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CHEMOTHERAPEUTICS, ANTICANCER

Cancer is second only to cardiovascular disease as the principal cause of human mortality (see Cardiovascular agents). As the median age of populations have risen, total deaths from cancer have increased. Treatment of cancer includes surgery, radiation, and chemotherapy. In those instances where a tumor is locally confined, has not metastasized, and is resectable, surgery alone or combined with local radiation may be curative. For the majority of patients, however, physicians are forced to rely on chemotherapy either as a means to attack residual disease following surgery and/or radiation, or as the primary treatment method. Chemotherapy encompasses the use of both cytotoxic agents and relatively nontoxic hormonal agents for the control of tumor growth (1).

Approaches to cytotoxic chemotherapy include special emphasis on drug targeting and toxicity alleviation. The directions in which new drug discovery strategies are moving and the criteria used for advancing compounds into clinical trials (2) are discussed herein, as are all of the drugs approved by the United States Food and Drug Administration (FDA) for the treatment of cancer as of this writing and those compounds in clinical trials.

1. Chemotherapeutic Agents

The majority of cytotoxic chemotherapeutic agents in clinical use were discovered empirically using cell cytotoxicity assays followed by assessment in an animal tumor model, usually an *in vivo* leukemia model such as L1210 or P388 (3). On the basis of the activity in those models and other murine solid tumor models, a large number of compounds advanced to human clinical trials where a low percentage were found to have sufficient activity in humans to justify approval as cancer chemotherapeutic agents. It is increasingly clear that these selection criteria were flawed (4). Concurrently, an increased knowledge of the biological complexity of cancer and the mechanism of action of drugs has permitted the design of more rational screens for the discovery of new lead structures and the design and synthesis of compounds targeted to specific receptors or enzymes involved in the pathogenesis of cancer (5).

At the preclinical level of discovery in the 1990s there is a greater reliance on the use of human tumor cell lines and clonogenic assays derived from primary explants (6). As the development of resistance to cytotoxic agents by tumor cells is better understood, it has become possible to assemble panels of cell lines consisting of a parent cell line and one or more resistant cell lines wherein the mechanism of resistance has been identified and quantitated, ie, expression of multidrug resistant (MDR) genes, increased glutathione [70-18-8] levels, and increased DNA repair. The use of mechanism-based screens such as specific oncogene tyrosine kinase assays, topoisomerase I and/or II assays, and tubulin assays has also become possible (5).

At the *in vivo* assay level, the classic ip-ip (interaperitoneal) *in vivo* model has been replaced as a selection criteria for advancement of new drug candidates to clinical trial. More stringent alternative models include subcutaneous or subrenal capsule implantation of tumor followed by intravenous drug dosing (7) and the human tumor xenograft models in nude mice (8).

Table 1. Antimetabolites[a]

Drug (trade name)	CAS Registry Number	Molecular formula	Molecular weight	Structure number	Disease	Toxic effects
5-azacitidine[b] (Mylosar)	[320-67-2]	$C_8H_{12}N_4O_5$	244.21	(**1**)	acute myelogenous leukemia	nausea, vomiting; he-patic dysfunction; myelosuppression
cytarabine USP[b] (Cytosar)	[147-94-4]	$C_9H_{13}N_3O_5$	243.22	(**2**)	acute granulocytic leu-kemia (adults); acute lymphocytic leukemia (children); Hodgkin's disease	bone-marrow depres-sion; hepatic toxic-ity; megaloblastosis; nausea; vomiting; diarrhea
gemcitabine[c]	[95058-81-4]	$C_9H_{11}F_2N_3O_4$	263.20	(**3**)	investigational drug; responses seen in Phase I trials in co-lon and nonsmall cell lung cancer	myelosuppression ob-served as dose limit-ing toxicity
floxuridine USP[d] (FUDR)	[50-91-9]	$C_9H_{11}FN_2O_5$	246.21	(**4**)	palliative treatment of gastrointestinal ad-enocarcinoma with liver metastases	severe hematological toxicity; gastrointes-tinal hemorrhage; nausea; vomiting; diarrhea; enteritis; stomatitis; erythema
fluorouracil USP[d] (Fluorouracil)	[51-21-8]	$C_4H_3FN_2O_2$	130.08	(**5**)	palliative treatment of carcinoma of colon, rectum, breast, stomach, and pan-creas	bone-marrow depres-sion; dermatitis; alo-pecia; nausea; vom-iting; diarrhea; stomatitis; anorexia; GI ulcers; skin pig-mentation
mercaptopurine USP[e] (Purinethol)	[6112-76-1]	$C_5H_4N_4S$	152.19	(**6**)	acute leukemia (more effective in children than in adults); chronic granulocytic leukemia	bone-marrow depres-sion; hepatic toxic-ity; anemia; gas-trointestinal (GI) ulceration; nausea; vomiting
thioguanine USP[e] (Tabloid)	[154-42-7]	$C_5H_5N_5S{\cdot}XH_2O$	167.19	(**7**)	acute leukemia; chronic granulocytic leukemia	bone-marrow depres-sion; stomatitis; an-orexia; nausea; vom-iting
methotrexate[f] USP (Methotrexate)	[59-05-2]	$C_{20}H_{22}N_8O_5$	454.46	(**8**)	acute lymphocytic leu-kemia; meningeal leukemia; choriocar-cinoma; chorioaden-oma destruens; lym-phosarcoma; osteogenic sarcoma; cancer of lung, neck, head, cervix; my-cosis fungoides; hy-datidiform mole high dose MTX fol-lowed by leucovorin rescue in nonmetas-tatic osteosarcoma	bone-marrow depres-sion; renal and he-patic toxicity; enteri-tis; stomatitis; alo-pecia; abdominal dis-tress; erythematous rash; oral and GI ul-ceration; diarrhea; nausea; vomiting
leucovorin[f] (calcium USP)	[58-05-9]	$C_{20}H_{21}CaN_7O_7$	511.51	(**9**)	high dose methotrex-ate rescue therapy in osteosarcoma	allergic sensitization

Table 1. ***Continued***

Drug (trade name)	CAS Registry Number	Molecular formula	Molecular weight	Structure number	Disease	Toxic effects
DDATHF[c] (Ly237147) (Lome-trexol sodium)	[120408-07-3]	$C_{21}H_{23}N_5Na_2O_6$	487.42	(**10**)	investigational drug	
trimetexate[g]	[52128-35-5]	$C_{19}H_{23}N_5O_3$	369.42	(**11**)	investigational drug; partial remissions in soft tissue sarcomas observed	myelosuppression; mu-cositis; nausea; vom-iting; skin rash
hydroxyurea USP[h] (Hydrea)	[127-07-1]	$CH_4N_2O_2$	76.05	(**12**)	chronic granulocytic leukemia; mela-noma; cancer of ovary, head, neck	vomiting; anorexia; fe-ver; bone-marrow depression; nausea; diarrhea

[a] See Figure 2.
[b] Upjohn.
[c] Lily.
[d] Hoffmann-La Roche.
[e] Burroughs Wellcome.
[f] Lederle.
[g] Parke-Davis.
[h] Bristol-Myers Squibb

In addition to a greater emphasis on *in vivo* evaluation as a means of assessing activity, there is also increased awareness of metabolism and pharmacokinetics in candidate selection (9). The use of prodrug strategies to improve water solubility, oral absorption, and other pharmaceutical properties has increased (10). Finally, the ability to assess potential toxic liabilities of a new drug candidate has improved as more predictive models for myelosuppression, ie, neutropenia and thrombocytopenia, emesis, and renal, cardiac, and hepatic toxicities, have been developed (11, 12).

The modern drug discovery team consists of medicinal chemists, biologists, metabolism and pharmacokinetics specialists, and toxicologists working together to improve drug selection.

Drugs used in cancer chemotherapy or clinical trials are classified according to primary underlying mechanisms of action. However, many drugs operate through multiple mechanisms. Mechanisms include those of antimetabolites, DNA alkylating and/or cross-linking agents, DNA binding/cleaving agents, DNA topoisomerase interactive compounds, agents which act on tubulin structure, and hormones (qv) (Fig. 1). In addition to those drugs which have already been approved by the FDA, a number of investigational drugs are undergoing clinical evaluation and many others are in the pipeline.

1.1. Antimetabolites

Antimetabolites, which represent one of the earliest groups of anticancer agents, are listed in Table 1. Structures are shown in Fig. 2.

