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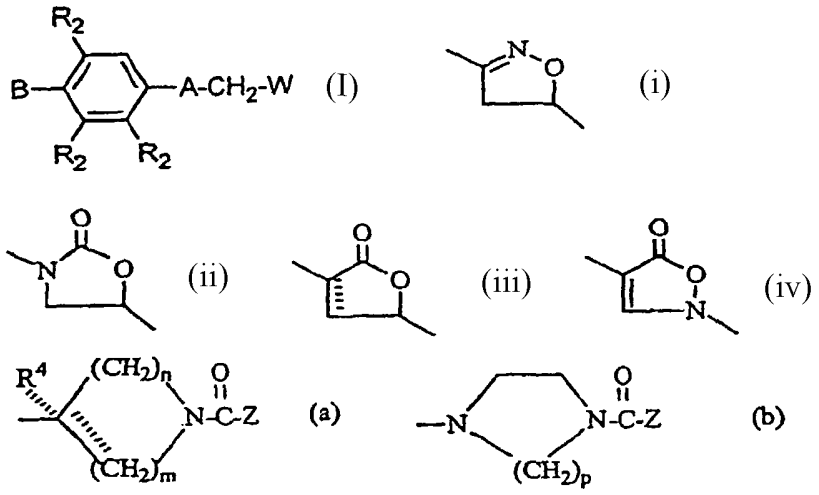
(54) **Title:** N-ARYL-2-OXAZOLIDINONE-5-CARBOXAMIDES DERIVATIVES WITH ANTIBACTERIAL ACTIVITY



(57) **Abstract:** The present invention provides antibacterial agents having the Formula (I) described herein or pharmaceutically acceptable salts thereof wherein: A is a structure I, ii, iii, or iv; Bis, W is-N(H)C(=X)-R_1, Het, or -Y-HET, in which the Het or -Y-HET is optionally substituted with =S or =O.

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N-ARYL-2-OXAZOLIDINONE-5-CARBOXAMIDE DERIVATIVES WITH ANTIBACTERIAL ACTIVITY

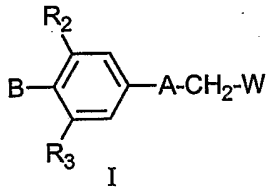
The present invention relates to novel N-Aryl-2-oxazolidinone-5-carboxamides, derivatives thereof, and their preparations. These compounds have potent antibacterial activity.

BACKGROUND OF THE INVENTION

The oxazolidinone antibacterial agents are a novel synthetic class of antimicrobials with potent activity against a number of human and veterinary pathogens, including Gram-positive aerobic bacteria such as multiply-resistant staphylococci and streptococci, anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as *Mycobacterium tuberculosis* and *Mycobacterium avium*.

SUMMARY OF THE INVENTION

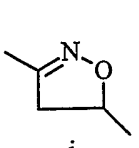
This invention provides compounds of Formula I.



I

or pharmaceutically acceptable salts thereof wherein:

A is a structure i, ii, iii, or iv;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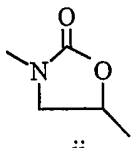
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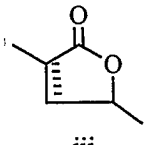
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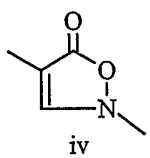
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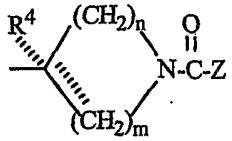
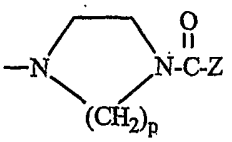
B is

(a) 

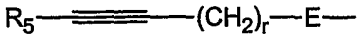
(b)  ;

W is –N(H)C(=X)-R_1, Het, or –Y-HET, in which the Het or –Y-HET is optionally substituted with =S or =O;

X is O or S;

Y is NH, O, or S;

Z is



E is CH_2 or C=O;

R_1 is a) H,

b) NH_2,

c) NHC_{1-4}alkyl,

d) C_{1-4} alkyl,

e) C_{2-4} alkenyl,

f) O-C_{1-4} alkyl,

g) S-C_{1-4} alkyl, or

h) $(CH_2)_s$ C_{3-6} cycloalkyl, in which each occurrence of alkyl or cycloalkyl in R_1 is optionally substituted by 1-3 halo;

Each R_2 and R_3 is independently hydrogen, halogen (F or Cl), methyl or ethyl;

R_4 is H, CH_3 or F;

R_5 is selected from H, aryl, and heteroaryl, each optionally substituted with 1-3 of R_6;

R_6 is halogen, $(CH_2)_mNHR_7$, $(CH_2)_pR_7$, CH_2-CHR_9-C(O)-R_8, OR_8, $S(O)_qR_7$, CN, $C(=O)R_9$, $C(=NR_{10})NHR_8$, or $C(=NR_{10})R_8$;

Each R_7 and R_8 is independently H, C_{1-6} alkyl, aryl, or heteroaryl;

R_9 is OH, OR_8, C_{1-6} alkyl, aryl, heteroaryl, or $N(R_7)(R_8)$;

R_{10} is OR_8 or $N(R_7)(R_8)$;

m is 0, 1, 2, 3, 4;

n is 0, 1, 2, 3, 4 with the proviso that m plus n is 2, 3, 4, or 5;

p is 1, 2, 3;

q is 0, 1, 2;

r and s are independently 0, 1, 2, 3, 4, 5 or 6.

Embodiments of the invention may include one or more of the following. r is 1, 2, 3, or 4. R_5 is phenyl optionally substituted with R_6. R_6 is $(CH_2)_mNHR_7$, such as $-CH_2-NH_2$. R_6 is $CH_2-CHR_9-C(O)-R_8$, such as $-CH_2-CH(NH_2)-C(O)-OH$ or $-CH_2-CH(NH_2)-C(O)-O-CH_3$. R_6 is OR_8, such as –OH or $-OCH_3$. R_6 is $C(=O)R_9$, such as $-C(O)-CH_3$.

Specific compounds of the invention include:

N-({(5S)-3-[4-(4-{6-[3-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-({(5S)-3-[3-fluoro-4-(4-hex-5-ynoylpiperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-({(5S)-3-[3-fluoro-4-(4-hept-6-ynoylpiperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[5-(4-hydroxyphenyl)pent-4-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[5-(3-hydroxyphenyl)pent-4-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-({(5S)-3-[4-(4-{5-[4-(aminomethyl)phenyl]pent-4-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[6-(4-hydroxyphenyl)hex-5-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[6-(3-hydroxyphenyl)hex-5-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-({(5S)-3-[4-(4-{6-[4-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[7-(3-hydroxyphenyl)hept-6-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[7-(4-hydroxyphenyl)hept-6-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-({(5S)-3-[4-(4-{7-[4-(aminomethyl)phenyl]hept-6-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-{[(5S)-3-(4-{4-[5-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pent-4-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

Methyl-4-{5-[4-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-5-oxopent-1-ynyl}-L-phenylalaninate;

N-{[(5S)-3-(4-{4-[5-(4-aminophenyl)pent-4-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-[((5S)-3-{3-fluoro-4-[4-(6-{4-[(methylamino)methyl]phenyl}hex-5-ynoyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

N-({(5S)-3-[3-fluoro-4-(4-{6-[4-(1H-imidazol-1-ylmethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-{[(5S)-3-(4-{4-[6-(4-acetylphenyl)hex-5-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-({(5S)-3-[4-(1-{6-[3-(aminomethyl)phenyl]hex-5-ynoyl}-3-methylazetidin-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanamide;

N-[((5S)-3-{3-fluoro-4-[4-(6-{4-[(1E)-N-hydroxyethanimidoyl]phenyl}hex-5-ynoyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

N-{[(5S)-3-(4-{4-[6-(3-cyanophenyl)hex-5-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

4-{5-[4-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-5-oxopent-1-ynyl}-L-phenylalanine;

N-[((5S)-3-{4-[4-(6-{4-[(Z)-amino(hydroxyimino)methyl]phenyl}hex-5-ynoyl)piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide hydrochloride;

N-({(5S)-3-[4-(4-{6-[3-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-2,3,5-trifluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide and

N-({(5S)-3-[4-(4-{6-[4-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-2,3,5-trifluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide.

Compounds of Formula I have antibacterial activity against a number of human and veterinary pathogens including Gram-positive aerobic bacteria such as multiply-resistant-staphylococci, streptococci and enterococci, Gram-negative organisms such as *H. influenzae* and *M. catarrhalis*, anaerobic organisms such as

Bacteroides spp. and *clostridia* spp., *Mycobacterium tuberculosis*, *M. avium* and *M.* spp. and in organisms such as *Mycoplasma* spp. For use as antibacterial agents the compounds of this invention can be administered orally or parenterally in a dosage range of about 0.1-100 mg/kg or preferably of about 1.0-50 mg/kg of body weight per day. Advantageously, the compound of the invention exhibit antibacterial activity against *S. aureus* resistant orgainsisms.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions are used, unless otherwise described.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_{i-j} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_{1-7} alkyl refers to alkyl of one to seven carbon atoms, inclusive.

The term "halo" refers to a halogen atom selected from Cl, Br, I, and F.

The term "alkyl" refers to both straight- and branched-chain moieties. Unless otherwise specifically stated alkyl moieties include between 1 and 6 carbon atoms.

The term "alkenyl" refers to both straight- and branched-chain moieties containing at least one –C=C–. Unless otherwise specifically stated alkenyl moieties include between 1 and 6 carbon atoms.

The term "alkoxy" refers to –O-alkyl groups.

The term "cycloalkyl" refers to a cyclic alkyl moiety. Unless otherwise specifically stated cycloalkyl moieties will include between 3 and 7 carbon atoms.

The term "amino" refers to $–NH_2$.

The term "aryl" refers to phenyl and naphthyl.

The term "het" refers to mono- or bicyclic ring systems containing at least one heteroatom selected from O, S, and N. Each monocyclic ring may be aromatic, saturated, or partially unsaturated. A bicyclic ring system may include a monocyclic ring containing at least one heteroatom fused with a cycloalkyl or aryl group. A bicyclic ring system may also include a monocyclic ring containing at least one heteroatom fused with another het, monocyclic ring system.

