Small Molecule Drug Discovery

Methods, Molecules and Applications

EDITED BY
ANDREA TRABOCCHI
ELENA LENCI

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Andrea Trabocchi

Department of Chemistry "Ugo Schiff"
University of Florence
Sesto Fiorentino, Florence
Italy

Elena Lenci

Department of Chemistry "Ugo Schiff"
University of Florence
Sesto Fiorentino, Florence
Italy

ELSEVIER

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Contributors

Michelle R. Arkin
Small Molecule Discovery Center and Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, CA, United States; Buck Institute for Research on Aging, Novato, CA, United States

Andrea Basso
Department of Chemistry and Industrial Chemistry, University of Genova, Genova, Italy

Pietro Capurro
Department of Chemistry and Industrial Chemistry, University of Genova, Genova, Italy

Stuart J. Conway
Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Oxford, United Kingdom

Margarida Espadinha
Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal

M. Isabel García-Moreno
University of Seville, Seville, Spain

José M. García Fernández
Institute for Chemical Research (IIQ), CSIC — University of Seville, Seville, Spain

Kamal Kumar
Max Planck Institute of Molecular Physiology, Dortmund, Germany; Aicuris Antiinfective Cures GmbH, Wuppertal, Germany

Elena Lenci
Department of Chemistry "Ugo Schiff", University of Florence, Sesto Fiorentino, Florence, Italy

Qingliang Li
National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Besthesda, MD 20894, United States

José L. Medina-Franco
Department of Pharmacy, School of Chemistry, Universidad Nacional Autónoma de México, Mexico City, Mexico

Carmen Ortiz Mellet
University of Seville, Seville, Spain

Amy Trinh Pham
School of Pharmacy, Health Sciences Campus, University of Waterloo, Waterloo, ON, Canada

Praveen P.N. Rao
School of Pharmacy, Health Sciences Campus, University of Waterloo, Waterloo, ON, Canada

Fernanda I. Saldívar-González
Department of Pharmacy, School of Chemistry, Universidad Nacional Autónoma de México, Mexico City, Mexico

Elena M. Sánchez-Fernández
University of Seville, Seville, Spain

Maria M.M. Santos
Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal

Arash Shakeri
School of Pharmacy, Health Sciences Campus, University of Waterloo, Waterloo, ON, Canada

Andrea Trabocchi
Department of Chemistry "Ugo Schiff", University of Florence, Sesto Fiorentino, Florence, Italy

Chris G.M. Wilson
Small Molecule Discovery Center and Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, CA, United States

Foreword

The discovery of new drugs is an endeavor of high scientific demand and societal relevance. It requires interdisciplinary research spanning the life sciences, chemistry, pharmcology, and even material science. It benefits mankind because the treatment of disease is one of societies' most urgent demands to science.

Among the pharmacopoeia available to us, small molecules historically are most prevalent, and they form the largest group of new chemical entities in medicinal chemistry research to this very day. Undoubtedly biologicals, in particular antibodies, have gained major importance and are here to stay, but it is also evident that small molecule drugs will remain to be of highest relevance in drug discovery in the foreseeable future.

Hence the science that underlies the discovery and development of new bioactive small molecules that can be considered drug candidates and that may inspire new approaches to the treatment of disease is of utmost importance and calls for continuous introduction of new methods and principles.

This necessity underlies the articles compiled in the book edited by Andrea Trabocchi and Elena Lenci. Collectively the authors shine light on a very impressive ensemble of some of the most relevant topics in contemporary medicinal chemistry and drug discovery. These include chemical synthesis, cheminformatics, and biophysical and computational methods and highlight individual case studies focusing on some of the greatest challenges in this science, as for instance Alzheimer disease.

The Editors have chosen the topics wisely and with deep insight into drug discovery. Thereby the book not only gives an overview of recent developments, it also guides the reader to the frontiers of medicinal chemistry research. It will be both entertaining to read and educative such that it will be of interest to the professional skilled in the art, as well as to newcomers to the field, in particular, advanced graduate and postdoctoral students.

