Pivaloyloxymethyl-modified isoprenoid bisphosphonates display enhanced inhibition of cellular geranylgeranylation

Nitrogenous bisphosphonate inhibitors of farnesyl disphosphate synthase have been used clinically for treatment of bone disease. Because many of their effects may be mediated by depletion of geranylgeranyl diphosphate, our group has sought compounds that do this more directly through inhibition of geranylgeranyl diphosphate synthase and we have discovered a number of isoprenoid-containing bisphosphonates that selectively inhibit this enzyme. These compounds have a high negative charge at physiological pH which is necessary for inhibition of the enzyme but may limit their ability to enter ccells. Therefore, chemical modifications that mask this charge may enhance their cellular potency. We now have synthesized nobel pivaloyloxymethyl-modified isoprenoid bisphosphonates and investigated their ability to inhibit protein geranylgeranylation within cells. We have found that addition of pivaloyloxymethyl moieties to isoprenoid pisphosphonates increases their potency towards cellular geranylgeranylation even though this modification decreases their in vitro and cellular activity which may serve as the basis for future development of more potent and/or drug-like inhibitors of geranylgeranyl diphosphate synthase.