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SYNTHESIS OF NOVEL YLIDENHYDRAZIDES OF 3-BENZYL-8-METHYLXANTHINYL-7-ACETIC ACID AS POTENTIAL BIOLOGICAL ACTIVE COMPOUNDS

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ABSTRACT

In this work, we have described the method of 3-benzyl-8-methylxanthinyl-7-acetohydrazide synthesis and studied its reaction with different aldehydes and ketones in acidic medium. As result, we obtained a series of novel ylidenhydrazides of 3-benzyl-8-methylxanthinyl-7-acetic acid. The structure of the synthesized substances was proved by IR and NMR spectra and elemental analysis and their individuality was confirmed by thin-layer chromatography.

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

INTRODUCTION

Some of the most widespread drugs are those, which contain in their structures a heterocyclic fragment (1-3). This could be explained by the fact that heterocycle containing compounds play an important role in the metabolic processes. Thus, NAD and NADP (coenzymes of dehydrogenases) are pyridine derivatives, vitamin B_6, which is rather important for amino acid metabolism is a pyrimidine derivative, and purine and xanthine heterocycles are part of the nucleotides (4, 5).

So chemical modification of well-known natural substances is one of the most promising ways for synthesis of novel less toxic biological active compounds, which are also potential medicines.

Xanthine derivatives are handy objects for pharmaceutical research. They are low-toxicity natural compounds with a wide spectrum of pronounced pharmacological properties (antioxidant, diuretic, antibacterial, anti-inflammatory, etc.) and high variability of chemical modification (6-8). At the same time, the hydrazine group is one of the most chemically active functional groups, which easily participates in reactions of nucleophilic addition (9, 10) and insertion of such functional fragment to the structure of xanthine molecule could have some positive effect on its synthetic potential (9-11).

In this article we have described the method of synthesis of hydrazide of 3-beznyl-8-methylxanthinyl-7-acetic acid and its N-substituted derivatives and have studied their physicochemical properties.

MATERIALS AND METHODS

Melting points were determined using the capillary method on DMP (M). ^{1}H NMR-spectra were recorded by Varian Mercury VX-200 device (company «Varian» – USA), solvent – (DMSO-*d6*), in-

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ternal standard – TMS. Chemical shifts are reported in ppm (parts per million) values. Infrared (IR) spectra were measured on a Bruker Alpha instrument using a potassium bromide (KBr) disk, scanning from 400 to 4000 cm^{-1}. Elemental analysis of obtained compounds was produced on device Elementar Vario L cube. Analytical thin-layer chromatography (TLC) was carried out on precoated plates, and spots were visualized with ultraviolet (UV) light. Systems, that were used for chromatography: «acetone-propanol-2» 5:2 ratio. All chemicals or reagents were purchased from standard commercial suppliers and treated with standard methods before use.

Propyl 3-benzyl-8-methylxanthinyl-7-acetate **3** was synthesized by a method that we have described earlier (12).

*Hydrazide of 3-benzyl-8-methylxanthinyl-7-acetic acid **4***

To heated suspension of 0.01 mmol ester **3** in 30 ml of propanol, 5 ml of hydrazine hydrate were added. The solution that formed was refluxed for 30 min. After cooling, a white solid was precipitated. It was filtered out, washed by water and dried at 80-85 °C.

Yield 89.1 %. M.p. >300 °C. R_f = 0.82. $C_{15}H_{16}N_6O_3$. Found, %: C, 55.17; H, 4.61; N, 25.30. Calculated, %: C, 54.87; H, 4.91; N, 25.60. IR-spectrum (ν, sm^{-1}): 3298 (NH), 3140 (NH), 3002 (CH_{arom}), 1710 (C=O), 1675 (C=O), 1640 (C=N), 1592 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.12 (1H, s, N^1H), 9.36 (1H, s, NH), 7.46-7.12 (5H, m, CH_{arom}), 5.12 (2H, s, N^3-CH_2), 4.98 (2H, s, N^7-CH_2), 4.52 (2H, ws, NH_2), 2.35 (3H, s, C^8-CH_3).

*General procedure for benzylidenhydrazides of -benzyl-8-methylxanthinyl-7-acetic acid synthesis **5a-l***

Method A. To the solution of 3.28 g (0.01 mole) hydrazide **4** in 15 ml 50 % acetic acid, 0.011 mole of aldehyde was added. The mixture was refluxed for 15-30 min. After cooling, a solid was precipitated. It was filtered out, washed by water and dried at 80-85 °C.

