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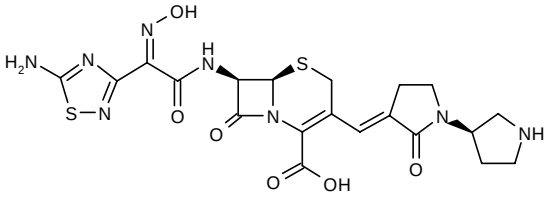
Ceftobiprole/Ceftobiprole Medocaril

Cephalosporin Antibiotic

Ceftobiprole

BAL-9141
Ro-63-9141

(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(hydroxyimino)acetamido]-3-[(*E*)-1-[3(*R*)-pyrrolidinyl]-2-oxopyrrolidin-3-ylidenemethyl]-3-cephem-4-carboxylic acid



$C_{20}H_{22}N_8O_6S_2$ Mol wt: 534.5758

CAS: 209467-52-7

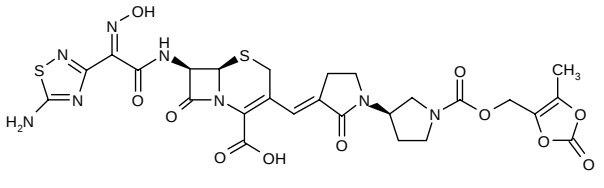
EN: 268124

Ceftobiprole Medocaril

BAL-5788
Ro-65-5788

(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(hydroxyimino)acetamido]-3-[(*E*)-1-[1-(5-methyl-2-oxo-1,3-dioxol-4-ylmethoxycarbonyl)pyrrolidin-3(*R*)-yl]-2-oxopyrrolidin-3-ylidenemethyl]-3-cephem-4-carboxylic acid

(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(hydroxyimino)acetamido]-3-[(3'*R*,*E*)-1'-(5-methyl-2-oxo-1,3-dioxol-4-ylmethoxycarbonyl)-2-oxo-1,3'-bipyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid



$C_{26}H_{26}N_8O_{11}S_2$ Mol wt: 690.6684

CAS: 376653-43-9
CAS: 252188-71-9 (as monosodium salt)

EN: 268124

Abstract

Over the past decade, resistance to antimicrobials has increased dramatically and is limiting the therapeutic options for the treatment and management of serious bacterial infections. Cephalosporins are commonly used to treat bacterial infections due to their broad spectrum of activity and low toxicity. However, the incidence of cephalosporin-resistant strains is increasing, thus decreasing the routine use of these agents. Researchers have focused on developing novel β-lactam antibiotics which are active against resistant bacteria. One particular novel agent is ceftobiprole, which is the first of a new class of parenteral cephem antibiotics. This fourth-generation cephalosporin was designed to have strong affinity for penicillin-binding proteins conferring resistance in staphylococci, pneumococci and other Gram-positive and Gram-negative pathogens, and was shown to have broad-spectrum efficacy and a low propensity to induce resistance *in vitro*. Ceftobiprole is administered *in vivo* as the water-soluble prodrug ceftobiprole medocaril, which is rapidly cleaved in plasma to form ceftobiprole. Ceftobiprole medocaril exhibited potent efficacy in animal infection models and proved safe and effective in a phase II trial in patients with complicated skin and skin structure infections. Ceftobiprole medocaril has advanced to phase III development for the treatment of bacterial infections, particularly those caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

Synthesis of Ceftobiprole

Ceftobiprole can be prepared by several different ways:

1) Cyclization of 3(*R*)-aminopyrrolidine-1-carboxylic acid allyl ester (I) with 2-bromo-4-chlorobutyryl chloride (II) by means of aqueous NaOH in dichloromethane gives the bipyrrolidine (III), which is treated with triphenylphosphine in dichloromethane to yield the phosphonium salt (IV). Condensation of compound (IV) with (*R*,*R*,*R*)-7-(*tert*-butoxycarbonylamino)-3-formyl-2-cephem-4-carboxylic acid diphenylmethyl ester (V) in refluxing THF affords the expected condensation product (VI). Double bond rearrangement of 2-cephem (VI) by oxidation at the sulfur atom with triphenylphosphine oxide and *meta*-chloroper-

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benzoic acid (MCPBA) in dichloromethane provides the sulfoxide intermediate (VII), which is subjected to deoxygenation by means of PBr_3 in dichloromethane/DMF to give the 3-cephem isomer (VIII). Selective deprotection of compound (VIII) by treatment with TFA and anisole in dichloromethane affords the 7-aminocephem-4-carboxylic acid (IX), which is condensed with 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(trityloxyimino)thioacetic acid *S*-(benzothiazol-2-yl)ester (X) –prepared by reaction of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(trityloxyimino)acetic acid 1-allyl-1-methylpyrrolidinium salt (XI) and 2,2'-dithiobis(benzothiazole) (XII) by means of triethylphosphite in acetonitrile– in DMF to yield the expected 7-acetamido derivative (XIII). Finally, this compound is deprotected first with bis(trimethylsilyl)acetamide (BSA) and bis(triphenylphosphine)palladium dichloride in dichloromethane to eliminate the allyloxycarbonyl group, and then with TFA and triethylsilane to eliminate the trityl group (1, 2). Scheme 1.

In addition, reaction of the phosphonium salt (IV) with 7-(*tert*-butoxycarbonylamino)-3-formyl-3-cephem-4-carboxylic acid diphenylmethyl ester (XIV) by means of *t*-BuOK in CH_2Cl_2/toluene/THF directly results in the 3-cephem (VIII) (3). Scheme 1.

2) Condensation of 7(*R*)-amino-3-(hydroxymethyl)-3-cephem-4-carboxylic acid (XV) with 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(trityloxyimino)thioacetic acid *S*-(benzothiazol-2-yl)ester (X) by means of tetramethyl guanidine in DMF and subsequent treatment with diphenyldiazomethane in CH_2Cl_2 gives 7(*R*)-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(trityloxyimino)acetamido]-3-(hydroxymethyl)-3-cephem-4-carboxylic acid diphenylmethyl ester (XVI), which is oxidized at the hydroxymethyl group with either TEMPO and NaOCl in CH_2Cl_2 or MnO_2 in THF/CH_2Cl_2 to yield the 3-formyl derivative (XVII). The condensation of the formyl group of (XVII) with the phosphonium salt (XVIII) by means of *t*-BuOK in dichloromethane/toluene/THF affords the protected cephem (XIX), which is finally deprotected by treatment with HCOOH and TFA in methyl phenyl ether/CH_2Cl_2 or triethylsilane and TFA in CH_2Cl_2 (4). Scheme 2.

