

Article

Evaluation of Anticonvulsant Activity of Dual COX-2/5-LOX Inhibitor Darbufelon and Its Novel Analogues

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Abstract: Neuroinflammation is an integral part of epilepsy pathogenesis and other convulsive conditions, and non-steroidal anti-inflammatory drugs (NSAIDs) present a potent tool for the contemporary search and design of novel anticonvulsants. In the present paper, evaluation of the anticonvulsant activity of the potential NSAID dual COX-2/5-LOX inhibitor darbufelone methanesulfonate using an scPTZ model in mice in dose 100 mg/kg is reported. Darbufelone possesses anticonvulsant properties in the scPTZ model and presents interest for in-depth studies as a possible anticonvulsant multi-target agent with anti-inflammatory activity. The series of 4-thiazolidinone derivatives have been synthesized following the analogue-based drug design and hybrid-pharmacophore approach using a darbufelone matrix. The synthesized derivatives showed a significant protection level for animals in the scPTZ model and are promising compounds for the design of potential anticonvulsants with satisfactory drug-like parameters.

Keywords: 4-thiazolidinones; darbufelone; dual COX-2/5-LOX inhibitor; pentylentetrazole seizure; anticonvulsant activity

1. Introduction

More than 70 million people suffer from epilepsy and seizure conditions, constituting nearly 1% of the global population [1]. The available schemes and protocols for the treatment of such pathologies are very often imperfect, therefore the research and development of innovative anticonvulsants are unmet and actual problems for medicinal chemists [2–5]. Recently, considerable attention in search of possible targets for the correction of epilepsy and related conditions has been focused on the neuroinflammation process which occurs due to many reasons, such as neuroinfection, strokes, and head injuries, and can initiate an inflammatory cascade in the central nervous system [6,7]. Neuroinflammation is a predictor of increased convulsive readiness [8] and key trigger for epilepsy pathogenic mechanisms such as the activation of microglia and microglial inflammatory mediators [9], the expression of circulating immune cells [10], cytokine and chemokine upregulation [11], free radical formation [12], and cyclooxygenases-1 and 2 (COX-1/2) upregulation, etc. [13,14]. Therefore, potential NSAIDs with different mechanisms of action

represent a powerful tool for modern anticonvulsant design [15,16]. A number of approved NSAIDs from many chemical chemotypes were evaluated in various screening convulsive models and were found to be effective, as well as prospects for subsequent experiments (Figure 1) [17–22].

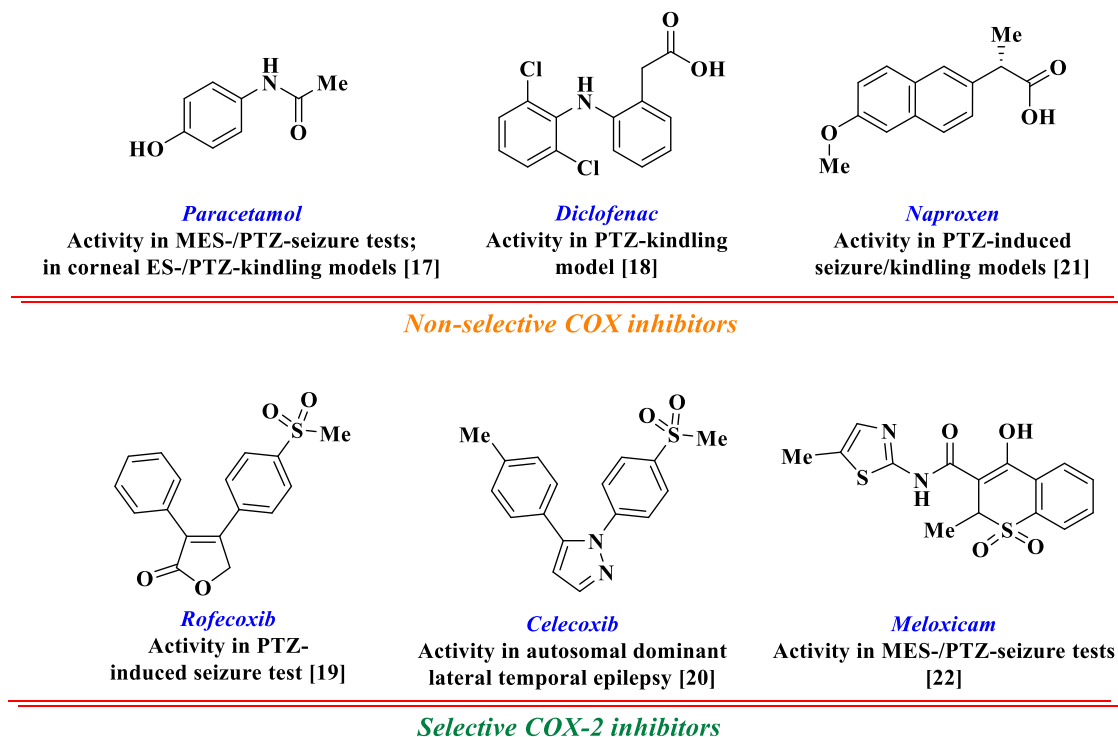


Figure 1. Anticonvulsant properties of marketed NSAIDs.

