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Research Article

Synthesis and anticonvulsant activity of 6-methyl-2-((2-oxo-2-arylethyl)thio) pyrimidin-4(3*H*)-one derivatives and products of their cyclization

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Abstract

The alkylation of 6-methyl-2-thioxo-2,3-dihydro-1*H*-pyrimidine-4-one phenacyl bromides under different conditions was investigated. It was found that during the reaction in the medium of DMF/K_2CO_3 a mixture of 2-(2-aryl-2-oxoethyl)thio-6-methyl-pyrimidine-4(3*H*)-one and 3-hydroxy-3-aryl-7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-a]pyrimidine-5-one was formed. The holding of the resulting mixture in the concentrated sulphuric acid leads to the formation of cyclization products - derivatives of 3-aryl-7-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one with high yields. Individual S-alkylated derivatives – 2-(2-aryl-2-oxoethyl)thio-6-methyl-pyrimidine-4(3*H*)-one - were obtained by reacting in methanol in the presence of sodium methoxide. Pharmacological screening of synthesized compounds for anticonvulsant activity on the model of pentylenetetrazole seizures in rats was carried out and some regularity "structure-activity" was established.

Keywords

synthesis, pyrimidine, thiazolopyrimidine, anticonvulsant activity

Introduction

Derivatives of 2-thiouracil are the subject of close attention of scientists from different countries, which is associated with a significant and varied spectrum of their biological activity. Its derivatives are known as antiviral (Ogilvie et al. 1984; Zenker 1990), antibacterial and anti-cancer agents (Prachayasittikul et al. 2011). Propylthiouracil is a known anti-thyroid agent (Azizi and Malboosbaf 2017). Derivatives of 2-thiopyrimidine-4-one are used in Alzheimer's disease (Zhi et al. 2013) and Parkinson's (Kumar et al. 2018) for the treatment of neurological diseases, migraines, depression and as tranquilizers (Wichmann et al. 1999; Abdallaa et al. 2012).

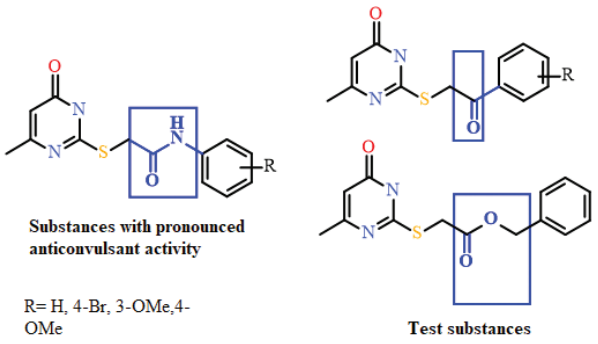


Figure 1. Pharmacophore fragments that may affect anticonvulsant activity.

The study of the influence of thiopyrimidines on the activity of the central nervous system continues to be one of the priority directions of research of this class of compounds, among which also has an anticonvulsant effect. The search for modern anticonvulsants, with fundamentally new mechanisms of action, remains an issue of the present day, since chronic and, especially, refractory forms of epilepsy are subjected to pharmacological correction with existing antiepileptic drugs (Beleza 2009).

Relying on its own positive experience with the search for anticonvulsants with a significant safety profile (Saidov et al. 2014; Severina et al. 2019) and the scientific findings of other researchers (Matias et al. 2017), it is likely that the presence of an exocyclic atom has a positive effect on the anticonvulsant activity of sulphur in the pyrimidine molecule. In previous studies (Severina et al. 2019), we have synthesized acetamide derivatives of 6-methyl-2-thiopyrimidine-4 (3*H*)-one (Fig. 1) with significant anticonvulsant activity on the pentylenetetrazole model of the seizures and on the model of maximum electric shock, as well a certain "structure-anticonvulsant activity" was detected.

In this study, we aimed to synthesize derivatives of 6-methyl-2-[(2-oxo-2-arylethyl)thio]pyrimidin-4(3*H*)–one and [(4-methyl-6-oxo-1H-pyrimidine-2-yl)thio] methylphenyl acetate, which are structural analogues of the previously studied acetamides (Fig. 1), and to investigate their anticonvulsant effect on pen tylenetrazole seizures in rats, which will allow to draw some conclusions about the effect of the modification of the amide fragment on the manifestation of activity.

