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(71) Applicant (for all designated States except US): **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MEINKE, Peter, T.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **LIU, Kun** [CN/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **XU, Libo** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **DEBENHAM, Sheryl, D.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

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(54) Title: ANTIBIOTIC COMPOUNDS

(57) Abstract: The present invention relates to novel carboxylic acid derivatives of thiazolyl peptide antibiotics capable of treating serious bacterial infections in mammals, and particularly, in humans. These carboxylic acid analogs can also be versatile intermediates for the preparation of new derivatives with useful antibacterial activity.



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TITLE OF THE INVENTION
ANTIBIOTIC COMPOUNDS

This application claims the benefit of US Provisional application 60/794,559,
5 filed April 24, 2006.

BACKGROUND OF THE INVENTION

Infections caused by bacteria are a growing medical concern as many of these
10 bacteria are resistant to various antibiotics. Such microbes include *Staphylococcus aureus*,
Staphylococcus hemolyticus, *Pediococcus spp.*, and *Streptococcus pyogenes*, *Streptococcus*
pneumoniae, *Pseudomonas aeruginosa*, *Vibrio cholerae*, *Vibrio parahemolyticus*, *Actinobacter*
calcoeticus, *Stenotrophomonas maltophilia*.

Many thiazolyl peptide antibiotics exhibit potent antibacterial activity against a
15 variety of Gram-positive bacteria, including multiple drug-resistant strains. Their poor water
solubility severely limits their usage as therapeutic agents. It is therefore desirable to prepare
derivatives with increased water solubility while maintaining potent antimicrobial activity.

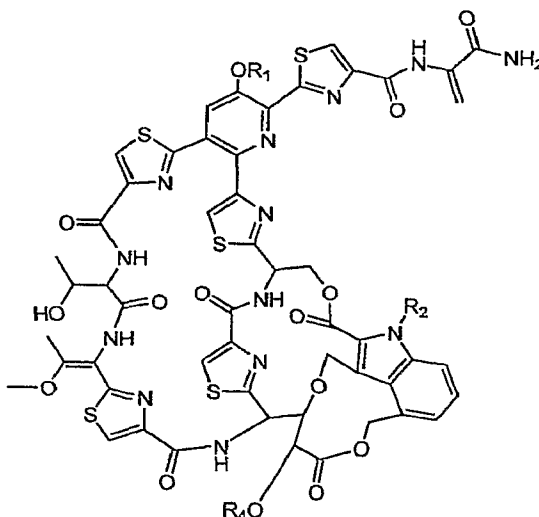
This invention relates to novel processes for preparing analogs of thiazolyl
peptide antibiotics, either through a two-step sequence via use of a versatile carboxylic acid
20 intermediate or in a one pot fashion by trapping the reaction intermediate directly using
appropriate nucleophiles. Many of the novel thiazolyl peptide antibiotics derived from the
claimed show much improved aqueous solubility over previously disclosed antibiotics (see
WO2004/004646, WO2002/14354, WO2002/13834, WO2000/68413, WO2000/14100,
WO2000/03722, WO2002/66046 and PCT US2005/33326, filed September 16, 2005). See also,
25 P. Hrnčiar et al., *J. Org. Chem.* 2002, 67(25), 8789-8793; B. Naidu, et al., *Bioorganic & Med.*
Chem. Ltrs. (2004), 14(22), 5573-5577; M. Pucci, et al., *Antimicrobial Agts. And Chemo.*,
(2004), 48(10), 3697-3701; B. Naidu, et al, *Tetrahedron Letters* (2004), 45(17), 3531, and
Tetrahedron Letters (2004), 45(5), 1059-1063; M. D. Lee et al., *J. Antibiotics* Aug. 1994, Vol.
47 No. 8 pages 901-908; T. Otani et al., *J. Antibiotics* 1998, Vol. 51 No. 8, pages 715-721; and
30 M. D. Lee et al., *J. Antibiotics* 1994, Vol. 47 No. 8 pages 894-900.

The novel processes described in this invention can be applied to various
thiazolyl antibiotics that have a dehydroalanine side chain, including nocathiacin-I, thiazomycin,
thiostrepton, GE2270A, A10255, S 54832, promothiocin, thioactin, siomycins,
berninamycin, thiopeptin, glycothiohexide, and nosiheptide.

SUMMARY OF THE INVENTION

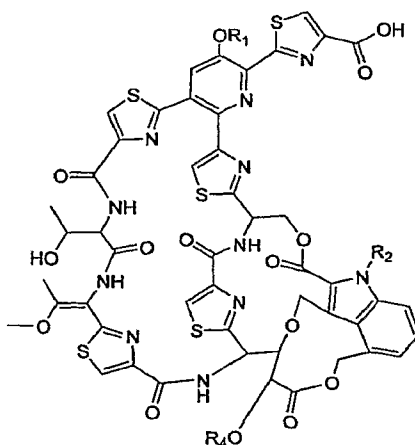
This invention relates to processes for making versatile carboxylic acid thiazolyl intermediates that provide an efficient means for making novel thiazolyl peptide derivatives.

- 5 The process for making carboxylic acid thiazolyl intermediates comprises the steps of
1) contacting a compound of formula I:



or a pharmaceutically acceptable salt, ester, enantiomer, diastereomer or mixture thereof,

- 10 with an anhydride in the presence of a base followed by aqueous hydrolysis to produce a compound of formula II:



Formula II

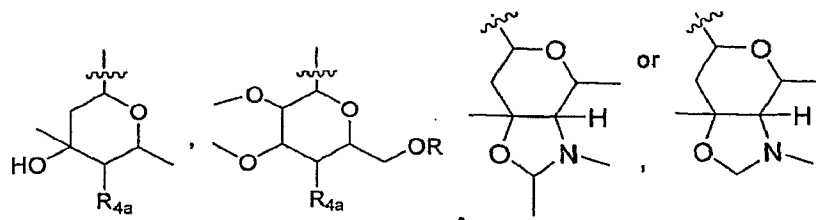
and 2) isolating the compound of formula II;

- 15 wherein:

R independently represents hydrogen, and C₁₋₁₂ alkyl;

R₁ represents hydrogen, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, said alkyl, cycloalkyl optionally substituted with 1 to 3 groups of R_a;

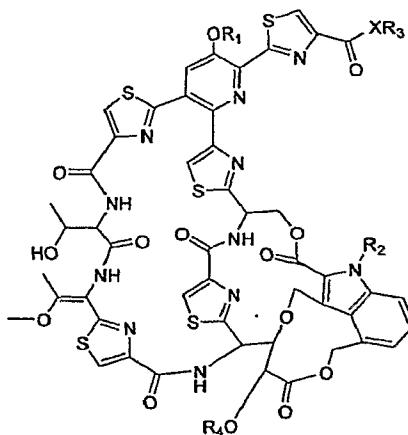
R₂ represents R₁ and OR₁;



R₄ represents hydrogen,

R_{4a} represents N(R)₂.

Another aspect of this invention comprises the step of coupling the compound of formula II with a nucleophile represented by R₃XH to produce a compound of formula III:



Formula III

or a pharmaceutically acceptable salt, ester, enantiomer, diastereomer or mixture thereof, wherein:

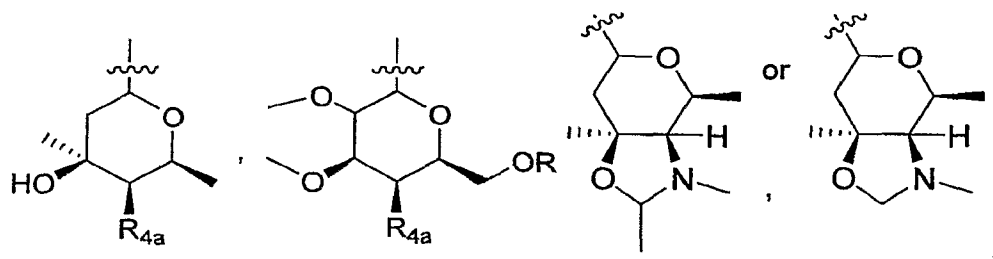
R independently represents hydrogen, and C₁₋₁₂ alkyl;

R₁ represents hydrogen, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, said alky, cycloalkyl optionally substituted with 1 to 3 groups of R_a;

R₂ represents R₁ and OR₁;

R₃X- represents -NR₅R₆, -NH(CR₇R₈)(CH₂)_nNH)_mC(O)NR₅R₆, -NHCR₇R₈R₉, -OR₅, and -SR₅;

R₄ represents hydrogen,



R_{4a} represents N(R)₂;

R₅ and R₆ independently represent hydrogen, C₁₋₁₂ alkyl, -(CH₂)_nC₅₋₁₀ heterocyclyl, -
 (CH₂)_nNR₇R₈, -(CH₂)_nNR(CH₂)_nNR₇R₈, -(CH₂)_nC(=CH₂)C(O)NR₇R₈, -
 (CH₂)_nC(=CH₂)CN, -(CH₂)_nNR(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nC₆₋₁₀ aryl, -
 (CH₂)_n(O(CH₂)₂)₁₋₆R₉, -(CH₂)_nNHC(O)(CH₂)_nNR₇R₈, -(CH₂)_nS(O)_p(CH₂)_nC₅₋₁₀
 heterocyclyl, -(CH₂)_nS(O)_p(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nS(O)_pC₁₋₆ alkyl, -(CH₂)_nNHNHR₁, -
 (CH₂)_nCHR₇CF₃, -C(O)C₅₋₁₀ heterocyclyl, -C(R)₂(CH₂)_nNHC(O)N(CH₂)_nC₅₋₁₀
 heterocyclyl, -C(R)₂(CH₂)_nOR, said aryl, and heterocyclyl optionally substituted with 1 to 3
 groups of R_a; said alkyl optionally substituted with 1 to 6 hydroxy and/or optionally substituted
 by one to three groups of R_a; or

R₅ and R₆ together with the nitrogen atom they are attached form a 5 to 10 heterocyclic ring
 optionally containing 1 to 2 additional heteroatoms selected from the group consisting of N, S
 and O and optionally substituted with 1 to 3 groups of R_a;

R₇ and R₈ independently represent hydrogen, hydroxyl, C₁₋₆ alkoxy, C₁₋₁₂ alkyl, -
 (CH₂)_nNR₅R₆, -(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nNHNHC(O)C₅₋₁₀

heterocyclyl, $-(CH_2)_nOR$, $-(CH_2)_nNHNHR_1$, $-C(O)C_{1-6}$ alkyl, $-C(O)C_{5-10}$ heterocyclyl, $-C(O)NH(CH_2)_nC_{5-10}$ heterocyclyl, $-C(O)(CH_2)_nN(R)_2$, $-(CH_2)_nS(O)p(CH_2)_nC_{5-10}$ heterocyclyl, $-(CH_2)_nS(O)p(CH_2)_nC_{6-10}$ aryl, $-(CH_2)_nS(O)p(CH_2)_nC_{1-6}$ alkyl, said aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^a ; said alkyl optionally substituted with 1 to 6 hydroxy and/or optionally substituted by one to three groups of R^a or

R_7 and R_8 together with the nitrogen atom they are attached form a 5 to 10 membered heterocyclic ring optionally containing 1 to 2 additional heteroatoms selected from the group consisting of N, S and O and optionally substituted with 1 to 3 groups of R^a ; or

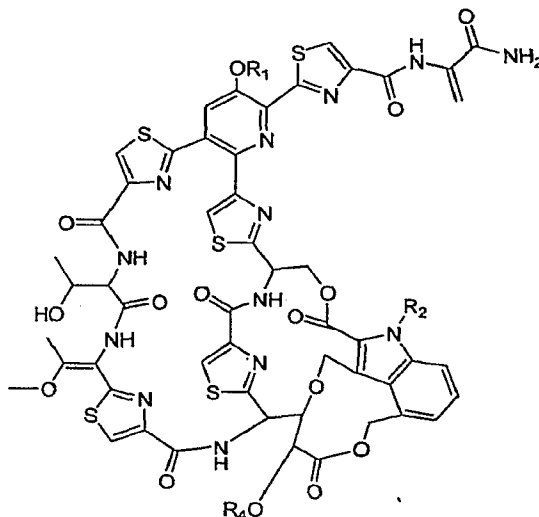
R_7 and R_8 together with the carbon atom they are attached form a 3 to 10 membered carbocyclic ring optionally and optionally substituted with 1 to 3 groups of R^a ;

R_9 represents hydrogen, C_{1-6} alkyl, $(CH_2)_nC_{5-10}$ heterocyclyl, $-C(O)OR$, CN, OR, said alkyl and heterocyclyl optionally substituted with 1 to 3 groups of R^a

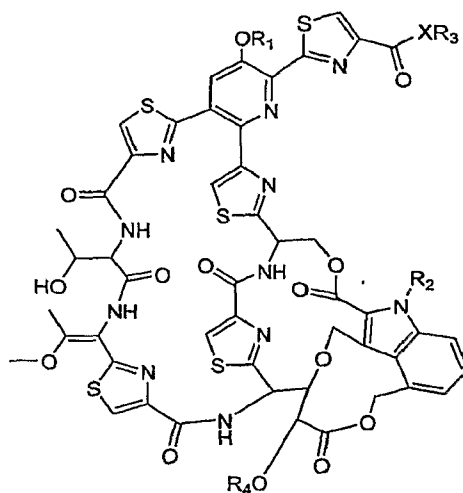
R^a represents hydrogen, halogen, $(CH_2)_nOR$, CF_3 , $(CH_2)_nC(O)OR$, $(CH_2)_nC(O)NR_7R_8$, $(CH_2)_nC_{5-10}$ heterocyclyl, $SO_2NR_5R_6$, $(CH_2)C_{6-10}$ aryl, $N(R)_2$, NO_2 , CN, $(C_{1-6}$ alkyl)O-, (aryl)O-, $(C_{1-6}$ alkyl)S(O) $_{0-2}$ -, C_{1-12} alkyl, said alkyl, heterocyclyl, and aryl optionally substituted with 1 to 4 groups selected from the group consisting of C_{1-6} alkyl, $(CH_2)_nOR$, $(CH_2)_nN(R)_2$, -O-, and

n represent 0-6, m represents 0-1, s represents 1-6, and p represents 0, 1 or 2.