Both primary enzymes COX-1 and COX-2, which catalyze the synthesis of inflammatory prostanoids and are main targets for NSAIDs, have been reported as potential neurotherapeutic targets for epilepsy correction and management [14,16,23].

In the aforementioned context, the darbufelone–NSAID, a dual inhibitor targeting COX-2 and 5-lipoxygenase (5-LOX), presents interest for study as a possible potential anticonvulsant. Darbufelone belongs to 4-thiazolidinone derivatives, and among this class of heterocycles, the thiazole-4-thiazolidinone hybrid molecules are known as an important source of drug-like molecules with various kinds of biological activities as well as polypharmacological agents [24–29]. The thiazole-4-thiazolidinone-bearing hybrids with promising anticonvulsant properties were identified and reported [26,30]. Among them the hit-compound Les-6222 (Figure 2) was found to be the most active in maximal electroshock seizures (MES) and pentylenetetrazole (PTZ) tests, and at doses of 50–150 mg/kg possessed equal activity compared to sodium valproate and carbamazepine.

Taking into account all the above reasons, herein we present a study of the anticonvulsant properties of darbufelone in a subcutaneous pentylenetetrazole (scPTZ) seizure model. Additionally, as a logical continuation, the other main goal of the current work was the synthesis of some darbufelone analogues and hybrids with thiazole moieties (Figure 2) and the evaluation of their anticonvulsant activity in scPTZ tests.

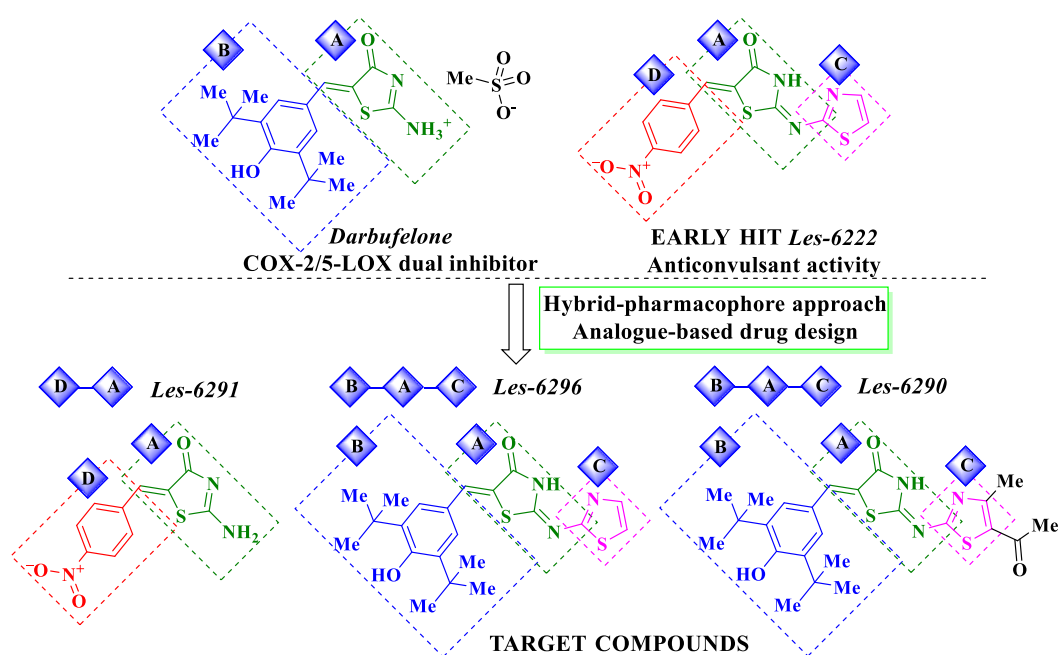


Figure 2. Background and design for the current work.

