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**WO 00/78309 A1**

(54) Title: INDOLE COMPOUNDS

(57) Abstract: This invention relates to the use of compounds as inhibitors of the fatty acid synthase FabH.

## INDOLE COMPOUNDS

### FIELD OF THE INVENTION

This invention relates to the use of compounds as inhibitors of the fatty acid synthase FabH.

5

### BACKGROUND OF THE INVENTION

The pathway for the biosynthesis of saturated fatty acids is very similar in prokaryotes and eukaryotes. However, although the chemical reactions may not vary, the organization of the biosynthetic apparatus is very different. Vertebrates and yeasts possess type I fatty acid synthases (FASs) in which all of the enzymatic activities are encoded on one or two polypeptide chains, respectively. The acyl carrier protein (ACP) is an integral part of the complex. In contrast, in most bacterial and plant FASs (type II) each of the reactions are catalyzed by distinct monofunctional enzymes and the ACP is a discrete protein. Mycobacteria are unique in that they possess both type I and II FASs; the former is involved in basic fatty acid biosynthesis whereas the latter is involved in synthesis of complex cell envelope lipids such as mycolic acids. There therefore appears to be considerable potential for selective inhibition of the bacterial systems by broad spectrum antibacterial agents (Jackowski, S. 1992. In *Emerging Targets in Antibacterial and Antifungal Chemotherapy*. Ed. J. Sutcliffe & N. Georgopapadakou. Chapman & Hall, New York; Jackowski, S. et al. (1989). *J. Biol. Chem.* 264, 7624-7629.)

The first step in the biosynthetic cycle is the condensation of malonyl-ACP with acetyl-CoA by FabH. In subsequent rounds malonyl-ACP is condensed with the growing-chain acyl-ACP (FabB and FabF, synthases I and II respectively). The second step in the elongation cycle is ketoester reduction by NADPH-dependent  $\beta$ -ketoacyl-ACP reductase (FabG). Subsequent dehydration by  $\beta$ -hydroxyacyl-ACP dehydrase (either FabA or FabZ) leads to trans-2-enoyl-ACP which is in turn converted to acyl-ACP by NADH-dependent enoyl-ACP reductase (FabI). Further rounds of this cycle, adding two carbon atoms per cycle, eventually lead to palmitoyl-ACP whereupon the cycle is stopped largely due to feedback inhibition of FabH and I by palmitoyl-ACP (Heath, et al, (1996), *J.Biol.Chem.* 271, 1833-1836). Fab H is therefore a major biosynthetic enzyme which is also a key regulatory point

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in the overall synthetic pathway (Heath, R.J. and Rock, C.O. 1996. *J.Biol.Chem.* 271, 1833-1836; Heath, R.J. and Rock, C.O. 1996. *J.Biol.Chem.* 271, 10996-11000).

5 The antibiotic thiolactomycin has broad-spectrum antibacterial activity both in vivo and in vitro and has been shown to specifically inhibit all three condensing enzymes. It is non-toxic and does not inhibit mammalian FASs (Hayashi, T. et al., 1984. *J. Antibiotics* 37, 1456-1461; Miyakawa, S. et al., 1982. *J. Antibiotics* 35, 411-419; Nawata, Y et al., 1989. *Acta Cryst. C*45, 978-979; Noto, T. et al., 1982. *J. Antibiotics* 35, 401-410; Oishi, H. et al., 1982. *J. Antibiotics* 35, 391-396.

10 Similarly, cerulenin is a potent inhibitor of FabB & F and is bactericidal but is toxic to eukaryotes because it competes for the fatty-acyl binding site common to both FAS types (D'Agno, G. et al., 1973. *Biochim. Biophys. Acta.* 326, 155-166). Extensive work with these inhibitors has proved that these enzymes are essential for viability. Little work has been carried out in Gram-positive bacteria.