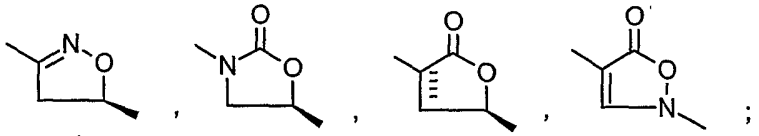
Examples of "het" include, but are not limited to, pyridine, thiophene, furan, pyrazoline, pyrimidine, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl,

5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 3-pyrazinyl, 4-oxo-2-imidazolyl, 2-imidazolyl, 4-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, 2-oxazolyl, 4-oxazolyl, 4-oxo-2-oxazolyl, 5-oxazolyl, 1,2,3-oxathiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazole, 4-isothiazole, 5-isothiazole, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isopyrrolyl, 4-isopyrrolyl, 5-isopyrrolyl, 1,2,3,-oxathiazole-1-oxide, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 5-oxo-1,2,4-oxadiazol-3-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 3-oxo-1,2,4-thiadiazol-5-yl, 1,3,4-thiadiazol-5-yl, 2-oxo-1,3,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,2,3,4-tetrazol-5-yl, 5-oxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 1,3,4,-oxadiazole, 4-oxo-2-thiazolinyl, 5-methyl-1,3,4-thiadiazol-2-yl, thiazoledione, 1,2,3,4-thiatriazole, 1,2,4-dithiazolone, phthalimide, quinolinyl, morpholinyl, benzoxazoyl, diazinyl, triazinyl, quinolinyl, quinoxalinyl, naphthyridinyl, azetidinyl, pyrrolidinyl, hydantoinyl, oxathiolanyl, dioxolanyl, imidazolidinyl, and azabicyclo[2.2.1]heptyl.

The term "heterocycle" refers to a fully saturated het, examples of which include, but are not limited to, morpholinyl, thiomorpholinyl, and tertrahydropyranyl.

Specific R_3 and R_4 substituents include H, F, Cl, Br, CN, NH_2, NO_2, CH_3.

Specific structures of A include



i , ii , iii , iv ;

Mammal refers to human or animals.

The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "O" for oxygen atom, "S" for sulfur atom, "N" for nitrogen atom, "h" for hour or hours and "rt" for room temperature) as described in J.Org.Chem., 67-1, 24A, 2002.

Other abbreviations and definitions used are defined as follows:

Hunig's base means diisopropylethyl amine;

HATU means O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexaflourophosphate;

in vacuo means at reduced pressure;

EDCI or EDC means 1-ethyl-3-(3-dimethylaminopropyl)carbodimide;

HOBT means hydroxybenztriazole;

Fmoc means 9-fluorenylmethoxycarbonyl;

trisamine resin means tris(2-aminoethyl)amine, polymer-bound;

DPPA means diphenylphosphoryl azide.

The compounds of the present invention can be converted to their salts, where appropriate, according to conventional methods.

The term "pharmaceutically acceptable salts" refers to acid addition salts useful for administering the compounds of this invention and include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, mesylate, maleate, malate, succinate, tartrate, citric acid, 2-hydroxyethyl sulfonate, fumarate and the like. These salts may be in hydrated form.

The compounds of Formula I of this invention contain a chiral center, such as at C-5 of the isoxazoline ring, and as such there exist two enantiomers or a racemic mixture of both. This invention relates to both the enantiomers, as well as mixtures containing both the isomers. In addition, depending on substituents, additional chiral centers and other isomeric forms may be present in any of A or R_1 group, and this invention embraces all possible stereoisomers and geometric forms in these groups.

The compounds of this invention are useful for treatment of microbial infections in humans and other warm blooded animals, under both parenteral and oral administration.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic

materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compound according to this invention.

The quantity of active component, that is the compound according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting, bacterial infections in warm-blooded animals, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 1.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., 2-4 four times per day.

The compounds according to this invention may be administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound or a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid

carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3.5-6. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compounds of this invention generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/mL to about 400 mg/mL of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds according to this invention are advantageously administered orally in solid and liquid dosage forms.

As a topical treatment an effective amount of Formula I is admixed in a pharmaceutically acceptable gel or cream vehicle that can be applied to the patient's skin at the area of treatment. Preparation of such creams and gels is well known in the art and can include penetration enhancers.

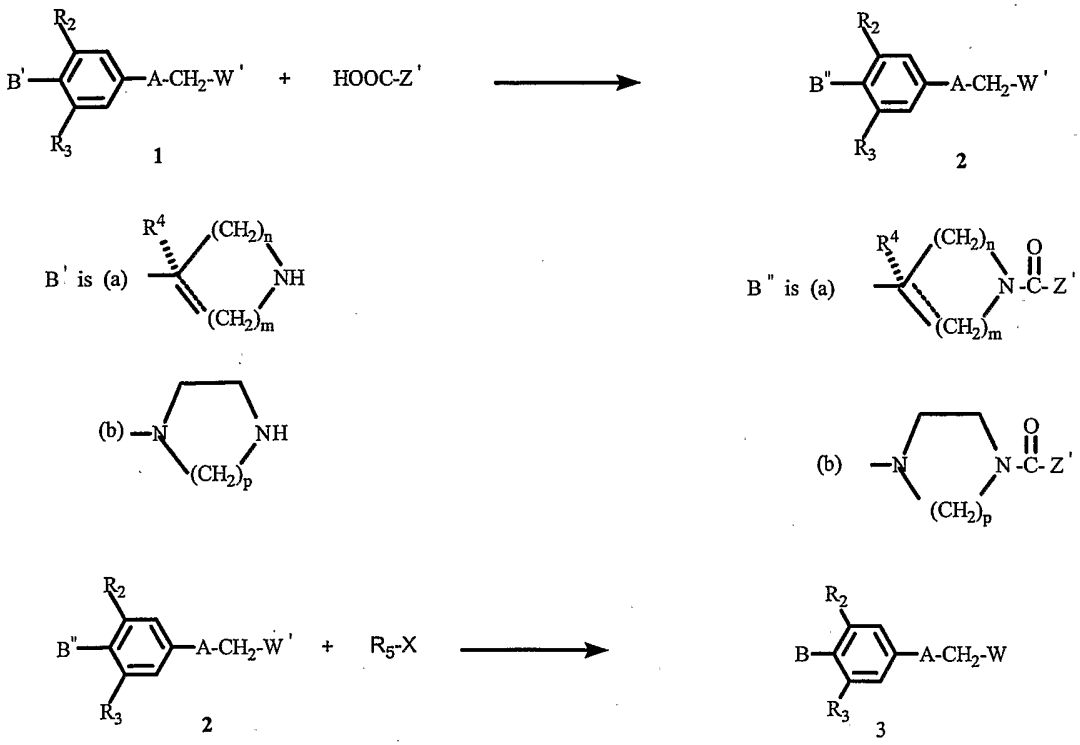
The oxazolidinone antibacterial agents of this invention have useful activity against a variety of organisms. The in vitro activity of compounds of this invention can be assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as described in "Approved Standard. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically", 3rd. ed., published 1993 by the National Committee for Clinical Laboratory Standards, Villanova, Pennsylvania, USA.

Compounds in this invention can be prepared as shown in Scheme I. In Scheme I an amine (**1**) is condensed with a suitably substituted alkyne carboxylic acid (HOOC-Z') to give an amide (**2**) where Z' represents Z of formula I in which R_5 is H. Amide **2** is coupled with R_5-L, where L represents a suitable coupling group such as halogen, trifluromethanesulfonate or the like. R_5-L may contain a suitable protecting group for hydroxy or amino substitutents that can be removed at an appropriate time in a manner that is compatible with other substituents on the molecule to give the title compound (**3**). A variety of reagents and reaction condensations can be used for the condensations of **1** with the carboxylic acids (HOO-Z'). These include but are not limited to the carbodiimides such as dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) which can be used

with promoters such as 4-(dimethylamino)pyridine (DMAP) or 1-hydroxybenzotriazole (HOBT) in solvents such as THF, DMF or pyridine at 0°C to 50°C. The terminal alkynes **2** can be coupled via a protocol using either $PdCl_2(PPh_3)_2$ or $Pd(dppf)Cl_2$ in the presence of Ph_3As, CuI, and Et_3N in DMF solvent at room temperature as has been described (de Kort, M., et.al., *J. Med. Chem.* **2000**, *43*, 3295).

By using the chemistry described in Scheme I and employing other side chains known in the literature or described in the examples other compounds of formula I can be prepared.

Scheme I



Suitable intermediates useful in preparating compounds of formula I and additional synthetic methods to assist in producing compounds of formula I may be found, for example, in the following publications each of which is hereby incorporated by reference.

U.S. Patent Nos. 5,225,565; 5,182,403; 5,164,510; 5,247,090; 5,231,188; 5,565,571; 5,547,950; 5,529,998; 5,627,181; 5,843,967; 5,861,413; 5,827,857; 5,869,659; 5,952,324; 5,968,962; 5,688,792; 6,069,160; 6,239,152; 5,792,765; 4,705,799; 5,043,443; 5,652,238; 5,827,857; 5,529,998; 5,684,023; 5,627,181;

5,698,574; 6,166,056; 6,194,441; 6,110,936; 6,069,145; 6,271,383; 5,981,528; 6,051,716; 6,043,266; 6,313,307; and 5,523,403.

U.S. Patent Application Publication 2002/0086900.

PCT Application and publications PCT/US93/04850, WO94/01110; PCT/US94/08904, WO95/07271; PCT/US95/02972, WO95/25106; PCT/US95/10992, WO96/13502; PCT/US96/05202, WO96/35691; PCT/US96/12766; PCT/US96/13726; PCT/US96/14135; PCT/US96/17120; PCT/US96/19149; PCT/US97/01970; PCT/US95/12751, WO96/15130, PCT/US96/00718, WO96/23788, WO98/54161, WO99/29688, WO99/03846, WO99/37641, WO99/37652, WO99/40094, WO97/30995, WO97/09328, WO01/81350, WO01/40236, WO00/21960 WO01/4022, and WO95/07271.

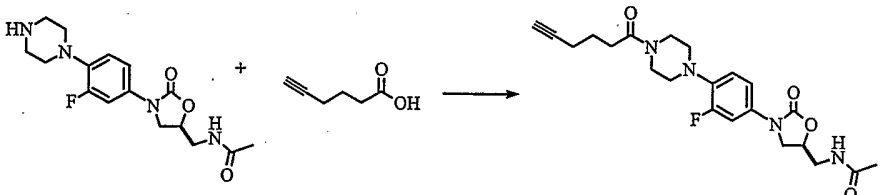
In some embodiments, the antibacterial compounds are prodrugs of the compounds of formula I. The expression "prodrug" denotes a derivative of a known direct acting drug, which is transformed into the active drug by an enzymatic or chemical process. Prodrugs of the compounds of formula I are prepared by modifying functional groups present on the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include, but are not limited to, compounds of structure (I) wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to the animal, cleaves to form the free hydroxyl, amino or sulfhydryl group, respectively. Representative examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups. See Notari, R. E., "Theory and Practice of Prodrug Kinetics," Methods in Enzymology, 112:309-323 (1985); Bodor, N., "Novel Approaches in Prodrug Design," Drugs of the Future, 6(3):165-182 (1981); and Bundgaard, H., "Design of Prodrugs: Bioreversible-Derivatives for Various Functional Groups and Chemical Entities," in Design of Prodrugs (H. Bundgaard, ed.), Elsevier, N.Y. (1985).

