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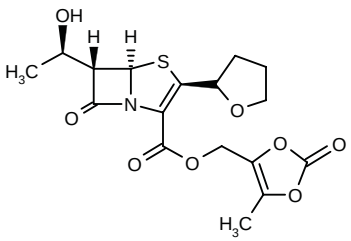
Faropenem Daloxate

Penem Antibiotic

Rec INNM

BAY-56-6854
SUN-A0026
SUN-208

(5*R*,6*S*)-6-[1(*R*)-Hydroxyethyl]-2-[2(*R*)-tetrahydrofuryl]-2-penem-3-carboxylic acid 5-methyl-2-oxo-1,3-dioxol-4-ylmethyl ester



$C_{17}H_{19}NO_8S$

Mol wt: 397.407

CAS: 141702-36-5

EN: 183599

Abstract

The penems are a class of β-lactam antibiotics which possess potent, broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria and are extremely stable to hydrolysis by β-lactamases. However, the currently available β-lactams are carbapenem antibiotics, which can only be formulated for parenteral administration, and therefore the search for potent, orally active β-lactams is ongoing. A novel β-lactam antimicrobial – the penem faropenem – has been developed and shown to have excellent activity against a wide range of bacteria, including extended-spectrum β-lactamase (ESBL)-producing strains. The prodrug, faropenem daloxate, is hydrolyzed in plasma to faropenem and was selected for clinical development in the treatment of community-acquired respiratory tract infections. This article discusses the synthesis, pharmacological actions and pharmacokinetics of this new agent.

Synthesis

Faropenem daloxate can be prepared by several related ways:

Treatment of the silylated azetidinone (I) with tritylmercaptan affords the tritylsulfanyl-azetidinone (II), which by reaction with $AgNO_3$ is converted into the silver salt (III). Compound (III) is coupled with tetrahydrofuran-2(*R*)-carbonyl chloride (IV) – obtained by treatment of carboxylic acid (V) with thionyl chloride – to provide the azetidinone thioester (VI) (1).

Alternatively, compound (VI) can be obtained by condensation of tetrahydrofuran-2(*R*)-thiocarboxylic *S*-acid (VII) – obtained by treatment of carboxylic acid (V) with hydrogen sulfide (1) – with silylated azetidinones (I) or (VIII) by means of NaOH in THF/water (2).

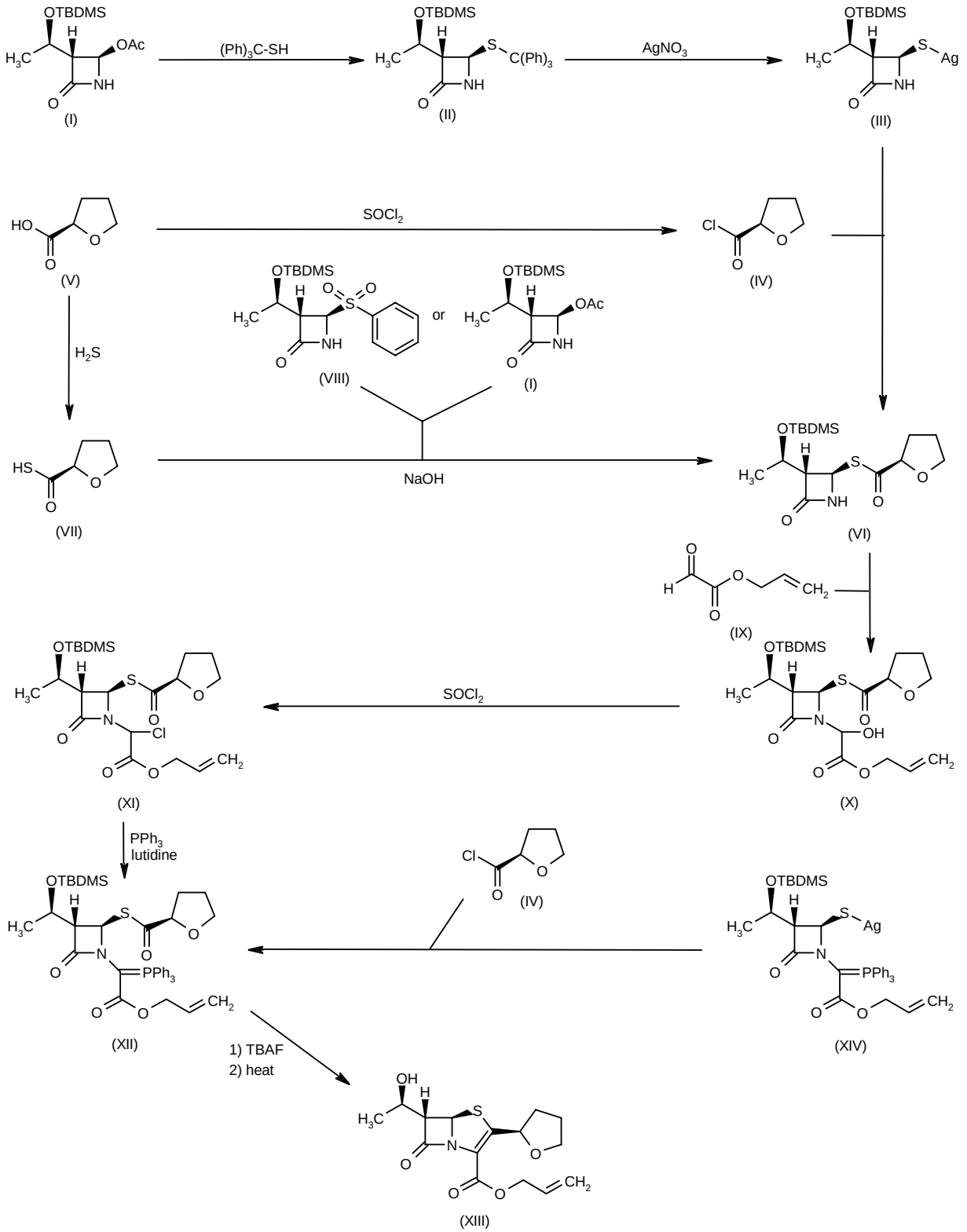
Condensation of azetidinone thioester (VI) with allyl glyoxylate (IX) in refluxing benzene gives the hydroxy ester (X), which is treated with $SOCl_2$ to yield the chloro ester (XI). Reaction of compound (XI) with triphenylphosphine and lutidine in hot THF provides the phosphoranylidene derivative (XII), which is converted into (5*R*,6*S*)-6-[1(*R*)-hydroxyethyl]-2-[2(*R*)-tetrahydrofuryl]penem-3-carboxylic acid allyl ester, faropenem allyl ester (XIII) by removal of the silyl protecting group with tetrabutylammonium fluoride, followed by cyclization in refluxing toluene (2). Scheme 1.

