Original Research

STUDY OF NEW DERIVATIVES OF 3-R-XANTHINES AS EFFECTIVE ANTIBACTERIAL AGENTS.

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ABSTRACT:

Antibiotics it is the most widely presented class of medicines which application allows to cope with various diseases of the caused cultures of pathogenic bacteria, mushrooms. Rather high prevalence among cultures is occupied: *Staphylococcus aureus*. This Pathogen provokes various abscesses, carbuncles and boils, pneumonia, eczema, pyoderma, cholecystitis, meningitis, peritonitis, a very dangerous hard treatable disease - staphylococcal septicemia, and other pathologies. *Escherichia coli* is the activator of the majority of infectious diseases of a digestive tract, possesses ability to invazirovat an intestines epithelium that is especially dangerous at chest and children's age. The *Pseudomonas aeruginosa* the activator of pyoinflammatory processes, causes to many percent of all intrahospital infections. *Candida* which in norm are in an organism, under certain conditions can roughly breed that often leads to candidiases. Despite the broad spectrum of antibacterial and antifungal agents, there are modern microbial strains possessing both single and multiple resistance to drugs used to treat them. Furthermore, many modern drugs have many side effects. In this connection there is a need for new low-toxic biologically active substances possessing pronounced fungicidal, bactericidal or bacteriostatic activity.

KEY WORDS: Antibacterial and antifungal agents, bactericidal or bacteriostatic activity, new xanthine derivatives.

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INTRODUCTION

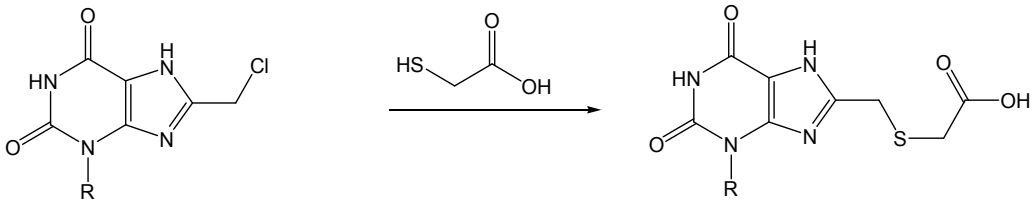
It is known that antibiotics it is the most widely presented class of medicines which application allows to cope with various diseases of the caused cultures of pathogenic bacteria, mushrooms. Rather high prevalence among cultures is occupied: *Staphylococcus aureus*. This Pathogen provokes various abscesses, carbuncles and boils, pneumonia, eczema, pyoderma, cholecystitis, meningitis, peritonitis, a very dangerous hard treatable disease - staphylococcal septicemia, and other pathologies [1;2]. *Escherichia coli* is the activator of the majority of infectious diseases of a digestive tract, possesses ability to invazirovat an intestines epithelium that is especially dangerous at chest and children's age [3]. The *Pseudomonas aeruginosa* the activator of pyoinflammatory processes, causes to 15-20% of all intrahospital infections [4; 5]. It is also known that sort mushrooms *Candida* which in norm are in an organism, under certain conditions can roughly breed that often leads to candidiases. Systematic fungal infections (fungemiya) are key causes of illness and mortality of patients with an immunodeficiency. Also, this fungus is the causative agent of intrahospital infections [6;7;8].

Despite the broad spectrum of antibacterial and antifungal agents, there are modern microbial strains possessing both single and multiple resistance to drugs used to treat them. Furthermore, many modern drugs have many side effects. In this connection there is a need for new low-toxic biologically active substances possessing pronounced fungicidal, bactericidal or bacteriostatic activity. In the development and delivery of chemotherapeutic agents of a new generation pays great attention to the study of natural substances, as well as their synthetic counterparts. In this regard interesting to consider and derivatives N- S- heterocyclic system xanthine which exhibit a broad spectrum of biological activity [9; 10; 11].

MATERIALS AND METHODS

For carrying out this scientific work a number of derivatives 3-R-8-hydroxymethylxanthines was synthesized and studying of their antimicrobic activity is carried out.

