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(54) Benævnelse: **CEFTOLOZAN/TAZOBACTAM TIL BEHANDLING AF INTRAPULMONALE INFEKTIONER**

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DESCRIPTION

Description

TECHNICAL FIELD

[0001] This disclosure relates to the treatment of intrapulmonary bacterial infections, including the treatment of nosocomial pneumonia infections, with a cephalosporin.

BACKGROUND

[0002] H. S. Sader et al., Antimicrobial Agents and Chemotherapy, (2011), vol. 55, no. 5, pages 2390-2394, concerns "Antimicrobial Activity of CXA-101, a Novel Cephalosporin Tested in Combination with Tazobactam against Enterobacteriaceae, Pseudomonas aeruginosa, and Bacteroides fragilis Strains Having Various Resistance Phenotypes".

[0003] Cubist Pharmaceuticals Corporate Presentation, Sep. 2011 concerns possible plans for development of Cubicin.

[0004] L. Zamorano et al., Clinical Microbiology and Infection, (2009), vol. 16, no. 9, concerns "Activity of the new cephalosporin CXA-101 (FR264205) against Pseudomonas aeruginosa isolates from chronically-infected cystic fibrosis patients".

[0005] C. Jacqueline et al., Abstracts Book, Interscience Conference on Antimicrobial Agents & Chemotherapy, US, (2010), vol. 50, pages B - 1401, concerns "Assessment of the In Vivo Activity of CXA-101 in a Murine Model of Pseudomonas aeruginosa Pneumonia: Comparison with Ceftazidime and Piperacillin-Tazobactam".

[0006] Y. Ge et al., Antimicrobial Agents and Chemotherapy, (2010), vol. 54, no. 8, pages 3427-3431, concerns "Pharmacokinetics and Safety of CXA-101, a New Antipseudomonal Cephalosporin, in Healthy Adult Male and Female Subjects Receiving Single- and Multiple-Dose Intravenous Infusions".

[0007] J. F. Marier et al., Abstracts Book, Interscience Conference on Antimicrobial Agents & Chemotherapy, US, (2010), vol. 50, pages A - 1391, concerns "Pharmacokinetics of a Novel Anti-Pseudomonal Cephalosporin, CXA-101, and Tazobactam (CXA/TAZ) in Healthy Adult Subjects".

[0008] B. Miller et al., Antimicrobial Agents and Chemotherapy, (2012) vol. 56, no. 6, pages 3086 - 3091, concerns "Pharmacokinetics and Safety of Intravenous Ceftolozane-Tazobactam in Healthy Adult Subjects following Single and Multiple Ascending Doses".

[0009] The cephalosporin (6R,7R)-3-[5-Amino-4-[3-(2-aminoethyl)ureido]-1-methyl-1H-pyrazol-2-ium-2-ylmethyl]-7-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(Z)-1-carboxy-1-methylethoxyimino]acetamido]-3-cephem-4-carboxylic acid (also referred to as "CXA-101" and previously designated FR264205) is an antibacterial agent. CXA-101 can be provided as the compound shown in Figure 1. The antibacterial activity of CXA-101 is believed to result from its interaction with penicillin binding proteins (PBPs) to inhibit the biosynthesis of the bacterial cell wall which acts to stop bacterial replication. CXA-101 can be combined (e.g., mixed) with a β-lactamase inhibitor ("BLI"), such as tazobactam. Tazobactam is a BLI against Class A and some Class C β-lactamases, with well established *in vitro* and *in vivo* efficacy in combination with active β-lactam antibiotics. The combination of CXA-101 and tazobactam in a 2:1 weight ratio is an antibiotic pharmaceutical composition ("CXA-201") for parenteral administration. CXA-201 displays potent antibacterial activity *in vitro* against common Gram-negative and selected Gram-positive organisms. CXA-201 is a broad-spectrum antibacterial with *in vitro* activity against Enterobacteriaceae including strains expressing extended spectrum β-lactamases-resistant (MIC_{90} = 1 µg/mL), as well as *Pseudomonas aeruginosa (P. aeruginosa)* including multi-drug resistant strains (MIC_{90}= 2 µg/mL). CXA-201 is a combination antibacterial with activity against many Gram-negative pathogens known to cause intrapulmonary infections, including nosocomial pneumonia caused by *P. aeruginosa.*

[0010] Intrapulmonary infections, such as nosocomial pneumonia, remain a major cause of morbidity and mortality, especially infections caused by drug resistant pathogens such as *P. aeruginosa.* One challenge in treating intrapulmonary infections with systemic administration of an antibiotic is determining the antibiotic dose that will provide a therapeutically safe and effective concentration of the antibiotic at the site of an infection on the mucosal side of the bronchi in the lung (i.e., in the bronchial secretions). Many antibiotics diffuse poorly from the bloodstream across the bronchi [e.g., Pennington, J. E., "Penetration of antibiotics into respiratory secretions," Rev Infect Dis 3(1):67-73 (1981)], which can result in the administration of higher doses of antibiotic than would be prescribed for a truly systemic infection. Furthermore, the purulent sputum that characterizes infected patients tends to compromise the potency of many antibiotics *(See e.g.,* Levy, J., et al., "Bioactivity of gentamicin in purulent sputum from patients with cystic fibrosis or bronchiectasis: comparison with activity in serum," J Infect Dis 148(6): 1069-76 (1983)). In some cases, the result is the prescription of large amounts of a systemically administered antibiotic to treat an intrapulmonary infection.

[0011] The efficacy of an antibiotic depends in part on the concentration of the drug at the site of action. Efficacy of antimicrobial therapy requires adequate antibiotic concentrations at the site of bacterial infection, and some authorities believe that epithelial lining fluid (ELF) concentrations are a reasonable surrogate for predicting effective concentrations for treating intrapulmonary infections such as pneumonia. For many antibiotics, clinical data correlating ELF concentrations to clinical outcome is unavailable and the clinical significance of differences

in pulmonary penetration of antibiotics is unknown or poorly characterized. Few studies have quantified the penetration of β-lactam agents into the lung, as measured by the ratio of area under the concentration-time curve (AUC) in ELF to AUC in plasma (AUC(ELF)/AUC(plasma) ratio). For some published studies, the concentration of antibiotics measured in the ELF of the lung has varied widely. For example, the reported penetration ratio of telavancin in healthy human volunteers ranges widely between 0.43 and 1.24 (Lodise, Gottfreid, Drusano, 2008 Antimicrobial Agents and Chemotherapy). Thus, predicting the penetration of a drug into the ELF *a priori,* based on the structure, molecular weight, size and solubility is difficult due to the limited data available on the effect of physicochemical properties on the lung penetration of drugs.

[0012] Accordingly, the efficacy of a particular drug in treating intrapulmonary infections, in particular nosocomial pneumonia, cannot be predicted solely on the basis of data, such as *in vitro* data relating to the activity of that drug against a particular bacterium, which does not give any indication as whether the drug will accumulate at a therapeutically safe and effective concentration at the site of an infection on the mucosal side of the bronchi in the lung (i.e., in the bronchial secretions). For instance, tigicycline, a glycylcycline antimicrobial, has *in vitro* activity against many species of Gram-positive and Gram-negative bacteria, including *P. aeruginosa,* and it has been approved by the FDA for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community acquired pneumonia. However, tigicycline is not approved for the treatment of nosocomial pneumonia, in view of an increased mortality risk associated with the use of tigicycline compared to other drugs in patients treated for nosocomial pneumonia.