I hope that this book will find widespread interest from practitioners in medicinal chemistry and simply curious scientists trying to get a glimpse at and an understanding of the science that drives small molecule drug discovery.

Herbert Waldmann
Max Plank Institute of Molecular Physiology
Dortmund, Germany
September 2019

Preface

The identification of novel molecular entities capable of specific interactions represents a significant challenge in early drug discovery. Despite the success of biopharmaceuticals, small molecules still dominate the market, being more than 95% of the top 200 most prescribed drugs in 2018. Small molecules are low-molecular-weight organic compounds that include natural products and metabolites, as well as drugs and other xenobiotics. The entire drug discovery process has changed a lot during the last decades due to the difficulties in finding new lead compounds for all those "undruggable" targets and for addressing complex oncology and CNS diseases. The rational design of ligands is still a powerful approach, especially in combination with computer-aided methods when the biological target is well-defined and structurally known. Nevertheless, new synthetic methods able to generate high-quality chemical libraries have been exploited over the last decades to meet the need of improving the quality and quantity of small molecules for biological screenings. Since the synthetic efforts characterized by the trial-and-error approach of the 1980s and combinatorial chemistry of the 1990s, new attitudes are now gaining wide attention in synthetic chemistry for small molecule drug discovery, in order to maximize the quality of libraries and reducing the waste of generating and screening random unnecessary compounds. New frontiers in the synthesis of small molecule libraries have been explored. Diversity-Oriented Synthesis has proven to be very effective to access large areas of the chemical space, primarily through the creation of many distinct molecular scaffolds. Also, Biology-Oriented Synthesis has been conceived with the purpose of taking inspiration from nature to select promising molecular scaffolds being related to natural products in terms of biological output. Today, an important part of modern medicinal chemistry is represented by computer-aided methods, for rational drug design (i.e, virtual screening), and for the smart design of small molecule libraries. As the number of publicly accessible biological data is rapidly increasing, chemoinformatics is gaining relevance as a tool for developing better chemical libraries.

The book is organized in three parts, exploring selected topics on small molecule drug discovery on key synthetic and screening methods, representative small molecule categories, and selected biomedical applications. The first part encompasses the methods for the synthesis, structure classification, and biological evaluation of small molecules. Specifically, Chapter 1 reports an in-depth overview of strategic approaches for the achievement of small molecules, and Chapter 2 gives a thorough account about most relevant chemical reactions for building small molecules. Chapters 3 and 4 report the chemoinformatic tools to assess chemical diversity of small molecule libraries and virtual screening methods, respectively. Chapter 5 concludes the first part on methods discussing screening approaches and biophysics of small molecules. In the second part, representative small molecule classes derived from natural products are reported. Chapter 6 describes the principles and applications of small molecule peptidomimetics, and Chapter 7 reports the chemistry of sp2-

iminosugars within the field of carbohydrates. Chapter 8 outlines the synthesis and structural features of small molecules characterized by spiroacetal moiety, and Chapter 9 reports the case study of centrocountins as nature inspired indoloquinolizines. The third part contains two selected case studies about the successful application of small molecules in biomedical research. Chapter 10 deals with PPIs as therapeutic targets for anticancer drug discovery and describes the case study of MDM2 and BET bromodomain inhibitors, and Chapter 11 is an account of the discovery of small molecules for the treatment of Alzheimer disease.

These presentations have been conceived for a broad readership and should interest not only those readers who currently work in the field of organic and medicinal chemistry addressing drug discovery, but also those who are considering this approach in the field of chemical biology, taking advantage of the use of small molecule as chemical probes for dynamically interrogating biological systems and for investigating potential drug targets. We hope these Chapters will stimulate further advances in the ever-developing field of small molecule drug discovery.