Synthesis of Ceftobiprole Medocaril

Ceftobiprole medocaril can be prepared by different ways:

1) Condensation of ceftobiprole (XX) with the mixed carbonate, carbonic acid 5-methyl-2-oxo-1,3-dioxol-4-ylmethyl 4-methylphenyl diester (XXI) in DMSO (5, 6). Scheme 3.

2) Condensation of 7(*R*)-amino-3-(hydroxymethyl)-3-cephem-4-carboxylic acid (XV) with 2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(trityloxyimino)thioacetic acid *S*-(benzothiazol-2-yl)ester (X) by means of tetramethyl guanidine in DMF and subsequent treatment with diphenyldiazomethane in CH_2Cl_2 gives 7(*R*)-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2(*Z*)-(trityloxyimino)acetamido]-3-(hydroxymethyl)-3-cephem-4-carboxylic acid diphenylmethyl ester (XVI), which is oxidized at the hydroxymethyl group with either TEMPO and NaOCl in CH_2Cl_2 or MnO_2 in THF/CH_2Cl_2 to yield the 3-formyl derivative (XVII). Condensation of the formyl group of compound (XVII) with [(3'*R*)-1'-(5-methyl-2-oxo-1,3-dioxol-4-ylmethoxycarbonyl)-2-oxo-1,3-bipyrrolidinyl-3-yl]triphenylphosphonium bromide (XXII) –obtained by condensation of the phosphonium salt (VII) with the mixed carbonate (XXI) by means of bis(triphenylphosphine)palladium chloride and Bu_3SnH in dichloromethane– using *t*-BuOK in dichloromethane/toluene/THF provides the protected cephem (XXIII), which is finally deprotected by treatment with triethylsilane and TFA (4). Scheme 4.

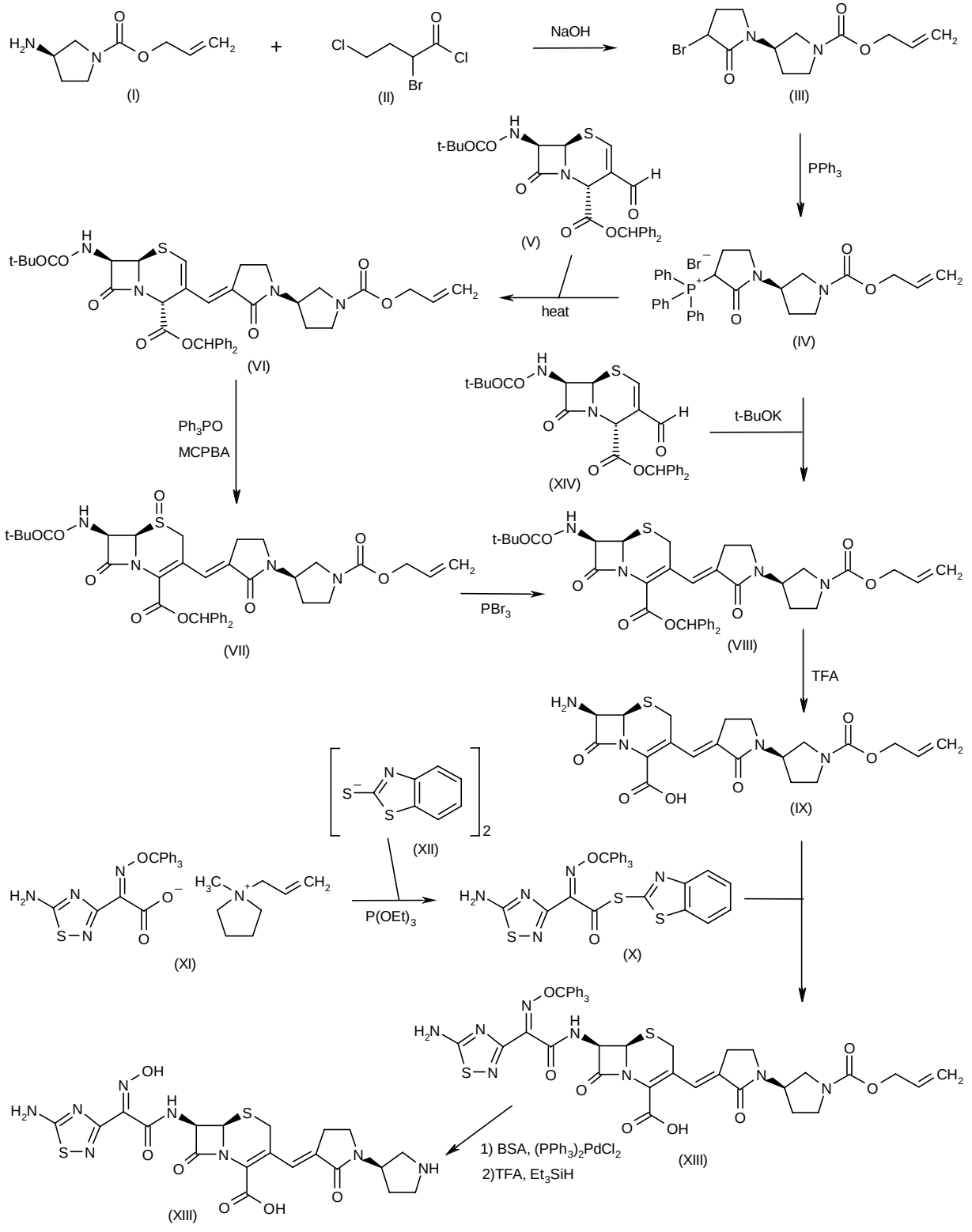
Introduction

Resistance to antimicrobials has become a significant problem over the past decade, with marked increases seen in methicillin-resistant *Staphylococcus aureus* (MRSA), intermediate- and high-level-resistant *S. aureus*, penicillin-resistant *Streptococcus pneumoniae* and vancomycin-resistant enterococci (VRE). Factors contributing to the emergence of antimicrobial resistance include antimicrobial usage patterns and the quality of infection control. However, even with improved controls and hospital hygiene, the incidence of MRSA, for example, continues to increase in both North America and Europe. The increase in resistant phenotypes limits treatment options and the management of serious Gram-positive infections has become extremely difficult. Thus, there is a crucial ongoing need for novel effective antibacterial agents (7).

