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Thiazole-Bearing 4-Thiazolidinones as New Anticonvulsant Agents

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Abstract: Here, we describe the synthesis and anticonvulsant activity of thiazole-bearing hybrids based on 2-imino-4-thiazolidinone and 2,4-dioxothiazolidine-5-carboxylic acid cores. The structure of target compounds was based on the following: (*i*) A combination of two thiazole cores; (*ii*) similarity to ralitolin's structure; (*iii*) the compliance with structural requirements for the new anticonvulsants. Target compounds were synthesized via known approaches based on Knoenavegel reaction, alkylation reaction, and one-pot three-component reaction. Anticonvulsant properties of compounds were evaluated in two different models—pentylenetetrazole-induced seizures and maximal electroshock seizure tests. Among the tested compounds 5*Z*-(3-nitrobenzylidene)-2-(thiazol-2-ylimino)-thiazolidin-4-one **Ib**, 2-[2,4-dioxo-5-(thiazol-2-ylcarbamoylmethyl)-thiazolidin-3-yl]-*N*-(2-trifluoromethylphenyl)acetamide **IId** and (2,4-dioxo-5-(thiazol-2-ylcarbamoylmethylene)-thiazolidin-3-yl)acetic acid ethyl ester **IIj** showed excellent anticonvulsant activity in both models. The directions of compounds modification based on SAR aspects were discussed. The results of the study provide a basis for further study of the anticonvulsant properties of selected thiazole-thiazolidinones.

Keywords: 4-thiazolidinones; thiazoles; synthesis; anticonvulsant activity

1. Introduction

Epilepsy is one of the most common chronic neurological diseases, affecting up to 1% of the human population [1]. According to the WHO, more than 50 million people worldwide suffer from epilepsy [2]. Over the last decades, more than 20 new anti-epileptic drugs from different chemical groups have been marketed, namely: Eslicarbazepine acetate [3], perampanel [4], ezogabine [5] etc. However, a significant part of patients cannot obtain a stable anticonvulsant effect under monotherapy [6], and about 30% of patients have refractory epilepsy and need treatment with drug combinations [7,8]. Increasing the frequency of attacks and side effects, the transformation of attacks and deterioration of the electroencephalogram are observed in some patients under anti-epileptic drug treatment. This is largely due to inadequate effectiveness of anticonvulsants, the need for their high doses, and as a result, their dose-dependent side effects, namely violations of behavioral reactions, emotional state, cognitive abilities, the development of encephalopathy, and mental disorders [9]. Thus, the search for new efficient and safety anticonvulsants is of special interest.

4-Thiazolidinones are a known class of drug-like molecules and improved drugs with a broad spectrum of biological effects [10,11], including anticonvulsant [12,13]. Thiazolidinone frame

is considered as cyclic mimetic of thiosemicarbazides and thioureas as well as (bio)isoster of hidantoin (imidazolidine-2,4-dione) [11]—approved scaffolds of known anticonvulsants and privileged (sub)structures for new anticonvulsants design [14–16]. "Fixation" of thiosemicarbazide/thiourea in a cyclic structure (thiazolidinone/thiazole core) and further optimization leads to activity increasing [17]. Moreover, the tendency to increase activity in the row: Thiazole–oxazole–4-thiazolidinone derivatives was described [18,19]. One of the main achievements in the anticonvulsant thiazolidinones area is the ralitolin - (2*Z*)-*N*-(2-chloro-6-methylphenyl)-2-(3-methyl-4-oxo-1,3-thiazolidine-2-ylidene)-acetamide and phenytoin - 5,5-diphenyl-2,4-imidazolidinedione, which are proved anticonvulsant drugs. Moreover, thiazolidinone derivatives correspond to the structural requirements to new anticonvulsant structure: (*i*) Contain cyclic imide or N-CO-CN fragments [20]; (*ii*) involve the combination of two aromatic rings as hydrophobic domain; (*iii*) contain N=C-NH moiety as hydrogen bonding domain; (*iv*) contain carbonyl group as the electron donor group [21–26] (Figure 1).

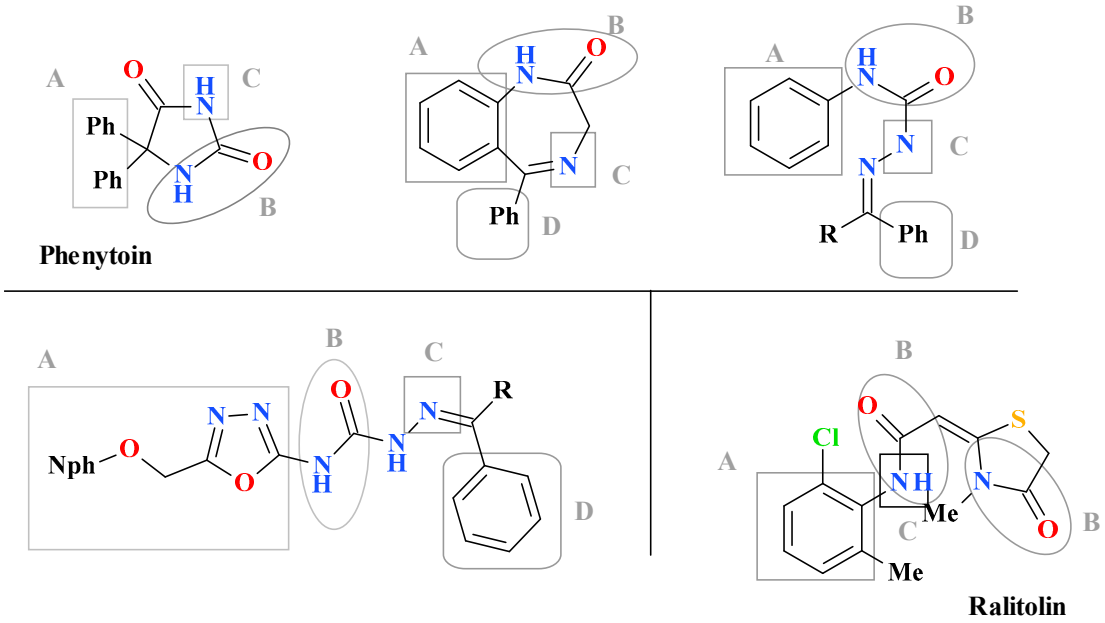


Figure 1. Structural features and "pharmacophore fragments" of the known anticonvulsants (fragments containing hydrophobic aromatic systems (**A**), a hydrogen-binding domain (**B**), an electron-donor fragment (**C**), a distal aromatic ring (**D**) adapted from [22,26].

