SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF 4-ACYL AND 4-SULFONYL DERIVATIVES OF PIPERAZINE-2,6-DIONE

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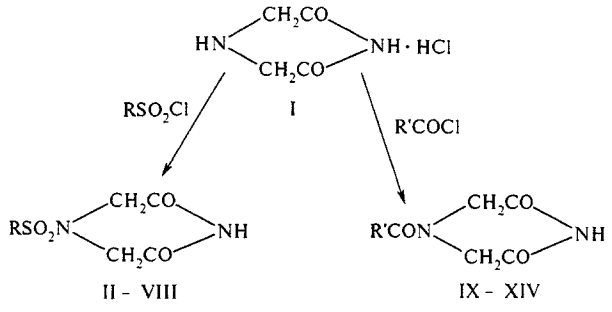
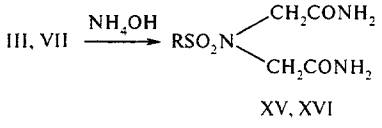
Piperazine-2,6-dione derivatives exhibit a broad spectrum of pharmacological activity [1 – 5]. However, the attention of researchers was drawn for the most part to the 1- and 4-alkyl and -aryl derivatives, while only a few data were reported on the 4-acyl and 4-sulfonyl substituted piperazine-2,6-diones [6]. We failed to find any data concerning the antiinflammatory properties of piperazine-2,6-diones.

The purpose of this work was to synthesize a series of 4-acyl and 4-sulfonyl derivatives of piperazine-2,6-dione and study their antiinflammatory activity.



R = C_5H_5 (II), 4-$CH_3C_6H_4$ (III), 4-$NO_2C_6H_4$ (IV), 3-$NO_2C_6H_4$ (V), 4-$CH_3CONHC_6H_4$ (VI), 2-naphthyl (VII), 2-fluorenyl (VIII);
R′ = 4-$CH_3C_6H_4$ (IX), 4-$CH_3CONHC_6H_4$ (X), $CH_3(CH_2)_6$ (XI), $CH_3(CH_2)_{12}$ (XII), $CH_3(CH_2)_{14}$ (XIII), 9-fluorenylmethyl (XIV).



R = 4-$CH_3C_6H_4$ (XV), 2-naphthyl (XVI).

Compounds II – VII were synthesized by condensation of piperazine-2,6-dione hydrochloride (I) with the corresponding arylsulfonyl chlorides in the presence of potassium bicarbonate (Schotten – Baumann reaction). The reaction was conducted at 20°C in a methanol – water medium; the target products were obtained at a yield of 65 – 86%.

We failed to obtain 4-(fluorenyl-2-sulfonyl)piperazine-2,6-dione (VIII) using the above procedure, apparently because of the low activity and solubility of fluorenyl-2-sulfonyl chloride under the conditions employed. Heating the reaction mixture to 30 – 40°C for 15 min probably led to a partial hydrolysis of the piperazine-2,6-dione ring; the resulting product mixture could not be separated. Compound VIII was successfully synthesized with a 97.2% yield by interaction of piperazine-2,6-dione hydrochloride (I) with fluorenyl-2-sulfonyl chloride in pyridine. Similar reactions in pyridine were used to obtain compounds IX – XIII (the yields ranged from 53 to 90%). Because we met considerable difficulties in attempts to prepare 9-fluorenylacetic acid chloroanhydride, 4-(9-fluorenylacetyl)piperazine-2,6-dione (XIV) was synthesized by the carbodiimide method. Ammonolysis of 4-sulfonyl piperazine-2,6-dione derivatives (III, VII) led to the corresponding diamides of iminodiacetic acids (XV, XVI).

The proposed structures of the synthesized compounds were confirmed by data of the ^{1}H NMR spectroscopy measurements; the purity and identity of the reaction products were checked by TLC (Tables 1 and 2).

