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SUBSTITUTED ANTHRAQUINONES IN G4-DNA DRUG DESIGN: A CONCISE REVIEW

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Abstract

DNA in the human telomere in the form of G-quadruplex (G4) has become an interesting target in cancer therapy since it plays a regulatory role in keeping the telomeres stable and regulating telomerase activity. Compounds consisting of anthraquinone-based structure and that have shown a high affinity to DNA due to the planar aromatic scaffold and the potentiality of binding G-quadruplex structures, have extensively been drawn as potent starting points to selectively stabilize G-quadruplex structures that occur in telomeres. The review indicates the latest achievements in the design, synthesis, and biological testing of the anthraquinone derivatives specifically oriented to act against human telomeric G4 DNA. A number of changes-amino-alkyl side chain, dimeric structures, and sugar conjugates- have enhanced their binding affinity and selectivity to duplex DNA and ability to kill cancer cells considerably. The derivatives, including 2,6-disubstituted-amino alkyl-amido, anthraquinones with neomycin-anthraquinone conjugates, can be mentioned as the derivatives capable of nanomolar to micromolar affinities toward G4-DNA and the capability to inhibit telomerase *in vitro*. Strong binding interactions and thermal stability of G4 structures, in particular, with the monovalent salt ions, such as Na^+ and K^+, are likewise well-documented by biophysical methods, including UV-Vis's spectroscopy, circular dichroism and fluorescence titrations. Cellular assays also show high therapeutic potentials of these compounds, which show reactive oxygen species (ROS), DNA damage and apoptosis in cancer cell lines. In addition to telomeric sequences, a few anthraquinone derivatives inhibit oncogene promoter G-quadruplexes extending the scope of their utility. Although the in vitro findings are encouraging, there are issues with regard to improved selectivity, toxicity and effective *in vivo* delivery. This review sums up the recent developments and provides future prospects of possible development of clinically useful G-quadruplex targeting anthraquinone therapeutics.

Keywords: Telomeric G-Quadruplex DNA, Anthraquinone Derivatives, Telomerase Inhibition, Cancer Therapeutics, DNA-Binding Ligands.

1. INTRODUCTION

1.1 The G Quadruplex DNA and Telomeres

G-quadruplexes G4s are four stranded nucleic acid structures that form in guanine rich sequences through Hoogsteen base pairing to generate G-tetrads, which are stabilized by monovalent cations such as K 1. In human beings, telomeric DNA includes TTAGGG tandem repeats that undergo intra or intermolecular G-quadruplex structures at chromosome ends.[1-4] The buildings may take an anti-parallel, parallel topology or a hybrid structure depending on the surroundings and the type of cation. Telomerase A (ribonucleoprotein reverse transcriptase) is expressed in ~80-85 of human cancers and regulates the extended length of telomeres, allowing them to avoid death.[5] By making the telomeric G4-DNA stable, telomerase is unable to elongate the telomeres resulting in replicative senescence or apoptosis among cancerous cells. In turn, the telomeric G-quadruplex-selective binding and stabilizing small molecules have been established to

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have a potential use as anticancer agents. The well-known anthraquinones are planar tricyclic compounds used as intercalators of DNA and inhibitors of topoisomerases. The anthraquinone scaffold (**Figure 1**) offers extensive 2-surface suitable to stacking with terminal G-tetrads of G-quadruplexes and docking grooves or loops of G4 DNA. A number of derivatives on which the stabilising effect includes mitoxantrone, doxorubicin and synthetic analogues have been known to resist G-quadruplex DNA and suppress telomerase as well as cell growth.[6, 7]

