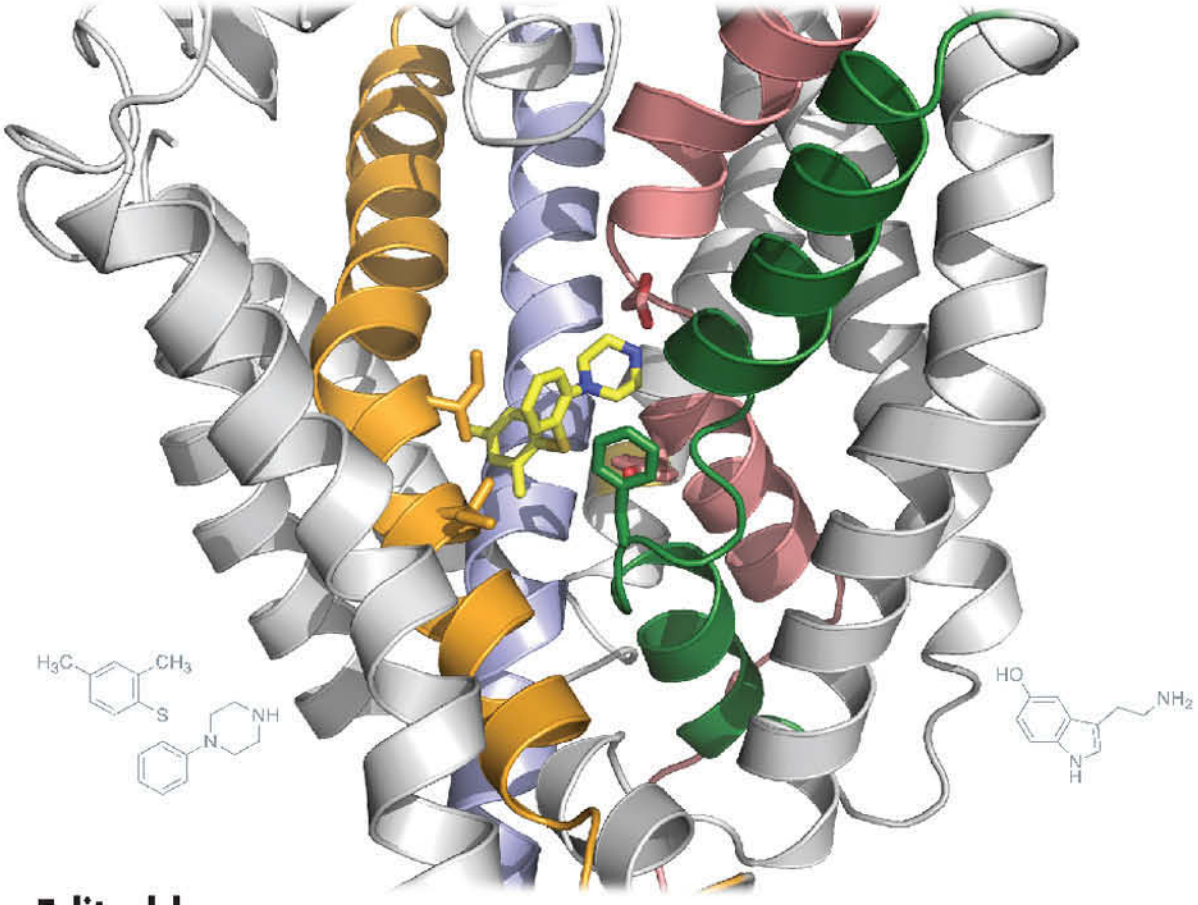
Textbook of

Drug Design and Discovery

Fifth Edition



Edited by

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Ulf Madsen

CRC Press
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Preface

Textbook of Drug Design and Discovery is meant to be used primarily in teaching at undergraduate and postgraduate level courses, where an insight into the complex process of the early drug design and discovery process is central. The chapters in the book are written by experts within their topic of expertise, and it is assumed that readers have a basic knowledge of organic and physical chemistry, biochemistry, and pharmacology.

The textbook covers a broad range of aspects related to the early drug design and discovery process, presented in an up-to-date review form, with an underlying and fundamental focus on the educational aspects. The first part of the book covers general aspects, methods, and principles within drug design and discovery and the second part exemplify important and recent medicinal chemistry developments for a number of specific targets and diseases.

To perform both academic and industrial medicinal chemistry research at the highest level, it is required to attract the attention of bright students, interested in the creative and fascinating nature of drug design. In order to reach this goal, it is of utmost importance to maintain focus on the integration of the scientific disciplines of chemistry and biology. Interesting developments in this regard is the increased interactions between academic and more industrial medicinal chemistry efforts, as seen in a number of public–private partnerships, often involving "big pharma" companies and universities around the world. Regardless of the setting, students should be taught that the conversions of hits into lead structures and further into drug candidates require the integration of a number of related scientific disciplines, such as advanced synthetic chemistry, computational chemistry, biochemistry, structural biology, and molecular pharmacology.

Clearly, the early processes of drug design and development are constantly undergoing changes, which call for a regular update of a textbook like this and are reflected in the current edition. This update includes chapters describing the particular challenges and aspects of developing peptide-based drugs, as well as a broader description of protein-based drugs. In addition, a chapter is devoted to the medicinal chemistry considerations in the pharmaceutical industry (Chapter 5), when developing hit compounds into lead compounds and later clinical candidates. These considerations are important for students to learn and understand and highlight putative distinctions between more academic medicinal chemistry endeavors and those ongoing in the pharmaceutical industry.