The classification of these drugs as antimetabolites stems from the mode of action as antagonists to the natural metabolic processes leading to either DNA, RNA, or protein synthesis (13) (see Nucleic acids; Proteins). They either inhibit function of a key enzyme involved in protein synthesis or are recruited into the cell division process as DNA synthesis terminators. For example, methotrexate (8) is a folic acid [59-30-3], $C_{19}H_{19}N_7O_6$, antagonist and has a 100,000-fold greater affinity for the enzyme, dihydrofolate reductase [9002-03-3] (DHFR), than does the enzyme's natural substrate, folic acid. Inhibition of DHFR function, ie, conversion of folic acid to folinic acid [58-05-9] (leucovorin) (9), results in the arrest of purine and pyrimidine synthesis which culminates in cell death. The use of high dose methotrexate treatment followed by leucovorin rescue, ie, toxicity amelioration, has resulted in significant improvements in the treatment of nonmetastatic

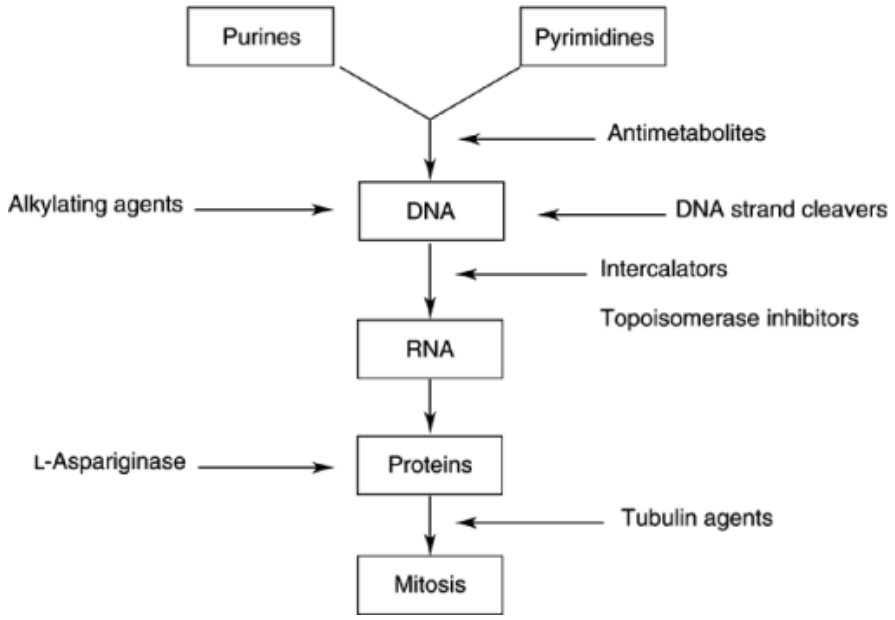


Fig. 1. Schematic of nucleic acid and protein synthesis and the steps leading to mitosis showing the common mechanisms of action and various classes of chemotherapeutic agents.

osteosarcoma. In the early 1990s, the use of high dose regimens followed by rescue with colony stimulating factors (CSFs) (14) has been extended to bone marrow transplantation.

Antimetabolites may be further classified as inhibitors of pyrimidine, purine, or glutamine metabolism. The compounds are cell cycle dependent.

1.2. DNA Alkylating/Cross-Linking Agents

This category includes compounds of diverse chemical classes (Table 2) eg, nitrosoureas (**13–16**) nitrogen mustards (**18–24**), mitomycins (**25–27**), and platinums (**28,29**), that have the ability to react covalently with DNA bases and to form inter- and intrastrand DNA cross-links (15–17). These compounds may also be responsible for the alkylation of proteins and protein–DNA linkages. The resulting lesions produced in the DNA result in disruption of cell growth and function, ultimately leading to cell death. The onset of action of this class of agents can be rapid, resulting in dramatic tumor shrinkage. However, because of the effects on normal cells, all compounds of this class are myelosuppressive and potentially teratogenic, mutagenic, and carcinogenic. In some cases the resulting myelosuppression has limited the ability of these drugs to be effective clinically. In other cases the rapid onset of resistance can occur; this limits utility as well as that of related analogues, because of cross resistance (18) (Fig. 3).

1.3. DNA Binding/Cleaving Agents

DNA binding and/or cleaving agents that have anticancer activity are listed in Table 3. Structures are shown in Fig. 4. All of the natural products (**31,32,35,36,38,39**) and analogues of natural products (**33,34,37**) in this category (Table 3) are able to bind DNA either as intercalators (**31–34**) or as minor groove binders

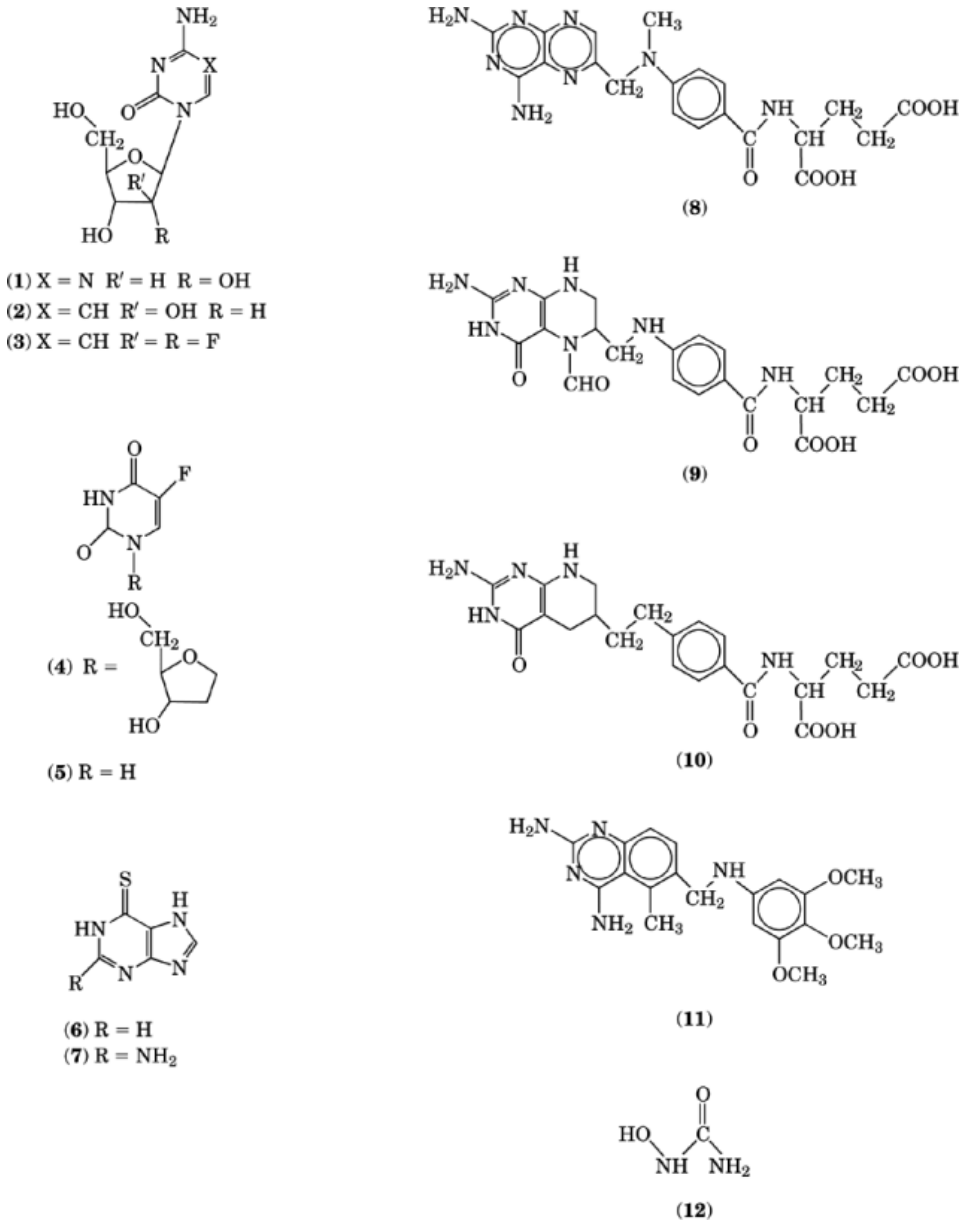


Fig. 2. Structures of antimetabolites listed in Table 1.

(**35–37**), hence inhibiting DNA dependant RNA synthesis (**15–17**). Both bleomycin (**35**) and esperamicin A_1 (**36**) cleave DNA by forming free radicals in the immediate vicinity of the sugar–phosphate backbone. Activity as antitumor agents is related to the ability to induce irreparable lesions in DNA (15, 19). Bleomycin generates oxygen free-radical species whereas esperamicin A_1 and a number of related natural products that include neocarzinostatin, dynemicin, and the calicheamicins, generate aryl diradical species, which abstract hydrogen atoms directly from the deoxyribose backbone (19). An analogue of the natural product CC1065 (**37**) has the

unique property of being a DNA alkylating agent which recognizes poly-AT regions of the minor groove of DNA. It remains to be seen if the high potency and unique modes of action ascribed to these novel classes of agents can translate into clinically useful drugs (Figure 4) (20).