Among different thiazolidinone subtypes, 5-substituted 2-amino(imino)-4-thiazolidinones [27] and 2-R-substituted-4-thiazolidinones are the most discussed compounds with confirmed anticonvulsant activity [28–31]. One of the efficient approaches for the design of new anticonvulsants is the combination of different heterocyclic cores, especially (thi)azoles in one molecule within a hybrid pharmacophore approach [19,21,31–36]. Highly active compounds with anticonvulsant activity have been identified among compounds combining thiazolidinone and quinazoline-4(3*H*)-one [37], thiobarbituric acid, triazole [27], benzodiazepine [19], coumarin [18], thiazole [31], thiadiazole [21], indole [30] fragments, etc. Very little data were published regarding the molecular mode/mechanism of action of thiazolidinone-based anticonvulsant agents. The anticonvulsant activity has been related to the ability to inhibit the oxidation of Krebs' cycle intermediates (pyruvate, a-ketoglutarate, citrate and b-hydroxybutyrate), in this study the prevalence of phenyl ring at C2 position was showed [38].

The present work is an extension of our ongoing efforts towards a search for new 4-thiazolidinone-based anticonvulsant agents [22,39]. Here, we addressed the design and synthesis of thiazole-thiazolidinones hybrids and evaluation of their anticonvulsant effects.

2. Materials and Methods

2.1. Chemistry

The starting (2,4-dioxothiazolidin-5-yl)-acetic acid, (2,4-dioxothiazolidin-5-ylidene)-acetic acid [40,41], and 2-(thiazol-2-ylimino)-thiazolidin-4-one [42] were obtained according to the known methods. Melting points were measured in open capillary tubes on a BUCHI B-545 melting point apparatus and were uncorrected. The elemental analyses (C, H, N) were performed using the Perkin-Elmer 2400 CHN analyzer and were within ± 0.4% of the theoretical values. IR spectra were recorded in KBr on a Nicolet iN10FX spectrometer. The ^{1}H NMR spectra were recorded on Varian Gemini 400 MHz and ^{13}C NMR spectra on Varian Mercury-400 100 MHz in DMSO-d_6 using tetramethylsilane as an internal standard. Chemical shifts are reported in ppm units with use of δ scale. Mass spectra were obtained using electrospray ionization (ESI) techniques on an Agilent 1100 Series LCMS.

2.2. General Procedure for the 5-(Het)Arylidene-2-(Thiazol-2-yl)Amino(Imino)-4-Thiazolidinones Synthesis (I)

A mixture of appropriate 2-(thiazol-2-ylimino)-thiazolidin-4-one (5 mmol), appropriate aromatic aldehyde or isatin (5 mmol), and anhydrous sodium acetate (5 mmol, 0.41 g) in glacial acetic acid (20 mL) was heated under reflux for 3 h. Precipitate obtained after cooling was filtered off, washed with methanol and recrystallized with DMF:ethanol (1:2) mixture or acetic acid.

5Z-(4-Fluorobenzylidene)-2-(thiazol-2-ylimino)-thiazolidin-4-one (**Ia**). Yield 76%, mp 238–240 °C. IR (cm^{-1}, KBr): 3080 (NH), 1716 (C=O), 1592 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.20 (d, 1H, *J* = 3.9 Hz, thiazol.), 7.25 (t, 2H, *J* = 7.8 Hz, arom.), 7.60 (d, 1H, *J* = 4.0 Hz, thiazol.), 7.65 (s, 1H, CH=), 7.70 (d, 2H, *J* = 7.9 Hz, arom.), 12.40 (brs, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.2, 167.3, 160.6 (d, *J* = 259 Hz), 159.3, 140.9, 133.0, 132.9, 131.1, 124.7, 118.0, 117.0 (d, *J* = 22 Hz). LCMS (ESI) m/z 306 (98.4%, (M + H)$^{+}$). Calcd. for $C_{13}H_8FN_3OS_2$: C, 51.14; H, 2.64; N, 13.76; Found: C, 51.00; H, 2.40; N, 14.00%.

5Z-(3-Nitrobenzylidene)-2-(thiazol-2-ylimino)-thiazolidin-4-one (**Ib**). Yield 82%, mp 216–218 °C, lit 231–233 °C [43]. IR (cm^{-1}, KBr):3085 (NH), 1707 (C=O), 1599 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.53 (d, 1H, *J* = 4.1 Hz, thiazol.), 7.73 (d, 1H, *J* = 4.0 Hz, thiazol.), 7.87 (s, 1H, CH=), 7.85 (t, 1H, *J* = 8.0 Hz, arom.), 8.07 (d, 1H, *J* = 8.2 Hz, arom.), 8.28 (d, 1H, *J* = 8.2 Hz, arom.), 8.50 (s, 1H, arom.), 12.80 (brs, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.1, 168.9, 166.9, 148.7, 141.0, 135.9, 131.3, 129.6, 124.9, 124.6, 118.2, 118.1, 110.8. LCMS (ESI) m/z 333 (100%, (M + H)$^{+}$). Calcd. for $C_{13}H_8N_4O_3S_2$: C, 46.98; H, 2.43; N, 16.86; Found: C, 46.80; H, 2.30; N, 17.10%.

5Z-(4-Dimethylaminobenzylidene)-2-(thiazol-2-ylimino)-thiazolidin-4-one (**Ic**). Yield 75%, mp 249–251 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.10 (s, 6H, 2 *CH_3), 6.85 (d, 2H, *J* = 7.9 Hz, arom.), 7.21 (d, 1H, *J* = 4.0 Hz, thiazol.), 7.45 (d, 2H, *J* = 8.0 Hz, arom.), 7.55 (s, 1H, CH=), 7.60 (d, 1H, *J* = 4.0 Hz, thiazol.), 12.40 (brs, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.1, 168.0. 159.6, 150.6, 149.1, 139.2, 131.0, 126.5, 118.6, 112.4, 107.9, 39.5. LCMS (ESI) m/z 331 (99.6%, (M + H)$^{+}$). Calcd. for $C_{15}H_{14}N_4OS_2$: C, 54.52; H, 4.27; N, 16.96; Found: C, 54.60; H, 4.50; N, 16.70%.