Andrea Trabocchi
Elena Lenci
Florence, September 2019

Abbreviations

(TR)-FRET	Time-resolved fluorescence resonance energy transfer
2D	Two-dimensional
3D	Three-dimensional
ACD	Available chemicals directory
ACE	Angiotensin-converting enzyme
ACh	Acetylcholine
AChE	Acetylcholinesterase
ACN	Acetonitrile
AcOH	Acetic acid
AD	Alzheimer disease
ADME	Absorption-distribution-metabolism-excretion
ADP	Adenosine diphosphate
AIDS	Acquired immunodeficiency syndrome
ALK	Anaplastic lymphoma kinase
AlphaScreen	Amplified luminescent proximity homogeneous assay
AMBER	Assisted Model Building with Energy Refinement
ANS	Anthocyanidin synthase
APDS/TRP	Alanine-proline-aspartate-serine/threonine-arginine-proline
ApoA1	Apolipoprotein A-1
APP	Amyloid precursor protein
APT1	Acyl protein thiosterase 1
APV	Amprenavir
AR	Androgen receptor
AS/MS	Affinity selection followed by mass spectrometry
ATP	Adenosine triphosphate
B/C/P	Build/couple/pair
BACE-1	Beta-site amyloid precursor protein cleaving enzyme 1
BAL	Backbone amide linker
BBB	Blood-brain barrier
BET	Bromodomain and extraterminal domain
Bcl-X_L	B-cell lymphoma
BCPs	Bromodomain-containing proteins
BEDROC	Boltzmann enhanced discrimination of ROC
BIOS	Biology-oriented synthesis
BLI	Bio-layer interferometry
BOP	Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
BRCA	Breast cancer gene
BRD	Bromodomain
BRET	Bioluminescence resonance energy transfer
BSA	Bovine serum albumin
BZD	Benzodiazepine
CAN	Ceric ammonium nitrate

CAS	Catalytic active site
CBD	Condition-based divergence
CCR2	Chemokine Receptor type 2
CCR5	Chemokine Receptor type 5
CDC	Cross-dehydrogenative couplings
CDK	Chemistry Development Kit
CDKs	Cyclin-dependent kinases
CDP	Consensus diversity plot
CETP	Cholesteryl ester transfer protein
CETSA	Cellular thermal shift assay
ChE	Cholinesterase
CHI	Chalcone isomerase
CHS	Chalcone synthase
CLL	B-cell chronic lymphocytic leukemia
clogP	Calculated octanol/water partition coefficient
CMC	Critical micelle concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxigenase
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CPA	Chiral phosphoric acid
CPAs	Carboxypeptidases A
Crm1	Chromosome region maintenance 1
Cryo-EM	Cryogenic electron microscopy
CS	Castanospermine
CSA	Camphorsulphonic acid
CSP	Chemical shift perturbation
CSR	Cyclic system recovery curves
CuAAC	Cu-catalyzed Azide Alkyne Click
CYP3A4	Cytochrome P450 3A4
DIPEA	*N*,*N*-Diisopropylethylamine
DCE	Dichloroethane
DCM	Dichloromethane
DCN	1,4-Dicyanonaphthalene
DDQ	Dichlorodicyanobenzoquinone
DECLs	DNA-encoded chemical libraries
DEEP-STD	Differential epitope mapping-STD
DIAD	Diisopropyl azodicarboxylate
DLS	Dynamic light scattering
DMAP	4-Dimethylaminopyridine
DMEDA	1,2-Dimethylethylenediamine
DMF	*N*,*N*-Dimethylformamide
DMPU	*N*,*N*′-dimethyl-*N*,*N*′-propylene urea
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DNJ	Deoxynojirimycin
DNP	Dictionary of Natural Products