Method B. To the solution (heated up to 50 °C) of 3.28 g (0.01 mole) hydrazide **4** in 70 ml aqueous dioxane (1:1), 3 ml of glacial acetic acid and 0.011 mole of aldehyde were added. The mixture was refluxed for 15-20 min. After cooling, a solid was precipitated. The solid was filtered out, washed by water and dried at 80-85 °C.

Ylidenhydrazides **5p-s** were synthesized by the same procedure. Ylidenhydrazides **5m-o** were obtained by method B, but the mixture of reagents was not refluxed. It was heated at 80 °C for 30 min.

*Benzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5a**)*

Yield 96.7 %. M.p. >300 °C. R_f = 0.96. $C_{22}H_{20}N_6O_3$. Found, %: C, 63.15; H, 5.14; N, 20.48. Calculated, %: C, 63.45; H, 4.84; N, 20.18. IR-spectrum (ν, sm^{-1}): 3290 (NH), 3120 (NH), 3040 (CH_{arom}), 1710 (C=O), 1680 (C=O), 1640 (C=N), 1592 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.78 (1H, s, CONH), 11.14 (1H, s, N^1H), 8.05 (1H, s, N=CH), 7.74-7.56 (2H, t, CH_{arom}), 7.51-7.16 (8H, m, CH_{arom}), 5.48 (2H, s, N^7-CH_2), 5.06 (2H, s, N^3-CH_2), 2.31 (3H, s, C^8-CH_3).

*4'-Methylbenzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5b**)*

Yield 81.6 %. M.p. 289-291 °C. R_f = 0.80. $C_{23}H_{22}N_6O_3$. Found, %: C, 63.87; H, 5.45; N, 19.82. Calculated, %: C, 64.17; H, 5.15; N, 19.52. IR-spectrum (ν, sm^{-1}): 3300 (NH), 3120 (NH), 3010 (CH_{arom}), 1722 (C=O), 1681 (C=O), 1620 (C=N), 1597 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.72 (1H, s, CONH), 11.17 (1H, s, N^1H), 7.96 (1H, s, N=CH), 7.62-7.51 (2H, t, CH_{arom}), 7.34-7.12 (7H, m, CH_{arom}), 5.46 (2H, s, N^7-CH_2), 5.09 (2H, s, N^3-CH_2), 2.28 (6H, s, CH_3).

*4'-Chlorobenzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5c**)*

Yield 85.2 %. M.p. >300 °C. R_f = 0.88. $C_{22}H_{19}ClN_6O_3$. Found, %: C, 58.30; H, 4.55; N, 18.34. Calculated, %: C, 58.60; H, 4.25; N, 18.64. IR-spectrum (ν, sm^{-1}): 3280 (NH), 3120 (NH), 3040 (CH_{arom}), 1720 (C=O), 1681 (C=O), 1650 (C=N), 1570 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.82 (1H, s, CONH), 11.12 (1H, s, N^1H), 8.69 (1H, s, N=CH), 7.89-7.81 (1H, d, CH_{arom}), 7.77-7.61 (1H, t, CH_{arom}), 7.54-7.38 (2H, m, CH_{arom}), 7.32-7.17 (5H, m, CH_{arom}), 5.47 (2H, s, N^7-CH_2), 5.04 (2H, s, N^3-CH_2), 2.33 (3H, s, C^8-CH_3).

*4'-Brombenzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5d**)*

Yield 84.3 %. M.p. >300 °C. R_f = 0.92. $C_{22}H_{19}BrN_6O_3$. Found, %: C, 53.05; H, 4.17; N, 16.67. Calculat-

ed, %: C, 53.35; H, 3.87; N, 16.63. IR-spectrum (ν, sm^{-1}): 3250 (NH), 3160 (NH), 3061 (CH_{arom}), 1710 (C=O), 1680 (C=O), 1630 (C=N), 1570 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.86 (1H, s, CONH), 11.18 (1H, s, N^1H), 8.62 (1H, s, N=CH), 7.82-7.51 (7H, m, CH_{arom}), 7.32-7.14 (2H, m, CH_{arom}), 5.49 (2H, s, N^7-CH_2), 4.99 (2H, s, N^3-CH_2), 2.31 (3H, s, C^8-CH_3).

