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Synthesis and anti-inflammatory activity of 1-acylaminoalkyl-3,4-dialkoxybenzene derivatives

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Abstract

New 1-acylaminoalkyl-3,4-dialkoxybenzene derivatives **17–31** were synthesized by the acylation of amines **9–16** with acyl chlorides. Amines **9–16** were obtained from aryl ketones **1–8**. Aryl ketones **1–8** were synthesized by the acylation of corresponding aromatic compounds. As it was preliminary predicted by PASS (Prediction of Activity Spectra for Substance) program, all 1-acylaminoalkyl-3,4-dimethoxy- and 3,4-diethoxybenzene derivatives possess anti-inflammatory activity. Activity of compounds **18**, **19**, **21**, **24**, **26**, **27**, **28**, **29** was similar to that of acetylsalicylic acid or ibuprofen however their acute toxicity was less than that of mentioned anti-inflammatory drugs.

A series of 1-acylaminoalkyl-3,4-dimethoxybenzene, 1-acylaminoalkyl-3,4-diethoxybenzene and 6-acylaminoalkyl-2,3-dihydro-1,4-benzodioxine derivatives have been synthesized. These compounds possess moderate or strong anti-inflammatory activity and low toxicity.

Keywords: 1-Acylaminoalkyl-3,4-dialkoxybenzene derivatives; *N*-acylation; Anti-inflammatory activity

1. Introduction

The search of biologically active compounds within the class of carboxamides is rather popular because of their easy synthesis and relative stability in biological media.

As a result of our investigations, it was also found out that a big number of 1,2-dialkoxybenzene derivatives possess high or moderate anti-inflammatory activity and low acute toxicity [1–3]. Some data on the possibility of anti-inflammatory activity of 1-acylaminoalkyl-3,4-dialkoxybenzene derivatives were also generated by PASS program [4] and kindly provided to us by SPECS, Rijswijk, the Netherlands. Due to this reason, we have performed the synthesis of amides **17–31** and investigated their anti-inflammatory activity in vivo.

2. Chemistry

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a FT-IR Spectrum BX (Perkin-Elmer, Sweden) in Nujol and ^{1}H-NMR spectra—on a BS-587A (80 MHz, Tesla, Czechoslovakia) with TMS as an internal standard. Chemical shifts (δ) are reported in ppm, coupling constants (J) are given in Hz. All new compounds were analyzed for C, H and N and the results were in an acceptable range.

Amides **17–31** have been synthesized by the acylation of amines **9–16** treating them with acyl chlorides in trichloromethane solution in presence of triethylamine. Amines **9–16** were obtained by the reaction of ketones **1**, **4–8** with formamide in formic acid with further hydrolysis of obtained formylamino derivatives or from aryl ketones **3**, **4** by reduction of their oximes with sodium in boiling butanol. Different ways of synthesis were used because ketones **3** and **4** were not stable under conditions of more convenient one step reductive amination. Aryl ketones **1–8** were synthesized by the acylation of corresponding aromatic compounds with acyl chlorides in dichloromethane solution in the presence of aluminum chloride (Scheme 1). Both means $\nu_{N\text{-}H}$ and $\nu_{C=O}$ in IR spectra of synthesized compounds depend on many factors and show no regularities. The ^{1}H NMR spectral data allow to make some conclusions about the symmetry of electron density dislocation and conformation of molecules of synthesized compounds. The means of chemical shift of hydrogen atoms of both CH_2O- or both CH_3O- groups are equal for both

