Eur J Med Chem (1996) 31, 625–628

Analgesic and antiinflammatory activity screening of 6-acyl-3-piperazinomethyl-2-benzoxazolinone derivatives

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(Received 26 September 1995; accepted 14 February 1996)

2-benzoxazolinone / acylation / analgesic / antiinflammatory

Introduction

Two main groups of analgesics on the market are the opioids, such as morphine and codeine, and the nonsteroidal antiinflammatory agents including aspirin, paracetamol and ibuprofen. The opioids act on the central nervous system which can result in dependence, hence limiting their clinical use [1]. The nonsteroidal antiinflammatory drugs act mainly peripherally by inhibiting prostaglandin synthesis, but unfortunately induce gastrointestinal lesions [2].

In the literature it is shown that acylahon of the benzoxazolinone moiety might be a means of alleviating these problems [3]. While compound A, with a hydrogen or methyl group on the nitrogen atom of the oxazolinone ring, shows favorable analgesic activity, compound B, with a (4-aryl-1-piperazinyl)alkyl moiety in addition to an acylic substituent fixed on the aromatic nucleus manifests significant analgesic activity (fig 1) [4].

On this basis, in recent years we reported that some derivatives of 2-benzoxazolinone have high analgesic and antiinflammatory activities [5–11], especially 6-acyl-3-[(4-substituted benzoyl)methyl]-2-benzoxazolinones with activity comparable to indomethacin [8]. These findings led us to synthesize new 6-acyl-3-arylpiperazinomethyl-2-benzoxazolinone derivatives and screen them for analgesic and antiinflammatory activities.

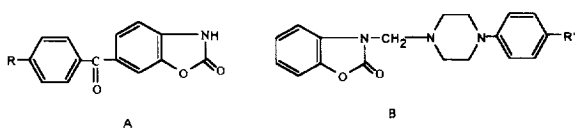
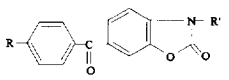


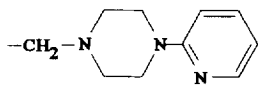
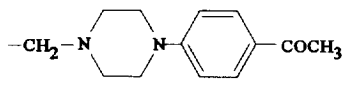
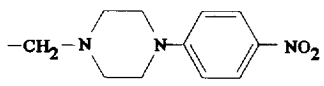
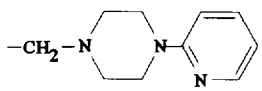
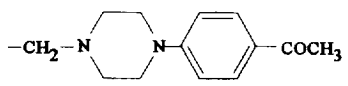
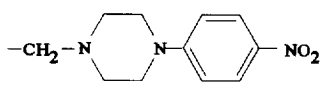
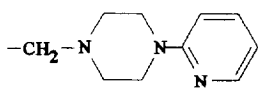
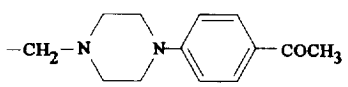
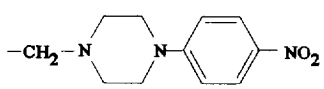
Fig 1.

Chemistry

Formulas, melting points % yields and crystallization solvents of the compounds are shown in table I. 6-Acyl derivatives of 2-benzoxazolinone were prepared by reacting 2-benzoxazolinone with aromatic acids in the presence of polyphosphoric acid. 3-Arylpiperazinomethyl)-2-benzoxazolinones were prepared from 6-acyl-2-benzoxazolinone, arylpiperazine derivatives and formaldehyde according to the Mannich reaction (scheme 1). The structures of the compounds were elucidated by spectral methods such as UV, IR, ^{1}H-NMR and elementary analyses. UV spectra of the compounds have two intense absorption bands, at 229 and 303 nm. In the IR spectra of the compounds, carbonyl stretching belonging to aromatic ketone was seen at about 1650 cm^{-1}, carbonyl stretching of lactam carbonyl appeared at around 1770 cm^{-1}, and aliphatic stretching bands belonging to piperazine ring were at about 2800 cm^{-1}. In the ^{1}H-NMR spectra of the compounds, the CH_2 protons of compounds **2–10** were seen at about 4.8 ppm as a singlet. The H_2 and, H_6 protons of the piperazine ring were seen at about 2.8 ppm, and the H_3 and, H_5 protons were observed at 3.5 ppm (table II).

Table I. 6-Acyl-3-substituted piperazinomethyl-2-benzoxazolinones **2** and **3a–i**.



