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(54) Title: ANTI-BACTERIAL AGENTS BASED UPON OXOANION BINDING

(57) Abstract: Compounds of the structure I are useful for treating bacterial growth. The compounds may be used to treat bacterial infections in human beings and to regulate biofilm formation. Pharmaceutical compositions comprising one or more such compounds are useful for treating bacterial infections in human beings.

ANTI-BACTERIAL AGENTS BASED UPON OXOANION BINDING

Background of the Invention

Field of the Invention

[0001] This invention relates to compositions and methods for controlling bacterial growth, and more particularly to anti-bacterial agents and their methods of use.

Description of the Related Art

[0002] Bacterial infections remain a public health concern, and indeed a growing one in view of increasing resistance to existing drugs by pathogenic bacteria. Drugs now in use fall into a relatively small number of chemical classes, and operate by one of a relatively small number of mechanisms. Development of resistance to one drug can therefore adversely affect the efficacy of others. Moreover, because bacteria can exchange genetic information, resistance can spread from one species to another.

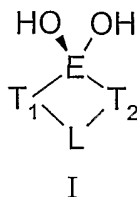
[0003] It is therefore desirable to have new classes of anti-bacterial agents based upon novel mechanisms of action, to which bacteria are unlikely to have resistance.

[0004] In addition, bacteria in nature commonly grow attached on solid surfaces in a mode of growth referred to as a biofilm. Bacteria within biofilms differ physiologically from those grown in liquid culture (planktonic cells) in having increased resistance to environmental stresses (such as antibiotic treatment). In clinical environments, biofilms of pathogenic bacteria lead to persistent and chronic infections refractory to treatment with conventional antibiotics. The U.S. Centers for Disease Control estimate that 60% of bacterial infections involve such biofilms. Industrially, biofilms contaminate and clog water lines, foul surfaces and contribute to corrosion and decay. Not all the consequences of biofilm formation are deleterious, however; for example, in bioproduction processes biofilms help in maintaining a stable population of cells as substrate passes through a bioreactor.

[0005] Consequently it is desirable not only to have new classes of anti-bacterial agents, but also to have ways of promoting and/or inhibiting the formation and maintenance of bacterial biofilms.

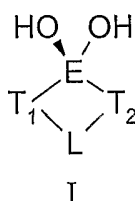
Summary of the Invention

[0006] A preferred embodiment provides a method of controlling bacterial growth, comprising exposing a bacterium to a compound of structure I

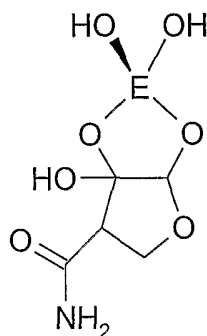


[0007] wherein E is selected from the group consisting of B, P, and S, T₁ and T₂ are each independently selected from the group consisting of O, NR, and CH₂, where R = H or C₁-C₈ alkyl, or C₁-C₈ oxoalkyl, and L is selected from the group consisting of ethylene, propylene, and four to six-membered alicyclic and aromatic rings, provided that structure I does not include AI-2-borate. Preferably, E is B (boron) or P (phosphorous). Preferably, T₁ and T₂ are O (oxygen). Preferably, the compound has a molecular weight less than about 750 Da, more preferably, less than about 500 Da. In preferred embodiments, bacterial growth is controlled by administering a therapeutically effective amount of the compound to a human infected with the bacterium.

[0008] Another preferred embodiment provides a pharmaceutical composition comprising a compound having structure I



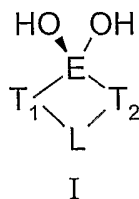
[0009] wherein E is selected from the group consisting of B, P, and S, T₁ and T₂ are each independently selected from the group consisting of O, NR, and CH₂, where R = H or C₁-C₈ alkyl, or C₁-C₈ oxoalkyl, and L is selected from the group consisting of ethylene, propylene, and four to six-membered alicyclic and aromatic rings, provided that structure I does not include AI-2-borate.. Preferably, L is tetrahydrofuran bearing a keto, a hydroxy, and a carboxamido functional group, T₁ and T₂ are oxygen, and E is B or P. More preferably, the compound has the following structure:



[0010] These and other embodiment are described in greater detail below.

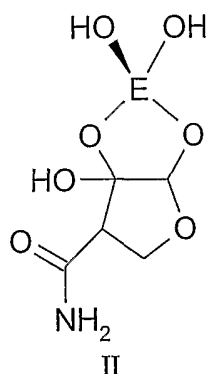
Detailed Description of the Preferred Embodiments

[0011] Preferred embodiments provide pharmaceutical compositions comprising compounds having the structure I:

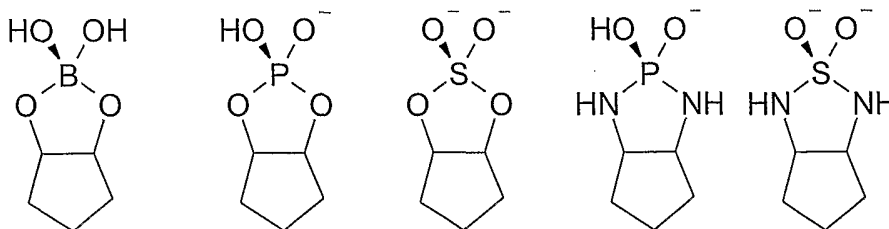


[0012] wherein E is selected from the group consisting of B, P, and S, T₁ and T₂ are each independently selected from the group consisting of O, NR, and CH₂, where R = H or C₁-C₈ alkyl, or C₁-C₈ oxoalkyl, and L is selected from the group consisting of ethylene, propylene, and four to six-membered alicyclic and aromatic rings, provided that structure I does not include AI-2-borate.