Table 2. DNA Alkylating/Cross-Linking Agents[a]

Drug (trade name)	CAS Registry Number	Molecular formula	Molecular weight	Structure number	Disease	Toxic effects
carmustine USP[b] (BiCNU)	[154-93-8]	$C_5H_9Cl_2N_3O_2$	214.05	(**13**)	Hodgkin's disease; non-Hodgkin's lym-phomas; meningeal leukemia; brain tu-mor; multiple mye-loma	bone-marrow depres-sion; hepatic toxic-ity; nausea; vomit-ing
lomustine USP[b] (CeeNU)	[13010-47-4]	$C_9H_{16}ClN_3O_2$	233.70	(**14**)	malignant brain tu-mors; Hodgkin's dis-ease	bone-marrow depres-sion; hepatic toxicity
tauromustine[c]	[85977-49-7]	$C_7H_{15}ClN_4O_4S$	286.73	(**15**)	investigational drug responses observed in malignant mela-noma	gastrointestinal; thrombocytopenia
streptozocin USP[d] (Zanosar)	[18883-66-4]	$C_8H_{15}N_3O_7$	265.22	(**16**)	metastatic islet cell carcinoma of the pancreas	bone-marrow depres-sion; renal and he-patic toxicity; nau-sea; vomiting
busulfan USP[e] (Myleran)	[55-98-1]	$C_6H_{14}O_6S_2$	246.29	(**17**)	chronic granulocytic leukemia; other myeloproliferative disorders	bone-marrow depres-sion; hyperuricemia; gynecomastia; amenorrhea; skin hyperpigmentation
cyclophosphamide USP[b] (Cytoxan)	[6055-19-2]	$C_7H_{15}Cl_2N_2O_2P$	279.10	(**18**)	acute and chronic lym-phocytic leukemia; lung cancer; rhab-domyosarcoma; neuroblastoma; ovarian and mam-mary carcinoma; multiple myeloma; lymphosarcoma; Burkitt's lymphoma; Hodgkin's disease; retinoblastoma; my-cosis fungoides	bone-marrow depres-sion; hepatictoxic-ity; cystitis; alope-cia; nausea; vomiting
ifosphamide USP[b] (Ifex)	[3778-73-2]	$C_7H_{15}Cl_2N_2O_2P$	261.09	(**19**)	germ cell testicular cancer; used in com-bination with mesna	myelosuppression; urotoxicity; alopecia; nausea; vomiting; CNS toxicities
mesna USP[b] (Mesnex)	[19767-45-4]	$C_2H_5NaO_3S_2$	164.17	(**20**)	prophylactic preven-tion of hemorrhagic cystitis	
mechlorethamine hydrochloride USP[f] (Must-argen)	[55-86-7]	$C_5H_{11}Cl_2N{\cdot}HCl$	192.52	(**21**)	Hodgkin's disease; non-Hodgkin's lym-phomas; lymphosar-coma; cancer of breast, ovary, lung; neoplastic effusion	bone-marrow depres-sion; nausea; vomit-ing; anorexia; diar-rhea; local irritation

Table 2. ***Continued***

Drug (trade name)	CAS Registry Number	Molecular formula	Molecular weight	Structure number	Disease	Toxic effects
chlorambucil USP[e] (Leukeran)	[305-03-3]	$C_{14}H_{19}Cl_2NO_2$	304.22	(**22**)	chronic lymphocytic leukemia; cancer of ovary, breast, testis; Hodgkin's disease; non-Hodgkin's lym-phomas	bone-marrow depres-sion; nausea; vomit-ing
melphalan USP[e] (Alkeran)	[148-82-3]	$C_{13}H_{18}Cl_2N_2O_2$	305.20	(**23**)	multiple myeloma; plasmacytic mye-loma; cancer of breast and ovary	bone-marrow depres-sion; nausea; vomit-ing; anorexia
thiotepa USP[g] (Thiotepa)	[52-24-4]	$C_6H_{12}N_3PS$	189.21	(**24**)	cancer of breast, ovary, lung, bladder; Hodgkin's disease; nonHodgkin's lym-phomas; neoplastic effusion	bone-marrow depres-sion; amenorrhea; anorexia; nausea; vomiting
mitomycin C USP[b] (Muta-mycin)	[50-07-7]	$C_{15}H_{18}N_4O_5$	334.33	(**25**)	chronic myelogenous leukemia; reticulum cell sarcoma; Hodg-kin's disease; non-Hodgkin's lympho-mas; cancer of stomach, pancreas, lung; epithelial tu-mors	bone-marrow depres-sion; renal toxicity; alopecia; stomatitis; anorexia; nausea; vomiting
BMY-25067[b]	[95056-36-3]	$C_{23}H_{25}N_5O_7S_2$	547.60	(**26**)	investigational drug	
KW2149[h]	[118359-59-4]	$C_{24}H_{34}N_6O_8S_2$	598.70	(**27**)	investigational drug	
cisplatin USP[b] (Platinol)	[15663-27-1]	$Cl_2H_6N_2Pt$	300.06	(**28**)	metastatic testicular tumors; metastatic ovarian tumors; ad-vanced bladder can-cer	nephrotoxicity; ototox-icity; myelosuppres-sion; nausea; vomit-ing; allergic reaction
carboplatin USP[b] (Paraplatin)	[41575-94-4]	$C_6H_{12}N_2O_4Pt$	371.25	(**29**)	recurrent ovarian carcinoma	bone-marrow suppres-sion; emesis; allergic reactions
dacarbazine USP[i] (DTIC)	[4342-03-4]	$C_6H_{10}N_6O$	182.18	(**30**)	malignant melanoma; Hodgkin's disease; soft tissue sarcomas	bone-marrow depres-sion; flulike syn-drome; alopecia; nausea; vomiting; anorexia

[a] See Figure 3.
[b] Bristol-Myers Squibb.
[c] Pharmacia.
[d] Upjohn.
[e] Burroughs Wellcome.
[f] Merck Sharp & Dohme.
[g] Lederle.
[h] Kyowa-Hakko.
[i] Dome.