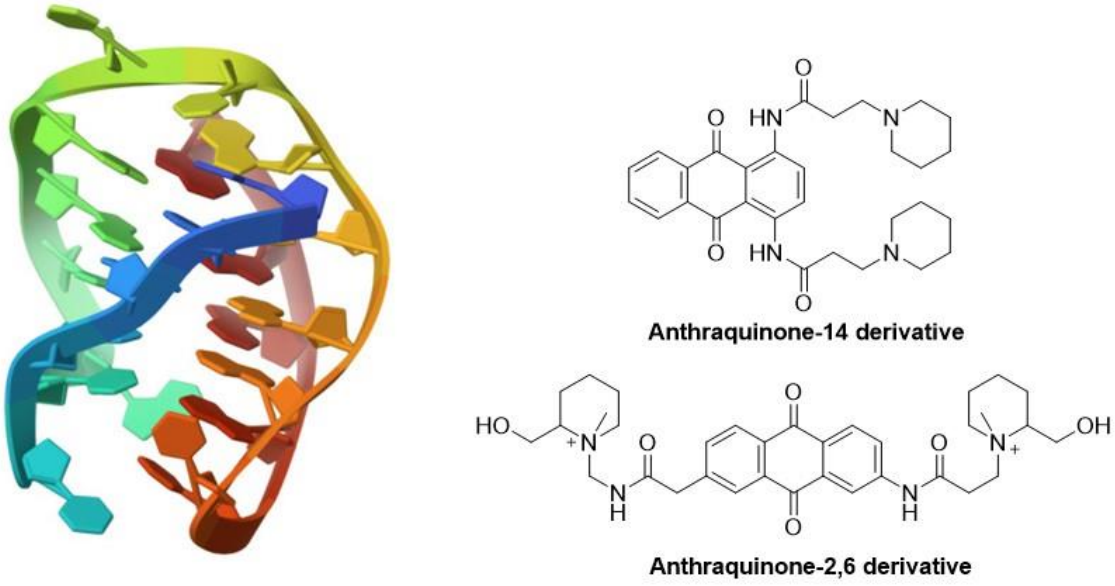

Figure 1: G-Quadruplex-DNA and Anthraqinone-based ligands targeting G4-DNA

2. TELOMERIC G4 SHORT DNA TARGETING ANTHRAQUINONE-BASED LIGANDS

2.1 Preliminary Findings: 2,6 Disubstituted aminoalkyl amido Anthraquinones

A 2,6 disubstituted aminoalkyl amido anthraquinone derivative (Figure 1) that stabilized telomeric G4 structures with $\Delta T_m \approx 20\,^{\circ}C$ and inhibited telomerase at ~23 μM concentration. These features established the anthraquinone scaffold as a G4-targeting pharmacophore. These attributes made anthraquinone a scaffold of G4 targeted pharmacophore.[4]

2.2 Dimeric and Side-chain Modified Anthraquinones

Dimeric derivatives; long chain amido anthraquinones and hydrophobic modications (e.g., Phe or Lys residues, tri N-methylpyrrole side chains) have subsequently been synthesized to enhance G4 vs duplex DNA selectivity and minimize toxicity. As an example, disubstituted anthraquinone tri-N methylpyrrole side chain (ANTP) displayed improved activity to c-Myc G4 ($3.8 \times 10^6\ M^{-1}$) and sufficient anticancer activity.[8]

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2.3 1,5 Bis[3 (diethylamino) propionamido] Anthracene 9,10 dione

A more recent derivative, 1,5-bis[3-(diethylamino)propionamido] anthracene-9,10-dione, was examined for binding to wHTel26 and HTel22 telomeric G4 in Na^+ and K^+ buffers. Biophysical assays revealed strong binding constants ($K_b \approx 10^5$–$10^7\ M^{-1}$), thermal stabilization ($\Delta T_m \sim 27.5\ °C$ in Na^+ and ~19.1 °C in K^+), spectral hypochromism and fluorescence quenching. Molecular docking suggested groove or loop-binding rather than end-stacking. In MCF-7 cancer cells, $IC_{50} \approx 8.4\ \mu M$ and apoptosis induction were observed.[9]

2.4 Neomycin-Anthraquinone Cyclo-conjugate

The conjoining of an aminosugar (neomycin) with anthraquinone resulted in a two-fold recognition ligand. This conjugate bound nano molar to human telomeric G4, ~1000 times greater than neomycin, anthraquinone, or mixtures alone (**Table 1**). The respective specificity and telomerase inhibition potential was found to be exceptional in the combined mode of the command by intercalation combined with groove binding.[10, 11]