DOS	Diversity-oriented synthesis
DPPH	Diphenyl-1-picrylhydrazyl
DR	Diabetic retinopathy
DRR	Double reactant replacement
DRV	Darunavir
DSF	Differential scanning fluorimetry
EC_{50}	Half maximal effective concentration values
ECFP	Extended-connectivity fingerprint
EeAChE	Electric eel acetylcholinesterase
EF	Enrichment factor
ELT	Encoded library technology
EMA	European Medicines Agency
ERα	Estrogen receptor α
ESIPT	Excited state intramolecular proton transfer
ET	Energy transfer
EYFP	Enhanced yellow fluorescent protein
FA	Fluorescence anisotropy
FACS	Fluorescence-activated cell sorting
FC	Fusicoccin
FDA	US Food and Drug Administration
FLIM	Fluorescence lifetime imaging microscopy
FP	Fluorescence polarization
FPV	Fosamprenavir
FRET	Fluorescence resonance energy transfer
GalNAc	*N*-Acetyl-d-galactosamine
GABA	Gamma-aminobutyric acid
GBSA	Generalized Born surface area
GFP	Green fluorescent proteins
GlcNAc	*N*-Acetyl-d-glucosamine
GluCl	Glutamate-gated chloride channel
GOLD	Genetic Optimisation for Ligand Docking
GPCRs	G protein—coupled receptors
GPx	Glutathione peroxidase
GSK3β	Glycogen synthase kinase 3β
GTM	Generative topographic mapping
H3R	Histamine H3 receptor
HAT	Hydrogen atom transfer
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HBA	Hydrogen bond acceptors
HBD	Hydrogen bond donors
hBuChE	Human butyrylcholinesterase
HCV	Hepatitis C virus
HCV NS3	Hepatitis C Virus nonstructural protein 3
HDx	Hydrogen/deuterium exchange
HER2	Human epidermal growth factor receptor 2
Hh	Hedgehog
HIV	Human immunodeficiency virus

HLMs	Human liver microsomes
HMG-CoA	3-Hydroxy-3-methyl glutaryl coenzyme A
HMQC	Heteronuclear Multiple Quantum Coherence
HO-1	Heme oxygenase-1
HPLC	High-performance liquid chromatography
HRP	Horseradish peroxidase
HSQC	Heteronuclear Single Quantum Coherence
hTR	Human telomerase RNA
HTRF	Homogeneous time-resolved FRET
HTS	High-throughput screening
ICR	Institute of Cancer Research
icv	Intracerebroventricular
IDH1	Isocitrate dehydroganse type 1
IDV	Indinavir
IMAP-FP	Ion affinity-based fluorescence polarization
IMCRs	Isocyanide-based multicomponent reactions
iNOS	Inducible nitric oxide synthase
ISC	Intersystem crossing
ITC	Isothermal titration calorimetry
IUPAC	International Union of Pure and Applied Chemistry
JAK2	Janus kinase 2
KAc	Acetylated lysine residues
KAHA	α-KetoAcid-HydroxylAmine
KATs	Lysine acetyltransferases
KDACs	Deacetylated by lysine deacetylases
KNIME	Konstanz Information Miner
LBVS	Ligand-based virtual screening
LC-MS	Liquid chromatography-mass spectrometry
LD_{50}	Lethal dose, 50%
LED	Light-emitting diode
LPS	Lipopolysaccharide
LSDs	Lysosomal storage diseases
LSF	Late-stage functionalization
LTP	Long-term potentiation
mAb	Monoclonal antibody
MACCS	Molecular ACCess System
MAO	Monoamine oxidase
MAPK	Mitogen-activated protein kinase
MB	Methylene blue
MCF-7	Michigan Cancer Foundation-7
***m*CPBA**	*m*-Chloroperoxybenzoic acid
MCR	Multicomponent reaction
MCR^2	Combining multicomponent reactions
MCSS	Maximum Common Substructure
MDM2	Mouse double minute 2 homolog
MeCN	Acetonitrile
MEK1/2	MAP (mitogen-activated protein) kinase/ERK (extracellular signal-regulated kinase) Kinase 1/2

