Progress in Drug Research

Fortschritte der Arzneimittelforschung

Progrès des recherches pharmaceutiques

Editor:
Ernst Jucker

38

Birkhäuser Verlag · Basel · Boston · Berlin

Progress in Drug Research
Fortschritte der Arzneimittelforschung
Progrès des recherches pharmaceutiques
Vol. 38

Progress in Drug Research
Fortschritte der Arzneimittelforschung
Progrès des recherches pharmaceutiques
Vol. 38

Edited by / Herausgegeben von / Rédigé par
Ernst Jucker, Basel

Authors / Autoren / Auteurs
S. Mitsuhashi, T. Kojima, N. Nakanishi, T. Fujimoto, S. Goto,
S. Miyusaki, T. Uematsu, M. Nakashima, Y. Asahina,
T. Ishisaki, S. Susue, K. Hirai, K. Sato, K. Hoshino, J. Shimada and
S. Hori · V. K. Singh · A. M. Cesura and A. Pletscher ·
M. D. Tricklebank, L. J. Bristow and P. H. Hutson

1992

Birkhäuser Verlag
Basel · Boston · Berlin

P.O. Box 133
4010 Basel
Switzerland

Printed in Germany on acid-free paper

ISBN 3-7643-2705-7
ISBN 0-8176-2705-7

Contents · Inhalt · Sommaire

Foreword

Volume 38 of "Progress in Drug Research" contains four reviews and the various indexes which facilitate its use and establish the connection with the previous volumes. The articles in this volume deal with novel quinolones and their antibacterial properties; neuropeptides and their immunoregulatory role; the new generation of monoamine oxidase inhibitors and their potential use in Parkinson's disease; and with alternative approaches to the discovery of novel antipsychotic agents. These four reviews present important tools in the search for new and useful medicines.

In the 32 years that "Progress in Drug Research" has existed, the Editor has enjoyed the valuable help and advice of many colleagues. Readers, the authors of the reviews, and, last but not least, the reviewers have all contributed greatly to the success of the series. Although the comments received so far have generally been favorable, it is nevertheless necessary to analyze and to reassess the current position and the future direction of such a review series.

So far, it has been the Editor's intention to help disseminate information on the vast domain of drug research, and to provide the reader with a tool with which to keep abreast of the latest developments and trends. The reviews in PDR are useful to the non-specialists, who can obtain an overview of a particular field of research in a relatively short time. The specialist readers of PDR will appreciate the reviews' comprehensive bibliographies, and, in addition, they may even get fresh impulses for their own research. Finally, the readers can use the 38 volumes of PDR as an encyclopedic source of information.

It gives me great pleasure to present this new volume to our readers. At the same time, I would like to express my gratitude to Birkhäuser Verlag, and, in particular, to Mrs. L. Koechlin and Mssrs. H.-P. Thür and A. Gomm. Without their personal commitment and assistance, editing PDR would be a nearly impossible task.

Basel, February 1992 DR. E. JUCKER

Vorwort

Der vorliegende 38. Band der «Fortschritte der Arzneimittelforschung» enthält vier Übersichtsartikel sowie die verschiedenen Register, welche das Arbeiten mit dieser Reihe erleichtern. Die Artikel dieses Bandes behandeln neuartige Chinolone mit bakteriziden Eigenschaften, Neuropeptide und ihre immunoregulierende Rolle, die neue Generation von Hemmstoffen der Monoaminoxidase B (MAO B) und ihrer potentiellen Möglichkeiten zur Behandlung des Parkinsonismus sowie alternative Wege zum Auffinden neuartiger Antipsychotika. In ihrer Gesamtheit stellen diese Referate ein wichtiges Hilfsmittel in der Suche nach neuen Arzneimitteln dar.

Seit der Gründung der Reihe sind 32 Jahre vergangen. In dieser langen Zeitspanne konnte der Herausgeber immer auf den Rat der Fachkollegen, der Leser und der Autoren zählen. Ihnen allen möchte ich meinen Dank abstatten. In diesem Dank sind auch die Rezensenten eingeschlossen, denn sie haben mit ihrer Kritik und mit ihren Vorschlägen wesentlich zum guten Gedeihen der PDR beigetragen. Viele Kommentare und Besprechungen waren lobend. Trotzdem ist es angebracht, die Frage nach dem Sinn und Zweck der «Fortschritte» zu stellen und zu überprüfen.

