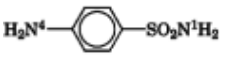
ANTIBACTERIAL AGENTS, SULFONAMIDES

1. Introduction

Sulfonamides derived from sulfanilamide (*p*-aminobenzenesulfonamide) are commonly referred to as sulfa drugs. Although several drug classes are characterized by the presence of a sulfonamide function, eg, hypoglycemics, carbonic anhydrase inhibitors, saluretics, and tubular transport inhibitors, the antibacterial sulfonamides have become classified as the sulfa drugs. Therapeutically active derivatives are usually substituted on the N^1 nitrogen; the N^4 position is generally unsubstituted. These features are illustrated by the structures of sulfanilamide [63-74-1] (**1**) and sulfadiazine [68-35-9] (**2**)



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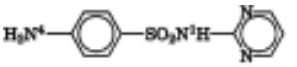

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Some related antibacterials are also included with the sulfonamides. The azo dye, Prontosil [103-12-8] (**3**) is metabolized to sulfanilamide *in vivo*, and was the progenitor of the sulfa drugs. Also, the antibacterial sulfones, eg, dapsone [80-08-8] (**4**), are believed to act in a similar fashion on enzymes involved with synthesis of folic acid, leading to bacterial growth inhibition.

(3)

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A monograph (1) covers the pioneering period of sulfa drug development and describes >5000 sulfanilamide derivatives, their preparation, properties, trade names, and biological testing. This review is remarkably complete through 1944. Several thousand additional derivatives have been made since, but no comparable coverage is available. A definitive account of medical applications up to 1960 has been published (2), and a review of experimental antibacterial aspects has been made (3). Chapters on general aspects of sulfonamides and sulfones have appeared (4–6). A review of the clinical efficacy of trimethoprim—sulfamethoxazole has been published (7).

The discovery of the sulfonamides, the first drugs to control systemic bacterial infections, had its origin in the investigation of organic dyes for chemotherapeutic purposes initiated by Paul Ehrlich and others in the first decade of the 1900s. The azo compound, Prontosil (**3**), was discovered by Domagk, Klarer and Mietzsch at the I. G. Farbenindustrie in Germany in 1935 (8) and found to cure bacterial septicemia. It was fortunate that animal tests were used in the screening procedure, because Prontosil (sulfamidochrysoidine) is inactive *in vitro*. Domagk received the 1939 Nobel Prize in Medicine for the discovery of the antibacterial effects of Prontosil. A group at the Pasteur Institute in Paris found that sulfanilamide, a metabolic product, was responsible for the activity (9), and was active against susceptible organisms both *in vitro* and *in vivo* (9,10). This marked the beginning of a worldwide effort to prepare and test derivatives and analogues of sulfanilamide. In <10 years, >5000 compounds of this type were synthesized, and they appear in the 1948 review (1). The effort to find compounds having a broader antimicrobial spectrum and improved therapeutic ratio resulted in the development and clinical use of the N^1-heterocyclic substituted sulfanilamides, exemplified by sulfapyridine [144-83-2], sulfathiazole [72-14-0], and sulfadiazine (all 2-substituted heterocycles). Later research has not produced sulfonamides having greater activity, but compounds having improved pharmacokinetic properties for specific uses have largely replaced the first used sulfonamides.

During 1935–1944, the most active period of investigation of sulfanilamide derivatives for systemic bacterial infections, the antimycobacterial activity of 4,4′-diaminodiphenylsulfone (DDS, dapsone) was discovered (11). Although neither this compound nor its derivatives proved to be clinically useful for human tuberculosis, it did evolve into the most important compound for leprosy (12). The *N,N′*-diacetyl derivative has also found use against certain resistant strains of falciparum malaria.

The sulfonamides are still important as antimicrobial agents, although they have been replaced in many systemic infections by other antibacterial agents and the natural and semisynthetic antibiotics. They are of great value in developing countries where problems of storage and lack of medical personnel make appropriate use of antibiotics difficult. They are especially useful in urinary tract infections. Their effectiveness has been enhanced by co-administration with dihydrofolate reductase inhibitors, and the combination of sulfamethoxazole [723-46-6] with trimethoprim [738-70-5] is of value in treatment of a number of specific microbial infections. The introduction of this combination (co-trimoxazole) in the late 1960s (1973 in the United States) resulted in increased use of sulfonamides.

The sulfonamides also remain clinically useful in the treatment of chancroid, the fungus-related nocardiosis (13), and infections due to *Chlamydia trachomatis*, such as lymphogranuloma venereum, trachoma, and inclusion conjunctivitis. In combination with pyrimethamine [58-14-0], they are recommended for toxoplasmosis (14) and have been used for chloroquine-resistant falciparum malaria (4,15). There has also been some use of sulfonamides for the prophylaxis of rheumatic fever. The sulfone, dapsone, remains an accepted treatment for all forms of leprosy (4), generally as part of a multi-drug therapeutic regimen. The sulfonamides in combination with trimethoprim is the agent of choice for the prevention and treatment of pneumonia caused by *Pneumocystis*

carinii (16). Like the sulfonamides, this drug combination is utilized for the treatment of sexually transmitted diseases caused by *C. trachomatis* (17).

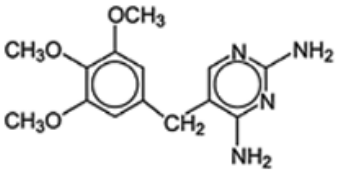
The clinical usefulness of the sulfonamides depends not only on antimicrobial effectiveness, but on other factors such as aqueous and liposolubility, protein-binding, half-life, and metabolism. Currently used sulfonamides vary widely in their absorption, distribution, and excretion patterns. Some of those in clinical practice, past or present, are listed in Tables 1 and 2. These can be grouped according to their rate of absorption and half-life. One group remains largely unabsorbed after oral administration, and is useful for gastrointestinal infections. A second group is characterized by high solubility, rapid absorption and renal excretion, mainly as unchanged drug, and is widely used for urinary tract infections. Another group is absorbed rapidly but excreted slowly, maintaining adequate blood levels for long periods; these drugs are useful for chronic infections and for prophylaxis. Sulfonamides with half-lives up to 10 h are considered short-acting, those with half-lives of 10–24 h are termed medium-acting, and those with half-lives of >24 h are long acting. This wide range of pharmacokinetic properties, along with their ease of administration, broad spectrum antimicrobial activity, and noninterference with host-defense mechanisms is responsible for their continued use five decades after their discovery. However, due to the high rates of resistance development, their utility is becoming more limited, especially in the case of serious infections.