*4'-Fluorobenzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5e**)*

Yield 90.5 %. M.p. >300 °C. R_f = 0.86. $C_{22}H_{19}FN_6O_3$. Found, %: C, 61.12; H, 4.11; N, 19.65. Calculated, %: C, 60.82; H, 4.41; N, 19.35. IR-spectrum (ν, sm^{-1}): 3317 (NH), 3139 (NH), 3036 (CH_{arom}), 1729 (C=O), 1683 (C=O), 1667 (C=N), 1590 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.79 (1H, s, CONH), 11.15 (1H, s, N^1H), 7.99 (1H, s, N=CH), 7.84-7.62 (2H, m, CH_{arom}), 7.39-7.18 (7H, m, CH_{arom}), 5.46 (2H, s, N^7-CH_2), 5.03 (2H, s, N^3-CH_2), 2.35 (3H, s, C^8-CH_3).

*3',4'-Difluorobenzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5f**)*

Yield 92.1 %. M.p. >300 °C. R_f = 0.82. $C_{22}H_{18}F_2N_6O_3$. Found, %: C, 58.71; H, 4.31; N, 18.28. Calculated, %: C, 58.41; H, 4.01; N, 18.58. IR-spectrum (ν, sm^{-1}): 3290 (NH), 3150 (NH), 3030 (CH_{arom}), 1717 (C=O), 1698 (C=O), 1669 (C=N), 1584 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.86 (1H, s, CONH), 11.15 (1H, s, N^1H), 7.97 (1H, s, N=CH), 7.89-7.72 (1H, m, CH_{arom}), 7.61-7.39 (2H, m, CH_{arom}), 7.34-7.12 (5H, m, CH_{arom}), 5.44 (2H, s, N^7-CH_2), 5.06 (2H, s, N^3-CH_2), 2.32 (3H, s, C^8-CH_3).

*4'-N',N'-Dimethylaminobenzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5g**)*

Yield 89.7 %. M.p. 283-285 °C. R_f = 0.82. $C_{24}H_{25}N_7O_3$. Found, %: C, 63.03; H, 5.78; N, 21.74. Calculated, %: C, 62.73; H, 5.48; N, 21.55. IR-spectrum (ν, sm^{-1}): 3290 (NH), 3130 (NH), 3047 (CH_{arom}), 1719 (C=O), 1700 (C=O), 1642 (C=N), 1576 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.49 (1H, s, CONH), 11.10 (1H, s, N^1H), 7.85 (1H, s, N=CH), 7.54-7.46 (2H, d, CH_{arom}), 7.38-7.19 (5H, m, CH_{arom}), 6.79-6.61 (2H, d, CH_{arom}), 5.45 (2H, s, N^7-CH_2), 5.07 (2H, s, N^3-CH_2), 2.94 (6H, s, N-CH_3), 2.34 (3H, s, C^8-CH_3).

*4'-Hydroxybenzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5h**)*

Yield 86.3 %. M.p. >300 °C. R_f = 0.90. $C_{22}H_{20}N_6O_4$. Found, %: C, 60.80; H, 4.36; N, 19.13. Calculated, %: C, 61.10; H, 4.66; N, 19.43. IR-spectrum (ν, sm^{-1}): 3300 (NH), 3140 (NH), 3020 (CH_{arom}), 1725 (C=O), 1689 (C=O), 1640 (C=N), 1590 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.59 (1H, s, CONH), 11.11 (1H, s, N^1H), 9.89 (1H, s, OH), 7.88 (1H, s, N=CH), 7.54-7.48 (2H, d, CH_{arom}), 7.34-7.19 (5H, m, CH_{arom}), 6.85-6.72 (2H, d, CH_{arom}), 5.45 (2H, s, N^7-CH_2), 5.05 (2H, s, N^3-CH_2), 2.34 (3H, s, C^8-CH_3).