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or

perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

Example 1: *N*-({(5*S*)-3-[3-Fluoro-4-(4-hex-5-ynoylpiperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide.

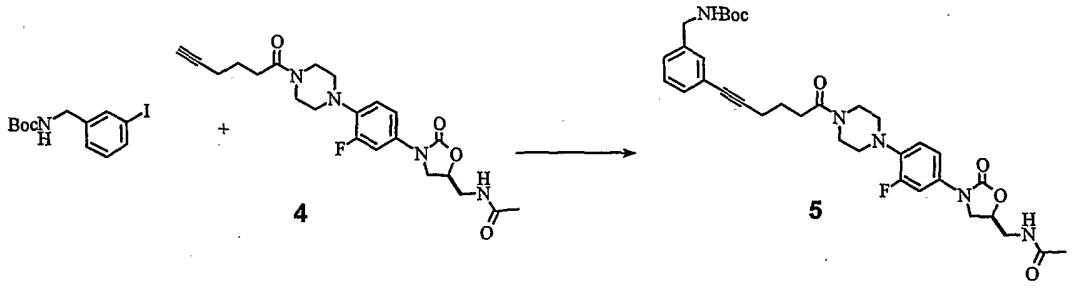


3 4

Amine 3 (U.S. Patent Application Publication 2002/86900) (3.0 g, 5.36 mmol), 5-hexynoic acid (0.66 g, 5.90 mmol), and Hunig's base (5 mL) were cooled to 0 °C in an ice bath and then diphenylphosphoryl azide (1.62 g, 5.90 mmol) was added dropwise via syringe. The reaction mixture was allowed to warm slowly to rt and then stirred 14h. The reaction mixture was diluted with EtOAc and water added. The water layer was extracted five times with EtOAc, the organic layers were combined and washed with water, saturated aqueous $NaHCO_3$, brine and dried over $MgSO_4$. The extract was concentrated in vacuo and then triturated with Et_2O to afford the desired amide **4**; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 8.24 (m, 1 H), 7.50 (dd, *J* = 16, 2 Hz, 1 H), 7.18 (dd, *J* = 2, 8 Hz, 1 H), 7.07 (dd, *J* = 12, 12 Hz, 1 H), 4.71 (m, 1 H), 4.08 (m, 1 H), 3.70 (dd, *J* = 8, 6 Hz, 1 H), 3.60 (m, 4 H), 3.40 (m, 2 H), 2.98-2.89 (m, 4 H), 2.81 (m, 1 H), 2.44 (t, *J* = 4 Hz, 2 H), 2.21 (dt, *J* = 4, 8 Hz, 2 H), 1.83 (s, 3 H), 1.69 (m, 2 H).

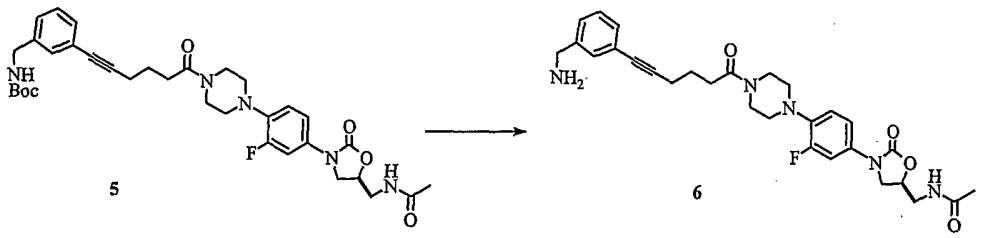
Example 2: N-({(5S)-3-[4-(4-{6-[3-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-3-fluorophen-yl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, 6.

Step 1: ***tert*-Butyl 3-{6-[4-(4-{(5*S*)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-6-oxohex-1-ynyl}phenylcarbamate, 5.**



tert-Butyl 3-iodobenzylcarbamate (0.67 mmol) was dissolved in 1 mL of dry DMF and the resultant solution was evacuated to 40mm pressure and then released to N_2 (g) three times. Triethylamine (1:8 ratio with DMF, 100 μL), $Pd(PPh_3)_2Cl_2$ (0.030 mmol), and CuI (0.067 mmol) were added. The resultant mixture evacuated to 40 mm pressure for *ca.* 30 seconds and then released to N_2 (g) . Finally, the alkyne **4** (0.67 mmol) in DMF (0.07 M) was added dropwise via an addition funnel over 40 minutes. The reaction mixture was stirred at room temperature for 18 hr and then diluted with ethyl acetate, poured into 0.1 M HCl and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$. The extract was concentrated and the product purified by Biotage chromatography (40M, product loaded onto SiO_2) with 2% $MeOH/CH_2Cl_2$ to afford the desired title compound: ^1H NMR (400 MHz, DMSO-*d6*) δ 8.24 (m, 1 H), 7.50 (dd, $J = 4$, 16 Hz, 1 H), 7.41 (m, 1 H), 7.26 (m, 3 H), 7.18 (m, 2 H), 7.05 (m, 1 H), 4.71 (m, 1 H), 4.08 (m, 3 H), 3.70 (dd, $J = 4$, 12 Hz, 1 H), 3.62 (m, 4 H), 3.40 (m, 2 H), 2.92 (m, 4 H), 2.47 (m, 4 H), 1.83 (s, 3 H), 1.79 (m, 2 H), 1.38 (s, 9 H).

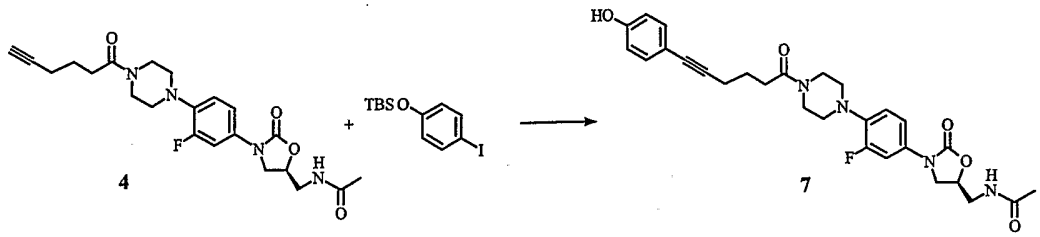
Step 2: **N-({(5S)-3-[4-(4-{6-[3-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-3-fluorophen-yl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, 6.**



The NBoc amine (**5**) was suspended in CH_2Cl_2 (ca. 5 mL) and treated with TFA (4 mL) at 0 °C to rt for 1.5 hr. The reaction mixture was concentrated in vacuo and subjected to Biotage chromatography with 5% $MeOH/CH_2Cl_2/NH_3$ to afford the free amine **6**: ^1H NMR (300 MHz, DMSO-*d6*) δ 8.24 (m, 1 H), 7.50 (dd, $J = 15$, 3 Hz, 1 H), 7.39 (m, 1 H), 7.29-7.22 (m, 3 H), 7.17 (dd, $J = 9$, 6 Hz, 1 H), 7.05 (m, 1 H), 4.71

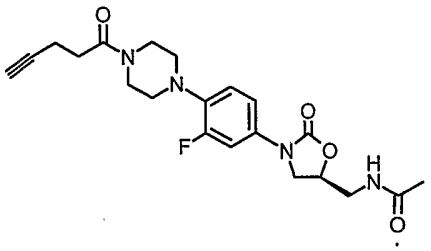
(m, 1 H), 4.08 (t, J = 9 Hz, 1 H), 3.71 (m, 3 H), 3.62 (m, 4 H), 3.40 (m, 2 H), 3.25 (bs, 2 H), 2.93 (m, 4 H), 2.47 (m, 2 H), 1.83 (s, 3 H), 1.79 (m, 2 H).

Example 3: N-{[(5*S*)-3-(3-Fluoro-4-{4-[6-(4-hydroxyphenyl)hex-5-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide, 7.



The title compound was prepared by coupling **4** (1.20 g, 2.79 mmol) with 4-*t*-butyldimethylsilyloxy-*p*-iodophenol (1.12 g, 3.34 mmol) as described in example 2, step 1, and deprotection of the intermediate silyl phenol with TBAF (3.0 mL of a 1.0 M solution in THF) in THF at 0 °C for 4 hr to afford the title compound **7.** ^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.72 (s, 1 H), 8.24 (m, 1 H), 7.50 (dd, J = 2, 16 Hz, 1 H), 7.20 (d, J = 12 Hz, 2 H), 7.18 (m, 1 H), 7.06 (dd, J = 12, 12 Hz, 1 H), 6.71 (d, J = 8 Hz, 2 H), 4.71 (m, 1 H), 4.08 (t, J = 8 Hz, 1 H), 3.70 (dd, J = 8, 12 Hz, 1 H), 3.62 (m, 4 H), 3.40 (t, J = 4 Hz, 2 H), 2.92 (m, 4 H), 2.49 (dd, J = 8, 8 Hz, 2 H), 2.42 (dd, J = 8, 8, 2 H), 1.83 (s, 3 H), 1.76 (m, 2 H).

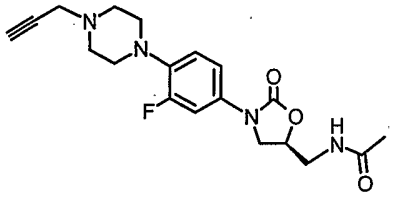
Example 4: N-[((5S)-3-{3-fluoro-4-[4-(4-pentynoyl)-1-piperazinyl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 8.



Prepared as in Example 1 with nonessential modifications but substituting pentynoic acid for hexynoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) d 8.24 (t, J = 4 Hz, 1 H), 7.50 (dd, J = 2, 16 Hz, 1 H), 7.18 (dd, J = 2, 8 Hz, 1 H), 7.07 (t, J = 8 Hz, 1 H), 4.71 (m, 1 H), 4.08 (t, J = 8 Hz, 1 H), 3.70 (dd, J = 8, 12 Hz, 1 H), 3.60 (m, 4 H), 3.40 (t, J = 4 Hz, 2 H), 2.97 (m, 2 H), 2.91 (m, 2 H), 2.78 (t, J = 4 Hz, 1 H), 2.59 (t, J = 4 Hz, 2 H), 2.83 (dt, J = 4, 8 Hz, 2 H), 1.83 (s, 3 H).

