The large synthetic potential and high biological potential in the series of 1,2,4-triazole derivatives cause favorable conditions for the search for new biologically active substances. A special attention is paid to the possibility of introducing various substituents at the stage of 1,2,4-triazole-3-thiol structure formation. At the same time, derivatives of xanthine are known as the basis for obtaining a wide range of drugs.

The aim of this work was the synthesis and properties’ study of new compounds in the series of esters of 2-[5-((theophylline-7’-yl)methyl)-4-R,1,2,4-triazole-3-ylthio]acetic acids.

Materials and methods. The strategy of the synthesis of all target products of the reaction was based on the use of theophylline as starting material. To obtain the intermediate thiol we used reactions of esterification, nucleophilic substitution, hydrazinolysis and intermolecular alkaline heterocyclic. The esters of 2-[5-((theophylline-7’-yl)methyl)-4-R,1,2,4-triazole-3-ylthio]acetic acid were obtained by two methods. The melting point was determined using capillary method on OptiMelt MPA 100 (SRS, USA). The structure of the compounds was confirmed with elemental analysis on Elemental Vario EL cube (Elementar Analysensysteme, Germany), IR spectra (4000–400 cm\(^{-1}\)) were taken off the module ALPHA-T of Bruker ALPHA FT-IR spectrometer (Bruker optics, Germany). Chromatmass-spectral studies were carried out on Agilent 1260 Series LC/MSD System.

Conclusion. The optimal conditions of obtaining esters of 2-[5-((theophylline-7’-yl)methyl)-4-R,1,2,4-triazole-3-ylthio]acetic acid have been determined. 15 not previously described compounds have been synthesized, its structure has been confirmed by physical and chemical methods of analysis. It has been established that the synthesis of esters of 2-[5-((theophylline-7’-yl)methyl)-4-R,1,2,4-triazole-3-ylthio]acetic acid proceeds with greater yield, if they are gotten directly from the thiol.

Key words: 1,2,4-triazole, theophylline, physical properties, organic synthesis, esters.

Current issues in pharmacy and medicine: science and practice 2017; 10 (2), 124–128
The creation of new highly effective medicines is one of the main tasks of modern pharmaceutical industry [5]. Significant interest in search for compounds with high pharmacological activity is paid to derivatives of 1,2,4-triazole and 1,3-dimethylxanthine [1,3,4,7]. Therefore, it was deemed appropriate to combine these two famous notions within a single molecule.

Ethers of 2-[(theophylline-7ʹ-yl)methyl]-4-R-1,2,4-triazole-3-ylthio]acetic acid are widely used in organic chemicals and pharmaceutical intermediates [2,3,7–11]. Ethers of 2-[(theophylline-7ʹ-yl)methyl]-4-R-1,2,4-triazole-3-ylthio]acetic acids is an understudied group of compounds, which creates conditions for their own data supplement information regarding this class of compounds.

**Aim of the work**

The aim of this work was the synthesis and properties’ study of new biologically active compounds in the series of esters of 2-[(theophylline-7ʹ-yl)methyl]-4-R-1,2,4-triazole-3-ylthio]acetic acid.

**Materials and methods**

To achieve this goal the following experimental methods of organic chemistry have been used: synthesis and chemical analysis with using IR-, ¹H NMR-spectroscopy, and chromatography-mass-spectrometry and elemental analysis.

The melting point was determined using capillary method on OptiMelt MPA 100 (SRS, USA). The structure of the compounds was confirmed with elemental analysis on Elemental Vario EL cube (Elementar Analysensysteme, Germany), IR spectra (4000–400 cm⁻¹) were taken off the module ALPHA-T of Bruker ALPHA FT-IR. ¹H ЯМР spectra were obtained with a spectrometer «Mercury 400» (Bruker optics, Germany).