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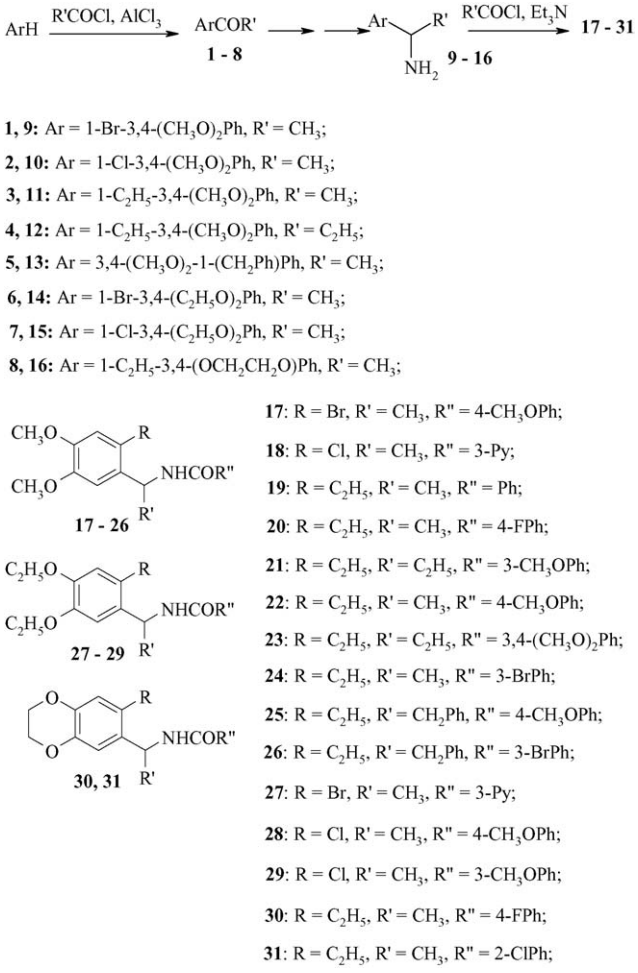

Scheme 1.

dimethoxybenzene derivatives **4**, **26** and cyclic compounds **30**, **31** and differ by 0.02–0.09 ppm for all remaining dimethoxy- and diethoxybenzene derivatives **5–7**, **9–25**, **27–29**. It means that CH_2O- and CH_3O- groups differ not only when electron donating (ethyl) and electron withdrawing (carbonyl) groups are attached to the same benzene ring but also even in the presence of two similar groups (ethyl and 2-aminoethyl) are there. The signal of CH_2 in ethyl group is usually triplet in the case of compounds **4**, **5**, **25**, **26** and it is multiplet in the case of compounds **11**, **12**, **19–24**. It means that hydrogen atoms of this group are different due to the conformation of compounds **11**, **12**, **19–24**. The form of signal of CH in aminoalkyl group (multiplet both for amines **9–16** and amides **17–31**) confirms this conclusion.

3. Experimental

3.1. Chemistry

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a FT-IR Spectrum BX (Perkin-Elmer, Sweden) in Nujol and ^{1}H-NMR spectra—on a BS-587A (80 MHz, Tesla, Czechoslovakia) with TMS as an internal standard. Chemical shifts (δ) are reported in ppm. All new compounds were analyzed for C, H and N and the results were in an acceptable range.

1-(2-Bromo-4,5-dimethoxyphenyl)-1-ethanone (**1**) [5], 1-(2-chloro-4,5-dimethoxyphenyl)-1-ethanone (**2**) [5], 1-(2-ethyl-4,5-dimethoxyphenyl)-1-ethanone (**3**) [6] and 1-(7-ethyl-2,3-dihydro-1,4-benzodioxin-6-yl)-1-ethanone (**8**) [7] were synthesized by the known methods. Experimental, physico-chemical and spectral data for compounds **4–7** and **9–31** are given in Table 1.

*1-(2-Ethyl-4,5-dimethoxyphenyl)-1-propanone (**4**), 1-(2-ethyl-4,5-dimethoxyphenyl)-2-phenyl-1-ethanone (**5**), 1-(2-bromo-4,5-diethoxyphenyl)-1-ethanone (**6**)* and *1-(2-chloro-4,5-diethoxyphenyl)-1-ethanone (**7**)* To a solution of 0.1 mol of aromatic compound and 0.11 mol of acyl chloride in 20 ml abs., dichloromethane 0.12 mol (16.0 g) of anhydrous aluminum chloride was added portionwise under stirring and at the temperature –5–0 °C (compounds **4**, **5**) or 5–10 °C (compounds **6**, **7**). Reaction mixture was stirred 4 h at room temperature and poured into 150 ml H_2O. Dichloromethane solution was washed with 10% sodium carbonate, dried and evaporated in vacuo. Obtained products were recrystallized from 2-propanol.