3-[4-Oxo-2-(thiazol-2-ylimino)thiazolidin-5-ylidene]-1,3-dihydroindol-2-one (**Id**). Yield 81%, mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.90 (d, 1H, *J* = 4.2 Hz, thiazol.), 7.00 (t, 1H, *J* = 8.8 Hz, arom.), 7.32 (t, 1H, *J* = 8.7 Hz, arom.), 7.40 (d, 1H, *J* = 4.0 Hz, thiazol.), 7.70 (d, 1H, *J* = 8.7 Hz, arom.), 8.85 (d, 1H, *J* = 8.7 Hz, arom.), 12.80 (brs, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.7, 168.4, 165.3, 156.8, 140.9, 132.5, 132.2, 131.4, 128.2, 118.6, 117.4, 110.4. LCMS (ESI) m/z 329 (96.5%, (M + H)$^{+}$). Calcd. for $C_{14}H_8N_4O_2S_2$: C, 51.21; H, 2.46; N, 17.06; Found: C, 51.00; H, 2.30; N, 17.30%.

3-Allyl-5-(4-hydroxybenzylidene)-2-(thiazol-2-ylimino)-thiazolidin-4-one (**Ie**). A mixture of the 1-allyl-3-thiazol-2-yl-thiourea (5 mmol, 1.0 g), *p*-hydroxybenzaldehyde (5 mmol, 0.61 g), chloroacetic acid (5 mmol, 0.47 g), and sodium acetate (5 mmol, 0.41 g) in 20 mL of acetic acid was heated under reflux for 3 h. Formed precipitate was filtered off, washed with acetic acid, water, ethanol, and diethyl ether and then recrystallized from a mixture of DMF:ethanol (1:2). Yield 69%, mp 219–221 °C. ^{1}H

NMR (400 MHz, DMSO-d_6): δ 4.53 (d, 2H, *J* = 4.8 Hz, CH_2), 5.18 (m, 1H, CH_2), 5,21 (d, 1H, *J* = 9.2 Hz, CH_2), 5.90 (m, 1H, CH), 7.42 (d, 1H, *J* = 4.2 Hz, thiazol.), 7.68 (d, 1H, *J* = 4.1 Hz, thiazol.), 6.94 (d, 2H, *J* = 8.1 Hz, arom.), 7.50 (d, 2H, *J* = 8.0 Hz, arom.), 7.73 (s, 1H, CH), 10.23 (s, 1H, OH).^{13}C NMR (100 MHz, DMSO-d_6): δ 169.0, 165.9, 165.9, 160.4, 154.5, 140.8, 133.9, 133.2, 131.9, 124.7, 118.2, 117.5, 116.9, 45.2. LCMS (ESI) m/z 344 (96.4%, $(M + H)^+$). Calcd. for $C_{16}H_{13}N_3O_2S_2$: C, 55.96; H, 3.82; N, 12.24; Found: C, 55.70; H, 3.50; N, 12.50%.

2.3. General Method for Amides of 2,4-Dioxothiazolidine-5-Carboxylic Acids Synthesis (II)

A mixture of 5 mmol of 2,4-dioxothiazolidine-5-carboxylic acid or 2,4-dioxothiazolidin-5-ylidene)-acetic acid, 12 mL of thionyl chloride in 30 mL of dioxane was heated under reflux for 1 h, cooled, and treated with 100 mL of hexane. The precipitate was separated by filtration. To the solution of 5 mmol of the corresponding 2-aminoazole, 1 mL of triethylamine in 10 mL of anhydrous dioxane the solution of appropriate 5 mmol acid chloride in 10 mL of the same solvent was added. The mixture was heated for 20 min at 90 °C, cooled and diluted with 100 mL of water. The formed precipitate was filtered and recrystallized from an appropriate solvent.

N-(Thiazol-2-yl)-2-(2,4-dioxothiazolidin-5-yl)-acetamide (**IIa**). Spectral and analytical data were described [40].

N-(Thiazol-2-yl)-2-(2,4-dioxothiazolidin-5-ylidene)-acetamide (**IIf**). Yield 72%, mp > 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.12 (d, 1H, *J* = 4.1 Hz, thiazol.), 7.43 (d, 1H, *J* = 4.0 Hz, thiazol.), 7.50 (s, 1H, CH), 11.2 (s, 1H, NH), 12.80 (brs, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 167.0, 164.6, 156.1, 138.7, 137.4, 121.3, 115.4. LCMS (ESI) m/z 256 (98.4%, $(M + H)^+$). Calcd. for $C_8H_5N_3O_3S_2$: C, 37.64; H, 1.97; N, 16.46; Found: C, 37.50; H, 1.80; N, 16.70%.

2-*(2,4-Dioxothiazolidin-5-ylidene)-N-(5-methyl-[1,3,4]thiadiazol-2-yl)-acetamide* (**IIg**). Yield 70%, mp > 250 °C. IR (cm^{-1}, KBr):3043 (NH), 1692, 1666, 1620, (C=O), 1573. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.67 (s, 3H, CH_3), 7.25 (s, 1H, CH=), 12.82 (brs, 1H, NH), 13.21 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.6, 166.8, 162.4, 160.6, 158.6, 141.8, 118.5, 15.4. LCMS (ESI) m/z 271 (98.3%, $(M + H)^+$). Calcd. for $C_8H_6N_4O_3S_2$: C, 35.55; H, 2.24; N, 20.73; Found: C, 35.40; H, 2.60; N, 20.40%.

N-[5-(4-Chlorobenzyl)-thiazol-2-yl]-2-(2,4-dioxothiazolidin-5-ylidene)-acetamide (**IIh**). Yield 74%, mp > 230 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.05 (s, 2H, CH_2), 7.20–7.32 (m, 6H, arom., CH), 12.62 (brs, 1H, NH), 12.76 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.8, 166.8, 158.4, 154.6, 146.6, 145.7, 140.8, 139.7, 131.6, 130.8, 130.3, 129.0, 31.6. LCMS (ESI) m/z 380/382 (99.8%, $(M + H)^+$). Calcd. for $C_{15}H_{10}ClN_3O_3S_2$: C, 47.43; H, 2.65; N, 11.06; Found: C, 47.20; H, 2.60;N, 10.90%.

2-(2,4-Dioxothiazolidin-5-ylidene)-N-[5-(3-trifluoromethylbenzyl)-thiazol-2-yl]-acetamide (**IIi**). Yield 73%, mp 262–264 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.22 (s, 2H, CH_2), 6.84 (s, 1H, CH), 7.45 (s, 1H, arom.), 7.62–7.71 (m, 4H, arom.), 12.35 (brs, 1H, NH), 12.83 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.0, 168.1, 163.6, 155.6, 140.3, 138.7, 137.3, 131.7, 131.4, 131.3 (q, *J* = 26 Hz), 125.4 (q, *J* = 280 Hz), 124.6, 120.8, 119.6, 114.7, 35.8. LCMS (ESI) m/z 414 (100%, $(M + H)^+$). Calcd. for $C_{16}H_{10}F_3N_3O_3S_2$: C, 48.49; H, 2.44; N, 10.16; Found: C, 48.20; H, 2.50;N, 10.40%.

