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The antimycobacterial derivatives against potential pathogenic strains: 2-Hydroxy-3-(4-phenylpiperazin-1-yl)-propylphenylcarbamates

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Abstract

According to our previous study 29 derivatives of 2-hydroxy-3-(4-phenylpiperazin-1-yl)-propylphenylcarbamates were tested for *in vitro* antimycobacterial activity against potential pathogenic strains *Mycobacterium kansasii* and *Mycobacterium avium*. The variations in group of compounds were by the substitution on phenyl rings. The Free-Wilson method was used to evaluate structure-antimycobacterial activity relationships. The advantage of compounds under study is in the activity against *M. kansasii*.

Keywords

Carbamates, propylphenylcarbamates, mycobacterium, potential pathogenic strains

Introduction

The return of tuberculosis to Europe and North America is one of the features of the period dating from 1985 In the developing countries, due to insufficient medical care, hygienic standards and compliance of the population with the treatment, a number of mycobacterial strains became resistant to modern chemical drugs. Due to the contemporary migration of population, infection was often transferred to Europe and North America. In addition, this unfavorable state is also being influenced by an increase in AIDS, which is often accompanied by mycobacterial diseasescaused by potential pathogenic strains. New mycobacterial diseases have occurred which were until recently considered intransferable to humans (mycobacterioses produced by potentially pathogenic strains). Mycobacterial diseases due to multiresistant strains of the complex *Mycobacterium avium* and *Mycobacterium intracellulare* are not frequent, but mostly fatal in the end. We have recently studied the derivatives of alkoxyphenylcarbamic acids [1-5]. The advantage of the derivatives of phenylcarbanic acids is the low toxicity. Goal of this study is determining of derivatives of 2-hydroxy-3-(4-phenylpiperazin-1-yl)-propyl-phenylcarbamates against *M. kansasii* and *M.avium t*o complete the results of previous study.

Results and Discussion

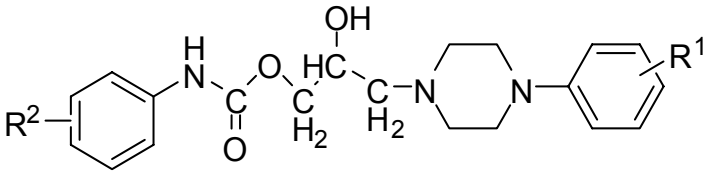
The values of antimycobacterial activity of derivatives of 2-hydroxy-3-(4-phenylpiperazin-1-yl)-propylphenylcarbamates are shown in Table 1. For the sake of comparison, we also included the values of MICs of the standard isoniazide (INH). The results revealed that the compounds exhibited in vitro activity against all tested mycobacterial strains. The values of MICs are generally within the range 8-1000 μmol/l. The compounds possessed a better activity against *M. kansasii* 235/80 and *M. avium* 330/88 than isoniazide. The influence of structural moiety on activity is analyzed by Free-Wilson approach (see Table 2). We did not study the influence on antimycobacterial activity of substitution on phenyl ring of 4-phenylpiperazine in the series of phenylcarbamic acid derivatives, yet. It seems

that the substitution R^1 in position 3 by trifluoromethyl increases the antimycobacterial activity. Trifluoromethyl is the strong electonaceptor and is more lipophilic than methyl or fluorine. The best substitution R^2 is by 4-propoxy- and 4-butoxy- group. The compounds of our study form the new promising group of antimycobacterials against *M.kansasii*. The activity against *M. avium* is not significant.

Experimental

Chemistry:

All compounds were prepared by coworkers of Čižmárik. Synthesis of compounds substituted by fluorine (R^1) was published [6]. Preparation of other compounds will be printed in other journals of chemistry. The structure of compounds is illustrated in Fig. 1.



R^1:		R^2:					
1	2-F	**a**	2-OCH_3	**d**	3-OCH_3	**h**	4-OCH_3
2	4-F	**b**	2-OC_2H_5	**e**	3-OC_2H_5	**i**	4-OC_2H_5
3	2-CH_3	**c**	2-OC_3H_7	**f**	3-OC_3H_7	**j**	4-OC_3H_7
4	3-CF_3			**g**	3-OC_4H_9	**k**	4-OC_4H_9

Fig. 1 Structure of derivatives of 2-hydroxy-3-(4-phenylpiperazin-1-yl)-propyl-phenylcarbamates

Microbiology:

For the evaluation of the antimycobacterial activity of the substances *in vitro*, the following strains were used*:* *Mycobacterium kansasii* CNCTC My 235/ 80, *Mycobacterium avium* CNCTC My 330/ 88, obtained from the Czech National

Collection of Type Cultures (CNCTC), National Institute of Public Health, Prague, and a clinical isolate of *Mycobacterium kansasii* 6 509/ 96. The antimycobacterial activities of the compounds was determined in the Šula semisynthetic medium (SEVAC, Prague). The compounds were added to the medium in Me_2SO at concentrations of 125, 64, 32, 16, 8, and 4 μmol/l. The minimum inhibitory concentrations (MIC, the lowest concentration of a substance, at which the inhibition of the growth occurred) were determined after incubation at 37 °C for 14 and 21 days. The results are summarized in Table 1.