Chemistry

All solvents and reagents were obtained from commercial sources. The reactions were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates, ethyl acetate-hexane solvent system (1: 1), iodine vapor as developer. The melting point (°C) was determined in a capillary using the electrothermal digital apparatus IA9100X1 (Bibby Scientific Limited, Staffordshire, UK). ^{1}H NMR spectra were recorded on a Varian Mercury-400 (Varian Inc., Palo Alto, CA, USA) spectrometer (400 MHz) in dimethyl sulfoxide (DMSO-d6) using tetramethylsilane (TMS) as an internal standard (chemical shifts in ppm). Elemental analysis were performed on a micro-analyzer Euro Vector EA-3000 (Eurovector SPA, Redavalle, Italy). Elemental analyzes were within ± 0.4% of theoretical values LC / MS was recorded using the RE SCIEX API 150EX chromatograph.

6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one(1) obtained by the method described in the literature (Barmaki et al. 2013).

General procedure for the synthesis of 2-(2-aryl-2-oxoethyl)thio-6-methylpyrimidin-4(3H)-one derivatives **(3.1–3.7)**. 2 mmol of 2-thiouracil **1** was dissolved in 6 ml of anhydrous methanol and sodium methoxide (118 mg, 2.2 mmol) was added followed by 2.2 mmol of the corresponding phenacyl bromide **2**. The mixture was stirred for 1 hour and 10 ml of water was added. The precipitate was filtered off, dried and recrystallized from a mixture of acetone and DMF.

6-Methyl-2-[(2-oxo-2-phenylethyl)thio]pyrimidin-4(3H)-one **(3.1)**.

Yield – 82%, m.p. = 182–4 °C. ^{1}HNMR (400 MHz, DMSO-d_6):12.55 (br. s, 1H, NH-3), 8.08 (d, *J* 7.5Hz, 2H, H-2',6'), 7.69 (t, *J* 7.2 Hz, 2H, H-3',5'), 7.53 (t, *J* 7.5 Hz, 1H, H-4'), 5.96 (s, 1H, CH-5), 4.74 (s, 2H, SCH_2), 1.95 (s, 3H, CH_3). Found, m/z: 261,2 [M+H]+. Anal. Calcd for $C_{13}H_{12}N_2O_2S$:C 59.98, H 4.65, N 10.76, S 12.32. Found: C 56.75, H 4.63, N 10.76,S 12. 27.

2-([2-(4-Bromophenyl)-2-oxoethyl]thio)-6-methylpyrimidin-4(3H)-one **(3.2)** *[19].*

Yield – 75%, m.p. = 160–2 °C.^{1}HNMR (400 MHz, DMSO-d_6): 12.52 (br. s, 1H, NH-3), 7.98 (d, *J*8.4 Hz, 2H, H-2',6'), 7.79 (d, *J* 8.4 Hz, 2H, H-3',5'), 5.96 (s, 1H, CH-5), 4.71 (s, 2H, SCH_2), 1.95 (s, 3H, CH_3). Found, m/z: 339,90 [M+H]+. Anal. Calcd for $C_{13}H_{11}BrN_2O_2S$: C 46.03, H 3.27, N 8.26,S 9.45.Found: C 45.84, H 3.25, N 8.23,S9.41.

2-([2-(3-Methoxyphenyl)-2-oxoethyl]thio)-6-methylpyrimidin-4(3H)-one **(3.3)**.

Yield – 78%, m.p. = 173–5 °C.^{1}HNMR (400 MHz, DMSO-d_6): 12.52 (br. s, 1H, NH-3), 7.61 (d, *J* 7.5 Hz, 1H, H-6'), 7.52 (s, 1H, H-2'), 7.41 (t, *J* 8.2 Hz, 1H, H-5'), 7.18 (d, *J* 7.5 Hz, 1H, H-4'), 5.97 (s, 1H, CH-5), 4.72 (s, 2H, SCH_2), 3.85 (s, 3H, OCH_3), 2.00 (s, 3H, CH_3). Found, m/z: 291,07 [M+H]+.Anal. Calcd for$C_{14}H_{14}N_2O_3S$:C57.92, H 4.86,N 9.65, S 11.04. Found: C 57.82, H 4.84, N 9.62, S 11.00.

