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SYNTHESIS OF 2(3H)-BENZOTHIAZOLINONE DERIVATIVES AS ANALGESIC AND ANTI-INFLAMMATORY AGENTS

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Abstract

In this study, we have synthesized new 1-(4-(2-oxobenzothiazolin-3-yl)butyl-4-substituted piperazine, 1-(4-(2-oxobenzothiazolin-3-yl)butanoyl-4-substituted piperazine and 3-(4-(2-oxo-1,3-benzothiazol-2(3H)-yl)butyl)-1,3-benzothiazol-2(3H)-one derivatives and screened for their analgesic and anti-inflammatory activities as well as gastric ulceration potential in animals. The chemical structures of these compounds were elucidated by their IR, 1H-NMR spectral data, and elementel analyses. None of the compounds except compound 5b, 5c caused gastric lesions or bleeding in test animals. Compound 6c was found to have the highest analgesic and anti-inflammatory activity among the synthesized compounds.

Key Words: *2(3H)-Benzothiazolinone, analgesic and anti-inflammatory activity.*

Analjezik ve Antienflamatuvar ajan olarak 2(3H)-Benzotiyazolinon Türevlerinin Sentezi

Bu çalışmada, yeni 1-(4-(2-oksobenzotiyazolin-3-il) butil-4-sübstitüepiperazin, 1-(4-(2-oksobenzotiyazolin-3-il) butanoil-4-sübstitüepiperazin ve 3-(4-(2-okso-1,3-benzotiyazol-2(3H)-yl)butil)-1,3-benzotiyazol-2(3H)-on türevleri sentezlenmiş ve bunların analjezik ve antienflamatuvar aktiviteleri ile deney hayvanlarında gastrik ülser oluşturma potansiyelleri incelenmiştir. Bileşiklerin kimyasal yapıları IR, 1H-NMR ve elementel analiz verileri ile kanıtlanmıştır. Bileşik 5b, 5c dışında, hiçbir bileşik gastrik lezyon veya kanamaya neden olmamıştır. Bileşik 6c, sentezlenen bileşikler arasında en yüksek analjezik ve antienflamatuvar aktiviteye sahiptir.

Anahtar Kelimeler: *2(3H)-Benzotiyazolinon, analjezik ve antienflamatuvar aktivite.*

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INTRODUCTION

Classical NSAIDs possessing anti-inflammatory, antipyretic and analgesic properties have been widely used for treatment of acute and chronic inflammatory diseases for a long time. However, the chronic use of these agents has limitations since they cause gastrointestinal and renal side-effects which are inseparable from their pharmacological activities, sometimes leading to hemorrhage and ulceration. Therefore, studies aimed better tolerated and more potent NSAIDs with fewer side effects as compared to currently used ones have been of interest for many years (1, 2).

In connection with these efforts, a large number of 2-oxobenzothiazoline derivatives bearing various substituents at position-3 have been reported to exhibit analgesic and anti-inflammatory activity. Doğruer et al. synthesized (2-benzothiazolinon-3-yl)acetamide derivatives indicating that these compounds showed potential analgesic and anti-inflammatory activity (3, 4). In addition, Önkol et al. demonstrated that 3-(2-oxobenzothiazolin-3-yl)butanoic acid derivatives resulted in greater analgesic activity than aspirin and dipyrone (5).

Recently, some studies developing better NSAIDs as COX-2 selective inhibitors have concentrated on the preparation of the amide derivatives of currently used NSAIDs such as indomethacin (6) and meclofenamic acid (7) and found that neutralization of these NSAIDs by preparing amide derivatives resulted compounds that selectively inhibited COX-2 but not COX-1. In our previous work, we also prepared and reported the analgesic activity of 3-(2-oxobenzothiazolin-3-yl)propanamide derivatives (8). Therefore, these finding prompted us to search for new compounds by preparing the amide derivatives of 3-(2-oxobenzothiazolin-3-yl)butanoic acid and 3-(4-aminobutyl)-2-oxobenzothiazoline derivatives to test their analgesic and anti-inflammatory activities.

