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MINI-REVIEW

Microbial transformations of antimicrobial quinolones and related drugs

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Abstract The quinolones are an important group of synthetic antimicrobial drugs used for treating bacterial diseases of humans and animals. Microorganisms transform antimicrobial quinolones (including fluoroquinolones) and the pharmacologically related naphthyridones, pyranoacridones, and cinnolones to a variety of metabolites. The biotransformation processes involve hydroxylation of methyl groups; hydroxylation of aliphatic and aromatic rings; oxidation of alcohols and amines; reduction of carboxyl groups; removal of methyl, carboxyl, fluoro, and cyano groups; addition of formyl, acetyl, nitrosyl, and cyclopentenone groups; and cleavage of aliphatic and aromatic rings. Most of these reactions greatly reduce or eliminate the antimicrobial activity of the quinolones.

Keywords Biotransformation · Ciprofloxacin · Enrofloxacin · Fluoroquinolones · Pradofloxacin

Introduction

The 4-quinolones are a large group of synthetic compounds that were originally developed as antimicrobial agents for infections of the urinary and respiratory tracts but are also effective for many other diseases [8]. More than 10,000 quinolones had already been synthesized by 1993 [56] and many others have been since then. Several are currently being used, in either human clinical or veterinary medicine, for treating infections caused by many Gram-negative and some Gram-positive bacteria [4, 59]. Their antibacterial activity is due to trapping of DNA in the complexes that it forms with DNA gyrase and topoisomerase IV during replication [13, 15, 23]. Some of the quinolones have antitumor, antiviral, antiallergic, antitubercular, immunomodulating, or antidiabetic activity [12, 38, 57], and may even be effective against malaria parasites [11, 20, 46]. Differences in antimicrobial activity of quinolones in vitro, which depend on the different substituents on the quinolone framework, are the basis for their classification into three or four "generations" [7, 13, 59]. Newer quinolones have been designed for enhanced activity against Gram-positive cocci and anaerobic bacteria and for better entry into bacterial cells [6, 19, 24].

Quinolones may enter the environment from hospital effluents and municipal wastewater [27, 97], sludge and farm wastes [17, 27, 45], and wastes from aquaculture operations [69]. They bind to organic matter and clay minerals [82]. Minimization of antibiotic residues in the environment by physical, chemical, or biological means is desirable to prevent further selection for resistance among pathogenic bacteria [41]. The products of degradation also should be identified to foster human risk assessment [44, 82] and ecotoxicological assessment [45].

In 1997, a study reported what appeared to be an extremely slow rate of degradation of a veterinary quinolone to CO_2 in soil [48]. However, several fungi, including species of *Cunninghamella* and *Umbelopsis* (Zygomycota); *Beauveria*, *Penicillium*, *Pestalotiopsis*, and *Trichoderma* (Ascomycota); and *Gloeophyllum*, *Phanerochaete*, and *Trametes* (Basidiomycota); and bacteria, including species of *Escherichia* and *Pseudomonas* (Proteobacteria) and *Microbacterium*, *Mycobacterium*, and *Streptomyces*

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(Actinobacteria); have been shown to biotransform quinolones and related compounds more rapidly by site-specific hydroxylations and other reactions. Microbial metabolites often are identical to metabolites produced by humans or experimental animals [18, 96]. Nearly all have much less antimicrobial activity for target bacteria than the parent drug, and some are totally inactive [89, 91]. Reactions such as *N*-oxidation [16, 33, 61] or *N*-acetylation [2, 32, 60, 61, 63] of quinolones that have a piperazine or alkylpiperazine group inactivate the drug by making it negatively charged at physiological pH and thus less able to enter a bacterial cell.

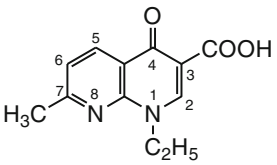
Photodegradation is another important process that may result in the inactivation of quinolones [83]; some of the products formed in the microbial biotransformation of piperazine side chains [49] are also formed by photodegradation in the environment [14]. Defluorination of fluoroquinolones may also occur in the light [25]. Photodegradation processes are more important in water [45, 79] or at the surface of the soil [80, 82].

This review will consider, in addition to the microbial transformations known for the quinolones, those of the related naphthyridones (including nalidixic acid), pyranoacridones (including acronycine), and cinnolones (including cinoxacin).

