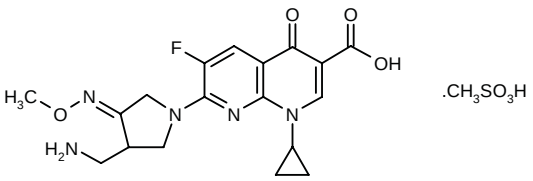
Drugs of the Future 1998, 23(11): 1199-1204

CCC: 0377-8282/98

SB-265805/LB-20304a

Naphthyridine Antibacterial

7-[3-(Aminomethyl)-4-(methoxyimino)pyrrolidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate



$C_{18}H_{20}FN_5O_4.CH_4O_3S$ Mol wt: 485.4906

CAS: 210353-53-0
CAS: 210353-55-2 (as trihydrate)
CAS: 210353-56-3 (as sesquihydrate)
CAS: 175463-14-6 (as free base)

EN: 226496

Synthesis

The addition of glycine ethyl ester (I) to 2-propenenitrile (II) by means of KOH in water gives *N*-(2-cyanoethyl)glycine ethyl ester (III), which is cyclized by means of di-*tert*-butyl dicarbonate yielding the protected pyrrolidinone (IV). The reduction of (IV) with $NaBH_4$ in ethanol affords the pyrrolidinol (V), which is further reduced with $LiAlH_4$ in THF and protected with di-*tert*-butyl dicarbonate to give the fully *N*-protected compound (VI). The oxidation of (VI) with pyridine/SO_3 complex yields the pyrrolidinone (VII), which is treated with *O*-methylhydroxylamine (VIII) to afford the correponding oxime (IX). The deprotection of (IX) with acetyl chloride in cool methanol gives 4-(aminomethyl)pyrrolidin-3-one *O*-methyloxime (X), which is finally condensed with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (XI) by means of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile (1,2). Scheme 1.

Description

White amorphous solid, m.p. 235-7 °C.

Introduction

Several new quinolone and naphthyridone derivatives have been developed and introduced on worldwide markets in recent years. These newer compounds represent important additions to the therapeutic armamentarium, especially for the oral treatment of serious infections, as shown in Table I. Most of the fluoroquinolones, however, are only somewhat active against the pathogenic Gram-positive cocci responsible for many respiratory tract infections. Based on this need for new compounds with increased activity against Gram-positive bacteria and with the potential to address the growing problem of bacterial resistance, scientists at LG Chemical initiated a program to synthesize novel fluoronaphthyridone compounds. A series of compounds was synthesized and subjected to *in vitro* and *in vivo* efficacy studies, culminating in the identification of the pyrrolidine-substituted fluoronaphthyridone compound LB-20304a as the most attractive candidate for further evaluation (2, 3).

LB-20304a was later licensed by LG Chemical to SmithKline Beecham for development and worldwide commercialization outside of Korea. Subsequent to this agreement, SmithKline Beecham has been a very active partner in the development of the compound, which was given the company development code name SB-265805 (4).

Pharmacological Actions

In vitro *studies*

SB-265805 displayed excellent activity against Gram-positive bacteria, with MIC values generally < 0.008 or 0.016 μg/ml. It had potent activity against resistant strains that are not susceptible to ciprofloxacin, including MRSA and MRSE. A structure-activity study confirmed that both the methyloxime group and the aminomethyl group are required for the antibacterial activity of the

