

Analgesic and Antiinflammatory Activities of Some New Mannich Bases of 5-Nitro-2-Benzoxazolinones

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In this study, the synthesis of a novel series Mannich bases of 5-nitro-3-substituted piperazino-methyl-2-benzoxazolinones are described. The structures attributed to compounds **3a-3k** were elucidated using IR, ¹H-NMR spectroscopic techniques besides elemental analysis. The compounds were examined for their in vivo antiinflammatory and analgesic activities in two different bioassays, namely, carrageenan-induced hind paw edema and p-benzoquinone-induced abdominal constriction tests in mice, respectively. In addition, the ulcerogenic effects of the compounds were determined. Among the tested derivatives most promising results were obtained for the compounds bearing electron-withdrawing substituents (F, Cl, COCH₃) in the ortho/para position of the phenyl nucleus on the piperazine ring at 3 position of benzoxazolinone moiety (**3a, 3b, 3c, 3d, 3h**). The analgesic activities of all compounds are higher than their antiinflammatory activities. Antiinflammatory inhibitory ratios for all compounds were above 30% for the last two measurements. Because of this compounds **3a, 3b, 3c, 3d** deserve attention and may be considered for further evaluation.

Key words: 5-Nitro-2-benzoxazolinone, Mannich reaction, Substituted piperazine, Analgesic-antiinflammatory activities

INTRODUCTION

Despite an ever growing body of knowledge about endogenous nociceptive and antinociceptive systems, clinical treatment of pain today is dominated by two main groups of analgesics: the opioids such as morphine and codeine and the non-steroidal antiinflammatory drugs including aspirin and ibuprofen. Given the reluctance to use opiates because of their liability towards physical dependence, tolerance, respiratory depression and constipation, and the limitations in efficacy of the peripheral analgesics associated to classical drawbacks i.e. gastrointestinal lesions (Calhoun *et al.*, 1995), the quest is to develop new potent analgesic agents with the efficacy of morphine without the undesired and use-limiting side effects. Because of this there has been a renewed interest for antiinflammatory agents endowed with either more

selective mechanisms (COX-1 vs. COX-2 inhibition) (Dannhardt and Kiefer, 2001) or novel modes of action. One of these novel action modes is inhibition of inducible nitric oxide synthase (NOS) which contributes acute and chronic inflammation (Kawanaka *et al.*, 2002). In this connection, it has been shown that some benzoxazolinone derivatives, as shown in general structure (Fig. 1), inhibit NOS and they constitute a novel class of non-aminoacid based NOS inhibitors (Shankaran, 1997).

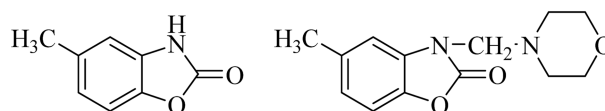


Fig. 1. Structures of benzoxazolinone derivatives

2-Benzoxazolinone ring has been investigated extensively for as analgesic and antiinflammatory agents and has become a promising group to prevent analgesia (Brunet *et al.*, 1980; Erdogan *et al.*, 1989; Gökhan *et al.*, 1999; Ünlü *et al.*, 2003). 5-Chloro-2-benzoxazolinone (chlorzoxazone) showing good muscle relaxant effect was also found during

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these researches. In addition researchers have revealed that different pharmacodynamic moieties of benzoxazolinones possess potent biological activities such as dopamine receptor agonist (Weinstok *et al.*, 1987), cardiotoxic (Von der Saal *et al.*, 1989), antihypertensive (Bonte *et al.*, 1990), antiulcer activities (Katsura *et al.*, 1991). Currently there is a considerable therapeutic interest on novel drugs containing 1-arylpiperazinyl moieties, in particular due to their effects on the central nervous system (Bonte *et al.*, 1992; Mokrosz *et al.*, 1992). The introduction of (4-aryl-piperazin-1-yl)alkyl moieties on various heterocyclic nuclei such as benzoxazolinones (Erdogan *et al.*, 1991; Gökhan *et al.*, 2003) oxazolopyridine (Flouzat *et al.*, 1993; Viaud *et al.*, 1995), pyridazine (Moreau *et al.*, 1996; Rohet *et al.*, 1997) and pyrazolotriazine (Mavel *et al.*, 1993) led to favourable antinociceptive compounds. Since varying substituents is a common method for drug design in medicinal chemistry and useful medical value of benzoxazolinones we have aimed to synthesize new 5-nitro-3-piperazinomethyl-2-benzoxazolinone derivatives and investigate the effect of molecular variation on the analgesic-antiinflammatory activities by *in vivo* methods.

