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Original Research Article

GUANINE-QUADRUPLEXES: BONDING, STRUCTURE AND BIOLOGICAL SIGNIFICANCE

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Abstract: The Guanine bases form non-canonical structures based on G-quartets was found in 1962. It is now well established that G-rich nucleic acids forms higher order structures called guanine quadruplexes. G-quadruplex structures show right-handed helicity due to hydrophobic stacking of two or more G-quartets. Little attention was paid to the of guanine tetrads structure and for more than 25 years this structure remained in search of functions. In this review the bonding in G-quartet, general features of quadruplex topology, structure and polymorphic behavior of G- quadruplex is described. In the quadruplex structure four guanines establish a cyclic array of hydrogen bonds from the Watson–Crick and the Hoogsteen bonding. A G-quartet is a planar association of four guanines held together by four central H-bonds between H1 of nitrogen and O6 of carbonyl group and also by four external H-bonds between H2 of amine and N7. Four guanine bases in a G-quartet can be brought together in monomer, dimmer or tetramer with parallel or antiparallel adjacent strands and structures can link up to provide different loop connectivities. The effect of guanine base modifications and metal cations on the G-guartets stability is described. The evidence of G-quadruplexes occurrence in human cells and anticipiated biological functions are highlighted.

Key Words : Guanine- Quadruplexes- structure, Quartet- bonding, G- quartet- stacking, quadruplex topology, G- quadruplex - Polymorphic Behavior, G-quadruplexes in human cell , Guanine Base Modifications- G Quartet.

Introduction: The duplex DNA structure elucidated by Watson – Crick in 1953 explains, folding of DNA, formation of compact chromatin structure and replication of genetic material very well [1]. The double helix is a right-handed spiral. The DNA strands wind around each other. The strands leave gaps between each set of phosphate backbones and reveal the sides of the bases inside. The two grooves twisting around the surface of the double helix, the major groove, is 22 Å wide and the the minor groove, is 12 Å wide. In 1979 Alexander Rich at Cambridge, discovered a new

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variety of DNA, termed as the Z-DNA [2]. Z-DNA consists of an alternating pyrimidine-purine sequence d(CGCGCG). Z-DNA structural features consist of the purine, deoxyguanosine and deoxycytidine, nucleosides having alternating syn-anti glycosidic angles. The glycosidic bond features are the same as glycosidic bond features of B DNA. Although A-T base pairings can exist within the Z-DNA helix but A-T base pairings destabilize the Z-DNA helix [2]. The most important feature of Z- DNA is that it is left handed unlike B- DNA. A few years after the discovery of the DNA *double helix* structure, it was shown that a triple helix could be formed by polynucleotide [3]. Two chains of the polyribonucleotide poly(rU) are able to simultaneously bind to one chain of poly(rA). This shows that double helices containing only purines in one chain could bind a third polynucleotide containing only pyrimidines (e.g., poly (dCT) binding to poly(dGA) • poly(dCT)) or only purines (e.g., poly(dG) binding to poly(dG) • poly(dC)) . The hydrogen bonding interactions involved in triple-helix formation are referred to as Hoogsteen hydrogen bonds. Hoogsteen discovered that in co crystals of adenine and thymine derivatives a hydrogen bonding pattern different from that of Watson-Crick base pairs was present. These hydrogen bonds are involved when a (third) strand of poly (dT) binds to a Watson-Crick-paired poly (dA) • poly(dT) double helix. Althoug in 1962, Gellert et al. [4] found that guanine bases form non-canonical structures based on G-quartets. Studies on guanosine-3'-phosphate showed that, this molecule aggregated into guanine tetrad structures [5]. The guanine tetrad arrangement has been shown in other guanine derivatives also. [6]. It is now well established that G-rich nucleic acids forms higher order structures called guanine quadruplexes. G-quadruplex structures show right-handed helicity due to hydrophobic stacking of two or more G-quartets. But little attention was paid to the of guanine tetrads structure. And for more than 25 years this structure remained in search of functions. Then suddenly, various functions of guanine tetrads were suggested , (1) responsible for the switch recombination that immunoglobulin heavy chains undergo to bring different constant regions next to variable regions during the differentiation of B lymphocytes [7] (2) shown to form at the telomeric ends of eukaryotic chromosomes [8,9] and in the promoter regions of oncogenes [10-12], (3) involved in the regulation of the insulin gene [13] The formation of quadruplex stucture has now been established *in vitro* as well as *in vivo* [14] The quadruple helix appears be a feature unique to cancer cells. If so, any treatments that target them will not harm healthy cells. Keeping the relevance of these sturctures, in this article we describe in detail of the bonding, structure and biological significance of the quadruplexes comprising of guanines.