*1-(2-Bromo-4,5-dimethoxyphenyl)ethylamine (**9**), 1-(2-chloro-4,5-dimethoxyphenyl)ethylamine (**10**), 1-(2-benzyl-4,5-dimethoxyphenyl)ethylamine (**13**), 1-(2-bromo-4,5-diethoxyphenyl)ethylamine (**14**), 1-(2-chloro-4,5-diethoxyphenyl)ethylamine (**15**), 1-(7-ethyl-2,3-dihydro-1,4-benzodioxin-6-yl)ethylamine (**16**)* A mixture of 0.07 mol of compound **1**, **2** or **5–8**, 13 g (0.28 mol) of formamide, 4 g (0.07 mol) of 85% formic acid was heated at 170–180 °C for 4 h, cooled to room temperature, triturated with 100 ml of water and refluxed with conc. HCl 2 h. To the obtained solution, sodium hydroxide was added to pH 13. Obtained amines **9**, **10**, **13–16** were extracted with toluene, dried over anhydrous sodium sulfate and isolated as hydrochlorides after treatment with anhydrous HCl gas.

*1-(2-Ethyl-4,5-dimethoxyphenyl)ethylamine (**11**), 1-(2-ethyl-4,5-dimethoxyphenyl)ethylamine (**12**)* A mixture of 0.04 mol of compound **3** or **4**, 11.8 g (0.17 mol) hydroxylamine hydrochloride and 120 ml pyridine was heated at 100 °C for 7 h, evaporated in vacuo and triturated with water. Obtained crystalline oximes were filtered off, dried, dissolved in 100 ml of boiling 1-butanol and treated portionwise with 4.5 g (0.195 mol) of sodium. 1-Butanol was removed in vacuo. Amines **11** and **12** were extracted with boiling toluene, cooled, dried over anhydrous sodium sulfate and isolated as hydrochlorides after treatment with anhydrous HCl gas.

*1-Acylaminoalkyl-3,4-dialkoxybenzenes (**17–31**)* A mixture of amine (hydrochloride or free base) **9–16** (0.01 mol), 0.01 mol corresponding acyl chloride, 0.025 mol triethylamine and 20 ml anhydrous trichloromethane was refluxed for 4 h. Then the reaction mixture was cooled, washed with water, dried over anhydrous sodium sulfate and evaporated in vacuo. Acyl derivatives **17–31** were obtained as solids after crystallization from 2-propanol.

Table 1
Experimental, physico-chemical and spectral data for compounds **4–7** and **9–31**