2. Materials and Methods

2.1. General Information

All materials were purchased from commercial sources and used without purification. Melting points were measured in open capillary tubes and are uncorrected. The elemental analyses (C, H, N) were performed using the Perkin–Elmer 2400 CHN analyzer (Perkin–Elmer, Norwalk, CT, USA) and were within 0.4% of the theoretical values. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE-400 spectrometer (Bruker, Bremen, Germany). All spectra were recorded at room temperature, except where indicated otherwise, and were referenced internally to solvent reference frequencies. Chemical shifts (δ) are quoted in ppm, and coupling constants (J) are reported in Hz. LC–MS spectra were obtained on a Finnigan MAT INCOS-50 (Thermo Finnigan LLC, San Jose, CA, USA). Solvents and reagents that are commercially available were used without further purification.

The procedure used for the synthesis of compound 1b was described in [31]; for compounds 3a,b, in [32]. The derivatives Les-6290, Les-6291, Les-6296 have been obtained from 3a,b and 2-aminothiazol-4(5H)-one (4) accordingly to the protocol described in [33].

2.2. Synthesis and Characterization of Compounds

2.2.1. Synthesis of (thiazol-2-ylamino/5-acetyl-4-methyl-thiazol-2-ylamino)-acetyl chlorides (2a,b)

A solution of chloroacetyl chloride (3 mmol) in 5 mL of dioxane was added to an appropriate mixture of 2-aminothiazole (1a) or 2-amino-4-methyl-5-acetylthiazole (1b) (3 mmol) and triethylamine (3 mmol) in 5 mL of dioxane and was later heated to 70–80 °C for 30 min, cooled, and poured into water (50 mL). The obtained powder was filtered off, washed with water, and recrystallized from ethanol.

2.2.2. Characterization of Compounds Les-6296, Les-6290, Les-6291

Les-6296: 5-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-2-(thiazol-2-ylimino)-thiazolidin-4-one. Yield 72%, yellow-brown powder, m.p. 170–172 °C; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 1.39, 1.41 (2*s, 18H, *t*-Bu), 7.38 (m, 1H, thiazol.), 7.45 (s, 1H, =CH), 7.60 (m, 1H, thiazol.), 7.64 (m, 2H, arom.), 8.00 (s, 1H, OH), 9.80, 12.21, 12.51 (3*s, 1H, NH); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): 30.3, 34.8, 117.6, 125.1, 127.3, 128.7, 133.7, 140.3, 144.6, 148.0, 162.7, 168.6, 192.4. Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_2\text{S}_2$: C, 60.69; H, 6.06; N, 10.11. Found: C, 60.60; H, 6.00; N, 10.19. ESI-MS m/z 416 (M+H) $^+$.

Les-6290: 2-(5-Acetyl-4-methylthiazol-2-ylimino)-5-(3,5-di-tert-butyl-4-hydroxybenzylidene)-thiazolidin-4-one. Yield 80%, yellow-brown powder, m.p. 158–160 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.26 (s, 3H, CH₃), 1.39 (s, 18H, t-Bu), 1.51 (s, 3H, CH₃), 7.38, 7.45 (2*s, 1H, =CH), 7.66 (s, 2H, arom.), 7.99 (s, 1H, OH), 9.80 (s, 1H, NH); ¹³C NMR (100 MHz, DMSO-*d*₆): 19.0, 35.0, 35.2, 39.6, 114.9, 123.5, 130.5, 132.0, 133.4, 143.8, 153.5, 165.1, 168.7, 174.5, 197.2. Anal. Calcd for C₂₄H₂₉N₃O₃S₂: C, 61.12; H, 6.20; N, 8.91. Found: C, 61.20; H, 6.30; N, 8.82. ESI-MS *m/z* 472 (M+H)⁺.

Les-6291: 2-Amino-5-(4-nitrobenzylidene)-thiazol-4-one. Yield 80%, yellow powder, m.p. > 240 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.68 (s, 1H, =CH), 7.81 (d, 2H, *J* = 8.5 Hz, arom.), 8.32 (d, 2H, *J* = 8.5 Hz, arom.), 9.34, 9.62 (2*s, 2H, NH₂); ¹³C NMR (100 MHz, DMSO-*d*₆): 129.4, 131.6, 135.4, 139.0, 145.8, 152.1, 180.3, 185.0. Anal. Calcd for C₁₀H₇N₃O₃S: C, 48.00; H, 3.22; N, 16.70. Found: C, 48.07; H, 3.32; N, 16.80. ESI-MS *m/z* 250 (M+H)⁺.