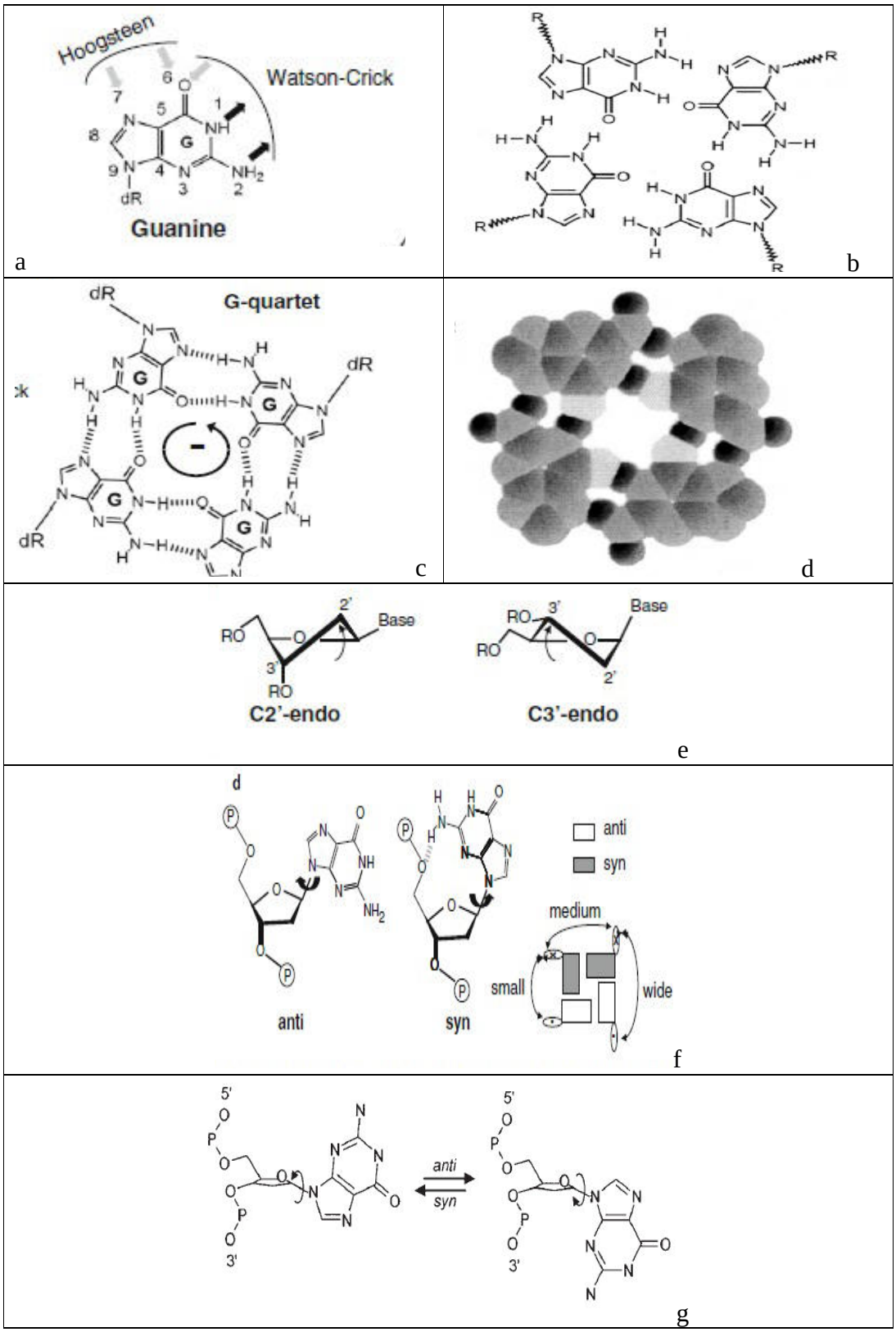
G- Quadruplex Structure: A G- quartet structure is formed when four guanines from different places along a G-rich strand are held together by a special type of hydrogen bonding. The G-quartet structures have been prepared in the laboratory by the folding of synthetic DNA strands rich in guanine. The G-quatet structures assemble into higher order structures. The higher order structures are called guanine quadruplexes. The G-quadruplex structures result from the hydrophobic stacking of two or more G-quartets. The G- quadruplex possess right-handed helicity. In the quadruplex structure four guanines establish a cyclic array of hydrogen bonds from the Watson–Crick and the Hoogsteen bonding (Fig. 1a). The hydrogen bonding scheme is shown in Figure 1b. A G-quartet is a planar association of four guanines held together by four central H-bonds between H1 of nitrogen and O6 of carbonyl group and also by four external H-bonds between H2 of amine and N7 (Fig. 1c). A space filling model reveling the hollow center is shown in Figure 1d. The nucleoside sugars (ribose or deoxyribose) can adopt several conformations. The two most favorable sugar conformations are C2'-endo (found in most DNA G-quadruplexes) and C3'-endo (found in most RNA structures) (Fig. 1e) [15]. The

guanine bases are covalently linked to the sugar via the glycosidic bond that can display two major different torsion angles: syn and anti (Fig. 1f). The anti conformation can be formed whatever the sugar conformation (C2'- or C3'-endo), whereas the syn position is unfavorable in the case of C3'-endo sugar conformation because of the steric hindrance between O3' and C5'. Despite this steric effect, the syn position is possible for guanine. Rotation around the glycosidic bond enables a guanine base to interconvert between syn and anti conformation is shown in Figure 1g.

Each G-quadruplex presents four grooves defined by two neighboring guanines in a G-quartet. According to their respective syn or anti conformations, grooves can be wide, medium, or small [16], contributing to the conformational diversity of G-quadruplex structures. However, this diversity is more limited in the case of tetramolecular quadruplexes; when all strands are parallel, all guanine in a quartet must adopt the same glycosidic bond angle, leading to all-syn or all-anti quartets (the latter being the general case), and all grooves are of medium size. The interplay between glycosidic torsion angles and strand polarities , indicated by (+) or (-) , give rise to different widths is shown in Figure 1h. Based on theoretical calculations it was once suggested that tracts of guanines favour formation of G-quadruplexes. Quadruplexes with four parallel strands in which all guanines adopt the *anti* conformation and that alternating *anti*/*syn* arrangements were restricted to intramolecular G quadruplexes with antiparallel strands [17]. It is easily realized that any G-quadruplex structure that contains antiparallel strands must have bases in both the *anti* and *syn* conformation in order to maintain the tetrad base-pairing scheme. There are examples of virtually any combination of glycosidic torsion angles. Several structures with exclusively *anti* [18-20] or *syn* [21] conformations have been characterized, as have structures with regularly alternating *anti*/*syn* conformations [22-27) or mixtures of *anti*/*syn* conformations within both guanine tracts and guanine tetrads [28-30].

The stacking of G-quartets is stabilized by monovalent (Rb^+, $NH4^+$, K^+, Na^+, Cs+, Li^+), divalent (Sr^{2+}, Ca^{2+}, Ba^{2+}, Mg^{2+}), or trivalent ($Tb^{3+,}$ $Eu^{3+)}$ [31,32] cations according to their ionic radii and their hydration energies. The order of cation ability to stabilize and/or to induce G-quadruplex structures is as follow: $K^+ > NH4^+ > Rb^+ > Na^+ > Cs^+ > Li^+$ for monovalent cations [33, 34] and $Sr^{2+} > Ba^{2+} > Ca^{2+} > Mg^{2+}$ for divalent cations [35]. G-quartet may be stack upon each other to form G-quartet core in presence of metal ion (Figure- 1i and Iii). The ion is bound between two G-quartets, co-ordinated (dashed lines) by eigth guanine O6 oxygen.

