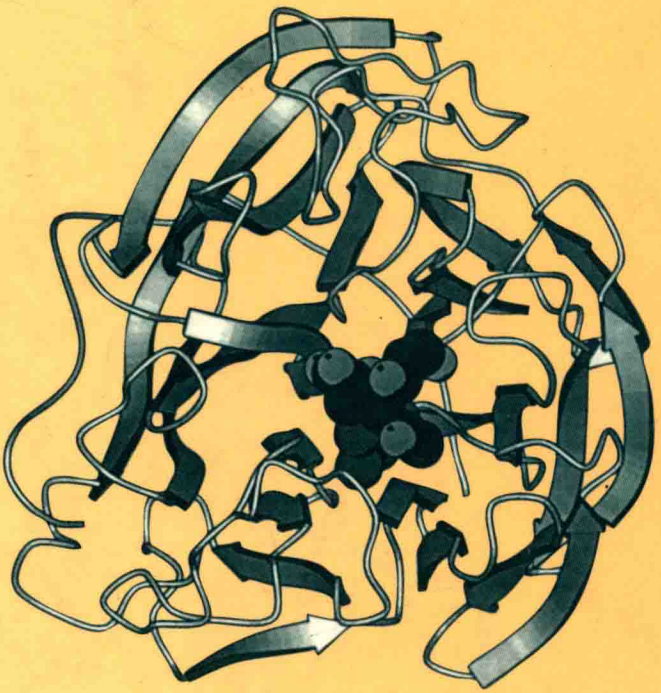
CARBOHYDRATES IN DRUG DESIGN



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MARCEL DEKKER, INC. NEW YORK · BASEL · HONG KONG

Library of Congress Cataloging-in-Publication Data

Carbohydrates in drug design/ edited by Zbigniew J. Witczak, Karl A. Nieforth.
p. cm.
Includes index.
ISBN 0-8247-9982-8 (hardcover: alk. paper)
1. Carbohydrate drugs. I. Witczak, Zbigniew J.
II. Nieforth, Karl A.
[DNLM: 1. Carbohydrates—chemistry. 2. Carbohydrates—therapeutic use. 3. Carbohydrates—pharmacokinetics. 4. Drug Design. QU 75 C26443 1997]
615'.3—dc21
DNLM/DLC
for Library of Congress

97-12543
CIP

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MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016
http://www.dekker.com

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

CARBOHYDRATES IN DRUG DESIGN

Preface

In the last four decades, carbohydrates, one of the most abundant natural product classes, have received considerably less attention from the majority of mainstream, synthetic chemists than other fields of natural product chemistry. Recently, this situation has changed and carbohydrate research is becoming a significant focus for synthetic chemists, particularly in medicinal and pharmaceutical chemistry. Within these disciplines, exciting new developments in the isolation and study of glycoproteins, glycopeptides and oligosaccharides have contributed to dramatic advances in our knowledge of the critical biological roles of these compounds.

Significant progress in this new field, glycobiology, and new discoveries of unique biological functions of carbohydrates have had a direct impact on a diverse group of biological studies from cancer to diabetes and cell-cell adhesion in inflammation and metastasis. Moreover, we have witnessed explosive developments in synthetic carbohydrate chemistry as efforts have been to expand our basic knowledge of relatively simple molecules such as KDO and sialyl Lewis^x, glycosylphosphatidylinositol (GPI) membrane anchors, Acarbose and other new antidiabetic agents as well as heparin oligosaccharides. Some of these new developments have major clinical implications and are the subject of chapters in this book. Other areas which are not part of this text, including macrolide antibiotics and modified aminoglycoside antibiotics, were not ignored; they were omitted because of limited space and scope of the book.

Carbohydrates have a long history of medicinal use as nutritional supplements, anticoagulants, plasma expanders, macrolide antibiotics, etc. and have recently been introduced as antidiabetics. The first of these, Acarbose, was introduced by Bayer in 1990 and approved by the FDA in 1995 for the USA market. The second was Voglibose, which was introduced in 1994 by Takeda Industries, and marketed only in Japan. A few other carbohydrate therapeutics based on oligosaccharides (heparin derivatives) and polysaccharides (glycans) are in the final phases of clinical trials or waiting approval.