**Synthesis and physical properties of esters of 2-[(theophylline-7ʹ-yl)methyl]-4-R-1,2,4-triazole-3-ylthio]acetic acid**

**A.** A mixture of 0.01 mole 2-[(theophylline-7ʹ-yl)methyl]-4-R-1,2,4-triazole-3-ylthio]actic acid, 35 ml of the appropriate alcohol (methanol, ethanol, propanol-1, propanol-2 and butanol-1) and 1 ml of concentrated sulfuric acid is boiled for 10 hours, the solvent is evaporated, the residue is neutralized with a solution of sodium hydroxide. Thus we receive compounds 1–15. The synthesized compounds are white crystalline substances, soluble in solutions of alkalis and carbonates of alkali metals, insoluble in water, soluble in organic solvents. For the analysis of esters are purified by recrystallization from the mixture ethanol–water 2:1.

**B.** To the solution of 0.01 mol sodium hydroxide in 5 ml of water the 0.01 mol of corresponding 7ʹ-(3-thio-4-R-1,2,4-triazole-3-ylthio]acetic acid
azole-5-yl)methyl)-theophylline was added in 50 ml of ethanol and 0.01 mol ethyl ether of 2-chloroacetic acid, boil for 1 hour, the solvent was evaporated and the residue was washed with water. Purified, crystallized from ethanol-water (3:1).

Sample mixing substances obtained by methods A and B gave no depression of melting point.

**Results**

The resulting compounds are white crystalline substances, practically insoluble in water, soluble in alcohols and 1,4-dioxane (*Table 1*). In the IR-spectra of the compounds the stretching vibrations of the groups C=O appear in the region of 1730–1715 cm⁻¹, bands of medium intensity at 1310–1250 cm⁻¹ at 1110 cm⁻¹ attributed to C-O-bond of esters group. Also fixed the deformation vibrations of the fragment N-CH₃ at 1426 cm⁻¹, a fragment of O-CH₃ at 1455 cm⁻¹ and fragment -CH₃ at 1375 cm⁻¹. A fragment of xanthine N-CH is recorded in the form of stretching vibrations at 2820–2730 cm⁻¹. Group -CH₂ is observed in the form of stretching vibrations at 2940–2915 cm⁻¹ (νₐs) at 2870–2845 cm⁻¹ (νₛ) and

![Chemical structure](image)

*Fig. 1. Synthesis of esters of 2-[5-((theophylline-7'-yl)methyl)-4-R-1,2,4-triazole-3-ylthio]acetic acid.*

**Table 1. Physical-chemical properties of the synthesized compounds**

<table>
<thead>
<tr>
<th>№</th>
<th>R</th>
<th>R₁</th>
<th>M. p., °C</th>
<th>Empirical formula</th>
<th>Yield, %</th>
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<tbody>
<tr>
<td>1</td>
<td>CH₃</td>
<td>CH₃</td>
<td>148–151</td>
<td>C₁₀H₁₄N₂O₄S</td>
<td>71</td>
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<tr>
<td>2</td>
<td>CH₃</td>
<td>C₂H₅</td>
<td>125–127</td>
<td>C₁₀H₁₅N₂O₄S</td>
<td>63</td>
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<tr>
<td>3</td>
<td>CH₃</td>
<td>C₃H₇</td>
<td>134–136</td>
<td>C₁₀H₁₇N₂O₄S</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>CH₃</td>
<td>C₂H₅⁻i</td>
<td>123–125</td>
<td>C₁₀H₁₇N₂O₄S</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
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<td>CH₃</td>
<td>117–119</td>
<td>C₁₀H₁₄N₂O₄S</td>
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<td>7</td>
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<td>C₂H₅</td>
<td>114–116</td>
<td>C₁₀H₁₄N₂O₄S</td>
<td>62</td>
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<tr>
<td>8</td>
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<td>CH₃</td>
<td>128–130</td>
<td>C₁₀H₁₄N₂O₄S</td>
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<td>C₂H₅</td>
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<td>C₁₀H₁₄N₂O₄S</td>
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<tr>
<td>11</td>
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<td>147–149</td>
<td>C₁₀H₁₄N₂O₄S</td>
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<td>C₂H₅</td>
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<td>104–107</td>
<td>C₁₀H₁₆N₂O₄S</td>
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<tr>
<td>13</td>
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<td>108–112</td>
<td>C₁₀H₁₄N₂O₄S</td>
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<td>C₂H₅⁻i</td>
<td>137–139</td>
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<td>71</td>
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<tr>
<td>15</td>
<td>C₂H₅</td>
<td>CH₃</td>
<td>128–130</td>
<td>C₁₀H₁₄N₂O₄S</td>
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</table>
the deformation vibration at 1480–1440 cm\(^{-1}\). Purine cycle causes the appearance of stretching vibrations in the high-bandwidth of C-H at 3060–3010 cm\(^{-1}\), deformation vibrations of C-H at 1000–960 cm\(^{-1}\), 875–775 cm\(^{-1}\) and vibrations of a ring in the middle lane at 1580–1520 cm\(^{-1}\).

