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Synthesis and anti-inflammatory activity of 5-(6-methyl-2-substituted 4-pyrimidinyloxymethyl)-1,3,4-oxadiazole-2-thiones and their 3-morpholinomethyl derivatives

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Abstract

The synthesis of 5-(6-methyl-2-substituted 4-pyrimidinyloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thiones and their 3-morpholinomethyl derivatives and the results of anti-inflammatory activity in vivo are described. Most of the tested compounds exhibited anti-inflammatory activity and some of them were more active than acetylsalicylic acid.

Keywords: 1,3,4-Oxadiazole-2-thiones; Aminomethylation; Anti-inflammatory activity

1. Introduction

Among derivatives of 1,3,4-oxadiazole-2-thione there is a large amount of compounds exhibiting anti-inflammatory activity [1–6]. 1,3,4-Oxadiazole-2-thiones containing the pyrimidine substituents in the 5th position of the oxadiazole ring possess the above-mentioned activity [7,8]. Previously we have reported on the synthesis and pharmacological properties of compounds containing both the pyrimidine and 1,3,4-oxadiazole moieties [8–11]. In continuation of our interest in the synthesis of biologically and chemically valuable compounds, now we report on the synthesis of compounds **5a**–**f** in which the pyrimidine and the 1,3,4-oxadiazole rings are separated by methyleneoxy group. We made an attempt to ascertain dependence of anti-inflammatory activity on the nature of various substituents, introduced into the 2nd position of pyrimidine ring. For structure–activity correlation the corresponding morfolinomethyl derivatives **6a**–**f** were also synthesized.

2. Chemistry

The ester **1** was chosen as a starting compound [12] (Fig. 1). 2-Alkylsulfanyl group is prone to be substituted with nucleophiles [13], thus the starting compound **1** was treated with different amines in order to synthesize esters **3b**–**f**. Unfortunately, from the resulting multicomponent slurry individual compounds were not isolated. Likely, in this case the nucleophilic attack occurred not only at the 2nd position of pyrimidine ring, but also at the 4th position and at the carbonyl group of ester too. When the direct synthesis of 2-amino substituted esters **3b**–**f** under treatment of the 2-methylsulfanyl derivative with different amines was unsuccessful, first we oxidized the 2-methylsulfanyl group into methylsulfonyl (better leaving group) [14]. This method of oxidation, i.e. oxidation of 2-alkylsulfanylpyrimidines with gaseous chlorine in water–alcohol solution into corresponding 2-alkylsulfonylpyrimidines, is reported in literature [15]. Further, the compound **2** was allowed to react with amines in dimethyl sulfoxide to give methyl (2-aminosubstituted 6-methyl-4-pyrimidinyloxy)acetates (**3b**–**f**). Hydrazides **4a**–**f** were obtained under the treatment of esters **1**, **3b**–**f** with hydrazine hydrate. Refluxing of hydrazides **4a**–**f** with

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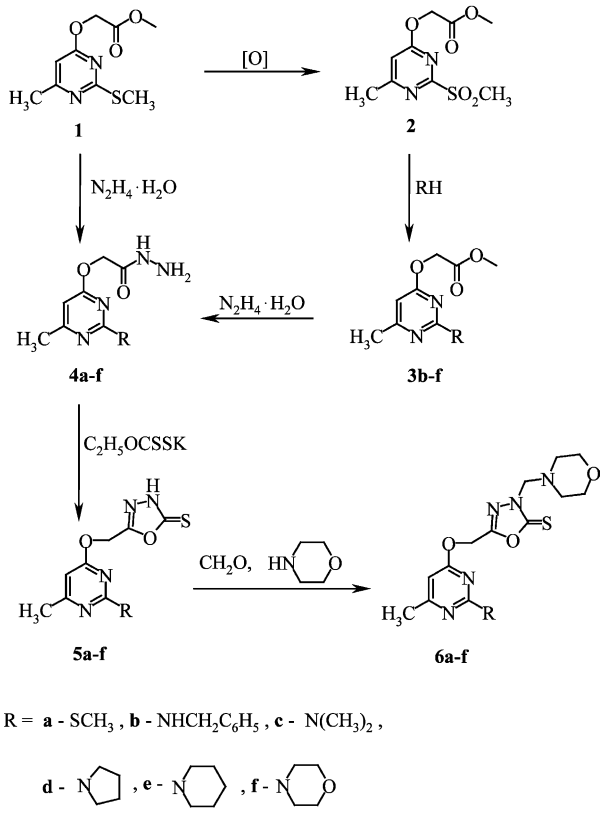