SUMMARY

[0013] The present invention provides ceftolozane (CXA-101) and tazobactam in a 2:1 (ceftolozane:tazobactam) weight ratio at a dose of 3.0 g for use in a method of treating nosocomial pneumonia caused by Gram-negative pathogens in a human, wherein the ceftolozane and tazobactam is administered intravenously once every 8 hours, and wherein the ceftolozane is in its free-base form or in its salt form. The invention is based in part on results from a human clinical study designed to assess the ELF penetration of CXA-201 in comparison to piperacillin/tazobactam, indicated for the treatment of nosocomial pneumonia. The study described herein quantified the penetration of CXA-201 into the lung, as measured by the ratio of area under the concentration-time curve (AUC) in epithelial lining fluid (ELF) to AUC in plasma (AUC(ELF)/AUC(plasma) ratio). The results of the study indicate that CXA-201 penetrated into the ELF of human patients, with a ceftolozane ELF/plasma AUC ratio of 0.48. The measured ELF concentrations of ceftolozane exceeded 8 µg/mL for 60% of the 8-hour dosing interval, a concentration that is predicted to inhibit 99% of *Pseudomonas aeruginosa* based on current surveillance data.

[0014] The study showed that CXA-201 penetrated well into the ELF of healthy volunteers compared to piperacillin/tazobactam, an agent widely used for treatment of lower respiratory

infections. The intrapulmonary pharmacokinetics measured in the study supports the use of CXA-201 as a parenteral (e.g., intravenous) antibiotic for treatment of intrapulmonary infections, such as nosocomial pneumonia or other lower respiratory tract infections.

BRIEF DESCRIPTION OF DRAWINGS

[0015]

Figure 1 is the chemical structure of a salt of ceftolozane hydrogen sulfate salt .

Figure 2A is a graph showing the ELF Concentration vs. Time Profile for ceftolozane hydrogen sulfate salt (Median and Range) for CXA-201.

Figure 2B is a graph showing the ELF Concentration vs. Time Profile for Tazobactam (Median and Range) for CXA-201.

Figure 3A is a graph showing the (Comparative) ELF Concentration vs. Time Profile for Piperacillin (Median and Range) for a piperacillin/tazobactam comparator (ZOSYN®).

Figure 3B is a graph showing the (Comparative) ELF Concentration vs. Time Profile for Tazobactam (Median and Range) for a piperacillin/tazobactam comparator (ZOSYN®).

Figures 4A and 4B are synthetic schemes for preparing ceftolozane hydrogen sulfate salt .

DETAILED DESCRIPTION

[0016] The present invention relates to ceftolozane (CXA-101) and tazobactam in a 2:1 (ceftolozane:tazobactam) weight ratio at a dose of 3.0 g for use in the treatment of nosocomial pneumonia caused by Gram-negative pathogens in a human, wherein the ceftolozane and tazobactam is administered intravenously once every 8 hours, and wherein the ceftolozane is in its free-base form or in its salt form. As used herein, the term "ceftolozane" means CXA-101 in a free-base or salt form, preferably a hydrogen sulfate form (illustrated in figure 1). In one embodiment, ceftolozane is CXA-101 in its free-base form. In another embodiment, ceftolozane is CXA-101 in its salt form, preferably a hydrogen sulfate form.

[0017] Ceftolozane (in free base or salt form, preferably hydrogen sulfate form) and tazobactam are in a 2:1 (ceftolozane:tazobactam) weight ratio. Provided herein are ceftolozane and tazobactam for use in methods of treating nosocomial pneumonia as defined by the claims. Ceftolozane hydrogen sulfate and tazobactam are in a 2:1 weight ratio. The combination of ceftolozane hydrogen sulfate and tazobactam in a 2:1 weight ratio is referred to herein and in the examples as "CXA-201."

[0018] The invention provides ceftolozane and tazobactam for use in a method of treating an intrapulmonary infection as defined in the claims. The method comprises administering ceftolozane in combination with tazobactam.

[0019] The invention comprises administering CXA-201 and the infection comprises Gram-negative bacteria.

[0020] In one embodiment, the amount of the ceftolozane in the ELF of the subject effective to treat an intrapulmonary infection is at least about 8 µg/ml. The ELF concentration of ceftolozane in the ELF may reach at least about 8 µg/ml after administration of ceftolozane (CXA-101) and tazobactam as defined by the claims. The subject is a human having nosocomial pneumonia. The subject (or patient) may, in some embodiments, have ventilator acquired pneumonia or hospital acquired pneumonia.

[0021] In the invention, the intrapulmonary infection is nosocomial pneumonia. The intrapulmonary infection may comprise *Pseudomonas aeruginosa, Enterobacteriaceae,* or a combination thereof. Typically, the intrapulmonary infection comprises *Pseudomonas aeruginosa.* The intrapulmonary infection may comprise a pathogen with minimum inhibitory concentration for CXA-201 of ≤ 8µg/ml. The intrapulmonary infection may comprise a pathogen with minimum inhibitory concentration for ceftolozane of ≤ 8µg/ml.

[0022] In another aspect, the invention provides ceftolozane, for use in a method of treating an intrapulmonary infection as defined by the claims. The ceftolozane is intravenously administered. The ceftolozane is administered once every 8 hours as an infusion. In some embodiments, the ceftolozane is intravenously administered as a 60-minute infusion.

[0023] In one embodiment, the ceftolozane is for use in a method of treating an intrapulmonary infection as defined in the claims. The ceftolozane is for use in a method of treating nosocomial pneumonia. The intrapulmonary infection may comprise *Pseudomonas aeruginosa, Enterobacteriaceae,* or a combination thereof. Typically, the intrapulmonary infection comprises *Pseudomonas aeruginosa.* The intrapulmonary infection may comprise a pathogen with minimum inhibitory concentration for ceftolozane and tazobactam of ≤ 8µg/ml. The intrapulmonary infection may comprise a pathogen with minimum inhibitory concentration for ceftolozane of ≤ 8µg/ml.

[0024] The invention also provides ceftolozane, for use in a method of treating an intrapulmonary infection, comprising administration of ceftolozane in combination with tazobactam as defined in the claims. The ceftolozane and tazobactam are intravenously administered. The ceftolozane and tazobactam are administered once every 8 hours as an infusion. In some embodiments, the ceftolozane and/or tazobactam is intravenously administered as a 60-minute infusion. Both the ceftolozane and tazobactam are intravenously administered. In some embodiments, both the ceftolozane and tazobactam are administered once every 8 hours as an infusion. In some embodiments, both the ceftolozane and

tazobactam are intravenously administered as a 60-minute infusion. The ceftolozane is for use in a method of treating an intrapulmonary infection as defined in the claims. The ceftolozane is for use in a method of treating nosocomial pneumonia. The intrapulmonary infection may comprise *Pseudomonas aeruginosa, Enterobacteriaceae,* or a combination thereof. Typically, the intrapulmonary infection comprises *Pseudomonas aeruginosa.* The intrapulmonary infection may comprise a pathogen with minimum inhibitory concentration for ceftolozane and tazobactam of ≤ 8µg/ml. The intrapulmonary infection may comprise a pathogen with minimum inhibitory concentration for ceftolozane of ≤ 8µg/ml.