*4'-Methoxybenzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5i**)*

Yield 95.5 %. M.p. >300 °C. R_f = 0.94. $C_{23}H_{22}N_6O_4$. Found, %: C, 61.57; H, 5.27; N, 19.12. Calculated, %: C, 61.87; H, 4.97; N, 18.82. IR-spectrum (ν, sm^{-1}): 3280 (NH), 3160 (NH), 3030 (CH_{arom}), 1700 (C=O), 1679 (C=O), 1660 (C=N), 1602 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.64 (1H, s, CONH), 11.13 (1H, s, N^1H), 7.95 (1H, s, N=CH), 7.68-7.55 (2H, d, CH_{arom}), 7.49-7.14 (5H, m, CH_{arom}), 7.07-6.86 (2H, d, CH_{arom}), 5.46 (2H, s, N^7-CH_2), 5.08 (2H, s, N^3-CH_2), 3.72 (3H, s, OCH_3), 2.29 (3H, s, C^8-CH_3).

*4'-Nitrobenzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5j**)*

Yield 91.7 %. M.p. >300 °C. R_f = 0.80. $C_{22}H_{19}N_7O_5$. Found, %: C, 57.56; H, 3.85; N, 20.95. Calculated, %: C, 57.26; H, 4.15; N, 21.25. IR-spectrum (ν, sm^{-1}): 3260 (NH), 3130 (NH), 2997 (CH_{arom}), 1703 (C=O), 1689 (C=O), 1642 (C=N), 1583 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 12.05 (1H, s, CONH), 11.14 (1H, s, N^1H), 8.12 (1H, s, N=CH), 8.39-8.16 (2H, d, CH_{arom}), 8.08-7.86 (2H, d, CH_{arom}), 7.39-7.11 (5H, m, CH_{arom}), 5.61 (2H, s, N^7-CH_2), 5.09 (2H, s, N^3-CH_2), 2.31 (3H, s, C^8-CH_3).

*3'-Nitrobenzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5k**)*

Yield 86.8 %. M.p. 293-294 °C. R_f = 0.92. $C_{22}H_{19}N_7O_5$. Found, %: C, 57.56; H, 4.45; N, 21.55. Calculated, %: C, 57.26; H, 4.15; N, 21.25. IR-spectrum (ν, sm^{-1}): 3340 (NH), 3120 (NH), 3030 (CH_{arom}), 1700 (C=O), 1680 (C=O), 1650 (C=N), 1590 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 12.01 (1H, s, CONH), 11.19 (1H, s, N^1H), 8.51 (1H, s, N=CH), 8.36-8.08 (3H, m, CH_{arom}), 7.75-7.61 (1H,

t, CH_{arom}), 7.41-7.15 (5H, m, CH_{arom}), 5.54 (2H, s, N^7-CH_2), 5.04 (2H, s, N^3-CH_2), 2.34 (3H, s, C^8-CH_3).

*3'-Methoxy-4'-hydroxybenzylidenhydrazide of -benzyl-8-methylxanthinyl-7-acetic acid (**5l**)*

Yield 80.1 %. M.p. 274-276 °C. R_f = 0.82. $C_{22}H_{22}N_6O_5$. Found, %: C, 60.03; H, 4.49; N, 18.47. Calculated, %: C, 59.73; H, 4.79; N, 18.17. IR-spectrum (ν, sm^{-1}): 3270 (NH), 3167 (NH), 3101 (CH_{arom}), 1712 (C=O), 1677 (C=O), 1650 (C=N), 1590 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.59 (1H, s, CONH), 11.15 (1H, s, N^1H), 9.51 (1H, s, OH), 7.89 (1H, s, N=CH), 7.34-7.19 (6H, m, CH_{arom}), 7.14-7.01 (1H, t, CH_{arom}), 6.82-6.71 (1H, d, CH_{arom}), 5.46 (2H, s, N^7-CH_2), 5.02 (2H, s, N^3-CH_2), 3.79 (3H, s, OCH_3), 2.39 (3H, s, C^8-CH_3).

*(3-Benzyl-8-methylxanthinyl-7)-acetic acid (2-chloro-quinolin-3-ylmethylene)-hydrazide (**5m**)*

Yield 89.4 %. M.p. 290-292 °C. R_f = 0.84. $C_{25}H_{20}ClN_7O_3$. Found, %: C, 59.52; H, 4.32; N, 19.23. Calculated, %: C, 59.82; H, 4.02; N, 19.53. IR-spectrum (ν, sm^{-1}): 3290 (NH), 3150 (NH), 3020 (CH_{arom}), 1700 (C=O), 1678 (C=O), 1640 (C=N), 1574 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 12.08 (1H, s, CONH), 11.15 (1H, s, N^1H), 8.91 (1H, s, N=CH), 8.45 (1H, s, CH_{arom}), 8.14-8.06 (1H, d, CH_{arom}), 8.01-7.74 (2H, m, CH_{arom}), 7.71-7.54 (1H, d, CH_{arom}), 7.39-7.16 (5H, m, CH_{arom}), 5.58 (2H, s, N^7-CH_2), 5.02 (2H, s, N^3-CH_2), 2.39 (3H, s, C^8-CH_3).

