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Preliminary communication

Synthesis and anti-inflammatory activity of *N*-substituted 2-oxo-2*H*-1-benzopyran-3-carboxamides and their 2-iminoanalogues

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Abstract – A series of *N*-arylsubstituted 2-imino-2*H*-1-benzopyran-3-carboxamides **3a** and **b** and 2-oxo-2*H*-1-benzopyran-3-carboxamides **4a**–**h** were synthesized and evaluated for their anti-inflammatory activity in carrageenan-induced rat paw oedema assays and in acetic acid-induced peritonitis tests in albino rats. The resulting products were found to be active anti-inflammatory agents and their effects were comparable to that of piroxicam as the reference compound. In the consideration of the efficacy of the compounds in these assays, 2-imino/oxo-2*H*-1-benzopyran-3-carboxamides **3a** and **b** and **4a**–**h** were further studied at graded doses for their acute toxicity (ALD_{50}) in albino mice and were essentially non-toxic at the highest dose tested. © 1999 Éditions scientifiques et médicales Elsevier SAS

coumarins / benzopyrans / amides / Knoevenagel condensation / anti-inflammatory activity

1. Introduction

Compounds comprising a coumarin (2-oxo-2*H*-1-benzopyran) backbone have a wide range of biological activities. Thus, among the natural and synthetic coumarin derivatives there are compounds possessing antimicrobial [1], antitumour [2], antiviral [3] and other [4] activities. Moreover, studies of the hydroalcohol extract of *Justicia pectoralis* (Eha) and its main constituents, coumarin (Cou) and umbelliferone (Umb), showed analgesic and anti-oedema activities on acetic acid-induced writhing in mice and on the carrageenan end dextran paw oedema in rats [5]. The Eha, Cou and Umb presented a significant anti-oedema effect in the carrageenan model but only Cou decreased the rat paw volume in the dextran model. Anti-inflammatory activity of coumarins isolated from *Santolina oblongifolia* Boiss was also reported [6]. The isolated coumarins identified as 7-methoxycoumarin (herniarin), 6,7-dihydroxycoumarin (aesculetin), 6-methoxy-7-glucosidylcoumarin (scopolin), and 6-hydroxy-7-methoxycoumarin (scopoletin) showed marked activity as inhibitors of eicosanoid-release from ionophore-stimulated mouse peritoneal macrophages. It was also revealed [7] that compounds containing a benzopyran moiety were potent and selective inhibitors of cyclooxygenase (COX). Of the 3-substituted coumarin derivatives, our attention was called to their *N*-substituted amide derivatives, since marked anti-inflammatory activity of structurally related *N*-substituted amides of 4-hydroxy-2-quinolone-3-carboxylic acids has been reported [8]. Also taking into consideration the fact that such anti-inflammatory drugs as mefenamic and meclofenamic acids [4] constitute derivatives of aromatic amino acids, *N*-substituted coumarin-3-carboxamide derivatives containing aromatic amino acid residues were selected as targets for our anti-inflammatory studies.

2. Chemistry

The general synthetic strategy employed to prepare *N*-substituted 2-imino/oxo-2*H*-1-benzopyran-3-carboxamide derivatives was based on Knoevenagel condensation [9, 10] of active methylene compounds. As shown in *figure 1*, 2-imino-2*H*-1-benzopyran-3-*N*-R-carboxamides **3a** and **b** were prepared by condensing *N*-substituted cyanoacetamides **1a** and **b** and salicylic aldehyde **2** to form the expected imino compounds using piperidine as

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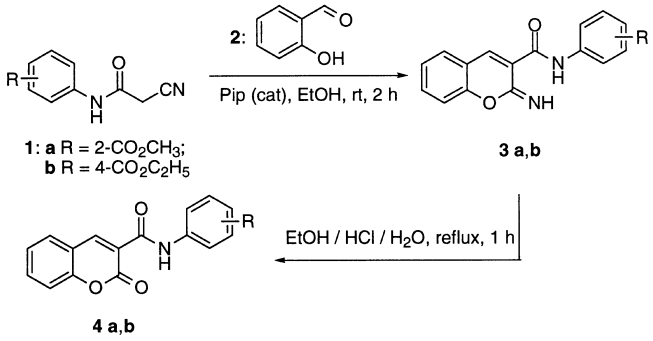

