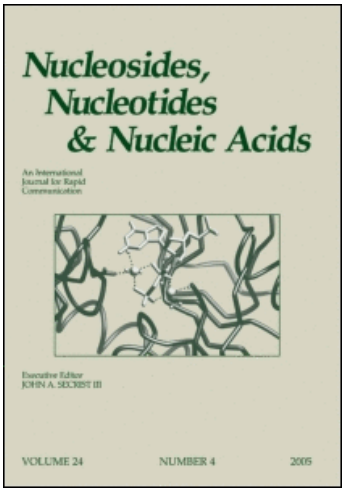


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# A Topological Classification of G-Quadruplex Structures

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# A TOPOLOGICAL CLASSIFICATION OF G-QUADRUPLEX STRUCTURES

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□ *A topological classification of most quadruplex structures is proposed, based on two main characteristics: 1) the relative orientation of the strands and 2) the nature of the loops connecting the strands.*

**Keywords** G-quadruplex; topological classification

G-quadruplexes showed a surprising structural variability.[1] Given the extreme complexity and variability of these structures, a classification taking into account all their aspects listed above is practically almost impossible. The lack of rules for their depiction makes cumbersome a comparison between results reported by different research groups taking into consideration the interdisciplinary interest in G-quadruplex structures. Since the number of structures being studied is rapidly increasing, the need now arises for a fast and easy comparison of the several complexes. Here we propose a topological classification of most of G-quadruplex structures which shows regard for two main characteristics: 1) the relative orientation of the strands and 2) the nature of the loops connecting strands.

## THE RELATIVE STRANDS ORIENTATION

Regarding this aspect, all theoretically possible cases have been observed. Quadruplex structures can be "parallel," "antiparallel" (two types), or "mixed parallel-antiparallel" (often labelled as 3+1). We suggest the

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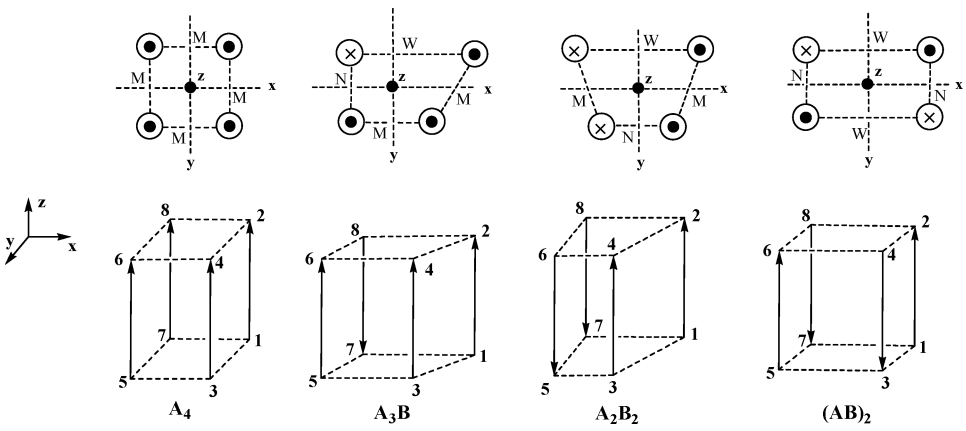


**FIGURE 1** Structures of the main four families and the ends numbering system proposed. Strands are arranged according the size of the grooves in the different complexes. The upper part of the figure shows an upside view of the structures where 5′ ends are indicated by an x and 3′ ends by a dot. N, M, and W indicate narrow, medium, and wide grooves, respectively.



following simple nomenclature: AAAA (or $A_4$) for parallel quadruplexes, AAAB (or $A_3B$) for mixed parallel-antiparallel ones and AABB (or $A_2B_2$) and ABAB [or $(AB)_2$] for the two types of antiparallel structures, in which A indicates strands pointing up and B strands pointing down (Figure 1). Owing to the different sizes of the grooves, these four main families are characterized by different symmetry properties. Limiting our discussion to axes, family $A_4$ shows a four-fold axis of symmetry (z axis), family $A_2B_2$ a two-fold axis of symmetry (y axis), family $(AB)_2$ three two-fold axes of symmetry (x, y, and z axes) while family $A_3B$ does not shows axes of symmetry.