[0025] In another aspect, the invention provides tazobactam, for use in a method of treating an intrapulmonary infection, comprising administration of tazobactam in combination with ceftolozane as defined in the claims. The tazobactam and ceftolozane is intravenously administered. In some embodiments, the tazobactam and ceftolozane is administered once every 8 hours as an infusion. In some embodiments, the tazobactam and/or ceftolozane is intravenously administered as a 60-minute infusion. Both the tazobactam and ceftolozane are intravenously administered. Both the tazobactam and ceftolozane are administered about once every 8 hours as an infusion. In another embodiments, both the tazobactam and ceftolozane are intravenously administered as a 60-minute infusion.

[0026] The tazobactam is for use in a method of treating an intrapulmonary infection as defined in the claims. The tazobactam is for use in a method of treating nosocomial pneumonia as defined in the claims. The intrapulmonary infection may comprise *Pseudomonas aeruginosa, Enterobacteriaceae,* or a combination thereof. Typically, the intrapulmonary infection comprises *Pseudomonas aeruginosa.* The intrapulmonary infection may comprise a pathogen with minimum inhibitory concentration for ceftolozane and tazobactam of ≤ 8µg/ml. The intrapulmonary infection may comprise a pathogen with minimum inhibitory concentration for ceftolozane of ≤ 8µg/ml.

[0027] In another aspect, the invention provides ceftolozane and tazobactam, as a combined preparation for simultaneous, separate or sequential use in a method of treating an intrapulmonary infection as defined in the claims. The ceftolozane and tazobactam are intravenously administered. In some embodiments, the ceftolozane and tazobactam are administered once every 8 hours as an infusion. In some embodiments, the ceftolozane and tazobactam, are intravenously administered as a 60-minute infusion.

[0028] In one embodiment, the ceftolozane and tazobactam are for use in a method of treating an intrapulmonary infection as defined in the claims. The intrapulmonary infection is nosocomial pneumonia. The intrapulmonary infection may comprise *Pseudomonas aeruginosa, Enterobacteriaceae,* or a combination thereof. Typically, the intrapulmonary infection comprises *Pseudomonas aeruginosa.* The intrapulmonary infection may comprise a pathogen with minimum inhibitory concentration for ceftolozane and tazobactam of ≤ 8µg/ml. The intrapulmonary infection may comprise a pathogen with minimum inhibitory concentration for ceftolozane of ≤ 8µg/ml.

[0029] Ceftolozane is administered in combination with tazobactam, e,g, CXA-201 is administered. 3.0 g of ceftolozane and tazobactam is administered every 8 hours. In one embodiment, the amount of the ceftolozane in the ELF of the subject effective to treat an intrapulmonary infection is at least about 8 µg/ml. The ELF concentration of ceftolozane in the ELF may reach at least about 8 µg/ml after administration of the ceftolozane. The subject is a human having nosocomial pneumonia. The subject (or patient) may, in some embodiments, have ventilator acquired pneumonia or hospital acquired pneumonia.

[0030] The safe and effective treatment of intrapulmonary infection with CXA-201 includes administration of an amount of the CXA-201 selected to provide a therapeutically effective dose of the CXA-201 antibiotic in the epithelial lining fluid (ELF). The penetration of CXA-201 into the ELF compared to a piperacillin/tazobactam comparator was assessed in a Phase 1 clinical study in healthy adult volunteers. The piperacillin/tazobactam comparator contained piperacillin/tazobactam in an 8:1 weight ratio with a total of 2.79 mEq of sodium per gram of piperacillin, FDA approved under the tradename ZOSYN® ("Zosyn"). The study results evaluate the penetration of intravenously administered CXA-201 into healthy human lungs, as measured by the ratio of area under the concentration-time curve (AUC) in epithelial lining fluid (ELF) to AUC in plasma (AUC(ELF)/AUC(plasma) ratio).

[0031] In the study, a 4.5 g amount of piperacillin/tazobactam incorporates the same dose of tazobactam (0.5 g) as 1.5 g of CXA-201. A multiple-dose regimen was used in this study to ensure that the concentrations of the analytes reached steady-state in both plasma and ELF prior to assessment. Healthy volunteers were chosen to standardize the subject population and minimize the variability associated with using actively ill patients. The objectives of the study included: (1) determination and comparison of the ELF to plasma concentration ratios of multiple-doses of intravenous CXA-201 compared to piperacillin/tazobactam in healthy adult volunteers, and (2) assessment of the safety and tolerability of multiple-doses of intravenous CXA-201 in healthy adult volunteers.

[0032] The study was a Phase 1 prospective, randomized (1:1), comparator controlled, open-label study of 50 healthy adult volunteers. Each healthy volunteer received 3 doses of either CXA-201(1.5 grams every 8 hours as a 60-minute infusion) or piperacillin/tazobactam (4.5 grams every 6 hours as a 30-minute infusion). Subjects received 3 doses of a study drug, underwent serial blood draws at planned plasma sampling timepoints, and underwent a single bronchoalveolar lavage (BAL) procedure at one of the scheduled timepoints (Table 1).

Table 1: Plasma Sampling and BAL Timepoints

Plasma Sampling Timepoints	**BAL Timepoints**
Intensive plasma sampling from all 25 subjects for one dosing interval	5 subjects per timepoint per treatment group; in hours from start of the third infusion
CXA-201	
0 (pre-PK dose trough) ,1,2,4,6,8 hours post start of infusion of the third dose of CXA 201	1,2,4,6,8 hours post start of infusion of the third dose of CXA 201

Piperacillin/tazobactam	
0 (pre-PK dose trough) ,0.5,1,2,4,6 hours post start of infusion of the third dose of piperacillin/tazobactam	0.5,1,2,4,6 hours post start of infusion of the third dose of piperacillin/tazobactam

[0033] A total of 51 subjects were enrolled; 25 in the CXA-201 group and 26 in the piperacillin/tazobactam group. Key Inclusion Criteria for the study were: (1) healthy adult male or non-pregnant females between 18 and 50 years, inclusive; (2) body mass index between 18.5 and 30; and (3) forced Expiratory Volume in 1 second (FEV1) ≥ 80%. Key Exclusion Criteria for the study were: (1) pregnancy or lactation; (2) clinically significant systemic disease or the existence of any surgical or medical condition that may have interfered with the distribution, metabolism, or excretion of CXA-201; (3) history of asthma or any restrictive or obstructive lung disease; (4) history of smoking or abuse of narcotics or alcohol; (5) positive test for human immunodeficiency virus, Hepatitis B surface antigen, or Hepatitis C antibodies; (6) any condition or situation where bronchoscopy was not advisable; and (7) impairment of renal function (CrCl < 90 mL/min).

