Synthesis and physical-chemical properties of (3-benzyl-8-propylxanthin-7-yl)acetohydrazide derivatives and their evaluation for antimicrobial and diuretic activities

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

One of the most important tasks of our indigenous pharmaceutical science is the necessity for new medicines because existing drugs are characterized by various side effects, resistance, high toxicity, and so on. New bioactive molecule synthesis utilizes substances of natural origin as well as chemically modified ones. Thus, the researcher's attention is mainly focused on 3-,7-,8-substituted derivatives of the natural heterocyclic xanthine system, which possess a wide range of pharmacological action. Synthesis of a novel of (3-benzyl-8-propylxanthin-7-yl)acetohydrazides with antimicrobial and diuretic activities described in the paper.

The aim of this work is to develop efficient methods for synthesis of (3-benzyl-8-propylxanthin-7-yl)acetohydrazide derivatives, and to study their physical-chemical properties.

Materials and methods. Two-hour boiling of propyl 2-(3-benzyl-8-propylxanthine-7-yl)acetate by excess hydrazine hydrate in propan-2-ol medium have yielded the key the key intermediate 2-(3-benzyl-8-propylxanthine-7-yl)acetohydrazide. Further transformation of the latter has led to formation of corresponding acetohydrazide derivatives achieved by the reaction with aliphatic, aromatic, heterocyclic aldehydes, and ketones. The structure and the relative configuration of the synthesized compounds were elucidated by analyzing their physical-chemical data.

Results. The synthesis and optimization of reaction conditions of (3-benzyl-8-propylxanthin-7-yl)acetohydrazide derivatives were conducted. The identification of all synthesized compounds was aided by various physical-chemical methods (thin layer chromatography, elemental analysis, IR, and ^{1}H NMR spectroscopy).

Conclusions. As a result of synthetic research the preparative synthesis method of (3-benzyl-8-propylxanthin-7-yl)acetohydrazide derivatives possessing antimicrobic, and diuretic activities was developed.

Key words: 3-benzylxanthine, acetohydrazide, physicochemical properties.

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Синтез і фізико-хімічні властивості іліденпохідних гідразиду 3-бензил-8-пропілксантиніл-7-ацетатної кислоти, що мають протимікробні та діуретичні властивості

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Створення нових лікарських препаратів – одне з найважливіших завдань вітчизняної фармацевтичної науки. Це зумовлено наявністю у препаратів небажаних побічних ефектів, набуттям резистентності, високою токсичністю тощо. Для створення біоактивних молекул застосовують і речовини природного походження, і нові синтезовані сполуки та продукти їхньої хімічної модифікації. У цьому аспекті увагу дослідників привертають 3-,7-,8-заміщені похідні природної гетероциклічної системи ксантину, що мають широкий спектр фармакологічної дії. Наведено синтез неописаних у фаховій літературі іліденгідразидів 3-бензил-8-пропілксантин-7-іл ацетатної кислоти, які характеризуються протимікробними та діуретичними властивостями.

Мета роботи – розроблення методів одержання іліденпохідних 3-бензил-8-пропілксантиніл-7-ацетатної кислоти та вивчення фізико-хімічних властивостей цих сполук.

Матеріали та методи. Як вихідну сполуку використали гідразид 3-бензил-8-пропілксантиніл-7-ацетатної кислоти, одержаний раніше двогодинним кип'ятінням н-пропілового естеру 3-бензил-8-пропілксантиніл-7-ацетатної кислоти з надлишком гідразин гідрату в середовищі пропан-2-олу. Надалі вивчили реакцію гідразиду 3-бензил-8-пропілксантиніл-7-ацетатної кислоти з аліфатичними, ароматичними, гетероциклічними альдегідами та кетонами, в результаті отримали відповідні іліденпохідні. Будова та індивідуальність синтезованих сполук підтверджена комплексом фізико-хімічних досліджень.

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Key words: 3-benzylxanthine, acetohydrazide, physicochemical properties.

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Результати. Здійснили синтез і визначили оптимальні умови перебігу реакцій одержання іліденпохідних 3-бензил-8-пропілксантиніл-7-ацетатної кислоти. За допомогою фізико-хімічних методів дослідження (хроматографія в тонкому шарі сорбенту, елементний аналіз, ІЧ- та ^{1}Н ЯМР-спектроскопія) встановили структуру та індивідуальність нових синтезованих сполук.

