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Synthesis of Some New Pyridylethylated Benzoxa(Thia)zolinones with Analgesic Activitiy

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Eighteen new 3-[2-(2-/4-pyridyl)ethyl]benzoxazolinone(benzothiazolinone) derivatives were synthesized by reacting 2-/4-vinylpyridine and appropriate benzoxazolinones and benzothiazolinones. The analgesic activities of these compounds were investigated by modified Koster and hot-plate tests. Test results revealed that most of the compounds at 100 mg/kg dose levels have higher analgesic activities than acetylsalicylic acid. Compounds with bromo substituents on the phenyl ring in the 6-position of the main ring seemed to show less activity than those with fluorinated ones. Compound **6b** showed remarkably high activity in the hot-plate test, although it was inactive in the Koster test. However compound **3a** had statistically significant high peripheral analgesic activity at all doses compared to other compounds, although it was inactive in the hot-plate test.

Key Words: 2-Benzoxazolinone, 2-Benzothiazolinone, Acylation, Pyridylethyl, Analgesic activity.

Introduction

In recent years considerable attention has been given to the search for new analgesic agents devoid of the side effects typical of morphine-like opioid agonists (such as respiratory depression, constipation and physical dependence) as well as of the gastro-intestinal problems associated with nonsteroidal anti-inflammatory drugs. In this regard a considerable number of 2-benzoxazolinone derivatives endowed with analgesic properties have been reported recently[1−5].

2-Benzoxazolinone is structurally related to 2,4-oxazolidindione, which forms the nucleus of a number of compounds with analgesic and anticonvulsant activities (Figure 1)[6]. Flouzat et al.[7] recently reported new potent analgesics corresponding to the general structure (**I**). These compounds, which contain a 5-membered N-substituted lactamic system, are characterized by the absence of either anti-inflammatory activity or affinity for opioid receptors. According to these results, 2-benzoxazolinone has become a promising group for preventing analgesia. In addition, 5-chloro-2-benzoxazolinone (chlorzoxazone) showing good muscle relaxant effects was found during this research.

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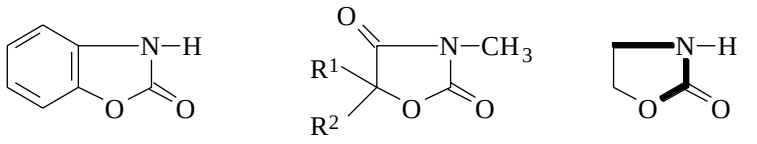
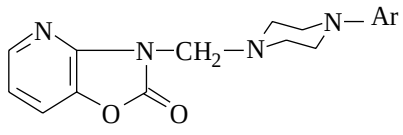


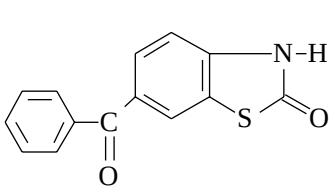
2-Benzoxazolinone Oxazolidinedione Common part

Figure 1

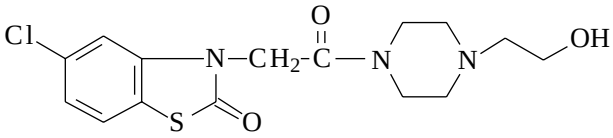
Benzothiazolinone derivatives have also been reported as potent analgesic agents[8,9]. In 1995, Ferreira et al. screened the anti-nociceptive activity of 6-benzoylbenzothiazolinone (**II**) and concluded that it might release an endogenous, opioid-like substance from the adrenal glands to exert anti-nociceptive activity [10]. On the other hand, the discovery of Tiaramide HCl (**III**) (4-[(5-chloro-2-oxo-3-benzothiazolinyl)acetyl]-1-piperazinylethanol hydrochloride) as a useful analgesic and anti-inflammatory agent has led to the synthesis of benzothiazolinone derivatives with the aim of obtaining better anti-inflammatory agents[11,12].



(I)



(II)



Tiaramide HCl

(III)

Previous studies on compounds carrying both 2-benzoxazolinone and ethylpyridine functions in the same molecule have shown that these functions possess analgesic and anti-inflammatory activities[4,5]. Since varying substituents is a common method for drug design in the medicinal chemistry, and as a continuation of previous studies, we aimed to synthesize new condensed oxazole derivatives and to test analgesic activity by *in vivo* tests.