The G- quartet structure are formed in vitro by a variety of biological , important guanine – rich sequences . The G- quartet structure might play a role in many functions of telomers , the nucleotides complexex at the end of linear chromosomes. The telomeric DNA sequences from most organisms consist of many tandem repeats of quanine- rich sequences, such as d (TTAGGG)n for human , d(TTGGGG)N for Tetrahymena , or d(TTTTGGGG)n for Oxytricha (where n is the number of tandem repeats) . The G- quartet structure was proposed for DNA sequences from an immunoglobulin switch region and shortly thereafter , the G-quartet structure was proposed as a general model for the structure of telomeric DNAs. Many different G- quartet structure have been observed in general G- quartet structures are very stable both thermodynamically and kinetically . The G-quartet may be stack upon each other to form G-quartet core (Fig- 1i) The G- quartet structures are prefentially stabilized by potassium ions , compared with sodium ions. Monovalent ions typically interact predominantly with the negatively charged phosphate groups on DNA. But in G- quartet structures the ions interact with eight carbonyl oxygens sandwiched between two co-planar G-quartets (Fig- 1i) In fact ,the ion – binding properties of G- quartets might be the most important factor [37].


Hoogsteen
Watson-Crick
Guanine
a
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G-quartet
dR
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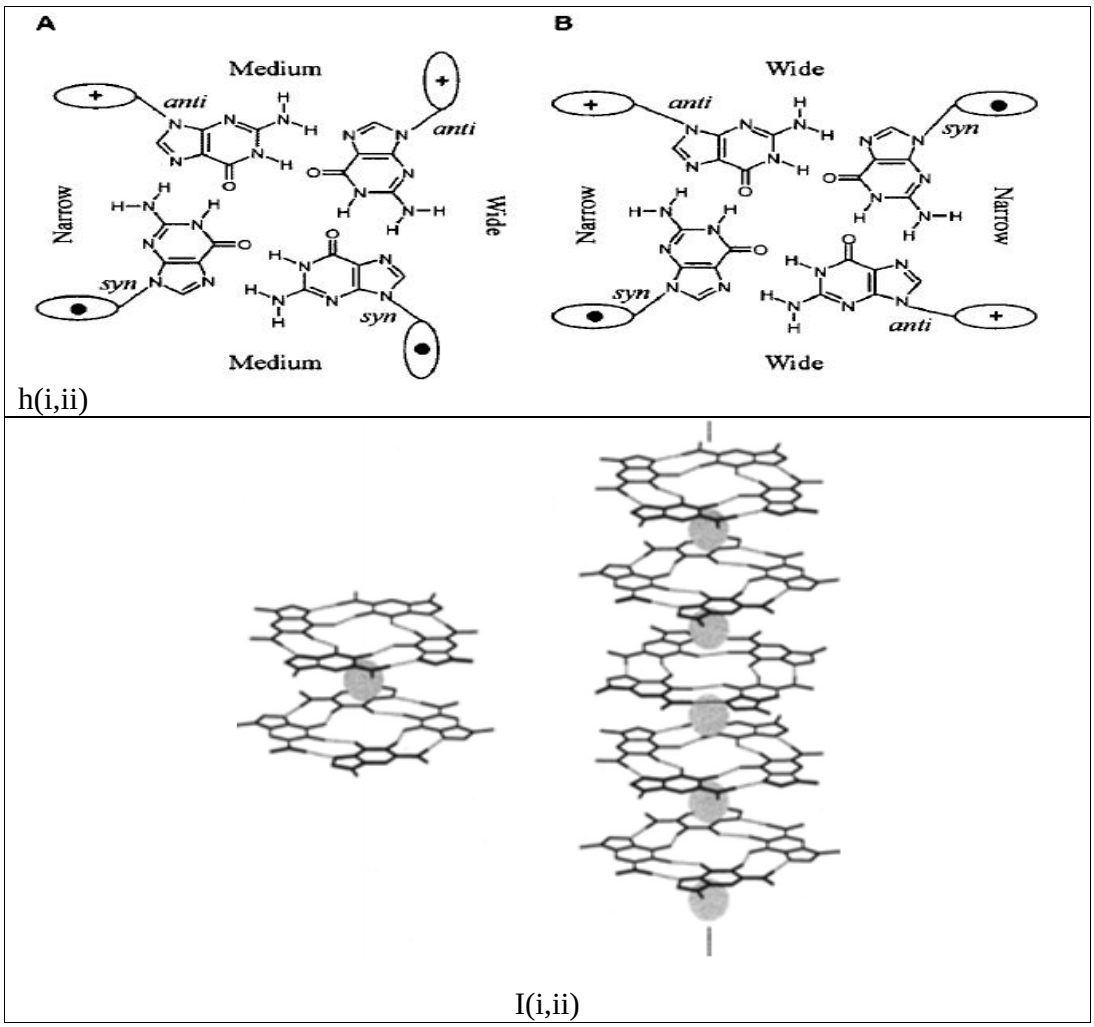

Figure 1: Guanine and G-quartet (a) chemical formula of canonical guanine and two hydrogen bonding faces (Watson – Crick and Hoogsteen) which are implicated in G-quartet formantion. Arrows indicate H-bond donors (in black) and acceptors (in gray), (b) the hydrogen bonding scheme in G- quartet (c) Classical G-quartet structure with anticlockwise rotation (-) of the donor NH to the acceptor C=O hydrogen bonds, (d) (c) Two most favorable sugar configurations og guanine of quarter : C2' or C3' endo, (d) A space filling model reveling the hollow center, (e) Two torsion single of guanine glycosidic bond (syn and anti) that determine groove dimension of G- quartet : wide , medium and small, (f) anti and syn conformation of guanine glycoside bond (g) Rotation around the glycosidic bond of a guanine base to interconvert between syn and anti conformation [36] , (h) The interplay between glycosidic torsion angles and strand polarities , indicated by (+) or (-) , give rise to different widths. (h-i) guanine tetrads with two pairs of adjacent parallel strands that have identical glycosidic torsion angles generated two medium groove , one wide groove , and one narrow groove , (h-ii) guanine tetrads with exclusively alternating antiparallel strands have two wide and two narrow grooves, (i) Stacking of G- quartet core in presence of metal ion.