2-([2-(4-Methoxyphenyl)-2-oxoethyl]thio)-6-methylpyrimidin-4(3H)-one **(3.4)**.

Yield – 78%,m.p. = 173–5 °C. ^{1}HNMR (400 MHz, DMSO-d_6): 12.52 (br. s, 1H, NH-3), 8.03 (d, *J* 9 Hz, 2H, H-2',6'), 7.06 (d, *J* 9 Hz, 2H, H-3',5'), 5.95 (s, 1H, CH-5), 4.70 (s, 2H, SCH_2), 3.86 (s, 3H, OCH_3), 1,99 (s, 3H, CH_3). Found, m/z: 291,07 [M+H]+.Anal. Calcd for$C_{14}H_{14}N_2O_3S$: C 57.92, H 4.86, N 9.65,S 11.04. Found: C 57.84, H 4.84, N 9.67,S 11.01.

2-([2-(4-Fluorophenyl)-2-oxoethyl]thio)-6-methylpyrimidin-4(3H)-one **(3.5)**.

Yield – 78%, m.p. = 173–5 °C. ^{1}HNMR (400 MHz, DMSO-d_6): 12.52 (br. s, 1H, NH-3), 8.03 (d, *J* 9 Hz, 2H, H-2',6'), 7.06 (d,*J* 9 Hz, 2H, H-3',5'), 5.95 (s, 1H, CH-5), 4.70 (s, 2H, SCH_2), 1.99 (c, 3H, CH_3). Found, m/z:279,02

[M+H]+.Anal. Calcd for$C_{13}H_{11}FN_2O_2S$: C 56.10, H 3.98, N 10.07, S 11.52. Found: C 56.01, H 3.96, N9.70,S 11.50.

2-([2-(4-Nitrophenyl)-2-oxoethyl]thio)-6-methylpyrimidin-4(3H)-one **(3.6)**.

Yield – 74%, m.p. = 197–9 °C. ^{1}HNMR (400 MHz, DMSO-d_6): 12.50 (br. s, 1H, NH-3), 8.12–8.08 (m, 2H, H-2',6'), 7.23–7.18 (m, 2H, H-3',5'), 5.84 (s, 1H, CH-5), 4.60 (s, 2H, SCH_2), 2.04 (s, 3H, CH_3). Found, m/z:306,05 [M+H]+.Anal. Calcd for$C_{13}H_{11}N_3O_4S$: C 51.14, H 3.63, N 13.76, S 10.50. Found: C51.00, H 3.62, N 13.78, S 10.48.

Benzyl [(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl) thio]acetate **(3.7)**.

Yield – 75%, m.p. = 175–5 °C. ^{1}HNMR (400 MHz, DMSO-d_6): 12.55 (br. s, 1H, NH-3), 7.42–7.22 (m, 5H, Ph), 5.96 (s, 1H, CH-5), 5.18 (s, 2H, SCH_2), 4.01 (2H, c, OCH_2), 2.05 (s, 3H, CH_3). Found, m/z:291,2[M+H]+.Anal. Calcd for$C_{14}H_{14}N_2O_3S$: C57.92, H 4.86,N 9.65, S 11.04. Found: C 57,87; H 4.84, N 9.69, S 11.02.

General procedure for the synthesis of 7-methyl-3-aryl-5H-thiazolo[3,2-a]pyrimidin-5-one derivatives **(5.1–5.4)**. A mixture of 7.34 mmol of 2-thiouracil **1** and 10.85 mmol of potassium carbonate in 10 mL of DMF was stirred at 70–80 °C. for 1 hour, the reaction mixture was cooled to room temperature, a solution of 7.34 mmol of the corresponding phenacyl bromide **2** in 10 mL of DMF was added, stirred for 3 hours (TLC). After cooling to room temperature, the reaction mixture was filtered and the filtrate was evaporated in vacuum; the residue was treated with 100 ml of cold water. The formed precipitate was filtered off, dried in air (mixture of products **3** and **4**). Then to the precipitate was added 10 ml of sulphuric acid was left to stand for 24 hours at room temperature. The mixture was poured into cold water and neutralized with aqueous sodium hydroxide solution. The formed precipitate was filtered off, washed with water and dried.