Fig. 1.

potassium *O*-ethylxanthate produced 1,3,4-oxadiazole-2-thiones **5a**–**f**. The latter were reacted with formaldehyde and morpholine in ethanol at 40 °C to give compounds **6a**–**f**. The structure of new compounds **2**, **3b**–**f**, **4b**–**f**, **5a**–**f**, **6a**–**f** was proved by the data of IR, ^{1}H NMR spectra and elemental analysis.

3. Experimental

3.1. Chemistry

Melting points (m.p.) were determined in open capillaries and are uncorrected. The IR spectra were measured on a Carl Zeiss Jena spectrofotometer Specord M 8O in Nujol, ^{1}H NMR spectra were recorded on a BS 567A (80 MHz, Tesla) with HMDSO as an internal standard. Chemical shifts (δ) are reported in ppm. The experimental values of microanalyses for compounds **2**, **3b**–**f**, **4b**–**f**, **5a**–**f**, **6a**–**f** agreed with the calculated ones. The properties of compounds are presented in Table 1. Compounds **1** and **4a** were synthesized as reported previously [12,16].

3.1.1. Methyl (6-methyl-2-methylsulfonyl-4-pyrimidinyloxy)acetate (2)

To a stirred suspension of 2.28 g (0.01 mol) of compound **1** in 30 ml 70% methanol at −5 °C temperature the gaseous chlorine was bubbled till the starting compound dissolved and the reaction product precipitated. Then the solid was filtered off, washed with 1% solution of $Na_2S_2O_3$, water and dissolved in chloroform. The solution was dried with Na_2SO_4 and evaporated, the residue was recrystallized.

^{1}H NMR ($CDCl_3$): 2.57 (s, 3H, CH_3), 3.25 (s, 3H, SO_2CH_3), 3.77 (s, 3H, OCH_3), 4.99 (s, 2H, OCH_2), 6.86 (s, 1H, CH).

3.1.2. Methyl (2-aminosubstituted 6-methyl-4-pyrimidinyloxy)acetates (3b–f)

To a suspension of 2.6 g (0.01 mol) of compound **2** in 3 ml of anh. DMSO 0.02 mol of corresponding amine (in the case of **3c**-solution of dimethylamine in anh. DMSO) was added. The reaction mixture was stirred at 50–70 °C temperature for 0.5 h, then cooled and poured into 100 ml of cold water. The solid was filtered off, washed with water and recrystallized.

^{1}H NMR, **3b** (CCl_4): 2.08 (s, 3H, CH_3), 3.44 (s, 3H, OCH_3), 4.43 (d, $J = 6$ Hz, 2H, $NHCH_2$), 4.55 (s, 2H, OCH_2), 5.78 (s, 1H, CH), 7.1 (s, 6H, Ar–H, NH).

Compound **3c** ($CDCl_3$): 2.26 (s, 3H, CH_3), 3.09 [s, 6H, $N(CH_3)_2$], 3.73 (s, 3H, OCH_3), 4.78 (s, 2H, OCH_2), 5.91 (s, 1H, CH).

Compound **3d** ($CDCl_3$): 1.6–2.06 [m, 4H, $(CH_2)_2$], 2.26 (s, 3H, CH_3), 3.25–3.65 [m, 4H, $N(CH_2)_2$], 3.73 (s, 3H, OCH_3), 4.79 (s, 2H, OCH_2), 5.93 (s, 1H, CH).

