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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL THIETAN-CONTAINING PYRIMIDINYLACETOHYDRAZIDE DERIVATIVES

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BACKGROUND

Antibiotic resistance is a worldwide problem. An emergence of new infections, a genetic transformation of known pathogens becomes a big challenge to the medical community. Many antimicrobial substances contain in their structure hydrazide, sulfur-containing fragments (Meshcheryakova et al., 2017), therefore it seems promising to use the pyrimidines as base objects for the synthesizing new biologically active substances.

Purpose of the Study:

To synthesize some novel acyl derivatives based on 2-[6-methyl-4-(thietan-3-yloxy) pyrimidine-2-ylthio]acetohydrazide and to investigate the antimicrobial activity of the synthesized compounds.

MATERIALS AND METHODS

Melting points were determined by open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on an InfraLUM FT-02 spectrophotometer. 1H NMR spectra were recorded on a Bruker AM-300 spectrometer using TMS as an internal standard. The purity of the compounds was checked by thin layer chromatography (TLC) on plate «Sorbfil» using ethyl acetate.

As starting compounds we have used 2-[6-methyl-4-(thietan-3-yloxy)pyrimidine-2-ylthio]acetohydrazide. Antimicrobial and antifungal activities of the compounds 1-6 were assayed using the agar diffusion and the twofold broth (pH 7.2–7.4) dilution methods (Mironov et al, 2012). Gram positive (*Staphylococcus aureus*) and gram negative (*Escherichia coli*, *Proteus vulgaris*, *Klebsiella pneumonia*, *Enterobacter aerogenes* and *Pseudomonas aeruginosa*) and lower fungi *Candida albicans* bacteria were used as test organisms. Ceftriaxone was used as reference drug

RESULTS

Treatment of 2-[6-methyl-4-(thietan-3-yloxy) pyrimidine-2-ylthio]acetohydrazide with acetic, propionic, maleic, succinic anhydrides in an inert solvent 1,4-dioxane at room temperature, with benzoyl chloride in a 1,4-dioxane medium during boiling in the presence of a 1.1-fold excess of triethylamine afforded the corresponding N,N'-diacylderivatives 2-6 (Fig. 1).

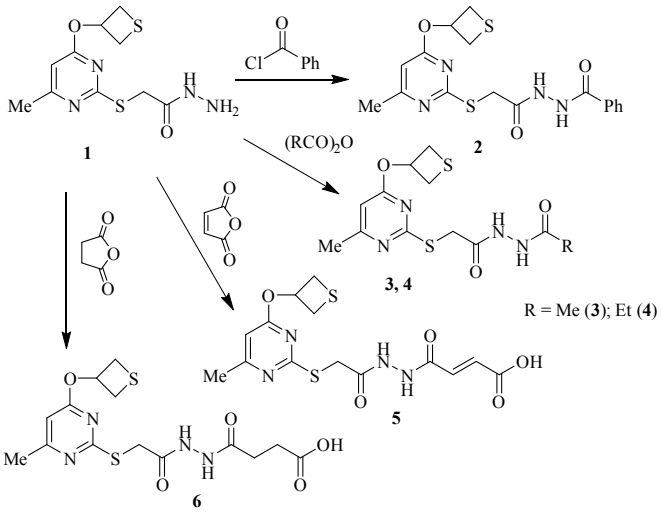

***Fig. 1.** Synthesis of thietan containing pyrimidinylacetohydrazide derivatives*

The formation of diacylderivatives is confirmed by 1H NMR spectra, in which signals of protons O-thietane fragment, methyl group, the proton in the fifth position of the pyrimidine ring are appeared.

As a result of researches it is established that benzoic, acetic, maleic acids residues in compounds 2, 3, 5 increase the activity in relation to St. aureus, P. vulgaris. Propionic acid residue in compound 4 increases the activity in relation to *E. coli*.

Minimum inhibitory concentration values are given in Table 1.

The investigation of antibacterial screening data revealed that the compound 5 showed good inhibition towards all tested gram-positive and gram-negative

Table 1. *Antimicrobial activity expressed as MIC (μg/ml)*

Compounds	MIC, mcg/mL						
	St. aureus	E. coli	P. vulgaris	K. pneumoniae	Ent. aerogenes	Ps. aeruginosa	C. albicans
1	50	0.5	5	0.05	0.05	0.05	0.05
2	5	0.5	0.5	0.05	0.05	5	0.5
3	5	0.5	0.5	0.05	0.05	0.05	0.5
4	50	0.05	5	5	0.5	0.05	0.5
5	5	0.5	0.05	0.05	0.05	0.5	0.05
6	5	0.5	0.5	0.5	0.05	5	0.5
Ceftriaxone	0.5	0.5	0.05	0.05	0.05	0.05	0.05

bacteria and lower fungi C. albicans at 0.5 μg/ml concentrations (Table 1).

CONCLUSION

1) Based on the activity of these compounds, we can propose structure-activity relationship.

2) Acyl derivatives based on 2-[6-methyl-4-(thietan-3-yloxy)pyrimidine-2-ylthio]acetohydrazide are promising for further in-depth research as potentially biologically active compounds

Keywords

pyrimidine, hydrazide, thietan, antimicrobial.