2.4. General Procedure for N3-Substituted 2,4-Dioxothiazolidine-5-Carboxamides Synthesis

A suspension of 10 mmol of an appropriate 2,4-dioxothiazolidine-5-carboxamide (**IIa** or **IIf**) in 15 mL ethanol was treated with 11 mmol (0.62 g) of KOH in 8 mL of the same solvent. The mixture was stirred for 2 h, and the precipitate was separated by filtration, washed with ethanol and ether. A mixture of N-potassium salt of appropriate 2,4-thiazolidinedione (5 mmol), N-substituted chloroacetamide or 4-fluorobenzyl chloride or chloroacetic acid ethyl ester (5.5 mmol), catalytic amount of potassium iodide and potassium carbonate in 15 mL of DMF-EtOH misxture (1:2) was heated under reflux for 3 h. Reaction product was filtered off after cooling and pouring into water, washed by water, ethanol, and diethyl ether and recrystallized.

2-[3-(4-Fluorobenzyl)-2,4-dioxothiazolidin-5-yl]-N-thiazol-2-yl-acetamide (**IIb**). Yield 79%, mp 236–238 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.12 (m, 1H, $CHCH_2$), 3.42 (dd, 1H, *J* = 15.9 Hz,

J = 4.2 Hz, $CHCH_2$), 4.51 (s, 2H, CH_2), 4,92 (dd, 1H, *J* = 9.9 Hz, *J* = 4.2 Hz, $CHCH_2$), 7.12 (d, 1H, *J* = 4.0 Hz, thiazol.), 7.36 (d, 2H, *J* = 8.6 Hz, arom.), 7.38 (d, 1H, *J* = 4.3 Hz, thiazol.), 7.70 (d, 2H, *J* = 8.7 Hz, arom.), 12.32 (brs, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.2, 168.4, 167.3, 163.8, 159.6 (d, *J* = 262 Hz), 138.2, 128.2, 121.4, 114.4 (d, *J* = 28 Hz), 45.0, 44.2, 37.6. LCMS (ESI) m/z 366 (96.3%, $(M + H)^+$). Calcd. for $C_{15}H_{12}FN_3O_3S_2$: C, 49.31; H, 3.31; N, 11.50; Found: C, 49.10; H, 3.50; N, 11.70%.

2-[2,4-Dioxo-5-(thiazol-2-ylcarbamoylmethyl)thiazolidin-3-yl]-N-(4-methoxyphenyl)acetamide (**IIc**). Yield 70%, mp > 240 °C. IR (cm^{-1}, KBr):3270 (NH), 1676, 1659, (C=O), 1577. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.08 (m, 1H, $CHCH_2$), 3.42 (dd, 1H, *J* = 15.2 Hz, *J* = 4.6 Hz, $CHCH_2$), 4,88 (m, 1H, $CHCH_2$), 4.58 (s, 2H, CH_2), 6.94 (d, 1H, *J* = 4.3 Hz, thiazol.) 7.12 (d, 2H, *J* = 4.1 Hz, thiazol.), 7.34 (d, *J* = 8.0 Hz, arom.), 7.56 (d, *J* = 8.1 Hz, arom.), 10.56 (s, 1H, NH), 12.54 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.1, 172.1, 168.4, 163.8, 157.9, 155.9, 138.2, 132.0, 121.2, 114.4, 114.3, 55.6, 45.0, 44.1, 37.8. LCMS (ESI) m/z 421 (98.0%, $(M + H)^+$). Calcd. for $C_{17}H_{16}N_4O_5S_2$: C, 48.56; H, 3.84; N, 13.32; Found: C, 48.40; H, 3.70; N, 13.50%.

2-[2,4-Dioxo-5-(thiazol-2-ylcarbamoylmethyl)-thiazolidin-3-yl]-N-(2-trifluoromethylphenyl)-acetamide (**IId**). Yield 68%, mp > 240 °C. IR (cm^{-1}, KBr):3310 (NH), 1682, (C=O), 1576. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.10 (m, 1H, $CHCH_2$), 3.46 (dd, 1H, *J* = 16.0 Hz, *J* = 4.2 Hz, $CHCH_2$), 4,92 (dd, 1H, *J* = 10.3 Hz, *J* = 4.2 Hz, $CHCH_2$), 4.36 (s, 2H, CH_2), 7.22 (d, 1H, *J* = 5.2 Hz, thiazol.) 7.47–4.50 (m, 2H, arom.), 7.70–7.73 (m, 3H, arom.) 10.00 (s, 1H, NH), 12.39 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.9, 172.0, 168.3, 165.7, 157.9, 138.2, 134.9, 133.5, 130.0 (q, *J* = 26 Hz), 127.6, 126.9, 123.9 (q, *J* = 272 Hz), 114.2, 45.1, 43.8, 37.8. LCMS (ESI) m/z 459 (96.8%, $(M + H)^+$). Calcd. for $C_{17}H_{13}F_3N_4O_4S_2$: C, 44.54; H, 2.86; N, 12.22; Found: C, 44.40; H, 2.60; N, 12.40%.

2-[2,4-Dioxo-5-(thiazol-2-ylcarbamoylmethyl)-thiazolidin-3-yl]-N-thiazol-2-yl-acetamide (**IIe**). Yield 73%, mp > 240°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.06 (m, 1H, $CHCH_2$), 3.40 (m, 1H, $CHCH_2$), 4.54 (s, 2H, CH_2), 4,98 (m, $CHCH_2$), 6.98-7.02 (m, 2H, thiazol.) 7.12 (d, 1H, *J* = 4.1 Hz, thiazol.), 7.32 (d, 1H, *J* = 3.8 Hz, thiazol.), 10.12 (s, 1H, NH), 12.58 (brs, 1H, NH). ^{13}C NMR(100 MHz, DMSO-d_6): δ. 173.9, 172.1, 168.3, 164.9, 157.9, 138.2, 114.4, 114.2, 45.2, 43.6, 37.LCMS (ESI) m/z 398 (100%, $(M + H)^+$). Calcd. for $C_{13}H_{11}N_5O_4S_3$: C, 39.29; H, 2.79; N, 17.62; Found: C, 39.40; H, 2.60; N, 17.50%.