EXPERIMENTAL

Chemistry

All chemicals were purchased locally from Merck AG and Aldrich Chemical. Melting points were determined with Electrothermal-9300 Digital Melting Point Apparatus and are uncorrected. IR spectra of the compounds were recorded on a Bruker Vector 22 (Opus Spectroscopic Software Version 2.0) FT IR spectrophotometer (KBr, ν, cm^{-1}). ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Bruker Avance DPX-400 NMR spectrometer using tetramethylsilane as the internal standard. All chemical shifts were recorded as δ (ppm). Microanalyses for C, H, N, were performed on Leco-932 at the TÜBİTAK Analytical Laboratory, Ankara, Turkey. Elemental analyses data for all compounds are within ±0.4% of the theoretical value. Synthesis of 2-oxobenzothiazoline (9), ethyl (2-oxobenzothiazolin-3-yl)butanoate (10), 4-(2-oxobenzothiazolin-3-yl)butanoic acid (5, 11, 12) were reported in the literature.

*Synthesis of 4-(2-oxobenzothiazolin-3-yl)butanamide derivatives (**5a-c**)*

0.012 mol of thionyl chloride was added to the solution of 0.01 mol 4-(2-oxobenzothiazolin-3-yl)butanoic acid in dichloromethane. The solution was refluxed for 5 h and then evaporated to dryness and residue was dissolved in dichloromethane and 0.01 mol of triethylamine and 0.01 mol of the appropriate amine derivative were added. After the reaction was complete, dichloromethane was evaporated to dryness, acetone was added to the residue and the precipitate formed was filtered off. Acetone was evaporated and the residue was recrystallized from the appropriate solvent.

*3-{4-[4-(4-Chlorophenyl)piperazin-1-yl]-4-oxobutyl}-1,3-benzothiazol-2(3H)-one (**5a**)*

Recrystallized from ethanol/ water to yield 45%. m.p.: 88-89 ^{o}C. FT-IR (KBr), cm^{-1} : 1682 C=O (ring), 1638 C=O (amide), ^{1}H-NMR (DMSO-d$_6$) δ: 7.47 (1H, dd, benzothiazolone H^7), 7.28 (1H, d, benzothiazolone H^4), 7.20 (1H, m, benzothiazolone H^5) , 7.06 (2H, d, phenyl H^3, H^5), 7,04-6,99 (1H, m, benzothiazolone H^6), 6.78 (2H, d, phenyl H^2, H^6), 3.78 (2H, t, N-CH$_2$-), 3.42-3.33 (4H, m, piperazine H^2, H^6), 2.96-2.89 (4H, m, piperazine H^3, H^5), 2.27 (2H, t, -CH$_2$CO-), 1.72-1.67 (2H, m, -CH$_2$CH$_2$CH$_2$-).

*3-{4-[4-(4-Fluorophenyl)piperazin-1-yl]-4-oxobutyl}-1,3-benzothiazol-2(3H)-one hydrochloride (**5b**)*

Recrystallized from ethanol/ water to yield 41%. m.p.: 85-86 ^{o}C. FT-IR (KBr), cm^{-1} : 2364 tert. amine salt, 1672 C=O (ring), C=O (amide), ^{1}H-NMR (DMSO-d$_6$) δ: 9.1 (1H, s, HCl), 7.48 (1H, dd, benzothiazolone H^7), 7.28 (1H, d, benzothiazolone H^4), 7,21 (1H, m, benzothiazolone H^5), 7,11-6,99 (5H, m, benzothiazolone H^6, phenyl H^2, H^3, H^5, H^6), 3.78 (2H, t, -N-CH$_2$-), 3.54-3.49 (4H, m, piperazine H^2, H^6), 3.05-3.01 (4H, m, piperazine H^3, H^5), 2.30 (2H, t, -CH$_2$CO-), 1.73-1.66 (2H, m, -CH$_2$CH$_2$CH$_2$-).