2.3. Pharmacology Assay

2.3.1. Animals

The experiments were conducted on random-bred male albino mice weighing 18–22 g purchased from the Animal House of the Central Research Laboratory of the Educational and Scientific Institute of Applied Pharmacy of the National University of Pharmacy, Kharkiv, Ukraine. The animals were housed in groups of 10 in standard plastic cages, at room temperature of 20 ± 2 °C, exposed to a 12:12 h light/dark cycle, with ad libitum standard laboratory food and water. All experiments were performed between 9 a.m. and 3 p.m. The tested groups consisting of 6–7 mice were chosen by means of a randomized schedule. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted, and were approved by the Local Ethical Committee in National University of Pharmacy, Kharkiv, Ukraine (Approval No: 3/2019).

2.3.2. Subcutaneous Pentylentetrazole Model (scPTZ)

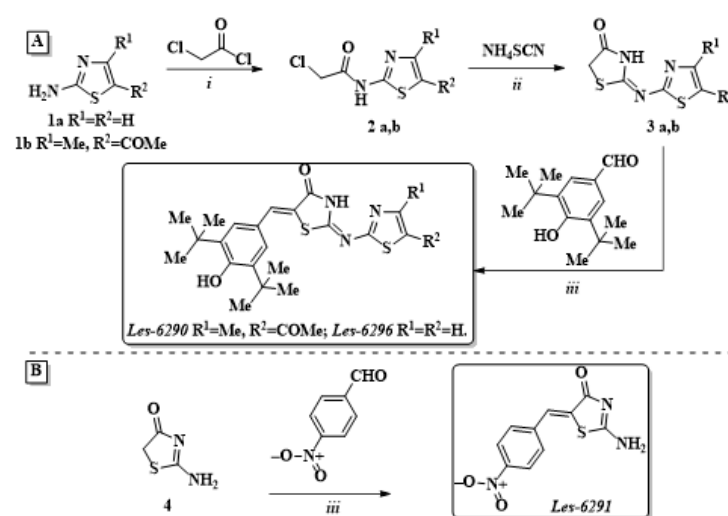
The scPTZ-induced seizures were performed by subcutaneous injection of PTZ (90 mg/kg). Animals were placed into the separate transparent plastic cylindrical containers and continuously monitored for 60 min. Sodium valproate (Depakine, Sanofi-Aventis, France) at a dose of 300 mg/kg [34] in the form of a syrup for oral administration, and phenytoin (Diphenin, Kyiv Vitamin Plant, Kyiv City, Ukraine) at a dose of 40 mg/kg [35] were used as reference drugs. Celecoxib (Celebrex, Pfizer, New York City, NY, USA)—selective COX-2 inhibitor with early described anticonvulsant properties [36] was used at a dose of 4 mg/kg for comparison. Darbufelone methanesulfonate and compounds Les-6290, Les-6291, and Les-6296 were administered once intragastrically (i.g.) in the form of an aqueous suspension stabilized with Tween-80 at a dose of 100 mg/kg 30 min before seizure induction [34]. The dose of test compounds at 100 mg/kg was selected for this screening study based on previous studies of a number of 4-thiazolidinone derivatives, in which the compounds showed a pronounced anticonvulsant effect [26,30]. The Les-6296 was further tested at a dose of 75 mg/kg (i.g.), which is equivalent to a dose of 100 mg/kg of darbufelone methanesulfonate. The Les-6291 was also administered i.g. at a dose of 53 mg/kg, which corresponds to a 40 mg/kg dose of phenytoin. The effectiveness of all substances were evaluated by the following indicators: latency period of first convulsions (latency), the number of clonic–tonic seizures in 1 mouse, percentage of animals in the group separately with clonic and tonic convulsions, severity of seizure—in points (1 point—single tremors; 2 points—“manege” running or “kangaroo” position; 3 points—clonic convulsions without lateral position; 4 points—clonic–tonic convulsions with lateral position; 5 points—tonic extension; 6 points—tonic extension, which led to the death of the animal), duration of convulsive period (period of seizures), life expectancy of animals to death (time to death), and lethality. If seizures were not observed for 1 h, the latency was considered to be 60 min [37]. For statistical analysis, STATISTICA 12.0 for Windows was used. Data are reported as the mean ± standard error of mean (mean ± SEM).

The level of statistical significance was considered as $p < 0.05$. Statistical differences between groups were analyzed using the parametric Student's *t*-test in cases of normal distribution; nonparametric Mann–Whitney U-tests in its absence. For the results in the alternative form (lethality, percentage of mice with clonic and tonic convulsions) the Fisher's angular transformation (with Yates's correction, if necessary) was used.