Still another aspect of this invention comprises contacting a compound of formula I:



with an anhydride in the presence of a base followed by addition of a nucleophile represented by R_3XH to produce a compound of formula III and isolating the compound of formula III:



Formula III

or a pharmaceutically acceptable salt, ester, enantiomer, diastereomer or mixture thereof,

wherein:

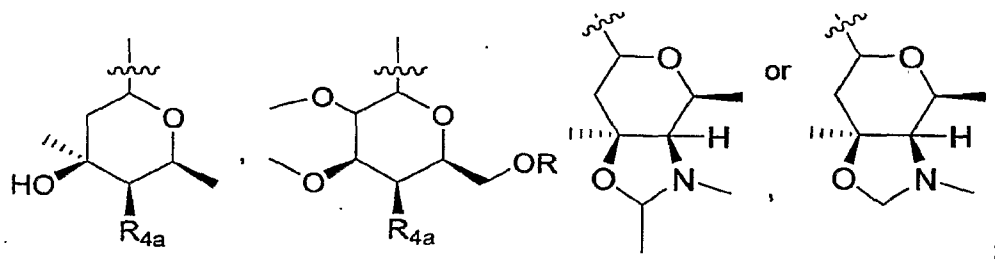
R independently represents hydrogen, and C₁-12 alkyl;

R₁ represents hydrogen, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, said alkyl, cycloalkyl optionally substituted with 1 to 3 groups of R^a;

5 R₂ represents R₁ and OR₁;

R₃X- represents -NR₅R₆, -NH(CR₇R₈)(CH₂)_n(NH)_mC(O)NR₅R₆, -NHCR₇R₈R₉, -OR₅, and -SR₅;

10 R₄ represents hydrogen,



R_{4a} represents N(R)₂;

15 R₅ and R₆ independently represent hydrogen, C₁₋₁₂ alkyl, -(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nNR₇R₈, -(CH₂)_nNR(CH₂)_nNR₇R₈, -(CH₂)_nC(=CH₂)C(O)NR₇R₈, -(CH₂)_nC(=CH₂)CN, -(CH₂)_nNR(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_n(O(CH₂)₂)₁₋₆R₉, -(CH₂)_nNHC(O)(CH₂)_nNR₇R₈, -(CH₂)_nS(O)_p(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nS(O)_p(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nS(O)_pC₁₋₆ alkyl, -(CH₂)_nNHNHR₁, -
 20 (CH₂)_nCHR₇CF₃, -C(O)C₅₋₁₀ heterocyclyl, -C(R)₂(CH₂)_nNHC(O)N(CH₂)_nC₅₋₁₀ heterocyclyl, -C(R)₂(CH₂)_nOR, said aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^a; said alkyl optionally substituted with 1 to 6 hydroxy and/or optionally substituted by one to three groups of R^a; or

25 R₅ and R₆ together with the nitrogen atom they are attached form a 5 to 10 heterocyclic ring optionally containing 1 to 2 additional heteroatoms selected from the group consisting of N, S and O and optionally substituted with 1 to 3 groups of R^a;

R₇ and R₈ independently represent hydrogen, hydroxyl, C₁₋₆ alkoxy, C₁₋₁₂ alkyl, -
 30 (CH₂)_nNR₅R₆, -(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nNHNHC(O)C₅₋₁₀

heterocyclyl, $-(CH_2)_nOR$, $-(CH_2)_nNHNHR_1$, $-C(O)C_{1-6}$ alkyl, $-C(O)C_{5-10}$ heterocyclyl, $-C(O)NH(CH_2)_nC_{5-10}$ heterocyclyl, $-C(O)(CH_2)_nN(R)_2$, $-(CH_2)_nS(O)p(CH_2)_nC_{5-10}$ heterocyclyl, $-(CH_2)_nS(O)p(CH_2)_nC_{6-10}$ aryl, $-(CH_2)_nS(O)p(CH_2)_nC_{1-6}$ alkyl, said aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^a ; said alkyl optionally substituted with 1 to 6 hydroxy and/or optionally substituted by one to three groups of R^a or

R_7 and R_8 together with the nitrogen atom they are attached form a 5 to 10 membered heterocyclic ring optionally containing 1 to 2 additional heteroatoms selected from the group consisting of N, S and O and optionally substituted with 1 to 3 groups of R^a ; or

R_7 and R_8 together with the carbon atom they are attached form a 3 to 10 membered carbocyclic ring optionally and optionally substituted with 1 to 3 groups of R^a ;

R_9 represents hydrogen, C_{1-6} alkyl, $(CH_2)_nC_{5-10}$ heterocyclyl, $-C(O)OR$, CN, OR, said alkyl and heterocyclyl optionally substituted with 1 to 3 groups of R^a

R^a represents hydrogen, halogen, $(CH_2)_nOR$, CF_3 , $(CH_2)_nC(O)OR$, $(CH_2)_nC(O)NR_7R_8$, $(CH_2)_nC_{5-10}$ heterocyclyl, $SO_2NR_5R_6$, $(CH_2)C_{6-10}$ aryl, $N(R)_2$, NO_2 , CN, $(C_{1-6}$ alkyl)O-, (aryl)O-, $(C_{1-6}$ alkyl)S(O) $_{0-2}$ -, C_{1-12} alkyl, said alkyl, heterocyclyl, and aryl optionally substituted with 1 to 4 groups selected from the group consisting of C_{1-6} alkyl, $(CH_2)_nOR$, $(CH_2)_nN(R)_2$, -O-; and

n represent 0-6, m represents 0-1, s represents 1-6, and p represents 0, 1 or 2.

DETAILED DESCRIPTION OF THE INVENTION

Several methods have been reported to synthesize water-soluble analogs of thiazolyl peptide antibiotics, including modifications of the dehydroalanine side chain of nocathiacin through an Amadori rearrangement sequence and a Michael addition reaction (see WO2004/004646, WO2002/14354, WO2002/13834, WO2000/68413, WO2000/14100, WO2000/03722, WO2002/66046 and PCT US2005/33326, filed September 16, 2005). See also, P. Hrnčiar et al., *J. Org. Chem.* 2002, 67(25), 8789-8793; B. Naidu, et al., *Bioorganic & Med. Chem. Ltrs.* (2004), 14(22), 5573-5577; M. Pucci, et al., *Antimicrobial Agts. And Chemo.*, (2004), 48(10), 3697-3701; B. Naidu, et al., *Tetrahedron Letters* (2004), 45(17), 3531, and *Tetrahedron Letters* (2004), 45(5), 1059-1063.) The Amadori sequence involves multiple steps,

harsh reaction conditions, and low overall yield, and can only generates N-(aminoethyl)-amides with a two-carbon linkage. Michael addition of amines and thiols to the dehydroalanine moiety in frozen water is efficient and provides good isolated yield of the desired adducts. However, the reaction is non-stereoselective and generates a 1:1 mixture of diastereomers.

5 The present invention relates to novel processes for preparing analogs of thiazolyl peptide antibiotics. One process is through a two-step sequence, the first of which results in the production of a versatile carboxylic acid intermediate in good synthetic yield. This carboxylic acid intermediate can then be used to couple with a variety of nucleophiles to generate water soluble analogs of the compound of formula III. The other process relates to a novel process for
10 preparing analogs of thiazolyl peptide antibiotics in a one-pot fashion wherein the nucleophile R_3XH is added directly to the reaction mixture of substrate and anhydride/base to generate analogs of thiazolyl peptide antibiotics of formula III. The methods described herein can be utilized for the synthesis of not only the Amadori products but also a variety of thiazolyl peptide derivatives that are not accessible using previously available methodologies. They also allow the
15 preparation of chiral Michael adducts.

For purposes of this invention, aqueous hydrolysis is performed in accordance with methods generally known in the art.

For purposes of this invention, useful anhydrides are trifluoroacetic anhydride (TFAA), pentafluoropropionic anhydride, chlorodifluoroacetic anhydride,
20 trichloroacetic anhydride, dichloroacetic anhydride, chloroacetic anhydride, benzoic anhydride, difluoro anhydride, and the like,, preferably TFAA. Generally, the ratio of anhydride to base ranges from 1:1 to 1:20.

For purposes of this invention, useful bases are pyridine, 4-pyrrolidinopyridine, 4-dimethylaminopyridine, 4-ethylpyridine, 4-isopropylpyridine, 4-
25 picoline, 3-picoline, and the like preferably pyridine.

An example of this invention is characterized by adding a base and an anhydride to an organic solution containing a compound of formula I at a temperature of about -25 °C to about 25 °C, preferably between about -5 °C to about 5 °C.

30 Organic solvents useful in this invention are C_3 to C_8 esters or ketones (e.g., methyl acetate, ethyl acetate, isopropyl acetate, acetone, methyl ethyl ketone and the like), ethers (e.g., tetrahydrofuran and dioxane), amides (e.g., dimethylformamide and dimethylacetamide),

and nitriles (e.g., acetonitrile and propionitrile), benzene, dimethylsulfoxide, or a mixture thereof.

Another example of a process of this invention is characterized by adding a base and an anhydride to an organic solution containing a compound of formula I at a temperature of about -5 °C to about 5 °C. The mixture is then allowed to warm to room temperature and stirred for several hours. Additional pyridine and anhydride can optionally be added. The reaction can be quenched using water while being kept in an ice bath. The crude acid product can be purified by HPLC and then utilized to couple with a variety of nucleophiles represented by R₃XH (e.g. alcohols, thiols, primary amines and secondary amines) to generate the compounds of formula III.

Alternatively, a base and an anhydride are added to an organic solution containing a compound of formula I at a temperature of about -5 °C to about 5 °C. The mixture is then allowed to warm to room temperature and stirred for several hours. It is then transferred (using a cannula for example) to an organic solution containing a nucleophile represented by R₃XH (e.g. alcohol, thiol, primary amine and secondary amine). The reaction mixture is stirred for several hours. The crude product can be purified by HPLC to generate a compound of formula III.

The invention is described herein in detail using the terms defined below unless otherwise specified.

The compounds of the present invention may have asymmetric centers, chiral axes and chiral planes, and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. (See E.L. Eliel and S.H. Wilen Stereochemistry of Carbon Compounds (John Wiley and Sons, New York 1994), in particular pages 1119-1190).

When any variable (e.g. aryl, heterocycle, R₄, R₁ etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight or branched. Preferred alkyl groups include lower alkyls which have from 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl and t-butyl. When substituted, alkyl groups may be substituted

with up to 5 substituent groups, selected from the groups as herein defined, at any available point of attachment. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group".

5 Cycloalkyl is a species of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings which are fused. Preferred cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. When substituted, cycloalkyl groups may be substituted with up to 3 substituents which are defined herein by the definition of alkyl.

10 The term "alkoxy" refers to those hydrocarbon groups having an oxygen bridge and being in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

15 "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. Preferably, alkenyl is C₂-C₆ alkenyl.

20 Preferably, alkynyl is C₂-C₆ alkynyl.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

25 The term heterocyclyl, heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term heterocyclyl, heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl,

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dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolanyl, imidazolyl, indolanyl, indolyl, isochromanyl, isoindolanyl, isoquinolanyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholanyl, naphthyridinyl, oxadiazolyl, 2-oxoazepanyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolanyl, quinolanyl, quinoxalanyl, tetrahydrofuryl, tetrahydroisoquinolanyl, tetrahydroquinolanyl, thiamorpholanyl, thiamorpholanyl sulfoxide, thiazolyl, thiazolanyl, thienofuryl, thienothienyl, and thienyl. An embodiment of the examples of such heterocyclic elements include, but are not limited to, azepanyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolanyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolanyl, imidazolyl, indolanyl, indolyl, isochromanyl, isoindolanyl, isoquinolanyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholanyl, naphthyridinyl, oxadiazolyl, 2-oxoazepanyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, 2-pyridinonyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolanyl, quinolanyl, quinoxalanyl, tetrahydrofuryl, tetrahydroisoquinolanyl, tetrahydroquinolanyl, thiamorpholanyl, thiamorpholanyl sulfoxide, thiazolyl, thiazolanyl, thienofuryl, thienothienyl, thienyl and triazolyl.

Preferably, heterocycle is selected from 2-azepinonyl, benzimidazolyl, 2-diazapinonyl, imidazolyl, 2-imidazolidinonyl, indolyl, isoquinolanyl, morpholanyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, 2-piperidinonyl, 2-pyrimidinonyl, 2-pyrrolidinonyl, quinolanyl, tetrahydrofuryl, tetrahydroisoquinolanyl, and thienyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolanyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolanyl, indolyl, isochromanyl, isoindolanyl, isoquinolanyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolanyl, quinolanyl, quinoxalanyl, tetrahydroisoquinolanyl, tetrahydroquinolanyl, thiazolyl, thienofuryl, thienothienyl, thienyl and triazolyl.

As used herein, unless otherwise specifically defined, substituted alkyl, substituted cycloalkyl, substituted aroyl, substituted aryl, substituted heteroaroyl, substituted heteroaryl, substituted arylsulfonyl, substituted heteroaryl-sulfonyl and substituted heterocycle include moieties containing from 1 to 3 substituents, substituents in addition to the point of attachment to the rest of the compound. Preferably, such substituents are selected from the group which includes but is not limited to F, Cl, Br, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, CN, (C₁-C₆ alkyl)O-, (aryl)O-, (C₁-C₆ alkyl)S(O)_m-, (C₁-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, (C₁-C₆ alkyl)C(O)-, (C₁-C₆ alkyl)OC(O)-, (C₁-C₆ alkyl)OC(O)NH-, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl and C₁-C₂₀ alkyl, (CH₂)_nOH, CF₃, (CH₂)_nC(O)OH, (CH₂)_nC(O)OC₁₋₆ alkyl, (CH₂)_nC(O)NR₇R₈, (CH₂)_nC₅₋₁₀ heterocyclyl, SO₂NR₅R₆, (CH₂)C₆₋₁₀ aryl, N(R)₂, NO₂, CN, (C₁₋₆ alkyl)O-, (aryl)O-, (C₁₋₆ alkyl)S(O)₀₋₂-, C₁₋₁₂ alkyl, said heterocyclyl, and aryl optionally substituted with 1 to 3 groups selected from the group consisting of (CH₂)_nOR, (CH₂)_nN(R)₂, -O-;

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T. W. et al. Protective Groups in Organic Synthesis Wiley, New York (1991). Examples of suitable protecting groups are contained throughout the specification.