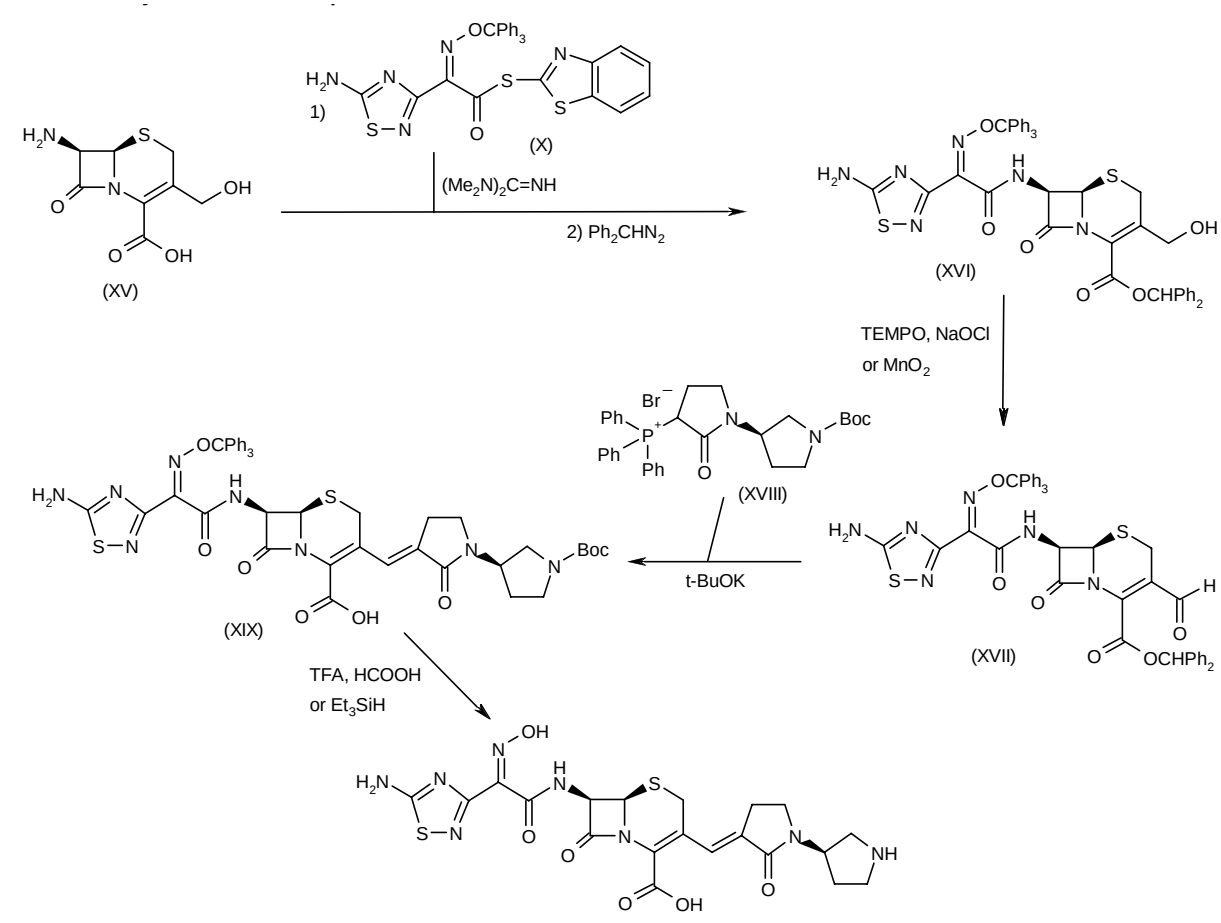
Cephalosporins are commonly used to treat bacterial infections due to their broad spectrum of activity and their low toxicity. In addition, patients allergic to penicillin depend on cephalosporins as agents that can be safely used. However, the incidence of cephalosporin-resistant strains, identified as early as 1992, is increasing. As a result, routine first-line use of β-lactam antibiotics has been significantly reduced or even abandoned in many centers, and other antimicrobials, sometimes with increased toxicity and/or suboptimal efficacy, are administered instead (8-13).

Researchers have focused on developing novel β-lactam antibiotics with activity against resistant bacteria. Until recently, these efforts were generally unsuccessful in discovering agents with improved efficacy against organisms such as MRSA (14). Ceftobiprole (BAL-9141, Ro-63-9141), a pyrrolidinon-3-ylidenemethyl-cephem, is the first of a new class of parenteral cephem antibiotics. This fourth-generation cephalosporin was designed to have strong affinity for penicillin-binding proteins PBP 2a and PBP 2x that confer resistance in staphylococci and pneumococci, respectively. It can also bind to relevant PBPs of most Gram-positive and Gram-negative bacteria and is resistant to many β-lactamases (15, 16). Ceftobiprole showed broad-spectrum activity against relevant resistant Gram-positive and Gram-negative pathogens *in vitro* and had a low liability to induce resis-

