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Signposts to Chiral Drugs

Organic Synthesis in Action

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Preface

Describing the intrinsic attraction of basic research in organic synthesis, Elias J. Corey, Nobel Laureate in 1990, wrote in 1988: “The appeal of a problem in synthesis and its attractiveness can be expected to reach a level out of all proportion to practical considerations, whenever it presents a clear challenge to the creativity, originality and imagination of the expert in synthesis” [1].

A few years earlier, Vladimir Prelog, Nobel Laureate in 1975, had expressed a similar opinion in his typical laconic way: “Any problem of organic chemistry is a scientific challenge if observed by scientific eyes” (According to notes made by V. Šunjić after a conversation at the Burgenstock Conference on Stereochemistry, 1972). Creativity and scientific challenge in synthetic organic chemistry, in particular, because of its frequent broad application, are repeatedly recognized by many others, organic and other chemists and even scientists from the other disciplines.

During 25 years of teaching an undergraduate course on “Synthetic Methods in Organic Chemistry” and a graduate (Ph.D.) course on “Stereoselective (previously asymmetric) Synthesis and Catalysis in Organic Chemistry”, at the Faculty of Natural Sciences and Mathematics, University of Zagreb, one of us (VŠ) encountered an interesting phenomenon. The undergraduate course, mostly based on retrosynthetic analysis using the problem-solving approach introduced by Warren [2, 3] and elaborated by others [4–7], differed in its pragmatic approach from the graduate course, which was based on the discussion of exciting chemistry in original papers and monographies [8–14]. There was a notably different response of the students during these two courses. While the undergraduates participated intensively in discussions of possible retrosynthetic paths and proposed new syntheses, the graduates, in spite of the inclusion of up-to-date, exciting examples of non-catalytic, catalytic and biocatalytic stereoselective transformations, were less inclined to interact. Obviously, the future “experts in synthesis” (Corey) greatly preferred lectures in which target structures were well defined, and the complex synthetic problem was clearly defined. This is the basic premise of the current monograph.

The concept of this book was born out of our joint experience in teaching and research in academic institutions on the one hand, and our combined, more than 40 years participation in research projects in small and large pharmaceutical companies on the other. The volume collects together exciting achievements in synthetic organic chemistry, as they appeared during the development of target molecules, mostly chiral, enantiopure drugs. Fifteen target structures are selected to demonstrate these synthetic achievements, some of them are established drugs, the others are candidates for drugs under clinical research, one a natural product with broad application and one a library of lead molecules. In the introduction, we describe the various stages of research towards a new drug entity (NDE), as organized within the innovative pharmaceutical industry. The search for hits, improvement of biological properties from hits to leads and selection of clinical candidates are outlined, followed by the various phases of clinical research.

The sequence of chapters is roughly based on the (potential) clinical indications, but each chapter is complete in itself. The chapter abstracts are structured to enable the interested reader to easily identify the synthetic achievements and biological profile of the specific compound or structural class presented. These include mechanistic and stereochemical aspects of enantioselective transformations, new methodologies such as click chemistry, multi-component syntheses and green chemistry criteria, as well as brief information on the biological targets, mechanisms of action and biological and therapeutic profiles of target structures. Presentation of synthetic chemistry in each chapter is guided by the concept inherent in modern organic chemistry, that mechanistic organization ties together synthesis, reactivity and stereoelectronic structures of the key reagents or intermediates [15].

In the chemical schemes in this book, all specific, defined compounds or chemical entities are consecutively designated with Arabic numbers, while general formulae are listed with Roman numbers.

We are very grateful to the support and assistance provided by the publisher, Springer, particularly that from Dr. Hans-Detlef Klueber and Dr. Andrea Schlitzberger. Finally, we hope you, the reader, will find much to interest and inform you as you browse through the book, both initially and as a subsequent reference text.

