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PHARMACOKINETIC MECHANISMS UNDERLYING DIFFERENCES IN THE BIOLOGICAL ACTIVITY OF POLYMORPHIC FORMS OF ETHYL 4-METHYL-2,2-DIOXO-1H-2λ⁶,1-BENZOTHAZINE-3-CARBOXYLATE

Introduction. The study investigated the relationship between crystal structure, pharmacokinetic parameters, and pharmacodynamic activity of polymorphic modifications of ethyl 4-methyl-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxylate. The relevance of the study is associated with the need to develop new non-steroidal anti-inflammatory drugs with improved efficacy and safety profiles. In this regard, derivatives of 1H-2λ⁶,1-benzothiazine are of particular interest, as pronounced analgesic and anti-inflammatory properties have previously been demonstrated for compounds of this class.

The aim of the study was to establish the relationship between crystal structure, pharmacokinetic parameters, and pharmacodynamic activity of polymorphic modifications of ethyl 4-methyl-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxylate.

Research Methods. The objects of the study were two polymorphic forms of ethyl 4-methyl-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxylate: the monoclinic form NI-75 and the orthorhombic form NI-77. Pharmacodynamic studies were performed using a carrageenan-induced inflammatory hyperalgesia and exudative reaction model in rats. Pharmacokinetic parameters were determined after single oral administration of the compounds to mice at a dose of 10 mg/kg using HPLC-MS analysis. The main pharmacokinetic parameters were calculated from concentration-time curves using non-compartmental analysis.

Results and Discussion. It was found that polymorphic modifications of the same compound differed significantly in pharmacological activity. The monoclinic form NI-75 exhibited markedly higher anti-exudative and analgesic activity compared with the orthorhombic form NI-77 and exceeded the efficacy of the reference drugs meloxicam and piroxicam. Pharmacokinetic analysis demonstrated that the major differences between the polymorphic forms were associated with the absorption stage. The monoclinic form was characterized by significantly higher absorption rate constant values, maximum plasma concentration, area under the pharmacokinetic curve, and bioavailability. At the same time, elimination and distribution parameters of both polymorphs did not differ significantly, indicating similar behavior of the compound after entering the systemic circulation.

The pharmacokinetic features were shown to correlate with X-ray crystallographic data. The denser molecular packing of the orthorhombic form probably complicates crystal lattice disruption and slows dissolution and absorption of the compound. In contrast, weaker intermolecular interactions in the monoclinic form may facilitate faster release and systemic absorption of the substance.

Conclusions. The obtained results demonstrate the important role of polymorphism in the formation of pharmacokinetic and pharmacodynamic properties of 1H-2λ⁶,1-benzothiazine derivatives and open prospects for the targeted search for new biologically active polymorphic modifications with optimized pharmacological characteristics.

KEY WORDS: pharmacokinetics; bioavailability; ethyl 4-methyl-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxylate; anti-inflammatory activity; analgesic activity; absorption; polymorphic modifications; non-steroidal anti-inflammatory drugs.

INTRODUCTION. The search for new biologically active compounds with anti-inflammatory and analgesic properties remains one of the key challenges of modern pharmacology.

Despite the wide range of currently available non-steroidal anti-inflammatory drugs (NSAIDs), their clinical use is frequently associated with gastrointestinal and cardiovascular adverse effects. This stimulates the development of novel heterocyclic systems capable of combining pronounced pharmacological

activity with an improved safety profile [1; 2]. Among the promising areas of medicinal chemistry, derivatives of 1*H*-2,1-benzothiazine-3-carboxylic acids and their functionalized analogs have attracted considerable attention. Compounds of this class have been reported to possess analgesic, anti-inflammatory, antioxidant, and antimicrobial activities [3]. Further investigations demonstrated that one of the most promising representatives, ethyl 4-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxylate, may exist in several polymorphic modifications differing in crystal packing organization. It is well known that polymorphism can significantly affect the physicochemical properties of pharmaceutical substances, including solubility, dissolution rate, and bioavailability [4]. In many cases, these factors determine pharmacokinetic behavior and, consequently, the intensity of pharmacological effects [5].

