Drugs of the Future 2002, 27(11): 1033-1038

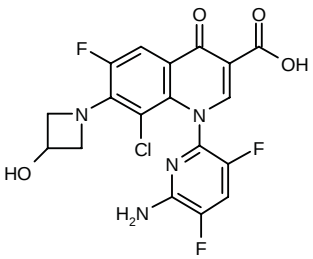
CCC: 0377-8282/2002

ABT-492

Quinolone Antibacterial

WQ-3034

1-(6-Amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3-hydroxyazetidin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid



$C_{18}H_{12}ClF_3N_4O_4$
Mol wt: 440.769
CAS: 189279-58-1
EN: 250845

Abstract

ABT-492/WQ-3034 is a novel fluoroquinolone that targets bacterial DNA topoisomerases and is undergoing clinical evaluation for the treatment of respiratory and urinary tract infections. In numerous *in vitro* studies, the new antibiotic has demonstrated excellent, broad-spectrum antibacterial and bactericidal activity, with particularly good activity against respiratory tract pathogens. ABT-492/WQ-3034 was generally more active than other quinolones and its spectrum included quinolone-sensitive and -resistant staphylococci and streptococci, vancomycin-sensitive and -resistant enterococci, anaerobic bacteria, *Pseudomonas aeruginosa*, *Enterobacteriaceae*, *Legionella,* mycobacteria and the causative organism of anthrax, *Bacillus anthracis*. ABT-492/WQ-3034 has also been tested in rodent infection models, including systemic, respiratory tarct and thigh infections. The new fluoroquinolone proved to be generally at least as active as the reference antibiotics following s.c. or p.o. administration.

Synthesis

ABT-492 can be prepared by two related ways:

1) Reaction of 2,3,5,6-tetrafluoropyridine (I) with benzylamine (II) in refluxing acetonitrile gives 2-(benzylamino)-3,5,6-trifluoropyridine (III), which is debenzylated with H_2 over Pd/C in methanol to yield 3,5,6-trifluoropyridine-2-amine (IV). Reaction of amine (IV) with 4-methoxybenzylamine (V) in *N*-methylpyrrolidone at 140 °C affords 3,5-difluoro-6-(4-methoxybenzylamino)pyridine-2-amine (VI), which is cyclized with 2-(3-chloro-2,4,5-trifluorobenzoyl)-3-ethoxyacrylic acid ethyl ester (VII) – obtained by condensation of 2-(3-chloro-2,4,5-trifluorobenzoyl)acetic acid ethyl ester (VIII) with triethyl orthoformate (IX) by means of acetic anhydride – in hot DMF in the presence of K_2CO_3 to provide the *N*-protected aminoquinolone derivative (X). Reaction of quinolone (X) with HCl in refluxing acetic acid gives 4-(6-amino-3,5-difluoropyridin-2-yl)-8-chloro-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (XI), which is finally condensed with 3-hydroxyazetidine (XII) by means of *N*-methylpyrrolidine in refluxing acetonitrile (1). Scheme 1.

2) Reaction of 2,3,5,6-tetrafluoropyridine (I) with ammonia in formamide gives the 2-aminopyridine derivative (IV), which is condensed with *tert*-butylamine (XIII) in *N*-methylpyrrolidone to yield 6-(*tert*-butylamino)-3,5-difluoropyridine-2-amine (XIV). Condensation of amine (XIV) with 2-(3-chloro-2,4,5-trifluorobenzoyl)-3-ethoxyacrylic acid ethyl ester (VII) gives the adduct (XV), which is cyclized by means of K_2CO_3 in DMF to afford the quinolone derivative (XVI). Treatment of quinolone (XVI) with HCl in AcOH produces simultaneous ester hydrolysis and *tert*-butyl group removal, providing 4-(6-amino-3,5-difluoropyridin-2-yl)-8-chloro-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (XI). Finally, this compound is condensed with 3-hydroxyazetidine (XII) by means of *N*-methylpyrrolidine in DMF (2). Scheme 2.

