LBRN Work-in-Progress

INBRE Seminar series

Available via Access Grid

Monday September 16, 2013

10:00 - 11:30AM

Total Synthesis and Biological Activity of Fusarochromanone

DR. ELAHE MAHDAVIAN

Department of Chemistry

LOUISIANA STATE UNIVERSITY SHREVEPORT

10:00 AM

~ ~ ~

Novel Peptidomimetics for Inhibition of EGFR Heterodimerization

DR. SEETHARAMA JOIS

Department of Basic Pharmaceutical Sciences

UNIVERSITY OF LOUISIANA MONROE

10:45 AM

Please check your local Access Grid Room or http://lbrn.lsu.edu for additional information

Total Synthesis and Biological Activity of Fusarochromanone

2

Elahe Mahdavian, PhD Department of Chemistry
LOUISIANA STATE UNIVERSITY SHREVEPORT

~~~

Mentor:

Christopher Kevil, PhD

Department of Molecular and Cellular Physiology

LSU Health Sciences Center in Shreveport

~~~

Fusarochromanone (FC101) is a small molecule fungal metabolite with a host of interesting biological functions, including very potent anti-angiogenic and anti-cancer activity. We report our successful synthesis of parent FC101 based on our synthetic methodology which utilizes the Sonogashira cross-coupling. We also report our progress towards the assessment of biological properties of the parent FC101. We have shown that FC101 exhibits very potent *in-vitro* growth inhibitory effect towards a number of human cancer cells. FC101 induces apoptosis and an increase in proportion of cells in the sub-G1 phase in cancer cells as evidenced by cell cycle profile analysis. We have also investigated the molecular mechanism and biological targets of FC101 through western blotting, photoaffinity labeling, and in-silico ligand-docking experiments. Based on our current results, we believe that FC101 is an excellent lead candidate for a small molecule anti-cancer agent that simultaneously affects angiogenesis signaling, tumor signal transduction, and apoptosis.

Novel Peptidomimetics for Inhibition of EGFR Heterodimerization

3

Seetharama Jois, PhD Department of Basic Pharmaceutical Sciences
UNIVERSITY OF LOUISIANA MONROE

~~~

Mentors:

Marcia Newcomer, PhD
Department of Biological Sciences
LSU

Maria da Graça H.Vicente, PhD
Department of Chemistry
LSU

~~~

Epidermal growth factor receptors (EGFRs) belong to the transmembrane receptor tyrosine kinase (RTK) family of receptors that mediate cell signaling resulting in cell growth, differentiation and motility. Deregulation of signaling due to mutation of the receptors and constitutive activation as well as dimerization has been reported in several types of cancers. HER2 is overexpressed in 20-30% of breast cancer. HER2 is known to exist in always open conformation without any known ligand and is the preferred partner among EGFRs for homo and heterodimerization which is stabilized by Protein-Protein interactions (PPI) of extracellular domain II and domain IV which leads to signaling. Domain IV of HER2 is a clinically validated target by antibody trastuzumab. Here we investigated the PPI of domain IV using molecular dynamics approach. We have designed several peptidomimetics to block the HER2 mediated dimerization resulting in antiproliferative activity for cancer cells. Among the compounds studied in this work, a peptidomimetic compound 21 with D-amino acid substitution exhibited antiproliferative activity in HER2 overexpressed breast, ovarian and lung cancer cell lines. Inhibition of dimerization was evaluated using pathhunter assay, proximity ligation assay and western blot analysis and correlated with antiproliferative activity against breast, ovarian and lung cancer cell lines.