NMR screening of new FPPS inhibitors

M. Grimaldi, I. Stillitano, A. Santoro, A.M. D'Ursi

Department of Pharmacy, University of Salerno, via Giovanni Paolo II, 132, 84084, Fisciano, Salerno, Italy,
dursi@unisa.it

Farnesyl pirophosphate synthase (FPPS) catalyzes the two step synthesis of the C15 isoprenoid farnesyl pyrophosphate. The precursors isopentenyl and dimethylallyl pyrophosphate are coupled to produce geranyl pyrophosphate, which is then condensed with an additional IPP to produce farnesyl pyrophosphate. FPPS is known to be the target of bisphosphonates used as osteoporosis therapeutic; however it is involved in several oncogenic processes, therefore is considered a new interesting target for the identification of new anticancer compounds. [1]

N6-Isopentenyladenosine (i6A) is a modified nucleoside exhibiting anti-tumor effects on human and murine cells.[2] Previously we demonstrated the structural interaction of i6A with the enzymatic pocket of FPPS by recording saturation transfer difference (STD) NMR experiments. Newly syntheized i6A analogs were obtained by chemical synthesis, modifying the N6 and the N1 position of adenosine. They were tested for their interaction with FPPS enzyme and their inhibitory capacity was assessed using a new developed FPPS assay based on the measurements of qualitative and quantitative NMR data.[3]

References

[1] - A. Szkopinska, D. Plochocka, Acta Biochim. Pol. **52**, 45-55 (2005).
[2] - E. Ciaglia, S. Pisanti, P. Picardi, C. Laezza, A. M. Malfitano, A. D'Alessandro, P. Gazzerro, M. Vitale, E. Carbone, M. Bifulco, Journal of Leukocyte Biology **94**, 1207-1219 (2013).
[3] - M. Scrima, G. Lauro, M. Grimaldi, S. Di Marino, A. Tosco, P. Picardi, P. Gazzerro, R. Riccio, E. Novellino, M. Bifulco, G. Bifulco, A. M. D'ursi J Med Chem. **25**, 57(18):7798-803 (2014).