ANTIBACTERIAL AGENTS, OVERVIEW

1. Introduction

Antibacterial agents are synthetic compounds derived from petrochemical sources and other small chemical building blocks that either kill or prevent the growth of bacteria. For the purposes of this survey, antibacterial agents are distinguished from antibiotics, antiseptics, disinfectants, and preservatives. Antibiotics are chemical substances isolated from natural sources, or their semisynthetic derivatives, that kill microorganisms or inhibit their growth (see also ANTIBIOTICS). Antiseptics are chemical substances with antimicrobial properties that are used on the surface of living tissues, such as the skin or mucous membranes. In contrast to antibacterial agents and antibiotics, antiseptics do not necessarily exhibit selective toxicity for the microbial cell relative to the host cell. Disinfectants are chemical substances that kill microorganisms when applied to inanimate objects. Preservatives are generally static agents that slow the decomposition of organic substances by inhibiting the growth of microorganisms.

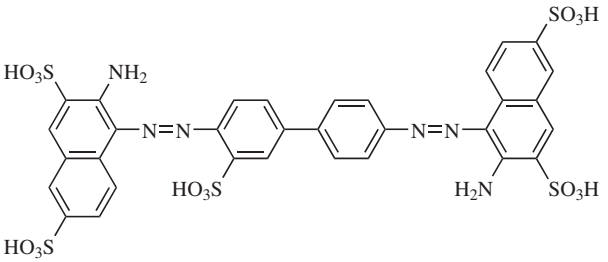
Antibacterial agents are commonly used to treat and/or prevent infections due to pathogenic bacteria in humans and animals. Although injectable dosage forms of some antibacterial agents have been developed, most of the drugs used in modern antibacterial chemotherapy were designed to achieve high systemic blood levels following oral administration. Consequently, antibacterial agents, with molecular weights in the range of 135–400 amu, tend to be less complex molecules than antibiotics. Given their synthetic origin, the antibacterial agents also contain few or no chiral centers, in contrast to antibiotics derived from natural sources, which frequently contain multiple contiguous stereocenters.

Thousands of analogues of antibacterial agents have been prepared in an effort to identify compounds with an enhanced spectrum of activity, improved pharmacokinetics, or a greater safety margin. Nevertheless, a relatively small number (~100) of antibacterial agents have been marketed for clinical or veterinary use.

The mechanism of action of antibacterial agents varies depending on the structural class. Some agents interfere with bacterial deoxyribonucleic acid (DNA) or protein synthesis (quinolones, oxazolidinones); others inhibit the activity of an enzyme or enzymes involved in bacterial cell metabolism (sulfonamides, diaminopyrimidines, nitrofurans, isoniazid, ethionamide). In the case of the sulfonamides and the antitubercular agents, the molecular target(s) are unique to the bacterial cell. The quinolones, oxazolidinones, and diaminopyrimidines are selectively toxic to bacteria owing to their greater affinity for the bacterial target than the mammalian counterpart. Some classes of antibacterial agents, such as the sulfonamides, nitrofurans, and oxazolidinones are bacteriostatic (ie, bacterial cell growth is inhibited). Others, such as the quinolones (against gram-positive and gram-negative bacteria) and isoniazid (against mycobacteria), are bactericidal (ie, bacteria are killed).

2. History

A systematic search for synthetic antiinfective agents began in the early 1900s with Ehrlich's pioneering research as Director of the Institute for Experimental Therapy in Frankfurt. In 1904, Ehrlich demonstrated the curative effect of the azo-dye trypan red (**1**) [574-64-1] in mice infected with trypanosomiasis (in humans, diseases such as sleeping sickness and Chagas' disease) (1). The drug was ineffective in humans, but this discovery proved that small molecular weight compounds were of value in the treatment of infectious diseases. Ehrlich's interest in organoarsenical compounds led to the subsequent discovery in 1909 of arsphenamine (Salvarsan) (**2**) [139-93-5] and neoarsphenamine (Neosalvarsan) (**3**) [457-60-3] as treatments for syphilis in humans (2), validating the scientific principles of chemotherapy he first enunciated in the late 1890s. During the next 20 years, the vast majority of research in antiinfective chemotherapy was directed toward the discovery of agents for the treatment of protozoal and parasitic diseases.



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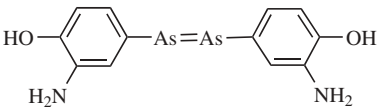

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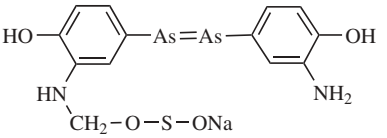
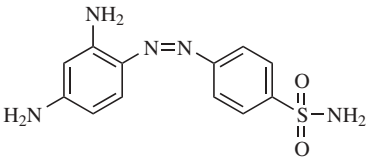


(**3**)

Application of Ehrlich's principles to antibacterial research began in the mid-1930s with the work of Domagk and colleagues at the German chemical firm, I.G. Farbenindustrie. Domagk led the group investigating the effects of various chemical dyes in experimental animal models of infection. In 1932, he discovered that the azo-dye, sulfamidochrysoidine (Prontosil) (**4**) [103-12-8], was effective in preventing death in mice infected with hemolytic streptococci and in rabbits infected with staphylococci (3). Subsequent clinical studies demonstrated the remarkable properties of this drug in the treatment of puerperal sepsis, meningitis and pneumonia (4). Later research by a French group at the Institute Pasteur showed that sulfamidochrysoidine was actually a prodrug, which is metabolized in the body to the bioactive compound sulfanilamide (5) [63-74-1] (5). The identification of the active metabolite facilitated the rapid development of the antibacterial sulfonamides (the sulfa drugs) derived from the sulfanilamide molecular template (6). One of these analogues, sulfamethoxazole (**6**), is still widely used in the clinic. Domagk's discovery proved that it was possible to discover small synthetic agents effective against bacterial infection, and stimulated interest in the identification of additional substances with broad-spectrum antibacterial activity.



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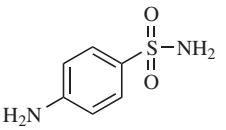

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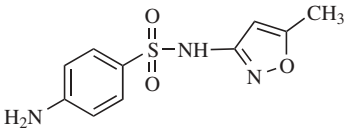
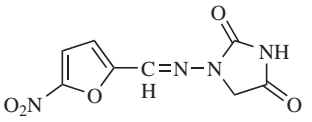


(**6**)

The work of Dodd, Stillman, and others on nitroheterocycle derivatives in the mid-1940s led to a number of nitrofuran drugs, among which nitrofurantoin (**7**) [67-20-9] and nitrofurazone (**8**) [59-87-0] are still used in clinical practice (7–9), in spite of multiple laboratory findings of mutagenicity (10,11). Nitrofurantoin, in particular, is active against a wide spectrum of gram-positive and gram-negative bacteria, including most urinary tract pathogens. Subsequently, the antitubercular effects of isoniazid (**9**) [54-85-3], pyrazinamide (**10**) [98-96-4] and ethionamide (**11**) [536-33-4] were described, based on earlier research that had uncovered the weak tuberculostatic activity of the structurally related compound, nicotinamide (**12**) (12–15). Optimization of the antimycobacterial activity of a series of ethylenediamine derivatives by Wilkinson and colleagues at Lederle Laboratories ultimately led to a structurally distinct antituberculous compound, ethambutol (**13**) [74-55-5] (16).



