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MINIREVIEW

Structure-Activity Relationships of the Fluoroquinolones

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INTRODUCTION

A comprehensive review of the structure-activity relationships, microbiology, and synthetic chemistry associated with the nalidixic acid-type antibacterial agents was published in 1977 (3). Since then, more than 5,000 new analogs have been described in the literature. In recent years, many clinically important antibacterial agents having a 1-substituted 1,4-dihydro-4-oxo-pyridine-3-carboxylic acid moiety and collectively known as quinolones have been discovered. These agents include norfloxacin (structure 1; Fig. 1) (35), pefloxacin (structure 2) (26), ofloxacin (structure 3) (44), ciprofloxacin (structure 4) (50), enoxacin (structure 5) (37), difloxacin (structure 6) (8), temafloxacin (structure 7) (28), lomefloxacin (structure 8) (31), fleroxacin (structure 9) (7), tosufloxacin (A-61827, T-3262) (structure 10) (J. M. Stamm, C. Vojtko, J. Weisz, C. Hanson, D. T. W. Chu, and P. B. Fernandes, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 132, 1985), and amifloxacin (structure 11) (49). Modification of the groups which occupy the N-1, C-6, C-7, and C-8 positions has been successful in yielding potent antibacterial agents. Most of these compounds are structurally characterized by the combination of the moiety (A) with a second aromatic or heteroaromatic ring (B) (structure 12; Fig. 1). Almost all of the clinically useful quinolones bear a fluorine atom at the C-6 position of the quinolone, naphthyridine, or benzoxazine ring system. Because of the presence of the C-6 fluorine atom, these antibacterial agents are generally described as fluoroquinolones. Figure 1 shows the various structures of the quinolones and fluoroquinolones mentioned in this review.

Recently, a short summary of the structure-activity relationships of these new fluoroquinolones was published (45). However, the rapid progress in quinolone research has resulted in many new interesting findings in relation to structure-activity relationships since that publication. In this minireview, we discuss the structure-activity relationships of the fluoroquinolones reported since 1970 up to the present time.

STRUCTURE-ACTIVITY RELATIONSHIPS

The mechanism of action of the quinolone antibacterial agents involves the inhibition of DNA gyrase (5, 10, 22, 29, 30, 32, 40, 43, 46, 51, 53). It is reasonable to assume that the antibacterial activity of quinolones is the result of the combination of bacterial cell penetration and DNA gyrase-inhibiting activities. A comparison between the MICs of and DNA gyrase inhibition by various quinolones to identify qualitatively features needed for these two activities has been reported (13). The study concluded that both gyrase inhibition and cell penetration are enhanced by the presence of a C-6 fluorine atom. With a similar set of data, a computed-automated structure evaluation program analysis concluded that cell permeability is predominantly controlled by the nature of the C-7 substituent (34). All of these conclusions, however, were based on the assumption that DNA gyrase isolated from various microbial sources exhibits identical sensitivities to quinolone antibacterial agents. Recent experimental results cast doubts on the validity of this assumption (38, 39, 53; L. L. Shen, L. A. Mitscher, P. N. Sharma, T. J. O'Donnell, D. T. W. Chu, C. S. Cooper, T. Rosen, and A. Pernet, Biochemistry, in press), although the conclusions for C-6 and C-7 substituents may be valid. In recent years, DNA gyrase inhibition assays have been routinely used as part of the screening of new quinolone derivatives, providing a structural lead for further modifications to enhance the antibacterial activities. Because there are few reported data on the inhibition of DNA gyrase isolated from different sources, as well as the fact that DNA gyrase-inhibiting activities account for only part of the antibacterial activities, the structure-activity relationships discussed in this review will be focused on MICs rather than on DNA gyrase inhibiting activities.

The general structure of the new potent quinolones is represented by structure 13 in Fig. 1. Nalidixic acid (structure 14) is the prototype for antibacterial agents of the naphthyridine class (structure 13, X = N), and oxolinic acid (structure 15) is the prototype of the quinolone class (structure 13, X = CH). Systematic modification studies on nalidixic acid have produced compounds with increased potency and spectrum and have greatly enhanced the therapeutic application of quinolones.