The following pages offer stimulating accounts of the rapidly developing and challenging field of the chemistry of carbohydrates presented by

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internationally recognized scholars. Significant developments in this fascinating arena review state-of-the-art technologies used to unravel mechanisms of actions, study conformational and steric effects, compare and contrast synthetic and enzymatic approaches and finally develop new leads in emerging fields of glycobiology.

Each of the authors has drawn heavily on existing literature and his or her own personal experiences to trace the discovery of new leads and the subsequent development of these leads. The reader is provided with an insight into the factors which led to these new, potentially therapeutic carbohydrates that might be applied in future discoveries. Every chapter provides an illustrative overview of the highly diverse, crucial functions played by mono-, oligo- and polysaccharides in biological systems, and the means by which these observations may be exploited by the imaginative biological chemist. The reader is afforded a glimpse into the bright future of carbohydrate therapeutics as discussions unfold on auranofin, Sucraflate, SLe^x, heparin pentasaccharide, gangliosides, β-glucans, new analogs of anthracycline antibiotics and pyrimidine nucleosides.

This volume is intended for all researchers and graduate students in carbohydrate chemistry, medicinal chemistry, biochemistry and glycobiology. We hope that this volume is found informative and useful to the community of researchers in both academic and industrial laboratories as well as other scientists involved in drug discovery and interested in staying abreast of the progress in the carbohydrate field.

We would like to thank the authors for their well-written articles and their patience during the editing process. We would also like to thank our colleagues who served as external referees for their very helpful suggestions and advice to improve the text. We hope that this book will be an important stimulus for new ideas in this exciting field of research. We believe that this is a challenging subject with a broad universe of interest which, because of its strong commercial potential, will quickly become a major interest of the chemical and pharmaceutical industries. Finally, we take this opportunity to make special mention of Professor Akira Hasegawa's chapter (Chapter 4, p. 137). Professor Hasegawa passed away on October 10, 1996, and we are privileged to have his contribution in this book.

Zbigniew J. Witczak
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Carbohydrates as New and Old Targets for Future Drug Design

Zbigniew J. Witczak
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1. INTRODUCTION

The long standing neglect of carbohydrates by the pharmaceutical and academic communities was most likely due to the underestimation of the biological importance of this class of natural compounds. Early considerations of carbohydrates as energy sources, structural components, and protective agents have been slowly refocused on the fact that they have significant diagnostic and therapeutic potential. New scientific evidence has suggested a relationship between carbohydrate structure and many biological functions. Recent developments show that the diversity and complexity of carbohydrates permit these molecules to carry out a wide range of functions. Studies continue unabated as do important, new developments with significant consequences in medicinal chemistry. Research on carbohydrates is now undergoing considerable growth and promises to be a major source of drug discovery leads [1-9]. One feature of the isolation of new carbohydrates from natural sources is that many belong to what, hitherto, were considered to be rare classes of sugars, i.e. amino-sugars, branched-chain sugars, deoxy sugars, thio-sugars, cyclitols including *myo*-inositols and higher sugars. However, it is remarkable how some of the unique carbohydrate properties can

evoke new concepts and technologies. The diversity and functional specialization of biologically active carbohydrate molecules seem now to be a hallmark and can be expected to bring about similar revolutions in clinical treatment. Such investigations have led to the discovery of new biosynthetic reactions and enzyme control mechanisms, and contribute to an understanding of certain fundamental processes, for example, in the interaction of cells with their environment and with other cells. The roles of carbohydrates in biological processes and diseases are becoming better understood.

Carbohydrate-containing biomolecules are found on all cell surfaces and because of their inherent structural diversity, many oligosaccharides are information carriers and recognition molecules through linkages with other components such as lipids and proteins. Many studies have revealed that carbohydrates provide signals for protein targeting and serve as receptors for binding toxins, viruses and hormones. They control vital events in fertilization and early development, regulate many critical immune system recognition events and target aging cells for destruction. Cell-cell interactions, such as antigen-antibody interactions and virus-host interactions are classical examples of the aforementioned biochemical functions. Another extremely important, recent discovery in cell-cell adhesion in inflammatory responses is the role of sialyl Lewis^x, (sLe^x) a terminal tetrasaccharide of glycolipids. Sialyl Lewis^x is displayed on the surface of white blood cells and is responsible for the repair of injured tissues. This particular discovery has significant potential in the development of new nonsteroidaal antiinflamatory drugs, as well as anticancer drugs designed to prevent the spread of cancer cells: metastasis.