Based on the mechanism of action, the sulfonamides are effective against microorganisms that depend on the synthesis of folic acid. Such organisms include gram positive and gram negative cocci and bacilli, mycobacteria, some large viruses, protozoa, and fungi (5). The action of the sulfonamides and related sulfones is bacteriostatic rather than bactericidal. These agents interfere with the synthesis of folic acid [59-30-3] by competing with *p*-aminobenzoic acid (PABA) [150-13-0] for the active site of the enzyme, dihydropteroate synthase. For a thorough discussion of the mechanisms of action postulated for the sulfonamides, see (18).

2. Therapeutic Aspects

Because of several unique properties, the sulfonamides continue to occupy an important place in antimicrobial therapy. Development of derivatives that remain largely unabsorbed in the intestinal tract makes them of particular advantage in causing local changes in the bacterial flora. Development of sulfonamides with high solubility in the urine and low renal toxicity has provided agents with effectiveness in chronic urinary tract infections. Also, the synergistic antibacterial effects of combinations with the dihydrofolate reductase inhibitors trimethoprim (**5**) and pyrimethamine (**6**) has given the sulfonamides a preferred

place in management of some specific microbial infections.



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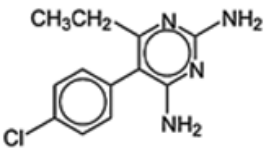

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2.1. Systemic Infections. The sulfonamides were the first drugs effective against bacterial septicemia (blood stream infections), and they have also been effective in tissue infections due to streptococci. However, the penicillins and other natural and semisynthetic antibiotics have generally displaced the sulfonamides for these uses. Nevertheless, the sulfonamides are of continuing value in the treatment of certain systemic infections. Sulfonamides, particularly sulfisoxazole and sulfadiazine, are used for the treatment of infections due to Nocardia species, occassionally in combination with cycloserine [68-41-7] (19,20). The poorly absorbed sulfonamides, phthalyl or succinyl sulfathiazole, phthalyl sulfacetamide [131-69-1], and sulfaguanidine, provide temporary inhibition of the intestinal microbial flora. This may be of value in preparing the bowel for surgery (20).

Sulfonamides in combination with dihydrofolate reductase inhibitors continue to be used in the treatment of several systemic infections. Co-trimoxazole is useful in the treatment of less serious cases of childhood pneumonia, particularly in the developing nations (6). It has also been used for the treatment of brucellosis, cholera, and malaria. Pyrimethamine in combination with sulfonamides has been employed for the protozoal diseases toxoplasmosis (13) and leishmaniasis.

2.2. Urinary Tract Infections. The sulfonamides have maintained an important place in treatment of urinary tract infections, where short acting, highly soluble drugs are required (21). Those most used in the United States are sulfisoxazole and sulfamethizole. *In vitro* serial dilution tests have shown that the combination of sulfamethoxazole and trimethoprim inhibits the growth of common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*. Therefore, for chronic urinary tract infection, co-trimoxazole is frequently employed.

Mixtures of sulfonamides (eg, the tri-sulfapyrimidines) have also been used for the treatment of urinary tract infections. Resistant organisms frequently result after use of sulfonamides as sole therapy, however.

2.3. Other Infections. Co-trimoxazole has been widely prescribed for otitis media, acute sinusitis, and chronic brochitis, particularly in patients with penicillin allergy. Similarly, the slowly excreted sulfonamides (eg, sulfamethoxypyridazine, sulfadimethoxine) have been used for treatment of sinusitis or otitis, or for prolonged maintenance therapy.

Sulfonamides have been shown to be valuable in the treatment of certain ocular infections. In particular, sulfisoxazole, sulfamethoxazole and sulfadiazine are effective for trachoma. Inclusion conjunctivitis is frequently treated with

sulfacetamide ointment. Oral administration of a sulfonamide, eg, sulfisoxazole, has been successful for treatment of lymphogranuloma venereum and chancroid. Dapsone and sulfonamides have also been used for treatment of the skin disorder dermatitis herpetiformis. Sulfonamides have been used for long term prophylaxis of rheumatic fever, but are being replaced by the penicillins for this purpose, except in cases of hypersensitivity to penicillin (21).

Co-trimoxazole is utilized as first-line therapy and for the prophylaxis of *P. carinii* pneumonia, a fungal infection common with AIDS patients (16). In addition, the combination is utilized for sexually transmitted diseases caused by *C. trachomatis* (17).

3. Physiochemical Properties

The sulfonamides are weak acids, the more important ones generally having a pK_a in the range of 5–8. This acidity, due to the sulfonamide function, makes the sulfonamides soluble in basic aqueous solution. The pK_a is modified by the presence of the N^1-substituent, but the clinically useful sulfonamides generally have pK_a values that give the compounds good solubility at physiologic pH. The N^4-acyl derivatives, such as succinylsulfathiazole, phthalylsulfathiazole , and salicylazosulfapyridine, are prodrugs that contain a free-carboxyl group and are soluble in the physiologic pH range. As pH is lowered, the solubility of the N^1-substituted sulfonamides reaches a minimum in the range of pH 3–5, which corresponds to the solubility of the neutral form. At this pH, either the sulfonamide molecule or its N^4-acetyl metabolic product may crystallize in the kidneys, giving rise to blockage and irritation. Because most of the sulfonamides have a free aromatic amino group that can be protonated, the sulfonamides are soluble as cations with pK_a of $\sim$2. Both their aqueous and liposolubilities have been thoroughly studied (22–24).

The amino group is readily diazotized in aqueous solution, and this reaction forms a basis for the assay of sulfonamides. Aldehydes also react to form anils, and the yellow product formed with 4-(dimethylamino)benzaldehyde can be used for detection in thin-layer and paper chromatography. Chromatographic retention values have been determined in a number of thin layer systems, and have been used as an expression of the lipophilic character of sulfonamides (25). These values have corresponded well with Hansch lipophilic parameters determined in an isobutyl alcohol–water system.

