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CCC: 0377-8282/98

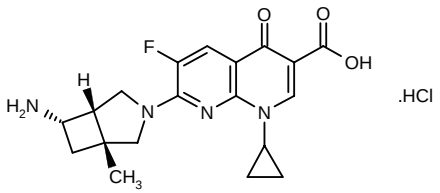
Ecenofloxacin Hydrochloride

Antibacterial
Naphthyridine

Prop INNM

CFC-222

(+)-(1*R*,5*S*,6*S*)-7-(6-Amino-1-methyl-3-azabicyclo[3.2.0]hept-3-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid hydrochloride



$C_{19}H_{21}FN_4O_3$.HCl Mol wt: 408.86

CAS: 162424-67-1
CAS: 162301-05-5 (as free base)
CAS: 186827-02-1 [as (1α,5α,6β)-isomer]
CAS: 186827-03-2 [as free base, (1α,5α,6β)-isomer]
CAS: 162301-08-8 [as (–)-isomer, free base]

EN: 224330

Synthesis

CFC-222 has been obtained by four closely related ways: Scheme 1.

1) The acylation of β-alanine (I) with tosyl chloride and NaOH in water gives the corresponding tosylate (II), which is esterified with $SOCl_2$ and ethanol as usual yielding the ethyl ester (III). The alkylation of the amido group of (III) with 2-methylallyl chloride (IV) by means of KI, K_2CO_3 and tetrabutylammonium iodide in acetonitrile affords the alkylated sulfonamide (V), which is condensed with pyrrolidine (VI) by means of $SOCl_2$ in dichloromethane to give the acylated pyrrolidine (VII). The cyclization of (VII) by means of trifluoromethanesulfonic anhydride and collidine in dichloromethane yields racemic *cis*-1-methyl-3-(*p*-toluenesulfonyl)-3-azabicyclo[3.2.0]heptan-6-one (VIII), which is converted to the corresponding oxime (IX) with hydroxylamine in pyridine. The reduction of (IX) with $NaBH_4$ and $NiCl_2$ affords racemic *cis*-1-methyl-3-(*p*-toluenesulfonyl)-3-azabicyclo[3.2.0]heptan-6-amine (X), which is submitted to optical resolution with L-tartaric acid to give pure (1*R*,5*S*,6*S*)-isomer (XI) (1). Elimination of the tosyl group of (XI) with concentrated HBr yields (1*R*,5*S*,6*S*)-3-azabicyclo[3.2.0]-heptan-6-amine (XII), which is finally condensed with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (XIII) by means of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and HCl in acetonitrile (1, 2).

2) The cyclization of the alkylated sulfonamide (V) to the racemic bicyclic ketone (VIII) can also be performed (with better yields) by direct cyclization with $SOCl_2$ and triethylamine (1).

3) The conversion of the racemic ketone (VIII) to the racemic amine (X) can also be performed by treatment of (VIII) with *O*-methylhydroxylamine in methanol to obtain the *O*-methyloxime (XIV), which is then reduced to amine (X) with $NaBH_4$ and trifluoroacetic acid (with poorer yields) (1, 2).

4) The optical resolution of racemic amine (X) can also be performed with *N*-tosyl-L-phenylalanine (2).

Introduction

Fluoroquinolone antibacterial agents such as ciprofloxacin, ofloxacin and lomefloxacin have been widely used in the treatment of various infections. Unfortunately, these compounds are only moderately active against anaerobic and Gram-positive bacteria as well as having somewhat unfavorable pharmacokinetics (*e.g.*, short serum half-lives), and thus newer fluoroquinolones with broader spectrums of activity and improved pharmacokinetics are clearly needed (3, 5).

CFC-222 (ecenofloxacin hydrochloride) is a novel fluoroquinolone with a bicyclic amide moiety at the 7 position of the naphthyridone ring. This compound was discovered at Cheil Jedang during research efforts targeted at improving the pharmacokinetics of ciprofloxacin and expanding its antibacterial efficacy to include Gram-positive and anaerobic bacteria, while maintaining its excellent activity against Gram-negative strains (3).