Example 5: N-[((5S)-3-{3-fluoro-4-[4-(3-phenylprop-2-ynyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 9.

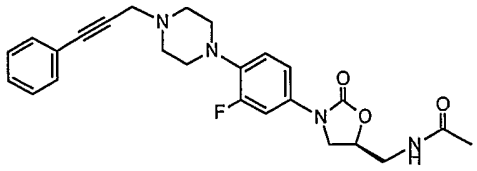
Step 1: N-({(5S)-3-[3-fluoro-4-(4-prop-2-ynylpiperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, 9A



9A

N-({(5S)-3-[3-fluoro-4-(1-piperazinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide hydrochloride (8.0 g, 21.4 mmol) was dissolved in DMF and treated with K_2CO_3 (15.0 g, 107 mmol) for 1 hr. After this period of time, the reaction was cooled to 0 °C and propargyl bromide (4.78 g of an 80% weight solution in toluene, 32.4 mmol) was added. The cooling bath was allowed to expire and the reaction was stirred 18 hr at rt at which time, TLC showed complete consumption of the starting material and formation of a new, single, higher Rf product. The reaction was quenched with water and the organic product extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford a yellow oil, which was purified by chromatography with 3% MeOH:CH_2Cl_2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (t, J = 4 Hz, 1 H), 7.48 (dd, J = 1, 12 Hz, 1 H), 7.16 (m, 1 H), 7.06 (t, J = 8 Hz, 1 H), 4.70 (m, 1 H), 4.08 (t, J = 8 Hz, 1 H), 3.70 (dd, J = 4, 6 Hz, 1 H), 3.40 (m, 2 H), 3.19 (m, 1 H), 2.99 (m, 4 H), 2.61 (m, 4 H), 1.83 (s, 3 H).

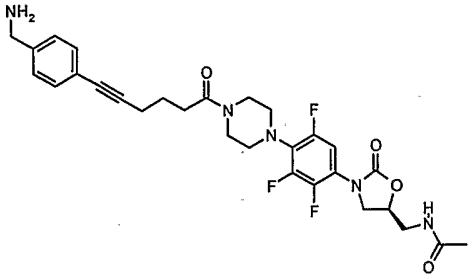
Step 2: *N*-[((5*S*)-3-{3-Fluoro-4-[4-(3-phenylprop-2-ynyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 9.



9

Prepared as in Example 2 with nonessential modifications but substituting the appropriate reactants; NMR (300 MHz, DMSO-*d6*) δ 8.24 (m, 1 H), 7.51-7.37 (m, 6 H), 7.17 (dd, *J* = 9, 3 Hz, 1 H), 7.07 (m, 1 H), 4.71 (m, 1 H), 4.08 (t, *J* = 9 Hz, 1 H), 3.70 (dd, *J* = 6, 9 Hz, 1 H), 3.59 (m, 2 H), 3.40 (m, 2 H), 3.03 (m, 4 H), 2.70 (m, 4 H), 1.83 (s, 3 H).

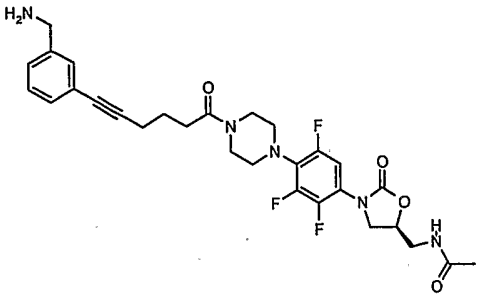
Example 6: N-({(5S)-3-[4-(4-{6-[4-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-2,3,5-trifluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, 10.



10

Prepared as in Example 2 with nonessential modifications but substituting the appropriate reactants. 1H NMR (300 MHz, DMSO-d6) δ 8.26 (t, J = 6.03 Hz, 1 H), 7.36 (m, 2 H), 7.24 (m, 1 H), 7.31 (d, J = 3.39 Hz, 2 H), 4.76 (m, 1 H), 4.06 (t, J = 8.67 Hz, 1 H), 3.70 (s, 2 H), 3.69 (m, 1 H), 3.58 (m, 4 H), 3.42 (m, 2 H), 3.34 (bs, 2 H), 3.13 (m, 4 H), 2.48 (m, 4 H), 1.85 (s, 3 H), 1.79 (m, 2 H).

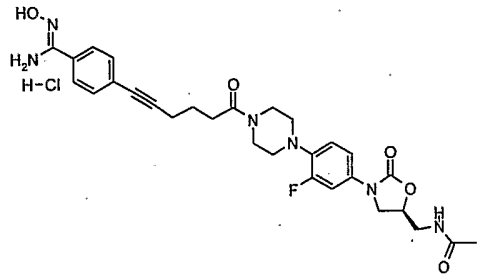
Example 7: N-({(5S)-3-[4-(4-{6-[3-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-2,3,5-trifluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, 11.



11

Prepared as in Example 2 with nonessential modifications but substituting the appropriate reactants. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (t, J = 5.84 Hz, 1 H), 7.38 (m, 1 H), 7.33 (m, 1 H), 7.27 (m, 2 H), 7.23 (m, 1 H), 4.75 (m, 1 H), 4.06 (t, J = 8.67 Hz, 1 H), 3.71 (m, 1 H), 3.69 (s, 2 H), 3.58 (m, 4 H), 3.41 (m, 2 H), 3.13 (m, 4 H), 2.79 (bs, 2 H), 2.45 (m, 4 H), 1.85 (s, 3 H), 1.79 (m, 2 H);

Example 8: N-[((5S)-3-{4-[4-(6-{4-[(Z)-amino(hydroxyimino)methyl]-phenyl}hex-5-ynoyl)piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-acetamide hydrochloride, 12.

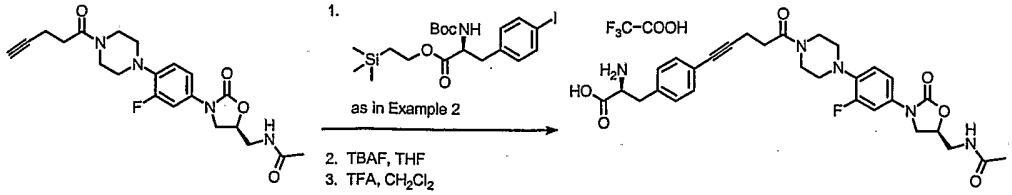


12

N-{[(5S)-3-(4-{4-[6-(3-cyanophenyl)hex-5-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide (0.300 g, 0.56 mmol) and hydroxylamine•HCl (86 mg, 1.24 mmol) in Et3N (1.29 mmol) and EtOH (2 mL) were heated at 75 °C. The reaction was monitored by TLC and found to be complete after 12 hr. The reaction was diluted with water and taken to pH 7.0 with conc. HCl and the crude product was purified by chromatography (5-6% MeOH:CH2Cl2 to afford the HCl•salt. ^{1}H NMR (400 MHz, DMSO-D$_6$) □ ppm 1.80 (d, J = 7.26 Hz, 2 H), 1.83 (s, 3 H), 2.93 (m, 4 H), 3.17 (d, J = 5.18 Hz, 1 H), 3.33 (s, 4 H), 3.40 (t, J = 5.49 Hz, 2 H), 3.62 (d, J = 4.56 Hz, 4 H), 3.70 (dd, J = 9.23, 6.32 Hz, 1 H), 4.08 (m, 1 H), 4.70 (m, 1 H), 5.87 (s, 2 H), 7.05 (t, J = 9.33 Hz, 1 H), 7.17 (dd, J = 8.81, 2.18 Hz, 1 H),

7.37 (m, 2 H), 7.50 (dd, J = 14.72, 2.49 Hz, 1 H), 7.64 (m, 1 H), 7.69 (s, 1 H), 8.24 (t, J = 5.81 Hz, 1 H), 9.70 (s, 1 H).

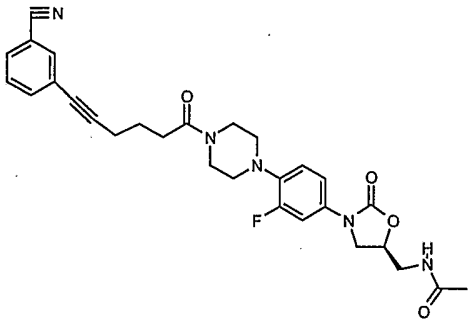
Example 9: 4-{5-[4-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl) piperazin-1-yl]-5-oxopent-1-ynyl}-L-phenylalanine, 13.



13

Prepared as in Example 2 with nonessential modifications but substituting the appropriate reactants. Subsequently, the silyl protecting group was removed with TBAF as in Example 3, and the Boc protecting group removed with TFA as described in Example 2. ^{1}H NMR (400 MHz, DMSO-d6) □ ppm 1.84 (s, 3 H), 2.66 (s, 4 H), 2.84 (dd, J = 13.99, 7.98 Hz, 1 H), 2.94 (d, J = 20.11 Hz, 4 H), 3.12 (dd, J = 13.89, 4.15 Hz, 1 H), 3.33 (s, 5 H), 3.39 (m, J = 6.01 Hz, 2 H), 3.63 (s, 4 H), 3.73 (dd, J = 8.81, 6.74 Hz, 1 H), 4.09 (t, J = 8.81 Hz, 1 H), 4.70 (m, 1 H), 7.01 (t, J = 9.02 Hz, 1 H), 7.15 (dd, J = 8.60, 1.76 Hz, 1 H), 7.22 (d, J = 8.09 Hz, 2 H), 7.28 (m, 2 H), 7.52 (dd, J = 14.82, 2.18 Hz, 1 H), 8.34 (t, J = 6.63 Hz, 1 H).

Example 10: N-{[(5S)-3-(4-{4-[6-(3-cyanophenyl)hex-5-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide, 14.

