UNIVERSITY GRADUATE SCHOOL BULLETIN
ANNOUNCEMENT

Florida International University
University Graduate School

Doctoral Dissertation Defense

Abstract

"Insight into the inhibition of ribonucleotide reductases by 2'-chloro-2'-deoxynucleotides and 2'-azido-2'-deoxynucleotides". Biomimetic studies with model substrates

by

Mukesh Madan Mudgal

Ribonucleotide Reductases (RNRs) are crucial enzymes that catalyze reduction of ribonucleotides to deoxyribonucleotides, required for the biosynthesis of DNA. Vital role played by RNR in the biosynthesis of DNA and its control on cell growth made it one of the main targets for anticancer therapy. Several laboratories clarified the aspects of reaction cascades at active site of RNR. Biochemical studies of RNR by Stubbe for the inactivation of RDPR by 2'-chloro-2'-deoxyuridine-5'-diphosphate emphasizes departure of chlorine as an anion, while biomimetic studies by Robins with 6'-*O*-nitro-2'-chloro-homonucleosides emphasizes the elimination of chlorine substituent from 2'-position as a radical. To clarify the ambiguity in the mechanism of inhibition of RNR by 2'-chloro-2'-deoxyuridine, biomimetic reactions with model 6-*O*-nitro-1,5-dideoxyhomosugar derivatives were investigated. The study includes several modes: (i) synthesis of 6-*O*-nitro-1,5-dideoxyhomosugar derivatives with chlorine, bromine or tosyl substituent at the C2 position with *ribo* and *arabino* configurations, (ii) biomimetic studies of 6-*O*-nitro-1,5-dideoxyhomosugar derivatives with Bu_3SnH/AIBN to provide chemical evidences to distinguish the nature of elimination of chlorine from 2'-chloro-2'-deoxyuridine upon its incubation with enzyme, and (iii) kinetic studies to differentiate between heterolytic or homolytic C2'-chlorine bond cleavage.

In the second half of this dissertation, azido and sulfenamide modified nucleosides and 2-azidolyxofuranoside derivatives have been synthesized with the azido or sulfenamide substitution at a specific site in the sugar or in the base moiety. The electron-induced site specific formation of neutral aminyl radicals (RNH●) and their subsequent reactions have been investigated using ESR spectroscopy. In 2'-AZdC the RNH● site is attached to a 2º C-atom, where as in 4'-AZdC, the RNH● site is attached to a 3º C-atom, respectively. These studies elucidated how stereo and electronic environment affect formation and subsequent reactivity of various types of RNH● generated from azidonucleosides. To avoid the interaction of transient radical with nucleoside heterocyclic bases, 2-azidolyxofuranoside derivatives as a simpler abasic model were synthesized and studied with ESR spectroscopy. Aminyl radical generated from 2-azidolyxofuranoside derivatives subsequently abstracted hydrogen from C5 intramolecularly. These studies were designed to understand the mechanism of damage in various DNA model structures.

Date: June 30, 2016
Time: 10.00 a.m.
Place: CP-320

Department: Chemistry and Biochemistry
Major Professor: Dr. Stanislaw Wnuk