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Review

Targeting c-MYC G-Quadruplexes for Cancer Treatment with Small Molecules

Prasanth Thumpati [1,*,†], Sachchida Nand Rai [2,†], Chandrabhan Prajapati [2], Kakarla Ramakrishna [3] and Santosh Kumar Singh [2,*]

[1] Department of Chemistry, Virginia Commonwealth University, Richmond, VA 23284, USA
[2] Centre of Experimental Medicine & Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India; sn.rai@bhu.ac.in (S.N.R.); cbbhu.123@bhu.ac.in (C.P.)
[3] KL College of Pharmacy, Koneru Lakshmaiah Education Foundation, Vaddeswaram 522302, India; kakarlaramakrishna@kluniversity.in
* Correspondence: prasanth.thumpati@gmail.com (P.T.); santosh.singh01@bhu.ac.in (S.K.S.)
† These authors contributed equally to this work.

Abstract: Novel therapies are required due to the rising cancer burden. Conventional chemotherapeutics tend to be particularly toxic, but there is a promising alternative for oncogenes, such as c-MYC. Often overexpressed in many cancer types, the potential c-MYC oncogene seems essential to the development of cancer. Targeting c-MYC protein directly was limited, but these DNA structures composed of guanine-rich sequences suppress c-MYC transcription. This review discusses recent advances in developing small compounds that selectively bind to and stabilize c-MYC G-quadruplexes (G4). These molecules have also shown promise for the inhibition of c-MYC signaling and inhibition of tumor growth, suggesting that G-quadruplex targeting could be a promising therapeutic for cancer.

Keywords: G-quadruplex; c-MYC; cancer; small molecules; G4 stabilizers; click chemistry; target guided synthesis

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1. Introduction

The subgroup of diseases called cancer is produced by epigenetic perturbations in gene expression, leading to runaway cellular growth [1,2]. Therefore, it is crucial to seek alternative therapies with minimal side effects, given the explosive nature of cancer that cannot be best addressed by radiotherapy, chemotherapy, and other alternative medicines [3]. Within the expansive landscape of the chemical universe, small molecules define a particularly cordoned-off realm. In recent years, small molecules came forth as a promising category of molecules with unique properties that can interact with DNA secondary structures, modulating their stability and dynamics. Their size, shape, and spatial orientation allow them to selectively bind to specific DNA secondary structures, stabilizing or destabilizing them. The ability of small molecules to target DNA secondary structures arises from their unique chemical properties [4]. Because of their specific chemical properties, small molecules can recognize and bind to DNA secondary structures through electrostatic interactions, hydrogen bonding, and π-π stacking, as well as van der Waals forces (Figure 1). These complexes with biological macrocycles can shift the secondary structure formation and melting balance by altering thermodynamic and kinetic parameters. Moreover, most of these DNA secondary structures, such as the Z-DNA helix implicated in gene expression and the G-quadruplex formed at telomeres, are integral to several biological functions, including gene control, telomere maintenance, and the stability of the genome.

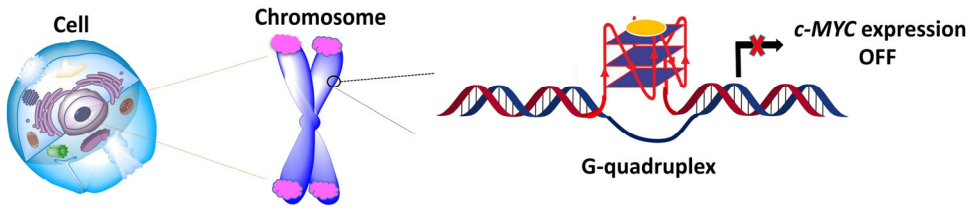

Figure 1. A schematic illustration of tiny molecules that stabilize the structure of the G-quadruplex.

Recently guanine-rich sequences of nucleic acids that can form the G-quadruplex secondary structures have become the hot targets for developing novel anticancer therapeutics [5]. Non-canonical structures of nucleic acid called G-quadruplexes have been formed by stacking guanine tetrads. They have gained interest as pharmacological targets, enabling novel therapeutic interventions for their essential roles in key cellular processes and disease conditions. Since interest in the molecular mechanism of the biological activity of G-quadruplexes grows, the development of novel approaches to modify their stability and binding through the use of macrocyclic molecules is highly desired. The unique three-dimensional structures and diverse chemical properties of macrocycles make them great candidates for regulating G-quadruplexes in a selective manner, which holds great promise for designing novel therapeutics for various disease conditions [6].

The human genome typically not only contains DNA sequences formed from G-quadruplex, which are known to promote cancer cell proliferation, but is also particularly abundant in protooncogene-promoter areas—such as c- MYC, c-KIT, BCL-2, VEGF, and RET—involved in cell proliferation and survival. Inhibiting the production of oncogenes and preventing the progression of cancer might be achieved by stabilizing G-quadruplexes [7].

The c-MYC gene encodes a protein that controls many essential cellular processes, including cell growth, division, and death. When c-MYC is overactive, it can lead to uncontrolled cell growth and cancer. Many genes are involved in regulating these basic cellular processes. The c-MYC G-quadruplex is a non-canonical DNA structure formed within the promoter region of the c-MYC oncogene [8]. This unique structure, characterized by stacked G-tetrads, is believed to play a crucial role in regulating c-MYC gene expression. The formation of this structure can act as a transcriptional "roadblock", potentially inhibiting the transcription of the c-MYC gene. Given the strong link between c-MYC overexpression and tumorigenesis, the c-MYC G-quadruplex has emerged as a significant target for cancer therapy. Key structural features of the c-MYC G-quadruplex include guanine-rich repeats, loop regions, and a parallel topology. The guanine-rich repeats form the core of the structure, while the loop regions, which can vary in length and sequence, influence the overall stability and conformation. The most common c-MYC G-quadruplex structure is considered to be parallel, where all strands run in the same direction [9]. The biological roles of c-MYC G-quadruplexes are multifaceted. Primarily, they are involved in transcriptional regulation. The formation of a G-quadruplex within the c-MYC promoter region can physically hinder the binding of RNA polymerase, thereby inhibiting transcription. Additionally, some studies suggest that G-quadruplexes can interact with chromatin-modifying proteins, potentially impacting the epigenetic landscape and gene expression regulation. Due to its role in cancer, stabilizing the c-MYC G-quadruplex through small molecule ligands is a promising therapeutic approach. By suppressing c-MYC expression, these ligands could potentially inhibit tumor growth. Understanding the structure and function of c-MYC G-quadruplexes offers valuable insights into cancer biology and opens new avenues for targeted cancer therapies [10].

Due to c-MYC encoding a transcriptional factor that controls the expression of multiple genes responsible for fundamental cellular functions, like progression of the

cell cycle, growth of the cell as well as differentiation, DNA replication, production of mRNA, and overall transcription, the deregulation of c-MYC is also implicated in numerous cancers [11–13]. c-MYC processes fundamental to cellular biology functions result in progressions of the cell cycle, growth of the cell and differentiation, apoptosis, metabolism, replication of DNA as well as the production of messenger RNA, and overall transcription [14,15]. G-quadruplex ligands will be briefly reviewed in this paper, with an emphasis on the progress made by macrocyclic ligands.

2. G-Quadruplex Topologies

Parallel G-quadruplexes consist of four strands arranged in a parallel orientation, with all guanine quartets facing the same direction. Antiparallel G-quadruplexes have strands that are arranged in an antiparallel orientation, with the guanine quartets alternating in direction. Hybrid G-quadruplexes contain both parallel and antiparallel strands, resulting in a more complex topology [16–18].

Ligand Selectivity and G-Quadruplex Topology

The topology of a G-quadruplex can significantly influence the binding selectivity of ligands. Different topologies may have distinct groove widths, loop lengths, and overall shapes, which can affect ligand binding affinity and specificity. Shape Complementarity. Ligands with shapes complementary to the G-quadruplex topology can bind more tightly and selectively. Electrostatic Interactions. Electrostatic interactions between the ligand and the G-quadruplex can also contribute to binding selectivity. Hydrogen Bonding. Hydrogen bonding between the ligand and the G-quadruplex can further enhance binding affinity and specificity. Impact on Drug Design. Understanding the impact of G-quadruplex topology on ligand binding is crucial for the rational design of potent and selective G-quadruplex ligands. By considering the specific topological features of the target G-quadruplex, researchers can design ligands with optimized shapes, charges, and hydrogen-bonding properties for G-quadruplex DNA-binding ligands [19].

Targeting secondary DNA structures represents a novel anticancer drug design and development approach. Diverse families of compounds that bind and/or stabilize G-quadruplex DNA over their duplex counterparts have been identified [20,21]. Most of these molecules contain extended aromatic structures with planar and electron-deficient ring systems for π-π stacking with a G-quartet platform instead of intercalating among the stacked base pairs of the DNA, as known for many duplex DNA-binding ligands (Figure 2) [22,23]. Additional side chains, appended to the molecular scaffolds, can participate in favorable electrostatic interactions among the loops and grooves of the quadruplex DNA, improving and enhancing double-stranded DNA-binding specificity and affinity [4,24]. Two criteria (i.e., electrostatics as well as π-stacking) have so far served as a guide for the logical design of G-quadruplex-interacting molecules (Figure 3) [25–29]. Several of these substances, such as anthraquinones, acridines, perylenes, and porphyrins, have polyaromatic heterocyclic ring structures [30–36].

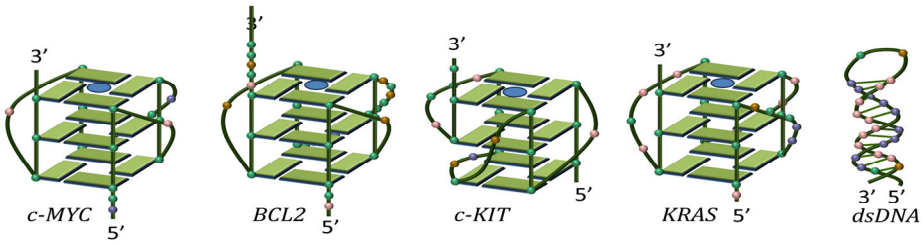

Figure 2. Representative topologies of G-quadruplex structures.

