

P024 Modifications to the chemical structure of bisphosphonates affects their potency and specificity for preventing prenylation of small GTPases

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Nitrogen-containing bisphosphonate drugs (N-BPs) suppress bone resorption by inhibiting FPP synthase, thereby indirectly preventing prenylation of all small GTPases in osteoclasts. NE10790, a phosphonocarboxylate analogue of the N-BP risedronate, inhibits Rab geranylgeranyl transferase (Rab GGTase), thereby specifically preventing the prenylation of Rab proteins. We have now confirmed that the anti-resorptive effects of NE10790 are due to inhibition of Rab GGTase, since osteoclasts derived from gunmetal mice (which have ~80% reduced Rab GGTase activity) are more susceptible to the effects of this compound on osteoclast function. We also examined the effects of removing or chemically modifying one or more of the phosphonate groups of these drugs on their potency and enzyme specificity. The monophosphonate analogue of risedronate weakly inhibited prenylation of Rabs, but not Rap1A, in J774 macrophages and osteoclasts, indicating that it inhibits Rab GGTase rather than FPP synthase. By contrast, the monophosphonate analogues of two other N-BPs did not affect protein prenylation. A phosphonophosphinate analogue of a potent N-BP also inhibited prenylation of Rap1A and Rab6, indicating inhibition of FPP synthase, but was 4-fold less potent than the parent N-BP. By contrast, a phosphonophosphinate analogue of a different N-BP, and bisphosphinate analogues of both N-BPs, were completely inactive. In summary, alterations to the phosphonate moieties of N-BPs reduces their ability to inhibit FPP synthase, and can generate compounds that specifically inhibit Rab GGTase.