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ADVANCES IN G-QUADRUPLEX CHEMISTRY: FROM MOLECULAR INSIGHTS TO MEDICINAL APPLICATIONS

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ABSTRACT
G-quadruplexes (G4s) are guanine-rich DNA and RNA structures stabilized by stacked guanine tetrads and metal cations. Once considered structural curiosities, they are now recognized as dynamic regulators of telomere function, oncogene transcription, and repeat-associated toxicity. Their structural diversity-spanning parallel, antiparallel, and hybrid conformations, has driven intense interest in ligand design. Medicinal chemistry has yielded diverse scaffolds such as acridines, carbazoles, naphthalene diimides, and natural macrocycles like telomestatin, each exploiting π–π stacking or groove interactions to stabilize specific G4 topologies. Importantly, several compounds have advanced beyond preclinical testing: quarfloxin (CX-3543) entered Phase II trials for neuroendocrine tumours, and CX-5461, initially described as a polymerase I inhibitor, is now recognized to act through G4 stabilization and is under clinical evaluation in haematological cancers. Together, these examples illustrate that G4-targeting chemistry is moving from concept to clinic. Beyond oncology, opportunities are emerging in neurodegenerative disease, viral infection, and cardiovascular disorders, underscoring the therapeutic versatility of these structures. Continued progress in structure-guided design and drug-like optimization will be key to realizing the full medicinal potential of G-quadruplex ligands. This review captures recent advances in G-quadruplex chemistry, spanning structural insights, ligand discovery, and translational applications, while highlighting future directions for their integration into mainstream drug discovery.

KEYWORDS: CX-5461; DNA; G-quadruplexes; Medicinal Chemistry; Oncogene regulation; Telomere stabilization.

1. INTRODUCTION

Guanine-rich nucleic acid sequences can fold into G-quadruplexes (G4s), formed by stacks of guanine tetrads linked through Hoogsteen hydrogen bonds and stabilized by monovalent cations such as potassium.[1] These noncanonical structures are abundant in telomeric DNA and the promoter regions of oncogenes, including *c-MYC*, *BCL-2*, *VEGF*, and *KRAS*.[2,3,4] Stabilization of G4s by small molecules presents a promising therapeutic approach. Telomeric G4 stabilization can inhibit telomerase, while promoter G4 stabilization can repress oncogene transcription.[2,4] For example, the quinoxaline derivative QN1 selectively downregulates *MYC* by binding its promoter G4 in triple-negative breast cancer models; additional scaffolds such as imidazole/carbazole hybrids and benzofuran derivatives highlight the chemical diversity of selective G4 ligands.[5] Beyond cancer, G4s also contribute to neurodegeneration. Expanded GGGGCC repeats in *C9orf72* fold into DNA and RNA G4s that drive pathology in ALS/FTD.[6,7] Structural studies reveal repeat-length dependent polymorphism: shorter sequences form antiparallel G4s, while longer repeats fold into tandem units; notably, fangchinoline induces parallel topology and enhances G4

stability in both DNA and RNA contexts.[8] Furthermore, small-molecule G4 ligands have ameliorated *C9orf72*-linked toxicity in cellular and animal ALS/FTD models.[9] This review highlights recent progress in G4 biology, ligand discovery, and therapeutic applications, underscoring their expanding role as druggable targets in medicinal chemistry.

2. G-QUADRUPLEX STRUCTURES AND TOPOLOGIES

G-quadruplexes (G4s) exhibit remarkable structural polymorphism, adopting diverse topologies depending on sequence composition, loop length, strand orientation, and ionic environment. Early crystallographic studies revealed the parallel-stranded human telomeric G4, stabilized by stacked guanine tetrads and potassium ions.[10] Nuclear magnetic resonance (NMR) investigations further demonstrated that the same telomeric sequence can adopt hybrid or antiparallel conformations under physiological conditions.[11,12] G4s are broadly classified into parallel, antiparallel, and hybrid/mixed topologies. Parallel structures, characterized by all strands oriented in the same direction, are frequently stabilized by short loops and favoured in K^+-rich environments.[10] Antiparallel G4s, in contrast, arise when strands alternate in direction, forming diagonal or lateral loops; such conformations were originally observed in sodium-stabilized telomeric repeats.[12] Hybrid structures, containing a mixture of parallel and antiparallel strands, represent physiologically relevant intermediates for telomeric sequences.[11]