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra were measured on a Hitachi R-22 spectrometer using DMSO-d_6 as the solvent and HMDS as the internal standard. The course of reactions was monitored and the purity of the reaction products was checked by TLC on Silufol UV-254 plates eluted in chloroform – acetone systems with the component ratios 1 : 2 (A); 2 : 1 (B); 1 : 3 (C); 3 : 1 (D), and 5 : 1 (E). The spots were visualized under UV illumination and by treating the chromatograms with a solution prepared using 1 g $CoCl_2$, 2 g $K_2Cr_2O_7$, 10 mg acetic acid, and 100 ml water (blue spots of cyclic imides and diamides). The data of elemental analysis agree with the results of analytical calculations.

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TABLE 1. Yields and Physicochemical Characteristics of the Synthesized Compounds

Compound	Yield, %	M.p., °C (solvent)	R_f (TLC system)	Empirical formula
II	83.6	201 – 202.5 (methanol – water)	0.31(E)	$C_{10}H_{10}N_2O_4S$
III	86.3	194 (acetone – water)	0.38(E)	$C_{11}H_{12}N_2O_4S$
IV	76.9	203 – 204 (acetone – water)	0.31(E)	$C_{10}H_9N_3O_6S$
V	64.4	189 – 190 (acetone – water)	0.66(B)	$C_{10}H_9N_3O_6S$
VI	82.6	240 – 244 (decomp.) (ethanol – water)	0.83(B)	$C_{12}H_{13}N_3O_5S$
VII	84.5	170 – 171.5 (acetone)	0.43(E)	$C_{14}H_{12}N_2O_4S$
VIII	97.2	237 – 239 (acetone – water)	0.51(E)	$C_{17}H_{14}N_2O_4S$
IX	83.0	137 – 139 (acetone – water)	0.68(C)	$C_{12}H_{12}N_2O_3$
X	61.5	220 – 225 (decomp.) (acetone – water)	0.84(B)	$C_{13}H_{13}N_3O_4$
XI	53.2	113 – 115 (acetone – water)	0.73(B)	$C_{12}H_{20}N_2O_3$
XII	71.3	114 – 116 (acetone – water)	0.39(E)	$C_{18}H_{32}N_2O_3$
XIII	89.8	98 – 100 (acetone – water)	0.41(E)	$C_{20}H_{36}N_2O_3$
XIV	65.6	192 – 193 (acetone – water)	0.62(D)	$Cl_9H_{16}N_2O_3$
XV	94.1	228 – 229 (methanol)	0.18(C)	$C_{11}H_{15}N_3O_4S$
XVI	78.1	220 – 222 (methanol – water)	0.11(A)	$C_{14}H_{15}N_3O_4S$

Table 1 lists the yields and physicochemical characteristics of the synthesized compounds. Table 2 presents parameters of their ^1H NMR spectra.

Piperazine-2,6-dione hydrochloride (I) was synthesized as described elsewhere [7].

Fluorenyl-2-sulfonyl chloride was obtained by the method described in [8], and 9-fluorenylacetic acid was synthesized according to [9].

Synthesis of 4-arylsulfonyl piperazine-2,6-dione derivatives (II – VII). To a solution of 6.0 g (40 mmole) of piperazine-2,6-dione hydrochloride (I) in 120 ml of a 70% aqueous methanol was added 4.0 g (40 mmole) of potassium bicarbonate and the mixture was kept for 1 h at 20°C (until carbon dioxide ceased to evolve). Then another 4.0 g (40 mmole) of sodium bicarbonate and 40 mmole of the corresponding arylsulfonyl chloride were added and the reaction mixture was stirred for 1 h and 20°C and allowed to stand for 12 h. The precipitated product was filtered, washed with water, dried, and recrystallized.

4-(Fluorenyl-2-sulfonyl)piperazine-2,6-dione (VIII). To a solution of 5.3 g (20 mmole) of fluorenyl-2-sulfonyl chloride obtained by heating in 10 ml of pyridine was added 3.0 g (20 mmole) of piperazine-2,6-dione hydrochloride (I) and the mixture was heated for 5 min (until complete dissolution of I). Then the mixture was allowed to stand for 12 h at 20°C, after which the precipitated product was washed with water and recrystallized.

