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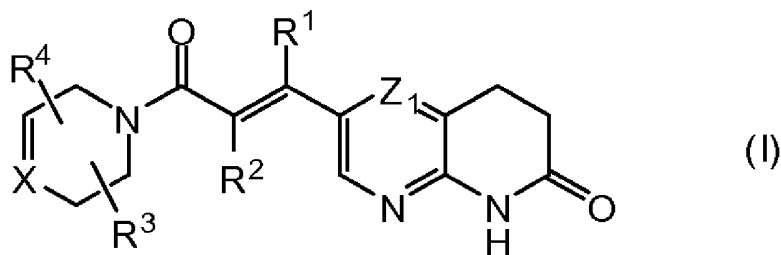
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(54) Title: ANTIBACTERIAL PIPERIDINYL SUBSTITUTED 3,4-DIHYDRO-1H-[1,8]NAPHTHYRIDINONES



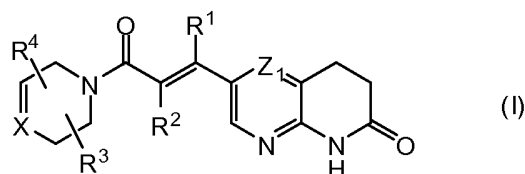
(57) **Abstract:** The present invention is related to novel compounds of formula (I) that inhibit the activity of the FabI enzyme which are therefore useful in the treatment of bacterial infections. It further relates to pharmaceutical compositions comprising these compounds, and chemical processes for preparing these compounds.

ANTIBACTERIAL PIPERIDINYL SUBSTITUTED
3,4-DIHYDRO-1H-[1,8]NAPHTHYRIDINONES

- 5 The present invention is related to novel compounds of formula (I) that inhibit the activity of the FabI enzyme which are therefore useful in the treatment of bacterial infections. It further relates to pharmaceutical compositions comprising these compounds, and chemical processes for preparing these compounds.
- 10 The compounds of the present invention are antibacterial compounds that inhibit the FabI protein, a NADH-dependent enoyl-acyl carrier protein (ACP) reductase enzyme in the fatty acid biosynthesis pathway. Fatty acid synthase (FAS) is involved in the overall biosynthetic pathway of saturated fatty acids in all organisms, but the structural organization of FAS varies considerably among them. The distinctive characteristics of
- 15 FAS of vertebrates and yeasts are that all enzymatic activities are encoded on one or two polypeptide chains, and that the acyl carrier protein (ACP) exists in the form of a complex. In contrast, in bacterial FAS, each of synthetic steps is catalyzed by a distinct, mono-functional enzyme and the ACP is a discrete protein. Therefore, it is possible to selectively inhibit bacterial FAS by blocking one of the synthetic steps
- 20 using an inhibitory agent. NADH-dependent enoyl-ACP reductase (Fab I) is involved in the last step of the four reaction steps involved in each cycle of bacterial fatty acid biosynthesis. Thus, the FabI enzyme is the biosynthetic enzyme in the overall synthetic pathway of bacterial fatty acid biosynthesis.
- 25 The FabI enzyme has been shown to constitute an essential target in major pathogens such as *E. Coli* (Heath *et al. J. Biol. Chem.* **1995**, 270, 26538; Bergler *et al. Eur. J. Biochem.* **2000**, 275, 4654). Hence, compounds that inhibit FabI may be useful as antibacterials.
- 30 Compounds having FabI enzyme inhibitory activity have been disclosed in WO-01/26652, WO-01/26654, and WO-01/27103. Substituted naphthyridinone compounds having FabI inhibitory activity have been disclosed in WO-03/088897, WO-2007/043835 and WO-2008/098374. International patent application WO 2007/053131 also discloses various naphthyridone compounds for potential use as
- 35 FabI inhibitors. However, none of these documents discloses a compound in which there is a cyclic amino group directly attached to a carbonyl moiety that is α to an alkene. International patent application WO 2011/061214 also discloses various

compounds for potential use as FabI inhibitors. However, this document does not disclose *inter alia* compounds in which there is a nitrogen-containing cyclic group containing a double bond or an additional nitrogen heteroatom.

5 The present invention relates to a compound of formula (I)



wherein

the --- bond represents a single bond or a double bond;

10 X represents carbon or nitrogen, and when X represents nitrogen then the --- bond represents a single bond;

Z₁ represents CH or N;

R¹ is hydrogen, C₁₋₄alkyl or halo;

R² is hydrogen, C₁₋₄alkyl or halo;

15 R³ is hydrogen, C₁₋₆alkyl, hydroxy or halo;

R⁴ is hydrogen, C₁₋₆alkyl, halo, aryl, aryloxy, arylcarbonyl, heteroaryl, C₁₋₆alkyl substituted with aryl or aryloxy, or C₁₋₆alkyl substituted with heteroaryl;

and when the substituents R³ and R⁴ are located on adjacent positions said R³ and R⁴ may be taken together to form a radical of formula =CH-CH=CH-CH= with the proviso

20 that X represents carbon and the --- bond represents a single bond;

aryl is phenyl; phenyl substituted with one, two or three substituents each individually selected from halo, hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, polyhaloC₁₋₄alkyl, polyhaloC₁₋₄alkyloxy, cyano, nitro, and amino;

heteroaryl is furanyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, 25 thiazolyl, triazolyl, tetrazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzo[1,3]dioxolyl, benzofuranyl, benzothiazolyl, indolyl, 2,3-dihydro-1H-indolyl, tetrahydrothiophenyl, or quinolinyl;

wherein each heteroaryl may be substituted with one or two substituents each independently selected from halo, cyano, C₁₋₄alkyl, C₁₋₄alkyloxy, 30 C₁₋₄alkylcarbonyl, or phenyl;

or a pharmaceutically acceptable acid addition salt thereof.

As used in the foregoing definitions :

- halo is generic to fluoro, chloro, bromo and iodo;
- C₁₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methyl-ethyl, 2-methylpropyl and the like;
- C₁₋₆alkyl is meant to include C₁₋₄alkyl and the higher homologues thereof having 5 or 6 carbon atoms, such as, for example, 2-methylbutyl, pentyl, hexyl and the like;
- polyhaloC₁₋₄alkyl is defined as polyhalo substituted C₁₋₄alkyl (as hereinabove defined) substituted with 2 to 6 halogen atoms such as difluoromethyl, trifluoromethyl, trifluoroethyl, and the like.

As used in the description, whenever the term “compound of formula (I)” is used, it is meant to include also the pharmaceutically addition salts the compounds of formula (I) are able to form and the solvates the compounds of formula (I) or the pharmaceutically acceptable acid addition salts of compounds of formula (I) are able to form.

The definition of “compounds of formula (I)” inherently includes all stereoisomers of the compound of formula (I) either as a pure stereoisomer or as a mixture of two or more stereoisomers. Enantiomers are stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a racemate or racemic mixture. Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers, *i.e.* they are not related as mirror images. If a compound contains a disubstituted cycloalkyl group, the substituents may be in the cis or trans configuration. Therefore, the invention includes enantiomers, diastereomers, racemates, cis isomers, trans isomers and mixtures thereof.

The absolute configuration is specified according to the Cahn-Ingold-Prelog system. The configuration at an asymmetric atom is specified by either R or S. Resolved compounds whose absolute configuration is not known can be designated by (+) or (-) depending on the direction in which they rotate plane polarized light. When a specific stereoisomer is identified, this means that said stereoisomer is substantially free, *i.e.* associated with less than 50%, preferably less than 20%, more preferably less than 10%, even more preferably less than 5%, in particular less than 2% and most preferably less than 1%, of the other isomers. Thus, when a compound of formula (I) is for instance specified as (R), this means that the compound is substantially free of the (S) isomer; when a compound of formula (I) is for instance specified as E, this means that the compound is substantially free of the Z isomer; when a compound of formula (I) is

for instance specified as *cis*, this means that the compound is substantially free of the *trans* isomer.

5 The terms “stereoisomers” or “stereochemically isomeric forms” hereinbefore or hereinafter are used interchangeably.

10 The absolute stereochemical configuration of the compounds of formula (I) and of the intermediates used in their preparation may easily be determined by those skilled in the art while using well-known methods such as, for example, X-ray diffraction.

10 Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

15 Furthermore, some compounds of formula (I) and some of the intermediates used in their preparation may exhibit polymorphism. It is to be understood that the present invention encompasses any polymorphic forms possessing properties useful in the treatment of the conditions noted hereinabove.

20 The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms that the compounds of formula (I) are able to form. These pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as
25 hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (*i.e.* ethanedioic), malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and
30 the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

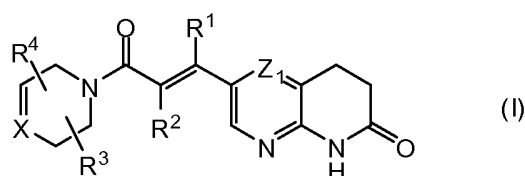
35 The compounds of formula (I) may exist in both unsolvated and solvated forms. The term ‘solvate’ is used herein to describe a molecular association comprising a

compound of the invention and one or more pharmaceutically acceptable solvent molecules, e.g. water or ethanol. The term 'hydrate' is used when said solvent is water.

The term "FabI" is art-recognized and refers to the bacterial enzyme believed to function as an enoyl-acyl carrier protein (ACP) reductase in the final step of the four reactions involved in each cycle of bacterial fatty acid biosynthesis. This enzyme is believed to be widely distributed in bacteria.

Compounds of formula (I) that may be mentioned include those in which:

- (i) Z_1 represents CH, and hence the compound of formula I represents the following:



wherein

- (ii) when R^1 or R^2 represent halo, then they are preferably F or Cl;
 (iii) R^1 represents hydrogen or C_{1-4} alkyl; and/or
 (iv) R^2 represents hydrogen or C_{1-4} alkyl.

Interesting compounds of formula (I) are those compounds of formula (I) wherein one or more of the following restrictions apply:

- a) R^1 and R^2 represent hydrogen; or
 b) R^3 represents hydrogen; or
 c) R^3 represents hydrogen, C_{1-4} alkyl or halo; or
 d) R^4 represents hydrogen; or
 e) R^4 represents aryl; or
 f) R^4 represents aryloxy, or arylcarbonyl; or
 g) R^4 represents C_{1-6} alkyl substituted with aryl or aryloxy; or
 h) R^4 represents heteroaryl; or
 i) R^4 represents C_{1-6} alkyl substituted with heteroaryl; or
 j) R^3 and R^4 are located on adjacent positions and taken together to form a radical of formula $=CH-CH=CH-CH=$ with the proviso that X represents carbon and the $\equiv$ bond represents a single bond; or
 k) heteroaryl represents furanyl, thiophenyl, pyrrolyl, triazolyl, oxadiazolyl, pyridinyl,

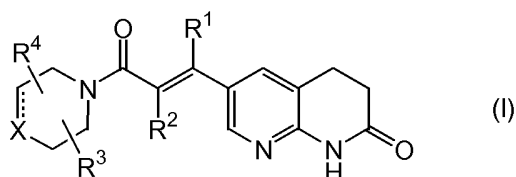
benzo[1,3]dioxolyl, benzofuranyl, benzothiazolyl, indolyl, 2,3-dihydro-1H-indolyl, tetrahydrothiophenyl, or quinolinyl; or

l) X represents carbon; or

m) X represents nitrogen and the ----- bond represents a single bond.

5

A first group of compounds are the compounds of formula (I)



wherein

10 the ----- bond represents a single bond or a double bond ;

X represents carbon or nitrogen, and when X represents nitrogen then the ----- bond represents a single bond;

R¹ is hydrogen;

R² is hydrogen;

15 R³ is hydrogen, C₁₋₆alkyl, or hydroxy;

R⁴ is hydrogen, aryl, aryloxy, arylcarbonyl, heteroaryl, C₁₋₆alkyl substituted with aryl or aryloxy, or C₁₋₆alkyl substituted with heteroaryl;

and when the substituents R³ and R⁴ are located on adjacent positions said R³ and R⁴ may be taken together to form a radical of formula =CH-CH=CH-CH= with the proviso

20 that X represents carbon and the ----- bond represents a single bond;

aryl is phenyl; phenyl substituted with one substituent selected from halo, hydroxy, C₁₋₄alkyloxy, or polyhaloC₁₋₄alkyl;

heteroaryl is furanyl, thiophenyl, pyrrolyl, triazolyl, oxadiazolyl, pyridinyl, benzo[1,3]dioxolyl, benzofuranyl, benzothiazolyl, indolyl, 2,3-dihydro-1H-indolyl, tetrahydrothiophenyl, or quinolinyl;

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wherein each heteroaryl may be substituted with one or two substituents each independently selected from halo, C₁₋₄alkyl, C₁₋₄alkyloxy, or phenyl;

or a pharmaceutically acceptable acid addition salt thereof.

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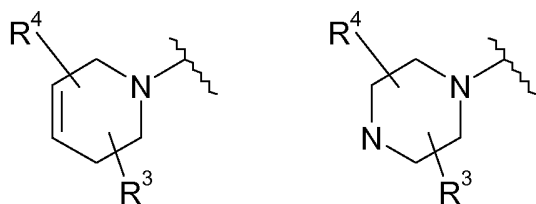
Compounds of formula (I) that may be mentioned include those in which X represents C, the ----- bond represents a single bond and R³ and R⁴ are present and located on adjacent positions, and taken together to form a radical of formula =CH-CH=CH-CH=.

However, compounds of formula (I) that are particularly preferred include those in which:

X represents C and the $\equiv$ bond represents a double bond; or

X represents N (in which case the $\equiv$ bond represents a single bond), and hence the

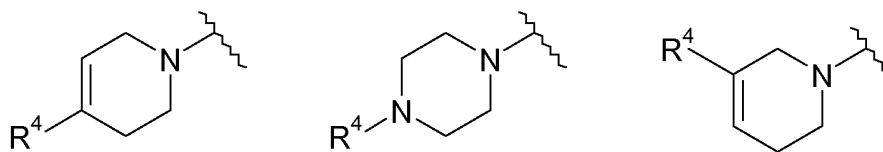
5 following X-containing rings are particularly preferred:



In this instance it is preferred that adjacent R^3 and R^4 groups are not taken together to form a radical.

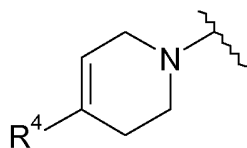
10 In compounds of formula (I), it is preferred that:

- (i) There is at least one R^3 or R^4 substituent present that does not represent hydrogen;
- (ii) One of R^3 and R^4 (e.g. R^3) represent hydrogen, C_{1-3} alkyl or hydroxy and the other one of R^3 and R^4 (e.g. R^4) represents a substituent other than hydrogen;
- 15 (iii) R^3 represents hydrogen, hydroxy or halo (e.g. fluoro) and most preferably represents hydrogen (i.e. R^3 is essentially not present);
- (iv) R^4 represents a substituent other than hydrogen (i.e. there is an R^4 substituent that is present, and does not represent hydrogen);
- (v) R^4 represents a substituent other than hydrogen, which is attached to X,
- 20 in which any of the above can be taken together or in combination. For instance, (iii), (iv) and/or (v) may be taken in combination to provide the particularly preferred compounds of formula (I) below:



25

in which R^4 represents a substituent other than hydrogen. The most preferred X-containing ring in the compounds of formula (I) is:



in which R^4 represents a substituent other than hydrogen. Particularly preferred substituents that R^4 (here and elsewhere) may represent include:

- 5 (i) optionally substituted aryl;
- (ii) optionally substituted heteroaryl
- (iii) C_{1-6} alkyl substituted by aryl, aryloxy or heteroaryl (which latter three aryl and heteroaryl moieties are themselves optionally substituted as defined herein);
- 10 (iv) aryloxy (in which the aryl moiety is optionally substituted as defined herein);
- (v) arylcarbonyl;

It is particularly preferred that the R^4 group contains an aromatic moiety, and hence (i),
 15 (ii), (iii), (iv) and (v) above are particularly preferred).

In the case when R^4 represents (i) above, then the aryl group is preferably phenyl, which group may be unsubstituted or substituted by one or two (e.g. one) substituent selected from halo (e.g. chloro), C_{1-4} alkyl, polyhalo C_{1-4} alkyl (e.g. $-CF_3$), C_{1-4} alkyloxy
 20 (e.g. $-OCH_3$).

In the case when R^4 represents (ii) above, then the heteroaryl group is preferably a monocyclic 5- or 6-membered ring containing one to four heteroatoms or a bicyclic 9- or 10-membered ring containing one to four heteroatoms (e.g. in the latter case, it may
 25 be a benzene ring fused to a 5- or 6-membered aromatic or non-aromatic ring), so forming e.g. a benzo[1,3]dioxolyl group, furanyl (e.g. 2- or 3-furanyl), pyridyl (e.g. 3-pyridyl), benzofuranyl (e.g. 2-benzofuranyl), which heteroaryl groups are optionally substituted by one or more (e.g. one) substituent(s) selected from C_{1-4} alkyloxy (e.g. $-OCH_3$).

30 In the case where R^4 represents (iii) above, then preferably the C_{1-6} alkyl group is methyl or ethyl, i.e. $-CH_3$ or $-CH_2CH_3$, which alkyl moiety is substituted with aryl (e.g. phenyl, such as unsubstituted phenyl or phenyl substituted with C_{1-4} alkyloxy, such as $-OCH_3$), aryloxy (e.g. in which aryl is phenyl, unsubstituted or substituted with one or

more (e.g. one) substituent selected from halo, such as fluoro) or heteroaryl (e.g. a 5- or 6-membered monocyclic heteroaryl group containing one or two (e.g. one) heteroatom(s) or a 9- or 10-membered bicyclic heteroaryl group containing one or two heteroatoms, so forming e.g. a benzofuranyl, benzothiazolyl, 2,3-dihydro-1H-indolyl, pyridinyl, thienyl, triazolyl, indolyl, quinolinyl, pyrrolyl and oxadiazolyl (which heteroaryl groups are unsubstituted or substituted with one or two substituents selected from halo (e.g. fluoro), C₁₋₄ alkyl (e.g. methyl) and unsubstituted phenyl).

In the case when R⁴ represents (iv) above, then the aryl group is preferably phenyl, which group is preferably unsubstituted.

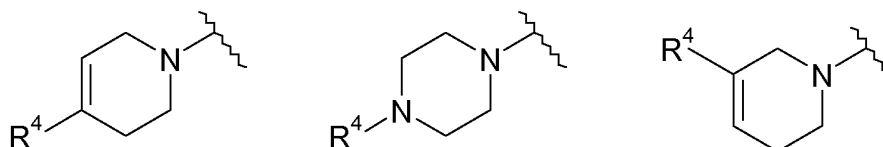
In the case when R⁴ represents (v) above, then the aryl group is preferably phenyl, which group is preferably unsubstituted.

Most preferably, the R⁴ group represents (i), (ii) or (iii) above and even more preferably, R⁴ represents (i) or (ii) above, i.e. aryl or heteroaryl. Even more preferably the R⁴ group represents (i) above, especially unsubstituted phenyl.

In compounds of formula (I) it is preferred that there is no R³ substituent present (or one R³ substituent that represents hydrogen) or there is one R³ substituent present (e.g. on X, when X is a carbon atom) that represents a substituent other than hydrogen (e.g. that represents C₁₋₃ alkyl or preferably hydroxy). It is especially preferred that there is no R³ substituent present. In compounds of formula (I) it is also preferred that there is one or two (e.g. one) R⁴ substituent(s) present, in which R⁴ is as hereinbefore defined.

It is especially preferred that there is one R⁴ substituent present that is located on the X moiety (e.g. on the C or N atom that X may represent), in which R⁴ does not represent hydrogen, but represent another substituent as defined herein.

It is stated hereinbefore that the following X-containing rings are particularly preferred:

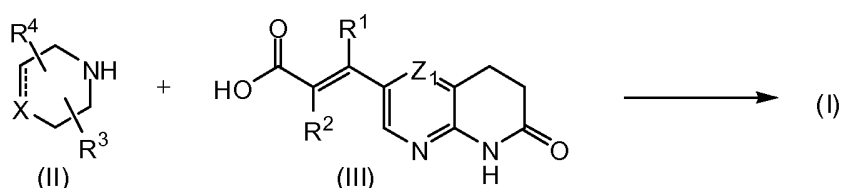


and particularly those in which R⁴ is as defined above. Such compounds which contain either a N(R⁴) moiety or a C(R⁴) moiety adjacent a double bond may be beneficial.

This is because the shape of the nitrogen atom (e.g. being more planar in nature, as

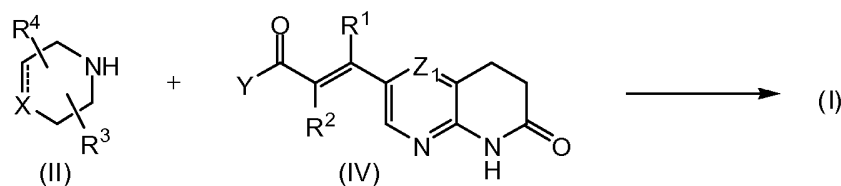
compared to a CR⁴ moiety that is not adjacent a double bond) or the presence of the double bond in the X-containing ring may help to orient the R⁴ group (if present) such that the compound overall (e.g. in view of the R⁴ substituent's orientation) displays better/improved binding properties to the FabI bacterial enzyme. Hence, these compounds of the invention may be advantageous in the sense that the presence of the double bond may lead to improved binding to/inhibition of the FabI enzyme. Consequently the compounds of the invention may be advantageous compounds (e.g. compared to known compounds) by virtue of these properties which may consequentially lead to better potency, efficacy, etc.

Compounds of formula (I) can generally be prepared by reacting an intermediate of formula (II) with an intermediate of formula (III), in at least one reaction-inert solvent and optionally in the presence of at least one suitable coupling reagent and/or a suitable base, the said process further optionally comprising converting a compound of formula (I) into an addition salt thereof, and/or preparing stereochemically isomeric forms thereof.



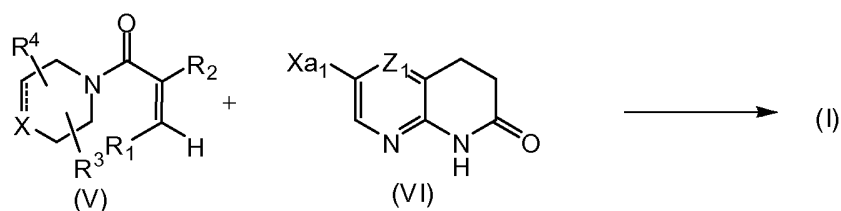
It may be convenient to activate the carboxylic acid of formula (III) by adding an effective amount of a reaction promoter. Non-limiting examples of such reaction promoters include carbonyldiimidazole, *N,N'*-dicyclohexyl-carbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydroxybenzotriazole, benzotriazolyl-oxytris (dimethylamino)-phosphonium hexafluorophosphate, tetrapyrrolidino-phosphonium hexafluorophosphate, bromotripyrrolidinophosphonium hexafluorophosphate, or a functional derivative thereof.

Compounds of formula (I) can also be prepared by reacting an intermediate of formula (II) with an intermediate of formula (IV), wherein Y represents hydroxy or halo. The reaction can be performed in a reaction-inert solvent such as, for example, dichloromethane or dimethylformamide and optionally in the presence of a suitable base such as, for example, diisopropylethyl-amine (DIPEA).



Compounds of formula (I) can also be prepared by reacting an intermediate of formula (V) with an intermediate of formula (VI),

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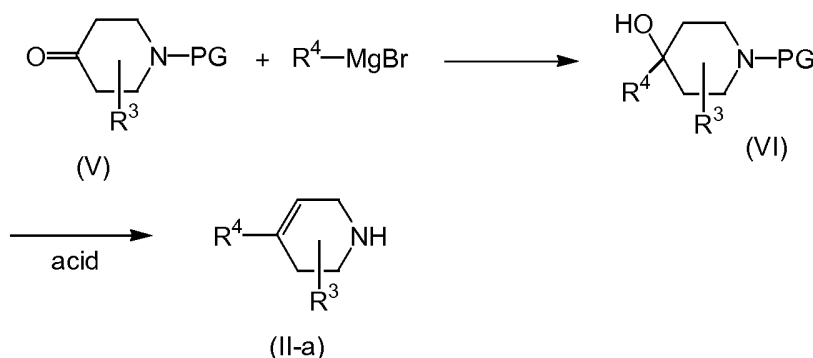


wherein X_{a1} represents a suitable leaving group such as a suitable halo group (e.g. chloro, iodo and, especially, bromo) and the other integers are as hereinbefore defined, under reaction suitable reaction conditions, for example under metal catalyst coupling reaction conditions (e.g. precious metal coupling reaction conditions, wherein the precious metal is e.g. palladium-based), in particular under Heck reaction conditions using preferably a palladium-based catalyst such as palladium acetate, tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) dichloride, [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride or the like (preferably, the catalyst is palladium acetate), for instance optionally in the presence of a suitable solvent (e.g. acetonitrile or the like), base (e.g. an amine base such as *N,N*-diisopropylamine or the like), and a ligand (e.g. triphenylphosphine, tri-*O*-tolylphosphine or the like). The reaction may be performed in a sealed tube and/or in a microwave.

The starting materials and some of the intermediates are known compounds and are commercially available or may be prepared according to conventional reaction procedures generally known in the art.

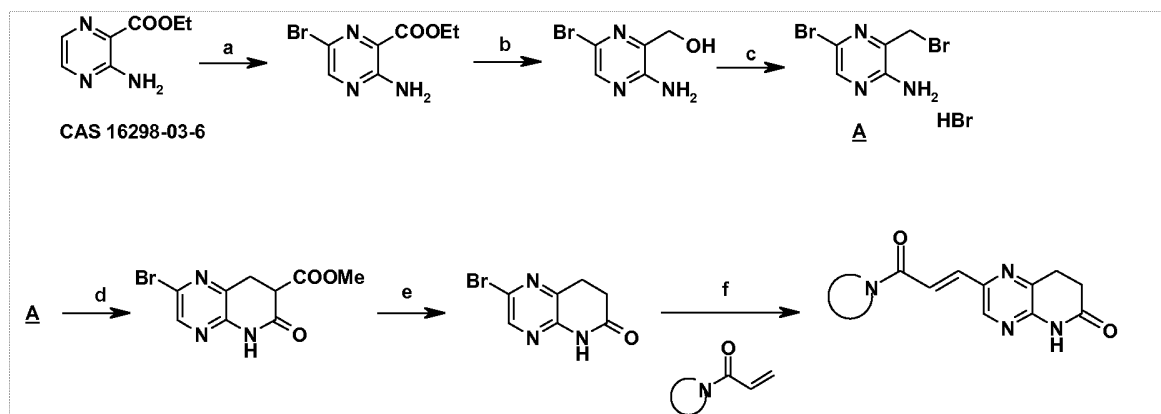
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Intermediates of formula (II-a), defined as intermediates of formula (II) wherein X represents carbon and R^4 is located at the 4-position of the piperidinyl ring, can be prepared according to the following general reaction scheme.



In the above reaction scheme, radical PG in intermediates (V) and (VI) is a nitrogen protecting group such as e.g. tert-butyloxycarbonyl that can easily be removed under acidic conditions. The organomagnesium reagent R⁴-MgBr can be obtained using art known organometallic reactions such as the Grignard reaction.

For the compounds in which Z₁ represents CH, intermediates (IV) and (VI) may be prepared as described herein, or according to conventional reaction procedures generally known in the art. For the corresponding intermediates in which Z₁ represents N, this may also be the case. However, such compounds may also be prepared in accordance with the following scheme:



Conditions :

a) NBS, ACN, reflux, 3 h, 70% ; b) LiAlH₄ 1M in THF, THF, 5°C to RT, o.n., 20%; c) PBr₃, DCM, RT, o.n., 90%; f) dimethyl malonate, NaOMe in MeOH, MeOH, RT, o.n., 25% ; g) NaOH, MeOH, reflux, 4h, HCl, reflux, o.n. ; h) DIEA, Pd(OAc)₂, tri-O-tolylphosphine, ACN, DMF, μ w, 180°C, 25 min.

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. Those compounds of

formula (I) that are obtained in racemic form may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative
5 manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will
10 be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds described herein are inhibitors of the FabI enzyme, as demonstrated in Pharmacological Example 1. In view of these FabI enzyme inhibiting properties the
15 compounds described herein 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,
20 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). Additionally, the compounds may be useful in combination with known
25 antibiotics.

Therefore the present invention also relates to compounds of formula (I) for use as a medicine especially for use in treating bacterial infections, in particular bacterial
30 infections caused by a bacterium that expresses a FabI enzyme. Subsequently the present compounds may be used for the manufacture of a medicine for treatment of bacterial infections, in particular bacterial infections caused by a bacterium that expresses a FabI enzyme.

35 Further, the present invention provides a method of treating bacterial infections which comprises administering to a subject in need thereof a FabI enzyme inhibiting compound of formula (I).

A subject in need of treatment has a bacterial infection or has been exposed to an infectious bacterium, the symptoms of which may be alleviated by administering a therapeutically effective amount of the compounds of the present invention. For example, a subject in need of treatment can have an infection for which the compounds of formula (I) can be administered as a treatment. In another example, a subject in need of treatment can have an open wound or burn injury, for which the compounds of formula (I) can be administered as a prophylactic. Typically a subject will be treated for an existing bacterial infection.

A subject can have a bacterial infection caused by *Bacillus anthracis*, *Citrobacter* sp., *Escherichia coli*, *Francisella tularensis*, *Haemophilus influenza*, *Listeria monocytogenes*, *Moraxella catarrhalis*, *Mycobacterium tuberculosis*, *Neisseria meningitidis*, *Proteus mirabilis*, *Proteus vulgaris*, *Salmonella* sp., *Serratia* sp., *Shigella* sp., *Stenotrophomonas maltophilia*, *Staphylococcus aureus*, or *Staphylococcus epidermidis*. Preferably, the subject is treated (prophylactically or therapeutically) for a bacterial infection caused by a bacterium that expresses a FabI enzyme.