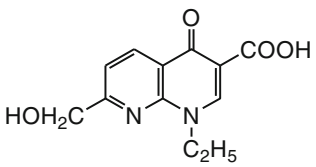
Transformation of first-generation quinolones and their analogs

Nalidixic acid (**I**), a derivative of 1,8-naphthyridine, inhibits DNA gyrase in Gram-negative bacteria [81]. It is usually considered the first of the quinolone-related compounds to be investigated as an antibacterial agent, starting in 1962, even though it is, strictly speaking, not a quinolone [43]. Nalidixic acid has been used against urinary tract infections caused by Gram-negative bacteria [71] and it also has antimalarial properties [20]. It is used in aquaculture in some countries [37].

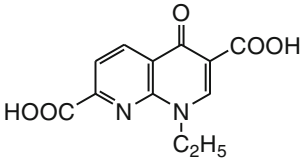
Many fungi, including *Penicillium adametzi*, transform nalidixic acid to pharmacologically interesting metabolites [29]. After 24 h, a culture of *P. adametzi* formed the 7-hydroxymethyl derivative (**II**) with a yield reaching 60 %; further oxidation led to the formation of the 3,7-dicarboxylic acid (**III**) [29]:



I

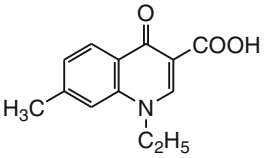


II

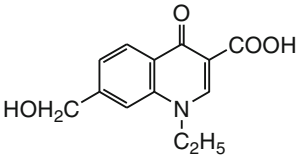


III

The microbial transformation of analogues of nalidixic acid has also been of interest. A growing culture of *P. adametzi* oxidized the methyl group of 3-carboxy-1-ethyl-7-methyl-4-quinolone (**IV**) to the alcohol, 3-carboxy-1-ethyl-7-hydroxymethyl-4-quinolone (**V**); the aromatic carbon atoms were not involved [35]:



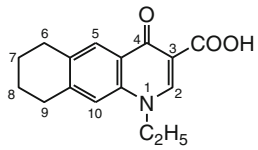
IV



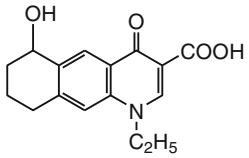
V

From the same substrate, the bacterium *Streptomyces surinam* formed a methyl ester. *P. adametzi* metabolized a similar compound that had a methoxyl group by demethylating it [35].

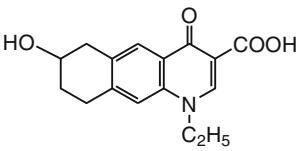
A more complicated quinolone with an additional saturated ring, 1-ethyl-4-oxo-1,4,6,7,8,9-hexahydrobenzo[*g*]quinoline-3-carboxylic acid (**VI**), was oxidized by three different microorganisms [35]. The fungus *Beauveria bassiana* ATCC 7159 (syn. *Sporotrichum sulfurescens*) introduced a hydroxyl group and formed the 6-hydroxy derivative (**VII**); *P. adametzi* formed the 7- and 8-hydroxy derivatives (**VIII** and **IX**); and *Streptomyces achromogenes* formed the 6-, 7-, and 8-hydroxy derivatives (**VII**, **VIII** and **IX**) [35]:



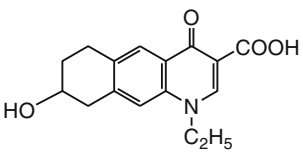
VI



VII

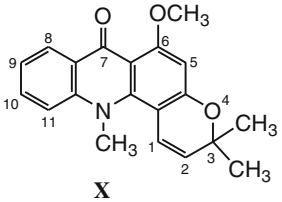


VIII

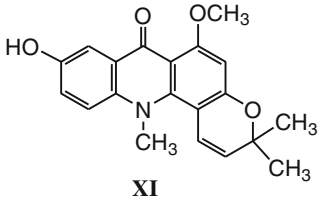


IX

Some derivatives of the natural product acronycine (**X**), a pyranoacridone alkaloid obtained from the bark of an Australian tree, have antitumor and antimalarial activity [9, 26, 58] but are not considered antibacterial agents. Acronycine is oxidized by cultures of fungi and bacteria by hydroxylation of the benzene ring [10]. The most active strain of the zygomycetous fungus *Cunninghamella echinulata* transformed the starting material into 9-hydroxyacronycine (**XI**), which is also the principal mammalian metabolite, with a yield of 30 % in 70 h [10]:

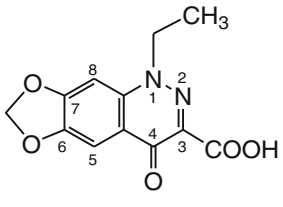


X

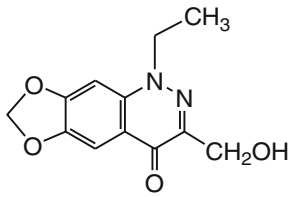


XI

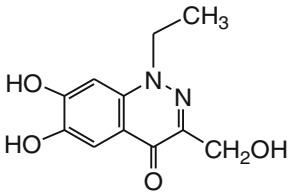
Cinoxacin (**XII**), a synthetic 4-cinnolone derivative with a dioxolo ring, was previously used for treating bacterial urinary tract infections [71, 78]. This drug was transformed by *B. bassiana* to two metabolites, 1-ethyl-1,4-dihydro-3-(hydroxymethyl)[1,3]dioxolo[4,5-*g*]cinnolin-4-one (**XIII**, yield 47.3 %) and 1-ethyl-1,4-dihydro-6,7-dihydroxy-3-(hydroxymethyl)cinnolin-4-one (**XIV**, yield 5.6 %), in 20 days [65]:



XII

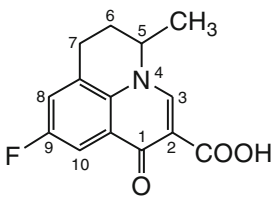


XIII

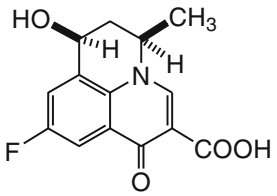


XIV

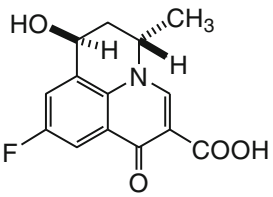
Flumequine (**XV**) is a fluoroquinolone antibacterial agent, produced as a racemic mixture of two isomers, which is used in many countries for aquaculture [37, 50, 69]. In the stereospecific transformation of the flumequine isomers by cultures of *Cunninghamella elegans*, two diastereomers of 7-hydroxyflumequine (**XVI**, yield 23 %, and **XVII**, yield 43 %) and also 7-oxoflumequine (**XVIII**, yield 11 %) were formed in 7 days [94]:



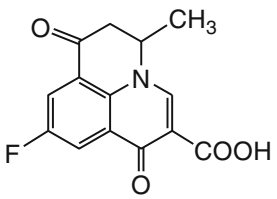
XV



XVI



XVII

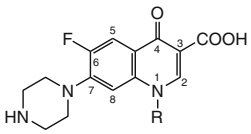


XVIII

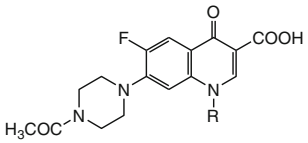
Transformation of norfloxacin, ciprofloxacin, and enrofloxacin

The fluoroquinolone norfloxacin (**XIX**), which has an *N*-ethyl group, a 3-carboxylic acid group, and a 7-piperazine ring, emerged in 1980 [40] as the earliest of the second-generation quinolones [13]. Norfloxacin is still used occasionally for treatment of some infections, including urinary tract infections [71] and conjunctivitis [54]. Laboratory and clinical tests have shown that it possesses antimalarial activity [20, 73] but may not be as effective as chloroquine [51].

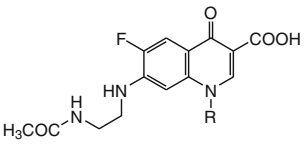
The transformation of norfloxacin by the fungus *Pestalotiopsis guepini* produced four metabolites, *N*-acetylnorfloxacin (**XX**, yield 55.4 %), desethylene *N*-acetylnorfloxacin (**XXI**, yield 8.8 %), *N*-formylnorfloxacin (**XXII**, yield 3.6 %) and 7-amino-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**XXIII**, yield 2.1 %) [63, 95], all of which are known from human and animal studies [18, 66]:



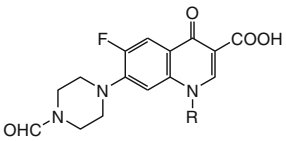
XIX, R=C_2H_5
XXV, R=cC_3H_5



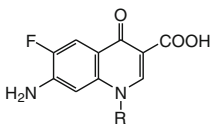
XX, R=C_2H_5
XXVI, R=cC_3H_5



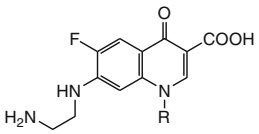
XXI, R=C_2H_5
XXVII, R=cC_3H_5



XXII, R=C_2H_5
XXVIII, R=cC_3H_5



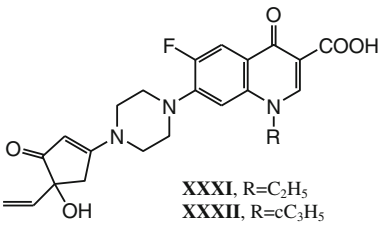
XXIII, R=C_2H_5
XXIX, R=cC_3H_5



XXIV, R=C_2H_5
XXX, R=cC_3H_5

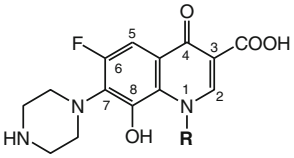
In an attempt to identify biotransformation products and the enzymes involved in their formation, a wood-decaying white-rot basidiomycete, *Trametes versicolor*, was grown in a medium containing norfloxacin [68]. It produced desethylene *N*-acetylnorfloxacin and 7-amino-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid from norfloxacin, plus desethylene norfloxacin (**XXIV**) [68]. Although these products have not been specifically tested, they most likely have less antibacterial activity than norfloxacin or none at all [18].

The fungus *Trichoderma viride*, when grown in a medium with norfloxacin for 16 days, formed a conjugate (**XXXI**, yield 42 %) that presumably originated from the reaction of norfloxacin with a cyclopentenone secondary metabolite of the fungus [64]:

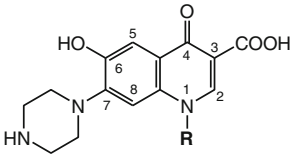


XXXI, R=C_2H_5
XXXII, R=cC_3H_5

Norfloxacin was transformed by cultures of a *Microbacterium* sp. from wastewater to four metabolites, *N*-acetylnorfloxacin, desethylene *N*-acetylnorfloxacin, 8-hydroxynorfloxacin (**XXXIII**), and the defluorinated compound 6-hydroxynorfloxacin (**XXXV**), in 14 days [36]:

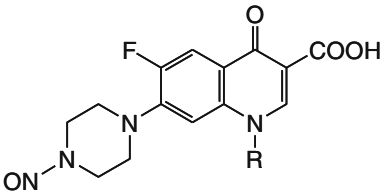


XXXIII, R=C_2H_5
XXXIV, R=cC_3H_5



XXXV, R=C_2H_5
XXXVI, R=cC_3H_5

Environmental mycobacteria are known to transform various aromatic compounds, including fluoroquinolones [16]. Transformation of norfloxacin by cultures of an environmental isolate of *Mycobacterium gilvum* led to the formation not only of *N*-acetylnorfloxacin (yield 20 %) but also of *N*-nitrosonorfloxacin (**XXXVII**, yield 5 %) [2]:



XXXVII, R=C_2H_5
XXXVIII, R=cC_3H_5

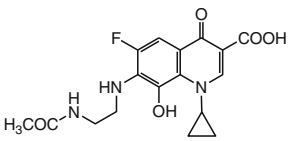
The *N*-acetylation of norfloxacin by cultures of an *Escherichia coli* strain, from wastewater, that has the variant aminoglycoside acetyltransferase gene *aac(6′)-Ib-cr* has also been observed [32].

Ciprofloxacin (**XXV**), which is similar to norfloxacin but has an *N*-cyclopropyl group, has a broad spectrum of activity and is widely prescribed for infections caused by many bacteria [76]. It shows antimalarial activity in vitro against chloroquine-sensitive strains of *Plasmodium falciparum* [20, 46], but it was unsuccessful for treating patients with chloroquine-resistant malaria [84]. Ciprofloxacin also has been shown to interrupt the cell cycle of tumor cell lines [38]. The metabolites found in urine, which include desethylene, sulfate, oxo, and formyl derivatives, have less activity for most of the target bacteria than ciprofloxacin [96]. The drug is degraded by sunlight when present in biological waste used as a soil amendment, but some of the photodegradation products still have antimicrobial activity [45].

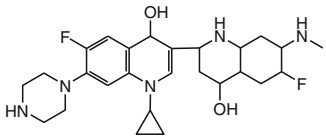
The wood-decaying brown-rot fungi are basidiomycetes that appear to produce hydroxyl radicals by a process involving Fenton-type chemistry [39, 74]. In a study of the oxidation of ciprofloxacin by the brown-rot basidiomycete *Gloeophyllum striatum*, 11 major metabolites and five trace metabolites were detected [93]. They included decarboxylated, defluorinated, and hydroxylated metabolites; some had lost all or part of the piperazine or the pyridine ring. One major metabolite (**XXXVI**) had a hydroxyl replacing fluorine at position C-6. Many of these metabolites are inactive as antibacterial agents [93, 96]. Several other basidiomycetes from agricultural and forest habitats are also able to degrade ciprofloxacin [93].

