SYNTHESIS, PHYSICAL, CHEMICAL AND BIOLOGICAL PROPERTIES OF 8-AMINO-7-[2-HYDROXY-3-(3,4-DIMETHYLPHENOXY)PROPYL]-3-METHYLXANTINES

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ABSTRACT

The problem of searching for biologically active compounds amidst xanthine derivatives is a crucial one and an issue for long-term investigation. Aiming to enlarge the chemical library of prospective bioactive compounds, we obtained a range of previously undescribed 8-amino derivatives of 7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl-1-]3-methylxanthine.

8-bromo-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl-1-]3-methylxanthine and its chemical modification were the object of the study. PTP-M device, Elementar Vario L cube, Bruker SF-400 were used to confirm the structure of synthesized compounds. The biological effects of synthesized compounds were predicted by the Prediction of Activity Spectra for Substances (PASS) program. Antioxidant activity was determined by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method.

In order to search for new biologically active compounds among xanthine derivatives, an 8-amino-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl]-3-methylxantines, never described before, was synthesized. The study of the reactions of 8-bromo-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl-1-]3-methylxanthine with primary, secondary and heterocyclic amines has shown that the substitution of the bromine atom in a position 8 by the amine residue occurs by heating the reagents in aqueous dioxane or ethanol. The structure of the synthesized compounds has been proved with certainty by elemental analysis and nuclear magnetic resonance (NMR) spectroscopy. The antioxidant activity of the obtained compounds has been explored. The priorities for further search of biologically active compounds in a range of xanthine derivatives have been set out.

Keywords: *synthesis, xanthine derivatives, NMR-spectroscopy, antioxidant activity*

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INTRODUCTION

It is well known that the most promising direction for the creation of new synthetic drugs is the structural modification of the known drugs of natural origin. The xanthine derivatives play a special part in this regard since a great number of effective drugs (diprophyllinum, etofylline, theofibrate, trental, etc.) has been created [1]. Earlier studies [2-6] indicate that various 8-substitutes of 7-(2-hydroxy-

3-ariloxypropyl)xanthine have low toxicity and exhibit distinctive diuretic, analgesic, anti-inflammatory, hypocholesterolemic activity. It was reported in the papers [7-10] that 8-amino-7-(2-hydroxy-3-oxypropyl)theophyllines appeared to be promising compounds for creating bronchodilators, anti-inflammatory, anti-anaphylactic and anti-asthmatic agents.

AIM

The aim of this work is to develop unique methods, never described in scientific papers before, to synthesize 8-amino derivatives of 7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl-1-]3-methylxanthine and to study their physical, chemical and biological properties.

MATERIALS AND METHODS

The melting point has been determined with the help of an open capillary method with PTP-M device. Elemental analysis has been performed with the help of the instrument Elementar Vario L cube, nuclear magnetic resonance (NMR) spectra have been measured by a spectrometer Bruker SF-400 [operating frequency of 300 MHz, solvent dimethyl sulfoxide (DMSO), internal standard – tetramethylsilane (TMS)]. These data correspond to the calculated elemental analysis.

Analytical data of synthesized compounds are shown in Table 1 and Table 2.

Synthesis of 8-bromo-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl-1-]3-methylxanthine (2).

A mixture of 49.0 g (0.2 mol) of 8-bromo-3-methylxanthine (1) [11], 39.16 g (0.22 mol) 3,4-dimethylphenoxymethyloxirane, 2 ml N,N-dimethylbenzylamine and 300 ml propanol-1 was boiled for 3 hours. After that, the mixture was cooled, then the sediment was filtered, rinsed in propanol-2, water, 5% ammonia solution, water, propanol-2 and then crystallized from the aqueous dioxane.

Synthesis of 8-amino-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl-1-]3-methylxanthines (3-9, 11-15).

The solution of 3.2 g (7.5 mmol) of bromoalcohol 2, 30 mmol of corresponding amine in a mixture of 20 ml of water and 30 ml of dioxane was boiled for 1 hour. After that, the mixture was cooled, then 100 ml of water were added. The sediment was filtered, rinsed in water and crystallized from the aqueous propanol-2 (3-7, 11, 12, 14, 15) or aqueous dioxane (8, 9, 13).