Previous pharmacological studies demonstrated that the monoclinic form of ethyl 4-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxylate (NI-75) and its orthorhombic form (NI-77), despite having identical chemical structures, differ substantially in their analgesic and anti-inflammatory activities. X-ray crystallographic analysis also revealed differences in intermolecular interactions and molecular packing density within the crystal lattice.

The aim of the article was to establish the relationship between crystal structure, pharmacokinetic parameters, and pharmacodynamic activity of polymorphic modifications of ethyl 4-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxylate.

RESEARCH METHODS. The objects of the study were polymorphic modifications of ethyl 4-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxylate synthesized at the Department of Pharmaceutical Chemistry of the National University of Pharmacy under the supervision of Professor I. V. Ukrainets. The chemical structure of the compound is presented in Figure 1.

The monoclinic polymorphic form (compound NI-75) and the orthorhombic form (compound NI-77) were obtained by crystallization from ethanol. It was found that heterogeneous crystallization from ethanol resulted in the formation of the monoclinic polymorphic form (M) of ethyl 4-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxylate, whereas homogeneous crystallization produced its orthorhombic form (O). The molecular and

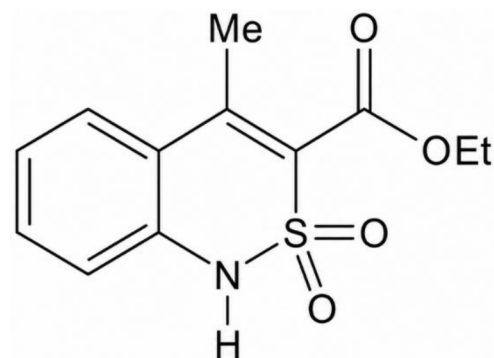


Fig. 1. Chemical structure of ethyl 4-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxylate

crystal structures of both forms were confirmed by X-ray crystallographic analysis, while phase purity was verified by powder X-ray diffraction.

Pharmacodynamic studies of the test samples were carried out on 140 male Wistar rats obtained from the vivarium of the State Institution "Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine" and housed under standard vivarium conditions at Pirogov National Medical University.

The experiments were conducted at the certified "Research Laboratory for Preclinical Investigation of Medicinal Products of the Department of Pharmacology" (Technical Competence Certificate № 171/23 dated December 6, 2023; valid until December 5, 2028).

The test samples were administered intragastrically to animals of the experimental groups as aqueous suspensions stabilized with 5 % aqueous Tween-80 solution (Sigma, USA), whereas animals of the control groups received equivalent volumes of water and Tween-80. Diclofenac sodium (Voltaren®, Novartis), meloxicam (Movalis®, Boehringer Ingelheim, Ingelheim am Rhein, Germany), and piroxicam (Sopharma AD, Bulgaria) were used as reference drugs. In pharmacodynamic studies, the compounds were administered at a dose of 20 mg/kg.

Anti-inflammatory and analgesic activities were evaluated using a model of inflammatory hyperalgesia and exudative reaction induced by subplantar injection of 0.1 mL of 1 % carrageenan solution (Sigma, USA) into the right hind paw of rats. Pain sensitivity was assessed by measuring the pain threshold using a Dolorimeter Baseline device (USA). Anti-exudative activity was determined 3 h after inflammation induction by measuring paw edema volume with a Plethysmometer (Ugo Basile, Italy). Both activities were compared

with the control and reference drug groups and expressed as percentages [6; 7].

Pharmacokinetic studies were performed on 104 outbred male white mice maintained under standard vivarium conditions with free access to food and water. Polymorphic forms NI-75 and NI-77 were administered orally at a dose of 10 mg/kg as suspensions stabilized with 0.5 % methylcellulose. Blood samples were collected at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 h after administration. The concentration of the studied compound was determined by HPLC-MS using an Agilent 1260 Infinity liquid chromatography system coupled with a 6530 Accurate Mass Q-TOF detector (Agilent Technologies, USA). For protein precipitation, 300 μ L of a mixture of 7 % perchloric acid and acetonitrile (60:40) was added to 200 μ L of serum, followed by centrifugation and filtration through a microporous filter. The analysis was performed using an injection volume of 20 μ L.

