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(54) Titre : POLYCETIDES POLYENIQUES ET METHODES DE PRODUCTION CONNEXES
(54) Title: POLYENE POLYKETIDES AND METHODS OF PRODUCTION

(57) Abrégé/Abstract:
Novel polyene polyketides, their pharmaceutically acceptable salts, prodrugs and derivatives have been found to have antibiotic activity. One method for obtaining the compounds is by cultivation of Amycolatopsis orientalis ATCC™ 43491 or a mutant or variant such as the strain IDAC-220604-1. Another method for obtaining the compounds is post-biosynthesis chemical modification of the compounds obtained by cultivation. Novel polynucleotide sequences and encoded proteins for the biosynthesis of the polyene polyketides are also presented.

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ABSTRACT

Novel polyene polyketides, their pharmaceutically acceptable salts, prodrugs and derivatives have been found to have antibiotic activity. One method for obtaining the compounds is by cultivation of *Amycolatopsis orientalis* ATCC™ 43491 or a mutant or variant such as the strain IDAC-220604-1. Another method for obtaining the compounds is post-biosynthesis chemical modification of the compounds obtained by cultivation. Novel polynucleotide sequences and encoded proteins for the biosynthesis of the polyene polyketides are also presented.

DEMANDES OU BREVETS VOLUMINEUX

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JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

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POLYENE POLYKETIDES AND METHODS OF PRODUCTION

FIELD OF THE INVENTION:

This invention relates to novel biologically active polyene polyketides, their pharmaceutically acceptable salts and derivatives, and to methods of obtaining them. One method for obtaining the compounds is by cultivation of *Amycolatopsis orientalis* ATCC™ 43491, the *Amycolatopsis orientalis* species having accession number IDAC 220604-01, or a mutant or variant of strain ATCC™ 43491 or strain IDAC 220604-1. Another method of producing these polyene polyketides involves expression of the biosynthetic gene cluster of the invention in transformed host cells. Another method of producing these polyene polyketide is by post-biosynthesis chemical modifications. The present invention further relates to *Amycolatopsis orientalis sp.* strains IDAC 220604-01, to the use of the polyene polyketides and their pharmaceutically acceptable salts and derivatives as pharmaceuticals, in particular to their use as inhibitors of bacterial cell growth and to pharmaceutical compositions comprising a polyene polyketide of the invention or a pharmaceutically acceptable salt or derivative thereof. Finally, the invention relates to novel polynucleotide sequences and their encoded proteins, which are involved in the biosynthesis of the polyene polyketides of the invention.

BACKGROUND OF THE INVENTION:

Polyketides are a diverse class of naturally occurring molecules typically produced by a variety of organisms, including fungi and mycelial bacteria, in particular actinomycetes. Although polyketides have widely divergent structures, they are classified together because they all share a common general biosynthetic pathway in which the carbon backbone of these molecules are assembled by sequential, step-

wise addition of two carbon or substitued two carbon units referred to as ketides. Polyene polyketides comprise a chain of ketide units that have been strung together by a series of enzymatic reactions by multimodular polyketide synthase proteins. Polyketides are usually found in their natural environment in trace amounts. Moreover, due to their structural complexity, poyketides are notoriously difficult to synthesize chemically. Nevertheless, many polyketides have been developed into effective drugs for the treatment of conditions such as bacterial and fungal infections, cancer and high cholesterol. Adriamycin, erythromycin, zocor and nystatin are but a few examples of polyketide molecules, which have been developed into valuable pharmaceuticals. Linearmycin A, having a 60 carbon chain and a degree of unsaturation of 15, is an example of a linear polyene polyketide reported to possess antifungal and antibacterial activity (Sakuda *et al.*, *Tetrahedron Letters*. Vol. 36, No. 16, 2777-2870 (1995); Sakuda *et al.*, *J. Chem Soc., Perkin Trans*. 1,2315-2319 (1996)).

Although large numbers of therapeutically important polyketides have been identified, there remains a need to obtain novel polyketides that have enhanced properties or possess completely novel bioactivities. The complex polyketides produced by modular Type I polyketide synthases (PKSs) are particularly valuable, in that they include compounds with known utility as antihelminthics, insecticides, immunosuppressants, cytotoxic, antifungal or antibacterial agents.

Because of their structural complexity, such novel polyketides are not readily obtainable by total chemical synthesis. The present invention addresses this need by providing a new class of polyketide compounds with therapeutic activity, together with means for their production. The compounds of the invention are prepared by fermentation or by fermentation followed by chemical modifications. The compounds of the invention may also be produced by appropriate application of recombinant DNA technology. A wide variety of polyketides can be prepared in a variety of different host cells provided one has access to nucleic acid compounds that encode PKS proteins and polyketide modification enzymes.

PKSs are large proteins that contain multiple enzymatic activities. PKSs catalyse the biosynthesis of polyketides through repeated, decarboxylative Claisen condensations between acylthioester building blocks, such as acetyl, butyryl, isobutyryl, propionyl, malonyl, hydroxymalonyl, methylmalonyl, and ethylmalonyl CoA.

PKS enzymes are generally classified into Type I or "modular" PKSs and Type II or "iterative" PKSs according to the polyketide synthetized and by the mode of synthesis. Type I PKSs are responsible for producing a large number of 12-, 14- and 16- membered macrolide antibiotics.

Type I or modular PKS enzymes are multifunctional proteins containing catalytic sites for acyl transferases (AT), acyl carrier protein (ACP), ketosynthase (KS), dehydratase (DH), and enoyl reductase (ER) activities. Type I enzymes are formed by a set of separate catalytic active sites for each cycle of carbon chain elongation and modification in the polyketide synthesis pathway. Each active site is termed a domain. A set of active sites or domains is termed a module. The typical modular PKS complex is composed of several large PKS polypeptides that act coordinately to achieve polyketide synthesis. Each PKS polypeptide can be segregated from amino to carboxy terminus into a loading module (found only in the first PKS polypeptide of the complex), multiple extender modules, and a releasing or thioesterase (TE) domain (generally found only in the final module of the terminal PKS polypeptide of the complex).

Generally, the loading module is responsible for binding the first building block used to synthesize the polyketide and transferring it to the first extender module. The AT domain of the loading module recognizes a particular acyl-CoA (usually acetyl or propionyl but sometimes butyryl, isobutyryl or other acyl-CoA) and transfers it as a thiol ester to the ACP domain of the loading module. The loading module may not encode a KS domain, or may encode a KS(Q) domain, a KS-like domain that carries an amino acid substitution at the active site cysteine residue (typically a glutamine residue, single letter code Q). KS(Q) domains decarboxylate the acylthioester of the loading domain before proceeding with chain elongation. For example, the loader module of the oleandomycin PKS complex initiates deoxyoleandolide synthesis by loading the ACP with a malonyl unit and performing a decarboxylation to generate acetyl-ACP (Shah, (2000), *J. Antibiotics*, Vol. 53, pp. 502-508).

The AT domain on each of the extender modules recognizes a particular extender-CoA (typically malonyl or alpha-substituted malonyl, i.e. methylmalonyl, ethylmalonyl, and 2-hydroxymalonyl) and transfers it to the ACP domain of that extender module to form a thioester. Each extender module is responsible for accepting a compound from a prior module, binding a building block, attaching the building block to the

compound from the prior module, optionally performing one or more additional functions, and transferring the resulting compound to the next module.

Each extender module of a modular PKS contains a KS, AT, ACP, and zero, one, two or three domains that modify the beta-carbon of the growing polyketide chain. A typical (non-loading) minimal Type I PKS extender module may contain a KS domain, an AT domain, and an ACP domain. Such domains are sufficient to activate a 2-carbon extender unit and attach it to the growing polyketide molecule. The next extender module, in turn, is responsible for attaching the next building block and transferring the growing compound to the next extender module until synthesis of the polyketide is complete.

Once the PKS is primed with acyl- and malonyl-ACPs, the acyl group of the loading module is transferred to form a thiol ester (trans-esterification) at the KS of the first extender module; at this stage, extender module one possesses an acyl-KS and a malonyl (or substituted malonyl)-ACP. The acyl group derived from the loading module is then covalently attached to the alpha-carbon of the malonyl group to form a carbon-carbon bond, driven by concomitant decarboxylation, and generating a new acyl-ACP that carries a backbone two carbons longer than the loading building block (elongation or extension) and side chains if a substituted malonyl unit is used for extension.

The polyketide chain, growing by two or more carbons with each extender module, is sequentially passed as covalently bound thiol esters from extender module to extender module, in an assembly line-like process. The carbon chain produced by this process alone would possess a ketone at every other carbon atom, producing a polyketone, from which the name polyketide arises. Most commonly, however, additional enzymatic activities modify the beta keto group of each two carbon unit just after it has been added to the growing polyketide chain but before it is transferred to the next module.

After traversing the final extender module, the polyketide encounters a releasing domain (TE) that cleaves the polyketide from the PKS and typically cyclizes the polyketide. Further, tailoring enzymes can modify the polyketide; these tailoring enzymes add carbohydrate groups, methyl groups, or make other modifications, i.e. oxidation or reduction, on the polyketide core molecule.

Type I PKSs displays a one-to-one correlation between the number and clustering of active sites in the primary sequence of the PKS and the structure of the polyketide backbone. The activities catalyzed by the domains within a type I PKS are often apparent in the structure of the growing polyketide chain; consequently, nucleotide sequence has become a predictive tool for deducing the biosynthetic route for these compounds (Rangaswamy et al, *Proc. Natl. Acad. Sci. USA,* (1998) Vol. 95, pp. 15469-15474).

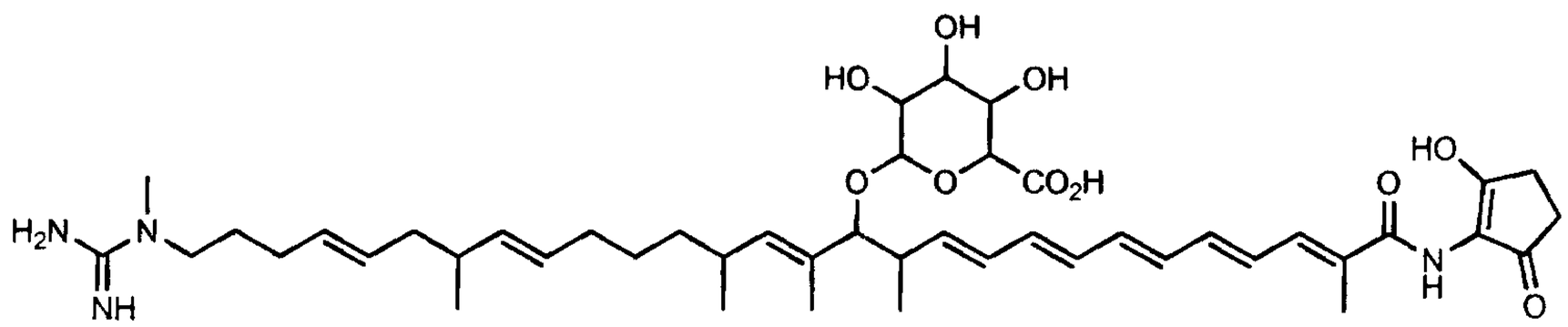
In Type I PKS polypeptides, the order of catalytic domains is conserved. When all beta-keto processing domains are present in a module, the order of domains in that module from N-to-C-terminus is always KS, AT, DH, ER, KR, and ACP. Some or all of the beta-keto processing domains may be missing in particular modules, but the order of the domains present in a module remains the same. The order of domains within modules is believed to be important for proper folding of the PKS polypeptides into an active complex. Importantly, there is considerable flexibility in PKS enzymes, this flexibility provides a means for genetically engineering novel catalytic complexes. By manipulating the polynucleotide sequences encoding the PKS polypeptide, genetically engineered novel PKSs can be achieved. Genetically engineering PKS enzymes can be achieved by the modification, addition or deletion of domains, or by replacing domains with domains taken from other Type I PKS enzymes. As well, this can also be achieved by deletion, addition or replacement of entire modules with modules taken from other sources. A genetically engineered PKS complex should, of course, have the ability to catalyze the synthesis of the product predicted from the genetic alterations made.

Alignment of the many available amino acid sequences for Type I PKS enzymes has approximately defined the boundaries of the various catalytic domains. Sequence alignments also have revealed linker regions between the catalytic domains and at the N- and C-termini of individual PKS polypeptides. The sequences of these linker regions are less well conserved than are those for the catalytic domains, which is in part how linker regions are identified. Linker regions can be important for proper association between domains and between the individual polypeptides that comprise the PKS complex. One can thus view the linkers and domains together as creating a scaffold on which the domains and modules are positioned in the correct orientation to be active. This organization and positioning, if retained, permits PKS domains of

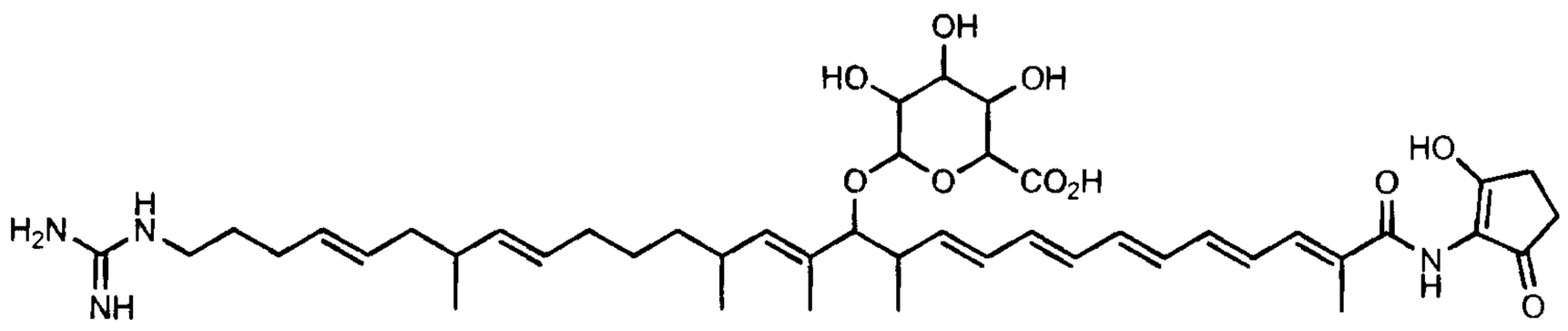
different or identical substrate specificities to be substituted (usually at the DNA level) between PKS enzymes by various available methodologies. In selecting the boundaries of, for example, an AT domain replacement, one can thus make the replacement so as to retain the linkers of the recipient PKS or to replace them with the linkers of the donor PKS AT domain, or, preferably, make both constructs to ensure that the correct linker regions between the KS and AT domains have been included in at least one of the engineering enzymes. Thus, there is considerable flexibility in the design of new PKS enzymes with the result that known polyketides can be produced more effectively, and novel polyketides can be made.

SUMMARY OF THE INVENTION:

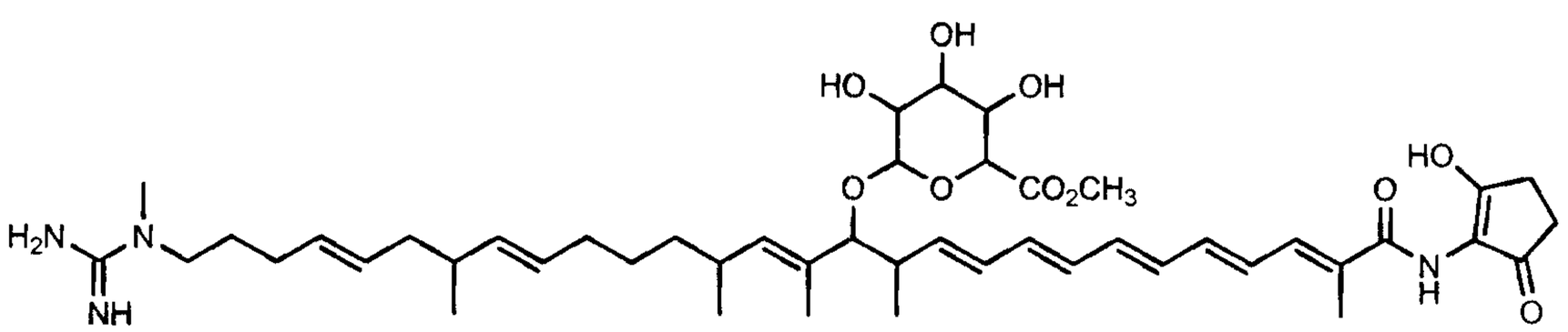
In one aspect of this embodiment the invention relates to novel polyene polyketides Compounds 1, 2, 3, 4, 5, 6 and 7:



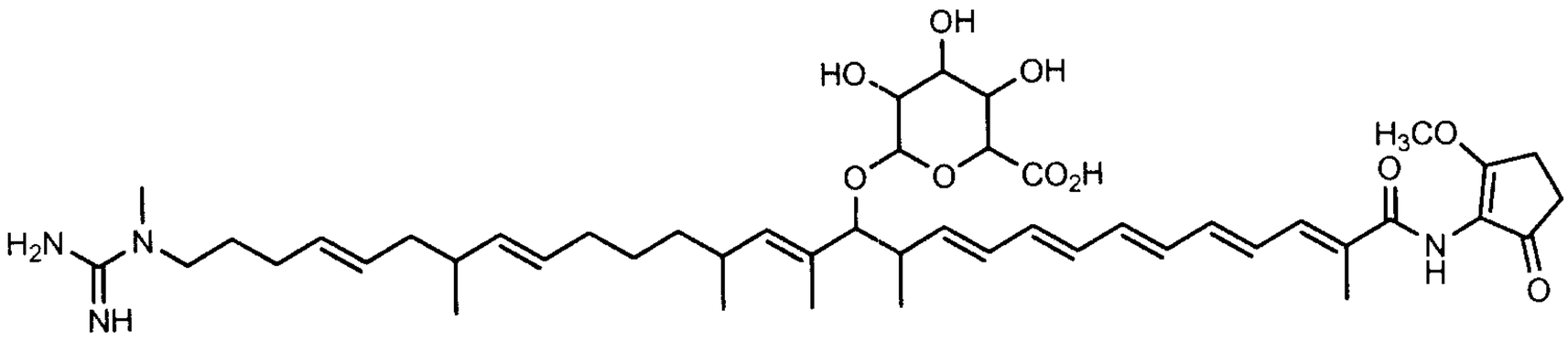
Compound 1;



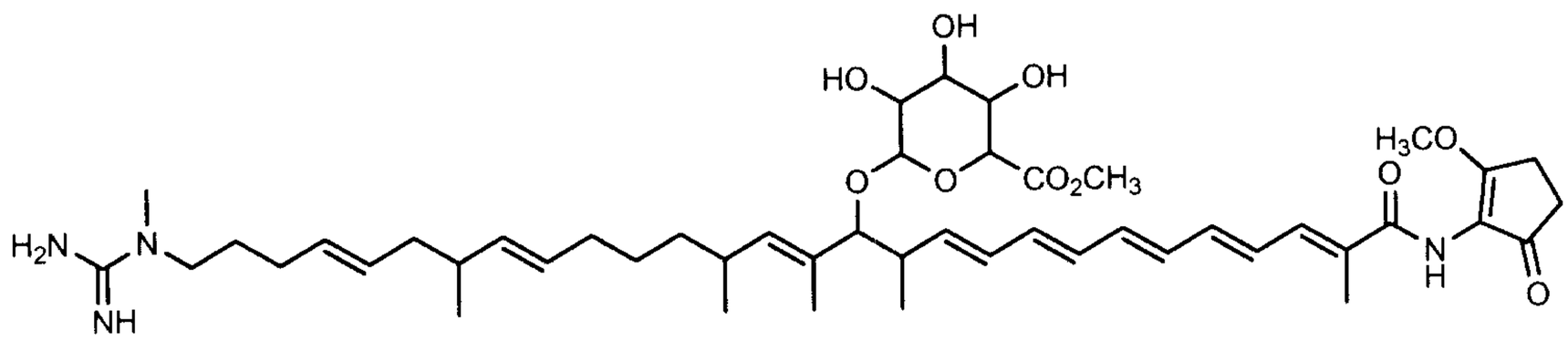
Compound 2;



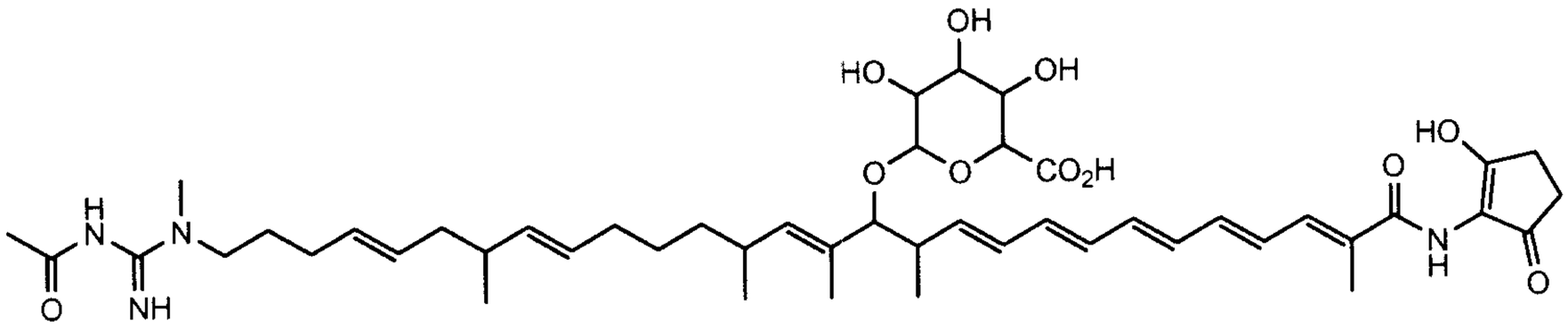
Compound 3;



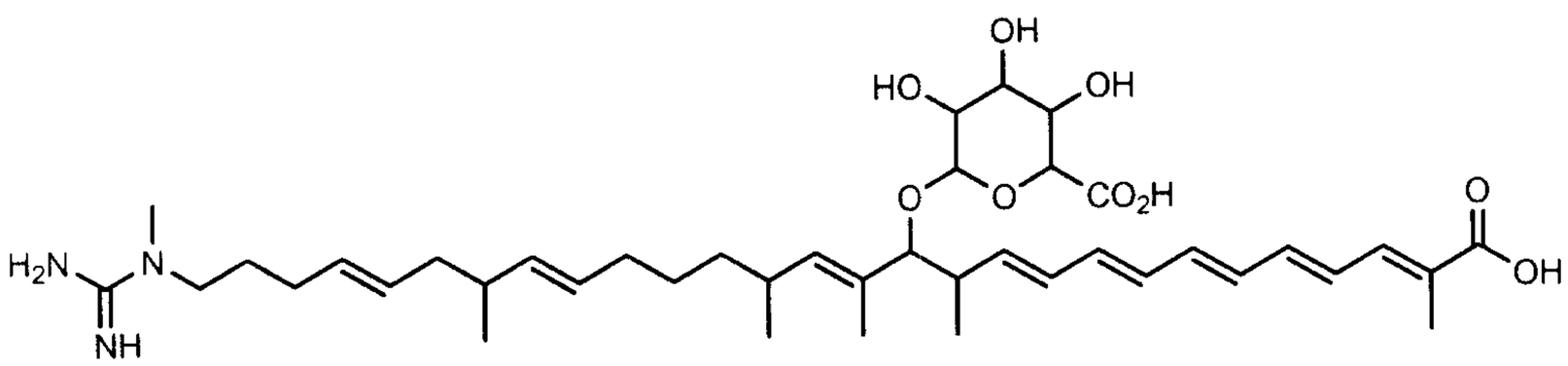
Compound 4;



Compound 5;



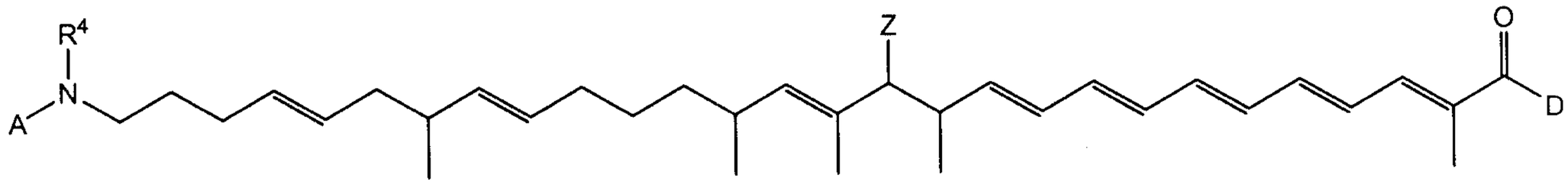
Compound 6;



Compound 7;

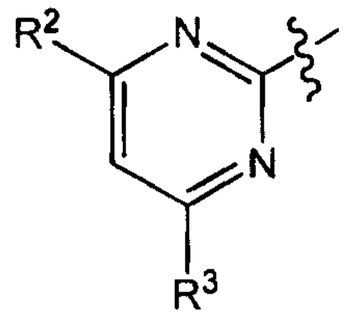
or a pharmaceutically acceptable salt or prodrug thereof.

In another aspect the invention provides polyene polyketides of Formula I, as illustrated below, which compounds may be derived by chemical modification of Compounds 1 to 7.



Formula I

wherein,
A is selected from $-C(NH)NHR^1$, CH_3, H or



;

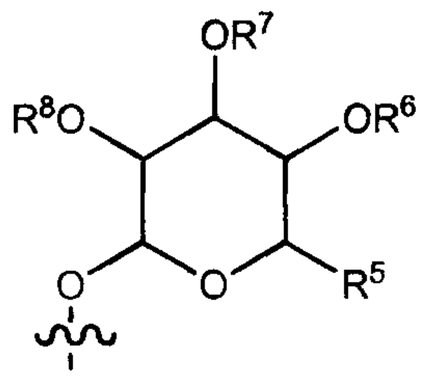
R^1 is selected from H, C_{1-6}alkyl, C_{6-10}aryl, $C(O)C_{1-6}$alkyl and $C(O)C_{6-10}$aryl;

R^2 and R^3 are each independently selected from H, C_{1-6} alkyl, C_{2-7} alkene and C_{6-10} aryl;

R^4 is selected from H or CH_3;

Z is OH or O when taken with adjacent carbon atom to form a carbonyl; or

Z may be a tetrahydropyranoxy of formula:



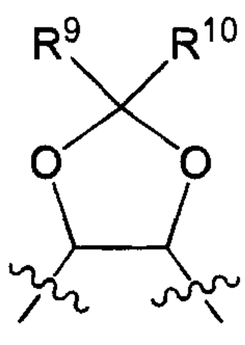
;

R^5 is selected from H, COOH, C_{1-6} alkyl or $C(O)OC_{1-6}$ alkyl;

R^6, R^7 and R^8 are each independently selected from H, C_{1-6} alkyl and $C(O)C_{1-6}$ alkyl; or

R^6 , R^7 and R^8 may each independently be absent when the adjacent oxygen and carbon atoms are taken together to form a carbonyl; or

R^6 , R^7 and R^8 may each independently be a bond when any of two neighboring R^6 , R^7 and R^8 are taken together with attached oxygen and carbon atoms to form a 1,3-dioxolane ring of formula:

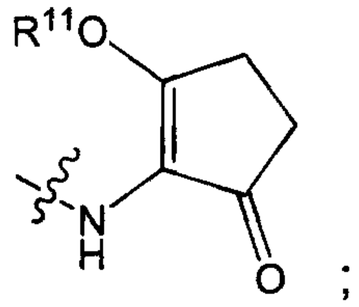


;

R^9 and R^{10} are each independently selected from H, C_{1-6} alkyl, C_{2-7} alkene and C_{6-10} aryl; or

R^9 and R^{10} are taken together with adjacent carbon atom to form a ring having from 5 to 7 carbons;

D is selected from OH, NH_2, $NH(C_{1-3}alkyl)$, $N(C_{1-3}alkyl)_2$, $OC_{1-3}alkyl$ or



;

R^{11} is selected from H or C_{1-3} alkyl;

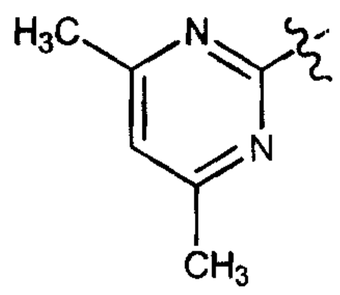
or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment the invention provides compounds of Formula I, wherein A is —$C(NH)NH_2$; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment of the invention provides compounds of Formula I, wherein A is H; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein A is —$C(NH)NHC(O)CH_3$; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein A is



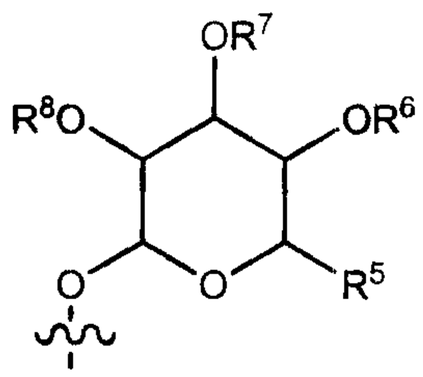
;

and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein R^4 is CH_3; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein R^4 is H; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

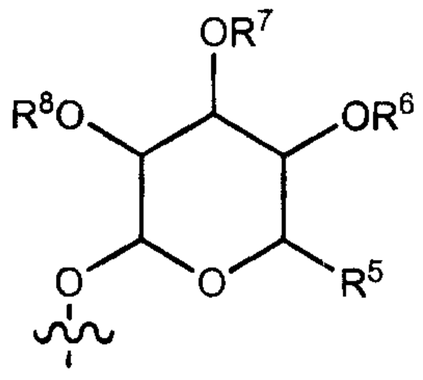
In a further embodiment the invention provides compounds of Formula I, wherein Z is



;

and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof. In a subclass of this embodiment R^6, R^7 and R^8 are each H, and R^5 is COOH, all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein Z is

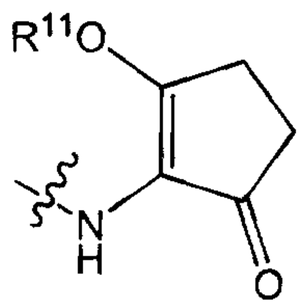


;

and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof. In a subclass of this embodiment R^6, R^7 and R^8 are each H, and R^5 is CO_2CH_3, all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein Z is OH and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

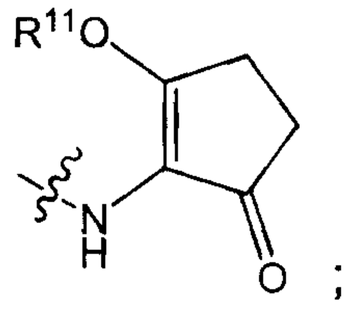
In a further embodiment the invention provides compounds of Formula I, wherein D is



;

and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof. In a subclass of this embodiment R^{11} is H and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein D is

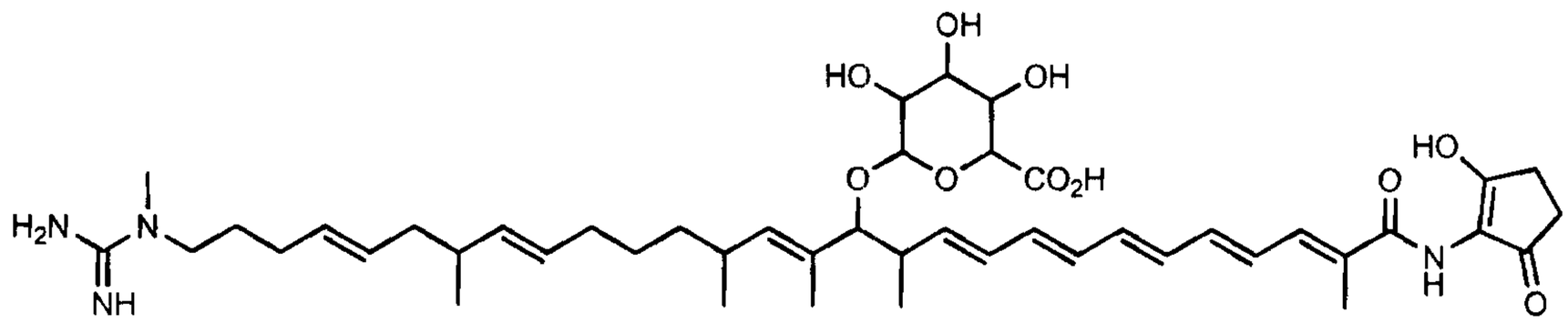


;

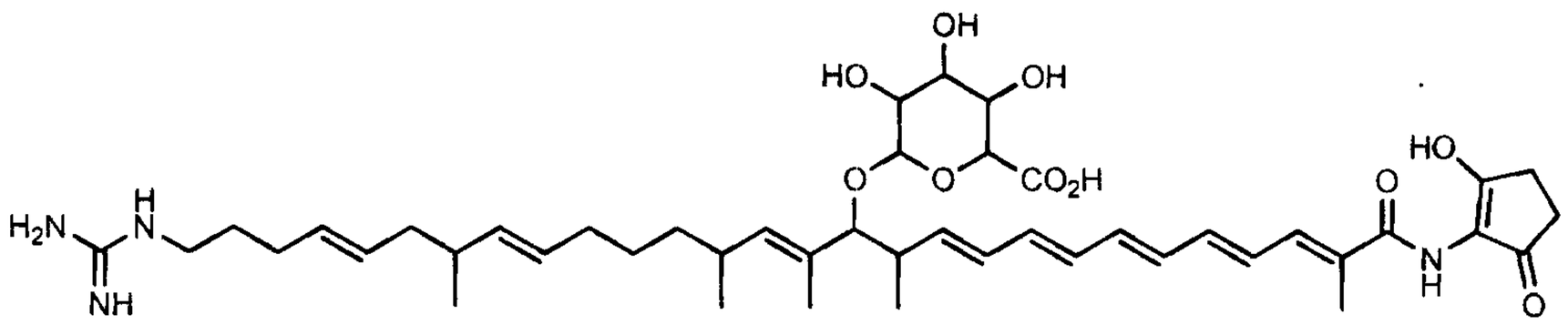
and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof. In a subclass of this embodiment R^{11} is CH_3 and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides compounds of Formula I, wherein D is OH; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

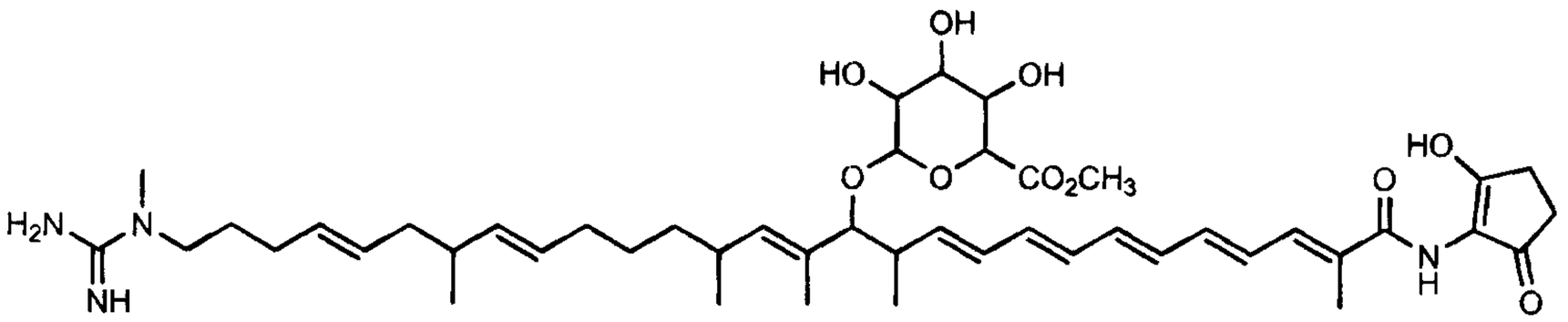
The following are exemplary compounds of the invention:



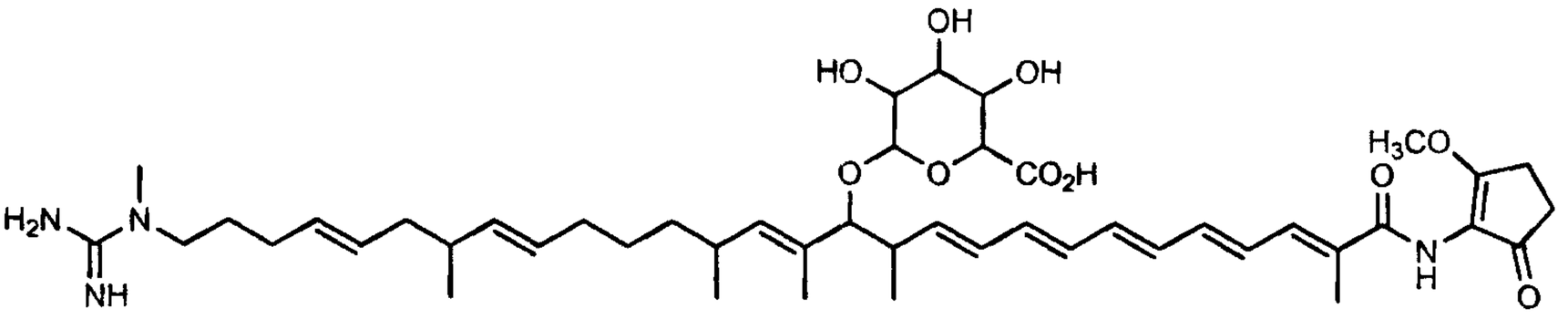
Compound 1;



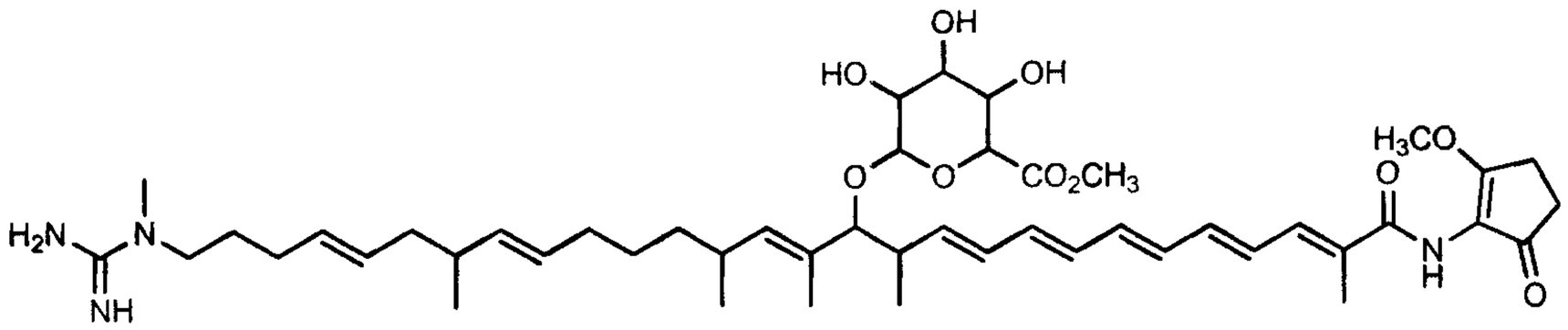
Compound 2;



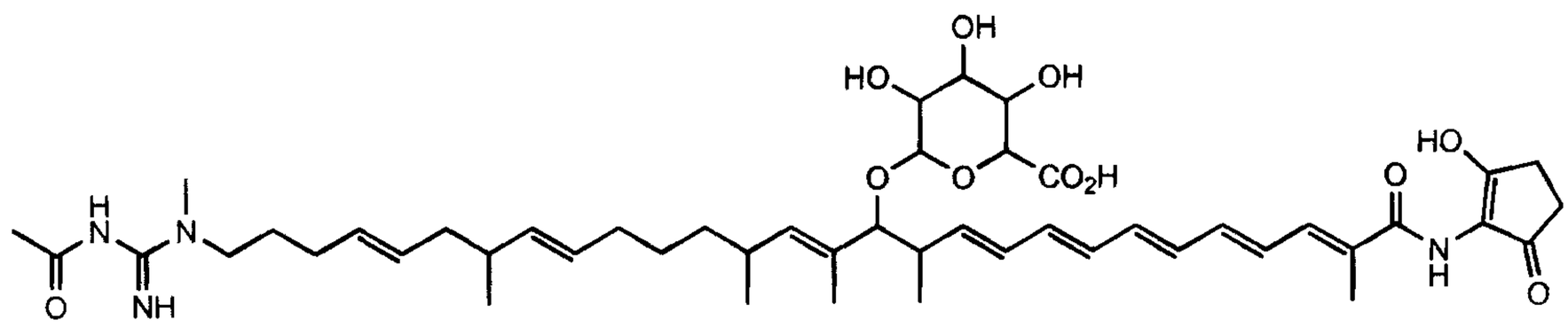
Compound 3;



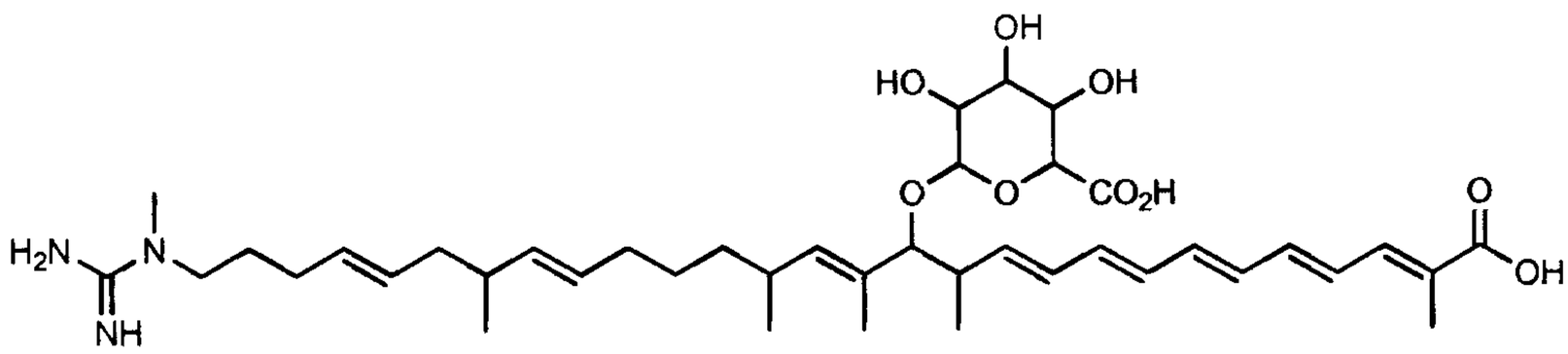
Compound 4;



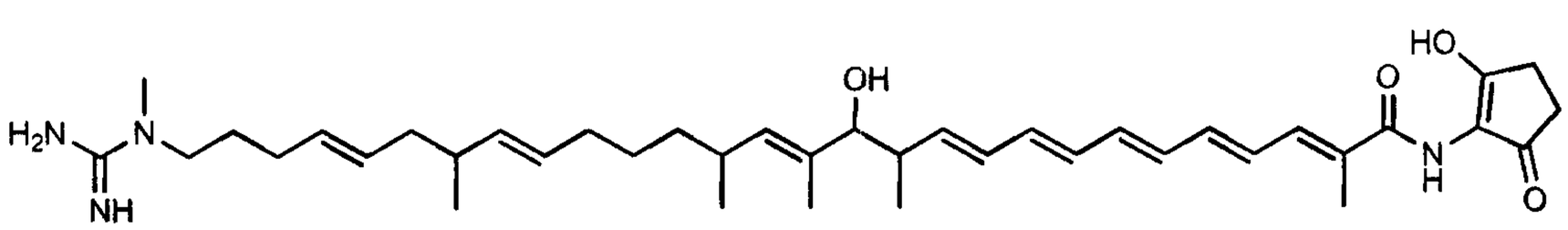
Compound 5;



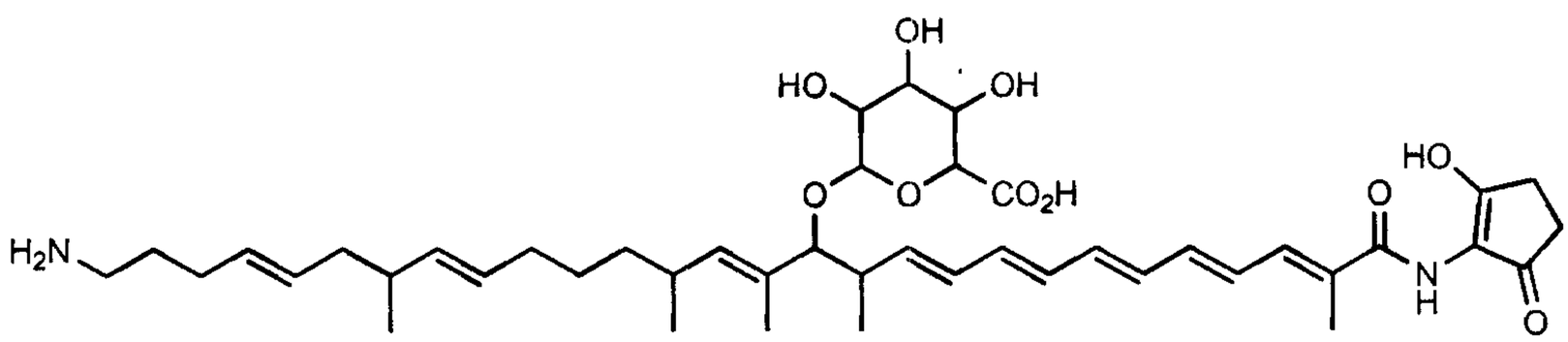
Compound 6;



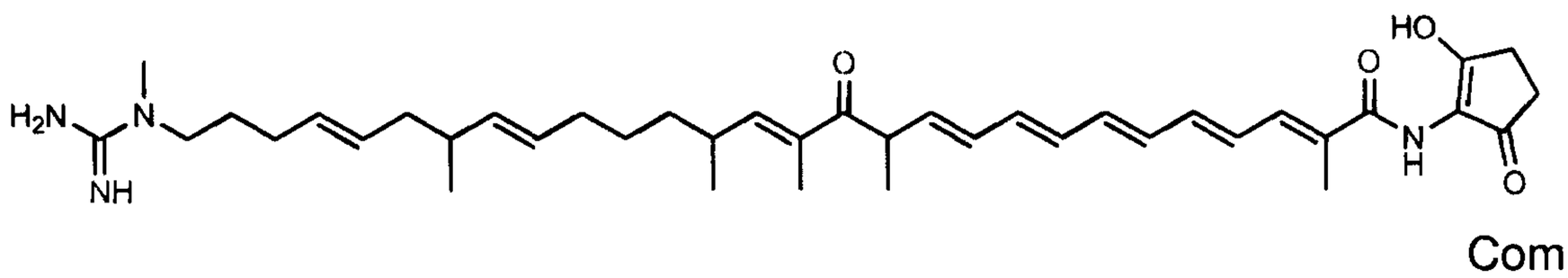
Compound 7;



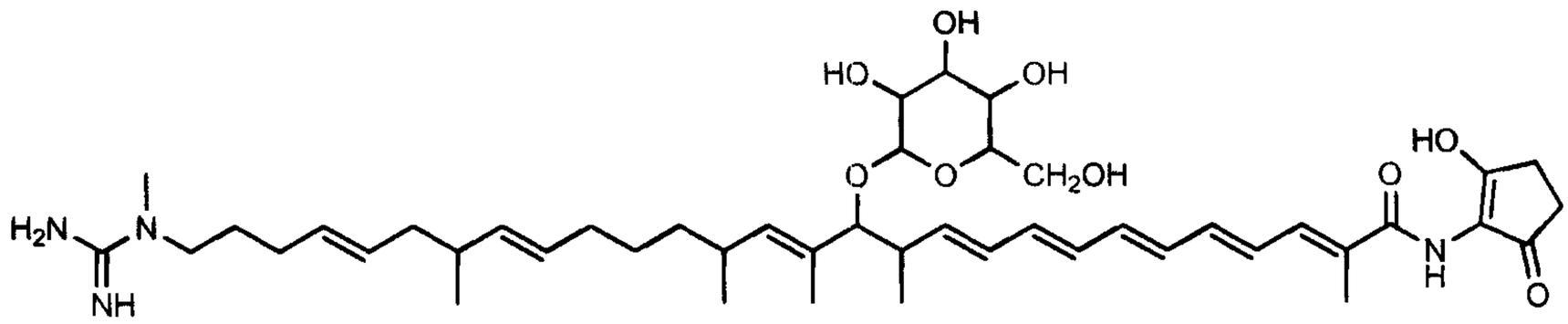
Compound 8;



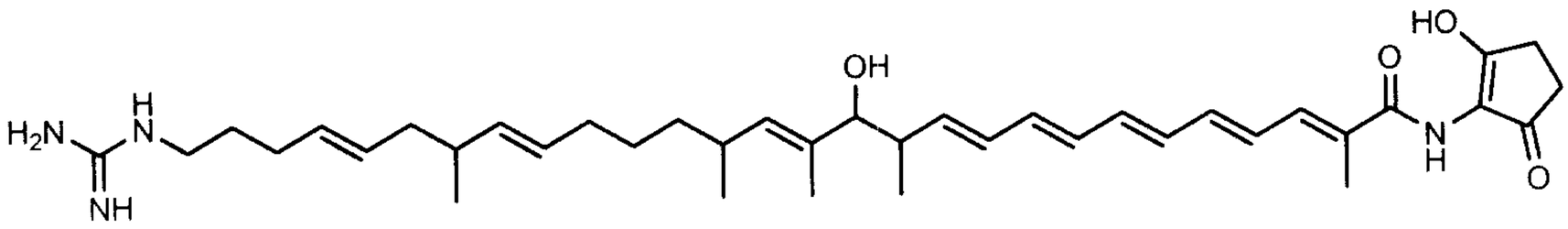
Compound 9;



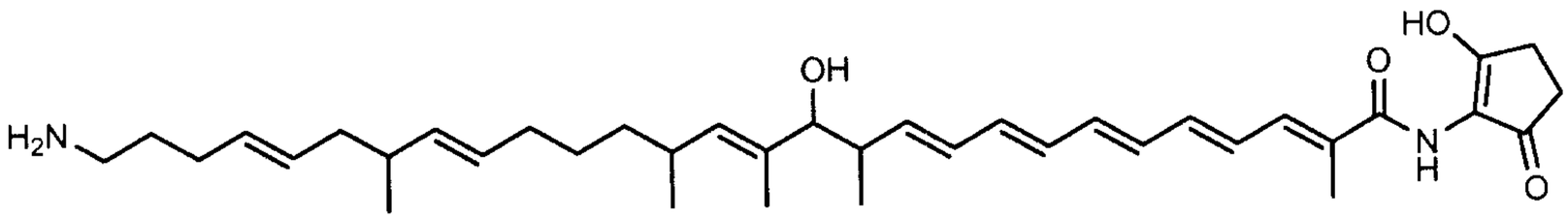
Compound 10;



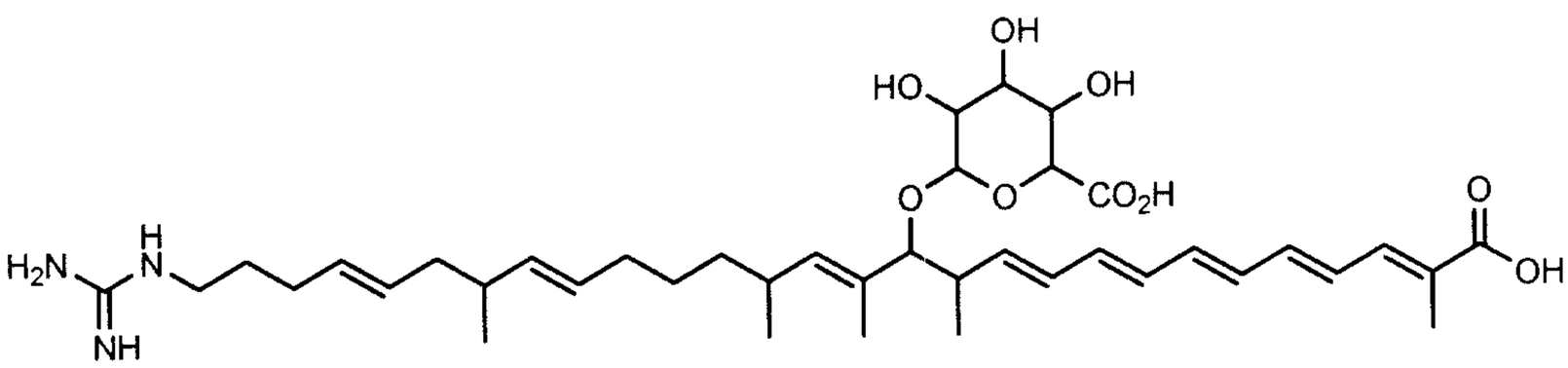
Compound 11;



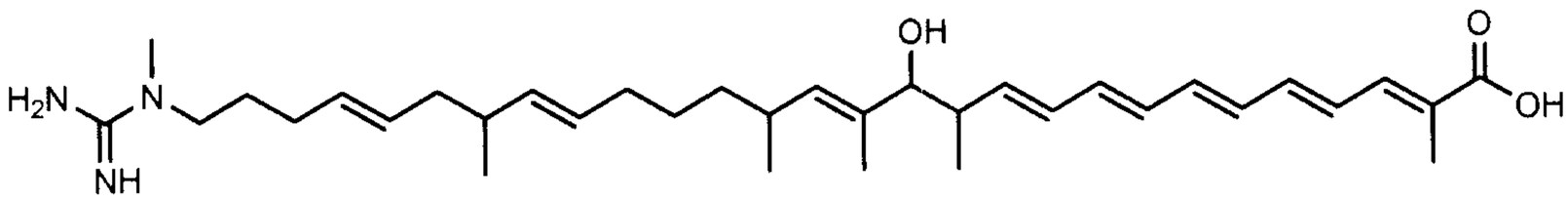
Compound 12;



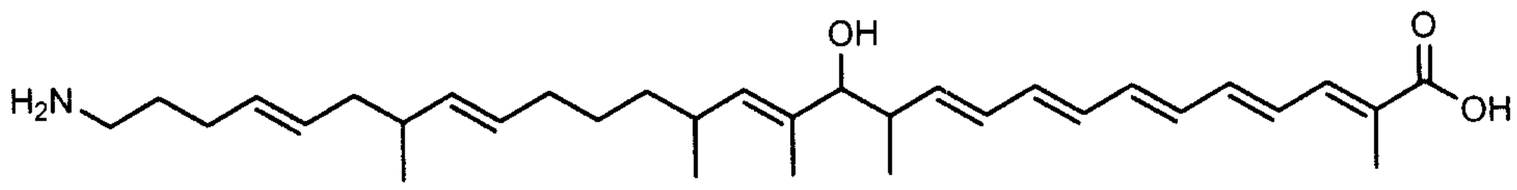
Compound 13;



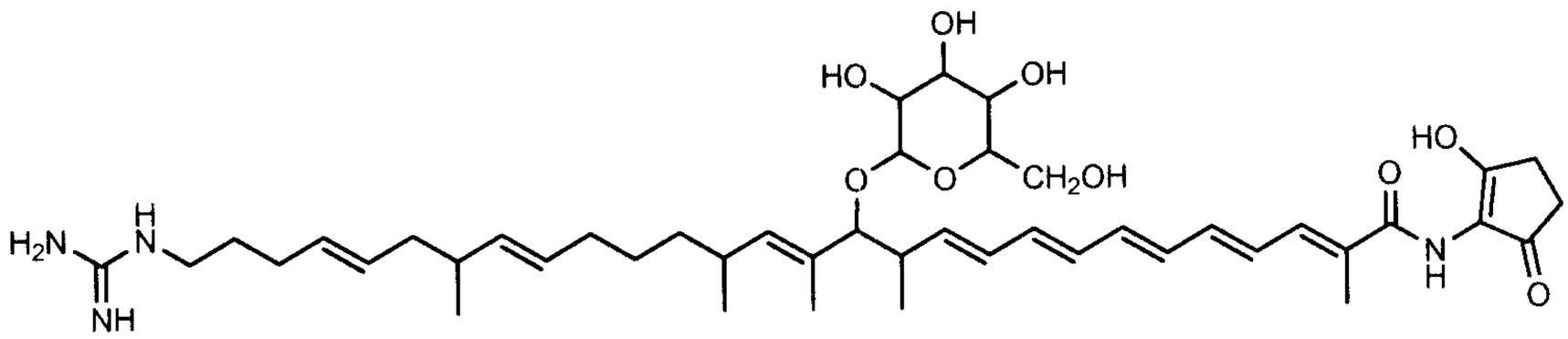
Compound 14;



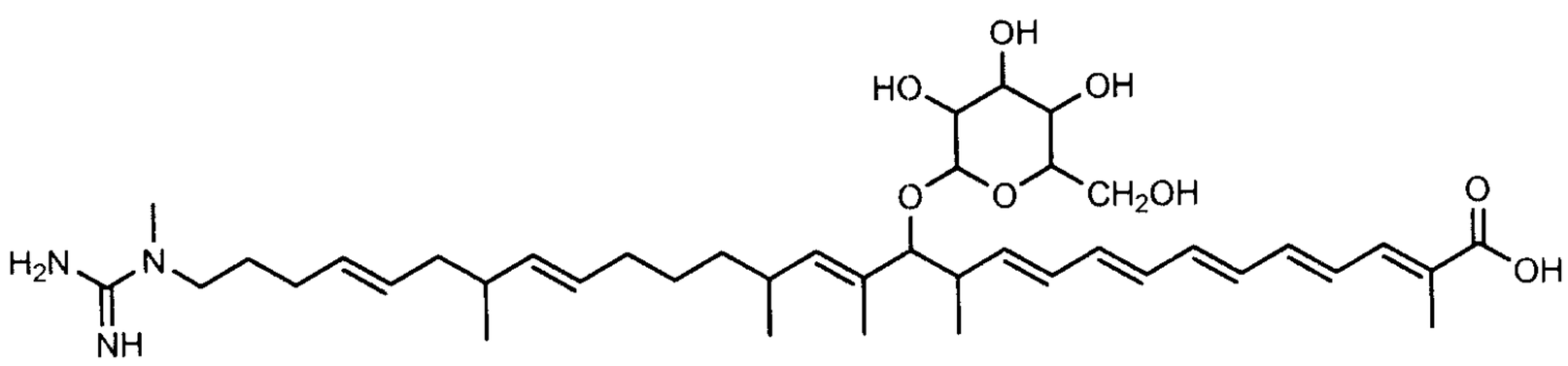
Compound 15;



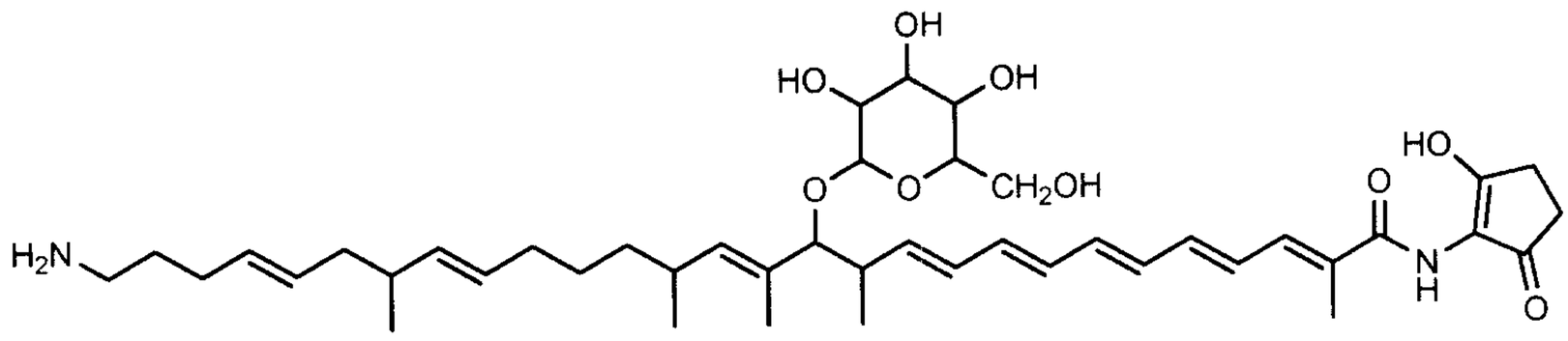
Compound 16;



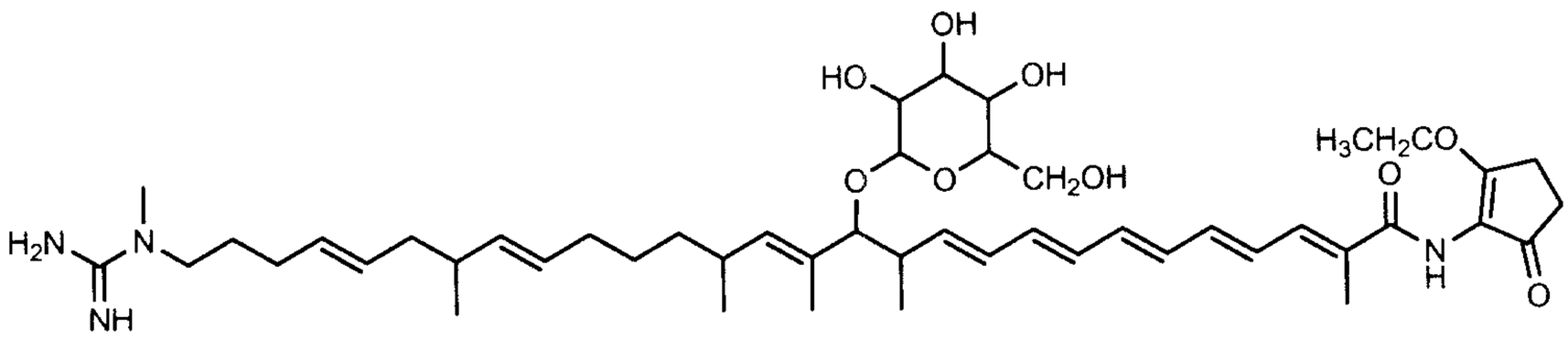
Compound 17;



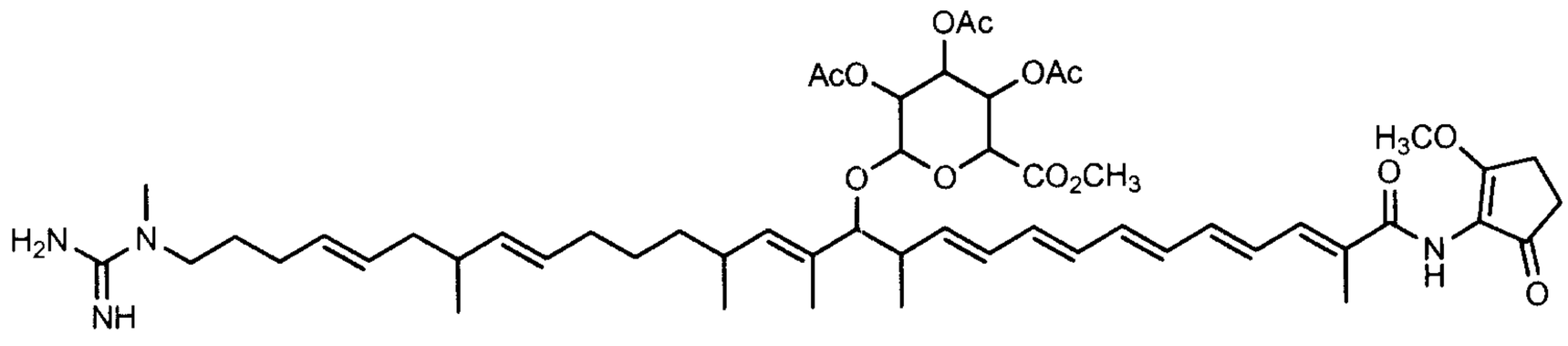
Compound 18;



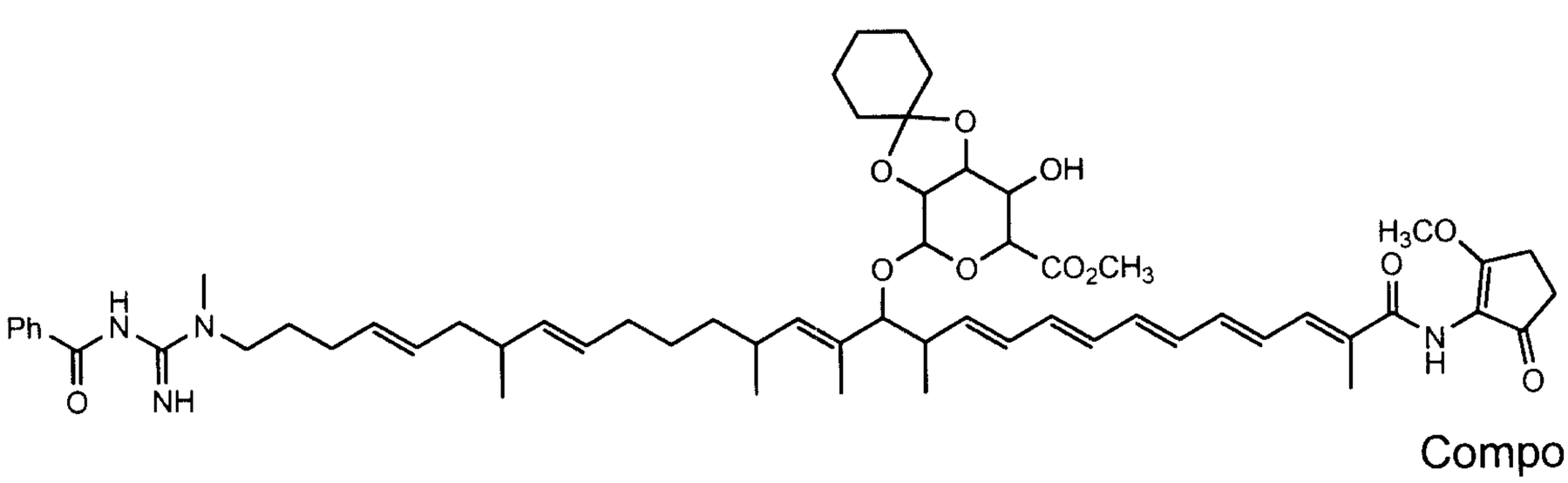
Compound 19;



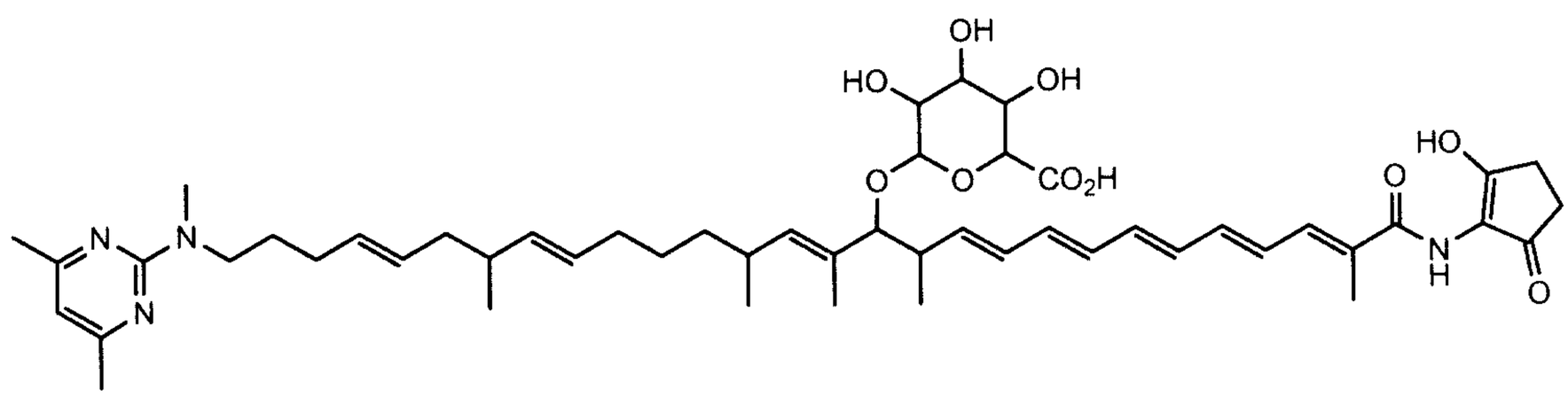
Compound 20;



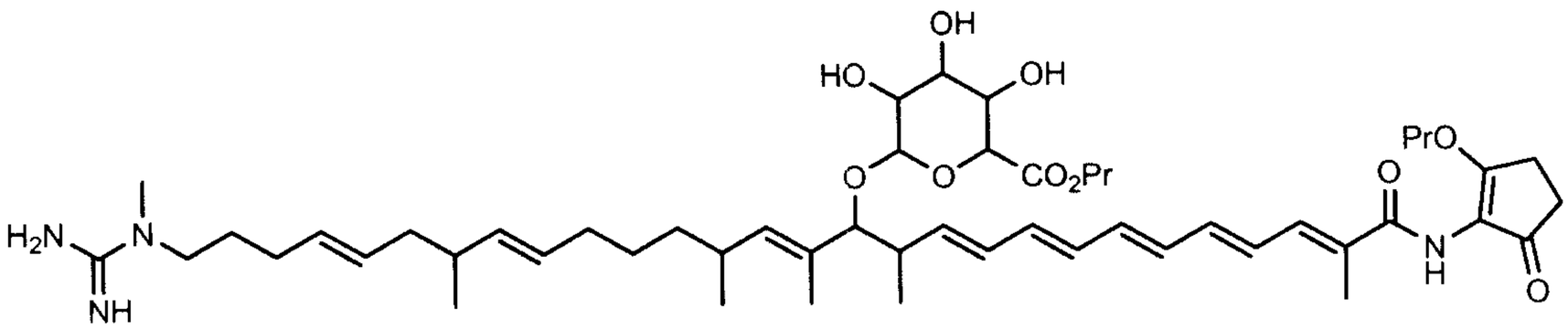
Compound 21;



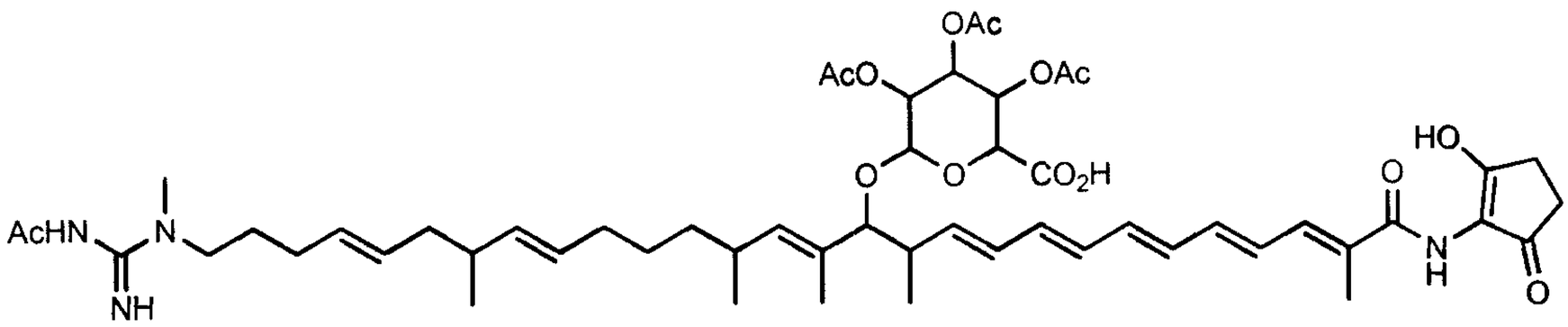
Compound 22;



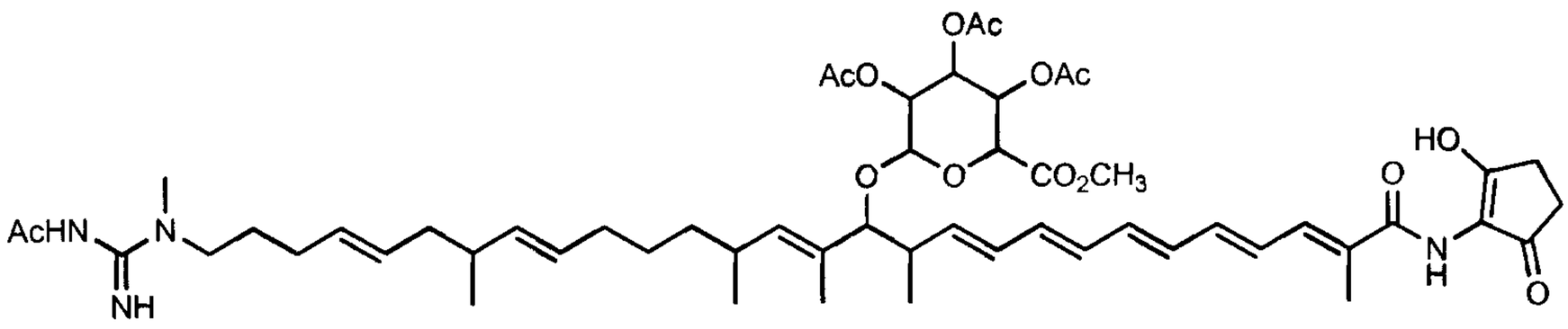
Compound 23;



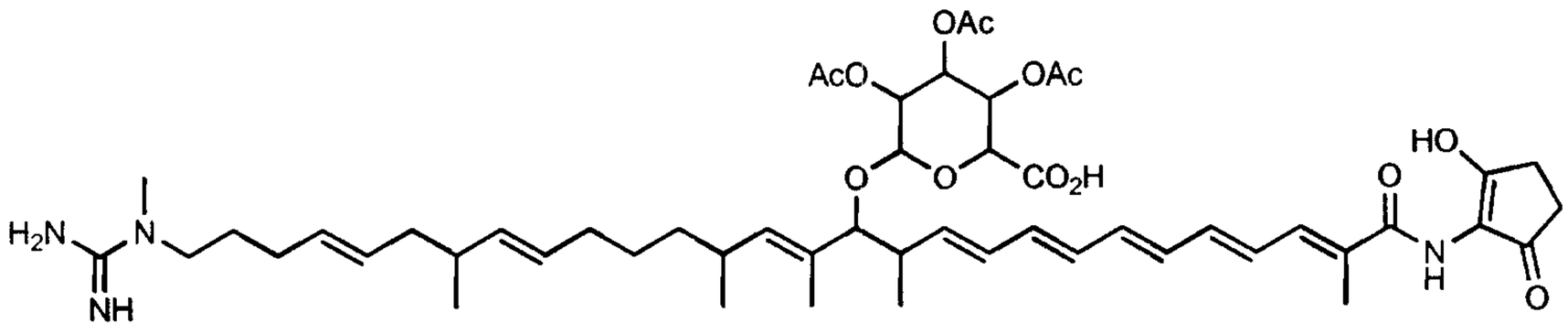
Compound 24;



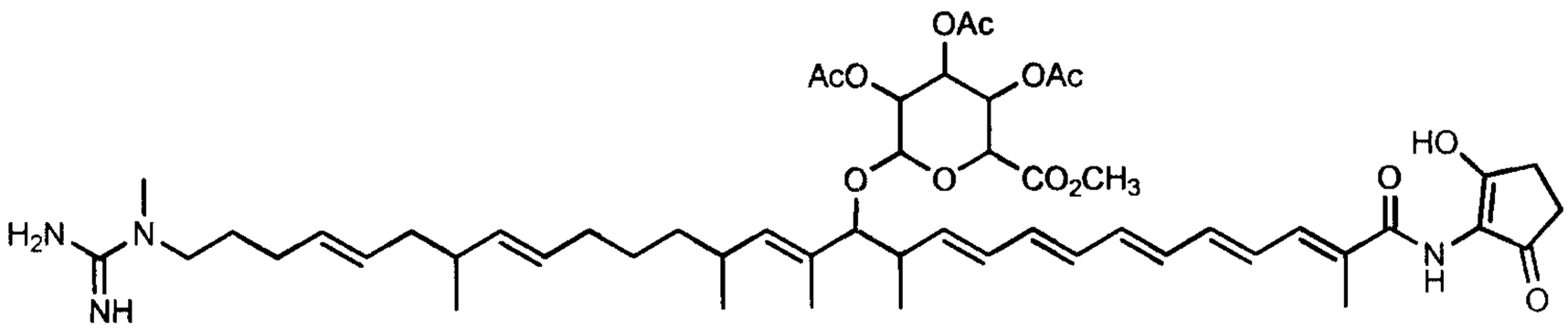
Compound 25;



Compound 26;



Compound 27 and



Compound 28;

or a pharmaceutically acceptable salt or prodrug of any one of Compound 1-28.

In a further aspect, the invention relates to a pharmaceutical composition comprising of a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, with a pharmaceutically acceptable carrier.

In an additional embodiment the invention relates to pharmaceutical compositions of polyene polyketides of the invention, comprising a therapeutically effective amount of the compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

The present invention further encompasses methods for producing the compounds of Formula I and related compounds, the method comprising: (a) cultivating

Amycolatopsis sp. strain under aerobic conditions in a nutrient medium comprising at least one source of carbon atoms and at least one source of nitrogen atoms, (b) isolating a compound of Formula I, from the bacteria cultivated in (a). In an aspect of the invention, the *Amycolatopsis orientalis* strain useful in the methods of the invention may be ATCC™ 43491 or a mutant thereof. In another embodiment, the strain is the *Amycolatopsis orientalis* strain deposited on June 22, 2004, at the International Depositary Authority of Canada (IDAC), Bureau of Microbiology, Health Canada, 1015 Arlington Street, Winnipeg, Manitoba, Canada R3E 3R2, and having accession no. 220604-01. In another aspect of the invention, the method of producing the compounds of Formula I comprises: (a) and (b) as described above and (c) chemically modifying the compound isolated in (b). In a further embodiment, the polyene polyketide generates a ^{1}H NMR spectra essentially as shown in any one of Figures 4 to 10. In a further embodiment, the polyene polyketide is any one of Compounds 1 to 7. In a further embodiment, the nutrient medium is selected from the media of Table 1.

The invention further provides a process for producing a polyene polyketide of the invention comprising cultivation of an *Amycolatopsis* strain in a nutrient medium comprising at least one source of carbon atoms and at least one source of nitrogen atoms, and isolation and purification of the polyene polyketide. In another embodiment, the strain is an *Amycolatopsis orientalis*. In a further embodiment, the strain is *Amycolatopsis orientalis* ATCC™ 43491 or a mutant thereof. In a further embodiment, the strain is the *Amycolatopsis orientalis* strain having accession no. 220604-01 deposited at the International Depositary Authority of Canada. In one embodiment, the carbon and nitrogen atoms sources are chosen from the components of Table 1. In a further embodiment, the nutrient medium is selected from the media of Table 1. In a further embodiment, the cultivation is carried out under aerobic conditions. In another embodiment, the cultivation is carried out at a temperature ranging from about 18°C to about 40°C. In another embodiment, the temperature range is 18°C to 29°C. In another embodiment, the cultivation is carried out at a pH ranging from about 6 to about 9.

The invention further provides polyene polyketides of Formula I that are a derivative or structural analog of any one of Compounds 1 to 7. In one embodiment the polyene polyketides of Formula I are produced by post-biosynthesis chemical modification of any one of Compounds 1 to 7. In another embodiment, the polyene

polyketides generate a ^{1}H NMR spectra essentially as shown in any one of Figures 4 to 10.

The invention further provides an *Amycolatopsis orientalis* strain having accession no. 220604-01 deposited at the International Depositary Authority of Canada.

The invention further provides Compounds 1 to 7, compounds of Formula I, or pharmaceutically acceptable salts or prodrugs thereof, for use as pharmaceuticals for the treatment of a bacterial infection in a subject. In another aspect, the invention provides the use of any one of Compounds 1 to 7, compounds of Formula I, or pharmaceutically acceptable salts or prodrugs thereof, for the manufacture of a medicament for the treatment of a bacterial infection in a subject.

The invention also provides methods of inhibiting bacterial cell growth, which comprise contacting said bacterial cell with a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof. The invention further encompasses methods for treating a bacterial infection in a subject, comprising administering to said subject suffering from said bacterial infection, a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof. Examples of bacteria organisms that may be treated or inhibited according to the methods of the invention include: *Streptococcus pneumoniae, Streptococcus pyogenes, Enterococcus faecalis*, *Enterococcus faecium, Klebsiella pneumoniae, Enterobacter spp., Proteus spp., Pseudomonas aeruginosa, E. coli, Serratia marcesens, Staphylococcus aureus,* Coagulase negative *Staphylococcus, Haemophilus infuenzae, Bacillus anthracis, Mycoplasma pneumoniae*, and *Staphylococcus epidermidis*.

The present invention also provides the biosynthetic locus responsible for producing the compounds of Formula I. Thus the invention provides polynucleotides and polypeptides useful in the production and engineering of compounds of Formula I. The present invention provides recombinant DNA vectors that encode all or part of the PKS enzymes useful for the production of polyketide compounds of Formula I. The invention also provides nucleic acid compounds that encode the specific domains of the PKS system useful for the production of polyketides of compound of Formula I. The recombinant DNA vectors, PKS enzymes, PKS systems and nucleic acid compounds encoding the domains of the PKS systems of the invention can be readily used, alone or in combination with nucleic acids encoding other PKS

domains, as intermediates in the construction of recombinant vectors that encode all or part of PKS enzymes that make novel polyketides selected from the compounds of Formula I.

The invention also provides isolated nucleic acids that encode all or part of one or more modules of the PKSs of the invention, each module comprising a ketosynthase activity, an acyl transferase activity, and an acyl carrier protein activity. The invention also provides isolated nucleic acids that encode all or part of a PKS loader module comprising an acyl transferase activity and an acyl carrier protein activity. Thus, in one aspect, the invention provides an isolated, purified or enriched nucleic acid encoding a domain of a polyketide synthase system for production of a polyene polyketide of claim 1, said nucleic acid comprising a sequence selected from the group consisting of: a nucleic acid encoding the acyl carrier protein of residues 47-109 of SEQ ID NO: 38; a nucleic acid encoding an acyl carrier protein having at least 69% identity to residues 47-109 of SEQ ID NO: 38; a nucleic acid encoding the acyl carrier protein of residues 1691-1753 of SEQ ID NO: 38; a nucleic acid encoding an acyl carrier protein having at least 73% identity to residues 1691-1753 of SEQ ID NO: 38; a nucleic acid encoding the acyl carrier protein of residues 3696-3758 of SEQ ID NO: 38; a nucleic acid encoding an acyl carrier protein having at least 77% identity to residues 3696-3758 of SEQ ID NO: 38; a nucleic acid encoding the acyl carrier protein of residues 1574-1636 of SEQ ID NO: 40; a nucleic acid encoding an acyl carrier protein having at least 78% identity to residues 1574-1636 of SEQ ID NO: 40; a nucleic acid encoding the acyl carrier protein of residues 3545-3607 of SEQ ID NO: 40; a nucleic acid encoding an acyl carrier protein having at least 76% identity to residues 3545-3607 of SEQ ID NO: 40; a nucleic acid encoding the acyl carrier protein of residues 5577-5639 of SEQ ID NO: 40; a nucleic acid encoding an acyl carrier protein having at least 78% identity to residues 5577-5639 of SEQ ID NO: 40; a nucleic acid encoding the acyl carrier protein of residues 1593-1655 of SEQ ID NO: 42; a nucleic acid encoding an acyl carrier protein having at least 76% identity to 1593-1655 of SEQ ID NO: 42; a nucleic acid encoding the acyl carrier protein of residues 1444-1506 of SEQ ID NO: 44; a nucleic acid encoding an acyl carrier protein having at least 82% identity to residues 1444-1506 of SEQ ID NO: 44; a nucleic acid encoding the acyl carrier protein of residues 3122-3184 of SEQ ID NO: 44; a nucleic acid encoding an acyl carrier protein having at least 69% identity to

residues 3122-3184 of SEQ ID NO: 44; a nucleic acid encoding the acyl carrier protein of residues 1597-1659 of SEQ ID NO: 46; a nucleic acid encoding an acyl carrier protein having at least 73% identity to residues 1597-1659 of SEQ ID NO: 46; a nucleic acid encoding the acyl carrier protein of residues 3235-3297 of SEQ ID NO: 46; a nucleic acid encoding an acyl carrier protein having at least 71% identity to residues 3235-3297 of SEQ ID NO: 46; a nucleic acid encoding the acyl carrier protein of residues 4956-5018 of SEQ ID NO: 46; a nucleic acid encoding an acyl carrier protein having at least 72% identity to residues 4956-5018 of SEQ ID NO: 38; a nucleic acid encoding the acyl carrier protein of residues 1582-1644 of SEQ ID NO: 48; a nucleic acid encoding an acyl carrier protein having at least 75% identity to residues 1582-1644 of SEQ ID NO: 48; a nucleic acid encoding the ketosynthase domain of residues 130-554 of SEQ ID NO: 38; a nucleic acid encoding a ketosynthase domain having at least 76% identity to residues 130-554 of SEQ ID NO: 38; a nucleic acid encoding the ketosynthase domain of residues 1771-2195 of SEQ ID NO: 38, a nucleic acid encoding a ketosynthase domain having at least 78% identity to residues 1771-2195 of SEQ ID NO: 38; a nucleic acid encoding the ketosynthase domain of residues 39-463 of SEQ ID NO: 40; a nucleic acid encoding a ketosynthase domain having at least 77% identity to residues 39-463 of SEQ ID NO: 40; a nucleic acid encoding the ketosynthase domain of residues 1657-2082 of SEQ ID NO: 40; a nucleic acid encoding a ketosynthase domain having at least 80% identity to residues 1657-2082 of SEQ ID NO: 40; a nucleic acid encoding the ketosynthase domain of residues 3628-4052 of SEQ ID NO: 40; a nucleic acid encoding a ketosynthase domain having at least 78% identity to residues 3628-4052 of SEQ ID NO: 40; a nucleic acid encoding the ketosynthase domain of residues 34-458 of SEQ ID NO: 42; a nucleic acid encoding a ketosynthase domain having at least 77% identity to residues 34-458 of SEQ ID NO: 42; a nucleic acid encoding the ketosynthase domain of residues 34-461 of SEQ ID NO: 44; a nucleic acid encoding a ketosynthase domain having at least 78% identity to residues 34-461of SEQ ID NO: 44; a nucleic acid encoding the ketosynthase domain of residues 1528-1952 of SEQ ID NO: 44; a nucleic acid encoding a ketosynthase domain having at least 76% identity to residues 1528-1952 of SEQ ID NO: 44; a nucleic acid encoding the ketosynthase domain of residues 34-460 of SEQ ID NO: 46; a nucleic acid encoding a ketosynthase domain having at least 77% identity to residues 34-460 of SEQ ID

NO: 46; a nucleic acid encoding the ketosynthase domain of residues 1682-2104 of SEQ ID NO: 46; a nucleic acid encoding a ketosynthase domain having at least 79% identity to residues 1682-2104 of SEQ ID NO: 46; a nucleic acid encoding the ketosynthase domain of residues 3317-3741 of SEQ ID NO: 46; a nucleic acid encoding a ketosynthase domain having at least 79% identity to residues 3317-3741 of SEQ ID NO: 46; a nucleic acid encoding the ketosynthase domain of residues 34-461 of SEQ ID NO: 48; a nucleic acid encoding a ketosynthase domain having at least 78% identity to residues 35-461of SEQ ID NO: 48; a nucleic encoding the acyl transferase domain of residues 567-990 of SEQ ID NO: 38; a nucleic acid encoding an acyl transferase domain having at least 58%identity to residues 567-990 of SEQ ID NO: 38; a nucleic acid encoding the acyl transferase domain of residues 2211-2638 of SEQ ID NO: 38; a nucleic acid encoding an acyl transferase domain having at least 57% identity to residues 2211-2638 of SEQ ID NO: 38; a nucleic encoding the acyl transferase domain of residues 474-872 of SEQ ID NO: 40; a nucleic acid encoding an acyl transferase domain having at least 60%identity to residues 474-872 of SEQ ID NO: 38; a nucleic encoding the acyl transferase domain of residues 2093-2495 of SEQ ID NO: 40; a nucleic acid encoding an acyl transferase domain having at least 61%identity to residues 2093-2495 of SEQ ID NO: 40; a nucleic encoding the acyl transferase domain of residues 4068-4489 of SEQ ID NO: 40; a nucleic acid encoding an acyl transferase domain having at least 59%identity to residues 4068-4489 of SEQ ID NO: 40; a nucleic encoding the acyl transferase domain of residues 475-892 of SEQ ID NO: 42; a nucleic acid encoding an acyl transferase domain having at least 57% identity to residues 475-892 of SEQ ID NO: 42; a nucleic encoding the acyl transferase domain of residues 478-905 of SEQ ID NO: 44; a nucleic acid encoding an acyl transferase domain having at least 58% identity to residues 478-905 of SEQ ID NO: 44; a nucleic encoding the acyl transferase domain of residues 1963-2383 of SEQ ID NO: 44; a nucleic acid encoding an acyl transferase domain having at least 58% identity to residues 1963-2383 of SEQ ID NO: 44; a nucleic encoding the acyl transferase domain of residues 472-883 of SEQ ID NO: 46; a nucleic acid encoding an acyl transferase domain having at least 61% identity to residues 472-883 of SEQ ID NO: 46; a nucleic encoding the acyl transferase domain of residues 2115-2523 of SEQ ID NO: 46; a nucleic acid encoding an acyl transferase domain having at least 63% identity to residues 2115-

2523 of SEQ ID NO: 46; a nucleic encoding the acyl transferase domain of residues 3752-4181 of SEQ ID NO: 46; a nucleic acid encoding an acyl transferase domain having at least 59% identity to residues 3752-4181 of SEQ ID NO: 46; a nucleic encoding the acyl transferase domain of residues 475-883 of SEQ ID NO: 48; a nucleic acid encoding an acyl transferase domain having at least 57% identity to residues 475-883 of SEQ ID NO: 48; a nucleic acid encoding the dehydratase domain of residues 1001-1101 of SEQ ID NO: 38; a nucleic acid encoding a dehydratase domain of having at least 64% identity to residues 1001-1101 of SEQ ID NO: 38; a nucleic acid encoding the dehydratase domain of residues 2647-2753 of SEQ ID NO: 38; a nucleic acid encoding a dehydratase domain of residues 2647-2753 of SEQ ID NO: 38; a nucleic acid encoding the dehydratase domain of residues 883-990 of SEQ ID NO: 40; a nucleic acid encoding a dehydratase domain of having at least 67% identity to residues 883-990 of SEQ ID NO: 40; a nucleic acid encoding the dehydratase domain of residues 2507-2614 of SEQ ID NO: 40; a nucleic acid encoding a dehydratase domain of having at least 69% identity to residues 2507-2614 of SEQ ID NO: 40; a nucleic acid encoding the dehydratase domain of residues 4497-4604 of SEQ ID NO: 40; a nucleic acid encoding a dehydratase domain of having at least 56% identity to residues 4497-4604 of SEQ ID NO: 40; a nucleic acid encoding the dehydratase domain of residues 901-1006 of SEQ ID NO: 42; a nucleic acid encoding a dehydratase domain of having at least 64% identity to residues 901-1006 of SEQ ID NO: 42; a nucleic acid encoding the dehydratase domain of residues 2395-2502 of SEQ ID NO: 44; a nucleic acid encoding a dehydratase domain of having at least 63% identity to residues 2395-2502 of SEQ ID NO: 44; a nucleic acid encoding the dehydratase domain of residues 895-1002 of SEQ ID NO: 46; a nucleic acid encoding a dehydratase domain of having at least 65% identity to residues 895-1002 of SEQ ID NO: 46; a nucleic acid encoding the dehydratase domain of residues 2534-2641 of SEQ ID NO: 46; a nucleic acid encoding a dehydratase domain of having at least 66% identity to residues 2534-2641 of SEQ ID NO: 46; a nucleic acid encoding the dehydratase domain of residues 4193-4300 of SEQ ID NO: 46; a nucleic acid encoding a dehydratase domain of having at least 65% identity to residues 4193-4300 of SEQ ID NO: 46; a nucleic acid encoding the dehydratase domain of residues 892-999 of SEQ ID NO: 48; a nucleic acid encoding a dehydratase domain of having at least 61% identity to residues 892-999 of SEQ ID

NO: 61; a nucleic acid encoding the ketoreductase domain of residues 1421-1628 of SEQ ID NO: 38; a nucleic acid encoding a ketoreductase domain having at least 62% identity to residues 1421-1628 of SEQ ID NO: 38; a nucleic acid encoding the ketoreductase domain of residues 3405-3622 of SEQ ID NO: 38; a nucleic acid encoding a ketoreductase domain having at least 69% identity to residues 3405-3622 of SEQ ID NO: 38; a nucleic acid encoding the ketoreductase domain of residues 1291-1501 of SEQ ID NO: 40; a nucleic acid encoding a ketoreductase domain having at least 64% identity to residues 1291-1501 of SEQ ID NO: 40; a nucleic acid encoding the ketoreductase domain of residues 3253-3470 of SEQ ID NO: 40; a nucleic acid encoding a ketoreductase domain having at least 69% identity to residues 3253-3470 of SEQ ID NO: 40; a nucleic acid encoding the ketoreductase domain of residues 5285-5502 of SEQ ID NO: 40; a nucleic acid encoding a ketoreductase domain having at least 71% identity to residues 5285-5502 of SEQ ID NO: 40; a nucleic acid encoding the ketoreductase domain of residues 1309-1517 of SEQ ID NO: 42; a nucleic acid encoding a ketoreductase domain having at least 62% identity to residues 1309-1517 of SEQ ID NO: 42; a nucleic acid encoding the ketoreductase domain of residues 1157-1366 of SEQ ID NO: 44; a nucleic acid encoding a ketoreductase domain having at least 69% identity to residues 1157-1366 of SEQ ID NO: 44; a nucleic acid encoding the ketoreductase domain of residues 2837-3048 of SEQ ID NO: 44; a nucleic acid encoding a ketoreductase domain having at least 67% identity to residues 2837-3048 of SEQ ID NO: 44; a nucleic acid encoding the ketoreductase domain of residues 1323-1523 of SEQ ID NO: 46; a nucleic acid encoding a ketoreductase domain having at least 63% identity to residues 1323-1523 of SEQ ID NO: 46; a nucleic acid encoding the ketoreductase domain of residues 2957-3166 of SEQ ID NO: 46; a nucleic acid encoding a ketoreductase domain having at least 65% identity to residues 2957-3166 of SEQ ID NO: 46; a nucleic acid encoding the ketoreductase domain of residues 4669-4879 of SEQ ID NO: 46; a nucleic acid encoding a ketoreductase domain having at least 66% identity to residues 4669-4879 of SEQ ID NO: 66; a nucleic acid encoding the ketoreductase domain of residues 1305-1512 of SEQ ID NO: 48; a nucleic acid encoding a ketoreductase domain having at least 61% identity to residues 1305-1512 of SEQ ID NO: 48; a nucleic acid encoding the enoyl reductase domain of residues 3060-3401 of SEQ ID NO: 38; a nucleic acid encoding an enoyl reductase domain

having at least 62% identity to residues 3060-3401 of SEQ ID NO: 38; a nucleic acid encoding the enoyl reductase domain of residues 2908-3249 of SEQ ID NO: 40; a nucleic acid encoding an enoyl reductase domain having at least 65% identity to residues 2908-3249 of SEQ ID NO: 40; a nucleic acid encoding the enoyl reductase domain of residues 4933-5281 of SEQ ID NO: 40; a nucleic acid encoding an enoyl reductase domain having at least 64% identity to residues 4933-5281 of SEQ ID NO: 40; a nucleic acid encoding the thioesterase domain of residues 1709-1921 of SEQ ID NO: 48; a nucleic acid encoding a thioesterase domain having at least 47% identity to residues 1709-1921 of SEQ ID NO: 48.

