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Review article

Targeting G-quadruplex nucleic acids with heterocyclic alkaloids and their derivatives

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ABSTRACT

G-Quadruplex nucleic acids or G-quadruplexes (G4s) are four-stranded DNA or RNA secondary structures that are formed in guanine-rich sequences. They are widely distributed in functional regions of the human genome, such as telomeres, ribosomal DNA (rDNA), transcription start sites, promoter regions and untranslated regions of mRNA, suggesting that G-quadruplex structures may play a pivotal role in the control of a variety of cellular processes. G-Quadruplexes are viewed as valid therapeutic targets in human cancer diseases. Small molecules, from naturally occurring to synthetic, are exploited to specifically target G-quadruplexes and have proven to be a new class of anticancer agents. Notably, alkaloids are an important source of G-quadruplex ligands and have significant bioactivities in anticancer therapy. In this review, the authors provide a brief, up-to-date summary of heterocyclic alkaloids and their derivatives targeting G-quadruplexes.

1. Introduction

The discovery of the right-handed double helical structure of B-form DNA has defined our molecular view of the genetic code since 1953 [1]. Other postulated DNA secondary structures, such as A-DNA, Z-DNA, H-DNA, cruciform and triplex structures, have provoked consideration of DNA as a more dynamic structure [2]. Found by Gellert and coworkers in 1962 [3], guanine-rich sequences can fold into a four-stranded DNA helical secondary structure termed a G-quadruplex. Its basic structural unit is the G-quartet, which are derived from the association of four guanines into a cyclic Hoogsteen hydrogen-bonding arrangement. The G-quartet, stabilized by monovalent cations, can form stacks that are extremely stable to thermal denaturation under conditions similar to cell physiological ones (Fig. 1).

The research course of G-quadruplex, beginning with structural determination *in vitro* to the discovery of its multifaceted modes of genome regulation in cells, has traversed a long way. This special structure differs from other nucleic acid secondary structures and is highly associated with human diseases (e.g., cancer [4], HIV [5], and diabetes [6]), which makes the G-quadruplex a potent therapeutic target. Therefore, a variety of small molecules have been identified and designed in an effort to target the G-quadruplex, specifically and effectively.

Alkaloids are an important class of small natural compounds that have diverse and significant biological activities, such as antimalarial and anticancer properties, which are due in part to their similarities with many natural and synthetic molecules with known biological activity [7]. Moreover, compounds that contain heterocyclic moieties often exhibit improved solubility and can facilitate salt formation. Both are known to be important for oral absorption and bioavailability [8]. With the characteristics of polymorphism, structural complexity, availability from natural sources and general low toxicity in normal cells, heterocyclic alkaloids and their derivatives have been investigated intensively for their potential to be G-quadruplex ligands by high throughput screening and other specific methods. This review is dedicated to the published research on heterocyclic alkaloids and their derivatives targeting G-quadruplex structures.

Abbreviations: G4s, G-quadruplexes; rDNA, ribosomal DNA; PQS, putative G-quadruplex forming sequences; POT1, the protection of telomeres 1; TRF1 and TRF2, the telomeric repeat binding factors 1 and 2; UTR, untranslated regions of mRNA; SAR, structural–activity relationship; $^{tel}IC_{50}$, the concentration required to produce 50% inhibition of telomerase; SPR, surface plasmon resonance; ITC, isothermal titration calorimetry.

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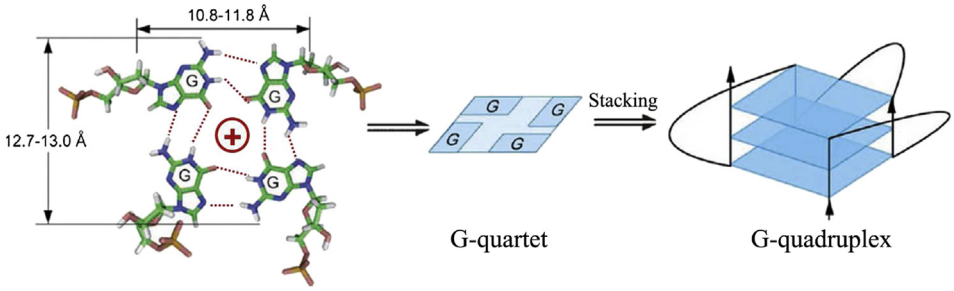


Fig. 1. Structures of G-quartet and G-quadruplex.

2. G-Quadruplexes as targets for drug design

2.1. Structure features of a G-quadruplex

A G-quadruplex can be viewed as an assembly of G-quartets, which is larger in size than that of a Watson–Crick base pair in a duplex helix [9]. By means of X-ray crystallography, NMR spectroscopy and other powerful technologies, the G-quadruplex structures have been resolved. These structures exhibit extensive structural diversity and polymorphism relative to duplex DNA which basically depends on six variable parameters [10]: (1) the component of oligonucleotide sequence (e.g., DNA G4, RNA G4 or DNA/RNA hybrid G4); (2) the number of oligonucleotide strands (e.g., intermolecular or intramolecular G4); (3) the orientation of strands (e.g., parallel, antiparallel, hybrid); (4) the type and size of intervening loops (e.g., diagonal loops, lateral loops and double chain reversal loops); (5) the angles of the glycosidic bonds (e.g., *syn*, *anti*); (6) the solution environment, such as the metal ions (e.g., Na^+, K^+, Sr^{2+}, Cu^{2+}), the molecular crowding and the presence of binding ligands. Some classification of G-quadruplexes is shown in Fig. 2.

2.2. Distribution, existence and biological role of the G-quadruplex

2.2.1. Distribution and existence of the G-quadruplex

Based on G-quadruplex search algorithms, computational surveys of the human genome have revealed that putative G-quadruplex forming sequences (PQS), carrying a signature motif $G_{\geq 3}N_xG_{\geq 3}N_xG_{\geq 3}N_xG_{\geq 3}N_x$, are prevalent in the genome, with an estimate of ~370,000 motifs [11–14]. These PQS are frequently within human telomeric DNA, rDNA, transcription start sites [15], the promoter regions [16], and untranslated regions of mRNA [17] suggesting that G4 structures may play a pivotal role in the control of a variety of cellular processes, including telomere maintenance, ribosome biogenesis, gene replication, transcription and translation. Strikingly, these structures are often over-represented in proto-oncogenes and apparently deleted in tumor suppressor genes, which suggests evolutionary selection for G-quadruplex structures based on their function; thus, G-quadruplexes may be required to control oncogene expression [14].

After the evidence of the *in vivo* existence of G-quadruplexes was established using specific antibodies against parallel and antiparallel G-quadruplexes formed in telomeric DNA of the ciliate *Stylonychia lemna* [18], directive and quantitative visualization of DNA G-quadruplex structures in human cells was recently reported [19]. With structure-specific antibodies BG4, the G-quadruplex was visualized forming in telomeres and outside of telomeres and formed in a replication-dependent manner in the cell cycle. More importantly, the increased BG4 foci number was observed after treatment with the G-quadruplex binding ligand, indicating that the small molecule could trap and stabilize a G-quadruplex in human cells. In addition, the practical high-throughput DNA sequencing showed the significant co-localization of PQS with antibody hf2 [20], γH2AX [21] and Pif1 DNA helicase [22]. All of these substantial evidences not only provide for the existence and location of G-quadruplexes in the genome but also implicate the profound function of G-quadruplexes. A specific small molecule could modulate these structures in cells, which strongly supports the therapeutic potential of targeting a G-quadruplex.

2.2.2. Biological role of the G-quadruplex in the human genome

Putative G-quadruplex sequences have been identified in the human genome with an enrichment in telomeres, rDNA, promoter regions, untranslated regions (UTR) of mRNA, first exons and first introns of many genes [23]. Such a distribution indicates a possible function of G-quadruplexes in cells and the potential for it to serve as a drug target.