Compound **3e** (CCl_4): 1.5 [s, 6H, $(CH_2)_3$], 2.1 (s, 3H, CH_3), 3.55 [s, 7H, OCH_3, $N(CH_2)_2$], 4.53 (s, 2H, OCH_2), 5.69 (s, 1H, CH).

Compound **3f** (CCl_4): 2.15 (s, 3H, CH_3), 3.56 [s, 11H, OCH_3, $N(CH_2)_2$, $O(CH_2)_2$], 4.58 (s, 2H, OCH_2), 5.81 (s, 1H, CH).

3.1.3. (2-Aminosubstituted 6-methyl-4-pyrimidinyloxy)acethydrazide (4b–f)

To a hot solution of 0.01 mol of ester **3b**–**f** in 10 ml of isopropanol 1.5 g (0.03 mol) of 99% hydrazine hydrate was added. The reaction mixture was stirred at reflux for 1 h and allowed to warm to room temperature (r.t.). The solid was filtered off, washed with ether and recrystallized.

^{1}H NMR, **4b** (CF_3COOH): 2.07 (s, 3H, CH_3), 4.33 (d, $J = 5$ Hz, 2H, $NHCH_2$), 4.84 (s, 2H, OCH_2), 5.99 (s, 1H, CH), 6.89 (s, 5H, Ar–H).

Compound **4c** (DMSO-d_6): 2.18 (s, 3H, CH_3), 3.04 [s, 6H, $N(CH_3)_2$], 4.25 (s, 2H, NH_2), 4.64 (s, 2H, OCH_2), 5.93 (s, 1H, CH), 9.38 (s, 1H, NH).

Compound **4d** (DMSO-d_6): 1.86 [s, 4H, $(CH_2)_2$], 2.17 (s, 3H, CH_3), 3.34 [s, 4H, $N(CH_2)_2$], 4.25 (s, 2H, NH_2), 4.64 (s, 2H, OCH_2), 5.93 (s, 1H, CH), 9,29 (s, 1H, NH).

Compound **4e** (CF_3COOH): 1.33 [s, 6H, $(CH_2)_3$], 2.01 (s, 3H, CH_3), 3.36 [s, 4H, $N(CH_2)_2$], 4.84 (s, 2H, OCH_2), 5.84 (s, 1H, CH).

Table 1
Properties of the compounds **2**–**6**

Comp.	Formula (molecular weight)	M.p. (°C) (solvent)	Yield (%)	IR, ν (cm^{-1})			
				NH	C=O	C=N	C=S
2	$C_9H_{12}N_2O_5S$ (260.3)	109–110 (benzene)	87		1760	1596	
3b	$C_{15}H_{17}N_3O_3$ (287.3)	88–89 (hexane)	85	3256	1756	1580	
3c	$C_{10}H_{15}N_3O_3$ (225.2)	38–40 (hexane)	58		1752	1592	
3d	$C_{12}H_{17}N_3O_3$ (251.3)	73–75 (hexane)	84		1752	1564	
3e	$C_{13}H_{19}N_3O_3$ (265.3)	59–60 (hexane)	88		1756	1564	
3f	$C_{12}H_{17}N_3O_4$ (267.3)	93–94 (hexane)	86		1744	1564	
4b	$C_{14}H_{17}N_5O_2$ (287.3)	156–158 (isopropanol)	76	3296	1648	1576	
4c	$C_9H_{15}N_5O_2$ (225.3)	143–145 (isopropanol)	83	3304, 3264, 3200	1676	1588	
4d	$C_{13}H_{17}N_5O_2$ (275.3)	151–153 (isopropanol)	76	3312, 3212	1672	1588	
4e	$C_{12}H_{19}N_5O_2$ (265.3)	151–152 (isopropanol)	68	3312, 3208	1680	1580	
4f	$C_{11}H_{17}N_5O_3$ (267.3)	186–188 (isopropanol)	80	3304, 3216	1672	1564	
5a	$C_9H_{10}N_4O_2S_2$ (270.3)	180–182 (isopropanol/water)	72			1576	1312
5b	$C_{15}H_{15}N_5O_2S$ (329.4)	166–168 (isopropanol/water)	67	3192		1588	1316
5c	$C_{10}H_{13}N_5O_2S$ (267.3)	183–185 (isopropanol/water)	56			1596, 1572	1324
5d	$C_{12}H_{15}N_5O_2S$ (293.4)	191–193 (isopropanol/water)	52			1576, 1540	1328
5e	$C_{13}H_{17}N_5O_2S$ (307.4)	163–165 (isopropanol/water)	73			1568, 1540	1320
5f	$C_{12}H_{15}N_5O_3S$ (309.4)	169–170 (isopropanol/water)	69			1590, 1576	1308
6a	$C_{14}H_{19}N_5O_3S_2$ (369.5)	125–127 (ethanol)	74			1580, 1546	1304
6b	$C_{20}H_{24}N_6O_3S$ (428.5)	120–122 (ethanol)	57	3248		1564	1316
6c	$C_{15}H_{22}N_6O_3S$ (366.4)	115–117 (ethanol)	66			1564	1312
6d	$C_{17}H_{24}N_6O_3S$ (392.5)	127–129 (ethanol)	61			1580, 1536	1316
6e	$C_{18}H_{26}N_6O_3S$ (406.5)	98–100 (ethanol)	74			1576, 1528	1324
6f	$C_{17}H_{24}N_6O_4S$ (408.5)	128–130 (ethanol)	74			1564	1344