Tab. 1: Minimum inhibitory concentration (μmol/l) of derivatives of phenylcarbamic acid

Compounds			*MIC(μmol/l)* Incubation time 14 d/21 d		
	R^1	R^2	*M. kansasii* My 235/ 80	*M. avium* My 330/ 88	*M. kansasii* 6 509/ 96
1a	2-F	2-OCH_3	250/500	500/1000	250/500
1b	2-F	2-OC_2H_5	250/500	n/1000	250/500
1c	2-F	2-OC_3H_7	250/250	250/500	125/125
1d	2-F	3-OCH_3	125/250	250/500	125/250
1e	2-F	3-OC_2H_5	125/125	500/500	125/125
2a	4-F	2-OCH_3	250/250	500/1000	500/500
2b	4-F	2-OC_2H_5	250/n	250/n	125/n
2c	4-F	2-OC_3H_7	62.5/n	125/n	32/62.5
2d	4-F	3-OCH_3	62.5/62.5	250/500	250/n
2e	4-F	3-OC_2H_5	n/n	n/1000	n/n
2f	4-F	3-OC_3H_7	62.5/125	125/n	125/125
2g	4-F	3-OC_4H_9	250/500	500/1000	500/500
2h	4-F	4-OCH_3	125/250	500/n	n/500
2j	4-F	4-OC_3H_7	32/62.6	n/n	62.5/n

2k	4-F	4-OC_4H_9	n/n	n/n	125/125
3d	2-CH_3	3-OCH_3	125/125	250/250	125/125
3e	2-CH_3	3-OC_2H_5	125/125	125/125	125/250
i	2-CH_3	4-OCH_3	125/250	250/250	125/250
3j	2-CH_3	4-OC_2H_5	250/250	250/250	125/125
4a	3-CF_3	2-OCH_3	125/n	n/n	125/125
4b	3-CF_3	2-OC_2H_5	125/125	125/n	62.5/62.5
4d	3-CF_3	3-OCH_3	32/62.5	n/n	32/62.5
4e	3-CF_3	3-OC_2H_5	32/32	n/n	32/32
4f	3-CF_3	3-OC_3H_7	16/32	n/n	32/32
4h	3-CF_3	4-OCH_3	16/32	32/62.5	16/32
4i	3-CF_3	4-OC_2H_5	32/62.5	32/62.5	32/62.5
4j	3-CF_3	4-OC_3H_7	32/n	62.5/n	32/n
4k	3-CF_3	4-OC_4H_9	32/62.5	n/n	32/32
INH			>250/>250	>250/>250	4/8

n: impossible to determine (low solubility of compounds or low growth of mycobacteria).

Calculation

For the calculations, the Multireg programme (Klemera) working under Microsoft Excel was employed. The Free-Wilson approach was used for QSAR analysis. Activity contribution and statistical significant of correlations are summarized in Table 2.

Tab. 2: Activity contribution of Free-Wilson analyzes and statistical significant of correlations.

	Δ log MIC (μmol/l) for incubation time 14 d / 21 d	
	M. kansasii My 235/80	*M. kansasii* 6 509/ 96
R^1: 2-F	0.241/0.292	0.206/0.328
4-F	0.052/0.039	0.176/0.261
2-CH_3	0.340/0.324	0.192/0.154
3-CF_3	-0.331/-0.428	-0.364/-0.413
R^2: 2-OCH_3	0.374/0.225	0.430/0.181
2-OC_2H_5	0.374/0.308	0.130/0.132
2-OC_3H_7	0.016/-0.052	-0.205/-0.089
3-OCH_3	-0.139//-0.117	-0.007/-0.084
3-OC_2H_5	-0.122/-0.323	-0.096/-0.284
3-OC_3H_7	-0.299/-0.166	-0.072/-0.285
3-OC_4H_9	0.410/0.508	0.450/0.415
4-OCH_3	-0.159/-0.039	-0.259/0.038
4-OC_2H_5	0.007/0.141	-0.109/0.069
4-OC_3H_7	-0.299/-0.392	-0.220/-
4-OC_4H_9	-0.108/-0.132	-0.100/0.053
μ_o	1.938/2.160	1.964/2.160
r	0.944/0.964	0.958/0.953
s	0.190/0.180	0.169/0.188
F	7.60/8.12	9.51/7.12
n	26/22	25/21

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