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Synthetic Efforts Toward a C7-alkyl Substituted Aziridinomitosene

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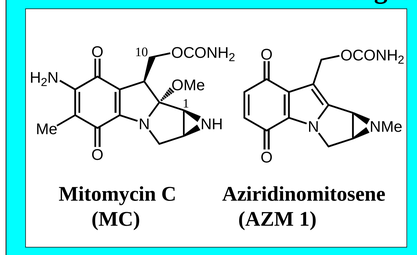
Abstract: Mitomycin C (MC) is a natural product that exhibits therapeutic cancer qualities by forming interstrand crosslinks with DNA in cancer cells, therefore inhibiting replication and cell growth. However, the clinical utility of MC is limited because of adverse side effects. It is hypothesized that MC toxicity arises from the reduction that is required before DNA adducts are formed. Aziridinomitosenes (AZMs), compounds structurally similar to MC, are able to alkylate DNA without reductive activation. Most notably, our synthetic AZMs have been shown to form DNA/protein crosslinks as well as DNA interstrand crosslinks in the absence of added reductant. In order to determine the mechanism by which these adducts form, several analogs with varying substitution at four separate electrophilic centers are being prepared. Synthetic efforts toward a C7-alkyl substituted AZM propagates testing that may potentially create more potent and less toxic anti-cancer agents. These and related studies will be presented.

Background



- Mitomycin C (MC) is a naturally occurring agent known to possess anti-cancer qualities
- Reductive activation of MC must occur before DNA alkylation
- MCs required reduction increases hematologic toxicity, limiting its clinical usefulness
- AZMs alkylate DNA similarly to MC, but do not require reductive activation

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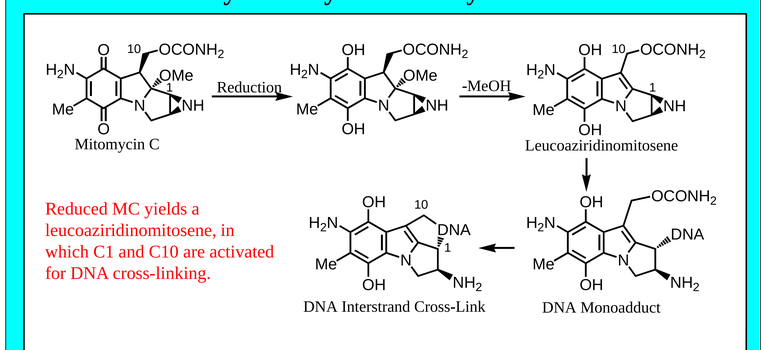
DNA Alkylation by Reductively Activated MC



Reduced MC yields a leucoaziridinomitosene, in which C1 and C10 are activated for DNA cross-linking.

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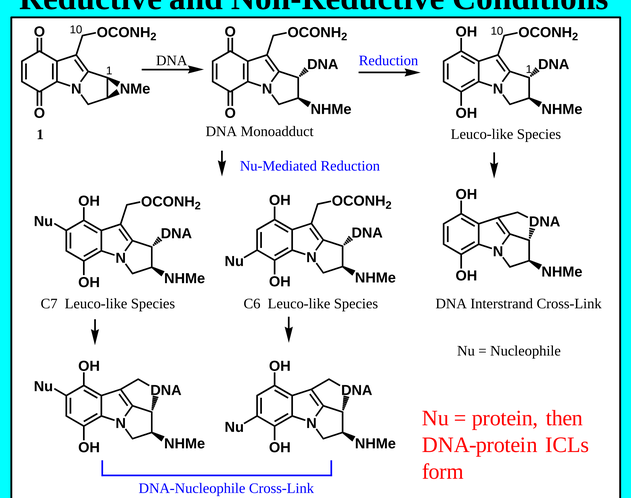
Proposed DNA Alkylation by Aziridinomitosene 1: Reductive and Non-Reductive Conditions



Nu = protein, then DNA-protein ICLs form

- Mechanism begins with acid catalyzed aziridine ring opening, followed by DNA alkylation
- Nucleophilic addition to the C6 or C7 position ring results in a reduced quinone ring
- Leucoaziridinomitosene formation prompts C10 carbamate departure, facilitating interstrand cross-link formation (ICL)

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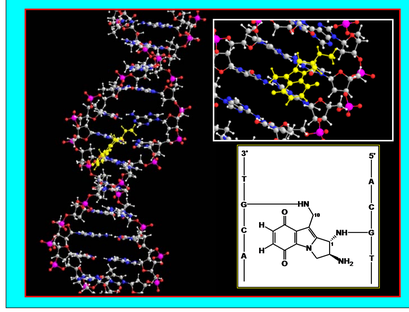
Molecular Model of DNA Interstrand Crosslink



- H-bonds direct AZM 1 to the minor groove of DNA
- AZM 1 selectively alkylates guanine bases, specifically 5'-d(CG) sequences
- DNA alkylation occurs at the C1 aziridine and C10 carbamate positions
- AZM 1 positions C6 and C7 are accessible to nucleophiles, such as proteins and thiols

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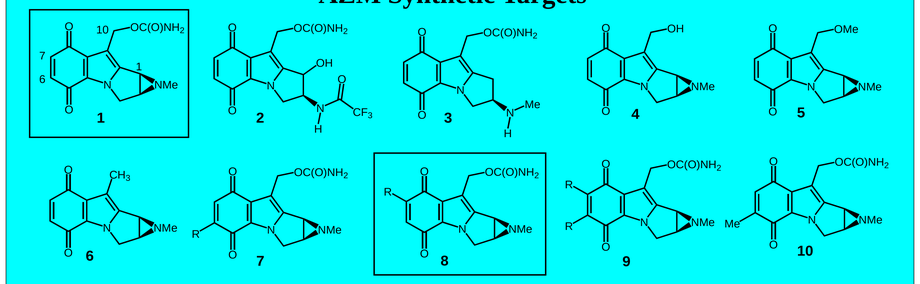
AZM Synthetic Targets