15 There is an unmet need for developing new classes of antibiotic compounds that are not subject to existing resistance mechanisms. No marketed antibiotics are targeted against fatty acid biosynthesis, therefore it is unlikely that novel antibiotics of this type would be rendered inactive by known antibiotic resistance mechanisms. Moreover, this is a potentially broad-spectrum target. Therefore, FabH inhibitors

20 would serve to meet this unmet need.

#### SUMMARY OF THE INVENTION

This invention comprises indole derivatives and pharmaceutical compositions containing these compounds, and their use as FabH inhibitors which are useful as antibiotics for the treatment of Gram positive and Gram negative

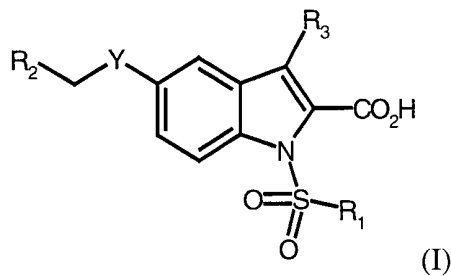
25 bacterial infections.

This invention further constitutes a method for treatment of a Gram negative or Gram positive bacterial infection in an animal, including humans, which comprises administering to an animal in need thereof, an effective amount of a compound of this invention.

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DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are represented by Formula (I):



wherein:

- 5         $R_1$  is selected from the group consisting of aryl, substituted aryl, heteroaryl,  $C_{1-10}$ alkyl, cycloalkyl, arylalkyl, heteroarylalkyl and heterocyclicalkyl;  
 $R_2$  is selected from the group consisting of aryl, substituted aryl, and heteroaryl;  
 $R_3$  is H, or lower alkyl;  
 10        Y is selected from the group consisting of  $CH_2$ ,  $NR_4$ , O, and S;  
 $R_4$  is selected from the group consisting of H, lower alkyl, CHO, and  $COR_1$ ;  
 or a pharmaceutically acceptable salt thereof.  
 Also included in the invention are pharmaceutically acceptable salt complexes.

- 15        As used herein, " $C_{1-10}$ alkyl" or "alkyl" means both straight and branched chain rings of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl and the like.

- The term "cycloalkyl" is used herein to mean cyclic rings, preferably of 3 to 8  
 20        carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.

The term "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean  $C_{1-10}$  alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.

- 25        As used herein, "aryl" means phenyl and naphthyl

As used herein, "heteroaryl" means a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group

consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, and benzimidazole.

As used herein, preferred aryl substituents include halo, including chloro, fluoro, bromo and iodo, in any combination.

As used herein, "lower alkyl" means C<sub>1-4</sub> alkyl.

The compounds of this invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Since the antibiotic compounds of the invention are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 95% pure, particularly at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 49% of a compound of the formula (I) or salt thereof.

