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Original article

SYNTHESIS and ANALGESIC and ANTI INFLAMMATORY ACTIVITY OF (6-ACYL-2-(3H)-BENZOTHIAZOLINON-3-YL) ACETAMIDE / PROPANAMIDE DERIVATIVES

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Abstract

In order to develop potent analgesic and anti-inflammatory compounds, we synthesized (6-acyl-2-benzothiazolinon-3-yl)acetamide / propanamide derivatives and screened their in vivo analgesic and anti-inflammatory activities at a single dose of 100 mg/kg in mice by p-benzoquinone-induced writhing test and Carrageenan induced hind paw edema model, respectively. We also determined for their gastric ulceration potential in the tested animals.1-[2-(6-(2-fluorobenzoyl)-2-benzothiazolinon-3-yl)acetyl]-4-(4-fluoro-phenyl)piperazine (Compound 7i) exhibited the highest analgesic and , anti-inflammatory.

Key words: *6-Acyl-2(3H)-benzothiazolinone, (6-Acyl-2-benzothiazolinon-3-yl)acetamide, (6-Acyl-2-benzothiazolinon-3-yl)propanamide, Analgesic and Anti-inflammatory activity.*

Analjezik ve Antienflamatuvar Ajan Olarak (6-Acyl-2-(3H)-Benzotiyazolinon-3-il) Asetamit/ Propanamit Türevlerinin Sentezleri

Etkili analjezik ve antienflamatuvar bileşikler geliştirmek amacıyla (6-açil-2-benzotiyazolinon-3-il)asetamit / propanamit türevleri sentez edilmiş ve bunların analjezik ve antienflamatuvar etkileri 100 mg/kg dozda fareler üzerinde test edilmiştir.Test edilen hayvanlarda gastrik lezyon etkileri değerlendirilmiştir. Bu çalışmada 1-[2-(6-(2-florobenzoil)-2-benzotiyazolinon-3-il)asetil]-4-(4-florofenil)piperazine (Bileşik 7i) bileşiğinin en yüksek analjezik ve antienflamatuvar etkiye sahip olduğu bulunmuştur.

Anahtar kelimeler: *6-Açil-2(3H)-benzotiyazolinon, (6-Açil-2-benzotiyazolinon-3-il)asetamit, (6-Açil-2-benzotiyazolinon-3-il)propanamit, Analjezik ve antienflamatuvar aktivite*

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INTRODUCTION

To search for new compounds with analgesic activity, and devoid of the side effects such as respiratory depression, constipation, and physical dependence as seen in morphine-like opioid agonists as well as the gastrointestinal irritation and kidney damage associated with nonsteroidal anti-inflammatory drugs has been of interest for many years. In this respect, 2-oxo-3H-benzothiazolines have attracted considerable attention.

Some of the 6-acyl-2-benzothiazolinone derivatives have been reported to have potent analgesic activity. Ferreira screened the antinociceptive activity of 6-benzoyl-2-benzothiazolinone (Figure1) in 1995, and concluded that it might release an endogenous opiod-like substance from the adrenal glands which might be responsible for the activity (1). Yous *et al.* have reported that 6-benzoyl-2-benzothiazolinone represents a new type of antinociceptive agent acting in periphery by inhibiting the cyclooxygenase pathway and also promoting the release of an opioid peptide (2).

Figure 1. 6-benzoyl-2-benzothiazolinone

Additionally, 6-Acyl-2-benzothiazolinone derivatives bearing the 2-pyridylethyl substituent at position 3 exhibited significant analgesic and anti-inflammatory activities (3).

We have been interested for a long time in developing compounds with potent analgesic and anti-inflammatory activity without GI liabilities exhibited by currently marketed NSAIDs (4-6). Our recent studies showed that (2-benzothiazolinon-3-yl)acetamides (7). and (2-benzothiazolinon-3-yl)propionamides (8,9) alleviated the induced pain and suppressed the induced inflammation with no observed acute toxicity in the tested animals. Also, we have reported that 6-acyl-2-benzothiazolinones having propanoic acid side chain might lead to further studies for developing better candidates with potent analgesic and anti-inflammatory activity than acetic acid derivatives (Figure 2) (10).

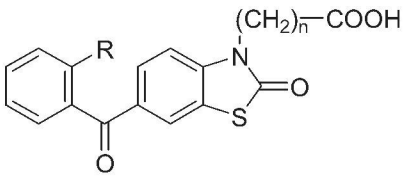


Figure 2. (6-acyl-2-benzothiazolinone-3-yl) acetic/propanoic acid derivative

Based on above findings, we decided to combine 6-acylbenzothiazolinone ring with acetamide and propanamide side chains at position 3 and comparative the analgesic and anti-inflammatory activities. On this basis, the synthesis of new (6-acyl-2-benzothiazolinon-3-yl)acetamide/propanamide derivatives (Figure 3) was reported in this study.

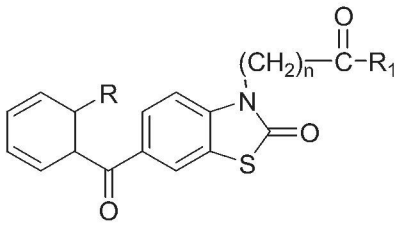


Figure 3. (6-acyl-2-benzothiazolinone-3-yl)acetamide/propanamide derivative)

MATERIALS AND METHODS

Apparatus

Melting points of the compounds were determined on Electrothermal 9200 melting points apparatus (Southent, Great Britain) and the values given are uncorrected.

The IR spectra of the compounds were recorded on a Bruker Vector 22 IR Spectrophotometer (Bruker Analytische Messtechnik, Karlrure, Germany).