Table 1: Anthraquinone based Ligand category

Ligand Class	Key Features	G4 Binding Role
2,6-Aminoalkyl Amido AQ	Cationic side chains	Electrostatic and H-bond groove binding
Neomycin–AQ conjugate	Sugar-quinone dual scaffold	Combined π-stacking + groove recognition
1,5-Bis-diethylamido AQ	Dual diethylamino propionamido	Strong G4 stabilization & telomerase inhibition
2,6-Dibromo AQ	Synthetic intermediate	Precursor for tailored ligand design

3. MECHANISMS OF BINDING AND STABILIZATION AT MOLECULAR LEVEL

3.1 Ligand Binding Modes

The mode of interaction of anthraquinones with the G4 DNA usually involves the 2-dimensional stacking interaction with the tetrads at the ends of G or interaction through groove/loop with help of the substituents. Several di-substituted derivatives show external groove, or loop binding by spectroscopic signature of hypochromism and absorbance shifts (617nm), fluorescence quenching, and CD response The conjugate of neomycin with anthraquinone provides two-point recognition: anthraquinone group is involved in recognition through π-stacking with G-tetrads whereas neomycin moiety can interact with groove or loop residues resulting in a nanomolar affinity and strong specificity.

3.2 Ion Modification: Na^+ vs. K^+

Anthraquinone derivatives often show stronger thermal stabilization (ΔT_m) in Na^+ than K^+ environments. For example, Dey's compounds enhanced ΔT_m by 34 °C in Na^+, but only ~21 °C in K^+. Similarly, the 1,5-substituted derivative had $\Delta T_m \approx 27.5$ °C in Na^+ vs ~19.1 °C in K^+. These differences reflect conformational topology changes—antiparallel forms in Na^+ vs hybrid or parallel in K^+—affecting ligand docking and stacking geometry.[12]

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3.3 Before and After the Kinetic and Thermodynamic Perspectives

The various binding constants (K_b) reported in literature vary between 10^2 and 10^8 M^{-1} with different substituents and ligand design. Neomycin-anthraquinone conjugate K_d was in the nanomolar range (10 nM^{-1}) as compared to simpler derivatives, which tend to fall in the micromolar and sub micromolar range.

Groove binding, the loop interaction and stacking events were established using molecular docking and uniquely molecular dynamics simulation. As an example, docking found important contacts between ligand and TTA loops or G quartet edges, which are in agreement with experimental CD and fluorescence measurements.

3.4 Biological Effects: Inhibition of telomerase, ROS, Apoptosis

Telomeric G4 structures that are in their stabilized forms are the inhibitors of telomerase binding and extension. Replication was blocked by polymerase stop assays and in cancer cell lines (e.g., MCF 7), these anthraquinone derivatives initiated the production of reactive oxygen species (ROS) and condensed their cell nuclei and initiated cell death (apoptosis), which was supported by viability assays and microscopy or qRT PCR of gene expression. The neomycin–anthraquinone conjugate also triggered telomerase inhibition and cytotoxicity consistent with G4 stabilization.[4]

4. MEDICAL IMPORTANCE AND POTENTIAL APPLICATIONS

4.1 Therapeutic Oncology

G4 stabilizing anthraquinones provide a specific and broad range anticancer approach, since telomerase is vital to the immortality of cancer cells, and is active in most cancers. Ligands of the neomycin anthraquinone conjugate and 2,6-disubstituted derivatives are highly binding and selective with in vitro potentials to inhibit tumor proliferation at low micromolar or nanomolar levels of concentration.[13]

4.2 Reducing Side Effect and Off Target Toxicity

One of the problems of chemotherapy with anthraquinone is the non-selective intercalation of DNA and systemic toxicity. Researchers are attempting to minimize off target effects by adding selectivity of G quadruplex over duplex DNA using modifications in side chain or by single designer hydrophobic residues or conjugation (e.g., aminoglycoside motif) to retain the anticancer activity.