Experimental

All chemicals were obtained from the Aldrich Chemical Co. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 1720X FT infrared spectrophotometer. In the IR spectra, all compounds displayed 2 carbonyl absorption bands at 1810-1672 cm^{-1} and 1681-1647 cm^{-1}. ^{1}H-NMR spectra were recorded using Bruker AC 80 (400) MHz FT NMR spectrometers using $CDCl_3$ and tetramethylsilane as internal standards. Microanalyses were performed by the Scientific and Technical Research Council of Turkey Instrumental Analysis Laboratory (TÜBİTAK). They also confirmed the postulated structure and were within ±0.4% of theoretical values. The purity of the compounds was assessed by Thin Layer Chromatography on silica gel HF $_{254+366}$ (Merck, silica gel, Type 60, 0.25 mm).

6-Acyl-2-benzoxazolinone (2-benzothiazolinone)

These were prepared by treating 2-benzoxazolinone (2-benzothiazolinone or chlorzoxazone) and carboxylic acid in polyphosphoric acid by the method reported earlier[3,13−16].

3-[2-(2-/4-pyridyl)]ethyl-6-acyl-2-benzoxazolinone/2-benzothiazolinone

To 2.5 mmol of 6-acyl-2-benzoxazolinone (2-benzothiazolinone) was added 7.5 mmol of 2- and/4-vinylpyridine, and the reaction mixture was heated under reflux in an oil bath until molten and then for a further 2 h. at 80 ° C. By adding a cold ethanol-water mixture, the product was separated, and the resulting precipitate was collected by filtration[17]. The crude product was recrystallized from different solvents.

Pharmacology

Male Swiss albino mice (20-25 g) were purchased from the animal breeding laboratories of Refik Saydam Hıfzısıhha Institute (Ankara, Turkey). All the animals were left 2 days in laboratory conditions for acclimatization and maintained on a standard pellet diet and water ad libitum before the day of experiment. On the last day food was withdrawn and they were given water only.

Analgesic activity[18]

A modified Koster test was used. Test samples and the reference compound were suspended in 0.5% carboxymethyl cellulose and administered to each mouse with a gastric gavage needle. The control group animals received the same volume of the dosing vehicle; 4-5 animals were used for the preliminary activity screening of the test samples (100 mg/kg). Those possessing more than 20% inhibitory effects were further evaluated in 2 different doses (50 mg/kg and 25 mg/kg) using groups of 6-7 animals. One hour after the administration of the test sample, each mouse was injected intraperitoneally with 3% (w/v) acetic acid solution (0.1 mL/10 g body weight). Starting 5 min after the acetic acid injection, the number of muscular contractions was counted for 10 min. A significant reduction in the level of writhing by any treatment compared to the vehicle-treated animals was considered a positive analgesic response. Analgesic activity was calculated using the formula:

Analgesic activity % :(n-n′)/n × 100

Where n and n' indicate the average number stretching movements in the control and test groups, respectively. Acetylsalicylic acid (ASA) (100 mg/kg, p.o.) was used as a reference analgesic and was administered according to the test protocol. On each day of testing 3 drug treated groups and 1 control group were used. A control group of 5 mice was used on each day of testing because the test is very susceptible to external conditions. At the end of the study, all results were corrected according to the single control group.

Constant temperature hot-plate test[19]

An HTC Inc. Mod. 35-D analgesiameter was set to give a plate temperature of 54 ± 0.5 °C. One hour after oral administration of the compounds (100 mg/kg), the animals were placed on the hot-plate and confined by a lidded perspex box in a compartment measuring 13.8 x 13.8 cm, and the latency to the first hind-paw lick was recorded. If no hind-paw lick occurred, the test was terminated after 30 s. Morphine was used as

