DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL ANTHRAQUINONE DERIVATIVESAS DUAL INHIBITORS OF TOPOISOMERASE 2 AND CASEIN KINASE 2

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Abstract - Cancer deaths rule the charts for over a decade with no persistent solution. In today's era of complex and heterogeneous diseases such as cancer, the concept of "single-target-single-compound" has proved less effective. This calls for dual targeting, wherein a single drug is so designed that it modulates the activity of multiple protein targets.
In the present work, 2 human proteins have been targeted to achieve anticancer effect – Human Topoisomerase 2 (Top2) and Human Casein Kinase 2 (CK2). While, Top2 helps in removing DNA tangles and supercoiling during cellular replication, CK2 is involved in the phosphorylation of multitude of protein targets.
Top2 are a group of enzymes capable of passing two duplex DNA segments through each other during cellular replication. The enzyme achieves this in three steps via the formation of the transient, short lived Top2 cleavage complex (Top2CC) which is then followed by the relegation step. Most of the Top2 inhibitors inhibit the enzyme function in a manner such that it increases the concentration of Top2CC and thereby prevents the relegation step. Over the years, Top2 has been a very popular and a highly successful target for achieving anticancer activity. The second protein targeted- CK2, is a highly conserved, ubiquitous serine/threonine kinase which phosphorylates more than 300 substrates. Although it is proven that CK2 by itself is not oncogenic, elevated levels of CK2 is observed in cancers. This shows that despite itself being non-oncogenic, CK2 rather regulates the activity of proteins which are under its control thereby altering the oncogenic potential of the cell.
In this study, considering all the designing aspects of Top2 and CK2 inhibitor, the moleculeswere designed, synthesized and tested for antiproliferative activity on HL60 and K562 leukemic cell lines. The compounds were also evaluated for their Top2 and CK2 enzyme inhibitory potential and were subjected to cell cycle analysis.