

2nd International Conference and Expo on

Drug Discovery & Designing

October 27-29, 2016 Rome, Italy

Inhibitors of Icmt and GGTase-I as anti-cancer drug targets

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Ras superfamily of small GTPases undergoes post-translational prenylation for their biological role. The majority of these prenylated proteins contain a C-terminal CaaX sequence, which serves as substrate for prenylation, involving covalent addition of either farnesyl (15-carbon unit, added when X=Ser, Ala or Met) or geranylgeranyl (20-carbon unit, added when X=Leu), catalyzed by protein FTase and protein GGTase-I, attaching the 15- and 20-carbon isoprenoid lipid to CaaX motifs, respectively. After covalent attachment, CaaX proteins undergo processing steps of proteolytic removal of the aaX tripeptide by the Rce1 followed by the carboxymethylation of the prenylcysteine residue by isoprenylcysteine carboxyl methyltransferase (Icmt). The fully processed CaaX proteins exhibit high affinity for cellular membranes and play critical roles in a wide variety of cellular processes, including transmembrane signaling, membrane trafficking and nuclear events. Studies have shown that Ras family members, particularly K-Ras, contribute to human tumorigenesis. In addition, the widespread GTPase activation in cancer, the major contribution of RhoC to metastasis of some solid tumors and Ral proteins activation in more than 90% of pancreatic duct adenocarcinoma cases triggered interest in identifying inhibitors of the enzymes involved for evaluation as therapeutic agents. Targeting inhibition of post-prenylation enzymes Rce1 and Icmt, offers a potential alternative to FTIs. This presentation shall cover the synthesis of natural and unnatural inhibitors of Icmt and GGTase-I.

Biography

Nisar Ullah has accomplished his PhD from University of Graz, Austria in 2001. He then assumed Post-doctoral positions in the McMaster University for a year followed by for another year in the University of Guelph. He joined KFUPM as an Assistant Professor in the year 2007 where he is currently a Professor of Organic Chemistry. His research is mainly centered on the synthesis of bio-active natural products and designed based drug development. He has authored more than 62 papers in reputed journals and has been serving as an Editorial Board Member in many journals including *Arkivoc*, ARKAT, USA, Inc.

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