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FINAFLOXACIN HYDROCHLORIDE

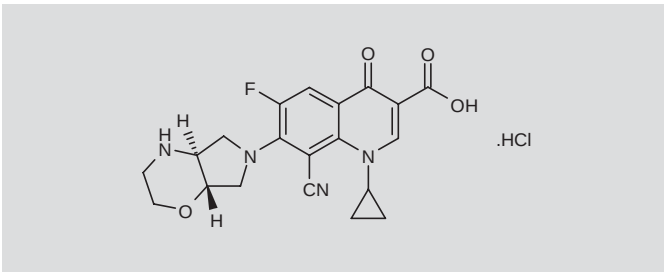
Rec INNM

Antibacterial Agent
Anti-Helicobacter pylori Agent
Quinolone

BY-377
BAY-35-3377 (former code name)

(–)-(4aS,7aS)-8-Cyano-1-cyclopropyl-6-fluoro-4-oxo-7-(perhydropyrrolo[3,4-*b*]-1,4-oxazin-6-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride

InChI=1/C20H19FN4O4/c21-14-5-11-17(25(10-1-2-10)7-13(19(11)26)20(27)28)12(6-22)18(14)24-8-15-16(9-24)29-4-3-23-15/h5,7,10,15-16,23H,1-4,8-9H2,(H,27,28)/t15-,16-/m0/s1



$C_{20}H_{20}ClFN_4O_4$
Mol wt: 434.849
CAS: 209342-40-5
EN: 295632

ABSTRACT

Finafloxacin hydrochloride, a novel 8-cyano subclass of fluoroquinolone, has demonstrated potent antibacterial activity in a range of in vitro and in vivo models against Gram-negative and Gram-positive bacterial isolates. The compound displayed superior bactericidal activity compared to other known fluoroquinolones, including ciprofloxacin and levofloxacin, at acidic conditions where other fluoroquinolones experience reductions in activity, thus rendering finafloxacin a good candidate for the treatment of bacterial infections in acidic environments. Finafloxacin is currently under clinical development for the treatment of urinary tract and gastrointestinal infections and Helicobacter pylori eradication.

SYNTHESIS

Finafloxacin hydrochloride can be synthesized by two closely related ways. Coupling of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (I) with (4aS,7aS)-octahydropyrrolo[3,4-*b*][1,4]oxazine (II) in the presence of triethylamine in acetonitrile and subsequent treatment of the resulting adduct (III) with hydrochloric acid in water gives finafloxacin hydrochloride (1, 2). Alternatively, condensation of the ethyl ester (IV) with the Boc-protected pyrrolo-oxazine (V) by means of DIPEA in dimethylphthalate (DMP) at 100 °C gives adduct (VI), which is hydrolyzed with lithium hydroxide to yield the corresponding free carboxylic acid (VII). Finally, acid (VII) is deprotected by treatment with hydrochloric acid in ethanol/ether (3). Scheme 1.

The 4-oxo-1,4-dihydroquinoline-3-carboxylate fragments, the free acid (I) and the ethyl ester (IV) can be synthesized as follows:

3,5-Dimethylfluorobenzene (VIII) is treated with chlorine in the presence of anhydrous $FeCl_3$ in either solvent-free conditions or in 1,2-dichloroethane to yield the 2,4-dichlorobenzene derivative (IX). Photochemical chlorination of compound (IX) affords 2,4-dichloro-3-(dichloromethyl)-1-fluoro-5-(trichloromethyl)benzene (X), which is further oxidized with concentrated sulfuric acid at 70 °C to give 2,4-dichloro-5-fluoro-3-formylbenzoic acid (XI) (1, 2). Aldehyde (XI) is next condensed with hydroxylamine hydrochloride (XII) in either an ethanolic NaOH basic media at 60 °C (1, 2) or in formic acid (2) to afford aldoxime (XIII) and the 3-cyanobenzoic acid derivative (XIV), respectively. Treatment of either of the two condensation products (XIII) and (XIV) with refluxing thionyl chloride affords the 3-cyanobenzoyl chloride derivative (XV) (1, 2), which is coupled with ethyl 3-(dimethylamino)acrylate (XVI) by means of DIEA in dichloromethane at 50 °C (1, 2) or triethylamine in toluene at 60-80 °C (3) to produce the 1,3-ketoester (XVII). Tertiary dimethylenamine (XVII) is converted to the secondary cyclopropylenamine (XIX) by treatment with cyclopropylamine (XVIII) in the presence of acetic acid in dichloromethane/water (1, 2) or in a mixture of ethanol/ether (3). Without isolation, intermediate (XIX) undergoes cyclization in the presence of potassium carbonate in *N*-methylpyrrolidone at 60-70 °C (1, 2) or in acetonitrile (3), affording the ethyl ester (IV).

