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Synthesis and physical-chemical research of 7-((3-thio-4-r-4*h*-1,2,4-triazole-5-yl)methyl) theophylline carbonyl derivatives

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Key words: *1,2,4-triazoles, Theophylline, Synthesis, IR Spectrometry, [1]H NMR Spectrometry.*

Aim. To analyze the carbonyl derivatives of 7-((3-thio-4-R-4*H*-1,2,4-triazole-5-yl)methyl)theophylline their mother substance was synthesized and its interaction with α-haloketones series was carried out.

Methods and results. The physical-chemical properties of the obtained compounds have been studied and their structures have been confirmed by elemental analysis, infrared spectrometry, ^{1}H NMR spectrometry, UV spectrophotometry and gas chromatography mass spectrometry. Preliminary computer study of acute toxicity and biological activity has been also carried out. It has been determined that the obtained compounds may exhibit diuretic and analeptic activity and 1,2,4-triazole fragment can theoretically increase it. Conclusion. Preliminary prediction of acute toxicity has showed that the compounds are low-toxic.

Синтез і фізико-хімічні дослідження карбонільних похідних 7-((3-тіо-4-R-4*H*-1,2,4-тріазол-5-іл)метил)теофіліну

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З метою дослідження карбонільних похідних 7-((3-тіо-4-R-4*H*-1,2,4-тріазол-5-іл)метил)теофіліну виконали синтез вихідної речовини та її взаємодію з рядом α-галогенкетонів. Досліджені фізико-хімічні властивості одержаних сполук і підтверджена їхня будова за допомогою елементного аналізу, ІЧ-спектрометрії, ^{1}Н ЯМР-спектрометрії, УФ-спектрофотометрії та хромато-мас-спектрометрії. Здійснили попереднє комп'ютерне дослідження гострої токсичності та біологічної активності. Встановили, що отримані сполуки можуть проявляти діуретичну й аналептичну активності, а фрагмент 1,2,4-тріазолу теоретично може підсилювати цю активність. Попереднє прогнозування гострої токсичності показало: сполуки належать до малотоксичних.

Ключові слова: *1,2,4-тріазол, теофілін, синтез, ІЧ-спектрометрія, [1]Н ЯМР-спектрометрія.*

Запорізький медичний журнал. – 2015. – №3 (90). – С. 103–106

Синтез и физико-химическое исследование карбонильных производных 7-((3-тио-4-R-4*H*-1,2,4-триазол-5-ил) метил)теофиллина

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С целью исследования карбонильных производных 7-((3-тио-4-R-4*H*-1,2,4-триазол-5-ил)метил)теофиллина проведен синтез исходного вещества и его взаимодействие с рядом α-галогенкетонов. Исследованы физико-химические свойства полученных соединений и подтверждено их строение с помощью элементного анализа, ИК-спектрометрии, ^{1}Н ЯМР-спектрометрии, УФ-спектрофотометрии и хромато-масс-спектрометрии. Проведённое предварительное компьютерное исследование острой токсичности и биологической активности. Установлено, что полученные соединения могут проявлять диуретические и аналептические активности, а фрагмент 1,2,4-триазола теоретически может усиливать эту активность. Предварительное прогнозирование острой токсичности показало, что соединения относятся к малотоксичным.

Ключевые слова: *1,2,4-триазол, теофиллин, синтез, ИК-спектрометрия, [1]Н ЯМР-спектрометрия.*

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1,2,4-Triazole derivatives are successfully used in medicine as antibacterial and antifungal agents. The combination of analeptic and diuretic effect of theophylline and triazole fragment may give unexpected results. Moreover, it is known that mesomeric effect manifestation, occurring in carbonyl group, shifts the electron density in the molecule. Therefore these derivatives spark the interest of scientific community. It is possible that carbonyl group contributes activity of transporting the agent through tissue. The manifestation of mesomeric effect in the carbonyl group provides great opportunity for the chemical molecule modification. In particular, ketones are featured by the reaction of reduction in H^+-ion excess and the reaction of hydrazinolysis thus creates a large amount of space for further research.

The goal

Synthesis, physical-chemical and predictive biological research of 7-((3-thio-4R-4*H*-1,2,4-triazole-5-yl)methyl)theophylline carbonyl derivatives.

Materials and methods

The study of physical-chemical properties of the obtained compounds has been carried out using methods listed in the State Pharmacopoeia of Ukraine. The melting point has been determined using capillary method on Stanford Research Systems Melting Point Apparatus 100, America. The structure of the compounds has been 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: API-ES; 6) scanning range m/z: 160-1000; 7) fragmentor: 10V; 8) positive polarity; 9) nitrogen temperature – 300 ˚C; 10) Nebulizer pressure 40 psig; 11) the rate of drying gas (nitrogen) - 10 l/min.