MATERIALS AND METHODS

Chemistry

All chemicals were purchased from Aldrich Chemical Co. Melting points were detected with a Thomas Hoover capillary melting point apparatus and are uncorrected. The IR spectra (KBr) were recorded on a Bruker Vector 22 FT-IR spectrophotometer. The ¹H-NMR spectra were obtained by Bruker AC 80 MHz and Bruker 400 MHz NMR instruments using CDCl₃ as solvent and tetramethylsilane as internal standard. Splitting patterns were designated as follows: s: singlet, d: doublet, t: triplet, q: quartet, and m: multiplet. All chemical shift values were recorded as δ (ppm). The purity of the compounds were controlled by thin layer chromatography (Merck, silicagel, HF₂₅₄₋₃₆₆, Type 60, 0.25 mm). The elemental analyses were performed on a Leco CHNS 932 analyzer at the Scientific and Technical Research Council of Turkey (TUBITAK), Instrumental Analysis Laboratory in Ankara.

5-Nitro-2-Benzoxazolinones

To a solution of 0,03 mol 4-nitro-2-aminofenol in 100 mL anhydrous tetrahydrofuran was added 0,045 mol 1,1-carbonyldiimidazole. The solution was refluxed on an oil bath for 4 h. The tetrahydrofuran was removed *in vacuo* and N,N-dimethylformamid added to the residue. After waited for one night in refrigerator, 5-nitro-2-benzoxazolinone was gained in dark yellow prismatic crystalline form (Abdelaal, 1992). C₇H₄FN₂O₄ (180), Yield: 62%. m.p 225-26°C, IR: 1746 (C=O), 11,8 (1H; s; NH); 8,2-7,0 (3H; m; Arom-H).

5-Methyl-3-substituted piperazinomethyl-2-benzoxazolinones

The title compounds were prepared by vigorously stirring a solution of 0.1 mole of the substituted piperazine derivative and 0.1 mol 5-nitro-2-benzoxazolinone in methanol 0.12 mol of formaline (37 % w/v) was added and the mixture refluxed in a water bath for 1 h. The reaction mixture was poured on to crushed ice and the resulting precipitate was filtered, dried and purified by crystallization with appropriate solvents

Pharmacology

Male Swiss albino mice (20-25 g) were purchased from the animal breeding laboratories of Refik Saydam Hizisihha Institute (Ankara, Turkey). The animals left for two days for acclimatization to animal room conditions and were maintained on standard pellet diet and water ad libitum. The food was withdrawn on the day before the experiment, but allowed free access of water. Test samples and reference compounds were suspended in 0.5% carboxymethyl cellulose and administered to each mouse by using gastric gavage needle. The control group animals, however, received same volume of dosing vehicle. In the pharmacological studies, the animals were first administered in 100 mg/kg (body weight) dose of the test drugs.

p-Benzoquinone-induced abdominal constriction test in mice

60 min after the oral administration of test samples, the mice were intraperitoneally injected with 0.1 mL/10 g body weight of 2.5% (v/v) p-benzoquinone (PBQ; Merck) solution in distilled water. 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) were counted for the next 15 min, starting on the 5th min after the PBQ injection. The data represent average of the total number of writhes observed (Okun, 1963). The antinociceptive activity was expressed as percentage change from writhing controls. Aspirin (ASA) was used as reference.

Carrageenan-induced paw edema model

For the determination of the effects on carrageenan-induced paw oedema the modified method of Kasahara *et al.* was employed. 60 min after the oral administration of either test sample or dosing vehicle, each mice was injected with freshly prepared (0.5 mg/25 μL) suspension of carrageenan (Sigma, St. Louis, Missouri, U.S.A.) in physiological saline (154 mM NaCl) into subplantar tissue of the right hind paw. As the control, 25 μL saline solution was injected into that of the left hind paw. Paw oedema was measured in every 90 min during 6 h after induction of inflammation. The difference in footpad thickness

between the right and left foot was measured with a pair of dial thickness gauge callipers (Ozaki Co., Tokyo, Japan). Mean values of treated groups were compared with mean values of a control group and analyzed using statistical methods (Yebilada, 2002) Indometacin (INDO) was used as a reference compound.

