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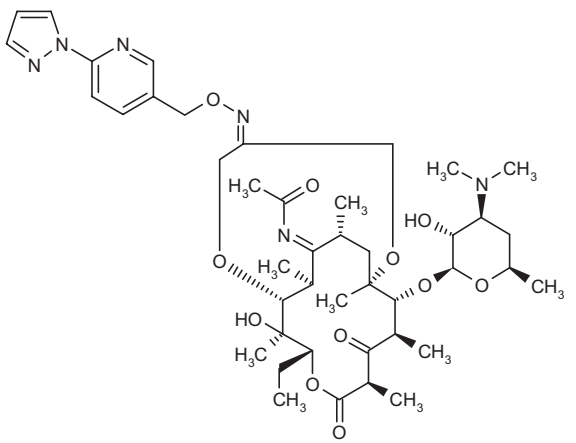
EDP-420

Ketolide Antibiotic

EP-013420 (former code name)
S-013420

9-(Acetylimino)-9-deoxo-3-des(hexopyranosyloxy)-3-oxo-6-*O*,11-*O*-[2-[6-(1*H*-pyrazol-1-yl)pyridin-3-ylmethoxyimino]propylene]erythromycin A



$C_{43}H_{64}N_6O_{11}$
Mol wt: 841.0021

CAS: 748796-41-0

CAS: 664180-95-0 (as monohydrate)

EN: 347484

Abstract

EDP-420 (formerly EP-013420, known as S-013420 at Shionogi) is a ketolide antibiotic in phase II clinical trials for the treatment of community-acquired pneumonia. The ketolides are the third generation of erythromycin derivatives, developed in response to the need to combat macrolide-resistant bacteria. Preclinical data indicate that EDP-420 is effective against many macrolide-resistant pathogens, particularly streptococci and staphylococci, and may have pharmacokinetic properties superior to the currently available ketolide telithromcyin.

Synthesis

Acylation of erythromycin oxime (I) with Ac_2O in the presence of DMAP gives the triacetyl derivative (II). Treatment of 2-methylene-1,3-propanediol (III) with Boc_2O under phase-transfer conditions provides the biscarbonate (IV), which is further coupled to the triacetylated erythromycin (II) in the presence of palladium catalyst to furnish the bridged diether (V). Methanolysis of the triacetyl compound (V) removes the *NO*-acetyl and 2'-*O*-acetyl groups, leading to the oxime (VI). Subsequent reduction of (VI) employing $TiCl_3$ with concomitant cleavage of the 3-cladinose moiety provides the imine (VII), which is then acetylated to the 3-hydroxy lactone (VIII) with Ac_2O and Et_3N (1). Dess-Martin oxidation of (VIII) leads to the ketolide (IX), which is further subjected to methanolysis to give (X) (1). Ozonolysis of the exocyclic methylene group of (X), followed by reductive work-up with PPh_3, provides the ketone (XI), which is finally condensed with the pyrazolylpyridinylmethoxy amine (XII) to give the title oxime (1, 2). Scheme 1.

Background

Erythromycin is a macrolide antibiotic that has been used for over 50 years for the treatment of bacterial infections, including ear, sinus, throat, respiratory tract, urinary tract and many wound and skin infections. Although erythromycin and other macrolides have saved many millions of lives, unfortunately, their frequent use has given rise to macrolide-resistant bacteria, particularly among streptococci, staphylococci and enterococci.

Macrolides inhibit protein synthesis in sensitive strains by binding to the 23S rRNA molecule of the 50S subunit of the bacterial ribosome, blocking the peptide exit tunnel, and so inhibiting translation (3, 4). Several different mechanisms of resistance have evolved, the most problematic of which are the expression of "*erm*" methyltransferases that modify the ribosome at the macrolide binding site to prevent binding, and the expression of "*mef*" multidrug efflux pumps. Of over 10,000 isolates of *Streptococcus pneumoniae* collected from patients who had community-acquired pneumonia in the year 2000 (206 centers in the U.S.), over 3,000 (about 30%) were erythromycin-resistant; of these, 71% were *mefA*, 17% *ermB* and 10% *mefA/ermB* (5).

