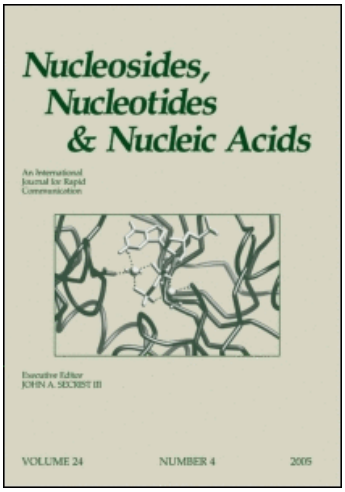

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Design, Synthesis and Tumor Specificity of Azomycin Ribo- and Acyclonucleosides

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To cite this Article Srivastava, Prem C. , Buchsbaum, Donald J. and Hasad, Ahmad(1991) 'Design, Synthesis and Tumor Specificity of Azomycin Ribo- and Acyclonucleosides', Nucleosides, Nucleotides and Nucleic Acids, 10: 1, 235 — 238
To link to this Article: DOI: 10.1080/07328319108046450
URL: http://dx.doi.org/10.1080/07328319108046450

NUCLEOSIDES & NUCLEOTIDES, 10(1-3), 235-238 (1991)

DESIGN, SYNTHESIS AND TUMOR SPECIFICITY OF AZOMYCIN RIBO- AND ACYCLONUCLEOSIDES

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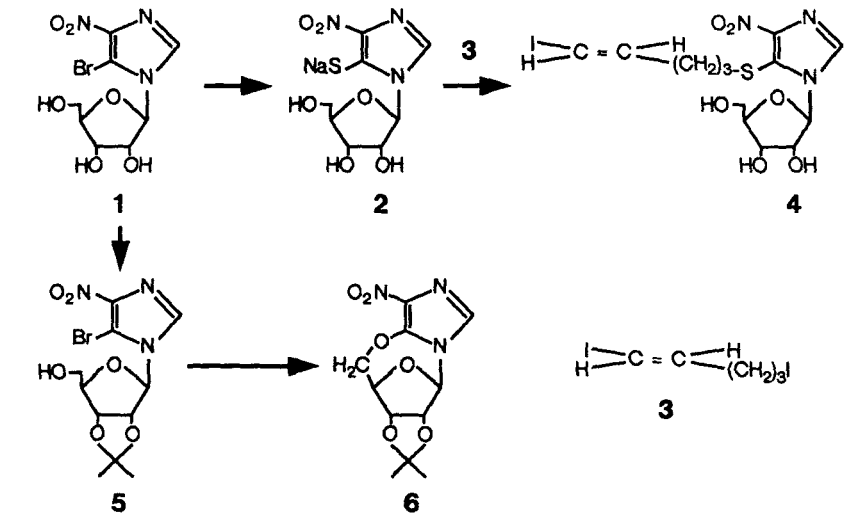
Abstract. Synthesis, structure elucidation, and *in vivo* tumor specificity of nitroimidazole ribo- and acyclonucleosides are described.

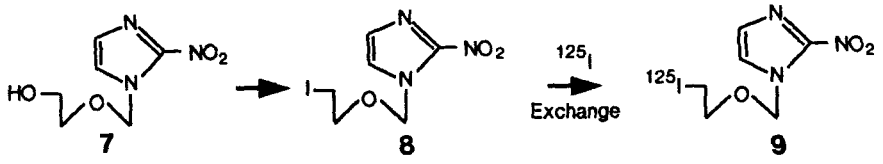
INTRODUCTION

Most solid tumors, unlike normal tissues, contain hypoxic cells due to insufficient blood supply. Several azomycin[1] (2-nitroimidazole) analogues are potentially capable of substituting for molecular oxygen and selectively bind and show cytotoxicity to hypoxic cells.[2,3] Generally, nucleosides show enhanced biological activity as compared to their parent aglycone because the glycosyl group increases the hydrophilicity which facilitates nucleoside transport[4] and provides a phosphorylation site for metabolic activation. It is implied that azomycin nucleoside analogues will show similar affinity but increased transport to hypoxic tumor cells as compared to their parent aglycones. The nucleosides with selective transport to and metabolism in hypoxic tumor cells may also become incorporated into nucleic acids and be trapped in the hypoxic microenvironment of tumors. Such nucleosides,

