Drug Disposition and Pharmacokinetics
From Principles to Applications

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Professor of Pharmacology and Physiology, University of Rochester, USA

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Preface

The origins of this book can be traced to a previous book with the same title written by one of us (S.H.C.) in 1974, second and third editions being published in 1977 and 1980. At the time, we were both in the early stages of what has become a very enjoyable career-long collaboration. Since that time newer approaches to the subject have been developed and many other books have been published. Mostly these have tended to be either very basic texts on pharmacokinetics, or weightier tomes, although some have been brief introductory texts, while yet others have concentrated on clinical applications. We have aimed to produce a book that takes the middle road, providing sufficient information and background to make it informative, clear, readable and enjoyable, without unnecessary complexity, maintaining the philosophy of the original *Drug Disposition and Pharmacokinetics*. Consequently, this book should be of benefit, in particular, to undergraduate and postgraduate students of science, including pharmacology, toxicology, medicinal chemistry and basic medical science, and students preparing for, and in, pre-professional programmes such as those in pharmacy, medicine and related disciplines, including dentistry and veterinary science, and environmental and public health. However, we are all life-long students, and thus this book is for anyone at any stage in his or her career wishing to learn about drug disposition and pharmacokinetics, that is, what happens to drug molecules in the body, but with strong emphasis on the pharmacological and clinical consequences of drug consumption, and so we expect our book to find readers among researchers, teachers and students in universities, in research institutes, in the professions, in industry, and in public laboratories employing toxicologists and environmental scientists in particular.

Clearly pharmacokinetics cannot be taught without recourse to mathematics. However, understanding the equations in this book requires little more than a basic knowledge of algebra, laws of indices and logarithms and very simple calculus. Anyone wishing to refresh his or her knowledge in these areas is recommended to read the Appendix. In a practical sense, it is important to be able to match standard equations to common graphical displays. There is little need in this context for the ability to derive complex equations. We believe in the old maxim, that a picture is worth a thousand words, and have noted that many of the principal pharmacokinetic relationships can be demonstrated empirically by the movement of dye into and out of volumes of water. We have used this approach to illustrate the validity of several models and further examples and colour plates can be found on the companion web site. This site also contains more mathematical examples, further equations and worked examples for readers who require them.

With few exceptions, we have adopted the system of pharmacokinetic symbols recommended by Aronson and colleagues (*Eur J Clin Pharmacol* 1988; 35: 1) where C represents concentration, A, is used for quantities or amounts, V for volumes of distribution, Q for flow rates, etc. First-order rate constants are either k or, if they are *elimination* rate constants, λ. Numbers have been used to designate compartments rather than letters (letters can lead to confusion, for example between plasma and peripheral) and for the exponents in multiple-compartment models. Thus, the variables for the biphasic decline of a two-compartment model are C_1, C_2, λ_1 and λ_2 rather than A, B, α and β, which may be familiar to some readers. It has not been possible to select a single convention for drug nomenclature. Rather, the names most likely to be familiar to readers around the world are used, and so we have leaned towards

recommended International Non-proprietary Names (rINN). In most instances this should not cause problems for the majority of readers: cyclosporin, cyclosporine and ciclosporin clearly refer to the same drug. Where names are significantly different, alternatives are given in parentheses, e.g. pethidine (meperidine), and in the Index.

We have designed this book to be read from beginning to end in the order that we have presented the material. However, there is extensive cross-referral between sections and between chapters – this should aid those readers who prefer to 'dip in,' rather than start reading from Page 1. Thus, Chapter 1 is a brief presentation of the general chemical principles underlying the key mechanisms and processes described in the later chapters, effectively a mini-primer in medicinal chemistry. Drug disposition and pharmacokinetics is a discipline within the life sciences that depends entirely on these and other chemical principles. Chapters 2 and 3, which detail distribution and fate of drugs, are largely descriptive. Pharmacokinetic modelling of drug and metabolites, including more advanced concepts of clearance can be found in Chapters 4– 7. Chapter 8 is devoted to bioavailability, particularly the influence of tablet formulation on concentrations of drugs in plasma and therefore on clinical outcome. The next four chapters (9–12) deal with what can be referred to as 'special populations' or 'special considerations': sex, disease, age and genetics in particular. The relationships between pharmacokinetics and pharmacological and clinical effects (PK-PD) are the topic of Chapters 13 and 14, whilst extrapolation from animals to human beings is considered in Chapter 15. The kinetics of macromolecules, including monoclonal antibodies, are considered in Chapter 16. The final chapters exemplify the importance of pharmacokinetics in three clinical areas, considering aspects of drug interactions, toxicity and therapeutic drug monitoring. Thus our sequence is from scientific preparation, through relevant science, to an introduction to clinical applications. The logical extension of the learning process in this area would be obtainable through one or more of the excellent texts available that focus on patient-care orientated pharmacokinetic research and practice.