The compounds of the present invention are basic therefore salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

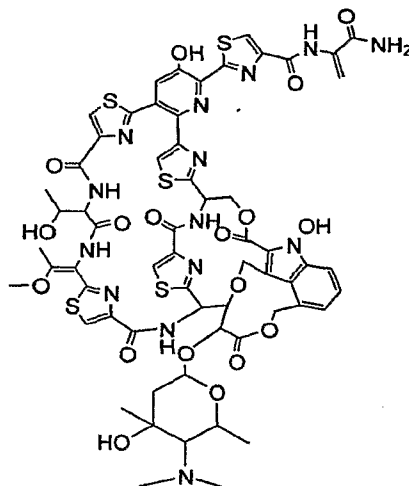
The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

Throughout the instant application, the following abbreviations are used with the following meanings:

DCM dichloromethane

	DIEA	diisopropylethylamine
	DMF	N,N-dimethylformamide
	DMAP	4-Dimethylaminopyridine
	DMSO	Dimethyl sulfoxide
5	DSC	N,N'-disuccinimidyl carbonate
	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride
	EI-MS	Electron ion-mass spectroscopy
	Et	ethyl
	EtOAc	ethyl acetate
10	EtOH	ethanol
	eq.	equivalent(s)
	FAB-MS	Fast atom bombardment-mass spectroscopy
	HOAc	acetic acid
	HOBT, HOBt	Hydroxybenztriazole
15	HPLC	High pressure liquid chromatography
	Me	methyl
	MeOH	methanol
	MF	Molecular formula
	MHz	Megahertz
20	MPLC	Medium pressure liquid chromatography
	NMM	N-Methylmorpholine
	NMR	Nuclear Magnetic Resonance
	Ph	phenyl
	Pr	propyl
25	prep.	Prepared
	PyBOP	(benzotriazole-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
	TEA	Triethylamine
	TFA	Trifluoroacetic acid
30	TFAA	trifluoroacetic anhydride
	THF	Tetrahydrofuran
	TLC	Thin layer chromatography
	TMS	Trimethylsilane

The compounds of the present invention can be prepared according to **Schemes 1-2**, using appropriate materials, and are further exemplified by the following non-limiting examples. Nocathiacin-I and the process for making can be found in US6,218,398, 6,287,827 and US2004/0018963 all incorporated herein by reference in their entirety. The structure of Nocathiacin I is:

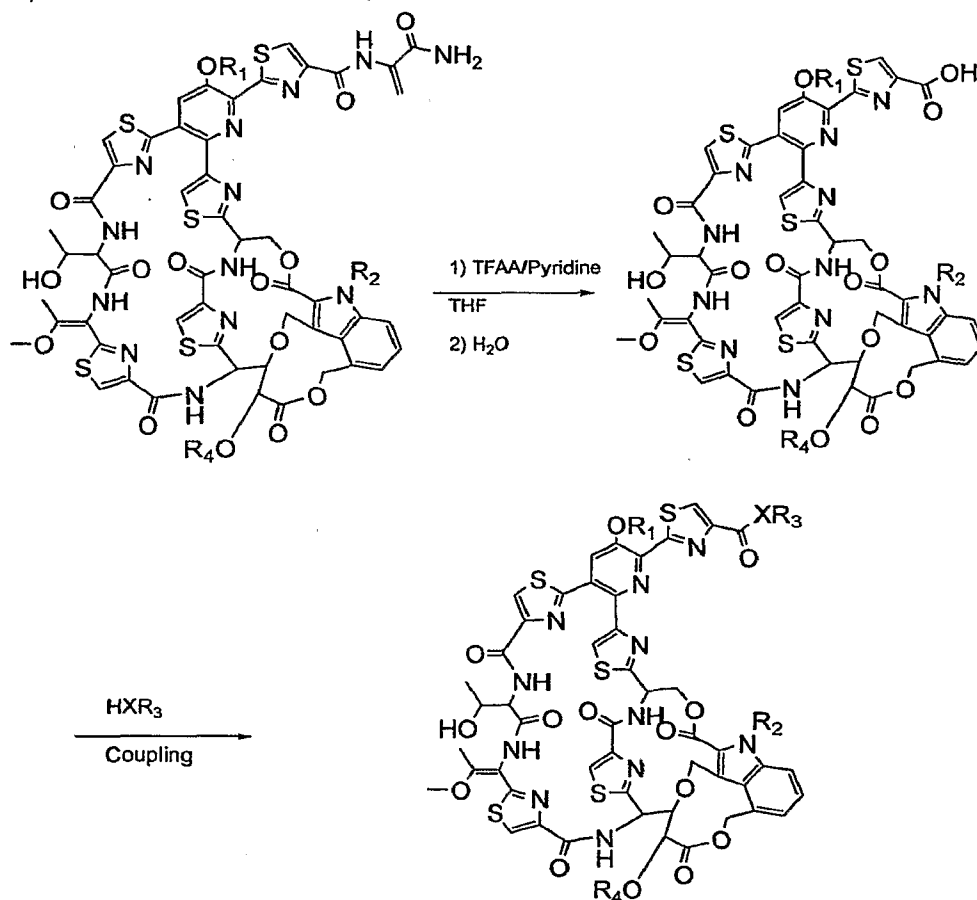


In Scheme 1, the carboxylic acid intermediate can be formed first, then coupled to a variety of nucleophiles, including alcohols, thiols, and primary and secondary amines, to generate esters, thioesters, and amides. In Scheme 2, the product can be obtained in a one-pot fashion. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The following examples further illustrate details for the preparation of compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare the compounds of the present invention. All temperatures are in degrees Celsius unless otherwise noted.

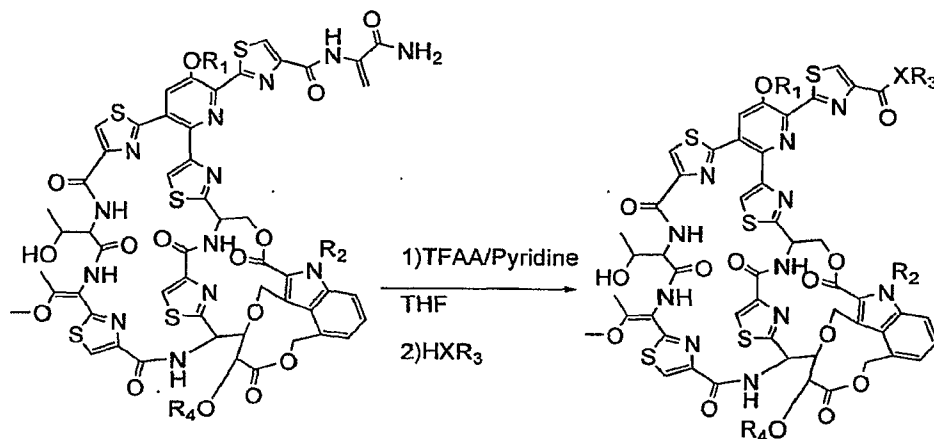
Processes for making compounds with substituents XR₃ are also disclosed in US6,218,398, 6,287,827 and US2004/0018963 all incorporated herein by reference in their entirety as well as exemplified in the non-limiting examples below. Coupling of XR₃H can be

performed, for example, with HOBt/EDC in DMF, PyBOP/DIEA in DMF or through a mixed anhydride intermediate in CH_2Cl_2 .

Scheme 1.

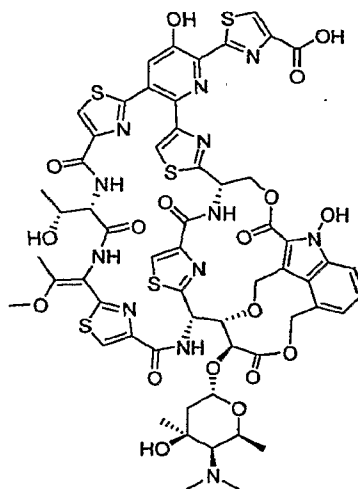


Scheme 2.



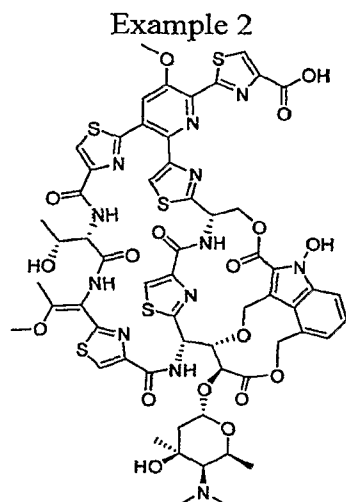
Example 1

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To a solution of nocathiacin-I (see B. Naidu, et al., Bioorganic & Medicinal Chemistry Letters (2004), 14(22), 5573-5577 and US6,218,398, both incorporated herein in their entirety for how to make nocathiacin I.) (100 mg, 0.07 mmol) in tetrahydrofuran (4 mL) at 0 °C were added pyridine (0.1 mL, 1.2 mmol) and trifluoroacetic anhydride (0.1 mL, 0.7 mmol) slowly. After addition, the reaction mixture was allowed to warm to room temperature and stirring was continued for 6 h. A second portion of pyridine (0.05 mL) and TFAA (0.05 mL) were added, and after 4 h the reaction was quenched by addition of a small amount of water while being kept in ice-bath and stirred for 30 minutes at room temperature. It was then concentrated until solid started to precipitate out. More water was added and the solid was collected by filtration. After

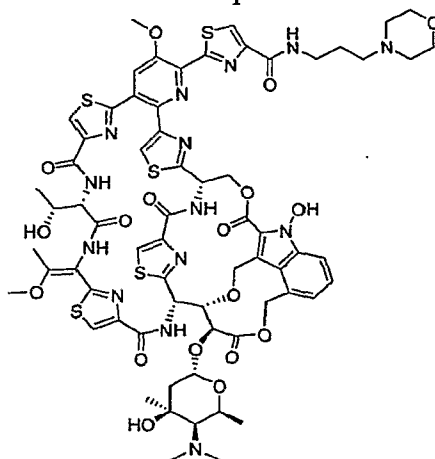
being washed with water, the solid was dissolved in methanol/chloroform, evaporated repeatedly until dry. The crude acid product was obtained as an orange crystalline solid (94 mg, 80% pure). LC-MS analysis indicated that this material consisted of approximately 1:1 acid and trifluoroacetylated acid, which can be used in the subsequent coupling reactions without further purification. An analytical sample was obtained by adding a drop of saturated sodium bicarbonate solution to 10 mg the mixed acid in DMSO, followed by reversed-phase HPLC purification. ¹H NMR (500 MHz, DMSO-*d*₆) 11.94 (s, 1H), 10.77 (s, 1H), 9.10 (s, 1H), 8.70 (s, 1H), 8.66 (s, 1H), 8.57 (m, 2H), 8.54 (s, 1H), 8.22 (s, 1H), 8.03 (s, 1H) (d, 1H, *J* = 9.5 Hz), 7.90 (s, 1H), 7.86 (d, 1H, *J* = 11.5 Hz), 7.75 (d, 1H, *J* = 8.5 Hz), 7.38 (m, 2H), 7.20 (d, 1H, *J* = 7 Hz), 6.38 (d, 1H, *J* = 12.0 Hz), 5.76 (dd, 1H, *J* = 11.0 and 4.5 Hz), 5.72 (d, 1H, *J* = 9.5 Hz), 5.24 (dd, 1H, *J* = 11.0 and 4.5 Hz), 5.06 (m, 2H), 5.00 (d, 1H, *J* = 8.0 Hz), 4.80 (d, 1H, *J* = 10.5 Hz), 4.54 (d, 1H, *J* = 11.0 Hz), 4.30 (d, 1H, *J* = 9.5 Hz), 4.26 (m, 1H), 4.16 (d, 1H, *J* = 10.5 Hz), 4.05 (d, 1H, *J* = 8.0 Hz), 3.92 (s, 3H), 3.13 (s, br, 1H), 2.89 (s, 3H), 2.87 (s, 3H), 2.13 (m, 1H), 2.01 (s, 3H), 1.95 (d, 1H, *J* = 14.5 Hz), 1.61 (s, 3H), 1.57 (s, br, 3H), 0.81 (d, 3H, *J* = 6.5 Hz). MS: 1369.71 (M+H)⁺, 685.42 ([M+2H]/2)⁺.



To a solution of Nocathiacin-I (6 g, 4.18 mmol) in benzene (150 mL) and methanol (24 mL) at 0 °C was added a solution of trimethylsilyl diazomethane in hexanes (2.0 M, 6.26 mL, 12.52 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. Volatiles were evaporated, and the solid residue was dried under vacuum overnight. Methyl-nocathiacin-I was obtained as a yellow powder (5.86 g, 80% pure by LC-MS), and was used in the next step without further purification.

To a solution of methyl-nocathiacin-I (5.86 g, 80% pure) in tetrahydrofuran (360 mL) at 0°C, was added pyridine (6.53 mL, 81 mmol) and trifluoroacetic anhydride (5.7 mL, 40 mmol) slowly. After addition, the reaction mixture was allowed to warm to room temperature and stirring was continued for 8 h. The reaction was quenched by adding small amount of water to it while being kept in ice-bath and stirred for 30 minutes at room temperature. It was then concentrated until solid started to precipitate out. More water was added and the solid was collected by filtration. After being washed with water, the solid was dissolved in dimethylsulfoxide and purified by reversed-phase HPLC (10-60% acetonitrile with 0.1% TFA). Product was obtained as a mixture of acid and trifluoroacetylated acid after lyophilization (2.56 g, 44% yield). For most of the coupling reactions, this intermediate gave satisfactory results because the trifluoroacetyl group can be easily removed with either sodium bicarbonate solution or N,N-diisopropylethylamine. An analytical sample was obtained similarly as described for example 1. ¹H NMR (500 MHz, CD₃OD) 8.94 (s, 1H), 8.62 (d, 1H, J = 9.5 Hz), 8.60 (s, 1H), 8.53 (s, 1H), 8.43 (s, 1H), 8.17 (s, 1H), 8.15 (d, 1H, J = 11.0 Hz), 8.00 (s, 1H), 7.95 (s, 1H), 7.91 (d, 1H, J = 7.0 Hz), 7.84 (d, 1H, J = 8.5 Hz), 7.43 (t, 1H, J = 7.8 Hz), 7.23 (d, 1H, J = 7.0 Hz), 6.14 (d, 1H, J = 12.5 Hz), 5.91 (dd, 1H, J = 9.3 and 1.8 Hz), 5.78 (dd, 1H, J = 10.5 and 5.0 Hz), 5.38 (dd, 1H, J = 11.5 and 5.0 Hz), 5.21 (m, 1H), 5.06 (d, 1H, J = 12.5 Hz), 4.96 (d, 1H, J = 10.5 Hz), 4.60 (d, 1H, J = 11.0 Hz), 4.41 (d, 1H, J = 9.5 Hz), 4.36 (dd, 1H, J = 10.5 Hz), 4.23 (s, 3H), 4.15 (m, 1H), 4.06 (dd, 1H, J = 9.8 and 1.8 Hz), 3.95 (s, 3H), 3.21 (m, 1H), 3.02 (s, 6H), 2.84 (m, 1H), 2.18 (m, 2H), 2.05 (s, 3H), 1.75 (s, 3H), 1.41 (d, 3H, J = 6.0 Hz), 1.00 (d, 3H, J = 7.0 Hz). MS: 1383.87 (M+H)⁺, 692.41 ([M+2H]/2)⁺.

