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(54) Title: FATTY ACID SYNTHASE INHIBITORS

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

FATTY ACID SYNTHASE INHIBITORS

FIELD OF THE INVENTION

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

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 β-ketoacyl-ACP reductase (FabG). Subsequent dehydration by β-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 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).

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. C45, 978-979; Noto, T. et al., 1982. J. Antibiotics 35, 401-410; Oishi, H. et al., 1982. J. Antibiotics 35, 391-396. 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'Agnolo, 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.

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 would serve to meet this unmet need.

SUMMARY OF THE INVENTION

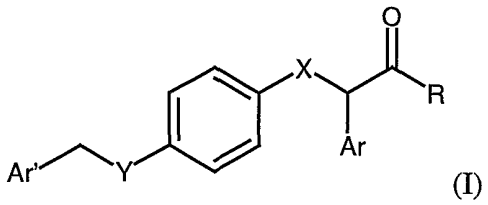
This invention comprises novel compounds and pharmaceutical compositions containing these compounds and their use as FabH inhibitors that are useful as antibiotics for the treatment of Gram positive and Gram negative bacterial infections.

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.

DETAILED DESCRIPTION OF THE INVENTION

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



(I)

wherein:

R is selected from the group consisting of OH, $NHSO_2R^1$, $NH(CH_2)_nAr''$, and $NHCR^2R^3CO_2H$;

X and Y are, independently, O, or S;

R^1 represents C_{1-10}alkyl, or Ar";

n represents an integer from 0 to 4;

Ar and Ar' are independently, selected from the group consisting of phenyl, thiophene, pyridine, pyrimidine, oxazole, and isoxazole; all of which can be substituted with one or more following groups selected from the group consisting of: fluoro, bromo, chloro, iodo; NO_2, CN, CO_2R^3, OR^4, NR^4R^5, C_{1-10}alkyl, C_{1-10}alkoxy, aryloxy, arylalkoxy, and heteroaryloxy;

Ar" is selected from the group consisting of phenyl, pyridine, and tetrazole, all of which can be optionally substituted by one or more of a group selected from the group consisting of: C_{1-4}alkyl, C_{1-4}alkoxy, fluoro, bromo, chloro, iodo, NO_2, NR^4R^5, CN, and CO_2R^4;

R^2 and R^3 represent $-(CH_2CH_2)_n-$ or any amino acid substituents, including chiral and racemic forms; R^4 and R^5 represents independently hydrogen, C_{1-10}alkyl.

Also included in the invention are pharmaceutically acceptable salt complexes.

As used herein, "alkyl" means both straight and branched chains of 1 to 6 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 alkyl may carry substituents such as hydroxy, carboxy, alkoxy, and the like.

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:
[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid;
N-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoyl}-methanesulfonamide;
N-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylsulfamoyl}-benzoic acid;
2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-N-(2,3,4-trifluoro-phenyl)-acetamide;
2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-N-(3-morpholin-4-yl-propyl)-2-phenyl-acetamide;

N-(2-Cyano-ethyl)-2-[4-(2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetamide;

2-[4-(2,6-Dichlrobenzyloxy)-phenylsulfanyl]-2-phenyl-N-[2-(1H-tetrazol-5-yl)-ethyl]-acetamide;

2-{4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl}-2-phenyl-N-(1H-tetrazol-5-yl)-acetamide;

1-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylamino}-cyclohexanecarboxylic acid;

1-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylamino}-cyclopropanecarboxylic acid;

N-[2-(5-Amino-tetrazol-2-yl)-ethyl]-2-[4-(2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetamide;

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-thiophen-3-yl-acetic acid;

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-N-(1H-tetrazol-5-yl)-2-thiophen-3-yl-acetamide;

[4-(2,6-Dichloro-benzyloxy)-phenoxy]-2-phenyl-acetic acid ;

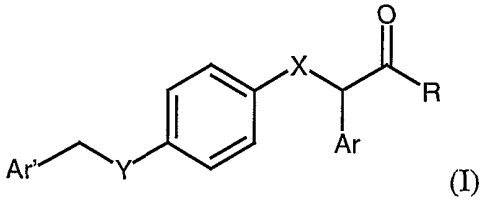
[4-(2,6-Dichloro-benzylsulfanyl)-2-phenoxy]-2-phenyl-acetic acid;

[4-(3-Amino-2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid; and

[4-(2,6-Dichloro-3-hydroxy-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid.