Table 1. The physicochemical characteristics of synthesized compounds (2-16)

Compound	m.p., °C	The empirical formula	Yield, %
2	224-225	$C_{17}H_{19}BrN_4O_4$	67.8
3	267-268	$C_{19}H_{25}N_5O_4$	86.2
4	210	$C_{20}H_{27}N_5O_4$	86.7
5	209-210	$C_{21}H_{29}N_5O_4$	87.1
6	215	$C_{21}H_{29}N_5O_4$	93.5
7	212-213	$C_{21}H_{29}N_5O_4$	80.6
8	211	$C_{22}H_{31}N_5O_4$	87.5
9	214-215	$C_{22}H_{31}N_5O_4$	90.6
10	176-177	$C_{19}H_{25}N_5O_4$	85.1
11	128-129	$C_{21}H_{29}N_5O_4$	86.6
12	202-203	$C_{21}H_{27}N_5O_4$	79.6
13	192	$C_{22}H_{29}N_5O_4$	80.0
14	196-197	$C_{23}H_{31}N_5O_4$	71.4
15	190-191	$C_{21}H_{27}N_5O_5$	86.7
16	248-249	$C_{17}H_{18}N_4O_4$	87.5 (A) 79.4 (B)

The method of obtaining oxazolinoxanthine 16 is similar – method A. It is crystallized from the aqueous dioxane.

Synthesis of 7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl-1-]8-dimethylamino-3-methylxanthine (10).

The mixture of 3.2 g (7.5 mmol) of bromoalcohol 2, 10 ml of 33 % solution of dimethylamine, 50 ml ethanol was heated for 5 hours in a steel autoclave at 160 °C. After that, the mixture was cooled, then 100 ml of water were added. The sediment was filtered, rinsed in water and crystallized from propanol-2.

Synthesis of 3,4-dimethylphenoxymethyl-8-methyl-2,3-dihydro-1,3-oxazolo[2,3-f]xanthine (16) – method B.

The solution of 4.2 g (10 mmol) of bromoalcohol 2, 4.2 g (40 mmol) triethylamine in 40 ml of dioxane was boiled for 3 hours. Then it was cooled and 200 ml of water were added. The sediment was filtered, rinsed in water and then crystallized from the aqueous dioxane.

Table 2. The values of the chemical shift in NMR-spectra of synthesized compounds (2-16)

