A hitchhiker's guide to G-quadruplex ligands

David Monchaud and Marie-Paule Teulade-Fichou*

Received 25th September 2007, Accepted 23rd October 2007
First published as an Advance Article on the web 14th November 2007
DOI: 10.1039/b714772b

Over the past decade, nucleic acid chemists have seen the spectacular emergence of molecules designed to interact efficiently and selectively with a peculiar DNA structure named G-quadruplex. Initially derived from classical DNA intercalators, these G-quadruplex ligands progressively became the focal point of new excitement since they appear to inhibit selectively the growth of cancer cells thereby opening interesting perspectives towards the development of novel anti-cancer drugs. The present article aims to help researchers enter this exciting research field, and to highlight recent advances in the design of G-quadruplex ligands.

Introduction

After one decade of speculation concerning its *in vivo* importance, G-quadruplex-DNA (Fig. 1) has attracted exceptional attention from all the nucleic acid research community. This peculiar DNA-arrangement has been thoroughly reviewed recently,[1] both in terms of structural investigations[2] and of biological implications[3] and also in terms of potential applications towards nano-technologies.[4]

Despite the fact that direct proof for its *in vivo* existence is still sparse,[5] a growing body of evidence for the biological relevance of G-quadruplex-DNA emerges from the recent literature: (*i*) the putative G-quadruplex-forming sequences are thoroughly distributed along the human genome (370 000 sequences,[6] probably even more[7]), and their involvement within an extended duplex-DNA is compatible with their folding into quadruplex-structures;[8] (*ii*) these sequences are particularly found at telomeric regions and gene promoters (more than 40% of human genome promoters present at least one quadruplex-forming sequence);[9] (*iii*) the putative quadruplex formation correlates with a certain gene expression level;[10] and (*iv*) an array of proteins with various

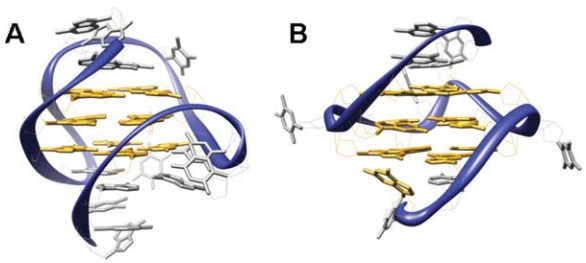


Fig. 1 Example of quadruplex-polymorphism: NMR structures of quadruplexes from the human telomeric (**A**, PDB entry: 2HY9) and c-myc (**B**, PDB entry: 1XAV) sequence (guanines in gold).

Institut Curie, CNRS UMR176, Section Recherche, Centre Universitaire Paris XI, Bât. 110, 91405, Orsay, France. E-mail: marie-paule.teulade-fichou@curie.fr; Fax: +33 1 69 07 53 81; Tel: +33 1 69 86 30 86

David Monchaud

David Monchaud received his PhD in organic chemistry in 2002 at the University of Geneva (Switzerland) with Professor Jérôme Lacour. After a first post-doctoral experience in medicinal chemistry with Professor Bernard P. Roques (Paris, France), he joined the group of Professor Jean-Marie Lehn at the College de France (Paris, France) for a second post-doctoral experience under the supervision of Dr Marie-Paule Teulade-Fichou on G-quadruplex ligands. He was then appointed as CNRS researcher, and recently, he moved with Dr Teulade-Fichou to the Institut Curie (Orsay, France) to develop an interfacial chemistry related to G-quadruplex-DNA.

Marie-Paule Teulade-Fichou

Marie-Paule Teulade-Fichou is a Research Director at CNRS and currently the co-director of the laboratory of Chemistry of the Institut Curie, France. She was educated at University P. & M. Curie in Paris and took up a position at CNRS, in 1986, to develop research on new organophosphorus compounds at the Ecole Polytechnique in the group of Prof. F. Mathey (Palaiseau). In 1991 she joined the group of Prof. J.-M. Lehn at the College de France, where she developed macrocyclic chemistry towards recognition of nucleic acids. Her current interest is focused on the design of new nucleic acid targeted drugs for anticancer research and for elucidating DNA-related molecular basis of cancer.

functions (nucleases, helicases, resolvases) has been shown to interact specifically with G-quadruplexes.[3f,k]

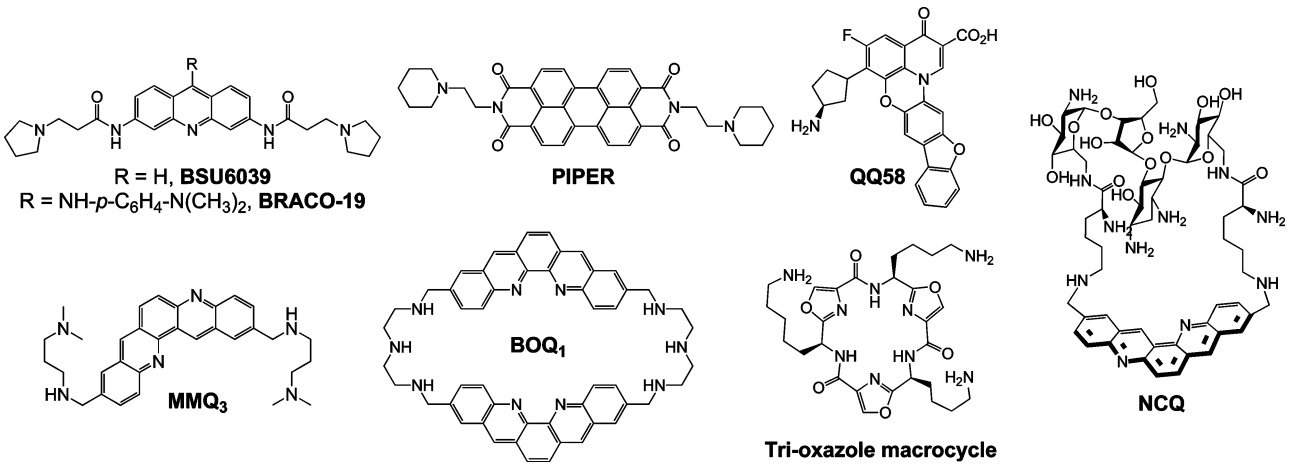
Most importantly, the implication of G-quadruplex is evoked in several biological dysfunctions that selectively alter the integrity of cancer cells.[3f,i,k] In particular, the formation of G-quadruplex-DNA at the end of telomeres has been reported not only to impede the telomerase association and activity (due to the enzyme inability to bypass the folded form of its DNA-substrate) but also severely to increase the genomic instability by hampering normal recognition of telomere-associated proteins with their targets.[3f,i,k] The regulatory potential of G-quadruplexes towards cancer cell growth is also strongly substantiated by their possible formation in the promoter regions of several human genes (such as the retinoblastoma susceptibility,[11] insulin,[12] muscle-specific,[13] vascular endothelial growth factor,[14] hypoxia inducible factor 1α,[15] fragile X mental retardation genes[5b,16]) and oncogenes (such as c-myc,[17] k-ras,[18] bcl-2,[19] c-kit,[20] or RET oncogenes[21]). Consequently, the possibility of building novel anti-cancer therapeutic strategies with G-quadruplex-DNA as the cornerstone is currently under investigation.

Therefore a general consensus is that G-quadruplex binders that stabilize the G-quadruplex structure could pave the way for the discovery of novel anti-cancer agents. The quadruplex-stabilization occurs, in most cases, *via* π–π stacking and electrostatic interactions resulting in the binding of the ligand (usually a flat aromatic molecule) on the G-quartet constitutive of the external-face of the quadruplex. This binding mode (external stacking) has been thoroughly discussed[1] since it represents a unique feature of quadruplex recognition as compared to other DNA forms. Given the large area of the G-quartet, an efficient G-quadruplex ligand should feature a large aromatic surface, much larger than that of a duplex binder to improve the aromatic–aromatic overlap and provide selectivity. Electrostatic interactions between positively charged ligands and the G-quadruplex-DNA scaffold also strongly participate in stabilization. However due to the polymorphism of the quadruplex backbone arrangement (Fig. 1)[2] and the lack of data on the electrostatic potential of the four grooves, these interactions are much less understood than those occurring with duplex-DNA. Finally, little is known concerning the influence of the central cations on ligand binding. So far, the rational design of G-quadruplex-interacting compounds has been guided by two criteria (*i.e.* π-stacking and electrostatics) but also by somewhat empirical approaches. Globally, the numerous ligands synthesized to date can be classified into four different categories on the basis of their cationic nature, *i.e.* cationic (1) upon *in situ* protonation of an amine appendage, (2) *via N*-methylation of an aza-aromatic moiety, (3) thanks to the presence of a metal centre, or (4) non-cationic ligands.

With the present article, our intention is not to cover exhaustively the G-quadruplex ligands field, but more to provide a field guide for bio-organic chemists allowing them to enter the exciting G-quadruplex ligand research area. The reader will find the structure, the essential biophysical and biological data and importantly, the references related to the most recently reported and cited ligands. It is also worth noting that the present article is focused on the structural design of ligands and on their molecular interactions with G-quadruplex, whereas the particular notion of telomerase inhibition, although mentioned, is not discussed in detail (for a recent review, see Ref. 3*k*).

