

Castillo Gra & Asociados
ABOGADOS

Señor Jefe

DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Santa Fe de Bogotá, D.C.

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Tramite : 001 MARCAS 1 REGISTRO/ 329 COMPLEMEN
Dependencia: 2010 DIVISION DE SIGNOS DISTINTIVOS

Folios: 34

Re.: 02-01-09
Expediente No. 00 - 38765

Solicitud de Patente

SMITHKLINE BEECHAM CORPORATION.

Debidamente traducida, adjunto acompaño la copia oficial de la solicitud de patente básica estadounidense No. 60/137.004, la cual le solicito agregar a este expediente para los efectos legales respectivos.

De Usted atentamente,

GERMAN CASTILLO GRAU

T.P.#2.978 del C.S.J.

Se desglosa original de este memorial para anexarlo al expediente de Patentes 00-39765
No se encontraron los anexos 10-04-03
Ej

00-39765

ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES LLEGUEN LOS PRESENTES:

MINISTERIO DE COMERCIO DE ESTADOS UNIDOS

Oficina de Patentes y Marcas Registradas de Estados Unidos

02 de junio de 2000

SE CERTIFICA QUE SE ADJUNTA AL PRESENTE DOCUMENTO UNA COPIA FIEL DE LOS ARCHIVOS DE LA OFICINA DE PATENTES Y MARCAS REGISTRADAS DE ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA QUE CUMPLIÓ LOS REQUISITOS PARA OTORGARLE UNA FECHA DE REGISTRO BAJO EL TITULO 35 DEL CODIGO DE ESTADOS UNIDOS NUMERAL 111.

NUMERO DE SOLICITUD: 60/137.004

FECHA DE REGISTRO: 1 de junio de 1999

(Sello de oblea)

Por Autoridad del
COMISIONADO DE PATENTES Y MARCAS REGISTRADAS

(Firma ilegible)

N. WOODSON

Funcionario que Certifica

Se retira en 2020
del exp. 99-77673

19-Oct-07

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3 1

"CERTIFICADO DE CORREO EXPRESO"

Número Etiqueta Porte "Correo Expreso" EM372546108US

Fecha de Depósito: 1 de junio, 1999

Por el presente certifico que este Documento o Derecho se está depositando en el mencionado Servicio Postal de los Estados Unidos "Correo Expreso Oficial Postal a Destinatario" servicio bajo 37 CFR 1.10 en la fecha arriba indicada y va dirigido a: Comisionado Asistente para Patentes, Washington, D.C. 20231.

Nombre de la persona remitente del Documento o Derecho.

(Letra de imprenta) *Texto ilegible*

Firma *Firma ilegible*

HOJA DE REMISION DE SOLICITUD PROVISIONAL

Esta es una solicitud para registrar una SOLICITUD PROVISIONAL de PATENTE bajo 37 CFR 1.53©.

Causa No.	P50936P		
INVENTOR(es) / SOLICITANTE(s)			
Apellido	Primer Nombre	Inicial Media	Residencia (Ciudad y estado o país extranjero)
MILLER	William	H	Collegeville, Pennsylvania 19426
NEWLANDER	Kenneth	A	West, Chester, Pennsylvania, 19382
SEEFELD	Mark	A	Phoenixville, Pennsylvania 19460

INHIBIDORES FAB I					
DIRECCION DE CORRESPONDENCIA SMITHKLINE BEECHAM CORPORATION Corporate Intellectual Property - UW2220 709 Swedeland Road King of Prussia					
				Teléfono No.	610-270-5022
				Fax No.	610-270-5090
Estado	PA	Código Postal	19406-2799	País	Estados Unidos de América

PARTES DE LA SOLICITUD ADJUNTAS (marque todo lo que aplica)					
☒ Especificación	Número de páginas	25	☐ Declaración Pequeña Entidad		
☐ Dibujos	Número de hojas		☒ Otro (especifique)		
			Resumen de 1 página		
METODO PAGO PARA REGISTRO DERECHOS ESTA SOLICITUD PROVISIONAL DE PATENTE					
☒ Por el presente documento el Comisionado está autorizado a cobrar			DERECHO POR REGISTRO \$150.00		
derechos de registro y abonarlos a la Cuenta de Depósito No. 19-2570			PROVISIONAL (\$)		

La invención se realizó por medio de una agencia del Gobierno de los Estados Unidos o bajo contrato con una agencia del Gobierno de los Estados Unidos.

☒ No.

☐ Sí, el nombre de la agencia del gobierno de los Estados Unidos y el número del contrato son:

Presentado respetuosamente,

Firma:

Firma ilegible

Mary E. McCarthy

Fecha: 1 junio 1999

Registro No.: 32.917

☐ Inventores adicionales nombrados por separado en hojas numeradas que aquí se adjuntan.

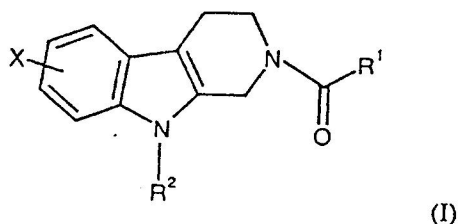
UNICAMENTE SOLICITUD PROVISIONAL DE REGISTRO

ENVIESE A: Comisionado Asistente para Patentes, Buzón Solicitud Provisional, Washington, D.C. 20231

N \mem\ptol\tr\50936p doc

REIVINDICACIONES:

1. Un compuesto según la fórmula (I)



donde:

R^1 es Ar o Het;

R^2 es H, C_{1-6} alquilo o Ar- C_{0-6} alquilo;

X es H, C_{1-4} alquilo, OR' , SR' , C_{1-4} alquilsulfonilo, C_{1-4} alquilsulfoxilo, CN, $N(R')_2$, $CH_2N(R')_2$, NO_2 , CF_3 , CO_2R' , $CON(R')_2$, COR' , $NR'C(O)R'$, F, Cl, Br, I o $CF_3S(O)r$;

R' es H, C_{1-6} alquilo o Ar- C_{0-6} alquilo; y

r es 0, 1, o 2;

o una sal farmacéuticamente aceptable del mismo.

2. Un compuesto según la reivindicación 1 donde R^1 es fenilo, sustituido o no sustituido por metilenodioxi, o por uno de los tres sustitutos seleccionados del grupo que consta de C_{1-4} alquilo, OR' , $N(R')_2$, F, Cl, Br, I y CF_3 en el que R' es H o C_{1-6} alquilo.
3. Un compuesto según la reivindicación 1 donde R^1 es bencimidazolilo o piridinilo sustituido o no sustituido por C_{1-4} alquilo, OR' , $N(R')_2$, F, Cl, Br, I y CF_3 en donde R' es H o C_{1-6} alquilo.
4. Un compuesto según la reivindicación 1 donde R^2 es H, C_{1-6} alquilo, o Ph- C_{0-6} alquilo.
5. Un compuesto según la reivindicación 1 donde X es H, C_{1-4} alquilo, OR' ,

P50936P

CN, N(R')₂, NO₂, CF₃, CO₂R', CON(R')₂, COR', F, Cl, Br o I donde R' es H, o C₁₋₆ alquilo.