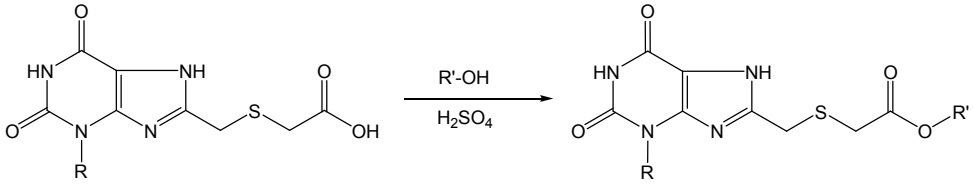
Reaction of 3-aryl(aralkyl)-8-chloromethylxanthines with excess boiling thioacetic acid were obtained 3-aryl(aralkyl)-8-methylthioacetic acid (**3.1; 3.2; 3.3**), the physico-chemical properties of which correspond to the structure.



3.1; 3.2 , 3.3

R = C_6H_5, $C_6H_4CH_3$-*n*, $CH_2C_6H_5$

Esterification of 3-phenyl-8-methylthioacetic acid (3.1) and 3-benzyl-8- methylthioacetic acid (3.3), Propyl and ethyl alcohol in the presence of a catalytic amount of sulfuric acid was obtained N-propyl ester of 3-phenyl-xanthine-8-methyl thioacetic acid (**3.19**) and methyl ester of 3-benzylxanthine-8-methylthioacetic acid (**3.22**).

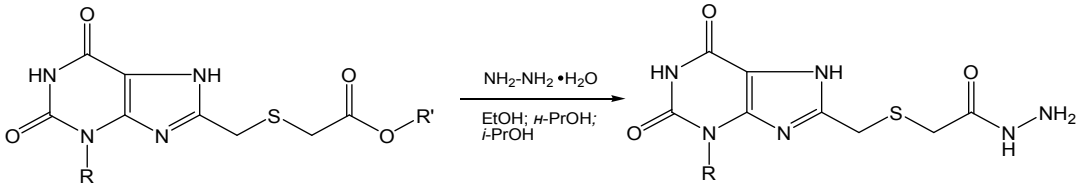


3.1-3.3 3.19, 3.22

R = C_6H_5, $CH_2C_6H_5$

R' = CH_3, C_3H_7-*n*

Reacting esters 3.22 with an excess of hydrazine hydrate in ethanol and propane were obtained hydrazide of 3-benzylxanthine-8-methylthioacetic acid (**3.28**)