4.3 Sophisticated Delivery and Combination tactics

New mechanisms are the use of anthraquinone payload with DNA nanostructures (and potentially aptamers, e.g., AS1411 aptamer, DNA tetrahedra), which are derived directly out of G quadruplex motifs, to provide more target specific delivery to tumor cells with less associated cardiotoxicity (as with doxorubicin mechanism). Such systems are not yet trained particularly on the treatment of ligands against anthraquinone G4, although these give an example of what might be used in the future.

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4.4 G Quadruplexes in the Promoters of Oncogenes beyond Telomeric Targets

Promoters of c-MYC, BCL 2, KRAS, c-KIT, VEGF and others have G quadruplex motifs. Stable-binding anthraquinones to promoter G4 structures (e.g., oncogene c MYC) have the potential to down-regulate oncogenes, provide multidimensional anti-cancer effects other than telomerase inhibition.[7]

4.5 A geriatric and Other Lesions

Even though the greater emphasis is put on cancer, G-quadruplexes are known to be involved in aging, genome instability, neurodegeneration, and other illnesses. In some of the discussions (e.g., in current literature), there is a proposal that unresolved G4 structures provide some contribution to the pathways of epigenomic instability and genome aging. Although anthraquinone is currently more under-explored in oncology, the application of G4-based targeting to the mentioned disease is one of its prospective applications.

5. RECENT ADVANCES AND FUTURE DIRECTIONS

5.1 High Resolution studies and New Structural Insights

Although anthraquinone targeting structures yet are only partially solved by NMR or crystallography, related G4 ligands, like Phen DC_3, have provided insights into the intercalation concept into how ligand induced G4 refolding can be conducted into new topologies (antiparallel, chair type). The above understandings guide the future directions of designing analogues of anthraquinone.

5.2 Ligand Libraries and Systematic Screening

Systematic screen and large review have now identified natural anthraquinones (e.g., aloe emodin, aloin), as well as synthetic variants with moderate and strong binding affinities to a wide range of telomeric and pathogenic oncogene G4s in humans.[6]

5.3 Enhanced Pharmacology

The focusses are on increasing water solubility and on minimizing aggregation, cell uptake, and selective binding. Dimerization, sidechain optimization, hetero-arene substitution, conjugation to sugar or peptide, and rational design, based on docking and molecular dynamics are current areas of development.

5.4 On the Way to Preclinical and Clinical Translation

Majority of anthraquinone G4-ligands are minimal in anti vitro or upstream pre-clinical development. Subsequent development after evaluation comprises animal tumor model assessment, pharmacokinetics, toxicity profile and mode of delivery. Translation will require the verification of G-quadruplex structure and ligand occupancy in live cells and tumors.

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6. SUMMARY AND CONCLUSIONS

Anthraquinone-based compounds form a pivotal class of telomeric G-quadruplex stabilizing ligands with significant anticancer potential. With a planar aromatic core complemented by substituent -aminoalkyl groups, hydrophobic residues, dimeric architectures, or conjugated molecules-their design strikes a balance between binding strength, G4 selectivity, and cell tolerability.

These compounds act by stabilizing telomeric G-quadruplexes, interfering with telomerase access, inducing oxidative stress and apoptotic pathways in cancer cells. Side-chain modification and conjugation afford improved specificity, reducing unwanted duplex binding and systemic toxicity. While still in early preclinical phases, anthraquinone G4 ligands are promising for targeted anticancer therapy.

Future studies should focus on high-resolution structural complexes, in vivo efficacy in animal models, pharmacokinetics, optimized delivery (e.g., nanoparticle/aptamer systems), and combination regimens. Moreover, exploring their roles beyond telomeres-in promoter G4s, genome stability, aging pathways-could broaden medical relevance.

In summary, anthraquinone-based G-quadruplex ligands represent a robust and evolving platform, leveraging structural DNA motifs to disable cancer proliferation and offering exciting avenues for therapeutic development in recent years.

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Declaration of competing interest

The author declares no known competing interests in this paper.

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