6. Un compuesto según la reivindicación 1 que es:

2- benzoil-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2- benzoil-9-metil-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2- benzoil-9-[(4-benciloxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2- benzoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(3,4-metilenodioxi)benzoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(2-hidroxi)benzoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(3-imidazo)benzoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(6-hidroxi)nicotinoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(6-amino)nicotinoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(3-amino)benzoil-9-metil-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(4-hidroxi)benzoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(4-metilamino)benzoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(4-amino)benzoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(4-cloro)benzoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(4-hidroxi)benzoil-9-[(4-trifluorometilfenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

2-(3,5-dicloro-4-hidroxi)benzoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola; o

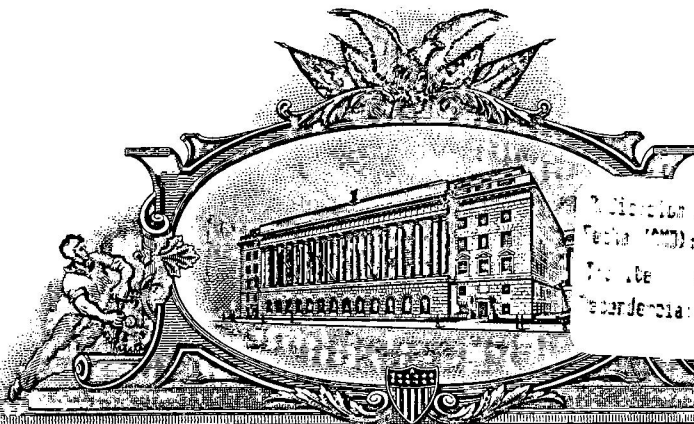
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2-(3-cloro-4-hidroxi)benzoil-9-[(4-hidroxifenil)metil]-1,3,4,9-tetrahidro-2H-pirido[3,4-b]indola;

o una sal farmacéuticamente aceptable del mismo.

7. Una composición farmacéutica que consta de un compuesto de acuerdo con la reivindicación 1 y un portador farmacéuticamente aceptable.
8. Un método para inhibir Fab I que comprende la administración a un sujeto con necesidad del mismo de un compuesto según la reivindicación 1.
9. Un método de tratamiento de infecciones bacterianas que comprende la administración a un sujeto con necesidad del mismo de un compuesto según la reivindicación 1.

PA 255865



Supervision: 88038765 88000001
Fecha (AMT): 2002-06-23 13:16:41
Tribunal: 001 MARCAS
Referencia: 0010 DIVISION DE SIGNOS DISTINTIVOS
Folios: 34
1 REGISTRO/ 329 COMPLEMEN

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 02, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/137,004

FILING DATE: June 01, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

N. Woodson
N. WOODSON
Certifying Officer

"EXPRESS MAIL CERTIFICATE"

"Express Mail" Mailing Label Number EM372546108US

Date Of Deposit 1 June 1999

I Herby Certify That This Paper Or Fee Is Being Deposited With The United States Postal Service "Express Mail Post Office To Addressee" Service Under 37 CFR 1.10 On The Date Indicated Above And Is Addressed To: Assistant Commissioner Of Patents, Washington, D.C. 20231.

Name Of Person Mailing Paper Or Fee
(Type Or Print) William E. McCarthy

Signature William E. McCarthy

PTO/SB/16(11-95)

Approved for use through 14/31/98. OMB 0651-0037

Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(b)(2).

Docket No.		P50936P		Type a plus sign (+) inside this box ->	+
INVENTOR(s) / APPLICANT(s)					
Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)		
MILLER	William	H	Collegeville, Pennsylvania 19426		
NEWLANDER	Kenneth	A	West Chester, Pennsylvania 19382		
SEEFELD	Mark	A	Phoenixville, Pennsylvania 19460		

TITLE OF THE INVENTION (280 characters max)

FAB I INHIBITORS

CORRESPONDENCE ADDRESS

SMITHKLINE BEECHAM CORPORATION

Corporate Intellectual Property - UW2220

709 Swedeland Road

King of Prussia

Telephone No. 610-270-5022

Facsimile No. 610-270-5090

State	PA	Zip Code	19406-2799	Country	United States of America
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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of Pages	25	☐ Small Entity Statement
☐ Drawings	Number of Sheets		☒ Other (specify)
1 page Abstract			

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 19-2570	PROVISIONAL FILING FEE AMOUNT (\$)	\$150.00
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____.

Respectfully submitted,

Signature:

Mary E. McCarthy
Mary E. McCarthy

Date:

1 June 1999

Registration No.:

32,917

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

SEND TO: Assistant Commissioner for Patents, Box Provisional Application, Washington, D.C. 20231.

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TITLE

Fab I Inhibitors

FIELD OF THE INVENTION

- 5 This invention relates to pharmaceutically active compounds which inhibit Fab I and are useful for the treatment of bacterial infections.

BACKGROUND OF THE INVENTION

- 10 While the overall pathway of saturated fatty acid biosynthesis is similar in all organisms, the fatty acid synthase (FAS) systems vary considerably with respect to their structural organization. Vertebrates and yeast possess a FAS in which all the enzymatic activities are encoded on one or two polypeptide chains, respectively, and the acyl carrier protein (ACP) is an integral part of the complex. In contrast, in bacterial FAS, each of the reactions is catalyzed by a distinct, mono-functional enzyme and the ACP is a discrete
- 15 protein. Therefore, there is considerable potential for the selective inhibition of the bacterial system by antibacterial agents.

- Fab I (previously designated EnvM) functions as an enoyl-ACP reductase (Bergler, et al, (1994), *J.Biol.Chem.* 269, 5493-5496) in the final step of the four reactions involved in each cycle of bacterial fatty acid biosynthesis. In this pathway, the first step is catalyzed
- 20 by β -ketoacyl-ACP synthase, which condenses malonyl-ACP with acetyl-CoA (FabH, synthase III). 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)
- 25 leads to trans-2-enoyl-ACP, which in turn is converted to acyl-ACP by NADH-dependent enoyl-ACP reductase (Fab I). Further rounds of this cycle, adding two carbon atoms per cycle, eventually lead to palmitoyl-ACP (16C), where upon the cycle is stopped largely due to feedback inhibition of Fab I by palmitoyl-ACP (Heath, et al, (1996), *J.Biol.Chem.* 271, 1833-1836). Thus, Fab I is a major biosynthetic enzyme and is a key regulatory point in the
- 30 overall synthetic pathway of bacterial fatty acid biosynthesis. Therefore, Fab I is an ideal target for antibacterial intervention.