Lipid solubilities of the sulfonamides vary over a wide range. Oil–water partition coefficients using an aqueous ethylene chloride system have been determined (22). The differences among individual members unquestionably influence their pharmacokinetics as well as antimicrobial activity. The longer acting sulfonamides with high tubular reabsorption generally have a high degree of liposolubility (4). Both antimicrobial activity and half-life of the drug are influenced by liposolubility, but these parameters are also dependent on the degree of ionization at physiologic pH, so no precise relation between activity and liposolubility has been established.

Numerous studies have been made to find a correlation between the physicochemical properties of the sulfonamides and their antibacterial activity. Rela-

tionships to the degree of ionization, lipid–water solubility, and protein binding have all been observed. The presence of a primary aromatic amino group has been found essential for activity, and the presence of N^1-substituents is a significant influence on the degree of acid dissociation of the sulfonamide group. As early as 1942, a study of the relationship between the pK_a and antibacterial activity of an extensive series of sulfonamides showed that a plot of log 1/MIC against pK_a was a parabolic curve, the maximum lying between pK_a 6.0 and 7.4 (26). The maximal activity was thus observed in compounds with a pK_a that fell in the physiologic pH range. The pK_a of most of the active sulfonamides found since then has been in this range as well. These findings (26) were related to the antimetabolite theory (27,28), regarding the structural similarity between the sulfonamide and the natural substrate, PABA, that it was replacing. The theory emphasized the need for polarization of the sulfonyl group, so that it should resemble as closely as possible the geometrical and electronic characteristics of the *p*-aminobenzoate ion. Subsequently, it has been shown using a small subset of sulfonamides, that high enzyme activity corresponds to compounds with highly polarized S–O bonds (high electron density on the oxygens). The extent of polarization was determined by measuring the symmetric stretching frequency values of the SO_2 group in the infrared spectra (29).

In another attempt to relate degree of ionization with antibacterial activity, the effect of pH of the medium on the antibacterial activity was studied (30,31). Activity increased with increase in pH only up to the point at which the drug was 50% ionized, and then decreased. The interpretation of this was that sulfonamides penetrate the bacterial cell in the unionized form, but once inside the cell, the equilibrium between ionized and unionized forms is reestablished, and the activity is due to the ionized form. For optimum activity, a sulfonamide should have a pK_a that provides half-dissociation at the physiologic pH in the area where it is absorbed. This observation also provided an explanation of the parabolic relationship between pK_a and MIC (26).

In subsequent studies attempting to find a correlation of physicochemical properties and antimicrobial activity, other parameters have been employed, such as Hammett σ values, electronic distribution calculated by molecular orbital methods, spectral characteristics, and hydrophobicity constants. No new insight on the role of physiochemical properties of the sulfonamides has resulted. Acid dissociation appears to play a predominant role, since it affects aqueous solubility, partition coefficient and transport across membranes, protein binding, tubular secretion, and reabsorption in the kidneys. An exhaustive discussion of these studies has been provided (18).

4. Biological Mechanism of Action

The sulfonamides act on microorganisms by limiting or halting growth rather than by a bactericidal action. They inhibit growth of bacteria *in vitro* only if the medium is free of inactivating substances, mainly peptones and PABA.

Woods and Fildes postulated that *p*-aminobenzoic acid PABA is an essential metabolite for the bacteria that are affected. Woods obtained evidence that PABA antagonizes the activity of sulfonamides and showed that PABA could completely

reverse the bacteriostatic activity of sulfanilamide against various bacteria *in vitro*. PABA was later isolated from the various tissues and fluids, and yeast extract, where antagonism to sulfanilamide was found. Further studies showed that inhibition of bacterial growth by sulfonamides in simple media can be reversed not only competitively by PABA, but also noncompetitively by compounds not structurally related to PABA, such as 1-methionine, 1-serine, glycine, adenine, guanine, and thymine (32). The finding that sulfanilamide-inhibited cultures accumulated 4-amino-5-imidazolecarboxamide ribotide (33), a precursor to purine biosynthesis (34), indicated that purine biosynthesis was affected by the sulfonamides.

The primary mode of action of the sulfonamides is, however, competition with PABA for incorporation into folic acid (21). The sulfonamides impede this synthesis and are therefore toxic to those bacteria that synthesize their own folic acid. Mammals cannot synthesize this and related vitamins and depend on food sources for them; the sulfonamides are therefore not toxic to mammals in this regard.

Subsequent knowledge of the structure, function, and biosynthesis of the folic acid coenzyme gradually allowed a picture to be formed regarding the step in this pathway that is inhibited by sulfonamides. The biosynthetic scheme for folic acid is shown in Figure 1. Sulfonamides compete in the step catalyzed by dihydropteroate synthase where condensation of PABA with hydroxymethyldihydropterin pyrophosphate takes place to form dihydropteroate (35). The 5-substituted-2,4-diaminopyrimidines, such as trimethoprim or pyrimethamine, block the production of tetrahydrofolic acid by inhibiting the enzyme dihydrofolate reductase. Thus, when they are used in combination, the sulfonamides and the 5-substituted-2,4-diaminopyrimidines block two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

Direct evidence of the inhibition of dihydropteroate and dihydrofolate synthesis was obtained (37) from work with enzymes from *Escherichia coli*. The synthesis of dihydropteroate from PABA is inhibited by a number of sulfonamides and, in general, the more potent inhibitors of folate biosynthesis are the better bacterial growth inhibitors. Subsequently, evidence was obtained of incorporation of sulfonamides (38,39) in the pteridine moiety to afford the metabolically inert 7,8-dihydropterin-sulfonamides which readily diffuse from the cell (40).

The gene encoding for dihydropteroate synthase from *E. coli* has been cloned and sequenced (41). The enzyme is composed of 282 amino acids. The crystal structure of the unliganded enzyme and the sulfanilamide-6-hydroxymethyl-7,8-dihydropterin-enzyme ternary complex from *E. coli* have been determined (42). The enzyme adopts a TIM-barrel type-fold with the active site located at the C-terminal end of the β-barrel. The data from the ternary complex indicates that sulfanilamide lies between the Arg 220 main chain and the Lys 221 side chain on one side and the Arg 63 side chain on the other (Fig. 2). The sulfonamide NH_2 donates a hydrogen bond to the Ser 219 carbonyl. In addition, one sulfonamide oxygen accepts a hydrogen bond from the guanidinium functionality of the Arg 63 side chain. The Phe 190 side chain appears to form a hydrophobic contact with sulfanilamide. The anilino nitrogen is a relatively distant 3.5 Å from the hydroxymethyl of the dihydropterin. The necessary displacement of pyropho-

sphate could only occur by "a small rearrangement" of the sulfonamide within the active site, to bring the reactive groups in close proximity. Comparison of this crystal data to that from the ternary complex with PABA indicates that the sulfonamides bind in the same location as the natural substrate. Binding and kinetic experiments of the dihydropteroate synthase enzyme from *Streptococcus pneumoniae* indicate that the target for sulfonamide inhibition is the enzyme-dihydropterinpyrophosphate binary complex (43).

