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Antifungal activity of thiosulfonates of monomeric type and rhamnolipids

Infections caused by fungi is growing and represent serious problem particularly in immunocompromised patients such as with burns, with AIDS, with cancers, and after term use of antibiotics or steroids. The use of classical antifungal has been often connected with the risk of serious side effects and may support the selection of resistant strains. Considering the clinical importance due to fungal infections and increasing drug resistance, is a need in the development of new, active, with minimum side effects antifungal agents. Allicin, a garlic thiosulfinate represents one of phyto-compounds, which showed antifungal properties, however is unstable. In our study we present antifungal activity of three stable, synthetic allicin analogs, esters of thiosulfonic acid.

The aim of this study was the development of methods of the synthesis of thiosulfonates of the monomeric type and the investigation the cytotoxicity *in vitro* and antimycotic activity of three new synthesized thiosulfonates.

Cytotoxicity of new synthetic thiosulfonates (M1, M4, M6) and *Pseudomonas* sp. rhamnolipids TL11 was determined *in vitro* on human lung cell line A549 and mouse fibroblast cells L929. Antifungal activity was tested according toM-27-A3 (CLSI, USA) microdilution method. Fungal strains *Aspergillus fumigatus*, *Cryptococcus neoformans* IHEM 14227, *Cryptococcus neoformans* IHEM 3969, *Geotrichum sp*. Lab. 1969, *Geotrichum capilar* Lab. 1967, *Trichosporon asahii* IHEM 17912 and *Candida albicans* ATCC 90028 were tested accordingly to the classical microdilution antifungal susceptibility protocol M27-A3 (CLSI, USA). Serial concentrations of tested compounds ranging from 3,125 to 100µg /ml were used. The minimal inhibitory concentrations. (MIC) end point was defined as the lowest drug concentration that inhibited 50% the growth when compared to the control.

Results: Thiosulfonates and rhamnolipids were characterized by low cytotoxicity. The spectrum of activity of M1, M4 and M6 compounds embraced *C. neoformans, T. asahii, Geotrichum. sp., A. fumigatus and C. albicans.* Activity of the compounds depended from time action, structure of compounds and on the type of the microorganism. It should be noted that the synthetic thiosulfonate M4 characterized the highest antifungal action (6,25-12,5 µg /ml). The range of action of the compound M1 for all strains was from12,5 µg to 25 µg /ml.

The activity of the compound M6 was similar, only *Cryptococcus neoformans* IHEM 3969 was more sensitive (6,26-12,5 µg/ml), whereas *Aspergillus fumigatus* was more resistant (50 µg/ml).

The rhamnolipids TL 11 antifungal properties were weakly than the remaining compounds (>100 µg/ml).

Synthetic derivatives of allicin at a concentrations 12,5-25 µg /ml, inhibited the growth of most tested fungal strains. M4 and M6 compounds even at a concentration of 6,25 ug/ml have shown activity against some species of fungi.