Synthesis of 4-acyl piperazine-2,6-dione derivatives (IX – XIII). To a solution of 20 mmole of the corresponding carboxylic acid chloroanhydride in 10 ml pyridine was added 3.0 g (20 mmole) of piperazine-2,6-dione hydrochloride (I) and the mixture was heated for 5 min (until complete dissolution of I). Then the mixture was allowed to stand for 12 h at 20°C, after which the precipitated product was washed with water and recrystallized.

4-(9-Fluorenylacetyl)piperazine-2,6-dione (XIV). To a mixture of 4.5 g (30 mmole) piperazine-2,6-dione hydrochloride (I) with 50 ml of pyridine, heated for 10 min, was added 6.7 g (30 mmole) of 9-fluorenylacetic acid and the solution was cooled to 0°C. To this solution was added 6.8 g (33 mmole) of N,N′-sicyclohexylcarbodiimide and the mixture was kept for 12 h at 4°C. Then pyridine was distilled off (to dryness) in vacuum and the product was dissolved in ethyl acetate and filtered. The filtrate was evaporated to dryness. The residue was washed with ether and dissolved in chloroform. The solution was filtered through a thin (2 – 3 cm) layer of silica gel 5/40. Finally, chloroform was distilled off and the product was recrystallized.

N-Substituted iminodiacetic acid diamides (XV, XVI). A mixture of 10 mmole of the corresponding 4-arylsulfonyl

TABLE 2. Parameters of the ^1H NMR Spectra of Compounds II – XVI

Compound	Chemical shift δ, ppm
II	3.98 (s, 4H, $COCH_2N$); 7.49 – 7.89 (m, 5H, C_6H_5); 11.20 (bs, 1H, NH)
III	2.36 (s, 3H, CH_3); 3.98 (s, 4H, $COCH_2N$); 7.41, 7.63 (4H, A_2B_2, C_6H_4); 11.49 (bs, 1H, NH)
IV	4.13 (s. 4H, $COCH_2N$); 8.00, 8.36 (4H, A_2B_2, C_6H_4); 11.15 (bs, 1H, NH)
V	4.09 (s, 4H, $COCH_2N$); 7.82 – 8.71 (m, 4H, C_6H_4); 11.23 (bs, 1H, NH)
VI	2.05 (s, 3H, CH_3); 3.98 (s, 4H, $COCH_2N$); 7.60 – 8.00 (m, 4H, C_6H_4); 10.36 (bs, 1H, CH_3CONH); 11.38 (bs, 1H, NH)
VII	4.02 (s, 4H, $COCH_2N$); 7.50 – 8.60 (m, 7H, arom. H); 10.94 (bs, 1H, NH)
VIII	4.01 (s, 2H, CH_2); 4.12 (s, 4H, $COCH_2N$); 7.40 – 8.10 (m, 7H, arom. H); 10.67 (bs, 1H, NH)
IX	2.32 (s, 3H, CH_3); 4.31 (s, 4H, $COCH_2N$); 7.20 – 7.45 (m, 4H, C_6H_4); 11.36 (bs, 1H, NH)
X	2.14 (s, 3H, CH_3); 4.42 (s, 4H, $COCH_2N$); 7.47, 7.73 (4H, A_2B_2, C_6H_4), 10.15 (bs, 1H, CH_3CONH); 11.40 (bs, 1H, NH)
XI	0.82 (t, 3H, CH_3); 1.23 (m, 10H, CH_2); 2.35 (2H, CH_2CO); 4.27 (s, 4H, $COCH_2N$); 11.29 (bs, 1H, NH)
XII	0.83 (t, 3H, CH_3); 1.20 (bs, 22H, CH_2); 2.28 (t, 2H, CH_2); 4.23 (s, 4H, $COCH_2N$); 11.27 (bs, 1H, NH)
XIII	0.82 (t, 3H, CH_3); 1.22 (bs, 26H, CH_2); 2.35 (t, 2H, CH_2); 4.27 (s, 4H, $COCH_2N$); 11.29 (bs, 1H, NH)
XIV	2.93 (d, 2H, CH_2); 4.22 (bs, 1H, CH); 4.35 (bs, 4H, $COCH_2N$); 6.97 – 7.87 (m, 8H, arom. H); 11.34 (bs, 1H, NH)
XV	2.38 (s, 3H, CH_3); 3.73 (c, 4H, $COCH_2N$); 7.18 (bs, 2H, NH_2); 7.39, 7.69 (4H, A_2B_2, C_6H_4); 8.00 (bs, 2H, NH)
XVI	3.85 (s, 4H, $COCH_2N$); 7.18 (bs, 2H, NH_2); 7.49 – 8.55 (m, 7H, arom. H overlap with 2H, NH_2)