5. Prevalence of Resistance

Resistance to sulfonamide antibacterial agents is rapidly developing among all major species of bacteria. Sulfonamides are utilized more in developing countries since they are relatively inexpensive, easily available, and easy to store. Consequently, strains isolated in developing countries tend to exhibit a higher level of resistance than those isolated from developed countries (44).

It was anticipated that combination therapy with trimethoprim and sulfamethoxazole would inhibit or slow the development of resistance. However, clinical data indicate that resistance to both agents developed rapidly (44). Resistance to trimethoprim-sulfamethoxazole, as well as other sulfonamides, of the respiratory pathogen *S. pneumoniae*, is found worldwide at levels of 9−>50% (44). In the United States, ∼26% of *S. pneumoniae* strains are resistant (45).

Resistance of two other common respiratory pathogens *Haemophilus influenzae* and *Moraxella catarrhalis* in the United States has dramatically increased from <5 (46)−33% (44). A collaborative European study in 1990 reported that 41% of *H. influenzae* isolates from Spain and 12% of isolates from Italy were resistant to trimethoprim-sulfamethoxazole (47). The prevalence of resistance for *M. catarrhalis* ranges from 2 to 50% (44).

The prevalence of resistance of urinary pathogens to trimethoprim-sulfamethoxazole varies greatly depending on the organism. For example, 25% of *E. coli* strains isolated from hospitalized patients in the United States were resistant, whereas the same study reports 100% of *P. aeruginosa* strains and 41% of enterococcal strains were resistant (48). In the United Kingdom, 50−60% of urinary pathogens from hospitalized patients were sulfonamide resistant (49). *Escherichia coli* isolates from elderly patients are more frequently resistant than those isolated from younger patients (44).

6. Mechanisms of Resistance

One of the principal limitations to sulfonamide therapy is the emergence of resistance. Resistance develops by several mechanisms: overproduction of PABA; reduced affinity for the dihydropteroate synthase enzyme; gene amplification that leads to an overproduction of enzyme; altered permeability of the organism to sulfonamides; and a bypass mechanism which allows the bacteria to utilize the folic acid present in the host (4). By far the most prevalent of resistance mechan-

ism in clinical isolates is the reduced affinity of sulfonamides for dihydropteroate synthase due to mutations in the target enzyme.

Duplication of amino acids Ile 66 and Glu 67 was found in dihydropteroate synthase from a laboratory-derived sulfonamide-resistant strain of *S. pneumoniae* (50). Site-directed mutagenesis removed this duplication and rendered the strain sulfonamide susceptible (51). A large number of clinical isolates of sulfonamide-resistant *S. pneumoniae* have 1–2 amino acid duplications in the sulfonamide active site region between amino acids 58 and 67. For example, repetition of either Ser 61 or Ser 62–Tyr 63 is a common mutation. These mutations affect the binding of sulfonamides by altering key interactions between the sulfonamide and the enzyme as well as modifying the conformation of the enzyme.

Resistance in some *E. coli* strains is due to the insertion of two amino acids after Phe 190, which is in close proximity to the sulfonamide binding site, thus altering the tertiary structure of the enzyme (42). In the enterobacteriaceae, the plasmid-borne resistance genes, sulI and sulII, encode for dihydropteroate synthase enzymes that are not inhibited by sulfonamides (52). Spontaneous mutants change Phe 28 to either Ile or Leu (53).

A two amino acid insertion (Ser-Gly) after residue 194, which is a highly conserved region of the dihydropteroate synthase enzyme has been shown to confer sulfonamide resistance in *Neisseria meningitidis* (54). Deletion of these two amino acids (Ser and Gly) results in a susceptible strain. Another common resistant strain of *N. meningitidis* has three point mutations at amino acids 31 (Phe to Leu), 84 (Pro to Ser) and 194 (Gly to Cys). Positions 31 and 184 are located in well-conserved regions of the enzyme. Site-directed mutagenesis studies have indicated that postions 31 and 194 effect resistance, whereas position 84 did not have an obvious effect (55).

Mutant strains of *P. carinii* have recently started to appear in AIDS patients that have been exposed to sulfonamides (56). These strains exhibit either a Thr 55 to Ala 55 or Pro 57 to Ser 57 mutation. From this study, 28% of patients with mutations failed treatment with sulfonamides. These mutations most likely represent the emergence of sulfonamide resistance in *P. carinii* since these changes are in the active site region of the enzyme (57).

Irrespective of the source of the enzyme, the sulfonamide-resistant dihydropteroate synthases exhibit normal binding to the natural substrate, PABA, despite the resemblance of substrate to inhibitor (53).

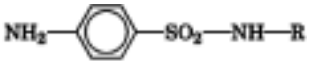
7. Structure–Activity Relationships

The following generalizations arose from a review of more than 5000 sulfonamides (1).

1. The amino and sulfonyl groups on the benzene ring should be in the 1,4 positions; the amino group should be unsubstituted or converted to a free amino *in vivo*.
2. Replacement of the benzene ring by other ring systems, or the introduction of additional substituents, decreases or abolishes activity.

3. Exchange of the SO_2NH by SOC_6H_4–p-NH_2, $CONH_2$, CONHR, or COC_6H_4R generally reduces activity.
4. N^1-Monosubstitution may result in greater activity, and will increase activity with a number of heterocycles; N^1-disubstitution in general leads to inactive compounds.

A later review (58) confirmed these generalizations. Replacement of the SO_2NH by $SO_2C_6H_4$– p-NH_2 gives the sulfones that show reduced activity for some bacterial species, but show good activity against leprosy and some strains of malarial organisms. General structures summarizing the essential features for activity of the sulfonamides (**7**) and sulfones (**8**) follow.



