

**MOLECULAR ASPECTS OF ANTICANCER
DRUG-DNA INTERACTIONS**

Volume 2

TOPICS IN MOLECULAR AND STRUCTURAL BIOLOGY

Series Editors

Stephen Neidle
Institute of Cancer Research
Sutton, Surrey, UK

Watson Fuller
Department of Physics
University of Keele, UK

Jack S. Cohen
Georgetown University
USA

Recent titles

Protein–Nucleic Acid Interaction
Edited by Wolfram Saenger and Udo Heinemann (1989)

Calcified Tissue
Edited by David W. L. Hukins (1989)

Oligodeoxynucleotides: Antisense Inhibitors of Gene Expression
Edited by Jack S. Cohen (1989)

Molecular Mechanisms in Muscular Contraction
Edited by John M. Squire (1990)

Connective Tissue Matrix, Part 2
Edited by David W. L. Hukins (1990)

New Techniques of Optical Microscopy and Microspectroscopy
Edited by Richard J. Cherry (1990)

Molecular Dynamics: Applications in Molecular Biology
Edited by Julia M. Goodfellow (1990)

Water and Biological Macromolecules
Edited by Eric Westhof (1993)

Topics in Molecular and Structural Biology

**MOLECULAR ASPECTS OF
ANTICANCER DRUG–DNA
INTERACTIONS
Volume 2**

Edited by

Stephen Neidle

*Institute of Cancer Research
Sutton, Surrey, UK*

and

Michael Waring

*Dept of Pharmacology
University of Cambridge*

M
MACMILLAN

© The contributors 1994

Softcover reprint of the hardcover 1st edition 1994

All rights reserved. No reproduction, copy or transmission of this publication may be made without written permission.

No paragraph of this publication may be reproduced, copied or transmitted save with written permission or in accordance with the provisions of the Copyright, Designs and Patents Act 1988, or under the terms of any licence permitting limited copying issued by the Copyright Licensing Agency, 90 Tottenham Court Road, London W1P 9HE.

Any person who does any unauthorised act in relation to this publication may be liable to criminal prosecution and civil claims for damages.

First published 1994 by
THE MACMILLAN PRESS LTD
Houndmills, Basingstoke, Hampshire RG21 2XS
and London
Companies and representatives
throughout the world

ISBN 978-1-349-13332-1 ISBN 978-1-349-13330-7 (eBook)
DOI 10.1007/978-1-349-13330-7
ISSN 0265-4377

A catalogue record for this book is available
from the British Library

Contents

<i>The Contributors</i>	viii
<i>Preface</i>	x
1 DNA topoisomerases <i>R. K. Ralph, W. Judd, Y. Pommier and K. W. Kohn</i>	1
1 Introduction	1
2 Topoisomerase I (top I)	3
3 Topoisomerase II (top II)	24
4 Conclusions	66
2 Cellular and molecular pharmacology of the anthrapyrazole antitumour agents <i>L. H. Patterson and D. R. Newell</i>	96
1 Introduction	96
2 Rationale for development of the anthrapyrazoles	96
3 Structural requirements for anthrapyrazole antitumour activity	98
4 Cellular pharmacology of the anthrapyrazoles	110
5 Molecular pharmacology of the anthrapyrazoles	112
6 Activation of anthrapyrazoles in biological systems	117
7 Preclinical and clinical pharmacology of the anthrapyrazoles	123
8 Conclusions	123
3 Calicheamicin <i>G. A. Ellestad and W.-d. Ding</i>	130
1 Introduction	130
2 Isolation, structure and chemistry	131
3 Affinity of calicheamicin γ_1^I for DNA	135
4 Plasmid DNA cleavage studies	136
5 DNA binding/cleavage specificity	137

6	Structural features important for DNA binding and discrimination	140
7	NMR evidence for solution conformation	141
8	Evidence for a hydrophobic contribution to the calicheamicin–DNA association	142
9	DNA cleavage chemistry	145
10	Mechanism of trisulfide cleavage	150
11	Biochemical basis for cytotoxicity	152
12	Summary	153
13	Addendum	161
4	Molecular pharmacology of intercalator–groove binder hybrid molecules <i>C. Bailly and J.-P. Hélichart</i>	162
1	Introduction	162
2	Isolexins, lexitropsins and combilexins	164
3	Naturally occurring multivalent molecules	167
4	Netropsin–acridine hybrid molecules	168
5	Distamycin–ellipticine hybrid molecules	178
6	Intercalator–peptide conjugates	181
7	Conclusion	186
5	Bleomycins: Mechanism of polynucleotide recognition and oxidative degradation <i>A. Natrajan and S. M. Hecht</i>	197
1	Introduction	197
2	Oxygen activation by iron bleomycin	200
3	Other metallobleomycins	209
4	Interaction of bleomycin with DNA	211
5	Nucleic acid degradation by bleomycin	224
6	Future prospects	233
6	Kinetic analysis of drug–nucleic acid binding modes: Absolute rates and effects of salt concentration <i>W. D. Wilson and F. A. Tanius</i>	243
1	Introduction	243
2	Nucleic acid binding modes	244
3	Ion effects on nucleic acid structure and interactions	246
4	Quantitative aspects	248
5	Methods	255
6	Applications to drug–nucleic acid complexes: Classical intercalation, threading intercalation and groove-binding	259
7	Association reactions	259
8	Dissociation reactions	262
9	Mechanism of nucleic acid–drug interactions	266

