https://doi.org/10.31925/farmacia.2019.2.9 **ORIGINAL ARTICLE**

THE ANALGESIC EFFECT OF 1,3-THIAZOLIDIN-4-ONE DERIVATIVES AS POTENTIAL MODULATORS OF THE SEROTONINERGIC SYSTEM

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Abstract

This study presents the synthesis and evaluation of the analgesic effect of 1,3-thiazolidin-4-one derivatives. Tested compounds were prepared by the cyclization reaction of appropriate N-substituted carboxylic acid hydrazide derivatives with mercaptoacetic acid. The purpose of this study was the evaluation of the analgesic properties of 1,3-thiazolidin-4-one derivatives. In addition to this, we tried to explain the role of serotonin receptors in the antinociceptive mechanisms of tested compounds. The experiments were carried out using male Albino Swiss mice (20-25g). The compounds were administered intraperitoneally (ip) and were analysed for analgesic activities in models of pain in mice. Additionally, they were tested for safety on the central nervous system of mice in selected behavioural tests. Our results revealed an interesting analgesic activity of the tested compounds. The tested derivatives showed low toxicity, reflected by their LD_{50} value. Moreover, none of these compounds exhibited neurotoxic properties or impaired the cognitive activity of mice, even at the highest doses used. All tested derivatives showed analgesic activity. Among the tested compounds, *N*-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl] acetamide seems to be the most effective painkiller. It has a pronounced antinociceptive effect towards thermal and mechanical pain stimulation. The present results support the idea that 5-HT receptors play an important role in the control of pain. The compounds that modulate 5-HT receptors activity may have clinical utility in pain therapy.

Rezumat

Acest studiu prezintă sinteza și evaluarea efectului analgezic a derivaților de 1,3-tiazolidin-4-onă. Compușii testați au fost sintetizați prin reacția de ciclizare a derivaților hidrazidici ai acidului carboxilic adecvați, N-substituiți cu acid mercaptoacetic. Scopul acestui studiu a fost evaluarea proprietăților analgezice a derivaților de 1,3-tiazolidin-4-onă. Suplimentar, am încercat să explicăm rolul receptorilor serotoninergici în mecanismele antinociceptive ale compușilor testați. Experimentele au fost efectuate utilizând șoareci masculi Albino Swiss (20 - 25 g). Compușii au fost administrați intraperitoneal (ip) și au fost testați pentru activități analgezice folosind modele de durere la șoareci. În plus, a fost evaluată siguranța la nivelul sistemului nervos central al șoarecilor în testele de comportament selectate. Rezultatele noastre au evidențiat o activitate analgezică interesantă a compușilor testați. Derivații testați au prezentat o toxicitate scăzută, reflectată de valoarea DL_{50}. Mai mult, chiar și la cele mai mari doze utilizate, nici unul dintre acești compuși nu a prezentat proprietăți neurotoxice sau de afectarea activității cognitive a șoarecilor. Toți derivații testați au prezentat activitate analgezică. Dintre compușii testați, se pare că N-[2-(4-metilfenil)-4-oxo-1,3-tiazolidin-3il] acetamida este cel mai eficient analgezic. Acesta are un efect antinociceptiv pronunțat în durerea indusă de stimuli mecanici și termici. Rezultatele prezentate susțin ideea că receptorii serotoninergici joacă un rol important în controlul durerii. Compușii care modulează activitatea receptorilor serotoninergici pot avea utilitate clinică în terapia durerii.

Keywords: 1,3-thiazolidin-4-one derivatives, pain, 5-hydroxytryptamine

Introduction

According to the definition of the International Association Study of Pain (IASP) "pain is the unpleasant and negative sensation which is associated with tissue damage or endangering their damage". Taking into consideration the highly subjective nature of pain symptoms, it is no doubt one of the most challenging to diagnose and treat health issues of the contemporary world [19, 27]. In reference to the duration of the pain, it can be classified into: acute and chronic. Acute pain is a protection and warning system which informs us about disorders in our body. If the pain stimulus is absent, the body reaction weakens or disappears. However, we must remember that untreated acute pain can transform into a chronic state which is a complex and recurrent condition [23]. Chronic pain frequently accompanies the inflammatory reaction and is associated with its mediators, such as

histamine, bradykinin, serotonin, leukotrienes, cytokine (TNF-alpha, IL-1, IL-6, IL-8, IL-15, IL-18 and other) which intensify pain perception [14]. In many cases, it is hard to find the cause of pain development, which in turn limits drug efficacy.