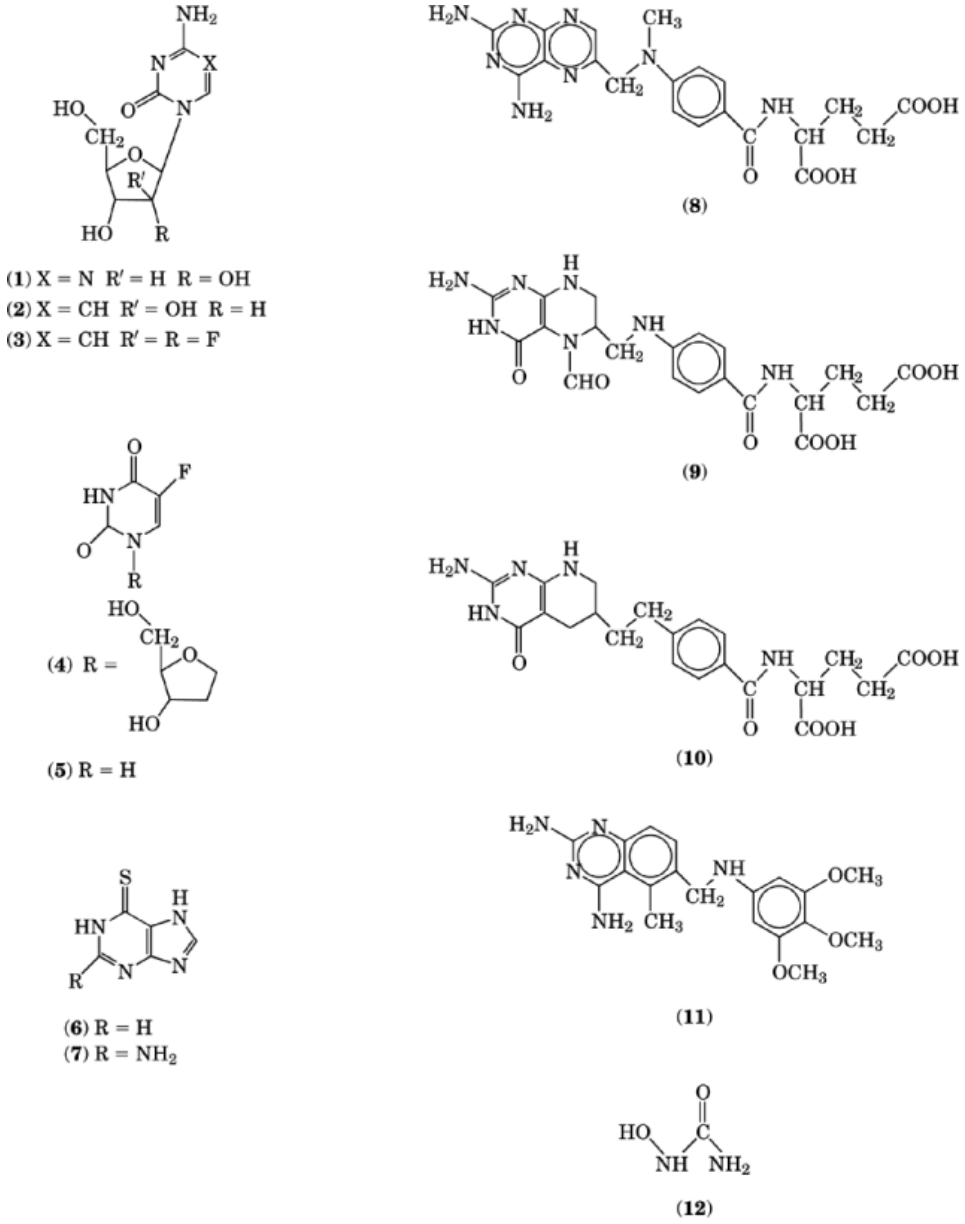


Fig. 3. Structures of DNA alkylating/cross-linking agents given in Table 2.

1.4. Topoisomerase Interactive Drugs

Topoisomerases I and II have emerged as interesting targets for the design of new anticancer agents (15, 21) (Table 4). Etoposide (**41**) and related epipodophyllotoxin analogues (**42,43**) produce DNA strand scission via the mediation of topoisomerase II. Additional work with other clinically active agents, such as adriamycin (**32**) and amsacrine (**47**), indicate that these compounds interact with topoisomerase also. A number of drugs are known to work on topoisomerase II only. However, camptothecin [7689-03-4] and its analogues, CPT 11 (**44**)

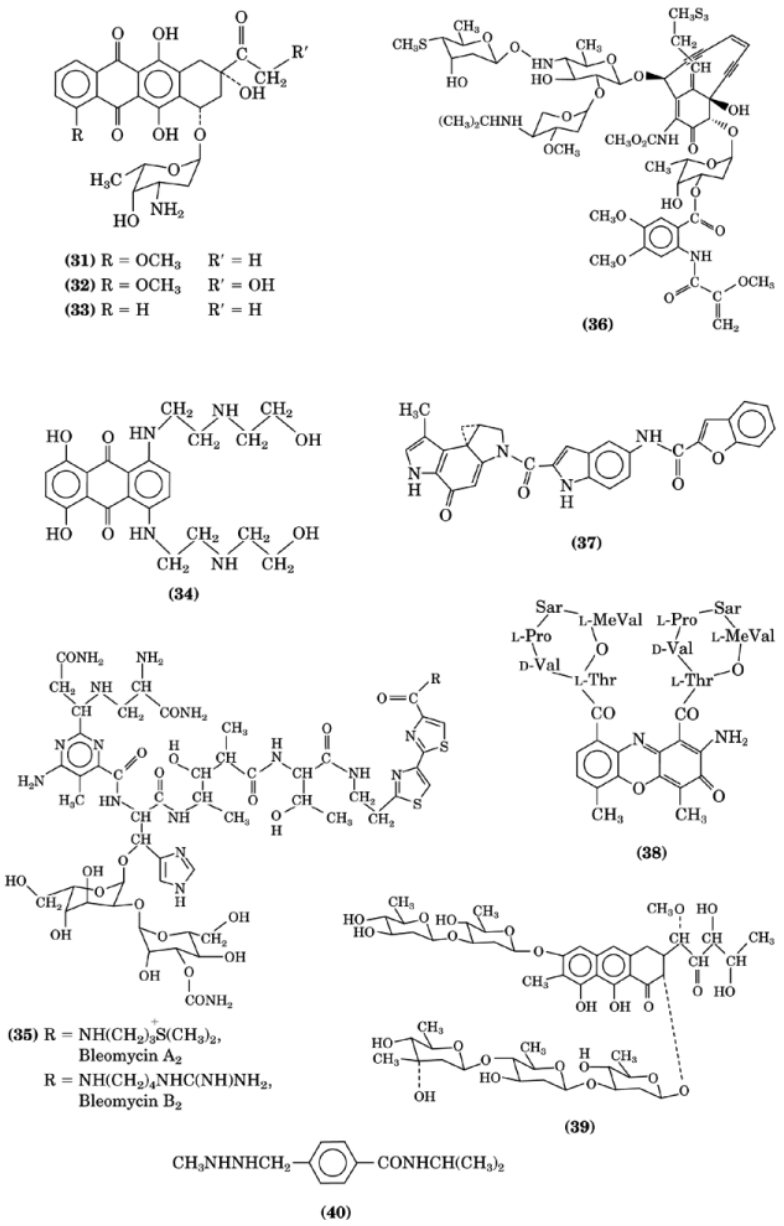


Fig. 4. Structures of DNA interactive agents are given in Table 3. In structure (**38**) L-MeVal is 1-*N*-methyl valine.

and topotecan (**45**), have been shown to target topoisomerase I (22). Encouraging solid tumor activity of these agents in Phase I trials has sparked an intense effort to identify further examples of topoisomerase I inhibitors (Fig. 5).

Table 3. DNA Interactive Agents[a]

Drug (trade name)	CAS Registry Number	Molecular formula	Molecular weight	Structure number	Disease	Toxic effects
daunorubicin hydrochloride USP[b] (Cerubidine)	[20830-81-3]	$C_{27}H_{29}NO_{10}\cdot HCl$	563.99	(**31**)	acute lymphocytic and granulocytic leuke-mia; lymphomas	bone-marrow depres-sion; cardiac toxic-ity; alopecia; stoma-titis; GI disturbance
doxorubicin USP[c] (Adriamycin)	[23214-92-8]	$C_{27}H_{29}NO_{11}$	543.53	(**32**)	soft-tissue and osteo-genic sarcomas; Hodgkin's disease; non-Hodgkin's lym-phomas; acute leuke-mia; cancer of thy-roid, breast, lung, genitourinary (GU) tract; Wilm's tumor; neuroblastoma	bone-marrow depres-sion; cardiac toxic-ity; alopecia; stoma-titis; GI disturbance
idarubicin hydrochloride[c] (Idamycin)	[57852-57-0]	$C_{26}H_{27}NO_9\cdot HCl$	533.96	(**33**)	acute myeloid leuke-mia in adults	bone-marrow suppres-sion; cardiotoxicity; nausea; vomiting; alopecia
mitoxanthrone hydrochloride USP[d] (Novantrone)	[70476-82-3]	$C_{22}H_{28}N_4O_6\cdot 2HCl$	517.41	(**34**)	acute nonlymphocytic leukemia including myelogenous pro-myelocytic, monocy-tic and erythroid acute leukemias	nausea; vomiting; alo-pecia; mucositis; sto-matitus; myelo-suppression; cardio-toxicity; allergic reaction; phlebitis
bleomycin sulfate USP[e] (Blenoxane)	[11056-06-7]	mixture of bleo-mycin A_2, B_2 as primary components		(**35**)	squamous cell carci-noma of head, neck, esophagus, skin, GU tract; testicular tu-mor; Hodgkin's lym-phomas	pulmonary fibrosis; skin reactions; alo-pecia; nausea; vom-iting; anorexia; fe-ver; stomatitis
esperamicin A_1[e]	[99674-26-7]	$C_{59}H_{80}N_4O_{22}S_4$	1324.41	(**36**)	investigational drug	
Adozelesin[f] (U73,975)	[110314-48-2]	$C_{30}H_{22}N_4O_4$	502.30	(**37**)	investigational drug	
dactinomycin USP[g] (Cosmegen)	[50-76-0]	$C_{62}H_{86}N_{12}O_{16}$	1255.43	(**38**)	Wilm's tumor; Ewing's tumor; choriocarci-noma; testicular car-cinoma; rhabdo-myosarcoma; neuroblastoma; melanoma; soft-tissue and osteo-genic sarcomas	bone-marrow depres-sion; renal and hepatic toxicity; alo-pecia; mental depression; stomati-tis; nausea; vomit-ing; diarrhea; an-orexia; local irritation
plicamycin USP[h] (Mithracin)	[18378-89-7]	$C_{52}H_{76}O_{24}$	1085.16	(**39**)	testicular tumors; hy-percalcemia and hy-percalciuria associ-ated with advanced malignancies	bone-marrow depres-sion; hepatic and renal toxicity; hypo-calcemia; hemor-rhage; stomatitis; nausea; vomiting; anorexia; diarrhea

Table 3. ***Continued***

Drug (trade name)	CAS Registry Number	Molecular formula	Molecular weight	Structure number	Disease	Toxic effects
procarbazine hydrochloride USP[i] (Matulane)	[366-70-1]	$C_{12}H_{19}N_3O{\cdot}HCl$	257.76	(**40**)	Hodgkin's disease; non-Hodgkin's lym-phomas; lung cancer	bone-marrow depres-sion; neurological and dermatological toxicity; nausea; vomiting

[a] See Figure 4.
[b] Wyeth-Ayerst.
[c] Adria.
[d] Lederle.
[e] Bristol-Myers Squibb.
[f] UpJohn.
[g] Merck Sharp & Dohme.
[h] Miles.
[i] Hoffmann-La Roche.

