Synthesis of triclosan derivatives and their antimycobacterial effect

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Introduction

Tuberculosis (TB) represents one of the leading causes of morbidity and mortality worldwide. Development of new potential drugs is essential because of the existence of latent TB and development of drug-resistant TB forms (multidrug-resistant TB, extensively drug-resistant TB and recently reported totally drug-resistant TB)[1, 2]. Triclosan (irgasan) is a broad spectrum antibacterial agent used in household products. Triclosan has been shown to inhibit InhA, an essential enoyl acyl carrier protein which leads to the lysis of *Mycobacterium tuberculosis*[3]. Esterification of triclosan to form its prodrugs can produce compounds with improved properties – enhanced bioavailability or absorption, higher activity and/or lower toxicity.

Results and discussion

It was prepared 28 triclosan esters based on various aliphatic, cycloaliphatic, aromatic and heteroaromatic acids. 5-Chloro-2-(2,4-dichlorophenoxy)phenyl 4-bromobenzoate (TRC-B-4Br) showed the best *in vitro* activity with minimum inhibitory concentrations (MIC) 16 μmol/L against *Mycobacterium tuberculosis* $H_{37}Rv$. Against next strains had the best activity 5-chloro-2-(2,4-dichlorophenoxy)phenyl isonicotinate (TRC-ISO). The MIC of TRC-ISO was similar for *M. kansasii* 6509/96 and better for *M. avium* and *M. kansasii* 235/80 with comparison of INH (Table 1).

Table 1. The most active derivatives

Code	MIC (μM)									
	***M. tuberculosis* 331/88**		***M. avium* 330/88**		***M. kansasii* 235/80**			***M. kansasii* 6509/96**		
	14 d	**21 d**	**14 d**	**21 d**	**7 d**	**14 d**	**21 d**	**7 d**	**14 d**	**21 d**
TRC-B-4Br	16	32	62.5	62.5	16	32	32	16	16	32
TRC-ISO	32	32	32	32	8	16	32	8	8	16
INH	0.5	0.5	> 250	> 250	> 250	> 250	> 250	4	8	8

Experimental methods

We used two synthetic procedures to obtain these esters. The first pathway consists in the reaction of triclosan (1 eq.) with various acyl chlorides (1.3 eq.) in presence of triethylamine (1.5 eq.). The second approach of the preparation triclosan esters is the Steglich esterification. Common yields were around 70 %. Synthesized derivatives were evaluated for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* $H_{37}Rv$, *M. avium* and two strains of *M. kansasii*.

Conclusions

The *in vitro* evaluation of 28 triclosan-based esters showed promising antimycobacterial activity. The further research of the most active analogues will continue, particularly with regard to cytotoxicity.

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Conflicts of interest: none.

References

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