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Identification of multivalent ligands of human farnesyl pyrophosphate synthase and tipping the affinity balance towards allosteric binding

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Human farnesyl pyrophosphate synthase (*hFPPS*) produces farnesyl pyrophosphate, an isoprenoid required for a variety of cellular processes including protein prenylation. Inhibition of *hFPPS*, and thus of prenylation of small GTPases, has been well established as the mechanism of action of the nitrogen-containing bisphosphonate (N-BP) drugs, currently best known for their anti-bone resorptive benefits. Inhibition of *hFPPS* also produces anticancer effects: N-BPs have shown to inhibit motility and viability of tumor cells and act in synergy with other anticancer agents both *in vitro* and *in vivo*. Furthermore, hFPPS is implicated in Alzheimer's disease (AD). Through analysis of polymorphisms in the *hFPPS* gene and mRNA levels in autopsy-confirmed subjects, we have established a genetic link between *hFPPS* overexpression and elevated levels of phosphorylated tau (P-Tau) in the human brain, the latter of which is a cellular hallmark of AD progression. The physicochemical properties of the current N-BP drugs, however, compromise their full pharmacological potential as *hFPPS* inhibiting agents. They have poor membrane permeability and extremely high affinity to bone, and thus their clinical usefulness is limited mainly to the treatment of osteoporosis and bone cancer metastasis. The poor drug-like properties of N-BPs are due to their highly charged bisphosphonate moiety, which mimics the pyrophosphate of *hFPPS* substrates, dimethylallyl pyrophosphate (DMAPP) and geranyl pyrophosphate (GPP). N-BPs bind to the DMAPP/GPP sub-pocket of *hFPPS* via Mg^{2+}-mediated interactions between their bisphosphonate moiety and two aspartate-rich motifs of the enzyme. Using a multistage screening method employing differential scanning fluorimetry, NMR spectroscopy, isothermal titration calorimetry, and X-ray crystallography, we have identified bisphosphonate compounds with dual binding modes: they bind to the enzyme's active site in the presence of Mg^{2+}, but also to a nearby allosteric inhibitory pocket in the absence of the metal ion. Furthermore, by removing a phosphonate group from the bisphosphonate moiety we have created monophosphonate inhibitors that bind exclusively to the allosteric pocket even in the presence of Mg^{2+}. Alternatively, modification of the side chain scaffold of the lead compounds has resulted in bisphosphonates that also bind only to the allosteric pocket. Further optimization of these compounds may lead to development of non-bisphosphonate human therapeutics for non-skeletal cancers and taupathy-associated neurodegeneration.

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