Compound (XII) can also be obtained by condensation of the silver salt of protected azetidinone (XIV) with tetrahydrofuran-2(*R*)-carbonyl chloride (V) (2). Scheme 1.

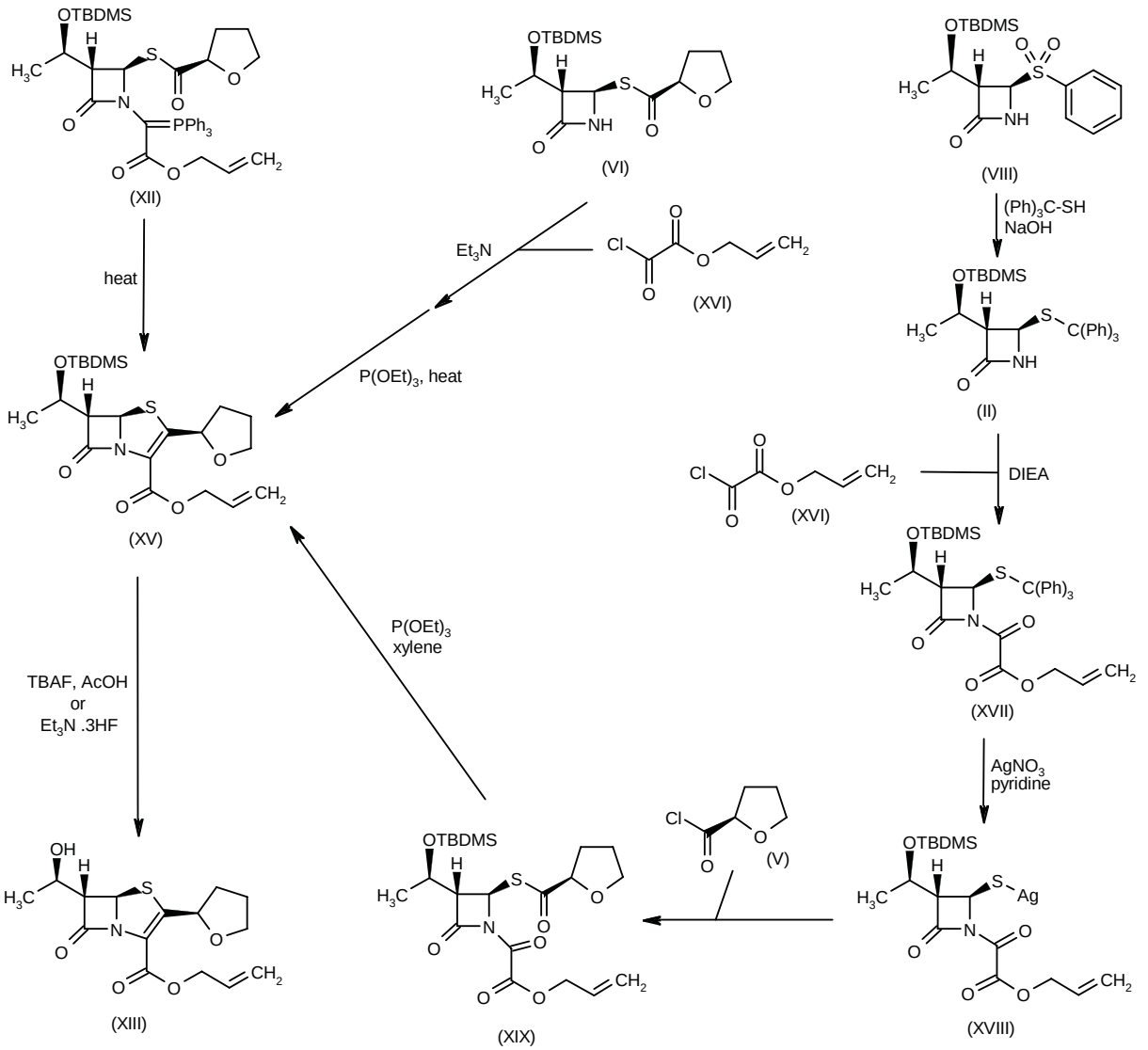
Alternatively, faropenem allyl ester (XIII) can also be prepared by cyclization of compound (XII) in refluxing benzene to yield silylated penem allyl ester (XV) (3, 4), which is then deprotected with either tetrabutylammonium fluoride in AcOH (3, 4) or triethylamine tris(hydrogen fluoride) in methyl isobutyl ketone or toluene (5). Scheme 2.