- Studies have shown that diazaborine antibiotics inhibit fatty acid, phospholipid and lipopolysaccharide (LPS) biosynthesis and that the antibacterial target of these compounds is Fab I. For example, derivative 2b18 from Grassberger, et al (1984) *J. Med Chem* 27 947-
- 35 953 has been reported to be a non-competitive inhibitor of Fab I (Bergler, et al, (1994), *J.Biol.Chem.* 269, 5493-5496). Also, plasmids containing the Fab I gene from diazaborine resistant *S. typhimurium* conferred diazaborine resistance in *E.coli* (Turnowsky, et al,

(1989), *J. Bacteriol.*, 171, 6555-6565). Furthermore, inhibition of Fab I either by diazaborine or by raising the temperature in a Fab I temperature sensitive mutant is lethal. These results demonstrate that Fab I is essential to the survival of the organism (Bergler, et al, (1994), *J. Biol. Chem.* 269, 5493-5496).

- 5 Importantly, it has now been discovered that certain compounds are Fab I inhibitors and have antibacterial activity, and, therefore, may be useful for the treatment of bacterial infections in mammals, particularly in man.

SUMMARY OF THE INVENTION

- 10 This invention comprises compounds of the formula (I), as described hereinafter, which inhibit Fab I and are useful in the treatment of bacterial infections.

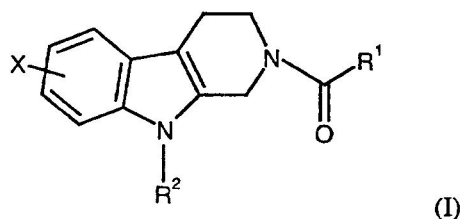
 This invention is also a pharmaceutical composition comprising a compound according to formula (I) and a pharmaceutically acceptable carrier.

 This invention is also a method of treating bacterial infections by inhibiting Fab I.

- 15 In a particular aspect, the compounds of this invention are useful as antibacterial agents.

DETAILED DESCRIPTION

 This invention comprises compounds of formula (I):



wherein:

- R¹ is Ar or Het;
 R² is H, C₁₋₆alkyl or Ar-C₀₋₆alkyl;
 X is H, C₁₋₄alkyl, OR', SR', C₁₋₄alkylsulfonyl, C₁₋₄alkylsulfoxyl, CN, N(R')₂,
25 CH₂N(R')₂, NO₂, CF₃, CO₂R', CON(R')₂, COR', NR'C(O)R', F, Cl, Br, I, or CF₃S(O)_r;
 R' is H, C₁₋₆alkyl or Ar-C₀₋₆alkyl; and
 r is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

- 30 Also included in this invention are pharmaceutically acceptable addition salts and complexes of the compounds of this invention. In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique racemic compound, as well as each unique nonracemic compound.

In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein

compounds may exist in tautomeric forms, such as keto-enol tautomers, such as 

and , each tautomeric form is contemplated as being included within this invention,

- 5 whether existing in equilibrium or locked in one form by appropriate substitution with R'. The meaning of any substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence.

- Also included in this invention are prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the active
10 parent drug according to formula (I) *in vivo*.

The compounds of formula (I) inhibit Fab I. Inhibition of this enzyme is useful in the treatment of bacterial infections. Also, the compounds of this invention may be useful as antifungal agents. Additionally, the compounds may be useful in combination with known antibiotics.

- 15 With respect to formula (I):

Suitably, R¹ is phenyl, unsubstituted or substituted by methylenedioxy or by one to three substituents selected from the group consisting of C₁₋₄alkyl, OR', N(R')₂, F, Cl, Br, I, and CF₃, in which R' is H or C₁₋₆alkyl.

- Alternately, R¹ is benzimidazolyl or pyridinyl, unsubstituted or substituted by
20 C₁₋₄alkyl, OR', N(R')₂, F, Cl, Br, I, and CF₃, in which R' is H or C₁₋₆alkyl.

Suitably, R² is H, C₁₋₆alkyl or Ph-C₀₋₆alkyl and X is H, C₁₋₄alkyl, OR', CN, N(R')₂, NO₂, CF₃, CO₂R', CON(R')₂, COR', F, Cl, Br or I, in which R' is H or C₁₋₆alkyl.

Representative of the novel compounds of this invention are the following is:

- 25 2-benzoyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;
2-benzoyl-9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;
2-benzoyl-9-[(4-benzyloxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;
2-benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;
30 2-(3,4-methylenedioxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;
2-(2-hydroxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;
2-(3-imidazo)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;
35

- 2-(6-hydroxy)nicotinoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole;
- 2-(6-amino)nicotinoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole;
- 5 2-(3-amino)benzoyl-9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole;
- 2-(4-hydroxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole;
- 2-(4-methylamino)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole;
- 10 2-(4-amino)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole;
- 2-(4-chloro)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole;
- 2-(4-hydroxy)benzoyl-9-[(4-trifluoromethylphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole;
- 15 2-(3,5-dichloro-4-hydroxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole; and
- 2-(3-chloro-4-hydroxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole;
- 20 or a pharmaceutically acceptable salt thereof.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of this invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984).

- 25 C₁₋₄alkyl as applied herein means an optionally substituted alkyl group of 1 to 4 carbon atoms, and includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl. C₁₋₆alkyl additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. C₀₋₄alkyl and C₀₋₆alkyl additionally indicates that no alkyl group need be present (*e.g.*, that a covalent bond is present).
- 30 Any C₁₋₄alkyl or C₁₋₆alkyl may be optionally substituted with the group R^x, which may be on any carbon atom that results in a stable structure and is available by conventional synthetic techniques. Suitable groups for R^x are C₁₋₄alkyl, OR', SR', C₁₋₄alkylsulfonyl, C₁₋₄alkylsulfoxyl, arylsulfonyl, arylsulfoxyl, C₁₋₄alkyl sulfonamides, aryl sulfonamides, -CN, N(R')₂, CH₂N(R')₂, -NO₂, -CF₃, -CO₂R', -CON(R')₂, -COR', -
- 35 NR'C(O)R', F, Cl, Br, I, or CF₃S(O)-, wherein R' and r are as defined for formula (I) compounds.

Halogen or halo means F, Cl, Br, and I.

Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or naphthyl substituted by one to three substituents, such as those defined above for alkyl, or substituted by methylenedioxy.