Determination of the ELF to plasma concentration ratios of multiple-doses of intravenous CXA-201 compared to piperacillin/tazobactam in healthy adult volunteers.

[0034] Plasma and BAL datapoints were used to construct one concentration-time profile in the ELF using the mean concentrations at each time point. After dosing, a single ELF sample was obtained by bronchoalveolar lavage (BAL) from each healthy volunteer at one of 5 scheduled time points (5 subjects/time point/treatment group). The ELF to plasma concentrations of multiple-doses was determined. Serial plasma samples were collected pre- and post-treatment over a 6-hour (piperacillin/tazobactam) or 8-hour (CXA-201) time period. Urea levels in the plasma and BAL were used to calculate the ELF drug concentrations (see Table 1). Pharmacokinetic parameters for ELF were calculated by non-compartmental analysis using the mean concentrations at each time point. The intrapulmonary penetration of CXA-201 into the ELF was determined by dividing the ELF AUC_{0-t} by mean plasma AUC_{0-t}.

[0035] The concentration of CXA-201 and piperacillin/tazobactam in ELF were estimated from the concentration of drug in BAL fluid, the volume of BAL fluid collected, and the ratio of urea concentration in BAL fluid to that in plasma. Calculation of ELF volume was determined by the urea dilution method, using urea as an endogenous marker of ELF recovered by BAL. Concentration of CXA-201 and piperacillin/tazobactam in ELF was estimated from the concentration of drug in BAL fluid, the volume of BAL fluid collected, and the ratio of urea concentration in BAL fluid to that in plasma. The following formulas represent these calculations:

$$\text{CXA-201 (CXA/T)} = [\text{CXA/T}]_{\text{BAL}} \times V_{\text{BAL}}/V_{\text{ELF}}$$

[0036] $[CXA/T]_{BAL}$ is the concentration of CXA-201 in BAL fluid; V_{BAL} is the volume of aspirated BAL fluid (total); V_{ELF} is $V_{BAL} \times [urea]_{BAL}/[urea]_{plasma}$, where $[urea]_{BAL}$ is the concentration of urea in the BAL fluid (supernatant) and $[urea]_{plasma}$ is the concentration of urea in the plasma specimens.

$$\text{Piperacillin/tazobactam} = [PIP/T]_{BAL} \times V_{BAL}/V_{ELF}$$

[0037] [PIP/T]BAL is the concentration of piperacillin/tazobactam in BAL fluid; V_{BAL} is the volume of aspirated BAL fluid (total); V_{ELF} is $V_{BAL} \times [urea]_{BAL}/[urea]_{plasma}$, where $[urea]_{BAL}$ is the concentration of urea in the BAL fluid (supernatant) and $[urea]_{plasma}$ is the concentration of urea in the plasma specimens.

[0038] No oral antibiotic therapy was permitted. Safety was monitored through the review of vital signs, laboratory and physical examinations and the occurrence of adverse events (AEs). Subjects who received three doses of study medication and had both BAL and plasma samples collected were included in the pharmacokinetic (PK) analysis population. All randomized subjects who received any dose (including partial doses) of study medication were included in the safety analysis population.

[0039] The results of the study (Table 2) indicate that CXA-201 penetrated well into ELF. The ceftolozane component of CXA-201 ELF/plasma AUC ratio was 0.48, compared to 0.26 for the piperacillin component of piperacillin/tazobactam. The ELF concentrations of ceftolozane exceeded 8 µg/mL for 60% of the 8-hour dosing interval. The plasma concentrations for ceftolozane were consistent with those seen previously at this dose.

[0040] The ELF concentration vs. time profiles for ceftolozane and tazobactam components of CXA-201 are shown in Figures 2A and 2B, respectively. Comparative data showing the ELF concentration vs. time profiles for piperacillin and tazobactam components of the comparator drug are shown in Figures 3A and 3B, respectively. The ELF to plasma penetration ratios are shown in Table 2.

[0041] The PK parameters were determined by non-compartmental PK analysis. PHOENIX® WinNonlin v 6.1 (PHARSIGHT®, Mountain View, California) was used for the derivation of all PK individual measures for each subject. The PK parameters for ELF were calculated by taking the mean concentrations of the 5 subjects at each time point and constructing a single profile over the duration of sampling. In the event that the urea concentrations determined in plasma or ELF were below quantifiable limits, thereby providing only an estimate of concentration, those values were not used in the calculation of mean concentration at that time point. The ceftolozane, piperacillin, and tazobactam PK parameters that were computed in plasma and ELF were:

- C_{max} (µg/mL): Maximum plasma and ELF concentration over the entire sampling phase directly obtained from the experimental plasma concentration time data, without

interpolation.

- T_{max} (hr): Sampling time at which C_{max} occurred, obtained directly from the experimental plasma and ELF concentration time data, without interpolation.
- C_{last} (µg/mL): Plasma or ELF concentration when last quantifiable concentration was observed, relative to the end of infusion.
- T_{last} (hr): Time when the last quantifiable concentration was observed.
- AUC_{0-t} (µg*hr/mL): An area under the concentration time curve from the time of the dose to the end of the dosing interval.
- Percent penetration into ELF: Calculated as the ratio of AUC_{0-tELF} and mean $AUC_{0-tPlasma}$.

Table 2: Summary of ELF to Plasma Penetration Ratios

Analyte	Mean Plasma AUC_{0-T} (µg*hr/mL)	ELF AUC_{0-T} (µg*hr/mL)	ELF Penetration Ratio
ceftolozane (in CXA-201)	158.5	75.1	0.48
Tazobactam (in CXA-201)	19.3	8.5	0.44
Piperacillin (in piperacillin/tazobactam)	357.3	94.5	0.26
Tazobactam (in piperacillin/tazobactam)	46.1	24.7	0.54

[0042] The ELF/plasma AUC ratio for the ceftolozane component of CXA-201 was 0.48, compared to 0.26 for the piperacillin component of the comparator drug (piperacillin/tazobactam). The ELF/plasma AUC ratio for tazobactam was 0.44 and 0.54 when given as part of CXA-201 and piperacillin/tazobactam, respectively. The ELF concentrations of ceftolozane exceeded 8 µg/mL for 60% of the 8-hour dosing interval. The plasma and ELF concentrations of tazobactam when given as piperacillin/tazobactam was approximately 2-fold higher than when an equivalent dose was given as CXA-201.

[0043] The results show that ceftolozane and tazobactam (i.e., administered as CXA-201) penetrated well into the ELF of healthy volunteers compared to piperacillin/tazobactam, an agent widely used for treatment of lower respiratory infections. CXA-201's intrapulmonary pharmacokinetics support use of CXA-201 as a parenteral (e.g., intravenous) antibiotic for treatment of lower respiratory tract infections, including infections caused by pathogens with minimum inhibitory concentrations of ≤ 8µg/ml. The concentrations of ceftolozane in ELF exceeded 8 µg/mL, a concentration that inhibits 99% of *P. aeruginosa,* for approximately 60% of the 8-hour dosing interval for the CXA-201 regimen of 1.5 grams every eight hours as a 60 minute infusion.

