ANTITUBERCULOSIS ACTIVITY OF NEW MEDICATIONS – DECAHYDROACRIDIN OF THIOSEMICARBAZONT DERIVATES

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Abstract: Our study established, that synthesis of antimicrobial medicines as acridin derivates is the perspective of future investigation in this direction.

The presence of a large number of publications of synthesis of antimicrobial drugs based on acridine derivatives indicates the prospect of studying the active substances of the middle class of compounds.

Preparations of derivatives of thiosemicarbazones of decahydroacridines are synthesized, the structure of the received drugs is confirmed using chromatographic mass spectrophotometric method at the Institute of Organic Chemistry of Academy of Sciences of Ukraine, it allowed to assert, that the product of the reaction is monotiosemicarbazone, which exhibit higher anti-TB activity, than well-known medical products.

During analysis of synthesied preparations TM 4/1, TT 1/1, TT 1/0 for sensitivity against Mycobacterium tuberculosis we discovered of some regularity in antimicrobial activity. Thus, preparation TT 1/0 in 100% cases had high activity against Mycobacterium tuberculosis strains resistant to streptomycin, rifampicin, ethambutol, isoniazid. But preparation TT 4/1 was active in 80% cases and TT 1/1 – in 20% only.

Key Words: Mycobacterium tuberculosis, synthesis of derivatives of acridine, streptomycin, rifampicin, ethambutol, sonasid.

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Introduction

Synthesis of effective and safe healing remedies requires obtaining new substances and the study of their activity.

The presence of a significant number of publications on the synthesis of antimicrobial drugs based on acridine derivatives indicates the potential of finding active compounds among

this class of compounds.

Preparations of derivatives of thiosemicarbazones of decahydroacridines are synthesized, the structure of the received drugs is confirmed using chromatographic mass spectrophotometric method at the Institute of Organic Chemistry of Academy of Sciences of Ukraine, it allowed to assert, that the product of the reaction is monotiosemicarbazone, which exhibit higher anti-TB activity, than well-known medical products.

On the basis of the analysis of synthesized preparations of TM 4/1. TT 1/1, 1/0 TT on the sensitivity of Mycobacterium tuberculosis (MBT) to their effects, revealed a corresponding pattern in the manifestation of these substances on anti-TB activity.

So the drug 1/0 in 100% of cases inhibited the growth of colonies of the office, which was resistant to the action of streptomycin, rifampicin, ethambutol, isoniazid, whereas TT 4/1 to 80%, and TT 1/1 to 20%.

The relevance of the work

Under the influence of the application of the Arsenal of anti-TB drugs, the possession of modern medicine, Mycobacterium tuberculosis (MBT) has not lost its pathogenic and virulent abilities.

On the contrary, the agent has acquired new morphological and cultural properties of the variability, drug resistance and aggressiveness. Therefore, the search for new effective drugs has important practical significance. Particularly promising in the use of derivatives of acridine observed Quaternary salt oxotetrahydrothiophene that characterizability a fairly high level of antimicrobial activity that was based on inactivation of the function of important cell components, particularly nucleic acids. An important property of the derivatives of acridine, which has found application in medical practice is their activity in the presence of plasma proteins that provides them with certain advantages in comparison with other antiseptics and disinfectants [1-5].

It is the indifference in relation to protein structures is the basis of selectivity of exposure to substances of this group on the function of cellular organisms. The specific point is, as proven in experiments, is the ability to specifically bind to nucleic acids by intercalation, which is that molecules of the active substance immersed nukleotidami pairs between the polynucleotide chain, causing local rosicruciana and the violation of the synthesis of nucleic acids, causing damage to the microbial cells. Intercalate derivatives of acridine molecule leads to inhibition of DNA synthesis and DNA - dependent RNA synthesis. This effect leads to inhibition of mitotic activity and replcement extra chromosomal genetic elements that are responsible for the death of the microorganism [6].