In metastasis cell surface carbohydrates change upon malignant transformation [10] and are responsible for the significant differences in surface properties between metastatic and nonmetastatic cells [10-12]. It is also well documented that the total and neuraminidase-releasable sialic acid contents of tumor cell surfaces are closely related to the metastatic potential of the tumor cells [13-18]. These important new discoveries are excellent, logical leads as key steps for rational design of anti-cancer agents for the treatment of metastatic tumors. Particularly, the development of specific cancer vaccines to induce an anticancer immune response now appears more feasible. This might also offer alternative treatments to chemotherapy and radiation therapy for metastatic cancers as well.

The ultimate goal of a cancer vaccine design is the generation of antigen (carbohydrates as targets) specific vaccines (active specific immunotheraphy ASI) by using chemically well-characterized synthetic antigens as active immunogens. The fact that particular antigens might be selective or, ideally, specific for cancer cells could prove very useful in stimulating antibody production and promoting active immunity against cancers.

Recent advances in monoclonal antibody technology together with rapid progress in synthetic and structural chemistry, have identified and characterized a number of tumor-associated antigens [19-23]. These new important discoveries in molecular biology, immunology, and synthetic carbohydrate chemistry offer great potential for further development of new and diverse cancer vaccines. The immunological and clinical aspects of cancer vaccine developments were reviewed [24].

Presently, there are several established carbohydrate-based products with "biopharmaceutical" applications as well as other new products with potential applications in medicine. Recently purified polysaccharides of bacterial origins, for example have been prepared for use as antigenic vaccines against pneumococcal and meningococcal infections. Due to the ability of certain polysaccharides to cross react with other antisera, they may also provide immunity against other infections.

Other artificial antigens, glycosylated recombinant proteins and immunoadjuvants are emerging as new areas of interest and extensive research.

Other glycobiology-related areas such as neurobiology, neuropathology, and neuropharmacology have investigated the important function of carbohydrates in the understanding of neurobiology. In recent years, neurobiotechnology companies have initiated rapid development of trophic factors and monoclonal antibodies based on recombinant techniques. In this context studies have been initiated of carbohydrates and other glycosylated compounds such as gangliosides, glycosaminoglycans, glycolipids, and lecitins, that may play a significant role in neuropathology or act as therapeutic agents in a wide range of disorders. Gangliosides are one of the leading examples of fast track development. Carbohydrate research in neurobiology may well soon give rise to interesting developments in the treatment of neurological disorders.

These new trends and directions in basic and applied research in multidisciplinary fields associated with the emerging field of glycobiology will provide tremendous opportunities for the development of new carbohydrate therapeutics. Present work suggests that these will include not only complex carbohydrate molecules but relatively simple small monosaccharide molecules as well.

2. CLASSIFICATION

Because of the multifunctionality of carbohydrates and for overall clarity, it is useful to classify biologically active carbohydrates according to their therapeutic activity such as antiinflammatory, anticancer, antidiabetic, anticonvulsant, antibiotic as well as antiviral. Traditional classification would divide the existing drugs or new analogs being developed as potential therapeutics into the following chemical classes of derivatives: mono- and disaccharides, oligosaccharides, and polysaccharides.

3. ANTICONVULSANT AGENTS

An example of a simple sugar with strong biological activity is a new prototype of an antiepileptic drug based on fructose, being developed by R.W. Johnson Pharmaceutical Institute under the generic name **Topiramate**.

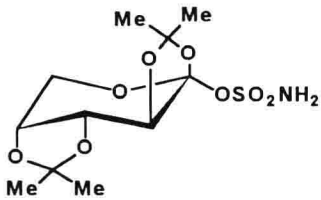

Fig. 1 Chemical structure of Topiramate.

Topiramate, a novel fructose sulfamate, is presently in late-phase clinical trials and has proven to be an effective anti-epileptic drug [25]. The anti-convulsant properties of Topiramate were discovered through biological screening. Recently, a carbocyclic analogue of Topiramate was also synthesized [26]. However, no biological data, were reported.

