

Antineoplastic Drugs

Organic Syntheses

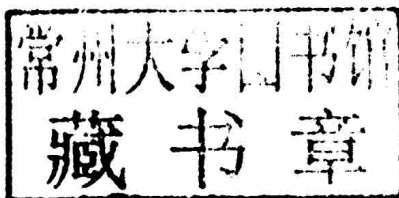
Daniel Lednicer



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Antineoplastic Drugs: Organic Synthesis

DANIEL LEDNICER



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Antineoplastic Drugs

*This book is dedicated to all of us Lednicers—Anne, Beryle,
Daniella, David, Lisa Grace, Oliver, Ruth, and Sylvie*

Preface

A recent perusal of the USAN Dictionary for new generic, or more precisely nonproprietary, names for drugs awarded over the past several decades, quite unexpectedly, turned up a sizeable group of recently named antineoplastic agents. The chemical structure of many of these new drug candidates comprised a collection of carbo- and heterocyclic moieties strung together in the form of a chain. The mechanisms by which those agents attack cancer cells were also quite novel.

The search for compounds for treating malignant cancer dates back to the early twentieth century. This effort has been at best a daunting task for chemists engaged in the search. The fact that cancer cells show few, if any, biochemical differences from normal cells complicated the task. When the search began in earnest in the late 1940s, chemists concentrated on the then-accepted means for finding new drugs: synthesizing assay candidates one at a time in pure form or alternatively supplying biologists with pure compounds isolated from plants, molds, or other natural sources. Those products were then tested one at a time *in vitro* or *in vivo* against neoplastic cells. This approach was rewarded with only moderate success. Many plant-derived antineoplastic drugs trace their origin to that period as do the agents which act by alkylating DNA. Management in both the private and public sectors eventually came to the conclusion that this method for finding new and better tolerated antineoplastic agents was giving scant return for the effort expended. Several changes, one in the method for synthesizing test material and the other to the screening assays, have inarguably resulted in the large list of new names in the USAN Dictionary.

Legislation and implementing regulations for the FDA approval process have also provided additional impetus for developing new antineoplastic drugs. The Orphan Drug Act recognized that pharmaceutical firms were loath to expend time and effort on drugs that would be used by a very small number of patients. In addition to some monetary awards, the Act provides special rules for approval of drugs for treating diseases suffered by 200,000 or fewer patients. The FDA Fast Track Development Program offers expedited requirements and review for drugs for treating serious, life-threatening medical conditions for which no other drug exists.

The appearance of the name in the USAN Dictionary served as the screen for selecting compounds in this compendium. Listing in the Dictionary requires only that the agent in question carries a generic name. The existence of such a designation is taken to indicate that the sponsor considers that the activity of the compound shows sufficient promise to be groomed for testing in the clinic.

Discussions of newly named potential therapeutic drugs have customarily sorted the compounds in chemical structure-based chapters. The structures of many of the antineoplastic agents in this monograph—a string of carbo- and heterocyclic moieties—would however make the conventional arrangement difficult. An alternative method for sorting compounds was chosen. Chapters in this volume list compounds that share the same

mechanism by which they attack neoplastic cells. The numbers of compounds listed in a given chapter, using that criterion, vary markedly: 41 pages for protein kinase and 5 pages for agents that inhibit histone deacetylase. The recently discovered kinase inhibitors comprise a major portion of the contents of this monograph. To provide context, the several opening chapters deal mainly with older neoplastic drugs and only a few of the newer antineoplastic drug candidates.

Many of the drugs for treating cancer, popularly known as “chemo,” comprise natural products. These widely used antineoplastic agents have been omitted since those drugs and their derivatives involve few, if any, chemical transformations. Drugs given short shrift include mainstay chemo compounds from plants and fermentation products such as the vinca alkaloids, doxorubicin, maytansine, and most recently paclitaxel.