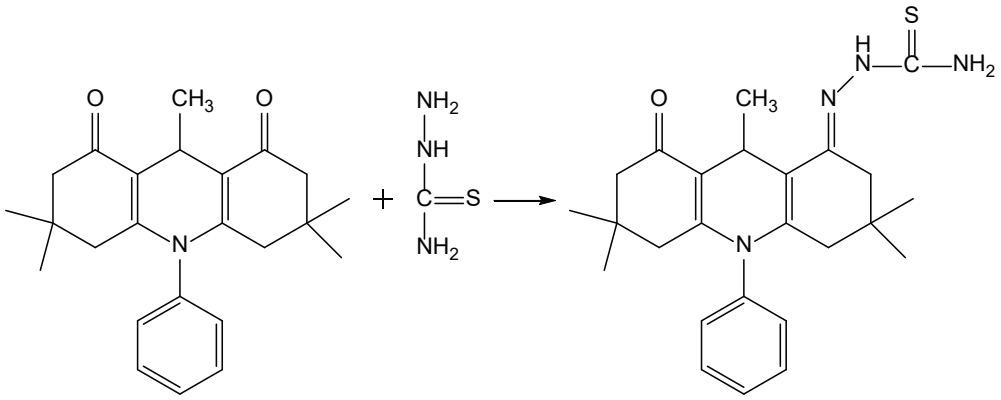
The purpose of the work

The synthesis and a study of antibacterial activity of new thiosemicarbazones drugs decadrononline and compare the data with other known anti-TB drugs.

Materials and methods

Conducted research synthesized drugs upgrade: tm4/1 (tiosemicarbazona N-phenyl-1-oxa-3,3 - dimethyltetradecyl bromide), TT/1/1 (tiosemicarbazona N-phenol-1,8-dioxo – 3,3,6,6,9 – pentamethyl octahedrally perchlorate), TT 1/0 (tiosemicarbazona-N - phenyl – 1,8 - pentamethyl decadron) on the sensitivity of Mycobacterium tuberculosis to their effects.

For synthesis of thiosemicarbazone was used N-phenol-1,8- dioxodecahydroacridine, which was synthesized according to the methodology: 0,01 mole of dioxodecahydroacridine dissolved during the heating in the minimum amount of ethanol, added dissolved in hot ethanol tiosemykarbazyd (0,025 mole) and heated with a reflux condenser during 30-40 min. Orange crystals dropped from the solution, which were recrystallized from alcohol [7]. Research by chromatographic mass spectrophotometric method at the Institute of Organic Chemistry of Academy of Sciences of Ukraine allowed to assert, that the product of the reaction is monotiosemicarbazone.



Research antimyocardial activity. To determine the resistance of MBT (Mycobacterium tuberculosis) to the action of the studied drugs the method used proportion method of Canetti (instruction on bacteriologic diagnostic of TB infection. The order of MH of Ukraine № 45 from 6.02.2002, Kyiv-118 C.).

In a sterile vial poured 4 ml of 2% sulfuric acid solution and adding it to the part of pathological material (sputum). Shaken for 3 minutes and then the material is sterile platinum loop was applied on solid egg medium of Levenshtein. The egg medium was placed in a thermostat at 37°C. Colonies of Mycobacterium tuberculosis detected at the 30th day.

Definition of sustainability the office regarding the investigated substances was performed so that solid media Lowenstein, which grew colonies of mycobacteria were given analyte separately (TM 4/1, 1/1 TT, TT 1/0) with concentrations 10^{-2}, 10^{-3}, 10^{-4} mol/l. In baklaboratorii made 39 samples from 13 cases in all three of the test substance. Parallel studies were conducted with well-known drugs streptomycin, rifampicin, ethambutol, isoniazid. The materials were placed in a thermostat at 37° C [8,9].

Results of investigation

The research results were analyzed after 30 days. It is established that the test substance showed different antibacterial activity.