Kristian Strømgaard
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Editors

Kristian Strømgaard is a professor of chemical biology in the Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, at the University of Copenhagen and a director of the Center for Biopharmaceuticals, Copenhagen, Denmark. He received his master's degree in chemical research from the Department of Chemistry at the University College London under the supervision of Professor C. Robin Ganellin. In 1999, he received his PhD in medicinal chemistry from the Royal Danish School of Pharmacy (now School of Pharmaceutical Sciences). Subsequently, Dr. Strømgaard carried out his postdoctoral studies with Professor Koji Nakanishi in the Department of Chemistry at Columbia University. During this period, his main focus was on medicinal chemistry studies of neuroactive natural products, with a particular emphasis on polyamine toxins and ginkgolides. In 2002, he returned to the Faculty of Pharmaceutical Sciences as an assistant professor and became an associate professor in 2004 and a professor in 2006. He is currently heading the Center for Biopharmaceuticals, which is an interdisciplinary center focusing on protein medicinal chemistry. The Strømgaard lab explores membrane-bound proteins and their downstream signaling proteins using a combination of chemical and biological approaches. In addition, Dr. Strømgaard is cofounder of a biotech company, Avilex Pharma, which explores peptide-based inhibitors of protein–protein interactions as a novel treatment for stroke.

Povl Krogsgaard-Larsen is a professor of medicinal chemistry in the Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, at the University of Copenhagen, Copenhagen, Denmark. In 1970, he received his PhD in natural product chemistry from the former Royal Danish School of Pharmacy. As an associate professor, he established a research program focusing on the conversion of naturally occurring toxins into specific pharmacological tools and therapeutic agents. Key lead structures in this research program were the *Amanita muscaria* constituents, muscimol and ibotenic acid, and the *Areca* nut alkaloid, arecoline, all of which interact nonselectively with GABA, glutamate, and muscarinic receptors, respectively. The redesign of muscimol resulted in a variety of specific GABA agonists, notably THIP and isoguvacine, and specific GABA uptake inhibitors, including nipecotic acid and guvacine. Ibotenic acid was converted into a broad range of subtype-selective glutamate receptor agonists, including AMPA, from which the AMPA receptor subgroup was named. Arecoline was redesigned to provide a variety of subtype-selective muscarinic agonists and antagonists. Whereas nipecotic acid was subsequently developed into the antiepileptic agent tiagabine, THIP is currently used in advanced clinical trials.

In 1980, Dr. Krogsgaard-Larsen received his DSc. He has published nearly 460 scientific papers and edited a number of books, and during the period 1998–2013, he was editor of the *Journal of Medicinal Chemistry*. He has been awarded honorary doctorates at the universities of Strasbourg (1992), Uppsala (2000), and Milan (2008), apart from receiving numerous other scientific awards and prizes. He is a member of a number of academies, including the Royal Danish Academy of Sciences and Letters. In 2002, he founded the Drug Research Academy as an academic/industrial research training center. He is currently chairman of the Brain Prize Foundation under the Lundbeck Foundation, member of the board of the Lundbeck Foundation, and deputy chairman of the Benzon Foundation. During the period 2003–2011, he was chairman of the Carlsberg Foundation.

Ulf Madsen is currently director at the School of Pharmaceutical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. In 1988, he received his PhD in medicinal chemistry from the Royal Danish School of Pharmacy, where he later became an associate professor in the Department of Medicinal Chemistry. Dr. Madsen has been a visiting scientist at the University of Sydney, Australia; at Johann Wolfgang Goethe University, Frankfurt, Germany; and at Syntex Research, California. He has extensive research experience with design and synthesis of glutamate receptor ligands. This includes structure activity studies and development of selective

ligands for ionotropic and metabotropic glutamate receptors, work that has led to a number of important pharmacological tools. Compounds with antagonist activities have shown neuroprotective properties in animal models and are consequently leads for potential therapeutic candidates. Projects involving biostructure-based drug designs have resulted in the development of important pharmacological agents with high subtype selectivity. The work generally involves the synthesis of heterocyclic compounds, the use of bioisosteric principles, and molecular pharmacology on native and recombinant receptors. The work has led to 120 scientific papers. Before becoming school director in 2012, Dr. Madsen was the associate dean at the former Faculty of Pharmaceutical Sciences and before that head of the Department of Medicinal Chemistry for nine years.

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1 Introduction to Drug Design and Discovery

Ulf Madsen and Povl Krogsgaard-Larsen

CONTENTS

1.1 MEDICINAL CHEMISTRY: AN INTERDISCIPLINARY SCIENCE

Therapeutic agents are chemical entities that prevent disease, assist in restoring health to the diseased, or alleviate symptoms associated with disease conditions. Medicinal chemistry is the scientific discipline that makes such drugs available either through discovery or design processes. Throughout history, drugs were primarily discovered by empirical methods, investigating substances or preparations of materials, such as plant parts or plant extracts, found in the local environment. Over the previous centuries, chemists developed methods for the isolation and purification of the active principles in medicinal plants. The purification and structure determination of natural products like morphine, hyoscyamine, quinine, and digitalis glycosides represent milestones in the field of drug discovery and the beginning of medicinal chemistry as a fascinating independent field of research (Figure 1.1).