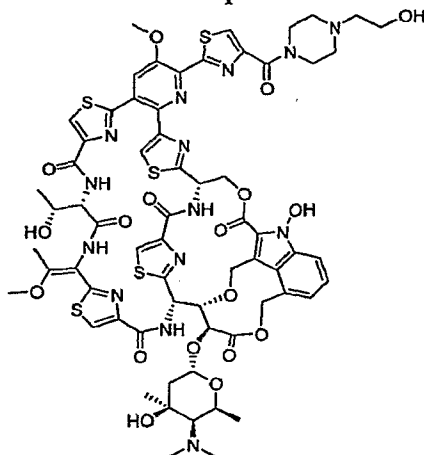
Example 3



The product of example 2 (1.04 g, 0.65 mmol) was mixed with *N*-(3-aminopropyl)morpholine (0.11 mL, 0.78 mmol), 1-hydroxybenzotriazole (0.088 g, 0.65 mmol) and EDC (0.18 g, 0.97 mmol) in anhydrous DMF (8 mL). After 1h, 2 mL of saturated sodium bicarbonate solution was added and the mixture was stirred at room temperature for 30 minutes to remove the trifluoroacetyl group. The reaction mixture was directly purified by reversed-phase HPLC (10-45% acetonitrile with 1% TFA). The desired compound was obtained as a light yellow solid after lyophilization (bis TFA salt, 0.64 g, 57% yield).

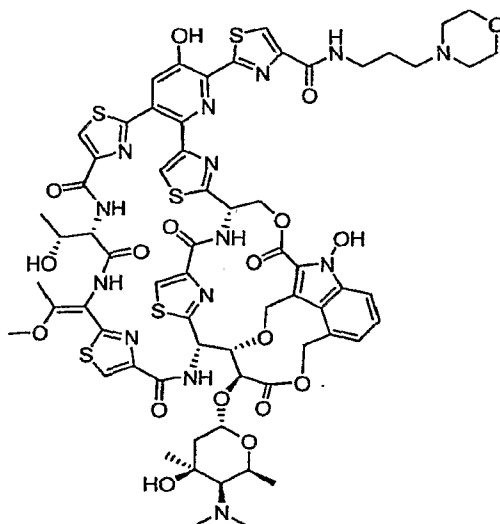
To convert to the HCl salt, the above obtained bis-TFA salt (0.64 g, 0.37 mmol) was dissolved in deionized water (130 mL) and passed through a column of AG1-X2 resin (Cl form, 40 g). Eluant and washings were combined and lyophilized to give the HCl salt of the desired compound as a light yellow fluffy solid (0.57 g, 98% yield). ¹H NMR (500 MHz, CD₃OD) 8.61 (d, 1H, J = 9.5 Hz), 8.60 (s, 1H), 8.45 (s, 1H), 8.42 (s, 1H), 8.18 (s, 1H), 8.13 (d, 1H, J = 11 Hz), 8.10 (s, 1H), 7.88 (s, 1H), 7.83 (d, 1H, J = 6.5 Hz), 7.82 (d, 1H, J = 8.5 Hz), 7.43 (t, 1H, J = 7 Hz), 7.23 (d, 1H, J = 7 Hz), 6.15 (d, 1H, J = 12.5 Hz), 5.91 (dd, 1H, J = 9.4 and 1.5 Hz), 5.77 (dd, 1H, J = 11.5 and 4.5 Hz), 5.42 (dd, 1H, J = 11.5 and 4.5 Hz), 5.21 (m, 1H), 5.07 (d, 1H, J = 13.0 Hz), 5.00 (d, 1H, J = 10.5 Hz), 4.61 (d, 1H, J = 11.0 Hz), 4.44 (d, 1H, J = 10.0 Hz), 4.38 (m, 1H), 4.32 (s, 3H), 4.29 (s, 1H), 4.15 (m, 1H), 4.07 (dd, 1H, J = 9.5 Hz), 3.96 (s, 3H), 3.87 (m, 2H), 3.54 (m, 2H), 3.19 (m, 4H), 3.02 (s, 6H), 2.78 (m, 1H), 2.17 (m, 3H), 2.07 (s, 3H), 2.04 (m, 1H), 1.75 (s, 3H), 1.41 (d, 3H, J = 6.0 Hz), 1.00 (d, 3H, J = 7.0 Hz). MS: 1509.44 (M+H)⁺, 755.67 ([M+2H]/2)⁺.

Example 4



The product of example 2 (30 mg, 0.020 mmol) was mixed with *N*-(2-hydroxyethyl)piperazine (3.2 mg, 0.024 mmol), 1-hydroxybenzotriazole (3.1 mg, 0.020 mmol) and EDC (5.8 mg, 0.03 mmol) in anhydrous DMF (0.4 mL). After 1h, the reaction mixture was deacylated with saturated sodium bicarbonate and purified by reversed-phase HPLC with a step gradient of 10-30% acetonitrile/water containing 0.1% TFA over 20 minutes. The product was obtained as a light yellow solid after lyophilization (bis TFA salt, 10.3 mg, 30% yield). ¹H NMR (500 MHz, CD₃OD) 8.62 (d, 1H, J = 9.0 Hz), 8.61 (s, 1H), 8.43 (s, 1H), 8.34 (s, br, 1H), 8.18 (s, 1H), 8.16 (d, 1H, J = 11.0 Hz), 8.02 (s, 1H), 7.91 (d, 1H, J = 7.0 Hz), 7.88 (s, 1H), 7.84 (d, 1H, J = 8.5 Hz), 7.44 (t, 1H, J = 7.8 Hz), 7.24 (d, 1H, J = 6.5 Hz), 6.15 (d, 1H, J = 12.5 Hz), 5.91 (dd, 1H, J = 9.5 and 2.3 Hz), 5.77 (dd, 1H, J = 10.3 and 5.0 Hz), 5.38 (dd, 1H, J = 11.3 and 5.0 Hz), 5.21 (m, 1H), 5.07 (d, 1H, J = 12.5 Hz), 4.97 (d, 1H, J = 11.0 Hz), 4.60 (d, 1H, J = 11.0 Hz), 4.41 (d, 1H, J = 9.5 Hz), 4.37 (m, 1H), 4.32 (d, 1H, J = 11.0 Hz), 4.25 (s, 3H), 4.15 (m, 1H), 4.07 (dd, 1H, J = 9.8 Hz), 3.96 (s, 3H), 3.87 (m, 2H), 3.20 (m, 2H), 3.02 (s, 6H), 2.84 (m, 1H), 2.17 (m, 2H), 2.05 (s, 3H), 1.75 (s, 3H), 1.42 (d, 3H, J = 6.0 Hz), 1.00 (d, 3H, J = 7.5 Hz). MS: 1495.8 (M+H)⁺, 748.8 ([M+2H]/2)⁺.

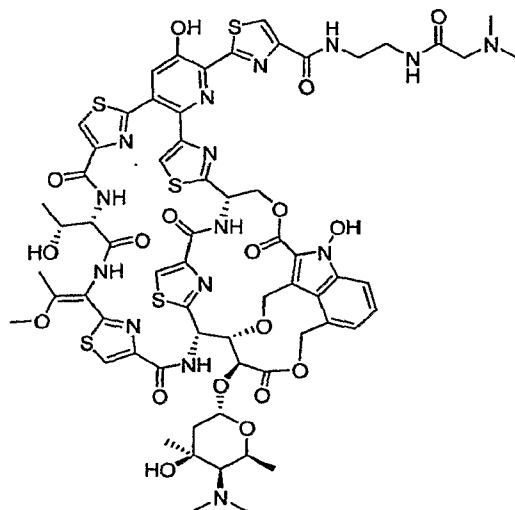
Example 5



The product of example 1 (630 mg, 0.43 mmol) was mixed with *N*-(3-aminopropyl)morpholine (75 mg, 0.52 mmol), 1-hydroxybenzotriazole (80 mg, 0.52 mmol) and EDC (125 mg, 0.65 mmol) in anhydrous DMF (3 mL). After stirring at room temperature for 1 h, the reaction mixture was deacylated with saturated sodium bicarbonate, and purified in multiple runs by

reversed-phase HPLC with a step gradient of 5-45% acetonitrile/water modified with 0.1% TFA over 20 minutes. The product was obtained as a light yellow solid after lyophilization (bis TFA salt, 270 mg, 41% yield). ¹H NMR (500 MHz, CD₃OD-*d*₄) 8.62 (d, 1H, J = 9.5 Hz), 8.56 (s, 1H), 8.43 (s, 1H), 8.41 (s, 1H), 8.19 (s, 1H), 8.14 (d, 1H, J = 11.0 Hz), 7.88 (s, 1H), 7.86 (d, 1H, J = 7.0 Hz), 7.84 (m, 2H), 7.43 (t, 1H, J = 8.0 Hz), 7.22 (d, 1H, J = 7.0 Hz), 6.13 (d, 1H, J = 13.0 Hz), 5.91 (dd, 1H, J = 9.5 and 2.0 Hz), 5.78 (dd, 1H, J = 11.0 and 5.0 Hz), 5.39 (dd, 1H, J = 11.3 and 5.3 Hz), 5.21 (m, 1H), 5.06 (d, 1H, J = 12.5 Hz), 4.96 (d, 1H, J = 10.5 Hz), 4.59 (d, 1H, J = 11.5 Hz), 4.42 (d, 1H, J = 10.0 Hz), 4.37 (m, 1H), 4.29 (d, 1H, J = 10.5 Hz), 4.05-4.18 (m, 4H), 3.96 (s, 3H), 3.80 (m, 2H), 3.53-3.60 (m, 4H), 3.29 (t, 2H, J = 7.8 Hz), 3.12-3.22 (m, 3H), 3.03 (s, 6H), 2.80 (m, 1H), 2.18 (s, 3H), 2.07 (s, 3H), 1.75 (s, 3H), 1.42 (d, 3H, J = 6.0 Hz), 1.00 (d, 3H, J = 7.0 Hz). MS: 1495.27 (M+H)⁺, 748.61 ([M+2H]/2)⁺.

Example 6

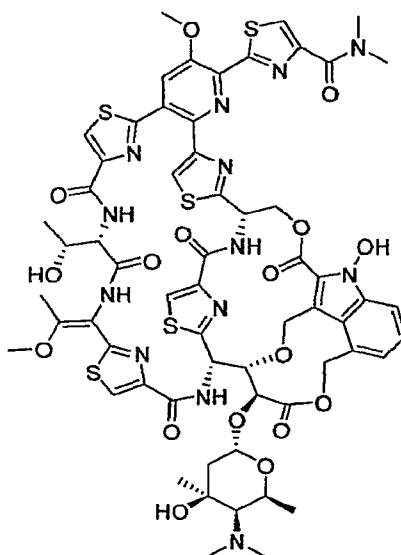


To a solution of the acid of example 1 (50 mg, 0.03 mmol) in anhydrous DMF were added N-(N,N-dimethylglycyl)-ethylenediamine (TFA salt, 12 mg, 0.045 mmol) (prepared from ethylenediamine and N,N-dimethylglycine) and PYBOP (19 mg, 0.036 mmol), followed by N,N-diisopropylethylamine (6.3 μ L, 0.036 mmol). After stirring at room temperature for 1 h, the reaction mixture was treated with saturated sodium bicarbonate, and purified by reversed-phase HPLC with a step gradient of 10-90% methanol/water modified with 0.1% TFA over 20 minutes. The product was obtained as a light yellow solid after lyophilization (bis TFA salt, 22 mg, 43% yield). ¹H NMR (600 MHz, CD₃OD) 8.86 (s, 1H), 8.60 (d, 1H, J = 9.6 Hz), 8.55 (s, 1H), 8.40 9s,

1H), 8.36 (s, 1H), 8.16 (s, 1H), 8.12 (d, 1H, J = 10.8 Hz), 7.88 (s, 1H), 7.84 (d, 1H, J = 6.6 Hz), 7.81 (d, 1H, J = 9.0 Hz), 7.80 (s, 1H), 7.41 (t, 1H, J = 7.8 Hz), 7.21 (d, 1H, J = 6.6 Hz), 6.12 (d, 1H, J = 12.6 Hz), 5.88 (d, 1H, J = 9.6 Hz), 5.75 (dd, 1H, J = 11.1 and 5.1 Hz), 5.37 (dd, 1H, J = 11.7 and 5.1 Hz), 5.19 (m, 1H), 5.04 (d, 1H, J = 12.6 Hz), 4.95 (d, 1H, J = 10.2 Hz), 4.57 (d, 1H, J = 11.4 Hz), 4.40 (dd, 1H, J = 9.6 Hz), 4.35 (m, 1H), 4.28 (d, 1H, J = 10.2 Hz), 4.12 (m, 1H), 4.05 (dd, 1H, J = 9.6 and 1.8 Hz), 3.93 (s, 3H), 3.89 (s, 3H), 3.60 (m, 2H), 3.18 (m, 1H), 3.00 (s, 6H), 2.90 (s, 6H), 2.77 (m, 1H), 2.15 (s, 2H), 2.04 (s, 3H), 1.73 (s, 3H), 1.39 (d, 3H, J = 6.0 Hz), 0.98 (d, 3H, J = 7.2 Hz). MS: 1497.66 (M+H)⁺, 749.21 ([M+2H]/2)⁺.