MFS Multifusion similarity maps
MMP Matrix metalloprotease
MptpA Low-molecular-weight protein-tyrosine phosphatase A
MptpB Low-molecular-weight protein-tyrosine phosphatase B
MRS Modular reaction sequences
MS Mass spectrometry
MST Microscale thermophoresis
MCC Matthews correlation coefficient
MOE Molecular Operating Environment
MTDLs Multi-target-directed ligands
MTT 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MUC1 Mucin 1
MW Molecular weight
NADPH Nicotinamide adenine dinucleotide phosphate hydrogen
NaN_3 Sodium azide
NF-κB Nuclear factor-kappa B
NFTs Neurofibrillary tangles
NHC *N*-heterocyclic carbene
NK1 Neurokinin 1 receptor
NMDA *N*-methyl-D-aspartate
NMDAR NMDA receptor
NMP N-Methyl-2-pyrrolidone
NMR Nuclear magnetic resonance
NN Neural network
NOR Novel object recognition
NPM Nucleophosmin
ORAC-FL Oxygen radical absorbance capacity
ORTEP Oak Ridge Thermal Ellipsoid Plot
P-3CR Passerini reaction
PADAM Passerini reaction/Amine Deprotection/Acyl Migration
PAINs Pan-assay interference compounds
PAMPA Parallel artificial membrane permeability assay
PBMC Peripheral blood mononuclear cells
PBSA Poisson-Boltzmann surface area
PCA Principal component analysis
PCIs Protein-chromatin interactions
PCR Polymerase chain reaction
PD Pharmacodynamics
PDB Protein Data Bank
PDE Phosphodiesterase
PDE5 Phosphodiesterase type 5
PET Positron emission tomography
PHFs Paired helical filaments
PIAs Phosphatidylinositol ether lipid analogues
PI3K Phosphoinositide-3-kinase
PK Pharmacokinetics
PMI Principal moment of inertia
PPI Protein-protein interaction

PS	Polystyrene
PSSC	Protein structure similarity clustering
PTP1B	Protein-tyrosine phosphatase 1B
PUMA	Platform for Unified Molecular Analysis
PVDF	Polyvinylidene difluoride
QSAR	Quantitative structure–activity relationship
RB	Rose bengal
RBs	Rotatable bonds
RCM	Ring closing metathesis
RF	Random forest
RGD	Arg-Gly-Asp
RIfS	Interference spectroscopy
RNA	Ribonucleic acid
ROC	Receiver operating characteristics
ROCS	Rapid Overlay of Chemical Structures
ROM	Ring opening metathesis
ROS	Reactive oxygen species
RTV	Ritonavir
RU	Response units
RXR	Retinoid X receptor
SAR	Structure–activity relationship
SBS	Society for Biomolecular Sciences
SBVS	Structure-based virtual screening
ScFv	Single-chain variable fragment
SCONP	Structural classification of natural products
SDS-PAGE	Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
SE	Shannon entropy
sEH	Soluble epoxide hydrolase
SET	Single electron transfer
SGLT2	Sodium-glucose linked transporter 2
SHG	Second harmonic generation
SIFt	Structural interaction fingerprint
SLL	Small lymphocytic lymphoma
SlogP	Octanol/water partition coefficient
SMM	Small molecule microarray
SOCE	Store-operated calcium entry
SOMs	Self-organizing maps
SPOS	Solid-phase organic synthesis
SPR	Surface plasmon resonance
SPRs	Structure–properties relationships
SPS	Solid-phase synthesis
SRR	Single reactant replacement
SQV	Saquinavir
STAT3	Signal transducers and activators of transcription 3
STD	Saturation transfer difference
SVM	Support vector machines
t-SNE	Distributed stochastic neighbor embedding
TASK3	TWIK-related acid-sensitive K^+ channel 3

TBAF	Tetrabutylammonium fluoride
TCM	Traditional Chinese medicine
TEM	Transmission electron microscopy
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
ThT	Thioflavin T
TINS	Target immobilized NMR screening
TNF-α	Tumor necrosis factor-α
TPP	Tetraphenylporphirine
TPSA	Topological polar surface area
TOS	Target-oriented synthesis
TRH	Thyrotropin-releasing hormone
TRK	Tropomyosin receptor kinase
TrxR	Thioredoxin reductase
U-5C-4CR	Ugi 5-center-4-component reaction
UDC	Ugi/deBoc/cyclization
Ugi-4CC	Ugi-4 component reaction
UNPD	Universal Natural Product Database
USR	Ultrafast shape recognition
UV-B	Ultraviolet B-rays
VE-PTP	Vascular endothelial-protein-tyrosine phosphatase
VHR	Vaccinia H1-related
WHO	World Health Organization
YFP	Yellow fluorescent protein

CHAPTER

Synthetic approaches toward small molecule libraries

1

Elena Lenci, Andrea Trabocchi

Department of Chemistry "Ugo Schiff", University of Florence, Sesto Fiorentino, Florence, Italy

1.1 Introduction

Drug discovery is the long and arduous process that can eventually bring molecules from the laboratories to the market. Although the number of new approved drugs showed about a 30% increase over 2017, marking a new record after 1996 [1], in general only 1 molecule out of 5000 hit candidates can reach the market [2].