Position 1. An earlier study indicated that substitution at the N-1 position is important for antibacterial activity (3). Quantitative structure-activity relationship analysis of a set of N-1-allyl and -alkyl derivatives suggested an optimum STERIMOL length of 0.42 nm, corresponding approximately to an ethyl group (20). STERIMOL is a program (48) that calculates a set of five parameters characterizing the size and shape of a substituent. The parameter *L* (STERIMOL length) is defined as the length of the substituent along the axis of the bond between the substituent and the parent molecule. Most of the marketed quinolones, such as norfloxacin, pefloxacin, and enoxacin, have an ethyl group at the N-1 position. Examples of bioisosteres of N-1-ethyl-substituted analogs are amifloxacin ($NHCH_3$), fleroxacin (C_2H_4F), and miloxacin (structure 16; Fig. 1) (1). Bioisosteres are molecules or fragments containing an identical number and arrangement of electrons (or, more broadly,

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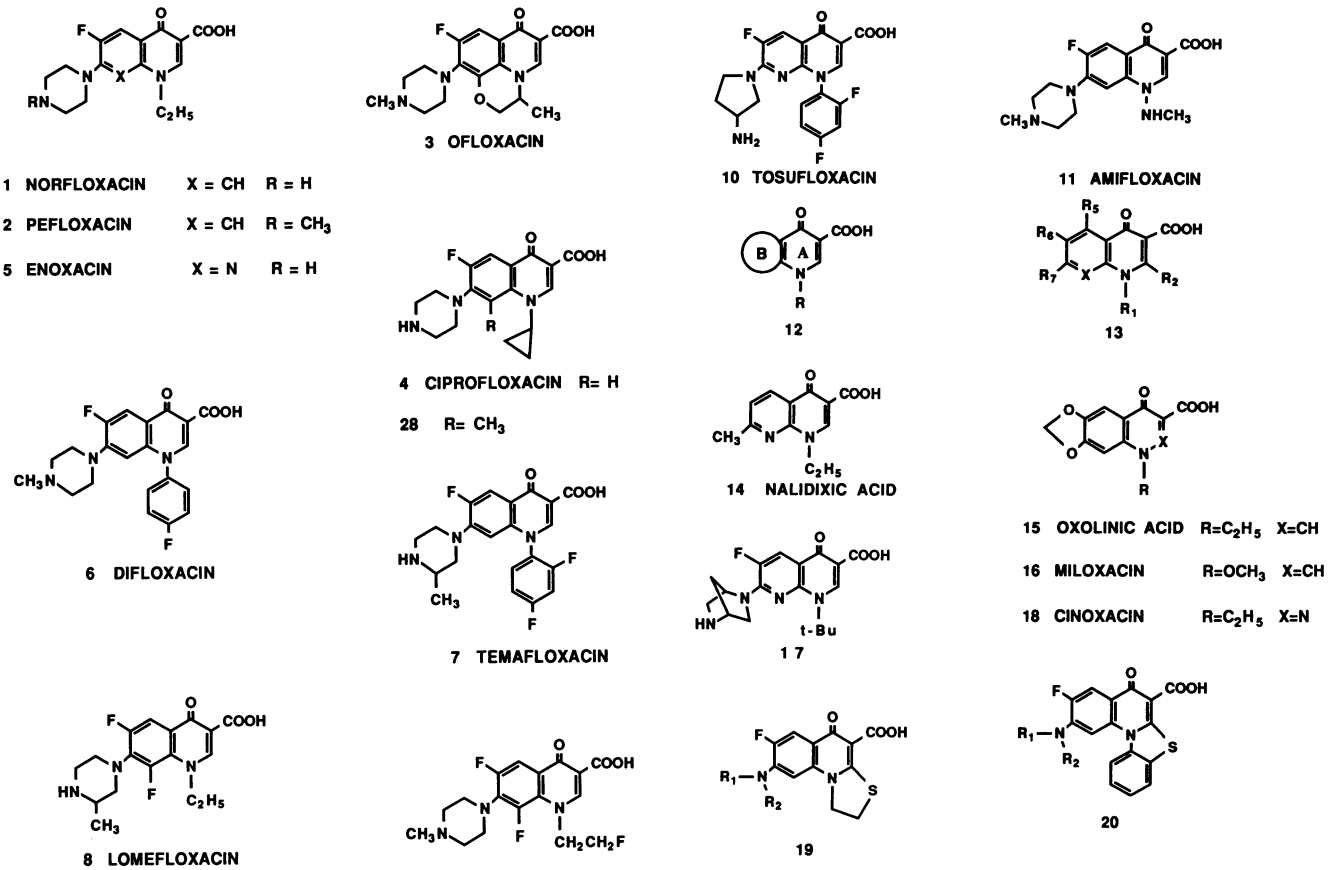

FIG. 1. Structures of various quinolones and fluoroquinolones.

retaining a major degree of similarity in steric or regional electronic configuration) and having similar chemical, physical, and biological activities.