[0013] Preferred L groups include ethylene, propylene, cyclopentyl, cyclohexyl, pyrrolidine, tetrahydrofuran, piperidine, pyran, dioxane, morpholine, pyrrole, furan, pyridine, pyrimidine, pyrazine, imidazole, thiazole, oxazole, purine, and indazole. Particularly preferred L groups include ethylene, propylene, cyclopentyl, cyclohexyl, pyrrolidine, tetrahydrofuran, piperidine, pyran, dioxane, and morpholine. Most preferred L groups include cyclopentyl, cyclohexyl, pyrrolidine, tetrahydrofuran, piperidine, pyran, dioxane, and morpholine. A particularly preferred compound has the structure II, where E is B or P:

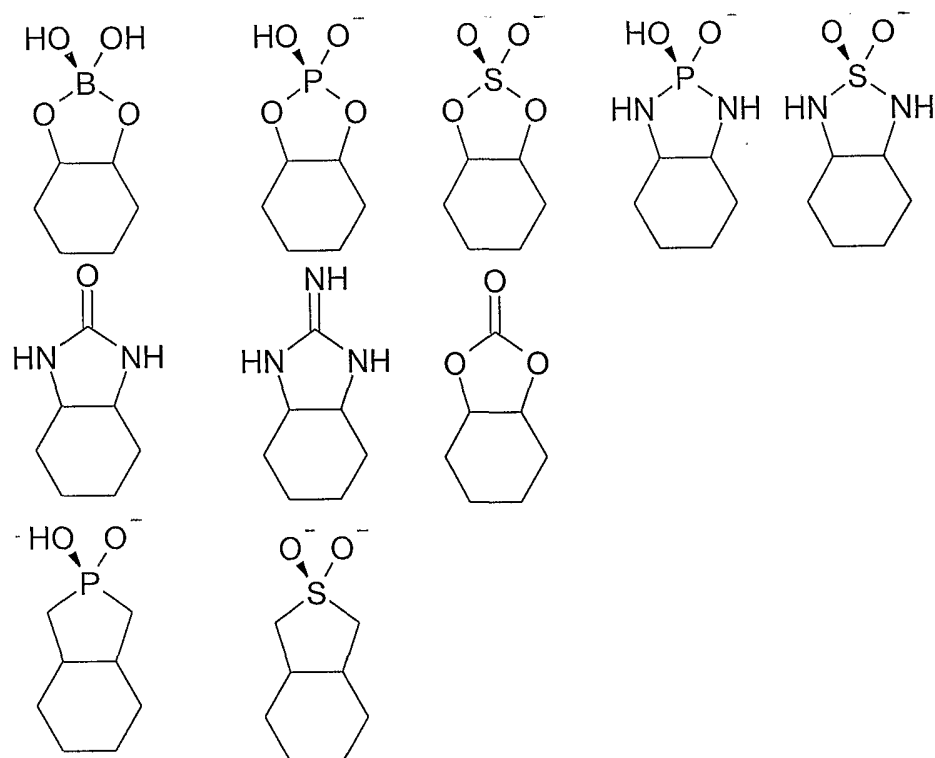


[0014] Other specific examples of preferred compounds include cyclic borate, sulfate, or phosphate esters and amides, as shown below for compounds derived from [3.3.0] bicyclooctane:

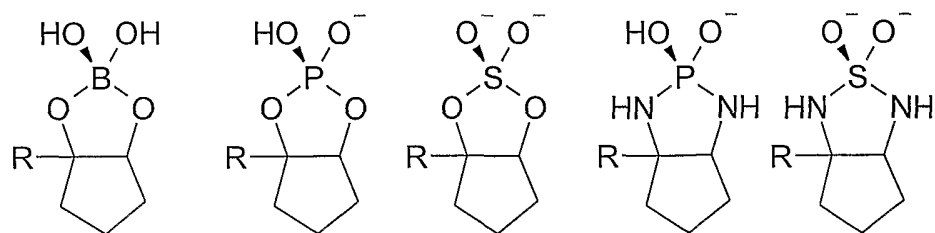


[0015] The unsubstituted five-membered ring in the above structures can incorporate one or more heteroatoms, with hydrogen-bonding heteroatoms such as O and N being particularly preferred. The unsubstituted five-membered ring in the above structures can also bear one or more substituents containing heteroatoms, again with hydrogen-bonding heteroatoms such as O and N being particularly preferred.

[0016] Additional preferred embodiments include compounds derived from [3.4.0] bicyclononane. Specific examples include the following:



[0017] Compounds having hydrogen-bonding substituents at a bridgehead position are also particularly preferred, in view of the strong H-bonding to this position evident in the structure found for the luxP-AI-2 co-crystal (discussed below). Examples of such compounds include the following, with R = OH or NH₂ being particularly preferred:



[0018] Methods of making various specific compounds are described in the Examples below. Methods of making the other compounds described herein may be undertaken by modifying the syntheses described in the Examples below in a manner known to those skilled in the art.

[0019] Specific compounds for a particular application are preferably selected with the aid of computer-aided drug design and/or combinatorial chemistry methods that are well-known to those skilled in the art. Computers and software suitable for carrying out computer-aided drug design are commercially available. Preferred computer packages include Sybyl version 6.8 from Tripos, Inc. and MacroModel version 8.0 from Schrodinger Software. Preferably, the heteroatoms are spatially disposed to interact with hydrogen-bonding groups on the LuxP protein.

[0020] One application of the present invention is in influencing the development or maintenance of biofilms, communities of bacteria that grow attached to solid surfaces. Bacteria within biofilms often exhibit greater resistance to antibiotic treatment than those living freely, and hence commonly lead to persistent and chronic infections refractory to treatment. The U.S. Centers for Disease Control estimate that 60% of bacterial infections involve such biofilms. Industrially, biofilms contaminate and clog water lines, foul surfaces and contribute to corrosion and decay. Not all the consequences of biofilm formation are deleterious, however; for example, in bioproduction processes biofilms help in maintaining a stable population of cells as substrate passes through a bioreactor.

[0021] Quorum-sensing influences biofilm formation, and therefore ways of promoting or impeding quorum-sensing also provide ways of controlling biofilm formation, including biofilm growth. For example, compounds of structure I can be used to affect biofilms by either stimulating their formation or hindering it. Methods for promoting or impeding biofilm formation are preferably practiced by exposing the bacteria to the compound in an amount that affects biofilm formation. Particular amounts for a given application may be determined by routine experimentation in a manner generally known to those skilled in the art.

[0022] Reference to a particular compound herein is to be understood as a reference to the compound itself and any salts thereof, and vice versa. Compounds that possess an acidic or basic group may form pharmaceutically-acceptable salts with pharmaceutically-acceptable cations or anions. Examples of pharmaceutically-acceptable cations include ammonium, tetramethylammonium, alkali metal (e.g. sodium, lithium and potassium) and alkaline earth metal (e.g. calcium, barium and magnesium), aluminum, zinc, and bismuth cations, and protonated forms of basic amino acids, such as arginine, lysine, and organic amines such as ethanolamine, ethylenediamine, triethanoleamine, benzylphenethylamine, methylamine, dimethylamine, trimethylamine, diethylamine, piperidine, morpholine, tris-(2-hydroxyethyl)amine, and piperazine.

[0023] Examples of pharmaceutically-acceptable anions include those derived from inorganic acids such as hydrochloric, hydrobromic, hydriodic, sulfuric, and phosphoric acid, as well as organic acids such as *p*-toluenesulfonic, methanesulfonic, oxalic, *p*-bromophenylsulfonic,

carbonic, succinic, citric, benzoic, and acetic acid, and related inorganic and organic acids. Such pharmaceutically-acceptable salts include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, ammonium, monohydrogenphosphate, dihydrogenphosphate, meta-phosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, hippurate, butyne-1,4-dioate, hexane-1,6-diospate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, α -hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate. It is understood that the above salts may form hydrates or exist in a substantially anhydrous form.

