CHAPTER

1

Medicinal Chemistry: Definitions and Objectives, Drug Activity Phases, Drug Classification Systems

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OUTLINE

Medicinal chemistry remains a challenging science which provides profound satisfaction to its practitioners. It intrigues those of us who like to solve problems posed by nature. It verges increasingly on biochemistry and on all the physical, genetic and chemical riddles in animal physiology which bear on medicine. Medicinal chemists have a chance to participate in the fundamentals of prevention, therapy and understanding of diseases and thereby to contribute to a healthier and happier life. **A Burger** [1]

I. DEFINITIONS AND OBJECTIVES

A. Medicinal Chemistry and Related Disciplines and Terms

A definition of medicinal chemistry was given by a IUPAC specialized commission: "*Medicinal chemistry* concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level. Emphasis is put on drugs, but the interests of the medicinal chemist are not restricted to drugs but include bioactive compounds in general. Medicinal chemistry is also concerned with the study, identification, and synthesis of the metabolic products of these drugs and related compounds" [2].

Drugs—natural and synthetic alike—are chemicals used for medicinal purposes. They interact with complex chemical systems of humans or animals. Medicinal chemistry is concerned with this interaction, focusing on the organic and biochemical reactions of drug substances with their targets. This is one aspect of drug chemistry.

Other important aspects are the synthesis and the analysis of drug substances. The two latter aspects together are sometimes called *pharmaceutical chemistry*, but the synthesis of drugs is considered by some people—mainly chemists—to be part of medicinal chemistry, denoting analytical aspects as pharmaceutical chemistry. In German faculties of pharmacy, the literal translations of pharmaceutical and medicinal chemistry—Pharmazeutische and Medizinische Chemie—are used synonymously.

The general study of drugs is called *pharmacy* or *pharmacology*. A common narrower definition of pharmacology concentrates on the fate and effects of a drug in the body. *Clinical chemistry*, a different subject, is concerned with the determination of physiological and pathophysiological parameters in body fluids, such as enzyme activities and metabolites in blood and urine. The term *biopharmacy* has been reserved for the investigation and control of absorption, distribution, metabolism, excretion, and toxicology (ADMET) of drug substances.

Some further terms are more or less synonymous with medicinal chemistry: *(molecular) pharmacochemistry, drug design, selective toxicity*. The French equivalent to medicinal chemistry is chimie thérapeutique, and the German terms are Medizinische/Pharmazeutische Chemie and Arzneimittelforschung.

In academia, medicinal chemistry is a major subject in most pharmacy faculties—both for undergraduates and in research—and in many chemistry faculties. In the pharmaceutical industry, medicinal chemistry is at the heart of the search for new medicines.

The main activities of medicinal chemists are evident in the analysis of their most important scientific journals (e.g., *Journal of Medicinal Chemistry, European Journal of Medicinal Chemistry, Bioorganic and Medicinal Chemistry, ChemMedChem, Archiv der Pharmazie, Arzneimittelforschung, Chemical and Pharmaceutical Bulletin*).

The *objectives of medicinal chemistry* are as easily formulated as they are difficult to achieve: find, develop, and improve drug substances that cure or alleviate diseases (see below, Section I.C.) and understand the causative and accompanying chemical processes (see below, Section III.A).

Medicinal chemistry is an interdisciplinary science covering a particularly wide domain situated at the interface of organic chemistry with life sciences such as biochemistry, pharmacology, molecular biology, genetics, immunology, pharmacokinetics, and toxicology on one side, and chemistry-based disciplines such as physical chemistry, crystallography, spectroscopy, and computer-based techniques of simulation, data analysis, and data visualization on the other side.

B. Drugs and Drug Substances

Drugs are composed of *drug substances* (syn. *active pharmaceutical ingredients, APIs*) and *excipients* (syn. *ancillary substances*). The combination of both is the work of pharmaceutical technology (syn. *galenics*) and denoted a *formulation*.

In 2014, the World Drug Index contained over 80,000 marketed and development drug substances [3]. The United States *Orange Book* listed approx. 3,500 products in 2014, and the United States Pharmacopeia contains monographs of approx. 1,400 small-molecules Active Pharmaceutical Ingredients (APIs) and 160 biologic drug substances [4]. In 2013 in Germany, the "Rote Liste" contained approximately 6,000 drugs in 7,500 formulations representing approximately 2,000 APIs [5]. The WHO Essential Medicines List held approximately 350 drug substances in 2013 that WHO claims sufficient for the treatment of approx. 90 percent of all diseases where drugs are useful [6].