The ^{1}H-NMR of the compounds spectra were recorded on a Bruker 400 MHz-NMR Spectrometer (Rheinstetten, Karlrure, Germany) using tetramethylsilane as an internal standard.

Elemental analyses were performed with Leco-932 (C,H,N,S,O-Elemental analyzer, St. Joseph, USA) at Scientific and Technical Research Council of Turkey, Instrumental Analysis Center (Ankara-Turkey) and within ± 0.4 % of the theoretical values.

Chemistry

Synthesis of 6-benzoyl-2-benzothiazolinone (11) 6-(2-fluorobenzoyl)-2-benzothiazolinone (11,12) (6-benzoyl-2-benzothiazolinon-3-yl)acetate, 6-(2-fluorobenzoyl-2-benzothiazolinon-3-yl)acetate, (6-benzoyl-2-benzothiazolinon-3-yl)acetic acid ,6-(2-fluorobenzoyl)-2-benzothiazolinon-3-yl)acetic acid, 3-(6-benzoyl-2-benzothiazolinon-3-yl)propionitrile, 6-(2-fluorobenzoyl-2-benzothiazolinon-3-yl)propionitrile, 3-(6-benzoyl-2-benzothiazolinon-3-yl)propionic acid and 6-(2-fluorobenzoyl-2-benzothiazolinon-3-yl)propionic acid (10) were synthesized according to the procedures previously published procedures.

Synthesis of 3-(6-acyl-2-benzothiazolinon-3-yl)acetamide (7a-l)

(6-Acyl-2-benzothiazolinon-3-yl)acetyl chloride derivative (5 mmol), potassium carbonate (15 mmol) and secondary amine derivative (15 mmol) were mixed in tetrahydrofuran (50 mL), refluxed for 3–8 h, and then poured into ice-water. The crude product precipitated was filtered and crystallized from appropriate solvents (Table 1).

Synthesis of 3-(6-acyl-2-benzothiazolinon-3-yl)propanamide (7m-z)

3-(6-Benzoyl-2-benzothiazolinon-3-yl)propionic acid (1.5 mmol) in dichloromethane (25 mL) was treated with triethylamine (4.5 mmol) and ethyl chloroformate (1.5 mmol) at 0°C. After stirring the reaction mixture for 30 min, an appropriate secondary amine derivative (4.5 mmol) was added to this solution. The final mixture was stirred for 24 h at 0°C and evaporated to dryness and the residue was treated with acetone. All solid materials thus obtained were filtered off and acetone was evaporated to dryness. The solid residue was crystallized from the appropriate solvents (Table 1).

Table 1. Synthesized 3-(6-acyl-2-benzothiazolinon-3-yl)acetamide derivatives (7a-l) and 3-(6-acyl-2-benzothiazolinon-3-yl)propanamide derivatives (7m-z) and their mps, crystallization solvents, yield percentages, and elemental analysis.

Comp.	R	R_1	n	Crys. Sol.	Yield %	Mp [°C]	Calcd/Found
7a	H	morpholine	1	Water	74	192-193	C:92.81/62.51, H:4.74/4.34, N: 7.32/6.63.
7b	H	phenylpiperazine	1	Acetone	51	128-130	C:68.25/67.79, H: 5.07/5.46, N: 9.18/8.75
7c	H	(4-fluorophenyl)piperazine	1	Ethanol	79	129-131	C:65.67/65.68, H:4.66/5.00, N: 8.84/8.74.
7d	H	(4-chlorophenyl)piperazine	1	Ethanol	21	162-164	C:63.47/63.82, H:4.51/4.90, N: 8.54/8.36.
7e	H	4-benzylpiperazine	1	2-Propanol	57	186-187	C:68.77/69.07, H:5.34/5.30, N: 8.91/8.84.
7f	H	(2-pyridyl)piperazine	1	Ethanol-Water	50	152-153	C:65.49/65.55, H:4.84/4.58, N:12.22/12.60.
7g	F	morpholine	1	Ethanol	68	197-198	C:59.99/54.59, H:4.28/4.38, N: 7.00/6.68.
7h	F	phenylpiperazine	1	Ethanol	54	146-148	C:65.67/66.05, H:4.66/4.62, N: 8.84/8.81.
7i	F	(4-fluorophenyl)piperazine	1	Ethanol	69	164-165	C:63.28/63.39, H: 4.29/4.02, N: 8.51/8.53
7j	F	(4-chlorophenyl)piperazine	1	Ethanol	30	127-129	C:61.23/61.40, H: 4.15/3.77, N: 8.24/8.04
7k	F	4-benzylpiperazine	1	Ethanol	73	184-185	C:66.24/66.31, H:4.94/4.84, N: 8.58/8.48.
7l	F	(2-pyridyl)piperazine	1	Ethanol	39	170-171	C:63.01/63.36, H:4.44/4.47, N:11.76/11.63.
7m	H	morpholine	2	Ethanol	71	115-118	C:63.62/63.48, H:5.08/4.56, N: 7.07/7.45.
7n	H	phenylpiperazine	2	Ethanol	47	165-167	C:68.77/68.55, H: 5.34/4.81, N: 8.91/8.89
7o	H	(4-fluorophenyl)piperazine	2	Ethanol	43	170	C:66.24/66.37, H:4.94/4.47, N: 8.58/8.60.