This volume focuses on the chemistry to prepare antineoplastic agents rather than a detailed account of the biology of those drugs. Since this is mainly a chemistry monograph, the bibliography is confined to sources for the description of the chemistry. The Internet provided the gist for the brief thumbnail description of the biological activity of the potential antineoplastic agent; they are thus not referenced. Not having a license to practice medicine, I take no blame or credit for the accuracy of the short notes about clinical trials that precede discussions of most of the compounds in this account. In the same vein, the chemistry is focused on the drug itself rather than its salts.

One more caveat is called for. The synthetic sequences that follow represent those presented in publication that have appeared in journals, largely the *Journal of Medicinal Chemistry*, *Bioorganic & Medicinal Chemistry*, and *Bioorganic & Medicinal Chemistry Letters*, as well as US Patents. It is more than likely that there will be more efficient schemes than those devised for drugs approved by the FDA by chemists in the sponsors' laboratories.

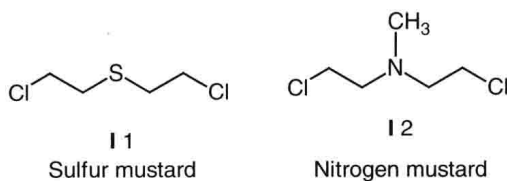
Daniel Lednicer

Introduction

Cancer has a long history as a scourge for mankind. Some prehistoric fossilized human bones, in fact, show growths that have been interpreted as malignant tumors. The term cancer actually encompasses a group of closely related diseases that have in common unregulated cell division. Many vital processes such as growth require the synthesis of new proteins. This process calls on instructions from DNA found in genes. In rough outline, cell division is normally directed by protein factors that are in turn controlled by two opposing genes. Proto-oncogenes control proteins that encourage cell proliferation, while those controlled by tumor suppressor genes tend to oppose the process. Any one of a number of stimuli, for example, chronic exposure to carcinogenic chemicals, can cause a proto-oncogene to mutate and become an oncogene. That oncogene then causes the proteins involved in cell division to become overactive. The cells whose growth has up to now been controlled escape the restraints on cell division and lose controls on proliferation. The now-cancerous cells often also lose many of functions they had played prior to becoming neoplastic. The absence of restraints in addition causes those cells to divide much more quickly than the normal progenitor; they then go on to form a malignant tumor. Untreated cancer virtually always causes premature death.

For centuries, the only means for treating the malignant tumors consisted of surgical extirpation of the lesion. Texts dating from Greco-Roman times describe excision of cancerous lesions; many of these sources refer to the recurrence of cancer within a short time after the surgery. Cancers of the circulatory system such as leukemias and lymphomas were considered a death warrant up to quite recent times because there was no visible tumor that could be removed. Today's greatly advanced surgical technique and adjuncts such as the sterile operating field and anesthesia made surgical removal of malignant tumors practical; surgery for treating solid tumors is now still the first-line treatment after a carcinoma has been identified. Unless caught at a very early stage, many cancerous lesions spread to other parts of the body by splitting off malignant daughter cells in a process called metastasis. Metastases spread throughout the body via the lymphatic and sometimes the circulatory system. The fact that surgeons now take special measures to insure that all cancer cells are excised helps avoid the spread of the cancer to other locations. The principal targets of anti-neoplastic drugs now comprise first the circulatory system cancer tumors not susceptible to surgical excision such as leukemia; metastases from solid tumors comprise an equally important target for these drugs. Antineoplastic agents are in addition also used following surgery to kill any cancer cells that had been left behind. These drugs are also not infrequently used to shrink tumors prior to surgery.

The beginning of antineoplastic therapy can be ironically traced back to the First World War when the Germans followed up their use of chlorine as a poison gas by what came to be called sulfur mustard (I-1). The name is said to come from the yellow-brown appearance of the substance while still liquid and the mustard-like odor. Exposure to this gas, now



Scheme 1 Methchloramine.

classed as a cytotoxic agent, caused large painful skin blisters; afflicted troops often lost eyesight. (A very moving larger-than-life-size John Singer Sargent painting depicts a line of gassed and blinded Great War soldiers.) The inhalation of the gas led to blister-like lesions in the lung. Postwar studies on individuals who were exposed to mustard gas showed a lowering of hematopoiesis—that is, the formation of blood cells. This was confirmed during the early 1940s by the examination of individuals who had been exposed to an inadvertent release of mustard gas.