[0024] The compounds described herein may be administered directly to subjects, preferably humans, and/or may be administered in the form of pharmaceutical compositions comprising one or more of the compounds. A preferred mode of administration of the compound is oral. Oral compositions preferably include an inert diluent and/or an edible carrier. The compound can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and/or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents. The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the compound, sucrose as a sweetening agent and preservatives, dyes and colorings and flavors.

[0025] The compound can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics. Preferred antibiotics for this purpose include aminoglycosides such as tobramycin, glycopeptides such as vancomycin, beta lactams such as amoxicillin, quinolones such as ciprofloxacin, macrolides such as azithromycin, tetracyclines, sulfonamides, trimethoprim-sulfamethoxazole, or chloramphenicol. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other

synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

[0026] In a preferred embodiment, the compound is prepared with carriers that protect it against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for the preparation of such formulations are known to those skilled in the art.

[0027] Pharmaceutical compositions are preferably administered to subjects, preferably humans, in an amount that is therapeutically effective to treat a bacterial infection. Therapeutically effective amounts can be determined by those skilled in the art by such methods as clinical trials. Dosage may be adjusted in individual cases as required to achieve the desired degree of target bacterial regulation. Sustained release dosages and infusions are specifically contemplated. Pharmaceutical compositions can be administered by any appropriate route for systemic, local or topical delivery, for example, orally, parenterally, intravenously, intradermally, subcutaneously, buccally, intranasally, by inhalation, vaginally, rectally or topically, in liquid or solid form. Methods of administering the compounds described herein may be by specific dose or by controlled release vehicles.

[0028] The pharmaceutical composition may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compound, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed methods.

[0029] In a particular case, the therapeutically effective amount of a pharmaceutical composition to be used in the treatment of a bacterial infection will typically vary with the severity of the infection and the route by which the drug is administered. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose range of the present compounds for a 70 kg person is from about 1 mg to about 2000 mg, in single or divided doses. Preferably, a daily dose range for a 70 kg person should be between about 5 mg and about 1500 mg, in single or divided doses. More preferably, a daily dose range for a 70 kg person should be between about 10 mg and about 1000 mg, in single or divided doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps

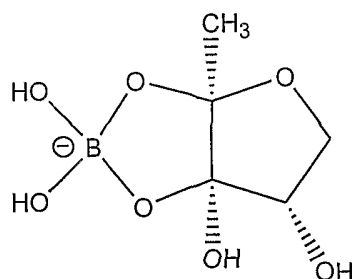
about 1 mg to about 200 mg for a 70 kg person, and increased up to about 1000 mg or higher depending on the patient's global response. It is further recommended that infants, children, patients over 65 years, and those with impaired renal or hepatic function, initially receive low doses, and that they be titrated based on individual response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust or terminate therapy in conjunction with individual patient response. The terms "therapeutic amount" and "therapeutically effective amount" are encompassed by the above-described dosage amounts and dose frequency schedules.

[0030] The instant invention is not bound by any theory of operation. The following discussion is provided for the benefit of those skilled in the art, and does not limit the scope of the claims.

[0031] Preferred pharmaceutical compositions are particularly useful for the treatment of bacterial infections. Bacteria sense their population density through a phenomenon called quorum-sensing, in which the bacteria synthesize and secrete low molecular weight compounds into the surrounding medium. By detecting the concentration of these signaling compounds in the medium they sense their population density, and express different genes in response to it.

[0032] Quorum-sensing controls not only light production in bioluminescent marine bacteria, where it was first discovered, but also production of exotoxins and other virulence factors in pathogenic bacteria. In many cases, modern drug design relies upon designing compounds that interact with targeted cellular constituents, such as enzymes, receptors, and periplasmic binding proteins, to block or otherwise alter the interaction between the target and the naturally-occurring compound it binds *in vivo*, the signaling compound in the case of quorum-sensing. Consequently, many strategies target the structure of both the signaling compound and its receptor as a way of designing agents that disrupt this interaction, for example, by competing with the signaling compound for the binding site on the receptor.

[0033] Recent work devoted to identifying a particularly important signaling compound known as autoinducer-2 (AI-2) is described in WO 00/32152. AI-2 is believed to control quorum sensing at least in part by interacting with LuxP (SEQ ID NO: 1), a periplasmic binding protein from *Vibrio harveyi* that is involved with quorum-sensing in this bacterium. Crystallographic work on a luxP-AI-2 co-crystal, which resulted from LuxP expressed by recombinant *Escherichia coli* in the presence of biologically-produced AI-2, yielded the following structure (hereinafter called "AI-2-borate") in which AI-2 (in the hydrated, *gem*-diol form of the keto group) binds at least in part to LuxP through the intermediacy of another species.



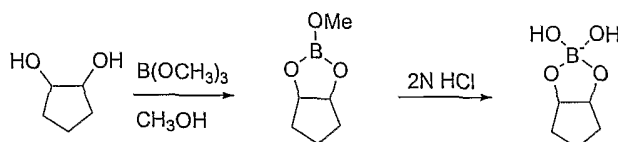
[0034] This intermediary species was initially believed to be a carbonate but subsequently recognized to be a borate moiety, with the borate possibly arising from adventitious borate derived from borosilicate glass used in the experimental work. See X. Chen, S. Schauder, N. Potier, A. Van Dorsselaer, I. Pelczer, B. Bassler, and F. Hughson, "Structural Identification of a Bacterial Quorum-Sensing Signal Containing Boron," *Nature*, Vol. 415, pp. 545-549 (2002),.

[0035] The interaction between the borate ester of 4,5-dihydroxy-5-methyl-3(2H)-furanone (in its hydrated form) and LuxP indicates that borate ester formation may have biological relevance to the functioning of autoinducer-2. Borate ester formation may be a specific example of a general characteristic of autoinducer-2's biological function, namely, as a chelating group for oxoanions such as borate, but including other oxoanions such as phosphate and sulfate. In nature, autoinducer-2 may function to present oxoanions to the autoinducer-2 receptor, with the oxoanion bound to autoinducer-2 either as a cyclic ester, as in the case of boron, or other structure.