1.5. Tubulin Active Drugs

Vinblastin (**48**) and vincristin (**49**), two very useful natural products derived from Vinca rosea (periwinkle plant), were discovered in the early days of cancer chemotherapy (Table 5), (Fig. 6).

(23). Vinblastin and vincristin are highly cell cycle dependent. They disrupt the mitotic spindle by promoting the disassembly of the microtubules essential for cell division. This results in cell death during replication. Vinblastin and vincristin differ minimally from one another structurally, but have different clinical utilities. A search for additional members of the Vinca alkaloid family has resulted in two new investigational drugs, vindesine (**50**) and navelbine (**51**) (24) (see Alkaloids), currently undergoing clinical trial. Initial results using navelbine indicate that this compound may find use in nonsmall cell lung cancer (25).

Taxol (**52**), a compound isolated from the pacific yew tree *Taxus brevifolia* (26), has shown high response rates in a variety of solid tumors including refractory ovarian cancer, refractory breast cancer, head and neck cancer, melanoma, and lung cancer. The mechanism of action for taxol is also linked with tubulin. However, unlike the Vinca alkaloids, taxol accelerates tubule formation and stabilizes it to depolymerization (27). The clinical development of taxol is dependent on identifying a renewable source. Once the FDA approves this drug for therapeutic use, large (kilogram) quantities are expected to be needed for the treatment of large patient populations. Approaches being investigated to address the problem of renewable source include cultivation, tissue culture, semisynthesis, and total synthesis (28). Resolution of supply problems also are needed to permit exploration of the full potential of this drug.

In addition to the Vinca alkaloids and taxol, a limited number of other cytotoxic agents have been demonstrated to act at the level of tubulin. This list includes colchicine [64-86-8] and the various podophyllotoxins and further underscores the importance of tubulin and microtubule formation as targets for anticancer drug action.

1.6. Hormones

Although not strictly cytotoxic, hormones (qv) have been used to control the environment of hormone dependent tumors such as those of the prostate, breast, and endometrium (29), ie, androgens are used to control the growth of estrogen dependent breast tumors, whereas estrogens control androgen dependent tumors of the prostate. Hormones that have anticancer activities are listed in Table 6. Structures are shown in Figure 7. In addition to the steroidal hormones (**57, 59–62**) several nonsteroidal hormones have been introduced (**54–56**) as have

Table 4. Topoisomerase Interactive Drugs[a]

Drug (trade name)	CAS Registry Number	Molecular formula	Molecular weight	Structure number	Disease	Toxic effects
etoposide USP[b] (Vepesid)	[33419-42-0]	$C_{29}H_{32}O_{13}$	588.56	(**41**)	refractory testicular tumors; small cell lung cancer	myelosuppression; mild to moderate nausea and vomit-ing; transient hypo-tension; allergic re-actions; alopecia
etoposide phosphate[b]	[117091-64-2]	$C_{29}H_{33}O_{16}P$	712.51	(**42**)	investigational drug; prodrug of etoposide	prodrug of etoposide
teniposide[b]	[29767-20-2]	$C_{32}H_{32}O_{13}S$	656.67	(**43**)	refractory acute lym-phocytic leukemia in children	myelosuppression; mild to moderate nausea and vomit-ing; transient hypo-tension; allergic re-actions; alopecia
CPT-11[c]	[100286-90-6]	$C_{33}H_{38}N_4O_6{\cdot}HCl$	622.78	(**44**)	investigational drug; topoisomerase I in-hibitor	
topotecan hydro-chloride[d]	[119413-54-6]	$C_{23}H_{23}N_3O_5{\cdot}HCl$	457.91	(**45**)	investigational drug; topoisomerase I in-hibitor	
elsamitrucin tartrate[b]	[123303-9S-7]	$C_{33}H_{35}NO_{13}{\cdot}C_4H_6O_4$	771.37	(**46**)	investigational drug	
amsacrine[e] (Amsidyl)	[51264-14-3]	$C_{21}H_{19}N_3O_3S$	393.46	(**47**)	investigational drug	

[a] See Figure 5.
[b] Bristol-Myers Squibb.
[c] Yakult Honsha.
[d] Smith Kline Beecham.
[e] Parke-Davis.

leutenizing hormone-releasing hormone (LHRH) agonists. These are often used in combinations. For example, LHRH analogues (**63,64**), antiestrogens (**54**), aromatase inhibitors (**62**), and progestins all are used in the control of breast cancer (30). LHRH analogues suppress estrogen production in the ovaries and are used in premenopausal breast cancer patients.

Aromatase inhibitors, which suppress estrogen production outside the ovaries, are useful for the treatment of tumors in postmenopausal women. Tamoxifen (**54**) is very well tolerated and is considered the drug of choice in post menopausal patients. The progestational agents medroxyprogesterone (**59**) and megestrol acetate (**60**) are used in the treatment of endometrial tumors to block overstimulation of the ovaries by estrogen. Megestrol acetate has been reported to have utility in reversing cachexia associated with cancer (31).

1.7. Miscellaneous Agents

Those chemotherapeutic agents, which do not fit into any of the classifications discussed, are listed in Table 7. Mitotane (**67**), a structural isomer of DDT, is used to induce chemical adrenalectomies in patients having adrenal cancer by reducing host levels of adrenocorticosteroids.

The retinoid isotretinoin (**68**) has been found to reduce the incidence of secondary malignancies in patients treated for head and neck cancer. In addition, the use of *trans*-retinoic acid in patients having M3 leukemia has been reported to induce complete, although temporary, remissions (32).

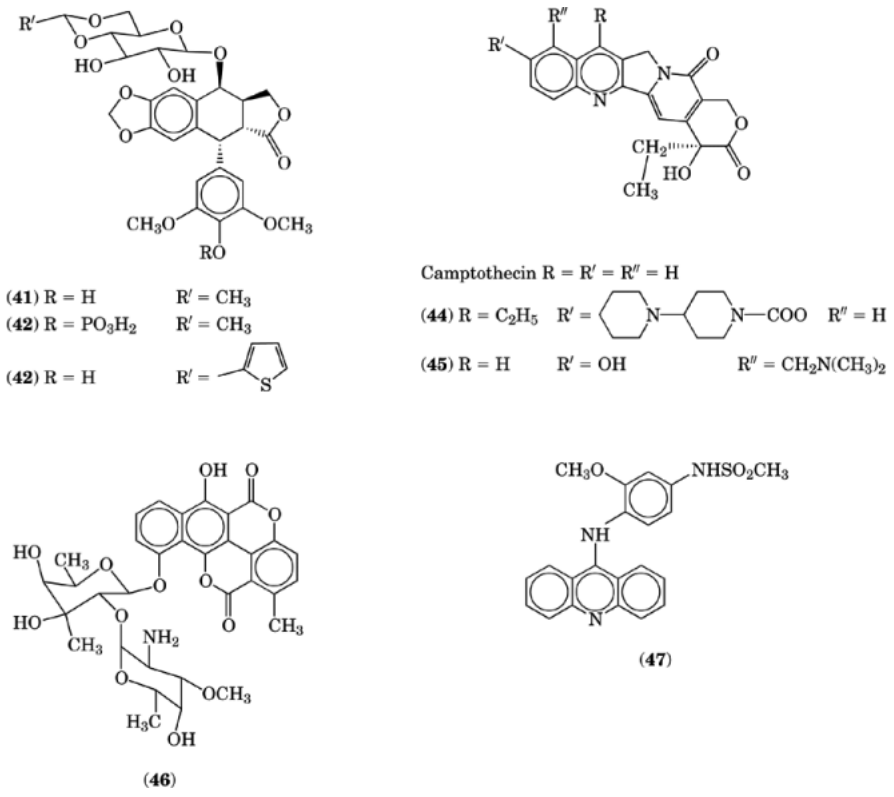
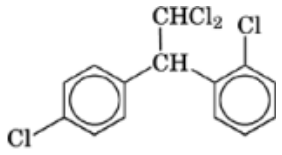
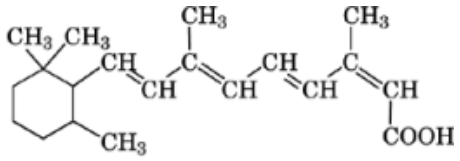


Fig. 5. Structures of topoisomerase interactive drugs given in Table 4.