*3-{4-[4-Benzylpiperazin-1-yl]-4-oxobutyl}-1,3-benzothiazol-2(3H)-one hydrochloride (**5c**)*

Recrystallized from ethanol/ water to yield 46%. m.p.: 245 ^{o}C. FT-IR (KBr), cm^{-1} : 2369 tert. amine salt , 1660 C=O (ring), 1647 C=O (amide), ^{1}H-NMR (DMSO-d$_6$) δ: 10.52-9.80 (1H, s, HCl), 7.48 (1H, dd, benzothiazolone H^7), 7.35-7.25 (6H, m, benzothiazolone H^4, phenyl H^2, H^3, H^4, H^5, H^6), 7,21 (1H, m, benzothiazolone H^5), 7.02 (1H, m, benzothiazolone H^6), 4.39-4.22 (1H, m, piperazine H^{2,6}) , 4.15 (2H, s, -N-CH$_2$-C$_6$H$_5$), 3.78-3.74 (3H, m, piperazine H^{2,6}, -N-CH$_2$-), 3.6-3.4 (2H, m, piperazine H^{2,6}), 2.78-2.75 (4H, m, piperazine H^3, H^5), 2.30 (2H, t, -CH$_2$CO-), 1.69-1.66 (2H, m, -CH$_2$CH$_2$CH$_2$-).

*4-(2-Oxobenzothiazolin-3-yl)butylamine derivatives (**6a-d**)*

A total of 0.01 mol of 2-oxobenzothiazoline, 0.03 mol of potassium carbonate, 0.01 mol 1-bromo-4-chlorobutane and 0.01 mol of the appropriate amine derivatives were placed in 30 ml acetone and refluxed for 8 h, and potassium salt was filtered off. Acetone was concentrated on a rotary evaporator and treated with 10% HCl. The precipitate formed was filtered and washed with acetone, dried and recrystallized from the appropriate solvent.

*3-[4-(4-(3-Chlorophenyl)piperazin-1-yl)butyl]-1,3-benzothiazol-2(3H)-one hydrochloride (**6a**)*

Recrystallized from acetone to yield 40%. m.p.: 225 °C. FT-IR (KBr), cm^{-1} : 2576, 2473 tert. amine salt 1660 C=O (ring), ^{1}H-NMR (DMSO-d_6) δ: 10.71-10.05 (1H, s, HCl), 7.66 (1H, dd, benzothiazolone H^7), 7.40-7.35 (2H, m, benzothiazolone H^5, H^4), 7.26-7.17 (2H, m, benzothiazolone H^6 and phenyl H^2), 7.02 (1H, d, phenyl H^6), 6.93 (1H, dd, phenyl H^4), 6.84 (1H, dd, phenyl H^5), 3.98 (2H, t, -N-$\underline{CH_2}$-), 3.86-3.83 (2H, m, piperazine $H^{3,5}$), 3.49-3.46 (2H, m, piperazine $H^{3,5}$), 3.14-3.03 (6H, m, piperazine H^2, H^6, -$\underline{CH_2}$-N-), 1.75-1.66 (4H, m, -$CH_2\underline{CH_2}\underline{CH_2}CH_2$-).

*3-[4-(4-(4-Chlorophenyl)piperazin-1-yl)butyl]-1,3-benzothiazol-2(3H)-one hydrochloride (**6b**)*