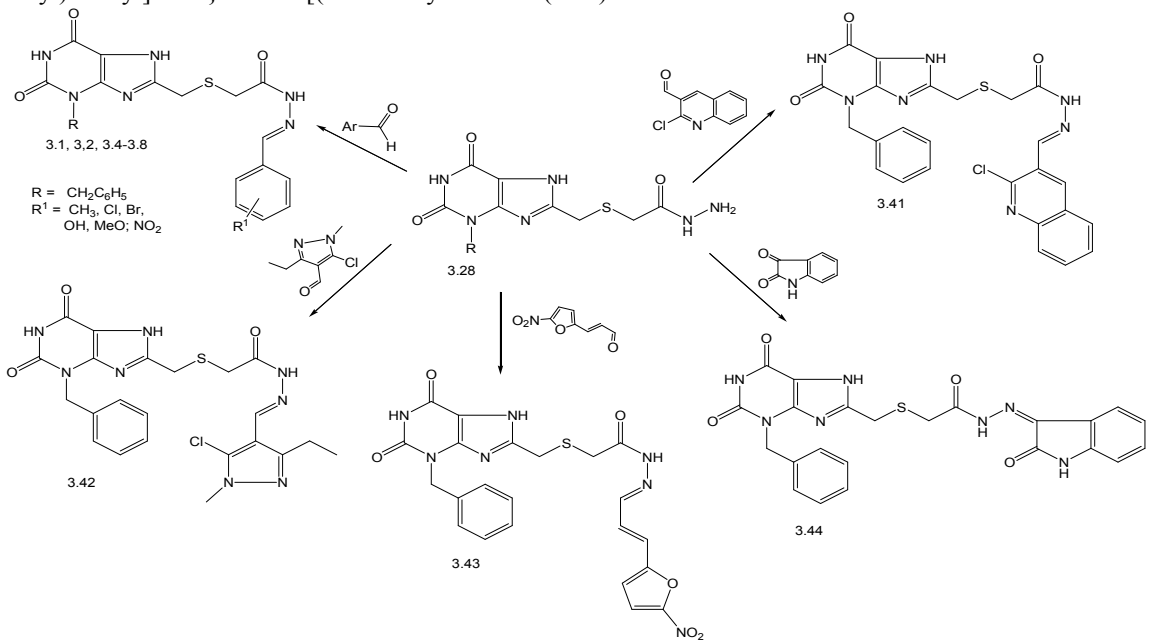
3.22

R = $CH_2C_6H_5$

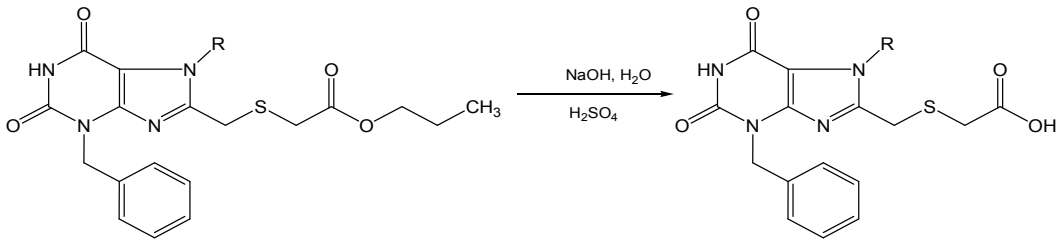
R' = CH_3

3.28

Reaction hydrazide (3.28) with an equimolar amount karbonilnogo connectings occurs when heated during 20-40 minutes delirium 50% acetic acid or dioxane in the presence of a catalytic amount of acetic acid Concentration to form the corresponding ylidenehydrazides: 2 - {[(3-benzylxanthine-8-yl)methyl] thio}-N '-[(1Z) phenylmethylliliden]acetohydrazide (**3.31**); 2 - {[(3-benzylxanthine-8-yl)methyl] thio}-N '-[(4-methyl-phenyl] methylliliden)acetohydrazide (**3.32**); 2 - {[(3-benzylxanthine-8-yl)methyl] thio}-N '-[(4-bromo-fenilschmetililiden) atsetogidrazid (**3.34**); 2 - {[(3-benzylxanthine-8-yl)methyl] thio} -N '- [(4-hydroxyphenyl] metililiden) atsetogidrazid (**3.35**); 2 - {[(3-benzyl-xanthine 8-yl)methyl] thio} -N '- [(4-methoxy-fenilschmetililiden) acetohydrazide (**3.36**); 2 - {[(3-benzylxanthine-8-yl)methyl] thio} -N '- [(4-nitrophenyl] methyliliden) acetohydrazide (**3.37**); 2 - {[(3-benzylxanthine 8-yl)methyl] thio} -N '- [(3-nitrophenyl] methyliliden) acetohydrazide (**3.38**); 2 - {[(3-benzyl-xanthine 8 -) methyl] thio} -N '- [(1Z) - (2-chloroquinoline-3-yl)methyliliden]acetohydrazide (**3.41**); 2 - {[(3-benzyl-xanthine-8-yl)methyl] thio} -N '- [(1Z) - (5- chloro-3-etil-1-methyl-1H-pyrazol-4-yl) methyliliden] acetohydrazide (**3.42**); 2 - {[(3-benzylxanthine-8-yl)methyl] thio} -N '- [(2E) -3-(5-nitrofuran-2-yl)prop-2-en-1-ililiden]acetohydrazide (**3.43**); 2 - {[(3-benzyl-xanthine-8-yl) methyl] thio} -N '- (2-oxo-2,3-dihydro-1H-indol-3-ylidene)acetohydrazide (**3.44**).

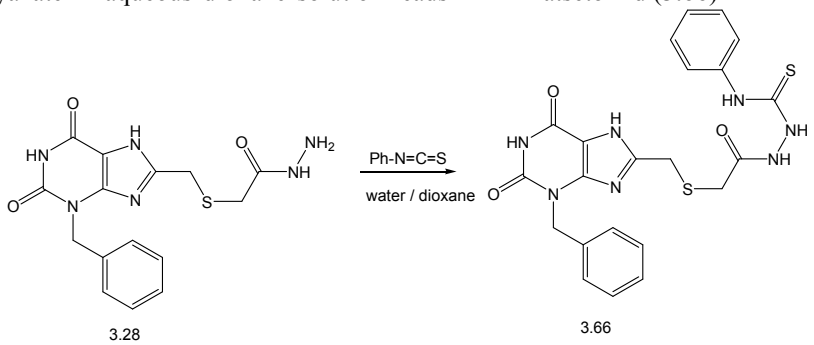


Alkaline hydrolysis of the 7-substituted derivatives as intermediates in synthesizing products (n-propyl ester 3,7-dibenzylxanthine-8-methylthioacetic acid) in water with subsequent neutralization delirium sulfate acid was obtained 3,7- dibenzyl xanthine-8-methy lthioacetic acid (**3.54**).