The novel agent sulofenur (**69**) has entered clinical trials based on its broad spectrum antitumor activity in tumor models, its unusual mechanism of action, and its lack of cross-resistance to other agents (33). In Phase I clinical trials, the drug was well tolerated and some clinical responses were noted.



(**67**)

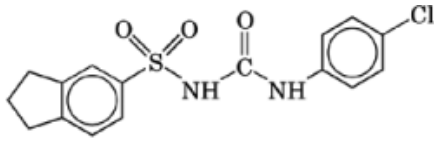


(**68**)

Table 5. Tubulin Active Drugs[a]

Drug (trade name)	CAS Registry Number	Molecular formula	Molecular weight	Structure number	Disease	Toxic effects
vinblastin sulfate USP[b] (Velban)	[143-67-9]	$C_{46}H_{58}N_4O_9 \cdot H_2SO_4$	909.06	(**48**)	Hodgkin's disease; lymphosarcoma; re-ticulum-cell sar-coma; neuroblas-toma; choriocarcinoma; carcinoma of breast, lung, oral cavity, testis, bladder; acute and chronic leuke-mia; histiocytosis; mycosis fungoides	leukopenia; neurologi-cal toxicity (pares-thesias, mental depression, loss of deep tendon re-flexes, etc); dysfunc-tion of autonomic nervous system (ileus, constipation, urinary retention, etc); alopecia; sto-matitis; nausea; vomiting; local irri-tation
vincristin sulfate USP[b] (Oncovin)	[2068-78-2]	$C_{46}H_{56}N_4O_{10} \cdot H_2SO_4$	923.04	(**49**)	acute leukemia in chil-dren; lymphocytic leukemia; Hodgkin's disease; non-Hodg-kin's lymphomas; Wilm's tumor; neuroblastoma; rhabdomyosarcoma.	neurological toxicity (paresthesias, foot drop, double vision, etc); constipation; ileus; alopecia; leu-kopenia (occasional);
vindesine sulfate[b] (Eldisine)	[59917-39-4]	$C_{43}H_{55}N_5O_7 \cdot H_2SO_4$	852.01	(**50**)	investigational drug	
navelbine[c] (Vinorelbine)	[71486-22-1]	$C_{45}H_{54}N_4O_8$	778.45	(**51**)	investigational drug; nonsmall cell lung cancer	
taxol[d]	[33069-62-4]	$C_{47}H_{51}NO_{14}$	853.92	(**52**)	investigational drug; refractory ovarian cancer; refractory breast cancer; mela-noma; lung cancer; head and neck can-cer	alopecia; neutropenia; hypersensitivity; mucositis; neuropa-thy
taxotere[e] (Docetaxol)	[114977-28-5]	$C_{43}H_{53}NO_{14}$	807.43	(**53**)	investigational drug	

[a] See Figure 6.
[b] Lilly.
[c] Pierre Fabre.
[d] Bristol-Myers Squibb.
[e] Rhône-Poulenc.



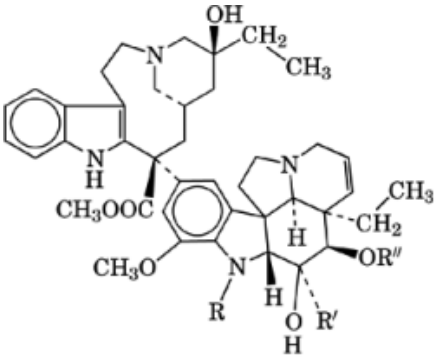
(**69**)

The enzyme L-asparaginase is the only biological agent included in this review. Most normal cells are capable of synthesizing their own L-asparagine; leukemic cells are deficient in this regard. Use of the enzyme

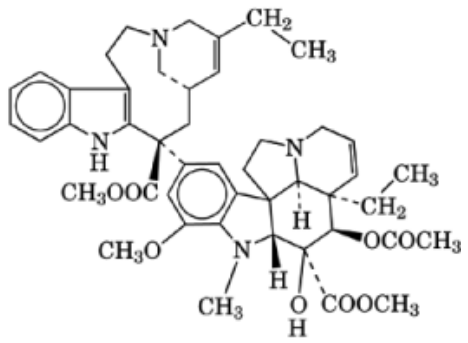
Table 6. Hormonal Therapy[a]

Drug (trade name)	CAS Registry Number	Molecular formula	Molecular weight	Structure number	Disease	Toxic effects
tamoxifen citrate USP[b] (Nolvadex)	[54965-24-1]	$C_{26}H_{29}NO{\cdot}C_6H_8O_7$	563.65	(**54**)	breast cancer	visual disturbances
diethylstilbestrol diphosphate USP[c] (Stilphos-trol)	[522-40-7]	$C_{18}H_{22}O_8P_2$	428.31	(**55**)	prostatic carcinoma	fluid retention; hyper-calcemia; common side effects of steroids
chlorotrianisene USP[c] (TACE)	[569-57-3]	$C_{23}H_{21}ClO_3$	380.87	(**56**)	androgen dependent carcinoma of the prostate	fluid retention; hyper-calcemia; common side effects of steroids
estradiol USP[d] (Estrace)	[50-28-2]	$C_{18}H_{24}O_2$	272.39	(**57**)	breast cancer; pros-tatic carcinoma	fluid retention; hyper-calcemia; common side effects of steroids
estramustine phosphate so-dium USP[e] (Emcyt)	[52205-73-9]	$C_{23}H_{30}Cl_2N{\cdot}Na_2O_6P$	564.35	(**58**)	prostatic carcinoma	side effects because of estradiol; increased dyspnea; nausea; vomiting
medroxyproges-terone acetate[f] (USP Depo-provera)	[71-58-9]	$C_{24}H_{34}O_4$	386.53	(**59**)	metastatic endome-trial carcinoma; renal carcinoma	fluid retention; hyper-calcemia; common side effects of steroids
megestrol acetate USP[d] (Megace)	[595-33-5]	$C_{24}H_{32}O_4$	384.51	(**60**)	carcinoma of the breast or endrome-trium	fluid retention; hyper-calcemia; common side effects of steroids
testolactone USP[d] (Teslac)	[968-93-4]	$C_{19}H_{24}O_3$	300.40	(**61**)	breast cancer	fluid retention; hyper-calcemia; common side effects of steroids
formestane[g] (Lentaron)	[566-48-3]	$C_{19}H_{26}O_3$	302.41	(**62**)	investigational drug; postmenopausal breast cancer	
goserelin USP[b] (Zoladex)	[65807-02-5]	$C_{59}H_{84}N_{18}O_{14}$	1269.43	(**63**)	prostatic carcinoma	bone pain; common hormonal side effects
leuprolide ace-tate USP[h] (Leupron)	[74381-53-6]	$C_{59}H_{84}N_{16}O_{12}{\cdot}C_2H_4O_2$	1269.47	(**64**)	prostatic carcinoma	common hormonal side effects
octreotide ace-tate USP[i] (Sandostatin)	[79517-01-4]	$C_{49}H_{66}N_{10}O_{10}S_2{\cdot}xC_2H_4O_2$	1019.24	(**65**)	mestastatic carcinoid tumors; vasoactive intestinal peptide-secretory tumors metastatic prostatic carcinoma in combi-nation with	nausea; diarrhea; loose stools; vomit-ing; abdominal pain; pain on injection
flutamide[j] (Eulexin)	[13311-84-7]	$C_{11}H_{11}F_3N_2O_3$	276.21	(**66**)	LHRH agonist	diarrhea

[a] See Figure 7.
[b] ICI.
[c] Marion-Merrill Dow.
[d] Bristol-Myers Squibb.
[e] Pharmacia.
[f] Upjohn.
[g] CIBA-GEIGY.
[h] TAP.
[i] Sandoz.
[j] Schering.



(**48**) R = CH_3 R′ = $COOCH_3$ R″ = CH_3CO^-
(**49**) R = CHO R′ = $COOCH_3$ R″ = CH_3CO^-
(**50**) R = CH_3 R′ = $CONH_2$ R″ = H



(**51**)

(**52**) R = C_6H_5 R′ = CH_3CO
(**53**) R = $OC(CH_3)_3$ R′ = H

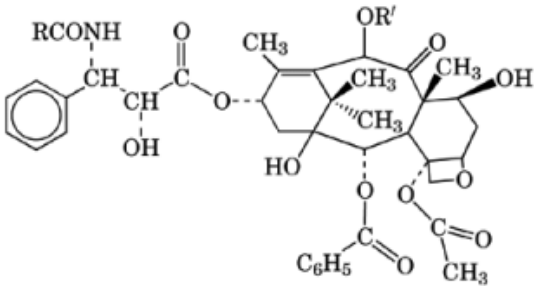


Fig. 6. Structures of tubulin active drugs listed in Table 5.

causes depletion of the exogenous L-asparagine necessary to the growth of the leukemia. Some remissions have been seen using this drug, however, they are usually transitory in nature because of the rapid emergence of resistance.