3-Phenyl-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one **(5.1)**.

Yield – 90%, m.p. = 126–8 °C. ^{1}HNMR (400 MHz, DMSO-d_6): 8.08 (d, *J* 7.5, 2H, H-2',6'), 7.69–7.60 (m, 3H, H-2, H-3',5'), 7,53 (t, *J* 7.5, 1H, H-4'), 6.07 (s, 1H, H-6), 2.20 (s, 3H, CH_3). Found, m/z:243,2 [M+H]+.Anal. Calcd for$C_{13}H_{10}N_2OS$: C64.44, H 4.16, N 11.56, S 13.23. Found: 64.20. H 4.14, N 11.59, S 13.18.

3-(4-Bromophenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one **(5.2)**[19].

Yield – 93%, m.p. = 110–11 °C.^{1} HNMR (400 MHz, DMSO-d_6): 7.75 (d, *J*8 Hz, 2H, H-2',6'), 7.69 (s, 1H, H-2), 7.65 (d, *J* 8 Hz, 2H, H-3',5'), 6.06 (s, 1H, H-6), 2.28 (s, 3H, CH_3).Anal. Calcdfor$C_{13}H_9BrN_2OS$: C 48.61, H 2.82, N 8.72, S 9.98.Found: C 48.48, H 2.80, N 8.74, S9.95.

3-(3-Methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one **(5.3)**.

Yield – 92%, m.p. = 114–6 °C. ^{1}HNMR (400 MHz, DMSO-d_6): 7.71 (d, *J* 7.5 Hz, 1H, H-6'), 7.69 (s, 1H, H-2), 7.50 (s, 1H, H-2'), 7,41 (t, *J* 8.2 Hz, 1H, H-5'), 7.18 (d, *J* 7.5, 1H, H-4'), 6.10 (s, 1H, H-6), 3.85 (s, 3H, OCH_3), 1.99 (s, 3H, CH_3). Anal. Calcdfor $C_{14}H_{12}N_2O_2S$: C 61.75, H 4.44, N 10.29, S11.77. Found: C61.50, H4.42, N10.31, S11.73.

3-(4-Methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one **(5.4)**.

Yield – 93%, m.p. = 118–20 °C. ^{1}HNMR (400 MHz, DMSO-d_6): 8.03 (d, *J* 9 Hz, 2H, H-2',6'), 7.69 (s, 1H, H-2), 7.06 (d, *J* 9 Hz, 2H, H-3',5'), 6.11 (s, 1H, H-6), 3.85 (s, 3H, OCH_3), 2.00 (s, 3H, CH_3). Anal. Calcdfor$C_{14}H_{12}N_2O_2S$: C 61.75, H 4.44,N 10.29,S 11.77. Found:C 61.54, H 4.43, N 10.33, S 11.76.

Anticonvulsant activity

The studies were performed on 65 white non-linear male rats weighing 130–150 g. Animals were bred in a vivarium at the Vinnitsa National Medical University, which is named after M.I. Pirogov. During the study, the animals were under standard vivarium conditions with free access to water and food and 12 hours of light (8:00 to 20:00). All experiments were carried out in accordance with the "Directive 2010/63 / EC of the European Parliament and of the Council of Europe on September 22, 2010 on the protection of animals used for scientific purposes", with the procedures and requirements of the State Expert Centre of the Ministry of Health of Ukraine and the rules of the European Convention on the protection of vertebrate animals used for experimental and other scientific purposes (Strasbourg, 1986), the Decree of the First National Congress on Bioethics (Kyiv, 2001), the National Congress of Ukraine on Bioethics (Kyiv, 2001) and Law of Ukraine No. 3447-IV "On protection of animals from cruel treatment" of 21.02.2006.