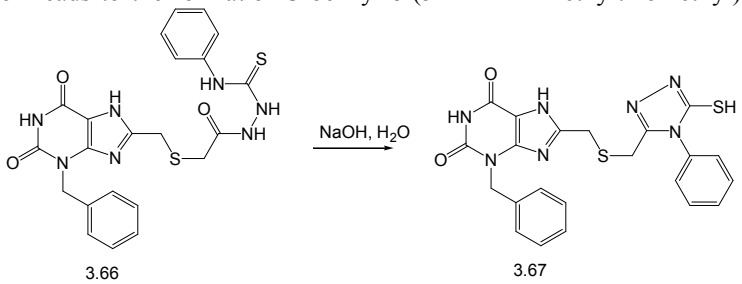


R = $CH_2C_6H_5$,

It has been established that a short boiling substance (3.28) with phenyl thioisocyanate in aqueous dioxane solution leads to the formation 2 - {[(3-benzyl-xanthine 8-yl) methyl] thio} -N - [(fenilkarbamo-tioil) amino] - atsetomid (**3.66**)



Alkaline carbothiamide (3.66) cyclization leads to the formation 3-benzyl-8-(5'-thio-4'-phenyl-[1,2,4] triazol-3'-yl-methylthiomethyl)xanthine (**3.67**)



To determine the antimicrobial and fungicidal activity used benchmark test culture as gram-positive and gram-negative bakterium that relate to the various properties on morphophysiological clinically significant groups of infectious agents. As a set of standard test cultures were strains of microorganisms: (Staphylococcus aureus ATCC 25923, Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853) and fungi (Candida albicans ATCC 885-653). Determining the antimicrobial activity of the test substances were determined by two fold serial dilutions in a liquid nutrient medium [12]. Defines the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBtsK) and minimum fungicidal concentration (MFtsK). Control of antimicrobial active substance relative to antimicrobial active substance relative to the test strains was performed according the order № 167 from 05.04.2007 Ukraine. On approval guidelines "Determining the sensitivity of microorganisms to antibiotics" [13].

RESULTS:

3.1

PMR N^7H(c, 1H) 13,49; N^1H(c, 1H) 11,18; OH(c, 1H) 12,67; CH_2(c, 2H) 3,85; 3,38; CH $_{aromatic}$ 7,53-7,36 (м, 5H).**PMR**. NH 3290; 3183; CH $_{aromatic}$ 3030; C=O 1695; 1679; C=N 1640; C=C 1584; C-S 730; Other signals 3600; 2950.

Tem.of melting 237-8

3.2

PMR N^7H(c, 1H) 13,48; N^1H(c, 1H) 11,21; OH(c, 1H) 12,67; CH_2(c, 2H) 3,78; 3,42; CH $_{aromatic}$ 7,49-7,01 (м,4H); CH_3(c, 3H) 2,38. **IR**. NH 3300; 3180;

CH $_{aromatic}$ 3020; C=O 1700; 1680; C=N 1652; C=C 1558; C-S 720; Other signals 3648; 2833. **Tem.of melting** 129-30

3.3

PMR N^7H(c, 1H) 13,48; N^1H(c, 1H) 11,16; OH(c, 1H) 12,67; CH_2(c, 2H) 5,10; 3,86; 3,41; CH $_{aromatic}$ 7,36-7,25 (м, 5H). **IR**. NH 3280; 3150; CH $_{aromatic}$ 3052; C=O 1710; 1694; C=N 1661; C=C 1564; C-S 743; Other signals 3610; 2960. **Tem.of melting** 241-2