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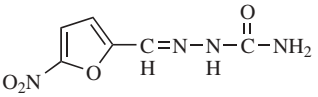

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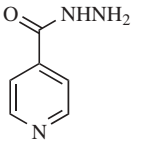

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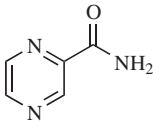

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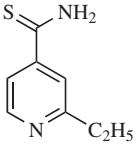

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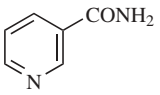

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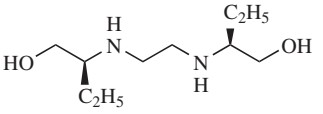
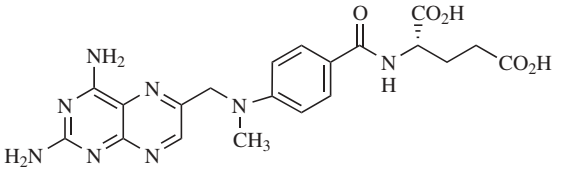


(**13**)

In the 1950s and 1960s, Hitchings and Elion of Wellcome Research Labs showed that selective inhibition of parasitic enzymes rather than the host enzymes could be exploited for chemotherapeutic ends. Through a series of iterative modifications of the non-selective dihydrofolate reductase inhibitor amethopterin (methotrexate) (**14**) [59-05-2], Hitchings discovered the simplified structure, pyrimethamine (**15**) [58-14-0], which is 2000-fold more selective for the dihydrofolate reductase from the malarial parasite, *Plasmodium berghei*, than the analogous mammalian enzymes (17). Despite increasing resistance to its action, pyrimethamine remains an important drug for the treatment of malaria in the tropical world. Further modification of the basic diaminopyrimidine scaffold led to trimethoprim (**16**) [738-70-5], which is particularly potent and selective for the dihydrofolate reductase from bacteria (18).



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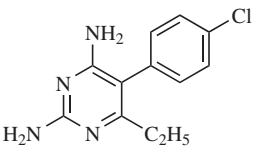

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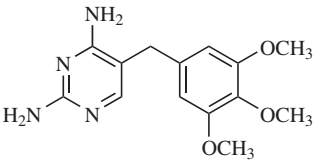
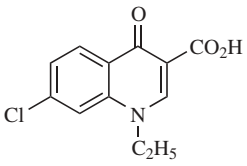


(**16**)

The next significant advance in the medicinal chemistry of antibacterial agents occurred in the late 1950s due to the astute observations of Lesher at Sterling-Winthrop Research Institute. As part of a study directed toward

the characterization of by-products in the synthesis of the antimalarial drug chloroquine, Lesher and his colleagues isolated 7-chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**17**) [16600-24-1], which showed weak *in vitro* antibacterial activity (19). Capitalizing on this discovery the Sterling chemists prepared a number of analogues, ultimately leading to the 1,8-naphthyridine derivative nalidixic acid (**18**) [389-08-2] (20). Although the antibacterial and pharmacokinetic properties of nalidixic acid limited its clinical use to gram-negative infections of the urinary tract, Lesher's discovery opened up a rich vein in antibacterial research, such that the quinolone class of antibacterial agents (including the 4-quinolones and 1,8-naphthyridine-4-ones) now accounts for 19.6% of the global antibacterial agents and antibiotics market (21). Structural modification of the quinolone nucleus afforded analogs, such as ciprofloxacin (**19**) [85721-33-1] and levofloxacin (**20**) [100986-85-4], with excellent oral bioavailability, good tissue distribution, prolonged serum half-lives and improved safety margins (22). Many of the newer quinolone antibacterial agents have increased activity against gram-positive bacteria (23).



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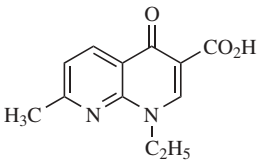

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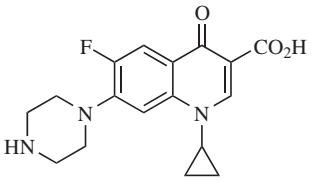

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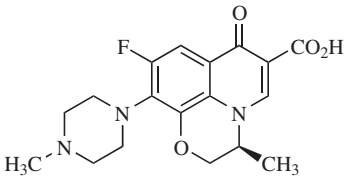
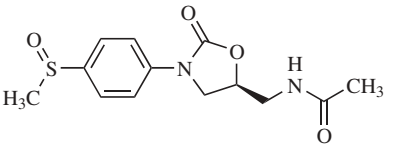


(**20**)

The dramatic increase in the prevalence of multidrug-resistant bacterial pathogens during the 1970s and 1980s was the stimulus for further research into new antibacterial agents at several pharmaceutical companies (24). The oxazolidinones emerged as a viable new class of synthetic antibacterial agents following broad screening of the DuPont Corporation compound library. Analogues such as DuP 105 (**21**) [96800-41-8] and DuP 721 (**22**) [104421-21-8] were attractive as potential drug development candidates because they were active against the important hospital pathogen, methicillin-resistant *Staphylococcus aureus* (25). A concerted effort at Pharmacia Corporation to improve the safety and aqueous solubility of the class led to the market introduction in 2000 of linezolid (**23**) [165800-03-3], with activity against vancomycin-resistant enterococci (26). Linezolid represented the first new class of antibacterial agent to gain FDA approval in 35 years (27).



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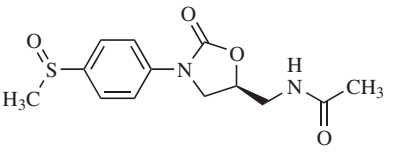

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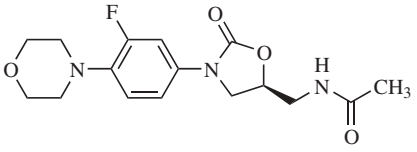


(**23**)

It is noteworthy that Domagk (1939) and Hitchings and Elion (1988) each received the Nobel Prize in Physiology or Medicine for their fundamental contributions to antibacterial chemotherapy. Table 1 lists years of historical significance to the development of selected synthetic antibacterial agents.

3. Nomenclature

Antibacterial agents are identified by three different types of names:

1. The chemical name is usually long and cumbersome and is based on conventional chemical nomenclature rules.
2. The generic name frequently has a common stem for a specific class of agents. For example, the generic names for the quinolone family end in

Table 1. **Year of Disclosure or Market Introduction of Selected Antibacterial Agents**

Antibacterial agent	CAS Registry Number	Year	
		Disclosure	Introduction
sulfamidochrysoidine	[103-12-8]	1932	1936
sulfapyridine	[144-83-2]	1938	
acetyl sulfisoxazole	[80-74-0]		1949
isoniazid	[54-85-3]		1952
pyrazinamide	[98-96-4]		1952
nitrofurantoin	[67-20-9]		1953
pyrimethamine	[58-14-0]	1950	
trimethoprim	[738-70-5]	1956	
nalidixic acid	[389-08-2]	1962	1965
trimethoprim–sulfamethoxazole	[8064-90-2]		1969
norfloxacin	[70458-96-7]	1978	1983
ciprofloxacin	[85721-33-1]	1983	1986
levofloxacin	[100986-85-4]	1987	1993
linezolid	[165800-03-3]	1995	2000

"-oxacin." Since this is a nonproprietary name, more than one brand name drug can have the same generic name.

3. The brand (trade) name is a proprietary name given by the manufacturer and is often based on commercial considerations.