The invention provides an isolated nucleic acid that encodes one or more open reading frames of PKS genes of the invention. Thus, in one aspect, the invention provides an isolated, purified or enriched nucleic acid encoding a polyketide synthase, useful in the production of polyene polyketide, said nucleic comprising a sequence selected from the group consisting of SEQ ID NOS: 38, 40, 42, 44, 46, 48 and a nucleic acid encoding a polyketide synthase selected from SEQ ID NOS: 37, 39, 41, 43, 45, 47 and a nucleic acid having at least 80% identity to a nucleic acid of a) or b). The invention also provides recombinant expression vectors containing these nucleic acids.

The invention provides a method of preparing polyketide compounds of Formula I, said method comprising transforming a host cell with a recombinant DNA vector that encodes at least one module of a PKS, said method comprising transforming a host cell with a recombinant DNA vector that encodes at least one module of a PKS, said module comprising at least one PKS domain of the invention, and culturing said host cell under conditions such that said PKS is produced and catalyzes synthesis of said polyketide. The invention also provides a method of preparing polyketide compounds of Formula I, said method comprising transforming a host cell with a recombinant DNA vector that encodes at least one gene of the invention, and culturing said host cell under conditions such that said polyketide is produced. In one aspect, the method is practiced with a *Streptomyces* host cell. In another aspect, the polyketide produced is a compound of Formula I. In another aspect, the polyketide produced is a polyketide related in structure to a compound described in any one of Examples 17 to 20.

The invention provides a set of genes in recombinant form sufficient for the synthesis of a compound of Formula I in a heterologous host cell. These genes and the methods of the invention enable one to create recombinant host cells with the ability to produce polyketides.

The invention provides recombinant PKS genes that produce a variety of polyketides that cannot be readily synthesized by chemical methodology alone. Moreover the present invention provides polyketides, some of which are produced only by fermentation and others of which are produced by fermentation and chemical modification. The invention allows direct manipulation of the genes and proteins for production of the compounds of Formula I via genetic engineering of the enzymes involved in the biosynthesis of a polyketide according to the invention.

The present invention provides recombinant DNA vectors that encode all or part of the PKS enzymes useful for the production of a polyketide of Formula I. The invention also provides nucleic acid compounds that encode the various domains of PKS systems useful for the production of a polyketide of Formula I. The recombinant DNA vectors, PKS enzymes, PKS systems and nucleic acid compounds encoding the domains of the PKS systems of the invention can be readily used, alone or in combination with nucleic acids encoding other PKS domains, as intermediates in the construction of recombinant vectors that encode all or part of PKS enzymes that make novel polyketides selected from the compounds of Formula I.

The invention also provides isolated nucleic acids that encode all or part of one or more modules of the PKSs of the invention, each module comprising a ketosynthase activity, an acyl transferase activity, and an acyl carrier protein activity. The invention also provides isolated nucleic acids that encode all or part of a PKS loader module comprising an acyl transferase activity and an acyl carrier protein activity. The invention provides an isolated nucleic acid that encodes one or more open reading frames of PKS genes of the invention. The invention also provides recombinant expression vectors containing these nucleic acids.

The invention provides a method of preparing a polyketide of Formula I, said method comprising transforming a host cell with a recombinant DNA vector that encodes at least one module of a PKS, said method comprising transforming a host cell with a recombinant DNA vector that encodes at least one module of a PKS, said module comprising at least one PKS domain from the PKS system of the invention, and

culturing said host cell under conditions such that said PKS is produced and catalyzes synthesis of said polyketide. In one aspect, the method is practiced using an *Amycolatopsis orientalis* organism for homologous expression of the modified endogenous gene cluster. In another aspect, the method is practiced with a *Streptomyces* host cell. The invention further provides a set of genes in recombinant form sufficient for the synthesis of a compound of Formula I. In one aspect the genes reside in an Amycolatopsis orientalis organism for homologous expression of the endogenous gene cluster. In another aspect, a Streptomyces host cell is transformed with a recombinant DNA vector containing the set of genes.

Thus, the invention provides recombinant PKS genes that produce a variety of polyketides that cannot be readily synthesized by chemical methodology alone. Moreover the present invention provides polyketides, some of which are produced only by fermentation and others of which are produced by fermentation and chemical modification.

BRIEF DESCRIPTION OF THE DRAWINGS:

Figure 1: Electrospray mass spectrum (Positive Ion Mode) of Compound 1.

Figure 2: Electrospray mass (ms/ms of m/z:837.50) spectrum (Positive Ion Mode) of Compound 1.

Figure 3: Electrospray mass spectrum (Negative Ion Mode) of Compound 1.

Figure 4: 500 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectrum of Compound 1 in d_4-MeOH.

Figure 5: 500 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectrum of Compound 2 in d_4-MeOH.

Figure 6: 500 MHz proton nuclear magnetic resonance (^{1}H NMR) spectrum of Compound 3 in d_4-MeOH.

Figure 7: 500 MHz proton nuclear magnetic resonance (^{1}H NMR) spectrum of Compound 4 in d_4-MeOH.

Figure 8: 500 MHz proton nuclear magnetic resonance (^{1}H NMR) spectrum of Compound 5 in d_4-MeOH.

Figure 9: 500 MHz proton nuclear magnetic resonance (^{1}H NMR) spectrum of Compound 6 in d_4-MeOH.

Figure 10: 500 MHz proton nuclear magnetic resonance (^{1}H NMR) spectrum of Compound 7 in d_4-MeOH.

Figure 11: biosynthetic locus producing compounds of Formula I in *Amycolatopsis orientalis*, showing a scale in base pairs units; the position of the three sequence of contiguous nucleic acids of SEQ ID NOS: 1, 24 and 49; the position and orientation of the 27 open reading frames of the biosynthetic locus identified by ORF number with the six polyketide synthase ORFs identified with PKSE designation; and the coverage of the biosynthetic locus by cosmids having deposit accession nos: IDAC 050903-01, IDAC 050903-02, IDAC 050903-03 and IDAC 050903-04.

Figures 12 to 18: multiple amino acid alignments comparing the domains of the polyketide synthase system of the biosynthetic locus for the production of the compounds of Formula I, wherein the asterisks (*) indicate positions which have a single, fully conserved residue, colons (:) indicate that one of the following strong groups is fully conserved: STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, and FYW, and periods (.) indicate that one of the following weaker groups is fully conserved: CSA, ATV, SAG, STNK, STPA, SGND, SNDEQK, NDEQHK, NEQHRK, FVLIM, and HFY.

Figures 12a and 12b: amino acid alignment comparing the twelve ketosynthase (KS) domains present in the polyketide synthase (PKS) system of ORFs 18 to 23 (SEQ ID NOS: 37, 39, 41, 43, 45 and 47). The boundaries and key residues of the KS domains were chosen as described by Kakavas *et al.*, *J. Bacteriol.*,179, 7515-7522 (1997) and indicated in black.

Figures 13a, 13b and 13c: amino acid alignment comparing the twelve acyl transferase (AT) domains present in the polyketide synthase system of ORFs 18 to 23 (SEQ ID NOS: 37, 39 41, 43, 45 and 47). The boundaries and key residues of the AT domains were chosen as described by Kakavas *et al.*, *supra* and indicated in black.

Figure 14: amino acid alignment comparing the eleven dehydratase (DH) domains present in the polyketide synthase system of ORFs 18 to 23 (SEQ ID NOS: 37, 39, 41, 43, 45 and 47). The boundaries and key residues of the DH domains were chosen as described by Kakavas *et al. supra* and indicated in black.

Figure 15: amino acid alignment comparing the three enoyl reductase (ER) domains present in ORFs 18 and 19 (SEQ ID NOS: 37 and 39) with the ER domains from

modules 5 and 15 of the nystatin biosynthetic locus as described by Brautaset *et al.*, *Chem. Biol.*, 7, 395-403 (2000). The boundaries and key residues of the ER domain were chosen as described by Kakavas *et al. supra* and indicated in black.

Figure 16: amino acid alignment comparing the twelve ketoreductase (KR) domains present in ORFs 18 to 23 (SEQ ID NOS: 37, 39, 41, 43, 45 and 47). The boundaries and key residues of the KR domains were chosen as described by Kakavas *et al. supra*, and Fisher *et al. Structure Fold Des.*, 8, 339-347 (2000) and indicated in black.

Figure 17: amino acid alignment comparing the thirteen acyl carrier proteins (ACP) domains present in ORFs 18 to 23 (SEQ ID NOS: 37, 39, 41, 43, 45 and 47). The boundaries and key serine residues of the ACP domains were chosen as described by Kakavas *et al. supra* and indicated in black.

Figure 18: amino acid alignment comparing the TE domain present in ORF 23 (SEQ ID NO: 47) with the TE domain from module 7 in the nystatin biosynthetic locus as described by Brautaset *et al. supra*. The boundaries and key residues of the TE domain were chosen as described by Kakavas *et al. supra* and indicated in black.

Figure 19: phylogenetic analysis of the twelve acyl transferase (AT) domains present in ORFs 18 to 23 (SEQ ID NOS: 37, 39, 41, 43, 45 and 47) along with a malonyl-specific and a methylmalonyl-specific AT domain present in modules 3 and 11 respectively of the nystatin PKS system as described by Brautaset *et al. supra*.

Figure 20a: biosynthesis of the 4-guanidino butyryl-CoA component of compounds of Formula I from arginine and involving ORF 7 (SEQ ID NO: 14) and ORF 25 (SEQ ID NO: 52). Figure 20b: biosynthesis of the polyketide core structure of compounds of Formula I involving the polyketide synthase system of ORFs 18 to 23 (SEQ ID NOS: 37, 39, 41, 43, 45 and 47) and incorporation of the 4-guanidino butyryl-CoA component of Figure 20a using ORF 24 (SEQ ID NO: 50).

Figure 21a: biosynthesis of the aminohydroxy-cyclopentenone moiety of compounds of Formula I using ORF 16 (SEQ ID NO: 33) and ORF 17 (SEQ ID NO: 35). Figure 21b: biosynthesis of the glucuronic acid component of compounds of Formula I using ORF 13 (SEQ ID NO: 27). Figure 21c: methylation, glycosylation and amide condensation of the polyketide core structure of compounds of Formula I using ORF 5 (SEQ ID NO: 10), ORF 14 (SEQ ID NO: 29) and ORF 15 (SEQ ID NO: 31) respectively.

Figure 22: inactivation of glycosyltransferase ORF 14 (SEQ ID NO: 29) and sugar oxidoreductase ORF 13 (SEQ ID NO: 27). Figure 22a: inactivation of the glycosyltransferase gene (SEQ ID NO: 30) disrupting the transfer of the sugar moiety onto the backbone of the polyketide core and producing the non-glycosylated Compound 8. Figure 22b: inactivation of sugar oxidoreductase gene product of ORF 13 (SEQ ID NO: 28) followed by transfer of the glucose onto the polyketide backbone chain by the glycosyltransferase gene product of ORF 14 (SEQ ID NO: 29) producing Compound 11.

Figure 23: inactivation of acyltransferase ORF 16 (SEQ ID NO: 33), acyl CoA ligase ORF 17 (SEQ ID NO: 35), or adenylating/condensing synthetase ORF 15 (SEQ ID NO: 31) so as to produce Compound 7.

Figure 24: incorporation of an amidino hydrolase to catalyze the conversion of 4-guanidinobutanamide to γ-amino butanamide resulting in production of Compound 9.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention relates to novel polyene polyketides, exemplified herein as Compound 1, Compound 2 and Compound 7, which are isolated from strains of actinomycetes, *Amycolatopsis* sp. such as *Amycolatopsis orientalis* ATCC™ 43491, or a mutant or a variant thereof.

The invention further relates to pharmaceutically acceptable salts and derivatives of Compound 1, Compound 2 and Compound 7, and to methods for obtaining such compounds. One method of obtaining the compounds is by cultivating *Amycolatopsis orientalis* ATCC™ 43491, or a mutant or a variant thereof, under suitable *Amycolatopsis sp.* culture conditions preferably using the fermentation protocol described herein below.

The invention also relates to polyene polyketides of Formula I, exemplified herein as Compounds 3, 4, 5 and 6, produced from Compound 1, Compound 2 or Compound 7 by selective chemical modification of Compound 1, Compound 2 or Compound 7 using techniques described herein and well known to those skilled in the synthesis of natural products.

The present invention also relates to pharmaceutical compositions comprising a polyene polyketide selected from any one of Compounds 1 to 7, pharmaceutically acceptable salts or prodrugs of any one of Compounds 1 to 7, and derivatives of any

one of Compounds 1 to 7 as defined by Formula I. In another aspect of the invention, Compounds 1 to 7 are each useful as antibacterial agents, and for use as inhibitors of bacterial cell growth. Accordingly, in an aspect the present invention relates to pharmaceutical compositions comprising any one of Compounds 1 to 7 of the invention together with a pharmaceutically acceptable carrier and methods of using the compositions as antibacterial agents to inhibit bacterial cell growth.

The following detailed description discloses how to make and use any of Compounds 1 to 7, compounds of Formula I and compositions containing these compounds to inhibit microbial growth.

Accordingly, certain aspects of the present invention relate to pharmaceutical compositions comprising the polyene polyketide compounds of the present invention together with a pharmaceutically acceptable carrier, methods of using the compositions to inhibit bacterial growth, and methods of using the pharmaceutical compositions to treat diseases, including cancer, and chronic and acute inflammation.

The present invention also provides the biosynthetic locus from *Amycolatopsis orientalis* strain ATCC™ 43491 which biosynthetic locus is responsible for producing the compounds of Formula I. Thus the invention provides polynucleotides and polypeptides useful in the production and engineering of compounds of Formula I.

Definitions

Molecular terms, when used in this application, have their common meaning unless otherwise specified.

Abreviations, as used herein, have the following meaning: Me refers to methyl (CH_3), Et refers to ethyl (CH_2CH_3), Pr refers to *n*-propyl ($CH_2CH_2CH_3$) and Ac refers to acetyl ($C(O)CH_3$).

The term alkyl refers to a linear or branched hydrocarbon groups. Examples of alkyl groups include, without limitation, methyl, ethyl, n-propyl, isopropyl, n-butyl, pentyl, hexyl, heptyl, cyclopentyl, cyclohexyl, cyclohexymethyl, and the like. Alkyl may optionally be substituted with substituents selected from acyl, amino, acylamino, acyloxy, carboalkoxy, carboxy, carboxyamido, cyano, halo, hydroxyl, nitro, thio, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, aryloxy, sulfinyl, sulfonyl, oxo, guanidino and formyl.

The term alkenyl refers to linear, branched or cyclic hydrocarbon groups containing at least one carbon-carbon double bond. Examples of alkenyl groups include, without limitation, vinyl, 1-propene-2-yl, 1-butene-4-yl, 2-butene-4-yl, 1-pentene-5-yl and the like. Alkenyl may optionally be substituted with substituents selected from acyl, amino, acylamino, acyloxy, carboalkoxy, carboxy, carboxyamido, cyano, halo, hydroxyl, nitro, thio, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, alkoxy, aryloxy, sulfinyl, sulfonyl, formyl, oxo and guanidino. The double bond portion(s) of the unsaturated hydrocarbon chain may be either in the cis or trans configuration.

The term cycloalkyl or cycloalkyl ring refers to a saturated or partially unsaturated carbocyclic ring in a single or fused carbocyclic ring system having from three to fifteen ring members. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclohexyl, and cycloheptyl. Cycloalkyl may optionally be substituted with substituents selected from acyl, amino, acylamino, acyloxy, carboalkoxy, carboxy, carboxyamido, cyano, halo, hydroxyl, nitro, thio, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, aryloxy, sulfinyl, sulfonyl and formyl.

The term heterocyclyl, heterocyclic or heterocyclyl ring refers to a saturated or partially unsaturated ring containing one to four hetero atoms or hetero groups selected from O, N, NH, NR^x, PO_2, S, SO or SO_2 in a single or fused heterocyclic ring system having from three to fifteen ring members. Examples of a heterocyclyl, heterocyclic or heterocyclyl ring include, without limitation, morpholinyl, piperidinyl, and pyrrolidinyl. Heterocyclyl, heterocyclic or heterocyclyl ring may optionally be substituted with substituents selected from acyl, amino, acylamino, acyloxy, oxo, thiocarbonyl, imino, carboalkoxy, carboxy, carboxyamido, cyano, halo, hydroxyl, nitro, thio, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, alkoxy, aryloxy, sulfinyl, sulfonyl and formyl.

The term amino acid refers to any natural amino acid, all natural amino acids are well known to a person skilled in the art.

The term halo is defined as a bromine, chlorine, fluorine or iodine.

The term aryl or aryl ring refers to common aromatic groups having “4n+2” electrons, wherein n is an integer from 1 to 3, in a monocyclic or conjugated polycyclic system and having from five to fifteen ring atoms. Aryl ring may include from 1 to 3 heteroatoms such as nitrogen, oxygen and sulphur atoms. Examples of aryl include,

without limitation, phenyl, naphthyl, biphenyl, terphenyl, furyl, pyrrollyl, thienyl, pyridyl, oxazolyl, imidazolyl, pyrazolyl and indolyl groups. Aryl may optionally be substituted with one or more substituent group selected from acyl, amino, acylamino, acyloxy, azido, alkythio, carboalkoxy, carboxy, carboxyamido, cyano, halo, hydroxyl, nitro, thio, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, aryloxy, sulfinyl, sulfonyl and formyl.

The compounds of the present invention can possess one or more asymetric carbon atoms and can exist as optical isomers forming mixtures of racemic or non-racemic compounds. The compounds of the present invention are useful as a single isomer or as a mixture of stereochemical isomeric forms. Diastereoisomers, i.e., nonsuperimposable stereochemical isomers, can be separated by conventional means such as chromatography, distillation, crystallization or sublimation. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes.

The invention embraces isolated compounds. An isolated compound refers to a compound which represents at least 10%, 20%, 50% and 80% of the compound of the present invention present in a mixture, provided that the mixture comprising the compound of the invention has demonstrable (i.e. statistically significant) biological activity including antimicrobial activity when tested in conventional biological assays known to a person skilled in the art.

As used herein, the term “treatment” refers to the application or administration of a therapeutic agent to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has a disorder, e.g., a disease or condition, a symptom of disease, or a predisposition toward a disease, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect the disease, the symptoms of disease, or the predisposition toward disease.

As used herein, a “pharmaceutical composition” comprises a pharmacologically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. As used herein, “pharmacologically effective amount,” “therapeutically effective amount” or simply “effective amount” refers to that amount of polyene polyketide effective to produce the intended pharmacological, therapeutic or preventive result. For example, if a given clinical treatment is considered effective when there is at least a 25% reduction in a measurable parameter associated with a

disease or disorder, a therapeutically effective amount of a drug for the treatment of that disease or disorder is the amount necessary to effect at least a 25% reduction in that parameter.

The term "pharmaceutically acceptable carrier" refers to a carrier for administration of a therapeutic agent. Such carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The term specifically excludes cell culture medium. For drugs administered orally, pharmaceutically acceptable carriers include, but are not limited to pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

The term "pharmaceutically acceptable salts" include acid addition salts and base addition salts. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Without being limited, examples of acid addition salts include hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulphuric, phosphoric, formic, acetic, citric, tartaric, succinic, oxalic, malic, glutamic, propionic, glycolic, gluconic, maleic, embonic (pamoic), methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic, cyclohexylaminosulfonic, stearic, algenic, β-hydroxybutyric, malonic, galactantic, galacturonic acid and the like. Suitable pharmaceutically-acceptable base addition salts of compounds of the invention include, but are not limited to, metallic salts made from aluminium, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, lysine, procaine and the like. Additional examples of pharmaceutically acceptable salts are listed in Berge SM et al., *Journal of Pharmaceutical Sciences*, (1977) Vol. 66 no 1, pp. 1-19. All of these salts may be prepared by conventional means form the corresponding compounds of Formula I by treating with the appropriate acid or base.

The term "isolated" polynucleotide or polypeptide means that the material is removed from its original environment, *e.g.* the natural environment if it is naturally-occurring. For example, a naturally-occurring polynucleotide or polypeptide present in a living organism is not isolated, but the same polynucleotide or polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of its natural environment.

The term "purified" polynucleotide or polypeptide does not require absolute purity; rather, it is intended as a relative definition. Individual nucleic acids obtained from a library have been conventionally purified to electrophoretic homogeneity. The purified nucleic acids of the present invention have been purified from the remainder of the genomic DNA in the organism by at least 10^4 to 10^6 fold. However, the term "purified" also includes nucleic acids which have been purified from the remainder of the genomic DNA or from other sequences in a library or other environment by at least one order of magnitude, preferably two or three orders of magnitude, and more preferably four or five orders of magnitude.

"Recombinant" nucleic acid means that the nucleic acid is adjacent to "backbone" nucleic acid to which it is not adjacent in its natural environment. "Enriched" nucleic acids represent 5% or more of the number of nucleic acid inserts in a population of nucleic acid backbone molecules. "Backbone" molecules include nucleic acids such as expression vectors, self-replicating nucleic acids, viruses, integrating nucleic acids, and other vectors or nucleic acids used to maintain or manipulate a nucleic acid of interest. Preferably, the enriched nucleic acids represent 15% or more, more preferably 50% or more, and most preferably 90% or more, of the number of nucleic acid inserts in the population of recombinant backbone molecules.

"Recombinant" polypeptides or proteins refer to polypeptides or proteins produced by the reassortment of sections of DNA or RNA sequences between at least two DNA or RNA molecules that are created by recombinant DNA techniques that are well known in the art. An extensive guide to such techniques is described in Sambrook *et al.*, (1989), Molecular Cloning: A Laboratory Manual, second edition, Cold Spring Harbor Laboratory Press. "Synthetic" polypeptides or proteins are those prepared by chemical synthesis.

A "coding sequence" or "sequence encoding" a particular polypeptide or protein, is a DNA sequence which is transcribed and translated into a polypeptide or protein when placed under the control of appropriate regulatory sequences.

Thus, as used herein, the term "polynucleotide encoding a polypeptide" encompasses a polynucleotide that includes only coding sequence for the polypeptide as well as a polynucleotide that includes additional coding and/or non-coding sequence.

The term "complement" and "complementary", refers to the ability of two single stranded nucleic acid fragments to sufficiently base pair with each other or to "hybridize" under certain stringent conditions. By way of example, and not limitation, a procedure of using high stringency is as follows: Prehybridizaion of filters containing DNA is carried out for 2 hrs. to overnight at 65^0 C in buffer composed of 6X SSC, 5X Denhardt's solution and 100 µg/ml denatured salmon sperm DNA. Filters are hybridized for 12 to 48 hrs at 65^0 C in prehybridization buffer mixture containing a labeled probe (e.g. 5-20 X 10^6 ^{32}P labeled probe). Washing of the hybridized filters is conducted at 37^0 C for 1 hr. in a solution of containing 2 X SSC, 0.1 % SDS. This is followed by a wash in 0.1 X SSC, 0.1 % SDS at 50^0 C for 45 min. followed by autoradiography. Other conditions for stringency are described in Sambrook *et al.*,*supra*.

Expression "control sequences" refers collectively to promoter sequences, ribosomal binding sites, polyadenylation signals, transcription termination sequences, regulatory regions, enhancers, and the like, which collectively provide for the transcription and translation of a coding sequence in a host cell. Not all these control sequences need always be present in a recombinant vector so long as the desired gene is capable of being transcribed or translated.

"Oligonucleotide" refers to a nucleic acid, generally of at least 10 to about 100 nucleotides, that are hybridizable to a genomic DNA molecule, a cDNA molecule, or an mRNA molecule encoding a gene or other nucleic acid of interest.

A promoter sequence is "operably linked to" a coding sequence recognized by RNA polymerase which initiates transcription at the promoter and transcribes the coding sequence into mRNA.

"Plasmids" are designated herein by a lower case p preceded or followed by capital letters and/or numbers. The starting plasmids herein are commercially available,

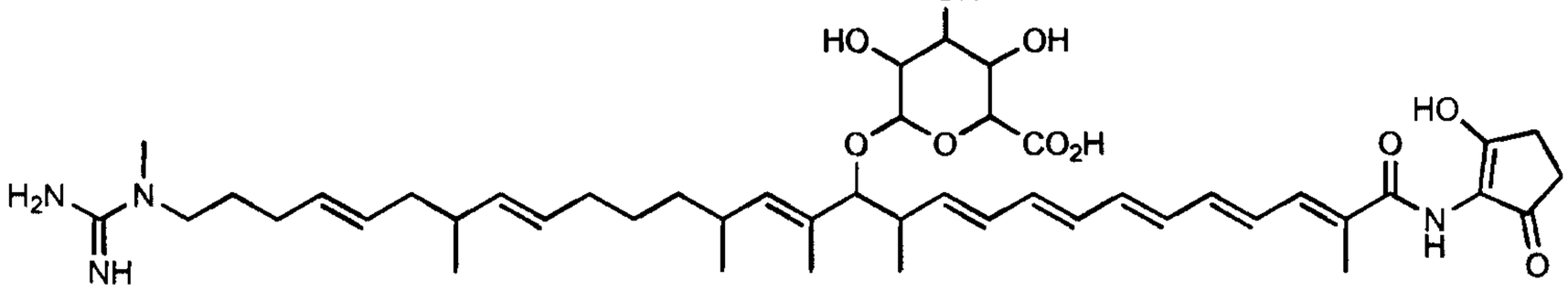
publicly available on an unrestricted basis, or can be constructed from available plasmids in accord with published procedures. In addition, equivalent plasmids to those described herein are known in the art and will be apparent to the skilled artisan.

"Digestion" of DNA refers to enzymatic cleavage of the DNA with a restriction enzyme that acts only at certain sequences in the DNA. The various restriction enzymes used herein are commercially available and their reaction conditions, cofactors and other requirements were used as would be known to the ordinary skilled artisan. For analytical purposes, typically 1 µg of plasmid or DNA fragment is used with about 2 units of enzyme in about 20 µl of buffer solution. For the purpose of isolating DNA fragments for plasmid construction, typically 5 to 50 µg of DNA are digested with 20 to 250 units of enzyme in a larger volume. Appropriate buffers and substrate amounts for particular enzymes are specified by the manufacturer. Incubation times of about 1 hour at 37°C are ordinarily used, but may vary in accordance with the supplier's instructions. After digestion the gel electrophoresis may be performed to isolate the desired fragment.

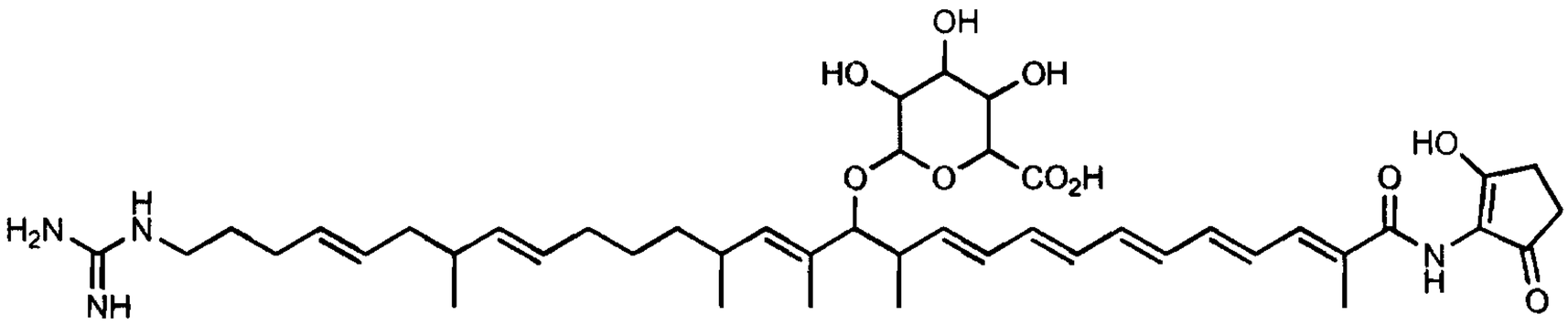
Unless otherwise indicated, all numbers expressing quantities of ingredients and properties such as molecular weight, reaction conditions, MIC and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in the present specification and attached claims are approximations. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of significant figures and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the examples, tables and figures are reported as precisely as possible. Any numerical values may inherently contain certain errors resulting from variations in experiments, testing measurements, statistical analysis and such.

Compounds of the invention

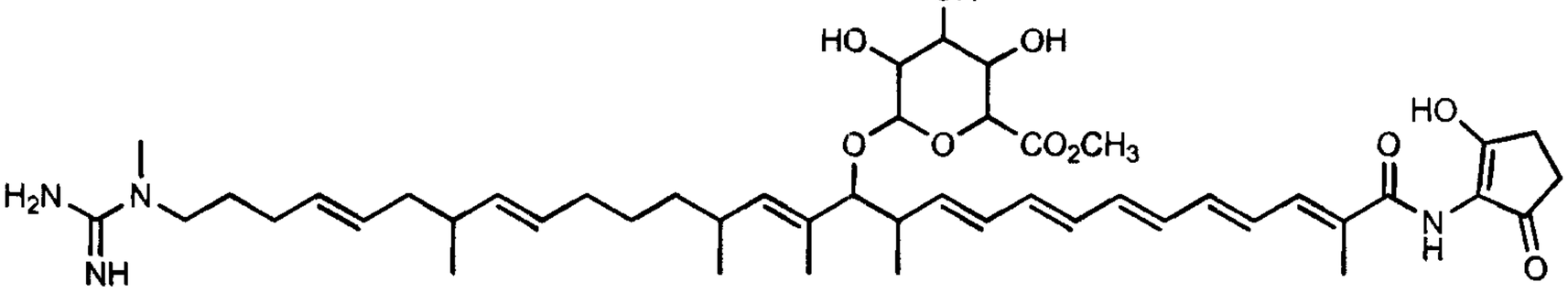
In one aspect of this embodiment the invention relates to novel polyene polyketides, referred to herein as Compounds 1 to Compound 7:



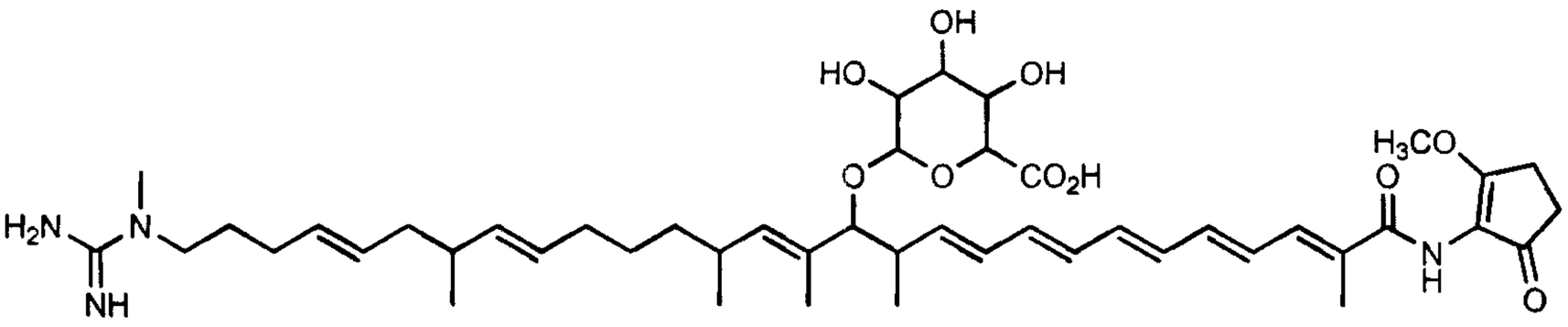
Compound 1;



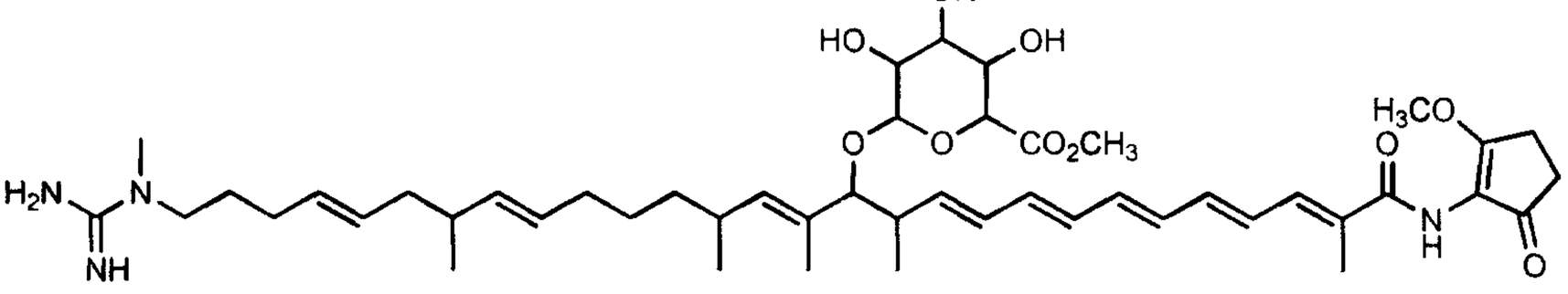
Compound 2;



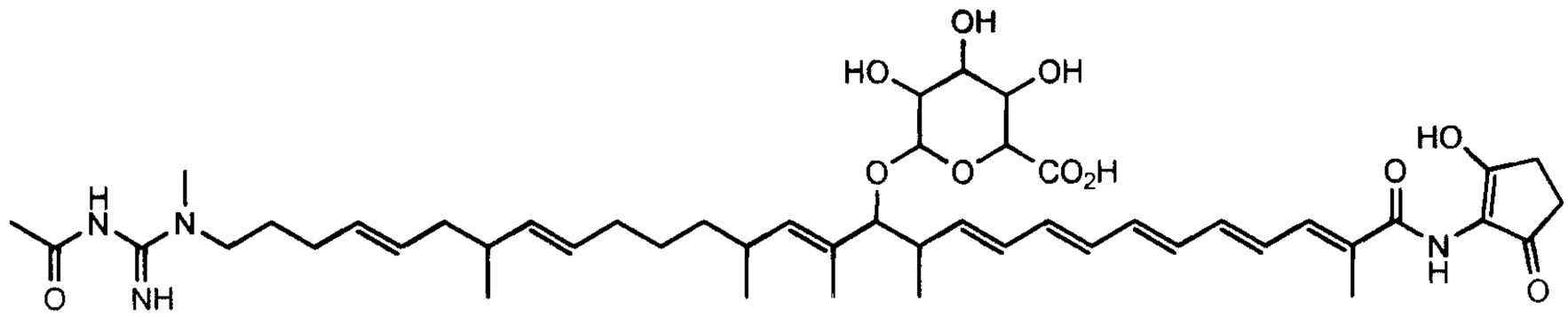
Compound 3;



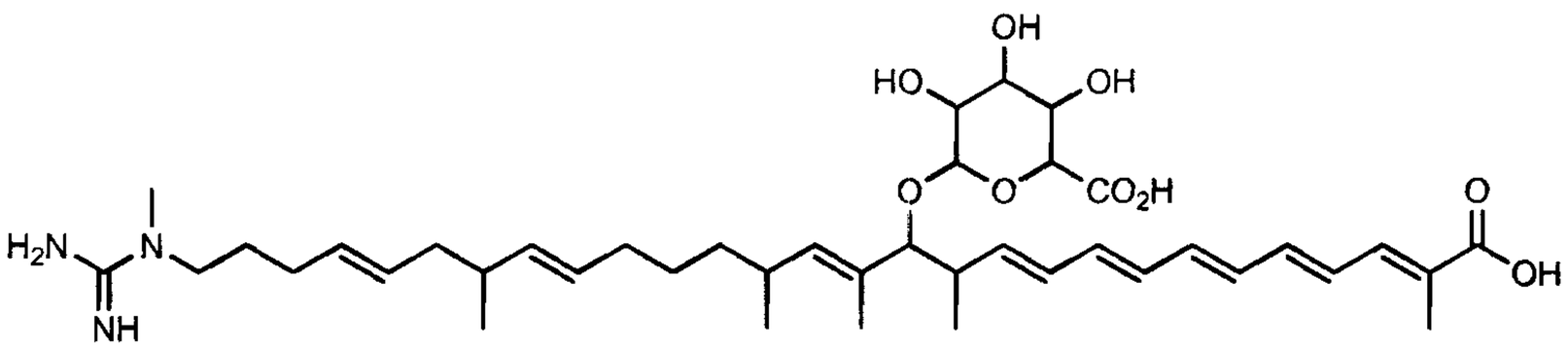
Compound 4;



Compound 5;



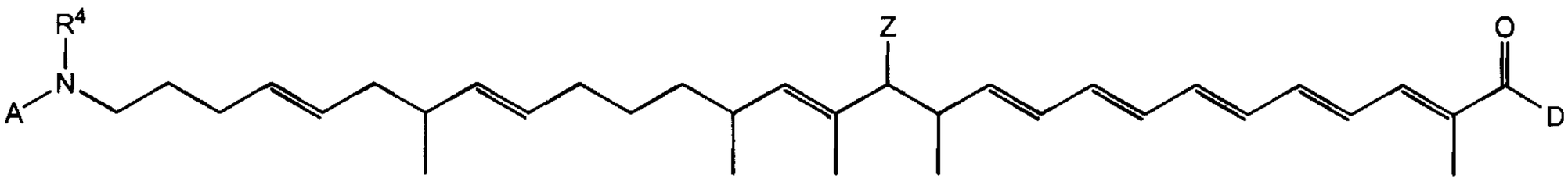
Compound 6;



Compound 7;

or, to a pharmaceutically acceptable salt or prodrug of any of Compounds 1 to 7. Compounds 1 to 7 may be characterized by any one or more of their physicochemical and spectral properties given below, such as mass, UV, and NMR spectroscopic data.

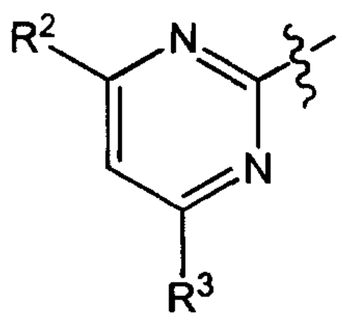
In another aspect the invention relates to derivatives of Compound 1 to 7, as represented by the polyene polyketides of Formula I:



Formula I

wherein,

A is selected from $-C(NH)NHR^1$, CH_3, H or



;

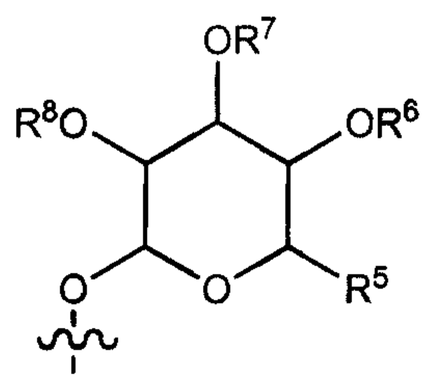
R^1 is selected from H, C_{1-6}alkyl, C_{6-10}aryl, $C(O)C_{1-6}$alkyl and $C(O)C_{6-10}$aryl;

R^2 and R^3 are each independently selected from H, C_{1-6} alkyl, C_{2-7} alkene and C_{6-10} aryl;

R^4 is selected from H or CH_3;

Z is OH or O when taken with adjacent carbon atom to form a carbonyl; or

Z may be a tetrahydropyranoxy of formula:



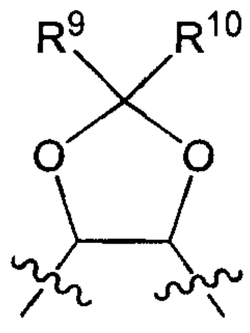
;

R^5 is selected from H, COOH, C_{1-6} alkyl or $C(O)OC_{1-6}$ alkyl;

R^6, R^7 and R^8 are each independently selected from H, C_{1-6} alkyl and $C(O)C_{1-6}$ alkyl; or

R^6 , R^7 and R^8 may each independently be absent when the adjacent oxygen and carbon atoms are taken together to form a carbonyl; or

R^6 , R^7 and R^8 may each independently be a bond when any of two neighboring R^6 , R^7 and R^8 are taken together with attached oxygen and carbon atoms to form a 1,3-dioxolane ring of formula:



;

R^9 and R^{10} are each independently selected from H, C_{1-6} alkyl, C_{2-7} alkene and C_{6-10} aryl; or

R^9 and R^{10} are taken together with adjacent carbon atom to form a ring having from 5 to 7 carbons;

D is selected from OH, NH_2, $NH(C_{1-3}alkyl)$, $N(C_{1-3}alkyl)_2$, $OC_{1-3}alkyl$ or

;

R^{11} is selected from H or C_{1-3} alkyl;

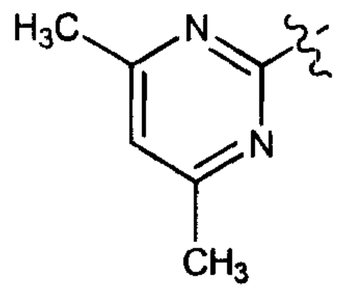
or a pharmaceutically acceptable salt or prodrug thereof.

In an embodiment the invention provides compounds of Formula I, wherein A is —C(NH)NH_2; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment of the invention provides compounds of Formula I, wherein A is H; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein A is —C(NH)NHC(O)CH_3; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein A is



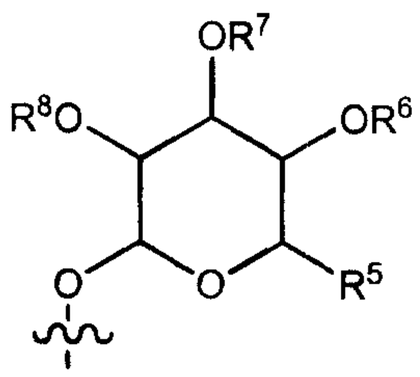
;

and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein R^4 is CH_3; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein R^4 is H; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

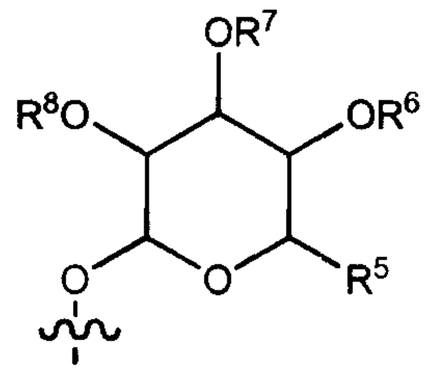
In a further embodiment the invention provides compounds of Formula I, wherein Z is



;

and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof. In a subclass of this embodiment R^6, R^7 and R^8 are each H, and R^5 is COOH, all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein Z is

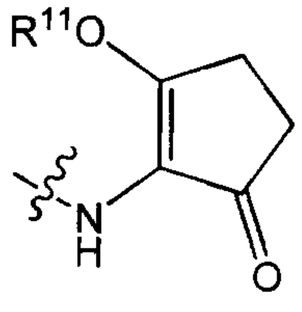


;

and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof. In a subclass of this embodiment R^6, R^7 and R^8 are each H, and R^5 is CO_2CH_3, all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein Z is OH and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

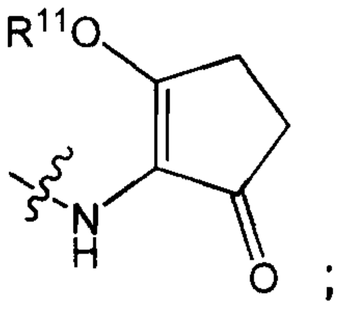
In a further embodiment the invention provides compounds of Formula I, wherein D is



;

and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof. In a subclass of this embodiment R^{11} is H and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In a further embodiment the invention provides compounds of Formula I, wherein D is

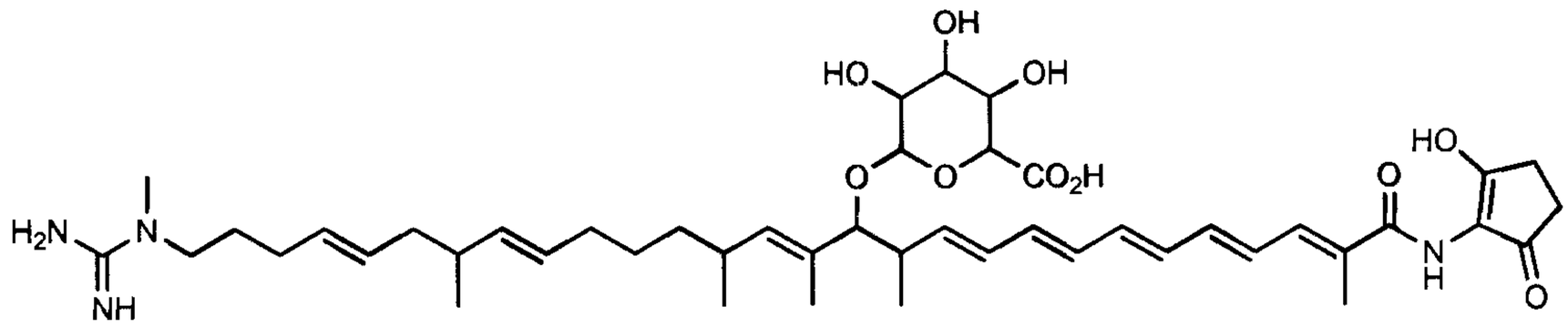


;

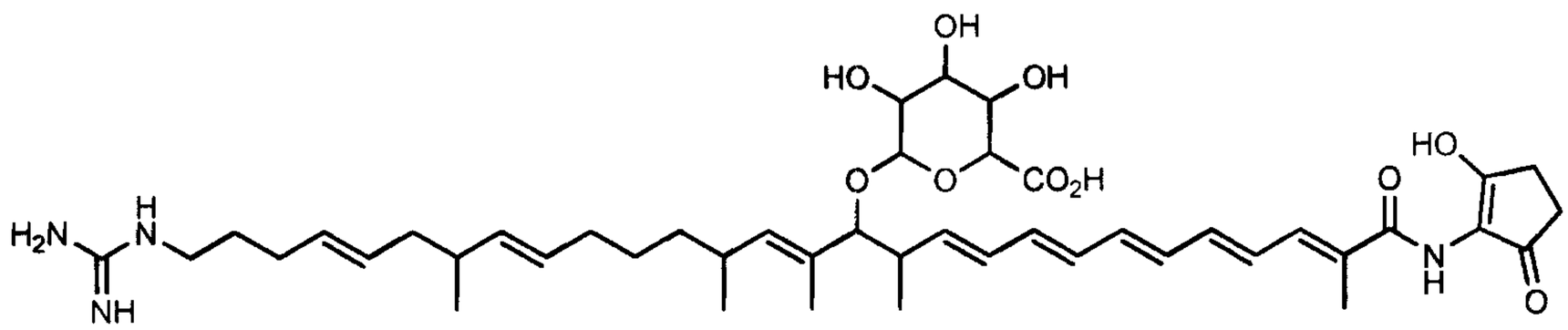
and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof. In a subclass of this embodiment R^{11} is CH_3 and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

In another embodiment the invention provides compounds of Formula I, wherein D is OH; and all other groups are as previously defined; or a pharmaceutically acceptable salt or prodrug thereof.

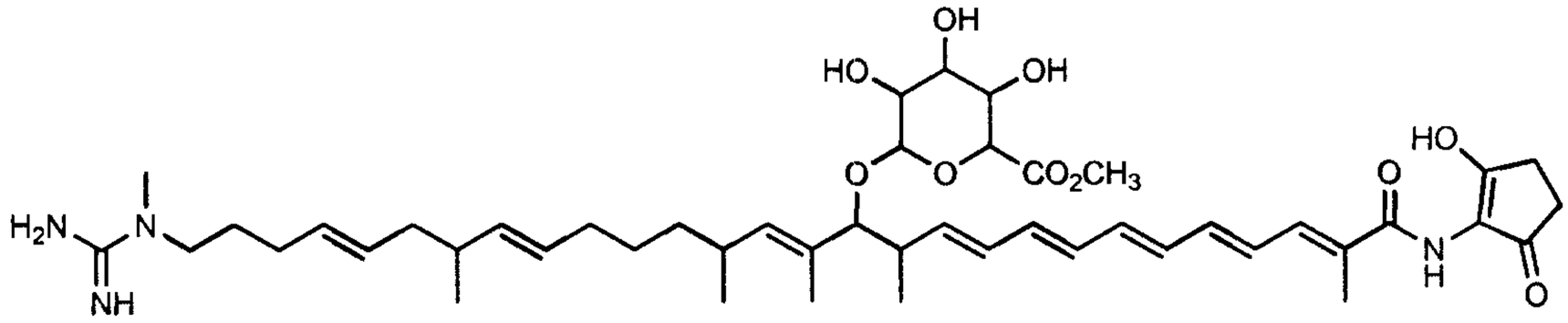
The following are exemplary compounds of the invention:



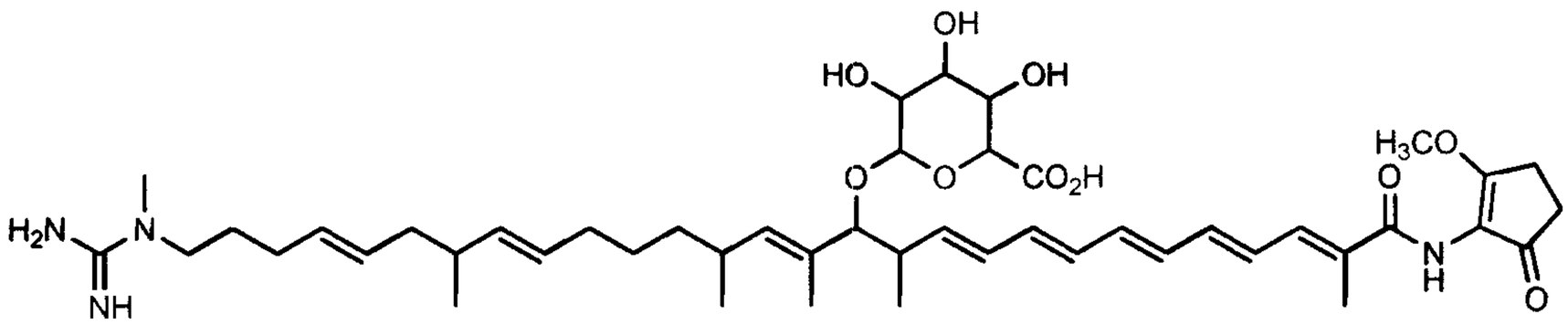
Compound 1;



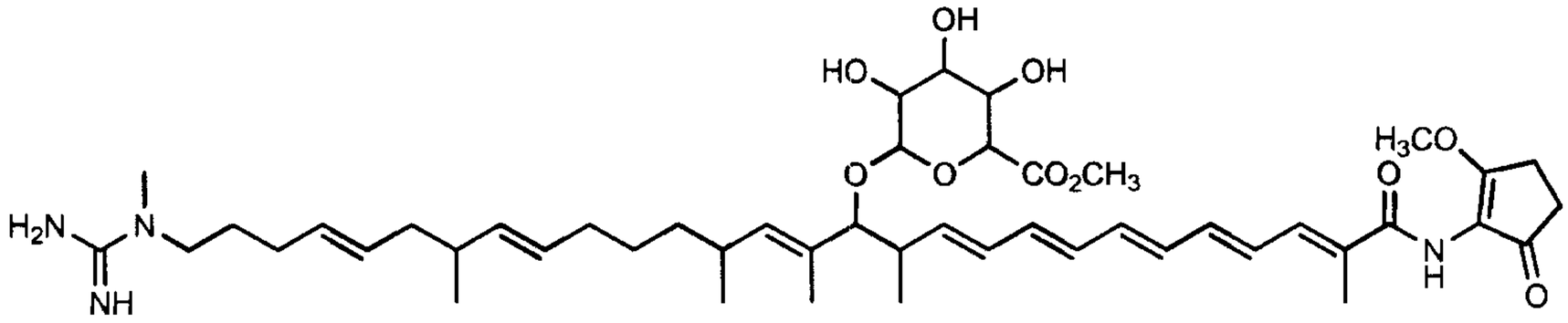
Compound 2;



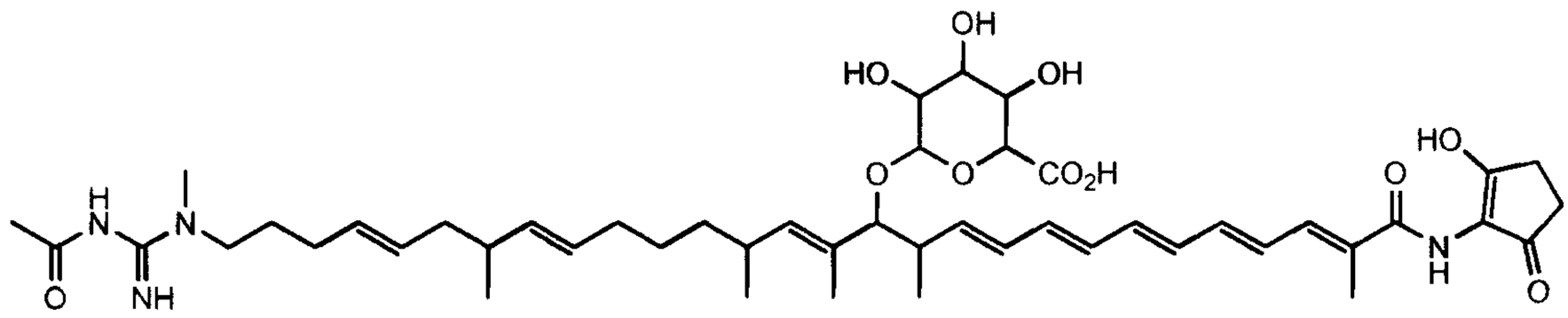
Compound 3;



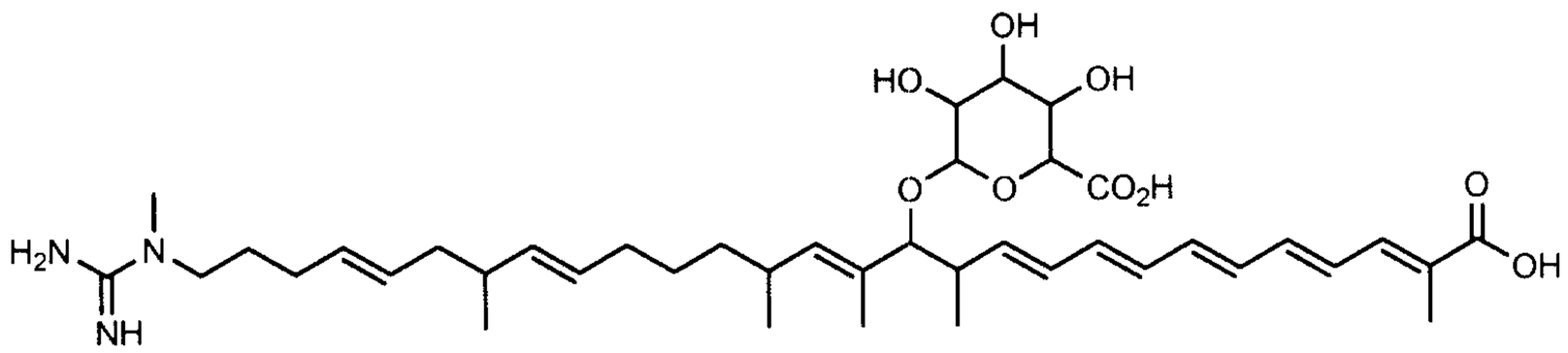
Compound 4;



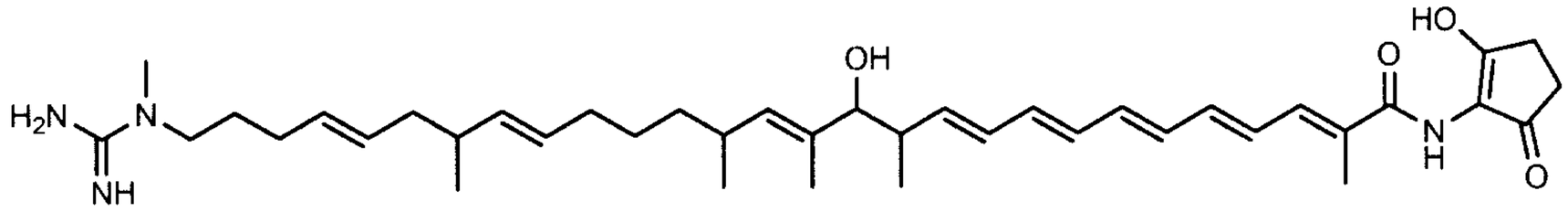
Compound 5;



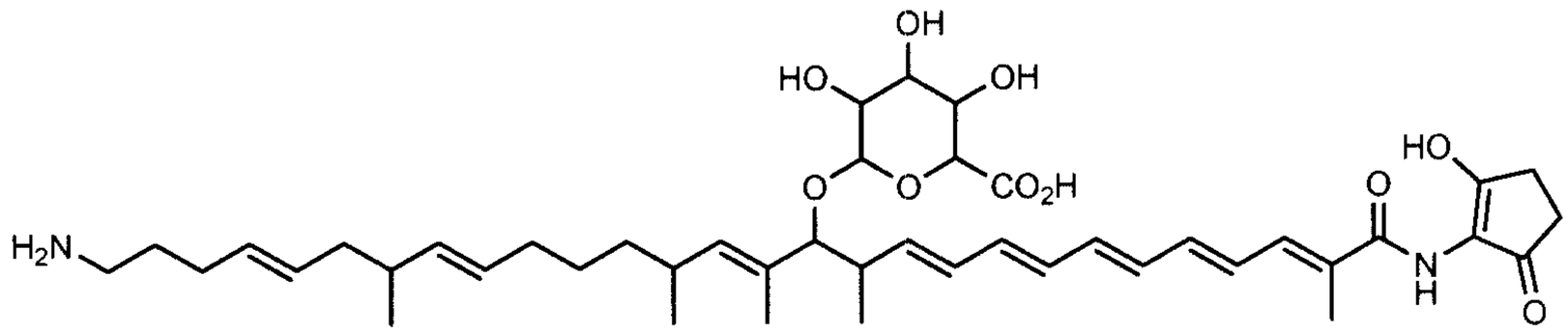
Compound 6;



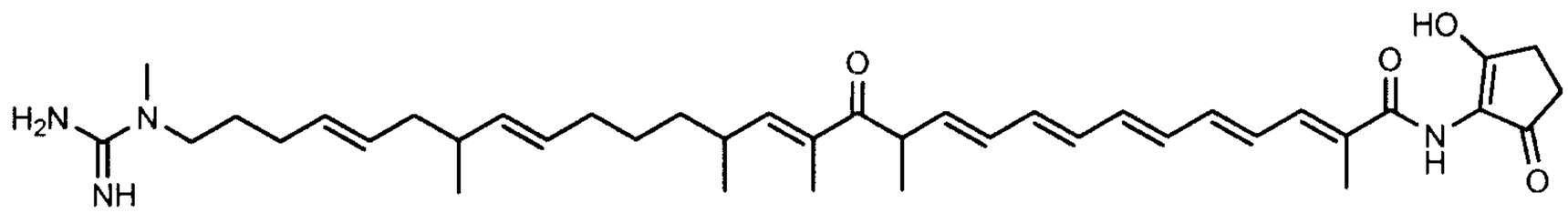
Compound 7;



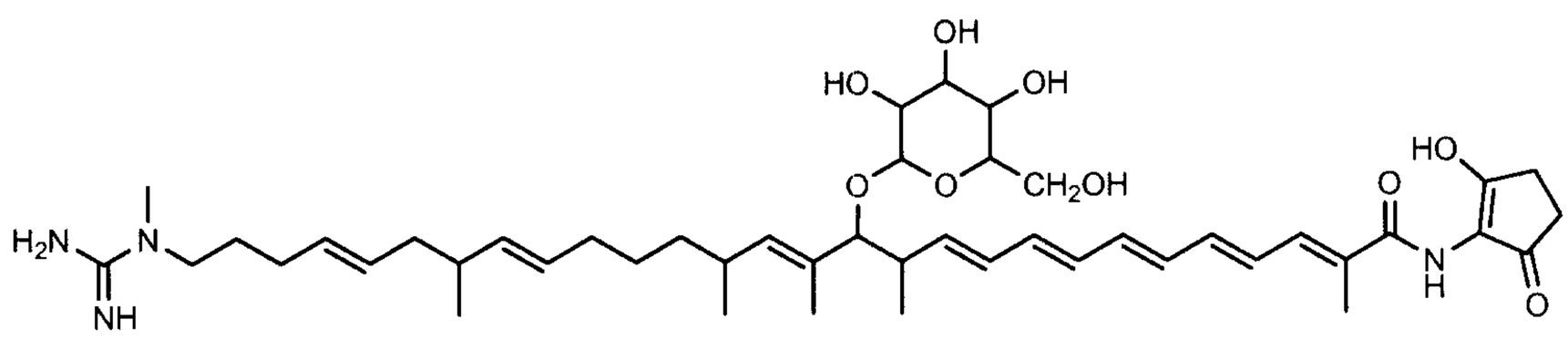
Compound 8;



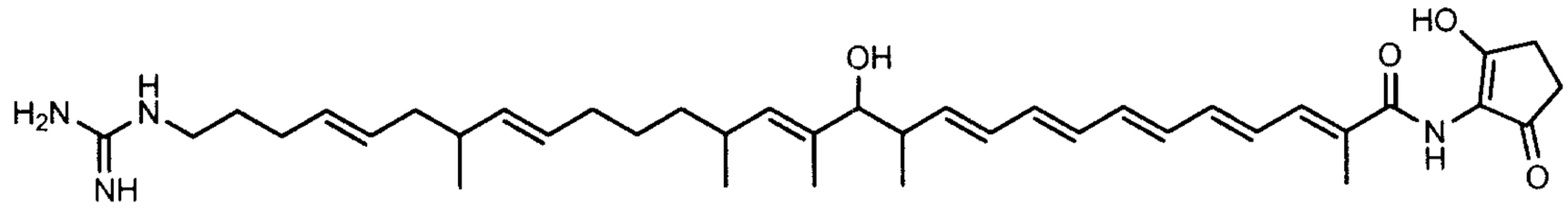
Compound 9;



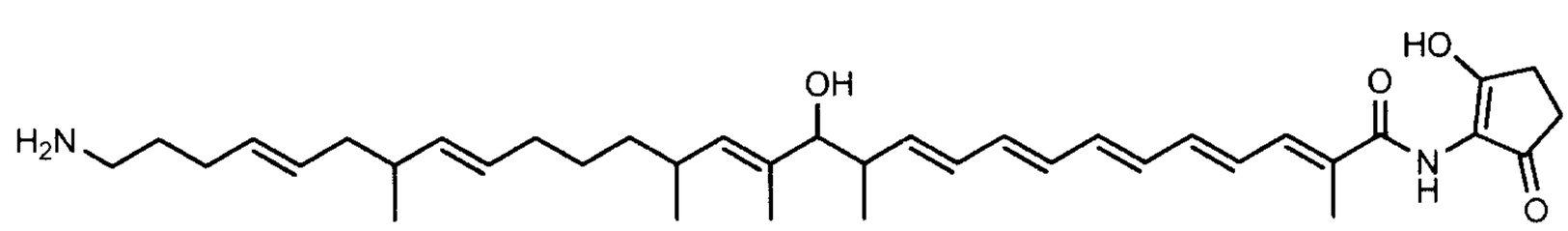
Compound 10;



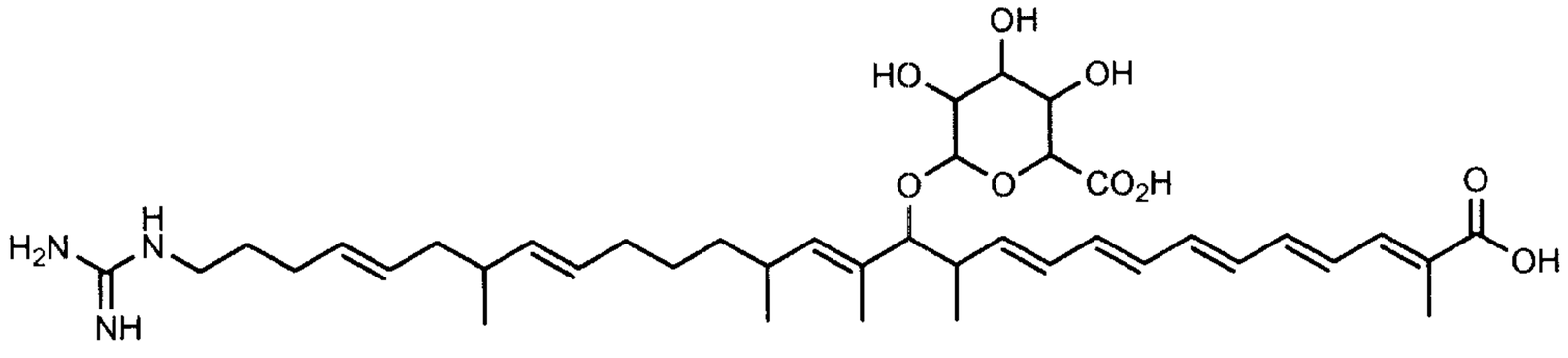
Compound 11;



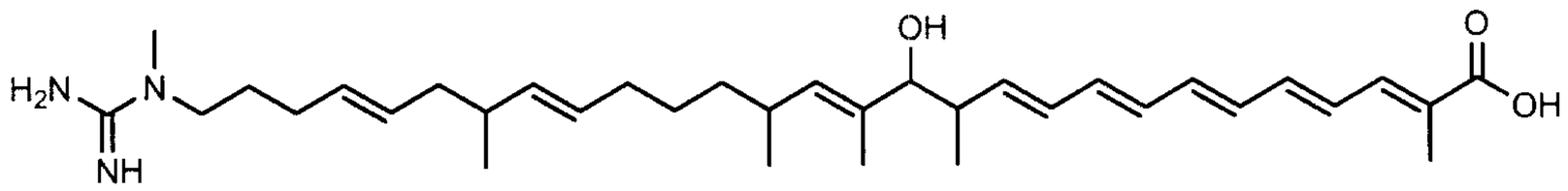
Compound 12;



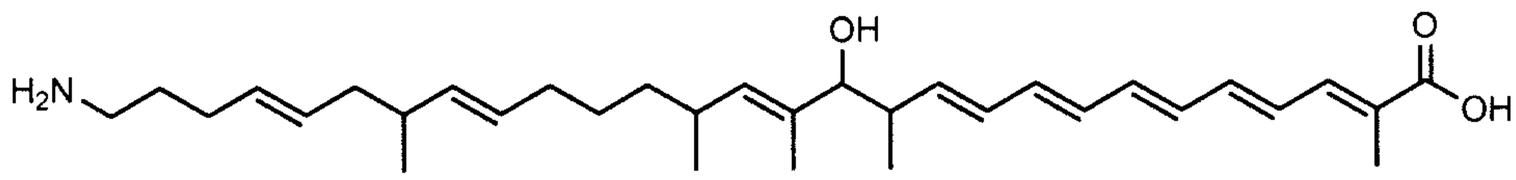
Compound 13;



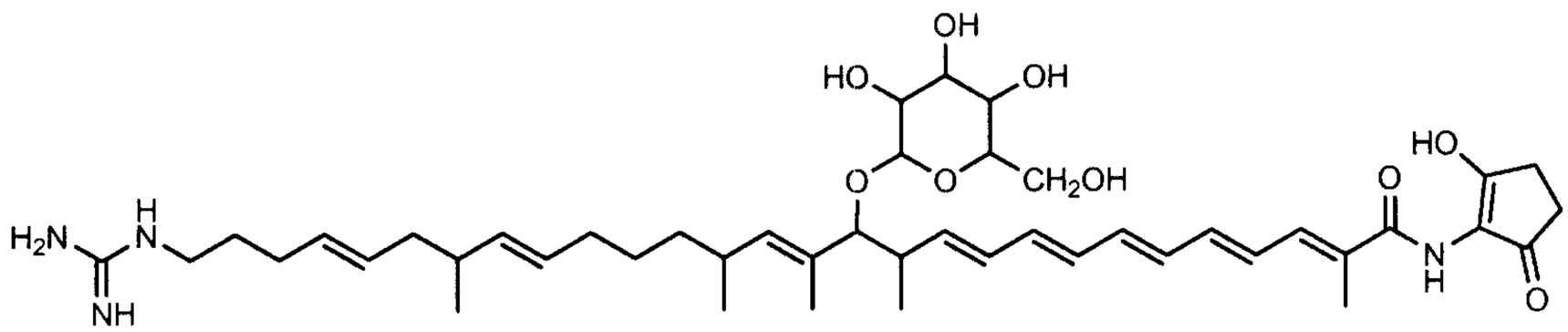
Compound 14;



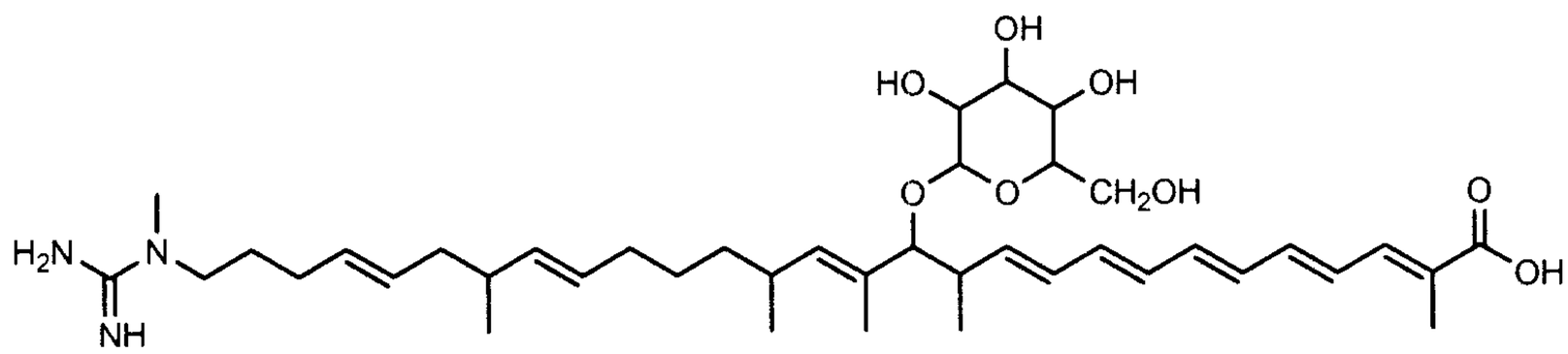
Compound 15;



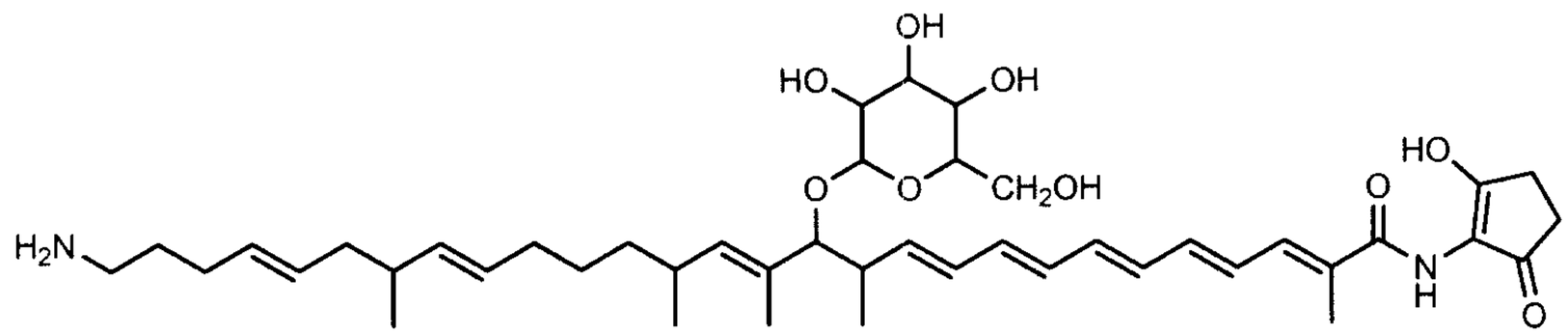
Compound 16;



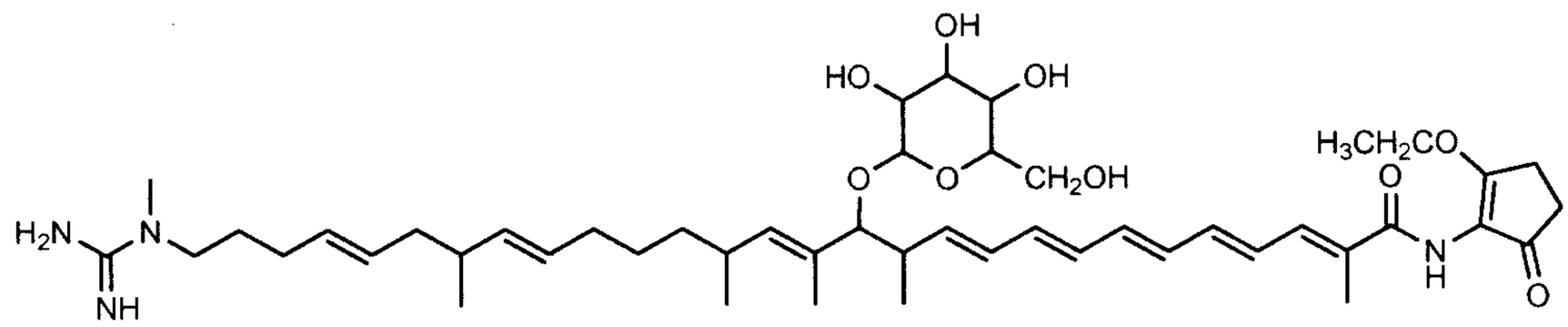
Compound 17;



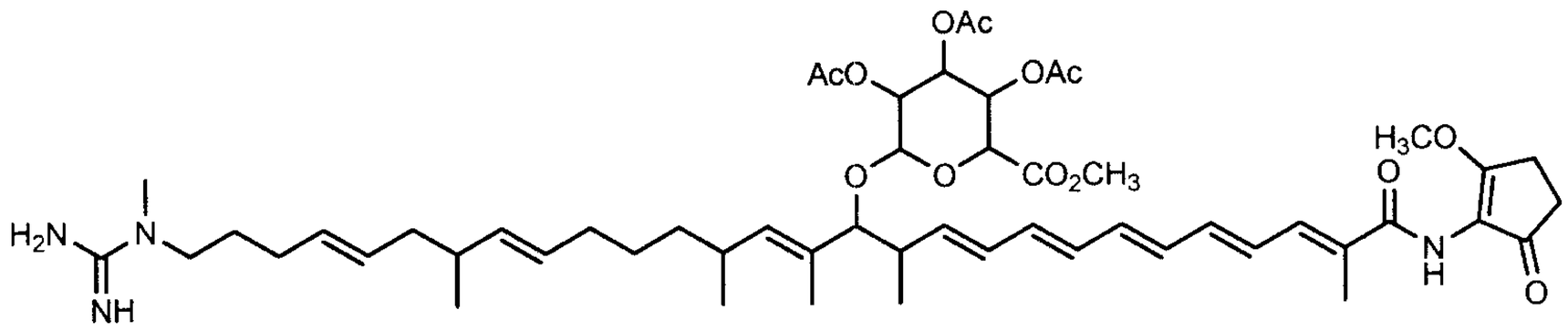
Compound 18;



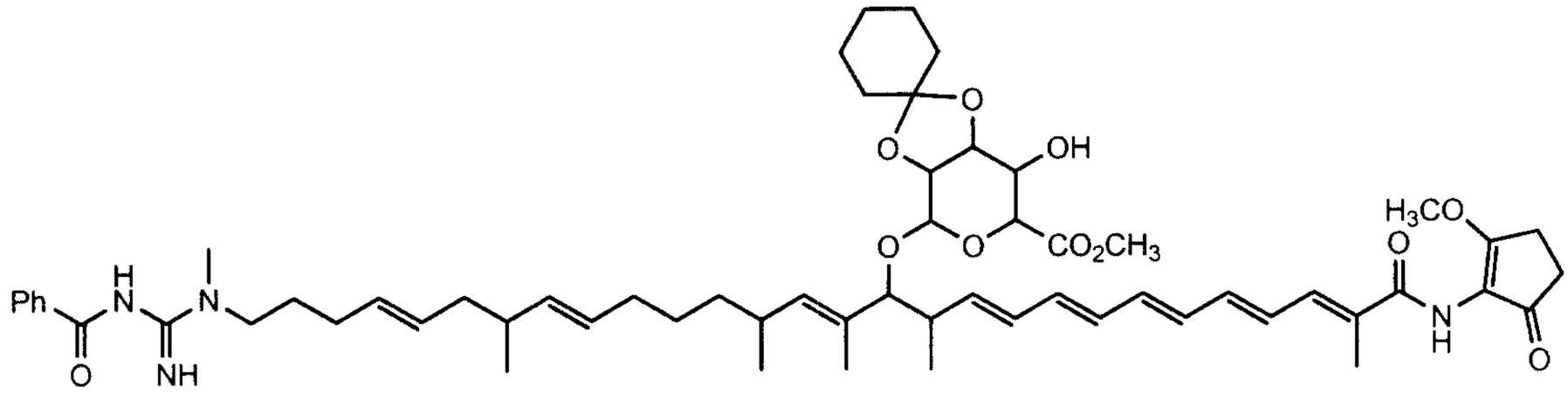
Compound 19;



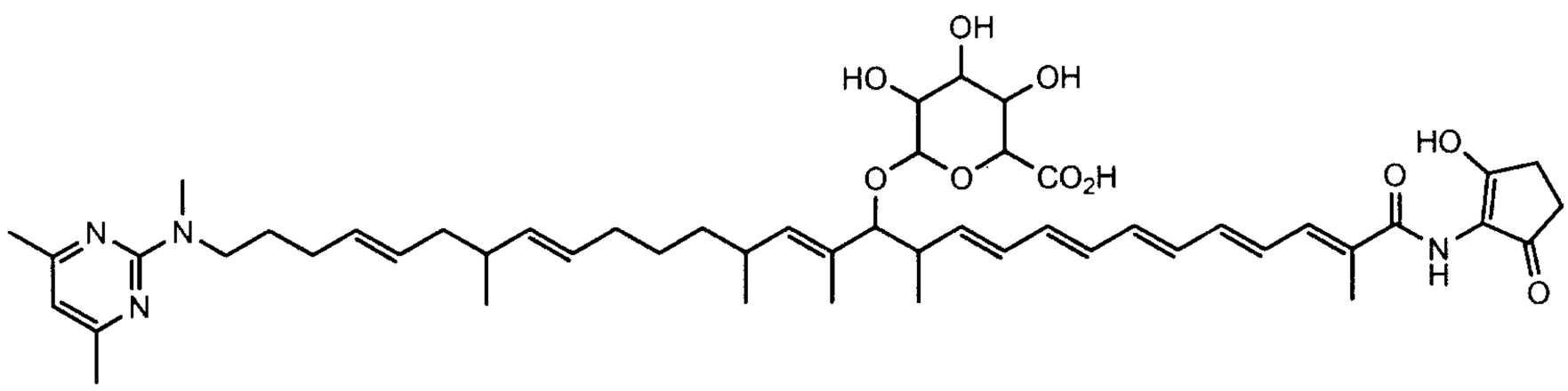
Compound 20;



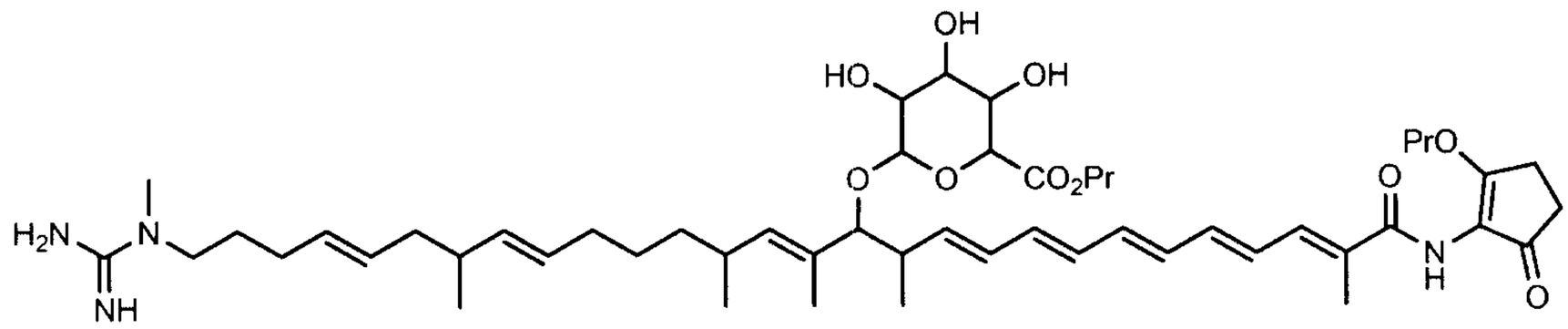
Compound 21;



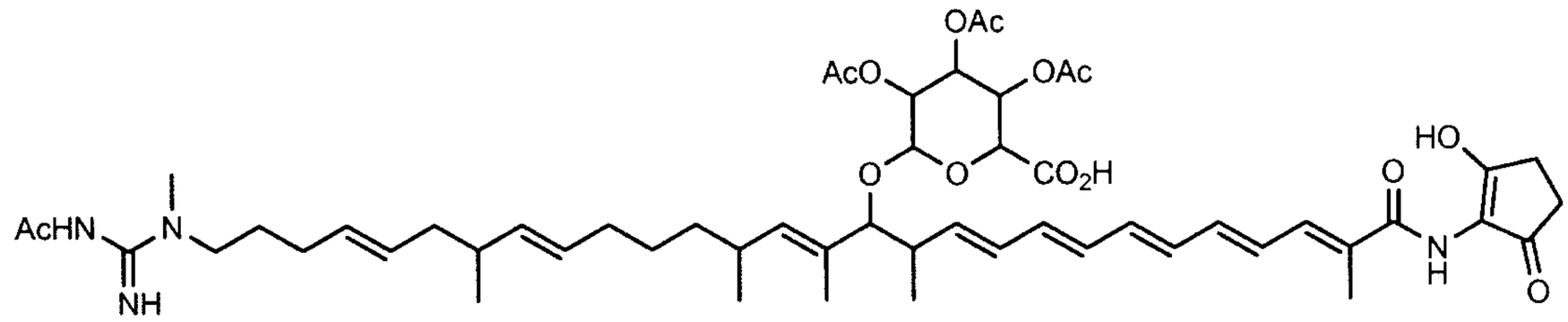
Compound 22;



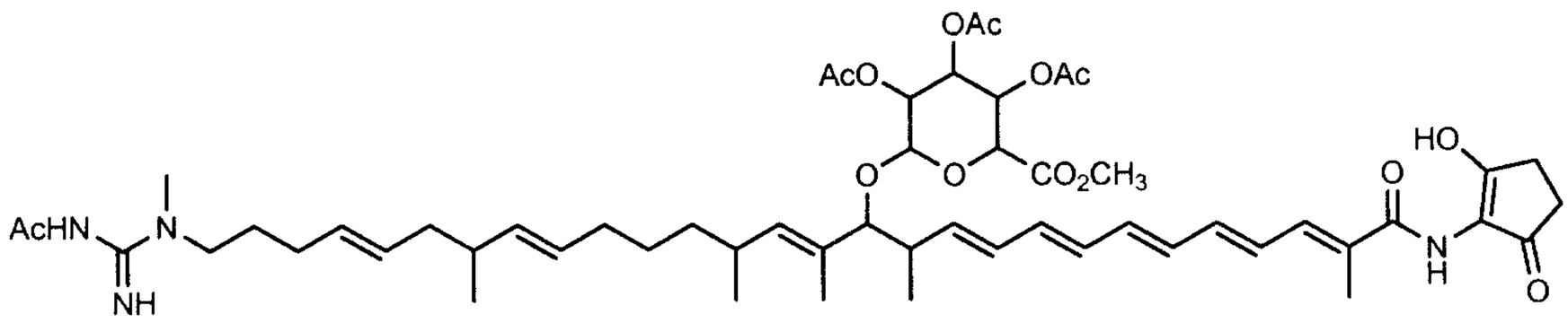
Compound 23;



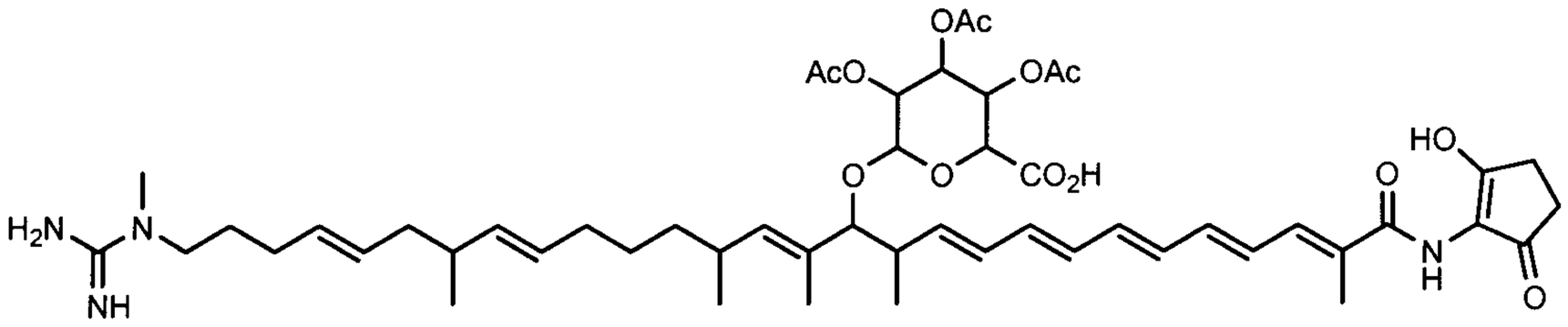
Compound 24;



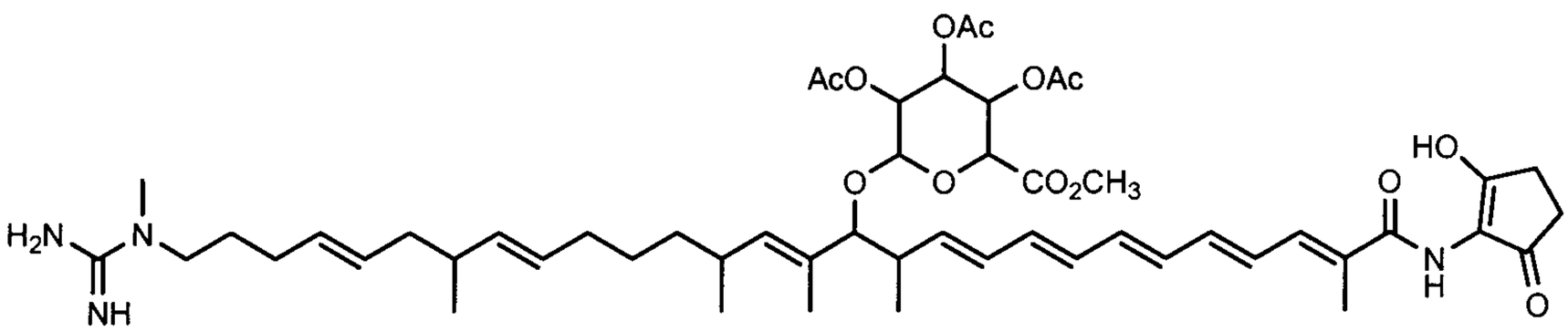
Compound 25;



Compound 26;



Compound 27 and



Compound 28;

or a pharmaceutically acceptable salt or prodrug of any one of Compound 1-28. Certain embodiments may exclude one or more of the compounds of Formula I.