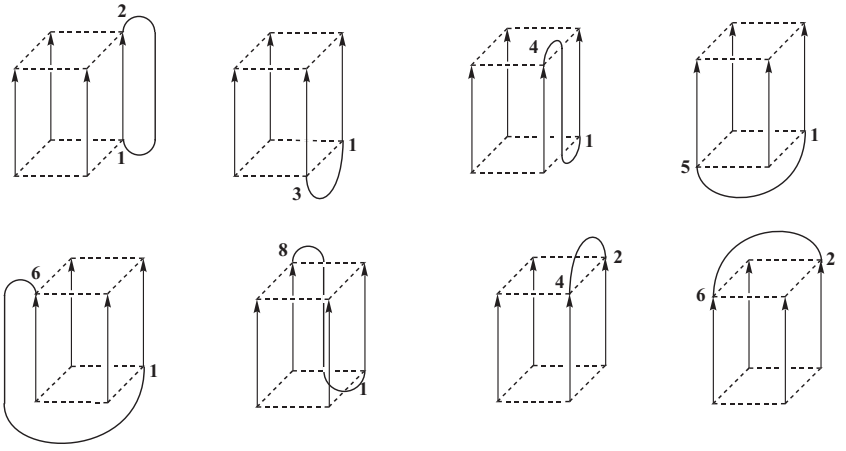

**FIGURE 2** Types of loops of the $A_4$ family.

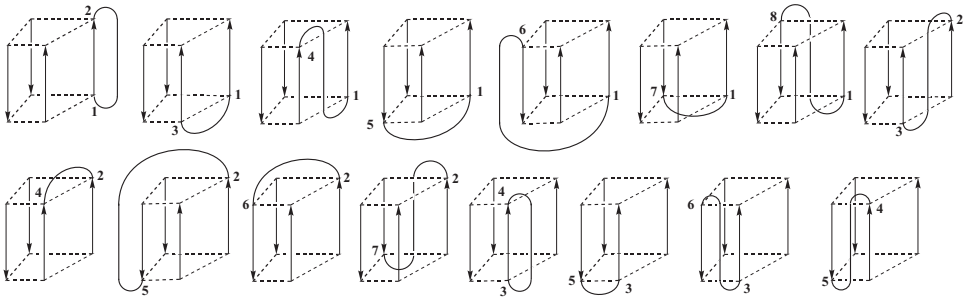

**FIGURE 3** Types of loops of the $A_2B_2$ family.

## THE NUMBER OF THE LOOPS CONNECTING STRANDS AND THEIR CONNECTIVITIES

Each of the four main families described above can be divided primarily in subfamilies according to the number of loops: one, two, three, or four and then to the loop connectivities. Taking into account the possible presence of 3′-3′ or 5′-5′ inversion of polarity sites, quadruplexes can show several types of loop connectivities being different for each of the four main families owing to the distinctive type of symmetry characterizing them. In order to classify all loop types is essential to indicate the eight ends (four 3′ and four 5′) in a quadruplex by numbers 1–8 (Figure 1). Conventionally, structures are arranged in such a way that most of the strands point up in 5′-3′ direction, then, numbers are assigned starting from the 5′ end of one strand pointing up and turning clockwise in such a way that smaller numbers are assigned to strands pointing up and ends in the underside are indicated by odd numbers, while ends in the upside by even numbers (Figure 1). This conventional numbering system allows us to identify each loop by a two-digit number indicating the connected ends. In Figures 2–4 are shown loops for $A_4$, $A_2B_2$ and $(AB)_2$ main families, respectively. Since each main family is characterized by distinctive symmetry properties, many loops turn out topologically equivalent. In these cases the correct loop number should be the lower one. For example, in family $A_4$ loops 24 and 46 are topologically equivalent since they result superimposable after a 90° clockwise rotation around the z axis of complex containing loop 24. On the other hand, loops 18 and 14 are not topologically equivalent since they cannot be superimposed by whichever structure rotation (Figure 5). It is evident that, in the

