

## Anthracyclines: Selected New Developments

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**Abstract:** Anthracycline antibiotics play an important role in cancer chemotherapy. The need for an improvement of their therapeutic index has stimulated an ongoing search for anthracycline analogues with improved properties. Analogue development was originally limited by a lack of information on the cellular drug target, nevertheless almost 20 years ago the mechanism of action of doxorubicin and daunorubicin was revealed and DNA topoisomerase II was recognised to be their main cellular target.

Several anthracyclines interfere with topoisomerase II functions by stabilizing a reaction intermediate in which DNA strands are cut and covalently linked to tyrosine residues of the enzyme. Investigations on the sequence specificity of doxorubicin *in vitro* and in nuclear chromatin of living cell have led to a molecular model of drug receptor on the topoisomerase II-DNA complex. Anthracyclines are likely placed at the interface between the DNA cleavage site and the active site of the enzyme, forming a DNA-drug-enzyme ternary complex. Moreover, a quite detailed structure-function relationship has been established for anthracyclines. First, drug intercalation is necessary but not sufficient for topoisomerase II poisoning; second, the removal of the 4-methoxy and 3'-amino substituents greatly increases the drug activity and third, the 3' substituent of the sugar moiety markedly influences the sequence selectivity of anthracycline-stimulated DNA cleavage. These relationships have been exploited during the last decade by several groups, including ours, in the search for new anthracycline drugs with lower side effects and higher activity against resistant cancer cells.

This review will focus on areas of the anthracycline field including synthesis of new analogues, new strategies of synthesis and recent developments in the area of drug delivery.

### INTRODUCTION

Anthracyclines are among the most utilised antitumor drugs ever developed [1-4]. The first identified anthracyclines, daunorubicin and doxorubicin, were isolated from pigment-producing *Streptomyces* spp. in the early 1960s and still remain in widespread clinical use today [5]. Anthracyclines are essential components of several curative drug combinations for the therapy of a number of tumors. It is a drug of primary use in the treatment of patients with lymphoma, breast cancer and sarcoma.

Although active against a variety of solid and haematological malignancies, their clinical use is hindered by tumor resistance and toxicity to healthy tissues.

Thus, the clinical success of doxorubicin, as well as its limitations in the clinical use has been the basis to find a "better doxorubicin" [6].

The research has moved in different directions: 1) the understanding of the mechanism of actions of anthracyclines; 2) the synthesis of analogues to improve the ability to form stable complexes with DNA-topoisomerase II, possibly leading to an increase in antitumor efficacy. Since doxorubicin

was discovered, more than two thousands of analogues have been reported. 3) Modify the pharmacokinetic properties and the delivery of the drugs to cancer cells in order to increase antitumor efficacy *in vivo* and/or reduce side effects.

From the chemical point of view all anthracyclines consist of an aglycone ring coupled with an aminosugar and their major molecular target that determines the clinical activity is the poisoning of DNA topoisomerase II [7]. A wealth of data shows that antitumor anthracyclines stabilize a topoisomeraseII-DNA covalent complex and hinder a specific step of the enzyme catalytic cycle, the resealing of DNA breaks [8-11]. This is followed by enhancement of DNA cleavage levels in living cells as well as in DNA fragments in the presence of purified topoisomerase II [10]. Thus, anthracyclines transform a harmless protein, topoisomerase II, into potent nuclear toxins that lethally damage the double helix [10].

The peculiarity of anthracyclines and, in general, of topoisomerase II poisons, is that their action is DNA sequence specific. Each topoisomerase II poison can stimulate DNA cleavage at certain sites, but not at all the sites recognized by the enzyme, suggesting that drug interactions depend on the local nucleotide base sequence.

Investigations on the sequence specificity of drug stimulation of topoisomeraseII-mediated cleavage have shed light on the drug mechanism of action [8,12] and have

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# Anthracyclines Current Status And New Developments