Compound **4f** (CF_3COOH): 2.05 (s, 3H, CH_3), 3.56 [s, 8H, $N(CH_2)_2$, $O(CH_2)_2$], 4.86 (s, 2H, OCH_2), 5.84 (s, 1H, CH).

Compound **5f** (CF_3COOH): 2.08 (s, 3H, CH_3), 3.63 [s, 8H, $N(CH_2)_2$, $O(CH_2)_2$], 5.13 (s, 2H, OCH_2), 5.91 (s, 1H, CH).

*3.1.4. 5-(2-Aminosubstituted 6-methyl-4-pyrimidinyloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thiones (**5a**–**f**)*

A mixture of 0.01 mol of compound **4a**–**f** and 1.6 g (0.01 mol) of potassium *O*-ethylxanthate in 70 ml ethanol was refluxed for 12 h. The solvent was evaporated, the residue was dissolved in 30 ml of water. The solution was acidified with concentrated HCl to pH 5. The solid formed was filtered off, washed with water and recrystallized.

^{1}H NMR, **5a** (DMSO-d_6): 2.29 (s, 3H, CH_3), 2.44 (s, 3H, SCH_3), 5.46 (s, 2H, OCH_2), 6.55 (s, 1H, CH).

Compound **5b** (CF_3COOH): 2.04 (s, 3H, CH_3), 4.29 (d, $J = 5$ Hz, 2H, $NHCH_2$), 5.06 (s, 2H, OCH_2), 5.88 (s, 1H, CH), 6.85 (s, 5H, Ar–H).

Compound **5c** (DMSO-d_6): 2.12 (s, 3H, CH_3), 3.04 [s, 6H, $N(CH_3)_2$], 5.37 (s, 2H, OCH_2), 6.01 (s, 1H, CH).

Compound **5d** (DMSO-d_6): 1.71–1.99 [m, 4H, $(CH_2)_2$], 2.2 (s, 3H, CH_3), 3.06–3.75 [m, 4H, $N(CH_2)_2$], 5.37 (s, 2H, OCH_2), 6.01 (s, 1H, CH).

Compound **5e** (CF_3COOH): 1.35 [s, 6H, $(CH_2)_3$], 2.01 (s, 3H, CH_3), 3.39 [s, 4H, $N(CH_2)_2$], 5.1 (s, 2H, OCH_2), 5.78 (s, 1H, CH).

*3.1.5. 5-(2-Aminosubstituted 6-methyl-4-pyrimidinyloxymethyl)-3-morpholinomethyl-2,3-dihydro-1,3,4-oxadiazole-2-thiones (**6a**–**f**)*

To a solution of 0.01 mol of compound **5a**–**f** in 100 ml of ethanol at 40 °C 1.13 ml (0.015 mol) of formalin and 0.87 g (0.01) of morpholine was added. The reaction mixture was stirred at this temperature for 1 h and cooled. The solid was filtered off, washed with ether and recrystallized.