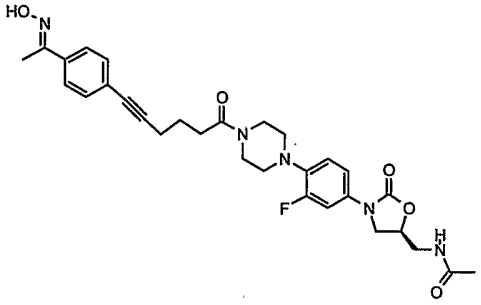


14

Prepared as in Example 2 with nonessential modifications but substituting the appropriate reactants (commerically available (3-cyano)iodobenzene was used in the Sonogashira coupling reaction). ^{1}H NMR (400 MHz, DMSO-d6) □ ppm 1.79 (m, 2

H), 1.83 (s, 3 H), 2.53 (d, J = 3.52 Hz, 4 H), 2.93 (m, 4 H), 3.40 (t, J = 5.49 Hz, 2 H), 3.62 (m, 4 H), 3.70 (dd, J = 9.12, 6.43 Hz, 1 H), 4.08 (m, 1 H), 4.70 (m, 1 H), 7.06 (t, J = 9.33 Hz, 1 H), 7.17 (m, 1 H), 7.50 (dd, J = 14.93, 2.49 Hz, 1 H), 7.56 (t, J = 7.88 Hz, 1 H), 7.74 (dt, J = 7.93, 1.43 Hz, 1 H), 7.81 (dt, J = 7.83, 1.37 Hz, 1 H), 7.90 (t, J = 1.45 Hz, 1 H), 8.24 (t, J = 5.80 Hz, 1 H).

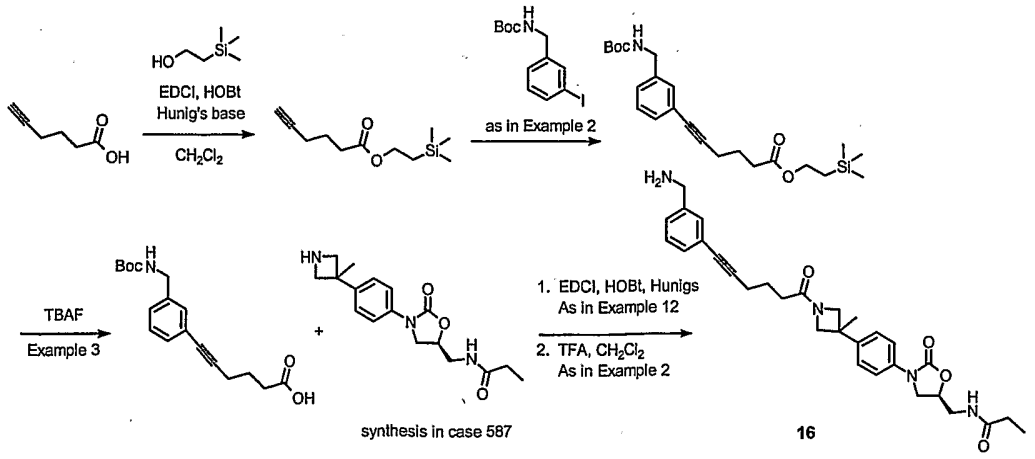
Example 11: N-[((5S)-3-{3-fluoro-4-[4-(6-{4-[(1E)-N-hydroxyethan-imidoyl]-phenyl}hex-5-ynoyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]-acetamide, HCl salt, 15.



15

N-[((5S)-3(4-[4-(6-{4-acetylphenyl}hex-5-ynoyl)piperazine-1-yl]-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide (220 mg, 0.40 mmol) was dissolved in 4 mL of a solution of 1:1 pyridine EtOH and treated with hydroxylamine•HCl (60 mg, 0.80 mmol). The reaction mixture was then heated to 50 °C for 2 hr at which time the reaction was complete. The reaction mixture was concentrated in vacuo and the organic product extracted with CH_2Cl_2. The combined organic layers were washed with 1 M HCl and brine and then dried over $MgSO_4$ and concentrated in vacuo to afford a white solid after trituration with Et_2O. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.31 (s, 1 H), 8.24 (t, J = 6 Hz, 1 H), 7.63 (m, 2 H), 7.50 (dd, J = 3, 15 Hz, 1 H), 7.40 (m, 2 H), 7.17 (m, 1 H), 7.05 (m, 1 H), 4.70 (m, 1 H), 4.08 (t, J = 9 Hz, 1 H), 3.70 (dd, J = 6, 8 Hz, 1 H), 3.62 (m, 4 H), 3.40 (m, 2 H), 3.37 (m, 4 H), 2.94 (m, 4 H), 2.13 (s, 3 H), 1.83 (s, 3 H), 1.80 (m, 2 H).

Example 12: N-({(5S)-3-[4-(1-{6-[3-(aminomethyl)phenyl]hex-5-ynoyl}-3-methylazetidin-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propan-amide, 16.



Prepared according to the following general procedure.

Step 1. 5-Hexynoic acid (44.6 mmol) and the alcohol (53.5 mmol) were stirred together at O °C and then HOBt (68.9 mmol), EDCI (53.5 mmol), and Hunig's base (133.8 mmol) were added successively. The ice bath was allowed to expire and the reaction warmed to rt and stirred 18 hr. After this period of time, the reaction mixture was poured into water and the organic product extracted with CH_2Cl_2; the combined organic layers were washed with 1M HCl, saturated aqueous $NaHCO_3$, water, and brine and then dried over $MgSO_4$ and filtered. The concentrated product was purified by chromatography to afford a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.08 (t, J = 8 Hz, 2 H), 2.79 (t, J = 2 Hz, 1 H), 2.34 (t, J = 4 Hz, 2 H), 2.17 (dt, J = 4, 8 Hz, 2 H), 1.66 (m, 2 H), 0.92 (m, 2 H), -0.01 (s, 9 H).

Step 2. The alkyne was coupled with *N*-Boc(3-iodo)benzyl amine according to the procedure outlined in Example 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 (m, 1 H), 7.22 (m, 4 H), 4.08 (m, 2 H), 2.43 (m, 2 H), 1.77 (m, 2 H), 1.37 (s, 9 H), 1.29 (m, 4 H), 0.92 (m, 2 H), -0.03 (s, 9 H).

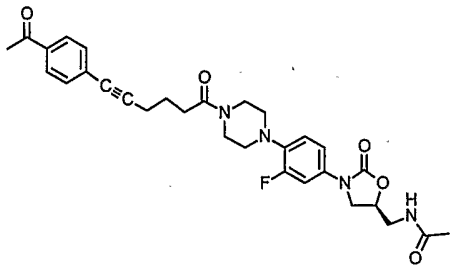
Step 3. The silyl protecting group was removed with TBAF according to the general procedure outlines in Example 3. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.1 (s, 1 H), 7.41 (t, J = 9 Hz, 1 H), 7.25 (m, 4 H), 4.10 (d, J = 6 Hz, 2 H), 2.45 (t, J = 6 Hz, 2 H), 2.38 (t, J = 9 Hz, 2 H), 1.76 (m, 2 H), 1.39 (s, 9 H).

Step 4. The amide bond forming reaction with the azetidine nitrogen **(case 587)** was performed according to the general procedure outlined in Example 12, step 1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (t, J = 4 Hz, 1 H), 7.49 (d, J = 8 Hz, 2 H), 7.41 (t,

J = 6 Hz, 1 H), 7.30 (d, J = 8 Hz, 2 H), 7.26-7.18 (m, 4 H), 4.72 (m, 1 H), 4.33 (d, J = 8 Hz, 1 H), 4.13 (d, J = 8 Hz, 1 H), 4.09 (m, 3 H), 4.04 (d, J = 8 Hz, 1 H), 3.86 (d, J = 8 Hz, 1 H), 3.74 (dd, J = 4, 6 Hz, 1 H), 3.42 (m, 2 H), 2.44 (t, J = 8 Hz, 2 H), 2.24 (dt, J = 8, 4 Hz, 2 H), 2.09 (q, J = 8 Hz, 2 H), 1.75 (m, 2 H), 1.53 (s, 3 H), 1.38 (s, 9 H), 0.95 (t, J = 8 Hz, 3 H).

Step 5. The Boc protecting group was removed as outline in Example 2 to afford the desire product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (t, J = 8 Hz, 1 H), 7.50 (d, J = 8 Hz, 2 H), 7.40 (s, 1 H), 7.30 (d, J = 8 Hz, 2 H), 7.26 (m, 3 H), 4.72 (m, 1 H), 7.32 (d, J = 8 Hz, 1 H), 4.13 (m, 3 H), 3.86 (d, J = 8 Hz, 1 H), 3.74 (s, 3 H), 3.60 (s, 2 H), 3.43 (m, 2 H), 2.44 (t, J = 8 Hz, 2 H), 2.25 (t, J = 8 Hz, 2 H), 2.09 (q, J = 8 Hz, 2 H), 1.76 (m, 2 H), 1.54 (s, 3 H), 0.96 (t, J = 8 Hz, 3 H).

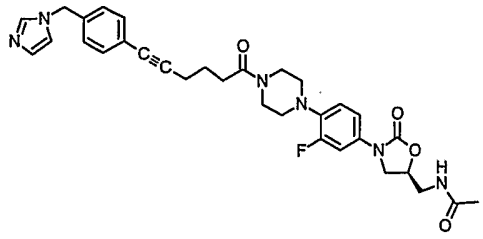
Example 13: *N*-{[(5S)-3-(4-{4-[6-(4-acetylphenyl)hex-5-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide, 17.



17

Prepared as in Example 2, step1, with nonessential modifications but substituting the appropriate reactants, (4-iodo)acetophenone was used in the Sonogashira coupling reaction. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (t, J = 8 Hz, 1 H), 7.92 (d, J = 8 Hz, 2 H), 7.54 (d, J = 8 Hz, 2 H), 7.50 (dd, J = 16, 4 Hz, 1 H), 7.17 (m, 1 H), 7.05 (dd, J = 12, 12 Hz, 1 H), 4.71 (m, 1 H), 4.08 (t, J = 8 Hz, 1 H), 3.70 (dd, J = 8, 10 Hz, 1H), 3.62 (m, 4 H), 3.40 (t, J = 4 Hz, 2 H), 2.93 (m, 4 H), 2.57 (s, 3 H), 2.53 (m, 4 H), 1.83 (s, 3 H), 1.82 (m, 2 H).

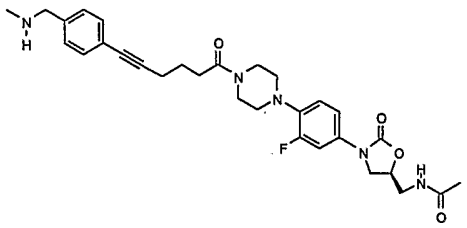
Example 14: N-({(5S)-3-[3-fluoro-4-(4-{6-[4-(1H-imidazol-1-ylmethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, 18.



