Anthracycline Antibiotics

Edited by

HASSAN S. EL KHADEM

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1982

ACADEMIC PRESS
A Subsidiary of Harcourt Brace Jovanovich, Publishers
New York London
Paris San Diego San Francisco São Paulo Sydney Tokyo Toronto

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

Library of Congress Cataloging in Publication Data
Main entry under title:

Anthracycline antibiotics.

"Papers presented in the symposium on anthracyclines, held in New York on August 24-25, 1981, and sponsored by the Carbohydrate and Medicinal Chemistry divisions of the American Chemical Society"--P.
Includes index.
1. Cancer--Chemotherapy--Congresses. 2. Anthracyclines --Testing--Congresses. 3. Structure-activity relationships (Pharmacology)--Congresses. I. El Khadem, Hassan Saad, Date. II. American Chemical Society. Division of Carbohydrate Chemistry. III. American Chemical Society. Division of Medicinal Chemistry. [DNLM: 1. Antibiotics, Antineoplastic. QV 269 A626]
RC271.A63A567 1982 615'.329 82-11548
ISBN 0-12-238040-1

PRINTED IN THE UNITED STATES OF AMERICA

82 83 84 85 9 8 7 6 5 4 3 2 1

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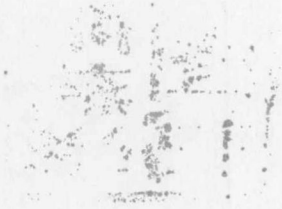
Academic Press Rapid Manuscript Reproduction



Based on the Symposium on Anthracyclines
Sponsored by the Carbohydrate and Medicinal Chemistry Divisions
of the American Chemical Society Held in New York, August 24–25, 1981

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Numbers in parentheses indicate the pages on which the authors' contributions begin.

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Foreword

This symposium, organized by The Division of Carbohydrate Chemistry in conjunction with The Division of Medicinal Chemistry of the American Chemical Society, focuses on a topic of high relevance to cancer therapy—the chemistry of anthracycline antibiotics. Both adriamycin (doxorubicin) and daunomycin (danorubicin) have been extensively studied clinically and have been rapidly accepted as major therapeutic tools in the treatment of cancer. They play a significant role in the effective treatment of acute leukemia, breast cancer, Hodgkins disease, non-Hodgkins' lymphomas, and sarcomas.

However, their extensive use is limited by the rather narrow spectrum of activity and dose-limiting toxicities. For example, the parent anthracyclines are not clinically useful against lung and colon tumors. The dose-limiting toxicity for these drugs is a cumulative cardiotoxicity. In addition, these exhibit conventional toxicities; for example, myelo-suppression, alopecia, and nausea and vomiting. Therefore, there is wide interest in developing new broad spectrum anthracyclines of low toxicity.

The present symposium is devoted to a survey of the recent international developments in the chemistry of anthracycline antibiotics. The topics include the following: new anthracycline analogs modified in both the aglycon and sugar portion of the molecule, total synthesis, microbial transformations, semisynthetic modifications, and "nonclassical" anthracyclines like aclacinomycins and nogalamycin.

These new developments in the chemistry of anthracyclines make feasible the synthesis of a wide variety of novel compounds for structure-activity/toxicity optimization. These widely divergent structural types might exert their antitumor activities by different mechanisms. Hence, it is reasonable to expect a separation of antitumor activity from toxicity, leading to drugs of enhanced therapeutic effectiveness.

V.L. Narayanan

Preface

Ten of the major papers presented in the symposium on anthracyclines held in New York on August 24–25, 1981, and sponsored by the Carbohydrate and Medicinal Chemistry Divisions of the American Chemical Society are published in this volume. Most of the authors have included in their papers data that had not been presented in the sessions to render the book more up-to-date.

The ten chapters comprising the present volume are authored by recognized authorities in the field of anthracycline chemistry, both in the United States and abroad. Their order follows roughly the logical order of presentation of the papers in the symposium.

Ven L. Narayanan, director of the Drug Synthesis and Chemistry Branch of NCI, who chaired the first session of the symposium, wrote an overview of the symposium for this volume. The first chapter gives an overview of the structure–antitumor activity relationships in anthracyclines as correlated by Naff, Plowman, and Narayanan. This is a very valuable chapter since it summarizes the extensive screening data available at the National Cancer Institute, an organization that runs the largest screening program in the world. Because of their unique position in the NCI, these authors were able to correlate the effect of the various structural changes that have been made in the hundreds of anthracycline molecules screened. As might be expected, this chapter is the longest in the book.

