Microwave-Assisted Synthesis of 1,3-Benzothiazol-2(3*H*)-one Derivatives and Analysis of Their Antinociceptive Activity

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Key words
- 1,3-benzothiazol-2(3*H*)-one
- tail flick test
- tail clip test
- hot plate test
- writhing test
- microwave-assisted synthesis

Abstract

A rapid and efficient method was developed for synthesis of 6-acyl-1,3-benzothiazol-2(3*H*)-one derivatives under microwave irradiation (MWI) conditions. The reaction times were shortened compared to conventional heating. Additionally, we synthesized acetic acid and acetamide derivatives of 1,3-benzothiazol-2(3*H*)-one, 6-acyl-1, 3-benzothiazol-2(3*H*)-one, 5-chloro-1,3-benzothiazol-2(3*H*)-one and 6-acyl-5-chloro-1,3-benzothiazol-2(3*H*)-one with the microwave-assisted method and analyzed their antinociceptive activity with the tail flick, tail clip, hot plate and writhing tests. Among the synthesized compounds, 3-[2-(4-ethylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (**6a**), 5-chloro-3-{2-oxo-2-[4-(propan-2-yl)piperazin-1-yl]ethyl}-1,3-benzothiazol-2(3*H*)-one (**7e**) and 3-[2-(4-butylpiperazin-1-yl)-2-oxoethyl]-5-chloro-1,3-benzothiazol-2(3*H*)-one (**8e**) showed significant antinociceptive activity in the tail clip, tail flick, hot plate and writhing tests.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAID), which are nonselective inhibitors of cyclooxygenases (COX-1 and COX-2), have been most widely used for the treatment of inflammatory diseases such as rheumatoid arthritis and osteoarthritis [1,2]. However, the chronic use of NSAIDs has certain limitations since they can result in gastrointestinal, renal and hematological toxicity [1–3]. Although the discovery of selective COX-2 inhibitors has solved some of these problems, COX-2 inhibitors cause serious cardiovascular complications [1,2]. Recently, NO-NSAIDs, dual COX/LOX inhibitors and anti-TNF therapy were found to be novel compounds allowing an effective anti-inflammatory therapy [1]. In addition, microsomal prostaglandin E2 synthase-1 (mPGES-1) and prostaglandin H2 synthase-1 (PGHS-1) as well as E prostanoid receptor (EP)were identified as promising therapeutic targets [2,4]. Consequently, there is an emerging need for developing new anti-inflammatory drugs with novel modes of action.

Tiaramide (**I**) (5-chloro-3-{2-[4-(2-hydroxyethyl)piperazin-1-yl]-2-oxoethyl}-1,3-benzothiazol-2(3*H*)-one hydrochloride) is a nonsteroidal anti-inflammatory drug developed and approved only in Japan. Tiaramide shows no inhibitory effect on COX enzymes and the mechanism of action has not yet been elucidated in detail. In 1985, Shizuko Takano reported that tiaramide inhibits platelet phospholipase A_2 through mechanisms other than blocking Ca-influx and intracellular Ca mobilization or calmodulin antagonism. Inomata and co-workers showed that tiaramide is a relatively safe alternative for Japanese patients with NSAID-induced urtiacaria and/or angioedema [5–7]. Previously, some tiaramide derivatives (**II**) were prepared in our laboratory and tested for their antinociceptive activity. Among these compounds, morpholin, 4-fluorophenylpiperazin, 4-chlorophenylpiperazin, 4-hydroxypiperidin and 4,6-dimethyl-2-pyridinamino derivatives were found to be more active than tiaramide and aspirin [8] (**Fig. 1**). S-14080 (6-benzoylbenzothiazolone) (**III**) was tested in clinical trials up to phase II as analgesic and was found to inhibit not only the inflammatory cascade of arachidonic acid, but also to induce the release of an opioid peptide in periphery [9,10]. In addition, Ünlü et al. synthesized 6-acyl-1,3-benzothiazol-2(3*H*)-one derivatives (**IV**) with acetic acid and propanoic acid moieties and per-

