

Synthesis and physicochemical investigation of some thiazepino[3,4-f] purine-2,4(3H, 10H)-dione derivatives

Veretenina A.A., Vasylyev D.A.

Department of Biological Chemistry, Zaporizhzhya State Medical University, Zaporizhzhya, Ukraine
Email: veretenina.a.a@zsmu.edu.ua

ABSTRACT

Ring systems are of great importance of bioorganic chemistry and consequently for the drug discovery procedures. Condensed moieties give molecules their basic form, determine their spatial conformation and keep substituents in their appropriate sites. In many biologically active structures, cyclic structures are directly involved in interactions with cell receptors, either through heteroatoms forming hydrogen bonds with appropriate protein residues or through hydrophobic interactions.

The chemistry of the xanthine derivatives, 1H-purine-2,6-dione has been a subject of constant attention due to their importance in biology and medicine. Hence, xanthine derivatives are possessing pharmaceutical implementation in a variety of substances acting on various phases of human metabolism.

KEY WORDS purine, thiazepine, synthesis.

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INTRODUCTION

The vital task of modern pharmacy is the development of new low-toxic and highly effective drugs for the prevention and treatment of various diseases. Amongst of 2,6-dioxopurine derivatives, many substances have been synthesized with hypotensive, diuretic, neuroleptic, anti-inflammatory, antiarrhythmic, hypolipidemic, antioxidant and other types of activity.

The preparation of derivatives of the newly synthesized system of thiazepino[3,4-f] purine-2,4 (3H, 10H)-dione is of undoubted interest in terms of the synthesis of potential biologically active compounds.

MATERIALS AND METHODS

The aim of the study is to develop preparative methods for the synthesis of previously undescribed [3-methyl-2,6-dioxo-7-(2-oxo-2-arylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]methylthioacetic acids (VI, VII) and derivatives of the previously undescribed heterocyclic system 1-methyl-7-aryl-(1H, 6H)-[1,4]thiazepino [3,4-f] purine-2,4(3H, 10H)-dione (VIII, IX).

The object of the study is 8-(hydroxymethyl)-3-methyl-3,7-dihydro-1H-purine-2,6-dione(I), on the basis of which 8-(hydroxymethyl)-3-methyl-7-(2-oxo-2-phenylethyl)-3,7-dihydro-1H-purine-2,6-dione(II) and 7-[2-(4-bromophenyl)-2-oxoethyl]-8-(hydroxymethyl)-3-methyl-3,7-dihydro-1H-purine-2,6-dione(III).

The reaction of the latter II, III with SOCl₂ yielded 8-(chloromethyl)-3-methyl-7-(2-oxo-2-phenylethyl)-3,7-dihydro-1H-purine-2,6-dione(IV) and 7-[2-(4-bromophenyl)-2-oxoethyl]-8-(chloromethyl)-3-methyl-3,7-dihydro-1H-purine-2,6-dione(V, Fig. 1). The interaction of IV, V with thioglycolic acid is realized by the formation of [3-methyl-2,6-dioxo-7-(2-oxo-2-arylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]methylthioacetic acids(VI, VII), the cyclization of which in acetic anhydride leads to the derivatives of 1-methyl-7-aryl-(1H, 6H)-[1,4]thiazepino[3,4-f]purine-2, 4(3H, 10H)-dione(VIII, IX, Fig. 1).

The structure of the synthesized compounds was established using elemental analysis and physicochemical methods: IR, NMR spectroscopy and mass spectrometry.

IR-spectra were recorded on a Bruker-ALPHA. NMR spectra were recorded on a Varian GEMINI-200 (operating frequency 200 MHz, solvent DMSO-d₆, internal standard TMS). Mass spectra were recorded on a Varian 1200L with direct sample injection into the ion source. The recording conditions were standard: accelerating voltage 3 kV, cathode emission current 1 mA, ionizing voltage 70 eV, elemental analysis was performed on an ELEMENTAR Vario EL cube.

8-(Hydroxymethyl)-3-methyl-3,7-dihydro-1H-purine-2,6-dione (I) was obtained by the method [8].