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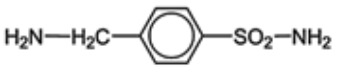
For the sulfonamides, the best activity is found where R is heterocyclic, but it can also be isocyclic (ie, contains carbon-only rings) or acyl. For the sulfones, R can be phenylene or a heterocycle; the parent dapsone, where R is phenyl, is the most active.

Other related structures may be active, but through a different mechanism. Separation of the amino group from the ring by CH_2 has provided an active sulfonamide, mafenide [138-39-6] (**9**). Replacement of the amino by amidino has also given an active sulfone, methyl p-amidinophenyl sulfone (**10**) [17574-50-4], for which no metabolite antagonist is known (1). Although not a sulfonamide, p-aminosalicylic acid [65-49-6] also has its action reversed by PABA. It has bacteriostatic action, but is most specific against mycobacteria (59).



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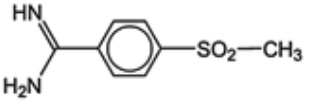

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8. Preparation and Manufacture

The most common method for the preparation of sulfonamides is by the action of N-acetylsulfanilyl chloride [121-60-8] with the appropriate amine (1). Excess amine or suitable base is used to neutralize the hydrochloric acid formed.

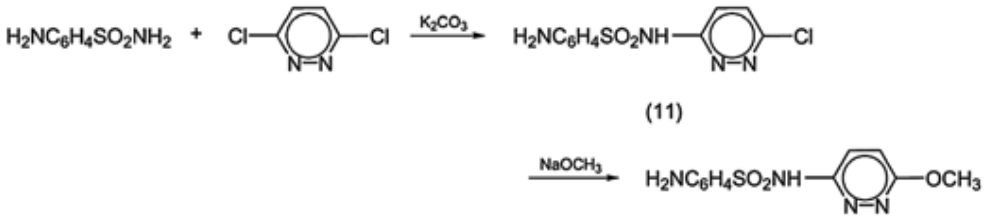
$$CH_3CONHC_6H_4SO_2Cl + RNH_2 \xrightarrow{\text{base}} CH_3CONHC_6H_4SO_2NHR + HCl$$

The resulting acetyl compound is usually hydrolyzed with aqueous alkali to give the free amine. Other N-acyl derivatives may be used, particularly for the less soluble succinyl and phthaloyl products. The use of p-nitrobenzenesulfonyl chloride, followed by reduction of the nitro to an amino function, is much more expen-

sive and is rarely used. *N*-Acetylsulfanilyl chloride is obtained by the chlorosulfonation of acetanilide [103-84-4], which is the basic material for most of the sulfonamides.

8.1. N^1-Heterocyclic Sulfanilamides. The parent sulfanilamide is manufactured by the reaction of *N*-acetylsulfanilyl chloride with excess concentrated aqueous ammonia, and hydrolysis of the product. Most heterocyclic amines are less reactive, and the condensation with the sulfonyl chloride is usually done in anhydrous media in the presence of an acid-binding agent. Use of anhydrous conditions avoids hydrolytic destruction of the sulfonyl chloride. The solvent and acid-binding functions are commonly filled by pyridine, or by mixtures of pyridine and acetone. Tertiary amines, such as triethylamine, may be substituted for pyridine. The majority of N^1-heterocyclic sulfanilamides are made by simple condensation with *N*-acetylsulfanilyl chloride and hydrolysis.

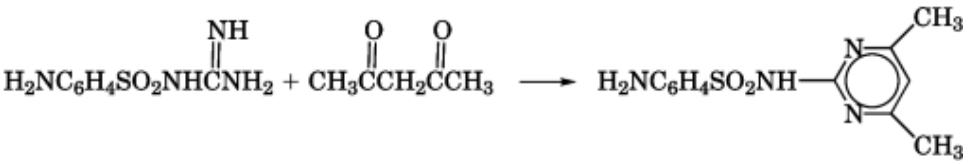
In a few cases, N^1-heterocyclic sulfanilamides have been prepared by the condensation of an active heterocyclic halide with the sulfonamide nitrogen of sulfanilamide or its *N*-acetyl derivative in the presence of an acid-binding agent. Sulfapyridine, sulfadiazine, and sulfapyrazine have been made by this method (1), but the most important application is probably for the synthesis of sulfachlorpyridazine [80-32-0] (**11**) and sulfamethoxypyridazine (**12**) (60).



(11)

(12)

N^1-Heterocyclic derivatives can be formed in some cases by a ring closure to give the heterocycle. Sulfadiazine, sulfamethazine, sulfamerazine [127-79-7], and sulfathiazole have been prepared in this fashion, but also by the usual procedure from the sulfonyl chloride and heterocyclic amine. The synthesis of sulfamethazine from sulfaguanidine is an example of the ring closure method.



8.2. N^1-Acylsulfanilamides. Only two examples of this class still have much use in the United States. Sulfacetamide is prepared by acetylation of N^4-acetylsulfanilamide in pyridine. The resulting N^1, N^4-diacetylsulfanilamide can be hydrolyzed selectively with alkali to give the monacetyl product. Its separation from regenerated sulfanilamide is easily achieved because of the greater

acidity of sulfacetamide. Sulfabenzamide [127-71-9] may be prepared in similar fashion.

Sulfaguanidine is prepared by condensation of *N*-acetylsulfanilyl chloride with guanidine in presence of alkali. The N^4-acetyl group is removed by acid or alkaline hydrolysis.

8.3. N^1-Heterocyclic-N^4-acylsulfanilamides. Two examples of this class still in use are succinylsulfathiazole and phthalylsulfathiazole. They are prepared by fusion of sulfathiazole with appropriate anhydrides.

8.4. Other Derivatives. Salicylazosulfapyridine (sulfasalazine) can be prepared by diazotization of sulfapyridine and coupling to salicylic acid. Mafenide is prepared by chlorosulfonating *N*-benzylacetamide, reaction of the resulting α-acetamido-*p*-toluenesulfonyl chloride with ammonia, and hydrolyzing the acetyl group.