Compd	Formula	Yield, (%)	M.p. (°C)	IR: (cm^{-1})	^{1}H-NMR:
4	$C_{13}H_{18}O_3$	78	43-44	1679 (C=O)	t 1.21 (6H, CH_3), k 2.82 and 2.92 (4H, CH_2), s 3.91 (6H, OCH_3), s 6.72 and 7.15 (2H, ArH)**
5	$C_{18}H_{20}O_3$	85	75-77	1688 (C=O)	t 1.15 (3H, CH_3), k 2.81 (2H, CH_2), s 3.85 and 3.91 (6H, OCH_3), s 4.18 (2H, CH_2Ph), s 6.72, 7.22 and 7.36 (1H, 5H and 1H, ArH)**
6	$C_{12}H_{15}BrO_3$	64	43-45	1690 (C=O)	t 1.41 (6H, CH_3), s 2.53 (3H, $COCH_3$), k 3.95 and 4.01 (4H, OCH_2), s 6.81 and 6.95 (2H, ArH)
7	$C_{12}H_{15}ClO_3$	72	36-38	1681 (C=O)	t 1.48 and 1.50 (6H, CH_3), s 3.11 (3H, $COCH_3$), k 4.12 and 4.21 (4H, OCH_2), s 7.02 (2H, ArH)***
9	$C_{10}H_{15}BrClNO_2$	61	215-216[h]	3408 (N-H)	d 1.43 (3H, $CHCH_3$), s 4.06 (6H, OCH_3), m 5.32-5.64 (1H, $CHCH_3$), s 6.95 and 7.10 (2H, ArH), br. s 8.91 (NH_2*HCl)*
10	$C_{10}H_{15}Cl_2NO_2$	56	252-254[h]	3406 (N-H)	d 1.55 (3H, $CHCH_3$), s 3.77 and 3.86 (6H, OCH_3), m 4.01-4.22 (1H, $CHCH_3$), s 7.09 and 7.83 (2H, ArH), br. s 10.57 (NH_2*HCl)*
11	$C_{12}H_{20}ClNO_2$	52	212-213[h]	3402 (N-H)	t 1.14 (3H, CH_2CH_3), d 1.50 (3H, $CHCH_3$), s 3.76 and 3.79 (6H, OCH_3), m 4.23-4.65 (1H, $CHCH_3$), s 6.80 and 7.38 (2H, ArH), br. s 8.55 (3H, NH_2*HCl)*
12	$C_{13}H_{21}NO_2$	48	oil	3356, 3289 (N-H)	t 0.89 and 1.20 (6H, CH_3), qt 1.69 (2H, $CHCH_2$), m 2.30-2.90 (4H, CH_2CH_3, NH_2) k 2.63 (2H, CH_2), m 3.95-4.22 (1H, $CHCH_3$), s 6.65 and 6.97 (2H, ArH)**
13	$C_{18}H_{24}ClNO_2$	58	208-210[h]	3399 N-H)	t 1.29 (3H, CH_2CH_3), m m 2.31-2.62 (2H, CH_2CH_3), m 3.13-3.55 (2H, CH_2Ph), s 3.90 and 3.93 (6H, OCH_3), m 5.45-5.61 (1H, $CHCH_3$), m 6.83-8.20 (8H, ArH, NH_2*HCl)*
14	$C_{12}H_{19}BrClNO_2$	51	229-231[h]	3422 (N-H)	t 1.32 (9H, CH_2CH_3), d 1.47 (3H, $CHCH_3$), t 4.02 and 4.08 (4H, OCH_2), m 4.26-4.77 (1H, $CHCH_3$), s 7.15 and 7.58 (2H, ArH), m 8.31-8.94 (NH_2*HCl)*
15	$C_{12}H_{19}Cl_2NO_2$	63	218-220[h]	3139 (N-H)	t 1.26 (9H, CH_2CH_3), d 1.46 (3H, $CHCH_3$), t 3.97 and 4.04 (4H, OCH_2), m 4.23-4.78 (1H, $CHCH_3$), s 6.85 and 7.49 (2H, ArH), m 8.40-9.04 (NH_2*HCl)*
16	$C_{12}H_{18}ClNO_2$	67	237-239[h]	3393 (N-H)	t 1.11 (3H, CH_2CH_3), d 1.46 (3H, $CHCH_3$), m 2.32-2.64 (2H, CH_2CH_3), t 4.21 (1H, $CHCH_3$), s 4.23 (4H, OCH_2), s 6.71 and 7.21 (2H, ArH), br. s 8.59 (NH_2*HCl)*
17	$C_{18}H_{20}BrNO_4$	83	169-170	3317 (N-H); 1632 (C=O)	d 1.61 (3H, $CHCH_3$), s 3.88, 3.94 and 3.96 (9H, OCH_3), m 5.44-5.65 (1H, $CHCH_3$), s 7.20 and 7.34 (2H, ArH), dd 7.06 and 8.00 (4H, ArH), m 7.85-8.25 (1H, NH)***
18	$C_{16}H_{17}ClN_2O_3$	86	168-170	3334 (N-H); 1636 (C=O)	d 1.64 (3H, $CHCH_3$), s 3.89 and 3.95 (6H, OCH_3), t 5.66 (1H, $CHCH_3$), s 7.22 and 7.35 (2H, ArH), m 7.40-8.78 (3H, Py), s 9.15 (1H, NH)***