7p	H	(4-chlorophenyl)piperazine	2	Ethanol	33	159-162	C: 64.09/64.52, H: 4.78/4.88, N: 8.30/7.98.
7q	H	4-benzylpiperazine	2	Ethanol	58	156	C:69.25/68.95, H: 5.60/5.95, N: 8.65/8.59
7r	H	(2-pyridyl)piperazine	2	Ethanol	33	128	C:65.77/65.77, H: 5.14/4.76, N: 7.93/7.95
7s	F	morpholine	2	Methanol	21	176	C:60.86/61.10, H: 4.62/4.33, N: 6.76/6.58
7t	F	phenylpiperazine	2	Methanol	19	166	C:66.24/66.36, H: 4.94/4.55, N: 8.58/8.53
7u	F	(4-fluorophenyl)piperazine	2	Ethanol	23	151	C:63.89/63.95, H: 4.57/4.16, N: 8.28/8.11
7v	F	(4-chlorophenyl)piperazine	2	Ethanol	16	155-158	C:61.89/62.30, H:4.42/4.12, N: 8.02/7.98.
7y	F	4-benzylpiperazine	2	Ethanol	28	120	C:66.78/66.39, H:5.20/5.48, N: 8.34/8.09.
7z	F	(2-pyridyl)piperazine	2	Acetone	70	250>	C:63.61/63.10, H: 4.79/4.53, N: 7.67/7.49

Table 2. IR and ^{1}H-NMR spectral data of the compounds **7a-z**.

Comp.	IR (KBr) cm^{-1}	^{1}H-NMR (ppm, δ)
7a	1662, 1647	$CDCl_3$, 7.94 (1H, d, H^7), 7.83 (1H, dd, $H^{4)}$, 7.80-7.77 (2H, m, benzoyl-$H^{2,6}$), 7.62 (1H, t, benzoyl-H^4),7.51 (2H,t, benzoyl-$H^{3,5}$), 7.14 (1H, d, H^5), 4.82 (2H, s, CH_2), 3.78-3.74 (4H, m, morpholinyl-O-CH_2), 3.67-3.63 (4H, m, morpholinyl-N-CH_2)
7b	1662, 1647	$CDCl_3$, 7.97 (1H, d, H^7), 7.83 (1H, dd, H^4), 7.78 (2H, d, benzoyl-$H^{2,6}$), 7.62 (1H, t, benzoyl-H^4),7.51 (2H, t, benzoyl-$H^{3,5}$), 7.32 (2H, t, phenyl-$H^{3,5}$),7.16 (1H, d, H^5), 7.02-6.93 (3H, m, phenyl-$H^{2,4,6}$), 4.87 (2H, s, CH_2), 3.83-3.79 (4H, m, piperazinyl-$H^{2(6)}$), 3.29 (2H, t, piperazinyl-$H^{3(5)}$), 3.21 (2H, t, piperazinyl-$H^{5(3)}$)
7c	1670, 1655	$CDCl_3$, 7.97 (1H, d, H^7), 7.83 (1H, dd, H^4), 7.80-7.77 (2H, m, benzoyl-$H^{2,6}$), 7.62 (2H, t, benzoyl-H^4), 7.51 (2H, t, benzoyl-$H^{3,5}$) 7.16 (1H, d, H^5), 7.04-6.99 (2H,m, phenyl-$H^{3,5}$), 6.94-6.90 (2H, m, phenyl-$H^{2,6}$), 4.87 (2H, s, CH_2), 3.83-3.79 (4H, m, piperazinyl-$H^{2,6}$), 3.20 (2H, t, piperazinyl-$H^{3(5)}$), 3.12 (2H, t, piperazinyl-$H^{5(3)}$)
7d	1672, 1657	$CDCl_3$, 7.97 (1H, d, H^7), 7.83 (1H, dd, H^4), 7.80-7.78 (2H, m, benzoyl-$H^{2,6}$), 7.62 (2H, t, benzoyl-H^4), 7.51 (2H, t, benzoyl-$H^{3,5}$), 7.27-7.25 (2H,m, phenyl-$H^{3,5}$), 7.17 (1H, d, H^5), 6.88 (2H, d, phenyl-$H^{2,6}$), 4.87 (2H, s, CH_2), 3.83-3.79 (4H, m, piperazinyl-$H^{2,6}$), 3.25 (2H, t, piperazinyl-$H^{3(5)}$), 3.18 (2H, t,