The term "treating" and "treatment", as used herein, refers to curative, palliative and prophylactic treatment, including reversing, alleviating, inhibiting the progress of, or preventing the disease, disorder or condition to which such term applies, or one or more symptoms of such disease, disorder or condition.

A "therapeutically effective amount" of a compound of the present invention is the quantity which, when administered to a subject in need of treatment, improves the prognosis of the subject, e.g. delays the onset of and/or reduces the severity of one or more of the subject's symptoms associated with a bacterial infection. The amount of the disclosed compound to be administered to a subject will depend on the particular disease, the mode of administration, and the characteristics of the subject, such as general health, other diseases, age, sex, genotype, body weight and tolerance to drugs. The skilled person will be able to determine appropriate dosages depending on these and other factors.

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.

Additionally the present invention provides pharmaceutical compositions comprising at least one pharmaceutically acceptable carrier and a therapeutically effective amount of

a compound of formula (I).

In order to prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with at least one pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for oral administration, rectal administration, percutaneous administration or parenteral injection.

For example in preparing the compositions in oral dosage form, any of the usual liquid pharmaceutical carriers may be employed, such as for instance water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid pharmaceutical carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their easy administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral injection compositions, the pharmaceutical carrier will mainly comprise sterile water, although other ingredients may be included in order to improve solubility of the active ingredient. Injectable solutions may be prepared for instance by using a pharmaceutical carrier comprising a saline solution, a glucose solution or a mixture of both. Injectable suspensions may also be prepared by using appropriate liquid carriers, suspending agents and the like. In compositions suitable for percutaneous administration, the pharmaceutical carrier may optionally comprise a penetration enhancing agent and/or a suitable wetting agent, optionally combined with minor proportions of suitable additives which do not cause a significant deleterious effect to the skin. Said additives may be selected in order to facilitate administration of the active ingredient to the skin and/or be helpful for preparing the desired compositions. These topical compositions may be administered in various ways, e.g., as a transdermal patch, a spot-on or an ointment. Addition salts of the compounds of formula (I), due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the pharmaceutical compositions of the invention in dosage unit form for ease of administration and uniformity of dosage. "Dosage unit form" as used herein refers to physically discrete units suitable as unitary

dosages, each unit containing a predetermined amount of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, 5 teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

For oral administration, the pharmaceutical compositions of the present invention may take the form of solid dose forms, for example, tablets (both swallowable and chewable forms), capsules or gelcaps, prepared by conventional means with pharmaceutically 10 acceptable excipients and carriers such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and the like), fillers (e.g. lactose, microcrystalline cellulose, calcium phosphate and the like), lubricants (e.g. magnesium stearate, talc, silica and the like), disintegrating agents (e.g. potato starch, sodium starch glycollate and the like), wetting agents (e.g. sodium laurylsulphate) and 15 the like. Such tablets may also be coated by methods well known in the art.

Liquid preparations for oral administration may take the form of e.g. solutions, syrups or suspensions, or they may be formulated as a dry product for admixture with water and/or another suitable liquid carrier before use. Such liquid preparations may be 20 prepared by conventional means, optionally with other pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methylcellulose, hydroxypropylmethylcellulose or hydrogenated edible fats), emulsifying agents (e.g. lecithin or acacia), non-aqueous carriers (e.g. almond oil, oily esters or ethyl alcohol), sweeteners, flavours, masking agents and preservatives (e.g. methyl or propyl 25 p-hydroxybenzoates or sorbic acid).

Pharmaceutically acceptable sweeteners useful in the pharmaceutical compositions of the invention comprise preferably at least one intense sweetener such as aspartame, acesulfame potassium, sodium cyclamate, alitame, a dihydrochalcone sweetener, 30 monellin, stevioside sucralose (4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose) or, preferably, saccharin, sodium or calcium saccharin, and optionally at least one bulk sweetener such as sorbitol, mannitol, fructose, sucrose, maltose, isomalt, glucose, hydrogenated glucose syrup, xylitol, caramel or honey. Intense sweeteners are conveniently used in low concentrations. For example, in the case of sodium saccharin, 35 the said concentration may range from about 0.04% to 0.1% (weight/volume) of the final formulation. The bulk sweetener can effectively be used in larger concentrations ranging from about 10% to about 35%, preferably from about 10% to 15%

(weight/volume).

The pharmaceutically acceptable flavours which can mask the bitter tasting ingredients in the low-dosage formulations are preferably fruit flavours such as cherry, raspberry,
5 black currant or strawberry flavour. A combination of two flavours may yield very good results. In the high-dosage formulations, stronger pharmaceutically acceptable flavours may be required such as Caramel Chocolate, Mint Cool, Fantasy and the like. Each flavour may be present in the final composition in a concentration ranging from about 0.05% to 1% (weight/volume). Combinations of said strong flavours are
10 advantageously used. Preferably a flavour is used that does not undergo any change or loss of taste and/or color under the circumstances of the formulation.

The compounds of formula (I) may be formulated for parenteral administration by injection, conveniently intravenous, intra-muscular or subcutaneous injection, for
15 example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form, e.g. in ampoules or multi-dose containers, including an added preservative. They may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as isotoning, suspending, stabilizing and/or dispersing agents. Alternatively, the
20 active ingredient may be present in powder form for mixing with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of formula (I) may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such
25 as cocoa butter and/or other glycerides.

Those of skill in the treatment of antibacterial diseases linked to the inhibition of the FabI enzyme will easily determine the therapeutically effective amount of a compound of formula (I) from the test results presented hereinafter. In general it is contemplated
30 that a therapeutically effective dose will be from about 0.001 mg/kg to about 50 mg/kg of body weight, more preferably from about 0.01 mg/kg to about 10 mg/kg of body weight of the patient to be treated. It may be appropriate to administer the therapeutically effective dose in the form of two or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms,
35 for example each containing from about 0.1 mg to about 1000 mg, more particularly from about 1 to about 500 mg, of the active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as the other medication, the patient may be taking, as is well known to those skilled in the art. Furthermore, said "therapeutically effective amount" may be lowered or increased depending on the response of the treated patient and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

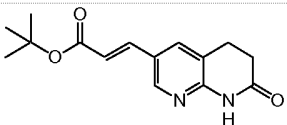
Compounds of formula (I) may have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the above-stated indications or otherwise. Particular compounds of formula (I) may exhibit such advantages, for instance the compounds in which the X-containing ring contains NR^4 and in particular those in which it contains a CR^4 moiety (e.g. in which X is CR^4), which is adjacent to a double bond. Any of these advantageous properties may be attributed to the presence of the moieties NR^4 or CR^4 adjacent to a double bond.

For instance, compounds of formula (I) may have the advantage that they have a good or an improved thermodynamic solubility (e.g. compared to compounds known in the prior art; and for instance as determined by a known method and/or a method described herein). Compounds of formula (I) may also have the advantage that they have a broad spectrum of activity against antibacterials (e.g. a broader spectrum of antibacterial activity compared to compounds known in the prior art; and for instance as determined by known tests and/or tests described herein). Compounds of formula (I) may also have the advantage that they have good or improved *in vivo* pharmacokinetics and oral bioavailability. They may also have the advantage that they have good or improved *in vivo* efficacy. For instance, the compounds of the invention may be adaptable for intravenous formulation/dosing and hence may exhibit an improved *in vivo* efficacy when administered intravenously. Particular compounds of formula (I) may exhibit such advantages, for instance the compounds in which the X-containing ring contains NR^4 and in particular those in which it contains a CR^4 moiety (e.g. in which X is CR^4), which is adjacent to a double bond. Any of these advantageous properties may be attributed to the presence of the moieties NR^4 or CR^4 adjacent to a double bond.

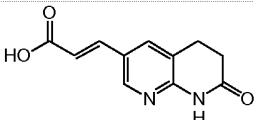
Experimental part

“DMF” is defined as *N,N*-dimethylformamide, “DCM” or “CH₂Cl₂” is defined as dichloromethane, “MeOH” is defined as methanol, “EtOH” is defined as ethanol,
 5 “MgSO₄” is defined as magnesium sulfate, and “THF” is defined as tetrahydrofuran, “HATU” is defined as 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-
 b]pyridinium 3-oxide hexafluorophosphate, “AcOEt” or “EtOAc” is defined as ethyl acetate, “DIPEA” is defined as diisopropylethylamine, “mp” is defined as melting
 point, “EDCI” is defined as *N*’-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine
 10 monohydrochloride, “HOBT” is defined as 1-hydroxy-1*H*-benzotriazole, “DIPA” is defined as diisopropylamine, “K₂CO₃” is defined as potassium carbonate, “TFA” is defined as trifluoroacetic acid, “NH₄OH” is defined as ammonium hydroxide,
 “NaHCO₃” is defined as carbonic acid monosodium salt, “KOH” is defined as potassium hydroxide, “AlCl₃” is defined as aluminum chloride, “NH₄Cl” is defined as
 15 ammonium chloride, “Et₂O” is defined as diethyl ether, “Na₂SO₄” is defined as sulfuric acid disodium salt, “CH₃CN” is defined as acetonitrile, “NaOH” is defined as sodium hydroxide.

A. Synthesis of the intermediates20 Example A.1

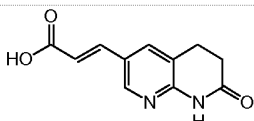
a) Preparation of		intermediate (1)
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A solution of 6-bromo-3,4-dihydro-1*H*-[1,8]naphthyridin-2-one (1.0 g, 4.4 mmol), *tert*-butyl acrylate (2.56 ml, 17.62 mmol) and *N,N*-diisopropylethylamine (1.46 ml, 8.81 mmol) in acetonitrile (20 ml) and DMF (7 ml) was stirred and degassed with nitrogen gas for 10 minutes. Tri-*o*-tolylphosphine (0.27 g, 0.88 mmol) and palladium (II)
 25 acetate (47% on Pd) (0.099 g, 0.44 mol) were added and the resulting mixture was microwaved (1600 W, 180°C, 35 minutes). The reaction mixture was evaporated till dryness, taken up in a mixture of DCM/methanol (8/2) (50 ml), filtered through a short pad of celite and washed with DCM. The organic layer was washed with water, dried over MgSO₄, filtered and evaporated to dryness. The residue was taken up in cold
 30 ethanol (10 ml) and stirred at 5°C for 5 minutes, the precipitate was filtered off, washed with cold ethanol (3 ml) and dried under vacuum to yield 950 mg intermediate (1).

b) Preparation of		intermediate (2)
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Intermediate (1) (4.1 g, 14.95 mmol) was dissolved in a mixture of trifluoroacetic acid (23.2 ml) in DCM (41 ml). The reaction was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure. The resulting solid was triturated with diethyl ether, filtered off and dried under vacuum to yield

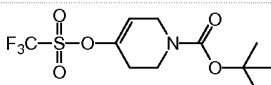
5 3.97 g of intermediate (2).

c) Preparation of		intermediate (3)
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Intermediate (2) was triturated overnight in a mixture of HCl in dioxane (4 M, 48 ml), the solid was filtered off, washed with diethyl ether and dried under vacuum to give 3.7 g of intermediate (3).

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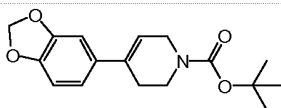
Example A.2

a) Preparation of		intermediate (4)
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Reaction under N₂. BuLi (1.6 M in hexane) (8.28 ml, 13.2 mmol) was added dropwise at -20°C to a solution of DIPA (1.86 ml, 13.2 mmol) in THF (20 ml) then the mixture was stirred at -20°C for 20 minutes. A solution of 1-*tert*-butoxycarbonyl-4-piperidone (2.2 g, 11.0 mmol) in THF (20ml) was then added at -78°C and the resulting mixture was stirred for 30 minutes at -78°C. A solution of 2-[*N,N*-bis(trifluoromethylsulfonyl)-amino]-5-chloropyridine (4.97 g, 12.1 mmol) in THF (10ml) was added at -78°C then the mixture was allowed to reach room temperature and was stirred overnight. The mixture was concentrated and the purification of the residue was carried out by flash chromatography over silica gel (silicagel 30µm, 80g, heptane/EtOAc 75/25). The desired product was collected and the solvent was evaporated, yielding 2.9 g of

15 intermediate (4).

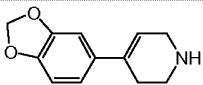
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b) Preparation of		intermediate (5)
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Reaction under N₂. Microwave conditions : Biotage initiator 60, 80°C, 20 minutes. A solution of intermediate (4) (0.3 g, 0.905 mmol) and 3,4-(methylenedioxy)phenyl boronic acid (0.18 g, 1.09 mmol) in K₂CO₃ (2 M, 0.905 ml) and ethylene glycol

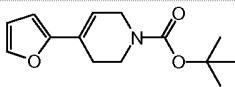
25

- dimethyl ether (3ml) was purged with N₂ for 10 minutes then tetrakis(triphenylphosphine)palladium(0) (0.105 g, 0.0905 mmol) was added. The mixture was irradiated following the conditions above, cooled to room temperature, water and EtOAc were added, the organic layer was separated, washed with water then brine, dried (MgSO₄) and evaporated till dryness. Purification of the residue was carried out by flash chromatography over silica gel (silicagel 10g, 15-40μm, heptane 100 to heptane/EtOAc 90/10) The pure fractions were collected and evaporated to dryness, yielding 0.17 g of intermediate (5).

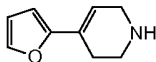
c) Preparation of		intermediate (6)
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- A solution of intermediate (5) (0.17 g, 0.56 mmol) in TFA (0.5 ml) and DCM (3 ml) was stirred at room temperature for 30 minutes, K₂CO₃ (10% aqueous solution) and DCM were added, the organic layer was separated, washed with water, dried (MgSO₄) and evaporated till dryness, yielding 0.11 g of intermediate (6).

15 Example A.3

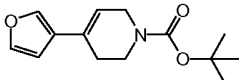
a) Preparation of		intermediate (7)
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- Reaction under N₂. Microwave conditions : 80°C, 20 minutes. A solution of intermediate (4) (0.3 g, 0.905 mmol) and furan-2-boronic acid (0.122 g, 1.09 mmol) in K₂CO₃ (0.905 ml) and ethylene glycol dimethyl ether (3 ml) was purged with N₂ for 10 minutes then tetrakis(triphenylphosphine)palladium(0) (0.105 g, 0.0905 mmol) was added. The mixture was irradiated following the microwave conditions above, cooled to room temperature, water and EtOAc were added, the organic layer was separated, washed with water then brine, dried (MgSO₄) and evaporated till dryness. Purification of the residue was carried out by flash chromatography over silica gel §10g, 15-40μm, heptane 100 to heptane/EtOAc 90/10). The pure fractions were collected and evaporated to dryness, yielding 0.1 g of intermediate (7).

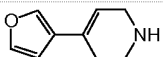
b) Preparation of		intermediate (8)
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- A solution of intermediate (7) (0.1 g, 0.401 mmol) in TFA (0.3 ml) and DCM (2 ml) was stirred at room temperature for 30 minutes, K₂CO₃ (10% aqueous solution) and DCM were added, the organic layer was separated, washed with water, dried (MgSO₄) and evaporated till dryness, yielding 0.046 g of intermediate (8).

Example A.4

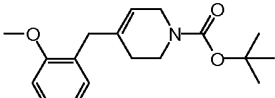
a) Preparation of		intermediate (9)
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Reaction under N₂. Microwave conditions : 80°C, 20 minutes. A solution of intermediate (7) (0.28 g, 0.845 mmol) and furan-3-boronic acid (0.104 g, 0.93 mmol) in K₂CO₃ (2 M, 0.845ml) and ethylene glycol dimethyl ether (3 ml) was purged with N₂ for 10 minutes then tetrakis(triphenylphosphine)palladium(0) (0.0977 g, 0.0845 mmol) was added. The mixture was irradiated following the conditions above, cooled to room temperature, water and EtOAc were added, the organic layer was separated, washed with water then brine, dried (MgSO₄) and evaporated till dryness. Purification of the residue was carried out by flash chromatography over silica gel (10g, 15-40μm, heptane 100 to heptane/EtOAc 90/10). The pure fractions were collected and evaporated to dryness, yielding 0.146 g of intermediate (9).

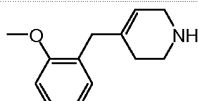
b) Preparation of		intermediate (10)
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A solution of intermediate (9) (0.146 g, 0.586 mmol) in TFA (0.5 ml) and DCM (3 ml) was stirred at room temperature for 30 minutes, K₂CO₃ (10% aqueous solution) and DCM were added, the organic layer was separated, washed with water, dried (MgSO₄) and evaporated till dryness, yielding 0.085 g of intermediate (10).

Example A.5

a) Preparation of		intermediate (11)
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Reaction under N₂. Microwave conditions : 80°C, 20 minutes. A solution of intermediate (4) (0.1 g, 0.302 mmol) and 2-methoxybenzylzinc chloride (0.724 ml, 0.93 mmol) in THF (0.5 ml) was degassed by N₂ bubbling for 10 minutes then 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.022 g, 0.03 mmol) was added. The mixture was irradiated following the conditions above, cooled to room temperature, water and EtOAc were added, the organic layer was separated, washed with water then brine, dried (MgSO₄) and evaporated till dryness, yielding intermediate (11).

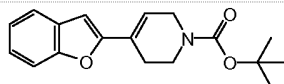
b) Preparation of		intermediate (12)
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A solution of intermediate (11) (0.232 g, 0.765 mmol) in TFA (0.6 ml) and DCM (5 ml) was stirred at room temperature for 45 minutes, K_2CO_3 (10% aqueous solution) and DCM were added, the organic layer was separated, washed with water, dried ($MgSO_4$) and evaporated till dryness, yielding 0.145 g of intermediate (12).

5

Example A.6

a) Preparation of



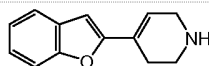
intermediate (13)

Microwave conditions : 80°C, 20 minutes. A solution of intermediate (4) (0.3 g, 0.905 mmol) and benzo[b]furan-2-boronic acid (0.176 g, 1.09 mmol) in K_2CO_3 (2 M, 0.905 ml) and ethylene glycol dimethyl ether (3 ml) was purged with N_2 for 10 minutes then tetrakis(triphenylphosphine)palladium(0) (0.105 g, 0.0905 mmol) was added. The mixture was irradiated following the conditions above, cooled to room temperature, water and EtOAc were added, the organic layer was separated, washed with water then brine, dried ($MgSO_4$) and evaporated till dryness. Purification of the residue was carried out by flash chromatography over silica gel (10g, 15-40 μ m, heptane 100 to heptane/EtOAc 90/10). The pure fractions were collected and evaporated to dryness, yielding 0.217 g of intermediate (13).

10

15

b) Preparation of



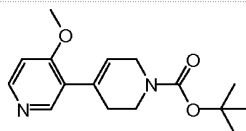
intermediate (14)

A solution of intermediate (13) (0.217 g, 0.725 mmol) in TFA (0.6 ml) and DCM (4 ml) was stirred at room temperature for 30 minutes, K_2CO_3 (10% aqueous solution) and DCM were added, the organic layer was separated, washed with water, dried ($MgSO_4$) and evaporated till dryness.

20

Example A.7

a) Preparation of

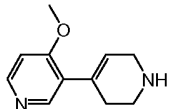


intermediate (15)

Reaction under N_2 . Microwave conditions : 400W, 80°C, 30 minutes. A solution of intermediate (4) (0.752 g, 1.36 mmol) and 4-methoxy-3-pyridinylboronic acid (0.25 g, 1.64 mmol) in K_2CO_3 (2 M, 1.36 ml) and ethylene glycol dimethyl ether (8 ml) was degassed with N_2 for 10 minutes then tetrakis(triphenylphosphine)palladium(0) (0.157 g, 0.0136 mmol) was added. The mixture was irradiated following the microwave conditions above, cooled to room temperature, water and EtOAc were

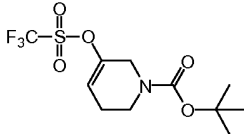
25

added, the organic layer was separated, washed with water then brine, dried (MgSO₄) and evaporated till dryness. Purification of the residue was carried out by flash chromatography over silica gel (30 g, 15-40μm, gradient elution from CH₂Cl₂ to CH₂Cl₂/MeOH/NH₄OH: 97/3/0.1) The pure fractions were collected and evaporated to dryness, yielding 0.19 g of intermediate (15).

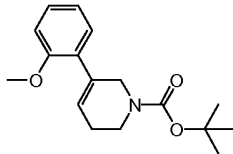
b) Preparation of		intermediate (16)
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A mixture of intermediate (15) (0.2 g, 0.689 mmol) and TFA (0.218 ml) in DCM (2 ml) was stirred at room temperature for 30 minutes then the reaction mixture was poured out into water and extracted with DCM. The organic layer was separated, washed with NaHCO₃ (10% aqueous solution) and water, dried (MgSO₄) and evaporated till dryness, yielding 0.11 g of intermediate (16).

Example A.8

a) Preparation of		intermediate (17)
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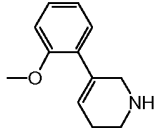
Reaction under N₂. BuLi (1.6M in hexane) (3.76 ml, 6.02 mmol) was added dropwise at -20°C to a solution of DIPA (0.846 ml, 6.02 mmol) in THF (10 ml) then the mixture was stirred at -20°C for 20 minutes. A solution of 1-N-Boc-3-piperidone (1.0 g, 5.02 mmol) in THF (10 ml) was then added at -78°C and the resulting mixture was stirred for 30 minutes at -78°C. A solution of 2-[N,N-bis(trifluoromethylsulfonyl)-amino]-5-chloropyridine (2.26 g, 5.52 mmol) in THF (5 ml) was added at -78°C then the mixture was allowed to reach room temperature and was stirred overnight. The reaction mixture was evaporated till dryness. The obtained residue was purified by normal phase on (silicagel, 450 g, 20-45μm, mobile phase (90% heptane, 10% AcOEt)). The desired fractions were collected and the solvent was evaporated, yielding 0.32 g of intermediate (17).

b) Preparation of		intermediate (18)
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Reaction under N₂. Microwave conditions : 80°C, 20 minutes. A solution of intermediate (17) (0.32 g, 0.966 mmol) and 2-methoxyphenylboronic acid (0.176 g,

1.16 mmol) in K_2CO_3 (2 M, 0.97 ml) and ethylene glycol dimethyl ether (3 ml) was purged with N_2 for 10 minutes then tetrakis(triphenylphosphine)palladium(0) (0.112 g, 0.097 mmol) was added. The mixture was irradiated following the microwave conditions above, cooled to room temperature, water and EtOAc were added, the organic layer was separated, washed with water then brine, dried ($MgSO_4$) and evaporated till dryness. Purification of the residue was carried out by flash chromatography over silica gel (10g, 15-40 μ m, heptane 100 to heptane/EtOAc 80/20). The pure fractions were collected and evaporated to dryness, yielding 0.22 g of intermediate (18).

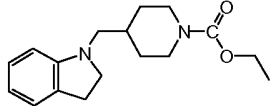
10

c) Preparation of		intermediate (19)
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A mixture of intermediate (18) (0.2 g, 0.76 mmol) and TFA (0.6 ml) in DCM (4 ml) was stirred at room temperature for 30 minutes then the reaction mixture was poured out into water and extracted with DCM. The organic layer was separated, washed with $NaHCO_3$ (10% aqueous solution) and water, dried ($MgSO_4$) and evaporated till dryness, yielding 0.13 g of intermediate (19).

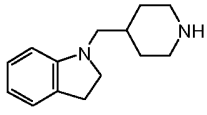
15

Example A.9

a) Preparation of		intermediate (20)
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A mixture of ethyl 4-formylpiperidine-1-carboxylate (0.10 mol) and 2,3-dihydro-1H-indole (0.10 mol) in methanol (250 ml) was hydrogenated at 50°C with Pd/C, 10% (3 g) as a catalyst in the presence of thiophene (4% solution, 2 ml). After uptake of hydrogen (1 equivalent), the catalyst was filtered off and the filtrate was evaporated, yielding 28 g of intermediate (20).

20

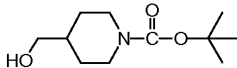
b) Preparation of	 .HCl	intermediate (21)
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A mixture of intermediate (20) (0.050 mol) and KOH (0.35 mol) in 2-propanol (150 ml) and H_2O (5 ml) was stirred and refluxed for 6 hours. The solvent was evaporated. Water was added to the residue and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent was evaporated. The residue was dissolved in 2-propanol and converted into the hydrochloric acid salt (1:2) with

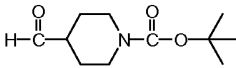
25

HCl/2-propanol. The precipitate was filtered off and dried, yielding 11.7 g of intermediate (21).

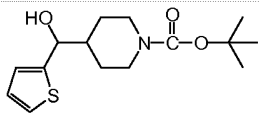
Example A.10

a) Preparation of		intermediate (22)
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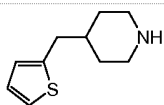
- 5 A solution of 4-piperidinemethanol (43.412 mmol) and di-*tert*-butyl dicarbonate (47.753 mmol) in CH₂Cl₂ (50 ml) was stirred at room temperature overnight. Water was added, the combined organic layer were washed with brine, dried (MgSO₄), and evaporated to give 10.61 g of intermediate (22).

b) Preparation of		intermediate (23)
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- 10 To methyl sulfoxide (86.766 mmol) in CH₂Cl₂ (43 ml) was added dropwise a solution of oxalyl chloride in CH₂Cl₂ (130 ml) at -70°C under N₂ then intermediate (22) (43.383 mmol) in CH₂Cl₂ (43 ml). The mixture was stirred for 15 minutes at -70°C. Triethyl-amine (216.914 mmol) was added dropwise. The mixture was stirred for 1 hour at -70°C and allowed to reach room temperature. The mixture was poured into water and extracted with CH₂Cl₂. The organic was washed with NaHCO₃, dried (MgSO₄), filtered and evaporated to dryness. Purification by chromatography : 90g of silica gel (15-40μm), eluent: CH₂Cl₂ (100%). The pure fractions were evaporated till dryness to give 8.18 g of intermediate (23).

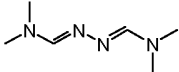
c) Preparation of		intermediate (24)
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- 20 2-Thienylmagnesium bromide in THF (50 mL, 50 mmol) was added dropwise to a solution of intermediate (23) (8.89 g, 41.68 mmol) in Et₂O (100 ml) cooled in a ice bath at 0°C and under a nitrogen atmosphere. The solution was stirred 2 hours at 0°C. An aqueous solution of NH₄Cl was added, the organic layer was extracted with DCM, dried (MgSO₄), filtered off and concentrated. The residue was purified by flash chromatography over silica gel (120 g, 15-40μm, heptane/EtOAc from 80/20 to 60/40).
- 25 Pure fractions were collected and concentrated to give 3.96 g of intermediate (24).

d) Preparation of		intermediate (25)
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Trifluoroacetic acid (8.81 ml, 114.32 mmol) was added dropwise to a solution of intermediate (24) (3.4 g, 11.43 mmol) and triethylsilane (18.21 ml, 114.32 mmol) in CH₂Cl₂ (35 ml). The resulting mixture was stirred at room temperature for 2 hours, and then K₂CO₃ (10% aqueous solution) was added. The organic layer was extracted with CH₂Cl₂, dried over magnesium sulfate, filtered and the solvent was evaporated to give a pale yellow oil. The reaction product was purified by flash chromatography over silica gel (90g, 15-40µm, CH₂Cl₂/MeOH/NH₄OH from 100/0/0 to 90/10/0.1). Pure fractions were collected and concentrated to give 1.12 g of intermediate (25).

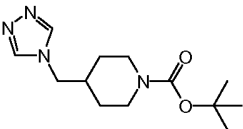
10 Example A.11

Preparation of		intermediate (26)
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Thionyl chloride (9 ml, 12.5 mmol) was added dropwise to 1,2-hydrazinedicarboxaldehyde (4.4 g, 50 mmol) in DMF (100 ml) at 10 °C. The mixture was stirred for 1.5 days and the precipitate was filtered off and washed with DMF (10 ml) and ether (10 ml). The solid was dried in vacuum, yielding 9.9 g of intermediate (26).

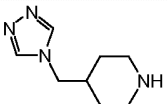
15

Example A.12

a) Preparation of		intermediate (27)
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A mixture of 4-aminomethyl-1-N-(tert-butoxycarbonyl)piperidine (3.5 mmol), intermediate (26) (4.2 mmol) and p-toluenesulphonic acid (catalytic quantity) in toluene (50 ml) was stirred and refluxed for 10 hours. After evaporation, the residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/MeOH 10/1). The product fraction were collected and the solvent was evaporated, yielding 0.46 g of intermediate (27).

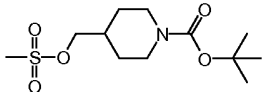
20

b) Preparation of		intermediate (28)
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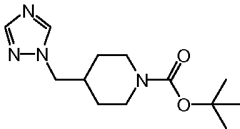
A mixture of intermediate (27) (0.3 g, 1.1 mmol) and TFA (1.25 g, 11 mmol) in DCM (20 ml) was stirred overnight. The solvent was evaporated. The residue was dissolved in water and adjust pH to 10 with Na₂CO₃ (aqueous solution). The mixture was extracted with CH₂Cl₂ (10 x 100 ml). The separated organic layer was dried (Na₂SO₄), filtered, and the solvent was evaporated to give 0.17 g of intermediate (28).

25

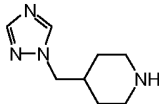
Example A.13

a) Preparation of		intermediate (29)
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To a solution of NaH (0.104 g, 2.6 mmol) in DMF (10 ml) was added drop wise a solution of 1*H*-1,2,4-triazole (0.207 g, 3 mmol) in DMF (5 ml) at room temperature. The resulting mixture was stirred for 30 minutes. Then intermediate (29) (0.587 g, 2 mmol) in DMF (5 ml) was added. The formed mixture was stirred for 5 hours at room temperature then heated at 80 °C overnight. The reaction mixture was cooled down at room temperature then treated with water (60 ml) and was extracted with EtOAc (3 x 40 ml). The combined organic layers were dried over Na₂SO₄, filtrated and the filtrate's solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: EtOAc). The product fraction were collected and the solvent was evaporated, yielding 0.42 g of intermediate (29).

