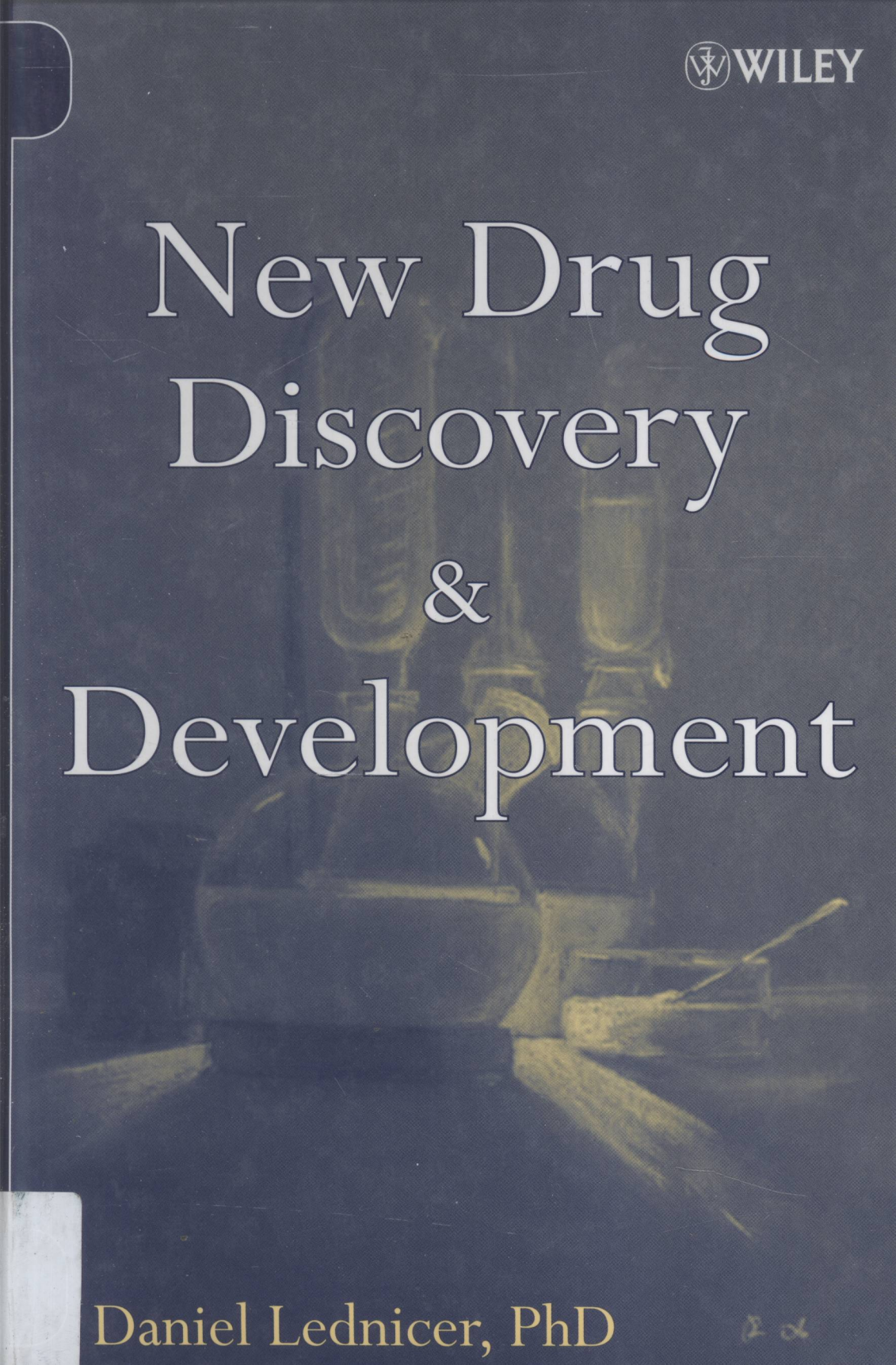
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New Drug Discovery and Development

