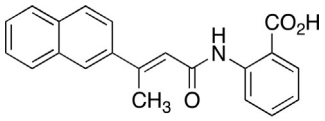
8.2 INHIBITORS OF TELOMERASE REVERSE TRANSCRIPTASE

Because human telomerase reverse transcriptase (hTERT) acts as a reverse transcriptase, it is not surprising that some nucleosides that inhibit HIV-1 reverse transcriptase, such as AZT, are also telomerase inhibitors, although with poor activity and selectivity. BIBR1532 (Sirong®) is a mixed-type noncompetitive inhibitor with a binding site distinct from the sites for deoxyribonucleotides and the DNA primer, respectively. This compound defined a novel class of telomerase inhibitors with mechanistic similarities to non-nucleosidic inhibitors of HIV1 reverse transcriptase.[188] It inhibits cell proliferation in lung, breast, fibrosarcoma, and prostate cancer cells through induction of *p21*, coupled with down-regulation of *c-Myc* and *hTERT* transcription.[189] However, its lengthy lag period poses a problem because in some cases it may be greater than the life expectancy of the patient.

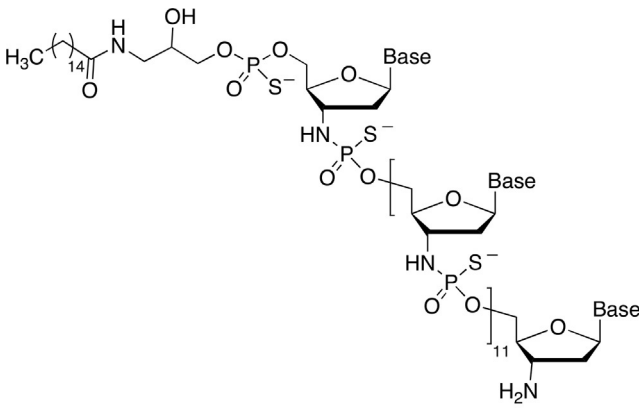


BIBR-1532

The selective inhibition of cancer cell growth through inhibition of hTERT by siRNA, antisense, or small-molecule inhibitors has been taken as a proof of principle that induction of telomere shortening is a viable therapeutic strategy in cancer.[190]

8.3 INHIBITORS OF THE RNA DOMAIN TEMPLATE

The human telomerase RNA component (hTR) has also been a target for antisense nucleotide approaches (for a more detailed discussion of antisense oligonucleotides, see Section 6 of Chapter 12). This hTR is not a messenger RNA and is not translated into a protein; therefore, these antisense oligomers will not have to compete with the ribosomal machinery and their toxicity will be low. Among the many antisense oligonucleotides targeted at hTR, the most advanced one is imetelstat (GRN-163 L), a 13-mer oligonucleotide belonging to the N3′–P5′ thiophosphoramidate (NPS) family that is covalently attached to a lipophilic palmitoyl moiety to enhance its potency.[191] Imetelstat has entered phase I and II clinical trials in patients with chronic lymphocytic leukemia, multiple myeloma (MM), and solid tumors,[192] but because of its hepatotoxicity, the FDA placed this drug on full clinical hold in 2014.



Imetelstat (GRN-163L)
Base sequence: 5'-Palm-TAGGGTTAGACAA-NH_2-3'