Telomeres are specialized DNA–protein structures located at the end of eukaryotic chromosomes. In mammalian cells, telomeres consist of tandem arrays of TTAGGG repeats (3–15 kb) ending with 35–600 nucleotide-long single stranded DNA on the 3′-oriented strand (3′-overhang). This G-overhang acts as a substrate for telomerase, a reverse transcriptase with an RNA component required for telomere extension [24]. The structure and stability of telomeres are closely related to cancer [25], aging [26], and genetic stability [27]. Due to the high contents of TTAGGG repeats and without the competition of its complementary strand on 3′-overhang, the existence of a G-quadruplex would be favored [25]. The formation of a G-quadruplex would provoke a profound influence on the telomere including: (1) It could inhibit telomerase activity by blocking the binding of telomerase to the single-stranded telomere substrate to elongate the telomeres [28]. Telomerase is abundantly expressed in 85% cancer cells relative to somatic cells making it an attractive target for specific targeting of a cancer cell. (2) Telomere uncapping by dissociation of the telomeric binding proteins (e.g., POT1, TRF1 and TRF2) from the telomere end [29] can lead to telomeric dysfunction characterized by end-to-end fusion, inappropriate recombination, anaphase bridges, and G-overhang degradation that either leads to apoptosis or senescence [30]. (3) Interfering with telomere replication by impairing replication fork progression is also possible [31]. These findings prompted an outburst of selective G-quadruplex interacting small molecules with the aim to develop a novel telomere based anticancer therapy. Recent comparative searches within the database of U.S. Food and Drug Administration-approved compounds have identified more than 750 telomerase inhibitors acting through G4 stabilization [32]. This research provides supplementary evidence for effective inhibition of telomere elongation by G-quadruplex ligands.

Several putative G-quadruplex sequences, besides the telomeric repeat, have been identified near the transcription starting site and gene promoters, indicating their key role in various gene regulations. These gene promoters include *c-MYC*, *c-KIT*, *BCL-2*, *K-RAS*,

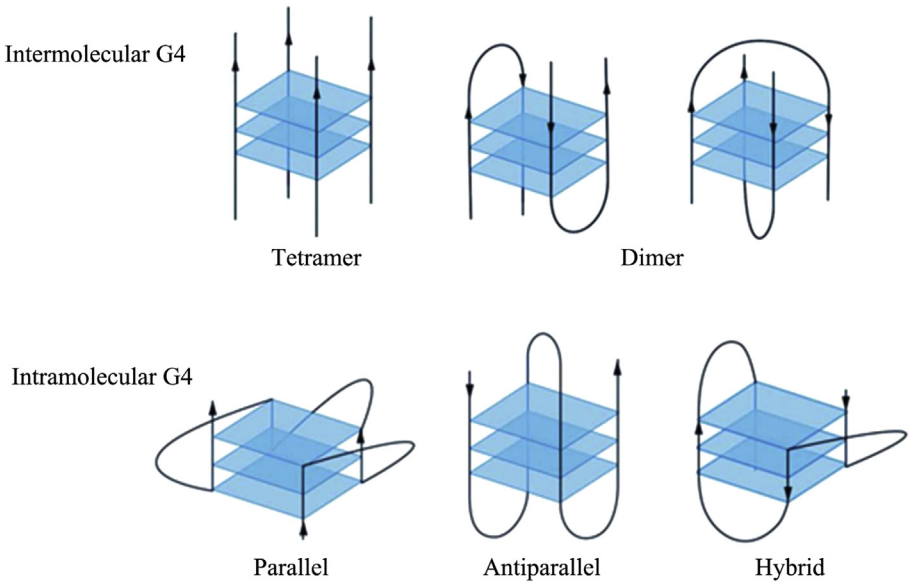
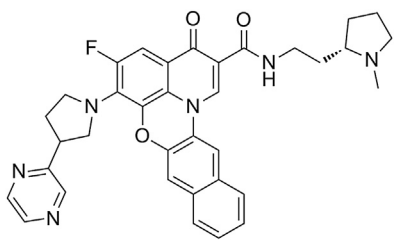


Fig. 2. Classification of G-quadruplex structures.

VEGF, *RB*, *PDGF-A*, *hTERT*, etc. Transcriptional repression of oncogenes through stabilization of these structures or blocking relative proteins binding to these structures could be a novel anticancer strategy [23]. The best characterized system in this regard is the *c-MYC* G-quadruplex. It was first demonstrated in 2002 that the G-quadruplex in the *c-MYC* promoter element was a silencer element and that stabilization with the G-quadruplex interactive molecule led to inhibition of *c-MYC* expression [33]. The ligand- or drug-mediated effect on *MYC* transcription by stabilization of the G-quadruplex has been independently demonstrated in subsequent works with the aim of developing an antitumor treatment.

G-Quadruplexes are also reported to form in the nontemplate strand of human ribosomal DNA (rDNA), which is a GC rich sequence [34]. Many studies have shown that a marked increase in rRNA synthesis is a general phenomenon in cancer and transcription of rDNA requires the stabilization of the G-quadruplex by nucleolin [35,36]. Consequently, extensive research efforts have been taken to disrupt the nucleolin–G-quadruplex complex for the inhibition of ribosome biogenesis. The best example of a small molecule that targets rDNA G-quadruplex is quarfloxin (**1**, Fig. 3), which was identified to disrupt nucleolin/rDNA G-quadruplex complexes to inhibit aberrant Pol I transcription in cancer cells. It is the first-in-class G-quadruplex-interacting compound that has reached Phase II clinical trials [37].

Similar to DNA, RNA can also form G-quadruplex structures. For example, RNA G-quadruplexes can be found clustered in the 3′-UTR, 5′-UTR [38] and open reading frame [39] of mRNA as well as in the telomeric repeat-containing RNA structure [40]. Studies on RNA G-quadruplexes have also revealed its important biological role in translation regulation and telomere maintenance [41]. For example, a G-rich sequence within the 5′-UTR of a human *NRAS* proto-oncogene could form a stable intramolecular G-quadruplex structure, even in the absence of K^+, and it has been demonstrated that RNA G-quadruplexes are able to affect the cap-dependent protein translation using a reporter gene assay in a cell-free translation system [42]. Another example comes from the intron 6 of *TERT* pre-mRNA, which contains several G-tracts that can fold into a G4, which can be stabilized by the triazine derivative to lead to a shift in the splicing pattern toward the production of a catalytically inactive form of *TERT* thus leading to down-regulation of telomerase activity [43]. Although many efforts are still to be made to rigorously validate RNA G-quadruplexes as drug targets for therapeutic intervention, the evidence that translational repression of target genes by some RNA G-quadruplex binding ligands open up new avenues in the design of drug candidates with specific targeting of RNA G-quadruplexes.



1 (Quarfloxin)

Fig. 3. The structure of quarfloxin.

2.3. Binding mode of G-quadruplex ligands

The unique structure and topology of G-quadruplexes provide great advantages for a small molecule to specifically target G-quadruplexes against duplex or other nucleic acid secondary structures and even target specific G-quadruplex structures. The interaction modes of small molecules with a G-quadruplex usually follow these several principles [44]: (1) They can stack with the G-quartet through π–π interactions. Ligands with an extended planar aromatic system, which are similar to a G-quartet in size and shape, facilitate stacking on the G-quartet. This aromatic system can be a rigid flat or twisted surface. (2) They can interact with the loops and grooves. Small molecules would interact with the loops and grooves of the G-quadruplex. Cationic substituents usually have stronger binding affinities with the anionic phosphate backbone. (3) They can interact with the negative electrostatic center of the G-quadruplex by electrostatic interaction with the cationic center of the aromatic core. Basic binding modes of G-quadruplex ligand are shown in Fig. 4.

3. Heterocyclic alkaloids and their derivatives binding to the G-quadruplex

3.1. Quinoline derivatives

Quinoline (1-azanaphthalene) is a heterocyclic aromatic nitrogen compound characterized by a double-ring structure that contains a benzene ring fused to pyridine at two adjacent carbon atoms. Quinoline compounds are widely used as "parental" compounds to synthesize molecules with medical benefits, especially with anti-malarial [45], anti-microbial [46] and anti-cancer activities [47]. A large number of structurally diverse quinoline derivatives have recently been examined for their modes of function in G-quadruplex targeting.

