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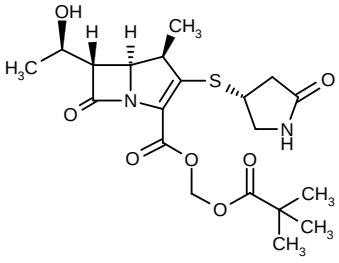
CCC: 0377-8282/98

CS-834

Carbapenem

(1*R*,5*S*,6*S*)-6-[1(*R*)-Hydroxyethyl]-1-methyl-2-[2-oxopyrrolidin-4(*R*)-ylsulfanyl]-1-dethia-1-carba-2-penem-3-carboxylic acid pivaloyloxymethyl ester



$C_{20}H_{28}N_2O_7S$ Mol wt: 440.51

CAS: 157542-49-9
CAS: 193811-33-5 (as free acid)
CAS: 129172-46-9 (as Na salt)
CAS: 179091-43-1 (as free acid monohydrate)

EN: 233813

Synthesis

CS-834 has been obtained by two different ways:

1) The mesylation of 4(*S*)-hydroxypyrrolidin-2-one (I) with mesyl chloride and triethylamine in pyridine gives the corresponding ester (II), which is treated with potassium thioacetate (III) in refluxing acetonitrile yielding 4(*R*)-(acetylsulfanyl)pyrrolidin-2-one (IV). The hydrolysis of (IV) with sodium methoxide in methanol followed by acidification with aqueous HCl affords 4(*R*)-sulfanylpyrrolidin-2-one (V), which is condensed with (1*R*,5*S*,6*S*)-2-(diphenoxyphosphoryloxy)-6-[1(*R*)-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-nitrobenzyl ester (VI) by means of ethyldiisopropylamine in acetonitrile to give (1*R*,5*S*,6*S*)-6-[1(*R*)-hydroxyethyl]-1-methyl-2-[5-oxopyrrolidin-3(*R*)-ylsulfanyl]-1-carba-2-penem-3-carboxylic acid *p*-nitrobenzyl ester (VII). The hydrogenolysis of (VII) with H_2 over Pd/C in THF/aqueous phosphate buffer yields the sodium salt (VIII), which is finally esterified with pivaloyloxymethyl iodide (IX) in dimethylacetamide (1-4). Scheme 1.

2) The esterification of 2(*R*)-[4-oxo-3(*S*)-[1(*R*)-(trimethylsilyloxy)ethyl]azetidin-2(*S*)-yl]propionic acid (X) with the already obtained pyrrolidinone (V) gives the expected thiopropionic ester (XI), which is acylated with oxalic acid monochloride monopivaloyloxymethyl ester (XII) by means of trimethylsilylchloride and triethylamine yielding the condensation product (XIII). The cyclization of (XIII) by means of methylphosphonic acid diethyl ester affords silylated CS-834 (XIV), which is finally deprotected with 1N HCl (2, 5). Scheme 2.

Description

Crystals, m.p. 189 C (1).

Introduction

Carbapenems are a class of β-lactam antibiotics with a broad spectrum of antimicrobial activity and bactericidal activity against both Gram-positive and Gram-negative strains. They are also extremely stable to hydrolysis by β-lactamases. Most carbapenems that have reached the market to date, however, are chemically unstable and can only be formulated for parenteral administration; thus, several laboratories are currently engaged in the search for orally active carbapenems.

As part of this search, scientists at Sankyo synthesized a novel class of 1β-methylcarbapenem derivatives (6) and found that compounds in this series possessed potent and balanced antibacterial activity and good stability to dehydropeptidase-I. The compounds were subjected to a prodrug approach in order to maximize their oral absorbability, and were then evaluated in terms of *in vitro* and *in vivo* antibacterial activity and pharmacokinetics. The most promising compound in this series, the pivaloyloxymethyl ester CS-834, was selected as a candidate for further development (1, 2).

Pharmacological Actions

CS-834 is an ester-type prodrug carbapenem antibiotic with a broad spectrum of potent activity, including resistant strains of bacteria against which previously described oral cephalosporins were found to be inactive (1). It acts as a prodrug of the sodium salt R-83201 [I] (2), and exerts it effects *in vivo* through conversion to the active metabolite (free acid) R-95867 [II].