Assessment of the safety and tolerability of multiple-doses of intravenous CX4-201 in healthy adult volunteers.

[0044] Among the subjects, 50 of the 51 (98%) subjects received all 3 doses of study medication and completed the BAL procedure. One subject prematurely discontinued piperacillin/tazobactam and terminated their participation in the study due to an AE of hypersensitivity that occurred during administration of the first dose. Demographics and baseline characteristics are summarized in Table 3, the two treatment arms were well balanced.

Table 3: Demographics and Baseline Characteristics (Safety Population)

	CXA-201 1.5 grams (N=25)	Piperacillin/ tazobactam 4.5 grams (N=26)
Sex, n (%)		
Female	11 (44.0)	11 (42.3)
Male	14 (56.0)	15 (57.7)
Age, years		
Mean (SD)	32.6 (7.8)	34.2 (8.5)
Minimum, Maximum	21, 47	22, 49
Race, n (%)		
White	20 (80.0)	21 (80.8)
Black or African American	2 (8.0)	2 (7.7)
Asian	1 (4.0)	0 (0.0)
	CXA-201 1.5 grams (N=25)	Piperacillin/ tazobactam 4.5 grams (N=26)
American Indian or Alaska Native	0 (0.0)	1 (3.8)
Native Hawaiian or Pacific Islander	1 (4.0)	0 (0.0)
Other	1 (4.0)	2 (7.7)
BMI, kg/m^2		
Mean (SD)	26.21 (2.6)	23.23 (2.4)
Minimum, Maximum	22.3, 30.0	20.6, 29.9

[0045] During the study, treatment-emergent AEs (TEAEs) occurred in 20.0% (5/25) of subjects receiving CXA-201 and 23.1% (6/26) of subjects receiving piperacillin/tazobactam. No serious AEs were reported in either treatment group. All AEs were mild in severity. The incidence and pattern of AEs were generally similar in the 2 treatment groups, Table 4.

Table 4: TEAEs by Preferred Term (Safety Population)

Subjects with at least 1 TEAE	*5 (20.0)*	*6 (23.1)*
Diarrhea	1 (4.0)	3 (11.5)
Viral Upper Respiratory Infection	1 (4.0)	0 (0)
Musculoskeletal Chest Pain	1 (4.0)	0 (0)
Somnolence	1 (4.0)	0 (0)
Hematuria	1 (4.0)	0 (0)
Cough	1 (4.0)	0 (0)
Type I Hypersensitivity	0 (0)	1 (3.8)
Alanine Aminotransferase Increased	0 (0)	1 (3.8)
Aspartate Aminotransferase Increased	0 (0)	1 (3.8)
Blood Creatine Phosphokinase Increased	0 (0)	1 (3.8)
Hyperkalemia	0 (0)	1 (3.8)

[0046] Eight subjects had TEAEs assessed as related to study drug; two in the CXA-201 group (diarrhea and somnolence in 1 subject each) and six in the piperacillin/tazobactam group (diarrhea in 3 subjects, type I hypersensitivity in 1 subject, blood creatine phosphokinase increased in 1 subject, and alanine aminotransferase increased, aspartate aminotransferase increased, and hyperkalaemia all in the same 1 subject). One piperacillin/tazobactam-treated subject discontinued study drug due to an adverse event, type I hypersensitivity. There were no clinically significant changes in safety laboratory assessments or vital signs.

[0047] CXA-201 appeared safe and well tolerated in this group of healthy adult subjects.

Determining appropriate dose

[0048] A Monte Carlo simulation was performed based on clinical trial data to predict an effective CXA-201 dose for treating nosocomial pneumonia using PHOENIX® NLME (PHARSIGHT®, Mountain View, CA) software, a tool for data processing and modeling for population PK/PD analysis. A population pharmacokinetic (PK) model was developed using the CXA-201 plasma concentration versus time data from a previously conducted Phase 2 study in patients with complicated intra abdominal infections. Estimates of clearance and volume of distribution along with the associated inter-individual variability were obtained from these analyses. The outputs from the PK population model served as inputs for a clinical trial simulation performed using PHARSIGHT® Trial Simulator (PHARSIGHT®) software, a tool for defining and testing interactive drug models, exploring and communicating study design attributes, and performing statistical and sensitivity analysis through graphical and statistical summaries. Based on the mean ELF penetration data, an ELF/Plasma AUC ratio of 0.48 for ceftolozane (modeled as a numerical range of 0.25-0.65) calculated from the ceftolozane ELF

study mentioned above was used to generate a random /Plasma AUC ratio from the range 0.25 - 0.65 for each simulated patient. This range reflects a conservative estimate of the potential distribution in a patient population. Using the results from the PK population model and the ELF/Plasma AUC ratio, the model simulated plasma and ELF concentration of CXA-201 versus time profiles for 1,000 hypothetical clinical trial patients with nosocomial pneumonia. The model evaluated the probability of clinical success of the 3.0 g every 8 hour (q8h) dose of CXA-201 against three key pathogens in nosocomial pneumonia. The MIC distribution for these pathogens was imputed from 2008 United States surveillance data. Clinical success was defined as the achievement of an ELF or plasma concentration of ceftolozane higher than the MIC(s) of the lower respiratory pathogen(s) for a given patient. *In vivo* models have demonstrated that, as for typical cephlaosporins, the relavent PK/PD driver for CXA-201 is the percentage of time above MIC during the dosing interval. The target is to achieve concentrations that exceed the MIC of the pathogen for 45-50% of the time between each q8H dose. Thus, a threshold of 50% time above the minimum inhibitory concentration [T>MIC] on Day 7 of treatment was used. Plasma and ELF concentrations were estimated at 15 time-points post-administration on Day 7 when dosed every 8 hours. The results of these simulations are shown in Table 5.

Table 5: Probability of Target Attainment versus Key Pathogens in Nosocomial Pneumonia Using the Simulated 3.0 g versus the 1.5 g Dose of Ceftolozane/tazobactam

Pathogen	**Dosing Regimen**	**50% T>MIC in Plasma**	**50% T>MIC in ELF**
P. aeruginosa	1.5 g q8h	98.2	94.6
	3.0 g q8h	99.4	98.5
E. coli	1.5 g q8h	96.3	94.2
	3.0 g q8h	98.8	95.5
K. pneumoniae	1.5 g q8h	90.2	87.3
	3.0 g q8h	92.6	89.3
Abbreviation: T > MIC = Time above minimum inhibitory concentration.			

[0049] These simulations demonstrate that the 3.0 g dose of CXA-201 administered every 8 hours is expected to provide adequate concentrations for treatment of the vast majority of lower respiratory infections caused by these pathogens.

[0050] Following these simulations, the safety and tolerability of a 10 day course of CXA-201 3.0 g IV q8h was evaluated in healthy human volunteers. Subjects were randomized to receive either 3.0 g (2.0/1.0 g) CXA-201 (n=8), 1.5 g (1.0/0.5 g) CXA-201 (n=4), or placebo (n=4). The data showed that CXA-201 was generally safe and well tolerated in this study. There were no serious adverse events or deaths reported in this study.