General features of quadruplex topology and structure : The one, two or four separate strands of DNA (or RNA) and can form Quadruplex. The quadruplex display a wide variety of topologies [38]. The topologies are consequence of various possible combinations of strand direction and also due to the variations in loop size and sequence. The quadruplex is formed by at least two stacked G-tetrads. The G- tetrads are held together by loops . The loops are arised from the intervening mixed- nucleotides which are not generally involved in the tetrads themselves. The difference in topologies rises due differnce in number of stacked G-tetrads, the polarity of the strands. The location and length of the loops also give rise to topologies.

A single stranded G-quadruplex-forming sequences can be described as follows:

G*a*N*1*G*b*N*2*G*c*N*3*G*d*,

where *a,b,c,d* are the number of G residues in each short G-motif, which are generally and directly involved in G-tetrad interactions. A G motif consists of four runs of at least three guanines per run, separated by other bases (N). $N_{1,}$ $N_{2,}$ and $N_{3,}$ are combination of any nucleoside bases, including G. These nucleoside bases are used in forming the loops. The G-tracts can be of unequal length. If one G tracts is longer than the others then some of the G residues can located in the loop regions. However it has been found that all G tracts within a quadruplex sequence are identical for vertebrate telomeric sequences. But this is not always the case for non-telomeric genomic sequences, and also for all telomeric sequences in some lower eukaryotics. In principle bimolecular (dimeric) and tetramolecular (tetrameric) quadruplexes can each be formed from the association of non-equal sequences. But almost all bimolecular quadruplexes reported to date are formed by the association of two identical sequences N_1 G_a N_2 G_bN_3, where *1 , 2 and 3* may or may not be zero. Tetramolecular quadruplexes may be formed by four N_1 G_m X_2 or $G_aN_1G_a$ strands associating together.

Polymorphic Behavior of G- quadruplex : The G- quartet structures shows polymorphic behavior. The four different potential sources of polymorphism are observed in G- quartet structures. Some of the independen polymorphic traits are discussed below.

1. Monomer, dimmer or tetramer: The four guanine bases in a G-quartet can be brought together in many different ways. A number of structures have been reported in which G-quartets forms in a complex consisting of four separate DNA stands. The sequences that readily forms the tetrameic structure are typically short oligonucleotides of the form d (N1GaN2) where 1,2 =0 or 1 and a = 3,4 or 5 . Most of the sequences studied are deoxyribonucleotides, although oligoribonucleotides form tetramers equally as well.

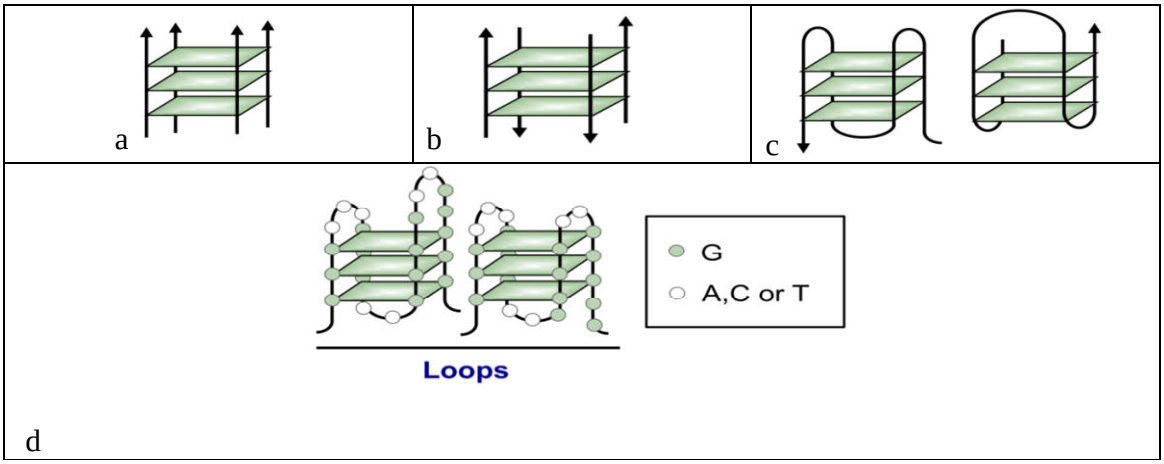

Figure -2 : Different strand polarity arrangement of (A) all strands parallel,(B) two parallel strands and two strand antiparallel, (c) monomeric form of G-quadruplexes , (D) Loops closure in monomeric form of G-quadruplexes[54].

2. Parallel or Ant parallel: G- quartet structures can form with the phosphodiester backbones running either parallel or antiparallel for adjacent strands (Figure- 2a and 2b) In tetramers , the strands directions have been experimentally verified . For dimmer or monomer forms there must however be at least two antiparallel sets of adjacent strands because of hairpin nature of these structures (Figure- 2c).

3.Loop Closure : For a given configuration of the G- quartet core , there are many ways that strings of guanine in dimeric or monomeric structures can link up to provide different loop connectivities . For example, in a dimmer structure formed by an sequence such a d(GGGGTTTTGGGG) the loop might be arranged in a head to head arrangement , a head to tail arrangement (Figure- 2d).