CS-834 has been tested against a wide range of clinically isolated bacteria. Using agar dilution methods, the

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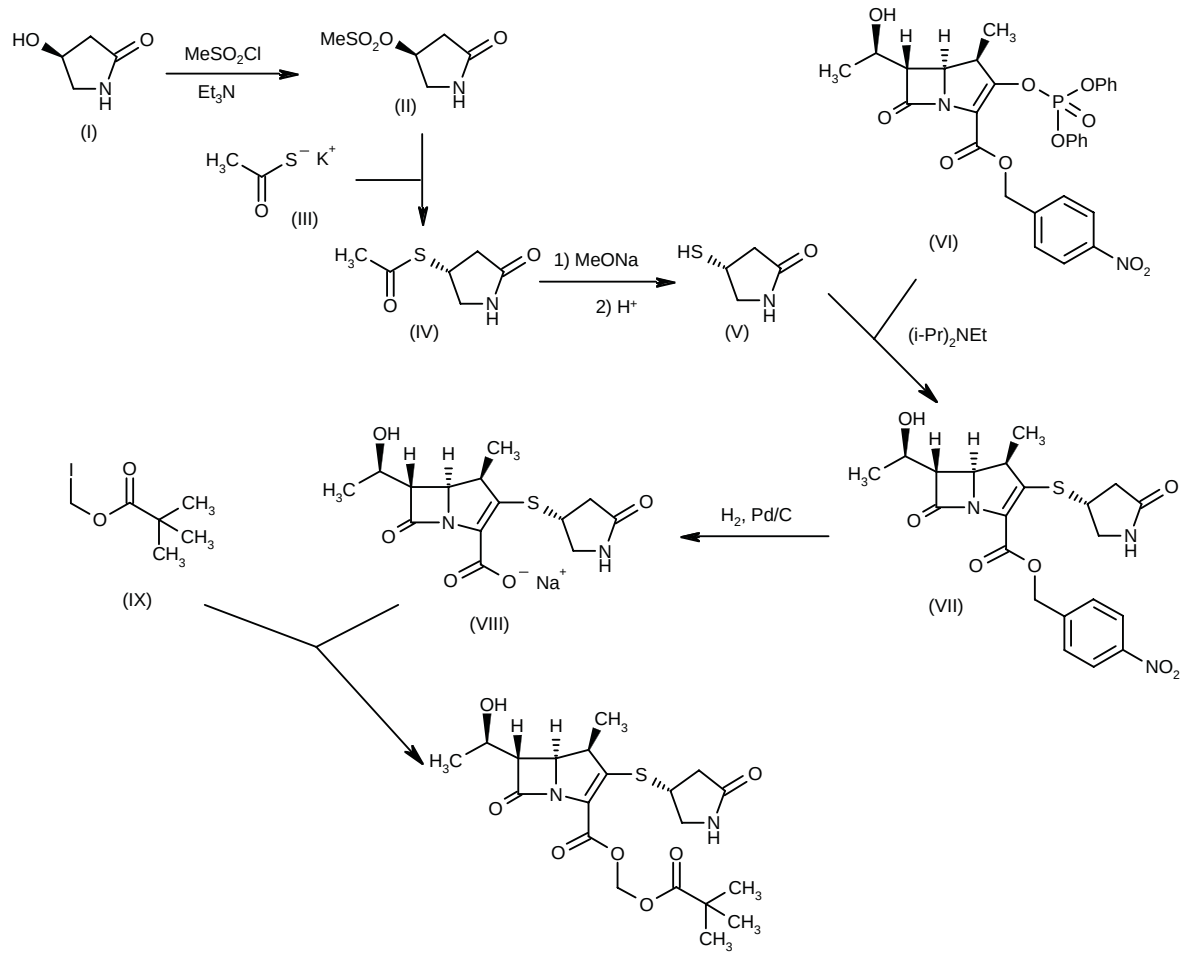
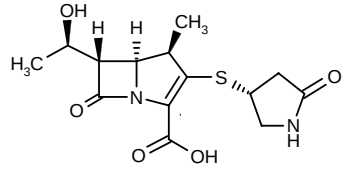
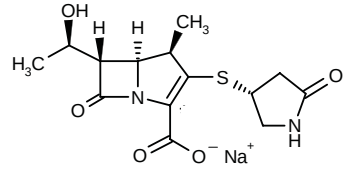
Scheme 1: Synthesis of CS-834