Pharmacokinetic parameters were calculated from concentration-time curves obtained after a single oral administration of the compounds. Pharmacokinetic characteristics were evaluated using an extravascular administration model with first-order absorption and elimination kinetics. The absorption (k_{abs}) and elimination (k_{el}) rate constants were determined by nonlinear approximation of the experimental data. T_{max} and C_{max} values were obtained directly from the concentration-time profiles. The area under the pharmacokinetic curve ($AUC_{0-\infty}$) and the area under the first moment curve ($AUMC_{0-\infty}$) were calculated using the trapezoidal method with extrapolation to infinity. Mean residence time (MRT) was determined as the $AUMC/AUC$ ratio. Pharmacokinetic analysis was performed using a non-compartmental approach [8; 9].

Statistical analysis of the obtained results was performed using nonparametric methods with the STATISTICA 10.0 software package. Data are presented as mean $\pm$ standard error of the mean (SEM). Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION. The results of the evaluation of the anti-inflammatory and analgesic activities of ethyl 4-methyl-2,2-dioxo-1*H*-2 λ^6 ,1-benzothiazine-3-carboxylate are presented in Table 1.

The studied crystalline modifications of ethyl 4-methyl-2,2-dioxo-1*H*-2 λ^6 ,1-benzothiazine-3-carboxylate (compounds NI-75 and NI-77) demonstrated markedly different biological properties. Thus, the orthorhombic form 2O (compound NI-77) exhibited moderate analgesic activity (66.0 %) and weak anti-inflammatory activity (anti-exudative activity of 30.7 %), whereas the monoclinic form 2M (compound NI-75), administered under the same conditions and at the same dose, demonstrated pronounced analgesic and anti-exudative effects, with analgesic and anti-inflammatory activities of 90.6 % and 85.8 %, respectively. These effects significantly exceeded not only those of piroxicam, but also those of meloxicam, which is considered more active in this regard ($p < 0.05$). These findings suggest that the crystal structure of benzothiazine-3-carboxylate esters plays an important role in determining their pharmacodynamic properties.

These findings prompted further investigation into the mechanisms underlying these differences. As a working hypothesis, we assumed that they could be associated with pharmacokinetic features of the investigated crystalline forms. To verify this assumption, a pharmacokinetic study was subsequently performed.

Table 1 – Anti-inflammatory activity of 4-methyl-2,2-dioxo-1*H*-2 λ^6 ,1-benzothiazine-3-carboxylate derivatives in comparison with reference drugs ($M \pm m$, $n = 7$)

Compound, laboratory code	<i>R</i> , form	Anti-inflammatory activity		Analgesic activity	
		Increase in edema volume	AEA (%)	pain threshold increment (ΔPT)	AA, (%)
NI-75	H (2M)	58.8 $\pm$ 5.81 ^{1,2,3}	85.8	30.0 $\pm$ 4.47 ^{1,2,3}	90.6
NI-77	H (2O)	286.7 $\pm$ 8.64 ^{1,2,3}	30.7	108.0 $\pm$ 8.60 ^{1,2,3}	66.0
Piroxicam	–	223.8 $\pm$ 6.13 ^{1,2,3}	45.9	164.0 $\pm$ 8.12 ^{1,2,3}	48.4
Meloxicam	–	131.3 $\pm$ 8.05 ^{1,2}	68.3	88.0 $\pm$ 11.,6 ^{1,2}	72.3
Diclofenac	–	91.05 $\pm$ 5.52 ^{1,3}	78.0	59.0 $\pm$ 9.27 ¹	81.4
Control	–	413.7 $\pm$ 32.2	0	318.0 $\pm$ 34.9	0

Notes:

¹ – statistically significant differences ($p < 0.05$) vs control group;

² – statistically significant differences ($p < 0.05$) vs diclofenac;

³ – statistically significant differences ($p < 0.05$) vs meloxicam.