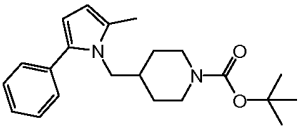
b) Preparation of		intermediate (30)
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To a mixture of intermediate (29) (2.15 g, 10 mmol) and triethylamine (1.52 g, 15 mmol) in CH₂Cl₂ (50 ml) was added drop wise methanesulfonyl chloride (1.37 g, 12 mmol) in a ice-water bath. After addition, the cooling bath was removed. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH₂Cl₂ (50 ml), then treated with brine (40 ml). The organic layer was separated, dried (Na₂SO₄), filtrated and the filtrate's solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: petroleum ether/EtOAc 1/1). The product fraction were collected and the solvent was evaporated, yielding 2.47 g of intermediate (30).

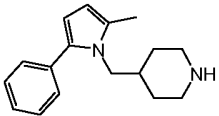
c) Preparation of		intermediate (31)
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The mixture of intermediate (30) (1.5 mmol), TFA (3 ml) and CH₂Cl₂ (20 ml) was stirred at room temperature overnight. The solvent was removed and the pH was adjusted to 8-10 with 2N NaOH and the reaction mixture was extracted with EtOAc (3 x 50ml), dried over anhydrous Na₂SO₄, then filtrated and concentrated to afford the product, yielding 0.13 g of intermediate (31).

Example A.14

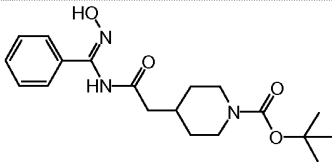
a) Preparation of		intermediate (32)
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- To a solution of NaH (0.104 g, 2.6 mmol) in DMF (10 ml) was added drop wise a solution of 2-methyl-5-phenyl-1*H*-pyrrole (0.472 g, 3 mmol) in DMF (5 ml) at room temperature. The resulting mixture was stirred for 30 minutes. Then intermediate (29) (0.587 g, 2 mmol) in DMF (5 ml) was added. The formed mixture was stirred for 5 hours at room temperature then heated at 80°C overnight. The reaction mixture was cooled down at room temperature then treated with water (60 ml). The water layer was extracted with EtOAc ₅ (3 x 40 ml). The combined organic layers were dried over Na₂SO₄, filtrated and the filtrate's solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: petroleum ether /EtOAc 10/1). The product fraction were collected and the solvent was evaporated, yielding 0.6 g of intermediate (32).

b) Preparation of		intermediate (33)
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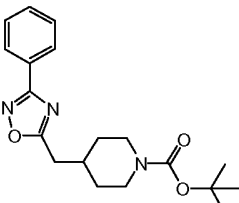
- To a solution of intermediate (32) (0.560 g, 1.57 mmol) in CH₃CN (5 ml) was added drop wise HCl (10 ml) at 0°C. After the addition, the mixture was refluxed for 1 hour. The reaction mixture was cooled to 0°C. Na₂CO₃ (8 g) was added. The mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic layer were dried over Na₂SO₄, filtrated and the filtrate's solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent : CH₂Cl₂/MeOH 20/1). The pure product fraction were collected and the solvent was evaporated, yielding 0.1 g of intermediate (33).

Example A.15

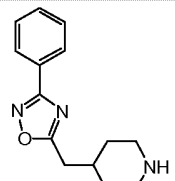
a) Preparation of		intermediate (34)
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- A mixture of 1-[(1,1-dimethylethoxy)carbonyl]-4-piperidineacetic acid (9.87 mmol), *N*-hydroxybenzenecarboximidamide (9.87 mmol), HATU (9.87 mmol) and DIPEA (20 mmol) in DCM (50 ml) was stirred at room temperature over night. NH₄Cl (50 ml) was added, the aqueous layer was extracted with CH₂Cl₂ (5 x 40 mL), the combined

organic layers were washed with saturated NaHCO_3 (90 ml) and brine (90 mm), dried over MgSO_4 and filtrated. The solvent was evaporated to give the product, yielding 1.92 g of intermediate.

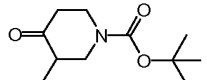
b) Preparation of		intermediate (35)
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- 5 A mixture of intermediate (34) (1.38 mmol), Burgess reagent (CAS 29684-56-8) (1.38 mmol) in THF (50 ml) under argon was stirred and refluxed overnight. The solvent was evaporated. The residue was dissolved in water and extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel
 10 (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10/1) to obtain 0.21 g of intermediate (35).

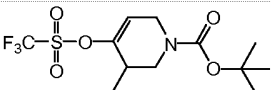
c) Preparation of		intermediate (36)
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- A mixture of intermediate (35) (0.3 g, 0.87mmol) and TFA (1 g, 8.7 mmol) in CH_2Cl_2 (20 ml) was stirred overnight. The solvent was evaporated. The residue was dissolved in water and adjusted pH to 10 with Na_2CO_3 . The mixture was extracted with CH_2Cl_2
 15 (10 x 100 ml). The separated organic layer was dried (Na_2SO_4), filtered, and the solvent was evaporated to give the product, yielding 0.14 g of intermediate (36).

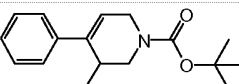
Example A.16

a) Preparation of		intermediate (37)
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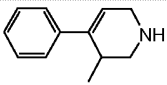
- A mixture of 1-benzyl-3-methyl-4-piperidone (2.0 g, 9.84 mmol), di-*tert*-butyl dicarbonate (2.36 g, 10.8 mmol) and Pearlman's catalyst (palladium(II)hydroxide) (0.35 g, 2.46 mmol) in EtOAc (50 ml) was hydrogenated (3 bar, room temperature)
 20 overnight in a Parr shaker. The reaction mixture was filtered through a short pad of celite, the cake was washed with EtOAc, the filtrate was washed with water then brine, dried (MgSO_4) and evaporated till dryness, yielding 2.2 g of intermediate (37).

b) Preparation of		intermediate (38)
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Reaction under N₂. BuLi (1.6M in hexane) (3.52 ml, 5.63 mmol) was added dropwise at -20°C to a solution of DIPA (0.791 ml, 5.63 mmol) in THF (8 ml) then the mixture was stirred at -20°C for 20 minutes. A solution of intermediate (37) (1.0 g, 4.70 mmol) in THF (10 ml) was then added at -78°C and the resulting mixture was stirred for 30 minutes at -78°C. A solution of *N*-phenyltrifluoromethanesulfonimide (1.92 g, 5.16 mmol) in THF (6 ml) was added at -78°C then the mixture was allowed to reach room temperature and was stirred overnight. The mixture was concentrated and purified by normal phase on (silicagel, 20-45μm, 450 g, mobile phase (80% heptane, 20% AcOEt)). The desired fractions were collected and the solvent was evaporated, yielding 1.7 g of intermediate (38).

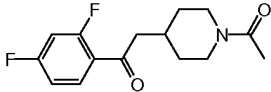
c) Preparation of		intermediate (39)
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Reaction under N₂. Microwave conditions : 80°C, 20 minutes. A solution of intermediate (38) (1.0 g, 1.45 mmol) and phenylboronic acid (0.194g, 1.59 mmol) in K₂CO₃ (1.45 ml) and ethylene glycol dimethyl ether (10 ml) was purged with N₂ for 10 minutes then tetrakis(triphenylphosphine)palladium(0) (0.167 g, 0.145 mmol) was added. The mixture was irradiated following the microwave conditions above, cooled to room temperature, water and EtOAc were added, the organic layer was separated, washed with water then brine, dried (MgSO₄) and evaporated till dryness, yielding 0.23 g of intermediate (39).

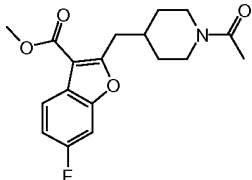
d) Preparation of		intermediate (40)
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A mixture of intermediate (39) (0.23 g, 0.841 mmol) and TFA (0.8 ml) in DCM (5 ml) was stirred at room temperature for 30 minutes then the reaction mixture was poured out into K₂CO₃ (10% aqueous solution) and extracted with DCM. The organic layer was separated, washed with water, dried (MgSO₄) and evaporated till dryness, yielding 0.143 g of intermediate (40).

Example A.17

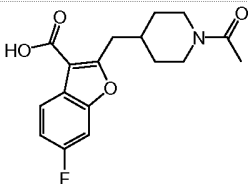
a) Preparation of		intermediate (41)
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- 1-Acetyl-4-piperidineacetic acid (1 mol) was stirred in 1,2-dichloroethane (1l) at room temperature, a solution of SOCl_2 (1.07 mol) in 1,2-dichloroethane (350 ml) was added dropwise over 30 minutes, then the reaction mixture was stirred and refluxed for 1.5
- 5 hour. After cooling, 1,3-difluorobenzene (1.2 mol) was added and AlCl_3 (288 g, 2.2 mol) was added dropwise. The reaction mixture was slowly brought to reflux, then stirred and refluxed for 2 hours. After cooling, the mixture was poured onto ice/ H_2O and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 600 ml). The organic layer was dried (MgSO_4), filtered and the solvent was evaporated.
- 10 The residue was stirred in DIPE at reflux, the DIPE was decanted off (4 x 500 ml) and the DIPE-layers were stirred overnight at room temperature. The precipitate was filtered off and dried in vacuum at 50°C . The obtained residue and the DIPE-filtrate were purified by column chromatography. The desired fractions were collected and the solvent was evaporated. The residue was crystallized from petroleum ether. The
- 15 precipitate was filtered off and dried in vacuum at 50°C , yielding 44.3 g of intermediate (41).

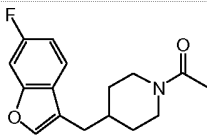
b) Preparation of		intermediate (42)
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- NaH (60%) (0.022 mol) was stirred in petroleum ether and then decanted (2 x). THF (40 ml) was added. A solution of methyl glycolate 98% (0.022 mol) in THF (40 ml)
- 20 was added dropwise (exothermic temperature rise to 26°C). The reaction mixture was stirred at room temperature for 2 hours. A solution of intermediate (41) (0.02 mol) in THF (40 ml) was added dropwise at $20^\circ\text{C}/25^\circ\text{C}$. The reaction mixture was stirred and refluxed for 20 hours, giving reaction mixture (I). NaH (60%) was stirred twice in petroleum ether and decanted twice. THF (40 ml) was added. Methyl glycolate 98% in
- 25 THF (40 ml) was added and the reaction mixture was stirred and refluxed for one hour, giving reaction mixture (II). Reaction mixture (I) was added and the whole was stirred and refluxed for another 24 hours. The mixture was cooled and the solvent was evaporated. The residue was partitioned between water and CH_2Cl_2 . The layers were separated. The aqueous layer was extracted with CH_2Cl_2 . The organic layer was

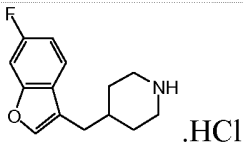
separated, dried (MgSO₄), filtered and the solvent was evaporated, yielding 6.2 g of intermediate (42).

c) Preparation of		intermediate (43)
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- 5 A solution of NaOH (0.038 mol) in H₂O (50 ml) was added to a solution of intermediate (42) (0.0186 mol) in MeOH (10 ml). The reaction mixture was stirred overnight at room temperature. Water (150 ml) was added, resulting in complete dissolution. The mixture was washed with CH₂Cl₂. The aqueous phase was acidified with concentrated hydrochloric acid, and this mixture was extracted three times with CH₂Cl₂. The organic layer was separated, dried (MgSO₄), filtered and the solvent was
- 10 evaporated, yielding 5.1 g of intermediate (43).

d) Preparation of		intermediate (44)
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- A mixture of intermediate (43) (0.016 mol) and Cu, powder (0.8 g) in quinoline (50 ml) was stirred for one hour at 210°C/220°C. The reaction mixture was cooled and the precipitate was filtered off. CH₂Cl₂ (100 ml) was added to the filtrate. The organic
- 15 phase was washed twice with HCl (20%, 200 ml), once with water, once with NaOH (10% aqueous solution), and again with water, dried (MgSO₄), filtered and the solvent was evaporated, yielding 3.4 g of intermediate (44).

e) Preparation of		intermediate (45)
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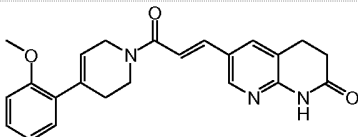
- A mixture of intermediate (44) (0.012 mol) in EtOH (20 ml) and HCl conc. (56 ml) was stirred and refluxed overnight. The reaction mixture was cooled and the solvent was
- 20 evaporated. The residue was dissolved in 2-propanone (15 ml), stirred at room temperature and the resulting precipitate was filtered off, stirred in CH₃CN, filtered off, washed with DIPE, then dried (vacuum, 100 °C), yielding: 2.06 g of intermediate (45).

- 25 Some intermediate compounds used in the preparation of the final compounds are commercially available such as 1,2,3,6-tetrahydro-4-(2-methoxyphenyl)-pyridine,

3-phenoxy piperidine, 1,2,3,4-tetrahydroisoquinoline, 4-phenyl piperidine,
 3-(4-piperidinyl)-phenol, phenyl-4-piperidinyl-methanone hydrochloride,
 1,2,3,6-tetrahydro-4-phenyl-pyridine, 4-(4-chlorophenyl)-4-piperidinol,
 4-benzyl piperidine, 4-(2-methoxyphenyl)-piperidine, 2-(4-piperidinylmethyl)-
 5 benzothiazole, 1,2,3,6-tetrahydropyridine, 4-(2-chlorophenyl)-1,2,3,6-tetrahydro-
 pyridine, 1',2',3',6'-tetrahydro-3,4'-bipyridine, 1,2,3,6-tetrahydro-4-[3-(trifluoromethyl)-
 phenyl]-pyridine, 1,2,3,6-tetrahydro-4-(3-methoxyphenyl)-pyridine, 1,2,3,6-tetrahydro-
 4-(4-methoxyphenyl)-pyridine, 1-(phenylmethyl)-piperazine, 1-phenylpiperazine,
 piperidine, 4-phenoxy-piperidine, 4-(2-phenoxy-ethyl)-piperidine hydrochloride,
 10 4-[2-(4-fluorophenoxy)ethyl]-piperidine hydrochloride, 4-[(4-fluorophenoxy)-methyl]-
 piperidine hydrochloride, 4-(phenyl-methyl)-piperidine, 1-(4-piperidinyl-methyl)-1*H*-
 indole, 2-(4-piperidinylmethyl)-quinoline.

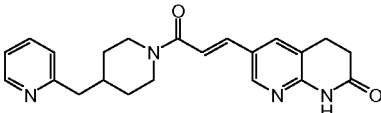
B. Synthesis of the final compounds

15 Example B.1

Preparation of		compound (2)
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A mixture of intermediate (2) (0.6 g, 1.81 mmol), 1,2,3,6-tetrahydro-4-(2-methoxy-
 phenyl)pyridine (0.0.479 g, 2.53 mmol), HOBT (0.293 g, 2.17 mmol), EDCI (0.415 g,
 2.17 mmol) and Et₃N (0.60 ml, 4.33 mmol) in DCM (12ml) and THF (12ml) was
 stirred for 24 hours at room temperature. water and DCM were added, the organic layer
 20 was separated, washed with water, dried (MgSO₄) and evaporated till dryness. The
 residue was crystallized from EtOH to give 0.47 g of compound (2).

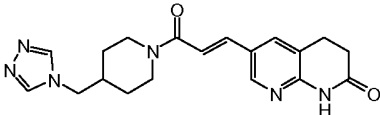
Example B.2

Preparation of		compound (35)
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2-(Pyridinylmethyl)piperidine (0.12 g, 0.72 mmol), intermediate (2) (0.17 g,
 25 0.80-mmol), EDCI (0.14 g, 0.72 mmol), HOBT (0.10 g, 10.72 mmol) and DIPEA
 (0.28-g, 2.16 mmol) in CH₂Cl₂ (50 ml) were stirred at room temperature overnight.
 The saturated NH₄Cl (50 ml) was added, the aqueous layer was extracted with CH₂Cl₂
 (2 x 20 ml). The combined organic layers were washed by NaHCO₃ (30 ml) and brine
 (30 ml), dried over MgSO₄, purified by column chromatography (eluent:

CH₂Cl₂/MeOH 20/1). The desired product fractions were collected and the solvent was evaporated, yielding 0.120 g of compound (35).

Example B.3

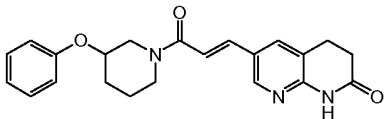
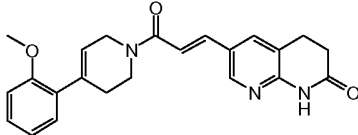
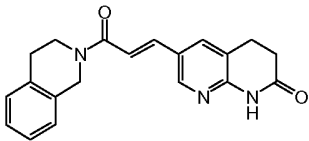
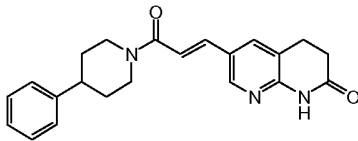
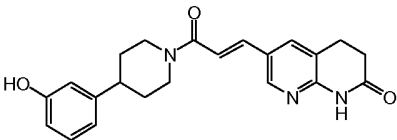
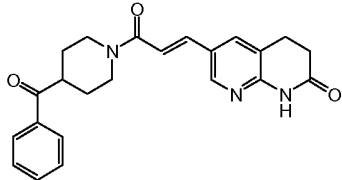
Preparation of		compound (38)
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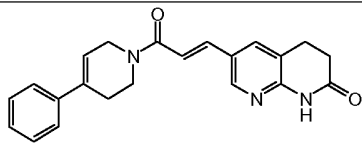
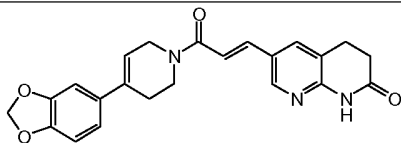
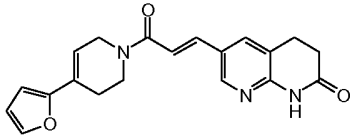
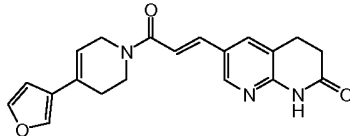
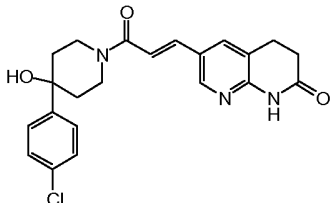
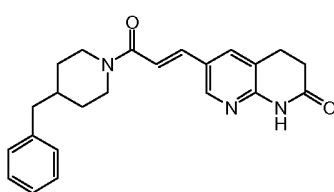
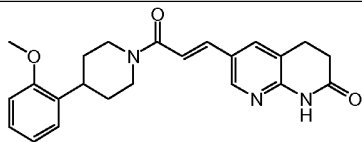
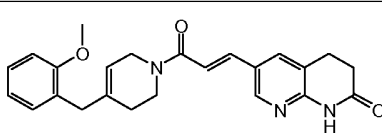
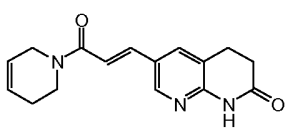
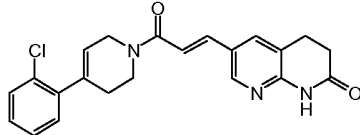
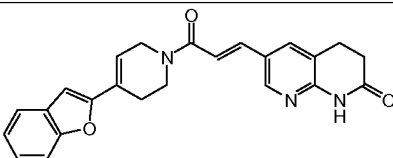
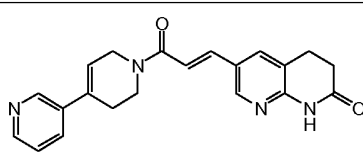
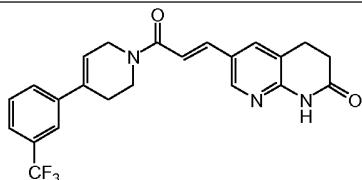
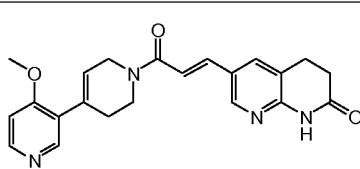
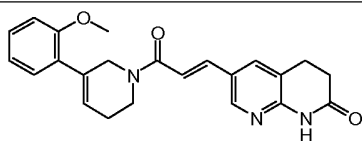
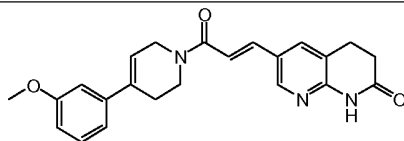
- 5 A solution of intermediate (28) (0.17 g, 1.12 mmol), intermediate (2) (0.24 g, 1.12 mmol), HATU (0.426 g, 1.12 mmol) and DIPEA (0.263 g, 2.04 mmol) in CH₂Cl₂ (50 ml) was stirred at room temperature overnight. The saturated NH₄Cl (50 ml) was added, the aqueous layer was extracted with CH₂Cl₂ (2 x 20 ml), washed with NaHCO₃ (30 ml) and brine (30 ml), dried (MgSO₄), purified by column chromatography over
 10 silica gel (eluent: CH₂Cl₂/MeOH 10/1). The product fractions were collected and the solvent was evaporated, yielding 20 mg of compound (38).

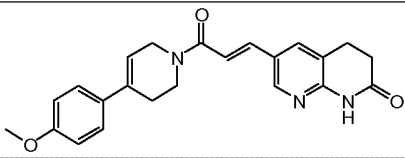
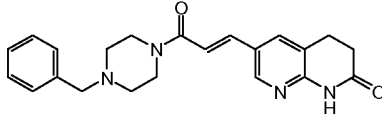
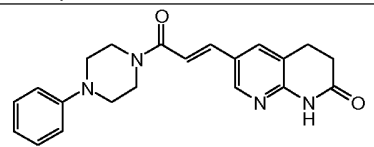
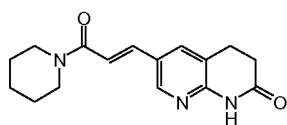
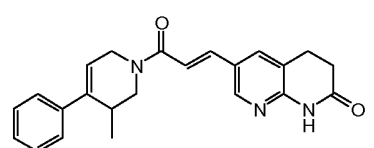
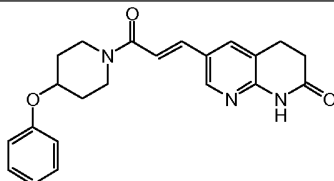
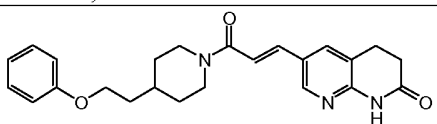
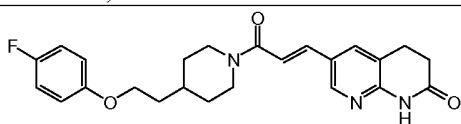
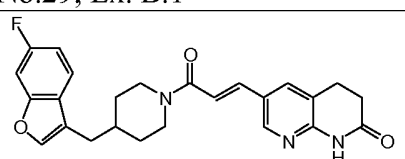
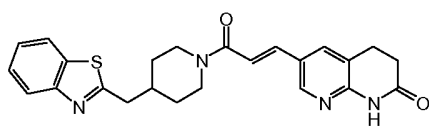
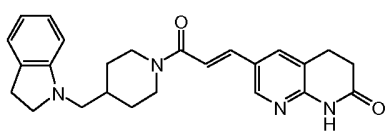
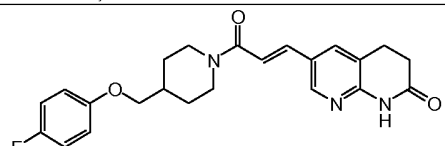
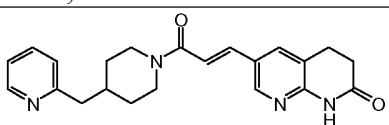
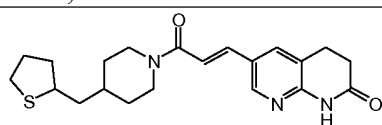
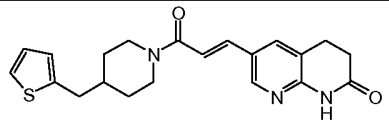
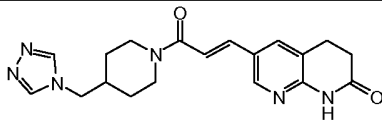
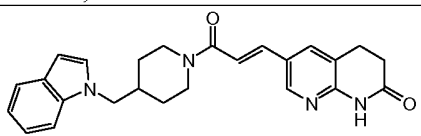
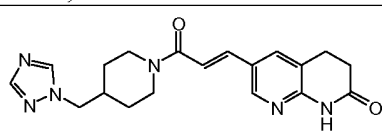
Table F-1 lists the compounds that were prepared according to one of the above Examples.

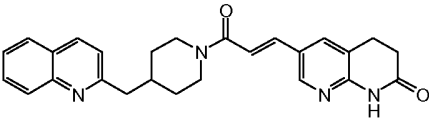
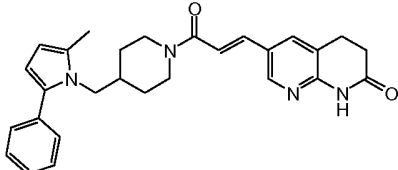
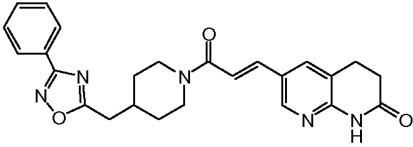
15

Table F-1

	
Co. No.1; Ex. B.1	Co. No.2; Ex. B.1
	
Co. No.3; Ex. B.1	Co. No.4; Ex. B.1
	
Co. No.5; Ex. B.1	Co. No.6; Ex. B.1

	
Co. No.7; Ex. B.1	Co. No.8; Ex. B.1
	
Co. No.9; Ex. B.1	Co. No.10; Ex. B.1
	
Co. No.11; Ex. B.1	Co. No.12; Ex. B.1
	
Co. No.13; Ex. B.1	Co. No.14; Ex. B.1
	
Co. No.15; Ex. B.1	Co. No.16; Ex. B.1
	
Co. No.17; Ex. B.1	Co. No.18; Ex. B.1
	
Co. No.19; Ex. B.1	Co. No.20; Ex. B.1
	
Co. No.21; Ex. B.1	Co. No.22; Ex. B.1

	
Co. No.23; Ex. B.1	Co. No.24; Ex. B.1
	
Co. No.25; Ex. B.1	Co. No.26; Ex. B.1
	
Co. No.27; Ex. B.1	Co. No.28; Ex. B.1
	
Co. No.29; Ex. B.1	Co. No.30; Ex. B.1
	
Co. No.31; Ex. B.1	Co. No.32; Ex. B.1
	
Co. No.33; Ex. B.1	Co. No.34; Ex. B.1
	
Co. No.35; Ex. B.2	Co. No.36; Ex. B.2
	
Co. No.37; Ex. B.1	Co. No.38; Ex. B.3
	
Co. No.39; Ex. B.2	Co. No.40; Ex. B.3

	
Co. No.41; Ex. B.3	Co. No.42; Ex. B.3
	
Co. No.43; Ex. B.3	

C. Compound identification

C1. LCMS

For LCMS-characterization of the compounds of the present invention, the following
5 methods were used.

General procedure A

The LC measurement was performed using a UPLC (Ultra Performance Liquid
Chromatography) Acquity (Waters) system comprising a binary pump with degasser,
10 an autosampler, a diode-array detector (DAD) and a column as specified in the
respective methods below, the column is hold at a temperature of 40°C. Flow from the
column was brought to a MS detector. The MS detector was configured with an
electrospray ionization source. The capillary needle voltage was 3 kV and the source
temperature was maintained at 130°C on the Quattro (triple quadrupole mass
15 spectrometer from Waters). Nitrogen was used as the nebulizer gas. Data acquisition
was performed with a Waters-Micromass MassLynx-Openlynx data system.

General procedure B

The HPLC measurement was performed using an Alliance HT 2795 (Waters) system
20 comprising a quaternary pump with degasser, an autosampler, a diode-array detector
(DAD) and a column as specified in the respective methods below, the column is hold
at a temperature of 30°C. Flow from the column was split to a MS spectrometer. The
MS detector was configured with an electrospray ionization source. The capillary
needle voltage was 3 kV and the source temperature was maintained at 100 °C on the
25 LCT (Time of Flight Zspray™ mass spectrometer from Waters. Nitrogen was used as
the nebulizer gas. Data acquisition was performed with a Waters-Micromass
MassLynx-Openlynx data system.

Method 1

In addition to the general procedure A : reversed phase UPLC was carried out on a Waters Acquity BEH (bridged ethylsiloxane/silica hybrid) C18 column (1.7 μm , 2.1 x 100 mm) with a flow rate of 0.35 ml/min. Two mobile phases (mobile phase A: 95 % 7 mM ammonium acetate / 5 % acetonitrile; mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 90 % A and 10 % B (hold for 0.5 minutes) to 8 % A and 92 % B in 3.5 minutes, hold for 2 min and back to the initial conditions in 0.5 min, hold for 1.5 minutes. An injection volume of 2 μl was used. Cone voltage was 20 V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.2 seconds using an interscan delay of 0.1 seconds.

Method 2

In addition to the general procedure A : reversed phase UPLC was carried out on a Waters Acquity BEH (bridged ethylsiloxane/silica hybrid) C18 column (1.7 μm , 2.1 x 100 mm) with a flow rate of 0.343 ml/min. Two mobile phases (mobile phase A: 95 % 7 mM ammonium acetate / 5 % acetonitrile; mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 84.2 % A and 15.8 % B (hold for 0.49 minutes) to 10.5 % A and 89.5 % B in 2.18 minutes, hold for 1.94 min and back to the initial conditions in 0.73 min, hold for 0.73 minutes. An injection volume of 2 μl was used. Cone voltage was 20V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.2 seconds using an interscan delay of 0.1 seconds.

