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Bogotá, D.C.

Re.: Código 02-01-329
Expediente No. 00-76.103
Solicitud de Patente
SmithKline Beecham Corporation

En relación con el Expediente de la referencia y con el fin de dar cumplimiento a la preceptuado por el artículo 4o. literal d.) numeral 3 de la Convención de París adjunto a este escrito sírvanse encontrar la copia certificada de la solicitud de patente de la cual se reivindica prioridad, la cual se encuentra debidamente traducida en sus apartes pertinentes.

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APPLICATION NUMBER: ***60/158,704***
FILING DATE: ***October 08, 1999***

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

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PROVISIONAL APPLICATION COVER SHEET

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

Docket No.	P51036P

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TITLE OF THE INVENTION (280 characters max)

Fab I Inhibitors

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ENCLOSED APPLICATION PARTS (check all that apply)

☑ Specification	Number of Pages	20	☐ Small Entity Statement
☐ Drawings	Number of Sheets		☐ Other (specify)

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

Respectfully submitted,
Signature: Mary E. McCarthy
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Date: October 8, 1999
Registration No.: 32,917

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

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TITLE

Fab I Inhibitors

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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 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 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) 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 overall synthetic pathwayof 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*, 947-953 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).

Recent studies have shown that Fab I is also the target for the broad spectrum antibacterial agent triclosan (McMurry, et al, (1998) *Nature 394*, 531-532). A crystal structure of the *E. Coli* Fab I complexed with NAD and triclosan shows that triclosan acts as a site-directed, very potent inhibitor of Fab I by mimicking its natural substrate (Levy, et al, (1999) *Nature 398*, 383-384). Ward, et al ((1999) *Biochem. 38*, 12514-12525) have shown that there is no evidence for the formation of a covalent complex between Fab I and triclosan, which would be analogous to the diazaborines; triclosan differs from these compounds in that it is a reversible inhibitor of Fab I. The structural data for the complex of Fab I with NAD and triclosan provides important information about Fab I as a therapeutic target.

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

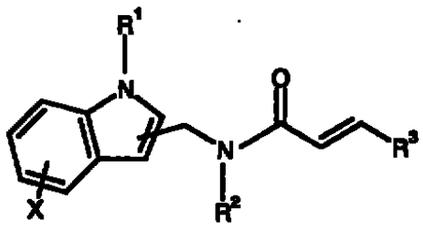
This invention comprises compounds of the formula (I), as described hereinafter, which inhibit Fab I and are useful in the treatment of bacterial infections.

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

DETAILED DESCRIPTION

This invention comprises compounds of formula (I):



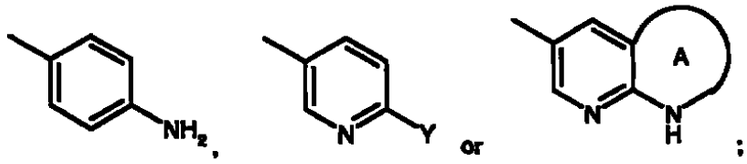
(I)

wherein:

R^1 is C_{1-4}alkyl;

R^2 is C_{1-4}alkyl;

R^3 is



; Y is H, NH_2 or NHC_{1-4}alkyl;

is a 5- or 6-membered alicyclic, aromatic or heteroaromatic ring;

X is H, C_{1-4}alkyl, OR', SR', 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 $-S(O)_rCF_3$;

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

r is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

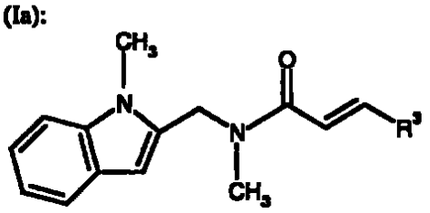
Also included in this invention are pharmaceutically acceptable addition salts and complexes of the compounds of this invention. In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique racemic compound, as well as each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

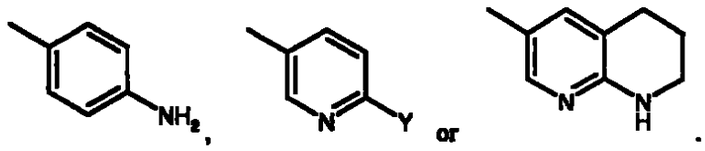
With respect to formula (I), this invention preferably includes compounds of formula (Ia):



(Ia)

in which R^3 is as defined for formula (I) compounds.