3. Results and Discussion

3.1. Chemical Synthesis and Drug-Likeness Properties

The general synthetic strategy of the present work included two approaches for target thiazole–4-thiazolidinone hybrids and darbufelone analogues: (1) based on a 4-thiazolidinone core formation with the next modification at the C-5 position of heterocycle (Scheme 1A); and (2) using of ready cyclic precursor (4) for modification at the C-5 position following Knoevenagel condensation (Scheme 1B).



Scheme 1. Synthetic pathways to target derivatives Les-6290, Les-6291, Les-6296. Reagent and conditions: (i) **1a,b** (10 mmol), ClCH₂COOH (10 mmol), Et₃N (10 mmol), dioxane anhydrous (10 mL), reflux, 30 min; (ii) **2a,b** (10 mmol), NH₄SCN (20 mmol), acetone (20 mL), reflux 3 h; (iii) **3a,b** or **4** (10 mmol), appropriate aromatic aldehyde (12 mmol), AcONa anhydrous (10 mmol), AcOH glacial (10 mL), reflux 3 h.

Initially, *N*-(thiazol-2-yl)- and *N*-(5-acetyl-4-methylthiazol-2-yl) 2-chloroacetamides (**2a,b**) were obtained from the appropriate aminothiazoles **1a,b** (Scheme 1A). The aforementioned acylation reaction was performed under reflux for 30 min due to weak reactivity of the amino groups of the compounds **1a,b**. Synthesized derivatives **2a,b** were utilized as equivalents of dielectrophilic synthon [C₂]²⁺ in the [2+3]-cyclocondensation reaction with ammonium thiocyanate in acetone providing the appropriate thiazole-bearing 4-thiazolidinones **3a,b**. Subsequently, compounds **3a,b**, and **4** were transformed in the Knoevenagel reaction (medium—glacial acetic acid; catalyst—anhydrous sodium acetate) to obtain the target hybrids Les-6290, Les-6291, Les-6296 (Scheme 1A,B).

The compound structures were characterized and confirmed using ¹H, ¹³C NMR, and LC–MS spectra.

The physicochemical properties of the darbufelone and derivatives Les-6290, Les-6291, and Les-6296 were determined based on Lipinski and Veber rules using the SwissAdme of Swiss Institute of Bioinformatics website [38] (Table 1).

Table 1. Drug-likeness parameters of the darbufelon and derivatives Les-6290, Les-6291, and Les-6296 according to Lipinski and Veber rules.

| Compounds/ Drugs | Lipinski Rules | | | | Veber Rules | | Violations of Rules |
|---------------------|----------------|-----------|---------|----------|-------------|------------|------------------------|
| | MW ≤ 500 | Log P ≤ 5 | NHD ≤ 5 | NHA ≤ 10 | NBR ≤ 10 | TPSA ≤ 140 | |
| Darbufelon | 332.46 | 2.88 | 2 | 3 | 3 | 100.98 | 0 |
| Les-6290 | 471.64 | 3.81 | 2 | 5 | 6 | 145.19 | 1 |
| Les-6291 | 249.25 | 1.19 | 1 | 4 | 2 | 126.57 | 0 |
| Les-6296 | 415.57 | 3.41 | 2 | 4 | 5 | 128.12 | 0 |

NHD: number of hydrogen bond donors; NHA: number of hydrogen acceptors; NBR: number of rotatable bonds; TPSA: total polar surface area.

All tested compounds complied with Lipinski's rule of five. Meanwhile, derivative Les-6290 had a total polar surface area value higher (145.16, accordingly) than limited (≤ 140), in line with Veber's rules.

3.2. Anticonvulsant Activity of Synthesized Compounds

The anticonvulsant activity of darbufelon and derivatives Les-6290, Les-6291, and Les-6296 were evaluated using an scPTZ test and studies results are presented in Figure 1 and Table 2. The reference drug, sodium valproate, showed an expressive anticonvulsant effect, maximally preventing seizures in animals. Meanwhile, the other reference drug, phenytoin, at a dose of 40 mg/kg, affected only the latent period of seizures, and increased them 1.73-fold. Additionally, the phenytoin impact on lethality decrease was inexpressive (only 19%), which could be explained by the predominant blocking of potential-dependent sodium channels [37], i.e., insufficient compliance of the PTZ-induced seizure mechanism.

