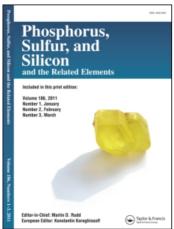
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# The Synthesis and Evaluation of Quaternary Pyridinium Bisphosphonates as Potent Anti-Resorptives

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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 pyridinium bisphosphonates 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.<sup>2,3</sup>

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<sub>2</sub>)<sub>3</sub>Ph. The least potent analogues were those with only small quaternary groups e.g. -CH<sub>2</sub>CH<sub>3</sub> or -(CH<sub>2</sub>)<sub>3</sub>SH.

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