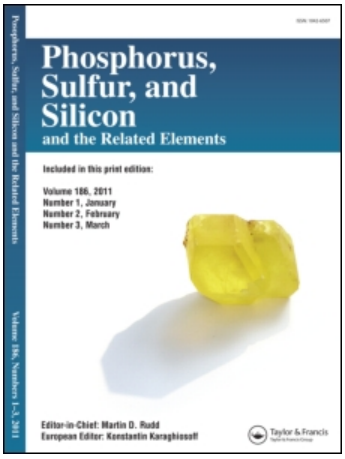

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

The Synthesis and Evaluation of Quaternary Pyridinium Bisphosphonates as Potent Anti-Resorptives

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To cite this Article Blackburn, G. M. , Carran, John , Brown, Richard , Xiong, Joanne , Watts, Donald , Russell, Graham and Ebetino, F. H.(1996) 'The Synthesis and Evaluation of Quaternary Pyridinium Bisphosphonates as Potent Anti-Resorptives', Phosphorus, Sulfur, and Silicon and the Related Elements, 111: 1, 64

To link to this Article: DOI: 10.1080/10426509608054693

URL: http://dx.doi.org/10.1080/10426509608054693

Phosphorus, Sulfur, and Silicon, 1996, Vol. 111, p. 64
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THE SYNTHESIS AND EVALUATION OF QUATERNARY PYRIDINIUM BISPHOSPHONATES AS POTENT ANTI-RESORPTIVES

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Abstract. Several novel quaternary pyridinium bisphosphonates have been synthesised and their efficacy as potential anti-resorptive bone agents have been tested in *Dictyostelium discoideum*. This assay has been shown to accurately reflect the potency of a bisphosphonic acid as an anti-resorptive compound. All the quaternary bisphosphonates are very potent growth inhibitors but results indicate that the more potent compounds are those containing hydrophobic, bulky groups.

Key Words: Bisphosphonate, Anti-resorptive, Dictyostelium, quaternary pyridinium.

INTRODUCTION

A hypothesis that the nitrogen functionality of the more potent N-heterocyclic bisphosphonate anti-resorptives should be positively charged for activity was tested by comparing the potency of the methyl quaternary pyridinium analogue of Risedronate with Risedronate itself in a rat model.[1]

This result indicated that quaternary pyridinium bisphosphonic acids were possible candidates as potent anti-resorptive agents. We thus set out to synthesise a range of quaternary pyridiniumbisphosphonates varying the nature of the quaternary group.

The potency of the bisphosphonates was estimated in our *Dictyostelium discoideum* growth inhibition assay. The inhibition of growth of this slime mould by bisphosphonic acids has been shown to correlate with the anti-resorptive potency of the compounds as estimated by other means.[2,3]

IC_{50} values of the bisphosphonic acids were estimated from growth and dose-response curves of the incubated mould.

CONCLUSION

All the quaternary analogues synthesised were potent growth inhibitors of *Dictyostelium*, and were substantially more potent than most of the early bisphosphonate anti-resorptives tested in the same assay.

The results show an increase in potency on increasing the size (and subsequently hydrophobicity) of the quaternary group e.g. $-(CH_2)_3Ph$. The least potent analogues were those with only small quaternary groups e.g. $-CH_2CH_3$ or $-(CH_2)_3SH$.

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