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Some New Mannich Bases of 5-Methyl-2-Benzoxazolinones With Analgesis and Anti-Inflammatory Activities

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The synthesis of a novel series of Mannich bases of 5-methyl-3-substituted piperazinomethyl-2-benzoxazolinones is described. The structures attributed to compounds **3c, 3d** and **3f-3n** were elucidated using IR and ^{1}H NMR spectroscopic techniques as well as elemental analysis. The compounds were examined for their in vivo anti-inflammatory and analgesic activities in 2 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 derivatives tested the most promising results were obtained for the compounds bearing electron-withdrawing substituents (F, Cl, $COCH_3$) in the para position of the phenyl nucleus on the piperazine ring at the 3 position of benzoxazolinone moiety (**3a**, **3c**, **3i**). The analgesic activities of all compounds are higher than their anti-inflammatory activities and therefore these high analgesic activities indicated that the compounds could a show central effect.

Key Words: 5-Methyl-2-Benzoxazolinone, Mannich Reaction, Analgesic, Anti-inflammatory Activities.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used. Despite their large number, none is very effective therapeutically, and almost all have several undesired, often serious, side effects[1] and so longterm administration is not advisable. Thus the need for new anti-inflammatory drugs is obvious. Therefore, there has been renewed interest in anti-inflammatory agents endowed with either more selective mechanisms (COX-1 vs. COX-2 inhibition)[2] or novel modes of action. One of these novel action modes is inhibition of inducible nitric oxide synthase (NOS), which contributes to acute and chronic inflammation[3−5]. In this

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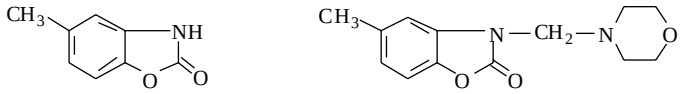
context, it has been shown that some benzoxazolinone derivatives, especially 5-methyl analogs, as shown in the general structure (Figure), inhibit NOS and they constitute a novel class of non-aminoacid NOS inhibitors[6].



Compound 2

Figure

Currently there is considerable therapeutic interest in novel drugs containing 1-arylpiperazinyl moieties, in particular, due to their effects on the central nervous system[7−10]. At the same time, the introduction of (4-aryl-piperazin-1-yl)alkyl moieties on various heterocyclic nuclei such as benzoxazolinones[11−12], oxazolopyridine[13−14], pyridazine[15−16] and pyrazolo-triazine[17] led to favorable antinociceptive compounds. As part of the continuing efforts of our laboratory to develop new analgesics, we initiated a research program based on the synthesis of benzoxazolinone derivatives substituted by arylpiperazinylalkyl chains[18−19] at the C-3 position. In this study, the effect caused by the introduction of arylpiperazinyl moieties at the C-3 position of 5-methyl-2-benzoxazolinones was evaluated.

Experimental

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 ^{1}H NMR spectra were obtained by Bruker AC 80 MHz and Bruker 400 MHz using $CDCl_3$ 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). Mass spectra were recorded on a Jeol AX505W mass spectrometer with electron ionization (EI). The purity of the compounds was determined by thin layer chromatography (Merck, silicagel, $HF_{254-366}$, 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 (TÜBİTAK), Instrumental Analysis Laboratory in Ankara.

5-Methyl-2-benzoxazolinone

A modification of the procedure described by Bywater[20] et al. was followed using 0.1 mol 4-methyl-2-aminophenol and 0.12 mol urea. The mixture was fused at 145-150 °C for 4 h in a preheated oil bath. The residue was recrystallized from water. [$C_8H_7NO_2$: Yield: 59.7% , mp 131-2 °C, IR: ν: 1791 cm^{-1}(C=O), ^{1}H-NMR: 2.4 (3H; s; 5-CH_3), 6.9-7.3 (3H; m; Arom-H.), 9.2 (1H; s; N-H).

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

The title compounds were prepared by vigorously stirring a solution of 0.1 mol of the substituted piperazine derivative and 0.1 mol of 5-methyl-2-benzoxazolinone in methanol. Then 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 onto crushed ice and the resulting precipitate was filtered, dried and purified by crystallization with appropriate solvents [21,22].