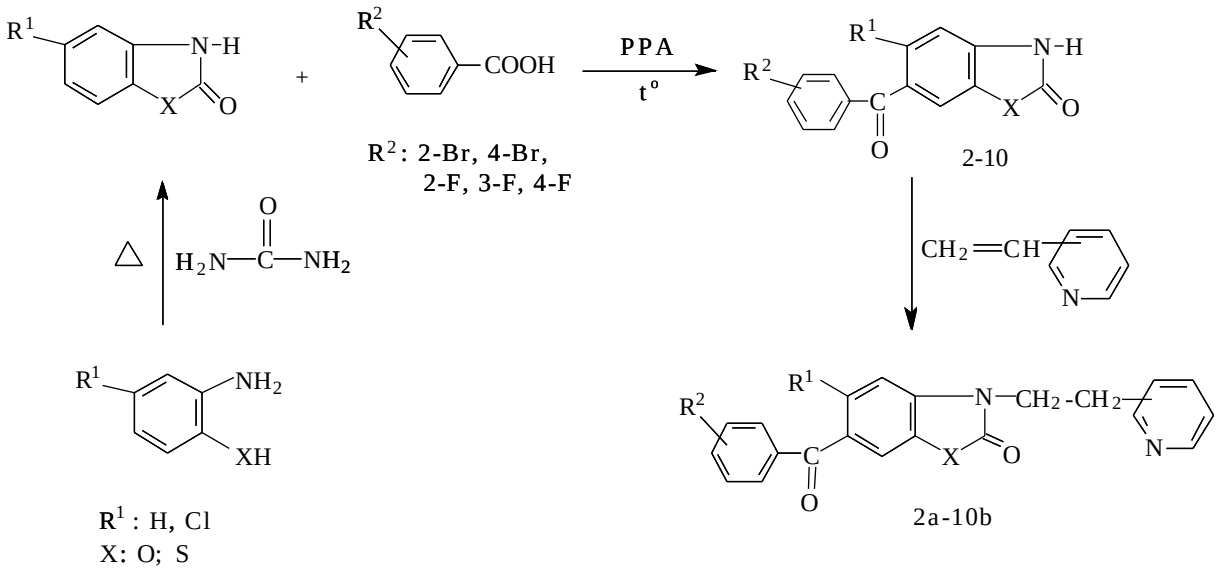
a reference analgesic and administered i.p. at 10 mg/kg. Analgesic activity was calculated according to the equation given above.

Statistical analysis

The statistical significance of test responses was evaluated by one way ANOVA followed by Tukey-Kramer post hoc test with the help of Instat computer software.

Results and Discussion

The synthesis of 2-benzoxazolinone (or 2-benzothiazolinone) was accomplished readily and practically through the reaction of urea with o-aminophenol (o-aminothiophenol) under heat. 6-Acyl-(5-chloro)-2-benzoxazolinone and 2-benzothiazolinone **2-10** required as starting materials were prepared from main compounds and appropriate carboxylic acids according to the method described in the literature[20]. They were converted into 3-[2-(2-and/or 4-pyridyl)ethyl]-2-benzoxazolinone (and 2-benzothiazolinone) in one step by reacting **2-10** with 2-and/or 4-vinylpyridine in an oil bath (Scheme)[17].



Scheme

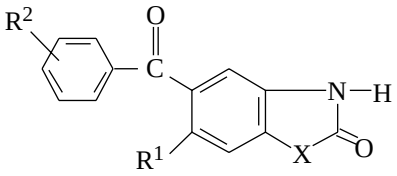
In acylation, since both the 3-nitrogen and 1-oxygen atoms are electron-donating, both the 5- and 6-positions are activated and therefore the regioselectivity in the C-acylation of benzoxazolinone could not be easily predicted.

However, it was reported that the substitution was directed by the nitrogen atom of the benzoxazolinone ring, and only the 6-acyl derivative was formed[21]. We also proved the formation product with ^{1}H-NMR parameters (chemical shifts and coupling constants)[22]. At the same time, the 6-acyl derivative was assigned by X-ray crystallographic analysis[23].

Characteristics belonging to the starting compounds are given in Table 1. Melting points, yields, formulas and spectral characterizations of the main compounds are shown in Table 2. In the ^{1}H-NMR spectra the protons neighboring the nitrogen atom in the benzoxazolinone/benzothiazolinone ring and the

other CH_2 protons were seen as triplet at approximately 4 ppm and 3 ppm, respectively. These results proved that 1,4-addition products were obtained from the reaction of the compounds **2-10** with 2-/4-vinylpyridine. The peaks associated with aromatic protons appeared in the expected regions and integral values. In addition, H-3 proton and H-3/H-5 protons of the pyridine were roughly seen as a doublet of doublets at 8.4 ppm and 8.5 ppm.

Table 1. Melting points, reaction yields and formulas and spectral data of starting compounds 2-10.



