Signposts to Chiral Drugs
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
February 2011

Vitomir Šunjić
Michael J. Parnham

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# Abbreviations and Acronyms

**A**
- **Aβ** : Amyloid-beta-peptide
- **AChE** : Acetylcholine esterase
- **ACL** : Assisted chemical ligation
- **Ac₂O** : 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
- **Bioisosteres** : 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
Cp₂TiH  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  Dihydropyrrane
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  Diethyamine
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(etas-tetrahydroindenyl)
EC₅₀  Effective concentration producing 50% of maximal response
EDG  Electron-donating group
Abbreviations and Acronyms

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 Fluorenlymethoxy carbonyl
Fuc-T alpha-1,3-Fucosyl transferase

**G**
GABA Gamma-aminobutyric acid
GCR Glucocorticoid receptor
GDP-fucose Guanidine diphosphate-beta-1-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)$_2$BCl Chlorodiisopinocampheyl borane

**L**
LacNAC $N$-acetyllactosamine
LBD Ligand-binding domain
LC/MS Liquid chromatography/mass spectrometry
LDA Li-diisopropylamide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>LDH</td>
<td>Layered double hydroxide</td>
</tr>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium hexamethyldisilazane</td>
</tr>
<tr>
<td>Log P</td>
<td>Logarithm of the ratio of the concentrations of the unionized solute in two solvents</td>
</tr>
<tr>
<td>LPPS</td>
<td>Liquid phase protein synthesis</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>Lithium tri-sec-butyl(hydrido)borate</td>
</tr>
<tr>
<td>LTC4, LTD4, LTE4</td>
<td>Leukotrienes C4, D4, E4</td>
</tr>
<tr>
<td>MAO</td>
<td>Monoamine oxidase</td>
</tr>
<tr>
<td>MCR</td>
<td>Multicomponent reaction</td>
</tr>
<tr>
<td>MDR</td>
<td>Multidrug resistance</td>
</tr>
<tr>
<td>Mesylate</td>
<td>Methanesulphonic ester moiety</td>
</tr>
<tr>
<td>MeQ</td>
<td>4′-Methyl-2′-quinolyl dihydroquinine</td>
</tr>
<tr>
<td>MsCl</td>
<td>Methanesulphonic acid chloride</td>
</tr>
<tr>
<td>N-Boc</td>
<td>N-Benzzyloxycarbonyl</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NCE</td>
<td>New chemical entity</td>
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<tr>
<td>NCL</td>
<td>Native chemical ligation</td>
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<tr>
<td>NDE</td>
<td>New drug entity</td>
</tr>
<tr>
<td>NLE</td>
<td>Non-linear effect</td>
</tr>
<tr>
<td>NME</td>
<td>New molecular entity</td>
</tr>
<tr>
<td>NMO</td>
<td>4-Methyl-morpholine-N-oxide</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methylpyrrolidine</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>OPMB</td>
<td>para-Methoxybenzyl</td>
</tr>
<tr>
<td>OTBS</td>
<td>O-tertiary-Butyldimethylsilyl</td>
</tr>
<tr>
<td>PADA</td>
<td>Dipotassium diazidocarboxylate</td>
</tr>
<tr>
<td>PCy3</td>
<td>Tricyclohexyl phosphine</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>PEGA</td>
<td>Poly[acryloyl-bis(aminopropyl)polyethylene glycol]</td>
</tr>
<tr>
<td>Peptone</td>
<td>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</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<td>P-gp</td>
<td>P-glycoprotein</td>
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<td>PHAL</td>
<td>Phthalazine</td>
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<td>Phen</td>
<td>1,10-Phenanthroline</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>PHN</td>
<td>Phenanthrenyl dihydroquinine</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PMB</td>
<td>para-Methoxybenzyl</td>
</tr>
<tr>
<td>PoC</td>
<td>Proof of concept</td>
</tr>
<tr>
<td>PPA</td>
<td>Polyphosphoric acid</td>
</tr>
<tr>
<td>PPARα</td>
<td>Peroxisome proliferator-activated receptor alpha</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium para-toluenesulphonate</td>
