IN VITRO EVALUATION OF ETHAMBUTOL ANALOGS AS DRUG PROTOTYPES AGAINST MULTIDRUG-RESISTANT MYCOBACTERIUM TUBERCULOSIS

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INTRODUCTION

Tuberculosis (TB) is one of the oldest diseases that still constitutes a serious pandemic, with a worrying increase of cases of multidrug-resistant TB (MDR, XDR, XXDR) to the available antimicrobials, and making the disease increasingly deadly and difficult to treat.

Taking into consideration our previous results, we have synthesized new 2-aminoalkanol, 1-aminoalkan-2-ol and 1,2-alkanediamine derivatives. All the obtained compounds were tested against the reference strain of M. tuberculosis (Mtbc) H37Rv (ATCC 27294) sensitive to the first-line drugs, and against the multi-resistant clinical isolate MDR-1576 (LACEN-PE-BR).

METHODOLOGY

The general synthetic procedure for obtaining compounds of type I and II is indicated in scheme 1. α-Amino acids of three different sizes (dodecyl, hexadecyl and octadecyl) were firstly alkylated to the carbamate, then the amino group was protected as a carbamate, followed by hydrolysis of the carbamate, leading to compounds 1. Reduction of compounds 1 gave compounds 2. Compounds 1 were alkylation to compounds 3-8, and reduced to the corresponding free alcohols 10-16. Diamines 17-23 were obtained in several steps from compounds 1.

The synthesis of type III compounds is indicated in scheme 2. They were obtained by directly opening of epoxides with the appropriate amines.

OBJECTIVE

The objective of this study was to obtain and evaluate the antimycobacterial activity of compounds related to sphingosine and ethambutol (EMB), as well as to determine their selectivity.

RESULTS

Sixty five compounds of types I, II and III were tested in vitro against Mtbc and the multi-resistant isolate MDR-1576. The minimum inhibitory concentration (MIC) was determined by the microdilution technique in culture broth. Cytotoxicity of compounds for normal cells was determined against murine macrophages J774A.1 (ATCC TIB-67).

All the compounds evaluated were active against both sensitive and MDR Mtbc strains, with similar potency or even better than EMB against the resistant strain MDR-1576. Compounds derived from 2-aminoalkanols showed greater activity against the sensitive strain, with MIC values varying from 1.5 to 16 µM. However, the alkan-1,2-diamines derivatives were those showed better activity against the MDR strain, with MIC values between 2 and 16 µM. With respect to cytotoxicity, the compounds showed CC50 values between 4.7 and 135 µM. The highest selectivity index of 15, was found for compound 3, which together with 2 have been selected for in vivo assays.

CONCLUSIONS

• Forty 2-aminoalkanols (type I compounds), seventeen alkan-1,2-diamines (type II) and three 1-aminoalkanols derivatives (type III), were obtained with good to excellent yields.
• Type I compounds showed the highest potency against the sensitive Mtbc strain, while those of type II were more active against the MDR strain.

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