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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.



WO 2007/127200 A2

TITLE OF THE INVENTION

ANTIBIOTIC COMPOUNDS

This application claims the benefit of US Provisional application 60/794,420, filed April 24, 2006.

5 Infections caused by bacteria are a growing medical concern as many of these 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 calcoaeticus*, *Stenotrophomonas maltophilia*.

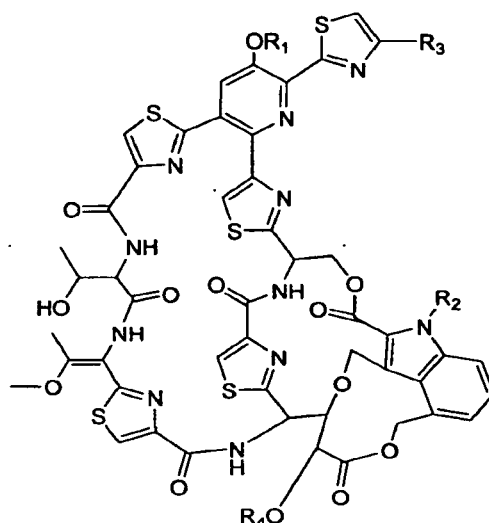
10 Many thiazolyl peptide antibiotics exhibit potent antibacterial activity against a variety of Gram-positive bacteria, including multiple drug-resistant strains. Their poor water solubility severely limits their usage as therapeutic agents.

 The present invention relates to novel thiazolyl peptide antibiotics capable of treating serious bacterial infections in mammals, and particularly, in humans. These analogs can
15 also be versatile intermediates for the preparation of new derivatives with useful antibacterial activity. Many of the novel thiazolyl peptide antibiotics of the present invention show much improved aqueous solubility (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;
20 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 M. D. Lee et al., *J. Antibiotics* 1994, Vol. 47 No. 8 pages
25 894-900. The antibiotics of this invention thus comprise an important contribution to therapy for treating infections which are resistant to various known antibiotics.

 The carboxylic acids of the claimed invention can be derived from thiazolyl antibiotics such as thiostrepton, GE2270A, A10255, S 54832, promothiocin, thioactin, siomycins, berninamycin, thiopeptin, nocaithiacins, glycothiohexide, and nosiheptide.

SUMMARY OF THE INVENTION

 This invention is concerned with novel thiazolyl-peptide antibiotics of the formula I:



I

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

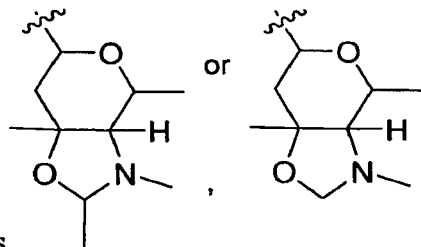
5 wherein:

R independently represents hydrogen, and C₁₋₁₂ alkyl;

R₁ represents hydrogen, C₁₋₆ alkyl, and C₃₋₆ cycloalkyl;

10 R₂ represents R₁ and OR₁

R₃ represents -C(O)NR₅R₆, -C(O)NHCR₇R₈(CH₂)_n(NH)_mC(O)NR₅R₆ or C(O)OR₅,



R₄ represents

;

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

10 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, -
 C(O)NH(CH₂)_nC₅₋₁₀ heterocyclyl, -C(O)(CH₂)_nN(R)₂, -(CH₂)_nS(O)_p(CH₂)_nC₅₋₁₀
 15 heterocyclyl, -(CH₂)_nS(O)_p(CH₂)_nNR₅R₆, -(CH₂)_nS(CH₂)_nNR₅R₆, -
 (CH₂)_nS(O)_p(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nS(O)_p(CH₂)_nC₁₋₆ alkyl, said aryl, and heterocyclyl
 optionally substituted with one or more groups of R^a; said alkyl optionally substituted with 1 to
 6 hydroxyl and/or optionally substituted by one to more groups of R^a or

20 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 one or more 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 one or more 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 one or more groups of R^a

30 R^a represents hydrogen, halogen, (CH₂)_nOR, CF₃, (CH₂)_nC(O)OR, (CH₂)_nC(O)NR₇R₈,
 (CH₂)_nC₅₋₁₀ heterocyclyl, SO₂NR₅R₆, (CH₂)_nC₆₋₁₀ 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, and p represents 0, 1 or 2.

DETAILED DESCRIPTION OF THE INVENTION

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".

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.

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.

"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.

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.

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, cinnoliny, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl. An embodiment of the examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnoliny, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl,

isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, 2-pyridinonyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl and triazolyl.

Preferably, heterocycle is selected from 2-azepinonyl, benzimidazolyl, 2-diazapinonyl, imidazolyl, 2-imidazolidinonyl, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, 2-piperidinonyl, 2-pyrimidinonyl, 2-pyrrolidinonyl, quinolinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, 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, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 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 4 substituents, preferably 1 to 3 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)₆₋₁₀ 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.

An embodiment of this invention is realized when R₁ represents -C₁₋₆ alkyl, preferably methyl, and C₃₋₆ cycloalkyl, and all other variables are as described herein.

Another embodiment of this invention is realized when R₁ represents H, and all other variables are as described herein.

Another embodiment of this invention is realized when R₂ represents OC₁₋₆ alkyl, preferably the alkyl is methyl, and all other variables are as described herein.

Another embodiment of this invention is realized when R₂ represents OH and all other variables are as described herein.

Another embodiment of this invention is realized when R₂ represents H and all other variables are as described herein.

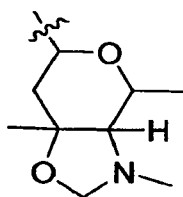
Another embodiment of this invention is realized when R₃ represents —C(O)NR₅R₆ and all other variables are as described herein.

Another embodiment of this invention is realized when R₃ is —(C(O)NH(CH₂)_nC₅₋₁₀ heterocyclyl and all other variables are as described herein. A sub-embodiment of this invention is realized when R₁ is H, or -C₁₋₆ alkyl, preferably methyl and R₂ is -OR, preferably R₂ is OH.

Another embodiment of this invention is realized when R_3 represents $-C(O)NHCR_7R_8(CH_2)_nC(O)NR_5R_6$, and all other variables are as described herein.

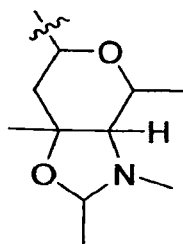
Another embodiment of this invention is realized when R_3 represents $-C(O)OR_5$, and all other variables are as described herein.

5 Another embodiment of this invention is realized when R_4 represents

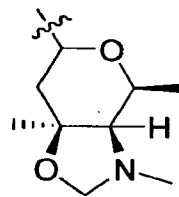


and all other variables are as described herein.

Another embodiment of this invention is realized when R_4 represents

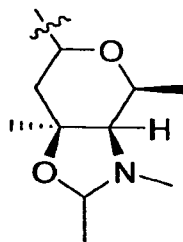


and all other variables are as described herein.



10 Another embodiment of this invention is realized when R_4 represents variables are as described herein.

Another embodiment of this invention is realized when R_4 represents



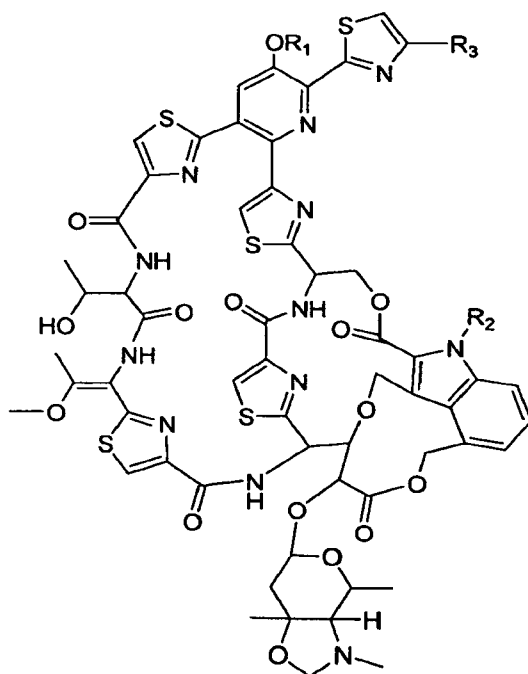
and all other variables are as described herein.

15 Another embodiment of this invention is realized when one of R_5 and R_6 is hydrogen and the other is C_{1-12} alkyl, $-(CH_2)_nC_{5-10}$ heterocyclyl, $-(CH_2)_nNR_7R_8$, $-(CH_2)_nNH(CH_2)_nNR_7R_8$, $-(CH_2)_nNH(CH_2)_nC_{5-10}$ heterocyclyl, $-(CH_2)_nC_{6-10}$ aryl, $(CH_2)(O(CH_2)_2)_{1-6}R_9$, $(CH_2)_nNHC(O)(CH_2)_nNR_7R_8$, $-C(O)C_{5-10}$ heterocyclyl, $-C(R)_2(CH_2)_nOR$ said heterocyclyl selected from the group consisting of pyrimidinyl,

morpholinyl, piperazinyl, pridinyl, pyrazolyl, indolyl, furanyl, isoindazolyl, pyrazinyl, pyrrolyl, imidazolyl, triazolyl or tetrazolyl and 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 ,

Another embodiment of this invention is realized when R_7 and R_8 are independently selected from the group consisting of hydrogen, C_{1-6} alkyl (said alkyl group optionally substituted with 1 to 6 groups of C_{1-4} alkoxy or OH), $-(CH_2)_nN(R)_2$, $-(CH_2)_nX$ (wherein X represents phenyl, pyrimidinyl, morpholinyl, piperazinyl, pridinyl, pyrazolyl, indolyl, furanyl, isoindazolyl, pyrazinyl, pyrrolyl, imidazolyl, triazolyl or tetrazolyl said X groups optionally substituted with 1 to 3 groups of R^a),

Still another embodiment of this invention is realized by structural formula II:

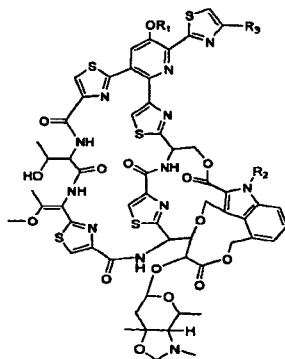


wherein R_3 is $-C(O)NHCR_7R_8(CH_2)_nC(O)NR_5R_6$, and all other variables are as described herein.