Suitably, with respect to formula (I), R^3 is:



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

3-(2-Aminopyridin-5-yl)-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]acrylamide;

4-Amino-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]cinnamamide; and

N-Methyl-N-[(1-methyl-1H-indol-2-yl)methyl]-3-(pyridin-3-yl)acrylamide;

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).

C_{1-4}alkyl 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. C_{1-6}alkyl additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. C_{0-4}alkyl and C_{0-6}alkyl additionally indicates that no alkyl group need be present (*e.g.*, that a covalent bond is present).

Any C_{1-4}alkyl or C_{1-6} alkyl 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 C_{1-4}alkyl, OR', SR', 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 $-S(O)_rCF_3$, 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.

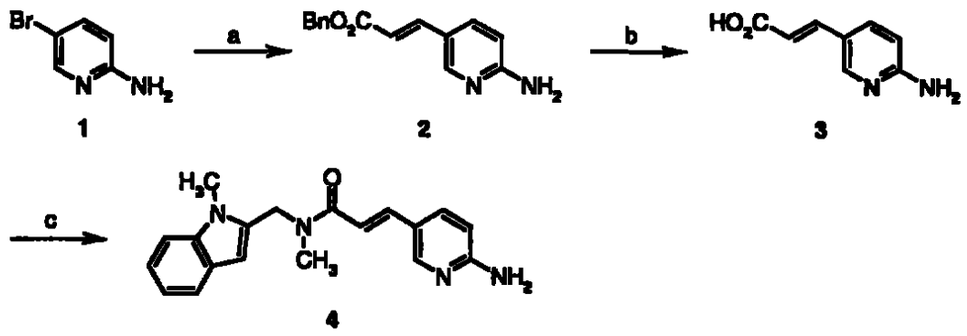
Het, or heterocycle, indicates an optionally substituted five or six membered monocyclic ring, or a nine or ten-membered bicyclic ring containing one to three heteroatoms chosen from the group of nitrogen, oxygen and sulfur, which are stable and available by conventional chemical synthesis. Illustrative heterocycles are benzofuryl, benzimidazolyl, benzopyranyl, benzothienyl, furyl, imidazolyl, indolinyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, pyrrolidinyl, tetrahydropyridinyl, pyridinyl, thiazolyl, thienyl, quinolinyl, isoquinolinyl, and tetra- and perhydro- quinolinyl and isoquinolinyl. 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.

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 C_{1-4}alkyl, Nph refers to 1- or 2-naphthyl and cHex refers to cyclohexyl. Tet refers to 5-tetrazolyl.

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, PPh_3 refers to triphenylphosphine, DIAD refers to diisopropyl 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 refers to pyridinium chlorochromate.

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

Scheme I



(a) benzyl acrylate, $Pd(OAc)_2$, P(o-tol)$_3$, $(i\text{-}Pr)_2NEt$, propionitrile; (b) 1.0 N NaOH, MeOH; (c) 1-methyl-2-(methylaminomethyl)indole, EDC, HOBt · H_2O, Et_3N, DMF.

A suitable haloaromatic derivative, for instance for instance 2-amino-5-bromopyridine (I-1), reacts with an appropriate α,β-unsaturated ester, for example benzyl acrylate, in a Heck-type reaction (see Heck, *Org. Reactions* 1982, 27, 345) to afford I-2. The reaction is mediated by a palladium(0) species, and generally is conducted in an inert solvent, such as CH_3CN, propionitrile, or toluene, in the presence of an appropriate acid scavenger, such as triethylamine (Et_3N) or diisopropylethylamine ($(i\text{-}Pr)_2NEt$). Typical sources of the palladium(0) species include palladium (II) acetate ($Pd(OAc)_2$) and palladium(II) chloride ($PdCl_2$), and oftentimes phosphine ligands, for instance triphenylphosphine (PPh_3) or tri-ortho-tolylphosphine (P(tol)$_3$), are included. The ethyl ester of I-2 is hydrolyzed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid I-3. The carboxylic acid of I-3 is converted to an activated form using, for example, EDC and HOBt, or $SOCl_2$, and the activated form is subsequently reacted with an appropriate amine, for instance 1-methyl-2-(methylaminomethyl)indole, in a suitable solvent such as DMF, CH_2Cl_2, or CH_3CN, to afford I-4. Depending on whether acid neutralization is required, an added base, such as triethylamine (Et_3N), diisopropylethylamine ($(i\text{-}Pr)_2NEt$), or pyridine, may be used.

