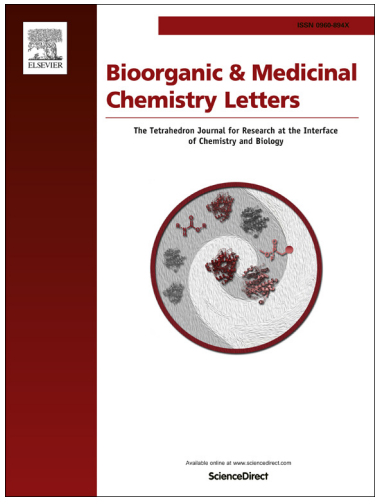

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Peptide chemistry applied to a new family of phenothiazine-containing inhibitors of human farnesyltransferase

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Abstract: Novel phenothiazine derivatives bearing an amino acid residue were synthesized via peptide chemistry, and evaluated for their inhibitory potential on human farnesyltransferase. The phenothiazine unit proved to be an important bulky unit in the structure of the synthesized inhibitors. Propargyl ester **20** bearing a tyrosine residue exhibited the best biological potential *in vitro* in the present study. Further syntheses and biological evaluation of phenothiazine derivatives are necessary in order to gain a full view of SAR in this family of farnesyltransferase inhibitors.

Key-words: farnesyltransferase inhibitor, phenothiazine, peptide coupling, activated ester

Over the years, farnesyltransferase (FTase) has generated much attention as a major target in the development of new anticancer agents.[1] It could be interesting also against Progeria and parasitic protozoa diseases such as malaria, Chagas diseases or Leishmanias.[2] This heterodimeric zinc metalloenzyme is one of the three prenyltransferases which catalyses covalent attachment of a prenyl unit (C15) from a farnesylpyrophosphate (FPP) to the free thiol group of the C-cysteine found in the terminal CAAX motif (where A are aliphatic amino acids, and X is a serine, a methionine or a glutamine for farnesyltransferase, and a leucine or an isoleucine for type I geranylgeranyltransferase(GGTase))[3] of a set of membrane small G-proteins. Many of these proteins, such as lamin A and B, Rac, Ras, RhoB or RhoE actively involved in many important cellular signaling pathways and in carcinogenesis. This protein farnesylation is critical for membrane binding and the biological function of G-proteins.[4] As one of the most important G-protein, Ras proteins have a well-established role in oncogenesis, and function as switches that control growth signal from cell surface receptors to nuclear transcription factors. It has been described that gene mutational activation of the Ras occurs in about 20% of pancreatic and colorectal adenocarcinoma,[5] as well as in many other human cancers.[6]

Inhibition of protein farnesyltransferase prevents membrane localization of Ras, and so constitutes a valid target for the conception of new cytostatic anticancer drugs,[7] and recent reviews report many data on SAR in these series.[8] The main FTase inhibitors (FTIs) that have undergone clinical development are non peptidic compounds such as Tipifarnib (R-115777),[9,10] BMS-214662[11] or Lonafarnib (SCH-66336)[10,12] (Figure 1).