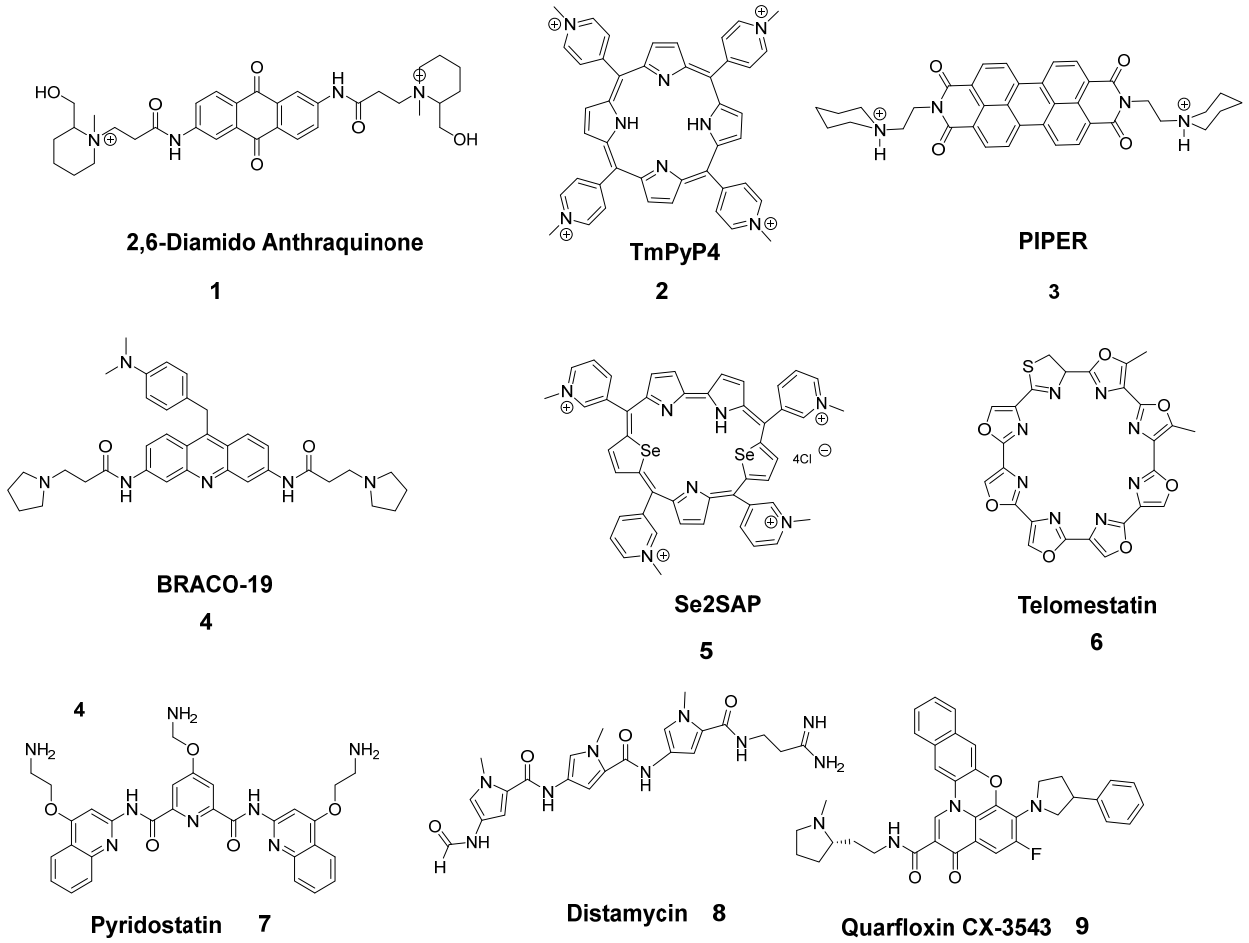

Figure 3. Structure of classical G-quadruplex-binding molecules.

The majority of small compounds that bind quadruplexes are designed with the following conditions: (i) extended (hetero) aromatic systems with planar end quartets and flanking bases facilitating π-stacking interactions; (ii) structures with a V or crescent shape with a quadruplex to maximum interactions; (iii) cationic side chains that interact electrostatically with the loop and groove regions' phosphate backbone; (iv) pharmaceutical action with increased bioavailability; and (v), thus, designing small molecules specifically targeting the G-quadruplex motif is still underway. Over the last few decades, significant progress has been made in the development of molecules that are small and able to bind to the nucleic acid structure, as well as the modification of the transcription process, making them an attractive target in drug discovery. Small molecules could be useful for the regulation of biological events as well as future therapeutic development by interfering with disease mechanisms. But, in the majority of instances, either the ligands' style of binding to the G-quadruplex is still unclear or they were made utilizing multistep syntheses with poor overall yields. We may learn more about the molecular mechanisms of G-quadruplex-mediated cancer treatment if a novel specialized G-quadruplex binder was designed and synthesized, revealing its mode of action at the level of transcription in cancer cells.

To date, numerous G-quadruplexes ligands are included in the G4LDB (G-quadruplex ligand database; http://www.g4ldb.org, access on 25 October 2024). TmPyP4 [37] **1**, PIPER [30] **2**, and 2,6-diamido anthraquinones **3** [37] are the first-known G-quadruplex-interacting ligands. Acridines such as BRACO-1939 **4** [34] and other tricyclic compounds were created as a result of the discovery of 2,6-diamido anthraquinone [37]. TmPyP4 has been used extensively as a standard reference for biological tests and is commercially accessible. In subsequent years, similar compounds, such as Se2SAP, were reported **5** [38].

Compound **6**, a natural product isolated from Streptomyces angulates, is a potent telomerase inhibitor [39]. As a macrocyclic chemical, telomestatin has, therefore, sparked interest in molecules that resemble half macrocycles, such as bisquinolinium compounds, like pyridostatin 7 [40]. Distamycin 8, a naturally occurring ds DNA binder, interacts with G-quadruplexes through a different groove binding mechanism [41]. However, because of its capacity to interact with G-quadruplexes in vivo, quarfloxin (CX-3543) 9, developed by Cylene Pharmaceuticals, advanced into phase II clinical trials (ClinicalTrials.gov identifier: NCT00780663), giving research on G-quadruplex-mediated gene regulation a fresh boost [42].

Currently, for G-quadruplex-targeting agents, the clinical translation for cancer treatment is a key focus, but there is still a long way to go. It is a big problem to successfully deliver these intricate molecules to target cells (especially tumor cells) [43]. They operate by cellular capture and nuclear localization once they are transferred. Moreover, they need to be metabolically stable to work as a treatment.

To obtain the most therapeutic benefits possible, we must make ligands that stick specifically to the target G-quadruplexes, with as little off-target activity and cellular toxicity as possible. There is also cancer cells' capacity for resistance, destabilizing G-quadruplex structures, or overexpressing drug efflux pumps, which can hamper the effectiveness of these agents. To navigate these obstacles, scientists are trying new tricks. Drug delivery, cell sorption, and stability can be enhanced with nanoparticle-based delivery systems. Targeted drug delivery can increase efficiency and mitigate off-target interactions [44]. With shrewd design, computational modeling, and relationship studies of structure and activity, one can come up with highly specific and active G-quadruplex ligands. Last but not least, combination therapies, where G-quadruplex ligands are used in combination with other drugs, could be more effective and overcome resistance [45]. With these problems and using these new techniques, the researchers can help by continuing to develop G-quadruplex-targeting drugs in clinical trials and ultimately offering new therapies to cancer patients.

A comparative analysis of G-quadruplex-targeting agents with conventional cancer therapies, such as chemotherapy, immunotherapy, and targeted therapy, provides valuable insights [46]. While traditional therapies have established clinical efficacy, they are often limited by severe side effects, drug resistance, and inconsistent response rates. G-quadruplex targeting, conversely, offers the potential for targeted therapy with reduced side effects and enhanced efficacy. It may also potentiate immunotherapy by modulating immune cell function or the tumor microenvironment. By integrating G-quadruplex-targeting agents into current treatment regimens, either as monotherapy or in combination with other therapies, we can potentially improve therapeutic outcomes and address the limitations of conventional approaches [47].

It is important to delve deeper into the cytotoxicity and selectivity of small molecule G-quadruplex ligands. A comprehensive analysis of these factors is essential for understanding their potential as effective cancer therapeutics [45]. Cytotoxicity: Cancer Cell Lines. We discuss the cytotoxic effects of these compounds on various cancer cell lines, including those with different levels of c-MYC overexpression. Mechanism of Cell Death. We explore the underlying mechanisms of cell death induced by these compounds, such as apoptosis, necrosis, or autophagy. Dose–Response Relationship. We analyze the dose–response relationship between the concentration of the compound and its cytotoxic effects. Selectivity: Normal Cells. We evaluate the cytotoxicity of these compounds on normal cells to assess their selectivity for cancer cells. Selectivity Indexes. We calculate the selectivity indexes of the compounds, which represent the ratio of the IC_{50} values for cancer cells to normal cells. Molecular Mechanisms of Selectivity. We investigate the molecular mechanisms underlying the selective cytotoxicity of G-quadruplex ligands, such as the

differential expression of G-quadruplex structures or DNA repair pathways. Non-Cytotoxic Compounds: Therapeutic Potential. We discuss the potential therapeutic applications of non-cytotoxic G-quadruplex ligands, such as their ability to modulate gene expression or inhibit cancer cell proliferation.

Combination Therapies. We explore the possibility of combining non-cytotoxic G-quadruplex ligands with other therapeutic agents to enhance their efficacy. Synergistic Effects. We investigate potential synergistic effects between G-quadruplex ligands and other anticancer drugs.

3. c-MYC G-Quadruplexes Stabilizing Small Molecules

The growing recognition of G-quadruplex structures as promising targets for cancer therapy has spurred the investigation of a wide array of small molecules as potential quadruplex stabilizers. Together, these moieties interact via the phosphate backbone, molecules of water that are inside the grooves, and G-quadruplexes tetrads to help stabilize G-quadruplexes [4]. Typically, G-quadruplex-stabilizing molecules have an aromatic core with side chains that are positively charged, which are either macrocyclic or polyaromatic. In context with this, we outline the design concepts that underlie the creation of c-MYC G-quadruplexes targeting ligands for the development of anticancer medications. [48]. This review provides an up-to-date account of the advancements in developing c-MYC G-quadruplex ligands, emphasizing their significance in therapeutic applications [49]. A summary of the very first compounds that bind G-quadruplexes is also provided. We anticipate that this comprehensive review will not only foster the design but also help in the development of effective small molecules, paving the way to exploit their therapeutic potential in cancer biology.

