(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 October 2010 (28.10.2010)

PCT

(10) International Publication Number
WO 2010/122456 A1

(51) International Patent Classification:
A61K 31/43 (2006.01) *A61P 31/06* (2006.01)
A61K 31/431 (2006.01)

(21) International Application Number:
PCT/IB2010/051623

(22) International Filing Date:
14 April 2010 (14.04.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/171,563 22 April 2009 (22.04.2009) US

(71) Applicant *(for all designated States except US)*: **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **WALLIS, Robert Steven** [US/US]; Pfizer Global Research and Development, 50 Pequot Avenue, New London, CT 06320 (US).

(74) Agent: **BENSON, Gregg C.**; PFIZER INC., Eastern Point Road MS9114, Groton, CT 06340 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2010/122456 A1

(54) **Title**: COMPOSITIONS OF SULOPENEM AND USE FOR TREATING TUBERCULOSIS

(57) **Abstract**: The present invention relates to methods of treating tuberculosis, including multi-drug resistant varieties and latent tuberculosis. More particularly, the present invention relates to a method of treating tuberculosis in a mammal comprising administering to said mammal in need thereof an effective amount of (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid ("sulopenem") or a pharmaceutically acceptable salt or prodrug thereof. The present invention also relates to a method of treating tuberculosis in a mammal comprising administering to said mammal in need thereof an effective amount of sulopenem or a pharmaceutically acceptable salt or prodrug thereof in combination with an agent useful in the treatment of tuberculosis. The present invention also relates to a pharmaceutical composition comprising (i) a therapeutically effective amount of sulopenem or a pharmaceutically acceptable salt or prodrug thereof (ii) a therapeutically effective amount of at least one other agent useful in the treatment of tuberculosis and (iii) one or more pharmaceutically acceptable carriers or vehicles.

COMPOSITIONS OF SULOPENEM AND USE FOR TREATING TUBERCULOSIS

Field of the Invention

The present invention relates to methods of treating tuberculosis, including multi-drug resistant varieties and latent tuberculosis. More particularly, the present invention relates to a method of treating tuberculosis in a mammal comprising administering to said mammal in need thereof an effective amount of (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid ("sulopenem") or a pharmaceutically acceptable salt or prodrug thereof. The present invention also relates to a method of treating tuberculosis in a mammal comprising administering to said mammal in need thereof an effective amount of sulopenem or a pharmaceutically acceptable salt or prodrug thereof in combination with an agent useful in the treatment of tuberculosis. The present invention also relates to a pharmaceutical composition comprising: (i) a therapeutically effective amount of sulopenem or a pharmaceutically acceptable salt or prodrug thereof; (ii) a therapeutically effective amount of at least one other agent useful in the treatment of tuberculosis and (iii) one or more pharmaceutically acceptable carriers or vehicles.

Background of the Invention

Tuberculosis (TB) kills approximately 1.6 million people worldwide each year, making it the second leading killer of adults behind HIV. Nearly 500,000 new cases of multidrug-resistant (MDR) TB occur each year and the recent emergence of extensively drug-resistant (XDR-TB) TB portends new epidemics of untreatable TB. (See Dorman, S. E. et al., Nat.Med 13:295-298 2007, Zignol, M. et al., J Infect.Dis 194:479-485, 2006).

Specifically, XDR-TB is a global health emergency. It first came to broad public attention following an outbreak of highly resistant TB in HIV-infected persons in KwaZulu-Natal, South Africa in 2005. 50,000 XDR cases are presently estimated in more than 50 countries. N. S. Shah *et al.*, *Emerg. Infect. Dis.* **13**, 380 (2007). It is thought that these represent only a small fraction of the true total, however, as the countries that likely are most affected lack necessary laboratory diagnostic facilities to identify XDR TB. The emergence of XDR TB has been particularly fueled by increased access to 2nd line TB drugs earlier in this decade in regions with high MDR prevalence, including China, the former Soviet Union, and parts of Asia (including India, Pakistan, Bangladesh, Iran, Indonesia, and Vietnam) and Africa (including South Africa, Nigeria, and Congo). These high burden countries account for >85% of the world's estimated

500,000 MDR TB cases. MDR rates in these regions continue to increase, fueling the spread of XDR TB. Iran, for example, now reports 10% of MDR strains are "super-XDR" with resistance to all 2nd line drugs. A. Velayati *et al.*, *Chest* (2009).

New drugs with potent anti-tuberculosis activity, especially against non-multiplying persisters, are needed to shorten the duration of treatment for TB and thereby facilitate the global implementation of directly-observed therapy. (See O'Brien, R. J. et al., Am.J.Respir. Crit Care Med. 163:1055-1058, 2001).

Currently, the treatment of drug-sensitive tuberculosis consists of administering a combination of at least the following drugs, isoniazid, rifampin, and pyrazinamide. For effective treatment, the above-mentioned drugs are given to a patient in an initial phase of treatment for 8 weeks, during which the drugs are used in combination to kill the rapidly multiplying population of *Mycobacterium tuberculosis* as well as to prevent the emergence of drug resistance. The initial phase of treatment is followed by a continuation or a sterilization phase for 18 weeks during which two or more sterilizing drugs (*e.g.* isoniazid and rifampin) are given to kill the intermittently dividing population (non-multiplying persisters) of *Mycobacterium tuberculosis*.

While the above-mentioned combination of drugs together provide treatment against sensitive *Mycobacterium tuberculosis* infection in 4 to 6 months time, such a combination therapy is not always successful, especially in patients harboring drug resistant strains. Also, the long duration of treatment consisting of six months may lead to unpleasant side effects. Further, compliance with the relatively long course of treatment is generally poor. Such non-compliance may lead to treatment failure resulting in development of drug resistance.

β-lactams are perhaps the most successful class of antimicrobials in general medicine. In certain clinical situations, their role can be further enhanced by combination with drugs of other classes. Combined with β-lactamase inhibitors (BLI, which avidly bind β-lactamases but not penicillin binding proteins), they have become first line treatments for otherwise resistant respiratory infections. Combined with inhibitors of bacterial protein synthesis (aminoglycosides and rifampin), β-lactams have made possible the accelerated cure of infections that would otherwise be difficult or impossible to eradicate, such as enterococcal and streptococcal endocarditis, and serious staphylococcal infections. This synergy has been attributed to the combined effects of drugs acting on the cell wall and on protein synthesis.

β-lactams have yet to be proven of value in TB, either alone or in specific combinations. This has been attributed to *blaC*, a mycobacterial gene encoding a highly active class A β-lactamase. A. R. Flores, L. M. Parsons, M. S. Pavelka, Jr., *Microbiology* **151**, 521 (2005) . BlaC shows unusually broad substrate specificity, including penicillins, cephalosporins, and carbapenems J. E. Hugonnet, J. S. Blanchard, *Biochemistry* **46**, 11998 (2007). However, the slow rate of hydrolysis of carbapenems (10^{-5} that of ampicillin) may explain the apparent partial activity of imipenem and meropenem *in vitro* and in experimental animals and patients. H. F. Chambers, et al, *Antimicrob. Agents Chemother.* **49**, 2816 (2005). Although MIC50 values of 4-8 μg/mL have been reported for this drug class, early studies indicated substantial variability due to drug instability *in vitro*. B. Watt, J. R. Edwards, A. Rayner, A. J. Grindey, G. Harris, *Tuber. Lung Dis.* **73**, 134 (1992). Part of the instability is likely due to slow hydrolysis by mycobacterial β-lactamases.

BlaC can be irreversibly inhibited by clavulanate at concentrations of 2.5 μg/mL. J. E. Hugonnet, J. S. Blanchard, *Biochemistry* **46**, 11998 (2007). Other BLIs such as sulbactam and tazobactam are also active, but only result in transient, reversible inhibition. Several small studies have conducted limited drug susceptibility testing of amoxicillin/clavulanate (AUGMENTIN) against clinical *M. tuberculosis* strains. G. Abate, H. Miorner, *J. Antimicrob Chemother* **42**, 735 (1998); J. S. Bergmann, G. L. Woods, *Int. J. Tuberc. Lung Dis.* **2**, 621 (1998); Dincer, A. Ergin, T. Kocagoz, *Int. J. Antimicrob. Agents* **23**, 408 (2004); J. E. Hugonnet, L. W. Tremblay, H. I. Boshoff, C. E. Barry, III, J. S. Blanchard, *Science* **323**, 1215 (2009). Although most strains would be considered susceptible based on plasma levels of amoxicillin (Cmax 10-12 μg/mL after 875 mg oral dosing), a substantial minority of strains fail to be inhibited by concentrations of 10 μg/mL or greater and would be considered resistant. This variability may explain the discrepant findings of two studies of the early bactericidal activity (EBA) of amoxicillin/clavulanate in patients with newly diagnosed drug-sensitive pulmonary TB, with one study showing the combination to be highly active, and the second, entirely inactive. H. F. Chambers, T. Kocagoz, T. Sipit, J. Turner, P. C. Hopewell, *Clin Infect Dis* **26**, 874 (1998); P. R. Donald *et al.*, *Scand. J. Infect Dis* **33**, 466 (2001). EBA primarily indicates activity against replicating, extracellular mycobacteria. Two studies have examined oral β-lactam/BLI effects against intracellular *M. tuberculosis*. In one, concentrations of 100 μg/mL of ampicillin/sulbactam were required for full activity in mouse macrophages K. Prabhakaran, E. B. Harris, B. Randhawa, *Int. J. Antimicrob*

Agents **13**, 133 (1999). In the second, oral administration of 875/125 mg amoxicillin/clavulanate failed to affect intracellular *M. tuberculosis* growth *ex vivo* using whole blood culture R. S. Wallis *et al.*, *J. Infect Dis.* **183**, 1300 (2001). Together, these studies indicate little or no role for current oral β-lactam/BLI combinations in TB, due to the inability to reach adequate concentrations in blood and target tissues.