		piperazinyl-$H^{5(3)}$)
7e	1674, 1647	$CDCl_3$, 7.96 (1H, d, H^7), 7.82-7.78 (3H, m, H^4, benzoyl-$H^{2,6}$), 7.62 (1H, t, benzoyl-H^4), 7.51 (2H, t, benzoyl-H3,5), 7.11 (1H, d, H5), 4.81 (2H, s, CH_2), 3.67-3.57 (6H, m, piperazinyl-$H^{2,6}$, benzyl-CH_2), 2.55-2.49 (4H, m, piperazinyl-$H^{3,5}$),
7f	1668, 1645	$CDCl_3$, 8.48 (1H, dd, pyridinyl-H^3) 8.22(1H,d, H^7), 8.07(1H, dd, H^4), 8.04-8.02 (2H, m, benzoyl-$H^{2,6}$), 7.87-7.73 (4H, m, benzoyl-$H^{3,4,5}$, pyridinyl-H^5), 7.39 (2H, d, H^5), 6.99-6.94 (2H, m, pyridyl-$H^{4,6}$), 5.12 (2H, s, CH_2), 4.05 (2H, t, piperazinyl-$H^{2(6)}$), 3.83 (2H, t, piperazinyl-$H^{6(2)}$), 1.86 (4H, m, piperazinyl-$H^{3,5}$)
7g	1673, 1651	$CDCl_3$, 7.96 (1H, s, H^7), 7.83 (1H, d, H^4), 7.57-7.52 (2H, m, benzoyl-$H^{3,6}$), 7.29(1H, t, benzoyl-H^4), 7.19 (1H, t, benzoyl-H^5), 7.12 (1H, d, H^5), 4.80 (2H, s, CH_2), 3.78-3.71 (4H, m, morpholinyl-O-CH_2), 3.65-3.62 (4H, m, morpholinyl-N-CH_2)
7h	1665	$CDCl_3$, 7.97 (1H, s, H^7), 7.84 (1H, dd, H^5), 7.59-7.52 (2H, m, benzoyl-$H^{3,6}$), 7.34-7.29 (4H, m, benzoyl-H^4, phenyl-$H^{3,4,5}$), 7.19 (1H, t, benzoyl-H^5),7.14 (1H, d, H^4), 6.97 (2H, d, phenyl-$H^{2,6}$), 4.86 (2H, s, CH_2), 3.80 (4H, m, piperazinyl-$H^{2,6}$), 3.28 (2H, t, piperazinyl-$H^{3(5)}$), 3.21 (2H, t, piperazinyl-$H^{5(3)}$)
7i	1659	$CDCl_3$, 7.97 (1H, s, H^7), 7.84 (1H, d, H^5), 7.57-7.53 (2H, m, benzoyl-$H^{3,6}$), 7.29 (2H, t, benzoyl-H^4) 7.19 (1H, t, benzoyl-H^5), 7.14 (1H, d, H^4), 7.01 (2H, t, phenyl-$H^{3,5}$), 6.93-6.89 (2H, m, phenyl-$H^{2,6}$), 4.85 (2H, s, CH_2), 3.79 (4H, m, piperazinyl-$H^{2,6}$), 3.18 (2H, t, piperazinyl-$H^{3(5)}$), 3.11 (2H, t, piperazinyl-$H^{5(3)}$)
7j	1664	$CDCl_3$, 7.96 (1H, s, H^7), 7.83 (1H,d, H^5), 7.59-7.52 (2H, m, benzoyl-$H^{3,6}$), 7.37-7.28 (6H, m, benzoyl-H^4,phenyl-H), 7.19 (1H, t, benzoyl-H^5), 7.10 (1H, d, H^4), 4.79 (2H, s, CH_2), 3.65 (6H, m, CH_2-benzyl, piperazinyl-$H^{2,6}$), 2.53-2.48 (4H, m, piperazinyl-$H^{3,5}$)
7k	1678, 1650	$CDCl_3$, 8.23 (1H, d, pyridinyl-H^3), 7.97 (1H, s, H^7), 7.84 (1H,d, H^5), 7.58-7.53 (3H, m, benzoyl-$H^{3,6}$, pyridinyl-H^5), 7.30 (1H, d, benzoyl-H^5), 7.19 (1H, m, benzoly-H^4), 7.14 (1H, d, H^4), 6.74-6.68 (3H, m, pyridinyl-$H^{4,6}$), 4.86 (2H,s, CH_2), 3.79-3.78 (6H, m, piperazinyl-H), 3.58-3.56 (2H, m, piperazinyl-H)
7l	1678, 1650	$CDCl_3$, 8.23 (1H, d, pyridinyl-H^3), 7.97 (1H, s, H^7), 7.84 (1H,d, H^5), 7.58-7.53 (3H, m, benzoyl-$H^{3,6}$, pyridinyl-H^5), 7.30 (1H, d, benzoyl-H^5), 7.19 (1H, m, benzoly-H^4), 7.14 (1H, d, H^4), 6.74-6.68 (3H, m, pyridinyl-$H^{4,6}$), 4.86 (2H,s, CH_2), 3.79-3.78 (6H, m, piperazinyl-H), 3.58-3.56 (2H, m, piperazinyl-H),
7m	1685, 1662	DMSO-d_6, 8.25 (1H, d, J=1.15 Hz, H^7), 7.90-7.79 (4H,m, $H^{4,5}$, benzoyl-$H^{2,6}$), 7.72-7.68 (3H, m, benzoyl-$H^{3,4,5}$), 4.35 (2H, t, N-CH_2), 3.66-3.65 (4H, m, morpholinyl-O-CH_2), 3.56-3.52 (4H, m, morpholinyl-N-CH_2), 2.92 (2H, t, CH_2-CO), Anal. Calcd. for $C_{21}H_{20}N_2O_4S$ (369.4), Calcd/Found: C: 63.62/63.48, H: 5.08/4.56, N: 7.07/7.45.
7n	1691, 1665	DMSO-d_6, 8.25 (1H, d, H^7), 7.89 (1H, dd, 6.73 Hz, H^4), 7.86-7.79 (3H, m, H^5, benzoyl-$H^{2,6}$), 7.71-7.68 (3H, m, benzoyl-$H^{3,4,5}$), 7.35 (2H, t, phenyl-$H^{3,5}$),7.06 (2H, d, phenyl-$H^{2,6}$), 6.93 (1H, t, phenyl-H^4), 4.38 (2H, t, N-CH_2), 3.72 (2H, t, piperazinyl-$H^{2(6)}$), 3.68 (2H, t, piperazinyl-$H^{6(2)}$), 3.24-3.19 (4H, m, piperazinyl-$H^{3,5}$), 2.98 (2H, t, CH_2CO)
7o	1690, 1667	DMSO-d_6, 8.26 (1H, d, H^7), 7.89 (1H, dd, H^4), 7.86-7.79 (3H, m, H^5, benzoyl-$H^{2,6}$), 7.72-7.68 (3H, m, benzoyl-$H^{3,4,5}$), 7.20-7.16 (2H, m, phenyl-$H^{3,5}$), 7.10-7.06 (2H, m, phenyl-$H^{2,6}$), 4.37 (2H, t, N-CH_2), 3.71(2H, t, piperazinyl-$H^{2(6)}$), 3.68 (2H, t, piperazinyl-$H^{6(2)}$), 3.17-3.12 (4H, m, piperazinyl-$H^{3,5}$), 2.98 (2H, t, CH_2CO)
7p	1672,	DMSO-d_6, 8.26 (1H, d, H^7), 7.89 (1H, dd, H^4), 7.86-7.79 (3H, m, H^5, benzoyl-$H^{2,6}$), 7.72-7.68 (3H, m, benzoyl-$H^{3,4,5}$), 7.38-7.35 (2H, m, phenyl-$H^{3,5}$), 7.08-