	δ-scale, ppm						
	NH (1H)	CH_{arom}	OH (d, 1H)	$N^7CH_2CHCH_2O$	N^3CH_3 (s, 3H)	Ar-CH_3 (s, 3H)	Other signals
2	11.26 (s)	7.0 (d, 1H); 6.69 (s, 1H); 6.61 (d, 1H)	5.42	4.39 (m, 1H); 4.26 (m, 2H); 3.93 (m, 2H)	3.31	2.17; 2.13	
3	10.64 (s); 6.80 (t)	7.0 (d, 1H); 6.67 (s, 1H); 6.60 (d, 1H)	5.47	4.20-3.95 (m, 3H); 3.90-3.75 (m, 2H)	3.29	2.16; 2.12	3.32 (m, 2H) – NCH_2; 1.13 (t, 3H) – CCH_3
4	10.63 (s); 6.82 (t)	7.0 (d, 1H); 6.66 (s, 1H); 6.58 (d, 1H)	5.50	4.15-4.0 (m, 3H); 3.95-3.80 (m, 2H)	3.28	2.16; 2.12	3.24 (m, 2H) – NCH_2; 1.54 (m, 2H) – CCH_2; 0.88 (t, 3H) – CCH_3
5	10.63 (s); 6.66 (t)	7.0 (d, 1H); 6.66 (s, 1H); 6.59 (d, 1H)	5.50	4.15-4.0 (m, 3H); 3.88-3.80 (m, 2H)	3.28	2.16; 2.12	3.31 (m, 2H) – NCH_2; 1.50 (m, 2H) – CCH_2; 1.30 (m, 2H) – CCH_2; 0.88 (t, 3H) – CCH_3
6	10.63 (s); 6.85 (s)	7.0 (d, 1H); 6.66 (s, 1H); 6.57 (d, 1H)	5.56	4.17-4.05 (m, 3H); 3.95-3.80 (m, 2H)	3.28	2.16; 2.12	3.12 (t, 2H) – NCH_2; 1.88 (m, 1H) – CCH; 0.89 (d, 6H) – CCH_3
7	10.62 (s); 6.53 (d)	6.99 (d, 1H); 6.66 (s, 1H); 6.58 (d, 1H)	5.54	4.20-4.0 (m, 3H); 3.95-3.75 (m, 3H) + NCH	3.27	2.16; 2.12	1.52 (m, 2H) – CCH_2; 1.13 (q, 3H) – CCH_3; 0.87 (q, 3H) – CCH_3
8	10.63 (s); 6.66 (t)	7.0 (d, 1H); 6.59 (s, 1H); 6.58 (d, 1H)	5.50	4.15-4.05 (m, 3H); 3.92-3.80 (m, 2H)	3.28	2.16; 2.12	3.27 (m, 2H) – NCH_2; 1.51 (m, 2H) – CCH_2; 1.25 (m, 4H) – CCH_2; 0.86 (t, 3H) – CCH_3
9	10.63 (s); 6.75 (t)	7.0 (d, 1H); 6.66 (s, 1H); 6.59 (d, 1H)	5.50	4.15-4.05 (m, 3H); 3.87-3.80 (m, 2H)	3.28	2.16; 2.12	3.29 (m, 2H) – NCH_2; 1.60 (m, 1H) – CCH; 1.39 (m, 2H) – CCH_2; 0.87 (d, 6H) – $C(CH_3)_2$
10	10.80 (s)	7.0 (d, 1H); 6.67 (s, 1H); 6.59 (d, 1H)	5.38	4.30-4.18 (m, 3H); 3.83-3.76 (m, 2H)	3.30	2.17; 2.13	2.95 (s, 6H) – $N(CH_3)_2$
11	10.82 (s)	6.99 (d, 1H); 6.64 (s, 1H); 6.57 (d, 1H)	5.38	4.29 (m, 1H); 4.14 (m, 2H); 3,79 (m, 2H)	3.28	2.16; 2.12	3.30 (m, 4H) – NCH_2; 1.10 (t, 6H) – $C(CH_3)_2$
12	10.64 (s)	7.0 (d, 1H); 6.66 (s, 1H); 5.58 (d, 1H)	5.38	4.32 (m, 2H); 4.14 (m, 1H); 3,82 (m, 2H)	3.28	2.16; 2.12	3.60 (m, 4H) – $N(CH_2)_2$; 1.80 (m, 4H) – $C(CH_2)_2$
13	10.87 (s)	7.0 (d, 1H); 6.65 (s, 1H); 6.58 (d, 2H)	5.40	4.39 (m, 1H); 4.13 (m, 2H); 3,84 (m, 2H)	3.31	2.16; 2.12	3.26 (m, 4H) – $N(CH_2)_2$; 3.08 (m, 2H) – NCH_2; 1.58 (m, 6H) – $C(CH_2)_3$

14	10.71 (s)	7.0 (d, 1H); 6.64 (s, 1H); 6.57 (d, 2H)	5.42	4.22 (m, 3H); 3,81 (m, 2H)	3.28	2.16; 2.13	3.52 (m, 4H) – $N(CH_2)_2$; 1.72 (s, 4H) – $C(CH_2)_2$; 1.55 (s, 4H) – $C(CH_2)_2$
15	10.95 (s)	7.0 (d, 1H); 6.67 (s, 1H); 6.58 (d, 1H)	5.40	4.42 (m, 1H); 4.16 (m, 2H); 3,88 (m, 2H)	3.31	2.17; 2.13	3.68 (m, 4H) – $N(CH_2)_2$; 3.37 (m, 2H) – OCH_2; 3.19 (m, 2H) – OCH_2
16	11.07 (s)	7.04 (d, 1H); 6.76 (s, 1H); 6.68 (d, 1H)	–	4.50 (t, 1H); 4.34 (m, 2H); 4.19 (m, 1H)	3.27	2.17; 2.13	5.78 (m, 1H) – OCH

The biological effects of synthesized compounds were predicted by the Prediction of Activity Spectra for Substances (PASS) program [12].

Antioxidant activity studying.