3.1. Macrocycles

Drawing inspiration from the seminal work on 5,10,15,20-tetrakis(Nmethyl-4-pyridyl) porphyrin (TmPyP4) **10**, macrocyclic ring systems, a type that uses a standard G-quadruplexes binder, have garnered a lot of interest as a potential platform for the production of G-quadruplex ligands [49,50]. The extended aromatic core of macrocyclic ligands effectively complements the planar surface area of G-tetrads within quadruplexes (Figure 4). At the same time, intercalation among double helix base pairs is prevented by their substantial steric barrier. TMPyP4 and its structural isomer TMPyP2 **11** exhibit distinct modes of DNA G-quadruplex stabilization. TMPyP4 interacts with the outer layer of guanine tetrads through external stacking, while TMPyP2 preferentially binds to the diagonal and middle TTA loops. This differential binding mode is attributed to the relative positions of the positively charged pyridinium side chains within the porphyrin macrocycle [51].

In vitro studies demonstrate TMPyP4's ability to suppress the activity of telomerase, downregulate hTERT expression and c-MYC, and impede cell proliferation in cancer. According to preclinical research, the first drug exhibits drug TMPyP2 and untreated controls in terms of tumor growth suppression and extended animal life expectancy. Nevertheless, TMPyP4 does not distinguish between various G-quadruplex topologies and shows very little preference for G-quadruplex structures against duplex DNA.

In subsequent years, similar to TMPy4 and TMPy2, Se2SAP **13** porphyrazines and metal-containing porphyrins were created as ligands that bind with G-quadruplexes. Haruo Seto demonstrated telomestatin **12**, and it has been demonstrated that a natural substance derived from Streptomyces anulates is a highly effective telomerase inhibitor. Cyclic naphthalene diimide (CNDI) **14** can bind to G-quadruplexes through its aromatic core, which interacts with the guanine bases in the quadruplex [52]. This interaction can stabilize the quadruplex structure and prevent it from unfolding.

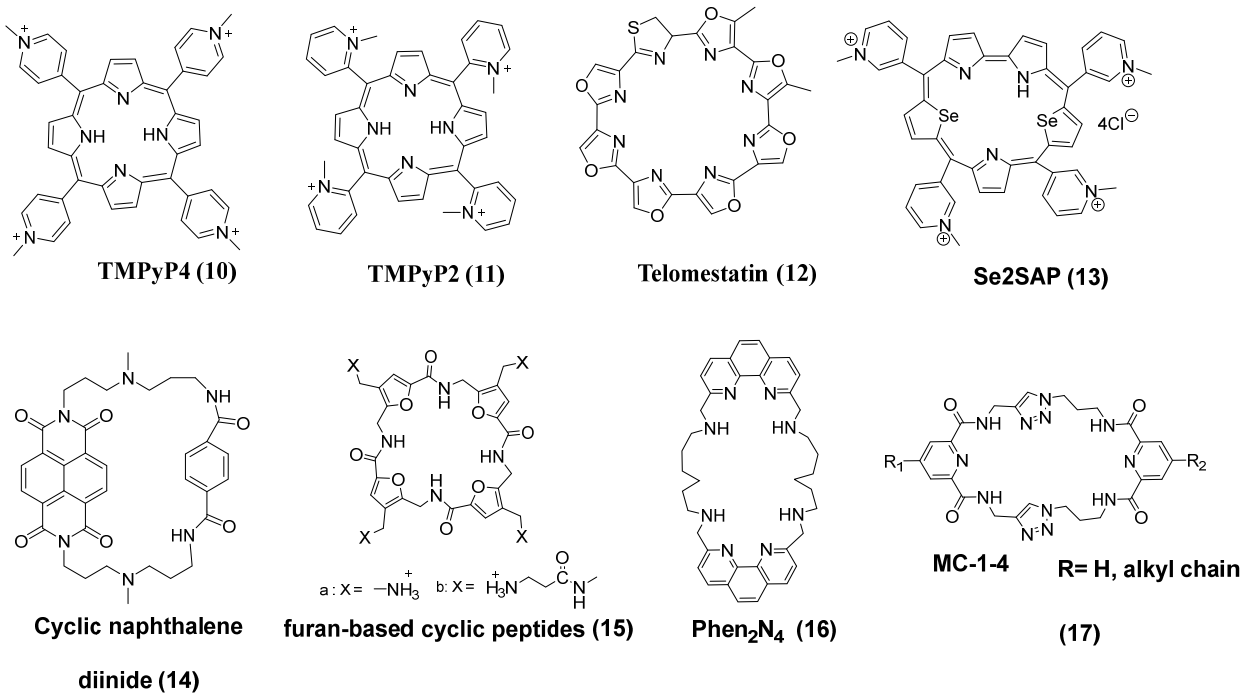

Figure 4. G-quadruplex binding macrocyclic ligands.

To enhance our understanding of macrocyclic G-quadruplex ligands, a detailed comparison of structural variations between compounds, like TMPyP4 and TMPyP2, is crucial. By examining specific structural features, such as the number and position of aromatic rings, the nature of substituents, and overall charge distribution, we can gain valuable insights into their binding preferences and biological activities [53]. For instance, the differential binding modes of TMPyP4 and TMPyP2, attributed to the relative positions of their pyridinium side chains, highlight the significant impact of structural variations on G-quadruplex recognition and stabilization. This knowledge can guide the rational design of novel G-quadruplex ligands with improved selectivity and efficacy.

Against this backdrop, a strong telomerase inhibitor, telomestatin, is a naturally occurring substance that was isolated from Streptomyces angulates. As a macrocyclic molecule, telomestatin has consequently garnered attention [53].

Furan-based cyclic homo-oligopeptides were developed by Chakraborty and Maiti in 2010 to target the c-MYC G-quadruplexes over ds DNA [54]. According to isothermal calorimetry studies (ITC), ligands, such as **15**, have a high affinity to the quadruplex over ds DNA. In addition, real-time PCR indicates that these ligands reduce c-MYC transcription in HeLa cells by around 90%. The luciferase test confirmed that the c-MYC oncogene is downregulated.

Carvalho et al. delved into a distinct class of macrocyclic compounds, macrocyclic phenanthroline **16**, possessing the capacity to stabilize c-MYC G-quadruplexes and telomeric G-quadruplexes in a FRET melting test with a ΔTm of 17.2 and 20.3 °C, respectively [55]. ΔTm, or a change in melting temperature, is a measure of the increase in thermal stability of a molecule, such as a G-quadruplex, when bound to a ligand. A higher DTm indicates stronger binding and greater stabilization. Furthermore, the authors employed a fluorescent intercalator displacement (FID) assay, revealing that macrocyclic compounds have strong binding affinity to c-MYC G-quadruplexes, as evidenced by their low EC50 values of 0.87 μM, and according to an in vitro investigation, the chemical can reduce Pif1 helicase's unwinding activity. While compound 3 demonstrated strong binding affinity to c-MYC G-quadruplexes, cytotoxicity assays revealed no significant impact on HeLa cancer cell

growth at low concentrations. In contrast, a separate study reported compound 3 to exhibit high cytotoxicity (IC_{50} < 0.01 μM) towards MCF-7 breast cancer cells, suggesting cell-type-dependent sensitivity to the compound. IC_{50} stands for an inhibitory concentration of 50%, which is a measure of the potency of a drug or compound. It represents the concentration required to inhibit a specific biological process or response by 50%. A lower IC_{50} value indicates a more potent compound.

In a recent study, Dash and coworkers used c-MYC and h-TELO G-quadruplexes as templates to develop a new class of peptidomimetic macrocycle **17** ligands by utilizing bifunctional building blocks of alkyne and azides [56,57].

3.2. Carbazole Derivatives/Four-Membered Heterocycles

Many synthetic and natural molecules that are biologically active use the carbazole ring system as a significant structural scaffold. These substances possess hepatoprotective, anti-protozoan, anti-inflammatory, antifungal, anticancer, antibacterial, and topoisomerase II inhibitory qualities [58,59].

Numerous 1,8-dipyrazolcarbazole (DPC) compounds have been found by Huang and colleagues as ligands of G-quadruplexes [60]. By adding the pyrazole scaffold, which is known to have anticancer properties, the ligand's overall pharmacological properties have improved. In HepG2, NCIH460, and HL60 cancer cell lines, compound **18** in the series has a significant antiproliferative effect; however, it is less cytotoxic to normal human umbilical vein endothelial cell lines. It also shows exon-specific regulation of the c-MYC gene in Burkitt's lymphoma cell lines (Ramos and CA46).

Carbazoles are an attractive option for quadruplex recognition owing to their planar aromatic ring structure developed bis-triazolyl carbazole derivative BTCf **19** using Cu(I)-catalyzed azide and alkyne cycloaddition (CuAAC) to target G-quadruplexes specifically [61]. Both in the presence and absence of K+ ions, the ligand exhibits a highly selective "turn-on" fluorescence response for the c-MYC quadruplex over ds DNA. In accordance with qRT-PCR and Western blot analysis, BTCf reduces c-MYC expression by 75% at the mRNA level and by 80% at the protein level. Carbazoles are an excellent choice for quadruplex recognition due to their planar aromatic ring system (Figure 5).

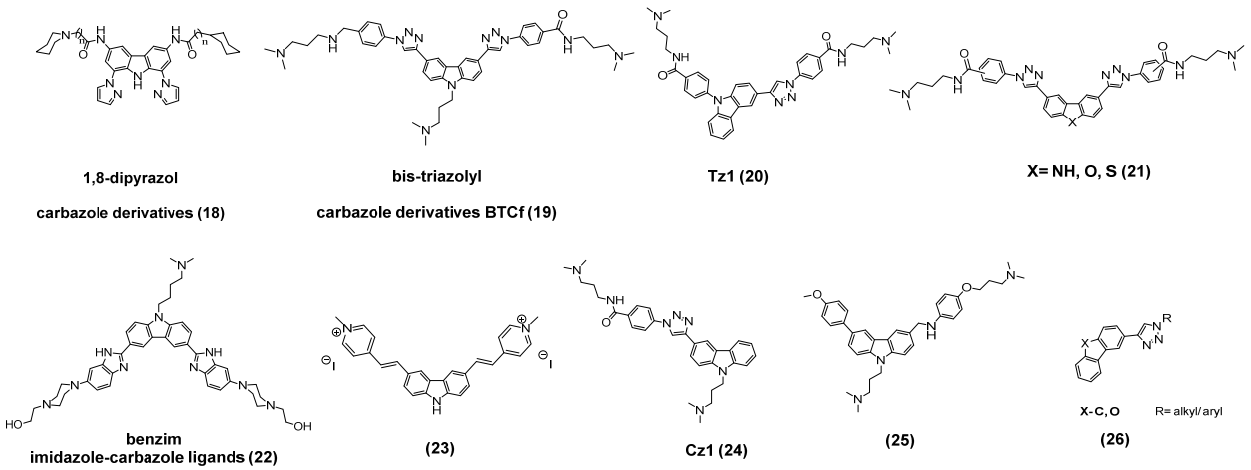

Figure 5. Carbazoles' structures demonstrate antiproliferative activity in cancer cells and a high capacity to stabilize c-MYC G-quadruplexes.

