Design and Synthesis of HIF-1 Inhibitors as Anti-Cancer Therapeutics

Zeus De los Santos[1], Sarah Burroughs[1], Jalisa Holmes[1], Binghe Wang[1*], Erwin Van Meir[2]

[1]Department of Chemistry, Georgia State University, Atlanta, Georgia 30302, USA

[2]Winship Cancer Institute, Emory University, Atlanta, GA 30322, USA

Hypoxia, or reduced of oxygen pressure, in healthy cells leads to cell necrosis and reoxygenation injuries; however, hypoxia is a prominent property of most solid tumors. The low oxygen pressure in cells activates the hypoxia-inducible factor (HIF) family of transcription factors, which induce targets genes that regulates adaptive biological processes such as anaerobic metabolism, cell motility and angiogenesis[1]. Overexpression of HIF-1α, a subunit of the HIF complex, has been linked to metastasis of tumor cells, and resistance to radio and chemotherapy. Because of this, HIF-1 has become an important therapeutic target for the inhibition of tumor growth by small molecules. It is our goal to design and synthesize novel small-molecules that disrupts HIF pathway mainly by targeting the HIF-1α subunit to prevent it from binding with the HIF-1β subunit that makes the HIF heterodimer and initiate its biochemical activity as a transcription factor that promote tumor cell growth. Mechanistic studies shows that these novel inhibitors do not primarily alter HIF-1 levels rather, they interfere with the HIF complex formation[1]. An initial HRE-alkaline phosphatase assay screening was done to find a lead compound.

A compound (KCN-1) with an IC_{50} of 0.4μM was tested and was found to be very potent in decreasing tumor size. Optimization of the said compound was subsequently done by dividing the compound into 4 parts (cores) and analogues have been made; the best compound made to date has an IC_{50} of 0.25μM.

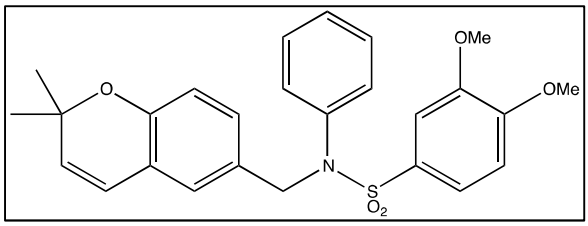

Figure 1 Molecular Structure of KCN-1

References:

1. Mooring, S.R.; Jin, H.; Devi, N.S.; Jabbar, A.A.; Kaluz, S.; Liu, Y.; Van Meir, E.G.; Wang, B., Design and Synthesis of Novel Small-Molecule Inhibitors of the Hypoxia Inducible Factor Pathway. *Journal of Medicinal Chemistry* **2011** *54* (24), 8471-8489.