In situ protonated G-quadruplex ligands

The key issue in the development of compounds that target G-quadruplex-DNA is to conceive large flat aromatic systems prone to π-stacking with a G-tetrad platform, while retaining reasonable water solubility. In other words, the molecule has to exhibit both hydrophobic and hydrophilic characteristics. A usual way to ensure this duality is to introduce protonable sidearms (*e.g.* amine groups) around an aromatic core; the molecule is then water-soluble, with the charge(s) far from the hydrophobic centre. This line was followed 10 years ago by Neidle, Hurley and co-workers with the promotion of a bisamidoanthraquinone as G-quadruplex ligand and telomerase inhibitor.[22] Besides this work, several pioneering reports concerning interaction of dyes with quadruplexes appeared in the literature and particularly worth mentioning is the study from Shafer and co-workers on DODC (3,3′-diethyloxadicarbocyanine).[23] The bisamido-anthraquinone family has been further developed and subsequently evaluated by cytotoxicity and direct telomerase inhibition assays, revealing IC_{50} values in the low micromolar range.[24] However, these studies concluded that the quadruplex- *vs.* duplex-DNA selectivity of this series was insufficient for further biological applications. To circumvent selectivity problems, Neidle and coworkers progressively modified the core and the sidearms of the initial ligands: from anthraquinone to fluorenone,[25] then acridone[26] and acridine.[27] A member of the 3,6-disubstituted acridine series was particularly useful for the G-quadruplex ligand design, **BSU6039** (Scheme 1), since a crystal structure of its complex with G-quadruplex was obtained (Fig. 2).[28] As expected, this structure showed an interaction dictated by hydrophobic–π-stacking interactions between the flat aromatic core of the ligand and two guanine residues of the accessible G-tetrad doubled by electrostatic interactions between the two protonable sidechains of the ligand and the quadruplex-grooves. On this basis, an optimized prototype was designed, **BRACO-19** (Scheme 1), able to interact concomitantly with three G-quadruplex grooves thanks to three side-arms.[29] This optimized target adaptation appears through the high level of quadruplex-stabilization, evaluated by FRET (fluorescence resonance energy transfer)-melting assay†,[30] ($\Delta T_{1/2} = 27$ °C) and selectivity evaluated by the SPR (surface plasmon resonance) method,[31] which revealed a 31-fold binding preference for the quadruplex-structure. In addition, a strong potency for telomerase inhibition was evaluated by TRAP (telomeric repeat amplification protocol)[3k,32] assay (IC_{50}-TRAP = 115 nM). Worth pointing out is that the TRAP assay has been very recently demonstrated to be somewhat biased by G-quadruplex-forming primers and thus may not fully reflect telomerase inhibition.[33] Nevertheless, TRAP results will be indicated here since they have been used as evaluation parameters in an overwhelming majority of the cited articles.[3k,33] Further biological investigations have recently demonstrated the efficiency of **BRACO-19** as an inhibitor of cancer cell proliferation,[34] which has been somewhat limited by pharmacological parameters (such as cellular uptake or membrane permeability).[35] These limitations seem to be on the way of being circumvented, by modification of the 9-amino substituent of the **BRACO-19** (from an aniline to a difluorobenzylamine group).[36] Thus, the simple acridine motif appears to be very valuable for G-quadruplex recognition, provided that its substitution pattern and the protonation ability of the central ring nitrogen are



Scheme 1 Selected cationic G-quadruplex ligands upon *in situ* protonation of amino-appendages.

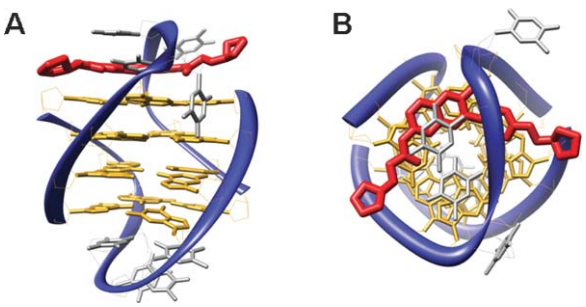


Fig. 2 Side- (**A**) and top-views (**B**) of the X-ray structure of **BSU6039** complex with bimolecular quadruplex-DNA $(d[G_4T_4G_4])_2$ (PDB entry: 1L1H).

optimized: the 2,7-dipropylamino-acridine being for example a very poor G-quadruplex ligand.[37]

Hurley's orientations pointed toward more extended aromatic molecules. In 1998, Fedoroff, Kerwin, Hurley and coworkers reported on the association studies of G-quadruplex-DNA and the perylene diimide **PIPER** (Scheme 1).[38] This molecule is characterized by a broader hydrophobic core, with two external amine appendages. This family of compounds was shown to be moderately active as telomerase inhibitors (IC_{50}-TRAP ~20 μM) but has been extensively studied by Hurley's then Kerwin's group, for the peculiar relationship between aggregation state and quadruplex- *vs.* duplex-DNA selectivity. Indeed the latter increases from almost none to 42-fold quadruplex selectivity under a free (pH 7) or aggregated state (pH 8.5).[17c,39] Recent extensions confirmed that hydrosolubility does not necessarily imply better *in vitro* characteristics, as demonstrated by multi-substituted perylene and coronene ligands, either symmetrically substituted[40] or not.[41]

Hurley's group also diverted the quinobenzoxazines from their usual anti-bacterial activity, to propose the fluoroquinolone **QQ58** (Scheme 1) as a G-quadruplex ligand.[42] A NMR study confirmed the stacking onto an external G-tetrad as the main binding mode, and extended biological investigations demonstrated the cellular activity of such ligands. Other compounds from various natural sources and well-known for their affinity for duplex-DNA have been tested as G-quadruplex ligands: these are intercalators such as **daunomycin**, which wonderfully crystallized as a trimer with G-quadruplex (Fig. 3),[43] or groove binders such as **distamycin**, whose NMR structure demonstrated quite a surprising binding mode with quadruplex, based on two molecules lying side by side in an anti-parallel fashion either in the groove[44] or on the terminal G-quartet.[45] Several flavonoid[46] or steroid derivatives,[47] as well as marine alkaloids such as **ascididemin** or **meridine**[48] have also been shown to bind quadruplexes with variable efficiency.

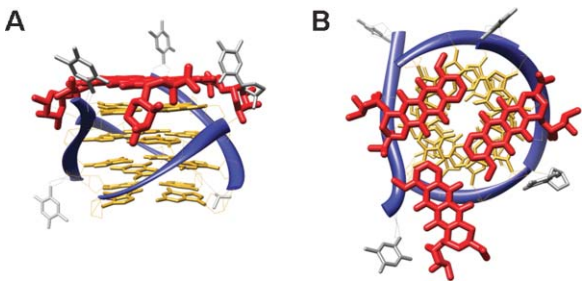


Fig. 3 Side- (**A**) and top-views (**B**) of the X-ray structure of the **daunomycin** trimer with tetramolecular quadruplex-DNA $(d[TG_4T])_4$ (PDB entry: 1O0 K).

Another dimension in the G-quadruplex ligand design was introduced in 2001 by Teulade-Fichou, Mergny and coworkers with the use of pentacyclic quinacridines that display a crescent shape likely to maximize the overlap with the guanines of the accessible G-quartet. $\mathbf{MMQ_3}$ (Scheme 1) was the leading compound of the quinacridine family, which shows remarkable G-quadruplex stabilization ($\Delta T_{1/2}$ = 20 °C) and high telomerase inhibitory activity (IC_{50}-TRAP = 28 nM).[49] Recently, an NMR structure was determined with $\mathbf{MMQ_1}$, the dipropylamino analogue of $\mathbf{MMQ_3}$, and a tetramolecular quadruplex (Fig. 4).[50] This study not only shows the simultaneous overlap of three guanines by the quinacridine unit, but also pinpointed the role of the protonated sidearms, which actively participate in quadruplex recognition *via* interactions in the grooves. A dimeric macrocyclic quinacridine was subsequently proposed, $\mathbf{BOQ_1}$ (Scheme 1), that proved to be an improved quadruplex-stabilizer ($\Delta T_{1/2}$ = 28 °C), with a better overall selectivity than the monomeric series (~10-fold, evaluated by SPR) and an efficient telomerase inhibitor (IC_{50}-TRAP = 130 nM).[51]

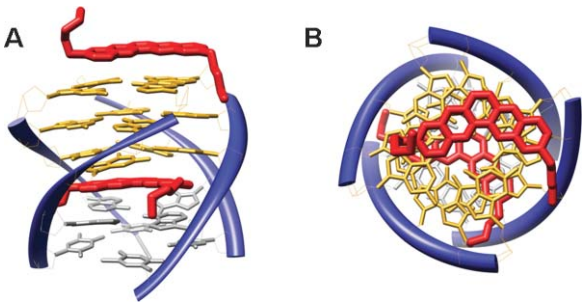


Fig. 4 Side- (**A**) and top-views (**B**) of the NMR structure of $\mathbf{MMQ_1}$ complex with tetramolecular quadruplex-DNA ($d[T_2AG_3T])_4$ (PDB entry: 2JWQ).

This selectivity, attributed to the enhancement of the ligand aromatic surface, is also likely a consequence of the steric hindrance of the macrocyclic scaffold that impedes duplex binding. Recently, it was suggested that $\mathbf{BOQ_1}$ can adopt a semi-closed conformation that might result in a particular binding mode, probably based on specific interactions with loops.[51c] Interestingly, the efficiency of such a dimeric macrocyclic scaffold appears clearly dependent on the nature of the aromatic unit, since macrocycles derived from quinacridine ($\mathbf{BOQ_1}$) or acridine (**BisA**)[37] are efficient quadruplex binders, whereas those comprised of phenanthroline or naphthalene units, which have poor ability to stack on DNA bases,[37,50] lead to more modest results.[52]

Subsequently, the crescent-shape particularity of quinacridine was found in several other ligands, such as indoloquinolines (such as **PSI99A**),[53] **cryptolepine** and analogues,[54] quindolines (such as **SYUIQ-5**) whose efficiency has been demonstrated on telomeric and *c-myc* promoter quadruplexes,[55] or triazacyclopentaphenantrene.[56]

Some of the previous examples perfectly illustrate the difficulty in obtaining ligands with high quadruplex-selectivity. Following the way paved by Wheelhouse and co-workers with biarylpyrimidines,[57] Neidle and co-workers succeeded in combining good overlap of G-quartet and simple synthetic access, with ligands assembled *via* click-chemistry.[58] The resulting bistriazole derivatives are good quadruplex-stabilizers ($\Delta T_{1/2}$ between 15 and 19 °C) with a high degree of selectivity but they appeared to be moderate telomerase inhibitors (IC_{50}-TRAP between 13 and 20 μM).

