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Synthesis of 1-methyl-4-(*N*-aroyl)-piperidinamides with anti-inflammatory and analgesic activities

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Abstract

Two series of 1-methyl-4-(*N*-aroyl)-piperidinamides were synthesized and evaluated for their anti-inflammatory and analgesic properties, as well as for their gastrointestinal irritation liability. A non-aromatic derivative, 1-methyl-4-(*N*-cyclohexanoyl)-piperidinamide, was synthesized and evaluated in order to obtain a more exhaustive knowledge of the structure–activity relationship.

Keywords: Piperidinamides; Anti-inflammatory agents; Analgesic agents

1. Introduction

Interesting anti-inflammatory and analgesic activities of some *N*-aroyl-cyclohexyl- and cyclohexenyl-amides, 3- or 4-methyl-substituted, **1**, **2** and **3** (Fig. 1) have been reported in a previous recent paper [1] from our laboratories. In particular, the compound **3a** showed an anti-inflammatory activity comparable with that of the indomethacin. Other compounds also exhibited notable pharmacological activities; the structure–activity relationships have been evaluated too.

In the present paper, the synthesis and pharmacological investigation of some new derivatives **4a–h** and **5a–h**, are presented. These new molecules **4** and **5** were obtained from the compounds having general structure **3** by substituting the carbon in position 4 of the cyclohexane with a nitrogen atom. Furthermore, to investigate the importance of the presence of the 4-(*N*-aroyl) moiety we synthesized the compound **6** (Fig. 2), in which this residue was substituted by a 4-(*N*-cyclohexanoyl) group.

2. Chemistry

The synthesis of piperidinamides **4a–h**, **5a–h** and **6** is depicted in Scheme 1. 1-Methylpiperidin-4-one **7**, which was commercially available, was readily converted into its oxyme hydrochloride **8** according to Adams et al. [2]. The reduction of **8** with sodium in boiling anhydrous ethanol [3,4] or with lithium aluminum hydride in anhydrous diethyl ether [5] led to 1-methyl-4-aminopiperidine **9** in moderate yield (ca. 50% in both cases). However, a long reflux time (20 h) was necessary when the second method was followed, because of the low oxyme solubility.

The preparation of piperidinamides **4a–h**, **5a–h** and **6** was performed by stirring **9** with an excess of the appropriate acyl chloride in anhydrous benzene at room temperature. Most of the (un)substituted benzoyl chlorides and the unsubstituted

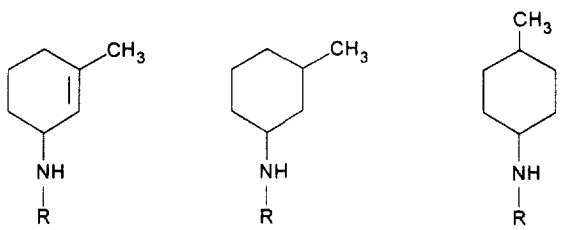

Fig. 1. *N*-Aroyl-cyclohexyl- and cyclohexenyl-amides 3- or 4-methyl-substituted **1**, **2** and **3** previously synthesized. Key: **a**, R = 4′-Cl–C_6H_4–CO–; **b**, R = 3′,4′,5′-$(CH_3O)_3$–C_6H_2–CO–; **c**, R-C_6H_5–CH=CH–CO–; **d**, R = 4′-Cl–C_6H_4–CH=CH–CO–; **e**: R = 3′,4′,5′-$(CH_3O)_3$–C_6H_2–CH=CH–CO–; **f**: R = 3′,4′-(CH_2O_2)–C_6H_3–CH=CH–CO–.

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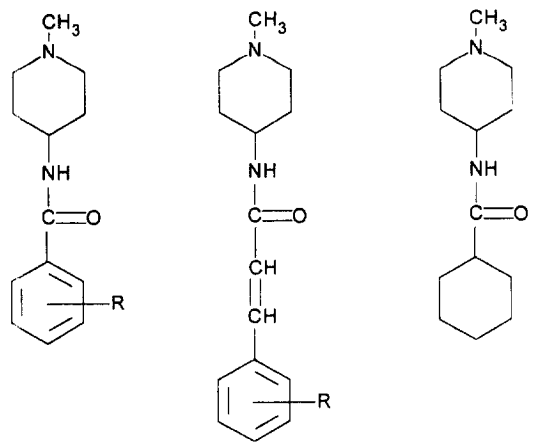


Fig. 2. 1-Methyl-4-(*N*-aroyl)-piperidinamides **4a–h** and **5a–h**, and 1-methyl-4-(*N*-cyclohexanoyl)-piperidinamide **6**. Key: **a**, R = 3′,4′,5′-$(CH_3O)_3$; **b**, R = 4′-Cl; **c**, R = 4′-F; **d**, R = 4′-Br; **e**, R = 2′,4′-dichloro; **f**, R = H; **g**, R = 4′-CH_3; **h**, R = 4′-NO_2.

cinnamoyl chloride used were commercially available, whereas the substituted cinnamoyl chlorides were prepared according to the procedure described by Koo et al. [6].

The physical characteristics and yields of piperidinamides **4a–h**, **5a–h** and **6** are reported in Section 5. The assigned structures were generally supported by IR, GC/MS data (Table 1), and ^1H and ^{13}C NMR (see Section 5) spectra. To correctly assign all ^1H NMR signals we also performed some COSY experiments on compounds **4d** and **6**.

3. Pharmacology

All compounds **4a–h**, **5a–h** and **6** were subjected to a series of in vivo tests in order to evaluate their pharmacological activity. The anti-inflammatory activity was studied by means of the carrageenin rat paw edema assay, whereas the acetic acid writhing test was used to assess the analgesic activity in mice. Higher molar doses were administered to rats in order to study the irritative and ulcerogenic action on the mucosa of the stomach and small intestine up to the distal ileum. Indomethacin was included in all tests as the reference drug.

4. Results and discussion

The results of the anti-inflammatory assay are shown in Table 2, and those of the analgesic assay in Table 3; the ulcerogenic activity is shown in Table 4.