One of quinoline compounds for G-quadruplex targeting is cryptolepine (5-methyl indolo[2,3b]-quinoline, **2**, Fig. 5). It is a natural alkaloid first isolated from the roots of *Cryptolepis triangularis* [48]. This flat tetracyclic compound has provided a potent platform that prefers GC over AT-rich duplex sequences, but it also recognizes triplex and quadruplex structures [49]. Several substituted cryptolepine analogs have been synthesized. The disubstituted derivatives, with two alkyl amino groups at the 2, 7-positions or at the 2, 10-positions (**3** and **4**), have been reported by Neidle et al. to have modest G-quadruplex stabilization and telomerase inhibition activity, with $^{tel}IC_{50}$ values in the range of 6–16 μM [50,51]. The 11-substituted cryptolepine analogs (**5**), designed and synthesized by our research group, significantly improved their ability to stabilize a G-quadruplex [52]. Electron-donating groups at the 11-position can enhance the basicity of the nitrogen atom in the pyridine ring, thus increasing the electrostatic interaction between the derivatives and the negative electrostatic center of the G-quadruplex. The most active compound, SYUIQ-05, showed an improved inhibitory effect on telomerase activity ($^{tel}IC_{50}$ = 0.44 μM) and induced a marked cellular senescence phenotype accompanied by a shortening of telomere length in K562 and SW620 cancer cells [53]. Furthermore, the introduction of a positive charge by methylation at the 5-N position of these compounds (**6**) showed significantly improved binding affinity to the G-quadruplex (approximately 5-fold higher than the non-methylated derivative) [54,55]. Recently, a series of peptidyl-benzofuroquinoline (P-BFQ) (**7**) conjugates were designed and synthesized to improve the selectivity of cryptolepine analogs. Positive charge and alkyl chain-length of the dipeptidyl side chain proved to be important for its interaction with the G-quadruplex; the most active compound with a dipeptide fragment of -Lys-Arg had the most potent inhibitory effect ($^{tel}IC_{50}$ = 5.5 μM) and 50 times higher selectivity for telomeric G-quadruplex against the duplex. Additionally, the cellular experiments also showed a promising anticancer effect [56].

A series of G-quadruplex ligands with two quinoline or methylated quinoline (quinolinium) side arms connected by different central aromatic linkers has appeared in recent years. These ligands show excellent binding affinity and selectivity due to their flexible structural conformations, which will contribute to groove and loop region interactions preserving the planarity and rigidity of each unit. Compound 12459 and 115405 are typical bis-quinoline triazine derivatives, presenting strong affinities to different G-quadruplex structures when compared with other forms of nucleic acids (**8** and **9**, Fig. 6). These two compounds act as human telomerase inhibitors at nanomolar concentrations ($^{tel}IC_{50}$ = 130 nM and 41 nM, respectively), active as antiproliferative agents on a panel of human cancer cell lines and also induce both telomere shortening and apoptosis in the human lung adenocarcinoma A549 cell line [57]. The biological effects of 12459, related with *hTERT* RNA alternative splicing [43] and short-term resistant [58–60], are further revealed by Riou et al. bis-quinolinium compounds with a pyridodicaboxamide core are latterly reported for the strong selectivity for G-quadruplex structures and strong inhibition of telomerase *in vitro* assays. The most active compound 307A (**10**) showed 50-fold selectivity towards a G-quadruplex with a $^{tel}IC_{50}$ value of 0.3 μM. It is also noteworthy that this ligand blocked cell proliferation, induced apoptosis, but not senescence and telomere shortening [61]. Experiences of these ligands led to further modification, especially to one of these derivatives, pyridostatin (**11**), which was used as a pioneering ligand to investigate the biological role of G-quadruplexes in cells and served as a potential anti-cancer agent. It stabilizes the human telomeric G-quadruplex with a maximum ΔT_m of 35 °C at 0.18 μM accompanied by a high level of selectivity over duplex DNA. The compound also induces telomere dysfunction by competing for the binding with telomere associated proteins such as human POT1 [62]. Pyridostatin also has been shown to alter transcription and replication of particular human genomic loci containing high G-quadruplex clustering within the coding region, which encompasses telomeres and selected genes such as the proto-oncogene *SRC* [21]. Recently, the compound also was confirmed to decrease Epstein–Barr virus-encoded nuclear antigen 1 (*EBNA1*) mRNA translation by stabilizing a RNA G-quadruplex within the open reading frame [63]. Another flexible structure was achieved by changing the aromatic core to a simple aliphatic diketene. M2 (**12**) is one of the bis-quinolinium diketene compounds that selectively binds to G-quadruplexes. M2 can even discriminate between specific G-quadruplex DNA structures. The binding affinity of M2 for *c-MYC* G-quadruplex DNA was over 200 times larger than that for telomere G-quadruplex DNA [64]. Further biophysical experiments revealed that the electrostatic surface of M2 was similar to 307A and 12459 and plays an important role in end-stacking binding to the G-quadruplex [65]. The great bioactivity of these compounds has promoted the development of various types of similar compounds, such as pyrimidine linked bis-aryl compounds [66], urea linked bis-phenyl compounds [67], bis-phenanthrolines [68] and bis-benzimidazoles [69].

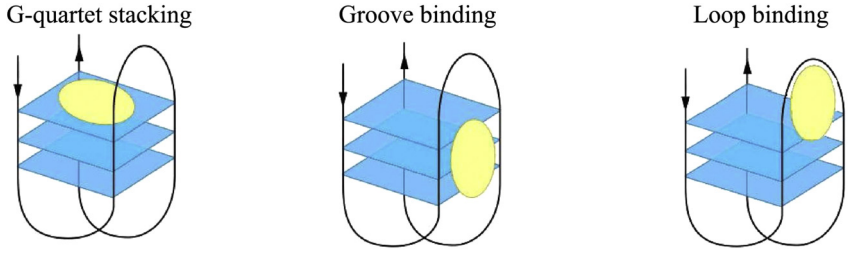


Fig. 4. Examples of binding mode of small molecule with G-quadruplex.

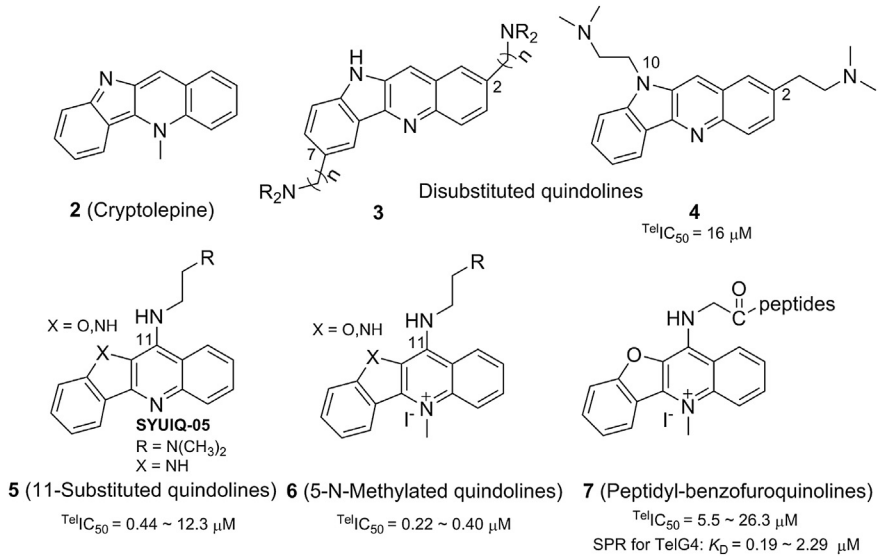


Fig. 5. Structures of quindoline derivatives: cryptolepine (**2**), disubstituted quindolines (**3** and **4**), 11-substituted quindolines (**5**), 5-N-methylated quindolines (**6**), and peptidyl-benzofuroquinolines (**7**).