Another-embodiment of this invention is realized when R_3 is — $C(O)NH(CH_2)_nX$, wherein X is selected from the group consisting of phenyl, pyrimidinyl, morpholinyl, piperazinyl, pridinyl, pyrazolyl, indolyl, furanyl, isoindazolyl, pyrazinyl, pyrrolyl, imidazolyl, triazolyl and tetrazolyl said X groups optionally substituted with 1 to 3 groups of R^a .

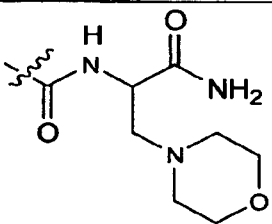
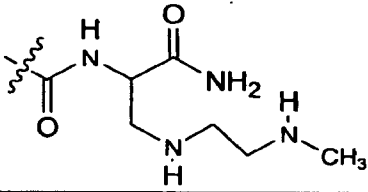
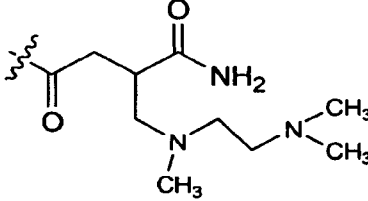
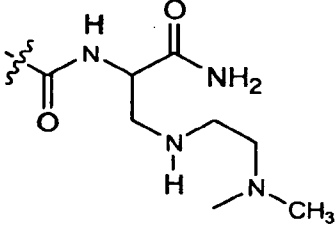
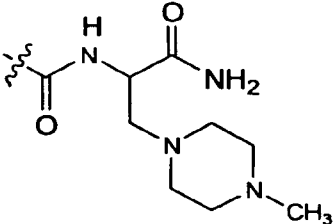
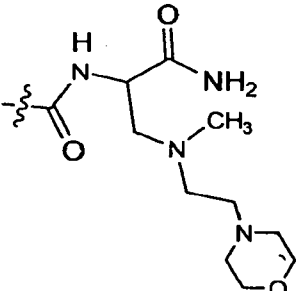
Preferred compounds of this invention are found in Table 1 below:

TABLE 1

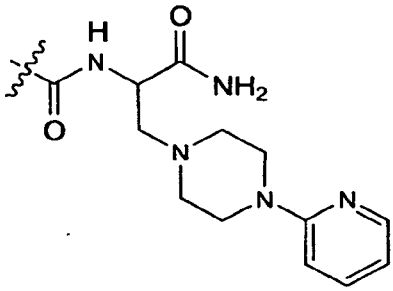
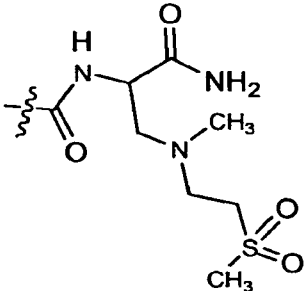
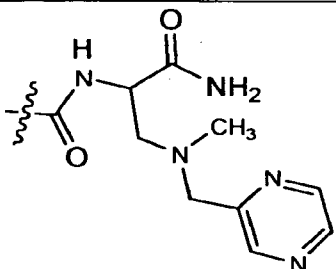
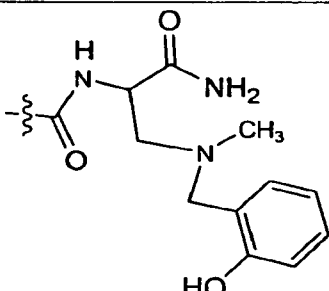
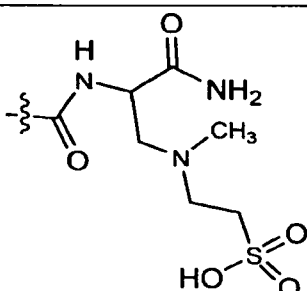


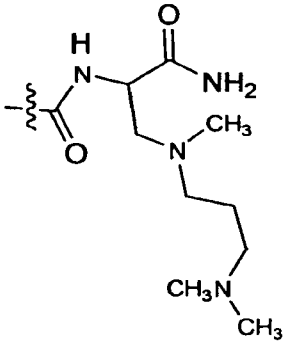
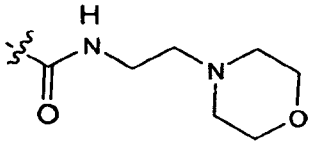
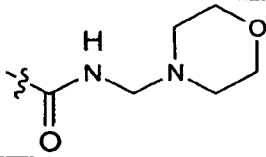
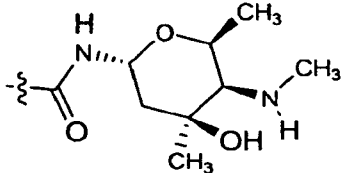
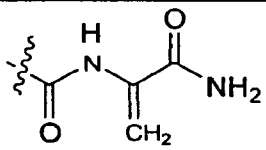
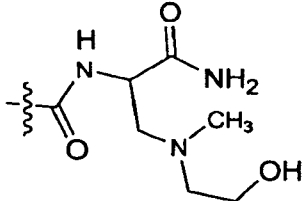
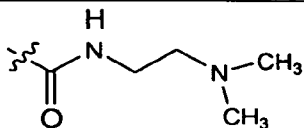
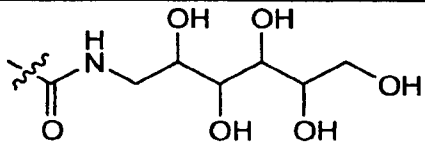
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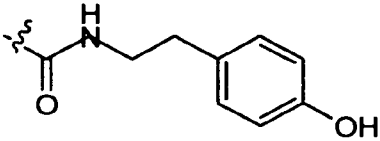
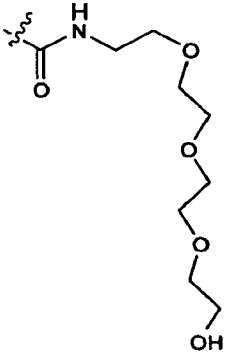
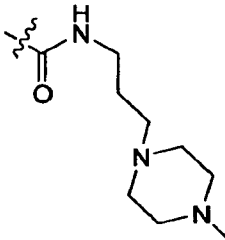
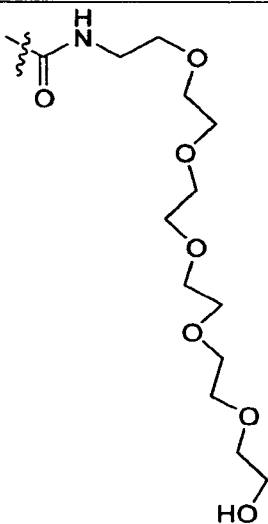
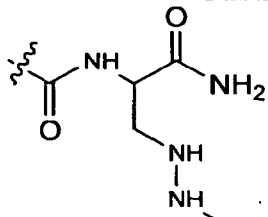
Compound	R ₁	R ₂	R ₃
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2	H	OH	
3	H	OH	C(O)NH ₂
4	H	OH	

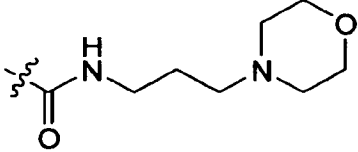
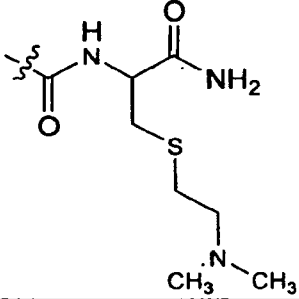
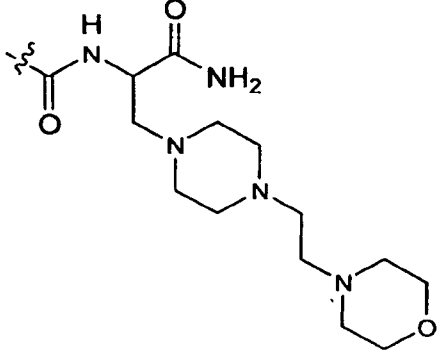
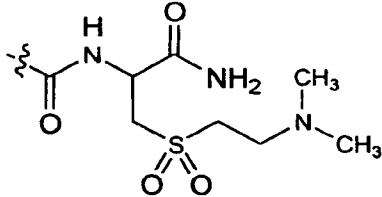
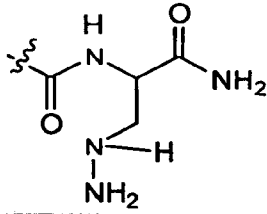
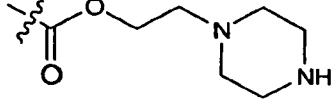
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6	H	OH	
7	H	OH	
8	H	OH	
9	H	OH	
10	H	OH	

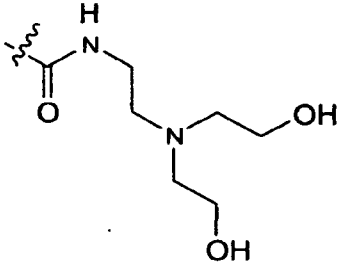
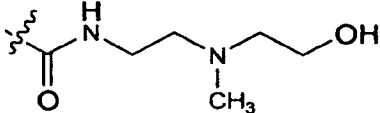
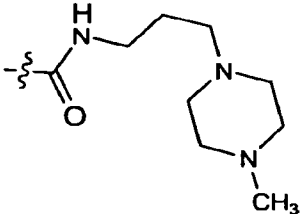
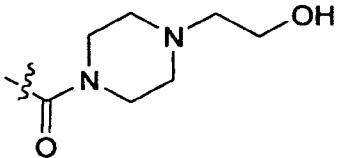
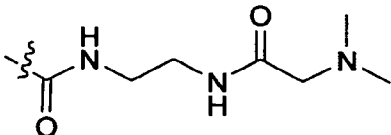
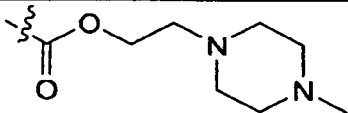
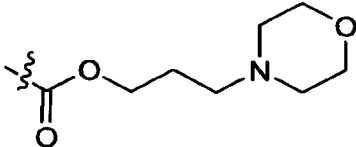
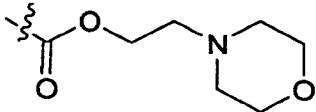
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12	H	OH	
13	H	OH	
14	H	OH	