Zagreb, Croatia — Vitomir Šunjić
February 2011 — Michael J. Parnham

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Contents

Abbreviations and Acronyms

A	
Aβ	Amyloid-beta-peptide
AChE	Acetylcholine esterase
ACL	Assisted chemical ligation
Ac_2O	Acetic anhydride
AD	Alzheimer's disease
ACE	Angiotensin-converting enzyme
ADME	Absorption–distribution–metabolism–excretion
agr	Accessory gene regulator
agrA (B,C,D)	Accessory gene regulator A (B,C,D)
AIDS	Acquired immunodeficiency syndrome
AIPs	Autoinducing peptides
Amberlyst 15	Sulphonic acid-based cationic ion exchange resin
4-AMS	Molecular sieves of 4Å
API	Active pharmaceutical ingredient
APP	Amyloid precursor protein
AT1	Angiotensin II type 1 receptor
AUC	Area under the curve
B	
BINA	2,2′-*bis* (Diphenylphosphino)-1,1′-binaphthyl
Bioisosters	Substituents or groups with similar physical or chemical properties that impart similar biological properties to a parent compound
Boc	Butoxycarbonyl
BOP-Cl	*bis*-(2-Oxo-3-oxazolidinyl)phosphonic chloride
C	
CBS-QB3	Complete basis set-quantum B3
CC	Clinical candidate
CD	Candidate drug

CL	Chemical ligation
Click chemistry	Reliable chemical transformations that generate collections of test compounds
CNS	Central nervous system
COD	1,5-Cyclooctadiene
Cp	Cyclopentadienyl
Cp_2TiH	Titanium(*bis*-cyclopentadienyl)hydride
CSA	Camphor sulphonic acid
CSP	Chiral stationary phase
CYP 3A4	Cytochrome P450
CYP/hERG	Cytochrome P450/human *ether-à-go go* related gene (potassium ion channel) drug–drug interaction screening assay

D

DEAD	Diethylazidodicarboxylate
DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene, strong crowded base
DCC	Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DHP	Dihydropyrane
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DHQ-PHN	Dihydroquinyl phenanthroline
DHQ-MeQ	Dihydroquinyl 4′-methyl-2′-quinolyl dihydroquinine
$(DHQ)_2$-PHAL	*bis*-Dihydroquinyl phthalazine
$(DHQD)_2$-PHAL	*bis*-Dihydroquinidyl phthalazine
DIA	Diethylamine
DIAD	Diisopropylazidocarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMSO	Dimethylsulphoxide
DMF	Dimethylformamide
DOS	Diversity-oriented synthesis
DPPA	Diphenylphosphorylazide
DPP-4	Dipetidyl peptidase 4
DTS	DNA-templated organic synthesis
DuPHOS	Chiral, bidentate phosphine ligand developed by DuPont company

E

EBTHI	Ethylene-*bis*(eta_5-tetrahydroindenyl)
EC_{50}	Effective concentration producing 50% of maximal response
EDG	Electron-donating group

e.e.	Enantiomeric excess
ESM	Electrospray mass spectrometry
EtOAc	Ethylacetate
EWG	Electron-withdrawing group

F

Fc	Ferrocene
FDA	Food and Drug Administration (USA)
FGI	Functional group interconversion
Fmoc	Fluorenylmethyloxycarbonyl
Fuc-T	alpha-1,3-Fucosyl transferase

G

GABA	Gamma-aminobutyric acid
GCR	Glucocorticoid receptor
GDP-fucose	Guanidine diphosphate-beta-L-fucose
GIP	Gastric inhibitory peptide
GLP1	Glucagon-like peptide 1
GMP	Guanosine monophosphate
GPCR	G-protein-coupled receptors
G3MP3	Gaussian method for very accurate calculation of energies

H

HAART	Highly active antiretroviral therapy
HBTU	*O*-Benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyl-uronium-hexafluorophosphate
HBP	Halogen-binding pocket
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HTS	High-throughput synthesis (or screen)
Hunig's base	*N*,*N*-diisopropylethylamine
5-HT	5-Hydroxytryptamine

I

IC_{50}	Concentration at which 50% inhibition of maximum response is achieved
Iosiphos	Ferrocene-based, chiral bidentate phosphine ligands
IPEA	Isopropylethyl amine
$(Ipc)_2BCl$	Chlorodiisopinocampheyl borane

L

LacNAC	*N*-acetyllactosamine
LBD	Ligand-binding domain
LC/MS	Liquid chromatography/mass spectrometry
LDA	Li-diisopropylamide

LDH	Layered double hydroxide
LDL	Low-density lipoprotein
LiHMDS	Lithium hexamethyldisilazane
Log P	Logarithm of the ratio of the concentrations of the un-ionized solute in two solvents
LPPS	Liquid phase protein synthesis
L-Selectride	Lithium tri-*sec*-butyl(hydrido)borate
LTC_4, LTD_4, LTE_4	Leukotrienes C_4, D_4, E_4