Figure 1. Synthesis of *N*-arylsubstituted 2-imino/oxo-2*H*-1-benzopyran-3-carboxamides **3a** and **b** and **4a** and **b**.

a catalyst in ethanol at room temperature [11, 12]. 2-Oxo-2*H*-1-benzopyran-3-*N*-R-carboxamides **4a** and **b** were obtained by acidic hydrolysis of the corresponding imino analogues **3a** and **b** employing a mixture of ethanol/water/≈ 32% hydrochloric acid and refluxing for 1 h.

The synthesis of coumarin-3-(*N*-2-carboxyphenyl) carboxamides **4c**–**h** was carried out as shown in *figure 2*. The precursor 2-carboxymalonanilic acid ester **5** [13] was

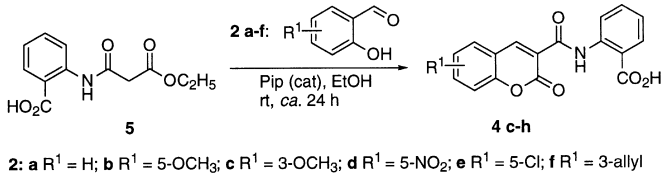

Figure 2. Synthesis of *N*-arylsubstituted 2-oxo-2*H*-1-benzopyran-3-carboxamides **4c–h**.

condensed with an equivalent amount of salicylic aldehydes **2a**–**f** to produce the desired coumarin derivatives **4c**–**h** utilizing piperidine as a catalyst in ethanol at room temperature. An alternative approach for synthesis of *N*-substituted coumarin-3-carboxamides of type **4**, based on rearrangements of 2-imino-2*H*-1-benzopyran-3-carboxamides under the action of anthranilic acid as *N*-nucleophile, has been recently developed [14] in our laboratory.

Physicochemical data for the compounds **3a** and **b** and **4a**–**h** are given in *table I*.

3. Pharmacology

The compounds synthesized were evaluated for their anti-inflammatory activity in carrageenan-induced rat paw oedema assays [15] and in acetic acid-induced peritonitis tests in albino rats [16]. 2-Imino/oxo-2*H*-1-benzopyran-3-carboxamides **3a** and **b** and **4a**–**h** were further studied for their acute toxicity [17]. Piroxicam was used as a control compound.

4. Results and discussion

Pharmacological results on anti-inflammatory activities and acute toxicity of the benzopyran derivatives **3a** and **b** and **4a**–**h** and piroxicam are summarized in *table II*.

In carrageenan-induced rat paw oedema assays, the compounds **4g**, **3b**, **4b**, and **4h** were found to be the most active anti-inflammatory agents at the graded dose 10 mg/kg po and exhibited 54 ± 6.50%, 51 ± 5.05%, 48 ± 6.51%, and 47 ± 7.13% inhibition of inflammation, respectively. Their effects were comparable to that of

Table I. Physicochemical data of the synthesized *N*-arylsubstituted 2-imino/oxo-2*H*-1-benzopyran-3-carboxamides **3a** and **b** and **4a–h**.

Compound	R^1	R	Molecular formula	Yield (%)	Recryst. solvent	M.p. (°C)
3a	H	2-CO_2CH_3	$C_{18}H_{14}N_2O_4$	74	*i*-PrOH	137–138
3b	H	4-$CO_2C_2H_5$	$C_{19}H_{16}N_2O_4$	82	*i*-PrOH	222–224
4a	H	2-CO_2CH_3	$C_{18}H_{13}NO_5$	87	*i*-PrOH	205–208
4b	H	4-$CO_2C_2H_5$	$C_{19}H_{15}NO_5$	85	*i*-PrOH	246–247
4c	H	2-CO_2H	$C_{17}H_{11}NO_5$	67	AcOH	275–276[a]
4d	6-OCH_3	2-CO_2H	$C_{18}H_{13}NO_6$	59	BuOH	124–125
4e	8-OCH_3	2-CO_2H	$C_{18}H_{13}NO_6$	67	BuOH	140–142
4f	6-NO_2	2-CO_2H	$C_{17}H_{10}N_2O_7$	63	BuOH	147–150
4g	6-Cl	2-CO_2H	$C_{17}H_{10}ClNO_5$	71	*i*-PrOH	232–235
4h	8-allyl	2-CO_2H	$C_{20}H_{15}NO_5$	54	MeCN	249–251

[a]Lit. [21] m.p. for **4c**: 279 °C.