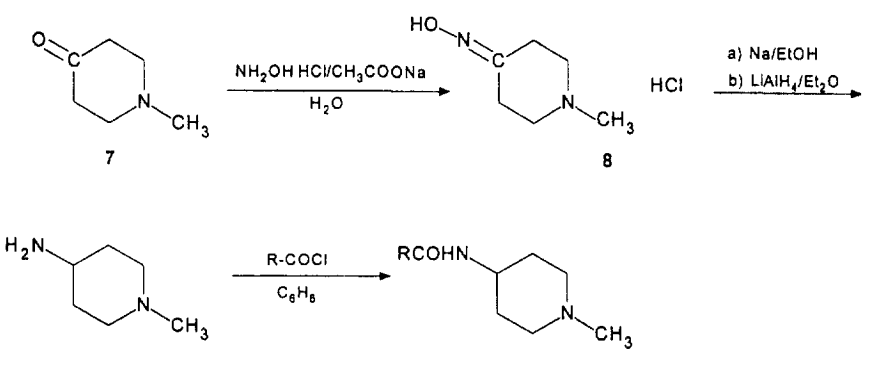
Anti-inflammatory and analgesic activities were evident in most of the tested compounds, though they were tested at a dosage more than ten times higher than the indomethacin used for comparison.

It is worth noting that derivatives **4a–h** and **5a–h** showed strongly different pharmacological profiles.

As regards the (un)substituted cinnamoyl derivatives **5a–h**, fairly good parallelism between anti-inflammatory and analgesic activities was found. In fact, in both tests the insertion of a substituent enhanced the pharmacological potency of the unsubstituted compound **5f**, although this effect was more evident in the anti-inflammatory activity test: the better results were shown by compounds bearing substituents with electron-drawing properties, such as compounds **5e,c,d** in the carrageenin rat paw edema test, and compounds **5b,d** in the writhing test. The methyl-substituted compound **5g** was completely lacking in anti-inflammatory activity, whereas its analgesic properties were not negligible.

On the contrary, no parallelism was found in the (un)substituted benzoyl series **4a–h**. In fact, in the anti-inflammatory activity test the better results were shown by the unsubstituted compound **4f**; the remaining compounds were less active. On the other hand, in the analgesic activity test compound **4f** was less active than many substituted compounds bearing electron-drawing substituents, such as **4b,c,d,e,h**. The methyl-substituted **4g** was scarcely active in both tests.

As regards the cyclohexanoyl derivative **6**, it showed some anti-inflammatory activity, whereas it was almost lacking in analgesic activity. As far as the ulcerogenic potency is concerned, all compounds are shown to be less ulcerogenic than indomethacin (at 14 μmol/kg), despite the severe dose used (375 μmol/kg). However, often it did not correspond to the anti-inflammatory and/or analgesic effect. In fact, the ulcerogenic potency of the most active compounds was not significantly different from that of compounds that were



Scheme 1. Synthesis of compounds **4a–h**, **5a–h** and **6**: (a) and (b) are alternative pathways.

Table 1
IR and GC/MS spectra of compounds **4a–h**, **5a–h** and **6**

Compound	t_r (min)	GC/MS Most important fragments (M^+/Z)	IR ν(N–H) (cm^{-1})	IR ν(C=O) (cm^{-1})
4a	25.7	308: (M^+); 211: [3′,4′,5′-$(CH_3O)_3$–C_6H_2–CO–NH_2]; 195: [3′,4′,5′-$(CH_3O)_3$–C_6H_2–CO]; 113: [$C_6H_{13}N_2$]	3280	1620
4b	16.8	252: (M^+); 156: [4′-Cl–C_6H_4–CO–NH_2]; 139: [4′-Cl–C_6H_4–CO]; 113: [$C_6H_{13}N_2$]	3310	1628
4c	9.9	236: (M^+); 140: [4′-F–C_6H_4–CO–NH_2]; 123: [4′-F–C_6H_4–CO]; 113: [$C_6H_{13}N_2$]	3310	1625
4d	14.4	296: (M^+); 200: [4′-Br–C_6H_4–CO–NH_2]; 184: [4′-Br–C_6H_4–CO]; 113: [$C_6H_{13}N_2$]	3310	1625
4e	14.3	286: (M^+); 190: [2′,4′-Cl_2–C_6H_3–CO–NH_2]; 173: [2′,4′-Cl_2–C_6H_4–CO]; 113: [$C_6H_{13}N_2$]	3240	1635
4f	5.3	218: (M^+); 121: [C_6H_5–CO–NH_2]; 113: [$C_6H_{13}N_2$]; 105: [C_6H_5CO]	3310	1628
4g	6.7	232: (M^+); 135: [4′-CH_3–C_6H_4–CO–NH_2]; 119: [4′-CH_3–C_6H_4–CO]; 113: [$C_6H_{13}N_2$]	3330	1625
4h	10.8	263: (M^+); 166: [4′-NO_2–C_6H_4–CO–NH_2]; 150: [4′-NO_2–C_6H_4–CO]; 113: [$C_6H_{13}N_2$]	3300	1625
5a	17.3	334: (M^+); 237: [3′,4′,5′-$(CH_3O)_3$–C_6H_2–CH=CH–CO–NH_2]; 221: [3′,4′,5′-$(CH_3O)_3$–C_6H_2–CO]; 113: $C_6H_{13}N_2$]	3270	1645
5b	7.4	278: (M^+); 181: [4′-Cl–C_6H_4–CH=CH–CO–NH_2]; 165: [4′-Cl–C_6H_4–CH=CH–CO]; 113: [$C_6H_{13}N_2$]	3250	1650
5c	13.4	262: (M^+); 165: [4′-F–C_6H_4–CH=CH–CO–NH_2]; 149: [4′F–C_6H_4–CO]; 113: [$C_6H_{13}N_2$]	3260	1650
5d	18.8	322: (M^+); 225: [4′-Br–C_6H_4–CH=CH–CO–NH_2]; 209: [4′-Br–C_6H_4–CO]; 113: [$C_6H_{13}N_2$]	3240	1640
5e	19.1	312: (M^+); 215: [2′,4′-Cl_2–C_6H_3–CH=CH–CO–NH_2]; 199: [2′,4′-Cl_2–C_6H_4–CO]; 113: [$C_6H_{13}N_2$]	3240	1650
5f	12.4	244: (M^+); 147: [C_6H_5–CH=CH–CO–NH_2]; 131: [C_6H_5–CH=CH–CO]; 113: [$C_6H_{13}N_2$]	3250	1650
5g	15.7	258: (M^+); 161: [4′-CH_3–C_6H_4–CH=CH–CO–NH_2]; 145: [4′-CH_3–C_6H_4–CH=CH–CO]; 113: [$C_6H_{13}N_2$]	3260	1640
5h	21.1	289: (M^+); 192: [4′-NO_2–C_6H_4–CH=CH–CO–NH_2]; 176: [4′-NO_2–C_6H_4–CH=CH–CO]; 113: [$C_6H_{13}N_2$]	3260	1650
6	4.8	224: (M^+); 127: [C_6H_{11}–CO–NH_2]; 113: [$C_6H_{13}CO$]; 111: [$C_6H_{11}CO$]	3280	1630

