Synthetic Substances - Antibacterial and Antifungal Potential Products

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***Abstract* — The paper presents the research results of a series of synthetic substances that have pronounced antibacterial and antifungal properties and can serve as a basis for obtaining and producing of new antibacterial and antifungal medicines.**

***Index Terms* — Antibacterial and antifungal synthetic substances.**

I. INTRODUCTION

One of the greatest scientific discoveries of the twentieth century can rightly be considered the antibacterial chemotherapy discovery that essentially changed the efficiency of treatment of the infectious diseases. However, antibacterial therapy continues to be an acute problem about the emergence and reemergence of many infections, the increase of the diseases caused by conditionally pathogenic bacteria, microorganisms' acquisition of resistance to antibacterial substances (8).

Solving of this problem is in permanent increasing of the antibacterial substances fund. Over the years 1990-2012 in the scientific laboratory "Hospital infections" of the Epidemiological chair of The State University of Medicine and Pharmacy "Nicolae Testemitanu" of the Republic of Moldova were studied hundreds of indigenous substances of synthetic origin with antibacterial and antifungal properties, which could be used in obtaining the new antibacterial and antifungal medicines (2, 3, 4, 5, 6, 7, 8, 9, 10, 13, 14).

II. MATERIALS AND METHODS

The researches on the antibacterial properties of the synthetic origin substances (Organic compounds) were realized applying the method of serial dilutions in liquid, as nutrient medium was used 2% meat - peptone broth (11). As reference cultures were used Gram-positive and Gram-negative microorganisms: S. aureus (Wood-46, Smith, 209-P), S. Saprophyticus, Streptococcus group A and G, E. faecalis, E. coli, S.typhimurium, K.pneumoniae, P. aeruginosa, P. vulgaris. The antifungal properties were investigated in broth Saburo on laboratory strains Aspergillus niger, Aspergillus fumigatus, Candida albicans and Penicillium.

Bacteriostatic activity was assessed in the absence of growth of microorganisms in the liquid nutrient medium and the bactericidal activity were based on the lack of growth of microorganisms on the solid nutrient medium - meat peptone agar after the repeated sowing and ulterior thermostating during 24 hours. The evaluation of the results for yeast and mycelium was done on agar Saburo after 7 and 14 days of incubation.

The study of the acute toxicity (LD 50) of the compounds was performed under general toxicity methodical recommendations on general toxicity of the pharmaceutical remedies (5, 12), on rats and white mice by introducing into the stomach of investigated substances in aqueous.

III. RESULTS AND DISCUSSION

1. New substances antibacterial from hydrazone class

1.1. Izonicotinoilhidrazone aldehyde 5-nitro-2-furan (Izohidrafural)

The substance is a new organic compound from the nitrofuran compounds seria (2, 3), synthesized at the inorganic and physical chemistry department of MSU. It is characterized by pronounced antibacterial activity, low toxicity and high stability. Compared to structural analogue - furacilinum, is 2-4 times more active and 9 times less toxic (Fig. 1).

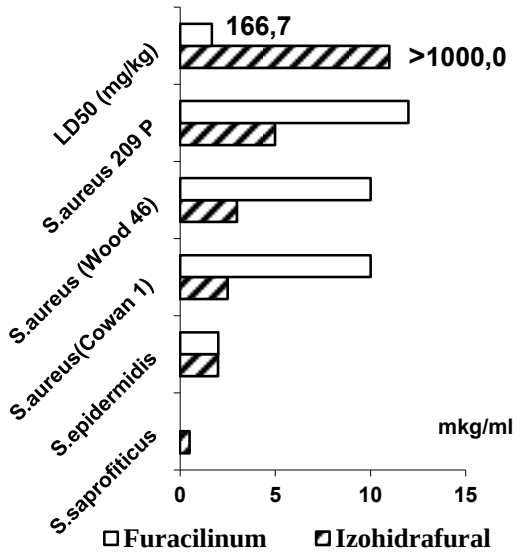

Fig. 1 Antibacterial activity and toxicity of Izonicotinoilhidrazone Aldehyde 5-nitro-2-furan

From this organic compound were prepared 2 new medicinal preparations - solution "Izofural - 0.05%" and ointment "Izofural - 0.1%", which have analogous furacillin properties, but exceed her activity 2 to 20 times towards the various Gram-positive and Gram-negative microorganisms species, while being 9 times less toxic (4, 5). Clinical tests proved the positive qualities of the obtained substances in the treatment of purulent wounds, burns, chronic tonsillitis, osteitis, periodontitis (1, 8).