Table II. Anti-inflammatory activities and acute toxicity of the benzopyran derivatives **3a** and **b** and **4a–h** and piroxicam.

Compound	Acute toxicity		Anti-inflammatory activity	
	Approximate LD_{50} (mg/kg) (in mice)		carrageenan-induced paw oedema	acetic acid peritonitis
			(Mean % inhibition ± SE)	
	po	ip	10 mg/kg po	
3a	> 1 000	> 700	19 ± 2.11	40 ± 6.43[b]
3b	> 1 000	> 700	51 ± 5.05	32 ± 6.89
4a	> 1 000	> 700	44 ± 7.21	39 ± 5.09
4b	> 1 000	> 700	48 ± 6.51	35 ± 1.02
4c	> 1 000	> 700	38 ± 1.01	42 ± 7.20
4d	> 1 000	> 700	30 ± 6.96	18 ± 4.63
4e	> 1 000	> 700	41 ± 6.42	32 ± 7.01[b]
4f	> 1 000	> 700	35 ± 7.11	29 ± 5.58[b]
4g	> 1 000	> 700	54 ± 6.50	35 ± 4.88[b]
4h	> 1 000	> 700	47 ± 7.13	31 ± 3.31[b]
Piroxicam	360[a]	> 1 000[a]	57 ± 6.61	29 ± 7.24[b]

[a]Data from ref. [22]; [b]$P < 0.05$ Student's *t* test versus controls.

piroxicam, the reference compound, which showed 57 ± 6.61% inhibition at the same dose level.

At the same dose level (10 mg/kg po), in acetic acid peritonitis tests, all compounds exhibited moderate to good anti-inflammatory activity. The most active compounds **4c**, **3a**, and **4a** showed 42 ± 7.20%, 40 ± 6.43%, and 39 ± 5.09% inhibition of inflammation, respectively. In this test, piroxicam revealed a protection of 29 ± 7.24%. All tested compounds were essentially non-toxic at the highest dose graded.

5. Conclusion

The products synthesized were found to be active anti-inflammatory agents and their effects were comparable to that of piroxicam as the reference compound. The most active compounds **3b**, **4a**, **4b** and **4g** have been marked for further detailed pharmacological studies to be evaluated for COX-2 and COX-1 inhibition in microsomal and cellular assays.

6. Experimental protocols

6.1. Chemistry

Melting points (°C) were measured with a Büchi melting point apparatus and were uncorrected. Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel (Merck, Kieselgel 60 F-254). ^{1}H-NMR spectra were recorded on a Varian WXR-400 spectrometer in DMSO-d_6 using TMS as an internal standard (chemical shifts in δ ppm), but a study on isomerization of benzopyran-2-imines in DMSO-d_6 has to be mentioned [18]. O'Callaghan et al. [18] revealed that when unsubstituted 2-imino-2*H*-1-benzopyran-3-carboxamide was dissolved in DMSO-d_6, NMR spectra showed that a mixture of 2-imino-2*H*-1-benzopyran-3-carboxamide and the isomeric 2-cyano-3-(2-hydroxyphenyl)prop-2-ene-1-carboxamide was present and other benzopyran-2-imines behaved similarly and the degree of isomerization varied considerably, depending on the nature and position of the substituents presented. In our case, isomerization of *N*-arylsubstituted 2-imino-2*H*-1-benzopyran-3-carboxamides **3a** and **b** did not occur in dimethyl sulfoxide-d_6 at room temperature and only starting materials were present. Mass spectra (MS) were obtained with a Finnigan MAT-4615B spectrometer at an ionization potential of 70 eV. Infrared spectra (IR) were recorded in KBr pellets on an IBM 486 PC computer-controlled Specord M-80 spectrometer. Elemental analyses were performed at the Microanalysis Laboratory, Kharkov State University, and the combustion analyses of all compounds synthesized indicated by the symbols of the elements were within ± 0.4% of theoretical values. The *N*-substituted cyanoacetamides **1a** and **b**, which are key intermediates for synthesis of the benzopyran-2-imines **3a** and **b**, were prepared according

to reported methods [19, 20] from ethyl cyanoacetate and methyl anthranilate or ethyl 4-aminobenzoate.