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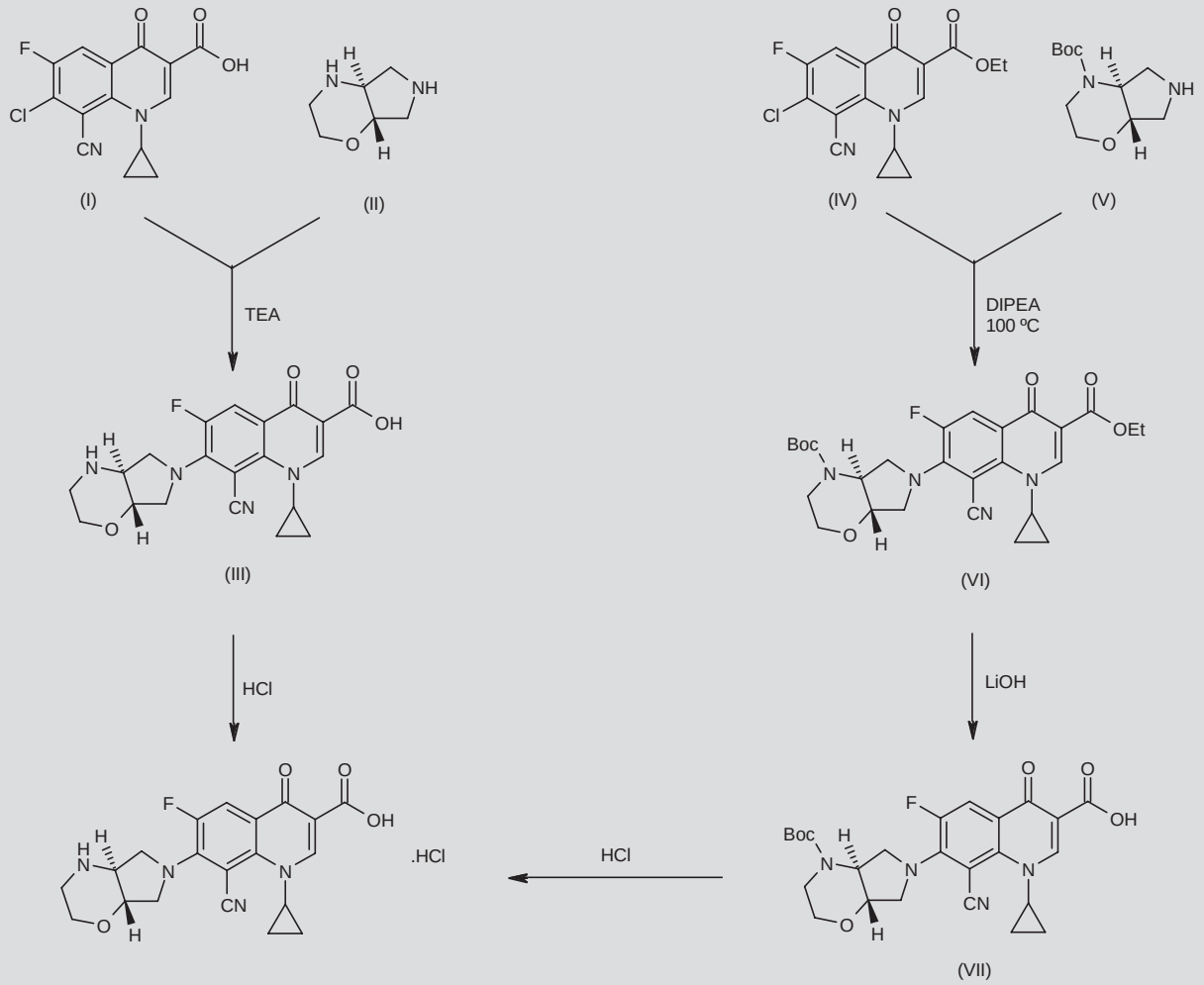
Scheme 1. Synthesis of Finafloxacin Hydrochloride