The situation is quite different for penems. Hugonnet recently reported clavulanate afforded 4 to 8-fold reductions in carbapenem MICs for *M. tuberculosis.* J. E. Hugonnet, L. W. Tremblay, H. I. Boshoff, C. E. Barry, III, J. S. Blanchard, *Science* **323**, 1215 (2009). The resulting MIC90 values are well below anticipated Cmax values in blood (for meropenem, for example, 0.9 µg/mL MIC90 *vs.* 25-50 µg/mL Cmax). Hugonnet further reported concentration-independent killing by meropenem/clavulanate in aerobic broth culture (consistent with T>MIC as the main determinant of efficacy), and concentration-dependent killing in hypoxic culture. These findings indicate the potential for bactericidal activity against diverse mycobacterial subpopulations *in vivo.* There are several caveats however. First and foremost is the requirement of meropenem for intravenous administration, which remains a critical obstacle that will prevent its wide use for M/XDR TB in regions of the world with greatest need. Secondly, although it appears that activity against *M. tuberculosis* is a general property of penems as a class, differences in MICs of up to 4-fold appear to exist among them; these have not been adequately studied. Some β-lactams have reduced intracellular penetration compared to established TB drugs. W. L. Hand, R. W. Corwin, T. H. Steinberg, G. D. Grossman, *Am Rev. Respir Dis* **129**, 933 (1984); M. B. Murdoch, L. R. Peterson, *Semin. Respir Infect* **6**, 112 (1991); this may prevent reaching adequate drug levels in granulomas. As a result, experimental validation is required to determine if the *in vitro* studies of Hugonnet predict efficacy in experimental animals or patients.

Hence, there is an urgent need to develop newer regimens that can be used to prevent, treat and/or reduce tuberculosis and/or eliminate the threat of multi-drug resistant tuberculosis or shorten the duration of treatment.

Summary of the Invention

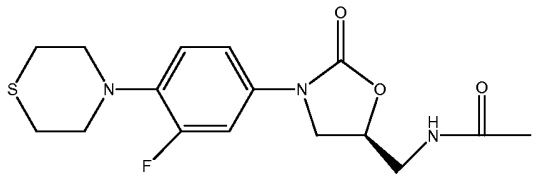
The present invention relates to a method of treating tuberculosis in a mammal comprising administering to the mammal in need thereof an effective amount of (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (“sulopenem”) or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the prodrug is (2-Ethyl-1-oxobutoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

In another embodiment, the prodrug is (2-Ethoxy-2-methyl-1-oxopropoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

In another embodiment, the method further comprising administering clavulanate to the mammal.

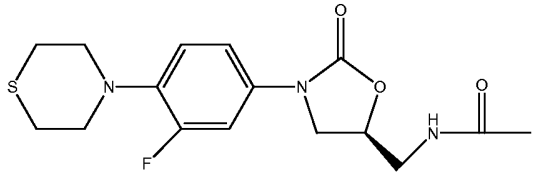
In another embodiment, the method further comprising administering a compound of formula (I) or a prodrug thereof or a pharmaceutically acceptable salt thereof:



(I)

to the mammal.

In another embodiment, the method further comprising administering clavulanate and a compound of formula (I) or a prodrug thereof or a pharmaceutically acceptable salt thereof:



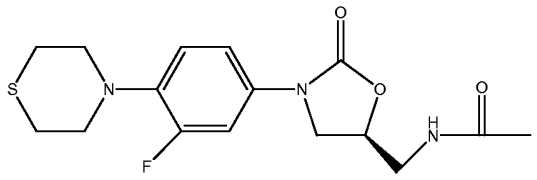
(I)

to the mammal.

In another embodiment, the present invention relates to a method of treating tuberculosis in a mammal comprising administering to the mammal in need thereof an effective amount of the prodrug (2-Ethyl-1-oxobutoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate and clavulanate to the mammal.

In another embodiment, the present invention relates to a method of treating tuberculosis in a mammal comprising administering to the mammal in need thereof an effective amount of the prodrug (2-Ethyl-1-oxobutoxy)methyl (5R,6S)-6-[(1R)-1-

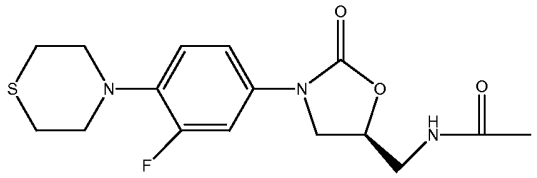
hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate and a compound of formula (I) or a prodrug thereof or a pharmaceutically acceptable salt thereof:



(I)

to the mammal.

In another embodiment, the present invention relates to a method of treating tuberculosis in a mammal comprising administering to the mammal in need thereof an effective amount of the prodrug (2-Ethyl-1-oxobutoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate, clavulanate, and a compound of formula (I) or a prodrug thereof or a pharmaceutically acceptable salt thereof:

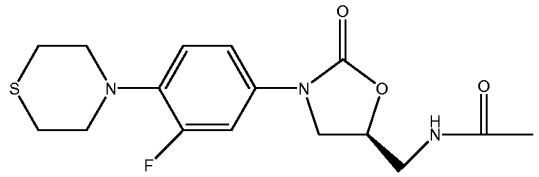


(I)

to the mammal.

In another embodiment, the present invention relates to a method of treating tuberculosis in a mammal comprising administering to the mammal in need thereof an effective amount of the prodrug (2-Ethoxy-2-methyl-1-oxopropoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate and clavulanate to the mammal.

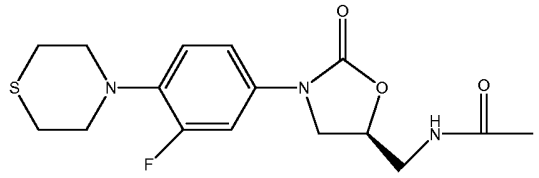
In another embodiment, the present invention relates to a method of treating tuberculosis in a mammal comprising administering to the mammal in need thereof an effective amount of the prodrug (2-Ethoxy-2-methyl-1-oxopropoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate and a compound of formula (I) or a prodrug thereof or a pharmaceutically acceptable salt thereof:



(I)

to the mammal.

In another embodiment, the present invention relates to a method of treating tuberculosis in a mammal comprising administering to the mammal in need thereof an effective amount of the prodrug (2-Ethoxy-2-methyl-1-oxopropoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate, clavulanate, and a compound of formula (I) or a prodrug thereof or a pharmaceutically acceptable salt thereof:



(I)

to the mammal.

In another embodiment, the tuberculosis comprises active tuberculosis or latent tuberculosis.

In another embodiment, the active tuberculosis comprises drug-sensitive tuberculosis, mono-drug resistant tuberculosis, multi-drug-resistant tuberculosis (MDR) or extensively drug-resistant tuberculosis (XDR).

In another embodiment, the tuberculosis is caused by a *Mycobacterium* infection selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium bovis* or other related mycobacterial species.

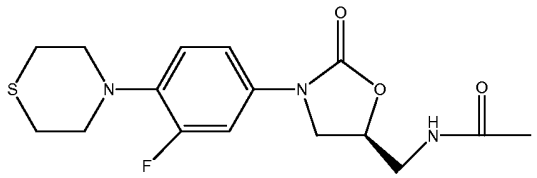
In another embodiment, the present invention relates to a pharmaceutical composition comprising (i) a therapeutically effective amount of (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid or a pharmaceutically acceptable salt or prodrug thereof; (ii) a therapeutically effective amount of at least one other agent useful in the treatment of tuberculosis; and (iii) one or more pharmaceutically acceptable carriers or vehicles.

In another embodiment, the present invention relates to a pharmaceutical composition comprising the prodrug (2-Ethyl-1-oxobutoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

In another embodiment, the present invention relates to a pharmaceutical composition comprising the prodrug (2-Ethoxy-2-methyl-1-oxopropoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

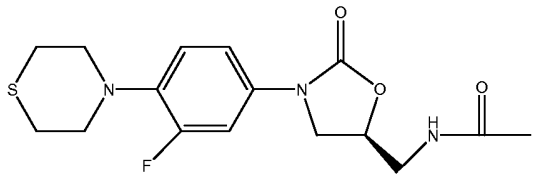
In another embodiment, the at least one other agent is clavulanate .

In another embodiment, the at least one other agent is a compound of formula (I) or a prodrug thereof or a pharmaceutically acceptable salt thereof:



(I).

In another embodiment, the at least one other agent is clavulanate and a compound of formula (I) or a prodrug thereof or a pharmaceutically acceptable salt thereof:



(I).

Brief Description of the Drawings

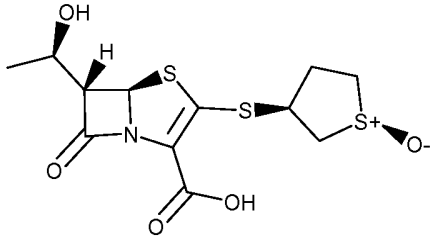
Figure I depict the results obtained in Example 5.

Figure II depict the results obtained in Example 6.