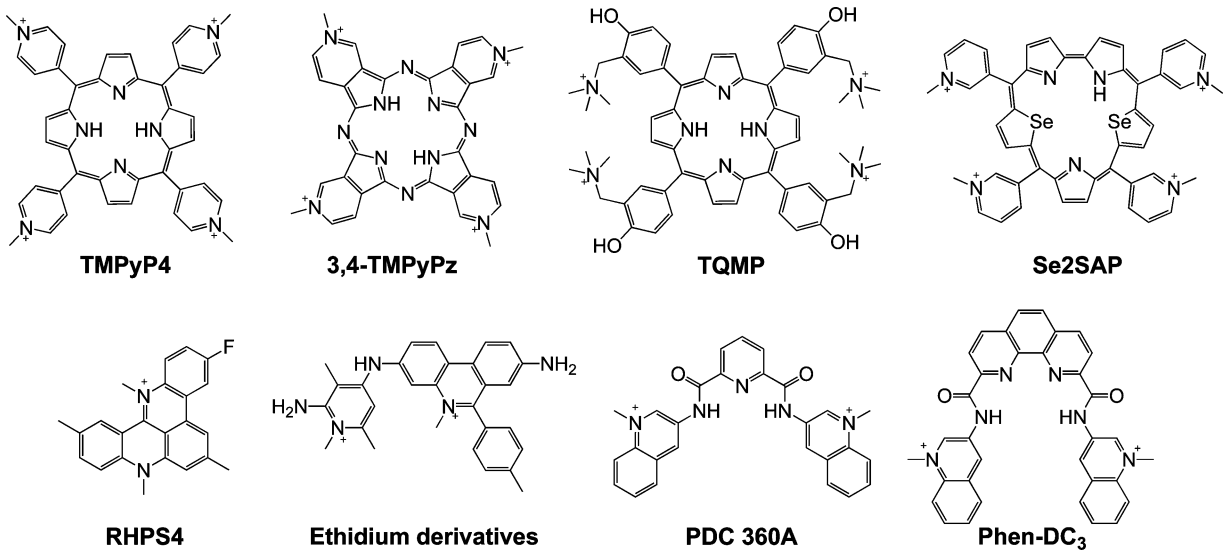
A novel trend in the G-quadruplex ligand design is currently emerging based on the enhancement of G-quadruplex recognition by the introduction of additional structural elements. This relies on the fact that quadruplex- *vs.* duplex-DNA selectivity has to be addressed in terms of the difference between the surface area of a G-quartet and of a base-pair, but also in terms of loop- and groove-recognition. This basic principle was applied to the conception of the neomycin capped quinacridine series (**NCQ**, Scheme 1) that has been designed to concomitantly target the G-quartet and the loop of a quadruplex structure with the quinacridine moiety and the neomycin motif respectively.[59] The preferential binding of **NCQ** to loop-containing quadruplexes as compared to non-loop containing ones was evidenced. This result along with the good quadruplex stabilization ability of the series ($\Delta T_{1/2}$ = 14 °C) and its strong telomerase inhibitory activity (IC_{50}-TRAP = 200 nM) fully validates this 'ditopic' design. The efficiency of **trioxazole macrocycles** (Scheme 1) originates probably in a similar phenomenon, thanks to the three amino appendages located on the same face of the macrocycle and putatively implicated in loop and groove interactions.[60] Interestingly, these secondary interactions raise the possibility of selectively stabilizing a particular type of quadruplex-DNA. This is illustrated by the binding preference of the tri-oxazole macrocycles for the quadruplex formed by the c-kit sequence as compared to the human telomeric one. This particular macrocyclic oligoamide scaffold has been very recently confirmed as valuable for the design of efficient G-quadruplex ligands by two independent studies.[61] Finally, Balasubramanian and coworkers also succeeded very recently in targeting another structural element of the quadruplex architecture, namely the central cation channel, thus opening interesting perspectives as for a ligand-mediated control of the quadruplex polymorphism.[62] However, and as mentioned above, interactions of ligands with peculiar quadruplex elements (*i.e.* loops, grooves, cation channel) are still poorly investigated, suffering from the availability of firm structural data.

Finally, an additional level of selectivity was very recently reached, with the use of isoalloxazines as c-kit selective quadruplex-ligand.[63] In this study, the duplex- *vs.* quadruplex-selectivity was combined with a clear intra-quadruplex selectivity (up to a 14-fold preference for the quadruplex formed by the c-kit sequence as compared to the human telomeric one), thereby opening an avenue to the design of a second generation of ligands able to selectively alter the expression of a given gene.

N-Methylated aromatic G-quadruplex ligands

Beyond quaternization of amine side-chains *via in situ* protonation, an alternative pathway was thoroughly exploited with the use of *N*-methylated ligands *i.e.* quaternized on the aromatic ring nitrogens. The success of this design relies on the double advantage of *N*-methylated aza-aromatic moieties, *i.e.* affording water solubility without the need for cationic side-chains and increasing the π-stacking ability of the ligand thanks to the reduction of the electron density of the aromatic part. **TMPyP4** (Scheme 2) is the pivotal example of this family of ligands. This tetracationic porphyrin has been extensively studied by Hurley's and co-workers;[14,17d,19b,21,64] **TMPyP4** has been shown for example to have a high affinity for G-quadruplex ($\Delta T_{1/2}$ = 17 °C), to efficiently inhibit telomerase (IC_{50}-TRAP = 6 μM), but also to downregulate the expression of oncogenes (such as *c-myc* or *k-ras*) and to convert antiparallel topologies to parallel forms of quadruplexes. Interestingly, despite the fact that **TMPyP4** soon became known to be poorly- to non-selective for quadruplex-structure,[65] the interest for this particular molecule has never declined, as can be seen by the recent controversy over the nature of the porphyrin-quadruplex complex. Indeed, the diverse binding modes of **TMPyP4** include intercalation between adjacent G-tetrads and stacking of the porphyrin onto the external G-quartet (Fig. 5).[66] Furthermore, X-ray studies have described an unexpected alternative binding mode based on external stacking onto the TTA nucleotides but without any direct contact with G-quartets.[67]

Several structurally-related ligands have been described over the past years: the porphyrin **TQMP**[68] and the porphyrazine **3,4-TMPyPz** (Scheme 2)[69] are two examples of tetracationic macrocycles, which have been shown to bind efficiently to quadruplex-DNA. In particular in the case of the porphyrazine derivative,



Scheme 2 Selected cationic G-quadruplex ligands upon *N*-alkylation of aza-aromatic appendages (counter-ions are Cl^- for **TMPyP4**, **3,4-TMPyPz** and **Se2SAP**, I^- for **TQMP**, **ethidium** derivatives and **PDC 360A**, $MeOSO_3^-$ for **RHPS4**, and $CF_3SO_3^-$ for **Phen-DC$_3$**).

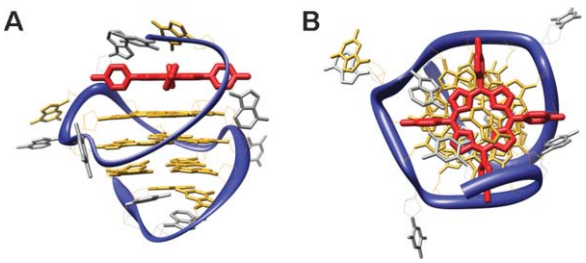


Fig. 5 Side- (**A**) and top-views (**B**) of the NMR structure of **TMPyP4** complex with c-myc derived quadruplex-DNA Pu24I (PDB entry: 2A5R).

a 100-fold increase in affinity as compared to **TMPyP4** has been measured by SPR, but also a significant improvement of the specific recognition of quadruplex-over duplex-DNA was observed (>30-fold preference for quadruplex-DNA). Very recently, **TMPyP4**-related porphyrins carrying 1 to 3 *N*-methylpyridinium arms,[70] as well as structurally-related corroles[71] have also been described.

Finally, an important breakthrough in the porphyrin series came with the design of a diselenosapphyrin **Se2SAP** (Scheme 2), with an expanded porphyrin core.[72] This ligand was shown to bind strongly and selectively to quadruplex-DNA (~50-fold preference for quadruplex-over duplex-DNA, evaluated by SPR) and to convert parallel (*c-myc* sequence) or anti-parallel (human telomeric sequence) topologies to a mixed anti-parallel/parallel hybrid structure. More importantly, this ligand was the first of a promising series able to discriminate among the various forms of the G-quadruplex-DNA. Nevertheless the very low-yielding preparation of the **Se2SAP** may be a serious drawback for future exploration of its biological potential.

Beyond the canonical macrocyclic pattern of porphyrins and derivatives, several small molecules have been reported with quite exceptional properties. Among the first was **RHPS4** (Scheme 2),[73] a *N*-methylated pentacyclic acridinium reported in 2000 by the Stevens group. *In vitro* studies (IC_{50}-TRAP = 330 nM) and *in cellulo* investigations demonstrated the ability of this highly condensed aromatic ligand to decrease telomere length and to act in synergy with the classical anti-cancer agent Taxol. Recently, **RHPS4** has also been reported as an efficient telomere uncapping agent, as well as a telomere binding proteins modulator.[74] Worth mentioning is that **RHPS4** is one of the rare ligands whose complex with G-quadruplex-DNA has been solved by NMR (Fig. 6).[75] As expected, the cationic molecule sandwiches the quadruplex-structure thanks to strong stacking interactions between the ligand and the two external G-quartets of the G-quadruplex.

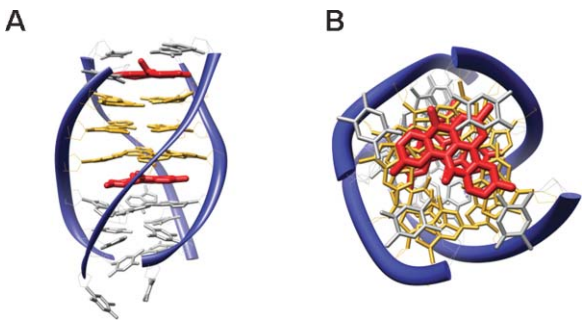


Fig. 6 Side- (**A**) and top-views (**B**) of the NMR structure of **RHPS4** complex with tetramolecular quadruplex-DNA $(d[T_2AG_3T])_4$ (PDB entry: 1NZM).