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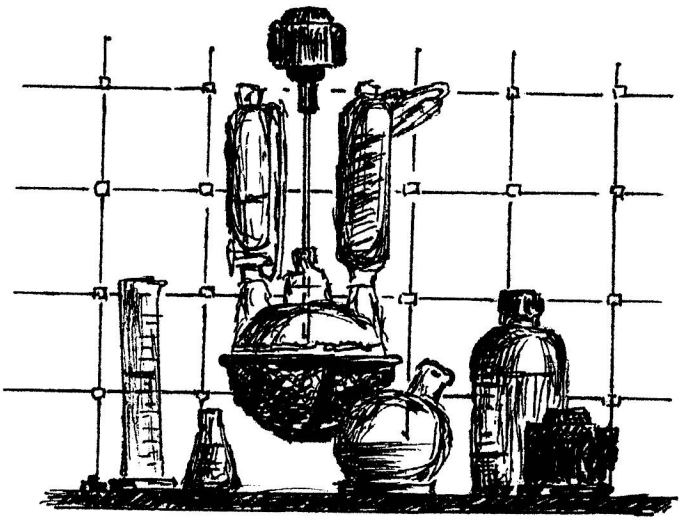
To the human curiosity that long ago led some individual to taste those berries and then millenia later prompted a chemist to follow a hunch in designing a molecule.



Preface

Therapeutic agents, more often called drugs, play an increasingly important role in our aging population. This is reflected most directly in the ever larger portion of family income spent on medicines, an increase that is only partly attributable to the rising cost of filling a prescription. The public and much of the media point to the greed of "big pharma," the small number of huge pharmaceutical companies, as the main cause of this price escalation. The companies in turn defend prices by citing the cost of research aimed at finding and developing new therapeutic agents. It can thus be instructive to set aside the heat of the argument and to take a closer look at the historical origins of some representative examples of the extensive pharmacopoeia available to physicians for treating their patients.

To that end, this volume presents a set of case histories that have led to families of drugs for treating many of mankind's ills. Some, for example the antibiotics, have contributed to a marked increase in longevity in the advanced world over the past half century. The effect of some other categories, for example the central analgesics, has been on patients' quality of life. The discovery of a new drug category inevitably leads to the development of related compounds as companies race to enter the burgeoning market. This account notes some of the entries that came after the pioneering drug, although not in the detail found in more specialized volumes.

The first chapter traces the development of the major classes of antibiotics used to treat infectious disease. The case histories provide interesting examples of the interplay between guided research and serendipity that marks much of drug research. The synthesis of the first effective antibacterial agent, the dye Prontosil, was prompted by the well-known affinity of stains for bacteria. It was found not much later that activity was in fact due to colorless sulfanilamide produced by cleavage of the dye by liver enzymes. The discovery and early development of penicillin took place in university laboratories. The antibiotic became a usable drug through involvement of industry at later stages. The second chapter deals with agents for treating the other major aspect of infectious disease, the virus. The great majority of antiviral drugs are of much more recent origin than antibiotics. This field of research interestingly received major stimulus from the AIDS epidemic. Some of the first antiviral drugs had their origin in anticancer research programs and reflect the reliance on screens that tested a wide variety of chemicals characteristic of the programs. The more recent antiviral compounds on the other

hand were designed to take advantage of newly gained insights into the molecular biology of viral infection.

The somewhat complex development of antihypertensive agents is considered in Chapter 3. Classes of drugs used to treat elevated blood pressure came from two disparate sources. A number were developed on the basis of the knowledge base in physiology and pharmacology that came out of basic research in academia and the NIH as well as industry. This provided the theoretical rationale for the early alpha blockers; the actual chemical compounds were found by random screening of products that came from the labs of organic chemists. In an interesting feedback, new compounds in this class, notably clonidine and prazocin, led to new insights into pharmacology. This motif is repeated in the calcium channel blockers, where a dihydropyridine found by random screening led to the elucidation of a new mechanism of action. The history of the angiotensin-converting enzyme (ACE) inhibitors and the more recent angiotensin antagonists drew heavily on the basic pharmacology of kidney function.

The deleterious effects of high levels of serum cholesterol were at least suspected by the middle of the nineteenth century. The development of compounds designed to lower cholesterol is found in Chapter 4. This seemingly simple end point led to the adoption of relatively straightforward animal screens intended to identify compounds that lowered serum cholesterol. A number of drugs that came out of this program are still in use. Several other agents were carefully designed to take advantage of the oxidation of cholesterol to bile acids by the liver. Acceptance was limited by the fact that treatment comprised taking these unpalatable powders in gram quantities. More recent work has been guided by new information on the biochemical mechanism involved in regulation of blood lipids. This insight led to the discovery of the statins, a class of drugs that has dramatically changed this area of therapy.