derivative III or VII in 10 ml of a 25% aqueous ammonia was boiled for 5 – 10 min and then kept at 20°C for 12 h. The precipitate was filtered, washed with methanol, and recrystallized.

EXPERIMENTAL PHARMACOLOGICAL PART

The antiinflammatory activity was studied on a model of carrageenan [10] and bentonite [11] induced foot edema in a group of male Wistar rats weighing 180 – 220 g. The synthesized compounds (at a dose of 1/50 – 1/60 of LD_{50}) and the reference drugs ibuprofen, sodium diclofenac, and indomethacin (at a dose of 1/10 of LD_{50} in mice) were introduced to animals perorally (1 h before carrageenan or bentonite injections) in the form of suspension in a 1% carboxymethyl cellulose solution Each compound was tested in a group of 6 animals.

It was established that compounds II, III, V – XI, and XIII – XVI exhibit more or less pronounced antiinflammatory activity (Table 3). The most active compounds (III and VII) exceeded all the reference drugs (ibuprofen, sodium diclofenac, and indomethacin) in efficacy (therapeutic ratio), and ibuprofen – in the activity.

Analysis of the structure – activity relationship showed that piperazine-2,6-dione hydrochloride (I) and the 4-sulfonyl derivatives of piperazine-2,6-dione (II, IV – VI, VIII) are inactive. Introduction of a CH_3 radical in the *para* position to benzene ring (III) or replacement of the benzene ring by naphthalene (VII) markedly increased the activity. Opening of the piperazine-2,6-dione ring in the most active compounds III and VII (leading to the corresponding diamides XV and XVI) significantly decreased the activity. However, the 4-acyl derivatives of piperazine-2,6-dione (IX – XIV) have also a rather low activity.

TABLE 3. Antiinflammatory Activity Toxicity of 4-Acyl and 4-Sulfonyl Piperazine-2,6-dione Derivatives in Rats