6.1.1. N-*arylsubstituted 2-imino-2*H-*1-benzopyran-3-carboxamides* **3a** *and* **b**

To a well-stirred solution of *N*-substituted cyanoacetamides **1a** and **b** (4 mmol) in 15 mL of ethanol, was added an equivalent amount of salicylic aldehyde **2** and a few drops of piperidine as a catalyst. The reaction mixture was stirred at room temperature for 2 h. The products, which precipitated in the course of the reactions were filtered and recrystallized from the proper solvent. Yields and physicochemical data of the synthesized *N*-substituted 2-imino-2*H*-1-benzopyran-3-carboxamides **3a** and **b** are listed in *table I*. **3a**: ^{1}H-NMR: δ 3.88 (s, 3H, C*H*$_3$); 7.13–7.25 (m, 3H, Ar*H*); 7.48–7.58 (m, 2H, Ar*H*); 7.70 (d, 1H, *J* = 7.9 Hz, Ar*H*); 7.88 (d, 1H, *J* = 7.9 Hz, Ar*H*); 8.42 (d, 1H, *J* = 8.41 Hz, Ar*H*); 8.50 (s, 1H, 4-C*H*); 8.79 (s, 1H, C=N*H*); 12.94 (s, 1H, N*H*). MS m/z 322 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3 300 (NH), 3 207 (NH), 3 041 (CH), 1 715 (C=O), 1 678 (C=O), 1 641 (C=N), 1 606 (C=C). Anal. $C_{18}H_{14}N_2O_4$ (C, H, N). **3b**: ^{1}H-NMR: δ 1.31 (t, 3H, *J* = 6.9 Hz, C*H*$_3$); 4.30 (q, 2H, *J* = 6.9 Hz, C*H*$_2$); 7.27–8.04 (m, 8H, Ar*H*); 8.59 (s, 1H, 4-C*H*); 9.32 (s, 1H, C=N*H*); 13.16 (s, 1H, N*H*). MS m/z 336 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3 315 (NH), 2 976 (CH), 1 704 (C=O), 1 688 (C=O), 1 644 (C=N), 1 593 (C=C). Anal. $C_{19}H_{16}N_2O_4$ (C, H, N).

6.1.2. N-*arylsubstituted 2-oxo-2*H-*1-benzopyran-3-carboxamides* **4a** *and* **b**

A solution of the corresponding 2-iminobenzopyran derivatives **3a** and **b** (4 mmol) in 15–20 mL of a mixture of ethanol/water/≈ 32% hydrochloric acid (30:1:1, v/v/v) was refluxed with vigorous stirring for 1 h. After cooling to room temperature the products precipitated were filtered and recrystallized from the appropriate solvent. Yields and physicochemical data of the synthesized *N*-substituted 2-oxo-2*H*-1-benzopyran-3-carboxamides **4a** and **b** are listed in *table I*. **4a**: ^{1}H-NMR: δ 3.92 (s, 3H, C*H*$_3$); 7.20–8.08 (m, 7H, Ar*H*); 8.61 (d, 1H, *J* = 8.2 Hz, Ar*H*); 9.04 (s, 1H, 4-C*H*); 12.16 (s, 1H, N*H*). MS m/z 323 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3 248 (NH), 3 042 (CH), 1 735 (C=O), 1 713 (C=O), 1 668 (C=O), 1 608 (C=C). Anal. $C_{18}H_{13}NO_5$ (C, H, N). **4b**: ^{1}H-NMR: δ 1.38 (t, 3H, *J* = 7.0 Hz, C*H*$_3$); 4.34 (q, 2H, *J* = 7.0 Hz, C*H*$_2$); 7.42–7.54 (m, 2H, Ar*H*); 7.72–8.06 (m, 6H, Ar*H*); 9.00 (s, 1H, 4-C*H*); 10.88 (s, 1H, N*H*). MS m/z 337 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3 250 (NH), 2 984 (CH) 1 704 (C=O), 1 671 (C=O), 1 596 (C=C). Anal. $C_{19}H_{15}NO_5$ (C, H, N).