L.A. Sorbera, M. del Fresno, R.M. Castañer, X. Rabasseda. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Intermediate (XIII)



Scheme 2: Synthesis of Intermediate (XIII)



Penem (XV) can also be synthesized by several related ways:

a) By coupling of azetidinone (VI) with allyl oxalyl chloride (XVI) in CH_2Cl_2 by means of Et_3N, followed by intramolecular Wittig cyclization by means of triethyl phosphite in refluxing xylene (2, 3). Scheme 2.

b) Substitution of phenyl sulfonyl group of azetidinone (VIII) by tritylmercaptan by means of NaOH in acetone/water provides tritylsulfanyl-azetidinone (II), which is condensed with allyl oxalyl chloride (XVI) by means of DIEA in CH_2Cl_2 to give the oxalyl amide (XVII). Compound (XVII) is then treated with $AgNO_3$ and pyridine in acetonitrile to provide the silver mercaptide (XVIII), which is acylated with tetrahydrofuran-2(*R*)-carbonyl chloride (IV) in acetonitrile to afford the penem precursor (XIX). Finally, compound (XV) is obtained by intramolecular Wittig cyclization of (XX) with $P(OEt)_3$ in refluxing xylene (6). Scheme 2.

Hydrolysis of faropenem allyl ester (XIII) to faropenem sodium (XX) can be performed under several different conditions: i) triphenylphosphine, sodium 2-ethylhexanoate and palladium tetrakis(triphenylphosphine) (1-3); ii) palladium tetrakis(triphenylphosphine) and sodium 4-(methoxycarbonyl)- 5,5-dimethylcyclohexane-1,3-dione enolate in several different solvents such as methyl acetate, ethyl acetate, tetrahydrofuran, dioxane,

sec-butanol, acetonitrile, acetone, 2-butanone, 1,2-dichloroethane, chlorobenzene, toluene, or ethylene glycol dimethyl ether (4); iii) triphenylphosphine and palladium tetrakis(triphenylphosphine) with sodium propionate, sodium acetate or sodium lactate in tetrahydrofuran or acetone (7); and iv) palladium acetate in the presence of $P(OBu)_3$ and sodium propionate in THF (8). Scheme 3.

Finally, faropenem daloxate can be directly obtained from faropenem sodium (XX) by esterification with 4-(iodomethyl)-5-methyl-1,3-dioxol-2-one (XXI) in DMF (9). Scheme 3.

Treatment of 4-(chloromethyl)-5-methyl-1,3-dioxol-2-one (XXII) with potassium formate (XXIII) by means of KI and $NaHCO_3$ in DMF affords the formyloxymethyl derivative (XXIV), which is converted into the hydroxymethyl derivative (XXV) by refluxing in MeOH. Coupling of compound (XXV) with oxalyl chloride (XXVI) in dichloromethane furnishes compound (XXVII), which is then condensed with protected azetidinone (VI) by means of Et_3N in dichloromethane to yield compound (XXVIII). Intramolecular Wittig cyclization of compound (XXVIII) by means of triethyl phosphite in refluxing xylene provides the silylated faropenem daloxate (XXIX) (10), which is finally deprotected by means of either Et_3N tris(hydrogen fluoride) in ethyl acetate (5) or tetrabutylammonium fluoride (TBAF) and AcOH in THF (10). Scheme 4.

Introduction

The growing problem of antimicrobial resistance to agents commonly used for respiratory tract infections is partly due to β-lactamase production by the causative microorganisms. A number of β-lactam antimicrobial agents with high potency, a broad spectrum of activity and stability to β-lactamases are available, including the parenteral carbapenems imipenem, meropenem and more recently ertapenem sodium but none can be administered orally. Faropenem is the world's first penem designed for the oral treatment of community-acquired respiratory tract infections and was launched in Japan in 1997. Faropenem showed potent activity against a wide variety of Gram-positive and Gram-negative bacteria, including extended-spectrum β-lactamase (ESBL)-producing strains. The mechanism of the stability against ESBL was elucidated by modeling the Michaelis complex of faropenem and Toho-1, an ESBL. Modeling of a complex of faropenem at the active site of a penicillin-binding protein 2 (PBP2) model suggested the characteristic affinity for faropenem with PBP2 of *Escherichia coli*. The prodrug faropenem daloxate, which is hydrolyzed in plasma to the active agent faropenem, was selected for further development.

