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Synthesis of 6,7-dialkoxy-2-arylmethylidene-2,3-dihydrobenzo[4,5]-imidazo[2,1-*b*][1,3]thiazol-3-ones exhibiting anti-inflammatory activity

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New 6,7-dialkoxy-2-arylmethylidene-2,3-dihydrobenzo[4,5]imidazo[2,1-*b*][1,3]thiazol-3-ones (**3a**–**h**, **4b**, **c**, **e**, **g**) were synthesized from 2-(5,6-dialkoxy-1*H*-benzo[*d*]imidazol-2-ylsulfanyl)acetic acids (**1**, **2**) and corresponding aromatic aldehydes in acetic anhydride. The compounds **3e**, **f** and **4b**, **g** were also synthesized from corresponding aromatic aldehydes and 6,7-dialkoxy-2,3-dihydrobenzo[4,5]imidazo[2,1-*b*][1,3]thiazol-3-ones (**5**, **6**) obtained by the cyclization of the acids **1** and **2** in acetic anhydride. The synthesized compounds **3a**–**h** and **4b**, **c**, **e**, **g** exhibit anti-inflammatory activity.

1. Introduction

Following reports of anti-inflammatory activity of 6-arylmethylidene-3-(2-pyrimidinyl)-5,6-dihydro[1,3]thiazolo [2,3-*c*][1,2,4]triazol-5-ones [1] the series of compounds containing similar structure – 6,7-dialkoxy-2-arylmethylidene-2,3-dihydrobenzo[4,5]imidazo[2,1-*b*][1,3]thiazol-3-ones (**3a**–**h**, **4b**, **c**, **e**, **g**) were synthesized and investigated for anti-inflammatory activity.

2. Investigations, results and discussion

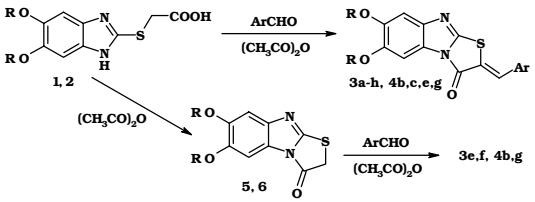
The target 6,7-dialkoxy-2-arylmethylidene-2,3-dihydrobenzo[4,5]imidazo[2,1-*b*][1,3]thiazol-3-ones (**3a**–**h**, **4b**, **c**, **e**, **g**) were synthesized by the reaction of the 2-(5,6-dialkoxy-1*H*-benzo[d]imidazol-2-ylsulfanyl)acetic acids (**1**, **2**) [2] with aromatic aldehydes in acetic anhydride. Some of these compounds (**3e**, **f**, **4b**, **g**) were also obtained by the reaction of corresponding aromatic aldehydes with the

Table 1: Experimental, physico-chemical and spectral data for compounds 3a–h and 4b, c, e, g