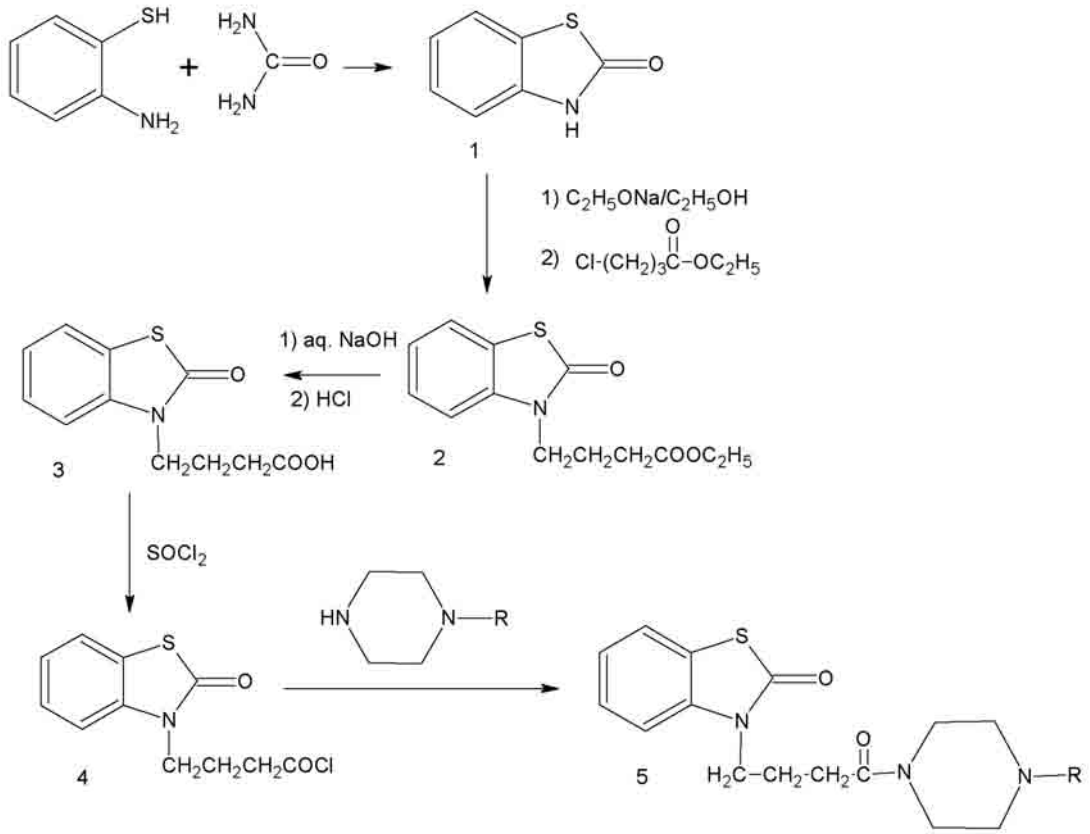
Recrystallized from acetone to yield 30%. m.p.: 212-213 °C. FT-IR (KBr), cm^{-1} : 2564, 2468 tert. amine salt 1653 C=O (ring), ^{1}H-NMR (DMSO-d_6) δ: 10.22-9.87 (1H, s, HCl), 7.68 (1H, dd, benzothiazolone H^7), 7.43-7.38 (2H, m, benzothiazolone H^5, H^4), 7.28 (2H, d, phenyl H^2, H^6) , 7.22 (1H, m, benzothiazolone H^6), 7.01 (2H, d, phenyl H^3, H^5), 4.01 (2H, t, N-$\underline{CH_2}$-), 3.81-3.70 (2H, m, piperazine $H^{3,5}$), 3.60-3.43 (2H, m, piperazine $H^{3,5}$), 3.16-2.88 (6H, m, piperazine H^2, H^6, -$\underline{CH_2}$-N-), 1.83-1.71 (4H, m, -$CH_2\underline{CH_2}\underline{CH_2}CH_2$-).