M

MAO	Monoamine oxidase
MCR	Multicomponent reaction
MDR	Multidrug resistance
Mesylate	Methanesulphonic ester moiety
MeQ	4′-Methyl-2′-quinolyl dihydroquinine
MsCl	Methanesulphonic acid chloride

N

N-Boc	*N*-Benzyloxycarbonyl
NBS	*N*-Bromosuccinimde
NCE	New chemical entity
NCL	Native chemical ligation
NDE	New drug entity
NLE	Non-linear effect
NME	New molecular entity
NMO	4-Methyl-morpholine-*N*-oxide
NMP	*N*-methylpyrrolidine
NNRTI	Non-nucleoside reverse transcriptase inhibitor

O

OPMB	*para*-Methoxybenzyl
OTBS	*O-tertiary*-Butyldimethylsilyl

P

PADA	Dipotassium diazidocarboxylate
PCy_3	Tricyclohexyl phosphine
PDC	Pyridinium chlorochromate
PEGA	Poly[acryloyl-*bis*(aminopropyl)polyethylene glycol]
Peptone	Various water-soluble protein derivatives obtained by partial hydrolysis of a protein by an acid or enzyme during digestion and used in culture media in bacteriology
PET	Positron emission tomography
P-gp	P-glycoprotein
PHAL	Phthalazine
Phen	1,10-Phenanthroline

PHN	Phenanthrenyl dihydroquinine
PK	Pharmacokinetics
PMB	*para*-Methoxybenzyl
PoC	Proof of concept
PPA	Polyphosphoric acid
PPARα	Peroxisome proliferator-activated receptor alpha
PPTS	Pyridinium *para*-toluenesulphonate
4-PPy	4-Phenylpyridine
PSA	Polar surface area
pTsOH	*para*-Toluenesulphonic acid

Q

QSAR	Quantitative structure–activity relationship

R

RAAS	Renin–angiotensin–aldosterone system
RaNi	Raney nickel catalyst
RCM	Ring closure metathesis
R&D	Research and development
REM	Regenerative Michael receptor
RT	Reverse transcriptase

S

SAR	Structure (biological) activity relationship
SCRAM	$[CpIrI_2]_2$ (Cp = cyclopentadienyl)
SERT	Plasma membrane serotonin transporter
SMB	Simulated moving bed chromatography
SPS	Solid phase synthesis
SPPS	Solid phase protein synthesis
SRS-A	Slow-reacting substance of anaphylaxis
SRS	Slow-reacting substance
SSRI	Selective serotonin uptake inhibitor

T

TACs	Tricyclic antidepressants
TBAB	*tetra-n*-Butylammonium bromide
TBAF	*tetra-n*-Butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyl-dimethylsilyl-chloride
TBSOTf	*tert*-Butyl-dimethylsilyl-trifluoracetate (triflate)
T2DM	Type 2 diabetes mellitus
TCEP	*tris*-(2-Carboxy)ethyl phosphine
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TFA	Trifluoracetic acid

TGS	Target-guided synthesis
THF	Tetrahydrofurane
THP	Tetrahydropyrane
TIS	Triisopropylsilane
TM	Target molecule
TM domain	Transmembrane domain
TMS	Trimethylsilyl group
TMSCl	Trimethylsilyl chloride
TMSI	Trimethylsilyl iodide
TON	Turnover number
Tosylate	Toluenesulphonic ester moiety
TPAP	Perruthenate complex
TriFer	Ferrocene-based C_2-symmetric diphosphine ligand
Triflate	Trifluoromethanesulphonic moiety
Triton B	Benzyl trimethyl ammonium hydroxide
TRPM8	Transient receptor potential cation channel subfamily M member 8
TsDPEN	(1*R*,2*R*)-N-(*p*-tolylsulphonyl)-1,2-diphenylethane
TsOH	Toluenesulphonic acid

Y

YMS	Culture medium supplemented with soybean peptones

Chapter 1
Organic Synthesis in Drug Discovery and Development

Abstract The discovery and development of a new drug entity (NDE) to become a marketable drug is a complex, costly and time-consuming process. It is subject to increasingly stringent regulations and high attrition, which squeeze the time available both for the development and sale of the final product within the remaining window of patent coverage.

Organic synthesis of NDEs is challenged by the creation of novel, biologically active, safe and suitably targeted molecules and the improvement of lead compounds, as well as by the need to scale up compound quantities for safety and clinical studies. Even though natural and biologically derived drug molecules are *en vogue*, small synthetic molecules are preferable for oral drug administration and organic synthesis is required to modify natural compounds.