Pharmacological Actions

CFC-222 is a novel fluoroquinolone antibacterial agent with potent, broad-spectrum antibacterial activity.

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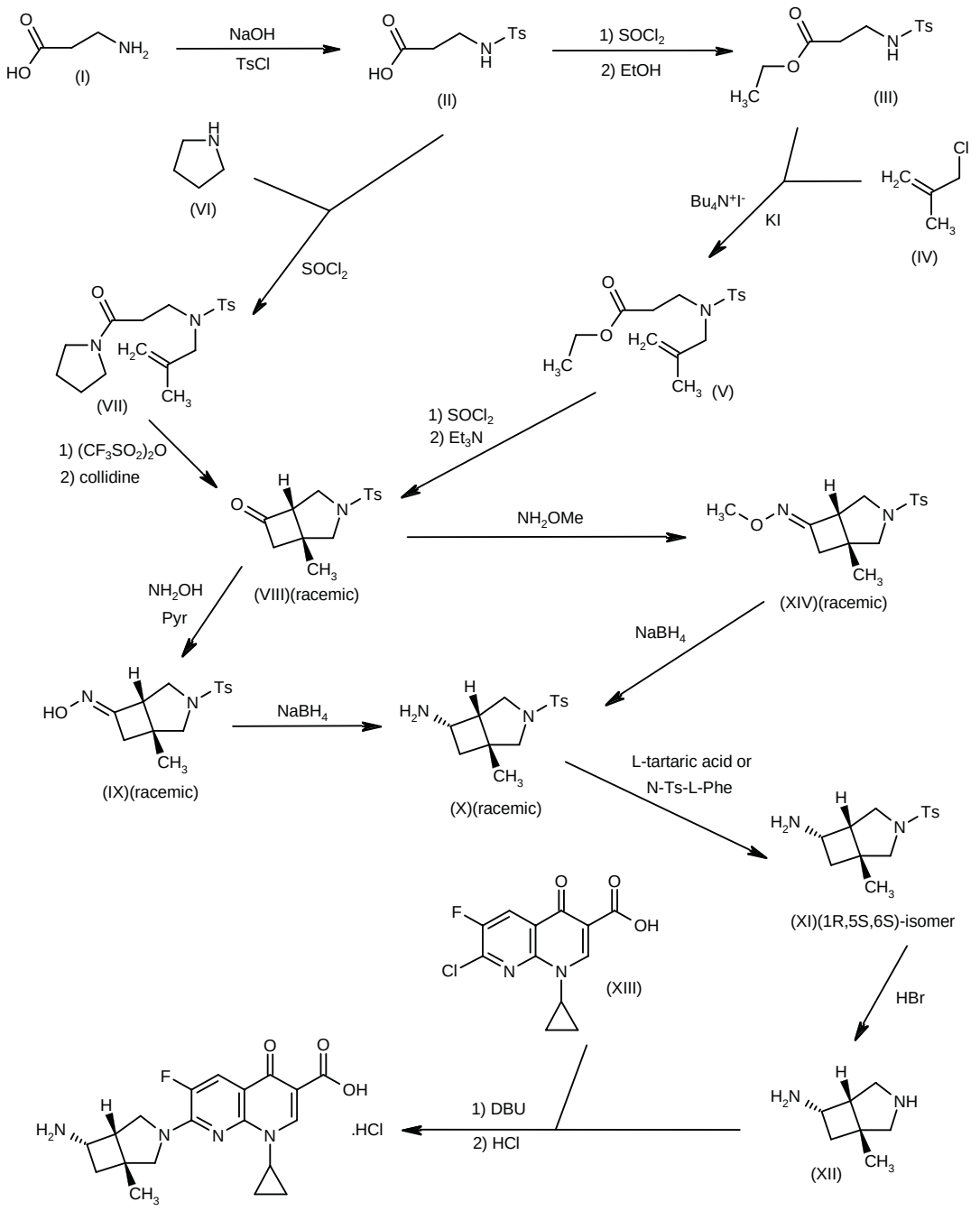
Scheme 1: Synthesis of Ecenofloxacin Hydrochloride



