Although many companies have developed major drug discovery programs screening for classical small-molecule inhibitors of telomerase activity, including focused sublibraries of reverse transcriptase inhibitors, a sufficiently potent and specific small-molecule inhibitor has not yet been found.

8.1 G-QUADRUPLEX LIGANDS

The substrate of telomerase is the single-stranded end of the telomeres, which must be in an unfolded, linear structure in order to fit the telomerase active site. The repeating G-rich sequences of telomeric DNA may form G-quadruplex structures in which four guanines are held in a planar rearrangement through the so-called Hoogsteen hydrogen bonding (Figure 7.28), with additional stabilization provided by a monovalent cation coordinated to the oxygen lone pairs. These secondary structures have been visualized with the selective antibody BG4.[177]

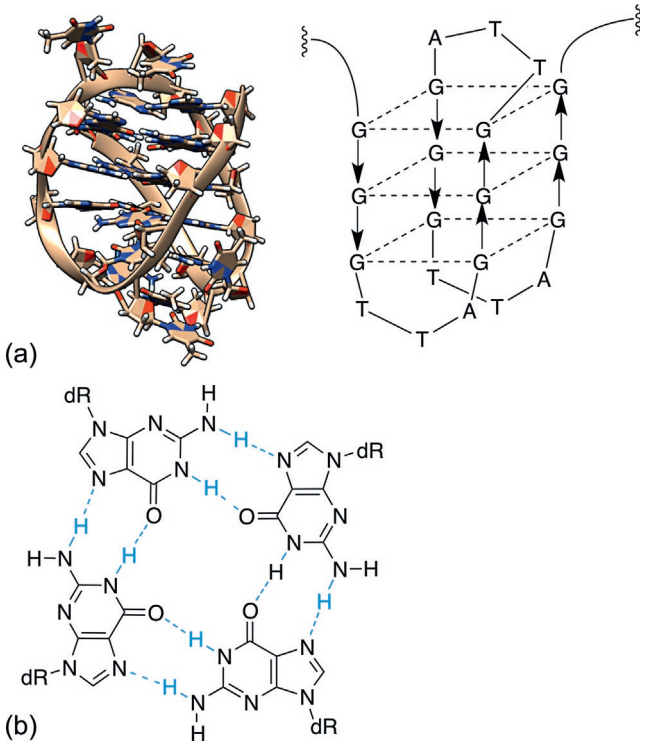

FIGURE 7.28

(a) Antiparallel DNA quadruplex. The three-dimensional structure was generated from Protein Data Bank reference 143D and displayed with Chimera 1.8.1. (b) Hydrogen bonding in DNA quadruplex.