Biologically orientated synthesis can generate compounds with multiple activities. The industrial use of genomics research to identify potential target proteins and of high throughput screening to test compounds, including synthesized libraries of DNA sequence-programmed small molecules, all increase the chance of identifying totally new NDEs.

Chirality of NDEs is crucial because of the three-dimensional nature of biological target molecules and 68% of the top 200 marketed drugs are optically pure. Consequently, the stereoselective approach to drug molecules will remain important for many years to come.

1.1 Introduction

The complexity of the process leading to the marketing of a new drug entity (NDE) and its introduction to therapy is well recognized. As a matter of fact, complexity has become synonymous with high risk and frequent failure, or attrition, in searching for an NDE. Currently, innovative pharmaceutical companies that are focused on the development of NDEs are facing huge financial and organizational problems. This is related to the decreasing likelihood of being able to introduce successfully a "blockbuster", or "$1 billion drug" to the world market. This situation is, in part, the consequence of the ever more stringent requirements of regulatory authorities in

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developed countries, primarily of the Food and Drug Administration (FDA) in the USA, concerning the required documentation for all phases of preclinical and clinical investigations of an NDE. In addition, the diseases for which new therapies are still needed are now generally complex chronic diseases, which are difficult to categorize and require long-term, safe drug treatment.

These factors also enhance the risk of investment in long-term NDE-orientated research and development (R&D) due to the prolonged period between the first patent application and the appearance of the drug on the market. Consequently, the number of new first-in-class drugs that have reached the market in the last decade has been steadily declining. As a result of new technological developments, interest and investment in biological (protein-based) drugs is increasing, partially because of their relative specificity and the expected higher price, which companies can set following their introduction to the market (see also Sect. 1.2). However, this approach too has its limitation as biologicals cannot usually be given orally and the pressure of reimbursement agencies is likely to reduce pricing in the future.

An NDE is expected to meet an unmet medical need or to improve therapy where existing drugs have proved ineffective due to lack of efficacy, development of resistance or tolerance, to unexpected toxic side-effects, or have shown incompatibility with other drugs. New pathological states or diseases are also being continuously revealed and require effective therapy.

In spite of all these incentives to the development and marketing of new drugs, the success rate is decreasing. Rapid progress in the sophistication of the technical and analytical methods used to monitor all NDE development steps has resulted in clearly safer drugs. But, at the same time, this has further contributed to the delay in the introduction of drugs to the world market. The span between the first patent claiming biological activity of the new chemical entity and its introduction to the market has been prolonged from less than 6–8 years in 1970–1990 to over 15 years today. Two economic drawbacks for innovative pharmaceutical companies have been the inevitable consequences: much higher investment is needed for the whole R&D process, and the periods available for exploration of the original drug under patent protection and for recovering this investment with drug sales are now much shorter.

In the next three sections, we briefly present some characteristics of the R&D process in the pharmaceutical industry and the specific approaches that are being taken to confront the scientific and organizational problems.

1.2 Synthetic Organic Chemistry in Pharmaceutical R&D

The discovery of a drug has always depended on creative thinking, good science and serendipity. Due to the ever more stringent criteria that need to be satisfied for the introduction of an NDE to the market, drug discovery has always had a high attrition rate. A key goal is therefore to reduce this attrition rate by transforming drug discovery into a high-throughput, rational process. This is possible at some

specific early stages during drug discovery, particularly with biological assays that identify numerous hit compounds and when the data accumulated support progress towards synthesis of a limited number of lead compounds.

To provide background information for the role of synthetic chemistry, some aspects of the R&D process in innovative pharmaceutical companies deserve comment. The complexity of the usual multidisciplinary research process in developing an NDE is presented schematically in Fig. 1.1.

The *organizational and value chain in pharmaceutical R&D* requires that a wide range of activities are interconnected, some of them loosely, the others strongly integrated. Individuals prepared to champion this progression are crucial, and they are recruited from among the scientists and physicians involved.

The importance of synthetic chemistry in the research shuttle arises from the need to access promptly the progressively increasing amounts of active substance or active pharmaceutical ingredient (API) that are required. This becomes most essential when approaching crucial activities such as safety studies (toxicology in animal species), and the development of suitable dosage forms and testing in human beings (clinical phases I–III). Lack of well-planned, timely delivery of reproducibly standardized API can result in long delays in the progression of the new product to the market, mainly by failing to arrive on time at the milestones of nomination for selection of a clinical candidate (CC) or a candidate drug (CD) [1]. The requirements for active substance at various points along the R&D shuttle process are presented in Fig. 1.2.