Ciprofloxacin is transformed by cultures of the zygomycete *Umbelopsis ramanniana* (syn. *Mucor ramannianus*) almost entirely to the much less active *N*-acetylciprofloxacin (**XXVI**, yield 89 %) [60]. The acetylated metabolite has an MIC for *E. coli* that is at least four times that of ciprofloxacin [70]. The transformation of ciprofloxacin by *P. guepini* produced four metabolites: *N*-acetylciprofloxacin (yield 52.0 %), desethylene-*N*-acetylciprofloxacin (**XXVII**, yield 9.2 %), *N*-formylciprofloxacin (**XXVIII**, yield 4.2 %) and 7-amino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**XXIX**, yield 2.3 %) [63]. This last metabolite, **XXIX**, is also produced by *G. striatum* [93]. Acetylation of the positively charged secondary amine on the piperazine ring makes the net charge of the molecule negative, so the drug is less able to enter a bacterial cell and thus has less activity [92]. Formylation of ciprofloxacin reduces activity somewhat against Gram-negative bacteria and desethylation reduces the activity even more [96]; both of these reactions also occur in humans. The loss of the piperazinyl group also probably reduces activity [18, 66, 93].

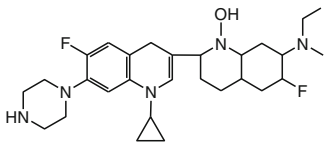
The basidiomycete *T. versicolor* transforms ciprofloxacin to 7-amino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**XXIX**), desethylene ciprofloxacin (**XXX**) and 8-hydroxyciprofloxacin (**XXXIV**), which are also produced by *G. striatum*; three novel metabolites of *T. versicolor* are desethylene *N*-acetyl-8-hydroxyciprofloxacin (**XXXIX**) and two unusual conjugates (**XL** and **XLI**) [68]:



XXXIX



XL



XLI

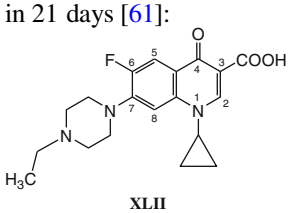
Cultures of the fungus *T. viride* grown in the presence of ciprofloxacin accumulated a cyclopentenone conjugate (**XXXII**, yield 31 %) in 16 days [64].

Ciprofloxacin, like norfloxacin, is *N*-acetylated by clinical and environmental cultures of *E. coli* that have the *aac(6′)-Ib-cr* gene [32, 70]. Fluoroquinolone resistance has already been found in pathogenic species of *Mycobacterium* [28]; a nonpathogenic strain of *M. gilvum* was found to transform ciprofloxacin to both *N*-acetylciprofloxacin (yield 5 %) and *N*-nitrosociprofloxacin (**XXXVIII**, yield 8 %) [3].

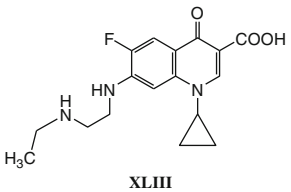
Enrofloxacin (**XLII**) is an antibacterial veterinary fluoroquinolone that is used to treat a great variety of diseases of livestock, companion animals, and fish [50, 55, 75]. It is degraded by various basidiomycetes from decaying wood and agricultural soils [49, 85, 91], and also by sunlight [79, 80].

A total of 137 metabolites, including ethylpiperazine and CO_2 [89], which are produced by *G. striatum* and other basidiomycetous fungi from enrofloxacin, have been identified in an outstanding series of investigations by Karl et al. [33] and Wetzstein et al. [89, 90] using high-performance liquid chromatography and high-resolution electrospray ionization mass spectrometry. The organism chosen for most of the work was *G. striatum*, which is able to biotransform enrofloxacin even in nutrient-free media [33, 89]. During the transformation of enrofloxacin by *G. striatum*, 87 metabolites were detected and identified [33, 89]; by using cultures of seven other basidiomycetes, 48 additional metabolites were found [90]. Hydroxyl radicals formed by Fenton chemistry are almost certainly involved in the biotransformation of enrofloxacin by these fungi [74]. The principal routes for enrofloxacin metabolism by *G. striatum* (Fig. 1) include oxidative decarboxylation followed by cleavage of the pyridone ring, defluorination at position C-6, hydroxylation at positions C-8 and C-7 with loss of the ethylpiperazine ring, removal of part of the ethylpiperazine ring, and N-oxidation [89, 91]. The metabolism of enrofloxacin by basidiomycetes from agricultural sites demonstrates the ability of these fungi to biodegrade veterinary fluoroquinolones that enter the environment [85, 90, 91].

