Synthesis, structure and properties of N-R-amides and hydrazides of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid

A. S. Gotsulya
Zaporizhzhia State Medical University, Ukraine

One of the most important tasks of modern pharmaceutical science is the search for new biologically active substances, which have high efficacy and low toxicity. Derivatives of 1,2,4-triazole and theophylline are a promising class of compounds for synthesis of biologically active substances on their basis, due to a wide range of biological activity of these heterocycles’ derivatives.

The purpose of work is the development of efficient methods for synthesis of new amides and hydrazides of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid (R = CH₂, C₆H₅, C₅H₄) with variation of the reactions conditions and the study of physical properties of the obtained compounds.

Materials and methods. As a key source of reagents we used 7’-(3-thio-4-R-4-H,1,2,4-triazole-5-yl)methyl)theophylline and esters of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid, which were obtained by known methods from readily available raw materials. By heating in ethanol medium the corresponding amines (ammonia, methylamine, ethylamine, monoethanolamine, diethanolamine), n-propyl ether 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid a series of amides of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid were obtained. Hydrazide of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid was synthesized by interaction of corresponding esters of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid with an aqueous solution of hydrazine hydrate in ethanol medium. The structure of the obtained compounds is confirmed by data of elemental analysis, ¹H NMR spectroscopy and IR-spectrophotometry. The individuality of substances is established by using high performance liquid chromatography with diode-array and mass spectrometric detection.

Results. Optimal methods of obtaining amides and hydrazides of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid have been developed. Getting investigated amides by two alternative ways of synthesis, it was established that the initial interaction of thiol with 2-chloroacetamide proceeds with high yield product of the reaction compared to the reaction between a corresponding ester with ammonia.

Conclusions. 15 amide and 3 hydrazide 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acids have been synthesized, their structure has been established and physical properties have been studied.

Key words: theophylline, 1,2,4-triazole, amides, hydrazide, synthesis, physical properties.

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Синтез, будова та властивості N-R-амідів і гідразидів 2-[4-R-5-(теофілін-7’-іл)-1,2,4-триазол-3-ілтіо]ациєтової кислоти

A. С. Гоцуля

Одним із найбажаніших завдань сучасної фармацевтичної науки є пошук нових біологічно активних речовин, які володіють високою ефективністю та низькою токсичністю. Похідні 1,2,4-триазолу та теофіліну є перспективним класом хімічних сполук, які володіють високою ефективністю та низькою токсичністю. Похідні 1,2,4-триазолу та теофіліну є перспективним класом хімічних сполук.

Мета роботи – розроблення ефективних методів синтезу нових амідів і гідразидів 2-[4-R-5-(теофілін-7’-іл)-1,2,4-триазол-3-ілтіо]ациєтової кислоти (R = CH₂, C₆H₅, C₅H₄) і дослідження фізичних властивостей сполук, що отримали.

Матеріали та методи. як ключові вихідні реагенти використали 7’-(3-тіо-4-R-4-H,1,2,4-триазол-5-іл)метил)теофілін та ефіри 2-[4-R-5-(теофілін-7’-іл)-1,2,4-триазол-3-ілтіо]ациєтової кислоти, котрі отримали за відомими методиками з доступної сировини.

Нагріванням в етаноліді відповідних амін (амоніак, метиламін, етиламін, моноетаноламін, діетаноламін), n-пропил ефір 2-[4-R-5-(теофілін-7’-іл)-1,2,4-триазол-3-ілтіо]ациєтової кислоти отримали ряд амідів 2-[4-R-5-(теофілін-7’-іл)-1,2,4-триазол-3-ілтіо]ациєтової кислоти. Взаємодією 7’-(3-тіо-4-R-4-H,1,2,4-триазол-5-іл)метил)теофіліну з 2-хлорacetамідом у присутності NaOH із високими виходами отримали відповідні аміди. Гідразиди 2-[4-R-5-(теофілін-7’-іл)-1,2,4-триазол-3-ілтіо]ациєтової кислоти синтезовано взаємодією відповідних ефірів 2-[4-R-5-(теофілін-7’-іл)-1,2,4-триазол-3-ілтіо]ациєтової кислоти з водним розчином гідразину гідрата в середовищі етанолу.

Результати. Розроблені оптимальні методи отримання амідів і гідразидів 2-[4-R-5-(теофілін-7’-іл)-1,2,4-триазол-3-ілтіо]ациєтової кислоти.

Висновки. Синтезовано 15 амідів і 3 гідразиди 2-[4-R-5-(теофілін-7’-іл)-1,2,4-триазол-3-ілтіо]ациєтової кислоти, встановлена їхня структура та вивчені фізичні властивості.

Ключові слова: теофілін, 1,2,4-триазол, аміди, гідразиди, синтез, фізичні властивості.

Synthesis, structure and properties of N-R-amides and hydrazides of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid

A. S. Гоцюля

One of the important tasks of modern pharmaceutical science is the search for new biologically active substances that have high efficiency and low toxicity [1,8,9]. The derivatives of 1,2,4-triazole-3-thiol and theophylline are a very promising class of chemical compounds for the synthesis of biologically active compounds based on them, due to the wide spectrum of biological activity of these heterocycles’ derivatives [2–7,10]. Objective reasons for the search for a number of 1,2,4-triazole-3-thiol and theophylline derivatives are the high synthetic and pharmacological potential of these heterocycles [2,5,7,10]. Our attention was drawn to previously unexplored amides and 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid.