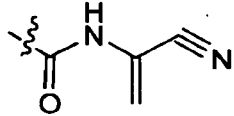
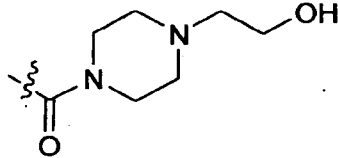
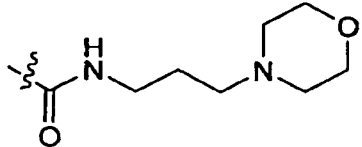
15	H	OH	
16	H	OH	
17	H	OH	
18	H	OH	
19	H	OH	

20	H	OH	
21	H	OH	
22	H	OH	C(O)OH
23	H	OH	
24	H	OCH ₃	
25	H	OCH ₃	
26	H	OCH ₃	
27	H	OH	
28	H	OH	

29	H	OH	
30	H	OH	
31	H	OH	
32	H	OH	
33	H	OH	

34	H	OH	
35	H	OH	
36	H	OH	
37	H	OH	
38	H	OH	
39	H	OH	

40	H	OH	
41	H	OH	
42	H	OH	C(O)NH ₂
43	H	H	
44	H	OH	
45	H	OH	
46	H	OH	
47	H	OH	
48	H	OH	
49	H	OH	-C(O)OMe

50	H	OH	
51	Me	OH	
52	Me	OH	

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

The compounds of this invention are a broad spectrum antibiotic useful in the treatment of bacterial infections. They demonstrate antibacterial activity primarily against *S.*

5 *aureus*, *E. faecalis*, *E. faecium*, *S. pneumoniae*, *B. subtilis* including species that are resistant to many known antibiotics. The minimum inhibitory concentration (MIC) values range from 0.0001 to less than 200 µg/mL for test strains such as *Staphylococcus aureus*, *Staphylococcus hemolyticus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *E. faecalis*. The compounds of the invention can be formulated in pharmaceutical compositions by combining the compounds with a pharmaceutically acceptable carrier. Examples of such carriers are set forth below.

15 The compounds may be employed in powder or crystalline form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically, orally and parenterally by injection (intravenously or intramuscularly).

20 Compositions for injection, one route of delivery, may be prepared in unit dosage form in ampules, or in multidose containers. The injectable compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain various formulating agents. Alternatively, the active ingredient may be in powder (lyophilized or non-lyophilized) form for reconstitution at the time of delivery with a suitable vehicle, such as sterile water. In injectable compositions, the carrier is typically comprised of sterile water, saline or another injectable liquid, e.g., peanut oil for intramuscular injections. Also, various buffering agents, preservatives and the like can be included.

Topical applications may be formulated in carriers such as hydrophobic or hydrophilic bases to form ointments, creams, lotions, in aqueous, oleaginous or alcoholic liquids to form paints or in dry diluents to form powders.

Oral compositions may take such forms as tablets, capsules, oral suspensions and oral solutions. The oral compositions may utilize carriers such as conventional formulating agents, and may include sustained release properties as well as rapid delivery forms.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated, the route and frequency of administration, the sensitivity of the pathogen to the Compound, the virulence of the infection and other factors. Such matters, however, are left to the routine discretion of the physician according to principles of treatment well known in the antibacterial arts.

The compositions for administration to humans per unit dosage, whether liquid or solid, may contain from about 0.01% to as high as about 99% of Compound I, one embodiment of the range being from about 10-60%. The composition will generally contain from about 15 mg to about 2.5 g of Compound I, one embodiment of this range being from about 250 mg to 1000 mg. In parenteral administration, the unit dosage will typically include pure Compound I in sterile water solution or in the form of a soluble powder intended for solution, which can be adjusted to neutral pH and isotonicity.

The invention described herein also includes a method of treating a bacterial infection in a mammal in need of such treatment comprising the administration of the compound of formula I to the mammal in an amount effective to treat the infection.

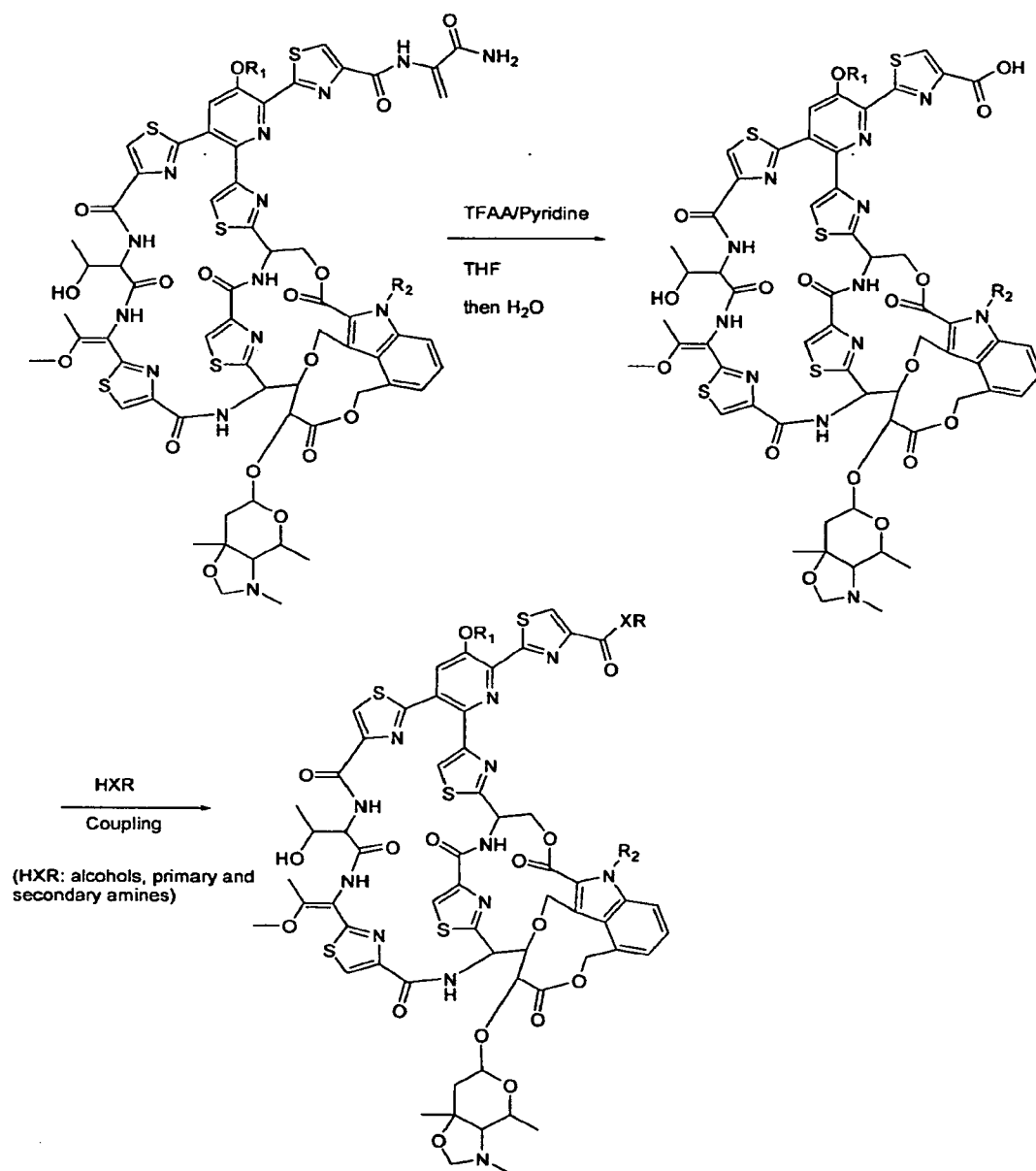
One embodiment of the methods of administration of a compound of formula I includes oral and parenteral methods, e.g., i.v. infusion, i.v. bolus and i.m. injection.

For adults, about 5-50 mg of a compound of formula I per kg of body weight given one to four times daily is preferred. The preferred dosage is 250 mg to 1000 mg of the antibacterial given one to four times per day. More specifically, for mild infections a dose of about 250 mg two or three times daily is recommended. For moderate infections against highly susceptible gram positive organisms a dose of about 500 mg three or four times daily is recommended. For severe, life-threatening infections against organisms at the upper limits of sensitivity to the antibiotic, a dose of about 1000-2000 mg three to four times daily may be recommended.