- Compounds differ in substitution at four sites involved in DNA crosslink formation: C1, C6, C7, and C10
- This study focuses on the synthesis of compounds 1 and 8

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Research Objectives

Objective 1: Synthesize the unsubstituted AZM 1

Objective 2: Synthesize the C7 alkyl substituted AZM 8

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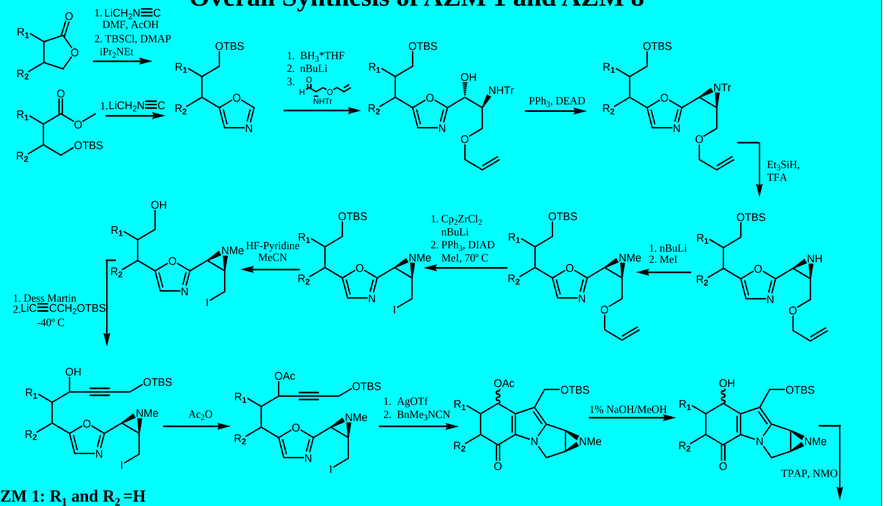
Overall Synthesis of AZM 1 and AZM 8



- **AZM 1: R_1 and R_2 =H**
- **AZM 8: R_1= variable alkyl group**
  R_2 = H

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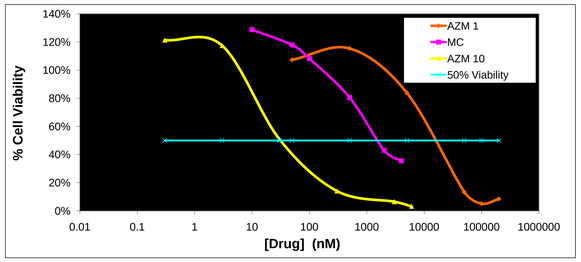
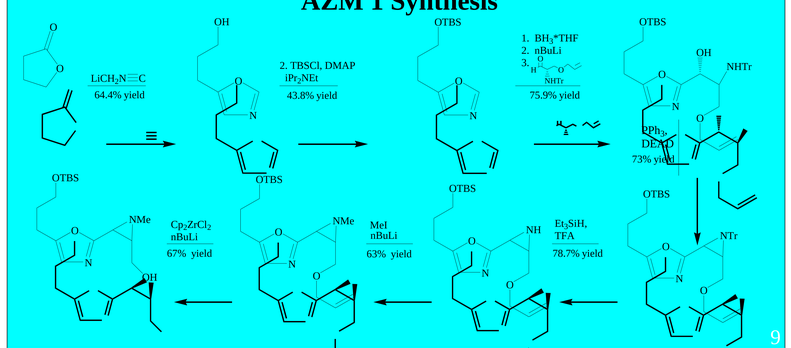
Aziridinomitosenes Potency



Cell Line (suspension)	IC_{50} Values (μM) MC	AZM 1	AZM 10
Jurkat (T-cell leukemia)[h]	1.98	24.4	0.11
YB 2/0 (B-cell leukemia)[r]	0.5	24.3	0.45
HL 60 (promyelocytic leukemia)[h,*]	0.07	2.7	0.003

** These studies were performed by Jamie Montgomery in collaboration with Dr. Richard Olson of MSTMRI and the Boise VA Medical Center. [r] = rat, [h] = human*

AZM 1 Synthesis



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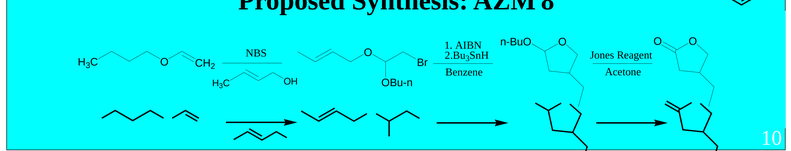
Proposed Synthesis: AZM 8



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Conclusions and Future Work

- AZM 1 has been previously shown to bind to DNA
- It is hypothesized that the C7 alkyl substituted AZM 8 will form DPCLs with depreciated efficacy because of steric constraints
- Goal 1: Complete synthesis of AZM 1
- Goal 2: Conduct synthesis for AZM 8 to investigate the role of the C7 site in DNA ICL formation
- Goal 3: By concurrently synthesizing AZM 1 and AZM 8, proper testing may be conducted to provide insight into the hypothesized nucleophile mediated DNA ICL formation

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