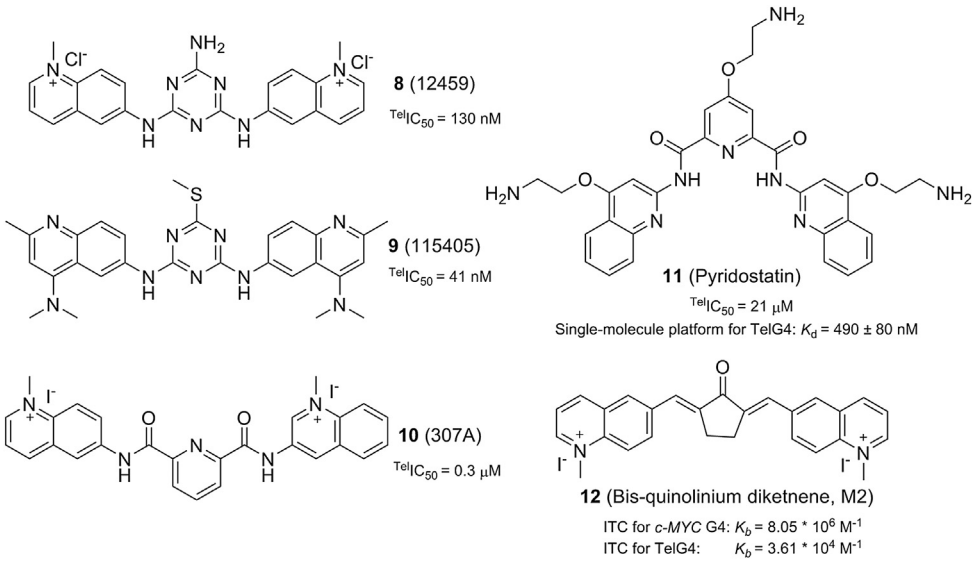


Fig. 6. Structures of bis-quinoline and bis-quinolinium derivatives: compound 12459 (**8**), compound 115405 (**9**), compound 307A (**10**), pyridostatin (**11**), and bis-quinolinium diketene, M2 (**12**).

3.2. Acridine and acridone derivatives

Acridine and acridone alkaloids are mostly synthesized by plants of the Rutaceae family. Most of these structures have exhibited high activity against malaria parasites, and some of them have been tested against tumoral cell lines, partly due to the planar structure of the tricycle rings conferring the ability to intercalate in the DNA and interfere with various metabolic processes both in prokaryotic and eukaryotic cells [70]. Neidle and co-workers first synthesized a series of 3, 6-disubstituted acridines to improve the G-quadruplex affinity (**13**, Fig. 7). Introduction of a side chain will increase the positive charge character of the core and enhance the electrostatic interaction with the negatively polarized G-quartet center. The most potent inhibitors have $^{tel}IC_{50}$ values against a telomerase of between 1.3 and 8 μM [71]. Later, a number of 3, 6, 9-trisubstituted acridines were designed and synthesized (**14**). The involvement of an anilino group at the 9-position significantly increased the basicity of the pyridine ring nitrogen and allowed the ligand core to be protonated at physiological pH values. Moreover, the anilino group at the 9-position provided an additional interaction with the third groove [72]. One of the most effective compounds termed BRACO-19, shows a strong binding affinity for G-quadruplex structure and high telomerase inhibitory activity (IC_{50} = 95 nM). Significant tumor growth inhibition by BRACO-19 was observed in early-stage xenograft tumors of nude mice [73]. The tricyclic system of acridines was subsequently modified to a pentacyclic system to enlarge the plane size for π-stacking. One member of N-methylated pentacyclic acridinium salts, RHPS4 (**15**), was found to exhibit notable telomerase inhibitory activity ($^{tel}IC_{50}$ = 330 nM by TRAP assay). RHPS4 has many pharmacological attributes, which make it an ideal telomere-targeting agent to eliminate a panel of cancer cells [74–76]. At the same time, it serves

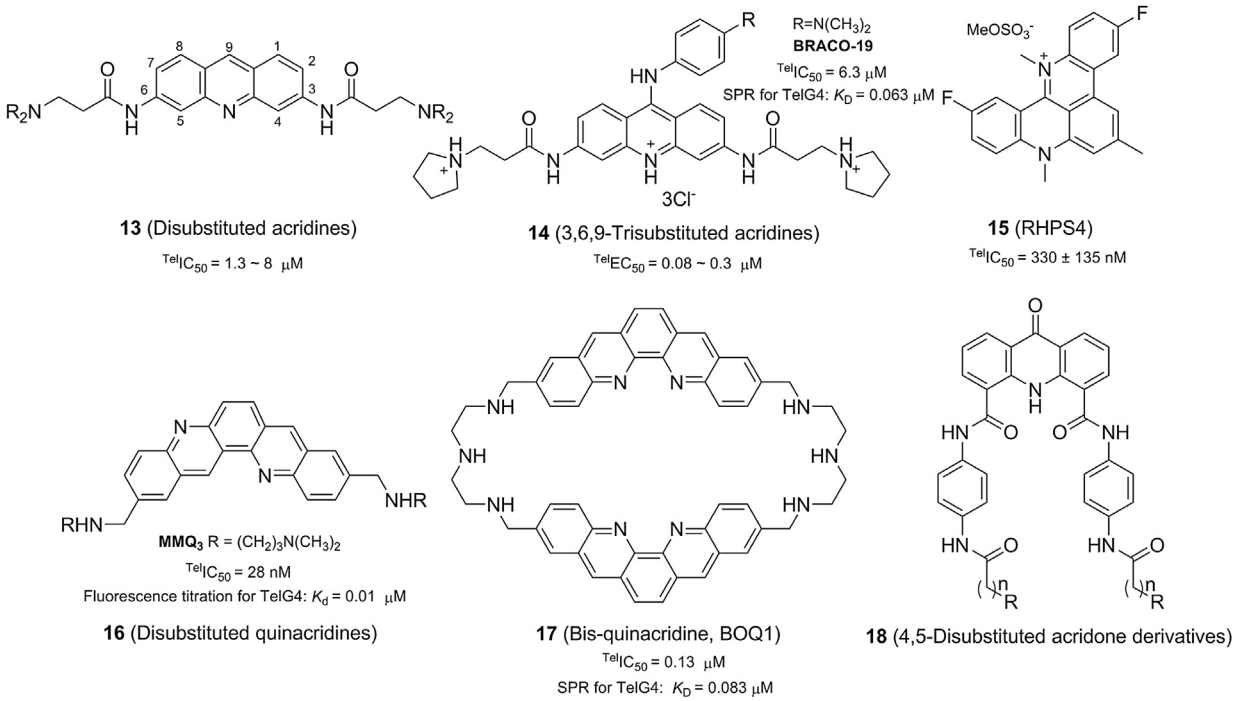


Fig. 7. Structures of acridine and acridone derivatives: disubstituted acridines (**13**), 3, 6, 9-trisubstituted acridines (**14**), RHPS4 (**15**), disubstituted quinacridines (**16**), bis-quinacridine, BOQ1 (**17**), and 4, 5-disubstituted acridone derivatives (**18**).

as a useful tool for investigating cancer related signaling pathway [77,78]. Mergny et al. introduced another class of pentacyclic ligands containing the crescent shaped dibenzophenanthroline (quinacridine) and extended amino side chains that maximize overlap with the G-quartet and electrostatic interaction with grooves (**16**) [79]. They found that with more cationic functional groups on the side chains, the binding affinity to intramolecular G-quadruplexes and telomerase inhibitory activity increased. For example, the most active compounds MMQ3 have a telomerase inhibitory value of 28 nM [80]. However, the charged side chains do not help to discriminate between the G-quadruplex and duplex structures. To improve the selectivity of these compounds, a cyclic bis-quinacridine (BOQ1) with two quinacridines connected by polyamine linkers, has been proposed (**17**) [81,82]. BOQ1 has better G-quadruplex stabilization than that of the monomeric series, most likely because the larger aromatic surface impedes its access to duplex DNA.