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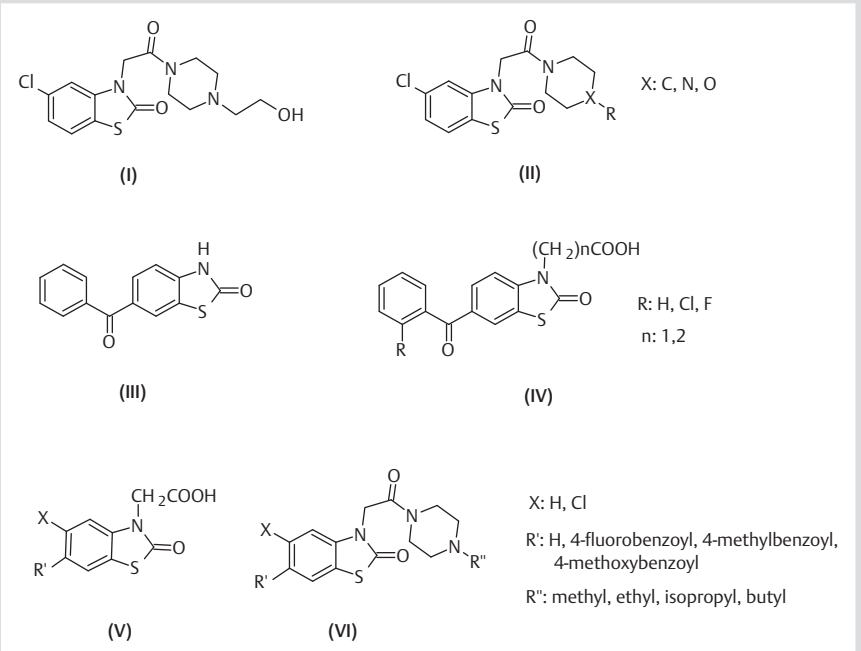


Fig. 1 Formulae of some 1,3-benzothiazol-2(3H)-one derivatives and the general structure of the synthesized compounds.

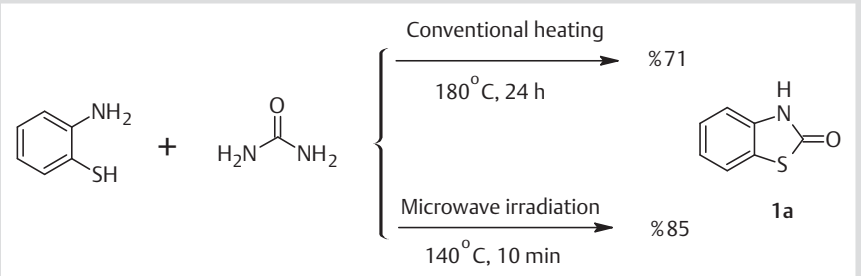


Fig. 2 Synthesis of 1,3-benzothiazol-2(3*H*)-one **1a**.

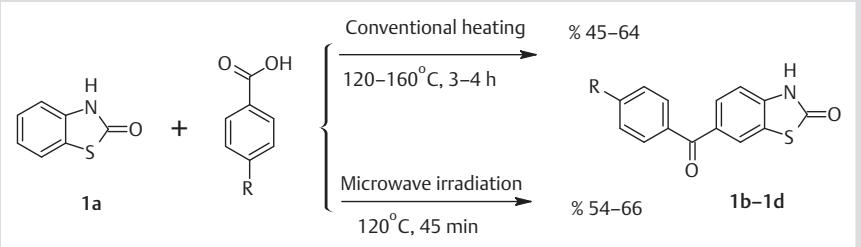


Fig. 3 Synthesis of 6-acyl-1,3-benzothiazol-2(3*H*)-one derivatives. R: 4-fluorobenzoyl **1b**, 4-methylbenzoyl **1c**, 4-methoxybenzoyl **1d**.

formed a preliminary screening of their in vivo analgesic and anti-inflammatory activity [11] (**Fig. 1**).

