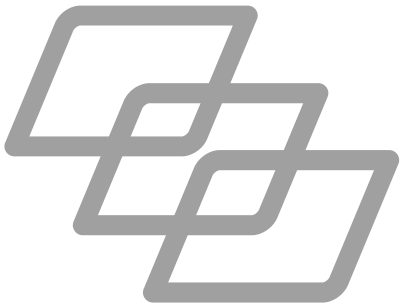

Південна
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«НОВІ ДОСЯГНЕННЯ У ГАЛУЗІ МЕДИЧНИХ ТА ФАРМАЦЕВТИЧНИХ НАУК»

ЗБІРНИК ТЕЗ НАУКОВИХ РОБІТ

18-19 листопада 2016 р.

Одеса

Громадська організація
«Південна фундація медицини»

ЗБІРНИК ТЕЗ НАУКОВИХ РОБІТ

УЧАСНИКІВ МІЖНАРОДНОЇ
НАУКОВО-ПРАКТИЧНОЇ КОНФЕРЕНЦІЇ

НОВІ ДОСЯГНЕННЯ У ГАЛУЗІ МЕДИЧНИХ ТА ФАРМАЦЕВТИЧНИХ НАУК

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Н 73 **Нові досягнення у галузі медичних та фармацевтичних наук:** матеріали міжнародної науково-практичної конференції (м. Одеса, 18-19 листопада 2016 року). – Одеса: ГО «Південна фундація медицини», 2016. – 104 с.

У збірнику представлені матеріали міжнародної науково-практичної конференції «Нові досягнення у галузі медичних та фармацевтичних наук», розглядаються загальні проблеми клінічної та профілактичної медицини, питання ветеринарної, фармацевтичної науки та інше.

Призначений для науковців, практиків, викладачів, аспірантів і студентів медичної, фармацевтичної та ветеринарної спеціальностей, а також для широкого кола читачів.

Організатори конференції не завжди поділяють думку учасників. У збірнику максимально точно відображається орфографія та пунктуація, запропонована учасниками.

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THE SEARCH OF BIOLOGICALLY ACTIVE COMPOUNDS IN A ROW OF 8-AMINO-7-(2-HYDROXY-2-PHENYLETHYL)-3-METHYLXANTHINES

Over the past decade the emerging global threat of antibacterial resistance has alarmingly come to the forefront. Antibiotics, thought one of the greatest medical discoveries of the 20th century, and still pivotal in medicine now, are becoming increasingly compromised. The diminishing effectiveness of many antibiotics is due to the emergence of antibacterial resistance, and although a natural phenomenon, the inappropriate use of antibiotics in both human beings and animals worldwide, has accelerated the emergence and spread of highly resistant bacterial clones [1, p. 692-701; 2, p. 15-21]. The speed at which bacteria have evolved to become resistant to antibiotics has surpassed the speed of drug discovery. This exacerbates the issue of resistance and stresses the need to preserve the efficacy of existing antibiotics. In short, without effective treatment, not only would bacterial epidemics become a substantial public health threat once again, but advances in modern medicine, ranging from minor surgery to cancer therapy, would also be jeopardised [3, p. 1057-1098].

Oxidative stress is characterized as an imbalance between the production of reactive species and antioxidant defence activity, and its enhanced state has been associated with many of the chronic diseases such as cancer, diabetes, neurodegenerative and cardiovascular diseases [4, p. 652-659].

Liver is a major organ attacked by ROS [5, p. 4850-4860]. Parenchymal cells are primary cells subjected to oxidative stress induced injury in the liver. The mitochondrion, microsomes and peroxisomes in parenchymal cells can produce ROS, regulating on PPARα, which is mainly related to the liver fatty

acid oxidation gene expression. Moreover, Kupffer cells, hepatic stellate cells and endothelial cells are potentially more exposed or sensitive to oxidative stress-related molecules. A variety of cytokines like TNF-α can be produced in Kupffer cells induced by oxidative stress, which might increase inflammation and apoptosis. With regard to hepatic stellate cells, the proliferation and collagen synthesis of hepatic stellate cells is triggered by lipid peroxidation caused by oxidative stress [6, p. 30-46; 7, p. 8082-8091; 8, p. 141-154].

Thus, creation of new modern drugs, that have antimicrobial, antifungal and antioxidant properties, is important and promising trend.