Neidle et al. also synthesized several series of 2, 6, 2, 7 and 3, 6-di-substituted acridone compounds, which show patterns of activity that are similar to their disubstituted acridine counterparts [83]. Particularly, a novel series of 4, 5-di-substituted acridone derivatives (**18**) were found to have high affinity for telomeric G-quadruplex DNA in classical and competition FRET assays, with improved selectivity compared with tri-substituted acridine compounds. Most of the compounds have distinguishing cytotoxicity between cancer cells and normal cell lines [84].

3.3. Isoquinoline and its derivatives

Isoquinoline is one of the most widely distributed alkaloids including benzylisoquinolines, protopines, benzo[c]phenanthridines, protoberberines, and many others. Berberine, palmatine, coralyne, and sanguinarine are important isoquinoline alkaloids with proven therapeutic potential especially for anti-cancer treatment (**19**, **20**, **21** and **22**, Fig. 8). The nucleic acid binding ability of these alkaloids has been intensely studied. Their binding affinities with G-quadruplexes follow the order: coralyne > sanguinarine > berberine > palmatine by calorimetric study and electrospray ionization mass spectrometry [85,86]. Those more planar compounds (coralyne and sanguinarine) are better ligands than the others, which may be due to the molecular planarity of these alkaloids. Importantly, a recent X-ray structure of human telomeric DNA and berberine, showed the presence of two berberine molecules directly interacting with each external G-tetrad by π-stacking [87]. This study provides an important clue for interpreting binding data of isoquinolines with a G-quadruplex. However, all these isoquinolines also showed a strong binding ability to duplex DNA [88].

Structural modifications of these isoquinoline alkaloids, including side chain introduction and scaffold revisions, have greatly improved the G-quadruplex selectivity. For example, several semi-synthetic berberine derivatives have been reported. The 13-substituted berberines were synthesized and found to better stabilize the G-quadruplex structure (**23**). In addition to stacking on the terminal G-tetrad, another dominant binding interaction comes from one of the four grooves of the quadruplex interacting with the side chain of piperidino-berberine [89]. Our research group synthesized 9-substituted berberines with an amino side chain [90] or aza-aromatic terminal group [91] (**24**). These compounds showed significant G-quadruplex binding and improved selectivity compare to berberine. Furthermore, modification of 9-substituted berberines yielded quinolino-benzo dihydroisoquindolium (QBDI) compounds (**25**), which have one more pyridine ring on the berberine scaffold. The increased aromaticity of the core of QBDI seems to enhance its interaction with the G-quadruplex [92]. What is particularly intriguing is that 9-substituted berberine and QBDI derivatives have high selectivity for G-quadruplex DNA to decrease *c-MYC* oncogene transcription up to 40%.

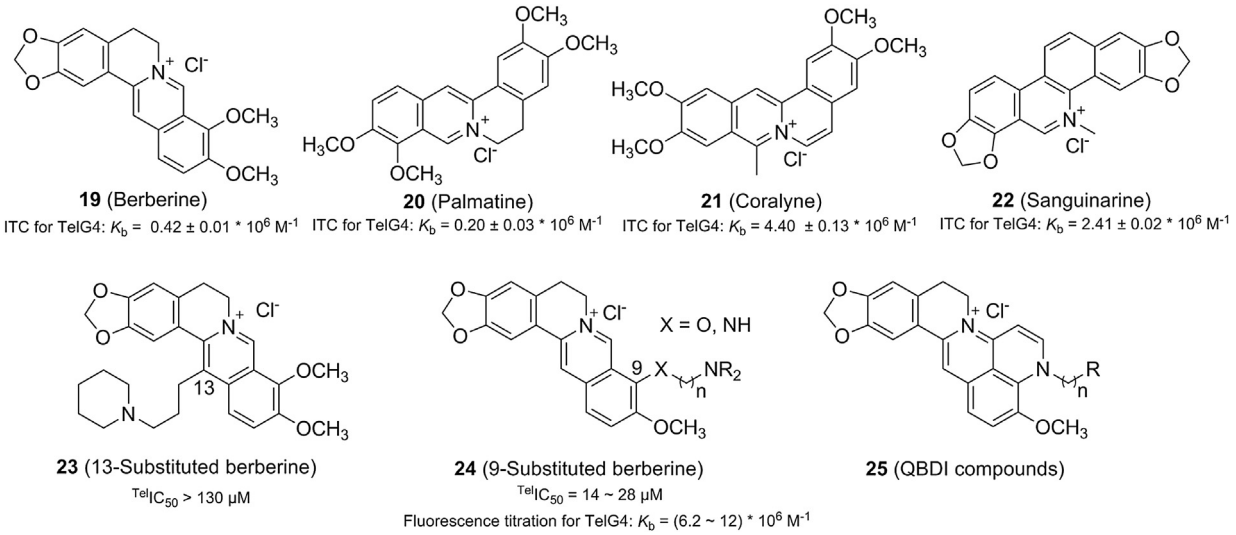


Fig. 8. Structures of isoquinoline derivatives: berberine (**19**), palmatine (**20**), coralyne (**21**), sanguinarine (**22**), 13-substituted berberine (**23**), 9-substituted berberine (**24**), and QBDI compounds (**25**).

3.4. Quinazoline and quinazolinone derivatives

Quinazolines and quinazolinones have attracted significant attention due to their diverse pharmacological activities such as antimalarial, anti-inflammatory and anticancer activities. Quinazolines and quinazolinones are also building blocks for approximately 150 naturally occurring alkaloids isolated from a number of families of the plant kingdom, from microorganisms and animals [93].

Quinazoline derivatives designed for G-quadruplex binding have arisen in recent years. A new series of G-quadruplex ligands that shares the quinazoline scaffold was synthesized, and its binding properties towards telomeric G-quadruplex DNA were reported by our research group [94]. This molecule has an "imitative" tetracyclic aromatic system formed through intramolecular hydrogen bonds, which enables the adoption of moderate twisted and co-planar conformations of the aryl groups and allows the ligand to stack well on the G-quartet. Therefore, these compounds effectively bind to telomeric G-quadruplexes but not to duplexes. The most effective compound, 11d, (**26**, Fig. 9) has a K_D value of 3.14×10^{-7} M. NMR and molecular docking indicate hydrogen bonding, π–π stacking interactions, and electrostatic interactions may account for the interaction. The compound also induces obvious cell senescence and telomere shortening of HL-60 cells at micromolar concentrations. More effective N-(2-(quinazolin-2-yl) phenyl)benzamide (QPB) derivatives (**27**) were subsequently achieved on the basis of previous compounds [95]. A feature of these compounds is their strong inducing ability, which lead to a