The planar aromatic ring structure of carbazoles makes them an excellent choice in quadruplex identification. Later in 2018, the same group used Cu(I) to catalyze cycloaddition to create derivatives of monotriazolyl carbazole **20** [62]. A derivative called Cz-1 demonstrated the highest rise in c-MYC G-quadruplex melting temperature permitted

by the FRET melting assay (Förster Resonance Energy Transfer), which is a spectroscopic technique used to measure distances between fluorophores. In a FRET melting assay, fluorescently labeled G-quadruplexes are monitored, as they denature with increasing temperature. The melting temperature (Tm) can be determined by measuring the decrease in the FRET signal, melting an assay (15.8 °C) in each of these tests. Cz1 inhibits c-MYC translation and transcription via binding to the G-quadruplex promoter based on scientific investigations, including Western blot, qRT-PCR, and CA46 exon-specific tests. In an alternate investigation, Dash and colleagues employed G-quadruplex-linked magnetic gold nanoparticles (NPs) to extract specific ligands from a set of tiny molecules. The same group also reported bis-triazolyl derivatives for selective recognition of the G-quadruplex by a competitive pulldown assay using gold-coated iron nanoparticle **21** [63,64].

Muniyappa and Bhattacharya (2018) showed that benzimidazole–carbazole ligand 22 binds to G-quadruplexes located in the promoter regions of human protooncogenes [65,66]. In lines of cancer cells, bis-benzimidazole decreases the expression of the c-MYC oncogene.

Yang revealed the 1:1 and 2:1 complexes of c-MYC G-quadruplex solution structures and the carbazole ligand BMVC **23** using NMR spectroscopy in 2019 [67]. BMVC is the first in vivo fluorescent probe designed especially to detect G-quadruplex structures in human telomeres. Additionally, research employing qRT-PCR and Western blot has shown that BMVC inhibits the c-MYC expression of MCF-7 breast cancer cells simultaneously at the mRNA and protein levels [68–70].

In another work, Dash et al. described a unique technique of target-guided synthesis (TGS) for G-quadruplex ligands [71,72]. They used DNA as a nanotemplate for in situ cycloaddition. The major lead compound Tz1 24, has a significant stabilization capability for the c-MYC G-quadruplexes, according to the FRET-based melting test. According to the fluorimetric titration data, the principal lead produced by TGS, Tz1, has a higher binding affinity for c-MYC G-quadruplexes than ds DNA. In HCT116 cells, the ligand dose dependently induces apoptosis and suppresses c-MYC expression.

In subsequent research, the selectivity of a range of carbazole derivatives for G-quadruplexes was designed and assessed via a FRET melting assay [73–75]. The most promising were compounds **25** and **26**, which displayed a lower melting point for double-stranded DNA and a comparatively high ΔTm value for G-quadruplex DNA (23.4 °C).

3.3. Ligands with Four or More Fused Aromatic Rings

Figure 6 provides a comprehensive overview of the structural diversity of c-MYC G-quadruplex ligands characterized by the presence of at least four interconnected aromatic rings. These compounds, derived from both natural and synthetic sources, exhibit a wide range of structural modifications, including variations in the number and arrangement of aromatic rings, the presence of functional groups, and the overall molecular shape. The intricate structural features of these ligands play a crucial role in their ability to bind and stabilize c-MYC G-quadruplexes, leading to the inhibition of c-MYC gene expression and ultimately contributing to their anticancer potential. By understanding the structure–activity relationships of these compounds, researchers can design and develop more potent and selective G-quadruplex ligands for cancer therapy. The aromatic tetracyclic molecules, such as indoloquinolines, have been the subject of much research and have demonstrated the ability to attach to a number of nucleic acid secondary structures [75]. Additionally, a number of investigations have demonstrated that their affinity and selectivity toward G-quadruplexes are subject to modification based on side chains.

Indoloquinolines are a class of compounds that have been shown to effectively bind and stabilize G-quadruplex structures, particularly those found in the c-MYC promoter region. Structural modifications to indoloquinolines can significantly impact their G-

quadruplex binding affinity and selectivity. For example, the addition of substituents to the indoloquinoline core can alter its electronic properties and steric hindrance, influencing its interaction with G-quadruplexes. Additionally, changes in the length and nature of side chains attached to the indoloquinoline scaffold can modulate its binding affinity and selectivity.

IC_{50} values, which represent the concentration of a compound required to inhibit cell growth by 50%, are often used to evaluate the potency of G-quadruplex ligands. Lower IC_{50} values indicate greater potency. By comparing the IC_{50} values of different indoloquinoline derivatives, it is possible to assess the impact of structural modifications on their therapeutic potential. Derivatives with lower IC_{50} values are generally considered to be more promising candidates for further development as anticancer agents.

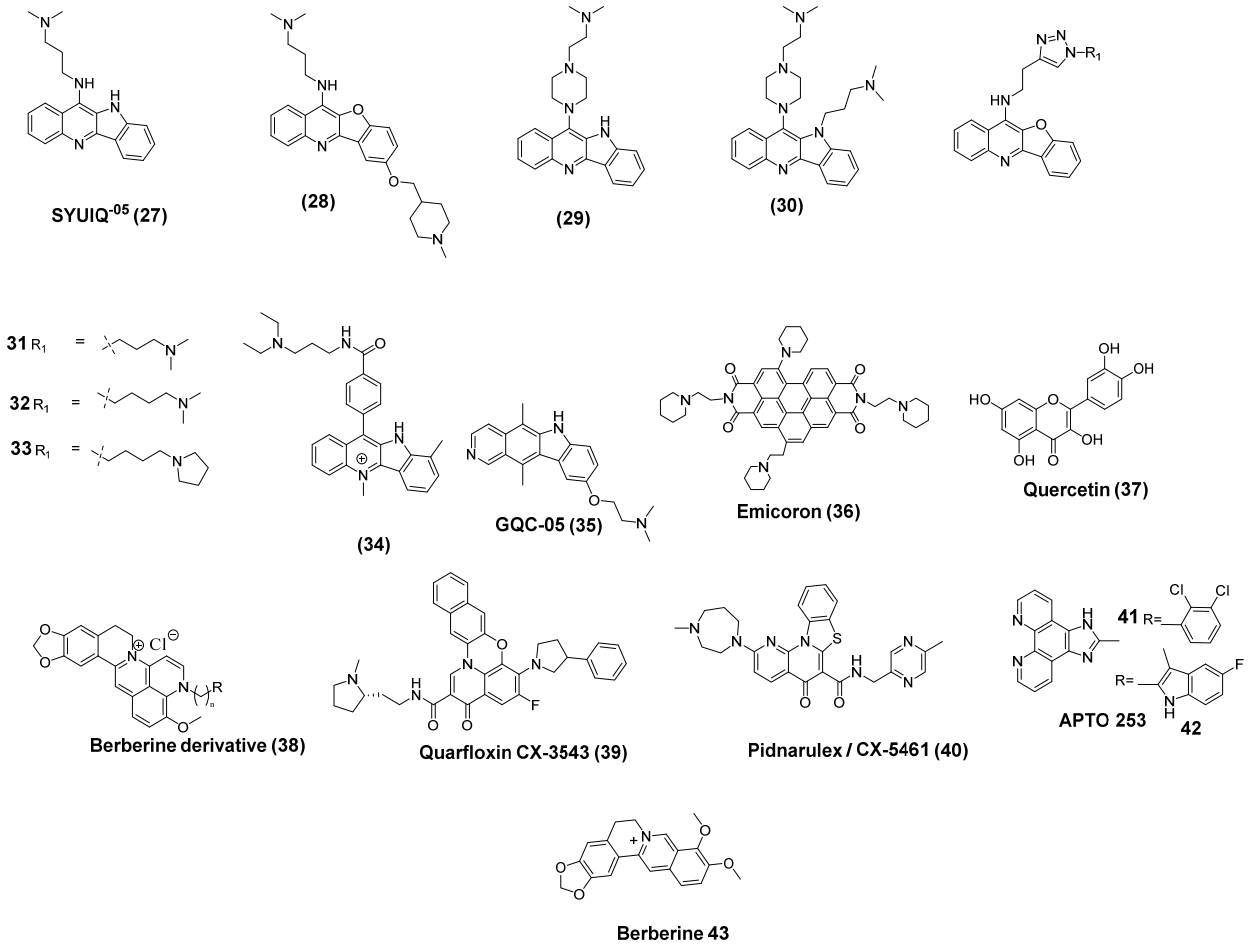

Figure 6. Structures of c-MYC G-quadruplex ligands that have four or more aromatic rings bonded together.

In order to increase lead **27** SYUIQ-5's anticancer activity, Liu et al. developed and investigated four disubstituted indoloquinoline series, consisting of paired substitutions in Positions 7 and 11, 8 and 11, and 9 and 11 [76–78]. Indoloquinoline 4 is a recognized binder of c-MYC G-quadruplexes that intercalates between the 30 outer tetrads of the G-quadruplexes and a pair of CG bases. Furthermore, strong electrostatic contacts are formed between the protonated quinoline nitrogen of the tetracyclic indoloquinoline, which is positively charged, and the carbonyl groups in guanine. Moreover, this substance demonstrated potent antiproliferative properties against multiple cell lines of cancer, demonstrating IC_{50} values between 0.24 and 4.8 μM. It has also been demonstrated to disrupt the connection and reduce c-MYC transcription in cancer cells.