Method 3

In addition to the general procedure B : reversed phase HPLC was carried out on a Waters X-bridge C18 column (3.5 μm , 4.6 x 100 mm) with a flow rate of 0.8 ml/min. Two mobile phases (mobile phase A: 100 % 7 mM ammonium acetate; mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 80 % A and 20 % B (hold for 0.5 minute) to 90 % B in 4.5 minutes, 90 % B for 4 minutes and reequilibrated with initial conditions for 3 minutes. An injection volume of 5 μl was used. Cone voltage was 20 V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.4 seconds using an interscan delay of 0.3 seconds.

Table C.1 : LC/MS data

Co. No.	Rt (min)	MH ⁺	LC/MS Method
12	2	390	2
15	1.85	325	2
17	3.46	404	1
19	2.66	432	2
21	3.46	400	1
26	2.4	326	3
31	2.33	361	1
39	2.57	417	2

C2. Melting points

- 5 For a number of compounds, melting points were obtained with a Kofler hot bench, consisting of a heated plate with linear temperature gradient, a sliding pointer and a temperature scale in degrees Celsius.

- For a number of compounds, melting points were determined using differential scanning calorimetry (DSC). Melting points were measured with a temperature
 10 gradient of 10 °C/minute. Maximum temperature was 400 °C.

The remaining melting points were determined using open capillary tubes.

Table C.2 : melting point data

Co. No.	Melting Moint	Method	Co. No.	Melting Moint	Method
1	76-77°C	-	23	258°C	Kofler
2	216.59°C	DSC	24	160°C	Kofler
3	278.46°C	DSC	25	151°C	Kofler
4	127.5-128.5°C	-	27	252°C	Kofler
5	114°C	Kofler	28	242.08°C	DSC
6	>260°C	Kofler	29	202.49°C	DSC
7	>260°C	Kofler	30	138°C	Kofler
8	133°C	Kofler	32	137-138°C	-
9	202.43°C	DSC	34	161.93°C	DSC
10	69.5-71°C	-	35	269.90°C	DSC
11	172°C	Kofler	36	187-188°C	Kofler

Co. No.	Melting Moint	Method	Co. No.	Melting Moint	Method
13	240°C	Kofler	37	177-178°C	-
14	225.34°C	DSC	38	165°C	Kofler
16	101.6-103.2°C	-	40	208°C	Kofler
18	196°C	Kofler	41	170.15°C	DSC
20	>260°C	Kofler	42	93-95°C	-
22	260°C	Kofler	43	180°C	Kofler

D. Pharmacological examples

D.1 FabI enzyme inhibition : *Staphylococcus aureus* FabI enzyme inhibition assay.

- FabI enzyme inhibition assays were carried out in half-area, 384-well microtitre plates.
- 5 Compounds were evaluated in 40- μ l assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-[2-acetamido]-2iminodiacetic acid), 250 μ M crotonoyl-CoA, 625 μ M NADH and 50 μ g/ml *S. aureus* ATCC 29213 FabI. Inhibitors were typically varied over the range of 50 to 0.39 μ M. The reaction mixtures were incubated for 30 minutes at room temperature and the reaction was stopped by adding 200 mM Tris buffer (pH
- 10 9.0) to create a pH-shift. The consumption of NADH was monitored by measuring the change in absorbance at 340. By comparing sample readings to those of negative (absence of compound) and positive (absence of enzyme) controls, the percent inhibition of enzymatic activity of the compounds was determined. A best-fit curve is fitted by a minimum of squares method. From this an IC₅₀-value (expressed in μ g/ml),
- 15 resulting in 50% inhibition of enzymatic activity, was obtained.

Table D.1 : *S. aureus* FabI IC₅₀ values

Co. No.	FabI IC ₅₀ μ g/mL	Co. No.	FabI IC ₅₀ μ g/mL
1	3.52	22	0.93
2	0.32	23	0.85
3	0.48	24	7.17
4	0.29	25	1.48
5	0.35	26	2.73
6	1.74	27	0.57
7	0.41	28	0.93
8	0.53	29	1.00
9	0.34	30	1.34
10	0.48	31	0.79

Co. No.	FabI IC ₅₀ µg/mL	Co. No.	FabI IC ₅₀ µg/mL
11	0.80	32	1.72
12	0.31	34	0.47
13	0.53	35	0.48
14	1.06	36	0.61
15	3.57	37	0.50
16	0.58	38	> 7.31
17	1.91	39	2.74
18	0.67	40	1.43
19	1.12	41	3.39
20	0.78	42	10.18
21	0.80		

D.2 In vitro method for testing compounds for antibacterial activity against various bacterial strains

Preparation of bacterial suspensions for susceptibility testing

- 5 The following bacteria were used: *Staphylococcus aureus* ATCC 29213, methicillin-resistant *Staphylococcus aureus* (MRSA) ATCC 700788 and *Escherichia coli* ATCC 35218. The bacteria used in this study were grown overnight in flasks containing 100 ml Mueller-Hinton broth (Difco cat. nr. 0757-17) in sterile de-ionized water, with shaking, at 37°C. Stocks were store at -70°C until use.
- 10 Bacteria were incubated on a tryptic soy agar plate containing 5% sheep blood (Becton Dickinson cat. nr. 254053) for 18-24 hours at 35°C in aerobic conditions (first passage). For the second passage, fresh Mueller-Hinton broth is inoculated with 5-10 colonies and grown overnight at 35°C until turbidity (reaching log-phase) in aerobic conditions is reached. The bacterial suspension is then adjusted to 0.5 McFarland
- 15 density and further diluted 1:100 in Mueller Hinton broth medium. This is used as inoculum.

The results (for STA ATCC 29213) are depicted in the table D2 below.

20 ***Antibacterial susceptibility testing: IC₉₀ determination***

MIC assays were performed by the broth microdilution method in a 96-well format (flat-bottom microtitre plates) with a final volume of 0.1 ml Mueller Hinton broth containing two-fold serial dilutions of compounds and inoculated with 5×10^5 CFU/ml of bacteria (standard inoculum size according to CLSI guidelines). Inhibitors are

typically varied over the range of 63 to 0.49 μ M. The final DMSO concentration in the assay was 1.25 % (maximum tolerable DMSO concentration = 6%). In the assays where the effect of human serum on the activity of the compounds against *S. aureus* was tested, human serum was added at a final concentration of 10 %. The plates were incubated at 35°C for 16-20 hours. At the end of incubation the bacterial growth was quantified fluorometrically. For this, resazurin was added to all wells and the plates were re-incubated. The incubation time is dependent on the type of bacteria. A change in color from blue to pink indicated the growth of bacteria. The fluorescence was read in computer-controlled fluorometer (Fluoroskan Ascent FL, Labsystems) at an excitation wavelength 540 nm and an emission wavelength of 590 nm. The % growth inhibition achieved by the compounds was calculated according to standard methods. The IC₉₀ (expressed in μ g/ml) was defined as the 90% inhibitory concentration for bacterial growth. A panel of reference compounds were simultaneously tested for QC approval.

The results are depicted in the table D2 below (STA + 10% HS).

Cytotoxicity Assays

Cytotoxicity of the compounds was evaluated using the MTT assay. Human HeLaM cells grown in 96-well plates were exposed to serial dilutions of the tested compounds (final volume of 0.2 ml) and incubated for 72 hours at 37°C and 5% CO₂. Inhibitors are typically varied over the range of 25 to 0.8 μ M. The final DMSO concentration in the assay is 0.5 %. MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole) was added and reduced to purple formazan only in living cells. Solubilization of the formazan crystals was achieved by adding 100 μ l 2-propanol. Cell viability was determined by measuring the absorbance of the reduced formazan, giving a purple color, at 540 nm and 690 nm. The absorbance measured at 690 nm was automatically subtracted from the absorbance at 540 nm, to eliminate the effects of non-specific absorption. The percent cytotoxicity achieved by the compounds was calculated according to standard methods. Cytotoxicity is reported as CC₅₀, the concentration that causes a 50% reduction in cell viability.

The results are depicted in the table D2 below (TOX HELAM).

Table D2 – data for representative examples

Cpd. No.	STA (361.159) IC90 µg/mL	STA + 10% HS (361.169) IC90 µg/mL	TOX HELAM (222.125) CC50 µg/mL
2	1.97	2.99	>9.78279
3	8.67	10.79	>8.37438
4	4.99	4.60	>9.07922
5	10.52	11.14	>9.48112
7	2.07	2.54	>9.02848
9	2.91	2.65	>8.77628
10	10.43	20.34	>8.77628
12	1.19	2.09	>9.43139
14	6.93	13.06	>10.1352
16	3.31	8.52	8.04
20	13.23	16.85	>9.80766
22	21.16	>24.5733	>9.78279
27	6.13	21.99	>9.38089
34	9.94	12.51	>10.2852
35	5.14	3.94	>9.45625
36	8.43	11.38	>9.68408
37	0.30	0.36	19.12

Example E5 **E.1 Thermodynamic Solubility/Solubility in Aqueous Solution**

The pH solubility profiling was carried out at ambient temperature for a period of 4 days. A saturation solubility study was carried out in order to determine maximum solubility in a particular buffer solution. The compound was added to respective buffer solution until saturation point is reached. This was followed by shaking the flask for 4

10 days at ambient temperature. After 4 days, the solutions were filtered and injected on UPLC and the concentration was determined using a generic HPLC method.

Results

	Co. No. 37
Buffer pH 2	<0.01
10% HP-β-CD buffer pH 2	NT
20% HP-β-CD buffer pH 2	NT
Buffer pH 4	<0.01
10% HP-β-CD buffer pH 4	0.63
20% HP-β-CD buffer pH 4	>1.202
Buffer pH 7.4	<0.01
10% HP-β-CD buffer pH 7.4	0.73
20% HP-β-CD buffer pH 7.4	>1.316

NT = not tested

5 E.2 Antimicrobial Spectrum of Activity

Minimum Inhibitory Concentrations (MICs) were determined in accordance with the Clinical and Laboratory Standards Institute (CLSI) methodology against aerobic bacteria (CLSI M07-A8) (see Clinical and Laboratory Standards Institute. 2009.

Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. CLSI document M07-A8, Vol. 29, No. 2.) by the broth microdilution method with cation-adjusted Mueller-Hinton broth (CA-MHB) medium for the majority of organisms, except for *Haemophilus influenza*, where Haemophilis test medium (HTM) broth was used. Descriptions of the individual organisms can be found in the table. Where possible, ATCC standard strains were tested.

The inoculum density for the susceptibility testing was standardized to give a final inoculum of approximately 5×10^5 CFU/mL. The broth MIC was determined as the lowest concentration of drug that prevented visible growth after 16-24 hours (species dependent) of incubation at 35°C-37°C.

20 Table: Description of individual organisms tested

Organism	Characteristics	MIC test medium
<i>Staphylococcus aureus</i>	ATCC 29213; reference strain MSSA	MHB
<i>Staphylococcus aureus</i>	ATCC 43300; reference strain MRSA	MHB
<i>Staphylococcus aureus</i>	NRS119; LZD-R; SCCmec IV; origin: US	MHB
<i>Staphylococcus aureus</i>	NRS120; LZD-R; SCCmec IV; origin: US	MHB

Organism	Characteristics	MIC test medium
<i>Staphylococcus aureus</i>	NRS121; LZD-R; SCCmec IV; origin: US	MHB
<i>Escherichia coli</i>	ATCC 25922; reference strain	MHB
<i>Escherichia coli</i>	Tol C mutant	MHB
<i>Haemophilus influenzae</i>	ATCC 49247; reference strain	HTM broth
<i>Moraxella catarrhalis</i>	ATCC 8176; b-lactamase negative	MHB

Stock solutions of the compounds were prepared in DMSO at concentrations of 1 mg/mL. Linezolid was prepared in DMSO at a concentration of 2 mg/mL. Stock solutions of all compounds were diluted into CA-MHB to give a range of two-fold dilutions, depending upon the sensitivity of the organism being tested.

Results (where available)

Organism	Compound No. and MIC ₉₀ (µg/ml)
	37
S.aureus ATCC 29213	0.125
S.aureus ATCC 43300	0.125
S.aureus NRS119	0.125
S.aureus NRS120	0.125
S.aureus NRS121	0.125
E. coli tolC mutant	>8
E. coli ATCC 25922	>8
H. influenza ATCC 49247	>8
M. catarrhalis ATCC 8176	1

E.3 In Vivo Pharmacokinetic and Oral Bioavailability

The in vivo pharmacokinetics and oral bioavailability of the compound of the examples was/is investigated in male Swiss mice (fed) following single intravenous (i.v.) bolus and oral (p.o.) administration. For the i.v. and p.o. solution formulations, the compound was/is dissolved in a 20% HP-β-CD solution. The pH of the formulations was/is around pH 4. All i.v. formulations were isotonic.

Results

	Co. No. 37
i.v.	
Dose (mg/kg)	2.5
n	3
C₀ (ng/mL)	2929
Plasma clearance Cl (L/h/kg)	0.33
Vd_z (L/kg)	1.3
AUC_{0-inf} (ng.h/mL)	7464
Half life (t_{1/2}) (h)	2.7
p.o.	
Dose (mg/kg)	10
n	3
C_{max} (ng/mL)	2950
T_{max} (h)	2.0
AUC_{0-inf} (ng.h/mL)	21394
Half life (t_{1/2}) (h)	3.2
Oral bioavailability (%)	72

E.4 In Vivo Efficacy

5 The concept of studying the in vivo effect of an antibacterial compound by treating intraperitoneally infected mice was introduced in 1911 for optochin against pneumococci (Morgenroth and Levy, 1911). The popularity of the model comes from the ease of its use with short-duration experiments, reproducible infections and simple end-points.

10 Method

Methicillin-sensitive *S. aureus* strain ATCC 29213 is used to infect female Swiss albino mice. A Brain Heart Infusion (BHI) broth bacterial culture is inoculated the day before infection, incubated at 37°C overnight and diluted in fresh BHI broth to the desired concentration. Intraperitoneal (i.p.) injection of $\sim 5 \times 10^9$ colony forming units (CFU) is performed in either of the lateral lower quadrants of the abdomen. After inoculation,

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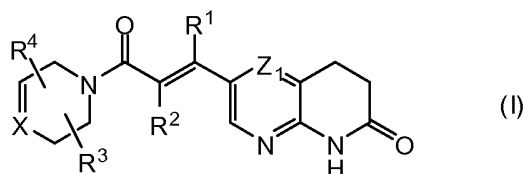
- mice are kept in their cages under daily observation for development of signs of infection or death. For the treatment of mice, both the p.o. and i.v. routes may be used and each mouse is treated individually by gavage or by i.v. injection. Both solutions and suspensions are tested in this model. The parameter used for monitoring the course of infection and the effect of treatment is death or survival of the animals over 3 days post-infection. As death could also be due to toxic side effects, a non-infected control group of 3 mice, treated with the highest dose of the compound tested, is included.

Results

- Compounds of the invention/examples display good *in vivo* efficacy properties, for instance compounds may exhibit such properties as measured by % survival (following the above test).

Claims

1. A compound of formula (I)



characterised in that:

X represents C and the $\text{---}=\text{---}$ bond represents a double bond; or

X represents N and the $\text{---}\text{---}$ bond represents a single bond;

and wherein

Z₁ represents CH or N;

R¹ is hydrogen, C₁₋₄alkyl or halo;

R² is hydrogen, C₁₋₄alkyl or halo;

R³ is hydrogen, C₁₋₆alkyl, hydroxy or halo;

R⁴ is hydrogen, C₁₋₆alkyl, halo, aryl, aryloxy, arylcarbonyl, heteroaryl, C₁₋₆alkyl substituted with aryl or aryloxy, or C₁₋₆alkyl substituted with heteroaryl;

and when the substituents R³ and R⁴ are located on adjacent positions said R³ and R⁴ may be taken together to form a radical of formula =CH-CH=CH-CH= with the proviso that X represents carbon and the $\text{---}\text{---}$ bond represents a single bond;

aryl is phenyl; phenyl substituted with one, two or three substituents each individually selected from halo, hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, polyhaloC₁₋₄alkyl, polyhaloC₁₋₄alkyloxy, cyano, nitro, and amino;

heteroaryl is furanyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, thiazolyl, triazolyl, tetrazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzo[1,3]dioxolyl, benzofuranyl, benzothiazolyl, indolyl, 2,3-dihydro-1H-indolyl, tetrahydrothiophenyl, or quinolinyl;

wherein each heteroaryl may be substituted with one or two substituents each independently selected from halo, cyano, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, or phenyl;

or a pharmaceutically acceptable acid addition salt thereof.

2. The compound as claimed in claim 1 wherein:

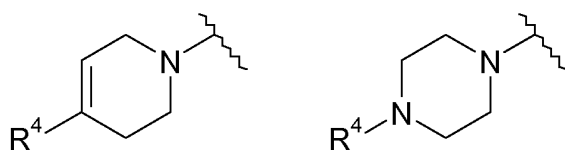
Z_1 represents CH;

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

R^2 is hydrogen or C_{1-4} alkyl.

5

3. The compound as claimed in claim 1 or claim 2 where the X-containing ring represents:



10

4. The compound as claimed in any one of claims 1 to 3 wherein R^1 is hydrogen and R^2 is hydrogen.

5. The compound as claimed in any one of claims 1 to 4 wherein R^3 represents hydrogen.

15

6. The compound as claimed in any one of claims 1 to 5 wherein R^4 is aryl.

7. The compound as claimed in any one of claims 1 to 5 wherein R^4 is heteroaryl.

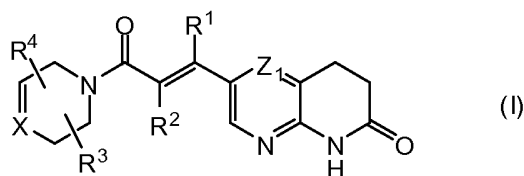
20

8. The compound as claimed in any one of claims 1 to 5 wherein R^4 is C_{1-6} alkyl substituted with aryl.

9. The compound as claimed in any one of claims 1 to 8 wherein X represents nitrogen and the --- bond represents a single bond.

25

10. A compound of formula (I)



(I)

30

wherein

the --- bond represents a single bond or a double bond;

X represents carbon or nitrogen, and when X represents nitrogen then the --- bond represents a single bond;

Z_1 represents CH or N;

5 R^1 is hydrogen, C_{1-4} alkyl or halo;

R^2 is hydrogen, C_{1-4} alkyl or halo;

R^3 is hydrogen, C_{1-6} alkyl, hydroxy or halo;

R^4 is hydrogen, C_{1-6} alkyl, halo, aryl, aryloxy, arylcarbonyl, heteroaryl, C_{1-6} alkyl substituted with aryl or aryloxy, or C_{1-6} alkyl substituted with heteroaryl;

10 and when the substituents R^3 and R^4 are located on adjacent positions said R^3 and R^4 may be taken together to form a radical of formula =CH-CH=CH-CH= with the proviso that X represents carbon and the --- bond represents a single bond;

aryl is phenyl; phenyl substituted with one, two or three substituents each individually selected from halo, hydroxy, C_{1-4} alkyl, C_{1-4} alkyloxy,

15 polyhalo C_{1-4} alkyl, polyhalo C_{1-4} alkyloxy, cyano, nitro, and amino;

heteroaryl is furanyl, thiophenyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, thiazolyl, triazolyl, tetrazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzo[1,3]dioxolyl, benzofuranyl, benzothiazolyl, indolyl, 2,3-dihydro-1H-indolyl, tetrahydrothiophenyl, or quinolinyl;

20 wherein each heteroaryl may be substituted with one or two substituents each independently selected from halo, cyano, C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, or phenyl;

or a pharmaceutically acceptable acid addition salt thereof.

25

11. The compound as claimed in claim 10 wherein:

Z_1 represents CH;

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

R^2 is hydrogen or C_{1-4} alkyl.

30

12. The compound as claimed in claim 10 or claim 11 (or, where appropriate, any one of claims 1 to 9) wherein

the --- bond represents a single bond or a double bond;

X represents carbon or nitrogen, and when X represents nitrogen then the ---

35 bond represents a single bond;

R^1 is hydrogen;

R^2 is hydrogen;

R³ is hydrogen, C₁₋₆alkyl, or hydroxy;

R⁴ is hydrogen, aryl, aryloxy, arylcarbonyl, heteroaryl, C₁₋₆alkyl substituted with aryl or aryloxy, or C₁₋₆alkyl substituted with heteroaryl;

and when the substituents R³ and R⁴ are located on adjacent positions said R³ and R⁴ may be taken together to form a radical of formula =CH-CH=CH-CH= with the proviso that X represents carbon and the --- bond represents a single bond;

aryl is phenyl; phenyl substituted with one substituent selected from halo, hydroxy, C₁₋₄alkyloxy, or polyhaloC₁₋₄alkyl;

heteroaryl is furanyl, thiophenyl, pyrrolyl, triazolyl, oxadiazolyl, pyridinyl, benzo[1,3]dioxolyl, benzofuranyl, benzothiazolyl, indolyl, 2,3-dihydro-1H-indolyl, tetrahydrothiophenyl, or quinolinyl; wherein each heteroaryl may be substituted with one or two substituents each independently selected from halo, C₁₋₄alkyl, C₁₋₄alkyloxy, or phenyl;

or a pharmaceutically acceptable acid addition salt thereof.

13. The compound as claimed in any of claims 10 to 12 wherein X represents carbon and the two --- bonds represent a single bond and R³ and R⁴ are located on adjacent positions and taken together to form a radical of formula =CH-CH=CH-CH=.

14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as claimed in any of claims 1 to 13.

15. A process for preparing a pharmaceutical composition as claimed in claim 14 wherein a therapeutically active amount of a compound as claimed in any of claims 1 to 13 is intimately mixed with a pharmaceutically acceptable carrier.

16. A compound of formula (I) as defined in any one of claims 1 to 13 for use as a medicine.

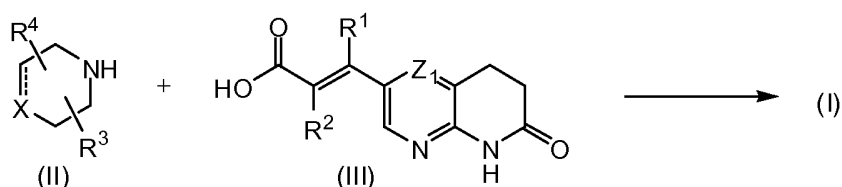
17. A compound of formula (I) as defined in any one of claims 1 to 13 for use in treating bacterial infections.

18. A compound as claimed in claim 17 wherein the bacterial infection is caused by a bacterium that expresses a FabI enzyme.

19. A process for preparing compounds of formula (I), as defined in claim 1 or claim 10:

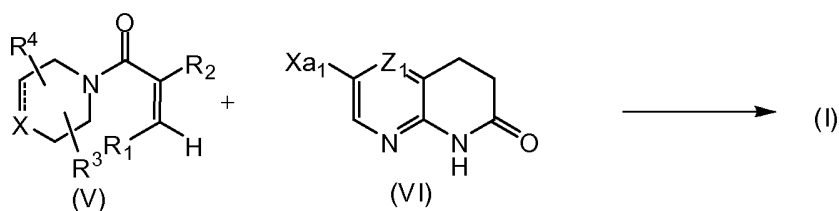
(i) by reacting an intermediate of formula (II) with an intermediate of formula (III),

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(ii) by reacting an intermediate of formula (V) with an intermediate of formula (VI),

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wherein X^{a1} represents a suitable leaving group and the other integers are as defined in Claim 1;

15

or; if desired; a compound of formula (I) is converted into a pharmaceutically acceptable acid addition salt, or conversely, an acid addition salt of a compound of formula (I) is converted into a free base form with alkali.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/065730

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 A61K31/4375 A61P31/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/061214 A1 (FAB PHARMA SAS [FR]; GERUSZ VINCENT [FR]; ESCAICH SONIA [FR]; OXOBY MA) 26 May 2011 (2011-05-26)	10-12, 14-19
Y	page 3, lines 29-31; claims 1-21; examples 3, 4, 5, 8, 9, 13, 14, 18, 25, 26, 27, 28; table 1	1-9, 13
Y	----- WO 2007/053131 A2 (AFFINIUM PHARM INC [CA]; SARGENT BRUCE JEREMY [GB]; PAULS HENRY [CA];) 10 May 2007 (2007-05-10)	1-9, 13
A	----- page 2, lines 3-6; claims 1, 39 ----- WO 2008/009122 A1 (AFFINIUM PHARM INC [CA]; PAULS HEINZ W [CA]; RAMNAUTH JAILALL [CA]; SA) 24 January 2008 (2008-01-24)	1-19
	the whole document -----	

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

21 September 2012

Date of mailing of the international search report

02/10/2012

Name and mailing address of the ISA/

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Authorized officer

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/065730

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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(19) 中华人民共和国国家知识产权局



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C07D 471/04 (2006. 01)

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A61P 31/04 (2006. 01)

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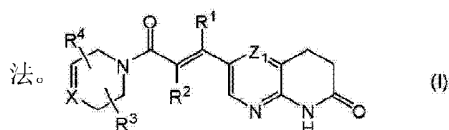
权利要求书3页 说明书36页

(54) 发明名称

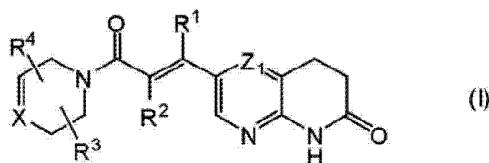
抗细菌的哌啶基取代的 3,4-二氢-1H-[1,8]
萘啶酮

(57) 摘要

本发明涉及新颖的抑制 Fab I 酶活性的式
(1) 化合物, 这些化合物因此对于治疗细菌感染
是有用的。本发明进一步涉及包含这些化合物的
药物组合物、以及用于制备这些化合物的化学方



1. 一种式 (I) 化合物



其特征在于：

X 表示 C 并且该 $\text{C}=\text{C}$ 键表示一个双键；或

m) X 表示 N 并且该 $\text{C}-\text{C}$ 键表示一个单键；

并且其中

Z_1 表示 CH 或 N；

R^1 是氢、 C_{1-4} 烷基或卤素；

R^2 是氢、 C_{1-4} 烷基或卤素；

R^3 是氢、 C_{1-6} 烷基、羟基或卤素；

R^4 是氢、 C_{1-6} 烷基、卤素、芳基、芳氧基、芳基羰基、杂芳基、用芳基或芳氧基取代的 C_{1-6} 烷基、或用杂芳基取代的 C_{1-6} 烷基；

并且当取代基 R^3 和 R^4 位于相邻的位置时，所述 R^3 和 R^4 可以一起形成一个式 =CH-CH= 的基团，其条件是 X 表示碳并且 $\text{C}=\text{C}$ 键表示一个双键；

芳基是苯基；用一个、两个或三个取代基取代的苯基，这些取代基各自独立地选自卤素、羟基、 C_{1-4} 烷基、 C_{1-4} 烷氧基、多卤代 C_{1-4} 烷基、多卤代 C_{1-4} 烷氧基、氰基、硝基和氨基；

杂芳基是呋喃基、苯硫基、吡咯基、吡啶基、咪唑基、异噁唑基、噻唑基、三唑基、四唑基、异噻唑基、噻二唑基、噁二唑基、吡嗪基、哒嗪基、嘧啶基、吡嗪基、苯并 [1,3] 二氧杂环戊烯基、苯并呋喃基、苯并噻唑基、吲哚基、2,3-二氢-1H-吲哚基、四氢苯硫基、或喹啉基；

其中每个杂芳基可以用一个或两个取代基取代，这些取代基各自独立地选自：卤素、氰基、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{1-4} 烷基羰基、或苯基；

或其药学上可接受的酸加成盐。

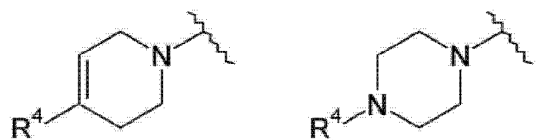
2. 如权利要求 1 所述的化合物，其中：

Z_1 表示 CH；

R^1 是氢或 C_{1-4} 烷基；

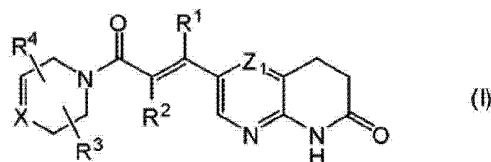
R^2 是氢或 C_{1-4} 烷基。

3. 如权利要求 1 或权利要求 2 所述的化合物，其中该含 X 的环表示：

4. 如权利要求 1 至 3 中任一项所述的化合物，其中 R^1 是氢并且 R^2 是氢。5. 如权利要求 1 至 4 中任一项所述的化合物，其中 R^3 表示氢。6. 如权利要求 1 至 5 中任一项所述的化合物，其中 R^4 是芳基。7. 如权利要求 1 至 5 中任一项所述的化合物，其中 R^4 是杂芳基。8. 如权利要求 1 至 5 中任一项所述的化合物，其中 R^4 是用芳基取代的 C_{1-6} 烷基。

9. 如权利要求 1 至 8 中任一项所述的化合物, 其中 X 表示氮并且该 --- 键表示一个单键。

10. 一种式 (I) 化合物



其中

该 --- 表示一个单键或双键；

X 表示碳或氮, 并且当 X 表示氮时, 则该 --- 表示一个单键；

Z₁ 表示 CH 或 N；

R¹ 是氢、C₁₋₄ 烷基或卤素；

R² 是氢、C₁₋₄ 烷基或卤素；

R³ 是氢、C₁₋₆ 烷基、羟基或卤素；

R⁴ 是氢、C₁₋₆ 烷基、卤素、芳基、芳氧基、芳基羰基、杂芳基、用芳基或芳氧基取代的 C₁₋₆ 烷基、或用杂芳基取代的 C₁₋₆ 烷基；

并且当取代基 R³ 和 R⁴ 位于相邻的位置时, 所述 R³ 和 R⁴ 可以一起形成一个式 = CH-CH = CH-CH = 的基团, 其条件是 X 表示碳并且 --- 键表示一个单键；