[I]

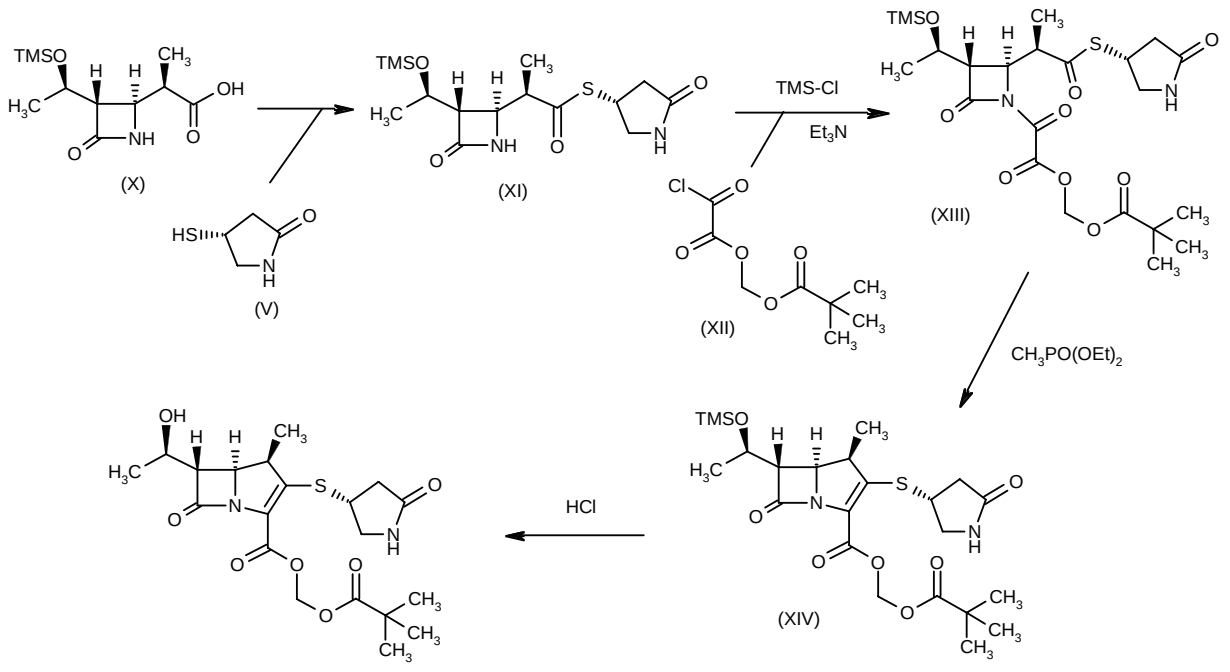


[II]

activity of the free acid R-95867 (MIC_{90} = 0.2 μg/ml) was superior to those of cefdinir, cefpodoxime and cefditoren (MIC_{90} = 0.39, 3.13 and 0.78 μg/ml, respectively) against methicillin-sensitive *Staphylococcus aureus* (MSSA). Like the reference β-lactams, R-95867 was ineffective against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) (7).

In another battery of *in vitro* tests, R-95867 gave mean MIC_{90} values of 32, ≤ 0.03, 0.06, 0.125, 0.5, 64 and 16 μg/ml against MRSA (26 isolates), *Escherichia coli* (12), *Salmonella* spp., *Klebsiella oxytoca* (25), *Enterobacter cloacae* (33), *Citrobacter freundii* (24) and *Serratia marcescens* (32), respectively. It was not active against *Pseudomonas aeruginosa*. Its activity was also evaluated against β-lactamase-producing strains of *E. coli* and *K. pneumoniae*. R-95867 was active against class A and C enzyme producers, including extended-spectrum β-lactamases; however, it was less active against class B and MOX-1-type class C enzyme-produc-

Scheme 2: Synthesis of CS-834



ing organisms (8). R-95867 exhibited a postantibiotic effect against both Gram-positive and Gram-negative organisms, in contrast to reference oral cephalosporins (cefteram, cefpodoxime, cefdinir and cefditoren), which had no such effect against Gram-negative bacteria (9).