Table 2
Carrageenin rat paw edema: anti-inflammatory activity

Compound	Dose (μmol/kg po)	Edema inhibition (%) relative to control at: 3rd hour	4th hour
Indomethacin	14	−63	−68
4a	150	−12	−8
4b	150	−42	−50
4c	150	−16	−28
4d	150	−38	−33
4e	150	−16	−12
4f	150	−67	−58
4g	150	−42	−34
4h	150	−53	−46
5a	150	−30	−20
5b	150	−46	−38
5c	150	−51	−52
5d	150	−37	−46
5e	150	−46	−54
5f	150	−28	−24
5g	150	−16	−10
5h	150	−42	−34
6	150	−46	−38

Table 3
Acetic acid writhing test: analgesic activity

Compound	Dose (μmol/kg po)	Mean No. of writhes in 25 min period after treatment ± S.E.	Decrease (%) relative to controls
Controls		45.6 ± 5.3	
Indomethacin	14	22.7 ± 4.1	−50
4a	150	37.3 ± 5.3	−18
4b	150	27.2 ± 2.9	−40
4c	150	24.7 ± 3.3	−46
4d	150	25.2 ± 3.7	−45
4e	150	23.2 ± 4.3	−50
4f	150	28.2 ± 5.6	−38
4g	150	34.1 ± 5.9	−25
4h	150	25.3 ± 5.1	−44
5a	150	38.6 ± 4.7	−15
5b	150	25.1 ± 2.4	−45
5c	150	37.5 ± 3.3	−18
5d	150	26.4 ± 5.1	−42
5e	150	40.1 ± 2.9	−12
5f	150	34.5 ± 3.7	−24
5g	150	30.0 ± 4.5	−34
5h	150	34.0 ± 3.8	−25
6	150	37.2 ± 4.9	−18

completely lacking in anti-inflammatory and analgesic activities (**4a**, **5a**,**g**).

These pharmacological results allow some preliminary conclusions about the structure–activity relationships:

– With respect to compounds of general structure **3** [1], the insertion of the nitrogen atom in the cyclohexane ring profoundly changed the pharmacological profile of that class of compounds. In fact, as regards compounds **3a**,**b** and the corresponding (un)substituted benzoyl series **4a–h**, the parallelism between the anti-inflammatory and the analgesic activities that was evident especially in compound **3a**, was completely lost in the new derivatives **4a–h**; as regards compounds **3c–f** and the corresponding (un)substituted cinnamoyl series **5a–h**, in the new derivatives the insertion of substituents on the aromatic ring enhanced the activity, whereas in compounds **3c–f** the most active was the unsubstituted **3c**.

– The presence of the vinyl group as a spacer between the aromatic and the carbamoyl-piperidinic rings completely

Table 4
Induction of gastric lesions in rats

Compound	Dose (μmol/kg po)	6th h after treatment, animals with:	
		Hyperemia (%)	Ulcers (%)
Indomethacin	14	80	60
4a	375	60	30
4b	375	60	40
4c	375	60	40
4d	375	30	20
4e	375	20	20
4f	375	40	30
4g	375	50	40
4h	375	30	20
5a	375	70	50
5b	375	30	20
5c	375	50	40
5d	375	40	20
5e	375	20	20
5f	375	50	30
5g	375	60	50
5h	375	30	30
6	375	40	40

changed the pharmacological behavior of the corresponding derivatives **4a–h** and **5a–h**: in the former series, the anti-inflammatory activity was reduced by the presence of substituents on the aromatic ring, whereas the analgesic activity was enhanced; in the latter series, both activities were enhanced by electron-drawing substituents, although some substituents were effective only in the anti-inflammatory activity test.

– The low pharmacological and ulcerogenic activities of the cyclohexanoyl derivative **6** suggest that the pharmacophorical portion of this class of compounds may be represented by the carbamoyl-piperidinic moiety.

A possible partial explanation for the different pharmacological behavior of the present piperidinamides with respect to the corresponding compounds of general structure **3** [1] can be provided by their structural resemblance to the central analgesic drug meperidine (Fig. 3). The target of the activity of compounds **4a–h**, **5a–h** and **6** may be multiple, acting both on the inflamed area of the body and on the central nervous system. These two activities could be differently affected by structural modifications, thus making the interpretation of the pharmacological data quite hard.

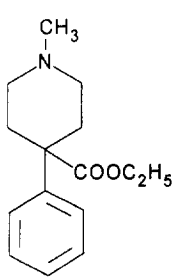


Fig. 3. Molecular structure of 1-methyl-4-phenyl-4-carboxyethylpiperidine (meperidine).

In conclusion, these series of amides provide preliminary information about the development of new selective anti-inflammatory and analgesic compounds. A more detailed pharmacological characterization is required to establish their mechanism of action.

5. Experimental

5.1. Chemistry

Precoated silica gel Merck 60 F254 plates were used for thin layer chromatography (TLC); components were detected using UV light (254 nm) and/or treatment with iodine vapors. Chromatographic and flash-chromatographic separations were performed in columns packed with silica gel 60, Merck 70–230 mesh ASTM and Merck 230–400 mesh ASTM, respectively. Melting points were determined using a Kofler hot-stage microscope and are uncorrected.

IR spectra were recorded on a Perkin-Elmer model 298 spectrophotometer, including solid samples in KBr pellets and analyzing liquid samples as films. GC/MS spectra were obtained from an HP5970A (Hewlett-Packard) apparatus, equipped with a capillary column HP-5 (25 m×0.2 mm×0.11 μm). The programmed temperature ranged from 100 to 300°C (10°C/min), the detector temperature was set to 300°C and the carrier gas was helium at a pressure of 10 psi.

The ^{1}H and ^{13}C NMR measurements were performed on a Bruker AMX 500 MHz spectrometer equipped with a Bruker X-32 computer, using $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. Chemical shifts are expressed in ppm downfield from tetramethylsilane and coupling constants *J* are expressed in hertz.

Commercially available solvents and chemicals were usually used for syntheses.

5.1.1. Synthesis of 1-methylpiperidin-4-one oxyme 8 [2]

9.0 g (131 mmol) of hydroxylamine hydrochloride and 13.0 g (95 mmol) of sodium acetate hydrate crystals ($NaC_2H_3O_2 \cdot 3H_2O$) were dissolved in 35 ml of water in a two-necked round-bottomed flask fitted with a thermometer and a mechanical stirrer.