Its activity was compared to that of ciprofloxacin, ofloxacin and lomefloxacin against clinical isolates of Gram-positive and Gram-negative organisms. The activity of the title compound was superior to that of the reference fluoroquinolones against all Gram-positive bacteria tested, and was especially potent in the case of *Streptococcus pneumoniae* (MIC_{90} = 0.2 μg/ml), *Staphylococcus aureus* (MIC_{90} = 0.2 μg/ml, ciprofloxacin-susceptible strains) and *Enterococcus faecalis* (MIC_{90} = 0.39 μg/ml). The title compound was less potent than ciprofloxacin, however, against *Escherichia coli* (MIC_{90} = 0.1 and 0.025 μg/ml for CFC-222 and ciprofloxacin, respectively) and other strains of *Enterobacteriaceae*. The activity of CFC-222 was not affected by inoculum

size, composition of the medium or presence of horse serum; like the other fluoroquinolones, however, its activity decreased significantly when pH of the medium was decreased from 7.0 to 6.0 (3, 4).

In another *in vitro* study, the compound was compared to the above fluoroquinolones and to sparfloxacin. CFC-222 was more active than ciprofloxacin and similar to sparfloxacin against Gram-positive bacteria such as *S. aureus* (both quinolone-susceptible and -resistant), *Staphylococcus epidermidis*, *S. pneumoniae* and *E. faecalis*. Its activity against Gram-negative strains (*e.g.*, *Enterobacteriaceae*) was comparable to that of sparfloxacin but less potent than that of ciprofloxacin, and its activity against *Pseudomonas aeruginosa* was inferior to that of both reference compounds (5). Especially good activity was observed against penicillin-resistant strains of *S. pneumoniae* (6).

The MBCs of CFC-222 were equivalent to or 2-fold higher than its MICs, similar to other fluoroquinolones. Time-kill curves for CFC-222 against *S. aureus*, *E. coli* and *P. aeruginosa* showed that the number of viable cells decreased rapidly during the period of incubation with CFC-222 at concentrations 1-4 times the MIC. The postantibiotic effect of the title compound was similar to that of ofloxacin. The mechanism of antibacterial activity of this fluoroquinolone was identified as bactericidal (7).

CFC-222 was also tested for its activity against 216 strains of *Mycoplasma in vitro*, and was compared to reference macrolides and tetracycline. The title compound gave MIC_{90} values of 0.78, 1.56 and 0.48 μg/ml, respectively, against *Mycoplasma pneumoniae* (33 strains), *Mycoplasma hominis* (47 strains) and *Ureaplasma urealyticum* (83 strains). Its activity was, in general, comparable to josamycin and superior to ofloxacin, ciprofloxacin, tetracycline, minocycline and erythromycin (8).

Oral administration of CFC-222 to mice imparted greater protection than ciprofloxacin, ofloxacin or lomefloxacin in a model of intraperitoneally inoculated systemic *S. aureus* infection. Its efficacy against Gram-negative (*e.g.*, *E. coli* or *Klebsiella pneumoniae*) infection in the same model was comparable to that of ciprofloxacin, although it was slightly less potent than the latter against *P. aeruginosa* (3, 4). Good oral antibacterial activity was seen in various other murine models of systemic infection with strains including *Enterobacter cloacae* MB4-03, *Streptococcus pyogenes* ATCC 8668 and *P. aeruginosa* MB4-16 (5).

The mean protective doses (PD_{50}) of CFC-222 in mice with systemic infections produced by *S. aureus* Smith, *S. aureus* TMS33 and *S. pyogenes* ATCC 8668 were 1.80, 1.96 and 2.31 mg/kg, respectively. The *in vivo* therapeutic efficacy of the compound was superior to that of ciprofloxacin, ofloxacin, lomefloxacin and sparfloxacin against Gram-positive bacteria (9).