METHODS OF PREPARATION

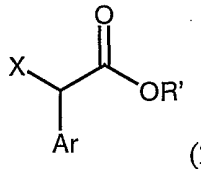
The present invention provides compounds of formula (I),



(I)

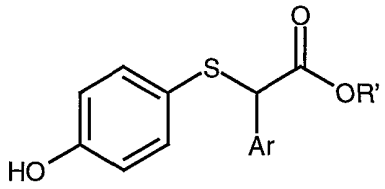
where R = OH, $NHSO_2R^1$, $NH(CH_2)_nAr''$, $NHCR^2R^3CO2H$, X and Y are O, S;

which can be prepared by reacting an alkyl α-haloaryl acetic acetate of Formula (2)



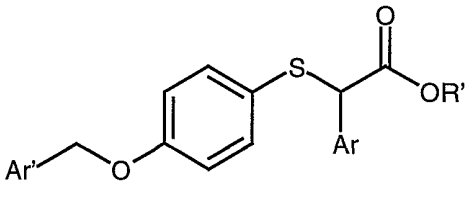
(2)

with 4-mercapto-phenol in presence of a base such as cesium carbonate in an appropriate solvent such as N,N'-dimethylformate affords a compound of Formula (3).



(3)

Alkylation of a phenol of Formula (3) with Ar'CH_2X in presence of a base such as cesium carbonate gives an ether of Formula (4).



(4)

Alternatively, a compound of Formula (4) can be prepared from a phenol (3) with Ar'CH_2OH under Mitsunobu conditions.

Hydrolysis of a compound of Formula (4) using a base such as lithium hydroxide in appropriate solvents such as tetrahydrofuran and water provides a compound of Formula (I), where R = OH, X = S, Y = O.

Treatment of an acid of Formula (I), where R = OH, X = S, Y = O, with a sulfonamide of Formula (5)

$R^1SO_2NH_2$ (5)

in presence of coupling reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and N,N'-dimethylaminopyridine in a solvent such

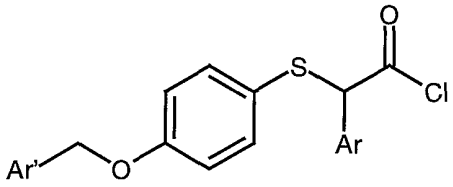
as dichloromethane at an appropriate temperature affords an acyl sulfonamide of Formula (I), where R = $NHSO_2R^1$, X = S, Y = O. Any ester function in R^1 can be hydrolyzed to the corresponding acid function using hydrolysis conditions described above.

Alternately, an acid of Formula (I) is coupled with an amino acid of Formula (6)

$NH_2CR^2R^3CO_2H$ (6)

gives a carboxy amide of Formula (I), where R = $NHCR^2R^3CO_2H$, X = S, Y = O.

Alternately, treatment of an acid of Formula (I) with thionyl chloride give an acid chloride of Formula (7)

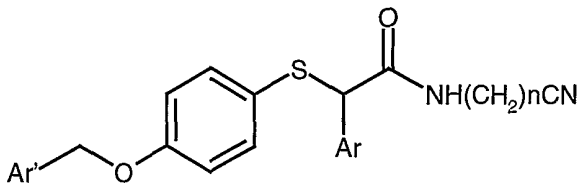


(7)

Coupling of an acid chloride of Formula (7) with an amine of Formula (8)

$NH_2(CH_2)_nCN$ (8)

affords an cyano amide of Formula (9).



(9)

Reacting of a cyano compound of Formula (9) with sodium azide in presence of a solvent such as N,N'-dimethylformate at an appropriate temperature provides a tetrazole of Formula (I), where Ar" = tetrazole, X = S, Y = O.

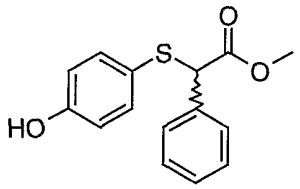
Alternately, direct coupling of an acid chloride of Formula (7) with an arylamine such 5-aminotetrazole in presence of an appropriate base such as triethylamine in a solvent such as dichloromethane affords a compound Formula (I), where R = $NH(CH_2)_nAr"$, n = 0, Ar" = tetrazole, X = S, Y = O.

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.

Example 1

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid

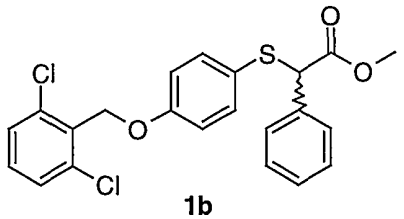


1a

(4-Hydroxy-phenylsulfanyl)-2-phenyl-acetic acid methyl ester 1(a).