Nach wie vor ist es unser Ziel, neueste Forschungsergebnisse in Form von Übersichten darzustellen und dem Leser auf diese Weise zu ermöglichen, sich verhältnismäßig rasch und mühelos über bestimmte Gebiete und Richtungen zu informieren. Es wird ihm somit die Möglichkeit gegeben, sich im komplexen Gebiet der Arzneimittelforschung auf dem laufenden zu halten und den Kontakt zur aktuellen Forschung aufrechtzuerhalten.

Die Übersichten der «Fortschritte» bieten dem Spezialisten eine wertvolle Quelle der Originalliteratur dar, erlauben ihm nützliche Vergleichsmöglichkeiten, und sie können u. U. seine eigene Forschung befruchten. Für alle Leser der «Fortschritte» stellt die Reihe mit ihren ausführlichen Verzeichnissen eine nützliche Quelle von enzyklopädischem Wissen dar, so daß das gesamte Werk auch als Nachschlagewerk dienen kann.

Zum Gelingen der Reihe haben nicht zuletzt auch die Mitarbeiter des Birkhäuser Verlages beigetragen. Erwähnt seien insbesondere Frau L. Koechlin und die Herren H.-P. Thür und A. Gomm; ihnen möchte ich auch an dieser Stelle meinen Dank aussprechen.

Basel, Februar 1992 Dr. E. JUCKER

Fluorinated quinolones – new quinolone antimicrobials

Editor: Susumu Mitsuhashi

Gunma University, School of Medicine, Episome Institute, Fujimi, Seta, Gunma 371-01, Japan

Preface

Paul Ehrlich started his research, called experimental chemotherapy, in 1902, and discovered Trypanrot in 1904 and Salvarsan in 1909. This was the first success of chemotherapy using man-made chemotherapeutic agents against microorganisms. Since the original observation by Fleming in 1929 of the effect of *Penicillium notatum* on a culture plate in his laboratory and the subsequent development by Florey and Chain in 1940 of the first clinically effective antibiotic-penicillin, enormous changes have occurred both in basic antibiotic research and in the practice of clinical medicine. The search for naturally occurring antibiotics has ranged widely over fungi, plants, soil, water and dust.

These chemotherapeutic agents including prontosil and antibiotics have led to dramatic and evolutional changes in medical therapeutics and prophylaxis.

After half a century of great success of antibiotics, the first drug of quinolone antibacterials, nalidixic acid, was discovered by G. Y. Lesher *et al.* in 1962. It is said that they noticed a marginal antibacterial activity of 1-ethyl-1, 4-dihydro-7-chloro-4-oxoquinoline-3-carboxylic acid, a by-product obtained in the process of the chloroquine synthesis and modified it to come up with nalidixic acid.

Norfloxacin having the 6-fluoro group and the 7-piperazinyl group was discovered in 1978. This was the start of the new quinolone era. Norfloxacin was about one order of magnitude more potent than old quinolones in antibacterial activity. Norfloxacin showed a broad antibacterial activity against gram-positive and gram-negative bacteria including *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Since the discovery of norfloxacin many pharmaceutical companies have tried to synthesize new quinolone derivatives with improved antibacterial activity and pharmacokinetic properties. These include ciprofloxacin, enoxacin, ofloxacin, pefloxacin, fleroxacin, amifloxacin, difloxacin, lomefloxacin, tosufloxacin, temafloxacin and sparfloxacin, and there are a number of other agents that are in a preclinical stage or in early clinical trial.

I wish to thank my colleagues who contributed papers on the history, structure-activity relationships, *in vitro* antibacterial activity, *in vivo* antibacterial activity, mechanisms of action and resistance, pharmacokinetics, and adverse effects of the new quinolones. I hope that this review will be valuable for clinical use and for the future progress of quinolone derivatives.