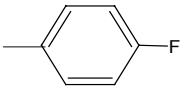
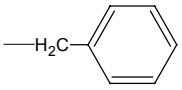
*3-[4-(4-(4-Fluorophenyl)piperazin-1-yl)butyl]-1,3-benzothiazol-2(3H)-one hydrochloride (**6c**)*

Recrystallized from acetone to yield 35.5%. m.p.: 216-217 °C. FT-IR (KBr), cm^{-1} : 2577 tert. amine salt, 1662 C=O (ring), ^{1}H-NMR (DMSO-d_6) δ: 10.16-9.55 (1H, s, HCl), 7.52 (1H, dd, benzothiazolone H^7), 7.26-7.23 (2H, m, benzothiazolone H^5, H^4), 7.06 (1H, m, benzothiazolone H^6) , 6.96-6.92 (2H, m, phenyl H^2, H^6), 6.87-6.83 (2H, m, phenyl H^3, H^5), 3.84 (2H, t, -N-$\underline{CH_2}$-), 3.57-3.54 (2H, m, piperazine $H^{3,5}$), 3.37-3.34 (2H, m, piperazine $H^{3,5}$), 3.01-2.83 (6H, m, piperazine H^2, H^6, -$\underline{CH_2}$-N-), 1.57-1.54 (4H, m, -$CH_2\underline{CH_2}\underline{CH_2}CH_2$-).

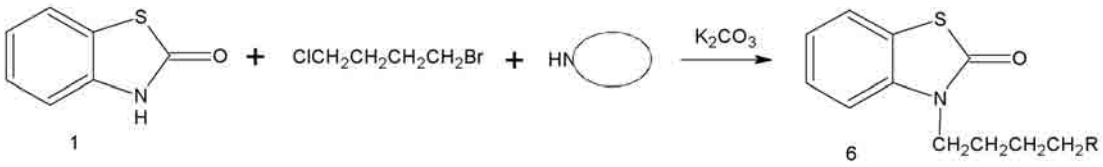
*3-(4-(2-Oxo-1,3-benzothiazol-2(3H)-yl)butyl)-1,3-benzothiazol-2(3H)-one (**6d**)*

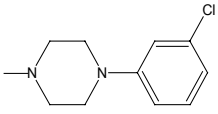
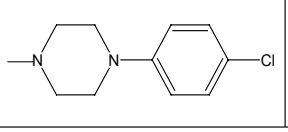
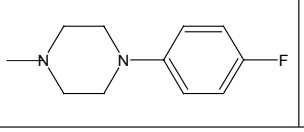
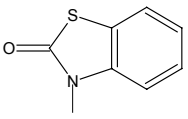
Recrystallized from butanol to yield 80%. m.p.: 170-171 °C. FT-IR (KBr), cm^{-1} : 1681 C=O (ring), ^{1}H-NMR (DMSO-d_6) δ: 7.64 (2H, dd, benzothiazolone H^7), 7.37- 7.35 (4H, m, benzothiazolone H^5, H^4), 7.20-7.18 (2H, m, benzothiazolone H^6), 4.09-3.86 (4H, m, -N-$\underline{CH_2}$-), 1.76-1.58 (4H, m, -CH_2-$\underline{CH_2}$-$\underline{CH_2}$-CH_2-) .



Comp.	5a	5b	5c
R			

Scheme 1. Synthetic route of the title compounds **(5a-c)**



Comp.	6a	6b	6c	6d
R				

Scheme 2. Synthetic route of the title compounds **(6a-d)**

Pharmacology

Animals

Male Swiss albino mice (The Animal Breeding Laboratories of Refik Saydam Hıfz-ı Sıhha Institute, Ankara, Turkey), weighing 20–25 g, were used for all experiments.The animals were kept in colony cages (six mice each), maintained on standard pellet diet, water ad libitum, and left for two days for acclimatization before the experimental session. The food was withdrawn on the day before the experiment, but free access of water was allowed. All experiments were carried out according to the suggested ethical guidelines for the care of laboratory animals.