6.1.3. N-*arylsubstituted 2-oxo-2*H-*1-benzopyran-3-carboxamides* **4c**–**h**

To a well-stirred solution of 2-carboxymalonanilic acid ester **5** [13] (4 mmol) in 10 mL of ethanol was added an equivalent amount of salicylic aldehydes **2a**–**f** and a few drops of piperidine as a catalyst. The reaction mixture was stirred at room temperature for ca. 1 day and then poured into water. The products precipitated were filtered and recrystallized from the suitable solvent. Yields and physicochemical data of the synthesized *N*-substituted 2-imino-2*H*-1-benzopyran-3-carboxamides **4c**–**h** are listed in *table I*. **4c**: ^{1}H-NMR: δ 7.15 (dd 1H, *J* = 8.0, 8.0 Hz, Ar*H*); 7.39 (m, 2H, Ar*H*); 7.56 (dd, 1H, *J* = 8.0, 8.0 Hz, Ar*H*); 7.73 (dd, 1H, *J* = 7.9, 7.9 Hz, Ar*H*); 7.94 (d, 1H, *J* = 8.2 Hz, Ar*H*); 8.05 (d, 1H, *J* = 8.2 Hz, Ar*H*); 8.65 (d, 1H, *J* = 8.3 Hz, Ar*H*); 8.85 (s, 1H, 4-C*H*); 13.52 (br s, 1H, N*H*). MS m/z 309 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3 266 (NH), 3 032 (CH), 1 731 (C=O), 1 696 (C=O), 1 673 (C=O), 1 608 (C=C). Anal. $C_{17}H_{11}NO_5$ (C, H, N). **4d**: ^{1}H-NMR: δ 3.95 (s, 3H, OC*H*$_3$); 7.14–7.32 (m, 4H, Ar*H*); 7.42 (d, 1H, *J* = 8.2 Hz, Ar*H*); 8.01 (d, 1H, *J* = 8.0 Hz, Ar*H*); 8.60 (d, 1H, *J* = 8.0 Hz, Ar*H*); 8.89 (s, 1H, 4-C*H*); 13.20 (s, 1H, N*H*). MS m/z 339 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3 287 (NH), 2 952 (CH), 1 726 (C=O), 1 694 (C=O), 1 675 (C=O), 1 614 (C=C). Anal. $C_{18}H_{13}NO_6$ (C, H, N). **4e**: ^{1}H-NMR: δ 3.95 (s, 3H, OC*H*$_3$); 7.15–7.44 (m, 4H, Ar*H*); 7.52 (d, 1H, *J* = 8.3 Hz, Ar*H*); 8.00 (d, 1H, *J* = 7.9 Hz, Ar*H*); 8.64 (dd, 1H, *J* = 8.0, 8.0 Hz, Ar*H*); 8.90 (s, 1H, 4-C*H*); 13.12 (s, 1H, N*H*). MS m/z 339 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3 291 (NH), 2 947 (CH), 1 730 (C=O), 1 689 (C=O), 1 677 (C=O), 1 604 (C=C). Anal. $C_{18}H_{13}NO_6$ (C, H, N). **4f**: ^{1}H-NMR: δ 7.21 (dd, 1H, *J* = 8.0, 8.0 Hz, Ar*H*); 7.60 (dd, 1H, *J* = 8.0, 8.0 Hz, Ar*H*); 7.71 (d, 1H, *J* = 8.2 Hz, Ar*H*); 8.02 (d, 1H, *J* = 7.9 Hz, Ar*H*); 8.46 (d, 1H, *J* = 8.3 Hz, Ar*H*); 8.72 (d, 1H, *J* = 7.9 Hz, Ar*H*); 8.95 (s, 1H, 5-C*H*); 9.10 (s, 1H, 4-C*H*); 13.21 (s, 1H, N*H*). MS m/z 354 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3 295 (NH), 3 085 (CH), 1 754 (C=O), 1 724 (C=O), 1 683 (C=O), 1 618 (C=C). Anal. $C_{17}H_{10}N_2O_7$ (C, H, N). **4g**: ^{1}H-NMR: δ 7.20 (t, 1H, *J* = 7.9 Hz, Ar*H*); 7.60–7.74 (m, 3H, Ar*H*); 7.98–8.06 (m, 2H, Ar*H*); 8.12 (s, 1H, 5-C*H*); 9.03 (s, 1H, 4-C*H*); 12.47 (s, 1H, N*H*). MS m/z 345, 343 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3 389 (OH + NH), 3 047 (CH), 1 736 (C=O), 1 689 (C=O), 1 671 (C=O), 1 607 (C=C). Anal. $C_{17}H_{10}ClNO_5$ (C, H, N). **4h**: ^{1}H-NMR: δ 3.63 (m, 2H, C*H*$_2$–CH=CH$_2$); 5.14 (m, 2H, CH$_2$–CH=C*H*$_2$); 6.03 (m, 1H, CH$_2$–C*H*=CH$_2$); 7.13 (dd, 1H, *J* = 8.0, 8.0 Hz, Ar*H*); 7.32 (dd, 1H, *J* = 7.9, 7.9 Hz, Ar*H*); 7.55 (m, 2H, Ar*H*); 7.78 (d, 1H, *J* = 8.0 Hz, Ar*H*); 8.03 (d, 1H, *J* = 7.9 Hz, Ar*H*); 8.76 (dd, 1H, *J* = 7.9, 7.9 Hz, Ar*H*); 8.98 (s, 1H, 4-C*H*); 12.53 (s, 1H, N*H*) MS m/z 349 ($M^{+\cdot}$). IR (KBr), cm^{-1}: ν 3 224 (NH), 2 942 (CH), 1 724 (C=O),