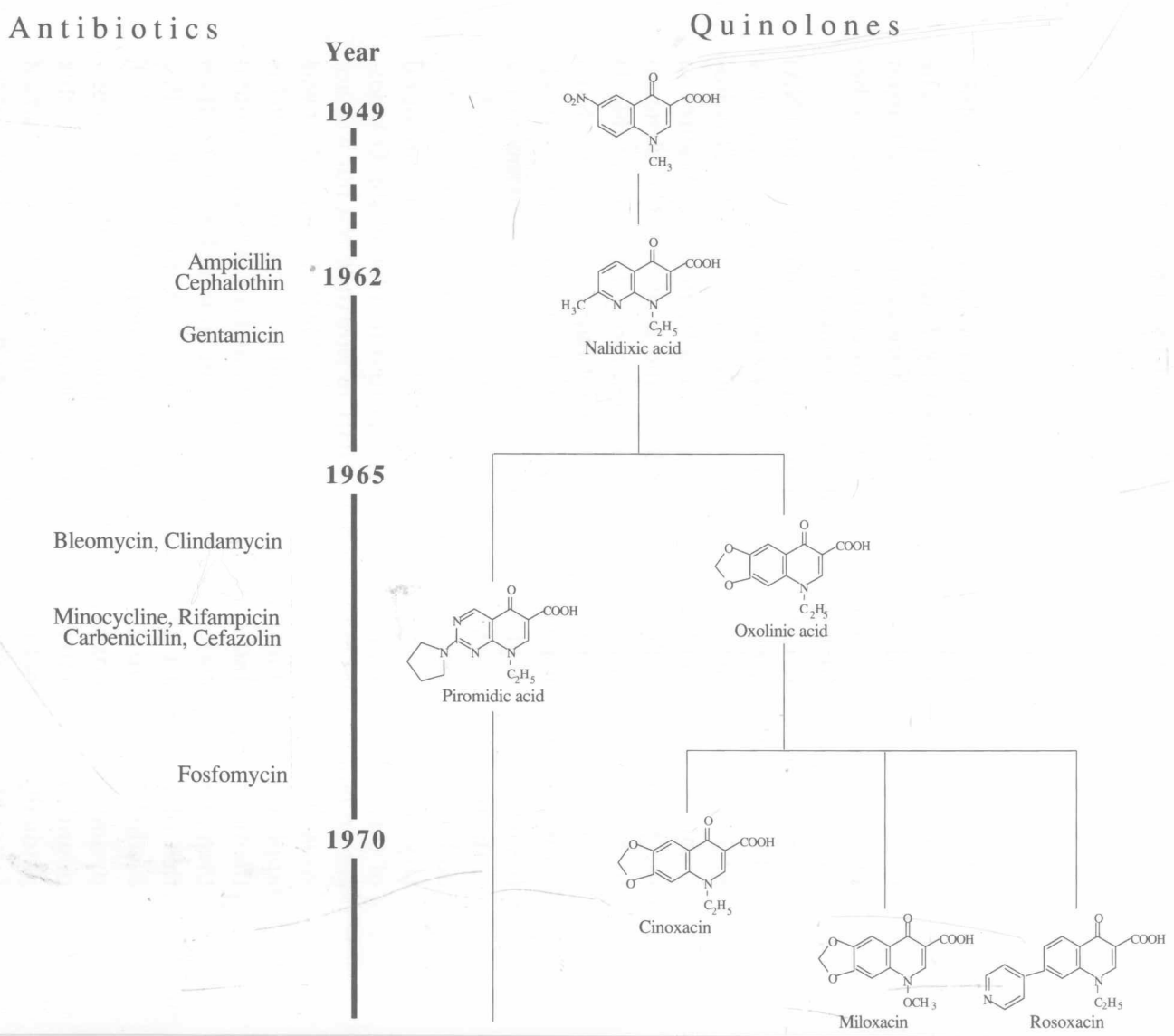
S. Mitsuhashi

History of quinolone antibacterials

By Tsuyoshi Kojima and Susumu Mitsuhashi
Gunma University, School of Medicine,
Episome Institute, Fujimi, Seta, Gunma 371-01, Japan

The first quinolone, 1-methyl-1,4-dihydro-6-nitro-4-oxoquinoline-3-carboxylic acid (Fig. 1), was reported by Price in 1949 [1]. The chemical modifications of the quinolone were carried out by Barton *et al.* in 1960 [2], but the derivatives were not clinically applicable because of their toxic effects on laboratory animals [3].