What makes a chemical "drug-like?" Because of the versatility of their molecular targets (see below), there can be no universal characteristic of drug substances. However, since the general structure of the target organisms is identical, generalizations as to drug substance structure are possible for biopharmacy [7,8]. For a chemical to be readily absorbed by the gut and distributed in the body, its size, hydrophilicity/lipophilicity ratio, stability toward acid media and hydrolytical enzymes, etc. have to meet defined physicochemical criteria. A careful analysis of reasons for drug attrition revealed that only 5 percent were caused by pharmacokinetic difficulties, whereas 46 percent were due to insufficient efficacy and 33 percent to adverse reactions in animals or humans [9]. Since both wanted and unwanted effects are due to the biological activity, 79 percent of drug candidates had unpredicted or wrongly predicted sum activities.

Predictions of toxicity from molecular features are still precarious [10–12]. Only rather general rules are for sure; such as avoidance of very reactive functional groups, for example, aldehyde because of oxidative instability and haptene nature; α,β-unsaturated carbonyl compounds and 2-halopyridines because of their unspecific reactivity as electrophiles. Torcetrapib is a typical example of toxicity—or adverse effects—challenges. It was an antiatherosclerotic drug candidate promising to become a blockbuster when in latter phase III of clinical trials, an increased risk of mortality led the company to discontinue its development. It was not clear whether the effects

were caused by the mechanism of action—inhibition of cholesteryl ester transfer protein—some other effect or an interaction with another drug. This is just one instance that "it isn't that simple [and] nothing's obvious and nothing's for certain" in rational drug development [13].

C. Stages of Drug Development

Most drugs were discovered rather than developed [14]. That is why a large number of drug substances are natural products or derivatives thereof. It is a matter of debate if ethnic medicines or nature still hold gems as yet undiscovered by pharmacy [15,16]. Synthetic substance collections ("libraries") have been created through (automated) organic chemistry. The very high number and diversity of natural and synthetic chemical entities is faced with an equally growing number of potential reaction partners (targets) from biochemical and pathophysiological research.

In virtual, biochemical and cell-based testing, compound selections are run against an isolated or physiologically embedded target that may be involved in the disease process [17]. Compounds that exceed a certain threshold value in binding to the target or modulation of some functional signal behind it, are called *hits*. If the identity and purity of the compound and the assay result are confirmed in a multipoint activity determination, the compound rises to the status of *validated hit*. From this one hopes to develop leads. A *lead* is a compound or series of compounds with proven activity and selectivity in a screen and fulfills some drug development criteria such as originality, patentability, and accessibility (by extraction or synthesis). Molecular variation hopefully tunes the physicochemical parameters so that it becomes suitable for ADME. An example of a small optimization algorithm is shown in Figure 1.1.

If the resulting *optimized lead* (*preclinical candidate*) displays no toxicity in cell and animal models, it becomes a *clinical candidate*. If this stands the tests of efficacy and safety in humans and overcomes marketing hurdles, a *new drug entity* will enter the treasure trove of pharmacy. Box 1.1 illustrates that activity is a necessary but not sufficient quality of medicines. There is, of course, no ideal drug in the real world, but one has to find a relative optimum. This often means developing a drug that has a different side-effect profile than drugs marketed for the same therapeutic indication so prescriptions can be tailored to the ways different patients react to a drug.

The role of medicinal chemistry is most prominent in steps one and two of drug development:

1. The discovery step, consisting of the choice of the therapeutic target (biochemical, cellular, or *in vivo* model; see below) and the identification or discovery and production of new active substances interacting with the selected target.
2. The optimization step that deals with the improvement of an active compound. The optimization process primarily takes into account the increase in potency, selectivity, and decrease in toxicity. Its characteristics are the establishment of structure–activity relationships, ideally based on an understanding of the molecular mode of action.