10

Example 7

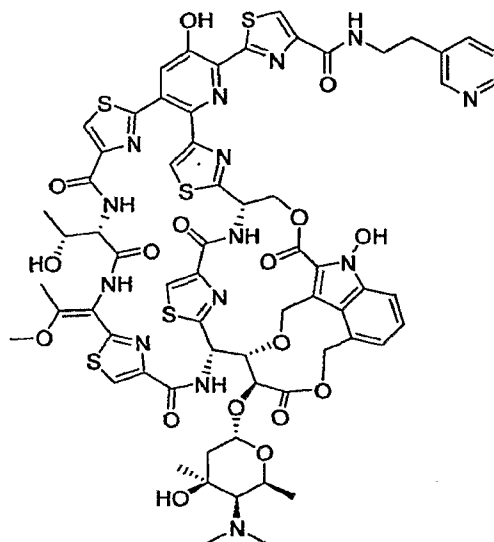


Following the procedure described for example 3 except using dimethylamine as the amine

15 component to afford the product as a yellow lyophilized solid. ¹H NMR (500 MHz, CD₃OD): δ 8.84 (s, 1 H); 8.64-8.60 (m, 2 H); 8.44 (s, 1 H); 8.19-8.13 (m, 3 H); 7.97 (s, 1 H); 8.15 (d, J = 5.0 Hz, 2 H); 7.84 (d, J = 8.2 Hz, 1 H); 7.44 (t, J = 7.3 Hz, 1 H); 7.24 (d, J = 6.9 Hz, 1 H); 6.14 (d, J = 12.3 Hz, 1 H); 5.91 (d, J = 8.7 Hz, 1 H); 5.77 (dd, J = 6.2 Hz, 1 H); 5.38 (dd, J = 4.3 Hz, 1 H); 5.22 (s, 1 H); 5.07 (d, J = 12.6 Hz, 1 H); 4.59 (d, J = 11.2 Hz, 1 H); 4.41-4.29 (m, 3 H); 4.21 (s, 3 H); 4.16-4.14 (m, 1 H); 4.07 (d, J = 9.6 Hz, 1 H); 3.95 (s, 3 H); 3.22 (s, 1 H); 3.16 (s, 2 H); 3.03 (s, 5 H); 2.85 (s, 1 H); 2.19 (s, 2 H); 2.05 (s, 3 H); 1.76 (s, 3 H); 1.41 (d, J = 5.7 Hz, 3 H); 1.00 (d, J = 7.1 Hz, 3 H).

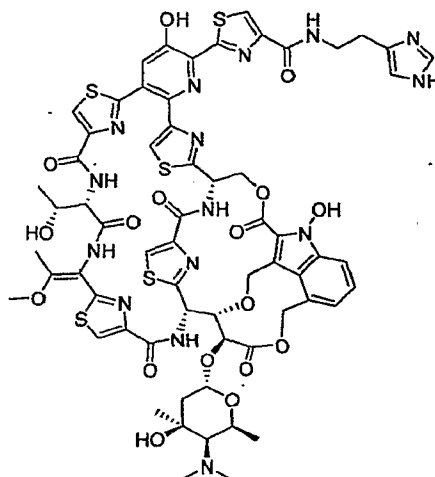
20

Example 8



- 5 Following the procedure described for example 5 except using 3-(2-aminoethyl)pyridine as the amine component to afford the product as a yellow lyophilized solid. ^1H NMR (500 MHz, CD_3OD): δ 8.86 (s, 1H); 8.79 (s, 1H); 8.69 (d, $J=3.2$ Hz, 1H); 8.60 (d, $J=9.4$ Hz, 1H); 8.55 (s, 1H); 8.48 (d, $J=8$ Hz, 1H); 8.41 (s, 1H); 8.30 (s, 1H); 8.17 (s, 1H); 8.12 (d, $J=10.9$ Hz, 1H); 7.94 (dd, $J=5.9, 7.7$ Hz, 1H); 7.83 (m, 4H); 7.41 (t, $J=7.1$ Hz, 1H); 7.21 (d, $J=7.1$ Hz, 1H); 6.12 (d, $J=12.4$ Hz, 1H); 5.89 (dd, $J=1.2, 9.6$ Hz, 1H); 5.76 (dd, $J=4.8, 10.3$, 1H); 5.37 (dd, $J=4.8, 11.4$ Hz, 1H); 5.20 (bs, 1H); 5.04 (d, $J=12.5$ Hz, 1H); 4.94 (d, $J=10.5$ Hz, 1H); 4.57 (d, $J=11.4$ Hz, 1H); 4.39 (d, $J=9.9$ Hz, 1H); 4.35 (m, 1H); 4.28 (d, $J=10.7$ Hz, 1H); 4.13 (m, 1H); 4.05 (dd, $J=1.6, 9.7$ Hz, 1H); 3.94 (s, 3H); 3.79 (bs, 2H); 3.44 (bs, 1H); 3.20 (m, 3H); 3.01 (s, 6H); 2.98 (m, 1H); 2.16 (s, 2H); 2.05 (s, 3H); 1.94 (m, 1H); 1.74 (s, 3H); 1.40 (d, $J=6$ Hz, 3H); 0.98 (d, $J=7$ Hz, 3H).

Example 9



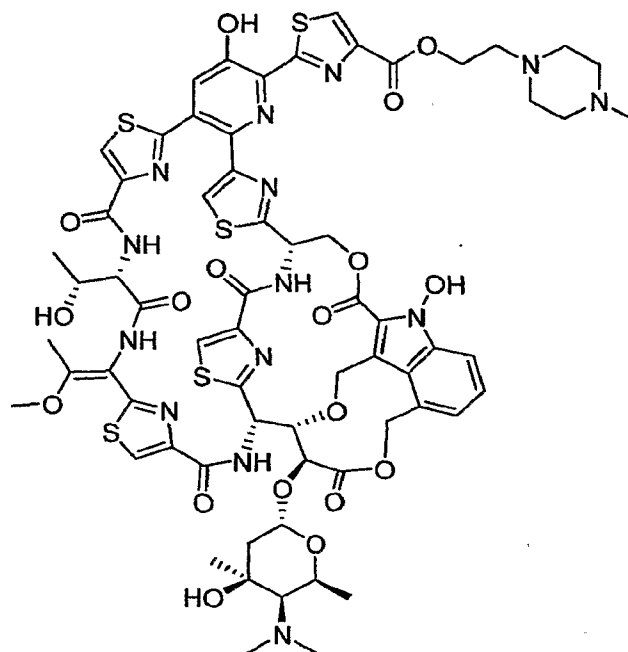
5

Following the procedure described for example 5 except using histamine as the amine component to afford the product as a yellow lyophilized solid. ^1H NMR (500 MHz, CD_3OD): δ 8.86 (s, 1 H); 8.82 (s, 1 H); 8.61 (d, $J = 9.5$ Hz, 1 H); 8.56 (s, 1 H); 8.41 (s, 1 H); 8.35 (s, 1 H); 8.17 (s, 1 H); 8.13 (d, $J = 11.2$ Hz, 1 H); 7.88-7.80 (m, 4 H); 7.41 (m, 2 H); 7.21 (d, $J = 6.9$ Hz, 1 H); 6.13 (d, $J = 12.4$ Hz, 1 H); 5.89 (d, $J = 9.3$ Hz, 1 H); 5.75 (dd, $J = 5, 11.3$ Hz, 1 H); 5.37 (dd, $J = 4.8, 11.5$ Hz, 1 H); 5.20 (s, 1 H); 5.04 (d, $J = 12.4$ Hz, 1 H); 4.95 (d, $J = 10.5$ Hz, 1 H); 4.58 (d, $J = 11.5$ Hz, 1 H); 4.40 (d, $J = 9.7$ Hz, 1 H); 4.35 (t, $J = 5.5$ Hz, 1 H); 4.29 (d, $J = 10.7$ Hz, 1 H); 4.06 (t, $J = 4.8$ Hz, 1 H); 4.05 (d, $J = 1.9, 9.6$ Hz, 1 H); 3.94 (s, 3 H); 3.76 (s, 2 H); 3.19 (s, 1 H); 3.08 (t, $J = 6.6$ Hz, 2 H); 3.00 (d, $J = 12.2$ Hz, 6 H); 2.80 (m, 1 H); 2.15 (s, 2 H); 2.04 (s, 3 H); 1.74 (s, 3 H); 1.40 (d, $J = 6.5$ Hz, 3 H); 0.98 (d, $J = 7.1$ Hz, 3 H).

10

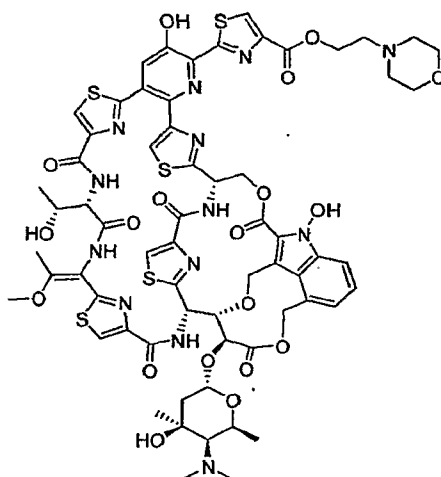
15

Example 10



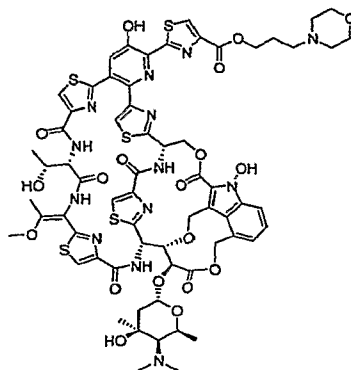
To a solution of the acid of example 1 (20 mg, 0.015 mmol), triethylamine (6.3 μ L, 0.045 mmol), and 4-dimethylaminopyridine (catalytic amount) in dichloromethane (1 mL) was isopropenylchloroformate (5 μ L, 0.045 mmol) at room temperature. After 5 minutes, 1-(2-hydroxyethyl)-4-methylpiperazine (43 mg, 0.15 mmol) was added. The reaction mixture was stirred at room temperature for 3 hours. The solvent was evaporated, and the residue was purified on preparative reversed-phase HPLC. The product was obtained as a light yellow solid after lyophilization. ^1H NMR (CD_3OD , 500MHz): d 8.61 (d, $J=9.5$, 1 H), 8.57 (m, 2 H), 8.43 (s, 1 H), 8.18 (s, 1 H), 8.14 (d, $J=11.0\text{Hz}$, 1 H), 7.87 (m, 1 H), 7.82 (m, 1 H), 7.42 (t, $J=7.8\text{Hz}$, 1 H), 7.22 (d, $J=7.0\text{ Hz}$, 1 H), 6.19 (d, $J=12.5\text{ Hz}$, 1 H), 5.90 (m, 1 H), 5.78 (dd, $J=10.5\text{ Hz}$, 4.5 Hz, 1 H), 5.39 (m, 1 H), 5.21 (s, 1 H), 5.06 (d, $J=12.5\text{ Hz}$, 1H), 4.96 (d, $J=10.5\text{Hz}$, 1 H), 4.57 (m, 3 H), 4.41 (d, $J=9.5\text{ Hz}$, 1 H), 4.37 (m, 1 H), 4.30 (d, 10.5 Hz, 1 H), 4.06 (m, 1 H), 3.95 (s, 3 H), 3.20 (s, 2 H), 3.02 (s, 6 H), 2.96 (m, 2 H), 2.89 (s, 3 H), 2.80 (m, 1 H), 2.17 (m, 2 H), 2.05 (s, 3 H), 1.75 (s, 3 H), 1.40 (d, $J=6\text{ Hz}$, 3 H), 0.99 (d, $J=7.5\text{ Hz}$, 3 H).

Example 11



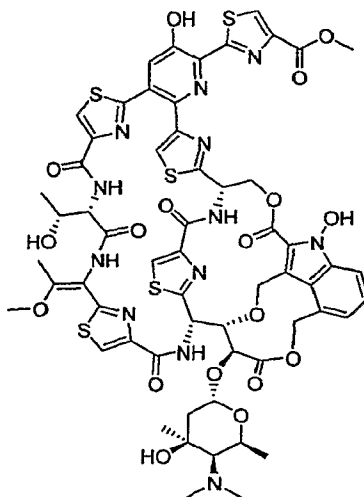
Following the procedure described for example 10 except using 1-(2-hydroxyethyl)-morpholine as the nucleophile to afford the product as a yellow lyophilized solid. ^1H NMR (500 MHz, CD_3OD): δ 8.66 (s, 1 H), 8.61 (d, $J=9.5$, 1 H), 8.55 (s, 1 H), 8.43 (s, 1 H), 8.18 (s, 1 H), 8.13 (d, $J=11.0\text{Hz}$, 1 H), 7.87-7.83 (m, 4 H), 7.42 (t, $J=7.8\text{Hz}$, 1 H), 7.21 (d, $J=7.0\text{ Hz}$, 1 H), 6.12 (d, $J=12.5\text{ Hz}$, 1 H), 5.90 (dd, $J=9.5\text{ Hz}$, 1.5 Hz, 1 H), 5.78 (dd, $J=10.5\text{ Hz}$, 4.5 Hz, 1 H), 5.39 (m, 1 H), 5.21 (m, 1 H), 5.06 (d, $J=12.5\text{ Hz}$, 1H), 4.79 (m, 1 H), 4.58 (d, $J=11\text{ Hz}$, 1 H), 4.40 (d, $J=9.5\text{ Hz}$, 1 H), 4.36 (m, 1 H), 4.27 (d, 10.5 Hz, 1 H), 4.13 (m, 1 H), 4.05 (m, 1 H), 3.95 (s, 3 H), 3.34 (m, 3 H), 3.20 (s, 2 H), 3.02 (s, 6 H), 2.80 (m, 1 H), 2.17 (d, $J=1.5\text{ Hz}$, 2 H), 2.06 (s, 3 H), 1.75 (s, 3 H), 1.41 (d, $J=6\text{ Hz}$, 3 H), 0.99 (d, $J=7.5\text{ Hz}$, 3 H).