The first drug of quinolone antibacterials is nalidixic acid (NA) which was found by Lesher *et al.* in 1962 [4]. It is said that they noticed a marginal antibacterial activity of 1-ethyl-1,4-dihydro-7-chloro-4-oxoquinoline-3-carboxylic acid, a by-product obtained in the process of the chloroquine synthesis and modified it to come up to NA [5]. It was mainly active against gram-negative rods (Table 1) [6], and not cross-resistant with existing antibacterial agents [7]. Such properties met a need to control infections due to antibiotic- and sulfonamide-resistant gram-negative bacteria which had been increasing at the time. NA was well absorbed orally and excreted into urine, bile and feces at high concentrations. NA got to be applied to urinary, biliary and intestinal tract infections in 1963 [8]. The second compound of this group is oxolinic acid (OA) reported in 1966 [9,10]. OA possessed more potent antibacterial activity *in vitro* than NA but was not so *in vivo*, because it was metabolically unstable [11]. Like NA, it was applied to limited infections. Piromidic acid (PA) reported in 1967 is the third compound of this group [12]. Its activity was more potent than that of NA against *staphylococci* but similar to or less potent than that of NA against gram-negative bacteria [7]. A metabolite of PA, 8-ethyl-5,8-dihydro-2-(3-hydroxy-1-pyrrolidinyl)-5-oxopyrido[2,3-d] pyrimidine-6-carboxylic acid was more potent than the parent compound, PA, in activity against gram-negative bacteria [13]. People gradually knew that the metabolism of quinolones was an important factor affecting their efficacy. PA was also a drug with a limited indication.


Antibiotics
Quinolones
Year
1949
1962
1965
1970
Ampicillin
Cephalothin
Gentamicin
Bleomycin, Clindamycin
Minocycline, Rifampicin
Carbenicillin, Cefazolin
Fosfomycin
Nalidixic acid
Piromidic acid
Oxolinic acid
Cinoxacin
Miloxacin
Rosoxacin

