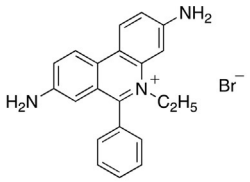
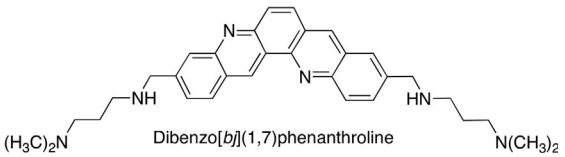
G-quadruplex-forming sequences in gene promoters are linked to the transcriptional activity of the proximal gene, as has been reported for cancer-related genes such as *c-Myc*, *c-Kit*, *k-Ras*, *VEGF*, *PDGF*, *HIF1α*, *Bcl-2* and *RET*. Following these findings, any molecule capable of interacting with a specific G-quadruplex could modulate the transcriptional activity of the associated gene.[178]

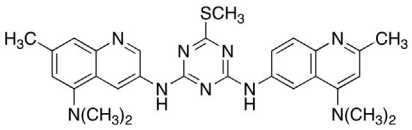
G-quadruplex ligands are often very similar to intercalating agents, and some of them, such as ethidium bromide, are prototype DNA intercalators. Nevertheless, the G-quadruplex nucleic acids have structural differences with the DNA double helix, and this provides a basis for selective recognition.[179] Most of the first-generation G-quadruplex ligands are polyaromatic molecules, such as dibenzophenanthroline and triazine derivatives, which interact by π-stacking and bear one or more substituents with positive charges, such as dibenzo[*bj*](1,7)phenanthroline and the quinoline-substituted compound 115405.[180] The natural product isolated from *Streptomyces anulatus* telomestatin is a potent G-quadruplex ligand that induces apoptosis of cancer cells through the displacement of POT1 (Protection of Telomere 1), a component of the protective telomeric protein shelterin[181] that modulates the activity of telomerase.[182] Shelterin is a protein complex with DNA remodeling activity that acts, together with several associated DNA repair factors, to change the structure of the telomeric DNA, thereby protecting chromosome ends. This complex is formed by six telomere-specific proteins that associate with the TTAGGG sequence. The shelterin subunits TRF1, TRF2, and POT1 recognize these repeats and are interconnected by shelterins TIN2, TPP1, and Rap1, forming a complex that allows cells to distinguish telomeres from sites of DNA damage. Without the protective activity of shelterin, telomeres are no longer hidden from the DNA damage surveillance and chromosome ends are inappropriately processed by DNA repair pathways. Many researchers suggest that shelterin dysfunction could play a major role in tumor formation. Specifically, induction of telomere uncapping due to abrogation of the TRF1 shelterin protein could be an alternative strategy to effectively kill cancer cells independently of the length of telomeres.[183]



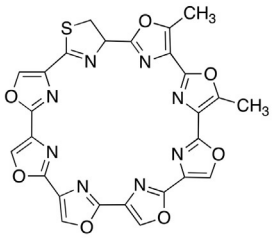
Ethidium bromide



Dibenzo[*bj*](1,7)phenanthroline



115405



Telomestatin

It has been shown that between telomestatin and a G-quartet are located potassium or ammonium cations and, consequently, the rational design of G-quadruplex binding ligands would have to consider the monovalent cation coordination capabilities of the possible ligands.[184] Some examples of second-generation G-quadruplex stabilizers[185] are also shown here.