III. Methods for producing the compounds of the invention by fermentation

The compounds of Formula I may be biosynthesized by various microorganisms. Microorganisms that may synthesize the compounds of the present invention include but are not limited to bacteria of the order Actinomycetales, also referred to as actinomycetes. Non-limiting examples of members belonging to the genera of Actinomycetes include *Nocardia, Geodermatophilus, Actinoplanes, Micromonospora, Nocardioides, Saccharothrix, Amycolatopsis, Kutzneria, Saccharomonospora, Saccharopolyspora, Kitasatospora, Streptomyces, Microbispora, Streptosporangium, Actinomadura*. The taxonomy of actinomycetes is complex and reference is made to Goodfellow (1989) Suprageneric classification of actinomycetes, *Bergey's Manual of Systematic Bacteriology,* Vol. 4, Williams and Wilkins, Baltimore, pp 2322-2339, and to Embley and Stackebrandt, (1994), and *The molecular phylogeny and systematics of the actinomycetes*, *Annu. Rev. Microbiol.* 48, 257-289 (1994), for genera that may synthesize the compounds of the invention.

Microorganisms biosynthetically producing compounds of Formula I are cultivated in culture media containing known nutritional sources for actinomycetes having assimilable sources of carbon, nitrogen plus optional inorganic salts and other known

growth factors at a pH of about 6 to about 9, non-limiting examples of growth media are provided in Table 1. Microorganisms are cultivated at incubation temperatures of about 20^0 C to about 40^0 C for about 3 to about 40 days.

The culture media inoculated with the microorganisms, which biosynthetically produce compounds of Formula I, may be aerated by incubating the inoculated culture media with agitation, for example shaking on a rotary shaker, or a shaking water bath. Aeration may also be achieved by the injection of air, oxygen or an appropriate gaseous mixture to the inoculated culture media during incubation.

After cultivation and production of compounds of Formula I, the compounds can be extracted and isolated from the cultivated culture media by techniques known to a skilled person in the art and/or disclosed herein, including for example centrifugation, chromatography, adsorption. For example, the cultivated culture media can be mixed with a suitable organic solvent such as n-butanol, n-butyl acetate and 4-methyl-2-pentanone, the organic layer can be separated for example, by centrifugation followed by the removal of the solvent, by evaporation to dryness or by evaporation to dryness under vacuum. The resulting residue can optionally be reconstituted with for example water, ethyl ether, ethanol acetate, methanol or a mixture thereof, and re-extracted in a two-phase system with a suitable organic solvent such as hexane, carbon tetrachloride, methylene chloride or a mixture thereof. After removal of the solvent, the compound of Formula I can be further purified by the use of standard techniques such as chromatography.

TABLE 1: Fermentation media

Component	CA	CB	GA[a]	JA	NA	OA	RM
pH[b]	**7**	**7**		**7.3**	**7**	**7**	**6.9**
Glucose	10		10			10	10
Sucrose		20	103				100
Cane molasses	15	5			10		
Corn starch				30			
Potato dextrin	40						
Corn steep liquor				15		3	
Yeast extract			5			3	5
Malt extract				35		3	
Pharmamedia™				15			
Glycerol					20	5	
N-Z Amine A	10						
Beef extract						3	

3010-5PCT-7CA

Component	CA	CB	GA[a]	JA	NA	OA	RM
Bacto-peptone		2			1		
Casamino acid			0.1		5		0.1
Thiamine						0.1	
$MgSO_4.7H_2O$	1	0.2					
$MgCl_2.6H_2O$			10.12				10.13
$CaCO_3$	2	5		2	4	2	
K_2SO_4			0.25				0.25
$FeSO_4.7H_2O$		0.1					
KI		0.5					
MOPS							21
Trace Elements Solution[c] ml/L			2				2

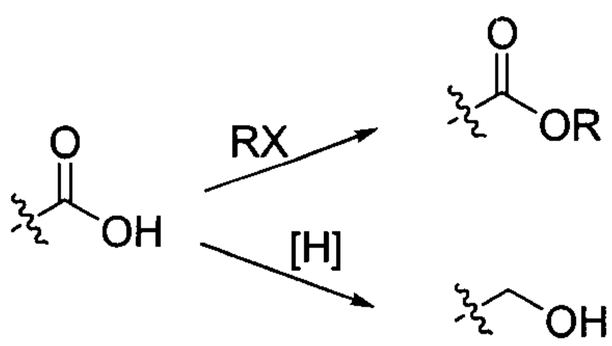
Unless otherwise indicated, all the components are in gm/L
To a liter of media GA add: 10 ml KH_2PO_4 (0.5% solution); 80 ml $CaCl_2.2H_2O$ (3.68% solution); 15 ml L-proline (20% solution); 100 ml TES buffer (5.73% solution, pH 7.2); 5 ml NaOH (1N solution).
The pH is adjusted as marked prior to the addition of $CaCO_3$.
Solution of trace elements contains: $ZnCl_2$ 40 mg; $FeCl_3.6H_2O$ (200 mg); $CuCl_2.2H_2O$ (10 mg); $(NH_4)_6Mo_7O_{24}.4H_2O$ (10 mg) per litre.

IV. Chemical modifications of Compounds 1 to 7

The compounds of Formula I that are biosynthesized by microorganisms may optionally be subjected to chemical modifications to form compounds that are derivatives or structural analogs of compounds of Formula I. Derivatives or structural analogs of compounds of Formula I having similar functional activities are within the scope of the present invention. Compounds of Formula I may optionally be modified using methods known in the art and described herein.

General principles of organic chemistry including functional moieties, reactivity and common protocols are described, for example, in Advanced Organic Chemistry 3rd Edition by Jerry March (1985). In addition, it will be appreciated by one of ordinary skill in the art that the synthetic methods described herein may use a variety of protecting groups, whether or not they are explicitly described. A "protecting group" as used herein means a moiety used to block one or more functional moieties such as reactive groups including oxygen, sulfur or nitrogen, so that a reaction can be carried out selectively at another reactive site in a polyfunctional compound. General principles for the use of protective groups, their applicability to specific functional groups and their uses are described for example in T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Edition, John Wiley & Sons, New York (1999),

Scheme 1: Modifications of acidic functions:

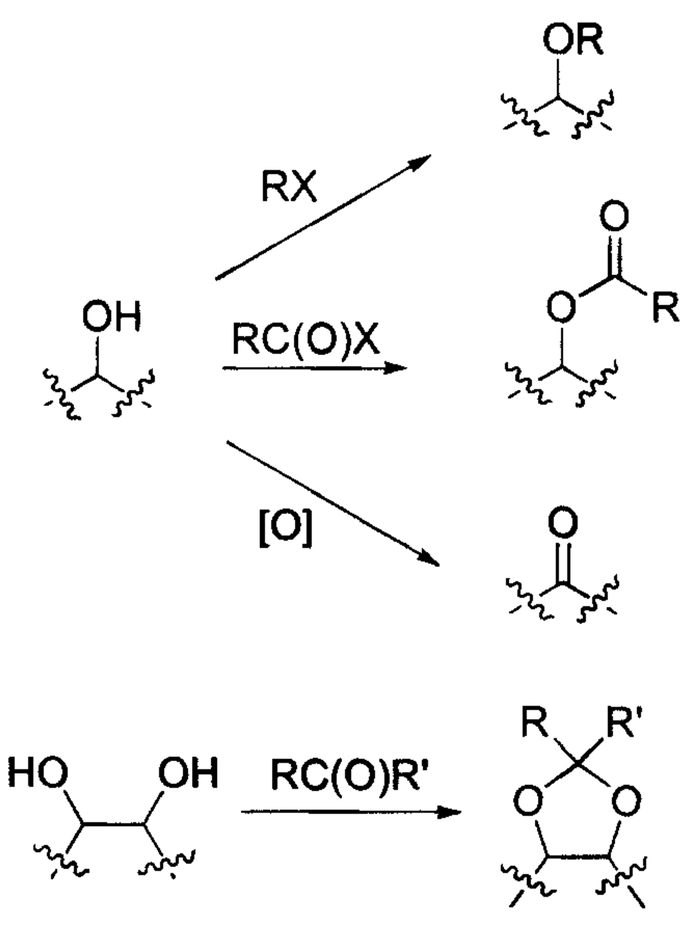


Scheme 1

wherein R is alkyl or aryl and X is a suitable leaving group

In Scheme 1, acidic functional groups are alkylated either individually or together. Simple ester is prepared from treatment of the carboxylic acid by an RX reagent such as diazoalkanes in the appropriate solvent. In Scheme 1, hydroxycyclopentenone is converted to alkoxycyclopentenone by similar treatment with the suitable RX reagent. In Scheme 1, carboxylic acids are also converted to alcohol by a reducing agent [H] such as lithiumaluminum hydride. Scheme 1 is used to obtain Compounds 3, 4, 5, 11 and 24 from Compound 1, Compounds 17, 18, 20, 26 and 28 respectively from Compounds 2, 7, 11, 25 and 27.

Scheme 2: Modifications to alcohol functions:



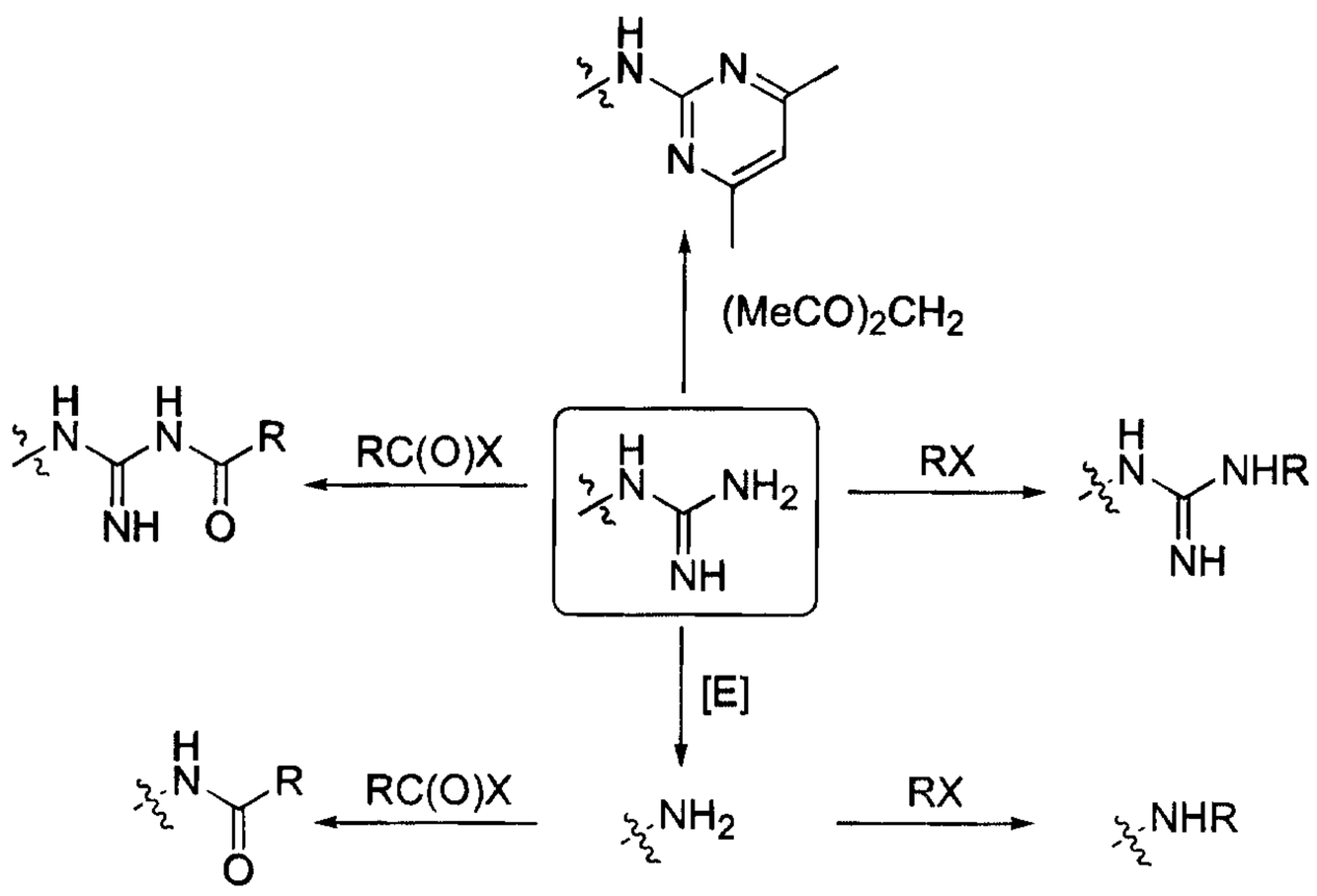
Scheme 2

wherein R and X are as in Scheme 1 and R' is alkyl, aryl or H

In Scheme 2, an alkylating agent such as methyliodide, converts alcohol to ether in the presence of a base such as potassium *tert*-butoxide. In Scheme 2, ester is obtained from the reaction of the alcohol with an activated carboxylic acid such as acid halides or anhydrides and N-hydroxysuccinimide esters in the presence of a base like diisopropylethylamine. In Scheme 2, a ketone is obtained from the oxidation of the alcohol by an oxidating agent [O] such as Dess-Martin (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)one) or Swern (oxalyl chloride and methylsulfoxide) reagents. In

scheme 2, a vicinal diol is converted to a 1,3-dioxolane ring by reaction with a ketone or an aldehyde (when R' is H) using an acid catalyst such as p-toluenesulfonic acid with removal of the water formed (like: Dean-Stark or molecular sieves). Scheme 2 is used to obtain Compound 10 from Compound 8, Compound 28 form Compound 3, Compounds 21 and 22 from Compound 5 and Compounds 25 and 27 from Compound 1.

Scheme 3: Modifications of guanidine group:



Scheme 3

wherein R and X are as in Scheme 1

In Scheme 3, a pyrimidine ring is obtained from the condensation of the guanidine group with a diketone, such as 2,4-pentadione in a solvent like ethanol under reflux. In Scheme 3, the guanidine functional group is enzymatically [E] hydrolyzed to amine in the appropriate conditions. In Scheme 3, the guanidine group or the amine group are alkylated by a suitable RX or acylated by a suitable RC(O)X in the presence of a base. Scheme 3 is used to produce Compounds 9, 13, 19 and 22 respectively from Compounds 2, 12, 17 and 5 and Compounds 6, 23 and 25 from Compound 1.

The following examples illustrate the invention but are not to be construed as limiting. Unless otherwise noted, all reagents were purchased from Sigma Chemical Co. (St. Louis, MO), (Aldrich).

Genes and proteins for producing the compounds of the invention

The invention also provides the genes and proteins forming the biosynthetic locus for the production of the compounds of Formula I.

Nucleic acid sequences encoding proteins involved in the biosynthesis of compounds of Formula I are provided in the accompanying sequence listing as SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57.

Polypeptides involved in the biosynthesis of compounds of Formula I are provided in the accompanying sequence listing as SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56.

One aspect of the present invention is an isolated, purified, or enriched nucleic acid comprising one of the sequences of SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57, the sequences complementary thereto, and isolated, purified or enriched nucleic acids having at least 70%, 75%, 80%, 85%, 90%, 95%, 97% or 99% identity to the above sequences as determined by analysis with BLASTN™ version 2.0 with the default parameters.

The isolated, purified or enriched nucleic acids may comprise DNA, including cDNA, genomic DNA, and synthetic DNA. The DNA may be double stranded or single stranded, and if single stranded may be the coding (sense) or non-coding (anti-sense) strand. Alternatively, the isolated, purified or enriched nucleic acids may comprise RNA. As discussed in more detail below, the isolated, purified or enriched nucleic acids of one of SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57 may be used to prepare one of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56 respectively or an isolated or purified polypeptide having at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% homology to the polypeptide of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56 as determined by analysis with BLASTP™ version 2.2.2 with the default parameters.

Accordingly, another aspect of the present invention is an isolated, purified or enriched nucleic acid which encodes one of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56 or an isolated or purified polypeptide having at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% homology to the polypeptide of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56 as determined by analysis with BLASTP™ version 2.2.2 with the default parameters. The coding sequences of these nucleic acids may be identical to one of the coding sequences of one of the nucleic acids of SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57 or may be different coding sequences which encode one of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56 or fragments comprising at least 50, 75, 100, 150, 200, 300 consecutive amino acids of one of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56 as a result of the redundancy or degeneracy of the genetic code. The genetic code is well known to those of skill in the art and can be obtained, for example, from Stryer, *Biochemistry*, 3rd edition, W. H. Freeman & Co., New York (1998).

The isolated, purified or enriched nucleic acid which encodes one of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, may include, but is not limited to: (1) only the coding sequences of one of SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57; (2) the coding sequences of SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57 and additional coding sequences, such as leader sequences or proprotein; and (3) the coding sequences of SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57 and non-coding sequences, such as introns or non-coding sequences 5' and/or 3' of the coding sequence.

The invention relates to polynucleotides based on SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57 but having polynucleotide changes that are "silent", for example changes which do not alter the amino acid sequence encoded by the polynucleotides of SEQ ID NOS: 3, 5, 7, 9, 11, 13,

15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57. The invention also relates to polynucleotides which have nucleotide changes which result in amino acid substitutions, additions, deletions, fusions and truncations of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56. Such nucleotide changes may be introduced using techniques such as site directed mutagenesis, random chemical mutagenesis, exonuclease III deletion, and other recombinant DNA techniques.

The isolated, purified or enriched nucleic acids of SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57, the sequences complementary thereto may be used as probes to identify and isolate DNAs encoding the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56 respectively. In such procedures, a genomic DNA library is constructed from a sample microorganism or a sample containing a microorganism capable of producing a polyketide. The genomic DNA library is then contacted with a probe comprising a coding sequence or a fragment of the coding sequence, encoding one of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, or a fragment thereof under conditions which permit the probe to specifically hybridize to sequences complementary thereto. In a preferred embodiment, the probe is an oligonucleotide of about 10 to about 30 nucleotides in length designed based on a nucleic acid of SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57. Genomic DNA clones which hybridize to the probe are then detected and isolated. Procedures for preparing and identifying DNA clones of interest are disclosed in Ausubel *et al.*, Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. (1997); and Sambrook *et al.*, Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbor Laboratory Press, (1989). In another embodiment, the probe is a restriction fragment or a PCR amplified nucleic acid derived from SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57.

The isolated, purified or enriched nucleic acids of SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57, the sequences

complementary thereto may be used as probes to identify and isolate related nucleic acids. In some embodiments, the related nucleic acids may be genomic DNAs (or cDNAs) from potential polyketide producers. In such procedures, a nucleic acid sample containing nucleic acids from a potential microbial producer of a compound of Formula I is contacted with the probe under conditions that permit the probe to specifically hybridize to related sequences. The nucleic acid sample may be a genomic DNA (or cDNA) library from the potential polyketide-producer. Hybridization of the probe to nucleic acids is then detected using any of the methods described above.

Hybridization may be carried out under conditions of low stringency, moderate stringency or high stringency. As an example of nucleic acid hybridization, a polymer membrane containing immobilized denatured nucleic acids is first prehybridized for 30 minutes at 45 °C in a solution consisting of 0.9 M NaCl, 50 mM NaH_2PO_4, pH 7.0, 5.0 mM Na_2EDTA, 0.5% SDS, 10X Denhardt's, and 0.5 mg/ml polyriboadenylic acid. Approximately 2 x 10^7 cpm (specific activity 4-9 x 10^8 cpm/ug) of ^{32}P end-labeled oligonucleotide probe are then added to the solution. After 12-16 hours of incubation, the membrane is washed for 30 minutes at room temperature in 1X SET (150 mM NaCl, 20 mM Tris hydrochloride, pH 7.8, 1 mM Na_2EDTA) containing 0.5% SDS, followed by a 30 minute wash in fresh 1X SET at Tm-10°C for the oligonucleotide probe where Tm is the melting temperature. The membrane is then exposed to autoradiographic film for detection of hybridization signals.

By varying the stringency of the hybridization conditions used to identify nucleic acids, such as genomic DNAs or cDNAs, which hybridize to the detectable probe, nucleic acids having different levels of homology to the probe can be identified and isolated. Stringency may be varied by conducting the hybridization at varying temperatures below the melting temperatures of the probes. The melting temperature of the probe may be calculated using the following formulas:

For oligonucleotide probes between 14 and 70 nucleotides in length the melting temperature (Tm) in degrees Celcius may be calculated using the formula: Tm=81.5+16.6(log [Na+]) + 0.41(fraction G+C)-(600/N) where N is the length of the oligonucleotide.

If the hybridization is carried out in a solution containing formamide, the melting temperature may be calculated using the equation Tm=81.5+16.6(log [Na +]) + 0.41(fraction G + C)-(0.63% formamide)-(600/N) where N is the length of the probe. Prehybridization may be carried out in 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 0.1 mg/ml denatured fragmented salmon sperm DNA or 6X SSC, 5X Denhardt's reagent, 0.5% SDS, 0.1 mg/ml denatured fragmented salmon sperm DNA, 50% formamide. The composition of the SSC and Denhardt's solutions are listed in Sambrook et al., *supra*. Hybridization is conducted by adding the detectable probe to the hybridization solutions listed above. Where the probe comprises double stranded DNA, it is denatured by incubating at elevated temperatures and quickly cooling before addition to the hybridization solution. It may also be desirable to similarly denature single stranded probes to eliminate or diminish formation of secondary structures or oligomerization. The filter is contacted with the hybridization solution for a sufficient period of time to allow the probe to hybridize to cDNAs or genomic DNAs containing sequences complementary thereto or homologous thereto. For probes over 200 nucleotides in length, the hybridization may be carried out at 15-25 °C below the Tm. For shorter probes, such as oligonucleotide probes, the hybridization may be conducted at 5-10 °C below the Tm. Preferably, the hybridization is conducted in 6X SSC, for shorter probes. Preferably, the hybridization is conducted in 50% formamide containing solutions, for longer probes.

All the foregoing hybridizations would be considered to be examples of hybridization performed under conditions of high stringency.

Following hybridization, the filter is washed for at least 15 minutes in 2X SSC, 0.1% SDS at room temperature or higher, depending on the desired stringency. The filter is then washed with 0.1X SSC, 0.5% SDS at room temperature (again) for 30 minutes to 1 hour. Nucleic acids which have hybridized to the probe are identified by conventional autoradiography and non-radioactive detection methods.

The above procedure may be modified to identify nucleic acids having decreasing levels of homology to the probe sequence. For example, to obtain nucleic acids of decreasing homology to the detectable probe, less stringent conditions may be used. For example, the hybridization temperature may be decreased in increments of 5 °C from 68 °C to 42

°C in a hybridization buffer having a Na+ concentration of approximately 1M. Following hybridization, the filter may be washed with 2X SSC, 0.5% SDS at the temperature of hybridization. These conditions are considered to be "moderate stringency" conditions above 50°C and "low stringency" conditions below 50°C. A specific example of "moderate stringency" hybridization conditions is when the above hybridization is conducted at 55°C. A specific example of "low stringency" hybridization conditions is when the above hybridization is conducted at 45°C.

Alternatively, the hybridization may be carried out in buffers, such as 6X SSC, containing formamide at a temperature of 42 °C. In this case, the concentration of formamide in the hybridization buffer may be reduced in 5% increments from 50% to 0% to identify clones having decreasing levels of homology to the probe. Following hybridization, the filter may be washed with 6X SSC, 0.5% SDS at 50 °C. These conditions are considered to be "moderate stringency" conditions above 25% formamide and "low stringency" conditions below 25% formamide. A specific example of "moderate stringency" hybridization conditions is when the above hybridization is conducted at 30% formamide. A specific example of "low stringency" hybridization conditions is when the above hybridization is conducted at 10% formamide.

Nucleic acids which have hybridized to the probe are identified by conventional autoradiography and non-radioactive detection methods.

For example, the preceding methods may be used to isolate nucleic acids having a sequence with at least 97%, at least 95%, at least 90%, at least 85%, at least 80%, or at least 70% homology to a nucleic acid sequence selected from the group consisting of the sequences of SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57, fragments comprising at least 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, 150, 200, 300, 400, or 500 consecutive bases thereof, and the sequences complementary thereto. Homology may be measured using BLASTN™ version 2.0 with the default parameters. For example, the homologous polynucleotides may have a coding sequence that is a naturally occurring allelic variant of one of the coding sequences described herein. Such allelic variant may have a substitution, deletion or addition of one or more nucleotides when compared to the nucleic acids of

SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 51, 53, 55, 57, or the sequences complementary thereto.

Additionally, the above procedures may be used to isolate nucleic acids which encode polypeptides having at least 99%, 95%, at least 90%, at least 85%, at least 80%, or at least 70% homology to a polypeptide having the sequence of one of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, or fragments comprising at least 50, 75, 100, 150, 200, 300 consecutive amino acids thereof as determined using the BLASTP™ version 2.2.2 algorithm with default parameters.

Another aspect of the present invention is an isolated or purified polypeptide comprising the sequence of one of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56 or fragments comprising at least 50, 75, 100, 150, 200 or 300 consecutive amino acids thereof. As discussed herein, such polypeptides may be obtained by inserting a nucleic acid encoding the polypeptide into a vector such that the coding sequence is operably linked to a sequence capable of driving the expression of the encoded polypeptide in a suitable host cell. For example, the expression vector may comprise a promoter, a ribosome binding site for translation initiation and a transcription terminator. The vector may also include appropriate sequences for modulating expression levels, an origin of replication and a selectable marker.

Promoters suitable for expressing the polypeptide or fragment thereof in bacteria include the *E.coli lac* or *trp* promoters, the lacI promoter, the lacZ promoter, the T3 promoter, the T7 promoter, the gpt promoter, the lambda P_R promoter, the lambda P_L promoter, promoters from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), and the acid phosphatase promoter. Fungal promoters include the α factor promoter. Eukaryotic promoters include the CMV immediate early promoter, the HSV thymidine kinase promoter, heat shock promoters, the early and late SV40 promoter, LTRs from retroviruses, and the mouse metallothionein-I promoter. Other promoters known to control expression of genes in prokaryotic or eukaryotic cells or their viruses may also be used.

Mammalian expression vectors may also comprise an origin of replication, any necessary ribosome binding sites, a polyadenylation site, splice donors and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. In some embodiments, DNA sequences derived from the SV40 splice and polyadenylation sites may be used to provide the required nontranscribed genetic elements.

Vectors for expressing the polypeptide or fragment thereof in eukaryotic cells may also contain enhancers to increase expression levels. Enhancers are cis-acting elements of DNA, usually from about 10 to about 300 bp in length that act on a promoter to increase its transcription. Examples include the SV40 enhancer on the late side of the replication origin bp 100 to 270, the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and the adenovirus enhancers.

In addition, the expression vectors preferably contain one or more selectable marker genes to permit selection of host cells containing the vector. Examples of selectable markers that may be used include genes encoding dihydrofolate reductase or genes conferring neomycin resistance for eukaryotic cell culture, genes conferring tetracycline or ampicillin resistance in *E. coli*, and the *S. cerevisiae* TRP1 gene.

In some embodiments, the nucleic acid encoding one of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, or fragments comprising at least 50, 75, 100, 150, 200 or 300 consecutive amino acids thereof is assembled in appropriate phase with a leader sequence capable of directing secretion of the translated polypeptides or fragments thereof. Optionally, the nucleic acid can encode a fusion polypeptide in which one of the polypeptide of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56 or fragments comprising at least 5, 10, 15, 20, 25, 30, 35, 40, 50, 75, 100, or 150 consecutive amino acids thereof is fused to heterologous peptides or polypeptides, such as N-terminal identification peptides which impart desired characteristics such as increased stability or simplified purification or detection.

The appropriate DNA sequence may be inserted into the vector by a variety of procedures. In general, the DNA sequence is ligated to the desired position in the vector following digestion of the insert and the vector with appropriate restriction

endonucleases. Alternatively, appropriate restriction enzyme sites can be engineered into a DNA sequence by PCR. A variety of cloning techniques are disclosed in Ausbel et al. Current Protocols in Molecular Biology, John Wiley 503 Sons, Inc. (1997) and Sambrook et al., Molecular Cloning: A Laboratory Manual 2d Ed., Cold Spring Harbour Laboratory Press, (1989). Such procedures and others are deemed to be within the scope of those skilled in the art.

The vector may be, for example, in the form of a plasmid, a viral particle, or a phage. Other vectors include derivatives of chromosomal, nonchromosomal and synthetic DNA sequences, viruses, bacterial plasmids, phage DNA, baculovirus, yeast plasmids, vectors derived from combinations of plasmids and phage DNA, viral DNA such as vaccinia, adenovirus, fowl pox virus, and pseudorabies. A variety of cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook, et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, N.Y., (1989).

Particular bacterial vectors which may be used include the commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC™ 37017), pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden), pGEM1 (Promega Biotec, Madison, WI, USA) pQE70, pQE60, pQE-9 (Qiagen), pD10, phiX174, pBluescript™ II KS, pNH8A, pNH16a, pNH18A, pNH46A (Stratagene), ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 (Pharmacia), pKK232-8 and pCM7. Particular eukaryotic vectors include pSV2CAT, pOG44, pXT1, pSG (Stratagene) pSVK3, pBPV, pMSG, and pSVL (Pharmacia). However, any other vector may be used as long as it is replicable and stable in the host cell.

The host cell may be any of the host cells familiar to those skilled in the art, including prokaryotic cells or eukaryotic cells. As representative examples of appropriate hosts, there may be mentioned: bacteria cells, such as *E. coli*, *Streptomyces*, *Bacillus subtilis*, *Salmonella typhimurium* and various species within the genera *Pseudomonas*, *Streptomyces*, and *Staphylococcus*, fungal cells, such as yeast, insect cells such as *Drosophila S2* and *Spodoptera Sf9*, animal cells such as CHO, COS or Bowes melanoma, and adenoviruses. The selection of an appropriate host is within the abilities of those skilled in the art.

The vector may be introduced into the host cells using any of a variety of techniques, including electroporation transformation, transfection, transduction, viral infection, gene guns, or Ti-mediated gene transfer. Where appropriate, the engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the genes of the present invention. Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter may be induced by appropriate means (e.g., temperature shift or chemical induction) and the cells may be cultured for an additional period to allow them to produce the desired polypeptide or fragment thereof. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract is retained for further purification. Microbial cells employed for expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents. Such methods are well known to those skilled in the art. The expressed polypeptide or fragment thereof can be recovered and purified from recombinant cell cultures by methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Protein refolding steps can be used, as necessary, in completing configuration of the polypeptide. If desired, high performance liquid chromatography (HPLC) can be employed for final purification steps. Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts (described by Gluzman, Cell, 23:175(1981)), and other cell lines capable of expressing proteins from a compatible vector, such as the C127, 3T3, CHO, HeLa and BHK cell lines.

The constructs in host cells can be used in a conventional manner to produce the gene product encoded by the recombinant sequence. Depending upon the host employed in a recombinant production procedure, the polypeptide produced by host cells containing the vector may be glycosylated or may be non-glycosylated. Polypeptides of the invention may or may not also include an initial methionine amino acid residue.

Alternatively, the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, or fragments comprising at least 50, 75, 100, 150, 200 or 300 consecutive amino acids thereof can be synthetically produced by conventional peptide synthesizers. In other embodiments, fragments or portions of the polynucleotides may be employed for producing the corresponding full-length polypeptide by peptide synthesis; therefore, the fragments may be employed as intermediates for producing the full-length polypeptides.

Cell-free translation systems can also be employed to produce one of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, or fragments comprising at least 50, 75, 100, 150, 200 or 300 consecutive amino acids thereof using mRNAs transcribed from a DNA construct comprising a promoter operably linked to a nucleic acid encoding the polypeptide or fragment thereof. In some embodiments, the DNA construct may be linearized prior to conducting an *in vitro* transcription reaction. The transcribed mRNA is then incubated with an appropriate cell-free translation extract, such as a rabbit reticulocyte extract, to produce the desired polypeptide or fragment thereof.

The present invention also relates to variants of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, or fragments comprising at least 50, 75, 100, 150, 200 or 300 consecutive amino acids thereof. The term "variant" includes derivatives or analogs of these polypeptides. In particular, the variants may differ in amino acid sequence from the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, by one or more substitutions, additions, deletions, fusions and truncations, which may be present in any combination.

The variants may be naturally occurring or created *in vitro*. In particular, such variants may be created using genetic engineering techniques such as site directed mutagenesis, random chemical mutagenesis, Exonuclease III deletion procedures, and standard cloning techniques. Alternatively, such variants, fragments, analogs, or derivatives may be created using chemical synthesis or modification procedures.

Other methods of making variants are also familiar to those skilled in the art. These include procedures in which nucleic acid sequences obtained from natural isolates are

modified to generate nucleic acids that encode polypeptides having characteristics which enhance their value in industrial or laboratory applications. In such procedures, a large number of variant sequences having one or more nucleotide differences with respect to the sequence obtained from the natural isolate are generated and characterized. Preferably, these nucleotide differences result in amino acid changes with respect to the polypeptides encoded by the nucleic acids from the natural isolates. For example, variants may be created using error prone PCR. In error prone PCR, DNA amplification is performed under conditions where the fidelity of the DNA polymerase is low, such that a high rate of point mutation is obtained along the entire length of the PCR product. Error prone PCR is described in Leung, D.W., *et al.*, Technique, 1:11-15 (1989) and Caldwell, R. C. & Joyce G.F., PCR Methods Applic., 2:28-33 (1992). Variants may also be created using site directed mutagenesis to generate site-specific mutations in any cloned DNA segment of interest. Oligonucleotide mutagenesis is described in Reidhaar-Olson, J.F. & Sauer, R.T., *et al.*, Science, 241:53-57 (1988). Variants may also be created using directed evolution strategies such as those described in US patent nos. 6,361,974 and 6,372,497. The variants of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, may be (i) variants in which one or more of the amino acid residues of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code.

Conservative substitutions are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Typically seen as conservative substitutions are the following replacements: replacements of an aliphatic amino acid such as Ala, Val, Leu and Ile with another aliphatic amino acid; replacement of a Ser with a Thr or vice versa; replacement of an acidic residue such as Asp or Glu with another acidic residue; replacement of a residue bearing an amide group, such as Asn or Gln, with another residue bearing an amide group; exchange of a basic residue such

as Lys or Arg with another basic residue; and replacement of an aromatic residue such as Phe or Tyr with another aromatic residue.

Other variants are those in which one or more of the amino acid residues of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56 includes a substituent group.

Still other variants are those in which the polypeptide is associated with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol).

Additional variants are those in which additional amino acids are fused to the polypeptide, such as leader sequence, a secretory sequence, a proprotein sequence or a sequence which facilitates purification, enrichment, or stabilization of the polypeptide.

In some embodiments, the fragments, derivatives and analogs retain the same biological function or activity as the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56. In other embodiments, the fragment, derivative or analogue includes a fused heterologous sequence which facilitates purification, enrichment, detection, stabilization or secretion of the polypeptide that can be enzymatically cleaved, in whole or in part, away from the fragment, derivative or analogue.

Another aspect of the present invention are polypeptides or fragments thereof which have at least 70%, at least 80%, at least 85%, at least 90%, or more than 95% homology to one of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, or a fragment comprising at least 50, 75, 100, 150, 200 or 300 consecutive amino acids thereof. Homology may be determined using a program, such as BLASTP version 2.2.2 with the default parameters, which aligns the polypeptides or fragments being compared and determines the extent of amino acid identity or similarity between them. It will be appreciated that amino acid "homology" includes conservative substitutions such as those described above.

The polypeptides or fragments having homology to one of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50,

52, 54, 56, or a fragment thereof may be obtained by isolating the nucleic acids encoding them using the techniques described above.

Alternatively, the homologous polypeptides or fragments may be obtained through biochemical enrichment or purification procedures. The sequence of potentially homologous polypeptides or fragments may be determined by proteolytic digestion, gel electrophoresis and/or microsequencing. The sequence of the prospective homologous polypeptide or fragment can be compared to one of the polypeptides of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 47, 50, 52, 54, 56, or a fragment thereof using a program such as BLASTP version 2.2.2 with the default parameters.

The PKS system of SEQ ID NOS: 37, 39, 41, 43, 45 and 47 may be modified to produce compounds of Formula I. Genetic modifications of PKS biosynthetic loci are well known in the art. The WO 01/34816 patent publication teaches the construction of a library of structural variants of the macrolide polyketide rapamycin derived from the genetic modification of genes in the locus that directs rapamycin synthesis. The genetic modifications taught include gene inactivations, gene insertions and gene replacements. These modifications, both individually and in combination at different positions within the rapamycin locus, resulted in alteration of polyketide starter units, chain length and hydroxyl sterospecificities in rapamycin. Similarly, McDaniel, *et.al.* [Proc Natl Acad Sci USA, 1999, 96:18646-51] generated a library of over 50 derivatives of the macrolide antibiotic erythromycin using a combination of genetic modifications including gene inactivations, macrolide chain length and hydroxyl sterospecificity modifications of the erythromycin biosynthesis genes. The PKS system of the invention may be genetically modified to produce compounds of Formula I. The biosynthetic locus of Example 1 is modified by deletion, mutagenesis, inactivation or replacement of one or more nucleic acid sequence that encode enzymatic activities. The modified gene locus of Example 1 produces compounds of Formula I that differ in size, degree of saturation and degree of oxidation. Compounds produced by these genetic modifications include, without limitations, Compounds 12, 14 and 16.

Pharmaceutical composition comprising the compounds of the invention

The compounds of the present invention, or pharmaceutically acceptable salts or prodrugs thereof, can be formulated for oral, intravenous, intramuscular, subcutaneous, topical or parenteral administration for the therapeutic or prophylactic treatment of diseases, particularly bacterial infections. For oral or parental administration, compounds of the present invention can be mixed with conventional pharmaceutical carriers and excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, wafers and the like. The compositions comprising a compound of this present invention will contain from about 0.1% to about 99.9%, about 5% to about 95%, about 10% to about 80% or about 15% to about 60% by weight of the active compound.

The pharmaceutical preparations disclosed herein are prepared in accordance with standard procedures and are administered at dosages that are selected to reduce, prevent, or eliminate bacterial infection (See, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA and Goodman and Gilman's the Pharmaceutical Basis of Therapeutics, Pergamon Press, New York, NY, for a general description of the methods for administering various antimicrobial agents for human therapy). The compositions of the present invention can be delivered using controlled (e.g., capsules) or sustained release delivery systems (e.g., bioerodable matrices). Exemplary delayed release delivery systems for drug delivery that are suitable for administration of the compositions of the invention (preferably of Formula I) are described in U.S. Patent Nos 4,452,775 (issued to Kent), 5,039,660 (issued to Leonard), 3,854,480 (issued to Zaffaroni).

The pharmaceutically-acceptable compositions of the present invention comprise one or more compounds of the present invention in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants and/or excipients, collectively referred to herein as "carrier" materials, and if desired other active ingredients. The compositions may contain common carriers and excipients, such as corn starch or gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid. The compositions may contain crosarmellose sodium, microcrystalline cellulose, sodium starch glycolate and alginic acid.

Tablet binders that can be included are acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Providone), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose.

Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicon fluid, talc, waxes, oils and colloical silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring or the like can also be used. It may also be desirable to add a coloring agent to make the dosage form more esthetic in appearance or to help identify the product comprising a compound of the present invention.

For oral use, solid formulations such as tablets and capsules are particularly useful. Sustained released or enterally coated preparations may also be devised. For pediatric and geriatric applications, suspension, syrups and chewable tablets are especially suitable. For oral administration, the pharmaceutical compositions are in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a therapeutically-effective amount of the active ingredient. Examples of such dosage units are tablets and capsules. For therapeutic purposes, the tablets and capsules which can contain, in addition to the active ingredient, conventional carriers such as binding agents, for example, acacia gum, gelatin, polyvinylpyrrolidone, sorbitol, or tragacanth; fillers, for example, calcium phosphate, glycine, lactose, maize-starch, sorbitol, or sucrose; lubricants, for example, magnesium stearate, polyethylene glycol, silica or talc: disintegrants, for example, potato starch, flavoring or coloring agents, or acceptable wetting agents. Oral liquid preparations generally are in the form of aqueous or oily solutions, suspensions, emulsions, syrups or elixirs may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous agents, preservatives, coloring agents and flavoring agents. Examples of additives for liquid preparations include acacia, almond oil, ethyl alcohol, fractionated coconut oil, gelatin, glucose syrup, glycerin, hydrogenated edible fats, lecithin, methyl cellulose, methyl or propyl *para*-hydroxybenzoate, propylene glycol, sorbitol, or sorbic acid.

For intravenous (IV) use, compounds of the present invention can be dissolved or suspended in any of the commonly used intravenous fluids and administered by

infusion. Intravenous fluids include, without limitation, physiological saline or Ringer's solution.

Formulations for parental administration can be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions or suspensions can be prepared from sterile powders or granules having one or more of the carriers mentioned for use in the formulations for oral administration. The compounds can be dissolved in polyethylene glycol, propylene glycol, ethanol, corn oil, benzyl alcohol, sodium chloride, and/or various buffers.

For intramuscular preparations, a sterile formulation of compounds of the present invention or suitable soluble salts forming the compound, can be dissolved and administered in a pharmaceutical diluent such as Water-for-Injection (WFI), physiological saline or 5% glucose. A suitable insoluble form of the compound may be prepared and administered as a suspension in an aqueous base or a pharmaceutically acceptable oil base, e.g. an ester of a long chain fatty acid such as ethyl oleate.

For topical use the compounds of present invention can also be prepared in suitable forms to be applied to the skin, or mucus membranes of the nose and throat, and can take the form of creams, ointments, liquid sprays or inhalants, lozenges, or throat paints. Such topical formulations further can include chemical compounds such as dimethylsulfoxide (DMSO) to facilitate surface penetration of the active ingredient.

For application to the eyes or ears, the compounds of the present invention can be presented in liquid or semi-liquid form formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints or powders.

For rectal administration the compounds of the present invention can be administered in the form of suppositories admixed with conventional carriers such as cocoa butter, wax or other glyceride.

Alternatively, the compound of the present invention can be in powder form for reconstitution in the appropriate pharmaceutically acceptable carrier at the time of delivery. In another embodiment, the unit dosage form of the compound can be a solution of the compound or a salt thereof in a suitable diluent in sterile, hermetically sealed ampoules.

The amount of the compound of the present invention in a unit dosage comprises a therapeutically-effective amount of at least one active compound of the present invention which may vary depending on the recipient subject, route and frequency of administration. A recipient subject refers to a plant, a cell culture or an animal such as an ovine or a mammal including a human.

According to this aspect of the present invention, the novel compositions disclosed herein are placed in a pharmaceutically acceptable carrier and are delivered to a recipient subject (including a human subject) in accordance with known methods of drug delivery. In general, the methods of the invention for delivering the compositions of the invention in vivo utilize art-recognized protocols for delivering the agent with the only substantial procedural modification being the substitution of the compounds of the present invention for the drugs in the art-recognized protocols.

Likewise, the methods for using the claimed composition for treating cells in culture, for example, to eliminate or reduce the level of bacterial contamination of a cell culture, utilize art-recognized protocols for treating cell cultures with antibacterial agents with the only substantial procedural modification being the substitution of the compounds of the present invention for the agents used in the art-recognized protocols.

The compounds of the present invention provide a method for treating microbial infections. As used herein the term unit dosage refers to a quantity of a therapeutically-effective amount of a compound of the present invention that elicits a desired therapeutic response. As used herein the phrase therapeutically-effective amount means an amount of a compound of the present invention that prevents the onset, alleviates the symptoms, or stops the progression of a bacterial infection. The term treating is defined as administering, to a subject, a therapeutically-effective amount of at least one compound of the present invention, both to prevent the occurrence of a bacterial infection, or to control or eliminate a bacterial infection. The term desired therapeutic response refers to treating a recipient subject with a compound of the present invention such that a bacterial infection is reversed, arrested or prevented in a recipient subject.

The compounds of the present invention can be administered as a single daily dose or in multiple doses per day. The treatment regime may require administration over extended

periods of time, e.g., for several days or for from two to four weeks. The amount per administered dose or the total amount administered will depend on such factors as the nature and severity of the infection, the age and general health of the recipient subject, the tolerance of the recipient subject to the compound and the type of the bacterial infection.

A compound according to this invention may also be administered in the diet or feed of a patient or animal. The diet for animals can be normal foodstuffs to which the compound can be added or it can be added to a premix.

The compounds of the present invention may be taken in combination, together or separately with any known clinically approved antibiotic to treat a recipient subject in need of such treatment.

Method of Inhibiting Bacterial Growth

In one embodiment, the present invention relates to a method for treating bacterial infection in a mammalian subject in need thereof, comprising the step of administering to the mammal a therapeutically effective amount of a polyene polyketide of Formula I, a compound as described herein, or a pharmaceutically acceptable derivative or prodrug thereof.

In another embodiment, the present invention relates to the use of a polyene polyketide of Formula I, a compound as described herein, or a pharmaceutical acceptable salt, derivative or prodrug thereof, as a pharmaceutical for treating bacterial infection in a mammalian subject in need thereof.

According to another embodiment, the invention provides a method of decreasing bacterial quantity in a biological sample. This method comprises the step of contacting the biological sample with a polyene polyketide of Formula I, a compound as described herein, or a pharmaceutically acceptable derivative or prodrug thereof. This method is effective if the number of bacteria decreases by at least 10%, and preferably more, e.g., 25%, 50%, 75% or even 100% after contacting the biological sample with a polyene polyketide of Formula I, a compound as described herein, or a pharmaceutically acceptable derivative or prodrug thereof.

These pharmaceutical compositions effective to treat or prevent a bacterial infection which comprise any one of Compounds 1 to 7, a compound of Formula I as described herein, or a pharmaceutically acceptable derivative or prodrug thereof in an amount sufficient to measurably decrease bacterial quantity, and a pharmaceutically acceptable carrier, are another embodiment of the present invention. The term "measurably decrease bacterial quantity", as used herein means a measurable change in the number of bacteria between a sample containing the inhibitor and a sample not containing the inhibitor.

Agents which increase the susceptibility of bacterial organisms to antibiotics are known. For example, U.S. Pat. No. 5,523,288, U.S. Pat. No. 5,783,561 and U.S. Pat. No. 6,140,306 describe methods of using bactericidal/permeability-increasing protein (BPI) for increasing antibiotic susceptibility of gram-positive and gram-negative bacteria. Agents that increase the permeability of the outer membrane of bacterial organisms have been described by Vaara, M. in Microbiological Reviews (1992) pp. 395-411, and the sensitization of gram-negative bacteria has been described by Tsubery, H., et al, in J. Med. Chem . (2000) pp. 3085-3092.

For the method of the invention related to treatment of subjects with a bacterial infection, a typical effective unit dose of any one of Compounds 1 to 7, a compound of Formula I as described herein or a pharmaceutically acceptable derivative or prodrug thereof given orally or parenterally would be from about 5 to about 100 mg/kg of body weight of the subject with a daily dose ranging from about 15 to about 300 mg/kg of body weight of the subject.

Another preferred embodiment of this invention relates to a method, as described above, of treating a bacterial infection in a mammal in need thereof, but further comprising the step of administering to the mammal an agent which increases the susceptibility of bacterial organisms to antibiotics.

According to another preferred embodiment, the invention provides a method, as described above, of decreasing bacterial quantity in a biological sample, but further comprising the step of contacting the biological sample with an agent which increases the susceptibility of bacterial organisms to antibiotics.

Methods of decreasing bacterial quantity are effective if the number of bacteria decreases at least 10%, and preferably more, e.g., 25%, 50%, 75% or even 100% after contacting the biological sample with any one of Compounds 1 to 7, a compound of Formula I as described herein, or a pharmaceutically acceptable derivative or prodrug thereof.

The pharmaceutical compositions and methods of this invention will be useful generally for controlling bacterial infections *in vivo*. Examples of bacterial organisms that may be controlled by the compositions and methods of this invention include, but are not limited to the following organisms: *Streptococcus pneumoniae, Streptococcus pyogenes, Enterococcus faecalis*, *Enterococcus faecium, Klebsiella pneumoniae, Enterobacter spp., Proteus spp., Pseudomonas aeruginosa, Escherichia coli, Serratia marcesens, Staphylococcus aureus, Haemophilus infuenzae, Bacillus anthracis, Mycoplasma pneumoniae*, and Coagulase negative *Staphylococcus* including *Staphylococcus epidermidis*. The compositions and methods will therefore be useful for controlling, treating or reducing the advancement, severity or effects of nosocomial or non-nosocomial infections. Examples of nosocomial uses include, but are not limited to, urinary tract infections, pneumonia, surgical wound infections, bacteremia and therapy for febrile neutropenic patients. Examples of non-nosocomial uses include but are not limited to urinary tract infections, pneumonia, prostatitis, skin and soft tissue infections and intra-abdominal infections.

In addition to the compounds of this invention, pharmaceutically acceptable derivatives or prodrugs of the compounds of this invention may also be employed in compositions to treat or prevent the above-identified disorders.

A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives or prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent

compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

Pharmaceutically acceptable prodrugs of the compounds of this invention include, without limitation, esters, amino acid esters, phosphate esters, metal salts and sulfonate esters.

Example 1: Genes and proteins for producing the compounds of the invention

Amycolatopsis orientalis ATCC™ 43491 was obtained from the American Type Culture Collection (P.O. Box 1549, Manassas, VA 20108, USA). The biosynthetic locus for the production of the compound of Formula I was identified in the genome of *Amycolatopsis orientalis* ATCC™ 43491 using the genome scanning method described in US patent publication 2003/0138810 A1, CA 2,352,451 and Zazopoulos *et. al.*, *Nature Biotechnol.*, 21, 187-190 (2003).

The biosynthetic locus spans approximately 100,000 base pairs of DNA and encodes 27 proteins. More than 10 kilobases of DNA sequence were analyzed on each side of the locus and these regions were deemed to contain primary genes or genes unrelated to the synthesis of the compound of Formula I. As illustrated in Figure 11, the locus is contained within three sequences of contiguous base pairs, namely Contig 1 having the 12,647 contiguous base pairs of SEQ ID NO: 1 and comprising ORFs 1 to 11 (SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23), Contig 2 having the 73,599 contiguous base pairs of SEQ ID NO: 24 and comprising ORFs 12 to 23 (SEQ ID NOS: 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 48), and Contig 3 having the 6,995 base pairs of SEQ ID NO: 49 and comprising ORFs 24 to 27 (SEQ ID NOS: 51, 53, 55 and 57). The order, relative position and orientation of the 27 open reading frames representing the proteins of the biosynthetic locus are illustrated schematically in Figure 11. The top line in Figure 11 provides a scale in base pairs. The black bars depict the three DNA contigs (SEQ ID NOS: 1, 24 and 49) that cover the locus. The empty arrows represent the 27 open reading frames of this biosynthetic locus. The black arrows represent the four deposited cosmid clones covering the locus.

The biosynthetic locus will further be understood with reference to the sequence listing which provides contiguous nucleotide sequences and deduced amino acid sequences of

the locus from *Amycolatopsis orientalis* ATCC™ 43491. The contiguous nucleotide sequences are arranged such that, as found within the biosynthetic locus, Contig 1 (SEQ ID NO: 1) is adjacent to the 5' end of Contig 2 (SEQ ID NO: 24), which in turn is adjacent to Contig 3 (SEQ ID NO: 49). The ORFs illustrated in Figure 11 and provided in the sequence listing represent open reading frames deduced from the nucleotide sequences of Contigs 1, 2 and 3 (SEQ ID NOS: 1, 24 and 49). Referring to the Sequence Listing, ORF 1 (SEQ ID NO: 3) is the polynucleotide drawn from residues 1 to 438 (sense/antisense strand) of SEQ ID NO: 1, and SEQ ID NO: 2 represents that polypeptide deduced from SEQ ID NO: 3. ORF 2 (SEQ ID NO: 5) is the polynucleotide drawn from residues 435 to 1544 of SEQ ID NO: 1, and SEQ ID NO: 4 represents the polypeptide deduced from SEQ ID NO: 5. ORF 3 (SEQ ID NO: 7) is the polynucleotide drawn from residues 1656 to 2171 of SEQ ID NO: 1, and SEQ ID NO: 6 represents the polypeptide deduced from SEQ ID NO: 7. ORF 4 (SEQ ID NO: 9) is the polynucleotide drawn from residues 2393 to 5203 of SEQ ID NO: 1, and SEQ ID NO: 8 represents the polypeptide deduced from SEQ ID NO: 9. ORF 5 (SEQ ID NO: 11) is the polynucleotide drawn from residues 6231 to 5419 of SEQ ID NO: 1, and SEQ ID NO: 10 represents the polypeptide deduced from SEQ ID NO: 11. ORF 6 (SEQ ID NO: 13) is the polynucleotide drawn from residues 6415 to 7104 of SEQ ID NO: 1, and SEQ ID NO: 12 represents the polypeptide deduced from SEQ ID NO: 13. ORF 7 (SEQ ID NO: 15) is the polynucleotide drawn from residues 7213 to 8874 of SEQ ID NO: 1, and SEQ ID NO: 14 represents the polypeptide deduced from SEQ ID NO: 15. ORF 8 (SEQ ID NO: 17) is the polynucleotide drawn from residues 9477 to 8938 of SEQ ID NO: 1, and SEQ ID NO: 16 represents the polypeptide deduced from SEQ ID NO: 17. ORF 9 (SEQ ID NO: 19) is the polynucleotide drawn from residues 9655 to 10323 of SEQ ID NO: 1, and SEQ ID NO: 18 represents the polypeptide deduced from SEQ ID NO: 19. ORF 10 (SEQ ID NO: 21) is the polynucleotide drawn from residues 11655 to 10516 of SEQ ID NO: 1, and SEQ ID NO: 20 represents the polypeptide deduced from SEQ ID NO: 21. ORF 11 (SEQ ID NO: 23) is the polynucleotide drawn from residues 11855 to 12610 of SEQ ID NO: 1, and SEQ ID NO: 22 represents the polypeptide deduced from SEQ ID NO: 23. ORF 12 (SEQ ID NO: 26) is the polynucleotide drawn from residues 520 to 32 of SEQ ID NO: 24, and SEQ ID NO: 25 represents the polypeptide deduced from SEQ ID NO: 26.

ORF 13 (SEQ ID NO: 28) is the polynucleotide drawn from residues 840 to 2165 of SEQ ID NO: 24, and SEQ ID NO: 27 represents the polypeptide deduced from SEQ ID NO: 28. ORF 14 (SEQ ID NO: 30) is the polynucleotide drawn from residues 2201 to 3424 of SEQ ID NO: 24, and SEQ ID NO: 29 represents the polypeptide deduced from SEQ ID NO: 30. ORF 15 (SEQ ID NO: 32) is the polynucleotide drawn from residues 3429 to 4994 of SEQ ID NO: 24, and SEQ ID NO: 31 represents the polypeptide deduced from SEQ ID NO: 32. ORF 16 (SEQ ID NO: 34) is the polynucleotide drawn from residues 4991 to 6199 of SEQ ID NO: 24, and SEQ ID NO: 33 represents the polypeptide deduced from SEQ ID NO: 34. ORF 17 (SEQ ID NO: 36) is the polynucleotide drawn from residues 6389 to 7924 of SEQ ID NO: 24, and SEQ ID NO: 35 represents the polypeptide deduced from SEQ ID NO: 36. ORF 18 (SEQ ID NO: 38) is the polynucleotide drawn from residues 8404 to 19908 of SEQ ID NO: 24, and SEQ ID NO: 37 represents the polypeptide deduced from SEQ ID NO: 38. ORF 19 (SEQ ID NO: 40) is the polynucleotide drawn from residues 19910 to 37081 of SEQ ID NO: 24, and SEQ ID NO: 39 represents the polypeptide deduced from SEQ ID NO: 40. ORF 20 (SEQ ID NO: 42) is the polynucleotide drawn from residues 37085 to 42292 of SEQ ID NO: 24, and SEQ ID NO: 41 represents the polypeptide deduced from SEQ ID NO: 42. ORF 21 (SEQ ID NO: 44) is the polynucleotide drawn from residues 42617 to 52411 of SEQ ID NO: 24, and SEQ ID NO: 43 represents the polypeptide deduced from SEQ ID NO: 44. ORF 22 (SEQ ID NO: 46) is the polynucleotide drawn from residues 52438 to 67737 of SEQ ID NO: 24, and SEQ ID NO: 45 represents the polypeptide deduced from SEQ ID NO: 46. ORF 23 (SEQ ID NO: 48) is the polynucleotide drawn from residues 67751 to 73516 of SEQ ID NO: 24, and SEQ ID NO: 47 represents the polypeptide deduced from SEQ ID NO: 48. ORF 24 (SEQ ID NO: 51) is the polynucleotide drawn from residues 939 to 16 of SEQ ID NO: 49, and SEQ ID NO: 50 represents the polypeptide deduced from SEQ ID NO: 51. ORF 25 (SEQ ID NO: 53) is the polynucleotide drawn from residues 2374 to 944 of SEQ ID NO: 49, and SEQ ID NO: 52 represents the polypeptide deduced from SEQ ID NO: 53. ORF 26 (SEQ ID NO: 55) is the polynucleotide drawn from residues 2600 to 2391 of SEQ ID NO: 49, and SEQ ID NO: 54 represents the polypeptide deduced from SEQ ID NO: 55. ORF 27 (SEQ ID NO: 57) is the

polynucleotide drawn from residues 3378 to 2614 of SEQ ID NO: 49, and SEQ ID NO: 56 represents the polypeptide deduced from SEQ ID NO: 57.

Some open reading frames provided in the Sequence Listing, namely ORF 2 (SEQ ID NO: 4), ORF 5 (SEQ ID NO: 10), ORF 12 (SEQ ID NO: 25), ORF 13 (SEQ ID NO: 27), ORF 15 (SEQ ID NO: 31), ORF 17 (SEQ ID NO: 35), ORF 19 (SEQ ID NO: 39), ORF 20 (SEQ ID NO: 41), ORF 22 (SEQ ID NO: 45), ORF 24 (SEQ ID NO: 50), ORF 26 (SEQ ID NO: 54) and ORF 27 (SEQ ID NO: 56) initiate with non-standard initiation codons (eg. GTG – Valine, or CTG – Leucine) rather than standard initiation codon ATG methionine. All ORFs are listed with the appropriate M, V or L amino acids at the amino-terminal position to indicate the specificity of the first codon of the ORF. It is expected, however, that in all cases the biosynthesized protein will contain a methionine residue, and more specifically a formylmethionine residue, at the amino terminal position, in keeping with the widely accepted principle that protein synthesis in bacteria initiates with methionine (formylmethionine) even when the encoding gene specifies a non-standard initiation codon (e.g. Stryer BioChemistry 3rd edition, 1998, W.H. Freeman and Co., New York, pp. 752-754).

Four deposits of E. coli DH10B vectors, each harbouring a cosmid clone of a partial biosynthetic locus for the compound of Formula I from *Amycolatopsis orientalis* (ATCC™ 43491) and together spanning the full biosynthetic locus for production of the compound of Formula I have been deposited with the International Depositary Authority of Canada, Bureau of Microbiology, Health Canada, 1015 Arlington Street, Winnipeg, Manitoba, Canada R3E 3R2 on September 5, 2003 and were assigned deposit accession numbers IDAC 050903-01, IDAC 050903-02, IDAC 050903-03 and IDAC 050903-04 respectively. The cosmid of deposit IDAC 050903-03 covers residue 1 to residue 8800 of Contig 1 (SEQ ID NO: 1). The cosmid of deposit IDAC 050903-01 covers residue 1600 of Contig 1 (SEQ ID NO: 1) to residue 19840 of Contig 2 (SEQ ID NO: 24). The cosmid of deposit IDAC 050903-02 covers the residue 14700 to residue 52230 of Contig 2 (SEQ ID NO: 24). The cosmid of deposit IDAC 050903-04 covers residue 41090 of Contig 2 (SEQ ID NO: 24) to residue 3378 of Contig 3 (SEQ ID NO: 49). The sequence of the polynucleotides comprised in the deposited strains, as well as the amino acid sequence

of any polypeptide encoded thereby are controlling in the event of any conflict with any description of sequences herein.

The deposit of the deposited strains has been made under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for Purposes of Patent Procedure. The deposited strains will be irrevocably and without restriction or condition released to the public upon the issuance of a patent. The deposited strains are provided merely as convenience to those skilled in the art and are not an admission that a deposit is required for enablement. A license may be required to make, use or sell the deposited strains, and compounds derived therefrom, and no such license is hereby granted.

In order to identify the function of the proteins coded by the genes forming the biosynthetic locus for the production of the compounds of Formula I the gene products of ORFs 1 to 27, namely SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 50, 52, 54 and 56, were compared, using the BLASTP version 2.2.6 algorithm with the default parameters, to sequences in the National Center for Biotechnology Information (NCBI) nonredundant protein database and the DECIPHER® database of microbial genes, pathways and natural products (Ecopia BioSciences Inc. St.-Laurent, QC, Canada).

The accession numbers of the top GenBank™ hits of this BLAST analysis are presented in Table 2 along with the corresponding E values. The E value relates the expected number of chance alignments with an alignment score at least equal to the observed alignment score. An E value of 0.00 indicates a perfect homolog. The E values are calculated as described in Altschul *et al. J. Mol. Biol.*, 215, 403-410 (1990). The E value assists in the determination of whether two sequences display sufficient similarity to justify an inference of homology.

Table 2

ORF	Family	# aa	Genbank homology	probability	% identity	% similarity	proposed function of GenBank match
1	UNBP	145	CAD60535.1, 194aa	1e-21	52/127(40.94%)	71 / 127 (55.91%)	Cinorf13 protein Streptomyces cinnamoneus
			NP_822919.1, 176aa	1e-06	36 / 113 (31.86%)	57 / 113 (50.44%)	hypothetical protein Streptomyces avermitilis
			NP_301329.1, 79aa	0.014	20 / 56 (35.71%)	29 / 56 (51.79%)	hypothetical protein Mycobacterium leprae
2	MEBA	369	CAB86101, 260aa	6.00E-05	69 /260 (26%)	97 / 260 (36%)	membrane protein
3	REQB	171	NP_301177.1, 132aa	4e-10	41 / 131 (31.3%)	73 / 131 (55.73%)	conserved hypothetical protein Mycobacterium leprae pir
			NP_218366.1, 132aa	4e-10	41 / 131 (31.3%)	73 / 131 (55.73%)	hypothetical protein Rv3849 Mycobacterium tuberculosis
			CAD60534.1, 163aa	2e-09	42 / 120 (35%)	61 / 120 (50.83%)	Cinorf12 protein Streptomyces cinnamoneus
4	REGD	936	AAC68887.1, 928aa	1e-149	345 / 919 (37.54%)	476 / 919 (51.8%)	putative transcriptional activator PikD Streptomyces venezuelae
			AAM88362.1, 945aa	1e-146	337 / 915 (36.83%)	469 / 915 (51.26%)	NbmM Streptomyces narbonensis
			NP_824077.1, 942aa	1e-138	343 / 933 (36.76%)	457 / 933 (48.98%)	LuxR-family transcriptional regulator Streptomyces avermitilis
5	MTNA	271	AAP36564.1, 237aa	6e-20	74 / 214 (34.58%)	99 / 214 (46.26%)	Homo sapiens guanidinoacetate N-methyltransferase
			NP_036925.1, 236aa	2e-20	72 / 214 (33.64%)	100 / 214 (46.73%)	guanidinoacetate methyltransferase Rattus norvegicus
			AAP36564.1, 237aa	6e-20	74 / 214 (34.58%)	99 / 214 (46.26%)	Homo sapiens guanidinoacetate N-methyltransferase
6	MEMO	229	NP_825904.1, 233aa	5e-23	71 / 187 (37.97%)	91 / 187 (48.66%)	putative membrane protein Streptomyces avermitilis
			NP_627542.1, 238aa	5e-19	64 / 191 (33.51%)	93 / 191 (48.69%)	putative membrane protein Streptomyces coelicolor
			AAN07910.1, 277aa	3e-17	58 / 181 (32.04%)	88 / 181 (48.62%)	AlbD Streptomyces noursei
7	TMOA	553	NP_828069.1, 565aa	0.0	328 / 548 (59.85%)	394 / 548 (71.9%)	putative amino oxidase Streptomyces avermitilis
			NP_625735.1, 565aa	0.0	325 / 548 (59.31%)	394 / 548 (71.9%)	putative amino oxidase Streptomyces coelicolor
			ZP_00086824.1, 560aa	1e-172	290 / 552 (52.54%)	371 / 552 (67.21%)	hypothetical protein Pseudomonas fluorescens
8	UNEW	179	ZP_00100936.1, 308aa	0.086	30 / 98 (30.61%)	49 / 98 (50%)	hypothetical protein Desulfitobacterium hafniense

ORF	Family	# aa	Genbank homology	probability	% identity	% similarity	proposed function of GenBank match
			NP_629948.1, 229aa	6e-55	120/225 (53.3%)	143/225 (63.56%)	two-component response regulator Streptomyces
			NP_628533.1, 226aa	1e-43	101/219 (46.12%)	130/219 (59.36%)	two-component response regulator Streptomyces
10	SPKF	379	NP_629947.1, 384aa	2e-34	93 / 216 (43.06%)	119 / 216 (55.09%)	putative two-component sensor Streptomyces coelicolor
			NP_823615.1, 384aa	4e-34	93 / 216 (43.06%)	122 / 216 (56.48%)	putative two-component sensor kinase Streptomyces
			NP_628532.1, 403aa	8e-29	87 / 231 (37.66%)	115 / 231 (49.78%)	putative two component sensor kinase Streptomyces
11	TESA	251	AAO65810.1, 267aa	8e-50	112 / 251 (44.62%)	139 / 251 (55.38%)	thioesterase; MonAX Streptomyces cinnamonensis
			NP_822128.1, 250aa	1e-48	107 / 242 (44.21%)	134 / 242 (55.37%)	thioesterase Streptomyces avermitilis
			NP_851508.1, 265aa	1e-47	103 / 225 (45.78%)	131 / 225 (58.22%)	probable thioesterase Streptomyces rochei
12	UNIQ	162	No hits	No hits	No hits	No hits	No hits
13	SOXA	441	AAF23790.1, 437aa	6e-88	176 / 436 (40.37%)	256 / 436 (58.72%)	UDP-glucose dehydrogenase Zymomonas mobilis
			NP_385188.1, 437aa	1e-87	180 / 438 (41.1%)	253 / 438 (57.76%)	UDP-GLUCOSE 6-DEHYDROGENASE Sinorhizobium
			ZP_00052125.1, 439aa	2e-87	182 / 434 (41.94%)	248 / 434 (57.14%)	hypothetical protein Magnetospirillum magnetotacticum
14	GTFA	407	AAM54103.1, 402aa	4e-67	165 / 409 (40.34%)	207 / 409 (50.61%)	glycosyltransferase Actinosynnema pretiosum subsp. auranticum
			AAM70336.1, 392aa	1e-16	103 / 418 (24.64%)	158 / 418 (37.8%)	CalG1 Micromonospora echinospora
			NP_624398.1, 407aa	1e-13	87 / 270 (32.22%)	122 / 270 (45.19%)	putative glycosyl transferase Streptomyces coelicolor
15	ADSN	521	AAG34183.1, 519aa	1e-111	223 / 515 (43.3%)	297 / 515 (57.67%)	SimL Streptomyces antibioticus
			AAG29784.1, 529aa	2e-76	178 / 510 (34.9%)	246 / 510 (48.24%)	putative ligase Streptomyces rishiriensis
			AAN65228.1, 527aa	4e-76	175 / 513 (34.11%)	246 / 513 (47.95%)	amide synthetase Streptomyces roseochromogenes subsp. oscitans
16	AYTP	402	NP_387095.1, 405aa	1e-101	190 / 382 (49%)	237 / 382 (62%)	5-aminolevulinic acid synthase Sinorhizobium meliloti
			BAA35068.1, 403aa	1e-101	191 / 400 (47%)	251 / 400 (62%)	5-aminolevulinate synthase Rhodopseudomonas palustris
			ZP_00011134.1, 443aa	1e-101	193 / 400 (48%)	249 / 400 (62%)	hypothetical protein Rhodopseudomonas palustris

ORF	Family	# aa	Genbank homology	probability	% identity	% similarity	proposed function of GenBank match
17	CALB	511	NP_631034.1, 511aa	1e-125	240 / 493 (48.68%)	298 / 493 (60.45%)	probable long-chain-fatty-acid-CoA ligase Streptomyces coelicolor
			NP_822779.1, 503aa	1e-123	236 / 491 (48.07%)	294 / 491 (59.88%)	putative long-chain fatty acid:CoA ligase Streptomyces avermitilis
			ZP_00059397.1, 557aa	1e-117	224 / 496 (45.16%)	291 / 496 (58.67%)	hypothetical protein Thermobifida fusca
18	PKSH	3834	AAF71776.1, 11096aa	0.0	1806 / 3951 (45.71%)	2169 / 3951 (54.9%)	NysC Streptomyces noursei
			AAF71776.1, 11096aa	0.0	1417 / 3280 (43.2%)	1733 / 3280 (52.84%)	NysC Streptomyces noursei
			AAF71776.1, 11096aa	0.0	1132 / 2687 (42.13%)	1387 / 2687 (51.62%)	NysC Streptomyces noursei
19	PKSH	5723	AAK73514.1, 10917aa	0.0	2653 / 5231 (50.72%)	3158 / 5231 (60.37%)	AmphC Streptomyces nodosus
			AAK73514.1, 10917aa	0.0	1682 / 3155 (53.31%)	2014 / 3155 (63.84%)	AmphC Streptomyces nodosus
			AAK73514.1, 10917aa	0.0	1643 / 3190 (51.5%)	1984 / 3190 (62.19%)	AmphC Streptomyces nodosus
20	PKSH	1735	NP_821593.1, 3564aa	0.0	876 / 1803 (48.59%)	1051 / 1803 (58.29%)	modular polyketide synthase Streptomyces avermitilis
			NP_821593.1, 3564aa	0.0	805 / 1750 (46%)	988 / 1750 (56.46%)	modular polyketide synthase Streptomyces avermitilis
			BAB69304.1, 3524aa	0.0	876 / 1803 (48.59%)	1051 / 1803 (58.29%)	modular polyketide synthase Streptomyces avermitilis
21	PKSH	3264	NP_824071.1, 3613aa	0.0	1600 / 3344 (47.85%)	1951 / 3344 (58.34%)	modular polyketide synthase Streptomyces avermitilis
			T17409, 4613aa	0.0	1562 / 3444 (45.35%)	1898 / 3444 (55.11%)	polyketide synthase type I - Streptomyces venezuelae
			T17409, 4613aa	0.0	492 / 994 (49.5%)	616 / 994 (61.97%)	polyketide synthase type I - Streptomyces venezuelae
22	PKSH	5099	CAB41041.1, 6797aa	0.0	2006 / 4012 (50%)	2442 / 4012 (60.87%)	polyketide synthase Streptomyces natalensis
			CAB41041.1, 6797aa	0.0	1105 / 2269 (48.7%)	1342 / 2269 (59.14%)	polyketide synthase Streptomyces natalensis
			CAB41041.1, 6797aa	0.0	541 / 881 (61.41%)	637 / 881 (72.3%)	polyketide synthase Streptomyces natalensis
23	PKSH	1921	NP_821593.1, 3564aa	0.0	888 / 1748 (50.8%)	1083 / 1748 (61.96%)	modular polyketide synthase Streptomyces avermitilis
			NP_821593.1, 3564aa	0.0	848 / 1757 (48.26%)	1030 / 1757 (58.62%)	modular polyketide synthase Streptomyces avermitilis
			BAB69304.1, 3524aa	0.0	888 / 1748 (50.8%)	1083 / 1748 (61.96%)	modular polyketide synthase Streptomyces avermitilis

ORF	Family	# aa	Genbank homology	probability	% identity	% similarity	proposed function of GenBank match
24	AYTF	307	AAK60008.1, 316aa	7e-12	83 / 312 (26.6%)	126 / 312 (40.38%)	malonyl-CoA:acyl carrier protein transacylase-like protein Streptomyces aureofaciens
			NP_657821.1, 314aa	2e-07	64 / 305 (20.98%)	118 / 305 (38.69%)	Acyl_transf, Acyl transferase domain Bacillus anthracis
			NP_228607.1, 293aa	4e-07	64 / 294 (21.77%)	118 / 294 (40.14%)	malonyl CoA-acyl carrier protein transacylase Thermotoga maritima
25	CALB	476	AAL35216.1, 540aa	3e-34	142 / 485 (29.28%)	224 / 485 (46.19%)	4-coumarate:CoA ligase Amorpha fruticosa
			AAC97600.1, 547aa	2e-33	132 / 487 (27.1%)	223 / 487 (45.79%)	4-coumarate:CoA ligase isoenzyme 2 Glycine max
			NP_821780.1, 518aa	3e-33	132 / 470 (28.09%)	201 / 470 (42.77%)	putative acyl-CoA synthetase, long-chain fatty acid:CoA ligase Streptomyces avermitilis
26	UNAC	69	AAC01708.1, 88aa	7e-06	32 / 70 (45.71%)	38 / 70 (54.29%)	unknown Amycolatopsis mediterranei
27	TESA	254	NP_824079.1, 252aa	4e-80	149 / 238 (62.61%)	172 / 238 (72.27%)	putative thioesterase Streptomyces avermitilis
			NP_822128.1, 250aa	7e-80	145 / 237 (61.18%)	170 / 237 (71.73%)	thioesterase Streptomyces avermitilis
			NP_821582.1, 255aa	2e-75	136 / 243 (55.97%)	169 / 243 (69.55%)	putative thioesterase Streptomyces avermitilis

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The ORFs encoding proteins involved in the biosynthesis of compounds of Formula I are assigned a putative function and grouped together in families based on sequence similarity to known proteins. To correlate structure and function, the protein families are given a four-letter designation used throughout the description and figures as indicated in Table 3. The meaning of the four letter designations is as follows: ADSN designates an amide synthetase; AYTF and AYTP designate acyltransferase activities; CALB designates an acylCoA ligase; GTFA designates a glycosyltransferase; MEBA and UNEW designate membrane proteins; MTNA designates a methyltransferase; PKSH designates a type I polyketide synthase system; REGD, REQB and RREB designate transcriptional regulators; SPKF designates a sensory protein kinase; TESA designates a thioesterase activity; TMOA designates an amino acid oxidase; UNIQ, UNBP and UNAC designate proteins of unknown function.

Table 3

Family	**Function**
ADSN	adenylating /condensing synthetase, amide synthetase, enzymes able to activate substrates as acyl adenylates and subsequently transfer the acyl group to an amino group of the acceptor molecule
AYTP	acyltransferase; pyridoxal phosphate dependent
AYTF	acyltransferase; acyl CoA-acyl carrier protein transacylase); includes malonyl CoA-ACP transacylases
CALB	acyl CoA ligase; shows similarity to plant coumarate CoA ligases, other aryl CoA ligases, yeast CoA synthetase and aminocoumarin ligases
GTFA	Glycosyltransferases
MEBA	membrane protein; putative transporter, permease;
MTNA	N-methyltransferase
PKSH	Polyketide synthase, type I
REGD	transcriptional regulator
REBQ	Regulator
RREB	Response regulator
SOXA	sugar oxidoreductase
SPKF	sensory protein kinase
TESA	Thioesterase
TMOA	amino acid monooxygenase
UNIQ	Unknown;
UNBP	Unknown
UNAC	Unknown
UNEW	Similarity to membrane proteins

Biosynthesis of the compounds of Formula I involves the action of a multimodular type I polyketide synthase system (PKS) corresponding to ORFs 18 to 23 (SEQ ID NOS: 37, 39, 41, 43, 45 and 47). Type I PKSs are large modular proteins that condense acyl thioester units in a sequential manner. PKS systems consist of one or more polyfunctional polypeptides each of which is made up of modules. Each type I PKS module contains three domains: a β-ketoacyl protein synthase (KS), an acyltransferase (AT) and an acyl carrier protein (ACP). Domains conferring additional enzymatic activities such as ketoreductase (KR), dehydratase (DH) and enoylreductase (ER) can also be found in the PKS modules. These additional domains result in various degrees of reduction of the β-keto groups of the growing polyketide chain. Each module is responsible for one round of condensation and reduction of the β-ketoacyl units. As a result, there is a direct correlation between the number of modules and the length of the polyketide chain as well as between the domain composition of the modules and the degree of reduction of the polyketide product. The final polyketide product is released from the PKS protein through the action of a thioesterase (TE) domain found in the ultimate module of the PKS system. The genetic organization of most type I PKS enzymes is colinear with the order of biochemical reactions giving rise to the polyketide chain. This feature allows prediction of polyketide core structure based on the architecture of the PKS modules found in a given biosynthetic pathway (Hopwood, *Chem. Rev.*, 97, 2465-2497 (1997)).

The PKS system in the biosynthetic locus for the production of the compounds of Formula I is composed of ORFs 18 to 23 (SEQ ID NOS: 37, 39, 41, 43, 45 and 47) and comprises a total of 12 modules as described below in Table 4. The first module contains only an ACP domain and corresponds to the loading module (module 0) whereas each of the remaining 12 modules contain domains KS, AT and ACP in various combinations with KR, DH and ER domains. The thioesterase domain present in ORF 23/module 12 indicates that this module is the ultimate one in the biosynthesis of the polyketide chain.

Table 4: Domain coordinates for PKS system

ORF Nos.	Amino acid coordinates	Domain	Module No.
18	47-109	ACP	0
	130-554	KS	1
	567-990	AT	
	1001-1101	DH	
	1421-1628	KR	
	1691-1753	ACP	
	1771-2195	KS	2
	2211-2638	AT	
	2647-2753	DH	
	3060-3401	ER	
	3405-3622	KR	
	3696-3758	ACP	
19	39-463	KS	3
	474-872	AT	
	883-990	DH	
	1291-1501	KR	
	1574-1636	ACP	
	1657-2082	KS	4
	2093-2495	AT	
	2507-2614	DH	
	2908-3249	ER	
	3253-3470	KR	
	3545-3607	ACP	
	3628-4052	KS	5
	4068-4489	AT	
	4497-4604	DH	
	4933-5281	ER	
	5285-5502	KR	
	5577-5639	ACP	
20	34-458	KS	6
	475-892	AT	
	901-1006	DH	
	1309-1517	KR	
	1593-1655	ACP	

ORF Nos.	Amino acid coordinates	Domain	Module No.
21	34-461	KS	7
	478-905	AT	
	1157-1366	KR	
	1444-1506	ACP	
	1528-1952	KS	8
	1963-2383	AT	
	2395-2502	DH	
	2837-3048	KR	
	3122-3184	ACP	
22	34-460	KS	9
	472-883	AT	
	895-1002	DH	
	1323-1523	KR	
	1597-1659	ACP	
	1682-2104	KS	10
	2115-2523	AT	
	2534-2641	DH	
	2957-3166	KR	
	3235-3297	ACP	
	3317-3741	KS	11
	3752-4181	AT	
	4193-4300	DH	
	4669-4879	KR	
	4956-5018	ACP	
23	35-461	KS	12
	475-883	AT	
	892-999	DH	
	1305-1512	KR	
	1582-1644	ACP	
	1709-1921	TE	

Multiple amino acid alignment of KS domains present in the PKS system, described in Figures 12a and 12b, shows an overall similarity of domains and conservation of amino acid residues and domain regions important for activity indicating that all KS domains are functional. Similarly, multiple amino acid alignment of AT domains (described in Figures 13a, 13b and 13c), DH domains (described in Figure 14), ER domains (described in Figure 15), KR domains (described in Figure 16), ACP domains (described in Figure 17) and TE domains (described in Figure 18) show an overall similarity of related domains and a high conservation of protein regions and of amino acid residues important for catalytic activity. The domains that occur only once in the PKS system, namely the thioesterase (TE) domain in ORF 23 (SEQ ID NO: 47) is compared to prototypical domains from the nystatin type I polyketide system (Brautaset, *supra*). Phylogenetic analysis of the AT domains in the PKS system was conducted to assess the nature of the β-keto acyl units that are incorporated in the growing polyketide chain. The AT domains of the PKS system were compared to two domains, AAF71779mod03 and AAF71766mod11 (National Center for Biotechnology Information (NCBI) nonredundant protein database), derived from the nystatin PKS system (Brautaset, *supra*) and responsible for the incorporation of malonyl-CoA and methylmalonyl-CoA respectively. Figure 19 shows the phylogenetic relatedness of the various AT domains indicating that, in the PKS system for production of compounds of Formula I, module 2 of ORF 18 (SEQ ID NO: 37), module 5 of ORF 19 (SEQ ID NO: 39), module 6 of ORF 20 (SEQ ID NO: 41), module 7 of ORF 21 (SEQ ID NO: 43) and module 12 of ORF 23 (SEQ ID NO: 47) incorporate methylmalonate in the polyketide backbone of compounds of Formula I, whereas all remaining AT domains, namely module 1 of ORF 18 (SEQ ID NO: 37), modules 3 and 4 of ORF 19 (SEQ ID NO: 39), module 8 of ORF 21 (SEQ ID NO: 43) and modules 9, 10 and 11 of ORF 22 (SEQ ID NO: 45) incorporate malonate extender β-keto acyl units in the polyketide backbone of compounds of Formula I.

Type I PKS domains and the reactions they carry out are well known to those skilled in the art and well documented in the literature (see, for example, Hopwood, *supra*). Those skilled in the art will readily appreciate that it is possible to determine the polyketide core structure produced by PKS system through domain analysis. The genes and proteins of the invention provide for biosynthesis of compounds of Formula I.

While not intending to be limited to any particular mode of action or biosynthetic scheme, Figures 20 and 21 describe production of Compound 1 using the genes and proteins of the invention. Figure 20b schematically describes a series of reactions catalyzed by the PKS system based on the correlation between the deduced domain architecture and the polyketide core of compounds of Formula I. Figure 20a describes a biosynthetic pathway for the production of the γ-aminobutyryl-CoA starter unit. Referring to Figure 20a, the amino acid monooxygenase of ORF 7 (SEQ ID NO: 14) catalyzes the decarboxylative oxidation of arginine forming 4-guanidinobutanamide that is further activated by the acyl CoA ligase of ORF 25 (SEQ ID NO: 52) to give 4-guanidinobutyryl-CoA. Referring to Figure 20b, the acyltransferase of ORF 24 (SEQ ID NO: 50) loads the 4-guanidinobutyryl-CoA extender unit onto the ACP domain of the loading module (module 0) of the type I polyketide synthase of ORF 18 (SEQ ID NO: 37). The polyketide chain continues to grow by the sequential condensation of malonyl-CoA and methylmalonyl-CoA extender units that are further reduced by specific domains to various degrees. The mature polyketide chain is then released through the action of the thioesterase domain found in module 12 of the type I polyketide synthase of ORF 23 (SEQ ID NO: 47). The polyketide core structure described in Figure 20b based on the architecture of the PKS system of the biosynthetic locus for the production of Compound 1 is entirely consistent with the polyketide portion of the chemical structure of Compound 1 as determined by MS sprectra data (Figures 1, 2 and 3), ^{1}H NMR (Figure 4) and ^{13}C NMR spectra data, demonstrating that the biosynthetic locus of the invention is responsible for the biosynthesis of Compound 1.

The biosynthetic locus contains genes involved in the synthesis of two other components found in the chemical structure of compounds of Formula I. Figure 21a describes a biosynthetic pathway for the production of the aminohydroxy-cyclopentenone moiety found in compounds of Formula I. Referring to Figure 21a, the pyridoxal phosphate dependent acyltransferase of ORF 16 (SEQ ID NO: 33) condenses glycine with succinyl-CoA forming 5-aminolevulinate. The 5-aminolevulinate intermediate is further activated through the action of the acyl CoA ligase of ORF 17 (SEQ ID NO: 35) forming 5-aminolevulinate-CoA, which in turn, cyclizes to produce aminohydroxycyclopentenone. Referring to Figure 21c, the

aminohydroxycyclopentenone moiety is activated and condensed to the carboxy terminus of the polyketide chain through the action of the adenylating/condensing synthetase of ORF 15 (SEQ ID NO: 31). Figure 21b describes the biosynthesis of the sugar component of compounds of Formula I. The sugar oxidoreductase of ORF 13 (SEQ ID NO: 27) oxidizes D-glucose to form D-glucuronic acid that is subsequently transferred onto a hydroxyl group of the polyketide core structure through the action of the glycosyltransferase of ORF 14 (SEQ ID NO: 29) as shown in Figure 21c. D-glucose derives from the primary metabolism of the microorganism and is expected to be activated by the primary metabolism enzyme nucleotidyl transferase that catalyzes the formation of NDP-D-Glucose. It is expected that the sugar oxidoreductase of ORF 13 (SEQ ID NO: 27) acts on NDP-D-Glucose to generate NDP-D-Glucuronic acid that is subsequently transferred onto the polyketide core structure through the action of the glycosyltransferase of ORF 14 (SEQ ID NO: 29).

The final modification of the polyketide core structure is the methylation reaction catalyzed by the N-methyltransferase of ORF 5 (SEQ ID NO: 10). Referring to Figure 21c, the N-methyltransferase of ORF 5 (SEQ ID NO: 10) catalyzes the transfer of a methyl group derived from S-adenosylmethionine onto the guanidine moiety or the polyketide structure. While Figure 21c describes the reactions catalyzed by the N-methyltransferase of ORF 5 (SEQ ID NO: 10), the adenylating/condensing synthetase of ORF 15 (SEQ ID NO: 31) and the glycosyltransferase of ORF 14 (SEQ ID NO: 29), the invention does not reside in the actual timing and order of the reactions, which may be different than as described in Figure 21c.

In regards to other ORFs forming the biosynthetic locus for production of the compounds of Formula I, the thioesterases of ORFs 11 and 27 (SEQ ID NOS: 22 and 56) are expected to have polyketide-priming editing functions; the regulator of ORF 3 (SEQ ID NO: 6), the transcriptional regulator of ORF 4 (SEQ ID NO: 8), the response regulator of ORF 9 (SEQ ID NO: 18) and the sensory protein kinase of ORF 10 (SEQ ID NO: 20) are expected to regulate synthesis of the compound of Formula I; and the membrane transporters of ORF 2 (SEQ ID NO: 4) and of ORF 8 (SEQ ID NO: 16) are expected to be involved in transmembrane transport.

The genes and proteins of the invention may be used to produce compounds of Formula I as described below in Examples 17 to 20.

Example 2: Production of Compounds 1, 2, 7, 8 and 15 by fermentation

Amycolatopsis orientalis ATCC™ 43491 was cultivated under aerobic conditions in an aqueous nutrient medium containing assimilable sources of carbon, assimilable sources of nitrogen, inorganic salts and vitamins. Preferred carbon sources are glucose, glycerol and the like. Preferred nitrogen sources are beef extract, malt extract, yeast extract, and the like. Representative media are provided in Table 1.

Compounds 1, 2, 7, 8 and 15 were produced by the following procedure: *Amycolatopsis orientalis* ATCC™ 43491 was maintained and sporulated on agar plates of ISP2 medium (Difco). The innoculum for the production phase was prepared by adding two loopfull of the spores obtained from the surface of the ISP2 agar plate to a 125-ml flask containing 25 ml of ITSB medium (Zahn et al. (2001). *Applied and Environmental Microbiology* 76, 377-386) composed of 30 g trypticase soy broth (Bacto), 3 g yeast extract, 2 g $MgSO_4$, 5 g glucose, 4 g maltose made up to one liter with distilled water. The flasks are shaken (250 rpm) for about 60 hours at 28 °C and then 10 ml of the culture is used to inoculate each 2-L flasks containing ten glass beads and 500 ml of sterile production medium OA consisting of glucose 10 g, glycerol 5 g, corn steep liquor 3 g, beef extract 3 g, malt extract 3 g, yeast extract 3 g, calcium carbonate 2 g, thiamine 0.1 g made up to one liter with distilled water (Kanzaki et al. (1998). *Biosci Biotechnol Biochem* 62; 438-442). The medium was adjusted at pH 7.0, and then 1 ml of silicon defoamer-oil (Chem Service) was added to each flask before sterilization. The fermentation batches are incubated aerobically under stirring (200 rpm) at 28°C for a period of 4 days. A fermentation period of 7 days without defoamer-oil was also used to produce Compound 1.