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activities of 8-amino-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl]-3-methylxantines were carried out as reported by Al-Omair et al. [13]: 1 ml of the test compound (2 μM) in methanol/DMSO (1:1) or standard (vitamin C) was added to 4 ml of 0.004% methanol solution of DPPH and vortexed carefully. After a 30-minute incubation at 30°C, the absorbance was recorded against control (methanol/DMSO 1:1) at 517 nm. Consequently, after an electron was transferred to the odd electron in DPPH•, the absorbance at 517 nm reduced steadily due to the increase of the nonradical DPPH forms. The percentage of inhibition of DPPH free radical was calculated by the equation:

$$I\% = \frac{A_{control} - A_{sample}}{A_{control}} \times 100\%,$$

where $A_{control}$ is the absorbance of the control and A_{sample} is the absorbance of the 8-amino-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl]-3-methylxantines.

Ascorbic acid was used as a reference substance for comparison.

The statistical program «STATISTICA® for Windows 6.0» was used for univariate analysis (mean, 5% truncated mean, standard deviation, standard error). $P<0.05$ was considered statistically significant.

RESULTS

As it is shown in Fig. 1, reaction of 8-bromo-3-methylxanthine (1) [11] with 3,4-dimethylphenoxymethyloxirane in 1-propanol in the presence of catalytic amount of N,N-dimethylbenzylamine leads to obtaining of the initial 8-bromo-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl-1-]3-methylxanthine (2).

The study of reactions of bromoalcohol 2 with primary and secondary amines has shown that the substitution of the bromine atom in a position 8 by the amine residue occurs by heating the reagents in aqueous dioxane (2:3) within 1 hour. Thus, were ob-