Research supported by the Office of Health and Environmental Research, U.S. Department of Energy, under contract DE-AC05-84OR21400 with Martin Marietta Energy Systems, Inc.



SCHEME I



SCHEME II

if appropriately radiolabeled, could be used as tumor markers for diagnosis or radiation killing of cancer cells. The ribonucleoside mimicking acyclonucleosides of azomycin, if recognized by relatively low substrate specificity enzymes of tumor may show improved tumor selectivity.

DISCUSSION

Several 5-substituted-4-nitroimidazole ribonucleosides[5] (Scheme I) and azomycin acyclonucleosides[6] (Scheme II) have been prepared. The syntheses of 5-(E-1-[^{125}I]iodo-1-penten-5-yl)thio-4-nitro-1-β-D-ribofuranosylimidazole([^{125}I]-IPTN, **4**) and 4'-deoxy-4'-[^{125}I]iodoazomycin acyclonucleoside (1-[2-deoxy-2-[^{125}I]iodoethoxy-methyl]-2-nitroimidazole, [^{125}I]-AcN, **9**) and their evaluation in laboratory tumor models is the subject of this discussion.

The [^{125}I]-IPTN was prepared via the following key steps: a) glycosylation[8,9] of 5-bromo-4-nitroimidazole, b) replacement of Br with SH, and c) alkylation of SH with E-1-[^{125}I], 5-diiodopentene.[10] The ß-configuration and the N^1-nitrogen position adjacent to the bromide leaving group as the site of glycosylation in 5-bromo-4-nitro-1-ß-D-ribofuranosylimidazole (1) was confirmed by its acetonation to 2',3'-O-isopropylidene derivative 5 followed by cyclization in dimethylformamide containing sodium hydride to yield 5,5'-anhydro-4-nitro-5-oxo-1-(2,3-O-isopropylidene-ß-D-ribofuranosyl)imidazole (6, mp 167-168°C).[5] The [^{125}I]-IPTN showed significant tumor uptake (1 h, 1.6% ID/gm) in Balb C mice bearing Line-1 lung carcinomas. The [^{125}I]-AcN prepared in high yield via hydroxyethoxymethylation of 2-nitroimadazole[6] followed by iodination (methyltriphenoxyphosphonium iodide) and exchange labeling with ^{125}I, was evaluated in nude mice bearing LS174T human colon cancer xenografts. The [^{125}I]-AcN, at 24 h after administration, showed high concentration (uptake) in the tumor (3.5% ID/gm), low concentration (less than 1% ID/gm) in stomach, small intestine, kidneys, bone, muscle, and liver, and insignificant (less than 0.1% ID/gm) concentration in the bone marrow. The [^{125}I]-AcN also showed activity in the blood, lungs, and spleen ($\sim$3.0% ID/gm, 24 h) due perhaps to *in vivo* deiodination or metabolism.

Recently, we have prepared 1-propargyloxymethylazomycin for the synthesis of azomycin acyclovinyl iodide[11] analogue to overcome *in vivo* deiodination. The enhanced uptake of [^{125}I]-AcN in tumor relative to most of the organs indicates potential utility of such agents in cancer diagnosis and therapy.

ACKNOWLEDGEMENT

Research at the Oak Ridge National Laboratory is supported by the Office of Health and Environmental Research, U.S. Department of Energy, under contract DE-AC05-84OR21400 with Martin Marietta Energy Systems, Inc., and research at the University of Michigan is supported by National Cancer Institute Grant CA44173.

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