These results led us to investigate the analgesic and anti-inflammatory activity of 6-acyl-2(3H)-benzothiazolone and its amide derivatives as a starting point for the discovery of new therapeutic agents. In this study, we describe the synthesis and preliminary evaluation of the biological activity of 1,3-benzothiazol-2(3*H*)-one, 6-acyl-1,3-benzothiazol-2(3*H*)-one, 5-chloro-1,3-benzothiazol-2(3*H*)-one and 6-acyl-5-chloro-1,3-benzothiazol-2(3*H*)-one and of their acetic acid and acetamide derivatives (**V** and **VI**) as molecules composed of tiaramide and 6-benzoyl-1,3-benzothiazol-2(3*H*)-one derived moieties (**Fig. 1**).

Materials and Methods

Detailed experimental protocols and physicochemical data of the synthesized compounds are available as Supporting Information.

Result and Discussion

The synthetic routes for the synthesized compounds are outlined in **Figs. 2–4**. The starting compound, 1,3-benzothiazol-2(3*H*)-one (**1a**), was synthesized by both conventional and microwave-assisted methods [12–14] (**Fig. 2**). Compound **1a** was prepared by reacting urea with o-aminothiophenol. Reagents were used in the same quantity for both methods. The conventional method was carried out with an external heat source (oil bath), and the yield was 71%. The microwave-assisted method relied on efficient internal heating with microwave irradiation (MWI) and the reaction time was reduced from 24 h to 10 min compared with the conventional heating method. The yield was 85% [12]. Microwave-assisted synthesis of **1a** has been developed in our laboratory. 5-Chloro-1,3-benzothiazol-2(3*H*)-one (**1e**) was also obtained with the microwave-assisted method as reported previously [15].

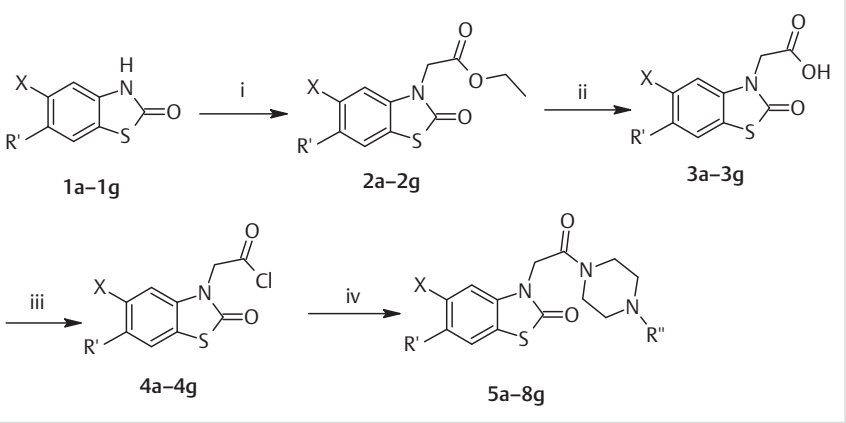


Fig. 4 Synthesis of acid and amide derivatives. Reagents: (i) ethyl bromoacetate, K_2CO_3, acetone, MWI; (ii) KOH, ethanol/water, MWI; (iii) $SOCl_2$, toluene, MWI; (iv) appropriate amine, K_2CO_3, THF, MWI.

Table 1 Comparable data for synthesis of 6-acyl-1,3-benzothiazol-2(3*H*)-one with conventional heating and microwave irradiation.