2. Toxicity

As a result of the life threatening nature of cancer and the general lack of therapeutically effective drugs for most cancers, doses of chemotherapeutic drugs in Phase I clinical trials are escalated until the emergence of a dose-limiting toxicity. The efficacy of these compounds in one or more tumor types is then established in Phase II/III clinical trials. The commonly observed dose-limiting toxicities include myelosuppression, gastrointestinal upset, and renal, hepatic, and cardiotoxicities.

The most common dose-limiting toxicity in cytotoxic chemotherapy is acute or cumulative suppression of bone marrow, ie, myelosuppression. To circumvent this, intermittent treatment schedules using suboptimal drug doses are often employed. Another approach involves either autologus, ie, derived from the same individual, or allogeneic, ie, derived from a different individual, bone marrow transplant accompanied by high dose therapy (34). Although therapeutic advantages have been achieved, patients are highly vulnerable to serious infections during the recovery period following reinfusion of bone marrow. When administered after infusion of the bone marrow, recombinant colony stimulating factors (CSFs) (14), granulocyte-macrophage-CSF

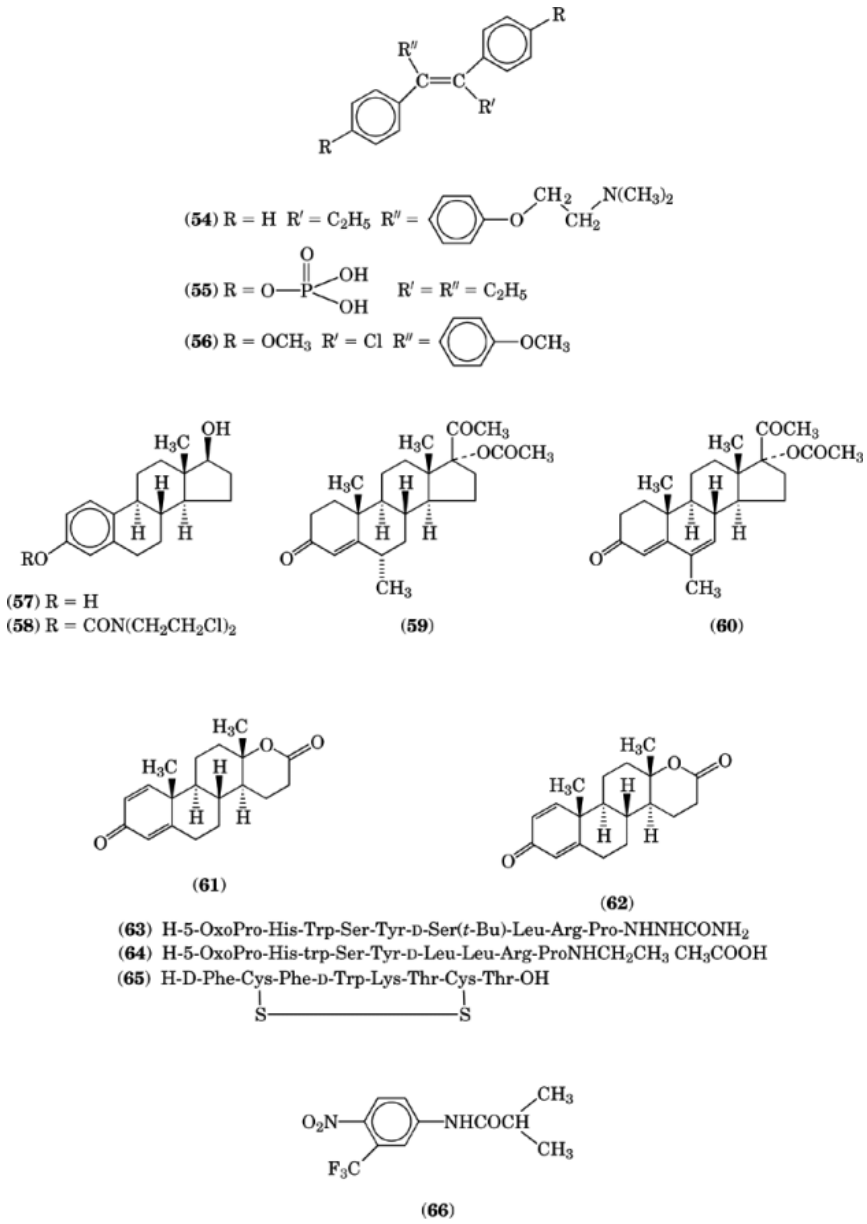


Fig. 7. Structures of hormone chemotherapeutic agents given in Table 6.

(GM-CSF), and macrophage-CSF (M-CSF) stimulate the growth of white blood cells, particularly granulocytes, macrophages, and monocytes, hence shortening the recovery period so patients suffer fewer infections.

Cumulative organ toxicity also presents a significant obstacle for effective chemotherapy. In many cases, the severity of the toxicity impedes the broader use of an agent. Other specific toxicities are associated with specific agents, for example cardiotoxicity with adriamycin (**32**), renal toxicity with *cis*-platinum (**28**), and neurotoxicity with vincristine (**49**).

Table 7. Chemotherapeutic Agents

Drug (trade name)	CAS Registry Number	Molecular formula	Molecular weight	Structure number	Disease	Toxic effects
mitotane USP[a] (Lyso-dren)	[53-19-0]	$C_{14}H_{10}Cl_4$	320.05	(**67**)	palliative treatment of inoperable adrenal cortical carcinoma	skin toxicity; vertigo; lethargy; somno-lence; anorexia; nau-sea; vomiting; diar-rhea
isotretinoin USP[b] (Accu-tane)	[4759-48-2]	$C_{20}H_{28}O_2$	300.44	(**68**)	investigational drug	
sulofenur[c]	[110311-27-8]	$C_{16}H_{15}ClN_2O_3S$	350.82	(**69**)	investigational drug; refractory ovarian carcinoma response seen in Phase I	anemia; methemoglo-binemia
asparaginase[d] (Elspar)	[9015-68-3]				acute lymphocytic leukemia	hepatic, renal, and pancreatic toxicity; neurological effects; hypersensitivity reactions; clotting ab-normalities; nausea

[a] Bristol-Myers Squibb.
[b] Hoffmann-La Roche.
[c] Lilly.
[d] Merck Sharp & Dohme.

2.1. Toxicity Amelioration

Cancer researchers traditionally have not focused their attention on the question of toxicity amelioration. This is partly attributed to the lack of predictive animal models for human toxicities. For example, the preclinical rat model, used as a predictor of myelosuppression, has failed to predict myelosuppression in humans in clinical trials. In addition, reduction of one toxicity may result in the emergence of another, more serious problem. Research efforts to address the problem of toxicity amelioration has progressed in several directions. The three most prominent areas are analogue synthesis, chemoprotection, and drug targeting.

2.1.1. Analogue Synthesis

Two notable examples, in which analogues have greater therapeutic indexes than the parent drugs, have been identified in Phase I trials. These are carboplatin (**29**) and adozelesin (**37**) (35). Carboplatin's approval was based on its comparable efficacy to cis-platinum (**28**) and its more favorable toxicity profile, ie, reduced and delayed episodes of emesis, reduced ototoxicity, etc. On the other hand, adozelesin, a totally synthetic analogue of natural product CC1065, has demonstrated a similar potency and antitumor activity profile as its natural prototype but is devoid of the delayed death liability associated with the parent drug in animals (36).

2.1.2. Chemoprotection

The success of chemoprotection depends on a detailed biochemical knowledge of the drug target. The pharmacological and metabolic fate of the parent drug, its relationship to the observed organ toxicity, and how the observed toxicity can be prevented/lessened by chemical intervention without affecting the antitumor activity of the parent drug are all important factors. Administering an antidote to the parent drug to minimize the specific drug toxicity to organs and the hematopoetic, ie, blood forming, system, is being studied in various cancer therapies. For example, leucovorin (**9**) rescue therapy has been used successfully in the clinic as an antidote to the toxic effects of high dose methotrexate (**8**). The antidote renders methotrexate ineffective against

the newly recruited stem cells after its initial cytotoxic insult. Other combinations under active clinical study to demonstrate effectiveness of chemoprotection are ifosphamide (**19**) and mesna (**20**) for hemorrhagic cystitis (37); cis-platinum (**28**) and WR-2721 [20537-88-6] for nephrotoxicity and neurotoxicity (38); and adriamycin (**32**) and ICRF-187 [24584-09-6] for cardiotoxicity (39).