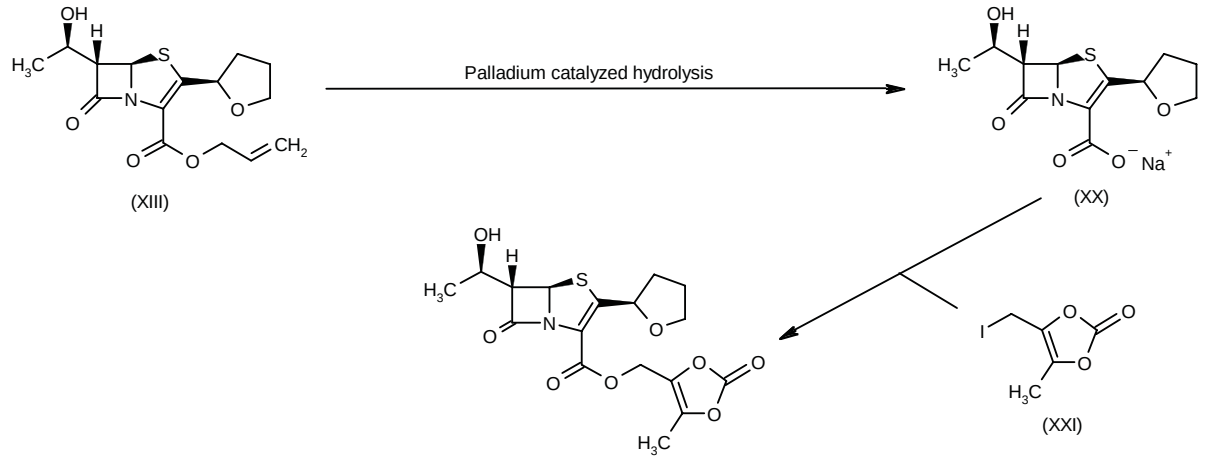
Pharmacological Actions

Faropenem exhibited potent activity against a wide range of Gram-positive and Gram-negative bacterial isolates. Results from an *in vitro* study examining the effects of the agent against a total of 5354 clinical isolates from 27 European hospital suggest that faropenem is a potential candidate for the treatment of community acquired infections particularly of the respiratory tract. Faropenem was effective against the following respiratory tract pathogens ($MIC_{50/90}$ mg/l): penicillin-susceptible (≤ 0.015/0.03), penicillin-intermediate (0.12/0.5) and penicillin-resistant (1/1) *Streptococcus pneumonia*, β-lactamase positive *Haemophilus catarrhalis* (0.06/0.5), *Moraxella catarrhalis* (0.06/0.5), *Escherichia coli* (0.5/1), *Klebsiella pneumoniae* (0.5/2), *Klebsiella oxytoca* (0.5/2) and *Citrobacter koseri* (0.5/2). Faropenem was 4-16-fold more potent than amoxicillin/ clavulanic acid against *E. coli*, *K. pneumoniae*, *K. oxytoca* and *C. koseri*. The agent also showed activity against β-hemolytic streptococci (MIC_{90} = 0.06 mg/l), *Streptococcus milleri* (MIC_{90} = 0.12 mg/l) and *Streptococcus viridans* (MIC_{90} = 1 mg/l). MIC_{90}s obtained for methicillin-susceptible and -resistant *Staphylococcus aureus* were 0.12 and > 32 mg/l, respectively, and MIC_{90}s for *Enterococcus faecalis* and *Enterococcus faecium* were 8 and > 32 mg/l, respectively. Faropenem was less active against the following isolates ($MIC_{50/90}$ mg/l): *Citrobacter freundii* (1/8), *Proteus mirabilis* (4/4), *Enterobacter* spp. (4/8), *Proteus vulgaris* (4/8) and *Morganella morganii* (4/8). MIC_{50}s ranging from 8 to > 32 mg/l and MIC_{90}s of 32 mg/l or greater were obtained against *Serratia* spp., *Acinetobacter* spp., *Burkholderia cepacia*, *Stenotrophomonas maltiphilia* and *Pseudomonas aeruginosa* (11). Several other studies have corroborated and/or extended these results (12-15) and faropenem also showed excellent activity against pediatric isolates of *E. coli*, *Klebsiella pneumoniae*, *M. catarrhalis*, *Haemophilus influenzae*, *S. pneumoniae*, groups A and B streptococci, *S. aureus* and *Staphylococcus epidermidis* (16).