	Conventional heating			Microwave irradiation		
Comp	**Reaction time**	**Yield (%)**	**Temp. (°C)**	**Reaction time**	**Yield (%)**	**Temp. (°C)**
1b	3 h	64	130–160 [19, 20]	45 min	54	120
1c	4 h	58	130–160 [19, 20]	45 min	65	120
1d	4 h	45 [21]	120–123 [22]	45 min	66	120

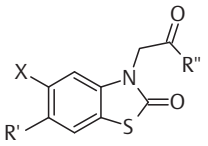
6-Acyl-1,3-benzothiazol-2(3*H*)-one derivatives are commonly prepared by reacting 1,3-benzothiazol-2(3*H*)-one with acyl halide and aluminum chloride (Friedel-Crafts acylation) [16, 17]. This procedure is hampered by significant consumption of $AlCl_3$. Ucar et al. suggested a new protocol in which $AlCl_3$ is used as well and which involves migration of the acyl group from the N-atom to the 6C-atom of the heterocyclic ring (Fries-Like rearrengement) [18]. Although total yield of the desired product was high, this method was rather time consuming and required 2 steps. An alternative method for obtaining 6-acyl-1,3-benzothiazol-2(3*H*)-one is acylation of 1,3-benzothiazol-2(3*H*)-one with benzoic acid derivatives in polyphosphoric acid (PPA) [11, 19–22]. PPA, however, is very viscous and is difficult to heat homogeneously with conventional methods. We therefore developed a rapid, practical and efficient microwave-assisted method for preparation of 6-acyl-1,3-benzothiazol-2(3*H*)-one derivatives (**1b–d**) in PPA (**Fig. 3**). MWI resulted in efficient heating of PPA and the use of Weflon™-coated stirring bars also positively affected homogeneous heating because they are strongly microwave-absorbing passive heating sources. The obtained yields (54–66%) were similar to the ones obtained with classical protocols (45–64%). The significant advantage of this procedure is its short duration. Synthesis of the 6-acyl-1,3-benzothiazol-2(3*H*)-one derivatives (**1b–d**) with the microwave-assisted method took only 45 min compared to 3 or 4 h with the conventional heating protocols (**Table 1**). The conventional method for synthesis of acyl derivatives has been reported earlier [19–22]. 5-Chloro-6-(4-fluorobenzoyl)-1,3-benzothiazol-2(3*H*)-one (**1f**) and 5-chloro-6-(4-methylbenzoyl)-1,3-benzothiazol-2(3*H*)-one (**1g**) were also synthesized with the microwave-assisted method. Although the reaction time, reagent quantities and temperature were varied, 5-chloro-6-(4-methoxybenzoyl)-1,3-benzothiazol-2(3*H*)-one was obtained neither with the conventional nor the microwave protocol.

Acetic acid derivatives (**3a–g**) were synthesized by alkaline hydrolysis of the corresponding ethyl esters (**2a–g**), which were prepared by reacting 1,3-benzothiazol-2(3*H*)-one and 5-chloro-1,3-benzothiazol-2(3*H*)-one (**1a–g**) with ethyl bromoacetate in the presence of potassium carbonate under MWI conditions, with good yields (**Fig. 4**). Acid derivatives were reacted with $SOCl_2$ to give acyl halides. The corresponding amides were obtained by reacting acyl halides with the appropriate amine under MWI conditions. Ethyl (2-oxo-1,3-benzothiazol-3(2*H*)-yl) acetate (**2a**) [23], ethyl (5-chloro-2-oxo-1,3-benzothiazol-3(2*H*)-yl)acetate (**2e**) [24], (2-oxo-1,3-benzothiazol-3(2*H*)-yl)acetic acid (**3a**) [23], (6-(4-methylbenzoyl)-2-oxo-1,3-benzothiazol-3-yl)acetic acid (**3c**) [19], (5-chloro-2-oxo-1,3-benzothiazol-3(2*H*)-yl)acetic acid (**3e**) [24] and 5-chloro-3-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1,3-benzothiazol-2(3*H*)-one (**5e**) [25–27] have been reported previously.