Gastric ulceration study

All the animals were sacrificed immediately after the last measurement under ether anesthesia and stomachs were removed. Then the stomachs were examined for lesions under a dissecting microscope. Stomachs exhibiting one or more ulcers were considered positive.

Statistical analysis of data

Data obtained from animal experiments were expressed as mean standard error (\pm SEM). Statistical differences between the treatments and the control were tested by two tailed Student's *t*-test. $p < 0.05$ was considered to be significant.

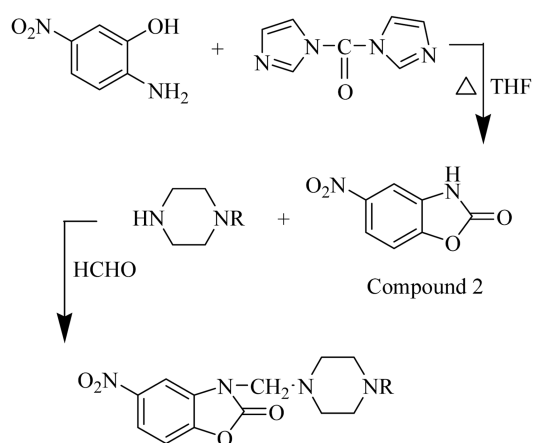
RESULTS AND DISCUSSION

We describe here a convenient approach to the preparation of 5-nitro-3-piperazinomethyl-2-benzoxazolinones 3a-3k in an attempt to find improved analgesic-antiinflammatory agents. One of the most interesting characteristic of these novel compounds is their basic nature, which differentiates them from the classical, acidic non steroidal antiinflammatory agents. It was of interest, therefore to study analgesic-antiinflammatory properties of these novel compounds. For the synthesis of the desired compounds Scheme 1 was followed. 5-Nitro-2-benzoxazolinones were prepared by reacting of 4-nitro-2-aminofenol and 1,1'-carbonyldiimidazole. The final compounds were prepared from 5-nitro-2-benzoxazolinone, arylpiperazine derivatives and formaldehyde according to the Mannich reaction in

61-85% yield (Table I). Melting points, yields %, formulas and spectral characterizations of the synthesized compounds are given in Table I. All spectral data are in accordance with the assumed structures. In the IR spectra of the compounds, no absorption bands were detected at 3100-3400 cm^{-1} , indicating the absence of an NH group which is an evidence for the addition reaction. The lactam C=O stretching band was seen at about 1746-1786 cm^{-1} and aliphatic stretching bands belonging to piperazine ring were appeared at about 2900 cm^{-1} . In the $^1\text{H-NMR}$ spectra of the compounds, the CH_2 protons of compounds 3a-3k were seen at about 4.7 ppm as a singlet. The H_2 and H_6 protons of the piperazine ring were seen at about 3.2 ppm and the H_3 and H_5 protons were observed at 2.7 ppm. The protons belonging to substituents attached to piperazine and aromatic ring protons were observed at the expected values.

Analgesic activities of the resulting compounds were investigated by p-benzoquinone-induced writhing test (Okun *et al.*, 1963) which is a well established method of testing the analgesic activity of compounds and sufficiently sensitive to detect the effect of analgesics which are less active than aspirin. Antiinflammatory activities of the compounds were assessed by utilizing carrageenan-induced hind paw edema model (Yesilada, 2002). Since the carrageenan edema has been used in the development of indometacin, many researchers adapted this procedure for screening potential antiinflammatory compounds. Carrageenan-induced edema is a non-specific inflammation maintained by the release of histamine, 5-hydroxytryptamine, kinins and later by prostaglandins (Tsurumi *et al.*, 1986). The inhibitory effect of acid NSAIDs, such as indometacin, is usually weak in the first phase (1-2 h), in contrast with their strong inhibition in the second phase (3-4 h) (Gavalas *et al.*, 1991). Good inhibition of the second phase of carrageenan-induced edema was observed for the compounds tested, suggesting that they interfere with prostaglandin synthesis (Table II).

