Principles of Medicinal Chemistry

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Preface

The first edition of *Principles of Medicinal Chemistry* was founded on the premise of presenting an account of drug properties based upon underlying chemical principles wherever possible. Although the existing literature has not provided the biochemical pathways by which drugs exert their effects in the complex world of the cell in many, or even in a majority of cases, much information of this kind is now known. Although this aspect of the subject is incomplete and will probably remain so for a considerable time to come, many of the principles relating biologic activity to molecular structure are known. Among these may be listed the stereochemical properties of the molecule, the ionization constants, the aqueous and lipid solubilities, the ability of the molecule to provide bonds of less than covalent strength for complexation with cellular macromolecules, and the ability of molecules to assume different structural conformations, with resultant energy changes, on forming these bonds. These aspects have been considered to a large extent in this treatment to provide a rational basis for the understanding of drug activity.

The text was originally written for courses in organic medicinal and pharmaceutical chemistry taken by pharmacy students, but it has enjoyed a much wider appeal. Students of chemistry, pharmacology, and those biologists with an appreciation of structural organic chemistry have found it useful. Various parts of the book have been used from high school level to graduate school level, so it is apparent that this treatment of the subject, with both a pervading consideration of fundamentals and an appreciation of clinical considerations, can stimulate the interest of students with varying educational backgrounds but a common desire to understand the complexities of drug action.

This edition has preserved the general structure of the first edition but has been thoroughly revised. New chapters have been added on anticancer agents and historical aspects of drugs derived from plants, from which has come much stimulation of research leading to many contemporary drugs. The chapter on diagnostic agents has been greatly expanded, and the chapter on molecular orbital theory has been broadened to one on quantitative structure–activity relationships. Part of one chapter has been devoted to antiparkinsonism agents, and a completely revised discussion of neuroleptics and anxiolytic agents has been written. The chapter on analgesic agents has now placed greater emphasis on stereochemical structure, and the discussion of autonomic drugs has been revised to reflect current categorization, although this field of drug activity may yet see significant change in the immediate future. An appendix on pKa values of representative drugs has also been included.

As in so many recent developments in science, the progress made in our knowledge of the biologic activity of organic compounds has been due to a synthesis of results from diverse fields, not only of pure science, but of applied and clinical studies. The medicinal chemist or pharmacologist who wishes to gain insight into this subject and to present it in an understandable manner to students, has a difficult task in the face of a voluminous literature scattered in diverse journals. The problem is magnified when results on the same drug are conflicting and where methods of bio-

logic testing, particularly with compounds having psychotic effects, are not standardized. For all these reasons, writing a "correct" and coherent account of drugs and their biologic activities requires considerable knowledge of several different fields to produce an authoritative treatment of a "borderline" discipline such as medicinal chemistry. For those authors who have contributed chapters to this book, and equally for those who have used the book and contributed comments, I have the greatest appreciation and wish to express the thanks that are due them. To the former, I wish also to recognize that special talent that can make the subject clear to the beginning student.

I wish also to acknowledge my indebtedness, as well as that of the contributing authors, to those who have assisted with the completion of the book: to those who have read or proofread chapters; to those colleagues, students, and librarians, who in the course of contacts, frequent or few, have contributed to the accumulation of facts and knowledge required; and to Professors John L. Neumeyer, David A. Williams, and the late G. B. Singh of Banaras Hindu University for most helpful discussions regarding scope and content of the book. Finally, I wish to acknowledge the cheerful and necessary assistance of the secretaries upon whom was placed ultimately most of the burden of putting the chapters in final form.

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Principles of Medicinal Chemistry

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Introduction and History

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Medicinal chemistry, according to Burger, "tries to be based on the ever-increasing hope that biochemical rationales for drug discovery may be found."[1] In contrast, he described pharmaceutical chemistry as being concerned primarily with modification of structures having known physiologic or pharmacologic effects and with analysis of drugs. Medicinal chemistry as practiced encompasses both definitions, but finding the biochemical pathways through which drugs exert their beneficial effects has become a dominating activity of the medicinal chemist. This activity has branched into two main directions: one essentially biologic and the other essentially physicochemical. The biologic direction has imposed the roles of enzymologist and pharmacologist on the medicinal chemist. The physicochemical direction has required that he become a quantum mechanician or spectroscopist. Attempts to correlate or reconcile the results of biochemical measurements with physicochemical calculations also occupy the attention of many medicinal chemists.