The discovery of potent quinolones with N-1-phenyl (8, 28) and N-1-cyclopropyl (50) substitutions indicated that with respect to an N-1 substituent, in addition to steric bulk, there are other factors, such as electronic π-donation and ideal spatial effects (8, 9, 14), that also have a great influence on their biological activities. The cyclopropyl group is by far the optimal group by virtue of its favorable combination of steric, spatial, and through-space electronic interactions. Ciprofloxacin, having an N-1-cyclopropyl substituent, is by far the most potent of the marketed quinolones in vitro against members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* (50). Difloxacin, having an N-1-*p*-fluorophenyl substituent, is the most active quinolone in vitro against *Chlamydia trachomatis* (6), *Legionella pneumophila* (16), and other intracellular pathogens (19). It also has excellent pharmacokinetic properties (27). The N-1-fluoro-substituted phenyl substitution may improve the in vitro efficacy of quinolones against anaerobic bacteria, as exemplified by tosufloxacin (17), difloxacin (18), and temafloxacin (28).

The introduction of a *t*-butyl group at N-1 produced quinolones with enhanced activity against gram-positive bacteria, with a minor reduction of activity against gram-negative bacteria, as exemplified by BMY 40062 (structure 17; Fig. 1) (D. Bouzard, P. DiCesare, M. Essiz, J. P. Jacquet, P. Remuzon, A. Weber, T. Oki, and P. Masuyoshi, 28th ICAAC, abstr. no. 962, 1988). This is another recent

result which indicated that a steric bulk factor at N-1 alone cannot account for optimal biological activity.

Position 2. Very few modifications have been explored at position 2. Cinoxacin (structure 18; Fig. 1), which has a nitrogen atom in position 2, has improved pharmacokinetic properties. However, it is less active in vitro than oxolinic acid. 5-Oxo-1,2-dihydro-5H-thiazolo[3,2-a]quinolone-4-carboxylic acid derivatives (structure 19) (S. Matsumura, M. Kise, M. Ozaki, S. Tada, K. Kazuno, H. Watanabe, K. Kunimoto, and M. Tsuda, U.S. patent 4,426,381, January 1984) and benzothiazolo[3,2-a]quinolones (structure 20) (9) possess good antibacterial activities. These derivatives have a sulfur atom positioned at C-2; the substituent is part of a ring system annealed to the benzene moiety. No clinical study on these compounds has been reported.

Position 3. Positions 3 and 4, having a link between the carboxylic acid group and the keto group, are generally considered necessary for the binding of quinolones to DNA gyrase (45). Classical studies have produced no active quinolones with a significant modification of the C-3 carboxylic acid group, with the exception of groups which are converted in vivo back to a carboxylic acid group (42). For example, replacement of the 3-carboxylic acid group of norfloxacin by a formyl group produced a compound with low antibacterial activity. However, the compound exhibited increased activity in vivo in a mouse infection model, owing to its rapid conversion into the 3-carboxylic acid group, to produce twice the concentration in serum as norfloxacin (36). The replacement of the 3-carboxylic acid function in these compounds by acidic groups such as sulfonic acid (2, 52), acetic acid (41), hydroxamic acid (41), and sulfonamide and phosphoric acid (52) resulted in a substantial decrease in antibacterial activities. A recent attempt to replace the 3-carboxylic acid group with a carboxylic acid-mimicking compound, 1-H-tetrazol-5-yl, resulted in a total loss of antibacterial activity (25).

A-62824 (structure 21; Fig. 1), in which the 3-carboxylic acid group of ciprofloxacin has been replaced by a bioisostere-fused isothiazolo ring, is substantially more potent (4 to 10 times) than ciprofloxacin and possesses enhanced activity against DNA gyrase (D. T. W. Chu, P. B. Fernandes, A. K. Claiborne, L. Shen, and A. Pernet, 27th ICAAC, abstr. no. 250, 1987). This discovery offers a new insight into the understanding of the structure-activity relationships among the quinolones. The isothiazolo ring system in structure 21 possesses an aromatic character, and the nitrogen proton is very acidic and can be considered to mimic carboxylic acid. The planarity between the 4-keto group and the enolized isothiazolo group may be important for binding to the DNA gyrase.

Position 4. Position 4 has not been extensively explored, and replacement of the 4-keto group with other groups so far has led to inactive compounds.

