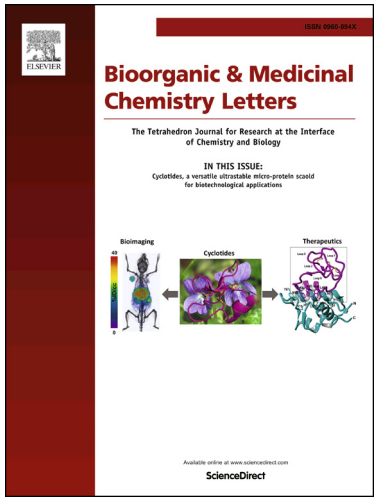

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Discovery of 5-((5-chloro-2-methoxyphenyl)sulfonamido)nicotinamide (SBI-425), a potent and orally bioavailable tissue-nonspecific alkaline phosphatase (TNAP) inhibitor

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Abstract— Tissue-nonspecific alkaline phosphatase (TNAP) is an ectoenzyme crucial for bone matrix mineralization via its ability to hydrolyze extracellular inorganic pyrophosphate (ePP_i), a potent mineralization inhibitor, to phosphate (P_i). By the controlled hydrolysis of ePP_i, TNAP maintains the correct ratio of P_i to ePP_i and therefore enables normal skeletal and dental calcification. In other areas of the body low ePP_i levels lead to the development of pathological soft-tissue calcification, which can progress to a number of disorders. TNAP inhibitors have been shown to prevent these processes via an increase of ePP_i. Herein we describe the use of a whole blood assay to optimize a previously described series of TNAP inhibitors resulting in 5-((5-chloro-2-methoxyphenyl)sulfonamido)nicotinamide (SBI-425), a potent, selective and oral bioavailable compound that robustly inhibits TNAP *in vivo*.

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