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.

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.

Typically, the amine is coupled via its free amino group to an appropriate carboxylic acid substrate using a suitable carbodiimide coupling agent, such as 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 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.

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 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 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 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 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 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 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 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, 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, such as lower alkanols or vegetable oils, and water-soluble non-toxic polymers, for example cellulose derivatives, such as methyl cellulose.

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, darcryocystitis), 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-His_{10}-*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-His_{10}-*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 (Sourse 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 were lysed and the sample centrifuged. The resulting supernatant was filtered and purified using three consecutive chromatography columns: ion-exchange (Sourse 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.

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. 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 ± 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 0.50 micromolar to about 0.05 micromolar.

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. 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 ± S.D. of duplicate determinations. Triclosan, a commercial antibacterial agent and inhibitor of FabI, is currently included in all assays as a positive control.

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 ± 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 10.0 micromolar to about 0.30 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 I, 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 µg/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 µg/mL. Most preferably, said compounds have a MIC value of less than 64 µg/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

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at either 300 or 360 MHz, and chemical shifts are reported in parts per million (:) 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 Hertz. $CDCl_3$ is deuteriochloroform, 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 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-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.

Preparation 1

Preparation of 1-methyl-2-(methylaminomethyl)indole

a) Ethyl 1-methylindole-2-carboxylate

NaH (60% dispersion in mineral oil, 8.02 g, 200.49 mmole) was washed with hexanes, then was suspended in dry DMF (530 mL). Solid ethyl indole-2-carboxylate (25.29 g, 133.66 mmole) was added portionwise over 5 - 10 min, allowing gas evolution to subside between additions. When the addition was complete, the yellow mixture was

stirred for 15 min, then methyl iodide (42 mL, 668.3 mmole) was added all at once. The reaction was exothermic, and the internal temperature rose to 40 - 45°C. After 1 hr, the reaction was quenched with 10% NH_4Cl (100 mL) and concentrated on the rotavap (high vacuum). The residue was partitioned between Et_2O(500 mL) and H_2O (100 mL), and the layers were separated. The Et_2O layer was washed with H_2O (100 mL), dried ($MgSO_4$), and concentrated to leave the title compound (27.10 g, quantitative) as a light yellow solid. This was used without further purification: TLC (10% EtOAc/hexanes) Rf = 0.39.

b) N,1-Dimethylindole-2-carboxamide

A suspension of ethyl 1-methylindole-2-carboxylate (27.10 g, 133.34 mmole) in 40% aqueous CH_3NH_2 (300 mL) and MeOH (30 mL) was stirred at RT. A solid tended to gradually creep up the walls of the flask, and was washed down periodically with MeOH. The flask was tightly stoppered to keep the material inside the flask. As the reaction proceeded, the solid dissolved, but eventually the product began to precipitate. The reaction was stirred at RT for 5 days, then was concentrated to remove approximately 200 mL of the solvent. The remaining residue was diluted with H_2O (300 mL), and the solid was collected by suction filtration and washed with H_2O. Drying at 50 - 60°C in high vacuum left the title compound (23.45 g, 93%) as a faintly yellow solid: ^1H NMR (300 MHz, $CDCl_3$) □ 7.63 (d, J = 8.0 Hz, 1 H), 7.27 - 7.43 (m, 2 H), 7.10 - 7.20 (m, 1 H), 6.80 (s, 1 H), 6.10 - 6.30 (m, 1 H), 4.06 (s, 3 H), 3.01 (d, J = 4.9 Hz, 3 H).

