Chirality in Drug Research

Edited by
Eric Francotte and Wolfgang Lindner

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Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data:
A catalogue record for this book is available from the British Library

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available in the Internet at <http://dnb.ddb.de>

Cover Design SCHULZ Grafik Design, Fußgönheim
Composition ProSatz Unger, Weinheim
Printing betz-druck GmbH, Darmstadt
Bookbinding Litges & Dopf Buchbinderei GmbH, Heppenheim

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN-13: 978-3-527-31076-0
ISBN-10: 3-527-31076-2

Contents

Preface

It are the 21 stereocenters in the gycopeptide antibiotics that give always raise to a headache for my students and it takes them some time to appreciate the incredible precision of complementarity in binding of these drugs to their bacterial targets.

The fascinating world of chirality in drug research, where microorganisms have been the masters for a long time, is brought to us in this new volume in the series, edited by Eric Francotte and Wolfgang Linder. There are three major parts to reflect the chiral research and technology of today. The first one is dealing with synthesis, the second with separation and the third one with analysis and modeling.

Here we learn how man created a methodology to get access to a chiral universe, so far property of nature. Research started by copying biological mechanisms or simply make use of natural sources. For instance microorganisms have been, and are still used to produce the desired structures. Today, highly sophisticated concepts of chiral catalysis, rather a pleonasm, are able to introduce almost all desired chirality at all locations in a synthetic molecule. Proof of the concept are numerous multi-step syntheses of complex natural compounds from a immensely broad variety of sources.

Even more impressive is the development of appropriate analytics. Modern NMR technology reveals such perfect complementarity as in the case of glycopeptides at levels of atomic resolution, providing virtual threedimensional models of ligand protein interaction. Bacterial resistance and means to cope with it, can be discussed by studying models of chiral interaction in the computer.

We have not always been in such a lucky position. Chirality and drugs are still related to each other by the tragedy of the sedative drug thalidomide, the "wrong" enantiomer being the cause for thousands of children being born disabled. But it lasted until recently that research showed that it would have been useless to separate the "wrong" enantiomer since the "good" one is immediately metabolized to the "bad" one in our body. The tragedy led to profound and sustainable change in the ways of thinking about individuality of molecules raising the concept of enantiomers being two different chemical entities at least with respect to drugs.

The historical perspective by Joseph Gal is therefore a perfect introductory chapter for the book.

We would like to express our gratitude to Renate Doetzer and Frank Weinreich from Wiley-VCH for their invaluable support in this project.

Raimund Mannhold, Düsseldorf
Hugo Kubinyi, Weisenheim am Sand
Gerd Folkers, Zürich

A Personal Foreword

Although the origin of chirality in life is still obscure, it is the source of diverse phenomena on the macromolecular and molecular level, governing our environment and the existence of living organisms. The principle of molecular chirality was established over a century ago by van't Hoff and LeBel, but awareness of how this characteristic affects the biological activity of molecules, is much more recent. Likewise, systematic investigation of the biological activity, including pharmacology and toxicology of individual stereoisomers, only recently became commonplace for all new chiral drugs. Due to increased interest in the consequences of chirality on physical and biological properties of molecules, the preparation of pure stereoisomers has become a topic of great importance, and methods of supplying optically pure isomers are being intensively pursued. In this context, there has been a rapid development of stereoselective synthetic methodologies, which have now reached a high degree of diversity and complexity. Developed synthetic approaches include those utilizing chiral building blocks or chiral auxiliaries, highly efficient catalytic processes, stereoselective enzymatic reactions and separation techniques. These different approaches are reviewed in dedicated chapters. Concomitantly, this trend created a rapid increase in the demand for stereoselective analysis techniques, capable of determining precisely the stereoisomeric composition of chiral compounds from synthesis, from biological assays and from pharmacological, metabolic and clinical studies. Among the different methodologies developed for this purpose, gas and liquid chromatographic separation on chiral stationary phases has attracted the attention of numerous research groups and is currently considered the method of choice for analyzing chiral compounds. Other techniques, such as capillary electrophoresis or sensors, have also been found to be useful for specific applications. The state-of-the-art for most of these analytical techniques is described in this book. Physical and chiroptical methods have also been intensively used for investigating and characterizing chiral drugs and are discussed as well. This book is meant to serve as a reference for scientists interested in the chirality-related aspects of chemistry and analysis.