Table 2. Anticonvulsant activity of the reference drugs, celecoxib, dual COX-2/5-LOX inhibitor darbufelone methanesulfonate and derivatives Les-6290, and Les-6291, Les-6296 in the scPTZ test. Each value represents the mean \pm S.E.M. obtained from 6 mice.

| Group of Animals | Dose, mg/kg | Number of Clonic-Tonic Seizures per Mouse | Mice with Seizures, % | | Seizure Severity, Points | Lethality, % |
|---------------------|----------------|--|-----------------------|----------|-----------------------------|--------------|
| | | | Clonic | Tonic | | |
| CP(PTZ) | 90 | 2.29 \pm 0.52 | 100 | 85.71 | 5.57 \pm 0.43 | 85.71 |
| SV | 300 | 0.00 \pm 0.00 ** | 0 ** | 0 ** | 0 ** | 0 ** |
| PHT | 40 | 1.17 \pm 0.17 | 100 | 66.67 | 5.00 \pm 0.63 | 66.67 |
| CXB | 4 | 2.00 \pm 0.37 | 100 | 66.67 | 4.67 \pm 0.62 | 50.00 |
| DAR | 100 | 1.17 \pm 0.17 | 100 | 100 | 4.00 \pm 0.00 * | 0.00 ** |
| Les-6290 | 100 | 1.67 \pm 0.56 | 83.33 ** | 50.00 | 3.67 \pm 0.84 * | 16.67 ** |
| | 100 | 1.00 \pm 0.00 * | 100 | 66.67 | 4.33 \pm 0.56 | 33.33 * |
| Les-6291 | 53 | 1.00 \pm 0.63 | 50.00 ** | 33.33 * | 2.50 \pm 1.20 * | 33.33 * |
| | 100 | 1.00 \pm 0.00 * | 100 | 33.33 * | 3.33 \pm 0.21 ** | 0.00 ** |
| Les-6296 | 75 | 0.83 \pm 0.17 * | 83.33 ** | 16.67 ** | 2.67 \pm 0.56 ** | 0.00 ** |

CP(PTZ), control pathology; SV, sodium valproate; PHT, phenytoin; CXB, celecoxib; DAR, darbufelone methanesulfonate; * $p < 0.05$; ** $p < 0.01$ compared to the group control pathology (CP (PTZ)).

The administration of the selective COX-2 inhibitor celecoxib at a dose of 4 mg/kg resulted in a moderate anticonvulsant activity in the scPTZ test. In the experimental conditions, by treatment of celecoxib, the proportion of animals with tonic seizures insignificantly reduced (at 19.04%); the animal lethality decreased (at 35.71%); and the period of latency was equal compared to the control pathology (PTZ)(CP(PTZ)) group.

Meanwhile, the administration of dual COX-2/5-LOX inhibitor darbufelone methanesulfonate at a dose of 100 mg/kg resulted in prolonging the latency 2.3-fold, reducing the severity of the seizures (at 28.18%), reducing the length of the seizure period by 9.76-fold, and showed an absolute protective effect on lethality (0%) compared to the CP(PTZ)-group. Additionally, the administration of darbufelone methanesulfonate led to prolonging the latency period by 2.09-fold and reducing the duration of the convulsive period by 7.86-fold in comparison with the animal group which received celecoxib. Considering the more pronounced anticonvulsant effect of darbufelone methanesulfonate, it is logical to

assume that both prostaglandins and leukotrienes play an important role in the mechanism of convulsive syndrome. Thus, dual impact on COX-2/5-LOX could be a more effective component for the presence of anticonvulsant effect than only the inhibition of prostaglandins synthesis.

The administration of Les-6291 at a dose of 100 mg/kg ($p < 0.05$) led to reducing the number of paroxysms per one animal by 2.29-fold. Additionally, the duration of the convulsive period was significantly reduced compared to both the CP(PTZ) group ($p < 0.01$) and the phenytoin group ($p < 0.05$). The life expectancy of animals to death was significantly ($p < 0.05$) reduced by 4.49-fold. However, the lethality to animals decreased, to 52.38% ($p < 0.05$). After the administration of the compound Les-6291 at a dose of 53 mg/kg (equivalent to a dose of 40 mg/kg of phenytoin), the latency period of the first convulsions was significantly ($p < 0.01$) increased by 7.36-fold; the number of clonic and tonic paroxysms was reduced to 50% and 52.38% accordingly, as well as the reduced severity of seizures (by 2.23-fold) and lethality (52.38%).

The derivative Les-6291 possessed anticonvulsant activity at both the used doses (100 and 53 mg/kg). A reduced number of animals with clonic seizures at 100.00% (for dose 100 mg/kg) and at 50.00% (for dose 53 mg/kg), with $p < 0.01$, as well as reducing the convulsive period duration to 0.10 ± 0.00 min (for dose 100 mg/kg) and to 7.08 ± 3.80 min (for dose 53 mg/kg), with $p < 0.05$, was observed in the experiment.

