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Synthesis and antinociceptive activity of (1-benzyl-2(3*H*)-benzimidazolon-3-yl) acetic acid derivatives

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Abstract

Eight (1-benzyl-2(3*H*)-benzimidazolon-3-yl)acetic acid derivatives have been synthesized and tested for antinociceptive activity in this study. All compounds but one, at the oral dose of 100 mg/kg were comparable with aspirin. Ethyl (1-benzyl-2(3*H*)-benzimidazolon-3-yl)acetate (**3**), 4-[(1-benzyl-2(3*H*)-benzimidazolon-3-yl)acetyl]morpholine (**6a**) and 1-[(1-benzyl-2(3*H*)-benzimidazolon-3-yl)acetyl]pyrrolidine (**6b**) have shown more potent antinociceptive activity than others.

Keywords: 2(3*H*)-Benzimidazolone derivatives; Antinociceptive activity

1. Introduction

Although there are many NSAIDs on the market, numerous research is being focused on these drugs due to the serious side effects of NSAIDs, i.e. gastrointestinal irritation and kidney damage. Therefore, developing new agents with or without minimal side effects is, at present, a diffuse research area.

Benzoxazolinones and benzothiazolones have emerged as one of the most promising groups for the development of potential antinociceptive anti-inflammatory agents. 6-Substituted benzoylbenzothiazolone derivatives have been reported as potent antinociceptive agents [1,2]. Bermann et al. [3], reported in 1982 high antinociceptive activity of 3-(4-arylpiperazin-1-yl)alkyl-2(3*H*)-benzoxazolone derivatives. In 1992, Şafak et al. [4] synthesized some 2-(3*H*)-benzoxazolones and showed that 3-(2-pyridinylethyl)-2-(3*H*)-benzoxazolone is the most active antinociceptive compound among other derivatives. Doğruer et al. [5] showed that *N*-(2-pyridinyl)-2-[2(3*H*)-benzazolon-3-yl]acetamides have high antinociceptive activity. *N*-[2-(4-methylpyridinyl)]-2-[2-(3*H*)benzoxazolon-3-yl]acetamide was found to be the most active compound. Antinociceptive activity of the 2(3*H*)-benzoxazolon-3-yl- and 2(3*H*)-benzothiazolon-3-yl-acetic acid derivatives have previously been reported in the literature [6–9].

However, *N*-alkylbenzimidazolone derivatives have been associated with various types of biological effects such as antihipertensive, broncholytic, vasodilator [10], antihistaminic [11,12] activities.

Chemical structures of known anti-inflammatory benzimidazolones are shown in Fig. 1 [13,14].

In addition, there are some (substituted-2(1*H*)-benzimidazolon-3-yl)acetic acid derivatives, which possess aldose reductase inhibitory activity [15]. However, not many studies on the antinociceptive activity of 2(3*H*)-benzimidazolon-3-yl-acetic acid derivatives have been carried out, but according to the papers cited above, it is predicted that there could be antinociceptive activity in benzimidazolone derivatives. Therefore here, some (1-substituted-2(3*H*)-benzimidazolon-3-yl)acetic acid

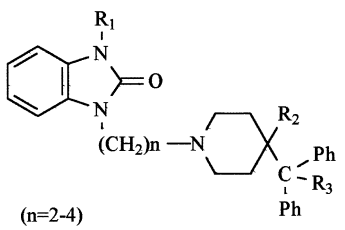

Fig. 1. Anti-inflammatory benzimidazolone derivatives.

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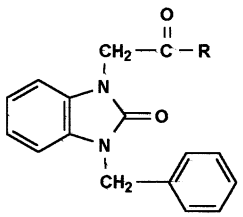
Table 1
Physical and chemical data of (1-substituted-2(3*H*)-benzimidazolon-3-yl)acetic acid derivatives



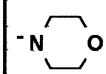
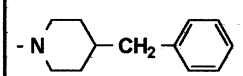
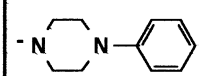
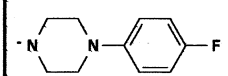
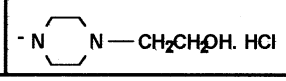
Comp. No.	R	Cryst. solvents	M. P. (°C) [Ref.]	Yield (%)	Formula
3	-OEt	Ethanol	125 [15]	60	$C_{18}H_{18}N_2O_3$
4	-OH	Ethanol	200 [15]	75	$C_{16}H_{14}N_2O_3$
6a		Methanol-water	175-78	69	$C_{20}H_{21}N_3O_3$
6b		Methanol	165-67	57	$C_{20}H_{21}N_3O_2$
6c		Methanol-water	184-87	78	$C_{28}H_{29}N_3O_2$
6d		Methanol	184-85	45	$C_{26}H_{26}N_4O_2$
6e		Methanol	163-64	89	$C_{26}H_{25}FN_4O_2$
6f		Ethanol	210-12	80	$C_{22}H_{26}N_4O_3$ .HCl