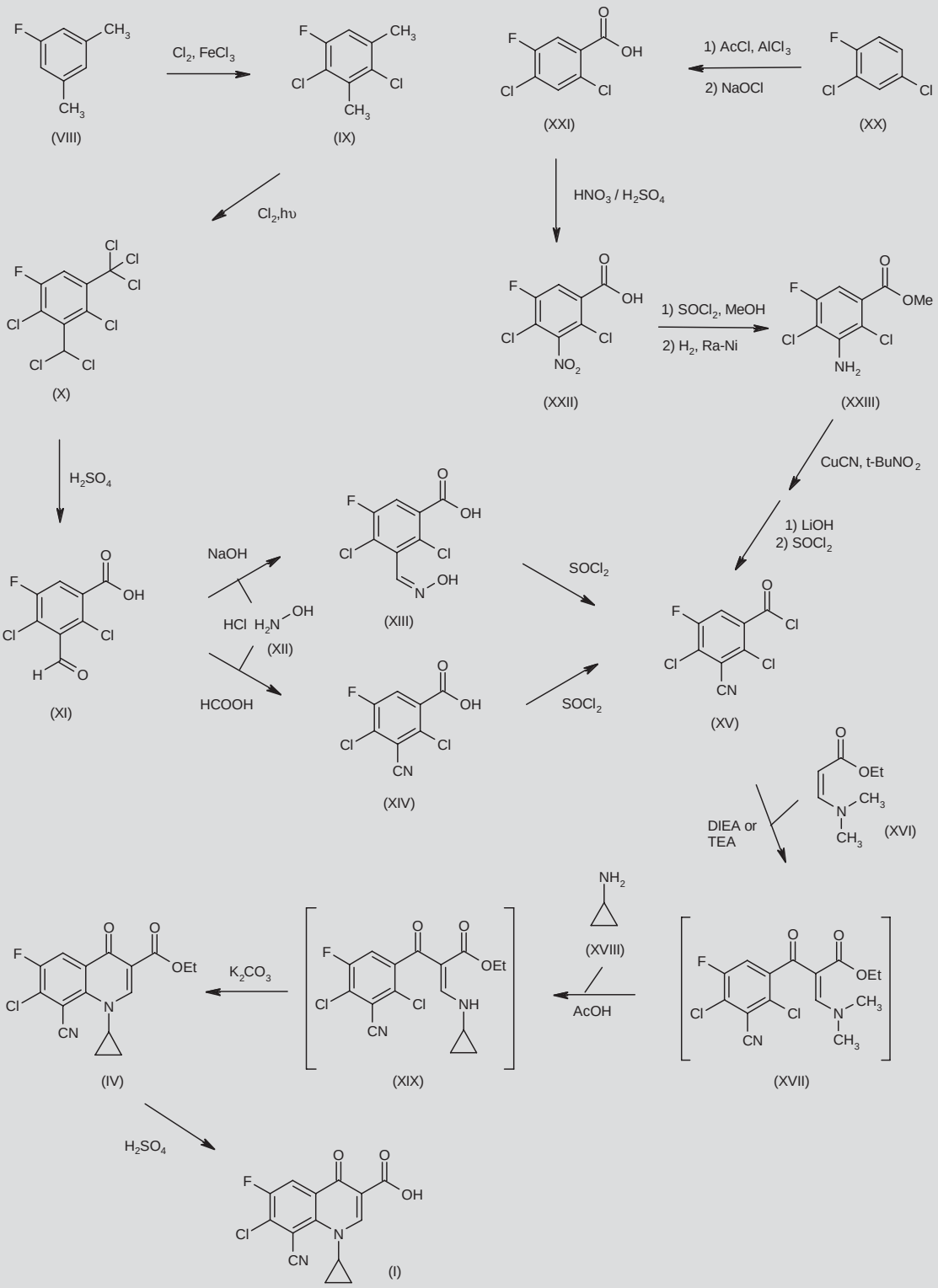


Compound (IV) is hydrolyzed in the presence of sulfuric acid in refluxing AcOH/water to yield the free carboxylic acid (I) (1, 2). Scheme 2.