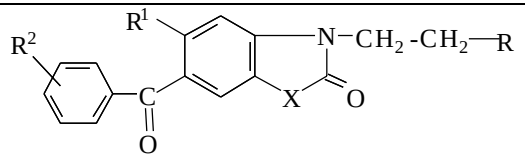
Comp. No.	R^2	R^1	X	Melting point	Yield %	Formula	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CHCl_3$-d_1) δ (ppm)
2	2-Br	H	O	196-198	40	$C_{14}H_8BrNO_3$	3312 1777 1656	6.05-7.6 (7H; m; Aro. prot.), 11-11.8 (1H; s; NH)
3	2-Br	Cl	O	206-207	65	$C_{14}H_7BrClNO_3$	3255 1780 1661	6.7-7.6 (6H; m; Aro. prot.), 11.2 11.6 (1H; s; NH)
4	4-Br	H	O	258-259	67	$C_{14}H_8BrNO_3$	Ref. 3	Ref. 3
5	2-F	Cl	O	185-186	20	$C_{14}H_7ClFNO_3$	Ref. 13	Ref. 13
6	3-F	Cl	O	183	21	$C_{14}H_7ClFNO_3$	Ref. 13	Ref. 13
7	4-F	Cl	O	235	20.5	$C_{14}H_7ClFNO_3$	Ref. 14	Ref. 14
8	2-F	H	S	174-176	64.73	$C_{14}H_8FNO_2S$	Ref 15	Ref 15
9	3-F	H	S	180-182	68	$C_{14}H_8FNO_2S$	Ref 16	Ref 16
10	4-F	H	S	232-233	56	$C_{14}H_8FNO_2S$	Ref 16	Ref 16

Compounds 4-10 were prepared previously [3,13,14-16]

The pharmacological profiles of centrally acting analgesics typically differ from those of peripherally acting ones. The mouse abdominal constriction test can be used to detect both peripherally and centrally acting analgesics, whereas the hot-plate test has been demonstrated to be predictive of centrally acting analgesics. Therefore the analgesic activity of the compounds was determined by both Koster and hot-plate tests.

Some consideration of the structure-activity relationships for this new series can be made on the basis of their pharmacological features. The substituents on the aromatic ring and the pyridine substituent were the determining factors for activity in the acetic acid writhing test. Most of the compounds (except for **4b**, **5a**, **6a** and **6b**) showed analgesic activity of varying magnitudes (36.1% -75.3%) at 100 mg/kg p.o. It is evident from the results that compounds **2a**, **2b**, **3a**, **3b** and **4a,** which were substituted with bromobenzoyl moiety, exhibited better analgesic activity (55.2%, 46.0%, 59.8%, 52.4% and 42.7%, respectively) when compared to the compounds **5a**, **6a** and **6b**, which possessed fluorobenzoyl moiety as a substituent (9.2%, 11.9% and 17.9%, respectively) for 2-benzoxazolinone ring. It was also noted that the presence of an electronegative atom, Cl, in the 5 position of 2-benzoxazolinone in compounds **3a**, **3b**, **7a** and **7b** provides better analgesic activity (59.8%, 52.4%, 50.5% and 61.7%, respectively) than unsubstituted benzoxazolinone derivatives (**2a**: 55.2% and **2b**: 46.0%) (Table 3).

Table 2. Melting points, reaction yields, formulas, IR and ^{1}H-NMR spectroscopic data of compounds 2a-10b.