[0036] Moreover, recognition of the role of 4,5-dihydroxy-5-methyl-3(2H)-furanone as a way of presenting oxoanions to a receptor may explain, at least in part, the activity of quorum-sensing inhibitors that incorporate a similar spatial disposition of functional groups. Thus, for example, preferred compounds as described herein having one or more heteroatoms in the five-membered ring, and therefore having similar hydrogen-bonding abilities to that found for the borate ester of 4,5-dihydroxy-5-methyl-3(2H)-furanone, have utility as competitive inhibitors of autoinducer-2 receptors, and therefore as therapeutic agents for controlling virulence by bacterial pathogens.

Examples

Example 1: Synthesis of borate esters



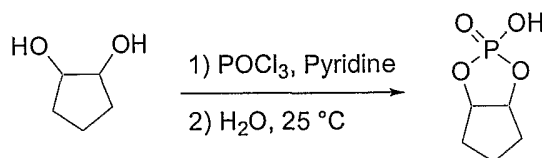
[0037] A mixture of diol (1 mmol) and trimethoxy borate (1.5 mmol) in methanol (5 mL) is heated at reflux until TLC reveals complete consumption of starting material. Removal of

the solvent *in vacuo* affords the product as its methyl ester, from which the corresponding acid can be isolated following acidification and warming.

Example 2: Alternative synthesis of borate esters

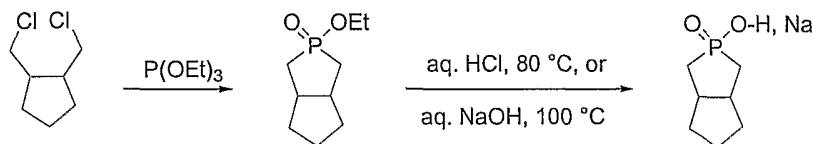
[0038] A diol (1 mmol) is added to a solution of 4 g borax in 15 mL of water optionally containing an organic co-solvent, with heating applied if necessary. The cyclic borate ester forms spontaneously, and can be precipitated by cooling and/or acidification of the solution and the product isolated by filtration. Borate esters can also be prepared by distillation of water from a mixture containing the diol and boric acid according to Organic Syntheses, CV 2, 106.

Example 3: Synthesis of phosphate esters



[0039] In a 2-l. round-bottomed flask, fitted with a reflux condenser, liquid-sealed mechanical stirrer, dropping funnel, and thermometer, are placed 1.5 moles of dry diol, 3.3 moles of pyridine, and 275 mL of dry benzene. The flask is immersed in an ice-salt mixture until the temperature has fallen to 5 °C at which time phosphorus oxychloride (153 g, 91 mL, 1 mole, b.p. 106–107°) with efficient stirring is added drop-wise at such a rate that the temperature does not exceed 10 °C. After the addition is completed the reaction mixture is heated slowly to the reflux temperature and held there for two hours. The mixture is cooled to room temperature, and 400–500 mL of water is added to dissolve the pyridine hydrochloride. The benzene layer is separated, washed with 100–150 mL of water, and dried over 20 g. of anhydrous sodium sulfate. The benzene and other low-boiling materials are removed *in vacuo* to afford the cyclic phosphate ester.

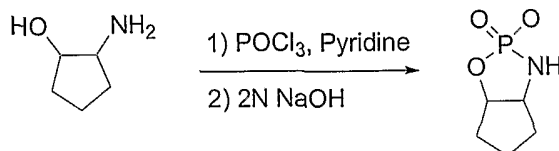
Example 4: Synthesis of cyclic phosphinates



[0040] A compound comprising two halomethyl substituents in a 1,2- or 1,3-relationship (e.g., 1,2-bis(chloromethyl)cyclopentane) (1 mmol) is treated with 0.5 mmol of triethyl phosphite in toluene (10 mL). The mixture is heated at reflux, the solvent removed *in vacuo*, and

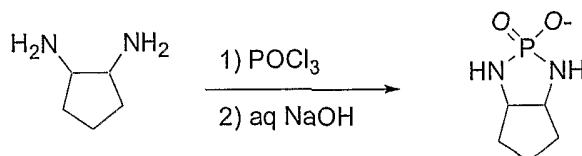
the crude product isolated as the diethyl ester. The free phosphinic acid and sodium phosphinate can be prepared by hydrolysis upon warming in either aqueous HCl or NaOH, respectively.

Example 5: Synthesis of cyclic phosphonamides



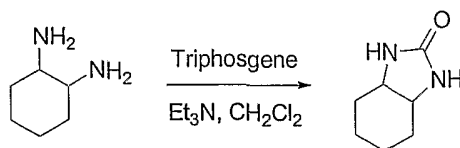
[0041] An ice-cooled solution of amino alcohol (15 mmol) and Et₃N (60 mmol) in dry CH₂Cl₂ (60 mL) is added to a solution of POCl₃ (22.7 mmol) in CH₂Cl₂ (40 mL) over a period of 10 min. Stirring is continued at 0°C until TLC indicates complete disappearance of the starting material. The mixture is then concentrated, and the crude chlorophosphoramidate hydrolyzed by treatment with 2N NaOH (10 mL) at room temperature for between 2 and 4 hours. The derived phosphonamide is isolated by reversed phase HPLC.

Example 6: Synthesis of cyclic phosphorodiamidates



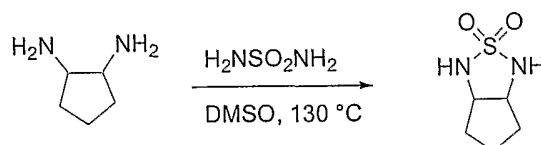
[0042] A solution of diamine (10 mmol) and triethylamine (40 mmol) in benzene (100 mL) is cooled to 0 °C and phosphorus oxychloride (POCl₃, 11 mmol) is introduced via syringe dropwise. After stirring at 0-5 °C for 2 hours, the mixture is allowed to warm to room temperature and stir for an additional 6 hours. The mixture is once again cooled to 0 °C, treated with 2N NaOH (20 mL), and then heated at 50 °C for 1-2 hours. The aqueous and organic phases are separated, and the product isolated by acidification of the aqueous solution.

Example 7: Synthesis of cyclic ureas



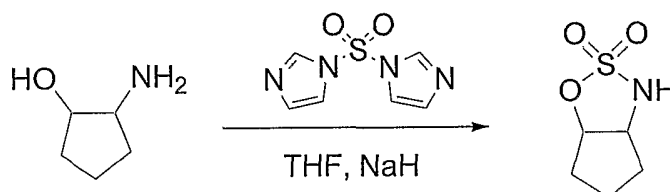
[0043] A solution of diamine (10 mmol) and triethylamine (40 mmol) in CH_2Cl_2 (100 mL) is cooled to 0 °C and triphosgene (11 mmol) is introduced portion-wise with stirring. After stirring at 0-5 °C for 2-5 hours, the mixture is quenched with methanol (20 mmol) and allowed to warm to room temperature. The mixture is treated with 2N HCl (20 mL) and the aqueous and organic phases are separated. The organic layer is dried over sodium sulfate and concentrated to provide the crude urea product, which is purified by silica gel chromatography or by crystallization.