*(3-Benzyl-8-methylxanthinyl-7)-acetic acid (5-chloro-1,3-dimethyl-1H-pyrazol-4-ylmethylene)-hydrazide (**5n**)*

Yield 79.5 %. M.p. 277-279 °C. R_f = 0.76. $C_{21}H_{21}ClN_8O_3$. Found, %: C, 53.49; H, 4.81; N, 24.20. Calculated, %: C, 53.79; H, 4.51; N, 23.90. IR-spectrum (ν, sm^{-1}): 3310 (NH), 3150 (NH), 3035 (CH_{arom}), 1723 (C=O), 1680 (C=O), 1655 (C=N), 1595 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.67 (1H, s, CONH), 11.14 (1H, s, N^1H), 7.88 (1H, s, N=CH), 7.42-7.10 (5H, m, CH_{arom}), 5.41 (2H, s, N^7-CH_2), 5.07 (2H, s, N^3-CH_2), 3.71 (3H, s, CH_3), 2.38 (6H, s, CH_3).

*(3-Benzyl-8-methylxanthinyl-7)-acetic acid (5-chloro-1-methyl-3-ethyl-1H-pyrazol-4-ylmethylene)-hydrazide (**5o**)*

Yield 74.7 %. M.p. 263-264 °C. R_f = 0.92. $C_{22}H_{23}ClN_8O_3$. Found, %: C, 55.05; H, 5.10; N, 23.50. Calculated, %: C, 54.72; H, 4.80; N, 23.20. IR-spectrum (ν, sm^{-1}): 3260 (NH), 3110 (NH), 3020 (CH_{arom}), 1710 (C=O), 1696 (C=O), 1633 (C=N), 1580 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.69 (1H, s, CONH), 11.11 (1H, s, N^1H), 7.86 (1H, s, N=CH), 7.35-7.16 (5H, m, CH_{arom}), 5.43 (2H, s, N^7-CH_2), 5.05 (2H, s, N^3-CH_2), 3.76 (3H, s, CH_3), 2.77 (2H, q, CH_2), 2.32 (3H, s, C^8-CH_3), 1.15 (3H, t, CH_3).

*(3-Benzyl-8-methylxanthinyl-7)-acetic acid [3-(5-nitro-furan-2-yl)-allylidene]-hydrazide (**5p**)*

Yield 76.3 %. M.p. 227-228 °C. R_f = 0.92. $C_{22}H_{19}N_7O_6$. Found, %: C, 55.05; H, 4.31; N, 20.24. Calculated, %: C, 55.35; H, 4.01; N, 20.54. IR-spectrum (ν, sm^{-1}): 3260 (NH), 3139 (NH), 3033 (CH_{arom}), 1700 (C=O), 1680 (C=O), 1660 (C=N), 1560 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.86 (1H, s, CONH), 11.14 (1H, s, N^1H), 7.82 (1H, s, N=CH), 7.74 (1H, d, CH), 7.41-7.15 (5H, m, CH_{arom}), 7.12 (1H, d, CH), 7.09-6.96 (2H, d, CH_{arom}), 5.39 (2H, s, N^7-CH_2), 5.06 (2H, s, N^3-CH_2), 2.29 (3H, s, C^8-CH_3).