2.1.3. Drug Targeting

Site-specific drug delivery involving a variety of approaches has been pursued to address the issue of drug toxicity in chemotherapy (40). Prodrug synthesis and liposome encapsulation of cytotoxic drugs, eg, adriamycin (**32**), have preceded more modern drug targeting approaches. The advent of hybridoma technology to produce large quantities of monoclonal antibodies directed toward antigenic epitopes on human cancer cells has made possible several novel approaches to selective delivery of cytotoxic agents to human tumors. The three most actively pursued research areas in this vein are the use of monoclonal antibody-drug conjugates (41), a combination approach involving the use of a targeted antibody–enzyme complex followed by administration of a suitable prodrug of an anticancer agent (42); and antibody-targeted radionuclides with α and β-particle emitting properties (43). *In vivo* results for antibody targeted cytotoxics against human tumor xenografts in nude mice have been very encouraging and several institutions are planning clinical trials to establish the proof of principle for such approaches. The antibody targeted radionuclides approach, which has been widely used in cancer diagnosis, is also showing promise for therapeutic utility (44).

3. Drug Resistance

Despite dramatic advances in the treatment of several human malignancies including Hodgkin's lymphomas and leukemias, drug resistance remains a pressing issue in cancer chemotherapy. Acquired or induced drug resistance afflicts practically all classes of cancer agents. It usually is manifested clinically subsequent to responsive therapy and cancer relapse following therapy often is fatal. The most recognized and studied mechanisms of drug resistance are attributed to multidrug resistance (MDR), gene amplification, DNA repair, topoisomerase II activity, and glutathione and metallothionein levels. Even with advances in understanding the biology and mechanism of drug resistance among different classes of antitumor agents, no real breakthrough appears imminent (45).

Research and clinical experience on drug resistance suggests that tumor cells are particularly adept at genetic selections leading to alterations in the structure, function, or synthesis of proteins involved in the antitumor drug action and detoxification. Multiple mechanisms of resistance have been shown to account for the resistance seen in the clinic (46).

3.0.4. Multidrug Resistance

MDR is characterized by reduced drug accumulation in tumor cells correlated with an enhanced drug efflux (47). This effect is common to a wide variety of cancer agents including the Vinca alkaloids, intercalators, and topoisomerase inhibitors. The drug efflux is attributed to the over expression of the MDR-1 gene, encoding a 170 kD glycoprotein (GP170) responsible for the energy (adenosine triphosphate) dependent nonspecific efflux of the drug from the MDR cells. In recent years, reversal of MDR by several classes of noncytotoxic agents, eg, verapamil [52-53-9], dipyridamole [58-32-2], progesterone [57-33-0], and dihydropyridine analogues, has been observed and studied at the preclinical level (48). Limited clinical trials are in progress to establish the validity of this approach. The exact mechanism of MDR reversal is not well understood but evidence suggests that these reversal agents either disrupt the efflux pump function or competitively inhibit drug binding to GP170 (49). The extent that MDR is responsible for the observed clinical resistance is being carefully monitored and evaluated.

3.0.5. Gene Amplification

This mechanism of drug resistance appears to be operative in drugs which act on *in vivo* enzymatic targets. For example, in the case of resistance to methotrexate (**8**), overexpression of the dihydrofolate reductase (DHFR) gene has been implicated. However, other mechanisms involving defects in drug uptake and polyglutamation also have been proposed and studied (50). Specifically, the multifactorial nature of methotrexate resistance represents a large therapeutic challenge. It is one example of how the heterogeneity of clinical resistance may be a serious problem.

3.0.6. DNA Repair

Resistance to alkylating agents, which constitute the bulk of chemotherapeutic agents, is ascribed to DNA repair and/or detoxification processes (51). Resistance usually manifests itself as an overproduction of repair enzymes. Overproduction of *O*-6 alkylguanosine transferase, an enzyme responsible for repairing lesions in DNA, is observed in resistance to nitrosoureas, mitomycin C (**25**), and melphlan (**23**). In the case of resistance to cis-platinum (**28**), tumors have demonstrated elevated levels of glutathione and the enzyme glutathione *S*-transferase. Glutathione is involved in both DNA repair and drug detoxification processes. Reversal of cis-platinum resistance has been observed in cells pretreated with glutathione depleting agents such as buthionine sulfoximine [5072-26-4].

4. Investigational Approaches

Chemotherapy has been impacted significantly by a small number of selected antitumor agents. In the 1970s it was adriamycin (**32**) and in the 1980s it was cis-platinum (**28**) and etoposide (**41**). Based on its unique mechanism of action and its clinical performance to date, taxol (**52**) may be the most important chemotherapeutic agent of the 1990s (26). However, the quest for novel chemotherapeutics still continues, guided by both rational mechanism-based screening and more relevant animal tumor models for preclinical evaluations. Approaches under investigation include the search for novel noncytotoxic agents which induce differentiation of cancer cells (52), inhibit tumor metastasis (53), and control growth factors (54). The dramatic advances made in recombinant DNA and hybridoma technology has caused a resurgence in the science of immunotherapy (see Immunotherapeutic agents) (55); the use of cytokines such as the interferons, interleukin-2 [85898-30-2] (IL-2), and tumor necrosis factor [138415-31-3] (TNF) as activators of the human immune system is under active study. The use of immunodulators, such as levamisole [14769-73-4], which stimulate and fortify the host's immunoreactivity toward tumors, also are being evaluated, but an unequivocal clinical demonstration of the effects of these biological response modifiers has not been made. In addition to use as selective drug delivery carriers, monoclonal antibodies are being employed as cytotoxic agents by the virtue of their natural effector mechanism (56). The clinical validity of all the above approaches are under careful scrutiny.

Resources are being marshalled to exploit and explore the possibility of cancer intervention at either the transcriptional or translational levels of gene activity. Specifically, as of 1992, antisense(RNA target) and antigene (DNA target) approaches (57, 58) are being pursued at a number of institutions and several investigative therapies are pending FDA approval for initiation of human clinical trials.

5. Economics of Cancer Chemotherapy

The increased use of chemotherapy as a modality in the treatment of cancer has caused a corresponding increase in the market for anticancer agents. Table 8 lists the estimated 1990 worldwide sales for the most commonly utilized chemotherapeutic agents. Data for Japan are not included because of differences in medical

Table 8. Antitumor Drug Sales, 1990[a]

Chemotherapeutic drug	$ × 10^6
Antimetabolites	
doxifluridine	112
fluorouracil	18
methotrexate	110
hydroxyurea	26
cytarabine	30
other	12
Total	*308*
Alkylating agents	
cis-platinum	192
carboplatin	191
mitomycin C	74
cyclophosphamide	54
ifosphamide	15
chlorambucil	13
thiotepa	13
melphalan	10
Total	*562*
DNA interactive drugs	
doxorubicin	150
epirubicin	110
mitoxanthrone	75
bleomycin	60
daunorubicin	18
Total	*413*
Topoisomerase inhibitors	
etoposide	260
Tubulin active dugs	
vincristine	30
vindesine	25
Total	*55*
Hormones[b]	
tamoxifen	540
leuprolide	170
flutamide	150
goserelin	112
medroxyprogesterone	92
estramustine	76
megestrol acetate	70
Total	*1210*

[a] Estimated worldwide sales excluding Japan. Based on audited sales adjusted for under reporting. Sales of less than 10 million per annum not included.
[b] Most hormonal agents are used for other indications. It is not possible to estimate usage for antitumor purposes.

and prescribing practices. Only a few anticancer drugs have achieved sales in excess of $100 million per year and many of the drugs discussed herein sell less than $10 million per year. Many of the approved drugs were introduced early on in cancer chemotherapy for the treatment of lymphomas and leukemias. Because of lack of patent coverage and the relatively small market size, these drugs are of relatively little commercial importance. Those agents which have achieved greater economic importance are newer, frequently used in combination chemotherapy, and of use in the treatment of solid tumors which comprise the bulk of reported cancer incidence. A number of the agents in clinical trials, such as taxol (**52**) and camptothecin analogues, are

expected to have considerable economic impact based on activity in the treatment of the more common human malignancies, eg, lung, breast, colon, and ovary.

In addition to the market for cancer chemotherapeutic drugs, there is also a growing market for biologicals such as the interferons, having combined 1990 sales of $\sim$\$560million, and the colony stimulating factors, G-CSF, GM-CSF, etc. It is reasonable to expect an overall doubling of this market in the 1990s.

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