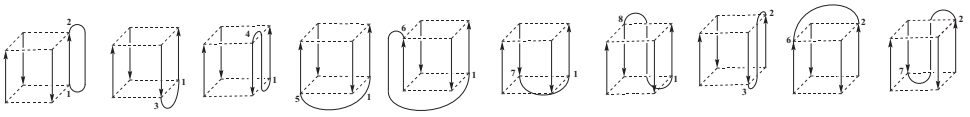

**FIGURE 4** Types of loops of the $(AB)_2$ family.

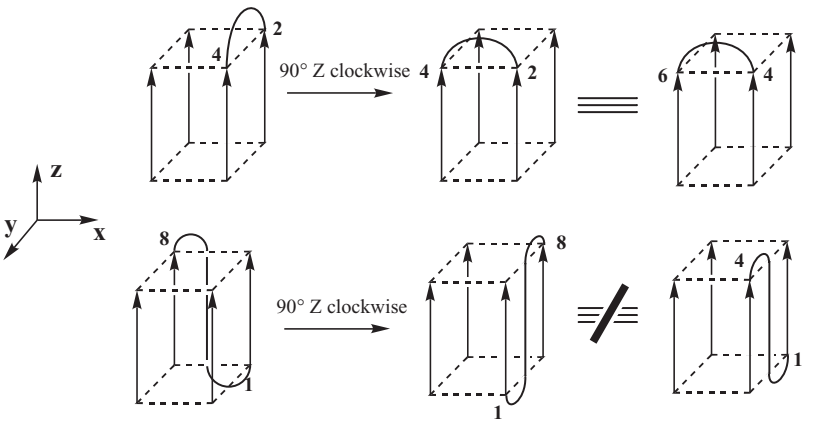


**FIGURE 5** Topological equivalence (see text).



case of quadruplexes containing more than one loop, the number of theoretically possible structures became dramatically large. Even though, the total number comes out seemingly unmanageable, every topological structure could be simply described by a train of two-digit numbers, from lowest to highest, each indicating a loop type. For example, quadruplex $(AB)_2$ 132857 contains the three loops 13, 28, and 57 and it matches the thrombin binding aptamer structure (TBA) (Figure 6). Should be noted that by using an alternative numbering system the name could be: $(AB)_2$ 134657. In this general case, is preferred the lowest number that is the first one. To date, only few structures have been investigated or proposed in comparison

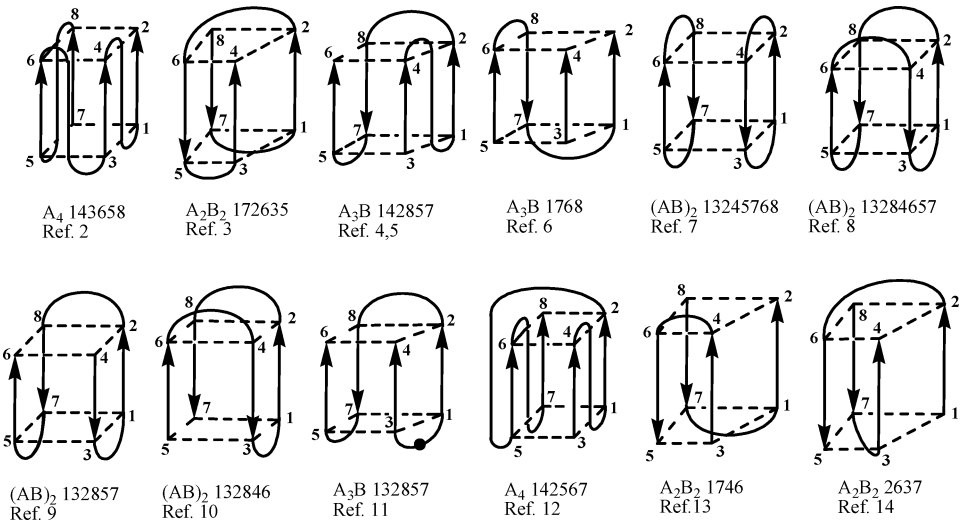


**FIGURE 6** Examples from the literature.

to the total number of topological possibilities. Some remarkable examples from literature[2–14] are showed in Figure 6, however some more complicated quadruplex structures could be classified only by an enhancement of the proposed classification, at the moment in progress.

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