Comp. No.	R^1	R^2	X	R^3	M.P (°C)	Yield (%)	Formula	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CHCl_3$-d_1) δ (ppm)
2a	H	2-Br	O	4-pyridyl	136-8[1]	85	$C_{21}H_{15}$ Br N_2O_3	1769[a], 1647[b]	2.9-3.2 (2H; t; CH_2-pyr.), 4.0-4.3 (2H; t; CH_2-N), 6.7-7.7 (9H; m; Arom-H., pyr.H_2, H_6), 8.4-8.6 (2H; d; pyr. H_3,H_5)
2b	H	2-Br	O	2-pyridyl	176-8[2]	95	$C_{21}H_{15}$ Br N_2O_3	1752[a], 1661[b]	3.1-3.4 (2H; t; CH_2-pyr.), 4.2-4.5 (2H; t; CH_2-N), 6.05-7.6 (10H; m; Arom-H., pyr.H_4, H_5, H_6), 8.4-8.6 (1H; d; pyr.H_3)
3a	Cl	2-Br	O	4-pyridyl	125-7[3]	40	$C_{21}H_{14}BrClN_2O_3$	1809[a], 1673[b]	2.9-3.2 (2H; t; CH_2-pyr.), 3.9-4.2 (2H; t; CH_2-N), 6.8-7.6 (8H; m; Arom-H., pyr.H_2, H_6), 8.4-8.6 (2H; d; pyr. H_3,H_5)
3b	Cl	2-Br	O	2-pyridyl	143-5[4]	43	$C_{21}H_{14}BrCl$ N_2O_3	1773[a], 1676[b]	3.1-3.4 (2H; t; CH_2-pyr.), 4.1-4.4 (2H; t; CH_2-N), 6.7 -7.7 (9H; m; Arom-H., pyr.H_4, H_5, H_6), 8.4-8.6 (1H; d; pyr.H_3)
4a	H	4-Br	O	4-pyridyl	185-7[5]	60	$C_{21}H_{15}$ BrN_2O_3	1756[a], 1650[b]	2.9-3.1 (2H; t; CH_2-pyr.), 3.9-4.1 (2H; t; CH_2-N), 6.7-7.8 (9H; m; Arom-H., pyr.H_2, H_6), 8.4-8.6 (2H; d; pyr. H_3,H_5)
4b	H	4-Br	O	2-pyridyl	155-7[1]	72	$C_{21}H_{15}BrN_2O_3$	1768[a], 1647[b]	3.1-3.4 (2H; t; CH_2-pyr.), 4.2-4.5 (2H; t; CH_2-N), 6.8-7.6 (10H; m; Arom-H., pyr.H_4, H_5, H_6), 8.4-8.6 (1H; d; pyr.H_3)
5a	Cl	2-F	O	4-pyridyl	139-1[1]	56	$C_{21}H_{14}ClFN_2O_3$	1790[a], 1668[b]	2.9-3.1 (2H; t; CH_2-pyr.), 3.9-4.1 (2H; t; CH_2-N), 6.7-7.8 (8H; m; Arom-H., pyr.H_2, H_6), 8.4 –8.6 (2H; d; pyr. H_3,H_5)
5b	Cl	2-F	O	2-pyridyl	101-3[1]	70	$C_{21}H_{14}ClFN_2O_3$	1780[a], 1660[b]	3.1-3.4 (2H; t; CH_2-pyr.), 4.2-4.5 (2H; t; CH_2-N), 6.8-7.6 (9H; m; Arom-H., pyr.H_4, H_5, H_6), 8.4-8.6 (1H; d; pyr.H_3)
6a	Cl	3-F	O	4-pyridyl	165-6[1]	92	$C_{21}H_{14}ClFN_2O_3$	1810[a], 1681[b]	2.9-3.1 (2H; t; CH_2-pyr.), 4.1-4.3 (2H; t; CH_2-N), 6.9-7.5 (8H; m; Arom-H., pyr.H_2, H_6), 8.4-8.6 (2H; d; pyr. H_3,H_5)
6b	Cl	3-F	O	2-pyridyl	115-6[1]	42	$C_{21}H_{14}ClFN_2O_3$	1673[b]	3.1-3.4 (2H; t; CH_2-pyr.), 4.1-4.3 (2H; t; CH_2-N), 6.9-7.5 (9H; m; Arom-H., pyr.H_4, H_5, H_6), 8.5-8.6 (1H; d; pyr.H_3)