The following example shows the difference between the three types of names for the same compound.

1. Chemical name—(*S*)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid
2. Generic name—levofloxacin
3. Trade name—Levaquin

Generic names are usually preferred in scientific communications, and will be used when applicable in this report.

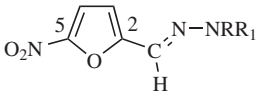
4. Classification of Antibacterial Agents

Antibacterial agents can be classified according to their molecular features. Agents within the same chemical family usually act by the same mechanism of action. However, since several chemical classes may exert the same, or closely related, mode of action, antibacterial agents may also be broadly classified according to the bacterial target affected. It is also possible to classify agents according to the therapeutic indication. For the purposes of this survey, antibacterial agents will be classified either according to the clinical indication for which the drug is used (eg, antitubercular agents), or according to the salient molecular features (eg, oxazolidinones).

4.1. Antitubercular Agents. The synthetic first-line antitubercular agents can be subdivided into two broad categories according to structure. The first group, consisting of isoniazid (**9**), pyrazinamide (**10**), and ethionamide (**11**) contain a heteroaryl hydrazide, amide, or thioamide. Isoniazid and ethionamide are metabolized by mycobacteria to electrophilic intermediates, which then inhibit the synthesis of mycolic acids essential to bacterial viability (28,29). Pyrazinamide has been shown to inhibit fatty acid synthesis by preventing the formation of precursors needed for the synthesis of mycolic acids (30). Conversion to pyrazinoic acid by a bacterial pyrazinamidase appears to be necessary, as mutations leading to the loss of enzymatic activity are a major mechanism of resistance. These agents all exhibit activity against *Mycobacterium tuberculosis*. Ethionamide also inhibits the growth of other slowly growing mycobacteria. Despite chemical similarities, these three agents do not always exhibit cross-resistance (31).

The second structural type of antitubercular agents is represented by ethambutol (**13**), which contains a symmetrical diamino-dihydroxy aliphatic chain. It has been proposed that ethambutol prevents mycobacterial cell wall synthesis by inhibiting the production of arabinan (32,33).

4.2. Nitrofurans. The nitrofuran class of antibacterial agents contain a 5-nitro-2-furanyl moiety. Compounds in this family (**7**,**8**) are usually hydrazone derivatives of 5-nitro-2-furancarboxaldehyde [698-63-5], of general structure (**24**). However, several compounds are olefinic derivatives, such as (**25**). An example of this type of nitrofuran is 3-(5-nitro-2-furyl)acrylamide (**26**) [710-25-8]. It has been shown that nitrofurans are converted by bacterial reductases to reactive intermediates that can inhibit a number of bacterial enzymes, including those responsible for DNA and ribonucleic acid (RNA) synthesis and carbohydrate metabolism (34). Due to the multiple mechanisms of action, resistance to the nitrofurans has not been a major concern. This class is active against a wide spectrum of gram-positive and gram-negative organisms, including enterococci and *Escherichia coli*, respectively, but has dropped out of widespread use in the United States for severe infections due to the discovery and development of new classes of agents.



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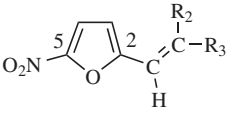

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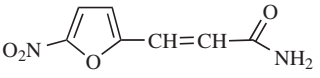
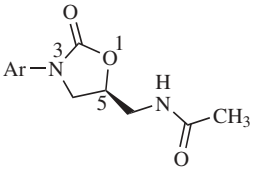


(**26**)

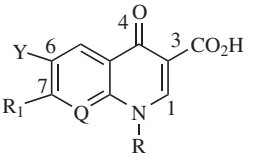
4.3. Oxazolidinones. The oxazolidinone class of antibacterial agents, exemplified by linezolid (**23**), contains a 3-aryl-5-acetamidomethyloxazolidin-2-one (**27**) pharmacophore essential for biological activity. These agents selectively bind to the P site of the 23S RNA component of the 50S ribosomal subunit, thus inhibiting protein synthesis at an early stage of translation, possibly by inhibiting translocation of fMet-tRNA (35). Oxazolidinones have microbiological activity against a variety of susceptible and multidrug-resistant gram-positive organisms.



(**27**)

4.4. Quinolones. The 4-quinolone class of antibacterial agents (**28**) contains a 3-carboxylic acid attached to the core quinolone (Q = CR_2) or naphthyridone (Q = N) nucleus. In addition, the N-1 nitrogen is arylated or alkylated. The moiety at C-7, appended to the core via a carbon or a nitrogen atom, generally contains a basic amine, which enhances the antibacterial spectrum as well as improving *in vivo* efficacy. Substitution of fluorine at C-6 (Y = F) usually leads to a compound with enhanced potency against gram-positive organisms when compared to the analogous des-fluoro analogue (Y = H). The quinolones target the essential bacterial type II topoisomerases, DNA gyrase and topoisomerase IV, the relative potency depending on the organism and the specific compound.

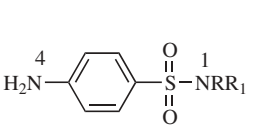
Quinolones are broad-spectrum bactericidal agents against a variety of gram-positive and gram-negative pathogens, including some anaerobic bacteria and intracellular pathogens.



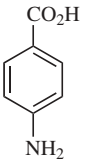
$Q = CR_2, N$
$Y = H, F$

(**28**)

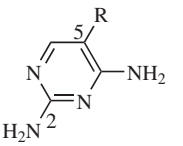
4.5. Sulfonamides and 2,4-Diaminopyrimidines. The sulfonamide class of antibacterial agents (**29**) includes N-1 derivatives of *para*-aminobenzenesulfonamide [sulfanilamide (**5**); $R = R_1 = H$]. Sulfonamides compete with *para*-aminobenzoic acid (PABA) (**30**) [150-13-0] for incorporation into folic acid in a reaction catalyzed by dihydropteroate synthase (36). The 5-substituted-2,4-diaminopyrimidines inhibit the enzyme dihydrofolate reductase, the next step in the biosynthesis of tetrahydrofolic acid. Combination therapy of sulfonamides and 5-substituted-2,4-diaminopyrimidines (**31**), such as pyrimethamine (**15**) and trimethoprim (**16**), is frequently employed, based on George Hitchings' concept of using two metabolite analogues for "sequential blocking" of enzymes in a biochemical pathway (37). In particular, the drug combinations, sulfadoxine-pyrimethamine and trimethoprim-sulfamethoxazole [8064-90-2] have been used to treat uncomplicated malaria and bacterial urinary tract infections, bronchitis and otitis media, respectively. These agents are bacteriostatic. Emergence of resistance to sulfonamides as well as the introduction of new classes of more potent antibacterial agents has diminished the clinical usefulness of this class.