Example 8: Synthesis of cyclic sulfamides



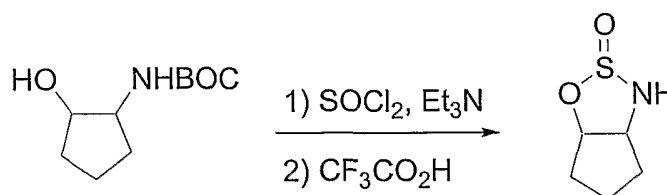
[0044] A diamine (1 mmol) in 10 mL of dimethyl sulfoxide (DMSO) is allowed to react with sulfamide (1.2 mmol) at 130 °C for 18-20 hours. The mixture is cooled, poured on to ice-cold sodium chloride solution extracted with diethyl ether. The combined organic extracts are then dried over anhydrous magnesium sulfate. Removal of drying agent and solvent *in vacuo* affords cyclic sulfamides.

Example 9: Synthesis of cyclic sulfamidates



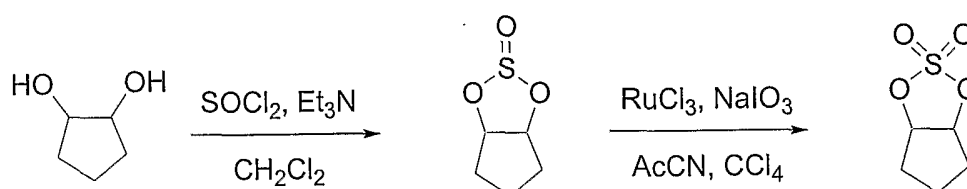
[0045] To a suspension of amino alcohol (2.5 mmol) in THF (15 mL) at room temperature is added NaH (7.52 mmol). After 15 minutes, a solution of 1,1'-sulfonyldiimidazole (3.23 mmol) in THF (7 mL) is added dropwise during 10 minutes and the mixture is stirred at room temperature for 15 hours. The reaction mixture is then quenched with methanol, the solvents evaporated *in vacuo*, and the residue purified silica gel chromatography to provide the cyclic sulfamidate.

Example 10: Synthesis of cyclic sulfamidites



[0046] The *t*-butoxycarbonyl (BOC) derivative (10 mmol) is dissolved in dry CH₂Cl₂ (100 mL) under an inert atmosphere and then cooled to -78°C. To the solution is then added triethylamine (200 mmol) via syringe and the resultant mixture is stirred for 5 minutes. After this time, distilled thionyl chloride (100 mmol) is added dropwise. The reaction is allowed to stir at -78 °C for 30 minutes before quenching with methanol (10 equivalents) at -78 °C. The mixture is then transferred onto CH₂Cl₂ and water. The organic layer is then dried over MgSO₄, concentrated and the product purified by column chromatography. Deprotection of the intermediate BOC material is achieved by allowing the material to react with a 50% solution of TFA in CH₂Cl₂ at 0 °C. Removal of TFA and solvent *in vacuo* affords the sulfamidite.

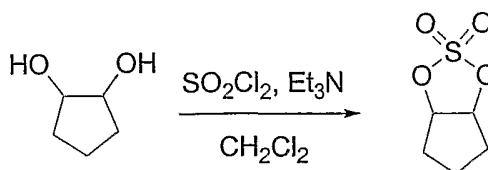
Example 11: Synthesis of cyclic sulfites and sulfates



[0047] An ice-cooled and magnetically stirred solution of diol (15.1 mmol) and Et₃N (60 mmol) in dry CH₂Cl₂ (60 mL) is added to a solution of SOCl₂ (22.7 mmol) in CH₂Cl₂ (40 mL) over a period of 10 min. Stirring is continued at 0°C until TLC indicates complete disappearance of the starting material. The mixture is diluted with CH₂Cl₂ (200 mL) and washed with water (2 × 100 mL) and brine (100 mL). The organic solution is dried (Na₂SO₄) and concentrated *in vacuo* to afford the cyclic sulfite, which is purified by a short column of silica gel.

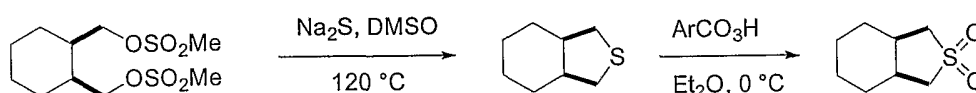
[0048] Oxidation of cyclic sulfite to cyclic sulfate: To a solution of the cyclic sulfite in a 1:1 mixture of CH₃CN/CCl₄ (100 mL) is added NaIO₄ (30.2 mmol), followed by a catalytic amount of RuCl₃ · 3H₂O (150 mg) and water (50 mL). The reaction mixture is stirred vigorously for 15 min at room temperature and then diluted with ether (800 mL). The organic layer is washed with water (2 × 200 mL) and brine (200 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Purification of the crude product by column chromatography provides the cyclic sulfate.

Example 12: Alternative synthesis of cyclic sulfates



[0049] An ice-cooled solution of diol (15 mmol) and Et_3N (60 mmol) in dry CH_2Cl_2 (60 mL) is added to a solution of SO_2Cl_2 (22.7 mmol) in CH_2Cl_2 (40 mL) over a period of 10 min. Stirring is continued at 0°C until TLC indicates complete disappearance of the starting material. The mixture is diluted with CH_2Cl_2 (200 mL) and washed with water (2×100 mL) and brine (100 mL). The organic solution is dried (Na_2SO_4) and concentrated in vacuo to afford the cyclic sulfate, which can be purified by a short column of silica gel to ensure removal of any residual Et_3N .

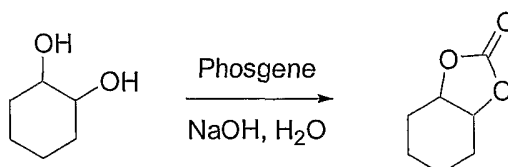
Example 13: Synthesis of *cis*-8-Thiabicyclo[4.3.0]nonane 8,8-dioxides



[0050] A 3-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, capillary tube, heating mantle, and 90° adapter connected to a condenser and receiving flask is charged with 240 g. (1.00 mole) of recrystallized sodium sulfide nonahydrate and 2 l. of dimethyl sulfoxide. As the mixture is stirred, the internal pressure is reduced to 30 mm., and heat is applied until 300–350 ml. of distillate is collected. After cooling to 40° , the capillary and take-off adapter are replaced with a thermometer and condenser, and 95 g. (0.32 mole) of *cis*-1,2-cyclohexanedimethanol dimethanesulfonate is introduced in one portion. The mixture is then stirred at 120° for 18 hours, cooled, and transferred to a 5-l. separatory funnel containing 1500 g. of ice. After 1 l. of hexane is added and the two-phase mixture well shaken, the aqueous phase is reextracted with hexane (500 ml.). The combined organic layers are washed with four 1-l. portions of water, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The sulfide is collected by bulb-to-bulb distillation at 0.05–0.1 mm. as a colorless liquid (30.8–31.6 g., 68.0–70.5%).