4. Syn or anti : The glycosidic conformation for a guanine in a G- quartet structure can adopt either the anti or more unusually , the syn conformation. Geomrtric constraints require that two adjacent guanines in a G- quartet on parallel strands have the same glycosidic conformation, but must have opposite glycosidic conformation if they are on antiparallel strands . There is a strong correlation between the glycosidic conformation and the relative strand direction, in all cases where both are known. The glycosidic conformations in tetrameric G- quartet structure with parallel strands are all anti . In G- quartet structure containing antiparallel strands , the observed glycosidic conformation angles are half syn and half anti , alternating syn – anti – syn- anti along the string of guanines [39-41] .

Guanine Base Modifications: Quadruplexes may incorporate unusual quartets with canonical nucleobases or guanine analogs. These modifications may affect the DNA quadruplex structure, its apparent melting temperature, and/or its association rate. During the last decade, several researchers [42-49] have been interested in investigating the effect of guanine analogs on G4 formation. The analogs presented here are classified according to their impact on H-bonds between guanine bases of the same quartet (Figure-3). 6-Thioguanine and O6-methylguanine disturb the central ring of H-bonds between O6 of carbonyl group and H1 of nitrogen from two neighboring guanine bases. Inosine and 7-deazaguanine disturb the internal ring of H-bonds between N7 and H2 of amine.8-Oxoguanine, 8-aminoguanine, 8-bromoguanine, and 8-methylguanine replace H8 of canonical guanine with bulkier and/or charged groups. The formation of a tetramolecular quadruplex containing a single modified base is possible [47]. The inner part of a G-quartet (i.e., the central ring of H-bonds) is crucial for its stability; disturbing this part not only leads to the loss of one H-bond, but may also alter coordination of the central cation with the carbonyl groups (in the case of 6-thioG and 6-methylG). Removal of the external ring of H-bonds generally leads to a moderate decrease in the association rate (observed in the case of inosine). 7-Deazaguanine not only prevents this external H-bond ring; it also perturbs the geometry/planarity of the quartet because of steric clashes, leading to a more severe effect on both association and dissociation rates. The modifications such as 8-aminoG, 8-bromoG, and 8-methylG generally favor G-quadruplex formation since they do not disturb the cyclic array of H-bonds of the G-quartet. However, position-dependent effects are found. It has been observed that 8-aminoguanine accelerates tetramolecular quadruplex formation when inserted at the 5’ end but has a detrimental effect on the thermal stability of the quadruplexes [48]. In contrast, the insertion of 8-aminoG at central positions (d-TGRGGT

where R = 8-aminoG) leads to an increase in the apparent melting temperature. The 8-bromoguanine and 8-methylguanine also stabilize and accelerate quadruplex formation by a factor of 10 [47] and 15 [50], respectively, when present at the 5' end. This insertion position of the modifications favors the formation of an all-syn quartet at the 5' end [43] that may suggest the implication of syn G at the 5' end in the nucleation process. This formation of all-syn quartet at the 5' end also stabilizes the complexes.

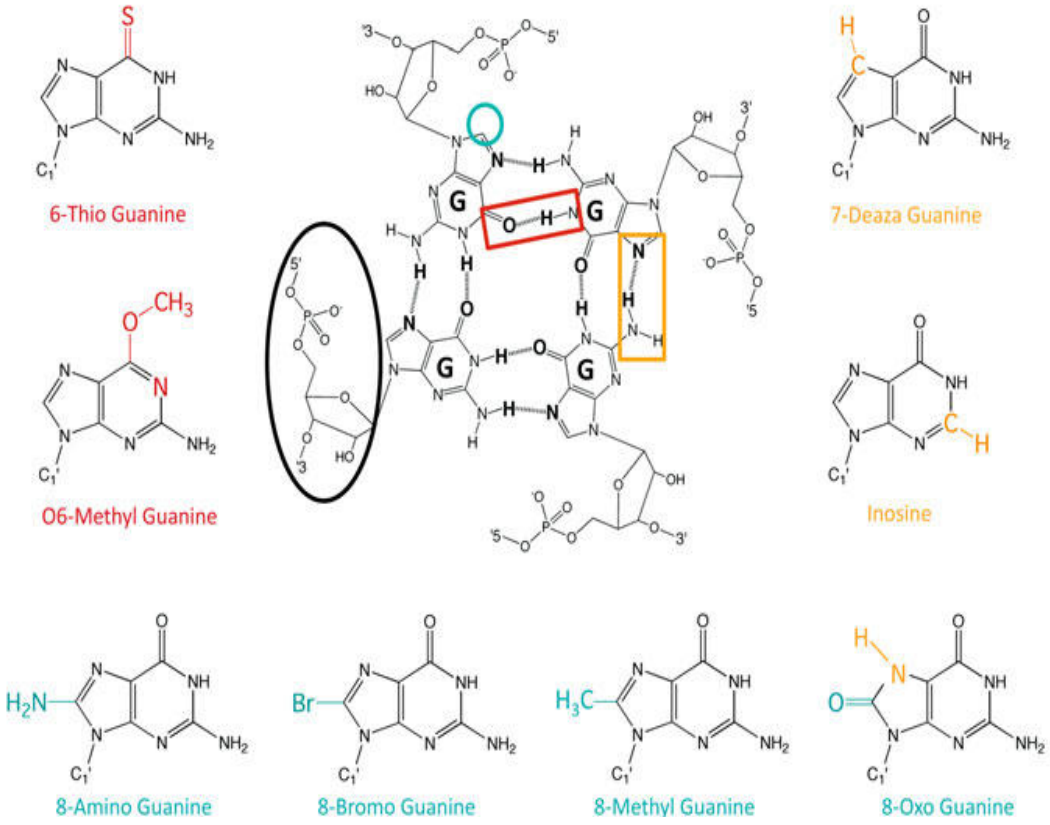

Figure-3 : G-quadruplex formation using modified guanine analogs

G-quadruplexes in human cell and its Relevance: In 2009 [51] scientists at the University of Cambridge, UK , has provided strong evidence of G-quadruplexes occurance in human cells and anticipiated that these unusual structures may have important biological functions [14]. The protective tips of chromosomal DNA, known as telomeres, are rich in guanine and so are likely candidates for G-quadruplex structures. In fact, studies in cancer cells have shown that small molecules that bind and stabilize G-quadruplex structures cause DNA damage at telomeres, supporting the argument [52]. Researchers have engineered an antibody that binds tightly and specifically to G-quadruplex structures and does not bind to double-stranded helical DNA. When the antibody are incubated with human cells in culture, they bound to many different sites in the chromosomes, only around a quarter of them in telomeres. The four-stranded packages of DNA, called G-quadruplexes, are formed by the interaction of four guanine bases that together make a square. They appear to be transitory structures, and are most abundant when cells are poised to divide. They form in