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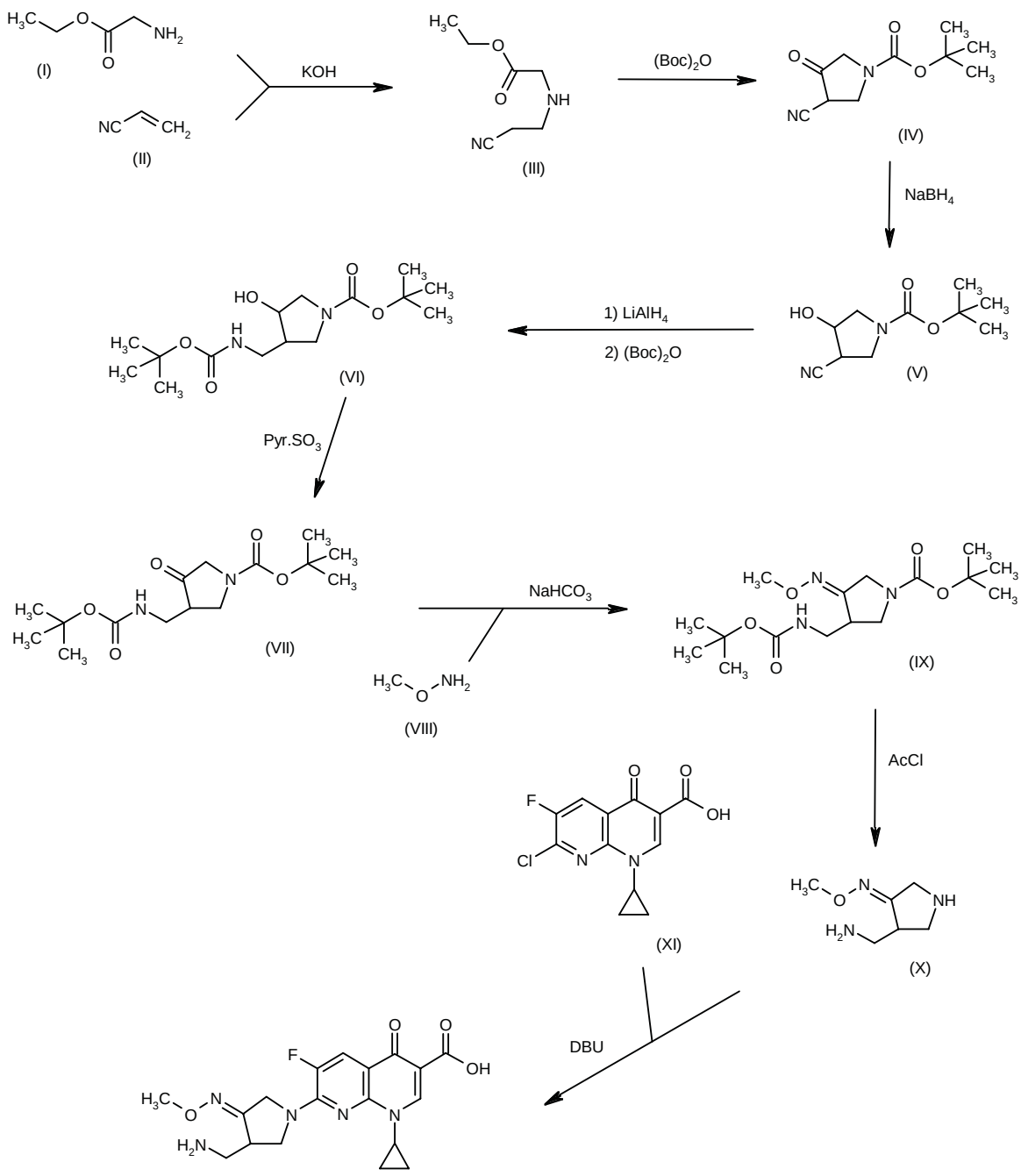
Scheme 1: Synthesis of LB-20304



compound, and furthermore that the two groups work in synergy (5).

The *in vitro* antibacterial activity of SB-265805 was evaluated against a panel of 1231 clinical isolates obtained from various Korean hospitals, and was compared to those of ciprofloxacin, sparfloxacin, lomefloxacin and ofloxacin. The study drug displayed the most potent activity of all compounds tested against Gram-positive bacteria, being more active than reference quinolones against methicillin-susceptible *Staphylococcus aureus* (MIC_{90} = 0.063 μg/ml), methicillin-susceptible *Staphylococcus epidermidis* (MIC_{90} = 0.13 μg/ml) and penicillin G-resistant *Streptococcus pneumoniae* (MIC_{90} = 0.031 μg/ml). Excellent activity was also observed against

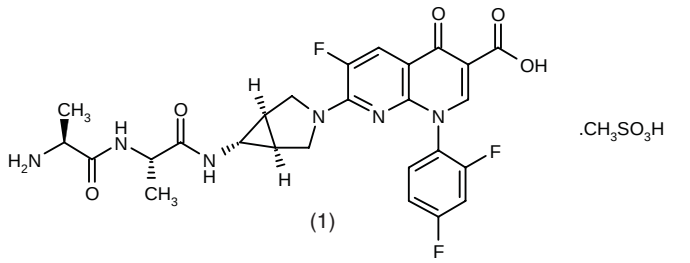
Table I: Fluoronaphthridones and naphthyridines launched and in clinical trials.