(**29**)



(**30**)

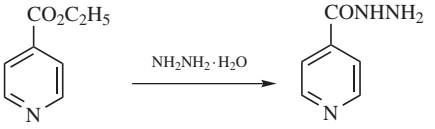


(**31**)

5. Preparation and Manufacture

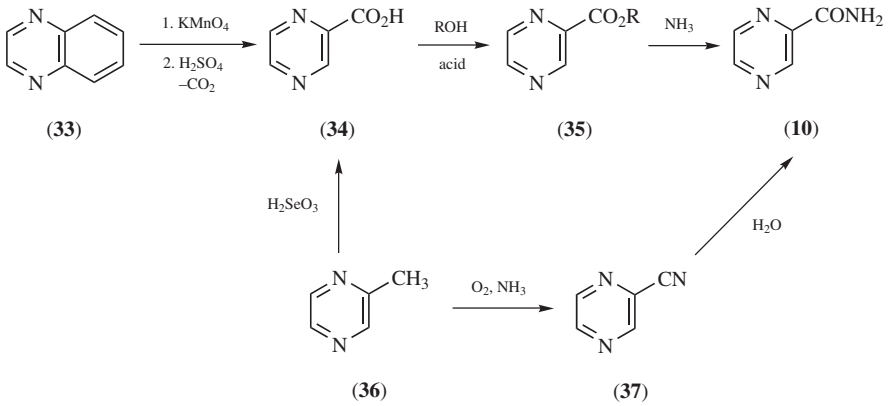
5.1. Antitubercular Agents. Isoniazid, pyrazinamide and ethionamide, related in structure, are manufactured by similar routes. Isoniazid (**9**) is prepared by condensation of ethyl isonicotinate (**32**) [1570-45-2] with hydrazine hydrate [7803-57-8] (eq. 1) (38), or alternatively by heating 4-cyanopyridine [100-48-1] with hydrazine hydrate in aqueous alkaline solution (39). A variation of this procedure involves the reaction of isonicotinic acid [55-22-1] with

hydrazine hydrate in the presence of a catalyst, such as alumina [1344-28-1], titanium tetrabutoxide [5593-70-4], or a sulfonic acid cation exchanger (40,41).



(32) (9) (1)

Pyrazinamide (**10**) is produced by ammonolysis of an alkyl ester of pyrazinoic acid (**35**) (eq. 2) (42,43). Alternatively, pyrazinamide can be obtained from the reaction of pyrazinecarbonitrile (**37**) [19847-12-2] with aqueous ammonia or by hydrolysis of pyrazinecarbonitrile under acidic or alkaline conditions (44–46). The alkyl pyrazinoates are produced by acid-catalyzed esterification of pyrazinoic acid (**34**) [98-97-5] in the presence of a lower alkanol (47). Pyrazinoic acid, in turn, is prepared by two general methods: 1) potassium permanganate [7722-64-7] oxidation of quinoxaline (**33**) [91-19-0], followed by decarboxylation of the intermediate pyrazine-2,3-dicarboxylic acid [89-01-0], and 2) oxidation of methylpyrazine (**36**) [109-08-0] with selenious acid [7783-00-8] in pyridine or, alternatively, reaction of ethylpyrazine [13925-00-3] with potassium permanganate (42,48). Pyrazinecarbonitrile is readily prepared by ammonoxidation of methylpyrazine (49).

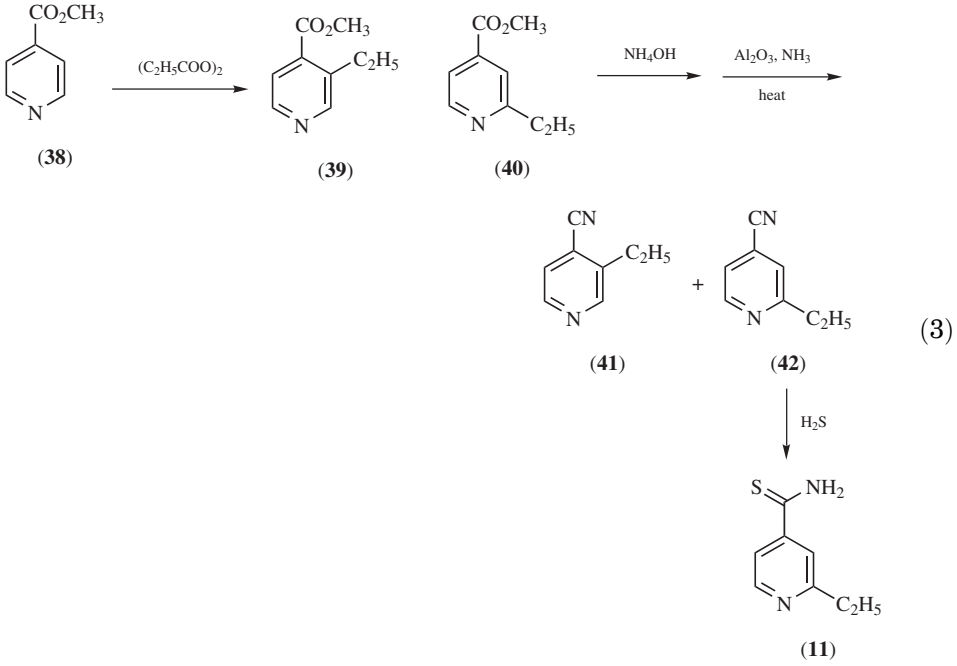


(33) (34) (35) (10)

(36) (37) (2)

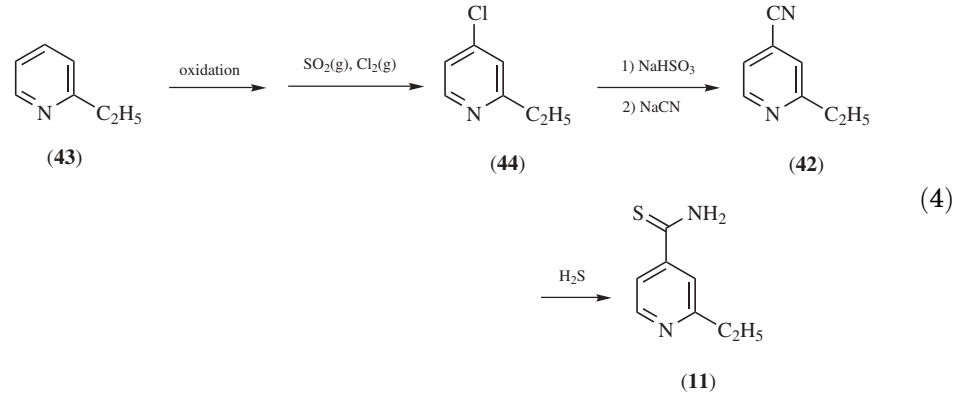
Two general methods are available for the preparation of ethionamide (**11**). Both routes converge at the key intermediate, 4-cyano-2-ethylpyridine (**42**) [1531-18-6], which is converted to ethionamide by treatment with hydrogen sulfide gas (50). In the first method, radical alkylation of methyl isonicotinate (**38**) [2459-09-8] with dipropionyl peroxide [3248-28-0] solution affords a mixture of 3-ethyl and 2-ethyl isomers (**39**) [13341-16-7] and (**40**) [1531-16-4], which can be converted to the corresponding 4-cyanopyridine derivatives (**41**) [13341-18-9] and (**42**) by condensation with ammonia, followed by dehydration of the resulting amide in the presence of alumina (eq. 3). Distillation of the mixture at atmospheric pressure affords 4-cyano-3-ethylpyridine (**41**) and the desired 4-cyano-2-ethylpyridine (**42**) in a ratio of 1:1.7 (50). Alternatively, 4-cyano-2-ethylpyridine can be prepared directly by radical alkylation of 4-cyanopyridine. The

reaction provides a 4:1 mixture of 4-cyano-2-ethylpyridine and 4-cyano-2,6-diethylpyridine [37581-44-5], which can be separated by distillation. 4-Cyanopyridine, in turn, is obtained by ammonoxidation of 4-picoline [108-89-4] (51).