The solution was then warmed up to about 40°C and 10.0 g (10.2 ml, 88 mmol) of 1-methylpiperidin-4-one **7** (previously distilled) were added. The mixture was vigorously stirred for 15 min, cooled to −5°C for 2 hours and then concentrated in vacuo to about 50% of its original volume. Precipitated white crystals were filtered, washed with water and recrystallized (white needles) from hot water or ethanol, to afford 1-methylpiperidin-4-one oxyme hydrochloride **8** (12.0 g, 73 mmol); yield 82%, m.p. 241–242°C.

5.1.2. Synthesis of 1-methyl-4-aminopiperidine 9

5.1.2.1. Method a [3,4]

15.0 g (653 mmol) of clean sodium (previously cut into small pieces) were added portionwise to a solution of 8.0 g

(48 mmol) of 1-methylpiperidin-4-one oxyme hydrochloride **8** in 170 ml of boiling anhydrous ethanol, keeping the vigorous reaction under control. When the sodium had reacted completely, the reaction mixture was cooled and diluted with a hydro-alcoholic solution (water/ethanol 1:1, 100–120 ml) and then acidified dropwise with conc. HCl under mechanical stirring until the solution resulted acid to litmus.

The white precipitate (NaCl) was filtered off and the solvent was evaporated in vacuo, giving a viscous oil, which was treated with diethyl ether (8–10 ml) and water (30 ml), the ethereal phase being discarded. The aqueous phase was basified dropwise with 2N NaOH until the solution resulted basic to litmus; it was then extracted with diethyl ether. The organic phase was dried with anhydrous sodium sulfate and evaporated in vacuo to give a mobile yellow oil. The crude oil was distilled in vacuo using a Kugelrohr apparatus (b.p. 50–53°C/5 mmHg) to yield 2.8 g (24 mmol, yield 50%) of 1-methyl-4-aminopiperidine **9**, as a mobile colorless oil.

5.1.2.2. Method b [5]

A suspension of 1-methylpiperidin-4-one oxyme hydrochloride **8** (3.6 g, 22 mmol) in anhydrous diethyl ether (10 ml) was added dropwise to a suspension of lithium aluminum hydride (1.0 g, 26 mmol) in anhydrous diethyl ether (10 ml), under vigorous stirring. The reaction mixture was refluxed for 20 h, until the TLC analysis (eluant ethyl acetate/diethyl ether 1:1) indicated the disappearance of the starting materials; it was then cooled to room temperature and cautiously quenched with water. The mixture was filtered through Celite and the filter cake (inorganic compounds) was washed with diethyl ether. The filtrate was dried on anhydrous sodium sulfate and concentrated in vacuo to give a mobile yellow oil, which was distilled in vacuo using a Kugelrohr apparatus to yield 1.25 g (22 mmol, yield 50%) of 1-methyl-4-aminopiperidine **9**, as a clear colorless oil.

*5.1.3. General procedure for the preparation of 1-methyl-4-(N-aroyl)-and 1-methyl-4-(N-cyclohexanoyl)-piperidinamides **4a–h**, **5a–h** and **6***

A solution of 1-methyl-4-aminopiperidine **9** (5 mmol) in anhydrous benzene (ca. 30 ml) was added dropwise, via an addition funnel, to an ice-cold solution of the appropriate acyl chloride (6 mmol) in the same solvent, under mechanical stirring. The mixture was allowed to warm to room temperature and was vigorously stirred for a time varying from 30 min to 2 h, until the TLC analysis (eluant ethyl acetate/diethyl ether 1:1) indicated the disappearance of the starting materials.

The abundant precipitate obtained was filtered, dried and then dissolved in H_2O (10–20 ml). The aqueous solution was washed with ethyl ether (10 ml), adjusted to pH 13–14 with 25% aqueous NaOH and then extracted with chloroform. The organic layer was dried (anhydrous sodium sulfate) and evaporated in vacuo to give the title products **4a–h**, **5a–h** and **6** (free bases) as white crystals or colorless needles, which did not need any further purification.

To enhance the reaction yield the initial filtrate was evaporated to dryness in vacuo, treated with a 10N NH_3 solution (30 ml) and extracted with diethyl ether. The organic phase was dried (anhydrous sodium sulfate) and evaporated in vacuo, to afford the crude amide compound, which was purified by silica gel chromatography or flash-chromatography using as eluant a mixture of ethyl acetate/diethyl ether. The appropriate fractions were collected and evaporated to afford the desired products **4a–h**, **5a–h** and **6**, which were stored together with the amounts obtained as described above.

*5.1.3.1. 1-Methyl-4-[N-(3′,4′,5′-trimethoxybenzoyl)]-piperidinamide **4a***

Formula $C_{16}H_{24}N_2O_4$, mol. wt. 308, m.p. 135–137°C, yield 93%.

^{1}H ($CDCl_3$): 1.76 (bq, 2H, J = 11.8 Hz, H_{ax}-3 and H_{ax}-5), 2.08 (bd, 2H, J = 11.8 Hz, H_{eq}-3 and H_{eq}-5), 2.28 (bt, 2H, J = 10.8 Hz, H_{ax}-2 and H_{ax}-6), 2.40 (s, 3H, N–CH_3), 2.97 (bd, 2H, J = 10.8 Hz, H_{eq}-2 and H_{eq}-6), 3.86 (s, 3H, 4′-OCH_3), 3.92 (s, 6H, 2 *m*-OCH_3), 4.03 (m, 1H, H-4), 6.21 (d, 1H, J = 6.8 Hz, NH), 7.02 (s, 2H, H-2′ and H-6′).

^{13}C ($CDCl_3$): 31.55 (2C, C-3 and C-5), 45.59 (N–CH_3), 46.34 (C-4), 54.46 (2C, C-2 and C-6), 56.37 (2C, 2 *m*-OCH_3), 60.86 (4′-OCH_3), 104.57 (2C, C-2′ and C-6′), 130.01 (C-1′), 153.13 (3C, C-3′, C-4′ and C-5′), 165.68 (CO).

*5.1.3.2. 1-Methyl-4-[N-(4′-chlorobenzoyl)]-piperidinamide **4b***

Formula $C_{13}H_{17}N_2OCl$, mol. wt. 252, m.p. 201–203°C, yield 88%.