8-(Hydroxymethyl)-3-methyl-7-(2-oxo-2-phenylethyl)-3,7-dihydro-1H-purine-2,6-dione (II) and 7-[2-(4-bromophenyl)-2-oxoethyl]-8-(hydroxymethyl)-3-methyl-3,7-dihydro-1H-purine-2,6-dione (III) were obtained by the method [8].

8-(Chloromethyl)-3-methyl-7-(2-oxo-2-arylethyl)-3,7-dihydro-1H-purine-2,6--diones (IV, V, Table 1).

A mixture of 0.01 mol 8-(hydroxymethyl)-3-methyl-7-(2-oxo-2-phenylethyl)-3,7-dihydro-1H-purine-2,6-dione (II) or 7-[2-(4-bromophenyl)-2-oxoethyl]-8-(hydroxymethyl)-3-methyl-3,7-dihydro-1H-purine-2,6-dione (III) and 100 ml of SOCl₂ are heated in a silicone bath at a temperature 85-90° C for 6 hours. SOCl₂ is distilled off in a water-jet vacuum pump. The dry residue is washed with diethyl ether. For analysis IV, V are crystallized from dioxane. Elemental analysis data and % yields are shown in Table 1.

[3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]methylthioacetic acid (VI), 7-[2-(4-bromophenyl)-2-oxoethyl]-3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl]methylthioacetic acid (VII, Table 1).

A mixture of 0.01 mol IV or V for 1 hour is boiled in 20 ml of mercaptoacetic acid. Filtered hot. Cool. The filtrate is diluted with 100 ml of distilled water. The precipitate is filtered off. For analysis, VI and VII are crystallized from ethanol (Table 1).

1-Methyl-7-phenyl-(1H, 6H)-[1,4]thiazepino [3,4-f]purine-2,4 (3H, 10H)-dione (VIII), 7-(4-bromophenyl)-1-methyl-(1H, 6H)-[1,4]-thiazepino [3,4-f]purine-2,4 (3H, 10H)-dione (IX), Table 1.

A mixture of 0.01 mol VI or VII, 1.5 g of freshly melted sodium acetate and 20 ml of acetic anhydride is boiled for 2.5 hours. The cooled reaction mixture is poured into 200 ml of distilled water and stirred until complete hydrolysis of acetic anhydride. The precipitate is filtered off. For analysis, compounds VIII, IX are crystallized from aqueous DMF (2: 1). Elemental analysis data and % yield are shown in Table 1.

7,8-Disubstituted-3-methyl-3,7-dihydro-1H-purine-2,6-dione (IV-VII). Derivatives of 1-methyl-7-aryl-(1H, 6H)-[1,4]thiazepino [3,4-f]purine-2,4 (3H, 10H)-dione (VIII, IX).

Table 1.

№	X	Mp., °C	Found, %				Formula	Calcd, %				Yield, %
			C	H	N	S		C	H	N	S	
IV	H	255-257	54,10	3,93	16,82		C ₁₅ H ₁₃ ClN ₄ O ₃	54,14	3,94	16,84		97
V	Br	259-261	43,74	2,92	13,58		C ₁₅ H ₁₂ BrClN ₄ O ₃	43,77	2,94	13,61		98
VI	H	249-250	52,52	4,13	14,44	8,24	C ₁₇ H ₁₆ N ₄ O ₅ S	52,57	4,15	14,43	8,26	62
VII	Br	256-258	43,67	3,23	11,96	6,85	C ₁₇ H ₁₅ BrN ₄ O ₅ S	43,69	3,24	11,99	6,86	60
VII	H	275-277	58,85	4,30	17,15	9,80	C ₁₆ H ₁₄ N ₄ O ₂ S	58,88	4,32	17,17	9,82	65
IX	Br	289-290	47,39	3,21	13,81	7,90	C ₁₆ H ₁₃ BrN ₄ O ₂ S	47,42	3,23	13,82	7,91	64

RESULTS AND DISCUSSION

We studied the reaction [8] of the previously described 8-(hydroxymethyl)-3-methyl-7-(2-oxo-2-arylethyl)-3,7-dihydro-1H-purine-2,6-diones (II, III) with an excess of thionyl chloride, which led to the production of 8-(chloromethyl)-3-methyl-7-(2-oxophenylethyl)-3,7-dihydro-1H-purine-2,6-dione (IV, Fig. 1) and 7-[2-(4-bromophenyl)-2-oxoethyl]-8-(chloromethyl)-3-methyl-3,7-dihydro-1H-purine-2,6-dione (V, Fig. 1).