	1640	7.06 (2H, m, phenyl-$H^{2,6}$), 4.37 (2H, t, N-CH_2), 3.71 (2H, t, piperazinyl-$H^{2(6)}$), 3.68 (2H, t, piperazinyl-$H^{6(2)}$), 3.25-3.19 (4H, m, piperazinyl-$H^{3,5}$), 2.98 (2H, t, CH_2CO)
7q	1693, 1667	DMSO-d_6, 8.26 (1H, d, H^7), 7.89-7.80 (4H, m, $H^{4,5}$, benzoyl-$H^{2,6}$), 7.72-7.67 (3H, m, benzoyl-$H^{3,4,5}$), 7.47-7.37 (5H, m, phenyl-H), 4.34 (2H, t, N-CH_2), 3.58 (1H, s, benzyl-CH_2), 3.56 (2H, t, piperazinyl-$H^{2(6)}$), 3.52 (2H, t, piperazinyl-$H^{6(2)}$), 2.90 (2H, t, CH_2CO), 2.43-2.39 (4H, m, piperazinyl-$H^{3,5}$)
7r	1671, 1645	DMSO-d_6, 8.26 (1H, d, J=1.62 Hz, H^7), 7.89-7.80 (4H, m, $H^{4,5}$, benzoyl-$H^{2,6}$), 7.72-7.67 (3H, m, benzoyl-$H^{3,4,5}$), 6.95 (2H, d, benzodioxol-$H^{4,7}$), 6.87-6.85 (1H, m, benzodioxol-H^6), 6.10 (2H, s, O-CH_2-O) 4.34 (2H, t, N-CH_2), 3.55 (2H, t, piperazinyl-$H^{2(6)}$), 3.51 (2H, t, piperazinyl-$H^{6(2)}$), 3.49 (1H, s, CH_2-benzodioxol), 2.90 (2H, t, CH_2CO), 2.40-2.38 (4H, m, piperazinyl-$H^{3,5}$)
7s	1683, 1661	DMSO-d_6, 8.29 (1H, s, H^7), 7.89 (1H, d, H^4), 7.82-7.78 (1H, m, H^5), 7.72-7.67 (2H, m, benzoyl-$H^{3,6}$), 7.54-7.50 (2H, m, benzoyl-$H^{4,5}$), 4.34 (2H, t, N-CH_2), 3.66-3.65 (4H, m, morpholinyl-O-CH_2), 3.55-3.51 (4H, m, morpholinyl-N-CH_2), 2.91 (2H, t, CH_2-CO)
7t	1683, 1636	DMSO-d_6, CDCl3, 8.17 (1H, s, H^7), 7.76 (1H, d, H^5), 7.69-7.67 (13H, m, H^5), 7.59-7.54 (2H, m, benzoyl-$H^{3,6}$), 7.41-7.37 (2H, m, benzoyl-$H^{4,5}$), 7.22 (2H, t, phenyl-$H^{3,5}$),6.93 (2H, d, phenyl-$H^{2,6}$), 6.80 (1H, t, phenyl-H^4), 4.23 (2H, t, N-CH_2), 3.58 (2H, t, piperazinyl-$H^{2(6)}$), 3.54 (2H, t, piperazinyl-$H^{6(2)}$), 3.10-3.05 (4H, m, piperazinyl-$H^{3,5}$), 2.84 (2H, t, CH_2CO)
7u	1691, 1670	DMSO-d_6, 8.17 (1H, s, H7), 7.76 (1H,d, H^5), 7.69-7.67 (1H, m, H^4), 7.58-7.54 (2H, m, benzoyl-$H^{3,6}$), 7.42-7.37 (2H, m, benzoyl-$H^{4,5}$), 7.08-7.06 (2H, m, phenyl-$H^{3,5}$), 6.97-6.93 (2H, m, phenyl-$H^{2,6}$), 4.22 ((2H, t, N-CH_2), 3.57 (2H, t, piperazinyl-$H^{2(6)}$), 3.53 (2H, t, piperazinyl-$H^{6(2)}$), 3.04-2.98 (4H, m, piperazinyl-$H^{3,5}$), 2.83 (2H, t, CH_2CO)
7v	1657	DMSO-d_6, 8.16 (1H, s, H^7), 7.75 (1H,d, H^5), 7.68-7.66 (1H, m, H^4), 7.57-7.53 (2H, m, benzoyl-$H^{3,6}$), 7.40-7.36 (2H, m, benzoyl-$H^{4,5}$), 7.24-7.21 (2H, m, phenyl-$H^{3,5}$), 6.94-6.92 (2H, m, phenyl-$H^{2,6}$), 4.21 ((2H, t, N-CH_2), 3.57 (2H, t, piperazinyl-$H^{2(6)}$), 3.52 (2H, t, piperazinyl-$H^{6(2)}$), 3.10-3.04 (4H, m, piperazinyl-$H^{3,5}$), 2.82 (2H, t, CH_2CO)
7y	1674, 1640	DMSO-d_6, 8.29 (1H, s, H^7), 7.88 (1H,d, H^5), 7.82-7.80 (1H, m, H^4), 7.70-7.66 (2H, m, benzoyl-$H^{3,6}$), 7.54-7.49 (2H, m, benzoyl-$H^{4,5}$), 7.45-7.37 (5H, m, phenyl-H), 4.33 (2H, t, N-CH_2), 3.58 (2H, s, CH_2-benzyl), 3.55 (2H, t, piperazinyl-$H^{2(6)}$), 3.51 (2H, t, piperazinyl-$H^{6(2)}$), 2.89 (2H, t, CH_2CO), 2.40-2.38 (4H, m, piperazinyl-$H^{3,5}$)
7z	1687, 1651	DMSO-d_6, 7.98 (1H, s, H^7), 7.84 (1H,d, H^5), 7.60-7.55 (2H, m, H4, benzoyl-H^3), 7.36-7.29 (2H, m, benzoyl-$H^{6,4}$), 7.22-7.18(1H, m, benzoly-H^5), 6.90-6.72 (3H, m, benzodioxol-$H^{4,6,7}$), 5.99(2H,s, O-CH_2-O), 4.35 (2H, t, N-CH_2), 3.68-3.41 (5H, m, piperazinyl-H), 3.38 (2H, s, CH_2-benzodioxol), 2.84 (2H, t, CH_2CO), 2.34-2.33 (3H, m, piperazinyl-H),