Sulfur mustard is a liquid with a low boiling point that is difficult and dangerous to handle. The nitrogen analogue (**1.2**) is a solid as its hydrochloride salt is much easier to handle and thus safer. This prompted pharmacologists Goodman and Gilman to launch a study to determine whether this compound, subsequently dubbed methchloramine, had the same effect on cancer as its sulfur predecessor. They consequently studied the effect of this compound on lymphomas, malignancies of blood cells that had been implanted in mice. They found that methchloramine markedly reduced the mass of cancerous tissue in that *in vivo* disease model. They and a group of physicians went on to administer the drug to a lymphoma patient. The drug now granted the generic name mustine dramatically reduced the mass of cancerous tissues. The 1946 paper announcing that result is now considered to mark the beginning of antineoplastic drug therapy [2]. Methloramine (Mustargen®) is still commonly used as a chemotherapy drug. (The class of anticancer compounds that act by alkylating DNA will be found in Chapter 1.) That section deals largely with older compounds since there is currently little research devoted to antineoplastic agents that act by alkylating DNA.

The central circumstance that makes the search for new antineoplastic agents so difficult lies in the fact that the properties of cancer cells are almost identical to those of their cancer-free counterparts [1]. In addition to alkylating agents, several other classes of antineoplastic drugs rely on the fact that cancerous tissue turns over at a considerably higher rate than normal tissue. As a result, cytotoxic chemicals will to some degree have a greater effect on cancerous tissues than on normal cells. The common side effects of the administration of many antineoplastic agents, such as loss of hair, dry mouth, and dry tear ducts, demonstrate that the selectivity of those drugs is not perfect; the drugs also attack normal cells that are turning over quickly.

An alternate approach for treating cancer involves the use of antimetabolites. Folic acid and some of its metabolites are an essential factor for many bodily processes. This class of compounds, known as folates, is essential for building and repairing DNA. A group of antineoplastic drugs, most of which have chemical structures that mimic folates, act as metabolic inhibitors of folate synthesis. Chapter 2 treats antineoplastic drugs that act by inhibiting that process. Each of the two purines and three pyrimidines that comprise the

coding bases in DNA in genes and the RNA that controls the construction of proteins is synthesized in the body by a set of specialized enzymes. Life as we know it is totally dependent on the six bases that form DNA and RNA. A collection of anticancer agents that inhibit the enzymes for building those substances is found in the same chapter.

Many of organs that comprise the sexual complex of women and men are studded with receptors for the agents that control their functions: the estrogens in women and androgens in men. Many, but not all, cancers of those organs retain those receptors and have become estrogen or androgen dependent. Chapter 3 describes hormone antagonists that have shown activity against hormone-dependent tumors. A sizeable number of those antineoplastic agents were elaborated in the 1970s up to the early 1990s as shown by the corresponding dates of the references.

When not involved in replication, DNA, a physically extremely long molecule, is supercoiled. The process of generating a new protein requires access to a relatively short sequence for copying to RNA that may be buried within the coil. The enzyme topoisomerase I expedites the process of bringing the required segment to the fore by cutting a strand in double-stranded DNA. The enzyme then temporarily marks the location of the cut and then reconnects the ends when the sequence has served its function. Closely related topoisomerase II cuts both strands at the same time. Topoisomerase inhibitors are discussed in Chapter 4.

The process of replication, called mitosis, involves the separation of the doubled cell nuclei. Chapter 5 describes drugs that interfere with this process. A set of very small fibers termed microfibers in the cell nucleus derived from the protein tubulin connect the doubled nuclei where they aid the separation of those entities. These structural elements are absorbed once mitosis is complete. One set of microtubules stabilizes the microfibers so that they are no longer absorbed, in effect halting mitosis. A second group of agents inhibit the formation of the microtubules.

