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4-(5-Chloro-2(3H)-benzoxazolon-3-yl) Butanoic Acid Derivatives: Synthesis, Antinociceptive and Anti-inflammatory Properties

In this study, 4-(5-chloro-2(3H)-benzoxazolone-3-yl)butanoic acid and its ethyl ester as well as its ten new amide derivatives have been synthesized. Their structures have been elucidated by IR, ^{1}H-NMR spectra and elemental analysis. The compounds were screened for antinociceptive and anti-inflammatory activities. The highest antinociceptive and anti-inflammatory activities were exhibited by Compound **11** which has carboxylic acid structure. A various decrease in antinociceptive and anti-inflammatory activity was observed by amidation of the carboxylic acid moiety of this compound.

Keywords: 2(3H)-Benzoxazolone; Butanamides; Synthesis; Antinociceptive; Anti-inflammatory

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Introduction

Considerable numbers of research efforts on developing new analgesic and anti-inflammatory drugs are being made since the many of the currently used non- steroidal anti-inflammatory drugs (NSAIDs) have serious side effects including gastrointestinal and renal toxicity. Therefore, developing agents without or with minimal side effects is an evolving area in the design of new NSAIDs.

Although 2(3H)-benzoxazolone derivatives which have been associated with various types of biological properties such as hypnotic, antipyretic, muscular relaxant and antibacterial [1–5], this class of compounds have emerged during the last two decades as potential analgesic and anti-inflammatory agents.

After the report made by Close and co-workers [6] on the analgesic activities of 2(3H)-benzoxazolones, they have been structurally modified at the positions 3, 5 and 6 in order to screen for their antinociceptive properties.

Renard [7] and Lespagnol [8] synthesized 3-alkanoic acid derivatives of 2(3H)-benzoxazolone with analgesic activity activities that were more potent than aspirin.

(6-Acyl-2(3H)-benzoxazolone-3-yl)alkanoic acid and ethyl ester derivatives also exhibited analgesic activity [9].

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Meanwhile, Dogruer reported the antinociceptive and anti-inflammatory activities of some (2(3H)-benzoxazolon-3-yl) and (2(3H)-benzothiazolon-3-yl)acetic acid derivatives [10–11]. Onkol and co-workers pointed out that (2(3H)-benzoxazolon-3-yl)propanamide and propanoic acid derivatives also had more pronounced antinociceptive and anti-inflammatory activity than the corresponding acetic acid derivatives [12–13].

These studies have directed us to synthesize new 2(3H)-benzoxazolone derivatives carrying butanamide moiety in the position 3 of the ring and to test their antinociceptive, anti-inflammatory activities at 100 mg/kg single dose.

Results and discussion

Chemistry

4-(5-chloro-2(3H)-benzoxazolon-3-yl)butanoic acid and its ethyl ester as well as its ten new amide derivatives were synthesized by using 2(3H)-benzoxazolone as the starting material. The chemical structures of the synthesized compounds are reported in Table 1 and a scheme of the synthetic route is shown in Figure 1.

In the synthesis of title compounds, the sodium salt of 5-chloro-2(3H)-benzoxazolone was prepared by treating 2(3H)-benzoxazolone with sodium ethoxyde in absolute ethanol and evaporated to dryness. Then, the sodium salt was reacted with ethyl 4-chlorobutanoate. The product of this reaction was hydrolyzed to free acid in the presence of acid catalyst. After treatment of free acid

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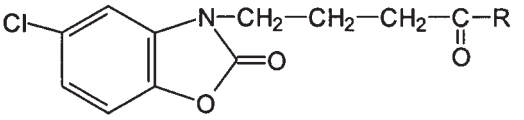
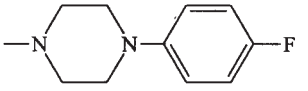
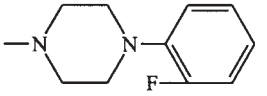
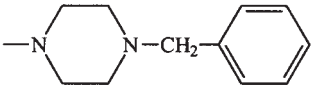
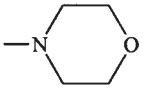
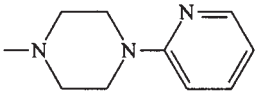
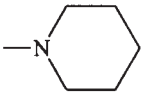
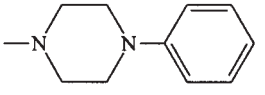
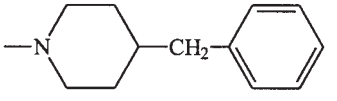
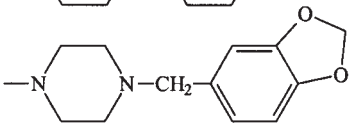
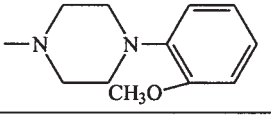
Table 1. Chemical structures of synthesized compounds.



