектроскопии, 1Н-ЯМР, 13С-ЯМР-спектроскопии, масс-спектроскопии и элементного анализа. Чистоту и индивидуальность подтверждали методами тонкослойной и высокоэффективной жидкостной хроматографий. Противоэпилептическую активность оценивали в тесте антагонизма с изониазидом (250 мг/кг, интраперитонеально) у мышей методом пробит-анализа. В результате исследования был получен N-(5-этил-1,3,4-тиадиазол-2-ил)-2-пропилпентанамид (вальпразоламид). ESI$^+$-масс-спектр N-(5-этил-1,3,4-тиадиазол-2-ил)-2-пропилпентанамида — *m/z* 256,1 $[M + H]^+$, MRM-переходы — *m/z* 256,1 — m/z 81,0 и *m/z* 130,1. Синтезированный вальпроат оказывал противоэпилептическое действие при изониазид-индуцированных судорогах у мышей. Значение ED_{50} (интраперитонеально, мыши) в тесте антагонизма с изониазидом составило 126,8 мг/кг (95% ДИ: 65,5–245,4). Терапевтический индекс был равен 7,3.

Ключевые слова: противоэпилептические средства, вальпроевая кислота, 1,3,4-тиадиазол

Вклад авторов: А. С. Малыгин — экспериментальное исследование, анализ результатов, обзор публикаций по теме статьи, написание текста; М. А. Демидова — концепция и дизайн исследования, написание и редактирование текста; С. Я. Скачилова, Е. В. Шилова — синтез и анализ соединения; все авторы участвовали в обсуждении результатов.

Соблюдение этических стандартов: исследование одобрено этическим комитетом Тверского государственного медицинского университета (протокол № 4 от 26 марта 2018 г.). Подопытных животных содержали согласно правилам лабораторной практики при проведении доклинических исследований в РФ (Приказ МЗ РФ № 199н от 01.04.2016 «Правила надлежащей лабораторной практики»). Все эксперименты осуществляли в соответствии с методическими рекомендациями по проведению доклинических исследований лекарственных средств с соблюдением «Европейской конвенции о защите позвоночных животных, используемых для экспериментов или в иных научных целях» (Directive 2010/63/EU).

✉ **Для корреспонденции:** Александр Сергеевич Малыгин
ул. Советская, д. 4, г. Тверь, 170100; dr.a.s.m@yandex.ru

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Over 75 million people worldwide suffer from epilepsy, and this number is continuously growing [1–2]. The key challenge of modern epileptology is drug resistance. Only 14.9% of epilepsy patients go into sustained remission. Seizures recur in 48.1% of patients, at a rate of up to 12 episodes a year [3–4]. Half of epilepsy patients are on multidrug antiseizure regimens. Some of them do not benefit from polytherapy or a regimen switch, which often result in a poor quality of life and an increased risk of adverse effects. Noncompliance is another serious concern: in Russia, 18.05% of epilepsy patients do not take their medications [5]. Optimization of antiepileptic pharmacotherapy is a crucial task facing epileptology.

Valproic (2-propylpentanoic) acid holds a special place in the arsenal of anticonvulsant drugs. It was first synthesized in 1882 by Beverly S. Burton and used as a solvent. Its anticonvulsant properties were discovered by accident in 1963 and have been used in clinical practice ever since [6]. Valproates are antiepileptic agents with a broad action spectrum and first-choice drugs in patients with various forms of epilepsy. Long-term studies have demonstrated the efficacy of valproates against all forms of generalized epilepsy [7–9]. However, these compounds have adverse effects, including acute and chronic toxicity [10–12]. Valproates are highly teratogenic and therefore are not recommended to women of reproductive age [13]. Safer anticonvulsants with improved efficacy can be developed by modifying the chemical structure of valproic acid [14].

The aim of the study was to develop a novel anticonvulsant from a group of thiadiazole-linked amide derivatives of valproic acid.

METHODS

Reagents

The following reagents were used: 2-amino-5-ethyl-1,3,4-thiadiazole (Acros Organics; Belgium), 2-propylpentanoic acid (Sigma Aldrich; USA), pyridine (LenReaktiv; Russia), isoniazid (Semashko Moschimfarmpreparaty; Russia), hydrochloric acid (LenReaktiv; Russia), 2-propanol (LenReaktiv; Russia), acetonitrile (LC-MS; Scharlau, Spain), ammonium acetate (Panreac AppliChem ITW reagents; USA), ethanol (Medchimprom; Russia), Milli-Q deionized water.