*(3-Benzyl-8-methylxanthinyl-7)-acetic acid [5-(4-nitro-phenyl)-furan-2-ylmethylene]-hydrazide (**5q**)*

Yield 71.5 %. M.p. 209-211 °C. R_f = 0.78. $C_{26}H_{21}N_7O_6$. Found, %: C, 59.50; H, 4.31; N, 18.29. Calculated, %: C, 59.20; H, 4.01; N, 18.59. IR-spectrum (ν, sm^{-1}): 3260 (NH), 3109 (NH), 3080 (CH_{arom}), 1713 (C=O), 1679 (C=O), 1658 (C=N), 1597 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.88 (1H, s, CONH), 11.15 (1H, s, N^1H), 7.96 (1H, s, N=CH), 8.31-8.16 (2H, d, CH_{arom}), 7.94-7.82 (2H, d, CH_{arom}), 7.43-7.37 (1H, d, CH_{arom}), 7.36-7.18 (5H, m, CH_{arom}), 7.14-7.06 (1H, d, CH_{arom}), 5.51 (2H, s, N^7-CH_2), 5.07 (2H, s, N^3-CH_2), 2.34 (3H, s, C^8-CH_3).

*3-benzyl-8-methylxanthinyl-7-N'-[2-oxo-2,3-dihydro-1H-indol-3-ylidene]acetohydrazide (**5r**)*

Yield 92.3 %. M.p. >300 °C. R_f = 0.86. $C_{23}H_{19}N_7O_4$. Found, %: C, 60.09; H, 3.89; N, 21.13. Calculated, %: C, 60.39; H, 4.19; N, 21.43. IR-spectrum (ν, sm^{-1}): 3300 (NH), 3180 (NH), 3050 (CH_{arom}), 1720 (C=O), 1680 (C=O), 1660 (C=N), 1590 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 12.72 (1H, s, NH), 11.32 (1H, s, CONH), 11.14 (1H, s, N^1H), 7.61-7.50 (1H, d, CH_{arom}), 7.48-7.19 (6H, m, CH_{arom}), 7.17-6.92 (1H, t, CH_{arom}), 6.91-6.83 (1H, d, CH_{arom}), 5.67 (2H, s, N^7-CH_2), 5.09 (2H, s, N^3-CH_2), 2.36 (3H, s, C^8-CH_3).

*(3-Benzyl-8-methylxanthinyl-7)-acetic acid [1-(4-amino-phenyl)-ethylidene]-hydrazide (**5s**)*

Yield 69.8 %. M.p. >300 °C. R_f = 0.72. $C_{23}H_{22}N_6O_3$. Found, %: C, 64.47; H, 5.45; N, 19.22. Calculated, %: C, 64.17; H, 5.15; N, 19.52. IR-spectrum (ν, sm^{-1}): 3250 (NH), 3140 (NH), 3020 (CH_{arom}), 1710 (C=O), 1692 (C=O), 1649 (C=N), 1587 (C=C). ^{1}H NMR-spectrum (δ-scale, ppm., solvent DMSO-d_6): 11.12 (1H, s, N^1H), 10.75 (1H, s, CONH), 7.52-7.46 (2H, d, CH_{arom}), 7.41-7.14 (5H, m, CH_{arom}), 6.59-6.52 (2H, d, CH_{arom}), 6.09 (2H, s, NH_2), 5.51 (2H, s, N^7-CH_2), 5.11 (2H, s, N^3-CH_2), 2.34 (3H, s, C^8-CH_3), 2.12 (3H, s, CH_3).

RESULTS AND DISCUSSION

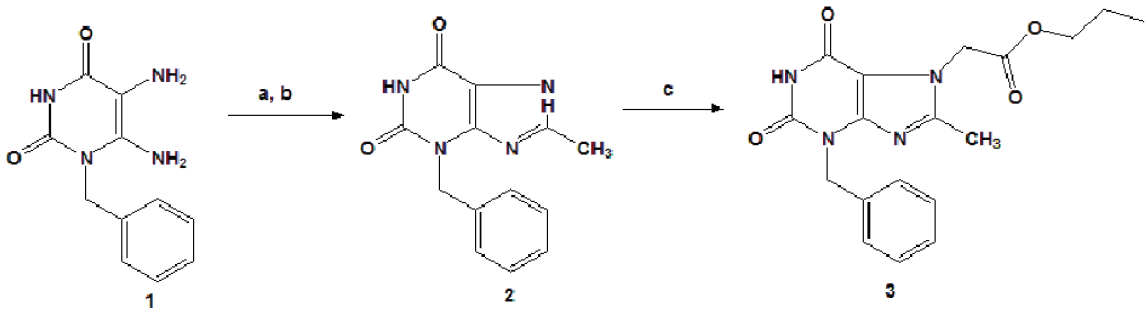
In the previous works we have described the method of propyl 3-benzyl-8-methylxanthinyl-7-acetate synthesis from 1-benzyl-5.6-diaminouracil (Fig. 1) (12).