c) 1-Methyl-2-(methylaminomethyl)indole

A 3-liter 3-necked roundbottom flask equipped with overhead stirring was charged with N,1-dimethylindole-2-carboxamide (23.45 g, 124.58 mmole) and anhydrous THF (170 mL). The solution was stirred while a solution of $LiAlH_4$ in THF (1.0 M, 250 mL, 250 mmole) was added via syringe. Gas was evolved during the addition of the first 50 mL of $LiAlH_4$ solution. When the addition was complete, the resulting light yellow solution was heated at gentle reflux. After 23 hr, the reaction was cooled in ice and quenched by the sequential dropwise addition of H_2O (9.5 mL), 15% NaOH (9.5 mL), and H_2O (28.5 mL). The mixture was stirred for 15 min, then was filtered through celite®, and the filter pad was washed thoroughly with THF. The filtrate was concentrated and the residue was flash chromatographed on silica gel (10% MeOH/$CHCl_3$ containing 0.5% conc. NH_4OH). The title compound (20.17 g, 93%) was obtained as a light yellow oil: ^1H NMR (300 MHz, $CDCl_3$) □ 7.56 (d, J = 7.8 Hz, 1 H), 7.02 - 7.35 (m, 3 H), 6.38 (s, 1 H), 3.88 (s, 2 H), 3.75 (s, 3 H), 2.49 (s, 3 H).

Preparation 2

Preparation of 3-(2-aminopyridin-5-yl)acrylic acid

a) Benzyl 3-(2-aminopyridin-5-yl)acrylate

A solution of 2-amino-5-bromopyridine (2.25 g, 13.0 mmole), benzyl acrylate (3.2 g, 19.7 mmole), $Pd(OAc)_2$ (0.31 g, 1.4 mmole), tri-*ortho*-tolylphosphine (0.73 g, 2.4 mmole), and diisopropylethylamine (3.5 mL, 20.0 mmole) in propionitrile (50 mL) was heated at reflux overnight. The dark mixture was filtered through celite®, and the filtrate was concentrated. Flash chromatography on silica gel (3% $MeOH/CH_2Cl_2$) gave the title compound (1.3 g, 39%): MS (ES) *m/e* 255 $(M + H)^+$.

b) 3-(2-Aminopyridin-5-yl)acrylic acid

A solution of benzyl 3-(2-aminopyridin-5-yl)acrylate (1.3 g, 5.1 mmole) and 1.0 N NaOH (10 mL, 10 mmole) in MeOH was heated at reflux overnight. The solution was concentrated in vacuo, and the residue was dissolved in H_2O. The pH was adjusted to 6 with dilute HCl, and the solid precipitate was collected by suction filtration and dried to give the title compound (0.6 g, 72%) as a white solid: MS (ES) *m/e* 165 $(M + H)^+$.

Example 1

Preparation of 3-(2-aminopyridin-5-yl)-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]acrylamide

EDC (0.70 g, 3.7 mmole) was added to a solution of 3-(2-aminopyridin-5-yl)acrylic acid (0.61 g, 3.7 mmole), 1-methyl-2-(methylaminomethyl)indole (0.65 g, 3.7 mmole), HOBt · H_2O (0.50 g, 3.7 mmole), and triethylamine (0.52 mL, 3.7 mmole) in DMF (30 mL) at RT. The reaction was stirred overnight, then was concentrated in vacuo. The residue was diluted with 5% $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$. Flash chromatography on silica gel (3% MeOH/CH_2Cl_2) gave a colorless semisolid which was triturated with Et_2O and dried. The title compound (1.0 g, 83%) was obtained as a white solid: ^1H NMR (300 MHz, $CDCl_3$) 8.20 (br s, 1 H), 7.45 - 7.70 (m, 3 H), 7.00 - 7.30 (m, 3 H), 6.69 (d, J = 15.4 Hz, 1 H), 6.30 - 6.50 (m, 2 H), 4.89 (s, 2 H), 4.67 (br s, 2 H), 3.68 (s, 3 H), 3.01 (s, 3 H); MS (ES) *m/e* 321 $(M + H)^+$. Anal. Calcd for $C_{19}H_{20}N_4O \cdot 0.40\ H_2O$: C, 69.66; H, 6.40; N, 17.10. Found: C, 69.99; H, 6.27; N, 16.84.

