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The susceptibility of certain microbial strains to some imidazolidine derivatives

Substituted derivatives of imidazolidine-2-thione are applied in medicine as thyroid inhibitors (mipimazole), antischistosomal drugs (niridazole) (7). The following derivatives of 2,5-dioxo-imidazolidine (hydantoin) are applicable in medicine as antiepileptic drugs – phenytoin, mephenytoin (4). The others were prepared and tested as antinematodal (1), broncholytic and antiepileptic (5) agents.

The imidazolidine ring is also the structural element of semisynthetic, broad- spectrum acylureidopenicillins – resistant due to β-lactamases azlocillin and mezlocillin (4). They preserve the useful antiGram-positive activity of ampicillin but have higher antiGram-negative potency. These drugs are used parentally with particular emphasis on Gram-negative bacteria, especially *Klebsiella pneumoniae* and the anaerobe, *Bacteroides fragilis*. Besides, from the literature data it follows that depending on the type of substituent certain derivatives of imidazolidine may also show antimicrobial properties (8).

The following compounds obtained due to the condensation reaction of N-arylethylenediamines with carbon disulfide (compounds I-VIII) were tested *in vitro* in relation to bacterial, fungal and moulds strains to exclude or confirm their potential antimicrobial activity:

I. 1-(2-methylphenyl)-imidazolidinethione-2;
II. 1-(2,3-dimethylphenyl)-imidazolidinethione-2;
III. 1-(2-methoxyphenyl)-imidazolidinethione-2;
IV. 1-(4-methoxyphenyl)-imidazolidinethione-2;
V. 1-(4-ethoxyphenyl)-imidazolidinethione-2;
VI. 1-(2-chlorophenyl)-imidazolidinethione-2;
VII. 1-(3-chlorophenyl)-imidazolidinethione-2;
VIII. 1-(2,6-dichlorophenyl)-imidazolidinethione-2.

Their chemical structures were confirmed on the basis of elemental analysis and spectral data: infrared (IR), nuclear magnetic resonance (^{1}H NMR) and mass spectra (MS). Their purity was tested by means of chromatography. All the compounds were characterized by solubility in methanol, dimethylformamide and dimethylsulfoxide. Three of the obtained derivatives (compounds I, II, V) are known (9) but the other (III, IV, VI, VII, VIII) have not been described in the literature yet and their synthesis will be described elsewhere.

MATERIAL AND METHODS

Assay of antimicrobial activity *in vitro*. The synthesized compounds were tested for their antimicrobial (antibacterial and antifungal) activities by disc-diffusion method by Kirby-Bauer, using

Mueller-Hinton medium for bacteria and the same medium with 4% glucose for fungi. The tested microorganisms were isolated from clinical specimens of the Laboratory of Medical Microbiology Department, Medical University of Lublin. The assayed collection included 54 strains of Gram-positive bacteria (*Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus agalactiae*), 52 strains of Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa, Proteus, spp., Klebsiella pneumoniae, Enterobacter aerogenes*), 6 strains of yeast-like fungi (*Candida albicans*), 3 strains of moulds (*Aspergillus spp.*) (Table).

In the disc-diffusion method, sterile paper disc (ϕ 5 mm) impregnated with dissolved in dimethylsulfoxide (DMSO) compound at concentrations of 100 μg ml^{-1} and 200 μg ml^{-1} were used. Discs containing DMSO were used as control. The microorganisms cultures were spread over the following appropriate media: Mueller-Hinton agar for *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Pseudomonas aeruginosa, Proteus* spp., *Klebsiella pneumoniae, Enterobacter aerogenes*, and Saburoud agar for the yeast-like fungi (*Candida albicans*) and for the moulds (*Aspergillus spp.*) in Petri dishes. Then, the paper discs impregnated with the solutions of the compound tested were placed on the surface of the media inoculated with the microorganism. The plates were incubated at 35°/24 h for the microorganisms cultures. After incubation, the zones of growth inhibition around the discs were observed indicating that the examined compound inhibits the growth of microorganism (2, 3, 6).

Table 1. Microorganism cultures used to microbiological screening

Group	Strain	Number of strains
Gram-positive bacteria	*Staphylococcus aureus*	21
	Staphylococcus epidermidis	15
	Streptococcus pyogenes	12
	Streptococcus agalactiae	6
Gram-negative bacteria	*Escherichia coli*	16
	Pseudomonas aeruginosa	12
	Proteus spp.	10
	Klebsiella pneumoniae	8
	Enterobacter aerogenes	6
Yeast-like fungi	*Candida albicans*	6
Moulds	*Aspergillus spp.*	3

RESULTS AND DISCUSSION

Antibacterial and antifungal activities of the obtained compounds were tested by the disc-diffusion method to Kirby-Bauer in relation to 54 Gram-positive and 52 Gram-negative bacterial strains, 6 strains of yeast-like fungi and 3 strains of moulds. It can be concluded from microbiological screening tests that compounds I–VIII in examined concentrations of 100 μg ml^{-1} and 200 μg ml^{-1} had no influence on the growth of microorganisms tested. The conducted tests enabled to limit the possible biological spectrum of activity of synthesized imidazolidine derivatives and exclude their potential antimicrobial activity.

CONCLUSION

1. All the tested compounds were inactive against of 54 Gram-positive and 52 Gram-negative bacterial strains, 6 strains of yeast-like fungi and 3 strains of moulds.

2. The microbiological screening tests enabled to limit the possible biological spectrum of activity of the tested compounds.

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SUMMARY

Substituted derivatives of imidazolidine-2-thione are applied in medicine as thyroid inhibitor (mipimazole) and antischisostomal drugs (niridazole). Besides, from the literature data it follows that depending on the type of substituent certain derivatives of imidazoline may show antimicrobial properties. The obtained compounds were tested for their potential antimicrobial activity. Microbiological tests conducted on 106 strains of bacteria, 6 strains of yeast-like fungi and 3 strains of moulds have shown that all the tested compounds in the examined concentrations (100 μgml^{-1} and 200 μgml^{-1}) had no influence on the growth of tested bacteria, yeast-like fungi and moulds.

Wrażliwość pewnych szczepów bakteryjnych na wybrane pochodne imidazolidyny

Podstawione pochodne imidazolidyno-2-tionu znalazły zastosowanie w medycynie jako tyreostatyki (mipimazol), leki stosowane w zwalczaniu przywr (niridazol). Ponadto z danych literatury wynika, że w zależności od podstawnika niektóre pochodne imidazolidyny mogą wykazywać aktywność przeciwdrobnoustrojową. Określono aktywność przeciwbakteryjną i przeciwgrzybiczą otrzymanych związków. Przeprowadzone na 106 szczepach bakteryjnych, 6 szczepach drożdżaków i 3 szczepach pleśni testy aktywności przeciwdrobnoustrojowej wykazały, że otrzymane związki w badanych stężeniach (100 μgml^{-1} i 200 μgml^{-1}) nie hamowały wzrostu bakterii, drożdżaków i pleśni.