3.19

PMR; N^7H(c, 1H) 13,48; N^1H(c, 1H) 11,24; CH_2(c, 2H) 3,85; 3,48; CH $_{aromatic}$ 7,52-7,34 (м, 5H); Other signals 3,96 (т, 2H)– O- CH_2; 1,56 (м, 2H) – O-C-CH_2; 0,88 (т, 3H) – CH3. **IR**. NH 3260; 3140; CH $_{aromatic}$ 3030; C=O 1725;1680; C=N 1660; C=C 1580; C-S 746; Other signals 2972; 975. **Tem.of melting** 158-60

3.22

PMR N^7H(c, 1H) 13,48; N^1H(c, 1H) 11,18; CH_2(c, 2H) 5,09; 3,86; 3,49; CH $_{aromatic}$ 7,33-7,27 (м, 5H); CH_3(c, 3H) 3,60. **IR**. NH 3260; 3150; CH $_{aromatic}$ 3020; C=O 1738; 1710; C=N 1665; C=C 1580; C-S 743; Other signals 2955; 994. **Tem.of melting** 235-6

3.28

PMR NH(c, 1H) 13,48; 11,15; 9,12; NH_2(пс, 2H) 4,27; CH_2(c, 2H) 5,11; 3,89; 3,20; CH $_{aromatic}$ 7,35-7,25 (м, 5H). **IR**. NH 3300; 3140; CH $_{aromatic}$ 3031; C=O 1720; 1673; C=N 1640; C=C 1580; C-S 748; Other signals 2968. **Tem.of melting** 264-5

3.31

PMR N^7H(c, 1H) 13,48; CONH(c, 1H) 11,46; N^1H(c, 1H) 11,16; N=CH(c, 1H) 8,10; CH $_{aromatic}$ 7,73-7,23 (м, 10H); CH_2(c, 2H) 5,02; 3,81; 3,19. **IR**. NH 3280; 3110; CH $_{aromatic}$ 3020; C=O 1720; 1688; C=N 1640; C=C 1553; C-S 755; Other signals 2960. **Tem.of melting** 263-4

3.32

PMR N^7H(c, 1H) 13,48; CONH(c, 1H) 11,24; N^1H(c, 1H) 11,10; N=CH(c, 1H) 8,04; CH $_{aromatic}$ 7,62-7,26 (м, 9H); CH_2(c, 2H) 5,09; 3,84; 3,52; Other signals 2,32 (c, 3H) – CH_3. **IR**. NH 3260; 3120; CH $_{aromatic}$ 3032; C=O 1720; 1667; C=N 1620; C=C 1551; C-S 744; Other signals 2980. **Tem.of melting** 262-4

3.34

PMR N^7H(c, 1H) 13,48; CONH(c, 1H) 11,44; N^1H(c, 1H) 11,12; N=CH(c, 1H) 7,92; CH $_{aromatic}$ 7,78-7,27 (м, 9H); CH_2(c, 2H) 5,09; 3,89; 3,22. **IR**. NH 3250; 3140; CH $_{aromatic}$ 3061; C=O 1715; 1670; C=N 1580; C=C 1552; C-S 744; Other signals 2990; 611. **Tem.of melting** 261-2

3.35

PMR N^7H(c, 1H) 13,47; CONH(c, 1H) 11,22; N^1H(c, 1H) 11,14; N=CH(c, 1H) 7,83; CH $_{aromatic}$ 7,48 (д, 2H); 7,32-7,08 (м, 5H); 6,74 (д,2H); CH_2(c, 2H) 5,06; 3,82; 3,79; Other signals 9,95 (c, 1H) –OH. **IR**. NH 3280; 3140; CH $_{aromatic}$ 3006; C=O 1715; 1666; C=N 1605; C=C 1540; C-S 744; Other signals 2960; 744. **Tem.of melting** 260-1

3.36

PMR N^7H(c, 1H) 13,48; CONH(c, 1H) 11,34; N^1H(c, 1H) 11,16; N=CH(c, 1H) 7,82; CH $_{aromatic}$ 7,62-6,92 (м, 9H); CH_2(c, 2H) 5,03; 3,98; 3,22; Other signals 3,54 (c, 3H) –O-CH_3. **IR**. NH 3280; 3140; CH $_{aromatic}$ 3006; C=O 1715; 1666; C=N 1605; C=C 1540; C-S 744; Other signals 2960; 744. **Tem.of melting** 203-5