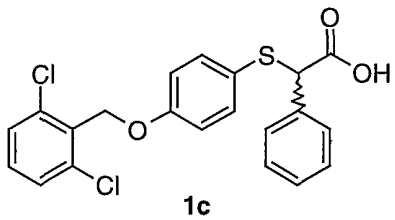
To a suspension of cesium carbonate (3.43 g, 10.5 mmol) in DMF (40 mL) was added 4-mercapto-phenol (1.33 g, 10.54 mmol). After stirring at room temperature under argon for 30 minutes, 2-bromo-2-phenyl-acetic acid methyl ester (2.42 g, 10.54 mmol) was added to the suspension and the resulting mixture was stirred at room temperature for 4 hours. The reaction was then quenched with water and extracted using EtOAc. The organic extracts were washed with water, brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, purification by flash column chromatography using an eluting system of hexane/EtOAc (4:1)

yielded 2.45 g (85%) of the title compound. ^{1}H NMR (400 MHz, CDCl3) δ •7.45-7.25 (m, 7H), 6.75 (d, 2H), 4.78 (s, 1H), 3.65 (s, 3H). MH+ 274.



1b

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid methyl ester 1(b). To a suspension of cesium carbonate (0.92 g, 2.81mmol) in DMF (14 mL) was added the above 1(a) (0.77 g, 2.81mmol). After stirring at room temperature under argon for 30 minutes, 2,6-dichlorobenzyl bromide (0.68 g, 2.81 mmol) was added to the suspension and the resulting mixture was stirred at room temperature for 5 hours. The reaction was then quenched with water and extracted using EtOAc. The organic extracts were washed with water, brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, purification by flash column chromatography using an eluting system of hexane/EtOAc (9:1) yielded 0.92 g (76%) of the title compound. ^{1}H NMR (400 MHz, CDCl3) δ •7.42-7.20 (m, 10H), 6.91 (d, 2H), 5.25 (s, 2H), 4.78 (s, 1H), 3.66 (s, 3H). MH+ 433.

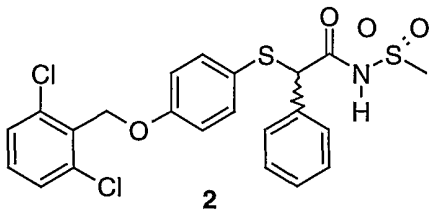


1c

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid 1(c). To a solution of the compound from 1(b) (430 mg, 0.99 mmol) in tetrahydrofuran (9 mL) and water (3 mL) was added lithium hydroxide monohydrate (420 mg, 9.90 mmol). The resulting solution was stirred at room temperature overnight. Water (20 mL) was then added to the reaction mixture. The aqueous layer was washed with EtOAc (20 mL x 2). The resulting aqueous layer was acidified with 1N HCl and the mixture was extracted with EtOAc. The organic extracts were washed with water, brine, and dried over $MgSO_4$. Removing the solvent under reduced pressure yielded

0.42 g (65%) of the title compound. ^{1}H NMR (400 MHz, $CHCl_3$) δ• 7.50-7.20 (m, 10H), 6.92 (d, 2H), 5.25 (s, 2H), 4.79 (s, 1H). MH+ 419.

Example 2

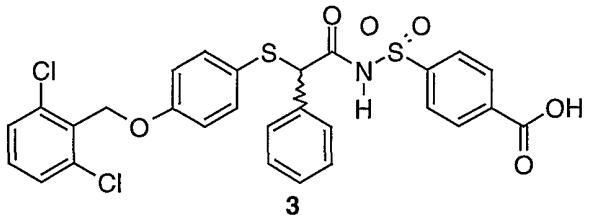


2

N-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoyl}-methanesulfonamide 2.

To a solution of the compound from 1(c) (180 mg, 0.43 mmol), methanesulfonamide (41 mg, 0.43 mmol) and DMAP (53 mg, 0.43 mmol) in dichloromethane (4.3 mL), was added at 0 °C 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (83 mg, 0.43 mmol). The resulting solution was stirred at room temperature overnight under argon. The reaction was quenched with 1N HCl and the mixture was extracted with EtOAc. The organic extracts were washed with brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, purification by preparative HPLC yielded 213 mg (65%) of the title compound. ^{1}H NMR (400 MHz, $CHCl_3$) δ •8.90 (br s, 1H), 7.40-7.15 (m, 10H), 6.90 (d, 2H), 5.20 (s, 2H), 4.78 (s, 1H), 3.02 (s, 3H). MH+ 496.