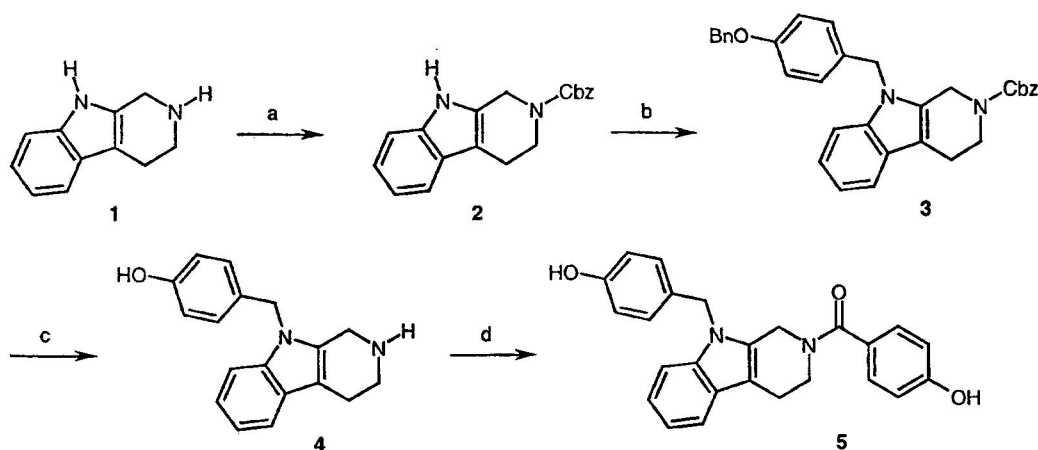
- 5 Het, or heterocycle, indicates an optionally substituted five or six membered monocyclic ring, or a nine or ten-membered bicyclic ring containing one to three heteroatoms chosen from the group of nitrogen, oxygen and sulfur, which are stable and available by conventional chemical synthesis. Illustrative heterocycles are benzofuryl, benzimidazolyl, benzopyranyl, benzothienyl, furyl, imidazolyl, indolyl, morpholyl, piperidinyl, piperazinyl, pyrrolyl, pyrrolidinyl, tetrahydropyridinyl, pyridinyl, thiazolyl, 10 thienyl, quinolyl, isoquinolyl, and tetra- and perhydro- quinolyl and isoquinolyl. Any accessible combination of up to three substituents on the Het ring, such as those defined above for alkyl, that are available by chemical synthesis and are stable are within the scope of this invention.

- 15 Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical, Bn refers to the benzyl radical, Me refers to methyl, Et refers to ethyl, Ac refers to acetyl, Alk refers to C₁₋₄alkyl, Nph refers to 1- or 2-naphthyl and cHex refers to cyclohexyl. Tet refers to 5-tetrazolyl.

- 20 Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, EDC refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride, HOBt refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DIEA refers to diisopropylethylamine, DEAD refers to diethyl azodicarboxylate, PPh₃ refers to triphenylphosphine, DIAD refers to diisopropyl 25 azodicarboxylate, DME refers to dimethoxyethane, DMF refers to dimethylformamide, NBS refers to N-bromosuccinimide, Pd/C refers to a palladium on carbon catalyst, PPA refers to polyphosphoric acid, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate, HF refers to hydrofluoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC 30 refers to pyridinium chlorochromate.

Compounds of the formula (I) are prepared by the general methods described in Scheme I.

Scheme I



- 5 Reagents and conditions: (a) N-(benzyloxycarbonyl)oxysuccinimide, Et₃N, DMF; (b) 4-benzyloxybenzyl chloride, NaH, DMF; (c) H₂, 10% Pd/C, HCl, MeOH, dioxane; (d) 4-hydroxybenzoic acid, EDC, HOBT · H₂O, (*i*-Pr)₂NEt, DMF.

- Commercially available 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (**I-1**) is
- 10 protected at the piperidine nitrogen with a suitable protecting group, for instance a benzyloxycarbonyl (Cbz) group, to afford **I-2**. The use of protecting groups to mask reactive functionality is well-known to those of skill in the art, and other protecting groups are listed in standard reference volumes, such as Greene, "Protective Groups in Organic
- 15 Synthesis" (published by Wiley-Interscience). The indole nitrogen is functionalized as appropriate with, for instance, alkyl groups, arylalkyl groups, acyl groups, or sulfonyl groups, to afford N-substituted derivatives. For example, the indole nitrogen can be alkylated with a suitable benzyl halide derivative, such as 4-benzyloxybenzyl chloride, to afford the benzylated derivative **I-3**. The alkylation reaction generally requires
- 20 deprotonation of the indole with a strong base, such as sodium hydride, LDA, or LiN(TMS)₂, and is typically conducted in a polar, aprotic solvent, usually THF, DMF, or mixtures thereof. The Cbz protecting group is removed by hydrogenation under acidic conditions, in the presence of a catalytic amount of palladium metal on activated carbon (Pd/C), to provide the amine hydrochloride **I-3**. Other standard methods for removal of a Cbz protecting group are described by Greene (cited above). The amine derivative is then
- 25 converted to amide **I-4** by reaction with an activated derivative of a suitable carboxylic acid. For example, 4-hydroxybenzoic acid is converted to an activated form by reaction with EDC and HOBT, and the activated form is subsequently reacted with amine **I-3** in a

suitable solvent such as DMF, CH_2Cl_2 , or CH_3CN . Depending on whether acid neutralization is required, an added base, such as triethylamine (Et_3N), diisopropylethylamine ($(i\text{-Pr})_2\text{NEt}$), or pyridine, may be used.

- 5 Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag), which are incorporated herein by reference.

- 10 Amide coupling reagents as used herein denote reagents which may be used to form peptide bonds. Typical coupling methods employ carbodiimides, activated anhydrides and esters and acyl halides. Reagents such as EDC, DCC, DPPA, PPA, BOP reagent, HOBt, N-hydroxysuccinimide and oxalyl chloride are typical.

- 15 Typically, the amine is coupled via its free amino group to an appropriate carboxylic acid substrate using a suitable carbodiimide coupling agent, such as $\text{N,N}'$ -dicyclohexyl carbodiimide (DCC), optionally in the presence of catalysts such as 1-hydroxybenzotriazole (HOBt) and dimethylamino pyridine (DMAP). Other methods, such as the formation of activated esters, anhydrides or acid halides, of the free carboxyl of a suitably protected acid substrate, and subsequent reaction with the free amine, optionally in the presence of a base, are also suitable. For example, a benzoic acid is treated in an
20 anhydrous solvent, such as methylene chloride or tetrahydrofuran (THF), in the presence of a base, such as N-methylmorpholine, DMAP or a trialkylamine, with isobutyl chloroformate to form the "activated anhydride", which is subsequently reacted with the free amine.

- 25 Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate
30 cation; or with an appropriate organic amine. Cations such as Li^+ , Na^+ , K^+ , Ca^{++} , Mg^{++} and NH_4^+ are specific examples of cations present in pharmaceutically acceptable salts.

- This invention also provides a pharmaceutical composition which comprises a compound according to formula (I) and a pharmaceutically acceptable carrier. Accordingly, the compounds of formula (I) may be used in the manufacture of a
35 medicament. Pharmaceutical compositions of the compounds of formula (I) prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent

or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also
5 be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in a
10 emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a
15 sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard
20 gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined
with excipients, such as cocoa butter, glycerin, gelatin or polyethylene glycols, and molded
25 into a suppository.

For topical administration, the compounds of this invention may be combined with diluents to take the form of ointments, gels, pastes, creams, powders or sprays. The compositions which are ointments, gels, pastes or creams contain diluents, for example, animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives,
30 polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures of these substances. The compositions which are powders or sprays contain diluents, for example, lactose, talc, silicic acid, aluminum hydroxide, calcium silicate and polyamide powder, or mixtures of these substances. Additionally, for topical ophthalmologic administration, the typical carriers are water, mixtures of water and water miscible solvents,
35 such as lower alkanols or vegetable oils, and water-soluble non-toxic polymers, for example cellulose derivatives, such as methyl cellulose.