In the twentieth century, a very large number of biologically active natural products were structurally modified in order to optimize their pharmacology and drug properties in general, and novel drugs were prepared by an increasing use of advanced synthetic methods. Moreover, the rapidly growing understanding of the nature of disease mechanisms, how cells function, and how drugs interact with cellular processes has led to the rational design, synthesis, and pharmacological evaluation of new drug candidates. Most recently, new dimensions and opportunities have emerged from a deeper understanding of cell biology, genetics, and biostructures.

Modern medicinal chemistry draws upon many scientific disciplines, with organic chemistry, physical chemistry, and pharmacology being of fundamental importance. But other disciplines such as biochemistry, molecular biology, toxicology, genetics, cell biology, biophysics, physiology, pathology, and computer modeling approaches play important roles. The key research objective of medicinal chemistry is to investigate relationships between chemical structure and biological effects. When the chemical structure of a particular drug candidate has been optimized to interact

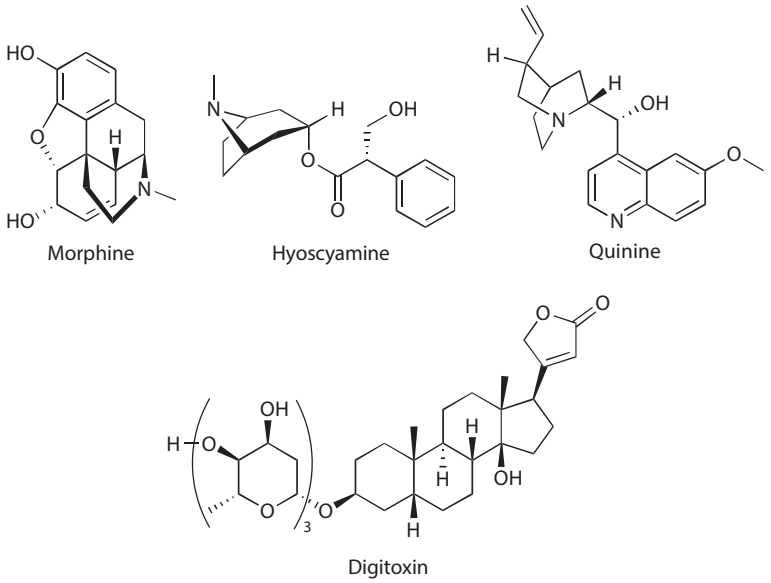


FIGURE 1.1 Chemical structures of four naturally occurring classical therapeutic agents.

with the biological target, the compound further has to fulfill a multifaceted set of criteria before it can be safely administered to patients. Absorption, distribution, metabolism, excretion (ADME), and toxicology studies in animals and humans are time-consuming research tasks which often call for redesign of the chemical structure of the potential therapeutic agent investigated. It is an iterative process which in reality ends up in an overall compromise with respect to multiple desired properties.

1.2 DRUG DISCOVERY: A HISTORICAL PERSPECTIVE

In early times, there was no possibility of understanding the biological origin of a disease. Of necessity, progress in combating disease was disjointed and empirical. The use of opium, ephedra, marijuana, alcohol, salicylic acid, digitalis, coca, quinine, and a host of other drugs still in use long predate the rise of modern medicine. These natural products are surely not biosynthesized by plants for our therapeutic convenience, but they normally have survival value to the plants in dealing with their own ecological challenges.

The presence of biologically active substances in nature, notably in certain plants, was in medieval times interpreted more teleologically. In the early sixteenth century, the Swiss-Austrian medical doctor and natural scientist Paracelsus formulated the "Doctrine of Signatures":

> Just as women can be recognized and appraised on the basis of their shape; drugs can easily be identified by appearance. God has created all diseases, and he also has created an agent or a drug for every disease. They can be found everywhere in nature, because nature is the universal pharmacy. God is the highest ranking pharmacist.

The formulation of this doctrine was in perfect agreement with the dominating philosophies at that time, and it had a major impact on the use of natural medicines. Even today, remanences of this doctrine can be observed in countries where herbal medical preparations are still widely used. Although the "Doctrine of Signatures" evidently is out of the conception of modern medicinal natural product research, the ideas of Paracelsus were the first approach to rational drug discovery.

More than 100 years ago, the mystery of why only certain molecules produced a specific therapeutic response was rationalized by the ideas of Emil Fischer and further elaborated by John Langley and Paul Ehrlich that only certain cells contained receptor molecules that served as hosts for the drugs. The resulting combination of drug and receptor created a new super molecule that had properties producing a response of therapeutic value. One extension of this conception was that the drug fits the target specifically and productively like "a key into its corresponding lock." When the fit was successful, a positive pharmacological action (agonistic) followed, analogous to opening the door. On the contrary, when the fit prevented the intrinsic key to be inserted an antagonist action resulted—i.e., the imaginative door could not be opened. Thus, if one had found adventitiously a ligand for a receptor, one could refine its fit by opportunistic or systematic modifications of the ligand's chemical structure until the desired function was obtained.