Basle and Vienna
June 2006

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Introduction

1
Chiral Drugs from a Historical Point of View

Joseph Gal

1.1
Introduction

Chiral molecules are constituents of a large proportion of therapeutic agents. In 1984 Simonyi surveyed a Swedish manual of drugs in clinical use and found that of a total of 666 drugs 355 (53%) had at least one chiral center; 181 drugs (27% of the total) were in use in single-enantiomer form while 174 (26%) were racemic [1]. In1987 Ariens and Wuis estimated that ca. 57% of marketed drugs are chiral (that is, are based on chiral molecules, be they racemic, single-enantiomeric, or some other mixture of chiral stereoisomers) [2]. They also showed that ca. 55% of the chiral drugs were used clinically in the racemic form and the remainder as single-enantiomers. Overall it appears, therefore, that by the end of the century ca. half of the chiral drugs were single-enantiomeric and the other half racemic.

The situation is different today. With rare exceptions new chiral drugs are developed in single-enantiomer form, and new racemic drugs are highly unlikely to appear. This is a profound change in drug development from a stereochemical viewpoint. How did we get here? What are the factors that have influenced the introduction and use of therapeutic agents based on chiral molecules? What is the history of chiral drugs?

1.2
A Word About Words

Before we attempt to answer the above questions, we need to examine briefly the terminology relevant to a discussion of chiral drugs. Specifically, the definition and usage of two important terms need to be clarified. *Chiral* was defined in one recent leading monograph on stereochemistry as follows: "Not superposable ... with its mirror image, as applied to molecules, conformations, as well as macroscopic objects, such as crystals" [3]. Mislow gave a shorter but essentially equivalent definition: "An object is chiral if and only if it is not superposable on its mir-

ror image; otherwise it is achiral" [4]. Thus, it is clear that *chiral* refers to a spatial property of objects, including molecules. Therefore, the term describes that nature of a molecule which makes it *non-superposable* on its mirror image, and *does not refer to the stereochemical composition of bulk material, i.e., drugs, compounds, substances, etc.* [5]. Thus, "chiral drug" does not tell us whether the drug is racemic, single-enantiomeric, or some other mixture of the stereoisomers. In the present article, therefore, *chiral* will be used strictly according to the definitions cited above, i.e., to refer to the chirality of individual molecules or other chiral *objects*. Thus, "chiral drug", "chiral substance", etc., will be used to indicate that the drug in question is composed of chiral molecules, but the enantiomer composition is not specified by this terminology.

There is however a great and obvious need for a convenient term to refer to chiral substances that are composed of only one of the two enantiomers. Numerous terms for this purpose have been introduced over many years, but the issue remains complex and largely unresolved. The present author recently discussed this issue in detail and introduced a new term for the purpose: *unichiral* [5]. In the present chapter *unichiral* will be used to specify the stereochemical composition of a chiral drug, substance, compound, sample, etc, as stereochemically homogeneous, i.e., consisting of a single-enantiomer (in the context where the term is used and within the limits of measurement) [5].

1.3 Old Chiral Drugs: Natural Remedies 3000BC–1900

For thousands of years, remedies from nature obtained from vegetable, animal, or mineral sources were relied upon for relief from human diseases. Such folk medicine was, by its very nature, inaccurate and unscientific and often had no rational basis. Moreover, the toxicity of many of the products was a serious problem; indeed, some of the pharmacologically active preparations were used as poisons. The advent of the printing press in the 15th century resulted in the wide dissemination of knowledge about natural medications and this in turn produced a considerable increase in the use, and misuse, of such remedies [6]. More rational therapy with purified natural products did not begin until the 1800s.

Despite the problems, however, some of the natural preparations were effective in relieving the symptoms and at times even eliminating the disease. In fact, we know today that the number of pharmacologically active substances produced by nature is large and the spectrum of biological activities of natural products is extraordinarily broad; for example, antimicrobial, antineoplastic, CNS-active, anti-inflammatory, cardiovascular, etc., are only a few of the therapeutic classes of drugs from nature [7].