[0051] In conclusion, given the pharmacokinetic simulations conducted, the favorable data from the intrapulmonary PK study and demonstrated safety and tolerability of the higher dose

of CXA-201 in the Phase 1 study mentioned above, the data provide justification for the use of 3.0 g CXA-201 IV q8h for the treatment of patients with nosocomial pneumonia caused by Gram-negative pathogens.

Preparing CXA-201

[0052] CXA-201 can be prepared by combining ceftolozane and tazobactam in a 2:1 weight ratio. CXA-201 can be obtained using methods described in US patent 7,129,232 and Toda et al., "Synthesis and SAR of novel parenteral anti-pseudomonal cephalosporins: Discovery of FR264205," Bioorganic & Medicinal Chemistry Letters, 18, 4849-4852 (2008).

[0053] According to the method disclosed in Toda et al., "Synthesis and SAR of novel parenteral anti-pseudomonal cephalosporins: Discovery of FR264205," Bioorganic & Medicinal Chemistry Letters, 18, 4849-4852 (2008), ceftolozane can be obtained by the synthetic schemes of Figures 4A and 4B. Referring to Figures 4A and 4B, synthesis of ceftolozane can be performed via activation of the thiadiazolyl-oximinoacetic acid derivative (I) with methanesulfonyl chloride and K_2CO_3 in DMA at 10°C, followed by coupling with the 7-aminocephem (II) by means of Et_3N in cold EtOAc/H_2O, affords amide (III) (1). Substitution of the allylic chloride of compound (III) with 4-[(N-Boc-aminoethyl)carbamoylamino]-1-methyl-5-tritylaminopyrazole (IV) in the presence of 1,3-bis(trimethylsilyl)urea (BSU) and KI in DMF then affords the protected pyrazolium adduct (V), which, after full deprotection with trifluoroacetic acid in anisole/CH_2Cl_2,can be isolated as the hydrogensulfate salt by treatment with H2SO4 in i-PrOH/H_2O (1, 2). Scheme 1. The pyrazolyl urea intermediate (IV) can be prepared as follows. Treatment of 5-amino-1-methylpyrazole (VI) with $NaNO_2$/HCl in water at 5°C gives the 4-nitrosopyrazole derivative (VII), which can be reduced to the diaminopyrazole (VIII) by catalytic hydrogenation over Pd/C in the presence of H_2SO_4. Selective acylation of the 4-amino group of compound (VIII) with phenyl chloroformate in the presence of NaOH in H_2O/dioxane at 10°C then yields the phenyl carbamate (IX). After protection of the free amine group of carbamate (IX) with chlorotriphenylmethane in the presence of Et_3N in THF, the resulting N-trityl derivative (X)can be coupled with N-Boc-ethylenediamine (XI) in the presence of Et_3N in DMF to afford pyrazolyl urea (IV).

Biological Activity Assay

[0054] The antibacterial activity of the CXA-201 or other compounds can be measured by the minimum inhibitory concentrations (MIC) of the compounds against various bacteria measured by using the broth microdilution method performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines with modifications as described below (CLSI guidelines can be derived from the CLSI document M7-A8 published in January 2009: "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved

Standard-Eighth Edition").

[0055] To prepare for MIC testing, individual colonies can be isolated by streaking frozen glycerol material containing Staphylococcus or Pseudomonas spp. onto rich, non-selective, tryptic soy agar containing 5% sheep's blood (TSAB), and incubated at 37°C for 18-24 hrs.

[0056] On the day of testing, primary cultures can be started by scraping off 5-10 colonies from the TSAB plates. The material can be suspended in ~5 mL of cation adjusted Mueller Hinton Broth (CAMHB) in 14 mL culture tubes and can be incubated at 37°C with aeration (200 rpm) for ~2 hrs until the OD600 was ≥0.1.

[0057] Inoculum cultures can be prepared by standardizing the primary cultures to OD600 = 0.1 and then adding 20 µL of the adjusted primary culture per 1 mL CAMHB for Pseudomonas and CAMHB plus 4% NaCl for MRSA so that the final inoculum density was ~10^5 colony forming units per milliliter. Diluted inoculum cultures can be used to inoculate 50 µL per well in 96 well broth microdilution assay plates. 50 µL of CAMHB that contained compound concentrations ranging from 64 - 0.06 µg/mL in two-fold dilutions can also be added to the broth microdilution assay plates for a final volume 100 µL per well, therefore final culture OD_{600} was approximately 0.001 and the final NaCl concentration for the MRSA strain was 2%.

[0058] Plates can be incubated for 18-20 hours at 37°C with aeration (200 rpm). Following incubation, growth can be confirmed visually placing plates over a viewing apparatus (stand with a mirror underneath) and then OD_{600} can be measured using a SpectraMax 340PC384 plate reader (Molecular Devices, Sunnyvale, CA). Growth was defined as turbidity that could be detected with the naked eye or achieving minimum OD_{600} of 0.1. MIC values were defined as the lowest concentration producing no visible turbidity.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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- US7129232B [0052]

Non-patent literature cited in the description

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- **PENNINGTON, J. E.**Penetration of antibiotics into respiratory secretionsRev Infect Dis, 1981, vol. 3, 167-73 [0010]
- **LEVY, J. et al.**Bioactivity of gentamicin in purulent sputum from patients with cystic fibrosis or bronchiectasis: comparison with activity in serumJ Infect Dis, 1983, vol. 148, 61069-76 [0010]
- **LODISE, GOTTFREID, DRUSANO**Antimicrobial Agents and Chemotherapy, 2008, [0011]
- **TODA et al.**Synthesis and SAR of novel parenteral anti-pseudomonal cephalosporins: Discovery of FR264205Bioorganic & Medicinal Chemistry Letters, 2008, vol. 18, 4849-4852 [0052] [0053]
- Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow AerobicallyCLSI document M7-A820090100 [0054]

CEFTOLOZAN/TAZOBACTAM TIL BEHANDLING AF INTRAPULMONALE INFEKTIONER

PATENTKRAV

1. Ceftolozan (CXA-101) og tazobactam i et 2:1 (ceftolozan:tazobactam) vægtforhold ved en dosis på 3,0 g til anvendelse i en fremgangsmåde til behandling af nosokomiel pneumoni forårsaget af gramnegative patogener hos et menneske, hvor ceftolozan og tazobactam administreres intravenøst hver 8. time, og hvor ceftolozan er i dets frie baseform eller i dets saltform.

2. Ceftolozan og tazobactam til anvendelse ifølge krav 1, hvor ceftolozan og tazobactam administreres intravenøst hver 8. time som en infusion.

3. Ceftolozan og tazobactam til anvendelse ifølge krav 2, hvor ceftolozan og tazobactam administreres som en 60-minutters infusion.

4. Ceftolozan og tazobactam til anvendelse ifølge et hvilket som helst af kravene 1 til 3, hvor den intrapulmonale infektion omfatter *Pseudomonas aeruginosa, Enterobacteriaceae* eller en kombination deraf.

5. Ceftolozan og tazobactam til anvendelse ifølge krav 4, hvor den intrapulmonale infektion omfatter *Pseudomonas aeruginosa.*

6. Ceftolozan og tazobactam til anvendelse ifølge et hvilket som helst af kravene 1 til 5, hvor ceftolozan er i dets frie baseform.