Pharmacology

Animals

Male Swiss albino mice (20–25 g) were used for all experiments. The animals were kept in colony cages (6 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 H_2O and 0.5% sodium carboxymethyl cellulose (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. Either Indomethacin (10 mg/kg) or acetyl salicylic acid (ASA) in 0.5% CMC (100 mg/kg) was used as reference drug.

p-Benzoquinone-induced writhing test

The test was performed according to the method of Okun *et al.* (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) solution in distilled H_2O (PBQ, Merck, Darmstadt, Germany). 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 5th min after the PBQ injection. The data represent average values of the total number of writhes observed. The analgesic activity was expressed as percentage change from writhing controls.

Carrageenan-induced hind paw edema test

The test was performed according to the method of Kasahara *et al* (14). The difference in footpad thickness between the right and left foot was measured with a pair of dial thickness gauge calipers (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 90min during 360 min after induction of inflammation, as described above.

Gastric side ulceration 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

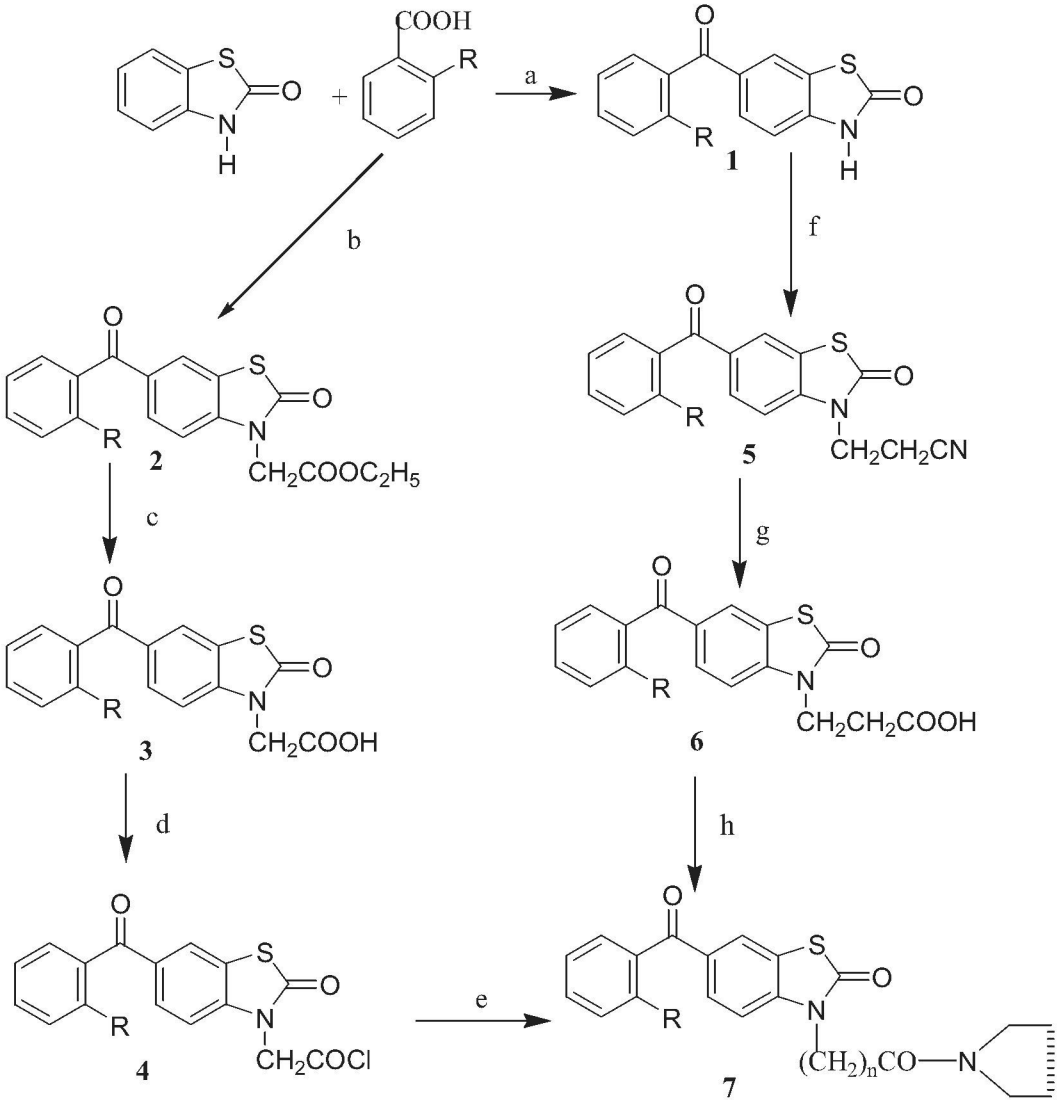
Data obtained from the animal experiments were expressed as the mean standard error (±SEM). Statistical differences between the treatments and the control were tested by ANOVA test. Data with $p < 0.05$ value was considered to be significant.