The most promising compound was indoloquinoline, which had two tertiary amines within the side chains. The melting temperature of c-myc G-quadruplexes is 26.6 °C using FRET. Moreover, compound **28** showed inhibition towards c-myc transcription and IC_{50} = 4.7 μM in the (RAJI) cell lines of Burkitt's lymphoma. Hurley et al. studied indoloquinolines with an 11-piperazinyl substitution in another study. The more interesting compounds comprised **29** and **30**, which could stabilize the c-MYC G-quadruplexes and had ΔTm values of 7 and 17 °C in a CD melting experiment. Furthermore, when evaluated for cytotoxicity in RAJI cell lines, both compounds had good IC_{50} values (2.3 and 3.1 μM, respectively) [79,80]. A higher ΔTm indicates a greater stabilization of the G-quadruplex structure, which can be attributed to the formation of hydrogen bonds or electrostatic interactions between the piperazinyl substituents and the G-quadruplex. This increased stability can lead to the inhibition of c-MYC transcription, ultimately contributing to the observed cytotoxicity of these compounds. During an alternate study, it was demonstrated that three hybrids of the bioisoster of triazole and indoloquinoline (compounds **31**, **32**, and **33**) could likewise downregulate c-MYC transcription and expression. This resulted in an increase in the melting point of c-MYC G-quadruplexes from 13 to 22 °C. Additionally, they demonstrated strong cytotoxicity for several cell lines of cancer (IC_{50} = 0.02–5.53 μM) and decreased cytotoxicity against non-malignant human cells [81].

N5-methylated indoloquinoline PIQ-4m (**34**) exhibited a strong c-MYC G-quadruplex binder in the thiazole orange (TO) displacement experiment, with an EC_{50} of 1.7 μM [82,83]. In a FRET melting test, a well-recognized c-MYC G-quadruplex binder, GQC-05 (**35**), is an indoloisoquinoline derivative that results in a ΔTm of 21 °C [84–86].

EMICORON (**36**), another polyaromatic substance, is a derivative of perylene diimide that binds to G-quadruplexes via π-π interactions with the terminal G-tetrads and promotes telomere uncapping [87,88]. Additionally, because of their positive charges, its side chains can attach to the G-quadruplex grooves. Research has shown that this substance can bind to the G-quadruplex promoters of c-MYC and BCL-2, which are oncogenes (ΔTm = 16.4 and 15.4 °C, respectively, in a FRET melting assay), as well as inhibit these oncogenes' expressions in cancerous cells.

Quercetin **37** has the strongest affinity for the c-MYC G-quadruplexes. According to NMR studies, quercetin stabilizes Pu24T G-quadruplexes by stacking at its 5′ and 3′ G-tetrads via π−π stacking interactions with no altering the G-quadruplex structure [89]. Moreover, quercetin's antiproliferative qualities in HeLa cells and its capacity to suppress c-MYC gene expression by stabilizing the c-MYC promoter G-quadruplexes were shown in in vitro investigations.

Another study identified **38** quinolino-benzo-[5,6]-dihydroisoquindolium, a series of chemicals derived from berberine, which is an alkaloid, that are molecules interacting with G-quadruplexes. The addition of an amino group and pyridine ring to berberine has improved its binding affinity as well as selectivity towards the c-MYC G-quadruplexes, even though berberine derivatives were previously demonstrated to be selective G-quadruplex binders over ds DNA [90,91]. This substance can cause dose-dependent apoptosis in cancer cells and raise the melting point of c-MYC G-quadruplexes by over 6 °C in CD research.

Fluoroquinolones are a different group of compounds that have the ability to target DNA. Two fluoroquinolone derivatives, quarfloxin (CX-3543) **39** and pidnarulex (CX-5461) **40,** have been created to selectively target G-quadruplex nucleic acids. For distinct G-quadruplexes, they result in ΔTm > 15 °C in a FRET melting experiment. To cure cancer, they began conducting clinical studies on people. Compound **39** advanced to a phase II clinical trial (NCT00780663) for treating neuroendocrine cancer, but the trial was terminated because of subpar clinical results [42,92,93].

Phenanthroimidazole derivatives have been demonstrated to have anticancer properties via a variety of methods, including binding to c-MYC G-quadruplexes. Six compounds with various substitutions in the benzene ring connected to the imidazole were examined by Wu et al. [94]. Chlorine-containing compounds showed the most potential derivatives. According to a FRET melting experiment, compound **41** has the ability to stabilize the G-quadruplexes within the promoter area of c-MYC and suppress its production (ΔTm = 4.4 °C). Additionally, this ligand demonstrated moderate toxicity towards non-cancer human keratinocyte HaCaT cells (IC_{50} = 16.8 M) and strong antiproliferative action against cancer cells (IC_{50} values of 1 μM). Another phenanthroimidazole derivative, APTO-253 (**41**), is entering phase I clinical trials for individuals with myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) (NCT02267863) [95]. According to the earliest published results, APTO-253 appears to be well tolerated at dosages as high as 150 mg/m^2. [96]. By triggering Krüppel-like factor (KLF) tumor suppressors, compound **42** has been shown to have antiproliferative action against human colon leukemia, non-small-cell lungs, and renal as well as prostate cancer cell lines. [97]. Additionally, compound **42** can cause cytotoxicity in several lymphoma cell lines and AML, exhibiting IC_{50} values ranging from 57 nM to 1.75 μM. Additionally, it lowers c-MYC expression in both proteins and mRNA [98], elaborating on the role of chlorine substitution in enhancing G-quadruplex binding affinity and selectivity. Additionally, it explores the possibility of additional mechanisms of action, such as the inhibition of other DNA or RNA targets or the modulation of cellular signaling pathways. Regarding therapeutic potential, it highlights the clinical significance of APTO-253, particularly its dual targeting of c-MYC G-quadruplexes and KLF tumor suppressors. There are implications for the observed cytotoxicity and antiproliferative effects of compound **42** in various cancer cell lines. Finally, the potential of these compounds as single agents or in combination therapies with other anticancer drugs should be considered.

Both conformers' PDB structures (7N7D and 7N7E) demonstrate that berberine (**43**) belongs to a naturally occurring substance that binds to G-quadruplexes [99]. According to CD research, this compound elevates the melting point of c-MYC G-quadruplexes by over 6 °C and has the ability to dose dependently cause apoptosis in cancer cells. Furthermore, after 14 days of therapy, compound **43** significantly reduced the growth of the tumor in mice implanted with cancer cells of the colon (CT26) in an in vivo study [100,101].

3.4. Ligands with Three Fused Aromatic Rings

Tricyclic compounds, like phenoxazine **44**, are components of well-known antibiotic and antitumor drugs (Figure 7). In the Ramos cell line compared to the CA46 cell line, where the NHEIII1 G-quadruplex-forming region in the promoter no longer regulates c-MYC transcription, this compound showed antiproliferative action and a larger inhibitory impact (by 25–40%) on c-MYC transcription. [102,103]. Additionally, compared to BCl2, VEGF, and HIF-1a promoters, **44** also showed increased c-MYC promoter amplification inhibitory efficacy using Taq polymerase [104]. In another study, two additional phenoxazines with distinct side chains were examined with an emphasis on lead **45**. In contrast to the lead compound (ΔTm = 18 °C), however, in a FRET melting test, these novel compounds did not result in larger fluctuations in the G-quadruplex Tm (ΔTm = 0 and 9 °C, respectively) [105].

Pelliccia et al. found that imidazole purine-type compounds may attach to c-myc G-quadruplexes. Compound **46** shows the Tm of the G-quadruplexes in a FRET melting assay (ΔTm = 12.8 °C for c-myc and 6.7 °C for BCl2, which downregulated the expression by 66 and 67%, respectively, in Jurkat cells at 25 μM [106]).

Based on the structure of **47**, four compounds were synthesized, and among all compounds, **48** showed a stronger affinity towards the c-myc G-quadruplex and showed

Tm 20 °C in comparison with other G-quadruplexes. In addition, it showed low cytotoxicity (IC_{50} = 2.1–4.2 μM) against cancer cells SiHa, HeLa, Huh7, and A375 and higher cytotoxicity (IC_{50} = 15.6–15.9 μM) against normal BJ fibroblasts and mesangial cell lines [107].

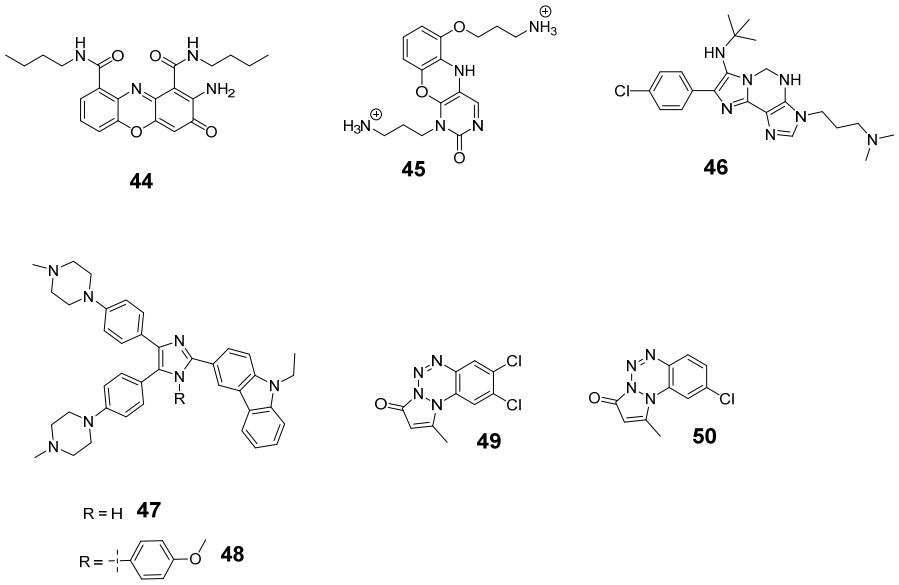

Figure 7. c-MYC G-quadruplex ligand structures, including three fused aromatic rings.

A study of the interaction between pyrazolo [1,2-a]benzo[1-4]tetrazin-3-one derivatives (PBTs) and the regulation of this oncogene transcription was conducted on a different class of compounds. The investigation shows that the substitution of chlorine atoms in C8 and C9 (**49**) and just in C8 (**50**) increases the G-quadruplex-stabilizing action of these derivatives (ΔTm = 4.0 and 1.9 °C, respectively).

Moreover, these atoms of chlorine are expected to interact with G-quadruplex adenine 3, according to molecular docking studies [108]. These substances showed potent antiproliferative action towards a variety of carcinoma cell lines in an MTT experiment; their IC_{50} values ranged from 17.7 to 20.5 μM for compound **49** and from 13.5 to 13.9 μM for compound 26 [109].