In this preliminary study, the antinociceptive activity of the title compounds was tested with the tail clip [28, 29], tail flick [30], hot plate [31, 32] and writhing tests [33] (**Table 2**). The tail clip, tail-flick and hot plate tests are used to assess central antinociceptive activity at the spinal level; the hot plate test also measures antinociceptive activity at the supraspinal level. The acetic acid-induced writhing test is used to assay peripheral antinociceptive activity, which typically mimics human clinical pain conditions [34–36]. Acetic acid-induced writhing behavior involves COXs and PGs. All compounds were administered at the same dose of 100 mg/kg except for **7a** and **5e**. Compounds **7a** and **5e** were tested at 25 mg/kg because the higher dose was found to be toxic to mice. In reference publications, aspirin has usually been used at a dose of 100 mg/kg.

All compounds except for **5d**, **6d**, **8f** and **3g** showed significant activity in the tail clip test. Compounds **5a** and **6a**, 1,3-benzothiazol-2(3*H*)-one derivatives, were more active than aspirin in the tail clip test. Compounds **5e**, **6e**, **7e**, **8e**, **5f**, **7f** and **7g**, 5-chloro-1,3-benzothiazol-2(3*H*)-one derivatives, were active as well with compound **6e** being the most active in the tail clip test. Compounds **6a**, **8a**, **6b**, **7b**, **6c**, **7c**, **7e**, **8e**, **5f** and **6g** at 100 mg/kg were at least as active as aspirin in the tail flick test with compounds **6a**, **6b**, **7b**, **7e** and **8e** being the most active ones. In the hot plate test, compounds **5a**, **6a**, **6c**, **3d**, **5e**, **6e**, **7e**, **8e** and **6g** at 100 mg/kg were at least as active as aspirin. Results from the writhing test indicated that 5-chloro-1,3-benzothiazol-2(3*H*)-

Table 2 Antinociceptive activity of the synthesized compounds.