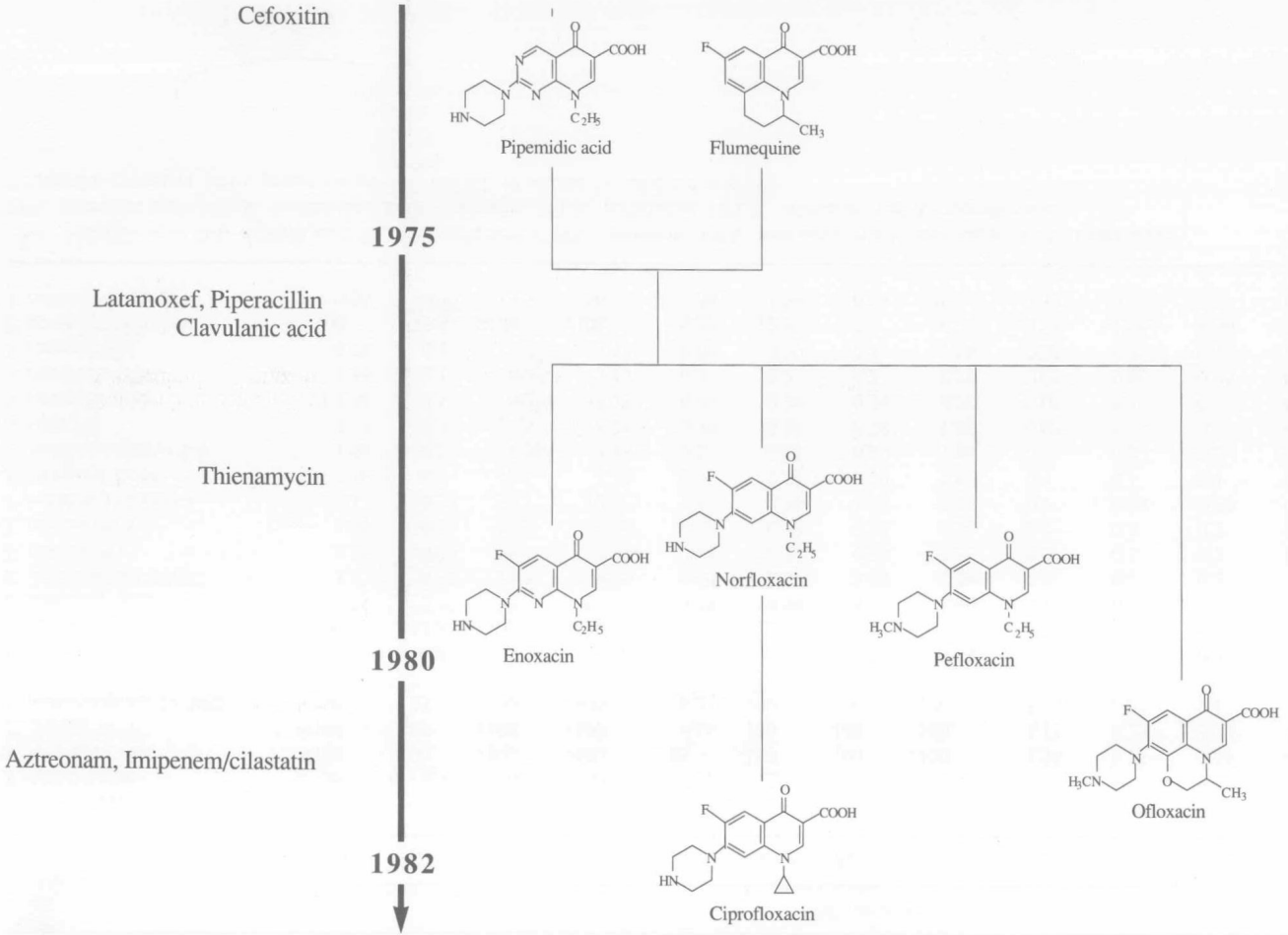


Figure 1
Schema of progress of quinolone antibacterials.

Table 1
Antibacterial activity of quinolones

Organism	MIC (μg/ml)*												
	NA	OA	PA	CINX	RSX	MLX	FLM	PPA	NFLX	ENX	PFLX	OFLX	CPFX
S. aureus 209P JC-1	50	1.56	6.25	>100	0.78	12.5	3.13	6.25	0.39	0.39	0.39	0.2	0.1
S. aureus Smith	25	1.56	6.25	100	0.39	12.5	6.25	12.5	0.78	0.78	0.39	0.2	0.2
S. pyogenes Cook	>100	100	>100	>100	25	>100	100	>100	1.56	3.13	3.13	0.78	0.39
E. faecalis 2473	>100	25	>100	>100	6.25	100	100	100	3.13	6.25	3.13	1.56	1.56
L. monocytogenes LI-2402	>100	25	100	>100	6.25	100	50	100	3.13	6.25	3.13	1.56	0.78
E. coli NIHJ JC-2	1.56	0.2	6.25	1.56	0.2	0.2	0.78	0.78	0.1	0.1	0.2	0.05	0.0063
E. coli N-51**	>100	12.5	>100	>100	25	12.5	12.5	25	0.78	1.56	0.78	0.78	0.2
C. freundii P-6801	6.25	0.39	25	12.5	0.78	0.39	25	1.56	0.1	0.1	0.2	0.1	0.0125
K. pneumoniae P-5709	3.13	0.39	12.5	3.13	0.39	0.39	0.78	1.56	0.1	0.2	0.2	0.1	0.025
E. cloacae 963	6.25	0.39	25	3.13	0.78	0.39	0.78	1.56	0.2	0.2	0.2	0.1	0.0125
S. marcescens S-9	1.56	0.2	12.5	6.25	0.39	0.78	0.78	3.13	0.2	0.2	0.2	0.2	0.05
P. mirabilis IFO3849-4	12.5	0.39	50	12.5	1.56	0.39	1.56	3.13	0.1	0.78	0.39	0.39	0.1
M. morganii Kono	1.56	0.1	12.5	3.13	0.39	0.39	0.78	1.56	0.1	0.1	0.1	0.1	0.0125
V. parahaemolyticus S-1	1.56	0.2	1.56	3.13	0.2	0.78	0.39	1.56	0.2	0.2	0.2	0.2	0.05
S. typhi 901	3.13	0.2	12.5	6.25	0.39	0.78	0.78	1.56	0.05	0.1	0.1	0.05	0.0063
S. paratyphi 1015	1.56	0.1	6.25	3.13	0.39	0.39	0.39	0.78	0.05	0.1	0.1	0.05	0.0125
S. enteritidis 1891	1.56	0.1	6.25	3.13	0.2	0.2	0.2	0.78	0.05	0.05	0.05	0.025	0.0031
S. sonnei EW33	0.78	0.1	0.78	3.13	0.05	0.39	12.5	1.56	0.05	0.05	0.1	0.025	0.0031
P. aeruginosa IFO3445	100	25	>100	>100	6.25	12.5	25	6.25	0.78	1.56	1.56	1.56	0.2
A. calcoaceticus P-6901	6.25	0.39	12.5	50	1.56	1.56	0.78	25	3.13	0.78	0.2	0.39	0.2