Equipment

The following equipment was used: an AB Sciex QTrap 3200 MD triple quadrupole mass spectrometer (Sciex; Singapore), an Agilent 1260 Infinity II high-performance liquid chromatography system (Agilent Technologies; Germany), TLC plates (silica gel 60 F 254) (Merck; Germany), a Bruker Avance-400 spectrometer (Bruker; Germany), an Agilent Cary 630 FTIR spectrometer (Agilent; Germany), an EA 1108 analyzer for elemental analysis (Carlo Erba Instruments; Italy), Acculab ALC-80d4 analytical scales (Acculab; USA), an Eppendorf 5810R centrifuge with a cooled rotor chamber (Eppendorf; Germany), a Millipore DirectQ UV water purification system (Millipore SAS; France), an Elmi V-3 vortex mixer (Elmi; Latvia), an Elmi S-3 shaker (Elmi; Latvia), a Thermit dry-block heater (DNA-Technology; Russia), Eppendorf (Eppendorf; Germany) and Black Thermo (Thermo Fisher Scientific; Russia) automated dispensers.

Identification methods

The chemical structure of the synthesized valproate (N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide) was studied using IR, proton NMR and 13C-NMR spectroscopy, mass-spectroscopy and elemental analysis. Purity of the obtained compound was evaluated by thin-layer (TLC) and high-performance liquid chromatography (HPLC).

Tests of antiepileptic activity

The antiepileptic activity of the synthesized valproate was tested using a valproate antagonist (isoniazid). Generalized tonic-clonic seizures were induced in male outbred SNK mice (19–21 g body weight, n = 40) by an intraperitoneal injection of 250 mg/kg isoniazid [15]. The animals were kept in a vivarium of Tver State Medical University at a constant temperature of 22 ± 2 °C under a 12/12 light/dark cycle (lights on from 08:00 to 20:00). The animals had free access to food and water. The mice were randomized into 5 groups: the control group (isoniazid-induced seizures) and experimental groups (intraperitoneal administration of 75, 150, 300 and 450 mg/kg valproate 40 min before the isoniazid injection). Video observation lasted for 3 hours to assess latency to the first seizure, record the onset of