^{1}H ($CDCl_3$): 1.58 (bq, 2H, J = 11.8 Hz, H_{ax}-3 and H_{ax}-5), 2.04 (bd, 2H, J = 11.8 Hz, H_{eq}-3 and H_{eq}-5), 2.14 (bt, 2H, J = 10.8 Hz, H_{ax}-2 and H_{ax}-6), 2.31 (s, 3H, N–CH_3), 2.82 (bd, 2H, J = 10.8 Hz, H_{eq}-2 and H_{eq}-6), 3.97 (m, 1H, H-4), 5.96 (d, 1H, J = 6.8 Hz, NH), 7.41 (d, 2H, J = 8.5 Hz, H-3′ and H-5′), 7.70 (d, 2H, J = 8.5 Hz, H-2′ and H-6′).

^{13}C ($CDCl_3$): 32.34 (2C, C-3 and C-5), 46.19 (N–CH_3), 46.79 (C-4), 54.48 (2C, C-2 and C-6), 128.29 (2C, C-3′ and C-5′), 128.78 (2C, C-2′ and C-6′), 133.14 (C-1′), 137.62 (C-4′), 165.80 (CO).

*5.1.3.3. 1-Methyl-4-[N-(4′-fluorobenzoyl]-piperidinamide **4c***

Formula $C_{13}H_{17}N_2OF$, mol. wt. 236, m.p. 218–219°C, yield 89%.

^{1}H ($CDCl_3$): 1.56 (bq, 2H, J = 11.5 Hz, H_{ax}-3 and H_{ax}-5), 2.02 (bd, 2H, J = 11.5 Hz, H_{eq}-3 and H_{eq}-5), 2.12 (bt, 2H, J = 10.8 Hz, H_{ax}-2 and H_{ax}-6), 2.30 (s, 3H, N–CH_3), 2.82 (bd, 2H, J = 10.8 Hz, H_{eq}-2 and H_{eq}-6), 3.95 (m, 1H, H-4), 6.02 (d, 1H, J = 6.8 Hz, NH), 7.08 (t, 2H, J = 8.8 Hz, H-3′ and H-5′), 7.76 (dd, 2H, J = 8.8, 5.1 Hz, H-2′ and H-6′).

^{13}C ($CDCl_3$): 32.26 (2C, C-3 and C-5), 46.12 (N–CH_3), 46.71 (C-4), 54.48 (2C, C-2 and C-6), 115.51 (d, 2C, $J_{C\text{-}F}$ = 22.9 Hz, C-3′ and C-5′), 129.18 (d, 2C, $J_{C\text{-}F}$ = 9.5 Hz,

C-2′ and C-6′), 130.91 (C-1′), 164.63 (d, J_{C-F} = 251.8 Hz, C-4′), 165.85 (CO).

5.1.3.4. 1-Methyl-4-[N-(4′-bromobenzoyl)]-piperidinamide ***4d***

Formula $C_{13}H_{17}N_2OBr$, mol. wt. 296, m.p. 260–262°C, yield 87%.

^1H ($CDCl_3$): 1.58 (bq, 2H, J = 12.0 Hz, H_{ax}-3 and H_{ax}-5), 2.04 (bd, 2H, J = 12.0 Hz, H_{eq}-3 and H_{eq}-5), 2.18 (bt, 2H, J = 11.3 Hz, H_{ax}-2 and H_{ax}-6), 2.34 (s, 3H, N–CH_3), 2.83 (bd, 2H, J = 11.3 Hz, H_{eq}-2 and H_{eq}-6), 3.98 (m, 1H, H-4), 5.98 (d, 1H, J = 6.8 Hz, NH), 7.58 (d, 2H, J = 8.5, H-3′ and H-5′), 7.64 (d, 2H, J = 8.5 Hz, H-2′ and H-6′).

^{13}C ($CDCl_3$): 32.30 (2C, C-3 and C-5), 46.17 (N–CH_3), 46.77 (C-4), 54.46 (2C, C-2 and C-6), 126.06 (C-4′), 128.49 (2C, C-3′ and C-5′), 131.78 (2C, C-2′ and C-6′), 133.56 (C-1′), 165.90 (CO).

5.1.3.5. 1-Methyl-4-[N-(2′,4′-dichlorobenzoyl)]-piperidinamide ***4e***

Formula $C_{13}H_{16}N_2OCl_2$, mol. wt. 287, m.p. 181°C, yield 90%.

^1H ($CDCl_3$): 1.62 (bq, 2H, J = 12.5 Hz, H_{ax}-3 and H_{ax}-5), 2.08 (bd, 2H, J = 12.5 Hz, H_{eq}-3 and H_{eq}-5), 2.20 (bt, 2H, J = 11.0 Hz, H_{ax}-2 and H_{ax}-6), 2.32 (s, 3H, N–CH_3), 2.84 (bd, 2H, J = 11.0 Hz, H_{eq}-2 and H_{eq}-6), 4.02 (m, 1H, H-4), 6.14 (d, 1H, J = 6.8 Hz, NH), 7.34 (d, 1H, J = 8.5 H-5′), 7.42 (s, 1H, H-3′), 7.62 (d, 1H, J = 8.5 Hz, H-6′).

^{13}C ($CDCl_3$): 32.05 (2C, C-3 and C-5), 46.22 (N–CH_3), 46.89 (C-4), 54.29 (2C, C-2 and C-6), 127.53, 129.99 and 131.21 (C-3′, C-5′ and C-6′), 131.24 (C-1′), 133.58 and 136.68 (C-2′ and C-4′), 164.79 (CO).

5.1.3.6. 1-Methyl-4-(N-benzoyl)-piperidinamide ***4f***

Formula $C_{13}H_{18}N_2O$, mol. wt. 218, m.p. 167–168°C (Ref. [7], 164–165°C), yield 86%.

^1H ($CDCl_3$): 1.60 (bq, 2H, J = 12.0 Hz, H_{ax}-3 and H_{ax}-5), 2.06 (bd, 2H, J = 12.0 Hz, H_{eq}-3 and H_{eq}-5), 2.18 (bt, 2H, J = 11.2 Hz, H_{ax}-2 and H_{ax}-6), 2.28 (s, 3H, N–CH_3), 2.84 (bd, 2H, J = 11.2 Hz, H_{eq}-2 and H_{eq}-6), 3.98 (m, 1H, H-4), 6.06 (d, 1H, J = 6.8 Hz, NH), 7.42 (t, 2H, J = 8.5 Hz, H-3′ and H-5′), 7.48 (t, 1H, J = 5 Hz, H-4′), 7.78 (d, 2H, J = 8.5 Hz, H-2′ and H-6′).