In 2001, Mergny and co-workers reported on the use of **ethidium** derivatives (Scheme 2) as G-quadruplex ligands.[76] The results obtained in terms of G-quadruplex stabilization ($\Delta T_{1/2} \sim 10$ °C) but mostly in terms of telomerase inhibition (IC_{50}-TRAP = 47 nM) and quadruplex- over duplex-selectivity were quite promising. However, the well-known toxic and mutagenic properties of **ethidium** bromide led these co-workers to develop a novel and safer series of G-quadruplex ligands, derived from triazine.[77] The member of the series known as **12459** and identified by FRET-melting screening was particularly interesting thanks to its ability to stabilize selectively G-quadruplex ($\Delta T_{1/2} = 8$ °C) and to strongly

inhibit telomerase activity (IC_{50}-TRAP = 130 nM). Nevertheless, triazines were also rapidly superseded by the emergence of a structurally-related bisquinolinium series containing a pyridodicarboxamide (**PDC**) core.[78] The **PDC** series has shown quite exceptional properties: the two leading compounds, **307A** and **360A** (Scheme 2), exhibit a high degree of quadruplex-stabilization ($\Delta T_{1/2}$ = 21 °C), an exquisite quadruplex-over duplex-selectivity (>150-fold) and induce efficient inhibition of telomerase (IC_{50}-TRAP = 300 nM). These results are particularly impressive with regard to the structural simplicity of the series and its two-step synthesis. These compounds have been subsequently shown to induce delayed growth arrest and apoptosis in immortalized cell lines.[78b] Remarkably, tritiated **360A** has been shown to localize preferentially at telomeric regions of chromosomes, thus providing new evidence of quadruplex existence in a cellular context.[79] The efficiency of **PDC** derivatives as G-quadruplex binders was also demonstrated recently *via* their ability to induce the challenging formation of tetramolecular quadruplexes and thus to act as molecular chaperones.[80] Finally, a recent extension of this family of ligands was achieved by the synthesis of phenanthroline analogues **Phen-DC** (Scheme 2) that show a perfect geometrical match with a G-quartet.[81] Remarkably, the selectivity of the **Phen-DC** series revealed to be higher than that of **telomestatin** (see below), thus confirming the great potential of the bisquinolinium compounds, which represent an ideal compromise between rapid synthetic access and efficient target recognition.[33,81]

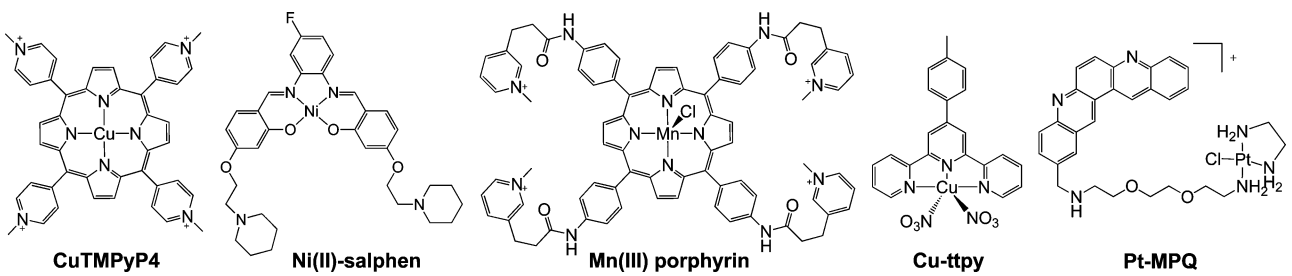
Various other cationic aromatics have also been tested for their ability to bind quadruplex-DNA. Most of these are, or are derived from, well-known duplex-DNA binders such as the anti-tumor agents diphenylcarbazoles (**BVMC**[82] or uncharged analogue[83]) and the bisintercalor **ditercalinium**.[84] Others are identified for specific biological activities such as the antibiotic **berberine** (either the 9-[85] or 13-substituted derivatives[86]) or the closely related **coralyne**.[87] A **fluorenylium** derivative, an oxidized derivative of the vasodilatator papaverine, was also studied.[88] Finally binding of several fluorescent dyes (carbocyanines[23b,89] and engineered derivatives[90] and Hoechst 3358[91]) known as duplex minor groove-binders have shown affinity for quadruplex-DNA. This suggests that external stacking on G-tetrads is not the unique mode for accommodating ligand and that groove interactions can be performed with suitably shaped ligands. A recent report from Wilson and coworkers highlights the use of bifuryl diamidine derivatives (like **DB832**) as agents interacting with the grooves of quadruplexes. In this latter case, the efficiency of the binding process clearly demonstrates that groove recognition is a very promising area that deserves further investigations.[31a]

Metallo-organic G-quadruplex ligands

An alternative to the use of classical organic molecules is currently emerging from the literature, with the use of metallo-organic complexes. This class of ligands is highly interesting thanks to their easy synthetic access and their very promising G-quadruplex binding properties. This approach is based on the assumption that the central metal centre could be positioned over the cation channel of the quadruplex, thereby optimizing the stacking interactions of the surrounding chelating agent with the accessible G-quartet.[92] Their cationic or highly polarized nature is also a clear advantage to promote the association with the negatively charged G-quadruplex-DNA.

The very first reported examples described the insertion of a metal in the central cavity of **TMPyP4**,[64b,c] and their use as Cu(II)-[93] (Scheme 3), Ni(II)- or Mn(III)-complexes.[94] **Mn-TMPyP4** deserves particular attention since it showed a ~10-fold preference for quadruplex-over duplex-DNA, as evaluated by SPR, despite modest telomerase inhibition (IC_{50}-TRAP = 26 μM).[94c] Among the subsequent examples of transition metal complexes like Ru(II)-,[95] Fe(III)-,[96] Zn(II)-[69,97] or Pt(II)-complexes,[98] **Ni(II)-salphen**[92] and **Mn(III)-porphyrin**[99] appeared to stand amongst the most potent reported G-quadruplex ligands (Scheme 3). Their performances are indeed impressive both in terms of quadruplex-stabilization ($\Delta T_{1/2}$ = 33 °C for Ni(II)) and quadruplex-selectivity that were evaluated by FRET-melting assay and SPR. Also worth pointing out is the spectacular 10000-fold quadruplex *vs.* duplex selectivity measured by SPR for the highly cationic **Mn(III)-porphyrin** complex. These compounds also display good level of telomerase inhibition (IC_{50}-TRAP = 120 and 580 nM for Ni(II) and Mn(III)-complexes respectively). Finally very simple structures such as Cu(II) and Pt(II)-terpyridine complexes that can be obtained in one-step or two-step processes have proved to be high-affinity and highly selective G-quadruplex ligands ($\Delta T_{1/2}$ = 15 °C for **Cu-ttpy**, selectivity ~22, Scheme 3).[100] Importantly, this study highlighted that the geometry of the metal centre is a key parameter governing selectivity.

Lastly, the use of a metal moiety grafted in the periphery of the central aromatic core of a G-quadruplex ligand has also been reported for various purposes. Fe(II) terminated appendages have been for example linked to a perylene or a naphthalene diimide core, in the design of probes devoted to quadruplex-selective chemical cleavage[101] or to electrochemical detection of immobilized quadruplex-DNA.[102] Pt(II) complexes have also been exploited to provide additional anchorage of a G-quadruplex binding motif inside the DNA target. This work was stimulated by previous



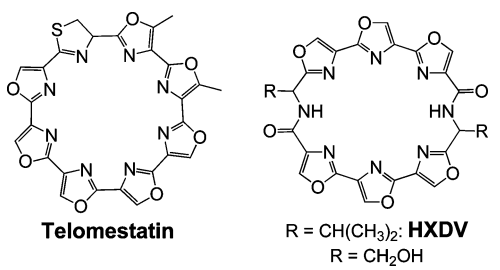
Scheme 3 Selected metallo-organinc G-quadruplex ligands (counter-ions are Cl^- for **CuTMPyP4**, **Mn(III) porphyrin**, and NO_3^- for **Pt-MPQ**).

investigations of Bombard and co-workers that demonstrated the ability of terminal G-quartets to be platinated.[103] This approach has led to the design of the hybrid compound **Pt-MPQ** (Scheme 3) that interacts with quadruplex-DNA *via* a dual covalent–non-covalent binding mode due to the concomitant presence of the quinacridine unit and the platinum moiety.[104] This unprecedented synergism between π-stacking-directed association and a covalent trapping mediated by a mono-functional Pt complex opens up new perspectives for the development of novel quadruplex-binding modes.

Neutral macrocyclic G-quadruplex ligands

Last but not least is the category of neutral ligands. This category is not the largest one but it includes the paradigm for G-quadruplex recognition namely **telomestatin** (Scheme 4). This natural molecule has been isolated from *Streptomyces annulatus* in 2001 by Shin-ya's group[105] and has been subsequently extensively studied since it appears to be one of the most interesting G-quadruplex ligands.[14,19b,21,33,61a,64d,f,72,105,106] Indeed, this polyheteroaromatic 24-membered ring greatly stabilizes G-quadruplex ($\Delta T_{1/2} = 24$ °C) and appears as one of the most selective G-quadruplex ligands: more than 70-fold, regardless of the evaluation technique used. The initial strong enthusiasm for telomestatin was justified by its complete absence of affinity for duplex-DNA due to its neutral character combined with its cyclic shape. The interest in this compound was also strongly stimulated by its exceptional activity as telomerase inhibitor (IC_{50}-TRAP = 5nM) even though some discrepancies in this value have been uncovered in subsequent studies. This efficiency is assumed to rely on a perfect shape adaptation between the macrocycle and its probable target, a G-quartet. Abundant biophysical and biological investigations have been performed and showed that **telomestatin** induces and greatly stabilizes G-quadruplex structures, even in salt-deficient conditions. In addition it inhibits the proliferation of telomerase-positive cells, *via* a modification of the conformation and of the length of telomeres, and a dissociation of telomere-related proteins from telomeres. Nevertheless, one major drawback is that **telomestatin** is difficult to obtain. Its total synthesis has been reported only recently, and the complexity of the proposed pathway seems hardly compatible with large-scale preparation.[107]

Among the few reports of **telomestatin**-like G-quadruplex ligands, two hexa-oxazole macrocyclic ligands have been independently reported by Rice and coworkers[108] and by Shin-ya, Nagasawa and coworkers.[109] These bisamide macrocycles only differ by the nature of the amino-acid used as building-block for their synthesis (*i.e.* valine R = $CH(CH_2)_3$) for **HXDV** or serine (R = CH_2OH, Scheme 4). **HXDV** for example has been found to greatly stabilize G-quadruplex structure ($\Delta T_{1/2} = 17$ °C), without any significant action on duplex- or triplex-DNA, and to have a high cytotoxicity against cancer cell lines. Very recent studies of the **HXDV** association with a quadruplex-forming sequence mimicking the human telomeric sequence confirmed its binding mode (external stacking) and binding stoichiometry (two molecules per quadruplex).[110] Interestingly, the high quadruplex-selectivity of **HXDV** was demonstrated to originate in its particular **telomestatin**-like concave shape.



Scheme 4 Neutral macrocyclic G-quadruplex-ligands.

Despite the fact that macrocyclic compounds like the mesoporphyrin IX **NMM** are known as very quadruplex-selective (counterbalanced by a low affinity),[65a,111] and despite the emergence of structurally-related compounds like **octaethylporphyrin** or related **cyclo[*n*]pyrroles**,[112] these ligands do not display the exceptional properties of **telomestatin**. This is why further examples of neutral polyheterocyclic macrocycles of high affinity and selectivity for G-quadruplex are impatiently expected, in order to better understand the molecular basis underlying their association with the target. Their binding mode, which is obviously purely driven by stacking forces, albeit eventual H-bonding cannot be excluded, represents also a unique feature of ligand–quadruplex interactions. Nevertheless one should be aware that the low (if any) water solubility of this class of compounds combined with sophisticated synthetic accesses might represent key issues for further developments.