Compound	R	Compound	R
1		7	
2		8	
3		9	
4		10	
5		11	—OH
6		12	$—OC_2H_5$

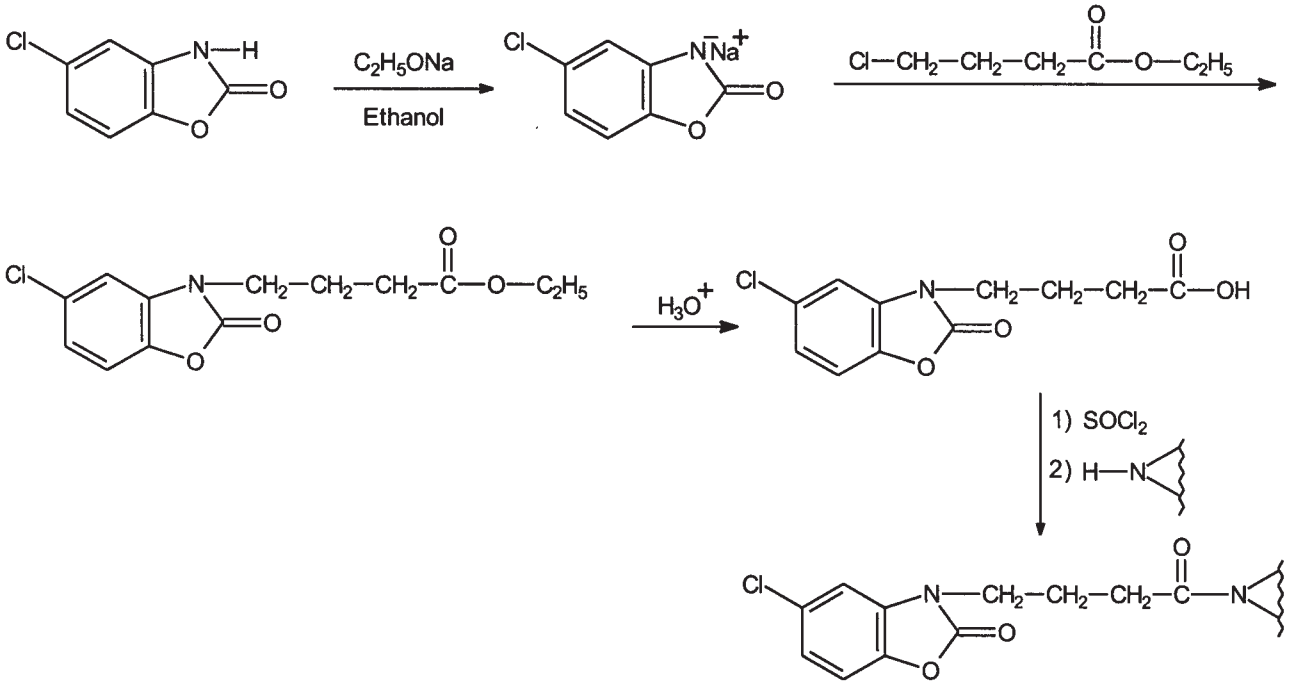


Figure 1. Synthetic route of the title compounds.

Table 2. Antinociceptive activity of compounds **1–12**.

