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Extended Abstract

Synthesis and Biological Evaluation of Aminobisphosphonates—Analogues of Incadronate †

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Bisphosphonates had been found to act as strong metal ion complexing agents with useful industrial and household applications. Today, they are a prominent class of organophosphorus drugs used to slow or prevent bone damage and, thus, are standardly applied for the prevention and treatment of osteopenia and osteoporosis. Despite this important medicinal use, they display a variety of physiologic activities, which make them promising anticancer, antiprotozoal, antibacterial, and antiviral agents. Consequently, their biological properties are still intensively studied, and these studies deliver promising drug candidates.

The three-component reaction between amines, triethyl orthoformate, and diethyl phosphite is perhaps the simplest and most commonly used reaction providing structurally variable aminomethylenebisphosphonates. It typically yields a complex mixture of products, which are not separated but immediately hydrolyzed with HCl to lead to the desired bisphosphonic acids in moderate to good yields.

A series of *N*-alkyl- and *N*-cycloalkylaminomethylenebisphosphonates, analogues of incadronate, have been obtained and evaluated for their anti-proliferative activity against a model mouse macrophage J774E. These cells originated from identical precursors as osteoclasts [1]. The in vivo studies were carried out on sheep. These animals were chosen because of sheep's similarity with humans in weight, bone and joint structure, and mechanisms of bone regeneration [2]. The metabolic rate of sheep (based on oxygen consumption per gram of body weight) is closer to that of man than that of a rat or dog model. Two of the most active compounds were used for fracture healing in sheep with steroid-induced osteoporosis. They demonstrated a mild antiosteoporotic activity that was documented using bone histopathology.

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