18

Prepared as in Example 2, step1, with nonessential modifications but substituting the appropriate reactants. The pyrazolylmethyl-iodo-benzene was obtained by alkylation of pyrrazole with 4-iodobenzyl bromide according to the literature procedure (OPPI, 2000, 32(4), 385). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (m, 1 H), 7.81 (m, 1 H), 7.50 (dd, J = 3, 15 Hz, 1 H), 7.38 (d, J = 9 Hz, 2 H), 7.20 (d, J = 9 Hz, 2 H), 7.15 (m, 1 H), 7.05 (m, 1 H), 6.94 (m, 1 H), 5.20 (s, 2 H), 4.70 (m, 1 H), 4.08 (dd, J = 9, 9 Hz, 1 H), 3.70 (dd, J = 6, 9 Hz, 1 H), 3.61 (m, 4 H), 3.40 (t, J = 6 Hz, 2 H), 2.94 (m, 4 H), 2.47 (m, 4 H), 1.83 (s, 3 H), 1.78 (m, 2 H).

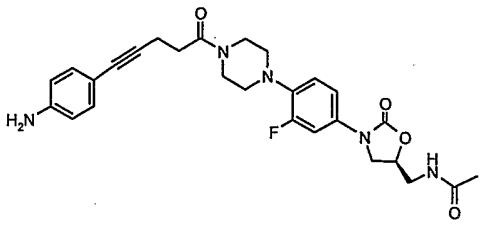
Example 15: N-[((5S)-3-{3-fluoro-4-[4-(6-{4-[(methylamino)methyl]phenyl}hex-5-ynoyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide, 19.



19

Prepared according to the steps outlined in Example 12 with nonessential modifications but substituting the appropriate reactants *N*-methyl-*N*-BOC-4-iodo benzylamine was used in the Sonogashira coupling reaction. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (t, J = 8 Hz, 1 H), 7.50 (dd, J = 4, 12 Hz, 1 H), 7.36 (s, 1 H), 7.28 (m, 4 H), 7.17 (dd, J = 4, 12 Hz, 1 H), 7.05 (t, J = 12 Hz, 1 H), 4.71 (m, 1 H), 4.08 (t, J = 8 Hz, 1 H), 3.70 (dd, J = 8, 10 Hz, 1 H), 3.64 (m, 4 H), 3.40 (t, J = 4 Hz, 2 H), 3.32 (bs, 1H), 2.94 (m, 5 H), 2.47 (m, 4 H), 2.25 (s, 3 H), 1.83 (s, 3 H), 1.79 (m, 2 H).

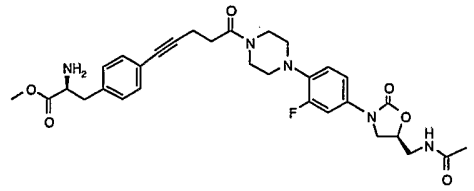
Example 16: N-{[(5S)-3-(4-{4-[5-(4-aminophenyl)pent-4-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide, 20.



20

Prepared as in Example 2, step1, with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.25 (m, 1 H), 7.51 (dd, *J* = 4, 16 Hz, 1 H), 7.16 (dd, *J* = 2, 4 Hz, 1 H), 7.08 (m, 1 H), 7.02 (d, *J* = 12 Hz, 2 H), 6.47 (d, *J* = 8 Hz, 2 H), 5.37 (s, 2 H), 4.71 (m, 1 H), 4.08 (t, *J* = 8 Hz, 1 H), 3.70 (dd, *J* = 8, 16 Hz, 1 H), 3.63 (m, 4 H), 3.40 (m, 2 H), 2.93 (m, 4 H), 2.60 (m, 4 H), 1.83 (s, 3 H).

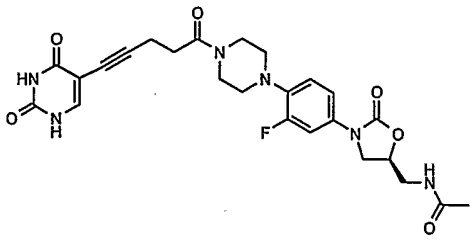
Example 17: methyl 4-{5-[4-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-5-oxopent-1-ynyl}-L-phenylalaninate, 21.



21

Prepared from commercially available *N*-(*tert*-butoxycarbonyl)-4-iodo-L-phenylalanine by Sonogashira coupling and subsequent removal of the Boc protecting group with TFA as in Example 2. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (m, 1 H), 7.50 (dd, *J* = 3, 15 Hz, 1 H), 7.27 (d, *J* = 9 Hz, 2 H), 7.19 (m, 1 H), 7.14 (d, *J* = 9 Hz, 2 H), 7.03 (m, 1 H), 4.71 (m, 1 H), 4.08 (dd, *J* = 9, 9 Hz, 1 H), 3.69 (dd, *J* = 6, 9 Hz, 2 H), 3.63 (m, 4 H), 3.56 (s, 3 H), 3.40 (m, 2 H), 2.94 (m, 4 H), 2.82 (dd, *J* = 6, 12 Hz, 2 H), 2.67 (m, 4 H), 2.66 (m, 2 H), 1.83 (s, 3 H).

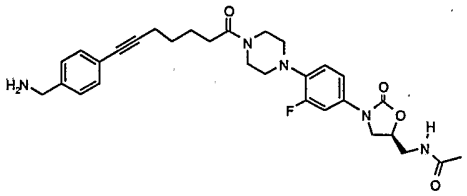
Example 18: N-{[(5S)-3-(4-{4-[5-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pent-4-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide, 22.



22

Prepared from the iodouracil by Sonogashira coupling as in Example 2, step 1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1 H), 11.15 (s, 1 H), 8.25 (t, J = 4 Hz, 1 H), 7.65 (d, J = 4 Hz, 1 H), 7.50 (dd, J = 4, 16 Hz, 1 H), 7.16 (dd, J = 2, 8 Hz, 1 H), 7.05 (t, J = 8 Hz, 1 H), 4.71 (m, 1 H), 4.08 (t, J = 8 Hz, 1 H), 3.70 (dd, J = 8, 10 Hz, 1 H), 3.62 (m, 4 H), 3.40 (t, J = 4 Hz, 2 H), 2.95 (m, 4 H), 2.61 (m, 4 H), 1.83 (s, 3 H).

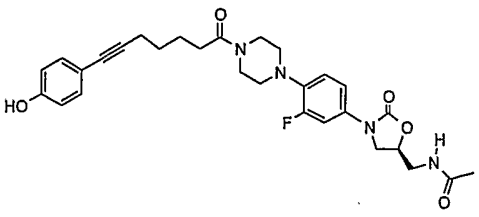
Example 19: N-({(5S)-3-[4-(4-{7-[4-(aminomethyl)phenyl]hept-6-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, 23.



23

Prepared as in Example 2 with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 8.21 (m, 1 H), 7.46 (m, 1 H), 7.29 (m, 4 H), 7.15 (m, 1 H), 7.00 (m, 1 H), 4.05 (m, 2 H), 3.67 (m, 2 H), 3.57 (m, 4 H), 3.37 (m, 3 H), 2.90 (m, 4 H), 2.40 (m, 4 H), 1.80 (s, 3 H), 1.63 (m, 2 H), 1.54 (m, 2 H).

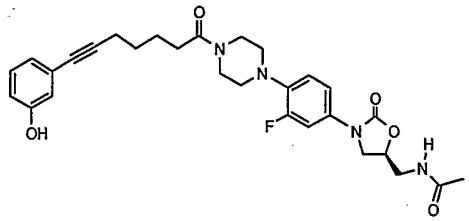
Example 20: N-{[(5S)-3-(3-fluoro-4-{4-[7-(4-hydroxyphenyl)hept-6-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide, 24.



24

Prepared as in Example 3 with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.71 (s, 1 H), 8.24 (m, 1 H), 7.50 (dd, J = 3, 9 Hz, 1 H), 7.18 (d, *J* = 9 Hz, 2 H), 7.14 (m, 1 H), 7.03 (dd, *J* = 9, 9 Hz, 1 H), 6.70 (d, *J* = 9 Hz, 2 H), 4.70 (m, 1 H), 4.08 (t, *J* = 9 Hz, 1 H), 3.70 (dd, *J* = 6, 9 Hz, 1 H), 3.60 (m, 4 H), 3.40 (t, *J* = 6 Hz, 2 H), 2.92 (m, 4 H), 2.40 (m, 4 H), 1.83 (s, 3 H), 1.65 (m, 2 H), 1.57 (m, 2 H).

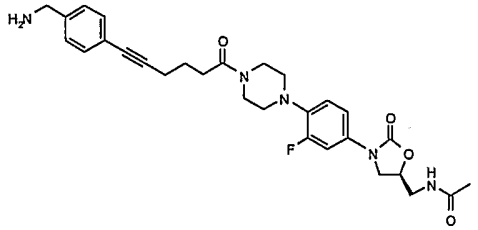
Example 21: N-{[(5S)-3-(3-fluoro-4-{4-[7-(3-hydroxyphenyl)hept-6-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide, 25.



25

Prepared as in Example 3 with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.52 (s, 1 H), 8.21 (m, 1 H), 7.46 (dd, *J* = 4, 16 Hz, 1 H), 7.12 (dd, *J* = 4, 8 Hz, 1 H), 7.08 (m, 1 H), 7.00 (dd, *J* = 12, 12 Hz, 1 H), 6.75 (d, *J* = 8 Hz, 1 H), 6.68 (m, 2 H), 4.67 (m, 1 H), 4.04 (t, *J* = 8 Hz, 1 H), 3.66 (dt, *J* = 8, 12 Hz, 1 H), 3.57 (m, 4 H), 3.36 (t, *J* = 8 Hz, 2 H), 2.88 (m, 4 H), 2.39 (m, 4 H), 1.79 (s, 3 H), 1.62 (m, 2 H), 1.53 (m, 2 H).

Example 22: N-({(5S)-3-[4-(4-{6-[4-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, 26.

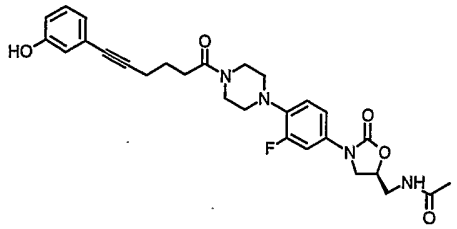


26

Prepared as in Example 2 with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 8.24 (m, 1 H), 7.50 (dd, *J* = 3, 15 Hz, 1 H), 7.32 (m, 4 H), 7.17 (dd, *J* = 2, 9 Hz, 1 H), 7.05 (m, 1 H), 4.71 (m, 1

H), 4.08 (t, J = 9 Hz, 1 H), 3.71 (m, 3 H), 3.62 (m, 4 H), 3.40 (m, 2 H), 3.30 (bs, 2 H), 2.96 (m, 4 H), 2.46 (m, 4 H), 1.83 (s, 3 H), 1.79 (m, 2 H).