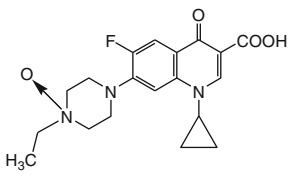
The zygomycete *U. ramanniana* transformed enrofloxacin (**XLII**) to three products, desethylene enrofloxacin (**XLIII**, yield 3.5 %), which is also produced by *G. striatum* [89], enrofloxacin *N*-oxide (**XLIV**, yield 62.0 %), also produced by *G. striatum* [33], and *N*-acetylciprofloxacin (**XXVI**, yield 8.0 %), in 21 days [61]:



XLII



XLIII

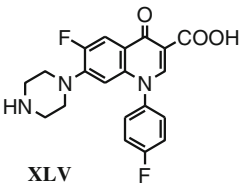


XLIV

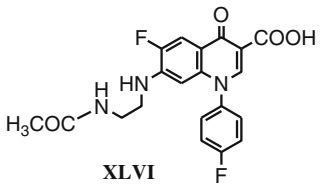
Transformation of sarafloxacin, danofloxacin, and marbofloxacin

Sarafloxacin (**XLV**) has been used as an antibacterial agent in poultry production [1, 31] and aquaculture [37, 50]. Because less than 1 % of sarafloxacin labeled with ^{14}C in the 2-position was degraded to detectable metabolites in soil [48], suggesting that this compound is especially persistent in the environment, the transformation of sarafloxacin was investigated with cultures of the wood-decaying white-rot basidiomycete *Phanerochaete chrysosporium* [47]. Six probable intermediate metabolites and CO_2 were produced from sarafloxacin [47].

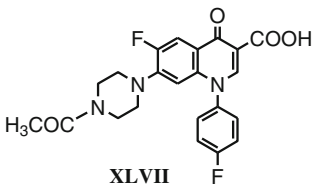
In another study, cultures of *U. ramanniana* formed two metabolites, which were identified as desethylene *N*-acetylsarafloxacin (**XLVI**, yield 26.0 %) and *N*-acetylsarafloxacin (**XLVII**, yield 15.0 %), in 18 days [62]:



XLV

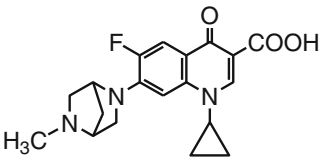


XLVI

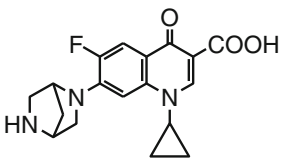


XLVII

Danofloxacin (**XLVIII**) is used for treating bacterial infections of cattle, pigs, and other livestock [52, 72]. To determine whether danofloxacin was likely to persist in the environment, cultures of several bacteria and fungi were grown with this drug [16]. The bacteria *Mycobacterium smegmatis* and *Pseudomonas fluorescens*, among others, produced two metabolites, *N*-desmethyldanofloxacin (**XLIX**) and 7-amino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**XXIX**) [16]:



XLVIII



XLIX

Marbofloxacin (**L**), a veterinary quinolone that is used mostly for treating bacterial infections in dogs and cats [53], is not only degraded photochemically in sunlight [79, 80] but also transformed biologically by *G. striatum*. Unpublished results obtained by mass spectrometry suggest that the fungal marbofloxacin derivatives formed may include 3-hydroxy (decarboxylated), 6-hydroxy and 5,6-