chromosomes and in telomeres, the caps on the tips of chromosomes that protect them from damage. Because cancer cells divide so rapidly, and often have defects in their telomeres, the quadruple helix might be a feature unique to cancer cells. If so, any treatments that target them will not harm healthy cells. The Unusual nucleic-acid structure may also have role in regulating some genes. The Four-strand DNA structure found in cells built using data from x-ray crystallography by Jean-Paul Rodriguez, and and Quadruple helix DNA discovered in human cells are shown in Figure-4

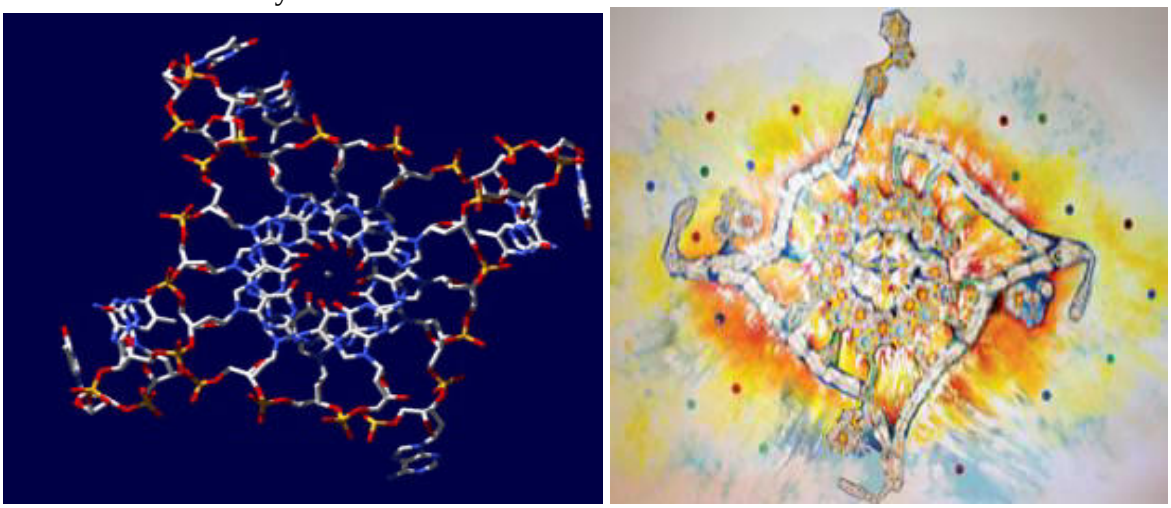

Figure-4 : Four-strand DNA structure found in cells built using data from x-ray crystallography b and Quadruple helix DNA discovered in human cells [14].

Many natural proteins have been identified that interact with quadruplex-DNA and Table-2 illustrates a range of protein activities that support the relevance of G-quadruplex DNA to replication and transcription.

Table 2: Selection of proteins that have been identified to interact with G-quadruplex DNA *in vitro* and that have been associated to G-quadruplex biology [53]

Protein	**Species**	**Type**	**Proposed function**
ATRX	Human	Nucleosome remodeling complex, possess homology with helicases	Modify epigenetic state at G-quadruplex sites and/or resolve G-quadruplexes.
BLM	Human Chicken	3′-to-5′ DNA helicase	Prevent genetic instability at G-quadruplex sites (not G-quadruplex specific).
DOG-1	*C. elegans*	5′-to-3′ DNA helicase (FancJ homologue)	Prevent genetic instability at G-quadruplex sites.
FANCJ	Human Chicken	5′-to-3′ DNA helicase	Prevent genetic and epigenetic instability at G-quadruplex sites (acting in concert with REV1 and/or WRN/BLM).
PIF1	*S. cerevisiae* Human	5′-to-3′ DNA helicase	Prevent genetic instability at G-quadruplex sites and inhibits telomere lengthening
RecQ	Gonococci *E. coli*	3′-to-5′ DNA helicase	Control G-quadruplex induced recombination events in pathogens
REV1	Chicken	Y family translesion polymerase	Prevent epigenetic instability at G-quadruplex sites
WRN	Human Chicken	3′-to-5′ DNA helicase	Prevent genetic instability at G-quadruplex sites (not G-quadruplex specific)

Conclusions: Guanine-rich DNA and RNA have the ability to form inter- and intramolecular four-stranded structures, referred to as G-quartets. G-quartets arise from the association of four G-bases into a cyclic Hoogsteen H-bonding arrangement, and each G-base makes two H-bonds with its neighbor G-base (N1 to O6 and N2 to N7). G-quartets stack on top of each other to give rise to tetrad-helical structures. The stability of G-quartet structures depends on several factors: the presence of the monovalent cations, the concentration of the G-rich oligonucleotides present, and the sequence of the G-rich oligonucleotides under study. Potassium with the optimal size to interact within a G-octamer greatly promotes the formation of G-quartet structures and increases their stability. Guanine base modifications **may** affect the DNA quadruplex structure, its apparent melting temperature, and/or its association rate. G-quartet oligodeoxynucleotides (GQ-ODNs) have been suggested to play a critical role in several biological processes including modulation of telomere activity, inhibition of human thrombin , HIV infection , HIV-1 integrase activity , human nuclear topoisomerase 1 activity , and DNA replication in vitro etc.