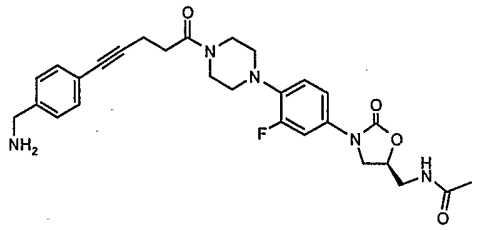
Example 23: N-{[(5S)-3-(3-fluoro-4-{4-[6-(3-hydroxyphenyl)hex-5-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide, 27.



23

Prepared as in Example 3 with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.56 (s, J = 1 Hz, 1 H), 8.24 (m, 1 H), 7.50 (dd, J = 4, 8 Hz, 1 H), 7.16 (dd, J = 4, 12 Hz, 1 H), 7.12 (m, 1 H), 7.03 (dd, J = 8, 8 Hz, 1 H), 6.78 (m, 1 H), 6.73 (m, 2 H), 4.71 (m, 1 H), 4.08 (t, J = 8 Hz, 1 H), 3.70 (dd, J = 8, 12 Hz, 1 H), 3.60 (m, 4 H), 3.40 (t, J = 4 Hz, 2 H), 2.92 (m, 4 H), 2.41 (m, 2 H), 1.83 (s, 3 H), 1.65 (m, 2 H), 1.57 (m, 2 H).

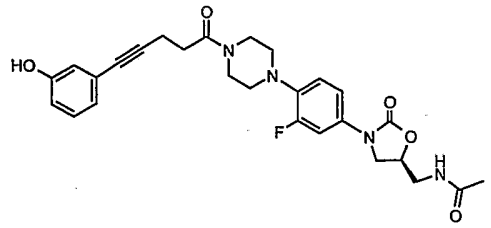
Example 24: N-({(5S)-3-[4-(4-{5-[4-(aminomethyl)phenyl]pent-4-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, 28.



28

Prepared as in Example 2 with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 8.24 (m, 1 H), 7.50 (dd, J = 2, 12 Hz, 1 H), 7.30 (m, 4 H), 7.17 (m, 1 H), 7.02 (m, 1 H), 4.70 (m, 1 H), 4.08 (m, 1 H), 3.71 (m, 3 H), 3.63 (m, 4 H), 3.40 (t, J = 6 Hz, 2 H), 2.95 (m, 4 H), 2.67 (m, 4 H), 2.65 (m, 2 H), 1.83 (s, 3 H).

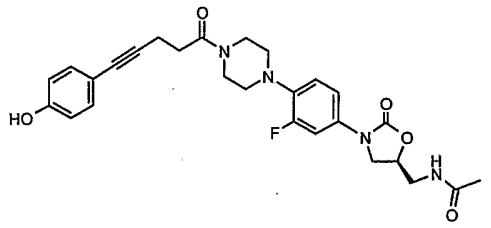
Example 25: N-{[(5S)-3-(3-fluoro-4-{4-[5-(3-hydroxyphenyl)pent-4-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide, 29.



29

Prepared as in Example 3 with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.57 (s, 1 H), 8.24 (m, 1 H), 7.49 (dd, *J* = 4, 16 Hz, 1 H), 7.17 (dd, *J* = 1, 8 Hz, 1 H), 7.12 (dd, *J* = 8, 8 Hz, 1 H), 7.03 (t, *J* = 8 Hz, 1 H), 6.78 (d, *J* = 8 Hz, 1 H), 6.74 (m, 2 H), 4.70 (m, 1 H), 4.08 (m, 1 H), 3.70 (dd, *J* = 8, 12 Hz, 1 H), 3.63 (m, 4 H), 3.40 (m, 2 H), 2.94 (m, 4 H), 2.66 (m, 4 H), 1.83 (s, 3 H).

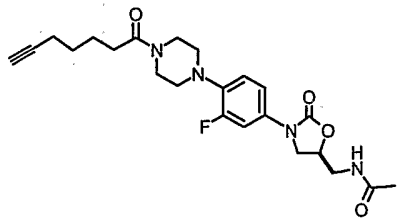
Example 26: N-{[(5S)-3-(3-fluoro-4-{4-[5-(4-hydroxyphenyl)pent-4-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide, 30.



30

Prepared as in Example 3 with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.72 (s, 1 H), 8.24 (m, 1 H), 7.50 (dd, *J* = 4, 16 Hz, 1 H), 7.17 (m, 3 H), 7.03 (dd, *J* = 8, 8 Hz, 1 H), 6.71 (d, *J* = 8 Hz, 2 H), 4.71 (m, 1 H), 4.08 (dd, *J* = 8, 8 Hz, 1 H), 3.69 (dd, *J* = 8, 12 Hz, 1 H), 3.63 (m, 4 H), 3.40 (t, *J* = 4 Hz, 2H), 2.94 (m, 4 H), 2.63 (m, 4 H), 1.83 (s, 3 H).

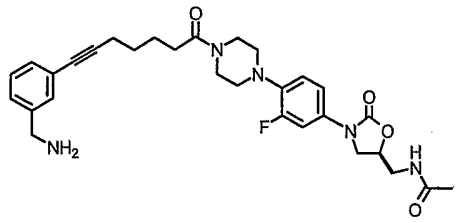
Example 27: N-({(5S)-3-[3-fluoro-4-(4-hept-6-ynoylpiperazin-1-yl)phenyl]-2-oxo-1,3- oxazolidin-5-yl}methyl)acetamide, 31.



31

Prepared as in Example 1 with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 8.24 (m, 1 H), 7.50 (dd, *J* = 3, 15 Hz, 1 H), 7.18 (dd, *J* = 3, 9 Hz, 1 H), 7.07 (dd, *J* = 9, 9 Hz, 1 H), 4.70 (m, 1 H), 4.08 (m, 1 H), 3.70 (dd, *J* = 6, 9 Hz, 1 H), 3.60 (m, 4 H), 3.40 (m, 2 H), 2.9 (m, 4 H), 2.77 (m, 1 H), 2.36 (m, 2 H), 2.19 (dt, *J* = 3, 6 Hz, 2 H), 1.83 (s, 3 H), 1.60 (m, 2 H), 1.48 (m, 2 H).

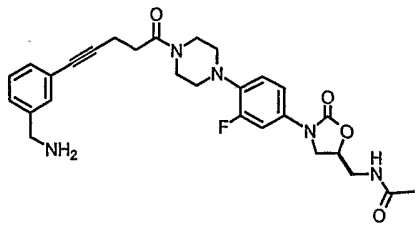
Example 28: N-({(5S)-3-[4-(4-{7-[3-(aminomethyl)phenyl]hept-6-ynoyl}-piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, 32.



32

Prepared as in Example 2 with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 8.24 (m, 1 H), 7.49 (dd, *J* = 15, 2 Hz, 1 H), 7.36 (bs, 1 H), 7.27-7.15 (m, 4 H), 7.03 (m, 1 H), 4.70 (m, 1 H), 4.08 (m, 1 H), 3.70 (m, 2 H), 3.68 (bs, 2 H), 3.59 (m, 4 H), 3.40 (m, 2 H), 2.92 (m, 4 H), 2.43 (m, 4 H), 1.83 (s, 3 H), 1.70-1.55 (m, 5 H).

Example 29: N-({(5S)-3-[4-(4-{5-[3-(aminomethyl)phenyl]pent-4-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}-methyl)acetamide, 33.

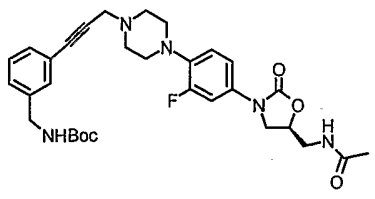


33

Prepared as in Example 2 with nonessential modifications but substituting the appropriate reactants; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.24 (m, 1 H), 7.50 (dd, *J* = 16, 4 Hz, 1 H), 7.36 (m, 1 H), 7.26 (m, 2 H), 7.21-7.15 (m, 2 H), 7.03 (dd, *J* = 8, 8 Hz, 1 H), 4.71 (m, 1 H), 4.08 (dd, *J* = 8 Hz, 1 H), 3.68 (m, 3 H), 3.64 (m, 4 H), 3.40 (m, 2 H), 2.95 (m, 4 H), 2.67 (m, 4 H), 1.83 (s, 3 H), 1.22 (bs, 2 H).

Example 30: *N*-({(5*S*)-3-[4-(4-{3-[3-(Aminomethyl)phenyl]prop-2-ynyl}-piperazin-1-yl)-3-fluorophen-yl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, 34.

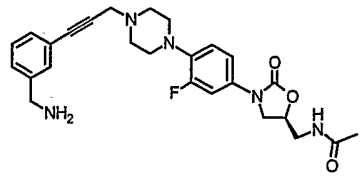
Step 1: ***tert*-butyl 3-{3-[4-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]prop-1-ynyl}benzylcarbamate, 34A**



34A

Prepared as in Example 2 with nonessential modifications but substituting the appropriate reactants; to afford the desired coupled product in 58-62% yield after Biotage chromatography with 3% MeOH/CH_2Cl_2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (m, 1 H), 7.47 (dd, *J* = 16, 4 Hz, 1 H), 7.43 (m, 1 H), 7.32 (m, 1 H), 7.31 (s, 2 H), 7.23 (m, 1 H), 7.17 (dd, *J* = 8, 2 Hz, 1 H), 7.07 (dd, *J* = 12, 12 Hz, 1 H), 4.70 (m, 1 H), 4.10 (m, 3 H), 3.70 (dd, *J* = 4, 8 Hz, 1 H), 3.60 (s, 2 H), 3.40 (m, 2 H), 3.02 (m, 4 H), 2.70 (m, 4 H), 1.83 (s, 3 H), 1.39 (s, 9 H).

Step 2 *N*-({(5*S*)-3-[4-(4-{3-[3-(Aminomethyl)phenyl]prop-2-ynyl}piperazin-1-yl)-3-fluorophen-yl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide, **34**.



34

The NBoc (**34A**) amine was suspended in CH_2Cl_2 (ca. 10 mL) and treated with TFA (4 mL) at 0 °C for 30 minutes. TLC analysis revealed that the reaction was complete after 1 hr. The crude reaction mixture was concentrated in vacuo and subjected to Biotage chromatography with 5-6% MeOH/CH_2Cl_2/NH_3 to afford the desired free amine (**4b**, 0.452 g, 0.94 mmol) in 32% yield after trituration with Et_2O; ^1H NMR (300 MHz, DMSO-*d6*) δ 8.24 (m, 1 H), 7.48 (m, 2 H), 7.30 (m, 3 H), 7.17 (dd, $J = 9$, 3 Hz, 1 H), 7.08 (m, 1 H), 4.70 (m, 1 H), 4.08 (dd, $J = 9$, 9 Hz, 1 H), 3.70 (m, 3 H), 3.59 (m, 2 H), 3.40 (m, 2 H), 3.03 (m, 4 H), 2.70 (m, 4 H), 2.24 (bs, 2 H), 1.83 (s, 3 H).