16

The compounds described herein are inhibitors of Fab I, and are useful for treating bacterial infections. For instance, these compounds are useful for the treatment of bacterial infections, such as, for example, infections of upper respiratory tract (e.g. otitis media, bacterial tracheitis, acute epiglottitis, thyroiditis), lower respiratory (e.g. empyema, lung abscess), cardiac (e.g. infective endocarditis), gastrointestinal (e.g. secretory diarrhoea, splenic abscess, retroperitoneal abscess), CNS (e.g. cerebral abscess), eye (e.g. blepharitis, conjunctivitis, keratitis, endophthalmitis, preseptal and orbital cellulitis, dacryocystitis), kidney and urinary tract (e.g. epididymitis, intrarenal and perinephric abscess, toxic shock syndrome), skin (e.g. impetigo, folliculitis, cutaneous abscesses, cellulitis, wound infection, bacterial myositis), and bone and joint (e.g. septic arthritis, osteomyelitis). Also, the compounds of this invention may be useful as antifungal agents. Additionally, the compounds may be useful in combination with known antibiotics.

The compounds of this invention are administered to the patient, in a manner such that the concentration of drug is sufficient to treat bacterial infections. The pharmaceutical composition containing the compound is administered at an oral dose of between about 10 mg to about 1000 mg, taken once or several times daily, in a manner consistent with the condition of the patient. Preferably, the oral dose would be about 50 mg to about 500 mg, although the dose may be varied depending upon the age, body weight and symptoms of the patient. For acute therapy, parenteral administration is preferred. An intravenous infusion of the compound of formula (I) in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. The precise level and method by which the compounds are administered is readily determined by one skilled in the art.

The compounds may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

Cloning of *S. aureus* FabI:

The *fabI* gene was cloned from the chromosomal DNA of *S. aureus* strain WCUH29 using the polymerase chain reaction. Amplification was performed using *Taq* DNA polymerase (BRL) and the following primers: 5'-CGCCTCGAGATGTTAAATCTTGAAAACAAAACATATGTC-3' and 5'-CGCGGATCCAATCAAGTCAGGTTGAAATATCCA-3' (*Xho*I and *Bam*HI sites underlined). The resulting fragment was then digested with *Xho*I and *Bam*HI and ligated into *Xho*I- and *Bam*HI-digested expression vector pET-16b (Novagen), producing pET-His₁₀-*fabI*. The gene sequence of *fabI* was confirmed by automated cycle sequencing using an Applied Biosystems model 377 machine. The untagged version of pET-*fabI* was

- constructed by digesting pET-His₁₀-*fabI* with *Nco*I and *Nde*I to remove a 97 bp fragment encoding the His 10 tag, the factor Xa cleavage site and the first 8 amino acids of FabI, and replacing it with a linker encoding the first 8 amino acids of FabI plus a glycine residue between the initiator methionine and the lysine at position 2. This plasmid was called pET-*fabI*. The linker was made by annealing the following two oligonucleotides: 5'-CATGGGCTTAAATCTTGAAAACAAAACA-3' and 5'-TATGTTTTGTTTTCAAGATTTAAGCC-3'. The linker sequence in pET-*fabI* was confirmed by dideoxy sequencing. Only native FabI was used for compound evaluation. For overproduction of native FabI, plasmid pET-*fabI* was transformed into BL21(DE3) (Novagen) cells, to form strain BL21(DE3):pET-*fabI*.

Purification of *S. aureus* FabI

- S. aureus* FabI was expressed as soluble protein to 10% of total cell protein, 400g cells being recovered from 15L fermentation in tryptone phosphate medium. The cells were lysed and the sample centrifuged. The resulting supernatant was filtered and purified using three consecutive chromatography columns: ion-exchange (Source 15Q), dye-affinity (Blue sepharose), and size exclusion chromatography columns (Superose 12). After each column the FabI containing fractions were pooled, concentrated, and checked for purity and biological activity.

Cloning of *E. coli* FabI:

- A PCR fragment of correct size for *E. coli* FabI was PCR amplified from *E. coli* chromosomal DNA, subcloned into the TOPO TA cloning vector, and verified by colony PCR + restriction endonuclease analysis. The presumptive *E. coli* FabI PCR fragment was subcloned into the expression vector pBluePet. The FabI clone was transformed into *E. coli* strain BL21(DE3). Small Scale expression studies show an over-expressed protein band of correct molecular weight (~28 Kda) for *E. coli* FabI clearly visible following Coomassie staining of SDS PAGE gels. DNA sequencing of the *E. coli* FabI expression constructs illustrated that no errors were apparent. N' terminal amino acid sequencing has confirmed the over-expressed protein band to be *E. coli* FabI.

Purification of *E. coli* FabI

- E. coli* FabI was expressed as soluble protein to 15% of total cell protein, 120g cells being recovered from 3L fermentation in shake flasks in modified terrific broth. The cells

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were lysed and the sample centrifuged. The resulting supernatant was filtered and purified using three consecutive chromatography columns: ion-exchange (Source 15Q), dye-affinity (blue sepharose), and size exclusion (superose 12). After each column the FabI containing fractions were pooled, concentrated and checked for purity and biological activity.

5

S aureus FabI Enzyme Inhibition Assay (NADH):

Assays were carried out in half-area, 96-well microtitre plates. Compounds were evaluated in 50-uL assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-[2-acetamido]-2-iminodiacetic acid), 4 % glycerol, 0.25 mM crotonoyl CoA, 1 mM NADH, and an appropriate dilution of *S. aureus* FabI. Inhibitors were typically varied over the range of 0.01-10 uM. The consumption of NADH was monitored for 20 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities were estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at t = 0 min. IC₅₀'s were estimated from a fit of the initial velocities to a standard, 4-parameter model and are typically reported as the mean ± S.D. of duplicate determinations. Triclosan, a commercial antibacterial agent and inhibitor of FabI, is currently included in all assays as a positive control. Compounds of this invention have IC₅₀'s from about 30.0 micromolar to about 0.015 micromolar.

20

S aureus FabI Enzyme Inhibition Assay (NADPH):

Assays were carried out in half-area, 96-well microtitre plates. Compounds were evaluated in 150-uL assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-[2-acetamido]-2-iminodiacetic acid), 4 % glycerol, 0.25 mM crotonoyl CoA, 50 uM NADPH, and an appropriate dilution of *S. aureus* FabI. Inhibitors were typically varied over the range of 0.01-10 uM. The consumption of NADPH was monitored for 20 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities were estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at t = 0 min. IC₅₀'s were estimated from a fit of the initial velocities to a standard, 4-parameter model and are typically reported as the mean ± S.D. of duplicate determinations. Triclosan, a commercial antibacterial agent and inhibitor of FabI, is currently included in all assays as a positive control.