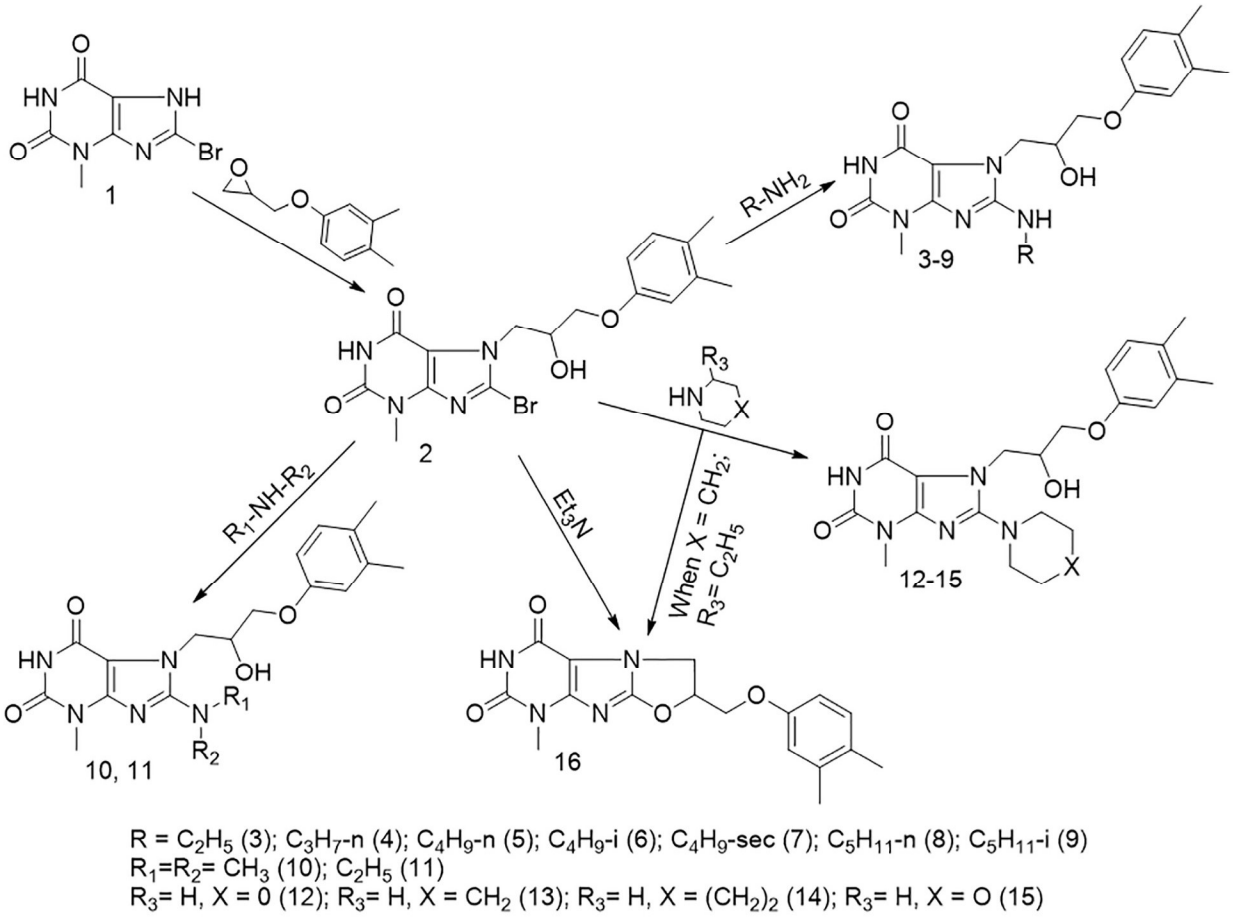

Fig. 1. Synthesis of 8-amino-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl]-3-methylxantines

tained the appropriate aminoxanthines 3-9, 11-16 with a high yield (Table 1). The 8-Dimethylaminoxanthine 10 was synthesized by heating bromoxanthine 2 with an excess of dimethylamine in ethanol in a steel autoclave at the temperature of 160 °C for 5 hours. It should be noted that the interaction of bromoalcohol 2 with 2-ethylpiperidine is carried out through the formation of 2-(3,4-dimethylphenoxy)methyl-8-methyl-2,3-dihydro-1,3-oxazolo[2,3-f]xanthine (16). This fact is explained by the steric effect of the ethyl group in a position 2 of a piperidine molecule.

In order to confirm the structure of oxazoline 16 we have carried out its counter synthesis through the reaction of bromoalcohol 2 with an excess of triethylamine in 1,4-dioxane. The samples of the mixing of compound 16 specimen which were obtained in different ways do not give the melting point depression (Table 1) and their NMR-spectra appeared to be identical. The obtained substances are white crystalline compounds insoluble in water and ether but soluble in hot alcohols, 1,4-dioxane, dimethylformamide and dimethylsulfoxide.

The structure of the synthesized substances has been proven by the NMR spectroscopy data (Table 2). The spectra have clear proton signals, which are substituents of an appropriate form and intensity and are located in the relevant part of the spectrum.

Further properties of the synthesized compounds were predicted by the PASS program. Thus, according to the PASS program prognosis the obtained compounds could have various activities (Table 3).

These data give us the reason to plan our further pharmacological investigation of the synthesized compounds 2-15 as vasodilator, diuretic, spasmolytic agents, compounds 3, 4, 6 anti-ischemic agents and 3,4-dimethylphenoxymethyl-8-meth-

Table 3. Data of PASS prediction for synthesized compounds (2-16)

Compound	Vasodilation, perifeal	Diuretic	Spasmolytic	Radiosensitizer	Antiishemic	Oxygen scavenger	Nootropic	Antipsychotic
2	0.517	0.552	0.303	0.790	0.232	0.278	–	–
3	0.673	0.518	0.545	0.652	0.565	–	0.320	–
4	0.638	0.550	0.490	0.642	0.558	0.263	0.323	–
5	0.686	0.532	0.489	0.666	0.362	0.274	–	–
6	0.646	0.425	0.430	0.583	0.557	–	0.392	–
7	0.606	0.409	0.643	0.513	0.295	0.289	–	–
8	0.695	0.517	0.488	0.668	0.355	0.285	–	–
9	0.615	0.415	0.509	0.585	0.348	–	0.387	–
10	0.654	0.594	0.404	0.611	0.310	0.286	–	–
11	0.633	0.572	0.624	0.619	0.329	0.273	–	–
12	0.773	0.627	0.528	0.674	0.346	–	0.481	–
13	0.775	0.637	0.544	0.669	0.344	–	0.487	–
14	0.775	0.637	0.544	0.669	0.344	–	0.487	–
15	0.697	0.587	0.479	0.740	0.344	–	0.436	–
16	–	–	–	0.245	–	0.332	–	0.631

yl-2,3-dihydro-1,3-oxazolo[2,3-f]xanthine – antipsychotic agent. The high probability of a radiosensitizing activity of the obtained compounds 2-15 was established, which can be used in oncology. In addition, the radiosensitizing activity may indirectly indicate the pro-oxidant activity of the synthesized substances.