7 Acridine-based anticancer drugs	<i>W. A. Denny and B. C. Baguley</i>	270
1	Introduction	270
2	9-Anilinoacridines	271
3	Acridinecarboxamides	279
4	Nitroacridines	284
5	Polyacridines	286
6	Acridines as carriers for other functionalities	291
7	Acridine alkaloids	295
8	Acridones	296
9	Conclusions	297
8 The mitomycins: Natural cross-linkers of DNA	<i>M. Tomasz</i>	312
1	Introduction	312
2	Reductive activation of mitomycins to bifunctional alkylating agents	314
3	Bioreductive alkylation products of mitomycins with DNA: Isolation and structure of the MC–DNA cross-link	318
4	Mechanism of the reductive alkylation of DNA	323
5	Acidic activation of mitomycin C: Switch of regioselectivity of alkylation from N ² to N-7 of guanine	326
6	Conformation of the mitomycin–DNA complex	328
7	DNA sequence specificity of the covalent reactions of mitomycin with DNA	335
8	Ternary mitomycin–DNA–protein interactions	341
9	Summary of the molecular details of mitomycin–DNA interactions: Significance for drug design	341
<i>Index</i>		351

The Contributors

Bruce C. Baguley
Cancer Research Laboratory
University of Auckland School of
Medicine
Private Bag 90192
Auckland
New Zealand

Christian Bailly
Department of Pharmacology
University of Cambridge
Tennis Court Road
Cambridge CB2 1QJ
UK

William A. Denny
Cancer Research Laboratory
Auckland Division Cancer Society of
New Zealand Inc.
Auckland Medical School
University of Auckland
Private Bag 90192
Auckland
New Zealand

Wei-dong Ding
Infectious Disease Research Section
Medical Research Division
Lederle Laboratories
American Cyanamid Company
Pearl River
New York 10965
USA

George A. Ellestad
Infectious Disease Research Section

Medical Research Division
Lederle Laboratories
American Cyanamid Company
Pearl River
New York 10965
USA

Sidney M. Hecht
Department of Chemistry
University of Virginia
Charlottesville
Virginia 22901
USA

Jean-Pierre Hénichart
Centre de Recherche INSERM
Place de Verdun
59045 Lille Cedex
France

Warren Judd
School of Biological Sciences
University of Auckland
Private Bag 92019
Auckland
New Zealand

Kurt W. Kohn
Laboratory of Molecular
Pharmacology
Development Therapeutics Program
National Cancer Institute
National Institutes of Health
Building 37 Room 5C25
Bethesda
Maryland 20892
USA

Anand Natrajan
Department of Biology
University of Virginia
Charlottesville
Virginia 22901
USA

David R. Newell
Division of Oncology
University of Newcastle upon Tyne
Cancer Research Unit
The Medical School
Framlington Place
The University
Newcastle-upon-Tyne NE2 4HH
UK

Laurence H. Patterson
Department of Pharmacy
School of Applied Sciences
De Montfort University
The Gateway
Leicester LE1 9BH
UK

Yves Pommier
Laboratory of Molecular
Pharmacology
Development Therapeutics Program
National Cancer Institute
Bethesda
Maryland 20892
USA

Raymond K. Ralph
School of Biological Sciences
University of Auckland
Private Bag 92019
Auckland
New Zealand

Fariar A. Tanious
Laboratory for Chemical and
Biological Sciences
Georgia State University
Atlanta
Georgia 30303
USA

Maria Tomasz
Department of Chemistry
Hunter College
City University of New York
695 Park Avenue
New York
New York 10021
USA

W. David Wilson
Department of Chemistry
Georgia State University
University Plaza
Atlanta
Georgia 30303
USA

Preface

DNA has long been a key target for cancer chemotherapy. Indeed, the first agents to be employed clinically in the treatment of human cancer (the nitrogen mustards) are DNA cross-linking agents. Spectacular advances have occurred during recent years in the treatment of childhood leukaemia and testicular cancer, largely as a result of the development of better DNA-interactive agents. Even though the majority of solid tumours remain resistant to chemotherapy, there is real promise that a new, third-generation of platinum compounds will prove successful in the treatment of ovarian cancer. Clinical advances in such key areas are the ultimate objective of much current research in cancer chemotherapy and biology. Future progress must surely result from wise application of the large body of fundamental knowledge being accumulated from studies in a whole range of disciplines. No one doubts that clinical success will increasingly depend upon the exploitation of such knowledge and on the interplay between it and more applied disciplines. This is especially important as the molecular and cellular bases of malignant cell growth become better understood. So the study of drug-DNA interactions has moved on from the position of a dozen years ago, when our understanding of the molecular basis of drug action was relatively poor, as were the prospects for rational design of new drugs, to a much more positive position with new horizons.

These two volumes survey our current knowledge about the mode of action of the major classes of DNA-interactive antitumour agents, and in so doing provide pointers for the discovery of new therapeutic substances. The reader will notice that certain related topics have been grouped together; indeed in one instance (that of topoisomerase inhibitors), what were originally planned as two separate chapters by different authors have been amalgamated into one (by mutual consent!) so as to produce a more balanced and co-ordinated treatment. Elsewhere the

relationships between topics may be less obvious, but we hope that our choices will stimulate cross-fertilization of ideas.

An enterprise involving many authors such as this requires the cooperation of all the contributors if it is to succeed. We are grateful to everyone for their efforts in ensuring delivery of their manuscripts promptly and for making our task as editors such a pleasurable one. Both of us are indebted to the Cancer Research Campaign for supporting work on drug–DNA interactions in our own laboratories over a number of years. To the hard-working staff of the Campaign, as well as to those who devote their lives to the alleviation of cancer at the bedside and in the laboratory, we dedicate this pair of volumes.

Sutton and Cambridge, 1993

S. N.
M. W.