The discovery of the pain-killing and soporific activity of the dried exudates of the flower pod of the poppy, papaver somniferum, took place well before recorded history. The isolation of the active principle from opium, as the crude substance was called, dates back to more recent times; that compound, morphine, was known in crystalline form by the early nineteenth century. As organic chemistry developed, chemists turned their attention to this molecule. They sought by manipulating the chemical structure to produce less addicting congeners that were active when taken by mouth. Chapter 5 first traces the development of several classes of analgesics built on the same complex carbon skeleton as the parent natural product. The account then switches to a series of purely synthetic compounds that to an organic chemist bear little resemblance to morphine. Many of these new compounds are several tens of orders of magnitude more potent than morphine. The goal of a nonaddicting opioid has however still not been met.

Nonopiate compounds for treating pain, often called peripheral analgesics, comprise one of the most widely prescribed classes of drugs. This usage is supplemented by consumption of a host of over-the-counter drugs. Drug development in this field has been a largely empirical enterprise. The discovery of the role of prostaglandins in pain and inflammation has guided some of the more recent research.

Drug discovery is anything but a linear process. Synthesis programs carefully designed to produce compounds active in a specific test more than occasionally lead to the discovery of an entirely new class of drugs. The chapter also traces the origin of the COX-2 nonsteroidal anti-inflammatory agents (NSAID) to a much earlier research program on anti-estrogens. The odyssey that weaved its way over the years through many different labs culminated in the discovery of celecoxib, more familiarly known as Celebrex. When first launched, this and its relatives were believed to present a significant advance over previously available NSAIDs.

The drugs whose development is considered in Chapter 7 share a common rather complex chemical structural framework. Small changes in the chemical structures, however, lead to quite disparate activities. The so-called sex steroids comprise a large subdivision of this class, which includes compounds with variously estrogenic, progestational, and androgenic activity. Research on this group was initially motivated by the involvement in reproductive function of steroids that had been isolated from animal blood and tissues. This work, perhaps not surprisingly, culminated in the development of the oral contraceptives. The resulting drugs, known collectively as "The Pill" have arguably brought about enormous changes in societal mores. The androgens and the related anabolic steroids are currently in the spotlight for their putative abuse among professional athletes. The clinical observation of the profound anti-inflammatory activity of high doses of the naturally occurring steroid, cortisone, led to a race among pharmaceutical companies for a practical means for producing the compound in large quantity. Once this was found, a correspondingly large effort was devoted in many labs to finding more potent congeners devoid of the classical side effects of cortisone. The first goal was eventually met, although side effects seemed to be inevitable with activity. The very potent agents were, however, well tolerated when applied topically. Those highly potent steroids are today widely used in anti-allergic nasal sprays.

Therapeutic goals provided the unifying theme for the first half dozen chapters, but the drugs discussed in Chapter 7 share a common structural element, the steroid nucleus. The very diverse set of compounds in Chapter 8 all come about from the search for agents to combat the adverse effects of histamine. This effort led not only to the familiar antihistamines, but also the tricyclic antipsychotic and antidepressant agents as well a series of antiulcer agents. Better understanding of the allergic action led to the recognition of the important role played by leukotrienes. This has resulted in the development of several anti-allergic leukotriene antagonists.

Each of the previous sections glosses over the various activities that take place between the identification of a new drug and its appearance on a pharmacy shelf. This therefore omits the enormous expenditure of time, effort, and money that must be spent in the process. Chapter 9 gives a brief overview of the many steps required before a drug is blessed with approval from the Food and Drug Administration and how these have changed over time.

This book is aimed at the informed layman, that is, an individual who, although not a chemist, has at least some background in the sciences. The use of technical terms and concepts is of course almost unavoidable in a book of this nature.

A deliberate attempt has been made to keep these to a minimum. The author, an organic chemist by training and persuasion, has included structural formulas in this account. The discussion is presented in terms that do not require reliance on those formulas. Structures have been included in the belief that they will provide additional insight to those readers who are conversant with that way of thinking. A brief review of conventions used to depict molecules is included in the Appendix for those whose exposure to organic chemistry was fleeting or largely forgotten.