RESULTS AND DISCUSSION

Chemistry

Synthesis of the title compounds **7a-l** was shown in Scheme 1. The starting material, 2-benzothiazolinone was synthesized according to the previously published method using 2-aminothiophenol and urea (14). 2-Benzothiazolinone was then reacted with benzoic acid derivatives in polyposphoric acid to obtain 6-acyl-2-benzothiazolinone (**1**) (11). The synthesis of ethyl (6-acyl-2-benzothiazolinon-3-yl)acetate (**2**) was performed by the reaction of 6-acyl-2-benzothiazolinone with ethyl bromoacetate. The acid hydrolysis of it gave (6-acyl-2-

benzothiazolinon-3-yl)acetic acid (**3**) (10). **3** was then treated with oxalyl chloride to prepare the corresponding acid chloride (**4**), which was then reacted (without subsequent purification) with appropriate amines to obtain resulting novel acetamide derivatives (**7a-l**) (Scheme 1). For preparation of the title propanamide derivatives, (6-acyl-2-benzothiazolinon-3-yl)propionic acid (**6**) was prepared subsequently acid hydrolyzed of corresponding propionitrile (**5**) which was obtained by the reaction of 6-acyl-2-benzothiazolinone with acrylonitrile [10]. Amidation of **6** with appropriate secondary amine in the presence of ethyl chloroformate in dichloromethane resulted in the synthesis of title propanamide (**7m-z**) with quantitative yield (Scheme 1).



Scheme 1. Synthetic route of the title compounds.

a:PPA, b: Ethyl bromoacetate, potassium carbonate, acetone, c: HCl, H_2O d: Oxalyl chloride, benzene, e: Potassium carbonate, sec.amine, THF, f: Acrylonitrile, TEA, ethanol, g: H_2SO_4 / H_2O / DMF, h: Ethyl cloroformate, sec. amine, dichloromethane

Data on the structure elucidation of the compounds synthesized were given in Table 1 and in Table 2.

Pharmacology

Analgesic activity of the compounds was tested using p-benzoquinone (PBQ)-induced writhing test (13). As shown in Table 3, all the compounds were evaluated for their analgesic activity at a single dose100 mg/kg. The active reference aspirin was included in the analgesic activity test for comparison.

As seen in Table 3, all the acetamide and propanamide derivatives showed lower analgesic activity than aspirin. 3-(6-(2-Fluorobenzoyl)-2-benzothiazolone-3-yl)acetamide derivatives were indicated higher than 3-(6-benzoyl)-2-benzothiazolone-3-yl)acetamide. In addition, 3-(6-acyl-2-benzothiazolone-3-yl)acetamide (**7a-l**) derivatives were showed higher activity than 3-(6-acyl-2-benzothiazolone-3-yl)propanamide (**7m-z**) derivatives. However, the fluoro substitution at the position two on 6-acyl group caused increase in the analgesic activity. Only, compound **7i** (52.8%) showed analgesic activity as well as aspirin. The compound having 6-(2-fluorobenzoyl) group and at the three position (4-fluorophenyl)piperazinyl moiety of 2-benzothiazolone.

Anti-inflammatory activity of the compounds synthesized was evaluated using carrageenan-induced hind paw edema model at 100 mg/kg dose (15). The active reference indomethacin was included in the anti-inflammatory activity test for comparison. It is known that an edema produced by carrageenan is a biphasic event and it is reported that the inhibitory effects of agents which act on the first stage of the carrageenan-induced hind paw inflammation are attributable to the inhibition of the chemical mediators such as histamine, serotonin and bradykinin (16,17). On the other hand, the second stage of the edema might be related to the arachidonic acid metabolites since it is inhibited by aspirin, indomethacin and other cyclooxygenase inhibitors. Anti-inflammatory activities of the synthesized compounds also demonstrated parallel results with their corresponding analgesic activities in which compounds **7i** and **7t** demonstrated the little lower but comparable activity to that of indomethacin. As seen in Table 3, these compounds exhibited considerable anti-inflammatory activities in the second phase of carrageenan-induced edema indicating that these compounds may exert their activities through the inhibition of enzymes which are important in the arachidonic acid cascade, therefore preventing the formation of inflammatory prostaglandins from arachidonic acid. In addition, the microscopic examination of the stomachs of tested animals resulted no gastric lesions and bleeding in most of the compounds.