Pharmacology

Male Swiss albino mice (20-25 g) were purchased from the animal breeding laboratories of the Refik Saydam Hıfzısıhha Institute (Ankara, Turkey). The animals were left for 2 days for acclimatization to animal room conditions and were maintained on a standard pellet diet and water ad libitum. The feeding was stopped on the day before the experiment, but they were allowed free access to water. Test samples and reference compounds were suspended in 0.5% carboxymethyl cellulose and administered to each mouse using a gastric gavage needle. The control group animals, however, received the same volume of dosing vehicle. In the pharmacological studies, the animals were first administered a 100 mg/kg (body weight) dose of the test drugs.

p-Benzoquinone-induced abdominal constriction test in mice[23]

One hour 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) was counted for the subsequent 15 min, starting 5 min after the PBQ injection. The data represent averages of the total numbers of writhes observed. The antinociceptive activity was expressed as percentage change from writhing controls. Aspirin (ASA) was used as a reference.

Carrageenan-induced paw edema model[24]

For the determination of the effects on carrageenan-induced paw edema the modified method of Kasahara et al. was employed. One hour after the oral administration of either the test sample or the dosing vehicle, each mouse was injected with a freshly prepared (0.5 mg/25 μL) suspension of carrageenan (Sigma, St. Louis, Missouri, USA) in physiological saline (154 mM NaCl) into the subplantar tissue of the right hind paw. As the control, 25 μL of saline solution was injected into the left hind paw. Paw edema was measured every 90 min for 6 h after the 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 the control group and analyzed statistically[22]. Indomethacine (INDO) was used as a reference compound.

Gastric ulceration study

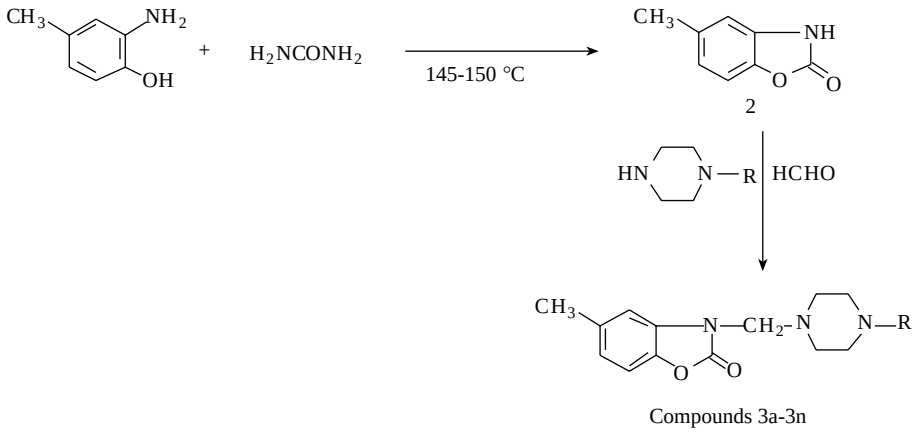
All the animals were sacrificed immediately after the last measurement under ether anesthesia and their stomachs were removed. The stomachs were examined for lesions under a dissecting microscope. Stomachs exhibiting one or more ulcers were considered positive.

Statistical analysis of data

Data obtained from animal experiments were expressed as mean standard error (±SEM). Statistical differences between the treatment and control groups were tested by two-tailed Student's t-test. $P < 0.05$ was considered significant.

Results and Discussion

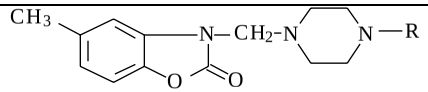
A series of novel derivatives of 5-methyl-3-substituted piperazinomethyl-2-benzoxazolinones was synthesized (Scheme) in an attempt to find improved analgesic-anti-inflammatory agents. One of the most interesting characteristics of these novel compounds is their basic nature, which differentiates them from the classical, acidic nonsteroidal antiinflammatory agents. It was of interest, therefore, to study the analgesic-antiinflamatory properties of these novel compounds.