Table 2
Antinociceptive activity of (1-substituted-2(3*H*)-benzimidazolon-3-yl)acetic acid derivatives

Comp. no.	Antinociceptive activity (%)
3	50.54 ± 18.39 *
4	46.83 ± 13.6 *
6a	58.78 ± 12.00 *
6b	56.72 ± 16.32 *
6c	14.68 ± 13.89
6d	46.83 ± 19.19 *
6e	45.59 ± 9.27 *
6f	40.19 ± 12.04
Aspirin	42.19 ± 16.39

* $P < 0.05$.

derivatives have been synthesized and were examined for their antinociceptive activity. The compounds synthesized are presented in Table 1 and the biological activity results are given in Table 2.

2. Chemistry

For the synthesis of the title compounds the reaction sequences outlined in Scheme 1 were followed, starting from 2(3*H*)-benzimidazolone, which was prepared by the reaction of *o*-phenylenediamine and urea. 2(3*H*)-Benzimidazolone was reacted with benzyl chloride to obtain 1-benzyl-2(3*H*)-benzimidazolone. The reaction of 1-benzyl-2(3*H*)-benzimidazolone with ethyl bromoacetate gave the ethyl (3-benzyl-2(3*H*)-benzimidazolone)acetate. Ethyl(3 - benzyl - 2(3*H*) - benzimidazolone)acetate was hydrolyzed and the carboxylic acid derivative was obtained. The title compounds were obtained by the reaction of corresponding secondary amines with the acid chloride, which was prepared by the reaction of the carboxylic acids with thionyl chloride. The chemical structures of the compounds have been elucidated by elemental analysis, IR and ^{1}H NMR spectral data.

3. Experimental

3.1. Chemistry

All chemicals were obtained from Aldrich (Steinheim, Germany). Melting points were determined with an Electrothermal melting point apparatus (Southend, UK) and are uncorrected.

