Kurt Housh

# TOWARDS THE SYNTHESIS OF 3-S-ALKYL-INDOLES AS POTENTIAL INHIBITORS OF ISOPRENYLCYSTEINE CARBOXYL METHYLTRANSFERASE

Isoprenylcysteine carboxyl methyl transferase (ICMT) catalyzes the methylation of the carboxyl terminus of over 100 cellular proteins, including the oncoprotein Ras. Ras is believed to be responsible for between 15 to 20% of all human cancers. Prior to methylation, Ras proteins must first be lipidated with a 15-carbon farnesyl group. This farnesyl group serves to help anchor the Ras proteins to the cell membrane. Studies have shown that blocking the methylation of Ras by ICMT leads to mislocalization of the Ras protein, followed by inhibition of tumor cell growth and apoptosis. A synthesis has been developed utilizing a 1-methyl-2-carboxyl-3-thioindole as a scaffold to build potential inhibitors of ICMT. Some key steps in the synthesis include: carboxylation of 1-methylindole, thiocyanation of 2-carboxyl indole, followed by the reductive removal of the cyano group and finally S-alkylation of the resulting free thiol group. This simple, four-step synthesis will allow for the facile synthesis of a large number of S-lipidated carboxyl indoles to fully probe the lipid-binding domain of ICMT and lead to further development of potent inhibitors of this enzyme.

ICMT is essential for subcellular localization of cellular proteins containing a C-terminal CaaX motif where C is cysteine, aa are aliphatic residues, and X can be one of several amino acid residues such as S, M or L. The CaaX motif signals the protein for a series of three postranslational modifications. After prenylation of the cysteine residue and endoproteolysis of the –aaX motif on Ras, ICMT catalyzes the methylation of the Ras protein. The most famous CaaX protein is the oncoprotein Ras. It has been shown the inhibition of ICMT results in

mislocalization of GFP-Ras fusion proteins and leads to growth inhibition and apoptosis of tumor cells.