Introduction

Structure-activity relationship studies at Wakunaga on a series of fluoroquinolones led to the selection of WQ-3034 for further development as the most promising candidate. WQ-3034 was subsequently licensed to Abbott for development, and is now referred to as ABT-492.

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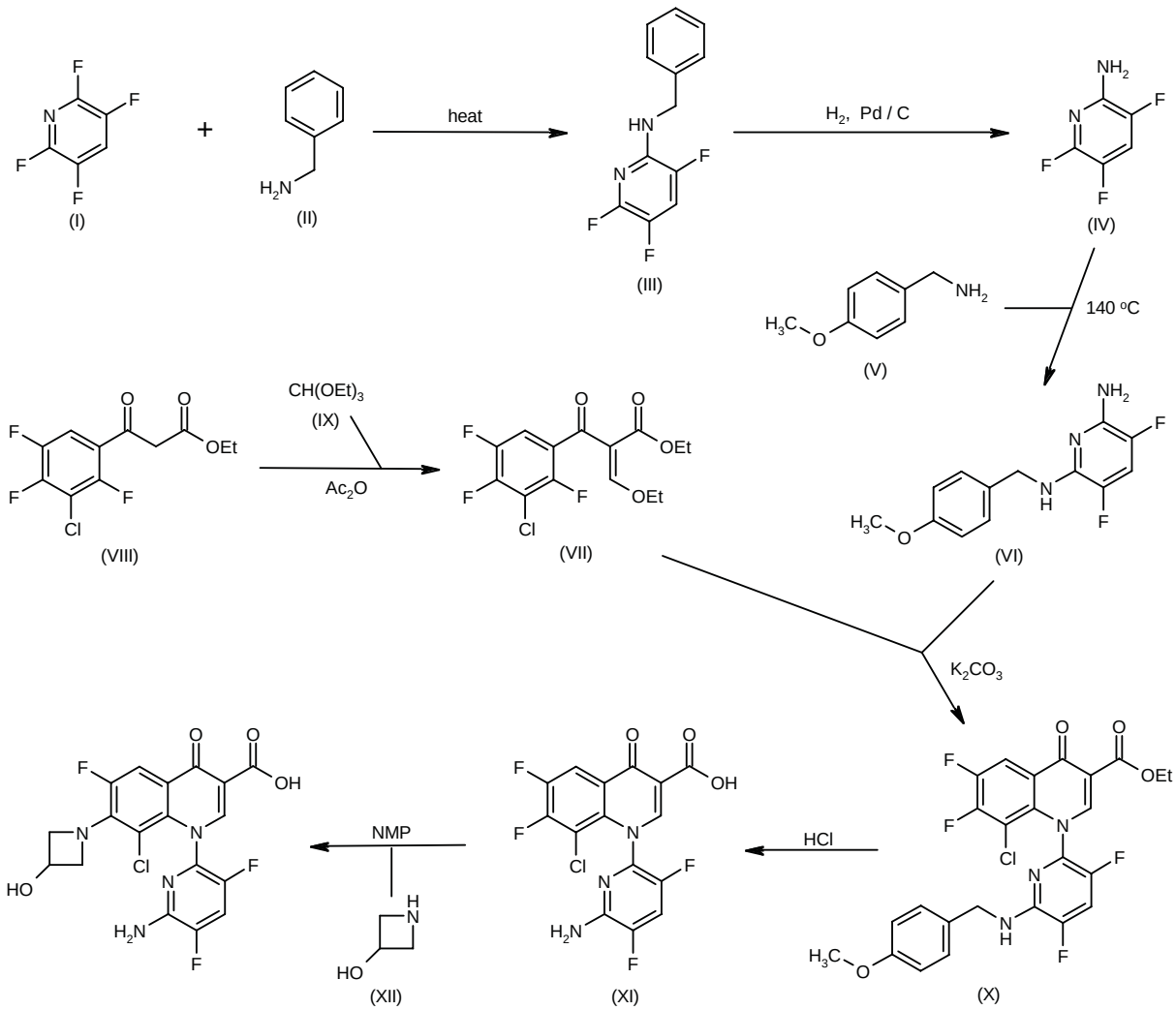
Scheme 1: Synthesis of ABT-492