Example 3

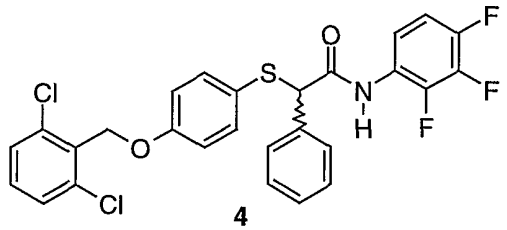


3

N-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylsulfamoyl}-benzoic acid 3.

Following the procedures of Example 2 except that 4-sulfamoyl-benzoic acid allyl ester was used in place of methanesulfonamide. The resulting compound was hydrolyzed by lithium hydoxide monohydrate as described in preparation of 1(c). Purification by preparative HPLC yielded 121 mg (40%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ •9.15 (br s, 1H), 8.20-7.90 (m, 4H), 7.35-7.10 (m, 10H), 6.72 (d, 2H), 5.18 (s, 2H), 4.69 (s, 1H). MH+ 602.

Example 4

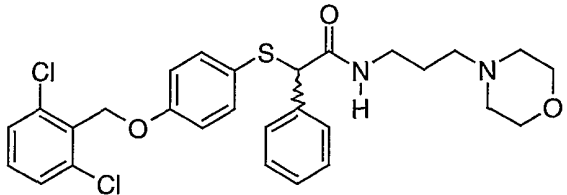


4

2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-N-(2,3,4-trifluoro-phenyl)-acetamide 4.

Following the procedures of Example 2 except that 2,3,4-trifluoro-phenylamine was used in place of methanesulfonamide. Purification by preparative HPLC yielded 178 mg (62%) of the title compound as a white solid. MH+ 548.

Example 5



5

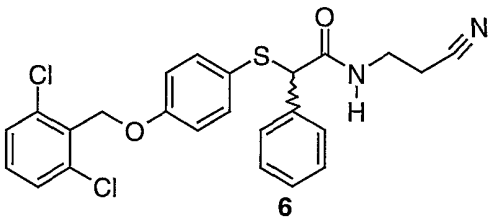
2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-N-(3-morpholin-4-yl-propyl)-2-phenyl-acetamide 5.

Following the procedures of Example 2 except that 4-(3-aminopropyl)morpholine was used in place of methanesulfonamide. Purification by preparative HPLC yielded 260 mg (60%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ• 7.75-7.20 (m,

10H), 6.90(d, 2H), 5.20 (s, 2H), 4.85 (s, 1H), 3.85 (m, 4H), 3.28 (m, 4H), 2.68 (m, 4H), 1.85 (m, 2H). MH+ 545.

Example 6

N-(2-Cyano-ethyl)-2-[4-(2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetamide

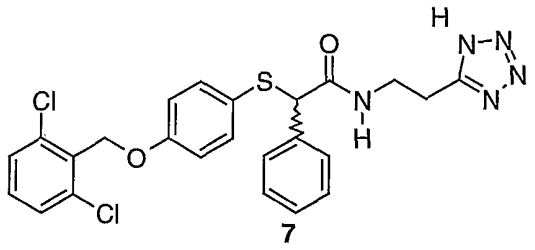


6

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetyl chloride 6(a). To the compound from 1(c) (0.42 g, 1.00 mmol) was added thionyl chloride (5 mL, 68.50 mmol) at room temperature. The resulting mixture was stirred at room temperature for 90 minutes. The solvent was then evaporated under vacuum and the crude product was used in the next reaction without further purification.

N-(2-Cyano-ethyl)-2-[4-(2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetamide 6(b). To a solution of the compound from 6(a) in THF (2 mL) were added 3-aminopropionitrile fumarate (128 mg, 1.00 mmol) and 1N NaOH (1.00 mL, 1.00 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. After the reaction was completed, water (5 mL) and dichloromethane (10 mL) were added. The aqueous layer was extracted with dichlromethane (10 mL x 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under vacuum. Trituration with dichloromethane yielded 0.31 g (65%) of the title compound as a white solid. MH+471.

Example 7

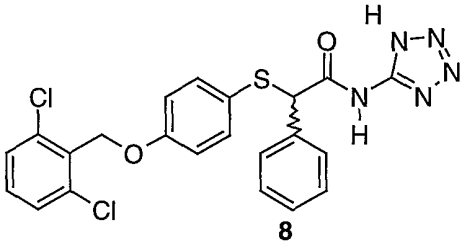


7

2-[4-(2,6-Dichlrobenzyloxy)-phenylsulfanyl]-2-phenyl-N-[2-(1H-tetrazol-5-yl)-ethyl]-acetamide 7.