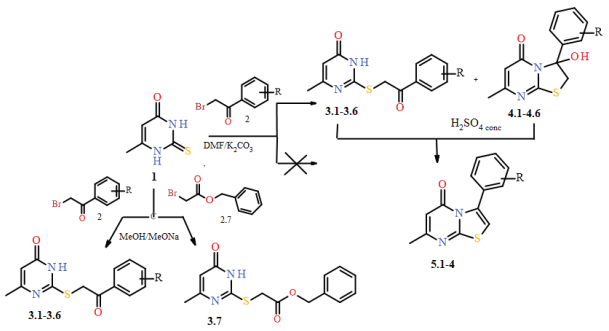
Animals were randomly assigned to experimental and control groups. The test substances were dissolved in 1% starch gel and injected with an oral cannula through a probe (volume 0.5 ml / 100 g body weight of rats). The screening dose for testing the compounds was 80 mg / kg. The reference compounds, phenobarbital and lamotrigine, were administered in the same way at their mean anticonvulsant doses of 20 mg / kg body weight, respectively (Metcalf et al. 2017). The determination of the experiment time was based on data relating to the peak of the anticonvulsant activity of the drug described in the literature (Fisher 1989). The control group received an equivalent amount of solvent. The attacks caused by pentylentetrazol between 9:00 and 11:00, in order to minimize the possible inconsistencies that arise as result of circadian rhythms (Loscher and Fiedler 1996).

The convulsive state in animals was modelled by single-dose subcutaneous administration of pentylenetetrazole (Sigma, USA) at a dose of 80 mg / kg. The manifestation of anticonvulsant activity was estimated by the dynamics of the latent period (from the introduction of the pentylenetetrazole to the start of the convulsions), the nature and duration of the trial in minutes, and the indicator of lethality. The intensity of convulsive attack was estimated using a 5-point scale, based on the following criteria (including the number of dead animals) (Gerald and Riffee 1973): 0 – no convulsive activity; 1 – hyperkinesia;

2 – trembling, twitching; 3 – clonic seizures of the forelegs with lifting on the hind legs; 4 – pronounced tonic-clonic seizures, falling of the animal to the side, an existing phase of tonic extension; 5 – repeated clonic-tonic seizures, loss of posture, death. Anti-convulsant effects were considered to protect animals from the development of clonic and tonic seizures, as well as lethality.

Results and discussion

Synthesis of the starting 6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one **1** was carried out according to the known method (Barmaki et al. 2013) by condensation of ethyl acetoacetate with thiourea in methanol. The next modification was carried out in several directions. Target phenacyl derivatives **3.1–3.6** were prepared by alkylation of 6-methyl-2-thiouracil **1** with substituted phenacyl bromides **2**. We attempted to carry out alkylation in a medium of DMF in the presence of an excess of potassium carbonate at a temperature of 70–80 °C, that is, under the usual conditions used for S -alkylation of thiopyrimidines (Kigundi et al. 2007; Ozerov et al. 2010; Severina et al. 2019). Since the sulphur atom of the starting thiouracil **1** is the most nucleophilic, the alkylation product should be 2-(2-aryl-2-oxoethyl)thio-6-methyl-pyrimidin-4(3*H*)-one **3** (see below). But according to the analysis of the ^{1}H NMR spectra, we received not individual substances, but a mixture of



products.