The pain modulation occurs both at the peripheral level as well as in the central nervous system. The presynaptic receptors like opioid μ and δ, 5-HT3, 5-HT2, GABA B, play important roles in this process [27]. In recent years, scientists switched their attention to serotonin receptors, (located in the central and peripheral nervous systems) specifically on synthetic substances that selectively stimulate or inhibit these receptors. The aforementioned neurotransmitter has a significant effect on many important vital functions, such as sleep, food intake, memory, feeling of pain, sexual behaviour [9]. This endogenous amine is also involved in the development of psychiatric disorders such as depression, schizophrenia, anxiety, sleep and appetite disorders. Therefore, many research centers in the world conduct intensive studies with the participation of 5-HT receptor modulators in a variety of disease conditions, including migraine, depression, psychosis, anxiety, and obesity [1, 10].

Interestingly, serotonin (5-HT) can exhibit pro-nociceptive properties at the periphery and anti-nociceptive effects directly within the spinal cord [2]. Recent studies demonstrated that the antagonists of receptor 5-HT3 are promising therapeutic agents in pain treatment in migraine and visceral discomfort associated with the irritable bowel syndrome. Substances with antagonistic properties towards the 5HT2 and/or 5-HT3 receptors proved to be efficient in the treatment of angina and glaucoma [24].

On the other hand, drugs such as ritanserin, which is a selective antagonist to the 5-HT2 receptor, found application in treating parkinsonism patients through efficient reduction of tremor and rigidity of muscles [18]. Another desired effect of the 5-HT2A receptor modulation is the control of the production of hepatic glucose, which might prove significant in the treatment of obesity and diabetes [32]. Some studies reported that 5-HT2A receptors may be involved in neuropathic pain regulation [33]. Taking into consideration the frequency of occurrence of pain and the limited ability of controlling it effectively, there is an urgent need for new analgesic drugs.

1,3-thiazolidiones are one of the most investigated class of compounds. 1,3-thiazolidin-4-ones are of great importance for the design and synthesis of new biologically active agents [20, 30]. Their biological properties proved more than promising. They cover the antiviral, antimicrobial, antihistaminic, anticancer, anticonvulsant cardio-protective, and antidiabetic activity [13, 20, 30]. Our earlier research concerning 2,3-disubstituted 1,3-thiazolidin-4-one derivatives confirmed their significant antimicrobial activity [26]. Among the twenty tested compounds, especially N-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide exhibited wide spectrum of bioactivity against Gram-positive bacteria (*Staphylococci*, *Streptococci*, *Micrococci*, and *Bacillus spp.)* and yeast belonging to *Candida spp*. [26].

The fact that the studied derivatives can easily penetrate into the central nervous system (CNS) has encouraged us to continue our research on their safety and antinociceptive activity. The evaluation of the analgesic activity of the new compounds was performed based on the results of the writhing and hot plate test. In our study, we also evaluated the potential toxic effect of the tested compounds on the central nervous system of mice based on the analysis of the results of selected behavioural tests.

Materials and Methods

Reagents

All required chemicals and solvents were purchased from Sigma-Aldrich (Munich, Germany) and Merck Co. (Darmstadt, Germany) and used without further purification. Melting points were determined with Fisher-Johns blocks (Fisher Scientific, Germany) and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on the Bruker Avance 300 apparatus (Bruker BioSpin GmbH, Germany) in DMSO-d_6 with TMS as the internal standard. The progress of the reaction and purity of obtained compounds were monitored by TLC using pre-coated aluminium sheet 60 F254 plates (Merck Co. USA), in a $CHCl_3$/C_2H_5OH (10:1, v/v) solvent system. The spots were detected by exposure to the UV lamp at 254 nm. The elemental analysis of obtained compounds was carried out with the AMZ 851 CHX analyser (PG, Gdańsk, Poland). The results of elemental analysis (C, H, N) were within ± 0.4% of the calculated values.

Preparation of 2,3-disubstituted 1,3-thiazolidin-4-one derivatives (5 - 8)

The synthesis was performed according to procedure described by Popiołek Ł *et al.* [32]. To the solution of corresponding *N*-substituted hydrazide derivatives (1 - 4) (10 mmol) in 1,4-dioxane (15 mL), mercapto-acetic acid (0.92 g, 10 mmol) was added dropwise. The mixture was stirred for 6 h at room temperature. Then the solvent was removed under reduced pressure to get a crude product which was purified by recrystallization from ethanol.

