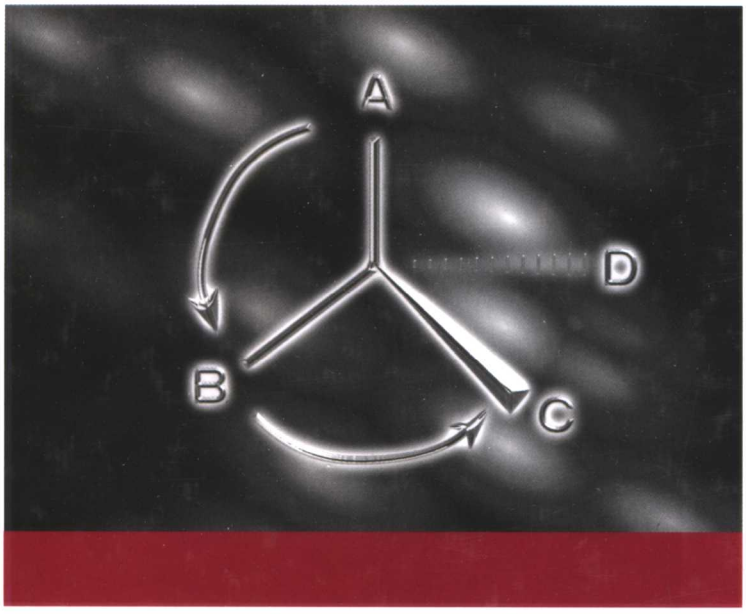
Edited by
Cynthia A. Challener

Chiral Drugs

手性药物手册



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PREFACE

Chiral molecules are ubiquitous in nature and have ever-increasing importance in the pharmaceutical industry. Actions taken by regulatory bodies throughout the world have resulted in drug companies focusing efforts on the development of single enantiomer products. In recent years, several valuable texts have been published that cover in detail the various sources and methods of preparation for obtaining optically active materials.

There has been a need, however, for a guide for workers in the pharmaceutical industry seeking information on commercially available chiral drugs and the processes for synthesizing them. The goal of this book is to present the chemical professional with a comprehensive listing of available chiral drugs including specific data of interest for each entry in the listing. This book is intended to complement the companion volume, *Chiral Intermediates*.

Part I of the book, divided into four chapters, provides an introduction to topics relevant to the field of chiral chemistry and includes a brief overview of chirality, a short discussion on the current market drivers in the area of chiral chemistry, and a basic presentation of the various sources and methods for obtaining chiral compounds.

This book will provide an introduction to the types of sources and methods currently in use for obtaining chiral molecules and will prove to be an invaluable resource for information on available chiral drugs. The reader is encouraged to investigate other sources for more detailed information on the technology and processes utilized for identifying, isolating, and preparing chiral pharmaceuticals and their corresponding intermediates.

FURTHER READING

Ager, D.J., (Ed.), *Handbook of Chiral Chemicals*, Marcel Dekker, Inc., New York, 1999.

Collins, A.N., Sheldrake, G.N., and Crosby, J., (Eds.), *Chirality in Industry*, John Wiley & Sons, New York, 1992.

Collins, A.N., Sheldrake, G.N., and Crosby, J., (Eds.), *Chirality in Industry II*, John Wiley & Sons, New York, 1997.

Sheldon, R.A., *Chirotechnology*, Marcel Dekker, Inc., New York, 1993.

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HOW TO USE THIS BOOK

Chiral Drugs is divided into four parts. A brief description of each part is given below.