Some investigators believe that the time is not yet appropriate to base a book on the basic principles behind the biochemical events leading to drug actions. No biochemical pathway of action for any drug has yet been completely explained, but, nevertheless, a rapidly increasing amount of biochemical information about drug action is now found in the literature. An amazing amount of insight into the behavior of drugs at the macromolecular level has been developed, and there is much direct and indirect evidence supporting these biochemical postulations of drug action. Perhaps a review of the historical development of our knowledge of enzymes and related aspects of interest to medicinal chemists, including enzyme activities and structure, and the effect of drugs on the activities, might provide a logical introduction to this volume. The effect of drugs on enzyme systems has occupied the greatest share of attention the medicinal chemist has devoted to interaction of drugs with cellular macromolecules. A brief survey of important events is given in Table 1-1.

A chronologic survey regarding important discoveries of drugs and other biologically important molecules can be found in Burger's *Medicinal Chemistry;* no attempt, therefore, has been made here to reproduce this information, but historical surveys can be found in most chapters. The primary function of the medicinal chemist is still to discover new drugs, but a knowledge of the underlying principles of biochemical action should be of immense value for the design of new drug molecules. Molecular orbital or other calculations designed to elucidate electronic and conformational aspects of molecules are now used to attempt to predict optimal structures for selective biologic activity, based on certain physical and biochemical properties.

In the so-called prescientific period, natural products having a history of folk remedies were in use, but very little of the drug therapy of today is based on these remedies. Some of the natural products currently used, either as such or as derivatives, were often used originally for other purposes, such as arrow poisons, as part of religious or other rituals, or even as cosmetics. Examples of such products include opium, belladonna, cinchona bark, ergot, curare, nutmeg, calabar bean, foxglove, and squill. Many drugs originally used as

TABLE 1-1. *Important Events Concerning Enzymes and Coenzymes*

1811	Kirchhoff observed that a glutinous component of wheat can convert starch to sugar and dextrin.
1825	Schwann described pepsin.
1830	Robiquet and Boutron discovered hydrolysis of amygdalin by bitter almonds. Liebig and Wohler (1837) and Robiquet (1838) named the enzyme "emulsin."
1831	Leuchs described the diastatic action of ptyalin.
1833	Payen and Persoz separated active amylase from malt.
1837	Berzelius described fermentation as a catalytic process.
1856	Corvisart described trypsin.
1858	Pasteur noted that a mold ferments *dextrorotatory* but not *levorotatory* tartaric acid.
1862	Danielewski separated pancreatic amylase from trypsin by adsorption.
1870	Liebig developed a purely chemical theory of enzyme action.
1878	Kuhne designated *unorganized ferments*, such as pepsin and diastase, as *enzymes*.
1894	Emil Fischer began investigations leading to present ideas of enzyme specificity.
1897	Buchner discovered that a cell-free yeast extract can cause alcoholic fermentation.
1897	Bertrand observed that certain enzymes require dialyzable substances to exert catalytic activity. These substances were called *coenzymes*.
1898	Croft-Hill performed the first synthesis catalyzed by an enzyme, that of isomaltose.
1902	Henri's work on invertase led to development of enzyme kinetics.
1903	Henri proposed that an enzyme and its substrate combine to form a complex.
1909	Sörensen pointed out the dependence of enzyme activity on pH.
1910	Hudson and Michaelis gave the first theoretical explanation of enzyme activity–pH curves.
1913	Michaelis and Menten treated the concept of an enzyme–substrate complex according to ideas of chemical equilibria.
1923	Barger and Stedman found physostigmine to be an inhibitor of cholinesterase.
1923	Ribonuclease, a phosphodiesterase enzyme, was discovered by Jones and Perkins.
1923	Hartridge and Roughton designed a rapid mixing device for measurement of rapid reactions and transient states.
1924	Kuhn recognized that the action of β-amylase on starch involves an inversion of configuration.
1925	Keilin employed spectrophotometry to characterize hemoproteins.
1925	Briggs and Haldane showed that a steady-state treatment could be applied to enzyme kinetics.
1925–1935	Protein nature of enzymes was demonstrated in several laboratories by work on flavins.
1926	Jansen and Donath isolated thiamine.
1926	Sumner prepared crystalline urease.
1930	Northrop crystallized pepsin.
1930	Lohmann showed that transfer of phosphate from adenosine triphosphate (ATP) to a phosphate receptor, in the hexokinase reaction, requires magnesium.
1930	Catalytic amines were used as carboxylase models by Langenbeck.
1931	Uridylic acid was first isolated as a constituent of nucleic acids by Levene and Bass.
1931	Aeschlimann showed that neostigmine inhibits cholinesterase.
1931–1936	Isolation and identification of the pyridine nucleotide coenzymes by Warburg and Christian and by von Euler, Albers, and Schlenk.
1932	Waugh and King showed that ascorbic acid undergoes reversible oxidation–reduction to dehydroascorbic acid.
1932	Warburg showed that "old yellow enzyme" contains riboflavin.
1932	Acetylcholinesterase was discovered in blood by Stedman and co-workers.
1933	The hypothesis that free thiol groups are essential for the activity of some enzymes was developed by Hellerman and his associates and by Bersin and Logemann.
1937	Hellerman proposed a metal bridge complex in arginase.
1938	Crystalline pyridoxine was isolated from natural sources by Gyorgy, Kuhn, and Wendt, and by Lepkovsky.
1938	Flavin adenine dinucleotide was isolated as the coenzyme of D-amino acid oxidase by Warburg and Christian.
1938	Use of electrophoresis was made by Tiselius to purify pepsin.
1940	Keilin and Mann found that carbonic anhydrase is a zinc-containing enzyme.
1940	Link found that Dicumarol is a vitamin K antagonist.
1940	Mann and Keilin reported the inhibition of carbonic anhydrase by sulfanilamide.
1940	Fildes theorized that substances structurally related to essential metabolites could be