Compd.	Formula	Yield (%) (from **1**, **2**/ from **5**, **6**)	M.p. (°C)	UV: λ_{max} (nm), (lg ε)	IR: $\nu_{C=O}$ (cm^{-1})	^{1}H NMR				
						RO	5-H	8-H	Ar-H	=CH
3a	$C_{18}H_{14}N_2O_3S$	78	286–287	291[a], 311(3.32), 335[a], 382[a]	1724	s[b] 3.67 and 3.72 CH_3O	s 7.00	s 7.52	s 7.22	s 8.11
3b	$C_{18}H_{13}FN_2O_3S$	58	275–278	288(3.69), 314(3.78), 330[a], 390[a]	1710	s 3.87 and 3.92 CH_3O	s 7.15	s 7.45	m[c] 7.24–7.31, 7.71–7.76 and 7.92–7.99	s 8.06
3c	$C_{16}H_{12}N_2O_4S$	54	259–262	279(3.87), 288(3.80), 360(4.15)	1712	s 3.68 and 3.72 CH_3O	s 7.01	s 7.47	m 6.30–6.45, 6.82–7.04 and 7.38–7.62	s 7.85
3d	$C_{17}H_{14}N_2O_4S$	49	251–252	280(3.16), 288(3.18), 373(3.41)	1711	s 3.67 and 3.72 CH_3O	s 7.00	s 7.50	m 6.02–6.18 and 6.83–7.08; s 2.17, CH_3	s 7.91
3e	$C_{16}H_{12}N_2O_3S_2$	69/76	282–284	278[a], 284(3.65), 358(3.73)	1700	s 3.67 and 3.72 CH_3O	s 7.00	s 7.52	m 6.78–7.73	s 8.17
3f	$C_{17}H_{13}N_3O_3S$	75/81	284–285	288[a], 321(3.59), 321(3.59)	1716	s 3.72 and 3.80 CH_3O	s 7.19	s 7.44	s 7.44, m 7.65–7.94 and 8.78–8.86	s 8.10
3g	$C_{17}H_{13}N_3O_3S$	55	285–286	305(3.49), 400(2.75)	1716	s 3.68 and 3.72 CH_3O	s 7.07	s 7.46	m 7.92–8.99	s 8.99
3h	$C_{17}H_{13}N_3O_3S$	50	274–275	301(4.03), 400(3.02)	1722	s 3.88 and 3.92 CH_3O	s 7.18	s 7.54	m 7.82–8.80	s 8.04
4b	$C_{20}H_{17}FN_2O_3S$	51/67	312–315	291[a], 313(4.08), 335[a], 388[a]	1727	t[d] 1.43 and 1.45 CH_3, k[e] 4.13 and 4.31 CH_2O	s 7.17	s 7.45	m 7.28–7.38 and 7.72–7.83	s 8.08
4c	$C_{18}H_{16}N_2O_4S$	64	247–249	290(3.00), 360(3.17)	1716	t 1.46 and 1.48 CH_3, k 4.08 and 4.13 CH_2O	s 7.10	s 7.42	m 6.65–6.70, 7.04–7.07 and 7.85–7.99	s 8.01
4e	$C_{18}H_{16}N_2O_3S_2$	67	239–242	289(2.81), 360(3.01)	1711	t 1.44 and 1.47 CH_3, k 4.09 and 4.12 CH_2O	s 7.12	s 7.44	m 7.24–7.28, 7.64–7.67 and 7.79–8.00	s 8.27
4g	$C_{19}H_{17}N_3O_3S$	54/71	243–244		1718	t 1.44 and 1.47 CH_3, k 4.09 and 4.12 CH_2O	s 7.09	s 7.46	m 7.90–8.39	s 8.89

[a] Shoulder, [b] Singlet, [c] Multiplet, [d] Triplet (J = 6 Hz), [e] Quartet (J = 6 Hz)

Scheme



1, 3a–h, **5**: R = CH_3
2, **4b**, **c**, **e**, **g**, **6**: R = C_2H_5
3a–h, **4b**, **c**, **e**, **g**: Ar = C_6H_5 (**a**), 4-FC_6H_4 (**b**), 2-furyl (**c**), 2-(5-methylfuryl) (**d**), 2-tienyl (**e**), 2-pyridyl (**f**), 3-pyridyl (**g**), 4-pyridyl (**h**)

6,7-dialkoxy-2,3-dihydrobenzo[4,5]imidazo[2,1-b][1,3]thiazol-3-ones (**5**, **6**) in acetic anhydride (scheme).

Compound **5** is known [3] and the new analogue **6** has been prepared by cyclisation of acid **2** in acetic anhydride. The yields of compounds **3e, f** and **4b**, **g** obtained from the acids **1** and **2** by the one-step synthesis were higher than those obtained by the two-step synthesis via isolation of the intermediate products **5** and **6** (51–78% and 45–65%, respectively).

The postulated structures of the newly synthesized compounds **3a–h**, **4b**, **c**, **e**, **g** and **6** are in agreement with their UV, IR and ^{1}H NMR spectral and elemental analysis data.

The means of $\nu_{C=O}$ in IR spectra of diethoxy derivatives **4b**, **c**, **e**, **g** are 2–17 cm^{-1} higher than those of analogous dimethoxy derivatives **3b**, **c**, **e**, **g**. The means of λ_{max} in UV spectra of these compounds follow the same trend and the means of lg ε – the opposite trend. The means of the chemical shift of 5-H hydrogen atom in the ^{1}H NMR spectra of the compounds **3a–h** are more sensitive to the nature of the substituent Ar than those of 8-H hydrogen atom (the variations are 7.00–7.19 and 7.44–7.54 ppm, respectively). The means of the chemical shift of 5-H and 8-H hydrogen atoms in the spectra of the compounds **4b**, **c**, **e**, **g** keep the some tendention (Table 1).

Most of the compounds **3** and **4** possess anti-inflammatory activity comparable with that of acetylsalicylic acid and the compounds **3c**, **g**, **h** are more active than ibuprofen. The anti-inflammatory activity of dimethoxy derivatives was equal to that of analogous diethoxy derivatives (in the case of the compounds **3b** and **4b**), or higher (in the case of the compounds **3c** and **4c**, **3e** and **4e**, **3g** and **4g**). The acute toxicity (LD_{50}) of the compounds **3c**, **g**, **h** was less than that of acetylsalicylic acid and significantly less than that of ibuprofen (Table 2).