The process of discovering, testing, and gaining approval for a new drug has changed a lot during the last century. From the isolation of active ingredients from traditional remedies and natural products, drug discovery has evolved into a multidisciplinary and complex process that brings together the efforts of biologists, pharmacologists, and chemists. Many different approaches nowadays can be applied in drug discovery. From one hand, the rational design of ligands remains the "gold standard" in medicinal chemistry, especially when the biological target is well defined and structurally known (Fig. 1.1, top) [3]. On the other hand, a parallel new approach has emerged, especially in those fields, such as cancer and neurodegenerative disorders, where the biological target or the mode of binding is not well known [4,5], or difficult to study in traditional drug discovery programs [6].

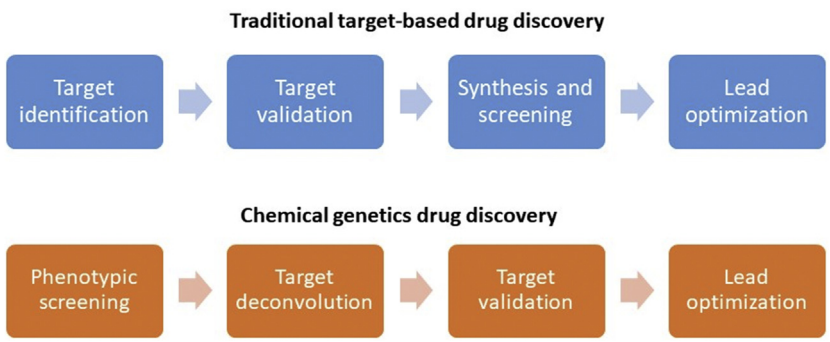

FIGURE 1.1

Comparison between conventional target-based and chemical genetics drug discovery approaches.

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When researchers are experiencing this impasse, one alternative, for the discovery of new targets and new lead compounds, is the application of large small molecules libraries in high-throughput screening (HTS), phenotypic assays, and chemical genetics studies (Fig. 1.1, bottom) [2,7–10]. The relevance of this approach is also highlighted by the emergence of international screening initiatives, such as EU-OPENSCREEN [11] or the European Lead Factory [12,13].

In both approaches, synthetic chemistry plays a key role in generating high-quality small molecules collections. In fact, despite the vast success of the biological drugs (monoclonal antibodies or recombinant proteins), the favorable pharmacokinetic properties of small molecules libraries allowed them to remain as the gold standard for the development of new medications, especially in the case of enzyme inhibitors. In fact, among the 59 new drugs approved by the FDA in 2018, 42 are small molecules and only 17 are biologic drugs [1]. In Table 1.1 are reported, for example, the 11 small molecules approved by the FDA as new drugs for cancer therapy in 2018.

Table 1.1 Small molecules approved by the FDA as new drugs for cancer therapy in 2018.