1. 2. Hydroxibenzil 2-methylene-1-aldehyde hydrazone 5-nitro-2-furan

The substance is an organic compound from the hydrazone class with a selective antimicrobial activity against Staphylococcus genus bacteria. It can be applied in medicine as antimicrobial drug used in the treatment of diseases induced by staphylococcal or as ingredient for creating selective nutrient media.

The mentioned compound shows so bacteriostatic as well bactericidal high activity towards the investigated strains of Staphylococcus (in concentrations 1.25 to 5.0 mg / ml). The obtained experimental results show that the bactericidal activity of the substance is 2-7 times higher than the structural analogue - furacilinum. At the same time, the toxicity of this compound is 6 times lower (LD 50 = 990 mg / kg) compared with furacilinum toxicity (LD 50 = 166.7 mg / kg).

2. Complexes of the zinc

2. 1. Bis [N [1] - (2-oxy-1-naphthyl) 5-nitro-2-furfurilidenhidrazonato] zinc

The certain substance is a new coordinative compound of zinc with derivative 5 nitrofuran, which can be used in medicine and pharmacy, as an active substance in elaboration of the new antimicrobial preparations. The compound manifests bacteriostatic and bactericidal activity in low concentrations (0.6 to 37.5 mg / ml) against Gram-positive microorganisms of the genus Staphylococcus and Streptococcus. Bactericidal activity of the mentioned substance is 8-33 times higher than furacilinum. Moreover, the compound is 6 times less toxic than furacilinum (Fig. 2).

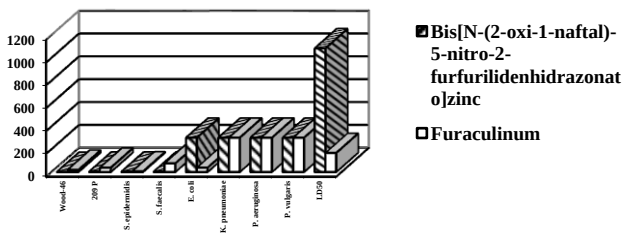

Fig. 2. Bactericide activity and toxicity of the Bis[N1-(2-oxi-1-naftil)5-nitro-2-furfurilidenhidrazonato]zinc

3. The complexes of copper

3. 1. Di(μ-O)di[N-(2-oxo-1-naftali)-N[1]-α-oxobenzalihidrazincupru]dihidrate

The obtained results denote that the complex manifests a selective activity towards the bakeries from the genus Staphylococcus. The activity of this is 2-4 times higher or remains as well as furacilinum action, used in medical practice.

The detected properties of the compound represent an interest for practical microbiology in the optimization of the selective properties of the nutrient media.

3.2. 3.5-Dibromsalicilidentiosemi-carbazidoamin cuprum dihydrate

The substance is a new coordinative compound of copper, which belongs to the class of thiosemicarbazone transition metal complexes with a large spectrum of antibacterial and antifungal action. It manifests the bactericidal activity in the limits of concentrations within 0.036 to 4000 mg / ml depending on the species of microorganisms and, respectively, antifungal activity in the concentration from 18.7 to 300 mg / ml.

Bactericidal activity towards Gram-positive microorganisms proved to be from 64 up to 4116 times and Gram-negative microorganisms from 2 to 297 times higher compared to furacilinum (Fig. 3) and antuifungical activity - from 1.6 up to 25.8 times higher in comparison with nystatinum (Fig. 4). However, the toxicity of certain compound is about 8 times lower in comparison with toxicity furacilinum.

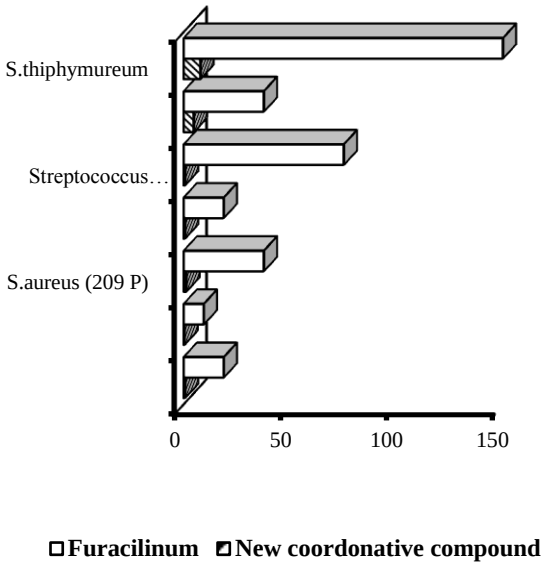

Fig. 3. Antibacterian activity of the intern compound of cuprum 3,5–Dibromsalicilidentiosemicarbazido-amincupru dihidrat