(38) (39) (40) (41) (42) (11) (3)

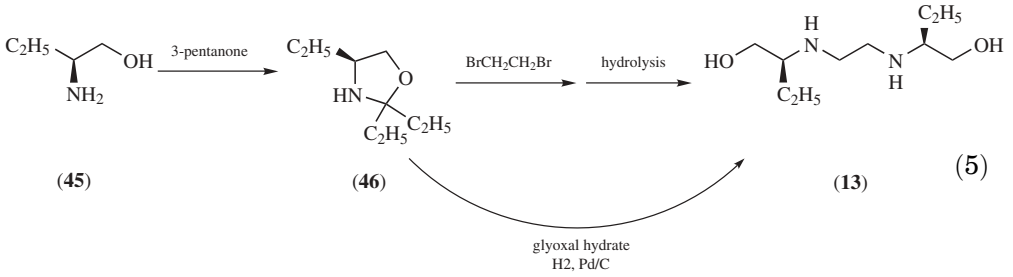
In the second general method, 2-ethylpyridine (**43**) [100-71-0] is converted to 4-cyano-2-ethylpyridine (**42**) through a series of steps, including oxidation to 2-ethylpyridine-*N*-oxide [4833-24-3], chlorination to give 4-chloro-2-ethylpyridine (**44**) [3678-65-7], treatment with an alkali metal bisulfite or pyrosulfite to give the intermediate 2-ethylpyridine-4-sulfonic acid [939-96-8], and finally reaction with an alkali metal cyanide (eq. 4) (52).



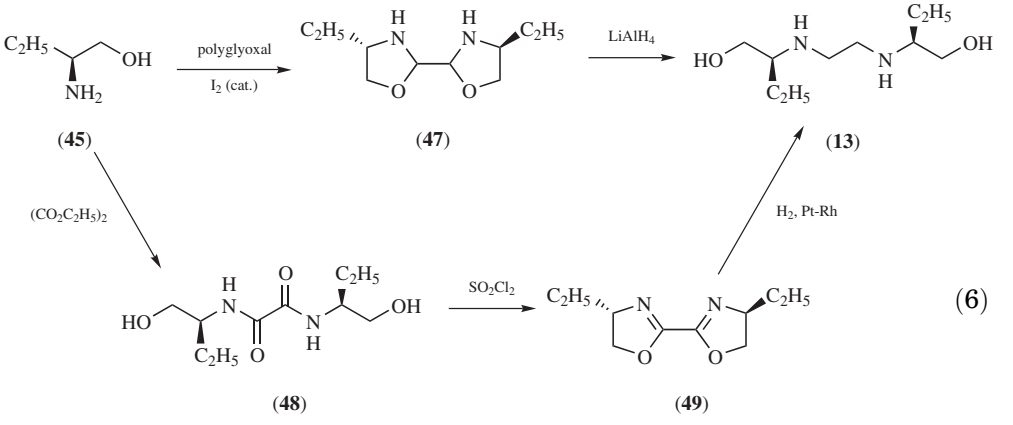
(43) (44) (42) (11) (4)

A number of methods for the manufacture of ethambutol (**13**), (+)-*N*,*N*′-bis[1-(hydroxymethyl)propyl]ethylenediamine, have been described. The vast majority begins with (+)-2-amino-1-butanol (**45**) [5856-62-2], obtained from

resolution of racemic 2-amino-1-butanol [96-20-8] with L-glutamic acid [56-86-0] (53). Direct alkylation of (+)-2-amino-1-butanol with 1,2-dichloroethane [107-06-2] has been reported to give a 42% yield of ethambutol (54). Other methods appear to be more amenable to large-scale synthesis, however. Condensation of (+)-2-amino-1-butanol (**45**) with 3-pentanone [96-22-0] to give (+)-2,2,4-triethyloxazolidine (**46**) [28507-97-3] followed by alkylation with 1,2-dibromoethane [106-93-4] and hydrolysis gives ethambutol (eq. 5) (55). Alternatively, ethambutol can be prepared by reductive alkylation of (+)-2,2,4-triethyloxazolidine (**46**) with glyoxal hydrate [631-59-4] in the presence of hydrogen gas and palladium on carbon as catalyst (56). Hydrogenolysis of D-4,4′-diethyl-2,2′-bisoxazoline (**49**) [36697-75-3] over Pt-Rh catalysts or lithium aluminum hydride reduction of (+)-4,4′-diethyl-2,2′-bisoxazolidine (**47**) [4486-39-9] also affords ethambutol (eq. 6) (57,58). D-4,4′-Diethyl-2,2′-bisoxazoline is prepared from (+)-2-amino-1-butanol by condensation with diethyl oxalate [95-92-1] followed by bis-cyclodehydration of the resulting glyoxalamide (**48**) [61051-11-4] with sulfuryl chloride [7791-25-5] (57). (+)-4,4′-Diethyl-2,2′-bisoxazolidine can be obtained from (+)-2-amino-1-butanol by treatment with polyglyoxal [25266-42-6] in the presence of catalytic iodine [7553-56-2] (59).



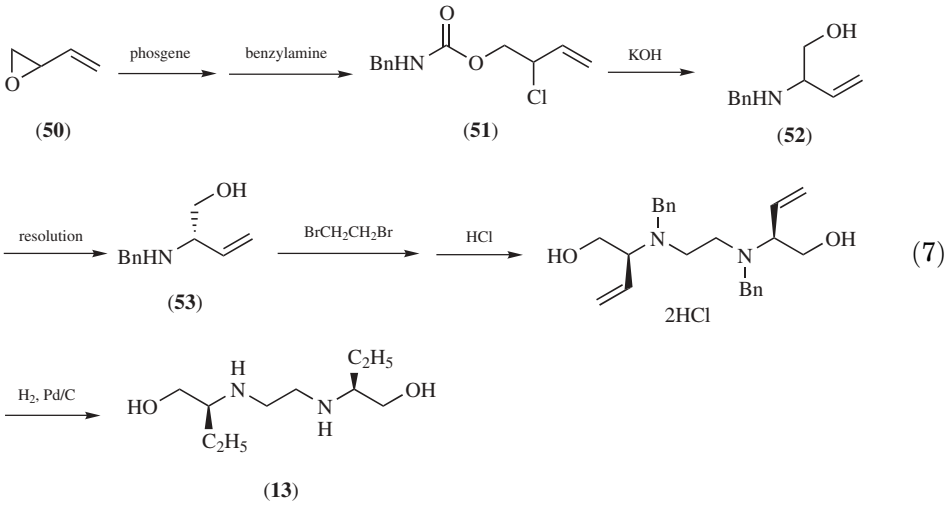
(**45**) (**46**) (**13**) (5)



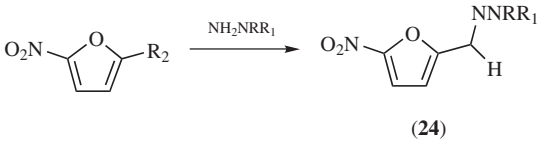
(**45**) (**47**) (**13**) (**48**) (**49**) (6)

Another approach to the preparation of ethambutol (**13**) uses butadiene monoepoxide (**50**) [930-22-3] (60) as an inexpensive source of the carbon atoms of the molecule (eq. 7). Treatment of butadiene monoepoxide with phosgene [75-44-5] followed by reaction with benzylamine [100-46-9] produces 2-chloro-3-butenyl benzylcarbamate (**51**) [50297-20-6], which on reaction with potassium hydroxide or sodium hydroxide in ethanol affords 2-benzylamino-3-buten-1-ol

(**52**) [50838-63-6] through displacement of chloride by the carbamate nitrogen followed by cyclic carbamate hydrolysis. Resolution with (+)-dibenzoyltartaric acid [17026-42-5] to give (+)-2-benzylamino-3-buten-1-ol (**53**) [50297-23-9], followed by reaction with 1,2-dibromoethane, and hydrogenation over palladium on carbon gives ethambutol (61).