Launched

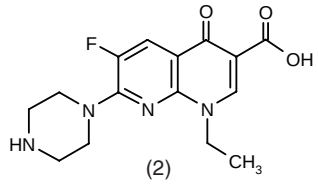
1. Alatrofloxacin mesilate
   Trovan
   Pfizer (1998)
2. Enoxacin
   Flumark
   Dainippon (1986)
3. Tosufloxacin tosilate
   Ozex; Tosuxacin
   Toyama; Dainabot (1990)
4. Trovafloxacin mesilate
   Trovan
   Pfizer (1998)

Clinical Trials

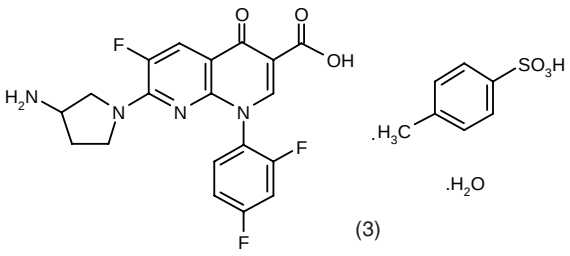
5. Ecenofloxacin HCl
   Cheil Jedang
6. SB-265805/LB-20304a
   SmithKline Beecham; LG Chemical



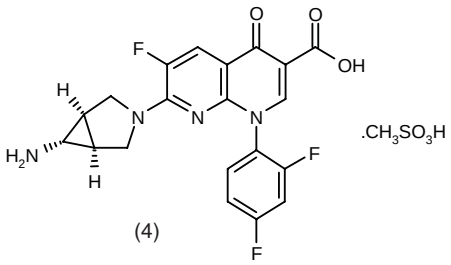
(1)



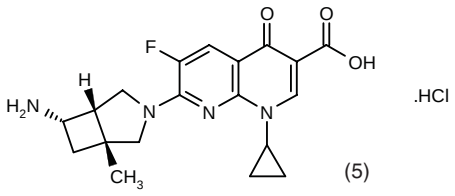
(2)



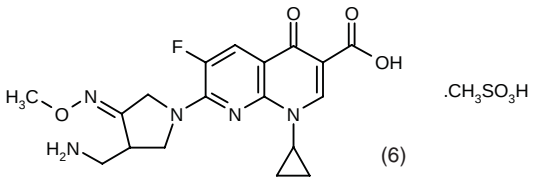
(3)



(4)



(5)



(6)

Streptococcus pyogenes, *Enterococcus faecalis* and *Enterobacteriaceae* (3).

The antibacterial activity of SB-265805 *in vitro* was 8-128 times more potent than that of grepafloxacin, trovafloxacin, sparfloxacin, ciprofloxacin and ofloxacin against clinical isolates of Gram-positive bacterial collected in Korea, again with especially good activity observed against penicillin-resistant *S. pneumoniae*. Its activity against Gram-negative species was equivalent to that of ciprofloxacin and superior to the other reference fluoroquinolones (6). In a subset of 335 Gram-positive clinical isolates with resistance to erythromycin, SB-265805 showed more potent activity than reference fluoroquinolones, azithromycin, clarithromycin, amoxicillin and cefdinir. SB-265805 showed MIC_{90} values of 0.063, 0.13, 0.31 and 0.063 μg/ml, respectively, for MSSA, MSSE, S. pneumoniae and *S. pyogenes*. Reference macrolide compounds (clarithromycin and azithromycin) were moderately active against erythromycin-susceptible bacteria, but were ineffective against resistant strains (7).