^{13}C ($CDCl_3$): 32.38 (2C, C-3 and C-5), 46.23 (N–CH_3), 46.61 (C-4), 54.51 (2C, C-2 and C-6), 126.84 (2C, C-3′ and C-5′), 128.53 (2C, C-2′ and C-6′), 131.37 (C-4′), 134.80 (C-1′), 166.89 (CO).

5.1.3.7. 1-Methyl-4-[N-(4′-methylbenzoyl)]-piperidinamide ***4g***

Formula $C_{14}H_{20}N_2O$, mol. wt. 232, m.p. 194–196°C, yield 92%.

^1H ($CDCl_3$): 1.58 (bq, 2H, J = 12.2 Hz, H_{ax}-3 and H_{ax}-5), 2.04 (bd, 2H, J = 12.2 Hz, H_{eq}-3 and H_{eq}-5), 2.16 (bt, 2H, J = 11.4 Hz, H_{ax}-2 and H_{ax}-6), 2.26 (s, 3H, N–CH_3), 2.40 (s, 3H, 4′-CH_3), 2.84 (bd, 2H, J = 11.4 Hz, H_{eq}-2 and H_{eq}-6), 3.98 (m, 1H, H-4), 6.02 (d, 1H, J = 6.8 Hz, NH), 7.22 (d, 2H, J = 8.5 Hz, H-3′ and H-5′), 7.64 (d, 2H, J = 8.5 Hz, H-2′ and H-6′).

^{13}C ($CDCl_3$): 21.39 (4′-CH_3), 32.41 (2C, C-3 and C-5), 46.22 (N–CH_3), 46.51 (C-4), 54.53 (2C, C-2 and C-6), 126.82 (2C, C-3′ and C-5′), 129.16 (2C, C-2′ and C-6′), 131.95 (C-1′), 141.75 (C-4′), 166.80 (CO).

5.1.3.8. 1-Methyl-4-[N-(4′-nitrobenzoyl)]-piperidinamide ***4h***

Formula $C_{13}H_{17}N_3O_3$, mol. wt. 263, m.p. 189–190°C, yield 84%.

^1H ($CDCl_3$): 1.62 (bq, 2H, J = 12.1 Hz, H_{ax}-3 and H_{ax}-5), 2.06 (bd, 2H, J = 12.1 Hz, H_{eq}-3 and H_{eq}-5), 2.18 (bt, 2H, J = 11.3 Hz, H_{ax}-2 and H_{ax}-6), 2.28 (s, 3H, N–CH_3), 2.84 (bd, 2H, J = 11.3 Hz, H_{eq}-2 and H_{eq}-6), 3.98 (m, 1H, H-4), 6.22 (d, 1H, J = 6.8 Hz, NH), 7.94 (d, 2H, J = 8.5, H-3′ and H-5′), 8.24 (d, 2H, J = 8.5 Hz, H-2′ and H-6′).

^{13}C ($CDCl_3$): 32.15 (2C, C-3 and C-5), 46.11 (N–CH_3), 47.14 (C-4), 54.42 (2C, C-2 and C-6), 123.78 (2C, C-3′ and C-5′), 128.12 (2C, C-2′ and C-6′), 140.29 (C-1′), 149.55 (C-4′), 164.88 (CO).

5.1.3.9. 1-Methyl-4-[N-(3′,4′,5′-trimethoxycinnamoyl)]-piperidinamide ***5a***

Formula $C_{18}H_{26}N_2O_4$, mol. wt. 334, m.p. 155–156°C, yield 91%.

^1H ($CDCl_3$): 1.76 (bq, 2H, J = 11.8 Hz, H_{ax}-3 and H_{ax}-5), 2.08 (bd, 2H, J = 11.8 Hz, H_{eq}-3 and H_{eq}-5), 2.28 (bt, 2H, J = 10.8 Hz, H_{ax}-2 and H_{ax}-6), 2.40 (s, 3H, N–CH_3), 2.97 (bd, 2H, J = 10.8 Hz, H_{eq}-2 and H_{eq}-6), 3.86 (s, 3H, 4′-OCH_3), 3.92 (s, 6H, 3′- and 5′-OCH_3), 4.03 (m, 1H, H-4), 6.21 (d, 1H, J = 6.8 Hz, NH), 7.02 (s, 2H, H-2′ and H-6′).

^{13}C ($CDCl_3$): 31.55 (2C, C-3 and C-5), 45.59 (N–CH_3), 46.34 (C-4), 54.46 (2C, C-2 and C-6), 56.37 (2C, 3′- and 5′-OCH_3), 60.86 (4′-OCH_3), 104.57 (2C, C-2′ and C-6′), 130.01 (C-1′), 153.13 (3C, C-3′, C-4′ and C-5′), 165.68 (CO).

5.1.3.10. 1-Methyl-4-[N-(4′-chlorocinnamoyl)]-piperidinamide ***5b***

Formula $C_{15}H_{19}N_2OCl$, mol. wt. 278, m.p. 242°C, yield 85%.

^1H ($CDCl_3$): 1.53 (bq, 2H, J = 12.0 Hz, H_{ax}-3 and H_{ax}-5), 1.99 (bd, 2H, J = 12.0 Hz, H_{eq}-3 and H_{eq}-5), 2.12 (bt, 2H, J = 11.2 Hz, H_{ax}-2 and H_{ax}-6), 2.28 (s, 3H, N–CH_3), 2.82 (bd, 2H, J = 11.2 Hz, H_{eq}-2 and H_{eq}-6), 3.92 (m, 1H, H-4), 5.56 (d, 1H, J = 6.8 Hz, NH), 6.34 (d, 1H, J = 15.3, C*H*=CH–CO), 7.32 (d, 2H, H-3′ and H-5′), 7.42 (d, 2H, H-2′ and H-6′), 7.56 (d, 1H, J = 15.3 Hz, C*H*=CH–CO).

^{13}C ($CDCl_3$): 32.35 (2C, C-3 and C-5), 46.21 (N–CH_3), 46.18 (C-4), 54.45 (2C, C-2 and C-6), 121.33 (CH=*C*H–CO), 128.92 (2C, C-3′ and C-5′), 129.06 (2C, C-2′ and C-6′), 133.32 (C-1′), 135.46 (C-4′), 139.67 (*C*H=CH–CO), 165.86 (CO).

5.1.3.11. 1-Methyl-4-[N-(4′-fluorocinnamoyl)]-piperidinamide ***5c***

Formula $C_{15}H_{19}N_2OF$, mol. wt. 262, m.p. 200–201°C, yield 86%.

