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Bioorganic Chemistry

Research Interests

Our group is interested in investigating chemically modified oligonucleotides to probe various biochemical processes. One of our projects involves the synthesis of oligonucleotides that are mimics of clinically relevant lesions formed during chemotherapy. This strategy requires skills in both solution-phase and solid-phase synthesis to prepare DNA duplexes that contain interstrand cross-links (ICL). These DNA probes will be used in studies that will advance our understanding of the mechanisms involved in their repair, an important step towards elucidating how some patients develop resistance to the effects of these chemotherapeutic agents. UV thermal denaturation (Tm), circular dichroism (CD), high field NMR and X-ray crystallography are some of the techniques that will be used to determine deviations of ICL DNA from unmodified DNA duplexes. In addition, biological assays will be carried out to probe the substrate specificity of various DNA repair enzymes towards our chemically synthesized ICL DNA duplexes. By exploring structure-activity relationships of modified nucleic acids though synthesis and biophysical chemistry, students will gain expertise in several other areas of interest to the pharmaceutical field (gene silencing, RNAi, drug discovery, etc).

Selected Publications

Wilds, C.J., Palus E. and Noronha A.M. (2007) "An Approach for the Synthesis of Duplexes Containing N3T-Alkyl-N3T Interstrand Cross-links via a Bisphosphoramidite Strategy", Canadian Journal of Chemistry, 85, 249-256.

Wilds, C.J., Booth, J.D., Noronha, A.M. (2006) "Synthesis of Oligonucleotides Containing an O6-G-alkyl-O6-G Interstrand Cross-Link", Tetrahedron Letters, 47, 9125-9128.

Li, F., Sarkhel, S., Wilds, C.J., Wawrzak, Z., Prakash, T.P., Manoharan, M and Egli, M. (2006) "2'-Fluoroarabino- and arabinonucleic acid show different conformations, resulting in deviating RNA affinities and processing of their heteroduplexes with RNA by RNase H", Biochemistry, 45, 4141-4152.

Wilds, C.J., Maier, M.A., Manoharan, M. and Egli, M. (2003) "Structural Basis for Recognition of Guanosine by a Synthetic Cytosine Analogue: Guanidinium G-Clamp", Helvetica Chimica Acta, 86, 966-978.

Wilds, C. J., Wawrzak, Z., Krishnamurthy, R., Eschenmoser, A. and Egli, M. (2002) "Crystal Structure of a B-form DNA Duplex Containing (L)-α-Threofuranosyl (3'->2') Nucleosides: A Four Carbon Sugar is Easily Accommodated into the Backbone of DNA", Journal of the American Chemical Society, 124, 13716-13721.