N-[2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl] acetamide (**5**)

CAS Registry Number: *1644570-76-2*. Analytical and spectral data is consistent with those reported in the literature [32]. Yield: 69%. M.p.: 202 - 204°C.

N-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl] acetamide (**6**)

CAS Registry Number: 1644570-74-0. Analytical and spectral data is consistent with those reported in the literature [32]. Yield: 81%. M.p.: 104 - 106°C.

N-[2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide (**7**)

CAS Registry Number: *1644570-79-5*. Analytical and spectral data is consistent with those reported in the literature [32]. Yield: 70%. M.p.: 176 - 178°C.

N-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide (**8**)

CAS Registry Number: *1644570-78-4*. Analytical and spectral data is consistent with those reported in the literature [32]. Yield: 87%. M.p.: 106 - 108°C.

Pharmacology assessment

Animals

Albino Swiss adult mice (20-25g) obtained from a licensed breeder (Breeding of Laboratory Animals, Jacek Kołacz, Poland) were housed in cages at room temperature of 22 ± 1°C with free access to water and food (Murigran pellets, Bacutil, Motycz). Animals were maintained under a 12h dark/light cycle (light phase 7 a.m. - 7 p.m.). After seven days of acclimatization to standardized laboratory conditions, the animals were divided into groups (8 animals per group) and prepared for the tests. The experiments were performed between 8 a.m. and 3 p.m., according to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals and to the European Community Directive for the Care and Use of Laboratory of 24 November 1986 (86/609/EEC), and approved by the Local Ethics Committee for Animal Experimentation of the Medical University of Lublin.

Drugs and substances

The following chemicals were used in the study: acetic acid (Sigma-Aldrich, Germany), L-5-HTP (5-hydroxy-L-tryptophan, Sigma-Aldrich, Germany), Tween 80 (Sigma, St. Louis, MO, USA). All the examined compounds (1,3-thiazolidin-4-one derivatives or thiazolidinones) were suspended in a small amount (3-4 drops) of Tween 80 and then diluted in the saline. At the respective time before the test, they were administered intraperitoneally (ip) to the maximum dose equivalent of 0.1 of their LD_{50}, in a volume of 0.1 mL/10 g of the body weight. The control animals received the same volumes of saline with small amount (3 - 4 drops) of Tween 80.

Behavioral experiments

The acute toxicity

The study was performed on mice, according to the Up-Down-Up method (guidelines OECD no. 425), as LD_{50} (95%CL) calculated for mortality (Table I). The thiazolidinones were administered in different doses, where 24h toxicity was recorded to identify the toxic doses. The pharmacological experiments were initiated with the doses corresponding to 0.1 of LD_{50} and were gradually reduced until the disappearance of the biological activity of the tested compounds.

Table I

The LD_{50} values and start doses of compounds 5-8 used in behavioural tests

No of compound	LD_{50} (mg/kg, ip)	The start dose of the compound used in experiments (mg/kg, ip)
5	1000	100
6	750	75
7	1000	100
8	1000	100

The antinociceptive activity

The compounds were examined in two analgesic tests - the writhing test and the hot plate test.

The writhing test is used to study the peripheral pain, induced by ip injection of acetic acid (0.6%), as a nociceptive stimulus, which induces characteristic writhing episodes (episodes of retraction of abdomen and stretching of hind limbs). The analgesic activity of the tested compounds was determined by the number of writhing episodes recorded during the 30min mice observation *vs*. control vehicle group [31].

The hot plate test is based on the use of thermal stimulus. The test was performed twice before the administration of the compounds. The mice showing time reaction under 4s were discarded. The animals were placed on a hot plate maintained at 55 ± 1°C (Ugo Basile hot/cold plate 35100, Italy). The reaction time was taken as the interval time from which the animal reached the hot plate until the moment in which it licked its feet or jumped out. Cut-off reaction time was +10s to avoid any tissue injury during the process. The time of the response was recorded after 15, 30, 60, 90, 120 and 180min after the administration of the tested compounds or saline. The analgesic effect of the derivatives was evaluated based on the response time of mice on a noxious thermal stimulus [15].

Assessment the safety of the test compounds on the central nervous system of mice

Motor function impairment was quantified with the chimney test [8]. In this test, 30 min after the administration of the investigated compounds, mice had to climb up backward in a plastic tube (inner diameter 3 cm, length 25 cm). Mice which were unable to get out of the chimney within 60s were considered to display motor impairment.