PART I

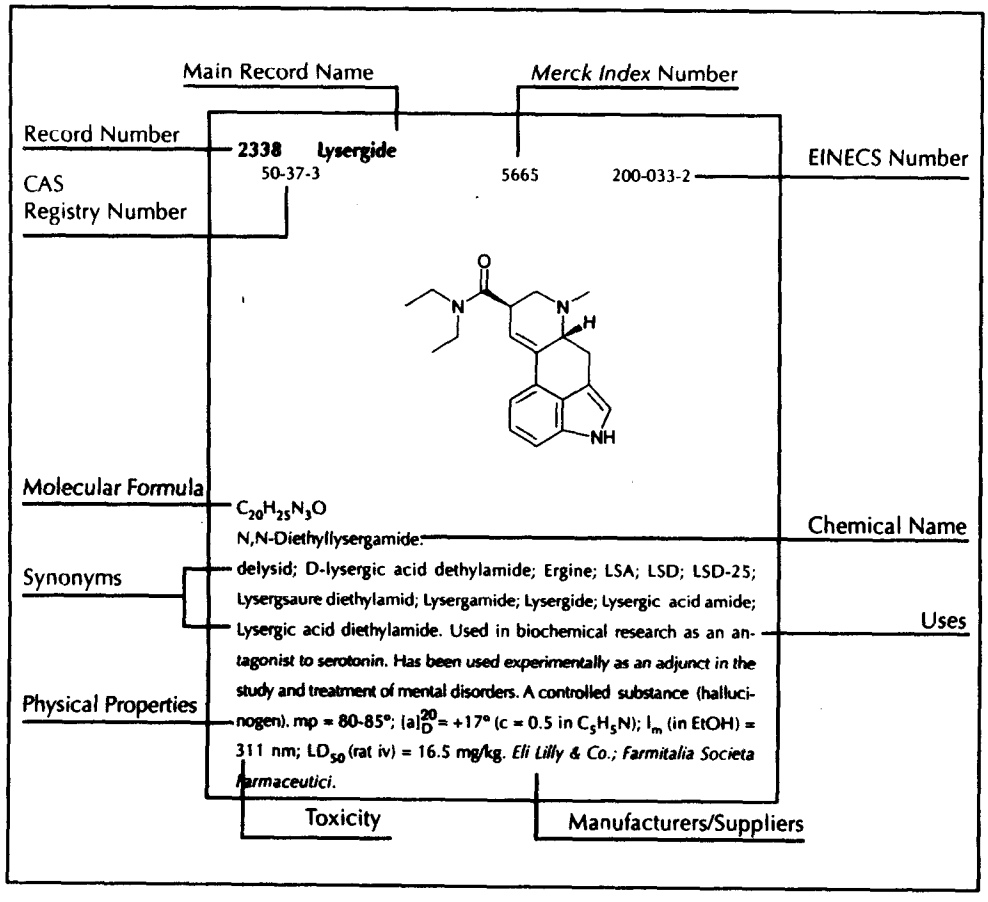
The four chapters in this part, entitled Chirality, provide an introduction to chiral chemistry. Chapter One, Overview of Chirality, introduces the reader to the definition of chirality, the importance of optical isomerism in chemistry and life science, issues involved in controlling chirality in synthesis, and methods for identifying the optical purity of a sample. Chapter Two, Drivers for the Chiral Market, describes key market issues, regulatory considerations, and recent technological developments in the field. Chapter Three, Sources of Chiral Compounds, discusses where the researcher can obtain chiral starting materials and derivatives as well as how to resolve racemic mixtures. Chapter Four, Methodologies for Obtaining Chiral Compounds, reviews methods for isolating optically active compounds as well as synthetic strategies.

PART II

The main entries in this part are classified according to therapeutic class. Each category lists the chemical name of the chiral drug in alphabetical order along with synonyms and other important data. Each record is identical in structure, enabling the reader to select specific information efficiently. A unique record number has been assigned to every record. The three indexes in Part III allow quick cross-referencing according to the record number in Part II by CAS Number, EINECS number, or synonym. The Manufacturer and Supplier Directory in Part IV provides convenient access to information on where and how to obtain the chiral compound of interest.

Record Structure

A typical record from the entries section of this book is shown below. The first line contains, in bold face, the record number (2338) and the name of the material (Lysergide). The second line gives the Chemical Abstracts Service (CAS) Registry Number for the compound (50-37-3), the corresponding *Merck Index* number, twelfth edition, (5665) and the European Inventory of Existing Commercial Chemical Substances (EINECS) number (200-033-2). These numbers always appear in the same position (left, center or right) enabling the reader to determine which source they belong to. Whenever CAS Registry Numbers are used in the text, they are always enclosed in brackets, for example [50-37-3]. The molecular formula and structure of the compound are provided. A list of synonyms follows, including proprietary names and other trivial names.



A description of the material and its known therapeutic uses then follows. Whenever possible, physical properties are presented. These include melting point, boiling point, and optical rotation, as well as density or specific gravity, uv absorption, solubility and acute toxicity, usually limited to oral dosage in rodents. Finally, the companies who supply the product are given.

PART III

This part contains three indexes. The purpose of each is described below:

- CAS Registry Number Index
  This index enables the reader to locate the record number and thereby find the main entry for a chiral drug based on its CAS Registry Number.

- EINECS Number Index
  This index enables the reader to locate the record number and thereby find the main entry for a chiral drug based on its EINECS number.