References:

[1].Watson JD and Crick FH , A structure of nucleic acids ; a structure for deoxyribose nucleic acid; *Nature* 1953, 171 : 737-738

[2]. Wang AHJ, Quigley GJ, Kolpak FJ, Crawford JL, van Boom JH, van der Marel G and Rich A, Molecular structure of a left-handed double helical DNA fragment at atomic resolution, *Nature* 1979, 282 : 680 – 686.

[3]. Frank-Kamenetskii MD, Mirkin SM, Triplex DNA structures, *Annu Rev Biochem.*, 1995, 64:65-95 and reference therein.

[4]. Gellert M, Lipsett MN, Davies DR , Helix formation by guanylic acid. *Proc Natl Acad Sci* USA, 1962, 48:2013–2018

[5]. Sasisekharan V, Zimmerman S and Davies DR , The structure of helical 5'-guanosine monophosphate, *J. Mol. Biol.* 1975, 92 : 171 – 179.

[6]. Guschlbauer W, Chantot JF and Thiele D, Fourstranded nucleic acid structures 25 years later: from guanosine gels to telomere DNA, *J. Biomol. Struct. Dyn*. 1990, 8: 491 – 511.

[7]. Sen D and Gilbert W, Formation of parallel four-stranded complexes by guanine-rich motifs in DNA and its implications for meiosis. *Nature* , 1988, 334 : 364 – 366.

[8]. Henderson E, Hardin CC, Walk SK, Tinoco I Jr and Blackburn EH , Telomeric DNA oligonucleotides form novel intramolecular structures containing guanine-guanine base pairs. *Cell*, 1987, 51: 899 – 908.

[9]. Sundquist WI and Klug A , Telomeric DNA dimerizes byformation of guanine tetrads between hairpin loops. *Nature* , 1989 , 342 : 825 – 829.

[10].Murchie AI and Lilley DM ,Retinoblastoma susceptibility genes contain 5' sequences with a high propensity to form guanine-tetrad structures, *Nucleic Acids Res.*, 1992, *20* : 49 –53.

[11]. Simonsson T, Pecinka P and Kubista M , DNA tetraplex formation in the control region of c-myc. *Nucleic Acids Res.*, 1998, 26 : 1167 – 1172.

[12]. Simonsson T and Sjöback R (1999). DNA tetraplex formation studied with fluorescence resonance energy transfer, *J. Biol. Chem.*, 1999, 274 : 17379 – 17383.

[13]. Hammond-Kosack MC, Kilpatrick MW and Docherty K , Analysis of DNA structure in the human insulin genelinked polymorphic region in vivo. *J. Mol. Endocrinol.*, 1992, 9 : 221 – 225.

[14]. Biffi G, Tannahill D, McCafferty J and Balasubramanian S, Quantitative visualization of DNA G-quadruplex structures in human cells, *Nature Chemistry*, 2013, 5 : 182–186

[15]. Smith FW, Lau FW, Feigon J , d(G3T4G3) forms an asymmetric diagonally looped dimeric quadruplex with guanosine 50-syn-syn-anti and 50-syn-anti-anti N-glycosidic

conformations. *Proc Natl Acad Sci USA*, 1994, 91(22):10546–10550
[16].Smith FW, Feigon J, Quadruplex structure of oxytricha telomeric DNA oligonucleotides. *Nature*, 1992, 356(6365):164–168
[17]. Mohanty D and Bansal M, Conformational polymorphism in G-tetraplex structures: strand reversal by base flipover or sugar flipover. *Nucleic Acids Res*., 1993, 21: 1767 – 1774.
[18]. Aboul-ela F, Murchie AI and Lilley DM, NMR study of parallel-stranded tetraplex formation by the hexadeoxynucleotide d(TG4T*), Nature*, 1992, 360 : 280 – 282.
[19]. Wang Y and Patel DJ , Guanine residues in d(T2AG3) and d(T2G4) form parallel-stranded potassium cation stabilized G-quadruplexes with anti glycosidic torsion angles in solution. *Biochemistry*, 1992, 31 : 8112 – 8119.
[20]. Wang Y and Patel DJ, Solution structure of a parallelstranded G-quadruplex DNA. *J. Mol. Biol.*, 1993a, 234:1171 – 1183.
[21]. Henderson E, Hardin CC, Walk SK, Tinoco I Jr and Blackburn EH , Telomeric DNA oligonucleotides form novel intramolecular structures containing guanine-guanine base pairs. *Cell*, 1987, 51 : 899 – 908.
[22]. Balagurumoorthy P, Brahmachari SK, Mohanty D, Bansal M and Sasisekharan V , Hairpin and parallel quartet structures for telomeric sequences, *Nucleic Acids Res.*, 1992, 20: 4061 – 4067.
[23]. Kang C, Zhang X, Ratliff R, Moyzis R and Rich A, Crystal structure of four-stranded Oxytricha telomeric DNA, *Nature* , 1992, 356 : 126 – 131.
[24]. Smith FW and Feigon J , Quadruplex structure of Oxytricha telomeric DNA oligonucleotides , *Nature*, 1992 , 356 : 164 – 168.
[25]. Smith FW and Feigon J, Strand orientation in the DNA quadruplex formed from the Oxytricha telomere repeat oligonucleotide d(G4T4G4) in solution, *Biochemistry*, 1993, 32: 8682 – 8692.
[26]. Greene KL, Wang Y and Live D , Influence of the glycosidic torsion angle on 13C and 15N shifts in guanosine nucleotides: investigations of G-tetrad models with alternating syn and anti bases. *J. Biomol.NMR*, 1995, 5*:* 333 – 338.
[27]. Catasti P, Chen X, Moyzis RK, Bradbury EM and Gupta G, Structure-function correlations of the insulin-linked polymorphic region, *J. Mol. Biol.*,1996, 264 : 534 – 545.
[28]. Smith FW, Lau FW and Feigon J , d(G3T4G3) forms an asymmetric diagonally looped dimeric quadruplex with guanosine 5'-syn-syn-anti and 5'-syn-anti-anti N-glycosidic conformations. *Proc. Natl. Acad. Sci.* USA, 1994, 91: 10546 – 10550.
[29]. Strahan GD, Shafer RH and Keniry MA, Structural properties of the [d(G3T4G3)]2 quadruplex: evidence for sequential syn-syn deoxyguanosines, *Nucleic Acids Res.*, 1994, 22: 5447 – 5455.
[30]. Wang Y and Patel DJ, Solution structure of the Oxytricha telomeric repeat d[G4(T4G4)3] G-tetraplex, *J. Mol.Biol*., 1995, 251 : 76 – 94.
[31]. Galezowska E, Gluszynska A, Juskowiak B , Luminescence study of G-quadruplex formation in the presence of Tb3+ ion, *J Inorg Biochem.*, 2007, 101(4) : 678–685
[32].Worlinsky JL, Basu S (2009) Detection of quadruplex DNA by luminescence enhancement of lanthanide ions and energy transfer from lanthanide chelates. *J Phys Chem B* 113(4):865–868
[33]. Huppert JL, Balasubramanian S, Prevalence of quadruplexes in the human genome. *Nucleic Acids Res.*, 2005, 33(9):2908–2916
[34]. Wong A and Wu G , Selective binding of monovalent cations to the stacking G-quartet structure formed by guanosine 50-monophosphate: a solid-state NMR study, *J Am Chem Soc.*, 2003, 125(45):13895–13905
[35]. Venczel EA, Sen D, Parallel and antiparallel G-DNA structures from a complex telomeric sequence, *Biochemistry*, 1993, 32(24):6220–6228