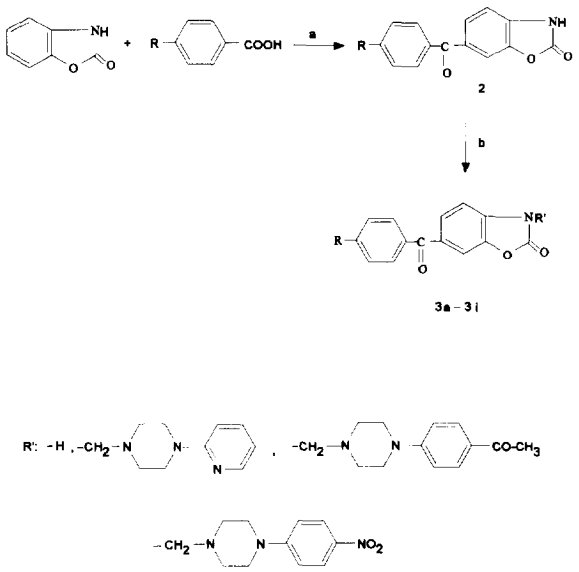
Comp no	*R*	*R'*	*Yield*[a] *(%)*	*Melting point*[b] *(°C)*	*Cryst sol*	*Molecular formula*[c]
2	Br	H	67	258–9	Ethanol	$C_{14}H_8BrNO_3$
3a	Br		72	186–7	Acetonitrile	$C_{24}H_{21}BrN_4O_3$
3b	Br		74	195–6	Acetonitrile	$C_{27}H_{24}BrN_3O_4$
3c	Br		66	205–7	Acetonitrile	$C_{25}H_{21}BrN_4O_5$
3d	Cl		70	175	Acetonitrile	$C_{24}H_{21}ClN_4O_3$
3e	Cl		72	203	Acetonitrile	$C_{27}H_{24}ClN_3O_4$
3f	Cl		73	209	Acetonitrile	$C_{25}H_{21}ClN_4O_5$
3g	OCH_3		69	149	Ethanol/water	$C_{25}H_{24}N_4O_3$
3h	OCH_3		71	158–9	Methanol	$C_{28}H_{27}N_3O_5$
3i	OCH_3		70	173–5	Methanol	$C_{26}H_{24}N_4O_6$

[a]Yields are of the products from first crystallization; [b]melting points were determined on a Thomas Hoover apparatus and are uncorrected; [c]C, H, N analyses were performed by the Scientific and Technical Research Council of Turkey (Gebze, Turkey).

Pharmacology

2-Benzoxazolinones have structural similarity to urethane, in fact they are cyclic urethanes. These chemical compounds are used as anticonvulsants and have analgesic activities. We therefore synthesized 2-benzoxazolinones with substituents at the 6 and 3 positions and investigated them for their analgesic activity using a modified Koster test and for their antiinflammatory activity using a Peacock Dial Thickness Gauge. The analgesic activities of the compounds were assayed using aspirin as reference analgesic. As can be seen in table III, the compounds **2**, **3a**, **3d**, **3f**, **3h** and **3i** showed analgesic activities higher than that of aspirin.

The compounds were then assayed for their inhibition of carrageenan-induced paw edema. Edema inhibition of compounds **2**, **3d**, **3f** and **3h** (used at 100 mg/kg) was significant when compared to inhibition obtained with indomethacin (used at 5 mg/kg) and compounds **3b**, **3c** and **3i** were equipotent with indomethacin (table III).



Scheme 1. a: PPA; b: HCHO, piperazines; R: -Br, -Cl, $-OCH_3$.

Experimental protocols

Chemistry

All chemicals were obtained from Aldrich Chemical Co (Steiheim, Germany). Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. UV spectra were recorded using a Shimadzu UV-160 A UV-visible spectrophotometer (10^{-4} mol/CH_3OH). IR spectra were taken on a FT 1720 X Infrared Spectrophotometer. ^{1}H-NMR spectra were recorded using a Bruker AC 80 MHz Spectrometer using DMSO-d_6 and $CDCl_3$-d_1 (with tetramethylsilane as internal standard). Chemical shift values were reported on a Perkin-Elmer Model 240C at the Scientific and Technical Research Council of Turkey (Gebze, Turkey). The purity of the compounds was determined by TLC on silica gel HF 254 (Merck) (benzene/methanol, 90:10).