Detailed Description of the Invention

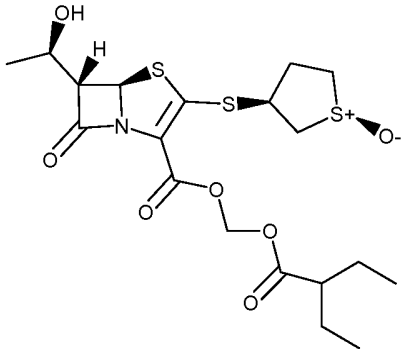
The present invention relates to a method of treating tuberculosis in a mammal comprising administering to said mammal in need thereof an effective amount of (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid ("sulopenem") or a pharmaceutically acceptable salt or prodrug thereof.

Sulopenem (chemical name (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid) also known as 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[[(1*R*,3*S*)-tetrahydro-1-oxido-3-thienyl]thio]-, (5*R*,6*S*)-, is a extended-spectrum antibiotic with the following chemical structure:



and is described in US5013729, which is incorporated by reference. Prodrugs of sulopenem are disclosed in, *e.g.*, US4952577; US5506225; WO1992/003444l; WO2004/067532; and WO2008001212, which are also incorporated by reference.

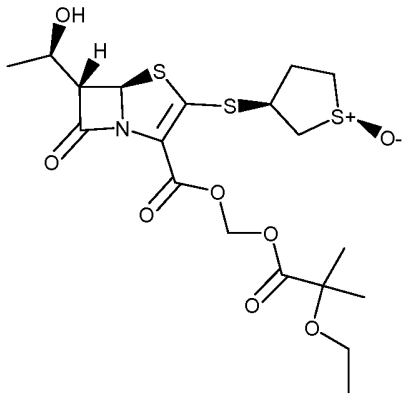
Preferable prodrugs are (2-ethyl-1-oxobutoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate also known as 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[[(1*R*,3*S*)-tetrahydro-1-oxido-3-thienyl]thio]-, (2-ethyl-1-oxobutoxy)methyl ester, (5*R*,6*S*)-with the following chemical structure:



;

and (2-ethoxy-2-methyl-1-oxopropoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-

[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate with the following chemical structure:



both of which are disclosed in WO2008001212, which is incorporated by reference.

Sulopenem prodrugs may be prepared from the free acid of sulopenem according to known methods such as those disclosed herein or in US3951954; US4234579; US4287181; US4452796; US4342693; US4348264; US4416891; US4457924; US5013729, and WO2008001212, all of which are incorporated by reference.

Sulopenem prodrugs may be amorphous or may exist as different crystal forms or polymorphs, including solvates and hydrates. Polymorphs of prodrugs form part of this invention and may be prepared by crystallization of a prodrug of the present invention under various conditions. Polymorphs may also be obtained by heating or melting a prodrug followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or other such techniques.

In one embodiment, the method further comprises administering clavulanate to the mammal. Clavulanic acid is a β-lactamase inhibitor and is included with the β-lactam antibiotic amoxycillin to counter a β-lactamase mediated resistance mechanism. Potassium clavulanate (hereinafter termed "clavulanate" unless a specific salt is identified) is its most common form, however other pharmaceutically acceptable salt(s) described below may be used.

In one embodiment, the method further comprises administering a compound of formula (I) to the mammal. The compound of formula (I) is disclosed in US 5880118, (incorporated in its entirety herein by reference) in Example 1, (S)-N-[[3-[3-fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. As described in more

detail below, the compound of formula (I) may be administered as the free base or in the form of a salt thereof.

The phrase “pharmaceutically acceptable salt(s)”, as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the above mentioned compounds.

For example, the above-mentioned compounds that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds of those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p toluenesulfonate and pamoate [i.e., 1,1’-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Examples of salts include, but are not limited to, acetate, acrylate, benzenesulfonate, benzoate (such as chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, and methoxybenzoate), bicarbonate, bisulfate, bisulfite, bitartrate, borate, bromide, butyne-1,4-dioate, calcium edetate, camsylate, chloride, caproate, caprylate, citrate, decanoate, dihydrogenphosphate, edetate, edislyate, estolate, esylate, ethylsuccinate, formate, fumarate, gluceptate, gluconate, glutamate, glycollate, glycollylarsanilate, heptanoate, hexyne-1,6-dioate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, γ-hydroxybutyrate, iodide, isobutyrate, isothionate, lactate, lactobionate, laurate, malate, maleate, malonate, mandelate, mesylate, metaphosphate, methane-sulfonate, methylsulfate, monohydrogenphosphate, mucate, napsylate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, nitrate, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, phenylacetates, phenylbutyrate, phenylpropionate, phthalate, phospate/diphosphate, polygalacturonate, propanesulfonate, propionate, propiolate, pyrophosphate, pyrosulfate, salicylate, stearate, subacetate, suberate, succinate, sulfate, sulfonate, sulfite, tannate, tartrate, teoclate, tosylate, triethiodode, and valerate salts.

The phrase “pharmaceutically acceptable salt(s)” also relates to base addition salts of the above-mentioned compounds. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts that are acidic in nature are

those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to, those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002). Methods for making pharmaceutically acceptable salts of compounds of formula (I) of the invention are known to one of skill in the art.

As used herein the terms ""formula (I)" and "formula (I) or pharmaceutically acceptable salts thereof"" are defined to include all forms of the compound of formula (I), including isomers, crystalline and non-crystalline forms, isomorphs, polymorphs, metabolites, solvates, hydrates and prodrugs thereof.

The term "solvate" is used herein to describe a noncovalent or easily reversible combination between solvent and solute, or dispersion means and disperse phase. It will be understood that the solvate can be in the form of a solid, slurry (e.g., a suspension or dispersion), or solution. Non-limiting examples of solvents include ethanol, methanol, propanol, acetonitrile, dimethyl ether, diethyl ether, tetrahydrofuan, methylene chloride, and water. The term "hydrate" is employed when said solvent is water.

A currently accepted classification system for organic hydrates is one that defines isolated site, or channel hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules.

When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

The compounds of formula (I) also include prodrugs. Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as "prodrugs". Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (Ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Some non-limiting examples of prodrugs in accordance with the invention include:

(i) where the compound of formula (I) contains a carboxylic acid functionality which is functionalized into a suitably metabolically labile group (esters, carbamates, etc.) compound of formula (I);

(ii) where the compound of formula (I) contains an alcohol functionality which is functionalized into a suitably metabolically labile group (ethers, esters, carbamates, acetals, ketals, etc.) compound of formula (I); and

(iii) where the compound of formula (I) contains a primary or secondary amino functionality, or an amide which are functionalized into a suitably metabolically labile group, e.g., a hydrolysable group (amides, carbamates, ureas, phosphonates, sulfonates, etc.) compound of formula (I).

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

The compounds of the formula (I) may exhibit the phenomena of tautomerism and structural isomerism. For example, the compounds of formula (I) of the invention may exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of compounds of formula (I) of the invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one

tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the compounds of formula (I) of the invention.

The compounds of the formula (I) may also include isotopically-labeled compounds, which are identical to those recited in formula (I) above, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that may be incorporated into compounds of formula (I) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as, but not limited to, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S and ^{18}F. Certain isotopically-labeled compounds of formula (I) of the invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labeled compounds of formula (I) of the invention may generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting an isotopically-labeled reagent for a non-isotopically-labeled reagent.

The compounds of formula (I) may exhibit polymorphism. Polymorphs of the compounds of formula (I) of the invention may be prepared by crystallization of a compound of formula (I) of the invention under various conditions. For example, there may be employed various solvents (including water) or different solvent mixtures for recrystallization; crystallization at different temperatures; various modes of cooling ranging from very fast to very slow cooling during crystallization. Polymorphs may also be obtained by heating or melting a compound of formula (I) of the invention followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or other such techniques.

The minimum amount of sulopenem or a pharmaceutically acceptable salt or prodrug thereof to be administered is an effective amount. The term "effective amount" means the amount of a compound of formula (I) of the invention which prevents the

onset of, alleviates the symptoms of, stops the progression of, and/or eliminates a TB infection in a mammal, e.g., a human.

A therapeutically effective amount of sulopenem or a pharmaceutically acceptable salt or prodrug thereof of the invention may possess the desired antitubercular properties.

The methods and compositions of the invention are particularly effective against tuberculosis including active tuberculosis and latent tuberculosis. In one example, the active tuberculosis comprises drug-sensitive tuberculosis, mono-drug-resistant tuberculosis, multi-drug-resistant tuberculosis and extensively drug-resistant tuberculosis. In another example, the present invention provides a method to completely eradicate drug-sensitive tuberculosis, mono-drug-resistant tuberculosis or multi-drug-resistant tuberculosis on completion of the treatment.

In addition, the methods and composition of the invention may be used in conjunction with diagnostic tests to identify the tuberculosis in the mammal which are known to those so skilled in the art. For example, the methods and compositions of the invention may be used in conjunction with the so-called line-probe assay (Hain Life-science GmbH) which may be used to identify genes linked with resistance to rifampin and isoniazid to indicate multi-drug-resistant tuberculosis and/or extensively drug-resistant tuberculosis. Other assays may also be used in conjunction with the methods and composition of the invention, which are known to those so skilled in the art.

In another embodiment, the methods and compositions of the invention are particularly effective against tuberculosis caused by a *Mycobacterium* infection selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium bovis* or other related mycobacterial species, which would be known by one skilled in the art. In one example, the present invention provides methods and compositions to prevent relapse of the *Mycobacterium* infection after completion of the treatment.