Висновки. У результаті синтетичного дослідження опрацювали препаративну методику синтезу іліденгідразидів 3-бензил-8-пропілксантиніл-7-ацетатної кислоти, які мають протимікробні та діуретичні властивості.

Ключові слова: 3-бензилксантин, іліденгідразиди, фізико-хімічні властивості.

Актуальні питання фармацевтичної і медичної науки та практики. 2021. Т. 14, № 1(35). С. 17–22

Синтез и физико-химические свойства илиденпроизводных гидразида 3-бензил-8-пропилксантинил-7-ацетатной кислоты, которые проявляют противомикробные и диуретические свойства

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Создание новых лекарственных препаратов – одна из важнейших задач отечественной фармацевтической науки. Это объясняется наличием у существующих препаратов нежелательных побочных эффектов, приобретением резистентности, высокой токсичностью и т. д. Для создания биоактивных молекул применяются и вещества природного происхождения, и новосинтезированные соединения и продукты их химической модификации. В этом плане внимание исследователей привлекают 3,7,8-замещенные производные природной гетероциклической системы ксантина, проявляющие широкий спектр фармакологической активности. Представлен синтез неописанных в специализированной литературе илиденгидразидов 3-бензил-8-пропилксантинил-7-ацетатной кислоты, которые проявляют противомикробную и диуретическую активности.

Цель работы – разработка методов получения илиденпроизводных 3-бензил-8-пропилксантинил-7-ацетатной кислоты и изучение физико-химических свойств этих соединений.

Материалы и методы. В качестве исходного соединения использован гидразид 3-бензил-8-пропилксантинил-7-ацетатной кислоты, полученный ранее двухчасовым кипячением н-пропилового эфира 3-бензил-8-пропилксантинил-7-ацетатной кислоты с избытком гидразингидрата в среде пропанола-2. В дальнейшем изучена реакция гидразида 3-бензил-8-пропилксантинил-7-ацетатной кислоты с алифатическими, ароматическими, гетероциклическими альдегидами и кетонами, в результате которой получены соответствующие илиденпроизводные. Строение и индивидуальность синтезированных соединений подтверждена комплексом физико-химических исследований.

Результаты. Осуществлен синтез и определены оптимальные условия протекания реакций получения илиденпроизводных 3-бензил-8-пропилксантинил-7-ацетатной кислоты. С помощью физико-химических методов исследования (хроматография в тонком слое сорбента, элементный анализ, ИК и ^{1}Н ЯМР-спектроскопия) установлены структура и индивидуальность новосинтезированных соединений.

Выводы. В результате синтетического исследования разработана препаративная методика синтеза илиденгидразидов 3-бензил-8-пропилксантинил-7-ацетатной кислоты, которые проявляют противомикробную и диуретическую активности.

Ключевые слова: 3-бензилксантин, илиденгидразиды, физико-химические свойства.

Актуальные вопросы фармацевтической и медицинской науки и практики. 2021. Т. 14, № 1(35). С. 17–22

In recent years, xanthine derivatives have attracted researchers' attention not only by their frequent occurrence in nature but also by their diverse pharmacological activities [1–5].

Xanthines, as important members of the purine family, are considered as key intermediates in the metabolism of nucleobases, because metabolic interconversions of adenine and guanine result in their formation [6,7]. In addition, xanthine, and its derivatives act as precursors in the synthesis of GMP, GDP, and GTP through the salvage pathways within cells [8]. Due to the aforementioned reasons, it is important to explore the use of xanthine derivatives in developing novel synthetic methods. Our interest is in finding effective acetohydrazides of (3-R-xanthine-7(8)-yl)alkanoic acids, and their structural analogs, because such compounds have been reported in the literature by their diverse biological activities.

Aim

Considering the abovementioned evidence, we made endeavors to synthesize a set of novel (3-benzyl-8-propylxanthin-7-yl) acetohydrazide derivatives and to study their physical-chemical properties.

Materials and methods

Unless otherwise indicated, reagents and solvents were purchased from commercial suppliers and used without further purification.

The starting material of (3-benzyl-8-propylxanthin-7-yl) acetohydrazide (1) was synthesized by boiling of n-propyl ester with hydrazine hydrate excess in propan-2-ol medium (*Fig. 1*).