Our examples come from our own experience, from literature of pivotal significance in the development of the subject, and from drugs that will be especially familiar to readers. Certain drugs stand out as demonstrating basic principles of widespread significance throughout the subject. They include propranolol, warfarin, digoxin, aspirin, theophylline and isoprenaline. It should be noted that these, and several other examples, can be considered as 'old' drugs. Some, indeed, such as isoprenaline and guanethidine, are obsolete as therapeutic agents, but still of paramount importance historically and as models. It was with these and other long-established drugs that principles of lasting significance were discovered. Of relevance to this is the fact that interest in this area of science undoubtedly existed among the ancients. More recently, Shakespeare referred to the risk–benefit ratio associated with alcohol consumption in *Macbeth*, and to the duration of action of the fantasy drug consumed by Juliet in *Romeo and Juliet*. Henry Bence Jones was probably the first to describe the rates of transfer of drugs between tissues, in work conducted in the 1860s, after he had developed assays for lithium and quinine. Awareness of the first-order removal of digoxin from the body originates from Gold *et al*. in the 1920s. However, it was in the 1930s that Widmark and Teorell first examined concentrations in blood. In the 1950s and 1960s, Brodie and Williams focused our interest on metabolism and metabolites, and then on quantitative pharmacology related to concentrations in blood. The big explosion of interest resulted from stirrings of pharmacokinetic thought in the colleges of pharmacy, and from the development of Clinical Pharmacology primarily in medical schools, in the 1960s, 1970s, and 1980s. It has been exciting to be associated with this dramatic development in medical science. Mathematical pharmacokinetics first gained prominence in relation to dosage form design, then to profiling of drugs in humans and control of clinical response, and, remarkably, only recently, in the process of new drug discovery.

We have not discussed bioanalysis, apart from a brief consideration of assay specificity in Chapter 19. However, it is important that the reader be aware that pharmacokinetic information can be no better than the quality of the concentration–time data provided. Thus, the pharmacokineticist should ensure that concentration data are from specific, precise and accurate assays, including their application to error-free timing of sample collections. Notes on other methods of drug investigation are to be found throughout the book, and

readers interested in particular methods should be able to access relevant information through the index and references.

We hope that you enjoy this book. We thank our various students in London, Gainesville, Rochester, and too many other locations to mention, for their help in formulating our understanding of our readers' needs in this subject area, and dedicate this book to them. We are immensely grateful to our publishers for their sage advice, and to our families for their support, tolerance and encouragement during the writing of this book.

Stephen H. Curry, Rochester, New York,
Robin Whelpton, London,
January 2010

About the Authors

Stephen Curry

Stephen has been Professor of Pharmacology at The London Hospital Medical College, Professor of Pharmaceutical Science at the University of Florida, and Adjunct Professor of Pharmacology and Physiology at the University of Rochester. He has also spent ten years with AstraZeneca and predecessor companies. He was honoured by the Faculty of Medicine of the University of London with the Doctor of Science Degree and is a Fellow of the Royal Pharmaceutical Society. He currently works in the field of technology transfer and translational science with early stage companies based on discoveries at the University of Rochester (PharmaNova) and Cornell University (ADispell). He can be contacted at www.stephenhcurry.com.

Robin Whelpton

After obtaining his first degree in Applied Chemistry, Robin joined the Department of Pharmacology and Therapeutics, London Hospital Medical College, University of London as research assistant to Professor Curry. Having obtained his PhD in pharmacology, he became lecturer and then senior lecturer before transferring to Queen Mary University of London, teaching pharmacology to preclinical medical students. He is currently a member of the School of Biological & Chemical Sciences and has a wealth of experience teaching drug distribution and pharmacokinetics to undergraduate and postgraduate students of medicine, pharmacology, biomedical sciences, pharmaceutical chemistry and forensic science.