3.37

PMR N^7H(c, 1H) 13,45; CONH(c, 1H) 11,82; N^1H(c, 1H) 11,16; N=CH(c, 1H) 7,98; CH $_{aromatic}$ 8,24-7,27 (м, 9H); CH_2(c, 2H) 5,11; 3,89; 3,28. **IR**. NH 3280; 3150; CH $_{aromatic}$ 3040; C=O 1710; 1680; C=N 1610; C=C 1584; C-S 737; Other signals 2970. **Tem.of melting** 265-6

3.38

PMR N^7H(c, 1H) 13,47; CONH(c, 1H) 11,52; N^1H(c, 1H) 11,14; N=CH(c, 1H) 8,42; CH $_{aromatic}$ 8,24 (т, 2H); 8,01 (д, 2H); 7,67 (м, 1H); 7,35-7,04 (м, 5H); CH_2(c, 2H) 5,01; 3,87; 3,71. **IR**. NH 3250; 3150; CH $_{aromatic}$ 3030; C=O 1710; 1680; C=N 1620; C=C 1530; C-S 734. Other signals 2960. **Tem.of melting** 265-6

3.41

PMR N^7H(c, 1H) 13,49; CONH(c, 1H) 11,82; N^1H(c, 1H) 11,14; N=CH(c, 1H) 8,40; CH $_{aromatic}$ 8,87 (д, 1H); 8,12-7,84 (м, 3H); 7,72 (т, 1H); 7,39-6,98 (м, 5H); CH_2(c, 2H) 4,99; 3,91; 3,78. **IR**. NH 3240; 3150; CH $_{aromatic}$ 3020; C=O 1700; 1674; C=N 1614; C=C 1583; C-S 738; Other signals 2970; 610. **Tem.of melting** 214-6

3.42

PMR N^7H(c, 1H) 13,34; CONH(c, 1H) 11,36; N^1H(c, 1H) 11,16; N=CH(c, 1H) 8,22; CH $_{aromatic}$ 7,51-7,09 (м, 5H); CH_2(c, 2H) 5,06; 3,88; 3,59; Other signals 3,32 (c, 3H) – N-CH_3; 2,84 (м, 2H) – CH_2; 1,14 (кв, 3H) – CH_3. **IR**. NH 3280; 3160; CH $_{aromatic}$ 3020; C=O 1700; 1682; C=N 1620; C=C 1540; C-S 730; Other signals 2971; 610. **Tem.of melting** 204-5

3.43

PMR N^7H(c, 1H) 13,42; CONH(c, 1H) 11,61; N^1H(c, 1H) 11,18; N=CH(c, 1H) 7,83; CH $_{aromatic}$ 7,39-7,21 (м, 5H); 7,14 (д, 1H); 6,98 (д, 1H); CH_2(c, 2H) 5,11; 3,93; 3,30; Other signals 7,72 (д, 1H) – CH; 3,57 (д, 1H) – CH. **IR**. NH 3240; 3140; CH $_{aromatic}$ 3033; C=O 1680; 1666; C=N 1610; C=C 1520; C-S 734; Other signals 2980; 1022. **Tem.of melting** 205-6

3.44

PMR N^7H(c, 1H) 13,38; CONH(c, 1H) 11,29; N^1H(c, 1H) 11,15; CH $_{aromatic}$ 7,52-7,26 (м, 7H); 7,16-6,96 (д, 2H); CH_2(c, 2H) 5,06; 3,92; 3,33; Other signals 12,53 (c, 1H) – NH. **IR**. NH 3250; 3120; CH $_{aromatic}$ 3030; C=O 1720; 1688; C=N 1614; C=C 1580; C-S 744; Other signals 2985. **Tem.of melting** 245-7

3.54

PMR NH(c, 1H) 11,22; CH $_{aromatic.}$ 7,61-6,79 (м, 10H); CH_2(c, 2H) 5,59 (N^7-CH_3); 5,09 (N^3-CH_3); 3,88 (S-CH_2); 3,44 (C^8-CH_2); Other signals 12,72 (c, 1H) – OH. **IR** NH 3140; CH $_{aromatic}$ 3010; C=O 1700; 1680; 1666; C=N 1640; C=C 1600; C-S 729; Other signals 3615; 2980. **Tem.of melting** 120-1