In continuation of our search for potential biological active compounds among 3-beznylxanthine derivatives we obtained hydrazide of 3-beznylxanthinyl-7-acetic acid **4** by the reaction of ester **3** with hydrazine hydrate (Fig. 2).

At ^{1}H NMR-spectra of hydrazide **4** signals of methyl and methylene groups of ester residue were absent, but signals of hydrazide residue protons at 9.37 ppm (1H, s) and 4.52 ppm (2H, w.s.) were present. These and also intensive singlet of methylene group, that combined with a Nitrogen atom at position 7, at 4.98 ppm proved the presence of acethydrazide residue in the structure of compound **4**.

At the next stage we studied the reaction of hydrazide **4** with aliphatic, aromatic and heterocyclic carbonyl-containing compounds and obtained appropriate ylidenehydrazides **5a-s** (Fig. 3). Reaction was conducted by reflux of reagents in 50 % acetic acid or aqueous dioxane in the presence of catalytic amount of glacial acetic acid.

Ylidenehydrazides **5a-s** are white, daffodil, yellow or orange crystal compounds, insoluble in wa-



a) acetic acid, reflux; b) NaOH, H_2O, reflux; c) propyl chloroacetate, $NaHCO_3$, DMF, reflux

Figure 1. Scheme of propyl 3-benzyl-8-methylxanthinyl-7-acetate synthesis

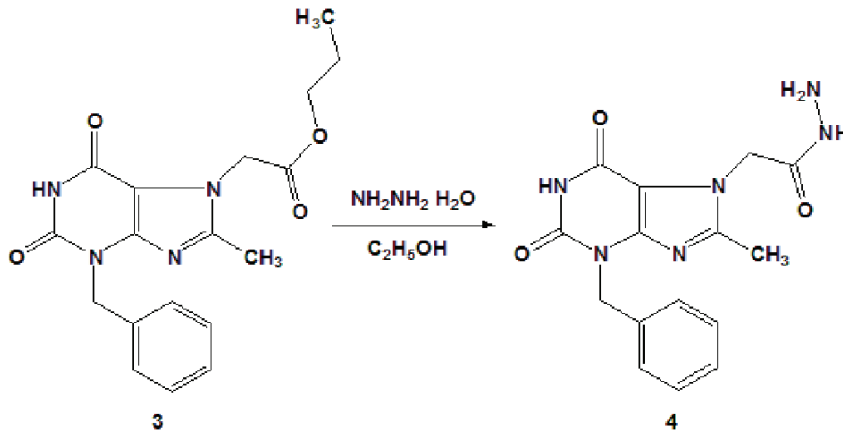


Figure 2. Scheme of hydrazide of 3-benzyl-8-methylxanthinyl-7-acetic acid synthesis