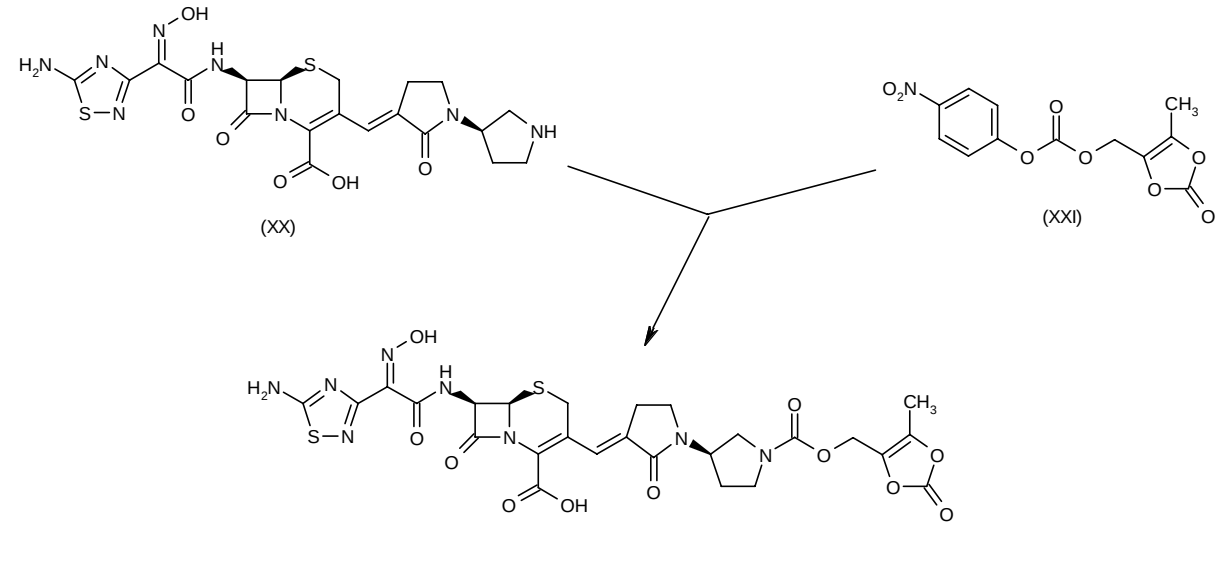
Scheme 1: Synthesis of Ceftobiprole



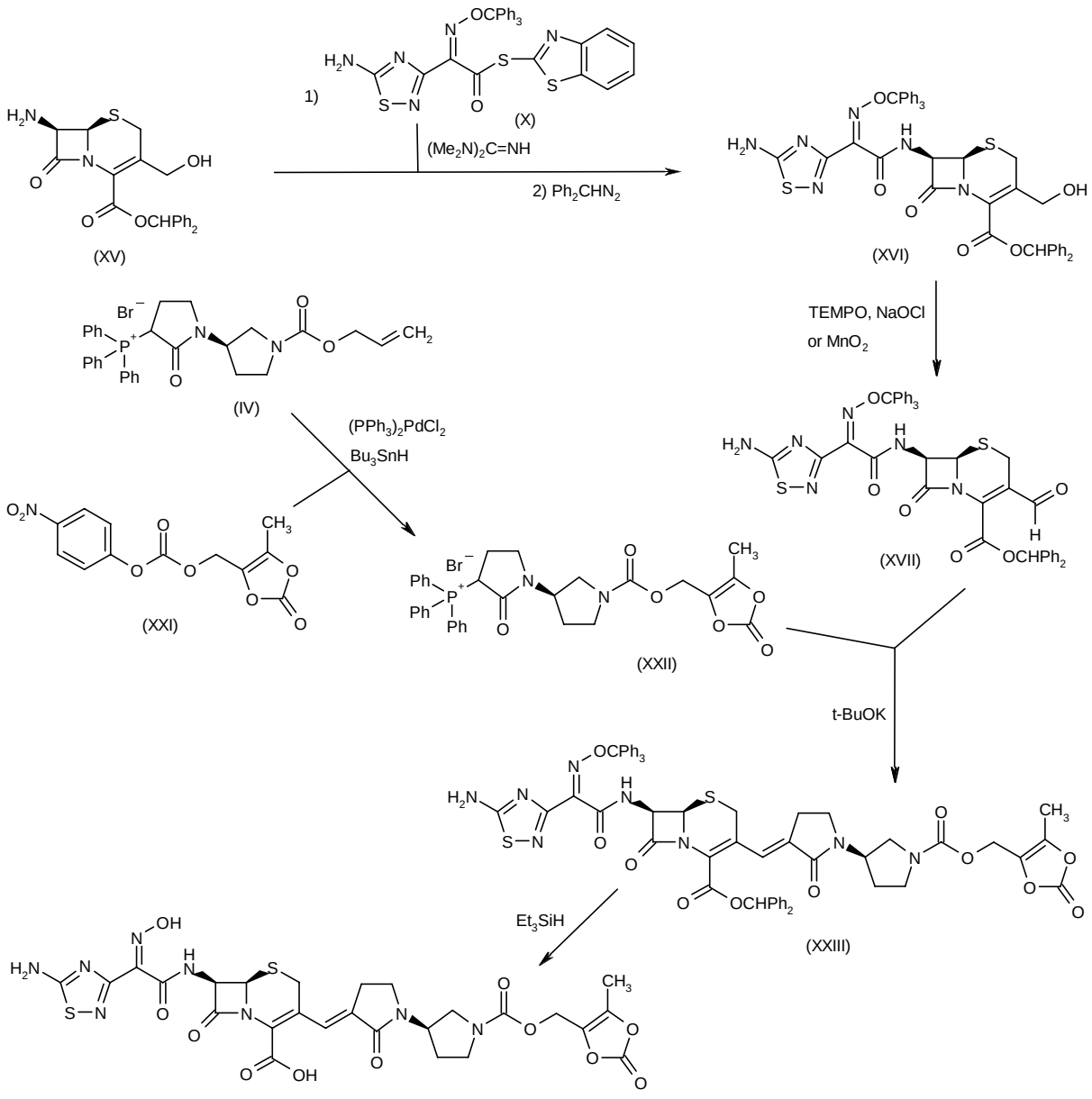
Scheme 2: Synthesis of Ceftobiprole



Scheme 3: Synthesis of Ceftobiprole Medocaril



Scheme 4: Synthesis of Ceftobiprole Medocaril



tance. The agent is administered *in vivo* as a water-soluble prodrug, ceftobiprole medocaril (BAL-5788, Ro-65-5788), which is rapidly cleaved in plasma to form ceftobiprole, diacetyl and CO_2. Ceftobiprole medocaril exhibited potent efficacy in animal infection models and was chosen for further development for the treatment of bacterial infections.

The chemical structures of ceftobiprole medocaril and other cephalosporins under development are shown in Table I.

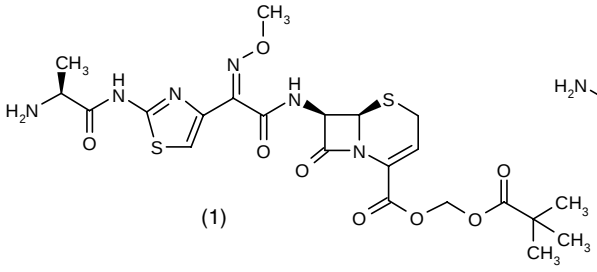
Pharmacological Actions

In vitro *activity*

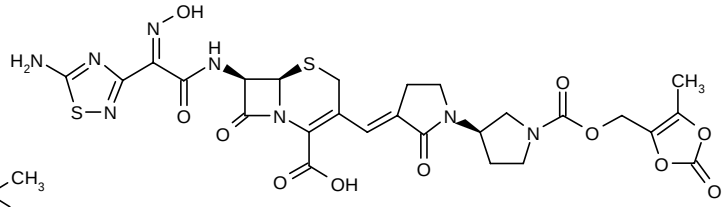
The *in vitro* activity of ceftobiprole was evaluated against several Gram-positive and Gram-negative pathogens and its activity compared to that of cefotaxime, cefepime, meropenem and ciprofloxacin. Ceftobiprole was shown to bind to essential PBPs, including PBP 2' present in *Staphylococcus epidermidis* (IC_{50} = 0.87 μM),

Table I: Cephalosporins under active development.