Comp.[a]	X	R′	R″	Tail Clip Test[b,c]	Tail Flick Test[b,c]	Hot Plate Test[b,c]	Writhing Test[c]
Control	–	–	–	3.11 ± 0.93	18.10 ± 2.91	7.15 ± 1.06	45.67 ± 6.69
3a	H	H	OH	18.94 ± 6.64 *	66.67 ± 8.60 *	12.03 ± 4.47	27.33 ± 6.07
5a	H	H	4-methylpiperazin-1-yl	95.93 ± 4.06 *	76.18 ± 6.84 *	42.58 ± 5.98 *	20.17 ± 4.40 *
6a	H	H	4-ethylpiperazin-1-yl	83.33 ± 16.66 *	100 *	71.21 ± 9.88 *	13.33 ± 4.91 *
7a**	H	H	4-(propan-2-yl)piperazin-1-yl	36.17 ± 7.17 *	33.33 ± 8.60	11.48 ± 3.40	31.50 ± 5.13
8a	H	H	4-butylpiperazin-1-yl	19.42 ± 6.57 *	83.98 ± 16.01 *	26.13 ± 9.03	23.00 ± 5.82 *
3b	H	4-fluorobenzoyl	OH	21.91 ± 7.30*	32.42 ± 7.23	7.06 ± 2.27	5.60 ± 1.84 *
5b	H	4-fluorobenzoyl	4-methylpiperazin-1-yl	11.62 ± 2.73 *	28.54 ± 6.18	18.76 ± 5.33	32.17 ± 4.78
6b	H	4-fluorobenzoyl	4-ethylpiperazin-1-yl	46.23 ± 16.37 *	100 *	22.51 ± 7.68	15.00 ± 5.15 *
7b	H	4-fluorobenzoyl	4-(propan-2-yl)piperazin-1-yl	25.04 ± 7.67 *	100 *	23.88 ± 5.92 *	7.83 ± 2.31 *
8b	H	4-fluorobenzoyl	4-butylpiperazin-1-yl	19.72 ± 4.77 *	20.77 ± 5.94	14.22 ± 3.35	31.50 ± 3.12
3c	H	4-methylbenzoyl	OH	50.46 ± 9.04 *	52.87 ± 8.66 *	11.47 ± 1.99	21.17 ± 4.71 *
5c	H	4-methylbenzoyl	4-methylpiperazin-1-yl	28.34 ± 6.31 *	55.51 ± 8.36 *	6.09 ± 1.98	14.83 ± 5.17 *
6c	H	4-methylbenzoyl	4-ethylpiperazin-1-yl	49.91 ± 16.16 *	83.33 ± 16.66 *	49.75 ± 1.54 *	22.33 ± 5.05 *
7c	H	4-methylbenzoyl	4-(propan-2-yl)piperazin-1-yl	59.90 ± 16.07 *	87.81 ± 10.94 *	29.69 ± 6.66 *	10.67 ± 2.65 *
8c	H	4-methylbenzoyl	4-butylpiperazin-1-yl	37.23 ± 12.55 *	73.53 ± 17.72 *	6.08 ± 2.14	23.80 ± 4.91 *
3d	H	4-methoxybenzoyl	OH	56.95 ± 16.80 *	43.29 ± 16.54 *	48.28 ± 12.97 *	22.60 ± 6.06 *
5d	H	4-methoxybenzoyl	4-methylpiperazin-1-yl	1.31 ± 0.31	35.47 ± 13.49	11.80 ± 4.06	45.00 ± 1.57
6d	H	4-methoxybenzoyl	4-ethylpiperazin-1-yl	1.47 ± 0.53	50.47 ± 18.65	18.71 ± 3.74 *	27.00 ± 4.37 *
7d	H	4-methoxybenzoyl	4-(propan-2-yl)piperazin-1-yl	21.89 ± 5.39 *	77.92 ± 14.36 *	22.81 ± 5.72 *	23.67 ± 5.77 *
8d	H	4-methoxybenzoyl	4-butylpiperazin-1-yl	52.66 ± 8.68*	52.66 ± 8.68 *	15.64 ± 3.79 *	19.00 ± 6.65 *
3e	Cl	H	OH	32.42 ± 8.33 *	46.77 ± 8.44 *	16.60 ± 5.55	7.17 ± 2.48 *
5e**	Cl	H	4-methylpiperazin-1-yl	73.04 ± 13.28 *	66.67 ± 21.07 *	31.80 ± 5.37 *	17.83 ± 6.89 *
6e	Cl	H	4-ethylpiperazin-1-yl	100 *	60.00 ± 22.35 *	46.30 ± 13.18 *	9.00 ± 2.91 *
7e	Cl	H	4-(propan-2-yl)piperazin-1-yl	91.84 ± 6.75 *	100 *	56.65 ± 15.72 *	0.83 ± 0.30 *
8e	Cl	H	4-butylpiperazin-1-yl	98.22 ± 1.77 *	100 *	52.69 ± 16.31 *	2.00 ± 0.55 *
3f	Cl	4-fluorobenzoyl	OH	27.23 ± 6.79 *	57.46 ± 18.21	10.91 ± 4.04	27.00 ± 5.81
5f	Cl	4-fluorobenzoyl	4-methylpiperazin-1-yl	83.33 ± 16.66 *	87.89 ± 12.10 *	30.11 ± 10.59	13.83 ± 4.07 *
6f	Cl	4-fluorobenzoyl	4-ethylpiperazin-1-yl	50.00 ± 9.12 *	76.98 ± 16.60 *	13.99 ± 2.44 *	19.00 ± 6.02 *
7f	Cl	4-fluorobenzoyl	4-(propan-2-yl)piperazin-1-yl	70.99 ± 7.42 *	64.48 ± 8.36 *	2.62 ± 0.44 *	25.00 ± 4.05 *
8f	Cl	4-fluorobenzoyl	4-butylpiperazin-1-yl	10.96 ± 3.85	63.44 ± 15.68 *	6.99 ± 1.89	25.67 ± 8.92
3g	Cl	4-methylbenzoyl	OH	6.55 ± 1.71	41.60 ± 15.89	5.22 ± 1.72	35.60 ± 3.57
5g	Cl	4-methylbenzoyl	4-methylpiperazin-1-yl	47.67 ± 18.53 *	74.91 ± 16.64 *	13.78 ± 4.39	18.00 ± 6.24 *
6g	Cl	4-methylbenzoyl	4-ethylpiperazin-1-yl	69.89 ± 19.10 *	84.12 ± 15.87 *	40.31 ± 14.06 *	30.17 ± 2.94
7g	Cl	4-methylbenzoyl	4-(propan-2-yl)piperazin-1-yl	71.87 ± 13.44 *	68.93 ± 19.72 *	7.10 ± 1.00	22.67 ± 5.28 *
8g	Cl	4-methylbenzoyl	4-butylpiperazin-1-yl	47.28 ± 17.90 *	10.64 ± 3.83	11.19 ± 2.72	14.83 ± 4.71 *
Aspirin	–	–	–	70.54 ± 14.57*	80.79 ± 13.16*	10.18 ± 1.96	16.78 ± 4.77*