The effects of 1,3-thiazolidin-4-one derivatives on cognitive activity was evaluated by the hole board test results. This test was performed according to the procedure described by Boissier and Simon [6, 7]. 30min after the application of tested substance, an animal was placed carefully in the center of the board (40×40 cm) with regularly arranged 16 holes. The frequency of spontaneous mice head

dipping into the holes was measured during a period of 5min.

The passive avoidance test is used to evaluate learning and memory disorders of mice [34]. The apparatus is divided into bright illuminated and dark compartments with a gate between them. During first day of test, 30min after intraperitoneal injection of compound, mice were placed in the bright compartment. When the animal naturally passed to the dark compartment, it received a mild electrical shock (0.5 mA, 1sec). After 24h the animal was placed again in the white compartment and observed for 180s. The animals that did not enter the dark part of the apparatus exhibited no impairment on the ability to memorise.

The antiserotonergic activity of the examined compounds was studied in the L-5-HTP -induced head-twitches test, according to Corne *et al*. [11]. L-5-HTP (180 mg/kg, ip) was given 30min after compounds administration and the number of rapid side-to-side head movement in mice was recorded for a period of 60min.

Data analysis

Behavioural data was analysed with Student's t-test or one-way analysis of variance – ANOVA followed by the Dunnett's *post-hoc* test. Results were expressed as the mean ± standard errors (SEM). The p-value less than 0.05 was chosen as indication of statistical significance.

Results and Discussion

Chemistry

In this research 2,3-disubstituted 1,3-thiazolidin-4-one derivatives (**5-8**) were synthesized by the cyclization reaction of *N*-substituted carboxylic acid hydrazide derivatives (1-4) with mercaptoacetic acid in the presence of 1,4-dioxane (Figure 1) [16]. The obtained compounds are stable solids at room temperature and their spectral data (^{1}H NMR, ^{13}C NMR) is in full agreement with the proposed structures. The synthesized compounds were evaluated for *in vivo* experiments.

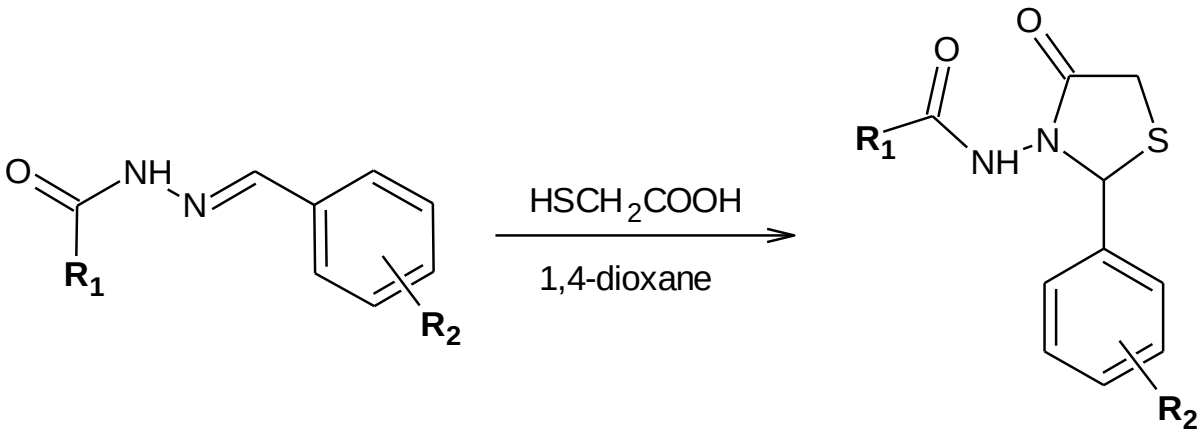


Figure 1.

Synthetic pathway to 2,3-disubstituted 1,3-thiazolidin-4-one derivatives

(Compound no. 1, 5: R_1 = Me*, R_2 = 3-NO_2-Ph*; Compound no. 2, 6: R_1 = Me, R_2 = 4-CH_3-Ph; Compound no. 3, 7: R_1 = Ph, R_2 = 3-NO_2-Ph; Compound no. 4, 8: R_1 = Ph, R_2 = 4-CH_3-Ph; * Me = methyl; * Ph = phenyl)