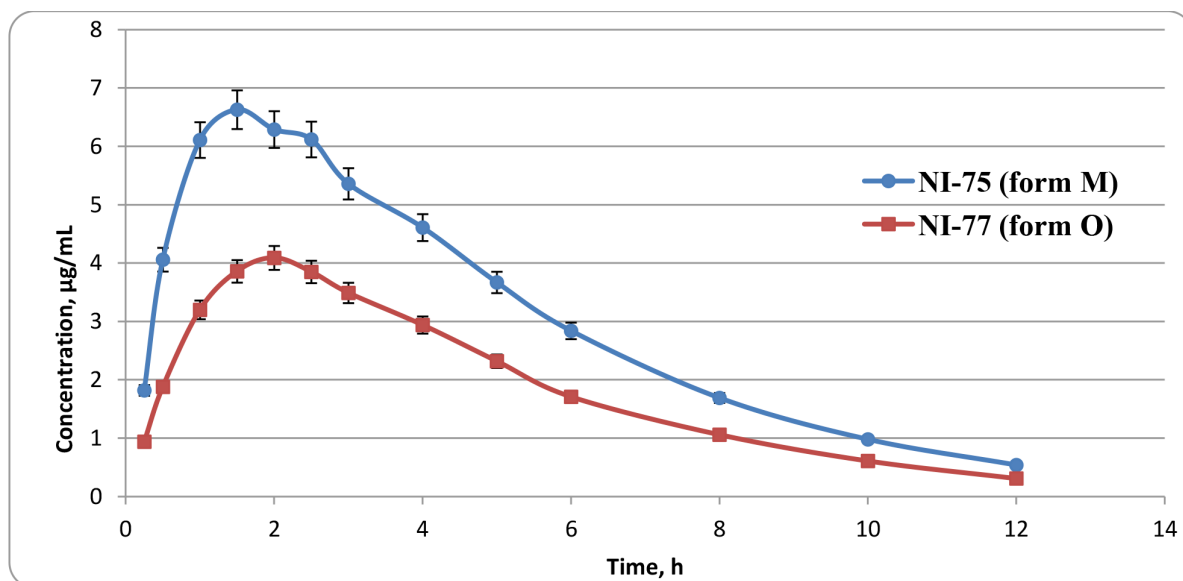


Fig. 2. Plasma concentration-time profiles of polymorphic forms of ethyl 4-methyl-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxylate (NI-75 and NI-77) following single oral administration at a dose of 10 mg/kg in mice. Data are presented as mean ± SEM (*n* = 8)

Following oral administration, both polymorphic forms produced typical concentration-time profiles consistent with one-compartment kinetics with first-order absorption (Figure 2). At the same time, the shapes of the curves and plasma concentration levels of NI-75 and NI-77 differed considerably.

The calculated pharmacokinetic parameters of polymorphic modifications of ethyl 4-methyl-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxylate indicate a significant influence of crystal structure on the absorption and bioavailability of the investigated compounds. The most pronounced differences were observed at the absorption stage, whereas elimination and distribution parameters showed almost no differences between the polymorphic forms (Table 2).

It was found that the monoclinic form M (NI-75), which had previously demonstrated more pronounced analgesic and anti-inflammatory activity, was characterized by a significantly higher absorption rate compared with the orthorhombic form O (NI-77). The monoclinic form NI-75 was absorbed considerably faster than the orthorhombic form NI-77. The absorption rate constant for form M was more than twofold higher than that of form O (2.241 ± 0.077 vs. 0.967 ± 0.067 h⁻¹; $p < 0.001$). These findings were consistent with the obtained *T*_{abs1/2} and *T*_{max} values. The maximum plasma concentration of NI-75 was reached within 0.9 h after administration, whereas for NI-77 this parameter was observed at 1.8 h.

Table 2 – Main pharmacokinetic parameters of 4-methyl-2,2-dioxo-1H-2λ⁶,1-benzothiazine-3-carboxylate derivatives (*M* ± *m*, *n* = 8)