Compound	Number of writhing ± SD	Antinociceptive activity (%)	Gastric lesion incidence in tested animals
Control	33 ± 4.86		0/6
1	23.5 ± 4.42	28.8**	0/6
2	13 ± 3.16	60.6***	2/6
3	18.5 ± 3.45	43.9***	1/6
4	28.0 ± 5.47	15.2	0/6
5	16 ± 4.47	51.5***	0/6
6	13 ± 2.76	60.6***	0/6
7	22.7 ± 2.73	31.2**	0/6
8	10.7 ± 2.50	67.6***	0/6
9	12.2 ± 2.14	63.0***	0/6
10	14 ± 3.74	57.6***	0/6
11	10 ± 2.00	69.7***	0/6
12	18.8 ± 3.43	43.0***	0/6
Aspirin	16.3 ± 3.39	50.6***	1/6

*: $p < 0.05$ **: $p < 0.01$ ***: $p < 0.001$

with $SOCl_2$, the amide derivatives were obtained by the reaction of acid chloride with appropriate amines.

In the IR spectra of butanamide derivatives, carbonyl stretching bands of the amide function were seen at about 1635–1650 cm^{-1} and the 2(3H)-benzoxazolone ring was seen at about 1760–1780 cm^{-1}. The data of the IR and ^{1}H-NMR spectra are presented in the monographs of the compounds.

Pharmacology

The antinociceptive and anti-inflammatory activities of the compounds were screened by the p-benzoquinone-induced stretching test and carrageenan- induced paw edema model using aspirin and indomethacin as the references, respectively.

According to the test results (Table 2 and 3), the highest antinociceptive and anti-inflammatory activities were exhibited by Compound **11**, which has carboxylic acid

Table 3. Anti-inflammatory activity of the compounds **1–12**.

Compound	Dose mg/kg	Swelling in thickness (× 10^{-2} mm) ± SEM (% Inhibition)			
		90 min	180 min	270 min	360 min
Control		40.2 ± 4.61	46.0 ± 4.07	52.8 ± 3.91	59.0 ± 4.03
1	100	32.2 ± 3.36 **(19.6)**	38.8 ± 2.49 **(15.6)**	39.0 ± 2.32 **(26.1)***	44.5 ± 1.96 **(24.5)****
2	100	32.7 ± 3.44 **(18.6)**	38.8 ± 3.55 **(15.6)**	39.2 ± 3.51 **(25.7)***	38.2 ± 2.65 **(35.2)****
3	100	34.5 ± 3.09 **(14.1)**	37.2 ± 1.11 **(19.1)**	40.5 ± 1.23 **(23.2)***	42.8 ± 1.74 **(27.4)****
4	100	36.7 ± 3.35 **(8.7)**	41.7 ± 3.38 **(9.3)**	42.8 ± 2.26 **(18.9)**	47.7 ± 3.72 **(19.1)**
5	100	35.2 ± 4.36 **(12.4)**	36.5 ± 2.57 **(20.6)**	38.0 ± 2.35 **(28.0)****	38.0 ± 3.49 **(33.9)****
6	100	31.3 ± 2.88 **(22.0)**	36.0 ± 3.25 **(21.7)**	36.0 ± 2.73 **(31.8)****	36.8 ± 3.88 **(37.6)****
7	100	33.8 ± 2.75 **(15.9)**	40.2 ± 2.49 **(12.6)**	41.5 ± 3.57 **(21.4)**	43.3 ± 2.49 **(26.6)****
8	100	34.3 ± 3.09 **(14.6)**	35.5 ± 2.23 **(22.8)***	35.2 ± 2.10 **(33.3)****	37.3 ± 2.23 **(36.7)*****
9	100	35.7 ± 3.84 **(11.1)**	36.3 ± 3.58 **(21.0)**	34.0 ± 3.52 **(35.6)****	36.3 ± 2.74 **(38.4)*****
10	100	36.5 ± 2.59 **(03.4)**	40.2 ± 2.98 **(14.1)**	41.0 ± 2.76 **(29.1)***	43.8 ± 4.39 **(34.8)****
11	100	34.2 ± 3.95 **(14.9)**	33.5 ± 3.80 **(27.1)***	35.0 ± 3.19 **(33.7)****	32.0 ± 1.61 **(45.7)*****
12	100	35.0 ± 3.45 **(12.9)**	40.0 ± 3.72 **(13.0)**	42.3 ± 3.53 **(19.8)**	43.0 ± 2.97 **(27.1)****
Indomethacin	10	26.5 ± 2.06 **(29.9)***	27.3 ± 1.91 **(41.7)****	27.2 ± 2.76 **(52.9)*****	29.0 ± 1.07 **(56.8)*****