[0051] Oxidation: A solution of the sulfide (43.0 g., 0.303 mole) in 1 l. of ether is cooled to 0° , stirred magnetically, and treated dropwise with 1.0 l. of 0.65 *N* ethereal monophtalic acid. The mixture is kept overnight at 0° , after which time the precipitated phthalic acid is separated by filtration and the filtrate is concentrated with a rotary evaporator. Bulb-to-bulb distillation of the residual oil at 0.05–0.1 mm. affords the sulfone as a colorless liquid (48.5–50 g., 92–95%). This product is crystallized from ether-hexane, yielding a colorless solid, m.p. $39\text{--}41^\circ$.

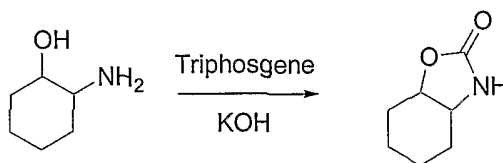
Example 14: Synthesis of cyclic carbonates



[0052] In a 5-l. three-necked flask, filled with nitrogen, 110 g. (1.0 mole) of recrystallized catechol is dissolved in 250 ml. of deaerated water containing 88 g. (2.2 moles) of sodium hydroxide. The flask is fitted with a gas inlet tube, a thermometer dipping into the liquid, and an efficient glass mechanical stirrer with a gas-tight rubber slip seal and is immersed in an ice-salt bath. A positive nitrogen pressure of about 1 cm. is maintained by attaching the inlet tube to a source of nitrogen through a line containing a T-tube dipping into mercury. A solution of 200–225 g. (2.0–2.3 moles) of commercial phosgene in 750 ml. of toluene is prepared at 0° by bubbling the gas into toluene in a tared flask, and the solution is added to the flask in portions of about 50 ml. with good mechanical stirring over a period of 60 to 75 minutes. During the addition the temperature is maintained at 0–5° by periodic addition to the mixture of clean cracked ice, free from dirt and iron rust. After addition of the toluene solution of phosgene is completed, the mixture is stirred at 0–5° for 1 hour and then allowed to come to room temperature. The mixture is filtered with suction, and the solid is pressed on the funnel to remove as much water as possible. The aqueous portion of the filtrate is separated, and the solid on the funnel is added to the toluene in the filtrate and dissolved by warming. The warm toluene solution is filtered and distilled under reduced pressure (water aspirator) until the product begins to crystallize. The residue is warmed to redissolve the solid, and then chilled. The *o*-phenylene carbonate is collected on a suction filter and dried in a vacuum desiccator; the yield is 98–110 g., m.p. 119–120°.

[0053] Concentration of the filtrate yields a second crop of impure product, which is recrystallized from toluene and then melts at 119–120°. The combined yield of pure white *o*-phenylene carbonate from the first and second crops is 107–116 g. (79–85%).

Example 15: Synthesis of cyclic urethanes



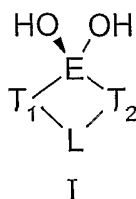
[0054] A 500-mL, single-necked, round-bottomed flask equipped with a 250-mL pressure-equalizing dropping funnel and a magnetic stirring bar is charged with (0.048 mmol) of amino alcohol, 70 mL of toluene, and 55 mL (0.12 mol) of 12.5% aqueous potassium hydroxide solution. The reaction flask is cooled to 0°C in an ice-water bath, the dropping funnel is charged with a solution of 50 mL (0.095 mol) of triphosgene (1.9 M in toluene), and the triphosgene solution is slowly added over 40 min with vigorous stirring to the two-phase reaction mixture. After the reaction is complete, the reaction mixture is stirred at 0°C for 1 hr and diluted with 130 mL of ethyl acetate. The mixture is transferred to a 1-L separatory funnel, and the layers are separated.

The organic layer is washed successively with 150 mL of saturated aqueous sodium bicarbonate solution and 150 mL of saturated sodium chloride solution. The organic layer is dried over magnesium sulfate, filtered, and concentrated by rotary evaporation to give the crude cyclic urethane that can be purified by silica gel chromatography or by crystallization.

[0055] It will be appreciated by those skilled in the art that various omissions, additions and modifications may be made to the processes described above without departing from the scope of the invention, and all such modifications and changes are intended to fall within the scope of the invention, as defined by the appended claims.

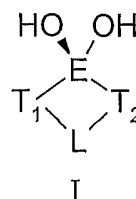
WHAT IS CLAIMED IS:

1. A method of controlling bacterial growth, comprising exposing a bacterium to a compound of structure I



wherein E is selected from the group consisting of B, P, and S, T₁ and T₂ are each independently selected from the group consisting of O, NR, and CH₂, where R = H or C₁-C₈ alkyl, or C₁-C₈ oxoalkyl, and L is selected from the group consisting of ethylene, propylene, and four to six-membered alicyclic and aromatic rings, provided that structure I does not include AI-2-borate.

2. The method of claim 1, wherein E is B.
3. The method of claim 2, wherein T₁ and T₂ are O.
4. The method of claim 1, wherein the compound has a molecular weight less than about 750 Da.
5. The method of claim 4, wherein the molecular weight is less than about 500 Da.
6. The method of claim 1, wherein E is P.
7. The method of claim 6, wherein T₁ and T₂ are O.
8. The method of Claim 1 comprising administering a therapeutically effective amount of the compound to a human.
9. The method of Claim 1 in which the bacterium is exposed to an amount of the compound that affects biofilm formation.
10. A pharmaceutical composition comprising a compound having structure I



wherein E is selected from the group consisting of B, P, and S, T₁ and T₂ are each independently selected from the group consisting of O, NR, and CH₂, where R = H or C₁-C₈ alkyl, or C₁-C₈ oxoalkyl, and L is selected from the group consisting of ethylene, propylene, and four to six-membered alicyclic and aromatic rings, provided that structure I does not include AI-2-borate.