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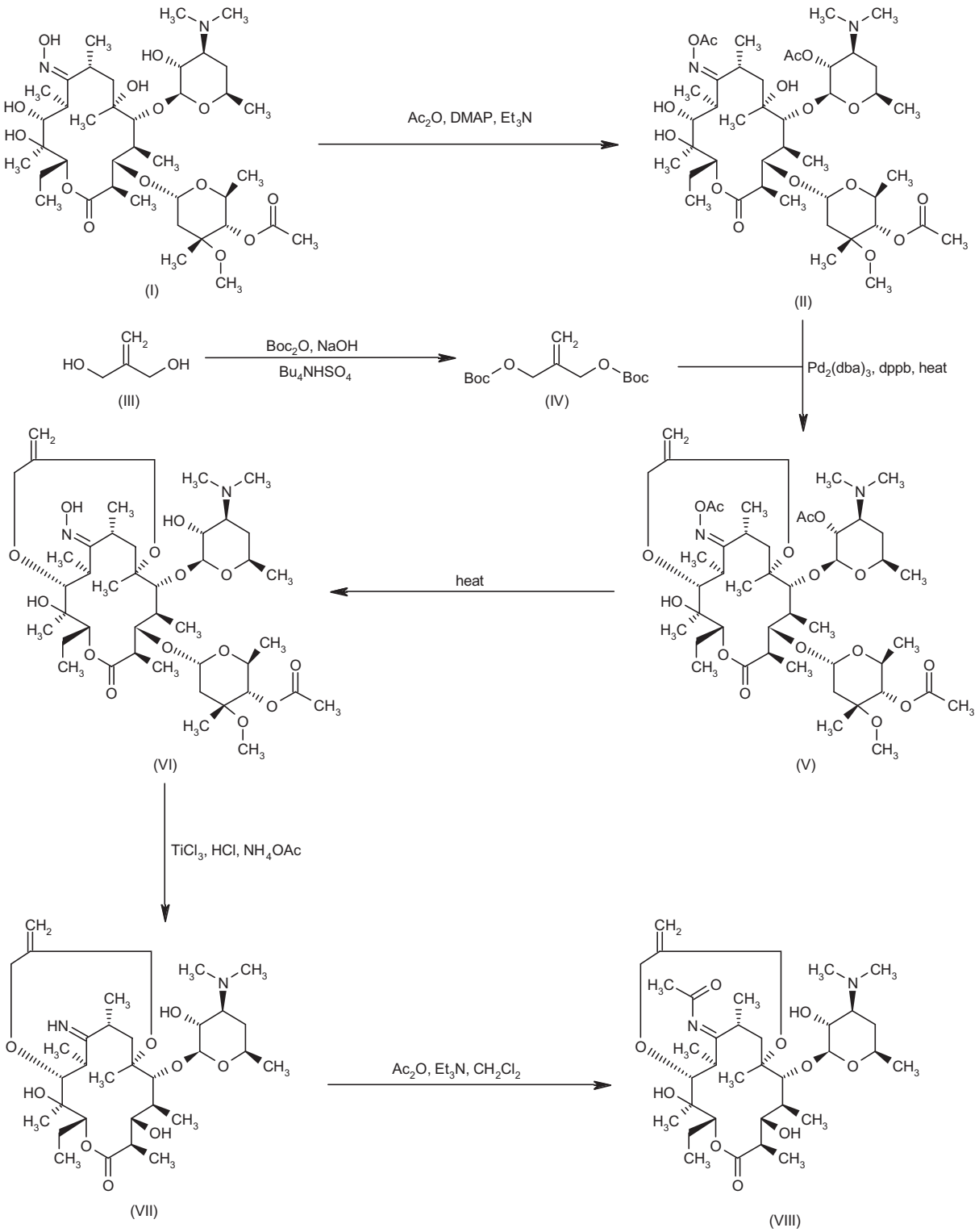
Scheme 1: Synthesis of EDP-420