7. Ceftolozan og tazobactam til anvendelse ifølge et hvilket som helst af kravene 1 til 6, hvor ceftolozan er i dets saltform.

8. Ceftolozan og tazobactam til anvendelse ifølge krav 7, hvor ceftolozan er i dets hydrogensulfatform.

9. Ceftolozan og tazobactam til anvendelse ifølge et hvilket som helst af kravene 1 til 8, hvor ceftolozan og tazobactam er i en farmaceutisk sammensætning.

DRAWINGS

Drawing

Figure 1

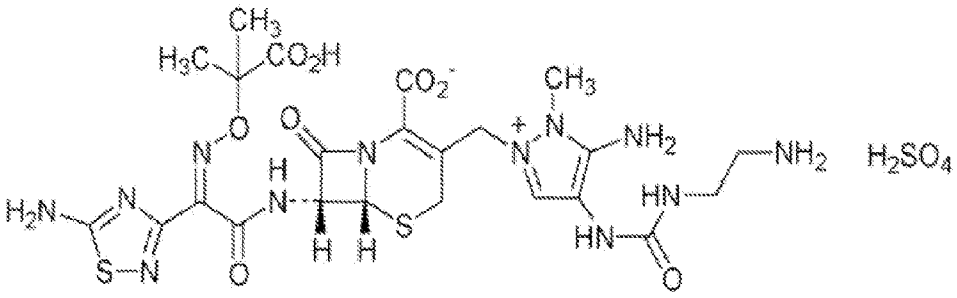
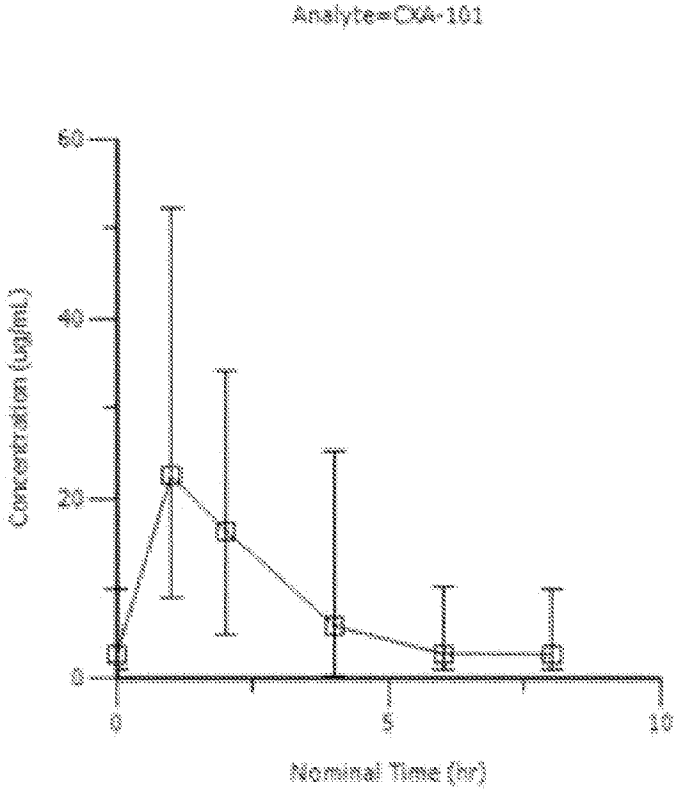


Figure 2A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60
40
20
0
Concentration (ug/mL)
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5
10
Nominal Time (hr)

Figure 2B

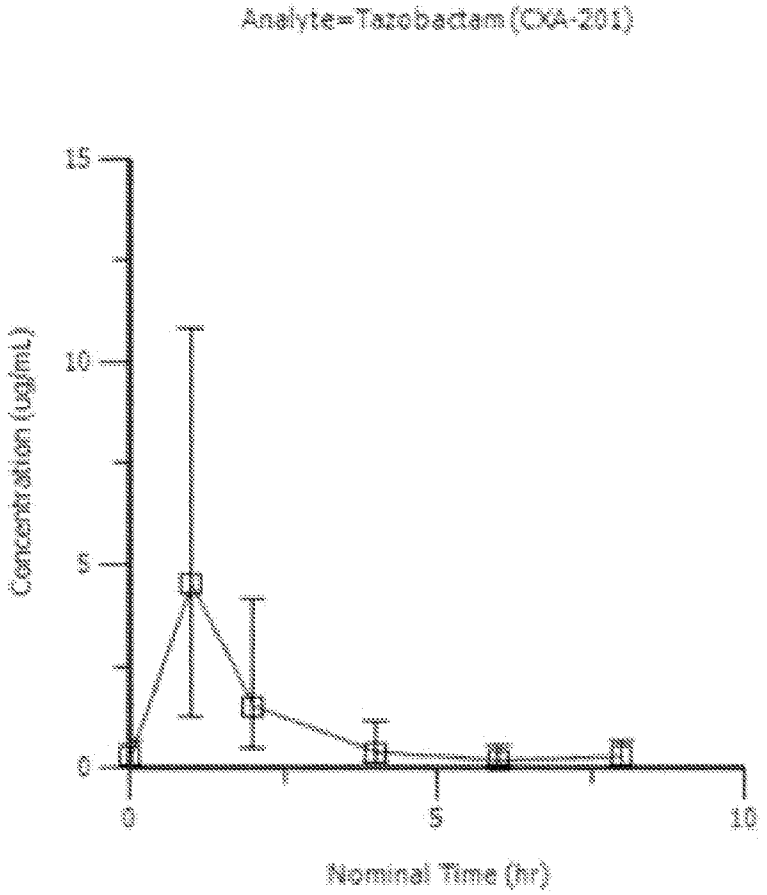

Analyte=Tazobactam (CXA-201)
Concentration (ug/mL)
15
10
5
0
0
5
10
Nominal Time (hr)

Figure 3A

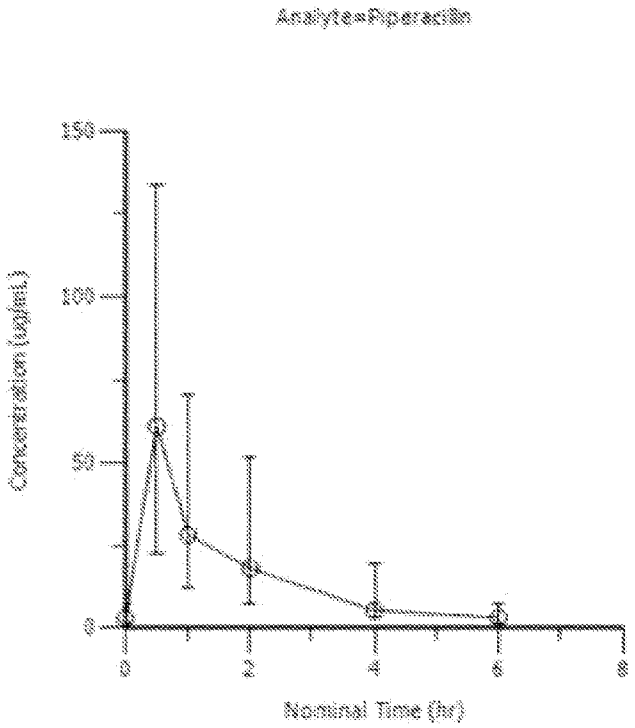

Analyte=Piperacillin
150
100
50
0
Concentration (ug/mL)
0
2
4
6
8
Nominal Time (hr)