A mixture of the compound from 6(b) (338 mg, 0.72 mmol), NaN_3 (468 mg, 7.20 mmol) and NH_4Cl (386 mg, 7.20 mmol) in DMF (7 mL) was heated at 110 °C for 26 h. After the reaction was completed, the reaction mixture was poured into water and made basic (pH = 14) with a 10% NaOH solution. The aqueous solution was washed with EtOAc and then acidified (pH = 6) with 1N HCl. The solution turned cloudy. It was extracted with EtOAc (15 mL x 3). The organic layers were dried over $MgSO_4$ and filtered and evaporated. The solid formed on standing. Trituration using hexane gave 277 mg (75%) of the title compound as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ •7.35-7.10 (m, 10H), 6.82)d, 2H), 5.20 (s, 2H), 4.69 (s, 1H), 4.40(m, 2H), 3.75 (m, 2H). MH+ 514.

Example 8



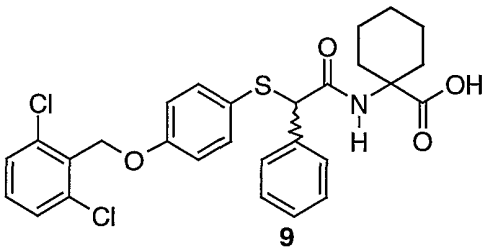
8

2-{4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl}-2-phenyl-N-(1H-tetrazol-5-yl)-acetamide 8.

To the compound 6(b) {prepared from the compound 1(c) (220 mg, 0.53 mmol) as described above} in dichloromethane (5 mL) were added triethylamine (0.37 mL, 2.63 mmol) and 5-aminotetrazole (82 mg, 0.79 mmol) at 0 °C. The reaction mixture

was stirred at room temperature overnight. Water (10 mL) and 1N HCl (10 mL) were then added. The aqueous layer was extracted with dichloromethane (10 mL x 3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated under vacuum. Purification by preparative HPLC yielded 77 mg (30%) of the title compound as a white solid. ^1H NMR (400 MHz, $CHCl_3$) δ •9.70 (br s, 1H), 7.30-7.05 (m, 10H), 6.75 (d, 2H), 5.20 (s, 2H), 5.15 (s, 1H) MH+ 486.

Example 9

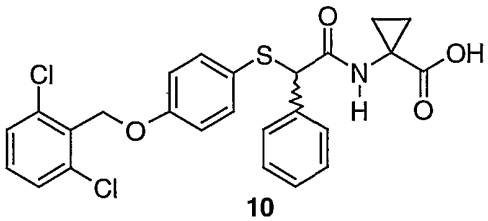


9

1-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylamino}-cyclohexanecarboxylic acid 9.

To the compound 6(b) {prepared from the compound 1(c) (320 mg, 0.76 mmol) as described above} in dichloromethane (7.6 mL) were added triethylamine (1.0 mL mL, 1.53 mmol) and 1-amino-cyclohexanecarboxylic acid (219 mg, 1.53 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. Water (10 mL) and 1N HCl (10 mL) were then added. The aqueous layer was extracted with dichloromethane (10 mL x 3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated under vacuum. Purification by preparative HPLC yielded 84 mg (20%) of the title compound as a white solid. ^1H NMR (400 MHz, $CHCl_3$) δ •8.00 (br s, 1H), 7.45-7.25 (m, 10H), 6.95 (d, 2H), 5.28 (s, 2H), 4.95 (s, 1H), 2.20-1.00 (m, 10H). MH+ 544.

Example 10

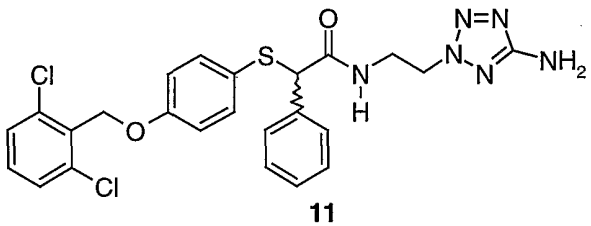


10

1-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylamino}-cyclopropanecarboxylic acid 10.

Following the procedures of Example 9 except that 1-amino-cyclopropanecarboxylic acid was used in place of 1-amino-cyclohexanecarboxylic acid. Purification by preparative HPLC yielded 42 mg (14%) of the title compound as a white solid. ^1H NMR (400 MHz, $CHCl_3$) δ •8.00 (br s, 1H), 7.45-7.25 (m, 10H), 6.95 (d, 2H), 5.28 (s, 2H), 4.95 (s, 1H), 0.6-0.3 (m, 4H). MH+ 502.