The obtained pharmacological results indicate that among the compounds, the derivative 2, which did not carry any substitution on the third position was found weaker than that bearing aminoalkyl residue on this position and some of the title compounds possess a good analgesic activity coupled with notable antiinflammatory properties. Moreover, all compounds showed a remarkable gastric tolerance except 3j. Some preliminary conclusions can be drawn as follows: As shown in Table II, most compounds showed potent inhibitory activities between 31.2 to 53.3% on 100 mg/kg dose. When substituents were taken into consideration within them, it was determined that substituted phenyl derivatives bearing piperazine ring (3a, 3b, 3c, 3d, 3f, 3g, 3h) had a stronger inhibitory effect on analgesic-antiinflammatory activity than that of the



Scheme 1. Synthesis of 5-nitro-3-piperazinomethyl-2-benzoxazolinones

Table I. Characterization and spectral data of compounds **3a-3k**

Comp.	R	Formula	M.p	Yield %	IR (KBr) n (cm ⁻¹)	¹ H-NMR (CHCl ₃ -d ₁) δ (ppm)
3a	4-Fluorophenyl	C ₁₈ H ₁₇ FN ₄ O ₄ (372.35) Calcd: C:58.06; H:4.60; N:15.05 Found:C:58.07; H:4.25; N:14.84	148-50 ¹	78	1783 ^a	8.2-6.8 (7H; m; Arom-H); 4.8 (2H; s; -CH ₂ -); 3.2-3.0 (4H; t; pip.H ₂ , H ₆); 3.0-2.8 (4H; t; pip.H ₃ , H ₅)
3b	2-Fluorophenyl	C ₁₈ H ₁₇ FN ₄ O ₄ (372.35) Calcd: C:58.06; H:4.60; N:15.05 Found:C:58.13; H:4.43; N:14.87	168-69 ²	71	1786 ^a	8.2-6.7 (7H; m; Arom-H); 4.8 (2H; s; -CH ₂ -); 3.4-3.0 (4H; t; pip.H ₂ , H ₆); 3.0-2.6 (4H; t; pip.H ₃ , H ₅)
3c	4-Chlorophenyl	C ₁₈ H ₁₇ ClN ₄ O ₄ (388.81) Calcd: C:55.60; H:4.41; N:14.41 Found:C:55.11; H:4.73; N:14.39	170-72 ²	81	1784 ^a	8.3-6.6 (7H; m; Arom-H); 4.8 (2H; s; -CH ₂ -); 3.5-3.0 (4H; t; pip.H ₂ , H ₆); 3.0-2.5 (4H; t; pip.H ₃ , H ₅)
3d	2-Chlorophenyl	C ₁₈ H ₁₇ ClN ₄ O ₄ (388.81) Calcd: C:55.60; H:4.41; N:14.41 Found:C:55.77; H:4.76; N:14.25	140-42	68	1787 ^a	8.3-6.8 (7H; m; Arom-H); 4.8 (2H; s; -CH ₂ -); 3.3-3.0 (4H; t; pip.H ₂ , H ₆); 3.0-2.6 (4H; t; pip.H ₃ , H ₅)