Example 31: Anti-bacterial activity:

The *in vitro* MICs of test compounds were determined by a standard agar dilution method. A stock drug solution of each analog was prepared in the preferred solvent, usually DMSO:H_2O (1:3). Serial 2-fold dilutions of each sample are made using 1.0 ml aliquots of sterile distilled water. To each 1.0 ml aliquot of drug was added 9 ml of molten Mueller Hinton agar medium. The drug-supplemented agar was mixed, poured into 15 x 100 mm petri dishes, and allowed to solidify and dry prior to inoculation.

Vials of each of the test organisms are maintained frozen in the vapor phase of a liquid nitrogen freezer. Test cultures are grown overnight at 35°C on the medium appropriate for the organism. Colonies are harvested with a sterile swab, and cell suspensions are prepared in Trypticase Soy broth (TSB) to equal the turbidity of a 0.5 McFarland standard. A 1:20 dilution of each suspension was made in TSB. The plates containing the drug supplemented agar are inoculated with a 0.001 ml drop of the cell suspension using a Steers replicator, yielding approximately 10^4 to 10^5 cells per spot. The plates are incubated overnight at 35°C.

Following incubation the Minimum Inhibitory Concentration (MIC μg/ml), the lowest concentration of drug that inhibits visible growth of the organism, was read and recorded.

The anti-bacterial activity for the example compounds is given in Table 1.

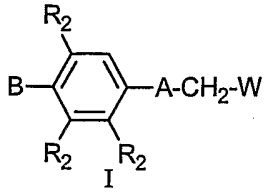
Table 1. Antibacterial Activity Minimum Inhibitory Concentration (μg/mL)

Compound No.	SAUR 9213 MIC	SPNE 9912 MIC	HINF 30063 MIC
4	4	1	64
6	2	1	16
7	4	1	>64
8	4	<0.5	>32
9	4	2	16
10	4	2	32
11	4	2	16
12	16	2	>64
13	>64	64	>64
14	8	2	>64
15	>16	2	>16
16	16	2	16
17	>64	2	>64
18	16	2	>64
19	4	0.25	32
20	4	2	64
21	32	4	>64
22	32	4	32
23	4	0.25	32
24	8	2	>64
25	8	2	>64
26	4	0.25	16
27	8	1	>64
28	4	0.5	16
29	4	1	>64
30	4	1	64

Compound No.	SAUR 9213 MIC	SPNE 9912 MIC	HINF 30063 MIC
31	4	1	64
32	4	2	64
33	4	1	16
35	64	16	>64
36	4	0.5	>64

We Claim:

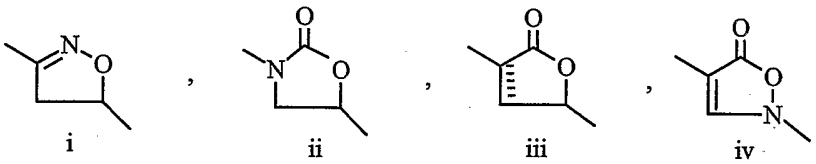
1. A compound of formula I



I

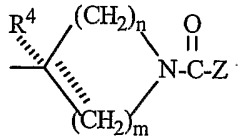
or pharmaceutically acceptable salts thereof wherein:

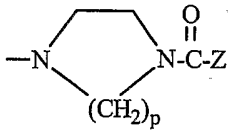
A is a structure i, ii, iii, or iv;



i ii iii iv

B is

(a) 

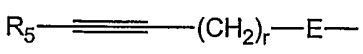
(b)  ;

W is –N(H)C(=X)-R_1, Het, or –Y-HET, in which the Het or –Y-HET is optionally substituted with =S or =O;

X is O or S;

Y is NH, O, or S;

Z is



E is CH_2 or C=O;

R_1 is a) H,

b) NH_2,

c) NHC_{1-4}alkyl,

d) C_{1-4} alkyl,

e) C_{2-4} alkenyl,

i) O-C_{1-4} alkyl,

j) S-C_{1-4} alkyl, or

k) $(CH_2)_s$ C_{3-6} cycloalkyl, in which each occurrence of alkyl or cycloalkyl in R_1 is optionally substituted by 1-3 halo;

Each R_2 is independently H, halogen, or C_{1-4} alkyl;

R_4 is H, CH_3 or F;

R_5 is selected from H, aryl, and heteroaryl, each optionally substituted with 1-3 of R_6;

R_6 is halogen, $(CH_2)_mNHR_7$, $(CH_2)_pR_7$, CH_2-CHR_9-C(O)-R_8, OR_8, $S(O)_qR_7$, CN, $C(=O)R_9$, $C(=NR_{10})NHR_8$, or $C(=NR_{10})R_8$;

Each R_7 and R_8 is independently H, C_{1-6} alkyl, aryl, or heteroaryl;

R_9 is OH, OR_8, C_{1-6} alkyl, aryl, heteroaryl, or $N(R_7)(R_8)$;

R_{10} is OR_8 or $N(R_7)(R_8)$;

m is 0, 1, 2, 3, 4;

n is 0, 1, 2, 3, 4 with the proviso that m plus n is 2, 3, 4, or 5;

p is 1, 2, 3;

q is 0, 1, 2;

r and s are independently 0, 1, 2, 3, 4, 5 or 6.

2. The compound of claim 1, wherein R_5 is phenyl optionally substituted with R_6.

3. The compound of claim 2, wherein R_6 is $(CH_2)_mNHR_7$.

4. The compound of claim 2, wherein R_6 is CH_2-CHR_9-C(=O)-R_8.

5. The compound of claim 4, wherein R_6 is $-CH_2$-$CH(NH_2)$-C(=O)-OH or $-CH_2$-$CH(NH_2)$-C(=O)-O-CH_3.

6. The compound of claim 2, wherein R_6 is OR_8.

7. The compound of claim 2, wherein R_6 is $C(=O)R_9$.

8. The compound of claim 1, wherein B is b and p is 2.

9. A compound selected from:

N-({(5S)-3-[4-(4-{6-[3-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-({(5S)-3-[3-fluoro-4-(4-hex-5-ynoylpiperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-({(5S)-3-[3-fluoro-4-(4-hept-6-ynoylpiperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[5-(4-hydroxyphenyl)pent-4-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[5-(3-hydroxyphenyl)pent-4-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-({(5S)-3-[4-(4-{5-[4-(aminomethyl)phenyl]pent-4-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[6-(4-hydroxyphenyl)hex-5-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[6-(3-hydroxyphenyl)hex-5-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-({(5S)-3-[4-(4-{6-[4-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[7-(3-hydroxyphenyl)hept-6-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-{[(5S)-3-(3-fluoro-4-{4-[7-(4-hydroxyphenyl)hept-6-ynoyl]piperazin-1-yl}phenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-({(5S)-3-[4-(4-{7-[4-(aminomethyl)phenyl]hept-6-ynoyl}piperazin-1-yl)-3-fluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-{[(5S)-3-(4-{4-[5-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pent-4-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

methyl 4-{5-[4-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-5-oxopent-1-ynyl}-L-phenylalaninate;

N-{[(5S)-3-(4-{4-[5-(4-aminophenyl)pent-4-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-[((5S)-3-{3-fluoro-4-[4-(6-{4-[(methylamino)methyl]phenyl}hex-5-ynoyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

N-({(5S)-3-[3-fluoro-4-(4-{6-[4-(1H-imidazol-1-ylmethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide;

N-{[(5S)-3-(4-{4-[6-(4-acetylphenyl)hex-5-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

N-({(5S)-3-[4-(1-{6-[3-(aminomethyl)phenyl]hex-5-ynoyl}-3-methylazetidin-3-yl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)propanamide;

N-[((5S)-3-{3-fluoro-4-[4-(6-{4-[(1E)-N-hydroxyethanimidoyl]phenyl}hex-5-ynoyl)piperazin-1-yl]phenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide;

N-{[(5S)-3-(4-{4-[6-(3-cyanophenyl)hex-5-ynoyl]piperazin-1-yl}-3-fluorophenyl)-2-oxo-1,3-oxazolidin-5-yl]methyl}acetamide;

4-{5-[4-(4-{(5S)-5-[(acetylamino)methyl]-2-oxo-1,3-oxazolidin-3-yl}-2-fluorophenyl)piperazin-1-yl]-5-oxopent-1-ynyl}-L-phenylalanine;

N-[((5S)-3-{4-[4-(6-{4-[(Z)-amino(hydroxyimino)methyl]phenyl}hex-5-ynoyl)piperazin-1-yl]-3-fluorophenyl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide hydrochloride;

N-({(5S)-3-[4-(4-{6-[3-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-2,3,5-trifluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide and

N-({(5S)-3-[4-(4-{6-[4-(aminomethyl)phenyl]hex-5-ynoyl}piperazin-1-yl)-2,3,5-trifluorophenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide.

10. A method for the treatment of microbial infections in mammals comprising administration of an effective amount of compound of claim 1 to said mammal.

11. The method of claim 10 wherein said compound of claim 1 is administered to the mammal orally, parenterally, transdermally, or topically in a pharmaceutical composition.

12. The method of claim 11 wherein said compound is administered in an amount of from about 0.1 to about 100 mg/kg of body weight/day.

13. The method of claim 11 wherein said compound is administered in an amount of from about 1 to about 50 mg/kg of body weight/day.

14. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/IB2004/000943

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/12 C07D413/10 C07D263/20 A61K31/496 A61P31/04

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)
IPC 7 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 practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 5 652 238 A (BRICKNER STEVEN J ET AL) 29 July 1997 (1997-07-29) claims 1,9	1-14
A	US 6 277 868 B1 (PLIUSHCHEV MARINA ET AL) 21 August 2001 (2001-08-21) claims 2,10	1-14
P,X	WO 03/082864 A (CADILA HEALTHCARE LTD ; LOHRAY BRAJ BHUSHAN (IN); LOHRAY VIDYA BHUSHAN) 9 October 2003 (2003-10-09) page 1, line 15 - line 17; claim 1; examples 44,80	1-14

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

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 2004	04/06/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Seelmann, I

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Int ional Application No
PCT/IB2004/000943

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