Scheme

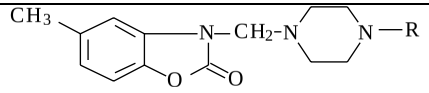
The synthesis pathway, leading to the title compounds, is given in Scheme. 5-Methyl-2-benzoxazolinone, starting material 2, was synthesized according to the literature method using 5-methyl-2-hydroxyaniline and urea[20]. The final compounds **3a-3n** were prepared from 5-methyl-2-benzoxazolinone, arylpiperazine derivatives and formaldehyde according to the Mannich reaction in 60-85% yield. The structure attributed to compounds **3c, 3d** and **3f-3n** was supported by the results of elemental analysis as well as by the IR and ^{1}H-NMR spectra. Melting points, yields % , formulae and spectral characterizations of the synthesized compounds are given in Table 1. 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 evidence for the additional reaction. The lactam C=O stretching band was seen at about 1780 cm^{-1} and aliphatic stretching bands belonging to a piperazine ring appeared at about 2900 cm^{-1}. In the ^{1}H-NMR spectra of the compounds, the CH_2 protons of compounds **3c, 3d** and **3f-3n** were seen at about 4.6-4.8 ppm as a singlet. The H_2 and H_6 protons of the piperazine ring were seen at about 2.3-3.0 ppm and the H_3 and H_5 protons were observed at 2.7-3.8 ppm. 5-Methyl protons bound to 2-benzoxazolinone appeared at approximately 2.2-2.4 ppm. In the EI-MS spectra of **3f**, **3k** and **3l**, molecular ion M^+ peaks, which appeared at different intensities confirmed the molecular weights of the examined compounds. In the spectra of compounds **3f** and **3k** the base peak resulted from loss of an amine moiety plus CH_2 group while in the spectra of compound **3l** the lost group was the base peak.

Table 1. Characterization and spectral data of compounds 3a-3n.



Comp.	R	Formula	M.p.	Yield %	IR (KBr) (cm^{-1})	^{1}H-NMR ($CHCl_3$-d_1) δ (ppm)
3a*	4-Fluorophenyl	$C_{19}H_{20}FN_3O_2$ (341,38)	167-68[1]	82	Ref. 21	
3b*	2-Fluorophenyl	$C_{19}H_{20}FN_3O_2$ (341,38)	144-45[1]	80	Ref. 21	
3c	4-Chlorophenyl	$C_{19}H_{20}ClN_3O_2$ (357,83) Calcd: C:63.77; H:5.63; N:11.74 Found: C:63.79; H:5.83; N:11.61	168-69[2]	79	1769[a] 1769[a]	2,35 (3H; s; -CH_3); 2,9-2,7 (4H; t; pip. H_2, H_6); 3,2-2,9 (4H; t; pip. H_3, H_5); 4,6 (2H; s; -CH_2-); 7,2-6,6 (7H; m; Arom-H.).
3d	3-Chlorophenyl	$C_{19}H_{20}ClN_3O_2$ (357.83) Calcd: C:63.77; H:5.63; N:11.74 Found: C:63.62; H:5.37; N:11.71	146-7[2]	69	1754[a]	2.3 (3H; s; 5-CH_3), 2.8 (4H; t; pip. H_2, H_6), 3.2 (4H; t; pip. H_3, H_5), 3.4 (2H; s; N-CH_2-C), 4.60 (2H; s; N-CH_2-N-), 6.6-7.4 (7H; m; Arom-H.)
3e*	2-Chlorophenyl	$C_{19}H_{20}ClN_3O_2$ (357,83)	159-60[2]	74	Ref. 22	
3f	2-Methoxyphenyl	$C_{20}H_{23}N_3O_3$ (353,42) Calcd: C:67.97; H:6.56; N:11.89 Found: C:67.42; H:5.32; N:11.85	156-58[1]	66	1778[a]	2,4 (3H; s; -CH_3); 2,9-2,7 (4H; s; pip. H_2, H_6); 3,2-3,0 (4H; s; pip. H_3, H_5); 3,8 (3H; s; -OCH_3), 4,7 (2H; s; -CH_2-); 7,3-6,7 (7H; m; Arom-H.)
3g	3-Methoxyphenyl	$C_{20}H_{23}N_3O_3$ (353,42) Calcd: C:67.97; H:6.56; N:11.89 Found: C:67.67; H:6.17; N:11.56	108-09[3]	60	1763[a]	2,2 (3H; s; -CH_3); 3,4-3,0 (4H; d; pip. H_3, 2,2 (3H; s; -CH_3); 3,4-3,0 (4H; d; pip. H_3, s; -OCH_3); 4,8 (2H; s; -CH_2-); 7,4-6,2 (7H; m; Arom-H.).
3h	2,3-Dimethylphenyl	$C_{21}H_{25}N_3O_2$ (351.42) Calcd: C:71.7; H:7.17; N:11.96 Found: C:71.67; H:7.23; N:11.82	141-2[3]	81	1764[a]	2.1 (3H; s; CH_3(o)-Ph-N), 2.2 (3H; s; CH_3(m)-Ph-N), 2.3 (3H; s; 5-CH_3), 2.9 (8H; s; pip. H_2, H_3, H_5, H_6), 4.6 (2H; s; N-CH_2-N-), 6.8-7.3 (6H; m; Arom-H.)