芳基是苯基；用一个、两个或三个取代基取代的苯基, 这些取代基各自独立地选自卤素、羟基、C₁₋₄ 烷基、C₁₋₄ 烷氧基、多卤代 C₁₋₄ 烷基、多卤代 C 烷氧基、氰基、硝基和氨基；

杂芳基是呋喃基、苯硫基、吡咯基、吡唑基、咪唑基、异噁唑基、噻唑基、三唑基、四唑基、异噻唑基、噻二唑基、噁二唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并 [1,3] 二氧杂环戊烯基、苯并呋喃基、苯并噻唑基、吲哚基、2,3-二氢-1H-吲哚基、四氢苯硫基、或喹啉基；

其中每个杂芳基可以用一个或两个取代基取代, 这些取代基各自独立地选自：卤素、氰基、C₁₋₄ 烷基、C₁₋₄ 烷氧基、C₁₋₄ 烷基羰基、或苯基；

或其药学上可接受的酸加成盐。

11. 如权利要求 10 所要求的化合物, 其中：

Z₁ 表示 CH；

R¹ 是氢或 C₁₋₄ 烷基；

R² 是氢或 C₁₋₄ 烷基。

12. 如权利要求 10 或权利要求 11 (或适当时, 权利要求 1 至 9 中任一项) 所述的化合物, 其中

该 --- 表示一个单键或双键；

X 表示碳或氮, 并且当 X 表示氮时, 则该 --- 表示一个单键；

R¹ 表示氢；

R² 表示氢；

R³ 是氢、C₁₋₆ 烷基、或羟基；

R⁴ 是氢、芳基、芳氧基、芳基羰基、杂芳基、用芳基或芳氧基取代的 C₁₋₆ 烷基、或用杂芳基取代的 C₁₋₆ 烷基；

并且当取代基 R^3 和 R^4 位于相邻的位置时,所述 R^3 和 R^4 可以一起形成一个式 $=CH-CH=CH-CH=$ 的基团,其条件是 X 表示碳并且 $\equiv$ 键表示一个单键;

芳基是苯基;用一个选自卤素、羟基、 C_{1-4} 烷氧基或多卤代 C_{1-4} 烷基的取代基取代的苯基;

杂芳基是呋喃基、苯硫基、吡咯基、三唑基、噁二唑基、吡啶基、苯并 [1,3] 二氧杂环戊烯基、苯并呋喃基、苯并噻唑基、吲哚基、2,3- 二氢 -1H- 吲哚基、四氢苯硫基、或喹啉基;

其中每个杂芳基可以用一个或两个取代基取代,这些取代基各自独立地选自:卤素、 C_{1-4} 烷基、 C_{1-4} 烷氧基、或苯基;

或其药学上可接受的酸加成盐。

13. 如权利要求 10 至 12 中任一项所述的化合物,其中 X 表示碳,这两个 $\equiv$ 键表示单键并且 R^3 和 R^4 位于相邻的位置并且一起形成一个式 $=CH-CH=CH-CH=$ 的基团。

14. 一种药物组合物,该组合物包括一种药学上可接受的载体以及一个治疗有效量的如在权利要求 1 至 13 中任一项所述的化合物。

15. 一种用于制备如权利要求 14 中所述的药物组合物的方法,其中将一个治疗有效量的如在权利要求 1 至 13 中任一项所述的化合物与一种药学上可接受的载体紧密混合。

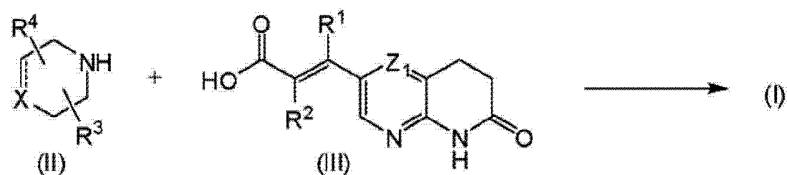
16. 如权利要求 1 至 13 中任一项所述的式 (I) 化合物,用于用作一种药物。

17. 如权利要求 1 至 13 中任一项所述的式 (I) 化合物,用于治疗细菌感染。

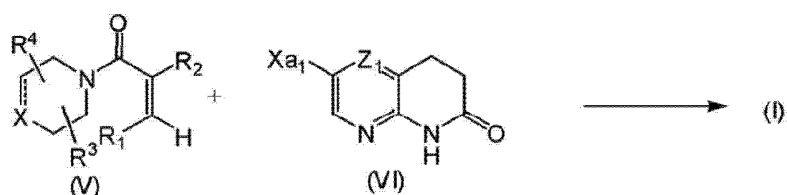
18. 如权利要求 17 所述的化合物,其中该细菌感染是由表达 Fab I 酶的细菌引起的。

19. 一种用于制备如在权利要求 1 或权利要求 10 中所定义的式 (I) 化合物的方法:

(i) 通过将一种式 (II) 的中间体与一种式 (III) 的中间体反应,



(ii) 通过将一种式 (V) 的中间体与一种式 (VI) 的中间体反应,



其中, X^{a1} 表示一个合适的离去基团并且其他整数是如在权利要求 1 中定义的;

或者;如果希望的话,将一种式 (I) 化合物转化成一种药学上可接受的酸加成盐,或者相反地,将一种式 (I) 化合物的酸加成盐用碱转化成一种游离碱。

抗细菌的嘧啶基取代的 3,4-二氢-1H-[1,8]萘啶酮

[0001] 本发明涉及新颖的抑制 FabI 酶活性的式 (I) 化合物, 这些化合物因此对于治疗细菌感染是有用的。本发明进一步涉及包含这些化合物的药物组合物、以及用于制备这些化合物的化学方法。

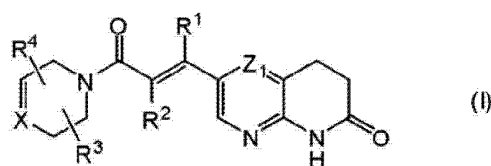
[0002] 本发明的化合物是抗细菌化合物, 这些化合物在脂肪酸生物合成途径中抑制 Fab I 蛋白, 一种 NADH 依赖性烯酰基-酰基载体蛋白 (ACP) 还原酶。在所有生物的饱和脂肪酸的总生物合成途径中涉及脂肪酸合酶 (FAS), 但是在它们中 FAS 的结构组织变化相当大。脊椎动物和酵母的 FAS 的明显特征是所有的酶活性编被码在一条或两条多肽链上, 并且酰基载体蛋白 (ACP) 以复合物的形式存在。相比之下, 在细菌 FAS 中, 每一个合成步骤由一种不同的单功能酶催化并且 ACP 是一种离散蛋白。因此, 有可能使用一种抑制剂通过阻断这些合成步骤之一来选择性地抑制细菌 FAS。在细菌脂肪酸生物合成的每个周期中所涉及的四个反应步骤的最后步骤中涉及 NADH 依赖性烯酰基-ACP 还原酶 (Fab I)。因此 Fab I 酶是在细菌脂肪酸生物合成的总合成途径中的生物合成酶。

[0003] 已经表明 Fab I 酶构成了主要病原体 (例如大肠杆菌) 中的重要靶标 (Heath (希斯) 等人, J. Biol. Chem. [生物化学杂志] 1995, 270, 26538; Bergler (伯格勒) 等人, Eur. J. Biochem. [欧洲生物化学杂志] 2000, 275, 4654)。因此, 抑制 Fab I 的化合物作为抗菌药物可以是有用的。

[0004] 在 WO-01/26652、WO-01/26654、和 WO-01/27103 中已经披露了具有 Fab I 酶抑制活性的化合物。在 WO-03/088897、WO-2007/043835 和 WO-2008/098374 中已经披露了具有 Fab I 抑制活性的取代的萘啶酮化合物。国际专利申请 WO2007/053131 还披露了不同的萘啶酮化合物用作 Fab I 抑制剂的潜在用途。然而, 这些文件均没有披露其中存在直接附接到羰基部分上的环状氨基基团的化合物, 该羰基部分为烯基的 α 位置。国际专利申请 WO2011/061214 还披露了不同的化合物用作 Fab I 抑制剂的潜在用途。然而, 这份文件未披露, 除其他之外, 存在含有一个双键或另外的氮杂原子的含氮环状基团的化合物。

[0005] 本发明涉及一种式 (I) 的化合物

[0006]



[0007] 其中

[0008] 该 --- 表示一个单键或双键;

[0009] X 表示碳或氮, 并且当 X 表示氮时, 则该 --- 表示一个单键;

[0010] Z_1 表示 CH 或 N;

[0011] R^1 是氢、 C_{1-4} 烷基或卤素;

[0012] R^2 是氢、 C_{1-4} 烷基或卤素;

[0013] R^3 是氢、 C_{1-6} 烷基、羟基或卤素;

[0014] R^4 是氢、 C_{1-6} 烷基、卤素、芳基、芳氧基、芳基羰基、杂芳基、用芳基或芳氧基取代的 C_{1-6} 烷基、或用杂芳基取代的 C_{1-6} 烷基；

[0015] 并且当取代基 R^3 和 R^4 位于相邻的位置时，所述 R^3 和 R^4 可以一起形成一个式 $=CH-CH=CH-CH=$ 的基团，其条件是 X 表示碳并且 $\equiv$ 键表示一个单键；

[0016] 芳基是苯基；用一个、两个或三个取代基取代的苯基，这些取代基各自独立地选自卤素、羟基、 C_{1-4} 烷基、 C_{1-4} 烷氧基、多卤代 C_{1-4} 烷基、多卤代 C_{1-4} 烷氧基、氰基、硝基和氨基；

[0017] 杂芳基是呋喃基、苯硫基、吡咯基、吡唑基、咪唑基、异噻唑基、噻唑基、三唑基、四唑基、异噻唑基、噻二唑基、噁二唑基、吡啶基、哒嗪基、嘧啶基、吡嗪基、苯并 [1,3] 二氧杂环戊烯基、苯并呋喃基、苯并噻唑基、吲哚基、2,3-二氢-1H-吲哚基、四氢苯硫基、或喹啉基；

[0018] 其中每个杂芳基可以用一个或两个取代基取代，这些取代基各自独立地选自：卤素、氰基、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{1-4} 烷基羰基、或苯基；

[0019] 或其药学上可接受的酸加成盐。

[0020] 如在先前的定义中所使用的；

[0021] - 卤素是氟代、氯代、溴代和碘代的属类；

[0022] - C_{1-4} 烷基定义了具有从 1 至 4 个碳原子的直链和支链饱和烷基，例如甲基、乙基、丙基、丁基、1-甲基乙基、2-甲基丙基等等；

[0023] - C_{1-6} 意在包括 C_{1-4} 烷基以及其具有 5 或 6 个碳原子的更高同系物，例如像 2-甲基丁基、戊基、己基等等；

[0024] - 多卤代 C_{1-4} 烷基定义为用 2 至 6 个卤素原子取代的多卤素取代的 C_{1-4} 烷基（如以上定义的），例如二氟甲基、三氟甲基、三氟乙基、等等。

[0025] 如在本说明书中使用的，无论何时使用术语“式 (I) 化合物”时，意在还包括该式 (I) 化合物能够形成的药学上可接受的加成盐以及该式 (I) 化合物的溶剂化物或该式 (I) 化合物能够形成的药学上可接受的酸加成盐。

[0026] “式 (I) 化合物”的定义固有地包括或是作为纯的立体异构体或是作为两种或多种立体异构体的混合物的所有式 (I) 化合物的立体异构体。对映异构体是彼此不重叠镜像的立体异构体。一对对映异构体的 1 : 1 混合物是一种消旋体或消旋混合物。非对映体（或非对映异构体）是不为对映异构体的立体异构体，即，它们是不相关的镜像。如果化合物包含一个二取代的环烷基，这些取代基可以处于顺式或反式构型。因此，本发明包括对映异构体、非对映异构体、消旋体、顺式异构体、反式异构体及其混合物。

[0027] 绝对构型是根据 Cahn-Ingold-Prelog 系统指定的。在不对称原子处的构型可以由 R 或 S 指定。绝对构型未知的、已拆分的化合物可以被指定为 (+) 或 (-)，取决于它们使平面偏振光旋转的方向。当鉴定一种特定立体异构体时，这意味着所述立体异构体基本上上无其他异构体，即，与其他异构体的关联小于 50%，优选地小于 20%，更优选地小于 10%，甚至更优选地小于 5%，特别是小于 2% 并且最优选地小于 1%。因此，例如当式 (I) 化合物被指定为 (R) 时，这意味着该化合物基本上上无 (S) 异构体；当式 (I) 化合物被指定为 E 时，这意味着该化合物基本上上无 Z 异构体；当式 (I) 化合物被指定为顺式时，这意味着该化合物基本上上无反式异构体。

[0028] 在上下文中，术语“立体异构体”或“立体化学同分异构体形式”可互换地使用。

[0029] 式 (I) 化合物以及在其制备中使用的中间体的绝对立体化学构型可以由本领域的普通技术人员使用熟知的方法 (例如像, X-射线衍射) 很容易地确定。

[0030] 一些式 (I) 化合物还可以按它们的互变异构形式存在。此类形式, 虽然没有在上述式中明确指出, 也旨在被包括在本发明的范围之内。

[0031] 此外, 一些式 (I) 化合物以及在其制备中使用的一些中间体可以呈现多晶型现象。应理解的是本发明包括在以上指出的处理条件中有用的任何多晶型加工特性。

[0032] 如在上文提及的药学上可接受的酸加成盐意为包括式 (I) 化合物能够形成的、治疗有活性的无毒的酸加成盐形式。可以方便地通过用这种适当的酸来处理碱形式而获得这些药学上可接受的酸加成盐类。适当的酸包括例如无机酸, 例如氢卤酸 (例如氢氯酸或氢溴酸)、硫酸、硝酸、磷酸等酸类; 或有机酸, 例如像乙酸、丙酸、羟基乙酸、乳酸、丙酮酸、草酸 (即乙二酸)、丙二酸、琥珀酸 (即丁二酸)、马来酸、富马酸、苹果酸、酒石酸、柠檬酸、甲磺酸、乙磺酸、苯磺酸、对甲苯磺酸、环己氨基磺酸、水杨酸、对氨基水杨酸、扑酸等酸类。

[0033] 相反地, 可以通过用适当的碱的处理将所述盐形式转化为游离碱形式。

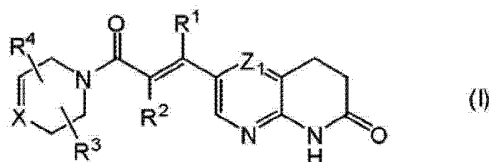
[0034] 这些式 (I) 化合物还可以按非溶剂化的和溶剂化两者的形式存在。在此使用术语 ‘溶剂化物’ 来描述包括本发明的化合物以及一种或多种药学上可接受的溶剂分子 (例如, 水或乙醇) 的分子缔合物。当所述溶剂是水时, 使用术语 ‘水合物’。

[0035] 术语 “Fab I” 是在本领域公认的并且是指被认为在细菌脂肪酸生物合成的每个周期中所涉及的四个反应的最终步骤中起作用的烯酰基-酰基蛋白 (ACP) 还原酶。这种酶被认为广泛地分布在细菌中。

[0036] 可以提及的式 (I) 化合物包括以下那些, 其中:

[0037] (i) Z_1 表示 CH, 并且因此式 I 的化合物表示如下:

[0038]



[0039] 其中

[0040] (ii) 当 R^1 或 R^2 表示卤素时, 则它们优选的是 F 或 Cl;

[0041] (iii) R^1 表示氢或 C_{1-4} 烷基; 和 / 或

[0042] (iv) R^2 表示氢或 C_{1-4} 烷基。

[0043] 感兴趣的式 (I) 化合物是那些式 (I) 化合物, 其中以下限制中的一者或多者适用:

[0044] a) R^1 和 R^2 表示氢; 或

[0045] b) R^3 表示氢; 或

[0046] c) R^3 表示氢、 C_{1-4} 烷基或卤素; 或

[0047] d) R^4 表示氢; 或

[0048] e) R^4 表示芳基; 或

[0049] f) R^4 表示芳氧基, 或芳基羰基; 或

[0050] g) R^4 表示用芳基或芳氧基取代的 C_{1-6} 烷基; 或

[0051] h) R^4 表示杂芳基 ;或

[0052] i) R^4 表示用杂芳基取代的 C_{1-6} 烷基 ;或

[0053] j) R^3 和 R^4 位于相邻的位置并且一起形成一个式 $=CH-CH=CH-CH=$ 的基团,其条件是 X 表示碳并且 --- 键表示一个单键 ;或

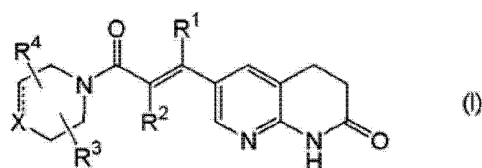
[0054] k) 杂芳基表示呋喃基、苯硫基、吡咯基、三唑基、噁二唑基、吡啶基、苯并 [1,3] 二氧杂环戊烯基、苯并呋喃基、苯并噻唑基、吲哚基、2,3- 二氢 -1H- 吲哚基、四氢苯硫基、或喹啉基 ;或

[0055] l) X 表示碳 ;或

[0056] m) X 表示氮并且该 --- 键表示一个单键。

[0057] 第一组化合物是式 (I) 化合物

[0058]



[0059] 其中

[0060] 该 --- 表示一个单键或双键 ;

[0061] X 表示碳或氮,并且当 X 表示氮时,则该 --- 表示一个单键 ;

[0062] R^1 表示氢 ;

[0063] R^2 表示氢 ;

[0064] R^3 是氢、 C_{1-6} 烷基、或羟基 ;

[0065] R^4 是氢、芳基、芳氧基、芳基羰基、杂芳基、用芳基或芳氧基取代的 C_{1-6} 烷基、或用杂芳基取代的 C_{1-6} 烷基 ;

[0066] 并且当取代基 R^3 和 R^4 位于相邻的位置时,所述 R^3 和 R^4 可以一起形成一个式 $=CH-CH=CH-CH=$ 的基团,其条件是 X 表示碳并且 --- 键表示一个单键 ;

[0067] 芳基是苯基 ;用一个选自卤素、羟基、 C_{1-4} 烷氧基或多卤代 C_{1-4} 烷基的取代基取代的苯基 ;

[0068] 杂芳基是呋喃基、苯硫基、吡咯基、三唑基、噁二唑基、吡啶基、苯并 [1,3] 二氧杂环戊烯基、苯并呋喃基、苯并噻唑基、吲哚基、2,3- 二氢 -1H- 吲哚基、四氢苯硫基、或喹啉基 ;

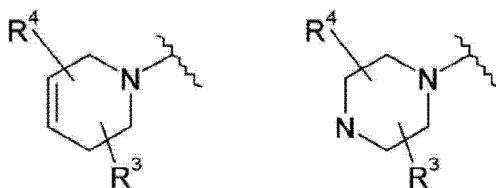
[0069] 其中每个杂芳基可以用一个或两个取代基取代,这些取代基各自独立地选自 :卤素、 C_{1-4} 烷基、 C_{1-4} 烷氧基、或苯基 ;

[0070] 或其药学上可接受的酸加成盐。

[0071] 可以提及的式 (I) 化合物包括以下那些,其中 X 表示 C,该 --- 键表示一个单键,并且 R^3 和 R^4 存在并且位于相邻的位置,并且一起形成一个式 $=CH-CH=CH-CH=$ 的基团。然而,特别优选的式 (I) 化合物包括以下那些,其中 :X 表示 C 并且该 --- 键表示一个双键 ;或

[0072] X 表示 N(在这种情况下,该 --- 键表示一个单键),并且因此以下含 X 的环是特别优选的 :

[0073]



[0074] 在这种情况下,优选的是相邻 R^3 和 R^4 的基团一起形成一个基团。

[0075] 在式 (I) 化合物中,优选的是:

[0076] (i) 存在至少一个不表示氢的 R^3 或 R^4 取代基;

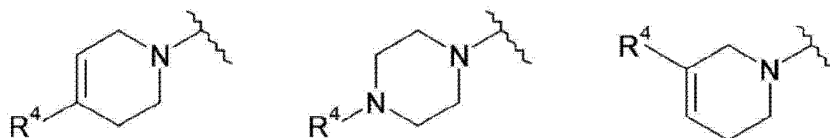
[0077] (ii) R^3 和 R^4 之一 (例如 R^3) 表示氢、 C_{1-3} 烷基或羟基,并且 R^3 和 R^4 中另一个 (例如 R^4) 表示一个非氢的取代基;

[0078] (iii) R^3 表示氢、羟基或卤素 (例如氟) 并且最优选地表示氢 (即, R^3 实质上不存在);

[0079] (iv) R^4 表示一个非氢的取代基 (即,有一个存在的并且不表示氢的 R^4 取代基);

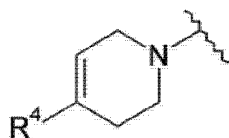
[0080] (v) R^4 表示一个非氢的取代基,该取代基附接到 X 上,其中以上任意者可以一起或以组合采取。例如能够以组合取 (iii)、(iv) 和 / 或 (v) 以提供以下特别优选的式 (I) 化合物:

[0081]



[0082] 其中 R^4 表示一个非氢的取代基。在该式 (I) 化合物中,最优选的含 X 的环是:

[0083]



[0084] 其中 R^4 表示一个非氢的取代基。 R^4 可以存在 (在此以及在别处) 的特别优选的取代基包括:

[0085] (i) 任选地取代的芳基;

[0086] (ii) 任选地取代的杂芳基

[0087] (iii) 被芳基、芳氧基或杂芳基 (这后三者芳基和杂芳基部分本身任选地如在此定义的进行取代) 取代的 C_{1-6} 烷基;

[0088] (iv) 芳氧基 (其中该芳基部分是如在此定义的任选地取代的);

[0089] (v) 芳基羰基;

[0090] 特别优选的是 R^4 包含一个芳香族部分,并且因此以上 (i)、(ii)、(iii)、(iv) 和 (v) 是特别优选的。

[0091] 在当 R^4 表示以上 (i) 的情况下,则该芳基基团优选地是苯基,该基团可以未被取代或被一个或两个 (例如一个) 选自卤素 (例如氯)、 C_{1-4} 烷基、多卤代 C_{1-4} 烷基 (例如 $-CF_3$)、 C_{1-4} 烷氧基 (例如 $-OCH_3$) 的取代基取代。

[0092] 在当 R^1 表示以上 (ii) 的情况下, 则该杂芳基基团优选地是含一个至四个杂原子的单环的 5 或 6 元环或含一至四个杂原子的 9 或 10 元环 (例如, 在后者的情况下, 它可以是一个稠和到 5 或 6 元芳香族或非芳香族环上的苯环), 从而形成例如苯并 [1,3] 二氧杂环戊烯基基团、呋喃基 (例如 2- 或 3- 呋喃基)、吡啶基 (例如 3- 吡啶基)、苯并呋喃基 (例如 2- 苯并呋喃基), 该杂芳基基团任选地被一个或多个 (例如一个) 选自 C_{1-4} 烷氧基 (例如 $-OCH_3$) 的取代基取代。

[0093] 在其中 R^1 表示以上 (iii) 的情况下, 则优选地该 C_{1-6} 烷基基团是甲基或乙基, 即, $-CH_3$ 或 $-CH_2CH_3$, 该烷基部分用以下项取代: 芳基 (例如苯基, 例如未取代的苯基或用 C_{1-4} 烷氧基, 例如 OCH_3 取代的苯基)、芳氧基 (例如, 其中芳基是苯基, 未取代或用 一个或多个 (例如) 选自卤素, 例如氟的取代基取代) 或杂芳基 (例如, 含有一个或两个 (例如一个) 杂原子的 5 或 6 元单环杂芳基基团或含有一个或两个杂原子的 9 或 10 元二环杂芳基基团, 从而形成例如苯并呋喃基、苯并噻唑基、2,3- 二氢 -1H- 吡啶基、吡啶基、噻吩基、三唑基、咪唑基、喹啉基、吡咯基、和噁二唑基 (这些杂芳基基团未被取代的或用 一个或两个选自卤素 (例如氟基)、 C_{1-4} 烷基 (例如甲基)、以及未取代的苯基的取代基取代)。

[0094] 在 R^1 表示以上 (iv) 的情况下, 则该芳基优选地是苯基, 该苯基优选地是未取代的。

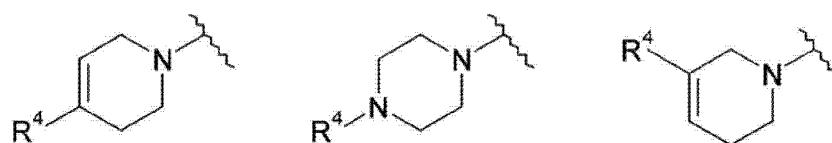
[0095] 在 R^1 表示以上 (v) 的情况下, 则该芳基优选地是苯基, 该苯基优选地是未取代的。

[0096] 最优选地, 该 R^1 基团表示以上的 (i)、(ii) 或 (iii) 并且甚至更优选地, R^1 表示以上 (i) 或 (ii), 即, 芳基或杂芳基。甚至更优选地, R^1 基团表示以上 (i), 尤其是未取代的苯基。

[0097] 在式 (I) 化合物中, 优选地是不存在 R^3 取代基 (或一个表示氢的 R^3 取代基) 或者存在一个 R^3 取代基 (例如在 X 上, 当 X 是一个碳原子时), 该取代基表示一个非氢的取代基 (例如, 表示 C_{1-3} 烷基或优选地羟基)。尤其优选的是不存在 R^3 取代基。在式 (I) 化合物中, 还优选的是存在一个或两个 (例如一个) R^4 取代基, 其中 R^4 是如以上定义的。尤其优选的是有一个在位于 X 部分 (例如, 在 X 可以表示的 C 或 N 原子上) 上存在的 R^4 取代基, 其中 R^4 不表示氢, 而是表示如在此定义的另一个取代基。

[0098] 以上已经陈述了以下含 X 的环是特别优选的:

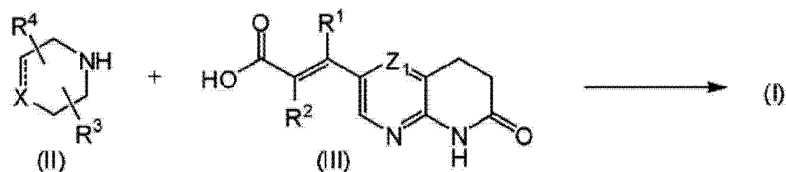
[0099]



[0100] 并且特别是其中 R^4 是如以上定义的那些。包含与一个双键相邻的一个 $N(R^4)$ 部分或 $C(R^4)$ 部分的此类化合物可以是有利的。这是因为氮原子的形状 (例如, 与一个不与双键相邻的 CR^4 部分相比在性质上更平面) 或在含 X 的环中存在双键可以有助于将该 R^4 基团 (如果存在的话) 定向, 这样使得该化合物总体上 (例如, 就 R^4 取代基的取向而言) 展示出与 Fab I 细菌酶更好的 / 改善的结合特性。因此, 本发明的这些化合物在存在引起对 Fab I 酶的改善的结合和 / 或抑制的双键的存在意义上可以是有利的。因此, 本发明的这些化合物因为可以必然导致更好的效能、疗效等的这些特性而可以是有利的化合物 (例如, 与已知的化合物相比)。

[0101] 式 (I) 化合物总体上可以通过使一种式 (II) 的中间体与一种式 (III) 的中间体在至少一种反应惰性的溶剂中并且任选地在至少一种适当的偶联试剂和 / 或一种适当的碱的存在下反应来制备, 所述方法进一步任选地包括将一种式 (I) 化合物转化成其加成盐, 和 / 或制备其立体化学同分异构的形式。

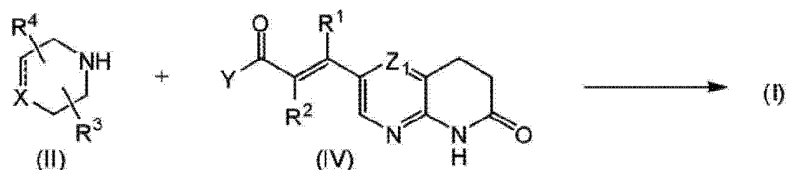
[0102]



[0103] 可以方便的是通过加入一个有效量的反应促进剂来活化式 (III) 的羧酸。此类反应促进剂的非限制性实例包括羰基二咪唑、N, N' - 二环己基碳二亚胺或 1-(3- 二甲基氨基丙基) - 3- 乙基碳二亚胺、羟基苯并三唑、苯并三唑基 - 氧基三 (二甲氨基) - 六氟磷酸磷、四吡咯烷基 - 六氟磷酸磷、溴三吡咯烷基六氟磷酸磷、或其功能衍生物。

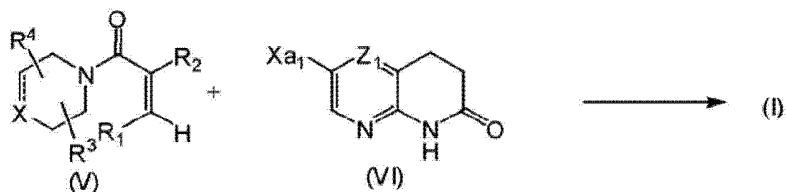
[0104] 式 (I) 化合物还可以通过使一种式 (II) 的中间体与一种式 (IV) 的中间体反应来制备, 其中 Y 表示羟基或卤素。该反应可以在一种反应惰性的溶剂 (例如像二氯甲烷或二甲基甲酰胺) 中并且任选地在一种适当的碱 (例如像二异丙基乙胺 (DIPEA)) 的存在下进行。

[0105]



[0106] 式 (I) 化合物还可以通过使一种式 (V) 的中间体与一种式 (VI) 的中间体反应来制备,

[0107]



