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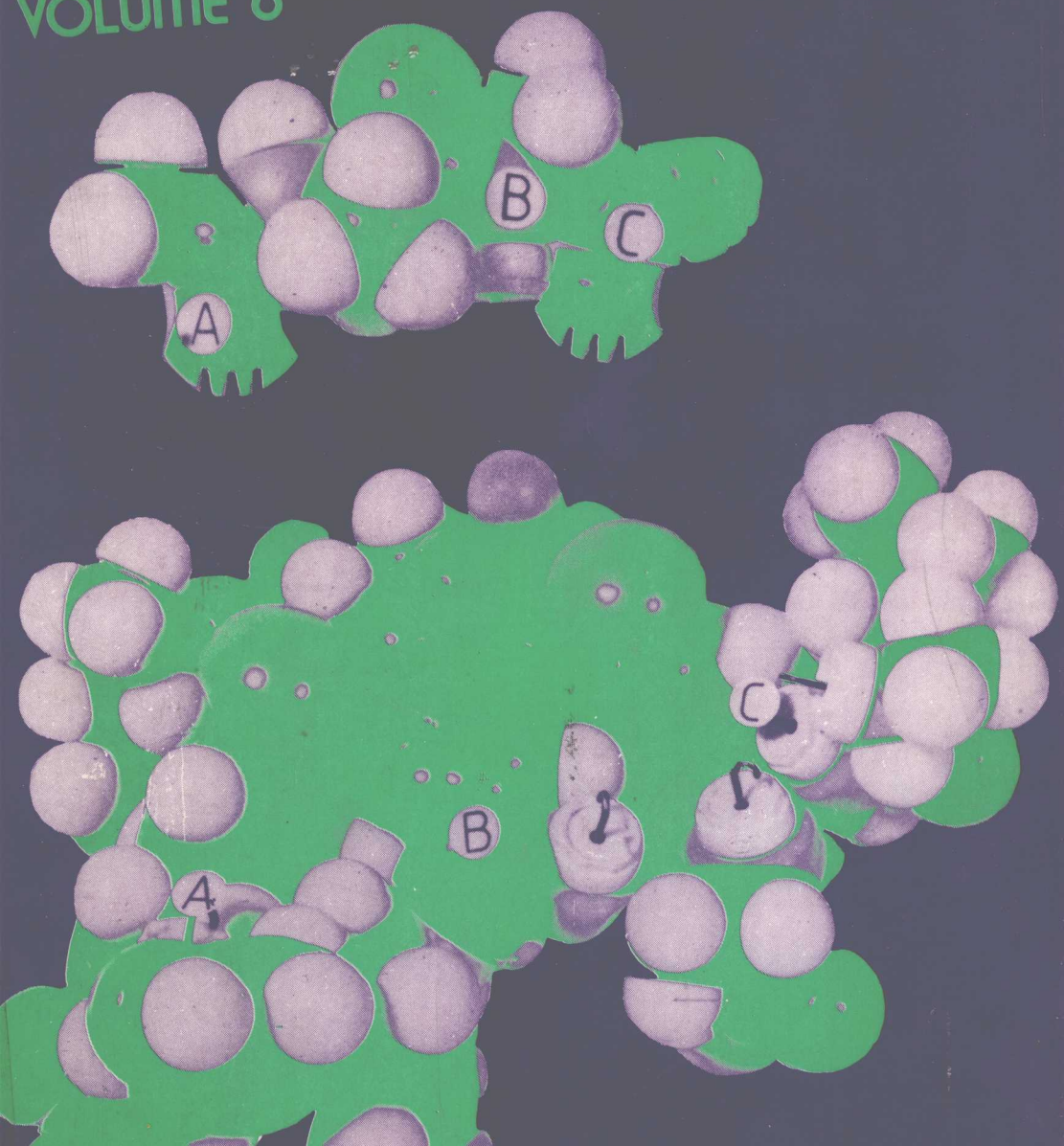
VOLUME 6



TOPICS IN ANTIBIOTIC CHEMISTRY
Vol. 6

TOPICS IN ANTIBIOTIC CHEMISTRY

Series Editor:
P. G. SAMMES, Head of Department of Organic Chemistry,
University of Leeds

The object of this international series is to keep all interested workers informed on the advances of our knowledge concerning the role of antibiotics in nature, and on the mechanisms by which they act against pathogenic organisms. Future volumes have been planned and will appear regularly.