Example 12



Following the procedure described for example 10 except using 1-(3-hydroxypropyl)-morpholine as the nucleophile to afford the product as a yellow lyophilized solid. ¹H NMR (500 MHz, CD₃OD): δ 8.61 (d, J=9.5, 1 H), 8.60 (s, 1 H), 8.55 (s, 1 H), 8.43 (s, 1 H), 8.18 (s, 1 H), 8.14 (d, J=11.0 Hz, 1 H), 7.87-7.82 (m, 4 H), 7.42 (t, J=7.8 Hz, 1 H), 7.21 (d, J=7.0 Hz, 1 H), 6.12 (d, J=12.5 Hz, 1 H), 5.90 (dd, J=9.5 Hz, 1.5 Hz, 1 H), 5.78 (dd, J=10.5 Hz, 4.5 Hz, 1 H), 5.39 (m, 1 H), 5.21 (s, 1 H), 5.06 (d, J=12.5 Hz, 1 H), 4.94 (d, J=10.5 Hz, 1 H), 4.58 (d, J=11 Hz, 1 H), 4.52 (t, J=6.0 Hz, 2 H), 4.41 (d, J=9.5 Hz, 1 H), 4.36 (m, 1 H), 4.28 (d, 10.5 Hz, 1 H), 4.13 (m, 1 H), 4.06 (m, 1 H), 3.95 (s, 3 H), 3.34 (m, 3 H), 3.20 (s, 2 H), 3.02 (s, 6 H), 2.81 (m, 1 H), 2.28 (m, 2 H), 2.17 (d, J=1.5 Hz, 2 H), 2.06 (s, 3 H), 1.75 (s, 3 H), 1.41 (d, J=6 Hz, 3 H), 0.99 (d, J=7.5 Hz, 3 H).

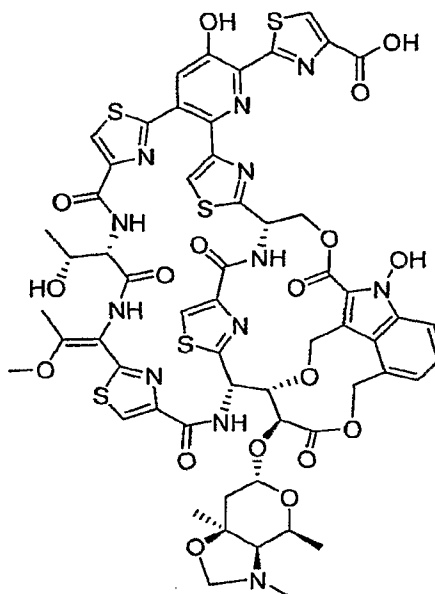
Example 13



One-pot procedure: To a suspension of nocathiacin-I (75 mg, 0.052 mmol) in THF (1 mL) was added anhydrous pyridine (84 μL, 1.04 mmol) to give a clear solution. Trifluoroacetic anhydride (72 μL, 0.72 mmol) was then introduced. The reaction mixture was stirred at room temperature for 1 hour before it was transferred to a solution of anhydrous methanol (200 μL) in THF (0.5 mL). After 10 minutes, the volatiles were removed in vacuo. The residue was treated with DIEA (0.1 mL) in a mixture of 1:1 mixture of water and acetonitrile (2 mL) for 10 minutes. Purification on preparative reversed phase HPLC generated the desired product (36 mg, 51 % yield) ¹H NMR (CD₃OD, 600 MHz) δ 8.82(s, 1 H), 8.59 (d, 9.6 Hz, 1 H), 8.51(s, 1 H), 8.48 (d,

6.6 Hz, 1 H), 8.41 (s, 1 H), 8.15 (s, 1 H), 8.11 (d, 10.8 Hz, 1 H), 7.83 (d, 6.6 Hz, 1 H), 7.80 (m, 3 H), 7.39 (t, 7.8 Hz, 1 H), 7.18 (d, 7.2 Hz, 1 H), 6.08 (d, 12.6 Hz, 1 H), 5.87 (d, 9.6 Hz, 1 H), 5.76 (m, 1 H), 5.35 (m, 1 H), 5.19 (m, 1 H), 5.02 (d, 12.6 Hz, 1 H), 4.91 (d, 10.2 Hz, 1 H), 4.54 (d, 9.6 Hz, 1 H), 4.38 (d, 9.6 Hz, 1 H), 4.33 (m, 1 H), 4.24 (d, 10.2 Hz, 1 H), 4.11 (m, 1 H), 4.02 (d, 9.6 Hz, 1 H), 3.97 (s, 3 H), 3.92 (s, 3 H), 3.18 (s, 1 H), 3.00 (s, 6 H), 2.78 (m, 1 H), 2.16 (m, 2 H), 2.04 (s, 3 H), 2.02 (s, 1 H), 1.73 (s, 3 H), 1.39 (d, 6.0 Hz, 3 H), 0.97 (d, 7.2 Hz, 3 H). LCMS: 1383.3 (M+H)⁺.

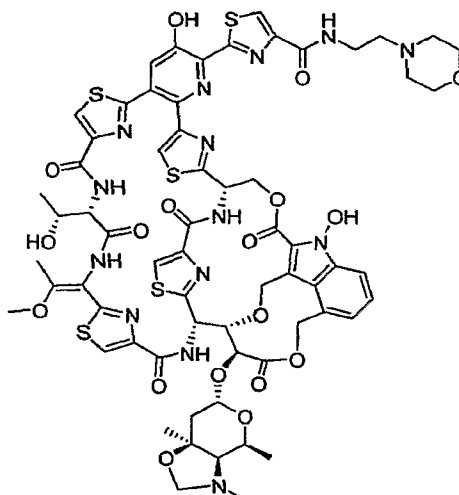
Example 14



To a solution of thiazomycin (0.5 g, 0.35 mmol) in tetrahydrofuran (30 mL) at 0 °C, was added pyridine (0.57 mL, 7 mmol) and trifluoroacetic anhydride (0.49 mL, 3.5 mmol) slowly. After addition, the reaction mixture was allowed to warm to room temperature and stirred for 6 h. Volatiles were evaporated and the residue was purified by reversed-phase HPLC with a linear gradient of 10 – 80% acetonitrile containing 0.1% TFA to give trifluoroacetylated thiazo acid (0.16 g, 31% yield). An analytical sample was obtained by adding a drop of saturated sodium bicarbonate solution to 5 mg the trifluoroacetylated thiazo acid in acetonitrile, followed by reversed-phase HPLC purification. ¹H NMR (500 MHz, CD₃OD): 8.58 (1 H, s), 8.54 (1 H, d, J = 9.7 Hz), 8.53 (1 H, s), 8.43 (1 H, s), 8.19 (1 H, t, J = 10.6 Hz), 8.17 (1 H, s), 7.80-7.90 (4 H,

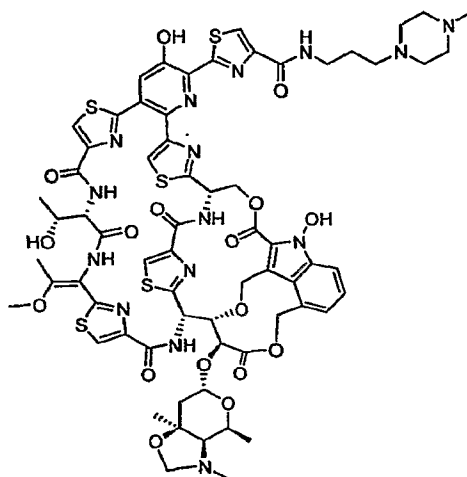
m), 7.42 (1 H, t, J = 7.7 Hz), 7.21 (1 H, d, J = 6.8 Hz), 6.07 (2 H, m), 5.78 (1 H, m), 5.38 (1 H, m), 5.10-5.04 (4 H, m), 4.95 (1 H, d, J = 11.4 Hz), 4.60 (1 H, d, J = 11.3 Hz), 4.53 (1 H, d, J = 9.7 Hz), 4.50 (1 H, d, J = 6.7 Hz), 4.35 (1 H, m), 4.30 (1 H, d, J = 10.6 Hz), 4.14 (1 H, m), 4.01 (1 H, d, J = 9.6 Hz), 3.95 (3 H, s), 3.42 (1 H, m), 2.95 (3 H, s), 2.85 (1 H, m), 2.49 (1 H, dd, J = 5.6, 15.6 Hz), 2.02 (3 H, s), 2.00 (1 H, m), 1.55 (3 H, s), 1.42 (3 H, d, J = 5.5 Hz), 0.89 (3 H, d, J = 6.6 Hz).

Example 15



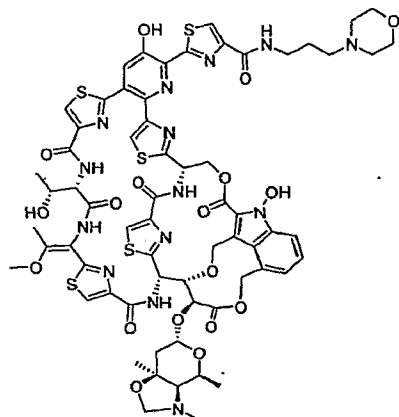
10 The product of example 1 (10.4 mg, 0.007 mmol) was mixed with 4-(2-aminoethyl)morpholine (1.5 μ L, 0.011 mmol) in anhydrous DMF (0.15 mL). To this was added PYBOP (5 mg, 0.009 mmol), and the mixture was stirred at room temperature for 1 h, followed by reversed-phase HPLC purification (10-80% acetonitrile with 1% TFA). The desired product was obtained as a light yellow solid after lyophilization (bis TFA salt, 4.5 mg, 42% yield). ^1H NMR (600 MHz, CD_3OD) δ 8.56 (1 H, s), 8.52 (1 H, d, J = 9.7 Hz), 8.45 (1 H, s), 8.40 (1 H, s), 8.16 (1 H, d, J = 11.2 Hz), 8.15 (1 H, s), 7.88 (1 H, s), 7.84 (1 H, d, J = 6.7 Hz), 7.80 (1 H, d, J = 9.2 Hz), 7.79 (1 H, s), 7.40 (1 H, t, J = 7.7 Hz), 7.20 (1 H, d, J = 7.0 Hz), 6.07 (1 H, d, J = 12.2 Hz), 6.03 (1 H, d, J = 9.5 Hz), 5.76 (1 H, dd, J = 4.7, 10.9 Hz), 5.37 (1 H, dd, J = 5.0, 11.1 Hz), 5.04 (2 H, m), 4.93 (1 H, d, J = 10.6 Hz), 4.57 (1 H, d, J = 11.5 Hz), 4.51 (1 H, d, J = 9.8 Hz), 4.40 (1 H, br), 4.34 (1 H, m), 4.28 (1 H, d, J = 10.6 Hz), 4.05 (2 H, m), 3.99 (1 H, dd, J = 2.0, 9.7 Hz), 3.93 (3 H, s), 3.83 (4 H, m), 3.45 (4 H, m), 3.41 (1 H, d, J = 1.6 Hz), 3.14 (2 H, m), 2.85 (4 H, m), 2.42 (2 H, m), 2.02 (3 H, d, J = 3.5 Hz), 1.96 (1 H, m), 1.84 (2 H, m), 1.50 (3 H, s), 1.41 (3 H, s), 0.83 (3 H, s).

Example 16



Following the procedure described for example 15 except using 1-(3-aminopropyl)-4-methylpiperazine as the amine component to afford the product as a yellow lyophilized solid. ¹H NMR (600 MHz, CD₃OD) δ 8.56 (s, 1 H), 8.51 (d, J = 9.3 Hz, 1 H), 8.40 (s, 1 H), 8.38 (s, 1 H), 8.16 (d, J = 9.8 Hz, 2 H), 8.15 (s, 1 H), 7.88 (s, 1 H), 7.84 (d, J = 6.6 Hz, 1 H), 7.81 (s, 1 H), 7.78 – 7.80 (2 H), 7.40 (t, J = 7.7 Hz, 1 H), 7.20 (d, J = 7.4 Hz, 1 H), 6.07 (d, J = 12.1 Hz, 1 H), 6.03 (d, J = 9.8 Hz, 1 H), 5.76 (dd, J = 4.5, 11.2 Hz, 1 H), 5.37 (dd, J = 5.3, 11.7 Hz, 1 H), 5.07-5.03 (3 H, m), 4.94 (d, J = 10.4 Hz, 1 H), 4.58 (d, J = 11.0 Hz, 1 H), 4.51 (d, J = 9.8 Hz, 1 H), 4.45 (m, 1 H), 4.34 (m, 1 H), 4.28 (d, J = 10.6 Hz, 1 H), 4.10 (m, 1 H), 4.00 (d, J = 10.0 Hz, 1 H), 3.93 (s, 3 H), 3.52 (t, J = 6.8 Hz, 2 H), 3.45 (m, 1 H), 2.91 (m, 4 H), 2.60 - 2.80 (8 H), 2.44 (m, 1 H), 2.02 (d, J = 3.2 Hz, 3 H), 1.88 – 2.00 (4 H), 1.52 (s, 3 H), 1.40 (s, 3 H), 0.86 (d, J = 6.8 Hz, 6 H).

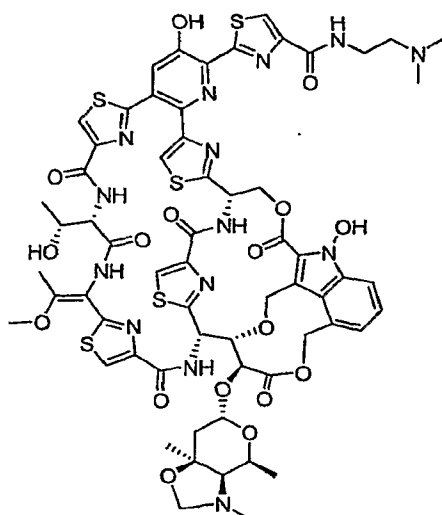
Example 17



Following the procedure described for example 15 except using N-(3-aminopropyl)morpholine as the amine component to afford the product as a yellow lyophilized solid. ¹H NMR (500 MHz, CD₃OD): δ 8.59 (s, 1 H); 8.55 (d, J = 9.7 Hz, 1 H); 8.44 (s, 1 H); 8.43 (s, 1 H); 8.19 (d, J = 11.0 Hz, 1 H); 8.17 (s, 1 H); 7.90 (s, 1 H); 7.86 (d, J = 6.9 Hz, 1 H); 7.82 (d, J = 8.7 Hz, 1 H); 7.81 (s, 1 H); 7.43 (t, J = 7.7 Hz, 1 H); 7.22 (d, J = 6.9 Hz, 1 H); 6.09 (d, J = 12.6 Hz, 1 H); 6.05 (d, J = 9.6 Hz, 1 H); 5.79 (dd, J = 4.8, 10.7 Hz, 1 H); 5.39 (dd, J = 5.0, 11.4 Hz, 1 H); 5.08-5.04 (m, 3 H); 4.97 (d, J = 10.7 Hz, 1 H); 4.60 (d, J = 11.6 Hz, 1 H); 4.53 (d, J = 9.7 Hz, 1 H); 4.36 (t, J = 5.4 Hz, 2 H); 4.30 (d, J = 10.7 Hz, 1 H); 4.08 (br, 2 H); 4.01 (dd, J = 2.0, 9.6 Hz, 1 H); 3.95 (s, 3 H); 3.80 (br, 2 H); 3.59 (t, J = 6.4 Hz, 2 H); 3.27 (t, J = 7.5 Hz, 2 H); 2.83 (br, 4 H); 2.43 (m, 1 H); 2.13 (m, 2 H); 2.05 (s, 3 H); 1.98 (m, 1 H); 1.94 (s, 1 H); 1.50 (s, 3 H); 1.43 (d, J = 6.7 Hz, 3 H); 0.83 (s, 3 H).