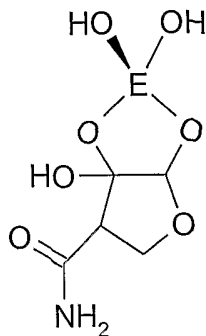
11. The pharmaceutical composition of claim 10, wherein L is selected from the group consisting of ethylene, propylene, cyclopentyl, cyclohexyl, pyrrolidine, tetrahydrofuran, piperidine,

pyran, dioxane, morpholine, pyrrole, furan, pyridine, pyrimidine, pyrazine, imidazole, thiazole, oxazole, purine, and indazole.

12. The pharmaceutical composition of claim 11, wherein L is selected from the group consisting of ethylene, propylene, cyclopentyl, cyclohexyl, pyrrolidine, tetrahydrofuran, piperidine, pyran, dioxane, and morpholine.

13. The pharmaceutical composition of claim 12, wherein L is tetrahydrofuran bearing a keto, a hydroxy, and a carboxamido functional group, T₁ and T₂ are oxygen, and E is B or P.

14. The pharmaceutical composition of claim 13, wherein the compound has the structure



SEQUENCE LISTING

<110> QUOREX PHARMACEUTICALS, INC.
 COOPER, Stephen R.
 YAGER, Kraig M.

<120> ANTI-BACTERIAL AGENTS BASED UPON
 OXOANION BINDING

<130> QUOREX.011VPC

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Pro	Val	Pro	Leu	Ser	Lys	Pro	Thr	Gln	Arg	Pro	Ile	Lys	Ile	Ser	Val
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Gln	Val	Phe	Thr	Arg	Pro	Asn	Ala	Asp	Ile	Lys	Gln	Gln	Ser	Leu	Ser
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Ser	Arg	Glu	Leu	Ala	Thr	Glu	Phe	Gly	Lys	Phe	Phe	Pro	Lys	His	Thr
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Tyr	Tyr	Ser	Val	Leu	Tyr	Phe	Ser	Glu	Gly	Tyr	Ile	Ser	Asp	Val	Arg
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Gly	Asp	Thr	Phe	Ile	His	Gln	Val	Asn	Arg	Asp	Asn	Asn	Phe	Glu	Leu
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Gly	Arg	Glu	Asp	Ile	Met	Ile	Asn	Gly	Trp	Gly	Gly	Gly	Ser	Ala	Glu
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			340												

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/27154

A. CLASSIFICATION OF SUBJECT MATTER				
IPC(7) : A61K 31/69				
US CL : 558/286, 287, 288, 291; 514/64				
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) U.S. : 558/286, 287, 288, 291; 514/64				
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 practicable, search terms used) Please See Continuation Sheet				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	Database Caplus on STN, Chemical Abstracts (Columbus, Ohio, USA), CA:103:47243, SAGULENKO et al 'Physicochemical properties of pyrocatechol borates of alkali metals' Viniti pp 4184 , 1984.	10		
X	Database Caplus on STN Chemical Abstracts (Columbus Ohio, USA, CA:111:166124, CODDINGTON et al 'High field boron-11 and carbon-13 NMR investigations of aqueous borate solutions and borate -diol complexes' Journal of Coordination Chemistry 20(1) pp 27-38, 1989.	10-12		
A	US 3,053,880 A (DALE, J.) 11 September 1962 (11/9/1962), column 1, lines 45-72 and column 2, lines 1-20	1-5 and 8-12		
A	US 3, 564,091 A (DEGRAY et al) 16 February 1971 (16/2/1971), columns 1-2.	1-5 and 8-12		
A	US 3,873,279 A (SINGER, M.) 25 March 1975 (25/3/75) column 2.	1-5 and 8-12		
A	US 3,325,262 A (DE GRAY et al) 13 June 1967 (13/6/67), column 1.	1-5 and 8-12		
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.				
<table border="0" style="width:100%;"> <tr> <td style="width:50%; vertical-align: top;"> * 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 application or patent 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 </td> <td style="width:50%; vertical-align: top;"> "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 </td> </tr> </table>			* 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 application or patent 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
* 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 application or patent 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 26 November 2002 (26.11.2002)		Date of mailing of the international search report 15 JAN 2003		
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer Jean F. Vollano <i>Jean F. Vollano</i> Telephone No. 703-308-1235		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/27154

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1. Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

- 2. Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3. Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

- 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
 - 2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
 - 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

 - 4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-5 and 8-12 (in part)
- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest.
 - No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US02/27154

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-5, 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group II, claim(s) 1, 4-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group III, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group IV, claim(s) 1-2, 4-5, 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are NR and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group V, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are NR and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group VI, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are NR and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group VII, claim(s) 1-2, 4-5, 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are CH2 and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group VIII, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are CH2 and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group IX, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are CH2 and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group X, claim(s) 1-2, 4-5, 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and NR and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group XI, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and NR and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group XII, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and NR and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group XIII, claim(s) 1-2, 4-5, 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and CH2 and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group XIV, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and CH2 and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group XV, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and CH2 and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group XVI, claim(s) 1-2, 4-5, 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are NR and CH2 and L is a non heterocyclic moiety (i.e. hydrocarbon).

INTERNATIONAL SEARCH REPORT

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Group XVII, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are NR and CH2 and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group XVIII, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are NR and CH2 and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group XIX, claim(s) 1-5 , 8-14 (in part) drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and L is the heterocyclic furan or tetrahydrofuran.

Group XX, claim(s) 1, 4-14 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and L is the heterocyclic furan or tetrahydrofuran.

Group XXI , claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and L is the heterocyclic furan or tetrahydrofuran.

Group XXII, claim(s) 1-2, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are NR and L is a non heterocyclic moiety (i.e. hydrocarbon).

Group XXIII, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are NR and L is the heterocyclic furan or tetrahydrofuran.

Group XXIV, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are NR and L is the heterocyclic furan or tetrahydrofuran.

Group XXV, claim(s) 1-2, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are CH2 and L is the heterocyclic furan or tetrahydrofuran.

Group XXVI, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are CH2 and L is the heterocyclic furan or tetrahydrofuran.

Group XXVII , claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are CH2 and L is the heterocyclic furan or tetrahydrofuran.

Group XXVIII, claim(s) 1-2, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and NR and L is the heterocyclic furan or tetrahydrofuran.

Group XXIX, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and NR and L is the heterocyclic furan or tetrahydrofuran.

Group XXX , claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and NR and L is the heterocyclic furan or tetrahydrofuran.

Group XXXI, claim(s) 1, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and CH2 and L is is the heterocyclic furan or tetrahydrofuran.

Group XXXII, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and CH2 and L is the heterocyclic furan or tetrahydrofuran.

Group XXXIII, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and CH2 and L is the heterocyclic furan or tetrahydrofuran.

Group XXXIV, claim(s) 1, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are NR and CH2 and L is the heterocyclic furan or tetrahydrofuran.