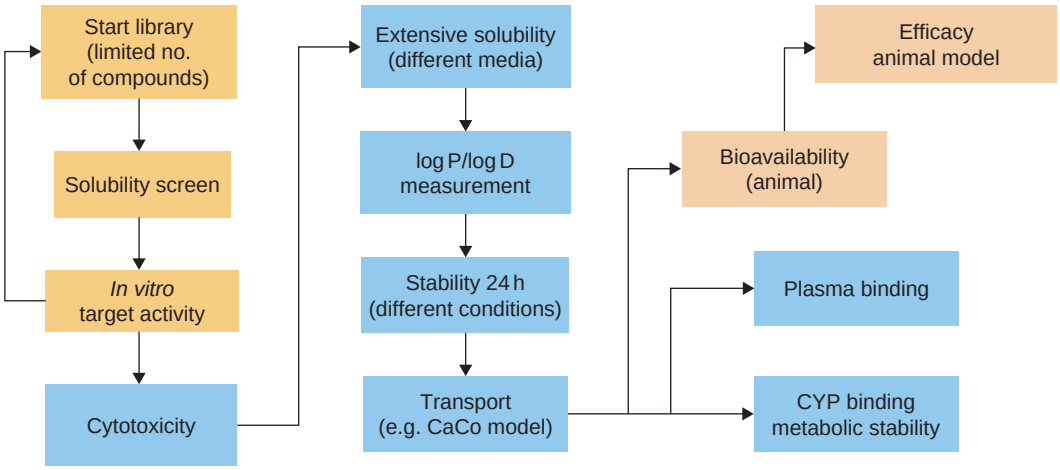

FIGURE 1.1 Example of an optimization algorithm. *Source: Adapted from a presentation by Dr. U. Heiser, Probiodrug AG, Halle, Germany, reproduced with permission.*

3. The formulation step, whose purpose is the continuation of the improvement of the pharmacokinetic properties and the fine-tuning of the pharmaceutic properties of active substances to render them suitable for clinical use. This can consist—to name just a few instances—of the preparation of better absorbed compounds, of sustained release formulations, and of water-soluble derivatives or in the elimination of properties related to the patient's compliance (irritation, painful injection, undesirable organoleptic properties). For an example, see Figure 1.2.

The main tasks of medicinal chemistry consist of the optimization of the following characteristics:

a. Higher affinity and target-intrinsic activation for better clinical activity so the dosage and nonspecific side effects will be as low as possible. There are no examples of drugs that are dosed below 10 mg/day that cause idiosyncratic adverse drug reactions. For drug substances that have to be given in higher doses—i.e., the majority—medicinal chemistry tries to find active derivatives that will be metabolized in a safe way [18]. This includes assaying for inhibition of or reaction with key enzymes of biotransformation, such as oxidases of the cytochrome type, some of which are highly demanded by food constituents and xenobiotics including drug substances [19]. Medicinal chemistry tries to prepare drugs that are not metabolized by bottleneck enzymic pathways [20].

b. Better selectivity, which may lead to a reduction of unwanted side effects. This sometimes entails the assaying of a very high number of other targets; for example, an antidepressive serotonin re-uptake inhibitor has to be tested against all subtypes of serotonin, adrenaline, and dopamine receptors, plus many other key receptors and enzymes.

BOX 1.1

THE IDEAL NEW DRUG SUBSTANCE

- New chemical entity for patentability and registration.
- Maximum four-step synthesis with, for example, no heavy metal catalysts and no environmentally problematic waste; no chromatographic purification steps; purity>99 percent.
- Stable up to 70°C even in humid air and light.
- Solid-state properties (crystalline, not polymorphous, not hygroscopic) that make it a perfect partner for (tablet) compaction.
- Solubility in water sufficient for the production of stable blood-isotonic solutions.
- Oral bioavailability .90 percent with no interindividual variation.
- Very high activity and pharmacokinetic profile enable once-a-day-dosage at 5–10 mg.