We found that the interaction of compounds IV, V with mercaptoacetic acid leads to the production of [3-methyl-2,6-dioxo-7-(2-oxo-2-arylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]methylthioacetic acids (VI, VII, Fig. 1). Heating the latter in acetic anhydride in the presence of anhydrous CH₃COONa is yielded by the formation of previously undescribed derivatives 1-methyl-7-aryl-(1H, 6H)-[1,4]thiazepino[3,4-f]purine-2,4 (3H, 10H)-dione (VIII, IX, Fig. 1).

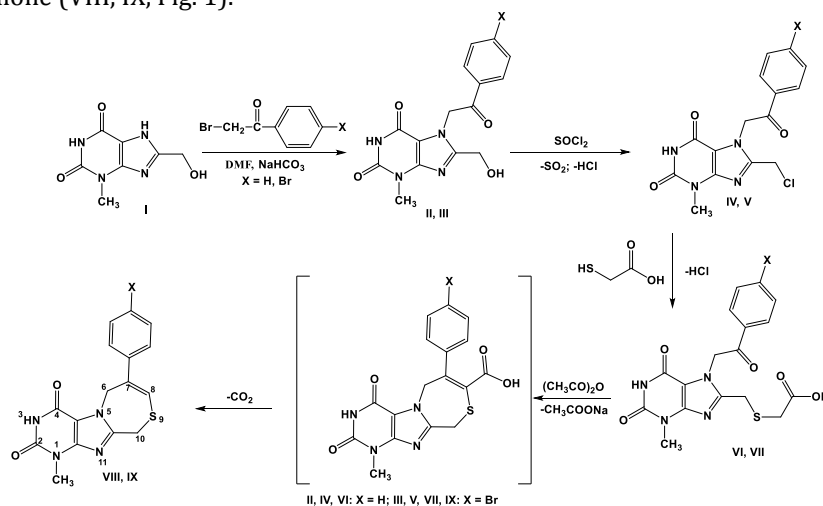


Fig1. Scheme of synthesis of 3-methyl-2,6-dioxo-7-(2-oxo-2-arylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl]methylthioacetic acids

The heterocyclization reaction of compounds VI, VII into thiazepino-[3,4-f] purine-2,4 (3H, 10H)-dione derivatives (VIII, IX) can be considered as a three-stage reaction.

At the first stage, the nucleophilic substitution of the chlorine atom in position 8 (-CH₂Cl) of compounds IV and V with the residue of thioglycolic acid occurs with the formation of compounds VI, VII (Fig. 1).

The second stage is characterized by intramolecular cyclization of VI, VII into the intermediate 1-methyl-2,4-dioxo-7-aryl-2,3,4,10-tetrahydro-(1H, 6H)-[1,4]-thiazepino[3,4-f]purine-8-carboxylic acids. The third stage consists in decarboxylation of the above acids to yield the final products (VIII, IX, Fig. 1).

To explain the mechanism of cyclization of compounds VI, VII to derivatives of thiazepino[3,4-f]purine-2,4 (3H, 10H) -dione (VIII, IX), we performed a quantum chemical calculation of the Hückel charges of compound VI (Table 2).

Table 2.

Quantum-chemical calculation of the charges of [3-methyl-2,6-dioxo-7-(2-oxo-2-phenylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl] methyl)-thioacetic acid (VI).