1

Chemical Introduction: Sources, Classification and Chemical Properties of Drugs

1.1 Introduction

Pharmacology can be divided into two major areas, pharmacodynamics (PD) – the study of what a drug does to the body and pharmacokinetics (PK) – the study of what the body does to the drug. Drug disposition is a collective term used to describe drug absorption, distribution, metabolism and excretion whilst pharmacokinetics is the study of the rates of these processes. By subjecting the observed changes, for example, in plasma concentrations as a function of time, to mathematical equations (models), pharmacokinetic parameters such as elimination half-life ($t_{1/2}$), volume of distribution (V) and plasma clearance (CL) can be derived. Pharmacokinetic modelling is important for the:

- Selection of the right drug for pharmaceutical development
- Evaluation of drug delivery systems
- Design of drug dosage regimens
- Appropriate choice and use of drugs in the clinic.

These points will be expanded in subsequent chapters.

A drug is a substance that is taken, or administered, to produce an effect, usually a desirable one. These effects are assessed as physiological, biochemical or behavioural changes. There are two major groups of chemicals studied and used as drugs. First, there is a group of pharmacologically interesting endogenous substances, for example acetylcholine, histamine and noradrenaline. Second, there are the non-endogenous, or 'foreign' chemicals (xenobiotics), which are mostly products of the laboratories of the pharmaceutical industry.

There are numerous ways in which drugs interact with physiological and biochemical process to elicit their responses. Many of these interactions are with macromolecules, frequently proteins and nucleic acids. *Receptors* are transmembrane proteins, with endogenous ligands typified by acetylcholine and noradrenaline (norepinephrine). Although substances may be present naturally in the body, they are considered drugs when they are administered, such as when adrenaline is injected to alleviate anaphylactic shock. Drugs can either mimic (agonists) or inhibit (antagonists) endogenous neurotransmitters. Salbutamol is a selective β_2-agonist whereas propranolol is a non-selective β-blocker. Some receptors are *ligand-gated ion channels*, for example the cholinergic nicotinic receptor, which is competitively antagonized by (+)-tubocurarine. *Enzymes*, either membrane bound or soluble, can be inhibited – for example neostigmine inhibits acetylcholinesterase

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and aspirin inhibits cyclooxygenase. Other proteins that may be affected are *voltage-gated (regulated) ion-channels* – a typical one being voltage-gated sodium channels which are blocked by local anaesthetics such as lidocaine (lignocaine). Antimalarials, chloroquine, for example, intercalate in DNA. Some drugs work because of their physical presence – often affecting pH or osmolarity – for example antacids to reduce gastric acidity or sodium bicarbonate to increase urinary pH and thereby increase salicylate excretion (Section 3.3.1.5).

1.1.1 Source of drugs

Primitive therapeutics relied heavily on a variety of mixtures prepared from botanical and inorganic materials. The botanical materials included some extremely potent plant extracts, with actions for example on the brain, heart and gastrointestinal tract, and also some innocuous potions, which probably had little effect. The inorganic materials were generally alkalis, which did little more than partially neutralize gastric acidity. Potassium carbonate (potash, from wood fires) was chewed with coca leaves to hasten the release of cocaine. Inevitably, the relative importance of these materials has declined, but it should be recognized that about a dozen important drugs are still obtained, as purified chemical constituents, from botanical sources and that alkalis still have a very definite value in certain conditions. Amongst the botanical drugs, are the alkaloids: morphine is still obtained from opium, cocaine is still obtained from coca leaves, and atropine is still obtained from the deadly nightshade (belladonna). Although the pure compounds have been prepared synthetically in the laboratory, the most economical source is still the botanical material. Similarly, glycosides such as digoxin and digitoxin are still obtained from plants. These naturally occurring molecules often form the basis of semisynthetic derivatives – it being more cost-effective than synthesis *de novo*.

Similar considerations apply with some of the drugs of zoological origin. For instance, while the consumption of raw liver (an obviously zoological material) was once of great importance in the treatment of anaemia, modern treatment relies on cyanocobalamin, which occurs in raw liver, and on hydroxycobalamin, a semisynthetic analogue. Another zoological example is insulin, which was obtained from the pancreatic glands of pigs (porcine insulin) but can now be genetically engineered using a laboratory strain of *Escherichia coli* to give human insulin.