Pharmacokinetic parameter	Form M (NI-75)	Form O (NI-77)	P
Absorption rate constant, k_{abs} , h ⁻¹	2.241 ± 0.077	0.967 ± 0.067	$p < 0.001$
Absorption half-life, $T_{abs1/2}$, h	0.348 ± 0.212	0.865 ± 0.093	$p < 0.01$
Time to maximum concentration, T_{max} , h	0.900	1.800	$p < 0.05$
Maximum concentration, C_{max} , μg/mL	6.724 ± 0.711	4.094 ± 0.314	$p < 0.05$
Area under the pharmacokinetic curve, $AUC_{0-\infty}$, μg · h/mL	55.70 ± 7.410	27.42 ± 3.254	$p < 0.01$
Bioavailability, <i>f</i>	0.850 ± 0.063	0.465 ± 0.178	$p < 0.05$
Elimination rate constant, <i>kel</i> , h ⁻¹	0.255 ± 0.210	0.255 ± 0.210	$p > 0.05$
Elimination half-life, $T_{el1/2}$, h	3.121 ± 0.210	3.121 ± 0.210	$p > 0.05$
Total clearance, <i>Cl</i> _{tot} , L/kg · h	0.175 ± 0.019	0.175 ± 0.019	$p > 0.05$
Steady-state volume of distribution, <i>V</i> _{dss} , L/kg	1.100 ± 0.131	1.100 ± 0.131	$p > 0.05$
Mean residence time, <i>MRT</i> , h	3.581 ± 0.086	6.722 ± 0.119	$p < 0.001$

The faster absorption of the monoclinic form was accompanied by higher systemic exposure of the compound. The $C_{\max}$ value for NI-75 reached $6.724 \pm 0.711 \mu\text{g/mL}$, whereas for the orthorhombic form it was $4.094 \pm 0.314 \mu\text{g/mL}$ ($p < 0.05$). A similar tendency was observed for the area under the pharmacokinetic curve: the $\text{AUC}_{0-\infty}$ value for NI-75 was more than twofold higher than that of NI-77 (55.70 ± 7.410 vs. $27.42 \pm 3.254 \mu\text{g}\cdot\text{h/mL}$; $p < 0.01$).

The differences between the polymorphic forms were also clearly reflected in their bioavailability. The bioavailability value (f) for the monoclinic form was 0.850 ± 0.063 , whereas for the orthorhombic form it was approximately 83 % lower. These findings indicate that the same administered dose of different polymorphic forms provides substantially different levels of active compound entering the systemic circulation.

At the same time, the parameters characterizing elimination and distribution of the compound remained nearly identical for both forms. The values of kel , $T_{1/2}$, total clearance (Cl_{tot}), and steady-state volume of distribution (V_{dss}) did not differ significantly ($p > 0.05$), indicating similar behavior of the compound after entering the systemic circulation. This suggests that polymorphism predominantly affects the absorption stage of the drug.

Interestingly, the orthorhombic form was characterized by a considerably longer mean residence time in the body. The MRT value for NI-77 was almost twofold higher than that for NI-75 (6.722 ± 0.119 vs. 3.581 ± 0.086 h; $p < 0.001$). This is probably associated with slower disruption of the crystal lattice and more gradual release of the compound [10].

The pharmacokinetic features of both polymorphs are in good agreement with the X-ray crystallographic data. Analysis of the crystal structure demonstrated that in

the monoclinic crystals, ethyl 4-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxylate molecules (compound NI-75) form infinite chains (Figure 3A) extending along the crystallographic direction. Molecules within each chain are interconnected, whereas no intermolecular interactions with adjacent chains were observed.

In contrast, in the orthorhombic form (compound NI-77) (Figure 3B), the ester molecules also form infinite chains along the crystallographic direction; however, in this case the molecules are linked not only within the same chain but also with neighboring chains, and these intermolecular interactions are stronger compared with those observed in the monoclinic form. In addition, the polymorphs differ in the type of molecular packing within the crystal lattice.

The denser molecular packing observed in the orthorhombic form probably complicates disruption of the crystal lattice and slows dissolution of the compound. In contrast, weaker interchain interactions in the monoclinic form may facilitate compound release and accelerate its absorption [11].

Thus, the results of the present study demonstrate that polymorphism of ethyl 4-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxylate significantly affects its pharmacokinetic characteristics, primarily the parameters of absorption and bioavailability. These differences most likely underlie the markedly different pharmacodynamic activities of the investigated polymorphic modifications.