Drug name	Phase	Company
1. Ceftizoxime alapivoxil	Preregistered	Asahi Kasei
2. Ceftobiprole medocaril	Phase III	Basilea Pharmaceutica
3. DA-7101*	Phase II	Dong-A
4. RWJ-54428	Phase I	Essential Therapeutics/R.W. Johnson
5. TAK-599/PPI-0903	Phase I	Peninsula Pharmaceuticals
6. LB-11058	Preclinical	LG Chem
7. RWJ-442831	Preclinical	Essential Therapeutics/R.W. Johnson



(1)



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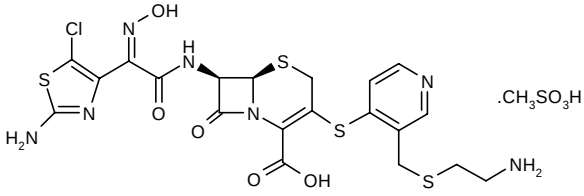
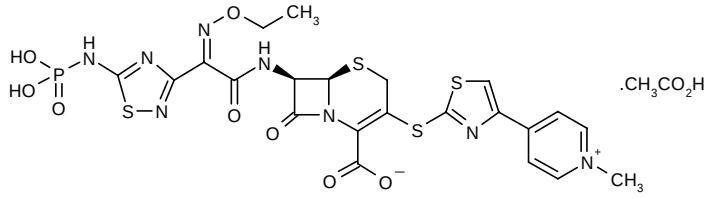


(4)



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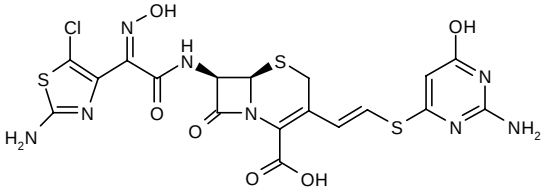
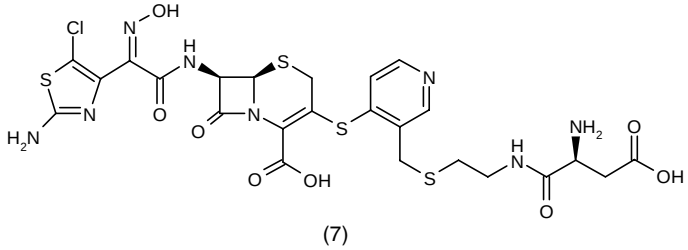


(6)



(7)

*Structure not yet detected

PBP 2x present in *S. pneumoniae* (IC_{50} = 0.27 μM) and PBP 1b in *Citrobacter freundii* (IC_{50} = 0.16 μM); however, ceftobiprole had low binding affinity for PBP 5 present in *Enterococcus faecium*. It was also shown to be stable toward β-lactamases. Ceftobiprole exhibited potent antibacterial activity against most Gram-positive bacteria tested, with the exception of ampicillin-resistant enterococci (particularly vancomycin-resistant *E. faecium*). The MIC_{90} obtained for the agent against 77 strains of MRSA was 4 μg/ml, as compared to > 64, > 32, > 32 and > 8 μg/ml, respectively, for cefotaxime, cefepime, meropenem and ciprofloxacin. Ceftobiprole exerted bactericidal activity against the MRSA strains. Development of resistance to ceftobiporole in MRSA was not seen. The agent was also more active than cefotaxime against penicillin-resistant *S. pneumoniae* (MIC_{90} = 2 μg/ml *vs.* 4 μg/ml for 20 strains). Activity was observed against ceftazidime-susceptible strains of *Pseudomonas aeruginosa* (MIC_{90} = 16 μg/ml for 60 strains) and Enterobacteriaceae, with the exception of *Proteus vulgaris* and some isolates producing extended-spectrum β-lactamases (ESBLs). Results obtained *in vitro* were confirmed *in vivo*. The antibiotic was very effective against septicemia in mice caused by methicillin-susceptible *S. aureus* (MSSA), MRSA, *Streptococcus pyogenes*, *S. pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, *C. freundii*, *Serratia*

marcescens and *Proteus mirabilis*. The agent was even active against septicemia caused by a penicillin-resistant strain of *S. pneumoniae* (23 F-CTR) that showed reduced susceptibility *in vitro* (MIC = 4 and 8 μg/ml for ceftriaxone and cefotaxime, respectively, *vs.* 1 μg/ml for ceftobiprole) and *in vivo* (ED_{50} = 8.8 and > 12 mg/kg, respectively, *vs.* 1 mg/kg s.c.) to third-generation cephalosporins. In addition, ceftobiprole (10 mg/kg i.p.) was more bactericidal than vancomycin (10 mg/kg i.p.) and linezolid (20 mg/kg i.p.) against a vancomycin-susceptible strain of *S. aureus* in *in vivo* experiments using a mouse model of subcutaneous abscesses (15).

Other *in vitro* studies examined the activity of ceftobiprole against 2,263 isolates, including 1,097 Gram-positive strains. The MIC_{90} (mg/l)/percent susceptibility values obtained were 0.5/100% for MSSA, 2/100% for MRSA, 0.25/100% for methicillin-susceptible coagulase-negative staphylococci (CoNS), 2/100% for methicillin-resistant CoNS (MR-CoNS), 0.25/100% for *S. pneumoniae*, 0.5/99% for viridans group streptococci, 0.015 or less/100% for β-hemolytic streptococci, 16/90% for *Enterococcus faecalis*, > 32/22% for *E. faecium*, 0.06/100% for *Haemophilus influenzae*, 0.05/100% for *Moraxella catarrhalis*, 0.06/100% for *Neisseria gonorrhoeae* and 0.004/100% for *Neisseria meningitidis*. The susceptibility of MRSA and MR-CoNS to ceftobiprole at 4 mg/l or less was superior to ceftriaxone and quinupristin/dalfopristin. At concentrations of 1 mg/l or less, 100% of *S. pneumoniae* were inhibited by ceftobiprole as compared to 90% and 98% with ceftriaxone and levofloxacin, respectively. Ceftobiprole exhibited potent activity against most wild-type enteric bacilli, but was only moderately active against nonfermentative Gram-negative strains and ESBL-producing *E. coli* or *K. pneumoniae* (16).