Table 1-1. *Important Events Concerning Enzymes and Coenzymes (Cont.)*

	chemotherapeutic by a competitive antagonism.
1941	Folic acid was isolated from natural sources by Mitchell, Snell, and Williams.
1943	Nachmansohn and Machado discovered that acetylation of choline by rabbit brain extracts does not proceed unless ATP is present as a source of energy.
1945	Lipmann showed that biologic acetylations require not only ATP but also another cofactor, which he called *coenzyme A*.
1945	Snell demonstrated coenzyme functions of pyridoxal phosphate.
1946	Diisopropyl phosphorofluoridate was found to be an inhibitor of cholinesterase by McCombie and Saunders.
1946	The structure of folic acid was determined at Lederle Laboratories.
1946	Use of an antimetabolite, methotrexate, for the treatment of leukemia was made by Farber and associates.
1948	O'Kane and Gunsalus showed that a factor later named *lipoic acid* is essential for oxidation of pyruvic acid.
1948	Enzymic incorporation of inorganic pyrophosphate into an organic molecule was noted by Kornberg on formation of ATP and nicotinamide mononucleotide from diphosphopyridine nucleotide (DPN).
1950	Michaelis and Wollman demonstrated free radical formation from α-tocopherol.
1950	Anionic and esteratic sites in acetylcholinesterase were recognized by Adams and Whittaker and by Wilson and Bergmann.
1950	An imidazole group was suggested as being at the active site of acetylcholinesterase by Wilson and Bergmann.
1951	Functions of glutathione in enzyme reactions and cell respiration were elaborated by Barron.
1951	Pyrithiamine was shown to be a thiamine antagonist by Cerecedo and co-workers.
1951	Amino acid sequence of insulin was established by Sanger and Tuppy.
1952	An azomethine chelation mechanism of action for pyridoxal was established by Metzler and Snell and others.
1954	Pullman, San Pietro, and Colowick established that the pyridine ring in the coenzyme DPN is reduced to a 1,4-dihydropyridine.
1954	Oxythiamine was shown to be a competitive inhibitor of thiamine by Naber and his researchers.
1954	The amino acid composition of crystalline carboxypeptidase was determined by Smith and Stockell.
1954	Vallee and Neurath showed that pancreatic carboxypeptidase contains 1 gram atom of zinc per mole of protein.
1954	Eigen and co-workers developed relaxation methods permitting the measurement of reaction rates with time constants as short as 10^{-10} s.
1955	Kosower concluded that reduction of the pyridine nucleotide coenzyme DPN involves the charge transfer type of complexing (Milliken, 1952).
1955	Kennedy and Weiss first demonstrated a cytidine nucleotide as an enzymic cofactor.
1956	Pyridine-2-aldoxime methiodide was found by Wilson to reactivate alkyl phosphate-inhibited acetylcholinesterase.
1956	Sutherland detected cyclic adenosine monophosphate (3′,5′-AMP) in animal tissues.
1957	Cunningham and Westheimer postulated the concerted action of a serine and a histidine residue in the active center of chymotrypsin.
1958	Koshland pointed out that enzyme proteins undergo conformational changes on binding of substrates to enzymes.
1958	Smith proposed that a high energy thiol ester bond is present in papain and is essential for its activity.
1958	Friden observed metal ion-induced aggregation with glutamic dehydrogenase.
1958	Kendrew and co-workers determined the structure of myoglobin to 2 Å resolution by x-ray crystallography.
1959	Metals associated with flavoproteins were found in several laboratories to be capable of oxidation–reduction during enzyme catalysis.
1960	Malmstrom used electron paramagnetic resonance (EPR) to determine the nature of ligands in metalloenzymes.
1960	Fine structure of a genetically modified enzyme, dihydropteroic acid synthetase, was determined by Hotchkiss and Evans.
1961	For enzyme studies, Baker, Shaw, and Singer developed active site-directed reagents.
1962	Baker showed that 4-iodoacetamidosalicylic acid is an active site-directed inhibitor of lactic dehydrogenase.
1962	Shaw showed that the chloromethyl ketone of tosylphenylalanine is an active site-directed inhibitor of chymotrypsin.
1962	Inhibition of dihydropteroic acid synthetase