This productive idea hardly changed for the next half century and assisted in the development of many useful drugs. However, a less fortunate corollary was that it led to some limitations of creativity in drug design. The drug and its receptor (whose molecular nature was unknown when the theory was formulated) were each believed to be rigid molecules precrafted to fit one another precisely. Today, we know that receptors are highly flexible transmembrane glycoproteins accessible from the cell surface that often comprise more than one drug compatible region. Further complexities have been uncovered continually. For example, a number of receptors have been shown to consist of clusters of proteins either preassembled or assembled as a consequence of ligand binding. The component macromolecules may be either homo- or heterocomplexes. The challenge of developing specific ligands for systems of this complexity may readily be imagined (Chapters 4 and 12).

The opposite extreme to "the lock and key model" is "the zipper model." In this view, a docking interaction takes place (much as the end of a zipper joins the talon piece) and, if satisfactory complementarity is present, the two molecules progressively wrap around each other and adapt to the steric and electrostatic needs of each other. A consequence of accepting this mutual adaptation is that knowledge of the receptor ground state may not be particularly helpful as it adjusts its conformation to ligand binding. Thus, in many cases, one now tries to determine the 3D structure of the receptor–ligand complex. In those cases where X-ray analysis remains elusive, modeling of the interactions involved is appropriate. This is the subject of Chapters 2 through 4.

Earlier, it was also noted that enzymes could be modulated for therapeutic benefit. Enzymatic proteins share many characteristics with receptors, although enzymes catalyze biochemical reactions. Receptor ligands interact with the receptor glycoproteins or with the interfaces between the macromolecular subunits of di- or polycomponent receptor complexes and modify the conformation and dynamics of these complexes. Thus, neither receptor agonists nor antagonists directly interfere with chemical reactions and generally are dissociated from the receptor recognition sites structurally unchanged.

The reaction mechanisms underlying the function of the vast majority of enzymes have been elucidated in detail, and based on such mechanistic information, it has been possible to design a variety of mechanism-based enzyme inhibitors, notably k_{cat} inactivators and transition-state analogs, many of which are in therapeutic use (Chapter 11). Until very recently, it was usually only possible to inhibit enzyme action rather than facilitate it. Actually, diseases frequently result from excessive enzymatic action, making selective inhibition of these enzymes therapeutically useful.

Much later, further classes of receptors were disclosed, explored, and exploited as therapeutically relevant pharmacological targets. This heterogeneous group of receptors comprises nuclear receptors operated by steroid hormones and other lipophilic biochemical mediators, a broad range of membrane-ion channels (Chapter 13), DNA or RNA (Chapter 22), and a number of other biostructures of known or unknown functions. These aspects will be discussed in different chapters of this book.

1.3 DRUG DEVELOPMENT PROCESS: AN OUTLINE

The stages through which a drug discovery/development project proceeds from inception to marketing and beyond are illustrated in Figure 1.2 and described briefly in the following text. The discovery and development process can be described by a number of individual steps, but is also a continuous and iterative process not necessarily performed in a strict stepwise process. From this outline, the complexity of the task of finding new therapeutic agents is evident:

- Target discovery comprises identification and validation of disease-modifying targets. Two major strategies are used for target identification and validation: (1) the molecular approach, with focus on the cells or cell components implicated in the disease and the use of clinical samples and cell models, and (2) the systems approach based on target discovery through the study of diseases in whole organisms.
- Before or after identification of target disease, establishment of a multidisciplinary research team, selection of a promising approach, and decision on a sufficient budget. Initiation of chemistry normally involves synthesis based on available chemicals, in-house chemical libraries, or collection of natural product sources. Start of pharmacology includes suitable screening methods and choice of receptor or enzymatic assays.
- Confirmation of potential utility of initial class(es) of compounds in animals, focusing on potency, selectivity, and apparent toxicity.
- Analog syntheses of the most active compounds, planned after careful examination of literature and patents. More elaborated pharmacology in order to elucidate the mode of action, efficacy, acute and chronic toxicity, and genotoxicity. Studies of ADME characteristics. Planning of large-scale synthesis and initiation of formulation studies. Application for patent protection.

These first project phases which typically last 4–5 years, are followed by highly time- and resource-demanding clinical, regulatory, and marketing phases which normally last 6–10 years:

- Very-large-scale synthesis in parallel or before clinical studies
- Phase I clinical studies which include safety, dosage, and blood level studies on healthy volunteers
- Phase II clinical studies focusing on efficacy and side effects on delimited groups of patients
- Phase III clinical studies which involve studies of range of efficacy and long-term and rare side effects on large patient groups
- Regulatory review
- Marketing and phase IV clinical studies focusing on long-term safety
- Distribution, advertisement, and education of marketing and information personnel

After these project stages from initiation to successful therapeutic application after approval, the patent protection expires, normally after 17–25 years, and generic competition becomes a reality.

This outline of a drug discovery and development process illustrates that, it takes many years to introduce a new therapeutic agent, and it must be kept in mind that most projects are terminated before marketing, even at advanced stages of clinical studies. The later a project fails the more expensive, and many efforts are done in order to consider as many potential failure problems as early as possible in the process. Especially forward translation of preclinical data to possible clinical outcome and back translation of clinical data to "humanized" preclinical data of more predictive value are important issues in the desire to avoid late failures.

Some of the aspects of drug discovery phase are described in more detail in the following sections.