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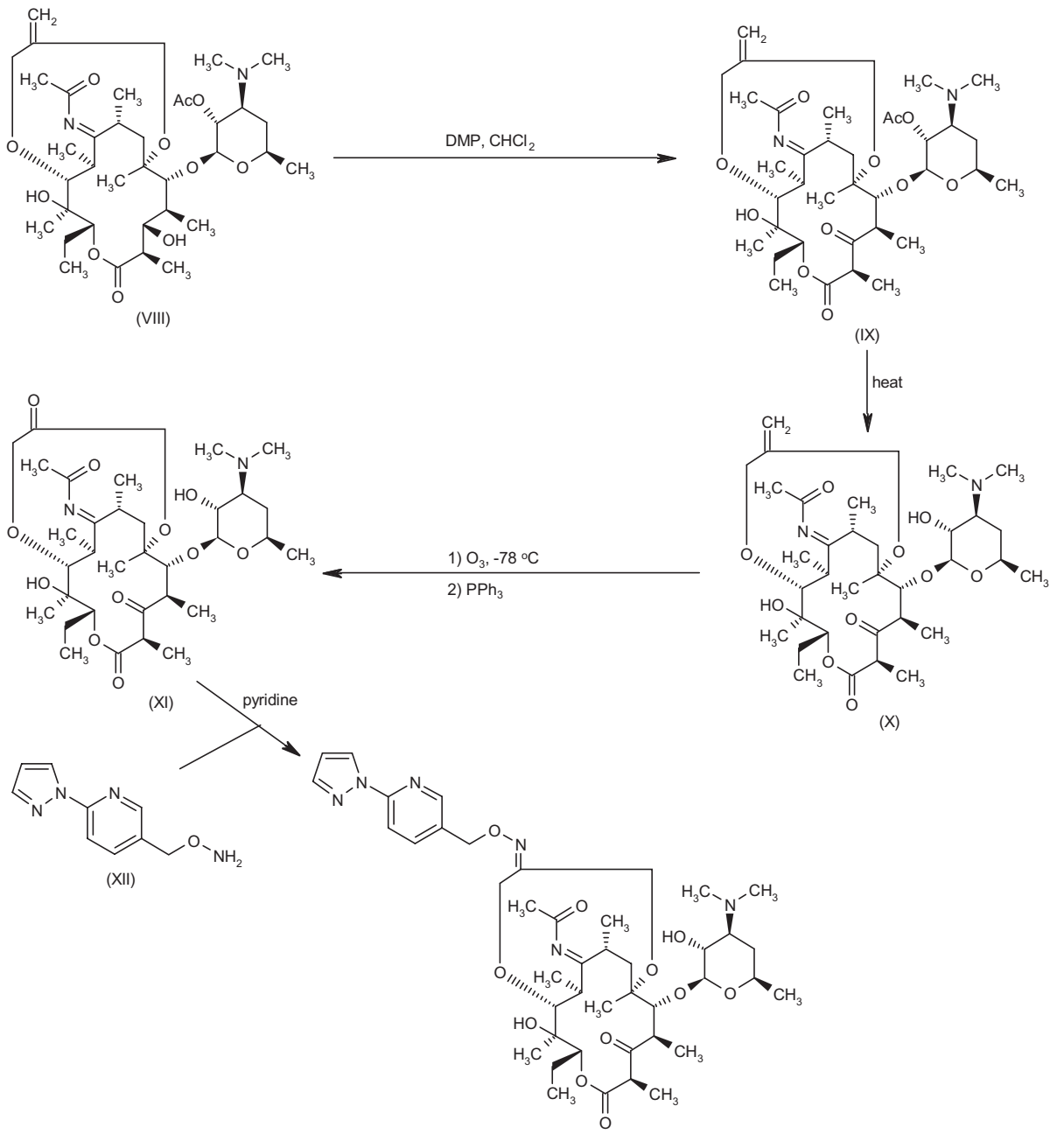
Scheme 1: Synthesis of EDP-420 (cont.)