Table 2. Contunie

Comp. No.	R^1	R^2	X	R^3	M.P (°C)	Yield (%)	Formula	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CHCl_3$-d_1) δ (ppm)
7a	Cl	4-F	O	4-pyridyl	174-6[4]	50	$C_{21}H_{14}ClFN_2O_3$	1782[a], 1671[b]	2.3-2.7 (2H; t; CH_2-pyr.), 3.4-3.7 (2H; t; CH_2-N), 6.5-7.3 (8H; m; Arom-H., pyr.H_2, H_6), 7.8-7.9 (2H; d; pyr. H_3,H_5)
7b	Cl	4-F	O	2-pyridyl	133-5[4]	30	$C_{21}H_{14}ClFN_2O_3$	1783[a], 1671[b]	3.1-3.4 (2H; t; CH_2-pyr.), 4.1-4.3 (2H; t; CH_2-N), 6.9-7.5 (9H; m; Arom-H., pyr.H_4, H_5, H_6), 8.5-8.6 (1H; d; pyr.H_3)
8a	H	2-F	S	4-pyridyl	196-8[4]	76	$C_{21}H_{15}FN_2O_2S$	1687[a], 1651[b]	2.8-3.1 (2H; t; CH_2-pyr.), 4.1-4.4 (2H; t; CH_2-N), 7.1-8.1 (8H; m; Arom-H., pyr.H_2, H_6), 8.3-8.5 (2H; d; pyr. H_3,H_5)
8b	H	2-F	S	2-pyridyl	104-6[4]	78	$C_{21}H_{15}FN_2O_2S$	1696[a], 1651[b]	2.8-3.3 (2H; t; CH_2-pyr.), 4.2-4.4 (2H; t; CH_2-N), 6.9-8.1 (9H; m; Arom-H., pyr.H_4, H_5, H_6), 8.3-8.5 (1H; d; pyr.H_3)
9a	H	3-F	S	4-pyridyl	177-8[2]	31	$C_{21}H_{15}FN_2O_2S$	1691[a], 1652[b]	2.6-3.1 (2H; t; CH_2-pyr.), 4.0-4.3 (2H; t; CH_2-N), 7.0-7.6 (8H; m; Arom-H., pyr.H_2, H_6), 8.1-8.3 (2H; d; pyr. H_3,H_5)
9b	H	3-F	S	2-pyridyl	107-9[4]	40	$C_{21}H_{15}FN_2O_2S$	1680[a], 1651[b]	2.5-2.9 (2H; t; CH_2-pyr.), 3.7-4.1 (2H; t; CH_2-N), 6.5-7.3 (9H; m; Arom-H., pyr.H_4, H_5, H_6), 7.9-8.2 (1H; d; pyr.H_3)
10a	H	4-F	S	4-pyridyl	145-7[4]	30	$C_{21}H_{15}FN_2O_2S$	1672[a], 1651[b]	2.8-3.2 (2H; t; CH_2-pyr.), 4.0-4.3 (2H; t; CH_2-N), 6.8-8.0 (8H; m; Arom-H., pyr.H_2, H_6), 8.1-8.4 (2H; d; pyr. H_3,H_5)
10b	H	4-F	S	2-pyridyl	158-1[4]	42	$C_{21}H_{15}FN_2O_2S$	1690[a], 1652[b]	3.0-3.3 (2H; t; CH_2-pyr.), 4.1-4.5 (2H; t; CH_2-N), 7.0-8.1 (9H; m; Arom-H., pyr.H_4, H_5, H_6), 8.3-8.5 (1H; d; pyr.H_3)

1: Chloroform-n-hexane, 2: Dioxan-water, 3: Isopropanol-water, 4. Ethanol-water, 5: Ethanol-acetone
a: lactam, b: ketone,

Table 3. Percentage analgesic activity of compounds 2a-10b.

Compounds	(% inh) (n = 4-5) 100 mg/kg	(% inh) (n = 5-6) 50 mg/kg	(% inh) (n = 5-6) 25 mg/kg
2 a	16.5 ± 0.9 (55.2%)	26.6 ± 2.2*** (27.7%)	22.2 ± 1.2*** (39.7%)
2 b	19.9 ± 2.1 (46.0%)	21.1 ± 1.1*** (42.7%)	22.2 ± 1.3*** (39.7%)
3 a	14.8 ± 2.7* (59.8%)	16.8 ± 1.0*** (54.3%)	10.8 ± 1.1*** (70.7%)
3 b	17.5 ± 1.9 (52.4%)	19.1 ± 1.6*** (48.1%)	31.2 ± 1.5 (15.2%)
4 a	21.1 ± 7.5 (42.7%)	20.4 ± 1.4*** (44.6%)	26.4 ± 1.2*** (28.3%)
4 b	36.0 ± 6.7 (2.2%)	—	—
5 a	33.4 ± 0.2 (9.2%)	—	—
5 b	23.5 ± 6.8 (36.1%)	18.6 ± 1.3*** (49.5%)	24.8 ± 1.0*** (32.6%)
6 a	32.4 ± 1.4 (11.9%)	—	—
6 b	30.2 ± 5.7 (17.9%)	—	—
7 a	18.2 ± 3.6 (50.5%)	25.5 ± 1.5*** (30.7%)	22.6 ± 2.2*** (38.6%)
7 b	14.1 ± 3.2* (61.7%)	13.7 ± 0.6*** (62.8%)	19.0 ± 2.3*** (48.4%)
8 a	23.5 ± 8.2 (36.1%)	18.4 ± 1.0*** (50.0%)	29.2 ± 1.0** (20.6%)
8 b	9.1 ± 3.6*** (75.3%)	22.8 ± 2.4*** (38.0%)	24.8 ± 1.0*** (32.6%)
9 a	21.5 ± 2.6 (41.6%)	25.4 ± 1.7 *** (30.9%)	24.4 ± 1.2*** (33.7%)
9 b	21.5 ± 2.8 (41.6%)	22.0 ± 1.4*** (40.2%)	16.8 ± 0.9*** (54.3%)
10 a	15.6 ± 2.6* (57.6%)	11.2 ± 1.3*** (69.6%)	16.8 ± 0.9*** (54.3%)
10 b	21.5 ± 7.0 (41.6%)	25.1 ± 1.4*** (31.8%)	26.4 ± 1.2*** (28.2%)
Control	36.8 ± 0.9		
ASA 100 mg/kg	15.9 ± 1.4* (56.8 %)		