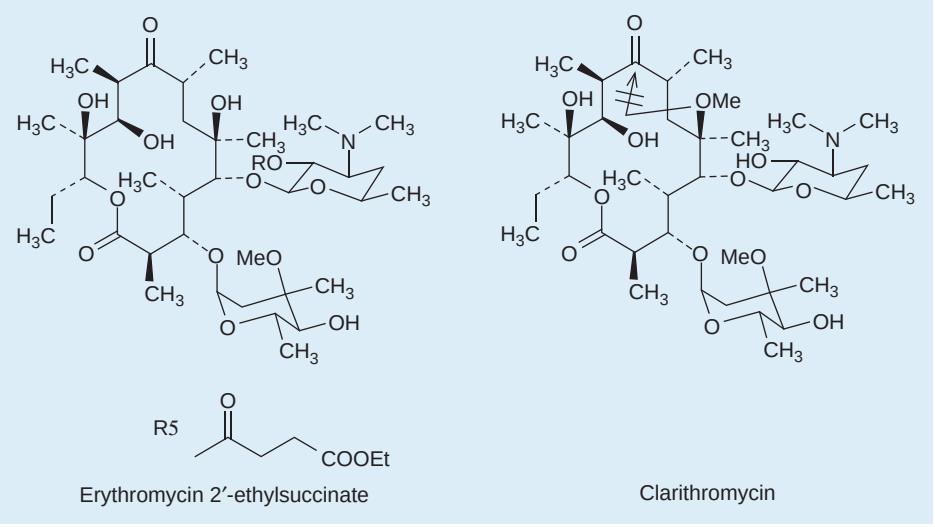

FIGURE 1.2 An example of fine-tuning of pharmacologically active chemicals: Erythromycin 29-ethylsuccinate and clarithromycin are semisynthetic derivatives of the macrolide antiinfective erythromycin. The small molecular change in the former leads to the elimination of bitterness which is important as this class of drugs is often used in pediatrics and administered as a syrup. In the latter, because hemiketal formation is no longer possible (arrow), clarithromycin is stable in the acidic milieu of the stomach (pH 2).

In spite of the high number of compounds, targets, and assays, the development pipeline of new chemical entities as drug substances has not got fuller in the past 20 years. For possible explanations, see the discussion of drug targets below and Ref. [9].

II. DRUG ACTIVITY PHASES

The progression of a drug into the body, to its target(s), and out again can be broken down into three mechanistically distinct phases, the second and third being partly simultaneous. During drug development, all three phases are investigated interdependently, because structural changes required for one phase must not abolish suitability in another phase.

A. The Pharmaceutical Phase

Drug substances are applied orally (preferred mode) or parenterally (e.g., by subcutaneous or intravenous injection, rectally, or through inhalation). A combination of the skills of medicinal chemists and pharmaceutical technologists has to provide the drug candidate in suitable formulations. For tablets, the drug substance needs to be crystalline and not have a low melting point. For injections, it should be water soluble (e.g., as a salt). The required structural features must be compatible with the pharmacological activity, of course.

B. The Pharmacokinetic Phase

For this phase, medicinal chemists and biopharmacists work together to design a compound that will have suitable ADME parameters. Sufficient solubility in an aqueous medium for absorption and blood transport has to be combined with sufficient lipophilicity for passage through cell membranes. If an active compound is too hydrophilic and at the same time contains a carboxylic acid group, for instance, conversion to a simple ester will facilitate absorption. Once in the blood, unspecific esterases will catalyze hydrolysis to the active carboxylic acid form. Such an ester is an instance of a *prodrug*.

Drug substances should remain active and in the body for a period of time that is neither too short nor too long. For many drugs, a metabolic and/or excretion rate that enables "once a day" dosage is sought. Sometimes this requires the identification of sites in the molecule that will be metabolized quickly with concomitant loss of activity. The vasodilator iloprost, for instance, was developed from the endogeneous mediator prostacyclin that has very short half-life both *in vivo* and on the shelf. Modification of several chemically and metabolically vulnerable positions yielded a stable and active derivative—a highly sophisticated product of synthetic medicinal chemistry (Figure 1.3) [21]. By contrast, sometimes functionality is introduced for the acceleration of biotransformation and excretion. Articaine is a local anesthetic of the anilide type. Systemically, it interferes with heart rate—an unwelcome side effect in dentistry. That is why articaine contains an additional ester group. Once in the blood stream, this will be hydrolyzed quickly to an inactive carboxylic acid (Figure 1.4) [22]. Medicinal chemistry here has come full circle, as anilide local anesthetics were developed from ester anesthetics like procain in order to prolong activity.

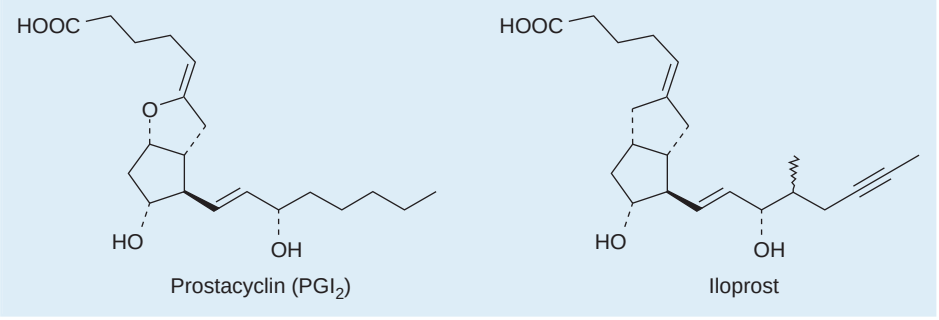

FIGURE 1.3 Prostacyclin and its synthetic analog, iloprost, that combines activity with sufficient *ex vivo* and *in vivo* stability.