In another embodiment, the present invention relates to a method of treating tuberculosis in a mammal comprising administering to the mammal in need thereof an effective amount of sulopenem or a pharmaceutically acceptable salt or prodrug thereof in combination with clavulanate or a compound of formula (I) or both.

Such combination treatment may be for simultaneous, separate or sequential use. In one embodiment, clavulanate or a compound of formula (I) may be administered prior to administration of sulopenem or a pharmaceutically acceptable salt or prodrug thereof. In another embodiment, clavulanate or a compound of formula (I) may be

administered after the administration of sulopenem or a pharmaceutically acceptable salt or prodrug thereof. In another embodiment, clavulanate or a compound of formula (I) may be administered at about the same time as administration of sulopenem or a pharmaceutically acceptable salt or prodrug thereof.

Separate administration of each compound, at different times and by different routes, in some cases would be advantageous. In addition, sulopenem or a pharmaceutically acceptable salt or prodrug thereof, clavulanate and the compounds of formula (I) may be administered by any route useful for administration to a mammal, which are known to those of skill in the art. Thus, the components in the combination *i.e.* sulopenem or a pharmaceutically acceptable salt or prodrug thereof, clavulanate and/or a compound of formula (I) need not be necessarily administered at essentially the same time or in any order. The administration can be so timed that the peak pharmacokinetic effect of one compound coincides with the peak pharmacokinetic effect of the other.

All the active ingredients can be formulated into separate or individual dosage forms which can be co-administered one after the other. Another option is that if the route of administration is the same (e.g. oral) two or more of the active compounds can be formulated into a single form for co-administration, both methods of co-administration, however, being part of the same therapeutic treatment or regimen.

The invention also relates to compositions of the invention which comprise (i) a therapeutically effective amount of sulopenem or a pharmaceutically acceptable salt or prodrug thereof, (ii) at least one other agent useful in the treatment of tuberculosis and (iii) a pharmaceutically acceptable carriers or vehicles (hereinafter “the compositions of the invention”).

Compositions of the invention that are suitable for administration to a patient in need thereof (e.g., a human) are also referred to herein as “pharmaceutical compositions of the invention.”

The pharmaceutical compositions of the invention may be in any form suitable for administration to a patient. For example, the pharmaceutical compositions of the invention may be in a form suitable for oral administration such as a tablet, capsule, pill, powder, sustained release formulations, solution, and suspension; for parenteral injection as a sterile solution, suspension or emulsion; for topical administration as an ointment or cream; or for rectal administration as a suppository. The pharmaceutical

compositions of the invention may be in unit dosage forms suitable for single administration of precise dosages.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

In one embodiment, the pharmaceutical compositions of the invention may be in the form of an oral dosage form. Non-limiting examples of oral dosage forms include such as, e.g., chewable tablets, capsules, pills, lozenges, troches, sachets, powders, syrups, elixirs, solutions and suspensions, and the like, in accordance with standard pharmaceutical practice. In another embodiment, the pharmaceutical compositions of the invention can also be delivered directly to a patient's gastrointestinal tract through a nasogastric tube.

Sulopenem or a pharmaceutically acceptable salt or prodrug thereof will be present in the pharmaceutical composition of the invention in an amount sufficient to provide the desired dosage amount in the range described herein. The proportional ratio of compound of formula (I) of the invention to excipients will naturally depend on the chemical nature, solubility and stability of the active ingredients, as well as the dosage form contemplated.

In general, a daily dose of the sulopenem prodrug for adults may be about 500 mgA (milligrams sulopenem equivalent) to about 6 gA, or about 1 gA to about 5 gA. A regimen of the sulopenem prodrug for adults may be about 500 mgA to about 1500 mgA administered twice a day in about 12 hour intervals. A regimen may be administered over a period of about one week to about two weeks. For certain infections, it may be necessary or desirable to use dosages outside these parameters.

A daily dosage of the sulopenem prodrug of the present invention can usually be administered from 1 to 4 times daily normally in equal doses. In some embodiments, the prodrug dosage can be about 500 to about 2500 mg BID or TID; about 800 mg to about 1 g BID; or about 2 g BID or TID for more serious infections. In some embodiments, the dosage can be about 7 to about 25 mg/kg BID; about 17 to about 45 mg/kg BID; or about 17 to about 45 mg/kg TID. In some cases, it may be necessary to use dosages outside these limits.

In some embodiments, treatment is initiated intravenously with sulopenem itself or other antibiotic and treatment is then continued with an oral prodrug of the present invention.

The pharmaceutical composition of the invention in a fixed dose combination may be prepared by conventional methods in the art. For e.g., a tablet form of the combination can be prepared by any one of skill in the art.

Oral administration is preferred.

Preferred agents useful for the treatment of tuberculosis in combination with sulopenem or a pharmaceutically acceptable salt or prodrug thereof may be clavulanate and the compound of formula (I).

Typically, an effective daily dose (i.e., total dosage over about 24 hours) of clavulanate for adults is about 125 to 250 mg with or without food. In some cases, it may be necessary to use dosages outside these limits.

Oral administration is preferred.

In addition, an effective daily dose (i.e., total dosage over about 24 hours) of the compound of formula (I) of the invention for adults is about 10 mg to about 2000 mg; about 25 mg to about 1000 mg; about 50 mg to about 500 mg; and 100 mg to about 500 mg with or without food. In some cases, it may be necessary to use dosages outside these limits.

A daily dosage of the compound of formula (I) is usually administered from 1 to 4 times daily in equal doses.

In one embodiment, a single dose of compound of formula (I) of the invention is administered per day (i.e., in about 24 hour intervals) (i.e., QD); in another embodiment, two doses of compound of formula (I) of the invention are administered per day (i.e., BID); in another embodiment, three doses of compound of formula (I) of the invention are administered per day (i.e., TID); and in another embodiment, four doses of compound of formula (I) of the invention are administered per day (i.e., (QID); in another embodiment a single dose of compound of formula (I) of the invention is administered every other day (i.e., in about 48 hour intervals), in another embodiment a single dose of compound of formula (I) of the invention is administered twice per week; in another embodiment a single dose of compound of formula (I) of the invention is administered thrice per week.

In one embodiment, the effective dose of the compound of formula (I) of the invention is administered BID in about 12 hour intervals.

In another embodiment, the effective dose of the compound of formula (I) of the invention is administered TID in about 8 hour intervals.

In another embodiment, the effective dose of the compound of formula (I) of the invention for is administered QID in about 6 hour intervals.

In one embodiment, an effective dose of the compound of formula (I) of the invention is about 25 mg to about 1000 mg administered per day to a subject in need of treatment for TB.

Oral administration is preferred.

The term "excipient" means an inert material that is combined with the compound of formula (I) to produce a pharmaceutical composition or oral drug dosage form.

The term "pharmaceutically acceptable excipient" means that the excipient must be compatible with other ingredients of the composition, and not deleterious to the recipient thereof. The pharmaceutically acceptable excipients are chosen on the basis of the intended dosage form.

The tablets, pills, capsules, and the like may contain excipients selected from binders such as polyvinylpyrrolidone, hydroxypropylmethyl cellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin, acacia, gum tragacanth, or corn starch; fillers such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch; disintegrants such as corn starch, potato starch, alginic acid, sodium starch glycolate, croscarmellose sodium and certain complex silicates; lubricants such as magnesium stearate, sodium lauryl sulfate and talc; and sweeteners such as sucrose lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both.

In the case of pediatric oral suspensions and sachets, these excipients may comprise suspending aids such as xantham gum or hydroxypropylmethylcellulose, glidants such as colloidal silica, diluents and bulking agents such as silicon dioxide, flavors such as bubble gum, orange, banana, raspberry and golden syrup or mixtures thereof, sweeteners such as aspartame or sugar, and stabilizers such as succinic acid. Powder or granular formulations, such as pediatric suspension formulations and sachets, may be manufactured using techniques which are generally conventional in the field of manufacture of pharmaceutical formulations and in the manufacture of dry formulations for reconstitution into such suspensions. For example a suitable technique is that of mixing dry powdered or granulated ingredients.

Sulopenem or a pharmaceutically acceptable salt or prodrug thereof can be prepared by methods known to those so skilled in the art. Specifically, sulopenem prodrugs of can be prepared, *e.g.*, from the free acid of sulopenem according to known methods such as those disclosed herein or in US3951954; US4234579; US4287181; US4452796; US4342693; US4348264; US4416891; US4457924; US5013729, and WO2008001212, all of which are incorporated by reference herein in their entireties.