^{1}H NMR, **6a** ($CDCl_3$): 2.39 (s, 3H, CH_3), 2.52 (s, 3H, SCH_3), 2.63–2.94 [m, 4H, $N(CH_2)_2$], 3.52–3.84 [m, 4H, $O(CH_2)_2$], 4.96 (s, 2H, NCH_2), 5.39 (s, 2H, OCH_2), 6.34 (s, 1H, CH).

Compound **6b** ($CDCl_3$): 2.27 (s, 3H, CH_3), 2.56–2.94 [m, 4H, $N(CH_2)_2$], 3.53–3.88 [m, 4H, $O(CH_2)_2$], 4.62 (d, $J = 6$ Hz, 2H, $NHCH_2$), 4.86 (s, 2H, NCH_2), 5.24 (s, 2H, OCH_2), 5.5–5.8 (m, 1H, NH), 5.98 (s, 1H, CH), 7.29 (s, 5H, Ar–H).

Compound **6c** ($CDCl_3$): 2.27 (s, 3H, CH_3), 2.62–2.94 [m, 4H, $N(CH_2)_2$], 3.12 [s, 6H, $N(CH_3)_2$], 3.5–3.88 [m, 4H, $O(CH_2)_2$], 4.94 (s, 2H, NCH_2), 5.31 (s, 2H, OCH_2), 5.88 (s, 1H, CH).

Compound **6d** ($CDCl_3$): 1.69–2.07 [m, 4H, $N(CH_2)_2$], 2.27 (s, 3H, CH_3), 2.58–2.9 [m, 4H, $N(CH_2)_2$], 3.31–3.83

[m, 8H, $N(CH_2)_2$, $O(CH_2)_2$], 4.94 (s, 2H, NCH_2), 5.31 (s, 2H, OCH_2), 5.89 (s, 1H, CH).

Compound **6e** ($CDCl_3$): 1.59 [s, 6H, $(CH_2)_3$], 2.25 (s, 3H, CH_3), 2.6–2.85 [m, 4H, $N(CH_2)_2$], 3.54–3.85 [m, 8H, $N(CH_2)_2$, $O(CH_2)_2$], 4.94 (s, 2H, NCH_2), 5.28 (s, 2H, OCH_2), 5.86 (s, 1H, CH).

Compound **6f** ($CDCl_3$): 2.27 (s, 3H, CH_3), 2.63–2.88 [m, 4H, CH_2–$N(CH_2)_2$], 3.54–3.95 {m, 12H, $N(CH_2)_2$, $2[O(CH_2)_2]$}, 4.94 (s, 2H, NCH_2), 5.28 (s, 2H, OCH_2), 5.95 (s, 1H, CH).

3.2. Pharmacology

For anti-inflammatory tests adult male and female Wistar strain rats weighing 140–150 g were used. All test compounds and the reference drug were administered orally suspended in 1% carboxymethylcellulose with one drop of Twin-80 solution. The effect of test compounds on decrease of rats paw oedema was compared with that of control rats. The anti-inflammatory activity was expressed as a decrease of rats paw oedema and is given in percentage. The data were evaluated statistically using Student's t-test. A level of $P < 0.05$ was adopted as 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. [17]. Carrageenin solution (1.0% in sterile 0.9% NaCl solution) was injected subcutaneously into the subplanar region of the hind paw (in a volume of 0.1 ml to each paw) 1 h after administration of the test compound. Control rats received only solution of 0.5% carboxymethylcellulose with one drop of Twin-80. The hind paw volume was measured with an electronic onkograph immediately before and 1, 2, 3 and 5 h after the carrageenin injection.

3.2.2. Bentonite test

Bentonite test was analogously produced (0.1 ml 5% solution) according to [18].

