Scientia Pharmaceutica (Sci. Pharm.) **72**, 43-49 (2004)

Influence of Lipophilicity on the Antimycobacterial Activity of the Hydrochlorides of Piperidinylethyl Esters of Ortho-Substituted Phenylcarbamic Acids

K. Waisser[1] , K. Dražková[1], Čižmárik J.[2], Kaustová J.[3]

[1]Department of Inorganic and Organic Chemistry, Charles University, Faculty of Pharmacy, Heyrovského 1203, CZ-500 05 Hradec Králové, Czech Republic

[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Commenius University, SK-832 32 Bratislava, Slovak Republic

[3]Department for the Diagnostics of Mycobacteria, Regional Institute of Public Health, Ostrava, Partyzánské nám. 7, CZ-728 892 Ostrava, Czech Republic

Abstract

A series of 14 hydrochlorides of piperidinylethyl esters of *ortho*-substituted phenylcarbamic acids were evaluated for *in vitro* antimycobacterial activity against the strains of *Mycobacterium tuberculosis*, *Mycobacterium kansasii* and *Mycobacterium avium*. *In vitro* antimycobacterial activity becomes higher with increasing hydrophobicity of the substituents. The alkoxy group is not necessary in order for the basic ethyl esters of phenylcarbamic acids to display antimycobacterial activity.

Key Words

phenylcarbamic acids, tuberculostatics, mycobacterium, *M. tuberculosis*

Introduction

The search for new antimycobacterially active compounds is undoubtedly one of the significant directions of current pharmaceutical

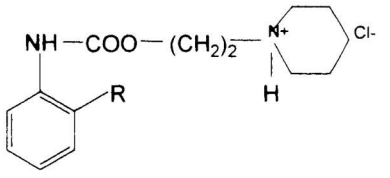
chemistry. Recently, an initial study of structure-antimycobacterial activity relationships of basic ethyl esters of alkoxy-substituted phenylcarbamic acids has been published [1]. The goal of this paper was to evaluate the structure-antimycobacterial activity relationships in the series of the hydrochlorides of piperidinylethyl esters of *ortho*-substituted phenylcarbamic acids. These compounds were originally studied as local anaesthetics because of their low toxicity [2].

Experimental

Chemistry. All compounds were prepared at the Department of Pharmaceutical Chemistry, Commenius University, Bratislava.[2-4]. The structures are depicted in Scheme 1.

Microbiology. To evaluate the *in vitro* antimycobacterial activity of the substances, the following strains were used: *Mycobacterium tuberculosis* CNCTC My 331/ 88, *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 were determined in the Šula semisynthetic medium (SEVAC, Prague). The compounds were added to the medium in Me_2SO solutions at the concentrations of 125, 64, 32, 16, 8, and 4 $\mu mol.l^{-1}$. The minimum inhibitory concentrations (MIC, the lowest concentration of a substance, at which the inhibition of the growth of mycobacteria occurred) were determined after incubation at 37 °C for 14 and 21 days. The results are summarized in Table 1.

Scheme 1



R = 1 -OMe, 2 -OEt, 3 -OPr, 4 -OBu, 5 -OPe, 6 -OHex, 7 -OHep, 8 -OOct, 9 -ONon, 10 -O-iPr, 11 -F, 12 -I, 13 -Me, 14 -Et

Results and discussion

All compounds are potential tuberculostatics. The hydrophobicity of the substituents (constants π) were taken from the literature[5,6]. For several alkoxy substituents, the hydrophobicity constants π were calculated by the method of Hansch [7], using the values of the known π constants of the most closely related alkoxy groups. The hydrophobicity substituent constants are summarized in Table 2.