3.66

PMR NH(c, 1H) 13,48; 11,14; 10,12; 9,79; 9,65; CH $_{aromatic.}$ 7,62-7,02(м, 10H); CH_2(c, 2H) 5,06; 3,89; 3,52. **IR**. NH 3260; 3140 CH $_{aromatic}$ 3022; C=O 1690; 1679; C=N 1620; C=C 1548; C-S 745; Other signals 2860. **Tem.of melting** 185-6

3.67

PMR. NH(c, 1H) 13,36; 11,12; CH $_{aromatic.}$ 7,72-7,08 (м, 10H); CH_2(c, 2H) 5,00; 3,72; 3,59; Other signals 13,82 (c, 1H) – SH. **IR**. NH 3290; 3130 CH $_{aromatic}$ 2987; C=O 1690; 1680; C=N 1630; C=C 1550; C-S 744; Other signals 2880. **Tem.of melting** 224-5

Table I: Results of the study of antimicrobial and antifungal activity 3- R -8-methylxanthinylthioacetic acids and their derivatives

Name	*E.coli*		*S.aureus*		*P.aeruginosa*		*C.albicans*	
	MIC, *mcg/ml*	MBtsC, *mcg/ml*	MIC, *mcg/ml*	MBtsC, *mcg/ml*	MIC, *mcg/ml*	MBtsC, *mcg/ml*	MIC, *mcg/ml*	MFtsC, *mcg/ml*
3.1	25	50	50	100	25	50	>200	>200
3.2	25	50	50	100	100	100	50	100
3.19	25	50	25	50	50	100	>200	>200
3.22	50	100	50	50	25	50	200	200
3.28	25	50	50	50	50	100	100	200
3.3	12,5	12,5	25	25	50	100	100	200
3.31	25	50	50	100	25	50	100	100
3.32	25	50	50	50	12,5	25	100	100
3.34	25	50	100	100	50	100	>200	>200
3.35	25	50	50	50	50	50	100	200
3.36	25	50	12,5	50	50	50	50	100
3.37	25	50	50	100	25	100	100	100
3.38	25	50	25	50	12,5	50	200	200
3.41	25	50	50	100	25	50	>200	>200
3.42	1,56	1,56	25	25	25	50	200	200
3.43	100	100	12,5	12,5	100	200	100	100
3.44	25	50	25	50	100	100	100	200
3.54	25	50	50	50	50	100	50	100
3.66	6,25	6,25	25	25	12,5	25	100	200
3.67	3,12	3,12	12,5	12,5	50	100	100	200

DISCUSSION:

As seen from the data shown in the table, almost all derivatives of 3-phenyl (4-methylphenyl, benzyl) xanthine-8-methylthioacetic acids to microorganisms that have been studied (Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans), exhibit weak activity. Of the total number of substances that can be studied to allocate connection (3.66) - {[(3-benzylxanthine 8-yl) methyl] thio} -N - [(phenylkarbamotioil)amino] acetamide, which influence the culture Escherichia coli in MBtsS 6,25 ug / ml and MIS 6,25 mcg / ml. Substance (3.67) - 3-benzyl-8-({[(4-phenyl-5-thio-4H-1,2,4-triazol-3-yl) methyl]thio} methyl) xanthine towards *E. coli* showed bactericidal and bacteriostatic effect in minimum inhibitory concentration of 3.12 mcg / ml, and 2 - {[(3-benzylxanthine-8-yl) methyl] thio} -N '- [(1Z) - (5- chloro-3-ethyl-1 methyl-1H-pyrazol-4-yl) -metililiden] - atsetogidrazid (3.42) against E. coli culture has an effect in MIC 1,56 mcg / ml and MBtsK 1,56 mcg / ml.

CONCLUSION:

By analyzing data obtained from the study, one can conclude that the 3-R-8-methylthioacetic acid and derivatives thereof exhibit antimicrobial activity in the presence of well-known substituents pharmacophores which contain the residue pyrazole, 5-nitrofuran, thiosemicarbazide, triazole, which are included in antimicrobials composition [14]. Since the unique biological effects of xanthine derivatives of the bicycle and is primarily in their role as agonists or antagonists of the [15-19] purine receptors. Consequently, the xanthine derivatives may have a regulatory effect on any of the functions of the human body. Given the fact that the bacterial lesions are often associated with a sharp decline in immunity. Relevant is the study of xanthine bicycle as a combination of drugs can simultaneously inhibit the growth of pathogenic organisms and stimulate the body's immune processes.

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