Group XXXV , claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are NR and CH2 and L is the heterocyclic furan or tetrahydrofuran.

Group XXXVI, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are NR and CH2 and L is the heterocyclic furan or tetrahydrofuran.

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Group XXXVII, claim(s) 1-5, 8-12 (in part) drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and L is the heterocyclic pyrrole or pyrrolidine.

Group XXXVIII, claim(s) 1, 4-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and L is the heterocyclic pyrrole or pyrrolidine.

Group XXXIX, claim(s) 1, 4-5, 8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and L is the heterocyclic pyrrole or pyrrolidine.

Group XL, claim(s) 1-2, 4-5, 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are NR and L is the heterocyclic pyrrole or pyrrolidine.

Group XLI, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are NR and L is the pyrrole or pyrrolidine.

Group XLII, claim(s) 1, 4-5, 8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are NR and L is the heterocyclic pyrrole or pyrrolidine.

Group XLIII, claim(s) 1-2, 4-5, 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are CH2 and L is the heterocyclic pyrrole or pyrrolidine.

Group XLIV, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are CH2 and L is the heterocyclic pyrrole or pyrrolidine.

Group XLV, claim(s) 1, 4-5, 8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are CH2 and L is the heterocyclic pyrrole or pyrrolidine.

Group XLVI, claim(s) 1-2, 4-5, 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and NR and L is the heterocyclic pyrrole or pyrrolidine.

Group XLVII, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and NR and L is the heterocyclic pyrrole or pyrrolidine.

Group XLVIII, claim(s) 1, 4-5, 8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and NR and L is the heterocyclic pyrrole or pyrrolidine.

Group XLIX, claim(s) 1, 4-5, 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and CH2 and L is pyrrole or pyrrolidine.

Group L, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and CH2 and L is the heterocyclic pyrrole or pyrrolidine.

Group LI claim(s) 1, 4-5, 8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and CH2 and L is the heterocyclic pyrrole or pyrrolidine.

Group LII, claim(s) 1, 4-5, 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are NR and CH2 and is the heterocyclic pyrrole or pyrrolidine.

Group LIII, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are NR and CH2 and is the heterocyclic pyrrole or pyrrolidine.

Group LIV, claim(s) 1, 4-5, 8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are NR and CH2 and L is the heterocyclic pyrrole or pyrrolidine.

Group XXXVII, claim(s) 1-5, 8-12 (in part) drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and L is the heterocyclic pyrrole or pyrrolidine.

Group LV, claim(s) 1-5, 8-12 (in part) drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and L is pyridine or piperidine.

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- Group LVI , claim(s) 1, 4-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and L is pyridine or piperidine.
- Group LVII , claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and L is pyridine or piperidine.
- Group LVIII, claim(s) 1-2, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are NR and L is pyridine or piperidine.
- Group LIX, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are NR and L is pyridine or piperidine.
- Group LX, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are NR and L is pyridine or piperidine.
- Group LXI, claim(s) 1-2, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are CH2 and L is pyridine or piperidine.
- Group LXII, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are CH2 and L is pyridine or piperidine.
- Group LXIII, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are CH2 and L is the pyridine or piperidine.
- Group LXIV, claim(s) 1-2, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and NR and L is pyridine or piperidine.
- Group LXV, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and NR and L is pyridine or piperidine.
- Group LXVI , claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and NR and L is pyridine or piperidine.
- Group LXVII , claim(s) 1, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and CH2 and L is pyridine or piperidine.
- Group LXVIII, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and CH2 and L is pyridine or piperidine.
- Group LXIX, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and CH2 and L is pyridine or piperidine.
- Group LXX, claim(s) 1, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are NR and CH2 and L is pyridine or piperidine.
- Group LXXI, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are NR and CH2 and is pyridine or piperidine.
- Group LXXII, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are NR and CH2 and L is pyridine or piperidine.
- Group LXXIII, claim(s) 1-5 , 8-12 (in part) drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and L is pyrimidine.
- Group LXXIV , claim(s) 1, 4-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and L is pyrimidine.
- Group LXXV , claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and L is pyrimidine.
- Group LXXXVI, claim(s) 1-2, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are NR and L is pyrimidine.

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Group LXXVII, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are NR and L is pyrimidine.

Group LXXVIII, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are NR and L is pyrimidine.

Group LXXIX, claim(s) 1-2, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are CH2 and L is pyrimidine.

Group LXXX, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are CH2 and L is pyrimidine.

Group LXXXI, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are CH2 and L is pyrimidine.

Group LXXXII , claim(s) 1-2, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and NR and L is pyrimidine.

Group LXXXIII, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and NR and L is pyrimidine.

Group LXXXIV , claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and NR and L is pyrimidine.

Group LXXXV, claim(s) 1, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are O and CH2 and L is pyrimidine.

Group LXXXVI, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are O and CH2 and L is pyrimidine.

Group LXXXVII, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are O and CH2 and L is pyrimidine.

Group LXXXVIII, claim(s) 1, 4-5 , 8-12 (in part), drawn to a compound of formula 1 wherein E is Boron and T1 and T2 are NR and CH2 and L is pyrimidine.

Group LXXXIX, claim(s) 1, 4-6, 8-12 (in part), drawn to a compound of formula 1 wherein E is Phosphorus and T1 and T2 are NR and CH2 and is pyrimidine.

Group XC, claim(s) 1, 4-5,8-12, drawn to a compound of formula 1 wherein E is a Sulfur and T1 and T2 are NR and CH2 and L is pyrimidine.

Groups XC1 to CVIII are the same as groups LXXII to XC except the L is dioxane.

Groups CIX to CXXVI are the same as groups LXXII to XC except the L is morpholine.

Groups CXXVII to CXLIV are the same as groups LXXII to XC except the L is pyrazine.

Groups CXLV to CLXII are the same as groups LXXII to XC except the L is imidazole.

Groups CLXIII to CLXXX are the same as groups LXXII to XC except the L is thiazole.

Groups CLXXXI to CXCVIII are the same as groups LXXII to XC except the L is purine.

Groups CXCIX to CCXVI are the same as groups LXXII to XC except the L is oxazole.

Groups CCXVII to CCXXXIV are the same as groups LXXII to XC except the L is indazole.

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The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The only structural feature that is common to all the alternatives is an OH group. This is not a large structural feature nor is it applicant's contribution to the art. There are thousands of compounds that have an OH in them and that also can control bacterial growth and therefore there is no special technical feature which unites the compound groups and there is no unity of invention since the groups are all structure groups.

Continuation of B. FIELDS SEARCHED Item 3:
EAST, CAS ONLINE, Beilstein

search terms: structure drawing, dihydroxy borate, bacterial, pharmaceutical, borate anion