

Apr 18th, 2:30 PM - 3:50 PM

Anthracenyl isoxazole amides (AIMs) stabilize quadruplex DNA structures in telomeric and c-MYC promotor sequences

Sascha Stump

University of Montana - Missoula, ss196343@umconnect.umt.edu

Matthew Jacob Weaver

The University of Montana

Nathan S. Duncan

The University of Montana

Alison King Kearns

The University of Montana

Philip Reigan

University of Colorado at Denver, Philip.Reigan@ucdenver.edu

See next page for additional authors

Follow this and additional works at: <http://scholarworks.umt.edu/gsrc>

Sascha Stump, Matthew Jacob Weaver, Nathan S. Duncan, Alison King Kearns, Philip Reigan, Nicholas R. Natale, and Howard Beall, "Anthracenyl isoxazole amides (AIMs) stabilize quadruplex DNA structures in telomeric and c-MYC promotor sequences" (April 18, 2015). *UM Graduate Conference (GradCon)*. Paper 22. <http://scholarworks.umt.edu/gsrc/2015/posters/22>

This Poster Presentation is brought to you for free and open access by ScholarWorks at University of Montana. It has been accepted for inclusion in UM Graduate Conference (GradCon) by an authorized administrator of ScholarWorks at University of Montana. For more information, please contact scholarworks@mail.lib.umt.edu.

Authors' Names

Sascha Stump, Matthew Jacob Weaver, Nathan S. Duncan, Alison King Kearns, Philip Reigan, Nicholas R. Natale, and Howard Beall

Anthracenyl isoxazole amides (AIMs) stabilize quadruplex DNA structures in telomeric and c-MYC promotor sequences

Stump, Sascha; Weaver, Matthew J.; Duncan, Nathan S.; Kearns, Alison K.; Reigan, Phillip; Natale, Nicholas R.; Beall, Howard D.

Department of Biomedical and Pharmaceutical Sciences, University of Montana

Approximately 23,000 people are affected by malignant brain and CNS tumors in the United States each year and those afflicted have a median survival rate of only 12–15 months due to the limited treatment options available. The anthracenyl isoxazole amides (AIMs) are a novel class of compounds that have been shown to possess significant anti tumor activity in the NCI 60 cell line panel and to inhibit growth of SNB-19 glioblastoma cells at low micromolar and nanomolar concentrations. The goal of our current research is to characterize the mechanism underlying the anti tumor activity of the AIMs. We hypothesize the mechanism of growth inhibition to involve binding and stabilization of a DNA tertiary structure known as a guanine quadruplex. Various regulatory regions of DNA, such the c-MYC oncogene promoter sequence and repeating sequences formed at the end of telomeres, adopt the quadruplex conformation. Stabilization of quadruplex structures by small-molecule binding ligands has been reported to modulate the expression of genes and inhibit telomerase activity. Down-regulation of certain oncogenes or the inhibition of telomerase can cause tumor cells to undergo apoptosis or become unable to efficiently replicate. To establish whether interactions between the AIMs and quadruplex-forming sequences act to stabilize the quadruplex tertiary structure, circular dichroism spectroscopy (CD) was employed. CD is a method that utilizes the differential absorbance of left and right circularly polarized light to examine the chiral structure of molecules. CD thermal melting studies were conducted to determine whether the AIMs would increase the melting temperature of quadruplex forming sequences as an indication of increased stability. Our results demonstrated the AIMs, at two equivalents, increase the melting temperature (T_m) of both the c-MYC promoter and telomeric sequences by approximately 2–3 °C with strong statistical significance and reproducibility. Utilizing CD allows the use of low micromolar concentrations of DNA and this method will be used in the future to rapidly develop additional structure-activity relationships between novel AIMs and quadruplex forming sequences. Our laboratory has also shown chemical shifts in the imino region upon treatment with the AIMs for both the c-MYC promoter and telomeric sequence by NMR, providing additional evidence of the AIMs interaction with quadruplex structures. Interestingly, fluorescence microscopy of SNB-19 cells treated with AIMs show their localization is primarily in the mitochondria, and mitochondrial DNA contains several other important quadruplex forming sequences. Mitochondrial-dependent apoptosis has been suggested for other quadruplex binding ligands and therefore our future work will examine the potential stabilization of mitochondrial quadruplexes by these and other novel AIMs.