*: $p < 0.05$ **: $p < 0.01$ ***: $p < 0.001$

structure. A various decrease in antinociceptive and anti-inflammatory activity was observed in the amide derivatives of these compounds. The amide derived from Compound **11** with 4-(2- or 4-flouorophenyl)piperazine resulted in the lowest antinociceptive and anti-inflammatory activity (Compound **1** and **7**). However, Compound **2**, **6**, **8**, **9**, **10** and **11** showed higher antinociceptive activity than aspirin, although anti-inflammatory activities of these compounds are lower than that of indomethacin. Compounds **2**, **6**, **8** and **9** showed the highest biological activity among the amide derivatives. The most active compounds except compound Compound **2** caused no gastric side effect. Therefore, we aim to search the inhibition effects of all compounds on COX enzymes.

Experimental

Chemistry

All the chemicals were purchased from E. Merck (Darmstadt, FRG) and Aldrich (Milwaukee, WI USA) locally. Melting points were determined on Electrothermal Melting Point Apparatus and are uncorrected. IR spectra were recorded on Bruker Vector 22. ^{1}H-NMR spectra were recorded on Bruker 400 MHz in DMSO-d_6 with tetramethylsilane as the internal standard. Elemental analyses were determined in Turkish Scientific and Technological Research Center, Ankara (Turkey), and the results were within the range of ± 0.4 % of calculated values.

Ethyl 4-(5-chloro-2(3H)-benzoxazolon-3-yl)butanoate (**12**) [14]

2(3H)-benzoxazolone (0.01 mol) was reacted with equimolar sodium ethoxyde in ethanol to synthesize sodium salt of 5-chloro-2(3H)-benzoxazolone. After evaporating to dryness an equimolar amount of ethyl 4-chlorobutanoate was added to the solution of sodium salt of 5-chloro-2(3H)-benzoxazolone in 30 mL DMF. The mixture was heated at 80 °C for 8 h., then cooled to room temperature and poured into ice-water. The precipitate formed was filtered and crystallized from ethanol-water (yield 85 %, m.p. 42 °C). ^{1}H-NMR (DMSO-d_6). – δ 7.31–7.11 (m, 3 H, 2-benzoxazolinone-H^{4-6-7}), 4.29 (q, 2 H, -O-CH_2-), 4.0 (t, 2 H, -N-CH_2-), 2.56 (t, 2 H, -CH_2-CO-), 2.23 (m, 2 H, -C-CH_2-C-), 1.41 ppm (t, 3 H, -O-C-CH_3). IR (KBr cm^{-1}). – 1778 (C=O lactam), 1724 (C=O ester). Anal. $C_{13}H_{14}ClNO_4$.

4-(5-Chloro-2(3H)-benzoxazolinon-3-yl)butanoic acid (**11**)

Ethyl [4-(5-chloro-2(3H)-benzoxazolinon-3-yl)]butanoate (0.01 mol) was dispersed in 30 mL concentrate HCl (37 %) and refluxed for 0.5 h. The mixture was cooled, filtered and the precipitate was crystallized from water (yield 95 %, m.p. 150 °C). ^{1}H-NMR (DMSO-d_6). – δ 7.22–6.96 (m, 3 H, 2-benzoxazolinone-H^{4-6-7}), 3.92 (t, 2 H, -N-CH_2-), 2.51 (t, 2 H, -CH_2-CO), 2.13 (m, 2 H, -C-CH_2-C-). IR (KBr cm^{-1}). – 1758 (C=O lactam), 1700 (C=O acid). Anal. $C_{11}H_{10}ClNO_4$.