Table 1. *In vitro* antimycobacterial activity (MIC, μmol/L) of the esters of phenylcarbamic acids after 14 and 21 days

Compound No.	***M. tuberculosis*** My 331/88		***M.avium*** My 330/88		***M. kansasii*** My 235/80		***M. kansasii*** My 6509/96	
	14	21	14	21	14	21	14	21
1	1000	>1000	500	500	1000	>1000	500	1000

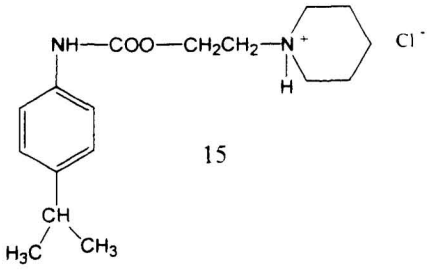
2	1000	>1000	1000	>1000	1000	>1000	1000	1000
3	250	500	500	1000	500	500	500	500
4	125	250	62,5		250	250	125	125
			62,5					
5	16	32	125	125	125	125	125	125
6	16	32	62,5		62,5		32	32
			62,5		62,5			
7	16	32	32	32	32	32	16	16
8	16	32	32	32	8	16	8	8
9	16	16	32	32	8	8	8	16
10	500	1000	1000	1000	1000	1000	1000	
							1000	
11	500	>1000	>1000	>1000	1000	>1000	500	
							1000	
12	250	500	500	1000	1000	1000	500	
							500	
13	500	1000	>1000	>1000	1000	1000	500	
							500	
14	500	1000	1000	>1000	1000	1000	500	
							1000	
15	62.5	125	125	250	250	250	125	
							250	
16	62.5	62.5	62.5	125	125	250	62.5	125
INH	2	2	250	250	250	250	8	
							8	

Table 2. Hydrophobicity substituent constants

R	Substituents constant π	R	Substituents constant π
O Me	-0.18	OOct	3.68
OEt	0.48	ONon	4.24
OPr	1.02	O-iPr	0.55
OBu	1.56	F	0
OPe	2.15	I	0.93
OHex	2.62	Me	0.84
OHept	3.15	Et	1.39

The results of the analysis confirm that the activity of the compounds increases with increasing hydrophobicity of the substituents (see Table 3). In the series under study, other substituents than the alkoxy group have been included as well. The value of the hydrophobicity π constant of iodine is similar to that of the propoxy group, and the respective antimycobacterial activities are also similar. Thus, we can conclude that the antimycobacterial activity is the function of hydrophobicity and, in contrast to what we had assumed before, it is independent of the size of the alkoxy group.

In order to gain insight into the behaviour of related compounds, substituted in other positions than *ortho*, we investigated two substances (15 and 16), substituted in positions *para* and *meta* on the phenyl ring. Both the compounds were antimycobacterially active, with the alkoxy group being not a part of the pharmacophore. The results will be used in the design of new antimycobacterial derivatives.



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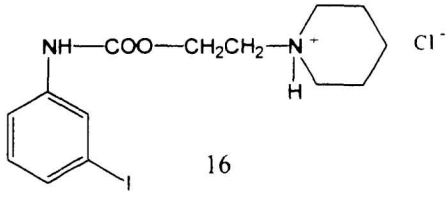

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Acknowledgements

The work was supported by the Ministry of Education of the Czech Republic (project No MSM 111600001) and by the grant Kontakt (78/ČR, 237/SR).

Table 3. Correlations of antimycobacterial activity (MIC, μmol/l) with the hydrophobicity substituent constants

Strains of mycobacterium	Time of incubation (d)	Regresion coefficients a	b	Statistical evidence r	s	n
M. tuberculosis My 331/88	14	-0.496 (±0.06	2.92 (±0.13)	0.914	0.316	14
M. tuberculosis My 331/88	21	-0.540 (±0.09)	3.22 (±0.19)	0.900	0.327	10

M. avium My 330/88	14	-0.402 (±0.07)	3.00 (±0.16)	0.880	0.318	12
M. avium My 330/88	21	-0.369 (±0.06)	2.86 (±0.15)	0.903	0.269	10
M. kansasii My 235/80	14	-0.559 (±0.05)	3.27 (±0.09)	0.959	0.236	14
M. kansasii My 235/80	21	-0.598 (±0.02)	3.40 (±0.05)	0.995	0.083	10
M. kansasii 6509/96	14	-0.528 (±0.05)	3.05 (±0.11)	0.947	0.257	14
M. kansasii 6509/96	21	-0.540 (±0.05)	3.16 (±0.11)	0.946	0.265	14

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Received September 12th, 2003
Accepted October 13th, 2003