Example 2

Preparation of 4-amino-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]cinnamamide

EDC (218 mg, 1.14 mmole) was added to a solution of 4-aminocinnamic acid hydrochloride (220 mg, 1.10 mmole), 1-methyl-2-(methylaminomethyl)indole (0.20 g, 1.15 mmole), HOBt · H_2O (154 mg, 1.14 mmole), and triethylamine (0.20 mL, 1.43 mmole) in DMF (20 mL) at RT. The reaction was stirred overnight, then was concentrated in vacuo. The residue was diluted with 5% $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine (2 x 30 mL) and dried over $MgSO_4$. Flash chromatography on silica gel (3% MeOH/CH_2Cl_2) gave the title compound (68 mg, 19%) as a yellow foam: ^1H NMR (360 MHz, DMSO-d_6, 330K) δ 7.46 (d, J = 7.8 Hz, 1 H), 7.42 (d, J = 15.3 Hz, 1 H), 7.37 (d, J = 8.3 Hz, 1 H), 7.32 (d, J = 8.5 Hz, 2 H), 7.06 - 7.15 (m, 1 H), 6.94 - 7.03 (m, 1 H), 6.81 (d, J = 15.3 Hz, 1 H), 6.58 (d, J = 8.5 Hz, 2 H), 6.33 (s, 1 H), 5.25 (br s, 2 H), 4.85 (s, 2 H), 3.70 (s, 3 H), 3.02 (s, 3 H); MS (ES) *m/e* 320 $(M + H)^+$. Anal. Calcd for $C_{20}H_{21}N_3O \cdot 0.20\ H_2O$: C, 74.37; H, 6.68; N, 13.01. Found: C, 74.21; H, 6.60; N, 12.80.

Example 3

Preparation of N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]-3-(pyridin-3-yl)acrylamide

EDC (0.22 g, 1.14 mmole) was added to a solution of *trans*-3-(3-pyridyl)acrylic acid (0.17 g, 1.14 mmole), 1-methyl-2-(methylaminomethyl)indole (0.20 g, 1.15 mmole), and HOBt · H_2O (0.15 g, 1.11 mmole) in DMF (10 mL) at RT. The reaction was stirred overnight, then was concentrated in vacuo. The residue was diluted with 5% $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$. Flash chromatography on silica gel (3% MeOH/CH_2Cl_2) followed by preparative TLC (3% MeOH/CH_2Cl_2) gave the title compound (0.14 g, 40%) as a white solid: ^1H NMR (360 MHz, $CDCl_3$) indicated an approximately 8:1 mixture of amide rotamers; for the major rotamer: . 8.79 (s, 1 H), 8.59 (d, J = 3.9 Hz, 1 H), 7.84 (d, J = 7.6 Hz, 1 H), 7.76 (d, J = 15.5 Hz, 1 H), 7.59 (d, J = 7.8 Hz, 1 H), 7.38 - 7.48 (m, 2 H), 7.19 - 7.27 (m, 1 H), 7.08 - 7.17 (m, 1 H), 6.98 (d, J = 15.5 Hz, 1 H), 6.51 (s, 1 H), 4.94 (s, 2 H), 3.73 (s, 3 H), 3.09 (s, 3 H); MS (ES) *m/e* 306 $(M + H)^+$. Anal. Calcd for $C_{19}H_{19}N_3O \cdot 0.20\ H_2O$: C, 73.86; H, 6.33; N, 13.60. Found: C, 73.52; H, 6.32; N, 13.43.

Example 4

Parenteral Dosage Unit Composition

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 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.

Example 5

Oral Dosage Unit Composition

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.

Example 6

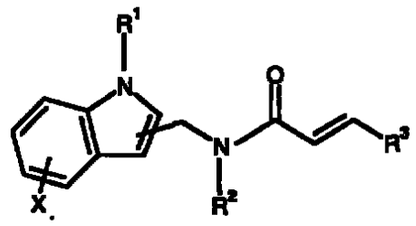
Oral Dosage Unit Composition

A tablet for oral administration is prepared by mixing and granulating 20 mg of sucrose, 150 mg of calcium sulfate dihydrate and 50 mg of the compound of Example 1 with a 10% gelatin solution. The wet granules are screened, dried, mixed with 10 mg starch, 5 mg talc and 3 mg stearic acid; and compressed into a tablet.