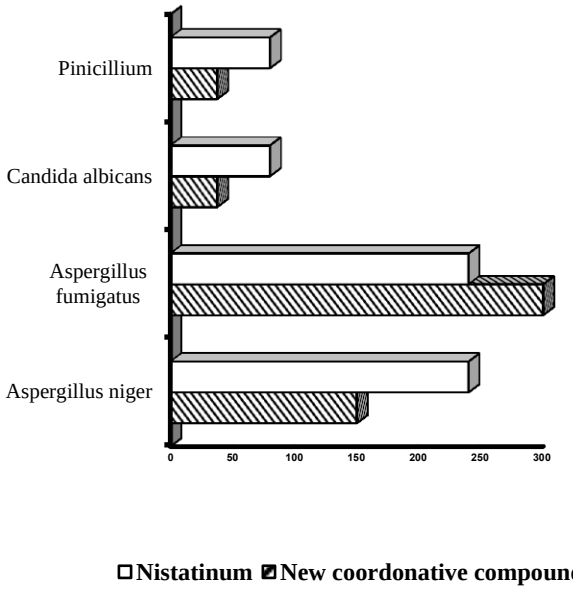

Fig.4. Antimycotic activity of the intern compound of cuprur 3,5-Dibromsalicilidentiosemicarbazidoamincupru dihidrat

3.3. Di(μ-O)-bis(3,5-dibromsalicili-dentiosemicarbazonatocuprum)

This substance is a new coordinative compound of copper, which belongs to the class of thiosemicarbazone transition metals. The certain compound manifests bactericidal activity in concentrations within 0.072 ... 600 mg / ml against Gram-positive and of 2 to 6.7 higher times towards Gram-negative microorganisms in comparison with its prototype - furacilinum (Fig. 5). Toxicity (LD 50) of the compound given is 1500 mg / kg.

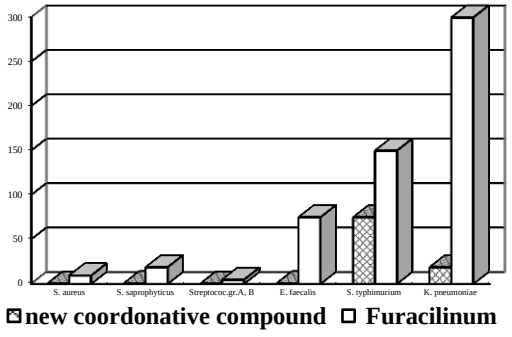

Fig. 5. Bactericidal activity of the Di (μ–O)–βισ (3,5-dibromsalicilidentiosemicarbazonatocupru)

3.4. Chloro-3,5-dibromsaliciliden-tiosemicarbazidocuprului

The certain substance is, also, from a new compound coordinative class of thiosemicarbazone transition metals that manifests a large spectrum of antibacterial and antifungal activity. Bacteriostatic activity occurs within limits from 0.018 to 150 mg / ml as against the Gram-positive and Gram-negative microorganisms with exception of P. aeruginisa, when DMI is 300 - 2000μg/ml (Fig. 6).

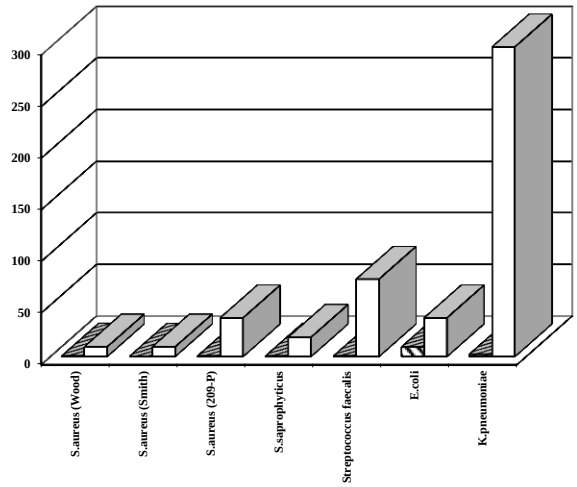

Fig. 6. Antibacterial activity of organic compounds Chloro-3,5-dibromsalicilidentiosemicarbazid

The compound manifests antifungal activity in the limits of concentrations within 18.7 to 300 mg / ml, which is 1.1 to 6.4 times higher than Nystatin activity (Fig.7).