5.2. Nitrofurans. The majority of the nitrofurans (**24**) are commercially prepared by the condensation of either 5-nitro-2-furancarboxaldehyde (**54**) or 5-nitro-2-furancarboxaldehyde diacetate (**55**) [92-55-7] with the appropriate hydrazine derivative (eq. 8). Nitrofurans (**25**) are prepared in a similar manner utilizing a carbon nucleophile in place of the hydrazine derivative.



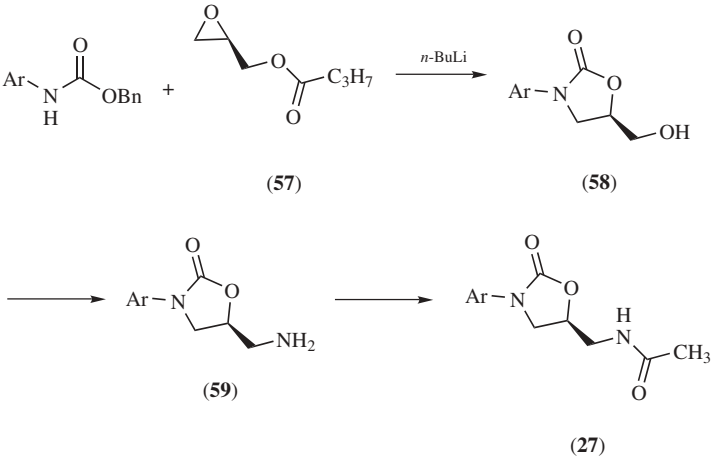
(8)

(**54**), R_2=CHO
(**55**), R_2=$CH(OC(O)CH_3)_2$

Nitrofurans (**54**) and (**55**) are commercially available but can also be prepared by nitration of 2-furancarboxaldehyde or the diacetate utilizing a variety of conditions.

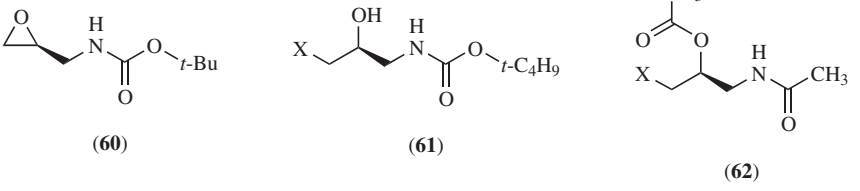
5.3. Oxazolidinones. In the typical drug discovery route for the synthesis of the oxazolidinone class of antibacterial agents, the oxazolidinone ring is formed by reaction of the anion of the appropriately substituted Cbz-protected aniline (**56**) with (*R*)-glycidyl butyrate (**57**) [60456-26-0] (eq. 9) (26). This reaction proceeds via epoxide opening by the carbamate anion, followed by cyclization to the oxazolidinone. The liberated benzyl alcohol anion cleaves the butyrate ester

to the alcohol. The resulting alcohol (**58**) is elaborated into amine (**59**), which is subsequently acetylated to afford (**27**).



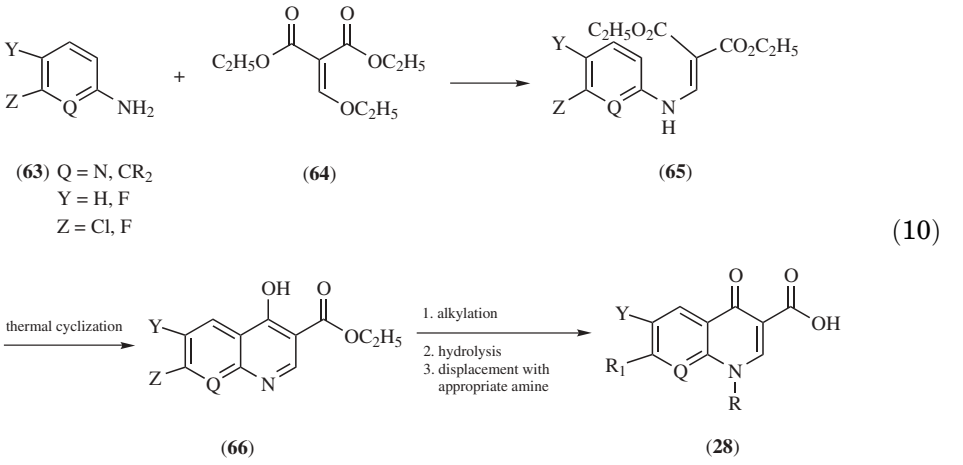
(9)

Several recent process patent applications have disclosed the condensation of carbamate (**56**) with nitrogen-containing three carbon reagents in place of (*R*)-glycidyl butyrate. Perrault and Gadwood describe the use of either (*S*)-Boc-protected glycidyl amine (**60**) [161513-47-9] or (*S*)-Boc-protected 1-amino-3-halo-2-propanol (**61**) to produce the Boc-protected aminomethyl oxazolidinone (62). Removal of the protecting group, followed by acetylation affords (**27**). A one-step process for the direct preparation of (**27**) from carbamate (**56**) utilizing (*S*)-*N*-{2-(acetyloxy)-3-chloropropyl}acetamide (**62**) [53460-78-9] or a similar derivative has also been disclosed (63).



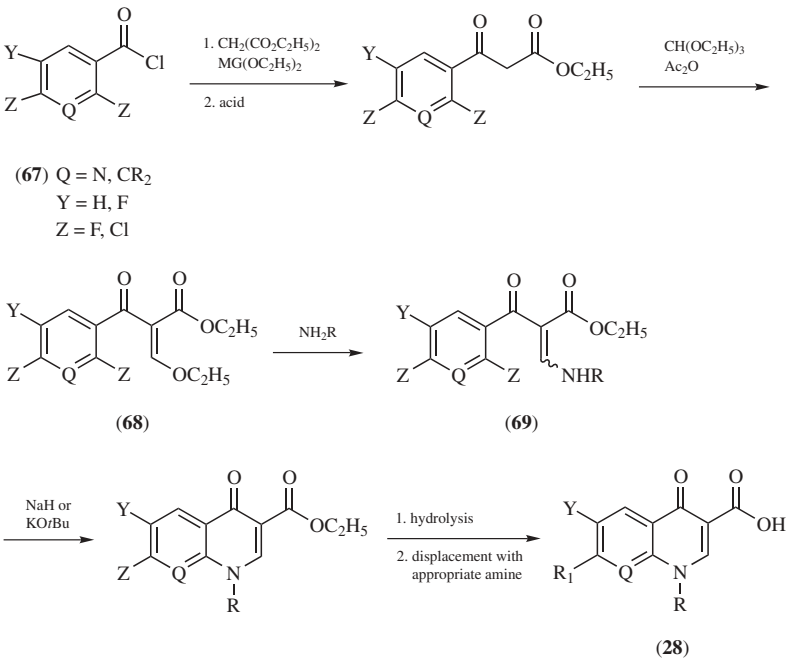
5.4. Quinolones. There are two common methods for the synthesis of the quinolone core structure. The earlier method relies on a Gould-Jacobs cyclization reaction between the appropriate aniline (**63**) and diethyl ethoxymethylenemalonate (**64**) [87-13-8] (eq. 10). Thermal cyclization of the resulting anilinomethylenemalonate (**65**) affords N-1 unsubstituted quinolone nucleus (**66**) (64). N-1 alkylation followed by hydrolysis and nucleophilic aromatic substitution with the appropriate amine produces the drug. Norfloxacin and other analogs of this type have been synthesized in this manner. However, this method is unsatisfactory for N-1 aryl substituents or for substituents that would be derived from an unreactive alkyl halide, such as cyclopropyl. In addition, there is the

potential for the formation of regioisomers during the cyclization of unsymmetrical anilines.