Volume 1 **The Aminoglycosides** – D. A. Cox, K. Richardson and B. C. Ross, Pfizer Central Research, Sandwich, Kent.

The Ansamycins – M. Brufani, University of Siena, Italy.

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Daunomycin and Related Antibiotics – F. Arcamone, Farmitalia-Ricerca Chemica, Milan.

Interactions of Daunomycin and Related Antibiotics with Biological Receptors – S. Neidle, Department of Biophysics, King's College, University of London.

Volume 3 **Mechanisms of Action of Nalidixic Acids and its Congeners** – G. C. Crumplin, J. M. Midgley and J. T. Smith, London University School of Pharmacy.

New β-Lactam Antibiotics – R. D. G. Cooper, The Lilly Research Laboratories, Eli Lilly Company, Indianapolis, Indiana.

Volume 4 **The Chemistry and Antimicrobial Activity of New Synthetic β-Lactam Antibiotics** – F. A. Jung, , W. R. Pilgrim, J. P. Poyser and P. J. Siret, I.C.I. Pharma S.A., Reims, France.

Volume 5 **Antibiotics and Peptidoglycan Metabolism** – J. M. Ghuysen, Faculté de Médicine, Institute de Botanique, Université de Liege.

The Vancomycin and Ristocetin Group of Antibiotics – D. H. Williams, V. Rajanada, M. P. Williamson and G. Bojesen, University Chemical Laboratory, Cambridge.

Properties and Action of Kirromycin (Mocimycin) and Related Antibiotics – A. Parmeggiani and G. Sander, Laboratoire de Biochemic, École Polytechnique, Palaiseau Cedex.

The Actinomycins – A. B. Mauger, Research Foundation of the Washington Hospital Center, Washington, D.C.

Volume 6 **Modern Synthetic Antifungal Agents** – G. J. Ellames, Searle Research & Development, G. D. Searle & Co. Ltd., High Wycombe, Buckinghamshire.

The Biochemistry of Nucleoside Antibiotics – J. Goodchild, Department of Medicinal Chemistry, Searle Research & Development, G. D. Searle & Co. Ltd., High Wycombe, Buckinghamshire.

Chemistry of Nucleoside Antibiotics – J. G. Buchanan and R. H. Wightman, Department of Chemistry, Heriot-Watt University, Riccarton, Currie, Edinburgh.

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Editor's Preface

The title of this series implies an emphasis on the chemistry of antibiotics and although this is certainly true it is apparent that reviews of other aspects of antibiotic properties have figured predominantly in previous volumes published in the series. Whereever possible authors have indicated the range of biological activities for different classes of compounds so that the complete series provides a useful library of reference for such information. The subject matter embraced by the title, *Topics in Antibiotic Chemistry*, has also been interpreted as widely as possible and has not been restricted to antibacterial agents or just natural products. This broadness of approach is reflected by the contents in this sixth volume of the series. In Part A, Dr George Ellames, of Searle Research and Development, High Wycombe, U.K., describes recent studies on synthetic antifungal agents, concentrating on the imidazole reagents most popularly prescribed for such infections. Emphasis is given to the range of microorganisms affected and the relevant safety levels at which these agents may be utilised. In view of the fact that over 20% of the world's population suffers from some form of fungal infection, this review has a very general interest.