</tr>
<tr>
<td>4-PPy</td>
<td>4-Phenylpyridine</td>
</tr>
<tr>
<td>PSA</td>
<td>Polar surface area</td>
</tr>
<tr>
<td>pTsOH</td>
<td>para-Toluenesulphonic acid</td>
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<td>Q</td>
<td>Quantitative structure–activity relationship</td>
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<tr>
<td>QSAR</td>
<td>Quantitative structure–activity relationship</td>
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<tr>
<td>R</td>
<td>Renin–angiotensin–aldosterone system</td>
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<tr>
<td>RaNi</td>
<td>Raney nickel catalyst</td>
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<tr>
<td>RCM</td>
<td>Ring closure metathesis</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research and development</td>
</tr>
<tr>
<td>REM</td>
<td>Regenerative Michael receptor</td>
</tr>
<tr>
<td>RT</td>
<td>Reverse transcriptase</td>
</tr>
<tr>
<td>S</td>
<td>Structure (biological) activity relationship</td>
</tr>
<tr>
<td>SAR</td>
<td>Structure (biological) activity relationship</td>
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<tr>
<td>SCRAM</td>
<td>[CpIrI$_2$]$_2$ (Cp = cyclopentadienyl)</td>
</tr>
<tr>
<td>SERT</td>
<td>Plasma membrane serotonin transporter</td>
</tr>
<tr>
<td>SMB</td>
<td>Simulated moving bed chromatography</td>
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<td>SPS</td>
<td>Solid phase synthesis</td>
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<td>SPPS</td>
<td>Solid phase protein synthesis</td>
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<tr>
<td>SRS-A</td>
<td>Slow-reacting substance of anaphylaxis</td>
</tr>
<tr>
<td>SRS</td>
<td>Slow-reacting substance</td>
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<tr>
<td>SSRI</td>
<td>Selective serotonin uptake inhibitor</td>
</tr>
<tr>
<td>T</td>
<td>Tricyclic antidepressants</td>
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<tr>
<td>TACs</td>
<td>Tricyclic antidepressants</td>
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<tr>
<td>TBAB</td>
<td>$tetra-n$-Butylammonium bromide</td>
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<td>TBS</td>
<td>$tert$-Butyldimethylsilyl</td>
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<td>TBSCl</td>
<td>$tert$-Butyl-dimethylsilyl-chloride</td>
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<tr>
<td>TBSOTf</td>
<td>$tert$-Butyl-dimethylsilyl-trifluoracetate (trflate)</td>
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<tr>
<td>T2DM</td>
<td>Type 2 diabetes mellitus</td>
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<tr>
<td>TCEP</td>
<td>$tris$-(2-Carboxy)ethyl phosphine</td>
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<tr>
<td>TEA</td>
<td>Triethylamine</td>
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<tr>
<td>TEMPO</td>
<td>2,2,6,6-Tetramethylpiperidine-1-oxyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoracetic acid</td>
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<tr>
<td>TGS</td>
<td>Target-guided synthesis</td>
</tr>
<tr>
<td>THF</td>
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<td>Triisopropylsilane</td>
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<td>Target molecule</td>
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<td>Transmembrane domain</td>
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<td>Trifluoromethanesulphonic moiety</td>
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<td>Triton B</td>
<td>Benzyl trimethyl ammonium hydroxide</td>
</tr>
<tr>
<td>TRPM8</td>
<td>Transient receptor potential cation channel subfamily M member 8</td>
</tr>
<tr>
<td>TsDPEN</td>
<td>(1R,2R)-N-(p-tolylsulphonyl)-1,2-diphenylethane</td>
</tr>
<tr>
<td>TsOH</td>
<td>Toluenesulphonic acid</td>
</tr>
<tr>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>YMS</td>
<td>Culture medium supplemented with soybean peptones</td>
</tr>
</tbody>
</table>