The procedure for the synthesis of (3-benzyl-8-propylxanthin-7-yl)acetohydrazide (1). A suspension of 3.84 g (0.01 mol) of propyl 2-(3-benzyl-2,6-dioxo-8-propyl-1,2,3,6-tetrahydro-7H-purin-7-yl)acetate was boiled under reflux in 30 ml of propan-2-ol. This mixture was heated for 15 min to form a clear solution. Then 5 ml of hydrazine hydrate was added and boiled for 45 minutes. After cooling the mixture to room temperature, the solution was poured into 100 ml of water. The precipitate was filtered, washed with water, and dried at 80–85 °C. Yield 87 %.

The chemical structure of (3-benzyl-8-propylxanthin-7-yl) acetohydrazide (1) was determined by ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum was revealed the appearance of a downfield singlet at δ 11.16 ppm, which confirms the uracil

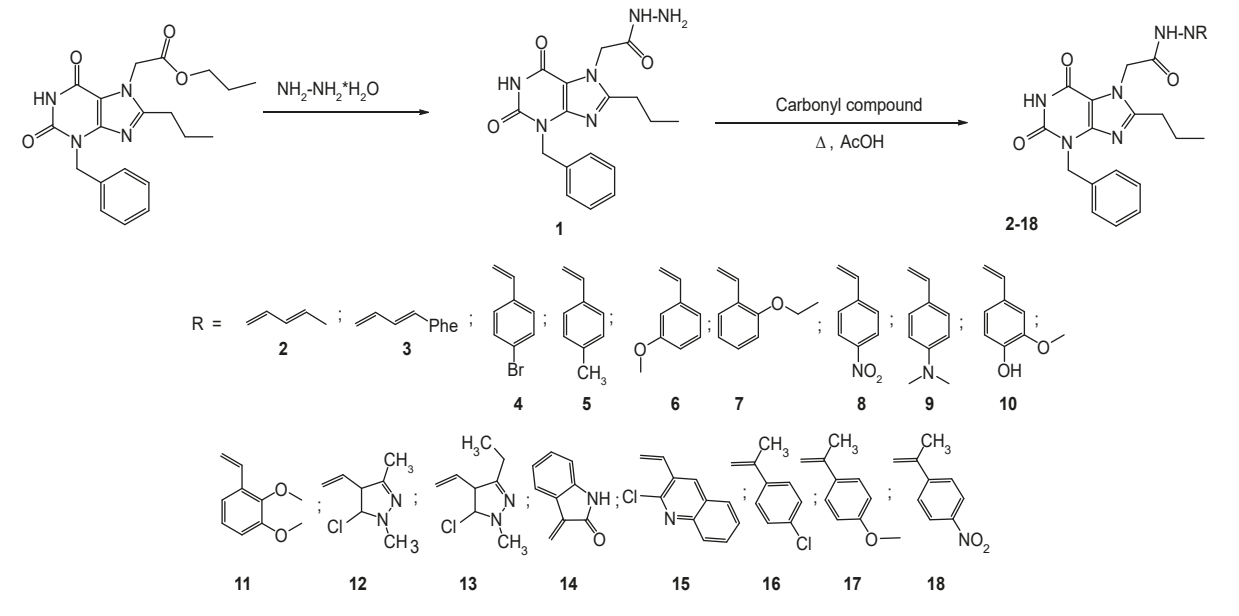

Fig. 1. Synthesis of (3-benzyl-8-propylxanthin-7-yl)acetohydrazide and its derivatives (**1–18**).

core of the investigated molecule. Broad singlet signal at δ 9.34 ppm was represented NH-group of hydrazide residue, whereas broad signal assigned for two protons of NH_2-group at δ 4.50–4.32 ppm. Signals of aromatic protons, methylene and methyl groups were recorded without anomalies in intensities, chemical shifts and cleavage at δ 7.27–7.10 ppm (m, 5H, Ar-H); 5.08 ppm (s, 2H, N^3CH_2); 4.98 ppm (s, 2H. N^7CH_2); 2.59 ppm (t, 2H, J = 7.41 *Hz*, C^8CH_2); 1,62 ppm (m, 2H, J = 7.42 *Hz*, C^8C-CH_2); 0,89 ppm (t, 3H, J = 7.38 *Hz*, C^8C-C-CH_3).