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E. coli FabI Enzyme Inhibition Assay:

Assays were carried out in half-area, 96-well microtitre-plates. Compounds were

evaluated in 150-uL assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-[2-acetamido]-2-iminodiacetic acid), 4 % glycerol, 0.25 mM crotonoyl CoA, 50 uM NADH, and an appropriate dilution of *E. coli* FabI. Inhibitors were typically varied over the range of 0.01-10 uM. The consumption of NADH was monitored for 20 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities were estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at $t = 0$ min. IC_{50} 's were estimated from a fit of the initial velocities to a standard, 4-parameter model and are typically reported as the mean $\pm$ S.D. of duplicate determinations. Triclosan, a commercial antibacterial agent and inhibitor of FabI, is currently included in all assays as a positive control. Compounds of this invention have IC_{50} 's from about 45.0 micromolar to about 2.0 micromolar.

Antimicrobial Activity Assay:

Whole-cell antimicrobial activity was determined by broth microdilution using the National Committee for Clinical Laboratory Standards (NCCLS) recommended procedure, Document M7-A4, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically". The compound was tested in serial two-fold dilutions ranging from 0.06 to 64 mcg/mL. Test organisms were selected from the following laboratory strains: *Staphylococcus aureus* Oxford, *Staphylococcus aureus* WCUH29, *Streptococcus pneumoniae* ERY2, *Streptococcus pneumoniae* 1629, *Streptococcus pneumoniae* N 1387, *Enterococcus faecalis* 1, *Enterococcus faecalis* 7, *Haemophilus influenzae* Q1, *Haemophilus influenzae* NEMC1, *Moraxella Catarrhalis* 1502, *Escherichia coli* 7623 AcrABEFD+, *Escherichia coli* 120 AcrAB-, *Escherichia coli* MG1655, *Escherichia coli* MG1658. The minimum inhibitory concentration (MIC) was determined as the lowest concentration of compound that inhibited visible growth. A mirror reader was used to assist in determining the MIC endpoint.

One skilled in the art would consider any compound with a MIC of less than 256 μ g/mL to be a potential lead compound. Preferably, the compounds used in the antimicrobial assays of the present invention have a MIC value of less than 128 μ g/mL. Most preferably, said compounds have a MIC value of less than 64 μ g/mL.

The examples which follow are intended in no way to limit the scope of this invention, but are provided to illustrate how to make and use the compounds of this invention. Many other embodiments will be readily apparent to those skilled in the art.

EXAMPLES

General

5 Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 300 MHz, and chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS). Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in
10 Hertz. CDCl_3 is deuteriochloroform, $\text{DMSO}-d_6$ is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Mass spectra were obtained using electrospray (ES) ionization techniques. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius. Analtech
15 Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Flash chromatography was carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Analytical HPLC was performed on Beckman chromatography systems. Preparative HPLC was performed using Gilson chromatography systems. ODS refers to an octadecylsilyl derivatized silica gel chromatographic support. YMC ODS-
20 AQ® is an ODS chromatographic support and is a registered trademark of YMC Co. Ltd., Kyoto, Japan. PRP-1® is a polymeric (styrene-divinylbenzene) chromatographic support, and is a registered trademark of Hamilton Co., Reno, Nevada. Celite® is a filter aid composed of acid-washed diatomaceous silica, and is a registered trademark of Manville Corp., Denver, Colorado.

25

Preparation 1Preparation of 9-[4-(hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole mono hydrochloride

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a) 2-Benzoyloxycarbonyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

To a stirred solution of 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (20.0 g, 116.2 mmole) in dry DMF (150 mL) at RT was added N-(benzyloxycarbonyloxy)succinimide (31.84 g, 127.76 mmole) and triethylamine (13.0 g, 127.76 mmole). After 12h, the reaction
35 contents were poured into H_2O (150 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phases were washed sequentially with H_2O and brine, then were dried over Na_2SO_4 . Concentration under reduced pressure gave a yellow oil. Purification on

silica (hexanes/EtOAc, 4:1) afforded the title compound (34.48 g, 97 %) as a white solid: MS (ES) m/e 307 (M + H)⁺.

- 5 b) 2-Benzyloxycarbonyl-9-[(4-benzyloxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole

To a stirred solution of 2-benzyloxycarbonyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole (17.75 g, 58.0 mmole) in dry DMF (150 mL) at was added 4-benzyloxybenzylchloride (14.85 g, 63.8 mmole). After 10 min, 60% NaH (2.78 g, 69.6 mmole) was added and the reaction slurry was allowed to warm to RT and stir for 12hr.

- 10 The reaction contents were poured into H₂O (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phases were washed sequentially with H₂O and brine, then were dried over Na₂SO₄. Concentration under reduced pressure gave a waxy solid. Purification on silica (hexanes/EtOAc, 4:1) afforded the title compound (27.13 g, 93 %) as a white solid: MS (ES) m/e 503 (M + H)⁺.

15

- c) 9-[4-(Hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole mono hydrochloride

To a solution of 2-benzyloxycarbonyl-9-[(4-benzyloxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole (5.0 g, 9.96 mmole) in methanol (25 mL) and dioxane (50 mL) containing HCl (10 mL, 1M in dioxane) at RT in a Parr hydrogenation flask was added 10% Pd/C (0.5 g). The reaction mixture was shaken under 45 psi of H₂ for 5 hr. The suspension was filtered through celite®, and the filter pad was washed with methanol. The filtrate was concentrated on the rotavap, and the residue was dried under high vacuum to afford the titled compound (2.79 g, 89%) as a white solid: MS (ES) m/e 279 (M + H - HCl)⁺.

25

Preparation 2

Preparation of 9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole mono hydrochloride

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- a) 2-Benzyloxycarbonyl-9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole

To a stirred solution of 2-benzyloxycarbonyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-*b*]indole (5.0 g, 16.3 mmole) in dry DMF (75 mL) at 5 °C was added 60% NaH (0.7 g, 17.5 mmole). After 10 min, methyl iodide (11.57 g, 81.5 mmole) was added and the reaction was allowed to warm to RT and stir for 12 hr. The reaction contents were poured into H₂O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed sequentially with H₂O and brine, then were dried over Na₂SO₄. Concentration

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under reduced pressure and purification on silica (hexanes/EtOAc, 1:1) afforded the title compound (5.17 g, 99 %) as a white solid: MS (ES) m/e 321 ($M + H$)⁺.

b) 9-Methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]-indole mono hydrochloride

- 5 To a solution of 2-benzyloxycarbonyl-9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole (5.17 g, 16.2 mmole) in methanol (100 mL), EtOAc (25 mL) and HCl (17 mL, 1M in dioxane) at RT in a Parr hydrogenation flask was added 10% Pd/C (0.5 g). The reaction mixture was shaken under 45 psi of H₂ for 6 hr. The suspension was filtered through celite®, and the filter pad was washed with methanol. The filtrate was concentrated on the
- 10 rotavap, and the residue was dried under high vacuum to afford the titled compound (3.19 g, 92%) as a white solid: MS (ES) m/e 187 ($M + H - HCl$)⁺.