An alternative pathway for the synthesis of intermediate (XV) proceeds as follows. Friedel-Craft's acylation of 2,4-dichloro-1-fluorobenzene (XX) with acetyl chloride in the presence of $AlCl_3$ and subsequent oxidation with sodium hypochlorite in 1,4-dioxane gives 2,4-dichloro-5-fluorobenzoic acid (XXI), which is nitrated with HNO_3/H_2SO_4 to give the nitrobenzoic acid (XXII). Esterification of compound (XXII) by means of thionyl chloride in methanol followed by hydrogenation in the presence of Raney-Ni in methanol yields amino ester (XXIII), which is subjected to a Sandmayer reaction with CuCN in the presence of 2-methyl-2-nitropropane (*t*-$BuNO_2$) in DMF at 60 °C. The intermediate thus obtained is then treated with lithium hydroxide in THF/water and the resulting carboxylic acid is finally chlorinated with thionyl chloride in toluene to afford acyl chloride (XV) (3). Scheme 2.

The pyrrolo-oxazine fragments, the free base (II) or the Boc-protected (V) can be synthesized as follows. Butene-1,4-diol (XXIV) is subjected to either of the two following alternative procedures: 1) treatment with mesyl chloride in the presence of Et_3N in CH_2Cl_2 and subsequent reaction with tosylamine, NaOH and tetrabutylammonium hydrogensulfate (TBAHS) in toluene/water at 40 °C (1, 2); or 2) chlorination with thionyl chloride followed by treatment with tosylamide by means of NaH in DMF (3) to afford 1-tosyl-2,5-dihydro-1*H*-pyrrole (XXV). Compound (XXV) is then epoxidated with *meta*-chloroperbenzoic acid (mCPBA) in refluxing dichloromethane to yield *cis*-*N*-tosyl-6-oxa-3-azabicyclo[3.1.0]hexane (XXVI) (1-3). Desymmetrization of intermediate (XXVI) is carried out by condensation with ethanolamine (XXVII) in refluxing dichloromethane to yield the racemic *N*-alkylated pyrrolidine derivative *rac*-(XXVIII), which by reaction with tosyl chloride in pyridine/THF at –10 °C affords the tosylate *rac*-(XXIX). Cyclization of the racemic (XXIX) by means of NaOH in THF/methanol at 0-3 °C gives the racemic pyrrolo-oxazine *rac*-(XXX), from which the desired enantiomer (4a*S*,7a*S*)-octahydropyrrolo[3,4-*b*][1,4]oxazine (XXX) is separated by chiral chromatography. Finally, compound (XXX) is detosylated by means of

Scheme 2. Synthesis of Intermediates (I) and (IV)



HBr/AcOH and anisole at 60 °C and the resulting dihydrobromide salt (XXXI) is treated with potassium hydroxide in isopropanol to afford the free base intermediate (II) (1). Scheme 3.

In an improved method for intermediate (II), compound (XXVI) is desymmetrized by coupling with (*R*)-phenylethylamine (XXXII) in water (2, 3), resulting in a mixture of diastereomers that is resolved by crystallization (2) or chromatography (3). The desired isomer (XXXIII) is *N*-acylated with chloroacetyl chloride (XXXIV) by means of triethylamine (2) or DIEA in THF (3) to afford the *N*-chloroacetyl amine (XXXV), which then cyclizes in the presence of sodium hydroxide (2) or potassium *tert*-butoxide in dichloromethane (3). The resulting bicyclic lactam (XXXVI) is reduced with $LiAlH_4$ in THF (3) or $NaBH_4$ in the presence of BF_3.THF complex (2) to give the pyrrolooxazine derivative (XXXVII) (2, 3), which is detosylated by treatment with HCl and subsequently with NaOH, yielding the free amine (XXXVIII). Finally, compound (XXXVIII) is subjected to hydrogenolysis over Pd/C in methanol to afford the target (4a*S*,7a*S*)-octahydropyrrolo[3,4-*b*][1,4]oxazine (II) (2). Scheme 3.

The Boc-protected compound (V) is obtained by subjecting *N*-alkylated derivative (XXXVII) to hydrogenolysis over Pd/C in methanol followed by treatment with *tert*-butoxycarbonyl anhydride in dichloromethane. The resulting fully protected intermediate (XXXIX) is finally detosylated with sodium naphthalenide (3). Scheme 3.