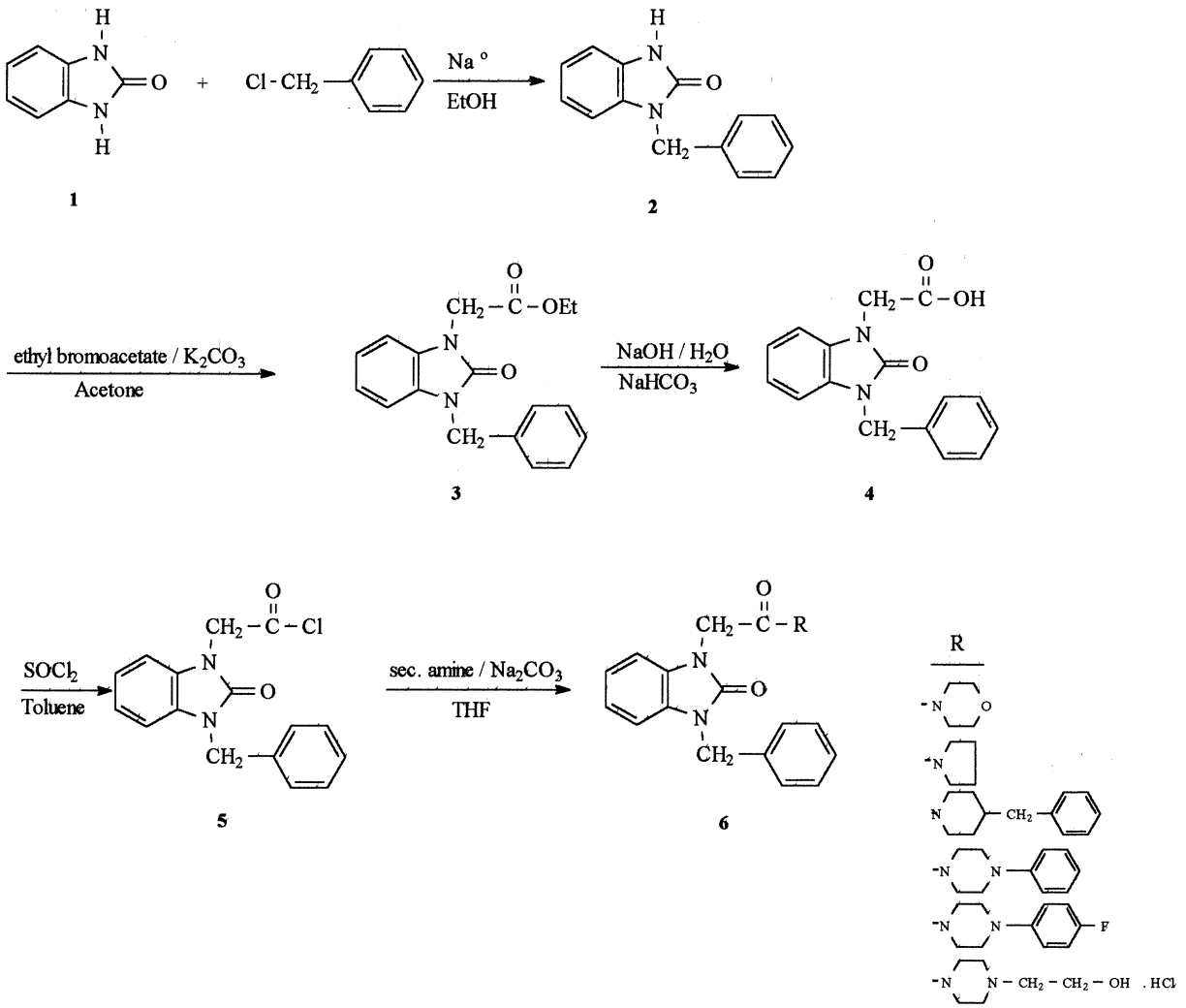
IR spectra were recorded on a Perkin–Elmer 1330 spectrometer (Überlingen, Germany) (KBr, ν (cm^{-1})). ^1H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer (Rheinstetten, Karlsruhe, Germany) using TMS as internal standard and DMSO-d_6. All chemical shifts were reported as δ (ppm) values. Elemental analyses were performed with Leco-932 (C,H,N,S-O-Elemental analyzer, St. Joseph, USA) at the Scientific and Technical Research Council of Turkey, Instrumental Analysis Center (Ankara, Turkey), and the results were within the range $\pm 0.4\%$ of the calculated values.

3.1.1. 1-Benzyl-2(3H)-benzimidazolone [16]

Metallic sodium (0.05 mol) was dissolved in 50 ml absolute ethanol and 0.1 mol of 2(3*H*)-benzimidazolone was added to this solution. Then having a clear solution, 0.1 mol of benzyl chloride was added. The final solution was refluxed for 8 h, and then evaporated to dryness. The residue was dissolved in 10% NaOH, filtered and acidified with 10% HCl. The solid material precipitate was crystallized from ethanol. M.p.: 196–198°C; see lit. [16] 197–200°C.

3.1.2. Ethyl(3-benzyl-2(3H)-benzimidazolon-3-yl)-acetate and (3-benzyl-2(3H)-benzimidazolon-3-yl)acetic acid [15]

Potassium carbonate (0.11 mol) was dispersed in 50 ml acetone and 3-benzyl-2(3*H*)-benzimidazolone (0.1 mol) was added to this mixture. Then the solution was stirred for 1 h and 0.15 mol of ethyl bromoacetate was added. The final solution was refluxed for 6 h and then cooled to room temperature. Ice water was added and stirred for 1 h. The precipitate was filtered and crystallized from ethanol. Part of the ester was hydrolyzed by heating with 10% NaOH and acidified with 20% HCl. The product was dissolved in $NaHCO_3$ and acidified with 10% HCl. The precipitate was filtered, washed with water to neutral pH and dried.



Scheme 1. Synthetic route of the title compounds.

3.1.3. (3-Benzyl-2(3H)-benzimidazolon-3-yl-)acetyl chloride

(3 - Benzyl - 2(3*H*)-benzimidazolon - 3 - yl)acetic acid (0.01 mol) was dispersed in 30 ml toluene, and 0.01 mol of thionyl chloride was added. The final solution was refluxed for 3 h, and then evaporated to dryness.