The title compound displayed bactericidal activity against *S. aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* in a time-kill study (8), as well as a pronounced postantibiotic effect against *S. aureus* and *E. coli* (9). The outstanding activity observed for SB-265805 against a panel of nearly 600 clinical isolates of *Streptococcus* spp., including 70 strains not susceptible to fluoroquinolones, indicates the clinical potential of this compound in the treatment of streptococcal infections. SB-265805 had significantly more potent antistreptococcal activity than ciprofloxacin, and was also more active than other newer fluoroquinolones such as moxifloxacin, sparfloxacin and grepafloxacin (10).

Pneumococci have been developing increasing resistance to existing antimicrobial agents, including penicillin

G and other β-lactam and non-β-lactam compounds. This increase has been most notable in South Africa, Spain, Central and Eastern Europe and parts of Asia, although an upward tendency has also been observed in the U.S. The mechanism of quinolone resistance in pneumococci is linked to mutations in the class II topoisomerase enzymes. Although the precise mechanism of enzymatic action of SB-265805 has not been defined, the compound has shown very low MICs against quinolone-resistant pneumococci in *in vitro* studies (11).

The activity of SB-265805 against respiratory tract pathogens was compared to that of 4 reference quinolones, 5 β-lactams and 2 macrolides. The activity of the new compound was more potent than that of any reference drug, including against resistant pathogens. It inhibited quinolone-resistant strains of *S. pneumoniae* (MIC_{90} = 0.5 μg/ml), penicillin-resistant and -susceptible *S. pneumoniae* (MIC_{90} = 0.03 μg/ml) and all strains tested of *Haemophilus influenzae* and *Moraxella catarrhalis* (concentrations < 0.016 μg/ml), being 1- to 8-fold more potent than any of the reference quinolones (12-14). At concentrations 2x and 4x the MIC, SB-265805 showed good bactericidal activity against *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. pyogenes* in a time-kill study. Both the title compound and ciprofloxacin reduced original bacterial counts by 3 $\log_{10}$ CFU/ml or higher at one dilution above bacteriostatic levels, with sustained prevention of regrowth lasting for 24 h (15).

SB-265805 also showed more potent activity than comparators against *Legionella pneumophila* (59 strains), *Chlamydia pneumoniae* (5 strains) and *Chlamydia trachomatis* (15 strains), with MICs of 0.004-0.015, 0.06-0.12 and 0.03-0.12 μg/ml, respectively (16). Tested against 219 strains of *Legionella* using a standard agar dilution procedure, SB-265805 was less active than rifampin and trovafloxacin but comparable to or more potent than reference fluoroquinolones, with MIC_{90}s in the range of 0.016-0.06 mg/l (17). The compound accumulated rapidly inside human macrophages in culture, reducing bacterial counts of *L. pneumophilia* growing inside human macrophages by more than 2 log at the concentration of 0.25 μg/ml. It reduced viable cell counts over 72 h by 80-100-fold, similar to ciprofloxacin, grepafloxacin and trovafloxacin and with more potent activity than erythromycin. These finding are consistent with the potent activity of SB-265805 against facultative intracellular pathogens such as *L. pneumophila* (18).

SB-265805 had excellent broad-spectrum, antimycoplasmal activity *in vitro* against clinically relevant strains of *Mycoplasma* and *Ureaplasma urealyticum*, being generally superior to ciprofloxacin, doxycycline and erythromycin (19). It was also moderately active against anaerobic bacteria (20).

Given that the problem of bacterial resistance is prevalent worldwide, an international study was conducted to assess the activity of SB-265805 against a total of 379 aerobic bacterial strains from Switzerland and the U.S. Of these isolates, 260 were Gram-negative and the remainder were Gram-positive. The compound demonstrated excellent activity, including against fastidious species such as pneumococci, *Haemophilus* spp. and *M. catarrhalis* (21).