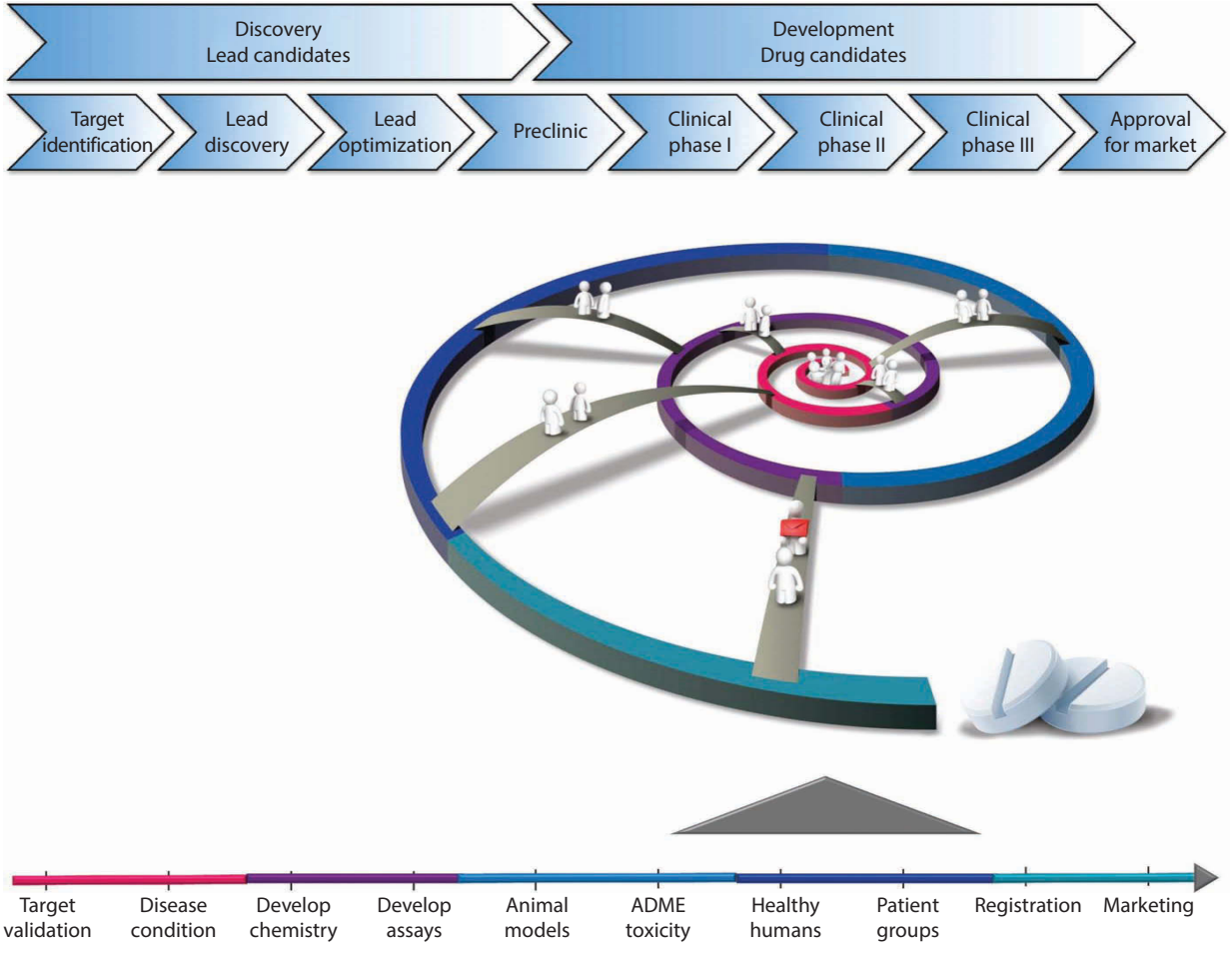


FIGURE 1.2 Outline of the drug discovery and development process with indication of individual steps (blue arrows). The lower multicolored timeline shows the process as a continuous flow which also involves iterative processes at all stages. The spiral representation illustrates such forward and backward translation of knowledge by bridges between the different stages of development.

1.4 DISCOVERY OF DRUG CANDIDATES

Prehistoric drug discovery started with higher plant and animal substances, and this continues today to be a fruitful source of biologically active molecules frequently belonging to unanticipated structural types. Adding to the long list of classical plant products that are still used in modern medicine, one can list many substances of more recent origin, including antibiotics such as penicillins, cephalosporins, tetracyclines, aminoglycosides, various glycopeptides, and many others (Chapter 23). Anticancer agents of natural origin comprise taxol, camptothecin, vinca alkaloids, doxorubicin, and bleomycin (Chapter 21). Among immunosuppressant agents, cyclosporine and tacrolimus deserve special mention.

Other sources of lead structures and drug candidates include endogenous compounds and other compounds with known activity at the target(s) in question, as well as screening programs. The role of natural products in target identification and as lead structures is further described in the following sections, whereas examples of use of other sources are described in different chapters throughout the textbook.

1.4.1 Natural Products: Role in Target Identification

Many naturally occurring compounds have potent and/or selective activity on different biological targets and are of potential therapeutic value. Most often these activities are toxic effects, since these compounds are either animal venoms (e.g., snake poison, spider, or wasp toxins) which can paralyze or kill prey or plant toxins preventing animals to eat the plants. However, toxicity is generally a matter of dose, and in some instances a toxin can be used as a drug in the appropriate dose.