Compounds 1, 2, 7, 8 and 15 could also be produced in other media including JA, GA, RM, NA, CA, and CB (Table 1). Compounds 1 and 2 were further produced as described above using a preferred strain, namely *Amycolatopsis orientalis* IDAC 220604-01.

Example 3: Purification of Compound 1, 2 and 7

Procedure 1: (for 12 x500mL of fermentation)

a) The whole fermentation broth at harvest was centrifuged at 3500 rpm for 20 minutes and the supernatant liquid was decanted and discarded. The residual mycelial pellet was treated with methanol (200 mL/L of original fermentation broth volume), stirred and centrifuged. The methanolic supernatant liquid was removed and the mycelial solid was extracted with acetone, the same manner as the methanol extraction. The combined methanol and acetone extracts are evaporated to dryness to a crude residue.

b) The crude residue of a) was partitioned between 100mL(per litre of fermentation) of chloroform ($CHCl_3$) and 100mL(per litre of fermentation) of methanol (MeOH) in water (3:2) buffered to pH 10 with ammonium hydroxide (NH_4OH) and at 10mM ammonium bicarbonate (NH_4HCO_3) salt concentration. The two layers were separated and the methanol: water layer evaporated to dryness. The residue from the upper phase was partitioned between n-butanol (100 ml/L of fermentation) and water (100 ml/L of fermentation), buffered as above. The butanol layer was concentrated to a orange-brown residue.

The residue was further purified by HPLC (Waters Autopurification System with ACD), using a Waters Xterra MS C18 column (5μ, 19 x 150 mm), and a gradient of 10mM aqueous NH_4HCO_3, pH 10/ acetonitrile 85:15 to 25:75 over 30 min at 19 mL/min, UV detector set at 261 nm. The sample was loaded as a suspension in DMSO/MeOH (3:1). The pooling of eluate gave samples of Compound 7 (< 1 mg, RT: 16-17 min) and a mixture of Compounds 1 and 2 (1.04 g, non-freezedried, RT: 11.8-12.1 min).

Alternatively, the first purification (step 2) was also accomplished using a Phenomenex Max-RP C12 column (4μ, 21.2 x 250 mm) using the gradient buffer (as above) and acetonitrile 89.5:10.5 to 20:80 over 25 minutes, with the same flow and UV detection. Fractions were collected at a retention time of 16.5-17 minutes (mixture of Compounds 1 and 2) and at RT: 21-22 minutes (Compound 7).

The mixture of Compounds 1 and 2 is further purified by HPLC (Waters Autopurification System with ACD), using a RCM Column (Novapak C-18, 6μ, 40 x 200 mm), and a gradient of 10mM aqueous ammonium acetate (NH_4OAc) to pH 5 with glacial acetic

acid / acetonitrile 80:20 to 20:80 over 25 min at 35 mL/min. Fractions were collected and freeze-dried to give pure Compound 1 (RT: 18.5-18.8 minutes, 224.5 mg) and pure Compound 2 (RT: 17.3-17.6 minutes, 34.6 mg).

Procedure 2:

The crude residue of 1 a) (see Procedure 1) was partitioned between 100mL(per litre of fermentation) of hexanes and 100mL(per litre of fermentation) of methanol (MeOH) in water (3:2) buffered to pH 10 with ammonium hydroxide (NH_4OH) and at 10mM ammonium bicarbonate (NH_4HCO_3) salt concentration. The two layers were separated and the methanol: water layer evaporated to dryness. The procedure was repeated and concentrated to dryness.

The crude residue was purified by solid phase extraction. Methanol washed Diaion® HP-20 resin (30mL) was added to the crude residue. The mixture was added to a column made of 75 mL of methanol washed HP-20 resin and eluted with a mixture of ethanol and pH 10 buffered aqueous ammonium carbonate following the following gradient:

Fraction	Ethanol	Aqueous	Volume
1	10	90	500
2	20	80	200
3	30	70	200
4	40	60	200
5	50	50	200
6	60	40	200
7	80	20	200
8	100	0	200

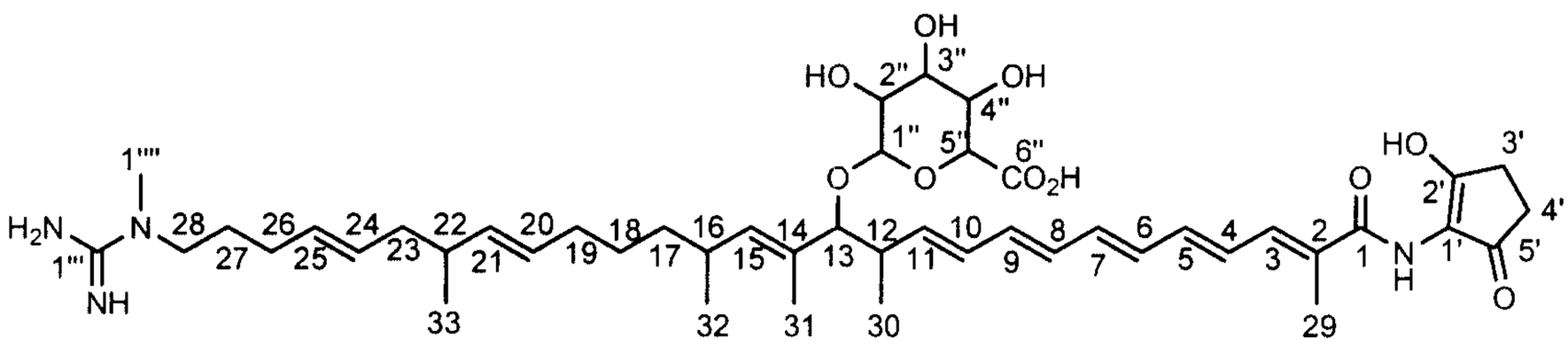
Fractions 4, 5 and 6 were combined and concentrated to give a mixture of Compounds 1 and 2 and Compound 7 was found in the concentrated fraction 7.

The mixture of Compounds 1 and 2 was further purified by HPLC (Waters Autopurification System with ACD), using a Symmetry C18 column (5μ, 30 x 100 mm), and a gradient of 10mM aqueous NH_4OAc, made to pH 5 with glacial acetic acid /

acetonitrile 74:26 to 50:50 over 20 min at 39 mL/min. The collection was triggered by UV 261 nm (PDA). The sample was loaded as a suspension in DMSO: MeOH (3:1). The pooling of eluates gave pure Compound 1 (RT: 14.9-15.2 min) and pure Compound 2 (RT: 14.1-14.2 min), generally with a ratio of 5:1. Compound 7 had a retention time of 13-14 minutes using the same conditions.

Example 4: Structure identification of Compounds 1, 2 and 7

Compounds 1, 2 and 7 were produced by fermentation as described in Example 2 and isolated as described in Example 3.



Compound 1

Compound 1 is named 3,4,5-trihydroxy-6-[1-[11-(2-hydroxy-5-oxocyclopent-1-enylcarbamoyl)-1-methyldodeca-2,4,6,8,10-pentaenyl]-2,4,10-trimethyl-16-(*N*-methyl-guanidino)-hexadeca-2,8,12-trienyloxy]-tetrahydropyran-2-carboxylic acid.

Compound 1 structure determination was based on mass, UV and NMR data. The NMR data detailed in Table 5 was collected at 500 MHz in d_4-MeOH including ^{1}H-NMR spectrum of Figure 4, and the multidimensional pulse sequences gCOSY, gDQCOSY, gHSQC, and gHMBC. The molecular formula of $C_{46}H_{68}N_4O_{10}$ and the chemical structure were established based the ^{1}H-NMR data, the COSY, HSQC and HMBC measured on about 500 μg of very pure material of structure illustrated above. The carbon assignments shown in Table 5 were made by virtue of the HSQC and HMBC. The straight chain nature of Compound 1 was supported by the fact that the two protons on each of the seven methylene groups were of almost indistinguishable chemical shift.

Table 5

^{1}H and ^{13}C NMR (δ, ppm) Data for Compounds 1 in MeOH-D_4			
Assignment	δ_H (ppm)	δ_C (ppm)	Group
1	–	170.1	C
2	–	138.8	C
3	7.09	135.2	CH
4	6.60	127.9	CH
5	6.38	132.5	CH
6	6.38	135.8	CH
7	6.56	127.9	CH
8	6.23	132.5	CH
9	6.23	131.3	CH
10	6.08	130.0	CH
11	5.51	137.9	CH
12	2.52	40.3	CH
13	3.58	93.8	CH
14	–	134.3	C
15	5.03	136.4	CH
16	2.32	32.2	CH
17	1.13	37.4	CH_2
18	1.29	37.3	CH_2
19	1.87	32.9	CH_2
20	5.24	135.9	CH
21	5.27	129.3	CH
22	2.11	37.3	CH
23	1.97	40.6	CH_2
24	5.41	130.0	CH
25	5.41	130.0	CH
26	2.01	29.6	CH_2
27	1.64	27.2	CH_2
28	3.34	48.2	CH_2
29	2.06	12.4	CH_3
30	1.21	17.4	CH_3
31	1.60	11.4	CH_3
32	0.92	20.7	CH_3
33	0.97	20.3	CH_3
1'	–	111.4	C
2'	–	199.3	C
3'	2.35	31.0	CH_2
4'	2.35	31.0	CH_2
5'	–	199.3	C
1''	4.20	102.9	CH
2''	3.27	74.6	CH

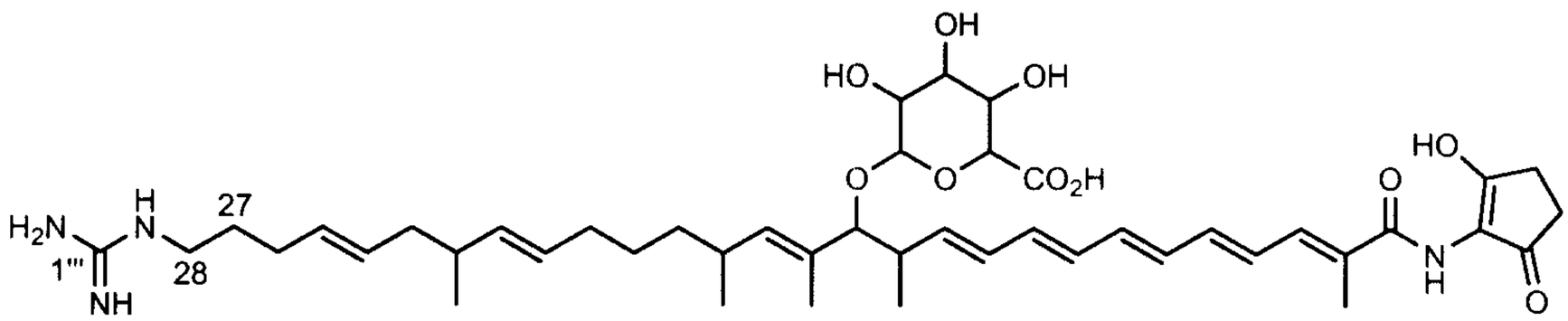
^{1}H and ^{13}C NMR (δ, ppm) Data for Compounds 1 in MeOH-D_4			
Assignment	δ_H (ppm)	δ_C (ppm)	Group
3''	3.36	77.6	CH
4''	3.41	72.9	CH
5''	3.40	76.2	CH
6''	–	176.1	C
1'''	–	157.7	C
1''''	3.00	35.8	CH_3

Mass spectra (Figures 1, 2, and 3) analysis shown in Table 6 gave a mass (m/z) of 836.4, which confirmed a molecular formula of $C_{46}H_{68}N_4O_{10,}$ and fragments that also confirmed structure assignment of Compound 1 including a sugar moiety.

Table 6

Mass Spectrometry data for Compound 1			
Figure	Ionization	Mass (m/z)	Fragment
1	+ mode (+ Q1)	837.5 823.7	$(M+H)^+$ $(M-CH_3)^+$
2	+ mode (+ EPI)	837.3 662.1 644.1	$(M+H)^+$ $(M\text{-sugar})^+$ $(M\text{-O-sugar})^+$
3	mode (- Q1)	835.3 821.5	$(M-H)^-$ $(M-CH_3)^-$

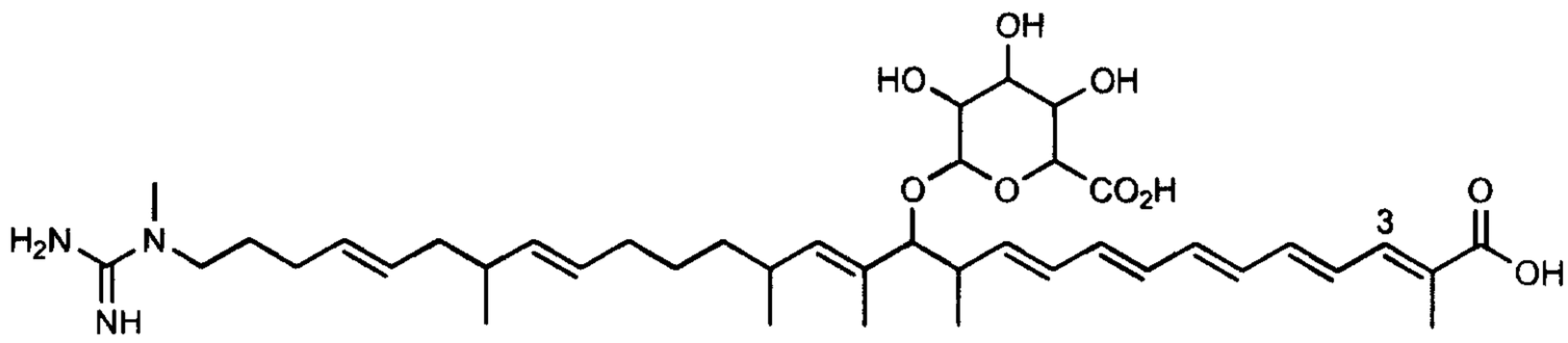
The UV spectrum for Compound 1 exhibited UV λ_{max} at 258.77 and 362.77 nm in methanol in accordance with the methylpentaene amide of the 2-aminocyclopenta-1,3-dione tautomer.



Compound 2

Compound 2 is named 6-{16-guanidino-1-[11-(2-hydroxy-5-oxocyclopent-1-enylcarbamoyl)-1-methyldodeca-2,4,6,8,10-pentaenyl]-2,4,10-trimethylhexadeca-2,8,12-trienyloxy}-3,4,5-trihydroxy-tetrahydro-pyran-2-carboxylic acid.

Structure of Compound 2 was confirmed by ^{1}H (Figure 5) and ^{13}C NMR. The signals of 1'''' carbon (35.8 ppm) and protons (singlet at 3.00 ppm) of Compound 1 (see Table 5) were absent from the spectra, which confirmed the absence of this CH_3 residue. Only small shifts in the guanidine area were observed in the ^{13}C NMR of Compound 2. No further changes from the structure of Compound 1 previously described were present.



Compound 7

Compound 7 is named 6-[1-(11-carboxy-1-methyldodeca-2,4,5,8,10-pentaenyl)-2,4,10-trimethyl-16-(*N*-methylguanidino)-hexadeca-2,8,12-trienyloxy]-3,4,5-trihydroxy-tetrahydropyran-2-carboxylic acid.

Structure analysis of Compound 7 was accomplished by spectral data analysis including ^{1}H NMR (Figure 10) and Mass spectra. The later gave a mass of 739.37 at negative ionization (ES-) and 741.53 at positive ionization (ES+), which is consistent with a molecular formula of $C_{41}H_{63}N_3O_9$ and a calculated mass of 741.95.

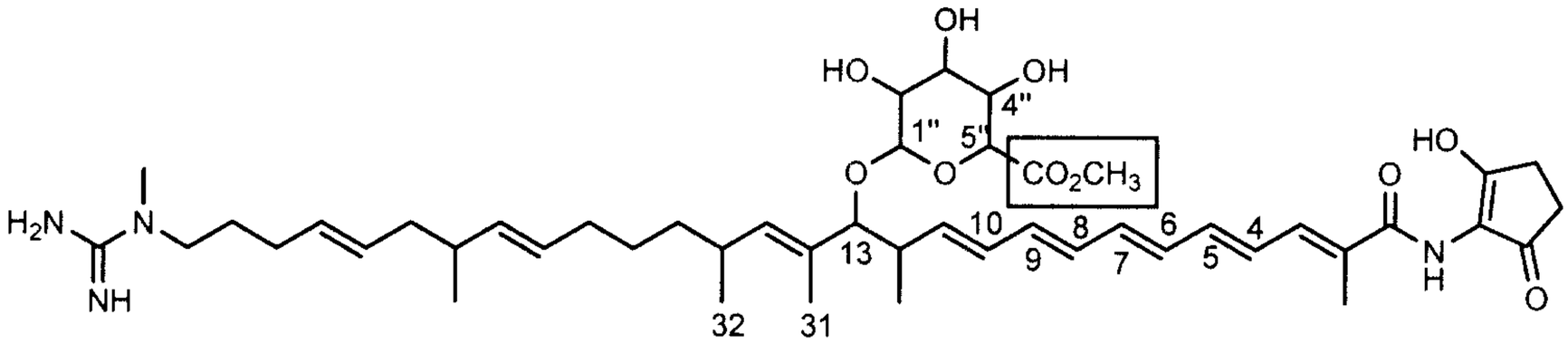
Analysis of the ^{1}H NMR (Figure 10) showed the absence of the signal at δ 2.35 ppm (Table 5) from the NMR spectrum of Compound 1. This signal was previously assigned to the two methylene groups of the cyclopentenone of Compound 1. An effect was also observed at position 3, which doublet (found at about 7.1 ppm in the case of Compound 1) has moved 0.1 ppm (to 7.0 ppm), the rest of the spectra remaining mostly the same.

Example 5: Preparation and identification of Compounds 3, 4 and 5

Compounds 3, 4 and 5 were prepared according to the following procedure. A 0.1M solution of sodium hydroxide in methanol (334 µL, Fisher Chemicals) was added to

Compound 1 (20 mg) in methanol (2 mL). Dimethyl sulfate (5.68 μL, Sigma) was added and the reaction stirred at room temperature for 24 hours. Additional sodium hydroxide in methanol (334 μL) and dimethyl sulfate (10 μL) were added and the reaction stirred for an additional 24 hours. A third portion of sodium hydroxide in methanol (400 μL) and dimethyl sulfate (15 μL) were added and the reaction mixture stirred for an additional 24 hours. The reaction was monitored by TLC (Merck Silica gel 60 F_{254}, eluting with 7 % methanol in chloroform) visualized under UV. The reaction was concentrated *in vacuo*. The crude residue was purified by multiple injection on an HPLC Waters Auto-Purification System using a Symmetry (C-18, 5μ, 30x100 mm) column and the following eluent: A (10mM ammonium acetate in water (10mM NH_4OAc)) and B acetonitrile (MeCN), 74:26 to 50:50 A:B gradient in 20 minutes, 40mL/min. The fractions having retention times 9.4, 11.5 and 15.5 minutes were collected to give respectively Compound 4 (0.53 mg), Compound 3 (5.36 mg) and Compound 5 (4.04 mg).

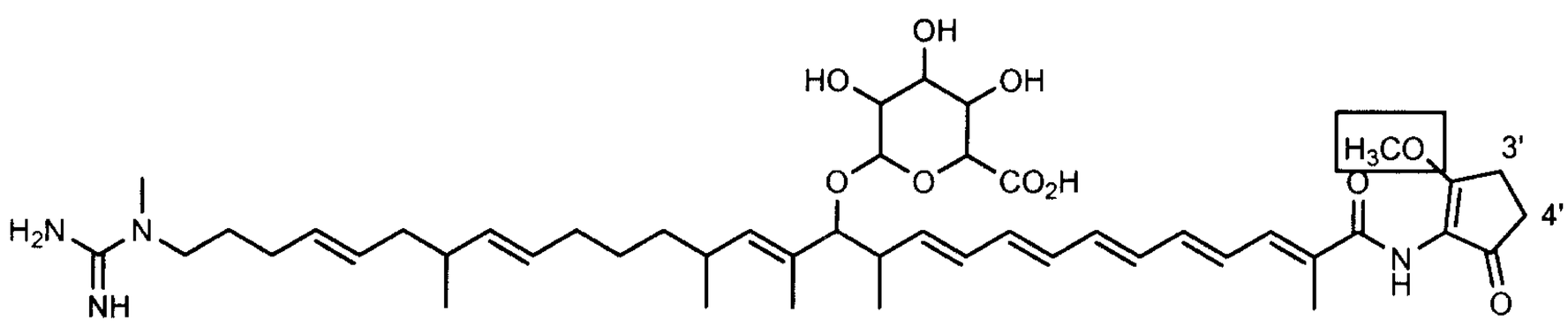
Structures of Compounds 3, 4 and 5:



Compound 3

Compound 3 is named 3,4,5-trihydroxy-6-[1-[11-(2-hydroxy-5-oxocyclopent-1-enylcarbamoyl)-1-methyldodeca-2,4,6,8,10-pentaenyl]-2,4,10-trimethyl-16-(*N*-methyl-guanidino)-hexadeca-2,8,12-trienyloxy]-tetrahydropyran-2-carboxylic acid methyl ester. Structure determination of Compound 3 was accomplished by spectral data analysis including ^1H NMR (Figure 6) and ^{13}C NMR and mass spectrometry. The molecular ion was found at mass 852.03 $(M+H)^+$ and 849.97 $(M-H)^-$, respectively for positive and negative ionization, which confirms a calculated molecular weight of 851.08, for $C_{47}H_{70}N_4O_{10}$ as molecular formula. The methyl group (in the squares) was easily assigned to the carboxylic ester from NMR chemical shifts, of the new methyl group (singlet at δ 3.73 ppm integrating for 3 protons) and of the surrounding proton and carbon atoms. The protons most affected were 4" and 5" (δ 3.40-3.48 ppm (Table 5)

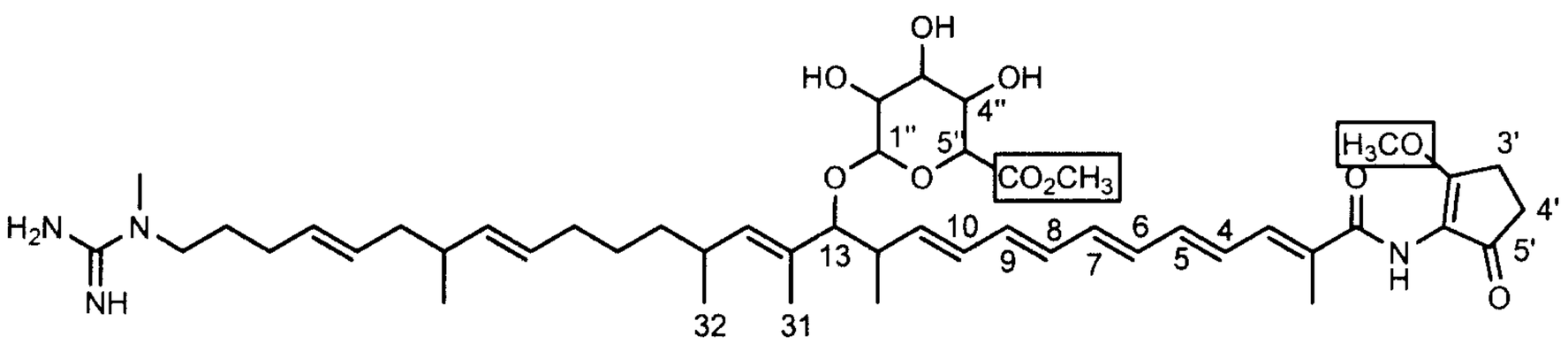
moved to δ 3.50-3.56 ppm), 1" (doublet δ 4.20 ppm (Table 5) moved to δ 4.26 ppm), 13 (doublet δ 4.58 ppm (Table 5) moved to δ 4.68 ppm) and 31 (δ 1.60 ppm (Table 5) moved to δ 1.52 ppm). Smaller effects were also observed at proton positions 4 to 10 and 32. These last effects might be due to a minor change in conformation and polarity difference between the carboxylic acid of Compound 1 and the ester of Compound 3.



Compound 4

Compound 4 is named 3,4,5-trihydroxy-6-[1-[11-(2-methoxy-5-oxo-cyclopent-1-enylcarbamoyl)-1-methyldodeca-2,4,6,8,10-pentaenyl]-2,4,10-trimethyl-16-(N-methyl-guanidino)-hexadeca-2,8,12-trienyloxy]-tetrahydropyran-2-carboxylic acid.

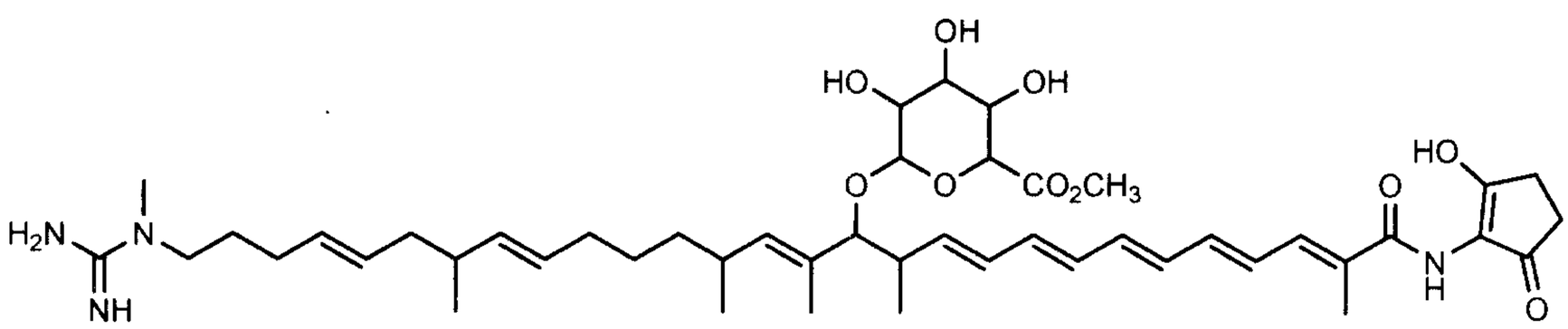
Structure determination of Compound 4 was accomplished by spectral data analysis including ^{1}H NMR (Figure 7) and ^{13}C NMR and mass spectrometry. The molecular ion was found at mass 852.03 $(M+H)^{+}$ and 849.98 $(M-H)^{-}$, respectively for positive and negative ionization, which confirms a calculated molecular weight of 851.08, for $C_{47}H_{70}N_4O_{10}$ as molecular formula. The ^{1}H NMR spectral analysis confirmed the presence of the methyl group (in the square) as a singlet integrating for three protons at 4.07 ppm. This methyl was also confirmed to be on the cyclopentenone as the two methylene groups were non-equivalent. In fact, in Compound 1, the two methylene groups from the cyclopentenone (positions 3' and 4') are equivalent (a 4 proton singlet at 2.35 ppm) due to the symmetry of the tautomeric forms. In Compound 4, the protons of these two positions appear as two separate triplets at 2.84 ppm and 2.52 ppm, integrating for two protons each.



Compound 5

Compound 5 is named 3,4,5-trihydroxy-6-[1-[11-(2-methoxy-5-oxo-cyclopent-1-enylcarbamoyl)-1-methyldodeca-2,4,6,8,10-pentaenyl]-2,4,10-trimethyl-16-(*N*-methyl-guanidino)-hexadeca-2,8,12-trienyloxy]-tetrahydropyran-2-carboxylic acid methyl ester. Structure determination of Compound 5 was accomplished by spectral data analysis including ^{1}H NMR (Figure 8) and ^{13}C NMR and mass spectrometry. The molecular ion was found at mass 866.06 $(M+H)^{+}$ and 863.89 $(M-H)^{-}$, respectively for positive and negative ionization, which confirms a calculated molecular weight of 865.11, for $C_{48}H_{72}N_4O_{10}$ as molecular formula. The ^{1}H NMR spectral analysis confirmed the presence of two methyl groups (in the square) as singlets integrating for three protons at 3.73 ppm and 4.07 ppm. One of the methyl (4.07 ppm) was confirmed to be on the cyclopentenone as the two methylene groups, as in Compound 4, were non-equivalent and appearing as two separate triplets at 2.84 ppm and 2.52 ppm, integrating for two protons each. The other methyl group (3.73 ppm) was confirmed as the methyl ester of the glucoronic acid (see Compound 3 determination above).

<u>Example 6</u>: Preparation of Compound 3 by esterification of Compound 1

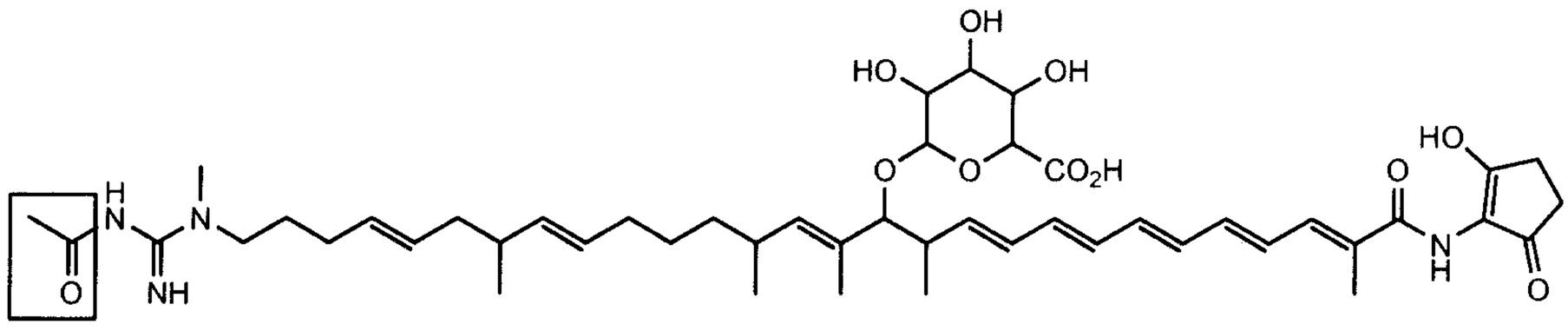


Compound 3

Diazomethane was generated by standard methods in an Aldrich diazomethane-generator [Z41, 173-6]. Approx. 2mL 5N sodium hydroxide was added dropwise to 450mg 1-methyl-3-nitro-1-nitrosoguanidine and the generated gaseous diazomethane

was condensed in 4 mL of diethyl ether at 0°C. The diazomethane solution was added dropwise to a solution of Compound 1 (10 mg) in 6 mL of methanol. The reaction was carried out at room temperature with magnetic stirring maintained for 15 minutes until completion. The reaction product was evaporated at 30°C under a gentle stream of N_2. The crude material was purified by multiple injections on HPLC using a YMC ODS-A 10×250mm column and a gradient of 5mM NH_4OAc / acetonitrile at 5mL/min (90:10 for 1min, 90:10 - 30:70 o. 20min). The combined yield of pure Compound 3 derived from two separate 10 mg batches was 0.99 mg.

Example 7: Preparation and identification of Compound 6



Compound 6

Compound 6 is named 6-{16-(N'-acetyl-*N*-methylguanidino)-1-[11-(2-hydroxy-5-oxocyclopent-1-enylcarbamoyl)-1-methyldodeca-2,4,6,8,10-pentaenyl]-2,4,10-trimethylhexadeca-2,8,12-trienyloxy}-3,4,5-trihydroxytetrahydropyran-2-carboxylic acid. Compound 6 was prepared by acetylation of Compound 1 using the following procedure. Acetic anhydride (3.38 μL, Sigma) was added to a solution of Compound 1 (20 mg) in methanol (2 mL) and the reaction stirred at room temperature for 72 hours. Additional portions of acetic anhydride (20 μL) were added after 24 and 48 hours. The reaction was monitored by TLC (Merck Silica gel 60 F_{254}, eluting with 7 % methanol in chloroform) visualized under UV. The reaction was concentrated *in vacuo*.

The crude residue was purified by multiple injection on an HPLC Waters Auto-Purification System using a Symmetry (C-18, 5μ, 30x100 mm) column and the following eluent: A (10mM ammonium acetate in water (10mM NH_4OAc)) adjusted to pH 5 with glacial acetic acid and B acetonitrile (MeCN), 74:26 to 50:50 A:B gradient in 20 minutes, 40mL/min. The fractions having retention times 9.4, 11.5 and 15.5 minutes were collected to give Compound 6 (6.43 mg).

Structure determination of Compound 6 was accomplished by spectral data analysis including ^{1}H NMR (Figure 9) and ^{13}C NMR and mass spectrometry. The molecular ion was found at mass 880.03 $(M+H)^{+}$ and 877.98 $(M-H)^{-}$, respectively for positive and negative ionization, which confirms a calculated molecular weight of 879.09, for $C_{48}H_{70}N_4O_{11}$ as molecular formula. Analysis of the ^{1}H NMR spectrum also confirmed the presence of an acetyl group as a singlet at 1.95 ppm integrating for 3 protons. No important changes were observed at other positions, which indicate this acetyl group is on the guanidine.

Example 8: Anti-microbial activity of Compounds 1 to 7

Antibacterial activity of Compounds 1 and 2 (Table 7) was measured by determining the minimal inhibitory concentration (MIC) necessary to obtain a complete inhibition of bacteria growth in eight indicator strains, namely *Staphylococcus aureus* (ATCC™ 6538P), , *Staphylococcus aureus MRS3* (ATCC™ 700699), *Staphylococcus epidermidis (ATCC™ 12228), Bacillus subtilis* (ATCC™ 23857), *Bacillus megaterium* (ATCC™ 14581), *Enterococcus faecalis VRE-1* (ATCC™ 29212), *Enterococcus faecalis VRE-2* (ATCC™ 51299) and *Micrococcus luteus* (ATCC™ 9341) . Indicator strains preparation and MIC determination were performed according to the National Committee for Clinical Laboratory Standards (NCCLS) guideline M7-A5 *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Fifth Edition.* (NCCLS document M7-A5, ISBN 1-56238-394-9; NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA).

Compounds 1 and 2 were prepared as 100x stock solution in DMSO, with concentrations ranging from 3.2 mg/ml to 0.003 mg/ml (a two-fold dilution series over 11 points). An aliquot of each 100x stock solution was diluted 50-fold in test medium described below to give a set of eleven (11) 2x solutions. 50 µl of each of the eleven 2x solutions was aliquoted into the corresponding well of a 12-well row, with the final well reserved for medium alone control.

Vancomycin (Sigma™) used as positive control compounds, was prepared as 2x stock solutions in Mueller-Hinton test medium ranging from 64 µg/ml to 0.06 µg/ml (a two-fold

dilution series over 11 points). An aliquot of 50 µl corresponding to each concentration (at 2x) was then transferred to 96-well microplates to obtain a series of eleven two-fold dilutions.

An isolated colony of each of the eight indicator strains was used to inoculate tubes containing 2 ml of test medium. Mueller-Hinton test medium was used for *Staphylococcus aureus* (ATCC™ 6538P), *Staphylococcus aureus MRS3* (ATCC™ 700699), *Staphylococcus epidermidis (ATCC™ 12228), Bacillus subtilis* (ATCC™ 23857), *Bacillus megaterium* (ATCC™ 14581) and *Micrococcus luteus* (ATCC™ 9341) indicator strains, and BHI test medium was used for *Enterococcus faecalis VRE-1* (ATCC™ 29212) and *Enterococcus faecalis VRE-2* (ATCC™ 51299) indicator strains. Cells were grown overnight at 28°C with shaking. Inoculum density for each indicator strain was adjusted to $0D_{600}$ = 0.1 in 5ml 0.85% saline, then further diluted 1/100 in appropriate medium. 50 µl of the final dilution (in test medium) of each indicator strain was added to each well of a 12-well row. This brings the final dilution of the test article or control compound in solution to 1x. The final inoculum is approximately 5 x 10^5 CFU/ml. The indicator strains were incubated with 11 concentrations of each of Compounds 1 and 2, Vancomycin (Sigma™) control compound and one media alone control. For MIC determination, assay plates were incubated at 35°C for 16 to 20 hours. The MIC for each indicator was assessed as the lowest concentration of compound resulting in total absence of growth and is shown below.

Table 7

Antibacterial activity of Compounds 1 and 2, MIC (µg/ml)			
Strain	Compound 1	Compound 2	Vancomycin
S. aureus ATCC™ 6538P	2	1	2
S. aureus ATCC™ 700699	4	2	4
S. epidermidis ATCC™ 12228	4	2	2
B. subtilis ATCC™ 23857	1	2	0.25
B. megaterium ATCC™ 14581	1	1	0.125
E. faecalis ATCC™ 29212	8-16	16	4
E. faecalis ATCC™ 51299	16	16	8-16
M. luteus ATCC™ 9341	4	1-2	1

Antibacterial activitiy of Compounds 3, 4, 5, 6 and 7 are accomplished using the same method in a panel of bacterial strains and Vancomycin as positive control.

Antibacterial efficacy of Compounds 1, 2, 3, 4, 5 and 6 on bacterial strain *Staphylococcus aureus* NRRL B-313 (ATCC™ 6538P) was determined at different pH concentrations. These results are shown in Table 8 together with the antibacterial activity of Compound 7 on the same strain.

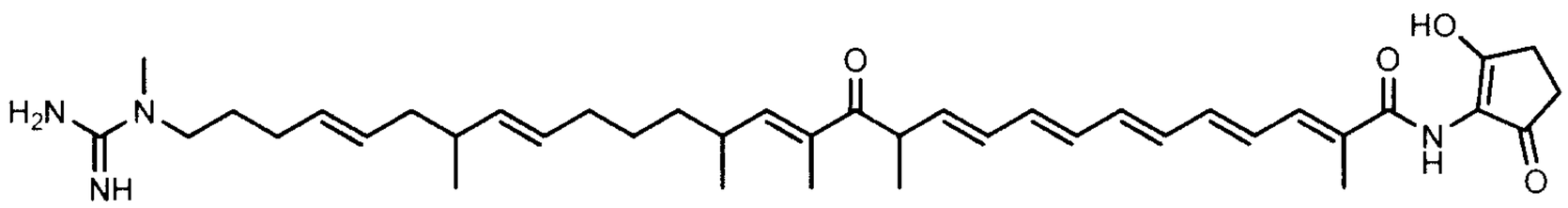
Table 8

Compounds 1 to 7 Antibacterial activity on *S. Aureus (ATCC™ 6538P)*, and effect of pH (MIC (µg/ml))

	1	2	3	4	5	6	7	Vancomycin
pH 5.0	0.125	0.0625	2	2	2	0.25	ND*	1
pH 6.0	0.25	0.125	4-8	2	4	0.5	ND*	1
pH 7.0	1	1	16	2	4	2	32-64	1

*ND: not determined

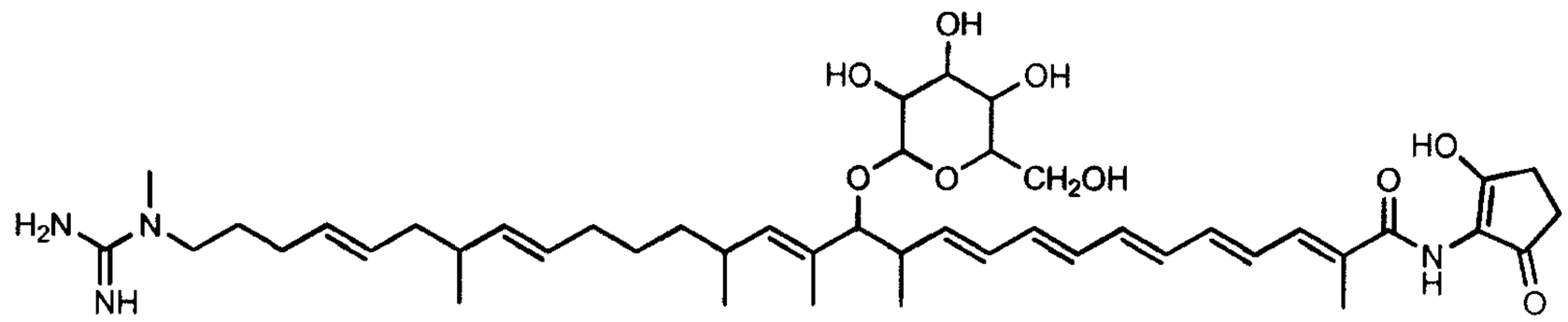
Example 9: Preparation of Compound 10 by oxidation of Compound 8



Compound 10

To a methylene choride solution of Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)one, Sigma-Aldrich Co.) is added a solution of Compound 8 in methylene chloride and the reaction stirred at room temperature for 1 hour. The mixture is diluted with diethyl ether and a saturated aqueous sodium bicarbonate solution containing sodium thiosulfate. Organic layer is separated and washed with saturated aqueous sodium bicarbonate, water and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude residue is purified by HPLC according to the procedure described in Example 5. Pure Compound 10 is obtained by pooling and concentrating the appropriate eluate fractions.

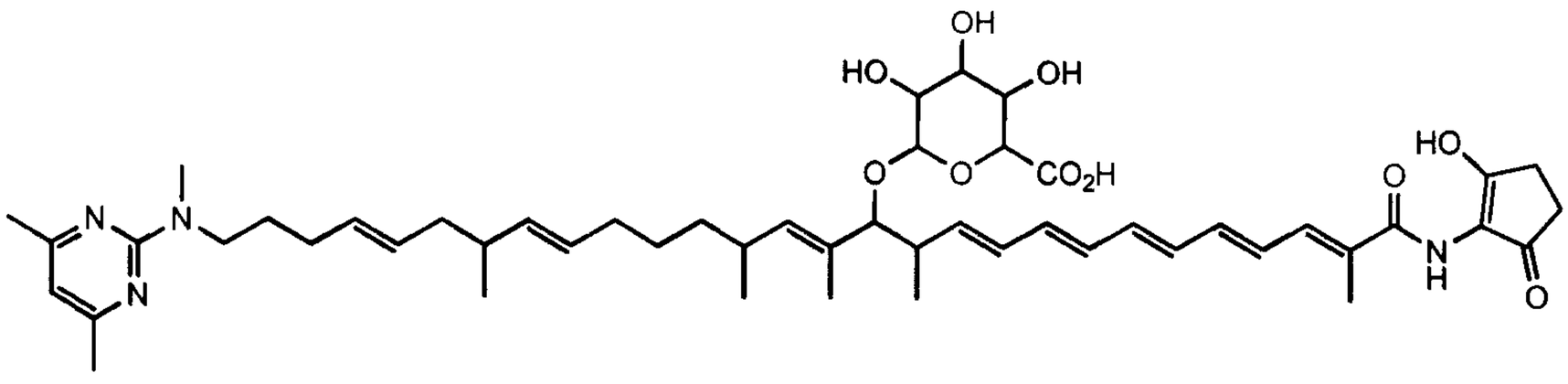
Example 10: Preparation of Compound 11 by reduction of Compound 1



Compound 11

LAH (lithium aluminum hydride) is added to a 0°C solution of Compound 1 in THF (tetrahydrofuran). After hydrogen gas has stopped evolving, the reaction is allowed to warm to room temperature and stirred overnight. Water is slowly added and 1M hydrochloric solution is used to acidify the solution carefully. The mixture is extracted three times with ethyl acetate. Organic layers are combined and washed with saturated aqueous sodium bicarbonate, water and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Pure Compound 11 is obtained by pooling and concentrating the appropriate fractions of HPLC purification according to Example 5.

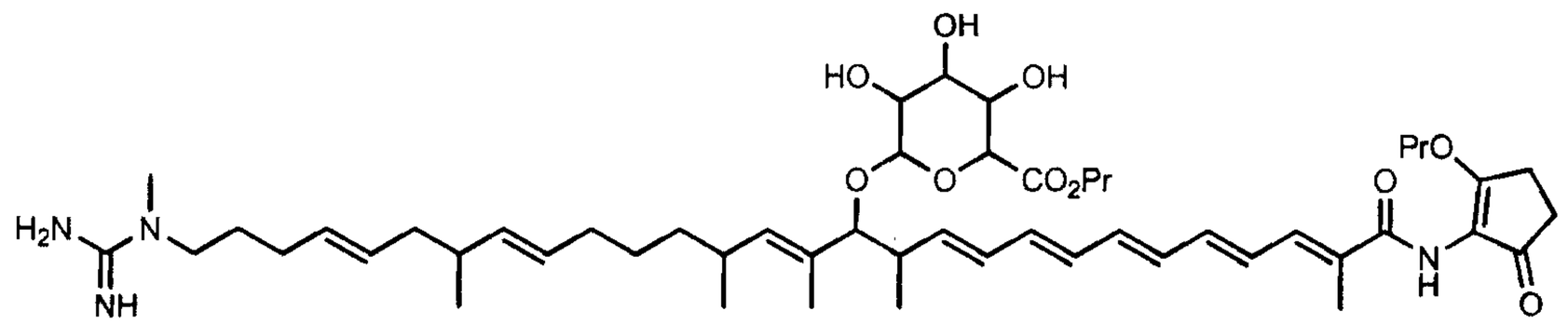
Example 11: Preparation of Compound 23 from Compound 1



Compound 23

Compound 23 is prepared by modification of the guanidino group of Compound 1 according to the procedure described in Argoudelis *et al.*, J. Antibiotics, Vol. XL, No. 6, June 1987, pp 750-760. A mixture of 200 mg of Compound 1 in 1.2 ml water, 1.0 ml of absolute ethanol,1.0 ml of 2,4-pentadione and 120 mg of sodium bicarbonate is stirred at 90 °C for 3 hours. The mixture is allowed to cool to room temperature, concentrated to dryness, dissolved in 5 ml of 2N acetic acid, and purified by HPLC as described in Example 5. Pure Compound 23 is obtained by pooling and concentrating the appropriate eluate fractions.

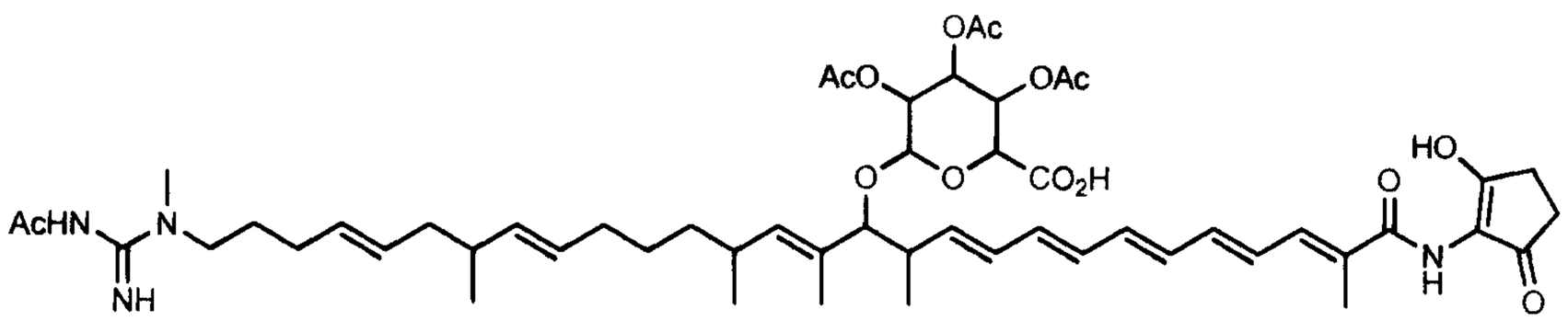
Example 12: Preparation of Compound 24 by alkylation of Compound 1



Compound 24

Compound 24 is prepared as follows. See Bartzatt et al., Biotechnol. Appl. Biochem. (2002) 36, 89-93. A Wheaton-type double-chamber device (Wheaton Co., Millville, NJ, U.S.A.) is utilized to generate diazopropane ($CH_3CH_2CHN_2$). Approx. 5.0 mg of Compound 1 is placed into an organic solvent (ethyl acetate/diethyl ether, 1:1, v/v) and the diazopropane gas formed is allowed to dissolve in the mixture. Diazopropane is generated by mixing 0.15 ml of 5 M NaOH with 0.15 g of 3-nitro-1-nitroso-1-propylguanidine. Excess diazoalkane and the solvent are removed by nitrogen gas flow or under vacuum. The remaining residue is dissolved in methanol, and the methanol solution is purified by HPLC as described in Example 5. Pure Compound 24 is obtained by pooling and concentrating the appropriate eluate fractions.

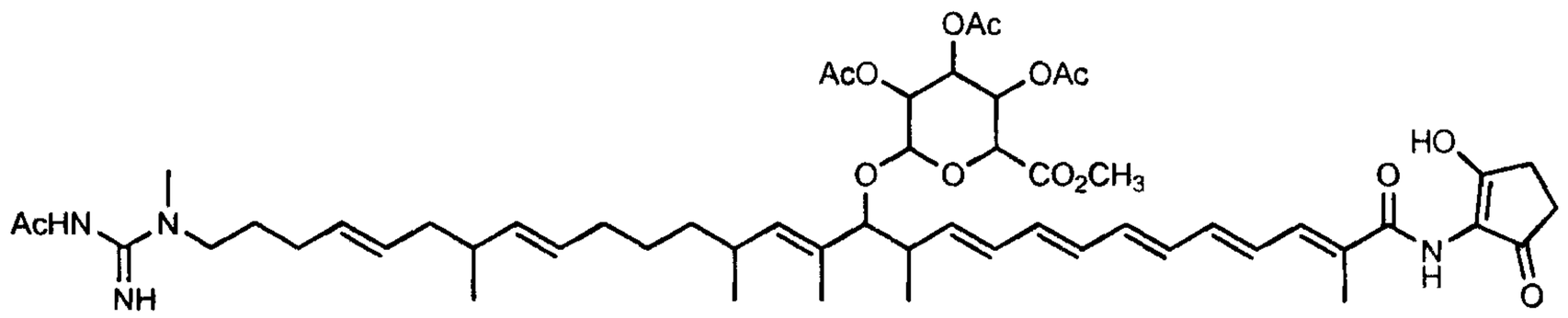
Example 13: Preparation of Compound 25 by acylation of Compound 1



Compound 25

Compound 25 is prepared by acylation of Compound 1 as follows. Acetic anhydride (4.5 equivalents) is added dropwise to a solution of 50 mg/ml of Compound 1 and in acetonitrile and pyridine (9:1). The mixture is stirred under reflux and monitored by TLC (see example 5). The solvent is removed under vacuum and the residue is dissolved in methanol. The methanol solution is purified by HPLC as described in Example 5. Pure Compound 25 is obtained by pooling and concentratin the appropriate eluate fractions.

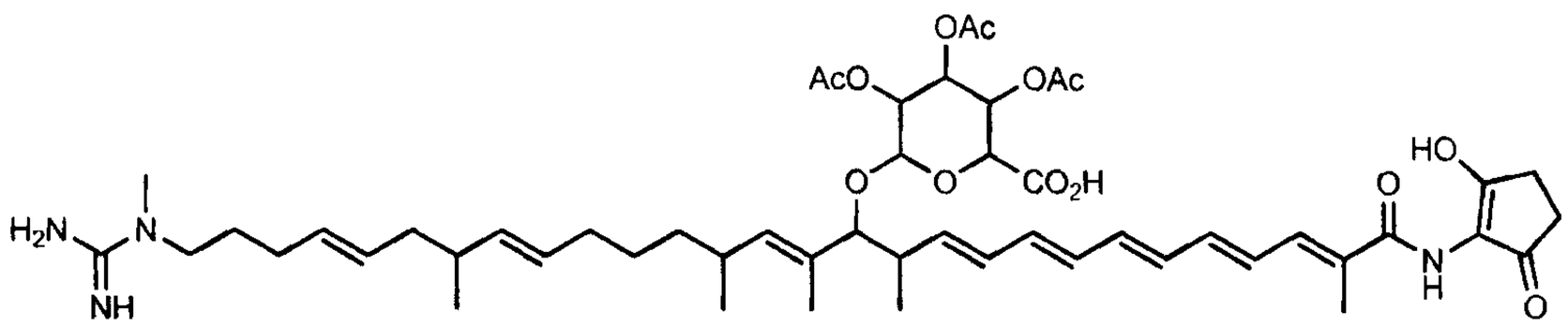
Example 14: Preparation of Compound 26 by esterification of Compound 25



Compound 26

To a solution of Compound 25 in diethyl ether/ethyl acetate (1/1) is added 1 equivalent of diazomethane in diethyl ether. The reaction mixture is allowed to stand at room temperature overnight. Excess diazomethane and the solvent are removed by nitrogen gas flow or under vacuum. The remaining residue is dissolved in methanol, and the methanol solution is purified by HPLC as described in Example 5. Pure Compound 26 is obtained by pooling and concentrating the appropriate eluate fractions.

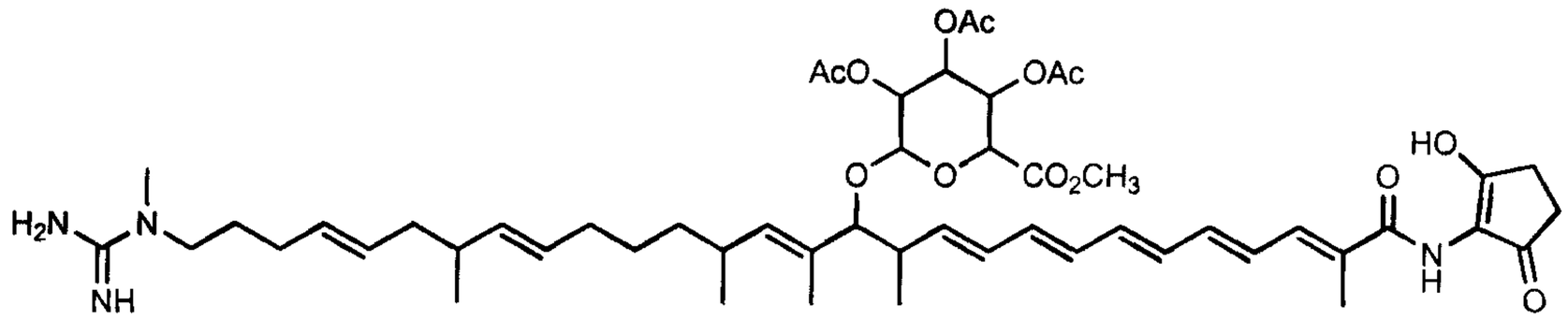
Example 15: Preparation of Compound 27 by acylation of Compound 1



Compound 27

Compound 27 is prepared by acylation of Compound 1 as follows. Acetic anhydride (3.2 equivalents) is added dropwise to a solution of 50 mg/ml of Compound 1 in acetonitrile. The mixture is stirred under reflux and monitored by TLC (see Example 5). The solvent is removed under vacuum and the residue is dissolved in methanol. The methanol solution is purified by HPLC as described in Example 5. Pure Compound 27 is obtained by pooling and concentrating the appropriate eluate fractions.

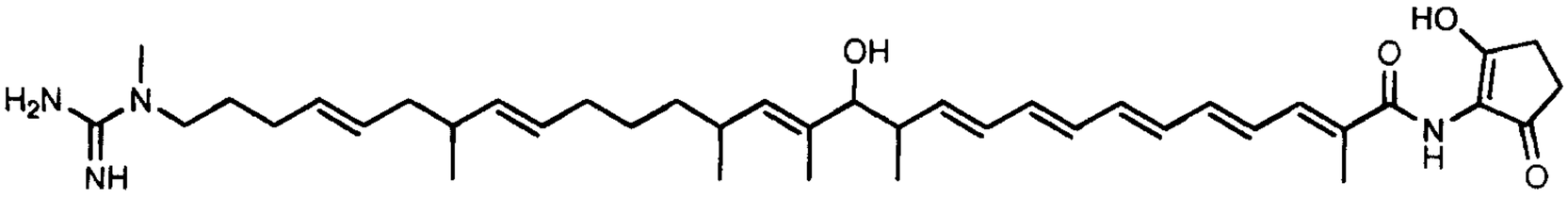
Example 16: Preparation of Compound 28 by esterification of Compound 27



Compound 28

To a solution of Compound 27 in diethyl ether is added 1 equivalent of diazomethane in diethyl ether. The reaction mixture is allowed to stand at room temperature overnight. Excess diazomethane and the solvent is removed by nitrogen gas flow or under vacuum. The remaining residue is dissolved in methanol, and the methanol solution is purified by HPLC as described in Example 5. Pure Compound 28 is obtained by pooling and concentrating the appropriate eluate fractions.

Example 17: Biosynthesis and Isolation of Compound 8



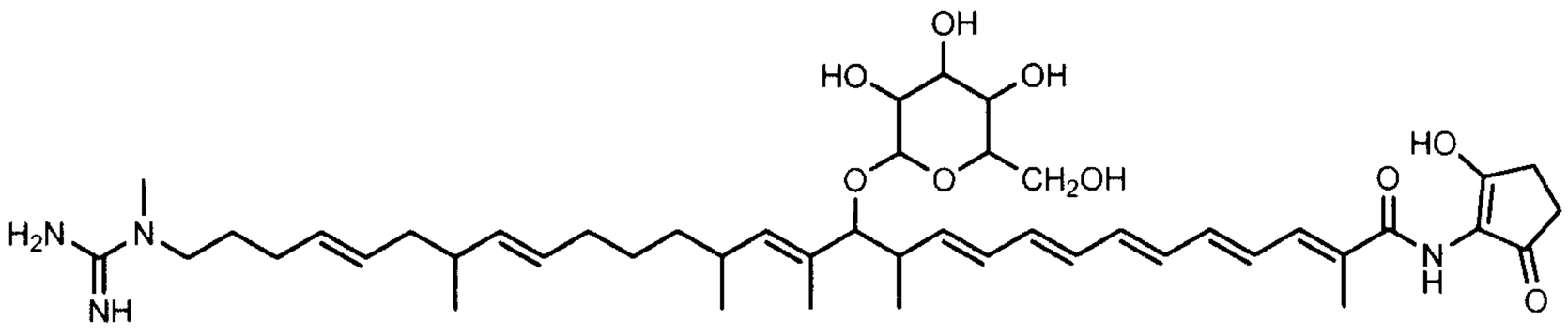
Compound 8

Compound 8 is produced by inactivation of glycosyltransferase ORF 14 (SEQ ID NO: 29) followed by fermentation as described in Example 2 and isolation of the compound as described in Example 3. Targeted inactivation of the gene product of ORF 14 (SEQ ID NO: 29) is achieved by insertional gene disruption using replicative plasmid-mediated homologous recombination. Inactivation of glycosyltransferase ORF 14 (SEQ ID NO: 29) is described in Figure 22a. Referring to Figure 22a, inactivation of the glycosyltransferase gene (SEQ ID NO: 30) disrupts the transfer of the sugar moiety onto the backbone of the polyketide core. The absence of the sugar moiety results in a non-glycosylated Compound 8. Insertional inactivation of glycosyltransferase genes involved in polyketide biosynthesis in streptomyces is known in the art. Blanco *et al.* (*Mol. Gen. Genet*. 262, 991-1000 (2000)), identified two genes of the mithramycin biosynthetic gene cluster as glycosyltransferases by the production of a non-glycosylated mithramycin upon inactivation of these genes. Similarly, Chen *et al.* (*Gene*

263, 255-64 (2001)) investigated genes responsible for glycosylation in the biosynthetic pathways encoding pikromycin, narbomycin, methymycin and neomethymycin by producing non-glycosylated analogs.

A plasmid for homologous recombination is constructed by cloning a kanamycin resistance marker between the left and right flanking regions of SEQ ID NO: 30. The construct is cloned into a delivery plasmid that is marked with thiostrepton resistance producing a disruption plasmid. The plasmid is introduced into *Amycolatopsis orientalis* by either PEG-mediated protoplast transformation or RK2-mediated conjugation. Spores from individual transformants or transconjugants are cultured on non-selective plates to induce recombination. This cycle is repeated three times to enhance the opportunity for recombination. Crossovers yielding targeted gene recombinants are then selected and screened using kanamycin and thiostrepton for single crossovers and kanamycin for double crossovers. Replica plating and southern hybridization are used to confirm the double crossover inactivation in *Amycolatopsis orientalis* transformants. The *Amycolatopsis orientalis* transformant is cultured as described in Example 2 and Compound 8 is isolated using the protocol of Example 3.

Example 18: Biosynthesis and Isolation of Compound 11



Compound 11

Compound 11 is produced by inactivation of inactivation of sugar oxidoreductase gene product of ORF 13 (SEQ ID NO: 27) followed by transfer of the glucose onto the polyketide backbone chain by the glycosyltransferase gene product of ORF 14 (SEQ ID NO: 29) as illustrated in Figure 22b. Referring to Figure 22b, glucuronic acid is synthesised by oxidation of glucose catalyzed by the sugar oxidoreductase gene product of ORF 13 (SEQ ID NO: 27). Inactivation of the ORF 13 (SEQ ID NO: 27) disrupts the conversion of glucose to glucuronic acid producing Compound 11 when the glucose

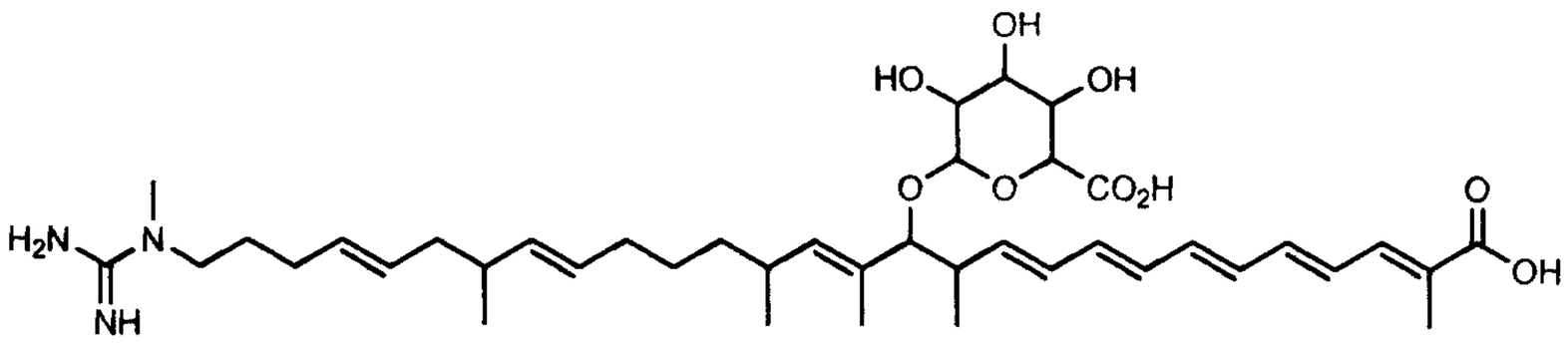
substrate is transferred onto the polyketide backbone chain by the glycosyltransferase gene product of ORF 14 (SEQ ID NO: 29). Targeted inactivation of the sugar oxidoreductase ORF 13 (SEQ ID NO: 27) is achieved by insertional gene disruption using replicative plasmid-mediated homologous recombination.

A plasmid for homologous recombination is constructed by cloning a kanamycin resistance marker between the left and right flanking regions of SEQ ID NO: 28. The construct is cloned into a delivery plasmid that is marked with thiostrepton resistance producing a disruption plasmid. The plasmid is introduced into *Amycolatopsis orientalis* by either PEG-mediated protoplast transformation or RK2-mediated conjugation.

Spores from individual transformants or transconjugants are cultured on non-selective plates to induce recombination. This cycle is repeated three times to enhance the opportunity for recombination. Crossovers yielding targeted gene recombinants are then selected and screened using kanamycin and thiostrepton for single crossovers and kanamycin for double crossovers. Replica plating and southern hybridization are used to confirm the double crossover inactivation in *Amycolatopsis orientalis* transformants.

The *Amycolatopsis orientalis* transformant is cultured as described in Example 2 and Compound 11 is isolated using the protocol of Example 3.

<u>Example 19:</u> Biosynthesis and Isolation of Compound 7



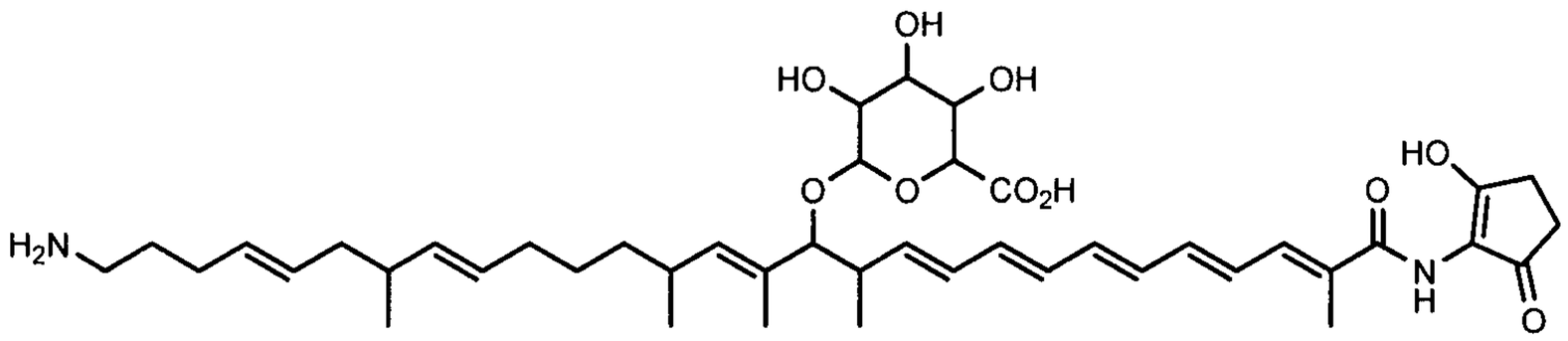
Compound 7

Compound 7 is also produced by inactivation of any one of acyltransferase ORF 16 (SEQ ID NO: 33), acyl CoA ligase ORF 17 (SEQ ID NO: 35), or adenylating/ condensing synthetase ORF 15 (SEQ ID NO: 31) followed by fermentation as described in Example 2 and isolation of the compound as described in Example 3. Referring to Figure 23, gene disruption of ORF 16 (SEQ ID NO: 34) results in the inactivation of the acyltransferase gene product of ORF 16 (SEQ ID NO: 33) preventing condensation of

succinyl-CoA and glycine to form 5-aminolevulinate. Gene disruption of ORF 17 (SEQ ID NO: 36) results in the inactivation of the acyl CoA ligase gene product of ORF 17 (SEQ ID NO: 35) preventing the conversion of 5-aminolevulinate to 5-aminolevulinate-CoA which cyclizes to form aminohydroxycyclopentenone. Gene disruption of ORF 15 (SEQ ID NO: 32) results in the inactivation of the adenylating/condensing synthetase gene product of ORF 15 (SEQ ID NO: 31) preventing transfer of the aminohydroxycyclopentenone unit to the polyketide chain. Compound 7 is provided by targeted inactivation of acyltransferase ORF 16 (SEQ ID NO: 33), acyl CoA ligase ORF 17 (SEQ ID NO: 35), or adenylating/condensing synthetase ORF 15 (SEQ ID NO: 31). Targeted inactivation of ORF 16, ORF 17 or ORF 14 (SEQ ID NO: 29) is achieved by insertional gene disruption using replicative plasmid-mediated homologous recombination.

A plasmid for homologous recombination is constructed by cloning a kanamycin resistance marker between the left and right flanking regions of SEQ ID NOS: 34, 36 or 32. The construct is cloned into a delivery plasmid that is marked with thiostrepton resistance producing a disruption plasmid. The plasmid is introduced into *Amycolatopsis orientalis* by either PEG-mediated protoplast transformation or RK2-mediated conjugation. Spores from individual transformants or transconjugants are cultured on non-selective plates to induce recombination. This cycle is repeated three times to enhance the opportunity for recombination. Crossovers yielding targeted gene recombinants are then selected and screened using kanamycin and thiostrepton for single crossovers and kanamycin for double crossovers. Replica plating and southern hybridization are used to confirm the double crossover inactivation in *Amycolatopsis orientalis* transformants. The *Amycolatopsis orientalis* transformant is cultured as described in Example 2 and Compound 7 is isolated using the protocol of Example 3.

Example 20: Biosynthesis and Isolation of Compound 9



Compound 9

Compound 9 is produced by incorporation of the amidino hydrolase of SEQ ID NO: 67 of co-pending application CA 2,453,071 (see below). The amidino hydrolase catalyzes the conversion of 4-guanidinobutanamide to γ-amino butanamide. The supplementation of SEQ ID NO: 67 of co-pending application CA 2,453,071 effects synthesis of γ-amino butanamide from 4-guanidino butanamide, as described in Figure 24. To promote catalytic activity of the amidinohydrolase enzyme, the N-methyltransferase of ORF 5 (SEQ ID NO: 10) is inactivated by insertional mutagenesis to prevent methylation of the guanidino group and thus avoid interference with the enzymatic activity of the amidino hydrolase SEQ ID NO: 67 of co-pending application CA 2,453,071. Referring to Figure 24, the γ-amino butanamide is converted by acyl CoA ligase ORF 25 (SEQ ID NO: 52) to form γ-aminobutyryl-CoA which is then tethered onto the ACP domain of module 0 of ORF 18 (SEQ ID NOS: 37) of the polyketide synthase enzyme through the action of acyltransferase ORF 24 (SEQ ID NO: 50).

To supplement amidinohydrolase activity, SEQ IS NO: 67 of co-pending application CA 2,453,071, *i.e* ORF 33 of a biosynthetic locus for the production of a polyketide in *Streptomyces aizunensis,* is cloned into vector pBW160 as described in Hussain and Ward (*Appl. Environ. Microbiol.* 69, 373-382 (2003)) and the vector transferred into *Amycolatopsis orientalis.* The vector contains inducible promoter elements placed upstream of the cloned amidinohydrolase gene. Transfer of the expression vector to *Amycolatopsis* host strain is achieved by direct transformation of mycelia and electroporation. Development of cloning vectors and transformation methods for amycolatopsis are described in Dhingra *et al.* (*J. Ind. Microbiol. Biotechnol.* 30, 195-204

(2003)). The *Amycolatopsis orientalis* transformant is cultured as described in Example 2 and Compound 9 is isolated using the protocol of Example 3.

The amidino hydrolase of SEQ ID NO: 67 of Canadian patent application 2,453,071 is defined in one letter code as follows:

MTAHPNGVTPPLPPTETDRTLHFAGPATFGRIPRIDQVEKTDIAVVGVPFDSGVTY
RPGARFGGNAIREASRTLRPYNPAQNVYPFHFSQVADAGDISANPFDLNDAVETIE
AAADDLISSGARLMTLGGDHTIALPMLRAVAKKHGPLAVLHFDAHLDTWDDYFGQ
QYTHGMPFRRAVEEGILDTSALSHVGTRGPIYGKKDLDDDEKLGFGIVTSADVMR
RGVDEVAQQLRERVGDRPLYISIDIDVLDPAHAPGTGTPEAGGLTSRELLEILRGLA
DCHLVSADIVEVAPAYDHADITSVAASHAAYELISIMSKQIAPVRWGATQ;

and is prepared synthetically or by using cosmid IDAC 250203-05, deposited on February 25, 2003, at the International Depositary Authority of Canada (IDAC), Bureau of Microbiology, Health Canada, 1015 Arlington Street, Winnipeg, Manitoba, Canada R3E 3R2, comprising the encoding nucleic acid.

While this invention has been particularly shown and described with reference to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

SEQUENCE LISTING

<110> ECOPIA BIOSCIENCES INC.
McAlpine, James B.
Farnet, Chris M.
Zazopoulos, Emmanuel
Sorensen, Dan

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65 70 75 80

Phe Leu Leu Ser Ala Gly Gly Ser Arg Arg Arg Val Ala Leu Asp Ala
85 90 95

Trp Leu Leu Leu Leu Val Cys Ala Ala Leu Ala Val Ala Met Phe Val
100 105 110

Val Pro Ala Ala Ser Arg Glu Gln Ala Phe Gly Val Gly Ala Ala Leu
115 120 125

Pro Ala Val Val Thr Glu Pro Gly Val Ala Leu Phe Phe Leu Val Asp
130 135 140

Ala Ala Tyr Gly Thr Tyr Thr Thr Val Gln Ala Ala Ser Trp Ala Leu
145 150 155 160

Arg Asp Ala Val Glu Thr Pro Leu Arg Val Arg Trp Gly Leu Arg Ile
165 170 175

Ala Ala Cys Gly Leu Ile Thr Leu Ala Val Thr Ser Val Ala Arg Phe
180 185 190

Gly Thr Ile Leu Val Arg Trp Ser Gly Gly Asp Val Pro Ser Ser Leu
195 200 205

Pro Val Ala Thr Ala Val Leu Val His Val Gly Ile Ile Leu Phe Met
210 215 220

Ala Gly Ile Thr Leu Val Gly Leu Leu Ala Val Leu Ala Ala Val Arg
225 230 235 240

Leu Trp Leu Arg His Arg Arg Arg Tyr Glu Asp Leu Arg Pro Leu Trp
245 250 255

Gly His Leu His Asp Val Phe Pro Gly Asp Ala Leu Tyr Ala Gly Gln
260 265 270

Arg Gly Gly Trp Leu Glu Glu Leu Ala Phe Trp Arg Met His Arg Arg
275 280 285

Tyr Trp Arg Arg Val Val Glu Ile Arg Asp Gly Leu Val Arg Leu Ser
290 295 300

Pro Tyr Leu Ala Asp Cys Gly Phe Val Glu Gly Arg Glu Arg Val Ser
305 310 315 320

Pro Glu Val Phe Arg Glu Ala Leu Ala Arg Leu Arg Ser Gly Glu Arg
325 330 335

Pro Thr Ser Arg Thr Ala Val Ala Val Ala Arg Pro Glu Gly Gln Asp
340 345 350

Val Glu Ala Asp Val Gly Glu Leu Val Thr Leu Ser Lys Thr Leu Arg
355 360 365

Ala

<210> 5
<211> 1110
<212> DNA
<213> Amycolatopsis orientalis

<400> 5
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cgatcgccgc gcgacccggc gatctgggcg ctggtcggct gcctggtgct gcggttgctg 120

accgcgcctt cgagcatggt ggcgctgcac gagttcaccg gagggacgct cgacgtcgac 180

accttccgcc tggtccagac ggtcgtgctc gacgccagcc tgttcttcct gctggtcttc 240

ttcctgctct ccgcgggcgg ctcgcggcgg cgggtggccc tcgacgcctg gttgctgcta 300

ctggtctgcg cggccctggc ggtggccatg ttcgtggtcc cggccgcgtc ccgcgagcag 360

gccttcggtg tcggcgcggc gctgccggcg gtcgtgacgg agccgggggt ggcgctcttc 420

ttcctggtcg acgcggcgta cggcacctac acgaccgtgc aggctgcgag ctgggcgctg 480

cgtgacgccg tggaaacccc gctccgggtc cgctgggggc tgcggatcgc cgcctgcggc 540

ctgatcacgc tcgcggtgac ctcggtcgcg cggttcggca cgatcctggt gcgctggtcc 600

ggcggcgacg tgccgtcgtc cctgccggtc gcgacggccg tgctggtcca cgtgggaatc 660

atcctgttca tggccgggat caccctggtc gggctgctcg ccgtgctcgc cgccgtcagg 720

ctgtggctgc ggcaccggcg gcggtacgag gatctgcgac cgctgtgggg gcacctgcac 780

gacgtgttcc ccggtgacgc gctgtacgcc gggcagcgcg gcggatggct ggaggaactc 840

gcgttctggc ggatgcatcg ccggtactgg cgaagggtcg tcgagatccg tgacggactg 900

gtccggctga gcccatacct ggccgactgc ggtttcgtcg aaggcaggga gcgggtttcg 960

cccgaggtct tccgcgaggc actggccagg ttgcggtcgg gggagcggcc gacctcgcgt 1020

accgcggtgg cggtggcgcg ccccgagggg caggacgtcg aggccgacgt cggggagctc 1080

gtcacgctgt cgaagacgct gcgcgcctga 1110

<210> 6
<211> 171
<212> PRT
<213> Amycolatopsis orientalis

<400> 6

Met Ala Ala Arg His Gly Phe Val Arg Asn Ser Ala Val Phe Leu Gly
1 5 10 15

Gly Ser Met Ser Arg Gln Asp Gly Pro Gly Arg Ser Leu Ala Glu Lys
20 25 30

Leu Asp His Leu Phe Ala His Val Thr Arg Arg Asn Gly Thr Glu Phe
35 40 45

Thr Tyr Glu Glu Val Ala Ser Ala Ile Thr Ala Glu Gly Val Thr Ile
50 55 60

Ser Gln Ser Tyr Val Trp Gln Leu Arg Lys Gly Lys Lys Asp Asn Pro
65 70 75 80

Thr Leu Lys His Leu Gln Gly Leu Ala Asp Phe Phe Gly Val Pro Val
85 90 95

Thr Tyr Phe Phe Asn Glu Asp Val Ser Asp Arg Val Asp Arg Gln Leu
100 105 110

Glu Tyr Leu Arg Ala Glu Gln Ala Arg Leu Arg Glu Leu Ala Glu Thr
115 120 125

Asp Glu Val Arg Leu Met Ala Met Arg Ala Gly Glu Leu Thr Thr Asp
130 135 140

Arg Arg Glu Leu Val Lys Asn Leu Leu Asp Val Val Trp Arg Asp Gln
145 150 155 160

Gln Ala Met Arg Glu Arg Gly Ser Lys Gln Asp
165 170

<210> 7
<211> 516
<212> DNA
<213> Amycolatopsis orientalis

<400> 7
atggcagcgc ggcacgggtt cgtgaggaac tcggcagtgt tcttgggagg cagcatgtcc 60

cggcaggacg gaccaggccg gagcctggcc gaaaaactcg accatctgtt cgcgcacgtc 120

acccggcgca acggcaccga gttcacgtac gaagaggtcg cgtccgcgat caccgccgag 180

ggtgtgacga tctcccagag ctacgtctgg cagctgcgca agggaaagaa ggacaacccg 240

acgctcaagc acctgcaagg gctggcggat ttcttcggtg tcccggtcac gtacttcttc 300

aacgaggacg tgagcgaccg ggtggaccgg cagctggagt acctgcgcgc ggaacaggcg 360

cggttgcgtg agctggccga aaccgacgag gtccgcctga tggccatgcg cgcgggcgag 420

ttgacgaccg atcgccgcga actggtgaag aacctcctcg acgtggtctg gcgggatcag 480

caggccatgc gagagcgtgg gtccaaacag gactga 516

<210> 8
<211> 936
<212> PRT
<213> Amycolatopsis orientalis

<400> 8

Met His Val Lys Ser Val Ile Arg Val Asp Gly Asp Val Arg Ala Arg
1 5 10 15

Ala Tyr Pro Arg Ala Glu Leu Leu Val Leu Arg Asp Phe Leu Thr Glu
20 25 30

Ser Glu Gln Gly Asn Ala Val Ala Ala Val Val Thr Gly Thr Ala Ala
35 40 45

Ser Gly Lys Ser Glu Leu Leu His Ala Phe Ala Gln Gln Cys Ala Glu
50 55 60

Ala Glu Ala Thr Val Met Ser Ala Leu Cys Val Glu Ala Glu Lys Asp
65 70 75 80

Leu Pro Phe Thr Ala Leu Phe Gln Leu Phe Arg Gly Pro Ala Leu Ser
85 90 95

Gly Asp Leu Arg Ala Lys Ala Ala Asp Leu Leu Thr Arg Ala Glu Arg
100 105 110

Thr Gly Leu Thr Gly Arg Pro Ser Thr His Leu Met Leu Asp Leu Leu
115 120 125

Glu Leu Val Arg Glu Leu Ala Ala His Arg Pro Val Val Val Leu Val
130 135 140

Asp Asp Phe His His Val Asp Thr Pro Ser Leu His Trp Leu Met Phe
145 150 155 160

Leu Met Arg Arg Met Arg Thr Met Asn Val Leu Val Val Leu Thr Glu
165 170 175

Ser Leu Ser Ala Lys Gln Thr Leu Pro Leu Leu Gly Ala Glu Tyr Leu
180 185 190

Arg Leu Pro His Cys Arg Arg Ile Arg Leu Lys Pro Leu Gly Arg Asp
195 200 205

Glu Val Ala Arg Phe Val Pro Pro Gly Gln Asp Asp Thr Leu Val Lys
210 215 220

Gly Leu His Glu Leu Ser Gly Gly Asn Pro Leu Leu Ala Gln Ala Leu
225 230 235 240

Leu Glu Asp Leu Arg Ala Ser Gly Val Pro Leu Ala Pro Glu Thr Arg
245 250 255

Pro Ile Pro Gly Asp His Tyr Cys Gln Ala Val Ala Ala Cys Leu Gln
260 265 270

Arg Gly Asp Gln Asp Thr Arg Thr Leu Ala Gly Val Leu Ala Val Leu
275 280 285

Gly Lys Gly Glu Thr Val Cys Leu Ala Val Arg Val Thr Gly Met Asp
290 295 300

Gln Arg Thr Ala Gly Arg Ala Ile Ala Leu Leu His Gln Val Gly Leu
305 310 315 320

Leu Asp Ala Gly Arg Phe Arg His Pro Met Thr Val Thr Ala Val Leu
325 330 335

Ala Asp Val Pro Val Ala Glu Arg Ala Arg Leu His Glu Arg Ala Ala
340 345 350

Val Leu Leu His His Asp Gly Ala Gly Ala Leu Asp Val Ala Arg His
355 360 365

Leu Val Ala Ala Asp Arg Ala Asp Arg Pro Trp Ala Val Pro Val Leu
370 375 380

Arg Thr Ala Ala Glu Leu Ala Lys Val Asp Asn Arg Thr Ser Phe Ala
385 390 395 400

Val Gln Cys Leu Lys Leu Ala Cys Arg Ser Cys Gly Asp Glu Ala Leu
405 410 415

Glu Val Glu Met Val Thr Gln Leu Ala Gly Leu Glu Trp Arg Asn Asn
420 425 430

Pro Ala Ile Gly Ala Val His Thr Asp His Leu Tyr Glu Ile Phe Leu
435 440 445

Ala Gly Gln Leu Pro Val Arg Ala Ala Ala Ile Leu Val Arg Phe Leu
450 455 460

Leu Trp His Gly Arg Thr Ala Glu Ala Gly Glu Val Leu Asp Lys Leu
465 470 475 480

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Ala Val Met Glu Pro Ser Ala Asp Asp Arg Thr Glu Ala Glu Leu Arg
                485                 490                 495

Ile Thr Arg Leu Phe Ile Leu Cys Ser Tyr Pro Val Leu Arg Asp Lys
            500                 505                 510

Leu Pro Ala Pro Ala Ala Lys Asp Arg Val Pro Ala Gln Ser Phe Asp
        515                 520                 525

Pro Asn Val Gln Ala Ala Met Ala Leu Ser Arg Ile Val Thr Asn Gly
    530                 535                 540

Pro Asp Asp Asp Ala Ile Ala Ser Ala Glu Asn Val Leu Lys Ser Ile
545                 550                 555                 560

Gln Leu Gly Asp Thr Met Val Glu Ser Val Arg Ser Ala Leu Phe Ala
                565                 570                 575

Leu Ile Tyr Ala Asp Arg Leu Asp Lys Ala Val Pro Trp Cys Glu Leu
            580                 585                 590

Leu Gln Gln Glu Ala Ala Asp Cys Asp Ala Pro Ser Trp Gln Ala Val
        595                 600                 605

Phe Ala Ala Ala Arg Ala Glu Met Ala Leu Arg Gln Gly Asp Leu Val
    610                 615                 620

Thr Ala Glu Lys Gln Ala Lys Ala Ala Leu Thr Phe Ile Thr Pro Gln
625                 630                 635                 640

Ser Trp Gly Val Ala Val Gly Val Pro Leu Ala Thr Leu Cys Leu Ala
                645                 650                 655

Ala Val Gly Met Gly Lys Phe Glu Glu Ala Ala Ser His Ile Asn Gln
            660                 665                 670

Pro Val Pro Ala Ser Met Leu Gln Thr Arg Phe Gly Leu His Tyr Leu
        675                 680                 685

Arg Ala Arg Gly Arg Leu Tyr Leu Glu Thr Asp Arg Val His Ala Ala
    690                 695                 700

Leu Gly Asp Phe Val Leu Cys Gly Glu Leu Ser Lys Ser Trp Asp Phe
705                 710                 715                 720

Asp Leu Pro Val Leu Val Pro Trp Arg Gly Asp Thr Ala Glu Ala Tyr
                725                 730                 735

Leu Arg Leu Gly Met Pro Glu Lys Ala Lys Ser Leu Leu Asp Glu Gln
            740                 745                 750

Leu Ala Lys Leu Ala Gly Ser Thr Ser His Val Arg Gly Ile Ser Leu
        755                 760                 765

Arg Leu Lys Ala Lys Ile Ala Glu Pro Gln Lys Arg Pro Glu Leu Leu
    770                 775                 780

Arg Glu Ala Val Lys Ile Phe Gln Ala Gly Gly Ile Arg Leu Glu Leu
785                 790                 795                 800

Ala Arg Ala Leu Gly Asp Leu Ser Arg Ala His Tyr Thr Leu Ala Glu
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805 810 815