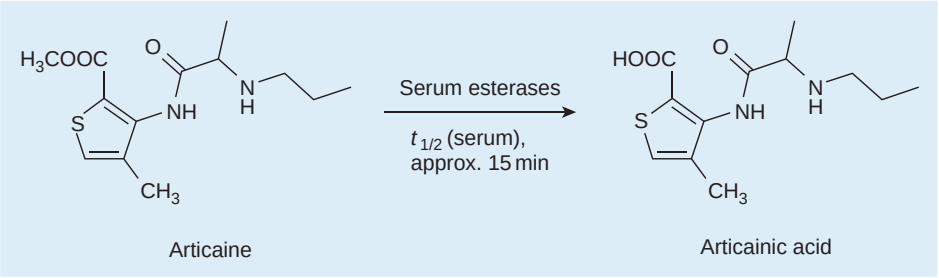

FIGURE 1.4 Articaine, a common local anesthetic dentists use, and its inactive metabolite that is formed off the scene of painful action. The value for $t_{1/2}$ is from the reference Oertel R, Ebert U, Rahn R, Kirch W. The effect of age on pharmacokinetics of the local anesthetic drug articaine. Reg Anesth Pain Med 1999;24:524–8.

C. The Pharmacodynamic Phase

While pharmacokinetics investigates what the body does to the drug, pharmacodynamics is concerned with what the drug does to the body. Most scientists who consider themselves medicinal chemists will be most comfortable with and interested in this phase. They will cooperate with biochemists and pharmacologists to elucidate mechanistic details of the interaction of the drug with its target(s), a topic we will treat in the Section III.

D. The Road to Successful Drug Development?

In the past years, many analyses have appeared that try to explain the dearth of new drug substances in the face of billions of dollars that have been spent, billions of assay data points that have been accumulated, and ten thousands of virtual and thousands of real hits that have been generated. By comparison, the Belgian medicinal chemist Paul Janssen and his relatively small group had tremendous success in the development of new drug entities and activities [23]. It was postulated that the individualization rather than integration of research guidelines into successive hypes (e.g., "as target subtype selective as possible"; "ADME rules have to be strictly adhered to"; "modeling programs automatically give a correct representation of molecules"; "the more combinatorial ligands, the more hits") is responsible for the disappointing state of drug discovery. What is needed is to keep what we already know about how successful drugs were actually discovered or invented [24], while providing an atmosphere of creativity in a team of scientists from various disciplines. Summarizing their long-lasting experiences in antibacterial research, an industrial team concluded that for this therapeutic area at least, synthesizing novel chemical structures that interact with and block *established* targets in new ways is a robust strategy [24,25].

So what does the increasing knowledge of targets mean for medicinal chemistry? This subject will be introduced in the following paragraphs and discussed in detail in later chapters.

III. DRUG CLASSIFICATION SYSTEMS

Classification systems help with understanding what a drug actually does at the molecular level (classification by target), and they are indispensable for categorizing the large number of drug substances (classification by clinical effect).

A. Classification by Target and Mechanism of Action

1. Targets

Targets are molecular structures, chemically definable by at least a molecular mass, that will undergo a specific interaction with chemicals that we call drugs because they are administered to treat or diagnose a disease [26]. To be meaningful, the interaction has to have a connection with the clinical effect(s). It is very challenging to prove that the interaction of a drug substance with a specific molecular target indeed triggers the clinical effect(s).

A clinically relevant target might consist not of a single biochemical entity but the simultaneous interference of a number of receptors. Only this multi-target interaction will give a net clinical effect that might be considered beneficial. It is only by chance that the current *in vitro* screening techniques will identify drugs that work through such targets.

The number of targets presently used is still open to discussion in medicinal chemistry, but various approaches concurred in finding several hundred. The number of potential targets, however, was estimated to be

several hundred thousand in view of the manifold protein complexes, splicing variants, and possible interventions with signaling pathways [26,27]. The problem with counting is two-fold: first, the identification of the reaction partners of drug substances in the body; and second, exactly what to define and count as the target. A target definition derived from the net effect rather than the direct chemical interaction will require input from systems biology, a research field that promises to affect the drug discovery process significantly [28]. At the other end of the scale of precision, we can define some targets very precisely on the molecular level. For example, we can say that dihydropyridines block the CaV1.2a splicing variant in heart muscle cells of L-type high-voltage activated calcium channels.

