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Molecular Docking and Synthesis of Nitrogen-Containing Bisphosphonates

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Abstract : The nitrogen-containing bisphosphonates (N-BPs) are well established as the treatments of choice for disorders of excessive bone resorption, myeloma and bone metastases, and osteoporosis. They inhibit farnesyl pyrophosphate synthase (FFPS), a key enzyme in the mevalonate pathway, resulting in inhibition of the prenylation of small GTP-binding proteins in osteoclasts and disruption of their cytoskeleton, adhesion/spreading, and invasion of cancer cells. A very few examples for synthesis of α-amino bisphosphonates based on several amino acids are known from the literature. In the present work, esters of aminoacid react with ketophsophonate (or their analog acid or acyl) to afford the desired products, α-iminophosphonates. The reaction of imine with dimethyl phosphate in the presence of catalytic amount of I2 give ester of α-aminobisphosphonate as sole product in good yield. Finally, we used computational docking methods to predict how several α-aminobisphosphonates bind to FPPS and how R and X influence. Pamidronate, β-aminobisphosphonate already marketed, was used as reference. These results are of interest since they represent a new and simple way to sythesize α-aminobisphosphonates with a free COOH group increased by R2 functionalisable and opening up the possibility of using the molecular docking to facilitate the design of other, novel FFPS inhibitors.

Keywords : drug research, cancer, α-amino bisphosphonates, molecular docking
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