Thereafter, the reaction of (3-benzyl-8-propylxanthin-7-yl)-acetohydrazide (1) with aliphatic, aromatic, heterocyclic carbonyl compounds was studied and the corresponding acetohydrazide derivatives **(2–18)** were obtained. The interaction of equimolar amounts of reactants was preceded in boiling water-dioxane medium for 30–40 minutes with acetic acid as a catalyst (*Fig. 1*).

The study of physical-chemical properties of the synthesized compounds was performed according to the State Pharmacopoeia of Ukraine (ed. 1). The melting point was determined by capillary method (2.2.14) on the PTP(M) device.

Infrared spectra were recorded on a Bruker Alpha (Bruker, Germany) in 4000–400 cm^{-1} with ATR (direct material input). ^{1}H-NMR spectra were recorded on Varian Mercury VX-200 spectrometer (Varian, USA) in DMSO-d_6 with TMS as an internal standard. Elemental analysis was performed on a Elementar Vario L cube analyzer (Elementar Analysensysteme, Germany). Binary mobile phase of benzene and propan-2-ol in 10 : 1 and 1 : 10 was used for chromatography. Chromatographic spots were visualized by UV light (200–300 nm).

Results

Synthesis (3-benzyl-8-propylxanthin-7-yl)acetohydrazide and its derivatives (**1–18**) showed in *Fig. 1*.

General procedure for the synthesis of (3-benzyl-8-propylxanthin-7-yl)acetohydrazide derivatives (2–18). To a solution of 3.56 g (0.01 mol) of 1 in 70 ml of aqueous dioxane (1:1) and heated to 50 °C was added 1 ml of glacial acetic acid and 0.011 mol of the corresponding aldehyde or ketone. The mixture was heated under a reflux condenser for 15–25 minutes. After cooling, the resulting product was precipitated. The crude product was filtered, washed with water, and dried at 80–85 °C.

Compounds **2–18** were pale-yellow, yellow or orange amorphous substances, insoluble in water, ethanol, diethyl ether, acetone, and soluble in DMF.

The structure of the synthesized compounds was confirmed by elemental analysis data (*Table 1*), and by IR- and ^{1}H NMR spectroscopy (*Tables 2, 3*).

In the IR spectra of compounds **2–18** (*Table 2*): υ_{max} (KBr, cm^{-1}): 3620–3600 (N–H stretching), 2989–2887 (al. C–H asymmetrical and symmetrical stretching), 1729–1677, 1670–1630, 1597–1570 (C=O, C=N, C=C stretching).

The ^{1}H NMR spectra of compounds **2–18** (*Table 3*) showed absence of the NH_2-group protons of the hydrazide residue, and NH-groups signal of the ylidene hydrazide residue was appeared as downfield singlet at δ 12.08–11.08 ppm. Signals of protons of methylidene groups were appeared as singlet at δ 8.61–7.85 ppm, protons of benzyl, propyl residue and uracil fragment of the molecule were recorded with the appropriate intensity and characteristic chemical shift.

Thus, ^{1}H NMR spectrum 2-(3-benzyl-8-propylxanthin-7-yl)-*N'*-[4-bromobenzyliden]acetohydrazide **(4)** was revealed the appearance of three proton singlets of NH groups: a substituent in the 7-position of the xanthine bicycle (11.82 ppm) and uracil fragment (11.08 ppm) and N = CH (7.98 ppm). Aromatic protons of the 4-bromobenzylidene moiety

Table 1. Physical-chemical characteristics of (3-benzyl-8-propylxanthin-7-yl)acetohydrazide derivatives **(2–18)**