BACKGROUND

Quinolones are a family of synthetic, broad-spectrum antibiotics that act as inhibitors of two key enzymes implicated in bacterial DNA metabolism: topoisomerase II (also known as DNA gyrase) and topoisomerase IV. Quinolones predominantly inhibit DNA gyrase in Gram-negative bacteria such as *Escherichia coli*, whereas in Gram-positive bacteria such as *Staphylococcus aureus* they target topoisomerase IV. DNA gyrase introduces negative supercoils into the DNA in an ATP-dependent manner, leading to bacterial chromosome condensation, whereas topoisomerase IV binds to DNA crossovers and facilitates the unlinking of replicated daughter chromosomes. Conformational changes induced in these enzymes following the binding of quinolones result in DNA breakage and inhibition of religation of the broken DNA strands. The formation of a complex among the enzyme, the quinolone and the DNA substrate prevents DNA replication and reversibly inhibits bacterial cell growth, which is considered responsible for the bacteriostatic action of quinolones. Resistance to quinolones may arise as a result of an accumulation of mutations in genes encoding DNA gyrase and topoisomerase IV (4).

The majority of quinolones developed for clinical use, including ciprofloxacin and levofloxacin, belong to the fluoroquinolone subfamily comprising a fluorine atom at position C-6 of the quinoline ring. Computer-based analyses suggested that increases in inhibitory activity of fluoroquinolones may be achieved by substitution of a fluorine or alkoxy group at the C-8 position of N-1 cyclopropyl fluoroquinolones. A novel 8-cyano subclass of fluoroquinolones was generated, including finafloxacin hydrochloride (BY-337, formerly BAY-35-3377), a novel broad-spectrum fluoroquinolone that displays improved antibacterial activity under slightly acidic pH conditions, where other marketed fluoroquinolones appear to exhibit a reduction in activity. Due to its mechanism of action, finafloxacin may represent a strong candidate for the treatment of bacterial infections in acidic environments such as gastrointestinal and urinary tract infections or persistent *Helicobacter pylori* infections (2). Finafloxacin is currently undergoing clinical development by MerLion Pharmaceuticals for *H. pylori* eradication.