*NA, Nalidixic acid; OA, oxolinic acid; PA, piromidic acid; CINX, cinoxacin; RSX, rosoxacin; MLX, miloxacin; FLX, flumequine; PPA, pipemidic acid; NFLX, norfloxacin; ENX, enoxacin; PFLX, pefloxacin; OFLX, ofloxacin; CPFX, ciprofloxacin.
**Quinolone-resistant DNA gyrase mutant of *E. coli* KL 16 selcted by nalidixid acid [34].

A series of studies on quinolone antibacterials revealed some structure-activity relationships: naphthylidine, quinoline and pyridopyrimidine are all appropriate as a basic ring, and the 3-carboxyl group and the 4-oxo group are necessary for activity [8]. Many quinoline, naphthylidine, cinnoline and pyridopyrimidine derivatives having the 3-carboxy and the 4-oxo groups were synthesized in the early 1970s; e.g. cinoxacin (CINX) [14], pipemidic acid (PPA) [15], flumequine [16], miloxacin [17], rosoxacin [18] etc. These were essentially similar to NA or OA in antibacterial activity. Among these compounds, CINX and PPA were considered to be up-graded because they were metabolically stable [10,19–21], and sufficient clinical effects were observed with relatively small daily doses. PPA had additional unique properties. It penetrated into various tissues very well [22] and was successfully applied to otitis media and sinusitis in addition to the local infections for which NA, OA and PA had been used. It may be worth stating that PPA is moderately active against bacteria highly resistant to NA and *Pseudomonas aeruginosa* which was insusceptible to most antibacterial agents available at that time [23]. Such characteristics of PPA appeared to be related to its piperazinyl group at position 7 of the pyridopyrimidine ring.

Norfloxacin (NFLX) having the 6-fluoro group and the 7-piperazinyl group was discovered in 1978 [24]. This was the start of the new quinolone era. NFLX was about one order of magnitude more potent than the old quinolones in antibacterial activity, and its antibacterial spectrum was broadened to gram-positive bacteria [25]. Furthermore, NFLX was metabolically stable and penetrated well into various tissues although its oral absorption was not very good and its antibacterial activity toward gram-positive bacteria was slightly weak [26]. It was, therefore, successfully used for the treatment of urinary tract infections.

