The Quinolones

THIRD EDITION

Edited by

VINCENT T. ANDRIOLE

THE QUINOLONES

Third Edition

To my family
who have supported and
encouraged me always
and in everything.

To my colleague, Susan Marino,
who has assisted me in
all professional activities.

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VINCENT T. ANDRIOLE

Yale University School of Medicine

ACADEMIC PRESS

San Diego London Boston New York Sydney Tokyo Toronto

This book is printed on acid-free paper. ∞

Academic Press
a Harcourt Science and Technology Company
525 B Street, Suite 1900, San Diego, California 92101-4495

http://www.academicpress.com

Academic Press Limited
Harcourt Place, 32 Jamestown Road, London NW1 7BY, UK

Library of Congress Catalog Card Number: 00-106606

International Standard Book Number: 0-12-059517-6

PRINTED IN UNITED STATES OF AMERICA
00 01 02 03 04 05 SB 9 8 7 6 5 4 3 2 1

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PREFACE

Substantial progress has been made in the development of newer quinolones since the last edition of *The Quinolones* was published. This progress occurred because the quinolone class of antibacterial agents has captured the interest of chemists, microbiologists, pharmacologists, and clinicians. Recent progress in molecular biology has provided new information and a better understanding of structure–activity relationships of the quinolone nucleus and its radicals. This progress has resulted in the approval of a few new compounds with improved mechanism of action and the potential for delaying the development of resistance by specific bacterial pathogens. A few of the newest quinolones developed recently—moxifloxacin, gatifloxacin, and gemifloxacin—provide a more potent spectrum of activity that includes penicillin-resistant pneumococci as well as good activity against anaerobes and decreased susceptibility to the development of resistance by some bacterial species. Trovafloxacin was the first quinolone that demonstrated improved penetration into the central nervous system and cerebrospinal fluid, and early clinical studies demonstrated excellent efficacy in pediatric patients with bacterial meningitis. The newest quinolones—moxifloxacin, gatifloxacin, and gemifloxacin—broaden the clinical utility of this class of antimicrobial agents as we enter an era of increasing bacterial resistance to the previously recommended "standard therapy." During this same period, we have learned much about quinolone toxicity as it relates to quinolone chemical structure and pharmacokinetics/pharmacodynamics in treated patients. Hopefully this knowledge will provide safer molecules for use in patients.

The excellent and very recent progress that has occurred warranted an update on the quinolones. This edition is intended to provide the newest and most cogent information on the quinolones—all of it readily available in one volume.

Once again, I am much indebted to my colleagues, each of whom contributed thorough reviews on the history, chemistry, and mechanism of action, *in-vitro* properties, mechanisms of bacterial resistance, pharmacokinetics, clinical overview (described in nine separate chapters, including pediatrics), toxicity, adverse effects and drug interactions, and the future prospects of the newer quinolones.

Clearly, our hope is that this work will serve as a ready resource for new and helpful information, and, in so doing, the efforts of my colleagues most certainly will have been worthwhile.

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CHAPTER I

The Quinolones

History and Overview

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The Quinolones, Third Edition

INTRODUCTION

The development of quinolone antibacterials, since the discovery of the naphthyridine agent nalidixic acid some 40 years ago [1], has progressed with periods of great clinical innovation, alternating with periods of apparent inactivity following unexpected recognition of rare, but severe, adverse reactions associated with specific agents. Initially, within a decade, the 4-quinolones oxolinic acid and cinoxacin, which had improved activity against a limited range of Gram-negative bacteria, had been synthesized. Parallel developments in Japan had yielded 7-piperazine-substituted compounds, such as pipemidic acid, which had limited activity against *Pseudomonas aeruginosa*. However, the breakthrough to broad-spectrum activity waited a further 10 years before fluorination, primarily at the 6-position, resulted in the fluoroquinolones. It is difficult to overestimate the clinical impact of the development of these agents.

Since the mid-1980s, the fluoroquinolones have become a major group of synthetic antibiotics with activity that ranges from the Enterobacteriaceae and opportunists such as *Pseudomonas aeruginosa*, to Gram-positive pathogens, including streptococci and staphylococci. These changes resulted in agents—for example, ciprofloxacin and ofloxacin (later the levo-isomer levofloxacin)—that are applicable across a broad range of indications, including those involving the genitourinary, respiratory, and gastrointestinal tracts, skin and soft tissues, and other structures. In most bodily tissues and fluids, the fluoroquinolones are characterized by excellent penetration and therapeutic ratios. Ciprofloxacin and ofloxacin revolutionized the management of many conditions previously amenable only to intravenous therapy or in which management has been compromised by bacterial resistance to standard agents, such as the β-lactams. Important examples include pyelonephritis, enteric fevers, prostatic infections, pulmonary exacerbations of cystic fibrosis, and nosocomial pneumonias.