Almost all compounds showed relatively low antioxidant properties, and their values were lower than the reference drug – ascorbic acid (Table 4). Their antioxidant activity was found to be within 2.17-39.88% (10^{-3}mol / l).

Compounds 3-9 showed medium antioxidant properties. All compounds showed a low antioxi-

Table 4. Biological activity of synthesized compounds p<0.01

Compound	AOA, %			Compound	AOA, %		
	C = 10^{-3} mol / L	C = 10^{-5} mol / L	C = 10^{-7} mol / L		C = 10^{-3} mol / L	C = 10^{-5} mol / L	C = 10^{-7} mol / L
2	2.17	-0.93	-2.17	10	4.67	5.67	4.36
3	35.91	4.02	-0.93	11	8.41	7.48	4.67
4	35.29	2.17	0.31	12	7.17	7.17	4.98
5	31.89	3.10	0.31	13	4.36	6.54	4.67
6	31.27	3.41	-0.93	14	7.17	6.85	5.30
7	29.72	4.02	-0.31	15	6.23	6.23	4.98
8	36.53	3.72	0.93	Ascorbic acid	92.11	47.08	0.95
9	39.88	7.48	3.12				

dant activity in concentrations of 10^{-5} and 10^{-7} mol / l. Compounds 2, 3, 6, 7 exerted a pro-oxidant effect in concentration of 10^{-7} mol / l and 8-bromo-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl-1-]3-methylxanthine (2) – in concentration of 10^{-5} mol / l.

DISCUSSION

As one can see from the data in Table 2, the spectrum of the initial bromoalcohol 2 is characterized by the presence of one-proton singlet at 11.26 ppm (N^1H) and three-proton singlet at 3.31 ppm (N^3CH_3), which prove the structure of the uracil moiety of the molecule. The aromatic protons resonate at 7.0 ppm (d, 1H); 6.69 ppm (s, 1H) and 6.61 ppm (d, 1H). The methyl groups bonded with the aromatic nucleus are fixed in the form of the intensive three-proton singlets at 2.17 ppm and 2.13 ppm. Proton of the secondary alcohol group is registered as a doublet at 5.42 ppm. Methylene and methine protons of N^7-propyl substituent are fixed in a form of multiplets at 4.39 ppm (1H); 4.26 ppm (2H) and 3.93 ppm (2H). The multiplicity of signals is explained by the presence of a chiral carbon atom in position 2 of the propyl residue. In the spectra of 8-aminosubstituted 3-15 (Table 1), the signals of substituent protons in the positions 1, 3, 7 are registered almost within the same areas of the spectrum in the corresponding shape and intensity. The signals of protons of amine residues in a position 8 are fully consistent with their structure. In the NMR spectrum of oxazolinoxanthine 16, the signal of an alcohol group proton is not detected. However, we can register a multiplet of the methine group proton bonded to the endocyclic oxygen atom at 5.78 ppm (1H). The protons of methylene groups form a triplet at 4.50 ppm (1H) and two multiplets at 4.34 ppm (2H) and 4.19 ppm (1H).

The analysis of the data concerning the study of the antioxidant activity (AOA) of the compounds under research (Table 4) shows that the insertion of primary amines into position 8 leads to an increase in the AOA index in the concentration of 10^{-3} mol / l. It should be noted that the branching of the carbon skeleton of primary amines does not significantly affect the AOA index. The insertion of a secondary or heterocyclic amine into position 8 does not lead to an increase of AOA. However, for the final conclusions it is necessary to conduct additional studies.

It should be noted that the data obtained did not confirm the assumption that radiosensitizing activity may indirectly indicate pro-oxidant activity. This assumption must be studied on another experimental model.

CONCLUSION

Accessible laboratory methods have been elaborated for synthesis of 8-amino-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl]-3-methylxantines, the structure of which has been proven by elemental analysis and NMR-spectroscopy data.

The PASS program prognosis confirmed that the obtained compounds could have vasodilation, anti-ischemic, spasmolytic, diuretic, antipsychotic, radiosensitizing activities.

The antioxidant activity of synthesized compounds has been studied and 8-i-pentenyl-7-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl-1-]3-methylxanthine (9) presented the best values in the concentrations of 10^{-3} and 10^{-5} mol / l.

It was founded that the insertion of primary amines into position 8 leads to an increase in the AOA index in the concentration of 10^{-3} mol / l.

Priorities for further research of biologically active compounds have been outlined.

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