Atom	Type	Charge	Atom	Type	Charge
N(1)	N Pyrrole	0.466125	C(23)	C Alkene	-0.0116197
C(2)	C Alkene	0.17683	C(24)	C Alkene	-0.133701
N(3)	N Imine	-0.571258	C(25)	C Carbonyl	0.608327
C(4)	C Alkene	0.15911	O(26)	O Carbonyl	-0.652522
N(5)	N Amide	0.413418	O(27)	O Carboxyl	-0.184456
C(6)	C Carbonyl	0.403022	H(28)	H Amide	0.0996286
O(7)	O Carbonyl	-0.889916	H(29)	H	0.0350845
N(8)	N Amide	0.313372	H(30)	H	0.0383767
C(9)	C Carbonyl	0.33604	H(31)	H	0.0380774
O(10)	O Carbonyl	-0.84051	H(32)	H	0.0212906
C(11)	C Alkene	-0.164925	H(33)	H	0.0329111
C(12)	C Alkene	-0.0540192	H(34)	H	0.0645333
C(13)	C Alkene	-0.10489	H(35)	H	0.043476
S(14)	S Thioether	0.138563	H(36)	H	0.02272
C(15)	C Alkene	-0.0348479	H(37)	H	0.0253183
C(16)	C Carbonyl	0.470463	H(38)	H	0.0249934
O(17)	O Carbonyl	-0.551402	H(39)	H	0.0250815
C(18)	C Alkene	0.00764578	H(40)	H	0.0269119
C(19)	C Alkene	-0.00620471	H(41)	H	0.0396023
C(20)	C Alkene	-0.0296107	H(42)	H	0.0272995
C(21)	C Alkene	-0.0104968	H(43)	H Carboxyl	0.211427
C(22)	C Alkene	-0.0292708			

Compound VI at position 7 contains a benzoylmethyl substituent in which there is a reactive carbonyl group.

There is a deficit of electrons on carbonyl carbon (+0.470463), and on oxygen (-0.551402), which indicates that carbon can undergo nucleophilic and oxygen electrophilic attacks.

In position 8 of compound VI there is a methylthioacetic acid residue (-CH₂-S-CH₂-COOH), in which there is a CH-acid center arising due to the acceptor effect of the sulfur atom (+0.138563), and on the other side of the carboxyl group (Fig. 1). Based on the data of calculation (VI), it can be assumed that first there is an electrophilic attack on the nucleophilic center of the carbonyl group with the formation of an intermediate conjugate acid, which, with the cleavage of the π -bond, passes into the corresponding carbocation, and therefore a whole positive charge arises on the carbon.

Subsequently, a nucleophilic attack of the electrophilic center proceeds with the elimination of water and simultaneous cyclization into an intermediate product, which is decarboxylated to form compound VII.

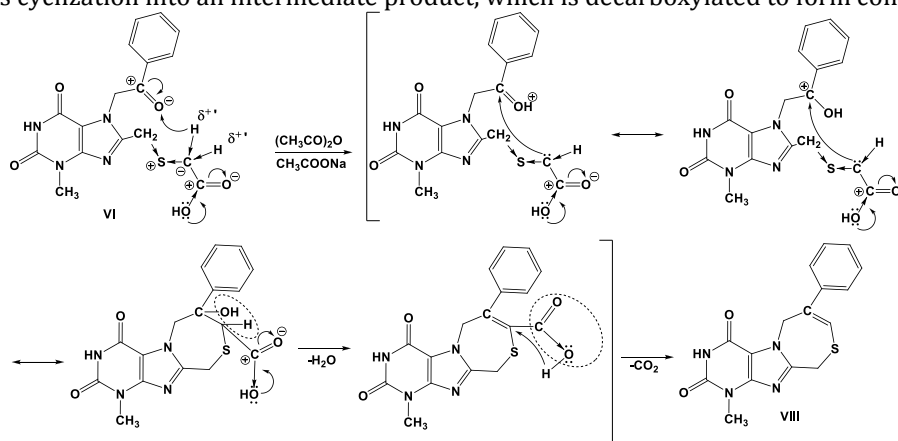


Fig.2 Scheme of the supposed mechanism of cyclization of compound (VI) to the thiazepino derivative [3,4-f] purine-2,4 (3H,10H)-dione (VII).

The NMR spectrum of 8-(chloromethyl)-3-methyl-7-(2-oxo-2-phenylethyl)-3,7-dihydro-1H-purine-2,6-dione (IV) shows the following signals: (s, N₁-H) - 11,15 ppm; (s, N₃-CH₃) - 3,43 ppm; (s, N₇-CH₃) - 5,97 ppm; (d, C₈-CH₂) - 4,89 ppm; (m, Ar) - 7,56-8,09 ppm.