1 684 (C=O), 1 657 (C=O), 1 600 (C=C). Anal. $C_{20}H_{15}NO_5$ (C, H, N).

6.2. Pharmacology

6.2.1. Anti-inflammatory activity

6.2.1.1. Carrageenan-induced rat hind paw oedema test

Experiments were carried out on groups of five Sprague-Dawley rats (140–160 g). The tested compounds and reference drug were administered orally (po) in 0.5% methylcellulose solution in water and 1 h later 0.1 mL of 1% carrageenan solution was injected under the plantar aponeurosis of the right hind paw of the rat by the method of Winter et al. [15]. The volume of the paw was measured before and 3 h after carrageenan treatment by a mercury plethysmometer. Anti-inflammatory activity was given as percentage of inhibition of oedema in treated groups compared with controls and was calculated according to the formula:

$$\% \text{ inhibition} = 100 \times [1 - (V_t/V_c)]$$

where V_t is the mean increase in paw volume of the rats treated with tested compounds and V_c is the mean increase in paw volume of the control group of rats.

6.2.1.2. Acetic acid peritonitis assay

This test was performed according to the procedure of Arrigoni-Martelli [16]. Groups of five rats were administered intraperitoneally (ip) with 10 mL/kg of 0.5% acetic acid solution 1 h after oral administration of the tested compounds. After 30 min, the rats were killed with diethyl ether and peritoneal exudate was collected and measured. The anti-exudate response was expressed as the inhibition percentage in comparison to the vehicle-treated control:

$$\% \text{ inhibition} = 100 \times [1 - (V_t/V_c)]$$

where V_t is the mean volume of the peritoneal exudate in treated rats and V_c is the mean volume of the peritoneal exudate in vehicle-treated rats.

6.2.1.3. Toxicity studies

All tested compounds were investigated for their acute toxicity and approximate lethal dose (ALD_{50}). Albino mice (either sex) weighing 20–25 g were used for the study. ALD_{50} values were determined by observing mortality within 24 h after drug administration [17].

6.2.1.4. Statistical calculation

Data are expressed as mean ± SE. The Student's *t* test was applied to determine the significance of the difference between the control and the treated groups. The difference in results was considered to be significant when $P < 0.05$.

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