Ser Gly Arg Ala Arg Thr Val Ala Arg Gln Ala Trp His Ile Ala Lys
820 825 830

Gly Cys His Ala Asp Val Ile Cys Arg Asp Leu Arg Leu Asp Gly Thr
835 840 845

Gly Asp Glu Gly Lys Pro Ala Ser Thr Ala Ala Glu Ile Ala Ala Ser
850 855 860

Gly Val Glu Arg Glu Leu Ile Glu Ser Leu Ser Glu Ala Glu Arg Arg
865 870 875 880

Val Ala Gly Leu Ala Ser Leu Gly His Thr Asn Arg Ala Ile Ala Ser
885 890 895

Lys Leu Tyr Ile Thr Val Ser Thr Val Glu Gln His Leu Thr Arg Val
900 905 910

Tyr Arg Lys Leu Asp Val Asn Arg Arg Arg Asp Leu Pro Ser Trp Leu
915 920 925

Gln Val Ser Val Val Asn Ser Ala
930 935

<210> 9
<211> 2811
<212> DNA
<213> Amycolatopsis orientalis

<400> 9
atgcacgtga aatcagtgat cagagtggac ggcgacgtcc gcgcgagggc gtatccccgc 60

gcggagctgc tggtcctgcg agacttcttg acggaatccg aacagggaaa cgccgtcgcg 120

gcggtggtca ccggaaccgc cgcgagcggg aaaagtgaac ttctgcacgc attcgcgcaa 180

caatgcgctg aagcggaagc aacggtgatg agcgcgcttt gcgtggaagc ggagaaggat 240

ctcccgttca ccgcgctgtt ccagcttttc cgtggcccgg cactgtccgg agatctgcgc 300

gcgaaggccg cggacctgct gacgcgggcc gaacggaccg ggctgaccgg gcggcccagc 360

acacatctca tgctcgacct gctggagctc gtgcgcgagc tcgccgcgca ccgtccggtc 420

gtggtcctgg tcgacgactt ccaccatgtg gacaccccgt cgttgcactg gctgatgttc 480

ctcatgcgcc gcatgcgcac gatgaacgtg ctcgtcgtgc tgacggagtc gttgtccgcc 540

aagcagacgt tgcccttgct gggcgccgag tacctccggc tcccgcactg ccgccggatc 600

cggctgaagc cgctgggccg cgacgaggtg gcccggttcg tcccgcccgg ccaggacgac 660

accctggtga agggcctgca cgagctcagc ggcgggaatc cgttgctggc tcaggcactc 720

ctcgaagatc tccgtgcctc gggcgtaccc ctcgcgcccg agacccggcc gatccccggc 780

gatcactact gccaggcggt ggcggcgtgt ctccagcgcg gcgaccagga cacccggacc 840

ctcgccggtg tcctcgcggt gctgggtaaa ggggaaacgg tctgcctcgc cgtccgggtg 900

accgggatgg accagcgcac cgccggccgt gcgatcgccc tcctgcacca ggtcggcctg 960

ctcgacgcgg gccggttccg gcatccgatg acggtgaccg cggtgctggc cgacgtcccg 1020

gtcgcggaac gcgcgcgact gcacgagcgc gccgcggtgc tcctgcatca cgacggcgcc 1080

ggcgcgctcg acgtggcccg ccacctcgtc gccgccgacc gggccgaccg gccgtgggcg 1140

gtgcccgtgc tgcgcaccgc ggccgaactg gccaaagtgg acaaccggac ctcgttcgcg 1200

gtccaatgcc tgaaactggc ctgccggtcg tgcggcgacg aagcgctcga ggtcgagatg 1260

gtgacccagc tcgccggcct ggaatggcgg aacaacccgg ccatcggcgc cgtgcacacg 1320

gaccacctct acgagatctt cctcgccggg cagctcccgg tgcgggccgc cgccatcctg 1380

gtgcggttcc tgctgtggca cggccgcacc gcggaagcgg gtgaggtgct cgacaagctc 1440

gccgtcatgg agccttcggc cgacgatcgc accgaggcgg aactgcgcat cacccggctg 1500

ttcattctct gttcctatcc cgttctgcgc gacaagctgc ctgccccggc cgcgaaggac 1560

cgcgttcccg cgcaatcctt cgaccccaac gtgcaggcgg cgatggcgct gagccggatc 1620

gtcacgaacg gccccgacga cgacgcgatc gcttcggctg agaacgtgct gaagagcatc 1680

cagctcggcg acacgatggt cgaatccgtg cgcagcgcgc tgttcgcgct catctacgcc 1740

gaccggctgg acaaggcggt gccgtggtgc gagctgctgc agcaggaggc cgccgactgc 1800

gacgcgccca gctggcaggc cgtgttcgcc gcggccaggg cggaaatggc gctgcgccag 1860

ggagatctgg tgacggcgga gaagcaggcc aaggcggcct tgacgttcat cacgccgcag 1920

agctggggcg tggccgtcgg agtcccgctg gcgacgctgt gcctcgccgc cgtcgggatg 1980

ggcaagttcg aggaggcggc gtcgcatatc aaccagccgg tgccggcctc gatgctgcaa 2040

acccggttcg gcctgcacta cctgcgcgcc cgcggcaggc tctacctgga gaccgaccgg 2100

gtgcacgccg cgctcggcga cttcgtcctg tgcggggaac tcagcaagag ctgggatttc 2160

gacctgccgg tgctggtgcc ctggcgcggc gacacggccg aggcgtacct ccggctcggc 2220

atgccggaga aggcgaagtc cctgctggac gagcagctcg cgaagctcgc cggctcgacg 2280

tctcatgtgc ggggaatctc gttgcggctc aaggccaaga tcgccgaacc gcagaagcgc 2340

ccggaattgc tgcgtgaagc ggtgaagatc ttccaggcgg gcggtatccg cctcgaactc 2400

gcccgcgcgc tcggcgatct cagccgcgcg cactacacgc tggccgagtc gggtcgcgcg 2460

cgcacggtgg cccggcaggc gtggcatatc gcgaagggtt gccacgccga cgtgatctgc 2520

cgggatctgc gtctcgacgg gacaggcgac gagggaaagc cggcgtccac cgcggcggag 2580

atcgccgcgt cgggcgtcga acgcgagctc atcgagtcgc tgagcgaggc cgagcgacgg 2640

gtcgccgggc tggcctccct cgggcacacg aaccgggcga tcgcgagcaa gctctacatc 2700

acggtgagca cggtcgaaca gcatctcacc cgcgtctatc gcaaactgga cgtcaaccgg 2760

cgccgggatc tcccgtcgtg gctccaggtt tcggtcgtca acagcgcctg a 2811

<210> 10
<211> 271
<212> PRT
<213> Amycolatopsis orientalis

<400> 10

Met Gln Arg Asn Phe Lys Glu Phe Lys Ile Thr Val Asp Pro Val Arg
1 5 10 15

Asp Asp Phe Leu Arg Ala Lys Gly Pro Gly Gln Arg Asn Leu Leu Leu
20 25 30

Gly Arg Ala Val Phe Glu Phe Ala Ser Asp Leu Glu His Leu Asp Thr
35 40 45

Ile Gln Gln Glu Phe Val Asp Gly Ser His Arg Pro Leu Ile Arg Arg
50 55 60

Asn Trp Gln Asp Ser Thr Ala Asp Tyr Ser Asp Pro Thr Gln Leu Leu
65 70 75 80

Ile Gln Gly Gln Gln Val Met Gln Asn Trp Glu Arg Pro Leu Met Lys
85 90 95

Val Leu Ala Glu Asn Ala Ala Ala Asn Gly Gly Asp Leu Leu Glu Val
100 105 110

Gly Phe Gly Met Gly Ile Ser Ala Thr Tyr Val Gln Asp Ala Gly Val
115 120 125

Arg Ser His Thr Leu Ile Glu Ile Asn Ser Glu Val Lys Ala Glu Phe
130 135 140

Glu Lys Trp Arg Ala Gln Trp Pro Asp Arg Asp Ile Arg Leu Glu Leu
145 150 155 160

Gly Ala Trp Gln Asp Val Leu Gly Gly Leu Gly Gln Tyr Asp Ala Ile
165 170 175

Leu Tyr Asp Thr Tyr Pro Thr Asp Glu Arg Glu Phe Ala Arg Thr Leu
180 185 190

Gly Pro Lys Ala Ile Val Leu Ala Ala Glu Phe Phe Glu His Ala Ala
195 200 205

Ala His Leu Arg Pro Gly Gly Val Phe Ser Tyr Tyr Thr Asn Glu Ile
210 215 220

Asp Ser Leu Ser Arg Ala His Gln Arg Ala Leu Leu Glu His Phe Ser
225 230 235 240

Ser Phe Arg Val Glu Val Val Arg Asp Leu Lys Pro Pro Ala Asp Cys
245 250 255

Thr Tyr Trp Trp Ala Gly Thr Met Ala Ala Val Thr Ala Val Lys

260 265 270

<210> 11
<211> 813
<212> DNA
<213> Amycolatopsis orientalis

<400> 11
cttgacggcg gtcacggcgg ccatcgtgcc cgcccaccag taggtgcagt cggccggcgg 60

cttcaggtcc cggacgacct ccacccggaa cgagctgaag tgttcgagca gggcgcgctg 120

gtgtgcccgg ctcagtgagt cgatttcgtt ggtgtagtag gagaagacgc caccgggacg 180

aaggtgggcg gcggcgtgct cgaagaattc ggccgccagc acgatggcct tcgggcccag 240

ggtcctggcg aattcccgct cgtcggtcgg ataggtgtcg tacaggatcg cgtcgtactg 300

gccgaggccg ccgagcacgt cctgccaggc gccgagttcc agccggatat cgcggtccgg 360

ccactgggca cgccatttct cgaactccgc cttcacctcg gagttgattt cgatcagggt 420

gtgcgaccgg acgcccgcgt cctggacgta ggtggccgaa atacccatcc cgaaaccgac 480

ttcgagcaga tccccgccgt tcgccgcggc gttttccgcc agcaccttca tcagcggccg 540

ttcccagttc tgcatcacct gctggccctg gatgagcagc tgcgtcggat cgctgtagtc 600

cgcagtgctg tcctgccagt tccggcggat cagcggccgg tgcgagccgt cgacgaattc 660

ctgctggatg gtgtccagat gttccagatc gctggcgaac tcgaacaccg cgcggccgag 720

aaggaggttg cgctggccgg gcccccttcgc ccggaggaag tcgtccctga ccgggtccac 780

cgttatcttg aattccttga agttccgttg cat 813

<210> 12
<211> 229
<212> PRT
<213> Amycolatopsis orientalis

<400> 12

Met Pro Gly Glu Thr Lys Asn Gln Asp Thr Asp Gly Arg Gly Ala Arg
1 5 10 15

Arg Arg Ser Val Val Ser Leu Ile Ala Asp Val Thr Val Pro Val Val
20 25 30

Val Tyr Tyr Ala Leu Leu Ala Phe Gly Trp Ser Ser Gly Ser Ala Leu
35 40 45

Val Ala Ala Thr Val Ala Ile Gly Val Leu Val Leu Ala Val Ala Val
50 55 60

Lys Glu Arg Arg Val Asp Gly Phe Gly Val Phe Val Leu Gly Val Cys
65 70 75 80

Ala Val Thr Leu Leu Val Ser Leu Val Ser Gly Asp Glu Arg Leu Leu
85 90 95

Leu Ala Lys Asp Pro Phe Thr Ser Gly Leu Ala Gly Ile Ala Phe Leu
100 105 110

Gly Ser Leu Val Phe Gly Lys Pro Val Thr Phe Phe Ile Ser Arg Arg
115 120 125

Ile Arg Ala Leu Thr Pro Ala Arg Arg Leu Gly Trp Asp Arg Leu Tyr
130 135 140

Ala Ala Glu Pro Glu Phe Arg Lys Leu His Arg Val Ser Thr Ala Gly
145 150 155 160

Trp Gly Val Val Leu Val Thr Glu Ser Ala Ala Arg Leu Val Leu Ile
165 170 175

Tyr Leu Leu Pro Ala Ser Val Met Val Gly Leu Ser Thr Ala Ile Glu
180 185 190

Leu Thr Ala Ile Thr Gly Val Val Ala Trp Thr Ile Trp Tyr Arg Arg
195 200 205

Arg Ser Ala Gly His Gly Leu Glu Lys Ser Leu Arg Thr Ala Asp Ala
210 215 220

Ala Pro Ala Ala Val
225

<210> 13
<211> 687
<212> DNA
<213> Amycolatopsis orientalis

<400> 13
atgccggggg aaaccaagaa ccaggacacc gacggccgcg gcgcgcgcag gcgctccgtc 60

gtatcgttga tcgccgacgt caccgtgccg gtcgtcgtct actacgcgct gctcgccttc 120

gggtggagca gcggctccgc cttggtggcg gccacggtcg ccatcggggt cctcgtgctc 180

gccgtcgcgg tcaaggaacg cagggtcgac ggcttcgggg tgttcgtgct cggagtctgc 240

gcggtgaccc tgctggtctc cttggtgagc ggggacgaac gcctgctgtt ggccaaggat 300

cccttcacca gcggcctggc cgggatcgcc ttcctcggca gcctcgtctt cgggaaaccg 360

gtgaccttct tcatctcccg ccggatccgg gcgctcaccc cggctcggcg cctgggctgg 420

gaccggctgt acgccgcgga acccgagttc cgcaaactgc atcgcgtctc caccgcgggc 480

tggggcgtgg tcctggtcac cgagtccgcc gcccggctcg tcctgatcta cctgctgccc 540

gcgtcggtga tggtcggcct gtccaccgcg atcgaactga ccgcgatcac cggcgtggtc 600

gcctggacca tctggtaccg gcgtcgctcc gccggccacg gtctggaaaa gtcgcttcgc 660

acggcggatg cggcgcccgc tgctgtc 687

<210> 14
<211> 553

<212> PRT
<213> Amycolatopsis orientalis

<400> 14

Met Thr Ala Ala Asp Phe Ala Pro Pro Leu Thr Thr Leu Cys Pro Asp
1 5 10 15

Phe Pro Phe Ala Tyr Asp Asp Trp Leu Ala His Pro Ala Gly Leu Gly
20 25 30

Glu Leu Pro Pro Asp Arg Leu Gly Gln Glu Val Ala Val Val Gly Gly
35 40 45

Gly Ile Ala Gly Val Val Ala Ala Tyr Glu Leu Leu Arg Leu Gly Leu
50 55 60

Lys Pro Val Val Tyr Glu Ala Gly Gln Ile Gly Gly Arg Met Arg Ser
65 70 75 80

Ile Pro Leu Ala Gly Glu Asp Gly Ala Val Ala Glu Met Gly Ala Met
85 90 95

Arg Phe Pro Pro Ser Ala Thr Thr Leu Tyr Arg Tyr Ile Asp Glu Val
100 105 110

Gly Leu Glu Thr Lys Pro Phe Ala Asn Pro Leu Ser Arg Ser Thr Ser
115 120 125

Thr Thr Val Ile Asn Leu Asp Gly Val Thr Tyr Arg Ala Arg Thr Pro
130 135 140

Ala Asp Leu Pro Ser Val Phe His Glu Val Asp Asp Ala Trp His Lys
145 150 155 160

Ala Leu Gln Glu Leu Ala Asp Leu Ser Thr Met Arg Asp Ala Ile Arg
165 170 175

Met Arg Asp Thr Ala Met Val Lys Ala Ile Trp Asn Arg Leu Leu Pro
180 185 190

Glu Leu Asp Asp Gln Ser Phe Tyr Gly Phe Leu Ala Arg Ser Thr Ala
195 200 205

Phe Ala Ser Phe Arg His Arg Glu Ile Phe Gly Gln Val Gly Phe Gly
210 215 220

Thr Gly Gly Trp Asp Thr Asp Phe Pro Asn Ser Val Leu Glu Ile Leu
225 230 235 240

Arg Val Ile Tyr Thr Gly Val Glu Glu Gly Pro Arg Gln Ile Ile Gly
245 250 255

Gly Cys Gln Gln Leu Pro Arg Arg Leu Trp Asn His Ala Pro Ala Ser
260 265 270

Ala Arg Phe Trp Pro Ala Gly Thr Ser Val Ala Ser Leu His Asp Gly
275 280 285

Ser Pro Arg Pro Ala Val Leu Gly Leu Arg Pro Ala Ala Asp Gly Phe
290 295 300

Ala Val Glu Asp Ala Asn Gly Asp Val Arg Thr Tyr Pro Ala Val Val
305 310 315 320

Phe Thr Ala Gln His Arg Val Leu Leu Thr Lys Ile Ala Gly Val Arg
325 330 335

Pro Leu Leu Pro Ala Asn Val Trp Thr Ala Leu Glu Arg Thr His Tyr
340 345 350

Met Gly Ala Ser Lys Leu Phe Val Pro Val Asp Arg Pro Phe Trp His
355 360 365

Asp Val Asp Pro Arg Thr Gly Glu Glu Leu Met Gly Met Thr Leu Thr
370 375 380

Asp Arg Thr Pro Arg Ser Val Tyr Leu Phe Asp Asp Gly Pro Asp Ser
385 390 395 400

Pro Ala Ala Leu Cys Leu Ser Tyr Thr Trp Asn Asp Asp Ser Leu Lys
405 410 415

Phe Ala Thr Leu Gly Pro Ala Asp Arg Leu Glu Leu Ala Leu Asp Ala
420 425 430

Leu Ala Asp Ile Tyr Pro Gly Val Asp Ile Arg Ser His Ile Thr Gly
435 440 445

Asp Pro Val Thr Val Thr Trp Glu Asn Glu Pro Asn Phe Gln Gly Ala
450 455 460

Phe Lys Ala Asn Leu Pro Gly Gln Tyr Arg Tyr Gln Arg Arg Leu Phe
465 470 475 480

Thr His Phe Arg Gln Asp Asp Leu Pro Ala Ala Gln Arg Gly Leu Phe
485 490 495

Leu Ala Gly Asp Asp Ile Ser Trp Met Gly Gly Phe Ala Glu Gly Ala
500 505 510

Val Thr Ser Ala Leu Asn Ala Val Trp Gly Thr Leu Arg His Leu Gly
515 520 525

Gly Ala Thr Asp Pro Arg Asn Pro Gly Pro Gly Asp Val Phe Asp His
530 535 540

Ile Ala Pro Ile Glu Leu Pro Glu Ser
545 550

<210> 15
<211> 1659
<212> DNA
<213> Amycolatopsis orientalis

<400> 15
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tacgacgatt ggctcgcgca tccggccggg ctcggtgagc tgccgccgga ccgcctcggc 120

caggaggtcg ccgtcgtcgg tggcgggata gcgggtgtgg tcgcggctta cgaactgctg 180

cgcctcggcc tgaaaccggt ggtctacgaa gcgggccaga tcggcgggcg gatgcgctcc 240

atccccttgg cgggcgagga cggcgcggtc gcggagatgg gcgcgatgcg gttcccgccc 300

tcggccacca ccctgtaccg gtacatcgac gaagtcggcc tggagaccaa gccgttcgcg 360

aacccgttgt cccgcagcac ttccaccacg gtgatcaacc tcgacggggt gacctaccgc 420

gcgcggaccc cggcggacct cccgtcggtg ttccacgagg tcgacgacgc ctggcacaag 480

gccctgcagg aactggccga tctgtccacc atgcgcgacg ccatccggat gcgcgacacc 540

gccatggtga aggcgatctg gaaccggctg ctgcccgaac tcgacgacca gtccttctat 600

ggtttcctgg cacggtcgac cgctttcgcc tccttccgcc atcgtgagat cttcggccag 660

gtcggcttcg gcaccggcgg ctgggacacc gatttcccca actccgtgct ggaaatcctc 720

cgcgtcatct acaccggtgt cgaggagggg ccgcggcaga tcatcggtgg ctgccagcaa 780

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gcggacgggt tcgccgtcga ggacgcgaac ggtgacgtgc ggacctatcc ggccgtggtc 960

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gacatctcgt ggatgggcgg cttcgccgaa ggggcggtca ccagcgcgct caacgcggtg 1560

tgggggacgc tgcgccatct cggcggggcc accgacccgc gtaatcccgg ccccggcgac 1620

gtcttcgacc acatcgcgcc gatcgaactg cccgagtcc 1659

<210> 16
<211> 179
<212> PRT
<213> Amycolatopsis orientalis

<400> 16

Met Ser Glu Ala Met Arg Asn Ala Leu Ile Leu Ser Gly Val Leu Leu
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Ala Leu Val Leu Phe Thr His Ile Gly Arg His Lys Ala His Leu Val
20 25 30

Ile Leu Ile Leu Pro Phe Phe Thr Cys Ala Leu Val Gly Trp Ala Val
35 40 45

Leu Tyr Asp Leu Lys Leu Thr Thr Pro Asn Thr Leu Ala Gly Leu Val
50 55 60

Gly Ile Ala Ala Gly Val Leu Ile Gly Trp Gly Leu Leu Lys Gly Thr
65 70 75 80

Lys Val Glu Trp Asp Gln Glu Lys Ser Ala Val Tyr Thr Arg Ala Gly
85 90 95

Trp Val Tyr Leu Gly Leu Trp Leu Phe Val Leu Val Gly Arg Leu Ile
100 105 110

Phe Val Tyr Thr Leu Glu His Ser His Ser Phe Ala Ala Asp Phe Gly
115 120 125

Lys Phe Leu Met Asp Thr Gly Ile Asp Ala Gly Gly Val Ser Ala Phe
130 135 140

Phe Val Thr Met Ala Leu Thr Met Val Ile Phe Arg Thr Ala Gly Val
145 150 155 160

Trp Val Tyr Arg Ala Lys Val Leu Arg Gln Ala Gln Arg Thr Pro Ser
165 170 175

Tyr Ala Ser

<210> 17
<211> 540
<212> DNA
<213> Amycolatopsis orientalis

<400> 17
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ttcacgcaca tcggtcgcca taaggcccac ctggtcatcc tgatcctgcc gttcttcacg 120

tgcgcgctgg tgggctgggc ggtcctctac gacctcaagc tgaccacgcc gaacacactg 180

gccgggctgg tcggcatcgc ggcgggcgtc ctgatcggct ggggattgct gaagggcacg 240

aaggtcgagt gggaccagga gaaatccgcc gtctacacca gggcgggctg ggtctacttg 300

ggactgtggc tgttcgtcct ggtcggacgg ctcatcttcg tctacaccct cgaacacagc 360

cactcgttcg cggccgactt cggcaagttc ctgatggaca ccgggatcga cgccggcggc 420

gtctccgcct tcttcgtcac catggcgctg acgatggtca tcttccgcac cgccggggtc 480

tgggtctacc gggccaaggt actcaggcag gctcagcgaa cccccagcta cgcgagctga 540

<210> 18
<211> 222
<212> PRT

<213> Amycolatopsis orientalis

<400> 18

Met Val Glu Glu Val Pro Pro Val Arg Ile Val Ile Ala Glu Asp Gln
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Ala Ala Val Arg Glu Gly Leu Ala Leu Leu Val Gly Thr Val Ala Gly
20 25 30

Ile Thr Val Val Gly Gln Ala Pro Asp Gly Glu Val Ala Val Arg Leu
35 40 45

Ala Gly Glu Leu Arg Pro Asp Val Val Leu Met Asp Leu Ser Met Pro
50 55 60

Arg Cys Asp Gly Val Glu Ala Thr Arg Arg Ile Lys Glu Arg His Pro
65 70 75 80

Glu Ile Glu Ile Val Val Leu Thr Thr Tyr Ala Asp Asp Asp Trp Val
85 90 95

Leu Arg Ala Leu Glu Ala Gly Ala Leu Gly Tyr Leu Thr Lys Ser Ala
100 105 110

Asn Lys His Glu Ile Gly Arg Ala Val His Ala Ala Ala Ala Gly Gln
115 120 125

Ala Leu Leu Asp Pro Gln Val Gln Arg Arg Val Leu Gly Ala Ala Leu
130 135 140

Thr Ser Ala Pro Ala Ser Ala Pro Pro Pro Glu Asp Asp Ala Asn Leu
145 150 155 160

Thr Lys Arg Glu Ala His Val Leu Thr Leu Ile Ala Ala Gly His Ser
165 170 175

Asn Lys Glu Ile Ala Ala Glu Leu Phe Val Ser Glu Thr Thr Val Lys
180 185 190

Ser His Ile Asn Arg Ile Phe Ala Lys Thr Gly Ser Arg Asp Arg Ala
195 200 205

Gln Ala Val Arg Tyr Ala Tyr Gln Ala Gly Tyr Val Arg Asp
210 215 220

<210> 19
<211> 666
<212> DNA
<213> Amycolatopsis orientalis

<400> 19
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gaaggactgg ccctcctggt ggggacggtc gcggggatca ccgtggtcgg ccaggcaccc 120

gacggcgagg tcgccgtgcg gctggccggg gaactgcgcc cggacgtcgt cctgatggat 180

ctctccatgc cccggtgcga cggcgtcgag gcgacccggc ggatcaagga acggcatccg 240

gagatcgaga tcgtcgtgct caccacctac gccgacgacg actgggtgct gcgcgcgttg 300

gaggccgggg cgttgggata cctgacgaaa tcggccaaca aacacgaaat cgggcgcgcg 360

gtacacgccg ccgcggcggg ccaggccctg ctcgatccgc aggtgcagcg acgggtgctc 420

ggcgccgccc tgacgtccgc gcccgcttcg gcgccaccgc cggaggacga cgcgaacctc 480

accaagcggg aagcccatgt gctgacgctg atcgcggcgg ggcacagcaa caaggagatc 540

gccgcggaac tgttcgtcag cgagacgacg gtcaagagcc atatcaaccg gatcttcgcc 600

aagacgggga gccgggatcg cgcgcaggcc gtccgttatg cctaccaagc gggctatgtg 660

cgggac 666

<210> 20
<211> 379
<212> PRT
<213> Amycolatopsis orientalis

<400> 20

Met Thr Asp Ala Val Ser Asp Glu Val Glu Glu Arg Arg Trp Arg Trp
1 5 10 15

Ala Ala Pro Ala Ala Gly Thr Ala Leu Leu Ala Val Thr Gln Met Thr
20 25 30

Ala Thr Val Pro Ala Gly Ala Gly Trp Leu Trp Val Leu Tyr Ala Val
35 40 45

Ser Ser Ala Ser Trp Leu Leu Trp Ile Gly Ile Ser Glu Arg Phe Pro
50 55 60

Arg Ala Ala Leu Leu Pro Leu Ala Ala Ala Ser Ala Val Pro Ala Phe
65 70 75 80

Gly Thr Gly Ala Ala Thr Asp Gly Thr Ala Val Ile Met Thr Cys Ile
85 90 95

Thr Leu Ala Ala Phe Ala Ser Arg Leu Glu Pro Gly Thr Val Ala Ile
100 105 110

Ile Ala Leu Met Val Phe Asp Ala Ala Ala Ile Val Val Ser Ser Leu
115 120 125

Leu Gly His Arg Pro Ser Glu Ala Trp Leu Gly Ala Leu Gly Ala Val
130 135 140

Val Ile Val Val Leu Val Gly Phe Thr Arg Arg Gly His Leu Thr Arg
145 150 155 160

Val Ala Gln Ala Glu Arg Leu Leu His Gln Glu Arg Leu Ala His Thr
165 170 175

Arg Gly Val Arg Ala Ala Thr Leu Asp Glu Arg Thr Arg Ile Ala Arg
180 185 190

Glu Ile His Asp Val Val Ala His Ser Leu Gly Ala Leu Arg Val Gln
195 200 205

Leu Glu Val Met His Thr Leu Leu Val Glu Glu Asn Asp Thr Glu Gly
210 215 220

Ala Leu Arg Ser Leu Ala Leu Ser Arg Ser Leu Ala Asp Gln Gly Leu
225 230 235 240

Ser Asp Val Arg Asp Ala Val Ala Ala Leu Arg Glu Asp Val Arg Ala
245 250 255

Leu Pro Asp Ala Leu Thr Glu Leu Val Arg Thr Phe Gly Arg Glu His
260 265 270

Asp Thr Pro Ala Asp Phe Thr Met Leu Gly Glu His Arg Asp Leu Pro
275 280 285

Ser Ala Gln Thr Ile Ala Leu Leu Arg Ile Cys Arg Glu Ala Leu Thr
290 295 300

Asn Ala Ala Lys His Ala Ala Gly Glu Ala Val Ser Val Glu Leu Glu
305 310 315 320

Tyr Pro Pro Asp Glu Val Arg Leu His Val Arg Asn Pro Leu Ala Ala
325 330 335

Ala Pro Asp Pro Gly His Thr Pro Gly Tyr Gly Leu Thr Gly Met Arg
340 345 350

Glu Arg Ile Glu Leu Val Asp Gly Thr Leu Val Thr Gly Pro Asp Gly
355 360 365

Arg Phe Trp Asp Val Thr Ala Arg Val Pro Gly
370 375

<210> 21
<211> 1140
<212> DNA
<213> Amycolatopsis orientalis

<400> 21
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gccgggacgg cgctgctggc cgtcacccag atgaccgcga ccgtaccggc cggcgccggc 120

tggctgtggg tgctctacgc ggtgtcgtcg gcgagctggc tgctgtggat cggcatcagc 180

gagcgcttcc cccgtgccgc cctgctcccg ctcgccgcgg cgagcgcggt ccccgccttc 240

ggtaccggcg ccgccaccga cggcaccgcc gtgatcatga cctgcatcac cctcgccgcg 300

ttcgcttcac ggctggagcc gggcaccgtc gcgatcatcg cgctgatggt cttcgacgcc 360

gccgccatcg tggtttccag cctgctcggc caccgtcctt cggaggcctg gctgggcgca 420

ctgggcgcgg tcgtcatcgt ggtcctcgtc ggattcaccc gccgcggtca tctgaccagg 480

gtcgcgcagg cggaacggtt gctgcaccag gaacggctgg cgcacacccg cggcgtgcgc 540

gcggcgacgc tggacgagcg cacccgcatc gcccgcgaga tccacgacgt cgtcgcccat 600

tccctcggcg cgctgcgggt ccagctggag gtgatgcaca ccctgctggt ggaggagaac 660

gacaccgaag gcgccctgcg ttcgctcgcg ctgtcgcgaa gtctcgccga ccaagggctc 720

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acgctggtca ccgggcccga cggccggttc tgggacgtca ccgcccgggt cccggggtag 1140

<210> 22
<211> 251
<212> PRT
<213> Amycolatopsis orientalis

<400> 22

Met Thr Ala Pro Ser Gly Asp Ala Gly Asp Trp Val Arg Val Phe Arg
1 5 10 15

Pro Gly Gly Pro Ser Val Pro Arg Leu Ile Cys Leu Pro Asp Ala Gly
20 25 30

Ala Ala Ala Asn Ala Phe Phe Pro Leu Ser Ala Ala Leu Ala Pro Gly
35 40 45

Ile Glu Val His Ala Val Gln Tyr Pro Gly Arg Gln Asp Arg Val Ala
50 55 60

Glu Pro Cys Ala Glu Asp Ile Gly Glu Leu Ala Asp Arg Val Thr Gly
65 70 75 80

Ala Leu Ala Leu Trp Glu Gly Ala Pro Phe Ala Val Tyr Gly His Gly
85 90 95

Met Gly Ala Val Val Gly Phe Glu Val Ala Arg Arg Leu Glu Gln Ala
100 105 110

Leu Thr Gly Ser Pro Val Ala Leu Ile Val Ser Gly Cys Pro Ala Pro
115 120 125

Ser Arg Ser Gly Thr Ala Gly Leu His Leu Leu Pro Asp Gln Asp Leu
130 135 140

Val Ala Glu Leu Tyr Ser Gln Arg Ala Ala Gly Ser Pro Gly Ala Arg
145 150 155 160

Asp Ala Glu Leu Leu Lys Ala Thr Phe Pro Ala Ile Arg Ala Asp Phe
165 170 175

Arg Ala Leu Ala Ala Tyr Arg Pro Glu Pro Ala Pro Pro Leu Arg Cys
180 185 190

Pro Val Thr Val Leu Val Gly Asp Ser Asp Pro Thr Val Ser Leu Asp
195 200 205

Glu Ala Arg Asp Trp His Glu Tyr Thr Thr Gly Pro Phe Asp Leu Gln
210 215 220

Val Phe Pro Gly Gly His Gly Phe Pro Glu Ala Arg Pro Glu Glu Phe
225 230 235 240

Ala Glu Val Val Thr Ala Ala Val Arg Arg Arg
245 250

<210> 23
<211> 753
<212> DNA
<213> Amycolatopsis orientalis

<400> 23
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gatcgggtcg cggaaccgtg cgccgaagac atcggggaat tggccgaccg ggtcaccggg 240

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atcgtgtccg gctgtcccgc cccgtcccgg tccggcaccg ccgggctcca cctgctgccg 420

gatcaggacc tcgtggccga gctgtactcg cagcgcgccg ccggctcgcc gggcgcgcgg 480

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ttcgacctcc aggtcttccc tggtgggcac ggttttccgg aggcgcgtcc cgaggagttc 720

gccgaggtgg tgaccgccgc ggtccggcgg cgg 753

<210> 24
<211> 73599
<212> DNA
<213> Amycolatopsis orientalis

<400> 24
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cgacacgcgg ctcaccgcca tgggcgccta cctgcgcttg ttcgccgact atgtgcccgc 73320

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ccggaccgaa tggcggtccg gctgggcctt gccgcacgac acggtggacg tcgaggggga 73440

tcacttcacg atgctggagc ggcatgccgg gacgaccgcc gaggccgtcc gggagtggct 73500

ggggcggctg gggtaacggc tgcgcgtgaa ccggtcgtgg gctgaaggct cccttcgccg 73560

cgtcttaagc ggtgaaagga gccttcgccc gcggcacag 73599

<210> 25
<211> 162
<212> PRT
<213> Amycolatopsis orientalis

<400> 25

Val Asp Thr Ser Thr Leu Ile Asn Ile Ala Val Ala Ile Ala Val Val
1 5 10 15

Val Tyr Val Ile Tyr Gln Arg Met Ser Trp Lys Pro Leu Glu Asn Val
20 25 30

Glu Ile Trp Gly Gly Pro Leu Thr Leu Val Ala Ile Gly Val Ile Gln
35 40 45

Met Arg His Leu Asp Thr Thr Ile Ser Val Thr Asp Ile Val Phe Leu
50 55 60

Gly Val Gly Leu Leu Val Ser Leu Leu Gly Gly Ala Ala Met Gly Ala
65 70 75 80

Met Thr Gln Leu Gln Arg Arg Gly Asp Lys Val Tyr Gln Arg Ile Gly
85 90 95

Val Val Gly Leu Ala Val Trp Val Gly Leu Leu Leu Val Arg Gly Val
100 105 110

Leu Gly Val Ile Gly His Phe Ala Gly Ala Thr Leu Thr Ser Gly Gly
115 120 125

Gly Thr Ile Leu Leu Ser Leu Gly Ala Asn Leu Met Ala Met Thr Leu
130 135 140

Val Leu Ser Ala Arg Leu Gly Gly Ala Lys Val Pro Gly Gly Ser Pro
145 150 155 160

Gln Arg

<210> 26
<211> 486
<212> DNA
<213> Amycolatopsis orientalis

<400> 26
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catcgccatc aggttcgcgc ccagcgagag caggatggtg ccgccgccgg aggtcagcgt 120

cgcgccggcg aagtgcccga tcacgccgag cacgccgcgg acgagcagca ggcccaccca 180

gacggcgagg ccgaccacgc cgatccgctg gtagaccttg tcgccgcgcc gctgcagctg 240

cgtcatcgcg cccatcgcgg cgccgccgag gagcgagacc agcaggccca ccccgaggaa 300

gacgatgtcg gtcacgctga tggtggtgtc cagatgccgc atctggatga ccccgatggc 360

gaccagggtg agcggcccgc cccagatctc cacgttctcc agcggcttcc agctcatgcg 420

ctggtagatc acgtagacga cgacggcgat ggcgaccgcg atgttgatca gcgtgctggt 480

gtccac 486

<210> 27
<211> 441
<212> PRT
<213> Amycolatopsis orientalis

<400> 27

Val Ala Val Val Gly Ala Gly Tyr Val Gly Leu Thr Thr Ala Ala Cys
1 5 10 15

Leu Ala Ser Leu Gly His Arg Val Arg Cys Thr Asp Ser Asp Arg Gly
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Lys Leu Ala Arg Leu Lys Arg Gly Glu Val Asp Ile Leu Glu Lys Gly
35 40 45

Leu Pro Gly Leu Val Ala Glu Gly Ile Ala Ala Gly Arg Leu Gly Phe
50 55 60

Val Glu Ser Ala Ala Glu Ala Val Glu Thr Ala Glu Ala Val Phe Leu
65 70 75 80

Cys Val Pro Thr Pro Met Gly Glu Gly Gly Met Ala Asp Leu Ser Ala
85 90 95

Val Ile Asp Val Ala Thr Lys Val Arg Asp Val Leu Ser Pro Gly Cys
100 105 110

Val Leu Val Asn Lys Ser Thr Val Pro Val Gly Thr Ala Ala Arg Val
115 120 125

Ala Ala Leu Leu Gly Arg Asp Asp Val Ala Val Val Ser Asn Pro Glu
130 135 140

Phe Leu Arg Glu Gly Thr Ala Val His Asp Phe Leu Asn Pro Asp Arg
145 150 155 160

Ile Val Val Gly Ser Asp Thr Arg Gly Pro Ala Glu Arg Val Ala Ala
165 170 175

Leu Tyr Ala Arg Leu Gly Ala Pro Thr Val Leu Thr Asp Ala Ala Ser
180 185 190

Ala Glu Met Val Lys Tyr Ala Ala Asn Cys Phe Leu Ala Thr Lys Leu
195 200 205

Ser Tyr Val Asn Ala Ile Ala Glu Leu Cys Glu Arg Leu Gly Ala Asp
210 215 220

Ile Gly Asp Val Thr Glu Gly Met Gly Tyr Asp Arg Arg Ile Gly Pro
225 230 235 240

Thr Phe Leu Ser Pro Gly Pro Gly Trp Gly Gly Ser Cys Leu Pro Lys
245 250 255

Asp Thr Met Ala Leu Lys Gln Val Ala Glu Val Ala Gly Phe Glu Phe
260 265 270

Gly Leu Leu Asp Glu Val Ile Ser Gly Asn Ala Lys Gln Ala Ser Arg
275 280 285

Val Val Glu Arg Ile Ala Val Ala Cys Gly Leu Asp Ala Asp Ala Asp
290 295 300

Leu Thr Gly Leu Arg Ile Gly Leu Leu Gly Leu Thr Phe Lys Ala Gly
305 310 315 320

Thr Asn Asp Leu Arg Asp Ser Pro Ala Leu Ser Val Ala Arg Leu Leu
325 330 335

Ala Glu Arg Gly Ala Glu Leu Thr Gly Tyr Asp Pro Gly Leu Thr Gly
340 345 350

Ala Glu Pro Pro Ile Pro Gly Val Arg Val Val Asp Asp Pro Tyr Tyr
355 360 365

Ile Ala Lys Asp Ala His Ala Leu Val Leu Leu Thr Asp Trp Pro Gln
370 375 380

Phe Arg Ala Leu Asp Trp Pro Arg Ile Ala Gly Leu Leu Glu Gly Pro
385 390 395 400

Val Val Ile Asp Thr Arg Asn His Leu Asp Pro Asp Ala Leu Ser Arg
405 410 415

Ala Gly Ile Ala Trp Arg Gly Phe Gly Arg Pro Pro Val Asp Pro Val
420 425 430

Arg Thr Pro Ser Leu Asp Pro Val Pro
435 440

<210> 28
<211> 1326
<212> DNA
<213> Amycolatopsis orientalis

<400> 28
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gaggtcgaca tcctggaaaa gggcctgccc ggtctggtcg ccgagggaat cgccgccgga 180

cggctcggtt tcgtcgagtc ggccgcggag gccgtcgaga ccgcggaggc cgtgttcctt 240

tgtgtaccca ccccgatggg cgagggcggg atggccgatc tgtcggccgt catcgacgtc 300

gcgaccaagg tccgtgacgt gctttcgccg ggttgtgtac tggtgaacaa gtcgaccgtg 360

ccggtcggga ccgcggccag ggtcgccgcg ctgctcggcc gggacgacgt cgcggtggtg 420

agcaatccgg agttcctccg cgagggcacc gccgtccacg acttcctcaa cccggaccgg 480

atcgtcgtcg gttccgacac gcgcggcccg gcggaacggg tcgcggcgct ctacgcccgg 540

ctcggcgccc cgacggtgct gaccgacgcg gcgagcgcgg agatggtcaa gtacgccgcc 600

aactgtttcc tcgcgacgaa actgtcctat gtgaacgcca tcgccgaact gtgcgagcgg 660

ctcggcgccg acatcggcga cgtcaccgaa ggcatgggct acgaccgccg gatcggcccg 720

acgttcctct cgccggggcc gggctggggc ggttcctgcc tgcccaagga caccatggcg 780

ctcaaacagg tcgccgaggt cgcgggtttc gagttcggcc tgctcgacga ggtcatctcg 840

ggcaacgcga aacaggcgtc ccgagtggtc gaacggatcg ccgtcgcctg tggactcgac 900

gcggacgcgg acctcaccgg cctgcggatc ggcctgctcg ggctgacctt caaggcgggc 960

accaacgacc tccgggattc cccggcgctc agcgtcgccc ggctgctggc cgagcgcggc 1020

gcggagctga ccggatacga ccccggtctc accggcgccg aacctccgat ccccggcgtc 1080

cgggtcgtcg acgaccccta ctacatcgcg aaggacgcgc acgcgctcgt cctgctgacc 1140

gattggccgc agttccgtgc cctcgactgg ccgcggatcg ccggtctgct cgaaggaccg 1200

gtcgtcatcg acacccgcaa ccacctcgac cccgacgcgc tcagccgggc cggcatcgcc 1260

tggcgcggct tcggcaggcc cccggtcgac ccggtgcgca cgccgtccct cgaccccgtt 1320

ccctga 1326

<210> 29
<211> 407
<212> PRT
<213> Amycolatopsis orientalis

<400> 29

Met Arg Val Leu Cys Thr Val Thr Gly Ser Gln Gly His Ala Arg Ala
1 5 10 15

Val Leu Pro Leu Ala Arg Ala Ala Ala Lys Ala Gly His Glu Val Leu
20 25 30

Val Val Thr Pro Pro Glu Leu Ala Asp Val Phe Glu Pro Gly Leu Met
35 40 45

Arg Ile Glu Pro Val Leu Pro Gly Met Val Glu Ala Ile Gly Arg Met
50 55 60

Val Gln Glu Arg Gln Glu Ala Glu Ala Ala Gly Thr Pro Arg Arg Val
65 70 75 80

Leu Asp Thr Arg Glu Gln Leu Ile Ala Thr Ala Ser Gly Pro His Val
85 90 95

Thr Thr Ala Tyr Gln Lys Leu Tyr Pro Leu Ala Lys Glu Phe Gln Pro
100 105 110

Asp Ile Val Leu Arg Asp Gly Ala Glu Leu Ser Gly Ala Leu Val Ala
115 120 125

Glu Gln Leu Gly Val Pro Tyr Ile Ser Ala Pro Ser Gly Ala Gly Asn
130 135 140

Leu Ile Asp Pro Ala Gly Leu Val Glu Pro Leu Asn Glu Arg Arg Gln
145 150 155 160

Glu Leu Gly Leu Ala Ala Glu Pro Asp Ala Gly Met Val His Arg Tyr
165 170 175

Gly Arg Phe Asp Cys Leu Pro Ala Asp Thr Ser Phe Ala Ala Phe Asp
180 185 190

Leu Pro Thr Pro Phe Thr Tyr Arg Gln Pro Ser Glu Val Ala Thr Gly
195 200 205

Glu Val Leu Pro Pro Glu Ile Ala Ala Leu Pro Ala Asp Arg Pro Leu
210 215 220

Val Leu Ala Ser Val Gly Thr Ala Leu Pro Met Leu Gly Ala Phe Lys
225 230 235 240

Ala Phe Gly Ile Asp Pro Pro Glu Glu Met Glu Asp Pro Asp Val Thr
245 250 255

Val Arg Ala Leu Ile Glu Gly Leu Ser Ser Val Asp Cys Ser Ala Val
260 265 270

Val Ala Thr Ala Gly Phe Pro Ile Gly Asp Val Glu Val Gly Asp Asn
275 280 285

Val Leu Val Val Glu Arg Met Pro Gln Pro Leu Leu Leu Glu Cys Ala
290 295 300

Gln Leu Phe Leu Thr His Ala Gly Tyr Asn Ser Ile Arg Glu Ala Leu
305 310 315 320

Arg Ala Gly Val Pro Met Ala Thr Leu Pro Gln Phe Gly Asp Gln Pro
325 330 335

His Asn Ala Arg Arg Ile Glu Glu Leu Gly Phe Gly Lys Gln Ile Pro
340 345 350

Ala Thr Thr Pro Glu Ala Val Ala Glu Thr Cys Arg Ala Val Leu Ala
355 360 365

Asp Ala Thr Ile Ala Ala Thr Val Ala Arg Ala Gln Arg Arg Ser Leu
370 375 380

Thr Met Pro Gly Val Glu Ser Ala Val Ala His Leu Glu Glu Leu Ala
385 390 395 400

Gly Arg Ala Ala Gly Thr Glu
405

<210> 30
<211> 1224
<212> DNA
<213> Amycolatopsis orientalis

<400> 30

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gccagggcgg cggcgaaggc gggccacgaa gtgctcgtcg tgaccccgcc ggaactggcc 120

gacgtcttcg aacccgggct gatgcggatc gaaccggtgc tcccggggat ggtcgaggcg 180

atcgggcgga tggtccagga acgccaggag gccgaagcgg ccgggacccc gcgccgggtg 240

ctggacacgc gcgaacagct gatcgccacc gcgagcggcc cgcacgtcac caccgcctac 300

cagaagctct acccactggc caaggagttt cagcccgaca tcgtgctgcg cgacggcgcg 360

gagctgtccg gcgcgctggt cgccgagcag ctcggcgtgc cctacatcag cgcgccgtcg 420

ggtgcgggca acctgatcga cccggcgggc ctggtggagc cgctgaacga gcgccgccag 480

gagctggggc tcgccgccga acccgacgcc gggatggtgc accgctacgg ccgtttcgac 540

tgcctgcccg ccgacacctc gttcgccgcc ttcgatctgc cgacgccgtt cacctaccgc 600

cagccgtcgg aggtggccac cggtgaggtc ctgccgccgg agatcgccgc attgcccgcg 660

gaccggccgc tggtgctcgc ctcggtcggc accgcgctgc ccatgctcgg cgcgttcaag 720

gccttcggca tcgacccgcc ggaggagatg gaagatcccg acgtcacggt gcgcgccctg 780

atcgaaggac tgtccagtgt ggactgttcg gcggtggtgg cgacggccgg gttcccgatc 840

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gagacctgcc gcgcggtgct ggccgacgcc acgatcgcgg ccaccgtcgc acgggcccaa 1140

cggcggagcc tgaccatgcc gggcgtggaa tccgccgtgg cccatctcga agagctcgcc 1200

ggccgggccg cgggaacgga gtag 1224

<210> 31
<211> 521
<212> PRT
<213> Amycolatopsis orientalis

<400> 31

Val Gln Ile Asp His Tyr Val Ser Gln Leu Leu Asp Val Leu Ser Thr
1 5 10 15

Arg Pro Asp Glu Ile Ala Leu Arg Tyr Gly Asp Glu Ala Leu Thr Ser
20 25 30

Ala Glu Phe Ala Ala Ala Ile Thr Gly Ala Ala Ala Ala Leu Arg Asp
35 40 45

Arg Gly Thr Gly Glu Gly Gly Val Val Ala Leu Leu Thr Val Gly Asn
50 55 60

Ser Pro Ala Thr Leu Ile Gly Arg Tyr Ala Ala Asn Leu Ile Gly Ala
65 70 75 80

Thr Val Val His Leu Arg Gly Ile Asn Ala Ala Asp Pro Leu Asp Glu
85 90 95

Leu Pro Val Ala Thr Gln Val Glu Ile Val Asp Asp Thr Gly Thr Thr
100 105 110

Val Leu Leu Thr Asp Ala Ala Asn Leu Asp Arg Ala Arg Lys Ile Arg
115 120 125

Asp Ala Met Ala Glu Pro Ala Ala Leu Ala Ala Phe Gly Asp Phe Gly
130 135 140

Asp Asp Val Ala Asp Leu Thr Gly Thr Ala Ser Glu Val Glu Pro Arg
145 150 155 160

Ala Glu Gly Thr Ala Val Leu Thr Tyr Thr Ser Gly Thr Thr Gly Arg
165 170 175

Pro Lys Gly Ile Gly Arg Gly Phe Gly Gly Leu Gly Ala Val Val Thr
180 185 190

Lys Ala Arg His Met Thr Glu Arg Cys Thr Met Leu Val Thr Thr Pro
195 200 205

Leu Ser His Ser Val Ser Ser Thr Val Asp Asp Ala Val Ala Ser Gly
210 215 220

Gly Met Ile Val Leu His Glu Gly Phe Asp Ala Gly Ala Val Leu Glu
225 230 235 240

Ala Val Glu Arg His Arg Val Asn Arg Val Tyr Leu Ala Thr Pro Gln
245 250 255

Leu Tyr Asp Leu Leu Asp His Pro Ala Leu Gly Thr Thr Asp His Ser
260 265 270

Ser Leu Arg Glu Leu Tyr Tyr Gly Gly Ser Pro Ala Ser Pro Val Arg
275 280 285

Leu Ser Arg Ala Ala Glu Val Phe Gly Ala Lys Leu Ile Gln Ile Tyr
290 295 300

Gly Thr Thr Glu Ser Trp Val Ile Ala Ala Leu Ser Pro Glu Glu His
305 310 315 320

Leu Lys Pro Glu Leu Leu Thr Thr Val Gly Lys Ala Val Pro Phe Val
325 330 335

Gln Val Gly Ile Arg Asp Pro His Val Arg His Glu Leu Pro Ala Gly
340 345 350

Lys Thr Gly Glu Ile Cys Val Arg Ser Pro Met Met Met Asp Gly Tyr
355 360 365

Trp Lys Arg Pro Asp Leu Thr Ser Lys Val Leu Ile Asp Gly Trp Leu
370 375 380

His Thr Gly Asp Val Gly Tyr Leu Asp Glu Asn Gly Tyr Leu Tyr Leu
385 390 395 400

Val Asp Arg Leu Ala Asp Met Ile Lys Thr Asn Gly Ile Lys Val Tyr
405 410 415

Pro Ala Glu Val Glu Asn Ala Leu Leu Ala His Pro Asp Val Ala Gln
420 425 430

Ala Ala Val Phe Gly Val Ala Asp Glu Asp Asn Val Glu Tyr Met His
435 440 445

Ala Ile Ala Val Pro Arg Arg Gly Arg Asp Val Asp Pro Ala Asp Leu
450 455 460

Ala Ala His Val Ala Arg Val Leu Ser Pro Ser His Val Pro Ala Glu
465 470 475 480

Ile Arg Leu Arg Ala Glu Leu Pro Leu Thr Asp Ala Gly Lys Pro Asp
485 490 495

Lys Leu Arg Leu Arg Glu Glu Ala Lys Pro Ala Thr Lys Ser Ser His
500 505 510

Ala Glu Pro Glu Ser Glu Leu Thr Ser
515 520

<210> 32
<211> 1563
<212> DNA
<213> Amycolatopsis orientalis

<400> 32
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atcgcgttgc gctacggcga cgaagcgctg acgtcggcgg aattcgccgc ggcgatcacc 120

ggtgccgccg ccgcgctgcg cgaccgcggg accggcgaag gcggggtggt ggccctgctg 180

accgtgggga acagcccggc gacgctgatc ggccggtacg ccgccaacct gatcggcgcc 240

accgtggtgc acctgcgcgg gatcaacgcc gccgatccgc tggacgaact cccggtcgcc 300

acgcaggtcg agatcgtcga cgacaccggc accaccgtcc tgctcaccga cgcggcgaac 360

ctcgaccggg ccaggaagat ccgcgacgcc atggcggaac cggcggcact ggcggctttc 420

ggggacttcg gtgacgacgt cgccgacctc accgggaccg cgagcgaggt cgagccgcga 480

gccgagggca ccgccgtgct gacctacacc agtgggacca ccggcaggcc caagggcatc 540

ggccgcgggt tcggcgggct gggcgcggtg gtcaccaagg cccggcacat gaccgagcgc 600

tgcacgatgc tggtcaccac gccgctcagc cattccgtct cgtccacagt ggacgacgcg 660

gtcgcctccg gcgggatgat cgtcctgcac gaggggttcg acgccggcgc cgtgctcgaa 720

gccgtggaac gccaccgggt caaccgggtc tacctggcca ccccgcagct ctacgacctg 780

ctcgaccatc cggcactggg caccaccgac cattccagcc tgcgcgagct gtactacggc 840

gggagcccgg cctccccggt gcggctctcc cgggccgcgg aggtgttcgg cgcgaagctg 900

atccagatct acggcaccac cgaaagctgg gtgatcgccg cgctttcgcc ggaagagcac 960

ctgaaaccgg aactgctcac cacggtcggc aaggcggtcc cgttcgtcca ggtcggcatc 1020

cgcgacccgc atgtgcggca cgagctgccc gccgggaaga ccggggagat ctgcgtccgg 1080

tcgccgatga tgatggacgg ttactggaag cggcccgacc tgacctcgaa ggtcctcatc 1140

gacggctggc tgcacaccgg cgacgtcggc tacctcgacg agaacggcta cctgtacctg 1200

gtcgaccggc tcgccgacat gatcaagacc aacggcatca aggtgtatcc ggccgaggtc 1260

gagaacgcgc tgctggccca tccggacgtc gcgcaggccg cggtgttcgg ggtcgccgac 1320

gaggacaacg tcgagtacat gcacgcgatc gcggtgccac gccgcggcag ggacgtggat 1380

cccgccgacc ttgccgcgca tgtcgcgcgg gtgctgtccc cgagccacgt gccggcggag 1440

atccggctcc gcgccgagct tccgctgacc gacgcgggga agccggacaa gctccgcctc 1500

cgcgaagagg cgaaacccgc caccaagtcc agccacgccg agccagagag cgagttgacg 1560

tca 1563

<210> 33
<211> 402
<212> PRT
<213> Amycolatopsis orientalis

<400> 33

Met Thr Thr Tyr Leu Glu Ser Phe Gln Arg Thr Leu Gln Gly Glu Val
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Leu Gln Lys Arg Asp Phe Leu Glu Ile Gly Arg Gln Ala Gly Arg Phe
20 25 30

Pro Ala Ala Ser Arg Tyr Glu Glu Ala Glu Ala Val Ala Glu Ile Asn
35 40 45

Val Trp Cys Ser Asn Asp Tyr Leu Gly Met Gly Gln His Pro Asp Val
50 55 60

Leu Ser Ala Met Lys Glu Ala Val Glu Arg Phe Gly Ala Gly Ala Gly
65 70 75 80

Gly Ser Arg Asn Ile Ala Gly Thr Asn His Tyr His Val Ala Leu Glu
85 90 95

Arg Glu Leu Ala Glu Leu His Gly Lys Glu Asp Ala Leu Leu Phe Thr
100 105 110

Ser Gly Tyr Thr Ala Asn Asp Gly Ser Leu Thr Val Leu Ala Gly Arg
115 120 125

Pro Glu Asp Cys Ile Val Phe Ser Asp Glu Lys Asn His Ala Ser Ile
130 135 140

Ile Asp Gly Leu Arg His Ser Gly Val Glu Lys Lys Ile Phe Arg His
145 150 155 160

Asn Asp Val Ala His Leu Ala Glu Leu Leu Ala Ala Ala Pro Ala Asp
165 170 175

Arg Pro Lys Met Ile Val Phe Glu Ser Val Tyr Ser Met Asn Gly Asp
180 185 190

Ile Ala Pro Leu Ala Glu Phe Ala Ala Leu Ala Lys Gln Tyr Asp Ala
195 200 205

Met Thr Tyr Val Asp Glu Val His Ala Val Gly Met Tyr Gly Pro Glu
210 215 220

Gly Ala Gly Ile Ala Ala Arg Glu Gly Ile Ala Asp Glu Phe Thr Val
225 230 235 240

Val Met Gly Thr Leu Ala Lys Gly Phe Gly Thr Thr Gly Gly Tyr Ile
245 250 255

Ala Gly Pro Ala Ala Leu Ile Asp Ala Val Arg Thr His Ser Arg Ser
260 265 270

Phe Ile Phe Thr Thr Ala Leu Pro Pro Ala Val Ala Ala Gly Ala Leu
275 280 285

Ala Ala Val Arg His Leu Arg Ser Ser Glu Arg Glu Arg Glu Ile Leu
290 295 300

Ala Asp Asn Ala Gln Leu Leu His Lys Leu Leu Ala Glu Arg Gly Ile
305 310 315 320

Pro Phe Leu Ser Asp Glu Ser His Ile Val Ser Ile Leu Val Gly Asp
325 330 335

Asp Ala Leu Cys Lys Lys Val His Glu Leu Leu Leu Gln Arg His Gly
340 345 350

Ile Tyr Ile Gln Ser Ile Asn Ala Pro Ser Val Pro Phe Gly Gln Glu
355 360 365

Ile Leu Arg Thr Ala Pro Ser Ala Val His Thr Gly Ser Asp Val Gln
370 375 380

Lys Met Val Glu Ala Leu Asp Gln Ile Trp Leu Asp Leu Gly Leu Pro
385 390 395 400

Arg Gly

<210> 34
<211> 1206
<212> DNA
<213> Amycolatopsis orientalis

<400> 34
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gacttcctgg agatcgggcg gcaggcgggc cggttcccgg cggccagccg gtacgaggag 120

gccgaagcgg tcgccgagat caacgtctgg tgcagcaacg actacctcgg catgggccag 180

cacccggacg tgctctccgc gatgaaggag gccgtcgagc ggttcggcgc cggggcgggc 240

ggttcacgca acatcgcggg caccaaccac taccacgtgg cgctcgaacg cgaactggcc 300

gaactgcacg gcaaagagga cgcgctgctc ttcacctccg gctacaccgc caacgacggt 360

tcgctgaccg tgctggcggg ccgccccgag gactgcatcg tgttctccga cgagaagaac 420

cacgcctcca tcatcgacgg gttgcggcac agtggtgtgg agaagaagat cttccgccac 480

aacgacgtcg cccatctggc cgagctgctc gccgccgccc cggcggaccg gccgaagatg 540

atcgtgttcg agtcggtcta ctcgatgaac ggcgacatcg cgccgctggc cgaattcgcc 600

gcgttggcga agcagtacga cgccatgacc tatgtggacg aagtgcacgc cgtcggaatg 660

tacgggcccg aaggtgccgg gatcgccgcg cgcgagggga tcgccgacga gttcaccgtc 720

gtgatgggca cgctggccaa gggtttcggc accaccggcg gatacatcgc cgggcccgcc 780

gcgctgatcg acgccgtgcg cacgcattcg cgatcgttca tcttcaccac cgcgctgccg 840

cccgccgtgg ccgccggagc gctcgccgcc gtccggcacc tgcgttcgtc ggagcgggag 900

cgcgagatcc tcgccgacaa cgcgcagctg ctgcacaaac tgctcgccga acgcggcatc 960

cccttcctct cggacgagtc gcatatcgtg tcgatcctgg tcggcgacga cgcgctctgc 1020

aagaaggtgc acgaactcct gttgcagcgg cacgggatct acatccagtc gatcaacgcg 1080

ccgagtgtcc cgttcggaca ggagatcctg cgcacggccc cgtcggcggt gcacaccggc 1140

agcgacgtgc agaagatggt cgaggcgctg gaccagatct ggctggatct cggtctgccg 1200

cgcggc 1206

<210> 35
<211> 511
<212> PRT
<213> Amycolatopsis orientalis

<400> 35

Val Ser Leu Ser Leu Ala Ala Val Leu Ala Asp Ser Ala Gly Arg Arg
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Pro Asp His Pro Ala Leu Val Phe Asp Gly Glu Pro Phe Ser Tyr Arg
20 25 30

Glu Leu Trp Ala Gly Ala Lys Arg Tyr Ala Ser Ala Leu Arg Asp Gln
35 40 45

Gly Val Ala Ala Gly Asp Arg Val Val Leu Leu Leu Pro Asn Thr Pro
50 55 60

Glu Phe Pro Met Val Tyr Phe Gly Ala Leu Ala Leu Gly Ala Val Val
65 70 75 80

Val Pro Val His Thr Leu Leu Val Ala Glu Glu Ile His Tyr Ile Leu
85 90 95

Thr Asp Cys Asp Ala Arg Val Leu Ile Cys Gly Ala Ala Leu Leu Glu
100 105 110

Gln Gly Gly Glu Ala Ala Asp Ala Ala Gly Val Glu Val Leu Thr Met
115 120 125

Leu Glu Asp Ser Asp Thr Gly Arg Val Arg Leu Asp Val Leu Ala Gly
130 135 140

Asp Ala Ala Glu Ile Glu Arg Tyr Glu Pro Arg Glu Pro Ser Asp Leu
145 150 155 160

Ala Leu Ile Leu Tyr Thr Ser Gly Thr Thr Gly Lys Pro Lys Gly Ala
165 170 175

Met Leu Thr His Leu Ser Ile Val Leu Asn Val Ser Thr Thr Met Leu
180 185 190

Ser Pro Phe Asp Phe His Ala Asp Asp Val Leu Leu Gly Cys Leu Pro
195 200 205

Leu Phe His Thr Phe Gly Gln Ile Cys Gly Met Ala Thr Cys Phe Arg
210 215 220

Ala Gly Ala Thr Met Val Leu Met Ser Arg Phe Asp Ala Arg Ala Ala
225 230 235 240

Leu Glu Leu Met Val Glu Gln Asn Cys Ser Leu Phe Met Gly Val Pro
245 250 255

Thr Met Tyr Val Ala Leu Leu Glu Ala Ala Glu Asp Glu Pro Arg Arg
260 265 270

Pro Lys Leu Asp Arg Ala Phe Ser Gly Gly Ser Ser Leu Pro Val Ala
275 280 285

Leu Leu Glu Arg Phe Glu Ala Val Phe Asp Cys Pro Ile Tyr Glu Gly
290 295 300

Tyr Gly Leu Thr Glu Thr Ser Pro Val Val Ala Tyr Asn Gln Arg Ala
305 310 315 320

Trp Pro Thr Arg Ala Gly Thr Val Gly Lys Pro Ile Trp Gly Val Asp
325 330 335

Val Ala Ile Ala Arg Ala Glu Thr Glu Asp Arg Ile Glu Pro Val Pro
340 345 350

Pro Gly Glu Val Gly Glu Ile Val Val Arg Gly His Asn Val Met Ala
355 360 365

Gly Tyr Leu Asn Arg Pro Glu Ala Thr Ala Ala Ala Ile Val Asp Gly
370 375 380

Trp Phe Arg Ser Gly Asp Leu Gly Phe Leu Asp Asp Asp Gly Tyr Leu
385 390 395 400

Ser Ile Val Asp Arg Lys Lys Asp Met Ile Leu Arg Gly Gly Tyr Asn

405 410 415

Val Tyr Pro Arg Glu Ile Glu Glu Val Leu Ala Arg His Pro Ala Ile
420 425 430

Ala Gln Val Ala Val Val Gly Val Pro Asp Glu Arg Tyr Gly Glu Glu
435 440 445

Ile Cys Ala Val Val Val Ala Ala Ser Asp Arg Glu Pro Gly Pro Glu
450 455 460

Leu Ala Ala Glu Leu Val Ala Trp Ser Lys Lys Arg Val Ala Ala Tyr
465 470 475 480

Lys Tyr Pro Arg Arg Val Glu Phe Leu Asp Ala Met Pro Leu Gly Pro
485 490 495

Ser Gly Lys Ile Leu Lys Arg Glu Leu Ala Glu Leu Leu Gly His
500 505 510

<210> 36
<211> 1533
<212> DNA
<213> Amycolatopsis orientalis

<400> 36
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gcgctcgtgt tcgacgggga accgttctcc taccgggaac tctgggccgg ggcgaagagg 120

tacgcctccg cgctccggga ccaggggggtc gccgccggcg accgggtcgt gctgctcctg 180

ccgaacacgc cggagttccc gatggtctac ttcggcgcgc tggcgctcgg cgcggtcgtc 240

gtgccggtgc acacgttgct cgtcgcggag gagatccact acatcctcac cgactgtgac 300

gcccgggtgc tgatctgcgg agccgccctg ctggagcagg gcggcgaggc cgccgacgcg 360

gccggtgtcg aagtcctgac gatgctggag gactccgaca ccggccgcgt ccgcctcgac 420

gtcctcgccg gggacgcggc cgagatcgag cggtacgaac cgcgtgaacc ctcggacctc 480

gcgctgatcc tctacacctc ggggaccacc ggcaaaccca agggcgcgat gctgacccac 540

ctgagcatcg tgctgaacgt ttccaccacg atgctgtcgc cgttcgactt ccacgccgac 600

gacgtgctgc tcggctgcct gccgctgttc cacaccttcg gccagatctg cgggatggcg 660

acctgtttcc gcgccggcgc gacgatggtg ctgatgtcgc ggttcgacgc gcgagccgcg 720

ctggaactga tggtggagca gaactgctcg ctgttcatgg gcgtgccgac gatgtacgtc 780

gcgttgctgg aggccgccga ggacgagccg cggcggccca aactcgaccg ggccttctcc 840

ggtggttcgt cgctgcccgt agcgctgctg gagcggttcg aggccgtgtt cgactgcccg 900

atctacgagg gatacggcct caccgagacc tcgcccgtgg tggcctacaa ccagcgcgcg 960

tggccgaccc gcgcgggcac cgtcggcaaa ccgatctggg gcgtggacgt cgccatcgcg 1020

cgcgccgaga ccgaagaccg gatcgaaccc gtgccgccgg gtgaggtcgg cgagatcgtc 1080

gtccggggcc acaacgtgat ggcgggctac ctgaaccgtc ccgaggccac ggcggccgcg 1140

atcgtggacg gctggttccg cagcggcgac ctaggcttcc tcgacgacga cggctatctg 1200

tccattgtgg accgtaagaa ggacatgatc cttcgcggcg gctacaacgt gtatccgcgc 1260

gagatcgagg aagtgctggc caggcatccc gcgatcgccc aggtcgcggt cgtcggcgtg 1320

ccggacgaac ggtacggcga ggagatctgc gccgtcgtgg tggccgcttc cgatcgggaa 1380

cccgggccgg aactggcggc ggaactcgtg gcgtggagca agaagcgcgt ggcggcctac 1440

aagtatccgc gccgcgtgga gttcctggac gcgatgccgc tcgggcccag cgggaagatc 1500

ctcaagcggg agctggcgga gctcctcggg cac 1533

<210> 37
<211> 3834
<212> PRT
<213> Amycolatopsis orientalis

<400> 37

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Pro Asp Trp Ala Thr Val Leu Ala Ala Phe Asp Glu Thr Pro Asp Gly
20 25 30

Glu Arg Arg Arg Ala Leu Ala Ala Leu Val Val Ala Glu Thr Glu Ala
35 40 45

Val Leu Glu Ala Lys Pro Gly Ala Gly Thr Ala Ala Pro Gly Thr Pro
50 55 60

Phe Ala Glu Leu Gly Phe Asp Ser Leu Ala Ala Val Glu Leu His Arg
65 70 75 80

Arg Ile Ser Ala Ala Thr Ala Leu Glu Leu Pro Val Thr Leu Val Phe
85 90 95

Asp His Pro Thr Pro Ser Ala Leu Ala Gly His Leu Arg Asp Leu Leu
100 105 110

Ala Gly Glu Ala Val Ala Glu Ile Glu Asp Tyr Gln Ala Ile Ala Asp
115 120 125

Asp Glu Pro Ile Ala Ile Val Gly Met Ala Cys Arg Tyr Pro Gly Gly
130 135 140

Ile Gly Ser Pro Glu Asp Leu Trp Arg Leu Val Thr Glu Gly Gly Asp
145 150 155 160

Ala Thr Ser Asp Phe Pro Ala Asp Arg Gly Trp Asp Val Glu Ser Leu
165 170 175

Tyr Asp Pro Asp Pro Gly Val Pro Gly Lys Thr Tyr Thr Arg Arg Gly
180 185 190

Gly Phe Leu Asp Gly Ala Gly Asp Phe Asp Ala Gly Phe Phe Gly Ile
195 200 205

Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln Gln Arg Leu Leu Leu
210 215 220

Glu Thr Ser Trp Glu Ala Phe Glu Arg Ala Gly Ile Asp Pro Ala Thr
225 230 235 240

Leu Arg Gly Ser Ala Thr Gly Val Phe Val Gly Ala Glu Thr Gln Glu
245 250 255

Tyr Gly Pro Arg Leu Gly Gly Ala Glu Glu Gly Leu Glu Gly Tyr Leu
260 265 270

Leu Thr Gly Asn Ala Ala Ser Val Ala Ser Gly Arg Val Ser Tyr Ala
275 280 285

Phe Gly Phe Glu Gly Pro Thr Val Thr Val Asp Thr Ala Cys Ser Ser
290 295 300

Ser Leu Val Ala Leu His Leu Ala Gly Gln Ala Leu Arg Leu Gly Glu
305 310 315 320

Cys Pro Ile Ala Val Ala Gly Gly Val Ala Val Met Ser Ser Pro Gly
325 330 335

Gly Phe Leu Ala Phe Ser Arg Gln Arg Gly Leu Ala Pro Asp Gly Arg
340 345 350

Cys Lys Pro Phe Ser Ala Ala Ala Asp Gly Thr Gly Trp Ser Glu Gly
355 360 365

Val Gly Met Leu Val Leu Glu Arg Leu Ser Asp Ala Arg Arg Asn Gly
370 375 380

His Arg Val Leu Ala Val Val Arg Gly Thr Ala Ile Asn Ser Asp Gly
385 390 395 400

Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Ala Ala Gln Gln Arg Val
405 410 415

Ile Arg Arg Ala Leu Ala Asn Ala Gly Leu Ala Pro Ser Glu Val Asp
420 425 430

Ala Val Glu Ala His Gly Thr Gly Thr Val Leu Gly Asp Pro Ile Glu
435 440 445

Ala Gln Ala Leu Leu Ala Thr Tyr Gly Arg Asp Arg Glu Arg Pro Leu
450 455 460

Leu Leu Gly Ser Val Lys Ser Asn Ile Gly His Thr Gln Ser Ala Ala
465 470 475 480

Gly Val Ala Gly Val Ile Lys Met Val Gln Ala Met Arg His Gly Val
485 490 495

Leu Pro Lys Thr Leu His Ala Asp Glu Pro Thr Pro Lys Val Ala Trp
500 505 510

Ser Ser Gly Ala Val Glu Leu Leu Asn Glu Thr Val Ala Trp Pro Glu

515 520 525

Asn Gly Ala Pro Arg Arg Ala Ala Val Ser Ser Phe Gly Met Ser Gly
530 535 540

Thr Asn Ala His Ala Val Leu Glu Gln Ala Pro Ala Glu Asp Glu Pro
545 550 555 560

Glu Pro Ser Pro Glu Ala Trp Pro Thr Trp Leu Phe Pro Val Ser Gly
565 570 575

Arg Asp Glu Lys Ala Leu Arg Arg Gln Ala Ala Arg Leu Arg Glu Ala
580 585 590

Leu Pro Asp Ser Asp Leu Pro Ala Ile Ala Ala Ala Leu Ala Thr Thr
595 600 605

Arg Ser Ala Leu Glu Trp Arg Ala Val Val Thr Val Ala Asp Arg Ala
610 615 620

Gly Leu Leu Ala Gly Leu Asp Ala Leu Ala Thr Gly Glu Ala Leu Pro
625 630 635 640

Ser Leu Val His Gly Thr Ala Arg Ile Gly Ile Val Phe Ser Gly Gln
645 650 655

Gly Ser Gln Arg Ala Gly Met Gly Arg Glu Leu His Arg Arg Phe Pro
660 665 670

Val Phe Ala Ala Ala Phe Asp Asp Ala Cys Gly His Leu Asp Leu Gln
675 680 685

Leu Asp Arg Pro Leu Ala Glu Ile Val Phe Ala Asp Glu Gly Thr Glu
690 695 700

Glu Ala Gly Leu Leu His Arg Thr Glu Tyr Ala Gln Cys Ala Leu Phe
705 710 715 720

Ala Val Glu Val Ala Leu Phe Arg Leu Tyr Glu His Trp Gly Leu Arg
725 730 735

Pro Asp Tyr Val Ala Gly His Ser Ile Gly Glu Leu Ala Ala Ala His
740 745 750

Val Ser Gly Met Leu Ser Leu Ser Asp Ala Ala Ala Leu Val Ala Ala
755 760 765

Arg Gly Arg Leu Met Gln Asp Thr Arg Glu Gly Gly Ala Met Leu Ala
770 775 780

Val Gln Ala Thr Glu Asp Glu Val Leu Pro Leu Leu Asp Glu Arg Leu
785 790 795 800

Ala Ile Ala Ala Val Asn Gly Pro Arg Ser Val Val Val Ser Gly Asp
805 810 815

Glu Ala Ala Val Glu Glu Val Ala Ala Ala Phe Ala Arg Arg Lys Thr
820 825 830

Lys Arg Leu Lys Val Ser His Ala Phe His Ser His His Met Asp Gly
835 840 845

Met Leu Asp Glu Phe Arg Arg Phe Ala Glu Ile Leu Thr Phe Arg Lys
850 855 860

Pro Val Ile Pro Leu Val Ser Thr Val Ser Gly Glu Leu Leu Thr Glu
865 870 875 880

Ala Thr Ala Pro Glu Tyr Trp Val Glu His Val Arg Arg Pro Val Arg
885 890 895

Phe Ala Asp Gly Val Arg Arg Leu Asp Glu Leu Gly Val Asp Val Leu
900 905 910

Leu Glu Leu Gly Pro Asp Ala Val Leu Thr Pro Met Ala Ala Glu Val
915 920 925

Leu Asp Gly Glu Gly Ala Ala Leu Val Pro Ser Leu Arg Gly Ser Arg
930 935 940

Pro Glu Ala Glu Ala Leu Ala Ala Ser Leu Ala Glu Leu Trp Val Arg
945 950 955 960

Gly Ala Glu Leu Gly Trp Pro Gln Val Phe Gly Ala His Pro Arg Ala
965 970 975

Asp Leu Pro Thr Tyr Ala Phe Glu Arg Gln Arg Tyr Trp Leu Ile Asp
980 985 990

Gln Asp Thr Ala Gly Asp Pro Gly Ala Tyr Gly Leu Gly Asp Thr Gly
995 1000 1005

His Pro Leu Leu Arg Ala Ser Val Thr Thr Ala Glu Asp Gly Ala
1010 1015 1020

Leu Leu Leu Leu Ser Gly Arg Leu Ser Pro Leu Thr Gln Pro Trp Leu
1025 1030 1035

Ala Asp His Val Val Gly Gly Asp Val Val Leu Pro Gly Thr Ala
1040 1045 1050

Leu Leu Glu Leu Ala Leu Arg Ala Ala Glu Leu Ala Gly Ala Gly
1055 1060 1065

Gly Val Glu Glu Leu Thr Leu Glu Val Pro Met Val Leu Ser Glu
1070 1075 1080

Ala Gly Val Gln Val Gln Val Ser Val Arg Asp Ser Gly Leu Leu
1085 1090 1095

Ile Phe Phe Arg Asp Thr Glu Asp Asp Glu Trp Thr Arg Cys Ala
1100 1105 1110

Ser Gly Thr Leu Gly Ala Ala Ala Pro Ala Pro Gly Phe Gly Ala
1115 1120 1125

Trp Pro Pro Ala Gly Glu Pro Leu Asp Leu Ser Asp Leu Tyr Asp
1130 1135 1140

Arg Leu Ala Asp Ser Gly Leu Asp Tyr Gly Pro Ala Phe Arg Cys
1145 1150 1155

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Leu Arg  Ala Ala Trp Arg Ser  Gly Asp Asp Leu Tyr  Ala Glu Val
    1160                 1165                 1170

Ala Ala  Val Pro Glu Thr Gln  Gly Gly Phe Gly Val  His Pro Ala
    1175                 1180                 1185

Leu Leu  Asp Ala Ala Leu His  Val Leu Glu Leu Gly  Ser Gly Gly
    1190                 1195                 1200

Gly Gly  Gly Pro Ala Ala Leu  Pro Phe Ala Trp Ser  Gly Val Thr
    1205                 1210                 1215

Leu His  Ala Arg Gly Ala Asp  Val Leu Arg Val Lys  Leu Glu Asn
    1220                 1225                 1230

His Val  Ala Gly Ala Glu Ala  Gly Thr Tyr Ser Val  Ser Leu Lys
    1235                 1240                 1245

Val Ala  Asp Gly Ala Gly Glu  Pro Val Ala Ser Val  Glu Ser Leu
    1250                 1255                 1260

Ala Leu  Arg Pro Leu Ser Thr  Ala Pro Arg Ala Gln  Asp Gly Ala
    1265                 1270                 1275

Leu Tyr  Gly Val Asp Trp Ile  Ser Leu Pro Gly Thr  Pro Gly Val
    1280                 1285                 1290

Ala Glu  Tyr Arg Leu Tyr Pro  Asp Leu Thr Ala Val  Asp Asp Val
    1295                 1300                 1305

Pro Pro  Val Val Ala Val Arg  Cys Thr Thr Leu Glu  Ser Val Leu
    1310                 1315                 1320

Asp Leu  Val Gln Thr Trp Leu  Ala Asp Asp Arg Phe  Ala Pro Ala
    1325                 1330                 1335

Arg Leu  Ala Leu Leu Thr Asp  Gly Ala Val Ala Thr  Glu Asn Pro
    1340                 1345                 1350

Asp Pro  Ala Ala Ala Ala Met  Trp Gly Leu Val Arg  Ser Ala Gln
    1355                 1360                 1365

Ala Glu  His Pro Asp Arg Leu  Val Leu Ala Asp Val  Thr Gly Glu
    1370                 1375                 1380

Asp Gly  Leu Ala Ala Gly Leu  Ala Ser Gly Glu Pro  Glu Phe Ala
    1385                 1390                 1395

Ala Arg  Asp Gly Ala Val Leu  Val Pro Arg Leu Thr  Arg Val Pro
    1400                 1405                 1410

Ser Pro  Ala Pro Ala Ser Phe  Thr Thr Gly Gly Thr  Val Leu Ile
    1415                 1420                 1425

Thr Gly  Gly Thr Gly Gly Leu  Ala Gly Leu Leu Ala  Arg His Leu
    1430                 1435                 1440

Val Glu  Arg His Glu Val Arg  Ser Leu Leu Leu Val  Ser Arg Arg
    1445                 1450                 1455

Gly Ala  Ala Gly Pro Leu Val  Asp Asp Leu Thr Ala  Leu Gly Ala
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    1460                1465                1470

Asp Val  Thr Val Ala Ala Cys  Asp Ile Ala Asp Arg  Glu Ser Val
    1475                1480                1485

Ala Ala  Leu Leu Ala Glu His  Pro Val Ser Ala Val  Val His Ala
    1490                1495                1500

Ala Gly  Val Leu Asp Asp Ala  Thr Ile Thr Thr Leu  Asp His Glu
    1505                1510                1515

Arg Leu  Ala Ala Val Leu Arg  Pro Lys Val Thr Gly  Ala Leu Val
    1520                1525                1530

Leu Asp  Glu Leu Thr Arg Asp  Leu Asp Leu Ser Ala  Phe Val Leu
    1535                1540                1545

Phe Ser  Ser Ser Ala Ala Thr  Phe Asp Gly Ala Gly  Gln Ala Asn
    1550                1555                1560

Tyr Ala  Ala Ala Asn Ala Phe  Leu Glu Ala Leu Ala  Leu Arg Arg
    1565                1570                1575

Arg Ala  Glu Gly Arg Pro Gly  Val Ala Leu Gly Trp  Gly Leu Trp
    1580                1585                1590

Ala Thr  Gly Met Gly Ala Arg  Leu Asp Glu Ala Gly  Leu Arg Arg
    1595                1600                1605

Ile Glu  Arg Ser Gly Gln Arg  Ala Leu Ser Glu Val  Asp Gly Leu
    1610                1615                1620

Ala Leu  Phe Asp Ala Ala Leu  Ala Ala Asp Arg Pro  Val Leu Leu
    1625                1630                1635

Pro Met  Arg Met His Arg Ala  Ala Leu Arg Ala Arg  Ala Ser Ala
    1640                1645                1650

Glu Gly  Leu Pro Ala Val Leu  Gly Gly Leu Val Arg  Val Thr Arg
    1655                1660                1665

Pro Ala  Pro Ser Ala Ala Pro  Arg Gly Leu Asp Glu  Ala Ala Leu
    1670                1675                1680

Leu Asp  Leu Val Arg Thr Thr  Val Ala Ala Val Leu  Gly His Pro
    1685                1690                1695

Asp Ala  His Ala Ile Asp Pro  Asp Arg Ala Phe Thr  Glu Val Gly
    1700                1705                1710

Phe Asp  Ser Leu Ala Ala Val  Glu Leu Arg Asn Arg  Leu Ile Ala
    1715                1720                1725

Ala Thr  Gly Leu Lys Ile Ala  Pro Thr Leu Val Phe  Asp His Pro
    1730                1735                1740

Asn Pro  Arg Ala Val Ala Ala  Phe Leu Ala Ala Gly  Ser Ala Pro
    1745                1750                1755

Val Arg  Asp Glu Pro Ala Ala  Pro Ala Glu Ala Asp  Glu Pro Ile
    1760                1765                1770
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Ala Ile  Ile Gly Met Ala Cys  Arg Tyr Pro Gly Gly  Val Ser Thr
    1775                 1780                 1785

Pro Asp  Asp Leu Trp Arg Leu  Val Ala Asp Gly Asn  Asp Gly Ile
    1790                 1795                 1800

Thr Arg  Phe Pro Glu Asn Arg  Gly Trp Asp Thr Asp  Gly Val Tyr
    1805                 1810                 1815

His Pro  Asp Ala Asp His Arg  Gly Thr Thr Tyr Val  Arg Glu Gly
    1820                 1825                 1830

Gly Phe  Leu His Asp Ala Gly  Gln Phe Asp Pro Gly  Phe Phe Gly
    1835                 1840                 1845

Ile Ser  Pro Arg Glu Ala Leu  Ala Met Asp Pro Gln  Gln Arg Leu
    1850                 1855                 1860

Leu Leu  Glu Ile Ser His Glu  Ala Val Glu Arg Ala  Gly Ile Asp
    1865                 1870                 1875

Pro Lys  Ser Leu Arg Gly Ser  Gly Thr Gly Val Phe  Ala Gly Val
    1880                 1885                 1890

Met Tyr  His Asp Tyr Ala Thr  Gly Leu Asn Arg Val  Pro Asp Asp
    1895                 1900                 1905

Val Glu  Gly Tyr Leu Gly Asn  Gly Thr Ser Ala Ser  Ile His Ser
    1910                 1915                 1920

Gly Arg  Val Ala Tyr Thr Phe  Gly Leu Glu Gly Pro  Ala Val Thr
    1925                 1930                 1935

Ile Asp  Thr Ala Cys Ser Ser  Ser Leu Val Ala Leu  His Leu Ala
    1940                 1945                 1950

Ala Gln  Ala Leu Arg Arg Gly  Glu Cys Ser Met Ala  Leu Ala Gly
    1955                 1960                 1965

Gly Val  Thr Val Met Ala Thr  Pro Glu Val Phe Val  Asp Phe Ser
    1970                 1975                 1980

Arg Gln  Arg Gly Leu Ala Pro  Asp Gly Arg Cys Lys  Ser Phe Ser
    1985                 1990                 1995

Asp Glu  Ala Asp Gly Thr Val  Trp Ser Glu Gly Val  Gly Met Leu
    2000                 2005                 2010

Leu Val  Glu Arg Leu Ser Asp  Ala Arg Arg Asn Gly  His Arg Val
    2015                 2020                 2025

Leu Ala  Ile Val Arg Gly Ser  Ala Val Asn Gln Asp  Gly Ala Ser
    2030                 2035                 2040

Asn Gly  Leu Thr Ala Pro Ser  Gly Pro Ser Gln Gln  Arg Val Ile
    2045                 2050                 2055