4-(5-Chloro-2(3H)-benzoxazolon-3-yl)butanamide derivatives (**1–10**) [10]

Thionyl chloride (0.012 mol) was added to the solution of 4-(5-chloro-2(3H)-benzoxazolon-3-yl)butanoic acid (0.01 mol) in dichloromethane. After refluxing for 5 h the solution was evaporated to dryness and the residue was dissolved in 30 mL dichloromethan. The solution of triethylamine (0.01 mol) and appropriate amine derivative (0.01 mol) in 20 mL dichloromethane was added dropwise to the solution with stirring at 0 °C. The solution was stirred for further 30 min. and evaporated to dryness. The residue was dissolved in 30 mL acetone, triethylamine hydrochloride was filtered off by suction filtration and then the product was collected by evaporating to dryness and crystallizing from appropriate solvent.

1-[4-(5-Chloro-2(3H)-benzoxazolon-3-yl)butanoyl]-4-(4-fluorophenyl)piperazine (**1**)

Crystallized from ethanol (yield 49 %, m.p. 69 °C). ^{1}H-NMR (DMSO-d_6). – δ 7.06–6.6 (m, 7 H, 2-benzoxazolinone-H^{4-6-7} and phenyl-H$^{2-3-5-6}$), 3.84 (t, 2 H, butanoyl-H^4), 3.65 (t, 2 H, piperazine-H$^{6(2)}$), 3.42 (t, 2 H, piperazine-H$^{2(6)}$), 2.94 (m, 4 H, piperazine-H$^{3-5}$), 2.31 (t, 2 H, -CH_2-CO-), 2.03 ppm (m, 2 H, butanoyl-H^3). IR (KBr cm^{-1}). – 1772 (C=O lactam), 1638 (C=O amide). Anal. $C_{21}H_{21}ClFN_3O_3$.

1-[4-(5-Chloro-2(3H)-benzoxazolone-3-yl)butanoyl]-4-benzylpiperazine (**2**)

Crystallized from ethanol (yield 55 %, m.p. 89 °C). ^{1}H-NMR (DMSO-d_6). – δ 7.32–7.06 (m, 5 H, phenylH$^{2-3-4-5-6}$), 7.06–6.85 (m, 3 H, 2-benzoxazolinone-H^{4-6-7}), 3.79 (t, 2 H, butanoyl-H^4), 3.51 (t, 2 H, piperazine-H$^{6(2)}$), 3.42 (s, 2 H, -N-CH_2-Ph), 3.29 (t, 2 H, piperazine-H$^{2(6)}$), 2.30 (m, 6 H, piperazine-H$^{3-5}$ and -CH_2-CO-), 1.97 ppm (m, 2 H, butanoyl-H^3). IR (KBr cm^{-1}). – 1784 (C=O lactam), 1637 (C=O amide). Anal. $C_{22}H_{24}ClN_3O_3$.

1-[4-(5-Chloro-2(3H)-benzoxazolon-3-yl)butanoyl]-4-(2-pyridinyl)piperazine (**3**)

Crystallized from ethanol (yield 55 %, m.p. 124 °C). ^{1}H-NMR (DMSO-d_6). – δ 8.12 (d, 1 H, pyridine-H^6), 7.39 (t, 1 H, pyridine-H^4), 6.81–7.07 (m, 3 H, 2-benzoxazolinone-H^{4-6-7}), 6.52 (m, 2 H, pyridine-H$^{3-5}$), 3.70 (t, 2 H, butanoyl-H^4), 3.64 (t, 2 H, piperazine-H$^{6(2)}$), 3.50 (t, 2 H, piperazine-H$^{2(6)}$), 3.40 (m, 4 H, piperazine-H$^{3-5}$), 2.31 (t, 2 H, -CH_2-CO-), 2.01 ppm (m, 2 H, butanoyl-H^3). IR (KBr cm^{-1}). – 1780 (C=O lactam), 1639 (C=O amide). Anal. $C_{20}H_{21}ClN_4O_3$.

1-[4-(5-Chloro-2(3H)-benzoxazolon-3-yl)butanoyl]-4-phenylpiperazine (**4**)

Crystallized from ethanol (yield 40 %, m.p. 105 °C). ^{1}H-NMR (DMSO-d_6). – δ 7.29–7.06 (m, 2 H, phenyl-H$^{2-6}$), 7.06–6.89 (m, 3 H, 2-benzoxazolinone-H^{4-6-7}), 6.89–6.64 (m, 3 H, phenyl-H^{3-4-5}), 3.83 (t, 2 H, butanoyl-H^4), 3.66 (t, 2 H, piperazine-H$^{6(2)}$), 3.45 (t, 2 H, piperazine-H$^{2(6)}$), 3.05 (m, 4 H, piperazine-H$^{3-5}$), 2.32 (t, 2 H, -CH_2-CO-), 2.02 ppm (m, 2 H, butanoyl-H^3). IR (KBr cm^{-1}). – 1780 (C=O lactam), 1639 (C=O amide). Anal. $C_{21}H_{22}ClN_3O_3$.