Mass spectra of the synthesized compounds are taken on Varian MAT-311A (Varian, Inc., USA) with direct induction of the sample in the ion source. Shooting conditions: accelerating voltage of 3 kV, a emission cathode current of 300 mA, toning voltage of 70 eV.

The sodium salt of theophylline, n-propyl ester of theophylline-7-acetic acid, hydrazide of theophylline-7-acetic acid and 2-(2-theophylline-7-yl)acetyl-N-methylhydrazide-carbothioamide has been obtained by the method described previously [1]. 2-(2-theophylline-7-yl)acetyl)-N-ethylhydrazide-carbothioamide, 2-(2-theophylline-7-yl)acetyl)-N-phenylhydrazinecarbothioamide, and 7-((3-thio-4-R-4*H*-1,2,4-triazole-5-yl) methyl)-theophylline have been also obtained.

1,3-Dimethyl-7-((5-(2-R1)-4-phenyl-4H-1,2,4-triazole-3-yl) methyl)-1H-purine-2,6(3H,7H)-dione (*table 1, 2*, compounds 1, 6, 11; 2, 7, 12)

0.01 mole sample of 7-((3-thio-4-R-4*H*-1,2,4-triazole-5-yl) methyl)theophylline (R = CH_3, C_2H_5, C_6H_5) is added to 0.01 mole aqueous solution of sodium hydroxide. Bromacetone/2-bromo-1-phenylethanone (R = oxopropylthio, oxo-2-phenylthio) in methanol is added to the resulting solution in equimolar amount. The solution was boiled up till pH = 6 - 8. Then it is cooled and the resulting precipitate is filtered, and washed well with water and dried completely to get white to yellow solid as desire compound. A mixture of methanol-water (3:1) is then recrystallized. Soluble in alcohol and DMF (*fig. 1*).

^{1}H NMR (DMSO-*d6*, 400 MHz), δ/ppm: *compound 1* – 2.23 (s, 2H, -CH_2C(O)), 3.19 (s, 3H, -N^3CH_3), 3.35 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.85 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH); *compound 6* – 2.23 (s, 2H, -CH_2C(O)), 3.19 (s, 3H, -N^3CH_3), 3.35 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.72 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH); *compound 11* – 2.35 (s, 2H, -CH_2C(O)), 3.21 (s, 3H, -N^3CH_3), 3.31 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.65 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH); *compound 2* – 2.23 (s, 2H, -CH_2C(O)), 3.19 (s, 3H, -N^3CH_3), 3.35 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.85 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH); *compound 7* – 2.23 (s, 2H, -CH_2C(O)), 3.19 (s, 3H, -N^3CH_3), 3.35 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.72 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH); *compound 12* – 2.35 (s, 2H, -CH_2C(O)), 3.21 (s, 3H, -N^3CH_3), 3.31 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.65 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH).

7-((5-(2-(4-R_1)-2-oxoethylthio)-4-R-4H-1,2,4-triazole-3-yl) methyl)-1,3-dimethyl-1H-purine-2,6 (3H, 7H)-dione (table 1,2, compounds 3, 8, 13; 4, 9, 14)

0.01 mole sample of 7-((3-thio-4-R-4*H*-1,2,4-triazole-5-yl) methyl) theophylline (R = CH_3, C_2H_5, C_6H_5) is added to the 0.01 mole aqueous solution of sodium hydroxide. 2-bromo-1-(4-R_1) ethanone (R_1 = fluorophenyl, methoxyphenyl) in methanol is added to the resulting solution in equimolar amount. The solution was boiled up till pH = 6-8. Then it is cooled and the resulting precipitate is filtered, and washed well with water and dried completely to get white to yellow solid as desire compound. A mixture of methanol-water (3:1) is then recrystallized. Soluble in alcohol and DMF (fig.1).

^{1}H NMR (DMSO-*d6*, 400 MHz), δ/ppm: *compound 3* – 2.23 (s, 2H, -CH_2C(O)), 3.19 (s, 3H, -N^3CH_3), 3.35 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.85 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH); *compound 8* – 2.23 (s, 2H, -CH_2C(O)), 3.19 (s, 3H, -N^3CH_3), 3.35 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.72 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH); *compound 13* – 2.35 (s, 2H, -CH_2C(O)), 3.21 (s, 3H, -N^3CH_3), 3.31 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.65 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH). *compound 4* – 2.23 (s, 2H, -CH_2C(O)), 3.19 (s, 3H, -N^3CH_3), 3.35 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.85 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH); *compound 9* – 2.23 (s, 2H, -CH_2C(O)), 3.19 (s, 3H, -N^3CH_3), 3.35 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.85 (c, 2H, -CH_2), 6.98 – 8,06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH); *compound 14* – 2.23 (s, 2H, -CH_2C(O)), 3.19 (s, 3H, -N^3CH_3), 3.35 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.85 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH).