^1H ($CDCl_3$): 1.60 (bq, 2H, J = 11.5 Hz, H_{ax}-3 and H_{ax}-5), 2.04 (bd, 2H, J = 11.5 Hz, H_{eq}-3 and H_{eq}-5), 2.22 (bt, 2H, J = 10.8 Hz, H_{ax}-2 and H_{ax}-6), 2.32 (s, 3H, N–CH_3), 2.86 (bd, 2H, J = 10.8 Hz, H_{eq}-2 and H_{eq}-6), 3.96 (m, 1H, H-4), 5.58 (d, 1H, J = 6.8 Hz, NH), 6.32 (d, 1H, J = 15.4, CH=C*H*–CO), 7.04 (t, 2H, J = 8.8 Hz, H-3′ and H-5′), 7.46 (dd, 2H, J = 8.8, 5.1 Hz, H-2′ and H-6′), 7.58 (d, 1H, J = 15.4, C*H*=CH–CO).

^{13}C ($CDCl_3$): 32.00 (2C, C-3 and C-5), 45.90 (N–CH_3), 46.03 (C-4), 54.36 (2C, C-2 and C-6), 115.83 (d, 2C, $J_{C\text{-}F}$ = 22.9 Hz, C-3′ and C-5′), 120.52 (CH=*C*H–CO), 129.48 (d, 2C, $J_{C\text{-}F}$ = 9.5 Hz, C-2′ and C-6′), 131.20 (C-1′), 139.71 (*C*H=CH–CO), 163.49 (d, $J_{C\text{-}F}$ = 252.0 Hz, C-4′), 165.03 (CO).

5.1.3.12. 1-Methyl-4-[N-(4′-bromobenzoyl)]-piperidinamide ***5d***

Formula $C_{15}H_{19}N_2OBr$, mol. wt. 323, m.p. 235–237°C, yield 84%.

^1H ($CDCl_3$): 1.56 (bq, 2H, J = 11.2 Hz, H_{ax}-3 and H_{ax}-5), 2.00 (bd, 2H, J = 11.2 Hz, H_{eq}-3 and H_{eq}-5), 2.12 (bt, 2H, J = 10.6 Hz, H_{ax}-2 and H_{ax}-6), 2.28 (s, 3H, N–CH_3), 2.80 (bd, 2H, J = 10.6 Hz, H_{eq}-2 and H_{eq}-6), 3.90 (m, 1H, H-4), 5.64 (d, 1H, J = 6.8 Hz, NH), 6.38 (d, 1H, J = 15.4, CH=C*H*–CO), 7.36 (d, 2H, J = 8.5 Hz, H-3′ and H-5′), 7.44 (d, 2H, J = 8.5 Hz, H-2′ and H-6′), 7.56 (d, 1H, J = 15.4 Hz, C*H*=CH–CO).

^{13}C ($CDCl_3$): 31.44 (2C, C-3 and C-5), 45.42 (N–CH_3), 45.78 (C-4), 54.09 (2C, C-2 and C-6), 121.45 (CH=*C*H–CO), 123.76 (C-4′), 129.12 (2C, C-3′ and C-5′), 132.01 (2C, C-2′ and C-6′), 133.76 (C-1′), 139.73 (*C*H=CH–CO), 164.95 (CO).

5.1.3.13. 1-Methyl-4-[N-(2′,4′-dichlorocinnamoyl)]-piperidinamide ***5e***

Formula $C_{15}H_{18}N_2OCl_2$, mol. wt. 314, m.p. 245°C, yield 87%.

^1H ($CDCl_3$): 1.64 (bq, 2H, J = 12.0 Hz, H_{ax}-3 and H_{ax}-5), 2.04 (bd, 2H, J = 12.0 Hz, H_{eq}-3 and H_{eq}-5), 2.25 (bt, 2H, J = 11.2 Hz, H_{ax}-2 and H_{ax}-6), 2.35 (s, 3H, N–CH_3), 2.92 (bd, 2H, J = 11.2 Hz, H_{eq}-2 and H_{eq}-6), 3.96 (m, 1H, H-4), 5.94 (d, 1H, J = 6.8 Hz, NH), 6.42 (d, 1H, J = 15.2 Hz, CH=C*H*–CO), 7.22 (d, 1H, J = 8.5 Hz, H-5′), 7.42 (s, 1H, H-3′), 7.48 (d, 1H, J = 8.5 Hz, H-6′), 7.90 (d, 1H, J = 15.2 Hz, C*H*=CH–CO).

^{13}C ($CDCl_3$): 31.58 (2C, C-3 and C-5), 45.58 (N–CH_3), 45.94 (C-4), 54.20 (2C, C-2 and C-6), 124.09 (CH=*C*H–CO), 127.34, 128.23 and 129.90 (C-3′, C-5′ and C-6′), 131.79 (C-1′), 135.23 and 135.59 (C-2′ and C-4′), 135.79 (*C*H=CH–CO), 164.49 (CO).

5.1.3.14. 1-Methyl-4-(N-cinnamoyl)-piperidinamide ***5f***

Formula $C_{15}H_{20}N_2O$, mol. wt. 244, m.p. 161–163°C, yield 83%.

^1H ($CDCl_3$): 1.60 (bq, 2H, J = 12.2 Hz, H_{ax}-3 and H_{ax}-5), 2.01 (bd, 2H, J = 12.2 Hz, H_{eq}-3 and H_{eq}-5), 2.18 (bt, 2H, J = 11.4 Hz, H_{ax}-2 and H_{ax}-6), 2.32 (s, 3H, N–CH_3), 2.84 (bd, 2H, J = 11.4 Hz, H_{eq}-2 and H_{eq}-6), 3.92 (m, 1H, H-4), 5.93 (d, 1H, J = 6.8 Hz, NH), 6.43 (d, 1H, J = 15.3 Hz, CH=C*H*–CO), 7.33 (m, 3H, H-3′, H-4′ and H-5′), 7.48 (d, 2H, J = 8.5 Hz, H-2′ and H-6′), 7.62 (d, 1H, J = 15.3 Hz, C*H*=CH–CO).

^{13}C ($CDCl_3$): 32.02 (2C, C-3 and C-5), 45.94 (N–CH_3), 46.05 (C-4), 54.40 (2C, C-2 and C-6), 120.91 (CH=*C*H–CO), 127.75 (2C, C-3′ and C-5′), 128.78 (2C, C-2′ and C-6′), 129.60 (C-4′) 134.87 (C-1′), 140.92 (*C*H=CH–CO), 165.28 (CO).