A study examined the activity of ceftobiprole *in vitro* against staphylococcal isolates selected to contain resistance mechanisms. Of the 53 stains for which MBCs were determined, 52 had an MBC/MIC ratio of 2 or less. Ceftobiprole was active against all strains (MIC_{90} = 1-2 μg/ml), including oxacillin-, linezolid-, quinupristin/dalfopristin- and vancomycin-resistant strains (MIC = 4 μg/ml or less) (17, 18).

The antistaphylococcal activity of ceftobiprole was compared *in vitro* to several other antibiotics against 126 MRSA and 151 CoNS. Ceftobiprole was active against all strains (MIC = 4 μg/ml or less), including vancomycin-intermediate and -resistant *S. aureus* (VISA and VRSA, respectively) and vancomycin-intermediate CoNS strains (MIC = 0.5-2 μg/ml). Linezolid, quinupristin/dalfopristin and daptomycin were also active against all strains (19).

Ceftobiprole was active against a VRSA strain (HMC3) containing genes conferring resistance to vancomycin, β-lactams, macrolides, tetracycline and aminoglycosides (*vanA*, *mecA*, *erm*(A), *erm*(B), *tet*(K), *aac*(6')-*aph*(2''), respectively); the strain also had alterations in GyrA and GrlB and was resistant to quinolones. Ceftobiprole was bactericidal against this strain with an MIC of < 2 mg/l (20).

The ability of ceftobiprole to select resistant mutations was examined in a study using 2 strains of MSSA, 3 strains of MRSA (2 VRSA and 1 VISA) and 2 and 3 strains of methicillin-susceptible and MR-CoNS, respectively. The agent was active against all strains (MIC = 0.25-2 μg/ml initially, 1-8 μg/ml after 50 days) and did not induce the development of endogenous resistance. In addition, clones with MICs > 4 times that of the parent were not selected for (21). Ceftobiprole was also shown to have a low liability to cause emergence of resistance in another study using MRSA strains 745 and $P8^{+}$-Hom and a methicillin-resistant *S. epidermidis* strain (22).

Ceftobiprole displayed potent antipneumococcal activity in several studies. In experiments comparing its activity with amoxicillin, imipenem, ertapenem, cefepime, ceftriaxone, cefotaxime, cefuroxime, cefdinir and other antimicrobials against 299 penicillin-susceptible, -intermediate and -resistant, macrolide-resistant and quinolone-resistant *S. pneumoniae* strains, ceftobiprole had the lowest MICs of all the class IV cephalosporins tested ($MIC_{50/90}$ = 0.016/0.016, 0.06/0.5, 0.5/1, 0.5/1 and 0.5/1 μg/ml for the respective strains). Ceftobiprole also displayed good bactericidal activity against pneumococci (23, 24). Moreover, ceftobiprole was shown to have a low risk of selecting for resistant clones in a study examining the activity of the agent against 10 pneumococcal strains (25).

Ceftobiprole is also active against other pathogens, including Gram-negative bacteria. The MICs and MBCs of ceftobiprole were determined against 150 Gram-negative bacteria and compared to other agents. Similar activity was observed for ceftobiprole, cefepime and ceftriaxone against *H. influenzae*, *K. pneumoniae* and ESBL-negative *Enterobacter cloacae* ($MIC_{50/90}$ = 0.125 μg/ml or less). All 3 agents were inactive against ESBL-positive *K. pneumoniae* ($MIC_{50/90}$ = 64/128 μg/ml for ceftobiprole and > 128/> 128 μg/ml for ceftriaxone and cefepime). Ceftobiprole and cefepime were similarly active against *P. aeruginosa* ($MIC_{50/90}$ = 2/8 μg/ml) (26).

The MIC_{50}s obtained for ceftobiprole against *Actinomyces* spp., *Clostridium* spp., Gram-positive anaerobic cocci, *Porphyromonas* spp., *Fusobacterium* spp., *Lactobacillus* spp., *Prevotella* spp. and *Veillonella* spp. were 1 mg/l or less. Ceftobiprole had an MIC_{50} of 16 mg/l for *Bacteroides fragilis* and other *Bacteroides* spp., but it was not active against cefoxitin-resistant *B. fragilis* (27).

Another study determined the activity of ceftobiprole against 57 strains of β-lactamase-producing Gram-negative bacteria, including *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *Klebsiella oxytoca*, *P. mirabilis* and *Aeromonas hydrophila*. The MICs for ceftobiprole against strains producing group 1 (CMY-2, CMY-7, DHA-1, FOX-1, FOX-2, LAT-1), 2b (HMS-1, LXA-1, SHV-1, TEM-1, TEM-2, TEM-90) and 2br (TEM-30-TEM-36) β-lactamases ranged from 0.06 to 2 mg/l. In contrast, the MIC range for LAT-2-producing *K. pneumoniae* (strain N10) was 32 mg/l and inconsistent activity was observed for ESBL-producing (group 2be β-lactamases) *E. coli*, *Klebsiella* and *P. mirabilis* (28). Against a range of ceftazidime-susceptible and -resistant *P. aeruginosa* clinical isolates, the antibiotic exhibited activity generally comparable to cefepime

and aztreonam, with $MIC_{50/90}$ values of 8/16 mg/l against ceftazidime-susceptible isolates and of 16/64 mg/l against ceftazidime-resistant isolates (29).

Ceftobiprole was reported to have species-dependent activity against Gram-negative nonfermenters in a study testing 244 strains, including *Achromobacter* spp., *Acinetobacter* spp., *Bordetella bronchiseptica*, *Burkholderia cepacia*, *Moraxella* spp., *Ochrobactrum anthropi*, *Oligella ureolytica*, *Pseudomonas* spp., *Ralstonia pickettii*, *Sphingomonas* spp. and *Weeksella virosa*, among others. The overall MIC_{50} and MIC_{90} values for the agent were 2 and 64 μg/ml, respectively. These values were comparable to those obtained for imipenem but lower than those observed for ciprofloxacin (30).