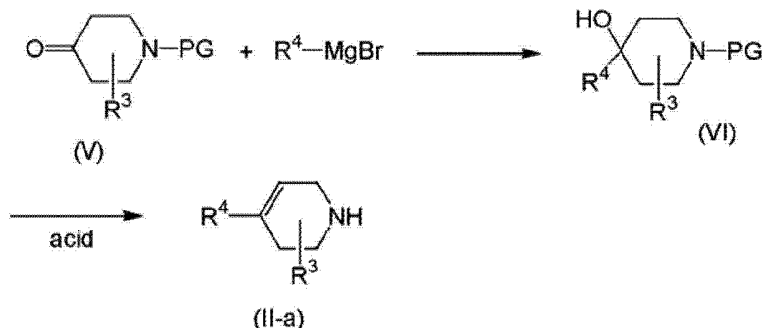
[0108] 其中 X_{a1} 表示一个合适的离去基团, 例如一个合适的卤素基团 (例如氯基、碘基并且尤其是溴基) 并且其他整数是如以上在反应适合的反应条件下定义的, 例如在金属催化剂偶联反应条件下 (例如, 贵金属偶联反应条件, 其中该贵金属是例如基于钯的), 特别是在使用以下优选地基于钯的催化剂赫克反应条件下: 例如乙酸钯、四 (三苯基膦) 钯 (0)、双 (三苯基膦) 钯 (II) 二氯化物、[1, 1' - 双 (二苯基膦基) 二茂铁] 钯 (II) 二氯化物、等等 (优选地该催化剂是醋酸钯), 例如任选地在一种适当的溶剂 (例如乙腈、等等)、碱 (例如胺碱, 例如 N, N- 二异丙基胺、等等) 以及一种配体 (例如, 三苯基膦、三 - O- 辛基膦、等等) 的存在下。该反应可以在一个密封管中和 / 或在微波中进行。

[0109] 这些起始材料以及一些中间体是熟知的化合物并且是可商购的或是可以根据本

领域中通常已知的常规反应程序可以制备的。

[0110] 式 (II-a) 的中间体, 定义为式 (II) 的中间体, 其中 X 表示碳并且 R^4 位于该吡啶环的 4 位上, 可以根据以下的总反应方案制备。

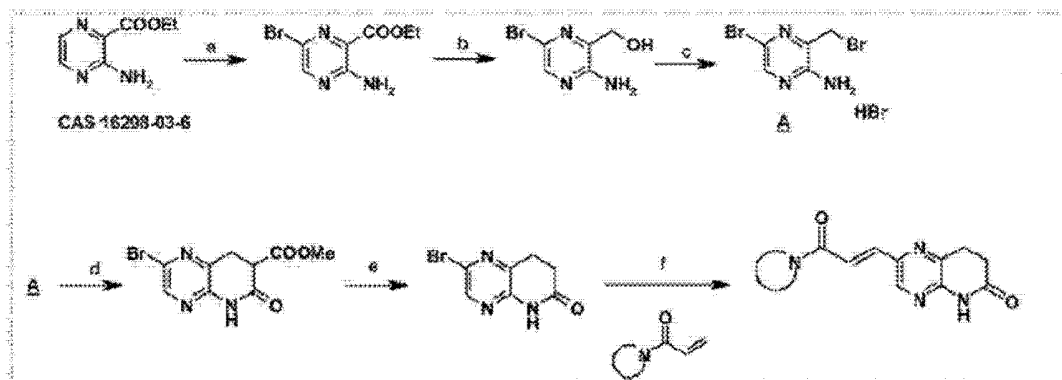
[0111]



[0112] 在以上反应方案中, 在中间体 (V) 和 (VI) 中的基团 PG 是一个在酸性条件下容易移除的氮保护基, 例如叔丁氧基羰基。使用本领域熟知的有机金属反应, 例如格利雅反应可以获得有机镁试剂 R^4-MgBr 。

[0113] 对于其中 Z_1 表示 CH 的化合物, 中间体 (IV) 和 (VI) 可以如在此描述的制备, 或根据本领域中通常已知的常规反应程序制备。对于其中 Z_1 表示 N 的相应中间体, 也可以是这种情况。然而, 此类化合物还可以根据以下的方案制备:

[0114]



[0115] 条件:

[0116] a) NBS、ACN、回流、3h、70% ; b) 在 THF 中 1M 的 $LiAlH_4$ 、THF、5℃至室温、o. n.、20% ; c) PBr_3 、DCM、RT、o. n.、90% ; f) 丙二酸二甲酯、在 MeOH 中 NaOMe、MeOH、RT、o. n.、25% ; g) NaOH、MeOH、回流、4h、HCl、回流、o. n. ; h) DIEA、 $Pd(OAc)_2$ 、三-O-甲基苯基膦、ACN、DMF、 μw 、180℃、25min。

[0117] 如在上文所述的方法中制备的式 (I) 化合物能够以对映异构体的外消旋混合物的形式合成, 这些对映异构体可以遵循领域中已知的拆分规程而得以彼此分离。以外消旋形式获得的式 (I) 的这些化合物可以通过分别与适合的手性酸发生反应而被转化为相对应的非对映异构体盐形式。随后例如通过选择性的或分步结晶将所述非对映异构盐形式进行分离, 并且对映体自此通过碱释放。分离式 (I) 化合物的对映异构体形式的替代方式涉及使用手性固定相液相色谱。所述纯的立体化学异构形式还可以衍生自适当起始材料的相

应的纯立体化学同分异构形式,其条件是该反应立体定向地发生。优选地如果一种特定的立体异构体是所希望的,所述化合物将通过立体定向的制备方法合成。这些方法将有利地采用对映异构体纯的起始材料。

[0118] 在此描述的化合物是 Fab I 酶的抑制剂,如在药理学实例 1 中所证明的。就这些 Fab I 酶抑制特性而言,在此描述的这些化合物对于治疗细菌感染是有用的。例如,这些化合物对于治疗细菌感染是有用的,例如像,上呼吸道感染(例如中耳炎、细菌性气管炎、急性会厌炎、甲状腺炎)、下呼吸道感染(例如,脓胸、肺脓肿)、心脏感染(例如感染性心内膜炎)、胃肠感染(例如分泌性腹泻、脾脓肿、腹膜后脓肿)、CNS(例如脑脓肿)、眼部感染(例如睑炎、结膜炎、角膜炎、内眼炎、前蜂窝织炎和眼眶蜂窝织炎)、肾和尿路感染(例如附睾炎、肾内和肾周脓肿、中毒性休克综合征)、皮肤炎症(例如脓疱病、毛囊炎、皮肤脓肿、蜂窝织炎、伤口感染、细菌性肌炎)、以及骨骼和关节感染(例如脓毒,性关节炎、骨髓炎)。此外,这些化合物可能在与已知的抗生素的组合中是有用的。

[0119] 因此,本发明还涉及式(I)化合物作为一种尤其是用于治疗细菌感染,特别是由表达 Fab I 酶的细菌引起的细菌感染的药物的用途。接着,本发明的化合物可以用于制造一种用于治疗细菌感染,特别是由表达 Fab I 酶的细菌引起的细菌感染的药物。

[0120] 此外,本发明提供了一种用于治疗细菌感染的方法,该方法包括向对其有需要的受试者给予一种抑制 Fab I 酶的式(I)化合物。

[0121] 需要治疗的受试者具有细菌感染或者已经暴露于传染性细菌,其症状可以通过给予一个治疗有效量的本发明的化合物来缓解。例如,对于治疗有需要的受试者可以具有一种该式(I)化合物可以作为治疗剂给药的感染。在另一个实例中,对于治疗有需要的受试者可以具有一种该式(I)化合物可以作为预防药的开放性创伤或烧伤。典型地,将治疗已存在生物感染的一位受试者。

[0122] 一位受试者可能具有由以下项引起的细菌感染:炭疽杆菌、枸橼酸杆菌属、大肠杆菌、土拉热弗朗西丝菌、流感嗜血杆菌、单核细胞增生李斯特菌、卡他莫拉菌、结核分枝杆菌、脑膜炎奈瑟菌、奇异变形菌、普通变形菌、沙门菌属、沙雷氏菌属、志贺氏菌属、嗜麦芽寡食单胞菌、金黄色葡萄球菌、或表皮葡萄球菌。优选地,针对由表达 Fab I 酶的细菌引起的细菌感染对受试者进行治疗(预防性地或治疗性地)。

[0123] 如在此使用的术语“治疗(treating)”和“治疗(treatment)”是指治疗性、缓解性以及预防性治疗,包括逆转(reversing)、缓解、抑制此类术语所适用的疾病、失调或病症的进展或此类疾病、失调或病症的一种或多种症状,或防止疾病、失调或病症或此类疾病、失调或病症的一种或多种症状。

[0124] 本发明的化合物的一个“治疗有效量”是一个当给予对治疗有需要的受试者时改善了该受试者的预后的量,例如延迟了该受试者的与细菌感染相关的一种或多种症状的发作和/或降低了其严重性。有待给予受试者的本披露的化合物的量将取决于具体的疾病、给药方式以及受试者的特征,例如总体健康状况、其他疾病、年龄、性别、基因型、体重以及对药物的耐受性。技术人员能够依赖于这些以及其他因素来确定合适的剂量。

[0125] 可以在若干生物测定之一中测试这些化合物以确定具有一种给定的药理效应的所需要的化合物的浓度。

[0126] 此外,本发明提供的药物组合物包括至少一种药学上可接受的载体以及一个治疗

有效量的式 (I) 化合物。

[0127] 为了制备本发明的药物组合物,将有效量的具体化合物(处于碱或酸加成盐形式)作为活性成分与至少一种药学上可接受的载体紧密混合,该载体取决于给药所希望的制剂形式可采用多种形式。这些药物组合物令人希望的地处于适合于、优选地适合于经口服、直肠给药、经皮给药或经肠胃外注射给予的单位剂型。

[0128] 例如,在制备处于口服剂型的组合物中,在口服液体制剂(例如悬浮液、糖浆、酏剂和溶液)的情况下,可以采用任何常用药物介质,例如像水、二醇类、油类、醇类等等;或者在粉剂、丸剂、胶囊、以及片剂的情况下,采用固体载体,例如淀粉、糖、高岭土、润滑剂、粘合剂、崩解剂等等。由于它们的给予方便,片剂和胶囊代表最有利的口服剂量单位形式,在此情况下显然采用固体药物载体。对于肠胃外注射组合物,该药物载体主要包含无菌水,尽管可以包含其他的成分以提高该活性成分的溶解度。注射溶液可以例如通过使用一种包含盐水溶液、葡萄糖溶液或两者的混合物的药物载体来制备。也可以采用适当的液体载体、助悬剂以及类似物制备注射悬浮剂。在适合于经皮给予的组合物中,该药物载体可以任选地包括渗透增强剂和/或适合的润湿剂,任选地与小比例的适合的添加剂组合,这些添加剂不会引起任何对皮肤的显著有害作用。所述添加剂可以选择为促进对皮肤给予该活性成分和/或可以有助于制备所希望的组合物。能以不同方式给予这些局部组合物,例如,作为透皮贴剂、喷滴剂(spot-on)、或软膏剂。式(I)化合物的加成盐显著地更适合于制备水性组合物,因为相对于相应碱形式其可溶性增加。

[0129] 为了便于给予和剂量的一致性,尤其有利的将本发明的药物组合物配制为单位剂型。如在此使用的“剂量单位形式”指的是适合作为单位剂量的物理离散单位,各单位包含预定量的活性成分,该预定量的活性成分经计算与所要求药物载体相结合而产生所希望的治疗效果。这样的单位剂型的实例是片剂(包括刻痕片剂或包衣片剂)、胶囊、丸剂、粉包、薄片、注射溶液或悬浮液、一茶匙容量、大汤匙容量等,及其分开的多个剂量(segregated multiples)。

[0130] 对于口服给药,本发明的药物组合物可以采取固体剂型,例如片剂(可吞咽和可咀嚼形式两者)、胶囊或软胶囊,通过常规的手段使用以下药学上可接受的赋形剂和载体制备:粘合剂(例如预胶化的玉米淀粉、聚乙烯吡咯烷酮、羟丙基甲基纤维素、等等)、填充剂(例如硬脂酸镁、滑石、硅石、等等)、崩解剂(例如马铃薯淀粉、羟基乙酸淀粉钠、等等)、湿润剂(例如月桂基硫酸钠)等等。合适的片剂还可以通过本领域熟知的方法包衣。

[0131] 用于口服给予的液体配制品可以采取例如溶液、糖浆、或悬浮液的形式,或者它们可以配制为一种干产品用于在使用前与水和/或另一种合适的液体载体混合。此种液体配制品可以通过常规的手段任选地与其他药学上可接受的添加剂制备,例如悬浮剂(例如山梨糖醇糖浆、甲基纤维素、羟丙基甲基纤维素或氢化的可食用脂肪)、乳化剂(例如卵磷脂或阿拉伯胶)、非水性载体(例如,杏仁油、油状酯或乙醇)、增甜剂、调味剂、掩蔽剂和防腐剂(例如,甲基或丙基对羟基苯甲酸酯或山梨酸)。

[0132] 在本发明的药物组合物中有用的药学上可接受的增甜剂优选地包含至少一种强烈的增甜剂,例如天冬酰苯丙氨酸甲酯、乙酰磺胺酸钾、环拉酸钠、阿力甜、双氢查耳酮增甜剂、莫内林、甜菊糖苷、三氯蔗糖(4,1',6'-三氯-4,1',6'-三脱氧半乳糖)或,优选地糖精、糖精钠或钙,以及任选地至少一种增量甜味剂,例如山梨糖醇、甘露醇、果糖、蔗糖、

麦芽糖、异麦芽酮糖醇、葡萄糖、氢化的葡萄糖浆、木糖醇、焦糖或蜂蜜。强烈的增甜剂合宜地以低浓度使用。例如，以糖精钠的形式，所述浓度可以范围从该最终配制品的约 0.04% 至 0.1%（重量 / 体积）。增量甜味剂能够以更大的浓度有效地使用，范围从约 10% 至约 35%，优选地从约 10% 至 15%（重量 / 体积）。

[0133] 在低剂量配制品中掩蔽苦味成分的药学上可接受的调味剂优选地是以下水果调味剂，例如樱桃、覆盆子、黑醋栗或草莓调味剂。两种调味剂的组合可以产生非常好的结果。在高剂量配制品中，可以要求更强的药学上可接受的调味剂，例如焦糖巧克力 (Caramel Chocolate)、冰薄荷 (Mint Cool)、Fantasy、等等。每种调味剂能够以范围约 0.05% 至 1%（重量 / 体积）的浓度在该最终组合物中存在。所述强调味剂的组合是有利地使用的。优选地，使用在该配制品的环境中不经受任何味道和 / 或颜色变化或损失的调味剂。

[0134] 式 (I) 化合物可以配制为用于通过注射、常规的静脉内、肌内或皮下注射，例如通过单次快速静脉注射或连续静脉输注而肠胃外给予。用于注射的配制品能够以单位剂型（例如以针剂）或多剂量容器（包括一种添加的防腐剂）而存在。它们可以采取例如在油或水载体中的悬浮液、溶液或乳液的形式，并且可以包含配制试剂，例如等渗剂、悬浮剂、稳定剂和 / 或分散剂。作为替代方案，该活性成分能以粉末的形式存在用于在使用前与一种适当的载体，例如灭菌无热原水混合。

[0135] 这些式 (I) 化合物还可以配制成直肠组合物，例如栓剂或保留灌肠剂，这些试剂包含常规的栓剂基础，例如可可油和 / 或其他甘油酯。

[0136] 在与这种 Fab I 酶的抑制相关的抗细菌疾病治疗中的普通技术人员将能够从下文所呈现的测试结果来确定一种式 (I) 化合物的治疗有效量。人体上，考虑了一个治疗有效剂量将是约 0.001mg/kg 至约 50mg/kg 待治疗的患者体重，更优选地从约 0.01mg/kg 至约 10mg/kg 体重。可以适当的是将该治疗有效的剂量在全天中以适当间隔以两个、或更多个亚剂量的形式给予。所述亚剂量可以配制为单位剂型，例如每一个包含从约 0.1mg 至约 1000mg、更特别是从约 1mg 至约 500mg 的活性成分 / 单位剂型。

[0137] 如本领域的普通技术人员所熟知的，给药的精确剂量和频率取决于使用的式 (I) 的具体化合物、正在被治疗的具体病症、正在被治疗的病症的严重性、具体患者的年龄、体重和总体身体健康状况、连同患者可以服用的其他药物。此外，所述“治疗有效量”可以降低或增加，这取决于所治疗的患者的反应和 / 或取决于对本发明的这些化合物开处方的医师的评估。因此在上文提到的有效每日剂量范围仅仅是指导。

[0138] 式 (I) 化合物具有的优点是与本领域中已知的化合物相比，无论用于以上陈述的适应症或其他适应症它们可以是更有效、更小毒性、更长效、更有效力、产生更少的副作用、更容易吸收、和 / 或具有更好的药物代谢动力学特征曲线（即，更高的口服生物利用度和 / 或更低的清除率）、和 / 或具有其他有用的药理学、物理、或化学特性。式 (I) 的具体化合物可以呈现这样的优点，例如其中含 X 的环含有与双键相邻的 NR^4 的化合物，并且特别是其中它包含一个与双键相邻的 CR^4 部分（例如，其中 X 是 CR^4 ）的那些。这些有利特性中的任一者可以归于存在与双键相邻的 NR^4 或 CR^4 。

[0139] 例如，式 (I) 化合物可以具有的优点是它们具有良好的或改进的热力学溶解度（例如，与本领域已知的化合物相比，并且例如由已知的方法和 / 或在此描述的方法确定的）。式 (I) 化合物还可以具有的优点是它们具有相对于抗菌药更宽的活性谱（例如，与

本领域已知的化合物相比更宽的抗菌活性谱,并且例如由已知的试验和/或在此描述的试验确定的)。式(I)化合物还可以具有的优点是它们可以具有良好或改进的体内药物代谢动力学以及口服生物利用度。它们还可以具有的优点是它们可以具有良好或改进的体内疗效。例如,本发明的化合物可以适用于静脉内配制/给药并且因此可以在静脉内给药时展示改进的体内疗效。式(I)的具体化合物可以呈现这样的优点,例如其中含X的环含有与双键相邻的NR⁴的化合物,并且特别是其中它包含一个与双键相邻的CR⁴部分(例如,其中X是CR⁴)的那些。这些有利特性中的任一者可以归于存在与双键相邻的部分NR⁴或CR⁴。

[0140] 实验部分

[0141] “DMF”定义为N,N-二甲基甲酰胺,“DCM”或“CH₂Cl₂”定义为二氯甲烷,“MeOH”定义为甲醇,“EtOH”定义为乙醇,

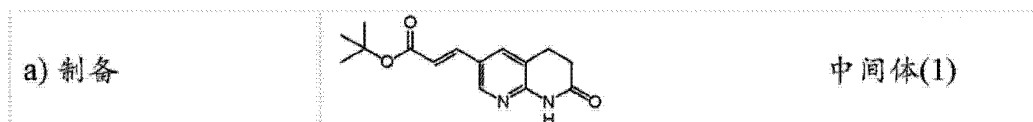
[0142] “MgSO₄”定义为硫酸镁,并且“THF”定义为四氢呋喃,

[0143] “HATU”定义为1-[双(二甲氨基)亚甲基]-1H-1,2,3-三唑[4,5-b]吡啶鎓3-氧化物六氟磷酸盐,“AcOEt”或“EtOAc”定义为乙酸乙酯,“DIPEA”定义为二异丙基乙胺,“mp”定义为熔点,“EDCI”定义为N’-(乙基碳亚胺酰基)-N,N-二甲基-1,3-丙二胺一氢氯化物,“HOBT”定义为1-羟基-1H-苯并三唑,“DIPA”定义为二异丙基胺,“K₂CO₃”定义为碳酸钾,“TFA”定义为三氟乙酸,“NH₄OH”定义为氢氧化铵,“NaHCO₃”定义为碳酸氢钠盐,“KOH”定义为氢氧化钾,“AlCl₃”定义为氯化铝,“NH₄Cl”定义为氯化铵,“Et₂O”定义为乙醚,“Na₂SO₄”定义为硫酸钠盐,“CH₃CN”定义为乙腈,“NaOH”定义为氢氧化钠。

[0144] A. 中间体的合成

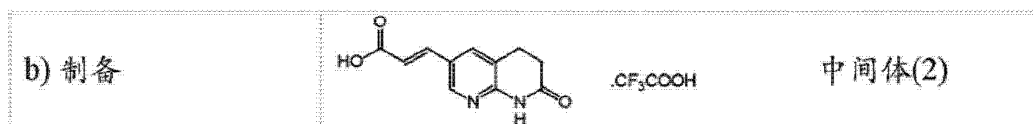
[0145] 实例 A.1

[0146]



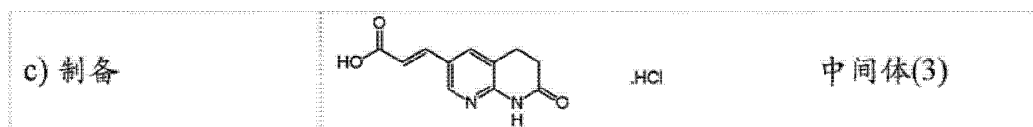
[0147] 将6-溴-3,4-二氢-1H-[1,8]萘啶-2-酮(1.0g,4.4mmol)、丙烯酸叔丁酯(2.56ml,17.62mmol)和N,N-二异丙基乙胺(1.46ml,8.81mmol)在乙腈(20ml)和DMF(7ml)中的溶液搅拌并且用氮气脱气10分钟。加入三-对甲苯基膦(0.27g,0.88mmol)和醋酸钯(II)(在Pd上47%)(0.099g,0.44mmol)并且将得到的混合物进行微波加热(1600W,180℃,35分钟)。将反应混合物蒸发至干,吸收在DCM/甲醇(8/2)(50ml)中,穿过短硅藻土垫过滤并且用DCM洗涤。将该有机层用水洗涤,用MgSO₄干燥,过滤并蒸发至干。将残余物在冷乙醇(10ml)中吸收并且在5℃下搅拌5分钟,将沉淀过滤出,用冷乙醇洗涤(3ml)并且在真空下干燥以产生950mg中间体(1)。

[0148]



[0149] 将中间体(1)(4.1g,14.95mmol)溶解在三氟乙酸(23.2ml)在DCM(41mL)的混合物中。将该反应在室温下搅拌30分钟。在减压下浓缩反应混合物。将得到的固体用乙醚研磨,过滤出并在真空下干燥以产生3.97g的中间体(2)。

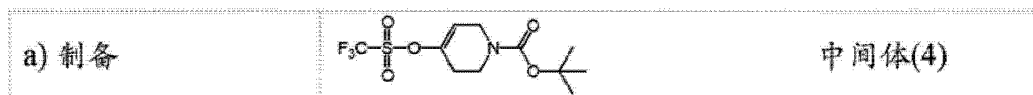
[0150]



[0151] 将中间体 (2) 在 HCl 于二噁烷 (4M, 48ml) 中的混合物中研磨过夜, 将固体过滤出, 用乙醚洗涤并且在真空下干燥以给出 3.7g 的中间体 (3)。

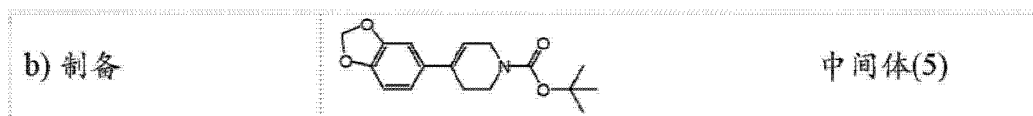
[0152] 实例 A. 2

[0153]



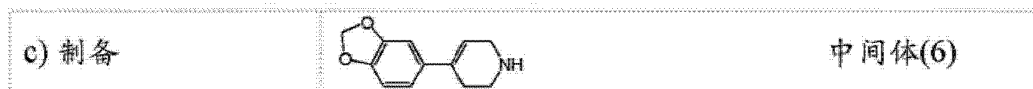
[0154] 在 N_2 下的反应。在 -20°C 下将 BuLi (1.6M 于己烷中) (8.28ml, 13.2mmol) 滴加至 DIPA (1.86ml, 13.2mmol) 于 THF (20ml) 中的溶液中并且然后将该混合物在 -20°C 下搅拌 20 分钟。然后在 -78°C 下加入 1-叔丁氧羰基-4-哌啶酮 (2.2g, 11.0mmol) 于 THF (20ml) 中的溶液并且将得到的混合物在 -78°C 下搅拌 30 分钟。然后在 -78°C 下加入 2-[N,N-双(三氟甲基磺酰基)-氨基]-5-氯吡啶 (4.97g, 12.1mmol) 在 THF (10ml) 中的溶液, 然后允许混合物达到室温并且搅拌过夜。将混合物浓缩并且通过快速色谱法在硅胶 (硅胶 $30\mu\text{m}$, 80g, 庚烷/EtOAc 75/25) 上进行残余物的纯化。收集所希望的产物并且将溶剂蒸发, 从而产生 2.9g 的中间体 (4)。

[0155]



[0156] 在 N_2 下的反应。微波条件: Biotage 引发器 60, 80°C , 20 分钟。将中间体 (4) (0.3g, 0.905mmol) 和 3,4-(亚甲二氧基) 苯基硼酸 (0.18g, 1.09mmol) 在 K_2CO_3 (2M, 0.905ml) 和乙二醇二甲醚 (3ml) 中的溶液用 N_2 吹扫 10 分钟, 然后加入四(三苯基磷) 钯 (0) (0.105g, 0.0905mmol)。将混合物按照以上的条件照射, 冷却到室温, 加入水和 EtOAc, 分离有机层, 用水然后盐水洗涤, 干燥 ($MgSO_4$) 并且蒸发至干。通过快速色谱法在硅胶 (硅胶 10g, $15-40\mu\text{m}$, 庚烷 100 至庚烷/EtOAc 90/10) 上进行残余物的纯化, 收集纯的部分并且蒸发至干, 从而产生 0.17g 的中间体 (5)。

[0157]

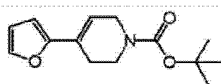


[0158] 将中间体 (5) (0.17g, 0.56mmol) 在 TFA (0.5ml) 和 DCM (3ml) 中的溶液在室温下搅拌 30 分钟, 加入 K_2CO_3 (10% 水溶液) 和 DCM, 将有机层分离, 用水洗涤, 干燥 ($MgSO_4$) 并且蒸发至干, 从而产生 0.11g 的中间体 (6)。

[0159] 实例 A. 3

[0160]

a) 制备

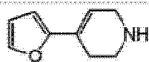


中间体(7)

[0161] 在 N_2 下的反应。微波条件: 80°C , 20 分钟。将中间体 (1) (0.3g, 0.905mmol) 和呋喃-2-硼酸 (0.122g, 1.09mmol) 在 K_2CO_3 (0.905ml) 和乙二醇二甲醚 (3ml) 中的溶液用 N_2 吹扫 10 分钟, 然后加入四(三苯基膦) 钯 (0) (0.105g, 0.0905mmol)。将混合物按照以上的微波条件照射, 冷却到室温, 加入水和 EtOAc, 分离有机层, 用水然后盐水洗涤, 干燥 ($MgSO_4$) 并且蒸发至干。通过快速色谱法在硅胶 (硅胶 § 10g, 15–40 μm , 庚烷 100 至庚烷 / EtOAc 90/10) 上进行残余物的纯化。收集纯的部分并且蒸发至干, 从而产生 0.1g 的中间体 (7)。

[0162]

b) 制备



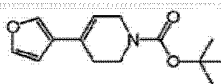
中间体(8)

[0163] 将中间体 (7) (0.1g, 0.401mmol) 在 TFA (0.3ml) 和 DCM (2ml) 中的溶液在室温下搅拌 30 分钟, 加入 K_2CO_3 (10% 水溶液) 和 DCM, 将有机层分离, 用水洗涤, 干燥 ($MgSO_4$) 并且蒸发至干, 从而产生 0.046g 的中间体 (8)。

[0164] 实例 A.4

[0165]

a) 制备

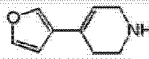


中间体(9)

[0166] 在 N_2 下的反应。微波条件: 80°C , 20 分钟。将中间体 (7) (0.28g, 0.845mmol) 和呋喃-3-硼酸 (0.104g, 0.93mmol) 在 K_2CO_3 (2M, 0.845ml) 和乙二醇二甲醚 (3ml) 中的溶液用 N_2 吹扫 10 分钟, 然后加入四(三苯基膦) 钯 (0) (0.0977g, 0.0845mmol)。将混合物按照以上的条件照射, 冷却到室温, 加入水和 EtOAc, 分离有机层, 用水然后盐水洗涤, 干燥 ($MgSO_4$) 并且蒸发至干。通过快速色谱法在硅胶 (10g, 15–40 μm , 庚烷 100 至庚烷 / EtOAc 90/10) 上进行残余物的纯化。收集纯的部分并且蒸发至干, 从而产生 0.146g 的中间体 (9)。

[0167]

b) 制备



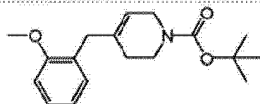
中间体(10)

[0168] 将中间体 (9) (0.146g, 0.586mmol) 在 TFA (0.5ml) 和 DCM (3ml) 中的溶液在室温下搅拌 30 分钟, 加入 K_2CO_3 (10% 水溶液) 和 DCM, 将有机层分离, 用水洗涤, 干燥 ($MgSO_4$) 并且蒸发至干, 从而产生 0.085g 的中间体 (10)。

[0169] 实例 A.5

[0170]

a) 制备

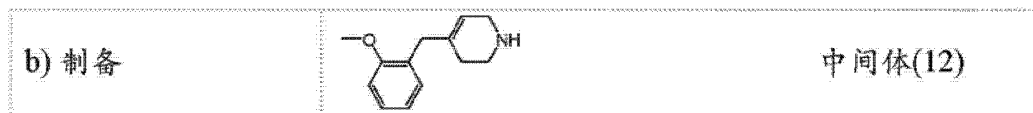


中间体(11)

[0171] 在 N_2 下的反应。微波条件: 80°C , 20 分钟。将中间体 (4) (0.1g, 0.302mmol) 和 2-甲氧基苄基氯化锌 (0.724ml, 0.93mmol) 在 THF (0.5ml) 中的溶液通过 N_2 鼓泡 10 分钟除