3.2.3. Acute toxicity

The tests of acute toxicity of the compounds were done on male BALB/C strain mice weighing 18–22 g. Groups of six mice were treated perorally with the test compound at various dose levels. The animals were watched for mortality and symptoms until 8th day [19].

4. Results and discussion

Anti-inflammatory activity was studied by carrageenin- and bentonite-induced paw oedema in rats. The inhibition of the oedema was measured after 1, 2, 3 and 5 h from the administration of test compounds. The data in the Table 2 are given as an arithmetical means of these measurements. As a reference substance in experiments an acetylsalicylic acid was used. Compounds **5f** and **6a** were the most active of all the tested ones. They showed anti-inflammatory activity higher than that of acetylsalicylic acid, i.e. they decreased carrageenin-induced oedema, 29.7 and 32.6% and bentonite-induced, 26.4 and 23.4%, respectively. Both of compounds have morpholine fragment as a substituent in the 2nd position of pyrimidine (**5f**) or in the 3rd position of oxadiazole ring (**6a**). Compound **6f** containing morpholine moiety in both above mentioned positions showed similar activity in bentonite test (decreased oedema

Table 2
Anti-inflammatory activity (50 mg kg^{-1} p.o.) and acute toxicity (LD_{50}) data for compounds **5**–**6**

Comp.	0.1 ml of 1% carrageenin solution		0.1 ml of 5% bentonite suspension		LD_{50} (mg kg^{-1})
	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	95.3	0	94.8	0	
5a	96.3	0	106.9	+12.1 [a]	
5b	110.4	+15.1 [a]	107.5	+12.2 [a]	
5c	77.9	17.4	76.5	18.3	>1000
5d	125.7	+30.4 [a]	75.5	19.3	
5e	95.0	0	94.6	0	
5f	65.6	29.7	68.9	26.4	800
6a	62.7	32.6	71.4	23.4	>1000
6b	109.3	+14.0 [a]	59.2	33.6	
6c	89.0	6.3	84.1	10.7	
6d	90.6	0	73.9	20.9	
6e	78.6	16.7	70.8	24.0	750
6f	77.5	17.8	67.5	27.3	>1000
Acetylsalicylic acid	77.2	19.8	74.7	21.6	1216

[a] Increase oedema.

Table 3
Data of elemental analysis of compounds

Compound	Brutto formula	Mol. Weight	Calculated / Found, %		
			C	H	N
2	$C_9H_{12}N_2O_5S$	260.3	41.53 / 41.97	4.64 / 4.65	10.76 / 10.94
3b	$C_{15}H_{17}N_3O_3$	287.3	62.70 / 62.76	5.96 / 6.02	14.62 / 14.92
3c	$C_{10}H_{15}N_3O_3$	225.2	53.32 / 53.37	6.71 / 6.67	18.65 / 18.69
3d	$C_{12}H_{17}N_3O_3$	251.3	57.36 / 57.40	6.82 / 7.02	16.72 / 16.93
3e	$C_{13}H_{19}N_3O_3$	265.3	58.85 / 58.82	7.21 / 7.28	15.83 / 15.69
3f	$C_{12}H_{17}N_3O_4$	267.3	53.92 / 53.82	6.41 / 6.28	15.72 / 15.72
4b	$C_{14}H_{17}N_5O_2$	287.3	58.52 / 58.38	5.96 / 6.12	24.37 / 24.25
4c	$C_9H_{15}N_5O_2$	225.3	47.99 / 48.10	6.71 / 6.70	31.09 / 31.14
4d	$C_{13}H_{17}N_5O_2$	275.3	52.58 / 52.64	6.82 / 7.06	27.87 / 28.61
4e	$C_{12}H_{19}N_5O_2$	265.3	54.32 / 54.41	7.21 / 7.28	26.39 / 26.49
4f	$C_{11}H_{17}N_5O_3$	267.3	49.43 / 49.22	6.41 / 6.37	26.20 / 26.22
5a	$C_9H_{10}N_4O_2S_2$	270.3	39.99 / 40.19	3.73 / 3.45	20.73 / 21.00
5b	$C_{15}H_{15}N_5O_2S$	329.4	54.70 / 54.73	4.59 / 4.45	21.26 / 21.30
5c	$C_{10}H_{13}N_5O_2S$	267.3	44.93 / 45.21	4.90 / 4.81	26.20 / 26.37
5d	$C_{12}H_{15}N_5O_2S$	293.4	49.13 / 49.35	5.15 / 5.18	23.87 / 23.74
5e	$C_{13}H_{17}N_5O_2S$	307.4	50.80 / 51.10	5.57 / 5.88	22.78 / 22.79
5f	$C_{12}H_{15}N_5O_3S$	309.4	46.59 / 46.72	4.89 / 4.92	22.64 / 22.57
6a	$C_{14}H_{19}N_5O_3S_2$	369.5	45.51 / 45.62	5.18 / 5.14	18.96 / 19.06
6b	$C_{20}H_{24}N_6O_3S$	428.5	56.06 / 55.80	5.65 / 5.64	19.61 / 19.45
6c	$C_{15}H_{22}N_6O_3S$	366.4	49.17 / 49.28	6.05 / 5.89	22.93 / 22.87
6d	$C_{17}H_{24}N_6O_3S$	392.5	52.03 / 51.94	6.16 / 5.91	21.41 / 21.50
6e	$C_{18}H_{26}N_6O_3S$	406.5	53.18 / 53.35	6.45 / 6.76	20.67 / 20.60
6f	$C_{17}H_{24}N_6O_4S$	408.5	49.99 / 50.09	5.92 / 5.85	20.57 / 20.56