The development of spontaneous bacterial resistance to SB-265805 and the existence of potential cross-resistance with other antimicrobial agents were evaluated in vitro. In 8 strains of bacteria, the frequency of mutation at concentrations 4x and 8x the MIC ranged from < 4.0 x 10^{-10} to 2.2 x 10^{-8}. Stepwise resistance resulted from the exposure of bacteria to increasing concentrations of the compound, as seen by the selection of organisms with higher MICs. The MICs for *S. aureus*, *S. pneumoniae*, *E. coli* and *P. aeruginosa* increased by 4- to 128-fold, although all strains with the exception of *P. aeruginosa* remained within the susceptibility range for the title compound even after repeated exposure. Resistant isolates selected by SB-265805 were cross-resistant with ciprofloxacin and *vice versa* (22).

In vivo *studies*

SB-265805 was effective in mice systemically infected with *S. aureus* giorgio and *P. aeruginosa* 1912E, giving oral ED_{50} values of 1.68 and 2.19 mg/kg, respectively. These values for ciprofloxacin were 14.0 and 3.11 mg/kg, respectively. The bactericidal activity of the compound was rapid at 1 and 2 MIC against *S. aureus*, *E. coli* and *P. aeruginosa* (23).

Pharmacokinetics and Metabolism

The pharmacokinetics of SB-265805 were evaluated in rats and dogs after oral and intravenous administration. In rats and dogs, total body clearance of the compound was 21.8 and 7.95 ml/min/kg, respectively, while apparent volume of distribution was 2265 and 4144 ml/kg, respectively. The terminal half-life was 93.6 min in rats and 363 min in dogs, and the bioavailability was 30.8% in rats and 81.1% in dogs. Drug concentrations in the liver, stomach, small intestine and kidney were 0.5-26.1 times greater than levels in plasma following administration to rats, but those in testes and brain were low to negligible. Urinary recovery at 48 h was 44% with i.v. administration and 14% with oral dosing, while 48-h biliary recovery was 6.4% for i.v. dosing and 4.5% for oral dosing in rats. Over the range of doses tested in rats (5-200 mg/kg i.v.), plasma concentrations decreased in a linear fashion indicating that drug distribution, metabolism and excretion were not affected by dose (24).

Phase I metabolism of SB-265805 was minimal in rats, dogs and humans, due to the lack of metabolism in the liver microsomes where it would normally occur. Phase I metabolism did occur via enzyme induction, however, as seen by a decrease in drug concentrations in rat microsomes treated with aroclor (24).

A high-performance liquid chromatographic assay has been developed and was used to determine drug levels in the plasma of rats and dogs (25).

Toxicity

Quinolone antibacterial agents exert their bactericidal activity by inhibiting bacterial DNA gyrase, an enzyme that controls the shape and functioning of bacterial DNA through its supercoiling and relaxing effects. At high concentrations, however, the quinolones have also been observed to inhibit the catalytic DNA strand passage activity of eukaryotic topoisomerase II, affecting the enyzme-mediated process of DNA cleavage and religation and ultimately converting topoisomerase II into a type of cellular poison. Thus, an evaluation of the potential for this adverse effect was considered opportune in the case of SB-265805. *In vitro* in cultures with *Micrococcus luteus*, the IC_{50} for SB-265805 for inhibition of the supercoiling activity of bacterial DNA gyrase was 11 μg/ml, compared to 84 μg/ml for ciprofloxacin. For human topoisomerase II, in contrast, ciprofloxacin induced DNA cleavage at the concentration of 644 μg/ml, while the title compound did not have this effect at concentrations of up to 10,000 μg/ml. Thus, the selectivity index of SB-265805 for bacterial DNA gyrase over human topoisomerase II was in excess of 909, *vs.* an index of just 7.7 for the reference quinolone. These findings indicate a reduced potential for cytotoxicity to eukaryotic cells with SB-265805 (26, 27).

In contrast to ciprofloxacin, which has epileptogenic potential, SB-265805 did not induce convulsions in mice even when coadministered with 4-biphenylacetic acid. The dose of SB-265805 inducing convulsions in 50% of the animals (CD_{50}) administered by intracerebral injection was 169 nmol; the CD_{50}s for ciprofloxacin and ofloxacin were 35 and 105 nmol, respectively (24).

Clinical Studies

SmithKline Beecham has initiated phase III clinical trials evaluating SB-265805 in the treatment of community-acquired infections (28).

Manufacturer

LG Chemical (KO); SmithKline Beecham (US).

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