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North Bethesda, Maryland

Contents

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Chapter 1

Antibiotics

The increase in life expectancy seen during the twentieth century in many parts of the world is by now too familiar to require lengthy discussion. Expectancy at birth in the United States, for example, increased by close to two decades from 49.2 years at the beginning of that century to 68.1 years in 1950.[1] This remarkable jump generally has been attributed to improvements in sanitation and the advent of drugs for the treatment of infectious disease. Many bacterial infections that required hospitalization before World War II are now treated with a course of antibiotics. Usage is so well accepted that treatment will involve prescription called into the pharmacy by the physician's office and self-administration at home. The isolation of pure penicillin in 1939 in England is often used to date the beginning of the development that has led to today's armamentarium of antibiotics drugs. However, the story in fact begins back in Germany in the early 1930s.

It was well recognized by then that the structure and enzyme systems that allow bacteria to thrive are very different from their mammalian counterparts. Scientists devoted considerable effort from the late nineteenth century on to the search of chemicals that would exploit those differences so as to specifically eradicate bacterial cells. A tantalizing early clue that such differences might exist lay in the stains that were used by microbiologists to study their prey. Drawing on the wealth of synthetic dyes produced by the burgeoning chemical industry in Germany in the nineteenth century, scientists had identified a series of substances that stained bacteria in preference to mammalian cells.[2] The key to finding a drug that would preferentially eradicate bacteria seemed to be to find a stain that would kill the cells that accepted that particular dye. The long search seemed to have finally borne fruit in 1932. Gerhard Domagk, working in a laboratory set up by I. G. Farben, discovered that the red dye Prontosil Rubrum (Fig. 1) protected mice that had been injected with otherwise lethal doses of staphylococci.[3] Use of the dye to treat successfully a human infection (Domagk's daughter) confirmed that this was indeed a therapeutic breakthrough. There had by then, however, been more than a few reports of seemingly miraculous cures of disease due to bacterial infection.

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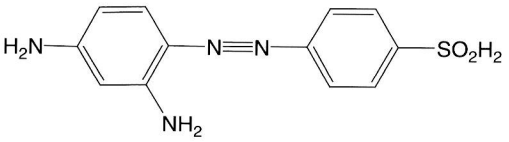
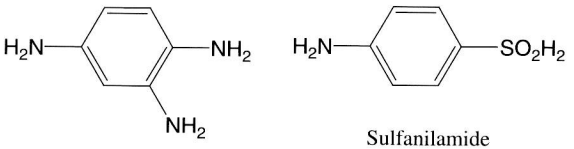


Prontosil Rubrum



Sulfanilamide

Figure 1 Prontosil Rubrum and its conversion to sulfanilamide.

The resulting skepticism from the inevitable failure of those earlier treatments led to surprisingly slow acceptance of the dye, by now simply called Prontosil. There was also the puzzling fact that the dye was only marginally effective in killing bacteria in vitro, that is, in the then standard test tube experiment for antibacterial activity. A group of scientists at the Pasteur Institute in France then showed that the dye molecule is transformed chemically in animals.[4,5] Liver enzymes, they found, split the molecule in two at the central nitrogen to nitrogen azo linkage (N=N). One of the halves, subsequently named sulfanilamide, turned out to be a fully effective antibacterial compound both in test tubes or when administered to infected mice. The other half showed no antibacterial activity whatsoever. This work incidentally gave birth to the discipline of drug metabolism. Prontosil was to be but the first case of a drug that needed to be modified by the body for activity.

An immediate result of this finding was the abandonment of Prontosil in favor of the chemically much simpler sulfanilamide. This drug can be synthesized from benzene in just a few steps.[6] In fact, this synthesis was for many years a laboratory exercise at the beginning of organic chemistry courses. It probably enticed more that one student, including the author, into a career in pharmaceutical research.

The discovery of sulfanilamide marked the beginning of the search for agents to treat infectious disease among compounds made from scratch by organic chemists. We come back to that story later. The discovery of the other important source of compounds that selectively kill microbes dates back to 1929 and Alexander Fleming's well-known serendipitous discovery. He noted a microbe-free clear zone around a mold colony that had contaminated a culture in a Petri dish, and correctly ascribed that to an antibiotic substance secreted by the mold. He named this unknown secretion penicillin after the producing mold, which he had identified as *Penicillium notatum*.[7] The imminence of World War II is said to have spurred the transition of what had been considered as simply an interesting laboratory observation into a useful antibiotic drug. Begining in about 1938, Howard Florey led the very major effort to isolate penicillin. This was finally accomplished in 1940, largely through the work of his Oxford collaborator Ernst Chain. The team isolated