6-Acyl-2-benzoxazolinones

The title compounds were synthesized by heating 2-benzoxazolinone (0.1 mol) with substituted benzoic acid (0.1 mol) in polyphosphoric acid (200 g) for 7 h. After cooling the solution was poured into ice-water. The crude product was extracted with dichloromethane (300 mL) and the organic layer washed twice with water and once with brine solution. The organic layer was dried over Na_2SO_4. Concentration of dichloromethane under reduced pressure gave a white solid which was recrystallized from ethanol.

6-Acyl-3-piperazinomethyl-2-benzoxazolinones

A solution of 6-acyl-2-benzoxazolinone (0.01 mol) in 30 mL methanol was refluxed with 0.01 mol piperazine derivatives and 1 mL (0.0013 mol) of 37% (w/w) formaldehyde for 30 min. Crude products were filtered and purified by crystallization with appropriate solvents.

Table II. IR and ^{1}H-NMR data of **2** and **3a–i**.

Comp no	*IR (cm^{-1})*				*^{1}H-NMR (ppm)*				
	Arom ketone	*Lactam C=O*	*Piperazine C-H*	*$-CH_2-$ (s)*	*Piperazine H^3, H^5 (m)*	*Piperazine H^2, H^6 (m)*	*Aromatic ring (m)*	*4-Acetylphenyl $-CH_3-$ (s)*	*4-Methoxyphen $-OCH_3-$ (s)*
1	1652	1790	–	–	–	–	7.08–8.00	–	–
2	1638	1792	2839	4.80	3.50	2.70	6.50–6.90	–	–
3	1660	1773	2838	4.75	3.40	2.90	6.80–7.90	2.50	–
4	1662	1773	2930	4.80	3.40	2.80	6.80–7.00	–	–
5	1637	1792	2829	4.80	3.50	2.80	6.50–7.90	–	–
6	1660	1771	2845	4.80	3.40	2.90	6.80–8.00	2.55	–
7	1662	1771	2940	4.90	3.50	2.85	7.00–8.20	–	–
8	1650	1767	2840	4.75	3.60	2.80	6.50–7.90	3.90	–
9	1662	1768	2846	4.75	3.40	2.80	6.50–7.90	2.50	3.90
10	1651	1768	2842	4.75	3.40	2.80	6.70–8.20	–	3.85

IR spectra were determined on a Perkin Elmer Model 457 IR in KBr, ^{1}H-NMR spectra were charted on a Bruker 80 MHz using tetramethylsilane as the internal standard and DMSO and $CDCl_3$; s: singlet, t: triplet, m: multiplet.

Table III. Analgesic activity and carrageenan paw edema inhibition of the assayed compounds.

Compound no[a]	*Analgesic activity (%)*	*Antiinflammatory activity (%)*
2	57.68	46.51
3a	48.69	18.60
3b	47.80	23.25
3c	48.69	23.25
3d	56.52	30.20
3e	47.82	–
3f	52.68	26.51
3g	36.52	10.93
3h	51.45	38.13
3i	60.59	23.25
ASA[a]	49.56	–
Indomethacin[b]	–	24.00

[a]100 mg/kg po; [b]5 mg/kg po.

Pharmacology

Female albino mice weighing 20 ± 2 g were used (local breed). Animals were housed in groups of six, with food and water ad libitum and allowed to get accustomed to their environment for two days before the experiments.

Analgesic activity [12]

A modified Koster test for screening analgesic activity was employed. Each compound was suspended in 5% gum-arabic syrup and given orally to mice in groups of six at a dose level of 100 mg/kg. One hour after this administration, stretchings were induced by ip injection of 3% solution of acetic acid at 300 mg/kg. Two control groups (n = 6) received gum-arabic syrup 1 h prior to injection of acetic acid. Animals were placed in glass cages 5 min after acetic acid injection and the number of 'stretchings' per animal was recorded during a 10 min period. Aspirin was used as a reference analgesic drug (100 mg/kg po).

Percent analgesic activity = $(n - n'/n) \times 100$

where n = mean number of stretches of control group, and n' = mean number of stretches of test group.

Antiinflammatory activity [13, 14]

Carrageenan-induced mouse paw edema (CPE) was measured using Peacock Thickness Gauge (0.01–10 mm). Sixty minutes after oral administration of the compounds (100 mg/kg), 0.01 mL of 2% carrageenan was injected subcutaneously into the plantar surface of the right hind paw. Two hours later the edema volume was measured. Results are expressed as % inhibition (table III). Six mice per group were used. Indomethacin (5 mg/kg ip injection) was used as a positive control.

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