Preparation 3

- 15 Preparation of 9-([4-(trifluoromethyl)phenyl]methyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]-indole mono hydrochloride

a) 2-Benzyloxycarbonyl-9-([4-(trifluoromethyl)phenyl]methyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

- 20 To a stirred solution of 2-benzyloxycarbonyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole (5.82 g, 19.0 mmole) in dry DMF (75 mL) at 5 °C was added 60% NaH (1.10 g, 28.5 mmole). After 10 min, 4-trifluoromethylbenzyl bromide (5.0 g, 20.9 mmole) was added and the reaction was allowed to warm to RT and stir for 12 hr. The reaction contents were poured into H₂O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined
- 25 organic phases were washed sequentially with H₂O and brine, then were dried over Na₂SO₄. Concentration under reduced pressure and purification on silica (hexanes/EtOAc, 4:1) afforded the title compound (8.73 g, 99 %) as a white solid: MS (ES) m/e 465 ($M + H$)⁺.

- 30 b) 9-([4-(Trifluoromethyl)phenyl]methyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]-indole mono hydrochloride

- To a solution of 2-benzyloxycarbonyl-9-([4-(trifluoromethyl)phenyl]methyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole (8.73 g, 18.81 mmole) in methanol (50 mL), dioxane (50 mL) and HCl (19 mL, 1M in dioxane) at RT in a Parr hydrogenation flask was added 10%
- 35 Pd/C (0.5 g). The reaction mixture was shaken under 45 psi of H₂ for 6 hr. The suspension was filtered through celite®, and the filter pad was washed with methanol. The filtrate was concentrated on the rotavap, and the residue was dried under high vacuum to afford the

titled compound (6.33 g, 92%) as a white solid: MS (ES) m/e 331 ($M + H - HCl$)⁺.

Preparation 4

5 Preparation of 2-benzoyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

a) 2-Benzoyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

To a stirred solution of 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (2.0 g, 11.6 mmole) in dry DMF (20 mL) at RT was added benzoic acid (1.56 g, 12.77 mmole), 1-hydroxybenzotriazole hydrate (1.72 g, 12.77 mmole) and diisopropylethylamine (1.65 g, 12.77 mmole). After 10 min, EDC (2.44 g, 12.77 mmole) was added and the reaction was allowed to stir for 12 hr. The reaction contents were poured into H₂O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed sequentially with H₂O and brine, then were dried over Na₂SO₄. Concentration under reduced pressure and purification on silica (hexanes/EtOAc, 1:1) afforded the title compound (3.0 g, 94 %) as a white solid: MS (ES) m/e 277 ($M + H$)⁺.

Example 1

20 Preparation of 2-benzoyl-9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

a) 2-Benzoyl-9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

To a stirred solution of 2-benzoyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole (3.0 g, 10.9 mmole) in dry DMF (75 mL) at 5 °C was added 60% NaH (0.52 g, 13.1 mmole). After 10 min, methyl iodide (7.80 g, 55 mmole) was added and the reaction was allowed to warm to RT and stir for 12 hr. The reaction contents were poured into H₂O (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed sequentially with H₂O and brine, then were dried over Na₂SO₄. Concentration under reduced pressure and purification on silica (hexanes/EtOAc, 1:1) afforded the title compound (3.14 g, 99 %) as a white solid: MS (ES) m/e 291 ($M + H$)⁺.

Example 2Preparation of 2-benzoyl-9-[(4-benzyloxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

5

a) 2-Benzoyl-9-[(4-benzyloxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

To a stirred solution of 2-benzoyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole (17.75 g, 58.0 mmole) in dry DMF (75 mL) at 5 °C was added 60% NaH (2.78 g, 69.6 mmole).

After 10 min, 4-benzyloxybenzyl chloride (14.85 g, 63.8 mmole) was added and the reaction was allowed to warm to RT and stir for 12 hr. The reaction contents were poured into H₂O (150 mL) and extracted with EtOAc (2 x 150 mL). The combined organic phases were washed sequentially with H₂O and brine, then were dried over Na₂SO₄.

Concentration under reduced pressure and purification on silica (hexanes/EtOAc, 1:1) afforded the title compound (26.61 g, 97 %) as a white solid: MS (ES) m/e 473 (M + H)⁺.

15

Example 3Preparation of 2-(3-amino)benzoyl-9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]-indole

20 a) 2-[3-(Amino)benzoyl]-9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]-indole (385820)

To a stirred solution of 9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]-indole mono hydrochloride (0.35 g, 1.59 mmole) in dry DMF (20 mL) at RT was added 3-aminobenzoic acid (0.24 g, 1.75 mmole), 1-hydroxybenzotriazole hydrate (0.24 g, 1.75 mmole) and diisopropylethylamine (0.45 g, 3.50 mmole). After 10 min, EDC (0.33 g, 1.75 mmole) was added and the reaction was allowed to stir for 12 hr. The reaction contents were poured into H₂O (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed sequentially with H₂O and brine, then were dried over Na₂SO₄.

Concentration under reduced pressure gave a yellow oil. Purification on silica (CHCl₃/CH₃OH, 95:5) afforded the title compound (0.45 g, 92 %) as a white solid: MS (ES) m/e 306 (M + H)⁺.

30

Example 4Preparation of 2-(4-hydroxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

a) 2-(4-Hydroxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

To a stirred solution of 9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]-indole monohydrochloride (0.50 g, 1.59 mmole) in dry DMF (25 mL) at RT was added 4-hydroxybenzoic acid (0.24 g, 1.75 mmole), 1-hydroxybenzotriazole hydrate (0.24 g, 1.75 mmole) and diisopropylethylamine (0.45 g, 3.50 mmole). After 10 min, EDC (0.33 g, 1.75 mmole) was added and the reaction was allowed to stir for 12 hr. The reaction contents were poured into H₂O (100 mL) and extracted with EtOAc (2 x 150 mL). The combined organic phases were washed sequentially with H₂O and brine, then were dried over Na₂SO₄. Concentration under reduced and purification on silica (hexanes/EtOAc, 1:2) afforded the title compound (0.55 g, 91 %) as a white solid: MS (ES) m/e 383 (M + H)⁺.

Example 5Preparation of 2-benzoyl-9-[4-(hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

a) 2-Benzoyl-9-[4-(hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

According to the procedure of Example 4, except substituting benzoic acid (0.21 g, 1.75 mmole) for 4-hydroxybenzoic acid, the title compound (0.60 g, 90 %) was prepared as a white solid following flash chromatography on silica gel (hexanes/EtOAc, 1:2): MS (ES) m/e 383 (M + H)⁺.

Example 6Preparation of 2-(3,4-methylenedioxy)benzoyl-9-[4-(hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

a) 2-(3,4-Methylenedioxy)benzoyl-9-[4-(hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

According to the procedure of Example 4, except substituting piperonylic acid

was prepared as an off-white solid following flash chromatography on silica gel (hexanes/EtOAc, 1:2): MS (ES) m/e 400 (M + H)⁺.