Dapsone has been prepared by a number of procedures (1,61). One procedure employs the reaction of 1-chloro-4-nitrobenzene with excess sodium sulfide to give the 4-amino-4′-nitrodiphenyl sulfide. This compound, after acetylation of the amino group, is oxidized with H_2O_2 to the sulfone. The nitro group is then reduced to amino, and hydrolysis of the acetyl gives the product.

$$O_2N—C_6H_4—Cl \xrightarrow{Na_2S} O_2N—C_6H_4—S—C_6H_4—NH_2 \xrightarrow{(CH_2CO)_2O}$$

$$O_2N—C_6H_4SC_6H_4NHCOCH_3 \xrightarrow{H_2O_2} O_2NC_6H_4SO_2C_6H_4NHCOCH_3 \xrightarrow[H^+]{H_2}$$

$$H_2NC_6H_4SO_2C_6H_4NH_2$$

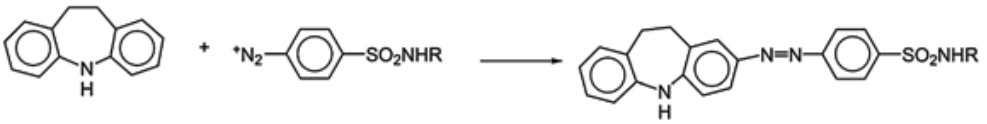
9. Economic Aspects

The production of sulfonamides increased rapidly after their introduction in the 1930s, and reached a maximum of 9000 t in 1943. An abrupt drop to less than one-half this amount occurred in 1944, with the commercial availability of penicillin. Contrary to some expectations that the sulfonamides would be totally replaced by antibiotics, their output has remained close to the 1944 level. Increased veterinary use, along with low cost and effectiveness of the sulfonamides has maintained a market for them. United States production figures of sulfonamides for selected years are shown in Table 3, in comparison with those for total antibiotics.The relative proportion of sulfonamides to total antibiotics is steadily decreasing due to the marketing of new agents from other classes of antimicrobial agents. The most recent figures released for sulfonamides also include those for other agents, such as antiprotozoan agents and other urinary tract antiinfective agents.

10. Analysis

Sulfonamides having a free *p*-amino group are readily assayed by titration with nitrous acid. The sulfonamide function may also be titrated with base, such as lithium methoxide. The majority of the sulfonamides listed in the U.S. Pharmacopeia 25, however, are assayed by chromatographic methods, particularly high performance liquid chromatography (63). Sulfonamides for which assays are listed in the U.S. Pharmacopeia 25–National Formulary 20 include the following: sulfacetamide, sulfabenzamide, sulfadiazine, sulfadoxine [2447-57-6], sulfamethazine, sulfamethizole, sulfamethoxazole, sulfapyridine, sulfasalazine, sulfathiazole, sulfisoxazole, sulfisoxazole acetyl [80-74-0], sulfaquinoxaline [59-40-5], mafenide acetate [13009-99-9], sulfadimethoxine, sulfacetamide sodium [127-56-0], sulfachlorpyridazine, silver sulfadiazine [22199-08-2], triple sulfa, dapsone, and various combinations with prednisolone, pyrimethamine, and trimethoprim.

Numerous spectophotometric methods have been reported for the determination of sulfonamides. A recent method utilized the reaction of the diazotized sulfonamide with iminodibenzyl (**13**), a novel coupling reagent, to produce a violet-colored azo product, which is stable for 2 h at room temperature (64). This technique is rapid, reproducible, sensitive and does not require heating or extractions.



(13)

11. Health and Safety Aspects

A small percentage of patients treated with sulfonamides have shown toxic effects, such as drug fever, rashes, mild peripheral neuritis, and mental disturbance. In general, these effects are more prevalent with higher blood levels, and may accompany poor excretion or overdosing (23). In 1966, the FDA required that two long-acting sulfonamides, sulfamethoxypyridazine and sulfadimethoxine carry a label warning of the possibility of death due to Stevens-Johnson syndrome, an extremely severe dermatologic reaction (65).

Crystalluria, due to formation of insoluble *N*-acetyl metabolic products, was one of the more serious toxic effects observed with sulfonamide therapy. This is much less of a problem than with the early sulfonamides, mainly because of the discovery of agents highly soluble at urinary pH, the development of long-acting sulfonamides that build up adequate blood levels at doses low enough to avoid crystallization, and the discovery of compounds that are excreted chiefly as highly soluble glucuronides. The danger of kidney blockage is also reduced by increasing fluid intake and by administering sodium bicarbonate to alkalinize the urine. The use of mixtures, such as triple sulfa, also reduces the possibility of crystallization in the kidneys.

Blood dyscrasias are quite uncommon, but if they occur may be serious enough to cause discontinuance of the therapy. Both topical and systemic administration of sulfonamides can cause hypersensitivity reactions, such as urticaria, exfoliative dermatitis, photosensitization, erythema nodosum, and in its most severe form, erythema multiformexudativum (Stevens-Johnson syndrome).

Sulfamethoxazole is metabolized primarily to the N-4 acetamide. In addition, a small amount is oxidatively metabolized by liver microsomes to the N-4 hydroxylamine (66). The hydroxylamine is capable of binding cellular macromolecules as well as being further transformed to a more reactive nitroso species (67). It has been postulated that the hydroxylamine metabolite may be responsible for adverse reactions in hypersensitive patients. There is a correlation between slow acetylation phenotype patients and a greater incidence of sulfonamide hypersensitivity (68). In these patients, a greater proportion of sulfamethoxazole is metabolized to the hydroxylamine.

Sulfamethoxazole and trimethoprim have exhibited drug-drug interactions with tolbutamide [64-77-7], phenytoin [57-41-0], warfarin [81-81-2] and glipizide [29094-61-9]. Sulfamethoxazole has been shown to inhibit the hydroxylation of tolbutamide *in vitro* (69). At clinically relevant concentrations, sulfamethoxazole moderately inhibits the activity of the CYP2C9 isoform of cytochrome P450 *in vitro* and trimethoprim strongly inhibits the activity of the CYP2C8 isoform (70). This may be the source of the drug–drug interactions.

In general, however, use of sulfonamide therapy is considered relatively safe.

