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Dissertation

Title *Molecular Recognition of Duplex and Quadruplex DNA by Small Molecules and its Application for Developing New Anticancer Therapies*

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Abstract

Human telomeres are the end caps of linear chromosomes. Under physiological conditions, telomere folds up into four stranded intramolecular structure called G-quadruplex. Formation of G-quadruplex has been associated with inhibiting telomerase enzyme found enriched in cancer cells and involved in cells' replications. Subsequently, G-quadruplex has become an active target for the development of anticancer agents. Small molecules stabilize G-quadruplex are potential for developing anticancer therapeutic agents acting by inhibiting telomerase.

In this work, several new benzoquinone derivatives were synthesized and their structures were elucidated using elemental analyses, IR, NMR and MS. Benzoquinone and its synthesized analogues were studied for their binding affinity and selectivity towards telomeric G-quadruplex DNA using UV-Vis absorption, fluorescence, circular dichroism, melting temperature and NMR. The results indicated that G-quadruplex DNA interacted with synthesized compounds in stoichiometric ratios ranged in 1:1 to 1:4. Binding affinities ranged between 5.60×10^4 - 1.33×10^7 M⁻¹. Compounds TQ8 and TQ6 showed the best stabilizing effects on G-quadruplex with changes in melting temperature (ΔT_m) of 21 and 10 °C, respectively. In addition, synthesized analogues showed good selectivity towards G-quadruplex DNA over duplex DNA.

Synthesized compounds were also tested against lung, breast, colorectal, prostate, pancreatic, colon and lymphoma cancer cell lines. Loss in cells' viabilities in the range of 25-100 % with IC₅₀'s between 6.18 and 100.0 µM were reported for synthesized analogues after 24 h relative to the control. These results revealed compounds of high potential for further processing as anticancer therapeutic agents.

Research Relevance and Potential Impact

Cancer is the third cause of death in UAE and worldwide. Therefore searching for new effective and selective anticancer drugs continued over decades as a topic of high importance in science. This work revealed compounds of high potential for further processing as anticancer agents. The study combined molecular recognition of G-quadruplex DNA and the effect of synthesized compounds on cancer cells in-vitro.

Relevant Publications

- Alaa A. Salem, Ismail M. El Haty, Ibrahim M. Abdou and Yaguang Mu, Interaction of human telomeric G-quadruplex DNA with thymoquinone: A possible mechanism for thymoquinone anticancer effect. *Biochimica Biophysica Acta (BBA)*, 2015. 1850 (2): p 329-342. Career

Career Aspirations

My dream is to be an active team player within an academic institution to contribute in the education development. On the other hand, I would like to use the experience and skills that I have gained during PhD and Post doctorate to synthesize new compounds that may help in developing anticancer therapies.