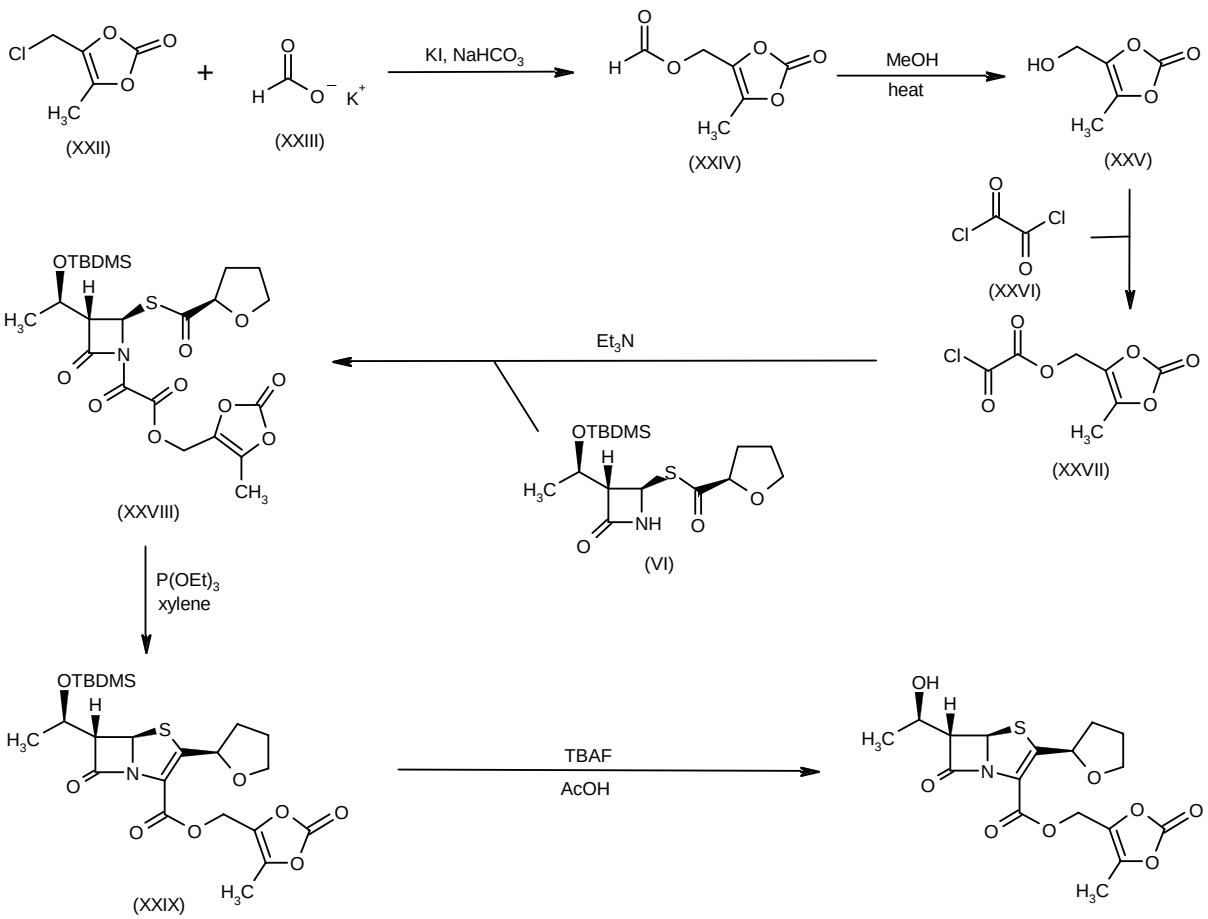
An *in vitro* study examining the activity of faropenem against oropharyngeal anaerobes reported potent broad spectrum activity of the agent. The MIC_{90} values for *Peptostreptococci*, *Prevotella* spp. and *Porphyromonas* and *Bacteroides* were 0.05-0.78, 0.1-0.2 and 3.13-6.25 mg/l, respectively. Moreover, faropenem was 256- and 16-fold more potent than ampicillin (1600 mg/l) and cefoxitin (MIC = 100 mg/l), respectively, against β-lactamase producing *Bacteroides fragilis* and 8-fold more potent than imipenem (MIC = > 200 mg/l) against metallo-β-lactamase-producing *B. fragilis*. Results also showed the agent's excellent stability against β-lactamase hydrolysis (17). Similarly, faropenem was found to be highly stable to penicillinase derived from *S. aureus* and *E. coli* and to cephalosporinase derived from *E. coli* and *P. vulgaris*. Moreover, there was a lower emergence of resistance in *S. aureus* strains as compared to the cephalosporins, cefixime, cefazolin and cefaclor (18).

Other studies have further compared the *in vitro* efficacy of faropenem with other antimicrobial agents. For example, faropenem was found to have activity comparable to imipenem but was more potent than oral β-lactams such as amoxicillin/clavulanate, ampicillin, cefuroxime,

Scheme 3: Synthesis of Faropenem Daloxate



Scheme 4: Synthesis of Faropenem Daloxate



ceftriaxone, cefaclor and cefdinir against penicillin-resistant and -susceptible *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* (15, 19). Faropenem-induced killing and eradication of penicillin-susceptible and -intermediate *S. pneumoniae* was shown to be comparable to eradication seen with high-dose amoxicillin and ceftriaxone (20). In addition, faropenem was 4- to 8-fold (MIC_{90} = 0.25 mg/l) more active than amoxicillin, cefuroxime and vancomycin against methicillin-susceptible *S. aureus*, *S. epidermidis* and *Staphylococcus haemolyticus*. Of the 31 methicillin-resistant *S. aureus* strains, 18 were inhibited by faropenem at concentrations of 2 μg/l or less and the MIC_{90}s for faropenem against methicillin-resistant *S. epidermidis* and *S. haemolyticus* were 0.25 and 2 mg/l, respectively (21).

An *in vitro* study compared the efficacy of faropenem with imipenem, amoxicillin/clavulanate, cefuroxime, ceftriaxone, cefixime and cefprozil against 174 characterized strains of *Enterobacteriaceae* (such as *E. coli*, *K. pneumoniae*, *Proteus mirabilis* and *Salmonella typhimurium*) that produce narrow spectrum β-lactamases, extended spectrum β-lactamases (ESBLs), plasmid-mediated and chromosomal AmpC β-lactamases and carbapenem-hydrolyzing β-lactamases. Faropenem ($MIC_{50/90}$ = 1/16 μg/ml) and imipenem (0.25/1 μg/ml) were found to be the most active agents followed by ceftriaxone (2/64 μg/ml), cefixime (8/>128 μg/ml), amoxicillin/clavulanate (32/128 μg/ml), cefuroxime (32/>258 mg/ml) and cefprozil (125/>256 μg/ml). Unlike the cephalosporins which displayed decreased activity when strains produced ESBL and high levels of AmpC, the activity of faropenem and imipenem was not affected. However, faropenem and imipenem were the least active agents against strains producing class A and B carbapenem-hydrolyzing β-lactamases (22).