1-[4-(5-Chloro-2(3H)-benzoxazolon-3-yl)butanoyl]-4-piperonylpiperazine (**5**)

Crystallized from ethanol (yield 63 %, m.p. 138 °C). ^{1}H-NMR (DMSO-d_6). – δ 7.06–6.87 (m, 3 H, 2-benzoxazolinone-H^{4-6-7}), 6.75 (s, 1 H, piperonyl-H^2), 6.67–6.52 (m, 2 H, piperonyl-H$^{5-6}$), 5.75 (s, 2 H, -O-CH_2-O-), 3.78 (t, 2 H, butanoyl-H^4), 3.51 (s, 2 H, -N-CH_2-Ph), 3.41–3.15 (m, 4 H, piperazine-H$^{2-6}$), 2.44–2.14 (m, 6 H, piperazine-H$^{3-5}$ and -CH_2-CO-), 1.96 ppm (m, 2 H, butanoyl-H^3). IR (KBr cm^{-1}). – 1776 (C=O lactam), 1634 (C=O amide). Anal. $C_{23}H_{24}ClN_3O_5$.

1-[4-(5-Chloro-2(3H)-benzoxazolon-3-yl)butanoyl]-4-(2-methoxyphenyl)piperazine (**6**)

Crystallized from ethanol-water (yield 48 %, m.p. 136 °C). ^{1}H-NMR (DMSO-d_6). – δ 7.22–6.62 (m, 7 H, 2-benzoxazolinone-H^{4-6-7} and phenyl-H$^{3-4-5-6}$), 3.90–3.56 (m, 7 H, butanoyl-H^4, piperazine-H$^{6(2)}$ and -O-CH_3), 3.45 (t, 2 H, piperazine-H$^{2(6)}$), 2.88 (m, 4 H, piperazine-H$^{3-5}$), 2.33 (2 H, t, -CH_2-CO-), 2.03 ppm (m, 2 H, butanoyl-H^3). IR (KBr cm^{-1}). – 1764 (C=O lactam), 1640 (C=O amide). Anal. $C_{22}H_{24}ClN_3O_4$.

1-[4-(5-Chloro-2(3H)-benzoxazolon-3-yl)butanoyl]-4-(2-fluorophenyl)piperazine (**7**)

Crystallized from ethanol (yield 55 %, m.p. 120 °C). ^{1}H-NMR (DMSO-d_6). – δ 7.08–6.63 (m, 7 H, 2-benzoxazolinone-H$^{4\text{-}6\text{-}7}$ and phenylH$^{3\text{-}4\text{-}5\text{-}6}$), 3.82 (t, 2 H, butanoyl-H^4), 3.64 (t, 2 H, piperazine-H$^{6(2)}$), 3.44 (t, 2 H, piperazine-H$^{2(6)}$), 2.92 (m, 4 H, piperazine-H$^{3\text{-}5}$), 2.31 (t, 2 H, -CH_2-CO-), 2.02 ppm (m, 2 H, butanoyl-H^3). IR (KBr cm^{-1}). – 1773 (C=O lactam), 1637 (C=O amide). Anal. $C_{21}H_{21}ClFN_3O_3$.

N-[4-(5-Chloro-2(3H)-benzoxazolon-3-yl)butanoyl]morpholine (**8**)

Crystallized from ethanol (yield 38 %, m.p. 123 °C). ^{1}H-NMR (DMSO-d_6). – δ 7.06–6.85 (m, 3 H, 2-benzoxazolinone-H$^{4\text{-}6\text{-}7}$), 3.85 (t, 2 H, butanoyl-H^4), 3.54 (m, 6 H, morpholine-H$^{2\text{-}6\text{-}5(3)}$), 3.26 (t, 2 H, morpholine-H$^{3(5)}$), 2.25 (t, 2 H, -CH_2-CO-), 2.02 ppm (m, 2 H, butanoyl-H^3). IR (KBr cm^{-1}). – 1775 (C=O lactam), 1654 (C=O amide). Anal. $C_{15}H_{17}ClN_2O_4$.