19	$C_{19}H_{23}NO_3$	71	134-135	3324 (N-H); 1628 (C=O)	t 1.36 (3H, CH_2CH_3), d 1.64 (3H, $CHCH_3$), m 2.61-3.02 (2H, CH_2CH_3), s 3.88 and 3.90 (6H, OCH_3), m 5.45-5.68 (1H, $CHCH_3$), s 6.88, 7.11 and 7.29 (2H, ArH), m 7.31-8.28 (6H, ArH, NH)***
20	$C_{19}H_{22}FNO_3$	82	113-115	3310 (N-H); 1634 (C=O)	t 1.35 (3H, CH_2CH_3), d 1.64 (3H, $CHCH_3$), m 2.52-2.97 (2H, CH_2CH_3), s 3.88 and 3.91 (6H, OCH_3), m 5.45-5.72 (1H, $CHCH_3$), s 6.88 and 7.27 (2H, ArH), m 7.08-8.32 (5H, ArH, NH)***
21	$C_{21}H_{27}NO_4$	59	178-180	3378 (N-H); 1646 (C=O)	t 1.08 and 1.34 (6H, CH_2CH_3), m 1.80-2.23 and 2.52-3.15 (4H, CH_2CH_3),s 3.87, 3.90 and 3.92 (9H, OCH_3), m 5.32-5.65 (1H, $CHCH_3$), s 6.88 and 7.26 (2H, ArH), m 7.05-7.54 (4H, ArH), m 7.83-8.25 (1H, NH)***
22	$C_{20}H_{25}NO_4$	78	125-127	3343 (N-H); 1647 (C=O)	t 1.34 (3H, CH_2CH_3), d 1.63 (3H, $CHCH_3$), m 2.61-3.12 (2H, CH_2CH_3), s 3.87, 3.90 and 3.94 (9H, OCH_3), m 5.45-5.68 (1H, $CHCH_3$), s 6.87 and 7.27 (2H, ArH), dd 7.05 and 7.99 (4H, ArH), br. s 8.00 (1H, NH)***
23	$C_{22}H_{29}NO_5$	54	165-168	3307 (N-H); 1620 (C=O)	t 1.08 and 1.36 (6H, CH_2CH_3), m 1.88-2.24 and 2.62-3.15 (4H, CH_2CH_3), s 3.87, 3.92, 3.91 and 3.95 (12H, OCH_3), m 5.20-5.65 (1H, $CHCH_3$), s 6.88 and 7.24 (2H, ArH), m 7.32-8.20 (5H, ArH, NH)***
24	$C_{19}H_{22}BrNO_3$	84	141-143	3309 (N-H); 1630 (C=O)	t 1.36 (3H, CH_2CH_3), d 1.66 (3H, $CHCH_3$), m 2.52-2.94 (2H, CH_2CH_3), s 3.87 and 3.91 (6H, OCH_3), m 5.50-5.70 (1H, $CHCH_3$), s 6.89, 7.26, m 7.32-8.20 (5H, ArH, NH)***
25	$C_{26}H_{29}NO_4$	71	157-160	3344 (N-H); 1629 (C=O)	t 1.27 (3H, CH_2CH_3), k 2.82 (2H, CH_2CH_3), m 3.10-3.47 (2H, CH_2Ph), s 3.90, 3.91 and 3.93 (9H, OCH_3), m 5.50-5.70 (1H, $CHCH_3$), m 6.83-8.20 (14H, ArH, NH)***
26	$C_{25}H_{26}BrNO_3$	65	153-155	3320 (N-H); 1635 (C=O)	t 1.28 (3H, CH_2CH_3), k 2.80 (2H, CH_2CH_3), m 3.15-3.49 (2H, CH_2Ph), s 3.90 (6H, OCH_3), m 5.53-5.94 (1H, $CHCH_3$), s 6.85 and m 7.09-8.04 (11H, ArH), m 8.18-8.39 (1H, NH)***
27	$C_{18}H_{21}BrN_2O_3$	59	148-149	3319 (N-H); 1636 (C=O)	t 1.43 and 1.48 (9H, CH_2CH_3), d 1.63 (3H, $CHCH_3$), t 4.12 and 4.21 (4H, OCH_2), m 5.42-5.71 (1H, $CHCH_3$), s 7.20 and 7.33 (2H, ArH), m 8.12-9.23 (4H, Py and NH)***
28	$C_{20}H_{24}ClNO_4$	87	163-165	3307 (N-H); 1629 (C=O)	t 1.43 and 1.48 (9H, CH_2CH_3), d 1.60 (3H, $CHCH_3$), s 3.96 (3H, OCH_3), t 4.12 and 4.21 (4H, OCH_2), m 5.50-5.89 (1H, $CHCH_3$), s 7.03 and 7.31 (2H, ArH), dd 7.05 and 8.04 (4H, ArH), m 7.92-8.31 (1H, NH)***
29	$C_{20}H_{24}ClNO_4$	85	149-150	3305 (N-H); 1634 (C=O)	t 1.43 and 1.48 (9H, CH_2CH_3), d 1.62 (3H, $CHCH_3$), s 3.95 (3H, OCH_3), t 4.12 and 4.21 (4H, OCH_2), m 5.47-5.74 (1H, $CHCH_3$), s 7.05 and 7.31 (2H, ArH), m 7.12-7.45 (4H, ArH), m 7.92-8.32 (1H, NH)***