The actual depth of detail used to define the target is primarily dependent on the amount of knowledge available about the target and its interactions with a drug. Even if the target structure has already been determined, the molecular effect of the drug could still not be fully described by the interactions with one target protein alone. For example, antibacterial oxazolidinones interact with 23S-rRNA, tRNA, and two polypeptides, ultimately leading to inhibition of protein synthesis [29]. In this case, a description of the mechanism of action that only includes interactions with the 23S-rRNA target would be too narrowly defined. In particular, in situations in which the dynamic actions of the drug substance stimulate or inhibit a biological process, it is necessary to move away from the description of single proteins, receptors and other targets to view the entire signal chain as the target. and so on to view the entire signal chain as the target.

Lists that classify all marketed drug substances according to target, with references, were published. An excerpt is given in Table 1.1 [26].

2. *Mechanisms of Action*

An effective drug target comprises a biochemical system rather than a single molecule. Present target definitions are static. We know this to be insufficient, but techniques to observe the dynamics of drug–target interactions are just being created. Most importantly, we are not able to gauge the interaction of the biochemical "ripples" that follow the drug's initial molecular effect. The first molecular step of drug activity consists in mass-action governed drug–target recognition. For clinically observable activity, a series of biochemical steps need to follow that have to shift physiological equilibria in a transient way. Indeed, the gap between chain and circles of molecular events and clinical effects is still wide open, as reflected by the complementarity of target and phenotypic-oriented drug discovery approaches [30].

Although the term "mechanism of action" itself implies a classification according to the dynamics of drug substance effects at the molecular level, the dynamics of these interactions are only speculative models at present, and so mechanism of action can currently only be used to describe static targets, as discussed above.

All drugs somehow interfere with signal transduction, receptor signaling, and biochemical equilibria. For many drugs we know—and for most we suspect—that they interact with more than one target. So there will be simultaneous changes in several biochemical signals, and there will be feedback reactions of the pathways disturbed. In most cases, the net result will not be linearly deducible from single effects. For drug combinations, this is even more complicated. Awareness is also increasing of the nonlinear correlation of molecular interactions and clinical effects. For example, the importance of receptor–receptor interactions (receptor mosaics) was summarized for G-protein-coupled receptors (GPCRs), resulting in the hypothesis that cooperativity is important for the decoding of signals, including drug signals [31]. Table 1.2 lists examples of dynamic molecular mechanisms of drugs. Table 1.1 is the excerpt of an attempt at a complete list of drug targets. Notably, inhibitors and antagonists by far outnumber effectors, agonists, and substitutes. It appears that reconstitution of biochemical and pharmacological balances is more easily achieved by blocking excessive or complementary pathways rather than by substitution or repair of deficient or defective biochemical input.

Greater knowledge of how drugs interact with the body (e.g., mechanisms of action, drug–target interactions) has led to a reduction of established drug doses and inspired the development of newer, highly specific drug substances with a known mechanism of action. However, a preoccupation with the molecular details has resulted in a tendency to focus only on this one aspect of the drug effects. For example, cumulative evidence suggests that the proven influence of certain psychopharmaceuticals on neurotransmitter metabolism has little to do with the treatment of schizophrenia or the effectiveness of the drug for this indication [32]. With all our efforts to understand the molecular basis of drug action, we must not fall into the trap of reductionism. For antibacterial research, multitargeting is now considered to be essential [33]. More generally, in recent years the limits of the reductionist approach in drug discovery have become painfully clear. Nobel laureate Roald Hoffmann put it this way: "Chemistry reduced to its simplest terms, is not physics. Medicine is not chemistry … knowledge of the specific physiological and eventually molecular sequence of events does not help us understand what [a] poet has to say to us" [34]. The cartoon (Figure 1.5) illustrates this point. Although it is too early for systems biology

TABLE 1.1 The Main Drug Target Classes with Examples of Targets and Ligands. A Full List Can Be Found in Ref. [26]