Preparation of test samples for bioassay

Test samples were suspended in a mixture of distilled water and 0.5% sodium carboxymethylcellulose (CMC) and were given orally to the test animals. The animals of the control group received the same experimental handling except that the drug treatment was replaced with appropriate volumes of the dosing vehicle. Indomethacin (10 mg/kg) or acetylsalicylic acid (ASA) in 0.5% CMC (100 mg/kg) was used as reference drug.

p-Benzoquinone-induced writhing test (13)

60 min after the oral administration of test samples, the mice were injected intraperitoneally with 0.1 mL/10 g body weight of 2.5% (v/v) *p*-benzoquinone (PBQ, Merck, Darmstadt, Germany) solution in distilled water. Control animals received an appropriate volume of dosing vehicle. The mice were then kept individually for observation and the total number of abdominal contractions (writhing movements) was counted for the next 15 min, starting on the fifth min after the PBQ injection. The data represent average values of the total number of writhes observed. The analgesic activity was expressed as the percentage differences in writhing numbers between compound's groups and control group.

Carrageenan-induced hind paw edema test (14, 15)

The test was performed according to the method of Kasahara et al. (15). The difference in footpad thickness between the right and left foot was measured with a pair of dial thickness gauge callipers (Ozaki Co., Tokyo, Japan). Mean values of treated groups were compared with mean values of a control group and analyzed using statistical methods. 60 min after the oral administration of the test sample or dosing vehicle, each mouse was injected with freshly prepared (0.5 mg/25 mL) suspension of carrageenan (Sigma, St. Louis, Mo, USA) in physiological saline (154 mM NaCl) into subplantar tissue of the right hind paw and 25 µL of saline solution was injected into that of the left hind paw as secondary control. Measurements were done and evaluated every 90 min during 360 min after induction of inflammation, as described above.

Gastric ulceration side effects

After the analgesic activity experiment, mice were killed under deep ether anesthesia and stomachs were removed. Then the abdomen of each mouse was opened through great curvature and examined under the dissecting microscope for lesion or bleedings.

Statistical analysis of data

Data obtained from the animal experiments were expressed as the mean standard error (±SEM). Statistical differences between the treatments and the control were tested by ANOVA test.

RESULTS AND DISCUSSION

The title amide derivatives were synthesized by the reaction of appropriate amine derivatives with 4-(2-oxobenzothiazolin-3-yl)butanoyl chloride in the presence of triethylamine. Analytical data for structure elucidation were given in Experimental Part. The preparation of resulting amide derivatives (**5a-c**) were outlined in Scheme 1. In the synthesis of amide derivatives (**5a-c**), commercially available 2-aminothiophenol was used as the starting material, and 4-(2-oxobenzothiazolin-3-yl)butanoic acid (**3**) was prepared by adapted procedures according to previously published methods (5, 9, 11, 12). **3** was then treated with thionyl chloride to prepare the corresponding acid chloride **4**, which was then reacted without subsequent purification with appropriate amine derivatives to obtain resulting novel amide derivatives **5a-c** (Scheme 1). Additionally, 2(3H)-oxobenzothiazoline **(1)** was also reacted with 1-bromo-4-chlorobutane and appropriate amine derivatives in the presence of potassium carbonate to obtain the 4-(2-oxobenzothiazolin-3-yl)butylamine derivatives **6a-d**, which are the reduced form of the previously obtained amide derivatives (Scheme 2).

In this preliminary screening study, analgesic and anti-inflammatory activities of the title compounds (**5-a-c**, **6a-d**) were assessed by *p*-benzoquinone-induced writhing test (13) and carrageenan-induced hind paw edema model (14, 15), respectively. As seen in Tables 1 and 2, the overall analgesic and anti-inflammatory activity of the compounds were lower than that of reference compounds aspirin and indomethacin. Analgesic activity results indicated that amide derivatives (**5a-c**) showed lower analgesic activity as compared to the corresponding amine derivatives (**6a-d**). For instance, compounds having 4-chlorophenylpiperazine (**5a**) and 4-fluorophenylpiperazine (**5b**) substituents at the amide portion resulted in lower analgesic activity when compared to their corresponding reduced forms **6b** and **6c**, respectively. Analgesic activity results of the compounds also showed good correlation with their anti-inflammatory activities tested by using the carrageenan-induced hind paw edema model. As seen in Table 2, the same derivatives **6b** and **6c** exhibited at 100 mg/kg the highest anti-inflammatory activity although it was way lower than that of the reference compound, indomethacin, tested at 10 mg/kg dose.