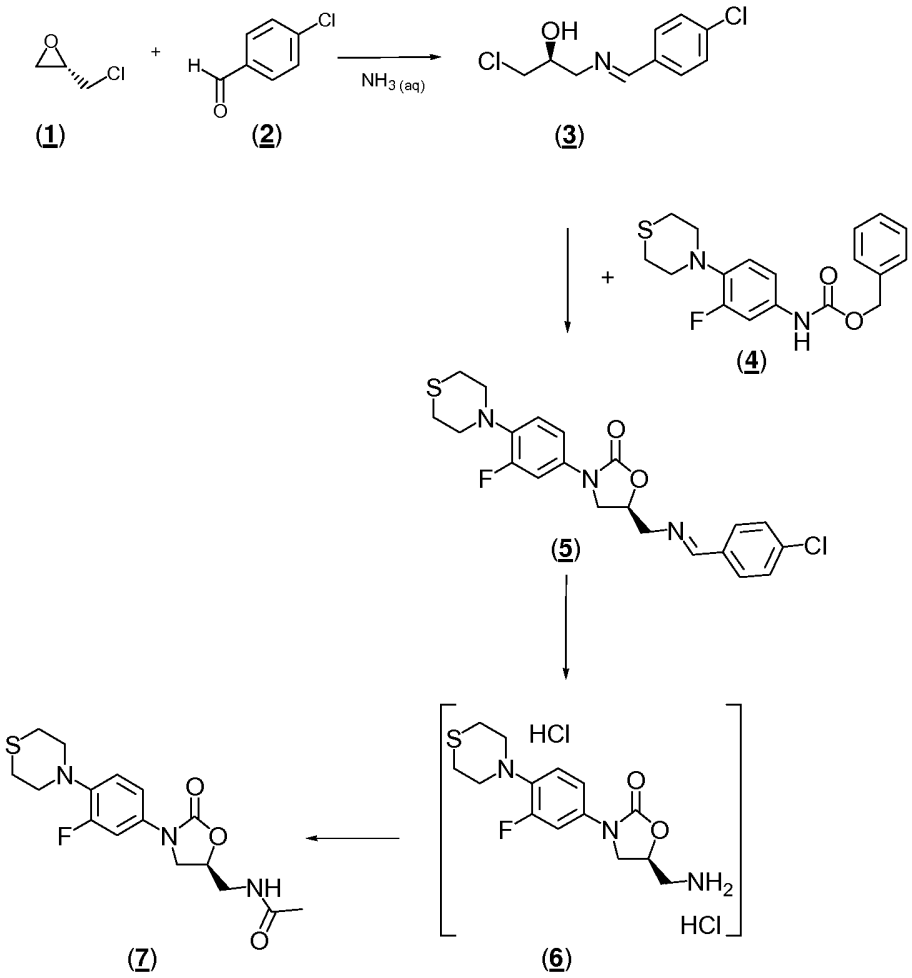
Clavulanate can be prepared by methods known to those so skilled in the art.

The compounds of formula (I) are readily prepared according to synthetic methods familiar to those skilled in the art. The compound of formula (I) can be prepared in a manner similar to that described for the preparation of Example 1 described in the Examples section in US5880118. In addition, the compound of formula (I) can be prepared by the processes set forth in WO97/37980 and WO99/24393, both of which are herein incorporated by reference.

Another example of the preparation of (*S*)-*N*-[[3-[3-fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide is as follows:

Scheme 1 illustrates a general synthetic sequence for preparing compounds of the present invention.

SCHEME I



Scheme 1 illustrates a method of synthesizing compounds of formula (I) of the invention in a multistep synthesis via a compound of formula 6. Referring to Scheme I, the synthesis begins with the formation of intermediate (3) by reacting (*S*)-epichlorohydrin (1) with a mixture of the appropriately substituted benzaldehyde derivative (2) (preferably 0.5 to 2 eq, most preferably 1 eq) and aqueous ammonia (preferably 0.5 to 3 eq, most preferably 1.5 eq). The reaction is best performed in both protic and aprotic non-nucleophilic and inert solvents such as alcohols (including C_1-C_6 branched and linear alcohols and polyols), ethers (including MTBE, THF, and other C_1-C_6 linear, branched and cyclic ethers) as well as chlorinated solvents such as methylene chloride. MTBE is a preferred solvent. Temperatures in a range from about 15 to about 60°C are preferred, most preferably between 30 to 50°C. After extractive isolation and concentration, the imine moiety (3) is obtained. It is then crystallized from a second

liquid phase, in the presence of non-polar hydrocarbon solvents such as, but not limited to, alkanes, mixtures of alkanes (hexane, heptane, octane, *iso*-octane and commercially available alkane mixtures), optionally in the presence of aprotic polar solvents, preferably ethereal solvents such as MTBE or aromatic solvents such as toluene or chlorinated solvents such as methylene chloride or mixtures thereof. Preferred solvents are a mixture of MTBE and heptane or a mixture of toluene and heptane. The crystallization process can be conducted at a temperature in a range from ambient temperature (about 18-25°C) to about 55°C, preferably in a range of 30 to 50°C, more preferably in a range of 38 to 45°C. This crystallization provides surprisingly high yield and affords significantly improved enantiomeric purity after isolation by filtration. (*S*)-epichlorohydrin (1) and benzaldehyde derivative (2) are commercially available or can be made by methods well known to those skilled in the art.

The substituted imine moiety (3) is coupled with carbamate (4) (which is known to those skilled in the art, for example see *J. Med. Chem.*, **1996**, *39*, (3), 680-685 and also Example 2 below, (preferably 1 to 3 eq, most preferably 1.5 to 2 eq)) to provide the corresponding (*S*)-oxazolidinone imine (5). The reaction is carried out preferably at a temperature in a range from ambient temperature to about 65°C in the presence of a base with pKa greater than 12, preferably a tertiary alkoxide base, most preferably lithium *tert*-butoxide and an aprotic non-nucleophilic solvent (preferably DMF, DMAc, , acetonitrile, C_1-C_6 linear, branched and cyclic ethers and/or chlorinated solvents and/ or mixtures of these solvents, most preferably MTBE or methylene chloride). Most preferably, the temperature is from about 30-60°C and the reaction time is 2 to 24 hours. Preferably, the (*S*)-oxazolidinone imine (5), after an aqueous extractive workup, is isolated by filtration from a 1:1 mixture of an ether (including MTBE, THF, and other C_1-C_6linear, branched and cyclic ethers) and water, most preferably MTBE. Alternatively, (5) is isolated after an aqueous extractive workup, by filtration or crystallization from an alcohol (including C_1-C_6linear, branched alcohols and polyols); most preferably isopropanol. Hydrolysis of compound (5) with an aqueous acidic solution provides compound (6) and subsequent acylation provides crude compound (7). Compound (5) is best hydrolyzed with a mixture of water and a strong acid such as hydrochloric acid and the substituted benzaldehyde byproduct is removed by extraction with a water immiscible organic solvent (preferably toluene, MTBE, methylene chloride or ethyl acetate), most preferably ethyl acetate. The resulting aqueous solution of amine hydrochloride (6) is preferably acylated with acetic anhydride, preferably in the presence

of water and a water-immiscible organic solvent (most preferably methylene chloride). The conversion of amine hydrochloride (6) to compound (7) is well known in the literature. (See Brickner, S.J. *et. al. J. Med. Chem.* **1996** *39* (3) 673-679, US Patent 5,837,870, US 5,688,792).

The examples provided below further illustrate and exemplify the compounds of formula (I) of the invention, compositions of the invention and methods of using the compound of the invention. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations.

Example 1

Preparation of (*S*)-1-chloro-3-[(4-chloro-*E*-benzylidene)-amino]-propan-2-ol

Method A

A 5L three neck round bottom flask equipped with a mechanical stirrer, thermocouple, reflux condenser and heating mantle is charged with 4-chlorobenzaldehyde (351.0 g, 2.5 mol, 1.0 eq.). MTBE (1.5 L) is then charged into the round bottom to give a homogeneous solution. Aqueous ammonia (28 wt%, 252.98 mL, 3.75 mol, 1.5 eq.) is added in a single portion resulting in a white precipitate that turned into a thin slurry within 15 minutes of stirring. (*S*)-(+)-epichlorohydrin (> 99 % ee, 196.0 mL, 2.5 mol, 1.0 eq.) is then slowly charged into the vessel. After 40 minutes, the contents are then slowly heated to 43°C. The reaction is stirred at 40°C for 18 hours at which time 8.4% area of epichorohydrin remained by GC. Upon cooling, the reaction mixture is transferred to a separatory funnel and the layers are separated. The lower aqueous layer is discarded. The organic layer is transferred to a 3L round bottom flask, concentrated *in vacuo* to about half the volume (800-900 mL) at which time *iso*-octane is slowly added from a feed tube (~750 mL) until cloudiness is observed. The biphasic mixture is seeded with ~4 mgs of the title compound. The reaction is cooled with an ice bath for 45 minutes while stirring. The precipitate is collected and rinsed with cold *iso*-octane (500 mL). The solid is dried for 18 hours at 50°C under vacuum to give 345.19 g (59% yield) of the title compound as a while solid. GC assay: 100%, 99.7% ee by Chiral SFC). GC (conditions: column - 30 meter HP-1, 0.25 mm ID and 0.25 micron film and 15 psi head pressure, 1.0 µl injection size; T_{ini} = 70°C, ramp of 20°C/min) T_R (epichlorohydrin) = 2.4 min, T_R (4-chlorobenzaldehyde) = 4.8 min and T_R (title compound) = 9.7 min; HPLC conditions: Chiralpak AD-H 250 mm X 4.6 mm column, eluting with 70% CO_2/ 30% MeOH at 3.0 mL/min, detecting at 255 nm. T_R [title

compound] = 3.9 min; T_R (enantiomer of title compound) = 2.8 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (bs, 2 H), 3.80 (m, 2 H), 4.15 (s, 1 H), 7.41 (d, J = 8 Hz, 2 H), 7.69 (d, J = 8 Hz, 2 H), 8.33 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.05, 63.09, 70.82, 128.93, 129.39, 134.08, 137.07, 162.30; IR (KBr Pellet) 1630 cm^{-1}.