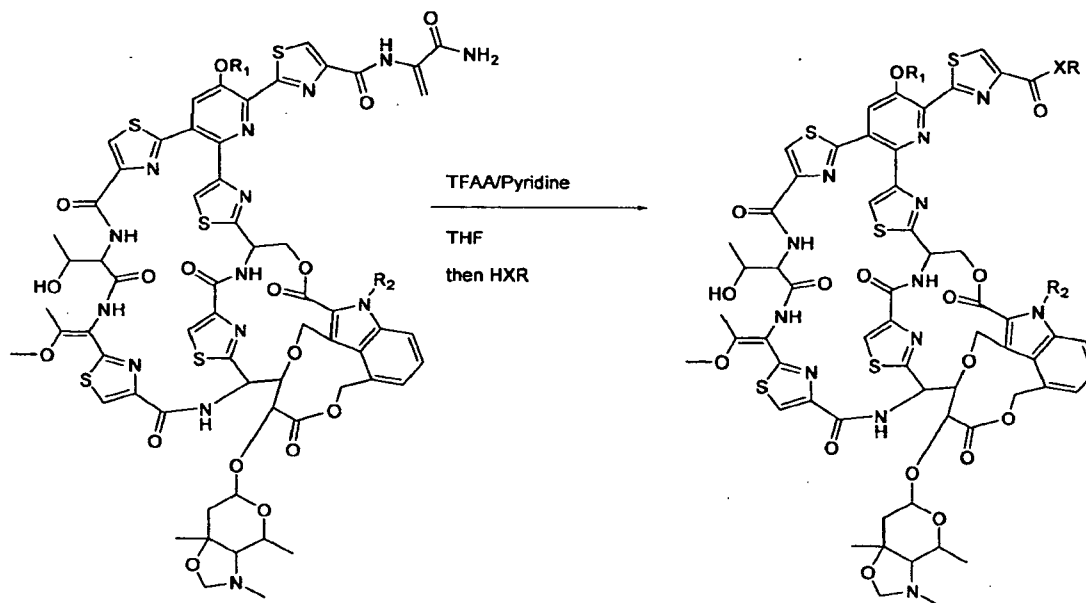
For children, a dose of about 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg is typically recommended.

The compounds of the present invention can be prepared according to **Schemes 1-3**, using appropriate materials, and are further exemplified by the following specific examples. 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.

Scheme 1.

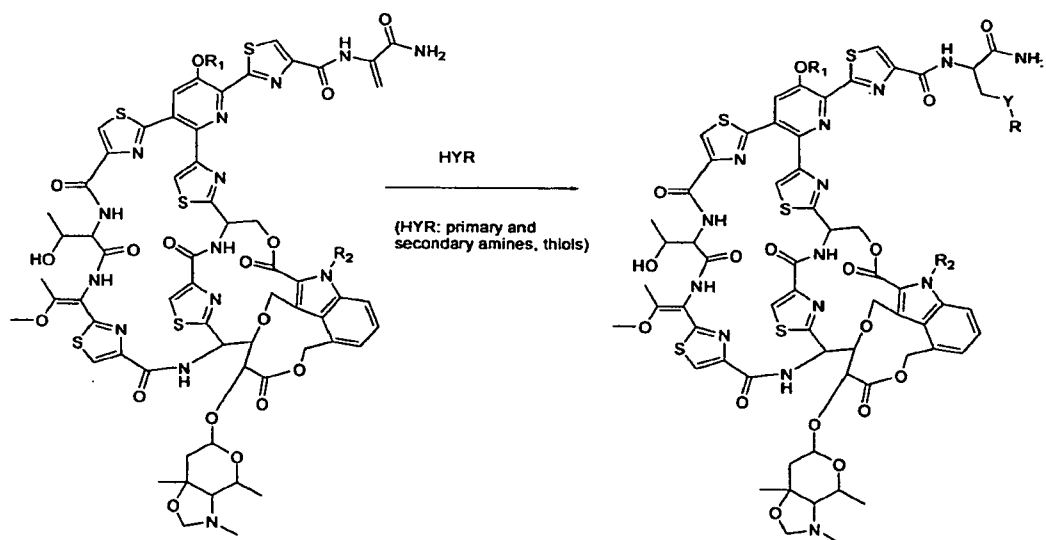


Scheme 2.

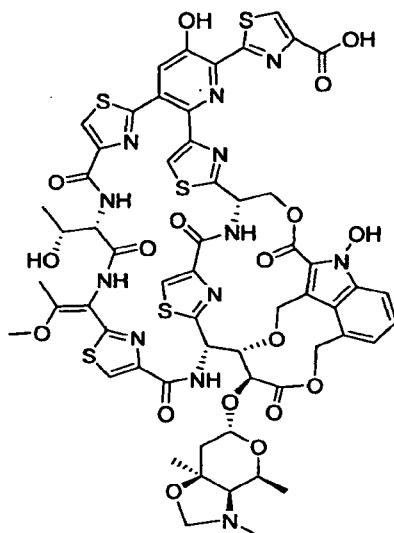


5

Scheme 3.



Example 1



5

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).

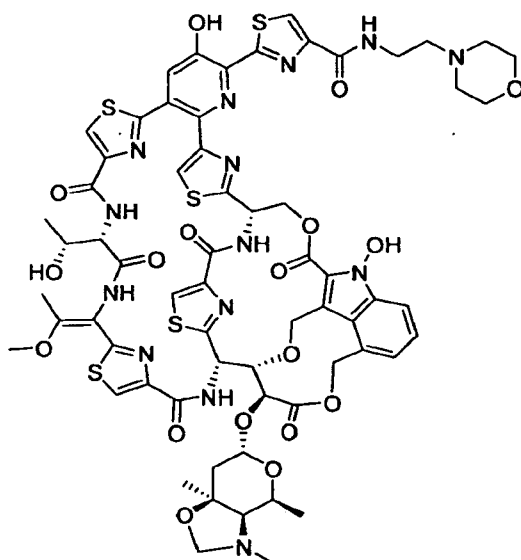
10

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).

15

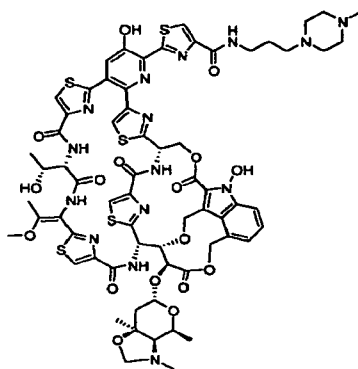
20

Example 2



- 5 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).

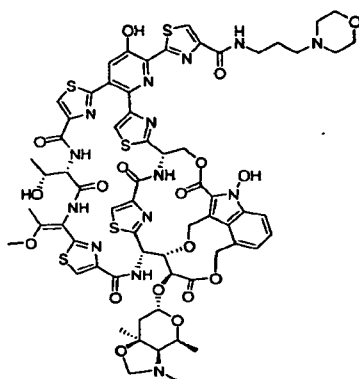
Example 3



- 5 Following the procedure described for example 2 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
- 10 (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).

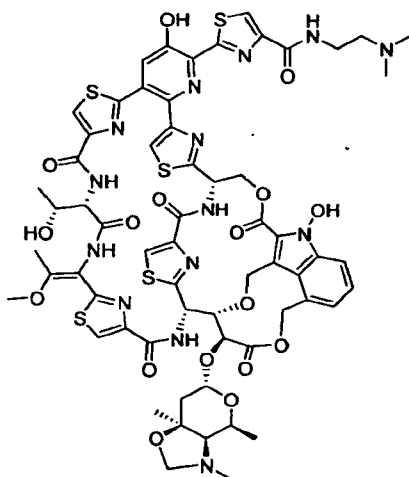
15

Example 4



- 5 Following the procedure described for example 2 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
- 10 (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
- 15 (d, J = 6.7 Hz, 3 H); 0.83 (s, 3 H).

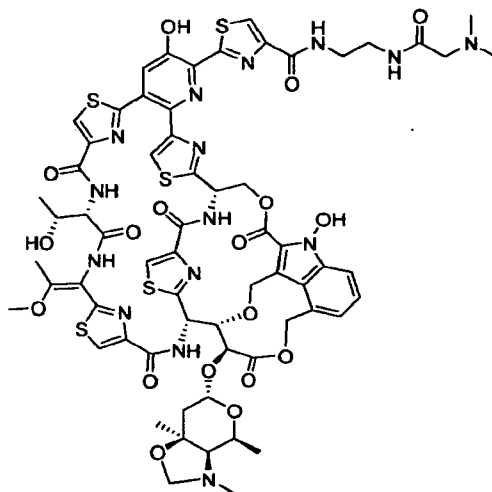
Example 5



- 5 Following the procedure described for example 2 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).

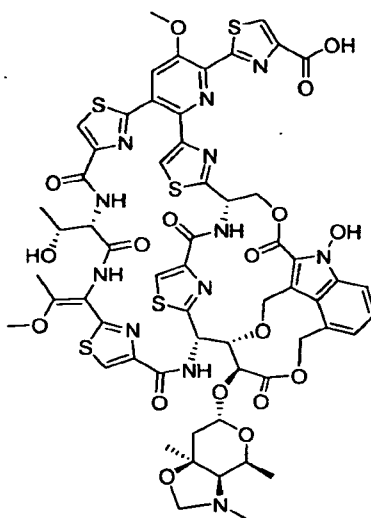
15

Example 6



5 Following the procedure described for example 2 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,
10 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
15 H).

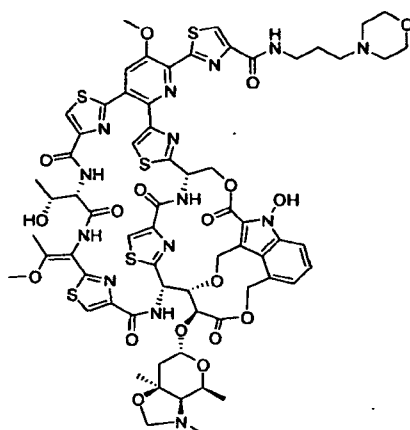
Example 7



5 To a solution of thiazomycin (0.5 g, 0.35 mmol) in benzene (20 mL) and methanol (4 mL) at 0 °C was added a 2.0 M solution of trimethylsilyl diazomethane in hexanes (0.7 mL, 1.39 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. Py-O-methyl thiazomycin was obtained as a yellow powder (0.45 g, 80% pure by LC-MS), and was used in
10 the next step without further purification.