Various biologically active natural products have played a key role in the identification and characterization of receptors, and such receptors are often named after these compounds (Chapter 12). Morphine is a classical example of a natural product used for receptor characterization. Radiolabeled morphine was shown to bind with high affinity to receptors in the nervous system, and these receptors are known as opiate receptors. More than three decades ago, the physiological relevance of these receptors was documented by the findings that endogenous peptides, notably enkephalins and endorphins, served as receptor ligands (agonists). Analogs of morphine have been useful tools for the demonstration of heterogeneity of opiate receptors (Chapter 19) (Figure 1.3).

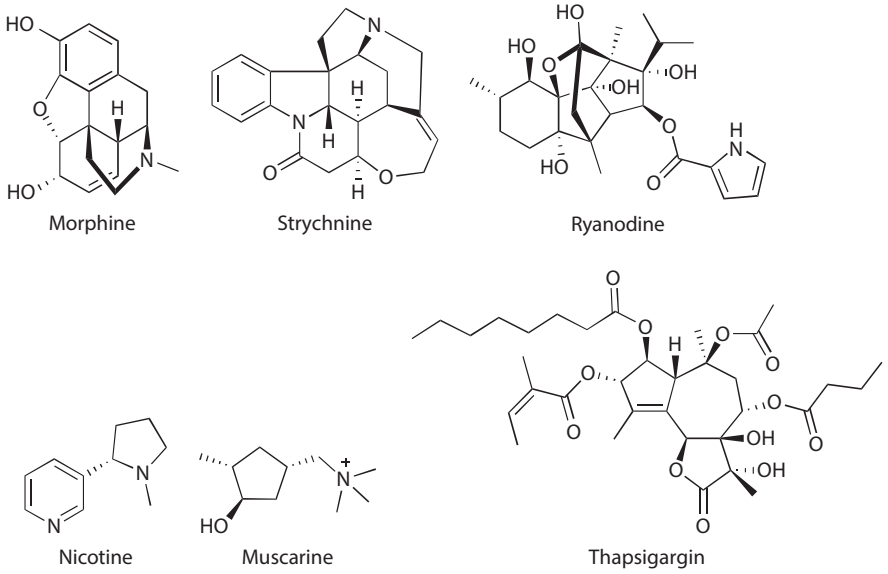


FIGURE 1.3 Chemical structures of morphine, strychnine, ryanodine, nicotine, muscarine, and thapsigargin.

The very toxic and convulsive alkaloid, strychnine, has been extensively studied pharmacologically. Using electrophysiological techniques and tritiated strychnine for binding studies, strychnine was shown to be an antagonist for the neuroreceptor mediating the inhibitory effect of glycine, through the $glycine_A$ receptor located primarily in the spinal cord.

Acetylcholine is a key transmitter in the central and the peripheral nervous system. Acetylcholine operates through multiple receptors, and the original demonstration of receptor heterogeneity was achieved using the naturally occurring compounds, nicotine and muscarine. Whereas the ionotropic class of acetylcholine receptors binds nicotine with high affinity and selectivity, muscarine specifically and potently activates the metabotropic class of these receptors. Using molecular biological techniques, a number of subtypes of both nicotinic and muscarinic acetylcholine receptors have been identified and characterized (Chapters 12 and 16).

The ryanodine receptor is named after the insecticidal naturally occurring compound, ryanodine. Extensive studies have disclosed that ryanodine interacts with high affinity and in a calcium-dependent manner with its receptor which functions as a calcium release channel. There are three genetically distinct isoforms of the ryanodine receptor which play a role in the skeletal muscle disorder, central core disease.

The sesquiterpene lactone, thapsigargin which is structurally unrelated to ryanodine, also interacts with an intracellular calcium mechanism. Thapsigargin has become the key pharmacological tool for the characterization of the sarco(endo)plasmic reticulum Ca^{2+} ATPase (SERCA). Thapsigargin effectively inhibits this ATPase, causing a rise in the cytosolic calcium level which eventually leads to cell death. Although the SERCA pump is essential for all cell types, attempts to target thapsigargin toward prostate cancer cells have been made based on a prodrug approach (see Chapter 10).

1.4.2 Natural Products as Lead Structures

Although a number of biologically active natural products have been indispensable as tools for identification and characterization of pharmacological and potential therapeutic targets, these compounds normally do not satisfy the demands on drugs for therapeutic use (Chapter 7).

Thus, although morphine is used therapeutically, it is not an ideal drug and has, to some extent, been replaced by a number of analogs showing lower side effects and higher degrees of selectivity for subtypes of opiate receptors (Chapter 19). Prominent examples are the μ-selective opiate agonist fentanyl and the experimental tool U50,488 which selectively activates the κ-subtype of opiate receptors (Figure 1.4).

The main psychoactive constituent of *Cannabis sativa*, the highly lipophilic tetrahydrocannabinol (THC), has been a useful tool for the identification of the two cannabinoid receptors, CB1 and CB2 receptors, operated by endocannabinoids. Since different preparations of *C. sativa* have psychoactive effects, health authorities in most countries have been reluctant to accept THC and analogs as therapeutic agents for the treatment of pain and other disease-related conditions. This may change with time, as medicinal chemists have synthesized a number of cannabinoid receptor ligands, including the receptor agonist CP55,940 which is markedly less lipophilic than THC (Chapter 19).