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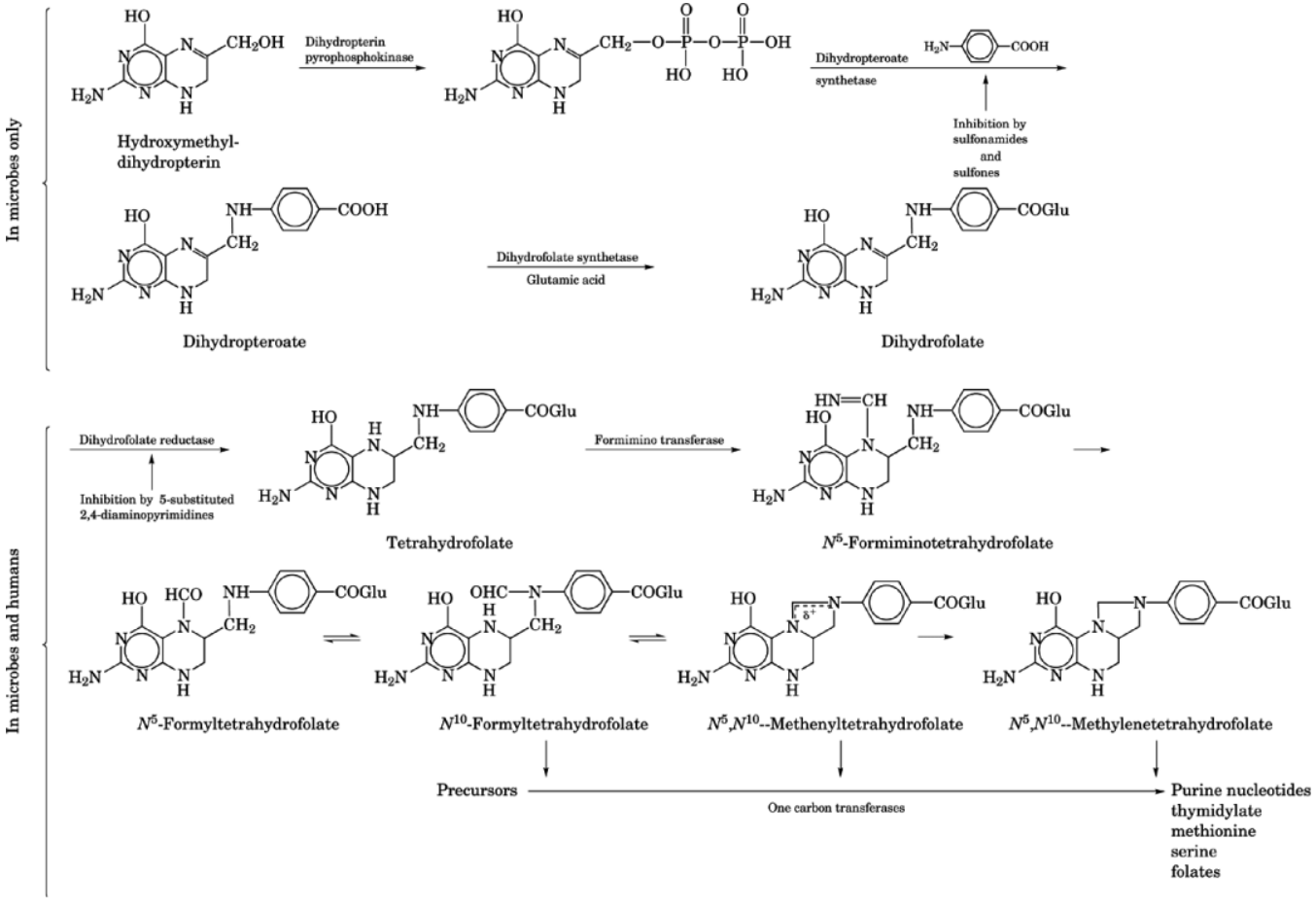


Fig. 1. Folate metabolism and sites of action of antifolates. Courtesy of Lea & Febiger (36).

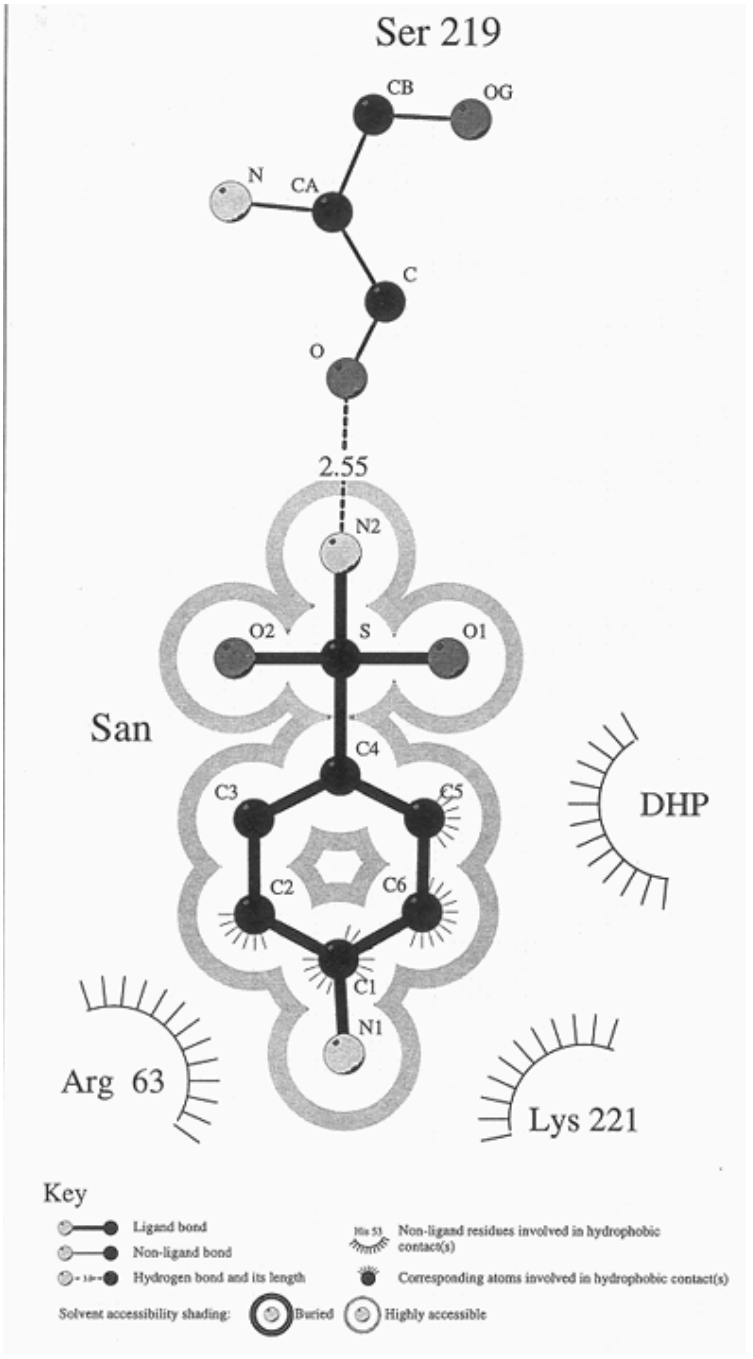
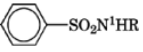


Fig. 2. Intermolecular interactions between sulfanilamide (San) and dihydropteroate synthase (DHP). Reprinted with permission from (42).