The analgesic activity

Particularly noteworthy is the analgesic activity exhibited by the tested compounds. All the 1,3-thiazolidin-4-one derivatives significantly reduced the number of writhing episodes in mice induced by intraperitoneal injection of 0.6% acetic acid. The compounds 5 and 6 were the most interesting, because they had the strongest analgesic effect through a wide range of doses (Figure 2A; ANOVA: $F_{(2.05)}$ = 8.629; p = 0.0003; Dunnett's post-hoc test; Figure 2B; ANOVA: $F_{(2.46)}$ = 13.493; p < 0.0001; Dunnett's post-hoc test). At the same time, the compounds 7 and 8 only at the highest dose (100 mg/kg bw) significantly reduced hyperalgesia in the mice in the writhing test (Figure 2C; ANOVA: $F_{(3.47)}$ = 12.517; p = 0.0003; Dunnett's post-hoc test; Figure 2D; ANOVA: $F_{(3.52)}$ = 4.410; p = 0.0267; Dunnett's post-hoc test).

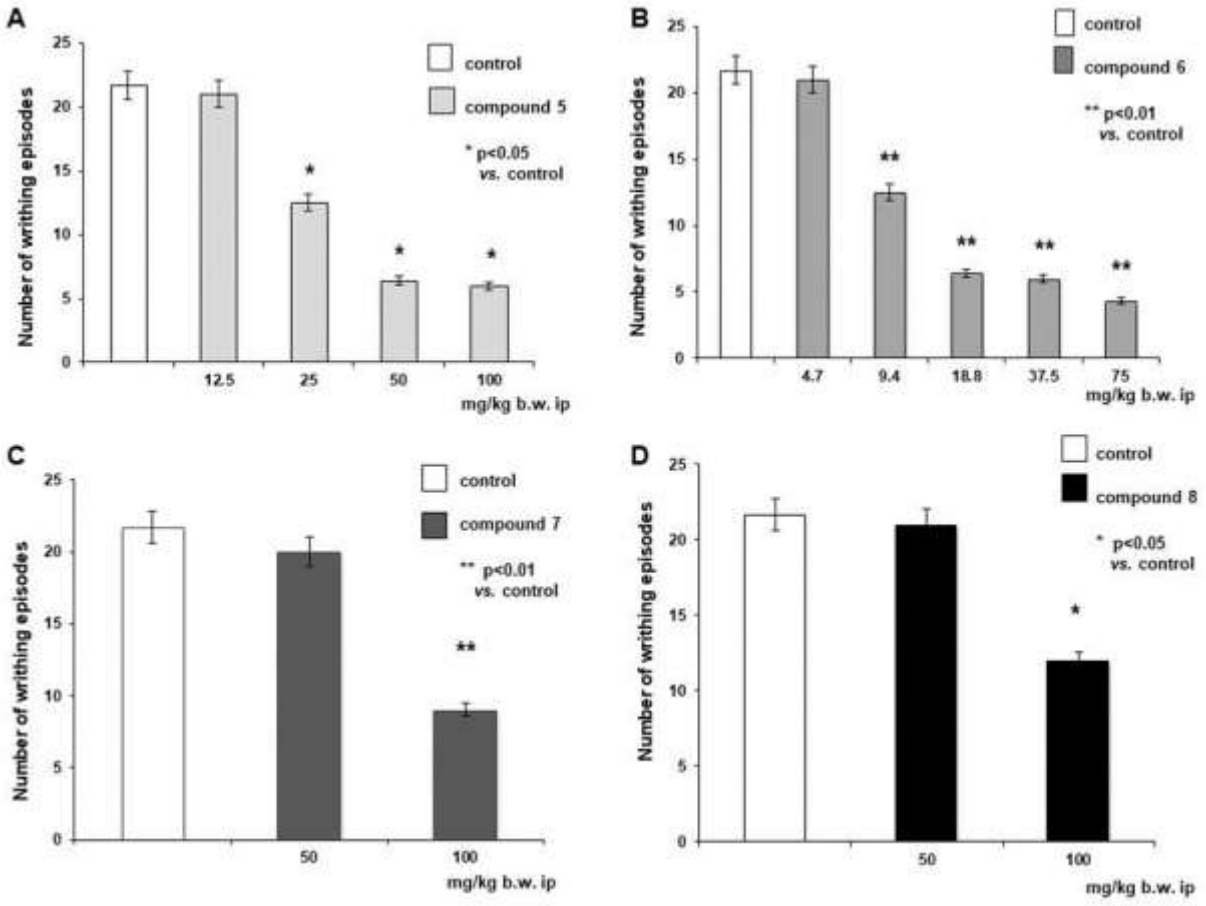


Figure 2.