27.3%), however, it was less active in carrageenin test (decreased oedema 17.8%). Compounds **5b**,**d** and **6b** showed the contrary effect. They increased the carragennin-induced oedema in rat's paw 15.1, 30.4 and 14.0%, respectively. Compounds **5a**,**b** showed the analogous results in bentonite test (increased oedema 12.1 and 12.2%, respectively). It may be stated, that introduction of benzylamino group into 2nd position of pyrimidine ring (compounds **5b** and **6b**) is unfavorable for anti-inflammatory effect. Morpholinomethyl derivatives **6a**,**e** exhibit stronger anti-inflammatory activity than corresponding oxadiazolethiones **5a**,**e**, while morpholinomethylated **6c** is less active than oxadiazolethione **5c**. Thus, the influence of morpholinomethyl substituent of oxadiazoles **6** towards anti-inflammatory activity is not clear expressed.

Compounds with higher expressed anti-inflammatory activity (**5c**,**f**, **6a**,**e**,**f**) were evaluated for their acute toxicity. The tests indicated, that compounds possess toxicity comparable to that of acetylsalicylic acid (Table 2).

References

[1] D.H. Boschelli, D.T. Connor, D.A. Bornemeier, R.D. Dyer, J.A. Kennedy, P.J. Kuipers, G.C. Okonkwo, D.J. Schrier, C.D. Wright, 1,3,4-Oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole analogs of the fenamates in vitro inhibition of cyclooxygenase and 5-lipoxygenase activities, J. Med. Chem. 36 (1993) 1802–1810.

[2] R. Kalsi, K. Pande, J.P. Barthwal, Synthesis of formazans of substituted oxadiazole-2(3H)-thiones, Indian J. Chem. 27B (1988) 197–199.

[3] I.P. Singh, A.K. Saxena, K. Shankar, Synthesis and anti-inflammatory activity of oxadiazoline thione hydrochlorides, Eur. J. Med. Chem.—Chim. Ther. 21 (1986) 267–269.

[4] R. Nigam, S. Swarup, V.K. Saxena, H.K. Singh, Synthesis and pharmacological screening of some new 2-thioxo-3-(substituted aminomethyl)-5-(3,5-dinitrophenyl)-1,3,4-oxadiazoles, J. Indian Chem. Soc. 69 (1992) 692–693.

[5] S. Saxena, M. Verma, A.K. Saxena, K. Shanker, 1,3,4-Oxadiazolethiones as inflammation inhibitors, Indian J. Pharm. Sci. 54 (1992) 1–3.