just enough pure penicillin to ascertain its near miraculous activity in humans.[8] Production of penicillin was transferred to the United States, because the British chemical industry was at that time fully tied up with war production. In its original form, *Penicillium notatum* grew best as a surface mat. Production in large quantities invoked visions of the use of shallow tanks with enormous surface areas, so the project was assigned to the U.S. Department of Agriculture Northern Laboratory in Peoria, Illinois, which had experience in industrial fermentation. There they devised a method for growing the mold as a submerged culture. By this and other means they greatly increased the yield of penicillin.[8,9] The method developed by USDA was then transferred to industry, and a large number of companies with expertise and facilities for fermentation were enlisted in the effort.[10] This even at one time included Schenley, better known as a producer of spirits.

Penicillin in the form used then had a number of very serious shortcomings. The drug had to be administered by injection as it was not orally active. The molecule is also very reactive, leading to poor stability. Early research aimed at producing more stable congeners led to several salts with improved stability. Reasons for the sensitivity of penicillins emerged with the determination of their chemical structure. The compounds are in essence comprised of two discrete connected pieces. The essential part consists of a fused ring structure called a beta-lactam. This is the reactive part that in the end kills bacteria; it also contributes to the lack of stability. The rest of the structure, which is also required for activity, consists of an organic acid connected through a chemical bond. Penicillin obtained from fermentation is a mixture of closely related compounds in which the invariant beta-lactam is hooked to slightly different acids. Penicillin G is one of the major components. Scientists had noted that they could increase the proportion of one or another congener by adding a large amount of that acid to the culture medium (Fig. 2).[11,12] This allowed them selectively to produce one or another of the congeners such as Penicillin V. These still, however, shared many of the same shortcomings. This included poor stability and lack of oral activity; the drugs were also not effective against a significant number of classes of bacteria. It had become apparent by 1960 that further improvements would require manipulation of the chemical structure.

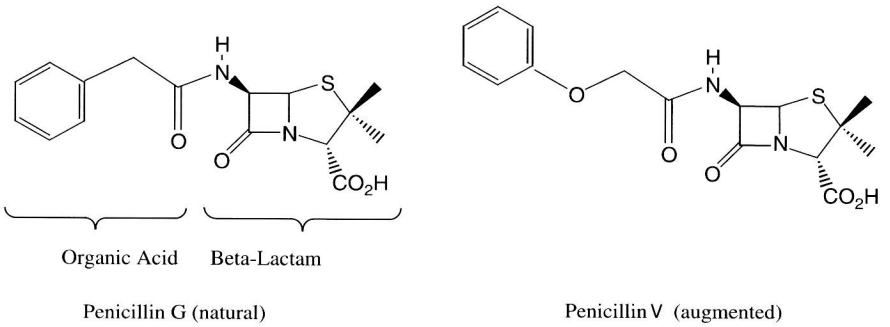


Figure 2 A penicillin from the naturally occurring complex and a typical augmented feeding product.

It was later established that the selectivity of the beta-lactam antibiotics traces back to the fact that bacteria are more closely related to plants than animals. Individual animal cells are surrounded by a membrane, whereas plants and thus bacteria depend on a wall for cell integrity. In bacteria that structure is composed of a dense network of protein filaments that is cross-linked by chemical bonds. A significant number of the amino acids that compose the proteins have chemical structures that are mirror images of those found in animals. The beta-lactams (penicillins and cephalosporins) are mistaken by bacterial enzymes as small pieces that will be used to form the cross-links. Once they get incorporated, they bring the process to a dead halt, causing the cell wall to rupture.[13] The drugs are thus selective, because mammals do not use cell walls and in addition utilize enzymes that do not recognize the mirror image amino acids used to make bacterial cell walls. The beta-lactam enzymes are consequently known for their very large safety margins. There is, however, a distinct portion of the population that is extremely allergic to these drugs.