The aim of our work was the synthesis of xanthine derivatives previously undescribed and the study of their biological action.

Materials and Methods. The melting point was determined by the open capillary method on a PTP-M device (a device for determining the melting temperature of solid substances, Russia). Elemental analysis was performed on an Elementar Vario L cube device (Germany), The NMR spectra were taken on a Bruker SF-400 spectrometer (Germany) (the working frequency – 400 MHz, the solvent – dimethylsulfoxide (DMSO), the internal standard – tetramethylsilane). The data of elemental analysis corresponded to the calculated ones.

Molecular descriptors have been calculated using the computer programs ALOGPS and DRAGON, whereas biological properties of the synthesized compounds have been calculated with the help of GUSAR and ACD / Percepta Platform.

The assessment of the antimicrobial and antifungal activity was carried out using the standard test strains of microorganisms obtained in the bacteriological laboratory of the SI «Zaporizhzhia Regional Laboratory Centre of the State Sanitary and Epidemiological Service of Ukraine». Such strains as *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853), *Candida albicans* (ATCC 885-653) were used in our studies. The sensitivity of microorganisms to the new promising antimicrobial compounds synthesized was determined according to the methodical recommendations [9, p. 1-38]. To incubate bacteria the Mueller-Hinton broth and agar (pH 7.2-7.4) were used, and for fungi the Sabouraud's medium (pH 6.0-6.8) was applied.

The minimal inhibitory concentration (MIC) was determined. Dimethylsulfoxide (DMSO) was used as a solvent for the compounds in our

studies, the initial solutions were adjusted to the concentration of 1 mg/ml. Additionally monitoring of nutrient media and the solvent was performed using conventional methods. As the reference drugs ampicillin (PJSC «Kyivmedpreparat», Ukraine) and nistatine (PJSC SIC «Borshchahivskiy CPP», Ukraine) were used.

Antioxidant activity (AOA) has been studied in vitro applying the method of nonenzymic initiation of free-radical oxidation [10, p. 1-26]. As reference substances for comparison were used Ascorbic acid and Thiotriazolinum.

The 2,2-diphenyl-1– picrylhydrazyl (DPPH) free radical scavenging activities of 8-aminoderivatives of 7-(2-hydroxy-2-phenylethyl)-3-methylxanthine were carried out as reported by Al-Omair et al. [11, p. 2591-2610]. 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:

$$I\% = \frac{Acontrol - Asample}{Acontrol} \times 100\%,$$

where Acontrol is the absorbance of the control and Asample is the absorbance of the aminoderivatives.

Results and Discussion. 8-Bromo-7-(2-hydroxy-2-phenylethyl)-3-methylxanthine previously synthesized [12, p. 660-663] by the interaction of 8-bromo-3-methylxanthine with phenyloxirane was selected as a starting compound. The reactions of bromoxanthine with the primary and secondary amines were studied. It has been found that regardless of the amine structure boiling of the synthons specified in the aqueous dioxane medium leads to formation of the corresponding 8-amino derivatives. The compounds obtained are white crystalline substances, insoluble in water and soluble in hot ethanol, propanol-2, dioxane-1,4, dimethylformamide, DMSO.

Further properties of the synthesized compounds were calculated. It has been found that all compounds satisfy to the Rule of five [13, p. 3-26], which means that the Lipinski index for all substances is 0. Further the Ghose filter

has been used. It should be noted that compounds 6 and 7 in terms of polar surfaces do not satisfy to all criteria the Ghose filter [14, p. 55-68].

8-Aminoderivatives of 7-(2-hydroxy-2-phenylethyl)-3-methylxanthine has been shown the antimicrobial and antifungal activity against *Staphylococcus aureus* and *Candida albicans,* and it is higher than that of the reference drugs – ampicillin and nistatine. Some regularities in the «chemical structure – biological activity» relationship have been determined.

The studies in vitro have shown that all the compounds in terms of AOA in concentration 10^{-3} mol / L exceed the standards of comparison.

The above facts clearly demonstrate reasonability and prospects for further search of antimicrobial, antifungal and antioxidant agents in the series of xanthines, especially among their 8-aminosubstituents. For final conclusions it is necessary to significantly expand both the spectrum of pathogenic microorganisms, and the number of the compounds synthesized.

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