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Characterization of novel PI3K family inhibitors as sensitizers to Doxorubicin

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Cancer is the leading cause of death in economically developedcountries and the second leading cause of death in developingcountries. Components of DNA damage response pathways have proven potential as therapeutic targets and this has fuelled researchers and pharmaceutical companies to develop inhibitors for the proteins involved in these pathways. One such protein is DNA-PK which has been the focus of several approaches including molecular modelling in attempts to expedite drug discovery. In my study, a set of novel benzoxazine derivatives synthesized in our lab were analysed for their protein/ligand interaction patterns following which four interesting compounds were selected for further examination. Detailed biological studies on the ability of these compounds to sensitize two human tumour cell lines, HT-29 and HCT-116, to the effects of the topoisomerase II poison Doxorubicin have been carried out. Cell cycle analysis, Apoptosis assay, γ-H2AX assay, Western Blotting and Mitotic catastrophe assays have been used to determine the exact mechanism of sensitization. Our studies indicate that two of compounds act through inhibition of DNA-PK and hence of DNA repair whereas two others act through an alternative pathway to enhance the effects of Doxorubicin.

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