A series of unrelated anticancer agents act at the level of the DNA within the cell nucleus. That DNA is tightly wrapped around a series of proteins that form a spindle-like structure known as histones. Reading the DNA code in response to a signal that calls for the production of a new protein is controlled by the series of acetyl groups attached to the histones. The enzyme histone deacetylase regulates the addition and deletion of those acetyl groups. Chapter 6 describes a number of inhibitors of the deacetylase enzyme that interfere with instructions for reading the genome.

Metalloproteinases are a family of related metal-containing enzymes that act on the extracellular matrix that holds cells together and in place. The process of dispersion of cancer to locations remote from the original tumor requires the disruption of the matrix. Chapter 7 describes a small group of compounds that inhibit those enzymes.

Kinases comprise a group of enzymes that connect a phosphate group to a specific amino acid on regulatory proteins. The resulting phosphorylated substrate then controls various cellular processes. The process of adding phosphate groups also serves as a means for signaling the start or ending of a process. The largest section by far in this compendium comprises two sizeable chapters on drugs that inhibit the action of kinases.

Chapter 8 describes a very large group of compounds that inhibit the binding to tyrosine kinases. It is noteworthy that close to half of those drugs have been approved by the FDA for treating patients with a narrowly defined cancers. The still sizeable number of compounds that inhibit other kinases and related proteins is to be found in Chapter 9.

No book of this nature is complete without a chapter that deals with compounds that cannot be included in the previous classes. Chapter 10, titled *Miscellaneous Agents*, describes a handful of such potential drugs.

The preponderant mode for prescribing drugs for treating most diseases called for prescribing a single drug that had been approved for that use by regulatory agencies. The administration of antineoplastic drugs, on the other hand, not infrequently leads to an initial shrinkage of the tumor. This is however too frequently followed by recurrence of the disease as the tumor develops resistance to the drug. This has led oncologists to administer a cocktail of drugs, each of which killed cells by different mechanisms. Before, too long cancer chemotherapy came to rely on sets of defined groups of drugs, cocktails, designated by acronyms. First-line treatment of Hodgkin's disease, for example, relied for a long time on the regime MOPP: mustine, Oncovin, procarbazine, and prednisone. It is of interest that a similar regime, administering a collection of antivirals that attack the virus by different mechanisms, is now used for treating HIV.

The US Food Administration generally grants fairly broad approvals for new drugs. This is applied to antineoplastic drugs as well. A new antineoplastic might, for example, be licensed for treating non-small cell lung cancer. Pressure from Congress and cancer support groups changed that practice in order to speed the approval of new antineoplastic agents. Approval currently more directly reflects the results of a clinical trial, or trials, where the drug in question showed a statistically significant more favorable outcome than that observed with other available treatments. The new drug will be typically approved for treating patients whose treatment with paclitaxel had failed. This volume is not a prescribing guide and thus steers away from those very detailed specifications; it merely states that a compound has been approved, occasionally indicating the organ.

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- [2] Goodman LS, Wintrobe MM, Dameshek W, Goodman MJ, Gilman A, McLennan MT, *JAMA*. **251**(17), 2255–2261 (1984, May 4).

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1

Alkylating Agents

An impressive number of cytotoxic compounds whose antineoplastic activity is due to their reactions with DNA have been studied in the clinic. Many of these comprise drugs that currently form part of the combinations used to treat neoplastic disease. This account however includes only a limited number of alkylating agents since this area has been well covered elsewhere.