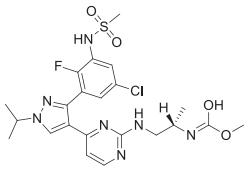
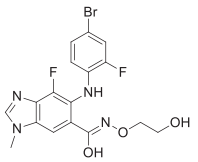
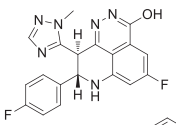
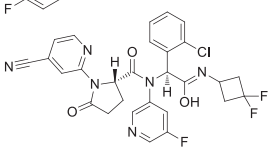
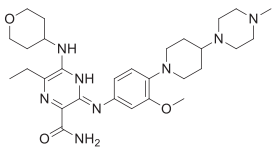
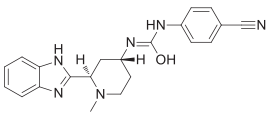
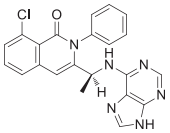
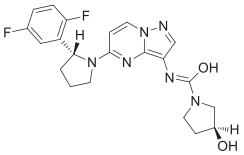
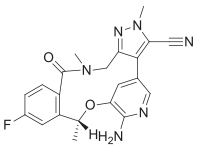
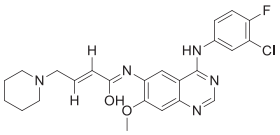
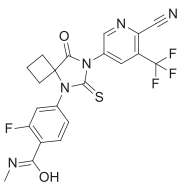
Name	Structure	Company	Biological effect
Encorafenib		Array	BRAF inhibitor. Used in combination with binimetinib for the treatment of BRAF-mutated melanoma
Binimetinib		Array	MEK1/2 inhibitor. Used in combination with Encorafenib for the treatment of BRAF mutated melanoma
Talazoparib		Pfizer	Poly (ADP-ribose) polymerase type 1 and 2 inhibitor. Used in the treatment of BRCA-mutated HER2-negative breast cancer
Ivosidenib		Agios	Isocitrate dehydrogenase type 1 (IDH1) inhibitor. Used in the treatment of acute myeloid melanoma
Gilteritinib		Astellas	FLT3, AXL, and ALK kinases inhibitor. Used in the treatment of acute myeloid melanoma

Table 1.1 Small molecules approved by the FDA as new drugs for cancer therapy in 2018.—*cont'd*

Name	Structure	Company	Biological effect
Glasdegib		Pfizer	Hedgehog (hh) signaling pathway inhibitor. Used in the treatment of acute myeloid melanoma
Duvelisib		Verastam	Phosphoinositide-3-kinase (PI3K) inhibitor. Used in the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma
Larotrectinib		Bayer and Loxo	Tropomyosin receptor kinase (TRK) A/B/C inhibitor. Used in the treatment of solid tumors that have the neurotrophic receptor tyrosine kinase gene fusion
Lorlatinib		Pfizer	ATP-competitive inhibitor of anaplastic lymphoma kinase (ALK) and c-Ros oncogene 1 (Ros)1. Used in the treatment of ALK-positive metastatic non—small cell lung cancer
Dacomitinib		Pfizer	Covalent ligand of human epidermal growth factor receptors Her-1, Her-2, and Her-4. Used in the treatment of metastatic non—small cell lung cancer
Apalutamide		Janssen	Androgen receptor (AR) antagonist. Used in the treatment of prostate cancer

Thus, to address this demand, very powerful synthetic methods are necessary for the generation of large small molecules libraries. Several efforts have been devoted to improve the quality and quantity of small molecules representing a library. In particular, during last decades, organic chemists have taken advantage of high-throughput synthesis methods, such as solid-phase techniques [14—17], and combinatorial chemistry [18,19]. Unfortunately, despite the apparent success, these chemistry approaches have not fulfilled the desired expectations as the automation of discovery processes has proven to be inefficient [20,21]. Thus, new frontiers in

the synthesis of small molecules libraries are being explored, with the aim of improving the quality of the small molecules representing a library, where the synthetic efforts are not guided by a specific core structure, but rather by concepts like molecular diversity (i.e., diversity-oriented synthesis) and bioactivity or biosynthetic pathway (i.e., biology-oriented synthesis). This chapter focuses on main synthetic approaches for the generation of large, high-quality small molecule collections, with an emphasis on organic synthesis and technical methods rather than assay results.

