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

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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). Chromate-mass-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 described previously 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.

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Синтез і властивості естерів 2-[4-R-5-(теофілін-7′-іл)-1,2,4-тріазол-3-ілтіо]ацетатної кислоти

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Великі синтетичні можливості та високий біологічний потенціал у ряду похідних 1,2,4-тріазолу зумовлюють сприятливі умови пошуку нових біологічно активних речовин. Особливу привабливість також викликає можливість уведення різних замісників на етапі формування структури 1,2,4-тріазол-3-тіолу. Водночас похідні ксантину відомі як основа для отримання широкого спектра лікарських засобів.

Мета роботи – синтез і вивчення властивостей сполук у ряду складних ефірів 2-[5-((теофілін-7'-іл)метил)-4-R-1,2,4-тріазол-3-ілтіо]ацетатної кислоти.

Матеріали та методи. Стратегія синтезу всіх цільових продуктів реакції базувалась на використанні теофіліну як вихідної речовини. Для отримання проміжного тіолу використані реакції етерифікації, нуклеофільного заміщення, гідразинолізу та внутрішньомолекулярної лужної гетероциклізації. Ефіри 2-[5-((теофілін-7'-іл)метил)-4-R-1,2,4-тріазол-3-ілтіо]ацетатної кислоти одержані за двома методами. Будова речовин підтверджена за допомогою елементного аналізу на приладі Elementar Vario EL cube (CHNS), ІЧ-спектри (4000–400 $см^{-1}$) зняті на модулі ALPHA-T спектрометра Bruker ALPHAFT-IR. ^{1}Н ЯМР спектри сполук записані за допомогою спектрометра «Mercury 400» (розчинник – ДМСО-d_6, внутрішній стандарт – тетраметилсилан). Хромато-мас-спектральні дослідження здійснили на приладі Agilent 1260 Series LC/MSD System.

Висновки. Встановили оптимальні умови отримання ефірів 2-[5-((теофілін-7'-іл)метил)-4-R-1,2,4-тріазол-3-ілтіо]ацетатної кислоти. Синтезували 15 сполук, що не описані в науковій літературі раніше, структура яких підтверджена фізико-хімічними методами аналізу. Встановили, що синтез ефірів 2-[5-((теофілін-7'-іл)метил)-4-R-1,2,4-тріазол-3-ілтіо]ацетатної кислоти перебігає з більшим виходом, якщо їх отримувати безпосередньо з тіолу.

Ключові слова: 1,2,4-тріазол, теофілін, фізичні властивості, органічний синтез, ефіри.

Актуальні питання фармацевтичної і медичної науки та практики. – 2017. – Т. 10, № 2(24). – С. 124–128

Синтез и свойства эфиров 2-[5-((теофиллин-7′-ил)метил)-4-R-1,2,4-триазол-3-илтио]ацетатной кислоты

А. С. Гоцуля

Большие синтетические возможности и высокий биологический потенциал в ряду производных 1,2,4-триазола обусловливают благоприятные условия для поиска новых биологически активных веществ. Особую привлекательность также вызывает возможность введения различных заместителей на этапе формирования структуры 1,2,4-триазол-3-тиола. В то же время производные ксантина известны как основа для получения широкого спектра лекарственных средств.

Цель работы – синтез и изучение свойств соединений в ряду сложных эфиров 2-[5-((теофиллин-7′-ил)метил)-4-R-1,2,4-триазол-3-илтио]ацетатной кислоты.

Материалы и методы. Стратегия синтеза всех целевых продуктов реакции базировалась на использовании в качестве исходного вещества теофиллина. Для получения промежуточного тиола были использованы реакции этерификации, нуклео-

фильного замещения, гидразинолиза и внутримолекулярной щелочной гетероциклизации. Эфиры 2-[5-((теофиллин-7′-ил) метил)-4-R-1,2,4-триазол-3-илтио]ацетатных кислот получены двумя методами. Строение веществ подтверждено с помощью элементного анализа на приборе Elementar Vario EL cube (CHNS), ИК-спектры (4000–400 см$^{-1}$) сняты на модуле ALPHA-T спектрометра Bruker ALPHA FT-IR. ^{1}Н ЯМР спектры соединений записаны с помощью спектрометра «Mercury 400» (растворитель – ДМСО-d_6, внутренний стандарт – тетраметилсилан). Хромато-масс-спектральные исследования проводили на приборе Agilent 1260 Series LC/MSD System.

Выводы. Установлены оптимальные условия получения эфиров 2-[5-((теофиллин-7′-ил)метил)-4-R-1,2,4-триазол-3-илтио] ацетатной кислоты. Синтезировано 15 ранее не описанных в научной литературе соединений, структура которых подтверждена физико-химическими методами анализа. Установлено, что синтез эфиров 2-[5-((теофиллин-7′-ил)метил)-4-R-1,2,4-триазол-3-илтио]ацетатной кислоты протекает с большим выходом, если их получать непосредственно из тиола.