CONCLUSIONS. Despite having identical chemical structures, polymorphic modifications of ethyl 4-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxylate differed significantly in their anti-inflammatory and analgesic activities. The monoclinic form

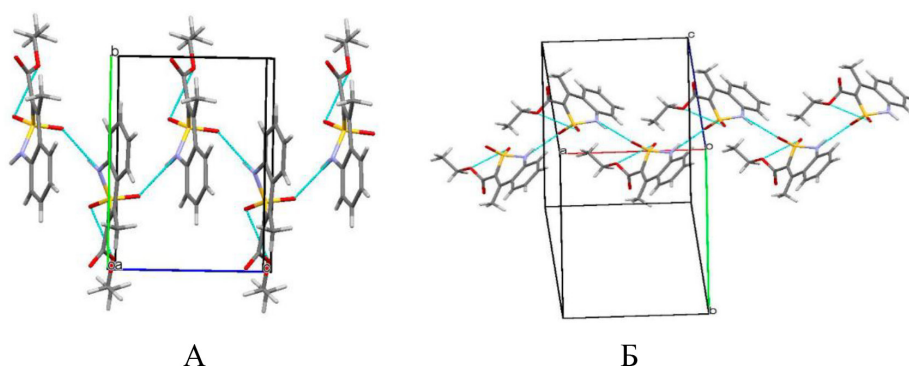


Fig. 3. Crystal structures of the monoclinic (A) and orthorhombic (B) polymorphic forms of ethyl 4-methyl-2,2-dioxo-1*H*-2λ⁶,1-benzothiazine-3-carboxylate [3]

NI-75 demonstrated more pronounced anti-exudative and analgesic effects compared with the orthorhombic form NI-77 and exceeded the activity of meloxicam and piroxicam.

The major pharmacokinetic differences between the polymorphic forms were associated with the absorption stage. The monoclinic form was characterized by a higher absorption rate, greater systemic exposure, and higher bioavailability, whereas elimination and distribution parameters did not differ significantly between the two forms.

A relationship between crystal packing features of the polymorphic modifications and their pharmacokinetic characteristics was established. The denser molecular packing of the orthorhombic form probably complicates crystal lattice disruption and slows absorption of the compound.

Further studies should focus on elucidating the role of polymorphism in the formation of pharmacokinetic and pharmacodynamic properties of 1*H*-2λ⁶,1-benzothiazine derivatives. Particular attention should be paid to the relationship between crystal organization, absorption rate, and the intensity of anti-inflammatory and analgesic activities. Such studies may provide a basis for predicting the biological activity of new polymorphic modifications and optimizing their pharmacological properties.

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COMPLIANCE WITH BIOETHICAL STANDARDS: All experimental procedures involving animals were performed in accordance with the general ethical principles for animal experimentation outlined in the European Convention for the Protection of Vertebrate Animals Used for Experimental

and Other Scientific Purposes (Strasbourg, 1986; revised in 1998) and the Law of Ukraine № 3447–IV “On Protection of Animals from Cruel Treatment” dated February 21, 2006, as amended. All animal experiments complied with the ARRIVE 2.0 guidelines for the humane treatment of animals used in experimental research. Compliance with these requirements was confirmed by the Bioethics Committee of Pirogov National Medical University, Vinnytsia, Ukraine (Protocol № 10, November 8, 2025).

AUTHOR

N. Voloshchuk – conceptualization, project administration, writing – Review & Editing; Olha Denysiuk – methodology, Writing – Original Draft, Supervision; Alexandr Il’chenko – data curation, investigation, resources; A. Saienko – investigation, Formal Analysis, Visualization.

CONTRIBUTIONS:

CONFLICT OF INTEREST: None declared.

AVAILABILITY OF PRIMARY DATA: The primary data that support the findings of this study are available from the corresponding author upon reasonable request, subject to applicable confidentiality requirements and ethical considerations.

INFORMATION ON THE USE OF ARTIFICIAL INTELLIGENCE: The authors of this manuscript certify that they did not use any generative artificial intelligence tools or services during the conduct of the study or the preparation of this manuscript for any of the tasks specified in the Generative Artificial Intelligence Delegation Taxonomy (GAIDeT, 2025). All stages of the work, from conceptualization to final editing of the manuscript, were carried out exclusively by the authors without the involvement of generative artificial intelligence.