The effect of 1,3-thiazolidin-4-ones on acetic acid-induced abdominal writhing in mice. (A) The influence of compound **5** at the doses 12.5, 25, 50, 100 mg/kg bw * p <0.05 *vs.* control group (Dunnett's test). (B) The impact of compound **6** at the doses 4.7, 9.4, 18.8, 37.5, 75mg/kg bw **p < 0.001 *vs.* control group (Dunnett's test). (C) The influence of compound **7** at the doses 50, 100 mg/kg bw ** p < 0.001 *vs.* control group (Dunnett's test). (D) The impact of compound **8** at the doses 50, 100 mg/kg bw * p < 0.05 *vs.* control group (Dunnett's test)

The results obtained in the hot plate test indicated a statistically significant antinociceptive effect of tested 5 and 6 compounds (the results are presented in Table II). The antinociceptive effect produced by compound 5 was constantly and significantly maintained throughout the experiment from 90 to 120min after substance administration (Table II; ANOVA: $F_{(4.95)}$ = 3.184; p = 0.0122; Dunnett's post-hoc test), whereas compound 6 showed antinociceptive activity 180min after its application (Table II; ANOVA: $F_{(2.42)}$ = 2.229; p = 0.0618; Dunnett's post-hoc test). Among all the 1,3-thiazolidin-4-one derivatives, compound 7 and 8 did not significantly extend the response time in hot plate test (Table II; ANOVA: $F_{(2.25)}$ = 2.197; p = 0.0590; Dunnett's post-hoc test; Table II; ANOVA: $F_{(2.25)}$ = 2.033; p = 0.0760; Dunnett's post-hoc test).

Table II

Evaluation of the anti-nociceptive effects of 1,3-thiazolidin-4-one derivatives (**5-8**) in hot plate test in mice

No of compound	**Dose** (mg/kg bw)	**Time reaction (s)**						
		Before treatment	**Time after injection**					
			15 min	**30 min**	**60 min**	**90 min**	**120 min**	**180 min**
saline	-	5.31 ± 0.49	5.34 ± 0.50	5.30 ± 0.50	5.31 ± 0.45	5.31 ± 0.45	5.33 ± 0.50	5.31 ±0.48
5	100	5.47 ± 0.39	5.87 ± 1.07	5.66 ± 0.73	7.45 ± 0.68	8.58 ± 0.44*	8.05 ± 0.76*	7.26 ±0.96
6	75	5.31 ± 0.49	5.90 ± 0.74	7.22 ± 0.53	7.64 ± 0.93	7.00 ± 1.14	7.0 ± 0.99	8.32 ± 0.76*
7	100	5.51 ± 0.29	5.08 ± 0.61	5.55 ± 1.12	5.97 ± 1.07	6.83 ± 1.07	8.13 ± 0.42	6.20 ± 0.75
8	100	5.04 ± 0.38	5.10 ± 0.84	6.20 ± 0.79	7.70 ± 0.89	7.42 ± 0.88	7.85 ± 0.86	7.37 ± 0.98

*p < 0.05 comparison of time reaction in control group of mice (Dunnett's test)

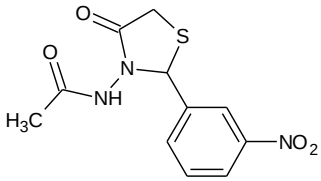
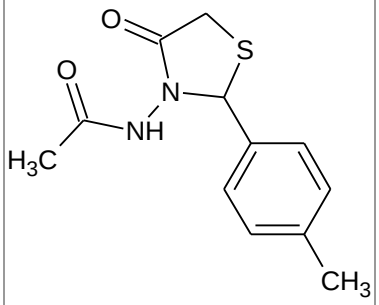
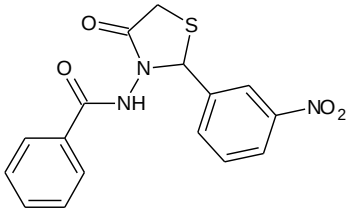
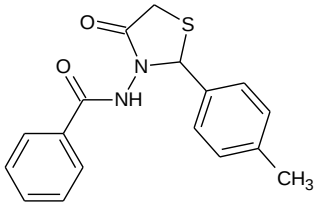
Influence of the test compounds on CNS of mice

The preliminary screening of novel compounds showed that 2,3-disubstituted-1,3-thiazolidin-4-ones (5-8) were safe. The LD_{50} values of acute toxicity tests were established at the level of 1000 mg/kg bw ip for 5, 7 and 8 derivatives and 750 mg/kg bw ip for derivative 6 (Table I).