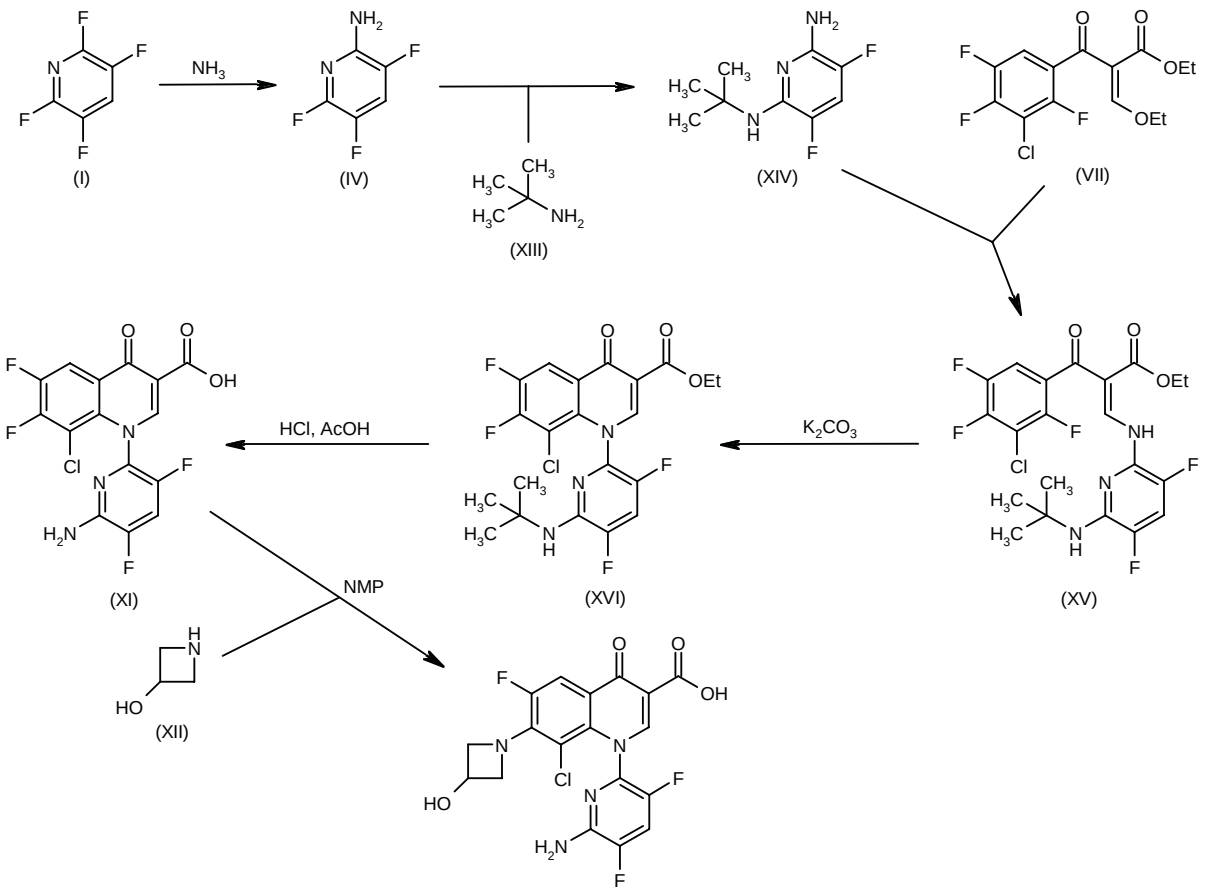


Pharmacological Actions

In preliminary *in vitro* testing for antibacterial activity, WQ-3034 proved to have excellent activity against laboratory strains of *Staphylococcus aureus* (MIC = 0.006 μg/ml), *Escherichia coli* (MIC = 0.05 μg/ml) and *Pseudomonas aeruginosa* (MIC = 0.39 μg/ml), and to be more active than levofloxacin, gatifloxacin or trovafloxacin against clinical isolates of *Streptococcus pneumoniae* (MIC_{90} = 0.025 μg/ml) and quinolone-resistant, methicillin-resistant *S. aureus* (MRSA; MIC_{90} = 6.25 μg/ml) (2). Like other fluoroquinolones, ABT-492 targets bacterial DNA topoisomerases. However, it was the most potent such antibiotic tested against *E. coli* topoisomerase IV (CC_{50} = 1.1 μg/ml) and *S. aureus* gyrase (CC_{50} = 0.57 μg/ml), while also having potent activity against *E. coli* gyrase (CC_{50} = 0.8 μg/ml) and *S. aureus* topoisomerase IV (CC_{50} = 1.7 μg/ml). Similar to other fluoroquinolones, it was highly selective relative to human topoisomerase II (CC_{50} > 100 μg/ml). It was suggested that its superior antibacterial activity compared to other fluoroquinolones may be explained, at least in part, by its potent inhibitory activity against the bacterial enzymes, and also that this profile may result in reduced selection of resistant mutants (3).

The antibacterial activity of ABT-492 has been extensively studied *in vitro* against a range of bacteria in comparison to other antibiotics. One particularly broad study determined the MICs against bacterial species known to cause community-acquired and nosocomial respiratory tract, urinary tract, skin and skin structure and anaerobic infections and bacteremia. ABT-492 demonstrated potent and broad-spectrum antibacterial and bactericidal activity and was more potent overall than trovafloxacin,

Scheme 2: Synthesis of ABT-492