Target class	Target subclass	Target example	Drug substance example (activity)
Enzymes	Oxidoreductases	Aldehyde dehydrogenase	Disulfiram (inhibitor)
	Transferases	Protein kinase C	Miltefosine (inhibitor)
	Hydrolases	Bacterial serine protease	β-Lactams (inhibitors)
	Lyases	DOPA decarboxylase	Carbidopa (inhibitor)
	Isomerases	Alanine racemase	D-cycloserine (inhibitor)
	Ligases (syn. synthases)	Dihydropteroate synthase	Sulphonamides (inhibitors)
Proteins	Growth factors	Vascular endothelial growth factor	Bevacizumab (antibody)
	Immunoglobulins	CD3	Muromonab-CD3 (antibody)
	Integrins	α4-Integrin subunit	Natalizumab (antibody)
	Tubulin	Human spindle	Vinca alkaloids (development inhibitors)
Substrates, metabolites	Substrate	Asparagine	Asparaginase (enhanced degradation)
	Metabolite	Urate	Rasburicase (enhanced degradation)
Receptors	Direct ligand-gated ion channel receptors	γ-Aminobutyric-acid (GABA)-	Barbiturates (allosteric agonists)
	G-protein-coupled receptors	Acetylcholine receptors	Pilocarpine (muscarinic receptor agonist)
		Opioid receptors	
		Prostanoid receptors	Buprenorphine (κ-opioid antagonist)
			Misoprostol (agonist)
	Cytokine receptors	TNFα receptors	Etanercept (receptor mimic)
	Integrin receptors	Glycoprotein IIb/IIIa receptor	Tirofiban (antagonist)
	Receptors associated with a tyrosine kinase	Insulin receptor	Insulin (agonist)
	Nuclear receptors, steroid hormone receptors	Mineralocorticoid receptor	Aldosterone (agonist)
	Nuclear receptors, other	Retinoic acid receptors	Isotretinoin (RARα agonist)
Ion channels	Voltage-gated Ca^{2+} channels	L-type channels	Dihydropyridines (inhibitors)
	K^+ channels	Epithelial K^+ channels	Diazoxide (opener)
	Na^+ channels	Voltage-gated Na^+ channels	Carbamazepine (inhibitor)
	Ryanodine-inositol 1,4,5-triphosphate receptor Ca^{2+} channel	Ryanodine receptors	Dantrolene (inhibitor)
	Transient receptor potential Ca^{2+} channel	TRPV1 receptors	Acetaminophen metabolite (inhibitor)
	Chloride channels	Mast cell chloride channels	Cromolyn sodium (inhibitor)
Transport proteins	Cation-chloride cotransporter family	Thiazide-sensitive NaCl symporter	Thiazide diuretics (inhibitors)
	Na^+/H^+ antiporters		Amiloride (inhibitor)
	Proton pumps	H^+/K^+ ATPase	Omeprazole (inhibitor)
	Eukaryotic (putative) sterol transporter (EST) family	Niemann-Pick C1 like 1 protein	Ezetimibe (inhibitor)
	Neurotransmitter/Na^+ symporter family	Serotonin/Na^+ symporter	Paroxetine (inhibitor)

(*Continued*)

TABLE 1.1 (Continued)

Target class	Target subclass	Target example	Drug substance example (activity)
DNA, RNA	Nucleic acids	Bacterial 16S-RNA	Aminoglycosides (protein synthesis inhibition)
	Ribosome	Bacterial 30S subunit	Tetracyclines (protein synthesis inhibition)
Physicochemical mechanism	Ion exchange	Hydroxide	Fluoride (enhanced acid stability of adamantine)
	Acid binding	In stomach	Hydrotalcite
	Adsorptive	In gut	Charcoal
	Surface-active	On oral mucosa	Chlorhexidine (disinfectant)
	Oxidative	On skin	Permanganate (disinfectant)
	Reductive	Disulphide bonds	*N*-acetylcysteine (mucolytic)
	Osmotically active	In gut	Lactulose (laxative)

TABLE 1.2 Examples of Dynamic (Process) Mechanisms of Drug Action

Dynamic mechanism	Example
Covalent modifications of the active center	Acylation of bacterial transpeptidases by β-lactam antibiotics
Drugs that require the receptor to adopt a certain conformation for binding and inhibition	Trapping of K^+ channels by methanesulphonanilide antiarrhythmic agents
Drugs that exert their effect indirectly and require a functional background	The catechol *O*-methyltransferase inhibitor entacapone, the effect of which is due to the accumulation of nonmetabolized dopamine
Anti-infectives that require the target organism to be in an active, growing state	β-Lactam antibacterials
Molecules requiring activation (prodrugs)	Enalaprilate, paracetamol
Modifications of a substrate or cofactor	Asparaginase, which depletes tumour cells of asparagine;[a] isoniazide, which is activated by mycobacteria leading to an inactive covalently modified NADH[b]
Simultaneous modulation of several signaling systems	GPCR receptor mosaics for the decoding of drug signals
Fluctuations of physiological signaling molecules	Dopamine fluctuations after administration of cocaine, followed by a gradual increase in steady state dopamine concentration[c]