Figure 3B

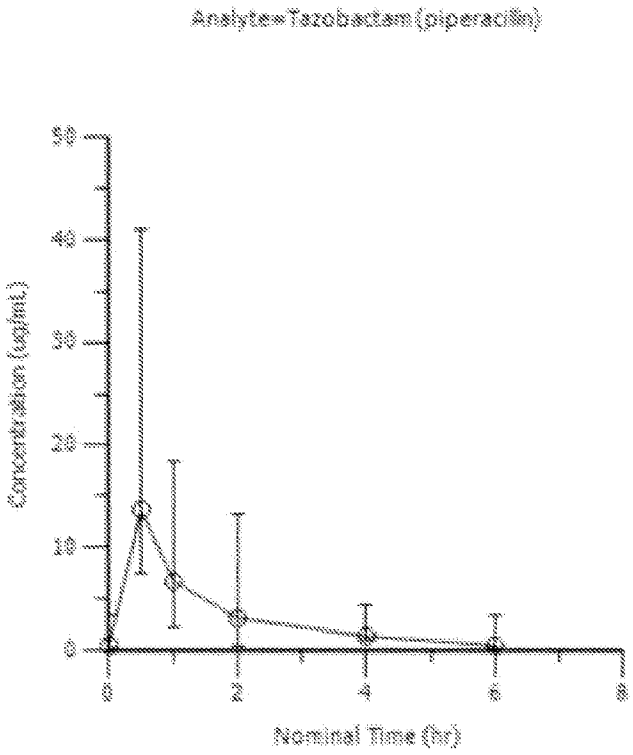
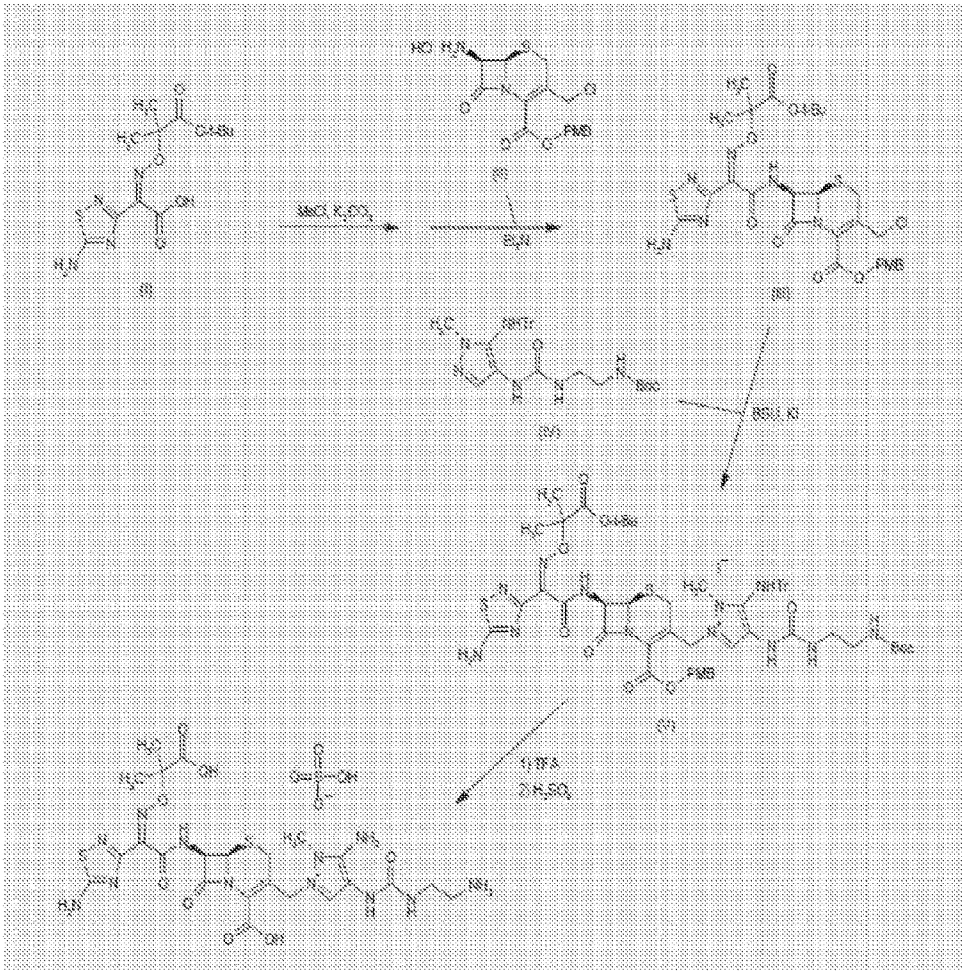
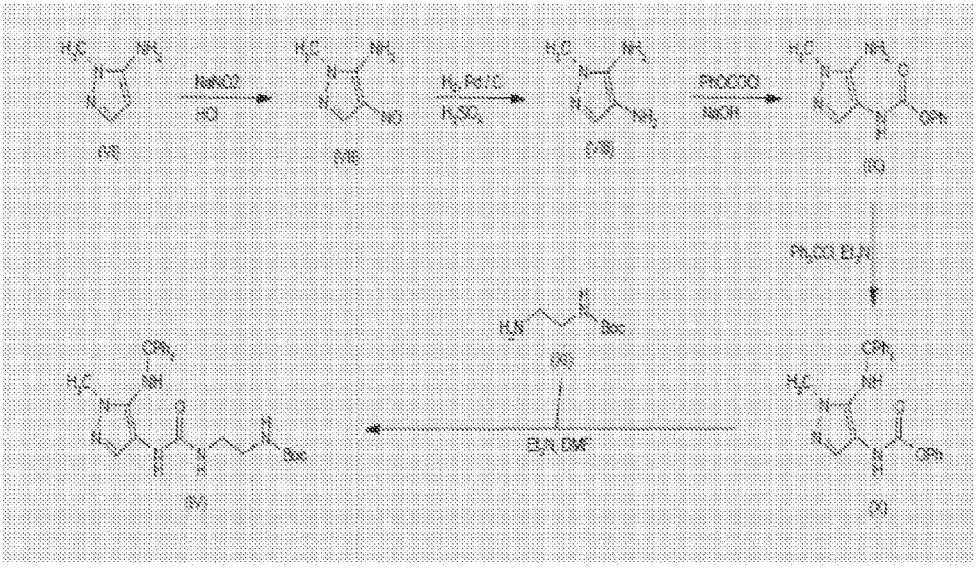

Analyte=Tazobactam (piperacillin)
Concentration (ug/mL)
50
40
30
20
10
0
0
2
4
6
8
Nominal Time (hr)

Figure 4A



Scheme 1

Figure 4B



Scheme 2