Example 11



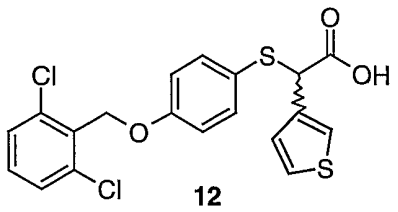
11

N-[2-(5-Amino-tetrazol-2-yl)-ethyl]-2-[4-(2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetamide 11.

Following the procedures of Example 9 except that 2-(2-amino-ethyl)-2H-tetrazol-5-ylamine was used in place of 1-amino-cyclohexanecarboxylic acid. Purification by preparative HPLC yielded 36 mg (34%) of the title compound as a white gum. ^1H NMR (400 MHz, $CHCl_3$) δ• 7.38-7.21 (m, 10H), 6.92(d, J = 8.6 Hz, 2H), 5.25 (s, 2H), 4.81 (s, 1H), 4.50 (m, 2H), 3.85 (m, 2H).

MH+ 529.

Example 12



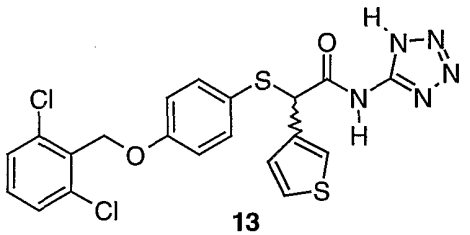
12

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-thiophen-3-yl-acetic acid (4-Hydroxy-phenylsulfanyl)-2-thiophen-3-yl-acetic acid methyl ester 12(a). To a suspension of cesium carbonate (3.30 g, 10.00 mmol) in DMF (50 mL) was added 4-mercapto-phenol (1.30 g, 10.00 mmol). After stirring at room temperature under argon for 30 minutes, 2-bromo-2-thiophen-3-yl-acetic acid methyl ester (2.35 g, 10.00 mmol) was added to the suspension and the resulting mixture was stirred at room temperature for 4 hours. The reaction was then quenched with water and extracted using EtOAc. The organic extracts were washed with water, brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, purification by flash column chromatography using an eluting system of hexane/EtOAc (4:1) yielded 2.10 g (75%) of the title compound.

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-thiophen-3-yl-acetic acid methyl ester 12(b). To a solution of the above 1(a) (0.63 g, 2.24mmol), 2,6-dichlorobenzyl alcohol (0.39 g, 2.24 mmol) and triphenylphosphine (0.65 g, 2.47 mmol) in THF (15 mL) was added dropwise diethyl azodicarboxylate (0.39 mL, 2.47 mmol) at 0 °C. After stirring at room temperature under argon overnight, the reaction was then quenched with water and extracted using EtOAc. The organic extracts were washed with water, brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, purification by flash column chromatography using an eluting system of hexane/EtOAc (9:1) yielded 0.60 g (61%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ• 7.35-7.10 (m, 8H), 6.81 (d, 2H), 5.20 (s, 2H), 4.78 (s, 1H), 3.56 (s, 3H).

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid 12(c). To a solution of the compound from 1(b) (500 mg, 1.14 mmol) in THF (9 mL) and water (3 mL) was added lithium hydroxide monohydrate (560 mg, 11.40 mmol). The resulting solution was stirred at room temperature overnight. Water (20 mL) was then added to the reaction mixture. The aqueous layer was washed with EtOAc (20 mL x 2). The resulting aqueous layer was acidified with 1N HCl and the mixture was extracted with EtOAc. The organic extracts were washed with water, brine, and dried over $MgSO_4$. Removing the solvent under reduced pressure yielded 0.42 g (65%) of the title compound. ^1H NMR (400 MHz, $CHCl_3$) δ• 7.35-7.11 (m, 8H), 6.92 (d, 2H), 5.20 (s, 2H), 4.79 (s, 1H). MH+ 425.

Example 13

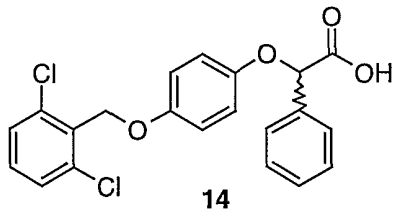


13

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-N-(1H-tetrazol-5-yl)-2-thiophen-3-yl-acetamide 13.

Following the procedures of Example 8 except that [4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-thiophen-3-yl-acetyl chloride was used in place of [4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetyl chloride. Purification by preparative HPLC yielded 41 mg (14%) of the title compound as a white solid. MH+ 492.

Example 14

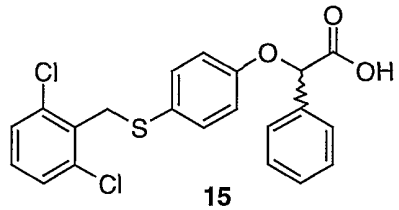


14

[4-(2,6-Dichloro-benzyloxy)-phenoxy]-2-phenyl-acetic acid 14.