The purpose of the work

The purpose of the work is the synthesis of new amides and hydrazides of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid and the study of their physical properties.

Materials and methods

As the key starting reagents, we used 7'-(3-thio-4-R-4H-1,2,4-triazol-5-yl)methyltheophylline ester 2-[4-R-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid, which were obtained by known methods from available raw materials. In the course of the research, it was found that by heating in ethanol, the corresponding amines (ammonia, methylamine, ethylamine, monoethanolamine, diethanolamine) from n-propyl ethers 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid are formed to 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid amides. The solvent was evaporated, the residue crystallized. Interactions of 7'-(3-thio-4-R-4H-1,2,4-triazol-5-yl)methyltheophylline with 2-chloroacetamide in the presence of NaOH in high yields yielded the corresponding amides (Fig. 1). Hydrazides 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid are synthesized by the interaction of the corresponding esters of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]-acetic acid with an aqueous solution of hydrazine hydrate in ethanol (Fig. 1).

The study of physical-chemical properties of the obtained compounds was carried out using methods listed in the State Pharmacopoeia of Ukraine. The melting point was determined using capillary method on Stanford Research Systems Melting Point Apparatus 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). Chromato-mass-spectral studies were carried out on the instrument Agilent 1260 Series LC/MSD System, method of ionization — electrospray (ESI).

Amides of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid. A. To 0.01 mol of ester of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid, 0.01 mol of amine and 35 ml of propanol-1 are added, then heat for 3 hours. Water is added to the cooled reaction medium. The resulting precipitate is filtered off and recrystallized from 1,4-dioxane (2–6, 8–12, 14–18) or ethanol (1, 7, 13). White crystals, slightly soluble in water and alcohols (Table 1). B. A mixture of 0.01 mol of ester and 10 ml of concentrated aqueous ammonia (25 %) is boiled for 12 hours.
Table 1. Amides and hydrazides of 2-[4-R-5-(theophyllin-7'-yl)-1,2,4-triazol-3-ylthio] acetic acid

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R₁</th>
<th>M. p., °C</th>
<th>Molecular formula</th>
<th>Yield, %</th>
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<tr>
<td>1</td>
<td>CH₃</td>
<td>H</td>
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<td>C₁₃H₁₈NO₅S</td>
<td>83</td>
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<tr>
<td>2</td>
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<td>CH₅</td>
<td>187–189</td>
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<tr>
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<td>C₅H₅</td>
<td>229–231</td>
<td>C₁₃H₁₆NO₅S</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
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<td>(C₃H₅)OH</td>
<td>211–213</td>
<td>C₁₃H₂₆NO₅S</td>
<td>77</td>
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<tr>
<td>5</td>
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<td>(C₃H₅)OH</td>
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<td>C₁₃H₂₆NO₅S</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
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<td>NH₂</td>
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<td>H</td>
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<td>C₁₃H₁₈NO₅S</td>
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<td>8</td>
<td>C₅H₅</td>
<td>CH₅</td>
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<tr>
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<td>18</td>
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<td>NH₂</td>
<td>239–241</td>
<td>C₁₃H₁₈NO₅S</td>
<td>79</td>
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</table>

Fig. 1. The scheme of the synthesis of amides and hydrazides of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazole-3-ylthio]acetic acid.
The resulting solution is evaporated; the residue is crystallized from ethanol. White crystals are insoluble in water and alcohols. Washed with ethanol and dried. White crystalline substances, practically insoluble in water and slightly soluble in alcohols.

**Results and their discussion**

The presence of the amide group in the IR-spectrum of the obtained compounds was confirmed by the presence of characteristic absorption bands in the region of 3132–3370 cm\(^{-1}\) (CONH\(_2\)) and in the region 1630–1675 cm\(^{-1}\) (CONH\(_2\)). The absorption band of the secondary amino group was observed in the range of 3165–3200 cm\(^{-1}\). The IR-spectrum of compounds 4, 5, 11, 12, 17, 18 in addition to the above has an additional absorption band within 950–890 cm\(^{-1}\), indicating the presence of OH-groups.

In the NMR \(^1\)H synthesized compounds, signals of protons with chemical displacements are present, which confirm the structure of the resulting compounds. Signals of protons of methylene groups (3.75–3.85 ppm), aromatic prototype multiplets – for compounds 13–18 (7.25–8.16 ppm). In addition, proton of amide NH-group (7.65–7.93 ppm), a proton of 

**Conclusions**

A universal method for the preparation of 2-[4-R-5-(theophylline-7'-yl)-1,2,4-triazol-3-ylthio]acetic acid amides and hydrazides was developed. It was established that while the interaction of the starting thiol with 2-chloroacetamide the product yields of the reaction are greater than in the reaction of the corresponding ester with ammonia.

**References**


Сведения об авторе:
Гоцуля А. С., канд. фарм. наук, доцент каф. токсикологической и неорганической химии, Запорожский государственный медицинский университет, Украина.

E-mail: andrey.goculya@gmail.com

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