Table 1

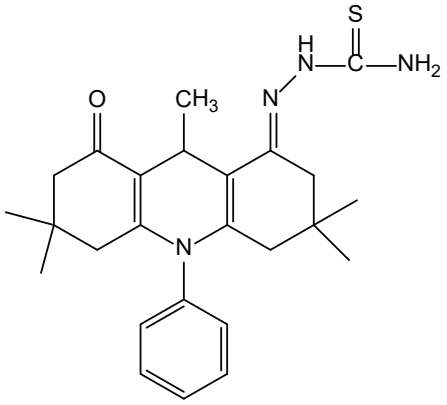
The results of the impact of drugs and test substances TM 4/1, 1/1 TT, TT 1/0 on the growth of pathogenic colonies MBT

№ N/p	The cases	The number of colonies GMT	Effect on MBC of the studied drugs and substances						
			Str	Rif	Eth	Iso	TM 4/1	TT 1/1	TT 1/0
1.	S. N. I.	+++	sensitive	sensitive	sensitive	standd	sensitive	sensitive	sensitive
2.	F. G. J.	+++	sensitive	sensitive	sensitive	standd	sensitive	stand	sensitive

3.	V.J.M.	+++	sensitive	sensitive	sensitive	sensitive	sensitive	sensitive	sensitive
4.	G.M.M.	+	sensitive	sensitive	sensitive	sensitive	sensitive	sensitive	sensitive
5.	G.N.G.	++++	sensitive	sensitive	sensitive	sensitive	sensitive	stand	sensitive
6.	V.A.E.	++	stand	sensitive	stand	stand	sensitive	stand	sensitive
7.	B.V.I.	++++	sensitive	stand	sensitive	sensitive	stand	stand	sensitive
8.	L.M.B.	+++	stand	sensitive	stand	stand	sensitive	sensitive	sensitive
9.	V.Z.I.	++++	sensitive	sensitive	sensitive	sensitive	sensitive	stand	sensitive
10.	I.O.M.	+++	sensitive	stand	stand	stand	stand	stand	sensitive
11.	V.N.I.	++++	sensitive	sensitive	sensitive	sensitive	stand	stand	sensitive
12.	M.V.I.	+++	sensitive	sensitive	sensitive	sensitive	sensitive	stand	sensitive
13.	S.I.I.	+++	stand	sensitive	sensitive	stand	stand	stand	sensitive

Marks: "+" - 25 colonies
Str – streptomycin
Rif – rifampicin
Eth – ethambutol
Iso – sonasid

Thiosemicarbazone dioxodecahydroacridine, which exhibits antimycobacterial activity, which differs that, obtained by the interaction N-phenol-1,8- dioxodecahydroacridine with thiosemicarbazide and isolated from the reaction mixture in the form of orange crystals, $C_{25}H_{34}N_4OS$, with the established molecular weight 437 hpoma-mass spectral analysis and the structural formula:



As the table 1 shows, the most pronounced antimyocardial the influence of the identified substance 1/0 TT was observed in 100% inhibition of all pathogenic colonies of MBT in the analyzed samples. Slightly lower activity was observed antimyocardial substance TM 4/1, which resulted in 80% suppression of growth of pathogenic MBT. Very low antimyocardial activity identified substance TT 1/1,as noted in 20% growth inhibition of the colonies of pathogenic MBT. It should be noted that the substance of TT 1/0 detected high antimyocardial activity as MBT strains that were resistant to streptomycin, rifampicin, ethambutol, isoniazid.

Conclusions

1. Synthesized preparations of derivatives of thiosemicarbazones of decahydroacridines are synthesized, the structure of the received drugs is confirmed using chromatographic mass spectrophotometric method at the Institute of Organic Chemistry of Academy of Sciences of Ukraine, it allowed to assert, that the product of the reaction is monotiosemicarbazone, which exhibit higher anti-TB activity, than well-known medical products.

2. On the basis of the analysis of "structure-activity" established by the leaders of the structure. So the drug 1/0 TT in 100% of cases inhibited the growth of colonies of the office, whereas TM 4/1 - 80%, TT 1/1 only 20%.

3. Substance 1/0 TT showed high antimyocardial activity as MBT strains that were resistant to the action of streptomycin, rifampicin, ethambutol, isoniazid.

Prospects for further research

Given that the synthesized tosaid decadrononline (TT 1/0) exhibits high anti-TB activity than known drugs, leading at the same time with a low level of toxicity, indicating the prospect for further research in the quality of medicines.

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