[6] D.H. Boschelli, D.T. Connor, C.R. Kostlan, J.B. Kramer, M.D. Mullican, J.C. Sircar, Preparation of (3,5-di-*tert*-butyl-4-hydroxyphenylthio)-1,3,4-thiadiazoles, oxadiazoles and analogs as anti-inflammatory agents, EP 449211 (1991) (C. A. 116 (1992) 6570).

[7] T.R. Belliotti, D.T. Connor, C.R. Kostlan, Preparation of 2-diazolyl-4,6-ditertiary-butyl-5-hydroxypyrimidines as cyclooxygenase and 5-lipoxygenase inhibitors, WO 9213844 (1992) (C. A. 118 (1993) 6990).

[8] M.M. Burbuliene, E. Udrenaite, P. Gaidelis, P. Vainilavicius, Reactions of 5-(2-dimethylamino-6-methyl-4-pyrimidinylsulfanylmethyl)-1,3,4-oxadiazole-2-thione with carbon electrophiles, Pol. J. Chem. 76 (2002) 557–563.

[9] G. Mekuskiene, P. Vainilavicius, A. Hetzheim, R. Sematovic, Synthesis of 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione, Khim. Geterotsikl. Soedin. (1993) 700–705 (Russ.) (C. A. 120 (1994) 8554).

[10] V. Jakubkiene, P. Vainilavicius, Reaction of 6-methyl-2-methylthio-3-(2-thioxo-1,3,4-oxadiazol-5-yl)methyl-4(3H)pyrimidinone with amines, Chem. Heterocycl. Comp. 34 (1999) 971–975 (C. A. 130 (1999) 338078).

[11] R. Smicius, V. Jakubkiene, M.M. Burbuliene, P. Vainilavicius, Reactions of 5-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidi-

nyl)-methyl-1,3,4-oxadiazole-2-thione with electrophiles, Monatsh. Chem. 133 (2002) 173–181.
[12] P. Vainilavicius, V. Sedereviciute, Selective O- and $N_{(3)}$-alkylation of 2-alkylthio-4-hydroxypyrimidines by alkyl haloacetates, Khim. Geterotsikl. Soedin. (1987) 1655–1658 (Russ.) (C. A. 109 (1988) 92927).
[13] V.P. Mamaev, O.A. Zagulyaeva, S.M. Shein, Nucleophilic substitution in azines, Khim. Geterotsikl. Soedin. (1973) 723–734 (Russ.) (C. A. 79 (1973) 77568).
[14] D.J. Brown, P.W. Ford, Simple pyrimidines. X. The formation and reactivity of 2-, 4-, and 5-pyrimidinyl sulfones and sulfoxides, J. Chem. Soc. C (1967) 568–572.
[15] Z. Budesinsky, J. Vavrina, Nucleophilic substitutions in the 2-methanesulfonylpyrimidine series, Collect. Czech. Chem. Commun. 37 (1972) 1721–1733.
[16] P. Vainilavicius, V. Sedereviciute, S. Mociskyte, Transformations of (6-methyl-2-methylthio-4-pyrimidinyloxy)- and (3,4-dihydro-6-methyl-2-methylthio-4-oxo-3-pyrimidinyl)acetic acid methyl esters, Khim. Geterotsikl. Soedin. (1992) 1655–1659 (Russ.) (C. A. 119 (1993) 160223).
[17] C.A. Winter, E.A. Risley, G.W. Nuss, Carrageenin-induced oedema in hind paw of the rat as an assay for anti-inflammatory drugs, Proc. Soc. Exp. Biol. Med. 111 (1962) 544–547.
[18] J. Marek, Bentonite-induced rat paw oedema as a tool for simultaneous testing of prophylactic and therapeutic effects of anti-inflammatory and other drugs, Pharmazie 36 (1981) 46–49.
[19] J.T. Litchfield, F.J. Wilkoxon, A simplified method of evaluating dose–effect experiments, Pharmacol. Exp. Ther. 96 (1949) 99–105.