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# Designing proteins for bone targeting

Sébastien A. Gittens[a,b], Geeti Bansal[c], Ronald F. Zernicke[d], Hasan Uludağ[a,b,c,*]

[a]*Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada*
[b]*Department of Biomedical Engineering, Faculty of Medicine, University of Alberta, Edmonton, Alberta, Canada*
[c]*Department of Chemical and Materials Engineering, Faculty of Engineering, University of Alberta, Edmonton, Alberta, Canada*
[d]*Department of Surgery, Faculty of Medicine and Faculties of Kinesiology and Engineering, University of Calgary, Calgary, Alberta, Canada*

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**Abstract**

Protein-based therapeutic agents intended for bone diseases should ideally exhibit a high affinity to bone tissue, so that their systemic administration will result in specific delivery to bone with minimal distribution to extra-skeletal sites. This was shown possible in the authors' lab by modifying a desired protein with bisphosphonates (BPs) that exhibit an exceptionally high affinity to the bone-mineral hydroxyapatite. In this review, we explore the potential applications of that concept by summarizing the bone diseases and candidate proteins that will benefit from the proposed bone delivery approach. A selective synopsis of BP synthesis is presented to highlight the synthesis of functional BPs suitable for covalent attachment to proteins. Finally, we present a summary of recent research results from the authors' laboratory emphasizing factors influencing bone affinity of the conjugates. We conclude with future research avenues that are considered critical for clinical entry of the BP-targeted therapeutic agents.


*Keywords:* Bone targeting; Drug delivery; Bisphosphonate synthesis; Disease-modifying proteinaceous drugs; Skeletal diseases

**Contents**



* Corresponding author. #526 Chemical and Materials Engineering Building, University of Alberta, Edmonton, AB, Canada T6G 2G6. Tel.: +1 780 492 0988; fax: +1 780 492 2881.
*E-mail address:* hasan.uludag@ualberta.ca (H. Uludağ).

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## 1. Introduction

An ideal therapeutic agent for bone diseases should restrict its pharmacological activity specifically to bone sites, with minimal effects at other non-skeletal sites. This requires the therapeutic agent to be localized to bones after systemic administration with minimal distribution to other sites. This is feasible if the therapeutic agent only exhibits a high affinity to bone tissue, so that it is bound and retained in bones [1]. Bone is distinguished from the rest of the body by the presence of a tissue-specific mineral, hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, which is not present in other tissues under normal circumstances, except pathological calcification at other tissues. Therefore, molecules with high affinity to hydroxyapatite are expected to be specifically delivered to bones after systemic distribution. Although hydroxyapatite is known for its binding capability to a wide variety of molecules (e.g., basis for utilization of hydroxyapatite-affinity chromatography), most therapeutic agents intended for bone diseases do not have a particular affinity to bone hydroxyapatite under the physiological conditions. This is because of a lack of a sufficiently high specific activity and competition from the other ions, organic molecules, and proteins present in the physiological milieu. One exception is a class of molecules known as bisphosphonates (BPs), which exhibits a strong affinity to bone mineral under physiological conditions. Systemic administration of BPs commonly results in 20–50% deposition of the molecules at bone tissues, with minimal accumulation at other sites (usually excreted in urine) [2]. BPs are structurally analogous to the endogenous inorganic phosphate, pyrophosphoric acid (Fig. 1). Replacement of the central oxygen (O) atom in the pyrophosphate with a carbon (C) in BPs allows one to incorporate additional functionalities to the BPs. Depending on the structural details of a BP [3],

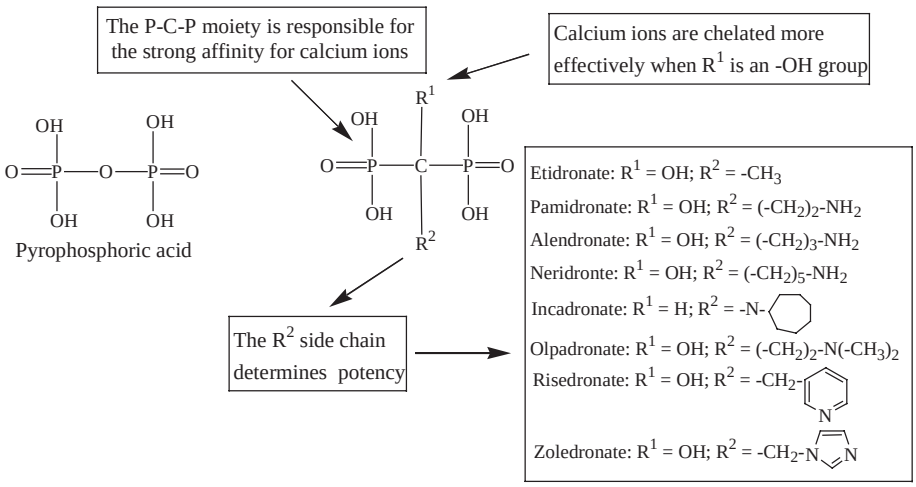


Fig. 1. The structure of pyrophosphoric acid and a geminal BP. Common members of the BP family are also shown.