In a test involving a variety of Gram-positive and Gram-negative anaerobic bacteria, most of the 63 strains tested were inhibited by R-95867 at a concentration of 0.5 μg/ml. The compound was stable to type-2e β-lactamases derived from *Bacteroides fragilis*, *Prevotella bivia* and *Prevotella intermedia*, but not to carbapenemases from *B. fragilis* (10).

The antibacterial activity of CS-834 compared favorably to that of imipenem and other reference β-lactams against clinical strains isolated from otitis media, pneumonia and respiratory tract infections (MIC_{90} = 0.5 μg/ml against penicillin-resistant *S. pneumoniae*). Its activity was more potent than that of the reference antibiotics against β-lactamase-producing strains of *Moraxella catarrhalis* (MIC_{90} = 0.125 μg/ml). R-95867 had high affinity for penicillin-binding proteins (PBPs) 2 and 4 in *H. influenzae*, and its activity was more potent than that of imipenem against this bacterial strain (11).

R-95867 also demonstrated potent antibacterial activity *in vitro* against *Helicobacter pylori*, with more potent effects than amoxicillin, clarithromycin or lansoprazole (MIC_{90} = 0.012, 0.10, 0.025 and 0.78 μg/ml, respectively) (12).

The prophylactic efficacy of CS-834 was demonstrated in mice with systemic infections produced by *S. aureus* Smith (ED_{50} = 0.018 mg), type III *S. pneumoniae* (ED_{50} = 0.16 mg), *S. pyogenes* C-203 (ED_{50} = 0.012 mg), *E. coli* KC-14 (ED_{50} = 0.067 mg) and *K. pneumoniae* KC-1 (ED_{50} = 0.28 mg). In most cases, its activity was superior to that of cefpodoxime proxetil, cefdinir, cefditoren pivoxil and/or levofloxacin (12).

In vivo in mice with systemic infections caused by 16 Gram-positive or Gram-negative pathogens, CS-834 was at least as active as, and in many cases more potent than, cefteram pivoxil, cefpodoxime proxetil, cefdinir and cefditoren pivoxil. This was especially true in the case of infections caused by *S. pneumoniae*, *E. coli*, *C. freundii* or *Proteus vulgaris* (13). The activity of CS-834 was also excellent in mice with pneumonia produced by penicillin-resistant *S. pneumoniae* (13, 14).

The activity of CS-834 was superior to that of all reference compounds except for cefditoren pivoxil in mice with *H. influenzae* respiratory infections, reflecting the high concentration of the active compound in the lungs. It was active against penicillinase-producing as well as penicillinase-nonproducing *H. influenzae*. Furthermore, the efficacy of CS-834 in murine models of respiratory tract infection was enhanced by its combination with cilastatin, and this combined effect was most pronounced with a dosing regimen of 3 times daily (14).

The antibacterial activity of CS-834 was compared to that of several fluoroquinolones (levofloxacin, ofloxacin, lomefloxacin, fleroxacin, ciprofloxacin, sparfloxacin and tosufloxacin) *in vitro* and *in vivo* in murine models of pneumonia. The therapeutic activity of title compound

was comparable to that of tosufloxacin and sparfloxacin and was superior to that of the other fluoroquinolones in mice infected with penicillin-susceptible and penicillin-resistant *S. penumoniae*. It also compared favorably to the fluoroquinolones in mice with experimental urinary tract infections and subcutaneous infections (15).

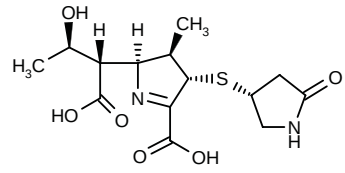
In a murine model of subcutaneous infection with *S. aureus*, CS-834 was more effective than cefteram pivoxil, cefpodoxime proxetil, cefdinir and cefditoren pivoxil in reducing viable cell counts in the skin when administered at a dose of 10 mg/kg x 4 or 50 mg/kg x 4. It also outperformed the same reference cephalosporins in several murine models of urinary tract infection caused by *E. coli*, *S. marcescens*, *K. pneumoniae* or *P. mirabilis* (16).