PRECLINICAL PHARMACOLOGY

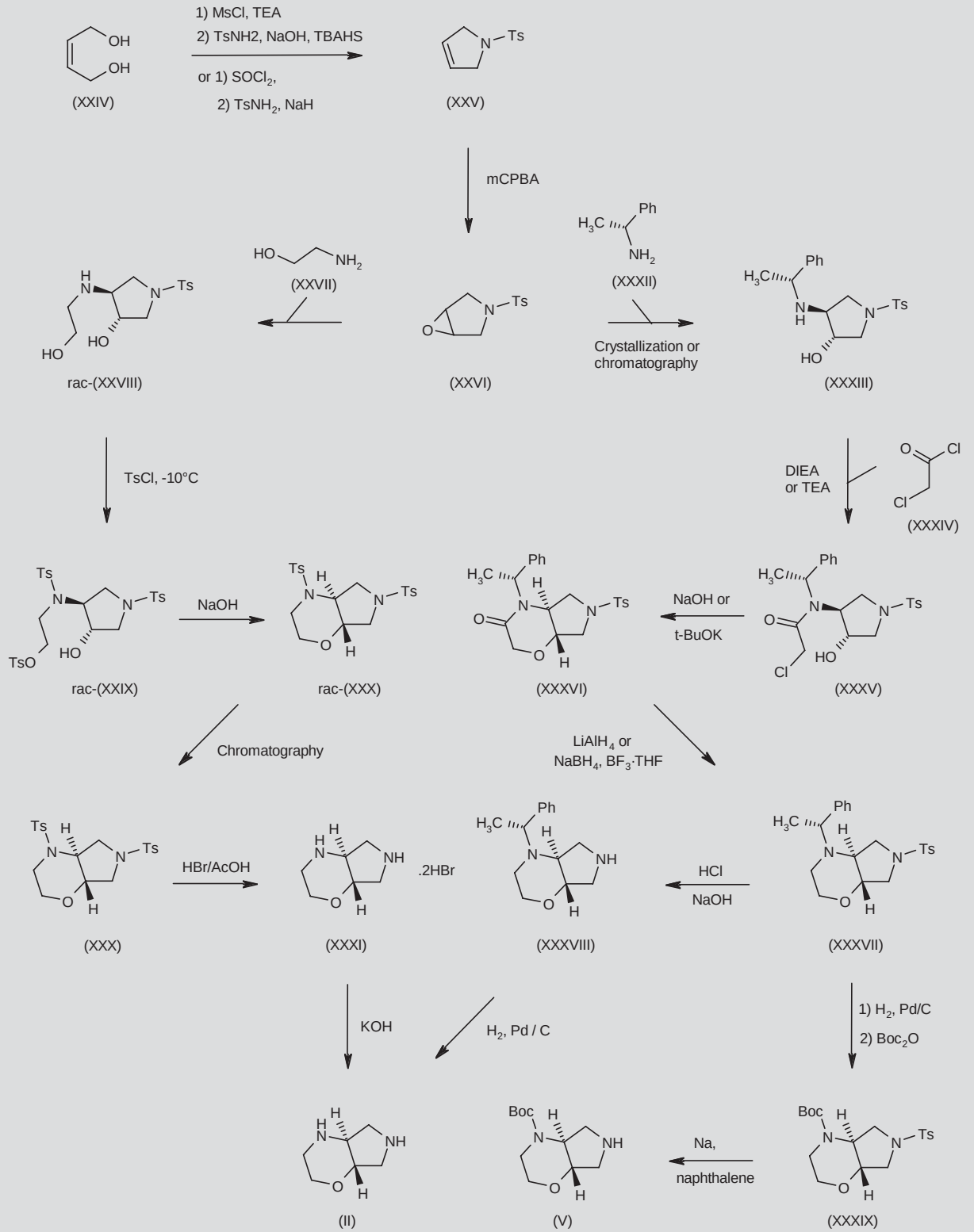
In vitro, the compound was found to exhibit increased solubility at neutral compared to acidic pH (12.5 and 4.3 mmol/mL, respectively, at pH 7.0 and 4.5) and displayed exceptional antibacterial activity at low pH against both Gram-negative bacteria such as *E. coli* ATCC 25922 (MIC = 0.06 and 0.008 µg/mL, respectively, at pH 7.2 and 5.8) and Gram-positive bacteria including *S. aureus* ATCC 29213 (MIC = 0.25 and 0.06 µg/mL, respectively, at pH 7.2 and 5.8). The antibacterial activity of finafloxacin under acidic conditions (pH 5.8) was shown to be superior compared to that of the fluoroquinolones ciprofloxacin and levofloxacin against a range of pathogenic bacteria, including various strains of *E. coli, Klebsiella pneumoniae*, *Pseudomonas aeruginosa, S. aureus, Staphylococcus saprophyticus* and *Enterococcus faecalis* (2)**.** Finafloxacin also displayed superior activity compared to ciprofloxacin in a study against a total of 100 clinical isolates of enterobacteria, including ciprofloxacin-susceptible strains of *E. coli, K. pneumoniae, Proteus mirabilis* and *Morganella morganii* (median MICs for finafloxacin and ciprofloxacin = 0.25 mg/L or less and ~0.87 mg/L, respectively, at pH 5.0), *S. aureus* (median MICs for finafloxacin = 0.125 and 0.031 mg/L, respectively, at pH 5.0 and 6.0, which were four dilution steps lower than those of ciprofloxacin), *S. saprophyticus* (finafloxacin was three and two dilution steps more active than ciprofloxacin at pH 5.0 and 6.0, respectively) and *Streptococcus agalactiae* (superior activity for finafloxacin was seen at pH 5.0 and 6.0). However, finafloxacin displayed comparable activity to ciprofloxacin against *P. aeruginosa* strains under acidic conditions (5).

A comparison of the bactericidal effects of finafloxacin and ciprofloxacin against Gram-negative and Gram-positive urinary tract infection (UTI) pathogens under physiological conditions and at varying pH revealed that, unlike ciprofloxacin, finafloxacin displayed increased activity in cation-adjusted Mueller Hinton broth at pH 5.8 compared to pH 7.2. Under conditions mimicking UTIs in synthetic urine, finafloxacin displayed more favorable bacteriostatic and bactericidal activity than ciprofloxacin, both qualitatively and quantitatively (6).

The activity of finafloxacin, evaluated using three different reference methods, namely Etest, Clinical Laboratories Standard Institute (CLSI) agar dilution (AD) and CLSI broth microdilution (BMD), against 39 strains of aerobic bacteria was found to be higher at slightly acidic pH. All three methods provided substantially equivalent results under neutral (pH 7.2) and acidic (pH 5.8) conditions (essential agreement ± 1 dilution = 88-100%) (7).