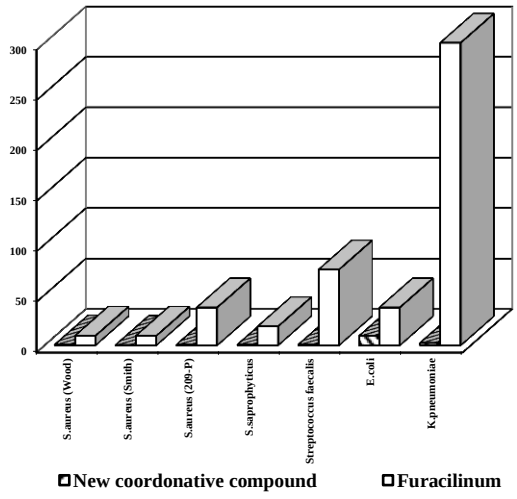

Fig. 7. Antifungal activity of organic compound Chloro-3,5-dibromsalicilidentiosemi-carbazidocuprum

4. ***Complexes of cobalt***

1. Bis [p-(5-nitrofuril-2-metilenhidrazonă) izatină] di (3-picoline cobalt) and **Bis [p - (5-nitrofuril-2-metilenhidrazonă) izatină] di (4-picoline cobalt).**

This compounds manifests bactericidal activity against Gram-positive and Gram-negative microorganisms in the concentration from 0.03 to 12.5 mg / ml, which is 16-40 times higher compared with

furacilinum. The certain substances belong to the class of substances with low toxicity (LD_{50} = 1960.0 mg / kg) (Fig. 8).

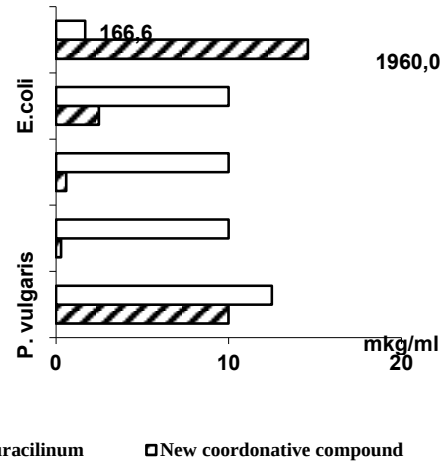

Fig. 8. Antibacterial activity of cobalt complexes

5. Compounds of nickel

5. 1. Salicilidentiosemicarbazido-[6 - (aminobenzensulfamido)-3-metoxipiridazin] nickel

New coordinative compound belong to the new class of salicyliden thiosemicarbazide transition metal complexes (9). This substance possess bacteriostatic and bactericidal activity in the concentrations within 0.06 ... 125 mg / ml against a large spectrum of Gram-positive and Gram-negative microorganisms. It is 2.6 to 41.6 times more active toward Gram-positive organisms and 2.4 - 10 times more active toward Gram-negative microorganisms in comparison with furacilinum (Fig. 9).

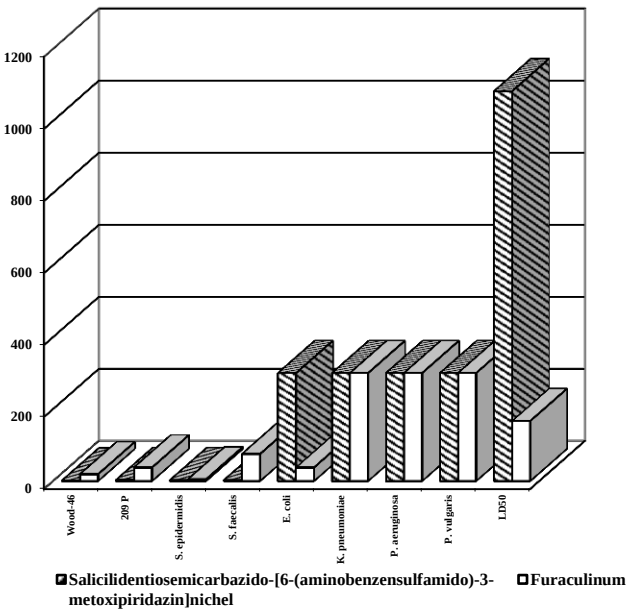

Fig. 9. Antibacterial activity Salicilidentio-semicarbazido-[6 - (aminobenzensulfamido)-3-metoxipiridazin] nickel