Most other naturally occurring drugs, including antibiotics (antimicrobial drugs of biological origin) and vitamins, are generally nowadays of known chemical structure, and although their synthesis in the laboratory is in most cases a chemical possibility, it is often more convenient and economical to extract them from natural sources. For the simpler molecules the converse may be true, for example chloramphenicol, first extracted from the bacterium, *Streptomyces venezuelae*, is totally synthesized in the laboratory. For some antibiotics, penicillins and cephalosporins for example, the basic nucleus is of natural origin, but the modern drugs are semisynthetic modifications of the natural product.

Amongst the naturally occurring drugs are the large relative molecular mass (M_r) molecules, such as peptides, proteins (including enzymes), polysaccharides and antibodies or antibody fragments. Some of these macromolecules, snake venoms and toxins such as botulinum toxin ($M_r \sim 150{,}000$) have long been known. The anticoagulant, heparin, is a heavily sulfated polysaccharide ($M_r \sim 3{,}000$–$50{,}000$). Peptide hormones used as drugs include insulin and human growth hormone. Streptokinase, urokinase and tissue plasminogen activator (tPA) are enzymes used as thrombolytic agents. Other therapeutic enzymes are the pancreatic enzymes given to sufferers of cystic fibrosis. Antibodies are a recent addition to macromolecular drugs. Digoxin-specific antibodies, or light-chain fragments (F_{ab}) containing the specific binding site, are used to treat poisoning by cardiac glycosides. Advances in molecular biology have led to the introduction of a number of monoclonal antibodies with a range of targets: various cancers, viruses, bacteria, muscular dystrophy, the cardiovascular and immune systems, to name but some. Furthermore, the antibodies can be

modified to carry toxins, cytokines, enzymes and radioisotopes to their specific targets. Monoclonal antibodies have the suffix *-mab* and the infix indicates the source of the antibody and the intended target; *-u-* indicates human and *-tu(m)-* that the target is a tumour. Thus, trastuzumab is a monoclonal antibody directed at (breast) cancer that has been 'humanized', *-zu-*; that is over 95% of the amino acid sequence is human. The prefix is unique to the drug.

With only minor exceptions, drugs are chemicals with known structures. Some of them are simple, some complex. Some of them are purely synthetic; some are obtained from crude natural products and purified before use. Most are organic chemicals, a few are inorganic chemicals. With all drugs, the emphasis is nowadays on a pure active constituent, with carefully controlled properties, rather than on a mysterious concoction of unknown potency and constitution.

1.2 Drug nomenclature and classification

Drug names can lead to confusion. Generally a drug will have at least three names, a full chemical name, a proprietary name, i.e. a trade name registered to a pharmaceutical company, and a non-proprietary name (INN) and/or an approved name. Names that may be encountered include the British Approved Name (BAN), the European Pharmacopoeia (EuP) name, the United States Adopted Name (USAN), the United States Pharmacopoeia (USP) name and the Japanese Approved Name (JAN). The WHO has been introducing a system of recommended INNs (rINN) and it is hoped that this will become the norm for naming drugs, replacing alternative systems. For example, lidocaine is classed as a rINN, USAN and JAN, replacing the name lignocaine that was once a BAN. Often 'ph' is replaced by 'f', as in cefadroxil, even though the group name is cephalosporins. We have elected to use amphetamine rather than amfetamine. Generally, the alternatives obviously refer to the same drug, such as ciclosporin, cyclosporin and cyclosporine. There are some notable exceptions, pethidine is known as meperidine in the United States and paracetamol as acetaminophen. Even a simple molecule like paracetamol may have several chemical names but the number of proprietary names or products containing paracetamol is even greater, including Panadol, Calpol, Tylenol, Anadin Extra. Spelling can also lead to apparent anomolies. For example, cefadroxine is a cephalosporin (Table 1.2). Therefore it is necessary to use an unequivocal approved name whenever possible.

A rigid system for the classification of drugs will never be devised. Increasingly, it is found that drugs possess actions which would permit their categorization in several groups in any one particular classification system. This is shown most strikingly by the use of lidocaine for both local anaesthetic and cardiac effects. Additionally, with constant changes in drug usage, it is not uncommon to find drugs of several different types in use for the same purpose. The number of examples within each type is of course very large. However, drugs are commonly grouped according to one of two major systems. These are on the basis of action or effect, and on the basis of chemistry. It is not possible to include all drugs in either of these groupings, and so a hybrid classification is necessary if all possibilities are to be considered. Table 1.1 shows an abbreviated pharmacological listing. The interpretation of this is quite straightforward, and it is presented as a general aid to the reader of later chapters of this book. Most of the examples quoted in later chapters are mentioned. Not so straightforward is the chemical listing shown in Table 1.2. It will be immediately noticed that while all of the groups of drugs in Table 1.2 are represented in Table 1.1, all of the types in Table 1.1 are not represented in Table 1.2, as a great many drugs are of chemical types of which there is only a single example, and Table 1.1 is only concerned with those chemical groups of drugs which are commonly known by their chemical names. Commonly encountered chemical groups are exemplified in Table 1.3.