3.5. Ligands with Two Fused Aromatic Rings

Quinazolines are heterocyclic molecules with an N atom frequently employed as a therapeutic agent [110,111]. Sysu12d **51** is a derivative of quinazoline that is 2,4-disubstituted and possesses the capacity to stabilize the Pu27 sequence's c-MYC G-quadruplexes [112]. Additionally, this mixture showed potent antiproliferative action against a variety of cancer cell lines, comprising IC_{50} values ranging from 3.1 to 6.3 μM. Using human liver cancer cell lines implanted in a naked mouse, Li et al. [113] demonstrated in another study that compound **52** could stabilize c-MYC G4 in a FRET melting experiment (ΔTm = 23.7 °C) and decrease tumor growth by 49% (10 mg/kg) and 58% (20 mg/kg) in an in vivo assay. Another quinazoline derivative, Sysu-ID-01 (**53**), also demonstrated binding to NM23-H2, downregulating c-MYC transcription and translation. But, compared to NM23-H2, its attachment with c-MYC G-quadruplexes is weaker (ΔTm = 9 °C) [114]. The two most promising compounds in this study, **54**, **55**, and **56**, inhibited the transcription of this gene while additionally displaying high as well as specific binding and an effect of stabilizing on c-MYC G-quadruplexes (ΔTm = 12.1 and 12.9 °C, respectively) [115]. Another isaindigotone derivative, compound **57**, discovered in a different work by Wang et al., can stop c-MYC transcription by cutting off the link among NM23-H2 along with c-MYC G-quadruplexes. And, it exhibits strong binding with the protein, but the binding is weak towards c-MYC

G-quadruplexes (ΔTm = 0.54 °C) [116]. Additionally, compound **57** has the ability to dose dependently elicit SiHa cell growth detention, apoptosis, and cell cycle arrest (Figure 8).

Naphthalene derivatives are compounds like quinoxaline or benzopyrazine. Their primary biological actions include antiviral, antibacterial, and antiparasitic properties; however, they also exhibit anticancer activity through various mechanisms [117,118]. According to Hu et al., a new quinoxaline that targets the G-quadruplexes within a specific gene promoter can inhibit c-MYC transcription [119]. Recently, ten distinct quinoxalines with various side chains along with the groups that donate electrons were synthesized for this investigation. They concluded that amino side chains were required for the compounds to bind to the G-quadruplexes and that more positively charged amino substituents improved the interactions with c-MYC G-quadruplexes. This was determined by studies of structure–activity relationships. The most effective compound was QN-1 (**58**). In contrast to other G-quadruplexes with distinct topologies, it was selective for c-MYC G-quadruplexes (KD = 1.3 μM) and firmly attached to it. Additionally, it has a more "drug-like" structure than the remaining G-quadruplex ligands. An experiment measuring cell proliferation using various cancer cell lines also demonstrated low IC_{50} values (0.7–0.9 μM) and higher values when compared to normal fibroblast cells (IC_{50} = 4.6 μM). Compound **58** also demonstrated concentration-dependent inhibition of c-MYC transcription, albeit with less potent effects on other oncogenes [119].

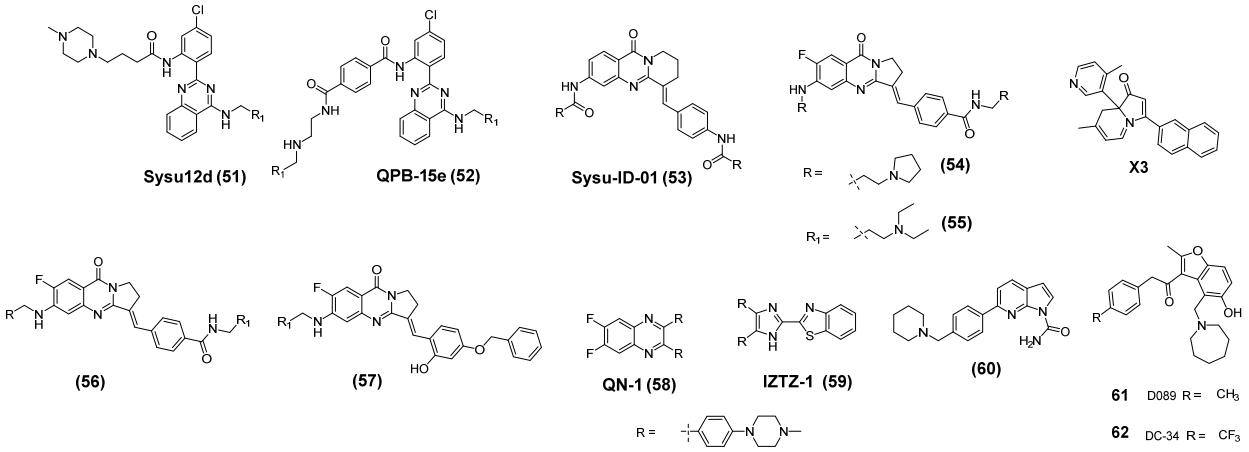

Figure 8. The structure of two joined aromatic c-MYC G-quadruplex ligands.

A promising G-quadruplex-binding motif is imidazole–benzothiazole. In light of this, IZTZ-1 (**59**) was created and investigated. In vitro, it demonstrated robust binding with c-MYC G-quadruplexes (ΔTm = 15 °C) along with growth-inhibiting properties for melanoma cells (IC_{50} = 2.2 μM). Additionally, **59** was shown to induce apoptosis and downregulate c-MYC transcription and expression using a flow cytometry assay and a dual luciferase reporter assay [120].

Derivative **60** of 7-azaindole-1-carboxamide was investigated to act like a dual G-quadruplex binder/PARP inhibitor. The investigation revealed that the substance forms a 2:1 ligand/G-quadruplex complex with Ka = 106.1 Mπ1 by stacking on the G-quadruplex tetrad through π-π interactions. Additionally, this compound exhibits 19.4 μM IC_{50} antiproliferative activity in HCC1937 cell lines [121].

To identify compound D089 (**61**), a targeted library comprising "drug-like" small molecules was employed throughout this study, a benzofuran derivative that binds c-MYC G-quadruplex sequences [122]. Moreover, this compound outperformed the well-researched G-quadruplex binder BRACO-19 (IC_{50} = 15.3 μM) regarding antiproliferative activity against myeloma cells (IC_{50} = 5.8 μM) [123]. By providing to the G-quadruplexes

in the promoter of c-MYC, DC-34 (**62**), a benzofuran derivative extremely similar to **61**, has been found in another study to inhibit c-MYC transcription selectively. It showed that a 2:1 complex with a ΔTm of 7.5 °C forms, covering the ligand with rearranged segments and stacking above two guanines at each end of the G-tetrad plane. Compared to analog **61**, this compound exhibits superior antiproliferative activity towards the cells of myeloma (IC_{50} of 3.4 μM) [124].

3.6. Flexible G-Quadruplex Ligands

Thiazoles are a group of anticancer chemicals [125,126]. Three thiazole polyamides, **63**, **64**, and **65**, were synthesized by Dutta et al. [125]. The selectivity of the latter compound **65** was demonstrated by the fact that it bound to c-MYC G-quadruplexes more strongly than duplex DNA and other gene promoter G-quadruplexes. In comparison to compounds **63** and **64**, compound **65** exhibited the greatest antiproliferative activity against cancer cells (IC_{50} values of 3.8 μM and 17.6 μM, respectively). However, these two compounds demonstrated negligible cytotoxicity aimed at non-malignant cells (IC_{50} > 50 M) (Figure 9).

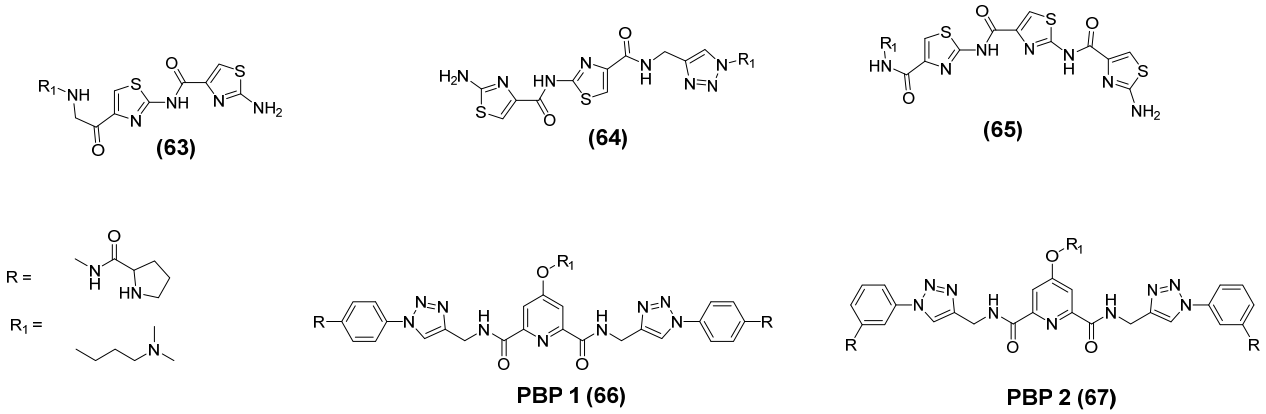

Figure 9. The structure of flexible c-MYC G-quadruplex ligands.

Two peptidomimetic derivatives that could attach to and stabilize G-quadruplex structures were created by Debnath et al. [127]. PBP1 (**66**) and PBP2 (**67**) were determined using a FRET melting experiment to show strong selectivity for c-MYC G-quadruplexes over duplex DNA. Furthermore, **66** and **67** demonstrated good affinities to different G-quadruplexes, with EC_{50} values for c-MYC G-quadruplexes of 8.5 μM and 1.3 μM, respectively, according to a thiazole orange displacement test. The IC_{50} values of compound **66** were greater than those of compound **67** (17.9 and 3.3 μM, respectively). Furthermore, these scientists also looked at the binding tendency of BCL2 G-quadruplexes and c-MYC G-quadruplexes, and they came to the conclusion that **67** is selective for c-MYC G-quadruplexes, whereas 66 shows no clear preference. Both compounds exhibited substantial cytotoxic action in MCF-7 breast cancer cells (IC_{50} = 3.8 and 7.1 M), moderate cytotoxicity with other cancer cell lines, and negligible cytotoxicity for normal cells [128].

3.7. Metal Ligand Complex

The beginning of this century saw the publication of the first G-quadruplex binders based on square planar metal complexes. Since then, hundreds of novel metal complex analogs have been found to bind to G-quadruplexes. G-quadruplexes are preferred over duplex DNA by Ni II, Cu II, Co III, and Pt II square planar complexes [129,130] (Figure 10).