The following three chapters describe work carried out by major pharmaceutical companies working in the anthracycline area. The chapter by Arcamone, Cassinelli, and Penco describes the recent developments in the chemistry of doxorubicin and related anthracycline glycosides. This work reviews research carried out in Farmitalia of Milan, following the development of the clinically successful doxorubicin. In his chapter Oki deals with the microbial transformation of anthracycline antibiotics and the development of new families of anthracyclines related to aclacinomycin. It will be recalled that the latter drug was developed by Sanraku-Ocean Company of Fujisawa, Japan, and has shown a great promise clinically in Japan. Wiley of the Upjohn Company discusses the research carried out by this company on nogalamycin and its analog.

The chapter by Acton, Mosher, and Gruber of SRI International discusses the development of several N-substituted anthracyclines with enhanced activity.

The next two chapters deal with the synthesis of the aromatic moieties of anthracyclines, namely, the anthracyclinones, and discuss various strategies developed toward their total synthesis. The first, by Kende, Rizzi, and King, deals with the total synthesis of deoxyanthracyclinones, while the second, by Swenton, deals with regiospecific conversion strategies for anthracyclinone synthesis using quinone bis- and monoketals.

The next three chapters deal with modifications in the sugar moiety of anthracyclines. The first, by Horton and Priebe, is on glycon- and C-14 -modified doxorubicin analogs having enhanced activity. This is followed by the chapter of Monneret, Boivin, Martin, and Pais on the synthesis of disaccharide analogs of aclacinomycins, and then the chapter by El Khadem, Matsuura, Swartz, and Cermak dealing with anthracycline analogs having monosaccharide and disaccharide moieties.

This volume includes the most comprehensive and up-to-date study of the structure – antitumor activity relationships in the area of anthracyclines, and although by its nature it does not attempt to cover all aspects of present day research in anthracyclines, it does offer the reader an insight on the recent developments in ten very active centers in the world.

Hassan S. El Khadem

Houghton, Michigan
April 1982

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ANTHRACYCLINES IN THE NATIONAL CANCER INSTITUTE PROGRAM

M. Benton Naff
Jacqueline Plowman
V. L. Narayanan

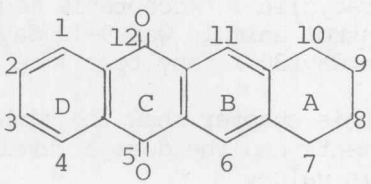
Developmental Therapeutics Program
Division of Cancer Treatment
National Cancer Institute
National Institutes of Health

The intense interest shown by researchers in the chemistry and biological activity of anthracyclines is illustrated by the wide variety and large numbers of these compounds submitted to the National Cancer Institute (NCI). Over a period of fifteen years, approximately four hundred anthracyclines became part of the program effort to develop agents superior to the clinically used adriamycin.

This paper presents and correlates chemical structures with anticancer data obtained in the in vivo P388 leukemia system for all anthracyclines screened by NCI*. The outcome of this testing was the selection of several anthracyclines for more extensive antitumor evaluation.

DEFINITIONS

For the purpose of this chapter an anthracycline is defined as an aglycone of four fused six-membered rings attached to at least one sugar moiety. The numbering pattern and letter designation of the rings in the aglycone are shown below:



**This excludes about 10% of the anthracyclines which are still classified.*

ISBN 0-12-238040-1

Rings B and D are aromatic, ring C quinoid and ring A non-aromatic. Two carbons in a side chain attached at the 9-position are numbered 13 and 14 proceeding along the chain away from the A-ring.

The aglycone core (rings BCD) of the anthracyclines tested by NCI differ in the number and/or the distribution of the phenolic hydroxyls (or methoxyls) on rings B and D. Only two anthracyclines had a change on the quinoid ring; in both, the 5-position oxygen was replaced by the isoelectronic NH group.

TESTING INFORMATION

Most of the anthracyclines were evaluated for antitumor activity against the i.p. implanted murine P388 lymphocytic leukemia*. Mice received an i.p. inoculum of 10^6 cells on day 0 and i.p. treatment with the anthracycline was initiated at least 24 hours later. Anthracyclines entering the program early in its history were administered daily for nine days starting on day 1 (Q01DX9,D-1). Later a more stringent delayed intermittent treatment schedule was employed with the anthracycline administered on days 5,9, and 13 (Q04DX3, D-5). Four or five doses of each anthracycline covering an 8-16 fold dosage range were initially evaluated. Median survival times of treated mice and non-treated controls were determined and the results expressed as a percent T/C where

$$\% \text{ T/C} = \frac{\text{median survival time of test animals X 100}}{\text{median survival time of control animals}}$$

A T/C value $\geq$ 120% is considered necessary to demonstrate activity, whereas a T/C value $<$ 85% indicates toxicity. Depending on compound availability, experiments in which the compound demonstrated initial activity were confirmed and inactive, non-toxic experiments were repeated using higher doses of the anthracycline. Acceptable median survival time range for control animals was 9-13 days. Experiments were terminated on day 30 if any test mice were still alive on that day.