5.1.3.15. 1-Methyl-4-[N-(4′-cinnamoyl)]-piperidinamide ***5g***

Formula $C_{16}H_{22}N_2O$, mol. wt. 258, m.p. 204–205°C, yield 90%.

^1H ($CDCl_3$): 1.52 (bq, 2H, J = 12.0 Hz, H_{ax}-3 and H_{ax}-5), 2.02 (bd, 2H, J = 12.0 Hz, H_{eq}-3 and H_{eq}-5), 2.12 (bt, 2H, J = 11.2 Hz, H_{ax}-2 and H_{ax}-6), 2.28 (s, 3H, N–CH_3), 2.38 (s, 3H, 4′-CH_3), 2.82 (bd, 2H, J = 11.2 Hz, H_{eq}-2 and H_{eq}-6), 3.94 (m, 1H, H-4), 5.51 (d, 1H, J = 6.8 Hz, NH), 6.34 (d, 1H, J = 15.2 Hz, CH=C*H*–CO), 7.18 (d, 2H, J = 8.5 Hz, H-3′, H-5′), 7.38 (d, 2H, J = 8.5 Hz, H-2′ and H-6′), 7.58 (d, 1H, J = 15.2 Hz, C*H*=CH–CO).

^{13}C ($CDCl_3$): 21.36 (4′-CH_3), 32.38 (2C, C-3 and C-5), 46.19 (2C, N–CH_3 and C-4), 54.47 (2C, C-2 and C-6), 119.75 (CH=*C*H–CO), 127.71 (2C, C-3′ and C-5′), 129.50 (2C, C-2′ and C-6′), 132.07 (C-1′), 139.87 (C-4′), 140.91 (*C*H=CH–CO), 165.36 (CO).

5.1.3.16. 1-Methyl-4-[N-(4′-nitrocinnamoyl)]-piperidinamide ***5h***

Formula $C_{15}H_{19}N_3O_3$, mol. wt. 289, m.p. 218–220, yield 80%.

^1H ($CDCl_3$): 1.62 (bq, 2H, J = 11.8 Hz, H_{ax}-3 and H_{ax}-5), 2.04 (bd, 2H, J = 11.8 Hz, H_{eq}-3 and H_{eq}-5), 2.18 (bt, 2H, J = 10.6 Hz, H_{ax}-2 and H_{ax}-6), 2.32 (s, 3H, N–CH_3), 2.84 (bd, 2H, J = 10.6 Hz, H_{eq}-2 and H_{eq}-6), 3.96 (m, 1H, H-4), 5.82 (d, 1H, J = 6.8 Hz, NH), 6.56 (d, 1H, J = 15.2 Hz, CH=C*H*–CO), 7.62 (m, 3H, H-3′, H-5′ and C*H*=CH–CO), 8.22 (d, 2H, J = 8.5 Hz, H-2′ and H-6′).

^{13}C ($CDCl_3$): 32.01 (2C, C-3 and C-5), 45.92 (N–CH_3), 46.37 (C-4), 54.28 (2C, C-2 and C-6), 124.09 (2C, C-3′ and C-5′),124.98 (CH=*C*H–CO), 128.27 (2C, C-2′ and C-6′), 138.37 (*C*H=CH–CO), 141.11 (C-1′), 164.03 (CO).

5.1.3.17. 1-Methyl-4-(N-cyclohexanoyl)-piperidinamide ***6***

Formula $C_{13}H_{24}N_2O$, mol. wt. 224, m.p. 183°C, yield 91%.

^1H (CDCl3): 1.22 (m, 3H, three cyclohexyl protons), 1.40 (m, 4H, H_{ax}-3, H_{ax}-5 and two cyclohexyl protons), 1.65 (m, 1H, one cyclohexyl proton), 1.78 (m, 4H, four cyclohexyl protons), 1.88 (bd, 2H, J = 11.8 Hz, H_{eq}-3 and H_{eq}-5), 2.06

(m, 3H, H_{ax}-2, H_{ax}-6 and one cyclohexyl proton), 2.24 (s, 3H, N–CH_3), 2.74 (bd, 2H, $J=10.6$ Hz, H_{eq}-2 and H_{eq}-6), 3.74 (m, 1H, H-4), 5.37 (d, 1H, $J=6.8$ Hz, NH).

^{13}C ($CDCl_3$): 25.69 (3C, C-3′, C-4′ and C-5′), 29.67 (2C, C-2′ and C-6′), 32.34 (2C, C-3 and C-5), 45.60 (N–CH_3), 46.14 (2C, C-4 and C-1′), 54.46 (2C, C-2 and C-6), 175.37 (CO).

5.2. Pharmacology

Tested compounds were administered orally by gavage in 1% methylcellulose suspension, using a dose of 150 μmol/kg (≅40 mg/kg).

Gastric ulcerogenic action was studied in rats which were treated orally with higher doses (375 μmol/kg, ≅100 mg/kg).

Indomethacin was included in all tests for comparison purposes at the dose level of 14 μmol/kg (5 mg/kg).

The following experimental procedures were employed.

5.2.1. Anti-inflammatory activity

The paw edema inhibition test was used on rats [8]. Groups of five rats of both sexes (body weight 180–250 g), pregnant females excluded, were given a dose of a test compound. Thirty minutes later, 0.2 ml of 1% carrageenin suspension in 0.9% NaCl solution was injected subcutaneously into the plantar aponeurosis of the hind paw. The paw volume was measured by a water plethysmometer (Socrel) and then measured again 1, 2, 3, and 4 h later. The mean increase of paw volume at each time interval was compared with that of the control group (five rats treated with carrageenan, but not treated with test compounds) at the same time intervals and percent inhibition values were calculated. The experimental results at the third and fourth hours are listed in Table 2.

5.2.2. Analgesic activity

The acetic acid writhing test was used on mice [9]. Groups of five mice (body weight 20–30 g) of both sexes, pregnant females excluded, were given a dose of a test compound. Thirty minutes later the animals were injected intraperitoneally with 0.25 ml/mouse of 0.5% acetic acid solution and writhes were counted during the following 25 min. The mean number of writhes for each experimental group and percent decrease compared with the control group (five mice not treated with test compounds) were calculated. The experimental results are listed in Table 3.

5.2.3. Ulcerogenic action

Groups of ten rats (body weight 180–250 g) of both sexes, pregnant females excluded, were treated with an oral dose of a test compound, except the control group [10]. All animals were sacrificed 6 h after dosing and their stomachs and small intestines were examined, using a 2×2 binocular magnifier, to assess the incidence of hyperemia and ulcers. All ulcers greater than 0.5 mm were recorded. The experimental results are listed in Table 4.

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