In murine models of systemic infection produced by *S. pyogenes* C-203 or *S. pneumoniae* type III, and of respiratory tract infection caused by *K. pneumoniae* B-54, CFC-222 showed more potent therapeutic efficacy than ofloxacin, ciprofloxacin, lomefloxacin and sparfloxacin. In mice with urinary tract infections caused by *E. coli*, CFC-222 was superior to all the reference compounds except sparfloxacin. Thus, the compound appears to be appropriate for use in the treatment of urinary and respiratory tract infections (10).

In mice with respiratory tract infections caused by nasal infection with *S. pneumoniae* type III, CFC-222 had greater therapeutic efficacy than reference fluoroquinolones. At a dose of 1.0 mg, its activity against *P. aeruginosa* GN11189 infections in mice was comparable to that of sparfloxacin and superior to that of ciprofloxacin and ofloxacin. In mice with *E. coli*-induced urinary tract infections, viable cell count decreased following treatment with CFC-222 at all doses tested; the activity of the compound in this model was similar to ofloxacin and ciprofloxacin but less potent than sparfloxacin (11).

Pharmacokinetics and Metabolism

The pharmacokinetics of CFC-222 in animal models have been described. The compound was administered as single oral doses (20 mg/kg) to mice, rats, beagle dogs and cynomolgus monkeys following an 18-h fast. CFC-222 was absorbed rapidly; peak concentrations (t_{max}) were reached within 0.25 h of dosing in both mice and rats, and within 2 h in both dogs and monkeys. C_{max} values were 4.9, 4.4, 5.0 and 6.0 mg/l in mice, rats, dogs and monkeys, respectively. Half-lives ranged from 4.5 h in rats to 6.2 h in monkeys. AUC values were much greater in dogs and monkeys (45.7 and 40.5 mg.h/l, respectively) than in mice and rats (12.7 and 15.2 mg.h/l, respectively). Plasma protein binding was moderate and did not show much interspecies variation. Renal excretion was not a major elimination route for CFC-222, as seen by low urinary excretion (10.5 and 8.7% in dogs and monkeys, respectively) (12).

In another pharmacokinetic study, radiolabeled CFC-222 was administered to rats (20 mg/kg p.o. or i.v.). The absolute bioavailability of the compound, as calculated from AUC and urinary recovery following administration by either route, was approximately 80%, indicating that the oral absorption of the compound is very good. The active drug was distributed extensively to the target organs (kidney, liver, lung, spleen and other tissues), with much lower levels of radioactivity detected in plasma, brain and fat tissues. The distribution pattern of total radioactivity in the body following 7-day dosing was similar to that after a single dose, indicating that little accumulation takes place following repeated administration of CFC-222 (13).

A metabolism study of CFC-222 was performed in male and female Sprague-Dawley rats. Following administration of oral doses of 20 mg/kg, urine, bile and feces were collected and analyzed for metabolites, the structures of which were determined by mass spectrometry. The parent drug, glucuronide conjugate (M1) and other minor metabolites were identified in bile. Parent drug and M1 were detected in urine, and only unchanged drug was

identified in feces. There were no gender-related differences in metabolic profiles, and the compound appears to undergo very little metabolic transformation (14).

Clinical Studies

The pharmacokinetics and safety of CFC-222 were evaluated in healthy male volunteers in a recent phase I study. Subjects were administered single oral doses of the compound (25, 50, 100, 200 or 400 mg) or placebo in a double-blind, randomized fashion. A separate study evaluated the effects of food on single oral doses of the compound (200 mg). CFC-222 was absorbed rapidly, with a t_{max} of less than 2 h. Plasma drug concentrations increased in a dose-related manner, and $t_{1/2}$ was in the range of 13.8-18.7 h, but was not related to dose. Approximately 20% of the administered dose was excreted in the urine as unchanged drug. $AUC_{(0-\infty)}$ and C_{max} in the fed and fasted state were bioequivalent. The compound was well tolerated and safe over the range of doses tested (15).

CFC-222 is undergoing phase II clinical testing in the U.K. and phase I trials in Korea. The compound is being evaluated for the treatment of community-acquired pneumonia, nocosomial pneumonia and urinary tract infections and is available for licensing and/or codevelopment worldwide (16).

Manufacturer

Cheil Jedang Corp. (KR).

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