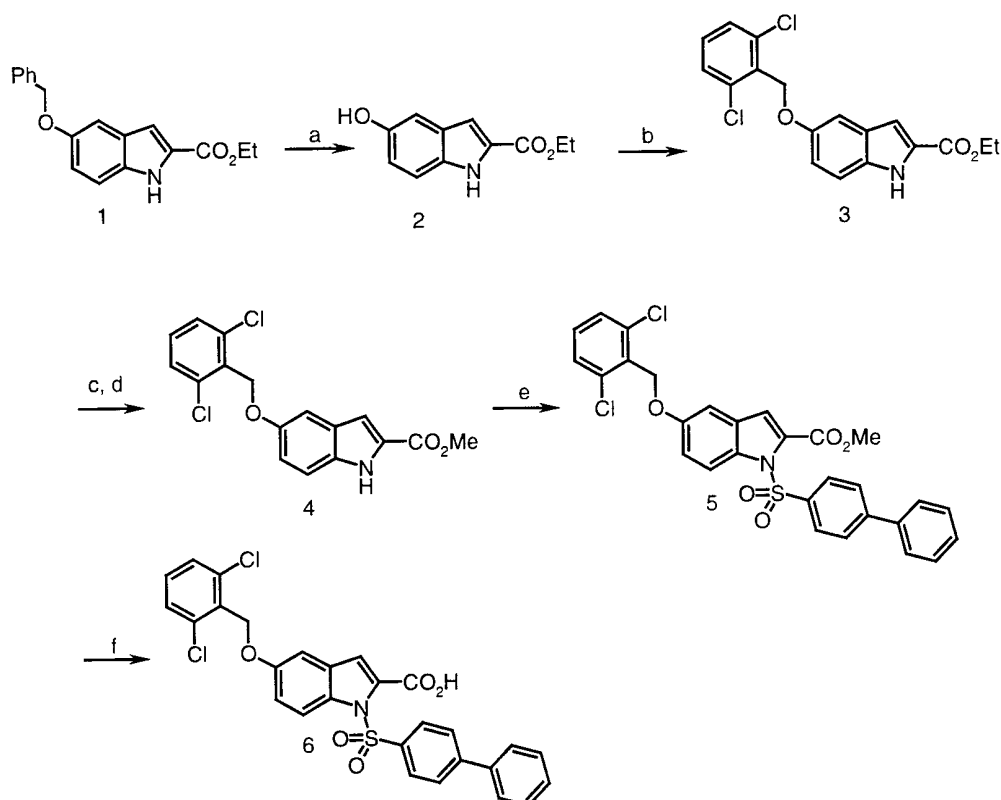
Preferred compounds of the present invention include:

5-(2, 6-dichlorobenzyloxy)-1-[(4-phenyl)phenylsulfonyl]indole-2-carboxylic acid;  
and

5-(2, 6-dichlorobenzyloxy)-1-[(4-phenoxy)phenylsulfonyl]indole-2-carboxylic acid.

Compounds of the Formula (I) wherein R<sub>1</sub> is substituted aryl, R<sub>2</sub> is 2, 6-dichlorophenyl, R<sub>3</sub> is H, and Y is O, were prepared by the method described in Scheme 1.

Scheme 1



- a) 10% Pd/C, H<sub>2</sub>, EtOH; b) 2, 6-dichlorobenzyl chloride, Cs<sub>2</sub>CO<sub>3</sub>, DMF; c) 1) aq. NaOH, THF, MeOH, 2) 10% HCl; d) MeOH, conc. H<sub>2</sub>SO<sub>4</sub>, reflux; e) 4-biphenylsulfonyl chloride, *t*-n-Bu<sub>4</sub>NHSO<sub>4</sub>, 50% KOH, PhH; f) 1) aq. NaOH, THF, MeOH, 2) 10% HCl.

Indole ethyl ester 1, Scheme 1, (Aldrich) was debenzylated *via* catalytic hydrogenation to provide the 5-hydroxy indole 2. The 5-hydroxyl was then  
 10 alkylated using the desired halide-containing reagent, in this example 2, 6-dichlorobenzyl chloride, using a suitable base such as cesium or potassium carbonate, providing indole 3. In this particular example, the ethyl ester was exchanged to a methyl ester by first saponification of ethyl ester 3 followed by reesterification to methyl ester 4. This ester exchange step is optional as the ethyl  
 15 ester may be carried through to the end of the synthesis if desired. Next, the indole was converted to the desired sulfonyl-containing derivative. In this example, indole 4 was reacted with 4-biphenylsulfonyl chloride under phase transfer catalysis conditions to provide biphenylsulfonamide 5. The 4-biphenylsulfonyl chloride used

in this example may be substituted by any desired sulfonyl chloride such as 4-phenoxyphenylsulfonyl chloride as illustrated in Example 2. The synthesis was completed by standard hydrolysis of the methyl ester providing the desired indole 2-carboxylic acid 6.

5

### SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, and all solvents are highest available purity unless otherwise indicated.