levofloxacin and ciprofloxacin. It was more potent than the other fluoroquinolones against quinolone-sensitive and -resistant staphylococci and streptococci (MIC_{90} < 0.008-0.5 μg/ml) and vancomycin-sensitive and -resistant enterococci (MIC_{90} = 0.25-32 μg/ml), as well as against anaerobic bacteria such as *Bacteroides fragilis* (MIC_{90} = 0.12 μg/ml) and *Clostridium* spp. (MIC_{90} = 0.015 μg/ml or less), and *Neisseria gonorrhoeae* (MIC_{90} = 0.004 μg/ml or less). Excellent activity was also found against *Enterobacteriaceae*, *P. aeruginosa*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Legionella pneumophila*. In most cases, the MBC values were the same as or only twice the MIC values (4).

The novel quinolone was tested against 4 isolates of *S. pneumoniae*, 2 sensitive to and the other 2 resistant to penicillin. ABT-492 was superior to levofloxacin in terms of MIC values (0.0078-0.0156 μg/ml *vs.* 1 μg/ml). Concentration-dependent bactericidal activity was seen for both ABT-492 and levofloxacin. After 2 h, near-maximal bactericidal activity was obtained at about 3 x the MIC for ABT-492 and about 2 x the MIC for levofloxacin (5). A similar study was performed using β-lactamase-negative and -positive strains of *H. influenzae*. As above, ABT-492 was more active than levofloxacin in terms of MIC values (0.0003125-0.00125 μg/ml *vs.* 0.015 μg/ml), but comparable concentration-dependent bactericidal activity was seen for both fluoroquinolones (6). Its bactericidal activity against quinolone-sensitive and -resistant respiratory tract pathogens was examined in another study. Compared to ciprofloxacin and moxifloxacin, ABT-492 had lower MICs against all strains tested except *P. aeruginosa*. Concentration-dependent bactericidal activity was seen at 2-64 x the MIC against quinolone-sensitive strains and was similar for ABT-492 and the other quinolones (7).