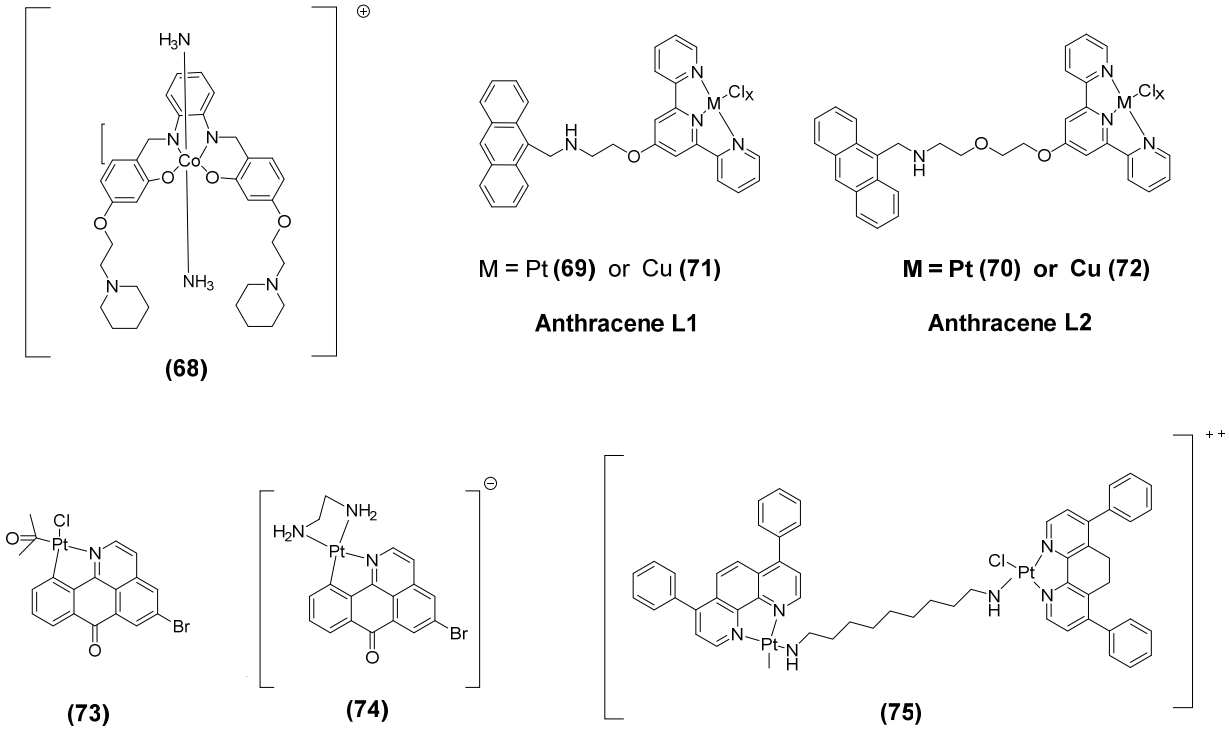

Figure 10. A metal complex structure that can bind to and stabilize c-MYC G-quadruplexes.

Compared to other complexes, Co III compounds containing NH3 as the coordinated ligand (**68**) comprised a greater affinity for c-MYC G-quadruplexes. The proposed binding mechanism states that the NH3 groups establish hydrogen bond interactions with the oxygen atoms in guanine and that the salphen ligand displays π-π stacking interactions with the G-tetrad. [131].

The anthracene-containing terpyridine ligand complexes of Cu II and Pt II (PtL1,2—**69** and **70**; and CuL1,2—**68** and **72**) are selective for G-quadruplexes rather than duplex DNA. In one investigation, the Pt complexes showed better G-quadruplex stabilization values in a FRET melting test when compared to the other complexes or the ligands without complexation with metals. Moreover, compared to Cu complexes, Pt complexes showed a greater affinity for c-MYC G-quadruplexes. The ΔTm values in Figure 11a–e further supported the authors' conclusion that the compounds with larger linkers (L2—**70** and **72**) had a greater affinity to bind to G-quadruplexes than the smaller ones (**69** and **71**) [132].

The possibility of additional platinum complexes with 5-bromooxoisoaporphine as ligands, [Pt(L)(DMSO)Cl] (**73**) and [Pt(L)(pn)]Cl (**74**)], to inhibit c-MYC expression by binding to its promoter G-quadruplexes was investigated. In an FID assay, complex 75 suppressed 99.9% of the levels of c-MYC protein and performed better than complex 73 in terms of selectivity towards c-MYC. Their cytotoxicity was evaluated using an MTT test, and it was revealed that the IC_{50} values for different carcinoma cell lines ranged from 5.1 to 31.1 μM. They showed incredibly low cytotoxicity for non-malignant cells [133].

Furthermore, in a FRET melting test, it was shown that dinuclear platinum complexes, such as 75, with a ΔTm of 8.5 °C, could stabilize G-quadruplex structures as well as bind to c-MYC G-quadruplexes more preferentially than duplex DNA. Through p-stacking and cross-linking with purines in G-quadruplexes via their alkyl chains, these complexes interacted with G-tetrads [134]. Recently, Dash and coworkers developed different strategies for stabilizing the G-quadruplexes for cancer treatment using copper-catalyzed click chemistry, and novel technologies are coming for cancer treatment [135–140].

4. Discussion

The escalating global burden of cancer necessitates the development of innovative therapeutic strategies. Because conventional chemotherapeutic drugs lack selectivity, they frequently show severe side effects along with toxicity. A critical factor in cancer cell proliferation is the dysregulation of genes, such as oncogenes, like c-MYC, which encode proteins involved in regulating cell growth and division [124]. While direct targeting of the c-MYC protein has proven hard due to the absence of a well-defined binding site, an alternate method has emerged: targeting the G-quadruplex structures produced inside the c-MYC promoter region [23].

Guanine-rich sequences give rise to non-canonical DNA structures called G-quadruplexes. These structures have been linked to a number of biological functions, such as telomere preservation, DNA replication, and gene transcription [23]. The nuclease hypersensitivity element III1 (NHE III1) is a guanine-rich region found in the c-MYC promoter that may create an intramolecular parallel G-quadruplex structure. Targeting this structure may be a viable cancer treatment approach since it has been demonstrated that the development of this G-quadruplex downregulates c-MYC transcription [141].

The number of tiny compounds that can bind with and stabilize c-MYC G-quadruplexes has increased in the past few years. These compounds have different chemical structures and differ in how selective they are for c-MYC G-quadruplexes compared to other G-quadruplex sequences [80]. These substances have been shown in several studies to suppress c-MYC expression both in vitro and in vivo, which lowers tumor development as well as cancer cell proliferation.

G-quadruplex stabilization significantly impacts c-MYC signaling and tumor progression, primarily by inhibiting the transcription of the c-MYC gene. The c-MYC promoter region contains multiple G-rich sequences prone to forming G-quadruplex structures. When these structures form, they can physically obstruct the binding site for RNA polymerase II, hindering the initiation of transcription. This reduction in c-MYC mRNA production leads to decreased c-MYC protein levels, which in turn impacts the expression of genes involved in cell cycle progression, DNA replication, metabolism, and angiogenesis. Ultimately, this can inhibit tumor cell growth and proliferation. Several factors influence G-quadruplex stabilization and c-MYC signaling, including G-quadruplex binding proteins, cellular environment, and small molecule G-quadruplex stabilizers. Targeting G-quadruplex formation in the c-MYC promoter is a promising strategy for cancer treatment, as it can selectively inhibit the expression of a key oncogene involved in tumor development [142]. Additionally, identifying G-quadruplex-forming sequences in cancer-related genes could serve as valuable biomarkers for cancer diagnosis and prognosis.

A significant barrier in creating drugs that target the c-MYC G-quadruplex is obtaining specificity [143]. In the human genome, G-quadruplexes are widely distributed, and several small molecules have the ability to bind to several G-quadruplex sequences. The therapeutic potential of these compounds may be limited by their lack of specificity, which may result in off-target effects. Researchers have looked at a number of strategies to deal with this problem, such as creating compounds that are more selective for c-MYC G-quadruplexes and employing tailored delivery methods [144].

Another important consideration is the efficacy of c-MYC G-quadruplex-targeting agents. While many compounds have shown promising in vitro activity, translating this activity into clinical efficacy can be challenging [106]. A number of factors, including pharmacokinetics, pharmacodynamics, and drug transport, are important in deciding how effective these drugs are. Efforts are underway to optimize the properties of c-MYC G-quadruplex ligands to improve their efficacy and bioavailability [144].

To comprehensively assess the therapeutic potential and limitations of G-quadruplex-targeting agents, a detailed analysis of their preclinical and clinical progress is essential. Preclinical studies in animal models have demonstrated the ability of these agents to inhibit tumor growth and metastasis, while also providing insights into their toxicity profiles. In clinical trials, G-quadruplex ligands have shown promising safety and tolerability profiles, with early-phase studies identifying potential dose-limiting toxicities [43]. Ongoing phase II clinical trials are evaluating their efficacy in specific tumor types and investigating their pharmacokinetic and pharmacodynamic properties in humans. However, challenges, such as drug delivery and the emergence of resistance mechanisms, remain significant obstacles. To address these challenges, researchers are exploring strategies to improve drug delivery and combination therapies with other anticancer agents to enhance efficacy and overcome resistance [45]. By addressing these challenges and leveraging innovative approaches, researchers aim to advance the clinical development of G-quadruplex-targeting agents and ultimately provide novel therapeutic options for cancer patients [145].

The field of G-quadruplex research has made significant strides in recent years, revealing the intricate role of these non-canonical DNA and RNA structures in various cellular processes. While the potential of targeting G-quadruplexes for therapeutic applications, particularly in cancer, is promising, the development of highly specific G-quadruplex ligands remains a significant challenge. Many compounds have been explored, but their lack of specificity for particular G-quadruplexes can lead to off-target effects and limit their therapeutic efficacy. Innovative approaches have emerged to address this limitation. One promising strategy involves the use of protein-based techniques, such as those described in [146,147]. These methods allow for the targeted manipulation of specific G-quadruplexes, offering greater precision and control. By fusing G4-stabilizing proteins with CRISPR-Cas9 or other targeting domains, researchers can selectively induce G4 formation at desired genomic loci. This approach has been successfully applied to study the functional consequences of G4 formation in various cellular processes, including cell proliferation, differentiation, and senescence. Additionally, the development of G-quadruplex-specific fluorescent probes has enabled the real-time visualization of G4 formation in living cells. By combining G4-binding aptamers with fluorescent proteins, researchers can directly detect and monitor G4 formation in RNA transcripts, providing valuable insights into the dynamic nature of these structures. While these advancements represent significant progress in the field of G-quadruplex research, several challenges remain. One major hurdle is the accurate prediction of G-quadruplex-forming sequences in the genome. Although computational tools can identify potential G4-forming sequences, experimental validation is often necessary to confirm their formation and biological relevance. Furthermore, the development of G4-specific ligands with high affinity and selectivity remains a priority.