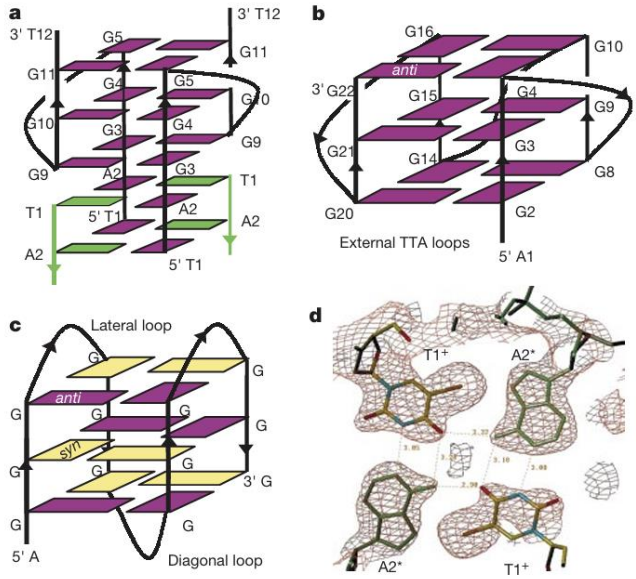

Figure 01: Schematic diagram of human telomeric quadruplex folding topologies.[10]

Beyond monomeric G4s, higher-order architectures can form through stacking interactions between multiple G4 units. Such multimeric G4s have been identified in extended telomeric repeats, where adjacent quadruplex units stack in tandem arrays.[13] Importantly, the ability of a given sequence to switch between conformations underlies the regulatory roles of G4s in transcription, replication, and genome stability. The structural adaptability of G4s also extends to RNA quadruplexes. Unlike DNA G4s, RNA G4s are predominantly parallel due to steric restrictions imposed by the ribose 2′-hydroxyl group.[14] RNA G4s have been detected in untranslated regions (UTRs) of mRNAs, where they modulate translation efficiency, splicing, and localization. Such findings emphasize that G4s in both DNA and RNA contexts are not static structures but dynamic entities with functional plasticity.

3. SMALL-MOLECULE LIGANDS TARGETING G-QUADRUPLEXES

Small molecules that stabilize G4s have been extensively studied as therapeutic leads. Binding occurs primarily via π–π stacking at the G-tetrad surface, groove interactions, or loop binding. One of the earliest scaffolds, quindoline derivatives, demonstrated potent stabilization of telomeric and promoter G4s, leading to suppression of *c-MYC* transcription.[5] Similarly, perylene diimides and naphthalene diimides show strong stacking interactions with telomeric G4s and inhibit telomerase activity.[15,16] Acridine-based ligands also display selectivity for G4s and effectively reduce cancer cell proliferation.[17] Natural products provide additional scaffolds. Telomestatin, a macrocyclic compound isolated from *Streptomyces anulatus*, is one of the most potent G4 stabilizers, inducing telomere dysfunction and apoptosis in cancer cells.[18] More recently, fangchinoline was identified as a G4 binder that shifts C9orf72 DNA and RNA G4s toward parallel topologies and improves their thermal stability, highlighting potential for neurodegenerative applications.[8] Crucially, ligand selectivity remains a challenge. Off-target interactions with duplex DNA can reduce specificity and increase toxicity.

4. THERAPEUTIC APPLICATIONS OF G-QUADRUPLEX TARGETING

4.1 Cancer

The overrepresentation of G4 motifs in oncogene promoters makes them attractive targets for anticancer therapy. Quindoline derivatives and acridine-based ligands have been shown to downregulate *MYC* and *BCL-2* expression.[5,17] Telomestatin induces telomere shortening and apoptosis, validating telomeric G4s as druggable structures.[18]

4.2 Neurodegenerative Disorders

Expanded GGGGCC repeats in *C9orf72* form G4s that contribute to ALS/FTD pathogenesis. Structural work has demonstrated repeat-length-dependent conformations, and small molecules, such as fangchinoline, can modulate these structures.[8] Importantly, the G4-binding ligand TMPyP4 reduces RNA foci and rescues neuronal toxicity in *C9orf72* ALS models.[9]

4.3 Infectious Diseases

Several viral genomes harbor G4 motifs that regulate replication and transcription. For example, G4s have been identified in HIV-1 long terminal repeats, and stabilization by small molecules suppresses viral replication.[19] Similarly, G4s in hepatitis C virus and herpesvirus genomes represent potential antiviral targets.