The use of compound Les-6290 led to a statistically significantly ($p < 0.01$) reduced number of animals with clonic seizures at 16.67%, and also reduced the number of mice with tonic convulsions compare with the CP (PTZ) group. Additionally, the administration of Les-6290 significantly reduced the number of animals with the most dangerous tonic seizures at 50% ($p < 0.01$), and at 16.67% with clonic seizures compared to the data obtained in the current experiment for the darbufelone-treated group. The severity of seizures statistically ($p < 0.05$) decreased by 1.52-fold, and lethality decreased to 69.04% compared with the CP(PTZ) group after administration of the compound Les-6290.

The compound Les-6296 was found to be the most potent in the experiment and showed expressive anticonvulsant activity at both doses (100 and 75 mg/kg), which was equivalent to a dose of darbufelone methanesulfonate. The administration of Les-6296 at both mentioned doses promoted full animal survival, reduced the seizure duration period, and reduced the severity of paroxysms. The use of compound Les-6296 (at a dose of 100 mg/kg) significantly ($p < 0.05$) led to a reduced number of animals with tonic convulsions. Meanwhile, administration at a dose of 75 mg/kg reduced the percentage of animals both with tonic (at 69.04%) and with clonic (at 16.67%) convulsions compared with the CP(PTZ) group. Additionally, compound Les-6296 in both administration doses reduced the percentage of animals with both clonic and tonic paroxysms and showed an absolute protective effect against lethality (0%) compared with the group treated with darbufelone.

It should be noted that the action of compounds Les-6290 and Les-6291 reduced the time to death at a dose of 100 mg/kg (Figure 3C). This observation does not mean that these compounds increase the risk of death, because, as shown in Table 2, they reduced the severity of seizures and significantly reduced the integral indicator—mortality. In particular, only one and two mice, from six in each group, died under the administration of compounds Les-6290 and Les-6291, respectively. Additionally, just these mentioned individual animals were characterized with convulsive syndrome which was more severe than in other animals. This led to fairly rapid death, the time of which did not exceed the fluctuations of the corresponding indicator of other groups. In the other animals treated with Les-6290 and Les-6291, the seizures stopped fairly quickly.