The study of \(^1\)H NMR spectra has been discovered and helps to analyze a number of patterns. The protons of the methyl radicals in the first and third position of the xanthine cycle reflected the characteristic singlet’s at 3.27 ppm and 3.40 ppm respectively. The proton at Carbon atom at the eighth position of the loop of theophylline resonates with 8.35 ppm. Protons of methylene group between the Carbon atom at the seventh position of theophylline and a Carbon atom in the fifth position of the 1,2,4-triazole resonate in the span of 6.20–6.17 ppm. Protons of the methyl radical in the fourth position of 1,2,4-triazole are placed in a strong field at 3.73 ppm. At the same time a quadruplet -CH\(_2\) - group and a triplet -CH\(_3\) resonates in the interval of 4.35 ppm and 1.21 ppm respectively. The protons of the phenyl radical are presented in the form of a number of signals, the second and sixth protons resonate doublet of doublets at 7.73 – of 7.69 ppm. Third and fifth protons resonate one multiplet’s 7.50–7.44 ppm; fourth proton is represented by a triplet at 7.69 ppm. The protons of esters group fragment –OCH\(_2\) resonates in the form of a singlet at 3.55 ppm. In the \(^1\)H NMR spectrum of compound (2), the signals of the protons of CH\(_2\)-CH\(_2\)- of esters group appear in the region of 1.31 ppm in the form of the singlet. The doublet in the region of 4.30 ppm assigned to the proton of CH\(_2\)-CH\(_2\) of esters group. The protons of the fragment (CH\(_3\))\(_2\)-CH- resonate in the form of a doublet at 1.25 ppm. Protons of esters group fragment with butyl component are recorded in the form of two multiplet’s when 4.12 ppm and of 1.43 ppm and a triplet at 0.90 ppm. As a result of mass spectrometric studies we have established the individual peaks of the synthesized substances: observed separation of the fragment, which is associated with carbonyl group.

**Conclusions**

The optimal conditions of obtaining esters of 2-[5-((theophylline-7'-yl)methyl)-4-R-1,2,4-triazole-3-ythio]acetic acid have been determined. It is established that the synthesis of esters of 2-[5-((theophylline-7'-yl)methyl)-4-R-1,2,4-triazole-3-ythio]acetic acid proceeds with greater yield, if they are gotten directly from the thiol. The general physical properties of the obtained compounds have been studied.

**Funding:** The research was carried out within the state budget scientific-research work “Synthesis of new biologically active substances - derivatives of 5-(alkyl-, aryl-, heteryl-) of 4-R-(amino)-1,2,4-triazolyl-3-thiones for the creation of original drugs with analgesic, actoprotective, antimicrobial, anti-inflammatory and diuretic effect” (0115U003470), 2015-2017, funded by the Ministry of Health of Ukraine.

**References**