Characterization of the antimicrobial activity of faropenem has been the focus of several studies. The bactericidal activity of faropenem against *S. pneumoniae* (ATCC 49619) and *H. influenzae* (ATCC 10211) was concentration- and time-dependent with EC_{50} values of 0.02 and 0.5 mg/l obtained, respectively (23).

The bactericidal and bacteriolytic action of faropenem was compared to amoxicillin against *S. pneumoniae* (No. 4241) in the presence and absence of sucrose (10%) and human serum (50%). Although human serum decreased the bactericidal activity of both agents, faropenem maintained its bactericidal activity. In contrast, while addition of sucrose to serum-containing media decreased the activity of amoxicillin, the bacteriolytic activity of faropenem was enhanced (24).

The bactericidal effect of faropenem was shown to be synergistic with host defense mechanisms. Treatment of *E. coli* (K12) with faropenem (1/8 x MIC) resulted in a time-dependent alteration in the morphology and structure of the bacterial surface from a normal rod-shape to a spherical-shape. Bulging *E. coli* were observed after 2 h of exposure to faropenem (1 x MIC) and cell lysis was seen after 4 h of exposure; treatment with faropenem at 4 x MIC resulted in spheroplast-like forms and cell lysis after only 2 h. The addition of complement resulted in an approximate 10-fold increase in the bactericidal activity of faropenem (7.5 x MIC). Results also showed that in the absence of faropenem, phagocytosed *E. coli* caused the lysis of macrophages. However, faropenem (1/8 -1/2 x MIC) prevented lysis of macrophages while phagocytosis of *E. coli* continued (25).

Faropenem has demonstrated a limited potency against *Pseudomonas aeruginosa* unlike other carbapenems such as imipenem and meropenem. The decrease in activity of the agent could be due to limited uptake, efficient efflux and/or a low affinity for penicillin-binding proteins. An *in vitro* study examined the activity of faropenem in a PAO1 background and in isogenic porin and efflux pump *P. aeruginosa* mutants. Results suggest faropenem does not pass through the OprD porin, that active efflux by MexAB-OprM plays a role in the intrinsic resistance of this species to the agent and faropenem may be a substrate for the EFN efflux pump (26).

A study using a rabbit immunogenicity model (rabbits sensitized with 4-6 intradermal injections over 4-9 weeks) and comparing faropenem with benzylpenicillin, cephalothin, cefazolin and imipenem showed that faropenem was less antigenic than other β-lactams. These results indicate that faropenem may have a lower propensity to elicit allergic reactions in patients previously sensitized to other β-lactam antibiotics (27).

Moreover, an *in vitro* study measuring the excitatory potential (*i.e.*, population spike amplitude) from the CA1 region of rat hippocampal slices demonstrated that faropenem had a lower potential to induce proconvulsive activity as compared to amoxicillin, penicillin and imipenem. The increases in population spike amplitude as compared to control following exposure to 2 μmol/l amoxicillin, penicillin, imipenem, the prodrug faropenem daloxate and faropenem were 300, 220, 220, 150 and 130%, respectively (28).

Pharmacokinetics

A randomized, double-blind, placebo-controlled study involving 48 young and elderly (18-86 years) male and female subjects examined the pharmacokinetics and safety and tolerability of single-dose faropenem daloxate (300 mg p.o. after an overnight fast). Faropenem daloxate was safe and well tolerated. No serious adverse events or laboratory findings were seen. However, 6 women treated with faropenem daloxate developed headaches as compared to only 1 in the placebo group. The pharmacokinetics of the agent were not affected by gender. $AUC_{0-\infty}$ and C_{max} values ranged from approximately 26-33 mg·h/l and 13-14 mg/l, respectively. A slight age-related increase in the $t_{1/2}$ value (0.88 ± 0.11 and 0.91 ± 0.13 h for young males and females, respectively *vs.* 1.32 ± 0.22 and 1.09 ± 0.12 h for elderly males and females, respectively) was observed although it was not considered clinically significant (29).

Box 1: Effect of faropenem daloxate compared to amoxicillin/clavulanic acid in healthy volunteers (30) [Prous Science Integrity®].