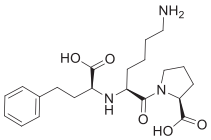
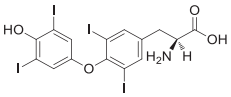
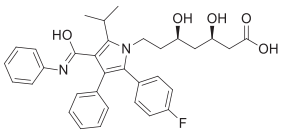
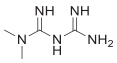
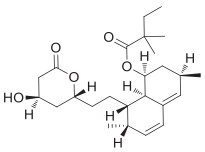
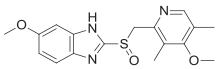
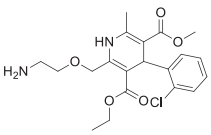
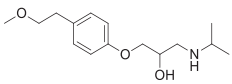
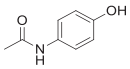
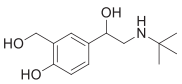
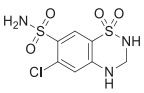
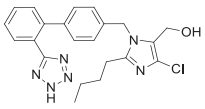
1.2 What is a small molecule?

Considering that there is no strict definition, the term small molecule can be referred to any organic compound with a molecular weight of less than 1500 Da [22]. The cutoff limit of 1500 Da is arbitrary, as in the literature it is possible also to find this limit fixed on 900−1000 Da, but it is correlated to the ability of small molecules to rapidly diffuse across cell membranes and reach the intracellular sites of action [22]. Small molecules are compounds that alter the activity or the function of a biological target, by interacting with a biological macromolecule, such as DNA, RNA, and proteins [23], often in a selective and dose-dependent manner, showing a beneficial effect against a disease, or a detrimental one (such as in the case of teratogens and carcinogens). Small molecules can be naturally occurring or of synthetic origin and can have a variety of different applications beyond drugs, as pesticides [24] or as probes and research tools to perturb biological systems in order to identify and discover novel biological targets, such as in the field of chemical genetics [2,7−10,25,26]. In fact, they work rapidly, reversibly, and in tunable conditions depending on the concentration, in contrast with genetic approaches, so they are better probes to analyze complex biological networks. In pharmacology, the term "small molecule" is used to differentiate drugs below 1000 Da from all the other classes of larger and complex biologic drugs that include antibodies, peptides, nucleic acid-based compounds, cytokines, replacement enzymes, polysaccharides, and recombinant proteins.

Biologic drugs have been increasing over the last decade, thanks to the advances of biotechnology and analytical techniques. Although they have some advantages over small molecules, such as their high specificity and biocompatibility, they often suffer of poor Absorption, Distribution, Metabolism, and Excretion (ADME) properties, and the oral delivery route remains practically unattainable, as most of them are still delivered using subcutaneous injections. Also, they are much more expensive as compared to low-molecular-weight drugs, and their structural characterization and quality control is more challenging.

Small molecules still dominate the market, as more than 95% among the top 200 most prescribed drugs in 2018 are small chemical entities [27]. In Table 1.2, the first 15 small molecules of this list are reported. Despite that, in the list of 15 top selling drugs of 2018, only five are small molecules (Table 1.3), whereas all the rest are

Table 1.2 First 15 small molecules of top 200 most prescribed drugs in 2018.

Name	Structure	Biological effect
Lisinopril		ACE inhibitor, used in the treatment of hypertension and symptomatic congestive heart failure
Levothyroxine		Natural thyroxine analogue, used in the treatment of hypothyroidism
Atorvastatin		3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor, used in the treatment of hyperlipidemic diseases
Metformin		Antihyperglycemic agent, used in the treatment of type II diabete
Simvastatin		3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor, used in the treatment of hypercholesterolemia
Omeprazole		proton-pump (potassium-transporting ATPase alpha chain 1) inhibitor, used for the treatment of gastric acid-related disorders
Amlodipine		calcium channel blocker, used in the treatment of high blood pressure and angina
Metoprolol		Beta-1 blocker, used in the treatment of angina, heart failure, and hypertension
Paracetamol		Antipyretic and analgesic
Salbutamol		Beta-2 adrenergic receptor agonist, bronchodilator, used in the treatment of asthma and Chronic Obstructive Pulmonary Disease (COPD)
Hydrochlorothiazide		Diuretic, used in the treatment of edema, hypertension, and hypoparathyroidism
Losartan		Angiotensin-receptor blocker, used in the treatment of hypertension

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