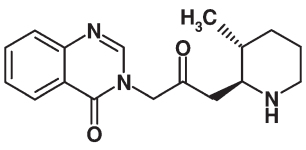
Chirality is a hallmark of many molecules from nature. Indeed, the number of chiral natural molecules is very large and the structural variety they represent is vast. Among such substances – be they small molecules or macromolecules – an overwhelming majority occur in unichiral form. For example, chiral α-amino acids

and the peptides and proteins containing them, sugars and their polysaccharides, steroids, antibiotics, and many other compounds from nature are unichiral. Another important aspect of many chiral molecules from nature is their *homochirality*. This means that related chiral molecules in the same chemical class usually have the same sense of chirality. For example, with rare exceptions α-amino acids occurring in nature consistently have the L configuration; similarly, monosaccharides are of the D configuration. Thus, both *unichirality* and *homochirality* are typical for compounds from nature: most of them occur in enantiomerically homogeneous form, and closely related molecules usually have the same sense of chirality.

In the light of the above, then, it is not surprising that many of the compounds used as therapeutic agents in natural remedies over the centuries and millennia have been chiral and that the vast majority of such substances occur in unichiral form. For thousands of years and until the beginning of the 19th century most such natural remedies were used as crude plant extracts rather than purified active principles. Obviously, in that "pre-scientific" era, the remedies were used without any clue as to the nature or identity of the active ingredient(s) within, let alone any understanding of the chirality of the molecules involved. Recognition of the existence of chiral drugs had to await a better understanding of chemical structure, i.e., the advent of modern organic chemistry and the discovery of molecular chirality (see below).

The number of pharmacologically active agents now known to be present in various old remedies is large [7] and many of these compounds are based on chiral molecules. Information about some of the earliest herbal remedies that contain chiral active ingredients goes back nearly 5000 years. A few examples of old therapies with chiral active ingredients are presented below.

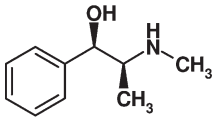
In a book about herbs, the Chinese scholar-emperor Shen Nung described in 2735 BC the beneficial effects of *Ch'ang Shan* in the treatment of "fevers" [8]. This preparation is the powdered root of a plant, *Dichroa febrifuga* Lour. Modern medicinal chemistry has identified several alkaloids with *antimalarial* properties in the plant, and it is therefore clear that the ancient use of Ch'ang Shan in fevers was not entirely without basis. One of the antimalarial compounds from Ch'ang Shan is *februgine* (*β*-dichroine), a relatively simple unichiral compound **1**. Modern attempts to develop these agents as antimalarial drugs failed, due to significant toxicity [8].



1

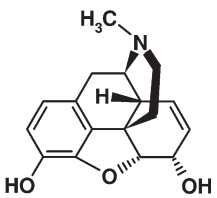
Shen Nung also observed the stimulant properties of another Chinese plant, Ma Huang, now known as *Ephedra sinica* [9]. The chief active ingredient, *ephedrine*, is a sympathomimetic amine, and therefore it is clear in this case also that the use of Ma Huang as a stimulant had a rational basis. The ephedrine molecule is simple and contains two chiral centers; the compound from *ephedra* is unichiral and has the 1*R*,2*S* configuration **2**. Ephedrine was first isolated from Ma Huang in 1887

[10], i.e., more than 4600 years after the effects of the compound were recorded. Ephedrine was introduced into medical practice during the 1920s [11] and for decades was widely used – as a CNS stimulant in narcolepsy, as a bronchodilator, in the treatment of Adams-Stokes syndrome with complete heart block, as a stimulant in some forms of depression, and in some other disorders – but more recently it has been largely replaced in most of these indications by other treatment modalities [12]. Ephedrine has also been widely available in "dietary supplements" for weight loss, increased energy, body building, etc. However, in the early 1990s concern arose over potentially serious adverse effects from such use of ephedrine, including cardiovascular, nervous-system, and other toxic effects, and in April 2004 the U.S. Food and Drug Administration (FDA) banned the sale in the United States of dietary supplements containing ephedrine or closely related compounds [13].