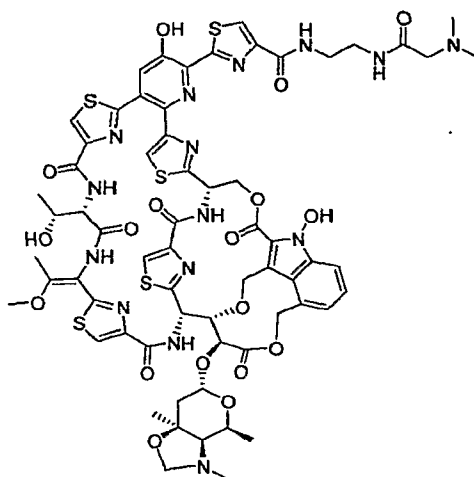
15

Example 18



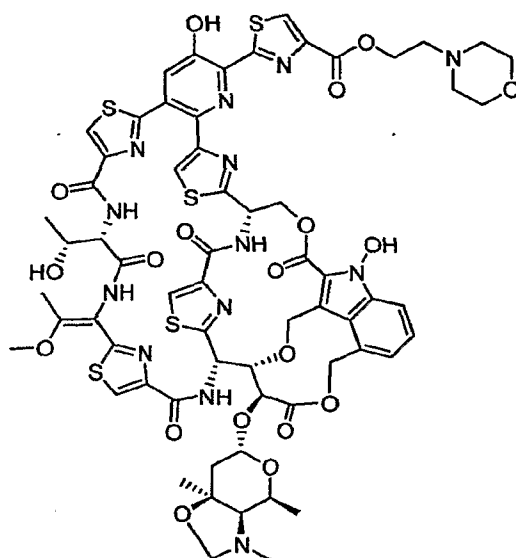
- 5 Following the procedure described for example 15 except using N,N-dimethylethylenediamine as the amine component to afford the product as a yellow lyophilized solid. ¹H NMR (600 MHz, CD₃OD): δ 8.56 (s, 1 H); 8.53 (d, J = 9.5 Hz, 1 H); 8.45 (s, 1 H); 8.40 (s, 1 H); 8.17 (d, J = 11.1 Hz, 1 H); 8.14 (s, 1 H); 7.88 (s, 1 H); 7.84 (d, J = 7.3 Hz, 1 H); 7.81 (d, J = 9.7 Hz, 1 H); 7.80 (s, 1 H); 7.40 (t, J = 7.6 Hz, 1 H); 7.20 (d, J = 6.8 Hz, 1 H); 6.06 (d, J = 12.1 Hz, 1 H);
- 10 6.02 (d, J = 9.4 Hz, 1 H); 5.75 (m, 1 H); 5.37 (m, 1 H); 5.03 (d, J = 12.5 Hz, 2 H); 4.93 (d, J = 10.7 Hz, 1 H); 4.57 (d, J = 11.1 Hz, 1 H); 4.51 (d, J = 9.9 Hz, 1 H); 4.34 (m, 1 H); 4.28 (d, J = 10.4 Hz, 1 H); 3.98 (d, J = 10.8 Hz, 2 H); 3.93 (s, 3 H); 3.82 (m, 2 H); 3.42 (m, 2 H); 3.00 (s, 6 H); 2.69 - 2.86 (br, 2 H); 2.38 (m, 1 H); 2.02 (s, 3 H); 1.92 (m, 1 H); 1.45 (s, 3 H); 1.41 (s, 3 H); 0.78 (s, 3 H).

Example 19



Following the procedure described for example 15 except using N,N-(dimethylglycyl)ethylenediamine as the amine component to afford the product as a yellow lyophilized solid. ¹H NMR (500 MHz, CD₃OD): δ 8.59 (s, 1 H), 8.58 (d, J = 8.4 Hz, 1 H); 8.42 (s, 1 H); 8.39 (s, 1 H); 8.21 (d, J = 11.1 Hz, 1 H); 8.16 (s, 1 H); 7.90 (s, 1 H); 7.87 (d, J = 6.7 Hz, 1 H); 7.83 (d, J = 6.6 Hz, 1 H); 7.81 (s, 1 H); 7.42 (t, J = 7.8 Hz, 1 H); 7.23 (d, J = 6.9 Hz, 1 H); 6.08 (d, J = 12.4 Hz, 1 H); 6.03 (d, J = 9.4 Hz, 1 H); 5.78 (dd, J = 5.1, 10.9 Hz, 1 H); 5.39 (dd, J = 5.3, 11.4 Hz, 1 H); 5.04 - 5.07 (2 H); 4.94 (d, J = 10.3 Hz, 1 H); 4.59 (d, J = 11.3 Hz, 1 H); 4.53 (d, J = 9.8 Hz, 1 H); 4.37 (m, 1 H); 4.29 (d, J = 10.4 Hz, 1 H); 4.00 (d, J = 10.2 Hz, 1 H); 3.95 (s, 3 H); 3.87 (m, 2 H); 3.62 (m, 2 H); 3.54 (m, 2 H); 2.89 (s, 6 H); 2.82 (m, 1 H); 2.54 (br, 2 H); 2.32 (m, 1 H); 2.04 (s, 3 H); 1.89 (m, 1 H); 1.38 - 1.47 (6 H); 0.71 (s, 3 H).

Example 20



5

One-pot procedure: To a suspension of thiazomycin (150 mg, 0.104 mmol) in dry THF (1 mL) was added anhydrous pyridine (84 μ L, 1.04 mmol) to give a clear solution. Trifluoroacetic anhydride (72 μ L, 0.72 mmol) was then introduced. The reaction solution was stirred at room temperature for 3 h, then transferred to a solution of 2-(4-morpholinyl)ethanol (0.2 mL) in THF (0.5 mL). After 10 minutes, the volatiles were removed in vacuo. The residue was purified by preparative reversed-phase HPLC to afford the desired product (53 mg, 36 % yield). LCMS:

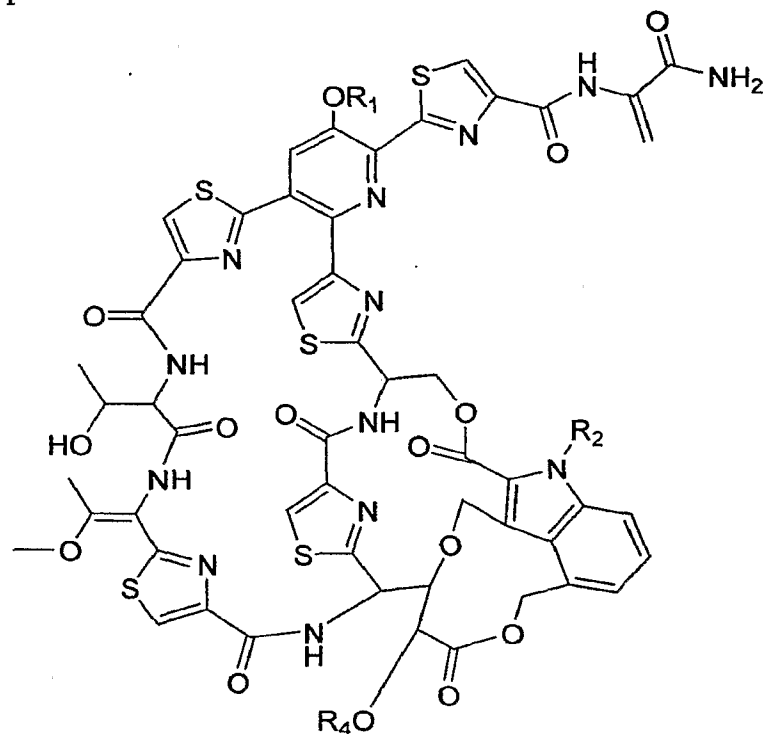
10

1480.9 (m/z); ^1H NMR (CD_3OD , 600 MHz) δ : 8.67 (s, 1 H), 8.56 (s, 1 H), 8.51 (d, 9.6 Hz, 1 H), 8.41 (s, 1 H), 8.16 (d, 9.6 Hz, 1 H), 8.15 (s, 1 H), 7.88 (s, 1 H), 7.84 (d, 6.6 Hz, 1 H), 7.80 (m, 2 H), 7.40 (t, 8.4 Hz, 1 H), 7.19 (d, 6.6 Hz, 1 H), 6.04 (m, 2 H), 5.77 (m, 1 H), 5.37 (m, 1 H), 5.07-5.02 (m, 3 H), 4.92 (d, 10.8 Hz, 1 H), 4.76 (m, 2 H), 4.56 (d, 5.4 Hz, 1 H), 4.50 (d, 10.2 Hz, 1 H), 4.47 (d, 6.0 Hz, 1 H), 4.33 (m, 1 H), 4.27 (d, 10.8 Hz, 1 H), 4.10 (m, 1 H), 3.93 (s, 3 H), 3.64 (m, 3 H), 3.38 (m, 1 H), 2.92 (s, 3 H), 2.81 (m, 1 H), 2.45 (m, 1 H), 2.02 (s, 3 H), 1.99 (m, 1 H), 1.52 (s, 3 H), 1.40 (d, 5.4 Hz, 3 H), 0.65 (d, 6.6 Hz, 3 H).

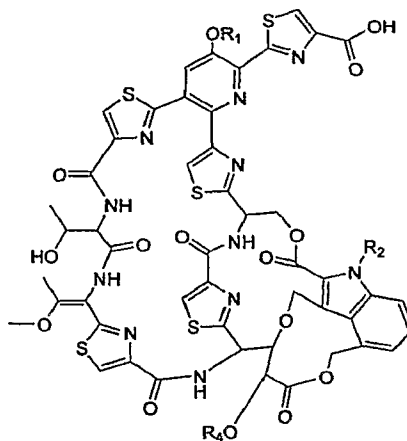
15

WHAT IS CLAIMED IS:

1. A process for making a compound of formula II, comprising the steps of
1) contacting a compound of formula I:



- 5 or a pharmaceutically acceptable salt, ester, enantiomer, diastereomer or mixture thereof,
- with an anhydride in the presence of a base followed by aqueous hydrolysis to produce a compound of formula II:



Formula II

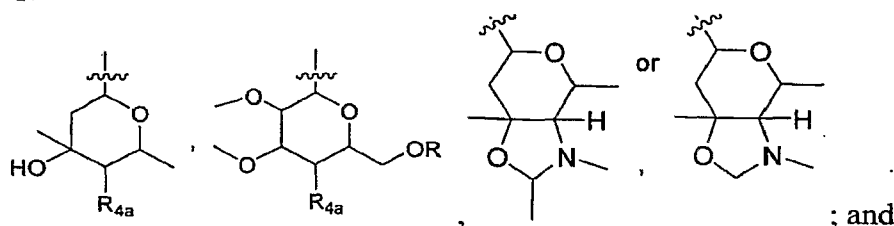
and 2) isolating the compound of formula II;

wherein:

R independently represents hydrogen, and C₁₋₁₂ alkyl;

R₁ represents hydrogen, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl, said alky, cycloalkyl optionally substituted with 1 to 3 groups of R^a;

R₂ represents R₁ and OR₁;



R₄ represents hydrogen,

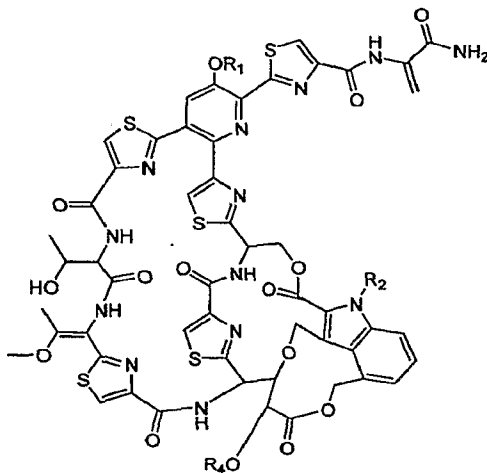
R_{4a} represents N(R)₂.

2. The process according to claim 1 wherein the anhydride is selected from the group consisting of trifluoroacetic anhydride, pentafluoropropionic anhydride, chlorodifluoroacetic anhydride, trichloroacetic anhydride, dichloroacetic anhydride, chloroacetic anhydride, benzoic anhydride, and difluoro anhydride and the base is selected from the group consisting of pyridine, 4-pyrrolidinopyridine, 4-dimethylaminopyridine, 4-ethylpyridine, 4-isopropylpyridine, 4-picoline, and 3-picoline.

3. The process according to claim 2 wherein the anhydride is trifluoroacetic anhydride, the base is pyridine, and the temperature is about -25 °C to about 25 °C.