The next significant advance occurred in the early 1990s with the synthesis of temafloxacin, which had four- to eightfold greater activity against *Streptococcus pneumoniae* and good activity against anaerobes, such as the *Bacteroides* and *Prevotella* spp. However, unexpected toxicity, in the form of hemolytic uraemic syndrome [2], resulted in its withdrawal only months after launch. In addition, the development of several other compounds with even greater anti-Gram-positive potency, notably sparfloxacin, sitafloxacin, and Bay 3118, has been either delayed or discontinued due to an unacceptable incidence of phototoxicity (and other adverse effects). By the mid-1990s, clinical development appeared to have halted, although molecules with differing sidechains and laboratory activity continued to be synthesized.

However, optimism again increased with the discovery of trovafloxacin, clinafloxacin, and grepafloxacin, only to be dampened at the end of the decade

by their abrupt withdrawal or suspension due to rare but severe adverse effects, including hepatotoxicity (trovafloxacin), significant QT prolongation and associated cardiac deaths (grepafloxacin), and serious phototoxicity and hypoglycemia (clinafloxacin). All of these agents had significantly greater potency against Gram-positive species, notably *S. pneumoniae*, and in the case of trovafloxacin at least proved highly clinically effective in pneumococcal infections. At a time when burgeoning global multidrug resistance among pneumococci had begun to compromise traditional therapy, this left a considerable hiatus in the range of potential alternatives to penicillin and macrolides.

Fortunately, the 8-methoxyquinolones moxifloxacin and gatifloxacin, which are highly potent against *S. pneumoniae* (10-fold greater than the earlier second-generation agents), clinically effective, and appear free from either significant or unexpected toxicity, have filled this therapeutic vacuum. Their proven activity against *S. pneumoniae*, coupled with maintained high potency against *Haemophilus influenzae* and *Moraxella catarrhalis*, and excellent penetration into respiratory tissues, including the intracellular habitat of *Chlamydia* and *Legionella* spp., suggests that, where ciprofloxacin was considered by many to be inappropriate for respiratory infections, 8-methoxyquinolone derivatives will now become agents of choice. They appear to limit emergence of resistance in Gram-positive species, which could prove a major advantage, compared with levofloxacin, which has also proven surprisingly clinically effective in respiratory infections despite a pneumococcal MIC typical of earlier second-generation agents. Further progress includes continued development of the naphthyridone subclass, notably gemifloxacin, which is characterized by a further 10-fold increase in anti-pneumococcal potency. Clinical trial results are awaited with interest.

The fluoroquinolones and their precursors have a number of predictable structure–activity and structure–adverse effect relationships relating to nuclear and sidechain configurations. Thus, design of new molecules can avoid many of the problems that have characterized previous members of the group. It may be anticipated that further modifications to the molecular structure will improve spectrum and activity while reducing the incidence of adverse effects.

Structure–Activity Relationships (SARs)

The 1,8 naphthyridines, 4-quinolones, cinnolines. fluoroquinolones, and fluorinated naphthyridones, together with their important sidechain substituent modifications and resultant structure–activity relationships are summarized in Table I. Modifications to the nucleus converting the naphthyridine nitrogen in the 8-position to a carbon reduced adverse reactions and increased activity against Gram-positive cocci, including both streptococci and *Staphylococcus aureus*, whereas either piperazine or other *N*-cyclic substitutions at the 7-position significantly increased potency against Gram-negative bacteria, including *P.*

TABLE I A Chemical and Functional Classification of Quinolones and Fluoroquinolones

Structure	Name		Antibacterial activity	Pharmacokinetics	Indications/comments
First-generation compounds (often all included as 4-quinolones)					
1,8 naphthyridine (carboxylic acid) 7-methyl 7-pyrrole	Nalidixic acid Piromidic acid		Enterobacteria only, no significant anti-Gram-positive activity	Orally absorbed, poor to moderate tissue penetration	UTI, shigellosis
1,2-cinnoline (carboxylic acid)	Cinoxacin				
4-quinolone (carboxylic acid)	Oxolinic acid				
7-piperazine (pyrido-pyrimidine)	Pipemidic acid		*P. aeruginosa* added		
6,7,8 sidechain substituents	Name	N-1 sidechain	Antibacterial activity	Pharmacokinetics	Indications/comments
Second-generation compounds (IIA) **A. Fluoroquinolones with enhanced but predominantly Gram-negative activity**					
6-Fluoro	Flumequine	–	Gram-negative: less active than piperazinyl derivatives	Improved absorption	Limited to UTI
6-Fluoro-7-piperazinyl	Ciprofloxacin Pefloxacin Norfloxacin Ofloxacin (Levofloxacin: Rufloxacin	Cyclopropyl Ethyl Ethyl 1-8 (O) cyclic ring L-isomer) 1-8 (S) cyclic ring	Enhanced anti-Gram negative potency, including *P. aeruginosa* plus some limited anti-Gram-positive activity	High absorption, ++ tissue penetration, variable elimination (renal/metabolic) with moderate to long T/2	UTI, STD, enteric infections, RTI (not 1° pneumococcal), invasive Gram-negative infections: osteomyelitis, skin and soft tissue, etc.