7-((4-R-5-(2-oxo-2-(thiophene-2-yl)thioethyl)-4H-1,2,4-triazole-3-yl)methyl)-1,3-dimethyl-1H-purine-2,6(3H, 7H)-dione (table 1, 2, compounds 5, 10, 15)

0.01 mole sample of 7-((3-thio-4-R-4*H*-1,2,4-triazole-5-yl) methyl)theophylline (R = CH_3, C_2H_5, C_6H_5) is added to 0.01 mole aqueous solution of sodium hydroxide. 2-bromo-1-(thiophene-2-yl)-ethanone in methanol is added to the resulting solution in equimolar amount. The solution was boiled up till pH = 6-8. Then it is cooled and the resulting precipitate is filtered, and washed well with water and dried completely to get white to yellow solid as desire compound. A mixture of methanol-water (3:1) is then recrystallized. Soluble in alcohol and DMF (fig/ 1).

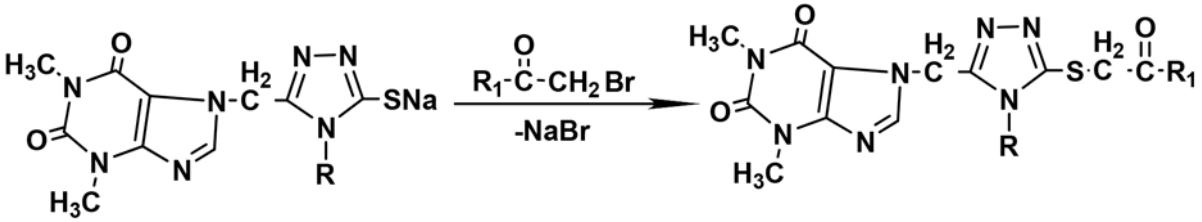
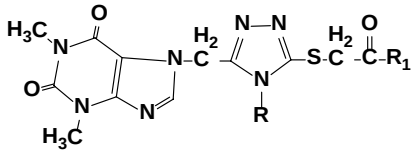


Fig 1. Synthesis of 7-((3-thio-4R-4*H*-1,2,4-triazole-5-yl)-methyl)theophylline carbonyl derivatives.

Table 1

Physical-chemical properties of the synthesized compounds



#	R	R_1	M. p. °C	Yield, %	Empirical formula
1	2	3	4	5	6
1	CH_3	CH_3	332-336 °C	86%	$C_{14}H_{17}N_7O_3S$
2	CH_3	C_6H_5	194-195 °C	83%	$C_{19}H_{19}N_7O_3S$
3	CH_3	C_6H_4–4-F	250-254 °C	94%	$C_{19}H_{18}FN_7O_3S$
4	CH_3	C_6H_4–4-OCH_3	179-181 °C	89%	$C_{20}H_{21}N_7O_4S$
5	CH_3	thiophen	181-183 °C	86%	$C_{17}H_{17}N_7O_3S_2$
6	C_2H_5	CH_3	258-261 °C	91%	$C_{15}H_{19}N_7O_3S$
7	C_2H_5	C_6H_5	164-166 °C	96%	$C_{20}H_{21}N_7O_3S$
8	C_2H_5	C_6H_4–F	156-158 °C	94%	$C_{20}H_{20}FN_7O_3S$
9	C_2H_5	C_6H_4–4-OCH_3	160-162 °C	85%	$C_{21}H_{23}N_7O_4S$
10	C_2H_5	thiophen	191-193 °C	93%	$C_{18}H_{19}N_7O_3S_2$
11	C_6H_5	CH_3	133-135 °C	92%	$C_{19}H_{19}N_7O_3S$
12	C_6H_5	C_6H_5	192-196 °C	87%	$C_{24}H_{21}N_7O_3S$
13	C_6H_5	C_6H_4–4-F	139-141 °C	90%	$C_{24}H_{20}FN_7O_3S$
14	C_6H_5	C_6H_4–4-OCH_3	204-206 °C	83%	$C_{25}H_{23}N_7O_4S$
15	C_6H_5	thiophen	165-167 °C	89%	$C_{22}H_{19}N_7O_3S_2$

