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Investigations into the Modification of DNA by Doxorubicin Analogs

Abstract. Doxorubicin (DOX) is an anthracycline chemotherapeutic that has seen widespread use to treat numerous cancer types. Its mechanism of action is still unclear, but is thought to include the intercalation of DNA, halting transcription and inducing apoptosis. Although DOX has shown strong antitumor activity, its usage is limited due to a dose-dependent onset of cumulative and irreversible life-threatening cardiac damage. Consequently, the harmful side effects necessitate the need for the production of new, less harmful anthracycline chemotherapeutics with greater effectiveness for the treatment of cancer. Three analogs of DOX (P-DOX, GPX-150 and GPX-160) have been synthesized and determined to have antitumor activity against multiple cancer cell lines. This study seeks to investigate the mechanism by which these analogs display their activity, specifically probing for DNA modification. Each compound was tested for and found to have greater DNA-modifying abilities than DOX by the alkaline COMET, DNA gel electrophoresis, and the K-SDS DNA-protein crosslinking assays. These and related experimental results will be presented.