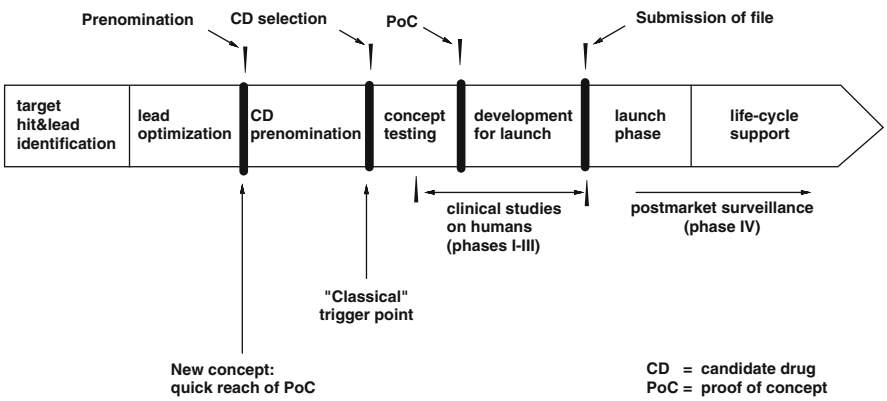

Fig. 1.1 R&D "shuttle" for delivering an NDE

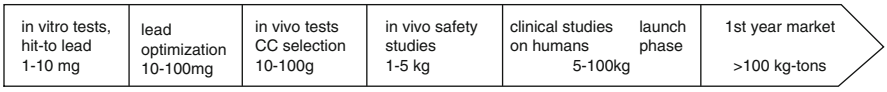

Fig. 1.2 Requirements for active compound along the R&D process

This scheme outlines the exponential requirements for the active substance over a period of approximately 10 years. The critical period for the research chemists on the project, however, lies between the selection of the lead and the clinical candidate. In this period, scale-up to kg production is undertaken for the process that was previously used for mg preparation. Besides the usual modification of the separate synthetic steps, often the complete synthetic scheme needs substantial modification to enhance efficiency, expressed as the average yield of the process, and to reach a reproducibly high level of purity of the final product. At this stage, initial consideration of the requirements for the future multi-kg production process is made. This includes planning the technological, ecological and economic aspects of the future process. The subsequent large-scale synthesis of API for clinical trials, these days, is usually contracted out to a specialized manufacturing company, for whom the research chemist will provide technical details.

Lead generation and, to a greater extent, *lead optimization* are the processes that make the most creative demands on the synthetic organic chemist. Lead generation is the process by which a series of compounds is identified that has the potential to be developed into a drug. Creativity is not only demanded in synthesizing a compound with the desired biological activity. The molecule must also have suitable physical properties for the route of administration planned, exert little or no toxicity and on administration, must be taken up efficiently into the body and distributed at adequate concentration to the desired site of action (pharmacokinetic properties).

The shuttle model in Fig. 1.2 is particularly challenged by the high attrition of the potential drug entities in the course of R&D process. Attrition of potential NDEs (termination of research projects due to their failure to satisfy the criteria set up for the different phases of the shuttle process) has various causes. Among them are toxicity in non-human tests (35%), lack of clinical efficacy (18%), unacceptable clinical safety (15%), together with unsatisfactory pharmacokinetic (PK) and bioavailability properties (9%). These data indicate that proof of concept (PoC) and clinical studies in humans are the stages at which most potential drugs fail to satisfy the criteria. Although synthetic chemistry is not directly involved in these activities, it is the basis for the unsuitable biological properties of the chemical entity. The only way to overcome the deficiencies is to design and synthesize new lead molecules.

Together with the identification of biological targets and lead optimization, the chemical synthesis of novel compounds forms one of the key steps in drug discovery (Fig. 1.1). According to Gillespie [2], the *attributes of a high-quality lead compound* are:

- Its synthetic tractability
- The patentability of the series around the lead
- Availability of chemistry space for optimization
- Acceptable solubility, permeability and protein binding
- Lack of inhibition of *cytochrome P450* (CYP; family of enzymes responsible for oxidative drug metabolism)