气,然后加入 1,1'-双(二苯基膦基)二茂铁二氯钯(II) (0.022g,0.03mmol)。将混合物按照以上的条件照射,冷却到室温,加入水和 EtOAc,分离有机层,用水然后盐水洗涤,干燥 (MgSO_4) 并且蒸发至干,从而产生中间体 (11)。

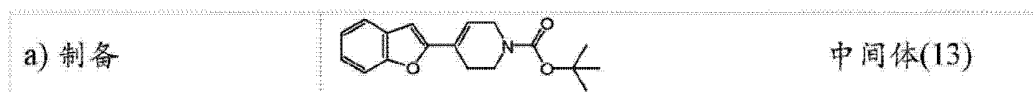
[0172]



[0173] 将中间体 (11) (0.232g,0.765mmol) 在 TFA(0.6ml) 和 DCM(5ml) 中的溶液在室温下搅拌 45 分钟,加入 K_2CO_3 (10%水溶液) 和 DCM,将有机层分离,用水洗涤,干燥 (MgSO_4) 并且蒸发至干,从而产生 0.145g 的中间体 (12)。

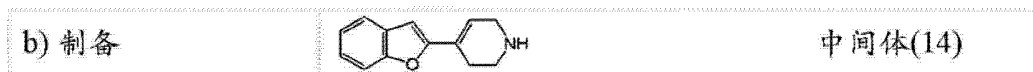
[0174] 实例 A.6

[0175]



[0176] 微波条件:80℃,20 分钟。将中间体 (4) (0.3g,0.905mmol) 和苯并[b]呋喃-2-硼酸 (0.176g,1.09mmol) 在 K_2CO_3 (2M,0.905ml) 和乙二醇二甲醚 (3ml) 中的溶液用 N_2 吹扫 10 分钟,然后加入四(三苯基膦)钯 (0) (0.105g,0.0905mmol)。将混合物按照以上的条件照射,冷却到室温,加入水和 EtOAc,分离有机层,用水然后盐水洗涤,干燥 (MgSO_4) 并且蒸发至干。通过快速色谱法在硅胶 (10g,15-40 μm ,庚烷 100 至庚烷/EtOAc90/10) 上进行残余物的纯化。收集纯的部分并且蒸发至干,从而产生 0.217g 的中间体 (13)。

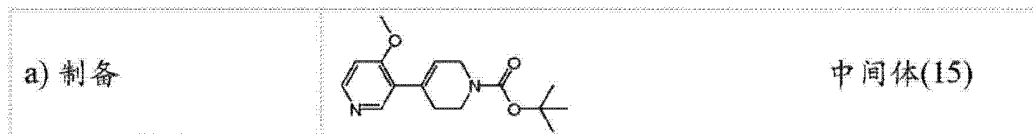
[0177]



[0178] 将中间体 (13) (0.217g,0.725mmol) 在 TFA(0.6ml) 和 DCM(4ml) 中的溶液在室温下搅拌 30 分钟,加入 K_2CO_3 (10%水溶液) 和 DCM,将有机层分离,用水洗涤,干燥 (MgSO_4) 并且蒸发至干。

[0179] 实例 A.7

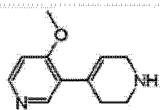
[0180]



[0181] 在 N_2 下的反应。微波条件:400W,80℃,30 分钟。将中间体 (4) (0.752g,1.36mmol) 和 4-甲氧基-3-吡啶基-硼酸 (0.25g,1.64mmol) 在 K_2CO_3 (2M,1.36ml) 和乙二醇二甲醚 (8ml) 中的溶液用 N_2 除气 10 分钟,然后加入四(三苯基膦)钯 (0) (0.157g,0.0136mmol)。将混合物按照以上的微波条件照射,冷却到室温,加入水和 EtOAc,分离有机层,用水然后盐水洗涤,干燥 (MgSO_4) 并且蒸发至干。通过快速色谱法在硅胶 (30g,15-40 μm ,从 CH_2Cl_2 至 $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$:97/3/0.1 梯度洗脱) 上进行残余物的纯化,收集纯的部分并且蒸发至干,从而产生 0.19g 的中间体 (15)。

[0182]

b) 制备



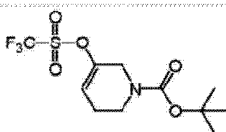
中间体(16)

[0183] 将中间体 (15) (0.2g, 0.689mmol) 和 TFA (0.218ml) 在 DCM (2ml) 中的混合物在室温下搅拌 30 分钟, 然后将该反应混合物倾倒入水中并且用 DCM 萃取。将该有机层分离, 用 NaHCO_3 (10% 水溶液) 和水洗涤, 干燥 (MgSO_4), 并且蒸发至干, 从而产生 0.11g 中间体 (16)。

[0184] 实例 A. 8

[0185]

a) 制备

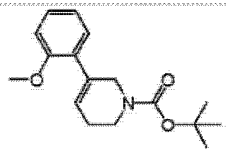


中间体(17)

[0186] 在 N_2 下的反应。将 BuLi (1.6M 于 THF 中) (3.76ml, 6.02mmol) 在 -20°C 下滴加至 DIPA (0.846ml, 6.02mmol) 于 THF (10ml) 中的溶液中并且然后将该混合物在 -20°C 下搅拌 20 分钟。然后在 -78°C 下加入 1-N-Boc-3-吡啶酮 (1.0g, 5.02mmol) 于 THF (10ml) 中的溶液并且将得到的混合物在 -78°C 下搅拌 30 分钟。然后在 -78°C 下加入 2-[N,N-双(三氟甲基磺酰基)-氨基]-5-氯吡啶 (2.26g, 5.52mmol) 在 THF (5ml) 中的溶液, 然后允许混合物达到室温并且搅拌过夜。将反应混合物蒸发至干燥。将得到的残余物通过正相色谱 (硅胶, 450g, 20-45 μm , 流动相 (90% 庚烷, 10% AcOEt)) 纯化。收集所希望的部分并且将溶剂蒸发, 从而产生 0.32g 的中间体 (17)。

[0187]

b) 制备

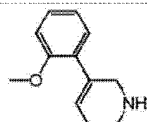


中间体(18)

[0188] 在 N_2 下的反应。微波条件: 80°C , 20 分钟。将中间体 (17) (0.32g, 0.966mmol) 和 2-甲氧基苯基硼酸 (0.176g, 1.16mmol) 在 K_2CO_3 (2M, 0.97ml) 和乙二醇二甲醚 (3ml) 中的溶液用 N_2 吹扫 10 分钟, 然后加入四(三苯基膦)钯 (0) (0.112g, 0.097mmol)。将混合物按照以上的微波条件照射, 冷却到室温, 加入水和 EtOAc, 分离有机层, 用水然后盐水洗涤, 干燥 (MgSO_4) 并且蒸发至干。通过快速色谱法在硅胶 (10g, 15-40 μm , 庚烷 100 至庚烷 / EtOAc 80/20) 上进行残余物的纯化, 收集纯的部分并且蒸发至干, 从而产生 0.22g 的中间体 (18)。

[0189]

c) 制备



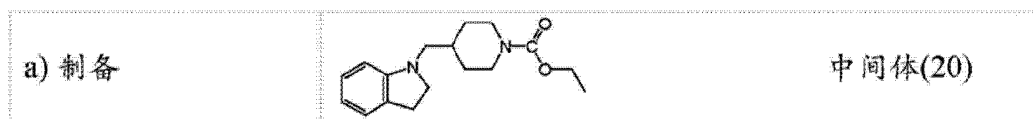
中间体(19)

[0190] 将中间体 (18) (0.2g, 0.76mmol) 和 TFA (0.6ml) 在 DCM (4ml) 中的混合物在室温下搅拌 30 分钟, 然后将该反应混合物倾倒入水中并且用 DCM 萃取。将该有机层分离, 用

NaHCO₃ (10%水溶液) 和水洗涤,干燥 (MgSO₄), 并且蒸发至干,从而产生 0.13g 中间体 (19)。

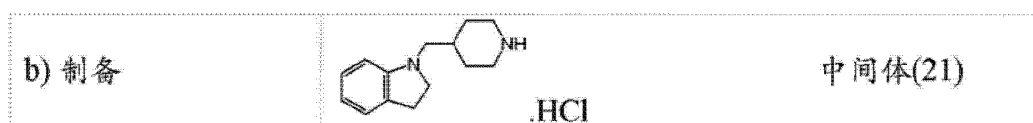
[0191] 实例 A. 9

[0192]



[0193] 将 4-甲酰基哌啶-1-羧酸乙酯 (0.10mol) 和 2,3-二氢-1H-吲哚 (0.10mol) 在甲醇 (250ml) 中的混合物在 50°C 下用 Pd/C, 10% (3g) 作为催化剂在噻吩 (4% 溶液, 2ml) 存在下氢化。吸收氢气 (1 当量) 后, 将该催化剂过滤出并将滤液蒸发, 从而产生 28g 的中间体 (20)。

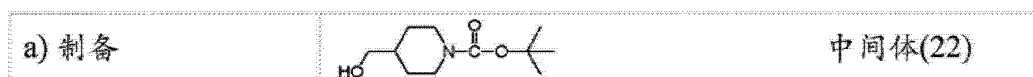
[0194]



[0195] 将中间体 (20) (0.050mol) 与 KOH (0.35mol) 在 2-丙醇 (150ml) 和 H₂O (5ml) 中的混合物搅拌并且回流 6 小时。将溶剂进行蒸发。将水添加至残余物, 并且将该混合物用 CH₂Cl₂ 萃取。将该分离的有机层干燥, 过滤并将该溶剂蒸发。将残余物溶解在 2-丙醇中并且用 HCl/2-丙醇转化为盐酸盐 (1:2)。将沉淀物过滤出并且干燥, 从而产生 11.7g 中间体 (21)。

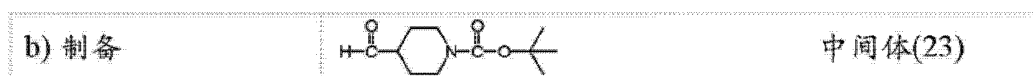
[0196] 实例 A. 10

[0197]



[0198] 将 4-哌啶甲醇 (43.412mmol) 和二碳酸二叔丁酯 (47.753mmol) 在 CH₂Cl₂ (50ml) 中的溶液在室温下搅拌过夜。加入水, 将合并的有机层用盐水洗涤, 干燥 (MgSO₄) 并蒸发以给出 10.61g 中间体 (22)。

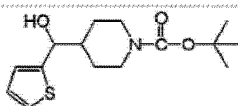
[0199]



[0200] 在 -70°C 并且在 N₂ 下向 CH₂Cl₂ (43ml) 中的二甲亚砜 (86.766mmol) 滴加草酰氯在 CH₂Cl₂ (130ml) 中的溶液然后滴加在 CH₂Cl₂ (43ml) 中的中间体 (22) (43.383mmol)。将该混合物在 -70°C 搅拌 15 分钟。滴加三乙胺 (216.914mmol)。将该混合物在 -70°C 下搅拌 1 小时并且允许达到室温。将混合物倾倒入水中并且用 CH₂Cl₂ 萃取。将该有机物用 NaHCO₃ 洗涤, 干燥 (MgSO₄), 过滤并蒸发至干。色谱提纯: 90g 硅胶 (15-40 μm), 洗脱液: CH₂Cl₂ (100%)。将纯的部分蒸发至干以给出 8.18g 的中间体 (23)。

[0201]

c) 制备

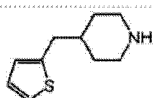


中间体(24)

[0202] 在 0℃ 并且在氮气氛围下, 将 THF (50mL, 50mmol) 中的 2-溴化噻吩基镁逐滴添加至冰浴中冷却的 Et₂O (100mL) 中的中间体 23 (8.89g, 41.68mmol) 的溶液中。在 0℃ 将该溶液搅拌 2 小时。加入 NH₄Cl 的水溶液, 将有机层用 DCM 萃取, 干燥 (MgSO₄), 过滤并且浓缩。将残余物通过快速色谱法在硅胶 (120g, 15-40 μm, 从 80/20 至 60/40 的庚烷/EtOAc) 上进行纯化。收集纯的部分并且浓缩以给出 3.96g 的中间体 (24)。

[0203]

d) 制备



中间体(25)

[0204] 将三氟乙酸 (8.81mL, 114.32mmol) 滴加到中间体 (24) (3.4g, 11.43mmol) 和三乙基硅烷 (18.21mL, 114.32mmol) 在 CH₂Cl₂ (35mL) 中的溶液里。将所得混合物在室温下搅拌 2 小时, 并且然后加入 K₂CO₃ (10% 水溶液)。将有机层用 CH₂Cl₂ 萃取, 在硫酸镁上干燥, 过滤并且蒸发溶剂以得到一种浅黄色油。将该反应产物通过快速色谱法在硅胶 (90g, 15-40 μm, 从 100/0/0 至 90/10/0.1 的 CH₂Cl₂/MeOH/NH₄OH) 上纯化。收集纯的部分并且浓缩以给出 1.12g 的中间体 (25)。

[0205] 实例 A. 11

[0206]

制备



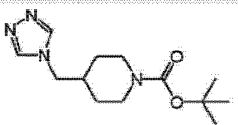
中间体(26)

[0207] 在 10℃ 下将亚硫酸二氯 (9mL, 12.5mL) 滴加到在 DMF (100mL) 中的 1,2-二甲酰肼 (hydrazinedicarbox-aldehyde) (4.4g, 50mmol) 中。然后将该混合物搅拌 1.5 天并且将沉淀过滤并用 DMF (10mL) 和醚 (10mL) 洗涤。将固体在真空中干燥, 从而产生 9.9g 中间体 (26)。

[0208] 实例 A. 12

[0209]

a) 制备

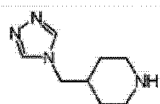


中间体(27)

[0210] 将 4-氨基甲基-1-N-(叔丁氧基羰基)哌啶 (3.5mmol), 中间体 (26) (4.2mmol) 和对甲苯磺酸 (催化量) 在甲苯 (50mL) 中的混合物搅拌并且回流 10 小时。蒸发之后, 将残余物通过柱色谱在硅胶 (洗脱液: CH₂Cl₂/MeOH 10/1) 上纯化。收集产物部分并且将溶剂蒸发, 从而产生 0.46g 的中间体 (27)。

[0211]

b) 制备



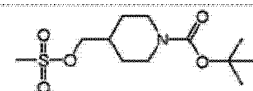
中间体(28)

[0212] 将中间体 (27) (0.3g, 1.1mmol) 和 TFA (1.25g, 11mmol) 在 DCM (20ml) 中的混合物搅拌过夜。将溶剂进行蒸发。将残余物溶解在水中, 并且 Na_2CO_3 (水溶液) 将 pH 调节到 10。将混合物用 CH_2Cl_2 (10x10ml) 萃取。将分离的有机层干燥 (Na_2SO_4), 过滤, 并将该溶剂蒸发以给出 0.17g 的中间体 (28)。

[0213] 实例 A. 13

[0214]

a) 制备

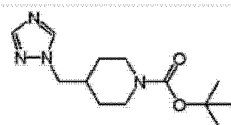


中间体(29)

[0215] 在室温下, 向 NaH (0.104g, 2.6mmol) 在 DMF (10ml) 中的溶液滴加 1H-1,2,4-三唑 (0.207g, 3mmol) 在 DMF (5ml) 中的溶液。将得到的混合物搅拌 30 分钟。然后添加在 DMF (5ml) 中的中间体 (29) (0.587g, 2mmol)。将形成的混合物在室温下搅拌 5 小时, 然后加热到 80 °C 过夜。将该反应混合物在室温下冷却, 然后用水 (30mL) 处理并且用 EtOAc (3x40ml) 萃取。将该合并的有机层用 Na_2SO_4 干燥, 过滤, 并蒸发滤液溶剂。将残余物通过柱色谱在硅胶 (洗脱液: EtOAc) 上进行纯化。收集产物部分并且将溶剂蒸发, 从而产生 0.42g 的中间体 (29)。

[0216]

b) 制备

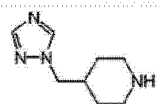


中间体(30)

[0217] 向中间体 (29) (2.15g, 10mmol) 和三乙胺 (1.52g, 15mmol) 在 CH_2Cl_2 (50ml) 中的混合物中滴加在冰浴中的甲磺酰氯 (1.37g, 12mmol)。添加之后, 将冷却浴移除。将混合物在室温下搅拌过夜。将反应混合物用 CH_2Cl_2 (50ml) 稀释, 然后用盐水 (40ml) 进行处理。分离有机层, 干燥 (Na_2SO_4), 过滤并将滤液溶剂蒸发。将该残余物通过柱色谱在硅胶 (洗脱液: 石油醚 / EtOAc 1/1) 上进行纯化。收集产物部分并且将溶剂蒸发, 从而产生 2.47g 的中间体 (30)。

[0218]

c) 制备



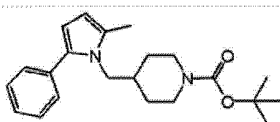
中间体(31)

[0219] 将中间体 (30) (1.5mmol)、TFA (3ml) 和 CH_2Cl_2 (20ml) 的混合物在室温下搅拌过夜。移除溶剂并且将 pH 用 2N NaOH 调节到 8-10 并且将反应混合物用 EtOAc (3x50ml) 萃取, 在无水 Na_2SO_4 上干燥, 然后过滤并且浓缩以得到该产物, 从而产生 0.13g 的中间体 (31)。

[0220] 实例 A. 14

[0221]

a) 制备

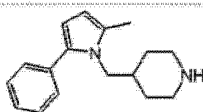


中间体(32)

[0222] 在室温下,向 NaH(0.104g, 2.6mmol) 在 DMF(10ml) 中的溶液滴加 2-甲基-5-苯基-1H-吡咯 (0.472g, 3mmol) 在 DMF(5ml) 中的溶液。将得到的混合物搅拌 30 分钟。然后添加在 DMF(5ml) 中的中间体 (29) (0.587g, 2mmol)。将形成的混合物在室温下搅拌 5 小时,然后加热到 80℃ 过夜。将该反应混合物在室温下冷却,然后用水 (30mL) 处理。将该水层用 EtOAc(3x40ml) 萃取。将该合并的有机层用 Na_2SO_4 干燥,过滤并蒸发滤液溶剂。将该残余物通过柱色谱在硅胶(洗脱液:石油醚/EtOAc10/1)上进行纯化。收集产物部分并且将溶剂蒸发,从而产生 0.6g 的中间体 (32)。

[0223]

b) 制备



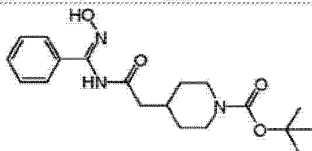
中间体(33)

[0224] 在 0℃ 下向中间体 (32) (0.560g, 1.57mmol) 在 CH_3CN (5ml) 中的溶液中滴加 HCl(10ml)。添加之后,将该混合物回流 1 小时。将反应混合物冷却至 0℃。添加 Na_2CO_3 (8g)。将该混合物用乙酸乙酯 (3x20ml) 萃取。将该合并的有机层用 Na_2SO_4 干燥,过滤并蒸发滤液溶剂。将残余物通过柱色谱在硅胶(洗脱液: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20/1)上纯化。收集纯的产物部分并且将溶剂蒸发,从而产生 0.1g 的中间体 (33)。

[0225] 实例 A. 15

[0226]

a) 制备

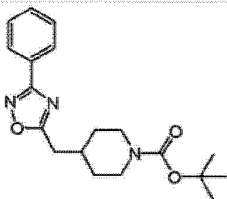


中间体(34)

[0227] 在室温下将 1-[(1,1-二甲基乙氧基)羰基]-4-哌啶乙酸 (9.87mmol)、N-羟基苯甲脒 (9.87mmol)、HATU(9.87mmol) 和 DIPEA(20mmol) 在 DMF(50mL) 中的混合物搅拌过夜。加入 NH_4Cl (50ml), 将水层用 CH_2Cl_2 (5x40mL) 萃取, 将合并的有机层用饱和 NaHCO_3 (90ml) 和盐水 (90mm) 洗涤, 用 MgSO_4 干燥并且过滤。蒸发溶剂以给出产物, 从而产生 1.92g 的中间体。

[0228]

b) 制备

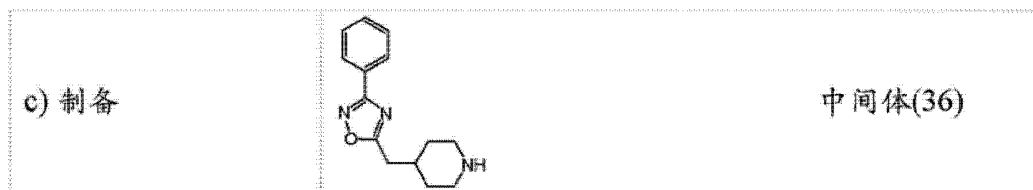


中间体(35)

[0229] 将中间体 (34) (1.38mmol)、伯吉斯试剂 (CAS29684-56-8) (1.38mmol) 在 THF(50ml) 中的混合物在氩气中搅拌并且回流过夜。将溶剂进行蒸发。将残余物溶解在水

中,并且用 CH_2Cl_2 (3x20ml) 萃取。将合并的有机层干燥 (Na_2SO_4), 过滤并将该溶剂蒸发。将残余物通过柱色谱在硅胶 (洗脱液: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10/1) 上纯化以获得 0.21g 的中间体 (35)。

[0230]



[0231] 将中间体 (35) (0.3g, 0.87mmol) 和 TFA (1g, 8.7mmol) 在 CH_2Cl_2 (20ml) 中的混合物搅拌过夜。将溶剂进行蒸发。将残余物溶解在水中, 并且用 Na_2CO_3 将 pH 调节到 10。将混合物用 CH_2Cl_2 (10x10mL) 萃取。将分离的有机层干燥 (Na_2SO_4), 过滤, 并将该溶剂蒸发以给出产物, 从而产生 0.14g 的中间体 (36)。

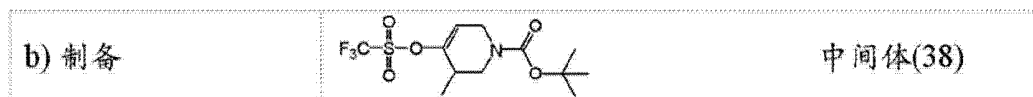
[0232] 实例 A. 16

[0233]



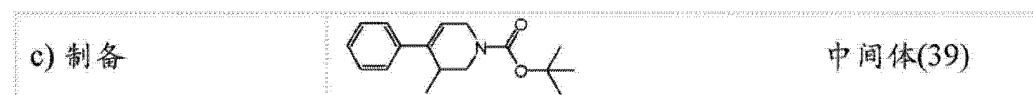
[0234] 将 1-苄基-3-甲基-4-哌啶酮 (2.0g, 9.84mmol) 二碳酸二叔丁酯 (2.36g, 10.8mmol) 和 Pearlman 催化剂 (氢氧化钯 (II)) (0.35g, 2.46mmol) 在 EtOAc (50ml) 中的混合物在帕尔振荡器 (Parr shaker) (3 巴, 室温) 中氢化过夜。将反应混合物通过短硅藻土垫过滤, 滤饼用 EtOAc 洗涤, 滤液用水然后用盐水洗涤, 干燥 (MgSO_4) 并且蒸发至干, 从而产生 2.2g 中间体 (37)。

[0235]



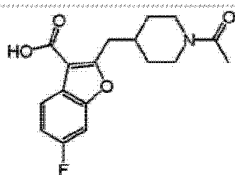
[0236] 在 N_2 下的反应。将 BuLi (1.6M 于 THF 中) (3.52ml, 5.63mmol) 在 -20°C 下滴加至 DIPA (0.791ml, 5.63mmol) 于 THF (8ml) 中的溶液中并且然后将该混合物在 -20°C 下搅拌 20 分钟。然后在 -78°C 下加入中间体 (37) (1.0g, 4.70mmol) 于 THF (10ml) 中的溶液并且将得到的混合物在 -78°C 下搅拌 30 分钟。然后在 -78°C 下加入 N-苄基三氟甲烷磺酰亚胺 (1.92g, 5.16mmol) 在 THF (6ml) 中的溶液, 然后允许混合物达到室温并且搅拌过夜。将混合物浓缩并且通过正相色谱 (硅胶, 450g, 20-45 μm , 流动相 (80% 庚烷, 20% AcOEt)) 纯化。收集所希望的部分并且将溶剂蒸发, 从而产生 1.7g 的中间体 (38)。

[0237]



[0238] 在 N_2 下的反应。微波条件: 80°C , 20 分钟。将中间体 (38) (1.0g, 1.45mmol) 和苯基硼酸 (0.194g, 1.59mmol) 在 K_2CO_3 (1.45ml) 和乙二醇二甲醚 (10ml) 中的溶液用 N_2 吹扫 10 分钟, 然后加入四 (三苯基膦) 钯 (0) (0.167g, 0.145mmol)。将混合物按照以上的微波条件照射, 冷却到室温, 加入水和 EtOAc, 分离有机层, 用水然后盐水洗涤, 干燥 (MgSO_4) 并且

c) 制备

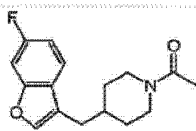


中间体(43)

[0247] 将 NaOH(0.038mol) 在 H₂O(50ml) 中的溶液添加至中间体 42(0.0186mol) 在 MeOH(10ml) 中的溶液中。将该反应混合物在室温下搅拌过夜。添加水(150ml), 从而导致完全溶解。将混合物用 CH₂Cl₂ 洗涤。将水层用浓盐酸酸化, 并且将该混合物用 CH₂Cl₂ 萃取三次。将有机层分离, 干燥(MgSO₄), 过滤并将溶剂蒸发, 从而产生 5.1g 的中间体(43)。

[0248]

d) 制备

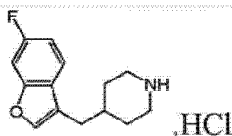


中间体(44)

[0249] 将中间体(43)(0.016mol) 与 Cu 粉末(0.8g) 在喹啉(50ml) 中的混合物在 210°C /220°C 搅拌一个小时。将反应混合物冷却并将沉淀过滤掉。将 CH₂Cl₂(100ml) 添加到该滤液中。将该有机相用 HCl(20%, 200ml) 洗涤两次, 用水洗涤一次, 用 NaOH(10% 水溶液) 洗涤一次, 并且再次用水洗涤, 干燥(MgSO₄), 过滤并且蒸发溶剂, 从而产生 3.4g 中间体(44)。

[0250]

e) 制备



中间体(45)

[0251] 将中间体(44)(0.012mol) 在 EtOH(20ml) 和浓 HCl(56ml) 中的混合物回流过夜。将该反应混合物进行冷却并将溶剂蒸发。将残余物溶解在 2-丙酮(15ml) 中, 在室温下搅拌并且将得到的沉淀过滤出, 在 CH₃CN 中搅拌, 过滤出, 用 DIPE 洗涤, 然后干燥(真空 100°C), 从而产生 2.06g 的中间体(45)。

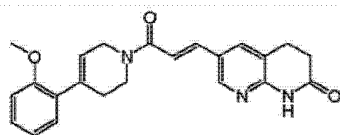
[0252] 在最终化合物的制备中所使用的一些中间体是可商购的, 例如 1,2,3,6-四氢-4-(2-甲氧苯基)-吡啶、3-苯氧基哌啶、1,2,3,4-四氢异喹啉、4-苯基哌啶、3-(4-哌啶基)-苯酚、苯基-4-哌啶基-甲酮盐酸盐、1,2,3,6-四氢-4-苯基-吡啶、4-(4-氯苯基)-4-哌啶醇、4-苄基哌啶、4-(2-甲氧苯基)-哌啶、2-(4-哌啶基甲基)-苯并噻唑、1,2,3,6-四氢吡啶、4-(2-氯苯基)-1,2,3,6-四氢-吡啶、1',2',3',6'-四氢-3,4'-联吡啶、1,2,3,6-四氢-4-[3-(三氟甲基)苯基]-吡啶、1,2,3,6-四氢-4-(3-甲氧苯基)-吡啶、1,2,3,6-四氢-4-(4-甲氧苯基)-吡啶、1-(苯基甲基)-哌啶、1-苯基哌啶、哌啶、4-苯氧基-哌啶、4-(2-苯氧基-乙基)-哌啶哌啶、4-[2-(4-氟苯氧基)乙基]-哌啶盐酸盐、4-[(4-氟苯氧基)-甲基]-哌啶盐酸盐、4-(苯基-甲基)-哌啶、1-(4-哌啶基-甲基)-1H-吡啶、2-(4-哌啶基甲基)-喹啉。

[0253] B. 最终化合物的合成

[0254] 实例 B0.1

[0255]

制备



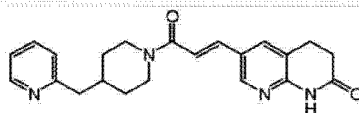
化合物(2)

[0256] 将中间体 (2) (0.6g, 1.81mmol) 1,2,3,6-四氢-4-(2-甲氧基-苯基)吡啶 (0.0.479g, 2.53mmol)、HOBt (0.293g, 2.17mmol)、EDCI (0.415g, 2.17mmol) 和 Et₃N (0.60ml, 4.33mmol) 在 DCM (12ml) 和 THF (12ml) 中的溶液在室温下搅拌 24 小时, 加入水和 DCM, 将有机层分离, 用水洗涤, 干燥 (MgSO₄) 并且蒸发至干。将残余物从 EtOH 中结晶以给出 0.47g 的化合物 (2)。

[0257] 实例 B. 2

[0258]

制备



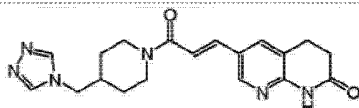
化合物(35)