[2,4-Dioxo-5-(thiazol-2-ylcarbamoylmethylene)-thiazolidin-3-yl]-acetic acid ethyl ester (**IIj**). Yield 70%, mp > 240 °C. IR (cm^{-1}, KBr):3178 (NH), 1736, 1686,1663, 1625 (C=O), 1579. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29 (t, 3H, *J* = 7.1 Hz, CH_3), 4.20 (q, 2H, *J* = 7.1 Hz, CH_2), 4.40 (s, 2H, $CHCH_2$), 7.13 (d, 1H, *J* = 4.1 Hz, thiazol.), 7.46 (d, 1H, *J* = 4.1 Hz, thiaz.), 7.48 (s, 1H, CH), 12.91 (s, 1H,). ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 167.0, 164.6, 162.0, 138.8, 138.7, 137.4, 121.3, 115.4, 62.2, 42.4, 14.4. LCMS (ESI) m/z 342 (97.2%, $(M + H)^+$). Calcd. for $C_{12}H_{11}N_3O_5S_2$: C, 42.22; H, 3.25; N, 12.31; Found: C, 42.00; H, 3.00; N, 12.60%.

2.5. Pharmacology

Adult random-bred albino-mice of either sex weighing 18–25 g, which were kept under the standard sanitary-hygienic conditions in the vivarium of the Central Research Laboratory of the National Pharmaceutical University (Ukraine), were used in the experiments. All animal procedures were approved by the institutional animal care and use committee and corresponding to the Law of Ukraine. During the experiment, the rules and principles adopted by the Helsinki Declaration on Humane Animal Welfare (2000), the Directive of the Council of the European Union on the protection of animals used for scientific purposes (2010) were observed. The animals were randomized into the next groups: Group 1—control group; Group 2—experimental group—mice treated with studied compounds or reference drugs.

The synthesized compounds were screened for their anticonvulsant activity by the pentylenetetrazole-induced (PTZ) seizures test and maximal electroshock seizure (MES) test [44,45]. Animals were administered the tested compounds once in the form of a thin suspencion stabilized with polysorbate-80 (Tween-80), at a dose of 100 mg/kg intragastrally.

In the *PTZ test*, in which seizures were induced by suppression of GABA-ergic inhibitory processes, sodium valproate (Depakin, Sanofi-Aventis, Gentilly, France) as a reference drug was administrated intragastrally (300 mg/kg) as an oral syrup. In the control group, the animals received purified water in an appropriate volume. Pentylenetetrazole (Corazol, Sigma-Aldrich, St. Louis, MO, USA) in the form of water solution (90 mg/kg) was injected subcutaneously 30 min after compound application. Subsequently, each mouse was placed in a separate cylindrical plastic container (5 L) and continuously monitored for 60 min.

MES test was used to evaluate the ability of compounds to prevent the generalization of seizure. Electroshock was applied via corneal electrodes. The ability of the compounds to prevent seizures was associated with the prevention of the spread of impulse through the nerve tissues. In the MES test, electric current-50 mA, a frequency 50 Hz during 0.2 s was used 30 min after the application of the tested compounds. Carbamazepine (Finlepsin, TEVA-Pharmaceuticals, Petah Tikva, Israel) was used as a reference drug and was administered intragastrically (40 mg/kg) in the form of a thin water suspension stabilized with a Tween-80 (polysorbate 80). The observation lasted 60 min. Latency of the convulsions; the number of clonic-tonic convulsions in one mouse; % of animals with clonic and tonic convulsions; the duration of the convulsive period (from the first to the last attack); and the lifetime of the animals before death (in mice with a lethal outcome) were calculated. The severity of seizures was evaluated according to a scale ranging from 1 to 6: 1—trembling; 2—circus movement; 3—clonic seizures; 4—clonic-tonic seizures with a lateral position; 5—tonic extension; 6—tonic extension leading to the animal's death. When seizures were not observed within 1 h, it was considered that the latent period was 60 min. The protection of animals from the development of clonic and tonic seizures and lethality were treated as the most significant indicators of anticonvulsant activity of the compounds [44].

Acute toxicity. The experiments were conducted on white male mice weighing 23–25 g. Compounds were dissolved in saline solution (0.9% NaCl) with l–2 drops of polysorbate 80 (Tween-80), after dissolution they were administered via intraperitoneal route. The LD_{50} was evaluated for 4 or 5 different doses each on 6 animals and calculated by the Litchfield-Wilcoxon method [46,47].

Statistical analysis was carried out using a Statistica 10.0 by the methods of variation statistics. The average values and standard errors were calculated. The significance of the differences between groups was estimated according to the Student's criterion (t) in the case of normal distribution, and according to the nonparametric Mann-Whitney criterion (U) in the case of the absence of normal distribution. The results, which were determined in an alternative form (presence/absence of a certain feature), were evaluated using the Fisher's criterion (φ) [48].

3. Results and Discussion

The design of molecule structure of target compounds was based on: Our former findings [22,39]; the compliance with structural requirements for potential anticonvulsants (see above); combination of thiazole and thiazolidinone cores in one molecule [49,50]; structural similarity with ralitolin (Figure 2).

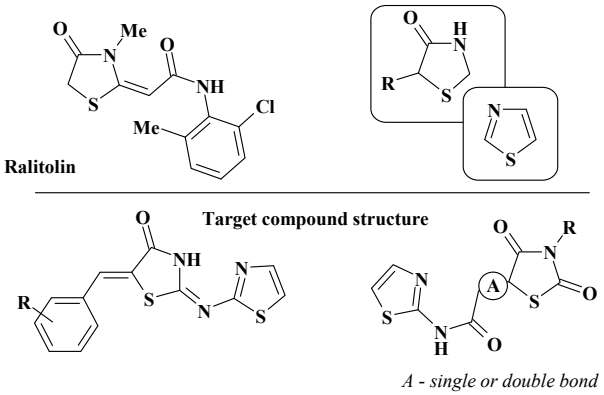
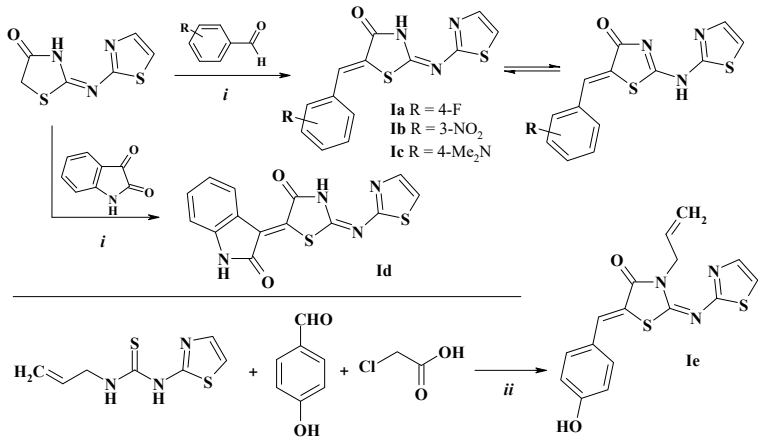


Figure 2. Structure of target compounds.