Table 1. Contunied



Comp.	R	Formula	M.p.	Yield %	IR (KBr) (cm^{-1})	^{1}H-NMR ($CHCl_3$-d_1) δ (ppm)
3i	4-Acetylphenyl	$C_{21}H_{23}N_3O_3$ (365.43) Calcd: C:69.02; H:6.34; N:11.50 Found: C:69.43; H:5.87; N:11.37	156-8[1]	83	1770[a]	2.3 (3H; s; 5-CH_3), 2.4 (3H; s; CO-CH_3), 2.8 (4H; t; pip. H_2,H_6), 3.3 (4H; t; pip. H_3,H_5), 4.65 (2H; s; N-CH_2-N-), 6.8-7.9 (7H; m; Arom-H.)
3j	2-Pyrimidinyl	$C_{17}H_{19}N_5O_2$ (339,39) Calcd: C:62.75; H:5.89; N:21.52 Found: C:62.92; H:5.49; N:21.21	170-1[1]	66	1776[a]	2.35 (3H; s; 5-CH_3), 2.8 (4H; t; pip. H_2,H_6), 3.8 (4H; t; pip. H_3,H_5), 4.6 (2H; s; N-CH_2-N-), 6.3-8.3 (6H; m; Arom-H.)
3k	3-Trifluoromethylphenyl	$C_{20}H_{20}F_3N_3O_2$ (391.39) Calcd: C:61.38; H:5.15; N:10.74 Found: C:61.63; H:4.85; N:10.52	159-60[4]	72	1757[a]	2.35 (3H; s; 5-CH_3), 2.8 (4H; t; pip. H_2, H_6), 3.2 (4H; t; pip. H_3, H_5), 4.7 (2H; s; N-CH_2-N-), 6.8-7.4 (7H; m; Arom-H.)
3l	2-Pyridyl	$C_{18}H_{20}N_4O_2$ (324.38) Calcd: C:66.65; H:6.21; N:17.17 Found: C:66.17; H:6.32; N:17.20	117-8[1]	70	1779[a]	2.35 (3H; s; 5-CH_3), 2.8 (4H; t; pip. H_2, H_6), 3.5 (4H; t; pip. H_3, H_5), 4.65 (2H; s; N-CH_2-N-), 6.5-8.2 (7H; m; Arom-H.)
3m	Benzyl	$C_{20}H_{23}N_3O_2$ (337.42) Calcd: C:71.19; H:6.87; N:12.45 Found: C:71.36; H:6.62; N:12.36	103-5[4] 103-5[4]	85 85	1786[a] 1786[a]	2.3 (3H; s; 5-CH_3), 2.4 (4H; t; pip. H_2, H_6), 2.8 (4H; t; pip. H_3, H_5), 3.4 (2H; s; N-CH_2-C), 4.60 (2H; s; N-CH_2-N-), 6.8-7.4 (8H; m; Arom-H.)
3n	Piperonyl	$C_{21}H_{23}N_3O_4$ (381.43) Calcd: C:66.13; H:6.08; N:11.02 Found: C:66.07; H:6.29; N:11.13	104-5[4]	63	1785[a]	2.2 (3H; s; 5-CH_3), 2.3 (4H; t; pip. H_2, H_6), 2.7 (4H; t; pip. H_3, H_5), 3.4 (2H; s; N-CH_2-C), 4.60 (2H; s; N-CH_2-N-), 5.8 (2H; s; O-CH_2-O), 6.7-7.3 (6H; m; Arom-H.)