[0259] 将 2-(吡啶基甲基)哌啶 (0.12g, 0.72mmol)、中间体 (2) (0.17g, 0.80mmol)、EDCI (0.14g, 0.72mmol)、HOBt (0.10g, 1.072mmol) 和 DIPEA (0.28g, 2.16mmol) 在 CH₂Cl₂ (50mL) 中在室温下搅拌过夜。加入饱和 NH₄Cl (50ml), 将水层用 CH₂Cl₂ (2x20mL) 萃取。将这些合并的有机层用 NaHCO₃ (30mL) 和盐水 (30mL) 洗涤, 用 MgSO₄ 干燥, 通过柱色谱 (洗脱液: CH₂Cl₂/MeOH 20/1) 纯化。收集所希望的产物部分并且将溶剂蒸发, 从而产生 0.120g 的化合物 (35)。

[0260] 实例 B. 3

[0261]

制备



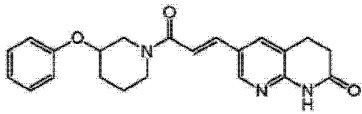
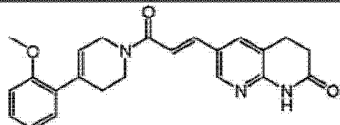
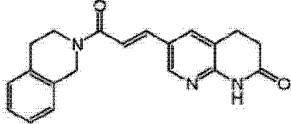
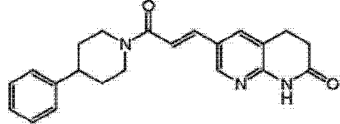
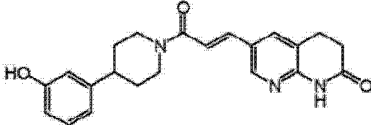
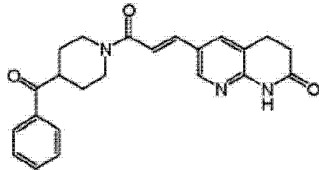
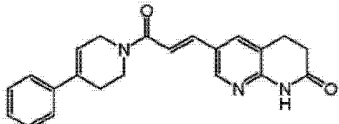
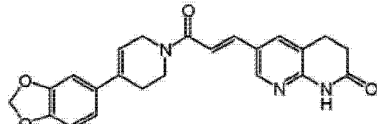
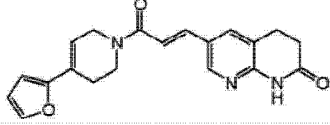
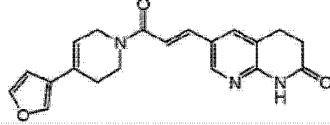
化合物(38)

[0262] 将中间体 (28) (0.17g, 1.12mmol)、中间体 (2) (0.24g, 1.12mmol)、HATU (0.426g, 1.12mmol) 和 DIPEA (0.263g, 2.04mmol) 在 CH₂Cl₂ (50ml) 中的溶液在室温下搅拌过夜。加入饱和的 NH₄Cl (50ml), 将水层用 CH₂Cl₂ (2x20mL) 萃取, 用 NaHCO₃ (30ml) 和盐水 (30ml) 洗涤, 干燥 (MgSO₄) 并且通过柱色谱法在硅胶 (洗脱液: CH₂Cl₂/MeOH 10/1) 上纯化。收集产物部分并且将溶剂蒸发, 从而产生 20mg 的化合物 (38)。

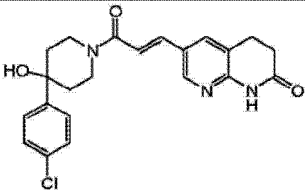
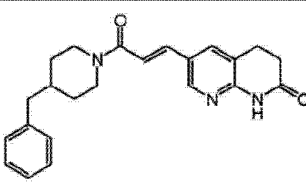
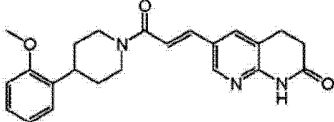
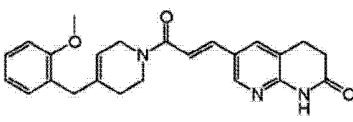
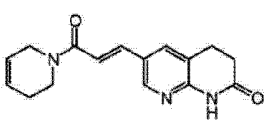
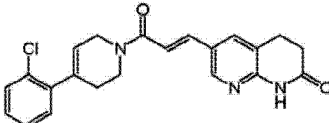
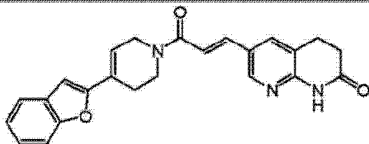
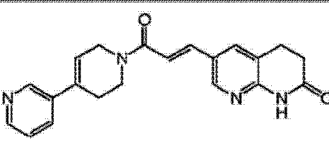
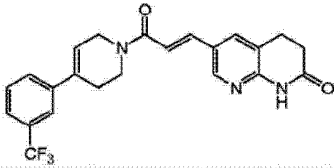
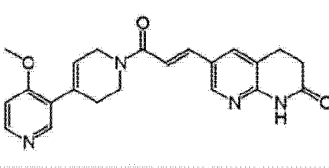
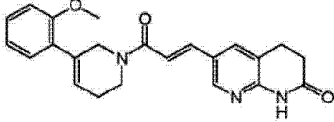
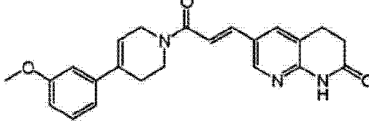
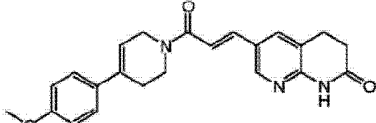
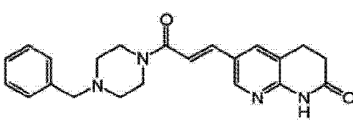
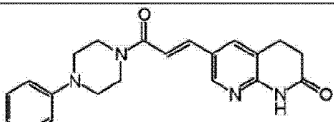
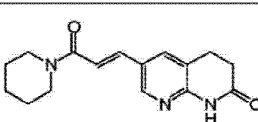
[0263] 表 F-1 列出了根据以上实例之一制备的化合物。

[0264] 表 F-1

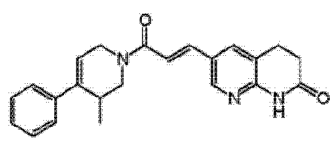
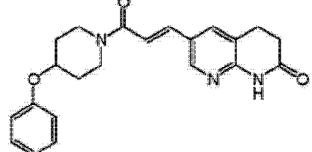
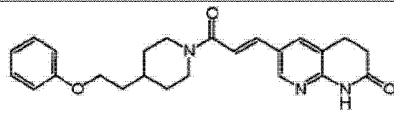
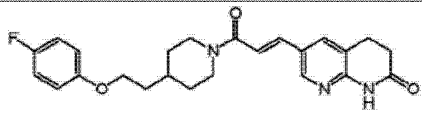
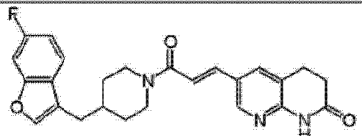
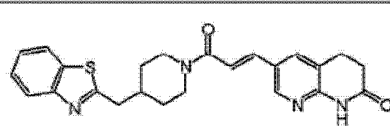
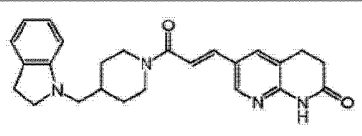
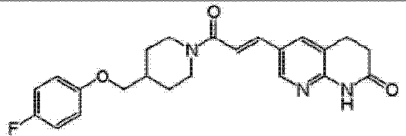
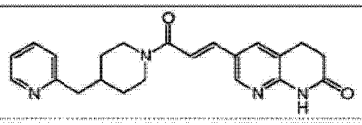
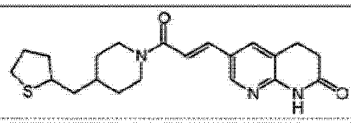
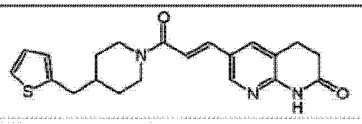
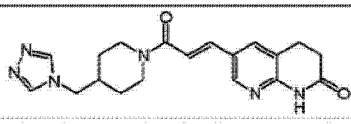
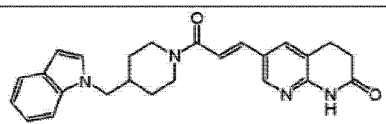
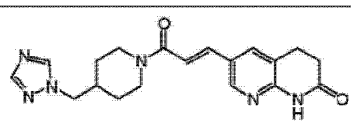
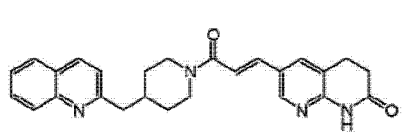
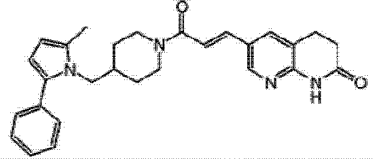
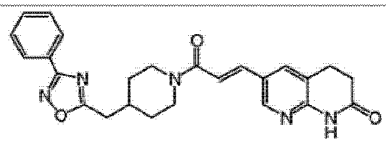
[0265]

 化合物编号 1; Ex. B.1	 化合物编号 2; Ex. B.1
 化合物编号 3; Ex. B.1	 化合物编号 4; Ex. B.1
 化合物编号 5; Ex. B.1	 化合物编号 6; Ex. B.1
 化合物编号 7; Ex. B.1	 化合物编号 8; Ex. B.1
 化合物编号 9; Ex. B.1	 化合物编号 10; Ex. B.1

[0266]

 化合物编号 11; Ex. B.1	 化合物编号 12; Ex. B.1
 化合物编号 13; Ex. B.1	 化合物编号 14; Ex. B.1
 化合物编号 15; Ex. B.1	 化合物编号 16; Ex. B.1
 化合物编号 17; Ex. B.1	 化合物编号 18; Ex. B.1
 化合物编号 19; Ex. B.1	 化合物编号 20; Ex. B.1
 化合物编号 21; Ex. B.1	 化合物编号 22; Ex. B.1
 化合物编号 23; Ex. B.1	 化合物编号 24; Ex. B.1
 化合物编号 25; Ex. B.1	 化合物编号 26; Ex. B.1

[0267]

	
化合物编号 27; Ex. B.1	化合物编号 28; Ex. B.1
	
化合物编号 29; Ex. B.1	化合物编号 30; Ex. B.1
	
化合物编号 31; Ex. B.1	化合物编号 32; Ex. B.1
	
化合物编号 33; Ex. B.1	化合物编号 34; Ex. B.1
	
化合物编号 35; Ex. B.2	化合物编号 36; Ex. B.2
	
化合物编号 37; Ex. B.1	化合物编号 38; Ex. B.3
	
化合物编号 39; Ex. B.2	化合物编号 40; Ex. B.3
	
化合物编号 41; Ex. B.3	化合物编号 42; Ex. B.3
	
化合物编号 43; Ex. B.3	

[0268]

[0269] C. 化合物鉴定

[0270] CI. LCMS

[0271] 关于本发明化合物的 LCMS 表征,使用以下方法。

[0272] 通用程序 A

[0273] 使用 UPLC(超高效液相色谱)Acquity(沃特斯公司)系统进行 LC 测量,该系统包括一个具有除气器的二元泵、一个自动进样器、一个二极管阵列检测器(DAD)以及一个如在以下对应的方法中详细描述的柱,该柱被保持在 40℃ 的温度。来自该管柱的流量被引至 MS 探测器。该 MS 探测器被配置为具有一个电喷雾电离源。毛细管针电压是 3kV 并且源温度在 Quattro(来自沃特斯公司的三级四极质谱仪)上保持在 130℃。使用氮气作为雾化器气体。用 Waters-Micromass MassLynx-Openlynx 数据系统进行数据采集。

[0274] 通用程序 B

[0275] 使用 Alliance HT2795(沃特斯公司)系统进行 HPLC 测量,该系统包括一个具有除气器的四元泵、一个自动进样器、一个二极管阵列探测器(DAD)以及一个在下面对应的方法中详细描述的柱,该管柱被保持在 30℃ 的温度。来自该柱的流被分流到 MS 光谱仪。该 MS 探测器被配置为具有一个电喷雾电离源。毛细管针电压是 3kV 并且源温度在 LCT(来自沃特斯公司的飞行时间 Zspray™(Time of Flight Zspray™)质谱仪)上保持在 100℃。使用氮气作为雾化器气体。用 Waters-Micromass MassLynx-Openlynx 数据系统进行数据采集。

[0276] 方法 1

[0277] 除了通用方法 A 之外,还有:在一个 Waters Acquity BEH(桥联的乙基硅氧烷/二氧化硅混合物)C18 管柱(1.7 μm, 2.1x100mm)上,以 0.35ml/min 的流速进行反相 UPLC。采用两个流动相(流动相 A:95% 7mM 乙酸铵/5% 乙腈;流动相 B:100% 乙腈)来运行梯度条件:从 90% A 与 10% B(持续 0.5 分钟),3.5 分钟后至 8% A 与 92% B 中持续 2min 并且 0.5min 后回到初始条件持续 1.5 分钟。使用 2 μl 的注射体积。用于阳离子化模式和阴离子化模式的锥孔电压是 20V。通过使用 0.1 秒的内扫描延迟在 0.2 秒内从 100 至 1000 的扫描获得质谱。

[0278] 方法 2

[0279] 除了通用方法 A 之外,还有:在一个 Waters Acquity BEH(桥联的乙基硅氧烷/二氧化硅混合物)C18 管柱(1.7 μm, 2.1x100mm)上,以 0.343ml/min 的流速进行反相 UPLC。采用两个流动相(流动相 A:95% 7mM 乙酸铵/5% 乙腈;流动相 B:100% 乙腈)来运行梯度条件:从 84.2% A 与 15.8% B(持续 0.49 分钟),2.18 分钟后至 10.5% A 与 89.5% B,持续 1.94min 并且 0.73min 后回到初始条件持续 0.73 分钟。使用 2 μl 的注射体积。用于阳离子化模式和阴离子化模式的锥孔电压是 20V。通过使用 0.1 秒的内扫描延迟在 0.2 秒内从 100 至 1000 的扫描获得质谱。

[0280] 方法 3

[0281] 除了通用方法 B 之外,还有:在一个 Waters X-桥 C18 柱(3.5 μm, 4.6x100mm)上,以 0.8ml/min 的流速进行反相 HPLC。采用两个流动相(流动相 A:100% 7mM 乙酸铵;流动相 B:100% 乙腈)来运行梯度条件:从 80% A 与 20% B(持续 0.5 分钟),4.5 分钟后至

90%, 90% B 持续 4min 并且与初始条件再平衡持续 3 分钟。使用 5 μ l 的注射体积。用于阳离子化模式和阴离子化模式的锥孔电压是 20V。通过使用 0.3 秒的内扫描延迟在 0.4 秒内从 100 至 1000 的扫描获得质谱。

[0282] 表 C.1: LC/MS 数据

化合物 编号	Rt (min)	MH ⁺	LC/MS 方法
12	2	390	2
15	1.85	325	2
17	3.46	404	1
19	2.66	432	2
21	3.46	400	1
26	2.4	326	3
31	2.33	361	1
39	2.57	417	2

[0284] C2. 熔点

[0285] 对于多个化合物, 使用 Kofler 热台获得了熔点, 该热台由一个具有线性温度梯度的经加热的板、一个滑动指针以及一个以摄氏度的温度标组成。

[0286] 对于多种化合物, 熔点是用差示扫描量热法 (DSC) 来确定的。使用 10°C / 分钟的温度梯度来测量熔点。最高温度是 400°C。

[0287] 其余的熔点使用开放的毛细管确定。

[0288] 表 C2: 熔点数据

化合物 编号	熔点 (Melting Moint)	方法	化合物 编号	熔点 (Melting Moint)	方法
1	76°C-77°C	-	23	258°C	Kofler
2	216.59°C	DSC	24	160°C	Kofler
3	278.46°C	DSC	25	151°C	Kofler
4	127.5°C- 128.5°C	-	27	252°C	Kofler
5	114°C	Kofler	28	242.08°C	DSC
6	> 260°C	Kofler	29	202.49°C	DSC
7	>260°C	Kofler	30	138°C	Kofler
8	133°C	Kofler	32	137°C-138°C	-
9	202.43°C	DSC	34	161.93°C	DSC
10	69.5°C-71°C	-	35	269.90°C	DSC
11	172°C	Kofler	36	187°C-188°C	Kofler
13	240°C	Kofler	37	177°C-178°C	-
14	225.34°C	DSC	38	165°C	Kofler
16	101.6°C- 103.2°C	-	40	208°C	Kofler
18	196°C	Kofler	41	170.15°C	DSC

[0290]	化合物编号	熔点 (Melting Moint)	方法	化合物编号	熔点 (Melting Moint)	方法
	20	> 260°C	Kofler	42	93°C-95°C	-
	22	260°C	Kofler	43	180°C	Kofler

[0291] D. 药理学实例

[0292] D. 1Fab I 酶抑制:金黄色葡萄球菌酶抑制测定。

[0293] FabI 酶抑制测定在半区 (half-area)、384 孔微滴定板上进行。化合物在 40- μ l 的测定混合物中评估,该混合物包含 100mM NaADA (pH6.5) (ADA = N-[2-乙酰氨基]-2-亚氨基二乙酸)、250 μ M 巴豆酰-CoA、625 μ M NADH 以及 50 μ g/ml 金黄色葡萄球菌 ATCC29213Fab I。抑制剂典型地是在 50 至 0.39 μ M 的范围内变化。将反应混合物在室温下培养 30 分钟并且通过添加 200mM Tris 缓冲液 (pH9.0) 产生 pH 偏移而停止反应。通过测量在 340 下的吸光度变化来监控 NADH 的消耗。通过将样品读数与阴性 (没有化合物) 和阳性 (没有酶) 对照的读数对比,确定这些化合物的酶活性的百分比抑制。通过最小二乘法拟合最佳拟合曲线。由此可以获得一个 IC_{50} 值 (以 μ g/ml 表达),引起 50%酶活性抑制。

[0294] 表 D.1:金黄色葡萄球菌 Fab I IC_{50} 值

[0295]	化合物编号	FabI IC_{50} μ g/mL	化合物编号	FabI IC_{50} μ g/mL
	1	3.52	22	0.93
	2	0.32	23	0.85
	3	0.48	24	7.17
	4	0.29	25	1.48
	5	0.35	26	2.73
	6	1.74	27	0.57
	7	0.41	28	0.93
	8	0.53	29	1.00
	9	0.34	30	1.34
	10	0.48	31	0.79
	11	0.80	32	1.72
	12	0.31	34	0.47

[0296]	化合物 编号	FabI IC ₅₀ µg/mL	化合物 编号	FabI IC ₅₀ µg/mL
	13	0.53	35	0.48
	14	1.06	36	0.61
	15	3.57	37	0.50
	16	0.58	38	> 7.31
	17	1.91	39	2.74
	18	0.67	40	1.43
	19	1.12	41	3.39
	20	0.78	42	10.18
	21	0.80		

[0297] D. 2 用于测试针对不同细菌菌株的多种化合物的抗菌活性的体外方法

[0298] 用于药敏试验的细菌悬浮液的制备

[0299] 使用了以下细菌：金黄色葡萄球菌 ATCC29213、耐甲氧西林金黄色葡萄球菌 (MRSA) ATCC700788 以及大肠杆菌 ATCC35218。将在这项研究中使用的细菌在 37℃、在去离子水中、在包含 100ml 米勒-海顿 (Mueller-Hinton) 肉汤 (Difco cat.nr. 0757-17) 的烧瓶中震荡下生长过夜。将多个储存物储存在 -70℃ 直到使用。

[0300] 在 35℃、在需氧条件 (第一代) 中, 将细菌在包含 5% 绵羊血液 (贝迪公司 (Becton Dickinson) 编号 254053) 的胰蛋白酶大豆琼脂平板上孵育 18-24 小时。对于第二代, 将新鲜的米勒-海顿肉汤用 5-10 个菌落接种并且在 35℃ 生长过夜直到在需氧条件中达到浊度 (达到对数期)。然后将该细菌悬浮液调节到 0.5 的麦克法兰 (McFarland) 密度并且进一步在马-欣二氏培养液介质中稀释为 1 : 100。这用作接种物。

[0301] 结果 (对于 STA ATCC29213) 在以下表 D2 中描述。

[0302] 抗细菌药敏试验 :IC₉₀ 测定

[0303] 用包含多种化合物的两倍连续稀释液的、最终体积为 0.1ml 的马-欣二氏培养液在 96 孔规格 (平底微滴定板) 中通过培养液微稀释法进行 MIC 测定并用 5×10^5 CFU/ml 的细菌 (根据 CLSI 指南的标准接种物容量) 接种。抑制剂典型地是在 63 至 0.49 µM 的范围内变化。在该测定中的最终 DMSO 浓度是 1.25% (最大容许 DMSO 浓度 = 6%)。在这些测定中试验了人血清对于抗金黄色葡萄球菌的化合物的活性的影响, 以 10% 的最终浓度添加人血清。将这些板在 35℃ 下孵育 16-20 小时。在孵育结束后, 通过荧光分析对细菌生长定量。为此目的, 将刃天青添加到所有的孔中并且将这些板再孵育。孵育时间取决于细菌的类型。颜色从蓝色变为粉红色表明了细菌生长。在激发波长 540nm 并且发射波长 590nm 处, 在计算机控制的荧光计 (Fluoroskan Ascent FL, 雷勃公司 (Labsystems)) 中读出该荧光。根据标准方法计算出由这些化合物实现的生长抑制百分数。将 IC₉₀ (以 µg/ml 代表) 定义为 90% 细菌生长抑制浓度。为了 QC 批准, 同时对一组参考化合物进行了试验。

[0304] 结果在以下表 D2 中描述 (STA+10% HS)。

[0305] 细胞毒性测定

[0306] 使用 MTT 测定法评估了这些化合物的细胞毒性。将生长在 96 孔板中的人 HeLaM 细胞暴露于连续稀释的试验化合物 (0.2ml 的终体积) 中并且在 37℃ 和 5% CO₂ 下孵育 72 小时。抑制剂典型地是在 25 至 0.8 µM 的范围内变化。在该测定中最终的 DMSO 浓度是 0.5%。

添加 MTT(3-(4,5-二甲基噻唑-2-基)-2,5-二苯四唑溴化鎘,一种四唑)并且其仅在活细胞中被还原为紫色甲月替。通过添加 100 μ l 2-丙醇实现甲月替晶体的溶解。通过测量所还原的甲月替的吸光度来测定细胞活力,在 540nm 和 690nm 处给出紫色。在 690nm 处的吸光度被自动地从 540nm 处的吸光度中减去以消除非特异性的效应。根据标准方法计算出由这些化合物实现的细胞毒性百分数。细胞毒性被记录为 CC_{50} ,是导引起胞活力下降 50% 的浓度。

[0307] 结果在以下表 D2 中描述 (TOX HELAM)。

[0308] 表 D2- 代表性实例的数据

[0309]

Cpd. No.	STA (361.159) IC90 μ g/mL	STA + 10% HS (361.169) IC90 μ g/mL	TOX HELAM (222.125) CC_{50} μ g/mL
2	1.97	2.99	> 9.78279
3	8.67	10.79	> 8.37438
4	4.99	4.60	> 9.07922
5	10.52	11.14	> 9.48112
7	2.07	2.54	> 9.02848
9	2.91	2.65	> 8.77628
10	10.43	20.34	> 8.77628
12	1.19	2.09	> 9.43139
14	6.93	13.06	> 10.1352
16	3.31	8.52	8.04
20	13.23	16.85	> 9.80766
22	21.16	> 24.5733	> 9.78279
27	6.13	21.99	> 9.38089
34	9.94	12.51	> 10.2852
35	5.14	3.94	> 9.45625
36	8.43	11.38	> 9.68408
37	0.30	0.36	19.12

[0310] 实例 E

[0311] E.1 热力学溶解度 / 水溶液中的溶解度

[0312] pH 溶解度特征曲线绘制 (profiling) 在环境温度下进行持续 4 天。进行饱和溶解度的研究以确定在一种特定的缓冲液溶液中的最大溶解度。将化合物添加到对应的缓冲液溶液中直至达到饱和点。这之后接着将烧瓶在环境温度下摇动 4 天。4 天之后,将溶液过滤并且注射到 UPLC 上并且使用通用的 HPLC 法确定浓度。

[0313] 结果

[0314]

	化合物编号 37
缓冲液pH 2	< 0.01
10% HP-β-CD缓冲液pH 2	NT
20% HP-β-CD缓冲液pH 2	NT
缓冲液 pH 4	< 0.01
10% HP-β-CD缓冲液pH 4	0.63
20% HP-β-CD缓冲液pH 4	> 1.202
缓冲液pH 7.4	< 0.01
10% HP-β-CD缓冲液pH 7.4	0.73
20% HP-β-CD缓冲液pH 7.4	> 1.316

[0315]

[0316] NT = 未测试

[0317] E. 2 抗微生物活性谱

[0318] 根据临床和实验室标准协会 (CLSI) 针对需氧细菌的方法 (CLSI M07-A8), 通过微量肉汤稀释法确定最小抑制浓度 (MIC) (参见临床和实验室标准协会 2009, 用于需氧生长的细菌的稀释抗微生物敏感性试验的方法, CLSI 文件 M07-A8, Vol. 29, No. 2), 该微量肉汤稀释法使用用于除了流感嗜血杆菌 (其中使用嗜血杆菌试验培养基 (HTM) 肉汤) 的大多数生物体的阳离子调节的米勒-海顿肉汤 (Mueller-Hinton broth) (CA-MHB)。生物个体的说明可以在下表中找到。适当时, 使用 ATCC 标准菌株。

[0319] 对敏感性试验的接种浓度进行标准化以给出大约 5×10^5 CFU/mL 的最终接种量。肉汤 MIC 确定为在 35°C - 37°C 下孵育 16-24 小时 (取决于物种) 之后防止的可见生长的最低药物浓度。

[0320] 表: 测试的生物个体的说明

[0321]

生物	特征	MIC 试验培养基
金黄色葡萄球菌	ATCC 29213; 参考菌株MSSA	MHB
金黄色葡萄球菌	ATCC 43300; 参考菌株MRSA	MHB
金黄色葡萄球菌	NRS119; LZD-R; SCCmec IV; origin: US	MHB
金黄色葡萄球菌	NRS120; LZD-R; SCCmec IV; origin: US	MHB
金黄色葡萄球菌	NRS121; LZD-R; SCCmec IV; origin: US	MHB
大肠杆菌	ATCC 25922; 参考菌株	MHB
大肠杆菌	Tol C mutant	MHB
流感嗜血杆菌	ATCC 49247; 参考菌株	HTM肉汤
卡他莫拉菌	ATCC 8176; b-内酰胺酶阴性	MHB

[0322] 在 DMSO 中以 1mg/mL 的浓度制备化合物的储备溶液。在 DMSO 以 2mg/mL 的浓度制备利奈唑胺。将所有化合物的储备溶液稀释到 CA-MHB 以给出二倍稀释的范围,取决于被测试生物的敏感性。

[0323] 结果 (如果有的话)

	生物	化合物编号和 MIC ₉₀ (μg/ml)
		37
[0324]	金黄色葡萄球菌 ATCC 29213	0.125
	金黄色葡萄球菌 ATCC 43300	0.125
	金黄色葡萄球菌 NRS119	0.125
	金黄色葡萄球菌 NRS120	0.125
	金黄色葡萄球菌 NRS121	0.125
	大肠杆菌 tolC 突变体	> 8
	大肠杆菌 ATCC 25922	> 8
	流感嗜血杆菌 ATCC 49247	> 8
	卡他莫拉菌 ATCC 8176	1

[0325] E.3 体内药物代谢动力学和口服生物利用度

[0326] 这些实例的化合物的体内药物代谢动力学和口服生物利用度在雄性瑞士小鼠 (饲养的) 中在单次静脉内 (i. v) 注射以及口服 (p. o) 给药后进行研究。对于 i. v 和 p. o. 溶液配制品, 将化合物溶解在 20% 的 HP-β-CD 溶液中。配方的 pH 是约 pH4。所有的 i. v. 配制品都是等渗的。

[0327] 结果

[0328]

	化合物编号 37
静脉内注射	
剂量 (mg/kg)	2.5
n	3
C ₀ (ng/mL)	2929
血浆清除率 Cl (L/h/kg)	0.33
Vd _z (L/kg)	1.3
AUC _{0-inf} (ng.h/mL)	7464
半衰期 (t _{1/2}) (h)	2.7
口服	
剂量 (mg/kg)	10
n	3
C _{max} (ng/mL)	2950
T _{max} (h)	2.0
AUC _{0-inf} (ng.h/mL)	21394
半衰期 (t _{1/2}) (h)	3.2
口服生物利用度 (%)	72

[0329]

[0330] E. 4 体内疗效测定

[0331] 1911 年针对肺炎双球菌的奥普托欣引入了通过腹膜内处理感染的小鼠研究体内抗菌化合物效果的概念 (Morgenroth 和 Levy, 1911)。模型的流行来自于其易于使用, 伴随短实验时期, 可再生的感染以及简单的终点。

[0332] 方法

[0333] 使用甲氧西林敏感的金黄色葡萄球菌菌株 ATCC29213 来感染雌性瑞士白化 (Swiss albino) 小鼠。在感染前一天接种脑心浸液 (BHI) 肉汤细菌培养液, 在 37°C 下孵育过夜并且在新鲜的 BHI 肉汤中稀释到所希望的浓度。腹膜内 (i. p.) 注射约 5x10⁹ 个集落形成单位 (CFU), 在腹部的任一侧的下象限进行。在接种之后, 将小鼠保持在其笼子中每天观察感染迹象的发展或死亡。对于小鼠的治疗, 可以使用 p. o. 和 i. v 两种途径并且对每只小鼠通过强饲法或通过 i. v. 注射单独地处理。在这个模型中测试了溶液和悬浮液两者。对

于监测感染过程和治疗效果所使用的参数是在感染后 3 天内动物的死亡或存活。因为死亡还可能是由于毒副作用, 包括一个具有 3 只用最高剂量的测试化合物处理的小鼠的非感染对照组。

[0334] 结果

[0335] 本发明 / 实例的化合物展示出良好的体内疗效特性, 例如, 化合物可以展示出如通过存活% (遵循以上试验) 测量的特性。