New 1-Hydroxy-1,1-bisphosphonates Derived from 1H-Pyrazolo[3,4-b]pyridine: Synthesis and Characterization

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A partir da 2-cloro-3-formilpiridina, sintetizou-se uma série de compostos derivados da 1H-pyrazolo[3,4-b]piridina de modo a obter os correspondentes 1-hidroxibisfosfonatos, uma classe de compostos com potencial interesse biológico. Os dados espectroscópicos foram utilizados na caracterização de todos os compostos e na identificação dos regioisômeros N-1 e N-2, e dos derivados mono- e bisfosfonatos. Estudos de difratometria de raios X do composto 7a confirmaram a estrutura proposta.

A number of 1H-pyrazolo[3,4-b]pyridine derivatives, starting from 2-chloro-3-formyl pyridine, was synthesized to obtain new 1-hydroxybisphosphonates, a class of compounds with potential biological interest. Spectroscopic data were used to characterize all compounds and to identify N-1 and N-2 regioisomers, and mono- and bisphosphonates derivatives. X-ray diffractometry studies of compound 7a confirmed the proposed structure.

Keywords: bisphosphonates, 1H-pyrazolo[3,4-b]pyridine, spectroscopic characterization, synthesis, X-ray diffractometry studies

Introduction

Bisphosphonates (BPs) are an important class of drugs known for their broad spectrum of therapeutical applications in the treatment and prevention of diseases of calcium metabolism.1-3 These compounds have high affinity for calcium and therefore to target the bone mineral, where they appear to be internalized selectively by bone-reabsorbing osteoclasts inducing their apoptosis.1-3 BPs were first developed in the mid 1960’s and have been used as an effective treatment for Paget’s disease.4 Further applications of BPs have been proven to succeed in the treatment of diseases characterized by abnormal calcium metabolism including hypercalcemia, osteoporosis, osteolysis, heterotopic calcification and ossification, bone metastases secondary to breast cancer and prostate cancer, inhibition of cell proliferation, invasion and adhesion to bone.2,5 BPs present several advantages in the treatment of bone diseases since they are bone-time specific, have minimal side effects, no known risk of carcinogenesis and antiresorptive efficacy equivalent or even greater than estrogens.2,6

The P–C–P bonds in BPs make them resistant to enzymatic hydrolysis and the nitrogen containing functional group of the alkyl moiety bound to the bisphosphonic structure improves their activity in the treatment of both primary and secondary bone disorders.1-3,7

The most potent BPs contain one or two nitrogen atoms