- Name and Synonym Index
  This is the master index containing all chemical and proprietary names found in Part II. It is the most convenient place for the reader to start if a name or synonym for a chiral molecule is known. This index enables the reader to locate the record number in Part II which relates to the main entry for that drug.

PART IV

This part contains a listing of companies that provide contract manufacturing services or products that support the production of chiral compounds. Each listing includes the company name, address and contact information. In most cases, a brief description of the products and services is provided as well. Arranged alphabetically by company name, this directory provides information to help the reader to contact the organization directly.

GLOSSARY OF UNITS

Name	Description
Mass	Unless otherwise specified, mass is expressed in a multiple of grams (g), such as micrograms (μg; 10^{-6} g), milligrams (mg; 10^{-3} g), grams (g; 10^{0} g), kilograms (kg; 10^{+3} g), etc.
Volume	Volume is expressed in liters (l) or milliliters (ml) unless otherwise specified.
Temperature	When no units are cited, the temperature given is in degrees Celsius (°C).
Melting point	Melting points are cited in degrees Celsius (°C) unless otherwise specified.
Boiling point	When measured at atmospheric pressure, boiling points are cited with no pressure, e.g. bp = 167°. At other pressures, the pressure is also cited, e.g. $bp_{0.01}$ = 167°.
Density	The measurement temperature is given as a superscript; thus a density of 1.123 measured at 25° will appear as $d^{25} = 1.123$. If the measurement was explicitly referenced to the density of water at 4°, the citation will carry both a superscript and a subscript, as in $d^{25}_{4} = 1.123$. Specific gravities are denoted by the abbreviation 'sg'.

Optical rotation — Denoted by the letter n, refractive indexes are usually determined at a temperature which is cited as a superscript, as in $n^{25} = 1.5432$. The wavelength of the light used in the measurement is cited as a subscript, as in $n_{546}^{25} = 1.5432$. Most commonly, the sodium D line (wavelength 549 nm) is used and in such cases, the subscript is a D, as in $n_D^{25} = 1.5432$.

Refractive index — As with refractive indexes, optical rotations (α) are cited with the measurement temperature superscripted, and the measurement wavelength (often the sodium D line) subscripted, as in $[\alpha]_D^{25} = 105°$. When mutarotation can occur, the rotation given is an equilibrium value, measured after some time interval, which is cited, as in $[\alpha]_D^{25} = 105°$(14 hr).

UV absorption — The ultraviolet absorption maxima given by the material are cited in nanometers (nm = 10^{-9} m) and the absorptivity (E, A, ε or log ε, all of which are unitless) may also be given.

Acute toxicity — Wherever possible the units of toxicity are LD_{50}, i.e. the dose which is lethal to 50% of the test animals. In most cases, acute toxicity is measured with the rat, orally administered, and the result is reported as LD_{50} (rat orl) = 50 mg/kg. Other species (for example, mus = mouse; rbt = rabbit; pgn = pigeon; gpg = guinea pig; m = male; f = female) are occasionally cited as are other administration routes (sc = subcutaneous; ihl = inhalation; ip = intraperitoneal; iv = intravenous). Chronic toxicity data are not given.

ABBREVIATIONS AND SYMBOLS

abs config	absolute configuration
abs	absolute
Ac –	acetyl (CH_3CO –)
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotrophic hormone
AIDS	acquired immunodeficiency syndrome
alc	alcohol, alcoholic
amp.(s)	ampule(s)
AMP	adenosine 5'-monophosphate
aq	aqueous
atm	atmosphere, atmospheric
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene ($C_{44}H_{16}P_2$)
BIPHEN	1,2-bis(diphenylphosphino)ethane ($C_{26}H_{28}P_2$)
Bn-	benzyl (C_7H_7 –)
BOC	tert-butoxycarbonyl ($C_5H_9O_2$ –)
bp	boiling point
BPH	benign prostatic hypertrophy
Bu –	butyl (C_2H_5 –)
Bz –	benzoyl (C_6H_5CO –)
c	concentration (g/100 ml), in rotations
C	Celsius (temperature scale)
cAMP	cyclic AMP
CBZ	carbobenzyloxy ($C_8H_7O_2$-)
CH_3CN	acetonitrile
C_5H_5N	pyridine