[a]*Graham ML. Pegaspargase: a review of clinical studies. Adv Drug Deliv Rev 2003;55:1293–302.*
[b]*Larsen MH, Vilchèze C, Kremer L, Besra GS, Parsons L, Salfinger M, et al. Overexpression of inhA, but not kasA, confers resistance to isoniazid and ethionamide in Mycobacterium smegmatis, M. bovis BCG, and M. tuberculosis. Mol Microbiol 2002;46:453–66.*
[c]*Heien ML, Khan AS, Ariansen JL, Cheer JF, Phillips PE, Wassum KM, et al. Real-time measurement of dopamine fluctuations after cocaine in the brain of behaving rats. Proc Natl Acad Sci USA 2005;102:10023–8.*

to provide clear-cut protocols for medicinal chemistry, translational medicine [35] and other integrative research efforts stress the functional as opposed to reductionist character of living systems, hopefully improving the success rate of drug research [36].

B. Other Classification Systems

From a pharmaceutical standpoint, many different criteria can be used to classify medications: type of formulation, the frequency with which it is prescribed or recommended, price, refundibility, prescription or nonprescription medication, etc. If a classification of the APIs is undertaken, numerous possibilities are revealed as well. At the end of the 19th century, drug substances were classified the same as other chemical entities: by nature of their primary elements, functional moieties, or organic substance class. Recently, the idea of classifying drug substances strictly according to their chemical constitution or structure has been revived. Databases attempt to gather

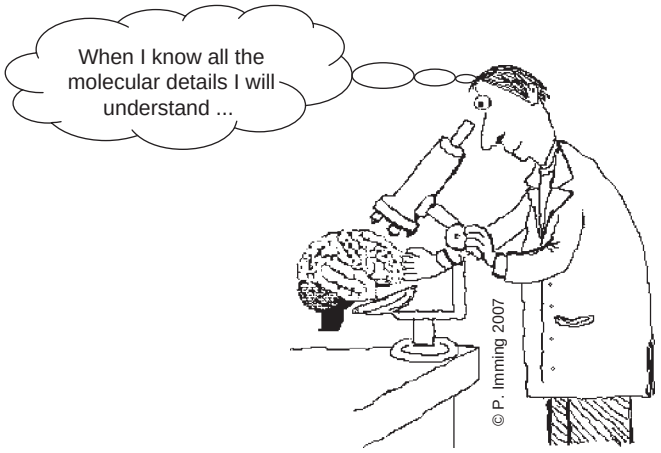

FIGURE 1.5 Searching for molecular mechanisms … "The meaning of the message will not be found in the chemistry of the ink." Sperry R. Brain circuits and functions of the mind. Cambridge: Cambridge University Press; 1990. *Source: Roger Sperry, neurophysiologist, Nobel Prize in Medicine, 1981.*

and organize information on existing or potential drug substances according to their chemical structure and diversity. The objective is to create—virtual or real—substance or fragment "libraries" that contain pertinent information about possible ligands for new targets (e.g., an enzyme or receptor) of clinical interest [37,38], and, more importantly, to understand the systematics of molecular recognition (ligand−receptor) [39,40].

The most commonly used classification system for drug substances is the *ATC system* [41]. It was introduced in 1976 by the Nordic Council on Medicines as a method for carrying out drug utilization studies throughout Scandinavia. In 1981, the World Health Organization recommended the use of the ATC classification for all global drug utilization studies, and in 1982 founded the WHO Collaborating Centre for Drugs Statistics Methodology in Oslo to establish and develop the method. The ATC system categorizes drug substances at five different levels according to (1) the organ or system on which they act (anatomy), (2) therapeutic and pharmacological properties, and (3) chemical properties. The first level comprises the main anatomical groups, while the second level contains the pharmacologically relevant therapeutic subgroup. The third level consists of the pharmacological subgroup, and the fourth the chemical subgroup. The fifth level represents the chemical substance (the actual drug entity). Drugs with multiple effects and different target organs can be found more than once within the system. The anti-inflammatory agent diclofenac, for instance, has three ATC numbers, one of them being M01AB05. This key breaks down to: M01 (musculo-skeletal system; anti-inflammatory and antirheumatic agents, nonsteroids); M01AB (acetic acid derivatives and related substances); and 05 (diclofenac in M01AB). The two other keys classify diclofenac as a topical agent and its use for inflammation of sensory organs.

While ATC is better suited if the emphasis is on therapeutic use, the TCAT system [26,42] puts the target chemistry first, particularly suiting the medicinal chemical approach.

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