Conclusions

In conclusion, targeting G-quadruplex-DNA represents a high scientific challenge since this particular DNA arrangement is highly polymorphic in nature and is weakly abundant as compared to canonical duplex-DNA. Nonetheless, over the past decade, the G-quadruplex ligand field has developed exponentially. A glimpse at the advances made in the design and the synthesis of G-quadruplex ligands leave us convinced that the development of compounds able to discriminate not only G-quadruplex from duplex-DNA, but between the various structures of G-quadruplexes is imminent.

In addition, results obtained quite convincingly pave the way for the exploitation of G-quadruplex ligands as tools to evaluate the therapeutic potential of telomeres and to help elucidate the complex interrelations with the telomere-interacting proteins such as telomerase and capping proteins. At the cellular level, it is already clear that G-quadruplex ligands act selectively on cancer cells and induce specific responses (telomere instability, focused DNA damage) that are different from those of classical duplex binders. Whether these effects result from the activation of telomere-associated pathways remains to be fully demonstrated. Overall research in the field of quadruplex ligands is getting more and more exciting as knowledge increases and as new drugs acting on DNA of cancer cells with a diminished toxicity are expected to be discovered. In the future, G-quadruplex chemists and biologists acting in conjunction, could very well provide new molecular principles that may find applications both in molecular and cellular biology and may contribute to the emergence of novel anti-cancer therapies.

Acknowledgements

The authors would like to thank Dr Nicolas Saettel for the creation of PDB figures, as well as Dr Jean-Louis Mergny and Anne

De Cian from the MNHN group, Drs Sophie Bombard, Jean-Francois Riou and Patrick Mailliet for scientific collaboration and fruitful discussions. The members of the Institut Curie group, particularly Hélène Bertrand, Clémence Allain, Guillaume Bordeau and Anton Granzhan, are greatly acknowledged for the scientific emulation and daily motivation. A special acknowledgement to Douglas Adams for the title inspiration and to Dr Jason Martin for careful reading of the manuscript.

† $\Delta T_{1/2}$ values indicated herein result from the FRET-melting assay performed with a tagged oligonucleotide that mimics the human telomeric sequence (F21T (*FAM*-$G_3[T_2AG_3]_3$-*Tamra*, with *FAM*: 6-carboxyfluorescein and *Tamra*: 6-carboxy-tetramethylrhodamine). The assay has been performed with 0.2 μM of DNA in presence of 1 μM of ligand. Cationic conditions used are 50 mM potassium cacodylate pH 7.4 for **BRACO-19**[29b] and **Ni(II)-salphen**,[92] 60 mM potassium cacodylate pH 7.4 for bis-triazole derivatives,[58] 10 mM lithium cacodylate pH 7.2, 100 mM NaCl for **MMQ_3**,[50] **Cu-ttpy**,[100] **TMPyP4**,[65b] **NCQ**[59] and **telomestatin**,[65b] 10 mM sodium cacodylate pH 7.2, 100 mM LiCl for **BOQ_1**,[51a] **ethidium** derivatives,[76] triazine **12459**[77a] and **360A**.[78b] The $\Delta T_{1/2}$ value indicated for **HXDV** has been evaluated *via* UV-melting experiments carried out with 4 μM of $[T_2AG_3]_4$ and 8 μM in ligand, in 10 mM EPPS buffer pH 7.5, 50 mM KCl, 0.1 mM EDTA.

Notes and references

1 *Quadruplex Nucleic Acid*, ed. S. Neidle and S. Balasubramanian, RSC publishing, Cambridge, 2006.

2 (*a*) S. Burge, G. N. Parkinson, P. Hazel, A. K. Todd and S. Neidle, *Nucleic Acids Res.*, 2006, **34**, 5402; (*b*) A. T. Phan, V. Kuryavyi and D. J. Patel, *Curr. Opin. Struct. Biol.*, 2006, **16**, 288; (*c*) D. J. Patel, A. T. Phan and V. Kuryavyi, *Nucleic Acids Res.*, 2007, DOI: 10.1093/nar/gkm711; (*d*) J. T. Davis, *Angew. Chem., Int. Ed.*, 2004, **43**, 668.

3 (*a*) L. H. Hurley, *Nat. Rev. Cancer*, 2002, **2**, 188; (*b*) S. Neidle and G. Parkinson, *Nat. Rev. Drug Discovery*, 2002, **1**, 383; (*c*) J.-L. Mergny, J.-F. Riou, P. Mailliet and M.-P. Teulade-Fichou, *Nucleic Acids Res.*, 2002, **30**, 839; (*d*) E. M. Rezler, D. J. Bearss and L. H. Hurley, *Annu. Rev. Pharmacol. Toxicol.*, 2003, **43**, 359; (*e*) S. Neidle and D. E. Thurston, *Nat. Rev. Cancer*, 2005, **5**, 285; (*f*) L. Oganesian and T. M. Bryan, *BioEssays*, 2007, **29**, 155; (*g*) N. Maizels, *Nat. Struct. Mol. Biol.*, 2006, **13**, 1055; (*h*) M. Fry, *Front. Biosci.*, 2007, **12**, 4336; (*i*) L. Kelland, *Clin. Cancer Res.*, 2007, **13**, 4960; (*j*) B. Pagano and C. Giancola, *Curr. Cancer Drug Targets*, 2007, **7**, 325; (*k*) A. De Cian, L. Lacroix, C. Douarre, N. Temine-Smaali, C. Trentesaux, J.-F. Riou and J.-L. Mergny, *Biochimie*, 2007, DOI: 10.1016/j.biochi.2007.07.011.

4 P. Alberti, A. Bourdoncle, B. Saccà, L. Lacroix and J.-L. Mergny, *Org. Biomol. Chem.*, 2006, **4**, 3383.

5 (*a*) C. Schaffitzel, I. Berger, J. Postberg, J. Hanes, H. J. Lipps and A. Pluckthun, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 8572; (*b*) J. C. Darnell, K. B. Jensen, P. Jin, V. Brown, S. T. Warren and R. B. Darnell, *Cell*, 2001, **107**, 489; (*c*) M. L. Duquette, P. Handa, J. A. Vincent, A. F. Taylor and N. Maizels, *Genes Dev.*, 2004, **18**, 1618; (*d*) K. Paeschke, T. Simonsson, J. Postberg, D. Rhodes and H. J. Lipps, *Nat. Struct. Mol. Biol.*, 2005, **12**, 847.

6 (*a*) A. K. Todd, M. Johnston and S. Neidle, *Nucleic Acids Res.*, 2005, **33**, 2901; (*b*) J. L. Huppert and S. Balasubramanian, *Nucleic Acids Res.*, 2005, **33**, 2908.

7 A. Bourdoncle, A. Estévez Torres, C. Gosse, L. Lacroix, P. Vekhoff, T. Le Saux, L. Jullien and J.-L. Mergny, *J. Am. Chem. Soc.*, 2006, **128**, 11094.

8 P. S. Shirude, B. Okumus, L. Ying, T. Ha and S. Balasubramanian, *J. Am. Chem. Soc.*, 2007, **129**, 7484.

9 J. L. Huppert and S. Balasubramanian, *Nucleic Acids Res.*, 2007, **35**, 406.

10 J. Eddy and N. Maizels, *Nucleic Acids Res.*, 2006, **34**, 3887.

11 A. I. Murchie and D. M. J. Lilley, *Nucleic Acids Res.*, 1992, **20**, 49.

12 A. Lew, W. J. Rutter and G. C. Kennedy, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 12508.

13 A. Yafe, S. Etzioni, P. Weisman-Shomer and M. Fry, *Nucleic Acids Res.*, 2005, **33**, 2887.

14 D. Sun, K. Guo, J. J. Rusche and L. H. Hurley, *Nucleic Acids Res.*, 2005, **33**, 6070.

15 R. De Armond, S. Wood, D. Sun, L. H. Hurley and S. W. Ebbinghaus, *Biochemistry*, 2005, **44**, 16341.

16 (*a*) M. Fry and L. A. Loeb, *Proc. Natl. Acad. Sci. U. S. A.*, 1994, **91**, 4950; (*b*) S. Khateb, P. Weisman-Shomer, I. Hershco-Shani, A. L. Ludwig and M. Fry, *Nucleic Acids Res.*, 2007, **35**, 5775–5788.

17 (*a*) T. Simonsson, P. Pecinka and M. Kubista, *Nucleic Acids Res.*, 1998, **26**, 1167; (*b*) A. Ambrus, D. Chen, J. Dai, R. A. Jones and D. Yang, *Biochemistry*, 2005, **44**, 2048; (*c*) A. Rangan, O. Y. Fedoroff and L. H. Hurley, *J. Biol. Chem.*, 2001, **276**, 4640; (*d*) A. Siddiqui-Jain, C. L. Grand, D. J. Bearss and L. H. Hurley, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 11593.

18 S. Cogoi and L. E. Xodo, *Nucleic Acids Res.*, 2006, **34**, 2536.

19 (*a*) J. Dai, T. S. Dexheimer, D. Chen, M. Carver, A. Ambrus, R. A. Jones and D. Yang, *J. Am. Chem. Soc.*, 2006, **128**, 1096; (*b*) T. S. Dexheimer, D. Sun and L. H. Hurley, *J. Am. Chem. Soc.*, 2006, **128**, 5404; (*c*) J. Dai, D. Chen, R. A. Jones, L. H. Hurley and D. Yang, *Nucleic Acids Res.*, 2006, **34**, 5133.

20 (*a*) S. Rankin, A. P. Reszka, J. Huppert, M. Zloh, G. N. Parkinson, A. K. Todd, S. Ladame, S. Balasubramanian and S. Neidle, *J. Am. Chem. Soc.*, 2005, **127**, 10584; (*b*) H. Fernando, A. P. Reszka, J. Huppert, S. Ladame, S. Rankin, A. R. Venkitaraman, S. Neidle and S. Balasubramanian, *Biochemistry*, 2006, **45**, 7854.

21 K. Guo, A. Pourpak, K. Beetz-Rogers, V. Gokhale, D. Sun and L. H. Hurley, *J. Am. Chem. Soc.*, 2007, **129**, 10220.

22 D. Sun, B. Thompson, B. E. Cathers, M. Salazar, S. M. Kerwin, J. O. Trent, T. C. Jenkins, S. Neidle and L. H. Hurley, *J. Med. Chem.*, 1997, **40**, 2113.