Finafloxacin displayed superior killing of adherent (difficult to kill) growth forms of *E. coli* (strain C600, membrane-adherent; strain 25922, catheter-adherent), as well as catheter-adherent populations of *S. aureus* (strain 29213), compared to ciprofloxacin, levofloxacin and moxifloxacin. Although all drugs (5 µg/mL) caused a significant reduction in cell viability by day 3, only finafloxacin had a rapid effect on cell viability (5-log reduction to below the detection limit of $< 10^2$ CFU/mL within 5 h) and was associated with no regrowth following treatment cessation (8).

Scheme 3. Synthesis of Intermediates (II) and (V)



The propensity for the development of finafloxacin resistance in *E. coli* 25922 was found to be very similar to that of ciprofloxacin and levofloxacin when compared at concentrations relative to the MIC under the prevailing conditions of pH; the limits of mutation prevention concentration (MPC) for all three compounds were lower at pH 5.8 than 7.2, where finafloxacin was also more active and thus more advantageous for the treatment of infections in acidic environments (9).

H. pylori bacteria are found in the acidic environment of the gastric mucosa, causing infections whose treatment may often lead to side effects and the development of crossresistance. The activity of finafloxacin against 36 clinical isolates of *H. pylori*, including fluoroquinolone-resistant strains, was tested using the Etest and CLSI AD methods. Following 3 and 5 days of incubation, MIC results showed good agreement between Etest and CLSI AD (particularly at 3 days, which was deemed the recommended incubation time for *H. pylori* in this study). Etest was found to be more efficient at detecting resistant subpopulations and may represent a useful tool for testing new antibacterial agents against *H. pylori* (10). The antimicrobial activity of finafloxacin, as determined by its MIC distribution, was found to increase in a stepwise manner as the pH became more acidic in a study using fluoroquinolone-susceptible and -resistant clinical isolates of *H. pylori* (11).

A comparative study of the activity of finafloxacin and other fluoroquinolones against bacterial and eukaryotic type II topoisomerases revealed that finafloxacin displayed a selectivity index for human topoisomerase II alpha of 250 (ratio over the activity of etoposide), which fell within the range of selectivity indices displayed by other fluoroquinolones (50-500). Finafloxacin was also found to be one of the most potent inhibitors of *E. coli* topoisomerase IV and DNA gyrase, with a high level of activity against both bacterial enzymes (cleavage detection limit [CDL] = 1 ng/mL for both enzymes; CL_{50} = 10 and 8 ng/mL against *E. coli* DNA gyrase and topoisomerase IV, respectively) (12).

In vivo finafloxacin (10 and 20 mg/kg p.o. b.i.d. for 10 days) displayed higher eradication rates than triple therapy with bismuth citrate (6.2 mg/kg), metronidazole (22.5 mg/kg) and amoxicillin trihydrate (50 mg/kg) once daily orally for 10 days in a mouse model of *Helicobacter felis* infection, which mirrors the etiology of clinical *H. pylori* infection in humans. Eradication rates achieved with finafloxacin in this model reached 100% compared to a 60% eradication rate observed following triple therapy (13). Pretreatment of mice bearing persistent *H. felis* infection with a subtherapeutic dose of finafloxacin (1 mg/kg) did not hamper the success of subsequent administration of a therapeutic dose of finafloxacin (10 mg/kg) (0% failure), unlike pretreatment with a subtherapeutic dose of ciprofloxacin (2.5 mg/kg), which caused 100% treatment failure of a subsequent ciprofloxacin therapeutic dose. This is indicative of lack of resistance selection during pretreatment with finafloxacin, but not ciprofloxacin (11).

Finafloxacin (10 mg/kg s.c.) also displayed superior efficacy compared to ciprofloxacin, levofloxacin and moxifloxacin in mouse models which reflect difficult-to-treat infections in humans, such as skin and skin structure infection (SSSI), peritonitis, catheter colonization (*S. aureus* DSM 11823), postoperative polymicrobial sepsis, infected abscess (*S. aureus* and *P. aeruginosa*) and *E. coli* pyelonephritis (14).

