Bioorganic & Medicinal Chemistry 21 (2013) 7330–7342

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Bis-phosphonium salts of pyridoxine: The relationship between structure and antibacterial activity

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ARTICLE INFO

Article history:
Received 9 July 2013
Revised 21 September 2013
Accepted 23 September 2013
Available online 1 October 2013

Keywords:
Quaternary phosphonium salts
Pyridoxine
Structure–activity relationship
Lipophilicity
Antibacterial activity

ABSTRACT

A series of 23 novel bis-phosphonium salts based on pyridoxine were synthesized and their antibacterial activities were evaluated in vitro. All compounds were inactive against gram-negative bacteria and exhibited the structure-dependent activity against gram-positive bacteria. The antibacterial activity enhanced with the increase in chain length at acetal carbon atom in the order *n*-Pr > Et > Me. Further increasing of length and branching of alkyl chain leads to the reduction of antibacterial activity. Replacement of the phenyl substituents at the phosphorus atoms in 5,6-bis(triphenylphosphonio(methyl))-2,2,8-trimethyl-4*H*-[1,3]-dioxino[4,5-*c*]pyridine dichloride (compound **1**) with *n*-butyl, *m*-tolyl or *p*-tolyl as well as chloride anions in the compound **1** with bromides (compound **14a**) increased the activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* up to 5 times (MICs = 1–1.25 μg/ml). But in practically all cases chemical modifications of compound **1** led to the increase of its toxicity for HEK-293 cells. The only exception is compound 5,6-bis[tributylphosphonio(methyl)]-2,2,8-trimethyl-4*H*-[1,3]dioxino[4,5-*c*]pyridine dichloride **(10a)** which demonstrated lower MIC values against *S. aureus* and *S. epidermidis* (1 μg/ml) and lower cytotoxicity on HEK-293 cells (CC_{50} = 200 μg/ml). Compound **10a** had no significant mutagenic and genotoxic effects and was selected for further evaluation. It should be noted that all bis-phosphonium salt based on pyridoxine were much more toxic than vancomycin.

1. Introduction

The widespread use of antibiotics has led to the multidrug-resistant (MDR) microbes due to various reasons including the increasing use of antibiotics in the medicine and agriculture. A striking change during the past quarter-century has been the increasing importance of infections caused by gram-positive bacteria.[1–4] Among gram-positive pathogens, *Staphylococcus aureus, Streptococcus pneumoniae* and, more recently, *enterococci*, each present global problem, for public health.[5–7]

Quaternary phosphonium salts are the promising type of antibacterial compounds. There are some examples in literature where phosphonium salts are used as antibacterial agents against different types of microorganisms.[8–14]

In our previous work the synthesis and antibacterial properties of phosphonium salts on the basis of pyridoxine were described.[15] In continuation of our studies in this article we optimized the chemical structure of the most active compound 5,6-bis(triphenylphosphonio(methyl))-2,2,8-trimethyl-4*H*-[1,3]-dioxino[4,5-*c*]pyridine dichloride (compound **1**). For this purpose we synthesized 23 bis-phosphonium salts on the basis of compound **1** (Fig. 1). The relationship of antibacterial activity of novel phosphonium salts of pyridoxine with their structure, lipophilicity, the nature of substituents at the phosphorus atom and the type of counterion were discussed.

2. Results and discussion

2.1. Chemistry

At the beginning of our study we tried to improve the lipophilicity of compound **1** by varying the substituent at the acetal carbon atom in the six-membered ring. The synthesis of acetals of bis-phosphonium salts—analogs of compound **1**, was carried out in three steps. In the first step, six-membered acetal (**3a**–**f**) was obtained by reacting compound **2** in benzene in the presence of threefold molar excess of toluenesulfonic acid with one to twofold molar excess of aldehyde at reflux temperature using a Dean–Stark trap. In the second step, chlorine derivatives (**4a**–**f**) were obtained via chlorination of the hydroxymethyl group of compounds (**3a**–**f**) using thionyl chloride as the chlorinating agent. Synthesis of quaternary phosphonium salts (**5a**–**f**) at the last stage were carried by

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0968-0896/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2013.09.056