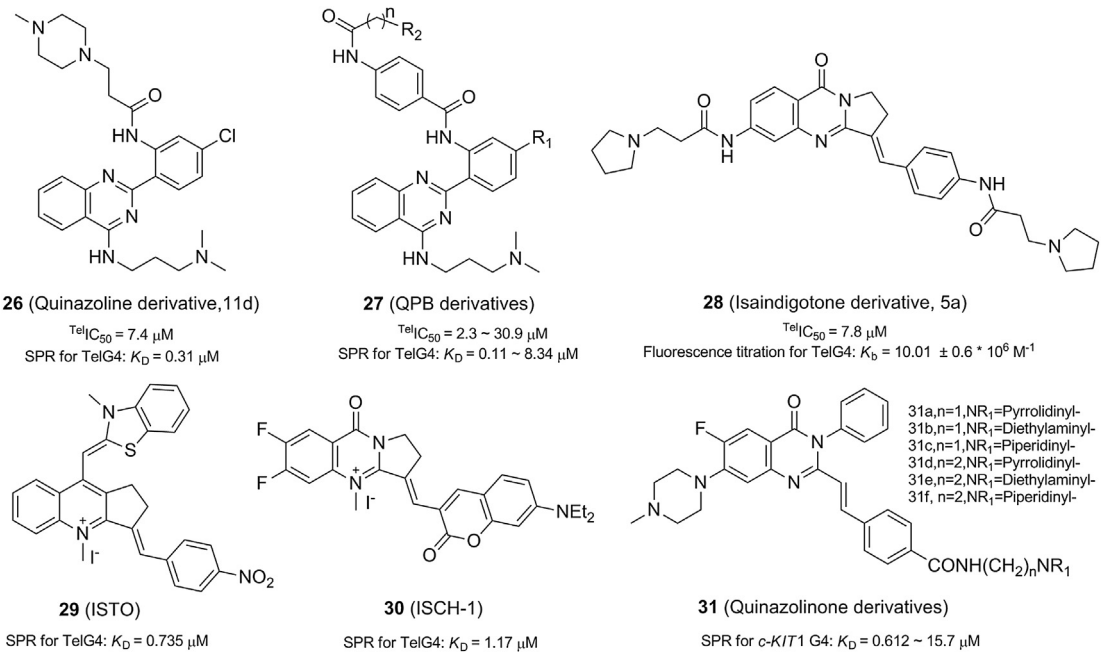


Fig. 9. Structures of quinazoline and quinazolinone derivatives: quinazoline derivative, 11d (**26**), QPB derivatives (**27**), isaindigotone derivative, 5a (**28**), compound ISTO (**29**), compound ISCH-1 (**30**), quinazolinone derivatives (**31**).

conversion of hybrid telomeric G-quadruplexes to parallel type. SAR (structural–activity relationship) analysis indicates that the existence of an additional phenyl group and a chlorine substituent could greatly increase the stability and inducing ability.

Isaindigotone is a quinazolinone alkaloid isolated from the root of the traditional Chinese herb *Isatis indigotica*, which has exerted excellent effects against influenza, epidemic hepatitis, and epidemic encephalitis [96]. Our group first synthesized a serious of isaindigotone derivatives to explore their effects on G-quadruplex stability and selectivity. The unfused aromatic rings and tethered side chains of these derivatives seemed to allow flexible and adaptive conformations, which will help for recognition of telomeric G-quadruplex cores and grooves in a 4:1 binding mode. Moreover, the most active compound 5a (**28**) significantly induced cell senescence and telomere shortening of HL-60 cells and CA46 cells at micromolar concentrations [97]. To better investigate how the planarity of an unfused aromatic ligand impacts its quadruplex binding properties, the aliphatic ring size in the middle core of these ligands was modified. We found that enlarging the ring will lead to decreased planarity of the ligand and result in decreased G-quadruplex binding affinity and stabilization ability [98]. In addition to being designed as potential anti-cancer drugs, the isaindigotone skeleton was also modified as a fluorescent probe for the detection of G-quadruplex structures. Incorporating thiazole orange (**29**) [99] or a coumarin–hemicyanine fluorophore (**30**) [100] to the isaindigotone framework lead to a big leap from colorimetric probe to colorimetric and fluorescent dual probe for detecting G-quadruplexes. In another series of quinazolinone derivatives (**31**) recently reported to stabilize *c-KIT* G-quadruplex, the best compound 31e reduced the transcription of *c-KIT* by 52.5% and exhibited significant cytotoxicity in a gastrointestinal stromal tumor cell line [101]. SAR analysis showed that the expanded aromatic system, via the introduction of a benzene ring, a benzylidene group and two cationic amino side chains into the quinazolone moiety, not only maximizes the stacking interaction of the derivatives with G-quartet but also incorporates features of flexibility that prevent it from intercalating into the duplex DNA.

3.5. Porphyrins and their derivatives

Porphyrins are a group of natural organic compounds. One of the best-known porphyrins is heme, which is the pigment in red blood cells [102]. The porphyrins were initially well known as duplex DNA binding agents [103]. Since then they have been thoroughly investigated for their interactions with G-quadruplex DNA following the pioneering work of Hurley group in 1999 [104]. The cationic *meso*-tetrakis-(N-methyl-4-pyridyl)-porphyrin TMPyP4 (**32**, Fig. 10) is the most representative example of this family and has been extensively investigated for its selectivity, binding mode and pharmacological effects. The TMPyP4 ring has been assumed to be appropriate to interact with the G-quartet of G-quadruplex structures through π–π stacking interactions. The

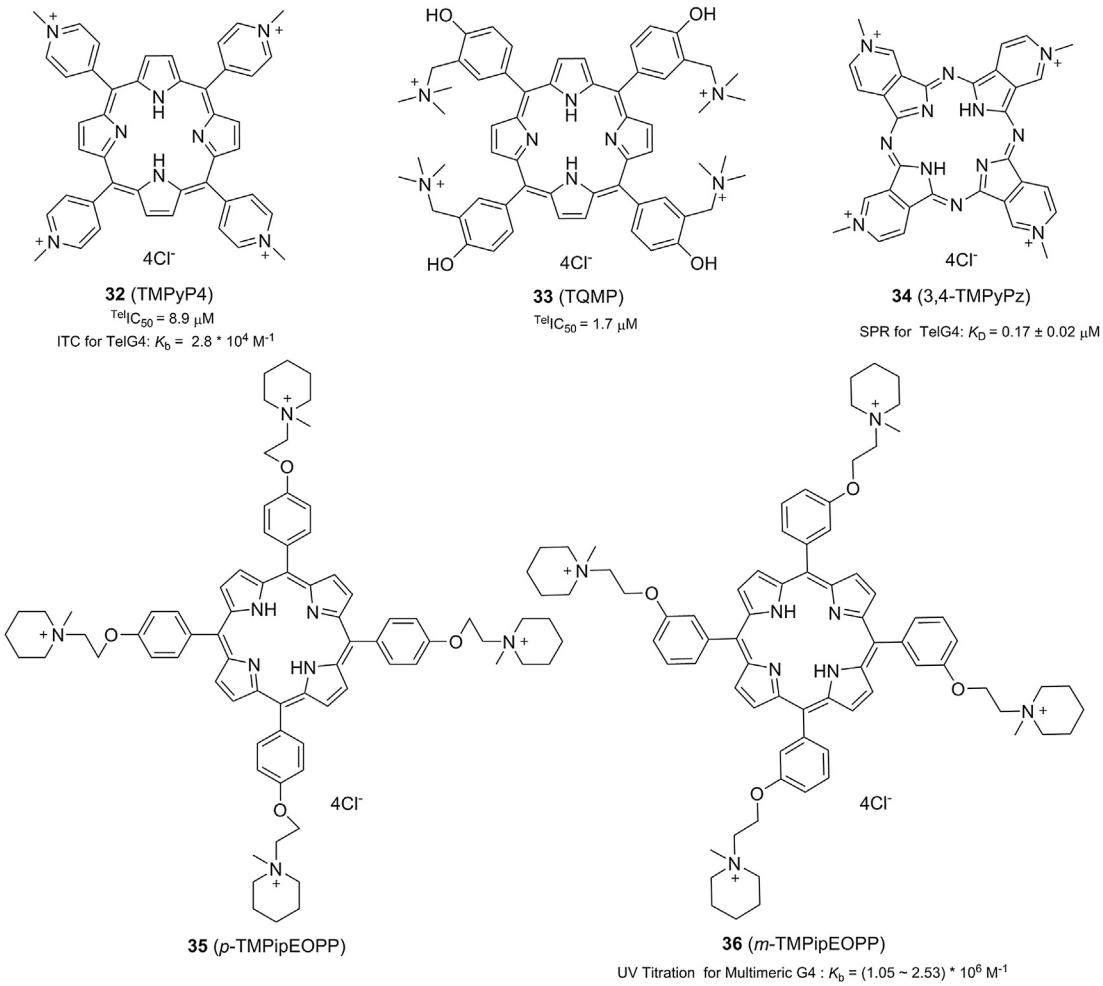


Fig. 10. Structures of porphyrin derivatives: TMPyP4 (**32**), TQMP (**33**), 3,4-TMPyPz (**34**), *p*-TMPipEOPP (**35**), and *m*-TMPipEOPP (**36**).