10

#### Example 1

#### Preparation of 5-(2, 6-dichlorobenzoyloxy)-1-[(4-phenyl)phenylsulfonyl]indole-2-carboxylic acid

##### a) Ethyl 5-hydroxyindole-2-carboxylate

A solution of 5-benzoyloxyindole-2-carboxylic acid ethyl ester (10 g, 34 mmol) in 250 mL of ethanol was treated with 10% Pd/C and hydrogenated under atmospheric pressure (double-walled balloon) for 20 h. The reaction mixture was diluted with EtOAc and filtered through Celite<sup>®</sup>. Evaporation of the filtrate *in vacuo* gave the title compound as a tan solid (7 g, 99%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.86 (br s, 1H), 7.29 (d, J = 8.80 Hz, 1H), 7.11 (s, 1H), 7.06 (s, 1H), 6.94 (d, J = 8.70 Hz, 1H), 4.83 (br s, 1H), 4.42 (q, J = 7.09 Hz, 2H), 1.41 (t, J = 7.08 Hz, 3H).

20

##### b) Ethyl 5-(2, 6-dichlorobenzoyloxy)indole-2-carboxylate

A solution of the compound of Example 1(a) (7 g, 34 mmol) in 100 mL of anhydrous DMF was treated with cesium carbonate (16.8 g, 52 mmol) and 2, 6-dichlorobenzyl chloride (7.38 g, 38 mmol) and stirred at room temperature for 20 h. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic extract was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo* to give a crude solid. Trituration of the solid with methylene chloride provided 7.61 g (61%) of the title compound as an off-white solid. ES (MS) m/e 364.2 [M+H]<sup>+</sup>.

30

## c) 5-(2, 6-Dichlorobenzyloxy)indole-2-carboxylic acid

A solution of the compound of Example 1(b) (7.61 g, 21 mmol) in anhydrous THF (100 mL) and methanol (50 mL) was treated with aqueous 1N NaOH (53 mL, 53 mmol) and stirred for 20 h. After removing the solvent mixture *in vacuo*, the  
5 resulting sodium salt was suspended in water and acidified with 10% HCl to afford the title compound (7g, 99%) as a white solid. ES (MS) m/e 336.2 [M+H]<sup>+</sup>.

## d) Methyl 5-(2, 6-dichlorobenzyloxy)indole-2-carboxylate

A solution of the compound of Example 1(c) in methanol (50 mL) and a  
10 catalytic amount of concentrated sulfuric acid (0.2 mL) was refluxed for 20 h. An off-white crystalline solid began to precipitate out upon cooling. The off-white crystalline solid (title compound) was collected by filtration. ES (MS) m/e 350.0 [M+H]<sup>+</sup>.

## 15 e) Methyl 5-(2, 6-dichlorobenzyloxy-1-[(4-phenyl)phenylsulfonyl]indole-2-carboxylate

A 50% KOH solution (3 mL) was added dropwise to a stirring mixture of the compound of Example 1(d) (1 g, 2.9 mmol) and *tert*-n-butylammonium sulfate (0.098 g, 0.29 mmol) in benzene. 4-Biphenylsulfonyl chloride (1.8 g, 7.2 mmol) was  
20 next added and the reaction mixture was stirred for 20 h. The reaction mixture was poured into water and extracted with methylene chloride. The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated *in vacuo*; the resulting residue was chromatographed over silica with 10:1:89, 10:3:87, 10:5:85, and 10:10:80 CH<sub>2</sub>Cl<sub>2</sub>-EtOAc-hexane to afford the title compound (1.32 g, 82%) as a light tan solid. ES  
25 (MS) m/e 566.2 [M+H]<sup>+</sup>.

## f) 5-(2, 6-Dichlorobenzyloxy)-1-[(4-phenyl)phenylsulfonyl]indole-2-carboxylic acid

Following the procedure of Example 1(c), except for substituting the compound of Example 1(b) with the compound of Example 1(e), the title compound  
30 was prepared as a white solid. ES (MS) m/e 552.0 [M+H]<sup>+</sup>.