3e	2-Methoxyphenyl	C ₁₉ H ₂₀ N ₄ O ₅ (384.39) Calcd: C:59.37; H:5.24; N:14.58 Found:C:59.56; H:5.20; N:14.33	136-38 ²	69	1780 ^a	8.2-6.6 (7H; m; Arom-H); 4.7 (2H; s; -CH ₂ -); 3.8 (3H; s; -OCH ₃); 3.3-3.0 (4H; s; pip.H ₂ , H ₆); 3.0-2.6 (4H; s; pip.H ₃ , H ₅)
3f	3-Methoxyphenyl	C ₁₉ H ₂₀ N ₄ O ₅ (384.39) Calcd: C:59.37; H:5.24; N:14.58 Found:C:59.62; H:5.56; N:14.50	162-63 ²	68	1787 ^a	8.2-6.2 (7H; m; Arom-H); 4.6 (2H; s; -CH ₂ -); 3.7 (3H; s; -OCH ₃); 3.3-2.9 (4H; t; pip.H ₂ , H ₆); 2.9-2.6 (4H; t; pip.H ₃ , H ₅)
3g	3-Trifluoromethylphenyl	C ₁₉ H ₁₇ F ₃ N ₄ O ₄ (422.36) Calcd: C:54.03; H:4.06; N:13.27 Found:C:53.66; H:4.07; N:13.12	162-64 ¹	71	1783 ^a	8.1-6.7 (7H; m; Arom-H); 4.7 (2H; s; -CH ₂ -); 3.3-3.0 (4H; d; pip.H ₂ , H ₆); 3.0-2.6 (4H; t; pip.H ₃ , H ₅)
3h	4-Acetylphenyl	C ₂₀ H ₂₀ N ₄ O ₅ (396.40) Calcd: C:60.60; H:5.09; N:14.13 Found:C:60.52; H:5.55; N:14.00	186-87 ²	85	1779 ^a	8.2-6.6 (7H; m; Arom-H); 4.7 (2H; s; -CH ₂ -); 3.6-3.1 (4H; t; pip.H ₂ , H ₆); 3.0-2.6 (4H; t; pip.H ₃ , H ₅); 2.4 (3H; s; -CH ₃)
3i	2-Pyridyl	C ₁₇ H ₁₇ N ₅ O ₄ (355.35) Calcd: C:57.46; H:4.82; N:19.71 Found:C:57.13; H:4.88; N:19.43	149-51 ¹	71	1784 ^a	8.1-6.4 (7H; m; Arom-H); 4.6 (2H; s; -CH ₂ -); 3.6-3.2 (4H; t; pip.H ₂ , H ₆); 2.8-2.4 (4H; t; pip.H ₃ , H ₅)
3j	Benzyl	C ₁₉ H ₂₀ N ₄ O ₄ (368.39) Calcd: C:61.95; H:5.47; N:15.21 Found:C:62.07; H:5.47; N:14.94	138-39 ³	61	1787 ^a	8.2-7.0 (7H; m; Arom-H); 4.7 (2H; s; -CH ₂ -); 3.5 (2H; s; benzyl -CH ₂); 3.0-2.6 (4H; t; pip.H ₂ , H ₆); 2.6-2.3 (4H; t; pip.H ₃ , H ₅)
3k	Piperonyl	C ₂₀ H ₂₀ N ₄ O ₆ (412.40) Calcd: C:58.25; H:4.89; N:13.59 Found:C:57.80; H:4.97; N:13.27	140-41 ³	62	1786 ^a	8.2-6.5 (6H; m; Arom-H); 5.8(2H; s; O-CH ₂ -O); 4.7 (2H; s; -CH ₂); 3.4 (2H; s; -CH ₂ -pip); 2.9-2.5 (4H; t; pip.H ₂ , H ₆); 2.8-2.2 (4H; t; pip.H ₃ , H ₅)