Design	Comparative, open, randomized clinical study
Population	Healthy male volunteers (n = 23)
Treatments	Faropenem daloxate, 300 mg p.o. b.i.d. x 8 d (n = 12) Amoxicillin, 875 mg p.o. b.i.d. + Clavulanic acid, 125 mg p.o. b.i.d. x 8 d (n = 11)
Adverse Events	F: 6/12 (50.0%) [headache 1/12 (8.3%), bitter taste 1/12 (8.3%), abdominal cramps 1/12 (8.3%), meteorism 1/12 (8.3%), soft stools 2/12 (16.7%), epididymitis 1/12 (8.3%) AC: 4/11 (36.4%) [rumbling noise of the stomach 1/11 (9.1%), meteorism 1/11 (9.1%), soft stools 4/11 (36.4%)
Results	No changes in the oropharyngeal microflora were seen in either group Presence of enterococci in the feces increased in both groups -*Bacteroides fragilis* and spp. increased in both groups -*Escherichia coli*: AC ≥ F Patients with *Clostridium difficile* in the feces: F(0/12) = AC (0/11) -overgrowth of *P. aeruginosa*: F (0/12) = AC (0/11) -overgrowth of multiresistant *Enterobacteriaceae*: F (0/12) = AC (0/11) Patients with *Citrobacter diversus* (new species) in the fecal flora @ 8 d: F (1/12 [8.3%]) ≥ AC (0%) -*Citrobacter freundii* (new species): AC (3/11 [27.3%]) ≥ F (3/12 [25.0%]) -*Enterococcus faecium* (new species): F (2/12 [16.7%]) ≥ AC (1/11 [9.1%]) -*Klebsiella pneumoniae* (new species): AC (4/11 [36.4%]) ≥ F (0%) -*Staphylococcus aureus* (new species): AC (1/11 [9.1%]) ≥ F (1/12 [8.3%]) -*Candida albicans/krusei* (new species): F (4/12 [33.3%]) ≥ AC (3/11 [27.3%]) All aerobic/anaerobic fecal colony counts were normalized @ 2 wks No changes in vital signs, ECG and laboratory parameters
Conclusions	Multiple doses of faropenem daloxate and amoxicillin clavulanic acid regimens were safe, well tolerated and resulted in minimal changes in normal intestinal microflora

A randomized, nonblinded study conducted in 12 healthy volunteers showed that multiple dosing with faropenem daloxate (300 mg b.i.d. for 8 days) or amoxicillin/clavulanic acid (875/125 mg b.i.d. for 8 days) had no effect on normal oropharyngeal flora and only minimally altered normal intestinal microflora. A transient increase in fecal enterococci was observed in both treatment groups. No overgrowth of *P. aeruginosa* or multiresistant *Enterobacteriaceae* was seen and no *C. difficile* were found (30) (Box 1).

A nonblinded, randomized, 4-way crossover study conducted in 8 healthy males examined the bioavailability and pharmacokinetics of single-dose faropenem daloxate (300 mg) administered orally or using an Enterion™ capsule to deliver the agent locally to the upper and lower small intestine or the ascending colon. The agent was well tolerated with no changes in vital signs, ECG or laboratory parameters observed. When compared to values obtained following oral administration, AUC and C_{max} values decreased when the agent was delivered to the upper (12 and 21%, respectively) and lower (22 and 34%, respectively) small intestine; the elimination $t_{1/2}$ of the agent was similar with all delivery routes (1.07-1.47 h). A marked decrease in bioavailability of 34% was observed when the agent was administered to the ascending colon (31).

Results of a study examining 1120 plasma samples from 18 volunteers participating in phase I trials indicated that there was no evidence of formation of antimicrobially active metabolites following administration of oral faropenem daloxate (150, 300 or 1200 mg) (32).

Food intake had no effect on the pharmacokinetics of single-dose faropenem daloxate (300 mg p.o.) according to results of a nonblinded, randomized, 2-way crossover study involving 12 healthy males who were administered the agent either after fasting or after a high-fat breakfast (about 1000 kcal; 55% fat). These results indicate the agent may be administered irrespective of food intake. The agent was well tolerated with no changes in vital signs, ECG or laboratory findings seen. Food intake slightly reduced the C_{max} from 10.7 to 9.2 mg/l at about 1.5 h postdosing. However, this alteration was concluded to be clinically insignificant. The AUC values obtained from fasted and fed subjects were 23.1 and 22.8 mg·h/l, respectively, and the $t_{1/2}$ value for both groups was 0.9 h (33) (Box 2).

A nonblinded, randomized, 3-way crossover study conducted in 11 healthy males examined the effects of pre- and cotreatment with a 10 ml suspension (600 mg magnesium hydroxide and 900 mg aluminum oxide) of Maalox® 70 on the pharmacokinetics, safety and tolerability of single-dose faropenem daloxate (300 mg). Maalox® 70 was given either 5 min before faropenem daloxate or q.i.d. after meals starting 48 h before faropenem daloxate and continued until evening when it was given 2 h after faropenem daloxate. Faropenem daloxate was well tolerated with no changes in vital signs, ECG or laboratory findings seen. Although the AUC and C_{max} of faropenem were decreased by 20% and 40%,

Box 2: Pharmacokinetics and safety of single-dose faropenem daloxate in healthy volunteers (33) [Prous Science Inegrity®].

Design	Randomized, crossover, open clinical study
Population	Healthy male Caucasian volunteers (n = 12)
Treatments	Faropenem daloxate, 300 mg (fasted) Faropenem daloxate, 300 mg + high-fat breakfast
Adverse Events	8/12 (66.7%) [meteorism 2/12 (16.7%)]
Results	No relevant changes in vital signs, ECG or laboratory parameters
Conclusions	Faropenem daloxate was safe and well tolerated in healthy volunteers

Table I: Pharmacokinetics of oral faropenem daloxate in young male subjects (values for elderly males in brackets) [Prous Science Integrity®].