The ketolides are a new generation of erythromycin analogues that have a keto group in place of the cladinose sugar at C-3, a bridge that spans two positions of the macrolide ring, and a heteroaromatic side-chain attached to the macrolide via a flexible linker. These modifications give the ketolides a broader antimicrobial spectrum than their progenitors, and due to additional points of contact with the ribosome, they are effective against many of the macrolide-resistant strains that have emerged in the past few years, including *S. pneumoniae mefA* (6, 7). Two such compounds are telithromycin (Ketek™, Levviax®; Sanofi-Aventis, Astellas Pharma), the only ketolide available on the market, and cethromycin (Advanced Life Sciences). A new ketolide, EDP-420 (formerly EP-013420, known as S-013420 at Shionogi), has an improved pharmacological profile relative to

telithromycin, cethromycin and clarithromycin (Biaxin™), including macrolide-resistant streptococci and a number of atypical pathogens. EDP-420 is in phase II clinical development as an oral antibiotic for the treatment of community-acquired pneumonia.

Preclinical Pharmacology

The activity of EDP-420 is comparable to that of telithromycin against many respiratory tract pathogens, and it has increased potency against certain macrolide-resistant streptococci. Against methicillin-susceptible *Staphylococcus aureus* and coagulase-negative staphylococci, erythromycin-susceptible *S. pneumoniae*, erythromycin-intermediate and -resistant *S. pneumoniae, Streptococcus pyogenes, Moraxella catarrhalis* and *Peptostreptococcus* spp., EDP-420 gave MIC_{90} values of 0.5 μg/ml or less, compared to 0.25 μg/ml or less for telithromycin; *Prevotella* spp. were more susceptible to EDP-420 than telithromycin (MIC_{90} = 0.125 μg/ml *vs.* 2 μg/ml). When tested against macrolide-resistant *mefA+, ermB+* and *ermTR+ S. pyogenes*, EDP-420 gave MIC values of 0.125-0.25, 1 and < 0.063-0.125 μg/ml, respectively, compared to values for telithromycin of 0.5-2, 16 and < 0.063-0.5 μg/ml (2, 8). EDP-420, like the other ketolides, is bactericidal, killing more than 99.9% of viable *S. pneumoniae* and *Haemophilus influenzae* within 4 h at 4 x MIC or less. The postantibiotic effect (PAE) in two strains of *H. influenza* exposed to 4 x MIC for 2 h was 4.3 and 2.2 h, comparable to that of telithromycin and exceeding that of clarithromycin (8).

EDP-420 was somewhat less potent than clarithromycin against *Mycobacterium avium* complex (MAC), with an MIC_{90} value of 8 μg/ml (9). The PAE for MAC 101, exposed at the MIC, 4 x MIC and 8 x MIC (2, 8 and 16 μg/ml, respectively) for 24 h was 17, 35 and 50 h, respectively, comparable to clarithromycin (28-42 h at 2 and 8 μg/ml) and azithromycin (28-38 h at 32 and 128 μg/ml) (10), suggesting that EDP-420 could be suitable for intermittent dosing. EDP-420 (0.5 x MIC) inhibited biofilm formation by MAC by 30-40% and reduced uptake of MAC 101 and MAC A5 into human bronchiolar cells from 11.5% (control) to 5.6% and from 9.7% to 3.3%, respectively, at 0.5 x MIC, whereas it had no effect on the uptake of the biofilm-deficient mutant strain MAC 5G4 (11).

EDP-420 has also exhibited promising activity against *Mycobacterium tuberculosis*, with an MIC value of 4 μg/ml (12).

Studies in mice indicated similar efficacy for EDP-420 and telithromycin against acute systemic infections caused by macrolide-susceptible *S. aureus* and resistant *mefE+ S. pneumoniae*, and against lung infection in mice caused by *H. influenzae* (2).