N-[4-(5-Chloro-2(3H)-benzoxazolon-3-yl)butanoyl]piperidine (**9**)

Crystallized from ethanol (yield 53 %, m.p. 63 °C). ^{1}H-NMR (DMSO-d_6). – δ 7.08–6.84 (m, 3 H, 2-benzoxazolinone-H$^{4\text{-}6\text{-}7}$), 3.79 (t, 2 H, butanoyl-H^4), 3.58–3.04 (m, 4 H, piperidine-H$^{2\text{-}6}$), 2.24 (t, 2 H, -CH_2-CO-), 1.97 (m, 2 H, butanoyl-H^3), 1.46 ppm (m, 6 H, piperidine-H$^{3\text{-}4\text{-}5}$). IR (KBr cm^{-1}). – 1782 (C=O lactam), 1641 (C=O amide). Anal. $C_{16}H_{19}ClN_2O_3$.

1-[4-(5-Chloro-2(3H)-benzoxazolon-3-yl)butanoyl]-4-benzylpiperidine (**10**)

Crystallized from ethanol (yield 35 %, m.p. 145 °C). ^{1}H-NMR (DMSO-d_6). – δ 7.29–6.79 (m, 8 H, 2-benzoxazolinone-H$^{4\text{-}6\text{-}7}$ and phenyl-H$^{2\text{-}3\text{-}4\text{-}5\text{-}6}$), 4.49 (s, 1 H, piperidine-H$^{2\text{-axial}}$), 3.78 (t, 2 H, butanoyl-H^4), 3.6 (s, 1 H, piperidine-H$^{2\text{-equatorial}}$), 2.77 (s, 1 H, piperidine-H$^{6\text{-axial}}$), 2.43 (m, 3 H, piperidine-H$^{6\text{-equatorial}}$ and -CH_2-Ph), 2.20 (t, 2 H, -CH_2-CO-), 1.97 (m, 2 H, butanoyl-H^3), 1.55 (m, 4 H, piperidine-H$^{3\text{-}5}$), 1.0 ppm (m, 1 H, piperidineH^4). IR (KBr cm^{-1}). – 1780 (C=O lactam), 1629 (C=O amide). Anal. $C_{23}H_{25}ClN_2O_3$.

Pharmacology

Antinociceptive activity [15–16]

Local breed male albino mice weighting 22 ± 2 g were used in these experiments. All the animals were housed in groups of six. They were allowed to get accustomed to their environment with free access to food and water for at least two days before the experiments. The synthesized compounds were administered orally (100 mg/kg) in carboxymethylcellulose (5 %) solution 1 hour prior to the intraperitoneal injection with 0.1 mL/10 g body weight of 2.5 % (v/v) p-benzoquinone (PBQ – Merck) solution in distilled water. The control group received carboxymethylcellulose (5 %) 1 h before p-benzoquinone injection. Animals were placed in cages after p-benzoquinone injection and the number of stretching per animal were recorded during the following 15 minutes. Percent analgesic activity was calculated as follows:

Percent antinociceptive activity = n-n′ / n × 100

n: Average number of stretching of control group
n′: Average number of stretching of test group

Anti-inflammatory activity [17]

Carrageenan-induced paw edema was employed for testing anti-inflammatory activity. Six mice per group were used. 60 min after oral administration of the compounds (100 mg/kg) carrageenan was injected subcutaneously (0.5 mg/25 µL) into the plantar surface of the right hind paw. Indomethacin was used as the reference. The differences in foot pad thickness between the right and left foot was measured in 90- minutes interval with a pair of dial thickness gauge calipers.

Gastric Side Effects

After the analgesic activity experiment mice were killed under deep ether anaesthesia and stomach was removed. Then the abdomen of each mouse was opened through great curvature and examined under a dissecting microscope for lesions or bleedings.

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