(continued on next page)

Table 1
(continued)

Compd	Formula	Yield, (%)	M.p. (°C)	IR: (cm^{-1})	^{1}H-NMR:
30	$C_{19}H_{20}FNO_3$	82	152-155	3329 (N-H); 1627 (C=O)	t 1.33 (3H, CH_2CH_3), d 1.56 (3H, $CHCH_3$), m 2.56-2.98 (2H, CH_2CH_3), s 4.31 (4H, OCH_2), m 5.45-5.63 (1H, $CHCH_3$), s 6.76, 7.11 and 7.52 (6H, ArH), br. s 7.9 (1H, NH)**
31	$C_{19}H_{20}ClNO_3$	77	105-108	3292 (N-H); 1640 (C=O)	t 1.33 (3H, CH_2CH_3), d 1.53 (3H, $CHCH_3$), m 2.68-2.98 (2H, CH_2CH_3), s 4.33 (4H, OCH_2), m 5.42-5.64 (1H, $CHCH_3$), s 6.75, 7.09 (2H, ArH), m 7.52-8.10 (5H, ArH, NH)**

[h] Hydrochloride.
Solvent: *DMSO, **$CDCl_3$,***$(CD_3)_2CO$;
Coupling: s - singlet, d - doublet (6 Hz for aliphatic hydrogens, 9 Hz for o-ArH and 2 Hz for m-ArH), t - triplet (6 Hz for aliphatic hydrogens); q - quartet (6 Hz for aliphatic hydrogens); qt - quintuplet (6Hz for aliphatic hydrogens), dd - double doublet (2 and 9 Hz for ArH), m – multiplet

3.2. Pharmacology

Adult male Wistar strain rats weighing 180–220 g and male BALB/C strain mice weighing 18–22 g were used. The animals were allowed food and water ad libitum. They were housed in rooms at 18–20 °C with a 12-h light/dark cycle and relative humidity of 55–60%. The animals were randomly allocated into groups at the beginning of all the experiments. All test compounds and the reference drugs were administered orally suspended in 0.5% carboxymethylcellulose solution. The data for activity and toxicity were evaluated statistically using Student's *t*-test. A level of $P < 0.05$ was adopted for the test of significance.

3.2.1. Carrageenin test

Carrageenin-induced hind-paw oedema in rats was produced by the method of Winter et al. [8]. Carrageenin solution (1.0% in sterile 0.9% NaCl solution) in a volume of 0.1 ml was injected subcutaneously into the subplantar region of the right hind paw 1 h after the administration of the test compound. Control animals received only 0.5% carboxymethylcellulose solution. Right hind paw volume was measured with an electronic onkograph immediately before and 1, 2, 3, and 5 h after the carrageenin injection. The cross-section was calculated from the experimental data of these measurements and was reported in relative units. The increase of results was matched with that of control rats. The values of arithmetical means of the measurements at each recording time (1, 2, 3, 5 h) were calculated. Each experiment was made with group of 10 animals (and one group of 10 animals was a control).

3.2.2. Bentonite test

Bentonite-induced hind paw oedema was studied analogously [9]. Bentonite suspension (5% in sterile 0.9% NaCl solution) in a volume of 0.1 ml was injected subcutaneously into the subplantar region of the left hind paw 1 h after the administration of the test compound. Control animals received only 0.5% carboxymethylcellulose solution. Left hind paw volume was measured with an electronic onkograph immediately before and 1, 2, 3, and 5 h after the carrageenin injection. The increase of results was matched with that of control rats. The values of arithmetical means of the measurements at each recording time (1, 2, 3, 5 h) were calculated. Each experiment was made with group of 10 animals (and one group of 10 animals was a control).

3.2.3. Acute toxicity

The tests of acute toxicity of the compounds were done on mice fasted for 24 h, water ad libitum. Groups of 6 mice were treated perorally with the test compound at various dose levels. The animals were watched for mortality and symptoms until 8th day [10].

4. Results and discussion

Anti-inflammatory activity was studied using carrageenin- and bentonite-induced paw oedema in rats. The inhibition of oedema was evaluated by the comparison of paw volume measured with an electronic onkograph immediately before and 1, 2, 3, and 5 h after the injection of carrageenin or bentonite. Obtained data are given as an arithmetical means of measurements (Table 2). Acetylsalicylic acid and ibuprofen were used as a reference drugs.