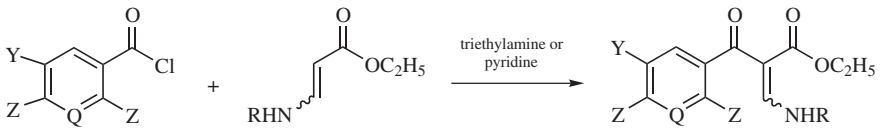


(10)

The most widely utilized methodology allows for greater flexibility and produces a wide variety of quinolones including the tricyclic analogues (eqs. 11 and 12). The ring closure occurs by an intramolecular nucleophilic aromatic substitution reaction of enamine (**69**) (65). In turn, enamine (**69**) may be prepared by two slightly different routes. Acid chloride (**67**) may be transformed into enamine (**69**) in several steps via the enol ether (**68**) or, alternatively, it may be converted to enamine (**69**) in one step by reaction with the appropriately substituted 3-aminoacrylate (**70**) (66). Ciprofloxacin, levofloxacin and numerous other quinolones have been synthesized via this type of nucleophilic aromatic substitution reaction.



(11)

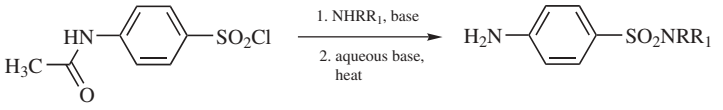


(12)

(**67**) Q = N, CR_2
Y = H, F
Z = F, Cl

(**70**) (**69**)

5.5. Sulfonamides and 2,4-Diaminopyrimidines. The sulfonamides (**29**) are usually prepared by the reaction of *N*-acetylbenzenesulfonyl chloride (**71**) [121-60-8] with the appropriate amine and an equivalent of base (or 2 equiv of the appropriate amine), followed by basic hydrolysis of the acetamide functionality (67) (eq. 13). The sulfonyl chloride is synthesized by chlorosulfonation of acetanilide [103-84-4].



(13)

(**71**) (**29**)

6. Economic Aspects

Worldwide sales of antiinfective agents for the treatment of bacterial diseases were estimated at 23.0 billion dollars for the 12-month period ending September 2002 (21). For the same period, sales of synthetic antibacterial agents reached $5.2 billion, constituting 22.6% of the global bacterial diseases antiinfective market (21) (Table 2). The increasing use of the quinolones for the treatment of community-acquired infections over the last decade has played a key role in expanding market share for the synthetic antibacterial agents. In particular, quinolone sales surpassed $4.5 billion for the year-ending September 2002,

Table 2. **World Market for Synthetic Antibacterial Agents**[a]

Structural classification	Sales (millions)[b]	% Change[c]
quinolones	4,593	7.4
trimethoprim combinations	189	−7.1
systemic nitrofurans[d]	144	10.2
antitubercular drugs[e]	141	2.4
oxazolidinones	108[f]	125.0
systemic sulfonamides	13	−22.0

[a] World market for the 12-month period ending September 2002 estimated at $5.2 billion (21).
[b] In U.S. dollars. See Ref. (21).
[c] Relative to the previous 12-month period
[d] Represents U.S. sales of Macrobid (nitrofurantoin hydrate/macrocrystals) for 2001 (68).
[e] May include sales of the antibiotic rifampin as part of a single ingredient or multidrug therapeutic regimen.
[f] See Ref. (69).

Table 3. **Relative Share of the Synthetic Antibacterial Agents Market for 2001**[a]

Company	Market share, %
Bayer	37
Ortho-McNeil	20
Daiichi	8
Bristol-Myers Squibb	6
Aventis	6
Procter & Gamble[b]	3
Pharmacia	2
Hoffmann-La Roche	2
Others	16

[a] See Ref. 69.
[b] Represents U.S. sales of Macrobid (nitrofurantoin hydrate/macrocrystals) for 2001 (68).

which represented 88.5% of sales for the synthetic antibacterial agent category and 19.6% of the overall bacterial diseases antiinfective market.

In contrast, annual sales of most of the other classes of synthetic antibacterial agents were comparatively low. The market for systemic sulfonamides and trimethoprim combinations continues to decrease due to resistance emergence in key bacterial pathogens. Sales of antitubercular drugs (including the antibiotic rifampicin) have been escalating as tuberculosis has reached epidemic proportions in portions of Eastern Europe, Asia, and Africa. Nevertheless, the market for antitubercular drugs remains modest due to their relatively low cost and the inadequate distribution networks in many developing nations. Annual U.S. sales of the systemic nitrofuran antibacterial agent, nitrofurantoin, continue to increase due to its effectiveness in the treatment of urinary tract infections. Sales of linezolid, the sole marketed oxazolidinone antibacterial agent, have increased since its introduction as the drug is approved for new clinical indications and in additional countries.

As would be expected from the above, companies engaged in the manufacture and/or sales of quinolone antibacterial agents dominate the synthetic antibacterial agents market (Table 3).

7. Therapeutic Utility

7.1. Antitubercular Agents. Treatment of infections caused by *M. tuberculosis* is most effective when multiple drugs are used for at least 4 months, due to the slow growth of mycobacteria and their propensity to develop resistance during monotherapy. Regimens recommended by The American Thoracic Society Medical Section of the American Lung Association (70) and The Tuberculosis Committee of the Infectious Disease Society of America in conjunction with the Division of Tuberculosis Elimination of the Centers for Disease Control and Prevention employ the use of three drug combinations unless that particular geographic region reports more than 4% of TB isolates resistant to isoniazid, in

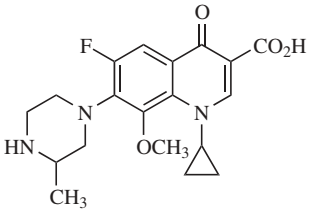
which case a four drug regimen is recommended (71). The most common combinations are isoniazid, rifampicin, and pyrazinamide, with the addition of either ethambutol or streptomycin depending upon geographical resistance profiles. A 6-month course of therapy is recommended unless multidrug-resistant bacteria are detected or treatment failure is observed, at which time at least two new agents are added to the regimen and treatment is continued for up to 18–24 months. Note that rifampicin and streptomycin are considered to be antibiotics, and, as such, are discussed in detail elsewhere. If a fully drug-susceptible strain is involved, a two drug regimen may be employed, such as rifampicin and isoniazid. Isoniazid alone for up to 12 months, or a rifampicin–pyrazinamide regimen for 2 months, has been recommended for prophylactic treatment of TB-infected asymptomatic HIV-infected patients (71,72).