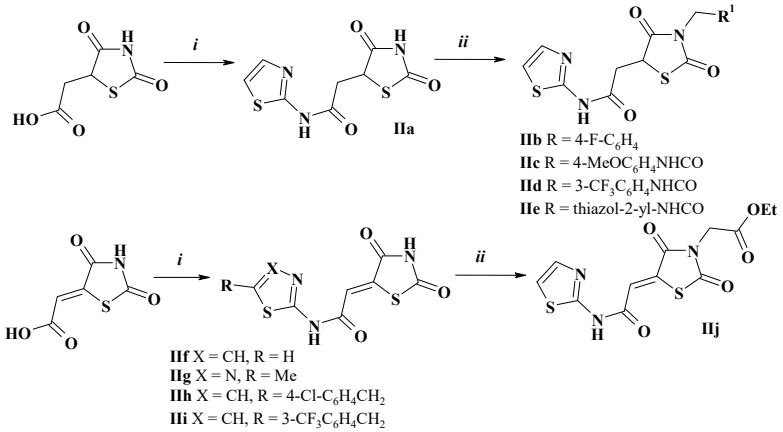
Target compounds belong to the two 4-thiazolidinone subtypes-2-imino-4-thiazolidinones **I** and 5-carboxymethyl(idene)-2,4-thiazolidinediones **II**. 2-Imino-4-thiazolidinones **I** were synthesized based on known approaches started from *N*-thiazolylchloroacetamide or disubstitutedthiourea [43,51]. Target compounds **Ib–Id** were obtained in the Knoevenagel reaction condition (Scheme 1), compound **Ie** was synthesized in one-pot three-component reaction of substituted thiourea, aldehyde and chloroacetic acid [51].



Scheme 1. Synthesis of 2-amino(imino)-4-thiazolidinones **I**. Reagents and conditions: (**i**) 2-(thiazol-2-ylimino)-thiazolidin-4-one (1.0 equiv), aromatic aldehyde (1.0 equiv), AcONa (1.0 equiv), AcOH, reflux, 3 h; (**ii**) 1-allyl-3-thiazol-2-yl-thiourea (1.0 equiv), *p*-hydroxybenzaldehyde (1.0 equiv), $ClCH_2COOH$ (1.0 equiv), AcONa (1.0 equiv), AcOH, reflux, 3 h.

Synthesized 4-thiazolidinones, bearing hydrogen atom on an exocyclic nitrogen atom (*N3*) can exist in the two tautomeric forms – 2-imino-4-thiazolidinones (exocyclic C=N bond) and 2-amino-4-thiazolidinones (endocyclic C=N bond) [52,53]. The form of compounds presentation (imino-form) was argued by previous data [51]. All synthesized compounds are in *Z*-isomeric form (thiazolidinone C5 double bond) [11,51,52].

(2,4-Dioxothiazolidin-5-yl)-acetic acid was used as starting reagents for synthesis of 2,4-thiazolidinedione-5-carboxylic acids amides **II** via known approach [40,54] (Scheme 2).



Scheme 2. Synthesis of 2,4-thiazolidinedione-5-carboxylic acids amides **II**. Reagents and conditions: (**i**) 1—2,4-dioxothiazolidine-5-carboxylic acid (1.0 equiv.), SOCl2, dioxane, reflux 1 h; 2—acid chloride (1.0 equiv.), amino-azole (1.0 equiv.), triethylamine (1.0 equiv.), dioxane, 30 min 90 °C; (**ii**) 1—appropriate 2,4-thiazolidinedione-5-carboxamide (1.0 equiv.), KOH (1.1 equiv.), EtOH, reflux 2h, 2—potassium salt of appropriate 2,4-azolidinedione-5-carboxamide (1.0 equiv.), appropriate chloride (1.1 equiv.), cat. amount KI and K2CO3, DMF:EtOH (1:2) mixture reflux, 3 h.

Amides **IIa** and **IIf** were utilized in the acylation reaction for the target *N3*-substituted compounds (**IIb-IIe**, **IIj**) synthesis. Structure of compounds was confirmed by physic-chemical data (see above).

The evaluation of anticonvulsant activity of the tested compounds was undertaken within the known anticonvulsant drug development program protocol [55]. The procedure involved PTZ-induced seizures and MES-test. For anticonvulsant activity study, *N*-unsubstituted 2-imino-thiazolidinones were used in the form of N-potassium salts.

At the first stage, a PTZ-induced seizures model was used. The mechanism of attack development was based on the suppressive effect of PTZ on GABA-receptors, resulting in a reduction in the inhibitory effect of GABA in the central nervous system [45]. Sodium valproate was used as a reference drug (Table 1). The anticonvulsant activity of the latter was associated with blockade of sodium channels, increased activity of glutamate decarboxylase, and suppression of GABA transaminase, which led to an increase in the level of GABA in the central nervous system [56]. At the experimental conditions, sodium valproate (300 mg/kg) showed good anticonvulsant effect: A significant decrease of the latent period of seizure development (by 6 times comparing to control); decrease (2.4 times) of the amount of clonic-tonic seizures per animal; decrease of the percentage of mice with clonic and tonic seizures (50 vs. 100% and 33.33 vs. 91.67%, $p < 0.01$); decreasing of the severity of the seizures by 2.8 times; decrease of the duration of the seizure period by 1.9 times; and decrease of the mortality. Among the tested compounds, three of the most active compounds **Ib**, **IId**, **IIj** were identified.

Compound **IIj** significantly reduced (by 3.3 times) the duration of the convulsive period (2.93 ± 1.99 min vs. 9.68 ± 1.96 min, $p < 0.05$) and the level of mortality by 2.5 times (33.33% vs. 83.33%, $p < 0.05$). The latent period, the proportion of animals with clonic seizures and severity of convulsion were decreased, but the compound's effect was inferior to the sodium valproate.

Compound **IId** significantly reduced (1.8 times) the proportion of animals with clonic seizures (50.00% vs. 91.67%, $p < 0.05$), reduced (1.5 times) the severity of the seizure (3.67 ± 0.88 vs. 5.58 ± 0.29 points, $p < 0.05$) and mortality by 5 times (16.67% vs. 83.33%, $p < 0.01$). The effect of compound **IId** was similar to the reference drug.