Enoxacin (ENX) [27] and pefloxacin (PFLX) [28] reported in 1979 and ofloxacin (OFLX) reported in 1981 [29] had the same antibacterial activity as NFLX and better oral absorption [26, 30]. Ciprofloxacin (CPFX) discovered in 1982 [31] showed more potent antibacterial activity than NFLX, ENX, PFLX and OFLX [30, 32]. All these compounds exhibit intrinsically similar antibacterial properties. The chemotherapeutic properties of these new quinolones called one's attention to this group of compounds [33]. Now, they have been widely used clinically for various kinds of bacterial infections including re-

spiratory tract infection. Since then, many new quinolone derivatives have been synthesized; e.g. lomefloxacin, fleroxacin, temafloxacin, DR-3355, tosufloxacin, sparfloxacin etc. The properties of these recent quinolones are described in the following sections of this review. The clinical values of these derivatives will be determined as they will be frequently used in the future.

References

1 J. R. Price: Aust. J. Sci. Res. *A 2*, 272 (1949).
2 N. Barton, A. F. Crowther, W. Hepworth, D. N. Richardson and G. W. Driver: Brit. Pat., 830, 832 (1960) [C. A. *55*, 7442 e (1961)].
3 J. K. Landquist: J. Chem. Soc. (C) 1971, 2735 (1971).
4 G. Y. Lesher, E. J. Froelich, M. D. Gruett, J. H. Bailey and R. P. Brundage: J. Med. Pharm. Chem. *5*, 1063 (1962).
5 G. C. Crumplin, J. M. Midgley and J. T. Smith: Topics in Antibiotic Chemistry, vol. 3 part A. John Wiley & Sons, New York 1980.
6 W. H. Deitz, J. H. Bailey and E. J. Froelich: Antimicrob. Agents Chemother. 1963, 583 (1964).
7 M. Shimizu, S. Nakamura and Y. Takase: Antimicrob, Agents Chemother. 1970, 117 (1971).
8 R. Albrecht: Prog. Drug Res. *21*, 9 (1977).
9 D. Kaminsky and R. I. Meltzer: U. S. Pat. 3, 287, 348 (1966) [C. A. *66*, 65399 u (1967)].
10 D. Kaminsky and R. I. Meltzer: J. Med. Chem. *11*, 160 (1968).
11 J. Edelson, C. Davison and D. P. Benziger: Drug Metab. Rev. *6*, 105 (1977).
12 S. Minami, T. Shono and J. Matsumoto: Chem. Pharm. Bull. *19*, 1426 (1971).
13 M. Shimizu, Y. Sekine, H. Higuchi, H. Suzuki, S. Nakamura and K. Nakamura: Antimicrob, Agents Chemother. 1970, 123 (1971).
14 W. A. White: Ger. Offen., 2, 005, 104 (104) [C. A. *73*, 77269 j (1970)].
15 J. Matsumoto and S. Minami: J. Med. Chem. *18*, 74 (1975).
16 J. F. Gerster: Ger. Offen., 2, 264, 163 (1973) [C. A. *79*, 92029 y (1973)].
17 H. Agui, T. Mitani, A. Iwazawa, T. Komatsu and T. Nakagome: J. Med. Chem. *20*, 791 (1977).
18 G. Y. Lesher and P.-M. Carabateas: Ger. Offen., 2, 224, 090 (1972) [C. A. *78*, 84280 n (1973)].
19 H. R. Black, K. S. Israel, R. L. Wolen, G. L. Brier, B. D. Obermeyer, E. A. Ziege and J. D. Wolny: Antimicrob. Agents Chemother. *15*, 165 (1979).
20 Y. Tochino, K. Sugeno, M. Doteuchi, H. Okabe, R. Norikura and H. Tanaka: Chemotherapy (Tokyo) *28* (S-4), 73 (1980).
21 M. Shimizu, S. Nakamura, Y. Takase and N. Kurobe: Antimicrob. Agents Chemother. *7*, 441 (1975).
22 M. Hashimoto, N. Morino, H. Miyazaki and A. Kagemoto: Chemotherapy (Tokyo) *23*, 2693 (1975).
23 M. Shimizu, Y. Takase, S. Nakamura, H. Katae, A. Minami, K. Nakata, S. Inoue, M. Ishiyama and Y. Kubo: Antimicrob. Agents Chemother. *8*, 132 (1975).