1.1 bis-Chloroethyl Amines

As noted in the Introduction, antineoplastic agents that include in their structure highly reactive chemical moieties comprise the earliest class of drugs for treating malignant tumors. This applies particularly to those cancers that afflict the system for producing and maintaining blood-forming tissues such as leukemia and lymphoma. The first of these agents, mustine (**1.1**), also known as mechlorethamine, was, as noted in the Introduction, actually developed empirically. An understanding of the mechanism by which alkylating agents kill cancer cells awaited the discovery of the structure of DNA in the 1950s as well as elaboration of the chemistry for studying that substance. The relatively large group of alkylating anticancer drugs was actually synthesized before their mode of action was fully understood. Many of those anticancer agents were designed as analogues of prior compounds that sported the chemically reactive chloroethyl group or some other highly reactive function.

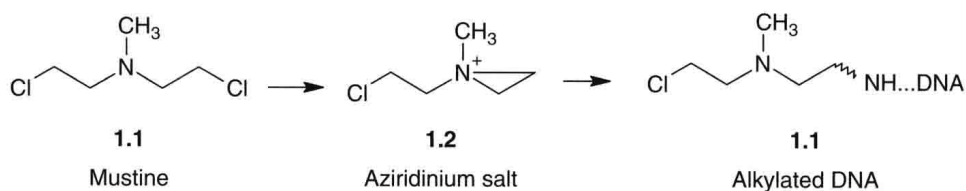
The alkylating agents as a class attack many tissues in the body that contains basic nitrogen. Those agents target all cells that are susceptible to alkylation, be they cancerous cells or unrelated normal cells. The latter circumstance leads to many classical side effects manifested by alkylating antineoplastic drugs, such as loss of hair, dry mouth, and dry eyes,

experienced by patients exposed to this class of antineoplastic agents. The effects on neoplastic cells are however more relevant to this discussion. Reaction with DNA is not a random process; it has been shown that alkylating agents react preferentially with the more electron-rich, more basic nitrogen atoms in DNA. The stacked bases between the two strands of that macromolecule in the helical arrangement constitute a particularly favorable configuration for attack on each of the two separate strands of DNA. Drugs that incorporate two alkylating moieties form a covalent bridge between the two strands of DNA. This effect is demonstrated by the significantly lower concentration of bifunctional agents required to kill cancer cells *in vitro* than that of molecules that include only a single reactive group. That cross-link inactivates alkylated DNA since almost all functions of DNA, such as replication, require access to a single strand. RNA, the counterpart directly involved in synthesizing new protein, can only read a single DNA strand. The affected cell then simply ceases to function and dies. Although very large number of alkylating drugs has been studied since the early 1940s, the present account is restricted to five subsets that illustrate research in this field.

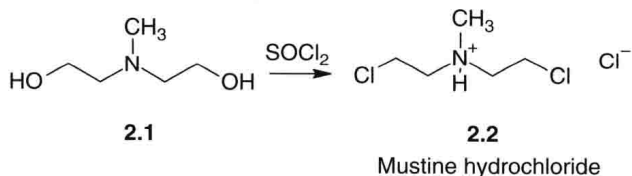
The chloroethyl group found in this subset of alkylating drugs does not react with DNA as administered. Instead, the basic nitrogen in mustine (**1.1**) displaces the side chain chlorine to form an aziridinium salt (**1.2**). The reaction of this activated species with nitrogen in DNA leads to ring-opened DNA adduct. The repetition of that sequence with the second chloroethyl function followed by the reaction of the new aziridinium function with alkylated DNA leads to cross-linked DNA.

The first recorded preparation of this rather venerable antineoplastic agent involves the reaction of methyl-bis(hydroxyethane) (**2.1**) with thionyl chloride. The starting diol is speculatively available from the reaction of methylamine and ethylene oxide. The resulting product, **mustine** (**2.2**), needs to be handled as a positively charged salt to prevent *ex vivo* aziridinium formation [1].

Cyclophosphamide is one of the best known and widely used antineoplastic agents. The drug comprises “C” in a large number of multidrug cocktails for treating cancer. One of the



Scheme 1.1 Aziridinium salt formation.



Scheme 1.2 *Synthesis of mustine.*