Table 1. **Sulfonamides of Structure** 

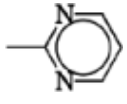
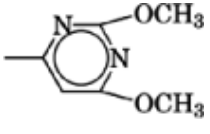
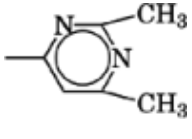
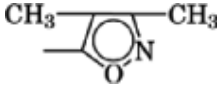
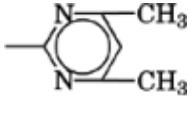
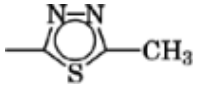
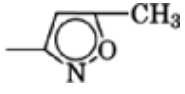
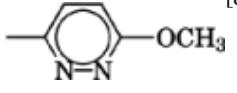
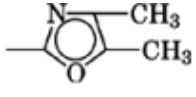
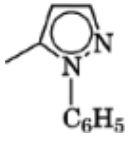
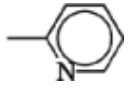
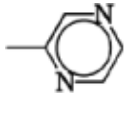
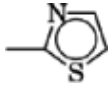
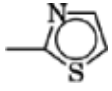
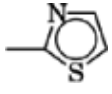
Generic name	R	CAS Registry Number	pK_a	Solubility in water, 25°C, mg/100 mL	Liposolubility, %[a]	Human plasma half-life[a], h	Protein binding[b] % bound
R′ = H							
sulfanilamide	H	[16-74-1]	10.5	750	71	9	9
sulfacetamide	—$COCH_3$	[144-80-9]	5.4	>670	2.0	7	9.5
sulfadiazine		[68-35-9]	6.5	8	26.4	17	37.8
sulfadimethoxine		[122-11-2]	6.1	<4.6	78.7	40	92.3
sulfaguanidine	—$C(NH)NH_2$	[57-67-0]	12.05	100		5	
sulfisomidine		[515-64-0]	7.4	~200	19	7.5	67
sulfisoxazole		[127-69-5]	5.0	350[c]	4.8	6	76.5
sulfamethazine		[57-68-1]	7.4	~100	82.6	7	66

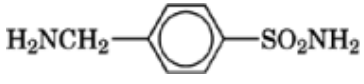
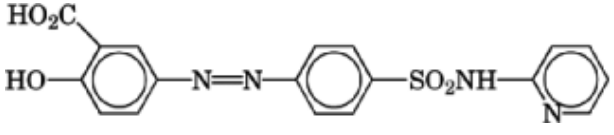
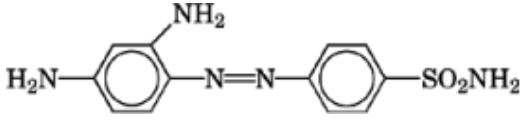
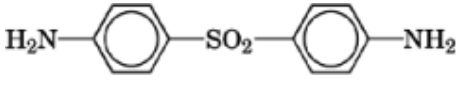
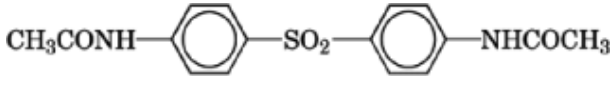
Table 1. (*Continued*)

Generic name	R	CAS Registry Number	pK_a	Solubility in water, 25°C, mg/100 mL	Liposolubility, %[a]	Human plasma half-life[a], h	Protein binding[b] % bound
sulfamethizole		[144-82-1]	5.5	25		2.5	22
sulfamethoxazole		[723-46-6]	6.0		20.5	11	60
sulfamethoxypyridazine		[80-35-3]	7.2	110 (pH5)	70.4	37	77
sulfamoxole		[729-99-7]	7.4	85	41.4	11	76.5
sulfaphenazole		[526-08-9]	6.1	150	69	10	87.5
sulfapyridine		[144-83-2]	8.4	30	14	9	70
sulfapyrazine		[116-44-9]	6.0	5			

sulfathiazole		[72-14-0]	7.25	60	15.3	4	68
$R' =$ phthalyl							
N^4-phthalylsulfathiazole		[85-73-4]	acid	sol (pH 7)			
$R' =$ succinyl							
N^4-succinylsulfathiazole		[116-43-8]	acid	20			

[a] Ref. 4, pp. 554–557; Determined by partition between ethylene dichloride and sodium phosphate buffer.
[b] At 1.0 μmol/mL.
[c] N'-acetylsulfisoxazole [80-74-0] water solubility = 7 mg/100 ml.

Table 2. **Sulfones and Other Structures Related to Sulfonamides**

Generic name	Structure	CAS Registry Number	Solubility in water, 25°C mg/100 mL	Human plasma half-life[a]
mafenide		[138-39-6]	sol (salt)	
sulfasalazine		[599-79-1]	sol (pH7)	
sulfamidochrysoidine (Prontosil)		[103-12-8]	sol (salt)	
dapsone[b]		[80-08-0]	insol	20 h[c]
acedapsone		[77-46-3]	0.3	43 d[d]

[a] Ref. 4, pp. 554–557.
[b] pK_a of protonated form = 1.3.
[c] Protein binding at 1.0 μmol/mL = 50% bound.
[d] Intramuscularly.

Table 3. **United States Production of Sulfonamides and Antibiotics, t**[a]

Drug	1943	1946	1956	1966	1975	1987	1994
total sulfa drugs	9077	4630	3462	4944	2122	5557[b]	4842[b]
total antibiotics	0	34.5	1784	8756	8312	16,099	41,608

[a] From Ref. 62.
[b] Also includes antiprotozoan agents and other urinary tract antiinfectives, but does not include the antileprotic sulfones.