23 (*a*) Q. Guo, M. Lu, L. A. Marky and N. R. Kallenbach, *Biochemistry*, 1992, **31**, 2451; (*b*) Q. Chen, I. D. Kuntz and R. H. Shafer, *Proc. Natl. Acad. Sci. U. S. A.*, 1996, **93**, 2635.

24 (*a*) P. J. Perry, S. M. Gowan, A. P. Reszka, P. Polucci, T. C. Jenkins, L. R. Kelland and S. Neidle, *J. Med. Chem.*, 1998, **41**, 3253; (*b*) P. J. Perry, A. P. Reszka, A. A. Wood, M. A. Read, S. M. Gowan, H. S. Dosanjh, J. O. Trent, T. C. Jenkins, L. R. Kelland and S. Neidle, *J. Med. Chem.*, 1998, **41**, 4873.

25 P. J. Perry, M. A. Read, R. T. Davies, S. M. Gowan, A. P. Reszka, A. A. Wood, L. R. Kelland and S. Neidle, *J. Med. Chem.*, 1999, **42**, 2679.

26 R. J. Harrison, A. P. Reszka, S. M. Haider, B. Romagnoli, J. Morrell, M. A. Read, S. M. Gowan, C. M. Incles, L. R. Kelland and S. Neidle, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5845.

27 (*a*) R. J. Harrison, S. M. Gowan, L. R. Kelland and S. Neidle, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2643; (*b*) M. A. Read, A. A. Wood, J. R. Harrison, S. M. Gowan, L. R. Kelland, H. S. Dosanjh and S. Neidle, *J. Med. Chem.*, 1999, **42**, 4538.

28 S. M. Haider, G. N. Parkinson and S. Neidle, *J. Mol. Biol.*, 2003, **326**, 117.

29 (*a*) C. M. Schultes, B. Guyen, J. Cuesta and S. Neidle, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4347; (*b*) M. J. B. Moore, C. M. Schultes, J. Cuesta, F. Cuenca, M. Gunaratnam, F. A. Tanious, W. D. Wilson and S. Neidle, *J. Med. Chem.*, 2006, **49**, 582.

30 (*a*) J.-L. Mergny and J.-C. Maurizot, *ChemBioChem*, 2001, **2**, 124; (*b*) A. De Cian, L. Guittat, M. Kaiser, B. Saccà, S. Amrane, A. Bourdoncle, P. Alberti, M.-P. Teulade-Fichou, L. Lacroix and J.-L. Mergny, *Methods*, 2007, **42**, 183.

31 (*a*) E. W. White, F. Tanious, M. A. Ismail, A. P. Reszka, S. Neidle, D. W. Boykin and W. D. Wilson, *Biophys. Chem.*, 2007, **126**, 140; (*b*) B. Nguyen, F. A. Tanious and W. D. Wilson, *Methods*, 2007, **42**, 150.

32 (*a*) N. W. Kim, M. A. Piatyszek, K. R. Prowse, C. B. Harley, M. D. West, P. L. C. Ho, G. M. Coviello, W. E. Wright, S. L. Weinrich and J. W. Shay, *Science*, 1994, **266**, 2011; (*b*) J. Cuesta, M. Read and S. Neidle, *Mini-Rev. Med. Chem.*, 2003, **3**, 11.

33 A. De Cian, G. Cristofari, P. Reichenbach, E. De Lemos, D. Monchaud, M.-P. Teulade-Fichou, K. Shin-ya, L. Lacroix, J. Lingner and J.-L. Mergny, *Proc. Natl. Acad. Sci. U.S.A.*, 2007, **104**, 17347–17352.

34 (*a*) A. M. Burger, F. Dai, C. M. Schultes, A. P. Reszka, M. J. Moore, J. A. Double and S. Neidle, *Cancer Res.*, 2005, **65**, 1489; (*b*) S. M. Gowan, J. R. Harrison, L. Patterson, M. Valenti, M. A. Read, S. Neidle and L. R. Kelland, *Mol. Pharmacol.*, 2002, **61**, 1154; (*c*) C. M. Incles, C. M. Schultes, L. R. Kelland and S. Neidle, *Mol. Pharmacol.*, 2003, **64**, 1101; (*d*) C. M. Incles, C. M. Schultes, H. Kempski,

