

Table VIII. Therapeutic Drugs that Target DNA Replication

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Inhibitors of Nucleotide Synthesis

Drug	Mechanism of Action	Therapeutic Applications
Methotrexate (MTX)	is a folic acid analogue that inhibits dihydrofolate reductase and the one carbon transfer reactions required for <i>de novo</i> synthesis of purines and thymidylate.	Childhood acute lymphoblastic leukemia; Choriocarcinoma; Some lymphomas and solid tumors; Psoriasis; Rheumatoid arthritis
Hydroxyurea (HU)	inhibits the enzyme ribonucleoside diphosphate reductase, which is required for reduction of ribonucleotides to deoxyribonucleotides.	Chronic myelogenous leukemia; Sickle cell disease
5-Fluorouracil (5-FU; FU)	is converted into 5-fluoro-2'-deoxyuridine monophosphate and inhibits thymidylate synthase. 5-FUTP is incorporated into DNA and RNA.	Several carcinomas (gastro-intestinal, head and neck, breast)

DNA Polymerase Inhibitors

Drug	Mechanism of Action	Therapeutic Applications
Cytosine Arabinoside (AraC)	is converted into the 5'-triphosphate form and competes with dCTP for incorporation into nascent DNA. This inhibits further DNA synthesis.	Acute myelocytic leukemia; Childhood leukemia
Acyclovir (Acy)	is a guanine nucleoside (lacking a cyclic sugar) that is selectively phosphorylated by viral thymidine kinases and selectively incorporated into DNA by viral DNA polymerases. This terminates further extension of the DNA strand.	Herpes Simplex Virus 1 and 2 infections; Varicella Zoster Virus infections
Ganciclovir (Gan)	acts as does Acyclovir, but it is recognized by human cytomegalovirus encoded enzymes more efficiently than those encoded by Herpes Simplex Virus types 1 and 2.	Cytomegalovirus infections in immuno-compromised patients
Foscarnet (FOS)	is a phosphonoformate salt that inhibits viral DNA polymerases by competitive binding to their pyrophosphate-binding sites	Cytomegalovirus infections in immuno-compromised patients
Gemcitabine (dFdC)	is a nucleoside analog that is incorporated into replicating DNA, resulting in partial chain termination and stalling of replication forks.	Pancreatic, lung and bladder cancers

DNA-Template Damaging Agents

Drug	Mechanism of Action	Therapeutic Applications
Cyclophosphamide	is a cyclic phosphamide with a <i>bis</i> -(2-chloroethyl) group that can be metabolized by cells into phosphoramidate mustard which alkylates macromolecules, including DNA, and cross-links the two DNA strands.	Breast cancer and other carcinomas; Burkitt's lymphoma and other non-Hodgkin's lymphomas
Bleomycin (BLM)	is a glycopeptide that forms complexes with Cu^{++} or Fe^{++} to generate O_2 free radicals that cause single and double-strand DNA breaks.	Testicular and ovarian cancer
Doxorubicin (Dox)	is an anthracycline that intercalates into DNA. In the presence of NADPH, it can generate free radicals that oxidize bases and produces single and double-strand DNA breaks.	Carcinomas including breast; Sarcomas including osteogenic; Hodgkin's and non-Hodgkin's lymphomas
Mitomycin C (MTC)	is a complex quinone that upon reduction alkylates and cross-links DNA.	Various carcinomas (e.g. cervical, stomach, breast, head and neck, and lung)
Cisplatin (CDDP)	is an inorganic complex of platinum that cross-links DNA.	Testicular and ovarian cancers; Lung, gastric, and bladder carcinomas

DNA Topoisomerase Inhibitors

Drug	Mechanism of Action	Therapeutic Applications
Camptothecin (CPT)	is a five-membered ring alkaloid that traps topoisomerase I-DNA complexes. This causes protein-linked DNA single-strand breaks and replication double-strand breaks.	Colon, lung and ovarian carcinomas; Leukemia and gastric cancer
Etoposide (VP-16)	is a complex sugar-ring structure that traps topoisomerase II-DNA complexes. This causes protein-linked DNA single- and double-strand breaks.	Testicular, lung and gastric cancers; Leukemia and sarcomas
Doxorubicin (Dox)	is an anthracycline that intercalates into DNA and traps topoisomerase II-DNA complexes. This causes protein-linked DNA single and double-strand breaks. It also generates free radicals.	Carcinomas including breast; Sarcomas including osteogenic; Hodgkin's and non-Hodgkin's lymphomas.
Daunorubicin	has the same mode of action as doxorubicin.	Leukemia