Following the procedures of Example 1 except that hydroquinone was used in place of 4-mercapto-phenol. Purification by preparative HPLC yielded 80 mg (54%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CHCl_3$) δ •7.70-7.22 (m, 8H), 6.95 (d, 2H), 5.65 (s, 1H), 5.21 (s, 2H). MH+ 403.

Example 15

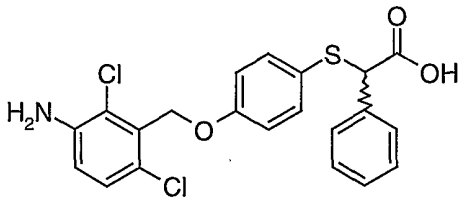


15

[4-(2,6-Dichloro-benzylsulfanyl)-2-phenoxy]-2-phenyl-acetic acid 15.

Following the procedures of Example 1 except that the order of alkylation was reversed. Purification by preparative HPLC yielded 240 mg (54%) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CHCl_3$) δ •7.75-7.12 (m, 10H), 6.85 (d, 2H), 5.65 (s, 1H), 4.30 (s, 2H). MH+ 419.

Example 16

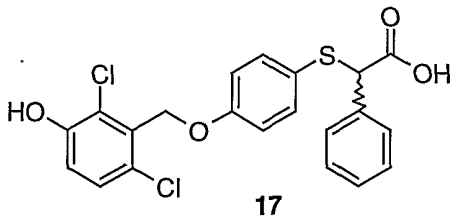


[4-(3-Amino-2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid

[4-(3-Amino-2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid methyl ester 16(a). To a solution of the above 1(a) (0.15 g, 0.59 mmol), (3-amino-2,6-dichlorophenyl)-methanol (0.14 g, 0.70 mmol) and triphenylphosphine (0.18 g, 0.70 mmol) in THF (5.8 mL) was added dropwise diethyl azodicarboxylate (0.13 g, 0.65 mmol) at 0 °C. After stirring at room temperature under argon overnight, the reaction was then quenched with water and extracted using EtOAc. The organic extracts were washed with water, brine, and dried over $MgSO_4$. After removing the solvent under reduced pressure, purification by flash column chromatography using an eluting system of hexane/EtOAc (9:1) yielded 0.16 g (61%) of methyl ester of the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ• 7.50-7.30 (m, 8H), 6.90 (d, 1H), 6.35 (br s, 2H), 6.80 (d, 2H), 5.12 (s, 2H), 4.70 (s, 1H).

[4-(3-Amino-2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid 16(b). Following the previous procedures of hydrolysis yielded 90 mg (57%) of the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ• 7.50-7.30 (m, 8H), 6.90 (d, 1H), 6.35 (br s, 2H), 6.80 (d, 2H), 5.12 (s, 2H). MH+ 434.

Example 17



17

[4-(2,6-Dichloro-3-hydroxy-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid 17.

Following the procedures of Example 16 except that [3-(*tert*-butyl-diphenyl-silanyloxy)-2,6-dichlorophenyl]-methanol was used in place of (3-amino-2,6-dichlorophenyl)-methanol. The resulting coupled compound (0.35 g, 0.53 mmol) was treated with TBAF (1M in THF, 1.1 mL, 1.07 mmol) in THF (5 mL). The resulting [4-(2,6-Dichloro-3-hydroxy-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid methyl ester was hydrolyzed as described in the previous examples. Purification by preparative HPLC yielded 32 mg (14%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, $CHCl_3$) δ• 7.40-7.18 (m, 8H), 6.90 (d, 1H), 6.80 (d, 2H), 5.12 (s, 2H), 4.70 (s, 1H). MH+ 435.

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 ß-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}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}C] acetyl-CoA substrate from [^{14}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 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, 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

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 polyvinylpyrollidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting 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 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 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 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 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 th 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 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 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.

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 body weight, depending on the route and frequency of administration..
Inhibitors of β-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 concentrations such as 0.01 to 10 mL/liter) to aid solubility and penetration of the β-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.

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 range of organisms including both Gram-negative organisms such as *Escherichia*

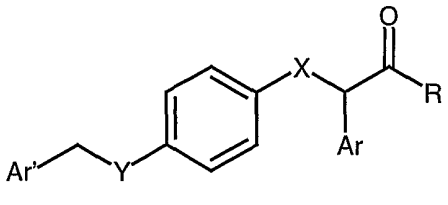
coli and Klebsiella pneumoniae and Gram-positive organisms such as *Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis and Enterococcus faecium*, including isolates resistant to existing antibiotics.