The two other articles concentrate on the nucleoside antibiotics. Interest on these agents is not only focused on their antibiotic properties but also on their potential use in cancer chemotherapy. The fundamental role played by nucleosides in cell reproduction and control processes is often enlightened by the use of nucleoside analogues. Part B, the first of these two reviews, is written by Dr. John Goodchild, also of Searle Research and Development, High Wycombe, U.K., and covers the biochemical role of such agents. Dr. Goodchild clearly presents modern thinking on the possible and preferred sites for attack and cases where selectivity of action may be anticipated. Part C, by Professor Grant Buchanan and Dr. Richard Wightman, of the Heriot-Watt University, Edinburgh, details chemical studies on the nucleoside antibiotics and on naturally-occurring analogues, thus fully complementing the discussion in Part B.

The target of Volume 6 follows that set in the earlier volumes, namely to keep all interested workers and students informed on the advances being made in our knowledge on the role antibiotics play in nature and the mechanisms by which they act.

Contributions to *Topics in Antibiotic Chemistry* are only sought from experts in the various fields. A further important requirement is that these experts must be actively engaged in research in the topic covered by their articles; a precedent set in Volume 1 and adhered to in all subsequent volumes.

Topics in Antibiotic Chemistry continues to attract the interest and enthusiasm of workers involved in this subject. I wish to thank all those who have made comments on the series and to extend an invitation for constructive and critical comments on the present volume. Suggestions for future articles will receive serious and careful consideration. As mentioned above, it is not our intention to restrict the scope of articles to purely chemical aspects of the subject but also to include those on associated areas of interest.

Despite my own shortcomings and distractions my publishers, Ellis Horwood Ltd. have continued to work efficiently and diligently in order to help this volume materialise. Finally may I thank all the contributors without whose efforts this volume would have been impossible.

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Part A

Modern Synthetic Antifungal Agents

by

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PART A

CONTENTS

1 INTRODUCTION

Fatalities caused by fungal disease are not a new burden; however the incidence of the systemic fungal infections that cause these fatalities has increased steadily in recent years. Ironically, it is believed that this is due largely to advances of modern medicine in other fields. In particular, the use in therapy of immunosuppressive and/or cytotoxic drugs, and the prolonged lifespan of patients with diseases displaying similar effects, are considered to have contributed to this observation by providing an increased number of 'compromised hosts'.

It is probably fair to say that the development of effective therapeutic agents for fungal disease has lacked the attention devoted to bacterial and, more recently, viral diseases. Fungal infections are considered less common than those caused by bacteria and viruses and have perhaps suffered from the view that they are often 'complications' rather than primary causes of illness. Also, the fungal diseases most frequently encountered are not the life-threatening systemic mycoses but are superficial infections which may disappear spontaneously without treatment.

Existing antifungal drugs probably owe more to serendipity than to rational drug design. One difficulty that confronts the designer of antifungal agents is that, unlike bacterial cells, both fungal and mammalian cells are eukaryotic. Therefore few differences readily present themselves as potential targets for selective chemotherapy. However, investigation of the modes of action of existing antifungal agents has led to increased understanding of the fungal cell and, with reference to the polyene macrolides and the imidazole-based antifungals, especially the structure of the fungal cell membrane. It is hoped that this increased understanding has already contributed to the next generation of chemical antifungals.

In concerning itself with modern synthetic antifungal agents this review will very largely discuss those containing the imidazole moiety. This naturally reflects the author's own interests, but a browse through the literature of the past dozen or so years will show that this view does have a certain validity. However, before a detailed examination of these agents, human fungal infections themselves will be considered. This will be followed by brief descriptions of the other main antifungal agents, that is, griseofulvin, flucytosine and the polyene macrolides. The imidazole-based antifungal agents currently available, that is, clotrimazole, miconazole and econazole, will then each be described in terms of their chemical synthesis, biological activity and clinical usefulness. The remainder of the review will discuss topics such as the possible mode of action of these compounds, the

screening processes involved in the search for novel compounds displaying antifungal activity, and a survey of the range of imidazole-based structures displaying such activity. There will also be a discussion of the compounds, notably ketoconazole, from which it is hoped will come the next generation of imidazole-based antifungal agents.