Example 10

5

Preparation of 2-(6-amino)nicotinoyl-9-[4-(hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

10 a) 2-(6-Amino)nicotinoyl-9-[4-(hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

According to the procedure of Example 4, except substituting 6-aminonicotinic acid (0.24 g, 1.75 mmole) for 4-hydroxybenzoic acid, the title compound (0.60 g, 87 %) was prepared as an off-white solid following flash chromatography on silica gel (hexanes/EtOAc, 1:2): MS (ES) m/e 399 (M + H)⁺.

15

Example 11

Preparation of 2-(4-methylamino)benzoyl-9-[4-(hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

20

a) 2-(4-Methylamino)benzoyl-9-[4-(hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

According to the procedure of Example 4, except substituting 4-methylaminobenzoic acid (0.26 g, 1.75 mmole) for 4-hydroxybenzoic acid, the title compound (0.61 g, 85 %) was prepared as an off-white solid following flash chromatography on silica gel (hexanes/EtOAc, 1:2): MS (ES) m/e 412 (M + H)⁺.

25

Example 12

30 Preparation of 2-(4-amino)benzoyl-9-[4-(hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

a) 2-(4-Amino)benzoyl-9-[4-(hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

35

According to the procedure of Example 4, except substituting 4-aminobenzoic acid (0.24 g, 1.75 mmole) for 4-hydroxybenzoic acid, the title compound (0.56 g, 80 %) was prepared as an off-white solid following flash chromatography on silica gel

Example 16

5 Preparation of 2-(4-hydroxy)benzoyl-9-([4-(trifluoromethyl)phenyl]methyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

a) 2-(4-Hydroxy)benzoyl-9-([4-(trifluoromethyl)phenyl]methyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole

10 According to the procedure of Example 4, except substituting 9-([4-(trifluoromethyl)phenyl]methyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]-indole monohydrochloride (0.50 g, 1.37 mmole) for 9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]-indole monohydrochloride, the title compound (0.55 g, 90%) was prepared as white solid following flash chromatography on silica gel (hexanes/EtOAc, 1:2): MS (ES) m/e 451 (M + H)⁺.

15 Example 17

Parenteral Dosage Unit Composition

20 A preparation which contains 20 mg of the compound of Example 1 as a sterile dry powder is prepared as follows: 20 mg of the compound is dissolved in 15 mL of distilled water. The solution is filtered under sterile conditions into a 25 mL multi-dose ampoule and lyophilized. The powder is reconstituted by addition of 20 mL of 5% dextrose in water (D5W) for intravenous or intramuscular injection. The dosage is thereby determined by the
25 injection volume. Subsequent dilution may be made by addition of a metered volume of this dosage unit to another volume of D5W for injection, or a metered dose may be added to another mechanism for dispensing the drug, as in a bottle or bag for IV drip infusion or other injection-infusion system.

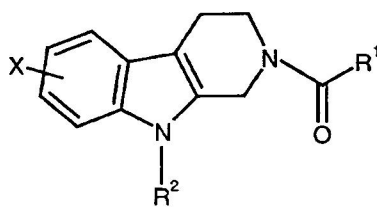
30 Example 18

Oral Dosage Unit Composition

35 A capsule for oral administration is prepared by mixing and milling 50 mg of the compound of Example 1 with 75 mg of lactose and 5 mg of magnesium stearate. The resulting powder is screened and filled into a hard gelatin capsule.

What is claimed is:

1. A compound according to formula (I):



wherein:

R^1 is Ar or Het;

R^2 is H, C_{1-6} alkyl or Ar- C_{0-6} alkyl;

X is H, C_{1-4} alkyl, OR', SR', C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfoxyl, CN, $N(R')_2$, $CH_2N(R')_2$, NO_2 , CF_3 , CO_2R' , $CON(R')_2$, COR' , $NR'C(O)R'$, F, Cl, Br, I, or $CF_3S(O)_r$;

R' is H, C_{1-6} alkyl or Ar- C_{0-6} alkyl; and

r is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which R^1 is phenyl, unsubstituted or substituted by methylenedioxy or by one to three substituents selected from the group consisting of C_{1-4} alkyl, OR', $N(R')_2$, F, Cl, Br, I, and CF_3 , in which R' is H or C_{1-6} alkyl.

3. A compound according to claim 1 in which R^1 is benzimidazolyl or pyridinyl, unsubstituted or substituted by C_{1-4} alkyl, OR', $N(R')_2$, F, Cl, Br, I, and CF_3 , in which R' is H or C_{1-6} alkyl.

4. A compound according to claim 1 in which R^2 is H, C_{1-6} alkyl or Ph- C_{0-6} alkyl.

5. A compound according to claim 1 in which X is H, C_{1-4} alkyl, OR', CN, $N(R')_2$, NO_2 , CF_3 , CO_2R' , $CON(R')_2$, COR' , F, Cl, Br or I, in which R' is H or C_{1-6} alkyl.

6. A compound according to claim 1 which is:
 2-benzoyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;
 2-benzoyl-9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;
 2-benzoyl-9-[(4-benzyloxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

2-benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

2-(3,4-methylenedioxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

5 2-(2-hydroxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

2-(3-imidazo)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

10 2-(6-hydroxy)nicotinoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

2-(6-amino)nicotinoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

2-(3-amino)benzoyl-9-methyl-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

15 2-(4-hydroxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

2-(4-methylamino)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

2-(4-amino)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

20 2-(4-chloro)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

2-(4-hydroxy)benzoyl-9-[(4-trifluoromethylphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

25 2-(3,5-dichloro-4-hydroxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole; or

2-(3-chloro-4-hydroxy)benzoyl-9-[(4-hydroxyphenyl)methyl]-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indole;

or a pharmaceutically acceptable salt thereof.

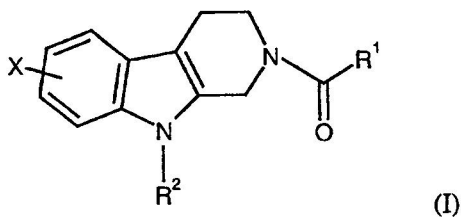
30 7. A pharmaceutical composition which comprises a compound according to claim 1 and a pharmaceutically acceptable carrier.

8. A method for inhibiting Fab I which comprises administering to a subject in need thereof a compound according to claim 1.

35 9. A method of treating bacterial infections which comprises administering to a subject in need thereof a compound according to claim 1.

ABSTRACT OF THE DISCLOSUREFab I Inhibitors

Compounds of the formula (I) are disclosed which are Fab I inhibitors and are useful in the treatment bacterial infections:



wherein:

R^1 is Ar or Het;

R^2 is H, C_{1-6} alkyl or Ar- C_{0-6} alkyl;

X is H, C_{1-4} alkyl, OR', SR', C_{1-4} alkylsulfonyl, C_{1-4} alkylsulfoxyl, CN, $N(R')_2$, $CH_2N(R')_2$, NO_2 , CF_3 , CO_2R' , $CON(R')_2$, COR' , $NR'C(O)R'$, F, Cl, Br, I, or $CF_3S(O)_r$;

R' is H, C_{1-6} alkyl or Ar- C_{0-6} alkyl; and

r is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

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