The bactericidal activity and synergistic action of ceftobiprole with gentamicin were examined using several strains of streptococci, enterococci and MRSA. Ceftobiprole was bactericidal against all streptococci and staphylococci and against some ampicillin-susceptible enterococci. No activity was seen, however, against ampicillin-resistant *E. faecium*. The agent was bactericidal against *E. faecalis* and some strains of *E. faecium* (–4.8 to –6.0 $\log_{10}$ CFU/ml). Gentamicin slightly enhanced but was not synergistic with, or had no effect on the activity of ceftobiprole against staphylococci. Early synergy at 4-8 h and indifference or synergy at 24 h were noted with gentamicin for all enterococci, including some VRE (31).

In vivo *activity*

Ceftobiprole medocaril was effective in the tissue cage rat model of chronic foreign body MRSA (MRGR3, isolated from catheter-related sepsis) infection; MIC/MBC values for ceftobiprole and vancomycin obtained *in vitro* were 1/4 and 1/2 μg/ml, respectively. Treatment of infected rats with ceftobiprole medocaril (equivalent to ceftobiprole 150 mg/kg i.p. b.i.d.) for 7 days significantly decreased tissue cage counts of viable MRGR3 by 0.68 ± 0.28 $\log_{10}$ CFU/ml as compared to untreated animals; treatment with vancomycin (50 mg/kg i.p.) decreased viable counts by 0.88 ± 0.22 $\log_{10}$ CFU/ml, which was not significantly different from values obtained for ceftobiprole medocaril-treated rats. No resistant colonies were observed (32).

Ceftobiprole medocaril (equivalent to ceftobiprole 2.1-78 mg/kg/day by s.c. injection starting 3 h postinoculation) was also effective in a leukopenic mouse model of acute pneumococcal pneumonia using the following clinical *S. pneumoniae* isolates: penicillin-, cefotaxime- and ceftriaxone-susceptible P-52181, penicillin-resistant, cefotaxime- and ceftriaxone-susceptible P-15986, and penicillin-, cefotaxime- and ceftriaxone-resistant P-40422 and P-40984. Survival rates at 10 days for ceftobiprole medocaril- and ceftriaxone (10-400 mg/kg/day)-treated mice ranged from 57 to 100% and from 13 to 100%, respectively, whereas all control mice died within 5 days of infection. Survival rates for mice infected with P-15986 and treated with ceftobiprole medocaril were significantly higher than in those treated with ceftriaxone (93% *vs.* 13%). No significant differences were noted in survival rates between mice infected with the other strains and treated with ceftobiprole medocaril or ceftriaxone, although markedly lower doses of the former agent provided comparable rates (33).

Ceftobiprole medocaril was as effective as cefepime and ceftriaxone in mouse models of pneumonia. Mice were infected with *H. influenzae*, *E. cloacae* or ESBL-negative or -positive *K. pneumoniae* and treated with ceftobiprole medocaril (71 mg/kg s.c. q.i.d.), cefepime (50 mg/kg i.p. q.i.d.) or ceftriaxone (50 mg/kg i.m. b.i.d.). All 3 antibiotics produced a significant reduction in viable counts for all strains except ESBL-positive *K. pneumoniae*, for which no effect was observed for any agent (34).

The efficacy of ceftobiprole was further demonstrated in a rat model of experimental endocarditis due to MRSA (COL Bla^+ and P8-Hom strains) and a rabbit model of aortic valve endocarditis due to MRSA (strain 76) or VISA (strain New Jersey [NJ]). Rats were administered ceftobiprole medocaril for 3 days starting 12 h after inoculation and were given a continuous infusion to achieve steady-state target serum levels of 5, 10 and 20 mg/l (72, 144 and 288 mg/kg every 24 h, respectively). Ceftobiprole medocaril was effective against both strains and eradicated more than 90% of cardiac vegetations, being significantly superior to amoxicillin/clavulanate (5/1; 1.2 g i.v. every 6 h) or vancomycin (1 g i.v. every 12 h). Similar efficacy was observed in rabbits treated with ceftobiprole medocaril (25 mg/kg t.i.d. for 4 days), where treatment significantly decreased vegetations of both strains as compared to controls (1.69 ± 2.36 $\log_{10}$ CFU/g *vs.* 6.84 ± 0.39 $\log_{10}$ CFU/g for MRSA, and 1.17 ± 1.65 $\log_{10}$ CFU/g *vs.* 6.83 ± 0.39 $\log_{10}$ CFU/g for VISA). Vancomycin (30 mg/kg i.v. b.i.d.) was only effective in animals infected with MSRA. The mortality rate for MRSA-infected animals was 50% for both ceftobiprole medocaril and vancomycin groups. In contrast, the mortality rates for VISA-infected animals treated with ceftobiprole medocaril and vancomycin were 8% and 67%, respectively. There was no emergence of ceftobiprole-resistant populations (35, 36).

Pharmacokinetics

The safety and pharmacokinetics of ceftobiprole were examined following administration of ceftobiprole medocaril as a single dose (ceftobiprole equivalents: 125, 250, 500, 750 and 1000 mg as a 200-ml infusion over 30 min) or multiple doses (ceftobiprole equivalents: 500 or 700 mg as a 200-ml infusion over 30 min once daily on days 1 and 8 and twice daily on days 2 and 7); the 2 studies involved 40 and 16 healthy male subjects, respectively. The antibiotic was well tolerated at all doses. No serious adverse events or significant trends or changes in laboratory parameters, vital signs or ECGs were observed. Taste disturbances, transient nausea and headache were the most frequent adverse events experienced. C_{max} and AUC values were dose-proportional over the dose range examined and the elimination half-life was approximately

3 h. The volume of distribution at steady sate (V_{ss}) and the volume of the adult extracellular water compartment were similar. Drug accumulation was negligible in the multiple-dose study. Free ceftobiprole was mainly eliminated in urine (> 70%). Renal clearance of the free agent corresponded to the normal adult glomerular filtration rate. Following infusion of 750 mg, mean plasma concentrations of ceftobiprole exceeded the MIC at which 100% of MRSA isolates are inhibited (4 μg/ml) for about 7-9 h in both studies, which corresponded to 58% and 75% of a 12-h dosing interval. Together, these results suggest that infusions of 750 mg b.i.d. would be optimal for the treatment of MRSA infections (37, 38).

