Bioorganic & Medicinal Chemistry 27 (2019) 100–109

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Synthesis and characterization of pyridoxine, nicotine and nicotinamide salts of dithiophosphoric acids as antibacterial agents against resistant wound infection

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ARTICLE INFO

Keywords:
Pyridoxine
Nicotine
Nicotinamide
Dithiophosphoric acids
Quaternary ammonium salts
Monoterpenes
Antibacterial agents
Wound infection
MRSA
Cytotoxicity

ABSTRACT

The pyridine-derived biomolecules are of considerable interest in developing medicinal compounds with various specific activities. Novel ammonium salts of pyridoxine, (*S*)-(–)-nicotine and nicotinamide with O,O-diorganyl dithiophosphoric acids (DTPA) were synthesized and characterized. The complexation of chiral monoterpenyl DTPA, including (*S*)-(–)-menthyl, (*R*)-(+)-menthyl, (1*R*)-*endo*-(+)-fenchyl, (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheolyl derivatives, with pyridoxine and nicotine provided effective antibacterial compounds **3a,b,e,f,** and **5a,b,d,f** with MIC values against Gram-positive bacteria as low as 10 μM (6 μg/mL). Two selected pyridoxine and nicotine salts based on menthyl DTPA **3a** and **5a** were similarly active against antibiotic-resistant bacteria from burn wounds including MRSA. The compounds had enhanced amphiphilic and hemolytic properties and effectively altered surface characteristics and matrix-secreting ability of *P. aeroginosa* and *S. aureus*. MBC/MIC ratios of **3a** and **5a** suggested the bactericidal mode of their action. Furthermore, the compounds exhibited moderate cytotoxicity towards human skin fibroblasts (IC_{50} = 48.6 and 57.6 μM, respectively, 72 h), encouraging their further investigation as potential antimicrobials against skin and wound infections.

1. Introduction

Natural products have been playing a key role in drug discovery and development. Plants, microorganisms, marine species are an important source of established and newly discovered bioactive compounds of diverse structure and activity, which are generally classified as alkaloids, polyphenols, terpenoids, and peptides.[1–4] Vitamins and vitamin-like compounds attract attention both as a precursor of bioactive derivatives[5] and cancer cell-targeted molecules.[6] Among them, pyridine based vitamins such as vitamin B_3 (nicotinic acid and nicotinamide) and vitamin B_6 (pyridoxine and its derivatives) are important cofactors in numerous enzymatic reactions in prokaryotic and eukaryotic cells with established transporters and an important role in supporting redox homeostasis.[7–9] Their modification and conjugation allow for the development of medicinal compounds which target and interfere with vitamin functions.

The vitamin B_3 and B_6 derivatives with antibiotic properties are of considerable interest in treating widespread and life-threatening viral and microbial infections with emerging resistance to existing medications.[1,10] Different nicotinic acid derivatives with antimicrobial activity were synthesized, such as *N*-acylhydrazones of nicotinic acid hydrazides,[11] 2-benzylsulfanyl-nicotinic acid based 1,3,4-oxadiazoles,[12] 2-amino-5-arylazo-6-aryl substituted nicotinic acid and pyrido[2,3-*d*] pyrimidine, transition metal complexes of Schiff-bases derived from 2-aminonicotinic acid and salicylaldehyde,[13] isonicotinic acid hydrazide (isoniazid) derivatives.[14] These compounds were active against Gram-negative and Gram-positive bacteria with minimal inhibitory concentrations (MIC) in the microgram and submicrogram ranges. 2-Thio- and *N*-substituted nicotinamide derivatives were synthesized as succinate dehydrogenase inhibitors against phytopathogenic fungi (IC_{50}

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https://doi.org/10.1016/j.bmc.2018.11.017
Received 20 August 2018; Received in revised form 29 October 2018; Accepted 13 November 2018
Available online 13 November 2018