Method B

A 5L three neck round bottom flask equipped with a mechanical stirrer, thermocouple, reflux condenser and heating mantle is charged with 4-chlorobenzaldehyde (375 g, 2.67 mol, 1.0 eq.). Methanol (0.75 L) is added to give a homogeneous solution after warming from 10 to 23°C. Aqueous ammonia (28.4 wt%, 264 mL, 3.95 mol, 1.5 eq.) is added in a single portion resulting in a biphasic solution forming after stirring for 15 minutes at 23 to 26°C. (*S*)-(+)-epichlorohydrin (99.3 % ee, 207 mL, 2.64 mol, 1.0 eq.) is then added in one portion. The reaction mixture is stirred at 23-24°C for 18 hours, then warmed to 40 to 45°C and stirred for 2.5 hours at which time 0.26% area of (*S*)-epichorohydrin remains by GC (GC conditions, 0.050 mL reaction mixture in 1 mL acetonitrile, inject 1 microliter; 15 M DB-1 column, 0.25 mm ID and 0.25 micron film and 15 psi head pressure, 1.0 µl injection size; T_{ini} = 38°C, ramp of 10°C/min) T_R (epichlorohydrin) = 1.1 min, T_R (4-chlorobenzaldehyde) = 6.9 min and T_R (title compound) = 16.0 min). The mixture is concentrated *in vacuo* to a total volume of 1250 mL. Toluene (250 mL) is added and the mixture concentrated *in vacuo* to a total volume of 1250 mL. Toluene (250 mL) is added and the mixture concentrated *in vacuo* to a total volume of 1145 mL. Toluene (355 mL) is added and the mixture concentrated *in vacuo* to a total volume of 900 mL. Toluene (600 mL) is added and the mixture concentrated *in vacuo* to a total volume of 1120 mL. While maintaining 45 to 50°C, heptane (1500 mL) is added. The resulting biphasic solution is cooled to 45°C and seeded. The mixture is then further cooled to 38°C over 1/2 hour while seeding after every 1 degree of cooling. The mixture is then further allowed to slowly cool to 23°C over 16 hours. The white crystals are then collected by vacuum filtration and washed with room temperature heptane (180 mL). The product is dried in a nitrogen stream to give the title compound (431.57 g, 70.4%). HPLC 95 area% [Kromasil 150 mm X 4.6 mm column, 254 nm, flow rate 1.5 mL/ min; A = 1000 mL water + 0.52 mL trifluoroacetic acid + 1.20 mL triethylamine; B = acetonitrile; Isocratic 47: 53 A: B for 5 min then gradient to 100% B over 5 min T_R [title compound] = 2.1 min; T_R (4-chlorobenzaldehyde) = 2.3 min]; 99.72% ee by Chiral SFC. Chiral HPLC conditions: Chiralpak AD-H 250 mm X 4.6 mm column, eluting with 70% CO_2/ 30% MeOH at 3.0

mL/min, detecting at 255 nm. T_R [title compound] = 3.9 min; T_R (enantiomer of title compound) = 2.8 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (bs, 2 H), 3.80 (m, 2 H), 4.15 (s, 1 H), 7.41 (d, J = 8 Hz, 2 H), 7.69 (d, J = 8 Hz, 2 H), 8.33 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.05, 63.09, 70.82, 128.93, 129.39, 134.08, 137.07, 162.30.

Method C

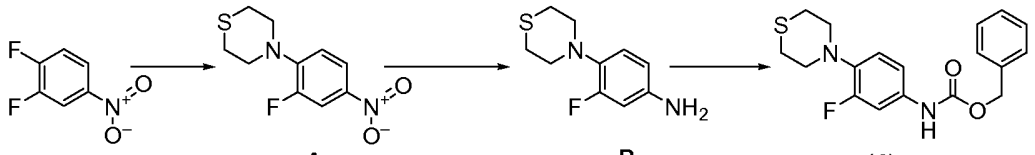
A 5L three neck round bottom flask equipped with a mechanical stirrer, thermocouple, reflux condenser and heating mantle is charged with 4-chlorobenzaldehyde (375 g, 2.67 mol, 1.0 eq.). MTBE (1.50 L) is then added to give a homogeneous solution after warming from 9 to 24°C. Aqueous ammonia (28.4 wt%, 265 mL, 3.97 mol, 1.5 eq.) is added in a single portion resulting in a biphasic solution forming after stirring for 15 minutes at 23 to 26°C. (*S*)-(+)-epichlorohydrin (99.3 % ee, 209 mL, 2.67 mol, 1.0 eq.) is then added in one portion. The reaction mixture is stirred at 23-24°C for 3 days. The phases are separated and the upper phase concentrated under atmospheric pressure from 2000 to 1000 mL total volume (boiling point 58 to 67°C). While maintaining 45 to 50°C, heptane (1700 mL) is added. The resulting biphasic solution is cooled to 45°C and seeded. The mixture is then further cooled to 38°C over 1/2 hour while seeding after every 1 degree of cooling. The mixture is then further allowed to slowly cool to 23°C over 1 hour. The snow white heavy crystals are then collected by vacuum filtration and washed with room temperature heptane (180 mL). The product is dried in a nitrogen stream to give the title compound (462.43 g, 74.7%). HPLC 94 area% [Kromasil 150 mm X 4.6 mm column, 254 nm, flow rate 1.5 mL/ min; A = 1000 mL water + 0.52 mL trifluoroacetic acid + 1.20 mL triethylamine; B = acetonitrile; Isocratic 47: 53 A: B for 5 min then gradient to 100% B over 5 min. T_R [title compound] = 2.1 min; T_R (4-chlorobenzaldehyde) = 2.3 min]; 99.92% ee by Chiral SFC. Chiral HPLC conditions: Chiralpak AD-H 250 mm X 4.6 mm column, eluting with 70% CO_2/ 30% MeOH at 3.0 mL/min, detecting at 255 nm. T_R [title compound] = 3.9 min; T_R (enantiomer of title compound) = 2.8 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (bs, 2 H), 3.80 (m, 2 H), 4.15 (s, 1 H), 7.41 (d, J = 8 Hz, 2 H), 7.69 (d, J = 8 Hz, 2 H), 8.33 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 47.05, 63.09, 70.82, 128.93, 129.39, 134.08, 137.07, 162.30.

Example 2

Preparation of (3-fluoro-4-morpholin-4-yl-phenyl)-carbamic acid benzyl ester

The title compound can be prepared according to the method described in *J. Med. Chem.*, **1996**, *39*, (3), 680-685 and depicted in SCHEME II.

SCHEME II



A B (4)

Additional methods for the conversion of intermediate A to 3-fluoro-4-thiomorpholin-4-ylaniline (B) are provided.

Method A

4-(2-Fluoro-4-nitrophenyl)thiomorpholine (A, 250 g, 1.03 mole) was charged into a mixture of dioxane (1400 mL), EtOH (1000 mL) and water (600 mL) in a 5000 mL three neck round bottom flask equipped with a mechanical stirrer. Into the stirred mixture was charged ammonium chloride (166 g, 3.1 moles) followed by iron powder (247 g, 4.25 moles), each in single portions. The reaction was warmed to reflux with vigorous stirring. The reaction was heated at reflux for a total of 16 hours and was then allowed to cool to room temperature. The dark mixture was diluted with EtOAc (800 mL), filtered through a pad of celite, and concentrated *in vacuo* to a pasty residue. The residue was partitioned between brine (1000 mL) and dichloromethane (750 mL). One filtration through celite removed particulates that were interfering with phase separation. The aqueous layer was then extracted with additional dichloromethane (750 mL). The combined organic layers were dried over anhydrous potassium carbonate and concentrated *in vacuo* to give 225 g of a dark solid. This crude material was dissolved in dichloromethane (1000 mL), treated with 200 g silica gel (230-400 mesh) and the mixture was concentrated to dryness. The plug was filtered over 500 g silica gel (230-400 mesh, packed as a slurry with 20% EtOAc/hexane) eluting with 20-30% EtOAc/hexane while collecting 1000 mL fractions. Fractions 3-11 were combined and concentrated to give 3-fluoro-4-thiomorpholin-4-ylaniline (B, 232 g, 106% yield) as an off-white solid. ^{1}H NMR indicated the desired material along with trace residual solvents to account for the greater than theoretical recovery. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.8 (m, 4H), 3.2 (m, 4H), 3.6 (s, 2H), 6.4 (m, 2H), 6.8 (m, 1H).

Method B

A 2000 mL Parr shaker flask was charged with 5% sulfided palladium on carbon (Johnson Matthey type A103038-5, 18 g) and 4-(2-fluoro-4-nitrophenyl)thiomorpholine (A, 60 g, 0.25 mole). The mixture was suspended in MeOH (1050 mL) and the reaction was hydrogenated at 50 PSI for 7 h. The catalyst was removed by filtration through

celite and the filter cake was washed well with fresh MeOH. The clear gray filtrate was concentrated *in vacuo* to give 3-fluoro-4-thiomorpholin-4-ylaniline (B, 51.3 g, 98% yield) as a gray solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.8 (m, 4H), 3.2 (m, 4H), 3.6 (s, 2H), 6.4 (m, 2H), 6.8 (m, 1H).