In the NMR spectrum of 7-[2-(4-bromophenyl)-2-oxoethyl]-8-chloromethyl-3-methyl-3,7-dihydro-1H-purine-2,6-dione (V) the following signals are recorded: the singlet of the protons of the methylene group C₈-CH₂-Cl at 4.94 ppm, the singlet of the protons of the methylene group in the third position (N₃-CH₃) at 3.40 ppm, the singlet of the protons of the methylene group of the substituent at position seven imidazole fragment - N₇-CH₂-C(O)-Ar at 5.96 ppm, multiplet of protons of the aromatic ring at 7.53-8.08 ppm, singlet of the proton of the uracil fragment (N₁-H) is recorded at 11.21 ppm.

Analysis of the NMR spectra of compounds IV, V indicates that the arrangement of the proton signals fully correspond to the proposed structures.

In the mass spectrum of 8-(chloromethyl)-3-methyl-7-(2-oxo-2-phenylethyl)-3,7-dihydro-1H-purine-2,6-dione (IV), a peak M⁺ with m/z 332:334, which corresponds to the gross composition C₁₅H₁₃ClN₄O₃. The presence of a phenyl radical is confirmed by the registration of an ion with m/z 255 - [M-C₆H₅]⁺. The presence of a substituent at the N₇ atom is fixed by ions with m/z 215: 217 - [M-C₆H₅O]⁺, m/z 214:216 - [M-C₆H₆O]⁺. Ions with m/z 286 - [M-CHCl]⁺, m/z 286, m/z 166 confirm the presence of a chloromethyl group at position 8 of purindione-2.6.

The structure of the uracil fragment is confirmed by fragment ions with m/z - 304:306, m/z 138, m/z 123, m/z 109, m/z 95, m/z 68. The scheme of mass decay of compound IV is shown in the scheme (Fig. 3).