In a mouse model of systemic infection caused by erythromycin-resistant *S. aureus*, oral administration of EDP-420 proved effective, with an ED_{50} of 8.51 mg/kg compared to 8.49, 47.7 and 5.87 mg/kg, respectively, for telithromycin, clarithromycin and levofloxacin. Against systemic infection caused by erythromycin-resistant (*ermB*) *S. pneumoniae*, the ED_{50} values were 3.27, 16.5, > 30 and 10.4 mg/kg for EDP-420, telithromycin, clarithromycin and levofloxacin, respectively. In rat lung infection models, EDP-420 compared favorably with telithromycin and clarithromyin in reducing viable counts of erythromycin-susceptible and -resistant *S. pneumoniae* and *H. influenzae* in the lungs (13).

EDP-420 or clarithromycin treatment (100 mg/kg/day for 28 days) of beige mice with bloodstream MAC infections showed comparable reductions in liver and spleen bacterial loads (9).

In a model of disseminated MAC infection in beige mice, EDP-420, either alone (100 mg/kg/day p.o. for 12 weeks) or in combination with mefloquine (40 mg/kg/day p.o. for 12 weeks) caused large reductions in bacterial load from 3.4 x 10^9 CFU/spleen for controls to 3.9 x 10^5 and 2.2 x 10^5 CFU/spleen, respectively. No EDP-420-resistant colonies could be isolated (14).

In a rabbit model of resistant pneumococcal meningitis, EDP-420 (30 mg/kg) crossed the blood-brain barrier to penetrate the meninges at 38% of serum levels and killed penicillin/quinolone-resistant *S. pneumoniae* at a rate of 4.8 $\log_{10}$ CFU/ml/8 h, showing comparable bactericidal activity to standard therapy with ceftriaxone + vancomycin (5.0 $\log_{10}$ CFU/ml/8 h) (15).

In vivo activity was also seen against intranasal *M. tuberculosis* infection in mice administered oral EDP-420, with comparable activity to clarithromycin and isoniazid (12).

In a mouse model of *S. pneumoniae* lung infection (using one macrolide-sensitive, two *mef+* and one *erm+* strain), infected animals were given doses ranging from 3.125 to 200 mg/kg. AUC/MIC and peak/MIC showed a good correlation with efficacy, AUC/MIC ratios of 4-73 producing bacteriostatic to bactericidal effects (16).

Pharmacokinetics and Metabolism

The compound has an excellent pharmacokinetic profile in mice, rats and dogs, generally comparable to telithromycin but with a longer half-life and higher accumulation in the lungs. Mice administered a single oral dose of either EDP-420 or telithromycin of 15 mg/kg had plasma C_{max} values of 2.45 and 5.54 μg/ml, AUC values of 13.18 and 15.90 μg.h/ml and $t_{1/2}$ values of 3.3 and 1.5 h, respectively. The ratios of lung tissue to plasma concentrations (based on AUC for lung tissue homogenates and plasma) were 9.8 and 2.2 for EDP-420 and telithromycin, respectively. The half-life in dogs given a dose of 5 mg/kg p.o. was much longer than that of telithromycin (10.8 h *vs.* 2.1 h) (2). In mice and rats administered a single oral dose of 10 mg/kg of EDP-420, excellent lung tissue to plasma AUC ratios were obtained (40.8 and 68.7, respectively), indicating preferential lung accumulation (13). Other studies in rats also revealed excellent distribution to the lung and epithelial lining fluid. Following single oral doses of 10 mg/kg to rats, peak plasma levels, $AUC_{0\text{-}24\ h}$ and $t_{1/2}$ values of 0.4 μg/ml, 3.8 μg.h/ml and 7.1 h, respec-

tively, were obtained. The lung to plasma AUC ratio was 224. Rats given doses of 10 and 30 mg/kg p.o. showed a ratio for drug accumulation in the epithelial lining fluid *versus* plasma of 17, and penetration of the epithelial lining fluid is expected to be even higher in humans, as for other macrolides (17).

Clinical Studies

Phase II clinical trials of EDP-420 for the treatment of community-acquired pneumonia are under way in the U.S., Canada and Japan (18-20).

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Enanta Pharmaceuticals, Inc. (US); licensed to Shionogi & Co., Ltd. (JP) for East Asia.

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