1.3 Properties of molecules

Drug molecules may be converted to other molecules either by spontaneous change (i.e. decomposition) or by enzymatic transformation. Enzymes are such efficient catalysts that the rate of a reaction may be increased

Table 1.1 Abbreviated listing of drug groups categorized on the basis of pharmacological use or clinical effect, with examples, or cross-referenced to the chemical types of Table 1.2

THE CENTRAL NERVOUS SYSTEM

General anaesthetics

I Gases – e.g. nitrous oxide
II Volatile liquids – e.g. halothane
III Intravenous anaesthetics, including some barbiturates

Hypnotics including some barbiturates and some benzodiazepines, and newer examples such as zolpidem

Sedatives including certain barbiturates, phenothiazines and benzodiazepines

Tranquillizers

I Major, including certain phenothiazines and butyrophenones
II Minor, including certain benzodiazepines
III Other, newer, examples, such as olanzepine

Antidepressants

I Dibenzazepines – e.g. nortriptyline
II Monoamine oxidase inhibitors – e.g. tranylcypromine
III Lithium
IV Other newer examples, such as fluoxetine

Central nervous system stimulants

I Amphetamine-related compounds – e.g methylphenidate and amphetamine
II Hallucinogens – e.g. lysergic acid diethylamide
III Xanthines – e.g. caffeine

Analgesics

I Narcotics – e.g. morphine and pethidine
II Mild analgesics, including salicylates

Miscellaneous centrally acting drugs, including respiratory stimulants (analeptics), anticonvulsants, certain muscle relaxants, drugs for Parkinson's disease, antiemetics, emetics and antitussives

CHEMOTHERAPY

Drugs used in the chemotherapy of parasitic diseases, including arsenicals
Drugs used in the chemotherapy of microbial diseases, including penicillins, cephalosporins and sulfonamides
Drugs used in the treatment of viral diseases, such as aciclovir
Drugs used in the treatment of fungal diseases, e.g. miconazole
Drugs used in the treatment of cancer, such as alkylating agents, antimetabolites, anthracycline derivatives, trastuzumab, hormone antagonists

PERIPHERAL SYSTEMS

Drugs acting at synapses and nerve endings

I Acetylcholine and analogues (parasympathomimetic agents)
II Anticholinesterase drugs – e.g. physostigmine
III Inhibitors of acetylcholine at parasympathomimetic nerve endings – e.g. atropine
IV Drugs acting at ganglia – e.g. nicotine
V Drugs acting at adrenergic nerve endings, including catecholamines and imidazolines
VI Neuromuscular blocking drugs – e.g. suxamethonium

Drugs acting on the respiratory system

I Bronchodilators – e.g. salbutamol
II Drugs affecting allergic responses – e.g. disodium cromoglycate
III Oral antiasthmatics e.g. montelukast

Autacoids and their antagonists

I Histamine and 5-hydroxytryptarnine
II Antihistamines – e.g. diphenhydramine

Drugs for the treatment of gastrointestinal acidity

e.g. ranitidine and omeprazole

Cardiovascular drugs

I Digitalis and digoxin
II Antiarrhythmic drugs – e.g. quinidine
III Antihypertensive drugs, including angiotensin-converting enzyme (ACE) inhibitors ('prils')
IV Vasodilators – e.g. glyceryl trinitrate
V Anticoagulants, including heparin and coumarins.
VI Diuretics, including thiadiazines
VII Lipid lowering drugs (e.g. 'statins')
VIII Thrombolytics (e.g. tissue plasminogen activator)

Local anaesthetics – e.g. lidocaine (lignocaine)

Locally acting drugs

e.g. gastric antacids and cathartics

Endocrinology

Hormones, hormone analogues and hormone antagonists, including steroids, sulfonylureas and biguanides (e.g. glipizide, thyroxine and insulin)

