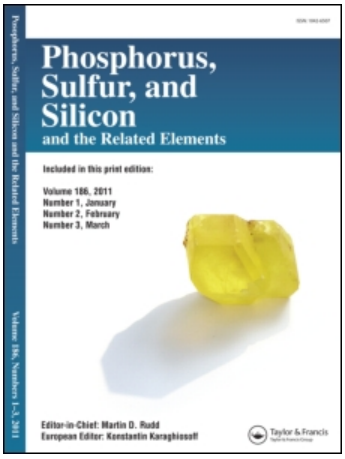

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Bisphosphonates and Novel Related Structural Classes for Bone Resorption Disorders

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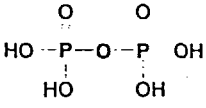
Bisphosphonates (BPs) are powerful inhibitors of bone resorption. They exert a strong affinity to bone mineral which allows the rapid and selective targeting to bone in vivo. We synthesized and evaluated two new classes of compounds: phosphono succinic acid (PSA) and phosphono glutaric acid (PGA) derivatives. In order to transfer the antiresorptive properties of bisphosphonates attempts have been made to elucidate the key elements of the putative BP pharmacophore. Whereas the new compounds revealed similar or better bone mineral affinity properties than BPs in vitro, the inhibition of endogenous bone resorption in vivo was less effective, but in contrast to BPs the effects were reversible after discontinuation of treatment, which suggests that these compounds are metabolically degradable.

Keywords: Bisphosphonates; osteoporosis; bone mineral affinity; bone resorption; calcium

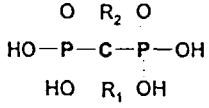
INTRODUCTION

Bisphosphonates (BPs) are very powerful inhibitors of bone resorption and their main therapeutic use is in diseases with high bone turnover such as Paget's disease, tumoral bone diseases and osteoporosis. BPs are

generally thought of as synthetic analogues of pyrophosphate where the P-C-P moiety acts as a bone hook and the R_1 chain determines the potency. In case of an amino or hydroxy group for R_2 binding can be enhanced further. This strong affinity for bone mineral allows the rapid and selective targeting to bone in vivo. However, the P-C-P bond is not metabolized and therefore the release of BPs occurs primarily during bone remodelling, accounting for the long half-life in humans. The charge and bulk of the P-C-P moiety may account for the poor intestinal absorption of approximately 1%. Looking at these features it appears that there might be a need for compounds with improved bioavailability and a shorter half-life due to metabolic degradation.



pyrophosphate



bisphosphonate

RESULTS AND DISCUSSION

The cellular and biochemical mechanisms of action of BPs are still not completely understood, but some important structure activity relationship (SAR) trends of this class of agents have emerged [1]. The incorporation of a hydroxyl group at C1 maximizes the affinity for hydroxyapatite and with the introduction of amino alkyl groups at C1 the antiresorptive potencies increases at least 10 fold.

To improve the poor oral bioavailability and the long half-life of BPs in humans we looked at different structural components that could replace the P-C-P moiety, but would still have a high affinity for bone mineral. Starting from phosphonoacetic acid which like non-geminal BPs

(1.2- and 1.3-BPs) shows only a low affinity to hydroxyapatite, we developed phosphonosuccinic acid (PSA) and phosphonoglutaric acid (PGA) derivatives. Figure 1 shows that these compounds are promising candidates for the replacement of the P-C-P group. Their bone mineral affinities are high and comparable to BPs or even better.

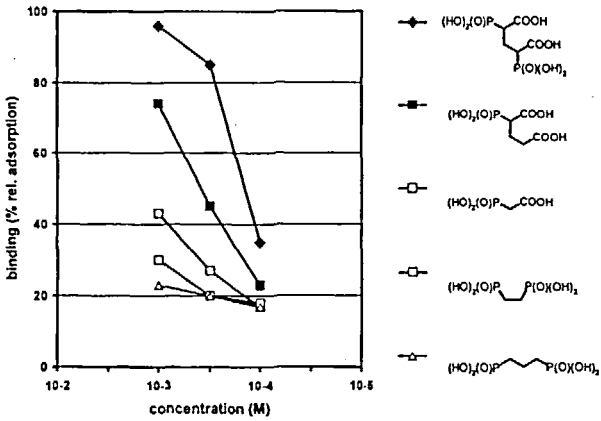


FIGURE 1: Binding on hydroxyapatite

To predict the effect on bone resorption of these new compounds we investigated the structure activity relationships of BPs and came to no clear cut conclusion. As long as there is no single molecular target identified that is responsible for the effects of BPs on the inhibition of bone resorption, the investigation of SAR will remain difficult.

However, we synthesized various PSA and PGA derivatives (figure 2) [2,3] and evaluated these compounds in vitro [4] and in vivo [5]. PSA and PGA derivatives inhibited in vitro osteoclast mediated pit formation

for up to 80% at 10^{-8}M. As in the case of BPs, different side chain substitutions resulted in marked differences in the antiresorptive potency. In vivo PSA derivatives inhibited unstimulated bone resorption at a relatively high dose of 2x200 mg/kg for up to 60%, whereas the effects with PGA derivatives were 10 times stronger.

FIGURE 2: PSA and PGA derivatives

CONCLUSIONS

The effects of these new compounds are only moderate when compared to BP. But in contrast to BPs, inhibition of bone resorption was reversible two days after treatment which suggests that these compounds are metabolically degradable. Thus, the results obtained are encouraging for further optimization of the antiresorptive properties of these compounds.

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