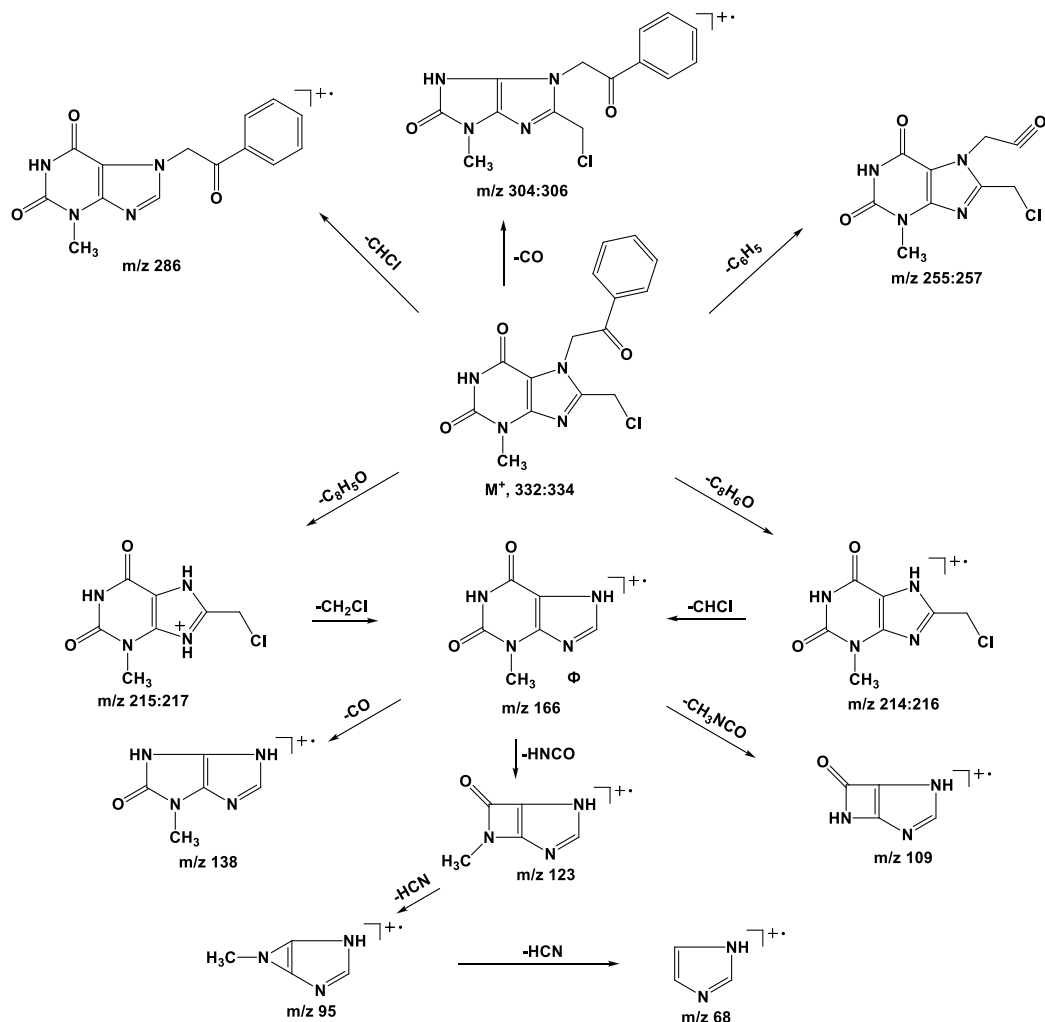


Fig. 3. Scheme of degradation of 8-(chloromethyl)-3-methyl-7-(2-oxophenylethyl)-3,7-dihydro-1H-purine-2,6-dione (VI) under of electron impact

In the NMR spectrum of compound VI, the following signals are recorded: singlet of protons of the methylene group (-S-CH₂COOH) at 3.31 ppm, singlet of protons (N₃-CH₃) at 3.35 ppm, singlet of protons (C₈-CH₂-S) - 3.98 ppm, the proton signal (N₇-CH₂(CO)Ar) - 5.94 ppm, the proton signals of the benzene ring in the form of a multiplet - 7.55-8.05 ppm. and the signal of the proton of the uracil fragment (N₁-H) - 11.08 ppm. The signal of the (-COOH) - group is broadened due to exchange with water molecules present in the solvent.

The following signals are recorded in the NMR spectrum of VII: singlet of protons of the methylene group (-S-CH₂-COOH) - 3.33 ppm, singlet of protons (N₃-CH₃) - 3.39 ppm, singlet of protons (C₈-CH₂-S) - 3.96 ppm, proton signal (N₇-CH₂(CO)Ar) - 5.98 ppm, benzene ring proton signals in the form of multiplet - 7.52-8.00 m. d., proton signal (N₁H) - 11.12 ppm.

In the NMR spectrum of 1-methyl-7-phenyl-(1H,6H)-[1,4]thiazepino[3,4-f]purine-2,4(3H, 10H)-dione (VIII), the following signals are recorded: (s, N₃-CH₃) - 3.10 ppm, singlets of protons of methylene groups in positions 6 and 10 of the thiazepine fragment at 5.62 ppm. and 4.51 ppm. respectively, the singlet of the proton [-S-CH=C(-C₆)Ar] at 6.23 ppm, the signals of the protons of the benzene ring appear as a multiplet - 7.22-7.55 ppm, and is also recorded the proton signal of the uracil moiety (N₁H) at 11.10 ppm.

In the NMR spectrum of 7-(4-bromophenyl)-1-methyl-(1H, 6H)-[1,4]thiazepino(3,4-f)purine-2,4(3H, 10H)dione (IX) the following signals: (s, N₁-CH₃) - 3.37 ppm, singlets of C₆ and C₁₀ protons at 5.60 ppm and 4.49 ppm. respectively, the singlet of the proton [-S-CH=C(C₆)Ar] is 6.21 ppm, the multiplet of the protons of the benzene ring is 7.20-7.59 ppm, the singlet of the proton of the uracil fragment (N₁-H) at 11.10 ppm.

CONCLUSION

1. The synthesis of 8-(chloromethyl)-3-methyl-7-(2-oxo-2-phenylethyl)-3,7-dihydro-1H-purine-2,6-diones has been carried out.
2. Developed a method for the synthesis of [3-methyl-2,6-dioxo-7-(2-oxo-2-arylethyl)-2,3,6,7-tetrahydro-1H-purin-8-yl] methylthioacetic acids.
3. A method was developed for the synthesis of derivatives of 1-methyl-7-aryl-(1H, 6H)-[1,4]thiazepino[3,4-f]-purine-2,4(3H, 10H)-dione.
4. The structure of the synthesized compounds was confirmed by the data of IR-, NMR-spectroscopy and mass spectrometry.

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