7.2. Nitrofurans. Urinary tract infections are the major area in which nitrofurans are used. Nitrofurantoin is specifically indicated for treatment of urinary tract infections caused by susceptible strains of *E. coli*, enterococci, *S. aureus*, *Klebsiella*, and *Enterobacter* species. Nitrofurantoin is not indicated for the treatment of more complicated renal infections, such as pyelonephritis or perinephric abscesses (73). Certain nitrofuran derivatives have been used in veterinary practice to treat or prevent protozoal and bacterial infections in both nonfood and food-producing animals. Use of these carcinogenic and teratogenic drugs, however, results in unacceptably elevated residues in edible tissues, leading to an FDA ban on the use of nitrofurans in food-producing animals in May 2002 (74).

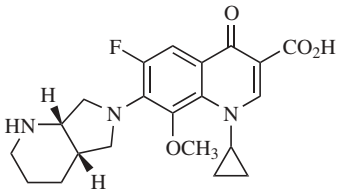
7.3. Oxazolidinones. Linezolid, the first and only oxazolidinone currently approved for therapeutic use by the regulatory agencies, represents the first new structural class of antibacterial agent in 35 years. Because it targets a stage of protein synthesis different from other agents, it does not demonstrate cross-resistance with any other antibiotic or antibacterial agent. Its *in vitro* antibacterial activity against susceptible and resistant gram-positive bacteria allows for its use in infections caused by organisms such as methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, and multidrug-resistant *Streptococcus pneumoniae*, organisms whose increase in prevalence has become a major health issue over the past 10 years. Linezolid is specifically indicated for the treatment of adult patients with infections caused by linezolid-susceptible strains of vancomycin-resistant *Enterococcus faecium*, including bacteremia (73). Linezolid can be used in both nosocomial and community-acquired pneumonia caused by *S. aureus* or *S. pneumoniae*, with combination therapy indicated if gram-negative organisms are present. It has been approved for treatment of both complicated and uncomplicated skin and skin structure infections caused by *S. aureus* or *Streptococcus pyogenes*.

7.4. Quinolones. Quinolones are broad-spectrum agents with antibacterial activity against both gram-positive and gram-negative bacteria, including anaerobic and intracellular pathogens. Their target of bacterial DNA topoisomerase means that they exhibit minimal cross-resistance with most other antibacterial agents, and generally retain activity against the penicillin-resistant streptococci that are becoming highly prevalent in community-acquired infections. Quinolones have been approved for multiple therapeutic indications, dependent upon the individual agent (73). Agents such as levofloxacin (**20**),

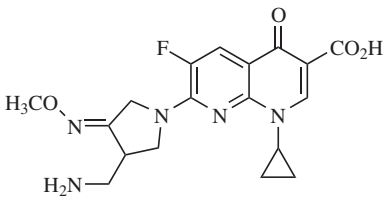
gatifloxacin (**72**) [112811-59-3], moxifloxacin (**73**) [151096-09-2], and gemifloxacin (**74**) [175463-14-6] are often considered to be "respiratory quinolones" with approved use for community-acquired infections such as acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, and community-acquired pneumonia. In addition, some quinolones have been approved for treatment of more serious infections including both complicated and uncomplicated skin and skin structure infections and nosocomial pneumonia. They may also be used to treat genitourinary tract infections including complicated and uncomplicated urinary tract infections (mild to moderate), acute pyelonephritis, prostatitis, various urethral and cervical infections, pelvic inflammatory disease, and uncomplicated cystitis.



(**72**)

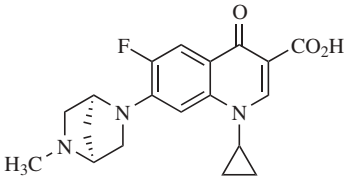


(**73**)

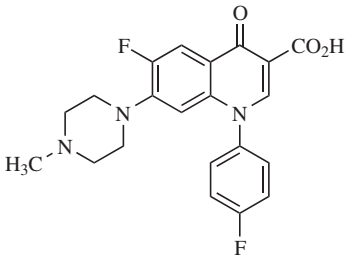


(**74**)

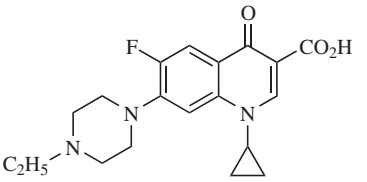
Additionally, six quinolones are marketed exclusively for use in veterinary medicine: danofloxacin (**75**) [112398-08-0], difloxacin (**76**) [98106-17-3], enrofloxacin (**77**) [93106-60-6], marbofloxacin (**78**) [115550-35-1], orbifloxacin (**79**) [113617-63-3], and sarafloxacin (**80**) [98105-99-8]. The human drugs, ciprofloxacin (**19**), ofloxacin (**81**) [82419-36-1], and trovafloxacin (**82**) [147059-72-1], are occasionally used in companion animal medicine (75).



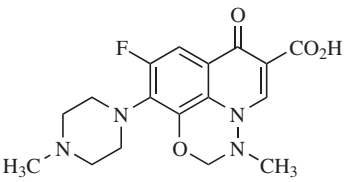
(**75**)



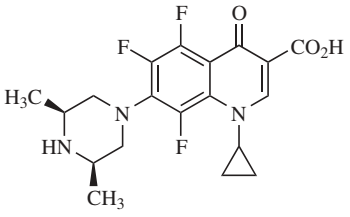
(**76**)



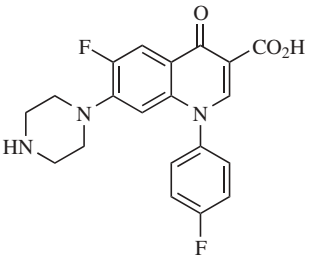
(77)



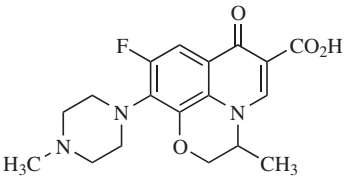
(78)



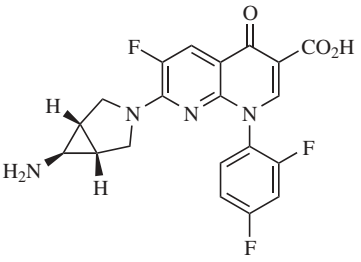
(79)



(80)



(81)



(82)

7.5. Sulfonamides and 2,4-Diaminopyrimidines. These agents have been surpassed as first line agents for most bacterial infections. However, sulfonamides alone are still utilized for the treatment of urinary tract infections due to susceptible enteric bacteria. The combination of a sulfonamide with trimethoprim, a dihydrofolate reductase inhibitor, can be used for treatment of a number of less serious microbial infections including urinary tract infections, acute otitis media due to susceptible strains of *S. pneumoniae* or *Haemophilus influenzae*, and acute exacerbations of chronic bronchitis in adults due to susceptible strains of *S. pneumoniae* or *H. influenzae*. This combination is also used for treatment of travelers' diarrhea in adults due to susceptible strains of enterotoxigenic *E. coli*, for shigellosis, and for enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei*. The combination of trimethoprim and sulfamethoxazole is the treatment of choice for *Pneumocystis carinii* pneumonia, and is also used as prophylaxis against this common fungal infection in immunocompromised or acquired immune deficiency syndrome (AIDS) patients (73).

Sulfonamide–trimethoprim combinations have been utilized for the treatment of bacterial disease in a variety of animal species (76–78).

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