In conclusion, the replacement of a fluorine substituent with a chlorine at the 4 position on the phenyl ring and also the replacement of the butyl with a butanone moiety caused a decrease in the analgesic and anti-inflammatory activity. In addition, as indicated in Table 1, all compounds except for **5b-c** did not cause any gastric lessions and bleeding in the stomachs of the tested animals. One can incline to say that straight alkyl chain derivatives are more active than amide derivatives.

Table 1. Effect of the synthesized compounds against *p*-benzoquinone-induced writhing in mice[a].

Compound	Dose (mg/kg)	Number of writhing ± SEM	Inhibitory ratio (%)	Ratio of ulceration	n
Control		47.9 ± 4.02		0/6	6
5a	100	42.2 ± 2.19	11.9	0/6	6
5b	100	39.9 ± 2.58	16.7	2/6	6
5c	100	43.2 ± 2.15	9.8	1/6	6
6a	100	34.9 ± 2.96	27.1	0/6	6
6b	100	29.8 ± 2.05	37.8**	0/6	6
6c	100	27.9 ± 2.54	41.8***	0/6	6
6d	100	51.1 ± 3.69	---	0/6	6
ASA	100	21.1 ± 1.82	55.5***	4/6	6

(** $p < 0.01$, *** $p < 0.001$).

[a]Analgesic activity of the compounds and aspirin was tested at 100 mg/kg dose as described in Experimental Part. $p < 0.5$ was found for all testing in comparison with control group.

Table 2. Effects of the synthesized compounds against carrageenan-induced paw edema in mice[a]

Compound	n	Dose (mg/kg)	Swelling thickness ($x10^{-2}$mm) ± SEM (Inhibition %)			
			90 min	180 min	270 min	360 min
Control	6		41.7 ± 3.15	49.3 ± 4.02	54.5 ± 3.97	63.2 ± 4.42
5a	6	100	42.2 ± 3.52 (0.0)	48.8 ± 3.68 (0.0)	51.3 ± 4.02 (5.9)	55.9 ± 3.95 (11.6)
5b	6	100	37.4 ± 3.13 (10.3)	39.6 ± 3.64 (19.7)	48.8 ± 3.59 (10.5)	51.5 ± 4.02 (18.5)
5c	6	100	48.3 ± 3.11 (0.0)	52.8 ± 3.65 (0.0)	57.1 ± 3.92 (0.0)	65.8 ± 4.02 (0.0)
6a	6	100	40.2 ± 2.16 (3.6)	43.3 ± 2.51 (12.2)	46.9 ± 2.78 (13.9)	49.9 ± 3.12 (21.0)
6b	6	100	31.8 ± 3.05 (23.7)	38.5 ± 3.26 (21.9)	39.9 ± 3.06 (26.8)	46.8 ± 3.92 (25.9)
6c	6	100	39.7 ± 2.10 (4.8)	41.5 ± 2.22 (15.8)	42.4 ± 3.02 (22.2)	43.7 ± 2.92 (30.9)**
6d	6	100	44.6 ± 2.98 (0.0)	49.5 ± 3.02 (0.0)	55.8 ± 3.15 (0.0)	67.9 ± 3.9 (0.0)
Indomethacin	6	10	31.6 ± 2.15 (24.2)*	32.1 ± 2.32 (34.9)**	31.4 ± 2.92 (42.4)***	32.7 ± 2.16 (48.3)***

(* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

[a] Anti-inflammatory activity of the compounds was tested at 100 mg/kg dose, and anti-inflammatory activity of the reference compound, indomethacin, was tested at 10 mg/kg doses as described in Experimental Part. $p < 0.5$ was found for all testing in comparison with control group.

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