[1]Acetone-water, [2]Methanol, [3]Ethanol, [4]Ethanol-water

[a]lactam

*Compounds 3a,3b,3e were prepared previously [21,22]

Analgesic activity of the resulting compounds was investigated by p-benzoquinone-induced writhing test[23], which is a well-established method of testing the analgesic activity of compounds and sufficiently sensitive to detect the effect of analgesics less active than aspirin. Antiinflammatory activities of the compounds were assessed by utilizing the carrageenan-induced hind paw edema model[24]. Since the carrageenan edema has been used in the development of indomethacine, many researchers have adapted this procedure for screening potential anti-inflammatory compounds. Carrageenan-induced edema is a nonspecific inflammation maintained by the release of histamine, 5-hydroxytryptamine, kinins and later by prostaglandins[25]. The inhibitory effect of NSAIDs, such as indomethacin, is usually weak in the first phase (1-2 h), in contrast with their strong inhibition in the second phase (3-4 h)[26]. Good inhibition of the second phase of carrageenan-induced edema was observed for the compounds tested, suggesting that they interfere with prostaglandin synthesis (Table 2).

On examination of the results, the derivative **2**, which did not carry any substitution on the third position, was found weaker than that bearing aminoalkyl residue on this position. It could be easily seen that most of the compounds exhibited antinociceptive activity in the writhing test, and some of them seemed to be more potent than aspirin under these test conditions. On the other hand, compound **3h** did not show any activity in the writhing test in comparison with the control. Viaud et al. suggested that the phenylpiperazinyl group enhanced the antinociceptive activity of the 2-oxo-1-aminoalkyl-oxazolo[5,4-b]pyridine derivatives synthesized[14]. As clearly seen, the oxazolo[5,4-b]pyridine-2-one ring is a bioisoster of a 2-benzoxazolinone ring system. Therefore, one can conclude that a phenylpiperazinyl moiety on the side chain may enhance the analgesic activity of these types of compounds. This finding is in good accordance with the data reported in our study. It was seen that the introduction of a phenylpiperazinyl group into the main skeleton (except **3h**) caused a noticeable increase in both analgesic and anti-inflammatory activity compared with the starting compound (compare **2**/ **3a**, **3b**, **3c**, **3d**, **3e**, **3i**, **3j**, **3k**), but no significant difference for the compounds carrying benzyl and 2-pyridyl was observed. The effect of substituents on the phenyl ring for the analgesic activity was examined. It appeared that the presence of an electron-donating substituent in the ortho position of the phenyl nucleus (**3f**, **3h**) abolished analgesic properties while electron-withdrawing ones led to increasing activity (**3b**, **3e**). Similarly, an electron-withdrawing substituent in the meta position (**3d**) also produced significant antinociceptive effects. The best analgesic activity was obtained for compounds with an electron-withdrawing substituent in the para position of the phenyl nucleus (**3a**, **3c**, **3i**). It was also noteworthy that the positions of fluorine and chlorine substitution (2-/4-Cl or 2-/4-F) on the phenyl group did not induce any remarkable change in the activity of the Mannich derivatives. A less remarkable but worthy of note result was obtained from the 2-pyrimidinyl substituent on the piperazine (**3j**). The compounds bearing acyclic residues as exemplified by structures 2-pyridyl and benzyl showed loss of activity, thus underscoring the importance of both the size and the shape of the auxiliary unit attached to the benzoxazolinone template.

Anti-inflammatory activity of the synthesized compounds was in parallel with their corresponding analgesic activities. Compound **3i** bearing acetylphenyl moiety was the most potent derivative in this series. It is well known the compounds with an anti-inflammatory effect can exhibit ulcerogenic properties. Therefore, the ulcerogenic activities of all the compounds were screened. In gastric ulceration studies, gastrointestinal bleeding was not observed at 100 mg/kg dose level for active compounds. Finally, among the compounds examined in this study, the compound **3i** possessed the most prominent and consistent activity. Compounds **3a** and **3b** deserve attention and may be considered for further evaluation. In conclusion, the

results suggested that the series of 5-methyl-2-benzoxazolinones had a superior analgesic activity profile and this indicated that these compounds may show activities via a central way.

Table 2. Percent analgesic activity and inhibition of carrageenan paw edema (CPE) of compounds 3a-3n.