In a comparative study with gatifloxacin and ciprofloxacin using over 900 bacterial pathogens, ABT-492 proved to be the most potent antibiotic, particularly against respiratory tract pathogens, giving MIC_{90} values of 0.002-0.012 μg/ml against *S. pneumoniae*, other streptococci, *Neisseria* spp., *Moraxella* spp., *H. influenzae* and *Staphylococcus* spp., MIC_{90}s of 1-2 μg/ml against other

Gram-positive bacteria, Gram-negative bacilli and anaerobic bacteria, and an MIC_{90} of 16 μg/ml against *Enterococcus* spp. (8). ABT-492 was also compared to ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin and moxifloxacin against 850, 450 and 430 clinically relevant isolates of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, respectively. The new fluoroquinolone was at least as potent as the reference antibiotics, giving MIC_{90} values against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* of 0.015, 0.03 and 0.015 μg/ml or less, respectively. Furthermore, ABT-492 retained activity against penicillin-, macrolide-, doxycycline- and ciprofloxacin-resistant *S. pneumoniae* (9). ABT-492 proved to be the most active antibiotic tested against ciprofloxacin-resistant *S. pneumoniae* clinical isolates (MIC_{90} = 0.25 μg/ml *vs.* 0.5-32 μg/ml for ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, penicillin, clarithromycin and trimethoprim/sulfamethoxazole) (10).

ABT-492 has also been compared to a variety of other quinolones for its efficacy against susceptible and resistant Gram-positive and Gram-negative microorganisms. As in other studies, ABT-492 was the most potent quinolone and exhibited excellent activity against both sensitive and resistant pathogens. The following MIC_{90} values were obtained against sensitive/resistant *S. pneumoniae*, *S. aureus*, *H. influenzae*, *E. coli*, *Klebsiella* spp. and *Enterococcus* spp.: 0.015/0.5 μg/ml, 0.008/1 μg/ml, 0.002/0.002 μg/ml, 0.06/8 μg/ml, 0.5/4 μg/ml and 0.06/8 μg/ml; ABT-492 showed comparable activity to cipro-floxacin against *P. aeruginosa* (MIC_{90} = 0.5 μg/ml) (11, 12).

The activity of ABT-492 against over 300 strains of microaerophilic and fastidious bacteria was compared to ampicillin/sulbactam, clindamycin, gatifloxacin, metronidazole and moxifloxacin in another *in vitro* study. The new fluoroquinolone was the most active overall, with MIC_{90} values of 0.5 μg/ml or less against all species tested except *Desulfomonas* spp. and *Actinobacillus actinomycetemcomitans*, for which MIC_{90} values of 4 μg/ml were obtained (13).

Excellent activity has also been reported against *Legionella*. Against *Legionella pneumophila*, *Legionella micdadei* and *Legionella dumoffii*, ABT-492 had superior activity to levofloxacin, gatifloxacin, moxifloxacin, ciprofloxacin, ofloxacin, azithromycin and clarithromycin, with an MIC_{90} of 0.004 mg/l or less. ABT-492 was as active as levofloxacin and more active than the other antibiotics against *Legionella longbeacheae*, with an MIC_{90} of 0.016 mg/l (14). In another study, ABT-492, but not gatifloxacin, moxifloxacin, levofloxacin, ofloxacin and ciprofloxacin, was able to inhibit the growth of erythromycin-susceptible or -resistant *L. pneumophila* and other species of erythromycin-resistant *Legionella* in human monocytes, and it was also the only agent capable of preventing regrowth of *L. pneumophila* following its removal. Moreover, the postantibiotic effect (PAE) of ABT-492 against *Legionella* spp. was at least 24 h and significantly longer than that of the other quinolones or macrolides. Thus, less frequent administration or shorter courses of therapy may be feasible for ABT-492 compared to the usual macrolide or quinolone therapy (15).