[36]. Simonsson T, G-Quadruplex DNA Structures–Variations on a Theme, *Biol. Chem.*, 2001, 382: 621 – 628 ·
[37]. Williamson J R, Guanine Quartets, Current Opinion in Structure Biology, 1993, 3: 357-362
[38]. Burge S, Parkinson GN, Hazel P, Todd AK and Neidle S , Quadruplex DNA: sequence, topology and structure, *Nucleic Acids Res.*, 2006, 34(19): 5402–5415
[39]. Scaria PV, Shire S J and Shafer RH , Quadruplex Structure of d(G3T4G3) Stabilized by K+ or Na+ is an Asymmetric Hairpin Dimer , *Proc. Nalt Acad Sci* , USA, 1992 , 89 : 10336- 10340.
[40]. Kang CH, Zhang X, Ralife R, Moyzis R and Rich A, Crystal Structure of Four Stranded Oxytrich- a Telomeric DNA , *Nature* , 1992 , 356 : 126-131.
[41].Smith FW and Feigon J, Quadruplex Structure of Oxytricha Telomeric DNA Oligonucleotids, *Nature*, 1992, 356: 164-168.
[42]. Szalai VA, Singer MJ, Thorp HH, Site-specific probing of oxidative reactivity and telomerase function using 7,8-dihydro-8-oxoguanine in telomeric DNA. *J Am Chem Soc.* 2002, 124(8) : 1625–1631
[43]. Esposito V, Randazzo A, Piccialli G, Petraccone L, Giancola C and Mayol L , Effects of an 8-bromodeoxyguanosine incorporation on the parallel quadruplex structure [d(TGGGT)]4. *Org Biomol Chem*. 2004, 2(3) : 313–318
[44]. Virgilio A, Esposito V, Randazzo A, Mayol L and Galeone A, 8-Methyl-20-deoxyguanosine incorporation into parallel DNA quadruplex structures. *Nucleic Acids Res.*, 2005, 33(19) : 6188–6195
[45]. Mekmaysy CS , Petraccone L, Garbett NC, Ragazzon PA, Gray R, Trent JO and Chaires JB, Effect of O6-methylguanine on the stability of G-quadruplex DNA. *J Am Chem Soc*. 2008, 130(21): 6710–6711
[46]. Matsugami A, Xu Y, Noguchi Y, Sugiyama H and Katahira M, Structure of a human telomeric DNA sequence stabilized by 8- bromoguanosine substitutions, as determined by NMR in a K+ solution, *FEBS J* 2007, 274(14) : 3545–3556
[47]. Gros J, Rosu F, Amrane S, Cian A D, Gabelica V, Lacroix L, and Mergny J L, Guanines are a quartet's best friend: impact of base substitutions on the kinetics and stability of tetramolecular quadruplexes. *Nucleic Acids Res.* 2007, 35(9): 3064–3075
[48]. Gros J, Aviñó A, Lopez de la Osa J, González C, Lacroix L, Pérez A, Orozco M, Eritja R and Mergny JL, 8-Amino guanine accelerates tetramolecular G-quadruplex formation,Chem Commun (Camb), 2008, 25 : 2926–8
[49]. Tran PLT, Virgilio A, Esposito V, Citarella G, Mergny JL and Galeone A, Effects of 8-methylguanine on structure, stability and kinetics of formation of tetramolecular quadruplexes. *Biochimie.*, 2011, 93(3) : 399–408
[50]. Amato J, Pagano B, Borbone N, Oliviero G, Gabelica V, Pauw ED, D'Errico S, Piccialli V, Varra M,Giancola C, Piccialli G, and Mayol L , Targeting G-quadruplex structure in the human c-Kit promoter with short PNA sequences, *Bioconjug Chem.*, 2011 22(4) : 654–663
[51]. Lipps H J and Rhodes D, G-quadruplex structures: in vivo evidence and function, Trends Cell Biol., 2009, 19 : 414–422.
[52]. Rodriguez R, Miller KM, Forment J V, Bradshaw C R, Nikan M and Britton S, Oelschlaegel T, Xhemalce B and Balasubramanian S and Jackson SP, Small molecule-induced DNA damage identifies alternative DNA structures in human genes, *Nature Chem. Biol*., 2012, 8 : 301–310.
[53]. Murat P and Balasubramanian' S, Existence and consequences of G-quadruplex structures in DNA, *Current Opinion in Genetics & Development*, 2014, *25* : 22–29
[54]. Maizels N and Gray LT , The G4 Genome, PLSO- Genetics, 2013, 9(4) : e1003468.