In the literature (Danelet al. 1998; Fadda et al. 2013; Abdel Moty et al. 2016) there is evidence that the reaction formed product **3** may be subject to intramolecular cyclization with the nitrogen N^1 and N^3 atoms, and it is difficult to stop the reaction at the stage of the formation of S-derivatives. This is precisely what happened in our attempt to get compound **3**. A similar result was obtained during the synthesis without heating: data of ^{1}H NMR spectra showed the formation of two reaction products in a ratio of 4:1. Danel et al. (1998) found that the N^3 atom is more reactive than N^1 due to the influence of the neighbouring carbonyl group, therefore we assumed that the reaction products are compounds of type **3** and **5**. In addition, a group of authors (Fadda et al. 2013) argues that boiling under the above conditions, 6-methyl-thiouracy **1** with phenacyl bromide **2** precisely results in the formation of 7-methyl-3-phenyl-5H-thiazolo[3,2-a] pyrimidine **5.1.** However, by analyzing the ^{1}H NMR spectra, the expected singlet signal of the proton at position 2 of the thiazole ring of compound **5.1** in the region characteristic of aromatic protons was not found. Instead, two single-protons doublets were recorded on the site 3.44–3.63 ppm. This indicates the probable occurrence of intramolecular cyclization with the formation of 3-hydroxy-3-aryl-7-methyl-2,3-dihydro-5*H*-thiazolo[3,2-a]pyrimidine-5-one 4 because their cyclic protons of the SCH_2 group are non-equivalents, whereas in the compound **3**, the protons are equivalent and form a two-proton singlet in the range of 4.6–4.7 ppm. Also, there is a singlet of the proton hydroxyl group at 3.08 ppm, which is typical for the OH group in the conditions of spectrum registration in DMSO-d6.

It should be noted that the above-mentioned heterocyclic reaction was previously studied by scientists in the example of 2-[2-(4-bromophenyl)-2-oxoethyl] thio-pyrimidine-4(3*H*)-ones (Frolova et al. 2016) and the possibility of product formation type **4** only in the presence of an electron-withdrawing CF_3 group at position 6 of the pyrimidine ring. In our study, products **4.1–4.6** were formed in the presence of 6 methyl radicals. Although there was a certain pattern of increasing the formation of cyclic form **4** in the presence of electron-acceptor substituents in the aryl radical: in the case of 4-nitrophenyl-**3.5/4.5** and 4-fluorophenyl derivatives **3.6/4.6**, the ratio of linear form to cyclic and singlets in ^{1}H NMR spectra was 1: 10 and 1.5: 10, respectively.

We did not see the need to divide the resulting mixture **3/4**, instead we were interested in the possible effect of the condensed thiazole ring on anticonvulsant activity, as there are indications about the promising nature of thiazolopyrimidine derivatives as metabotropic glutamate receptor antagonists (Wichmann et al. 1999). Therefore, we treated the resulting mixture of compounds **3/4.1–4** with concentrated sulphuricacid, which led to the formation of derivatives of 3-aryl-7-methyl-5*H*-thiazolo[3,2-a]pyrimidin-5-one **5.1–5.4** with high yields (Tab. 1). The successful completion of complete cyclization and dehydration is evidenced by the appearance on ^{1}H NMR spectra of compounds **5.1–5.4** of the singlet signal of the proton in the 2 position of the thiazole ring at 7.56 ppm, the disappearance of two doublets at 3.44–3.63 ppm and a singlet of OH group at 3.08 ppm. The individuality and purity of compounds **5.1–5.4** was proved by chromatographic mass spectrometry.

To obtain the targeted 2-[2-aryl-2-oxoethyl]thio-pyrimidine-4(3*H*)-ones, **3.1–3.6**, we tried to change the alkylation conditions using methanol as a solvent and sodium methoxide as a catalyst without heating the reaction mixture. The reaction time was determined by thin-layer chromatography and was 1 hour. Under these conditions, we were able to obtain S - derivatives **3.1** in individual form with satisfactory yields and with sufficient purity, which is confirmed by the data of chromagraphic mass spectrometry.

Nine synthesized compounds from the groups of phenacyl derivatives and their cyclization products containing phenyl **3.1, 5.1**, 4-bromophenyl **3.2, 5.2**, 3-methoxy**3.3**, **5.3** and 4-methoxy-phenylene **3.4, 5.4**, and benzyl acetate fragment **3.7** were considered on the anticonvulsant activity on the

Table 1. Influence of synthesized compounds **3.1–3.4, 3.7** and **5.1–5.4** on seizures induced by the administration of pentylenetrazole in rats.