6. Sulphanilamide derivatives

6.1. N-(5-nitro-2-furfuriliden)-4-aminobenzensulfamide

Mentioned derivatives are a new group of organic biologically active compounds from sulfanilamide class. Proximate analogues are known as the class of sulphanilamide, which are widely used in medical practice.

The investigations *in vitro* (6, 7, 8, 13) have demonstrated that this organic compound manifests a large spectrum of antibacterial activity. The bactericidal activity of these compounds towards Gram-positive microorganisms occurs at concentrations from 9.35 to 2000 mg / ml and against Gram-negative microorganisms in the concentration of 1000-2000 mg / ml, that is higher than prevailing traditional sulfanilamide's activity from 2 to 428 times, depending on the species of microorganisms (Fig. 10).

6. 3. Naftalidentiosemicarbazidaţi copper (II) that contain sulphanilamide

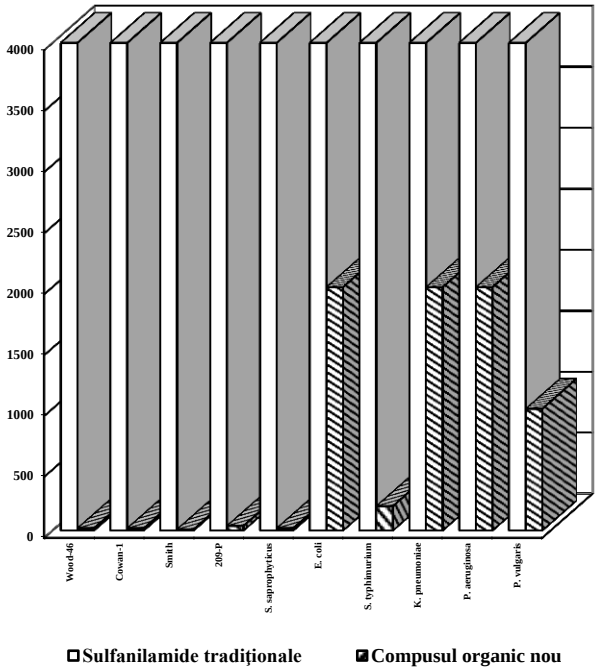

Fig. 10. Antibacterial activity N-(5-nitro-2-furfuriliden) - 4-aminobenzensulfamide

Obtained substances belong to a number of biologically active copper coordination compounds. The proximate analogues of these compounds are traditional sulfanilamide. The mentioned compounds possess the bacteriostatic and bactericidal activity in concentrations from 0.00012 to 2000 mg / ml against Gram-positive and Gram-negative bacteria, while sulfanilamide traditional activity is manifested in the higher concentrations of 4000

mg / ml. The toxicity (LD 50) of certain compounds is 4750 mg / kg (11), (Fig. 11).

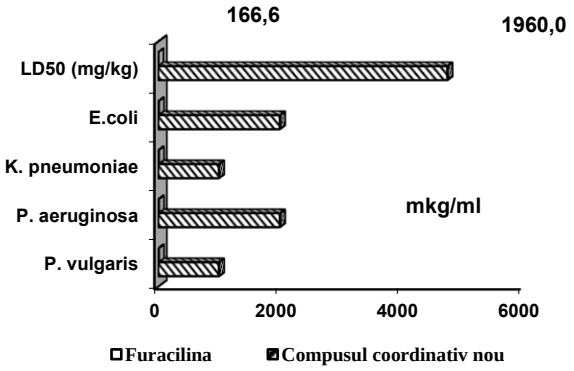

Fig. 11. Antibacterial activity of the Naftalidentiosemicarbazide of copper (II) which contain sulphanilamide

IV. CONCLUSION

The results of researches have demonstrated that various organic compounds or coordinative new substances, which are synthesized in diverse scientific laboratories, provide bactericidal and fungicidal properties and, however, inoffensive, which can serve as a basis in obtaining and producinf of antibacterial and antifungal remedies. Already developed preparations from these substances have been shown to be highly effective, practical harmless, and also available for population.

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