Arg Arg  Ala Leu Ala Asp Ala  Gly Leu Lys Pro Ser  Glu Val Asp
    2060                 2065                 2070
```

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Ala Val  Glu Ala His Gly Thr  Gly Thr Pro Leu Gly  Asp Pro Ile
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Glu Ala  Gln Ala Met Leu Ala  Thr Tyr Gly Gln Asp  Arg Asp Arg
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Pro Leu  Trp Leu Gly Ser Leu  Lys Ser Asn Leu Gly  His Thr Gln
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Ala Ala  Ala Gly Val Gly Gly  Ile Ile Lys Met Val  Gln Ala Met
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His His  Gly Val Leu Pro Arg  Thr Leu Asn Leu Gly  Thr Pro Thr
    2135                 2140                 2145

Thr Lys  Val Asp Trp Thr Ser  Gly Asn Val Ser Leu  Leu Ser Glu
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Pro Val  Ala Trp Pro Glu Thr  Gly Gly Pro Arg Arg  Ala Ala Val
    2165                 2170                 2175

Ser Ser  Phe Gly Ile Ser Gly  Thr Asn Ala His Val  Val Leu Glu
    2180                 2185                 2190

Gln Ala  Glu Pro Val Glu Lys  Ser Thr Ser Asp Thr  Ser Pro Leu
    2195                 2200                 2205

Gly Gly  Asp Val Leu Pro Phe  Val Leu Ser Gly Lys  Thr Ser Ala
    2210                 2215                 2220

Ala Leu  Ala Ala Gln Ala Asp  Arg Leu Ala Gly His  Leu Ala Gly
    2225                 2230                 2235

Asp Val  Ser Leu Pro Ala Val  Ala Arg Ala Leu Ala  Val Thr Arg
    2240                 2245                 2250

Ser Ala  Leu Asp His Arg Ala  Val Val Val Ala Gly  Asp Arg Ala
    2255                 2260                 2265

Gly Leu  Thr Ala Gly Leu Arg  Ala Leu Ala Asp Ala  Val Pro Ala
    2270                 2275                 2280

Pro His  Val Val Asp Gly Val  Ala Glu Asn Gly Lys  Ala Val Phe
    2285                 2290                 2295

Val Phe  Pro Gly Gln Gly Ser  Gln Trp Thr Gly Met  Ala Val Asp
    2300                 2305                 2310

Leu Leu  Gly Ser Ser Ala Val  Phe Ala Glu Ala Met  Ala Asp Cys
    2315                 2320                 2325

Glu Ala  Ala Leu Leu Ser His  Leu Asp Trp Lys Leu  Thr His Val
    2330                 2335                 2340

Leu Ser  Asp Ala Ala Ala Leu  Glu Arg Val Asp Val  Val Gln Pro
    2345                 2350                 2355

Val Leu  Phe Ala Val Met Val  Ser Leu Ala Arg Leu  Trp Arg Ala
    2360                 2365                 2370

Cys Gly  Ile Glu Pro Ala Ala  Val Val Gly His Ser  Gln Gly Glu
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Ile Ala Ala Ala Cys Val Ala Gly Ala Leu Ser Leu Glu Asp Ala
2390 2395 2400

Ala Arg Val Val Cys Leu Arg Ser Lys Ala Ile Leu Ala Leu Ser
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Gly Leu Gly Gly Met Val Ser Val Ala Ala Ser Glu Asp Arg Val
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Arg Glu Leu Leu Pro Asp Gly Val Ser Val Ala Val Val Asn Gly
2435 2440 2445

Pro Ala Ser Val Val Val Ser Gly Asp Val Ala Gly Leu Glu Ala
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Leu Leu Lys Arg Cys Glu Leu Leu Asp Val Arg Ala Lys Arg Val
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Pro Val Asp Tyr Ala Ser His Ser Ala His Val Asp Ala Ile Glu
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Gln Gln Val Val Thr Ala Leu Ser Gly Ile Met Pro Arg Glu Ala
2495 2500 2505

Glu Leu Pro Met Tyr Ser Thr Val Thr Gly Glu Pro Ile Asp Thr
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Thr Thr Leu Asp Ala Ala Tyr Trp Phe Arg Asn Leu Arg Ala Thr
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Val Arg Phe Asp Gln Ala Val Arg Arg Leu Ile Ala Asp Gly Phe
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Arg Phe Phe Val Glu Thr Ser Pro His Pro Val Leu Val Ala Gly
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Ala Ser Leu Arg Arg Asp Glu Gly Gly Pro Thr Arg Phe Val Thr
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Ser Leu Ala Glu Ala His Val His Gly Leu Ser Pro Asp Trp Ala
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Ala Leu Leu Pro Glu Ala Gly Trp Val Asp Leu Pro Pro Tyr Ala
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Phe Gln His Gln Glu Phe Trp Leu Thr Asp Ala Gly Glu Pro Gly
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Asp Ala Ala Gly Phe Gly Leu Gly Ala Thr Gly His Pro Leu Leu
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Gly Arg Ile Ser Thr Ala Ala Gln Pro Trp Leu Ala Asp His Ala
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Val Gln Gly Val Val Leu Leu Pro Gly Thr Ala Phe Val Glu Leu
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Ala Leu Gln Ala Gly Thr His Ala Gly Cys Gly Arg Ile Asp Glu
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Leu Thr Leu Glu Ala Pro Leu Pro Leu Pro Glu Gln Gly Gly Val
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Arg Val Gln Val Val Leu Gly Ser Glu Val Asn Gly Arg Arg Glu
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Val Thr Val His Ser Gln Ala Glu Ser Gly Asp Asp Thr Trp Val
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Arg His Ala Ser Gly Phe Leu Thr Ser Ala Glu Thr Pro Gly Glu
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Gly Leu Thr Glu Trp Pro Pro Ala Gly Ala Thr Ser Ala Asp Leu
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Asp Gly Phe Tyr Ala Asp Ala Glu Ala Gln Gly Tyr Gly Tyr Gly
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Pro Ala Phe Gln Gly Leu Arg Ala Ala Trp Thr Leu Gly Ser Asp
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Val Phe Ala Glu Val Val Leu Pro Asp Ala Glu Gly Ala Asp Arg
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Phe Gly Leu His Pro Ala Leu Leu Asp Ala Ala Leu His Ala Leu
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Gly Thr Val Arg Ser Gly Asp Gly Ala Glu Leu Pro Phe Ala Trp
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Thr Gly Val Thr Val His Ala Val Gly Ala Thr Ala Leu Arg Val
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Arg Leu Thr Val Gly Thr Asp Thr Val Ala Val Thr Ala Ala Asp
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Pro Ala Gly Ala Pro Val Ala Thr Val Glu Gly Leu Val Thr Arg
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Pro Ala Ala Leu Pro Gly Ser Arg Arg Pro Asp Ser Leu Phe Arg
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Val Asp Trp Thr Pro Val Ser Thr Pro Glu Ala Val Glu Thr Pro
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Ile Pro Asp Val Val Leu Val Pro Val Gly Ala Glu Ala Gly Asp
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Val Leu His Thr Arg Gly Ala Val Ala Asp Val Arg Asp Leu Pro
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Pro Asp Arg Ile Val Leu Leu Asp Ser Asp Thr Asp Leu Pro Pro
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Trp Arg Asp Gly Glu Leu Leu Val Pro Arg Leu Ala Lys Val Ser
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Ala Pro Arg Arg Gly Thr Leu Glu Glu Leu Ala Leu Val Pro Ala
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Pro Thr Ala Ala Arg Pro Leu Ala Asp Gly Glu Val Arg Ile Gln
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Val Arg Ala Ala Gly Ile Asn Phe Arg Asp Val Leu Ile Thr Leu
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Asp Met Tyr Pro Glu Asp Lys Ala Val Met Gly Ser Glu Gly Ala
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Gly Ile Val Thr Glu Ile Gly Ser Gly Val Thr Gly Leu Lys Pro
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Gly Asp Arg Val Phe Gly Leu Phe Asp Gly Ala Phe Gly Pro Val
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Ala Ile Ala Asp Arg Arg Thr Val Thr Glu Met Pro Val Asp Trp
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Tyr Tyr Gly Leu Val Asp Leu Gly Gly Leu Arg Pro Gly Glu Lys
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Val Leu Ile His Gly Ala Thr Gly Gly Val Gly Met Ala Ala Val
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Gln Leu Ala Arg His Leu Gly Ala Glu Val Phe Ala Thr Ala Ser
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Pro Gly Lys Trp Glu Val Leu Arg Gly Leu Gly Phe Asp Asp Glu
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His Ile Ala Ser Ser Arg Thr Leu Asp Phe Glu Asp Arg Phe Gly
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Arg Met Asp Val Val Leu Asp Ser Leu Ala Lys Glu Phe Val Asp

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Pro Gly  Val Thr Tyr Arg Ala  Phe Asp Leu Leu Asp  Ala Gly Arg
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Pro Arg  Ile Gly Glu Ile Leu  Ala Glu Leu Leu Asp  Leu Phe Gly
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Ala Gly  Ser Leu Thr Val Pro  Arg Pro Thr Val Trp  Asp Ala Arg
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Arg Ala  Pro Glu Val Phe Arg  Phe Met Ser Gln Ala  Lys His Ile
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Gly Lys  Asn Val Leu Thr Ile  Pro Ser Thr Met Asp  Gly Asn Gly
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Thr Val  Leu Ile Thr Gly Ala  Thr Gly Thr Leu Gly  Ala Leu Val
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Ala Arg  His Leu Val Thr Val  Arg Gly Val Arg His  Leu Leu Leu
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Val Gly  Arg Arg Gly Arg Ala  Ala Ala Gly Met Ala  Glu Leu Glu
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Ala Glu  Leu Thr Ala Ala Gly  Ala Ser Val Thr Ile  Ala Ala Cys
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Asp Ala  Ala Asp Arg Ala Ala  Leu Ala Ala Leu Leu  Ala Thr Val
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Pro Ala  Glu His Pro Leu Ala  Gly Val Val His Ala  Ala Gly Val
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Leu Asp  Asp Gly Leu Val Ala  Thr Leu Thr Pro Glu  Arg Leu Ala
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Lys Val  Leu Arg Pro Lys Val  Asp Ala Ala Val Asn  Leu His Glu
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Leu Thr  Arg Asp Ala His Leu  Ala Glu Phe Val Leu  Phe Ser Ser
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Ala Ala  Gly Ala Phe Gly Asp  Ala Gly Gln Gly Asn  Tyr Ala Ala
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Ala Asn  Ser Phe Leu Asp Ser  Leu Ala Arg His Arg  Arg Ala Gln
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Gly Leu  Pro Ala Val Ser Leu  Ala Trp Gly Phe Trp  Ala Glu Leu
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Ser Gly  Met Thr Gly His Leu  Gly Glu Ala Asp Leu  Ala Arg Leu
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Lys Arg Ser Gly Met Ser Pro Leu Ser Thr Glu Asp Gly Leu Leu
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Leu Met Asp Ala Ala Arg Ala Gly Tyr Glu Pro Ala Pro Leu Pro
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Met His Ile Asp Leu Ala Ala Leu Arg Gly Glu Glu Val His Pro
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Leu Leu Arg Gly Leu Val Lys Ala Pro Val Arg Arg Ala Ala Ala
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Ala Thr Gly Thr Gln Ser Glu Gly Leu Ala Asp Arg Leu Ala Gly
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Leu Ala Pro Ala Ala Arg Gly Arg Ala Leu Leu Asp Leu Ile Arg
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Ala Asn Val Ala Ala Val Leu Gly Phe Gly Ser Pro Glu Gln Val
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Gly Val Arg Gln Ala Phe Arg Glu Leu Gly Phe Asp Ser Leu Ser
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Ala Val Glu Leu Arg Asn Arg Leu Asn Ala Ala Thr Gly Leu Arg
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Ala Glu Thr Leu Gly Asp Arg Leu Ala Pro Ala Glu Glu Ala Val
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Ala Asp Arg Leu Arg Glu Ala Gly Val Leu Asp Leu Leu Thr Arg
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Leu Ala Asp Pro Gly Tyr Arg Pro Thr Glu Ser Pro Asp Gly Ala
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<400> 39

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Asn Arg Arg Leu Thr Gly Glu Pro Ile Ala Ile Ile Gly Met Ala Cys
35 40 45

Arg Tyr Pro Gly Gly Val Arg Ser Pro Glu Glu Leu Trp Asp Leu Val
50 55 60

Ala Gly Glu Arg Thr Gly Leu Thr Gly Phe Pro Val Asp Arg Gly Trp
65 70 75 80

Asp Leu Asp Gly Leu Tyr Asp Pro Glu Gln Gly Lys Pro Gly Lys Ser
85 90 95

Tyr Val Arg Glu Gly Gly Phe Leu His Asp Ala Ala Arg Phe Asp Pro
100 105 110

Ala Phe Phe Gly Ile Ser Pro Arg Glu Ala Leu Ala Met Asp Pro Gln
115 120 125

Gln Arg Leu Leu Leu Glu Ile Ser Trp Glu Ala Ile Glu Arg Ala Gly
130 135 140

Ile Ala Pro Asp Ser Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly
145 150 155 160

Val Ile His Asn Glu Tyr Ser Ala Ile Ala Gly Thr Pro Pro Ala Asp
165 170 175

Leu Glu Pro Tyr Leu Gly Asn Gly Ser Phe Ala Ser Ile Ala Ser Gly
180 185 190

Arg Val Ser Tyr Thr Phe Gly Leu Glu Gly Pro Ala Val Thr Val Asp
195 200 205

Thr Ala Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Ala Gln Ala
210 215 220

Leu Arg Gln Gly Glu Cys Ser Leu Ala Leu Ala Gly Gly Val Thr Val
225 230 235 240

Met Ala Asn Pro Ala Ala Phe Val Asp Phe Ser Arg Gln Arg Gly Leu
245 250 255

Ala Ala Asp Gly Arg Ile Lys Ala Phe Ala Glu Ala Ala Asp Gly Thr
260 265 270

Ala Trp Gly Glu Gly Ala Gly Met Leu Leu Val Glu Arg Leu Ser Asp
275 280 285

Ala Arg Arg Asn Gly His Arg Val Leu Ala Val Val Arg Gly Ser Ala
290 295 300

Val Asn Gln Asp Gly Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Leu
305 310 315 320

Ser Gln Gln Arg Val Ile Arg Gln Ala Leu Ala Asn Ala Arg Leu Ala
325 330 335

Pro Ser Asp Val Asp Ala Met Glu Ala His Gly Thr Gly Thr Arg Leu
340 345 350

Gly Asp Pro Ile Glu Ala Gln Ala Leu Leu Ala Thr Tyr Gly Gln Asp
355 360 365

Arg Thr Thr Pro Leu Trp Leu Gly Ser Val Lys Ser Asn Ile Gly His
370 375 380

Ser Gln Ala Ala Ala Gly Val Ala Ser Ile Ile Lys Leu Val Glu Ala
385 390 395 400

Met Arg His Gly Val Leu Pro Lys Thr Leu His Val Asp Ala Pro Thr
405 410 415

Ser His Val Asp Trp Ser Glu Gly Ala Val Ser Leu Leu Thr Glu Ala
420 425 430

Glu Pro Trp Pro Lys Thr Asp Arg Pro Arg Arg Ala Ala Val Ser Ser
435 440 445

Phe Gly Ile Ser Gly Thr Asn Ala His Val Val Leu Glu Gln Pro Thr
450 455 460

Ala Glu Glu Glu Pro Pro Ser Thr Phe Ala Gly Pro Val Pro Phe Val
465 470 475 480

Leu Ser Gly Lys Thr Glu Ala Ala Leu His Glu Gln Val Ala Arg Val
485 490 495

Arg Glu Leu Ala Arg Asp Ser Asp Val Thr Ala Ala Asp Leu Ala Phe
500 505 510

Ser Leu Ala Thr Thr Arg Thr Ala Leu Asp His Arg Ala Ala Leu Val
515 520 525

Gly Thr Leu Asp Asp Leu Leu Thr Ala Thr Leu Val Glu Gly Arg Ala
530 535 540

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Thr Asp Gly Gly Thr Ala Phe Leu Phe Thr Gly Gln Gly Ser Gln Arg
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Leu Gly Met Gly Arg Glu Leu Ala Glu Arg Phe Pro Val Phe Ala Gln
                565                 570                 575

Ala Phe Asp Asp Val Ser Ser Arg Phe Glu Arg Pro Ile Ala Glu Leu
            580                 585                 590

Ser Ala Glu Glu Leu Asn Gln Thr Ala Asn Thr Gln Cys Ala Leu Phe
        595                 600                 605

Ala Phe Glu Val Ala Leu Phe Arg Leu Val Glu Asn Trp Gly Leu Arg
    610                 615                 620

Pro Asp Phe Leu Ala Gly His Ser Val Gly Glu Ile Ala Ala Ala His
625                 630                 635                 640

Val Ala Asp Val Leu Ser Leu Asp Asp Ala Val Thr Leu Val Ser Ala
                645                 650                 655

Arg Gly Arg Leu Met Gln Ala Leu Pro Thr Gly Gly Ala Met Val Ala
            660                 665                 670

Leu Gln Ala Thr Glu Ala Glu Val Ala Pro Leu Leu Thr Asp Arg Val
        675                 680                 685

Ser Leu Ala Ala Ile Asn Gly Pro Glu Ser Val Val Val Ser Gly Asp
    690                 695                 700

Glu Glu Ala Val Ala Ala Val Val Ser His Phe Glu Gly Arg Lys Ser
705                 710                 715                 720

Lys Arg Leu Thr Val Ser His Ala Phe His Ser Pro Leu Met Glu Pro
                725                 730                 735

Met Leu Asp Asp Phe Arg Ala Val Val Glu Gly Leu Thr Phe Ala Glu
            740                 745                 750

Pro Arg Ile Pro Ile Val Ser Gly Gly Leu Ala Glu Val Ser Thr Ser
        755                 760                 765

Asp Tyr Trp Val Arg His Val Arg Asp Ala Val Arg Phe His Asp Ser
    770                 775                 780

Val Glu Phe Leu Lys Ala Glu Gly Val Thr Arg Phe Leu Glu Ile Gly
785                 790                 795                 800

Pro Asp Ala Val Leu Thr Ala Met Ala Lys Glu Ser Ala Glu Asp Ala
                805                 810                 815

Val Val Leu Pro Ala Ser Arg Arg Asp Arg Pro Glu Val Thr Thr Leu
            820                 825                 830

Leu Thr Ala Val Ala Gly Leu His Val His Gly Ala Glu Val Asp Trp
        835                 840                 845

Ala Pro Leu Phe Asp Gly Ala Arg Arg Val Asp Leu Pro Thr Tyr Pro
    850                 855                 860

Phe Gln Tyr Glu His Phe Trp Leu Glu Ser Gly Ala Ala His Arg Asp
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865 870 875 880

Val Ser Ala Ala Gly Leu Asp Ala Ser Pro His Ala Leu Leu Ala Ala
885 890 895

Ala Val Arg Pro Ala Gly Glu Asp Glu Ile Leu Leu Thr Gly Arg Ile
900 905 910

Ser Leu Ser Thr Leu Pro Trp Leu Ala Asp His Val Val Gly Gly Asn
915 920 925

Val Leu Leu Pro Gly Thr Ala Phe Ala Glu Leu Ala Leu Ala Ala Ala
930 935 940

Asp Glu Ala Gly Cys Glu Ala Val Glu Glu Leu Asn Leu Glu Ala Pro
945 950 955 960

Leu Val Leu Pro Glu Lys Gly Gly Val Gln Leu Gln Val Ala Val Gly
965 970 975

Ala Ala Asp Asp Gln Gly Arg Arg Ser Val Thr Val His Ala Arg Pro
980 985 990

Glu Asp Asp Gly Phe Trp Val Arg His Ala Ser Gly Val Leu Gly Thr
995 1000 1005

Ala Val Ser Thr Gln Asp Glu Met Ile Glu Trp Pro Pro Ser Gly
1010 1015 1020

Ala Glu Pro Val Asp Leu Glu Gly Phe Tyr Pro Asn Leu Ala Ala
1025 1030 1035

Glu Gly Leu Gly Tyr Gly Pro Ala Phe Gln Gly Val Arg Ala Val
1040 1045 1050

Trp Thr Arg Asp Gly Asp Val Phe Ala Glu Val Gln Val Asp Asp
1055 1060 1065

Thr Pro Gly Thr Phe Gly Ile His Pro Ala Leu Phe Asp Ser Ala
1070 1075 1080

Leu His Ala Ile Gly Val Gly Glu Ser Arg Gly Leu Glu Ile Pro
1085 1090 1095

Phe Ala Trp Ser Asp Leu Arg Leu His Ala Asp Gly Ala Thr Val
1100 1105 1110

Leu Arg Val Arg Leu Ser Pro Ala Gly Asp Gly Ala Val Ser Val
1115 1120 1125

Phe Ala Thr Asp Pro Ala Gly Ala Pro Val Leu Ser Val Gly Ser
1130 1135 1140

Leu Ser Leu Arg Ala Pro Val Ala Ala Thr Ala Ser Leu Pro Arg
1145 1150 1155

Asp Ser Leu Phe Arg Val Thr Trp Thr Pro Val Thr Val Pro Ala
1160 1165 1170

Gly Ala Gly Glu Pro Thr Val Glu Ser Phe Val Asp Phe Asp Asp
1175 1180 1185

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Val Arg  Gln Ala Thr Ala His  Ala Arg Gln Ile Ala  Val Glu Pro
    1190                 1195                 1200

Gly Glu  Ala Pro Val Val Phe  Leu Thr Ser Gly Ala  Phe Thr Asp
    1205                 1210                 1215

Pro Ala  Gln Ala Ser Val Trp  Gly Leu Met Arg Ser  Ala Arg Glu
    1220                 1225                 1230

Glu Tyr  Pro Gly Arg Phe Val  Leu Val Asp Ala Asp  Asp Pro Ala
    1235                 1240                 1245

Thr Leu  Thr Ala Gly Leu Leu  Ala Gly Ile Val Ala  Ser Gly Glu
    1250                 1255                 1260

Thr Glu  Ala Ile Val Arg Glu  Gly Glu Val Arg Val  Pro Arg Leu
    1265                 1270                 1275

Thr Pro  Val Arg Gly Gly Glu  Thr Gly Pro Gly Trp  Asp Pro Glu
    1280                 1285                 1290

Gly Thr  Val Leu Ile Thr Gly  Gly Thr Gly Ala Leu  Ala Thr Glu
    1295                 1300                 1305

Leu Ala  Arg His Leu Val Thr  Arg Arg Gly Val Arg  Asn Leu Ile
    1310                 1315                 1320

Leu Ala  Gly Arg Arg Gly Pro  Ala Ala Glu Gly Ala  Ser Glu Leu
    1325                 1330                 1335

Ala Ala  Glu Leu Ala Asp Leu  Gly Ala Gln Ala Arg  Ile Val Ala
    1340                 1345                 1350

Cys Asp  Val Ala Asp Arg Asp  Gln Leu Thr Ala Leu  Leu Asp Gly
    1355                 1360                 1365

Val Pro  Leu Thr Ala Val Val  His Ala Ala Gly Val  Leu Asp Asp
    1370                 1375                 1380

Gly Leu  Leu Ala Asp Leu Thr  Arg Asp Arg Phe Glu  Thr Val Leu
    1385                 1390                 1395

Arg Ser  Lys Val Asp Gly Ala  Ile Leu Leu Asp Glu  Leu Ala Gly
    1400                 1405                 1410

Asp Ala  His Leu Val Phe Phe  Ser Ser Ala Ala Gly  Val Leu Gly
    1415                 1420                 1425

Ser Ala  Gly Gln Ala Asn Tyr  Ala Ala Ala Asn Ala  Ala Leu Asp
    1430                 1435                 1440

Ala Val  Ala Ala Arg Arg Arg  Glu Arg Gly Leu Pro  Ala Thr Ser
    1445                 1450                 1455

Leu Ala  Trp Gly Leu Trp Glu  Thr Gly Asp Gly Met  Ala Gly Ala
    1460                 1465                 1470

Leu Ala  Gly Thr Asp Arg Ala  Arg Met Ala Gly Ser  Gly Leu Leu
    1475                 1480                 1485
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Pro Leu  Pro Val Gly Asp Ala  Leu Thr Leu Phe Asp  Phe Ala Val
    1490                 1495                 1500

Gly Ala  Glu Glu Val Leu Phe  Val Pro Met Arg Leu  Asp Val Pro
    1505                 1510                 1515

Ala Leu  Arg Ala Ser Ala Thr  Asp Val Pro Leu Leu  Arg Ala Phe
    1520                 1525                 1530

Ala Gly  Lys Ser Arg Arg Thr  Ala Ser Ala Ala Pro  Ala Ala Arg
    1535                 1540                 1545

Glu Leu  Arg Asp Arg Leu Ala  Ser Leu Pro Thr Glu  Glu Arg Gly
    1550                 1555                 1560

Arg Glu  Leu Leu Ala Leu Val  Arg Gly Gln Val Ala  Glu Val Leu
    1565                 1570                 1575

Gly His  Arg Asp Ala Gly Ala  Val Glu Pro Ala Arg  Pro Phe Arg
    1580                 1585                 1590

Glu Leu  Gly Phe Asp Ser Leu  Thr Ala Val Glu Leu  Arg Asn Gly
    1595                 1600                 1605

Leu Asn  Ala Ala Ser Gly Leu  Arg Leu Pro Ala Thr  Ala Val Phe
    1610                 1615                 1620

Asp His  Pro Thr Pro Lys Ala  Leu Ala Asp Leu Leu  Ala Ala Glu
    1625                 1630                 1635

Leu Phe  Gly Ala Ala Pro Glu  Ala Pro Val Gln Gly  Pro Ala Met
    1640                 1645                 1650

Ala Ala  Asp Glu Pro Ile Ala  Ile Ile Gly Met Ala  Cys Arg Tyr
    1655                 1660                 1665

Pro Gly  Gly Val Ala Ser Pro  Glu Asp Leu Trp Arg  Leu Val Ala
    1670                 1675                 1680

Glu Gly  Arg Asp Gly Ile Ser  Leu Phe Pro Ala Asp  Arg Gly Trp
    1685                 1690                 1695

Asp Val  Asp Gly Leu Tyr Asp  Pro Asp Pro Gly Lys  Ala Gly Lys
    1700                 1705                 1710

Ser Tyr  Val Arg Glu Gly Gly  Phe Leu His Glu Ala  Gly Asp Phe
    1715                 1720                 1725

Asp Ala  Gly Phe Phe Gly Ile  Ser Pro Arg Glu Ala  Leu Gly Met
    1730                 1735                 1740

Asp Pro  Gln Gln Arg Leu Leu  Leu Glu Val Ser Trp  Glu Ala Phe
    1745                 1750                 1755

Glu Arg  Ala Gly Ile Asp Pro  Gly Thr Leu Arg Gly  Ser Asp Thr
    1760                 1765                 1770

Gly Val  Phe Ala Gly Gln Met  Tyr His Asp Tyr Leu  Thr Gly Ala
    1775                 1780                 1785

Thr Val  Val Pro Asp Asp Val  Glu Gly Tyr Leu Gly  Thr Gly Asn
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    1790                1795                1800

Ser Gly  Ser Val Leu Ser Gly  Arg Val Ser Tyr Thr  Phe Gly Leu
    1805                1810                1815

Glu Gly  Pro Ala Val Thr Val  Asp Thr Ala Cys Ser  Ser Ser Leu
    1820                1825                1830

Val Ala  Leu His Leu Ala Ala  Gln Ala Leu Arg Arg  Gly Glu Cys
    1835                1840                1845

Ser Leu  Ala Leu Ala Gly Gly  Val Thr Val Met Ala  Thr Pro Glu
    1850                1855                1860

Thr Phe  Val Asp Phe Ser Arg  Gln Arg Gly Leu Ala  Pro Asp Gly
    1865                1870                1875

Arg Ser  Lys Ser Phe Ser Asp  Gly Ala Asp Gly Thr  Ser Trp Ser
    1880                1885                1890

Glu Gly  Val Gly Met Leu Leu  Val Glu Arg Leu Ser  Asp Ala Glu
    1895                1900                1905

Arg Asn  Gly His Arg Ile Leu  Ala Val Val Arg Gly  Ser Ala Val
    1910                1915                1920

Asn Gln  Asp Gly Ala Ser Asn  Gly Leu Thr Ala Pro  Asn Gly Pro
    1925                1930                1935

Ser Gln  Gln Arg Val Ile Arg  Arg Ala Leu Ala Asp  Ala Arg Leu
    1940                1945                1950

Glu Pro  Ser Glu Val Asp Ala  Val Glu Ala His Gly  Thr Gly Thr
    1955                1960                1965

Thr Leu  Gly Asp Pro Ile Glu  Ala Gln Ala Leu Leu  Ala Thr Tyr
    1970                1975                1980

Gly Gln  Gly Arg Glu Asp Ala  Ala Leu Trp Leu Gly  Ser Ile Lys
    1985                1990                1995

Ser Asn  Ile Gly His Ser Gln  Ala Ala Ala Gly Val  Ala Gly Val
    2000                2005                2010

Ile Lys  Met Val Glu Ala Met  Arg Arg Gly Val Leu  Pro Lys Thr
    2015                2020                2025

Leu His  Val Thr Glu Pro Ser  Ser His Val Asp Trp  Thr Ala Gly
    2030                2035                2040

Ala Val  Ser Leu Leu Thr Glu  Ala Arg Leu Trp Pro  Asp Ala Gly
    2045                2050                2055

Arg Pro  Arg Arg Ala Ala Val  Ser Ser Phe Gly Ile  Ser Gly Thr
    2060                2065                2070

Asn Ala  His Val Val Leu Glu  Gln Gly Pro Ala Pro  Val Glu Ala
    2075                2080                2085

Ile Glu  Ser Gly Glu Gly Pro  Ala Ala Phe Val Leu  Ser Ala Gly
    2090                2095                2100
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Ser Glu  Ala Ala Leu His Asp  Gln Ala Ser Arg Leu  Arg Asp Phe
    2105                 2110                 2115

Leu Ala  Glu Thr Pro Ala Ala  Leu Ala Asp Val Ala  Phe Ser Leu
    2120                 2125                 2130

Ala Thr  Thr Arg Ala Ala Leu  Glu His Arg Ala Ala  Val Val Ala
    2135                 2140                 2145

Ala Asp  Arg Glu Thr Leu Leu  Ala Ala Leu Glu Asn  Leu Thr Val
    2150                 2155                 2160

Thr Gly  Arg Ala Thr Glu Gly  Arg Thr Ala Phe Leu  Phe Thr Gly
    2165                 2170                 2175

Gln Gly  Ser Gln Arg Leu Gly  Met Gly Leu Gln Leu  Ala Glu Arg
    2180                 2185                 2190

Phe Pro  Val Phe Ala Ala Ala  Tyr Asp Glu Val Cys  Ser Arg Phe
    2195                 2200                 2205

Glu Gln  Pro Leu Arg Asp Leu  Thr Ala Glu Glu Leu  Asn Gln Thr
    2210                 2215                 2220

Ala Asn  Thr Gln Cys Ala Leu  Phe Ala Leu Glu Val  Ala Leu Phe
    2225                 2230                 2235

Arg Leu  Val Glu Ser Trp Gly  Val Arg Pro Asp Phe  Leu Ala Gly
    2240                 2245                 2250

His Ser  Val Gly Glu Ile Ala  Ala Ala His Val Ala  Gly Val Leu
    2255                 2260                 2265

Ser Leu  Asp Asp Ala Val Thr  Leu Val Ser Ala Arg  Gly Arg Leu
    2270                 2275                 2280

Met Gln  Ala Leu Pro Thr Gly  Gly Ala Met Val Ala  Leu Gln Ala
    2285                 2290                 2295

Thr Glu  Ala Glu Val Thr Pro  Leu Leu Thr Glu Arg  Val Ser Leu
    2300                 2305                 2310

Ala Ala  Ile Asn Gly Pro Glu  Ser Val Val Val Ser  Gly Glu Glu
    2315                 2320                 2325

Asp Ala  Val Ala Ala Val Val  Ser Gln Phe Glu Gly  Arg Lys Ser
    2330                 2335                 2340

Lys Arg  Leu Thr Val Ser His  Ala Phe His Ser Pro  Leu Met Glu
    2345                 2350                 2355

Pro Met  Leu Asp Glu Phe Arg  Val Val Ala Asp Ser  Leu Ser Tyr
    2360                 2365                 2370

Ala Ala  Pro Arg Ile Pro Ile  Val Ser Gly Gly Leu  Ala Glu Val
    2375                 2380                 2385

Ser Thr  Ser Asp Tyr Trp Val  Arg His Val Arg Asp  Ala Val Arg
    2390                 2395                 2400
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Phe His  Asp Ser Val Lys Phe  Leu Glu Ala Glu Gly  Val Thr Arg
    2405                 2410                 2415

Phe Leu  Glu Ile Gly Pro Asp  Gly Val Leu Thr Ala  Met Ala Lys
    2420                 2425                 2430

Glu Thr  Ala Glu Asp Ala Val  Val Val Pro Ala Leu  Arg Arg Asp
    2435                 2440                 2445

Arg Pro  Glu Val Glu Thr Leu  Leu Thr Ala Val Ala  Gly Leu His
    2450                 2455                 2460

Val His  Gly Val Gly Val Asp  Leu Thr Ala Leu Leu  Gly Gly Gly
    2465                 2470                 2475

Ser Pro  Val Asp Leu Pro Thr  Tyr Ala Phe Gln His  Arg Arg Phe
    2480                 2485                 2490

Trp Leu  Ser Ser Ala Gly Gly  Ala Ala Gly Asp Val  Thr Ala Ala
    2495                 2500                 2505

Gly Leu  Gly Thr Thr Asp His  Pro Leu Leu Gly Ala  Ala Ala Ala
    2510                 2515                 2520

Leu Pro  Gly Asp Gly Gly Phe  Leu Leu Thr Gly Arg  Leu Ser Gly
    2525                 2530                 2535

His Ala  Gln Pro Trp Leu Ala  Glu His Arg Val Gly  Gly Val Val
    2540                 2545                 2550

Leu Leu  Pro Gly Thr Ala Phe  Val Glu Ile Ala Leu  Arg Ala Gly
    2555                 2560                 2565

Asp Glu  Ala Gly Cys Gly His  Leu Glu Asp Leu Thr  Leu Glu Ala
    2570                 2575                 2580

Pro Leu  Val Leu Pro Glu Arg  Gly Ala Thr Gln Leu  Ser Val Leu
    2585                 2590                 2595

Val Gly  Ala Ala Asp Asp Thr  Gly Arg Arg Thr Ile  Glu Ile His
    2600                 2605                 2610

Ser Arg  Glu Glu Gly Glu Asp  Gly Trp Gln Arg His  Ala Thr Gly
    2615                 2620                 2625

Leu Leu  Ser Ala Ala Gly Ala  Val Glu Pro Ala Gly  Leu Thr Thr
    2630                 2635                 2640

Trp Pro  Pro Gln Asn Ala Glu  Ala Val Pro Val Gly  Asp Val Tyr
    2645                 2650                 2655

Glu Arg  Leu Ala Ala Thr Gly  Leu Glu Tyr Gly Pro  Ala Phe Arg
    2660                 2665                 2670

Gly Leu  Arg Ala Ala Trp Arg  Ala Gly Glu Asp Leu  Phe Ala Glu
    2675                 2680                 2685

Val Glu  Leu Pro Glu Asp Gln  His Ser Asp Ala Ala  Arg Phe Gly
    2690                 2695                 2700

Val His  Pro Ala Leu Leu Asp  Ala Ala Leu His Thr  Leu Gly Leu
```

2705 2710 2715

Ala Gly Gly Gly Asp Gly Thr Arg Leu Pro Phe Ala Trp Ser Gly
2720 2725 2730

Val Arg Leu His Ala Ala Gly Ala Thr Arg Leu Arg Val Arg Leu
2735 2740 2745

Arg Pro Ser Gly Pro Asp Gly Phe Glu Val Leu Val Ala Asp Gly
2750 2755 2760

Thr Gly Arg Pro Val Val Ser Ala Glu Glu Leu Thr Leu Arg Glu
2765 2770 2775

Ile Ser Gly Asp Ala Leu Ala Arg Lys Gly His Asp Ser Leu Tyr
2780 2785 2790

Arg Val Ala Trp Arg Pro Val Pro Leu Pro Glu Thr Gly Glu Thr
2795 2800 2805

Leu Pro Ala Glu Ser Val Phe Ser Val Pro Arg Gly Gly Asp Ser
2810 2815 2820

Ala Glu Arg Val His Glu Thr Thr Ala Ala Val Leu Glu Val Val
2825 2830 2835

Gln Arg Arg Leu Glu Asp Glu Pro Gly Gly Pro Leu Val Val His
2840 2845 2850

Thr Arg Gly Gly Val Ala Ala Gly Asp Gly Glu Ala Val Thr Asp
2855 2860 2865

Leu Ala His Ala Ala Val Trp Gly Leu Val Arg Ala Ala Gln Ser
2870 2875 2880

Glu Asn Pro Gly Arg Phe Leu Leu Val Asp Ala Glu Thr Leu Pro
2885 2890 2895

Asp Gly Arg Ile Leu Ala Ile Asp Glu Pro Gln Ile Ala Leu Arg
2900 2905 2910

Asp Gly Arg Ala Leu Ala Pro Arg Leu Ala Thr Thr Ala Ser Ser
2915 2920 2925

Thr Glu Leu Thr Pro Pro Glu Gly Ala Trp Arg Leu Asp Thr Thr
2930 2935 2940

Gly Arg Gly Thr Leu Glu Asn Leu Thr Leu Val Pro Ser Pro Glu
2945 2950 2955

Ala Val Ala Pro Leu Ala Glu Gly Glu Val Arg Ile Ala Val Arg
2960 2965 2970

Ala Ala Gly Leu Asn Phe Arg Asp Val Leu Ile Ala Leu Gly Met
2975 2980 2985

Tyr Pro Gly Ala Ala Thr Leu Gly Ser Glu Gly Ala Gly Val Val
2990 2995 3000

Thr Glu Ile Gly Pro Gly Val Thr Gly Leu Asp Val Gly Asp Arg
3005 3010 3015

Val Phe Gly Leu Met Ser Asn Gly Phe Gly Pro Gln Val Val Thr
3020 3025 3030

Asp His Arg Thr Leu Ala Lys Met Pro Glu Asp Trp Ser Phe Ala
3035 3040 3045

Thr Ala Ala Ser Val Pro Ile Val Phe Leu Thr Ala Tyr Tyr Gly
3050 3055 3060

Leu Phe Asp Leu Ala Arg Leu Glu Ala Gly Glu Ser Ile Leu Val
3065 3070 3075

His Ala Ala Ala Gly Gly Val Gly Met Ala Ala Thr Gln Leu Ala
3080 3085 3090

Arg His Ala Gly Ala Glu Val Phe Gly Thr Ala Gly Pro Gly Lys
3095 3100 3105

Trp Asp Thr Leu Arg Ala Asn Gly Phe Asp Asp Thr His Leu Ser
3110 3115 3120

Ser Ser Arg Asp Leu Gly Phe Glu Glu Lys Phe Arg Asp Ala Thr
3125 3130 3135

Gly Gly Arg Gly Val Asp Val Val Leu Asn Ser Leu Ala Gly Asp
3140 3145 3150

Tyr Val Asp Ala Ser Leu Arg Leu Leu Ala Pro Gly Gly Arg Phe
3155 3160 3165

Ala Glu Met Gly Lys Thr Asp Ile Arg Glu Pro Gly Glu Thr Gly
3170 3175 3180

Val Glu Tyr His Pro Phe Asp Val Ile Asp Ala Gly Pro Glu Arg
3185 3190 3195

Ile His Glu Met Leu Ala Ala Leu Leu Glu Leu Phe Ala Ala Gly
3200 3205 3210

Ala Leu Thr Pro Leu Pro Val Thr Gly Trp Asp Val Arg Arg Gly
3215 3220 3225

Pro Asp Ala Phe Arg Phe Leu Ser Gln Ala Lys His Val Gly Lys
3230 3235 3240

Asn Val Leu Thr Met Pro Ala Ala Leu Asp Pro Asp Gly Thr Val
3245 3250 3255

Leu Val Thr Gly Gly Thr Gly Ala Leu Gly Ala Leu Phe Ala Arg
3260 3265 3270

His Leu Val Arg Glu Arg Gly Val Arg Arg Leu Leu Leu Ala Ser
3275 3280 3285

Arg Arg Gly His Asp Ala Pro Gly Val Pro Glu Leu Val Ala Glu
3290 3295 3300

Leu Thr Glu Ala Gly Ala Ser Val Thr Val Glu Ala Cys Asp Ala
3305 3310 3315

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Ala Asp  Arg Gly Ala Leu Ala  Ala Val Leu Ala Gly  Ile Pro Ala
    3320                 3325                 3330

Ala His  Pro Leu Thr Gly Val  Val His Thr Ala Gly  Val Leu Asp
    3335                 3340                 3345

Asp Gly  Leu Val Gly Ser Leu  Thr Pro Glu Arg Leu  Ala Lys Val
    3350                 3355                 3360

Leu Arg  Pro Lys Val Asp Ala  Ala Leu Asn Leu His  Glu Leu Thr
    3365                 3370                 3375

Ser Gly  Ala Asp Leu Ala Glu  Phe Val Val Phe Ser  Ser Ala Ala
    3380                 3385                 3390

Gly Val  Phe Gly Asn Ala Gly  Gln Ala Asn Tyr Ala  Ala Ala Asn
    3395                 3400                 3405

Gly Phe  Leu Asp Ala Leu Ser  Val Arg Arg Ala Ala  His Gly Leu
    3410                 3415                 3420

Pro Ala  Arg Ser Leu Ala Trp  Gly Leu Trp Ala Glu  Thr Gly Gly
    3425                 3430                 3435

Met Gly  Gly Thr Leu Gly Glu  Ala Glu Leu Ala Arg  Met Ala Gln
    3440                 3445                 3450

Ser Gly  Thr Ala Ala Leu Ser  Thr Gln Asp Gly Leu  Glu Leu Phe
    3455                 3460                 3465

Asp Ala  Ala Gly Ala Leu Ala  Glu Pro Val Leu Val  Pro Met Arg
    3470                 3475                 3480

Leu Asp  Val Thr Ala Met Gly  Gly Asp Gly Leu Pro  Pro Leu Leu
    3485                 3490                 3495

Arg Gly  Leu Ala Arg Gly Pro  Val Arg Arg Ala Ala  Ser Ala Gly
    3500                 3505                 3510

Ala Ala  Gly Asp Ala Asp Ser  Leu Arg Asp Arg Leu  Leu Ala Val
    3515                 3520                 3525

Pro Val  Ala Asp Arg Glu Thr  Leu Leu Val Asp Leu  Val Arg Thr
    3530                 3535                 3540

His Ser  Ala Thr Val Leu Gly  His Thr Ala Ala Asp  Ala Val Glu
    3545                 3550                 3555

Ala Thr  Arg Ser Phe Gln Glu  Ile Gly Phe Asp Ser  Leu Thr Ala
    3560                 3565                 3570

Val Glu  Leu Arg Asn Arg Leu  Thr Ala Ala Thr Gly  Leu Arg Leu
    3575                 3580                 3585

Pro Ala  Thr Leu Ile Phe Asp  Tyr Pro Thr Pro Glu  Ala Leu Ala
    3590                 3595                 3600

Ala His  Ile Gly Glu Gly Val  Leu Gly Ala Gln Gly  Gly Pro Glu
    3605                 3610                 3615

Thr Gly  Gln Ala Ala Val Thr  Ala Asp Glu Pro Ile  Ala Ile Val
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    3620                3625                3630

Ala Met  Ser Cys Arg Phe Pro  Gly His Ala Asp Thr  Pro Glu Arg
    3635                3640                3645

Leu Trp  Ala Leu Leu Ala Glu  Gly Arg Asp Ala Leu  Gly Glu Phe
    3650                3655                3660

Pro Ala  Asp Arg Gly Trp Asp  Leu Glu Arg Leu Phe  Asp Thr Asp
    3665                3670                3675

Pro Asp  Arg Arg Gly Thr Ser  Tyr Thr Arg Gln Gly  Ala Phe Leu
    3680                3685                3690

Glu Thr  Ala Gly Asp Phe Asp  Ala Gly Phe Phe Gly  Ile Ser Pro
    3695                3700                3705

Arg Glu  Ala Leu Ala Met Asp  Pro Gln Gln Arg Leu  Leu Leu Glu
    3710                3715                3720

Thr Ser  Trp Glu Ala Phe Glu  Arg Ala Gly Ile Asp  Pro Ala Thr
    3725                3730                3735

Leu Arg  Gly Ser Arg Thr Gly  Val Phe Ala Gly Val  Met Asp Asn
    3740                3745                3750

Glu Tyr  Val Ser Gly Ser Ala  Glu Val Pro Asp Gly  Val Glu Gly
    3755                3760                3765

Tyr Leu  Ala Thr Gly Thr Ser  Ala Ser Val Ala Ser  Gly Arg Val
    3770                3775                3780

Ser Tyr  Thr Phe Gly Leu Glu  Gly Pro Ala Val Thr  Val Asp Thr
    3785                3790                3795

Ala Cys  Ser Ser Ser Leu Val  Ala Leu His Leu Ala  Ala Gln Ala
    3800                3805                3810

Leu Arg  Gln Gly Glu Cys Ser  Leu Ala Leu Ala Gly  Gly Val Thr
    3815                3820                3825

Val Met  Ala Thr Pro Gly Thr  Phe Val Glu Phe Ser  Arg Gln Arg
    3830                3835                3840

Gly Leu  Ala Ala Asp Gly Arg  Cys Lys Ala Phe Ala  Asp Gly Ala
    3845                3850                3855

Asp Gly  Thr Gly Trp Gly Glu  Gly Ala Gly Met Leu  Leu Val Glu
    3860                3865                3870

Arg Leu  Ser Asp Ala Arg Arg  Asn Gly His Pro Val  Leu Ala Val
    3875                3880                3885

Leu Arg  Gly Ser Ala Val Asn  Gln Asp Gly Ala Ser  Asn Gly Leu
    3890                3895                3900

Thr Ala  Pro Asn Gly Pro Ser  Gln Gln Arg Val Ile  Arg Gln Ala
    3905                3910                3915

Leu Ala  Asn Ala Arg Leu Glu  Pro Ser Glu Val Asp  Ala Val Glu
    3920                3925                3930
```

```
Ala His  Gly Thr Gly Thr Thr  Leu Gly Asp Pro Ile  Glu Ala Gln
    3935                 3940                 3945

Ala Leu  Leu Ala Thr Tyr Gly  Gln Asp Arg Glu Arg  Pro Leu Leu
    3950                 3955                 3960

Leu Gly  Ser Val Lys Ser Asn  Ile Gly His Thr Gln  Ala Ala Ala
    3965                 3970                 3975

Gly Val  Ala Gly Val Ile Lys  Met Val Leu Ala Met  Arg His Gly
    3980                 3985                 3990

Thr Leu  Pro Arg Thr Leu His  Val Asp Thr Pro Thr  Ser Arg Val
    3995                 4000                 4005

Asp Trp  Ala Ala Gly Arg Ile  Glu Leu Ala Thr Glu  Pro Thr Gln
    4010                 4015                 4020

Trp Pro  Glu Thr Gly Gly Pro  Arg Arg Ala Ala Val  Ser Ser Phe
    4025                 4030                 4035

Gly Met  Ser Gly Thr Asn Ala  His Val Val Leu Glu  Gln Ala Glu
    4040                 4045                 4050

Ala Val  Glu Thr Arg Asp Glu  Thr Ser Pro Gly Leu  Leu Gly Asp
    4055                 4060                 4065

Val Val  Ala Trp Pro Leu Ser  Ala Lys Glu Pro Glu  Ala Val Ala
    4070                 4075                 4080

Ala Gln  Ala Ala Arg Leu Lys  Ser Phe Leu Thr Gly  Glu Arg Pro
    4085                 4090                 4095

Ala Asp  Val Ala Tyr Ser Leu  Ala Thr Ala Arg Thr  Thr Leu Glu
    4100                 4105                 4110

His Arg  Ala Val Val Val Gly  Glu Asp Pro Ile Ala  Gly Leu Ala
    4115                 4120                 4125

Ala Leu  Ala Ala Gly Glu Pro  Ser Gly Ser Val Val  Thr Gly Thr
    4130                 4135                 4140

Ala Thr  Ser Gly Lys Ala Val  Phe Val Phe Pro Gly  Gln Gly Ser
    4145                 4150                 4155

Gln Trp  Ala Gly Met Ala Val  Glu Leu Leu Ala Ser  Ala Pro Val
    4160                 4165                 4170

Phe Ala  Glu Ser Met Ala Glu  Cys Glu Ala Ala Leu  Leu Ser Tyr
    4175                 4180                 4185

Val Asp  Trp Lys Leu Thr Glu  Val Leu Ser Asp Ala  Thr Ala Leu
    4190                 4195                 4200

Glu Arg  Val Asp Val Val Gln  Pro Ala Leu Phe Ala  Val Met Val
    4205                 4210                 4215

Ser Leu  Ala Arg Leu Trp Arg  Ala Ser Gly Ile Glu  Pro Ala Ala
    4220                 4225                 4230
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Val Val  Gly His Ser Gln Gly  Glu Ile Ala Ala Ala  Cys Val Ala
    4235                 4240                 4245

Gly Ala  Leu Ser Leu Asp Asp  Ala Ala Arg Val Val  Cys Leu Arg
    4250                 4255                 4260

Ser Lys  Ala Ile Thr Ala Leu  Ser Gly Arg Gly Gly  Met Val Ser
    4265                 4270                 4275

Val Ala  Ala Pro Glu Ala Gln  Val Arg Glu Ile Leu  Pro Glu Gly
    4280                 4285                 4290

Val Ser  Leu Ala Ala Val Asn  Gly Pro Ala Ser Val  Val Val Ser
    4295                 4300                 4305

Gly Asp  Val Ala Gly Leu Asp  Ala Leu Met Thr Ala  Cys Glu Ala
    4310                 4315                 4320

Ser Gly  Leu Arg Ala Lys Arg  Ile Pro Val Asp Tyr  Ala Ser His
    4325                 4330                 4335

Ser Ala  His Val Asp Ala Ile  Glu Gln Asp Val Leu  Ala Ala Leu
    4340                 4345                 4350

Asp Gly  Ile Glu Pro Arg Ala  Pro Glu Ile Pro Phe  Tyr Ser Thr
    4355                 4360                 4365

Val Ala  Gly Glu Pro Leu Asp  Pro Val Val Asp Ala  Ala Tyr Trp
    4370                 4375                 4380

Phe Arg  Asn Leu Arg Gly Thr  Val His Phe Gly Gln  Ala Val Arg
    4385                 4390                 4395

Arg Leu  Leu Asp Asp Gly Phe  Arg Phe Phe Val Glu  Ala Ser Pro
    4400                 4405                 4410

His Pro  Val Leu Val Thr Gly  Ile Ala Asp Thr Ala  Glu Asp Ala
    4415                 4420                 4425

Gly Glu  Arg Ala Val Ala Val  Gly Ser Leu Arg Arg  Asp Glu Gly
    4430                 4435                 4440

Gly Pro  Leu Arg Phe Leu Thr  Ser Leu Ala Glu Ala  His Val His
    4445                 4450                 4455

Gly Leu  Ser Pro Asp Trp Ala  Ala Leu Ala Pro Gly  Thr Arg Val
    4460                 4465                 4470

Asp Leu  Pro Thr Tyr Ala Phe  Gln His Glu His Tyr  Trp Leu Arg
    4475                 4480                 4485

Thr Arg  Ser Ser Ala Asp Pro  Gly Gln Ala Gly Leu  Asp Asp Gly
    4490                 4495                 4500

Gly His  Pro Leu Leu Gly Ala  Val Val Pro Leu Ala  Gly Ser Asp
    4505                 4510                 4515

Gly Leu  Val Ala Thr Gly Arg  Ile Ser Ala Arg Asn  Gln Thr Trp
    4520                 4525                 4530

Leu Pro  Asp His Ala Val Gly  Gly Ala Leu Leu Leu  Pro Gly Ala
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    4535                4540                4545

Ala Leu  Val Asp Leu Ala Leu  Thr Val Gly Glu Arg  Thr Gly Cys
    4550                4555                4560

Gly Arg  Ile Ala Glu Leu Thr  Ile Glu Ala Pro Leu  Val Leu Gly
    4565                4570                4575

Glu Ser  Gly Ser Ala Arg Leu  Gln Val Thr Val Gly  Ala Ser Ala
    4580                4585                4590

Asp Asp  Gly Thr Arg Glu Val  Ala Val Tyr Ser Arg  Asp Glu Thr
    4595                4600                4605

Ala Gly  Thr Asp Trp Ile Arg  His Ala Thr Gly Leu  Leu Ala Ala
    4610                4615                4620

Asp Gly  Glu Thr Pro Val Ala  Asp Leu Thr Gln Trp  Pro Pro Ala
    4625                4630                4635

Gly Ala  Glu Pro Ile Ser Leu  Glu Gly His Tyr Glu  Gly Leu Ala
    4640                4645                4650

Glu Leu  Gly Tyr Gly Tyr Gly  Pro Ala Phe Arg Gly  Leu Arg Ala
    4655                4660                4665

Val Trp  Arg Arg Gly Asp Asp  Val Phe Ala Glu Val  Ala Leu Pro
    4670                4675                4680

Glu Asp  Arg Ile Ala Glu Ala  Ala Ala Phe Gly Leu  His Pro Ala
    4685                4690                4695

Leu Leu  Asp Ala Ala Leu His  Ala Leu Gly Phe Gly  Met Leu Pro
    4700                4705                4710

Asp Asp  Gly Arg Leu Arg Leu  Pro Phe Ala Trp Asn  Glu Val Ser
    4715                4720                4725

Leu Ser  Ala Val Gly Ala Pro  Ser Leu Arg Val Arg  Leu Ser Pro
    4730                4735                4740

Ala Gly  Glu Asp Ala Val Ala  Val Asp Leu Ala Asp  Thr Ala Gly
    4745                4750                4755

Ala Pro  Val Ala Ser Ile Gly  Ser Val Val Phe Arg  Pro Val Ala
    4760                4765                4770

Glu Ala  Gln Leu Ala Gly Ala  Arg Arg Asp Pro Ala  Asp Ser Leu
    4775                4780                4785

Phe Gln  Ile Gln Trp Thr Asp  Leu Ser Ala Lys Asp  Val Val Ala
    4790                4795                4800

Pro Ala  Val Val Val Leu Gly  Glu Asp Cys Ala Asp  Leu Ala Glu
    4805                4810                4815

Leu Ala  Ala Asp Leu Asp Ala  Gly Arg Pro Ala Pro  Asp Val Val
    4820                4825                4830

Leu Thr  Thr Cys Ala Pro Val  Thr Gly Asp Ile Ala  Glu Gly Ala
    4835                4840                4845
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His Ala  Ala Ala Arg Asp Ala  Leu Thr Leu Val Gln  Asn Trp Leu
    4850                 4855                 4860

Ala Asp  Glu Arg Phe Ser Gly  Ala Arg Leu Val Phe  Arg Thr Ser
    4865                 4870                 4875

Gly Ala  Val Ser Val Ala Ala  Asp Glu Pro Val Ser  Asp Pro Ala
    4880                 4885                 4890

Asn Ala  Thr Val Trp Gly Leu  Val Arg Thr Ala Gln  Glu Glu Asn
    4895                 4900                 4905

Pro Gly  Arg Phe Gly Leu Leu  Asp Thr Asp Gly Ser  Glu Ala Val
    4910                 4915                 4920

Leu Gly  Ala Ala Leu Ala Leu  Asp Glu Pro Gln Leu  Ala Leu Arg
    4925                 4930                 4935

Ala Gly  Thr Val Leu Gly Ala  Arg Leu Val Lys Ala  Ser Ala Asp
    4940                 4945                 4950

Thr Ala  Leu Val Pro Pro Pro  Gly Ser Arg Ala Trp  Thr Val Asp
    4955                 4960                 4965

Thr Leu  Gly Gly Gly Thr Leu  Glu Asn Leu Val Leu  Arg Asp Arg
    4970                 4975                 4980

Pro Asp  Leu Leu Ala Pro Leu  Ala Asp Gly Gln Val  Arg Ile Ala
    4985                 4990                 4995

Val Arg  Ser Ala Gly Leu Asn  Phe Arg Asp Val Val  Val Ala Leu
    5000                 5005                 5010

Gly Leu  Val Pro Gly Gln Glu  Gly Ile Gly Gly Glu  Gly Ala Gly
    5015                 5020                 5025

Val Val  Thr Glu Thr Gly Pro  Gly Val Thr Asp Leu  Ala Pro Gly
    5030                 5035                 5040

Asp Arg  Val Leu Gly Met Phe  Asp Ala Ser Phe Gly  Pro Ile Ala
    5045                 5050                 5055

Val Ala  Asp Arg Lys Leu Ile  Ala Pro Val Pro Asp  Asp Trp Ser
    5060                 5065                 5070

Phe Thr  Glu Ala Ala Ser Ala  Pro Val Ala Phe Leu  Thr Ala Tyr
    5075                 5080                 5085

Val Gly  Leu Ala Asp Leu Gly  Glu Leu Arg Pro Gly  Gln Thr Val
    5090                 5095                 5100

Leu Ile  His Ala Ala Ala Gly  Gly Val Gly Met Ala  Ala Val Gln
    5105                 5110                 5115

Leu Ala  Arg His Phe Gly Ala  Glu Ile Tyr Val Thr  Ala Ser Pro
    5120                 5125                 5130