2 FUNGI PATHOGENIC TO MAN

Fungal infections in man are generally divided into three main groups; cutaneous, subcutaneous and systemic. There follows a brief description of the most common infections in each category.

2.1 Cutaneous mycoses

Cutaneous mycoses are the superficial fungal infections and these tend to be classified by the site of infection rather than by the agent responsible. They include such common infections as athlete's foot, ringworm and thrush. These are extremely widespread and, although seldom disabling, are rightly considered a major hazard to public health both in terms of man-hours lost and in terms of psychological distress. These superficial fungi live in the keratinous layer of the skin and produce enzymes that break down the keratin, thus giving rise to lesions. They can be further sub-divided into the candidal infections and the dermatophytoses, or tineas.

The descriptions that follow owe a great deal to two dermatological texts, that is, *Synopsis of Dermatology*, by Stewart, Danto and Maddin [1], and *Dermatology – An Illustrated Guide*, by Fry [2].

2.1.1 *Candidiasis*

(a) *Candida vaginitis*

This infection was described in 1977 as having reached near epidemic proportions in the United Kingdom [3]. Only the dermatophytoses are more common fungal infections. In 1973 it was estimated that one in seven women of child-bearing age suffer from this disease [4]. The incidence of the infection appears to be highest during pregnancy [5] and it is reported [6] that children born to women infected with the organism responsible, *Candida albicans*, have a thirty-five times greater chance of developing thrush than other newborns. Many of those children that appear to be unaffected are found to be carrying the fungus in the gastrointestinal tract. This often leads to the vagina eventually being infected via the perineum. The affected area develops a pimply rash which forms lesions leading to a white, curdy discharge and often an intense itching and burning sensation. Candida vaginitis has recently been discussed in greater detail by Hurley and De Louvois [7].

(b) *Intertrigo*

The lesions caused by this infection may occur on the submammary, perianal and perivulval skin. The infection appears as a tender, reddened, macerated area which is, again, pruritic.

(c) *Perleche*

This infection is characterised by fissuring inflammation at the corners of the

mouth. It is particularly prevalent amongst the elderly who may have lost their natural teeth, as this causes the folding of the skin around the mouth to increase.

(d) *Thrush*

Although commonly used to describe many of the above and other superficial candidal infections, this term is correctly restricted to oral candidiasis. The infection is characterised by creamy white plaques on the mucosal surfaces.

2.1.2 *Dermatophytoses*

These infections are generally found to be caused by *Trichophyton, Epidermophyton* or *Microsporum* species. Often referred to as tineas, after the latin *tinea* or gnawing worm, these ringworm diseases are the most common fungal infections.

(a) *Tinea capitis*

This disease is more commonly known as ringworm of the scalp and is characterised by patchy loss of hair, with or without inflammation. The organisms responsible are most usually *Microsporum canis* or *Microsporum audouini.* The disease is found to be very widespread in the Third World and amongst socially deprived groups. The most common sufferers are children, who may suffer additional damage psychologically through attempts at containment by isolation.

(b) *Tinea corporis*

This infection may be located over any smooth area of the body surface and its physical appearance probably gives rise to the term ringworm. When caused by *Microsporum* species this infection appears as red, circular patches with pale centres and blistery surrounds. They may be numerous but tend to be uniform in size and less than three inches in diameter. When caused by *Trichophyton* species these patches tend to be larger and less regular in shape.

(c) *Tinea cruris*

This is the second most frequently encountered of the tineas and is more commonly known as ringworm of the groin. The infection appears as a reddening of the skin with a raised scaly circumference to the affected area. The disease is more common amongst men than women.

(d) *Tinea pedis*

This infection is usually caused by either *Trichophyton rubrum* or *Trichophyton mentagrophytes* and is commonly known as athlete's foot. Although found throughout the world, this infection appears to be most common in temperate regions. In 1969 it was estimated that up to 70% of the general population showed signs of tinea pedis [8]. The disease usually manifests itself in the form of white, macerated tissue between the toes.