H. Koehler, L. R. Kelland and S. Neidle, *Mol. Cancer Ther.*, 2004, **3**, 1201; (*e*) M. Gunaratnam, O. Greciano, C. Martins, A. P. Reszka, C. M. Schultes, H. Morjani, J.-F. Riou and S. Neidle, *Biochem. Pharmacol.*, 2007, **74**, 679.
35 S. Taetz, C. Baldes, T. E. Mürdter, E. Kleideiter, K. Piotrowska, U. Bock, E. Haltner-Ukomadu, J. Mueller, H. Huwer, U. F. Schaefer, U. Klotz and C.-M. Lehr, *Pharm. Res.*, 2006, **23**, 1031.
36 C. Martins, M. Gunaratnam, J. Stuart, V. Makwana, O. Greciano, A. P. Reszka, L. R. Kelland and S. Neidle, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2293.
37 P. Alberti, J. Ren, M.-P. Teulade-Fichou, L. Guittat, J.-F. Riou, J. B. Chaires, C. Hélène, J.-P. Vigneron, J.-M. Lehn and J.-L. Mergny, *J. Biomol. Struct. Dyn.*, 2001, **19**, 505.
38 O. Y. Fedoroff, M. Salazar, H. Han, V. V. Chemeris, S. M. Kerwin and L. H. Hurley, *Biochemistry*, 1998, **37**, 12367.
39 (*a*) J. T. Kern and S. M. Kerwin, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3395; (*b*) J. T. Kern, P. W. Thomas and S. M. Kerwin, *Biochemistry*, 2002, **41**, 11379; (*c*) C. L. Mazzitelli, J. S. Brodbelt, J. T. Kern, M. Rodriguez and S. M. Kerwin, *J. Am. Soc. Mass Spectrom.*, 2006, **17**, 593.
40 (*a*) L. Rossetti, M. Franceschin, S. Schirripa, A. Bianco, G. Ortaggi and M. Savino, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 413; (*b*) M. Franceschin, A. Alvino, V. Casagrande, C. Mauriello, E. Pascucci, M. Savino, G. Ortaggi and A. Bianco, *Bioorg. Med. Chem.*, 2007, **15**, 1848; (*c*) W. Tuntiwechapikhul, T. Taka, M. Béthencourt, L. Makonkawkeyoon and T. Randall Lee, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4120; (*d*) C. Sissi, L. Lucatello, A. P. Krapcho, D. J. Maloney, M. B. Boxer, M. V. Camarasa, G. Pezzoni, E. Menta and M. Palumbo, *Bioorg. Med. Chem.*, 2007, **15**, 555.
41 (*a*) M. Franceschin, E. Pascucci, A. Alvino, D. D'Ambrosio, A. Bianco, G. Ortaggi and M. Savino, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2515; (*b*) H. Dincalp, N. Avcibasi and S. Icli, *J. Photochem. Photobiol., A*, 2007, **185**, 1.
42 (*a*) W. Duan, A. Rangan, H. Vankayalapati, M.-Y. Kim, Q. Zeng, D. Sun, H. Han, O. Y. Fedoroff, D. Nishioka, S. Y. Rha, E. Izbicka, D. D. Von Hoff and L. H. Hurley, *Mol. Cancer Ther.*, 2001, **1**, 103; (*b*) A. K. Mehta, Y. Shayo, H. Vankayalapati, L. H. Hurley and J. Schaefer, *Biochemistry*, 2004, **43**, 11953.
43 G. R. Clark, P. D. Pytel, C. J. Squire and S. Neidle, *J. Am. Chem. Soc.*, 2003, **125**, 4066.
44 A. Randazzo, A. Galeone and L. Mayol, *Chem. Commun.*, 2001, 1030.
45 M. J. Cocco, L. A. Hanakahi, M. D. Huber and N. Maizels, *Nucleic Acids Res.*, 2003, **31**, 2944.
46 (*a*) W. Li, M. Zhang, J.-l. Zhang, H.-q. Li, X.-c. Zhang, Q. Sun and C.-m. Qiu, *FEBS Lett.*, 2006, **580**, 4905; (*b*) H. Sun, Y. Tang, J. Xiang, G. Xu, Y. Zhang, H. Zhang and L. Xu, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3586.
47 B. Brassart, D. Gomez, A. De Cian, R. Paterski, A. Montagnac, K.-H. Qui, N. Temine-Smaali, C. Trentesaux, J.-L. Mergny, F. Gueritte and J.-F. Riou, *Mol. Pharmacol.*, 2007, **72**, 631.
48 L. Guittat, A. De Cian, F. Rosu, V. Gabelica, E. De Pauw, E. Delfourne and J.-L. Mergny, *Biochim. Biophys. Acta*, 2005, **1724**, 375.
49 J.-L. Mergny, L. Lacroix, M.-P. Teulade-Fichou, C. Hounsou, L. Guittat, M. Hoarau, P. B. Arimondo, J.-P. Vigneron, J.-M. Lehn, J.-F. Riou, T. Garestier and C. Hélène, *Proc. Natl. Acad. Sci. U. S. A.*, 2001, **98**, 3062.
50 C. Hounsou, L. Guittat, D. Monchaud, M. Jourdan, N. Saettel, J.-L. Mergny and M.-P. Teulade-Fichou, *ChemMedChem*, 2007, **2**, 655.
51 (*a*) M.-P. Teulade-Fichou, C. Carrasco, L. Guittat, C. Bailly, P. Alberti, J.-L. Mergny, A. David, J.-M. Lehn and W. D. Wilson, *J. Am. Chem. Soc.*, 2003, **125**, 4732; (*b*) C. Allain, D. Monchaud and M.-P. Teulade-Fichou, *J. Am. Chem. Soc.*, 2006, **128**, 11890; (*c*) V. Gabelica, E. S. Baker, M.-P. Teulade-Fichou, E. De Pauw and M. T. Bowers, *J. Am. Chem. Soc.*, 2007, **129**, 895.
52 (*a*) T. Paris, J.-P. Vigneron, J.-M. Lehn, M. Cesario, J. Guilhem and C. Pascard, *J. Inclusion Phenom. Macrocyclic Chem.*, 1999, **33**, 191; (*b*) A. Granzhan, D. Monchaud and M.-P. Teulade-Fichou, *in preparation*.
53 P. Alberti, P. Schmitt, C.-H. Nguyen, C. Rivalle, M. Hoarau, D. S. Grierson and J.-L. Mergny, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1071.
54 (*a*) V. Caprio, B. Guyen, Y. Opoku-Boahen, J. Mann, S. M. Gowan, L. M. Kelland, M. A. Read and S. Neidle, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2063; (*b*) B. Guyen, C. M. Schultes, P. Hazel, J. Mann and S. Neidle, *Org. Biomol. Chem.*, 2004, **2**, 981; (*c*) L. Guittat, A. Alberti, F. Rosu, S. Van Miert, E. Thetiot, L. Pieters, V. Gabelica, E. De Pauw, A. Ottaviani, J.-F. Riou and J.-L. Mergny, *Biochimie*, 2003, **85**, 535.
55 (*a*) J.-L. Zhou, Y.-J. Lu, T.-M. Ou, J.-M. Zhou, Z.-S. Huang, X.-F. Zhu, C.-J. Du, X.-Z. Bu, L. Ma, L.-Q. Gu, Y.-M. Li and A. S.-C. Chan, *J. Med. Chem.*, 2005, **48**, 7315; (*b*) J.-M. Zhou, X.-F. Zhu, Y.-J. Lu, R. Deng, Z.-S. Huang, Y.-P. Mei, Y. Wang, W.-L. Huang, Z.-C. Liu, L.-Q. Gu and Y.-X. Zeng, *Oncogene*, 2006, **25**, 503; (*c*) T.-M. Ou, Y.-J. Lu, C. Zhang, Z.-S. Huang, X.-D. Wang, J.-H. Tan, Y. Chen, D.-L. Ma, K.-Y. Wong, J. C.-O. Tang, A. S.-C. Chan and L.-Q. Gu, *J. Med. Chem.*, 2007, **50**, 1465; (*d*) J.-N. Liu, R. Deng, J.-F. Guo, J.-M. Zhou, G.-K. Feng, Z.-S. Huang, L.-Q. Gu, Y.-X. Zeng and X.-F. Zhu, *Leukemia*, 2007, **21**, 1300.
56 J. Hooda, D. Bednarski, L. Irish and S. M. Firestine, *Bioorg. Med. Chem. Lett.*, 2006, **14**, 1902.
57 (*a*) P. M. Murphy, V. A. Phillips, S. A. Jennings, N. C. Garbett, J. B. Chaires, T. C. Jenkins and R. T. Wheelhouse, *Chem. Commun.*, 2003, 1160; (*b*) R. T. Wheelhouse, S. A. Jennings, V. A. Phillips, D. Pletsas, P. M. Murphy, N. C. Garbett, J. B. Chaires and T. C. Jenkins, *J. Med. Chem.*, 2006, **49**, 5187.
58 A. D. Moorhouse, A. M. Santos, M. Gunaratnam, M. Moore, S. Neidle and J. E. Moses, *J. Am. Chem. Soc.*, 2006, **128**, 15972.
59 M. Kaiser, A. De Cian, M. Sainlos, C. Renner, J.-L. Mergny and M.-P. Teulade-Fichou, *Org. Biomol. Chem.*, 2006, **4**, 1049.
60 K. Jantos, R. Rodriguez, S. Ladame, P. S. Shirude and S. Balasubramanian, *J. Am. Chem. Soc.*, 2006, **128**, 13662.
61 (*a*) P. S. Shirude, E. R. Gillies, S. Ladame, F. Godde, K. Shin-ya, I. Huc and S. Balasubramanian, *J. Am. Chem. Soc.*, 2007, **129**(39), 11890–11891; (*b*) T. K. Chakraborty, A. Arora, S. Roy, N. Kumar and S. Maiti, *J. Med. Chem.*, 2007, **50**(23), 5539–5542.
62 R. Rodriguez, G. Dan Pantoş, D. P. N. Gonçalves, J. K. M. Sanders and S. Balasubramanian, *Angew. Chem., Int. Ed.*, 2007, **46**, 5405.
63 M. Bejugam, S. Sewitz, P. S. Shirude, R. Rodriguez, R. Shahid and S. Balasubramanian, *J. Am. Chem. Soc.*, 2007, **129**(43), 12926–12927.
64 (*a*) F. Xiaoguang, Huan, R. T. Wheelhouse and L. H. Hurley, *J. Am. Chem. Soc.*, 1999, **121**, 3561; (*b*) E. Izbicka, R. T. Wheelhouse, E. Raymond, K. K. Davidson, R. A. Lawrence, D. Sun, B. E. Windle, L. H. Hurley and D. D. Von Hoff, *Cancer Res.*, 1999, **59**, 639; (*c*) D.-F. Shi, R. T. Wheelhouse, D. Sun and L. H. Hurley, *J. Med. Chem.*, 2001, **44**, 4509; (*d*) M.-Y. Kim, M. Gleason-Guzman, E. Izbicka, D. Nishioka and L. H. Hurley, *Cancer Res.*, 2003, **63**, 3247; (*e*) C. L. Grand, T. J. Powell, R. B. Nagle, D. J. Bearss, D. Tye, M. Gleason-Guzman and L. H. Hurley, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 6140; (*f*) W. Liu, D. Sun and L. H. Hurley, *Nucleosides, Nucleotides Nucleic Acids*, 2005, **24**, 1801; (*g*) M. W. Freyer, R. Buscaglia, K. Kaplan, D. Cashman, L. H. Hurley and E. A. Lewis, *Biophys. J.*, 2007, **92**, 2007.
65 (*a*) J. Ren and J. B. Chaires, *Biochemistry*, 1999, **38**, 16067; (*b*) A. De Cian, L. Guittat, K. Shin-ya, J.-F. Riou and J.-L. Mergny, *Nucleic Acids Symp. Ser.*, 2005, **49**, 235; (*c*) D. Monchaud, C. Allain and M.-P. Teulade-Fichou, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4842.
66 (*a*) I. Haq, J. O. Trent, B. Z. Chowdury and T. C. Jenkins, *J. Am. Chem. Soc.*, 1999, **121**, 1768; (*b*) C. Wei, G. Jia, J. Yuan, Z. Feng and C. Li, *Biochemistry*, 2006, **45**, 6681; (*c*) A. T. Phan, V. Kuryavyi, H. Y. Gaw and D. J. Patel, *Nat. Chem. Biol.*, 2005, **1**, 167.
67 G. N. Parkinson, R. Gosh and S. Neidle, *Biochemistry*, 2007, **46**, 2390.
68 P. Wang, L. Ren, H. He, F. Liang, X. Zhou and Z. Tan, *ChemBioChem*, 2006, **7**, 1155.
69 D. P. N. Gonçalves, R. Rodriguez, S. Balasubramanian and J. K. M. Sanders, *Chem. Commun.*, 2006, 4685.
70 D. P. N. Gonçalves, S. Ladame, S. Balasubramanian and J. K. M. Sanders, *Org. Biomol. Chem.*, 2006, **4**, 3337.
71 B. Fu, J. Huang, L. Ren, X. Weng, Y. Zhou, Y. Du, X. Wu, X. Zhou and G. Yang, *Chem. Commun.*, 2007, 3264.
72 (*a*) J. Seenisamy, S. Bashyam, V. Gokhale, H. Vankayalapati, D. Sun, A. Siddiqui-Jain, N. Streiner, K. Shin-ya, E. White, W. D. Wilson and L. H. Hurley, *J. Am. Chem. Soc.*, 2005, **127**, 2944; (*b*) E. M. Rezler, J. Seenisamy, S. Bashyam, M.-Y. Kim, E. White, W. D. Wilson and L. H. Hurley, *J. Am. Chem. Soc.*, 2005, **127**, 9439.
73 (*a*) J. Stanslas, D. J. Hagan, M. J. Ellis, C. Turner, J. Carmichael, W. Ward, T. R. Hammonds and M. F. G. Stevens, *J. Med. Chem.*, 2000, **43**, 1563; (*b*) J. C. Cookson, R. A. Heald and M. F. G. Stevens, *J. Med. Chem.*, 2005, **48**, 7198; (*c*) J. C. Cookson, F. Dai, V. Smith, R. A. Heald, C. A. Laughton, M. F. G. Stevens and A. M. Burger, *Mol. Pharmacol.*, 2005, **68**, 1551.

74 (*a*) P. Phatak, J. C. Cookson, F. Dai, V. Smith, R. B. Gartenhaus, M. F. G. Stevens and A. M. Burger, *Br. J. Cancer*, 2007, **96**, 1223; (*b*) E. Salvati, C. Leonetti, A. Rizzo, M. Scarsella, M. Mottolese, R. Galati, I. Sperduti, M. F. Stevens, M. D'Incalci, M. Blasco, G. Chiorino, S. Bauwens, B. Horard, E. Gilson, A. Stoppacciaro, G. Zupi and A. Biroccio, *J. Clin. Invest.*, 2007, **117**(11), 3236–3247.

75 (*a*) E. Gavathiotis, R. A. Heald, M. F. G. Stevens and M. S. Searle, *Angew. Chem., Int. Ed.*, 2001, **40**, 4749; (*b*) E. Gavathiotis, R. A. Heald, M. F. G. Stevens and M. S. Searle, *J. Mol. Biol.*, 2003, **334**, 25.

76 F. Koeppel, J.-F. Riou, A. Laoui, P. Mailliet, P. B. Arimondo, D. Labit, O. Petitgenet, C. Hélène and J.-L. Mergny, *Nucleic Acids Res.*, 2001, **29**, 1087.

77 (*a*) J.-F. Riou, L. Guittat, P. Mailliet, A. Laoui, E. Renou, O. Petitgenet, F. Megnin-Chanet, C. Hélène and J.-L. Mergny, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 2672; (*b*) D. Gomez, N. Aouali, A. Londono-Vallejo, L. Lacroix, F. Mégnin-Chanet, T. Lemarteleur, C. Douarre, K. Shin-ya, P. Mailliet, C. Trentesaux, H. Morjani, J.-L. Mergny and J.-F. Riou, *J. Biol. Chem.*, 2003, **278**, 50554; (*c*) D. Gomez, T. Lemarteleur, L. Lacroix, P. Mailliet, J.-L. Mergny and J.-F. Riou, *Nucleic Acids Res.*, 2004, **32**, 371; (*d*) C. Douarre, D. Gomez, H. Morjani, J.-M. Zham, M.-F. O'Donohue, L. Eddabra, P. Mailliet, J.-F. Riou and C. Trentesaux, *Nucleic Acids Res.*, 2005, **33**, 2192.