Ключевые слова: 1,2,4-триазол, теофиллин, физико-химические свойства, органический синтез, эфиры.

Актуальные вопросы фармацевтической и медицинской науки и практики. – 2017. – Т. 10, № 2(24). – С. 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 sinton within a single molecule.

Ethers of 2-[5-((theophylline-7′-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-[5-((theophylline-7′-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-[5-((theophylline-7′-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-, ^{1}H 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 spectrometer (Bruker optics, Germany).

Gear Liquid Chromatography System with Mass spectrometric detector (Agilent Technologies, USA): Agilent 1260 Infinity HPLC System (degasser, binary pump, autosampler, thermostat column, diode-array detector); single quadrupole mass spectrometer Agilent 6120 with electrospray ionization (ESI); Open LAB CDS Software. Terms of HPLC-MS study: 1) binary gradient – A: H_2O (0.1 % solution of HCOOH), B: CH_3CN (0.1 % solution of HCOOH); 2) Column: Zorbax SB-C18; 30 mm × 4.6 mm × 1.8 mm; 3) column temperature: 40 °C; 4) DAD: 210, 254 nm; 5) ion source: APIES; 6) scanning range m/z: 160–1000; 7) fragmentor: 10 V; 8) positive polarity; 9) nitrogen temperature – 300 °C; 10) Nebulizer pressure 40 psig; 11) the rate of drying gas (nitrogen) – 10 l/min.

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 esterification reaction, nucleophilic substitution, hydrazinolysis and intermolecular alkaline heterocyclic [6]. 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 first method (A) involves the interaction of 7'-((3-thio-4-R-1,2,4-triazole-5-yl)methyl)theophylline with ethyl ether of bromacetic acid in the presence of equimolecular amount of alkali. The second method (B) involves esterification 2-[5-((theophylline-7′-yl)methyl)-4-R-1,2,4-triazole-3-ylthio]acetic acid with methanol, ethanol, propanol-1, propanol-2 and butanol-1 in the presence of a catalytic amount of concentrated sulfuric acid. Synthesis of 2-[5-((theophylline-7′-yl)methyl)-4-R-1,2,4-triazole-3-ylthio]acetic acid was carried out by known method in double excess of sodium hydroxide with 2-chroacetic acid [6].

After the reaction, the excess alcohol is evaporated; the residue first washed thoroughly with a solution of sodium bicarbonate, then with water, precipitation was filtered, washed with water and dried. For the analysis the esters *1–15* were purified by recrystallization from a mixture ethanol–water 3:1.

The purity and structure of the obtained compounds has been confirmed using ^{1}H NMR spectroscopy, elemental analysis, IR spectrophotometry and gas chromatography-mass spectrometry.

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

A. A mixture of 0.01 mole 2-[5-((theophylline-7′-yl)methyl)-4-R-1,2,4-triazole-3-ylthio]acetic 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 hydrogencarbonate. 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 3:1.

B. To the solution of 0.01 mol sodium hydroxide in 5 ml of water the 0.01 mol of corresponding 7'-((3-thio-4-R-1,2,4-tri-

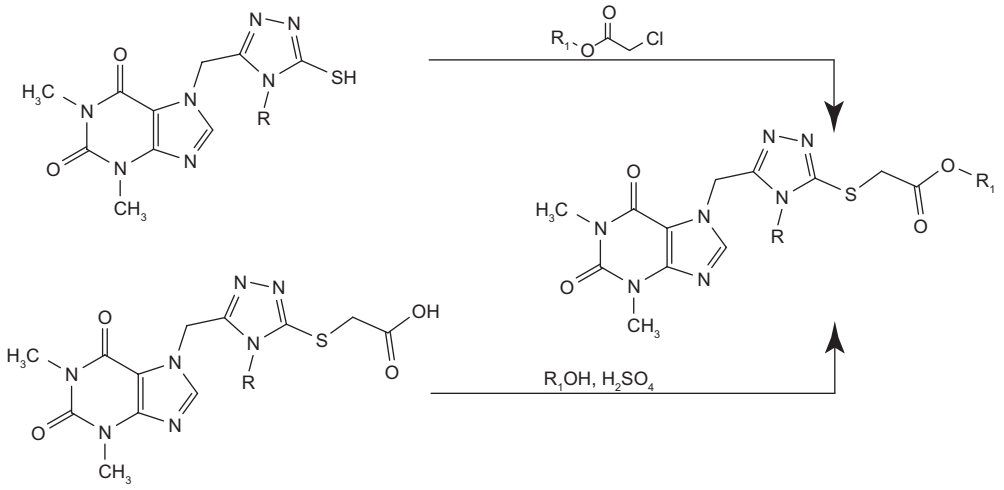


Fig. 1. Synthesis of esters of 2-[5-((theophylline-7'-yl)methyl)-4-R-1,2,4-triazole-3-ylthio]acetic acid.