All publications, including but not limited to patents and patent 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 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 the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound according to Formula (I):



(I)

wherein:

R is selected from the group consisting of OH, $NHSO_2R^1$, $NH(CH_2)_nAr''$, and $NHCR^2R^3CO_2H$;

X and Y are, independently, O, or S;

R^1 represents C_{1-10}alkyl, or Ar";

n represents an integer from 0 to 4;

Ar and Ar' are independently, selected from the group consisting of phenyl, thiophene, pyridine, pyrimidine, oxazole, and isoxazole; all of which can be substituted with one or more following groups selected from the group consisting of: fluoro, bromo, chloro, iodo; NO_2, CN, CO_2R^3, OR^4, NR^4R^5, C_{1-10}alkyl, C_{1-10}alkoxy, aryloxy, arylalkoxy, and heteroaryloxy;

Ar" is selected from the group consisting of phenyl, pyridine, and tetrazole, all of which can be optionally substituted by one or more of a group selected from the group consisting of: C_{1-4}alkyl, C_{1-4}alkoxy, fluoro, bromo, chloro, iodo, NO_2, NR^4R^5, CN, and CO_2R^4;

R^2 and R^3 represent $-(CH_2CH_2)_n-$ or any amino acid substituents, including chiral and racemic forms; R^4 and R^5 represents independently hydrogen, C_{1-10}alkyl;

or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable salt complex thereof.

2. A compound according to claim 1 selected from the group consisting of:

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid;

N-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoyl}-methanesulfonamide;

N-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylsulfamoyl}-benzoic acid;

2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-N-(2,3,4-trifluoro-phenyl)-acetamide;

2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-N-(3-morpholin-4-yl-propyl)-2-phenyl-acetamide;

N-(2-Cyano-ethyl)-2-[4-(2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetamide;

2-[4-(2,6-Dichlrobenzyloxy)-phenylsulfanyl]-2-phenyl-N-[2-(1H-tetrazol-5-yl)-ethyl]-acetamide;

2-{4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl}-2-phenyl-N-(1H-tetrazol-5-yl)-acetamide;

1-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylamino}-cyclohexanecarboxylic acid;

1-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylamino}-cyclopropanecarboxylic acid;

N-[2-(5-Amino-tetrazol-2-yl)-ethyl]-2-[4-(2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetamide;

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-thiophen-3-yl-acetic acid;

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-N-(1H-tetrazol-5-yl)-2-thiophen-3-yl-acetamide;

[4-(2,6-Dichloro-benzyloxy)-phenoxy]-2-phenyl-acetic acid ;

[4-(2,6-Dichloro-benzylsulfanyl)-2-phenoxy]-2-phenyl-acetic acid;

[4-(3-Amino-2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid; and

[4-(2,6-Dichloro-3-hydroxy-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid.

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

4. A method of treatment according to Claim 1 wherein the compound of Formula (I) is selected from the group consisting of:

[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid;
N-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoyl}-methanesulfonamide;
N-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylsulfamoyl}-benzoic acid;
2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-N-(2,3,4-trifluoro-phenyl)-acetamide;
2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-N-(3-morpholin-4-yl-propyl)-2-phenyl-acetamide;
N-(2-Cyano-ethyl)-2-[4-(2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetamide;
2-[4-(2,6-Dichlrobenzyloxy)-phenylsulfanyl]-2-phenyl-N-[2-(1H-tetrazol-5-yl)-ethyl]-acetamide;
2-{4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl}-2-phenyl-N-(1H-tetrazol-5-yl)-acetamide;
1-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylamino}-cyclohexanecarboxylic acid;
1-{2-[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-ethanoylamino}-cyclopropanecarboxylic acid;
N-[2-(5-Amino-tetrazol-2-yl)-ethyl]-2-[4-(2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetamide;
[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-2-thiophen-3-yl-acetic acid;
[4-(2,6-Dichloro-benzyloxy)-phenylsulfanyl]-N-(1H-tetrazol-5-yl)-2-thiophen-3-yl-acetamide;
[4-(2,6-Dichloro-benzyloxy)-phenoxy]-2-phenyl-acetic acid ;
[4-(2,6-Dichloro-benzylsulfanyl)-2-phenoxy]-2-phenyl-acetic acid;
[4-(3-Amino-2,6-dichloro-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid; and
[4-(2,6-Dichloro-3-hydroxy-benzyloxy)-phenylsulfanyl]-2-phenyl-acetic acid.