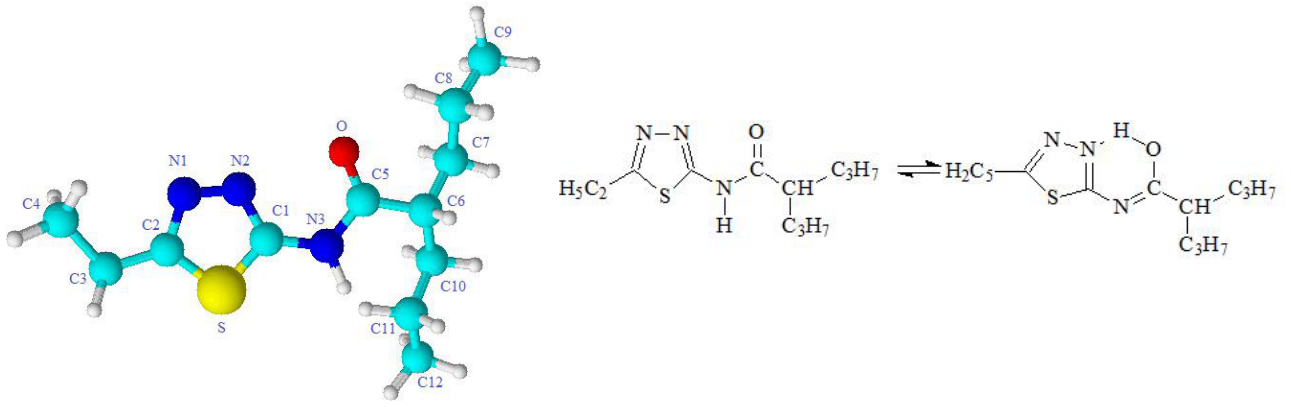

Fig. 1. N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide

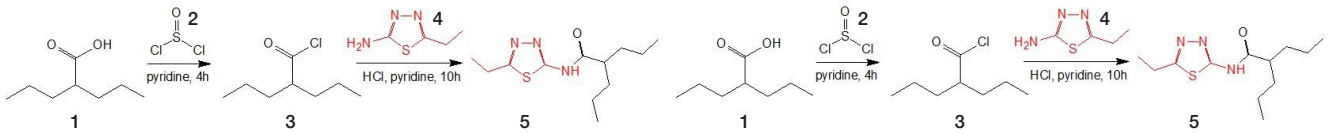

Fig. 2. A schematic representation of N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide synthesis. **1** — 2-propylpentanoic acid; **2** — thionyl chloride; **3** — 2-propylpentanoic acid chloroanhydride; **4** — 2-amino-5-ethyl-1,3,4-thiadiazole; **5** — N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2- propyl pentane amide

clonic and tonic seizures and the outcomes (death or survival). We also calculated ED_{50} (the median effective doze required to ensure survival of 50% of the animals in the test) and the therapeutic index (TI = DL_{50}/ED_{50}, i.e. the ratio of the median lethal dose to the median effective dose).

Statistical analysis

Statistical analysis was carried out in BioStat 2009 (AnalystSoft; USA). The results of the experiment were analyzed using descriptive statistics. The normality of data distribution was tested using the Shapiro-Wilk test. Group means were compared by one-way ANOVA with post-hoc Tukey HSD. Categorical variables were compared using Fisher's exact test. In this work, the data are presented as $m \pm$ SEM. Finney Probit analysis was applied to calculate ED_{50}.

RESULTS

Synthesis

Fig. 1 shows the synthesized thiadiazole-linked amide derivative of valproic acid, N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide. Its molecular formula is $C_{12}H_{21}N_3OS$. The laboratory name for the compound is valprazolamide (VPZ).

The synthesis of this novel anticonvulsant agent can be broken down in the following stages: halogenation of 2-propylpentanoic acid by thionyl chloride; stochiometric interaction of the resulting 2-propylpentanoic acid chloroanhydride with 2-amino-5-ethyl-1,3,4-thiadiazole; acidification of the reaction mix by HCl (pH lowered to 1–2) at 5 °C for getting a crystalline precipitate (Fig. 2).

The synthesized compound was purified as described below. Water-soluble impurities were removed by washing the reaction product with cooled water; then, the product was refiltered and recrystallized in 2-propanol after preliminary vacuum-drying at 10 mmHg until its mass was constant (67% yield). Purification quality was assessed with TLC and HPLC.

Description and identification of N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide

The synthesized pharmaceutical substance is a yellowish-white crystalline powder with a molar mass of 255.14 g/mol and a melting point of 93–94 °C. The powder is barely soluble in water but well soluble in alcohol, acetonitrile and other organic solvents.

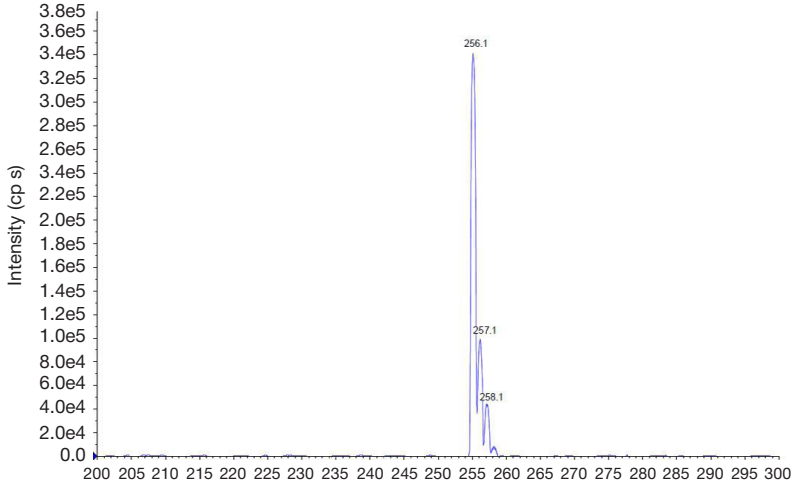

Fig. 3. ESI$^+$-mass-spectrum of N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide ($[M + H]^+$)