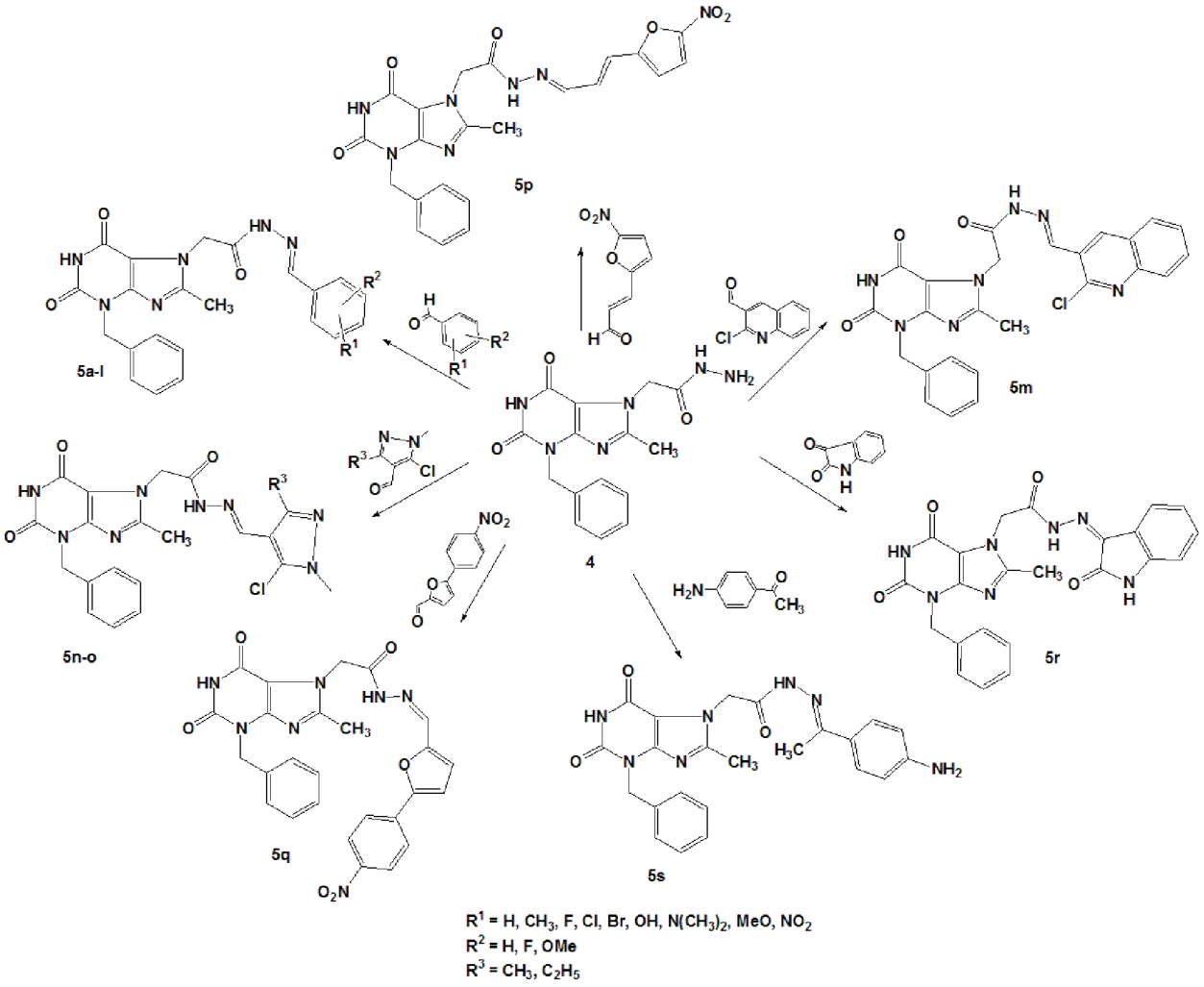


Figure 3. Scheme of ylidenhydrazides of 3-benzyl-8-methylxanthinyl-7-acetic acid synthesis

ter, diethyl ether, soluble in DMSO, ethanol and propanol.

In IR-spectra of compounds **5a-s** were present strips of absorption of N–H, C=O, C=C and C=N.

In ^{1}H NMR-spectra of ylidenehydrazides in comparison with initial hydrazide spectrum was absent signal of NH_2-group. At the same time, singlets of methine groups protons (at interval 8.91-7.82 ppm) were registered. Protons of NH-group of hydrazide residue resonated at a more weak field at 12.08-11.49 ppm.

In the spectra of all ylidenehydrazides signals of appropriate ylidene residues protons were also registered.

Thus, presence of 4-hydroxybenzylidene fragment of the ^{1}H NMR-spectra of compound **5h** was proved by singlet of OH-group proton (at 9.89 ppm) and two doublets of protons of p-substituted benzylidene residue (at 7.54-7.48 ppm and 6.85-6.72 ppm). Substituents at 4 position of benzene ring of compounds **5b**, **5g** and **5i** were proved by singlets of methyl at 2.28 ppm (compound **5b**) and 2.94 ppm (compound **5g**) and methoxy groups at 3.72 ppm (compound **5i**).

Synthesis of 3-benzyl-8-methylxanthinyl-7-N'-[2-oxo-2,3-dihydro-1H-indol-3-ylidene]acetohydrazide (compound **5r**) was confirmed by the presence of a signal of NH-group of indole fragments at 12.72 ppm and increasing of the aromatic proton multiplet intensity up to 9.

CONCLUSIONS

The developed method could be used for hydrazides and ylidenhydrazides of 3-aralkylxanthinyl-7-acetic acids synthesis. The PASS program prognosis confirmed that obtained compounds could have anti-bacterial and antifungal activities, which would be researched in further studies.

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