By 1940 sulfanilamide had come into widespread use particularly in treating war wounds. The drug was used both as a tablet and sprinkled directly onto open lesions. Although the drug saved numerous lives, many types of bacteria were immune to its action. Chemists in a number of pharmaceutical laboratories then tried to make changes in the molecule in attempts to broaden its activity against other classes of bacteria (Fig. 3). Systematic work showed that there was only a single place on the molecule that could be manipulated and still retain antibacterial activity. Hundreds of analogues of sulfanilamide such as sulfathiazole were probably prepared in a number of laboratories between 1940 and the late 1950s, by which time the work was finally abandoned.[14] No fewer than 27 of these were granted nonproprietary names, which is often an indication that the sponsor intends to test the compound in the clinic. At least eight of these so-called sulfa drugs are currently used in the clinic.

The antibacterial activity and selectivity of this class of drugs again depends on the fact that bacteria uniquely rely on biochemical processes that have no counterpart in more complex organisms (Fig. 4). Folic acid, perhaps better known as one of the B vitamins, is an essential factor in various metabolic processes such as formation of red blood cells and DNA itself. Over the course of evolution many organisms have lost the ability to make this compound and rely on obtaining it in food. Bacteria, on the other hand, synthesize this vitamin from scratch. An important biochemical step involves hooking a small molecule, PABA (para-aminobenzoic acid), onto the growing molecule. The chemical structures of the sulfa drug are similar enough to PABA to cause bacterial enzymes to incorporate these molecules.

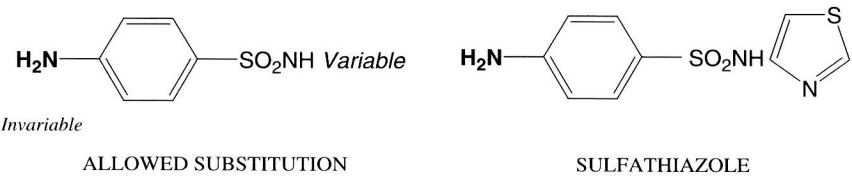


Figure 3 Sites that may be modified on sulfa drugs.

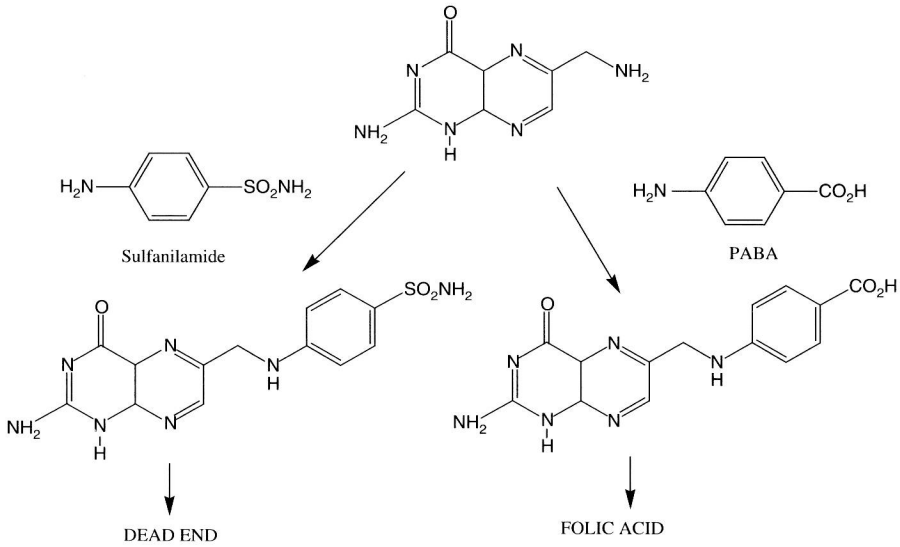


Figure 4 Sulfa drugs' mode of action.

However, the resulting product can go no further, in effect causing the bacterium to die for lack of folic acid.[15]

One of the sulfa drugs, sulfamethoxazole, is a constituent of combination tablets, such as Bactrim®, that still comprise first-line treatment for urinary infections. The other active ingredient, trimethoprim, originates in work carried out by future Nobel Prize winner George Hitchings at Burroughs Wellcome in the late 1950s.[16] Taking their cue from compounds involved in enzyme action, he and his associates prepared a congener called pyrimethamine.[17] This agent proved to inhibit bacterial growth by interfering with an enzyme, dihydrofolate reductase (DHFR), involved further down the line in the synthesis of folic acid. Further work along the same lines led to the synthesis of trimethoprim. The combination tablet exploits the fact that each of the active ingredients inhibits bacterial growth by interfering with different enzymes that bacteria need survive (Fig. 5). This combination has been used for treating HIV/AIDS opportunistic infections.