4.4 Cardiovascular Disorders

G4 motifs have been discovered in the promoters of genes involved in vascular homeostasis and proliferation. The *PDGFR-β* promoter contains a unique cluster of quadruplex structures, and ligand-induced stabilization downregulates gene expression, suppressing smooth muscle proliferation associated with atherosclerosis.[20] These findings indicate that G4s could be harnessed to regulate pathological vascular remodelling.

4.5 Parasitic Infections

G4-forming sequences have been reported in the genomes of protozoan parasites such as *Plasmodium falciparum*. Quadruplexes within subtelomeric regions modulate antigenic variation by influencing *var* gene switching. Stabilization of these motifs reduces parasite survival and virulence, suggesting novel antiparasitic strategies.[21]

4.6 Metabolic Diseases

High-throughput sequencing has identified G4 motifs in the regulatory regions of genes implicated in metabolic disorders, including diabetes and obesity. Although still at an exploratory stage, the potential to target these structures to modulate transcription of metabolic regulators presents an emerging therapeutic avenue.[22]

5. CLINICALLY EVALUATED AND EMERGING G4 TARGETING COMPOUNDS

Several G-quadruplex (G4) stabilizing ligands have progressed into advanced preclinical and clinical evaluation. Quarfloxin (CX-3543) was the first G4 ligand to enter human trials, reaching Phase II for neuroendocrine tumors, although development was discontinued due to pharmacokinetic limitations.[23]

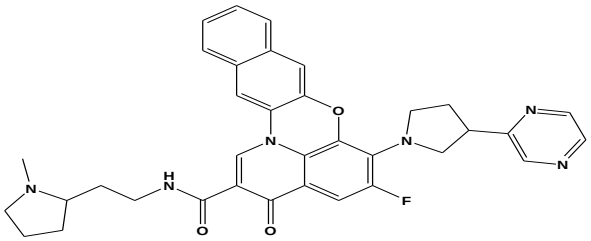

Figure 02: Structure of Quarfloxin.[23]

CX-5461, initially described as an RNA polymerase I inhibitor, was later shown to act via G4 stabilization and is currently undergoing clinical evaluation in haematological malignancies.[24]

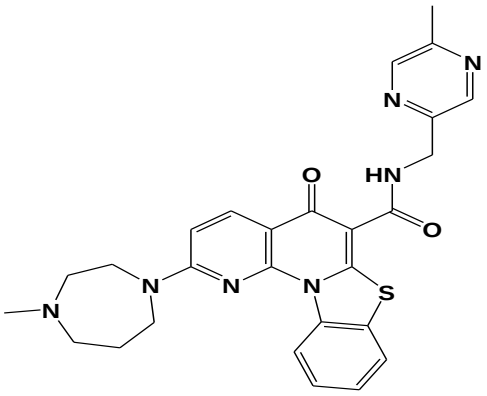

Figure 03: Structure of CX-5461.[24]

More recently, QN-302 (SOP1812), a naphthalene diimide derivative targeting hTERT promoter G4s, received orphan drug designation by the U.S. FDA for pancreatic cancer and is advancing toward Phase I trials.[25]

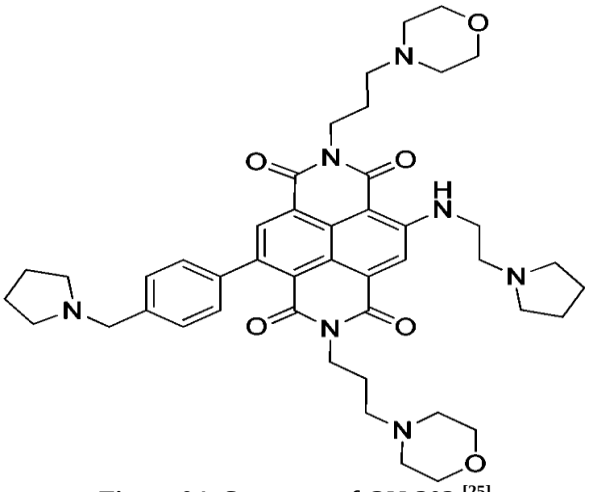

Figure 04: Structure of QN-302.[25]

In addition to these, several preclinical scaffolds remain highly influential. Telomestatin, a macrocyclic natural

product, exhibits potent telomeric G4 stabilization and induces cancer cell apoptosis, though it has not yet entered clinical studies.[26]