Taking into consideration the molecular weight of obtained derivatives and values of Clog P of tested compounds, we can conclude that they can penetrate into the CNS (Table III). All compounds (5-8) did not show neurotoxic effects as they did not impair the mouse motor coordination (at the highest used doses).

Table III

The chemical structure, molecular weight, molecular formula and Clog P values of compounds **5-8** used in behavioural tests

Compound No	Chemical structure	Molecular weight	Molecular formula	ClogP
5		281.29	$C_{11}H_{11}N_3O_4S$	1.04
6		250.32	$C_{12}H_{14}N_2O_2S$	1.40
7		343.36	$C_{16}H_{13}N_3O_4S$	0.87
8		312.39	$C_{17}H_{16}N_2O_2S$	3.31

This is a very important effect from the pharmacological point of view (Table IV; Student's t-test: (5) p = 0.7317; t = 0.3498; (6) p > 0.9999; t = 0.000; (7) p = 0.9131; t = 0.1111; (8) p = 0.5238; t = 0.6538).

Table IV

Effect of compounds 5-8 on results chimney and passive avoidance test in mice

No of compound	Dose (mg/kg)	Chimney test (sec)	Passive avoidance test (sec)
saline	-	6.8 ± 0.5	180 ± 0.0
5	100	7.2 ± 0.9	180 ± 0.0
6	75	7.0 ± 1.0	180 ± 0.0
7	100	7.0 ± 0.9	180 ± 0.0
8	100	7.3 ± 0.5	180 ± 0.0

Moreover, none of the tested compounds administered at the maximal dose (0.1 of their LD_{50}, see Table III) affected the cognitive activity of mice in the hole-board test and their memory in the passive avoidance test (Tables V; Student's t-test: (5) p = 0.8205; t = 0.2319; (6) p = 0.7078; t = 0.3831; (7) p = 0.8831; t = 0.1500; (8) p = 0.3866; t = 0.8984 and Table IV; Student's t-test: (5) p = 0.9114; t = 0.1136; (6) p = 0.9464; t = 0.06866; (7) p = 0.7390; t = 0.3410; (8) p = 0.9909; t = 0.01168).

Table V

The effect of tested derivatives (5-8) on the cognitive activity in the hole board test in mice

No of compound	Dose (mg/kg bw)	The average number of head-dipping	
		Mean ± SEM	%
saline	-	56.1 ± 7.8	100 ± 13.9
5	100	54.1 ± 5.0	96.4 ± 8.9
6	75	56.9 ± 7.3	101.4 ± 13.0
7	100	58.4 ± 5.6	104.1 ± 10.0
8	100	47.6 ± 5.4	84.8 ± 9.6

The compounds 5 (100 mg/kg bw) and 6 (75 mg/kg bw) significantly reduced the number of episodes of head twitches induced in mice by administration of L-5-HTP. The aforementioned action may suggest that these compounds may affect the serotonergic neurotransmission (Figure 3A; ANOVA: $F_{(3.47)}$ = 9.003; p = 0.0015; Dunnett's post-hoc test; Figure 3B; ANOVA: $F_{(3.47)}$ = 5.381; p = 0.0130; Dunnett's post-hoc test). The remaining 1,3-thiazolidin-4-one derivatives (7, 8) had no significant impact on the results of this test (Figure 3C; ANOVA: $F_{(3.47)}$ = 0.724; p = 0.4962; Dunnett's post-hoc test).