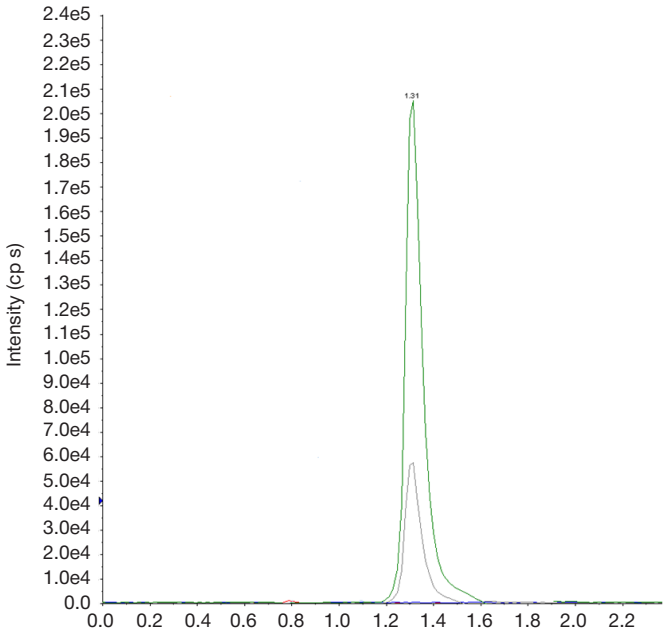

Fig. 4. A chromatogram of N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide

The chemical structure of N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide ($C_{12}H_{21}N_3OS$) was confirmed by elemental analysis and spectroscopy. The predicted content of C in $C_{12}H_{21}N_3OS$ was 56.44%; H, 8.29%; N, 16.45%; O, 6.26%; S, 12.56%. According to the results of the elemental analysis, the actual content of the elements was as follows: C, 56.39%; H, 8.34%; N, 16.41%; O, 6.26%; S, 12.60%, which was consistent with the chemical structure of the synthesized compound.

Spectroscopy results are shown below. IR spectra (KBr pelleting technique), ν/cm^{-1}: 3302, 3030 (NH), 2981, 2959, 2860 (CH), 1545 (NHCO); ^{1}H-NMR (400 MHz, DMSO-d_6) δ ppm: 0.97 (s, 3H, CH_3), 1.33 (s, 2H, CH_2), 1.41–1.50 (m, 4H), 2.65 (s, 2H, CH_2), 10.63 (s, 1H, NH); ^{13}C-NMR (400 MHz, DMSO-d_6) δ ppm: 13.48, 13.66, 20.06, 24.70, 35.27, 43.22, 155.85, 156.5, 175.00; ESI+MS: *m/z* 256.1 ([M + H]$^+$); MRM transitions: *m/z* 256.1 →m/z 81.1 and *m/z* 130.1. ESI$^+$ MS for N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide is shown in Fig. 3.

Purity of the synthesized anticonvulsant agent was assessed by HPLC at 50 °C using a Phenomenex synergi 4 μm C18 Fusion column (2 × 50 mm). For elution, 90 : 10 methanol : deionized water and 0.1% ammonium acetate were used. Retention time was 1.31 min (Fig. 4).

Antiepileptic activity tests in a mouse model of isoniazid-induced seizures

Intraperitoneal administration of 250 mg/kg isoniazid induced generalized tonic-clonic seizures resulting in the death of all control animals. An injection of VPZ given 40 min before isoniazid administration had a dose-dependent effect on the progression of isoniazid-induced seizures in mice ($p < 0.0001$; one-way ANOVA). A 75 mg/kg VPZ dose significantly increased seizure latency (by 1.5-fold) in the experimental groups in comparison with the control animals, but did not prevent seizures or animal death. At 150 and 300 mg/kg, VPZ increased seizure latency and reduced the death rate. In a test with 450 mg/kg VPZ, no seizures were observed for 3 h following isoniazid administration (see Table).

Probit analysis revealed that ED_{50} of intraperitoneally injected VPZ was 126.8 mg/kg (95% CI: 65.5–245.4) in the test with VPZ antagonist. The therapeutic index was 7.3.