Comp.	Mp. °C	R_f	Anal. calcd. %			Formula	Found. %			Yield. %
			C	H	N		C	H	N	
1	3	4	5	6	7	8	9	10	11	12
2	237–239	0.78	61.71	5.91	2.54	$C_{21}H_{24}N_6O_3$	61.75	5.95	2.58	80
3	222–225	0.80	66.34	5.54	17.82	$C_{26}H_{26}N_6O_3$	66.37	5.57	17.86	82
4	276–279	0.56	55.04	4.39	16.02	$C_{24}H_{23}BrN_6O_3$	55.08	4.43	16.06	83
5	240–242	0.54	65.45	5.68	18.29	$C_{25}H_{26}N_6O_3$	65.49	5.72	18.33	80
6	233–235	0.63	63.24	5.48	17.67	$C_{25}H_{26}N_6O_4$	63.28	5.52	17.71	82
7	204–206	0.56	63.89	5.74	17.16	$C_{26}H_{28}N_6O_4$	63.92	5.78	17.20	86
8	281–283	0.80	58.85	4.70	19.98	$C_{24}H_{23}N_7O_5$	58.89	4.74	20.03	90
9	292–295	0.68	64.00	5.96	20.7	$C_{26}H_{29}N_7O_3$	64.05	6.00	20.11	85
10	244–246	0.56	61.18	5.30	17.9	$C_{25}H_{26}N_6O_5$	61.22	5.34	17.13	84
11	108–110	0.72	61.85	5.55	16.62	$C_{26}H_{28}N_6O_5$	61.89	5.59	16.66	85
12	267–270	0.64	55.55	5.03	22.51	$C_{23}H_{25}ClN_8O_3$	55.59	5.07	22.55	90
13	261–263	0.58	56.37	5.29	20.89	$C_{24}H_{27}ClN_8O_3$	56.41	5.33	21.93	84
14	255–257	0.68	61.81	4.74	20.16	$C_{25}H_{23}N_7O_4$	61.85	4.78	20.20	80
15	262–264	0.66	61.15	4.52	18.46	$C_{27}H_{24}ClN_7O_3$	61.19	4.56	18.50	82
16	247–249	0.54	60.87	5.7	17.01	$C_{25}H_{25}ClN_6O_3$	60.91	5.11	17.05	86
17	235–238	0.72	63.88	5.74	17.16	$C_{26}H_{28}N_6O_4$	63.92	5.78	17.20	81
18	280–282	0.68	59.59	4.96	19.43	$C_{25}H_{25}N_7O_5$	59.63	5.00	19.47	84

Table 2. IR-spectra of (3-benzyl-8-propylxanthin-7-yl)acetohydrazide derivatives **(2–18)**

Comp.	υ, cm^{-1}					
	NH	Ar-H	C=O	C=N	C=C	Other
2	3320; 3170	3032	1708; 1693	1670	1580	2930
3	3290; 3120	3040	1710; 1680	1640	1592	2920
4	3260; 3150	2987	1720; 1691	1654	1589	2910; 717
5	3250; 3160	3061	1710; 1680	1630	1570	2980; 730
6	3290; 3130	3047	1719; 1700	1642	1576	2967
7	3250; 3120	3010	1700; 1690	1667	1584	2887
8	3280; 3160	3030	1700; 1679	1660	1592	2960; 1251
9	3260; 3130	2997	1703; 1689	1642	1583	2910
10	3290; 3150	3020	1700; 1678	1640	1574	3600; 754
11	3310; 3150	3035	1723; 1680	1655	1595	2989; 715
12	3260; 3110	3020	1710; 1696	1633	1580	2971; 788
13	3270; 3140	3010	1720; 1690	1670	1590	2950
14	3260; 3139	3033	1700; 1680	1660	1560	2940
15	3260; 3109	3080	1713; 1679	1658	1597	2987
16	3270; 3150	3030	1715; 1679	1666	1574	2910
17	3300; 3180	3050	1720; 1680	1660	1590	2980
18	3250; 3140	3020	1710; 1692	1649	1587	3610

Table 3. ^{1}H NMR-spectra of (3-benzyl-8-propylxanthin-7-yl)acetohydrazide derivatives (**2–18**)