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ВІННИЦЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ М. І. ПИРОГОВА

ФАРМАКОКІНЕТИЧНІ МЕХАНІЗМИ ВІДМІННОСТЕЙ БІОЛОГІЧНОЇ АКТИВНОСТІ ПОЛІМОРФНИХ ФОРМ ЕТИЛ-4-МЕТИЛ-2,2-ДІОКСО-1Н-2 λ ⁶,1-БЕНЗОТІАЗИН-3-КАРБОКСИЛАТУ

Анотація

Вступ. У роботі досліджено взаємозв'язок між кристалічною структурою, фармакокінетичними параметрами та фармакодинамічною активністю поліморфних модифікацій етил-4-метил-2,2-діоксо-1Н-2 λ ⁶,1-бензотіазин-3-карбоксилату. Актуальність дослідження зумовлена необхідністю пошуку нових нестероїдних протизапальних засобів (далі – НПЗЗ) із покращеним профілем ефективності та безпеки, оскільки застосування традиційних НПЗЗ нерідко супроводжується розвитком гастроінтестинальних і серцево-судинних побічних реакцій. Особливий інтерес у цьому аспекті становлять похідні 1Н-2 λ ⁶,1-бензотіазину, для яких раніше було показано виражену анальгетичну та протизапальну активність.

Мета дослідження – встановлення взаємозв'язку між кристалічною структурою, фармакокінетичними параметрами та фармакодинамічною активністю поліморфних модифікацій етил-4-метил-2,2-діоксо-1Н-2 λ ⁶,1-бензотіазин-3-карбоксилату.

Методи дослідження. Об'єктами дослідження були дві поліморфні форми етил-4-метил-2,2-діоксо-1Н-2 λ ⁶,1-бензотіазин-3-карбоксилату: моноклінна форма NI-75 і орторомбічна форма NI-77. Фармакодинамічні дослідження проведено на моделі карагенін-індукованої запальної гіпералгезії та ексудативної реакції в щурів. Фармакокінетичні параметри визначали після одноразового перорального введення сполук мишам у дозі 10 мг/кг із використанням ВЕРХ-МС-аналізу. Розрахунок основних параметрів фармакокінетики здійснювали методом pop-compartmental analysis за результатами концентраційно-часових кривих.

Результати й обговорення. Встановлено, що поліморфні модифікації тієї самої сполуки суттєво різняться за вираженістю фармакологічної активності. Моноклінна форма NI-75 проявляла значно вищу антиексудативну й анальгетичну активність порівняно з орторомбічною формою NI-77 і перевищувала за ефективністю референс-препарати Мелоксикам і Піроксикам. Фармакокінетичне дослідження показало, що основні відмінності між поліморфними формами локалізуються на стадії абсорбції. Для моноклінної форми були характерні значно вищі значення константи абсорбції, максимальної концентрації у плазмі крові, площі під фармакокінетичною кривою та біодоступності. Водночас параметри елімінації та розподілу для обох поліморфів практично не відрізнялися, що свідчить про однакову поведінку сполуки після її потраплення в системний кровотік.

Показано, що особливості фармакокінетики узгоджуються з даними рентгеноструктурного аналізу. Більш щільна упаковка молекул в орторомбічній формі, імовірно, ускладнює руйнування кристалічної решітки та сповільнює розчинення і абсорбцію речовини. Натомість слабші міжмолекулярні взаємодії в моноклінній формі сприяють швидшому вивільненню та надходженню сполуки в системний кровотік.

Висновки. Отримані результати свідчать про важливу роль поліморфізму у формуванні фармакокінетичних і фармакодинамічних властивостей похідних 1Н-2 λ ⁶,1-бензотіазину та відкривають перспективи цілеспрямованого пошуку нових біологічно активних поліморфних модифікацій з оптимізованими фармакологічними характеристиками.

КЛЮЧОВІ СЛОВА: фармакокінетика; біодоступність; етил-4-метил-2,2-діоксо-1Н-2 λ ⁶,1-бензотіазин-3-карбоксилат; протизапальна активність; анальгетична активність; абсорбція; поліморфні модифікації; НПЗЗ.

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