2

Another millennia-old unichiral drug is the opioid agent morphine. *Opioid* refers broadly to all compounds related to opium (a more recent definition states that the term *opioid* includes any compound that interacts with the brain's opioid receptors) [14]. Opium powder is the dried juice from the unripe seed capsule of the poppy *Papaver somniferum* and its name is derived from the diminutive of the Greek word *opos*, i.e. juice. Opium has analgesic, euphoric, and other effects and contains many alkaloids, including morphine **3** and codeine **4**. Poppy juice is mentioned in the writings of the Greek philosopher and naturalist Theophrastus (ca. 371–287 BC), but evidence has been found suggesting that opium may have been known much earlier, to ancient civilizations in Egypt and Mesopotamia (Fig. 1.1) [14, 15]. Within the Arab–Islamic civilization, whose rise began in the 7th century, opium came to be used mainly as a constipant to control dysentery [16]. The arrival of the Islamic armies and their influence in Europe in the 16th century (Constantinople fell to the Ottoman Turks in 1453 and the first siege of Vienna by the Ottoman army took place in 1529) brought opium to Europe. Laudanum, a somewhat purified opium concentrate, was compounded by Paracelsus (Theophrastus Bombastus von Hohenheim, 1493–1541), a Swiss alchemist and physician, and the smoking of opium became openly popular during the 1700s; however, opium may have been extensively but less openly used in Europe in earlier times [17].



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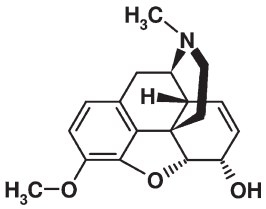


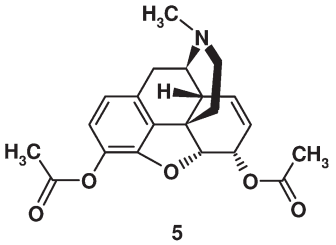
4

Fig. 1.1 Frieze from the palace of Assyrian king Sargon II, in Khorsabad (in modern-day Iraq), depicting two priests. Note the poppy heads carried by the priest on the right. 8th century BC. Musée du Louvre, Paris, Antiquités orientales. Photograph: Service de documentation photographique de la Réunion des Musées Nationaux, Château de Versailles. (Reprinted from Lydia Mez-Mangold, *A History of Drugs*, F. Hoffmann-La Roche & Co., Ltd, Basle, Switzerland, 1971, with permission).

Morphine, the most important alkaloid in opium, was obtained as a purified powder from opium in 1805 by Friedrich Wilhelm Sertürner (1783–1841), a German pharmacist's assistant [18]. He named it *morphium* after Morpheus, the Latin god of dreams, so named by Ovid using a Greek word. Later, the great French chemist and physicist Joseph-Louis Gay-Lussac (1778–1850), who was a strong supporter of Sertürner in his priority claim for the isolation of the substance over French pretenders, renamed the drug *morphine*, against the wishes of Sertürner [19]. The morphine molecule is a pentacyclic tertiary amine with five chiral centers **3** and the natural product is the levorotatory enantiomer.

The invention of the hypodermic needle and syringe in the middle of the 19th century resulted in the widespread use of morphine, and addiction became a common problem. An early – and false – hope to circumvent the addiction liability of morphine was provided by a most unlikely candidate: heroin. This compound, the diacetyl derivative of morphine **5**, is a potent opiate narcotic first synthesized in 1874 via acetylation of morphine, and was introduced into medical practice in 1898 as a cough suppressant [10]. Heroin is a *semisynthetic* drug, i. e., a chemically modified derivative of a natural product, and retains the stereochemistry of mor-

phine. Heroin may have been the first synthetic unichiral drug introduced in clinical medicine.



5

Heroin was actively marketed to physicians by its manufacturer, as an advertisement from ca. 1900 shows (Fig. 1.2). The drug was touted as a "non-addicting" morphine analog that could safely replace morphine and thereby eliminate the latter's addiction problem [20]. This claim turned out to be tragically mistaken and today heroin is the most important abused opioid, with grave social, economic, and medical consequences. Another chiral drug, methadone, a totally synthetic opiate agonist, has been recruited to fight heroin addiction. Methadone was first synthesized, in the racemic form, in the 1940s and was later shown to have stereoselective opioid agonist properties, concentrated nearly exclusively in the (*R*)-(-) enantiomer **6** [21]. Methadone is used in the racemic form in the U.S. as an analgesic and in the treatment of opiate addiction, but in some other countries the pharmaceutical product is the unichiral *levo* form [22].

Perhaps the most fascinating old chiral drug, from a historical point of view, is quinine. Its earliest history is obscure, but it is known that by the early 1600s it was being used by South American natives in Peru, Ecuador, and neighboring regions

Fig. 1.2 Drug advertisement ca. 1900. (Reprinted from Roy Porter (Ed.), *Cambridge Illustrated History of Medicine*, Cambridge University Press, Cambridge, 1996, with permission).