Comp.	δ. ppm						
	CONH (s, 1H)	N^{1}H (s, 1H)	N=CH (s, 1H)	Ar-H	CH_2	CH_3	Others
2	11.71	11.17	7.89	7.35–7.18 (m, 5H)	5.46 (s, 2H); 5.11 (s, 2H); 2.71–2.58 (t, 2H J = 7.46 *Hz*); 1.76–1.61(m, 2H J = 7.44 *Hz*)	1.86 (d, 3H J = 7.32 *Hz*) 0.92 (t, 3H J = 7.42 *Hz*)	–
3	11.67	11.19	7.86	7.62–7.49 (m, 3H); 7.46–7.14 (m, 5H); 7.04-6.96 (d, 2H)	5.48 (s, 2H); 5.09 (s, 2H); 2.69–2.59 (t, 2H J = 7.36 *Hz*); 1.74–1.60(m, 2H J = 7.35 *Hz*)	0.91 (t, 3H J = 7.33 *Hz*)	7.09 (d, 1H) – CH; 6.85 (d, 1H) – CH
4	11.82	11.08	7.98	7.71–7.61 (m, 4H); 7.27–7.19 (m, 5H)	5.48 (s, 2H); 5.06 (s, 2H); 2.67–2.58 (t, 2H J = 7.44 *Hz*); 1.74–1.58(m, 2H J = 7.41 *Hz*)	0.92 (t, 3H J = 7.42 *Hz*)	–
5	11.81	11.12	7.99	7.80–7.67 (m, 2H); 7.37–7.18 (m, 7H)	5.49 (s, 2H); 5.07 (s, 2H); 2.66–2.56 (t, 2H J = 7.37 *Hz*); 1.72–1.59(m, 2H J = 7.36 *Hz*)	2.43 (s, 3H); 0.91 (t, 3H J = 7.32 *Hz*)	–
6	11.66	11.08	8.35	7.44–7.24 (m, 6H); 7.11–6.92 (m, 3H)	5.44 (s, 2H); 5.06 (s, 2H); 2.67–2.55 (t, 2H J = 7.35 *Hz*); 1.69–1.56(m, 2H J = 7.34 *Hz*)	0.91 (t, 3H J = 7.38 *Hz*)	3.84 (s, 3H) – OCH_3
7	11.68	11.09	8.37	7.40–7.21 (m, 6H); 7.09–6.88 (m, 3H)	5.45 (s, 2H); 5.08 (s, 2H); 2.68–2.55 (t, 2H J = 7.36 *Hz*); 1.68–1.55(m, 2H J = 7.38 *Hz*)	0.92 (t, 3H J = 7.33 *Hz*)	4.07 (q, 2H) – OCH_2 1.32 (t, 3H) – $OCCH_3$
8	12.03	11.12	8.43	8.38–8.19 (d, 2H); 8.02–7.88 (d, 2H); 7.36–7.19 (m, 5H)	5.54 (s, 2H); 5.02 (s, 2H); 2.67–2.59 (t, 2H J = 7.39 *Hz*); 1.73–1.59(m, 2H J = 7.36 *Hz*)	0.90 (t, 3H J = 7.38 *Hz*)	–
9	11.43	11.09	7.85	7.54–7.41 (d, 2H); 7.38–7.19 (m, 5H); 6.76–6.63 (d, 2H)	5.42 (s, 2H); 5.06 (s, 2H); 2.69–2.56 (t, 2H J = 7.43 *Hz*); 1.74–1.58(m, 2H J = 7.39 *Hz*)	0.90 (t, 3H J = 7.37 *Hz*)	2.99-2.87 (s, 6H) – $N\text{-}CH_3$
10	11.56	11.01	7.89	7.38–7.17 (m, 5H); 6.82–6.75 (m, 3H)	5.44 (s, 2H); 5.07 (s, 2H); 2.69–2.54 (t, 2H J = 7.36 *Hz*); 1.72–1.60(m, 2H J = 7.36 *Hz*)	0.92 (t, 3H J = 7.36 *Hz*)	3.74 (s, 3H) – OCH_3
11	11.69	11.09	8.30	7.38–7.19 (m, 5H); 7.12–7.03 (m, 3H)	5.47 (s, 2H); 5.06 (s, 2H); 2.66–2.58 (t, 2H J = 7.42 *Hz*); 1.72–1.59(m, 2H J = 7.35 *Hz*)	0.90 (t, 3H J = 7.38 *Hz*)	3.82 (s, 3H) – OCH_3 3.72 (s, 3H) – OCH_3
12	11.67	11.14	7.88	7.42–7.10 (m, 5H)	5.41 (s, 2H); 5.07 (s, 2H); 2.68–2.59 (t, 2H J = 7.36 *Hz*); 1.71–1.59(m, 2H J = 7.34 *Hz*)	3.71 (s, 3H); 0.91 (t, 3H J = 7.32 *Hz*)	2.58 (s, 3H) – $N\text{-}CH_3$
13	11.69	11.11	7.86	7.4–7.16 (m, 5H)	5.43 (s, 2H); 5.05 (s, 2H); 2.67–2.57 (t, 2H J = 7.37 *Hz*); 1.72–1.61(m, 2H J = 7.31 *Hz*)	3.76; (s, 3H); 0.92 (t, 3H J = 7.33 *Hz*)	2.77 (q, 2H) – $N\text{-}CH_2$; 1.15 (3H. т) – $N\text{-}C\text{-}CH_3$
14	11.32	11.14	–	7.61–7.50 (1H. д); 7.48–7.19 (6H. м); 7.17–6.92 (1H. т); 6.91–6.83 (1H. д)	5.37 (s, 2H); 5.09 (s, 2H); 2.66–2.57 (t, 2H J = 7.34 *Hz*); 1.73–1.63(m, 2H J = 7.37 *Hz*)	0.91 (t, 3H J = 7.39 *Hz*)	12.72 (s, 1H) – NH
15	12.08	11.15	8.61	8.45 (s, 1H); 8.1–8.06 (d, 1H); 8.01–7.74 (m, 2H); 7.71–7.54 (d, 1H); 7.39–7.16 (m, 5H)	5.49 (s, 2H); 5.08 (s, 2H); 2.65–2.54 (t, 2H J = 7.36 *Hz*); 1.71–1.61(m, 2H J = 7.33 *Hz*)	0.91 (t, 3H J = 7.32 *Hz*)	–
16	11.87	11.02	–	7.97–7.83 (d, 2H); 7.49–7.41 (d, 2H); 7.37–7.19 (m, 5H)	5.52 (s, 2H); 5.08 (s, 2H); 2.67–2.57 (t, 2H J = 7.44 *Hz*); 1.72–1.61(m, 2H J = 7.42 *Hz*)	2.25 (s,3H); 0.91 (t, 3H J = 7.41 *Hz*)	–
17	11.08	10.86	–	7.81–7.68 (d, 2H); 7.40–7.19 (m, 5H); 6.9–6.91 (d, 2H)	5.51 (s, 2H); 5.09 (s, 2H); 2.67–2.56 (t, 2H J = 7.43 *Hz*); 1.72–1.59(m, 2H J = 7.38 *Hz*)	2.23 (s,3H); 0.91 (t, 3H J = 7.39 *Hz*)	–
18	11.12	10.75	–	7.52–7.46 (d, 2H); 7.41–7.14 (m, 5H); 6.59–6.52 (d, 2H)	5.49 (s, 2H); 5.07 (s, 2H); 2.68–2.57 (t, 2H J = 7.36 *Hz*); 1.72–1.60(m, 2H J = 7.37 *Hz*)	2.26 (s,3H); 0.91 (t, 3H J = 7.31 *Hz*)	–