3. Experimental

3.1. Chemistry

M.p.'s were determined in open capillaries and are uncorrected. The UV spectra were recorded on a Lambda 20 (Perkin-Elmer, Sweden), IR spectra – on a Spectrum BX FT-IR (Perkin-Elmer, Sweden) in nujol and ^{1}H NMR spectra – on a BS–587A (80 MHz, Tesla, Czechoslovakia) in $CDCl_3$ with TMS as an internal standart. 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.

2-(5,6-Dialkoxy-1*H*-benzo[*d*]imidazol-2-ylsulfanyl)acetic acids (**1**, **2**) [2] and 6,7-dimethoxy-2,3-dihydrobenzo[4,5]imidazo[2,1-*b*][1,3]thiazol-3-one (**5**) [3] were synthesized by the known methods.

3.1.1. 6,7-Dialkoxy-2-arylmethylidene-2,3-dihydrobenzo[4,5]imidazo[2,1-b][1,3]thiazol-3-ones (**3a–h**, **4b**, **c**, **e**, **g**)

A mixture of 0.83 g (0.01 mol) anh. sodium acetate, 0.01 mol 2-(5,6-dialkoxy-1*H*-benzo[*d*]imidazol-2-ylsulfanyl)acetic acid (**1** or **2**) or 6,7-dialkoxy-2,3-dihydrobenzo[4,5]imidazo[2,1-*b*][1,3]thiazol-3-one (**5** or **6**), 0.015 mol of the corresponding aromatic aldehyde and 15 ml acetic anhydride was heated at 100 °C for 0.5 h. Then the reaction mixture was cooled and the precipitate obtained was recrystallized from dimethylformamide (Table 1).

3.1.2. 6,7-Diethoxy-2,3-dihydrobenzo[4,5]imidazo[2,1-b][1,3]thiazol-3-one (**6**)

A mixture of 20 ml acetic anhydride, 5 ml pyridine and 1.2 g (0.004 mol) 2-(5,6-diethoxy-1*H*-benzo[d]imidazol-2-ylsulfanyl)acetic acid (**2**) was heated at 90 °C for 0.5 h, cooled and poured into water. The precipitate was filtered off and recrystallized from ethanol. Yield: 0.75 g (67%), m.p.: 165–167 °C. ^{1}H NMR: 1.47 (t (6 Hz), 6 H, CH_3), 4.08 (k (6 Hz), 4 H, OCH_2), 4.31 (s, 2 H, SCH_2), 7.10 (s, 1 H, Ar-H), 7.44 (s, 1 H, Ar-H). IR (cm^{-1}): 1732 (C=O). UV [λ_{max} (lg ε)]: 250 (3.31), 302 (2.89). $C_{13}H_{14}N_2O_3S$.

3.2. Pharmacology

Adult male Wistar strain rats weighing 180–220 g and male BALB/C strain micesweighing 18–22 g were used. The animals were alowed 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. Carrageenin-induced hind-paw oedema in rats was produced by the method of Winter et al. [4]. 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

Table 2: Anti-inflammatory activity (50 mg/kg p.o.) and acute toxicity (LD_{50}) data for compounds 3a–h and 4b, c, e, g

Compd.	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	45.01	0	43.10	0	
3a	41.22	8.4	39.72	7.9	
3b	33.70	25.2	31.77	26.3	2780
3c	31.86	29.2	21.47	50.2	>2000
3d	39.83	11.5	38.58	10.5	
3e	33.60	25.4	28.31	34.2	>2000
3f	41.90	7.3	39.57	8.2	
3g	25.74	42.8	27.59	36.0	2545
3h	26.33	41.5	28.36	34.2	>2000
4b	33.44	25.7	31.51	26.9	
4c	34.70	22.9	35.69	17.2	
4e	33.80	24.5	35.91	16.7	
4g	34.38	23.6	34.27	20.5	
Acetylsalicylic acid	36.09	19.8	33.80	21.6	1216
Ibuprofen	27.10	38.0	34.18	20.7	500

volume was measured with an electronic onkograph immediately before and 1, 2, 3, and 5 h after the carrageenin injection. The increase observed was compared with that of control rats. Each experiment was made with 5 groups of rats, 10 animals each (the first one served as control). Bentonite-induced hind paw oedema was analogously studied [5]. Bentonite suspension (5% in sterile 0.9% NaCl solution) in a volume of 0.1 ml was used. The data were evaluated statistically using Student's t-test. A level of $p < 0.05$ was adopted as the test of significance. 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 day 8 [6].

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