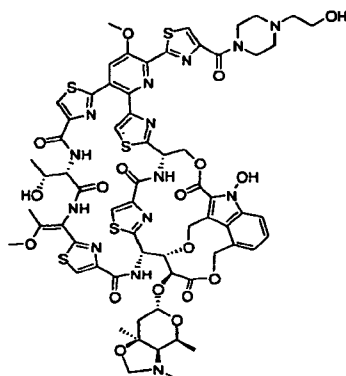
To a solution of Py-O-methyl thiazomycin (0.05 g, 80% pure) in tetrahydrofuran (3.3 mL) at 0 °C were added pyridine (0.056 mL, 0.69 mmol) and trifluoroacetic anhydride (0.048 mL, 0.35 mmol) slowly. After addition, the reaction mixture was allowed to warm to room temperature and stirring was continued 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. Purification by reversed-phase HPLC (10-60% acetonitrile with 0.1% TFA) yielded product as a mixture of O-methyl thiazo acid and trifluoroacetylated O-methyl
15 thiazo acid after lyophilization (0.01 g, 21% yield).
20

Example 8



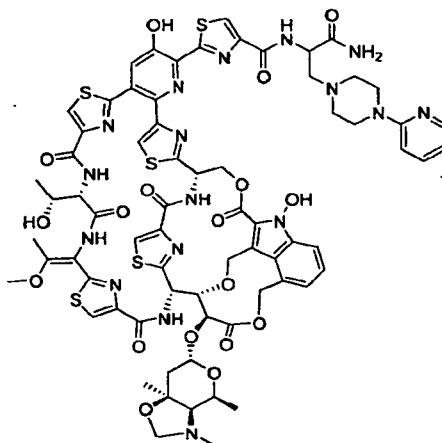
Coupling of the product of example 7 with N-(3-aminopropyl)morpholine using the procedure as described in example 2, followed by reversed-phase HPLC purification, yielded the desired product as a light yellow solid after lyophilization. ¹H NMR (500 MHz, CD₃OD): δ 8.61 (s, 1 H); 8.57 (d, J = 9.1 Hz, 1 H); 8.45 (s, 1 H); 8.42 (s, 1 H); 8.20 (d, J = 10.9 Hz, 1 H); 8.16 (s, 1 H); 8.11 (s, 1 H); 7.88 (s, 1 H); 7.83 (d, J = 7.5 Hz, 1 H); 7.81 (d, J = 8.2 Hz, 1 H); 7.42 (t, J = 7.7 Hz, 1 H); 7.23 (d, J = 6.9 Hz, 1 H); 6.08 (d, J = 12.6 Hz, 1 H); 6.04 (d, J = 9.4 Hz, 1 H); 5.78 (dd, J = 5.2, 10.7 Hz, 1 H); 5.42 (dd, J = 5.1, 11.4 Hz, 1 H); 5.06 (d, J = 12.7 Hz, 1 H); 5.04 (m, 1 H); 4.98 (d, J = 10.6 Hz, 1 H); 4.61 (d, J = 11.5 Hz, 1 H); 4.55 (d, J = 9.7 Hz, 1 H); 4.38 (t, J = 5.5 Hz, 1 H); 4.32 (s, 3 H); 4.28 (d, J = 10.7 Hz, 1 H); 4.00 (d, J = 7.8 Hz, 1 H); 3.95 (s, 3 H); 3.84 (br, 2 H); 3.54 (t, J = 6.8 Hz, 2 H); 3.17 (m, 2 H); 2.82 (m, 1 H); 2.52 (m, 1 H); 2.33 (m, 1 H); 2.05 (s, 6 H); 1.88 (m, 1 H); 1.40 – 1.44 (6 H); 0.71 (s, 3 H).

Example 9



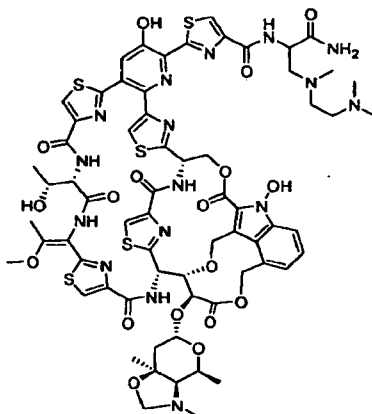
- 5 Coupling of the product of example 7 with *N*-(2-hydroxyethyl)piperazine using the procedure as described in example 2, followed by reversed-phase HPLC purification, yielded the desired product as a light yellow solid after lyophilization. ¹H NMR (500 MHz, CD₃OD): δ 8.62 (s, 1 H); 8.59 (d, J = 9.5 Hz, 1 H); 8.42 (s, 1 H); 8.29 (s, 1 H); 8.22 (d, J = 11.0 Hz, 1 H); 8.15 (s, 1 H); 8.01 (s, 1 H); 7.91 (d, J = 6.9 Hz, 1 H); 7.89 (s, 1 H); 7.83 (d, J = 8.2 Hz, 1 H); 7.43 (dd, J = 7.0, 8.4 Hz, 1 H); 7.23 (d, J = 6.8 Hz, 1 H); 6.07 (d, J = 12.4 Hz, 1 H); 6.02 (d, J = 11.1 Hz, 1 H); 5.76 (dd, J = 5.2, 10.7 Hz, 1 H); 5.37 (dd, J = 5.4, 11.7 Hz, 1 H); 5.06 (d, J = 12.6 Hz, 1 H); 5.02 (d, J = 5.7 Hz, 1 H); 4.92 (d, J = 10.7 Hz, 1 H); 4.59 (m, 4 H); 4.52 (d, J = 9.7 Hz, 1 H); 4.37 (t, J = 5.5 Hz, 1 H); 4.30 (d, J = 10.6 Hz, 1 H); 4.24 (s, 3 H); 4.06 (m, 1 H); 4.00 (d, J = 9.8 Hz, 1 H); 3.95 (s, 3 H); 3.82 (m, 3 H); 2.86 (m, 1 H); 2.44 (s, 4 H); 2.29 (m, 1 H); 2.04 (s, 3 H); 1.86 (m, 1 H); 1.43 (d, J = 6.5 Hz, 3 H); 1.37 (s, 3 H); 0.67 (s, 3 H).
- 10
- 15

Example 10

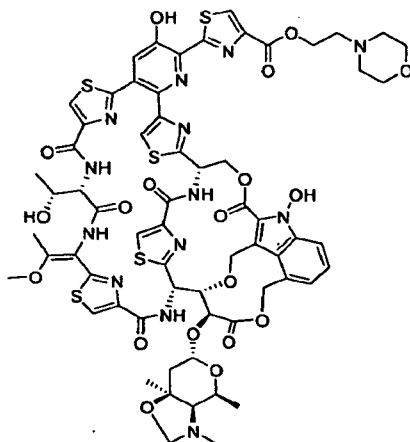


To a solution of 1-(2-pyridyl)piperazine (11 mg, 0.07 mmol) in water (0.5 mL) at room temperature were added thiazomycin (10 mg, 0.07 mmol) and triethylamine (0.005 mL). The reaction mixture was stirred for 5 minutes, and then kept at -20 °C for 16 hours. Purification by reversed-phase HPLC yielded the product as a yellow solid (4.4 mg, 40% yield). ¹H NMR (600 MHz, CD₃OD): δ 8.56 (s, 1 H); 8.51 (d, J = 9.7 Hz, 1 H); 8.47 (s, 1 H); 8.41 (s, 1 H); 8.16-8.14 (m, 2 H); 8.05 (s, 1 H); 7.87 (s, 1 H); 7.83 (s, 1 H); 7.80 (d, J = 9.0 Hz, 2 H); 7.72 (br, 1 H); 7.40 (t, J = 7.7 Hz, 1 H); 7.20 (d, J = 6.9 Hz, 1 H); 7.06 (br, 1 H); 6.80 (s, 1 H); 6.07 (d, J = 12.4 Hz, 1 H); 6.04 (d, J = 11.4 Hz, 1 H); 5.76 (m, 1 H); 5.37 (dd, J = 5.5, 11.8 Hz, 1 H); 5.06 (d, J = 7.6 Hz, 1 H); 5.03 (d, J = 12.5 Hz, 2 H); 4.94 (d, J = 10.6 Hz, 1 H); 4.56 (d, J = 11.3 Hz, 1 H); 4.51 (d, J = 9.7 Hz, 1 H); 4.47 (s, 1 H); 4.33 (s, 1 H); 4.28 (d, J = 10.6 Hz, 1 H); 4.11 (s, 1 H); 3.99 (d, J = 7.7 Hz, 1 H); 3.93 (s, 3 H); 3.39 (m, 1 H); 2.92 (s, 3 H); 2.81 (m, 1 H); 2.46 (dd, J = 5.2, 15.2 Hz, 1 H); 2.02 (d, J = 7.8 Hz, 3 H); 2.00 (m, 1 H); 1.98 (d, J = 7.1 Hz, 1 H); 1.52 (s, 3 H); 1.40 (s, 3 H); 0.87 (d, J = 6.7 Hz, 3 H).

Example 11



Following the procedure described for example 9 except using trimethylethylenediamine as the amine component to afford the product as a yellow lyophilized solid. ¹H NMR (500 MHz, CD₃OD): δ 8.60 (s, 1 H); 8.55 (d, J = 9.3 Hz, 1 H); 8.50 (s, 1 H); 8.44 (s, 1 H); 8.20 (d, J = 11.0 Hz, 1 H); 8.19 (s, 1 H); 7.92 (s, 1 H); 7.87 (d, J = 6.5 Hz, 1 H); 7.85 (d, J = 8.5 Hz, 1 H); 7.83 (s, 1 H); 7.44 (t, J = 7.7 Hz, 1 H); 7.24 (d, J = 7.2 Hz, 1 H); 6.11 (d, J = 12.6 Hz, 1 H); 6.07 (d, J = 11.6 Hz, 1 H); 5.80 (dd, J = 4.9 Hz, 11.3 Hz, 1 H); 5.41 (dd, J = 4.8, 11.3 Hz, 2 H); 5.10-5.06 (m, 3 H); 4.98 (d, J = 10.5 Hz, 2 H); 4.84 (m, 1 H); 4.61 (d, J = 11.0 Hz, 2 H); 4.55 (d, J = 9.7 Hz, 1 H); 4.46 (m, 1 H); 4.37 (m, 1 H); 4.32 (d, J = 10.7 Hz, 2 H); 4.11 (m, 1 H); 4.03 (d, J = 9.8 Hz, 1 H); 3.97 (s, 3 H); 3.38 (m, 1 H); 3.26-3.18 (m, 2 H); 2.94 (d, J = 3.6 Hz, 12 H); 2.87 (m, 4 H); 2.72-2.68 (m, 1 H); 2.47 (s, 3 H); 2.06 (s, 3 H); 2.01 (m, 1 H); 1.54 (s, 3 H); 1.45 (s, 3 H); 0.88 (s, 3 H).