and the substituent in the third position were resonated as two multiplets at δ 7.71–7.61 ppm (m, 4H) and 7.27–7.19 ppm (m, 5H) respectively. Methylene protons were registered as singlets for substituents in positions 7 (5.48 ppm s, 2H) and 3 (5.06 ppm, s, 2H) of xanthine moiety, and triplet (2.67–2.58 ppm, t, 2H) and multiplet (1.74–1.58 ppm, m, 2H) for the propyl radical at C8. The presence of the CH_3 group was confirmed by a three-proton triplet at 0.92 ppm (s, 3H).

Discussion

Biological activity of synthesized (3-benzyl-8-propylxanthin-7-yl)acetohydrazide derivatives was predicted by using PASS software [9]. All the compounds showed a good probability of antimicrobial activity (compounds **4–6**, **8–10**, **14**), which makes a good foundation for the in-depth investigation for compounds with high antimicrobial activity. The results of the study of antibacterial and fungicidal activities were described in our previous work [10].

The reason for an in-depth study of the diuretic activity of the synthesized compounds was based on a molecular docking investigation. Interaction of (3-benzyl-8-propylxanthin-7-yl) acetohydrazide (**1**) and its derivatives (**2–5**, **7–9**, **12–14**, **16**, **17**) with the A_1 adenosine receptor has resulted in high affinity values. This result confirms the trend discovered in earlier *in vitro* study of diuretic activity of the compound **1** [11]. In conclusion, derivatives of (3-benzyl-8-propylxanthin-7-yl)acetohydrazide could be a promising starting material for further structural optimization to obtain new and more potent diuretic agents [12].

Conclusions

1. Preparative methods for the synthesis of the novel (3-benzyl-8-propylxanthin-7-yl)acetohydrazide and its derivatives have been developed.

2. The structures of the synthesized compounds was confirmed by various physical-chemical methods.

3. Within the investigated substances we identified compounds displayed good antimicrobial and diuretic activity.

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