The nicotine acetylcholine receptors (nAChRs) have become important targets for therapeutic approaches to treat pain, cognition disorders, depression, schizophrenia, and nicotine dependence. For several reasons, nicotine has limited utility as a therapeutic agent, and a wide variety of nAChR agonists have been synthesized and characterized (Chapter 16). (–)-Cytisine is a naturally occurring toxin acting as a partial nAChR agonist. Using (–)-cytisine as a lead structure, varenicline was developed as a partial nAChR agonist showing a balanced agonist/antagonist profile for smoking cessation. Muscimol is another example of a naturally occurring toxin which has been extensively used as a lead for the design of specific GABA receptor agonists and GABA uptake inhibitors (Chapter 15). Muscimol which is a 3-isoxazolol bioisostere (see Section 1.4.3.1) of GABA, is a

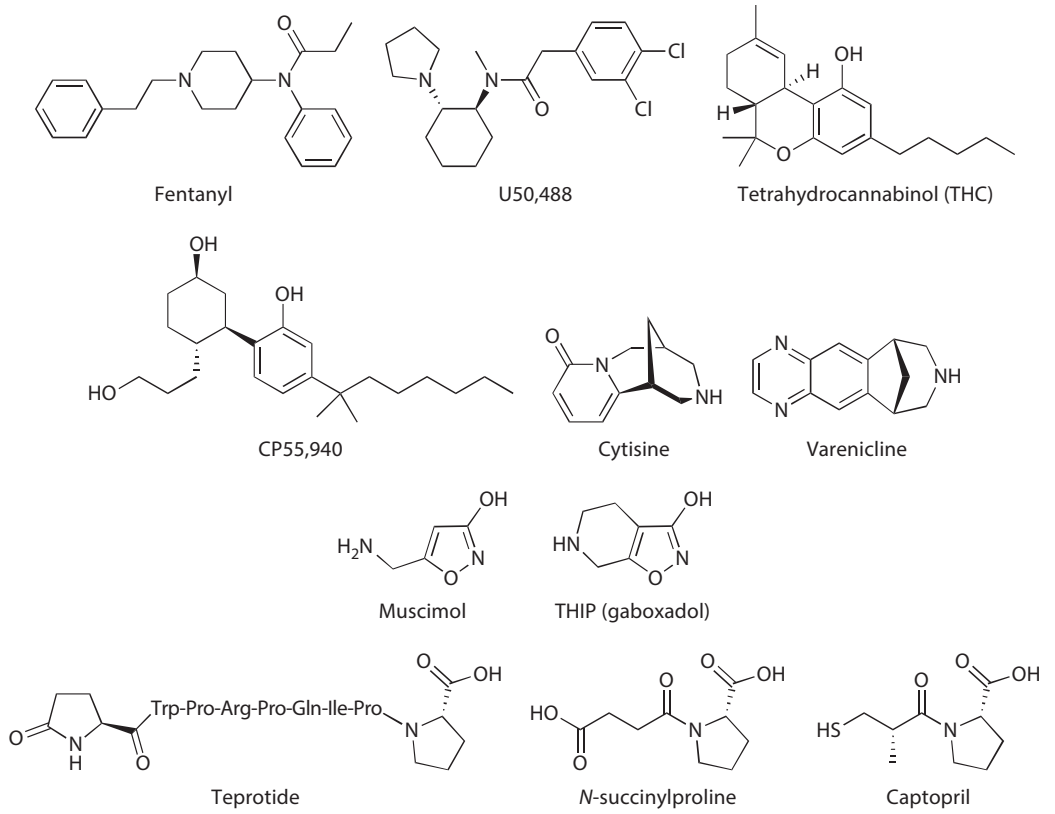


FIGURE 1.4 Chemical structures of fentanyl, U50,488, tetrahydrocannabinol (THC), CP55,940, cytisine, varenicline, muscimol, THIP (gaboxadol), teprotide, *N*-succinylproline, and captopril.

constituent of the mushroom *Amanita muscaria*. Muscimol is toxic, it is metabolically unstable, and it interacts with the different GABA synaptic mechanisms and with a broad range of $GABA_A$ receptor subtypes. The cyclic analog of muscimol, THIP (gaboxadol), is highly selective for the therapeutically interesting extrasynaptic $GABA_A$ receptors. Gaboxadol is a clinically active nonopioid analgesic and a nonbenzodiazepine hypnotic which at present is in clinical trials (see also Chapter 15).

The angiotensin-converting enzyme (ACE) is a zinc carboxypeptidase centrally involved in the regulation of blood pressure and is an important target for therapeutic intervention. Peptide toxins from the Brazilian pit viper, *Bothrops jararaca*, and the synthetic peptide analog, teprotide, are inhibitors of ACE (Figure 1.4), but are not suitable for therapeutic use. Systematic molecular dissection of teprotide led to the nonpeptide ACE inhibitor, *N*-succinylproline which was converted into the structurally related and much more potent analog, captopril, that is now marketed as an effective antihypertensive drug.

1.4.3 Basic Principles in Lead Development and Optimization

Potency, efficacy, and selectivity are essential but certainly not the only parameters to fulfill for a pharmacologically active compound to become a therapeutic drug. A large number of additional requirements have to be met, and the most important ones have been summarized in the acronym, ADME or ADME-Tox (ADME and toxicity). Obviously, the drug must reach the site of action in a timely manner and in sufficient concentration to produce the desired therapeutic effect.

After oral administration, one of many routes of administration, the drug must survive the acidic environment of the stomach. In the small intestine, the bulk of absorption takes place. Here, the pH is neutral to slightly acidic. In the gastrointestinal system metabolism can take place. The presence of digestive enzymes creates particular problems for polypeptide drugs which may call for other routes of administration, as the gut wall is rich in oxidative enzymes.