binding modes as well as the binding stoichiometry in TMPyP4-G-quadruplex complexes continue to be controversial in recent years, the binding modes including intercalation between adjacent G-quartets [105], stacking onto external G-quartets [106], and external stacking on TTA nucleotides without any direct interaction with G-quartets [107] have been discussed. TMPyP4 was also found to stabilize different G-quadruplexes, to convert anti-parallel topologies into parallel G-quadruplex forms [106], to inhibit telomerase with an $^{tel}IC_{50}$ of 6 μM [108], to down-regulate oncogenes, such as, *c-MYC* [109] and *KRAS* [110], and kill a panel of cancer cells [111–113]. Particularly, TMPyP4 was reported to destabilize the G-quadruplex of both the DNA and the RNA $(CGG)_n$ repeats of *FMR1* [114,115], and to unfold RNA G-quadruplexes, such as the one present in the *MT3-MMP* mRNA, this led to enhanced levels of translation in a dual reporter gene construction [116], indicating a complicated interaction mode of TMPyP4 with the G-quadruplex. TMPyP4 was also found to promote the formation of the i-motif DNA structure, which is a DNA secondary structure formed by C-rich strands [117,118]. Based on the non-selective interaction of TMPyP4 with duplex DNA, DNA G-quadruplex, RNA G-quadruplex and even i-motif, more details are needed to validate the interaction properties and biological effects of cationic porphyrins.

To identify porphyrin derivatives with improved binding selectivity for G-quadruplexes, further studies have been performed with a primary focus on the synthesis of metal–porphyrin complexes and modification at the N-methylpyridyl positions. TQMP (**33**) shows 30-fold more selectivity than TMPyP4 through efficient groove and loop binding, which mainly depends on a flexible positively charged ammonium group and the phenolic hydroxyl group of the ligand [119]. Tetramethylpyridinium porphyrazine, TMPyPz (**34**), shows 100-fold higher binding affinity to human telomeric G-quadruplexes and higher selectivity towards the G-quadruplex over duplex DNA (by up to 30-fold) [120]. Recently, a cationic porphyrin derivative with four large side arm substituents termed *p*-TMPipEOPP (**35**) and *m*-TMPipEOPP (**36**) were synthesized and investigated for their specific recognition and stabilization of monomeric and multimeric G-quadruplexes [121–123]. *p*-TMPipEOPP was shown to bind to multimeric G-quadruplexes by two modes: sandwich-like end-stacking mode and pocket-dependent intercalative mode, while *m*-TMPipEOPP binds to multimeric G-quadruplexes by a side binding mode. These results indicate that the slight structural difference accounts for the markedly different multimeric G-quadruplex recognition specificities of porphyrin derivatives.

3.6. Macrocyclic alkaloids and their derivatives

An effective telomeric G-quadruplex stabilizer termed telomestatin (**37**, Fig. 11), which is a macrocyclic natural product, was isolated from *Streptomyces anulatus* in 2001 by Shin-ya et al. [124]. This stabilizer is composed of six oxazole rings and one thiazolone ring. The hydrophobicity, near complete flatness, and the optimal size of telomestatin provide effective overlap with the four guanines when it stacks on top of the G-quartets using π-stacking interactions. One telomestatin molecule stacks at each terminal G-quartet within a quadruplex to give a 2:1 complex [125]. Due to its unique structural features, telomestatin exerts high selectivity towards G-quadruplex over duplex DNA (>70-fold preference) and shows the greatest *in vitro* telomerase inhibitory activity ($^{tel}IC_{50}$ = 5 nM) of the reported telomeric G-quadruplex ligands [126]. Biological studies reveled that telomestatin effectively interacted with telomeric G-quadruplex, dissociated TRF2 and

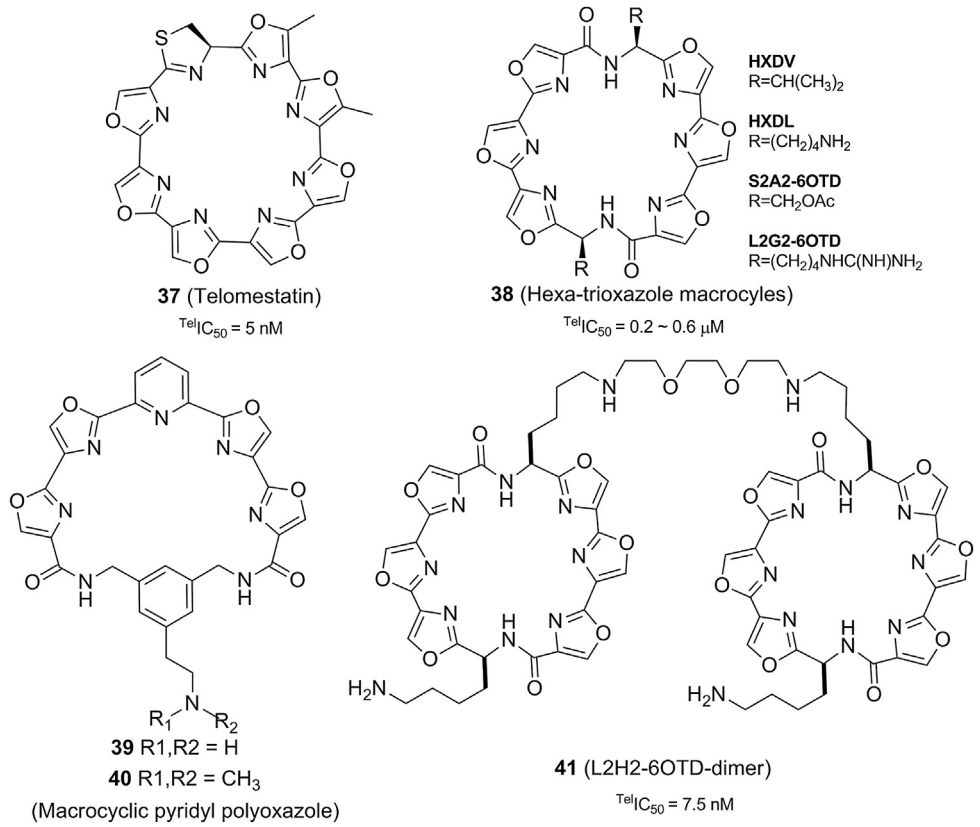


Fig. 11. Structures of macrocyclic alkaloids and their derivatives: telomestatin (**37**), hexa-trioxazole macrocycles (**38**), macrocyclic pyridyl polyoxazole (**39** and **40**), and L2H2-6OTD-dimer (**41**).

POT1 proteins from the telomere and thus led to telomere shortening and cancer cell growth suppression [29]. Because telomestatin has anti-proliferative activities against a wide range of cancer cell lines, including cancer stem cell [127], while it has little effect on normal cells, this macrocycle is an interesting anti-cancer agent [126,128,129]. Due to the low productivity rate and the poor water solubility of telomestatin, synthesis of telomestatin-like compounds has attracted much research attention.

Hexa-trioxazole macrocycles (**38**), composed of two symmetric trioxazoles linked by amino acids, was found to stabilize G-quadruplexes significantly by binding at both external sides of G-quartets [130]. The amino side chain makes HXDV more water soluble and improves its interaction with the G-quadruplex [131]. Especially, a pyridyl-polyoxazole moiety linked by a 1,3-bis(aminomethyl) phenyl group with a 5-(2-aminoethyl)-substituent (**39**) or a 5-(2-dimethylaminoethyl)-substituent (**40**) displayed great cytotoxic potency (with an average IC_{50} value of 30 nM and 40 nM, respectively), and **39** exhibited exquisite selectivity to stabilize the G-quadruplex DNA while **40** stabilizes G-quadruplex RNA more effectively [132]. A 6OTD-dimer (**41**) linked by a bis-amide linker was synthesized for dual stacking at both ends of the G-quartets. It was more selective towards the G-quadruplex than the monomer and showed potent inhibitory activity against telomerase, with an $^{tel}IC_{50}$ value of 7.5 nM [133]. Although the limited availability from natural sources and the poor scalability in chemical synthesis along with its intrinsic characteristics such as low water solubility hamper further biological development of telomestatin, the macrocyclic ligands show effective binding ability and biological effects to inhibit cancer cells. Macrocycles with better pharmacological and physicochemical properties are highly expected in the near future.