Ala Lys  Trp Asp Thr Leu Arg  Ala Met Gly Phe Asp  Asp Asp His
    5135                 5140                 5145
```

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Ile Ala  Ser Ser Arg Thr Leu  Asp Phe Glu Asp Lys  Ile Arg Glu
    5150                 5155                 5160

Ala Thr  Gly Gly Arg Gly Val  Asp Leu Val Leu Asp  Ser Leu Ala
    5165                 5170                 5175

Arg Glu  Phe Val Asp Ala Ser  Leu Arg Leu Val Arg  Glu Gly Gly
    5180                 5185                 5190

Arg Phe  Val Glu Met Gly Lys  Thr Asp Ile Arg Asp  Ala Asp Glu
    5195                 5200                 5205

Val Ala  Ala Ala His Pro Gly  Val Thr Tyr Arg Ala  Phe Asp Leu
    5210                 5215                 5220

Ile Asp  Ser Gly His Asp Arg  Ile Gln Glu Ile Leu  Gly Glu Leu
    5225                 5230                 5235

Leu Ala  Leu Ala Asp Lys Asp  Val Val Arg Pro Leu  Pro Thr Thr
    5240                 5245                 5250

Ala Trp  Asp Val Arg Arg Ala  Pro Glu Ala Phe Arg  Phe Leu Ser
    5255                 5260                 5265

Gln Ala  Lys His Thr Gly Lys  Ile Val Leu Glu Pro  Pro Ala Val
    5270                 5275                 5280

Leu Asp  Pro Glu Gly Thr Val  Leu Ile Thr Gly Gly  Thr Gly Val
    5285                 5290                 5295

Leu Gly  Gly Leu Phe Ala Arg  His Leu Val Thr Ala  His Gly Val
    5300                 5305                 5310

Arg Arg  Leu Leu Leu Thr Ser  Arg Arg Gly Leu Asp  Ala Glu Gly
    5315                 5320                 5325

Ala Arg  Glu Leu Val Ala Asp  Leu Thr Gly Leu Gly  Ala Thr Val
    5330                 5335                 5340

Thr Val  Val Ala Cys Asp Val  Ala Asp Arg Ala Ala  Val Ala Gly
    5345                 5350                 5355

Leu Leu  Gly Ser Val Pro Pro  Glu His Pro Leu Thr  Ala Val Val
    5360                 5365                 5370

His Thr  Ala Gly Val Leu Asp  Asp Gly Leu Ile Pro  Ala Leu Thr
    5375                 5380                 5385

Pro Asp  Arg Leu Gly Thr Val  Phe Arg Pro Lys Val  Asp Ala Ala
    5390                 5395                 5400

Val His  Leu His Glu Leu Thr  Arg Asp Leu Gly Leu  Ala Ala Phe
    5405                 5410                 5415

Val Leu  Phe Ser Ser Ser Ala  Ala Thr Phe Gly Ala  Ala Gly Gln
    5420                 5425                 5430

Gly Asn  Tyr Ala Ala Ala Asn  Ala Phe Leu Asp Ala  Leu Ala Gln
    5435                 5440                 5445

His Arg  Arg Ala Glu Gly Leu  Ala Gly Gln Ala Leu  Ala Trp Gly
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Phe Trp Ala Glu Arg Ser Ala Met Thr Gly His Leu Asp Glu Ala
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Asp Val Ala Arg Met Lys Arg Ser Gly Val Ser Pro Leu Ser Ser
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Val Asp Gly Leu Ala Leu Phe Asp Ala Ala Ala Glu Arg Asp Val
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Ala Ala Leu Val Pro Val His Leu Asp Thr Ala Ala Leu Arg Gly
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Gln Thr Glu Val Pro Ala Leu Leu Arg Val Leu Ala Gly Ala Pro
5525 5530 5535

Ala Lys Arg Val Ala Gly Ala Ala Ala Thr Ser Gly Pro Ser Leu
5540 5545 5550

Ala Gln Arg Leu Ala Ala Leu Pro Ala Ala Asp Arg Glu Pro Phe
5555 5560 5565

Leu Leu Asp Leu Val Arg Ser His Ala Ala Ala Ala Leu Gly His
5570 5575 5580

Ala Ser Val Ala Lys Val Gly Pro Glu Leu Ala Phe Arg Asp Leu
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Gly Phe Asp Ser Leu Thr Ala Val Glu Leu Arg Asn Arg Leu Gly
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Ala Ala Thr Gly Leu Arg Leu Pro Ser Thr Leu Val Phe Asp Gln
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Pro Ser Pro Ala Ala Leu Ala Arg His Leu Leu Ala Glu Leu Gly
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Glu Pro Ala Gly Ala Glu Pro Glu Val Ala Val Leu Ala Asp Leu
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Asp Arg Leu Glu Thr Ala Leu Ala Ala Ala Val Thr Asp Asp Glu
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Thr Ala Asp Arg Ile Thr Asp Arg Leu Arg Ala Val Leu Ala Arg
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Trp Thr Glu Ala Arg Gly Pro Ala Glu Asp Glu Gly Asp Gly Asp
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Glu Phe Gly Arg Ser
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35 40 45

Val Arg Ser Pro Glu Gln Leu Trp Asp Leu Val Ala Ser Gly Thr Asp
50 55 60

Ala Leu Ser Glu Phe Pro Gly Asp Arg Gly Trp Asp Leu Gly Gly Leu
65 70 75 80

Phe Asp Pro Asp Pro Asp Thr Pro Gly Lys Thr Tyr Val Ser Glu Gly
85 90 95

Gly Phe Leu Tyr Glu Ala Gly Asp Phe Asp Ala Ala Phe Phe Gly Ile
100 105 110

Ser Pro Arg Glu Ala Gln Ala Met Asp Pro Gln Gln Arg Leu Leu Leu
115 120 125

Glu Ala Ala Trp Glu Val Leu Glu Arg Ala Gly Ile Asp Pro Ala Thr
130 135 140

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Leu Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Val Ile His Asn Asp
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Tyr Thr Gly Val Leu Thr Asp Ile Pro Pro Glu Leu Glu Pro Tyr Leu
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Gly Asn Gly Asn Phe Ser Ser Val Ala Ser Gly Arg Ile Ala Tyr Thr
            180                 185                 190

Leu Gly Leu Glu Gly Pro Ala Val Ser Val Asp Thr Ala Cys Ser Ser
        195                 200                 205

Ser Leu Val Ala Leu His Leu Ala Ala Gln Ser Leu Arg Arg Glu Glu
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Cys Thr Leu Ala Leu Val Gly Gly Val Asn Val Met Thr His Pro Ala
225                 230                 235                 240

Ala Phe Val Asp Phe Ser Arg Gln Arg Gly Leu Ala Ala Asp Gly Arg
                245                 250                 255

Cys Lys Ala Phe Ala Asp Ala Ala Asp Gly Thr Gly Trp Gly Glu Gly
            260                 265                 270

Val Gly Met Leu Leu Val Glu Arg Leu Ser Asp Ala Gln Arg Asn Gly
        275                 280                 285

His Gln Val Leu Ala Val Leu Arg Gly Ser Ala Ile Asn Gln Asp Gly
    290                 295                 300

Ala Ser Asn Gly Leu Thr Ala Pro Asn Gly Pro Ala Gln Gln Arg Val
305                 310                 315                 320

Ile Arg Gln Ala Leu Ala Asp Ala Arg Leu Ser Pro Gly Gln Val Asp
                325                 330                 335

Val Val Glu Gly His Gly Thr Gly Thr Thr Leu Gly Asp Pro Ile Glu
            340                 345                 350

Ala Gln Ala Leu Leu Ala Thr Tyr Gly Gln Asp Arg Glu Arg Pro Leu
        355                 360                 365

Leu Leu Gly Ser Leu Lys Ser Asn Ile Gly His Thr Gln Ala Ala Ala
    370                 375                 380

Gly Val Gly Gly Val Ile Lys Met Val Gln Ala Ile Arg His Gly Ile
385                 390                 395                 400

Ala Pro Arg Thr Leu His Val Asp Ala Pro Ser Ser His Val Asp Trp
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Ser Ala Gly Glu Val Ser Leu Leu Thr Gly Glu Gln Pro Trp Pro Glu
            420                 425                 430

Thr Gly Glu Pro Arg Arg Ala Gly Val Ser Ser Phe Gly Ile Ser Gly
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Thr Asn Ala His Val Ile Leu Glu Gln Ala Pro Ala Val Glu Val Glu
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Ser Leu Val Asp Thr Arg Val Leu Asp Ser Ala Val Leu Pro Phe Val
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Leu Ser Gly Arg Ser Glu Glu Ala Leu Ala Ala Gln Ala Ser Lys Leu
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Leu Ala Glu Thr Arg Ser Ala Leu Pro His Arg Ala Val Val Leu Ala
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Glu Asp Leu Gly Glu Leu Leu Gly Gly Leu Arg Ser Leu Ala Glu Gly
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Glu Pro Ala Ala Arg Val Leu Thr Gly Thr Ala Glu Ala Gly Lys Ala
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Val Phe Val Phe Pro Gly Gln Gly Ser Gln Trp Val Gly Met Ala Glu
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Glu Leu Leu Leu Ser Ala Pro Val Phe Ala Glu Ser Met Ala Glu Cys
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Glu Arg Ala Leu Ser Ser Phe Val Asp Trp Lys Leu Ser Asp Val Leu
595 600 605

Ser Asp Ala Ala Ala Leu Glu Arg Val Asp Val Val Gln Pro Val Leu
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Phe Ala Val Met Val Ser Leu Ala Arg Leu Trp Arg Ala Cys Gly Val
625 630 635 640

Glu Pro Ala Ala Val Val Gly His Ser Gln Gly Glu Ile Ala Ala Ala
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Cys Val Ala Gly Ala Leu Ser Leu Asp Asp Ala Ala Arg Leu Val Cys
660 665 670

Leu Arg Ser Lys Ala Ile Leu Ala Leu Ser Gly Arg Gly Gly Met Val
675 680 685

Ser Val Ala Ala Ser Glu Asp Arg Val Arg Glu Leu Leu Pro Ala Gly
690 695 700

Val Ser Val Ala Ala Val Asn Gly Pro Ser Ala Val Val Val Ser Gly
705 710 715 720

Asp Val Ala Gly Leu Glu Ala Leu Leu Lys Arg Cys Glu Leu Leu Asp
725 730 735

Val Arg Ala Lys Arg Ile Pro Val Asp Tyr Ala Ser His Ser Ala His
740 745 750

Val Asp Ala Ile Glu Gln Glu Val Leu Ser Ala Leu Ala Gly Ile Ser
755 760 765

Pro Gln Ala Pro Val Ile Pro Phe Tyr Ser Thr Val Thr Asp Glu Pro
770 775 780

Leu Glu Leu Asp Ala Ala Tyr Trp Phe Arg Asn Leu Arg Gly Thr Val
785 790 795 800

Arg Phe Ala Ala Thr Val Asp Arg Leu Leu Glu Asp Gly Phe Arg Phe
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Phe Val Glu Ala Ser Pro His Pro Val Leu Val Pro Gly Ile Ser Glu
820 825 830

Glu Ala Ile Ala Leu Gly Ser Leu Arg Arg Gly Glu Gly Gly Ala Glu
835 840 845

Arg Phe Val Ala Ser Leu Ala Glu Ala His Thr Gln Gly Leu Ser Pro
850 855 860

Ser Trp Ser Ala Val Leu Pro Pro Ala Glu Arg Val Asp Leu Pro Thr
865 870 875 880

Tyr Ala Phe Gln His Lys Arg Phe Trp Leu Glu Ala Gly Thr Ala Ser
885 890 895

Gly Asp Ala Ser Ala Phe Gly Gln Thr Val Val Asp His Pro Leu Leu
900 905 910

Gly Ala Ala Leu Pro Leu Ala Asp Gly Asp Gly Leu Val Leu Thr Gly
915 920 925

Arg Ile Ser Pro Asp Thr Gln Pro Trp Leu Val Asp His Thr Val Leu
930 935 940

Asp Thr Val Leu Leu Pro Gly Thr Ala Phe Val Glu Leu Val Leu Arg
945 950 955 960

Ala Gly Arg Glu Ala Gly Cys Asp Gly Val Asp Glu Leu Thr Leu Glu
965 970 975

Ala Pro Leu Val Leu Asp Gly Pro Val Ala Leu Gln Val Val Leu Gly
980 985 990

Glu Pro Asp Glu Arg Gly Arg Arg Ala Val Ser Val His Ser Arg Pro
995 1000 1005

Glu Asp Ser Asp Glu Pro Trp Thr Arg Asn Ala Gln Gly Thr Leu
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Ser Ala Gly Thr Pro Ser Thr Val Ser Leu Ala Glu Trp Pro Pro
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Pro Gly Ala Ala Glu Ala Pro Glu Ser Asp Leu Tyr Asp Arg Phe
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Ala Glu Leu Gly Leu Ala Tyr Gly Pro Val Phe Gln Gly Leu Arg
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Ala Ala Trp Arg Gln Gly Asp Asp Val Phe Ala Glu Val Asp Leu
1070 1075 1080

Pro Glu Glu Glu Glu Ala Asp Arg Phe Gly Val His Pro Ala Leu
1085 1090 1095

Leu Asp Ala Ala Leu His Thr Leu Gly Leu Gly Ala Gln Asp Glu
1100 1105 1110

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Thr Val  Arg Leu Pro Phe Thr  Trp Ser Gly Val Thr  Leu His Ala
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Thr Gly  Ala Ser Lys Leu Arg  Val Arg Leu Thr Pro  Thr Ala Asp
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Gly Gly  Ser Leu Thr Val Ala  Asp Glu Thr Gly Ala  Pro Val Leu
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Thr Val  Gly Glu Leu Gly Leu  Arg Pro Ile Ser Pro  Ala Gln Leu
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Gly Arg  His Arg Asp Ser Leu  Phe Arg Leu Asp Trp  Val Pro Ala
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Pro Val  Gly Pro Ala Pro Glu  Glu Pro Gly Val Trp  Arg Cys Pro
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Glu Gly  Glu Leu Arg Pro Val  Leu Glu Glu Val Leu  Lys Arg Ile
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Gln Ala  Asp Ser Thr Ala Thr  Thr Val Val Leu Thr  Ser Gly Ala
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Val Ala  Ser Ala Ser Pro Asp  Pro Val Ala Ala Ala  Val Trp Gly
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Leu Val  Arg Ser Ala Gln Ala  Glu His Pro Gly Arg  Phe Val Leu
    1250                1255                1260

Ile Asp  Ala Arg Thr Glu Asp  Glu Val Arg Thr Ala  Leu Ala Thr
    1265                1270                1275

Gly Glu  Ala Gln Val Ala Val  His Asp Gly Lys Pro  Leu Val Pro
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Arg Leu  Ala Arg Val Ala Ala  Ala Asp Ala Gly Glu  Pro Asp Trp
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Thr Pro  Asp Asp Val Val Leu  Ile Thr Gly Gly Thr  Gly Arg Leu
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Gly Gln  Ala Leu Ala Arg His  Leu Ala Val Arg His  Gly Val Arg
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Gly Leu  Val Leu Thr Gly Arg  Thr Gly Gly Gly Ala  Glu Asp Leu
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Val Ala  Asp Leu Ala Glu Leu  Gly Thr Gln Val Thr  Val Ala Ala
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Cys Asp  Val Ala Asp Pro Asp  Ala Val Arg Ala Leu  Leu Ala Ala
    1370                1375                1380

His Pro  Val Thr Ala Val Val  His Ala Ala Ala Val  Leu Asp Asp
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Gly Leu  Val Asp Gly Leu Thr  Pro Asp Arg Leu Gly  Thr Val Leu
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Ala Pro  Lys Ala Asp Gly Ala  Arg Val Leu His Glu  Leu Ala Gly
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Pro Val  Arg Arg Phe Val Thr  Phe Ser Ser Ala Ala  Gly Val Phe
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Gly Asn  Pro Gly Gln Ala Gly  Tyr Ala Ala Ala Asn  Ala Tyr Ala
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Asp Ala  Leu Met Leu Arg Arg  Arg Ala Glu Gly Leu  Pro Gly Val
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Ser Leu  Ala Trp Gly Phe Trp  Ala Glu Arg Ser Lys  Leu Thr Gly
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Asp Leu  Asp Asp Thr Asp Val  Arg Arg Met Ala Arg  Ala Gly Val
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Thr Ala  Leu Ser Thr Glu Glu  Gly Leu Ala Leu Phe  Asp Ala Ala
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Val Ala  Gly Gly Asp Gly Leu  Leu Val Pro Ala Lys  Ile Asp Leu
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Thr Ala  Phe Arg Gly Arg Pro  Ala Ala Glu Ile Pro  Ala Leu Leu
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Gly Thr  Ala Glu Ala Leu Lys  Arg Asp Leu Ala Gly  Lys Pro Glu
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Ala Glu  Arg Val Arg Leu Leu  Glu Glu Val Val Arg  Ile Arg Val
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Ala Ala  Val Leu Gly His Glu  Ser Ala Asp Ala Ile  Ala Gly Asp
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Arg Gly  Phe Leu Glu Leu Gly  Phe Asp Ser Leu Thr  Ala Val Glu
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Leu Arg  Asn Arg Leu Ala Glu  Ala Thr Gly Leu Arg  Leu Pro Pro
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Thr Leu  Val Phe Asp Arg Pro  Asn Ala Gly Ala Leu  Ala Ala Tyr
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Leu Ala  Ala Glu Leu Ala Thr  Glu Thr Ala Gly Pro  Ala Leu Asp
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Ala Glu  Leu Asp Arg Phe Ala  Ala Ala Leu Thr Ala  Ala Asp Pro
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Gly Glu  Ala Glu Arg Ala Arg  Leu Ala Ala Arg Leu  Arg Ala Leu
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Leu Gly  Thr Leu Gln Gly Gly  Glu Asp Pro Ala Gly  Glu Ile Asp
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35 40 45

Val Arg Gly Pro Glu Gln Leu Trp Asp Leu Val Ala Ala Gly Thr Asp
50 55 60

Ala Val Gly Gly Phe Pro Ala Asp Arg Gly Trp Asp Val Glu Ala Leu
65 70 75 80

Tyr Asp Pro Asp Pro Ala Arg His Gly Lys Thr Tyr Thr Arg Glu Gly
85 90 95

Gly Phe Leu Tyr Asp Ala His Glu Phe Asp Ala Ala Phe Phe Gly Ile
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Ser Pro Arg Glu Ala Leu Thr Val Asp Pro Gln Gln Arg Leu Leu Leu
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Val Arg Gly Ser Arg Thr Gly Val Phe Ala Gly Val Met Tyr Asn Asp
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Tyr Gly Ser Arg Leu Asp Pro Arg Ala Glu Glu Leu Arg Glu Phe Glu
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Gly Tyr Leu Gly Asn Gly Ser Ala Gly Ser Val Ala Ser Gly Arg Val
180 185 190

Ala Tyr Thr Phe Gly Leu Glu Gly Pro Ala Val Thr Ile Asp Thr Ala
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Cys Ser Ser Ser Leu Val Ala Leu His Leu Ala Ala Glu Ser Leu Arg
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Arg Gly Glu Ser Thr Leu Ala Leu Ala Gly Gly Val Thr Val Met Ala
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Ser Pro Glu Thr Phe Val Glu Phe Ser Arg Gln Arg Gly Met Ala Pro
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Asp Gly Arg Cys Lys Pro Phe Ala Asp Ala Ala Asp Gly Thr Gly Trp
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Ala Glu Gly Ala Gly Ile Leu Leu Leu Glu Arg Leu Ser Asp Ala Arg

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2___

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

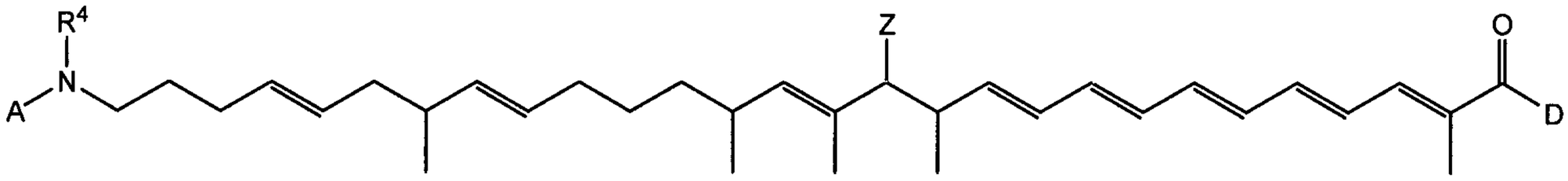
THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

NOTE: For additional volumes please contact the Canadian Patent Office.

We claim:

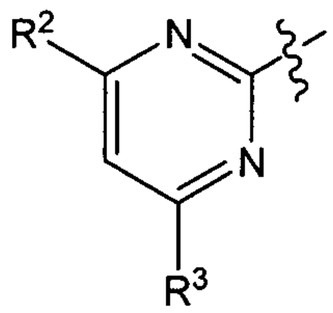
1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



Formula I

wherein,

A is selected from $-C(NH)NHR^1$, CH_3, H and



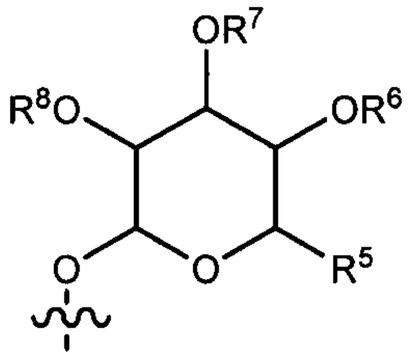
;

R^1 is selected from H, C_{1-6}alkyl, C_{6-10}aryl, $C(O)C_{1-6}$alkyl and $C(O)C_{6-10}$aryl;

R^2 and R^3 are each independently selected from H, C_{1-6} alkyl, C_{2-7} alkene and C_{6-10} aryl;

R^4 is selected from H and CH_3;

Z is OH; or Z is O when taken with adjacent carbon atom to form a carbonyl; or Z is a tetrahydropyranoxy of formula:



; wherein

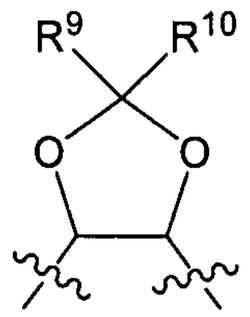
R^5 is selected from H, COOH, C_{1-6} alkyl and $C(O)OC_{1-6}$ alkyl;

R^6, R^7 and R^8 are each independently selected from H, C_{1-6} alkyl and

$C(O)C_{1-6}$ alkyl; or

R^6 , R^7 and R^8 may each independently be absent when the adjacent oxygen and carbon atoms are taken together to form a carbonyl; or

R^6 , R^7 and R^8 may each independently be a bond when any of two neighboring R^6 , R^7 and R^8 are taken together with attached oxygen and carbon atoms to form a 1,3-dioxolane ring of formula:



;

R^9 and R^{10} are each independently selected from H, C_{1-6} alkyl, C_{2-7} alkene and C_{6-10} aryl; or

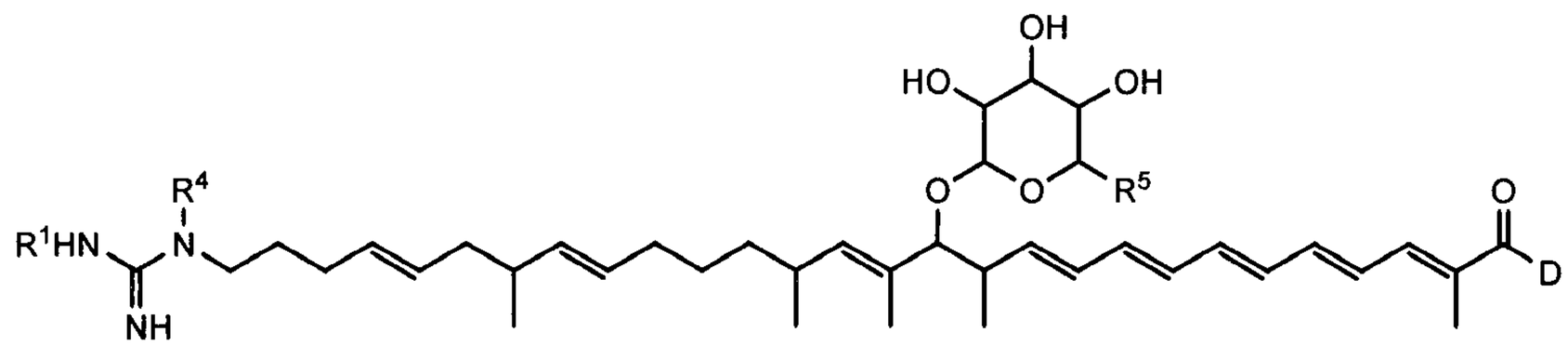
R^9 and R^{10} are taken together with adjacent carbon atom to form a ring having from 5 to 7 carbons;

D is selected from OH, NH_2, $NH(C_{1-3}alkyl)$, $N(C_{1-3}alkyl)_2$, $OC_{1-3}alkyl$ and

; and

R^{11} is selected from H and C_{1-3} alkyl.

2. An isolated compound of Formula II, or a pharmaceutically acceptable salt thereof:



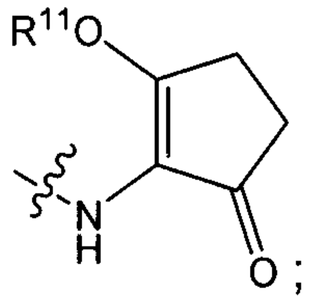
Formula II

wherein, R^1 is selected from H and $C(O)C_{1-3}$alkyl;

R^4 is selected from H and CH_3;

R^5 is selected from C(O)OH and $C(O)OC_{1-3}$alkyl;

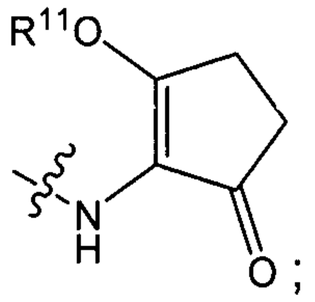
D is selected from OH and the cyclopentenone of the formula:



wherein R^{11} is selected from H and C_{1-3}alkyl.

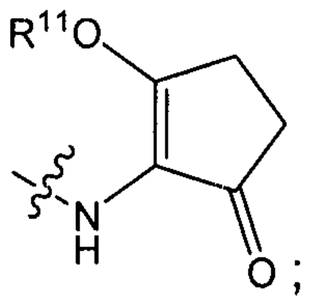
3. A compound of claim 2 wherein

wherein D is



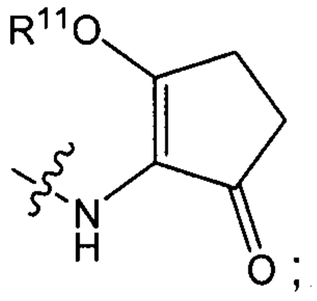
R^1 and R^{11} are H; R^4 is CH_3; and R^5 is C(O)OH, or a pharmaceutically acceptable salt thereof.

4. A compound of claim 2 wherein D is



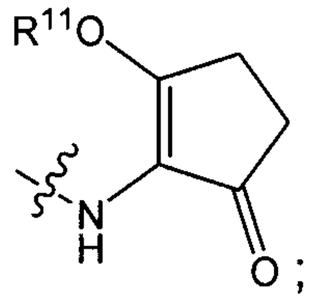
R^1, R^4 and R^{11} are H and R^5 is C(O)OH, or a pharmaceutically acceptable salt thereof.

5. A compound of claim 2 wherein D is



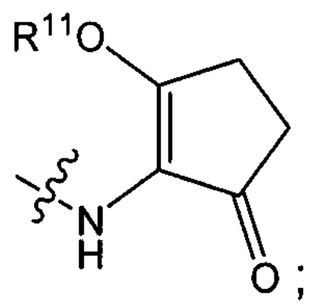
R^1 and R^{11} are H, R^4 is CH_3 and R^5 is $C(O)OCH_3$, or a pharmaceutically acceptable salt thereof.

6. A compound of claim 2 wherein D is



R^1 is H; R^4 and R^{11} are CH_3; and R^5 is C(O)OH; or a pharmaceutically acceptable salt thereof.

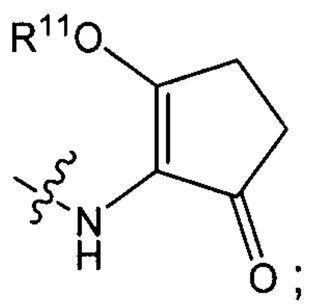
7. A compound of claim 2 wherein D is



R^1 is H; R^4 and R^{11} are CH_3; and R^5 is $C(O)OCH_3$; or a pharmaceutically acceptable salt thereof.

8. A compound of claim 2 wherein

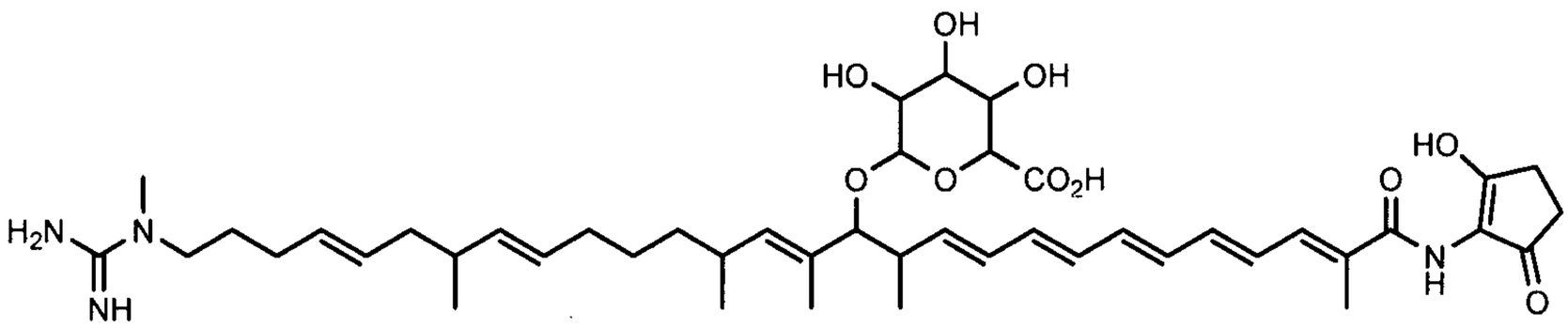
wherein D is



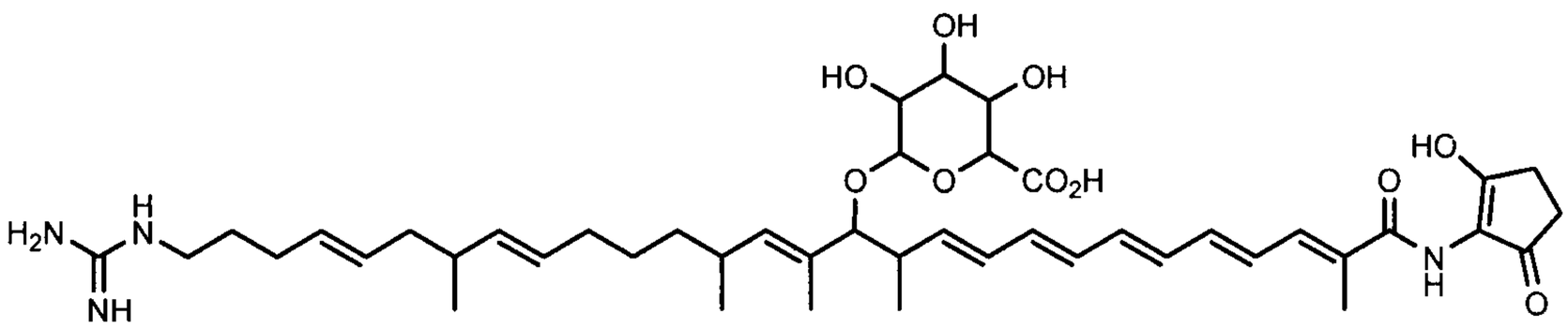
R^1 is $C(O)CH_3$; R^4 is CH_3; R^5 is C(O)OH; and R^{11} is H; or a pharmaceutically acceptable salt thereof.

9. The compound of claim 2, wherein D is OH, R^1 is H, R^4 is CH_3 and R^5 is C(O)OH, or a pharmaceutically acceptable salt thereof.

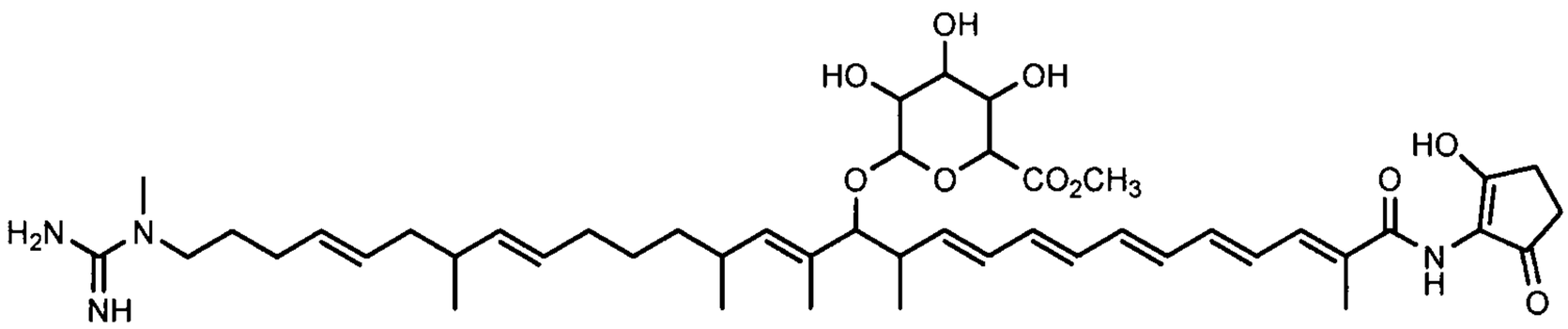
10. A compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:



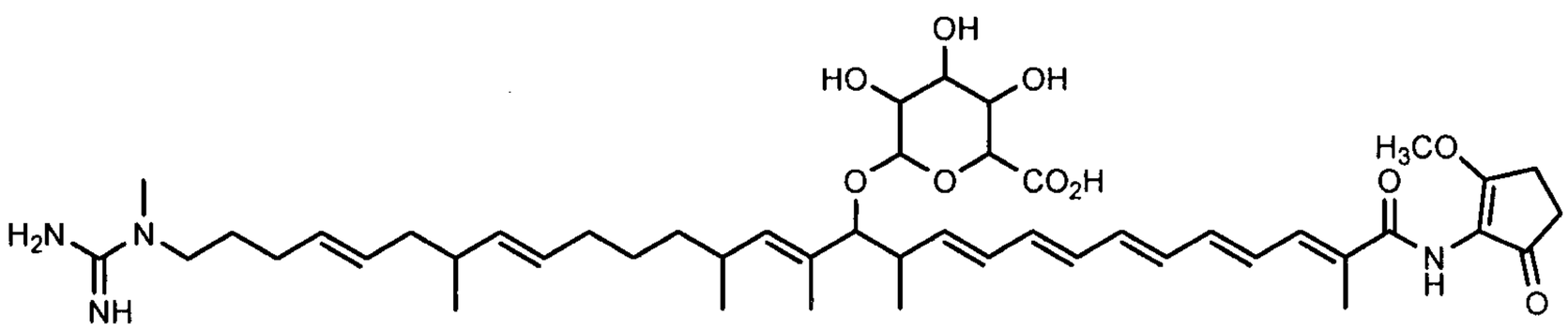
Compound 1;



Compound 2;



Compound 3;



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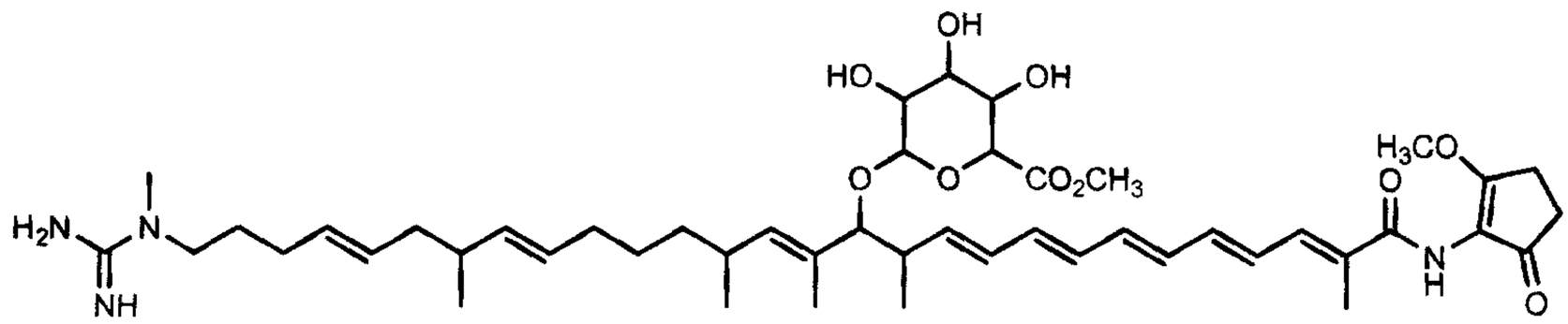

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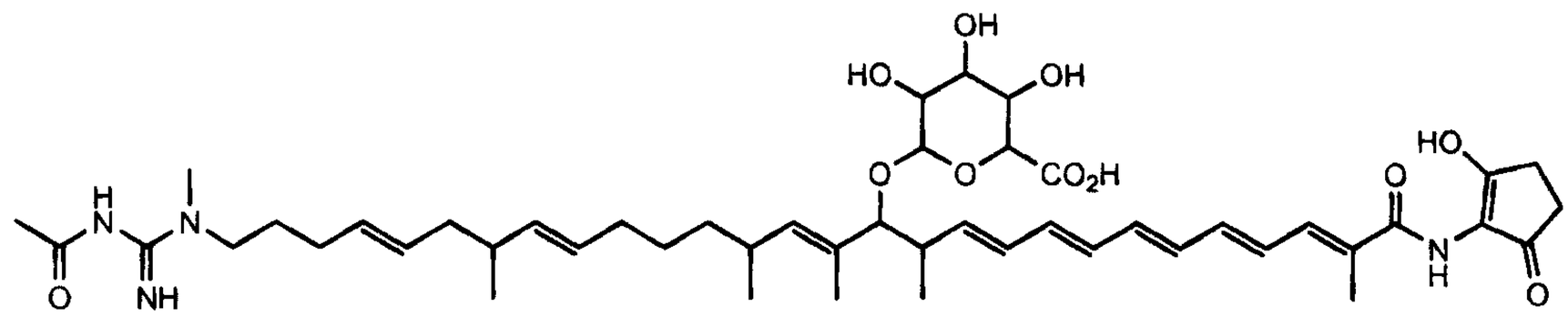

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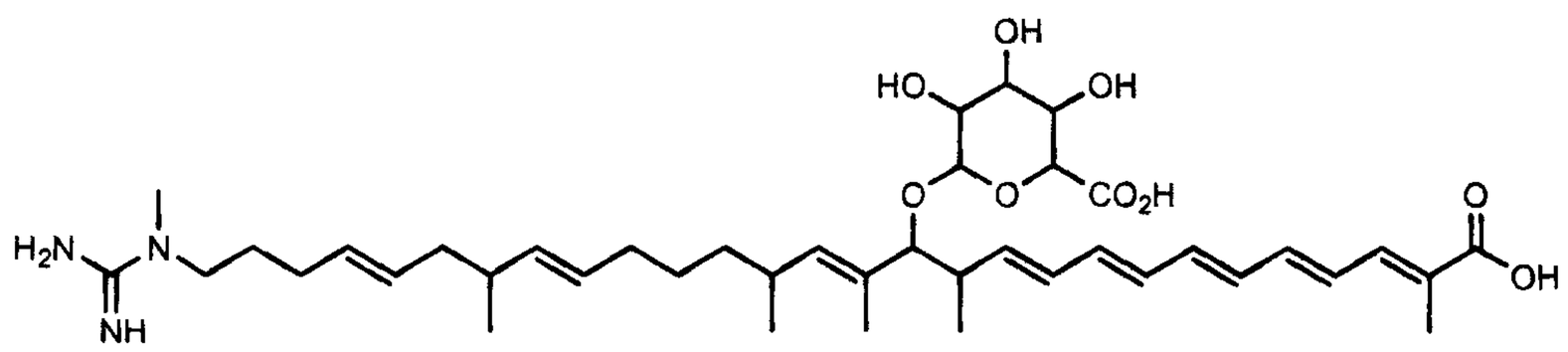

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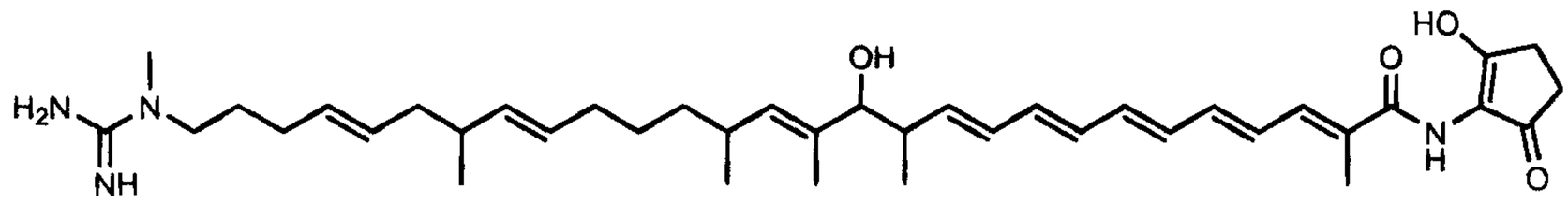

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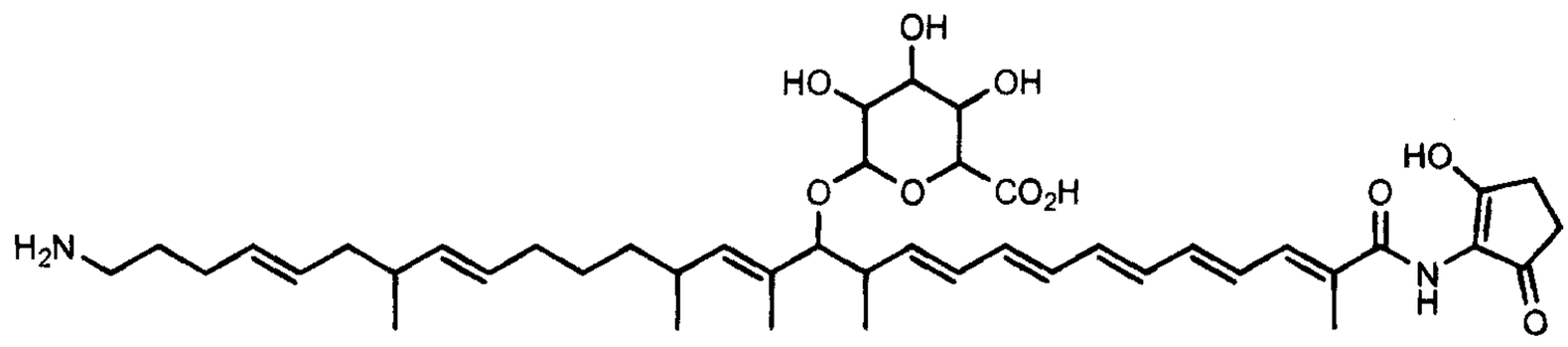

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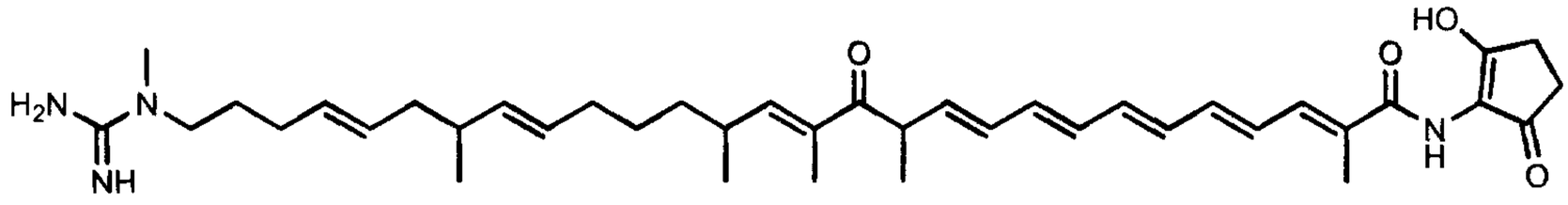

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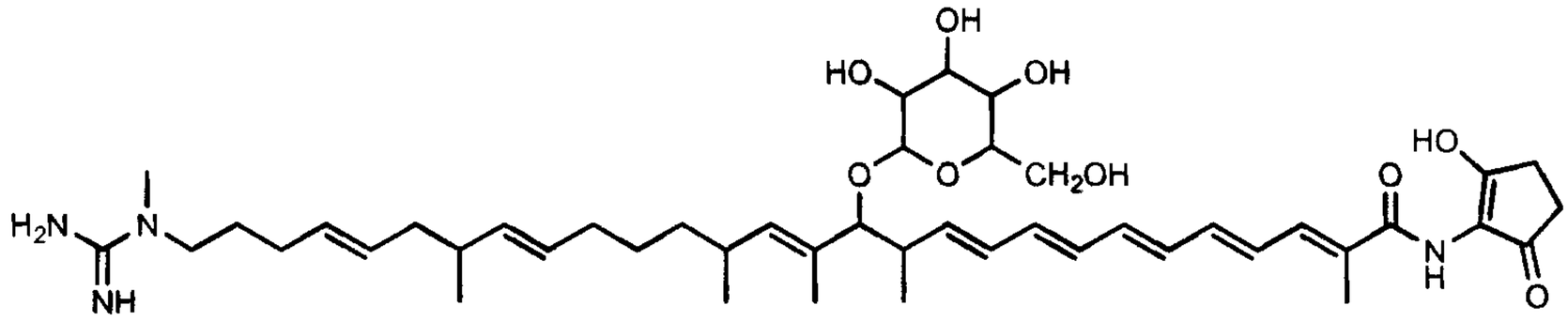

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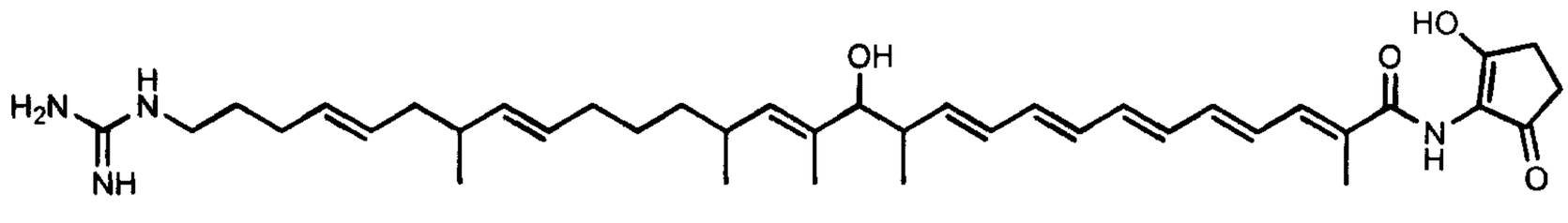

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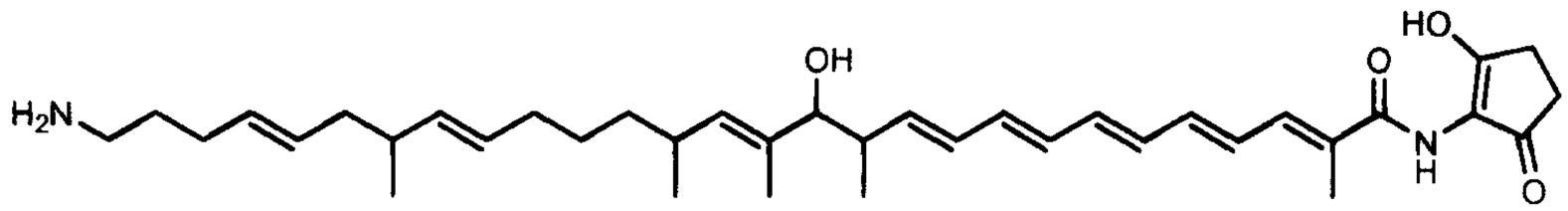
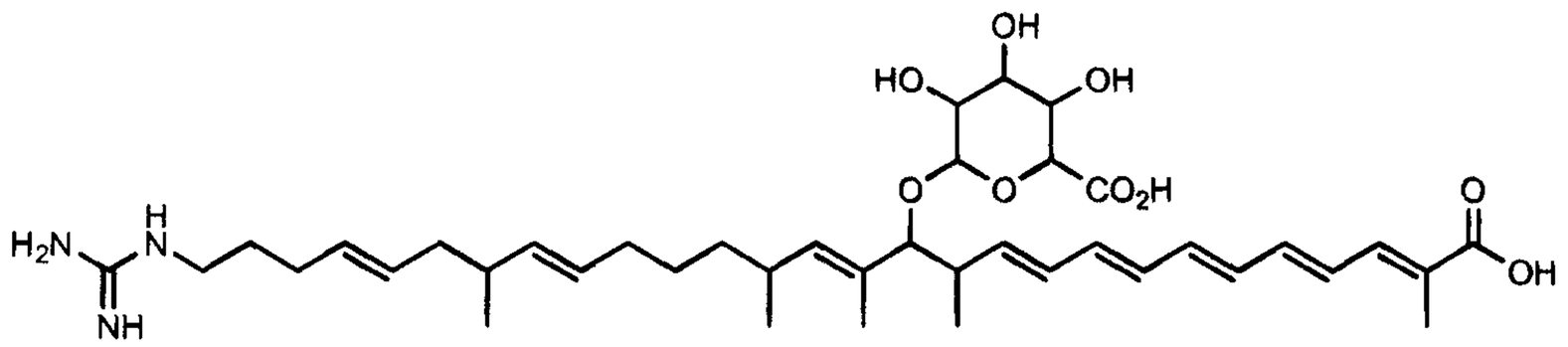


Compound 13;



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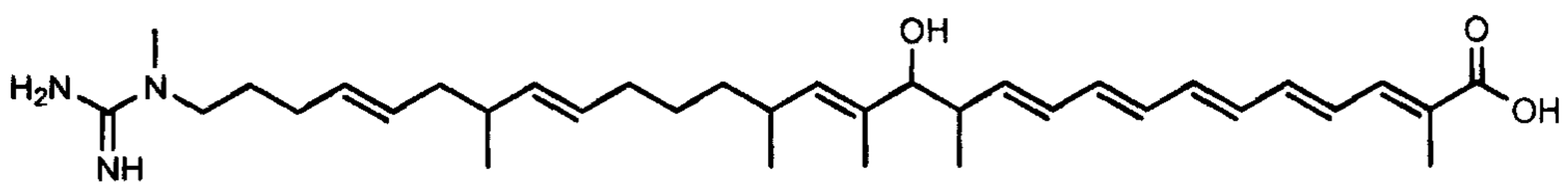

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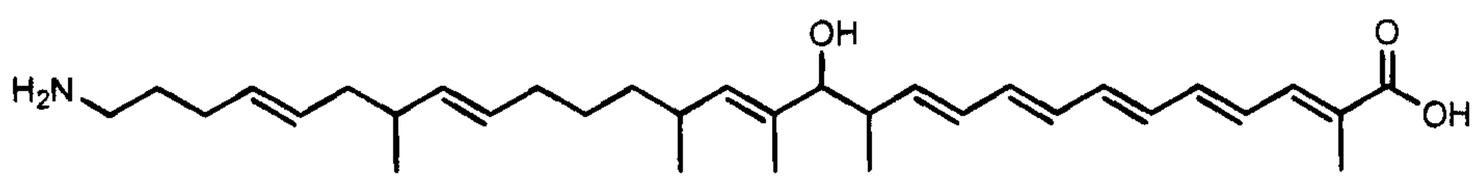

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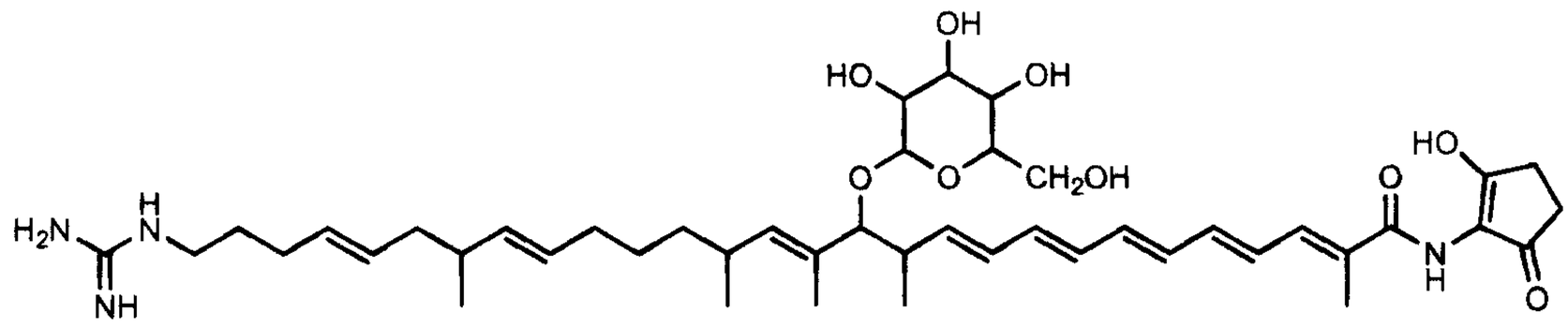

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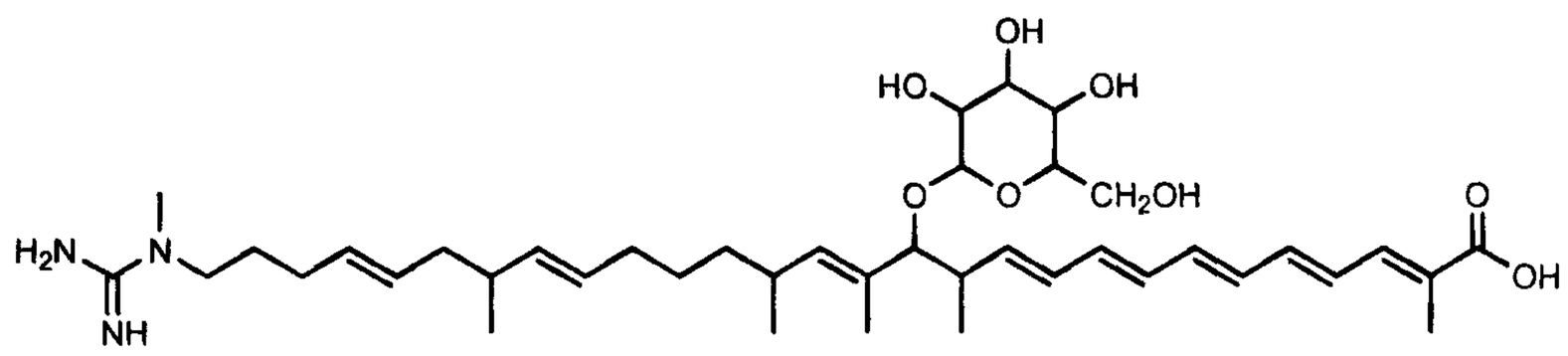

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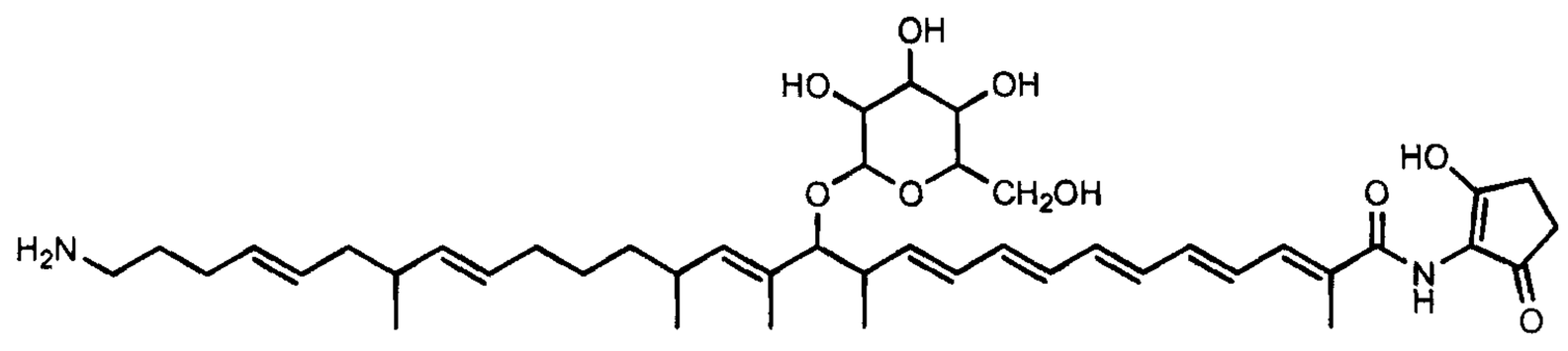

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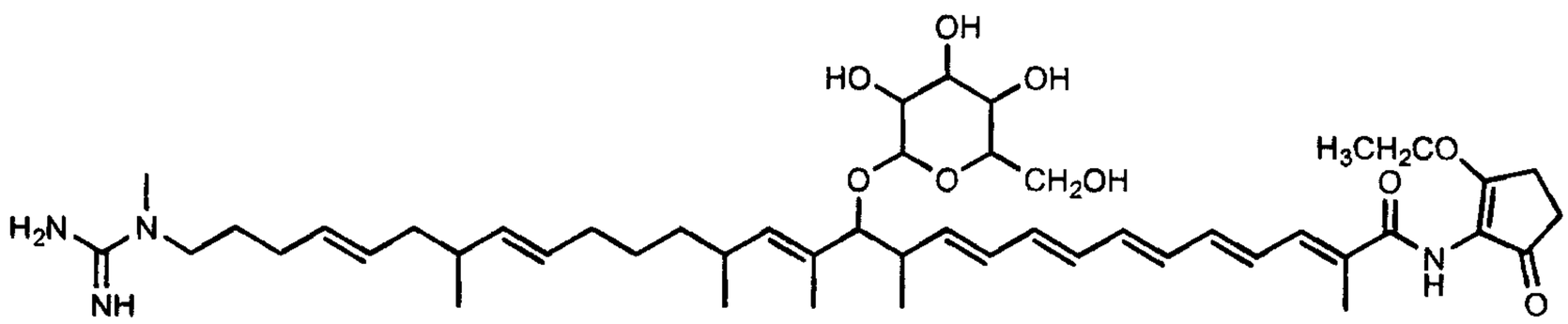

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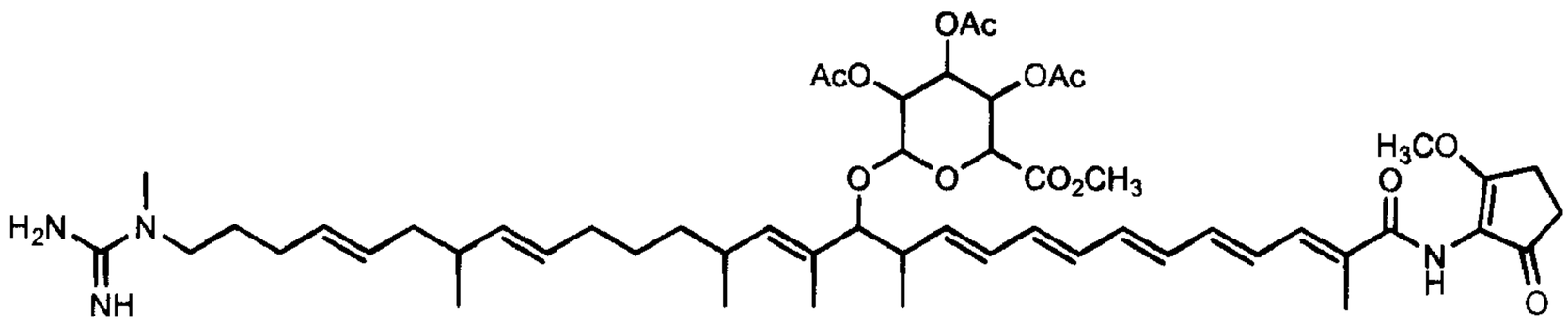

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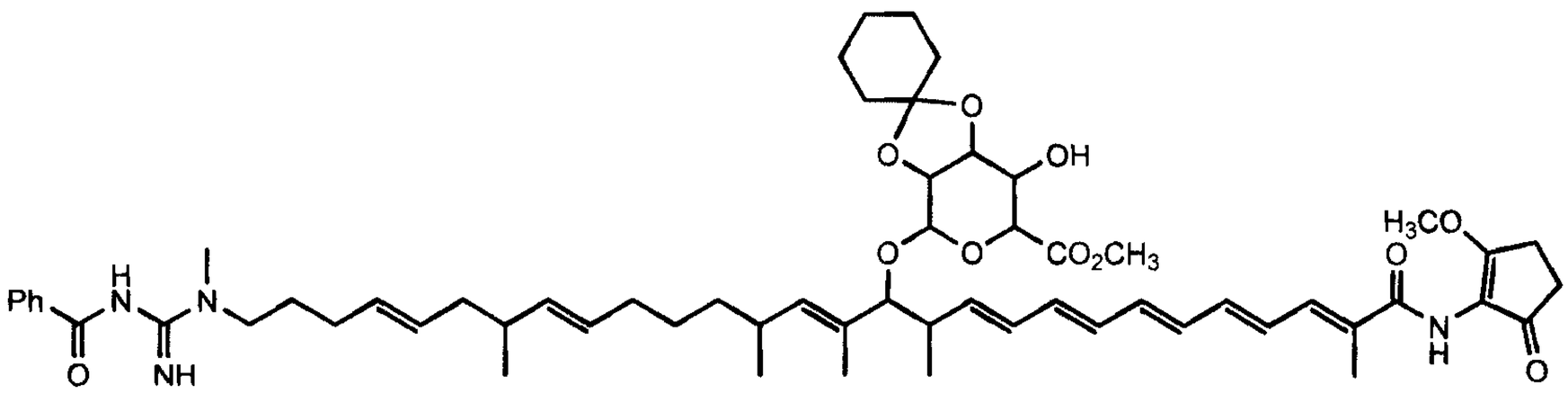

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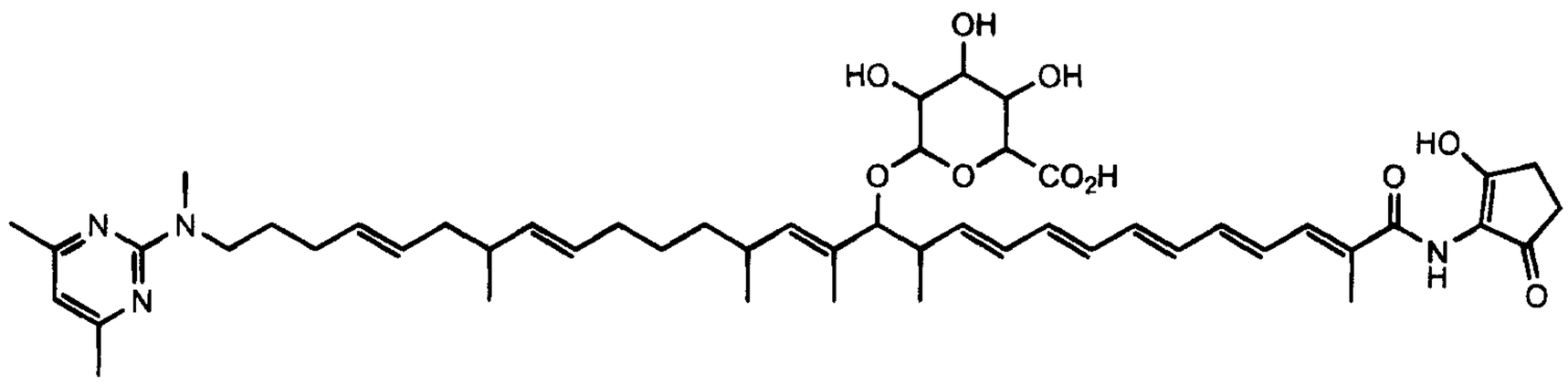

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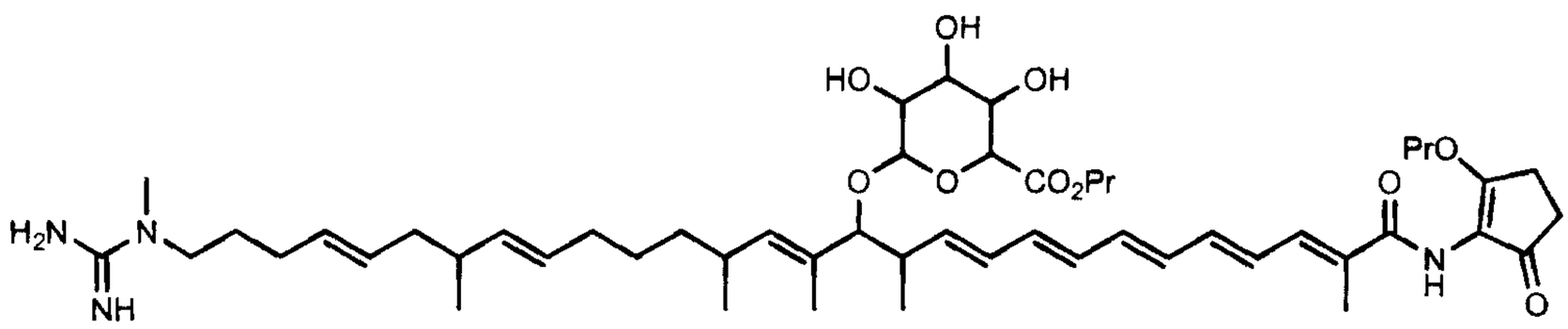

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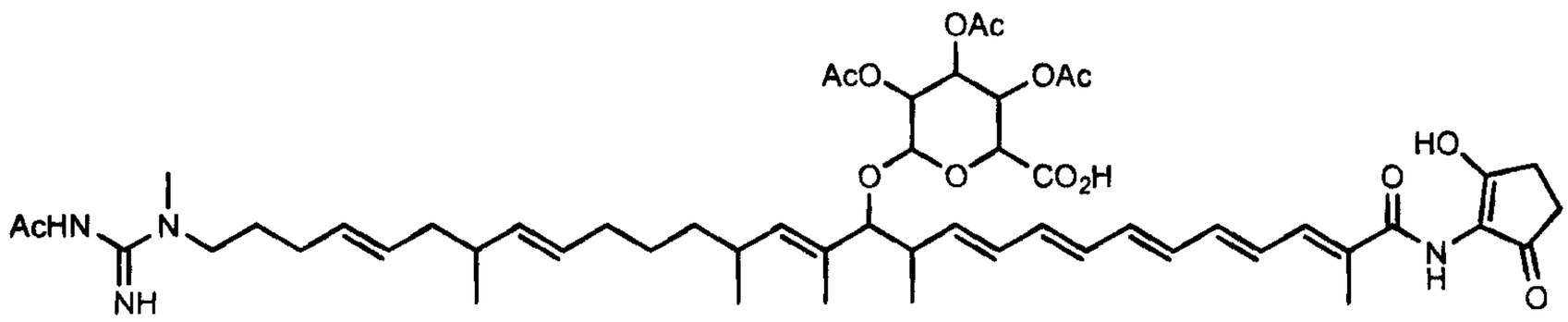

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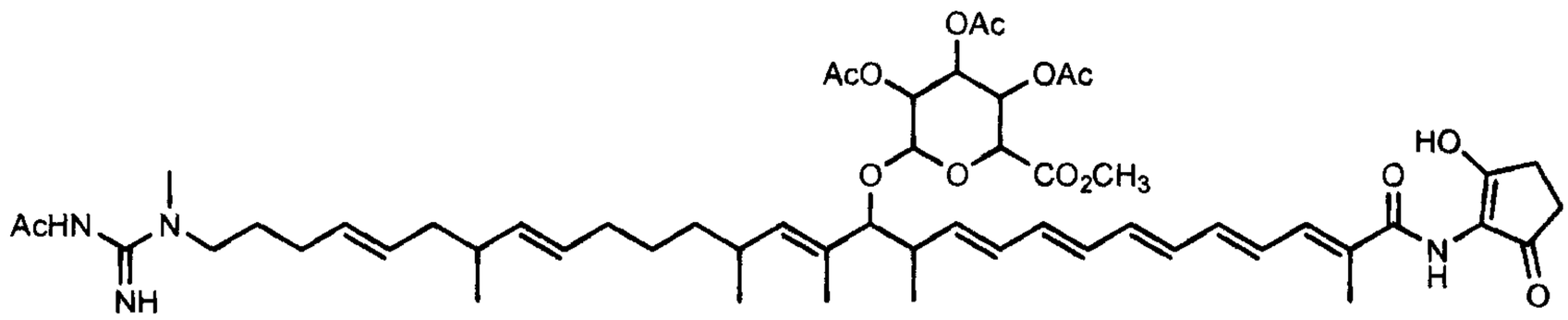

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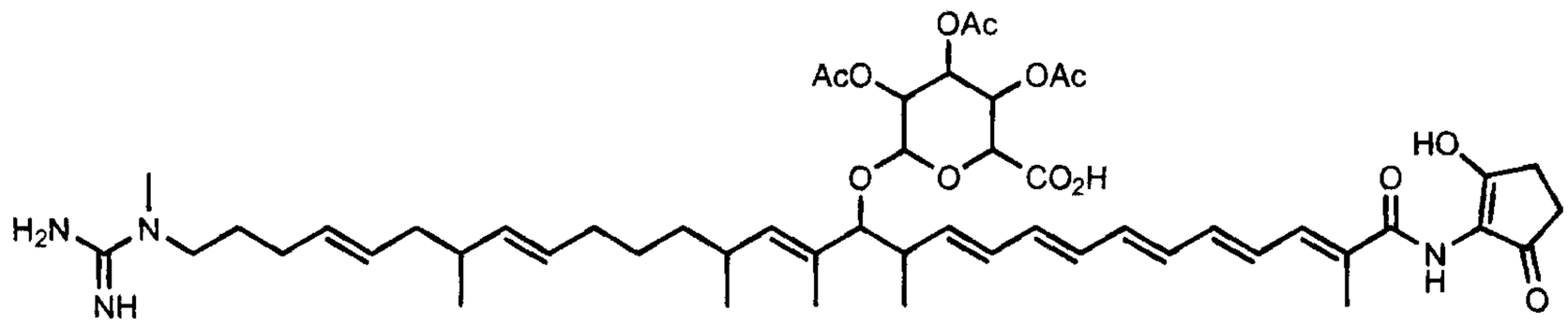
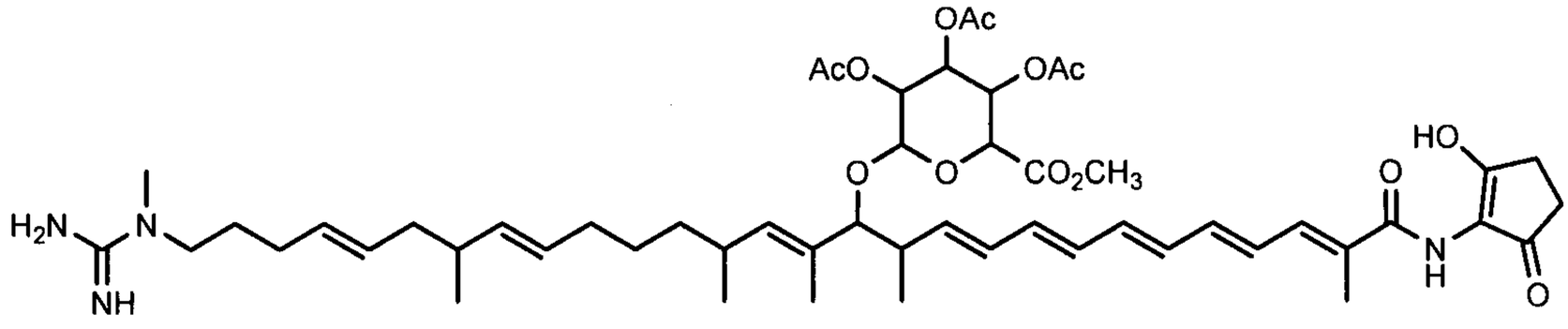


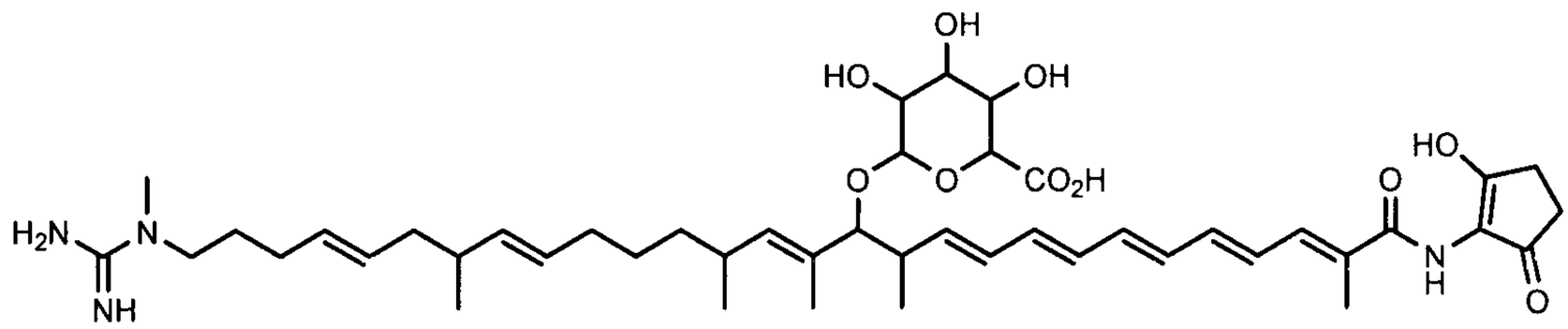
Compound 27; and

10



Compound 28.

11. A compound of claim 2, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:



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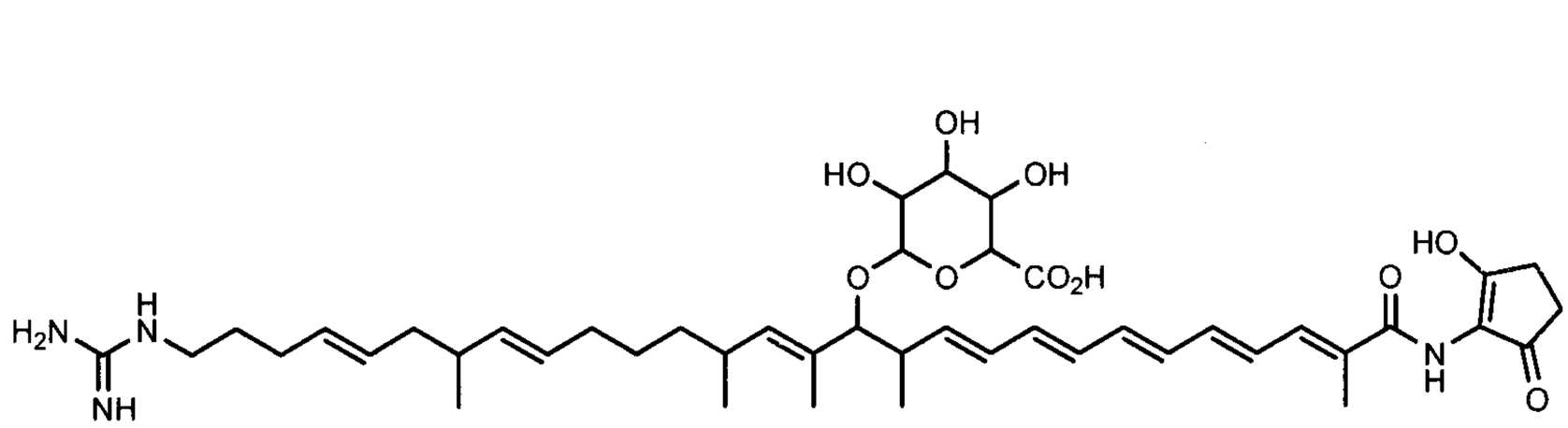

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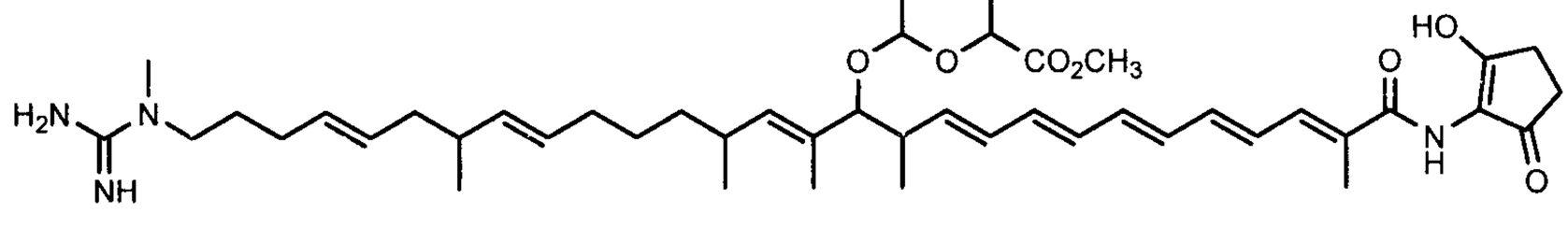

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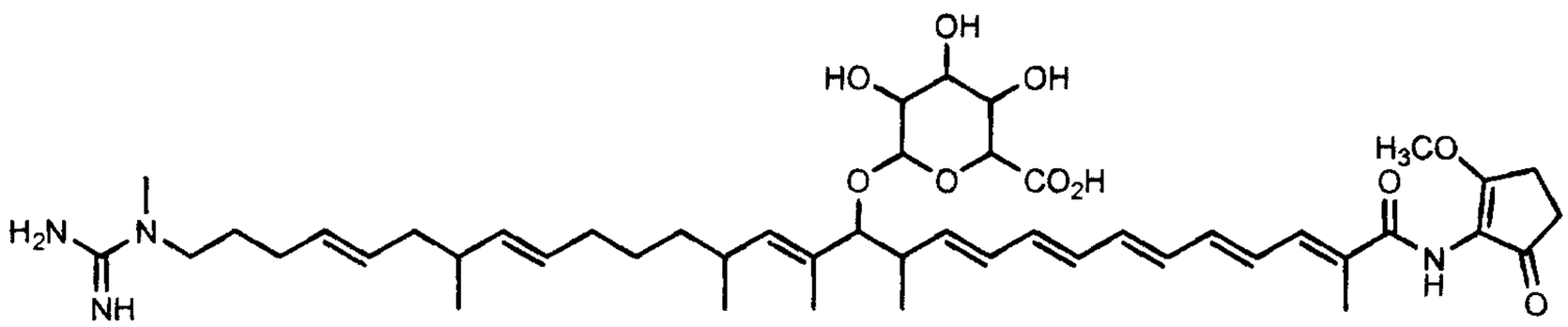
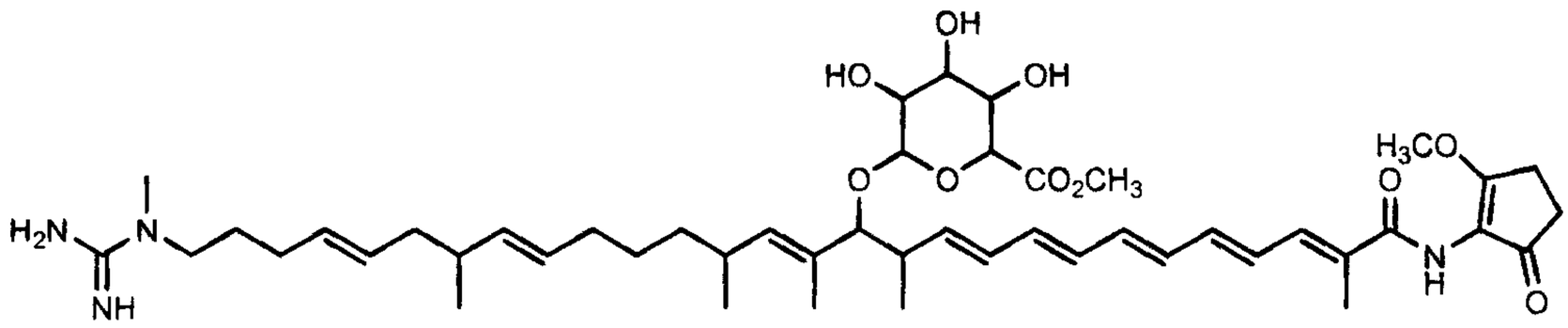
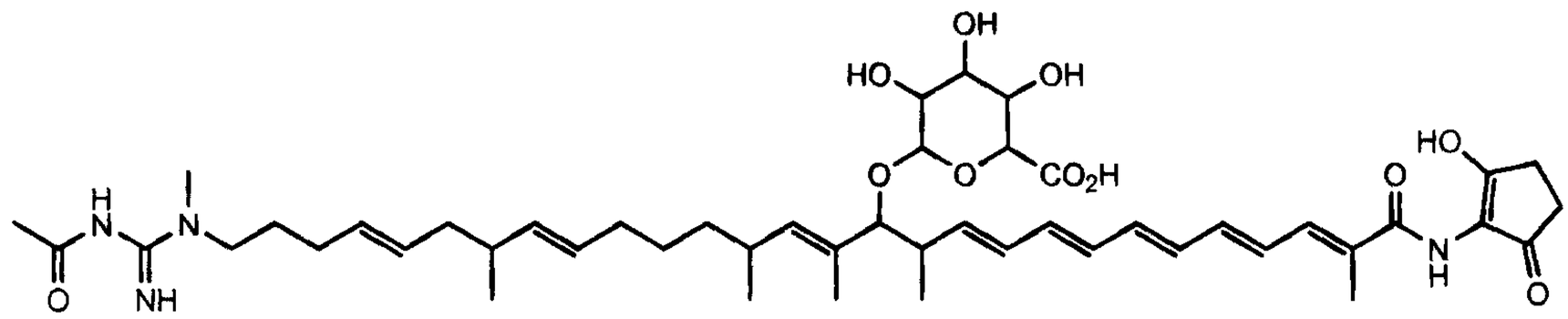


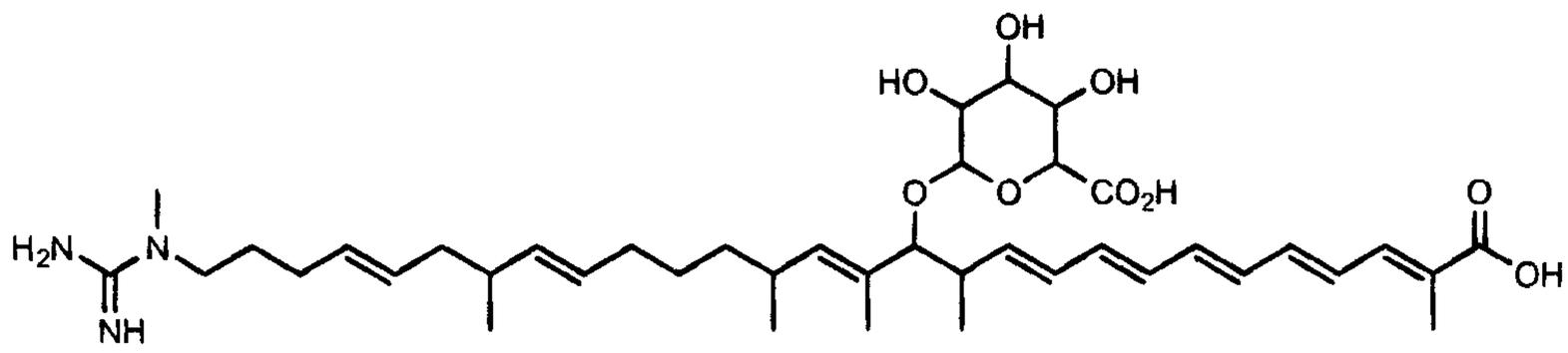
Compound 4;



Compound 5;



Compound 6; and



Compound 7.

12. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

13. A pharmaceutical composition comprising a compound of claim 2 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

14. A pharmaceutical composition comprising a compound of claim 10 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

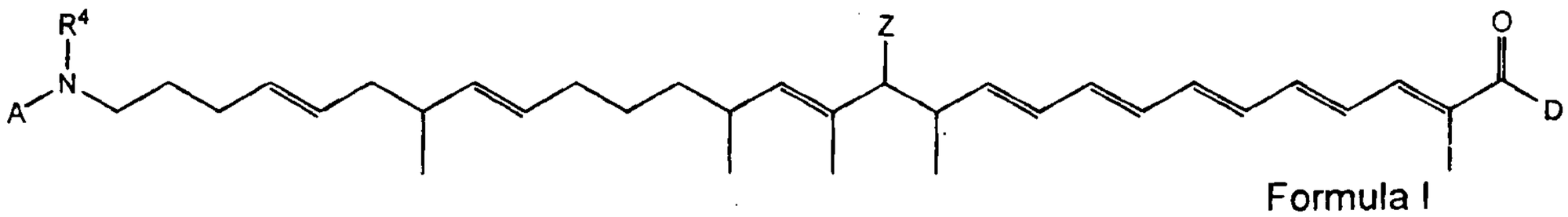
15. A pharmaceutical composition comprising a compound of claim 11 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

16. A polyene polyketide selected from Compounds 1, 2 and 7 as defined in claim 11, wherein said polyene polyketide is obtained by a method comprising:

a) cultivating a *Amycolatopsis orientalis* strain, wherein said cultivation is performed under aerobic conditions in a nutrient medium comprising at least one source of carbon atoms and at least one source of nitrogen atoms; and

b) isolating a polyene polyketide of claim 11 selected from Compounds 1, 2 and 7, from the bacteria cultivated in step (a).

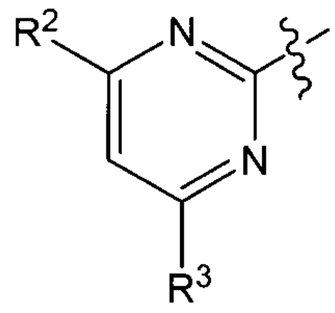
17. A polyene polyketide of Formula I



Formula I

wherein,

A is selected from $-C(NH)NHR^1$, CH_3, H and



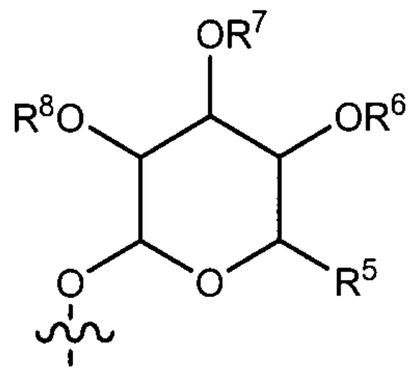
;

R^1 is selected from H, C_{1-6}alkyl, C_{6-10}aryl, $C(O)C_{1-6}$alkyl and $C(O)C_{6-10}$aryl;

R^2 and R^3 are each independently selected from H, C_{1-6} alkyl, C_{2-7} alkene and C_{6-10} aryl;

R^4 is selected from H and CH_3;

Z is OH; or Z is O when taken with adjacent carbon atom to form a carbonyl; or Z is a tetrahydropyranoxy of formula:



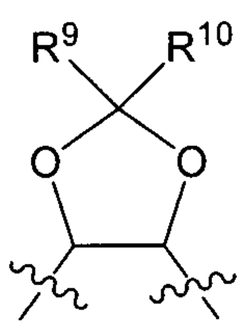
; wherein

R^5 is selected from H, COOH, C_{1-6} alkyl and $C(O)OC_{1-6}$ alkyl;

R^6, R^7 and R^8 are each independently selected from H, C_{1-6} alkyl and $C(O)C_{1-6}$ alkyl; or

R^6 , R^7 and R^8 may each independently be absent when the adjacent oxygen and carbon atoms are taken together to form a carbonyl; or

R^6 , R^7 and R^8 may each independently be a bond when any of two neighboring R^6 , R^7 and R^8 are taken together with attached oxygen and carbon atoms to form a 1,3-dioxolane ring of formula:

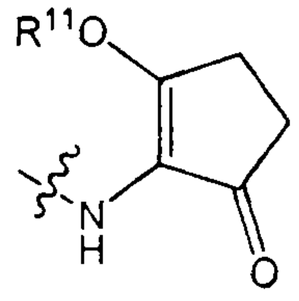


;

R^9 and R^{10} are each independently selected from H, C_{1-6} alkyl, C_{2-7} alkene and C_{6-10} aryl; or

R^9 and R^{10} are taken together with adjacent carbon atom to form a ring having from 5 to 7 carbons;

D is selected from OH, NH_2, $NH(C_{1-3}alkyl)$, $N(C_{1-3}alkyl)_2$, $OC_{1-3}alkyl$ and



; and

R^{11} is selected from H and C_{1-3} alkyl,

wherein said polyene polyketide is obtained by a method comprising:

a) cultivating a *Amycolatopsis orientalis* strain, under aerobic conditions in a nutrient medium comprising at least one source of carbon atoms and at least one source of nitrogen atoms; and

b) isolating a polyene polyketide of claim 11 selected from compounds 1, 2 and 7, from the bacteria cultivated in step (a); and

c) chemically modifying the polyene polyketide of paragraph (b) to obtain a polyene polyketide of Formula I.

18. The polyene polyketide of claim 16 that generates a ^1H NMR spectra essentially as shown in Figure 4.

19. The polyene polyketide of claim 16 that generates a ^1H NMR spectra essentially as shown in Figure 5.

20. The polyene polyketide of claim 16 that generates a ^1H NMR spectra essentially as shown in Figure 10.

21. The polyene polyketide of claim 17 that generates a ^1H NMR spectra essentially as shown in Figure 6.

22. The polyene polyketide of claim 17 that generates a ^1H NMR spectra essentially as shown in Figure 7.

23. The polyene polyketide of claim 17 that generates a ^1H NMR spectra essentially as shown in Figure 8.

24. The polyene polyketide of claim 17 that generates a ^{1}H NMR spectra essentially as shown in Figure 9.

25. A process of producing a compound of claim 1 comprising the steps of:

a) cultivating an Amycolatopsis strain in a nutrient medium comprising at least one source of carbon atoms and at least one source of nitrogen atoms;

b) isolating a compound selected from the group consisting of Compound 1, 2, 7, 8 and 15 as defined in claim 10; and

c) chemically modifying the compound of paragraph b) to produce a compound of claim 1.

26. A process of producing a compound of claim 10 selected from the group consisting of Compounds 1, 2, 7, 8 and 15 comprising the steps of:

a) cultivating an *Amycolatopsis* strain in a nutrient medium comprising at least one source of carbon atoms and nitrogen atoms; and

b) isolating the compound of claim 10 selected from the group consisting of Compounds 1, 2, 7, 8 and 15.

27. The process of claims 25 or 26 wherein the *Amycolatopsis* strain is *Amycolatopsis orientalis.*

28. The process of any one of claim 25-27, wherein the *Amycolatopsis* strain is *Amycolatopsis orientalis* ATCC 43491 or a mutant or variant thereof.

29. The process of any one of claim 25-28, wherein the *Amycolatopsis* strain is *Amycolatopsis orientalis* having accession number IDAC 220604-01, or a mutant or variant thereof.

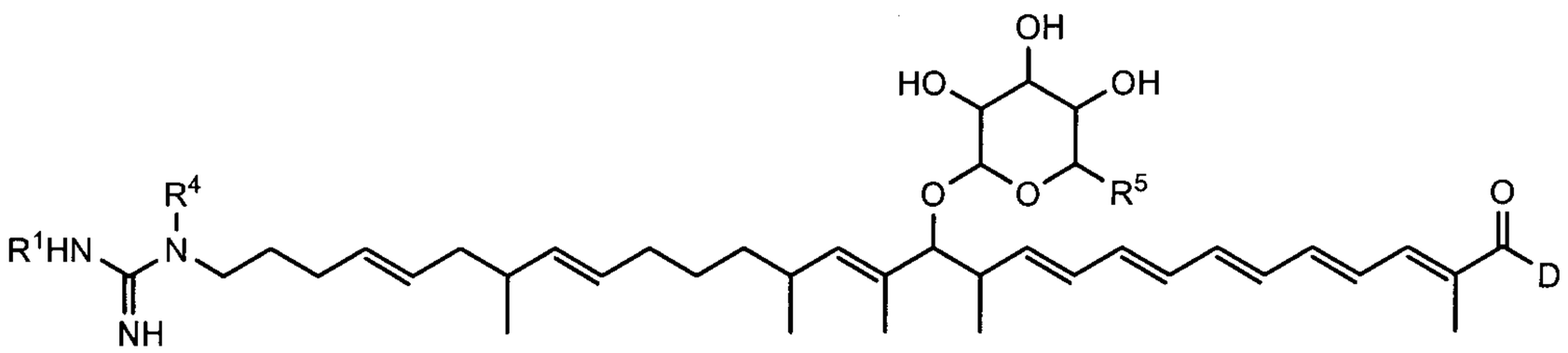
30. The process of any one of claims 25-29, wherein the cultivating step occurs under aerobic conditions.

31. The process of any one of claims 25-30, wherein said cultivation is carried out at a temperature ranging from 18°C to 40°C.

32. The process of any one of claims 25-31, wherein said cultivation is carried out at a pH ranging from 6 to 9.

33. *Amycolatopsis orientalis sp.* having IDAC Accession No. 220604-01.

34. Use, as an antibacterial agent, of a compound of Formula II:



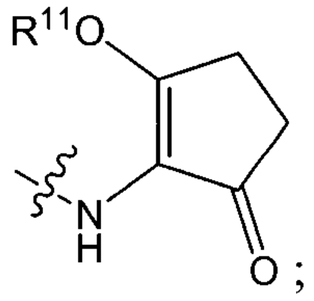
Formula II

wherein, R^1 is selected from H and $C(O)C_{1-3}$alkyl;

R^4 is selected from H and CH_3;

R^5 is selected from C(O)OH and $C(O)OC_{1-3}$alkyl;

D is selected from OH and the cyclopentenone of the formula:

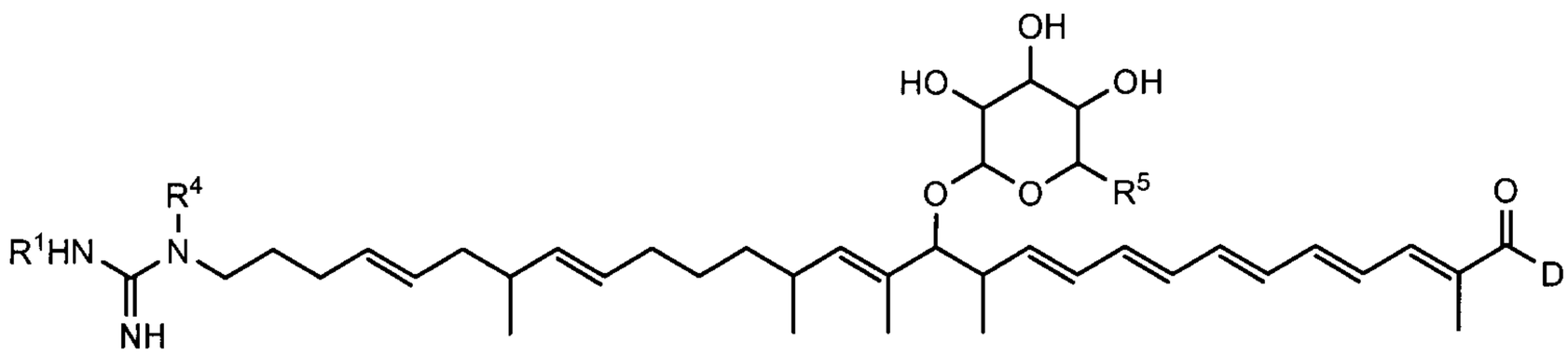


;

wherein R^{11} is selected from H and C_{1-3}alkyl.

35. Use of a compound of any one of claims 3-9 and 11 to inhibit bacterial growth.

36. Use, in the treatment of bacterial infection, of a compound of Formula II:



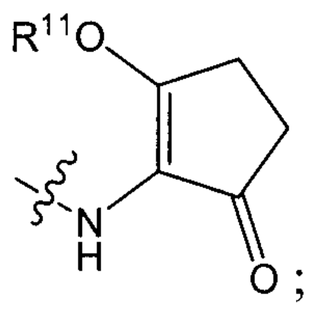
Formula II

wherein, R^1 is selected from H and $C(O)C_{1-3}$alkyl;

R^4 is selected from H and CH_3;

R^5 is selected from C(O)OH and $C(O)OC_{1-3}$alkyl;

D is selected from OH and the cyclopentenone of the formula:



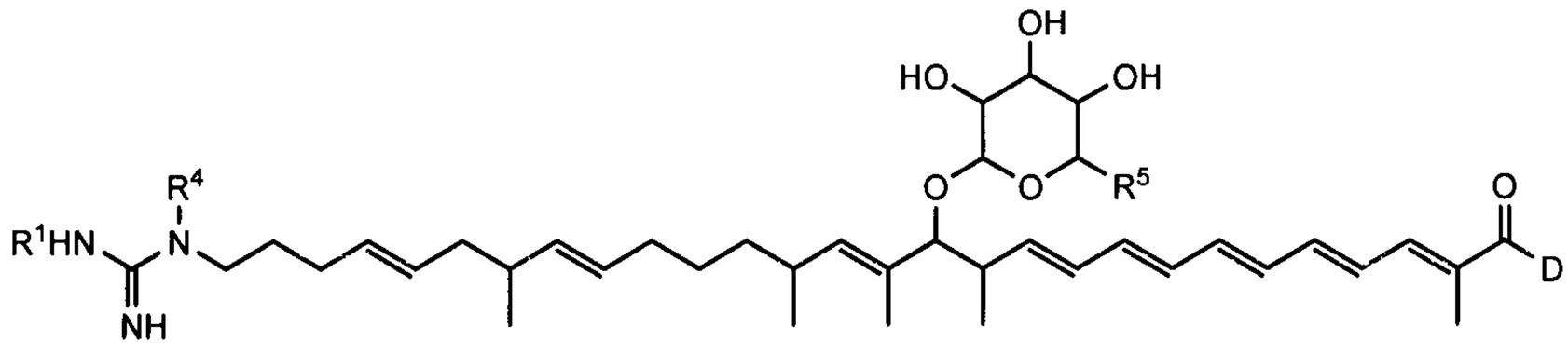
wherein R^{11} is selected from H and C_{1-3}alkyl.

37. Use of a compound of claim 3-9 and 11 in the treatment of bacterial infection in a subject.

38. Use of a compound of claim 11 in the treatment of bacterial infection in a mammal.

39. Use of a compound of any one of claims 3-9 and 11 in the preparation of a medicament to treat bacterial infection.

40. Use in the preparation of a medicament for the treatment of bacterial infection, of a compound of Formula II:



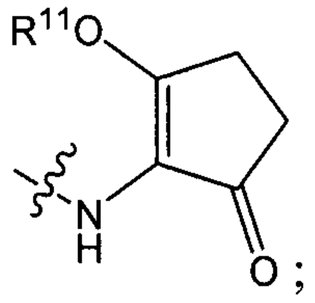
Formula II

wherein, R^1 is selected from H and $C(O)C_{1-3}$alkyl;

R^4 is selected from H and CH_3;

R^5 is selected from C(O)OH and $C(O)OC_{1-3}$alkyl;

D is selected from OH and the cyclopentenone of the formula:



wherein R^{11} is selected from H and C_{1-3}alkyl.

41. Use according to any one of claims 35-40 wherein the bacterial growth or bacterial infection involves a bacterial strain selected from the group consisting of *Streptococcus pneumoniae, Streptococcus pyogenes, Enterococcus faecalis*, *Enterococcus faecium, Klebsiella pneumoniae, Enterobacter spp., Proteus spp., Pseudomonas aeruginosa, E. coli, Serratia marcesens, Staphylococcus aureus,* Coagulase negative *Staphylococcus, Haemophilus infuenzae, Bacillus anthracis, Mycoplasma pneumoniae*, and *Staphylococcus epidermidis*.

42. Use according to any one of claims 35-40 wherein the bacterial growth or bacterial infection involves a strain selected from the group consisting of *Staphylococcus aureus, Staphylococcus epidermidis, Bacillus subtilis, Bacillus megaterium, Enterococcus faecalis and Micrococcus luteus.*

43. Use of any one of claims 41 or 42 wherein the bacterial strain is *Staphylococcus aureus*.

44. Use of a pharmaceutical composition according to claim 15 in the treatment of bacterial infection.

45. Use of a pharmaceutical composition according to claim 15 in the preparation of a medicament for the treatment of bacterial infection.

46. Use according to claim 44 or 45 wherein the bacterial infection involves a strain selected from the group consisting of *Streptococcus pneumoniae, Streptococcus pyogenes, Enterococcus faecalis*, *Enterococcus faecium, Klebsiella pneumoniae, Enterobacter spp., Proteus spp., Pseudomonas aeruginosa, E. coli, Serratia marcesens, Staphylococcus aureus,* Coagulase negative *Staphylococcus, Haemophilus infuenzae, Bacillus anthracis, Mycoplasma pneumoniae*, and *Staphylococcus epidermidis.*

47. Use according to claim 44 or 45 wherein the bacterial infection involves a strain selected from *Staphylococcus aureus, Staphylococcus epidermidis, Bacillus subtilis, Bacillus megaterium, Enterococcus faecalis and Micrococcus luteus.*

Figure 1

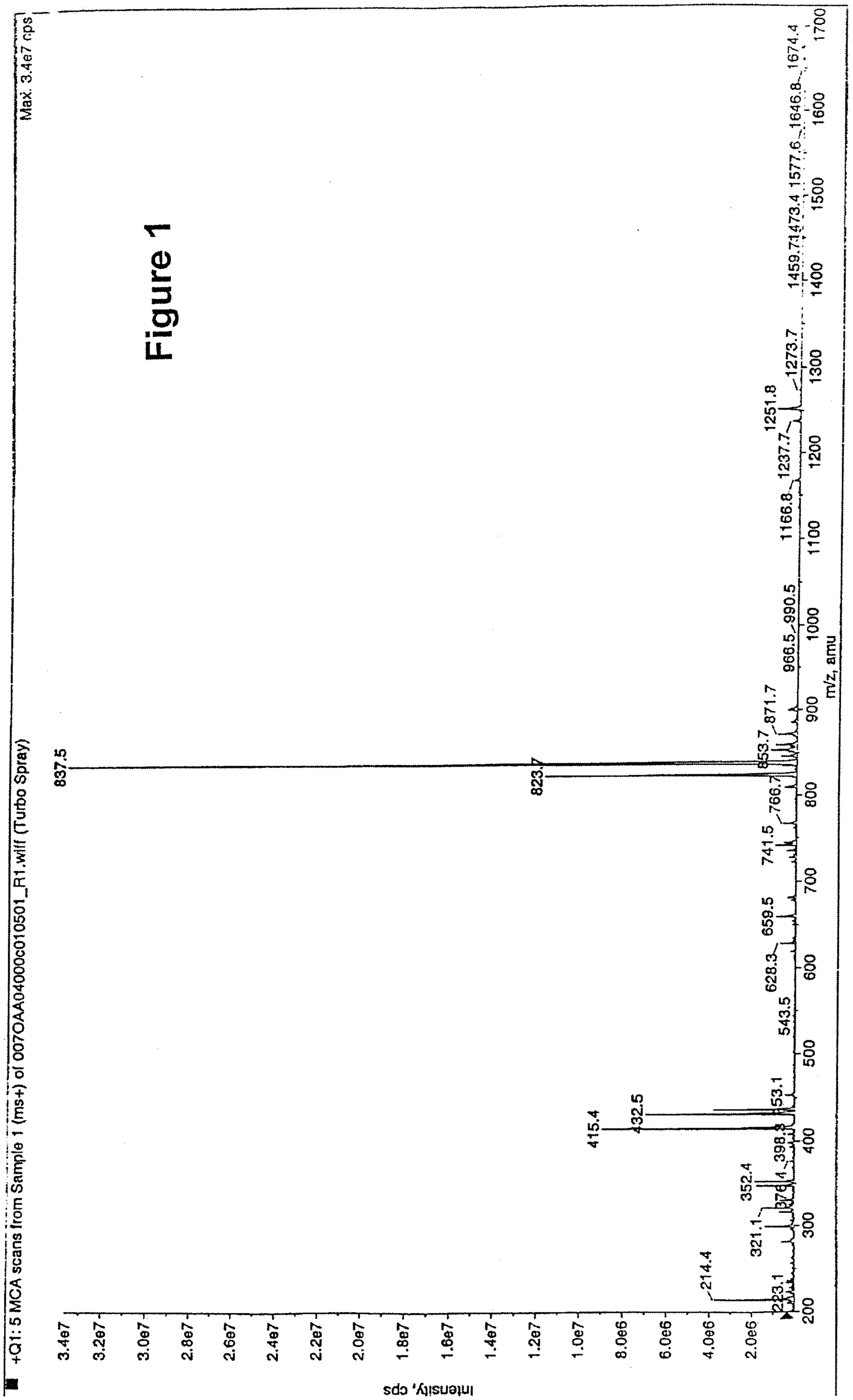
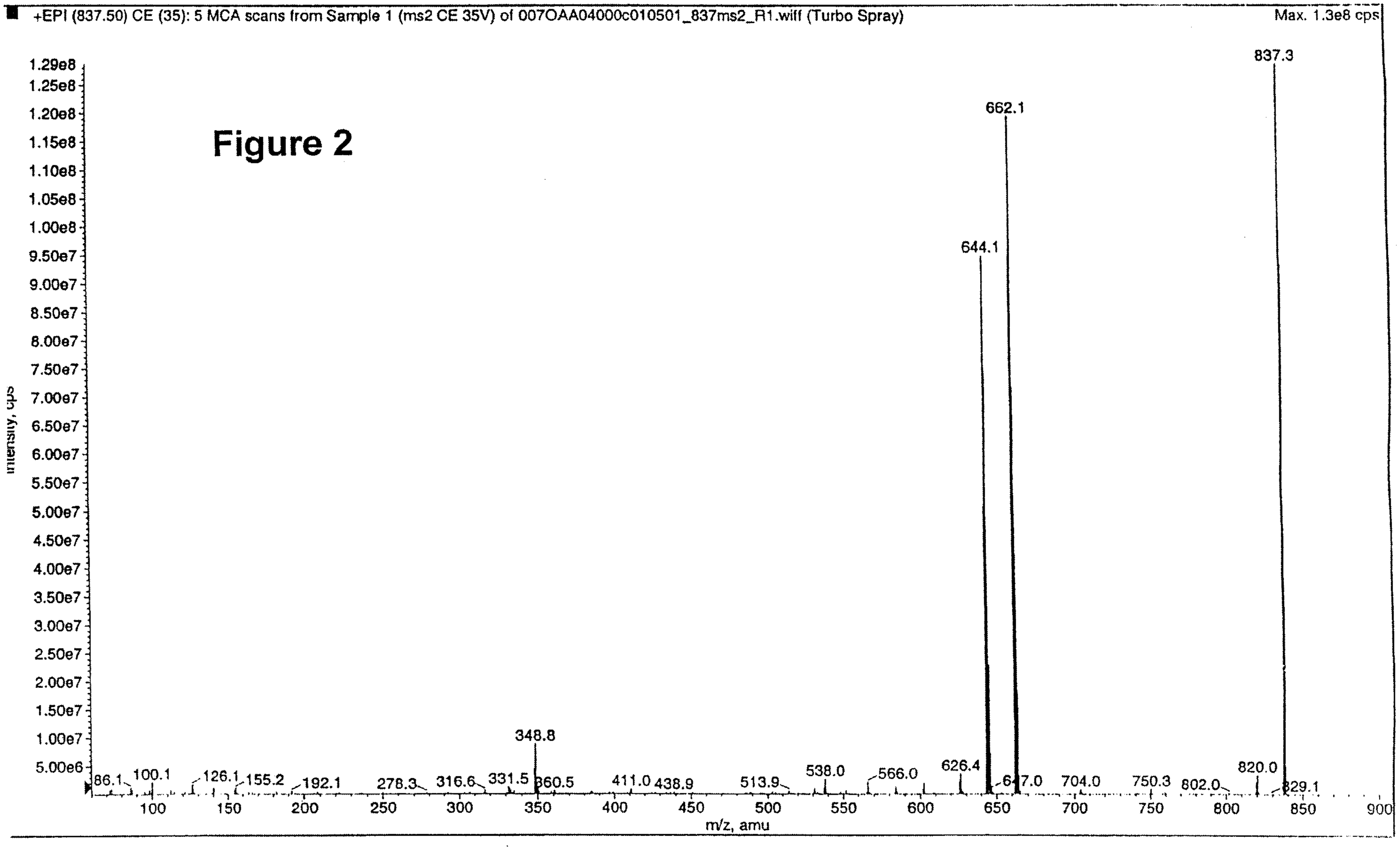

Max. 3.4e7 cps
+Q1: 5 MCA scans from Sample 1 (ms+) of 007OAA04000c010501_R1.wiff (Turbo Spray)
Intensity, cps
m/z, amu

Figure 2



CA 02484638 2004-11-18

Figure 3

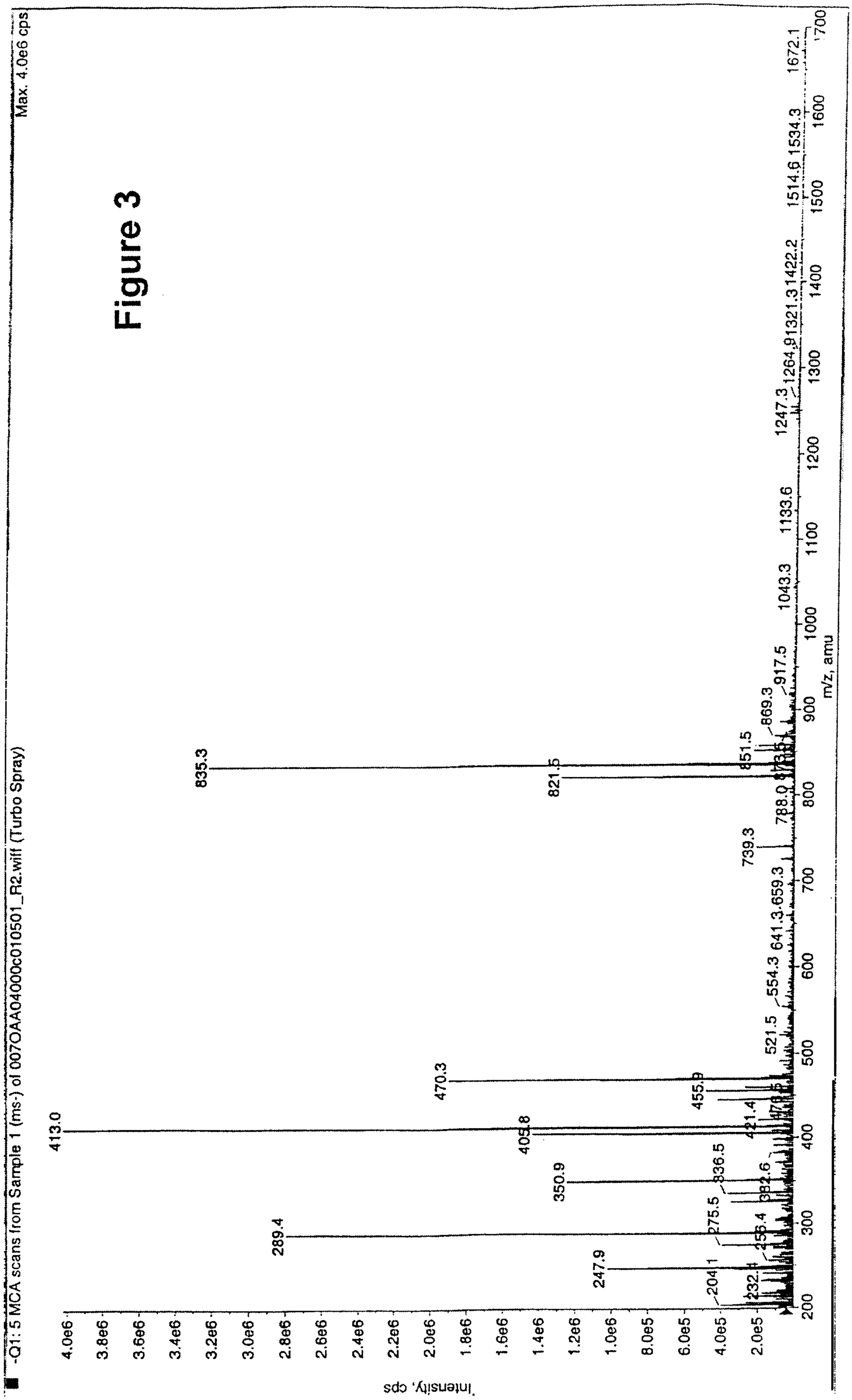
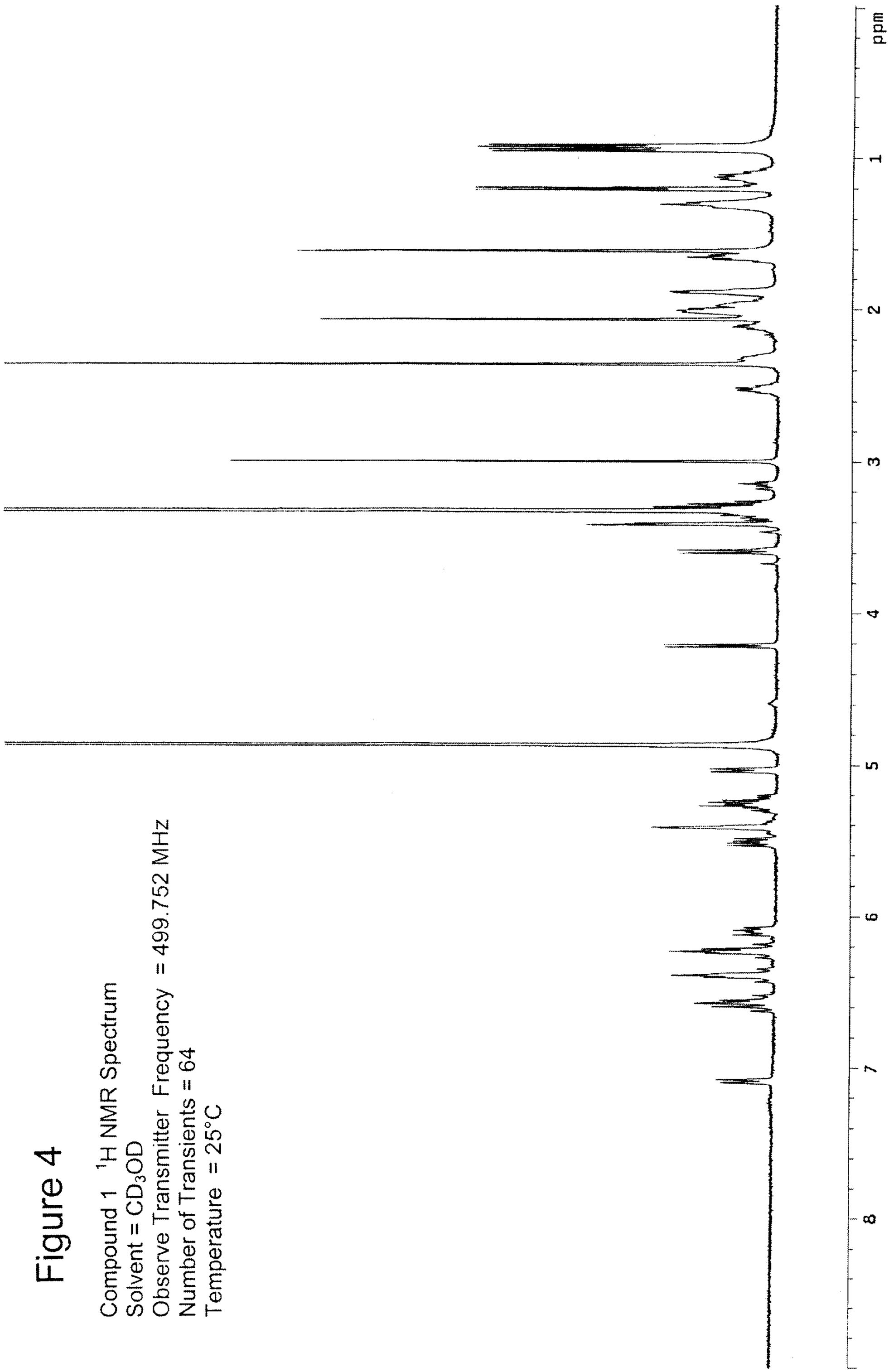

-Q1: 5 MCA scans from Sample 1 (ms-) of 007OAA04000c010501_R2.wiff (Turbo Spray)
Max. 4.0e6 cps
Intensity, cps
m/z, amu

Figure 4

Compound 1 ^1H NMR Spectrum
Solvent = CD_3OD
Observe Transmitter Frequency = 499.752 MHz
Number of Transients = 64
Temperature = 25°C



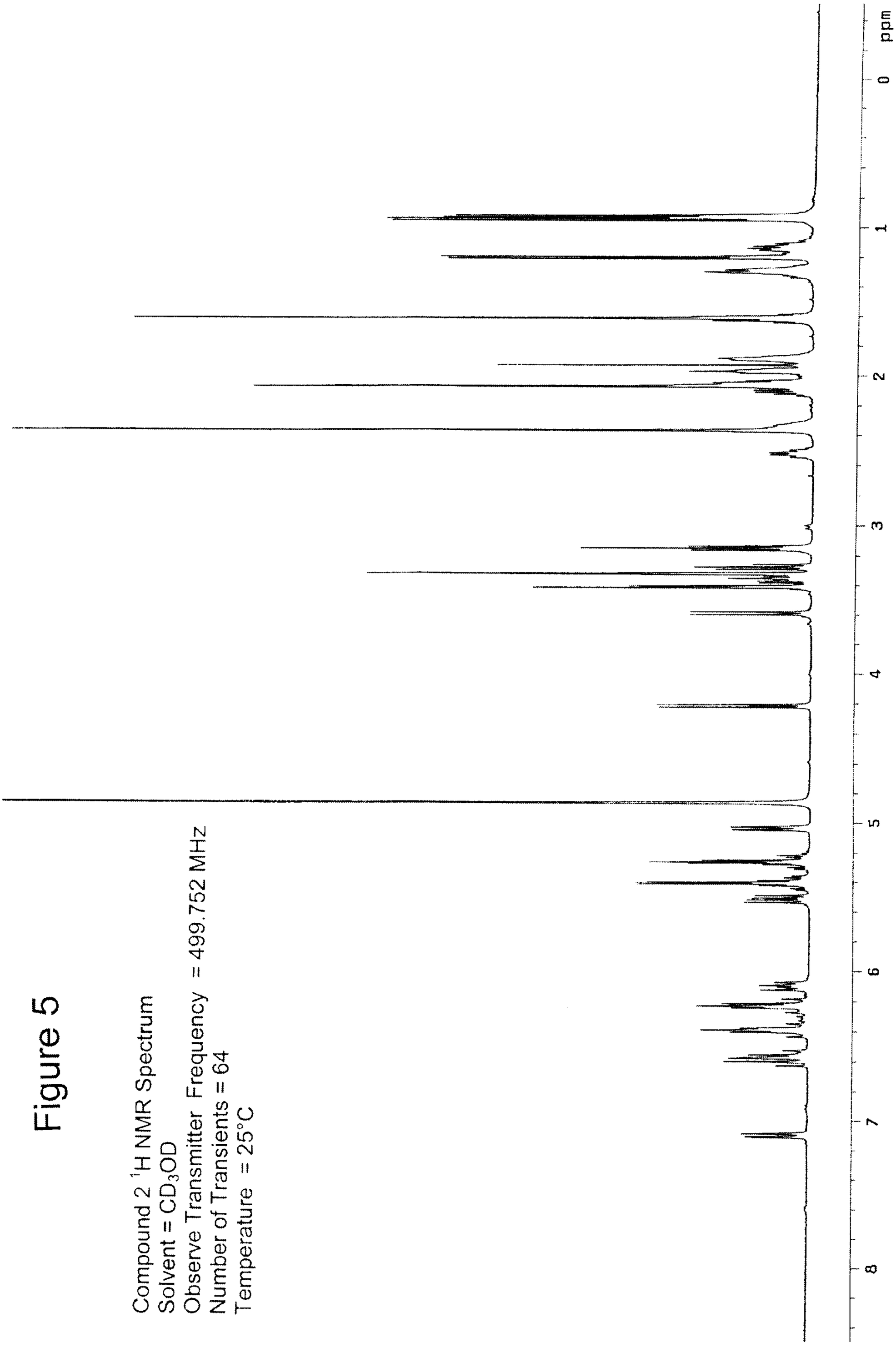

ppm
0
1
2
3
4
5
6
7
8
Compound 2 ^{1}H NMR Spectrum
Solvent = CD_3OD
Observe Transmitter Frequency = 499.752 MHz
Number of Transients = 64
Temperature = 25°C

Figure 5

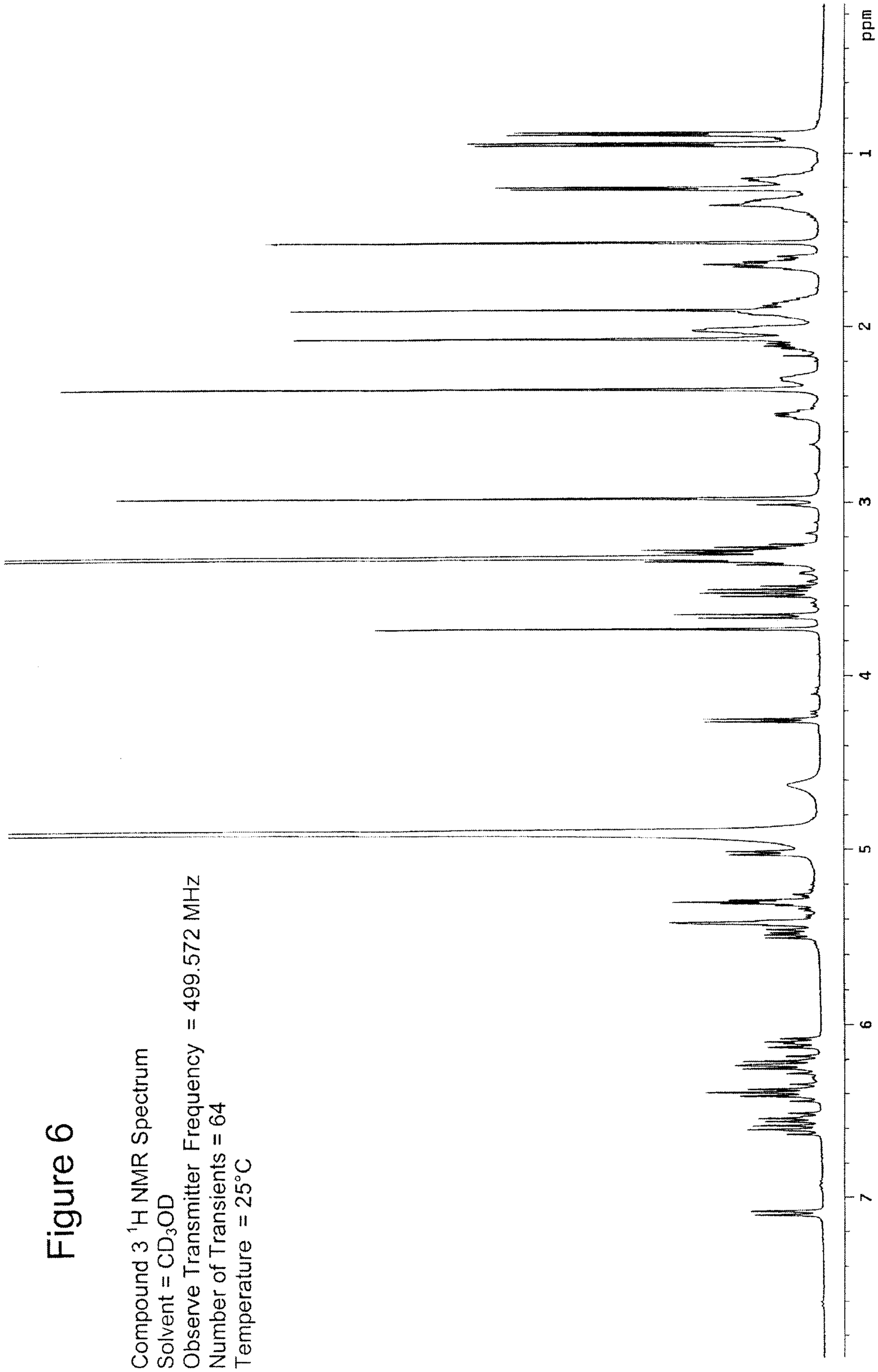

ppm
1
2
3
4
5
6
7
Compound 3 ^{1}H NMR Spectrum
Solvent = CD_3OD
Observe Transmitter Frequency = 499.572 MHz
Number of Transients = 64
Temperature = 25°C

Figure 6

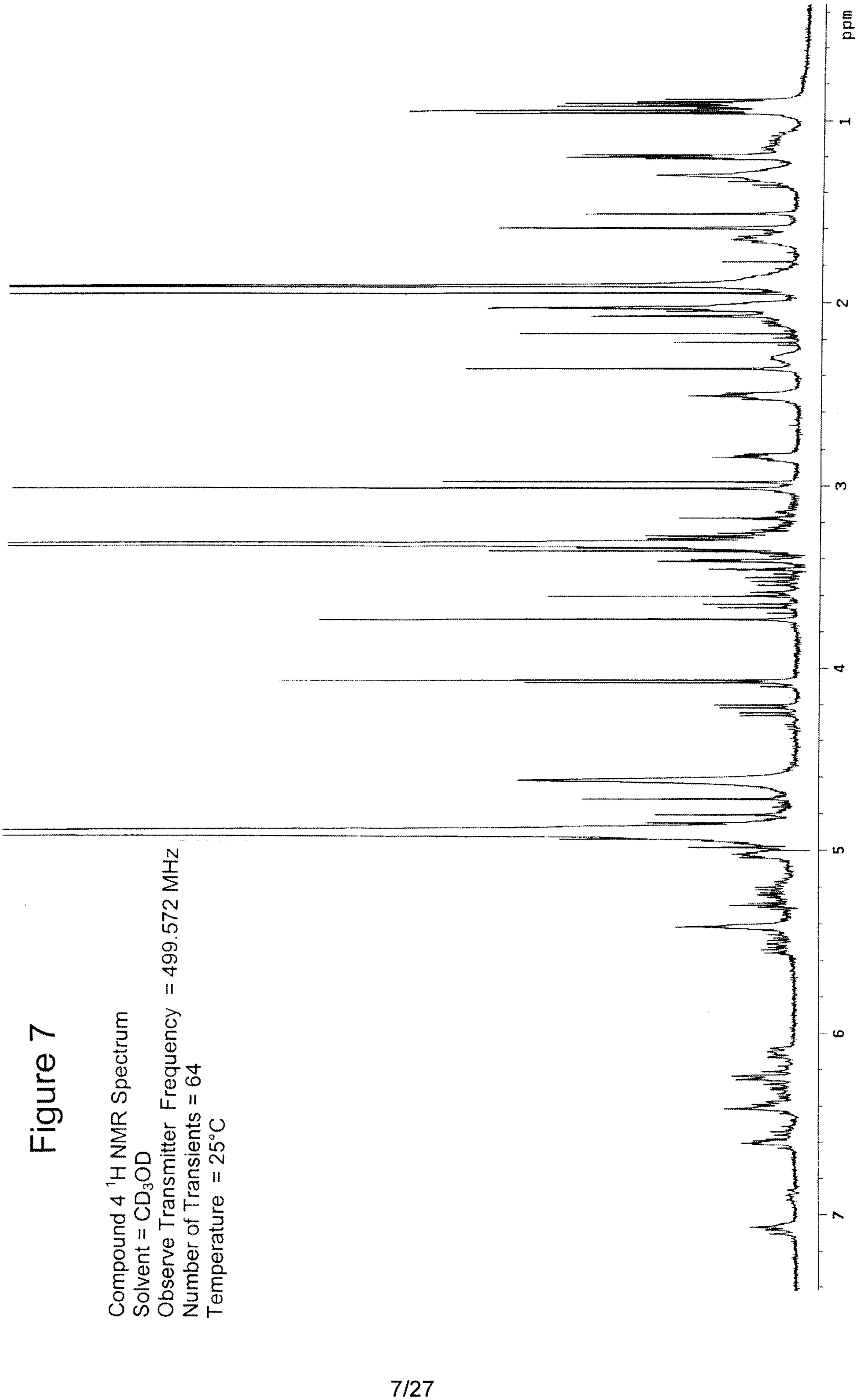
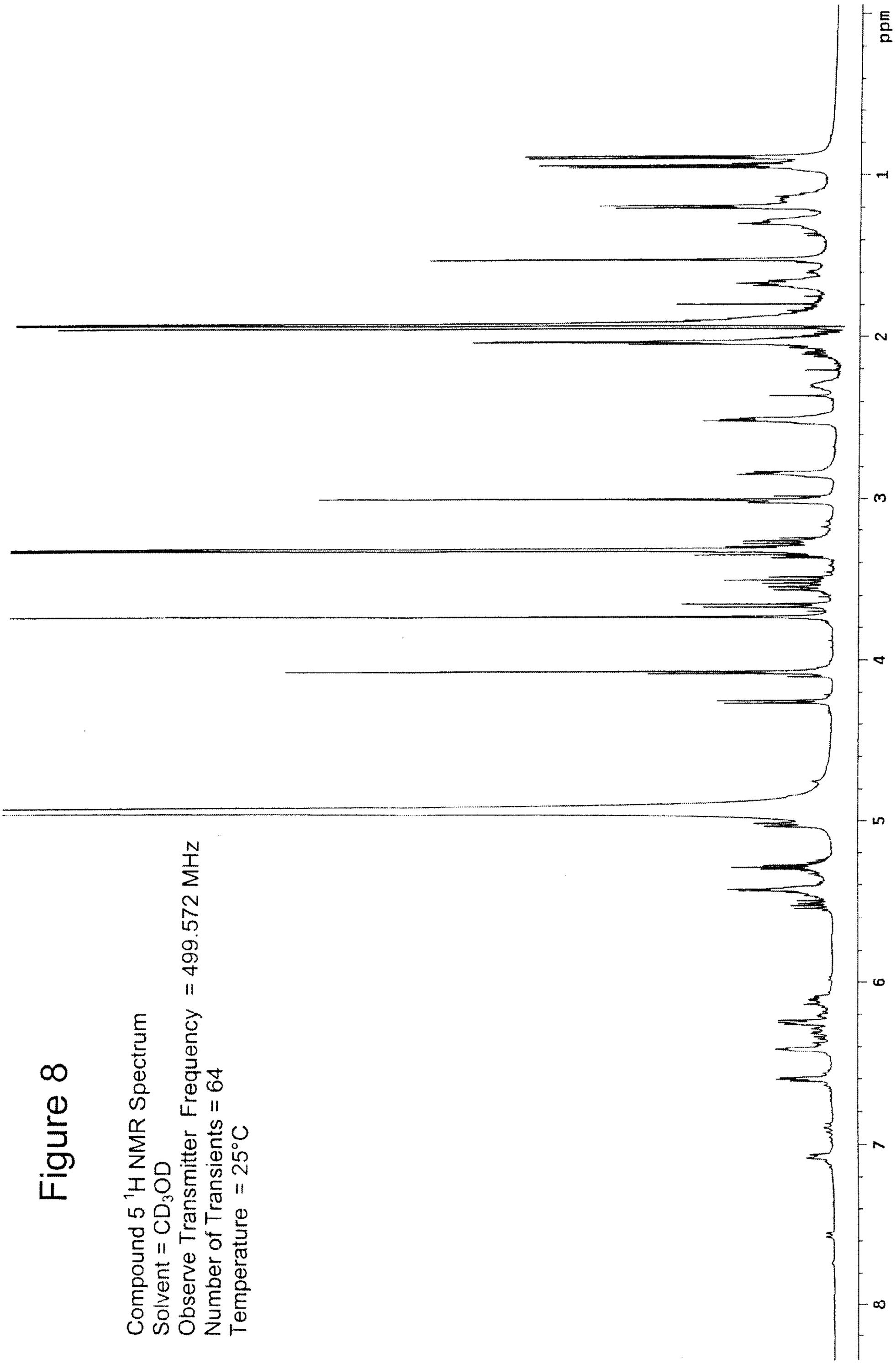

ppm
1
2
3
4
5
6
7
Compound 4 ^{1}H NMR Spectrum
Solvent = CD_3OD
Observe Transmitter Frequency = 499.572 MHz
Number of Transients = 64
Temperature = 25°C

Figure 7

Figure 8

Compound 5 ^{1}H NMR Spectrum
Solvent = CD_3OD
Observe Transmitter Frequency = 499.572 MHz
Number of Transients = 64
Temperature = 25°C



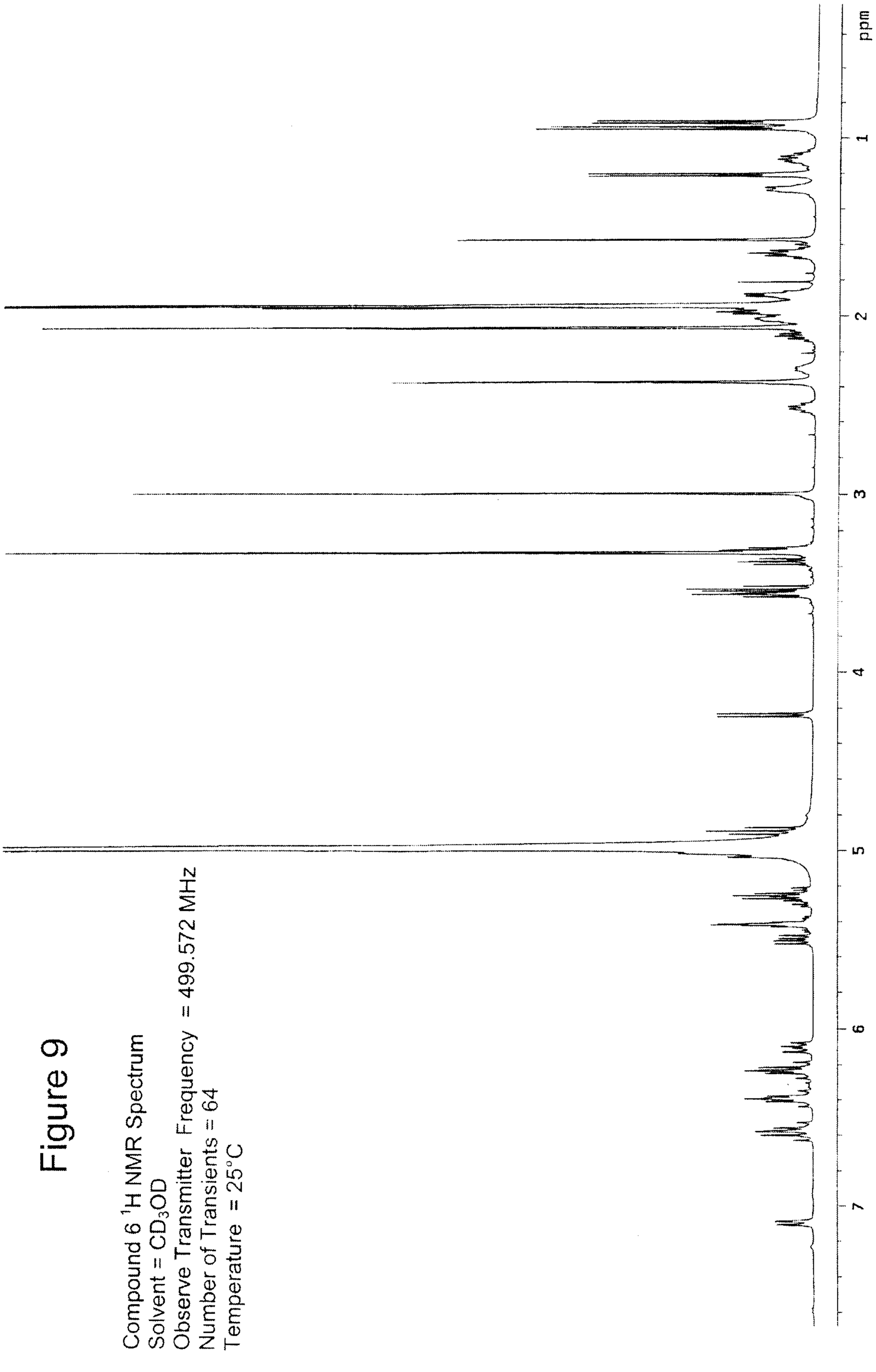


Figure 9

Compound 6 ^{1}H NMR Spectrum
Solvent = CD_3OD
Observe Transmitter Frequency = 499.572 MHz
Number of Transients = 64
Temperature = 25°C

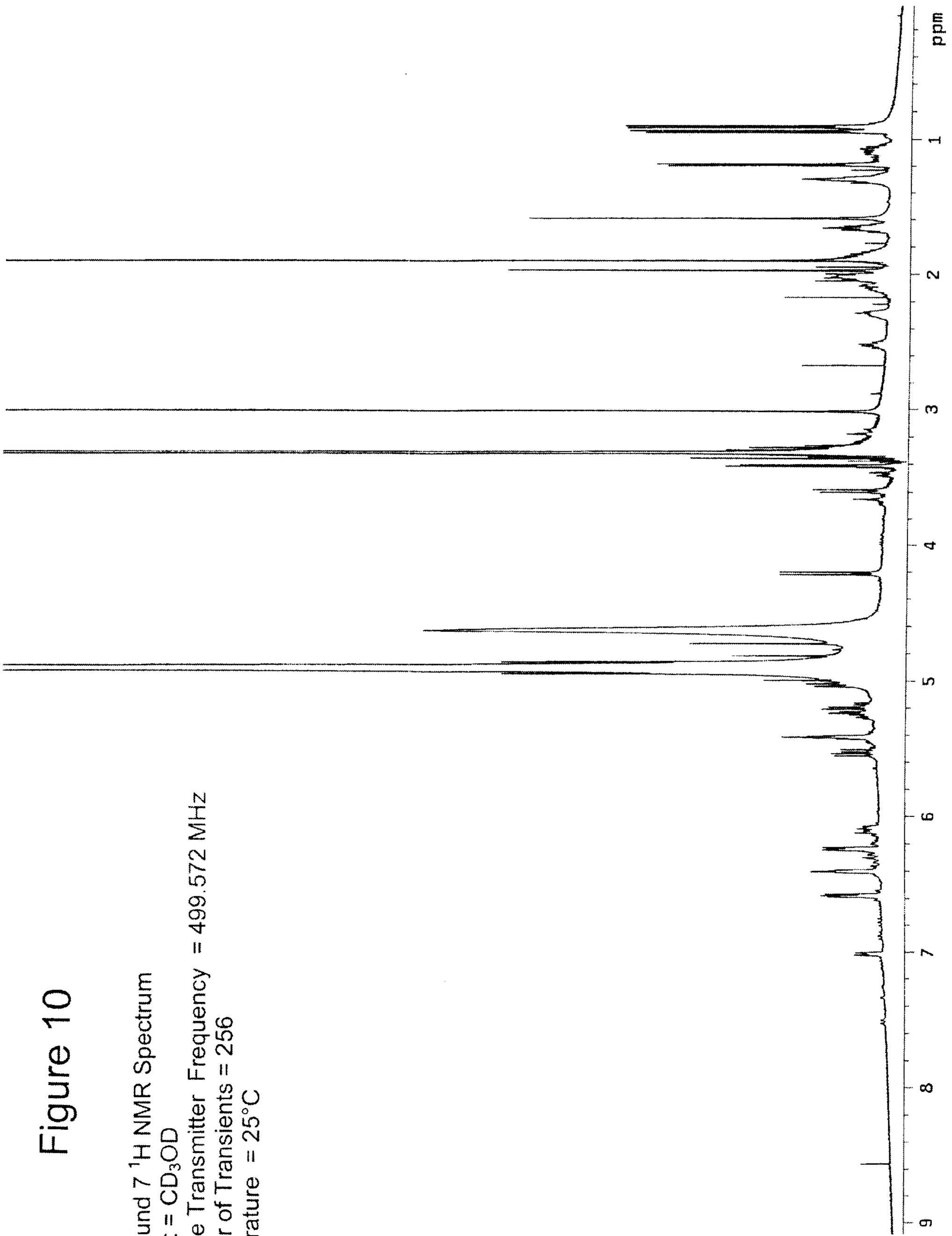


Figure 10

Compound 7 ^{1}H NMR Spectrum
Solvent = CD_3OD
Observe Transmitter Frequency = 499.572 MHz
Number of Transients = 256
Temperature = 25°C

Figure 11

Biosynthetic locus for production of the compound of Formula I

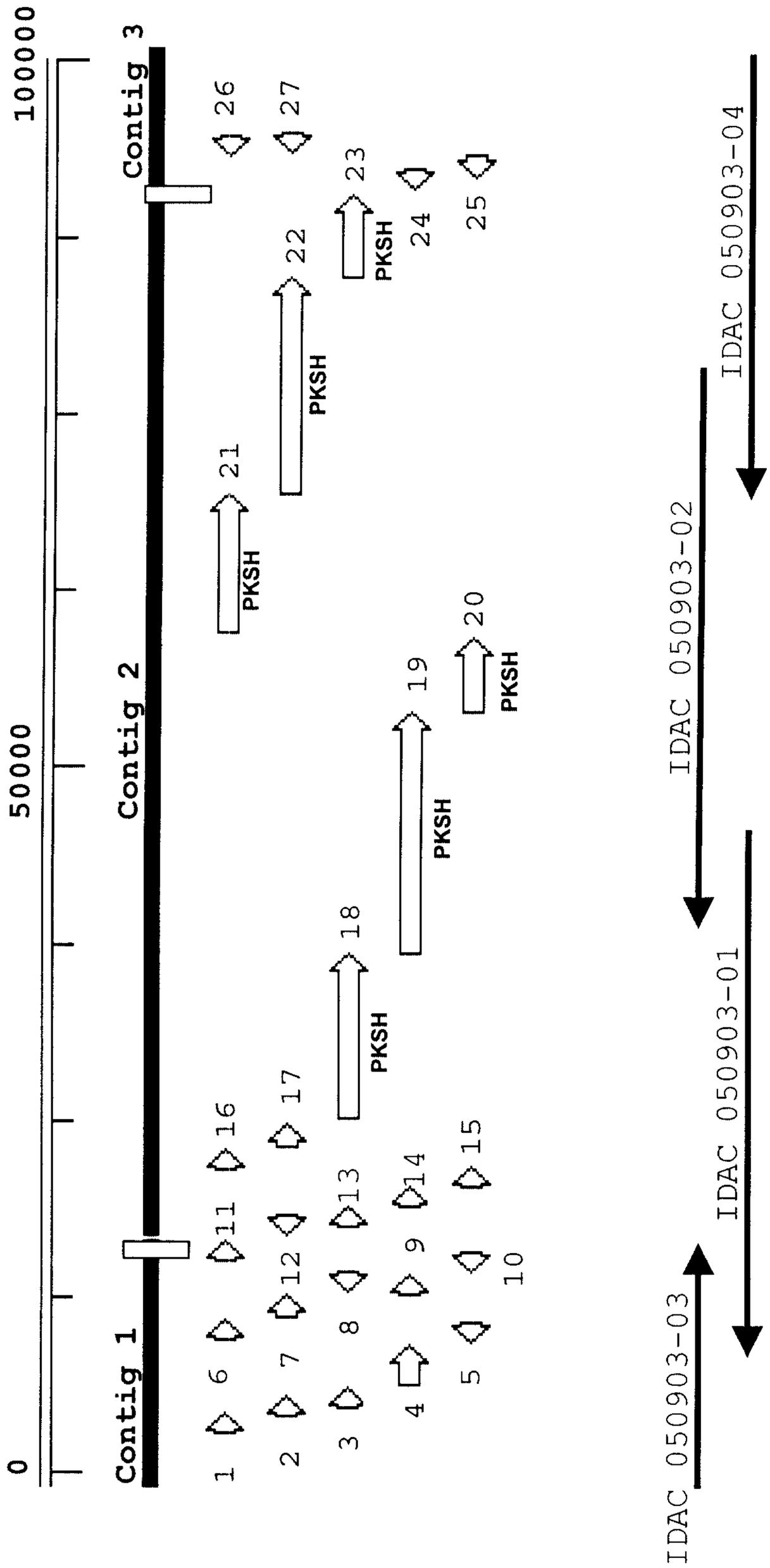


Figure 12a

```
ORF 22_KS02          PIAIIGMACRYPGGVTSPEELWDLVAAGRDGVSEFPVNRGW--EDVYDAD
ORF 22_KS03          PIAIVGMACRFPGGVRSPEDLWRLVSEGRDGITPFPADRGWDVEGLYDPE
ORF 19_KS01          PIAIIGMACRYPGGVRSPEELWDLVAGERTGLTGFPVDRGWDLDGLYDPE
ORF 18_KS02          PIAIIGMACRYPGGVSTPDDLWRLVADGNDGITRFPENRGWDTDGVYHPD
ORF 19_KS02          PIAIIGMACRYPGGVASPEDLWRLVAEGRDGISLFPADRGWDVDGLYDPD
ORF 23_KS01          PIAIVGMACRYPGGVASPEDLWRMVETGGDGISGFPVDRGWDLEALYDPD
ORF 20_KS01          PIAVVGMSCRFPGGVRSPEQLWDLVASGTDALSEFPGDRGWDLGGLFDPD
ORF 21_KS01          PIAIIGMACRYPGGVRGPEQLWDLVAAGTDAVGGFPADRGWDVEALYDPD
ORF 22_KS01          PIAIIGMACRFPGGVRSPEDLWELVAEGRDGISGFPADRGWDLSALYDPT
ORF 19_KS03          PIAIVAMSCRFPGHADTPERLWALLAEGRDALGEFPADRGWDLERLFDTD
ORF 18_KS01          PIAIVGMACRYPGGIGSPEDLWRLVTEGGDATSDFPADRGWDVESLYDPD
ORF 21_KS02          PIAIVAMSCRFPGGITDPEKFWDFVADGGDAMAAFPGDRGWDLDALYDPD
                     ***:::.*:**:**    *: :* ::      .   ** :***    :::.

