Abstract: Reductive activation of Mytomycin C (MC), a commonly used anticancer agent, results in the formation of DNA interstrand crosslinks (ICLs). These crosslinks result in apoptosis of the cell. However, reductive activation is thought to be the cause of many of the adverse side effects caused by MC. Aziridinomitoines (AZMs) are structurally similar to MC, but can alkylate DNA and form ICLs under non-reductive conditions. The synthetic AZM currently being used has four electrophilic sites that are able to alkylate DNA: C1, C6, C7, and C10. It is hypothesized that the C6 and C7 electrophilic sites on the quinone ring of the AZM are responsible for the formation of the DNA/protein adducts. To test this, methyl substituted variations of the AZM, in which the methyl group is used to block either C6 or C7, have been prepared and will be tested to determine the fate of the AZM analogs in the presence of nucleophiles. Details and relevant studies will be presented.

Background

- Mitomycin C (MC) is a naturally occurring anti-cancer agent exhibiting the ability to form DNA interstrand crosslinks, thereby, causing cell apoptosis.
- MC requires reductive activation in order to alkylate and bind to the DNA, which is believed to result in the adverse effects caused by the drug.
- Aziridinomitoines (AZMs) are structurally similar to MC and share many of its key characteristics, but they do not require reductive activation.

Sequence Specific Interstrand Crosslinks

- Interstrand crosslinks (ICLs) result in cell death by forming a clasp between the two helical strands of DNA and preventing it from unzipping and replicating.
- MC are specific to the CG sequence of DNA in terms of forming these ICLs.
- As seen in the figure on the left, AZMs are also specific to the CG sequence of DNA.

Proposed DNA alkylation by an AZM

- The proposed mechanism involves monoalkylation of the DNA followed by nucleophilic attack of the quinone ring.
- With the C6-methyl substituted AZM, the nucleophilic attack occurs at the C7 position with the opposite being true of the C7-methyl substituted AZM. It is hypothesized that a methyl group in both positions would prevent nucleophilic attack, thus, preventing DNA crosslinking.

Synthetic Targets

- C6-methyl substituted AZM
- C7-methyl substituted AZM
- Di-methyl substituted AZM

NMR of the Final Product To Date

Research Objectives

1) Synthesize the C6-methyl substituted AZM
2) Test each AZM derivative in the presence of nucleophiles

OBJECTIVE 1:

Synthesis of the C6-methyl substituted AZM

Conclusions and Future Work

- The C6 and C7-methyl substituted analogs have previously been found to bind with DNA and form a crosslink between the two helical strands.
- The synthesis of the AZM derivatives must be completed in order to determine the effect the methyl group has under nucleophilic attack.

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