Example 3

Preparation of (5*S*)-5-{[(4-chlorobenzylidene)amino]methyl}-3-(3-fluoro-4-thiomorpholin-4-ylphenyl)-1,3-oxazolidin-2-one

The title compound in Example 2 (194 g, 0.56 mole), and the title compound of Example 1 (195 g, 0.84 mole), and lithium *tert*-butoxide (116 g, 1.4 mole) were charged into a 3000 mL three neck round bottom flask under nitrogen. The reactants were slurried with methyl *tert*-butyl ether (1200 mL) and the mixture was warmed to 56°C and stirred for 2 h as a yellow solid gradually formed. The reaction was cooled to room temperature, and diluted with 1200 mL water. The mixture was then stirred vigorously over 60 min as the solid changed from dark yellow to a more pale yellow solid. The mixture was cooled to 10°C, filtered, and the filter cake was washed with ice cold methyl *tert*-butyl ether (450 mL). The resulting light yellow solid was dried in air for 30 min, then placed in a vacuum oven and dried at 40°C overnight to afford the title compound (243 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.8 (m, 4H), 3.2 (m, 4H), 3.9 (m, 2H), 4.1 (m, 2H), 5.0 (m, 1H), 6.9 (m, 1H), 7.2 (m, 1H), 7.4 (m, 3H), 7.6 (m, 2H), 8.4 (s, 1H).

Example 4

Preparation of *N*-{[(5*S*)-3-(3-fluoro-4-thiomorpholin-4-ylphenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide

The title compound in Example 3 (243 g, 0.56 mole) was combined with EtOAc (1300 mL) and water (1300 mL) in a 5000 mL three neck round bottom flask equipped with a mechanical stirrer. The mixture was treated drop-wise with 12N HCl (140 mL, 1.68 moles) and the mixture was stirred vigorously for 1 hour at room temperature. The layers were separated and the aqueous layer was washed with EtOAc (1 x 500 mL). The resulting aqueous solution containing (*S*)-5-(aminomethyl)-3-(3-fluoro-4-thiomorpholinophenyl)oxazolidin-2-one hydrochloride was combined with a mixture of dichloromethane (1800 mL) and MeOH (120 mL), and the vigorously stirred mixture was charged with acetic anhydride (132 mL, 1.4 mole) in one portion and subsequently treated drop-wise with 10 N NaOH (200 mL, 2.0 mole) over 15 min. An extremely thick reaction mixture resulted from addition of the base, which gradually thinned as the pH

rose and the acylation rapidly progressed. The reaction was stirred vigorously for 1 hour after the mixture resolved to two phases. At that time, 10 M NaOH (160 mL, 1.6 mole) was added drop-wise to the mixture until the pH was stable at 7. The layers were separated, the aqueous layer was extracted with dichloromethane (250 mL), and the combined organic layers were dried over anhydrous potassium carbonate. The volatiles were removed *in vacuo* to give an off-white solid which was titrated with methyl *tert*-butyl ether (250 mL), collected, and dried *in vacuo* to give title compound (5) (186.1 g, 94% yield) as a fine white solid with greater than 98% HPLC purity (retention time = 3.93 minutes, HPLC conditions reported below).

The crude solid was dissolved in warm 6% methanol in dichloromethane (1250 mL) in a 5000 mL three neck round bottom flask equipped with a mechanical stirrer. The solution was warmed to reflux, diluted by the portion-wise (500 mL) addition of 2500 mL isopropanol (IPA), and, in order to maintain reflux, the temperature was ramped to 50-70°C. On completion of this addition of IPA, the reflux condenser was replaced with a short-path distillation head and distillation was continued into a cooled flask. During distillation, a 500 mL portion of fresh IPA was added after 500 mL of distillate was collected to maintain between 2000 and 2500 mL IPA present at all times. After this addition (internal flask temperature dropped to 60°C) the mixture became slightly cloudy and remained so for the balance of the distillation, becoming increasingly cloudy as the distillate temperature exceeded 70°C; particulate matter appeared as the distillate temperature exceeded 75°C. The temperature controller was ramped to 85°C and held there until the conclusion of the distillation. When the distillate was clearly isopropanol alone (82-83°C) the volume was reduced to 2500 mL hot IPA, the heating mantle was removed, stirring was discontinued, and the paddle was removed from the flask. The mixture was allowed to continue to crystallize as the flask cooled. The white crystalline solid was then collected by filtration, washed with methyl *tert*-butyl ether (250 mL), and dried *in vacuo* at 40°C to afford 180 g (91% yield) of the title compound in greater than 99% HPLC purity (retention time = 3.93 minutes, HPLC conditions reported below). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.8 (s, 3H), 2.7 (m, 4H), 3.2 (m, 4H), 3.4 (m, 2H), 3.7 (m, 1H), 4.7 (m, 1H), 7.1 (m, 1H), 7.15 (m, 1H), 7.2 (m, 1H), 8.2 (m, 1H). Mass Spec. $C_{16}H_{20}FN_3O_3S$: m/z 354.1 (M+1).

HPLC conditions for analyses mentioned in the text: HP Series 1100; Column: Symmetry C8 5uM 4.6 x 50 mm; Flow rate 1.2 mL/min; Solvent A: water with 0.1% formic acid, Solvent B: acetonitrile with 0.1% formic acid; Injection volume = 10 uL of 1

mg/mL (acetonitrile); Gradient: Solvent B 0-100% over 7 minutes then 100% B for 1 minute; wavelength = 254 nm.

Example 5

Example 5 illustrates the anti-mycobacterial effect of sulopenem, both alone, and when co-administered with clavulanic acid. Example 5 utilized the BACTEC™ MGIT™ 960 Mycobacterial system that is commercially available from Becton Dickinson. This product is routinely used to diagnose tuberculosis and to identify drug resistance. The reader's attention is directed to www.bd.com/ds/technicalcenter for a copy of the user's manual and further details regarding this system and how to carry out testing. This particular experiment utilized the protocol of the BD TB SIRE® susceptibility test for streptomycin, isoniazid, rifampin, and ethambutol resistance, except that it substituted a range of concentrations of sulopenem and a single concentration of clavulanic acid in the protocol to determine the minimal inhibitory concentration (MIC). MIC for *M. tuberculosis* is defined as that drug concentration which reduces mycobacterial viability by 2 $\log^{10}$ (100-fold). This historically has been determined by performing colony counts in the presence and absence of drug on solid agar medium. In clinical practice, this technique has been largely replaced by the BD SIRE method, which compares time to positivity in MGIT of drug-containing cultures with a 100-fold diluted growth control.

The MGIT system detects microbial growth as oxygen is consumed in a sealed culture tube containing an oxygen-quenched fluorophor (i.e. oxygen consumption causes fluorescence). The MGIT 960 instrument measures fluorescence hourly and reports out the time when fluorescence reaches predetermined threshold. This signifies microbial growth and is defined as "positivity". *M. tuberculosis* H37Rv (available from www.ATCC.org) was the strain of mycobacterium used in the experiment. *M. tuberculosis* stock culture was prepared by inoculating approximately 100 colony forming units (CFU) into a MGIT tube and harvesting 1 day after the culture was identified as positive, as per BD SIRE protocol. Such cultures typically contain approximately 10^5 CFU per ml of stock when serial dilutions are plated and colonies counted on 7H10 agar medium. For this experiment, stock solutions of sulopenem 100ug/ml, and clavulanic acid, 100ug/ml, were also prepared. Cultures were performed in duplicate and reported as their mean. Cultures were inoculated with 12 ul *M. tuberculosis* stock. Sulopenem concentrations of 0, 0.125, 0.25, 0.5, 1, 2, 4, and 8 ug/ml were tested. Each concentration was tested alone, and with clavulanic acid 2.5 ug/ml.

Figure I, infra, depict the results that were obtained from this experiment. As indicated in the left panel of Figure I, time to positivity is highly inversely correlated with log inoculum volume. Two data points for this culture stock are indicated by dotted lines: 0.12 μl (positive in 11 days) and 12 μL (positive in 6 days). The two inocula differ in volume by 100-fold. This difference forms the basis of the definition of MIC for *M. tuberculosis* (the minimal concentration capable of reducing CFU number 100-fold). In the right panel, time to positivity is indicated for MGIT cultures inoculated with 12 μL of this stock, to which specific concentrations of sulopenem were added, either alone (black symbols), or with clavulanic acid 2.5 μg/mL (red symbols). As of day 19, 2-fold greater concentrations (8 and 4 mg/μL) have remained without detectable growth. Dotted lines indicate the sulopenem concentrations required to reduce the apparent mycobacterial inoculum 100-fold: 2.2 μg/mL when tested alone, and 1.5 μg/ml when combined with clavulanic acid. These values are defined as the MIC.

Example 6

This experiment examined the capacity of sulopenem, plus clavulanic acid, to kill intracellular *M. tuberculosis* in whole blood culture. Bactericidal activity was measured as previously described by Wallis et al the Journal of Infectious Disease, 183:1300-1303, (2001) with the substitution of MGIT 960 for Bactec TB-460 (Becton Dickinson). Briefly, *M. tuberculosis* H37Rv was grown in MGIT tubes until positive (as described in Example 5). The following day, the stock was frozen in aliquots at -70°C until needed. A titration experiment was performed in which serial 10-fold volumes of stock from 500 to 0.005 μλ were inoculated into MGIT tubes in duplicate to determine the general relationship between inoculum size and time-to-positivity (TTP) and the specific volume predicted to be positive in 5.5 days (21 μλ). Stock solutions of sulopenem and clavulanic acid were prepared at 100 μg/ml in tissue culture medium (RPMI 1640, developed at Roswell Park Memorial Institute and currently available from Sigma Aldrich).