78 (*a*) T. Lemarteleur, D. Gomez, R. Paterski, E. Mandine, P. Mailliet and J.-F. Riou, *Biochem. Biophys. Res. Commun.*, 2004, **323**, 802; (*b*) G. Pennarun, C. Granotier, L. R. Gauthier, D. Gomez, F. Hoffschir, E. Mandine, J.-F. Riou, J.-L. Mergny, P. Mailliet and F. D. Boussin, *Oncogene*, 2005, **24**, 2917.

79 C. Granotier, G. Pennarun, L. Riou, F. Hoffshir, L. R. Gauthier, A. De Cian, D. Gomez, E. Mandine, J.-F. Riou, J.-L. Mergny, P. Mailliet, B. Dutrillaux and F. D. Boussin, *Nucleic Acids Res.*, 2005, **33**, 4182.

80 A. De Cian and J.-L. Mergny, *Nucleic Acids Res.*, 2007, **35**, 2483.

81 A. De Cian, E. DeLemos, J.-L. Mergny, M.-P. Teulade-Fichou and D. Monchaud, *J. Am. Chem. Soc.*, 2007, **129**, 1856.

82 (*a*) C.-C. Chang, J.-Y. Wu, C.-W. Chien, W.-S. Wu, H. Liu, C.-C. Kang, L.-J. Yu and T.-C. Chang, *Anal. Chem.*, 2003, **75**, 6177; (*b*) C.-C. Chang, I.-C. Kuo, I.-F. Ling, C.-T. Chen, H.-C. Chen, P.-J. Lou, J.-J. Lin and T.-C. Chang, *Anal. Chem.*, 2004, **76**, 4490; (*c*) C.-C. Chang, C.-W. Chien, Y.-H. Lin, C.-C. Kang and T.-C. Chang, *Nucleic Acids Res.*, 2007, **35**, 2846; (*d*) D.-Y. Yang, T.-C. Chang and S.-Y. Sheu, *J. Phys. Chem. A*, 2007, **111**(38), 9224–9232.

83 N. Dias, U. Jacquemard, B. Baldeyrou, C. Tardy, A. Lansiaux, P. Colson, F. Tanious, W. D. Wilson, S. Routier, J.-Y. Mérour and C. Bailly, *Biochemistry*, 2004, **43**, 15169.

84 C. Carrasco, F. Rosu, V. Gabelica, C. Houssier, E. De Pauw, C. Garbay-Jaureguiberry, B. Roques, W. D. Wilson, J. B. Chaires, M. J. Waring and C. Bailly, *ChemBioChem*, 2002, **3**, 1235.

85 W.-J. Zhang, T.-M. Ou, Y.-J. Lu, Y.-Y. Huang, W.-B. Wu, Z.-S. Huang, J.-L. Zhou, K.-Y. Wong and L.-Q. Gu, *Bioorg. Med. Chem.*, 2007, **15**, 5493.

86 (*a*) M. Franceschin, L. Rossetti, A. D'Ambrosio, S. Schirripa, A. Bianco, G. Ortaggi, M. Savino, C. Schultes and S. Neidle, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1707; (*b*) K. C. Gornall, S. Samosorn, J. Talib, J. B. Bremner and J. L. Beck, *Rapid Commun. Mass Spectrom.*, 2007, **21**, 1759.

87 F. Xing, G. Song, J. Ren, J. B. Chaires and X. Qu, *FEBS Lett.*, 2005, **579**, 5035.

88 (*a*) B. Juskowiak, E. Galezowska, N. Koczorowska and T. W. Hermann, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3627; (*b*) E. Galezowska, A. Masternak, B. Rubis, A. Czyrski, M. Rybczyńska, T. W. Hermann and B. Juskowiak, *Int. J. Biol. Macromol.*, 2007, **41**(5), 558–563.

89 (*a*) J. Ren and J. B. Chaires, *J. Am. Chem. Soc.*, 2000, **122**, 424; (*b*) S. M. Kerwin, D. Sun, J. T. Kern, A. Rangan and P. W. Thomas, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2411; (*c*) C.-P. Li, J.-H. Huang, A.-C. Chang, Y.-M. Hung, C.-H. Lin, Y. Chao, S.-D. Lee, J. Whang-Peng and T.-S. Huang, *Pharm. Res.*, 2004, **21**, 93.

90 J. A. Schouten, S. Ladame, S. J. Mason, M. A. Cooper and S. Balasubramanian, *J. Am. Chem. Soc.*, 2003, **125**, 5594.

91 S. Maiti, N. K. Chaudhury and S. Chowdhury, *Biochem. Biophys. Res. Commun.*, 2003, **310**, 505.

92 J. E. Reed, A. A. Arnal, S. Neidle and R. Vilar, *J. Am. Chem. Soc.*, 2006, **128**, 5992.

93 (*a*) L. R. Keating and V. A. Szalai, *Biochemistry*, 2004, **43**, 15891; (*b*) S. E. Evans, M. A. Mendez, K. B. Turner, L. R. Keating, R. T. Grimes, S. Melchoir and V. A. Szalai, *JBIC, J. Biol. Inorg. Chem.*, 2007, **12**(8), 1235–1249.

94 (*a*) C. Vialas, G. Pratviel and B. Meunier, *Biochemistry*, 2000, **39**, 9514; (*b*) A. Maraval, S. Franco, C. Vialas, G. Pratviel, M. A. Blasco and B. Meunier, *Org. Biomol. Chem.*, 2003, **1**, 921; (*c*) I. M. Dixon, F. Lopez, J.-P. Estève, A. M. Tejera, M. A. Blasco, G. Pratviel and B. Meunier, *ChemBioChem*, 2005, **6**, 123.

95 C. Rajput, R. Rutkaite, L. Swanson, I. Haq and J. A. Thomas, *Chem.–Eur. J.*, 2006, **12**, 4611.

96 T. Ohyama, Y. Kato, H. Mita and Y. Yamamoto, *Chem. Lett.*, 2006, **35**, 126.

97 L. Ren, A. Zhang, J. Huang, P. Wang, X. Weng, L. Zhang, F. Liang, Z. Tan and X. Zhou, *ChemBioChem*, 2007, **8**, 775.

98 J. E. Reed, S. Neidle and R. Vilar, *Chem. Commun.*, 2007, 4366.

99 I. M. Dixon, F. Lopez, A. M. Tejera, J.-P. Estève, M. A. Blasco, G. Pratviel and B. Meunier, *J. Am. Chem. Soc.*, 2007, **129**, 1502.

100 H. Bertrand, D. Monchaud, A. De Cian, R. Guillot, J.-L. Mergny and M.-P. Teulade-Fichou, *Org. Biomol. Chem.*, 2007, **5**, 2555.

101 W. Tuntiwechapikul, J. T. Lee and M. Salazar, *J. Am. Chem. Soc.*, 2001, **123**, 5606.

102 S. Sato, H. Kondo, T. Nojima and S. Takenaka, *Anal. Chem.*, 2005, **77**, 7304.

103 (*a*) S. Redon, S. Bombard, M.-A. Elizondo-Riojas and J.-C. Chottard, *Nucleic Acids Res.*, 2003, **31**, 1605; (*b*) I. Ourliac-Garnier, M.-A. Elizondo-Riojas, S. Redon, N. P. Farrell and S. Bombard, *Biochemistry*, 2005, **44**, 10620; (*c*) I. Ourliac-Garnier and S. Bombard, *J. Inorg. Biochem.*, 2007, **101**, 514.

104 H. Bertrand, S. Bombard, D. Monchaud and M.-P. Teulade-Fichou, *JBIC, J. Biol. Inorg. Chem.*, 2007, **12**, 1003.

105 K. Shin-ya, K. Wierzba, K.-I. Matsuo, T. Ohtani, Y. Yamada, K. Furihata, Y. Hayakawa and H. Seto, *J. Am. Chem. Soc.*, 2001, **123**, 1262.

106 (*a*) M.-Y. Kim, H. Vankayalapati, K. Shin-ya, K. Wierzba and L. H. Hurley, *J. Am. Chem. Soc.*, 2002, **124**, 2098; (*b*) F. Rosu, V. Gabelica, K. Shin-ya and E. De Paw, *Chem. Commun.*, 2003, 2702; (*c*) K. Shin-ya, *Biosci., Biotechnol., Biochem.*, 2005, **69**, 867; (*d*) N. Binz, T. Shalaby, P. Rivera, K. Shin-ya and M. A. Grotzer, *Eur. J. Cancer*, 2005, **41**, 2873; (*e*) H. Tahara, K. Shin-ya, H. Seimiya, H. Yamada, T. Tsuruo and T. Ide, *Oncogene*, 2006, **25**, 1955; (*f*) T. Tauchi, K. Shin-Ya, G. Sashida, M. Sumi, S. Okabe, J. H. Ohyashiki and K. Ohyashiki, *Oncogene*, 2006, **25**, 5719; (*g*) D. Gomez, M.-F. O'Donohue, T. Wenner, C. Douarre, J. Macadre, P. Koebel, M.-J. Giraud-Panis, H. Kaplan, A. Kolkes, K. Shin-ya and J.-F. Riou, *Cancer Res.*, 2006, **66**, 6908; (*h*) D. Gomez, T. Wenner, B. Brassart, C. Douarre, M.-F. O'Donohue, V. El Khoury, K. Shin-ya, H. Morjani, C. Trentesaux and J.-F. Riou, *J. Biol. Chem.*, 2006, **281**, 38721.

107 T. Doi, M. Yoshida, K. Shin-ya and T. Takahashi, *Org. Lett.*, 2006, **8**, 4165.

108 G. Singh Minhas, D. S. Pilch, J. E. Kerrigan, E. J. LaVoie and J. E. Rice, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3891.

109 M. Tera, Y. Sohtome, H. Ishizuka, T. Doi, M. Takagi, K. Shin-ya and K. Nagasawa, *Heterocycles*, 2006, **69**, 505.

110 C. M. Barbieri, A. R. Srinivasan, S. G. Rzuczek, J. E. Rice, E. J. LaVoie and D. S. Pilch, *Nucleic Acids Res.*, 2007, **35**, 3272.

111 (*a*) H. Arthanari, S. Basu, T. L. Kawano and P. H. Bolton, *Nucleic Acids Res.*, 1998, **26**, 3724; (*b*) F. Rosu, V. Gabelica, C. Houssier, P. Colson and E. De Pauw, *Rapid Commun. Mass Spectrom.*, 2002, **16**, 1729.

112 E. Shammel Baker, J. Tae Lee, J. L. Sessler and M. T. Bowers, *J. Am. Chem. Soc.*, 2006, **128**, 2641.