C_6H_6	benzene
C_7H_8	toluene
cc	cubic centimeters (milliters)
CCK	cholecystokinin
CCL	*Candida* cylindrical lipase
CCl_4	carbon tetrachloride
CCK	cholecystokinin
CH_2Cl_2	methylene chloride
$CHCl_3$	chloroform
cm	centimeter
CNS	central nervous system
CoA	coenzyme A
COD	cyclooctadiene
COMT	catechol-O-methyltransferase
CPMA	chiral mobile phase additive
CPMP	Commission on Proprietary Medicinal Products
CSP	chiral stationary phase
d	dextro(rotatory)
d	density
dec	decompose, decomposition
DIPAMP	1,2-bis(methylanisylphenylphsophino)ethane ($C_{28}H_{28}O_2P_2$)
DIPT	diisopropyltartrate
dl-	racemic
DL-	racemic
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DOPA	dihydroxyphenylalanine
(E)-	(entgegen) opposite
EC	Enzyme Commision
ee	enantiomeric equivalent
e.g.	for example
ED	effective dose
EDTA	ethylenediamine tetraacetic acid
EINECS Substances	European Inventory of Existing Commercial Chemical
endo-	stereochemical descriptor
Et-	ethyl (C_2H_5 –)
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
exo-	stereochemical descriptor
F	Fahrenheit (temperature scale)
FMOC	fluoromethoxycarbonyl ($C_2F_3O_2$-)

g	gram(s)
g/l	grams/liter
gal	gallon(s)
GI	gastrointestinal
GLC	gas liquid chromatography
gpg	guinea pig
H_2O	water
H_2SO_4	sulfuric acid
HCl	hydrochloric acid
HIV	human immunodeficiency virus
HKR	hydrolytic kinetic resolution
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
hmtr	hamster
hr	hour
HT	hydroxytryptamine (serotonin)
ihl	inhalation
inj.	injection
im	intramuscular
ip	intraperitoneal
iPr –	isopropyl ($(CH_3)_2CH$ –)
IR	infrared
iv	intravenous
kcal	kilocalories
l	liter, levo(rotatory)
λ (lambda)	wavelength
LC	lethal concentration
LC_{50}	median lethal concentration
LD	lethal dose
LD_{50}	median lethal dose
log	common logarithm
LSR	lanthnide shift reagent
MAO	monoamine oxidase
max	maximum, maxima
Me –	methyl (CH_3 –)
Me_2CO	acetone
MeOH	methanol
MEUF	micellar enhanced ultrafiltration
mg	milligram
min	minimum, minima, minute
MLD	minimum lethal dose
mp	melting point
µg	microgram
mµ	millimicron (nanometer)
Ms-	mesyl (CH_3O_2S-)
mus	mouse

N	normal, normality
NBD	norbornadiene
nm	nanometer (10^{-9} m)
NMO	N-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
NSAID	non-steroidal anti-inflammatory drug
NSC	National Service Center (of the National Cancer Institute)
NTP	normal temperature, pressure
o-	ortho
OD	optical density
orl	oral
p-	para
pgn	pigeon
Ph-	phenyl (C_6H_5-)
pH	acid-base scale (log of reciprocal hydrogen ion concentration)
pK	log of the reciprocal of the dissociation constant
PLE	pig liver esterase
PMA	Pharmaceutical Manufacturing Association
pOH	acid-base scale (log of reciprocal hydroxyl ion concentration)
ppb	parts-per-billion
PPL	porcine pancreatic lipase
ppm	parts-per-million
Pr-	propyl (C_3H_7 –)
(R)	rectus (stereochemical descriptor)
rbt	rabbit
Rh2(MEOX)4	Doyle dirhodium catalyst
RNA	ribonucleic acid
(S)	sinister (stereochemical descriptor)
S-	symmetical
sc	subcutaneous
sec	second
sec-	secondary
SG, sg	specific gravity
SOM	site directed mutagenesis
spp.	species (plural)
STP	standard temperature, pressure
tabl.	tablet
TBHP	tert-butyl hydroperoxide
temp	temperature
tert-	tertiary
THF	tetrahydrofuran
THP	tetrahydopyranyl (C_5H_7O-)
Ts-	tosyl ($C_7H_7O_2S$-)
TSCA	Toxic Substances Control Act

UK	United Kingdom
USA	United States of America
USAN	United States Adopted Names
USP	United States Pharmacopeia
UV	ultraviolet
v/v	volume in volume
VIS	visible
viz	namely
w/w	weight in weight
w/v	weight in volume
wt	weight
(Z)-	(zusammen) on the same side
>	greater than
<	less than
~	approximately
Å	Angstrom units (10^{-8} cm)

CONTENTS