4. ANTIVIRAL AGENTS

The potent and selective influenza neuraminidase inhibitor, **4-Guanidino Neu-5Ac2en** (K_i viral = 0.1 nm; K_i human = 100 nm) inhibits the replication of both

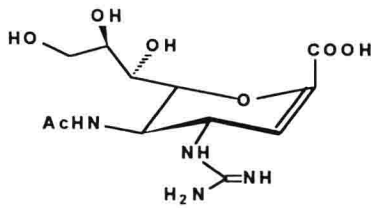

Fig. 2 Chemical structure of **4-Guanidino-NEU5AC2en**.

influenza A and B viruses in cell culture and is efficacious in animal models when administered intranasally [27-28]. A group of researchers headed by von Itzstein [29-31] developed this synthetic derivative currently being tested by Glaxo. Most importantly, the design of this compound is based on protein structure data from a complex of influenza sialidase with an inhibitor [32]. (See Chapter 2 by von Izstein and Kiefel). C-Glycoside analogues of sialic acid previously synthesized by two research groups [33-34] have been recently tested together with new analogs as potential influenza inhibitors [35]. The results are very encouraging for predicting the active site of the receptor as well as biologically active conformations capable of receptor binding. Another category of simple monosaccharides with potentially, multiple biological activities are the azasugars.

Azasugars (see Chapter 11 by van den Broek) belong to the polyhydroxypiperidine and polyhydroxypyrrolidine groups. This class of sugar analogues is represented by a well known family of

Fig.3 Chemical structures of Deoxyfuconojirimycin (left) and α-Homofuconojirimycin (right).

specific glucosidase inhibitors derived from nojirimycin and its reduced form, 1-deoxynoijrimycin, with potential as antidiabetic [36] and antitumor [37] agents. Because some derivatives have exhibited activity against the human immunodeficiency virus (HIV) [38-41], there has been a tremendous effort recently in the search for new azasugars and their analogues [42-51]. Among other azasugars, piperidine analogs with the same secondary hydroxyl groups absolute configuration as fucose are very powerful inhibitors of most fucosidases [52].

Deoxyfuconojirimycin [53-54] and **α -Homofuconojirimycin** [55] both have K_i of 10^{-8} mol dm^3 or less against a number of fucosidases and are the most potent fucosidase inhibitors yet reported. The research group from Organon Int. [56] reported an extensive review of the chemistry of azasugars and their biological activities as potential inhibitors of N-glycoprotein processing glycosidases and HIV-I infections.

The interest in this group of derivatives has been further illustrated in research reports from many active industrial laboratories [57].

Two of the representatives of this class are **Castanospermine** and **Swainsonine** which are drug candidates for treating cancer and viral infections [58-61]. The first one was isolated in 1981 from the seeds of the Australian tree *Castanospermum australe*, and inhibits a number of glycosidases. It was also isolated (1988) from the dried pods of *Alexa leiopetala*. The first synthesis of castanospermine [58] and determination of absolute configuration was reported by Bernotas and Ganem [62]. Castanospermine is also is a strong inhibitor of various intestinal glucosidases.

Fig. 4 Chemical structures of (-) Swainsonine (left) and (+) Castanospermine (right).

The hydroxyl group with the (S)-configuration on C-1 of castanospermine is essential for optimal glucosidase activity just as is the hydroxyl group on C-6 of deoxynojirimycin. The inhibitory effects of various castanospermine derivatives on glucosidases, fucosidases, and mannosidases have demonstrated that alterations of configuration in the piperidine ring as well as removal of the hydroxyl groups lead to significantly weaker α-, and β-glycosidase inhibition. Because of its toxicity, which is probably due to nonspecific inhibition of various glucosidases, castanospermine is unsuitable for therapeutic use in diabetes.

The second representative of bicyclic pyrrolidine derivatives is swainsonine, a powerful inhibitor of α-D-mannosidases which are involved in the biosynthesis of glycoproteins [63]. It may be utilized in cancer chemotheraphy [64-65]. Surprisingly, glucosidases are not inhibited by swainsonine. It also was shown that swainsonine effectively inhibits human B cell development .

Recently, new sulfated polysaccharides from the lentinan and curdlan groups were reported to have high anti-HIV activity and low anticoagulant activity [66]. Similarly, ribofuranan and dextran sulfates also had high anti-HIV activity, however, with simultaneously high anticoagulant activity. It was assumed that this particular effect may be attributed to the flexible backbone containing oxymethylene groups between the glucopyranose rings. It now seems unlikely that sulfated polysaccharides with potent anticoagulant side effects will not be used as future anti-AIDS drugs. New prototypes of semisynthetic oligosaccharides as glycoconjugate vaccines [67] offer

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