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Compounds having 2-benzothiazolinone nucleus **8a-10b** exhibited some analgesic activity, from moderate to significant levels (36.1% -75.3%).

Compounds **3a**, **7b** and **10a** caused reductions in the number of abdominal constrictions of 59.8%, 61.7% and 57.6%, respectively, and thus these compounds appeared to be more active than ASA at this dose level. Compound **8b**, however, emerged as a compound of particular interest at 100 mg/kg (75%) since most of the treated animals were protected from the effects of the noxious chemical stimulus. It is significant

to note from the observation that the compounds carrying 2-ethylpyridine group in the 3 position (**5b**, **6b**, **7b**, **8b** and **9b**) showed more analgesic activity (36.1%, 17.9%, 61.7%, 75.3% and 41.6% respectively) in comparison to compounds carrying the 4-ethylpyridine group among the compounds having fluorobenzoyl moiety in the 6 position, whereas substitution with the 4-ethylpyridyl group as seen in compounds **2a**, **3a** and **4a** bearing bromobenzoyl moiety in the 6 position exhibited maximal analgesic activity (55.2%, 59.8% and 42.7%). According to ED_{50} values (95% confidence interval) and while compounds **3a** [32.8 mg (9.6-111 mg)] and **7b** [28.8 mg (22.4-37.2 mg] are equally potent, compound **10a** [7.5 mg (3.0 mg-18.5 mg), which bears 4-fluorobenzoyl in the 6 position and 4-pyridyl in the 3 position of the benzothiazolinone ring, is the most potent analgesic agent in this series.

Constant temperature hot-plate test results (Figure 2) were in good accordance with the Koster analgesic activity test for compounds **7a**, **7b**, **8a**, **10a** and **10b**. Furthermore, compound **6b** showed remarkably high activity (154%) in the hot-plate test although it was inactive in the Koster test. As seen in Table 4, compound **3a** has significantly high peripheral analgesic activity at all doses compared to other compounds, although it was inactive in the hot-plate test. The lack of activity in the hot-plate test for this compound, which was associated with a potent antinociceptive property in the acetic acid writhing test, was in favor of a peripherally acting agent without central analgesic effects.

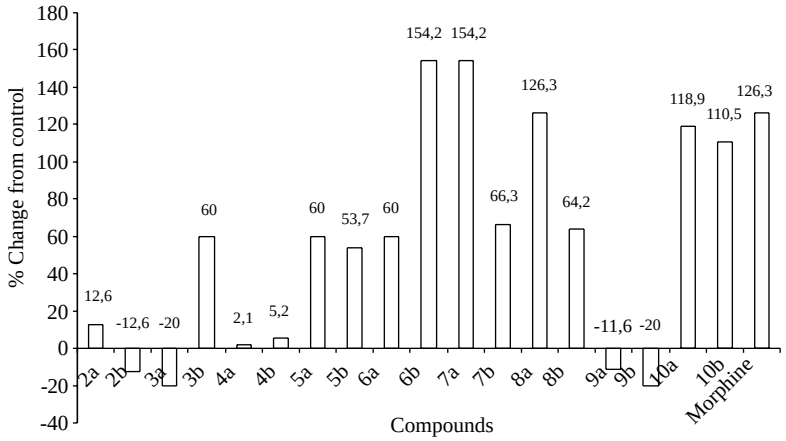


Figure 2. Constant temperature hot plate test.