Table 2

Elementary analysis

№ п/п	Estimated, %				Found, %			
	C	H	N	S	C	H	N	S
1	46.27	4.72	26.98	8.82	46.15	4.73	26.91	8.83
2	53.64	4.50	23.04	7.54	53.52	4.49	23.10	7.53
3	51.46	4.09	22.11	7.23	51.35	4.10	22.15	7.24
4	52.74	4.65	21.53	7.04	52.59	4.66	21.47	7.05
5	47.32	3.97	22.72	14.86	47.40	3.97	22.76	14.90
6	47.73	5.07	25.98	8.5	47.65	5.06	26.02	8.49
7	54.66	4.82	22.31	7.30	54.76	4.83	22.35	7.31
8	52.51	4.41	21.43	7.01	52.40	4.42	21.37	4.43
9	53.72	4.94	20.88	6.83	53.85	4.93	20.92	6.82
10	48.53	4.30	22.01	14.39	48.41	4.31	21.60	4.32
11	53.64	4.50	23.04	7.54	53.71	4.49	22.99	7.55
12	59.13	4.34	20.11	6.58	59.04	4.33	20.06	6.59
13	57.02	3.99	19.40	6.34	26.96	3.98	19.44	3.97
14	58.02	4.48	18.94	6.20	58.11	4.49	18.96	4.48
15	53.54	3.88	19.87	12.99	53.68	3.89	19.89	3.90

^{1}H NMR (DMSO-d_6, 400 MHz), δ/ppm: *compound 5* – 2.23 (s, 2H, -CH_2C(O)), 3.19 (s, 3H, -N^3CH_3), 3.35 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.85 (s, 2H, -CH_2), 6,98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH); *compound 10* – 2.23 (s, 2H, -CH_2C(O)), 3.19 (s, 3H, -N^3CH_3), 3.35 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.72 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH); *compound 15* – 2.35 (s, 2H, -CH_2C(O)), 3.21 (s, 3H, -N^3CH_3), 3.31 (s, 3H, -N^1CH_3), 3.43 (t, 3H, -$N^{4'}CH_3$), 4.65 (s, 2H, -CH_2), 6.98 – 8.06 (m, 8H, Ar-H), 8.44 (s, 1H, =CH).

Results and Conclusions

The first stage defines the optimal conditions of ketone bromating (acetone, acetophenone, 4-methoxyacetophenone, 4-fluoroacetophenone, 1-thiophene-2-yl-ethanone) [8,9]. The next step is the reaction of resulting thiol and brominated ketone.

The row of various signals is observed in the ^{1}H NMR spectra of the resulting compounds. In the part of a strong magnetic field the signals of –CH_2-group are recorded in a singlet in the range at 4.85 – 4.65 ppm. Proton signals of –CH_3 groups of xanthine synthon are manifested with intense singlet in the range at 3.35 – 3.19 ppm (corresponding to N^1CH_3 and N^3CH_3). Methoxy group proton signals are recorded in the form of intense singlet at 3.81 ppm. –CH_3 radical of triazole synthon in fourth position is confirmed with intense triplet at 3.43 ppm. The presence of C_2H_5-radical is confirmed by proton triplet of CH_3– group at 1.25 – 1.30 ppm and quadruplet protons and –CH_2-fragment at 4.08 ppm. Aromatic protons C_6H_4-4-OCH_3 and C_6H_4-4-F

fragments form a multiplet in the range at 7.46–6.98 ppm and 8.06–7.27 ppm respectively. Proton of – CH-group of imidazole fragment is featured by a signal at 8.44 ppm. The chemical shift of methylene protons due to the ketone carbonyl occurs in the region of 2.15–2.23 ppm.

In the IR spectra of S-ethanones 7-((3-thio-4-R-4*H*-1,2,4-triazole-5-yl)methyl)-theophylline one can observe specific absorption bands of C=N and C=C groups at 1614–1580 and 1518–1474 cm^{-1}, stretching vibrations of aromatic CH-fragment 3095–3028 cm^{-1} and CF-fragment at 1143 cm^{-1}. Stretching vibration of ketone carbonyl is strongly marked in the range at 1682–1672 cm^{-1} and aromatic OCH_3-group 2825 cm^{-1}.

S-CH_2-fragment is directly linked to the carbonyl group as it causes deformation vibrations at 1425–1410 cm^{-1}.

A specific pattern has been found according to the results of previous studies of acute toxicity. Toxicity of ketones with acetophenone, 4-fluoro-4-acetophenone or methoxy acetophenone fragment in their structure, was increased depending on R, a number of C_6H_5 – CH_3 – C_2H_5. Toxicity of ketones with a piece of acetone or 1-thiophene-2-yl-ethanone was increased, depending on R, a number of CH_3 – C_6H_5 – C_2H_5. The lowest toxicity in the study belongs to ketone #12 (1992 mg / kg), and the highest toxicity belongs to ketone #10 (723.9 mg / kg). Acute toxicity was calculated for oral administration. According to Sidorov's classification the compounds can be classified as low-toxic and mildly toxic which makes it reasonable to use it in further research.

Summary

The optimum reaction conditions of 7-((3-thio-4R-4*H*-1,2,4-triazole-5-yl) methyl)theophylline and electrophilic reagents – aliphatic, aromatic and heterocyclic α-bromoketones have been studied. A mass spectrometric-chromatographic research of the synthesized compounds has been carried out whereas their structure has been confirmed using ^{1}H NMR and IR spectroscopy.

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