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: 1480.9 (m/z); ^1H NMR (CD₃OD, 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).

The antibacterial activity of the compounds of Formula I can be determined using the assay methods described below.

MATERIALS:

Cation-Adjusted Mueller Hinton Broth (MH; BBL)
 50% Lysed Horse Blood (LHB; BBL) (stored frozen)
 RPMI 1640 (BioWhittaker)
 Human Serum (Pel-Freez)
 RPMI 1640 (BioWhittaker)

Haemophilus Test Medium (HTM, Remel)

Trypticase Soy Broth (TSB, 5 mL/tube; BBL)

0.9% Sodium Chloride (Saline; Baxter)

Trypticase Soy + 5% Sheep Blood Agar Plates (TSA; BBL)

5 Sabouraud Dextrose Agar Plates (BBL)

Chocolate Agar Plates (BBL)

2X Skim Milk (Remel)

Microbank Beads (Kramer Scientific)

MIC 2000 Microtiter plate inoculator.

10 2X Trypticase Soy Broth (TSB, BBL) + 15% glycerol/50% horse serum.

96-Well Microtiter plates, lids, inoculum trays (Dynex Laboratories)

8-Channel Finn Multichannel pipettor, 0.5-10 µL volume

METHODS:

15 MEDIA PREPARATION

Cation-Adjusted Mueller Hinton Broth (BBL): Prepared according to manufacturer's instructions (22 gms dissolved in 1000 mL water; autoclaved 22 minutes). Stored refrigerated. Filter-sterilized before use using a Corning 0.45 Tm cellulose acetate filter.

20 50% Lysed Horse Blood: Defibrinated horse blood is diluted 1:1 with sterile distilled water; frozen, thawed and re-frozen (at least 7 times), then centrifuged. Stored frozen at -20 °C.

Cation-Adjusted Mueller Hinton + 2.5% Lysed Horse Blood: Aseptically add 5 mL 50% lysed horse blood to 100 mL Cation-Adjusted Mueller Hinton Broth. Filter-sterilize before use using a
25 Corning 0.45 Tm cellulose acetate filter.

Cation-Adjusted Mueller Hinton + 50% Human Serum: Aseptically add 50 mL Human Serum to 50 mL 2X Cation-Adjusted Mueller Hinton Broth. Filter-sterilize before use using a Corning
30 0.45 Tm cellulose acetate filter.

Haemophilus Test Medium (Remel): Received prepared from manufacturer. Filter-sterilized before use using a Corning 0.45 Tm cellulose acetate filter.

0.9% Sodium Chloride (Saline; Abbott Labs): Received prepared from manufacturer.

2X Skim Milk (Remel): Received prepared from manufacturer.

All agar plates are received prepared from manufacturer.

5

CONDITIONS AND INOCULUM	FOR REPRESENTATIVE STRAINS
<i>BACILLUS</i> , <i>STAPHYLOCOCCUS</i> , <i>ENTEROCOCCUS</i> : <i>ESCHERICHIA</i> :	INCUBATION CONDITIONS, 35°C; MICS READ AT 18-22 HOURS; CATION-ADJUSTED MUELLER HINTON (CAMHB; BBL); INOCULUM = 10 ⁵ CFU/ML
<i>STREP. PNEUMONIAE</i> :	INCUBATION CONDITIONS, 35°C; MICS READ AT 22-24 HOURS; CATION-ADJUSTED MUELLER HINTON+ 2.5% LYSED HORSE BLOOD (LHB); INOCULUM = 10 ⁵ CFU/ML
<i>HAEMOPHILUS INFLUENZAE</i> :	INCUBATION CONDITIONS, 35°C; MICS READ AT 18-22 HOURS; HAEMOPHILUS TEST MEDIUM (HTM; REMEL); INOCULUM = 10 ⁵ CFU/ML
<i>CANDIDA</i> :	INCUBATION CONDITIONS, 35°C; MICS READ AT 24 HOURS; RPMI 1640 MEDIUM (BIOWHITTAKER) INOCULUM = 10 ³ CFU/ML

HIGHEST CONCENTRATION OF ANTIBIOTIC TESTED = 64 µG/ML (WHEN STARTING FROM A 1 MG/ML SOL'N IN 50% DMSO)

FINAL CONCENTRATION OF DMSO PER WELL = 3.2%

SELECTION AND MAINTENANCE OF ISOLATES

The type of strains listed above can be obtained from publicly available sources.

The strain of *Haemophilus influenzae* used in to assay the compound of this invention is a mouse pathogen used for *in vivo* testing at Merck. The *Escherichia coli* strain used in to assay the compound of this invention is a cell wall permeable strain. The *Candida albicans* strain is used as a control. These culture are maintained as frozen stocks at -80 °C in a) Microbank beads; b)

10

2X Skim Milk; or c) in 2X Trypticase Soy Broth + 15% glycerol/50% horse serum (*Haemophilus* and *Streptococcus pneumoniae*).

INOCULUM PREPARATION

5 Selected isolates are sub-cultured onto either Chocolate Agar Plates (*Haemophilus influenzae*), onto Trypticase Soy + 5% Sheep Blood Agar Plates (*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus*, *Bacillus*) or onto Sabouraud Dextrose Agar (*Candida*) and incubated at 35°C. *Haemophilus* and *Streptococcus pneumoniae* are incubated in 5% CO₂; all other isolates are incubated in ambient air. Isolates are
10 sub-cultured 2X before assay.

Colonies are selected from plates and used to prepare an inoculum equivalent to a 0.5 McFarland standard in Trypticase Soy Broth. An inoculum with a density equivalent to a 1.0 McFarland standard is prepared for *Streptococcus pneumoniae*. The inoculum density for all cultures is ~10⁸ CFU/mL in TSB. This TSB inoculum is diluted 1:10 in sterile saline (4 mL
15 inoculum + 36 mL saline; equivalent to ~10⁷ CFU/mL) and kept on ice until used to inoculate microtiter plates.

Colony counts are performed on randomly-selected isolates to confirm CFU/well (TSB inoculum plated out 10⁻⁵, 10⁻⁶ onto either TSA II + 5% SB or onto chocolate agar plates, incubated overnight, 35°C, CO₂)

20

PLATE FILLING

All wells of 96-well microtiter plates (Dynex) are filled with 100 TL media. *Haemophilus* test media plates are prepared to test *Haemophilus influenzae*; Cation-Adjusted Mueller Hinton + 5% Lysed Horse Blood plates are prepared to test *Streptococcus pneumoniae*;
25 Cation-Adjusted Mueller Hinton Broth plates are prepared to test *Enterococcus*, *Staphylococcus aureus*, *Escherichia coli* and *Bacillus subtilis*. RPMI 1640 is used to test *Candida*. The MICs against *S. aureus* Smith are determined in Cation-adjusted Mueller Hinton and in Cation-Adjusted Mueller Hinton + 50% Human Serum, to determine if the compound is inactivated by some component in serum (indicated by an increase in the MIC). Filled plates are wrapped in
30 plastic bags (to minimize evaporation), stored frozen and thawed before use.

PREPARATION OF COMPOUNDS

The compounds are prepared on a weight basis. Compounds are prepared to 2-10 mg/mL in 100% DMSO, then diluted to 1mg/mL in a 1:1 dilution of DMSO/2x CAMHB (final

concentration=50%DMSO/50% CAMHB). Compounds are serially diluted 1:1 in 50% DMSO/50% CAMHB in BD Biosciences Deep Well Polypropylene 96 well plates (starting concentration 1-5 mg/mL).

5 MICROBROTH DILUTION ASSAY

Using a Finn Automated Multichannel Pipette, (0.5-10 μ L volume) 6.4 TLs of antimicrobial working solutions are added to wells of filled microtiter plates (concentration of antimicrobial in first well = 512-64 microg/mL; concentration of DMSO = 3.2%).

Antimicrobials are added in this manner to keep constant the amount of DMSO in each well (to
10 keep compounds solubilized and to account for the possibility of non-specific killing by the DMSO. The last row contains a growth control of 3.2% DMSO.

Controls (Penicillin G and chloramphenicol) are run with each assay. The controls are prepared in the same manner as described for the compounds of the invention. Ertapenem is included as a control for the serum protein binding assay.

15

PLATE INOCULATION

All wells of microtiter plates are inoculated with (saline-diluted) culture using the MIC 2000 System, an automated plate inoculating device which delivers an inoculum of 1.5 TL per well. Plates are incubated at 35°C in ambient air. An uninoculated plate is also incubated as
20 a sterility check. Results are recorded after 22-24-hours' incubation. Plates were read to no growth. The MIC is defined as the lowest antimicrobial level which resulted in no growth after 22-24-hours' incubation.

The Compounds of formula I demonstrate antibacterial activity against various strains of *S. aureus*, *E. faecalis*, *E. faecium*, *B. subtilis* and *S. pneumoniae*. Compounds of
25 formula I also demonstrate antibacterial activity against various species that are resistant to many known antibiotics such as methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococcus sp.* (VRE), multidrug-resistant *E. faecium*, macrolide-resistant *S. aureus* and *S. epidermidis*, and linezolid-resistant *S. aureus* and *E. faecium*. The minimum inhibitory concentration (MIC) values for these test strains range from 0.0001 to 200 μ g/mL. MICs are
30 obtained in accordance to the NCCLS guidelines. Select compounds of this invention have been found to have minimum inhibitory concentration (MIC) values that are at least a 10 fold improvement over the compounds disclosed in P. Hrnčiar, et. al., J. Org. Chem. 2002, 67, 8789-8793 against tested strains. See Table 2 where compounds A and B (Examples 5 and 3 of

claimed invention) were compared with compound C (example 7 of J. Org. Chem. 2002, 67, 8789-8793).