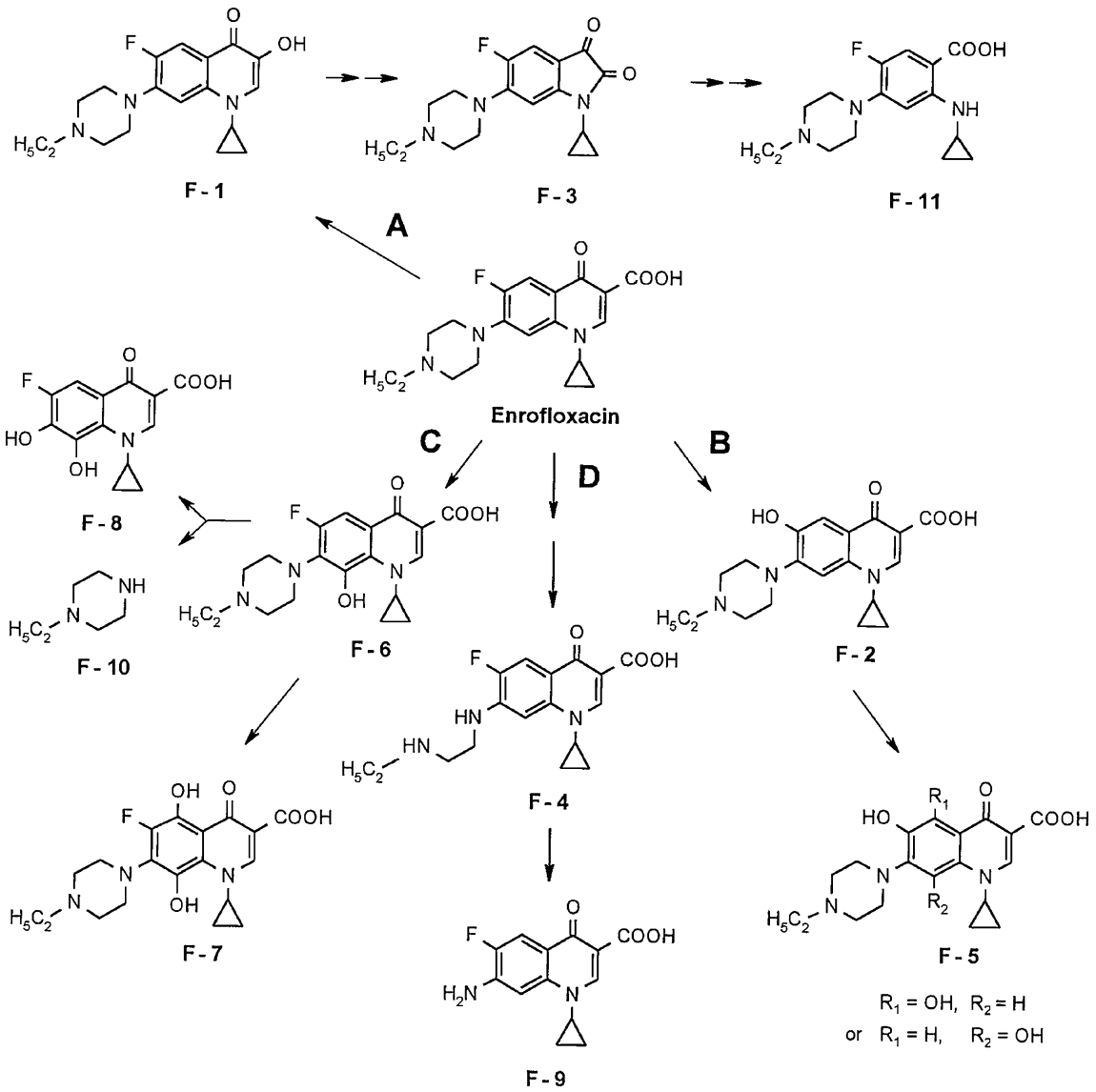
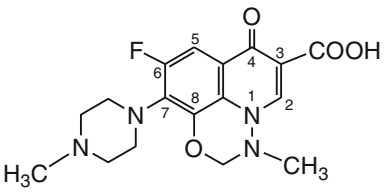


Fig. 1 Principal routes of enrofloxacin biotransformation in the basidiomycete *Gloeophyllum striatum* (N-oxidation is not shown). Reprinted with permission from Wetzstein et al. [89]. Copyright 1997 by ASM Press

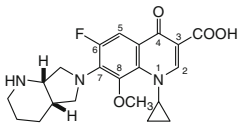
dihydroxy (both defluorinated), desethylene, 7-amino (missing most of the *N*-methylpiperazine group), 3,6-dihydroxy (decarboxylated and defluorinated), and an N_1–H, 8-hydroxy derivative [H.-G. Wetzstein, personal communication]:



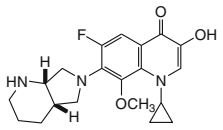
L

Transformation of moxifloxacin and pradofloxacin

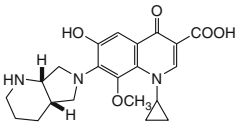
Moxifloxacin (**LI**), an 8-methoxyfluoroquinolone (BAY 12-8039), is used clinically for treating bacterial infections of the respiratory tract, especially those caused by Gram-positive cocci and anaerobes, and those of the skin [34, 67]. It is biotransformed by cultures of *G. striatum*; several metabolites, including 3-hydroxy-decarboxymoxifloxacin (**LII**), 6-hydroxy-defluoromoxifloxacin (**LIII**), and the demethylated derivative 8-hydroxymoxifloxacin (**LIV**), all with either low antimicrobial activity or none [67], were produced in 3 days [87]:



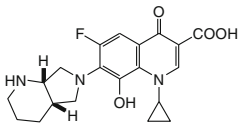
LI



LII

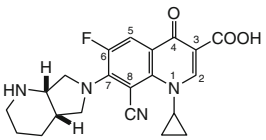


LIII

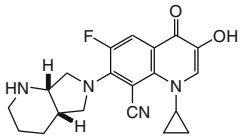


LIV

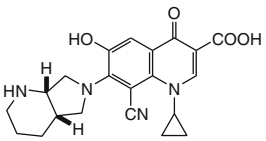
Pradofloxacin (**LV**) is a veterinary fluoroquinolone with a cyano group on the C-8 position, developed for treating bacterial infections in dogs and cats [77, 86]. Especially because of the cyano substituent, pradofloxacin had been expected to be more biodegradable than most other fluoroquinolones [92]. Transformation of pradofloxacin by *G. striatum* produced six major metabolites, probably arising from hydroxyl radical reactions, in 16 days [92]. As expected, the pathways were similar to those for enrofloxacin metabolism depicted in Fig. 1. The major metabolites, with their steady-state concentrations, were 3-hydroxy-decarboxypradofloxacin (**LVI**, 3.0 %), 6-hydroxy-defluoropradofloxacin (**LVII**, 9.0 %), 5,6-dihydroxy-defluoropradofloxacin (**LVIII**, 3.0 %), 8-hydroxy-decyanopradofloxacin (**LIX**, 1.0 %), 7-amino-8-cyano-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**LX**, 1.0 %) and 6-[(*E*/*Z*)-1-cyano-2-hydroxyethenyl]-1-cyclopropyl-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid (**LXI**, 1.0 %) [92]:



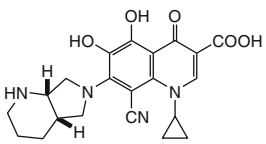
LV



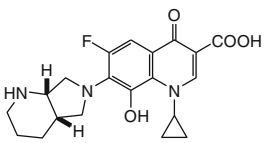
LVI



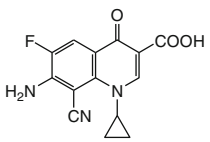
LVII



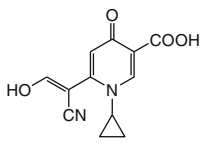
LVIII



LIX



LX



LXI

At least four of the six major pradofloxacin metabolites lack substantial antimicrobial activity; the other two metabolites (**LVII** and **LVIII**) are unstable [88, 92]. The unique feature of this fungal biotransformation occurs after the pyrrolodinopiperidine group at position C-7 is removed, when the benzo ring is cleaved [92]. The product of this cleavage, **LXI**, was isolated by HPLC and identified by the exact mass, NMR spectrum, and FT-IR spectrum [92]. Cleavage of aromatic benzo rings by fungi was previously demonstrated in aromatic hydrocarbons [30] and had been proposed to occur also in the fungal transformation of quinolones [33], but this paper [92] was the first to show the isolation and identification of a cleavage product of the benzo ring of a quinolone.

Concluding remarks

Quinolones include several widely used antibacterial agents, which are not only distributed by physicians, pharmacists and small-animal veterinarians, but are also used in large-scale livestock production and aquaculture in many countries [5, 50, 82]. They may be partially degraded by photochemical processes when exposed to sunlight [79, 80, 82]. Although the fully synthetic structures of quinolones were once thought by some to be non-biodegradable [91], recent work has shown that all parts of these molecules can be degraded by fungi [92] and that quinolone-degrading basidiomycetes are abundant in agricultural sites [85, 90, 91]. Some bacteria found in the environment, including mycobacteria, can also inactivate quinolones [2, 3, 32, 36].

Because of the serious problem of drug resistance among pathogenic bacteria [15], new antimicrobials that are able to restrict selection for resistance are needed [21, 24]. Improved design of the chemical structure of quinolones by considering structure–activity relationships of substitutions at various positions [56, 88] should help to solve some of the problems caused by emerging resistance [4, 22] and adapt quinolones for new applications [11, 12, 57]. Consideration of the mutant prevention concentration of a drug for a target bacterium and appropriate dosing levels may allow the mutant selection window to be narrowed [21, 86, 88]. It is also possible that new quinolone derivatives obtained by regio- and stereospecific microbial transformation [42] combined with chemical synthesis may be useful in developing new antimicrobial, antiparasitic, antiviral, and antitumor drugs.

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