Position 5. Limited investigations have been done on the C-5 position. Small substituents, such as nitro, amino, halo, and alkyl groups, have been synthesized. The C-5-amino substitution may enhance absorption or tissue distribution. Although some reports have suggested that substitution at the C-5 position reduces antibacterial activity (33, 47), 5-aminoquinolones (structures 22 and 23; Fig. 1) have been reported (12) to have in vitro antibacterial activity far superior to that of ciprofloxacin. The amino group at the C-5 position in the 6,8-difluoroquinolone series may enhance in vitro potency.

Position 6. Of the various C-6 substituents (H, F, Cl, Br, CH_3, SCH_3, $COCH_3$, CN, and NO_2), the addition of a fluorine atom resulted in a dramatic increase in antibacterial potency (35). The fluoro group at position C-6 seems to improve both the DNA gyrase complex binding (2- to 17-fold) and cell penetration (1- to 70-fold) of the corresponding derivatives with no substitution at the C-6 position (13). Because of such an enhancement of antibacterial potency, nearly all of the recently synthesized quinolones carry a C-6 fluorine substituent.

Position 7. Modification at the C-7 position of the quinolone molecule has been extensively studied. Norfloxacin, having a C-7-piperazinyl group in addition to a C-6 fluorine substituent, has antibacterial potency far superior to that of the earlier classical quinolones against gram-positive and gram-negative bacteria, including many strains of *P. aeruginosa*. In general, quinolones with small or linear C-7 substituents (H, Cl, CH_3, $NH_2CH_2CH_2NH_2$, $NHCH_3$, and $NHNH_2$) possess moderate to weak biological activities. Quinolones having a five- or six-membered heterocyclic ring with or without a substitution at the C-7 position (pyrrolidinyl, pyrrolyl, thiazolidinyl, thiomorpholinyl, and piperazinyl) have good antibacterial activities. The most common C-7 substituents are (i) piperazin-1-yl (found in norfloxacin, ciprofloxacin, and enoxacin), (ii) 4-methyl-piperazin-1-yl (found in pefloxacin, ofloxacin, difloxacin, fleroxacin, and amifloxacin), (iii) 3-aminopyrrolidin-1-yl (found in tosufloxacin and AM-1091 [PD 127391]) (structure 24; Fig. 1) (K. Hirai, T. Ishizaki, T. Koibe, K. Iwase, M. Hosaka, Y. Niwata, Y. Asahina, S. Suzue, and K. Masurzawa, 26th ICAAC, abstr. no. 436, 1986; M. A. Cohen, G. B. Mailloux, P. A. Bien, S. L. Yoder, and C. L. Heifetz, Abstr. Annu. Meet. Am. Soc. Microbiol. 1988, A17, p. 3), (iv) 3-ethylaminomethyl-pyrrolidin-1-yl (found in PD 117558) (structure 25) (14), (v) 3-methylpiperazin-1-yl (found in lomefloxacin and temafloxacin), and (vi) pyrrolyl (found in irloxacin) (structure 26) (4).

In general, the substitution of methyl at the C-4 position of the piperazinyl group enhances the gram-positive antibacterial activity of the parent compound, with a slight decrease in gram-negative activity, especially against *P. aeruginosa*. The LogP (partition coefficient, octanol:water) of derivatives with a 4-methypiperazin-1-yl group is generally higher than that of the piperazinyl group analogs. These compounds, exemplified by difloxacin and pefloxacin, are well absorbed and have high levels in serum and a long half-life in serum. They undergo enterohepatic circulation to a substantial degree (27). It is surprising to find that 3-methylpiperazin-1-yl substitution does not cause the same increase in LogP but allows good oral absorption characteristics to be retained. The quinolones with a substitution of the 3-ethylaminomethylpyrrolidin-1-yl group at the C-7 position have improved gram-positive activity. The substitution of a 3-aminopyrrolidin-1-yl group at the C-7 position of quinolones generally enhances the overall spectrum of activity. However, this substitution may make the molecules less water soluble at pH 7.4 and may cause potential absorption problems in humans.