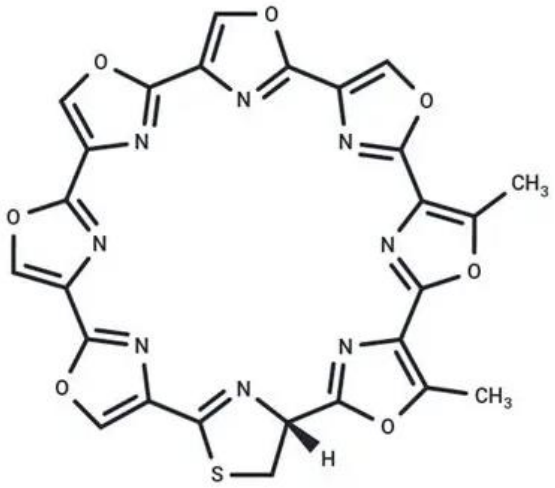

Figure 05: Structure of Telomestatin.[26]

Pyridostatin (PDS) selectively stabilizes telomeric and promoter G4s, demonstrating strong anticancer activity in vitro and in vivo models.[27]

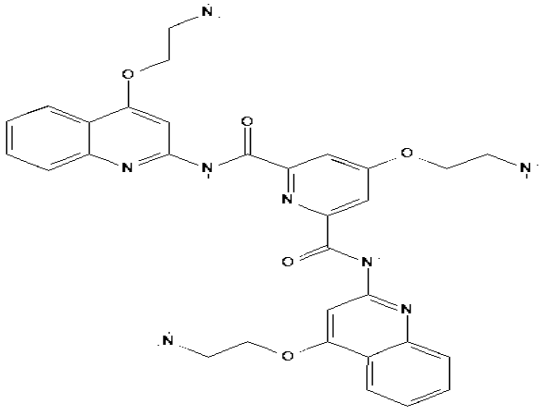

Figure 06: Structure of Pyridostatin.[27]

Similarly, derivatives such as BMSG-SH-3 have been optimized to promote G4 formation and trigger apoptosis in tumor cells.[28]

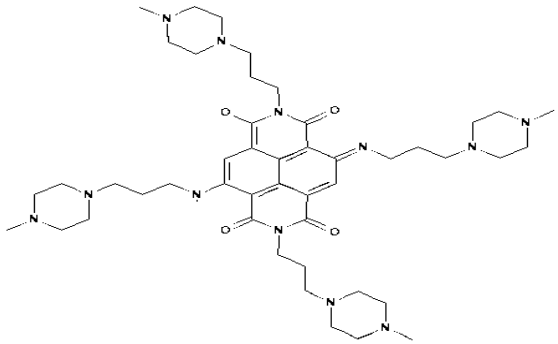

Figure 07: Structure of BMSG-SH-3.[28]

Interestingly, drug repurposing screens have identified FDA-approved compounds, including prochlorperazine, promethazine, and chlorpromazine, as G4 stabilizers with potential anticancer utility.[29] Collectively, these advances highlight how G4-targeting agents are transitioning from conceptual frameworks to tangible therapeutic candidates, with CX-5461 and QN-302 representing the most clinically advanced molecules to date.

6. CHALLENGES AND FUTURE DIRECTIONS

Despite significant progress, challenges remain for translating G4 ligands into clinical therapies. Selectivity for specific G4 topologies over duplex DNA remains limited. Pharmacokinetic issues, including poor solubility and stability, hinder drug-like optimization. Moreover, the polymorphic and context-dependent nature of G4 folding complicates target validation. Future opportunities lie in structure-guided ligand design, chemo proteomics for in-cell mapping of G4 interactions, and AI-driven drug discovery to predict ligand-G4 binding modes. Novel modalities such as oligonucleotide therapeutics and CRISPR-based editing could synergize with G4 targeting, expanding the therapeutic scope.

7. CONCLUSION

G-quadruplexes represent an expanding frontier in medicinal chemistry. Their enrichment in telomeric regions, oncogene promoters, and pathogenic repeat expansions provides unique therapeutic entry points in cancer, neurodegeneration, and infectious diseases. Advances in structural biology have revealed G4 polymorphism and dynamics, while small-molecule ligands have validated their draggability in preclinical models. Although challenges in selectivity and pharmacokinetics persist, integration of chemical biology, structural methods, and innovative drug design approaches holds promise for translating G4 targeting into clinical therapies.

8. ACKNOWLEDGMENT

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9. CONFLICT OF INTEREST

The authors declare no conflict of interest.

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