## Example 2



Preparation of 5-(2, 6-dichlorobenzyloxy)-1-[(4-phenoxy)phenylsulfonyl]indole-2-carboxylic acid

a) Methyl 5-(2, 6-dichlorobenzyloxy)-1-[(4-phenoxy)phenylsulfonyl]indole-2-carboxylate

5           Following the procedure of Example 1(e), except for substituting 4-biphenylsulfonyl chloride with (4-phenoxy)phenylsulfonyl chloride, the title compound was prepared as a colorless glassy foam. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.04 (d, J = 9.87 Hz, 1H), 7.96 (d, J = 8.80 Hz, 2H), 7.40 (m, 4H), 7.20 (m, 5H), 7.03 (d, J = 8.32 Hz, 2H), 6.98 (d, J = 8.84 Hz, 2H), 5.28 (s, 2H), 3.95 (s, 3H).

10

b) 5-(2, 6-Dichlorobenzyloxy)-1-[(4-phenoxy)phenylsulfonyl]indole-2-carboxylic acid

          Following the procedure of Example 1(c), except for substituting the compound of Example 1(b) with the compound of Example 2(a), the title compound  
15 was prepared as an off-white glassy foam. ES (MS) m/e 568.0 [M+H]<sup>+</sup>.

### Example 3

Preparation of 5-(2,6-Dichlorobenzyloxy)-1-(naphthalene-1-sulfonyl)-1H-indole-2-carboxylic acid

20           Following the general procedure as described in Example 1 and Example 2, above, using 1-naphthalenesulphonyl chloride, the title compound was prepared as a white solid. ES (MS) m/e 526.0 [M+H]<sup>+</sup>.

### Example 4

25 Preparation of 5-(2,6-Dichlorobenzyloxy)-1-(naphthalene-2-sulfonyl)-1H-indole-2-carboxylic acid

          Following the general procedure as described in Example 1 and Example 2, above, using 2-naphthalenesulphonyl chloride, the title compound was prepared as a white solid. ES (MS) m/e 526.0 [M+H]<sup>+</sup>.

30

Biological Assay:

FabH was assayed in a coupled format using his-tagged *S.aureus* FabD, and acyl carrier protein (ACP) purchased from Sigma. Lyophilized ACP was reduced using  $\beta$ -mercaptoethanol in phosphate buffer. Malonyl-CoA, and FabD were added to the reduced ACP, thus generating malonyl-ACP. After the FabD reaction reached equilibrium, [ $^{14}\text{C}$ ] acetyl-CoA and inhibitors were added, and the reaction started by the addition of FabH. TCA precipitation and filtration was used to separate [ $^{14}\text{C}$ ] acetyl-CoA substrate from [ $^{14}\text{C}$ ] acetoacetyl-ACP product.

Secondary and tertiary screens of suitable reproducibility, sensitivity, throughput and analytical power to progress primary screen hits are characterized, validated and in current use. Compounds are evaluated against purified mammalian fatty acid biosynthetic enzymes, *E.coli* FabH, FabB and a human lung cell cytotoxicity assay. In addition, whole-cell antibacterial activity is determined against a range of clinically relevant wild type and efflux impaired bacteria using standard and novel fluorescence based technologies. The FabH assay has been thoroughly characterized kinetically and a reaction mechanism proposed. Detailed studies have generated novel data about mechanism of inhibition by tool compounds, including thiolactomycin. Screens in use are of direct relevance to the therapeutic goal - eradication of bacteria from sites of infection ('cure'). Several state-of-the-art animal models of bacterial infection are available, meaningful and in current use in this and numerous other studies at SB. Extensive prior experience with known antibacterials confirm that bacterial kill *in vitro* and in animal models is an excellent indicator of bacterial kill *in vivo* and cure of infection.