The potential of ABT-492 for the treatment of acute and chronic sinusitis was evaluated using 300 aerobic and anaerobic isolates from antral puncture specimens. Excellent activity against all pathogens was found, with MIC_{90} values for *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, *S. aureus*, *Eikenella corrodens*, *Fusobacterium nucleatum*, *Prevotella* spp., *Peptostreptococcus* spp., *Propionibacterium* spp. and *Veillonella* spp. of 0.001, 0.008, 0.015, 0.008, 0.015, 0.015, 0.5, 0.008, 0.03 and 1 μg/ml, respectively. Overall, ABT-492 was more active than the other fluoroquinolones tested against aerobic bacteria and it was the most active agent against the anaerobic strains (16).

The *in vitro* activity of ABT-492/WQ-3034 has also been tested against mycobacteria and compared to other quinolones by Japanese researchers. WQ-3034 and levofloxacin showed similar activity against *Mycobacterium tuberculosis* and *Mycobacterium avium* complex and were more potent than ciprofloxacin, but less so than sparfloxacin. Intracellular antimycobacterial activity was also demonstrated in macrophage and alveolar cell lines. Combinations of WQ-3034 and clarithromycin or rifampicin resulted in reduced activity against extracellular *M. avium* complex, whereas significantly potentiated activity was seen in combination with isoniazid (17, 18).

Bacillus anthracis is a potential biological weapon and the search continues for possible effective treatments. ABT-492 was therefore evaluated for its efficacy against *B. anthracis* in comparison to clarithromycin, erythromycin and ciprofloxacin. The MIC_{90} value for ABT-492 (0.0625 μg/ml) was similar to that of ciprofloxacin (0.0312 μg/ml) and superior to those of the other agents (0.125-2 μg/ml) (19).

The *in vivo* activity of ABT-492 has also been assessed in several rodent models of systemic, respiratory tract and thigh infection. ABT-492 and other fluoroquinolones were compared in mice with systemic infections caused by Gram-positive microorganisms following administration at 1 and 5 h postinfection. ABT-492, trovafloxacin and gemifloxacin were more active than gatifloxacin, levofloxacin and moxifloxacin in these murine infections. ABT-492 gave ED_{50} values of < 3.1-20.5, 3.3-35.0, 0.2-94.7 and 38.8-66.1 mg/kg, respectively, against infections caused by *S. pneumoniae*, *Streptococcus pyogenes*, *S. aureus* and *Enterococcus faecalis*. ABT-492 also gave higher C_{max} and AUC values compard to gemifloxacin, gatifloxacin, levofloxacin and moxifloxacin following an oral dose of 25 mg/kg, while trovafloxacin gave lower C_{max} but higher AUC values compared to ABT-492 (20). ABT-492 provided 100% survival in experimental murine respiratory tract infections due to *S. pneumoniae*, *versus* 86% survival on sparfloxacin following a dose of 12.5 mg/kg p.o. at 4, 24 and 48 h after infection. ABT-492, but not sparfloxacin, was also effective in reducing lung bacterial counts (21). Another study in neutropenic mice with thigh infection caused by *S. pneumoniae* established that the

AUC_{24}/MIC was better correlated with efficacy than the C_{max}/MIC for ABT-492 administered s.c. (5-200 mg/kg over 24 h) (22).

Finally, rats with lung infection caused by *H. influenzae* or *S. pneumoniae* and mice with pyelonephritis caused by *E. coli*, *P. aeruginosa* or *E. faecalis* were treated with ABT-492, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, trovafloxacin or ciprofloxacin orally once daily for 2 days. ABT-492 was generally comparable to if not superior to the other agents, with ED_{50} values ranging from 4.0 mg/kg/day against *E. coli* pyelonephritis to 55.8 mg/kg against *E. faecalis* pyelonephritis (23).

ABT-492 is reportedly in phase II trials for the treatment of respiratory and urinary tract infections.

Source

Wakunaga Pharmaceutical Co., Ltd. (JP); licensed to Abbott Laboratories Inc. (US).

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