ORF 22_KS02          PGKVGKSYAREGGFLHDAGEFDAAFFGISPREALAMDPQQRLLLETSWEV
ORF 22_KS03          ASRPGTSCTRYGGFLHDAGDFDPGFFGISPREALAMDPQQRLLLETSWEA
ORF 19_KS01          QGKPGKSYVREGGFLHDAARFDPAFFGISPREALAMDPQQRLLLEISWEA
ORF 18_KS02          ADHRGTTYVREGGFLHDAGQFDPGFFGISPREALAMDPQQRLLLEISHEA
ORF 19_KS02          PGKAGKSYVREGGFLHEAGDFDAGFFGISPREALGMDPQQRLLLEVSWEA
ORF 23_KS01          PDKQGTSYVSQGGFLHDVAEFDPAFFGISPREALAMDPQQRLLLETSWEA
ORF 20_KS01          PDTPGKTYVSEGGFLYEAGDFDAAFFGISPREAQAMDPQQRLLLEAAWEV
ORF 21_KS01          PARHGKTYTREGGFLYDAHEFDAAFFGISPREALTVDPQQRLLLETAWEA
ORF 22_KS01          GEKPGTSYCREGGFLDGAGEFDPAFFGISPREALAMDPQQRLLLEISWET
ORF 19_KS03          PDRRGTSYTRQGAFLETAGDFDAGFFGISPREALAMDPQQRLLLETSWEA
ORF 18_KS01          PGVPGKTYTRRGGFLDGAGDFDAGFFGISPREALAMDPQQRLLLETSWEA
ORF 21_KS02          PAHLGTTYAREGGFLDDAGGFDAAFFGISPREALAMDPQQRLLLETSWEA
                         *.:    *.**  .  **..*********  :********* : *.

ORF 22_KS02          FERAGIDPHAVRGSKTGVFAGVMYHDYAARLNSVPEDV---EGYLGTGNS
ORF 22_KS03          FERAGIDPATLRGSATGVFAGAMYHDYVSRLTEIPADL---EGYLGTGNS
ORF 19_KS01          IERAGIAPDSLRGSRTGVFAGVIHNEYSAIAGTPPADL---EPYLGNGSF
ORF 18_KS02          VERAGIDPKSLRGSGTGVFAGVMYHDYATGLNRVPDDV---EGYLGNGTS
ORF 19_KS02          FERAGIDPGTLRGSDTGVFAGQMYHDYLTGATVVPDDV---EGYLGTGNS
ORF 23_KS01          IERAGIDPGSLKGSRTGVFAGLMYHDYVSGLTEIPDEV---GGYLGTGNS
ORF 20_KS01          LERAGIDPATLRGSRTGVFAGVIHNDYTGVLTDIPPEL---EPYLGNGNF
ORF 21_KS01          FERAGIDPLSVRGSRTGVFAGVMYNDYGSRLDPRAEELREFEGYLGNGSA
ORF 22_KS01          FERAGIDPGSLRGSRTGVFAGVMYHDYVSRLAAIPEEL---EGYLGTGNS
ORF 19_KS03          FERAGIDPATLRGSRTGVFAGVMDNEYVSGSAEVPDGV---EGYLATGTS
ORF 18_KS01          FERAGIDPATLRGSATGVFVGAETQEYGPRLGGAEEGL---EGYLLTGNA
ORF 21_KS02          FERAGIDPATLRGSATGVFVGASFQNYGLDAVDAPEGT---EGYFLTGTA
                     .***** * :::** ****.*   ::*                  *: .*.

ORF 22_KS02          GSVISGRLAYTFGLEGPAVSIDTACSSSLVAMHLAGQALRQGECSLAVAG
ORF 22_KS03          GSVISGRLAYAFGLEGPAVSIDTACSSSLVAMHLAAQALRQGECGLALAG
ORF 19_KS01          ASIASGRVSYTFGLEGPAVTVDTACSSSLVALHLAAQALRQGECSLALAG
ORF 18_KS02          ASIHSGRVAYTFGLEGPAVTIDTACSSSLVALHLAAQALRRGECSMALAG
ORF 19_KS02          GSVLSGRVSYTFGLEGPAVTVDTACSSSLVALHLAAQALRRGECSLALAG
ORF 23_KS01          GSIASGRVSYTFGFEGPALTVDTACSSSLVTLHLAAQALRRGECDLALSG
ORF 20_KS01          SSVASGRIAYTLGLEGPAVSVDTACSSSLVALHLAAQSLRREECTLALVG
ORF 21_KS01          GSVASGRVAYTFGLEGPAVTIDTACSSSLVALHLAAESLRRGESTLALAG
ORF 22_KS01          GSVVSGRVAYTFGLEGPAVTIDTACSSSLVALHLAAQALRQGECSMALAG
ORF 19_KS03          ASVASGRVSYTFGLEGPAVTVDTACSSSLVALHLAAQALRQGECSLALAG
ORF 18_KS01          ASVASGRVSYAFGFEGPTVTVDTACSSSLVALHLAGQALRLGECPIAVAG
ORF 21_KS02          TAVVSGRLSYTFGLEGPAVTIDTACSSSLVALHLAAQALRRGECSLALAG
                      :: ***::*::*:***::::***********::***.::**  *. :*: *
```

Figure 12b

```
ORF 22_KS02          GVTVMATPNTFIEFSRQRGMATDGRCKSFAEAADGTGWGEGVGMLLLERL
ORF 22_KS03          GVAVMSTPDTFIEFSRQRGMAPDGRIKAFSETADGTAWGEGVGMLLLERL
ORF 19_KS01          GVTVMANPAAFVDFSRQRGLAADGRIKAFAEAADGTAWGEGAGMLLVERL
ORF 18_KS02          GVTVMATPEVFVDFSRQRGLAPDGRCKSFSDEADGTVWSEGVGMLLVERL
ORF 19_KS02          GVTVMATPETFVDFSRQRGLAPDGRSKSFSDGADGTSWSEGVGMLLVERL
ORF 23_KS01          GVTVMFTPGTFVEFSRQRGMAPDGRCKPFAEEADGTGWSEGVGMLLVERL
ORF 20_KS01          GVNVMTHPAAFVDFSRQRGLAADGRCKAFADAADGTGWGEGVGMLLVERL
ORF 21_KS01          GVTVMASPETFVEFSRQRGMAPDGRCKPFADAADGTGWAEGAGILLLERL
ORF 22_KS01          GVAVMSTPDTFVDFSRQRGLAADGRCKSYSDGADGTSWAEGVGMLLVEKL
ORF 19_KS03          GVTVMATPGTFVEFSRQRGLAADGRCKAFADGADGTGWGEGAGMLLVERL
ORF 18_KS01          GVAVMSSPGGFLAFSRQRGLAPDGRCKPFSAAADGTGWSEGVGMLVLERL
ORF 21_KS02          GVTVMANPAAFVEFSRQRGLAPDGRCKAFADAADGTAWSEGAGILLVERL
                     ** **  *  *: ******:*.*** *.::  **** *.**.*:*::*:*

ORF 22_KS02          SDARRNGHRVLAVVRGSAVNQDGASNGLTAPNGPSQQRVIRQALAQAGLR
ORF 22_KS03          SDARRNGHRVLAVLRGTAVNQDGASNGLTAPNGPSQQRVIRQALAQAGLR
ORF 19_KS01          SDARRNGHRVLAVVRGSAVNQDGASNGLTAPNGLSQQRVIRQALANARLA
ORF 18_KS02          SDARRNGHRVLAIVRGSAVNQDGASNGLTAPSGPSQQRVIRRALADAGLK
ORF 19_KS02          SDAERNGHRILAVVRGSAVNQDGASNGLTAPNGPSQQRVIRRALADARLE
ORF 23_KS01          SDARRNGHPVLAVLRGSAVNQDGASNGLTAPNGPSQQRVIREALADARLT
ORF 20_KS01          SDAQRNGHQVLAVLRGSAINQDGASNGLTAPNGPAQQRVIRQALADARLS
ORF 21_KS01          SDARRHGHPVLAVVRGTAVNQDGASSGLTAPNGPSQQRVIRQALDSAGLA
ORF 22_KS01          SDARRLGHEVLAVVSGSAVNQDGASSGLSVPNGPSQQRVIRQALENARLS
ORF 19_KS03          SDARRNGHPVLAVLRGSAVNQDGASNGLTAPNGPSQQRVIRQALANARLE
ORF 18_KS01          SDARRNGHRVLAVVRGTAINSDGASNGLTAPNGAAQQRVIRRALANAGLA
ORF 21_KS02          SDARRLGHPVLALVRGSAVNQDGASNGLSAPNGPSQQRVIRQALANAGFA
                     ***.* ** :**:: *:*:*.****.**:.*.* :******.** .* :

ORF 22_KS02          PSDVDAVEAHGTGTTLGDPIEAQALLATYGQDR--EEPLWLGSVKSNLGH
ORF 22_KS03          PSDVDAVEAHGTGTTLGDPIEAQALLATYGQDR--EEPLWLGSVKSNLGH
ORF 19_KS01          PSDVDAMEAHGTGTRLGDPIEAQALLATYGQDR--TTPLWLGSVKSNIGH
ORF 18_KS02          PSEVDAVEAHGTGTPLGDPIEAQAMLATYGQDR--DRPLWLGSLKSNLGH
ORF 19_KS02          PSEVDAVEAHGTGTTLGDPIEAQALLATYGQGRE-DAALWLGSIKSNIGH
ORF 23_KS01          TADVDVVEAHGTGTTLGDPIEAQALLATYGKGRPSDRPLWLGSIKSNLGH
ORF 20_KS01          PGQVDVVEGHGTGTTLGDPIEAQALLATYGQDR--ERPLLLGSLKSNIGH
ORF 21_KS01          PHQVDVVEAHGTGTTLGDPIEAQALLAAYGQER--VRPLWLGSLKSNVGH
ORF 22_KS01          AGQIDVVEGHGTGTTLGDPIEAQALLATYGREKSADRPLWLGSLKSNIGH
ORF 19_KS03          PSEVDAVEAHGTGTTLGDPIEAQALLATYGQDR--ERPLLLGSVKSNIGH
ORF 18_KS01          PSEVDAVEAHGTGTVLGDPIEAQALLATYGRDR--ERPLLLGSVKSNIGH
ORF 21_KS02          PSDVDAVEAHGTGTSLGDPIEAQALLAAYGGER--EHPLWLGSVKSNLGH
                     . ::*.:*.*****  *********:**:**  :    .* ***:***:**

ORF 22_KS02          TQAAAGVAGVIKMVEAMRHGVLPRTLHVDEPSSHVDWTGGAVSLVTESRE
ORF 22_KS03          TQAAAGVASVIKMVEAMRHGVLPRTLHVDEPSSHVDWTEGAVSLLTETRD
ORF 19_KS01          SQAAAGVASIIKLVEAMRHGVLPKTLHVDAPTSHVDWSEGAVSLLTEAEP
ORF 18_KS02          TQAAAGVGGIIKMVQAMHHGVLPRTLNLGTPTTKVDWTSGNVSLLSEPVA
ORF 19_KS02          SQAAAGVAGVIKMVEAMRRGVLPKTLHVTEPSSHVDWTAGAVSLLTEARL
ORF 23_KS01          TQAAAGVAGIIKMVQALRSGILPRSLHAETPSSHVDWSAGAVSLLAEARP
ORF 20_KS01          TQAAAGVGGVIKMVQAIRHGIAPRTLHVDAPSSHVDWSAGEVSLLTGEQP
ORF 21_KS01          SQAAAGVGGVIKMVQAIRHGIAPMTLHVDTPTSKVDWEAGSVELLTEARP
ORF 22_KS01          SQSAAGVGGVIKMVQAIRHGILPRTLHAEDPSSKVDWSAGAVELLTEARG
ORF 19_KS03          TQAAAGVAGVIKMVLAMRHGTLPRTLHVDTPTSRVDWAAGRIELATEPTQ
ORF 18_KS01          TQSAAGVAGVIKMVQAMRHGVLPKTLHADEPTPKVAWSSGAVELLNETVA
ORF 21_KS02          TQSASGVAGVIKMVQAIRHGVLPRTLHVDAPTTEVDWTAGDVRLLTEPVD
                     :*:*:**..:**:* *:: *  * :*:   *:..* *  * : *

ORF 22_KS02          WPDTGRPRRAGVSSFGISGTNAHTIIEAV
ORF 22_KS03          WPDTGRPRRAGVSSFGISGTNAHVVLEAD
ORF 19_KS01          WPKTDRPRRAAVSSFGISGTNAHVVLEQP
ORF 18_KS02          WPETGGPRRAAVSSFGISGTNAHVVLEQA
ORF 19_KS02          WPDAGRPRRAAVSSFGISGTNAHVVLEQG
ORF 23_KS01          WPELDRPRRAAVSSFGISGTNAHVVLEAA
ORF 20_KS01          WPETGEPRRAGVSSFGISGTNAHVILEQA
ORF 21_KS01          WPETGEPRRAGISSFGVSGTNAHVIVEQA
ORF 22_KS01          WPETGQPRRAGVSSFGVSGTNAHTIIEQA
ORF 19_KS03          WPETGGPRRAAVSSFGMSGTNAHVVLEQA
ORF 18_KS01          WPENGAPRRAAVSSFGMSGTNAHAVLEQA
ORF 21_KS02          WPDTGRPRRAGVSSFGVSGTNVHTLIEEV
                     **.  . ****.:****:****.*.::*
```

Figure 13a

```
ORF_19_AT01                GPVPFVLSGKTEAALHEQVARVR-ELARDSDVTAADLAFSLATTRTALDH
ORF_22_AT01                GAVPAVLSGKTAEALRDQVVRLRSHILARPELSVADVAASLATTRVLHEH
ORF_19_AT02                GPAAFVLSAGSEAALHDQASRLR-DFLAETPAALADVAFSLATTRAALEH
ORF_22_AT02                DVPPWPLSGKTEEALRAQASRLHDHLLATPEVTAADVALSLT-ARADLEH
ORF_21_AT02                TWVPWVLSAKTEEALRSQASRLHAQLEEHP-GDDSDIAYTLATARAGLEI
AAF71776_ATMA03|NYST       GVVPLPLSGKSPEALRDQAARLLAGLAERPALRPLDLGYSLATTRSAFDH
ORF_22_AT03                DVLAFPLSAKTQDALREQAARLRARLLTGHAPELADVAQTLA-TRGLFEH
ORF_18_AT01                PTWLFPVSGRDEKALRRQAARLR---EALPDSDLPAIAAALATTRSALEW
ORF_20_AT01                -VLPFVLSGRSEEALAAQASKLAAYLTGEP--APKAIARALAETRSALPH
ORF_23_AT01                -ATPWLLSARTPEALRARAAQLRSFVDLPG--AAATLA-----ARPLFGH
ORF_18_AT02                -VLPFVLSGKTSAALAAQADRLAGHLAGDV--SLPAVARALAVTRSALDH
ORF_19_AT03                -VVAWPLSAKEPEAVAAQAARLKSFLTGE---RPADVAYSLATARTTLEH
ORF_21_AT01                -VTPLVLSARSAEALRAQSARLREHLRQTE--SLTDTAFSLATSRAALEH
AAF71775_ATMM01|NYST       -ALPWIVSGHSPQALRDQAAALAARVETDPALRPQDIGHTLHTARALLER
                                 :*.    *:  :   :                    .     :*

ORF_19_AT01                RAALVGT-LDDLLT----------ATLVEGRA-TDGGTAFLFTGQGSQR
ORF_22_AT01                RGAIVAADRDQLLAGLDILAAGATTAGVSQGVA-TDGRTAFLFTGQGSQR
ORF_19_AT02                RAAVVAADRETLLAALEN--------LTVTGRA-TEGRTAFLFTGQGSQR
ORF_22_AT02                RAVLVAGDRDGLLATLDALAHGETTEGIVRGTARHTGRTAFLFTGQGSQR
ORF_21_AT02                RAAVTGPDRLRELALLAEG----TPSAAVLRGALTAGAPGFLFTGQGSQK
AAF71776_ATMA03|NYST       RAVVLATDRADAVRALTALAAADADLSAVVGDT-RTGRHAVLFSGQGSQR
ORF_22_AT03                RAVVTAGDRDGLLDALAALAGG-EPGDFVTGLAKPGGKLAFLFTGQGSQR
ORF_18_AT01                RAVVTVADRAGLLAGLDALATGEALPSLVHGTA----RIGIVFSGQGSQR
ORF_20_AT01                RAVVLAEDLGELLGGLRSLAEGEPAARVLTGTAEA-GKAVFVFPGQGSQW
ORF_23_AT01                RAAIVGDPR----AALDALATGKPSNLLIEGTAQS-GKAVFVFPGQGSQW
ORF_18_AT02                RAVVVAGDRAGLTAGLRALADAVPAPHVVDGVAEN-GKAVFVFPGQGSQW
ORF_19_AT03                RAVVVGEDP---IAGLAALAAGEPSGSVVTGTATS-GKAVFVFPGQGSQW
ORF_21_AT01                RAVVVAEAD----ASLDALAAGAPAAGLVEGIALPPGKVAFVFPGQGSQW
AAF71775_ATMM01|NYST       RAVVVAPDRAELLAATHELAAGRSANAVVEGLADVEGRTVFVFPGQGSQW
                           *..:                                :      .:*.*****

ORF_19_AT01                LGMGRELAERFPVFAQAFDDVSSRFERPI----------AELSAEE--LN
ORF_22_AT01                RGMGRELAERFPVFAEAFDDVCARFERPI----------KELSTEE--LN
ORF_19_AT02                LGMGLQLAERFPVFAAAYDEVCSRFEQPL----------RDLTAEE--LN
ORF_22_AT02                LGMGRELAERFPVFAEVYDEVCSRFEQPL----------RDLSAEE--LN
ORF_21_AT02                PGMGAELAARFPVFAAAFDEVCAHLDPRLGLSL-----REVLETER--VH
AAF71776_ATMA03|NYST       LGMGRELYERFPVFAEALDVAIDHLDAALPAQASLREVMWGDDVEL--LD
ORF_22_AT03                AGMADELSAAFPVFARTFGEICARFDTLLDRPLR-----EALAGDL--VD
ORF_18_AT01                AGMGRELHRRFPVFAAAFDDACGHLDLQLDRPLAEIVFADEGTEEAGLLH
ORF_20_AT01                VGMAEELLLSAPVFAESMAECERALSSFVDWKLS---DVLS---DAAALE
ORF_23_AT01                VGMAEELLLSAPVFAESMAECEQALSSFVDWKLS---DVLS---DAAALE
ORF_18_AT02                TGMAVDLLGSSAVFAEAMADCEAALLSHLDWKLT---HVLS---DAAALE
ORF_19_AT03                AGMAVELLASAPVFAESMAECEAALLSYVDWKLT---EVLS---DATALE
ORF_21_AT01                AGMALELKDSSPVFRAALLDCERALSSFVDWKLT---DVLG---DATALE
AAF71775_ATMM01|NYST       VGMGAQLLDESAVFAERIAECAAALAEFTDWSLV---DVLRGVVGAPSLE
                            **. :*    .**          :                      :.

                             M1          M2                 M3
                            -----      --------           -----
ORF_19_AT01                QTANTQCALFAFEVALFRLVENWGLRPDFLAGHSVGEIAAAHVADVLSLD
ORF_22_AT01                QTANTQCALFAFEVALFRLVESWGVRPDFLAGHSIGEIAAAHVAGVFNLD
ORF_19_AT02                QTANTQCALFALEVALFRLVESWGVRPDFLAGHSVGEIAAAHVAGVLSLD
ORF_22_AT02                QTANTQCALFALEVALFRLVESWGVRPDFLAGHSVGEIAAAHVAGVLSLD
ORF_21_AT02                ETAFAQCALFAVEVALFRLLESWGVRPALLLGHSVGEIAAAHVAGVLSLA
AAF71776_ATMA03|NYST       ETGWTQPALFAVEVALFRLVESWGVRPDFVAGHSIGEIAAAHVVGVFSLE
ORF_22_AT03                RTEYTQCAMFAVEVALFRLVESRGVRPDFLAGHSIGELAAAHVAGVWSLE
ORF_18_AT01                RTEYAQCALFAVEVALFRLYEHWGLRPDYVAGHSIGELAAAHVSGMLSLS
ORF_20_AT01                RVDVVQPVLFAVMVSLARLWRACGVEPAAVVGHSQGEIAAACVAGALSLD
ORF_23_AT01                RVDVVQPVLFAVMVSLARLWRACGVEPAAVVGHSQGEIAAACVAGALSLD
ORF_18_AT02                RVDVVQPVLFAVMVSLARLWRACGIEPAAVVGHSQGEIAAACVAGALSLE
ORF_19_AT03                RVDVVQPALFAVMVSLARLWRASGIEPAAVVGHSQGEIAAACVAGALSLD
ORF_21_AT01                RVDVVQPALFAVNVSLAALWRACGVEPDAVTGHSQGEIAAAYVSGALSLA
AAF71775_ATMM01|NYST       RVDVVQPASFAVMVSLAALWGSRGVLPDAVVGHSQGEIAAAVVSGALSLR
                           ..  .* . **. *:*  *    *: *  : ***  **:*** * .  .*
```

Figure 13b

```
ORF_19_AT01              DAVTLVSAPGRLM-QALPTGGAMVALQATEAEVAPLLTDR---VSLAAIN
ORF_22_AT01              DAVKLVAAPGRLM-QALPTGGAMVALQATEAEVFPLLTDR---VSLAAIN
ORF_19_AT02              DAVTLVSAPGRLM-QALPTGGAMVALQATEAEVTPLLTER---VSLAAIN
ORF_22_AT02              DAVTLVSAPGRLM-QALPTGGAMVALRATEAEVTPLLTER---VSIAAIN
ORF_21_AT02              DAATMVEAPGRLM-GALPSRGVMIALQANEDEVTPLPTER---VSIAAVN
AAF71776_ATMA03|NYST     DACRLVAAPATLM-QALPTGGAMIAIQAAEDEVTQHLTDD---VSIAAVN
ORF_22_AT03              DACTVVAAPGRLM-QALPSGGAMIAVQATEEEVRPLIDDET--VSIAAIN
ORF_18_AT01              DAAALVAAPGRLM-QDTREGGAMLAVQATEDEVLPLLDER---LAIAAVN
ORF_20_AT01              DAARLVCLPSKAI-LALSGRGGMVSVAASEDRVRELLPAG---VSVAAVN
ORF_23_AT01              DAARVVCLPSKAI-LALSGLGGMVSVAASEDRVRELLPAG---VSVAAVN
ORF_18_AT02              DAARVVCLPSKAI-LALSGLGGMVSVAASEDRVRELLPDG---VSVAVVN
ORF_19_AT03              DAARVVCLPSKAI-TALSGRGGMVSVAAPEAQVREILPEG---VSLAAVN
ORF_21_AT01              DAAKVVALPAKAI-LALSGAGGMVAVALGRDDVLPRLTEWGDRIAVAAVN
AAF71775_ATMM01|NYST     DGARVVALPSQAIGRALAGRGGMMSVALSVDVLEPRLVEFEGRVSVAAVN
                         *.  :*  *.  :       * *:::      :           :::*.:*

                                                          M4
                                                          ----
ORF_19_AT01              GPESVVVSGDEEAVAAVVSHF--EGRKSKRLTVSHAFHSPLMEPMLDDFR
ORF_22_AT01              GPESVVLSGDEDAVAAVVSRF--EGRKHKRLAVSHAFHSPLMEPMLDDFR
ORF_19_AT02              GPESVVVSGEEDAVAAVVSQF--EGRKSKRLTVSHAFHSPLMEPMLDEFR
ORF_22_AT02              GPESVVVSGDEDAVAAVV-----EGRKHKRLTVSHAFHSPLMEPMLDEFR
ORF_21_AT02              GPEAVVLSGDEDAVTAVVDRF--ADRKSKRLVVSHAFHSPLMEPMLADFR
AAF71776_ATMA03|NYST     GPTSVVVSGAESAARTVADRLAENGRKTTRLRVSHAFHSPLMDPMLAEFR
ORF_22_AT03              GPVSVVVSGEEAAVTALAAGFAERGRKTKRLTVSHAFHSPLMDGMLGEFR
ORF_18_AT01              GPRSVVVSGDEAAVEEVAAAF--ARRKTKRLKVSHAFHSHHMDGMLDEFR
ORF_20_AT01              GPSAVVVSGDVAGLEALLKRCELLDVRAKRIPVDYASHSAHVDAIEQEVL
ORF_23_AT01              GPSAVVVSGDVAGLEALLKRCELLDVRAKRIPVDYASHSAHVDAIEQEVL
ORF_18_AT02              GPASVVVSGDVAGLEALLKRCELLDVRAKRVPVDYASHSAHVDAIEQQVV
ORF_19_AT03              GPASVVVSGDVAGLDALMTACEASGLRAKRIPVDYASHSAHVDAIEQDVL
ORF_21_AT01              GPASVVVSGDPEALDGLVSACEADGVRARRIPVDYASHSPQVDVLREELL
AAF71775_ATMM01|NYST     GPRSVVVAGEPEALDALHARLTADDIRARRIAVDYASHSHQVEDLHEELL
                         ** :**::*   .   :         :  *: *.:* :*  :: :  :.

ORF_19_AT01              AVVEGLTFAEPRIPIVS------GGLAEVSTSDYWVRHVRDAVRFHDSVE
ORF_22_AT01              AVADSLSYAAPRIPIVS------GGLADVSTSDYWVRHVRDAVRFHDSVK
ORF_19_AT02              VVADSLSYAAPRIPIVS------GGLAEVSTSDYWVRHVRDAVRFHDSVK
ORF_22_AT02              TVVEGLTFAAPRIPIVS------GGLAEVSTSDYWVRHVRDAVRFHDSVK
ORF_21_AT02              RVVSGLSFSEPRIPIVSTVT--GRSDPEIASPGYWVRHVREAVRFHDAIR
AAF71776_AT03|NYST       AVAEGLSYATPTLPVVSNLTGRLATADDLCSAEYWARHVREAVRFADGVS
ORF_22_AT03              AVLDGIAAADPRIPLVSTLTGDPLTGDQARSSEYWVRHVRDAVRFCDAIR
ORF_18_AT01              RFAEILTFRKPVIPLVSTVSG--ELLTEATAPEYWVEHVRRPVRFADGVR
ORF_20_AT01              SALAGISPQAPVIPFYSTVTD-EPLE---LDAAYWFRNLRGTVRFAATVD
ORF_23_AT01              SALAGISPQAPVIPFYSTVTD-EPLE---LDAGYWFRNLRGTVRFAATVD
ORF_18_AT02              TALSGIMPREAELPMYSTVTG-EPIDTTTLDAAYWFRNLRATVRFDQAVR
ORF_19_AT03              AALDGIEPRAPEIPFYSTVAG-EPLDP-VVDAAYWFRNLRGTVHFGQAVR
ORF_21_AT01              GLLDGVEHHASTVPFYSAVTG-EPLDTAGLTPEYWFRNLRATVRFDRSVR
AAF71775_AT01|NYST       EVLAELAPRTSEVPFFSTVTG-DWLDTARMDAGYWFRNLRGRVRFADAVA
                               :    . :*. *                . ** .::*  *:*   :

ORF_19_AT01              F--LKAEGVTRFLEIGPDAVLTAM-----AKESAE----DAVVLPASRRD
ORF_22_AT01              F--LETEGVTRFLEIGPDAVLTAM-----AQESTE----GAVVVAASRRN
ORF_19_AT02              F--LEAEGVTRFLEIGPDGVLTAM-----AKETAE----DAVVVPALRRD
ORF_22_AT02              F--LEAEGVTRFLEIGPDGVLTAM-----AQDSLE----DAVVVPALRRD
ORF_21_AT02              FAEAEAEGVRAFVELGPEGVLSAM-----AKDFLE----DTVLIPTLRGE
AAF71776_AT03|NYST       T--LENEGVTTFLELGPDGVLSAM-----AQQSLTG---DAATVPALRKD
ORF_22_AT03              T--LEAQGVRRYLELGPDAPLTALGEHCVTNESTVD---AQLFVPSLRAG
ORF_18_AT01              R--LDELGVDVLLELGPDAVLTPM-----AAEVLDGE--GAALVPSLRGS
ORF_20_AT01              R--LLEDGFRFFVEASPHPVLVPG-----ISE-------EAIALGSLRRG
ORF_23_AT01              R--LLEDGFRFFVETSPHPVLVPG-----ISE-------DAVALGSLRRG
ORF_18_AT02              R--LIADGFRFFVETSPHPVLVAG-----LTELVEEAAVPAVALASLRRD
ORF_19_AT03              R--LLDDGFRFFVEASPHPVLVTG-----IADTAEDAGERAVAVGSLRRD
ORF_21_AT01              R--LLDDGHRFFVEASAHPVLTGS-----VTETIEERGAHAVALGSLRRD
AAF71775_AT01|NYST       D--LLAAEYRAFVEVSSHPVLTMA-----VLDLIEEAGVTAVATGTLRRD
                                     :* ...  *           :               : *
```

Figure 13c

```
ORF_19_AT01              RPEVTTLLTAVAGLHVHGAEVDWAPLFDG--ARRVDLPTYPFQYEHFWL-
ORF_22_AT01              RAEDVTLLAAVSTLHVHGASVDWTPLLAG--ARRVDLPTYAFQHRRFWL-
ORF_19_AT02              RPEVETLLTAVAGLHVHGVGVDLTALLGG--GSPVDLPTYAFQHRRFWL-
ORF_22_AT02              KPEVTTLLTAVAGLHVHGAGVDWSPLSAG--ARRVDLPTYAFQRTEFWL-
ORF_21_AT02              RPEVAALATTLGRLHVHGVGIDWAGVFDGVQASRVTLPTYPFEHRHFWL-
AAF71776_AT03|NYST       RDEETSALTALAHLHTAGLRVDWAAFFAGSGATRVDLPTYAFQHATYWP-
ORF_22_AT03              RSDVESFVTALARLHVDGVRVDWAKALPG---RKIDLPTYAFQHERFWL-
ORF_18_AT01              RPEAEALAASLAELWVRGAELGWPQVFGA--HPRADLPTYAFERQRYWL-
ORF_20_AT01              EGGAERFVASLAEAHTQGLSPSWSAVLPP--AERVDLPTYAFQHKRFWLE
ORF_23_AT01              EGGAERFVASLAEAHVHGLSPAWSSILPT--ADWVDLPTYPFQRKRFWLE
ORF_18_AT02              EGGPTRFVTSLAEAHVHGLSPDWAALLPE--AGWVDLPPYAFQHQEFWLT
ORF_19_AT03              EGGPLRFLTSLAEAHVHGLSPDWAALAP---GTRVDLPTYAFQHEHYWLR
ORF_21_AT01              EGGPRRFLTSLAEAHVRGLRPDWAALWPT--ATRVDLPTYAFQRVPYWLD
AAF71775_AT01|NYST       QGGAGRFLLSAAEVFVRGVDVDWAGAFEGTGAARVDLPTYAFQRERYWNT
                         .         : .    . *      .               **.*.*:    :*
```

Figure 14

```
ORF 22_DH02          AGLSDAGHPLLGGAVTLPDSGGTVFTGRLSLAAQPWLADHAVGFTVLLPG
ORF 22_DH03          LGQSPAGHPLLGAAVEAPDSGAVLFTGRLSVQEQPWLADHVVAGTTLLPG
ORF 20_DH01          FGQTVVDHPLLGAALPLADGDGLVLTGRISPDTQPWLVDHTVLDTVLLPG
ORF 23_DH01          FGQTVVDHPLLGAVVAVPGTGGLLYTGRISLETHPWLADHAVSGTVLVPG
ORF 18_DH02          FGLGATGHPLLTAATALPGSGGLLLTGRISTAAQPWLADHAVQGVVLLPG
ORF 19_DH03          AGLDDGGHPLLGAVVPLAGSDGLVATGRISARNQTWLPDHAVGGALLLPG
ORF 21_DH02          FGLGEAGHALLGAAVPVPGGSGISFTGRLSLRAQPWLAEHVVLGTALLPG
ORF 19_DH02          AGLGTTDHPLLGAAAALPGDGGFLLTGRLSGHAQPWLAEHRVGGVVLLPG
ORF 22_DH01          LGLGATDHPLLGAVVTMADAHGVLLTGRLSLAAQPWLAGHVVAGHVLLPG
ORF 19_DH01          AGLDASPHALLAAAVRPAGEDEILLTGRISLSTLPWLADHVVGGNVLLPG
ORF 18_DH01          YGLGDTGHPLLRASVTTAEDGALLLSGRLSPLTQPWLADHVVGGDVVLPG
                      *     *.** .    .       :**:*    .**   * *    ::**

ORF 22_DH02          TAFVDLALAAGRRHGRVVLDELTLESPLVLPEHGGVDLRVWVREPDDTGA
ORF 22_DH03          TAFVELALRAGELTGCAAVDELTLEAPLVLPDHGGTALRIVAAAPDETGR
ORF 20_DH01          TAFVELVLRAGREAGCDGVDELTLEAPLVLDG--PVALQVVLGEPDERGR
ORF 23_DH01          TAFVELALAAGTQVDCALLDELTLEAPLVLEEGTDVRLSVELGDADVDGR
ORF 18_DH02          TAFVELALQAGTHAGCGRIDELTLEAPLPLPEQGGVRVQVVLG-SEVNGR
ORF 19_DH03          AALVDLALTVGERTGCGRIAELTIEAPLVLGESGSARLQVTVGASADDGT
ORF 21_DH02          TAFVDLALHAGDRAGCGTVAELTLEAPLALPESGDVRLHVTVGEPGEDGG
ORF 19_DH02          TAFVEIALRAGDEAGCGHLEDLTLEAPLVLPERGATQLSVLVGAADDTGR
ORF 22_DH01          TAFVDLVLHAGDKVDCGIVEELTLREPLVLPEHDALSLQLVVGAPDETGR
ORF 19_DH01          TAFAELALAAADEAGCEAVEELNLEAPLVLPEKGGVQLQVAVGAADDQGR
ORF 18_DH01          TALLELALRAAELAGAGGVEELTLEVPMVLSEA-GVQVQVSVRDSG----
                     :*: ::.* ..    .    : :*.:. *: *        : :     .

ORF 22_DH02          CAVSVHS
ORF 22_DH03          RALDVYS
ORF 20_DH01          RAVSVHS
ORF 23_DH01          REVGVYS
ORF 18_DH02          REVTVHS
ORF 19_DH03          REVAVYS
ORF 21_DH02          RTIEIHS
ORF 19_DH02          RTIEIHS
ORF 22_DH01          RTVGVHS
ORF 19_DH01          RSVTVHA
ORF 18_DH01          --LLIFF
                       : :.
```

Figure 15

```
ORF 18_ER02              QLAWRDGELLVPRLAKVSTDGTLTPPEGP--WVLDAPRRGTLEELALVPA
ORF 19_ER03              QLALRAGTVLGARLVKASADTALVPPPGSRAWTVDTLGGGTLENLVLRDR
ORF 19_ER02              QIALRDGRALAPRLATTASSTELTPPEGA--WRLDTTGRGTLENLTLVPS
AAF71767_ER01|NYST       QAVVREGTVRVGRLARLDSGRGLVPPPGT-PWRLGSRAKGSLDGLALLPH
AAF71776_ER03|NYST       QLALRDGGVLAARLARFDTAAALTPPADR-AWRLDSTAKGSLNGLALTPY
                         * . * *     **.   :   *.** .   * :.:   *:*: *.*

ORF 18_ER02              PTAARPLADGEVRIQVRAAGINFRDVLITLDMYPE-DKAVMGSEGAGIVT
ORF 19_ER03              PDLLAPLADGQVRIAVRSAGLNFRDVVVALGLVP--GQEGIGGEGAGVVT
ORF 19_ER02              PEAVAPLAEGEVRIAVRAAGLNFRDVLIALGMYP--GAATLGSEGAGVVT
AAF71767_ER01|NYST       PEARRPLTGHEVRVGIRAAGLNFRDVLNALGMYPG-DAGLFGSEAAGVVV
AAF71776_ER03|NYST       PAALAPLTGHEVRVEVRAAGLNFRDVLNALGMYPGDDVGSFGSEAAGVVV
                         *    **:  :**: :*:**:*****: :*.: *  .   :*.*.**:*.

ORF 18_ER02              EIGSGVTGLKPGDRVFGLFDGAFGPVAIADRRTVTEMPVDWTFAEAAALP
ORF 19_ER03              ETGPGVTDLAPGDRVLGMFDASFGPIAVADRKLIAPVPDDWSFTEAASAP
ORF 19_ER02              EIGPGVTGLDVGDRVFGLMSNGFGPQVVTDHRTLAKMPEDWSFATAASVP
AAF71767_ER01|NYST       EVGPEVTGLAPGDRVMGMLFGGFGPLGIADARLLTPVPADWSWETGASVP
AAF71776_ER03|NYST       EVGPEVTGLAPGDQVMGMITGSFGSLAVDDARRLARLPEDWSWETGASVP
                         * *. **.*  **:*:*::  .**.  : * : :: :* **::  .*: *

ORF 18_ER02              VVFLTAYYGLVDLGGLRPGEKVLIHGATGGVGMAAVQLARHLGAEVFATA
ORF 19_ER03              VAFLTAYVGLADLGELRPGQTVLIHAAAGGVGMAAVQLARHFGAEIYVTA
ORF 19_ER02              IVFLTAYYGLFDLARLEAGESILVHAAAGGVGMAATQLARHAGAEVFGTA
AAF71767_ER01|NYST       LVFLTAYYALKELGGLRAGEKVLVHAGAGGVGMAAIQIARHVGAEVFATA
AAF71776_ER03|NYST       LVFLTAYYALKELGGLRAGEKVLVHAGAGGVGMAAIQIARHVGAEVFATA
                         :.***** .* :*. *..*:.:*:*..:***** *:*** *:** ***:: **

ORF 18_ER02              SPGKWEVLRGLGFDDEHIASSRTLDFEDRF-----GR-MDVVLDSLAKEF
ORF 19_ER03              SPAKWDTLRAMGFDDDHIASSRTLDFEDKIREATGGRGVDLVLDSLAREF
ORF 19_ER02              GPGKWDTLRANGFDDTHLSSSRDLGFEEKFRDATGGRGVDVVLNSLAGDY
AAF71767_ER01|NYST       SEGKWDVLRSLGVADDHIASSRTLDFEAAFAEVAGDRGLDVVLNALSGEF
AAF71776_ER03|NYST       SEGKWDVLRSLGVADDHIASSRTLDFEAAFAEVAGDRGLDVVLNSLAGDF
                         . .**:.**. *. * *:***** *.**  :     .* :*:**::*: ::

ORF 18_ER02              VDASLRLLGEGGRFVEMGKTDIRDADEVAAAHPGVTYRAFDLLDAGRPRI
ORF 19_ER03              VDASLRLVREGGRFVEMGKTDIRDADEVAAAHPGVTYRAFDLIDSGHDRI
ORF 19_ER02              VDASLRLLAPGGRFAEMGKTDIREPGE-----TGVEYHPFDVIDAGPERI
AAF71767_ER01|NYST       VDASMRLLGDGGRFLEMGKTDIRAADSVP---DGLSYHSFDLGMVDPEHI
AAF71776_ER03|NYST       VDASMRLLGDGGRFLEMGKTDIRAADSVP---DGLSYQSFDLAWVVPETI
                         ****:**:  **** ******** ...      *: *:.**:       *

ORF 18_ER02              GEILAELLDLFGAGSLTVPRPTVWDARRAPEVFRFMSQAKHIGKNVLTIP
ORF 19_ER03              QEILGELLALADKDVVRPLPTTAWDVRRAPEAFRFLSQAKHTGKIVLEPP
ORF 19_ER02              HEMLAALLELFAAGALTPLPVTGWDVRRGPDAFRFLSQAKHVGKNVLTMP
AAF71767_ER01|NYST       QRMLLDLVELFDRGALAALPVRSWDVRRAGEAFRFMSLAQHIGKIVLTVP
AAF71776_ER03|NYST       GTMLAELMDLFRTGALRPLPVRTWDVRHAKDAFRFMSMAKHIGKIVLTLP
                           :*  *: *   . :       **.*:. :.***:* *:* ** **  *
```

Figure 16

```
ORF18_KR01          TGGTVLITGGTGGLAGLLARHLVERHEVRSLLLVSRRG----AAGPLVDD
ORF19_KR03          PEGTVLITGGTGVLGGLFARHLVTAHGVRRLLLTSRRGLDAEGARELVAD
ORF18_KR02          GNGTVLITGATGTLGALVARHLVTVRGVRHLLLVGRRGRAAAGMAELEAE
ORF19_KR02          PDGTVLVTGGTGALGALFARHLVRERGVRRLLLASRRGHDAPGVPELVAE
ORF21_KR02          PGKTVLVTGGTGALGALVARHLVTARGVTRLLLVSRRGLEAEGAKDLVAD
ORF22_KR01          -DGTVLVTGGTGALGADLARHLVRSRGVRRLLLTSRRGAAAPGADTLTRE
ORF22_KR02          PEGTVLLTGATGALGRSLASHLVSGHGVRHLLLVSRSGAAAHGAKDLLAE
ORF20_KR01          PDDVVLITGGTGRLGQALARHLAVRHGVRGLVLTGRTGG---GAEDLVAD
ORF23_KR01          -DDVVLITGGTGLLGAAVAKHLVVTHGVRSLVLLSRSGASAPGAAALADE
ORF22_KR03          TDGAVLITGGTGALGAALARHLVTAHGKTRLVLAGRRGPDAPGAGELADE
ORF19_KR01          PEGTVLITGGTGALATELARHLVTRRGVRNLILAGRRGPAAEGASELAAE
ORF21_KR01          PRGTVLVTGGTGAVAAHVARWLAG-NGAGHLVLTSRRGAAAEGAAELSDE
                       .**:**.** :.   .*  *.  .    *:* .* *    .   *  :

ORF18_KR01          LTALGADVTVAACDIADRESVAALL----AEHPVSAVVHAAGVLDDATIT
ORF19_KR03          LTGLGATVTVVACDVADRAAVAGLLGSVPPEHPLTAVVHTAGVLDDGLIP
ORF18_KR02          LTAAGASVTIAACDAADRAALAALLATVPAEHPLAGVVHAAGVLDDGLVA
ORF19_KR02          LTEAGASVTVEACDAADRGALAAVLAGIPAAHPLTGVVHTAGVLDDGLVG
ORF21_KR02          LTAAGADVTVEACDVADRAALEAALAG----HELTAVVHTAGVLDDGLVD
ORF22_KR01          LTALGAEVRIEACDAADRDALAALLA----DQPITLAVHAAGVLDDGLIG
ORF22_KR02          LTGLGASVVLESCDVADREALAGLLAGIDPGHPLTGVVHAAGVLDDGLID
ORF20_KR01          LAELGTQVTVAACDVADPDAVRALLA----AHPVTAVVHAAAVLDDGLVD
ORF23_KR01          LTGMGAEVRILACDAADREALRQVLA----AHPVTGVVHAAGVLDDGLIT
ORF22_KR03          LRGLGAEVAVIACDAADREALRRLLA----EHPVTGVVHAAGVLDDVVLD
ORF19_KR01          LADLGAQARIVACDVADRDQLTALLDG----VPLTAVVHAAGVLDDGLLA
ORF21_KR01          LAGLGARVTFAACDVADRDALAAVLA----EYPPNAVVHTAGVGATASLA
                     *   *: . . :** **   :   *            .**:*.*     :

ORF18_KR01          TLDHERLAAVLRPKVTGALVLDELTRDLDLSAFVLFSSSAATFDGAGQAN
ORF19_KR03          ALTPDRLGTVFRPKVDAAVHLHELTRDLGLAAFVLFSSSAATFGAAGQGN
ORF18_KR02          TLTPERLAKVLRPKVDAAVNLHELTRDAHLAEFVLFSSAAGAFGDAGQGN
ORF19_KR02          SLTPERLAKVLRPKVDAALNLHELTSGADLAEFVVFSSAAGVFGNAGQAN
ORF21_KR02          SLTPERLAKVLRPKVDAALNLHELAG--DVEEFVLFSSASATFGNPGQAN
ORF22_KR01          DLSAERLTAVLRSKVDAAVHLHELLG--DT-ELVLFSSAAGVFGNEGQAN
ORF22_KR02          SLTPERFDAVLRPKADAALNLHELAG--DVDEFVLFSSAAGTFGNAGQAN
ORF20_KR01          GLTPDRLGTVLAPKADGARVLHELAG--PVRRFVTFSSAAGVFGNPGQAG
ORF23_KR01          AQTPERLDRVLAPKVDAAVNLHELLP--DAAPFVMFSSAAGVFGNPGQSG
ORF22_KR03          GLTPDRLDAVLRPKVDAAVNLHELAG--DVDEFVLFSSAAGTFGNPGQAN
ORF19_KR01          DLTRDRFETVLRSKVDGAILLDELAG---DAHLVFFSSAAGVLGSAGQAN
ORF21_KR01          ETGPAELADALAAKAGGAAHLDELLEGAELDAFVLFSSNAGVWGGAGQGA
                          .:  .: .*. .*  *.**        :* ** * :. .  **.

ORF18_KR01          YAAANAFLEALALRRRAEGRPGVALGWGLWATG--MGARLDEAGLRRIER
ORF19_KR03          YAAANAFLDALAQHRRAEGLAGQALAWGFWAERSAMTGHLDEADVARMKR
ORF18_KR02          YAAANSFLDSLARHRRAQGLPAVSLAWGFWAELSGMTGHLGEADLARLKR
ORF19_KR02          YAAANGFLDALSVRRAAHGLPARSLAWGLWAETGGMGGTLGEAELARMAQ
ORF21_KR02          YAAANAFLDALARHRHAQGLPATSLAWGLWATDGGMTGELSDTDLARMGR
ORF22_KR01          YAAANAFLDALARHRQANGLPGTALAWGMWAS--GMG-DALTA------R
ORF22_KR02          YAAANAFLDALAQHRQANGLPARSLAWGLWDTDDGMDASAAVA------R
ORF20_KR01          YAAANAYADALMLRRRAEGLPGVSLAWGFWAERSKLTGDLDDTDVRRMAR
ORF23_KR01          YAAANAFVDALVERRRADGAAAASLAWGLWATTSAMTG---SADVDRMAR
ORF22_KR03          YAAANAFLDALARHRHAHGLPATSLAWGLWAG-DGMAGGMSGRDLDRMSA
ORF19_KR01          YAAANAALDAVAARRRERGLPATSLAWGLWETGDGMAGALAGTDRARMAG
ORF21_KR01          YGAANAALDALAERRRARGLPATSVAWGLWGGGSGLAG---QDDVDRLRR
                    *.***.   :::   :*    * .. ::.**:*      :

ORF18_KR01          SGQRALSEVDGLALFDA
ORF19_KR03          SGVSPLSSVDGLALFDA
ORF18_KR02          SGMSPLSTEDGLLLMDA
ORF19_KR02          SGTAALSTQDGLELFDA
ORF21_KR02          TGIAALTPEAGLALFDA
ORF22_KR01          PGFPALSTEDGMALFDA
ORF22_KR02          LTGSGLTTEEGLHLFDT
ORF20_KR01          AGVTALSTEEGLALFDA
ORF23_KR01          AGLTGLSTEEGLDLLDA
ORF22_KR03          SGAGALSTEEGLALFDL
ORF19_KR01          SGLLPLPVGDALTLFDF
ORF21_KR01          LGLAAMDPALAVSALVQ
                          :    .:  :
```

Figure 17

```
ORF 22_AC02          AAVLGYSGPEDVPSDRAFTELGFDSLTSVDLRNRLNSATGLRLPATLVFD
ORF 22_AC03          AGVLGHAGPEQVDPDKAFTELGFDSLAAVELRNRVNEATGLRLPATLVFD
ORF 18_AC02          AAVLGFGSPEQVGVRQAFRELGFDSLSAVELRNRLNAATGLRLPATVVFD
ORF 19_AC03          AAALGHASVAKVGPELAFRDLGFDSLTAVELRNRLGAATGLRLPSTLVFD
ORF 21_AC01          AAVLGHGGAAAVEPDRAFRDLGFDSLTAVEVRDRLAAATGLRLPATLVFD
ORF 19_AC01          AEVLGHRDAGAVEPARPFRELGFDSLTAVELRNGLNAASGLRLPATAVFD
ORF 18_AC01          AAVLGHPDAHAIDPDRAFTEVGFDSLAAVELRNRLIAATGLKIAPTLVFD
ORF 20_AC01          AAVLGHESADAIAGDRGFLELGFDSLTAVELRNRLAEATGLRLPPTLVFD
ORF 22_AC01          AIVLGHLGSEAIDAGKPFQELGFDSLAAVELRNRLTEVTGLRLAATLVFD
ORF 23_AC01          AAVLGHDGADAIDAGVAFLELGFDSLTAVDLRNRLAASTGLRLPPSLVFD
ORF 19_AC02          ATVLGHTAADAVEATRSFQEIGFDSLTAVELRNRLTAATGLRLPATLIFD
ORF 21_AC02          AAALGHAGAGAIDPGKGFVELGMDSLSAVELRNQLCALSGLKLSTTVVFD
ORF 18_AC00          AVLEAKPGAGTAAPGTPFAELGFDSLAAVELHRRISAATALELPVTLVFD
                     *    .             * ::*:*:*::*:::   :    :.*.:. : :**

ORF 22_AC02          HPNSDAVVARLR
ORF 22_AC03          HPTTTAVAELVG
ORF 18_AC02          HPTPTALAETLG
ORF 19_AC03          QPSPAALARHLL
ORF 21_AC01          HPSASALAGHLV
ORF 19_AC01          HPTPKALADLLA
ORF 18_AC01          HPNPRAVAAFLA
ORF 20_AC01          RPNAGALAAYLA
ORF 22_AC01          YPTPLVLAEHLL
ORF 23_AC01          HPTPLAVAERIS
ORF 19_AC02          YPTPEALAAHIG
ORF 21_AC02          HPNPAALAGHLA
ORF 18_AC00          HPTPSALAGHLR
                      *.. .:.  :
```

Figure 18

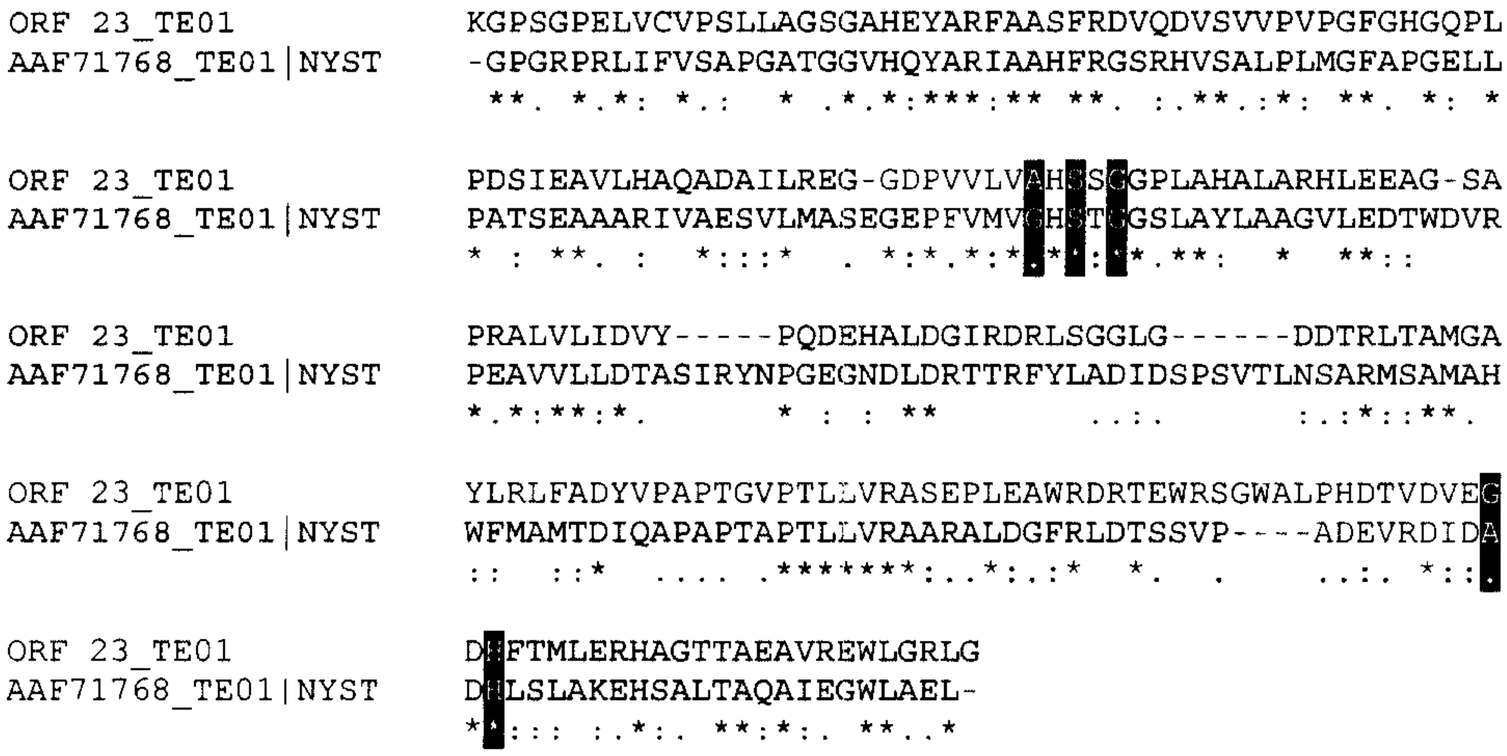

ORF 23_TE01 KGPSGPELVCVPSLLAGSGAHEYARFAASFRDVQDVSVVPVPGFGHGQPL
AAF71768_TE01|NYST -GPGRPRLIFVSAPGATGGVHQYARIAAHFRGSRHVSALPLMGFAPGELL
ORF 23_TE01 PDSIEAVLHAQADAILREG-GDPVVLVAHSSGGPLAHALARHLEEAG-SA
AAF71768_TE01|NYST PATSEAAARIVAESVLMASEGEPFVMVGHSTGGSLAYLAAGVLEDTWDVR
ORF 23_TE01 PRALVLIDVY-----PQDEHALDGIRDRLSGGLG------DDTRLTAMGA
AAF71768_TE01|NYST PEAVVLLDTASIRYNPGEGNDLDRTTRFYLADIDSPSVTLNSARMSAMAH
ORF 23_TE01 YLRLFADYVPAPTGVPTLLVRASEPLEAWRDRTEWRSGWALPHDTVDVEG
AAF71768_TE01|NYST WFMAMTDIQAPAPTAPTLLVRAARALDGFRLDTSSVP----ADEVRDIDA
ORF 23_TE01 DIFTMLERHAGTTAEAVREWLGRLG
AAF71768_TE01|NYST DILSLAKEHSALTAQAIEGWLAEL-

Figure 19

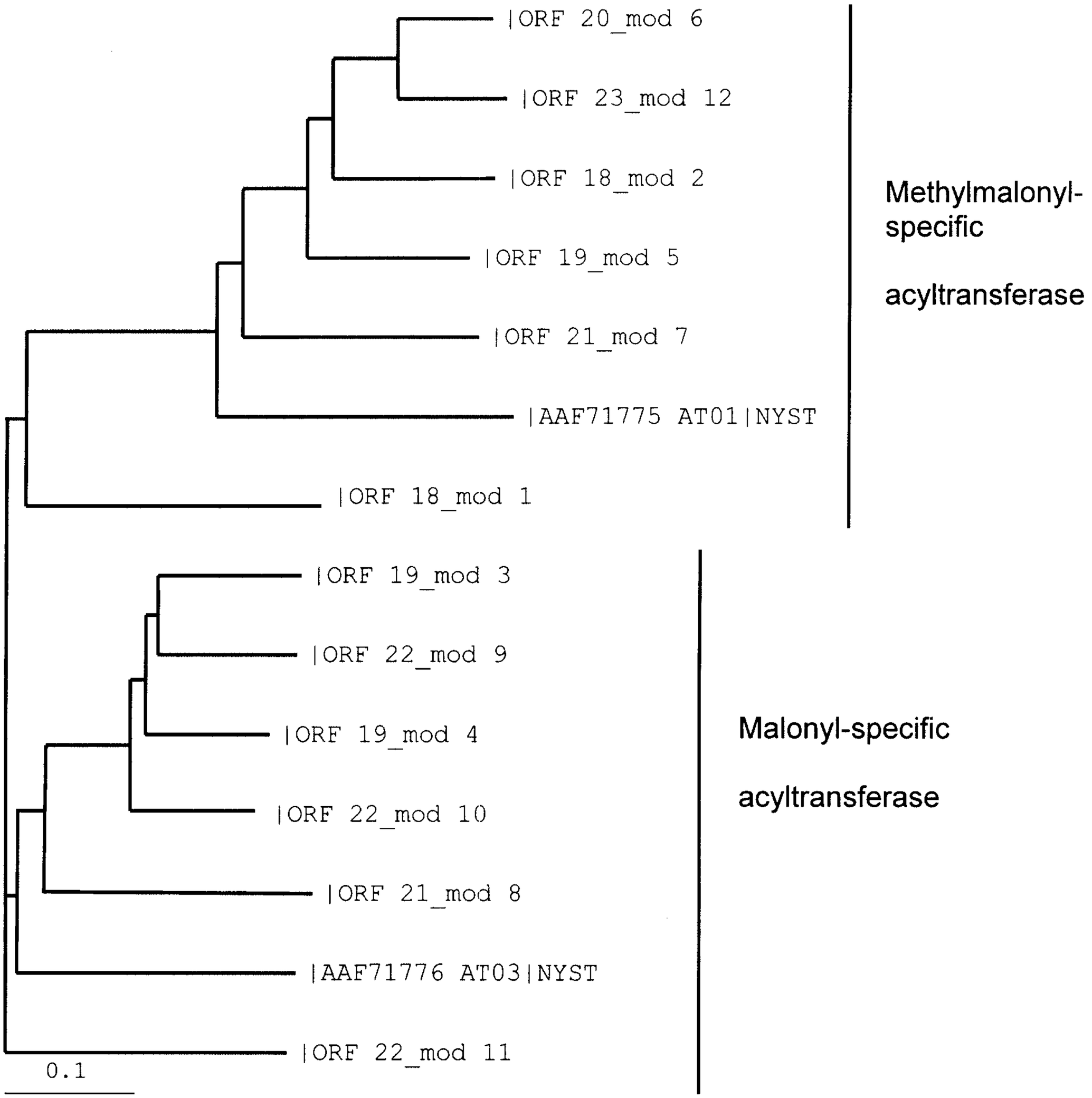

|ORF 20_mod 6
|ORF 23_mod 12
|ORF 18_mod 2
|ORF 19_mod 5
|ORF 21_mod 7
|AAF71775 AT01|NYST
|ORF 18_mod 1
Methylmalonyl-specific acyltransferase
|ORF 19_mod 3
|ORF 22_mod 9
|ORF 19_mod 4
|ORF 22_mod 10
|ORF 21_mod 8
|AAF71776 AT03|NYST
|ORF 22_mod 11
Malonyl-specific acyltransferase
0.1

Figure 20

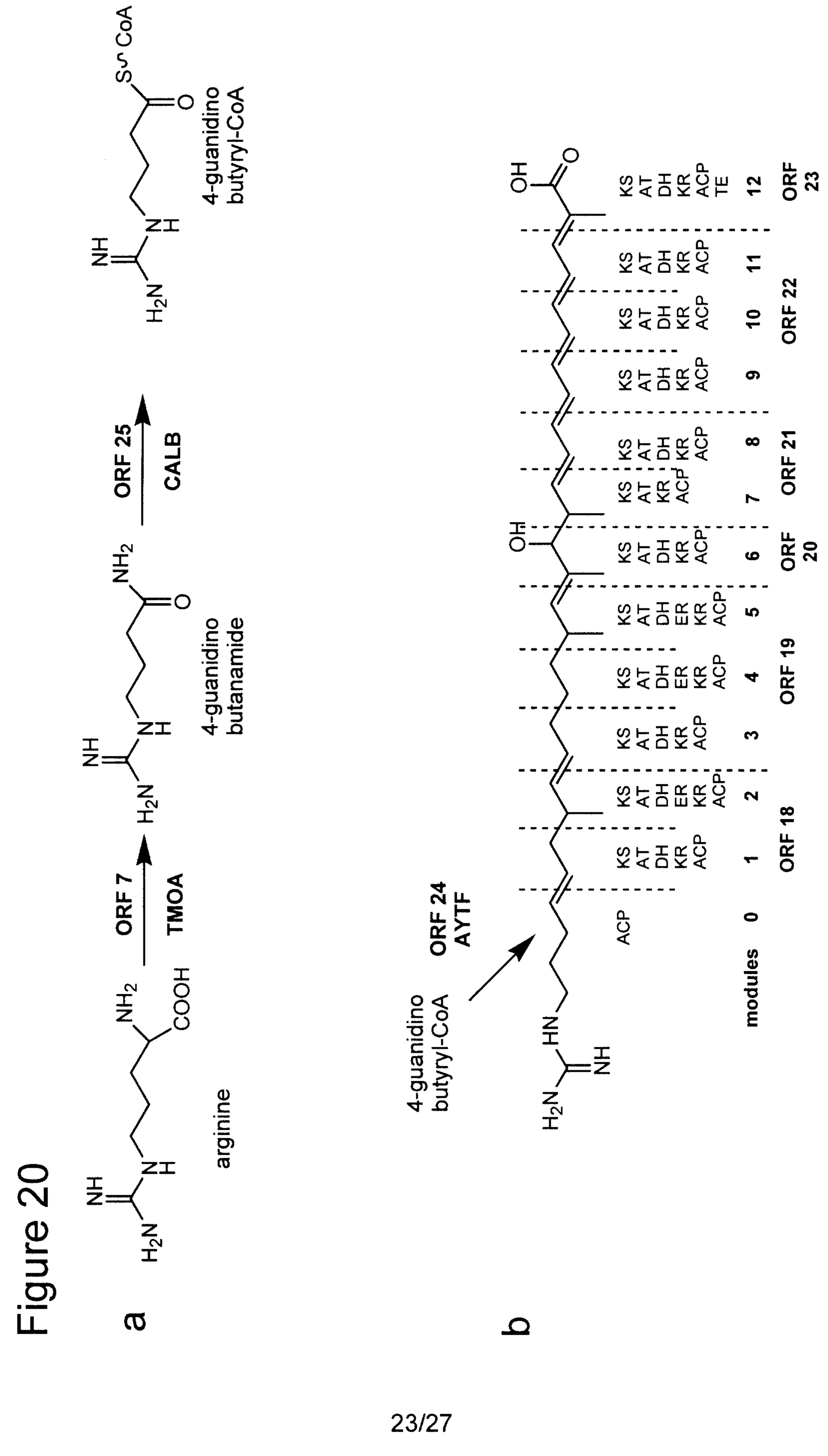
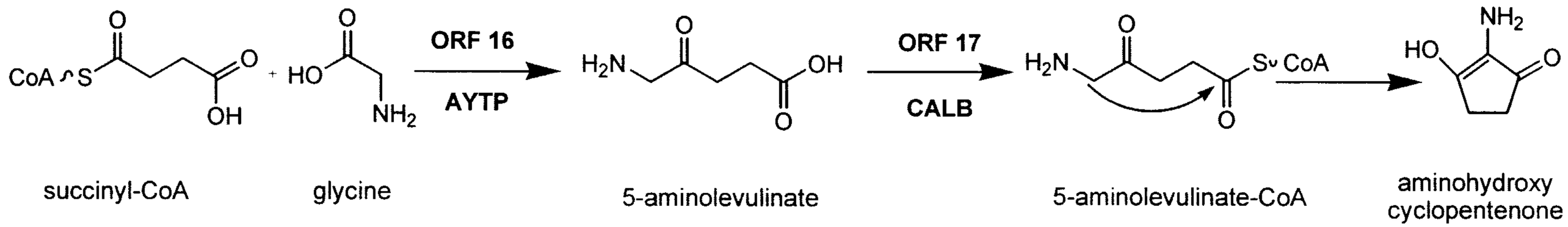
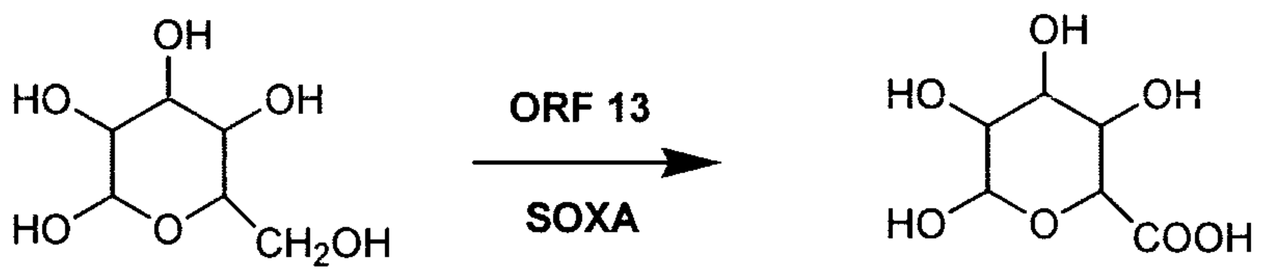

a
arginine
ORF 7
TMOA
4-guanidino butanamide
ORF 25
CALB
4-guanidino butyryl-CoA
ORF 24
AYTF
4-guanidino butyryl-CoA
b
modules 0 1 2 3 4 5 6 7 8 9 10 11 12
ORF 18
ORF 19
ORF 20
ORF 21
ORF 22
ORF 23
KS AT DH ER KR ACP TE

Figure 21

a



b



c

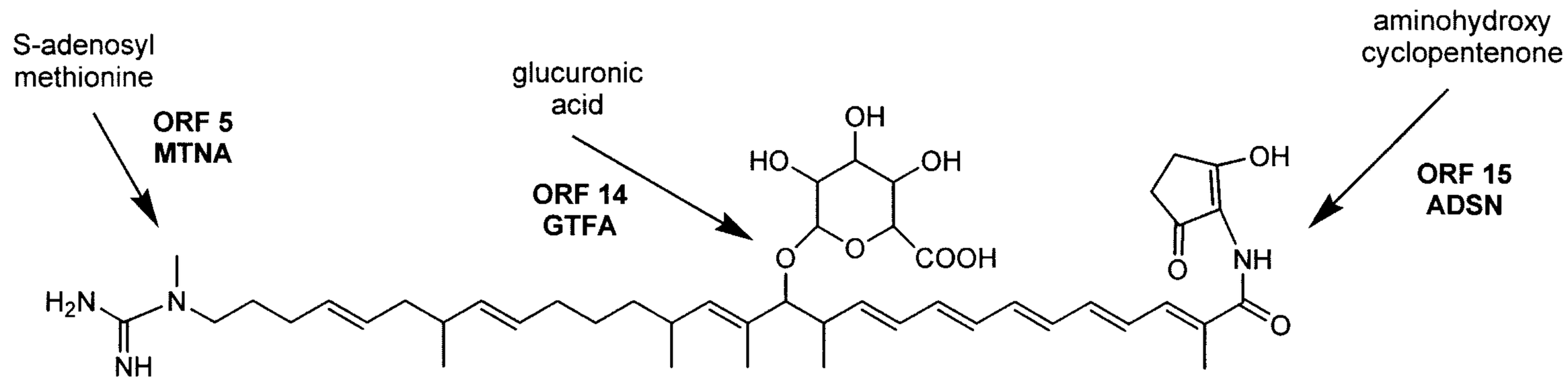


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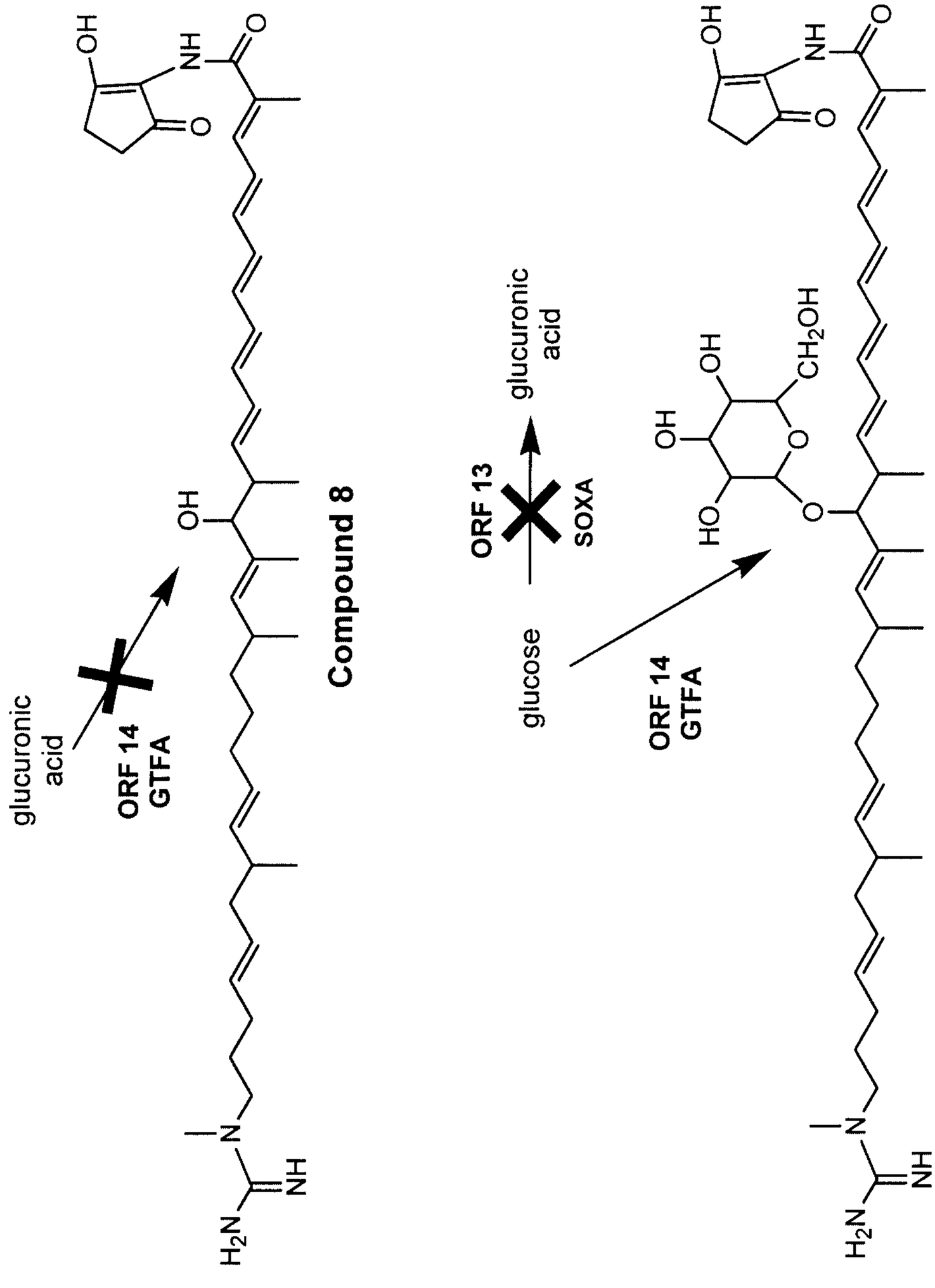
Figure 22


a
glucuronic acid
ORF 14 GTFA
Compound 8
ORF 13 SOXA
glucose
ORF 14 GTFA
Compound 11
b

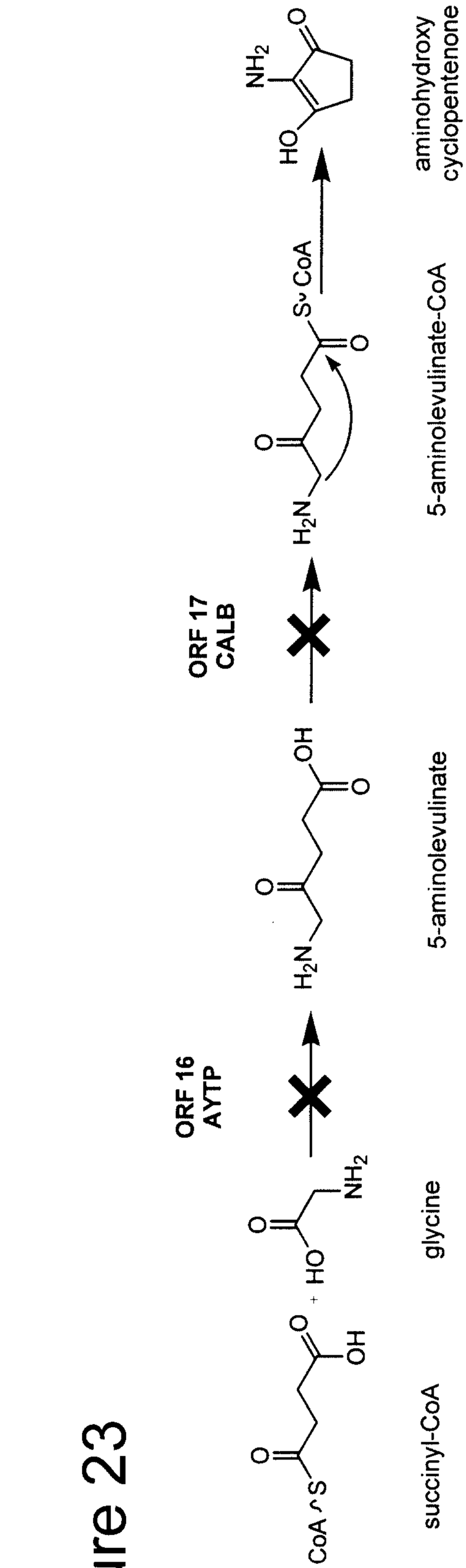

ORF 17
CALB
ORF 16
AYTP
glycine
5-aminolevulinate
succinyl-CoA
5-aminolevulinate-CoA
aminohydroxy
cyclopentenone
aminohydroxy
cyclopentenone
ORF 15
ADSN
Compound 7

Figure 23

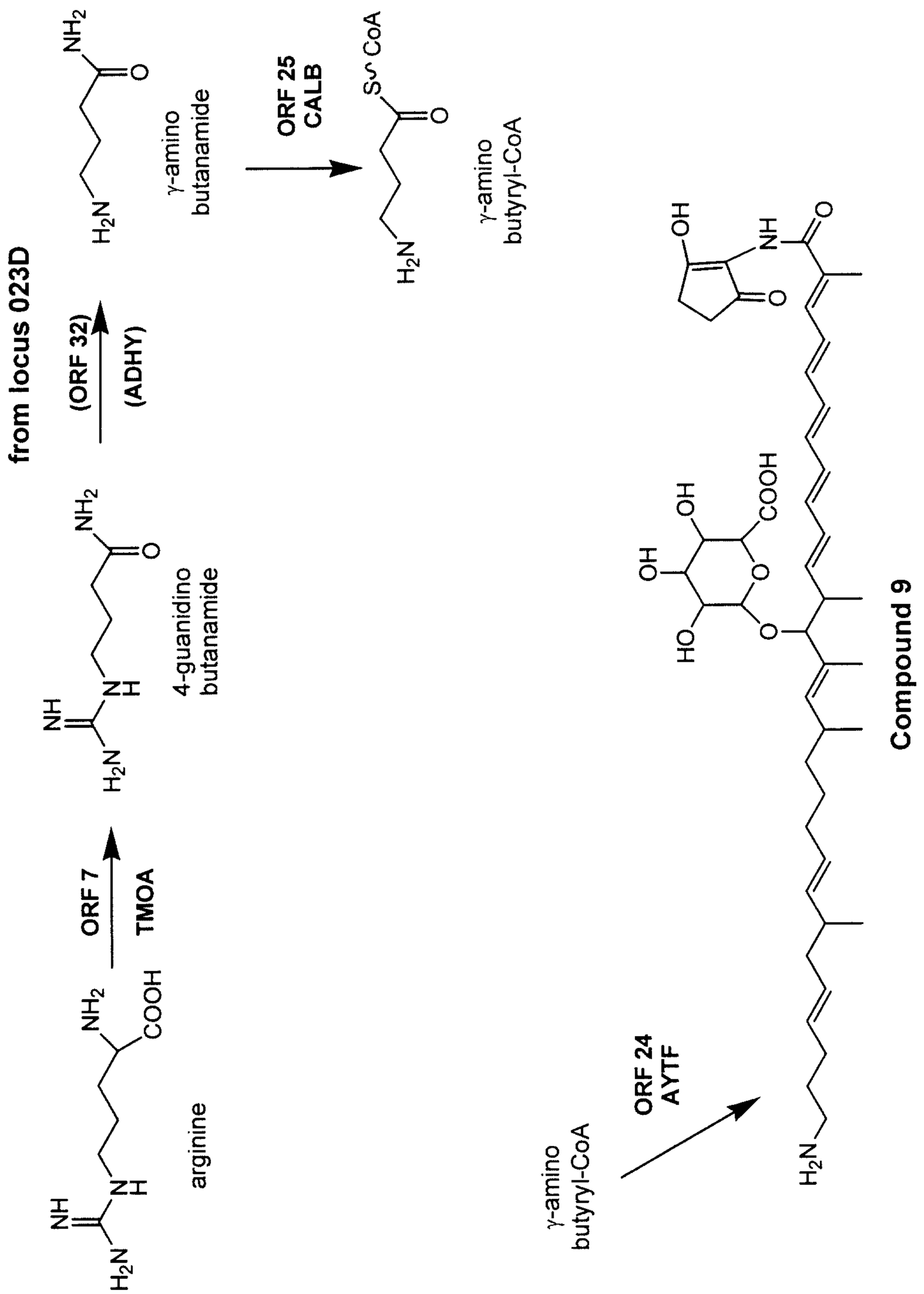

from locus 023D
(ORF 32)
(ADHY)
4-guanidino butanamide
γ-amino butanamide
ORF 25
CALB
γ-amino butyryl-CoA
ORF 7
TMOA
arginine
ORF 24
AYTF
Compound 9

Figure 24