The present invention also provides a pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof and a pharmaceutically acceptable carrier. The compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The antibiotic compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

The composition may be formulated for administration by any route, such as  
5 oral, topical or parenteral, especially oral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops,  
10 impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may  
15 be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for  
20 example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the  
25 form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate  
30 gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for

example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter  
5 or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in  
10 water for injection and filter sterilized before filling into a suitable vial or ampoule and sealing. The solution preferably contains a buffer (such as phosphate) to keep the pH in the range of about 3.5 to 7. DMSO or alcoholic solvents may also be present (at concentrations such as 0.01 to 10 mL/liter) to aid solubility and penetration of the compound of Formula (I). Advantageously, agents such as a local  
15 anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same  
20 manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilized by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

25 The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 1 to 140 mg/kg of  
30 body weight, depending on the route and frequency of administration..

Inhibitors of  $\beta$ -ketoacyl-ACP Synthase (FabH) can be administered by injection in solutions either intravenously, intramuscularly, intraperitoneally, or orally. The solution preferably contains a buffer (such as phosphate) to keep the pH in the range of about 3.5 to 7. DMSO or alcoholic solvents may also be present (at  
5 concentrations such as 0.01 to 10 mL/liter) to aid solubility and penetration of the  $\beta$ -ketoacyl-ACP Synthase (FabH) inhibitor.

No unacceptable toxicological effects are expected when a compound of formula (Ia) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof is administered in the above-mentioned dosage range.

10 The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or compounds which enhance the antibacterial activity of a compound of formula (I) may be employed.

The antibiotic compounds of the present invention are active against a wide  
15 range of organisms including both Gram-negative organisms such as *Escherichia coli* and *Klebsiella pneumoniae* and Gram-positive organisms such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis* and *Enterococcus faecium*, including isolates resistant to existing antibiotics.

All publications, including but not limited to patents and patent  
20 applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

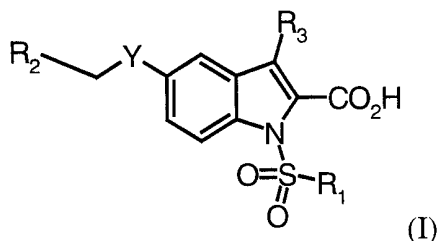
The above description fully discloses the invention including preferred  
25 embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims.

Without further elaboration, it is believed that one skilled in the area can, using the preceding description, utilize the present invention to its fullest extent.

Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of  
30 the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed is:

1. A method of treating bacterial infections by administering to a patient in need thereof an effective amount of a compound of Formula (I):



5

wherein:

R<sub>1</sub> is selected from the group consisting of aryl, substituted aryl, heteroaryl, C<sub>1-10</sub>alkyl, cycloalkyl, arylalkyl, heteroarylalkyl and heterocyclicalkyl;

10 R<sub>2</sub> is selected from the group consisting of aryl, substituted aryl, and heteroaryl;

R<sub>3</sub> is H, or lower alkyl;

Y is selected from the group consisting of CH<sub>2</sub>, NR<sub>4</sub>, O, and S; and

R<sub>4</sub> is selected from the group consisting of H, lower alkyl, CHO, and COR<sub>1</sub>; or a pharmaceutically acceptable salt thereof.

15

2. A method of treatment according to Claim 1 wherein the compound of Formula (I) is 5-(2, 6-dichlorobenzoyloxy)-1-[(4-phenyl)phenylsulfonyl]indole-2-carboxylic acid.

3. A method of treatment according to Claim 1 wherein the compound of Formula (I) is 5-(2, 6-dichlorobenzoyloxy)-1-[(4-phenoxy)phenylsulfonyl]indole-2-carboxylic acid.

20

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/17244

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/40

US CL :514/419

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. : 514/419

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)

STN (REGISTRY(structure))

search terms: none (no compounds found)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,482,960 A (BERRYMAN et al) 09 January 1996, col. 5-10.	1-3

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	*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
*A* document defining the general state of the art which is not considered to be of particular relevance	*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
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Date of the actual completion of the international search

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