These results suggest that the 2-benzo(thia)oxazolinone ring may play a significant role in the management of pain. The structure-activity relationships of our series of derivatives are not fully understood. This is due to the partially contradictory results so far obtained. Convergent results indicate that compound **3a** has a peripheral analgesic activity, while compound **6b** shows a remarkably high effect on central analgesic activity. However, the mechanism underlying their antinociceptive activity remains to some degree unknown. A role by other systems that implicate dopaminergic, seratonergic or noradrenergic interactions cannot be ruled out. Thus further studies are essential to ascertain the mechanisms involved in the analgesic properties of the ring system.

References

1. H. Erdoğan, M. Debaert and J.C.Cazin, **Arzneim.-Forsch./Drug Res**. **41,** 73-76 (1991).

2. E. Palaska, S. Ünlü, H. Erdoğan, C. Şafak, B. Gümüşel and R. Demirdamar, **Eur. J. Med. Chem**. **28**, 963-967 (1993).
3. N. Gökhan, H. Erdoğan, N.T. Durlu and R. Demirdamar, **Eur. J. Med. Chem**. **31,** 625-628 (1996).
4. N. Gökhan, H. Erdoğan, N.T. Durlu and R.Demirdamar, **Archiv der Pharmazie Pharm. and Medicinal Chem**. **332,** 43-50 (1999).
5. E. Palaska, N. Gökhan, H. Erdoğan, B.C. Tel and R.Demirdamar, **Arzneim.-Forsch./Drug Res**. **49,** 754-758 (1999).
6. W.J. Close, B.D. Tiffany and M.A. Spielman, **J. Am. Chem. Soc**. **71,** 1265, (1949).
7. C. Flouzat, Y. Besson, A. Mattio, J. Bonnet and G. Guillaumet, **J. Med. Chem. 36,** 497-503 (1993).
8. D. Lesieur, C. Lespagnol and S.Yous, Eur. Patent No. 395 526 (1990). (Chem. Abstr. 114 164208x, 1991).
9. Fujisawa Pharmaceutical Co. Ltd., Jpn. Kokai Tokkyo Koho JP 5 953 475 [8453475] (1984) (Chem Abstr. 101 90983d, 1984).
10. S.H. Ferreira, B.B. Lorenzotti, M. Devissaguet, D. Lesieur and Y.Tsouderos, **Br. J. Pharmacol. 114,** 303-308 (1995).
11. T. Takashima, Y. Kadoh, S. Kumada, T. Takashima, Y. Kadoh and S. Kumada, **Arzneim.-Forsch./Drug Res. 22,** 711-715 (1992).
12. K. Tsurumi, Y. Hiramatsu, M. Nozaki, M. Hayashi and H. Fujimura, **Arzneim.-Forsch./Drug Res. 22,** 716-724 (1972).
13. G. Pilli, H. Erdoğan and R. Sunal, **Arzneim.-Forsch./Drug Res**. **43,** 12-15 (1993).
14. A. Temizer, N. Özaltın and H. Erdoğan, **Port. Electroc. Acta 5,** 33-41 (1987).
15. O.I. Petrov, A.T. Antonova, V.B. Kalcheva and C.G. Veleva, **Dokl. Bulg. Akad. Nauk. 47,** 31-34 (1994).
16. H. Uçar, K. Van Derpoorten, P. Depovere, D. Lesieur, M. Isa, B. Masereel, J. Delarge and J. H. Poupaert, **Tetrahedron 54,** 1763-1772 (1998).
17. S.L. Shapiro, I.M. Rose and L. Freedman, L, **J. Am. Chem. Soc. 79,** 2811-2814 (1957).
18. R. Koster and M. Anderson, **Fed. Proc. 18,** 412 (1959).
19. J.H. Rosland, S. Hunskaar, O.J. Broch and K. Hole,.**Pharmacol. Toxicol. 70,** 31-37 (1992).
20. J.P. Bonte, D. Lesieur, C. Lespagnol and J.C. Cazin, **Eur. J. Med. Chem.-Chim. Ther. 9,** 491-498 (1974).
21. H. Aichaoui, J.H. Poupaert, D. Lesieur and J.P. Hénichart, **Tetrahedron 47,** 6649-6654 (1991).
22. N. Gökhan, H. Erdoğan, N.T. Durlu and R. Demirdamar, **Il Farmaco 54,** 112-115 (1999).
23. P.G. Mairesse, J.C. Boivin, D.J. Thomas, M.C. Bermann, J.P. Bonte and D. Lesieur, **Acta Cryst**. **C40,** 1019-1020 (1984).