Unless the drug acts as a substrate for active energy-requiring uptake mechanisms which normally facilitate uptake of, for example, amino acids and glucose, it must be significantly unionized to penetrate cell membranes in order to enter the blood stream. Following absorption, the blood rapidly presents the drug to the liver, where Class I metabolic transformations (oxidation, hydrolysis, reduction, etc.) and in some cases phase II transformations (glucuronidation, sulfation, etc.) take place. The polar reaction products from these reactions are typically excreted in the urine or feces.

The rate of absorption of drugs, their degree of metabolic transformation, their distribution in the body, and their rate of excretion are collectively named pharmacokinetics. This is in effect the influence of the body on a drug as a function of time. The interaction of the drug with its targets, and the consequences of this interaction as a function of time are pharmacodynamics.

Both of these characteristics are alone governed by the drug's chemical structure. Thus, the medicinal chemist is expected to remedy any shortcomings by structural modification. In addition to ADME-Tox, a number of other characteristics must also be satisfactory, such as

- Freedom from mutagenesis
- Freedom from teratogenicity
- Chemical stability—shelf stability
- Synthetic or biological accessibility
- Acceptable cost
- Ability to patent
- Clinical efficacy
- Solubility
- Satisfactory taste (per oral administration)
- Ability to formulate satisfactorily for administration
- Freedom from idiosyncratic problems

A number of strategies are used by the medicinal chemists in order to optimize lead compounds in order to fulfill all these requirements related to optimization of desired activities and minimization of undesired effects:

- Variation of substituents—change of size, shape, and polarity
- Extension/contraction of structure—change chain size or ring size
- Ring closure/ring variation/ring fusion
- Simplification of structure
- Rigidification of structure

Examples of such modification are presented especially in Chapters 15 through 19, and generally these efforts aim toward optimizing the active conformation and physicochemical properties of the drugs with the essential and necessary pharmacophoric groups present. A very versatile principle for variation of molecules, functional groups, and substituents with focus on optimizing biological activity is the use of bioisosteres (see Section 1.4.3.1). Furthermore, stereochemical control of drug interactions with the chiral environment is essential as described in Section 1.4.3.2 and subsequent sections.

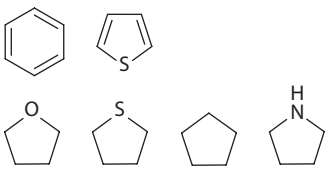
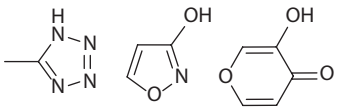
These challenges emphasize the key importance of scientists trained in interdisciplinary medicinal chemistry in drug discovery projects.

1.4.3.1 Bioisosteres

Bioisosteric replacement, also named molecular mimicry, is one of the most widely used principles for optimization of drug molecules. Bioisosteres are molecules in which atoms or functional groups are modified in order to obtain new molecules with a biological activity related to the parent molecule. The purpose is to obtain drug molecules with improved biological properties. Bioisosteric replacement can change a number of physicochemical properties of the resulting molecules compared to the parent molecule: size, shape, electronic distribution, solubility, pK_a, and chemical reactivity. These changes may lead to changes in the pharmacodynamics as well as pharmacokinetic properties, e.g., changes in potency, selectivity, bioavailability, and metabolism.

Bioisosteres have been classified as either classical or nonclassical. In classical bioisosterism, similarities in certain physicochemical properties have enabled investigators to successfully exploit several monovalent isosteres. These can be divided into the following groups: (1) fluorine versus hydrogen replacements; (2) amino-hydroxyl interchanges; (3) thiol-hydroxyl interchanges; and (4) fluorine, hydroxyl, amino, and methyl group interchanges (Grimm's hydride displacement law, referring to the different number of hydrogen atoms in the isosteric groups to compensate for valence differences). The nonclassical bioisosteres include all those replacements that are not defined by the classical definition of bioisosteres. These isosteres are capable of maintaining similar biological activity by mimicking the spatial arrangement, electronic properties, or some other physicochemical properties of the molecule or functional group that are of critical importance. A number of classical and nonclassical bioisosteres are shown in Table 1.1 representing only a selection of more commonly used bioisosteres. The concept of nonclassical bioisosterism, in particular,

TABLE 1.1
Examples of Bioisosteric Replacements

Classical	
Monovalent	—F —OH —NH_2 —CH_3 —Cl —SH
atoms and groups	—Br —*i*—Pr
	—I —*t*—Bu
Bivalent	—CH_2— —O— —S— —Se— —NH—
atoms and groups	—$COCH_2R$ —CONHR —COOR —COSR
Trivalent	—N= —P= —CH= —As=
atoms and groups	
Ring equivalents	
Nonclassical	
Hydroxyl group	—OH —CH_2OH —NHCOR —$NHSO_2R$ —$NHCONH_2$
Carbonyl group	CO C=C$(CN)_2$ —SO_2NRR' CONRR′ =CHCN
Carboxylic acid	—COOH —SO_2NHR —SO_2OH —PO_3H_2 —CONHOH
	
Halogen	—X —CF_3 —CN —$N(CN)_2$ —$C(CN)_3$
Spacer group	—$(CH_2)_3$—