Compound*	Average percentage decrease in edema volume (against control)							
	Carrageenan edema				Bentonite edema			
	1 h	2 h	3 h	5 h	1 h	2 h	3 h	5 h
II*	29.3 ± 3.7 $p < 0.05$	22.8 ± 0.9 $p < 0.05$	22.9 ± 1.6 $p < 0.01$	0	26.7 ± 2.0 $p < 0.01$	0	2.6 ± 0.8 $p < 0.05$	18.5 ± 1.3 $p < 0.01$
III	67.2 ± 4.2 $p < 0.01$	69.5 ± 5.3 $p < 0.01$	88.6 ± 7.0 $p < 0.01$	80.0 ± 6.9 $p < 0.01$	56.7 ± 4.3 $p < 0.01$	54.6 ± 4.9 $p < 0.01$	59.0 ± 5.1 $p < 0.01$	79.0 ± 6.8 $p < 0.01$
V	0	20.6 ± 1.6 $p \leq 0.05$	14.3 ± 2.3 $p < 0.05$	1.5 ± 0.1 $p < 0.04$	0	5.0 ± 0.3 $p < 0.05$	38.5 ± 3.2 $p < 0.05$	35.9 ± 2.8 $p < 0.05$
VI	0	30.6 ± 2.8 $p < 0.05$	8.6 ± 0.9 $p < 0.05$	0	20.0 ± 1.8 $p < 0.05$	27.3 ± 1.9 $p < 0.05$	28.3 ± 2.0 $p < 0.05$	29.0 ± 3.1 $p < 0.05$
VII	64.3 ± 5.2 $p < 0.01$	75.0 ± 6.3 $p < 0.01$	62.9 ± 5.3 $p < 0.05$	63.9 ± 5.4 $p < 0.01$	66.5 ± 5.9 $p < 0.01$	63.9 ± 5.8 $p < 0.01$	87.9 ± 7.6 $p < 0.01$	79.5 ± 7.0 $p < 0.01$
VIII	0	5.8 ± 0.2 $p < 0.05$	7.1 ± 0.8 $p < 0.05$	0	10.6 ± 0.9 $p < 0.05$	31.2 ± 2.8 $p < 0.01$	49.3 ± 3.6 $p < 0.05$	19.5 ± 2.1 $p < 0.05$
IX	18.5 ± 1.5 $p < 0.05$	0	2.8 ± 0.1 $p < 0.05$	41 ± 0.6 $p < 0.05$	40.0 ± 3.6 $p < 0.01$	42.6 ± 3.9 $p < 0.01$	29.4 ± 3.6 $p < 0.05$	23.1 ± 1.9 $p \leq 0.05$
X	0	0	0	0	23.5 ± 1.9 $p < 0.05$	14.4 ± 0.9 $p < 0.05$	29.6 ± 3.0 $p < 0.01$	10.6 ± 0.9 $p < 0.05$
XI	0	0	0	0	0	0	10.8 ± 0.9 $p \geq 0.05$	6.0 ± 0.2 $p \geq 0.05$
XIII	22.5 ± 1.9 $p < 0.01$	5.0 ± 0.2 $p < 0.05$	0	22.6 ± 1.8 $p < 0.05$	0	0	0	28.6 ± 3.2 $p < 0.05$
XIV	0	16.2 ± 1.5 $p < 0.05$	14.3 ± 1.2 $p < 0.05$	17.0 ± 1.2 $p < 0.01$	11.8 ± 0.9 $p < 0.01$	0	14.8 ± 1.3 $p < 0.05$	23.1 ± 1.6 $p < 0.01$
XV	5.8+0.6 $p < 0.05$	50.0 ± 4.7 $p < 0.01$	48.7 ± 5.2 $p < 0.01$	52.8 ± 4.6 $p < 0.01$	77.5 ± 6.9 $p < 0.01$	51.9 ± 6.2 $p < 0.01$	43.2 ± 3.9 $p < 0.01$	52.8 ± 4.6 $p < 0.05$
XVI	0	0	0	0	12.8 ± 0.6 $p \geq 0.05$	1.9 ± 0.1 $p \geq 0.05$	11.5 ± 0.6 $p > 0.05$	3.6 ± 0.1 $p > 0.05$
Ibuprofen (80 mg/kg)	28.4 ± 2.9 $p < 0.01$	30.6 ± 2.0 $p < 0.01$	31.2 ± 2.8 $p < 0.01$	32.9 ± 3.0 $p < 0.01$	21.6 ± 1.9 $p < 0.01$	24.3 ± 3.0 $p < 0.01$	23.6 ± 1.9 $p < 0.01$	24.0 ± 3.0 $p < 0.01$
Sodium diclofenac (25 mg/kg)	40.3 ± 3.9 $p < 0.01$	45.8 ± 3.2 $p < 0.01$	52.6 ± 4.9 $p < 0.01$	59.8 ± 4.9 $p < 0.01$	41.3 ± 3.9 $p < 0.01$	44.2 ± 3.9 $p < 0.01$	49.5 ± 3.6 $p < 0.05$	56.5 ± 4.8 $p < 0.01$
Indomethacin (5 mg/kg)	18.3 ± 1.30 $p < 0.05$	23.2 ± 1.9 $p < 0.01$	29.9 ± 3.0 $p < 0.01$	35.8 ± 3.0 $p < 0.05$	26.4 ± 1.9 $p < 0.01$	29.2 ± 2.0 $p < 0.01$	32.3 ± 3.0 $p < 0.05$	48.6 ± 4.0 $p < 0.01$

* Compounds I, IV, and XII exhibited no antiinflammatory activity.

Thus, the results of our experiments show that the class of piperazine-2,6-diones of the type studied may contain effective antiinflammatory agents.

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