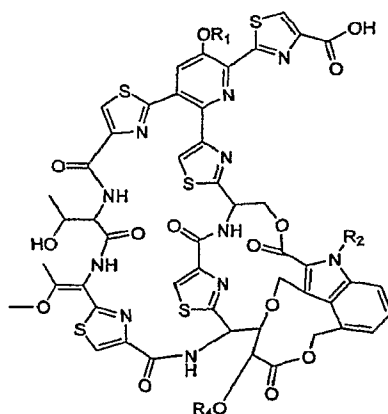
4. A process for making a compound of formula III comprising the steps of:

1) contacting a compound of formula I:



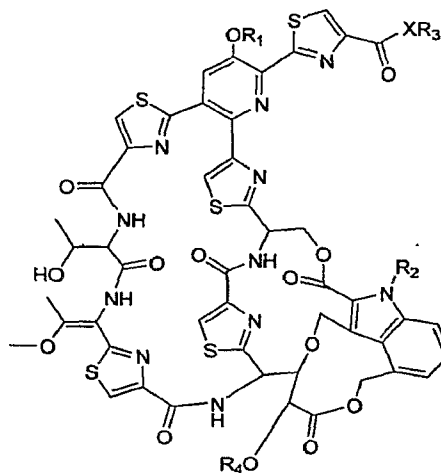
or a pharmaceutically acceptable salt, ester, enantiomer, diastereomer or mixture thereof,

- 5 with an anhydride in the presence of a base followed by aqueous hydrolysis to produce a compound of formula II:



Formula II

- 2) isolating the compound of formula II; and
10 3) coupling the compound of formula II with a nucleophile represented by R_3XH to produce a compound of formula III:



Formula III

or a pharmaceutically acceptable salt, ester, enantiomer, diastereomer or mixture thereof,
wherein:

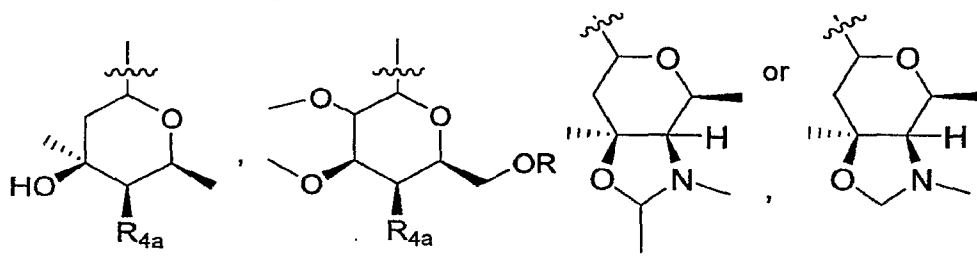
5 R independently represents hydrogen, and C₁-12 alkyl;

R₁ represents hydrogen, C₁-6 alkyl, and C₃-6 cycloalkyl, said alky, cycloalkyl optionally substituted with 1 to 3 groups of R_a;

10 R₂ represents R₁ and OR₁;

R₃X- represents -NR₅R₆, -NH(CR₇R₈)(CH₂)_n(NH)_mC(O)NR₅R₆, -NHCR₇R₈R₉, -OR₅, -C(O)OR₅, and -SR₅;

15 R₄ represents hydrogen,



R_{4a} represents N(R)₂;

R₅ and R₆ independently represent hydrogen, C₁₋₁₂ alkyl, -(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nNR₇R₈, -(CH₂)_nNR(CH₂)_nNR₇R₈, -(CH₂)_nC(=CH₂)C(O)NR₇R₈, -
 5 (CH₂)_nC(=CH₂)CN, -(CH₂)_nNR(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_n(O(CH₂)₂)₁₋₆R₉, -(CH₂)_nNHC(O)(CH₂)_nNR₇R₈, -(CH₂)_nS(O)_p(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nS(O)_p(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nS(O)_pC₁₋₆ alkyl, -(CH₂)_nNHNHR₁, -(CH₂)_nCHR₇CF₃, -C(O)C₅₋₁₀ heterocyclyl, -C(R)₂(CH₂)_nNHC(O)N(CH₂)_nC₅₋₁₀ heterocyclyl, -C(R)₂(CH₂)_nOR, said aryl, and heterocyclyl optionally substituted with 1 to 3
 10 groups of R^a; said alkyl optionally substituted with 1 to 6 hydroxy and/or optionally substituted by one to three groups of R^a; or

R₅ and R₆ together with the nitrogen atom they are attached form a 5 to 10 heterocyclic ring optionally containing 1 to 2 additional heteroatoms selected from the group consisting of N, S
 15 and O and optionally substituted with 1 to 3 groups of R^a;

R₇ and R₈ independently represent hydrogen, hydroxyl, C₁₋₆ alkoxy, C₁₋₁₂ alkyl, -(CH₂)_nNR₅R₆, -(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nNHNHC(O)C₅₋₁₀ heterocyclyl, -(CH₂)_nOR, -(CH₂)_nNHNHR₁, -C(O)C₁₋₆ alkyl, -C(O)C₅₋₁₀ heterocyclyl, -
 20 C(O)NH(CH₂)_nC₅₋₁₀ heterocyclyl, -C(O)(CH₂)_nN(R)₂, -(CH₂)_nS(O)_p(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nS(O)_p(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nS(O)_p(CH₂)_nC₁₋₆ alkyl, said aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^a; said alkyl optionally substituted with 1 to 6 hydroxy and/or optionally substituted by one to three groups of R^a or

R₇ and R₈ together with the nitrogen atom they are attached form a 5 to 10 membered heterocyclic ring optionally containing 1 to 2 additional heteroatoms selected from the group consisting of N, S and O and optionally substituted with 1 to 3 groups of R^a; or

R₇ and R₈ together with the carbon atom they are attached form a 3 to 10 membered carbocyclic
 30 ring optionally and optionally substituted with 1 to 3 groups of R^a;

R₉ represents hydrogen, C₁₋₆ alkyl, (CH₂)_nC₅₋₁₀ heterocyclyl, -C(O)OR, CN, OR, said alkyl and heterocyclyl optionally substituted with 1 to 3 groups of R^a

R^a represents hydrogen, halogen, (CH₂)_nOR, CF₃, (CH₂)_nC(O)OR, (CH₂)_nC(O)NR₇R₈, (CH₂)_nC₅₋₁₀ heterocyclyl, SO₂NR₅R₆, (CH₂)C₆₋₁₀ aryl, N(R)₂, NO₂, CN, (C₁₋₆ alkyl)O-, (aryl)O-, (C₁₋₆ alkyl)S(O)₀₋₂-, C₁₋₁₂ alkyl, said alkyl, heterocyclyl, and aryl optionally substituted with 1 to 4 groups selected from the group consisting of C₁₋₆ alkyl, (CH₂)_nOR, (CH₂)_nN(R)₂, -O-; and

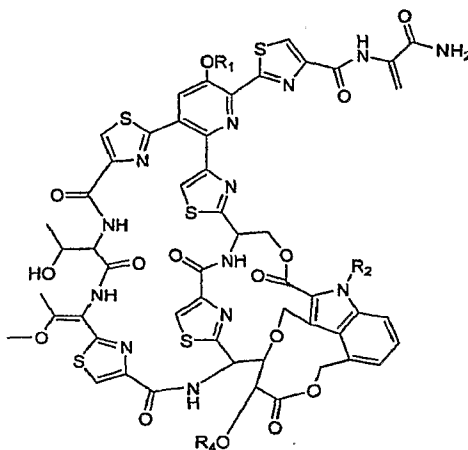
n represent 0-6, m represents 0-1, s represents 1-6, and p represents 0, 1 or 2.

5. The process according to claim 4 wherein the anhydride is selected from the group consisting of trifluoroacetic anhydride, pentafluoropropionic anhydride, chlorodifluoroacetic anhydride, trichloroacetic anhydride, dichloroacetic anhydride, chloroacetic anhydride, benzoic anhydride, and difluoro anhydride and the base is selected from the group consisting of pyridine, 4-pyrrolidinopyridine, 4-dimethylaminopyridine, 4-ethylpyridine, 4-isopropylpyridine, 4-picoline, and 3-picoline.

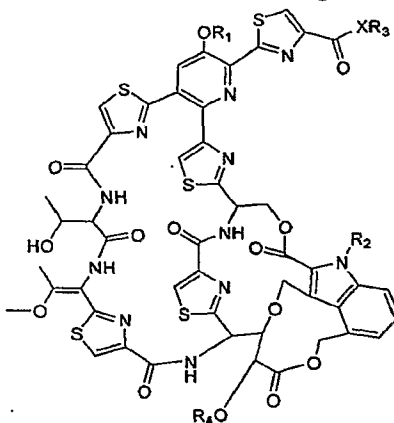
6. The process according to claim 5 wherein the anhydride is trifluoroacetic anhydride, the base is pyridine, and the temperature is about -25 °C to about 25 °C.

7. A process for making a compound of formula III comprising the steps of:

1) contacting a compound of formula I:



with an anhydride in the presence of a base followed by addition of a nucleophile represented by R_3XH to produce a compound of formula III and isolating the compound of formula III:



Formula III

- 5 or a pharmaceutically acceptable salt, ester, enantiomer, diastereomer or mixture thereof,
wherein:

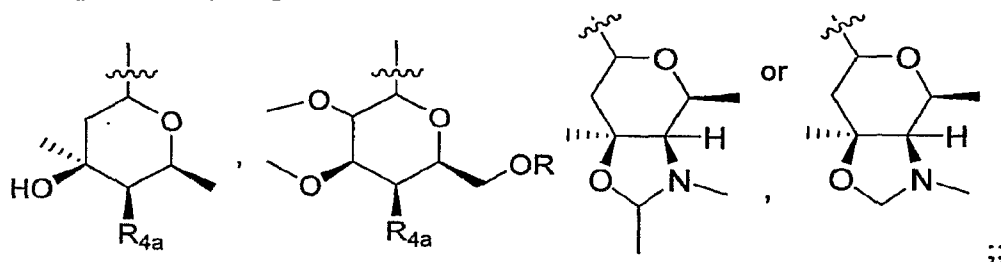
R independently represents hydrogen, and C_{1-12} alkyl;

- 10 R₁ represents hydrogen, C_{1-6} alkyl, and C_{3-6} cycloalkyl, said alkyl, cycloalkyl optionally substituted with 1 to 3 groups of R_a ;

R₂ represents R₁ and OR₁;

- 15 R₃X- represents -NR₅R₆, -NH(CR₇R₈)(CH₂)_n(NH)_mC(O)NR₅R₆, -NHCR₇R₈R₉, -OR₅, -C(O)OR₅, and -SR₅;

R₄ represents hydrogen,



R_{4a} represents N(R)₂;

R₅ and R₆ independently represent hydrogen, C₁₋₁₂ alkyl, -(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nNR₇R₈, -(CH₂)_nNR(CH₂)_nNR₇R₈, -(CH₂)_nC(=CH₂)C(O)NR₇R₈, -
 5 (CH₂)_nC(=CH₂)CN, -(CH₂)_nNR(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_n(O(CH₂)₂)₁₋₆R₉, -(CH₂)_nNHC(O)(CH₂)_nNR₇R₈, -(CH₂)_nS(O)_p(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nS(O)_p(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nS(O)_pC₁₋₆ alkyl, -(CH₂)_nNHNHR₁, -(CH₂)_nCHR₇CF₃, -C(O)C₅₋₁₀ heterocyclyl, -C(R)₂(CH₂)_nNHC(O)N(CH₂)_nC₅₋₁₀ heterocyclyl, -C(R)₂(CH₂)_nOR, said aryl, and heterocyclyl optionally substituted with 1 to 3
 10 groups of R^a; said alkyl optionally substituted with 1 to 6 hydroxy and/or optionally substituted by one to three groups of R^a; or

R₅ and R₆ together with the nitrogen atom they are attached form a 5 to 10 heterocyclic ring optionally containing 1 to 2 additional heteroatoms selected from the group consisting of N, S
 15 and O and optionally substituted with 1 to 3 groups of R^a;

R₇ and R₈ independently represent hydrogen, hydroxyl, C₁₋₆ alkoxy, C₁₋₁₂ alkyl, -(CH₂)_nNR₅R₆, -(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nNHNHC(O)C₅₋₁₀ heterocyclyl, -(CH₂)_nOR, -(CH₂)_nNHNHR₁, -C(O)C₁₋₆ alkyl, -C(O)C₅₋₁₀ heterocyclyl, -
 20 C(O)NH(CH₂)_nC₅₋₁₀ heterocyclyl, -C(O)(CH₂)_nN(R)₂, -(CH₂)_nS(O)_p(CH₂)_nC₅₋₁₀ heterocyclyl, -(CH₂)_nS(O)_p(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nS(O)_p(CH₂)_nC₁₋₆ alkyl, said aryl, and heterocyclyl optionally substituted with 1 to 3 groups of R^a; said alkyl optionally substituted with 1 to 6 hydroxy and/or optionally substituted by one to three groups of R^a or

R₇ and R₈ together with the nitrogen atom they are attached form a 5 to 10 membered heterocyclic ring optionally containing 1 to 2 additional heteroatoms selected from the group consisting of N, S and O and optionally substituted with 1 to 3 groups of R^a; or
 25

R₇ and R₈ together with the carbon atom they are attached form a 3 to 10 membered carbocyclic ring optionally and optionally substituted with 1 to 3 groups of R^a;
 30

R₉ represents hydrogen, C₁₋₆ alkyl, (CH₂)_nC₅₋₁₀ heterocyclyl, -C(O)OR, CN, OR, said alkyl and heterocyclyl optionally substituted with 1 to 3 groups of R^a

R^a represents hydrogen, halogen, (CH₂)_nOR, CF₃, (CH₂)_nC(O)OR, (CH₂)_nC(O)NR₇R₈, (CH₂)_nC₅₋₁₀ heterocyclyl, SO₂NR₅R₆, (CH₂)C₆₋₁₀ aryl, N(R)₂, NO₂, CN, (C₁₋₆ alkyl)O-, (aryl)O-, (C₁₋₆ alkyl)S(O)₀₋₂-, C₁₋₁₂ alkyl, said alkyl, heterocyclyl, and aryl optionally substituted with 1 to 4 groups selected from the group consisting of C₁₋₆ alkyl, (CH₂)_nOR, (CH₂)_nN(R)₂, -O-; and

n represent 0-6, m represents 0-1, s represents 1-6, and p represents 0, 1 or 2.

8. The process according to claim 7 wherein the anhydride is selected from the group consisting of trifluoroacetic anhydride, pentafluoropropionic anhydride, chlorodifluoroacetic anhydride, trichloroacetic anhydride, dichloroacetic anhydride, chloroacetic anhydride, benzoic anhydride, and difluoro anhydride and the base is selected from the group consisting of pyridine, 4-pyrrolidinopyridine, 4-dimethylaminopyridine, 4-ethylpyridine, 4-isopropylpyridine, 4-picoline, and 3-picoline.

9. The process according to claim 8 wherein the anhydride is trifluoroacetic anhydride, the base is pyridine, and the temperature is about -25 °C to about 25 °C.

10. The process according to claim 7 wherein the coupling is performed using HOBT/EDC in DMF, PyBOP in DIEA or TEA/cat. DMAP in CH₂Cl₂.