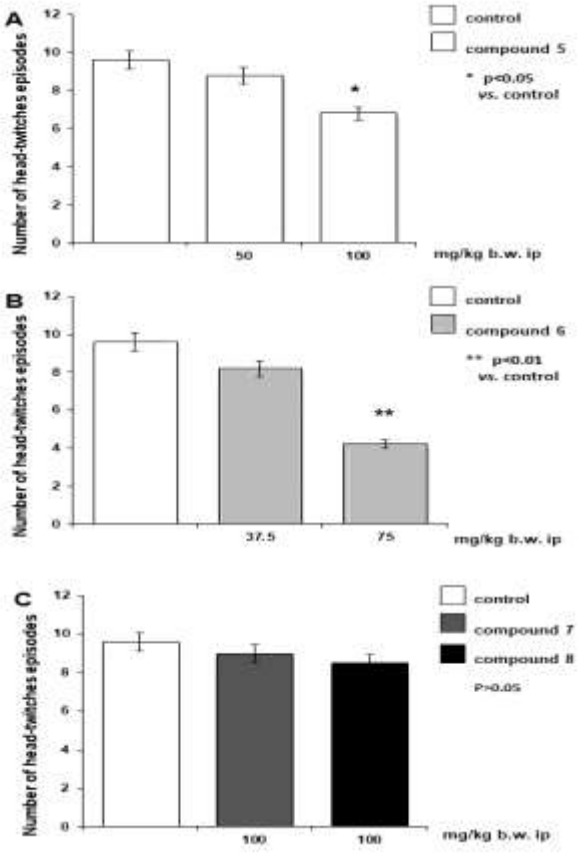


Figure 3.

The effect of 1,3-thiazolidin-4-ones on head-twitches episodes in mice after the L-5-HTP administration. (A) The influence of compound **5** at the doses 50, 100 mg/kg bw * $p < 0.05$ *vs*. control vehicle-treated group (Dunnett's test). (B) The influence of compound **6** at the doses 37.5, 75 mg/kg bw * $p < 0.01$ *vs*. control vehicle-treated group (Dunnett's test). (C) The impact of compound **7** and **8** at the doses 100 mg/kg bw $p > 0.05$ *vs*. control vehicle-treated group (Dunnett's test)

Despite the similar chemical structure, the studied derivatives showed different analgesic activities. Particularly noteworthy is the analgesic activity of the tested compounds 5 (N-[2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl] acetamide) and 6 (N-[2-(4-methylphenyl)-4-oxo-1,3-thiazolidin-3-yl] acetamide). Both exhibited an analgesic effect in a wide range of doses. They also significantly reduced the number of writhing episodes in mice in the acute, chemical model of pain [4]. It could be assumed that in case of these compounds, analgesia can result from the inhibition of the inflammatory reaction in visceral tissues [4]. The same compounds also confirmed their central analgesic activity. The hot plate test was used to verify this thesis. Compounds 5 and 6 showed delayed duration of the analgesic action.

Considering the results of the head twitch test, we suppose that the action discussed above may be related to the modulation of pain based on the serotoninergic system because the same compounds significantly reduced the number of head twitch episodes in mice induced by the L-5-HT precursor [5, 17]. The rhythmic paroxysmal rotational head movement observed in the tested mice after the administration of 5-hydroxytryptophan is a result of the activation of the 5-HT2A receptor by generated serotonin, which by the activation of appropriate receptors, plays a very important role in pain modulation [21, 22]. Our results show that the compounds with the strongest analgesic effect may modulate 5-HT2 receptors.

In recent years, a lot of attention is focused on the use of drugs capable of either selectively stimulating or inhibiting certain serotonin receptor subtypes and their role in acute and chronic pain [3, 12, 16, 25, 28, 35]. Interestingly, the activation of the same receptor subtype at the CNS level might induce variable effects depending on the physiological or pathophysiological status of the animal administered agonists. This is observed specifically with 5-HT7 receptor agonists which cause pronociceptive action in healthy rats while alleviating hyperalgesia following a nerve lesion in neuropathic animals [29, 35].

The purpose of this study was also to determine the safety of the tested compounds towards the central nervous system of the mice, given that pain-limiting drugs can lead to cognitive impairment. Further, preclinical studies showed that the substances which modulate the 5-HT2 receptor can affect learning and cognition. None of 1,3-thiazolidin-4-one derivatives administered at the maximum dose (0.1 of their LD_{50}, see Table III) disturbed the mice's motor coordination, cognitive activity, or memory (Tables IV and V, respectively), which emphasizes the unique nature of these compounds. It is also worth mentioning that the significant analgesic potential of the tested compounds proves to be at equally high rate as its safety. Moreover, the modulation of 5-HT2A receptors by new 1,3-thiazolidin-4-one derivatives has no impact on memory, nor cognitive activity of mice, which is very important due to the fact that these receptors are located in the brain.

Conclusions

Due to the fact that pain therapy is now one of the challenges of modern medicine, it seems to be important to search for new compounds with analgesic potential. The present work shows that the tested compounds are safe and have the analgesic activity. The results of our research suggest that the 5-HT2A receptor modulation by the new 1,3-thiazolidin-4-one derivatives may have an important role in pain treatment. Further studies on these compounds could provide key information that would later on be used in creating effective as well as safe analgesic drugs.

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Conflict of interest

The authors declare no conflicts of interest.

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