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Novel Bisphosphonates Derived from 1*H*-Indazole, 1*H*-Pyrazolo[3,4-*b*]Pyridine, and 1*H*-Pyrazolo[3,4-*b*]Quinoline

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ABSTRACT: *Novel tetraethyl ethylene-1,1-bisphosphonate esters derived from 1H-indazole, 1H-pyrazolo[3,4-b]pyridine, and 1H-pyrazolo[3,4-b]quinoline were synthesized by a Michael addition reaction of tetraethyl ethylidene-1,1-bisphosphonate with the corresponding heterocycle, using conventional heating and microwave-assisted methods. The microwave-assisted method provides shorter reaction times and better yields. The hydrolysis of bisphosphonates afforded the corresponding bisphosphonic acids or salt, using concentrated hydrochloric acid or TMSBr/collidine, respectively. All new compounds were fully characterized, and their structures were assigned using ^{1}H, ^{31}P, and ^{13}C NMR and IR spectroscopies and mass spectrometry. The molecular structure of compound* **6** *was confirmed by X-ray diffraction studies.* © 2015 Wiley Periodicals, Inc. Heteroatom Chem. 27:3–11, 2016; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21282

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INTRODUCTION

Bisphosphonates are an important class of organophosphorus drugs known by their broad spectrum of therapeutic applications in the treatment of diseases characterized by abnormal calcium metabolism, due to their high affinity for calcium and target the bone mineral [1–5]. Bisphosphonates present other therapeutic applications against pathogenic agents due to their antiparasitic [6–8], herbicidal [9] and antibacterial activities [10]. Bisphosphonates were also studied as ligands for radioactive metal complexes [11, 12] and as chelating agents for the treatment of human metal intoxications [13].

The activity of bisphosphonates, in the treatment of bone disorders, is improved by the presence of a nitrogen containing group bonded to an alkyl moiety or to a heteroaromatic cycle [14–16]. Indazole, pyrazolo[3,4-*b*]pyridine, and pyrazolo[3,4-*b*]quinoline are heteroaromatic compounds with two or three nitrogen atoms in an aromatic moiety, resembling the heteroaromatic part of the most potent third-generation bisphosphonates, and are promising moieties for drug discovery.

Indazole, pyrazolo[3,4-*b*]pyridine and pyrazolo [3,4-*b*]quinoline have been studied, and a large