Table 1-1. *Important Events Concerning Enzymes and Coenzymes (Cont.)*

	was established as mode of action of the sulfonamide drugs by Woods.
1963	Merrifield developed a method of solid phase peptide synthesis used to prepare insulin and ribonuclease.
1965	Strominger and Tipper found that transpeptidase is selectively acylated by the β-lactam ring of penicillin and cephalosporin antibiotics.
1965	Species differences among dihydrofolate reductases were recognized as a basis for chemotherapy by Hitchings.
1966	Incorporation of nitroxide radicals in proteins as environmental probes for electron spin resonance studies was described by McConnell.
1968	Interaction of rifamycin with bacterial RNA polymerase was found by Wehrli *et al.*
1969	Bactericidal effect of rifampicin was recognized as due to inhibition of ribonucleic acid nucleotidyltransferase by Lancini *et al.*
1969	Knowledge of the enzymes required for the biosynthesis of dihydropteroic acid established by Richey and Brown.
1970	An altered dihydrofolate reductase was found to be associated with drug resistance in plasmodia by Ferone *et al.*

folk remedies, on the other hand, have been abandoned.

Development of drug therapy could not progress until knowledge of anatomy and physiology had reached the status of sciences. The empiric observations of Harvey and Sydenham were of great importance to this development in the seventeenth century. The work of Magendie (1783–1855), an instructor of anatomy in Paris, probably represents the first application of the experimental method to medicine. He administered a Javanese arrow poison (nux vomica) to animals by various routes and described the resulting convulsions and asphyxia. This was probably the first experiment in drug absorption. By removing or sectioning the spinal cord, he concluded that this was the site of action of the active component. This was subsequently isolated and named strychnine. Magendie and his students studied a number of other drugs and physiologic problems, and they isolated several other alkaloids. He eventually published a formulary based on pure compounds.

Following the French Revolution, the sciences broke with their previous dependence on logic rather than observation and became more empiric, a development necessary for real advance. The study and classification of diseases made considerable progress during the first half of the nineteenth century, and a new spirit of inquiry developed. Ineffective remedies were recognized as such and discarded. Although the German university system was well established by 1850, and definite programs of research were instituted, much of the drug discovery in the nineteenth century resulted from the investigations of either amateurs or investigators in the chemical industry, then mainly concerned with dyes. It was not until well into the twentieth century that the search for new drug entities or classes took place in university laboratories.

The first use of synthetic organic chemicals for interference with life processes was probably when ether and chloroform were introduced for anesthesia during the first half of the nineteenth century. In consequence, early efforts to find synthetic drugs were concentrated on anesthetics and hypnotics and eventually analgesics. Chloral hydrate appeared in 1869 and paraldehyde in 1882, and the sulfone hypnotics were discovered by accident in 1888. The local anesthetic properties of ethyl p-aminobenzoate were known in 1890 and led to the development of procaine hydrochloride (Novocain), the structure of which is based on some features of the cocaine molecule. Cocaine was introduced as a local anesthetic in 1884.

Phenacetin also appeared during this period, and its discovery resulted from observations of the hydroxylation and conjugation of aniline in the animal body. This was probably the first drug to be designed as a result of knowledge of a biochemical transformation. Aspirin was introduced in 1899, and it resulted from an attempt to reduce the nausea caused by the salicylates, which had been used as antipyretics. Antipyrine was discovered from investigations of the chemistry of quinine, at this time, and the urethane hypnotics also resulted from the study of compounds produced by the chemical industry.

The next period in the development of medicinal agents was dominated by Paul Ehrlich. He was appointed Director of the Institute for Experimental Therapy in Frankfurt in 1899, at the age of 45. By this time, synthetic analgesics, anesthet-