*3.1.4. (3-Benzyl-2(3H)-benzimidazolon-3-yl)acetamide derivatives (**6a–6f**)*

(3-benzyl-2(3*H*)-benzimidazolon-3-yl-)acetyl chloride (0.01 mol), 0.011 mol of Na_2CO_3 and 0.01 mol of an appropriate secondary amine were mixed in 30 ml tetrahydrofurane, refluxed for 8 h and stirred for 12 h at room temperature. Then the eventual mixture was filtered. The filtrate was evaporated to dryness and 100 ml of water was added. This mixture was extracted three times with 30 ml of chloroform. The chloroform extracts were pooled, dried with sodium sulfate, filtered and evaporated to dryness. The residue was crystallized from appropriate crystallization solvents. Compound **6f** was characterized as its hydrochloride salt, that was prepared by treatment of reaction product in alcohol with alcoholic HCl.

3.1.5. Spectral data of the compounds

The IR spectra of the benzimidazolone derivatives exhibited the following characteristic bands (cm^{-1}): heterocyclic carbonyl: 1660–1650, amide carbonyl: 1710–1690. The ^1H NMR spectra did not exhibit any peculiar features, thus only the spectrum of compound **6a** is indicated as an example: δ 7–8 (m, 9H, aromatic H); 5.1 (s, 2H, N–CH_2–CO–); 4.82 (s, 2H, N–CH_2–∅); 3.65 (m, 4H, CH_2–O–CH_2); 2.51 (m, 4H, CH_2–N–CH_2).

3.2. Biology

3.2.1. Materials

Swiss albino mice of both sexes (25 ± 5.0 g), which are a local breed, were employed. The animals were housed in groups of eight with food and tap water ad libitum and were received to the laboratory at least 2 days before the experiments to allow them to get accustomed to the environment. The food was withdrawn one day before the experiment, but they were allowed free access to tap water. The experiments were performed in full awareness of the test animals. Acetic acid (Merck A.G), carboxymethyl cellulose sodium salt (CMC Na) (Aldrich), aspirin (Bayer), gauge callipers (Peacock, Ozaki Co., Tokyo) were used.

3.2.2. Methods

3.2.2.1. Antinociceptive activity test. A modified Koster's test was employed [4]. Koster test was first used by Koster et al. in mice at 60 mg/kg acetic acid (0.6% solution) given by i.p. injection to produce repeated characteristic stretching movements [17]. This method was modified later by Şafak et al. [4] using acetic acid at a dose level of 300 mg/kg (3% solution). Acetylsalicylic acid (ASA) was used as reference [18].

Each compound was suspended in 0.5% carboxymethyl cellulose to form a solution at the concentration 10 mg/ml and given orally to mice in groups of six at a dose of 100 mg/kg. One hour after this administration; pain was induced by intraperitoneal injection of 3% solution of acetic acid at 300 mg/kg. The control group animals received carboxymethyl cellulose 1 h prior to injection of acetic acid. Animals were placed in private cages 5 min after acetic acid injection and the number of 'stretching' per animal was recorded during the following 10 min period; percent analgesic activity was calculated by using the formula:

$$\text{Percent anti-nociceptive activity} = \frac{n - n'}{n} \times 100$$

where n is the average number of 'stretching' of the control group, and n' is the average number of 'stretching' of the test group.

According to this calculation maximum antinociceptive activity could be 100%, whereas it equals 0% in the control. The reference drug was administered according to the test protocol.

3.2.2.2. Statistical analysis. Data were expressed as means $\pm$ S.E.M. Statistical comparisons were made by one way analysis of variance (ANOVA) following by a post hoc Dunnett Multiple Comparisons test. A P value of < 0.05 was considered indicative of statistical significance.

4. Results and discussion

The antinociceptive activities of the compounds are shown in Table 2. All the compounds except compound **6c** were shown to be equally potent in comparison with aspirin. Compounds **3**, **6a** and **6b** are the more promising ones and slightly more potent than the others.

Antinociceptive activities of compounds **3**, **4**, **6a**, **6b**, **6d** and **6e** were significantly different from the control group. However, for these compounds there was no statistical difference from aspirin.

In the literature, 2(3*H*)-benzothiazolone acetic acids, which have morpholine, pyrrolidine and phenylpiperazine rings on the side chain were reported to exhibit high antinociceptive activity. In our study, 4-[(1-benzyl-2(3*H*)benzimidazolon-3-yl)acetyl]morpholine and 4-[(1-benzyl - 2(3*H*)benzimidazolon - 3 - yl)acetyl]pyrrolidine also showed higher activity than the others. Therefore, one can be inclined to say that morpholine and pyrrolidine rings on the side chain may be critical for antinociceptive activity in this kind of compounds.

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