Group of animals	Number of rats	Dose, mg/kg	Duration of latent period, min	Duration of seizures, min	Lethality abs. units	Intensity of seizures, (points)
Control	10	80	4.7 ± 0.30	9.70 ± 0.90	10 (100%)	4.96
3.1	5	80	12.0 ± 1.8*	12.4 ± 0.7	2 (40%)	3.0
3.2	5	80	15.2 ± 1.2*	11.6 ± 3.1	2 (40%)	3.0
3.3	5	80	6.2 ± 1.8*	8.2 ± 1.2	2 (40%)	2.6
3.4	5	80	5.80 ± 1.0	17.8 ± 3.4*	3 (60%)	2.8
3.7	5	80	12.0 ± 1.6*	15.4 ± 3.0	2 (40%)	3.4
5.1	5	80	8.6 ± 0.5*	15.0 ± 3.7*	4 (80%)	3.6
5.2	5	80	5.6 ± 0.4*	8.4 ± 1.2	5 (100%)	4.6
5.3	5	80	9.0 ± 1.5*	18.6 ± 3.7*	5 (100%)	4.6
5.4	5	80	8.8 ± 1.1*	12.6 ± 2.9	4 (80%)	4.4
Phenobarbital	5	20	30.0	0	0	0
Lamotrigine	5	20	27.6 ± 0.8*	2.40 ± 0.40*	1 (20%)	2.20

Note: * statistically significant result ($p \leq 0.05$) relative to control animals.

pentylenetrazole seizures models in rats. The choice of compounds for screening was based on the previously obtained data (Severina et al. 2019) on the positive effect of these radicals in the structural analogues of the 6-methyl-2-thiopyrimidine-4 (3H)-one acetamide compounds studied.

In the control group, the administration of pentylenetetrazole induced seizure in all animals. At the same time, the duration of the latent period of convulsions amounted to an average of 4.7 minutes, and the length of the trial - 9.7 minutes (Tab. 1). The convulsion syndrome that developed in the rats of this group, accompanied by pronounced tonic-clinical convulsions, which was periodically repeated, there was a clearly expressed phase of tonic extension (opisthotonus). Mortality in this group was 100%. Phenobarbital prevented the development of convulsive syndrome in all animals. At the same time, with the introduction of lamotrigine in rats, pentylenetetrazole induced some manifestations of the convulsive condition (convulsive jerking, jumps and tonic contractions of the anterior limbs), but the duration of the latent period was statistically significantly lengthened (5.8 times), the degree of manifestation of convulsions, and the total duration of the trial were significantly lower than in the control group. The drug prevented mortality in 80% of animals.

All investigated compounds did not show a significant anticonvulsant effect. In all studied groups of animals, seizures appeared after the administration of pentylenetrazole and the compounds studied, and significant lethality was observed (Tab. 1). Compounds 3.1 and 3.2 though, increased the duration of the latent period with respect to control by 2.5 and 3.2 times, respectively, and a 60% mortality rate, but increased the length and severity of the trial. The obtained results in comparison with the previous ones (Severina et al. 2019) allow confirming the positive effect on the manifestation of the anticonvulsant action of the acetamidic fragment and the reduction of activity as a result of its modification.

In addition, it can be stated that compounds with condensed thiazolopyrimidine fragment **5.1–5.4** do not have an anticonvulsant effect in any of the indicators and do not protect the animals from death against the background of administration of pentylenetetrazole.

Conclusion

It was found that for the preparation of individual 2-(2-aryl-2-oxoethyl)thio-6-methyl-pyrimidin-4(3*H*)-one alkylation of 6-methyl-2-thioxo-2,3-dihydro-1*H*-pyrimidine-4-onephenacyl bromides should be carried out in methanol in the presence of sodium methoxide. In the course of the alkylation in DMF/K_2CO_3 a mixture of 2-(2-aryl-2-oxoethyl)thio-6-methyl-pyrimidin-4(3*H*)-one and 3-hydroxy-3-aryl-7-methyl-5*H*-thiazolo[3,2-a]pyrimidine-5-ones, treatment of which with concentrated sulphuric acid allows to get 3-aryl-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one with high outputs. On the model of pentylenetrazole seizures in rats, in comparison with reference phenobarbital and lamotrigine, the synthesized compounds did not show significant anticonvulsant activity.

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