Table 3. Analgesic and Anti-inflammatory activities of the synthesized compounds (**7a-z**)

Comp.	**Dose (mg/kg)**	**Number of writhing ± SEM Inhibitory ratio (%)**	**Ratio of ulceration**	**Swelling thickness (x10^{-2}mm) ± SEM (inhibition %)**			
				90 min	**180 min**	**270 min**	**360 min**
Control		52.5 ± 4.64	0/6	46.9 ± 3.37	54.0 ± 3.37	57.8 ± 3.65	65.6 ± 4.68
7a	100	46.5 ± 3.88 (11.4)	0/6	49.9 ± 4.02	55.0 ± 4.10	59.3 ± 4.02	66.2 ± 3.97
7b	100	43.8 ± 2.93 (16.6)	0/6	51.1 ± 2.98	56.7 ± 3.01	58.8 ± 3.13	66.9 ± 3.82

7c	100	31.4 ± 2.97 **(40.2)****	0/6	35.8 ± 2.98 (23.7)	37.9 ± 2.15 **(29.8)***	39.3 ± 2.19 **(32.0)****	41.1 ± 2.72 **(37.3)****
7d	100	33.2 ± 2.95 **(36.8)***	0/6	37.4 ± 2.06 (20.3)	40.1 ± 2.97 (25.7)	43.4 ± 2.91 **(24.9)***	45.5 ± 2.98 **(30.6)***
7e	100	41.4 ± 2.19 (21.1)	0/6	47.7 ± 3.01	57.8 ± 3.12	60.1 ± 3.45	68.8 ± 3.92
7f	100	40.8 ± 3.02 (22.3)	3/6	43.3 ± 2.15 (7.7)	47.7 ± 2.92 (11.7)	50.1 ± 3.01 (13.3)	54.4 ± 3.11 (17.1)
7g	100	42.8 ± 3.17 (18.5)	1/6	46.6 ± 4.01	48.9 ± 3.97 (9.4)	50.1 ± 4.12 (13.3)	56.8 ± 4.26 (13.4)
7h	100	40.3 ± 5.52 (23.2)	0/6	46.6 ± 3.45	49.7 ± 2.92 (7.9)	53.3 ± 2.01 (7.8)	55.7 ± 2.87 (15.1)
7i	100	24.8 ± 2.98 **(52.8)*****	0/6	37.9 ± 3.94 (19.2)	39.2 ± 2.22 **(27.4)***	37.8 ± 2.13 **(34.6)****	38.9 ± 2.34 **(40.7)*****
7j	100	30.3 ± 2.61 **(42.3)****	0/6	35.7 ± 3.95 (23.9)	39.5 ± 3.14 (26.9)	38.8 ± 2.13 **(32.9)****	40.1 ± 2.94 **(38.9)****
7k	100	37.8 ± 4.84 (28.0)	0/6	45.3 ± 2.97 (3.4)	47.7 ±3.02 (11.7)	49.8 ± 3.11 (13.8)	51.3 ± 3.17 (21.7)
7l	100	36.7 ± 4.15 (30.1)	2/6	35.5 ± 1.98 (24.3)	38.8 ± 2.01 (28.1)	41.1 ± 2.39 (28.9)	44.2 ± 2.10 **(32.6)****
7m	100	47.5 ± 4.00 (9.5)	0/6	48.3 ± 2.86	54.8 ± 4.05	58.5± 3.32	67.0 ± 4.73
7n	100	53.2 ± 3.13	1/6	45.1 ± 2.10	52.4 ± 2.02	54.4 ± 3.58	64.2 ± 3.69
7o	100	43.6 ± 3.28 (16.9)	0/6	37.1 ± 2.15 (20.9)	39.5 ± 3.07 (26.8)	41.0 ± 2.68 (29.1)	48.2 ± 3.64 (26.5)
7p	100	46.6 ± 5.61 (11.2)	2/6	50.5 ± 1.75	55.1 ± 2.77	58.47 ± 2.75	68.5 ± 3.15
7q	100	52.6 ± 4.11	0/6	45.2 ± 1.53	52.5 ± 2.20	56.7 ± 2.66	64.0 ± 3.63
7r	100	53.2 ± 5.14	0/6	49.3 ± 2.15	54.3 ± 2.76	58.2 ± 2.69	66.4 ± 3.64
7s	100	31.3 ± 4.15 **(40.4)****	1/6	36.7 ± 2.20 (21.7)	39.1 ± 2.76 **(27.6)***	41.0 ± 2.21 **(29.1)***	42.0 ± 2.73 **(35.9)***
7t	100	38.3 ± 2.80 **(27.1)***	0/6	35.6 ± 1.51 (24.0)	38.4 ± 2.68 **(28.9)***	38.7 ± 2.03 **(33.1)****	39.8 ± 2.61 **(39.3)****

7u	100	53.1 ± 6.42	0/6	48.3 ± 1.73	54.5 ± 2.61	60.1 ± 2.75	70.5 ± 4.96
7v	100	30.8 ± 4.04 **(41.3)*****	0/6	36.0 ± 1.47 (23.2)	37.3 ± 2.00 **(30.9)****	37.3 ± 2.19 **(35.5)****	43.4 ± 3.58 **(33.8)****
7y	100	35.1 ± 4.23 **(33.1)****	0/6	34.3 ± 2.86 (26.8)	40.6 ± 3.67 (24.8)	40.7 ± 3.72 (29.6)	46.4 ± 4.67 **(29.2)***
7z	100	49.8 ± 5.33	0/6	49.7 ± 2.92	55.4 ± 3.16	60.6 ± 3.72	72.3 ± 5.64
Indomethacin	10	-	-	33.5 ± 2.89 **(28.6)***	34.0 ± 2.02 **(37.0)****	35.3 ± 2.05 **(38.9)*****	35.6 ± 2.38 **(45.7)*****
ASA	100	23.8 ± 1.74 **(54.7)*****	5/6	-	-	-	-

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