Sulopenem	Clavulanic	Sulo	Clavulanic	Blood	H37Rv	RPMI-1640	total
ug/ml	ug/ml	ul	ul	ul	ul	ul	ul
0	0	0.0	0.0	300.0	21.0	279.0	600
1	2.5	6.0	15.0	300.0	21.0	258.0	600
5	2.5	30.0	15.0	300.0	21.0	234.0	600

Whole blood cultures consisted of 300 μl heparinized blood, the specified volume of mycobacterial stock, sulopenem, clavulanic acid, and tissue culture medium as indicated above. Cultures were maintained at 37°C with slow constant mixing for 72 hrs, at which time the cells were sedimented, the liquid phase removed, and blood cells lysed by hypotonic lysis. Bacilli recovered after washing were inoculated into MGIT. Log change in viability during whole blood culture was calculated as log(*final*) – log(*initial*), where *final* and *initial* are the volumes corresponding to TTP values of the completed cultures and the inoculum, respectively, based on the titration curve. Data are presented as mean of duplicate cultures.

As indicated in the figure 2 infra, in the absence of added antibiotics, there was growth of approximately 0.5 log of *M. tuberculosis* H37Rv over 72 hrs. Therapeutic concentrations of sulopenem plus clavulanic acid resulted in bactericidal activity of approximately -0.5 log. These findings indicate the ability of sulopenem plus clavulante to kill intracellular *M. tuberculosis* at clinically meaningful concentrations in blood.

The above protocol was repeated with sulopenem and (S)-N-[[3-[3-fluoro-4-(4-thiomorpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, the structure of which is disclosed on page 5, at line 12. This combination of agents was not synergistic.

All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated herein by reference in their entireties.

What is claimed:

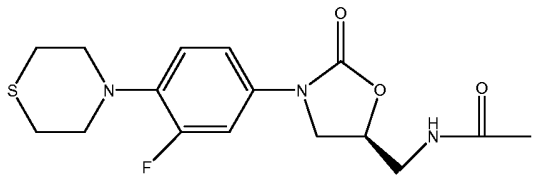
1. A method of treating tuberculosis in a mammal comprising administering to the mammal in need thereof an effective amount of (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid or a pharmaceutically acceptable salt or prodrug thereof.

2. The method of claim 1, wherein the prodrug is (2-Ethyl-1-oxobutoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

3. The method of claim 1, wherein the prodrug is (2-Ethoxy-2-methyl-1-oxopropoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

4. The method according to any of claims 1-3, further comprising administering clavulanate to the mammal.

5. The method according to any of claims 1-4, further comprising administering a compound of formula (I) or a prodrug thereof or a pharmaceutically acceptable salt thereof:



(I)

to the mammal.

6. The method according to any of claims 1-5, wherein the tuberculosis comprises active tuberculosis or latent tuberculosis.

7. The method of any of claims 1-5, wherein the active tuberculosis comprises drug-sensitive tuberculosis, mono-drug resistant tuberculosis, multi-drug-resistant tuberculosis (MDR) or extensively drug-resistant tuberculosis (XDR).

8. The method of any of claims 1-5, wherein the tuberculosis is caused by a *Mycobacterium* infection selected from the group consisting of *Mycobacterium tuberculosis*, *Mycobacterium bovis* or other related mycobacterial species.

9. A pharmaceutical composition comprising (i) a therapeutically effective amount of (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid or a pharmaceutically

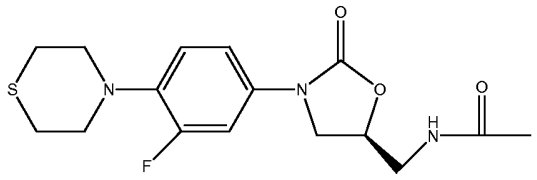
acceptable salt or prodrug thereof; (ii) a therapeutically effective amount of at least one other agent useful in the treatment of tuberculosis; and (iii) one or more pharmaceutically acceptable carriers or vehicles.

10. The composition of claim 9, wherein the prodrug is (2-Ethyl-1-oxobutoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

11. The composition of claim 9, wherein the prodrug is (2-Ethoxy-2-methyl-1-oxopropoxy)methyl (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[[(1R,3S)-tetrahydro-1-oxido-3-thienyl]thio]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

12. The composition of claim 9, 10 or 11, wherein the at least one other agent is clavulanate.

13. The composition of claim 9, 10, 11 or 12, wherein the at least one other agent is a compound of formula (I) or a prodrug thereof or a pharmaceutically acceptable salt thereof:



(I).

FIG. 1

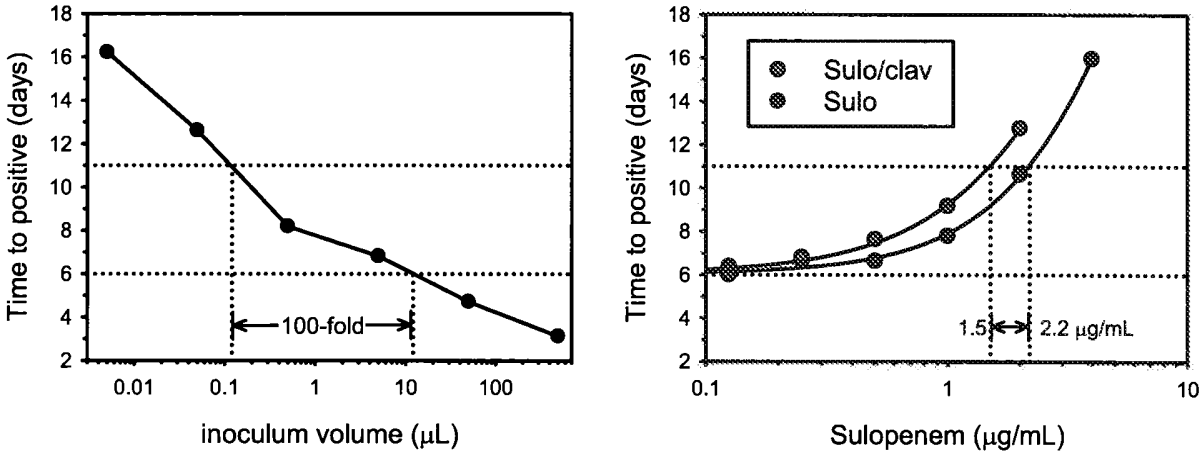
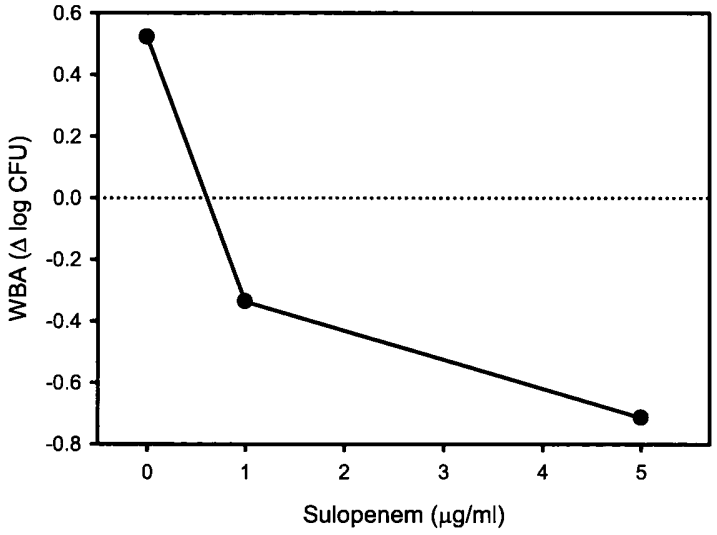

Time to positive (days)
18
16
14
12
10
8
6
4
2
0.01
0.1
1
10
100
100-fold
inoculum volume (µL)
Sulo/clav
Sulo
1.5
2.2 µg/mL
0.1
1
10
Sulopenem (µg/mL)

FIG. 2



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/051623

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/43 A61K31/431 A61P31/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHAMBERS HENRY F ET AL: "Imipenem for treatment of tuberculosis in mice and humans." ANTIMICROBIAL AGENTS AND CHEMOTHERAPY JUL 2005 LNKD- PUBMED:15980354, vol. 49, no. 7, July 2005 (2005-07), pages 2816-2821, XP002586671 ISSN: 0066-4804 * abstract	1-13

-/--

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2010	29/06/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Zimmer, Barbara

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/051623

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HUGONNET JEAN-EMMANUEL ET AL: "Irreversible inhibition of the mycobacterium tuberculosis beta-lactarnase by clavulanate" BIOCHEMISTRY, vol. 46, no. 43, October 2007 (2007-10), pages 11998-12004, XP002586672 ISSN: 0006-2960 page 12003, left-hand column, paragraph discussion	1-13
Y	HUGONNET J -E ET AL: "Meropenem-clavulanate is effective against extensively drug-resistant Mycobacterium tuberculosis" SCIENCE 20090227 AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE USA LNKD-DOI:10.1126/SCIENCE.1167498, vol. 323, no. 5918, 27 February 2009 (2009-02-27), pages 1215-1218, XP002586673 cited in the application * abstract page 1217, right-hand column - page 1218, left-hand column	1-13
Y	KOSOWSKA-SHICK KLAUDIA ET AL: "Comparative antipneumococcal activities of sulopenem and other drugs." ANTIMICROBIAL AGENTS AND CHEMOTHERAPY JUN 2009 LNKD- PUBMED:19307366, vol. 53, no. 6, 23 March 2009 (2009-03-23) , pages 2239-2247, XP002586674 ISSN: 1098-6596 * abstract page 2245 - page 2246	1-13
Y	BARRY P J ET AL: "Novel agents in the management of Mycobacterium tuberculosis disease." CURRENT MEDICINAL CHEMISTRY 2007 LNKD-PUBMED:17691942, vol. 14, no. 18, 2007, pages 2000-2008, XP002586675 ISSN: 0929-8673 * abstract page 2002, right-hand column, paragraph 2	1-13