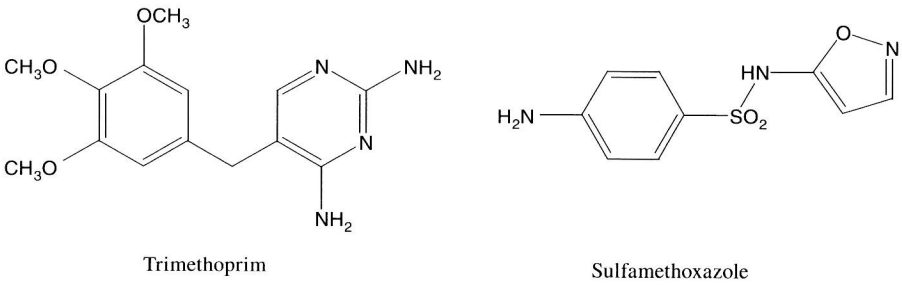


Figure 5 Active ingredients in Bactrim.

Isolated reports of unusual side effects came with widespread use of sulfa drugs.[18] Very high doses caused some patients to excrete water and others to show a drop in blood sugar levels. Chemists in pharmaceutical laboratories seized on these apparent side effects to develop entirely new classes of drugs. By manipulating the chemical structures, scientists at Hoechst came up with a compound that normalized blood sugar in adult onset diabetics. This drug, chlorpropamide, in which the all-essential amino group is replaced by methyl, is virtually devoid of antibacterial activity. Replacement of the sulfonamide (SO_2NH_2) by a sulfonylurea function ($SO_2NHCONH_2$) proved crucial for antidiabetic activity and was present in the widely marketed drug tolbutamide.[19] The only drugs available in the 1940s for treating conditions that required loss of body water, the diuretics, included mercury in their chemical composition. Scientists at Merck, led by Sprague, were able to introduce changes on the structure of the sulfa drugs to produce a well-tolerated diuretic drug. These principally involved adding an additional sulfonamide onto the parent molecule. This compound, chloraminophenamide, also devoid of antibacterial activity, is no longer in use. It has been superseded by hydrochlorothiazide, which was first synthesized by chemists at Ciba. This drug, often better known by its acronym, HCTZ (Fig. 6), is still used as first-line treatment of patients with mildly elevated blood pressure.[20]

The discovery of penicillin led to the recognition of the ability of fungi to protect themselves against microorganisms by secreting compounds that inhibit bacterial replication and in fact often kill off those threatening organisms. Penicillin itself showed that such antibiotics may act specifically on enzymes that do not have counterparts in mammals. This property, shared with the sulfa drugs, led to low toxicity to humans. The search for new molecules in this class turned to the

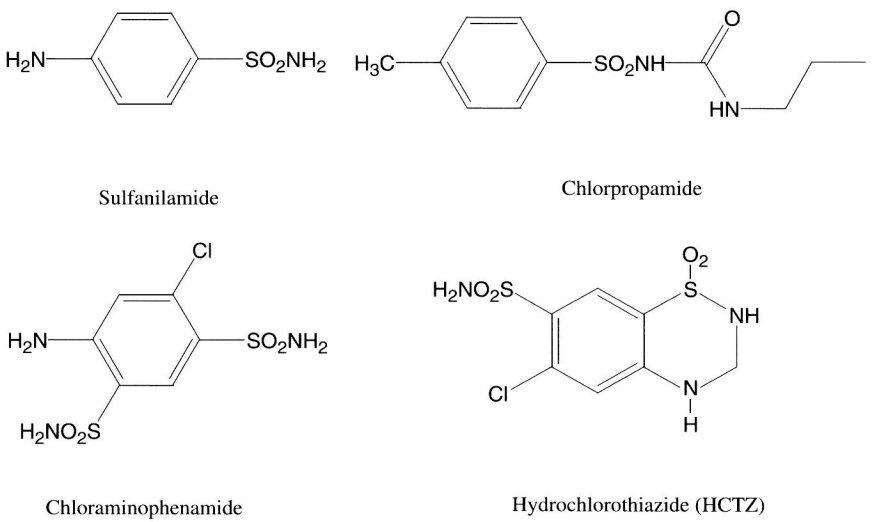


Figure 6 Nonantibiotic drugs related to sulfonamides.

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