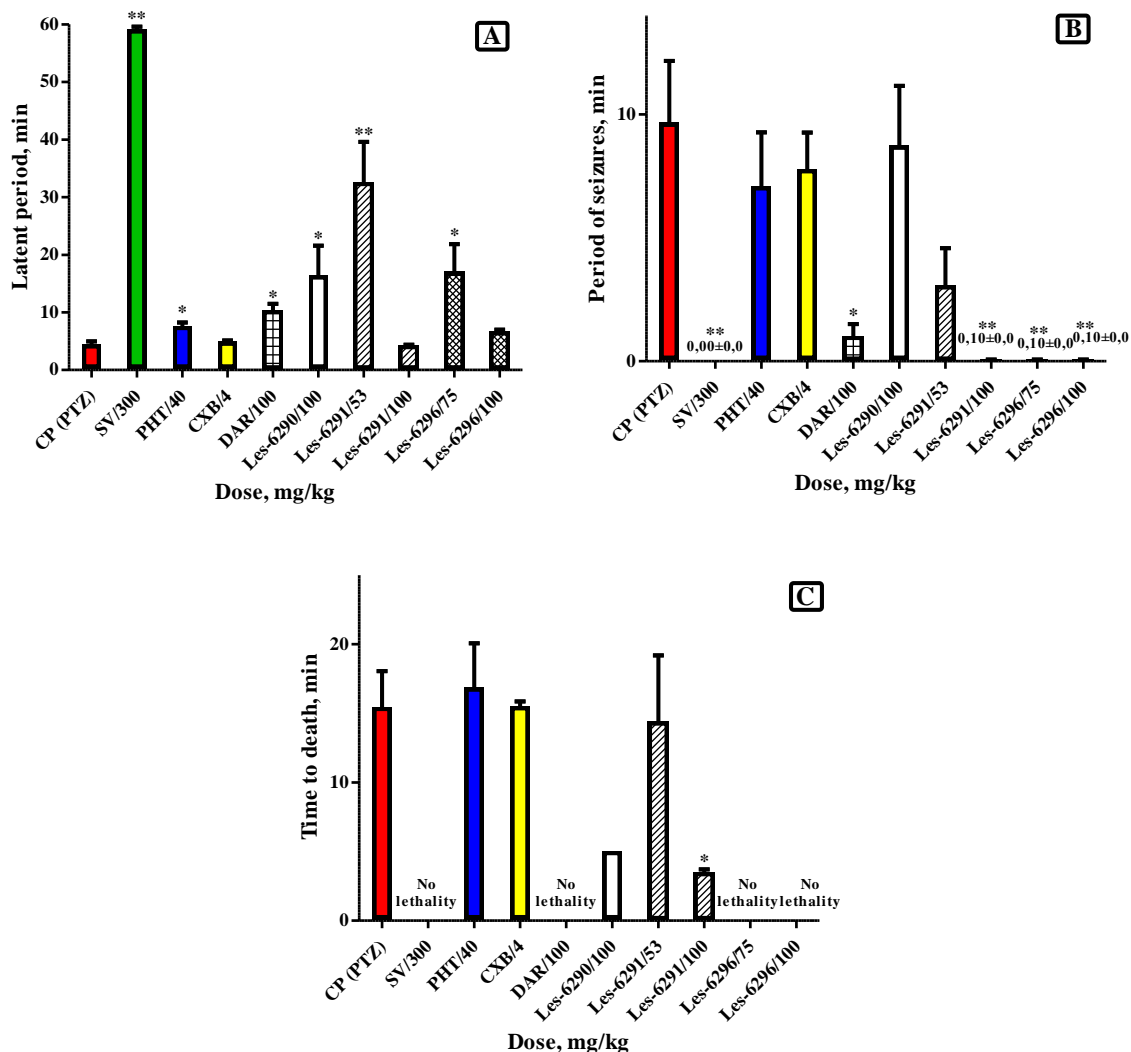


Figure 3. Anticonvulsant activity of the reference drugs, celecoxib, dual COX-2/5-LOX inhibitor darbufelone methanesulfonate and derivatives Les-6290, Les-6291, and Les-6296 in the scPTZ test: (A) latency to the first seizure episode; (B) duration (period) of seizures; (C) time to death. Each value represents the mean ± S.E.M. obtained from 6 mice. CP(PTZ), control pathology; SV, sodium valproate; PHT, phenytoin; CXB, celecoxib; DAR, darbufelone methanesulfonate; * $p < 0.05$; ** $p < 0.01$ compared to the group control pathology (CP (PTZ)).

In a series of darbufelone and synthesized 4-thiazolidinone hybrids/analogues, the following sequence of decreasing anticonvulsant activity potency was observed: Les-6296 (75 mg/kg) > darbufelone methanesulfonate (100 mg/kg) > Les-6296 (100 mg/kg) > Les-6290 (100 mg/kg) > Les-6291 (53 mg/kg and 100 mg/kg). From the structure–activity relationship, it should be noted that presence of the thiazol-2-yl-amine substituent at position C-2 and 3,5-di-*tert*-butyl-4-hydroxybenzylidene moiety in position C-5 into 4-thiazolidinone molecule are optimal for anticonvulsant effects.

In this study, it was established that the selective COX-2 inhibitor celecoxib, dual COX-2/5-LOX inhibitor darbufelone methanesulfonate, and its derivatives, significantly reduced scPTZ-induced seizures in mice. The remarkable role of neuroinflammation in epileptogenesis was confirmed [6–8]. Therefore, anti-inflammatory agents would make a significant contribution to reductions in the progression of seizures in various experimental models [15–19]. The moderate protective effect of celecoxib has been confirmed in our study, which corresponds with literature data about the protective role of COX-2 inhibitors in the PTZ models [20,36,39]. This stimulates further research in the synthesis of new anticonvulsants with anti-inflammatory properties, especially among 4-thiazolidinones with polypharmacological properties.

4. Conclusions

In the present work, anticonvulsant activity screening study of dual COX-2/5-LOX inhibitor darbufelone methanesulfonate, as well as the design and synthesis of structural analogues of darbufelone, and evaluation of their anticonvulsant properties were described. Darbufelone possesses anticonvulsant properties in the scPTZ model in mice at doses of 100 mg/kg and presents interest for in-depth studies as a possible anticonvulsant multi-target agent with anti-inflammatory activity. Structure analogues/hybrids of darbufelone with thiazole moieties at position C-2 of the basic molecule, especially compound Les-6296, demonstrated a significant protection level for animals in the scPTZ model, which was equal to or more potent than for darbufelone alone. The described structure analogues/hybrids of darbufelone with thiazole moieties are promising compounds for the design of potential anticonvulsants with satisfactory drug-like parameters.

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