The above description fully discloses how to make and use the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprises the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound according to formula (I):



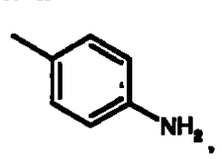
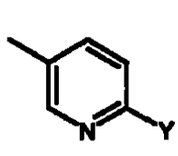
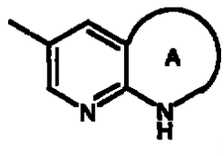
(I)

wherein:

R^1 is C_{1-4}alkyl;

R^2 is C_{1-4}alkyl;

R^3 is



or

;

Y is H, NH_2 or NHC_{1-4}alkyl;

is a 5- or 6-membered alicyclic, aromatic or heteroaromatic ring;

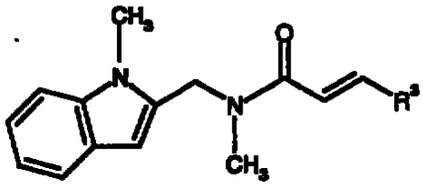
X is H, C_{1-4}alkyl, OR', SR', CN, $N(R')_2$, $CH_2N(R')_2$, NO_2, CF_3, CO_2R', $CON(R')_2$, COR', $NR'C(O)R'$, F, Cl, Br, I or $-S(O)_rCF_3$;

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

r is 0, 1 or 2;

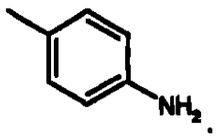
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 of formula (Ia):

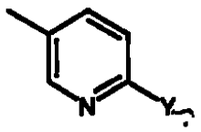


(Ia).

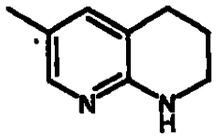
3. A compound according to claim 1 in which R^3 is:



4. A compound according to claim 1 in which R^3 is:



5. A compound according to claim 1 in which R^3 is:



6. A compound according to claim 1 which is:

3-(2-Aminopyridin-5-yl)-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]acrylamide;

4-Amino-N-methyl-N-[(1-methyl-1H-indol-2-yl)methyl]cinnamamide; or

N-Methyl-N-[(1-methyl-1H-indol-2-yl)methyl]-3-(pyridin-3-yl)acrylamide;

or a pharmaceutically acceptable salt thereof.

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

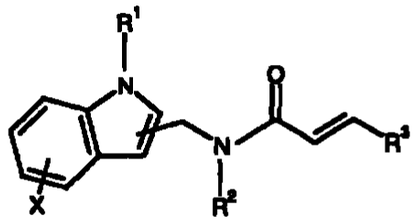
8. A method for inhibiting Fab I which comprises administering to a subject in need thereof a compound according to claim 1.

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 DISCLOSURE

Fab I Inhibitors

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



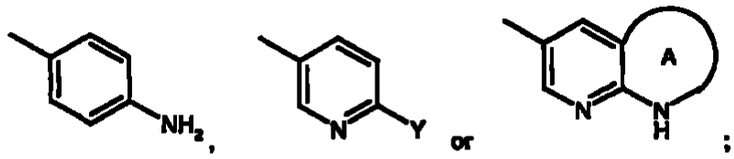
(I)

wherein:

R^1 is C_{1-4}alkyl;

R^2 is C_{1-4}alkyl;

R^3 is



Y is H, NH_2 or NHC_{1-4}alkyl;

is a 5- or 6-membered alicyclic, aromatic or heteroaromatic ring;

X is H, C_{1-4}alkyl, OR', SR', 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 $-S(O)_rCF_3$;

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

r is 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

ESTADOS UNIDOS DE AMERICA

A TODOS A QUIENES LLEGUE EL PRESENTE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Marcas y Patentes

28 de septiembre de 2000

LA PRESENTE CERTIFICA QUE LA ADJUNTA ES UNA COPIA TOMADA DE LOS REGISTROS DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS, DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA Y LA CUAL CUMPLE CON LOS REQUISITOS PARA QUE LE SEA CONFERIDA UNA FECHA DE RADICACIÓN SEGÚN 35 USC 111.