DISCUSSION

Candidate anticonvulsant agents must be effective against refractory epilepsy, have fewer side effects and better tolerability, as well as the ability to slow down progression of the disease and modify its course. Additional advantages include linear pharmacokinetics, simplicity of titration in the clinical setting, ancillary therapeutic effects such as relief of neuropathic pain. Such candidates are usually searched for among novel molecules or developed based on the derivatives of known anticonvulsants.

The possibility of creating new-generation valproates has been shown in the literature [16]. The teratogenicity of their amide analogs is significantly lower than that of valproic acid [17]. Valproic acid amides demonstrate antiepileptic [18], antineuropathic [19–20], antiviral [21–22] and some other properties. A number of 1,3,4-thiadiazole derivatives, including those that contain a valproic acid residue, have been reported to exert anticonvulsant activity [23]. The majority of such derivatives have higher bioavailability and are less toxic than their analogs. This is also true for the valproate synthesized in this study, containing 1,3,4-thiadiazole. Using a mouse model, researchers have demonstrated that DL_{50} of an intraperitoneally injected 1,3,4-thiadiazole-linked amide derivative of valproic acid is 1.8 times higher than that of valproic acid [24]. The antiepileptic effect of the synthesized valproate has been confirmed in maximal electroshock seizure models and pentylenetetrazole-induced seizure models in mice [25–26]. Considering that VPZ was the most active in a test with a GABAA-receptor antagonist (pentylenetetrazole), we studied the effect of this valproate on the seizures induced by another GABA antagonist isonicotinylhydrazide (isoniazid). The proconvulsant effect of isoniazid is linked to the inhibition of GABA synthesis resulting from isoniazid antagonism towards pyridoxal phosphate, a coenzyme of glutamate decarboxylase that catalyzes glutamate conversion into GABA. Antituberculous therapy with isoniazid can cause serious complications in the form of seizures often described as status epilepticus. Isoniazid-induced seizures are poorly controlled by conventional anticonvulsants and cannot always be prevented by pyridoxine intake [27–28]. Valproates are known to inhibit development of isoniazid-induced seizures in a dose-dependent fashion [29]. Our study demonstrates that an injection of N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide before seizure modeling increased latency to the first seizure and reduced the death rate in mice in the isoniazid test. Based on these findings, N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide can be considered a candidate antiepileptic drug with an improved safety profile.

CONCLUSIONS

The results of the study confirm that modification of valproic acid with 1,3,4-thiadiazole holds promise for discovering novel anticonvulsant candidate drugs. The advantage of the synthesized N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide is its

Table. The effect of N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide (VPZ) on the latency to the first seizure and survival of mice in the test with the VPZ antagonist isoniazid (250 mg/kg injected intraperitoneally)

Test	Dose, mg/kg	LS1, min *m* ± SEM	Number of surviving mice /total number of mice	Survival, %
NaCl IS + INH	–	31.25 ± 2.03	0/8	0
VPZ + INH	75	47.75 ± 2.42*	0/8	0
VPZ + INH	150	72.13 ± 4.28*	5/8	62.5#
VPZ + INH	300	93.75 ± 4.77*	7/8	87.5#
VPZ + INH	450	–	8/8	100#

Note: * — statistically significant difference between the experimental group and the control animals (mice with isoniazid-induced seizures treated with NaCl IS before the isoniazid injection) ($p < 0.05$; one-way ANOVA with post-hoc Tukey HSD); # — statistically significant difference between the experimental group and the control ($p < 0.05$; Fisher's exact test). VPZ is valprazolamide (N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide); INH is isoniazid; NaCl IS is the isotonic solution of sodium chloride; LS1 is latency to the first seizure.

ability to prevent development of isoniazid-induced seizures. The compound is not soluble in water, which is a disadvantage, since it hinders manufacturing of its injectable formulations. Further research will be focused on the improvement of the compound's biological and pharmaceutical properties by loading it onto β-cyclodextrin nanocapsules. Methods of N-(5-ethyl-1,3,4-thiadiazol-2-yl)-2-propyl pentane amide identification can also be applied to test its originality and used in pharmacokinetic studies.

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