TABLE 2

Compound A

5	<u>Organism</u>	<u>Strain</u>	<u>Serum %</u>	<u>MIC ug/mL</u>
	Enterococcus Faecalia	CLB 21560	0	0.01595
	Staphylococcus Aureus	CL 5814	0	0.00565
	Staphylococcus Aureus	CL 8260	0	0.0075
	Staphylococcus Aureus	MB 2865	50	0.03

10

Compound B

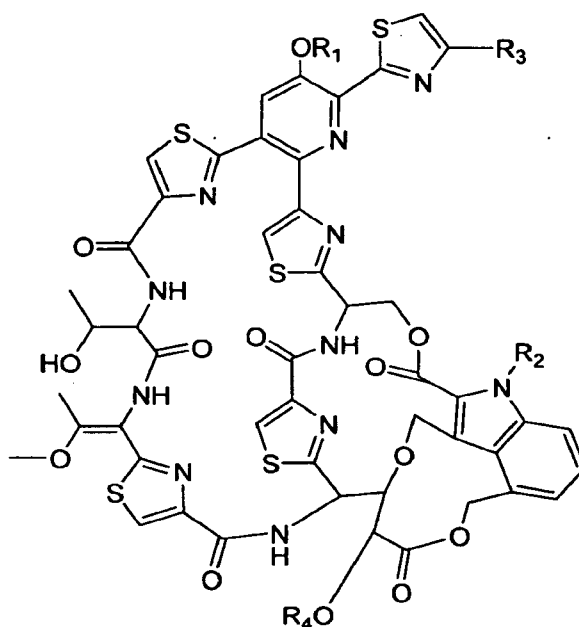
	<u>Organism</u>	<u>Strain</u>	<u>Serum %</u>	<u>MIC ug/mL</u>
	Enterococcus Faecalia	CLB 21560	0	0.0325
	Staphylococcus Aureus	CL 5814	0	0.0075
15	Staphylococcus Aureus	CL 8260	0	0.015
	Staphylococcus Aureus	MB 2865	50	0.06

Compound C

	<u>Organism</u>	<u>Strain</u>	<u>Serum %</u>	<u>MIC ug/mL</u>
20	Enterococcus Faecalia	CLB 21560	0	0.25375
	Staphylococcus Aureus	CL 5814	0	0.030475
	Staphylococcus Aureus	CL 8260	0	0.125475
	Staphylococcus Aureus	MB 2865	50	0.14

WHAT IS CLAIMED IS:

1. A compound of structural formula I:



I

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

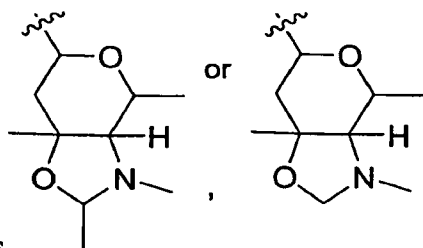
wherein:

R independently represents hydrogen, and C₁-12 alkyl;

- 10 R₁ represents hydrogen, C₁-6 alkyl, and C₃-6 cycloalkyl;

R₂ represents R₁ and OR₁

R₃ represents -C(O)NR₅R₆, -C(O)NHC(R₇R₈)(CH₂)_n(NH)_mC(O)NR₅R₆ or C(O)OR₅,



- 15 R₄ represents ;

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

15 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, -C(O)NH(CH₂)_nC₅₋₁₀ heterocyclyl, -C(O)(CH₂)_nN(R)₂, -(CH₂)_nS(O)_p(CH₂)_nC₅₋₁₀
 20 heterocyclyl, -(CH₂)_nS(O)_p(CH₂)_nNR₅R₆, -(CH₂)_nS(CH₂)_nNR₅R₆, -(CH₂)_nS(O)_p(CH₂)_nC₆₋₁₀ aryl, -(CH₂)_nS(O)_p(CH₂)_nC₁₋₆ alkyl, said aryl, and heterocyclyl optionally substituted with one or more groups of R^a; said alkyl optionally substituted with 1 to 6 hydroxyl and/or optionally substituted by one to more groups of R^a or

25 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 one or more groups of R^a; or

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

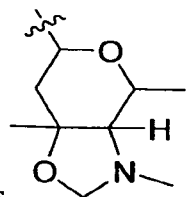
R^a represents hydrogen, halogen, (CH₂)_nOR, CF₃, (CH₂)_nC(O)OR, (CH₂)_nC(O)NR₇R₈, (CH₂)_nC₅₋₁₀ heterocyclyl, SO₂NR₅R₆, (CH₂)C₆₋₁₀ aryl, N(R)₂, NO₂, CN, (C₁₋₆ alkyl)O-, (aryl)O-, (C₁₋₆ alkyl)S(O)₀₋₂-, C₁₋₁₂ alkyl, said alkyl, heterocyclyl, and aryl optionally substituted with 1 to 4 groups selected from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

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

2. The compound according to claim 1 wherein R₁ represents H or C₁₋₆ alkyl and R₂ represents OH or OC₁₋₆ alkyl.

3. The compound according to claim 1 wherein R₃ represents -C(O)NR₅R₆.

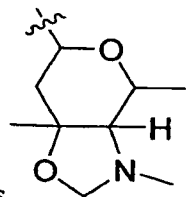
4. The compound according to claim 3 wherein R₃ is -(C(O)NH(CH₂)_nC₅₋₁₀ heterocyclyl, R₁ is hydrogen or C₁₋₆ alkyl, R₂ is -(CH₂)_nOR, and R₄



represents

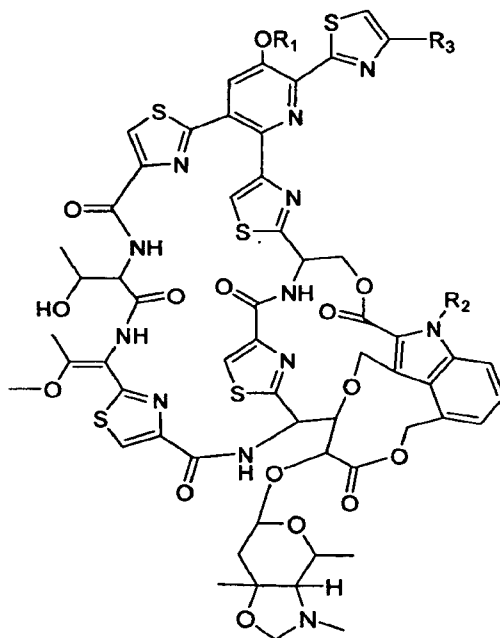
5. The compound according to claim 4 wherein R₁ is methyl and R₂ is -(CH₂)_nOR.

6. The compound according to claim 1 wherein R₃ represents C(O)NHC(R₇R₈)(CH₂)_nC(O)NR₅R₆, R₁ is hydrogen or C₁₋₆ alkyl, R₂ is -OR, and R₄

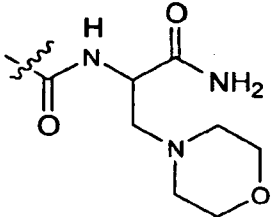
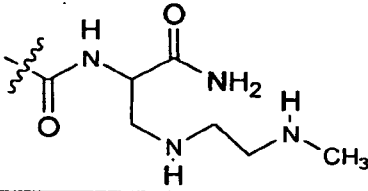
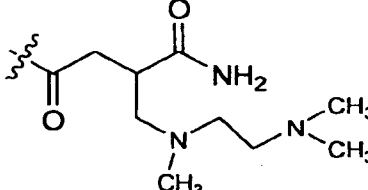
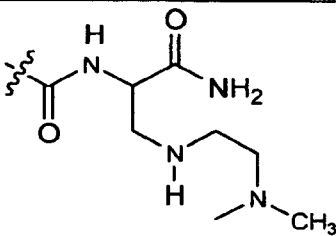
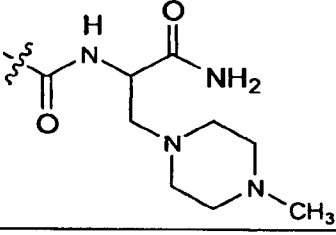
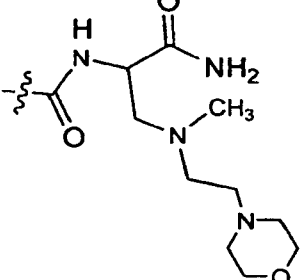


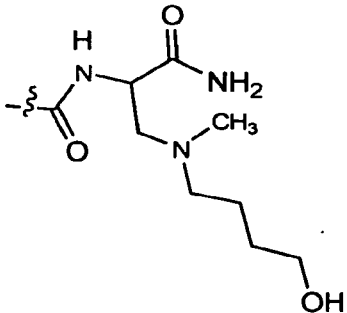
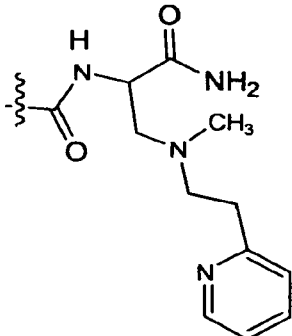
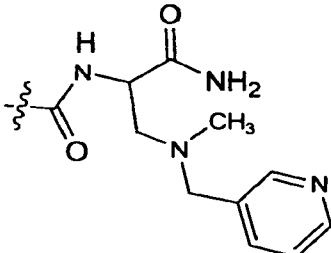
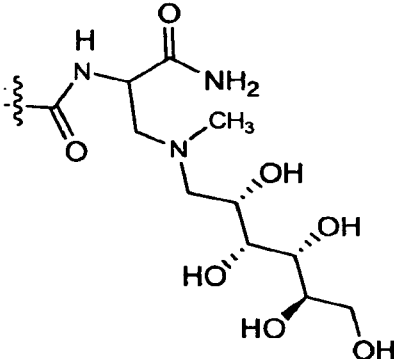
represents