NÚMERO DE SOLICITUD *60/158,704*

FECHA DE RADICACIÓN: *08 de octubre de 1999*

Por Autoridad del

COMISIONADO DE MARCAS Y PATENTES

(FIRMA) H. L. JACKSON

Oficial de Certificaciones

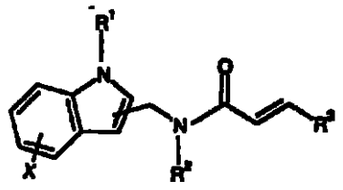
(SELLO DORADO DE OBLEA)

* * * *

INHIBIDORES DE FAB I

REIVINDICACIONES:

1. Un compuesto según la fórmula (I):



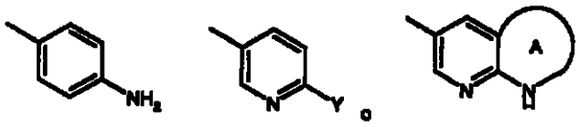
(I)

en donde:

R^1 es alquil C_{1-4}

R^2 es alquil C_{1-4}

R^3 es



Y es H, NH_2 o NHCalquilC_{1-4};

es un anillo alicíclico, aromático o heteroaromático de 5 o 6 miembros;

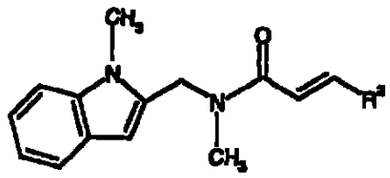
X es H, alquilC$_{1-4}$, OR', SR', CN N(R')$_2$, CH$_2$N(R')$_2$, NO$_2$, CF$_3$, CO2R', CON(R')$_2$, COR', NR'C(O)R, F, Cl, Br, I o -S(O)rCF$_3$;

R' es H, alquil C$_{1-6}$ o -alquilC$_{0-6}$-Ar; y

R es 0, 1 o 2;

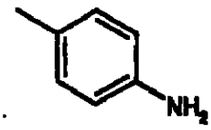
o una sal farmacéuticamente aceptable de lo mismo.

2. Un compuesto según la reivindicación 1 de la fórmula (Ia):

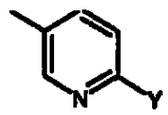


(Ia).

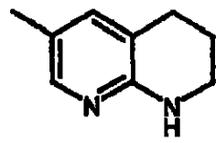
3. Un compuesto según la reivindicación 1 en el cual R^3 es:



4. Un compuesto según la reivindicación 1 en el cual R^3 es:



5. Un compuesto según la reivindicación 1, en el cual R^3 es:



6. Un compuesto según la reivindicación 1, que es:

3-(2-Aminopiridin-5-il)-N-metil-N-[(1-metil-1H-indol-2-il)metil]acrilamida;

4-Amino-N-metil-N-[(1-metil-1H-indol-2-il)metil]cinamamida; o

N-Metil-N-[(1-metil-1H-indol-2-il)metil[3-(piridin-3-il)acrilamida;

o una sal farmacéuticamente aceptable de lo mismo.

7. Una composición farmacéutica que comprende un compuesto según la reivindicación 1 y un portador farmacéuticamente aceptable.

8. Un método para inhibir Fab I que consiste en administrara un sujeto que lo requiera, un compuesto según la reivindicación 1.

9. Un método para el tratamiento de infecciones bacterianas que consiste en administrar a un sujeto que lo requiera, un compuesto según la reivindicación 1.

125 126

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

136

2020
Bogotá, D.C.

Doctor
GERMAN CASTILLO GRAU
Apoderado

REFERENCIA:	Radicación No.	00076103
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	0243
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que:

Debe allegar copia del documento en que consta la cesión del derecho a la patente otorgado por el inventor al solicitante o a su causante. (Art.26-k).

En cumplimiento del artículo 39 de la Decisión 486 de la Comisión de la Comunidad Andina, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la Resolución Reglamentaria No. 210 del 15 de enero del 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 06 FEB. 2001.

Se recuerda al interesado que debe presentar, dentro de los dieciséis meses siguientes contados a partir de la fecha de presentación de la solicitud cuya prioridad se invoca, copia de la misma certificada por la autoridad que la expidió, un certificado de la fecha de presentación de esa solicitud expedida por la misma autoridad y, en los casos en que haya lugar, la traducción simple del capítulo reivindicatorio. El incumplimiento de éste plazo, acarreará la pérdida de la prioridad invocada.

C.T./C.J: 202012/202022

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