Intravenous administration of finafloxacin (1 mg/kg) in mice was shown to confer 80% protection against infection with *E. faecalis* 27159 compared to < 20% protection seen with other fluoroquinolones. In an *E. coli* DSM 10650 mouse infection model, lower doses of finafloxacin (0.1 and 0.5 mg/kg) resulted in 60% and 100% survival of infected animals, respectively. In a mouse model of *Moraxella catarrhalis* infection, oral administration of finafloxacin (10 and 25 mg/kg) at 30 min postinfection caused a greater reduction in the number of viable bacteria in the lungs of infected animals compared to other fluoroquinolones (15).

PHARMACOKINETICS AND METABOLISM

Pharmacokinetic analysis of orally administered finafloxacin (1 mg/kg) in CFW-1 mice which had previously been infected i.p. with a bacterial suspension of either *E. coli* DSM 10650 or *E. faecalis* 27159 revealed higher area under the curve (AUC) and peak serum concentration (C_{max}) values (0.571 mg.h/L and 0.364 mg/L, respectively) compared to moxifloxacin (0.153 mg.h/L and 0.172 mg/L, respectively), ciprofloxacin (0.104 mg.h/L and 0.035 mg/L, respectively) and levofloxacin (0.223 mg.h/L and 0.182 mg/L, respectively). Following oral administration of finafloxacin, the C_{max} values displayed dose-dependency over a dose range of 0-225 mg/kg (15).

SAFETY

Toxicological profiling of finafloxacin in predictive in vitro and ex vivo toxicity assays revealed that the compound has a low potential for the development of undesirable side effects commonly associated with the use of other fluoroquinolones. In the J774.A1 mouse macrophage cell line, finafloxacin treatment for 72 h demonstrated a low cytotoxic effect (EC_{50} = 100 µg/mL; no observable effect concentration [NOEC] = 30 µg/mL). Finafloxacin was deemed nonphototoxic in the mouse fibroblast cell line 3T3 (EC_{50} > 100 µg/mL administered at 1 h following UV irradiation for 20 or 60 min). The compound was also not hepatotoxic in primary rat hepatocytes at concentrations up to 100 µg/mL and displayed no toxicity in primary human and dog chondrocytes (NOEC > 100 µg/mL) (16).

CLINICAL STUDIES

The safety, tolerability and pharmacokinetic profile of finafloxacin was evaluated in humans for the first time in a phase I trial in healthy volunteers (17). Participants (N = 75) received a single oral dose of finafloxacin (dose range: 25-800 mg as tablets) or repeated doses for 7 consecutive days (dose range: 150-800 mg). Finafloxacin administration did not elicit any relevant changes in laboratory test parameters. Treatment-related adverse events included headache, tiredness, cranial pressure, diarrhea and nausea, which were observed in 35 of 75 subjects. Single doses of 100, 200, 400 and 800 mg finafloxacin displayed C_{max} values of 1.0, 1.9, 5.1 and 9.5 µg/mL, respectively, with respective half-lives ($t_{1/2}$) of 5.8, 5.0, 10.1 and 10.5 h. In the repeated-dose cohorts, C_{max} values of 4.0, 6.8 and 9.0 µg/mL, respectively, were recorded at doses of 300, 600 and 800 mg, with corresponding $t_{1/2}$ values of 6.5, 8.7 and 13.8 h. Total body clearance for the 400- and 800-mg doses was estimated to be 28.0 and 35.8 L/h, respectively, and the median urinary recovery values for these doses ranged from 26.99% to 34.75% (18).

The urinary pharmacokinetics and bactericidal activity (measured as urinary bactericidal titers, UBT) of the highest single oral dose of finafloxacin (800 mg) used in the previous study were subsequently evaluated in a phase I trial in healthy individuals (N = 6). Finafloxacin was well tolerated, with a mean maximum concentration in urine reaching 150 mg/mL (4-8 h postadministration). Quantification of the bactericidal activity of finafloxacin ex vivo against a panel of UTI pathogens, including various strains of *E. coli*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa* and *E. faecalis*, revealed UBT values that were highest for the Gram-negative *E. coli* ATCC25922 strain (> 2048) and *K. pneumoniae* (512), and comparable for the other uropathogens tested (UBT range: 32-64) at 0-4 h after dosing (19).

Two phase II clinical trials that were initiated in 2008 and recently completed aimed to evaluate the bacteriological eradication rates of finafloxacin and ciprofloxacin in female patients with lower uncomplicated UTI (20) and compare the eradication rates of *H. pylori* with finafloxacin in combination with amoxicillin or esomeprazole (21).

SOURCES

MerLion Pharmaceuticals (SG); licensed from Bayer.

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