¹Ethanol, ²Methanol, ³Ethanol-water.^alactam.

aliphatic substituted piperazine derivatives (**3j**, **3k**). According to this, we suggested that the phenyl group was an important structural characteristic of the analgesic-antiinflammatory action of these derivatives. Then the effect of substituents on the phenyl ring was investigated. It was clear that compounds bearing fluoro and chloro residues (**3a-3d**) displayed the best activity. By contrast, acetylphenyl (**3h**) or trifluoromethylphenyl (**3g**) analogs were less active, which can be hypothesized that the

larger substituents cause decreasing of the activity for this series (Revised), may be detrimental to the overall activity. Among the compounds It appeared that presence of an electron withdrawig substituents in the para position of the phenyl nucleus led to more active compounds (**3a**, **3c**) compared with ortho substituted derivatives (**3b**, **3d**). If the piperazine portion was substituted with 2-pyridil bearing lone pair of electrons (**3i**) and electron donating group such as 2-methoxyphenyl (**3e**); observed efficacy decreased

Table II. Percent analgesic activity and inhibition of carrageenan paw edema (CPE) of the compounds **2**, **3a-3k**

Comp. No	Antiinflammatory Activity ^c				Analgesic Activity	Ratio of ulceration
	Swelling in thickness (x 10 ⁻² mm)±SEM (% inhibition)					
	90 min	180 min	270 min	360 min	Number of writhing ± SEM (% Inhibition)	
Control	41.7 ± 4.13	47.7 ± 4.36	54.2 ± 4.95	59.0 ± 5.31	44.3 ± 3.84	0/6
2	41.2 ± 4.03 (1.2)	44.8 ± 4.31 (6.1)	49.7 ± 4.84 (8.3)	54.0 ± 4.80 (8.5)	33.7 ± 1.94 (23.9**)	0/6
3a	28.3 ± 2.06 (32.1)	30.7 ± 2.51 (35.6)*	34.7 ± 2.14 (35.9)**	36.0 ± 2.98 (38.9)**	20.7 ± 1.33 (53.3***)	0/6
3b	29.8 ± 2.14 (28.5)	33.5 ± 1.98 (29.8)	38.7 ± 1.89 (28.6)*	38.0 ± 1.79 (35.6)**	22.7 ± 2.52 (48.8***)	0/6
3c	29.3 ± 2.91 (29.7)	32.8 ± 3.06 (31.2)	35.8 ± 2.04 (33.9)*	38.7 ± 2.42 (34.4)**	21.7 ± 2.03 (51.0***)	1/6
3d	31.0 ± 3.13 (25.7)	36.3 ± 3.15 (23.9)	38.0 ± 2.5 (29.9)*	38.8 ± 1.70 (34.2)**	24.2 ± 1.56 (45.4***)	0/6
3e	37.2 ± 3.47 (10.8)	40.0 ± 3.29 (16.1)	42.5 ± 3.78 (21.6)	45.5 ± 3.45 (22.9)	27.7 ± 3.14 (37.9*)	0/6
3f	30.5 ± 2.64 (26.9)	35.0 ± 2.81 (26.6)	37.7 ± 2.63 (30.4)*	40.5 ± 2.80 (31.4)*	25.2 ± 2.10 (43.1***)	0/6
3g	35.7 ± 2.80 (14.4)	39.8 ± 2.70 (16.6)	44.7 ± 2.94 (17.5)	46.8 ± 3.46 (20.7)	28.5 ± 2.41 (35.7**)	0/6
3h	32.8 ± 3.17 (21.3)	35.7 ± 2.46 (25.2)	38.0 ± 3.08 (29.9)*	41.2 ± 3.07 (30.2)*	25.8 ± 3.57 (41.8**)	1/6
3i	36.2 ± 2.69 (13.2)	40.7 ± 2.64 (14.7)	43.2 ± 2.77 (20.3)	45.8 ± 2.09 (22.3)	27.5 ± 2.75 (37.9*)	1/6
3j	41.2 ± 3.54 (14.9)	44.0 ± 4.39 (7.8)	48.5 ± 4.29 (10.5)	51.3 ± 4.14 (13.1)	38.2 ± 2.95 (13.8)	2/6
3k	38.2 ± 3.83 (8.4)	43.7 ± 3.83 (8.4)	48.2 ± 4.16 (11.1)	50.8 ± 5.28 (13.9)	30.5 ± 2.99 (31.2*)	0/6
ASA					21.3 ± 1.80 (51.9***)	2/6
INDO	30.7 ± 4.18 (29.5)*	33.0 ± 3.38 (30.6)*	35.3 ± 3.31 (41.9)**	34.2 ± 3.11 (42.7)***	-	-

*p<0.05, **p<0.01, ***p<0.001.

slightly compared to *o*-/*p*-fluoro(chloro)phenyl and 4-acetylphenyl groups.

A quiet similar pattern of antiinflammatory activity was observed with that of analgesic activity. Although not significant, inhibitory ratios for all compounds were above 30% for the last two measurements. However, the inhibitory effects of **3a** and **3b** reached to significant values after 360 min. Among the compounds examined in this study, the compounds **3a**, **3b**, **3c**, **3d** and **3f** possessed the most prominent and consistent activity. Compounds **3a**, **3b**, **3c**, **3d** deserve attention and may be considered for further evaluation.

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