	Anti-inflammatory Activity Swelling in thickness (x 10^{-2} mm) ± SEM (% inhibition)				Analgesic Activity	
Comp. No.	90 min	180 min	270 min	360 min	Number of writhings ± SEM (% Inhibition)	Ratio of ulceration
Control	43.7 ± 4.63	52.5 ± 5.09	58.7 ± 5.74	62.8 ± 4.28	44.2 ± 1.78	0/6
2	36.7 ± 4.2 (19.3)	41.3 ± 4.3 (20.1)	46.3 ± 3.9 (19.8)	51.3 ± 4.4 (19.8)	32.5 ± 4.2 (29.3)	0/6
3a	28.5 ± 3.22 (34.8)	36.0 ± 3.13 (31.4)	36.6 ± 3.35 (38.2)	37.7 ± 4.49 (39.9)	10.8 ± 1.22 (75.6)	0/6
3b	33.8 ± 3.44 (22.7)	35.0 ± 4.00 (33.3)	36.7 ± 2.43 (37.5)	38.7 ± 2.63 (38.4)	12.2 ± 1.58 (72.4)	0/6
3c	36.2 ± 2.55 (17.2)	39.8 ± 2.59 (24.2)	44.0 ± 2.52 (25.0)	47.5 ± 3.09 (24.4)	18.2 ± 2.21 (58.8)	0/6
3d	33.8 ± 3.1 (25.7)	35.7 ± 2.3 (30.9)	37.8 ± 2.7 (34.5)*	43.7 ± 2.9 (31.7)*	21.5 ± 2.4 (53.3)*	0/6
3e	34.8 ± 3.95 (20.4)	43.2 ± 4.02 (17.7)	46.7 ± 3.82 (20.4)	49.8 ± 3.32 (20.7)	20.2 ± 2.06 (54.3)	0/6
3f	37.2 ± 4.19 (14.9)	41.3 ± 4.04 (21.3)	46.5 ± 3.84 (20.8)	49.8 ± 3.52 (20.7)	30.2 ± 3.07 (31.7)	0/6
3g	38.0 ± 5.05 (13.0)	41.5 ± 4.91 (20.9)	45.5 ± 4.85 (22.5)	50.2 ± 4.73 (20.1)	25.7 ± 2.40 (41.9)	2/6**
3h	43.2 ± 4.1 (5.1)	47.5 ± 3.6 (8.1)	52.8 ± 3.6 (8.5)	57.2 ± 3.4 (10.6)	35.7 ± 4.7 (22.4)	1/6
3i	29.7 ± 2.5 (34.7)	33.0 ± 2.4 (36.2)	36.3 ± 2.5 (37.1)**	40.2 ± 2.9 (37.2)**	23.2 ± 2.8 (49.6)***	0/6 0/6
3j	36.8 ± 3.0 (19.1)	37.7 ± 2.2 (27.1)	40.0 ± 2.6 (30.7)*	41.4 ± 2.3 (35.5)**	25.7 ± 2.2 (44.1)**	0/6
3k	35.2 ± 4.3 (22.6)	39.8 ± 3.6 (23.0)	42.0 ± 3.9 (27.2)	44.3 ± 3.7 (30.8)*	28.5 ± 2.7 (38.0)*	0/6
3l	35.3 ± 3.9 (22.4)	39.2 ± 3.8 (24.2)	43.5 ± 4.0 (24.6)	46.3 ± 3.2 (27.7)*	35.3 ± 3.7 (23.2)	0/6
3m	41.3 ± 3.3 (9.2)	45.5 ± 3.6 (11.2)	49.8 ± 3.8 (13.7)	54.7 ± 3.6 (14.5)	37.0 ± 3.2 (19.6)	3/6
3n	37.5 ± 3.4 (17.6)	40.8 ± 3.6 (21.1)	44.8 ± 3.4 (22.3)	46.7 ± 3.6 (27.0)	31.0 ± 2.8 (32.6)*	0/6
INDO 10 mg	30.7 ± 4.2 (29.7)	33.0 ± 3.4 (37.1)*	35.3 ± 3.3 (39.9)**	34.2 ± 3.1 (45.5)***	-	0/6
ASA 100 mg	-	-	-	-	21.5 ± 2.2 (51.4)***	1/6

* $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$

The structure-activity relationships of our series of derivatives (**3a-3n**) are not fully understood. The mechanism underlying their analgesic activity remains to some degree unknown. A role of 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.

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