Among tested compounds, the compound **Ib**, which affected all of the studied parameters at the level of the sodium valproate, was the most active. It significantly reduced the latent period (43.59 ± 10.58 min vs. 5.63 ± 0.76 min, $p < 0.05$); the amount of clonic-tonic convulsion per animal was 6.8 times lower (0.50 ± 0.34 vs. 3.42 ± 0.47, $p < 0.01$); the portion of animals with clonic and tonic seizures was lower at 3 and 5.5 times, respectively (33.33% vs. 100% and 16.67% vs. 91.67%, $p < 0.01$); the severity of the convulsion was 3.7 times lower (1.50 ± 1.03 vs. 5.58 ± 0.29, $p < 0.01$) as well as the duration of the convulsive period (6.9 times, 1.40 ± 1.38 min vs. 9.68 ± 1.96 min, $p < 0.01$). The mortality under compound's action was decreased at 66.7% (16.67% vs. 83.33%, $p < 0.01$). These were confirmed by our primary data [22].

Seven compounds: **Ie**, **IIb**, **IIf**, **IIe**, **IIg**, **IIh**, and **IIi** did not show either anticonvulsant or pro-convulsive activity. For the two compounds **Ia** and **Ic,** the minor anticonvulsant properties were established since they significantly affected only one or two of the studied parameters. There was a significant decrease in the control of the number of convulsion per animal and the decrease in the duration of the convulsive period under compound **Ia** action. Compound **Ic** contributed to the lengthening of the latent period and the decrease in the amount of clonic-tonic convulsions per mouse.

Compounds **Id** and **IIc** showed pro-convulsant properties. Compound **IIc**, which showed moderate pro-convulsant properties, was characterized by a significant reduction in the life of animals before death and, accordingly, the duration of the convulsive period. In all animals, under compound **IIc** action the most severe tonic convulsions were observed. Compound **Id** induced the development of tonic seizures in 100% of cases, indicating its pro-convulsant properties.

Table 1. Anticonvulsant effect of tested compounds in PTZ model.

Group	*n*	Latent Period, min	Number of Clonic-Tonic Seizures per Mouse	% of Mice with Seizures		Severity of Seizures, Points	Period of Seizures, min	Time to Death, min	Mortality, %
				Clonic	Tonic				
Control	12	5.63 ± 0.76	3.42 ± 0.47	100	91.67	5.58 ± 0.29	9.68 ± 1.96	15.71 ± 2.70	83.33
SV	12	34.06 ± 7.87 **	1.42 ± 0.53 *	50 **	33.33 **	2.00 ± 0.64 **	5.10 ± 2.24 *	20.9	8.33 **
Ia	6	9.58 ± 2.11	1.50 ± 0.34 **	100 ##	83.33	5.50 ± 0.50 ##	2.92 ± 2.62 *	12.61 ± 3.32	83.33 ##
Ib	6	43.59 ± 10.58 *	0.50 ± 0.34 **	33.33 **	16.67 **	1.50 ± 1.03 **	1.40 ± 1.38 **	26.98	16.67 **
Ic	6	20.26 ± 8.57 *	1.50 ± 0.34 **	83.33	66.67	4.17 ± 0.98	4.66 ± 2.99	11.72 ± 4.15	50.00
Id	6	3.89 ± 1.38 ##	2.17 ± 0.31	100 ##	100 ##	5.67 ± 0.33 ##	6.87 ± 2.37	10.76 ± 2.31	83.33 ##
Ie	6	12.73 ± 9.46 #	2.67 ± 0.88	83.33	66.67	4.17 ± 0.98	7.97 ± 2.92	9.51 ± 3.10	50.00
IIb	6	15.55 ± 9.20	1.50 ± 0.56 *	83.33	83.33	4.67 ± 0.99 #	4.41 ± 3.65 *	10.35 ± 5.46	66.67 ##
IIc	6	5.51 ± 2.30 #	2.17 ± 0.75	100 ##	100 ##	5.33 ± 0.42 ##	2.25 ± 1.36 *	4.91 ± 1.62 *	66.67 ##
IId	6	16.92 ± 8.90	2.33 ± 0.76	83.33	50.00 *	3.67 ± 0.88 *	7.64 ± 2.79	9.23	16.67 **
IIe	6	13.33 ± 9.37	2.17 ± 0.70	83.33	66.67	4.17 ± 0.98	4.64 ± 1.86	12.22 ± 2.79	50.00
IIf	6	4.29 ± 0.66 ##	1.83 ± 0.31 *	100 ##	83.33	5.17 ± 0.54 #	7.38 ± 2.63	11.74 ± 3.22	66.67 ##
IIg	6	3.63 ± 1.17 ##	2.67 ± 0.92	100 ##	66.67	4.67 ± 0.62 #	8.39 ± 2.74	10.59 ± 4.42	50.00
IIh	6	3.43 ± 0.46 ##	2.00 ± 0.52	100 ##	66.67	5.00 ± 0.63 #	7.06 ± 5.33	13.72 ± 7.55	66.67 ##
IIi	6	14.81 ± 9.17	2.50 ± 0.76	83.33	83.33	4.50 ± 0.96 #	8.45 ± 3.99	15.34 ± 5.02	50.00
IIj	6	6.37 ± 2.05 #	2.00 ± 0.52	100 ##	83.33	4.50 ± 0.50 #	2.93 ± 1.99 *	11.38 ± 4.18	33.33 *

SV—Sodium valproate; data are given as (M ± m); * $p < 0.05$; ** $p < 0.01$compared to the control; # $p < 0.05$; ## $p < 0.01$compared to sodium valproate.

At the second stage, the most active compounds **Ib**, **IId,** and **IIj** were selected to evaluate their anticonvulsant action in the MES model. The results of the experiment are shown in the Table 2.Carbamazepine was used as a reference drug, due to its ability to block sodium channels that play a leading role in the development of primary-generalized convulsions [57].There was a significant reduction of the severity of the convulsion by 1.2 times (4.78 ± 0.28 vs. 5.53 ± 0.13 points, $p < 0.05$), the duration of the convulsive period by 2.4 times (0.10 ± 0.03 vs. 0.24 ± 0.03 min, $p < 0.01$) and the duration of the recovery period by 1.9 times (0.41 ± 0.14 vs. 0.80 ± 0.16 min, $p < 0.01$) under carbamazepine treatment.

Table 2. Anticonvulsant effect of tested compounds in MES model.