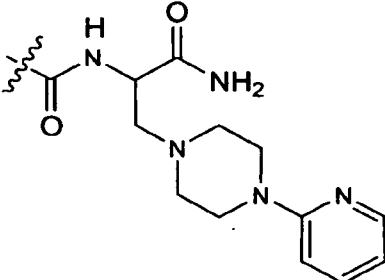
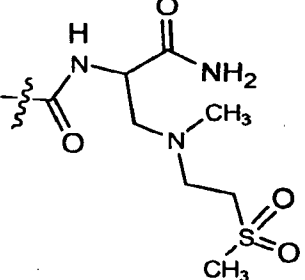
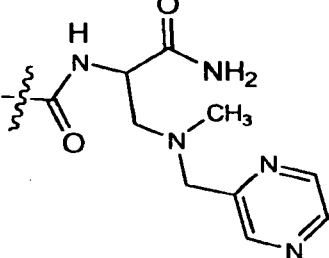
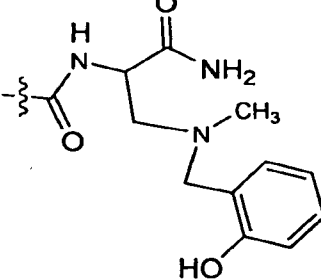
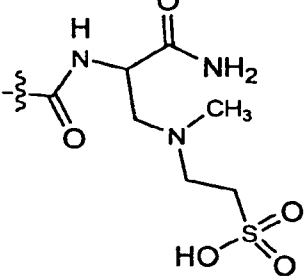
7. The compound according to claim 1 represented by structural formula II:

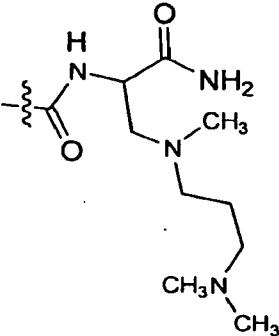
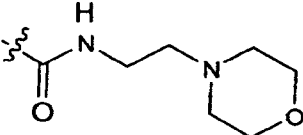
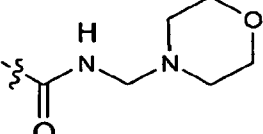
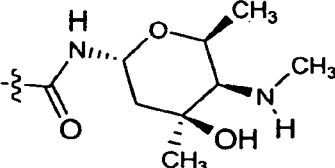
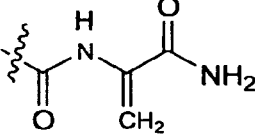
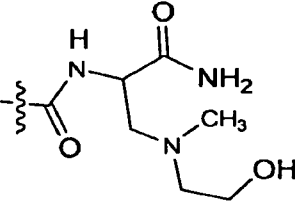
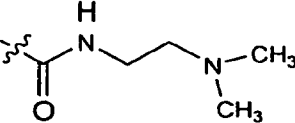
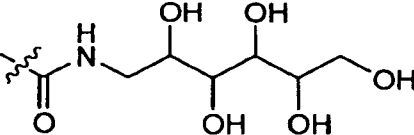


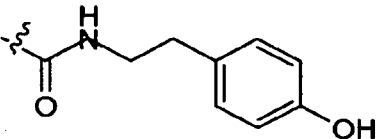
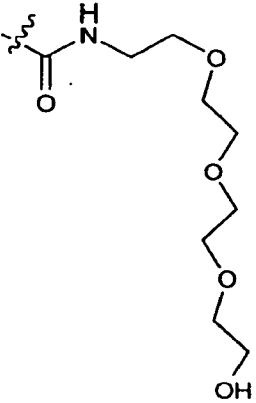
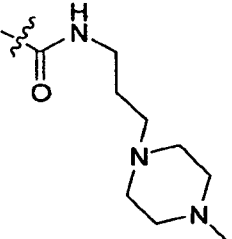
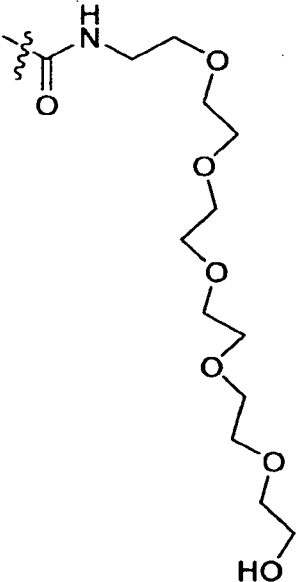
Compound	R ₁	R ₂	R ₃
1	-CH ₃	-OCH ₃	
2	H	OH	
3	H	OH	C(O)NH ₂
4	H	OH	

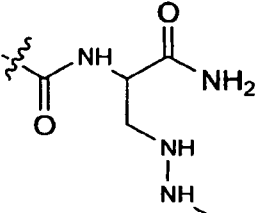
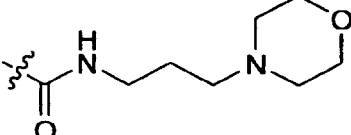
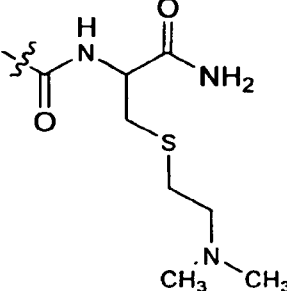
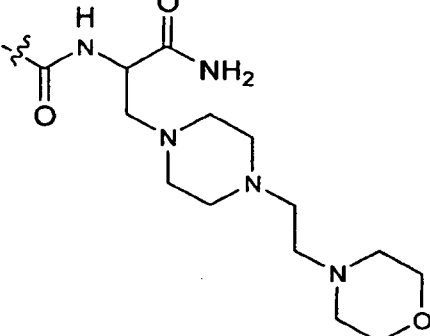
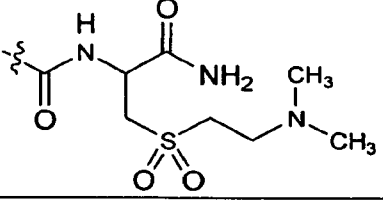
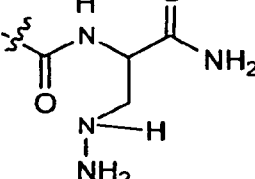
5	H	OH	
6	H	OH	
7	H	OH	
8	H	OH	
9	H	OH	
10	H	OH	

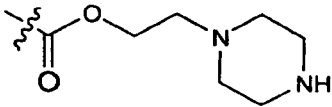
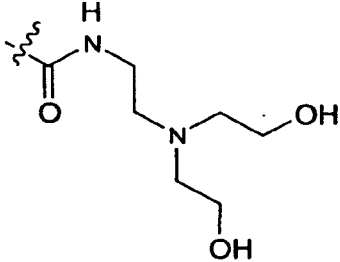
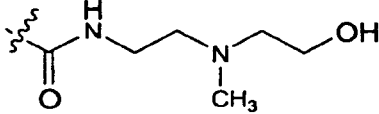
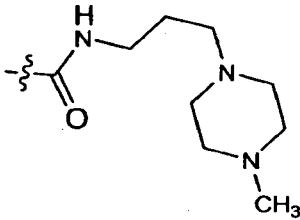
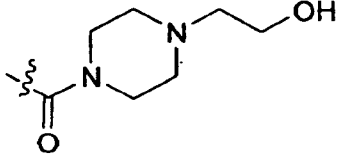
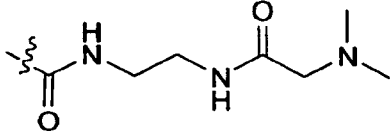
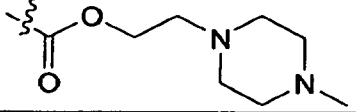
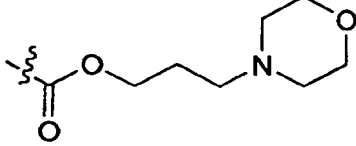
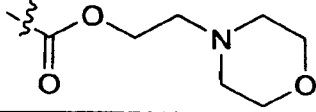
11	H	OH	
12	H	OH	
13	H	OH	
14	H	OH	

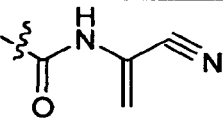
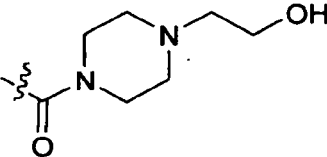
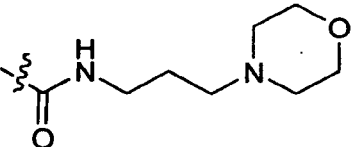
15	H	OH	
16	H	OH	
17	H	OH	
18	H	OH	
19	H	OH	

20	H	OH	
21	H	OH	
22	H	OH	C(O)OH
23	H	OH	
24	H	OCH ₃	
25	H	OCH ₃	
26	H	OCH ₃	
27	H	OH	
28	H	OH	

29	H	OH	
30	H	OH	
31	H	OH	
32	H	OH	

33	H	OH	
34	H	OH	
35	H	OH	
36	H	OH	
37	H	OH	
38	H	OH	

39	H	OH	
40	H	OH	
41	H	OH	
42	H	OH	C(O)NH ₂
43	H	H	
44	H	OH	
45	H	OH	
46	H	OH	
47	H	OH	
48	H	OH	

49	H	OH	-C(O)OMe
50	H	OH	
51	Me	OH	
52	Me	OH	

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

8. A pharmaceutical composition which is comprised of a compound
5 in accordance with Claim 1 and a pharmaceutically acceptable carrier.

9. Use of a compound of formula I of claim 1 in the manufacture of a
medicament for inhibiting bacterial infections.

10. A pharmaceutical composition comprising a compound according
10 to claim 1 useful for inhibiting bacterial infections.