3.7. Other alkaloids

In addition to the alkaloids mentioned above, several interesting heterocyclic alkaloids have been identified and tested for their G-quadruplex binding ability. Distamycin A (**42**, Fig. 12) is an oligopeptide antibiotic biosynthesized by *Streptomyces distallicus* that has been known to bind to the minor groove in the A/T rich region of duplex DNA in a drug/DNA stoichiometry of 2:1 [134]. Randazzo et al. first reported the NMR structure of distamycin A/$[d(TGGGGT)]_4$ complex and confirmed that distamycin A was a typical groove binder of a G-quadruplex [135]. The binding mode was that four distamycin A molecules formed two dimers and bound simultaneously to two opposite grooves of the quadruplex in a 4:1 binding mode [136]. Another natural antibiotic actinomycin D (**43**) was found to be a telomeric G-quadruplex binder with intrinsic association constants of approximately $2 \times 10^5\ M^{-1}$, a 2:1 molecularity [137] and to be a *c-MYC* G-quadruplex stabilizer to decrease *c-MYC* transcription [138]. The nonplanar steroidal derivatives were reported as G-quadruplex stabilizers in recent years. Steroid FG (**44**), a funtumine derivative substituted with a guanylhydrazone moiety, stabilized telomeric G-quadruplexes with a moderate ΔT_m of 13.8 °C at 10 μM concentration and induced a degradation of the telomeric G-overhang and telomere shortening in HT1080 tumor cells [139]. Two other non-planar compounds without side chains, peimine (**45**) and peiminine (**46**), showed a selective stabilizing effect on parallel stranded G-quadruplexes and interact with telomeric G-quadruplexes by a groove binding mode [140]. These studies provided novel insight into the development of non-planar G-quadruplex stabilizing ligands.

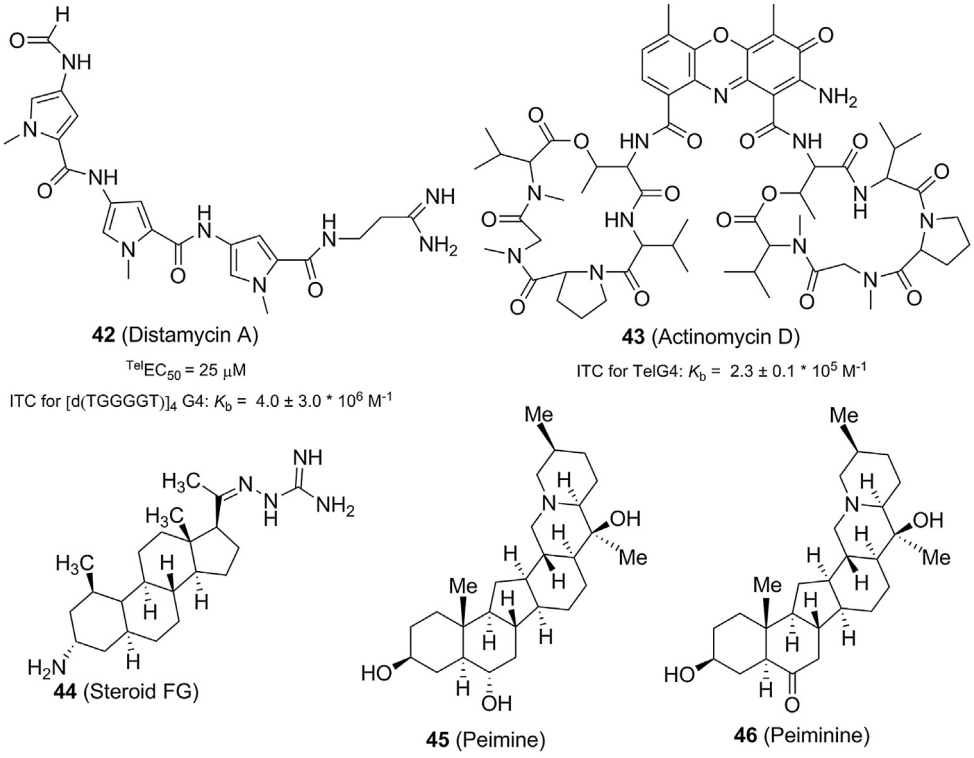


Fig. 12. Structures of distamycin A (**42**), actinomycin D (**43**), steroid FG (**44**), peimine (**45**) and peiminine (**46**).

4. Conclusions and perspectives

Over the past decades, G-quadruplex research has rapidly moved from fundamental to clinical studies. Research data on the structure and biological functions of the G-quadruplex, the innovation of new methods and the upgrading of fine equipment have sped up the development of this field. The G-quadruplex ligands have been shown to shorten telomeric length, to repress the transcriptions of certain oncogenes and to suppress the translation of RNA by binding to and stabilizing the G-quadruplex structures. The consequence of these biological effects can lead to anti-cancer activity. Further validation of the existence of G-quadruplexes *in vivo* and the uncovering of the biological role as a potential anti-cancer drug target, has encouraged scientists to discover novel chemical entities that can bind to the G-quadruplex. However, up to date, the clinical trials of DNA G-quadruplex binders are rarely reported. The reasons are complex, including inherent difficulties in drug discovery process, difficulties in translation from *in vitro* data to *in vivo* data and the side-toxicity of the small molecules because of their poor selectivity, or nonspecific interactions with the duplex DNA.

The basic element of nitrogen heterocycles greatly promotes alkaloids to be excellent G-quadruplex ligands by π–π stacking with the G-quartet. Alkaloids provide the types of skeletons that greatly match with the G-quadruplex structure. Many studies have reported effective G-quadruplex ligands are modified from alkaloids. Moreover, with the advantage of polymorphism, heterocyclic alkaloids provide a huge library for the large scale screening of potential G-quadruplex ligands. In this review, we focus on the design ideas and biological application of various kinds of heterocyclic alkaloids. These compounds include quinolines, acridines, acridones, isoquinolines, quinazolines, quinazolinones, porphyrins, macrocyclic alkaloids and their derivatives. Most of these compounds have a planar conjugated chromophore, which help to achieve excellent π–π stacking with the G-quartet, such as the quindoline and acridine derivatives. The planar molecules with positive charge usually show a higher affinity with G-quadruplex by extra electrostatic interaction, such as the acridinium and porphyrin derivatives. However, most of these compounds inevitably exhibit certain interaction with duplex DNA. In contrast, compounds with flexible skeletons or non-planer structures, such as bis-quinoline, bis-quinolinium and steroid, show higher selectivity towards G-quadruplex. Thus, more efforts could be taken to develop these types of heterocyclic alkaloids and explore their biological effects on G-quadruplex targeting. This may be a new way to develop more promising drugs targeting G-quadruplex.

For the design of more effective and promising G-quadruplex ligands, there remain other challenges, including: (1) Biological functions of G-quadruplexes in cancer cell as well as normal somatic cell require further illumination. (2) More valid methods are needed for evaluating the *in vivo* effects of G-quadruplex ligands. (3) Highly selectivity compounds for a given class of G-quadruplex is needed. There is still a long way to go, however, given the rapidly accumulating data on G-quadruplex structure and biological functions and rapid development of G-quadruplex ligands, we are confident that a wealth of new drugs that are less cytotoxic and have higher selectivity will emerge in the near future.

Acknowledgments

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