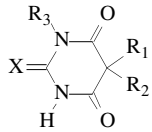
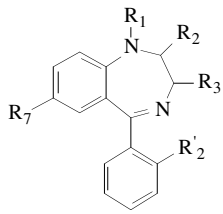
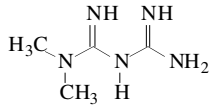
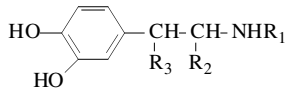
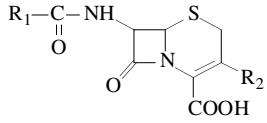
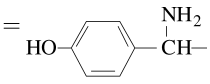
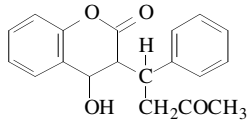
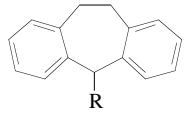
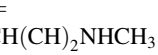
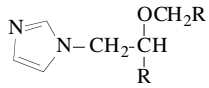
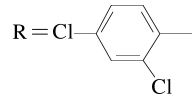
Biological response modifiers

e.g. interferon, adalimumab

Immunosuppressants

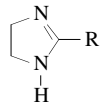
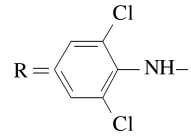
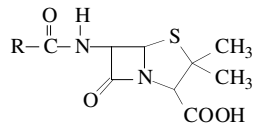
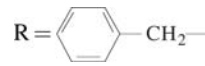
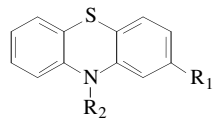
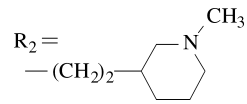
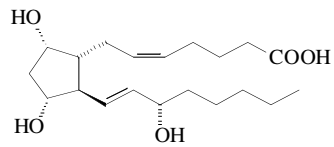
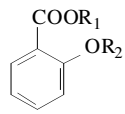
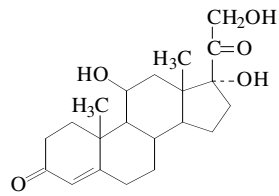
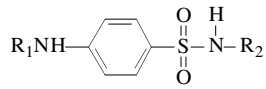
e.g. ciclosporin

Table 1.2 Some groups of drugs classified on chemical structure rather than pharmacological properties or uses

Group	Parent structure	Chemical example	Uses and examples
Barbiturates		Phenobarbital $R_1 = C_2H_5$ $R_2 = C_6H_5$ $R_3 = H$ $X = O$	As hypnotics and sedatives (pentobarbital) As anticonvulsants (phenobarbital) As general anaesthetics (thiopental)
Benzodiazepines		Lorazepam $R_1 = H$ $R_2 = O$ $R_3 = OH$ $R_7 = Cl$ $R'_2 = Cl$	As anxiolytics (diazepam) As hypnotics (temazepam)
Biguanides		Metformin (as drawn)	As oral hypoglycaemics
Catecholamines		Adrenaline $R_1 = CH_3$ $R_2 = H$ $R_3 = OH$	Sympathomimetic amines
Cephalosporins		Cefadroxil $R_1 =$  $R_1 = CH_3$	As antimicrobial drugs
Coumarins		Warfarin (as drawn)	As anticoagulants
Dibenazazepines		Nortriptyline R = 	As antidepressants
Imidazoles		Miconazole R = 	As antifungal drugs

(*continued*)

Table 1.2 (*Continued*)

Group	Parent structure	Chemical example	Uses and examples
Imidazolines		Clonidine 	As antihypertensive drugs
Macromolecules: Polysaccharides, peptides, proteins, enzymes, antibodies		Heparin, insulin, trastuzumab	In control of blood clotting, diabetes, cancer, rheumatoid arthritis and other conditions
Penicillins		Penicillin G 	As antimicrobial drugs
Phenothiazines		Thioridazine $R_1 = SCH_3$ 	As antihistamines (promethazine) As antipsychotics (thioridazine) As antiemetics (trifluoperazine)
Prostaglandins		$PGF_{2\alpha}$ (as drawn)	As uterine stimulants and other procedures
Salicylates		Aspirin $R_1 = H$ $R_2 = COCH_3$	As antipyretic, anti-inflammatory and antipyretic drugs
Steroids		Hydrocortisone (as drawn)	Anti-inflammatory drugs
Sulfonamides		Sulfacetamide $R_1 = H$ $R_2 = COCH_3$	As antimicrobial drugs