[a] All synthesized compounds were tested at 100 mg/kg. [b] The results are expressed as percentage of the maximal possible effect (%MPE ± SE). [c] All values are given as X ± standard error. n: 6. *$p < 0.05$. ** Compounds **7a** and **5e** were tested at 25 mg/kg because a dose of 100 mg/kg was found to be toxic to mice

one acid and amide derivatives (**3e-8e**) showed the highest antinociceptive activity. Compounds **3b**, **6b** and **7b** with a 4-fluorobenzoyl moiety were significantly active in the writhing test. Additionally, compounds **6a**, **5c**, **7c**, **5f** and **8g** had moderate antinociceptive activity and showed higher activity if compared to the aspirin and control groups whereas 6-(4-methoxybenzoyl)-1,3-benzothiazol-2(3*H*)-one derivatives had no a significant activity in all used tests.

Conclusions

Tiaramide is a nonsteroidal anti-inflammatory drug developed and approved only in Japan. S-14080, 6-benzoylbenzothiazolone, was tested in clinical trials up to phase II as an analgesic. This led us to investigate the analgesic and anti-inflammatory activity of 6-acyl-2(3H)-benzothiazolone and its amide derivatives composed of a tiaramide and 6-benzoylbenzothiazolone moiety. We synthesized acetic acid and acetamide derivatives of 1,3-benzothiazol-2(3*H*)-one, 6-acyl-1,3-benzothiazol-2(3*H*)-one, 5-chloro-1,3-benzothiazol-2(3*H*)-one and 6-acyl-5-chloro-1,3-benzothiazol-2(3*H*)-ones and assayed their antinociceptive activity with the tail flick, tail clip, hot plate and writhing tests with the intention of comparing their central and peripheral effects.

Our results showed that compounds **6a**, **7e** and **8e** were more active than aspirin at 100 mg/kg in the tail clip, tail flick, hot plate and writhing tests. These results suggest that these 3 compounds could possibly be both central and peripheral antinociceptive agents. Compounds **6b**, **7b**, **7c**, **6e** and **5f** have both central

and peripheral antinociceptive activity as well. On the other hand, compounds **5a**, **8a**, **6c** and **6g** could be centrally acting antinociceptive agents whereas compounds **3b**, **3e** and **5c** are likely to act at the periphery.

In conclusion, the synthesized compounds could provide a starting point for the design and development of new and more active antinociceptive agents. The mode of action of these compounds remains to be studied.

Acknowledgements

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Conflict of Interest

The authors declare that they have no conflict of interest.

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