A study comparing the pharmacokinetics of ceftobiprole following administration of a single dose of ceftobiprole medocaril (ceftobiprole equivalent: 750 mg as a constant 30-min infusion) in 12 male and 12 female subjects showed that gender influences the pharmacokinetics of the agent. Plasma C_{max} and AUC values in males and females following the infusion were 65.6 and 79.3 μg/ml and 137 and 157 μg·h/ml, respectively. The elimination half-life values and total systemic clearance in males and females were 3.4 and 2.8 h and 5.5 and 4.9 l/h, respectively, and a significant difference was found between V_{ss} in males and females (17 and 12 l, respectively). However, if clearance and V_{ss} were corrected for body weight and C_{max} and AUC values normalized to doses of 1 mg/kg body weight, no significant gender differences were observed in V_{ss} and C_{max}. Approximately 92% and 96% of the free drug was recovered in urine in males and females, respectively. It was concluded that although systemic exposure to ceftobiprole was about 15% higher in females, this difference was related to lower body weight and thus an inferior V_{ss} in females. The differences were not considered to be clinically significant and therefore no dose adjustments were recommended for female subjects (39).

A study in 20 healthy male subjects with normal renal function and mild, moderate or severe renal impairment (creatinine clearance: > 80, 51-80, 31-50 and < 30 ml/min, respectively) administered a single i.v. dose of ceftobiprole medocaril (ceftobiprole equivalent: 250 mg infused over 30 min) indicated that dose adjustments were required in subjects with renal dysfunction based on creatinine clearance. A correlation was found between creatinine clearance and systemic drug clearance. The renal state of the subject influenced clearance, elimination half-life and urinary excretion of the free drug. Based on an MIC value of 4 μg/ml as a target systemic exposure for at least 6 h, the dose adjustments suggested according to creatinine clearance were 750 mg b.i.d., 500 mg b.i.d. and 250 mg once daily, respectively, for subjects with mild, moderate and severe renal impairment (40).

The pharmacokinetics of ceftobiprole were reported from a study conducted in 20 patients with Gram-positive (including MRSA) complicated skin and skin structure infections administered ceftobiprole medocaril (ceftobiprole equivalent: 750 mg as a 30-min infusion b.i.d. for at least 7 days). Drug accumulation was negligible since plasma ceftobiprole concentrations were comparable on days 2 and 7. The mean C_{max} value at steady state on day 7 was 64.4 ± 31.9 μg/ml, which was similar to values obtained in other studies in heathy volunteers (60.6 ± 9.99 μg/ml); an AUC value of 136 ± 34 μg·h/ml was obtained in patients with infections, which was also similar to values reported for healthy subjects. The mean plasma concentration of ceftobiprole at 10 h after the start of infusion (80% of the 12-h dosing period) was 2.31 ± 1.31 μg/ml. A low inter- and intrasubject variability of 30% was seen, which was comparable to variability in healthy subjects (41).

In order to select a dosing schedule for phase II trials, pharmacokinetic data from 12 subjects participating in a multiple-dose phase I trial and administered ceftobiprole medocaril (ceftobiprole equivalents: 500 and 750 mg b.i.d. as a 30-min infusion for 8 days) were used to predict target attainment rates for various time periods during which the concentration remains above the MIC. A 2-compartment model best fit the phase I pharmacokinetic data. Using Monte Carlo simulations together with *in vitro* MIC data reported for ceftobiprole, it was concluded that a dosing schedule of 750 mg b.i.d. would be appropriate (42).

Clinical Studies

A phase II study in 40 patients with complicated skin and skin structure infections examined the efficacy and safety of ceftobiprole medocaril (750 mg b.i.d. by 30-min infusion for 7-14 days, with prolongation up to 21 days). The majority of infections were caused by streptococci and staphylococci, including 4 patients with MRSA infections. Treatment was well tolerated. Of the 40 patients in the intent-to-treat population, 35 were clinically evaluable and all were cured; 28 of these patients had pathogens isolated from baseline cultures and 23 were microbiologically evaluable, with 21 reported as eradication, presumed eradication or colonization (without signs or symptoms of infection). Of the 15 and 4 patients with MSSA and MRSA infections, respectively, none failed treatment and 12 and 4 were cured, respectively; 3 and 0 of these patients, respectively, were unevaluable. Of the 6 patients with infections due to streptococci (*Streptococcus constellatus*, *Streptococcus intermedius*, *Streptococcus equisimilis*, *S. pyogenes*), 5 were cured and 1 was unevaluable. Each of the single patients with infections caused by *Staphylococcus schleiferi*, *Staphylococcus lugdunensis* and *C. freundii* were cured. All baseline pathogens were susceptible to ceftobiprole and no increase in MIC was observed during treatment. These pathogens included: MSSA (n=53; MIC = 0.125-1 μg/ml), MRSA (n=21; MIC = 0.5-2 μg/ml), CoNS (n=24; MIC = 0.0625-2 μg/ml), *S. intermedius* (n=4; MIC = 0.0625-0.125 μg/ml), *S. pyogenes* (n=2; MIC = 0.0080 μg/ml or less), *S. equisimilis* (n=2; MIC = 0.0080 μg/ml or less), *S. constellatus* (n=1; MIC = 0.125 μg/ml), *Acinetobacter* spp. (n=3; MIC = 0.25-0.5 μg/ml), *E. faecalis* (n=2; MIC = 0.25 μg/ml), *B. cepacia* (n=2; MIC = 2 μg/ml), *E. cloacae* (n=1; MIC = 0.125

μg/ml), *K. oxytoca* (n=1; MIC = 0.125 μg/ml), *P. vulgaris* (n=1; MIC > 16 μg/ml) and *Providencia rettgeri* (n=1; MIC > 16 μg/ml) (43).

A multicenter, randomized, controlled phase III trial has been initiated to determine the efficacy and safety of ceftobiprole medocaril as compared to vancomycin in approximately 700 patients with complicated skin and skin structure infections. The primary efficacy endpoint for the STRAUSS (Study of Ceftobiprole in Resistant *Staphylococcus aureus* Skin and Skin Structure Infections) study is clinical outcome at the test-of-cure visit between 7 and 14 days after the end of treatment. Other studies in patients with severe infections are also planned (44).

Ceftobiprole medocaril was granted fast track designation by the FDA for the treatment of complicated skin and skin structure infections due to MRSA and for the treatment of hospital-acquired pneumonia, including ventilator-associated pneumonia due to suspected or proven MRSA (44).

Basilea gained the global manufacturing and marketing rights to the antibiotic last year when Roche decided not to exercise its opt-in right to ceftobiprole (45).

Source

Basilea Pharmaceutica AG (CH); licensed from F. Hoffmann La Roche AG (CH).

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