Group	No	Strength	Preference for c-Myc-$_{G4}$ (KD, Ka, Tm)	In Vitro and In Vivo Studies	Ref
	28	ΔTm = 26.6 °C		Decrease c-MYC Expression Cytotoxicity activity (IC $_{50}$ 4.7 µM) Inhibits tumor growth	90
	29	ΔTm = 7 °C	No	Cytotoxicity activity (IC $_{50}$ 2.3-3.1 µM)	91,92
	30	ΔTm = 17 °C	No	Cytotoxicity activity (IC $_{50}$ 2.3-3.1 µM)	
	31	ΔTm = 22 °C	Yes	Cytotoxicity activity (IC $_{50}$ 0.02-5.53 µM)	94
	32	ΔTm = 16.6 °C	Yes	Decrease c-MYC Expression	
	33	ΔTm = 13.37 °C	Yes	Inhibits tumor growth	
	39	ΔTm = >15 °C		Decrease c-MYC Expression Induces apoptosis Inhibits RNA polymerase I activity Inhibits formation of G4- complexes Reached Phase II clinical trials	103
	10		No	Reduce telomerase activity Inhibit Cancer cell growth Decrease c-MYC and h-TERT Inhibits tumor growth	60,61
Macrocycles					
	16	ΔTm = 17.2 °C	No	Decrease c-MYC Expression Decrease Pif1 helicase activity Cytotoxicity activity (IC$_{50}$ < 0.01 µM in MCF cells.	66

(**a**)

Group	No	Strength	Preference for c-Myc-G4 (KD, Ka, Tm)	In Vitro and In Vivo Studies	Ref
Ligands with four or more fused aromatic rings	**27**		Yes	Decrease c-MYC Expression Antiproliferative activity (0.24-4.8 µM)	89
	40	ΔTm = >15 °C	No	Toxic against BRCA 1/ 2 deficient cells Inhibits RNA polymerase I and Topoisomerase II Phase I clinical trial Induce G4-mediated DNA damage	104
	41	ΔTm = 4.4 °C		Decrease c-MYC Expression Cytotoxicity activity (IC$_{50}$ 1.1 µM) Inhibits tumor growth in zebrafish model	105
	APTO		No	Decrease in c-MYC Expression in mRNA Cytotoxicity activity Phase I clinical trial	100-101
	43	ΔTm = 10 °C	Yes	Inhibits cell growth	113
	36	ΔTm = 16.4 °C	No	Decrease c-MYC Expression & BCL-2 Cytotoxicity effect and Inhibits the tumour growth	100-101
	43	ΔTm = >6 °C	No	Decrease c-MYC Expression & *HIF1α*	103
	44		Yes	Decrease c-MYC Expression by 25-40%	116, 117
	46	ΔTm = 12.8 °C	No	Decrease c-MYC & BCL2Expression Cytotoxicity activity (IC$_{50}$ 17.0 µM)	119
	48	ΔTm = 20 °C	Yes	Decrease c-MYC Expression Cytotoxicity activity (IC$_{50}$ 2.1-4.2 µM) Inhibits tumor growth	120

(**b**)

Figure 11. *Cont.*

Group	No	Strength	Preference for c-Myc-G4 (KD, Ka, Tm)	In Vitro and In Vivo Studies	Ref
Ligands with three fused aromatic rings	**47**	ΔTm = 4 °C	Yes	Decrease c-MYC Expression	121
	50	ΔTm = 1.9 °C	Yes	Cytotoxicity activity (IC_{50} 3.4 µM)	122
	24	ΔTm = 15.8 °C	Yes	Cytotoxicity activity in HeLa (IC_{50} 3.2 µM)	83
	20	ΔTm = 0.17 °C	-	Decrease c-MYC Expression Cytotoxicity activity in HCT 116 Cells (IC_{50} 2.1 µM)	74
	25	ΔTm = 23.4 °C	-	Decrease c-MYC Expression Cytotoxicity activity in HeLa (IC_{50} 2.5 µM)	85
	23	ΔTm = 36 °C	Yes	Decrease c-MYC Expression	79
	51	ΔTm = 15.0 °C	-	Decrease c-MYC Expression Downregulate the RNA Polymerase I Transcription	118

(**c**)

Group	No	Strength	Preference for c-Myc-G4 (KD, Ka, Tm)	In Vitro and In Vivo Studies	Ref
Ligands with two Fused aromatic Rings	**57**	Binding affinity to NM23-H2 protein (KD 3.1 µM)	No	Decrease c-MYC Expression Induce cell cycle arrest & apoptosis Cytotoxicity	129
	58	KD 1.3 µM	Yes	Decrease c-MYC Expression Cytotoxicity (IC_{50} 0.7-0.9 µM) Inhibits the tumor growth	133
	59	ΔTm = 15 °C	Yes	Decrease c-MYC Expression Cytotoxicity (IC_{50} 2.2 µM) Inhibits the tumor growth	134
	60	Ka = $10^{6.1}$ M^{-1}	No	Dual G4/PARP Inhibitor Cytotoxicity (IC_{50} 19.4 µM)	135
	61		Yes	Decrease c-MYC Expression Antiproliferative activity (IC_{50} 5.8 µM)	136
	62	ΔTm = 7.5 °C	Yes	Decrease c-MYC Expression Cytotoxicity (IC_{50} 3.4 µM)	137

(**d**)

Group	No	Strength	Preference for c-Myc-G4 (KD, Ka, Tm)	In Vitro and In Vivo Studies	Ref
	65	ΔTm = 22 °C	Yes	Decrease c-MYC Expression Cytotoxicity (IC_{50} 3.4 µM)	139
Flexible Ligands	**66**	ΔTm = 15 °C	No	Decrease c-MYC Expression	141
	67	ΔTm = 6 °C		Cytotoxicity (IC_{50} 3.8 and 7.1 µM in MCF-7 cells)	142
	69	ΔTm = 10.2°C			
	70	ΔTm = 15.6 °C			
	71	ΔTm = 2.0 °C	No	Decrease c-MYC Expression	143
	72	ΔTm = 7.3 °C			
Metal Complexes	**73**			Decrease c-MYC Expression	
	74		-	Cytotoxicity (IC_{50} 10.1 and 5.1 µM in Hep-G2 cells)	147

(**e**)

Figure 11. (**a**–**e**) Information on the best c-MYC G-quadruplex ligand properties [60,61,66,74,79,83,85,89–92,94,100,101,103–105,113,116–122,129,133–137,139,141–143,147].

Overall, targeting c-MYC G-quadruplexes represents a promising approach for cancer therapy. The development of small compounds that may bind as well as stabilize these structures has advanced significantly, but there are still obstacles in the way of reaching the best possible specificity, effectiveness, and delivery. Addressing these issues and clarifying the molecular processes behind the anticancer effects of c-MYC G-quadruplex ligands should be the main goals for upcoming studies. By doing so, it may be possible to develop effective and selective c-MYC G-quadruplex-targeting drugs to improve patient outcomes.

5. Future Perspectives

To further advance the field of c-MYC G-quadruplex targeting for cancer therapy, future research should focus on developing compounds with improved selectivity, cellular uptake, and targeted delivery. Enhancing the affinity, solubility, stability, and cell permeability of these molecules is crucial for their efficacy. Additionally, exploring combination therapies with other anticancer treatments and conducting extensive in vivo studies and clinical trials will be essential to translate these promising findings into effective clinical applications [46]. The future of cancer treatment holds significant promise and is driven by advancements in nanotechnology, drug delivery systems, and innovative therapeutic approaches, like photodynamic therapy (PDT). Nanoformulations offer a promising strategy to overcome limitations associated with drug delivery, enhancing their efficacy and reducing side effects [148]. By optimizing nanoformulations and exploring combination therapies, researchers aim to improve cancer treatment outcomes. Additionally, innovative therapeutic approaches with a minimally invasive nature and potential for targeted therapy make it a compelling approach, particularly when combined with other modalities [149]. Ongoing research in cancer, including developing innovative photosensitizers and advanced drug delivery systems, is expanding its application to various cancer types and other diseases. While substantial progress has been made, further clinical studies are necessary to fully realize the potential of innovative therapeutic approaches and optimize their therapeutic benefits.

While small molecule-based approaches targeting c-MYC G-quadruplexes are promising, they often lack specificity. Including alternative methods, like bimolecular fluorescence complementation and CRISPR-based techniques, would provide a more comprehensive understanding of the field and highlight the potential limitations of small molecule approaches [150,151].

The future of targeting c-MYC G-quadruplexes for cancer treatment holds immense potential. To maximize the therapeutic benefits of these compounds, further research is needed to optimize their delivery systems, improve their bioavailability, and minimize potential side effects. The development of novel techniques has led to the identification of a diverse range of biomarkers capable of selectively recognizing distinct G-quadruplex structures, significantly advancing the field of cancer research [152–154]. By addressing these challenges, researchers can develop more effective and targeted therapies. Additionally, exploring combination therapies with other anticancer agents and investigating the mechanisms of action in greater detail will provide valuable insights into the clinical potential of these compounds. Ultimately, integrating multidisciplinary approaches, including medicinal chemistry, pharmacology, and clinical research, will be essential to translate these promising findings into clinically effective treatments for cancer patients.

6. Conclusions

Finding c-MYC G-quadruplex-targeting agents has been quite successful, and many promising compounds have been discovered. Although we have made great strides in finding molecules that can stabilize c-MYC G-quadruplexes, there remains a need for even

greater specificity, efficacy, and delivery. Future research should enhance specificity by developing molecules that selectively target c-MYC G-quadruplexes over other G-quadruplex structures throughout the genome. Additionally, increasing the potency and efficacy of these compounds to achieve clinically meaningful responses is crucial. Overcoming challenges associated with the delivery and bioavailability of G-quadruplex-targeting agents is another important area of focus. Furthermore, elucidating the precise mechanisms by which these compounds interact with G-quadruplexes and exert their anticancer effects can provide valuable insights for future drug development. Exploring synergistic interactions between G-quadruplex-targeting agents and other therapeutic modalities may enhance their effectiveness. By closing these gaps, researchers can establish pathways towards efficient and selective c-MYC G-quadruplex-targeting agents with real promise for multiple cancers.

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