The tables of this chapter show the highest % T/C obtained in the two experiments and the dosage level (optimal dose) which produced this value.

**CANCER CHEMOTHERAPY REPORTS PART 3, Vol. 3, No. 2, p. 9 (1972).*

COMPARISON OF ACTIVITIES

Adriamycin was selected as the parent for comparisons of activities. The % T/C of an anthracycline analog was divided by the average % T/C of adriamycin (determined in over 200 experiments) to provide a number referred to as the analog to parent ratio (A/P ratio). An A/P ratio >1.00 indicates that the analog is superior to adriamycin.

Data on two of the best known anthracylines are shown in Table I:

TABLE I

NSC	COMPOUND	Daily Schedule Q01DX9 D-1			Intermittent Schedule Q04DX3 D-5		
82151	daunomycin	0.79[a]	179[b]	1.00[c]	0.82[a]	143[b]	8.00[c]
123127	adriamycin	1.00	226	1.00	1.00	174	8.00

These are average values from many tests of daunomycin and adriamycin.

a. A/P analog to parent ratio

b. % T/C test animal survival divided by control animal survival both measured in days and the fraction multiplied by 100.

c. optimum dose (mg/kg/injection).

The same order for A/P ratio, % T/C, and optimum dose is used for all the tables in this chapter.

Note, that the term activity refers to the A/P ratio, throughout the discussions to the tables.

SYMBOLS FOR TABLES

R's are hydrogen unless another group is indicated in the table column. The designation of the orientation of a group as above or below the plane of the aglycone is indicated by a wedge ◄ (above) and by a dotted line ..... (below). Haworth projection formulas are used for sugars.

A cartwheel ⊕ by the dose means that of the two experiments run on the same schedule the highest T/C of the first experiment differed from that of the second by at least 20%.

An ↑ alongside the dose indicates the optimum T/C was not attained in the experiment.

Special designations are interpreted in table footnotes as necessary.

The NSC symbol is an abbreviation identifying the National Cancer Institute acquisition number.

APPROACH TO STUDY AND ORGANIZATION OF CONTENTS

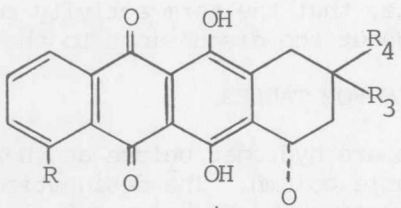
All the anthracyclines in the NCI program were categorized into tables according to structural types. Screening data were added and each table analyzed. Proprietary compounds were then eliminated and the truncated tables became the basis for discussion.

The organization of the main body of this chapter is under the heading of "Structure-Activity Correlations". It consists of a series of structural formulas each followed by an applicable table and an appropriate statement or discussion of the table. A summary encompassing the main points of the discussion concludes the chapter.

STRUCTURE-ACTIVITY CORRELATIONS

Figure 1 is the structural formula for Tables II through VIII.

AGLYCONE A =



SUGAR =

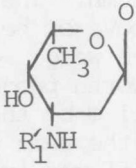


FIGURE 1

TABLE II HETEROATOM MONOSUBSTITUTION ; A-RING 9-POSITION

refer to figure 1. R=OCH_3

NSC	R_1'	R_3,R_4	Q01DX9	D-1		Q04DX3	D-5	
268708		... OH,H	1.04	236	12.50	1.04	181	75.00
268709		▬ OH,H	0.76	173	6.25			
281634		$-OCH_3$ [a]				0.61	107	50.00↑
265493	TFA [b]	= O	0.46	104	1.56			
272678	TFA	= NHOH	0.56	128	25.00			
272679	TFA	∿∿NHOH,H	0.51	116	25.00↑			

Table II emphasizes the importance of the 9-hydroxyl group. Note that the best A/P ratio results if the hydroxyl lies below the plane of the aglycone as in NSC-268708.

(a) NSC-281634 has a 9,10 position double bond.
(b) TFA is the trifluoroacetyl group.