The effects of the development of carrageenin- and bentonite-induced oedema caused by p.o. administration of the test compounds as well as the reference drug at a dose of 50 mg/kg are given in Table 2. Each reported value is expressed as the percentage inhibition of the mean increase of paw volume in treated animals as compared with untreated controls. Also the LD_{50} mg/kg doses are given.

All tested 1,2-dimethoxybenzene derivatives **17–26** and 1,2-diethoxybenzene derivatives **27–29** possess moderate (**17, 19–21, 23, 25, 27, 28**) or strong (**18, 22, 24, 26, 29**) anti-inflammatory activity. Both cyclic analogues—2,3-dihydro-1,4-benzodioxine derivatives possess week (**30**) or no (**31**) anti-inflammatory activity. The activity of compounds **17**, **19–22**, **23**, **27**, **28** is comparable to that of acetylsalicylic acid or higher and the compounds **18**, **24**, **26**, **27** possess the anti-inflammatory activity comparable to that of ibuprofen. By the summarized results of both carragenin and bentonite tests, compound **29** was more active than ibuprofen. The influence of substituents in structure of tested compounds is not clearly expressed, although some observations could be mentioned. The activity of the derivatives of compound **19** with various substituents into benzene ring of acyl group was less (4-F, **20**) or equal (4-CH_3O, **22**; 3-CH_3O, **24**) to that of unsubstituted compound **19**. Benzyl derivative **25** was less active than its structural analogue **22** containing methyl group. However benzyl derivative **26** possessed the some activity like their

Table 2
Anti-inflammatory activity (50 mg/kg p.o.) and acute toxicity (LD_{50}) data for compounds **17-31**

Compound	0.1 ml of 1% carrageenin solution		0.1 ml of 5% bentonite suspension		LD_{50} (mg/kg)
	Cross-section of rat paw (relative units)	Inhibition of rat paw oedema (%) over control	Cross-section of rat paw (relative units)	Inhibition of rat paw oedema (%) over control	
Control	85.41	0	82.32	0	
17	68.84	19.4	65.12	20.9	
18	56.63	33.7	57.79	29.8	>1500
19	60.21	29.5	59.11	28.2	>1500
20	66.02	22.7	62.72	22.6	
21	58.16	31.9	65.53	20.4	>1500
22	62.43	26.9	58.36	29.1	
23	71.83	15.9	70.22	14.7	
24	58.59	31.4	54.99	33.2	>1500
25	65.51	23.3	68.00	17.4	
26	57.05	33.2	53.34	35.2	>1500
27	62.26	27.1	60.59	26.4	
28	67.13	21.4	63.80	22.5	
29	57.75	35.9	51.78	37.1	>1500
30	67.56	20.9	76.72	6.8	
31	81.22	4.9	82.32	0	
Acetylsalicylic acid	68.50	19.8	64.54	21.6	1216
Ibuprofen	52.95	38.0	65.28	20.7	500

analogue **24** containing methyl group. Dimethoxyphenyl derivative **20** was more active than their cyclic analogue—2,3-dihydro-1,4-benzodioxine derivative **30**. Ethyl derivative **22** possess higher activity than bromo derivative **17**.

Evaluation of acute toxicity of most active compounds (**18**, **19**, **21**, **24**, **26, 29**) showed that all the compounds selected for this study have low toxicity (LD_{50} > 1500 mg/kg), i.e. they are less toxic than acetylsalicylic acid and much less toxic than ibuprofen (Table 2).

In conclusion, the results of this study demonstrate that 1-acylaminoalkyl-3,4-dialkoxybenzene derivatives are the subject of further more detailed examination.

5. Activity prediction

Data on the possibility of anti-inflammatory activity of 1-acylaminoalkyl-3,4-dialkoxybenzene derivatives were generated by PASS program [4] and kindly provided by SPECS, Rijswijk, the Netherlands. Computerized system PASS predicts more than 100 pharmacological effects, mechanisms of action and specific toxicities simultaneously. More information on PASS is available in Refs. [11,12] and Internet [13]. Authors are grateful to SPECS company for the permision for use and publication of prediction results.

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