Group	*n*	% of Mice with Seizures		Severity of Seizures, Points	Period of Seizures, min	Recovery Period (Lateral Position), min	Ttime to Death, min	Mortality, %
		Clonic	Tonic					
Control	17	100	100	5.53 ± 0.13	0.24 ± 0.03	0.80 ± 0.16	0.30 ± 0.03	52.94
CM	14	100	92.86	4.78 ± 0.28 *	0.10 ± 0.03 **	0.41 ± 0.14 **	0.32 ± 0.02	35.71
Ib	14	100	78.57 **	4.57 ± 0.33 *	0.08 ± 0.03 **	0.27 ± 0.27 **	0.28 ± 0.03	35.71
IId	14	100	85.71 *	5.00 ± 0.33	0.13 ± 0.03 *	0.23 ± 0.03 **	0.30 ± 0.02	57.14
IIj	14	100	78.57 **	4.71 ± 0.34	0.10 ± 0.03 **	0.32 ± 0.10 **	0.26 ± 0.01	42.86

CM—carbamazepine; data are given as (M ± m); * $p < 0.05$; ** $p < 0.01$compared to the control.

Compound **IIj** reduced of the percentage of animals with tonic seizures (78.57% vs. 100%, $p < 0.01$) and decreased the duration of tonic and clonic seizures by 2.4 and 2.5 times respectively (0.10 ± 0.03 vs. 0.24 ± 0.03 min and 0.32 ± 0.10 vs. 0.80 ± 0.16 min, $p < 0.01$). Under compound **IId** action reduction of the percentage of mice with tonic seizures by 14.3% (85.71 vs. 100%, $p < 0.05$), decreasing of the duration of tonic extension by 1.8 times (0.13 ± 0.03 vs. 0.24 ± 0.03 min, $p < 0.05$) and clonic convulsions by 3.5 times (0.23 ± 0.03 vs. 0.80 ± 0.16 min, $p < 0.01$) were observed. Compound **Ib** significantly decreased the amount of mice with tonic seizures by 21.4% (78.57% vs. 100%, $p < 0.01$), the duration of tonic extension and clonic seizures by 3 and 2.9 times, respectively (0.08 ± 0.03 vs. 0.24 ± 0.03 min and 0.27 ± 0.27 vs. 0.80 ± 0.16 min, $p < 0.01$), and the severity of convulsions by 1.2 times (4.57 ± 0.33 vs. 5.53 ± 0.13 points, $p < 0.05$). Thus, all three compounds possess the anticonvulsant properties in the MES model, the compounds' activities was not inferior to carbamazepine.

The most active of the synthesized compounds were evaluated for their approximate LD_{50} (intraperitoneal administration) in mice [46,47]. Tested compounds were relatively non-toxic and well tolerated by the experimental animals as demonstrated by their LD_{50} (**Ib**—263 ± 27.1 mg/kg, **IId**—610 ± 40.5 mg/kg, **IIj**—320 ± 31.5 mg/kg).

The analysis of the structure-activity relationships in the group of 2-imino-4-thiazolidinones (**I**) reveled the following patterns: The presence of nitrobenzylidene fragment at C5 position of main core are preferred for anticonvulsant activity realization. The replacement of the nitro-group by fluorine atom (compound **Ia**) or dimethylamino group (compound **Ic**) led to reduction of the anticonvulsant effect. The introduction of the substituent in the N3 position of the thiazolidinone core led to only imino-form of compounds and the impossibility of amino-iminotautomeric transformation. Such modification of 2-iminothiazolyl-4-thiazolidinones led to a decrease of anticonvulsant activity (compound **Ie**). The replacement of the arylidene fragment by isatine moiety that can be treated as annulation of benzylidene fragment (compound **Id**), and it was not the optimal direction for compound structure modification. Compound **Id** possesses even pro-convulsant activity. For such group of compounds **I** with different substituent in the C5 benzylidene fragment the strong antimicrobial activity [43,58] and inhibition of *SHP-2* (non receptor protein tyrosine phosphatase that mediates cell signaling by growth factors and cytokines acting via the *RAS/MAP kinase* pathway [59]) also was detected. These alone with a new trend in the creation of new anticonvulsants [60] can be treated as a benefit, especially within a polypharmacological approach [10,11], when the compound possessed several types of activity and can be used as a baseline for further optimization.

For the 2,4-thiazolidinone-5-carboxylic acid derivatives (**II**), the next aspects of structure-activity relationships were funded: The complication of C5 moiety (compounds **IIh** and **IIi**) led to activity decreasing; the presence of *N3* substituent was essential (crucial decreasing of activity of **IIf** compare to **IIj**). The nature of the substituents in the *N3* fragment also plays a significant role: The absence of C=O group (compound **IIb**), as well as the replacement of CF_3 (**IId**) group by OMe group (**IIc**) provided the activity decreasing. Saturated analogs (with C5-single bond) of compound **IIj** also possessed the strong anticonvulsant activity [61] that confirmed the potency of such direction for the new anticonvulsants design.

Hit-compounds **Ib**, **IId,** and **IIj** showed pronounced anticonvulsant properties in both the PTZ-model and the MES-test. It can be assumed that these compounds have a mixed mechanism of action aimed at increasing the inhibitory processes in the central nervous system by increasing GABA-ergic activity, and reducing the processes of excitation in the CNS by blocking the sodium channels. The results of the study provide a basis for further study of the anticonvulsant properties of thiazole-thiazolidinones.

4. Conclusions

The present work reports the design and synthesis, and anticonvulsant activity evaluation of two series of thiazole-bearing 4-thiazolidinones, namely 2-imino-4-thiazolidinones and 2,4-dioxothiazolidine-5-carboxamides. The design of the compounds' structure was based on structural requirements for anticonvulsant structures, similarity to ralitoline—known anticonvulsant drug, and a combination of two azole cores. The study of the anticonvulsant activity was undertaken in pentylenetetrazole-induced seizures assay and maximal electroshock seizure test. Among the tested compounds 5*Z*-(3-nitrobenzylidene)-2-(thiazol-2-ylimino)-thiazolidin-4-one **Ib**, 2-[2,4-dioxo-5-(thiazol-2-ylcarbamoylmethyl)-thiazolidin-3-yl]-N-(2-trifluoromethylphenyl)-acetamide **IId,** and [2,4-dioxo-5-(thiazol-2-ylcarbamoylmethylene)-thiazolidin-3-yl]-acetic acid ethyl ester **IIj** showed excellent anticonvulsant activity in both assays and possessed relatively low acute toxicity. Some structure-activity relationship findings were discussed as well as directions for such compounds modification. The results of the study provide a basis for further study of the anticonvulsant properties of selected thiazole-thiazolidinone hybrids.

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