Position 8. Among many modifications investigated at the C-8 position, replacement of C-8 with a nitrogen atom or substitution with a halogen atom may provide clinically useful quinolones. In general, when compared with analogs with no substitution at the C-8 position, C-8-fluoro or -chloro derivatives are more active in vivo, owing to better oral absorption. They are a little less active in vitro. Lomefloxacin, fleroxacin, PD 117558, compounds shown as structures 22 and 23, and PD 117596 (structure 27; Fig. 1) (Cohen et al., Abstr. Annu. Meet. Am. Soc. Microbiol. 1988) have a

C-8-fluoro substitution, and AM-1091 (PD 127391) has a C-8-chloro substitution. Ofloxacin, having an oxygen substituted at the C-8 position, where the substituent is part of a ring system annealed to the basic pyridone moiety, is somewhat more potent than norfloxacin in vitro and has outstanding in vivo efficacy. Substitution at the C-8 position by a methyl group produces analogs having in vitro and in vivo activities comparable to those of the unsubstituted quinolone exemplified by compound 28 (Fig. 1) (K. Ohmori, F. Mukai, K. Ohguro, S. Kawabata, M. Kurosumi, H. Yamashita, H. Miyamoto, H. Ueda, H. Tamaoka, K. Nakagawa, and Y. Yabunchi, 28th ICAAC, abstr. no. 954, 1988). A number of naphthyridines in which C-8 is replaced by a nitrogen atom have excellent activity in vitro and in vivo, as exemplified by tosufloxacin. In general, however, with similar substitutions at N-1, C-5, C-6, and C-7, naphthyridine analogs are less active in vitro than their quinolone counterparts. This inferior in vitro activity is overcome by better absorption to enhance in vivo activity.

Monocyclic quinolones. Ro-13-5478 (structure 29; Fig. 1) was found to have antibacterial activity similar to that of nalidixic acid (23). It inhibits DNA supercoiling catalyzed by DNA gyrase and produces DNA cleavage. So far, no monocyclic analogs have been shown to have activity equal to that of the newer fluoroquinolones.

Chiral quinolones. Nearly all clinically useful quinolones developed to date are either achiral or racemic mixtures. Recently, the optical enantiomers of ofloxacin (15, 39, 51) and S-25930 (structure 30; Fig. 1) (24) were prepared; the *S* enantiomers have greater biological activity (10- to 100-fold). These compounds have the methyl substituent positioned above the plane of the quinolone nucleus. The *R* enantiomer of 7-(2-substituted pyrrolidin-1-yl) derivative compound 31 (Fig. 1) was reported to be 10- to 60-fold more active than the *S* enantiomer (C. S. Cooper, D. T. W. Chu, P. B. Fernandes, E. Pihuleac, and A. Pernet, 25th ICAAC, abstr. no. 130,, 1985). Chiral recognition is important when the chiral group is in close proximity to the quinolone nucleus, such as at N-1 or C-7. When the chiral group is farther away, as with the 3-ethylaminomethylpyrrolidin-1-yl in CI-934 (structure 32) (11), the 3-methylpiperazin-1-yl in temafloxacin (structure 7) (D. T. W. Chu, P. B. Fernandes, A. K. Claiborne, R. Z. Maleczka, P. Klock, L. Shen, J. Patel, and A. Pernet, 26th ICAAC, abstr. no. 428, 1986), and the 3-aminopyrrolidin-1-yl in tosufloxacin (structure 10) (T. Rosen, I. M. Lico, D. T. W. Chu, P. B. Fernandes, L. Shen, and A. G. Pernet, 3rd Chem. Congr. North Am., abstr. no. Medi-49, 1988), only minor improvements in antibacterial activities over those of their antipodes have been observed.

CONCLUSIONS

The new fluoroquinolones are potent synthetic antibacterial agents with broad spectra, including most urinary tract and gastrointestinal tract bacterial pathogens, *Neisseria gonorrhoeae*, and many other difficult-to-treat bacteria. Modifications of every position in the standard quinolone molecule, with the exception of the C-4 position, have been successful. Fluoroquinolones that possess a dipolar ion are generally more active at higher pHs. However, difloxacin is more active at pH 7.2 than at pH 8.8 (E. St. Martin, J. Stamm, E. McDonald, C. Vojtko, and P. B. Fernandes, 24th ICAAC, abstr. no. 74, 1984). E-3846 (structure 33), which does not appear to possess a dipolar ion, is more potent at lower pHs (21). The recent important advance in structure-activity relationship is the discovery of A-62824 (structure 21) and its related analogs. By use of the bioisosteric replacement strategy, the 3-carboxylic group has been successfully modified. A clever refinement of the many mentioned structure modifications to generate quinolones with lower central nervous system side effects, greater water solubility, and improved pharmacokinetics and activity against streptococci and anaerobes will remain the focus of many medicinal chemists.

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