

Molecular Docking Studies on the Interactions of Human Farnesyl Pyrophosphate Synthase with α -Aminobisphosphonates Compounds

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The nitrogen-containing bisphosphonates (N-BPs) are a major class of drugs for the treatment of diseases characterized by excessive bone resorption. Farnesyl pyrophosphate synthase (FPPS), one of the key enzymes involved in the mevalonate pathway, is the major molecular target of N-BPs. From the comparative docking study of our compounds with many structurally related lead compounds such as zoledronate and pamidronate we could observe how our compounds might bind to the FPPS binding site, based on the knowledge of the structure of similar active sites. We redocked zoledronate and pamidronate into the active site of the enzyme, and then we replaced with our compounds in order to compare the binding mode of both ligand and the test compound.

Keywords: Cancer, FPPS, α -aminobisphosphonates, Molecular Docking, Lipophilicity

INTRODUCTION

Bisphosphonates (BPS) are the current drugs of choice for the treatment of diseases characterized by excessive resorption of bone, such as postmenopausal osteoporosis, Paget's disease, or tumor associated osteolysis. In oncology, their role in metastatic bone disease is well established, but there is increasing interest in their potential role in preventing and treating cancer-induced bone loss and their possible anti-tumor effects¹⁻³. These drugs are non hydrolyzable analogues of the endogenous pyrophosphate in which the oxygen bridge is replaced by a carbon atom. Attached to the bridging carbon atom are two substituents, forming a general "P-C-P" structure (scheme1.A)⁴.

Bisphosphonates (BPS) are divided into two classes according to their chemical structure and mechanism of action: non nitrogen containing BPS such as etidronate and clodronate that are of low potency and inhibit osteoclast function via metabolism into toxic ATP-metabolites and nitrogen-containing BPS (NBPS), such as zoledronate and pamidronate that inhibit the enzyme of the mevalonate biosynthetic pathway farnesyl pyrophosphate synthase (FPPS) (Fig.1), which catalyzes the condensation of the isoprenoid dimethylallyl diphosphate (DMAPP) with isopentenyl diphosphate (IPP) to form geranyl diphosphate (GPP), which then condenses with a second IPP molecule to form farnesyl diphosphate(FPP)^{5,6}.

The biological activity of bisphosphonates has been found to be dependent on the structure⁷, lipophilicity⁸, and bone binding affinity⁹ of the compounds. For example, the structure of the side chain of bisphosphonates is important in determining the potency of individual bisphosphonates in biological models, and this includes a potential role for the side chain in modulating bone binding. In general, the oxygen/nitrogen containing bisphosphonates exhibits high bone binding affinities, which might be expected to reduce efficacy. However, some of these molecules are very potent and the difference in potency has been attributed to the inhibition of FPPS. While the latter property is of course critical for their use in treating bone-related diseases, for further more general development as anticancer agents¹⁰, it might be desirable to have more lipophilic species. Small

changes in the structure in the R₁ or R₂ moiety can lead to extensive alterations in their physicochemical, biological, therapeutic, and toxicological characteristics. For these reasons, it appears there is a need for more N-BP compounds with a greater margin between the inhibitions of cancer, and improved bioavailability.

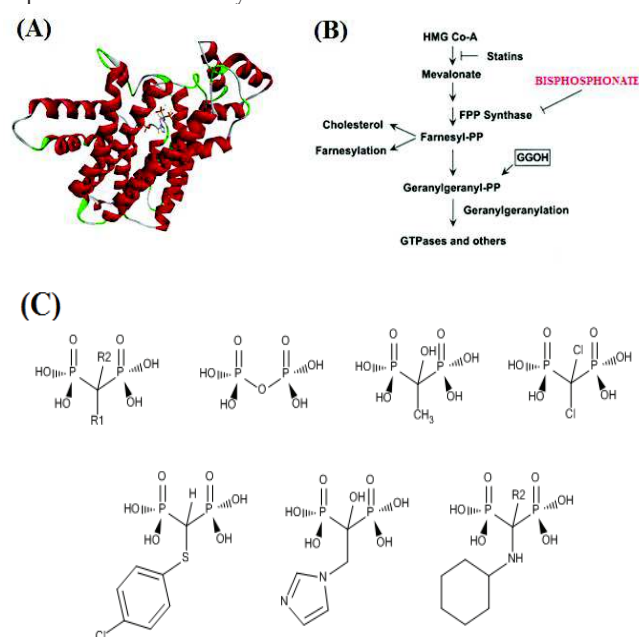


Fig.1 (A) Ribbon representation of the human FPPS (PDB code 2I1B) (B) Schematic representation of intracellular effects of N- BPs. (C) Pyrophosphate and bisphosphonate structures.

In this study, computations on the interactions at the active site of FPPS were carried out for ten ligands. All these ligands have shown to be competitive inhibitors for the FPPS activity which were synthesized in our research group. The availability of several co-crystallized structures for both FPPS with different inhibitors makes it possible to apply a molecular docking protocol to explore the protein-ligand interactions. The study also focuses on the comparison between the inhibitory potentials of novel

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