Excellent activity was obtained with CS-834 in the treatment of mice infected with a penicillin-resistant strain of *Streptococcus pneumoniae*. The compound was administered twice daily at doses of 0.4, 2 or 10 mg/kg for 2 days beginning 24 h after bacterial inoculation. The activity of CS-834 was better than any other cephem tested in this model (cefteram pivoxil, cefpodoxime proxetil, cefdinir and cefditoren pivoxil), and was also superior in cases of infection with penicillin-sensitive strains of *S. pneumoniae*. At all 3 doses, CS-834 significantly decreased the number of viable cells in lungs and blood, with maximum decreases obtained at doses of 10 and 50 mg/kg p.o. These results indicate the therapeutic potential of CS-834 in the treatment of *S. pneumoniae* infections (17).

Pharmacokinetics and Metabolism

During early studies of CS-834 which led to the selection of this compound for development, its pharmacokinetics were evaluated in dogs. The compound was found to have a C_{max} of 6.1 μg/ml and a $t_{1/2}$ of 0.90 h following oral administration as the sodium salt R-83201 at a dose of 10 mg/kg. The absolute bioavailability of CS-834 (10 mg/kg p.o.) in dogs was 50%, and urinary recovery following oral administration to mice was 46% (1, 2).

In another study in various animal species, the safety, pharmacokinetics and metabolism of CS-834 were evaluated. Compound was administered as single oral or i.v. doses of R-83201, the sodium salt of the parent acid. Plasma concentrations of R-83201 peaked at 45 min to 2 h after dosing in mice, rats, rabbits, dogs and monkeys. Elimination half-life was species-dependent, ranging from 0.61 h in rats to 1.05 h in monkeys. The absorption ratio, calculated as $AUC_{(p.o.)}/AUC_{(i.v.)}$ x 100, ranged from 26.8% in rats to 62.0% in mice. In dogs, the relationship between dose and AUC was linear up to 10 and 100 mg/kg, respectively, for i.v. and p.o. dosing. Serum protein binding was less than 20% in all laboratory species. Following dosing of CS-834 to rats and dogs, the principal metabolites in plasma and urine were R-83201 and R-99861 [III], the β-lactam-opened form of the latter. No renal toxicity was observed in rabbits administered single doses of R-83201 up to 400 mg/kg i.v., nor were any toxicological



[II]

changes observed in rats given repeated oral doses of up to 1000 mg/kg/day for 4 weeks (18).

Clinical Studies

Based on the favorable activity of CS-834 in preclinical models, and especially on the basis of its excellent activity against penicillin-resistant *S. pneumonia*, which has become a serious clinical problem in many countries in recent years, this compound was advanced to clinical testing (17).

In a pilot clinical trial enrolling healthy male volunteers, the safety and pharmacokinetics of single (50, 100, 200 or 400 mg) and multiple (150 mg t.i.d. x 7 days) oral doses of CS-834 were evaluated. Plasma concentrations of R-95867 peaked at 1.1-1.7 h after dosing of CS-834 in a fasting state, and declined thereafter in a monoexponential fashion. Maximum concentrations (C_{max}) of R-95867 in serum were 0.51, 0.97, 1.59 and 2.51 μg/ml, respectively, following administration of CS-834 at doses of 50, 100, 200 and 400 mg. Title compound was orally well absorbed and converted readily to R-95867, the active metabolite, during absorption through the intestinal wall. $T_{1/2}$ was approximately 0.7 h, and was nearly constant. AUC was dose-proportional ranging from 50-400 mg.h/ml. Thirty to 35% of the dose was recovered in urine over the 24 h following single-dose administration of CS-834. Pharmacokinetic parameters (AUC, C_{max}, $t_{1/2}$ and urinary recovery) were not affected by food intake. When title compound was coadministered with probenecid, $t_{1/2}$ was prolonged; C_{max} and AUC for R-95867 increased by 1.5-fold and 2.1-fold, respectively, upon coadministration with probenecid. Pharmacokinetic values in the multiple-dose study did not differ significantly from those in the single-dose arm, and no drug accumulation was observed. Some participants in the multiple-dose trial had mild transient soft stools, and 1 subject had elevated levels of serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase. No other abnormal laboratory findings or objective symptoms were reported, and the drug was generally well tolerated (19, 20).

CS-834 is currently in phase II evaluation in Japan and in phase I in the U.S. (21).

Manufacturer

Sankyo Co., Ltd. (JP).

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