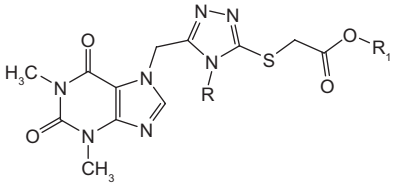
azole-5-yl)methyl)-theophylline was added in 50 ml of ethanol and 0.01 mol ethyl ether of 2-chloracetic acid, boil for 1 hour, the solvent was evaporated and the residue was washed with water. Purified, crystallized from ethanol-water (3:1).

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-CH_3 at 1426 cm^{-1}, a fragment of O-CH_3 at 1455 cm^{-1} and fragment -CH_3 at 1375 cm^{-1}. A fragment of xanthine N-CH is recorded in the form of stretching vibrations at 2820–2730 cm^{-1}. Group -CH_2- is observed in the form of stretching vibrations at 2940–2915 cm^{-1} (ν_{as}) at 2870–2845 cm^{-1} (ν_s) and

Table 1. Physical-chemical properties of the synthesized compounds



№	R	R_1	M. p., °C	Empirical formula	Yield, %
1	CH_3	CH_3	148–151	$C_{14}H_{17}N_7O_4S$	71
2	CH_3	C_2H_5	125–127	$C_{15}H_{19}N_7O_4S$	63
3	CH_3	C_3H_7	134–136	$C_{16}H_{21}N_7O_4S$	82
4	CH_3	C_3H_7-i	123–125	$C_{16}H_{21}N_7O_4S$	85
5	CH_3	C_4H_9	117–119	$C_{17}H_{23}N_7O_4S$	69
6	C_2H_5	CH_3	130–132	$C_{15}H_{19}N_7O_4S$	77
7	C_2H_5	C_2H_5	114–116	$C_{16}H_{21}N_7O_4S$	62
8	C_2H_5	C_3H_7	128–130	$C_{17}H_{23}N_7O_4S$	79
9	C_2H_5	C_3H_7-i	136–138	$C_{17}H_{23}N_7O_4S$	71
10	C_2H_5	C_4H_9	112–114	$C_{18}H_{25}N_7O_4S$	82
11	C_6H_5	CH_3	147–149	$C_{19}H_{19}N_7O_4S$	80
12	C_6H_5	C_2H_5	104–107	$C_{20}H_{21}N_7O_4S$	74
13	C_6H_5	C_3H_7	108–112	$C_{21}H_{23}N_7O_4S$	77
14	C_6H_5	C_3H_7-i	137–139	$C_{21}H_{23}N_7O_4S$	71
15	C_6H_5	C_4H_9	128–130	$C_{22}H_{25}N_7O_4S$	68

Cont. Table 1

№	Found, %				Estimated, %			
	C	H	N	S	C	H	N	S
1	44.24	4.53	25.89	8.43	44.32	4.52	25.84	8.45
2	45.87	4.86	24.87	8.16	45.79	4.87	24.92	8.15
3	47.24	5.19	24.03	7.86	47.17	5.20	24.06	7.87
4	47.09	5.21	24.10	7.88	47.17	5.20	24.06	7.87
5	48.55	5.51	23.20	7.60	48.45	5.50	23.26	7.61
6	45.71	4.86	24.94	8.16	45.79	4.87	24.92	8.15
7	47.26	5.21	24.01	7.86	47.17	5.20	24.06	7.87
8	48.34	5.49	23.31	7.62	48.45	5.50	23.26	7.61
9	48.35	5.49	23.30	7.62	48.45	5.50	23.26	7.61
10	49.56	5.80	22.48	7.37	49.64	5.79	22.51	7.36
11	51.57	4.35	22.16	7.23	51.69	4.34	22.21	7.26
12	52.63	4.66	21.57	7.03	52.74	4.65	21.53	7.04
13	53.82	4.95	20.84	6.82	53.72	4.94	20.88	6.83
14	53.81	4.93	20.91	6.84	53.72	4.94	20.88	6.83
15	54.53	5.20	20.32	6.64	54.65	5.21	20.28	6.63

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 groups resonated 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 7.65–7.58 ppm. Protons of the fragment -S-CH_2- represented by a singlet in the interval of values of 4.09 is 4.03 ppm. Protons of esters group fragment – OCH_3 resonate in the form of the singlet at 3.55 ppm. In the ^{1}H NMR spectrum of compound (2), the signals of the protons of CH_3-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_3 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-ylthio]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-ylthio]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.

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