**American Chemical Society.  
Meeting, Waldemar Priebe**



## **Anthracyclines Current Status And New Developments:**

**Anthracyclines** Stanley T. Crooke, Steven D. Reich, 1980-01-01      **Anthracycline Antibiotics in Cancer Therapy**  
Franco M. Muggia, Charles W. Young, Stephen K. Carter, 2012-12-06 F M MUGGIA When faced with the inadequacies of current cancer treatment we prefer to look at what the future may hold Quite often we take for granted the past preferring research into totally new areas However the persistent development of fertile soil may yield surprising rewards for those who choose to build on the knowledge of the past hence this symposium on anthracycline antibiotics Although the anthracycline antibiotics represent much of the present and future of cancer treatment their actual use stretches back barely two decades to the pioneering efforts of Aurelio Di Marco who characterized the antitumor properties of daunomycin and adriamycin The clinical application of these two compounds heralded a decade of excitement among oncologists dealing with pediatric tumors breast cancer leukemias and lymphomas and opened new hope for patients afflicted with sarcomas and a variety of other tumors that had been deemed resistant to chemotherapy These successes were tempered with the realization that the antitumor effect of anthracyclines could be achieved at times only at the very high price of risking cardiac decompensation and almost invariably with the occurrence of alopecia and other acute toxicities This record of past achievements and problems has slowly given way to a present increasingly illuminated by our ability to modify the distressing toxicities of these agents Detailed clinical studies supplemented by ingenious laboratory models have gradually elucidated mechanisms and risk factors implicated in the cardiomyopathy      **Journal of the National Cancer Institute** ,1988      **Antineoplastic Agents**  
Stanley T. Crooke, Archie W. Prestayko, 2013-10-22 Cancer and Chemotherapy Volume III Antineoplastic Agents is a collection of articles that deals with the treatment of cancer using drugs The collection describes the various drugs that are used the therapeutic approaches being taken and agents that are being developed Part I is a general review of anti cancer drugs as regards their action mechanisms pharmacokinetics pharmacology known toxicities and clinical utility These drugs include alkylating agents such as mitomycin C and nitrosoureas plant alkaloids such as maytansine antibiotics such as anthracyclines platinum containing complexes antimetabolites and hormones Part II examines the molecular pharmacology of some major drug classes namely bleomycin and anthracycline The text also discusses the chemistry mechanism and any structure activity relationships found in these drug classes Part III discusses in detail the clinical pharmacology of some antitumor drugs for example cisplatin and nitrosoureas The text includes the clinical applications biochemistry metabolism and the use of mathematical models in interpreting or describing resulting data The book is helpful for pharmacologists molecular biologists and scientists involved in cancer research      Cancer Treatment Reports ,1981      Cancer Chemotherapy 1 Franco M. Muggia, 2012-12-06 Where do you begin to look for a recent authoritative article on the diagnosis or management of a particular malignancy The few general oncology textbooks are generally out of date Single papers in specialized journals are informative but seldom comprehensive these are more often preliminary reports on a very limited number of patients

Certain general journals frequently publish good indepth reviews of cancer topics and published symposium lectures are often the best overviews available Unfortunately these reviews and supplements appear sporadically and the reader can never be sure when a topic of special interest will be covered Cancer Treatment and Research is a series of authoritative volumes which aim to meet this need It is an attempt to establish a critical mass of oncology literature covering virtually all oncology topics revised frequently to keep the coverage up to date easily available on a single library shelf or by a single personal subscription We have approached the problem in the following fashion First by dividing the oncology literature into specific subdivisions such as lung cancer genitourinary cancer pediatric oncology etc Second by asking eminent authorities in each of these areas to edit a volume on the specific topic on an annual or biannual basis Each topic and tumor type is covered in a volume appearing frequently and predictably discussing current diagnosis staging markers all forms of treatment modalities basic biology and more

**Anthracycline Antibiotics** Hassan Saad El Khadem,1982  
**Anthracycline and Anthracenedione-based Anticancer Agents** J. William Lown,1988 *Future Trends in Chemotherapy, 6, 1984-1986* Aldo Bertelli,1985 *Studies in Natural Products Chemistry* Atta-ur- Rahman,1988

*Anthracycline Antibiotics* American Chemical Society. Meeting, Waldemar Priebe,1995 Developed from a symposium at the 205th National Meeting of the ACS in Denver March 1993 held to bring together researchers who are involved in the direct design and synthesis of new drugs with researchers who are investigating biochemical processes and mechanisms of action The volume covers research relevant to the development of novel anthracyclines such as the synthesis of promising new analogs studies of mechanisms of action and new approaches to improving properties for this class of compounds by using different drug delivery and tumor targeting systems Annotation copyright by Book News Inc Portland OR

Adriamycin M. Ogawa,Franco M. Muggia,Marcel Rozencweig,1984 **DUECR**,1986 **Stereoselective Synthesis** Atta-ur Rahman,1989 Section 1 *Publications* University of Iowa. Department of Internal Medicine,1986 Each vol consists of papers reprinted from various periodicals etc **Recent Advances in Chemotherapy: Antimicrobial (3 v.)** Jōji Ishigami,1985 **Cancer and Chemotherapy: Antineoplastic agents** Stanley T. Crooke,Archie W. Prestayko,1980

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