Dose	C_{max} (μg/ml)	t_{max} (h)	AUC (μg·g/ml)	$t_{1/2}$ (h)
		Single dose		
300 mg	11.1-15.0 (13.8)	0.8-1.8 (1.4)	22.0-26.0 (32.8)	0.9-1.1 (1.3)
600 mg	23.5	1.0	45.7	1.2
1200 mg	40.2	1.0	101	1.4
		Multiple dose		
300 mg b.i.d.	9.6	0.6-1.0	18.3	1.0-1.2
600 mg b.i.d.	23.1	0.8-1.5	40.3	0.9-1.6
1200 mg b.i.d.	41.3	0.8-1.5	92.2	0.9-1.1

Ranges from minimum and maximum values obtained in different trials are shown. Values refer to faropenem free acid. C_{max}, peak plasma concentrations; t_{max}, time to peak plasma concentrations; AUC, area under the plasma concentration-time curve; $t_{1/2}$, elimination half-life. (Refs. 29, 33-37).

respectively, when faropenem daloxate and Maalox® 70 were administered together, these parameters were only decreased by 8% and 25% when the agents were administered 2 h apart. This effect was not thought to be due to changes in intragastric pH but rather to absorption effects between faropenem daloxate and Maalox® 70. It was concluded that these changes were not clinically significant since the T>MIC value was not decreased with either cotreatment (34).

A nonblinded, randomized, 2-way crossover study conducted in 11 healthy males reported that there were no clinically significant interactions when faropenem daloxate (single dose corresponding to 300 mg faropenem) was administered with probenecid (500 mg 1 h before faropenem daloxate and 500 mg at 3 and 7 h). The AUC (22.0 ± 1.28 *vs.* 54.6 ± 1.21 mg·h/l) and $t_{1/2}$ (1.07 ± 1.75 *vs.* 2.33 ± 1.15 h) values of faropenem were approximately doubled with concomitant probenecid administration although C_{max} for the agent was only slightly increased (13.4 ± 1.44 *vs.* 17 1.28 mg/l). These changes were considered clinically irrelevant since the $t_{1/2}$ of faropenem was only 2.3 h with coadministration and no accumulation of faropenem is expected (35).

Another nonblinded, randomized, 3-way crossover study involving 11 healthy males reported that there were no clinically significant interactions when faropenem daloxate (single dose corresponding to 300 mg faropenem p.o.) was given concomitantly with furosemide (40 mg). Faropenem was well tolerated with no changes in vital signs, laboratory parameters or ECG noted. Treatment with furosemide alone or together with faropenem daloxate both resulted in an increase in the excretion of urine and electrolytes. AUC, C_{max} and terminal $t_{1/2}$ values were similar for both agents when given alone or in combination. It was concluded that no dose adjustment is required when faropenem daloxate and furosemide are administered concomitantly (36).

Table I shows the main pharmacokinetic properties of faropenem daloxate after oral administration to healthy male volunteers (29, 33-37) (Box 3).

Clinical Studies

Faropenem daloxate is in phase III clinical trials in Europe and the U.S. for the treatment of respiratory tract infections and is expected to be launched in 2004 (38-41).

Source

Suntory Ltd. (JP); licensed worldwide to Bayer AG (DE).

Box 3: Pharmacokinetics and safety of multiple-dose faropenem daloxate in healthy volunteers (37) [Prous Science Inegrity®].

Design	Randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Healthy male volunteers (n = 24)
Treatments	Faropenem daloxate, 300 mg p.o. b.i.d. x 8 d (n = 6) Faropenem daloxate, 600 mg p.o. b.i.d. x 8 d (n = 6) Faropenem daloxate, 1200 mg p.o. b.i.d. x 8 d (n = 6) Placebo (n = 6)
Withdrawals	1/24 (4.2%)
Adverse Events	F300: 2/6 (33.3%) [abdominal pain 1/6 (16.7%), headache 1/6 (16.7%), dyspepsia 1/6 (16.7%), nausea 1/6 (16.7%), hypesthesia 1/6 (16.7%), rhinitis 1/6 (16.7%), skin disorder 1/6 (16.7%)] F600: 4/6 (66.7%) [abdominal pain 1/6 (16.7%), accidental injury 1/6 (16.7%), injection site pain 1/6 (16.7%), thrombophlebitis 1/6 (16.7%), diarrhea 2/6 (33.3%), dyspepsia 1/6 (16.7%), rhinitis 1/6 (16.7%), contact dermatitis 1/6 (16.7%), rash 1/6 (16.7%)] F1200: 5/6 (41.7%) [back pain 2/6 (33.3%), accidental injury 1/6 (16.7%), headache 1/6 (16.7%), leg pain 1/6 (16.7%), diarrhea 4/6 (66.7%), vomiting 1/6 (16.7%)] P: 5/6 (41.7%) [asthenia 1/6 (16.7%), palpitations 1/6 (16.7%), diarrhea 2/6 (33.3%), flatulence 3/6 (50.5%), nausea 1/6 (16.7%), liver function test abnormal 1/6 (16.7%), CK increased 1/6 (16.7%)
Results	No relevant changes in vital signs, ECG and laboratory parameters No patients with *Pseudomonas aeruginosa* overgrowth or potentially multiresistant *Enterobacteriaceae* Decrease in *Clostridium* spp. Enterococci overgrowth/*E. faecium* selection rate: F (7/12 [58.3%]) Resistant oropharyngeal bacteria overgrowth rate: F (0/18)
Conclusions	Faropenem daloxate was safe and well tolerated in healthy volunteers and had only minor effects on endogenous flora after oral administration

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